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P-手性化合物的不对称催化合成研究进展

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摘要 *P*-手性结构单元广泛存在于具有生物活性和药物活性的化合物中, 并且 *P*-手性化合物可用作不对称催化的手性配体或有机小分子催化剂. 因而, 近二十年来 *P*-手性化合物的不对称合成引起了化学家的广泛关注. 利用动力学拆分和动态动力学拆分的策略, 以不对称的方式构建新的 P—C、P—O 或 P—N 键, 将外销旋的仲膦、其硼烷加合物或其氧化物转变为相应的 *P*-手性化合物是合成该类化合物最有效、最直接的方法之一. 此综述从动力学拆分和动态动力学拆分两个策略出发, 介绍 *P*-手性化合物的不对称过渡金属催化合成方法及最新研究进展. 根据亲电试剂的不同, 将反应分为芳基化反应、对活泼烯烃或炔烃的加成反应、烷基化反应以及其它反应. 此外, 还介绍了通过构建不对称 P—C 键将前手性的伯膦转变为 *P*-手性仲膦的反应.

关键词 *P*-手性化合物; 过渡金属催化; 不对称催化; 动力学拆分; 动态动力学拆分

Research Progress on Catalytic Asymmetric Synthesis of *P*-Chiral Compounds

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Abstract *P*-Chiral compounds are a valuable class of privileged structures in pharmaceutically and biologically active compounds and also serve as powerful and versatile ligands or organocatalysts in asymmetric synthesis. Therefore, their asymmetric synthese has gained increasing attention in the past two decades. By means of kinetic resolution (KR) or dynamic kinetic resolution (DKR) strategy, racemic secondary phosphines, their borane-adducts or their oxides can be transformed to the associated compounds with *P*-chirality, which serves as a straightforward and efficient protocol to construct a *P*-chiral center. The recent achievements of the transition-metal-catalyzed asymmetric syntheses of *P*-chiral compounds based on KR and DKR of racemic secondary phosphines, their borane-adducts and their oxides in the past two decades are summarized. Meanwhile, arylation, addition to activated alkenes or alkynes, alkylation and other reactions are covered respectively based on the varied reaction partners. These reaction entails the formation of new P—C, P—O and P—N bonds in an asymmetric manner. What's more, the transformation of prochiral primary phosphines to *P*-chiral secondary phosphines is mentioned in the miscellaneous reaction section.

Keywords *P*-chiral compounds; transition-metal-catalysis; asymmetric catalysis; kinetic resolution; dynamic kinetic resolution

1 Introduction

P-Chiral stereogenic centers are an integral part of many pharmaceuticals, pesticides and biologically active molecules as their core subunits. On the other hand, as powerful ligands and organocatalysts, *P*-chiral compounds play an important part in asymmetric catalysis.[1] Hence, the development of efficient strategies for the syntheses of

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P-chiral compounds has attracted broad attention of synthetic chemists, and a number of research articles have uncovered progresses in this field.

Traditional synthetic methods mainly rely on resolution processes and chiral auxiliary-induced diastereoselective synthesis, both of which need to use stoichiometric amounts of chiral reagents. Asymmetric catalysis, which has the advantages of high synthetic efficiency and chirality economy, has been established as an indispensible methodology to produce a plenty of enantioenriched compounds in the domain of synthetic chemistry. There is no doubt that asymmetric catalysis offers a more powerful and promising alternative for the efficient synthesis of *P*-chiral compounds. In a broad sense, the catalytic asymmetric reactions for building *P*-chirality could be classified into four categories: (1) desymmetrization reactions, (2) kinetic resolution (KR) of racemic secondary phosphine oxides, (3) dynamic kinetic resolution (DKR) of racemic secondary phosphines, their borane complexes, and their oxides, and (4) other miscellaneous reactions. The first approach usually requires the desymmetric functionalization of prochiral P(V) compounds. In the KR processes, only 50% racemic phosphine oxides could be converted to the desired chiral products. As a result, 2 equiv. of racemic secondary phosphine oxides is required to ensure high yields and enantioselectivities. Compared with KR processes, the DKR processes are recognized to be more ideal because 100% racemic phosphines or their derivatives could be transformed to the target enantio-enriched products in theory. Given that most examples of the KR, and the DKR of secondary phosphines and their derivatives are based on transition-metal-catalysis, there is a serious problem that must be addressed. Both the phosphorus-containing starting materials and products, which can serve as new ligands, would coordinate to the transition metal centers competitively with the original chiral ligands. The desired metal-ligand complex catalysts may be destroyed and thus some new but undesired catalysts may be generated. As a result, both the yields and the asymmetric induction would be diminished.

Since reactions concerning desymmetrization have received sustained attention and a comprehensive review has been published,[2] this review mainly focuses on transition metal-catalyzed KR and DKR of racemic secondary phosphines and their derivatives, and has been divided into two sections dealing with these two processes, respectively. Moreover, some interesting miscellaneous reactions have been described in an additional section.

2 Kinetic resolution of secondary phosphine oxides

As bench stable phosphorus-containing prochiral nucleophiles, secondary phosphine oxides usually enjoy the advantages of odorlessness and low toxicity. They exist in a tautomeric equilibrium with their trivalent phosphinous acid tautomers in the presence of acids, bases or transition metals (Figure 1). The phosphorus atom of the trivalent tautomers could ligate to a variety of transition metals, which enables them to react with various electrophiles. However, it is a challenging task to realize their KR or DKR because of their elusive degree of racemization, deterring them from being used in the preparation of *P*-chiral compounds. Since Tan group[3] pioneered the KR of racemic secondary phosphine oxides in a guanidinium-catalyzed asymmetric phospha-Mannich reaction capable of generating *P*-chiral *α*-amino tertiary phosphine oxides in 2009, several examples based on KR of secondary phosphine oxides have been published in recent years. This section has been subdivided into three parts: asymmetric arylation, asymmetric addition to alkynes, and asymmetric alkylation, based on the nature of the electrophilic partners.

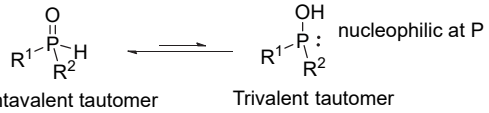
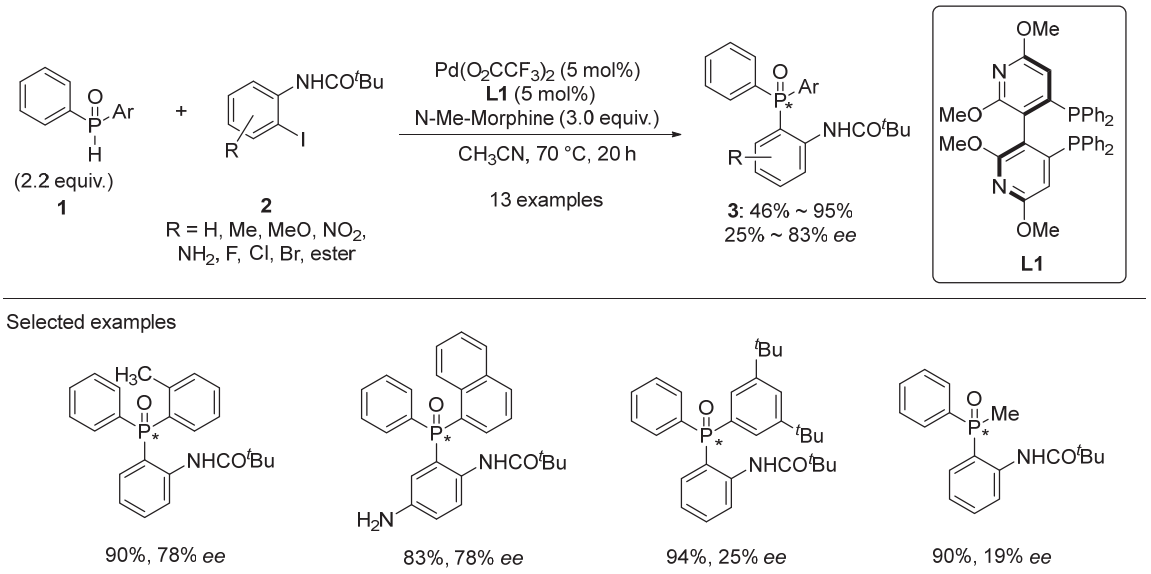


Figure 1 Tautomerism of secondary phosphine oxides

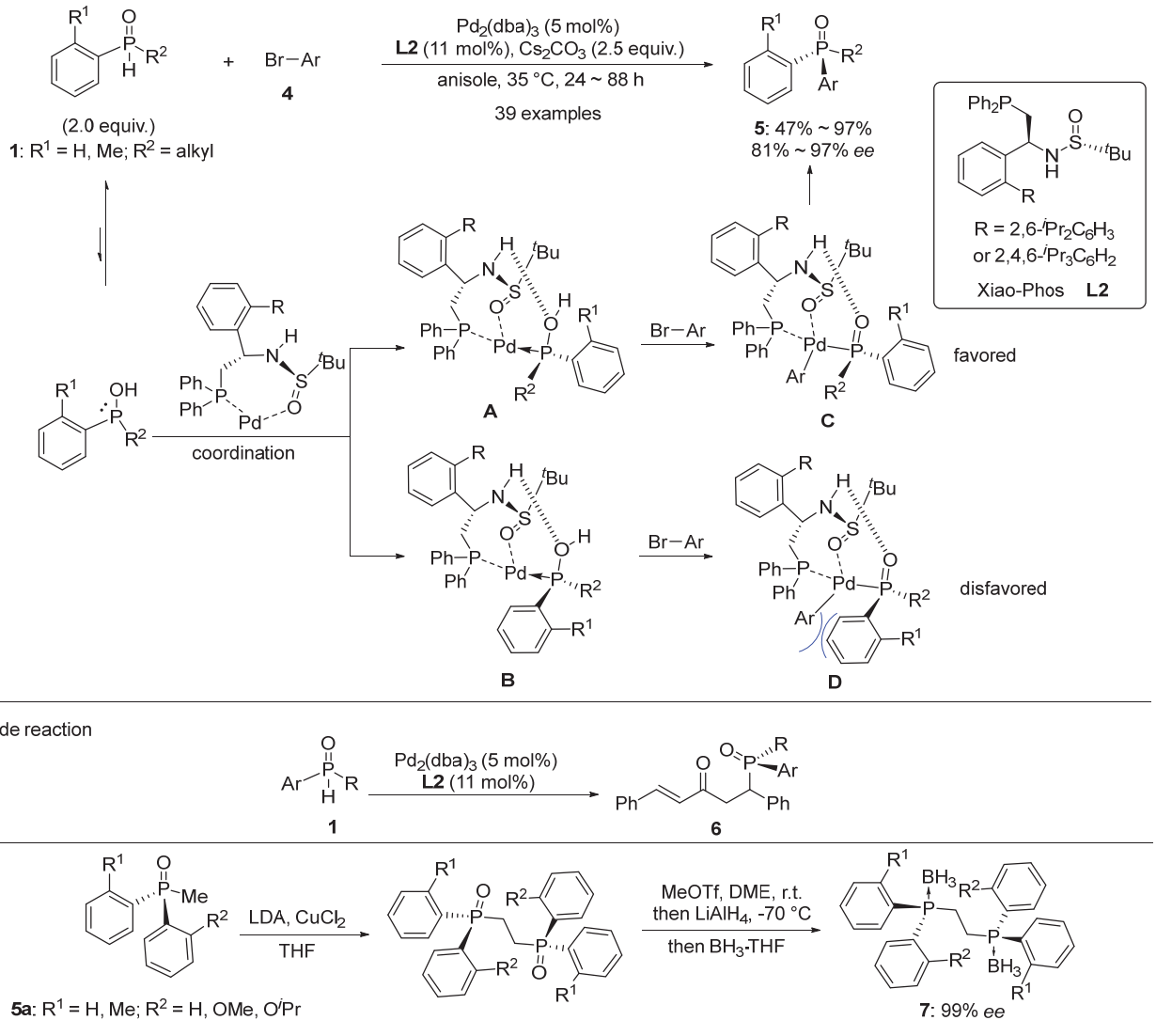
2.1 Asymmetric arylation reaction

Cai group focused on developing new methodologies for the asymmetric cross-coupling reactions of aryl halides with a heteroatom nucleophile. In 2016, Cai group[4] employed *N*-(2-iodoaryl)pivalamides **2** as novel electrophiles to develop a asymmetric cross-coupling reaction with diarylphosphine oxides **1**, which enabled the enantioselective synthesis of *P*-chiral triarylphosphine oxides **3** (Scheme 1). In the presence of 5 mol% Pd(II)-**L1** complex and 3.0 equiv. of *N*-methyl morphine, the KR of **1** furnished coupling products **3** in moderate to high yields with moderate to high enantioselectivity. It was found that *N*-(2-bromoaryl)pivalamides were much less reactive under the best reaction conditions. The bulky *ortho*-pivalamide moiety in coupling partners **2** served as an important directing group for high asymmetric induction. The use of (3,5-di-*tert*-butylphenyl)(phenyl)phosphine oxide as a prenucleophile suffered from very poor enantioselectivity, indicating that the *ortho* group on the aromatic substituent of **1** was also important for enantioselectivity control. Probably, it was because bulky substrates and congested coupling partners reduced the coordination capacity of starting materials **1** and products **3** to Pd(II). Thus, the competitive ligand exchange between **L1** and **1** or **3**, which was harmful to enantioselectivity, was avoided. In addition, methylphenylphosphine oxide was also inefficient substrate because of the very poor enantioselectivity in the reaction.

The kinetic separation of alkylarylphosphine oxides, which were not compatible with Cai's protocol, was achieved by Zhang group three years later, who developed a Pd-catalyzed asymmetric cross-coupling reaction between racemic alkylarylphosphine oxides **1** and *ortho*-, *meta*-, or *para*-substituted aryl bromides **4** (Scheme 2).[5]



Scheme 1 Pd(II)-catalyzed asymmetric arylation of diarylphosphine oxides



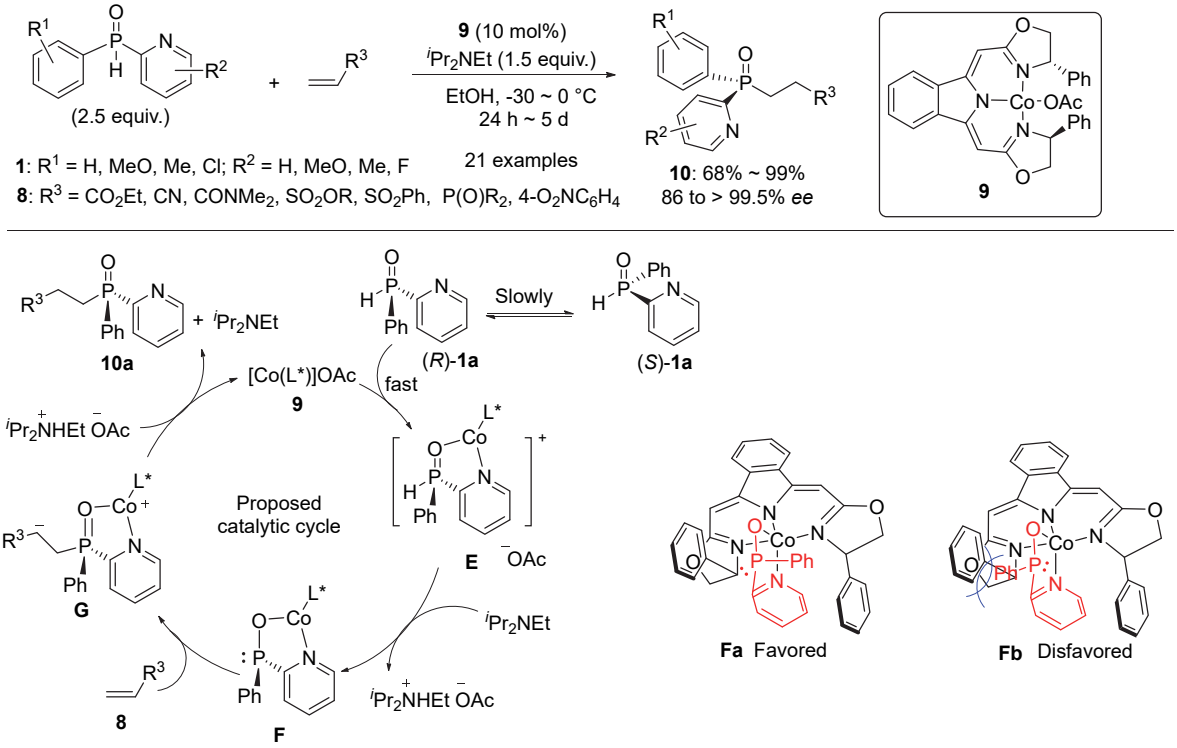
Scheme 2 Pd(0)-catalyzed asymmetric arylation of alkylarylphosphine oxides

P-chiral alkyldiarylphosphine oxides **5** were obtained in up to 97% yield and 97% *ee*. Zhang group developed a series of sulfinamidephosphine type ligands for asymmetric metal catalysis. Their own Xiao-Phos **L2**, a typical chiral organocatalyst,[6] was employed as a chiral ancillary ligand for the first time. It is worthy to mention that as a hemilabile ligand, Xiao-Phos made a significant contribution to both the catalytic activity and the asymmetric induction. A tentative mechanism based on experimental observations and DFT calculation results was proposed. Both the P atom and the sulfinamide moiety in Xiao-Phos **L2** could coordinate to Pd with the latter in a flexible manner. The trivalent tautomers of **1** coordinated to Pd to form intermediates **A** and **B**. The hydrogen bond between the O atom of **1** and the sulfinamide NH secured the stability of the intermediates **A** and **B**. Then, the oxidative addition of aryl bromides **4** to **A** and **B** gave intermediates **C** and **D**, respectively. The temporary departure of the sulfinamide moiety from Pd provided a vacant coordination site for the oxidative addition process. **C** was instable because of the spatial repulsion between the two aryl groups. The reductive elimination of the stable intermediate **D** delivered the desired products **5**. In this KR process, the two configurations of racemic alkylarylphosphine oxides **1** were identified selectively, which was the key to achieving excellent enantioselectivity. In addition, a side addition reaction between **1** and dba, referred to as an asymmetric hydrophosphinylation reaction, was observed in this reaction. The potential application of this protocol was showcased by two-step transformations of **5a** to an array of DiPAMP-type ligands **7**.

2.2 Asymmetric addition to activated alkenes or alkynes

In 2021, Zhang, Duan and co-workers[7] developed a cobalt-catalyzed enantioselective addition of secondary phosphine oxides **1** to activated olefins **8** (Scheme 3). The cobalt complex of boxmi ligand **9** was chosen as the best chiral catalyst. The 2-pyridinyl moiety in **1**, which could coordinate to the metal catalyst, was essential for the reaction to proceed smoothly. Meanwhile, this reaction had a wide substrate scope on electrophiles **8** with various electron-deficient alkenes (such as acrylate esters, acrylonitrile, acrylamide, sulfonate, arylsulfoxide, phosphine oxide, phosphinate, and even substituted styrene) well tolerated. A possible reaction mechanism was proposed with **1a** as a model substrate. Only (*R*)-**1a** could coordinate to the cobalt catalyst **9** to form P(V) intermediate **E**, which was then deprotonated by the base $^{i}Pr_2NEt$ to generate P(III) intermediate **F**. The favored configuration of **F** served as the active nucleophile to attack alkene **8** to yield intermediate **G**, the protonation of which would release the desired product **10a**.

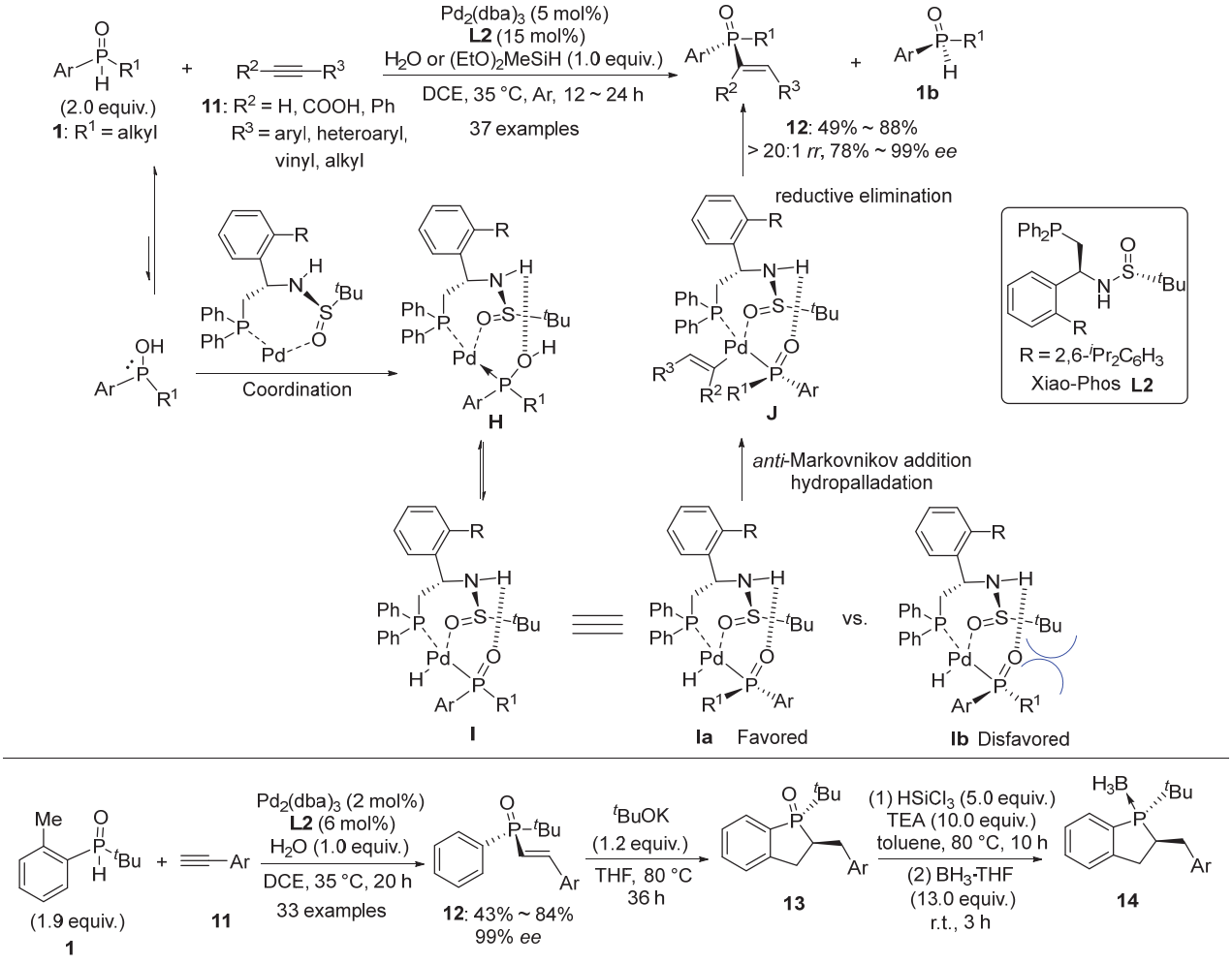
Given the particular utility of alkenylphosphine oxides, especially the *P*-chiral ones, as versatile synthetic building blocks in organic chemistry,[8] methods for facile construction of these compounds have gained increasing attention. Hydrophosphinylation of alkynes is appreciated as one of the most direct and atom-efficient strategies. Inspired by the side enantioselective hydrophosphinylation reaction in Scheme 2, Zhang group[9] disclosed a highly regio- and



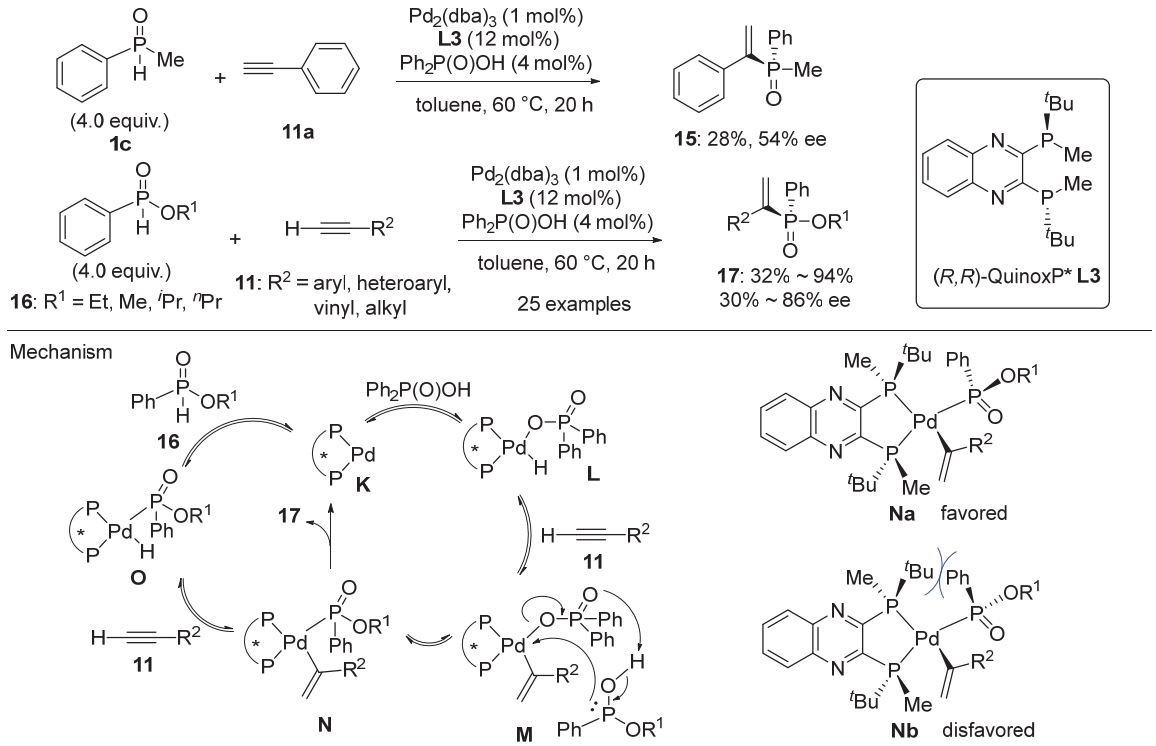
Scheme 3 Co(II)-catalyzed asymmetric addition of secondary phosphine oxides to activated alkenes

enantioselective addition reaction of alkylarylphosphines **1** to various alkynes **11** using nearly the same Xiao-Phos **L2**-$Pd_2(dba)_3$ catalytic system (Scheme 4). Upon the coordination of **1** to Pd(0)-**L2**, intermediate **H** was generated, which had an equilibrium with Pd-H species **I**. The use of water or $(EtO)_2MeSiH$ as additional hydrogen source enabled the equilibrium to favor the generation of the latter. Meanwhile, the steric hindrance between the large alkyl substitution of **1** and the *t*-butyl moiety of sulfinyl group in **L2** enabled the identification of the two configurations of **1**, which acted as the key step for the enantioselective discrimination. The *syn*-selective hydropalladation of **11** using the more favored Pd-H species **Ia** worked well to furnish *anti*-Markovnikov addition intermediate **J**, which then underwent reductive elimination to form the target products **12**. In particular, both terminal and internal alkynes **11**, and whether (hetero)aryl or alkyl ones, were accommodated in this protocol. The reaction showed good functional group compatibility of **11** with amine, ester, alcohol, nitro, halides. With respect to **1**, both diarylphosphine oxides and dialkylphosphine ones suffered from low efficiency with very poor yields. Other types of secondary phosphine reagents, such as aryl phosphinates and phosphine borane adducts, were not compatible, either. The former gave trace amount of desired products and the latter were thoroughly inert. In most cases, the *ee* values of the *P*-stereogenic adducts **12** and the recovered optically pure secondary phosphine oxides **1b** were higher than 90%. Due to the versatility of the *P*-chiral scaffolds in **12** and **1b**, several associated products were transformed to some potentially useful molecules in 99% *ee*. In 2022, this protocol was employed by the same group to assemble a set of novel *P*-chiral monophosphorus ligands (Xie-phos) **14**.[10] The benzophospholane framework was rapidly synthesized via a simple base-mediated intramolecular cyclization from *P*-stereogenic adducts **12**. The obtained products **14** served as efficient ligands in many catalytic asymmetric reactions (such as α-arylation of amides and the domino Heck/Suzuki reaction).

In 2020, Wang group[11] exploited a (*R*,*R*)-QuinoxP* **L3**-$Pd_2(dba)_3$ catalytic system to facilitate the hydrophosphinylation of phenylacetylene **11a**, affording Markovnikov adduct **15** albeit in low yields with moderate enantioselectivity (Scheme 5). Contrary to Zhang's protocol in Scheme 4, aside from alkylarylphosphine oxides **1**, aryl phosphinates **16** were also feasible in this protocol. By using phenylphosphinates **16** as the secondary phosphine reagents, a variety of alkynes **11** underwent hydropho-



Scheme 4 Pd(0)-catalyzed asymmetric hydrophosphinylation of alkylarylphosphine oxides



Scheme 5 Pd(0)-catalyzed asymmetric hydrophosphorylation of aryl phosphinates

sphorylation smoothly to deliver *P*-chiral alkenylphosphinates **17** in satisfactory results, all of which were Markovnikov adducts. The employment of $Ph_2P(O)OH$ as an additive was beneficial to enhance the yields. The proposed mechanism showed that the reaction began with the generation of chiral palladium complex **K**, followed by the oxidative addition of the oxygen-hydrogen bond of $Ph_2P(O)OH$ to Pd(0) to afford Pd-H species **L**. Then the *syn*-hydropalladation of **11** occurred to generate the Markovnikov addition intermediate **M**, the subsequent ligand exchange of which with the trivalent form of phenylphosphinate **16** gave intermediate **N**. Another pathway, which was the direct oxidative addition of **16** to Pd to generate intermediate **O**, was also possible. Then the Markovnikov addition of **O** furnished the same intermediate **N**. Upon reductive elimination of the favored configuration of **N**, the desired alkenylphosphinate products **17** were obtained.

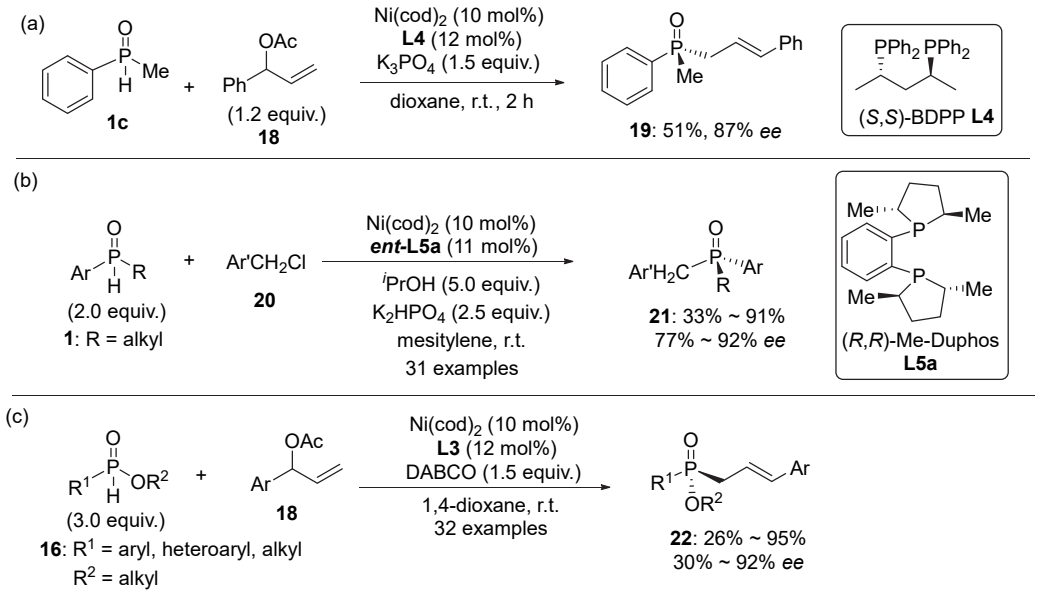
2.3 Asymmetric alkylation

Catalytic asymmetric allylic alkylation is recognized as a powerful strategy to incorporate the synthetically useful allyl group into various targets.[12] In 2019, Zhang group[13] uncovered an Ni-catalyzed enantioselective allylic alkylation of alkylarylphosphine oxides **1**, which generated enantioenriched tertiary phosphine oxides featuring *P*-chirality and a linear allyl group (Scheme 6a). By using (*S*,*S*)-BDPP **L4** as the chiral ligand, K_3PO_4 as the base, and allylic acetate **18** as the allyl reagent, exclusively linear product **19** was obtained in 51% yield and 87% *ee*. It was envisioned that this reaction proceeded through a KR process. Interestingly, when the base was switched to KOAc, a more promising DKR reaction was observed, which was discussed in detail in section 3.3.

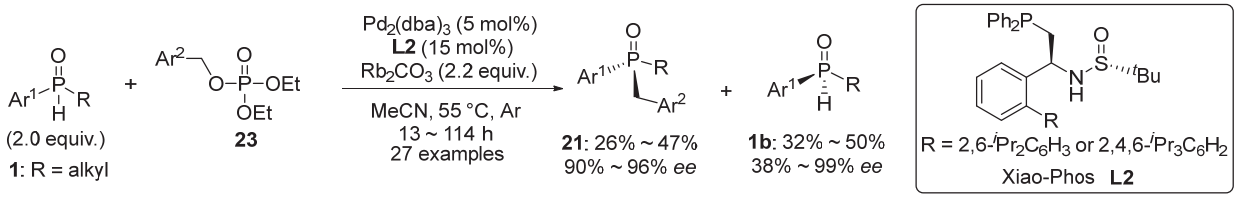
Benzylation was more challenging than the corresponding allylation. In 2022, the same group successfully extended their catalytic system to enantioselective benzylation of alkylarylphosphine oxides **1** by switching the chiral ligand to (*S*,*S*)-Me-Duphos ***ent*-L5a** (Scheme 6b).[14] It should be mentioned that only benzyl chlorides **20** were effective electrophiles to produce the desired *P*-chiral benzylated products **21**. Benzyl acetates, methyl carbonates, benzyl phosphates, and even the more labile benzyl bromides were all inert under the optimum reaction conditions.

The reaction protocol was also extended by the same group to the enantioselective allylic alkylation of *H*-phosphinates **16**, which was less nucleophilic than secondary phosphine oxides **1** (Scheme 6c).[15] 3.0 equiv. of *H*-phosphinates **16** was required to obtain high yields of the desired allylic *P*-chiral phosphinates **22**. The reaction of allylic acetate **18** with aryl group replaced by alkyl one did not occur. Meanwhile, the use of internal alkene moiety in place of terminal alkene moiety in **18** proved infeasible.

In 2021, Liu, Zhang and co-workers[16] also documented the catalytic asymmetric benzylation reaction of alkylarylphosphine oxides **1** by utilizing their own Xiao-Phos **L2**-$Pd_2(dba)_3$ catalytic system (Scheme 7). By employing benzyl phosphates **23** as the competent benzylation reagents, a typical KR process of racemic secondary phos-



Scheme 6 Ni(II)-catalyzed asymmetric allylation and benzylation



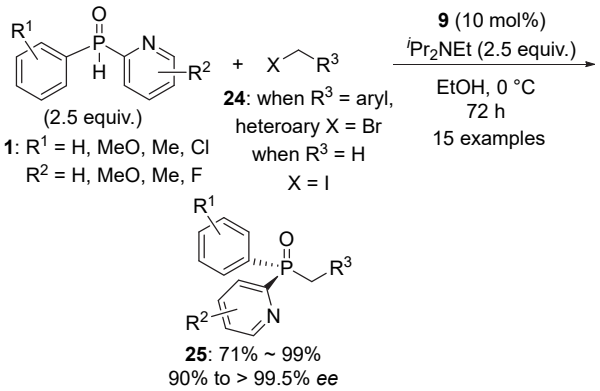
Scheme 7 Pd(0)-catalyzed asymmetric benzylation of alkylarylphosphine oxides

phines **1** proceeded smoothly to deliver enantioenriched *P*-benzylated products **21**. In most cases, both the obtained tertiary phosphine oxides **21** and the recovered chiral secondary phosphine oxides **1b** were delivered in high yields with excellent enantioselectivity.

Examples in Schemes 6 and 7 focused on the substitution of secondary phosphine oxides containing one aryl and one alkyl group. The asymmetric reaction of secondary phosphine oxides bearing two aryl moieties was more difficult because it was difficult to distinguish the two aryl groups of similar size. In 2020, enantioselective allylation of diarylphosphine oxides with Morita-Baylis-Hillman carbonates was described by Zhang group by using their own Le-Phos as an organocatalyst.[17] By virtue of the coordination ability of 2-pyridinyl unit, Zhang, Duan and co-workers also uncovered a cobalt-catalyzed enantioselective nucleophilic alkylation of diarylphosphine oxides **1** (Scheme 8).[7] Both benzyl bromides and methyl iodide were feasible electrophiles to give the desired *P*-chiral tertiary phosphine oxides **25** in up to 99% yield and 99.5% *ee*.

3 Dynamic kinetic resolution of secondary phosphines, their borane complexes, and their oxides

Racemic secondary phosphines can coordinate to some transition metals (such as Pd, Pt, Ni, Ru, and Cu), which



Scheme 8 Co(II)-catalyzed asymmetric alkylation of secondary phosphine oxides

will enable the acidification of the phosphorous-hydrogen bond and thus facilitate their deprotonation in the presence of a mild base. Given the possibility of the non-enantioselective background reaction, facile deprotonation was necessary for the asymmetric reaction. The transition metal-phosphido species generated *in situ* enjoys the advantage of low barrier to pyramidal inversion (Figure 2) and there is a rapid equilibrium between the two epimers of the transition metal-phosphido species, which will allow various electrophiles to be used in a DKR process. Therefore, the racemic secondary phosphines are converted to optically active tertiary phosphines. What's more, the reac-

tion partners as well as the chiral ligand must be bulky, which will aid in tertiary phosphines dissociation and thus avoid product inhibition. The main drawbacks associated with secondary phosphines are their toxicity and liability. In some cases, their borane complexes which are air-stable serve as promising alternatives.

In the DKR process of secondary phosphines, the transition metal-phosphido species has low barrier to pyramidal inversion. As a result, the disfavored enantiomer of the starting materials can be transformed to the favored one to undergo the subsequent reaction. However, the trivalent form of secondary phosphine oxides enjoys relatively high barrier to pyramidal inversion in most cases. As a result, a KR process usually occurs. The disfavored enantiomer of the starting materials cannot be transformed to the favored one with only the latter undergo the subsequent reaction to give the associated enantioenriched products. Against all odds, some protocols for the DKR of secondary phosphine oxides have also been successfully explored. This section has been subdivided into four parts: asymmetric arylation, asymmetric addition to *α*,*β*-unsaturated compounds, asymmetric alkylation, and asymmetric reactions to construct *P*-chiral P—O or P—N bond.

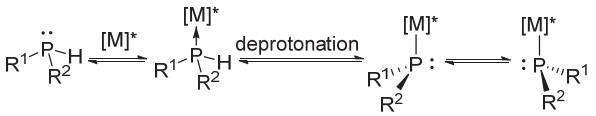


Figure 2 Racemization of the metal-phosphido species derived from secondary phosphines

3.1 Asymmetric arylation

In 2002, Glueck group[18] reported an example of enantioselective cross-coupling reaction of racemic (2,4,6-triisopropylphenyl)methylphosphine **26** with aryl iodides **27** catalyzed by a complex Pd((*R*,*R*)-Me-Duphos)(Ph) (**I**) **29a**, which was derived from chiral bisphosphine ligand (*R*,*R*)-Me-Duphos **L5a** (Scheme 9a). Soon afterwards, it was found that the Pd(0) precursor (Pd((*R*,*R*)-Me-Duphos)(*trans*-stilbene) (**30a**)) had nearly the same catalytic efficiency.[19] The combined use of a sterically demanding aryl substituent in **26** and aryl iodide **27** bearing a *para* electron-donating group resulted in the highest enantioselectivity, up to 88% *ee*. The reaction was initiated by the oxidative addition of aryl iodides **27** to **30a**, giving intermediate **P**. The replacement of iodide with **26** yielded the cation species **Q** and its triflate salt was isolated successfully. Then the deprotonation of **Q** generated the Pd-phosphido species **R**. There was a rapid epimerization in **R** and the reductive elimination of the major diastereoisomer produced the favored enantiomer of the tertiary phosphine (**28**).

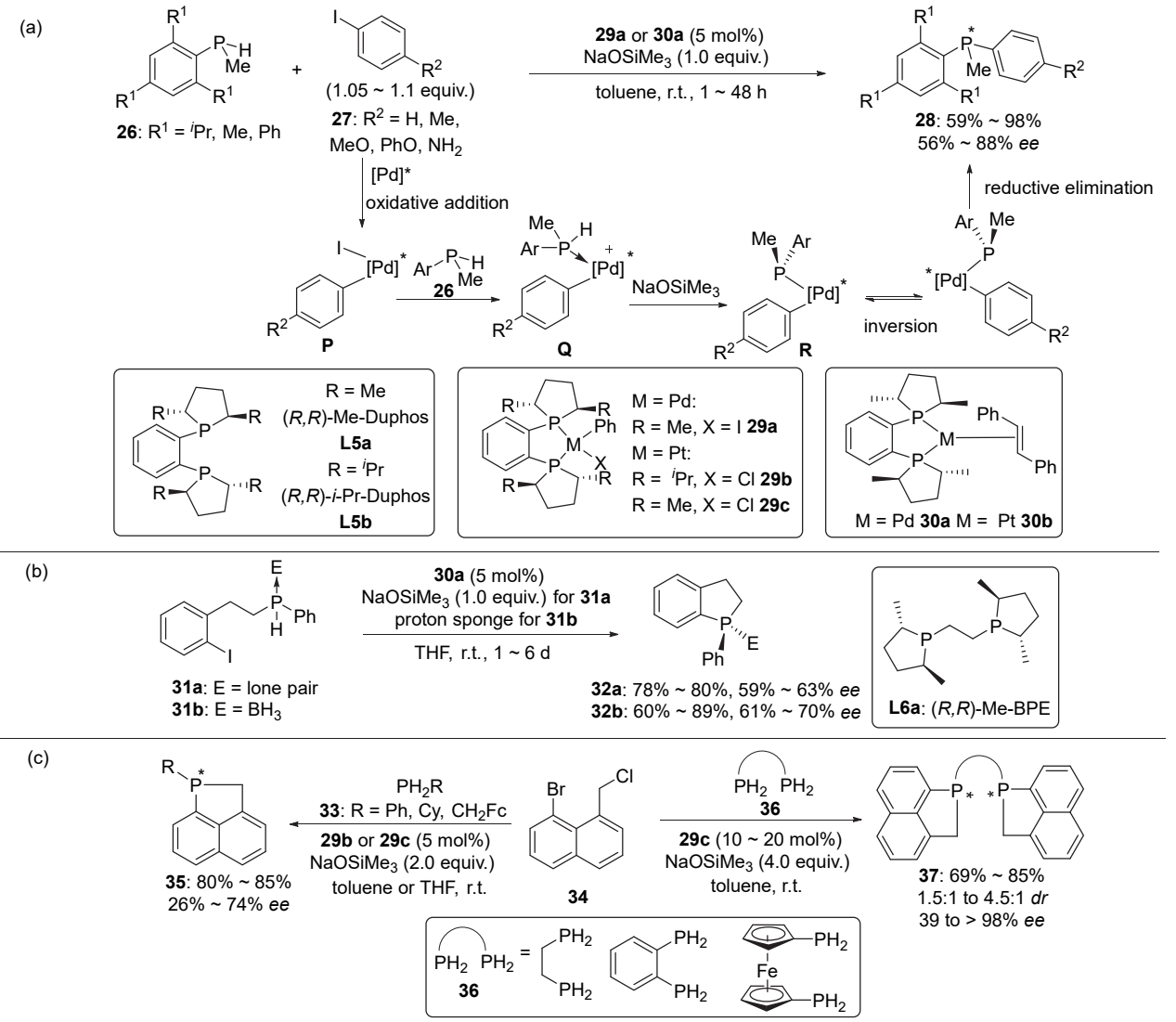
This strategy was then extended by the same group to forge benzophospholanes **32** containing a P-Chirality. Secondary phosphine **31a** was used as substrate while **30a** was used as the catalyst precursor (Scheme 9b).[20] Phosphine borane complex **31b**, an alternative of air-sensitive **31a**, was also suitable substrate, providing enantioenriched product **32b** in similar enantioselectivity. It was deduced that the real active species in the reaction of **31b** was **31a**, which was formed by reversible and unfavorable dissociation of borane from **31b**. Some investigations revealed that switching the chiral ligand of **30a** to (*R*,*R*)-Me-BPE **L6a** was also viable albeit with lower enantioselectivity (36%～40% *ee*).

Contrary to Duphos and BPE, *P*-chiral 1-phosphaacenaphthenes **35** may be a type of useful ligands with reduced conformational flexibility because of the fused naphthalene. In 2008, Glueck group[21] uncovered an enantioselective tandem reaction between primary phosphines **33** and 1-bromo-8-chloromethylnaphthalene **34**, including an alkylation and an arylation process (Scheme 9c). **30a** was an unsuitable catalyst precursor because the reaction was unselective. Complexes **29b** and **29c**, in which the transition metal was switched to Pt, were chosen as compatible catalysts to assemble **35** in an enantioselective way. It should be noted that the successful assembly of C_2-symmetric diphosphines **37** at ambient temperature was also enabled by using bis(primary) phosphines **36** as substrates.

By using a catalytic system prepared *in situ* from $Pd_2(dba)_3$•$CHCl_3$, (*R*,*R*)-Et-FerroTANE (**L7**) and LiBr, Helmchen group[22] disclosed an asymmetric cross-coupling reaction between diarylphosphines **26** and aryl iodides **27** featuring an *ortho*-substituent (Scheme 10a). When R^1 in **26** was replaced by an electron-donating group (such as methoxyl), dramatic decrease of enantioselectivity was observed. This reaction provided a handle for the asymmetric syntheses of phosphinooxazoline (PHOX) ligands **38**. By employing aryl iodide **27a** as the coupling partner, both of the two diastereomers of **38** were obtained.

Inspired by the success of Pd-(*R*,*R*)-Et-FerroTANE (**L7**) complex-catalyzed asymmetric arylation of secondary phosphines **26**, Toste group[23] accomplished an enantioselective coupling reaction of silylphosphines **39** with aryl iodides **40** bearing a bulky *ortho*-amide substituent (Scheme 10b). The complex ((*R*,*R*)-Et-FerroTANE)$PdCl_2$ (**41**) was used as the best catalyst. The addition of **40** to **41** yielded intermediate **S**, which underwent transmetalation reaction with silylphosphines **39** to give Pd-phosphido species **T**. Then after reductive elimination, tertiary phosphines with a *P*-chiral center were obtained. Quenching the reaction with S_8 provided air-stable products **42** in up to 97% *ee*. The *ortho*-amide moiety in **40** was pivotal for the high enantioselectivity. It was postulated that the oxygen atom of the amide moiety could coordinate to Pd to form a five-membered palladacycle, which may play an important role in the enantioselective determining step. What's more, both electron-rich (**43a**) and electron-deficient (**43b** and **43c**) heteroarenes were acceptable coupling partners under the optimum reaction conditions.

In 2016, the Cu-catalyzed asymmetric arylation of alkylarylphosphine oxides **1** through a DKR process was revealed by Gaunt group, who employed diaryliodonium

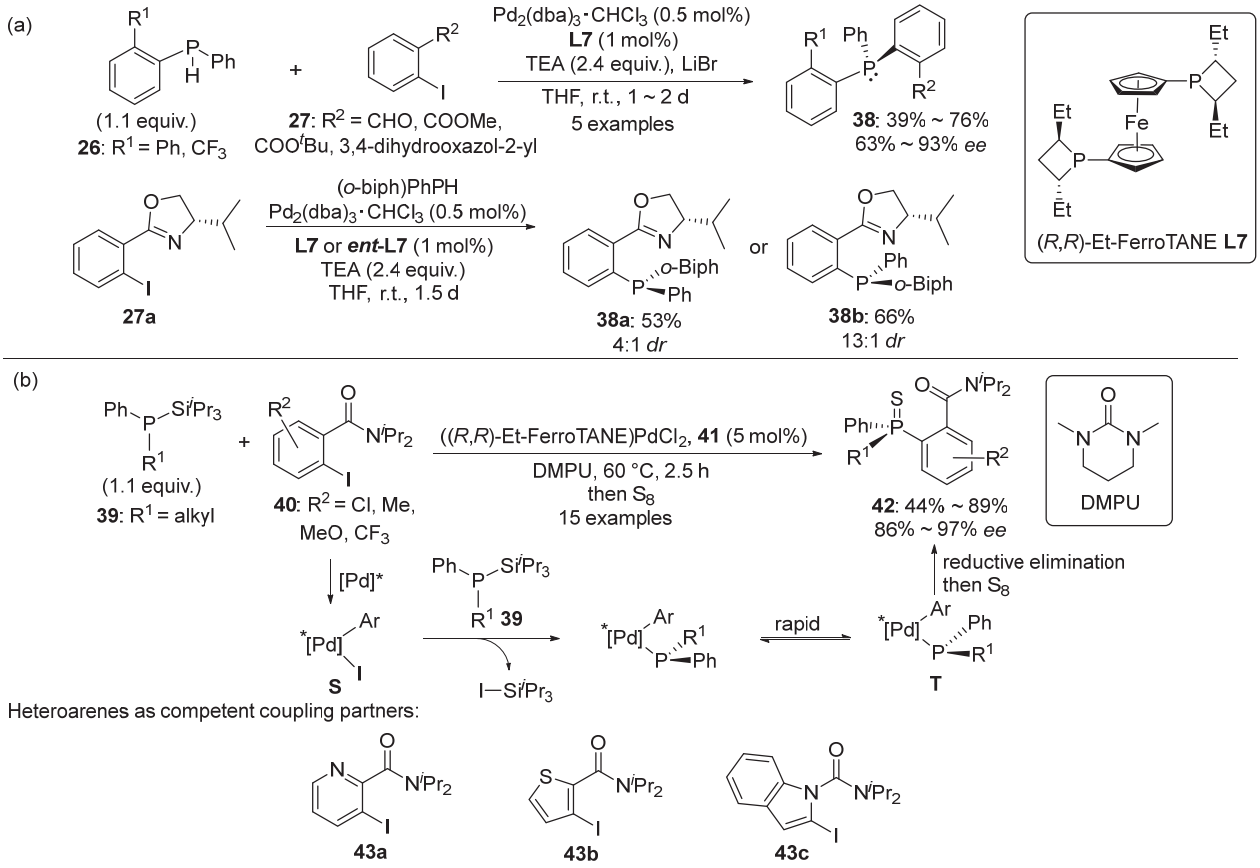


Scheme 9 Pd and Pt-catalyzed asymmetric arylation of secondary phosphines and their borane complexes

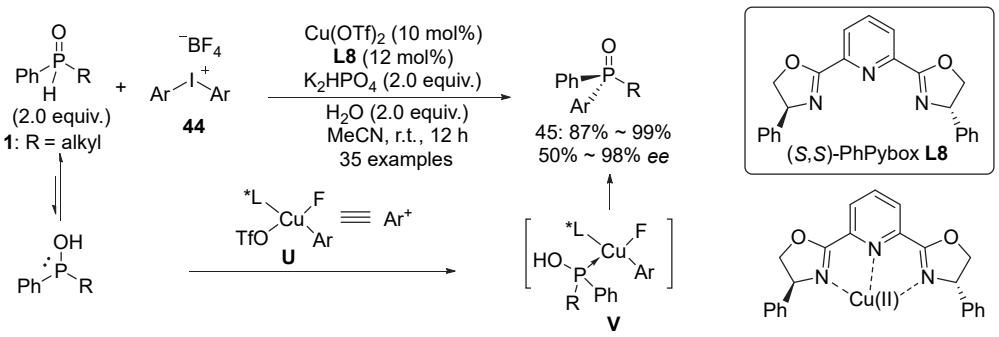
salts **44** as the arylation reagents and (*S*,*S*)-PhPybox **L8** as the chiral ligand (Scheme 11).[24] The combination of diaryliodonium salts **44** and Cu catalyst gave a putative Cu-aryl species **U**, which was supposed to be an aromatic electrophile equivalent. Then the trivalent phosphinous acid form of **1** bound to **U** to form intermediate **V**. Upon an enantio-controlled reductive elimination process, the desired *P*-chiral products **45** were produced. The rigid chelation of tridentate ligand **L8** with copper offered an ideal model for high asymmetric induction. It is worth noting that the reaction was accompanied by an oxidative side reaction, which afforded corresponding phosphinates as side products. As a result, 2 equiv. of **1** was required to offset the deleterious oxidative side reaction. Meanwhile, the acid generated through the oxidation pathway resulted in the racemization of **1**, which was pivotal for the DKR of **1**.

3.2 Asymmetric addition to *α*,*β*-unsaturated compounds or alkyne

Early in 2000, by utilizing Pt((*R*,*R*)-Me-Duphos)(*trans*-stilbene) (**30b**) as the catalyst precursor, Glueck group[25-26] developed an stereocontrolled Michael type reaction of secondary phosphines with activated olefins (such as acrylonitrile and *tert*-butyl acrylate) to build up tertiary phosphines with a *P*-chiral center. However, the enantioselectivity was very poor. In 2012, Leung group[27] discovered that *C*,*P*-palladacycle **47** served as an efficient catalyst for the asymmetric hydrophosphination of enones **46** (Scheme 12). When methylphenylphosphine **26a** was employed as the substrate, a DKR process was carried out to provide tertiary phosphines **48** bearing adjacent P-chiral and C-chiral centers in up to 91∶9 *dr* and 82% *ee*. The proposed mechanism showed that the displacement of acetonitrile in **47** by **26a** initiated the reaction, which was followed by the binding of enones **46**, yielding the intermediate **X**. Upon deprotonation of **X** by a mild base, Pd-phosphido species **Y** was furnished. The intramolecular 1,4-addition reaction of **Y** underwent a six-member ring transition state to afford intermediate **Z** with good control of stereoselectivity, which would lead to the expected adduct **48**.



Scheme 10 Pd-catalyzed asymmetric arylation of secondary phosphines and silylphosphines

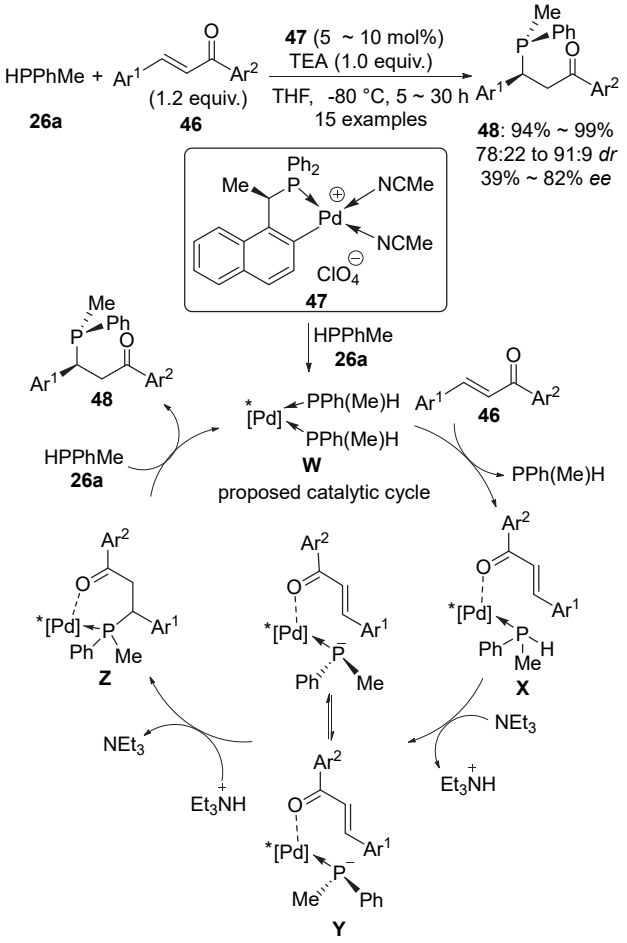


Scheme 11 Cu(II)-catalyzed asymmetric arylation of alkylarylphosphine oxides with diaryliodonium salts

In 2014, Duan Group found a very similar chemistry (Scheme 13a).[28] By employing NCN pincer-Pd complexes **50** as the catalyst, a good enantioselective 1,4-addition of methylphenylphosphine **26a** to enones **46** was also disclosed. However, the diastereoselectivity was very poor albeit with good enantioselectivity. Notably, by replacing the catalyst with PCP pincer-Pd complex **52a** and the nucleophile with isopropylphenylphosphine **26b**, an excellent diastereo- and enantioselective hydrophosphination reaction worked well to furnish the desired adducts **51**. The synthetic application of this strategy was demonstrated by the facile synthesis of optically pure *P*-chiral bisphosphine **54**, which was a potential ligand for the preparation of pincer metal catalysts with *P*-Chirality.[29]

It was difficult to realize the Pd-catalyzed asymmetric hydrophosphination of *α*,*β*-unsaturated ketones carrying a 2-pyridyl moiety at the *β*-position.[30] The main obstacle is that the phosphorus and the nitrogen atoms in the products could tightly bind to Pd center and thus the catalyst's activity was inhibited. PCP pincer-Pd complex **52a** successfully tackled this problem. Enones **46a** bearing a 2-pyridyl group and isopropylphenylphosphine **26b** were employed as the appropriate substrates by Xiao, Duan and co-workers and the products **55** were provided in ＞20∶1 *dr* and 99% *ee* (Scheme 13b).[31]

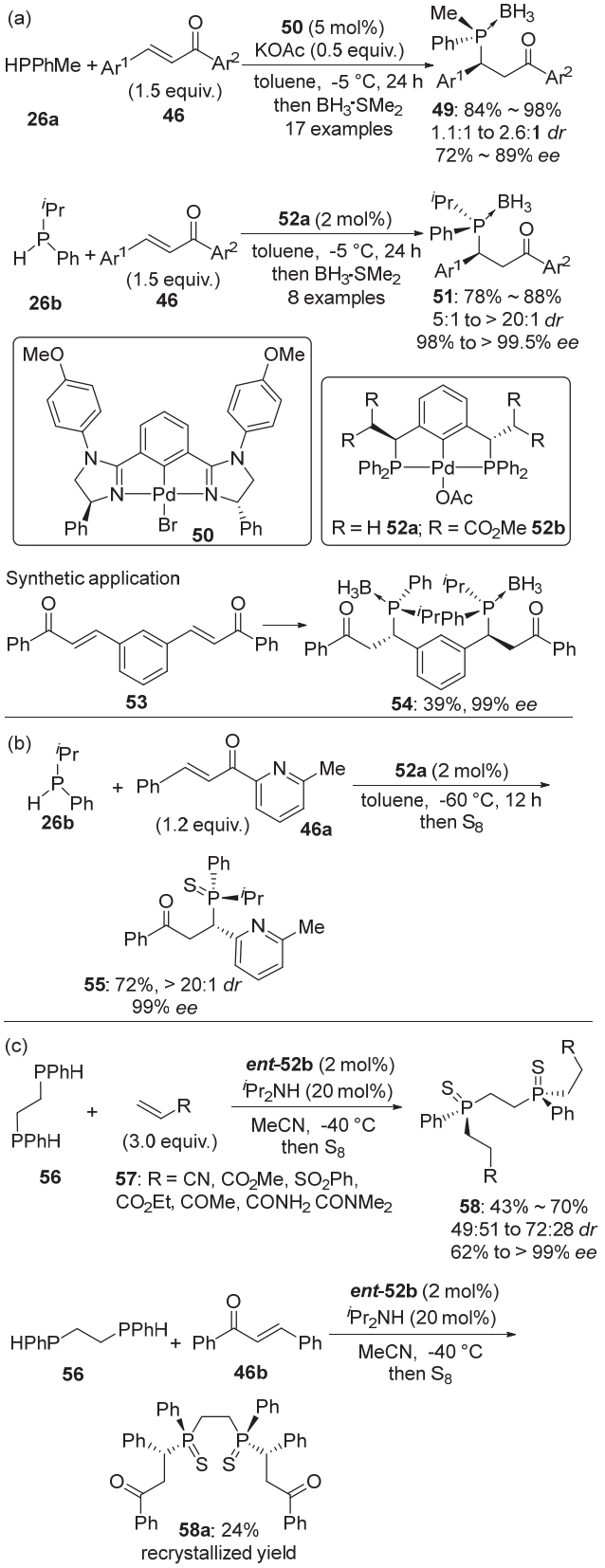
The synthesis of free *P*-chiral 1,2-diphosphines was also achieved by using PCP pincer-Pd complex ***ent*-52b** as the catalyst and bis(phenylphosphino)ethane **56** as the nucleo-



Scheme 12 Palladacycle-catalyzed asymmetric 1,4-addition of methylphenylphosphine to enones

phile (Scheme 13c).[32] Under mildly basic conditions, the asymmetric addition of various activated olefins **57** was enabled, affording *P*-chiral 1,2-diphosphines **58** in good to excellent enantioselectivity. Disappointingly, the diastereoselectivity was moderate, which was largely attributed to the conflicting influences between the chiral mono-hydrophosphinated intermediate and the chiral Pd catalyst in the second hydrophosphination. The utility of *trans*-chalcone **46b** as a Michael acceptor enabled the generation of 1,2-diphosphines **58a** bearing four stereogenic centers, which was the first example for the direct construction of both *C*- and *P*-chiral free 1,2-diphosphines.

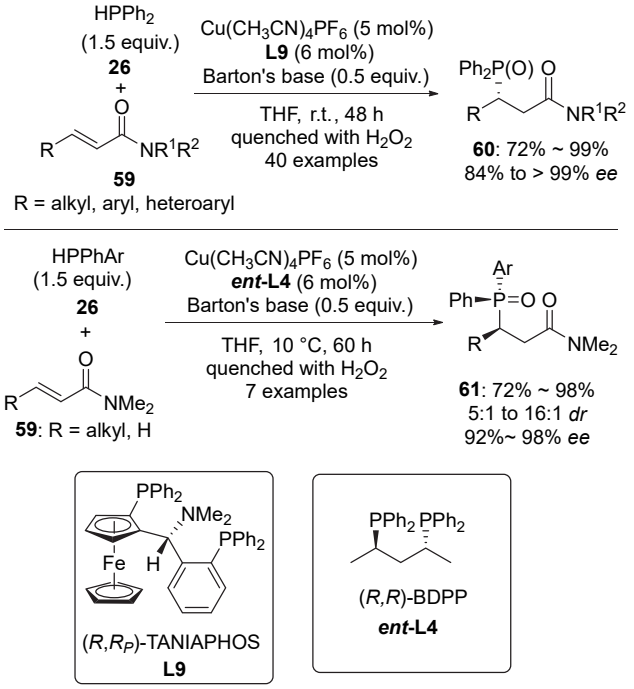
Compared to *α*,*β*-unsaturated ketones, *α*,*β*-unsaturated amides were supposed to be less efficient electrophiles in catalytic asymmetric conjugate addition of secondary phosphines because of their low electrophilicity. In 2020, Yin group[33] disclosed an asymmetric 1,4-addition of diphenylphosphine **26** to *α*,*β*-unsaturated amides **59** catalyzed by Cu(I)-bisphosphine complexes (Scheme 14). The scope of the nucleophiles was extended to unsymmetrical diarylphosphines **26**. A DKR reaction occurred smoothly with the assistance of chiral ligand (*R*,*R*)-BDPP ***ent*-L4** to provide *P*-stereogenic tertiary phosphine oxides **61** after an oxidation protection with good to high diastereoselectivity



Scheme 13 Pincer Pd-catalyzed asymmetric hydrophosphination

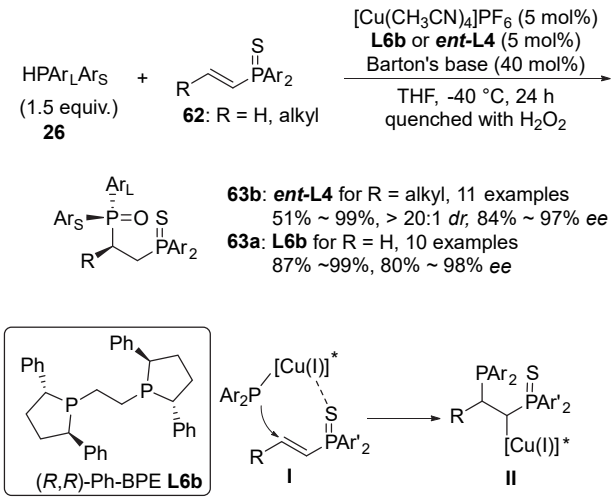
and high enantioselectivity. The reaction relied upon the activation of diphenylphosphine **26** by coordination to

copper(I) catalyst, followed by deprotonation with Barton's base. Thus a copper(I)-PPhAr species was generated and proposed as the reactive nucleophile under the mild basic reaction conditions. ^{1}H NMR spectroscopic experiments confirmed that the efficient deprotonation of **26** required the precoordination of **26** to Cu(I)-bisphosphine complex. The success of this reaction relied on the high nucleophilicity of the copper(I)-PPhAr species generated *in situ*, which compensated for the low electrophilicity of *α*,*β*-unsaturated amides **59**. Meanwhile, the high stereoselective control in this reaction benefited from the experimental fact that the catalyst Cu(I)-bisphosphine complex was relatively stable in the presence of excessive **26**. The tight binding of bisphosphine ligand to copper(I) suppressed the ligand exchange between original ligands ***ent*-L4** and **26**, which would lead to reduced enantioselectivity.



Scheme 14 Cu(I)-Catalyzed asymmetric hydrophosphination of *α*,*β*-unsaturated amides

α,*β*-Unsaturated phosphine oxides are another type of inert Michael acceptors that are hardly used in conjugate hydrophosphination also due to their low electrophilicity. By switching the electrophiles from *α*,*β*-unsaturated phosphine oxides to *α*,*β*-unsaturated phosphine sulfides **62**, Yin group[34] succeeded in developing an efficient Cu(I)-catalyzed asymmetric conjugate addition of diarylphosphines **26** to construct chiral 1,2-bisphosphines **63** featuring a stereogenic phosphorus center, which represented a class of important and powerful ligands used in asymmetric catalysis (Scheme 15). The chiral ligand (*R*,*R*)-Ph-BPE **L6b** was found to be effective for the enantioselective addition of terminal olefins **62** (R=H), while the (*R*,*R*)-BDPP ***ent*-L4** ligand was optimal for the asymmetric hydrophosphination of non-terminal olefins **62** (R=alkyl). The difference of



Scheme 15 Cu(I)-catalyzed asymmetric hydrophosphination of *α*,*β*-unsaturated phosphine sulfides

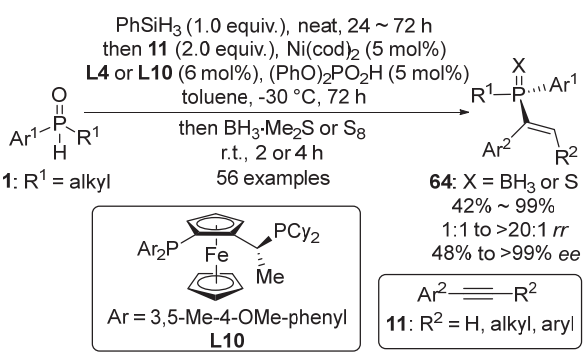
the steric hindrance effects between the two aryl rings of **26** should not be too small to achieve the DKR process. Under the optimum reaction conditions, both the diastereoselectivity and the enantioselectivity were high to excellent in most cases.

It was deduced that the "soft-soft interaction" between Cu(I) and sulfur atom was crucial for the activation of *α*,*β*-unsaturated phosphine sulfides **62**. The coordination of diarylphosphines **26** to Cu(I)-bisphosphine complex was indispensible for their deprotonation by Barton's base. The resulting Cu(I)-PAr$_2$ species was captured by mass spectrum and ^{31}P spectrum. The nucleophilic Cu(I)-PAr$_2$ species **I** attacked *α*,*β*-unsaturated phosphine sulfides **62** via a six-member ring transition state to afford intermediate **II**, the protonation of which afforded the expected products.

In 2021, Zhang group[35] uncovered a Ni-catalyzed enantioselective hydrophosphination of unactivated alkynes **11** (Scheme 16). Bench-stable secondary phosphine oxides **1** were employed as the starting materials. They were reduced by $PhSiH_3$ and the *in situ* generated secondary phosphines served as the real nucleophiles, which bypassed the isolation and purification of toxic secondary phosphines. Ni was a relative "hard" metal, the use of which would eliminate the possible background reactions because the *in situ* generated secondary phosphines and the products **64** were relatively "soft" and their coordination ability to Ni was weak. When R^1 in **1** was a secondary alkyl group, (*S*,*S*)-BDPP **L4** was chosen as the best ligand, and when R^1 was a primary alkyl group, **L10** performed best. Under the optimum reaction conditions, the Markovnikov *cis*-adducts **64** was obtained in up to >99% *ee* and >20∶1 *rr*. The adducts **64** could be easily transformed to various potential bidentate chiral ligands, organocatalyst, as well as transition-metal complexes.

3.3 Asymmetric alkylation

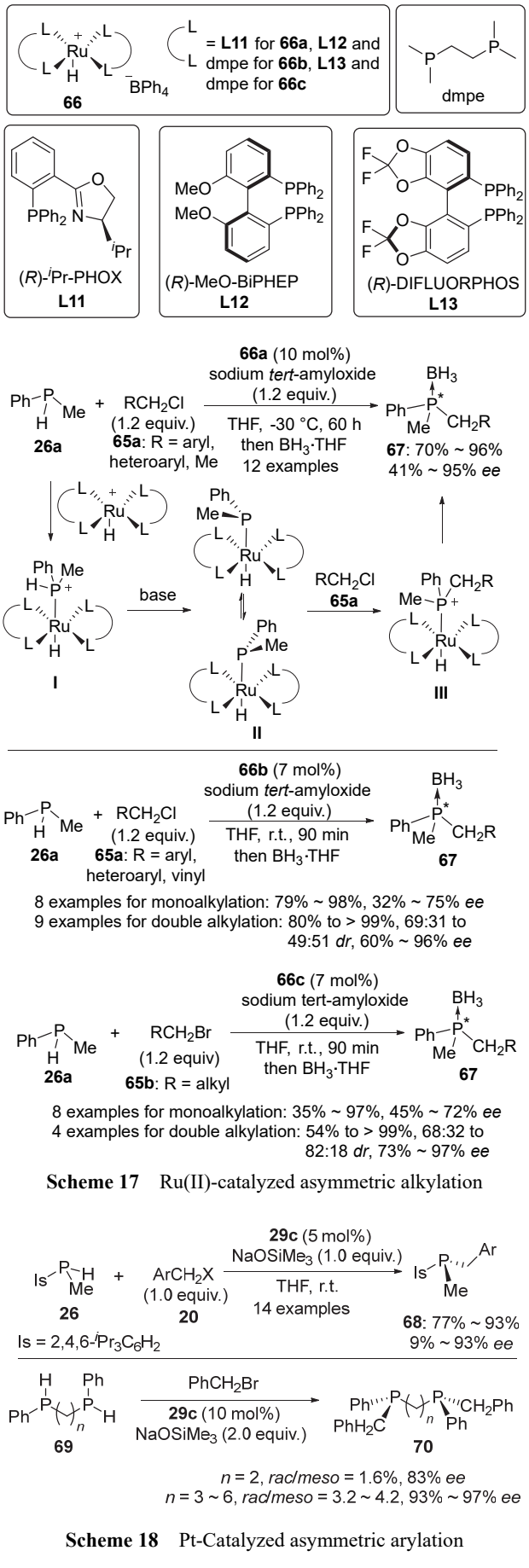
In 2006, Bergman, Toste and co-workers[36] designed



Scheme 16 Ni(II)-catalyzed asymmetric hydrophosphination of alkynes

and synthesized a myriad of chiral hydrido ruthenium compex **66** and applied them as catalysts for the novel catalytic asymmetric alkylation reaction (Scheme 17). The complex **66a** employing (*R*)-^{i}Pr-PHOX **L11** as the chiral bidentate ligand performed best for the enantioselective alkylation of methylphenylphosphine **26a**. Based on some control experiments, a tentative mechanism was proposed. The coordination of **26a** to Ru(II), an electron-rich transition metal, gave rise to intermediate **I**, which was deprotonated by sodium *tert*-amyloxide to yield highly nucleophilic Ru(II)-phosphido complex **II**. There was a rapid equilibrium between the two epimers of **II** through pyramidal inversion, which entailed its substitution reaction with **65a** in a enantioselective manner. Remarkably, the reaction exhibited an unusual temperature dependence. When lowering the reaction temperature from room temperature to −30 ℃, a reversed enantio-introduction was observed. What's more, the scope of the electrophiles was mainly confined to benzylic chlorides, which significantly limited the application of this protocol. Soon after, the same group developed two coordinatively unsaturated complexes **66b** and **66c**, in which two different bisphosphine ligands were used to address these problems.[37] The combination of chiral bisphosphine (*R*)-MeO-BiPHEP **L12** (in **66b**) or (*R*)-DIFLUORPHOS **L13** (in **66c**) and an achiral ligand 1,2-bis(dimethylphosphino)ethane (dmpe) created an asymmetric environment around Ru center through the synergistic interaction between the two ligands. The former complex **66b** was effective for the enantioselective substitution of benzylic chlorides and allylic chloride **65a** at ambient temperature, while the latter complex **66c** allowed the asymmetric alkylation with less activated alkyl bromides **65b**.

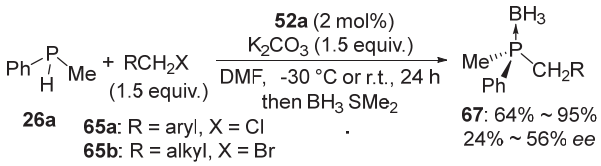
The aforementioned catalyst precursor Pt((*R*,*R*)-Me-Duphos)(Ph)(Cl) **29c** could also catalyze the asymmetric alkylation of arylmethylphosphine **26** to yield *P*-chiral tertiary phosphines **68** (Scheme 18).[38-39] The catalytic system could also be extended to double alkylation of bis(secondary phosphines).[40-42] By using bis(phenylphosphino)alkanes **69** as a model, the effect of linker length on stereoselectivity and cooperative reactivity was studied.[43] It was a substrate-controlled reaction for n=2 while it was a catalyst-controlled reaction for n=3～6.



Scheme 17 Ru(II)-catalyzed asymmetric alkylation

Scheme 18 Pt-Catalyzed asymmetric arylation

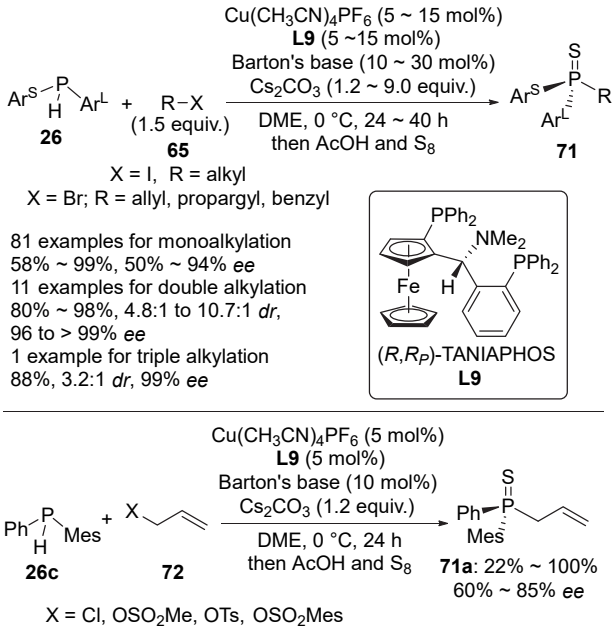
In 2013, Xu, Duan and co-workers[44] realized a PCP pincer Pd **52a**-catalyzed enantioselective alkylation of methylphenylphosphine **26a** with alkyl halides **65** (Scheme 19). Both benzyl chlorides **65a** and alkyl bromides **65b** were viable under the optimum reaction conditions to deliver the desired products **67** as borane-adducts in high yields, albeit with low to moderate enantioselectivity.



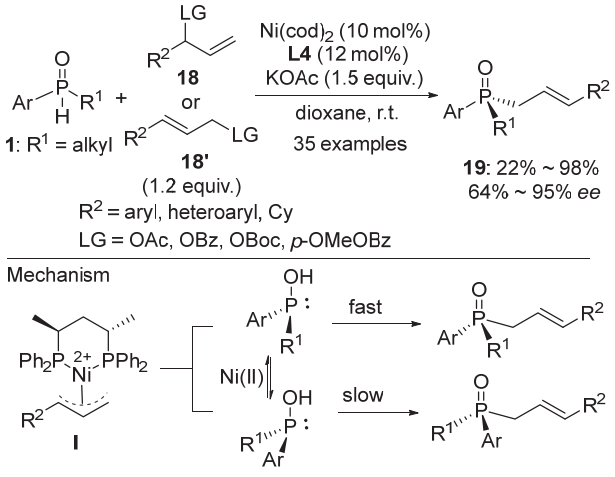
Scheme 19 Pincer Pd-catalyzed asymmetric alkylation

In 2021, Yin group[45] accomplished a highly enantioselective alkylation reaction of sterically demanding diarylphosphines **26** with alkyl halides **65** by employing a chiral Cu(I) complex, which allowed direct access to optically active *P*-stereogenic tertiary phosphines **71** (Scheme 20). The combination of 5 mol% $Cu(CH_3CN)_4PF_6$ and 5 mol% (R,R_P)-TANIAPHOS **L9** was identified to be the best choice and enabled the smooth reaction of a myriad of alkyl halides **65**, including benzyl bromides, allyl bromides, propargyl bromides, and alkyl iodides. By increasing the catalyst loading to 10～15 mol%, the extension of this protocol to double and triple alkylation was accomplished in excellent enantioselectivity, albeit with moderate diastereoselectivity. They also tried other electrophiles **72** (such as allyl chloride, allyl mesylate, allyl tosylate, and allyl 2,4,6-trimethylbenzenesulfonate), but inferior results were obtained. Based on control experiments, a tentative mechanism was proposed with HPPhMes **26c** as a model substrate. The activation and the following deprotonation of **26c** were ensured by its coordination to Cu(I)-(R,R_P)-TANIAPHOS **L9** complex. The resulting Cu(I)-PPhMes species had two diastereoisomers **IIa** and **IIb**, both of which could proceed a S_N2 substitution with alkyl halides **65**. However, the former was fast and the latter was very slow, which gave rise to the high asymmetric induction in this protocol. The use of stoichiometric **26c** did not have an obvious disturbing effect on the enantio-control of this reaction owing to the fact that the copper(I)-**L9** complex was highly catalytically active and rather stable in the presence of excessive **26c**. The synthetic utility of this protocol was demonstrated by the synthesis of structurally diversified Cu(I) complexes directly from the obtained *P*-chiral products.

As shown in Scheme 6a, the use of KOAc in place of K_3PO_4 resulted in DKR of alkylarylphosphine oxides **1**. The best catalytic system was comprised of 10 mol% $Ni(cod)_2$, 12 mol% (*S*,*S*)-BDPP **L4**, and 1.5 equiv. of KOAc (Scheme 21).[13] The linear selective allylation of **1** with various allylic esters **18** delivered (*E*)-form products **19** exclusively. The leaving group of **18** (such as OAc, OBz, OBoc, and *p*-methoxyl-OBz) had no impact on the enantioselectivity and when esters **18** were displaced by



Scheme 20 Cu(I)-catalyzed asymmetric alkylation



Scheme 21 Ni(II)-catalyzed asymmetric allylation of secondary phosphine oxidates

linear allylic esters **18'**, the same products were obtained with the same enantioselectivity, indicating that π-allyl Ni intermediate **I** was involved in the mechanism. The racemization of **1** was enabled by the Ni(II) complex in the

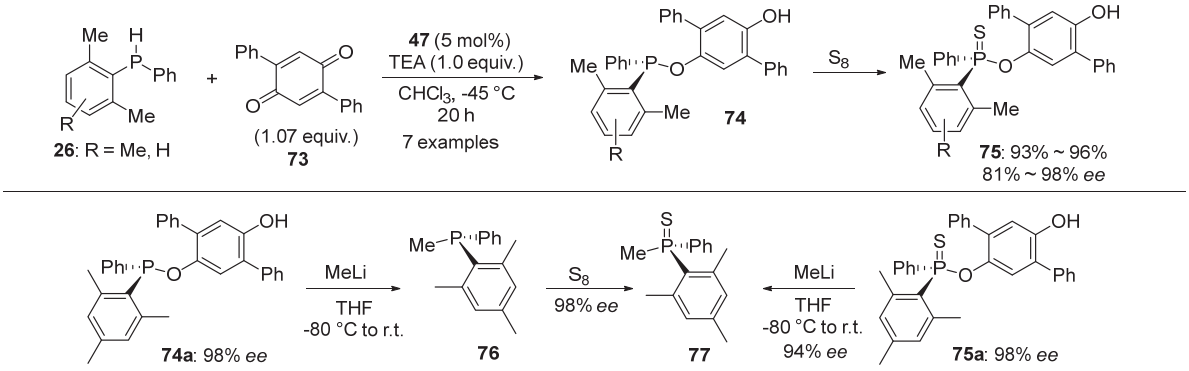
presence of KOAc. The trivalent tautomers of **1** with *S* configuration could react with intermediate **I** in a much faster rate than those with *R* configuration, whereby the DKR of **1** took place efficiently to furnish the *P*-chiral products **19**.

3.4 Asymmetric reaction to construct *P*-chiral P—O bond and P—N bond

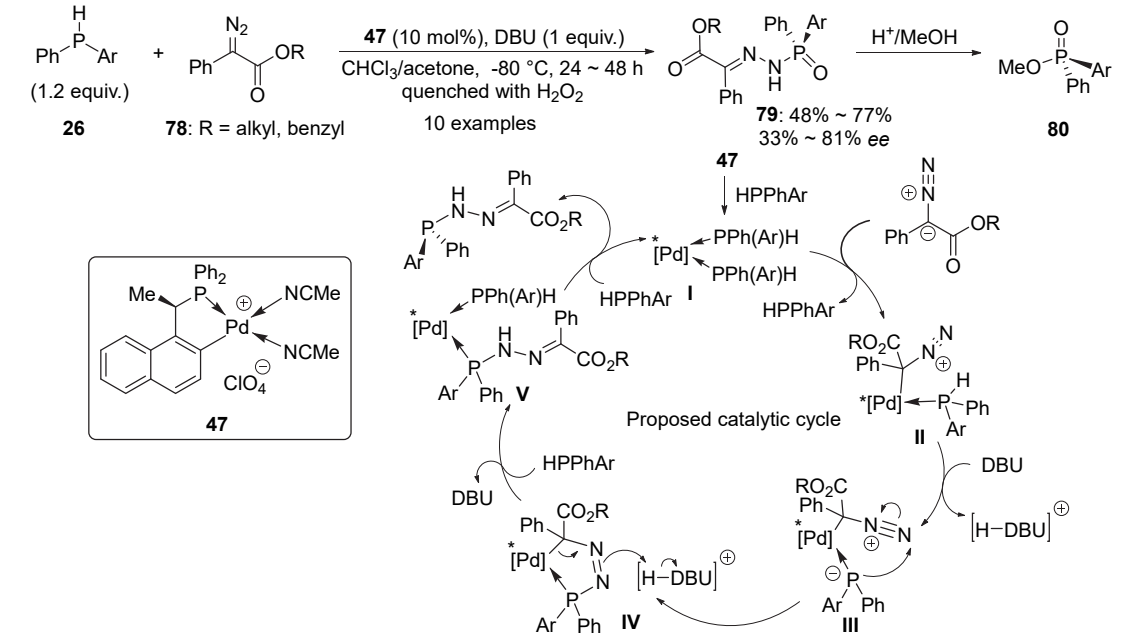
The aforementioned reports mainly focused on the construction of enantioenriched all-carbon attached tertiary phosphines. During the study on Pd-catalyzed enantioselective hydrophosphination of *α*,*β*-unsaturated compounds, Leung, Hayashi and co-workers[46] found that when diarylphosphines **26** in which one of the two aromatic ring was sterically congested, and benzoquinones **73** were subjected to the reaction conditions, an unusual 1,6-addition rather than 1,4-addition occurred, whereby a DKR of **26** incorporating asymmetric C—O bond formation was established (Scheme 22). In the presence of 5 mol% phosphapalladacycle complex **47** and 1.0 equiv. of triethylamine (TEA), a variety of **26** was successfully transformed to *P*-chiral diarylphosphinites **74**. In most cases, the yields and the enantioselectivity of the products as sulfides **75** were excellent. However, the less congested **26** with an *ortho*-monosubstituted aryl ring gave rise to a significant decrease in enantioselectivity. The use of diphenylphosphine even led to diphosphinite and diphosphine via an oxidation process rather than the desired product. Given that the phenoxide moiety was a good leaving group, the product **74a** and its sulfide **75a** were easily converted into phosphine **76** and its sulfide **77** with high enantiomeric purity, exemplifying the versatile utility of this protocol in organic synthesis.

Given that *P*-chiral aminophosphinites (or their oxides) are ubiquitous in a variety of bioactive compounds[47] and appreciated as efficient chiral ligands or organocatalysts in the field of asymmetric catalysis,[48] extensive attentions have been devoted to their preparation. The nucleophilic substitution of $ClPR^1R^2$ with amine is a typical strategy for the synthesis of racemic aminophosphinites. However, the configuration of $ClPR^1R^2$ is instable, which deters the substitution reaction from being extended to its asymmetric version.[49] The dynamic kinetic asymmetric transformation of racemic secondary phosphines could provide a straightforward access to *P*-chiral aminophosphinites. In 2020, by exploiting the electrophilic capability of diazoesters **78**, Pullarkat, Leung, and co-workers[50] disclosed an asymmetric hydrazonation of racemic unsymmetrical diarylphosphines **26**, furnishing *P*-chiral phosphinic hydrazones **79** in moderate enantioselectivity (Scheme 23). Catalyst screening established that the Pd complex **47** performed the best. It should be mentioned that only diarylphosphines **26** bearing a substituent on the *m*-position of aryl ring were perfect substrates. Diarylphosphines decorated with an *o*-substituent were thoroughly incompetent nucleophiles because of their steric hindrance, which made the diazo compounds **78** disable to coordinate to the catalyst. As for the *p*-substituted counterparts, it was difficult to differentiate the two aryl groups and diminished enantioselectivity was obtained. What's more, replacing either of the aryl rings with an alkyl one led to extremely low reaction rate, as well as the erosions in both yield and enantioselectivity. By some control experiments, a reaction pathway was proposed in which both of the two starting materials first coordinated to the catalyst to form intermediate **II**, which was subsequently deprotonated by 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). The resulting intermediate **III** then underwent an intramolecular nucleophilic addition to provide intermediate **IV**. Finally, **IV** retrieved the proton from DBU•H^+ to produce the target molecules. The potential application of this methodology was exemplified by a single-step transformation of **79** to valuable *P*-chiral diarylphosphinates **80** without any loss of enantioselectivity.

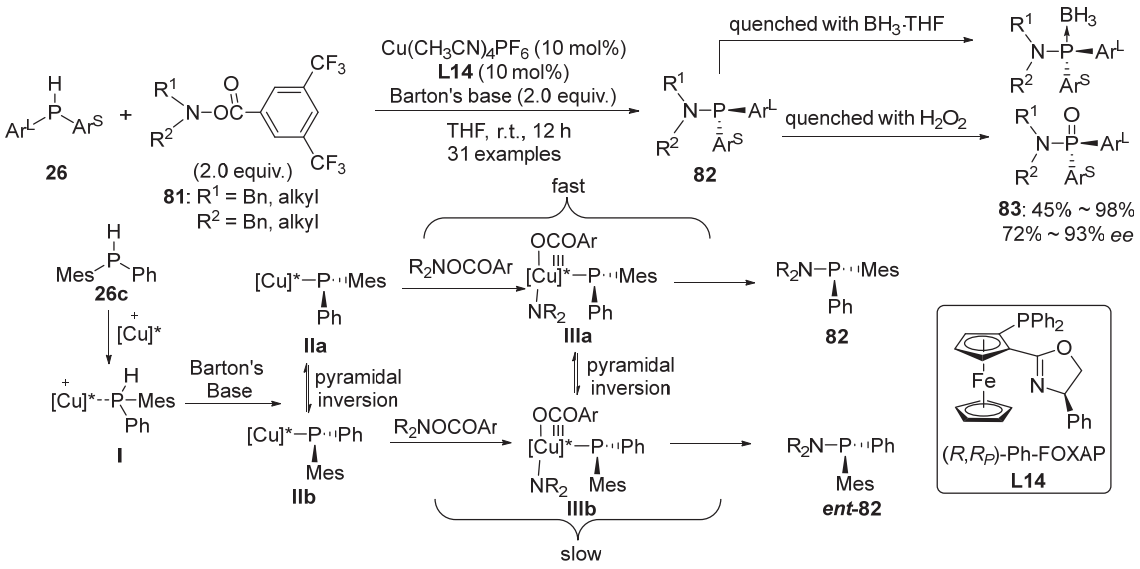
However, there is a lack of general strategies for the catalytic asymmetric synthesis of *P*-chiral aminophosphinites from unsymmetrical diarylphosphines. This problem was successfully addressed by Yin group in 2022. By employing *O*-benzoyl hydroxylamines **81** as electrophilic reaction partners, and the complex of $Cu(CH_3CN)_4PF_6$ and (R,R_P)-Ph-FOXAP **L14** as the catalyst, various *P*-chiral aminophosphinites **82** were furnished in high yields with high enantioselectivity (Scheme 24).[51] It is noteworthy that alkylarylphosphines were unsatisfactory substrates with only trace desired products obtained. This is a limitation of this strategy, so it should be overcome in the future. Bulky either R^1 or R^2 substituents in **81**, and sterically congested Ar^L group in **26** were necessary for high enantioselectivity. Control experiments indicated that this reaction was nei-



Scheme 22 Pd-catalyzed asymmetric 1,6-addition of 2,5-diphenylbenzoquinones



Scheme 23 Pd-catalyzed asymmetric hydrazonation

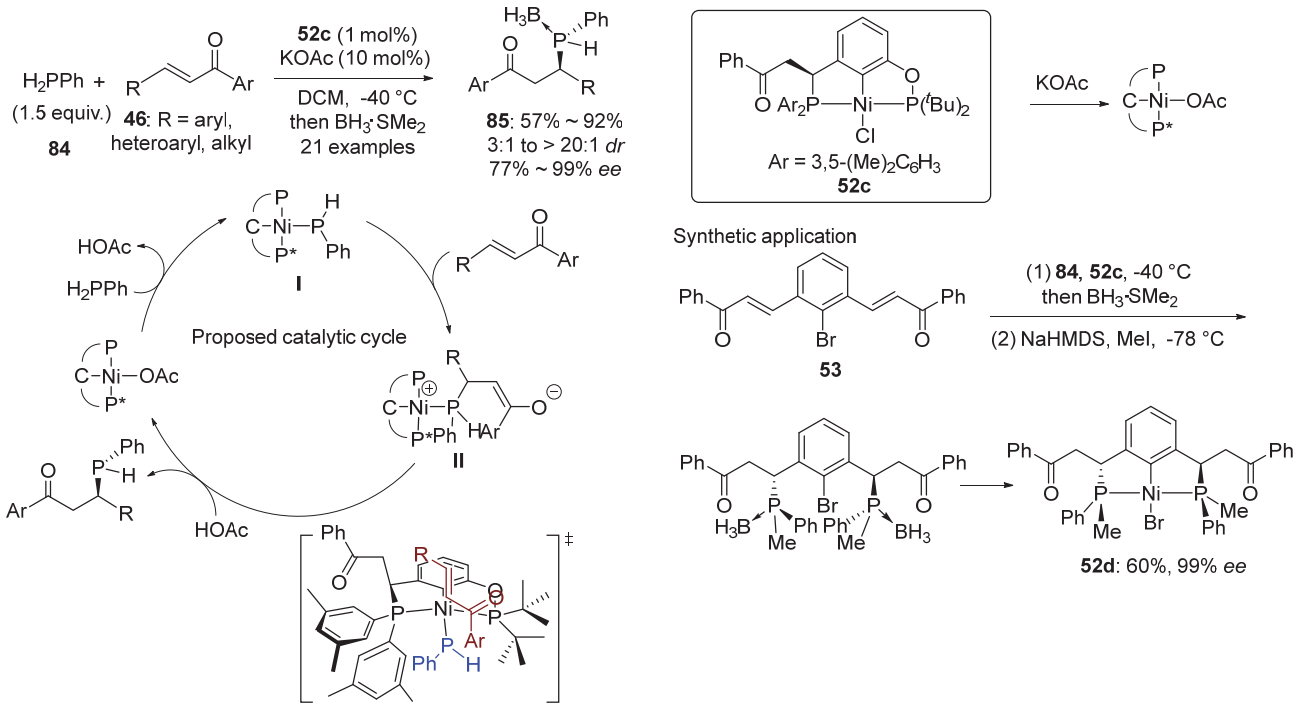


Scheme 24 Cu(I)-catalyzed asymmetric amination

ther a simple S_N2 substitution nor a radical-based process. Based on NMR studies, a plausible two-electron redox mechanism with HPPhMes **26c** as a model substrate was proposed. The Cu-phosphido species **IIa** and **IIb** were obtained through the coordination of **26c** to the Cu(I) catalytic complex and the following deprotonation by Barton's base, the interconversion of which was enabled via a pyramidal inversion. Then the oxidative addition and the following reductive elimination of the former were much faster than the latter, realizing the DKR of **26c** and successfully delivering the desired products **82**.

4 Miscellaneous reactions

Compared to the configurational stability of *P*-chiral tertiary phosphines, the tendency of secondary phosphines to be racemized arising from their low inversion barrier makes the catalytic asymmetric synthesis of *P*-chiral secondary phosphines from primary phosphines more challenging.[52] Early in 2003, Lebel group[53] found that phenylphosphine borane could be methylated stereoselectively in the presence of a chiral phase-transfer catalyst, although the enantioselectivity of the product was very low. In transition metal catalysis, the rotation around the metal-P bond in the metal-phosphido intermediate was relatively easy because of the small size of primary phosphine, which gave rise to low stereoselectivity. Considering this, Wang, Duan and co-workers[54] designed and synthesized an excellent PCP′ pincer Ni complex **52c** bearing a large



Scheme 25 Ni(II)-catalyzed asymmetric hydrophosphination of primary phosphines

P(3,5-Me_2-Ph)$_2$ group and an even larger OP^{t}Bu$_2$ moiety to facilitate the asymmetric addition of phenylphosphine **84** to electron-deficient alkenes **46** (Scheme 25). The enantiomerically enriched products **85** were obtained in up to 99% *ee* and >20∶1 *dr* after a BH_3 protection. Transphosphination between phenylphosphine **84** and the catalyst afforded Ni-phosphido species **I**, which attacked the *β*-position of **46** to produce intermediate **II**. After protonolysis with HOAc, *P*-chiral secondary phosphines were released, which were unstable and prone to racemize at room temperature. As a result, the protection with BH_3 to form stable borane complex **85** was necessary. As displayed in Scheme 25, a favored transition state was proposed to account for the stereochemistry in this reaction. The obtained optically pure *P*-chiral secondary phosphines could be easily converted into *P*-chiral tertiary phosphines via a simple alkylation reaction. The rapid construction of Pincer-Ni-Br complex **52d** featuring four stereocenters by a three-step reaction sequence starting from bisenone **53** showcased the synthetic application of this protocol.

5 Summary and outlook

In the past two decades, the catalytic asymmetric synthesis of *P*-chiral compounds received continuous attention from synthetic chemists. Various stereoselective methodologies based on KR or DKR of secondary phosphines or their derivatives were developed. The reaction scope was no longer confined to C-based electrophilic partners and was successfully extended to O-based and N-based electrophilic reagents. More importantly, these new methodologies have been applied in the efficient syntheses of some useful molecules or complexes for asymmetric synthesis scenarios. However, some challenging issues still exist, which need to be tackled in future. First, the scope of secondary phosphines or their derivatives in disclosed methodologies was mainly limited to unsymmetrical diarylphosphines. Some examples with simple arylalkylphosphines were also reported but with limited success. Evidently, the reactions with unsymmetrical dialkylphosphines in asymmetric catalysis are unknown, whereby new catalytic asymmetric systems or new chiral catalysts are required. Second, given that *P*-chiral compounds serve as potentially important chiral ligands, significant efforts should be deployed to the application of these compounds in efficient syntheses of diversified transition metal-ligand complexes to enrich the arsenal of the catalysts in asymmetric synthesis. Third, more powerful catalytic complexes and more mild reaction conditions are required to precisely control the stereoselectivity of the products as >99% *ee* is usually requested for chiral ligands. Definitely, the rapid availability of diversified P-chiral compounds from asymmetric catalysis would greatly contribute to the development of asymmetric catalysis and medicinal chemistry.

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