Letter

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Axially Chiral Biaryl Monophosphine Oxides Enabled by Palladium/WJ-Phos-Catalyzed Asymmetric Suzuki-Miyaura Cross-coupling

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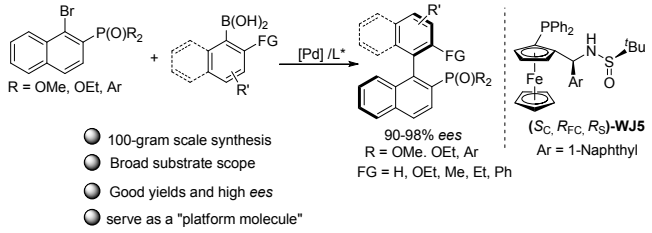
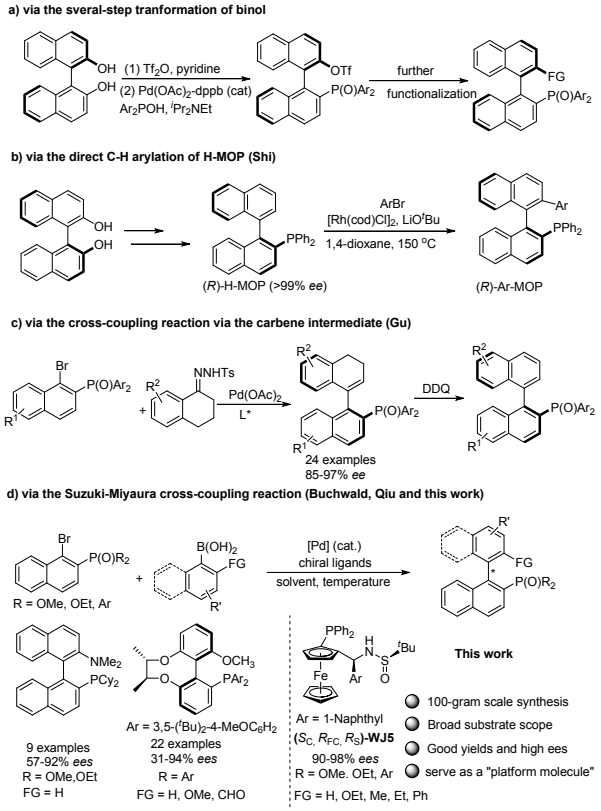
ABSTRACT: A highly enantioselective palladium/WJ-Phos-catalyzed Suzuki-Miyaura coupling reaction for efficient construction of axially chiral biaryl monophosphine oxides was developed. A series of axially chiral biaryl monophosphine oxides were obtained in good yields and with high enantioselectivities. The practicability of this reaction was validated in the straightforward synthesis of axially chiral biaryl monophosphine ligand and demonstrated by a 100-gram-scale synthesis. Moreover, various functionalizations of the product make it as a platform molecule for synthesis of other chiral biaryl phosphines.



KEYWORDS: *Suzuki coupling, Palladium, axially chiral compounds, Asymmetric catalysis, Phosphine*

The axially chiral biaryl monophosphines and their oxides have emerged as powerful chiral ligands and catalysts in asymmetric catalysis.[1,2] Therefore, the development of new methods for their synthesis have received much attention[1,2] and several strategies have been developed. For example, the classic strategy for synthesis of these compounds relies on multi-step synthesis from chiral Binols (Scheme 1a).[1h] Very recently, the group of Shi developed an elegant rhodium(I)-catalyzed direct arylation of (*R*)-H-MOP without erosion of the *ee* value, which provides a facile access to aryl-substituted binapthyl monophosphines (Scheme 1b).[3] In 2016, Gu and co-workers developed an efficient palladium-catalyzed asymmetric synthesis of axially chiral 1-vinylnaphthalen-2-yl phosphine oxides from aryl bromides and hydrazones.[2j] Further oxidation of the products allows to get the axially chiral biaryl compounds by using DDQ with good chiral retention (Scheme 1c). Besides the above strategies, the palladium-catalyzed asymmetric Suzuki-Miyaura coupling of 1-bromo-naphth-2-yl phosphine oxide or phosphonate with *ortho*-substituted arylboronic acids have attracted much attention. Early in 2000, Buchwald reported the first example of this type of reaction, delivering the corresponding phosphonate in 57-92% *ees*, which upon further reaction with Grignard reagent to furnish the desired aryl phosphine oxides (Scheme 1d).[2b] Subsequently, Qiu and coworkers realized the Pd-catalyzed direct asymmetric Suzuki-coupling between *ortho*-substituted arylboronic acids and 2-diarylphosphinyl-1-naphthyl bromides with the use of chiral bridged atropisomeric monophosphine or Cy-MOP as the chiral ligand.[2g] The existence of an *ortho* formyl or alkoxy group in arylboronic acids is crucial for the coupling efficiency and enantioselectivity (Scheme 1d). Considering the broad applications of phosphine-containing axial chiral binaphthyl compounds, it would be exciting to find a robust catalyst system to improve the substrate scope and especially applicable in large-scale synthesis.



Scheme 1. Synthetic protocols for axially chiral biaryl monophosphine (oxides).

Over the past few years, we designed and developed a series of new chiral sulfinamidephosphine (Sadphos) ligands such as Ming-Phos,[4] Xiang-Phos,[5] PC-Phos,[6]

Xu-Phos[7] and WJ-Phos[8] which have demonstrated good performance in asymmetric transition metal catalysis.[9] Inspired by these successes, we wondered whether these preeminent chiral ligands could address the limited scope of palladium-catalyzed Suzuki-Miyaura coupling reaction. Herein, we present a highly enantioselective Suzuki coupling reaction by using WJ-Phos as chiral ligand, which provides a facile access to various substituents atropisomers phosphine oxides in good yields and high *ee* values (Scheme 1d).

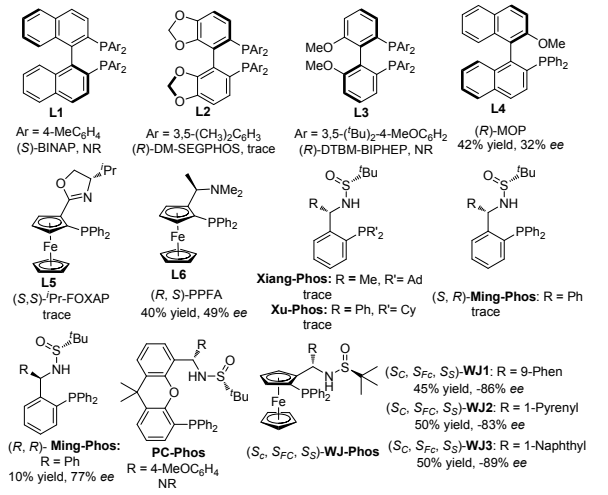
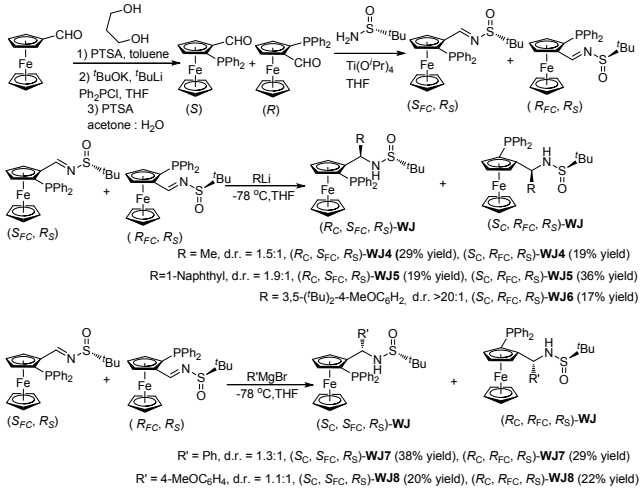


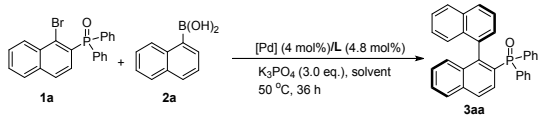
Figure 1. Screened ligands.



Scheme 2. Synthesis of different diastereoisomers of WJ-Phos ligands.

With 2-diphenylphosphinyl-1-naphthyl bromide **1a** and 1-naphthylboronic acid **2a** as model substrates, a series of chiral ligands were investigated (Figure 1). It was observed that, axially chiral bisphosphine ligands L1-L3 are inefficient. However, the product **3aa** was obtained in 42% yield and 32% *ee* when axially chiral monophosphine ligand (*R*)-MOP (L4) was used as chiral ligand. Next, ferrocene-based N, P ligands L5-L6 were investigated and only (*R*)-(*S*)-PPFA gave the product **3aa** in 40% yield with 49% *ee*. Then we focus on our developed Sadphos as chiral ligand, among which the palladium catalyzed derived from Ming-Phos, Xiang-Phos, Xu-Phos and PC-Phos all showed low catalytic activity. Fortunately, the ferrocene derived **WJ-Phos** gave promising result and the desired product **3aa** was obtained in 50% yield and 89% *ee*. Inspired by this result, we further developed a new synthetic route for **WJ-Phos**, which could easily deliver a pair of diastereomers. Gratifyingly, new synthesis of **WJ-Phos** could be realized from commercially available ferrocenecarboxaldehyde.[8,10] A series of **WJ-Phos** was obtained with highly diastereoselective addition of ArLi, AlkylLi or ArMgBr to chiral sulfinyl imine (Scheme 2), which the absolute structure was established by the X-ray structures of (R_C, S_{FC}, R_S)-**WJ5** and (S_C, R_{FC}, R_S)-**WJ5**, respectively (Scheme 2).[11]

Table 1. Optimization of reaction conditions.[a]



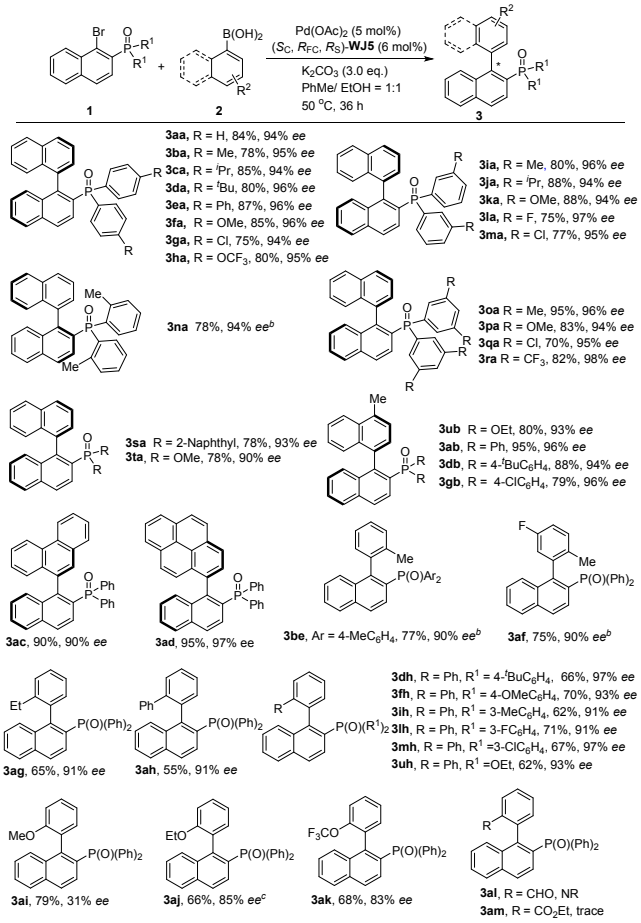
Entry	[M]	L	Solvent	Yield (Ee) [%][b,c]
1	Pd2(dba)3	(R_C, S_{FC}, R_S)-**WJ4**	PhMe	Trace (--)
2	Pd2(dba)3	(S_C, R_{FC}, R_S)-**WJ4**	PhMe	20 (-7)
3	Pd2(dba)3	(R_C, S_{FC}, R_S)-**WJ5**	PhMe	Trace (--)
4	Pd2(dba)3	(S_C, R_{FC}, R_S)-**WJ5**	PhMe	55 (90)
5	Pd2(dba)3	(S_C, R_{FC}, R_S)-**WJ6**	PhMe	45 (92)
6	Pd2(dba)3	(S_C, S_{FC}, R_S)-**WJ7**	PhMe	Trace (--)
7	Pd2(dba)3	(R_C, R_{FC}, R_S)-**WJ7**	PhMe	47 (79)
8	Pd2(dba)3	(S_C, S_{FC}, R_S)-**WJ8**	PhMe	Trace (--)
9	Pd2(dba)3	(R_C, R_{FC}, R_S)-**WJ8**	PhMe	53 (82)
10	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe	77 (92)
11	Pd(PPh3)2Cl2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe	NR (--)
12	Pd(PhCN)2Cl2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe	35 (86)
13	Pd(PPh3)4	(S_C, R_{FC}, R_S)-**WJ5**	PhMe	NR (--)
14	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	DCE	30 (89)
15	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	THF	50 (91)
16	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	EtOH	69 (94)
17	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe/ EtOH = 1:1	76 (94)
18[d]	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe/ EtOH = 1:1	80 (94)
19[de]	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ5**	PhMe/ EtOH = 1:1	84 (94)
20[de]	Pd(OAc)2	(S_C, R_{FC}, R_S)-**WJ6**	PhMe/ EtOH = 1:1	78 (95)

[a]Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1a**, 0.4 mmol of **2a**, 3.0 equiv of K3PO4, 4 mol% of catalyst ([Pd] to L = 1:1.2) in 2.0 mL solvent at 50 ºC for 36 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]3.0 equiv of K2CO3. [e]5 mol% of catalyst ([Pd] to L = 1:1.2). NR = no reaction. dba = dibenzylideneacetone, DCE = 1,2-dichloroethane.

We firstly investigated the performance of this series of new **WJ-Phos** in the asymmetric suzuki coupling reaction (Table 1, entries 1-9). (S_C, R_{FC}, R_S)-**WJ5** bearing 1-naphthyl group gave the best result, delivering product **3aa** in 55% yield with 90% *ee* (Table 1, entry 4). Although the *ee* value can reach 92% when (S_C, R_{FC}, R_S)-**WJ6** was used, the yield of the reaction was low (Table 1, entry 5). With the use of (S_C, R_{FC}, R_S)-**WJ5** as the chiral ligand, different palladium salts were then investigated (Table 1, entries 10-13). The yield of **3aa** was significant increased to 77% with 92% *ee*

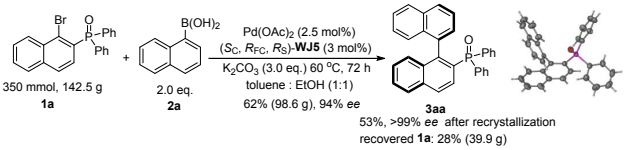
when $Pd(OAc)_2$ was used (Table 1, entry 10). Next, the solvent effect were studied (Table 1, entries 14–17) and a mixture of PhMe/EtOH(1:1) could deliver the product **3aa** in 76% yield with 94% *ee*. Further changing the base to K_2CO_3 and slightly increasing the catalyst loading delivered **3aa** in 84% yield with the same *ee* value (Table 1, entries 18–19). Under these conditions, 78% yield of **3aa** could be obtained by using (S_C, R_{FC}, R_S)-**WJ6** as the ligand (Table 1, entries 20).

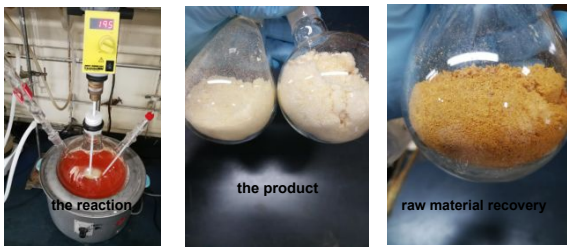
Having established the optimized reaction conditions, we next set out to test the scope of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction (Scheme 3). The reactions of 2-diarylphosphinyl-1-naphthyl bromide with either electron-donating groups (e.g., Me, ^{i}Pr, ^{t}Bu, Ph and OMe), or electron-withdrawing groups (e.g., Cl, OCF_3) at the *para*-position of the phenyl ring could furnish the corresponding products **3ba–3ha** in 75-87% yields with 94–96% *ees*. As highlighted in Scheme 3, the *meta*-substituent of the phenyl ring were also compatible to furnish the products **3ia–3ma** in 75–88% yields with 94–97% *ees*. It is worth to note that the reaction with *ortho*-substituent of the phenyl ring could deliver the product **3na** in 78% yield with 94% *ee* by the use of (S_C, S_{FC}, S_S)-**WJ3** as the chiral ligand. Both the disubstituted arylphosphine oxide and the β-naphthyl phosphine oxides worked smoothly to give the corresponding products **3oa–3sa** in 70–95% yields with 93–98% *ees*. To our delight, the reactions of dimethyl 1-bromo-2-naphthylphosphonate and diethyl 1-bromo-2-naphthylphosphonate with 1-naphthylboronic furnished **3ta** and **3ub** in moderate yields with 90$ and 93% *ee,* respectively. With respect to other substituents of arylphosphine oxide with 4-methyl-1-naphthaleneboronic acid could also participate in this reaction, delivering the products (**3ab–3gb**) in 79–95% yields with 94–96% *ees*. Both 9-phenanthracenylboronic acid and 1-pyrenylboronic acid with diphenylphosphine oxides were tolerated under the reaction conditions, providing the products **3ac** and **3ad** in 90–95% yields with excellent enantioselectivity (90–97% *ees*). It is noteworthy that different *ortho* substituted phenylboronic acids were also suitable for this reaction and the corresponding coupling products **3be–3mh** were obtained in good yields with up to 97% *ee*. In addition, when diethyl 1-bromo-2-naphthylphosphonate with 2-biphenylboronic acid were employed as the coupling partners, the product **3uh** was furnished in moderate yield with 93% *ee*. The *ortho*-methoxy, ethoxy, trifluoromethoxy substituted phenylboronic acids were examined under the standard condition and the corresponding products **3ai–3ak** were obtained in good yields with up to 85% *ee*. Unfortunately, the aldehyde or ester derived phenylboronic acids were not suitable for this reaction (**3al–3am**). The brominated substrates based on phenyl ring were also investigated under standard conditions. Although the reaction proceeded smoothly, the products did not show any *ee* due to the low rotation barrier (see Supporting Information). At present, there are few reports on the coupling of 2-diarylphosphinyl-1-naphthyl bromide or 2-dialkoxyphosphinyl-1-naphthyl bromide with naphthalene boronic acid or *ortho* substituted phenylboronic acid in one catalytic system. We were very glad to make up for this shortcoming by using (S_C, R_{FC}, R_S)-**WJ5** chiral ligand.



[a] Condition: Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.4 mmol of **2**, 3.0 equiv of K_2CO_3, 5 mol% of catalyst ([Pd] to L = 1:1.2) in 2.0 mL solvent at 50 ºC for 36 h. [b] with the use of (S_C, S_{FC}, S_S)-**WJ3** as the chiral ligand. [c] with the use of (S_C, R_{FC}, R_S)-**WJ6** as the chiral ligand.

Scheme 3. Substrate scope with respect to the phosphine oxides and boronic acids. [a]

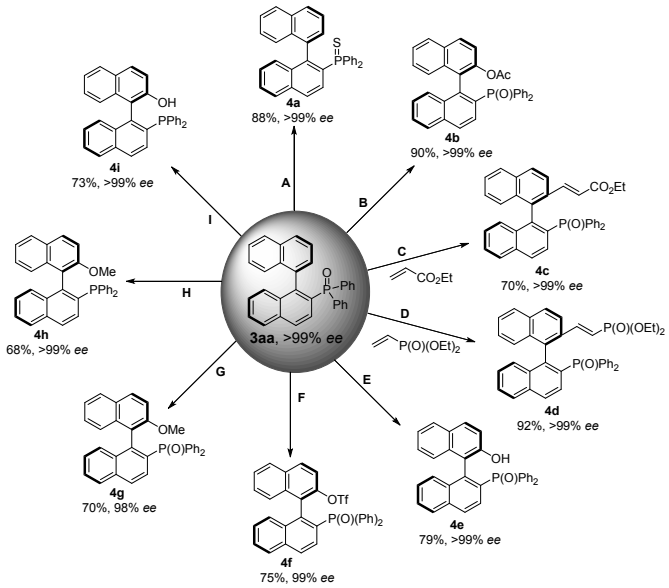




Scheme 4. 100-gram scale synthesis.

As an indication of the possible practical potential of this catalyst system, the screening reactions were carried out on a 100-gram-scale synthesis (Scheme 4). A 350 mmol scale reaction of **1a** (142.5 g) with two equivalents of **2a** worked smoothly under the catalysis of 2.5 mol% of

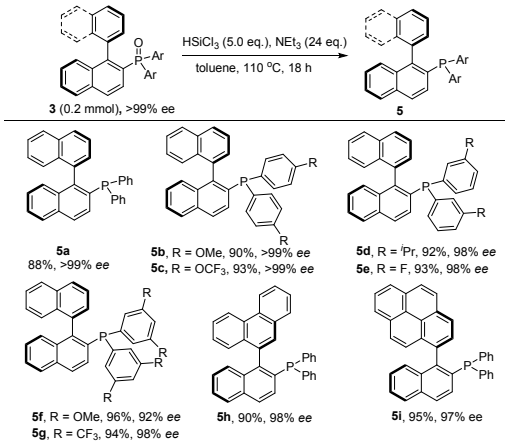
$Pd(OAc)_2$/(S_C, R_{FC}, R_S)-**WJ5**, delivering 98.6 g of **3aa** in 62% yield with 94% *ee* (53% yield, >99% *ee* after recrystallization) and 28% of **1a** was recovered. The absolute configuration was determined by X-ray diffaction analysis of product **3aa**.[11] To demonstrate that product **3aa** could be used as a "platform molecule", several transformations were then carried out (Scheme 5). Firstly, the product **3aa** could be reduced[12] then oxidized in the presence of sulfur to obtained the phosphine sulfide product **4a** in a high yield without loss the enantiopurity.[13] Secondly, the phosphine compounds **4b**, **4c**, **4d** and **4e** were achieved in >99% *ee*[14] by Pd(II)-catalyzed $Ph_2(O)P$-directed C-H acetoxylation, hydroxylation and olefination of **3aa**, respectively. The $Ph_2(O)P$ group not only acts as the directing group but also serves to construct the alkene-phosphine ligands. The products **4f**, **4g**, **4h**, **4i** with high enantioselectivity delivered by the product **4e**[12, 15] under the corresponding conditions.



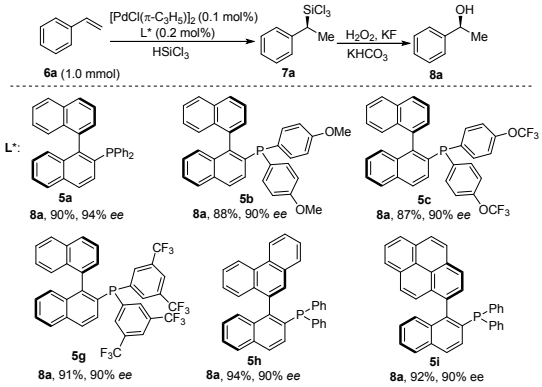
Conditions: [A]: 1) $HSiCl_3$ (5.0 eq.), NEt_3 (24 eq.), toluene, 110 °C, 18 h; 2) S, THF, rt. [B]: $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (3.0 eq.). [C]: Ac-Gly-OH (20 mol%), $Pd(OAc)_2$ (10 mol%), AgOAc (5.0 eq.). [D]: Ac-Gly-OH (20 mol%), $Pd(OAc)_2$ (10 mol%), AgOAc (5.0 eq.). [E]: $(CF_3CO_2)_2Pd$ (10 mol%), $PhI(CF_3CO_2)_2$ (1.5 eq.), CH_3NO_2. [F]: 1) $(CF_3CO_2)_2Pd$ (10 mol%), $PhI(CF_3CO_2)_2$ (1.5 eq.), CH_3NO_2; 2) Tf_2O, Py, DCM. [G]: 1) $(CF_3CO_2)_2Pd$ (10 mol%), $PhI(CF_3CO_2)_2$ (1.5 eq.); 2) CH_3I, K_2CO_3. [H]: 1) $(CF_3CO_2)_2Pd$ (10 mol%), $PhI(CF_3COO)_2$ (1.5 eq.); 2) CH_3I, K_2CO_3; 3) $HSiCl_3$, NEt_3. [I]: 1) $(CF_3CO_2)_2Pd$ (10 mol%), $PhI(CF_3CO_2)_2$ (1.5 eq.), CH_3NO_2; 2) $HSiCl_3$, NEt_3.

Scheme 5. Transformations of 3aa.

Gratifying, the products of this palladium-catalyzed suzuki coupling reaction could also be readily reduced under mild reaction conditions delivered the monophosphine ligand with good yield and high *ee* value (Scheme 6).[12] Notably, the reduced products **5a-5c** were achieved in 88%-93% yield without loss of *ees*. But the products **5d-5e**, **5g-5i** were delivered in 90%-96% yield with slightly declined *ees*. Unfortunately, the [1,1'-binaphthalen]-2-ylbis(3,5-dimethoxyphenyl)phosphine was obtained in 96% yield with 92% *ee*. These monphophines ligands could be used in palladium-catalyzed asymmetric hydrosilylation of olefins (Scheme 7).[16] It is interesting to find that most of these ligands could deliver the product in high yields with high enantioselectivity.

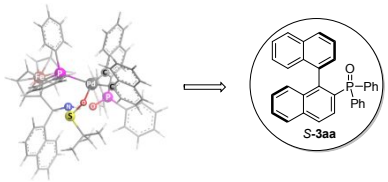


Scheme 6. Synthesis of Binaphthyl monophosphines via the reduction of 3.



Scheme 7. Testing the developed phosphine ligand libraries.

In light of the absolute configurations of the chiral ligand (S_C, R_{FC}, R_S)-**WJ5** and the product *S*-**3aa**, a chirality induction model of palladium atom clamped into an 8-membered ring by P and O coordination was proposed (Scheme 8).[4c, 8, 17] In this transition state, the steric resistance between naphthyl ring of substrate **2a** and diphenylphosphine oxide of substrate **1a** is more smaller, which upon reductive elimination should release the product *S*-**3aa**.



Scheme 8. Proposed Asymmetric Induction Model.

In summary, we have developed a operational simplicity, highly enantioselective palladium-catalyzed Suzuki-Miyaura cross-coupling reaction by using **WJ-Phos** as chiral ligand, which provides a facile access to various substituents axially chiral biaryl monophosphine oxides in good yields and high *ee* values. In light of the

synthetic applications of the axially chiral biaryl monophosphine ligand, this approach can be expected to applying in wide-ranging synthetic applications.

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Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information: Experimental procedures, spectroscopic data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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