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P-Chiral Phosphines Enabled by Palladium/Xiao-Phos-Catalyzed Asymmetric P–C Cross-Coupling of Secondary Phosphine Oxides and Aryl Bromides

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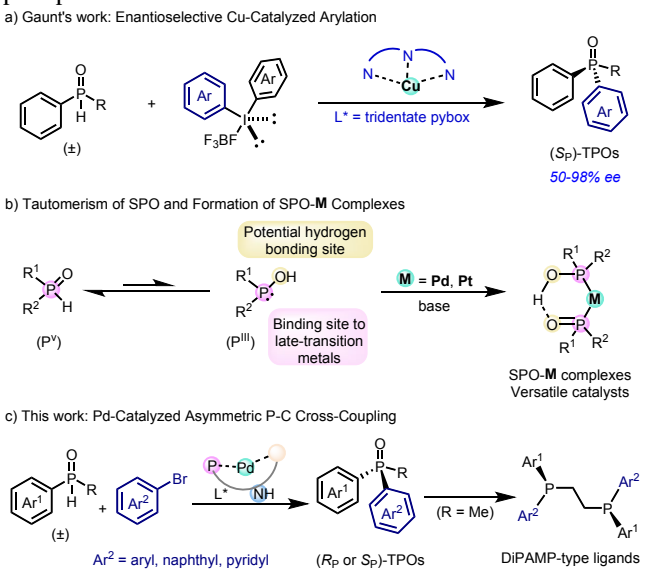
ABSTRACT: The development of transition metal-catalyzed methods for the synthesis of P-chiral phosphine derivatives pose considerable challenge. Herein we present a direct Pd/Xiao-Phos-catalyzed cross-coupling reaction of easily accessible secondary phosphine oxides and aryl bromides, which provides a rapid access to P-chiral phosphine oxides. The reaction proceeds efficiently with a wide array of reaction partners to deliver various tertiary phosphine oxides in up to 96% yield and 97% ee. Moreover, the synthesis of DiPAMP ligand and its analogues was also realized, which demonstrates a suitable pathway to switching the branched chain of DiPAMP.

INTRODUCTION

Chiral phosphine compounds have seen widespread applications in chiral introduction. They can be used as a ligand for metal catalysts[1] or directly as an organocatalyst[2]. However, the great majority of chiral phosphines commonly used today are axial-chiral or planar-chiral or C-stereogenic phosphines. The lack of concise and efficient methods for their enantioselective synthesis inhibits P-stereogenic phosphines to continue their early promising applications.[3] Classical synthetic methods usually rely on resolution processes or the use of chiral auxiliaries.[4] In past years, alternative methods such as desymmetrization, addition of specified phosphine derivatives to alkenes or benzoquinones have been developed.[5] Besides, employing alkene, alkyne and imine hydrophosphination to build phosphine compounds have also been realized,[6] while most of them are not for building P-chirality or hampered in selectivity. In addition, general methods relying on P–C cross-coupling events catalyzed by transition metals have been the object of extensive investigations for some time.[7,8] The difficulties encountered in this process are that the initial and final phosphorus compounds coordinate to metal catalysts competitively with chiral ligands, thus eroding the enantioselectivity. Bulky substrates or the *ortho*-functionalized coupling partners are usually required to compensate for the insufficient coordination capacity of the chiral ligands. Therefore, it is still highly desirable to develop alternative strategies for synthesis of P-stereogenic phosphine compounds.

Recently, Gaunt and co-workers[9] reported an elegant copper/pybox-catalyzed enantioselective arylation of secondary phosphine oxides (SPOs) with diaryliodonium salts to access P-stereogenic tertiary phosphine oxides (TPOs)

Scheme 1. Enantioselective synthesis of P-chiral phosphines.



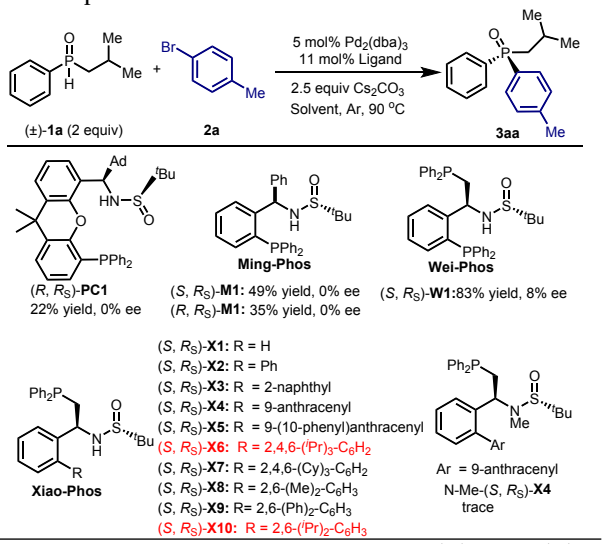
(Scheme 1a). The rigid chelation of tridentate pybox with copper provides a favorable condition for high enantioselectivity. The air stability of SPOs[10] used in this reaction largely stems from the unique tautomerism between the pentavalent and the trivalent tautomer.[11] The tautomeric equilibrium can be shifted toward to the trivalent phosphinous acid form in the presence of bases or transition metals.[12] Either of the chelating sites (O, P) could coordinate with transition metal, whereas the phosphorus atom coordinates well to the soft metal ions (**M**) and the

oxygen atom can act as a potential hydrogen bond acceptor (Scheme 1b). The resulting SPO-**M** complexes are known as versatile catalysts in transition metal-catalyzed cross-coupling reactions.[13] In view of the possibility that the excessive SPOs competitively bind to the metals with chiral ancillary ligands, using racemic SPOs as cross-coupling partners to implement a palladium catalyzed asymmetric process might be very difficult. The tight binding of the chiral ligand to the metal, as with Gaunt's work, is indeed an effective method. However, choosing a flexible chiral ancillary ligand to deftly circumvent this effect is also an alternative pathway. Having this in mind, we report here our efforts to develop a Pd-catalyzed asymmetric P–C cross-coupling of easily available racemic SPOs and aryl halides (Scheme 1c). The chiral sulfinamidephosphine (**Sadphos**) type ligands (**Xiao-Phos**) used here belong to a class of hemilabile ligands.[14] The coordination of its sulfinamide moiety is highly fluxional and labile in nature, thus providing a dynamic environment for metal-catalyzed reactions. In addition, **Xiao-Phos** was previously used as an organocatalyst[15] in our group and it's the first time acting as chiral ancillary ligand in asymmetric metal-catalysis.

RESULT AND DISSCUSION.

Optimization of Reaction Conditions. Our initial ligand screening was performed by using racemic SPO (±)-**1a** and 4-bromotoluene **2a** as model reaction. Tridentate pybox and bidentate N, N-ligands (**L1–L4**) all failed to promote the reaction (Figure S1, supporting information). Other commercially available ligands such as bidentate N, P-ligands (**L5–L8**), P, P-ligands (**L10–L12**) as well as monodentate binol-derived phosphoramidite (**L9**) were also examined. Unfortunately, very low ee was observed in some cases, indicating the asymmetric P–C cross-coupling reaction is indeed very challenging (for more details, please see Supporting Information). Over the past 6 years, a series of novel chiral ligands (**Sadphos**) have been developed in our laboratory, which showed good performance in asymmetric metal catalysis (Au, Cu, Pd).[16] However, (*R*, R_S)-**PC1**, which worked well in asymmetric palladium-catalyzed arylation of general sulfenate anions for the synthesis of chiral sulfoxides,[16g] was found inefficient in this palladium-catalyzed reaction. (*R*, R_S)-**M1** and (*S*, R_S)-**M1** also gave racemic product in low yield. Bisphosphine (*S*, R_S)-**W1** provided excellent conversion, but only 8% ee was obtained. The ee was slightly increased to 19% when **Xiao-Phos** ((*S*, R_S)-**X1**) was used (Table 1, entry 1). Of interest, the introduction of a phenyl group at *ortho*-position of the side aryl ring ((*S*, R_S)-**X2**) significantly improved the ee to 66% but only a modest yield was obtained (Table 1, entry 2). Having observed the *ortho*-substituent effect, we next focused on variation of the *ortho*-aryl group. Further increasing the steric hindrance of *ortho*-aryl group, structured as **X3**, **X4**, both allowing enantioselectivity increasing (Table 1, entries 3–4). Interestingly, no product of **3aa** was formed when using N-methylated ligand N-Me-**X4**, which indicated that the NH might play some role for the catalytic activity. With the use of **X4** as ligand, lowering the reaction temperature from 90 to 80 °C slightly decreased the yield but improved the ee from 75% to 85%

Table 1. Optimization of reaction conditions.[a]

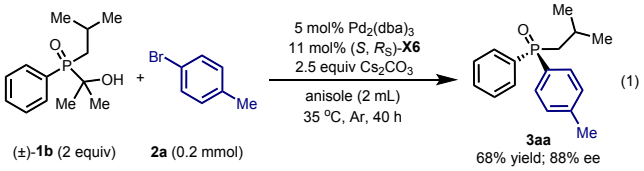


Entry	Ligand	Solvent	yield (%)[b]	ee (%)[c]
1	(*S*,R_S)-**X1**	toluene	52	19
2	(*S*,R_S)-**X2**	toluene	38	66
3	(*S*,R_S)-**X3**	toluene	43	69
4	(*S*,R_S)-**X4**	toluene	39	75
5[d]	(*S*,R_S)-**X4**	toluene	31	85
6[d]	(*S*,R_S)-**X4**	$PhCF_3$	90	71
7[d]	/	$PhCF_3$	13	/
8[e]	(*S*,R_S)-**X4**	$PhCF_3$	87	74
9[e]	(*S*,R_S)-**X5**	$PhCF_3$	94	75
10[e]	(*S*,R_S)-**X6**	$PhCF_3$	66	87
11[e]	(*S*,R_S)-**X7**	$PhCF_3$	68	84
12[e]	(*S*,R_S)-**X8**	$PhCF_3$	69	80
13[e]	(*S*,R_S)-**X9**	$PhCF_3$	62	73
14[e,f]	(*S*,R_S)-**X6**	acetone	97	54
15[e]	(*S*,R_S)-**X6**	anisole	83	84
16[g,h]	(*S*,R_S)-**X6**	anisole	73	90
17[g]	(*S*,R_S)-**X10**	anisole	70	92

[a]Reactions performed at 0.2 mmol scale in solvent (2 mL) for 40 h. [b]Isolated yield. [c]Enantiomeric excesses were determined by HPLC on chiral stationary phases. [d]80 °C. [e]70 °C. [f]For 10 h. [g]35 °C. [h]For 60 h.

(Table 1, entries 5). However, further screening of conditions including aryl electrophile **2**, palladium sources, and bases could not bring both better results in yield and selectivity (for additional details, please see Supporting Information). A reverse trend of ee value and yield was observed in solvent screening under the same catalytic system conditions, which is largely due to the different catalytic activities of SPO-**M** complexes in different solvents (for additional details, please see Supporting Information, Table S1). Although the background reaction was still high in trifluorotoluene solvent, **3aa** was afforded with very high yield and maintained a relatively good ee value (Table 1, entry 6–7). Further lowering the temperature to 70 °C slightly increase the ee to 74% (Table

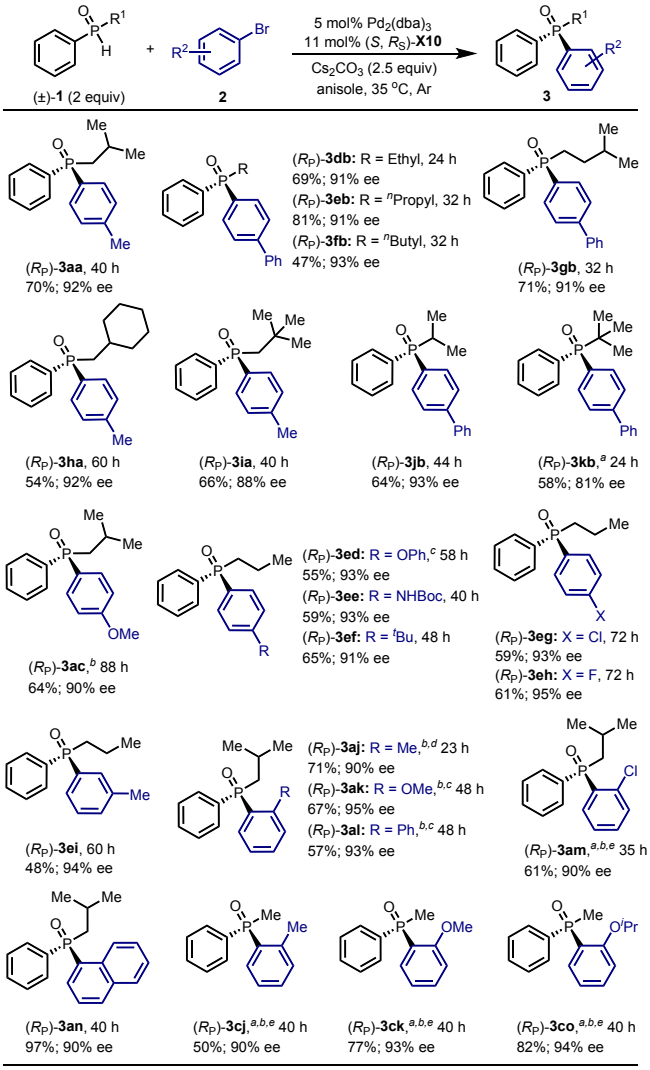
1, entry 8). Continuing to change the substitution pattern of *ortho*-aryl group found that a relatively better result (66% yield, 87% ee) could be obtained when **X6** (with 2,4,6-(^{i}Pr)$_3$-C$_6$H$_2$ as the *ortho*-aryl group) was used (Table 1, entries 9–13). Interestingly, when using **X6** as the chiral ligand, **3aa** was isolated in 97% yield after only 10 hours in acetone albeit with moderate ee (Table 1, entry 14). Further investigation of the reaction time and temperature in acetone could not bring better results (for additional details, please see Supporting Information, Table S2). There was also a dramatic increase in the yield of **3aa** and the selectivity was maintained when using anisole as solvent (Table 1, entry 15). Moreover, 90% ee and 73% yield was obtained in anisole when lowering the reaction temperature from 70 °C to 35 °C with elongated reaction time (Table 1, entry 16). Besides, compared with **X6**, ligand **X10** slightly enhanced the activity in the absence of *para*-isopropyl in the side aryl group (Table 1, entry 17).



With the fact that SPO **1a** could react with acetone to form adduct **1b** under basic conditions.[11,17] A control experiment was carried out using the adduct **1b** instead of **1a** with anisole as solvent. A comparable yield of **3aa** was obtained with slightly reduced ee value after 40 hours, which might be attributed to the *in-situ* generated acetone during the reaction (eq 1).

Scope of the SPOs and Aryl Bromides. With the optimal reaction conditions in hand, we firstly investigated the scope of the SPO by changing the alkyl substituent on the phosphine atom (Table 2). The desired TPOs (R_P)-**3db–3gb** bearing linear alkyl chain were obtained from moderate to high yield with 91–93% ee when (±)-**1d–1g** were used. SPOs with cyclohexylmethyl and neopentyl group were also suitable substrates to give moderate yields of (R_P)-**3ha** and (R_P)-**3ia** with 92% ee and 88% ee, respectively. With steric hindrance closely adjacent to P atom, isopropyl-derived SPO (±)-**1j** is applicable to this asymmetric cross coupling process, delivering the desired (R_P)-**3jb** in 64% yield and 93% ee. The bulky *tert*-butyl-substituted SPO (±)-**1k**, a previously reported challenging substrate,[9] also worked to afford the desired product (R_P)-**3kb** in moderate yield with 81% ee. The effect of substituent on the aryl bromide was then investigated. Aryl bromides with a variety of substituents at the *para*-position was transformed to the corresponding product (R_P)-**3ac** and (R_P)-**3ed–3eh** in moderate yield with high enantioselectivity (90–95% ee) under modified conditions. *Meta*-substituted aryl bromide showed relatively low reaction efficiency but still in high enantioselectivity under the reaction conditions. For example, product (R_P)-**3ei** was afforded in 48% yield and 94% ee. When the scope was extended to *ortho*-substituted aryl bromides, (S, R_S)-**X6** showed better enantioselectivity even in higher temperature. Product (R_P)-**3aj–3al** were obtained in 57-71% yield with 90-95% ee. Besides, using a mixture of solvent (anisole/acetone = 4/1) could improve the yield of (R_P)-**3am** to 61% yield with 90% ee. In addition, the steric hindrance effect appeared again when1-bromonaphthalene was examined. Increasing the equivalents of **1a** was necessary, delivering (R_P)-**3an** in 97% yield with 90% ee. Remarkably, this reaction produced (R_P)-**3cj–3co**[18] in 50-82% yield with 90-94% ee, which provided a rapid access to useful enantioenriched PAMP and analogues.

Table 2. Scope of the SPOs and aryl bromides.

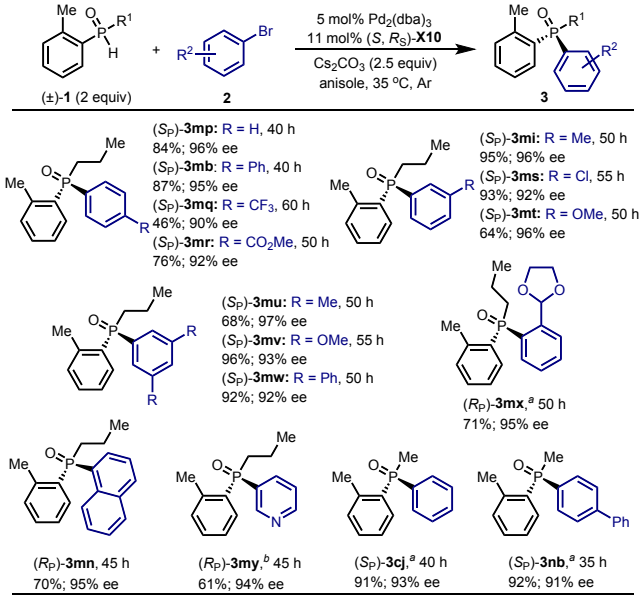


[a]mixed solvent (anisole/acetone) was used, for details, see supporting information. [b](S, R_S)-**X6** was used. [c]50 °C. [d]70 °C. [e]80 °C.

The introduction of an *ortho*-methyl group to the aromatic ring of SPOs led to a great improvement in enantioselectivity and activity (Table 3). Electron-withdrawing groups, such as trifluoromethyl and ester group, in the *para* position of aryl bromides were well tolerated, and the coupling products (S_P)-**3mq–3mr** were isolated in moderate to good yield with excellent enantioselectivity. *Meta*-substituted aryl bromides were also applicable to this process. For example, methyl,

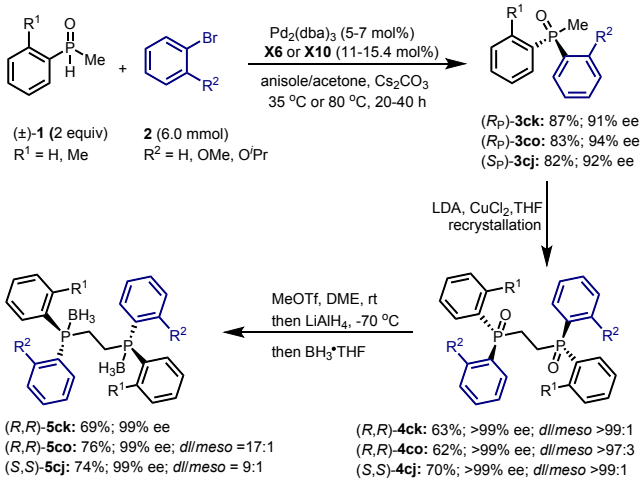
chloro, methoxy substituted and disubstituted aryl bromides were all compatible, delivered the desired product (S_P)-**3mi–3mw** in excellent yield and ee. Sterically bulky substrates such as *ortho*-acetal substituted and naphthalene both gave very good results ((R_P)-**3mx**, 71% yield, 95% ee and (R_P)-**3mn**, 70% yield, 95% ee). The acetal group provided a handle for the further transformations. Pyridine group was also suitable coupling partner to furnish SPO (R_P)-**3my** in 61% yield with 94% ee. Similarly, (S_P)-PAMP analogues (S_P)-**3cj**[18] and (S_P)-**3nb** were both achieved in 91-92% yields and 91-93% ee.

Table 3. Scope of the SPOs and aryl bromides.



[a]mixed solvent (anisole/acetone) was used, for details, see supporting information. [b]60 °C.

Scheme 2. Gram-Scale Synthesis and Synthetic Applications: DiPAMP type ligands.



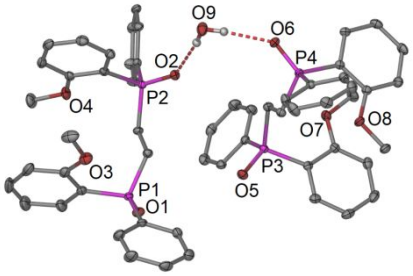


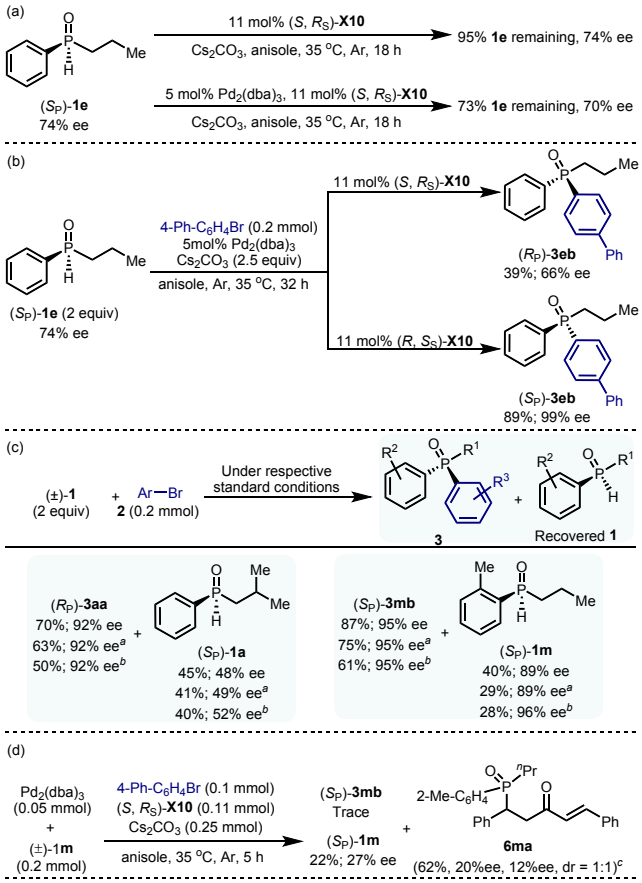
Figure 1. X-ray structure of **4ck** confirmed the absolute stereochemistry.

Gram-scale Synthesis and Synthetic Applications. To demonstrate the practicability of our method, gram scale preparation of enantioenriched tertiary methylphosphine oxides was conducted under modified conditions, delivered the corresponding product without loss of the enantioselectivity (Scheme 2). Further transformation of these enantioenriched tertiary methylphosphine oxides to DiPAMP ligands and its analogues was then carried out.[19] The dimerization of the enantioenriched product **3** gave the chiral bisphosphine oxides (**4ck**, **4co** and **4cj**) in almost enantiomerically pure level, and only minor amount of *meso* compounds remained after recrystallization. Subsequent stereo-controlled reduction took place with inversion of configuration at the P-center and efficiently delivered the DiPAMP–BH_3 adducts after borane protection (**5ck**, **5co** and **5cj**) with very high enantioselectivity.[20] Thus providing a facile route to vary the branched chain of DiPAMP. In addition, the absolute configuration of product **4ck** was unambiguously determined to be (*R, R*) by single crystal XRD analysis (Figure 1),[21] from which we can determine the absolute configuration of the product **3ck** and then tentatively assign other TPOs a relative configuration by analogy to **3ck**.

Mechanistic Studies. With the facts that the product ee was influenced by the amount of SPOs and the SPOs are configurationally stable according to the literature, the possible mechanism was initially thought to be a kinetic resolution process. To probe this hypothesis, we firstly tested the stability of enantioenriched SPO (S_P)-**1e** under reaction systems and a very low degree of racemization was observed in the presence of palladium (Scheme 3a). We also showed that the reaction of (S_P)-**1e** with (*R, S*$_S$)-**X10**·$Pd_2(dba)_3$ leads to the productive, matched formation of the product (S_P)-**3eb** with higher enantioselectivity. While under the mismatched conditions (with (*S, R*$_S$)-**X10**·$Pd_2(dba)_3$), the enantiomer (R_P)-**3eb** was obtained in greatly reduced yield and enantioselectivity from the fewer matched (R_P)-**1e** and the possible weak racemization of (S_P)-**1e** (Scheme 3b). We then turned our attention to the basic piece of data (yield and ee) of both recovered starting materials and products under their respective standard conditions (Scheme 3c). The ees of recovered *ortho*-substituted aryl SPOs (S_P)-**1m** and **1n** are higher than **1a** and **1e** (for more basic data, please see Supporting

Information, Section 10), these results might indicate that the reactions of the *ortho*-substituted aryl SPOs might undergo the kinetic resolution process, but simple aryl alkyl SPOs might undergo very minor dynamic kinetic resolution. We also performed the reaction by using stoichiometric catalysts (Scheme 3d), and were surprised to find that almost no target product **3mb** was detected, instead, a large number of Michael-addition type product **6ma** was obtained. The low ee value of **6ma** indicated that it might stem from palladium-catalyzed enantioselective hydrophosphination reaction, which can also be demonstrated by enantiomeric excess of recovered **1m**. Given that the enantioselective hydrophosphination reaction must also occurred in the catalytic system, and was obviously prior to the target coupling reaction, which might explain why only a very weak racemization was observed in scheme 3a (mismatched condition under (S_P)-**1e** and (*S*, R_S)-**X10**).

Scheme 3. Mechanistic Research Experiments.



[a]1.8 equivalents of (±)-**1** were used. [b]1.5 equivalents of (±)-**1** were used. [c]Isolated yield was based on Dibenzylideneacetone (dba) and contained a small amount of double hydrophosphination product.

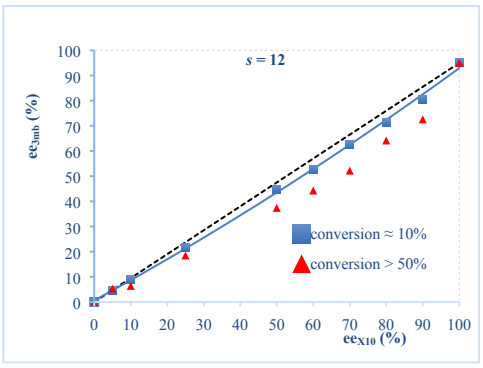
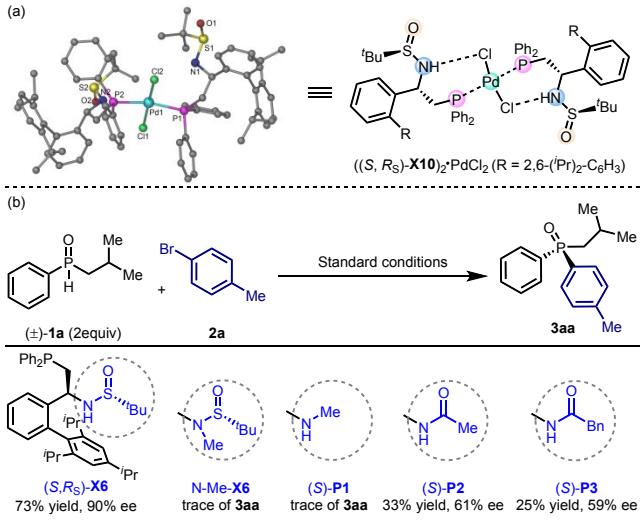


Figure 2. Product ee (ee_{3mb}) as a function of catalyst ee (ee_{X10}). selectivity factors: $s = \ln[(1 - C)(1 - ee_{1m})]/\ln[(1 - C)(1 + ee_{1m})]$. C represents conversion of **1m**.

As Xiao-Phos was firstly used as chiral ancillary ligand in Pd-catalyzed asymmetric reaction. We were very interested in its coordination pattern, and we managed to get its palladium complex by using $Pd(CH_3CN)_2Cl_2$ ((*S*, R_S)-**X10**)$_2$·$PdCl_2$, Scheme 4a)[22]. The formation of intermolecular hydrogen bonds between NH and Cl might helped stabilize the complex. However, the palladium complex prepared with palladium (0) was very unstable and difficult to separate. In addition, it is worth noting that although the palladium (II) could also perform good enantioselectivity, the catalytic efficiency was very low (for additional details, please see Supporting Information, Table S3 and Section 10). Therefore, we speculated that the complex obtained above is a stable form but was not really a catalytic active species and the stable coordination modes of palladium with different valence states may be different in our system. The nonlinear effect studies have also shown that the obtained complex might not really an active species in the reaction process (Figure 2, for additional details, please see Supporting Information, Section 10). The observed negative nonlinear effect at high conversion was due to the intrinsic kinetics of the enantioconvergent process, rather than to the presence of more than one unit of the chiral ligands in coordination with palladium.[23] Because almost no nonlinear effect was detected at low conversion, we hinted the opportunity that the sulfinamide moiety might occupy one coordination site of palladium in a very flexible manner during the reaction.[14] And it was precisely the highly fluxional and labile in nature that made such palladium complex cannot be isolated in a stable form.

Scheme 4. Study on coordination pattern of Xiao-Phos.



In order to gain insight into the coordination properties of the sulfinamide moiety and its role in the reaction, the modification of (*S*, R_S)-**X6** was investigated (Scheme 4b). Both N-methylated ligand N-Me-**X6** and further removal of the sulfinyl group **P1** blocked the reactions, suggested that these two parts play a crucial role in the catalytic activity. We next used acyl instead of chiral sulfinyl group, the ligands **P2** and **P3** both led to significantly low yield and enantioselectivity which showed the importance of sulfinamide moiety again. Due to the diversity of coordination modes (O, S or N) of sulfinamide moiety, we were not sure what the actual coordination pattern existed in the reaction, but it did play a very important role in the efficiency and enantioselectivity of the reaction. On the other hand, according to our previous studies on the coordination pattern of palladium with chiral sulfinamidephosphine ligands,[16g,i] we speculated that was the oxygen atom in sulfinamide moiety coordinate with palladium.

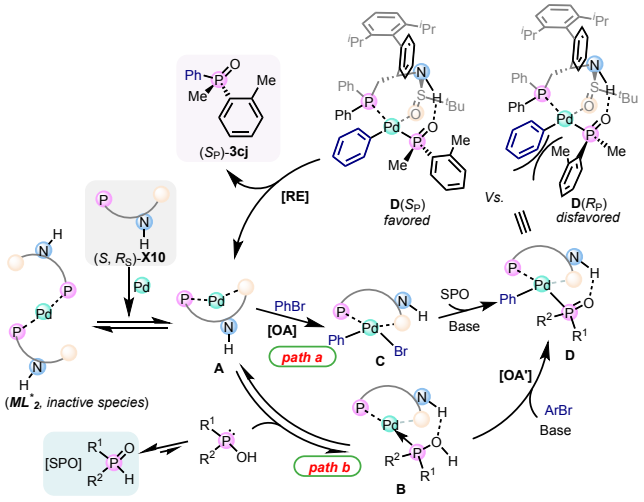


Figure 3. Tentative mechanism.

As to the possible mechanism of the stereoselective cross-coupling process (Figure 3), a dynamic coordination equilibrium might exist and the palladium complex **A** having the P atom and sulfinamide moiety coordinate to palladium participated in the catalytic cycle. Following the classical coupling steps (path a), the oxidative addition of aryl bromide to palladium complex **A** leaded to the formation of intermediate **C**, which further evolved into intermediate **D** through transmetalation. Our initial assumption was that the hydrogen bond interactions between sulfinamide NH and the oxygen of the SPO might exist in the resulting intermediate **D** and contribute to the stability of the transition state. On the other hand, the more competitive hydrophosphination reaction (scheme 3d) indicated that the reaction preferred the b route to some extent. The coordination of SPO to palladium center (intermediate **B**) through the trivalent phosphinous acid form took precedence over oxidative addition step of aryl bromide. In this case, the sulfonamide might temporarily leave to provide a vacant coordination site for incoming aryl bromide to give the same intermediate **D**. The instability of **D**(R_P) might due to the steric effect between two aromatic rings in the approximately planar coordination of Pd. Reductive elimination from the more favored intermediate **D**(S_P) gave the corresponding (S_P)-**3cj** (Bromobenzene, (±)-**1n** along with the Pd°–(*S*, R_S)-**X10** chiral system was selected as model), which was in agreement with the formation of the major experimental enantiomer.

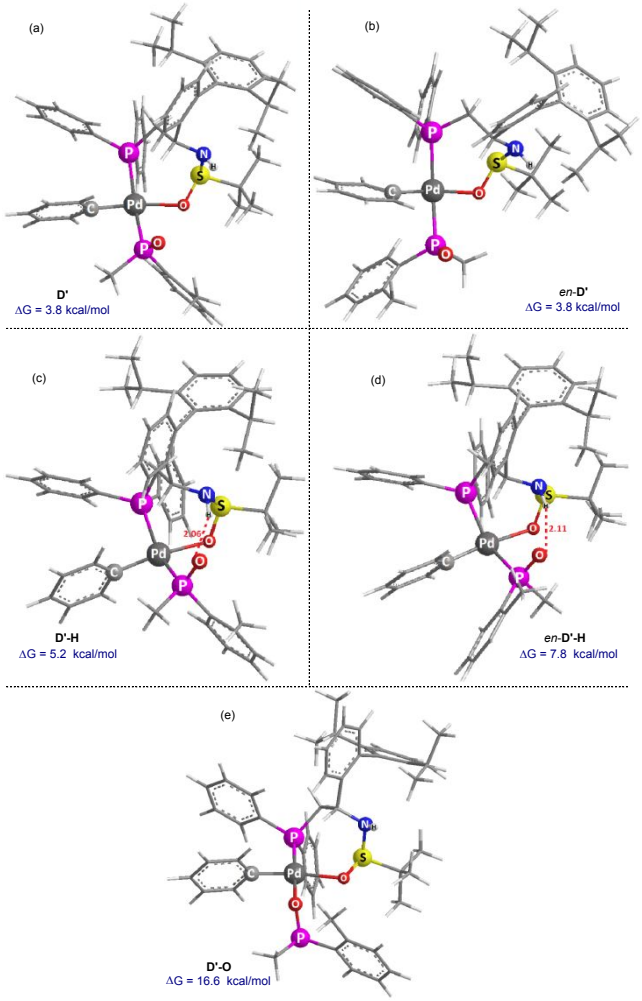


Figure 4. The optimized structures of intermediate **D** at B3LYP/6-31G(d)-SDD level in anisole (bromobenzene, (±)-**1n** along with the Pd⁰–(*S*, R_S)-**X10** chiral system was selected as the model).

DFT calculations at B3LYP/6-31G(d)-SDD level were then carried out to locate intermediate **D** using Gaussian 09 software.[24] The reaction of bromobenzene, (±)-**1n** along with the Pd⁰–(*S*, R_S)-**X10** chiral system was selected as the model, which has shown good performance in the reaction (Tables 3). The solvent effects, anisole, were included with the SMD approach.[25] The other calculation details were provided in the supporting information. Both intermediates **D'** and *en*-**D'** corresponding to each product (S_P and R_P) were located, in which divalent Pd coordinates with P and O atom in (*S*, R_S)-**X10**, aromatic ring from bromobenzene, and **1n** (Figure 4). The relative free energies based on the initial structures (*int*-**A** + (±)-**1n** + PhBr) are both 3.8 kcal/mol for **D'** and *en*-**D'**. Another pair of **D** intermediates with H-bond interactions were located as well (Figure 4), the bond distances between NH group and O atom in SPO are 2.06 Å for **D'-H** (corresponds to **D**(S_P) in figure 3) and 2.11 Å for *en*-**D'-H** (corresponds to **D**(R_P) in figure 3). However, they are less stable conformations compared to **D'** and *en*-**D'**, the relative free energies are 5.2 and 7.8 kcal/mol. Since N-Me-**X6** is not active and only gives a trace amount of the product, while the **X6** gives 73% yield and 90% ee (Scheme 4), the intermediate **D** containing the H-bond interactions (**D'-H** and *en*-**D'-H**) should be invoked to account for the observed enantioselectivity, as it does show some energy bias towards the right enantiomer. This might be indicative that the NH moiety functions as a proton shuttle in the reaction. The O atom in SPO as coordination site with palladium was also considered, and the higher instability of **D'-O** (relative free energy 16.6 kcal/mol) rules out the O-coordination possibility of SPO (For additional details, please see Supporting Information, Section 10).

CONCLUSION

In summary, we have developed an asymmetric Pd/Xiao-phos-catalyzed P–C cross-coupling for the efficient synthesis of highly enantioenriched P-stereogenic phosphine oxides. **Xiao-Phos** contributes significantly to the catalytic activity and enantioselectivity control. Moreover, this method could be applied to the enantioselective synthesis of PAMP oxide and opens up a facile route to DiPAMP-type ligands with diverse branched chain, thus promotes the diversity and high utility in asymmetric catalysis of these ligands. The further application of **Xiao-Phos** in other asymmetric metal-catalyzed reaction is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, optimization tables, characterization data for all the products (PDF).

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Author Contributions

Notes

The authors declare no competing financial interests.

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