CellPress

Chem Catalysis

Perspective

Transition metal-catalyzed enantioselective C–P coupling reactions for the construction of P-stereogenic centers

Cheng Luan,[1,2,3,4] Chang-Jiang Yang,[1,4] Lin Liu,[1] Qiang-Shuai Gu,[3,*] and Xin-Yuan Liu[2,*]

SUMMARY

The transition metal-catalyzed C–P coupling reaction represents an effective strategy for the construction of P-stereogenic centers. These reactions involve different stereochemical mechanistic details depending on the phosphorus starting materials employed. The stereospecific transition metal-catalyzed C–P coupling of enantioenriched P-stereogenic compounds was mainly investigated in the early days. With the development of asymmetric catalysis, corresponding efficient kinetic resolution and dynamic kinetic asymmetric C–P coupling of racemic P-stereogenic starting compounds have recently been disclosed. This perspective discusses the impressive advances and provides an outlook on the directions of further developments.

THE BIGGER PICTURE

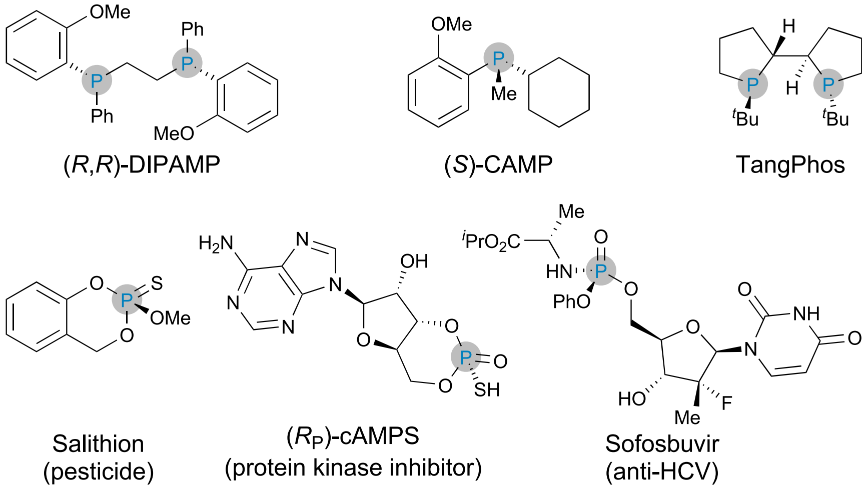
Challenges and opportunities:

- The replacement of precious metals (platinum, palladium, ruthenium, etc.) with earth-abundant first-row transition metals, such as copper, nickel, and cobalt, as catalysts for developing enantioselective C–P coupling is an appealing future direction.
- Extraordinary efforts are still required to expand the scopes of both phosphorus starting materials as well as electrophiles.
- Enantioselective C–P cross-coupling reactions that embody dynamic kinetic resolution or DyKAT of racemic phosphorus starting materials are greatly appealing in terms of both reaction efficiency and practicality.

INTRODUCTION

P-stereogenic centers are key structure motifs in many natural products,[1] pharmaceuticals,[2] and chiral ligands (Figure 1).[3,4] Traditionally, the construction of P-stereogenic centers has been considered to be challenging, and classical methods toward these compounds mainly rely on resolutions with stoichiometric chiral reagents or using chiral auxiliaries attached to the starting materials.[5–7] Over the past 2 decades, many powerful strategies have been developed for the catalytic enantioselective synthesis of P-stereogenic compounds,[8] including the desymmetrization of prochiral phosphorus substrates,[9–17] the hydrophosphination of alkenes or alkynes,[9,18–26] the C–P coupling reactions,[27,28] and other miscellaneous reactions.[4,29–35] Most of these existing methods have relied on asymmetric transition metal catalysis, while a relatively small yet significant portion of them are metal-free strategies.[13,14,17,24,30,31,33–35] In this context, transition metal-catalyzed enantioselective C–P coupling reactions represent straightforward methods for the expedient construction of P-stereogenic centers, and significant progress has been made in the recent few years. This perspective aims to provide a concise overview and the major advances in the aspect with particular emphasis on mechanistic insights concerning stereochemical control. The current challenges as well as an outlook of future trends are also presented.

In principle, the development of transition metal-catalyzed enantioselective C–P coupling is closely associated with the intrinsically unique structural and stereochemical features of various phosphorus functionalities, particularly in the presence of transition metals. For example, the typical inversion barrier of a tertiary phosphine is more than 30 kcal/mol at room temperature (Figure 2A),[36] which means a very low pyramidal inversion rate. However, metal-phosphido species are known to be configurationally labile[37] and undergo rapid pyramidal inversion (the inversion


(R,R)-DIPAMP

(S)-CAMP

TangPhos

Salithion
(pesticide)

(R_{P})-cAMPS
(protein kinase inhibitor)

Sofosbuvir
(anti-HCV)

Figure 1. Representative chiral P-stereogenic molecules

barriers for some certain Pd and Pt phosphides are around 15 kcal/mol) (Figure 2B).[38] In addition, phosphine oxides are generally more configurationally stable than trivalent phosphines. Yet transition metals have been reported to facilitate the configurational equilibration of phosphinous acids, thus indirectly promoting the racemization of corresponding phosphine oxides through tautomerization (Figure 2C).[39,40] These tactics have been successfully exploited in developing transition metal-catalyzed enantioselective C–P coupling reactions. In this perspective, these reactions are classified into three categories according to the different starting phosphorus compounds.

ENANTIOENRICHED P-STEREOGENIC COMPOUNDS

Historically, the transition metal-catalyzed stereospecific C–P cross-coupling of enantioenriched secondary phosphine derivatives was developed to obtain P-stereogenic molecules in the early days. This strategy relies on the maintenance of the stereochemical integrity at the phosphorus center during both the transmetalation step for the metal–P bond formation and the reductive elimination step for the C–P bond formation. Thus, the stereospecific transformation is undoubtedly an effective method to access P-stereogenic compounds. This is particularly true if the enantioenriched starting materials are readily available. Early explorations by Xu and coworkers revealed that enantiopure phosphinate esters underwent Pd-catalyzed stereospecific P-arylation[41,42] and alkenylation[43] with complete retention of configuration at the phosphorus centers (Figure 3A). By assuming a stereoretentive reductive elimination, the authors deduced a front-sided attack of Pd by the lone pair of the trivalent phosphonite tautomer for the Pd–P bond formation.[41] In addition, the Pd-catalyzed stereospecific P-arylation of enantioenriched secondary phosphine oxides (SPOs) with aryl halides was also reported for the synthesis of P-stereogenic tertiary phosphine oxides with retention of stereochemistry.[44–46] Besides Pd catalysts, a chiral Ni catalyst (1) was disclosed by Yang and coworkers[47] for the stereoretentive P-arylation of an enantioenriched secondary phosphine oxide with 2-naphthonitrile (the absolute configuration of the product should be revised to S_{P} instead of the originally assigned R_{P} on the basis of reported optical rotation data[48]) (Figure 3B). Although only a single substrate was demonstrated, this coupling reaction exhibited intriguing dependence on the catalyst stereochemistry: an achiral Ni catalyst led to a racemic product, and the enantiomer of Ni catalyst **1** did not work at all.

[1] School of Science and Institute of Scientific Research, Great Bay University, Dongguan 523000, China

[2] Shenzhen Grubbs Institute and Department of Chemistry, Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen 518055, China

[3] Academy for Advanced Interdisciplinary Studies and Department of Chemistry, Southern University of Science and Technology, Shenzhen 518055, China

[4] These authors contributed equally

*Correspondence:
guqs@sustech.edu.cn (Q.-S.G.),
liuxy3@sustech.edu.cn (X.-Y.L.)

https://doi.org/10.1016/j.checat.2022.09.048

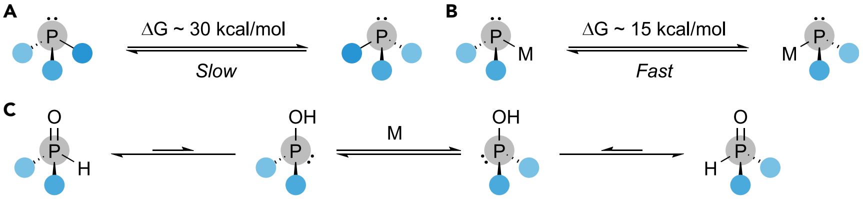


Figure 2. Configurational stability of phosphorus compounds
(A) The pyramidal inversion of common tertiary phosphines is slow.
(B) The metal-phosphido species are generally configurationally labile.
(C) Transition metals can promote the racemization of phosphine oxides by facilitating the configurational equilibration of their phosphinous acid tautomers.

It is noteworthy that the P-configuration can be affected by reaction conditions. In this respect, Imamoto and coworkers observed that the stereochemistry in Pd-catalyzed arylation of enantioenriched secondary phosphinite-boranes with aryl iodides was largely dependent on the solvent used.[49,50] Acetonitrile led to complete retention of the P-configuration, whereas tetrahydrofuran gave rise to nearly complete inversion (Figure 3C). The authors proposed that the ready phosphinite deprotonation in polar acetonitrile favored the front-sided Pd–P bond formation, resulting in configurational retention. By contrast, in the less polar solvent tetrahydrofuran, concerted phosphinite deprotonation and Pd–P bond formation likely occurred from the two sides of the P–H bond, respectively, causing configurational inversion. Besides, in a similar reaction, Livinghouse and coworkers showed that a catalytic amount of copper iodide could effectively suppress the base-mediated racemization of enantioenriched secondary phosphine–boranes via a configurationally stable Cu phosphide-borane intermediate (Figure 3D).[51] Thus, the corresponding P-stereogenic tertiary phosphine-boranes were obtained in high enantioselectivity with retention of the P-configuration. Recently, the Pd-catalyzed stereoretentive P-arylation of enantioenriched secondary dialkyl phosphines-boranes with aryl halides has also been developed.[52]

RACEMIC SECONDARY PHOSPHINES AND SURROGATES

Racemic P-stereogenic compounds are no doubt much more readily accessible than enantioenriched ones, so they are more ideal starting materials for preparing enantioenriched P-stereogenic molecules. Thus, transition metal-catalyzed enantioselective C–P coupling of racemic secondary phosphines has been intensively investigated. A noteworthy feature of these reactions involves the configurational equilibration of the *in situ* generated diastereomeric metal-phosphido complexes, which interconvert rapidly via the pyramidal inversion of the phosphorus centers. Accordingly, dynamic kinetic asymmetric transformations (DyKATs)[53] are achieved when the subsequent C–P bond formation from one diastereoisomeric complex is significantly faster than that from the other (Figures 4A and 5A). We will discuss the enantioselective C(sp^2)–P and C(sp^3)–P coupling reactions separately in the following subsections.

Enantioselective C(sp^2)–P coupling

Palladium-catalyzed enantioselective cross-coupling reactions of racemic secondary phosphines with aryl halides are a powerful strategy for the construction of P-stereogenic centers. The enantioselective C(sp^2)–P bond formation is generally proposed to proceed via the oxidative addition of a chiral Pd catalyst with an aryl halide followed by transmetalation of the racemic phosphine to form diastereomeric

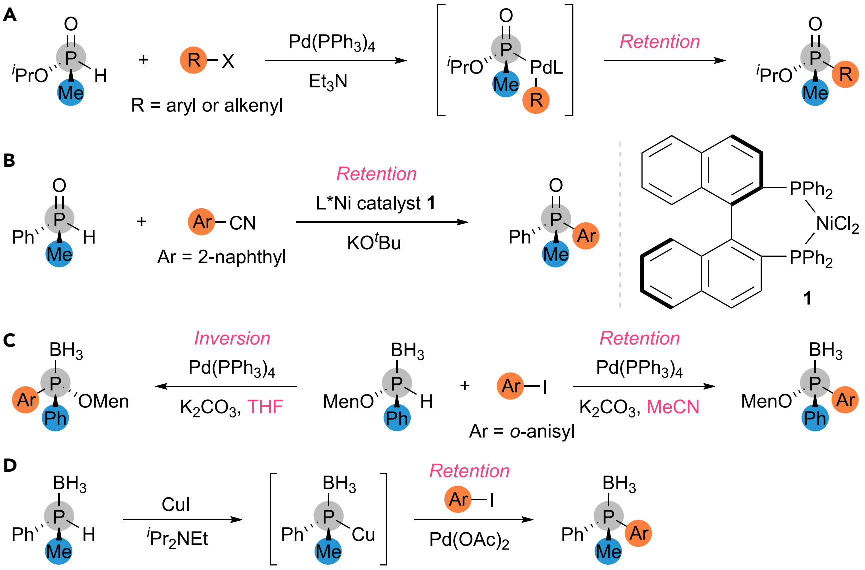


Figure 3. Stereoselective functionalization of enantioenriched P-stereogenic compounds

(A) Pd-catalyzed stereoretentive P-arylation and -alkenylation of enantioenriched phosphinate esters.

(B) Ni-catalyzed stereoretentive P-arylation of an enantioenriched phosphine oxide.

(C) The solvent effect on the stereochemistry of Pd-catalyzed P-arylation of enantioenriched secondary phosphinite-boranes.

(D) The suppression of base-mediated racemization of enantioenriched secondary phosphine-boranes by CuI.

Pd-phosphido intermediates in the presence of a base, one of which then selectively undergoes reductive elimination to afford the enantioenriched product (Figure 4A).

In this aspect, Glueck and coworkers pioneered the enantioselective C(sp^2)–P coupling of racemic secondary aryl phosphines with aryl halides using chiral Pd catalyst **2** (Figures 4B and 4E).[54] Mechanistic studies suggested that the inversion rates of the P-stereogenic centers in the diastereomeric Pd-phosphido intermediates were much faster than those of the ensuing reductive elimination processes, which signified Curtin-Hammett kinetics leading to the DyKAT of racemic secondary phosphines.[55] However, ligand substitution at the Pd center by the chiral phosphine products might occur in the reaction, rendering the reaction mechanism much more complicated than expected.[56] A similar enantioselective C–P cross-coupling of racemic diaryl phosphines with aryl iodides was also achieved by Helmchen and his coworker.[57] With chiral Pd complex **3** (Figures 4C and 4E) as the catalyst and lithium halides as an additive, the reaction delivered enantioenriched P-stereogenic triaryl phosphines in high enantioselectivity.

Although successes have been made in enantioselective C(sp^2)–P coupling of racemic secondary phosphines, their direct use is often troubled with two common problems: (1) the displacement of chiral ligands by racemic secondary phosphines[56,58] resulting in unsatisfactory enantioselectivity, and (2) the tendency toward undesired oxidation by oxygen, especially of those alkyl-substituted secondary phosphines.[59] In this vein, Toste, Bergman, and coworkers uncovered a Stille-type cross-coupling of racemic tertiary silylphosphines with 2-iodobenzamide catalyzed by chiral Pd catalyst **4** (Figures 4D and 4E), yielding P-stereogenic tertiary phosphines in good yield with excellent enantioselectivity.[60] Key to good enantiocontrol

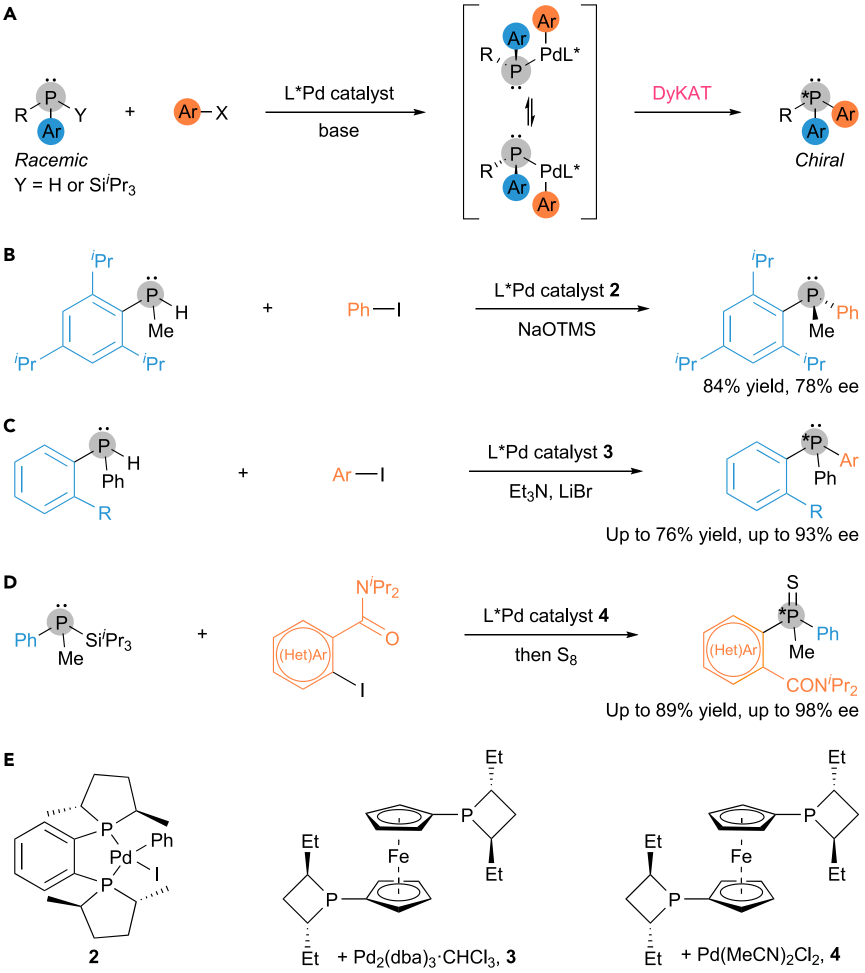


Figure 4. Enantioselective C(sp^2)–P coupling of racemic secondary phosphines and surrogates

(A) A general scheme for Pd-catalyzed enantioselective C(sp^2)–P coupling of racemic secondary phosphines and surrogates.

(B and C) Pd-catalyzed enantioselective C(sp^2)–P coupling of racemic secondary phosphines.

(D) Pd-catalyzed enantioselective Stille-type C(sp^2)–P cross-coupling of racemic tertiary silylphosphines.

(E) Representative chiral Pd catalysts.

is the use of bulky tertiary silylphosphines as secondary phosphine surrogates and the introduction of *ortho*-amide directing groups to coordinate with Pd in the reaction.

Enantioselective C(sp^3)–P coupling

In addition to the abovementioned ligand displacement by either the starting secondary phosphines or the tertiary phosphine products, the C(sp^3)–P coupling with alkyl electrophiles may also suffer from their relatively high innate nucleophilicity that likely brings about nonstereoselective background alkylation reactions and/or overalkylation side reactions. Nonetheless, compared with neutral secondary phosphines, the corresponding metal-phosphido complexes generally possess enhanced nucleophilicity and diminished pyramidal inversion barriers, thus rendering the development of transition metal-catalyzed enantioselective C(sp^3)–P coupling very promising (Figure 5A).[27,28] In this regard, Glueck and coworkers pioneered the use of chiral Pt catalysts to achieve enantioselective C(sp^3)–P coupling.

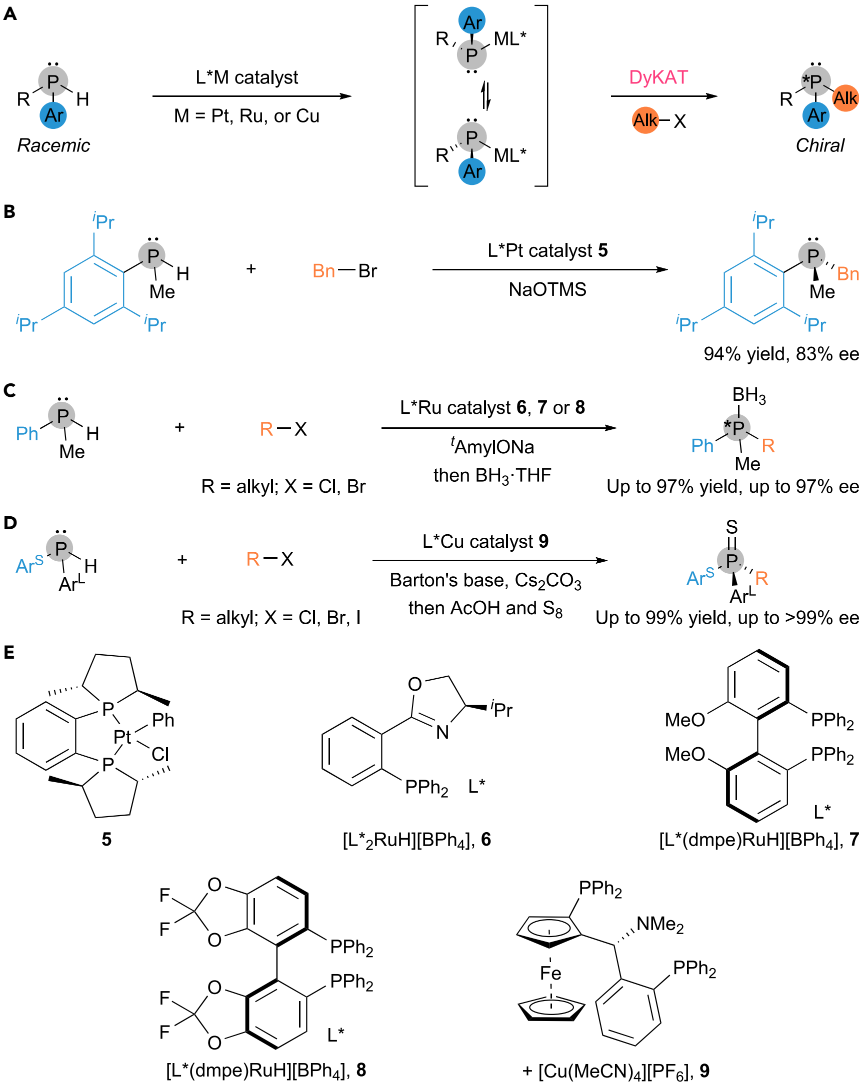


Figure 5. Enantioselective C(sp^3)–P coupling of racemic secondary phosphines

(A) A general scheme for transition metal-catalyzed enantioselective C(sp^3)–P coupling of racemic secondary phosphines.

(B) Pt-catalyzed enantioselective C(sp^3)–P coupling of racemic bulky secondary methylarylphosphines.

(C) Ru-catalyzed enantioselective C(sp^3)–P coupling of racemic methylphenylphosphines.

(D) Cu-catalyzed enantioselective C(sp^3)–P coupling of bulky aryl-substituted racemic secondary phosphines.

(E) Representative chiral transition metal catalysts.

Particularly, they discovered Pt complex **5** (Figures 5B and 5E) as an effective catalyst for the reaction of racemic bulky secondary methylarylphosphines with benzylic halides.[61] Mechanistic investigations revealed the formation of the major product enantiomer from the major Pt-phosphido intermediate diastereomer, possibly indicating that the enantioselective reaction was thermodynamically enantiocontrolled.[62] At the same time, Toste, Bergman, and coworkers independently reported chiral Ru catalyst **6** (Figures 5C and 5E) for the enantioselective C(sp^3)–P coupling of racemic methylphenylphosphines with benzyl chlorides.[63] Later, they developed second-generation chiral mixed ligand Ru catalysts **7** and **8** (Figures 5C and 5E) to

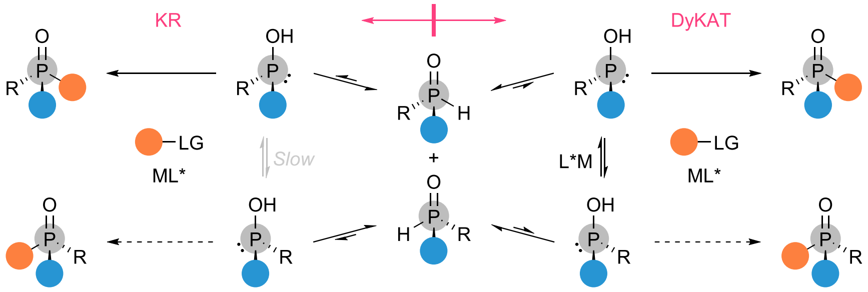


Figure 6. Enantioselective C–P coupling of racemic SPOs and *H*-phosphinates

achieve the enantioselective C(sp^3)–P coupling at ambient conditions and to accommodate less activated alkyl halides.[58]

Regarding other transition metal catalysts, Duan, Xu, and coworkers developed a Pd-catalyzed C(sp^3)–P coupling of racemic methylphenylphosphines with benzyl chlorides and alkyl bromides, albeit with low to moderate enantioselectivity.[64] Very recently, Yin and coworkers achieved enantioselective C(sp^3)–P coupling of bulky aryl-substituted racemic secondary phosphines with a wide variety of alkyl halides using chiral Cu catalyst **9** (Figures 5D and 5E).[65] Mechanistic studies indicated the weak and uncompetitive coordinating ability of the starting bulky secondary phosphine, thus emphasizing the importance of chiral catalyst **9** in enantiocontrol.

RACEMIC SPOs AND *H*-PHOSPHINATES

SPOs as well as the structurally analogous pentavalent *H*-phosphinates are much more resistant to oxidation in air and much less toxic than secondary phosphines. In addition, these pentavalent tetracoordinate organophosphorus compounds and their trivalent tricoordinate counterparts can be readily interconverted to each other through facile redox processes. Thus, these two types of compounds, especially SPOs, constitute excellent starting compounds for developing enantioselective C–P coupling methodologies and have recently received increasing interest (Figures 7A and 8A). SPOs usually exhibit very high configurational stability,[66] and thus, chirality retention is commonly observed in transition metal-catalyzed C–P coupling reactions where kinetic resolution of SPOs is achieved. Nonetheless, fast epimerization of corresponding phosphinous acid tautomers catalyzed by transition metals has been occasionally observed, which may lead to the establishment of dynamic kinetic asymmetric C–P coupling reactions in some circumstances (Figure 6).

Enantioselective C(sp^2)–P coupling

In 2016, Guant and coworkers reported the enantioselective C(sp^2)–P coupling of alkylarylphosphine oxides with diaryliodonium salts (DAISs) catalyzed by Cu catalyst **10** (Figures 7B and 7F).[67] Two equivalents of SPOs were typically employed, and the recovered SPOs were found to be of low enantiopurity or racemic. They ascribed the racemization of SPOs to the generation of acidic phosphorus compounds by side oxidation reactions. Nevertheless, in this work, they finally failed to achieve the dynamic kinetic resolution (DKR) of SPOs. Interestingly, Yang and coworkers recently achieved the dynamic kinetic asymmetric C(sp^2)–P coupling of *H*-phosphinates using chiral Cu catalyst **11** (Figures 7C and 7F).[40] Intramolecular aryl iodides were employed as the arylation reagents, and thus, the reaction gave rise to a panel of P-stereogenic phosphorus heterocycles. Their mechanistic results clearly suggested the racemization of the starting *H*-phosphinates was promoted by chiral copper catalysts, lending support for the DyKAT nature.

As for Pd catalysis, Cai and coworkers developed kinetic resolution of racemic diaryl SPOs with aryl iodides using chiral Pd catalyst **12** in 2016 (Figures 7D and 7F).[68] A bulky protected *ortho*-amino group in the aryl iodides was found to be essential for obtaining good yet still nonideal enantioselectivity. Later, Zhang and coworkers accomplished highly enantioselective kinetic resolution of alkylarylphosphine oxides with (hetero)aryl bromides using chiral Pd catalyst **13** (Figures 7E and 7F).[69] Subsequent control experiments demonstrated standard kinetic resolution of *ortho*-substituted aryl SPOs, while the reactions of simple aryl SPOs were complicated by the minor racemization of the starting materials. The nature of this racemization process as to whether it involved transition metal catalysis or not remained unknown.

Enantioselective C(sp^3)–P coupling

In 2021, Zhang, Liu, and their coworker also realized the enantioselective C(sp^3)–P coupling of alkylaryl SPOs with benzyl phosphates using chiral Pd catalyst **13** or **14** (Figures 7F, 8B, and 8G).[70] In contrast to their previous enantioselective C(sp^2)–P coupling, the racemization of simple aryl SPOs was not observed, and thus, excellent kinetic resolution of these SPOs was achieved. At the same time, Duan, Zhang, and coworkers achieved the enantioselective C(sp^3)–P coupling of phenylpyridyl SPOs with (hetero)benzyl bromides as well as methyl iodides using chiral Co catalyst **15** (Figures 8C and 8G).[71] The pyridine motifs in the substates were demonstrated to be indispensable for achieving high enantioselectivity and were proposed to coordinate to the Co catalyst, assisting the enantiodiscrimination. In addition, the outstanding kinetic resolution of the starting SPOs was once again experimentally validated.

Concerning DyKATs, Zhang and coworkers disclosed an enantioselective C(sp^3)–P coupling of alkylaryl SPOs with racemic allylic acetates using chiral Ni catalyst **16** (Figures 8D and 8G).[39] The use of potassium acetate as the base additive proved to be essential for the Ni-catalyzed racemization of starting SPOs. Accordingly, switching the base to potassium phosphate resulted in the standard kinetic resolution of the starting SPOs under the otherwise identical reaction conditions. Although interesting, the additive effect seemed to be limited to this particular reaction since excessive amounts of *H*-phosphinates[72] and alkylaryl SPOs[73] were employed in their following enantioselective C(sp^3)–P coupling works with chiral Ni catalysts **17** and **18** (Figures 8E–8G), respectively. In particular, the authors observed significant kinetic resolution of the starting SPOs in the enantioselective benzylation reaction.

SUMMARY AND OUTLOOK

Great progress has been made in transition metal-catalyzed C–P coupling reactions for constructing P-stereogenic centers in the past 2 decades, providing a straightforward and powerful strategy for synthesizing enantioenriched P-stereogenic molecules. This perspective summarizes both the early developments and the recent achievements in this field, in which sporadic efforts have been devoted to the synthesis of P-stereogenic chiral ligands for synthetic applications. Despite the significant advances achieved in these aspects, several remaining challenges and opportunities as detailed below are still to be addressed in future developments.

First, the replacement of precious metals (platinum, palladium, ruthenium, etc.) with earth-abundant first-row transition metals, such as copper,[74] nickel,[75] and cobalt,[76] as catalysts[77] for developing enantioselective C–P coupling is an appealing future

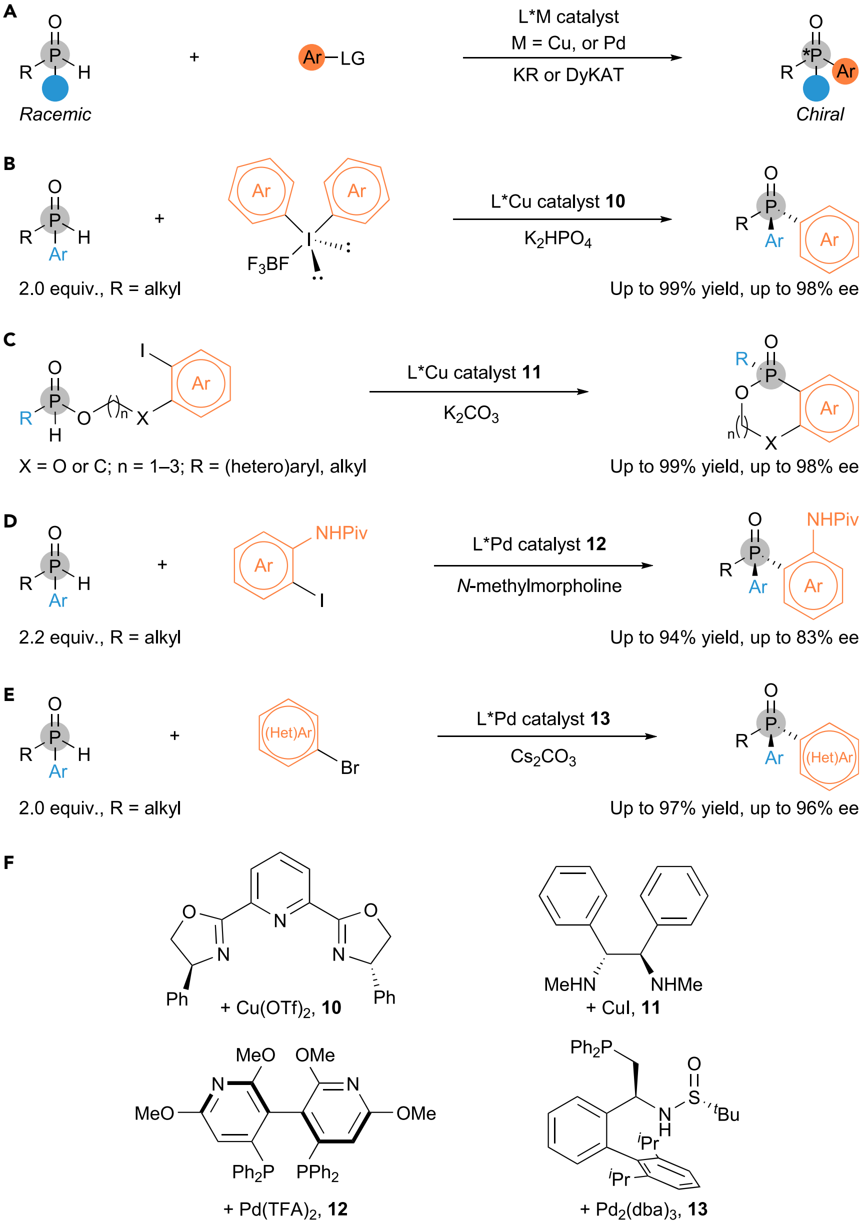


Figure 7. Enantioselective C(sp^2)–P coupling of racemic SPOs and *H*-phosphinates

(A) A general scheme for transition metal-catalyzed enantioselective C(sp^2)–P coupling of racemic SPOs and *H*-phosphinates.

(B) Cu-catalyzed enantioselective C(sp^2)–P coupling of racemic SPOs with DAISs.

(C) Cu-catalyzed enantioselective intramolecular C(sp^2)–P coupling of racemic SPOs with aryl iodides.

(D and E) Pd-catalyzed enantioselective C(sp^2)–P coupling of SPOs with aryl iodides or (hetero)aryl bromides.

(F) Representative chiral transition metal catalysts.

direction. The benefits are obviously not limited to cost or availability since Glueck and coworkers have demonstrated copper catalysts with weaker metal-ligand bonds and faster substitution processes, resulting in more active catalysts.[78] Rational catalyst designs as well as mechanistic studies are essential to reach this target, which remain largely underdeveloped at the present stage.

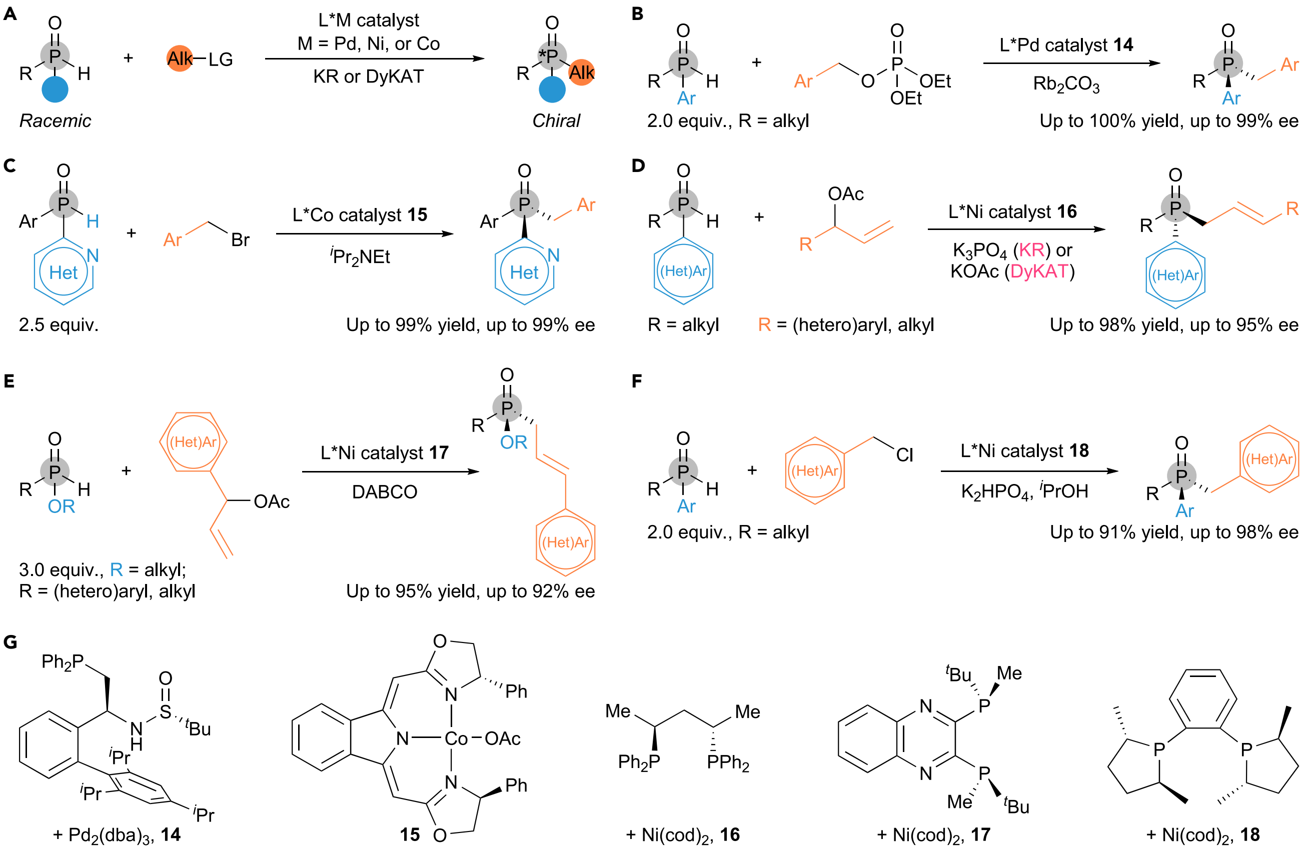


Figure 8. Enantioselective C(sp^3)–P coupling of racemic SPOs and *H*-phosphinates

(A) A general scheme for transition metal-catalyzed enantioselective C(sp^3)–P coupling of racemic SPOs and *H*-phosphinates.

(B) Pd-catalyzed enantioselective C(sp^3)–P coupling of racemic SPOs with benzyl phosphonates.

(C) Co-catalyzed enantioselective C(sp^3)–P coupling of racemic pyridyl-substituted SPOs with benzyl bromides.

(D–F) Ni-catalyzed enantioselective C(sp^3)–P coupling of racemic SPOs or *H*-phosphinates with allylic acetates or (hetero)benzyl chlorides.

(G) Representative chiral transition metal catalysts.

Second, extraordinary efforts are still required to expand the scopes of phosphorus starting materials and electrophiles. Although a number of synthetic methods have been established, most of them deal with diaryl- or alkylaryl-substituted secondary phosphines or corresponding oxides. Particularly, some of these known methods require very bulky aryl[54,61,65] or coordinating pyridyl[71] substituents for attaining high enantioselectivity. With regard to the electrophiles, limitations may include particular directing groups on aryl halides[57,60] or the accommodation of only primary electrophiles. Therefore, breakthroughs toward more efficient catalytic systems, particularly the ones invoking distinct mechanistic pathways, for the enantioselective synthesis of structurally diverse P-stereogenic compounds are expected to render the C–P cross-coupling strategy more general and powerful.

Third, enantioselective C–P cross-coupling reactions that embody DKR or DyKAT of racemic phosphorus starting materials are greatly appealing in terms of both reaction efficiency and practicality.[53] The enhanced epimerization of metal-phosphido intermediates provides a generally applicable strategy for developing enantioconvergent C–P cross-coupling of secondary phosphines. However, this mechanism does not apply to SPOs or *H*-phosphinates. Although transition metal-catalyzed epimerization of phosphinous acid tautomers has been reported,[39,40] the underlying exact mechanism as well as how to deliberately and efficiently recruit it for developing transition metal-catalyzed enantioconvergent C–P cross-coupling reaction has so far remained unclear, and thus, it merits additional efforts in this aspect.

Arguably, the surge in interest in P-stereogenic compounds has largely been fueled by the recent advances in transition metal-catalyzed C–P coupling reactions. With the subsequent intensive studies in catalytic methods for the enantioselective synthesis of P-stereogenic compounds, it is expected that increasing attention will be drawn to their wide applications in related areas.

ACKNOWLEDGMENTS

Financial support from the National Key R&D Program of China (2021YFF0701604 and 2021YFF0701704), the National Natural Science Foundation of China (22025103, 21831002, 22001109, 22271133, and 22101122), Guangdong Innovative Program (2019BT02Y335), Guangdong Provincial Key Laboratory of Catalysis (2020B121201002), Shenzhen Special Funds (JCYJ20200109141001789), and Great Bay University is gratefully acknowledged.

AUTHOR CONTRIBUTIONS

Conceptualization, Q.-S.G. and X.-Y.L.; writing – original draft, C.L., C.-J.Y., and L.L.; writing – review & editing, Q.-S.G. and X.-Y.L.; supervision, Q.-S.G. and X.-Y.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Petkowski, J.J., Bains, W., and Seager, S. (2019). Natural products containing 'rare' organophosphorus functional groups. Molecules *24*, 866. https://doi.org/10.3390/molecules24050866.
2. J.-L. Montchamp, ed. (2015). Phosphorus Chemistry I: Asymmetric Synthesis and Bioactive Compounds (Springer). https://doi.org/10.1007/978-3-319-15473-2.
3. Grabulosa, A. (2011). *P*-Stereogenic Ligands in Enantioselective Catalysis (The Royal Society of Chemistry). https://doi.org/10.1039/9781849732703.
4. Dutartre, M., Bayardon, J., and Jugé, S. (2016). Applications and stereoselective syntheses of P-chirogenic phosphorus compounds. Chem. Soc. Rev. *45*, 5771–5794. https://doi.org/10.1039/c6cs00031b.
5. Pietrusiewicz, K.M., and Zablocka, M. (1994). Preparation of scalemic P-chiral phosphines and their derivatives. Chem. Rev. *94*, 1375–1411. https://doi.org/10.1021/cr00029a009.
6. Kolodiazhnyi, O.I. (1998). Asymmetric synthesis of organophosphorus compounds. Tetrahedron: Asymmetry *9*, 1279–1332. https://doi.org/10.1016/s0957-4166(98)00089-5.
7. Lemouzy, S., Giordano, L., Hérault, D., and Buono, G. (2020). Introducing chirality at phosphorus atoms: an update on the recent synthetic strategies for the preparation of optically pure P-stereogenic molecules. Eur. J. Org. Chem. *2020*, 3351–3366. https://doi.org/10.1002/ejoc.202000406.
8. Kolodiazhnyi, O.I. (2017). Asymmetric Synthesis in Organophosphorus Chemistry: Synthetic Methods, Catalysis, and Applications (Wiley). https://doi.org/10.1002/9783527341542.
9. Ye, X., Peng, L., Bao, X., Tan, C.-H., and Wang, H. (2021). Recent developments in highly efficient construction of P-stereogenic centers. Green Synth. Catal. *2*, 6–18. https://doi.org/10.1016/j.gresc.2020.12.002.
10. Diesel, J., and Cramer, N. (2019). Generation of heteroatom stereocenters by enantioselective C–H functionalization. ACS Catal. *9*, 9164–9177. https://doi.org/10.1021/acscatal.9b03194.
11. Zhu, R.-Y., Liao, K., Yu, J.-S., and Zhou, J. (2020). Recent advances in catalytic asymmetric synthesis of *P*-chiral phosphine oxides. Acta Chim. Sinica *78*, 193–216. https://doi.org/10.6023/a20010002.
12. Zhu, R.-Y., Chen, L., Hu, X.-S., Zhou, F., and Zhou, J. (2020). Enantioselective synthesis of *P*-chiral tertiary phosphine oxides with an ethynyl group via Cu(I)-catalyzed azide–alkyne cycloaddition. Chem. Sci. *11*, 97–106. https://doi.org/10.1039/c9sc04938j.
13. Huang, Q.-H., Zhou, Q.-Y., Yang, C., Chen, L., Cheng, J.-P., and Li, X. (2021). Access to *P*-stereogenic compounds *via* desymmetrizing enantioselective bromination. Chem. Sci. *12*, 4582–4587. https://doi.org/10.1039/d0sc07008d.
14. Yang, G.-H., Li, Y., Li, X., and Cheng, J.-P. (2019). Access to P-chiral phosphine oxides by enantioselective allylic alkylation of bisphenols. Chem. Sci. *10*, 4322–4327. https://doi.org/10.1039/C8SC05439H.
15. Genov, G.R., Douthwaite, J.L., Lahdenperä, A.S.K., Gibson, D.C., and Phipps, R.J. (2020). Enantioselective remote C–H activation directed by a chiral cation. Science *367*, 1246–1251. https://doi.org/10.1126/science.aba1120.
16. Song, S.-Y., Li, Y., Ke, Z., and Xu, S. (2021). Iridium-catalyzed enantioselective C–H borylation of diarylphosphinates. ACS Catal. *11*, 13445–13451. https://doi.org/10.1021/acscatal.1c03888.
17. Huang, Z., Huang, X., Li, B., Mou, C., Yang, S., Song, B.-A., and Chi, Y.R. (2016). Access to P-stereogenic phosphinates via N-heterocyclic carbene-catalyzed desymmetrization of bisphenols. J. Am. Chem. Soc. *138*, 7524–7527. https://doi.org/10.1021/jacs.6b04624.
18. Liu, X.-T., Wu, Y., and Zhang, Q.-W. (2021). Nickel-catalyzed asymmetric synthesis of *P*-stereogenic vinyl phosphines. Synlett *33*, 301–306. https://doi.org/10.1055/a-1695-4979.
19. Liu, X.-T., Han, X.-Y., Wu, Y., Sun, Y.-Y., Gao, L., Huang, Z., and Zhang, Q.-W. (2021). Ni-catalyzed asymmetric hydrophosphination of unactivated alkynes. J. Am. Chem. Soc. *143*, 11309–11316. https://doi.org/10.1021/jacs.1c05649.
20. Yue, W.-J., Xiao, J.-Z., Zhang, S., and Yin, L. (2020). Rapid synthesis of chiral 1,2-bisphosphine derivatives through

copper(I)-catalyzed asymmetric conjugate hydrophosphination. Angew Chem. Int. Ed. Engl. *59*, 7057–7062. https://doi.org/10.1002/anie.201916076.

21. Li, Y.B., Tian, H., and Yin, L. (2020). Copper(I)-catalyzed asymmetric 1, 4-conjugate hydrophosphination of *α*, *β*-unsaturated amides. J. Am. Chem. Soc. *142*, 20098–20106. https://doi.org/10.1021/jacs.0c09654.

22. Dai, Q., Liu, L., Qian, Y., Li, W., and Zhang, J. (2020). Construction of P-chiral alkenylphosphine oxides through highly chemo-regio-and enantioselective hydrophosphinylation of alkynes. Angew Chem. Int. Ed. Engl. *59*, 20645–20650. https://doi.org/10.1002/anie.202009358.

23. Yang, Z., Gu, X., Han, L.-B., and Wang, J.J. (2020). Palladium-catalyzed asymmetric hydrophosphorylation of alkynes: facile access to *P*-stereogenic phosphinates. Chem. Sci. *11*, 7451–7455. https://doi.org/10.1039/d0sc01049a.

24. Maiti, R., Yan, J.-L., Yang, X., Mondal, B., Xu, J., Chai, H., Jin, Z., and Chi, Y.R. (2021). Carbene-catalyzed enantioselective hydrophosphination of *α*-bromoenals to prepare phosphine-containing chiral molecules. Angew Chem. Int. Ed. Engl. *60*, 26616–26621. https://doi.org/10.1002/anie.202112860.

25. Wang, C., Huang, K., Ye, J., and Duan, W.-L. (2021). Asymmetric synthesis of P-stereogenic secondary phosphine-boranes by an unsymmetric bisphosphine pincer-nickel complex. J. Am. Chem. Soc. *143*, 5685–5690. https://doi.org/10.1021/jacs.1c02772.

26. Long, J., Li, Y., Zhao, W., and Yin, G. (2022). Nickel/Brønsted acid dual-catalyzed regio- and enantioselective hydrophosphinylation of 1, 3-dienes: access to chiral allylic phosphine oxides. Chem. Sci. *13*, 1390–1397. https://doi.org/10.1039/d1sc05651d.

27. Glueck, D. (2007). Metal-catalyzed asymmetric synthesis of P-stereogenic phosphines. Synlett *2007*, 2627–2634. https://doi.org/10.1055/s-2007-991077.

28. Glueck, D.S. (2008). Catalytic asymmetric synthesis of chiral phosphanes. Chem. Eur. J. *14*, 7108–7117. https://doi.org/10.1002/chem.200800267.

29. Kolodiazhnyi, O.I. (2012). Recent developments in the asymmetric synthesis of *P*-chiral phosphorus compounds. Tetrahedron: Asymmetry *23*, 1–46. https://doi.org/10.1016/j.tetasy.2012.01.007.

30. Wang, M., Zhang, L., Huo, X., Zhang, Z., Yuan, Q., Li, P., Chen, J., Zou, Y., Wu, Z., and Zhang, W. (2020). Catalytic asymmetric synthesis of the anti-COVID-19 drug remdesivir. Angew Chem. Int. Ed. Engl. *59*, 20814–20819. https://doi.org/10.1002/anie.202011527.

31. Qiu, H., Dai, Q., He, J., Li, W., and Zhang, J. (2020). Access to *P*-chiral *sec*- and *tert*-phosphine oxides enabled by Le-Phos-catalyzed asymmetric kinetic resolution. Chem. Sci. *11*, 9983–9988. https://doi.org/10.1039/d0sc04041j.

32. Li, Y.-B., Tian, H., Zhang, S., Xiao, J.-Z., and Yin, L. (2022). Copper(I)-catalyzed asymmetric synthesis of *P*-chiral aminophosphinites. Angew Chem. Int. Ed. Engl. *61*, e202117760. https://doi.org/10.1002/anie.202117760.

33. Zhang, Y., Yuan, J., Huang, G., Yu, H., Liu, J., Chen, J., Meng, S., Zhong, J.-J., Dang, L., Yu, G.-A., and Che, C.-M. (2022). Direct visible-light-induced synthesis of P-stereogenic phosphine oxides under air conditions. Chem. Sci. *13*, 6519–6524. https://doi.org/10.1039/d2sc00036a.

34. Forbes, K.C., and Jacobsen, E.N. (2022). Enantioselective hydrogen-bond-donor catalysis to access diverse stereogenic-at-P(V) compounds. Science *376*, 1230–1236. https://doi.org/10.1126/science.abp8488.

35. Formica, M., Rogova, T., Shi, H., Sahara, N., Farley, A.J.M., Christensen, K.E., et al. (2021). Catalytic enantioselective nucleophilic desymmetrisation of phosphonate esters. ChemRxiv. https://doi.org/10.26434/chemrxiv-2021-5714s-v2.

36. Baechler, R.D., and Mislow, K. (1970). Effect of structure on the rate of pyramidal inversion of acyclic phosphines. J. Am. Chem. Soc. *92*, 3090–3093. https://doi.org/10.1021/ja00713a028.

37. Rogers, J.R., Wagner, T.P.S., and Marynick, D.S. (1994). Metal-assisted pyramidal inversion in metal–phosphido complexes. Inorg. Chem. *33*, 3104–3110. https://doi.org/10.1021/ic00092a015.

38. Zhuravel, M.A., Glueck, D.S., Zakharov, L.N., and Rheingold, A.L. (2002). Palladium(II) terminal phosphido complexes derived from cyclometalated dimesitylphosphine: synthesis, structure, and low-barrier phosphorus inversion. Organometallics *21*, 3208–3214. https://doi.org/10.1021/om020249k.

39. Liu, X.-T., Zhang, Y.-Q., Han, X.-Y., Sun, S.-P., and Zhang, Q.-W. (2019). Ni-catalyzed asymmetric allylation of secondary phosphine oxides. J. Am. Chem. Soc. *141*, 16584–16589. https://doi.org/10.1021/jacs.9b08734.

40. Li, Y., Jin, X., Liu, P., Zhang, H., Yu, X., Liu, Y., Liu, B., and Yang, W. (2022). Copper-catalyzed dynamic kinetic C–P cross-coupling/cyclization for the concise asymmetric synthesis of six-seven- and eight-membered *P*-stereogenic phosphorus heterocycles. Angew Chem. Int. Ed. Engl. *61*, e202117093. https://doi.org/10.1002/anie.202117093.

41. Xu, Y., and Zhang, J. (1986). Stereochemistry at the phosphorus atom during palladium-catalyzed formation of carbon phosphorus bonds and mechanistic implications. J. Chem. Soc. Chem. Commun. 1606. https://doi.org/10.1039/c39860001606.

42. Zhang, J., Xu, Y., Huang, G., and Guo, H. (1988). Palladium-catalyzed synthesis of chiral, nonracemic isopropyl arylmethylphosphinates. Tetrahedron Lett. *29*, 1955–1958. https://doi.org/10.1016/S0040-4039(00)82088-2.

43. Xu, Y., Wei, H., Zhang, J., and Huang, G. (1989). An efficient synthesis of chiral, nonracemic isopropyl alkenylmethylphosphinates via palladium route. Tetrahedron Lett. *30*, 949–952. https://doi.org/10.1016/S0040-4039(00)95287-0.

44. Bloomfield, A.J., and Herzon, S.B. (2012). Room temperature, palladium-mediated *P*–arylation of secondary phosphine oxides. Org. Lett. *14*, 4370–4373. https://doi.org/10.1021/ol301831k.

45. Han, Z.S., Wu, H., Xu, Y., Zhang, Y., Qu, B., Li, Z., Caldwell, D.R., Fandrick, K.R., Zhang, L., Roschangar, F., et al. (2017). General and stereoselective method for the synthesis of sterically congested and structurally diverse *P*-stereogenic secondary phosphine oxides. Org. Lett. *19*, 1796–1799. https://doi.org/10.1021/acs.orglett.7b00568.

46. Chrzanowski, J., Krasowska, D., Urbaniak, M., Sieroń, L., Pokora-Sobczak, P., Demchuk, O.M., and Drabowicz, J. (2018). Synthesis of enantioenriched aryl-*tert*-butylphenylphosphine oxides via cross-coupling reactions of *tert*-butylphenylphosphine oxide with aryl halides. Eur. J. Org. Chem. *2018*, 4614–4627. https://doi.org/10.1002/ejoc.201800698.

47. Sun, M., Zhang, H.-Y., Han, Q., Yang, K., and Yang, S.-D. (2011). Nickel-Catalyzed C–P cross-coupling by C–CN bond cleavage. Chem. Eur. J. *17*, 9566–9570. https://doi.org/10.1002/chem.201101930.

48. Korpiun, O., Lewis, R.A., Chickos, J., and Mislow, K. (1968). Synthesis and absolute configuration of optically active phosphine oxides and phosphinates. J. Am. Chem. Soc. *90*, 4842–4846. https://doi.org/10.1021/ja01020a017.

49. Oshiki, T., and Imamoto, T. (1992). Unprecedented stereochemistry of the electrophilic arylation at chiral phosphorus. J. Am. Chem. Soc. *114*, 3975–3977. https://doi.org/10.1021/ja00036a054.

50. Imamoto, T., Oshiki, T., Onozawa, T., Matsuo, M., Hikosaka, T., and Yanagawa, M. (1992). Synthesis and reactions of optically active phosphine-boranes. Heteroat. Chem. *3*, 563–575. https://doi.org/10.1002/hc.520030519.

51. Al-Masum, M., Kumaraswamy, G., and Livinghouse, T. (2000). A new synthetic route to *P*-chiral phosphine-boranes of high enantiopurity via stereocontrolled Pd(0)-Cu(I) cocatalyzed aromatic phosphorylation. J. Org. Chem. *65*, 4776–4778. https://doi.org/10.1021/jo0003605.

52. Wang, C., Yue, C.-D., Yuan, J., Zheng, J.-L., Zhang, Y., Yu, H., Chen, J., Meng, S., Yu, Y., Yu, G.-A., and Che, C.-M. (2020). Synthesis of *P*-chiral phosphine compounds by palladium-catalyzed C–P coupling reactions. Chem. Commun. *56*, 11775–11778. https://doi.org/10.1039/d0cc05340f.

53. Bhat, V., Welin, E.R., Guo, X., and Stoltz, B.M. (2017). Advances in stereoconvergent catalysis from 2005 to 2015: transition-metal-mediated stereoablative reactions, dynamic kinetic resolutions, and dynamic kinetic asymmetric transformations. Chem. Rev. *117*, 4528–4561. https://doi.org/10.1021/acs.chemrev.6b00731.

54. Moncarz, J.R., Laritcheva, N.F., and Glueck, D.S. (2002). Palladium-catalyzed asymmetric phosphination: enantioselective synthesis of a P-chirogenic phosphine. J. Am. Chem. Soc. *124*, 13356–13357. https://doi.org/10.1021/ja0267324.

55. Blank, N.F., Moncarz, J.R., Brunker, T.J., Scriban, C., Anderson, B.J., Amir, O., Glueck,

D.S., Zakharov, L.N., Golen, J.A., Incarvito, C.D., and Rheingold, A.L. (2007). Palladium-catalyzed asymmetric phosphination. Scope, mechanism, and origin of enantioselectivity. J. Am. Chem. Soc. *129*, 6847–6858. https://doi.org/10.1021/ja070225a.

56. Blank, N.F., McBroom, K.C., Glueck, D.S., Kassel, W.S., and Rheingold, A.L. (2006). Chirality breeding via asymmetric phosphination. Palladium-catalyzed diastereoselective synthesis of a P-stereogenic phosphine. Organometallics *25*, 1742–1748. https://doi.org/10.1021/om050993f.

57. Korff, C., and Helmchen, G. (2004). Preparation of chiral triarylphosphines by Pd-catalysed asymmetric P–C cross-coupling. Chem. Commun. *2004*, 530–531. https://doi.org/10.1039/b315009g.

58. Chan, V.S., Chiu, M., Bergman, R.G., and Toste, F.D. (2009). Development of ruthenium catalysts for the enantioselective synthesis of P-stereogenic phosphines via nucleophilic phosphido intermediates. J. Am. Chem. Soc. *131*, 6021–6032. https://doi.org/10.1021/ja9014887.

59. Rauhut, M.M., and Currier, H.A. (1961). Oxidation of secondary phosphines to secondary phosphine oxides. J. Org. Chem. *26*, 4626–4628. https://doi.org/10.1021/jo01069a102.

60. Chan, V.S., Bergman, R.G., and Toste, F.D. (2007). Pd-catalyzed dynamic kinetic enantioselective arylation of silylphosphines. J. Am. Chem. Soc. *129*, 15122–15123. https://doi.org/10.1021/ja076457r.

61. Scriban, C., and Glueck, D.S. (2006). Platinum-catalyzed asymmetric alkylation of secondary phosphines: enantioselective synthesis of P-stereogenic phosphines. J. Am. Chem. Soc. *128*, 2788–2789. https://doi.org/10.1021/ja058096q.

62. Scriban, C., Glueck, D.S., Golen, J.A., and Rheingold, A.L. (2007). Platinum-catalyzed asymmetric alkylation of a secondary phosphine: mechanism and origin of enantioselectivity. Organometallics *26*, 1788–1800. https://doi.org/10.1021/om061116s.

63. Chan, V.S., Stewart, I.C., Bergman, R.G., and Toste, F.D. (2006). Asymmetric catalytic synthesis of *P*-stereogenic phosphines via a nucleophilic ruthenium phosphido complex. J. Am. Chem. Soc. *128*, 2786–2787. https://doi.org/10.1021/ja058100y.

64. Li, C., Li, W., Xu, S., and Duan, W. (2013). Pd-catalyzed asymmetric alkylation of methylphenylphosphine with alkyl halides for the synthesis of P-stereogenic compounds. Chin. J. Org. Chem. *33*, 799–802. https://doi.org/10.6023/cjoc201301050.

65. Zhang, S., Xiao, J.-Z., Li, Y.-B., Shi, C.-Y., and Yin, L. (2021). Copper(I)-catalyzed asymmetric alkylation of unsymmetrical secondary phosphines. J. Am. Chem. Soc. *143*, 9912–9921. https://doi.org/10.1021/jacs.1c04112.

66. Shaikh, T.M., Weng, C.-M., and Hong, F.-E. (2012). Secondary phosphine oxides: versatile ligands in transition metal-catalyzed cross-coupling reactions. Coord. Chem. Rev. *256*, 771–803. https://doi.org/10.1016/j.ccr.2011.11.007.

67. Beaud, R., Phipps, R.J., and Gaunt, M.J. (2016). Enantioselective Cu-catalyzed arylation of secondary phosphine oxides with diaryliodonium salts toward the synthesis of P-chiral phosphines. J. Am. Chem. Soc. *138*, 13183–13186. https://doi.org/10.1021/jacs.6b09334.

68. Zhang, Y., He, H., Wang, Q., and Cai, Q. (2016). Asymmetric synthesis of chiral P-stereogenic triaryl phosphine oxides via Pd-catalyzed kinetic arylation of diaryl phosphine oxides. Tetrahedron Lett. *57*, 5308–5311. https://doi.org/10.1016/j.tetlet.2016.10.048.

69. Dai, Q., Li, W., Li, Z., and Zhang, J. (2019). P-Chiral phosphines enabled by palladium/Xiao-Phos-catalyzed asymmetric P–C cross-coupling of secondary phosphine oxides and aryl bromides. J. Am. Chem. Soc. *141*, 20556–20564. https://doi.org/10.1021/jacs.9b11938.

70. Dai, Q., Liu, L., and Zhang, J. (2021). Palladium/Xiao-Phos-catalyzed kinetic resolution of *sec*-phosphine oxides by *P*-benzylation. Angew Chem. Int. Ed. Engl. *60*, 27247–27252. https://doi.org/10.1002/anie.202111957.

71. Wu, Z.-H., Cheng, A.-Q., Yuan, M., Zhao, Y.-X., Yang, H.-L., Wei, L.-H., Wang, H.-Y., Wang, T., Zhang, Z., and Duan, W.-L. (2021). Cobalt-catalysed asymmetric addition and alkylation of secondary phosphine oxides for the synthesis of *P*-stereogenic compounds. Angew Chem. Int. Ed. Engl. *60*, 27241–27246. https://doi.org/10.1002/anie.202111137.

72. Zhang, Q., Liu, X.-T., Wu, Y., and Zhang, Q.-W. (2021). Ni-catalyzed enantioselective allylic alkylation of *H*-phosphinates. Org. Lett. *23*, 8683–8687. https://doi.org/10.1021/acs.orglett.1c02986.

73. Cai, W.-Q., Wei, Q., and Zhang, Q.-W. (2022). Ni-catalyzed enantioselective benzylation of secondary phosphine oxide. Org. Lett. *24*, 1258–1262. https://doi.org/10.1021/acs.orglett.2c00209.

74. Zhou, H., Li, Z.-L., Gu, Q.-S., and Liu, X.-Y. (2021). Ligand-enabled copper(I)-catalyzed asymmetric radical C(sp^3)–C cross-coupling reactions. ACS Catal. *11*, 7978–7986. https://doi.org/10.1021/acscatal.1c01970.

75. Tasker, S.Z., Standley, E.A., and Jamison, T.F. (2014). Recent advances in homogeneous nickel catalysis. Nature *509*, 299–309. https://doi.org/10.1038/nature13274.

76. Pellissier, H. (2020). Enantioselective cobalt-catalysed transformations. In Cobalt Catalysis in Organic Synthesis: Methods and Reactions, M. Hapke and G. Hilt, eds. (Wiley), pp. 337–416. https://doi.org/10.1002/9783527814855.ch10.

77. Bullock, R.M., Chen, J.G., Gagliardi, L., Chirik, P.J., Farha, O.K., Hendon, C.H., Jones, C.W., Keith, J.A., Klosin, J., Minteer, S.D., et al. (2020). Using nature's blueprint to expand catalysis with Earth-abundant metals. Science *369*, eabc3183. https://doi.org/10.1126/science.abc3183.

78. Glueck, D.S. (2021). Catalytic asymmetric synthesis of P-stereogenic phosphines: beyond precious metals. Synlett *32*, 875–884. https://doi.org/10.1055/s-0040-1707309.