Chiral ligands designed in China

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ABSTRACT

Asymmetric catalysis has become an indispensable and productive field within the Chinese organic chemistry society. The design of chiral ligands is one of the most prominent research areas in this field. Since the late 1990s, Chinese organic chemists have developed numerous chiral ligands possessing novel chiral skeletons and design concepts. Some of these ligands have been widely adopted and can be regarded as ‘privileged ligand’, which have shown excellent performance in many asymmetric catalytic reactions. In this review, we provide an overview of the chiral ligands designed by Chinese scientists with the aim of promoting the development of this area in China and with the hope of encouraging more scientists across the world to use these ligands when designing asymmetric reactions.

Keywords: chiral ligand, asymmetric catalysis, transition metal, Lewis acid, enantioselective

INTRODUCTION

Catalysts are integral to reaction development and industrial processes, since they are able to improve the reactivity and selectivity of specific chemical transformations by increasing reaction yield, allowing lower reaction temperatures and decreasing the amounts of waste byproducts. The steric and electronic properties of metal catalysts can usually be dramatically affected by ligands that coordinate to the metal center. Therefore, ligands, much like a chemist’s hands, manipulate metal-catalysed reactions by controlling the reactivity and selectivity. In other words, chiral ligands provide a chiral environment for the metal being used. Based on this principle, enantioselective catalytic reactions have been developed since the 1950s by intricately designing chiral ligands [1,2]. Interest in this field has accelerated at a phenomenal rate due to increasing demand for enantiomerically pure pharmaceuticals, agrochemicals, flavors and other fine chemicals [1–4].

Thousands of chiral ligands with diverse structures and applications in asymmetric reactions have been developed over the past decades, among which several successful examples have been applied in industrial processes [5–8]. However, many of the present metal-catalysed asymmetric reactions are still far from satisfactory for practical applications. For example, some of the problems associated with today’s ligands are limited substrate and reaction scope. Therefore, the design and preparation of new chiral ligands to improve the utility, activity and selectivity of their related metal catalysts are still challenges for organic chemists.

Since the late 1990s, organic chemistry in China has progressed rapidly due to increasing investment in basic science research by the government. Asymmetric catalysis is one of the most developed and productive research fields in the Chinese organic chemistry community. Numerous chiral ligands bearing novel chiral skeletons and design concepts have been developed by Chinese scientists over the past two decades. A number of them have the potential to be applied in industry and have become well known as so-called ‘privileged ligands’. An overview of efficient chiral ligands developed in China will not only help readers track the development of chiral chemistry in China, but will also encourage chemists to develop new efficient chiral ligands. This review summarizes efficient chiral ligands developed by Chinese chemists in the past 20 years, as well as their representative applications in asymmetric catalysis.

Chiral ligands can be classified into several groups according to their molecular skeleton: chiral spiro ligands (axial chirality); chiral biphenyl ligands (axial chirality); metalloocene-based chiral ligands...
(planar chirality); and chiral ligands with only central chirality. Additionally, Chinese chemists have contributed greatly to the area of unique chiral ligands bearing olefin-coordinating groups. Thus, these types of ligands are discussed in a separate section, even though some of them possess axial chirality (e.g. a biphenyl or binaphthyl backbone). Due to the limitation imposed by article length, only representative applications of some excellent ligands will be discussed. Fortunately, previous reviews and books on related ligands help to alleviate this problem. Chiral organocatalysts and asymmetric reactions developed by Chinese chemists will not be discussed.

**LIGANDS WITH SPIRO BACKBONES**

A great number of chiral ligands as well as chiral catalysts have been reported over the past few decades; however, only a handful bearing particular core structures can be regarded as truly successful as they demonstrate proficiency in a variety of mechanistically unrelated reactions. The spiro backbone, which is present in molecules bearing axial chirality, is completely rigid. However, the use of this skeleton for the design of chiral ligands by chemists occurred much later than that of other kinds of skeletons. This type of chiral skeleton has been well developed by Chinese chemists, especially the spirobiindane skeleton developed by Zhou and co-workers. Ligands bearing this backbone have been found to be highly active and enantioselective in a variety of mechanistically unrelated reactions. In this section, chiral ligands derived from four kinds of spiro skeletons are discussed. Much of this work is based on the elegant ligand design of Chan/Jiang, Zhou and Ding.

**Chiral ligands based on spiro[4.4]nonane**

Chan and Jiang developed the first spiro ligands, **SpiroOP** [9,10] and **SpiroNP** [11], which possess axial chirality and central chirality (Fig. 1). These bisphosphinite ligands have shown excellent enantio-inducing features in the Rh-catalysed hydrogenation of dehydro amino acids. These seminal works promoted the development of chiral spiro ligands for use in transition-metal-catalysed asymmetric reactions. Following Chan’s work, a large number of studies concerning spiro ligands and their application have been reported [12,13].

**Chiral ligands based on 1,1′-spirobiindane scaffold**

The chiral 1,1′-spirobiindane scaffold developed by the Zhou group, which possesses high rigidity, perfect $C_2$ symmetric, simple chirality and can be easily modified, has proved to be an ideal chiral ligand backbone. More than 100 chiral spiro ligands have been designed and prepared using single or multiple steps starting from readily available 1,1′-spirobiindane-7,7′-diol (**SPINOL**). These ligands include diimines **SIDIM**s [14], bisoxazolines **SpiroBOX**s [15], phosphate-oxazolines **SIPHOX**s [16], amino-phosphines **SpiroAP** [17], benzylamino-phosphine **SpiroBAP** [18], diphosphines **SDP**s [19] and a wide range of monodentate phosphines **OPPh$_2$** (R)-**SpirOP**

![Figure 1. Applications in Rh-catalysed hydrogenation with **SpirOP** and **SpiroNP**.](https://academic.oup.com/nsr/article-abstract/4/3/326/3861357)
phosphorous ligands such as SITCPs [20], ShiPs [21], FuPs [22] and SIPHOS [23] (Fig. 2). Chiral spiro ligands have been applied to a variety of mechanistically unrelated reactions and exhibit unique enantioselectivity and reactivity. For example, they can be applied to different metal-catalysed hydrogenations, Cu- and Fe-catalysed carbene insertion reactions, Pd-catalysed umpolung allylations, Ni-catalysed three-component coupling reactions, Rh-catalysed additions of arylborons and hydrosilylation/cyclizations. The chiral spirobipindane has become a ‘privileged’ chiral scaffold. Zhou has composed several elegant reviews to summarize his work [24,25]. We herein describe the significant contributions that Zhou and co-workers have contributed to the chemical community.

Reliable and efficient methods for the construction of carbon–heteroatom (C–X) bonds are highly desirable due to their importance in organic compounds. One of the most efficient approaches to the formation of such bonds is insertion of carbenes into heteroatom–hydrogen bonds (X–H, X = O, N, S, etc.) using Cu-catalysis. Remarkable advances have been made by the Zhou group in this area (Fig. 3). By using chiral spiro bisoxazoline ligands SpiroBOXs (diimine ligand SIDIM for Si-H bonds [15]), a series of catalytic asymmetric insertions of α-diazoesters into N–H, O–H, S–H, and B–H, Ar–H bonds have been developed with high enantioselectivities [16,26–28]. Mechanistic studies showed that the excellent performance of Zhou’s catalyst could be attributed to a novel dinuclear biscooperative catalysis.

Alkenylation is one of the most important reactions in organic synthesis because the vinyl group of the products can be further transformed into various functional groups, so asymmetric alkenylation has attracted much attention. The Zhou group has applied spiro monophosphorus ligands, SIPHOS and SITCP, to two types of Ni-catalysed asymmetric alkenylations (Fig. 4). The first type of asymmetric alkenylation involves three-component addition vinylation using alkyl zinc as the trigger nucleophile, giving good to excellent ees [29,30]. The second alkenylation is a hydrovinylation of α-alkyl vinylarenes. Employing 1 atm of ethylene as a vinyl source, the desired products bearing an all-carbon quaternary stereocenter could be prepared efficiently with high enantioselectivities [31].

The asymmetric hydrogenation of ketones is at the center of asymmetric catalysis. Noyori has developed a highly efficient Ru-catalyst for this reaction (TONs of up to 2 400 000) [32]. Zhou et al. have also carried out some intriguing research using the group’s own Ru catalysts bearing spiro ligands. In 2010, Zhou and co-workers embarked on the design of ligands for Ir-catalysed asymmetric hydrogenations (Fig. 5). Firstly, a SpiroAP ligand bearing amine and phosphine groups was found to be an excellent ligand for the Ir-catalysed asymmetric hydrogenation of exo-cyclic α,β-unsaturated ketones and simple ketones, with up to a 10 000 S/C ratio [33]. After gaining a deep understanding of the hydrogenation mechanism with Ir/SpiroAP, Zhou developed a second-generation ligand for this asymmetric transformation. To avoid the coordination of two
ligands with the iridium metal center, an additional pyridine group was linked to the amino group, giving rise to a tridentate N,N,P-ligand SpiroPAP. The corresponding iridium catalyst of this ligand catalyzes the asymmetric hydrogenation of ketones with excellent enantioselectivities (up to 99.9% ee) and extremely high turnover numbers (TONs of up to 4 550 000). This catalyst has been applied to a variety of substituted ketones for the efficient preparation of useful chiral building blocks [34]. Very recently,
a highly efficient method for the kinetic resolution of racemic aliphatic alcohols, without requiring conversion of the hydroxyl group, has been realized by Zhou using this Ir catalyst. Interestingly, this method involves hydrogenation mediated by a remote ester group via selective reduction of an in-situ reversibly formed (R)-lactone. This method provides chiral \( \delta \)-alkyl-\( \delta \)-hydroxy esters and \( \delta \)-alkyl-1,5-diols in good yields with high enantioselectivities and with a high TON (52000) \[35\].

Zhou’s spiro ligands have been widely used by other organic chemists. They have become important ligands for organic chemists trying to promote higher enantioselectivity. Zhou’s chiral spirobiindane backbone has also been applied in ligands and organocatalysts designed by other groups. This privileged and elegant chiral skeleton will no doubt continue to show its impressive power in more asymmetric reactions.

One example using the spirobiindane skeleton to design new ligands, besides those describe by Zhou et al., can be seen in Fig. 6. Recently, You et al. developed elegant spiro cyclopentadienyl ligands (SCPs) by combining the 1,1’-spirobiindane and cyclopentadienyl scaffolds. These ligands were applied in rhodium-catalysed asymmetric oxidative couplings of biaryl compounds giving satisfying yields (up to 97%) of the desired products with excellent enantioselective control (up to 94% ee) \[36\].

### Figure 5
Ir-catalysed hydrogenation of ketones with high TONs.

### Figure 6
Chiral Spiro Cp Ligands with 1,1’-spirobiindane scaffold.
**Figure 7.** Synthesis of SpinPHOX ligands.

**Chiral ligands based on spiro[4,4]-1,6-nonadiene and spiroketal scaffolds**

Ding et al. designed a novel class of chiral phosphine–oxazoline ligands, SpinPHOX, based on the spiro[4,4]-1,6-nonadiene backbone [37], which could be prepared in five steps from readily available racemic spiro[4,4]nonane-1,6-dione (Fig. 7). The cationic iridium/SpinPHOX complexes were found to be highly efficient for the asymmetric hydrogenation of a broad range of substrates.

Ketimines [37], acyclic α,β-unsaturated carbonyl compounds [38,39] and α,β-unsaturated exocyclic carbonyl compounds, especially challenging α-alkyldiene lactam substrates with six- or seven-membered rings [40], can be hydrogenated to give the corresponding optically active products in excellent yields and enantioselectivities (Fig. 8).

Interestingly, when α,α′-bis(2-hydroxyarylidene) ketones are used as substrates, the iridium/SpinPHOX complex is highly efficient for asymmetric hydrogenation to give the corresponding aromatic spiroketals in high yields with excellent diastereo- and enantioselectivities (Fig. 9). The catalyst plays a dual role in the reaction acting as catalyst for both the hydrogenation of C=C bonds and the subsequent spiroketalization of the bisphenolic ketones. More importantly, two of the desired products could be transformed to a novel type of spiroketal bisphosphine ligand that has a large dihedral angle. X-ray structure analysis of SKP revealed a much larger intramolecular P,P distance than those reported for the analogous ligands SPANphos and Xantphos. The larger P,P distance in SKP favours the adoption of an intramolecular trans-chelating mode or coordination with metals as a monodentate ligand. The fact that the PdCl₂ complex of SKP features a trans-spanning chelating coordination proved these hypotheses [41].

When this SKP ligand was applied in a Pd-catalysed asymmetric allylic amination of Morita–Baylis–Hillman adducts (Fig. 10), the corresponding optically active β-arylamino acid esters were obtained in good yields and with high regio- and enantioselectivities [42]. Mechanistic studies revealed a cooperative action between...
Asymmetricallylic substitutions with Ir/SpinPHOX.

the organo- and organometallic catalysts, which was most likely responsible for its high activity (TON up to 4750), as well as excellent regio- and enantioselectivities. This novel mechanism may inspire the development of more interesting and novel catalysts and organometallic reactions. Based on the key intermediate generated in the allylic amination of Morita—Baylis—Hillman adducts, Ding et al. designed the first highly chemo-, regio- and enantioselective alkoxy carbonylation—amination cascade process of terminal allenes with arylamines, carbon monoxide and methanol via oxidative SKP/Pd(II) catalysis with a Cu(II) salt as the oxidant [43]. Very recently, the Ding group has developed a palladium-catalysed asymmetric allyl–allyl cross-coupling of acetates of racemic Morita–Baylis–Hillman adducts and allylB(pin) using SKP as a chiral ligand. This asymmetric reaction provided a series of chiral 1,5-dienes bearing a vinylic ester functionality in good yields, highly branched regioselectivities and uniformly excellent enantioselectivities [44].

Shortly following the discovery of these diphosphine ligands bearing a large bite-angle, two applications of these ligands have been reported (Fig. 11). In collaboration with Ding, Zhou demonstrated that SKP is an excellent ligand for the Au-catalysed asymmetric cyclopropanation of alkenes with diazo oxindoles [45]. Nakao further realized a Pd-catalysed asymmetric aminocyanation of alkenes by employing SKP as the chiral ligand [46].

In addition, Ding et al. have also developed a spiro bisoxazoline ligand based on a spiroketal skeleton, named SPANBox (Fig. 12). The Zn complex of this ligand shows excellent catalytic activity and provides an excellent chiral environment for the α-hydroxylatin of β-ketoesters. The reaction could be carried out with a low catalyst loading (0.1 mol%) and products could be obtained with up to 99% yield and 98% ee [47].

LIGANDS WITH BIPHENYL BACKBONES

Chiral ligands with biphenyl and binaphthyl backbones are the most widely studied and used ligands in asymmetric catalysis. This is because these skeletons are highly rigid and can be easily modified at the 3,3′-positions, which are close to the reaction center. Chinese organic chemists have also developed several novel types of ligands belonging to this
Figure 13. Transition-metal-catalysed enantioselective reactions with P-Phos.

Figure 14. Asymmetric addition reactions of azomethine ylides with TF-BiphamPhos.

Normal axially fixed chiral ligands

Over the last three decades, tremendous success has been achieved with the use of axially chiral ligands such as Binap, MeO-Biphep and Segphos. In
contrast, the catalytic properties of transition-metal complexes with chiral phosphate ligands embodying heterocyclic moieties such as pyridyl rings remain relatively unexplored. Replacing traditional carbocyclic biaryl backbone in chiral phosphate ligands with diheteroaryl backbone may provide the following desirable features: (i) more interesting chemistry may be introduced by the additional functionality of the heteroaryl rings in the ligand; and (ii) recycling of the catalysts may be possible via a simple acid extraction process (if the ligand possesses basic sites). The most famous axially chiral ligand bearing a heterocyclic backbone, P-Phos, developed by Albert S.C. Chan (Fig. 13), has provided very high levels of absolute stereocontrol in the Ru-catalysed enantioselective hydrogenations of \( \alpha, \beta \)-unsaturated acids and \( \beta \)-keto esters, and simple ketones [48]. Excellent catalytic activity and enantioselectivities have also been obtained with these types of ligands in the Rh-catalysed asymmetric hydrogenation of dehydro-\( \alpha \)-and \( \beta \)-amino acids [49] and the Ir-catalysed asymmetric hydrogenation of heterocycles [50,51]. In addition, P-Phos has also been used successfully in the Cu-catalysed asymmetric hydrosilylation of a series of substrates [52–54] and Ni-catalysed cross-coupling reactions [55].

The Wang group has designed an efficient axially chiral \( P,N \) ligand named TF-BiphamPhos [56]. It behaves as an excellent ligand for Cu-catalysed asymmetric reactions of azomethine ylides, including \([3 + 2]\) cycloadditions, Michael additions and Mannich-type additions (Fig. 14). The free amine \( \text{NH}_2 \) may also act as a hydrogen bond donor for control of the electrophiles. \([3 + 2]\) cycloaddition is one of the most important reactions for the construction of cyclic compounds. For azomethine ylides derived from amino esters other than glycinate, however, it used to be difficult to achieve high efficiency and excellent enantio-/diastereoselectivity. When a TF-BiphamPhos/Cu complex was used in this reaction, excellent reactivity, selectivity and structure scope were uniformly observed for various azomethine ylides, especially those derived from amino esters [57]. Although azomethine ylides are widely used in 1,3-dipolar cycloaddition reactions to construct five-membered pyrrolidine frameworks, direct catalytic asymmetric \([6 + 3]\) cycloaddition reactions to build larger, enantio-enriched heterocyclic molecules have been met with little success [58]. Wang et al. have described two types of asymmetric \([3 + 6]\) cycloaddition of imino esters with readily available fulvenes or 2-acyl cycloheptatrienes catalysed by Cu/TF-BiphamPhos. A broad range of substrates can undergo cycloaddition under mild reaction conditions with good yields, excellent diastereoselectivities and high enantioselectivities. An unprecedented substrate-controlled catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides employing 2-ester cycloheptatrienes has been disclosed [59].

The Cu(I)/TF-BiphamPhos complex can also catalyse the direct asymmetric Mannich reaction (Fig. 15) of glycine Schiff bases with N-tosylamines. A broad range of substrates are tolerable to the reaction conditions, furnishing anti-adducts of various \( \alpha, \beta \)-diamino acid esters in good yields with up to 94:6 diastereoselectivity and 97% ee [60]. A novel catalytic asymmetric Michael addition of azomethine ylide with \( \beta \)-substituted alkylidene bisphosphonates was also realized using this chiral catalyst [61]. The optimized system provides a unique and facile access to enantioenriched unnatural \( R \)-amino acid derivatives containing gem-bisphosphonates (gem-BPs) in high yields with excellent diastereo- and enantioselectivities. Wang has
also successfully developed an asymmetric construction of highly functionalized spiro compounds using a Cu(I)/TF-BiphamPhos-catalysed tandem reaction protocol [62]. In 2003, the Shi group developed the first axially chiral biphenyl bis-NHC ligand (Fig. 16). The rhodium complex of this ligand has shown good catalytic activity and provides a well-defined chiral environment for the asymmetric hydrosilylation of ketones [63]. Kinetic resolution of secondary alcohols was feasible with a Pd complex of Shi’s biphenyl bis-NHC [64]. Palladium complexes with different counter-ions could also be applied in the addition of aryloboronic acids or enolate nucleophiles to $\alpha,\beta$-unsaturated compounds or imines [65–67]. Excellent yields and enantioselectivities were observed for all of these reactions.

You et al. synthesized a series of novel N-aryl phosphoramidite ligands, THQphos, from enantiopure BINOL and 2-methyl-1,2,3,4-tetrahydroquinoline [68]. Their catalytic mechanisms in iridium-catalysed allylic alkylation reactions were studied. Density Functional Theory (DFT) calculations and X-ray crystallographic analyses of the ($\pi$-allyl)$--\text{Ir}$ complexes revealed that the active iridacycle was formed via $\text{C}(\text{sp}^3)\text{H}$ bond activation [69]. A wide variety of substrates, including ortho-substituted cinnamyl carbonates, offered high regio- and enantioselectivities in iridium-catalysed allylic alkylation reactions (Fig. 17). These ligands were found to be efficient for the iridium-catalysed dearomatic allylation of various aromatic heterocycles and naphthalene to give a series of chiral heterocycle skeletons with high diastero- and enantioselectivities. These compounds are useful intermediates for the total synthesis of natural and pharmaceutical products [70,71].

**Axially unfixed or $D_2$-symmetric chiral biphenyl ligands**

Biphenyl compounds bearing hydrogen atoms at the 6,6' positions usually have an unfixed axis and are named *tropos* compounds. W. Zhang et al. developed a novel type of chiral *tropos* biphenyl phosphine–oxazoline ligand (BiphPHOS) (Fig. 18). When this type of ligand coordinates to metals such as Pd(II) and Ir(I), only (aS)-complexes are formed, possibly due to steric hindrance presents in the (aR)-complexes [72]. The iridium complex (aS)-Ir/BiphPHOS behaved as an efficient catalyst for the asymmetric hydrogenation of a series of exo-cyclic olefins [73,74].

Based on a similar chiral chelation-inducement principle, W. Zhang et al. developed another novel type of chiral biphenyl ligand bearing four identical oxazoline groups at four *ortho* positions (Fig. 19).

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**Figure 17.** Iridium-catalysed allylic substitutions reactions with THQphos.

**Figure 18.** *Tropos* BiphPHOS ligands and applications in asymmetric hydrogenation.

**Figure 19.** Tetraoxazoline ligands for highly enantioselective Wacker-Type cyclization.
Figure 20. $D_2$-Phosphoramidites ligands for enantioselective Cu-catalysed addition of organometallic reagents.

Figure 21. Design and applications of chiral oxovanadium(IV) complexes.

There is no axial chirality in the ligand due to molecular symmetry when it is coordinated with one or two palladium ions. Axial chirality can be induced by destroying the molecular symmetry [75]. These types of ligands have been successfully applied in palladium-catalysed asymmetric Wacker-type cyclizations.

Following a similar design concept (Fig. 20), when the $D_{2h}$-symmetric [1,1′-biphenyl]-2,2′,6,6′-tetrals react with a chiral phosphorous source, a trans-(aR)-phosphoramidite with one of four possible configurations is obtained as the major isomer [76]. The application of these ligands in Cu-catalysed asymmetric 1,4-additions of hard organometallic reagents revealed their excellent environment for enantioinduction [77].

The Chen [78] and Uang groups [79] found that chiral vanadyl complexes were promising catalysts for the oxidative coupling of 2-naphthols.
These two groups have independently designed similar oxovanadium complexes of chiral Schiff bases for use in an asymmetric variant. The Gong group proposed that the enantioselectivity could be improved by introducing another suitable chiral center in close proximity to the naphthoxy or phenoxo group(s) (Fig. 21). Based on this idea, they designed novel bi-2-naphthol oxovanadium(IV) complexes (V1) [80]. In the oxovanadium complexes derived from binaphthol, the (R)-configuration of the axial chirality matches (S)-amino acids and so favours stereocenters. In 2004, the same group developed achiral biphenol oxovanadium(IV) complexes (V2) which are structurally similar to V1, except that the binaphthyl unit of V1 is replaced with a conformationally flexible biphenyl unit [81]. CD spectral and experimental studies indicated that the axial chirality (aR) of the vanadium complex V2 is created from the chiral amino acid groups (S) and is essential for the stereocenters. Excellent enantioselectivities for a large number of mono- and di-substituted 2-naphthols can be obtained using 5 mol% of the optimal catalyst V2. A bimetallic intramolecular radical–radical coupling mechanism has been proposed based on kinetic studies, cross-coupling experiments and HRMS spectral (High Resolution Mass Spectrometry) studies of the reaction [82].

**LIGANDS WITH METALLOCENE BACKBONES**

Great advances in the use of planar chiral ligands have been made within the last few decades. Some of these chiral ligands have shown excellent activity to promote metal-catalysed asymmetric reactions [6], such as Ugi’s base-derived bisphophine ligand Josiphos. The metallocene is the most popular backbone for these types of ligands, especially ferrocene, which is commercially available and inexpensive. Therefore, metallocene-based chiral ligands have attracted much attention from Chinese organic chemists. An overview of metallocene-based chiral ligands developed by Chinese scientists is provided in this section with topics ranging from ferrocene-derived chiral ligands with/without planar chirality to ruthenocene-derived chiral ligands.

**Ferrocene-derived chiral ligands without planar chirality**

Ferrocene-based phosphine–oxazoline ligands have been well studied, including ligands with/without planar chirality. Although these ligands have shown excellent enantioinduction for the allylic substitution of 1,3-disubstituted allylic esters, the preferential formation of branched products is always challenging.
Figure 25. Pd-catalysed [3 + 2] cycloaddition with SiocPhox.

Figure 26. Pd-catalysed cyclopropanation of acyclic amides with SiocPhox.

Figure 27. Cu-catalyzed propargallic substitutions and cycloadditions with tridentate \( P,N,N \)-ligands.

when unsymmetrical substrates are used (Fig. 22). This is rationalized by the fact that the R group of the unsymmetrical allyl is positioned on the P side of the allyl-Pd intermediate, and the stronger trans effect of P compared to N causes the C-atom trans to P to be the site of nucleophilic attack. On the basis of steric considerations, the Hou and Dai groups designed cyclic phosphonates using the bulky RL groups on the P to push the R group to the oxazoline side, in order to control regioselectivity for the branched product [83]. Although the reaction of BINOL with a ligand precursor did not give the cyclic phosphonate as envisaged, a phosphonamidate with a free OH group on the BINOL moiety was obtained (SiocPhox). In this case, a new chiral center was formed on the P atom and four diastereoisomers were obtained by using the binols with two different configurations. The free OH functionality was retained, which is crucial for Pd-catalysed asymmetric allylic substitution reactions and particularly for amination reactions.

All four diastereoisomers of SiocPhox gave branched allylic alkylation products with good regio- and enantioselectivity (Fig. 23). Ligands \((S,S_{phos},R_a)-SiocPhox\) and \((S,R_{phos},S_{a})-SiocPhox\) gave better results in alkylation reactions, while \((S,R_{phos},R_a)-SiocPhox\) and \((S,S_{phos},S_{a})-SiocPhox\) were better in amination reactions [84]. The difference between these two sets of ligands can be explained by the possible formation of a hydrogen bond between the free OH group of the ligand and the amine nucleophile in the amination reaction. Control experiments with O-methyl protected SiocPhox support their proposal.

The use of other carbon nucleophiles and 2-aryl-but-3-en-2-yl acetate [85,86] also gives the desired products with excellent branched regioselectivity and good enantiomeric excesses (Fig. 24). The chiral center present in the nucleophiles was controlled by the SiocPhox ligand, resulting in the successful construction of quaternary stereocenters or the kinetic resolution of \( \beta \)-chiral ketones [87,88]. The generation of contiguous stereogenic centers in the products was realized via the reaction of ketones with
allylic substrates. Branched anti-products were obtained in excellent regio-, diastereo- and enantioselectivities [89,90].

The SiocPhos ligands have also been applied successfully to a highly diastereo- and enantioselective palladium-catalysed asymmetric [3 + 2] cycloaddition reaction of vinylaziridines with enones using a single activator [91]. The free OH group of the ligand may act as a hydrogen bonding group that anchors and activates the $\alpha, \beta$-enones (Fig. 25).

In most cases involving Pd-catalysed allylic alkylation reactions, the products are formed via attack of nucleophiles to the terminal carbon of $\pi$-allyl-Pd intermediates. The formation of cyclopropane via attack of nucleophiles at the central carbon of $\pi$-allyl-Pd intermediate is rare. When N,N-diphenyl acrylonitrile reacted with monosubstituted allylic substrates, an interesting asymmetric cyclopropanation reaction occurred in the presence of a Pd/SiocPhos catalyst and LiCl additive (Fig. 26). Cyclopropane derivatives with three chiral centers were obtained with high diastereo- and enantioselectivities [92].

**Figure 28.** Cu-catalyzed allylic substitution with $P,S$-ligands.

**Figure 29.** Synthesis of bisphosphine-thiourea ligand (zhaoPhos).

**Figure 30.** Rh-catalysed asymmetric hydrogenations with zhaoPhos.

**Figure 30.** Rh-catalysed asymmetric hydrogenations with zhaoPhos.

**Ruthenocene-derived planar chiral ligands**

Hu *et al.* developed Ugi amine-derived tridentate $P,N,N$-ligands, which were easily prepared in three-step reactions. Interestingly, Hu developed a Cu-catalysed [3 + 3] cycloaddition of propargyl esters with cyclic enamines for the preparation of chiral bicyc[n,3,1] compounds by employing a ferrocene tridentate ligand and attack at the $\alpha$ and $\gamma$ positions [93]. These chiral tridentate $P,N,N$-ligands also demonstrated excellent catalytic activity for Cu-catalysed propargylic aminations [94]. Subsequently, Hu developed other types of tridentate $P,N,N$-ligands which do not possess planar chirality [95–100]. These simple ligands have been applied in several Cu-catalysed propargylic substitutions and cycloadditions, affording important chiral building blocks and heterocycles with excellent ee (Fig. 27).

Chen has developed several $P,S$-ligands derived from Ugi’s base and has applied them to a Pd-catalysed asymmetric allylic substitution (Fig. 28) [101,102]. The application of these ligands in other asymmetric reactions is worthy of further exploration [103].

X. Zhang *et al.* combined metal catalysis and organocatalysis to develop a novel chiral bisphosphine–thiourea ligand. The ligand consists of a chiral ferrocenyl bisphosphine scaffold that acts as the coordinating functionality and a tunable thiourea as a hydrogen bond donor [104]. The ligand was easily prepared from readily accessible Ugi’s amine (Fig. 29).

This chiral bisphosphine–thiourea ligand (zhaoPhos) was applied in the rhodium-catalysed asymmetric hydrogenations of $\beta,\beta$-disubstituted nitroalkenes [104], unprotected NH imines [105], $\beta$-amino nitroolefins [106], $\alpha,\beta$-unsaturated amides and esters [107], maleimides, 3-aryl succinimides and 3-methyl succinimides [108] and heteroarenes such as isquinolines and quinolones [109] (Fig. 30).

**Ruthenocene-derived planar chiral ligands**

The distance between the two cyclopentadienyl rings of ruthenocene is approximately 10% longer
Figure 31. W. Zhang’s ruthenocene-derived ligands in asymmetric catalysis.

Figure 32. Design of $N,N'$-dioxide ligands and their applications.
Ligands with chiral carbon

Most chemists are concerned with developing new ligands for organometallic reactions; however, Lewis acid-catalysed reactions are also very important in organic synthesis. Such reactions include addition reactions, Diels-Alder reactions and so on. Privileged chiral ligands including Salen, BOX, PyBOX and Binol derivatives are often used in Lewis acid-catalysed asymmetric reactions but there are still some reactions for which they are ineffective. Research is currently being carried out to solve these problems.

Feng and co-workers developed well-designed N,N'-dioxide ligands bearing not only chiral carbon atoms, but also chiral nitrogen atoms [116]. It acts as a tetradentate ligand coordinating to a metal center via four oxygen atoms of two amide groups and two amine oxides. The multidentate, hard and neutral properties of these ligands allow facile and strong coordination with hard Lewis acid metal ions. Their C$_2$-symmetry and the ability to easily modify their structure mean that the chiral environment of these ligands can be altered to be suitable for different substrates and reactions. Due to these characteristics, such ligands are privileged chiral ligands for a wide range of asymmetric catalytic reactions (Fig. 32).

Feng’s N,N'-dioxide ligands can be prepared practically over four simple steps from readily available cyclic chiral amino acids, such as L-proline, L-pipecolic acid, L-ramipril and (S)-tetrahydroisoquinoline-3-carboxylic acid (Fig. 33). Efficient metal catalysts generated from these ligands have been reported, by coordination of the ligand to a wide variety of metal ions, including rare-earth metals (e.g. Sc$^{3+}$, Y$^{3+}$, La$^{3+}$, Nd$^{3+}$, Sm$^{3+}$, Eu$^{3+}$, Gd$^{3+}$, Yb$^{3+}$), transition metals (e.g. Ti$^{4+}$, Fe$^{3+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Cu$^+$, Zn$^{2+}$, Ag$^+$, Au$^+$) and main group metals (e.g. Mg$^{2+}$, In$^{3+}$) etc. These catalysts have been applied in many Lewis-acid-catalysed reactions [116,117]. For some of these reactions, the catalyst loading can be lowered to 0.05 mol%, for example in the Roskamp-Feng reaction [118] and haloamination [119]. The following work describes recent advances reported by Feng and co-workers.

![Figure 33. Preparation of N,N'-dioxide ligands.](image)

![Figure 34. Sc(III)-catalysed enantioselective α-arylation with N,N'-dioxide.](image)
Chiral Lewis acid catalyst of a \( N,N' \)-dioxide-Sc(OTf)_3 complex bearing tetrahydroisoquinoline backbones performed well in the reaction of \( N \)-unprotected 3-substituted oxindoles with diaryl iodonium triflates under mild reaction conditions (Fig. 34). This new asymmetric catalytic strategy for the \( \alpha \)-arylation of carbonyl compounds gave chiral oxindole derivatives bearing a quaternary center with high enantioselectivity and reactivity (up to 99% ee and 99% yield) [120].

Feng has developed mild and highly enantioselective Claisen rearrangements of both propargyl and allyl vinyl ethers accelerated by a readily available chiral nickel(II)/\( N,N' \)-dioxide complex (Fig. 35). A wide range of substrates were tolerated with the products being obtained in high yield and enantioselectivity. An asymmetric allyl vinyl rearrangement could be carried out with a low catalyst loading of 0.5 mol% [121].

Ring-opening reactions of cyclopropane derivatives are an important class of transformation for the construction of chiral \( \gamma \)-functionalized compounds. The Feng group has applied a chiral \( N,N' \)-dioxide/scandium(III) complex as a highly efficient catalyst to the first asymmetric ring-opening reaction of cyclopropyl ketones with primary amines. Interestingly, an asymmetric catalytic synthesis of chiral 2,4,5-trisubstituted 2,3-dihydropyrroles with excellent enantioselectivities (up to 97% ee) [122]. When thiols, alcohols and carboxylic acids were used as nucleophiles, the corresponding sulfoxides, ethers and esters were obtained in up to 99% yield and 95% ee [123].

Chiral cyclobutanes are present in a wide range of bioactive molecules. The Feng group developed a \( [2 + 2] \) cycloaddition of alkynes with cyclic enol silyl ethers by using a chiral \( N,N' \)-dioxide/Zn(NTf₂)₂ complex as a highly efficient catalyst (Fig. 37). It is noteworthy that a wide range of alkynes, including terminal alkynes and internal alkynes, can be used in this reaction. A series of fused cyclobutenes were obtained in good yields with high enantioselectivities (up to 97%) [124]. Furthermore, the products can be easily transformed into fused cyclobutane derivatives via conjugate addition.

Relay catalysis, a strategy for combining two catalytic cycles into one reaction, can construct complex structures efficiently. Very recently, the Feng group developed two examples of gold(I)/chiral \( N,N' \)-dioxide–nickel(II) relay catalysis (Fig. 38). One is an asymmetric tandem hydroalkoxylation(hydroamination)/inverse-electron-demand hetero-Diels-Alder reaction, which provides spiroketals and spiroaminals in high yields with up to >99% ee [125]. The other is an asymmetric tandem intermolecular hydroalkoxy-
The remote control of enantioselection is difficult due to the long communication distance between the reactive site of the substrate and the chiral center of the catalyst. The development of highly efficient catalysts to overcome this challenge is of great importance and highly desirable. The introduction of an additional side-arm group to the ligand may allow for tuning of the electronic properties, the chiral spaces and the shapes of the catalytic site of the complex. Based on the bisoxazoline framework, the Tang group has developed two series of ligands using this side-arm strategy, namely trisoxazoline (TOX) ligands and side-armed bisoxazoline (SaBOX) ligands [127]. The ‘side arm’ may adopt different roles in different environments; for example, it can act as a ligating group, a steric group or a directing group, depending on the metal and the functionality at the side arm (Fig. 39). Metal catalysts based on these ligands have proven to be highly efficient for a number of asymmetric transformations, including Friedel–Crafts reactions, Kinugasa reactions, Nazarov reactions, 1,2-Stevens rearrangements, Cannizzaro reactions, cyclopropanations and ring-openings of cyclopropane [128]. In comparison to the parent BOX ligands, the metal catalysts based on these TOX and SaBOX ligands usually exhibit higher efficiency and diastereo- and enantioselectivity. These ligands are prominently used for the remote control of enantioselection in conjugate additions to alkylidene malonates and ring-opening/cyclization cascades of cyclopropanes, for which high stereoselectivity is usually difficult to achieve due to poor chiral communication.

The side-arm strategy has also been applied in the design of well-known chiral mono-phosphoramidate ligands, phosphoric acid organocatalysts and many other chiral ligands (Fig. 40). The work of Tang and other groups has demonstrated that the side-arm strategy can be employed as a general principle for ligand and catalyst design. Herein we discuss four of the aforementioned reactions. In the addition reaction of 2-methylidemalonate, the coordination of both ester groups of malonate to the metal center, forming a rigid six-member ring (Fig. 41, mode A) is crucial for the activation of substrates. Figure 42 clearly shows that the catalytic results of TOX ligands are much better than that of BOX due to the presence of the side arm [129,130].

Similarly, cyclopropane-1,1-dicarboxylates can also bind to the metal center (Fig. 41, mode B), and good discrimination between the two enantiomers of cyclopropane is most likely established with the assistance of side-arm groups, thus enabling asymmetric transformations based on (dynamic) kinetic resolution of racemic 2-substituted cyclopropane-1,1-dicarboxylates [131]. A series of efficient and highly enantioselective ring-opening reactions and ring-opening/cyclizations (ring expansions) were developed for the preparation of useful building blocks or skeletons of bioactive molecules (Fig. 43). In all the reported examples, the TOX and SaBOX ligands gave the desired products with higher diastereo- and enantioselectivity compared to the corresponding BOX ligand [132–138]. It should be noted that, for Ni(II)-catalysis, TOX is usually used as a tridentate ligand. The DFT calculations indicated that the benzene ring of the
Figure 43. Ring-opening reactions and ring expansions with ligand TOX or SaBOX.

Figure 44. The control of cis/trans selectivity for cyclopropanation.
reactivity. This unique model provides a new basis for ligand design.

Intermolecular hydrogen bonding was also discovered in another structurally related ligand. When DopenPhos was used as a ligand to promote the Rh-catalysed asymmetric hydrogenation of \( \alpha \)-substituted ethenylphosphonic acids, Ding found that DopenPhos was hydrolysed in situ to give a chiral monodentate secondary phosphine oxide (SPO) ligand (Fig. 48). High efficiency and enantioselectivity have been achieved using SPOs as chiral ligands, affording optically active phosphonic acids with high ee values and a turnover number of up to 10 000 [146]. These SPO ligands were also found to be highly enantioselective in the Rh-catalysed asymmetric hydrogenation of \( \alpha \)-arylacrylic acids and \( \beta \)-arylbuto-3-enolic acids [147].

**Ligands with chiral phosphorus**

P-chiral phosphine ligands have proved to be highly efficient for asymmetric hydrogenation and cross-coupling reactions due to the electron-rich and bulky character of the phosphine groups. The first chiral phosphorus ligand applied in an industrial process, DIPAMP, belongs to this family of chiral ligands. Imamoto and X. Zhang have contributed greatly to this area of research. Recently, the Tang group in China has also become active in this area.

W. Tang designed a series of novel P-chiral monophosphorus ligands [148]. One salient structural feature of Tang’s ligands is the rigid framework of the 2,3-dihydrobenzo[\( d \)][1,3]oxaphosphole structure on the upper aryl ring. This group defines the orientation of the phosphorus atom for metal coordination. Such rigidity limits the preferred configuration of the corresponding complex. Another important advantage of Tang’s ligands is that the upper aryl ring can be easily modified, allowing fine-tuning of the overall steric environment (Fig. 49).

These ligands exhibit high efficiency in asymmetric Suzuki-Miyaura coupling reactions, enabling the construction of an array of chiral biaryl products in high yields and excellent enantioselectivities (up to 99% ee) under mild conditions [148]. Interestingly, computational studies have revealed that a \( \pi - \pi \) or polar–\( \pi \) interaction between the two coupling partners can enhance the enantioselectivity. This asymmetric coupling reaction has been employed in the total syntheses of the chiral biaryl natural products korupensamine A and B, allowing a concise and stereoselective synthesis of michelamine B [149]. The W. Tang group has further applied their chiral phosphine ligands to the efficient synthesis of P-chiral biaryl phosphonates via a palladium-catalysed asymmetric cyclization of diaryl 2-bromo arylphosphonates [150] as well as to the synthesis of a series of chiral tricyclic phenanthrene derivatives bearing an all-carbon...
quaternary center via a palladium-catalysed dearomatic cyclization Heck reaction [151]. The former method provides convenient access to various P-chiral biaryl monophosphines, while the latter method has provided a new strategy for the efficient synthesis of terpenes and steroids. Recently, a highly enantioselective alkene aryloxyarylation that has led to the formation of a series of 1,4-benzodioxanes, a 1,4-benzoazoxine and chromans containing quaternary stereocenters has been realized with high enantioselectivities and good yields [152]. The application of this method to the synthesis of the chiral chroman core structure of α-tocopherol has also been demonstrated (Fig. 50).

The application of Tang’s monophosphine ligands in asymmetric Ni-catalysed intramolecular and intermolecular cascade addition reactions has also been successful (Fig. 51). The first highly enantioselective Ni-catalysed reductive cyclization of alkynones was realized by employing the ligands AntPhos or BI-DIME. Chiral tertiary allylic alcohols with various alkyl/aryl substituents bearing furan/pyran rings were efficiently prepared with excellent yields and ee values. Mechanistic studies demonstrated that a Ni catalyst with a single chiral monophosphine ligand may be the active catalyst species [153]. An intermolecular alkylative alkyne–aldehyde cross-coupling was also developed by employing a BI-DIME/Ni catalyst. This three-component reaction gave the desired chiral tetrasubstituted olefinically allylic alcohol with excellent regio- and enantioselectivities [154].

The BI-DIME ligand was also found to be the superior ligand for the Rh-catalysed asymmetric hydroboration of α-arylenamides with (Bpin)2 as the reagent (Fig. 52). This method provides a succinct synthesis of a series of chiral α-amino tertiary boronic esters in good yields, and with excellent Markovnikov selectivities and enantioselectivities [155].

In 2013, the Tang group designed a novel bisphosphine ligand with a deep and well-defined chiral pocket by installing R groups that protrude directly towards the substrate coordination site (Fig. 53). This ligand, named WingPhos, has shown high efficiency in the rhodium-catalysed asymmetric hydrogenation of (E)-baryl-N-acetyl enamides, cyclic β-aryl enamines and heterocyclic β-aryl enamines, giving hydrogenated products with excellent enantioselectivities at high s/c ratios (up to 10 000 TON) [156]. This method holds promise for the practical synthesis of various chiral β-arylamine compounds. When this type of bisphosphine ligand was used in the Rh-catalysed addition of aryloboronic acids to trifluoromethyl aryl ketones, high yields and excellent ees were also observed [157].
Ligands with chiral sulfur

Ligands with chiral sulfur groups have not been significantly studied in past but have recently gained more attention. Chinese scientists have contributed greatly to the development of chiral ligands containing chiral sulfoxide or sulfinamide building blocks. Several types of useful ligands possessing different properties have been developed by combining one of these two chiral groups with other coordinating groups. It is worth mentioning that the use of stereogenic sulfoxide or sulfinamides as key chiral directing groups is advantageous to design chiral sulfur ligands allowing easy and practical synthesis.

J. Zhang et al. [158] designed new types of chiral sulfinamide monophosphine ligands (Ming-Phos), and synthesized two sets of diastereomeric (R,R)- and (S,R)-configured Ming-Phos ligands using a two-step procedure (Fig. 54).

A polymer-supported-Ming-Phos gold catalyst was developed using an efficient method, in which the chiral ligand can easily copolymerize with styrene with minimal cross-linking [159]. For the gold(I)-catalysed asymmetric cycloaddition reaction of 2-(1-alkynl)-alk-2-en-1-ones with various nitriles, both Ming-Phos enantiomers ((R,R)-Ming-Phos and (S,R)-Ming-Phos) furnished the desired cycloadducts in high yields (up to 99%) and with excellent diastereo- and enantioselectivities (up to 99% ee). Compared with homogeneous catalysts, the polymer-bound gold catalysts exhibited similar catalytic activity (74–89% yield, 90–99% ee). Moreover, this polymer-bound gold catalyst can be recycled eight times with no loss of enantioselectivity; it is applicable to large-scale synthesis (Fig. 55).

Ming-Phos ligands have also been applied to a copper(I)-catalysed asymmetric [3 + 2] cycloaddition reaction of azomethine ylides with β,β,β-trifluoromethyl β,β-disubstituted enones (Fig. 56). This reaction provides a scalable and efficient synthesis of highly substituted pyrrolidines with trifluoromethylated, all-carbon quaternary stereocenters in good yields with >20:1 d.r. and 98% ee [160].

Xiang-Phos, derived from Ming-Phos, contains P substituents bearing more sterically bulky adamantyl groups (Fig. 57). Its application in gold-catalysed asymmetric [2 + 2] cycloadditions between 3-styrylindoles and N-allenyl oxazolidinone gave chiral cyclobutane products in good yields with up to 95% ee [161].

The W. Xiao group has also designed new types of P-sulfinyl ligands [162–164] that have shown excellent enantioselectivity in Pd-catalysed asymmetric allylic substitutions (Fig. 58). Very recently, P,S-ligands were developed by the same group for similar reactions [165,166]. A Michael addition/allylic...
Figure 59. Pd-catalysed asymmetric allylic substitution with hybrid P,S ligands.

Figure 60. Rh-catalysed asymmetric additions with SOP ligands.

Figure 61. Cu-catalysed asymmetric additions of boron with SOP ligands.

Substitution cascade cyclization was realized using this ligand, furnishing the desired chiral terahydroquinoline products in good yield with excellent diastereo and enantioselectivities (Fig. 59) [165].

In 2010, the Liao group developed novel types of simple chiral tert-butanesulfinylphosphine (SOP) ligands that bear chirality at the sulfur atom [167]. The RH complexes of these ligands were found to be efficient catalysts for the Rh-catalysed 1,4-addition of arylboronic acids to electron-deficient olefins and 1,2-addition to ketones (Fig. 60). Excellent activities and enantioselectivities in these reactions were demonstrated. Good regioselectivity could be achieved with the preferential formation of the 1,4 addition adducts of $\beta,\gamma$-unsaturated $\alpha$-ketoamide substrates when the SOP ligand, $o,o'$-bis(sulfoxide) phosphine, was used [168].

These novel types of SOP ligands were also suitable for the Cu-catalysed asymmetric addition of boron to different double bonds (Fig. 61). High yields and enantioselectivities were realized for the hydroboration of imines and para-quinone methides, the borylstannation of alkenes [169] and allylboration of alkenes with Pd catalyst cooperation [170].

Liao has also developed a novel tridentate bis(sulfoxide) phosphine ligand [171]. Interestingly, when this ligand was applied in Pd-catalysed allylic substitutions with unprotected indoles, Liao discovered that it acts as a bidentate P,S-ligand with the free sulfoxide forming a hydrogen bond with indole (Fig. 62). This represents the first ligand promoted palladium-catalysed DYKAT of racemic unsymmetrical 1,3-disubstituted allylic acetates with indoles.

In the same year, the Liao group also prepared a simple bis-sulfoxide ligand, the Rh complex of which could also catalyse the 1,4-addition of arylboron [172]. When it was evaluated in addition to chromone, one of the most challenging substrates in this field, high catalytic activity and selectivity were observed (Fig. 63). It is noteworthy that the Y. Zhou group developed a facile synthesis of a series of axially chiral biphenyl bis-sulfoxide ligands in the same year.

LIGANDS WITH OLEFIN COORDINATED CONSTRUCTION

Since the pioneering work of the Hayashi and Carrera groups, olefin-type chiral ligands, including
Figure 63. Rh-catalysed 1,4-addition of arylboron with bis-sulfoxide ligands.

Figure 64. Rh-catalysed asymmetric additions with sulfoxide-olefin ligands.

Figure 65. Two types of allylic amine-derived chiral sulfonamide-olefin ligands.

Subsequently, Xu demonstrated that chiral sulfonamide-olefins based on a homoallylic amine backbone also displayed promising catalytic activities and enantioselectivities in the aforementioned reaction. Xu’s simple ligands can be prepared by Zn-mediated allylation of chiral N-tert-butanesulfinylimines at room temperature [175,176]. Du and co-workers independently described the development of similar chiral sulfonamide–olefin ligands bearing an allylic amine backbone that showed success in the same reaction [177]. Later, Xu et al. developed two types of allylic amine-derived chiral sulfonamide-olefin ligands: linear and β-substituted species (Fig. 65).

Xu’s linear sulfonamide–olefin ligands display great catalytic activities and enantioselectivities in Rh-catalysed 1,4-addition reactions of α,β-unsaturated olefins [178] and 1,2-addition reactions of activated ketones [179–181]. A broad range of useful product classes can be accessed via Xu’s catalytic 1,2-additions. All of these procedures give chiral tertiary alcohols in good yields with very high enantioselectivities (Fig. 66).

Xu’s branched ally-type sulfonamide-olefins have proved to be some of the best ligands for the Rh-catalysed asymmetric addition of arylborons to ketimines (challenging substrates due to their electronic and steric nature) [182,183]. Five- and six-membered ketimine substrates bearing aromatic, aliphatic and electron-withdrawing R groups are able to react with the nucleophiles in the presence of Xu’s ligands to give chiral tertiary amines (Fig. 67).

chiral diene ligands and hybrid olefin chiral ligands, have attracted much attention, especially from Chinese organic chemists. Different types of chiral olefin ligands designed by Chinese scientists have been developed and found to be useful for asymmetric catalysis. An overview on olefin-type chiral ligands developed by Chinese scientists is provided in this section, ranging from S-olefin and P-olefin chiral ligands to chiral diene ligands.

S-olefin coordinated ligands

In 2011, the groups of Liao [173], Wan [174], Xu [175,176] and Du [177] independently reported their simple and readily prepared chiral sulfoxide–olefin ligands. These ligands have proved to be remarkably efficient ligands for Rh-catalysed asymmetric addition reactions providing addition products with excellent enantioselectivities (Fig. 64). Interestingly, Liao found that the enantioselectivity could be reversed by simply changing the substituents at the olefin bond. This has the advantage of eliminating the need to prepare the ligands in both enantiomerically pure forms. At the same time, the Wan and Xu groups reported the preparation of similar ligands and the application in the same reaction [174–176].
Differing from the application in addition reactions, Du developed a highly enantioselective asymmetric allylic substitution cyclization reaction by employing Rh/sulfinamide-olefin ligands as chiral catalysts [184] (Fig. 68).

**P-olefin coordinated ligands**

Several phosphine–olefin and phosphite–olefin ligands have also been developed by the Du and Xu groups (Fig. 69). These ligands have also shown good activity in Rh-catalysed additions of arylboronic acids [185,186]. In addition, the application of Du’s ligands in Pd-catalysed allylic substitutions reveals that they are also suitable ligands for Tsuji-Trost reactions [187–190].

**Olefin–olefin coordinated ligands**

Significant progress has been made in the development of chiral diene ligands for asymmetric catalysis. These ligands have shown even better selectivity and catalytic activity than phosphine ligands in Rh-catalysed addition reactions. The design and synthesis of new chiral diene ligands have therefore received much attention. Differing from other well-known diene ligands, Lin discovered a new type of C2-symmetric chiral diene ligand bearing a non-bridged bicyclic [3.3.0] framework [191]. The two cis-fused cyclopentene rings in the molecule exhibit a characteristic wedge structure, which provides a good chiral environment and exerts excellent enantiocontrol in the reaction when two double bonds are coordinated to the metal. This class of diene ligands can be prepared from 1,5-cyclooctadiene via octahydropentalene-1,4-diol over several steps (Fig. 70). It has demonstrated high catalytic activity and enantioselectivity in Rh-catalysed arylations and alkenylations of various substrates (Fig. 71) [191–193].

Later, the Lin group prepared aqueous soluble bicyclic[3.3.0] diene ligands [194]. The first Rh-diene-catalysed aqueous asymmetric 1,4-addition of α,β-unsaturated carbonyl compounds with arylboronic acids was realized using Lin’s hydrophilic bicyclo[3.3.0] diene ligand (Fig. 72). In 2010, the first palladium-diene-catalysed asymmetric Suzuki-Miyaura coupling reaction was reported by the Lin group [195]. A number of functionalized biaryls were obtained in high yields and with moderate to high enantioselectivities. This study opens a new avenue for the application of chiral diene ligands in asymmetric Pd-catalysis (Fig. 73).

Lin has also designed a new class of monosubstituted C1-symmetric dicyclopentadiene-type diene ligands [196]. These ligands have also been applied successfully in asymmetric arylation reactions (Fig. 74).

The Du Group has prepared several chiral linear 1,5-hexadiene ligands (Fig. 75). Interestingly, these ligands can also promote the Rh-catalysed addition of arylboron to unsaturated cyclic carbonyl...
Figure 69. Olefin ligands developed by Du and Xu.

Figure 70. The preparation of chiral diene ligands.

Figure 71. Rh-catalyzed arylation and alkenylation with chiral diene ligands.

Figure 72. Rh-diene-catalyzed aqueous asymmetric 1,4-addition.

Figure 73. The first Pd-diene-catalyzed asymmetric Suzuki-Miyaura coupling reaction.

Figure 69. Olefin ligands developed by Du and Xu.

Figure 70. The preparation of chiral diene ligands.

Figure 71. Rh-catalyzed arylation and alkenylation with chiral diene ligands.

Figure 72. Rh-diene-catalyzed aqueous asymmetric 1,4-addition.

Figure 73. The first Pd-diene-catalyzed asymmetric Suzuki-Miyaura coupling reaction.

compounds to give the corresponding arylation products in high yields and ees [197]. However, poor results were obtained when these ligands were applied to the Rh-catalyzed arylation of imines. Chiral binaphthyl diene ligands designed by Du [198] showed good performance in this reaction (Fig. 76). Interestingly, no catalytic activity is observed when ligand with no aryl groups at 3,3′-positions are used. Although this ligand is not a particularly excellent ligand for Rh-catalyzed arylation reactions, it has become a ‘privileged ligand’ for borane-catalyzed metal-free asymmetric hydrogenation.

Frustrated Lewis pairs (FLP) have become a popular research topic because of their unique character. This unique character arises from the steric bulk and strong Lewis acidity of the electron-deficient triaryl borane. In 2013, Du reported that his group’s chiral binaphthyl diene ligand was able to react with HB(C6F5)2 for the in-situ generation of a chiral bisborane catalyst that can be used for the asymmetric hydrogenation of imines [199]. After this discovery, a series of substrates including heterocycles and silyl enol ethers were hydrogenated using Du’s catalyst [200–202]. With regard to the hydrogenation of N-heterocycles, the nitrogen atom may act as a Lewis base, while tBu3P is employed as
a Lewis base for the hydrogenation of enol ethers [203]. In general, high yields and moderate to excellent enantioselectivities could be obtained under Du’s conditions (Fig. 77).

Very recently, Du developed a novel type of axially chiral diyne ‘ligand’ (Fig. 78). The corresponding diboran catalyst that is generated in situ is more rigid than that of the axially chiral diene, limiting the preferred configuration of the borane catalyst. This chiral diyne has performed as an excellent ‘ligand’ in the borane-catalysed asymmetric hydrogenation of silyl enol ethers [204]. When Du’s ‘ligands’ were applied in the asymmetric hydrosilylation of ketones [205], the chiral diyne provided better reactivity and enantioselectivity than chiral diene ligands. This can most likely be attributed to the electronic and/or steric differences between the alkenylborane and alkylborane.

**CONCLUSION**

In conclusion, significant contributions to the development of novel and efficient chiral ligands have been reported by Chinese scientists. Chinese organic chemists have developed a series of versatile and well-known chiral spiro ligands that have shown extremely good activity in asymmetric hydrogenations, carbene insertions and many other reactions.

The development of novel axially chiral biphenyl ligands has also proved fruitful, with applications in asymmetric hydrogenations, cycloadditions, oxidations and conjugate additions. Metallocene-based planar chiral ligands, some of which have shown unique properties in Pd-catalysis, have attracted the attention of Chinese scientists. Ligands bearing chiral phosphine and sulfur groups have also shown good performance in asymmetric hydrogenations, dipolar cycloadditions, cross-couplings, arylboron additions and borylations of double bonds. Several novel chiral dienes and diynes behave as excellent chiral ligands for Rh-catalysed arylations and borane-catalysed hydrogenations. Ligands for use with asymmetric Lewis acid catalysis have also seen significant advances and have been applied in numerous asymmetric catalytic reactions.

There can be no doubt that many of these ligands are ‘chiral-privileged ligands’ and are essential backbones for many catalyst complexes. Several ligand design strategies and concepts developed by Chinese chemists can be employed as general rules for the design of new ligands and catalysts. We envisage that even more significant contributions to this area of research are forthcoming and that some of the ligands...
ligands developed in China will be able to be applied to industrial processes.

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