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Enantioselective Synthesis of Axially Chiral Biaryl Monophosphine Oxides via Direct Asymmetric Suzuki Coupling and DFT Investigations of the Enantioselectivity

Yougui Zhou,[†] Xuepeng Zhang,[‡] Huiyi Liang,[†] Zhenkun Cao,[†] Xiaoyu Zhao,[†] Yuwei He,[†] Shouliang Wang,[†] Jiyan Pang,[†] Zhongyuan Zhou,[§] Zhuofeng Ke,*[,‡] and Liqin Qiu*[,†,∥,⊥]

[†]School of Chemistry and Chemical Engineering, Guangdong Engineering Research Center of Chiral Drugs, Sun Yat-Sen University, Guangzhou 510275, People's Republic of China

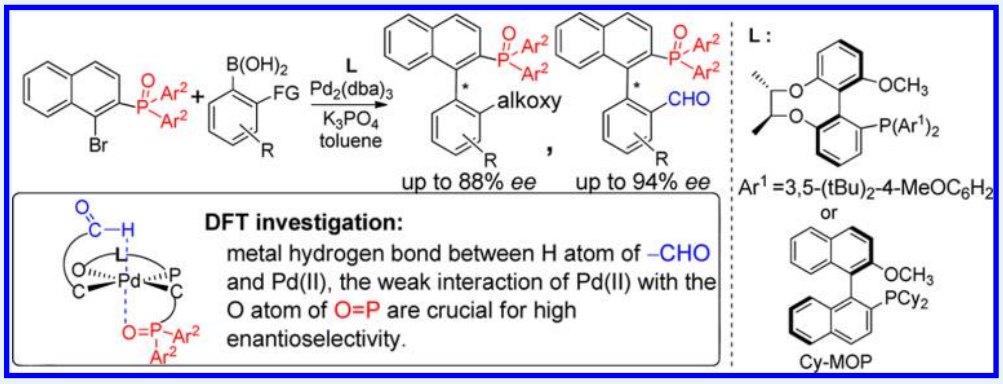
[‡]MOE Key Laboratory of Bioinorganic and Synthetic Chemistry/KLGHEI of Environment and Energy Chemistry, Sun Yat-sen University, Guangzhou 510275, People's Republic of China

[§]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, People's Republic of China

[∥]Huizhou Research Institute of Sun Yat-Sen University, Dayawan, Huizhou, People's Republic of China

[⊥]Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai People's Republic of China

Supporting Information



ABSTRACT: Direct asymmetric Suzuki coupling between arylboronic acids and 2-diarylphosphinyl-1-naphthyl bromides was successfully developed for the first time with the use of Pd−**L1** or Pd−(Cy-MOP) as the catalyst. A variety of axially chiral 2-functionalized-2′-diarylphosphinyl-1,1′-biaryls were afforded in 34−99% yields with up to 94% ee. This methodology provides a highly efficient and practical strategy for the synthesis of novel axially chiral biaryl monophosphine oxides and the corresponding phosphines. The existence of an ortho formyl group in arylboronic acids greatly improves the coupling efficiency and permits further versatile transformations in organic synthesis. Density functional calculations were used to determine the origin of stereoselectivity during the reductive elimination step of the closely related coupling of 2-formylphenylboronic acid with naphthylphosphonate bromide. These studies indicate that both the significant transition metal hydrogen bond between the H atom of the formyl group and palladium(II) and the weak interaction between the Pd center and the phosphoryl oxygen atom in the transition state are crucial for high enantioselectivity of the coupling products.

KEYWORDS: *asymmetric catalysis, biaryls, computational chemistry, phosphine oxides, Suzuki coupling*

INTRODUCTION

Axially chiral 2-functionalized-2′-diarylphosphino-1,1′-biaryl ligands (MOP type ligands) have attracted much attention because of their high efficiency in transition-metal-catalyzed asymmetric reactions.[1,2] Indeed, the chiral functionalized biaryl monophosphine oxides are important intermediates for the preparation of MOP type ligands. The commonly used synthetic protocol for these compounds relies on a coupling reaction of axially chiral biaryl halides or biaryl triflates with diarylphosphinic chlorides or diarylphosphine oxides (Scheme 1A);[3] however, a multistep synthesis was often required to obtain these biaryl halide or biaryl triflate substrates, or even resolution of racemic materials was involved in some procedures.[4] This results in material waste and thus would

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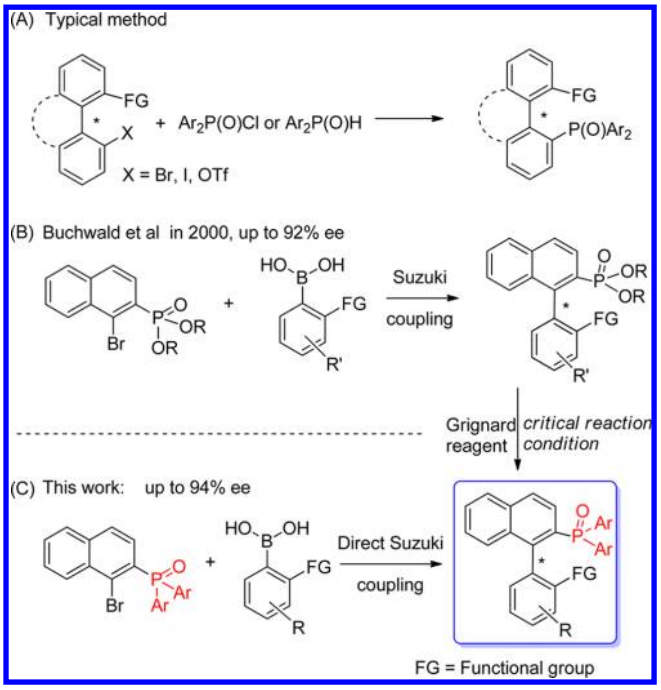
Scheme 1. Synthetic Protocols for Axially Chiral Biaryl Monophosphine Oxides



lead to low efficiency of the whole synthetic process. A convenient preparation for novel axially chiral functionalized phosphine oxides remains of significance and a challenge.

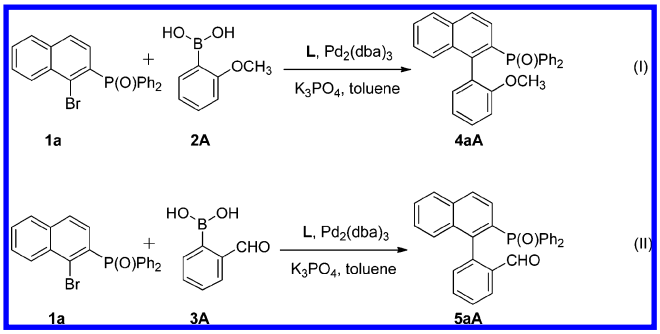
Enantioselective metal-catalyzed Suzuki coupling has become one of the most used protocols in the synthesis of axially chiral biaryls.[5] In 2000, Buchwald first reported a Pd-catalyzed asymmetric Suzuki coupling of dialkoxyphosphinyl (P(O)-$(OR)_2$)-substituted naphthyl bromides with ortho-alkyl-substituted arylboronic acids. A number of enantioenriched biaryl phosphonates were obtained with up to 92% ee.[6] The phosphonate moiety in the coupling product was successfully converted to the corresponding phosphine oxide, too. However, the reaction conditions, such as solvent, reaction temperature and reaction time, were critical for the conversion to avoid erosion of the enantiomeric purity (Scheme 1B).

We recently established a Pd-(chiral bridged atropisomeric monophosphine) catalyst system[7] and a Pd−(Cy-MOP) catalyst system[8] for asymmetric Suzuki coupling of P(O)-$(OR)_2$-substituted naphthyl bromides with ortho-substituted arylboronic acids. These catalyst systems afforded the coupling products with excellent ee's (both up to 97% ee). Herein, we report a subsequent finding that direct asymmetric Suzuki coupling generates axially chiral biaryl monophosphine oxides containing various functional groups using these two catalyst systems (Scheme 1C). To our knowledge, this represents the first example of enantioselective synthesis of 2-functionalized-2′-diarylphosphinyl-1,1′-biaryls via this catalytic route.

RESULTS AND DISCUSSION

Establishment of Catalyst System. We have embarked on a Pd-catalyzed Suzuki coupling of 2-diphenylphosphinyl-1-naphthyl bromide **1a** with 2-methoxyl phenylboronic acid **2A** (Scheme 2, reaction I) and 2-formyl phenylboronic acid **3A** (Scheme 2, reaction II) for the synthesis of racemic monophosphine oxides **4aA** and **5aA**. It was observed that, with the combination of toluene, K_3PO_4, $Pd_2(dba)_3$, and Sphos,

Scheme 2. Synthesis of Racemic Biaryl Monophosphine Oxides



both the coupling racemic products **4aA** and **5aA** were obtained smoothly in 90% yield for 72 h at 60 and 90 °C, respectively.

With this approach in hand, we began to seek efficient asymmetric catalytic systems used in reactions I and II for affording the axially chiral biaryl monophosphine oxides **4aA** and **5aA**. A variety of chiral ligands (Figure 1, **L1**−**L15**)[9] were

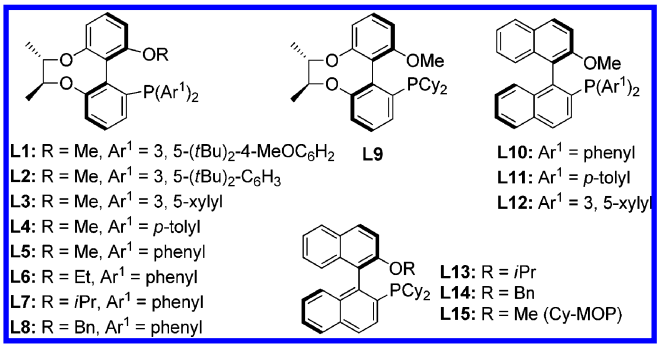


Figure 1. Monophosphine ligands **L1**−**L15**.

examined in toluene with K_3PO_4 as the base and $Pd_2(dba)_3$ as the palladium source (Table 1). **L1** and **L15** (Cy-MOP) were found to be the best choice for reaction I and reaction II, respectively.

For reaction I, ligands **L1**−**L8** were found to give better ee values than those of BINOL-derived MOP's **L10**−**L15** (Table 1, entries 1−11 vs entries 13−18). This demonstrates that the chiral bridged biphenyl skeleton in **L1**−**L8** is beneficial for acquiring high enantioselectivity in this reaction. **L1** provided the best result at 30 °C within 48 h (Table 1, entry 1). When the reaction temperature was decreased to 10 °C, the reaction became sluggish, and there was no beneficial effect toward the enantioselectivities (Table 1, entry 2). When the temperature was increased to 60 °C, **1a** was consumed completely in 24 h; however, the ee value decreased slightly (Table 1, entry 3, 64% ee). When the reaction was conducted at 30 °C for 24 h, only 40% yield was obtained (Table 1, entry 4). When the 3,5-$(t\text{Bu})_2$-4-MeO-C_6H_2 group attached to the phosphorus atom in **L1** was changed to a 3,5-$(t\text{Bu})_2$-C_6H_3 group (**L2**), the same ee value was given, but the yield dropped (Table 1, entry 4 vs entry 5). It indicates that a high electron density of the attached aryl group enhances the reaction rate.[10] **L3**, **L4**, and **L5** possessing less bulky aryl groups at this place provided lower enantioselectivities (Table 1, entries 6−8). This shows that a bigger aryl group is somewhat helpful to better enantioselection. The influence of an alkoxy or aryloxy group linked at

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Table 1. Ligand Screening

reaction I[a]						reaction II[a]					
entry	L	*t*, °C	time, h	yield, %[b]	ee, %[c]	entry	L	*t*, °C	time, *h*	yield %[b]	ee %[c]
1	**L1**	30	48	95	68 (−)	19	**L1**	90	72	69	80 (84[d], *R*)
2	**L1**	10	120	44	68 (−)	20	**L2**	90	72	53	80 (*R*)
3	**L1**	60	24	95	64 (−)	21	**L3**	90	72	55	84 (*R*)
4	**L1**	30	24	40	68 (−)	22	**L4**	90	72	45	86 (*R*)
5	**L2**	30	24	30	68 (−)	23	**L5**	90	72	50	85 (*R*)
6	**L3**	30	48	95	64 (−)	24	**L6**	90	72	50	83 (*R*)
7	**L4**	30	48	95	61 (−)	25	**L7**	90	72	20	77 (*R*)
8	**L5**	30	48	95	62 (−)	26	**L8**	90	72	20	79 (*R*)
9	**L6**	30	48	95	62 (−)	27	**L9**	90	72	40	67 (*R*)
10	**L7**	30	48	90	63 (−)	28	**L10**	90	72	45	67 (*R*)
11	**L8**	30	48	90	65 (−)	29	**L11**	90	72	39	65 (*R*)
12	**L9**	30	48	66	36 (+)	30	**L12**	90	72	39	55 (*R*)
13	**L10**	30	48	44	44 (−)	31	**L13**	90	72	80	77 (*R*)
14	**L11**	30	48	89	45 (−)	32	**L14**	90	72	75	79 (*R*)
15	**L12**	30	48	79	41 (−)	33	**L15**	90	72	95	84 (*R*))
16	**L13**	30	48	94	8 (−)	34	**L15**	70	72	95	89 (*R*)
17	**L14**	30	48	94	39 (−)	35	**L15**	50	72	93	93 (99[e], *R*)
18	**L15**	30	48	80	36 (−)	36	**L15**	30	48	0	

[a]Reaction conditions: **1a** (0.5 mmol), **2A** or **3A** (1.0 mmol); K_3PO_4 (1.5 mmol); ligand (4.8 mol %); Pd (4 mol %); toluene (4 mL). [b]Yields were determined by HPLC and NMR analysis of the crude reaction mixture. [c]Determined by HPLC. [d]The reaction was conducted at 50 °C. [e]99% ee and 62% overall yield after recrystallization once from methylene chloride and hexanes. The absolute configuration of **5aA** was determined by X-ray crystallography.[11]

Table 2. Optimization Experiments[a]

entry	palladium	base	solvent	reaction	yield %[b]	ee %[c]
1	$Pd_2(dba)_3$	K_3PO_4	toluene	I	95	68 (−)
				II	93	93 (*R*)
2	$Pd_2(dba)_3$	K_3PO_4	THF	I	60	62 (−)
				II	65	92 (*R*)
3	$Pd_2(dba)_3$	K_3PO_4	dioxane	I	77	62 (−)
				II	74	92 (*R*)
4	$PdCl_2$	K_3PO_4	toluene	I	traces	nd
				II	traces	nd
5	$Pd(OAc)_2$	K_3PO_4	toluene	I	87	68 (−)
				II	80	93 (*R*)
6	$Pd(CF_3COO)_2$	K_3PO_4	toluene	I	89	68 (−)
				II	80	92 (*R*)
7		K_3PO_4	toluene	I	0	nd
				II	0	nd
8	$Pd_2(dba)_3$	K_2CO_3	toluene	I	54	67 (−)
				II	90	92 (*R*)
9	$Pd_2(dba)_3$	KF	toluene	I	43	67 (−)
				II	81	93 (*R*)
10	$Pd_2(dba)_3$	CsF	toluene	I	39	67 (−)
				II	85	91 (*R*)

[a]Reaction conditions: **1a** (0.5 mmol), **2A** or **3A** (1.0 mmol), base (1.5 mmol), ligand (4.8 mol %), Pd (4 mol %), solvent (4 mL); reaction I (used **L1** as ligand) was run at 30 °C for 48 h, reaction II (used **L15** as ligand) was run at 50 °C for 72 h. [b]Yields were determined by HPLC and NMR analysis of the crude reaction mixture. [c]Determined by HPLC.

the 2′-site of the ligands was also tested (**L5**−**L8**). When a MeO or EtO group was introduced (**L5** and **L6**), **4aA** resulted, in 95% yield. When more sterically congested counterparts were instead employed (**L7** and **L8**), dehalogenation of the starting material **1a** became significant. This resulted in a lower yield of the coupling product, despite giving higher ee values (Table 1, entries 8, 9 vs 10, 11). In place of a 3,5-(tBu)$_2$-4-MeOC$_6$H$_2$ group in **L1** with an electron-rich cyclohexyl group, disappointingly, poor yield and enantioselectivity were observed (Table 1, entry 12).

For reaction II, coupling product **5aA** was provided with enantioselectivity in the range of 67−86% ee when the reaction was conducted at 90 °C for 72 h with chiral bridged **L1**−**L9** as the ligands. However, the reaction yields of **5aA** were poor because of serious dehalogenation (Table 1, entries 19−27). Similar phenomena were also observed using BINOL derived **L10**−**L12** as the ligands (Table1, entries 28−30). Ligands with

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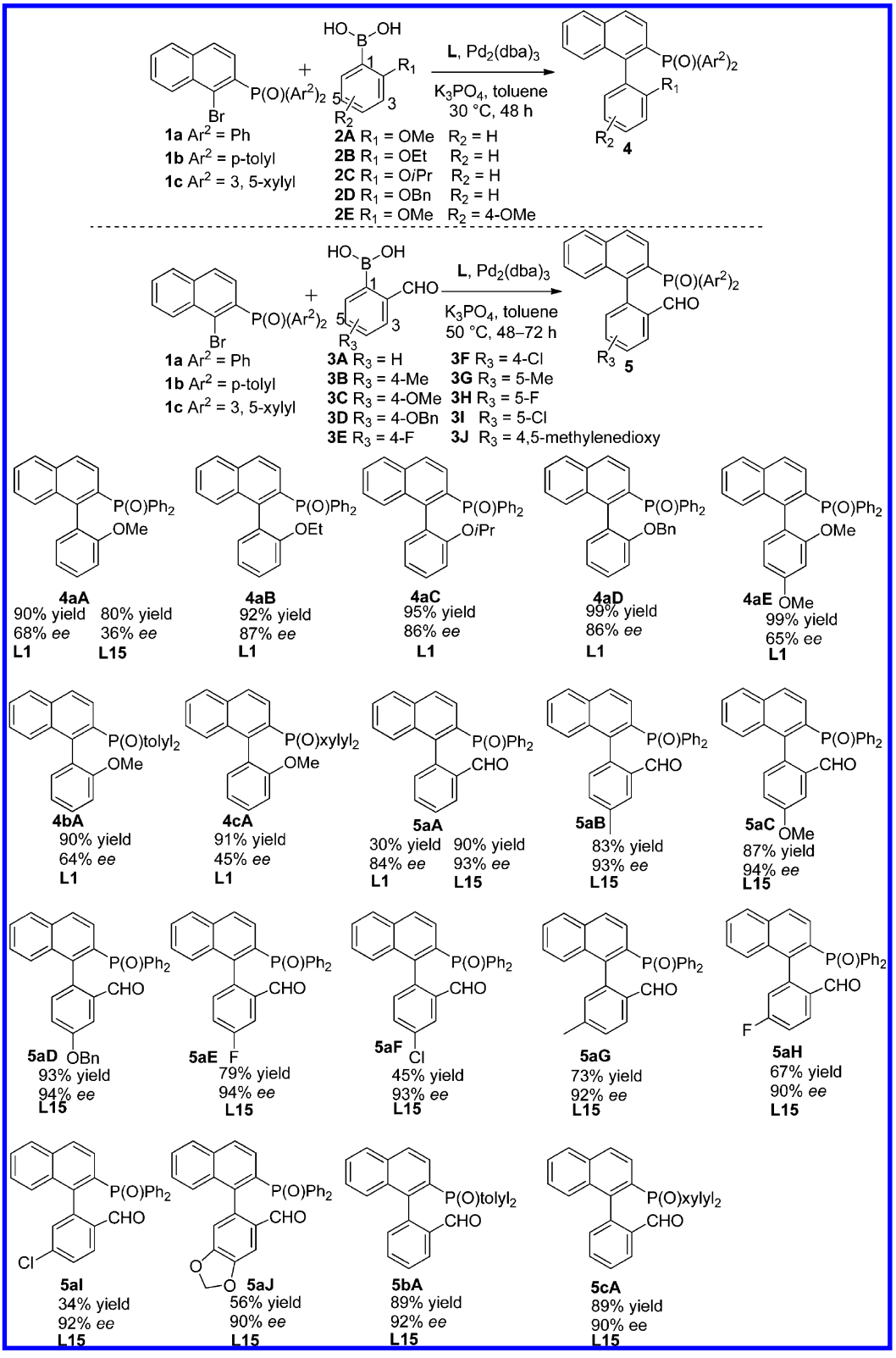
Scheme 3. Synthesis of Axially Chiral Biaryl Monophosphine Oxides via the Suzuki Reaction[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** or **3** (2.0 mmol), K_3PO_4 (3.0 mmol), ligand (4.8 mol %), Pd (4 mol %), toluene (8 mL). Yields are combined isolated values; ee values were determined by HPLC.

the electron-rich dicyclohexylphosphino group (**L13**–**L15**) gave better yields of **5aA**, with 77–84% ee (Table 1, entries 31–33). **L15** (Cy-MOP) exhibited the best efficiency among them (Table 1, entry 33). Using **L15** (Cy-MOP) as the ligand, the reaction proceeded smoothly with excellent enantioselectivity (89% ee) at 70 °C (Table 1, entry 34). Higher ee value (93% ee) was afforded at a lower temperature 50 °C (Table 1, entry 35). The reaction did not proceed when the reaction

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temperature was further decreased to 30 °C, (Table 1, entry 36).

In addition to the ligand screening, the effects of solvents, Pd sources, and bases were investigated. The results are illustrated in Table 2. Toluene was found superior to THF and dioxane solvents. Although the product enantioselectivities were not affected, dehalogenation of **1a** became serious when THF or dioxane was used (Table 2, entries 1−3). Further survey of palladium sources indicated that $Pd_2(dba)_3$ exhibited better catalytic performance than $Pd(OAc)_2$, $PdCl_2$, and $Pd(CF_3COO)_2$ (Table 2, entries 4−6). A control experiment showed that the reaction did not proceed in the absence of palladium (Table 2, entry 7). Commonly available inorganic bases were also screened. K_3PO_4 was found to be better than K_2CO_3, KF, and CsF (Table 2, entries 8−10).

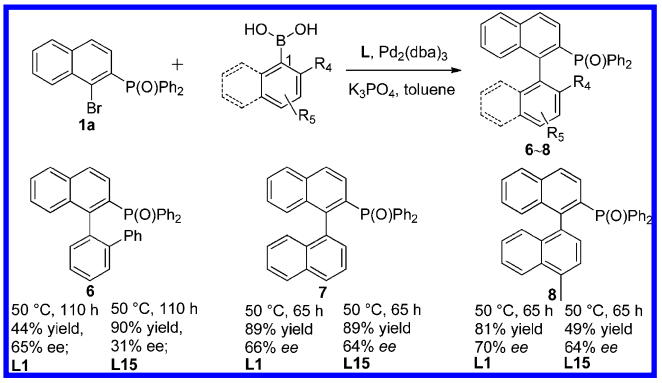
Substrate Scope. Having established the optimal conditions, the substrate scope of the reactions was explored (Scheme 3). Using **L1** as the ligand, coupling products **4aB**, **4aC**, **4aD**, and **4aE** were afforded in 90−99% yields. Interestingly, the ee values of **4aB**, **4aC**, and **4aD** were higher than those of **4aA** and **4aE**. These results suggest that larger 2-alkoxy group of the arylboronic acids has a positive influence on the enantioselectivity; however, for the coupling of **1b** (Ar^2 = *p*-tolyl), **1c** (Ar^2 = 3,5-xylyl) with **2A**, the ee values of the corresponding products **4bA** and **4cA** dropped to 64% and 45%, respectively. This implies that the more sterically congested Ar^2 group at the aryl bromide has a negative effect on the enantioselectivity.

When substituted 2-formyl phenylboronic acids with electron-donating or electron-withdrawing groups (Scheme 3, **3A**−**3J**) were employed as the coupling partners, interestingly, the coupling products **5aA**−**5aJ** (Scheme 3) were obtained in moderate-to-good yield with excellent ee's (90−94% ee's) with the use of ligand **L15** (Cy-MOP). It suggests that the formyl group at the 2-position of arylboronic acids shows an astonishing positive effect on high level of enantioselectivity. Use of chloro-substituted 2-formyl phenylboronic acids resulted in relatively lower yields of the coupling products (**5aF** and **5aI**) due to self-coupling reaction of the boronic acids. It is worth noting that reactions of **1b** (Ar^2 = *p*-tolyl) and **1c** (Ar^2 = 3,5-xylyl) with **3A** could also provide the corresponding products **5bA** and **5cA** in 89% yields with slightly lower ee's (92% and 90% ee's, respectively) than that of **5aA** (93% ee). This demonstrates that the steric effect of the Ar^2 group on substrate **1** is not significant for the catalytic performance.

Moreover, biphenyl-2-ylboronic acid, 1-naphthenyl boronic acid, and 4-methylnaphthalen-1-yl boronic acid were also evaluated (Scheme 4). Ligand **L1** showed higher efficacy than **L15** (Cy-MOP) for the coupling reactions of these arylboronic acids with **1a**. The ee values of the corresponding coupling products **6**, **7**, and **8** were also lower than those of **5aA**−**5aJ**, **5bA**, and **5cA**. It also reveals the importance of the formyl group of the arylboronic acids in acquiring high enantioselectivity in this reaction.

Application Exploration. To test the practicality of the methodology, a scaled-up reaction was performed. Coupling of **1a** (5 mmol) with **3A** (10 mmol) gave product **5aA** without erosion in either the yield (90%) or enantioselectivity (93% ee). By means of single crystallization in layering dichloromethane/hexane mixtures, enantiopure crystals of **5aA** were obtained (99% ee). The absolute configuration was confirmed in the *R* form by single-crystal X-ray diffraction.[11]

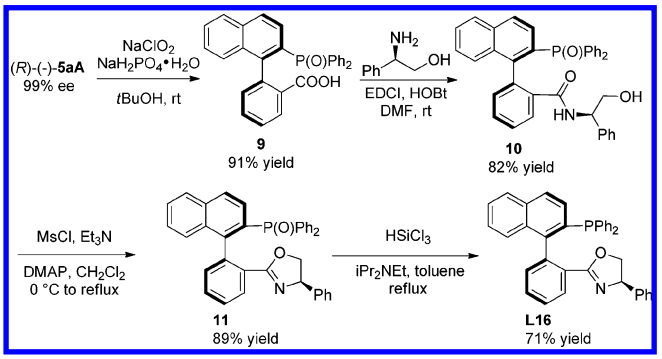
Scheme 4. Synthesis of Axially Chiral Biaryl Monophosphine Oxides[a]



[a]Reaction conditions: **1a** (1.0 mmol), boronic acid (2.0 mmol), K_3PO_4 (3.0 mmol), ligand (4.8 mol %), Pd (4 mol %), toluene (8 mL). Yields are combined isolated values; ee values were determined by HPLC.

With the aid of this newly developed method, a new chiral phosphine−oxazoline ligand **L16** was prepared from **5aA** (Scheme 5). Oxidation of **5aA** by sodium chlorite afforded

Scheme 5. Preparation of Chiral Phosphine−Oxazoline Ligand L16



compound **9**, which was converted into amide **10** in 82% yield. The amide was subjected to oxazoline ring formation by treatment with triethylamine and methanesulfonyl chloride in dichloromethane to give oxazoline **11**. Following reduction of **11** with $HSiCl_3$, a new ligand **L16** was obtained in 71% yield.[12]

COMPUTATIONAL STUDIES ON THE ENANTIOSELECTIVITIES IN SUZUKI REACTIONS

Buchwald's publication[5e,6] suggested that in the asymmetric Suzuki reaction of 2-alkyl or 2-alkoxy substituted arylboronic acid with aryl halide, a $P(O)(R)_2$ (R = alky or alkxoy), or C(O)NRR′ group at the 2-position of the aryl halide is significant for reaching high levels of enantioselectivity because of a Pd···O interaction between the palladium(II) atom and the oxygen atom belonging to the $P(O)(R)_2$ or C(O)NRR′. However, in our catalyst system, high enantioselectivities were given in the coupling reactions of 2-diarylphosphinyl-1-naphthyl bromide (**1**) with 2-formylphenylboronic acids (**3**). In contrast, using 2-alkoxy phenylboronic acids as substrates instead, only moderate ee values of the coupling products were observed. It is tempting to speculate that a formyl group at the 2-position of the boronic acids greatly improves the levels of enantioselectivity.

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To provide insight into the nature of the 2-position formyl group and the selectivity in the reaction, computational studies were performed with the DFT B3LYP methods.[13,14] The effective core potential (ECP) basis sets lanl2dz with double-ζ basis sets were employed for the Pd and P atoms and the splitting polarization basis sets 6-31G(d) were adopted for C, H, and O atoms.

As a starting point of our computational studies, X-ray crystallographic data were employed in the modeling of the transition states. We recently reported a closely related reaction of dimethyl-(1-bromo-2-naphthyl)phosphonate with 2-formylphenylboronic acid catalyzed by the Pd−(Cy-MOP) complex, which could also afford the coupling product **12** in the *R* configuration (Figure 2).[8,15] Thus, for the sake of calculation expense, we chose this closely related reaction to carry out detailed computational investigations.

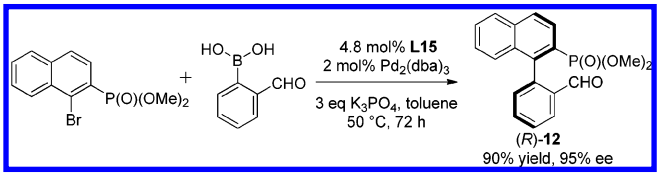

Figure 2. The Pd−(Cy-MOP)-catalyzed reaction of dimethyl-(1-bromo-2-naphthyl)phosphonate with 2-formylphenylboronic acid.

DFT calculations were carried out to explore the transition state structures and their relative free energies. Previous research indicated that the enantioselectivities of the products in Suzuki−Miyaura reactions were determined in the step of the reductive elimination.[5e,j,16] In the prototypical transition state for the reductive elimination, both the formylphenyl and the naphthylphosphonate addends are coordinated with the palladium(II) ion. In addition, the formyl and phosphonate substituents on the formylphenyl and naphthylphosphonate addends, respectively, can be either above or below the plane defined by the palladium(II) ion and two bounded carbon atoms. Meanwhile, the formyl group can be inclined away from or toward the palladium(II) ion. Finally, the ligand in the Pd−(Cy-MOP) complex can be monodentate or bidentate. Consequently, a total of 64 transition structures can be generated from these orientations discussed above (see the Supporting Information). However, a general principle can be conducted on the analysis of the relative free energies of these transition structures. The computational result indicates that the Pd−(Cy-MOP) complex prefers a bidentate ligand and the formyl group is more inclined to interact with the palladium(II) ion with the H atom (See the Supporting Information). Therefore, 16 selected transition structures of different orientations were analyzed (Figure 3).

As shown in Figure 3, the TS2 of enantiomer of R is the most stable transition state, which is consistent with the configuration of the major product in the X-ray crystallography experiment. In addition, distribution analysis (eq 1) based on these results was conducted to predict the ee value.

$$\mathrm{ee} = \frac{C_R - C_S}{C_R + C_S} = \frac{\sum_{\Delta G_R^{\neq}} \exp(-\Delta G_R^{\neq}/RT) - \sum_{\Delta G_R^{\neq}} \exp(-\Delta G_S^{\neq}/RT)}{\sum_{\Delta G_R^{\neq}} \exp(-\Delta G_R^{\neq}/RT) + \sum_{\Delta G_R^{\neq}} \exp(-\Delta G_S^{\neq}/RT)} \quad (1)$$

The calculated value is 88% ee in favor of *R* stereochemistry at 25 °C, which is in good agreement with the selectivity found by experiment of 95% ee.[15]

The Stability of the Transition State TS2. The calculation results predict the experimental enantioselectivity of *R* well. The ligand in the Pd−(Cy-MOP) complex is more inclined to coordinate with the palladium(II) ion with both the P atom and the O atom, which further supports our experimental finding that one molecule of palladium(II) is limited to coordinate with one molecule of the ligand for the sake of steric hindrance and entropy effect. Our calculations suggest that a transition state with a monodentate ligand is usually higher in energy than its corresponding bidentate one.[5e]

Interestingly, TS2 possesses a distorted octahedron configurationa in which a bidentate ligand and two carbon atoms bind to the palladium center on the equatorial plane, and the C−H motif of the formyl group and the phosphoryl P═O of the phosphonate group are located on two elongated axial position, respectively. Similar distorted octahedral configurations were observed from TS6, TS10, and TS14, in which they also have relatively lower transition state energies. It should be noted that the fulfilled $4dz^2$ orbital of the Pd atom is inclined to capture the electron-deficient H atom in the formyl group, and a typical three-center, four-electron transition metal hydrogen bond is generated. As shown in Figure 3, the distance between the H atom and the Pd atom is 2.45 Å, and that of Pd−C is 2.98 Å in TS2, which indicates that this significant transition metal hydrogen bond plays an important role in the stabilization of TS2. Moreover, there also exists a weak interaction between Pd atom and the phosphoryl P═O group, with a Pd···O distance of 2.92 Å. NBO population analysis indicates that there is a remarkable second-order perturbation energy between the phosphoryl and Pd center to stabilize the transition state structure. Finally, the origin of the enantioselectivity can be interestingly figured out by a comparison between TS2 and TS7 (the former is the most stable transition state for the product with *R* stereochemistry, and the latter is the most stable transition state for the product with *S* stereochemistry).

As can be seen from Figure 4, TS2 possesses a distorted octahedron configuration, whereas TS7 adopts a tetragonal pyramid configuration without the weak interaction between the Pd atom and the phosphoryl group (Pd···O═P distance, 3.55 Å). TS2 and TS2-O are two types of distorted octahedral transition states for the product with *R* stereochemistry; however, the Pd atom is more inclined to form a transition metal hydrogen bond (Figure 4, TS2), rather than interact with the formyl oxygen atom (Figure 4, TS2-O). The lone pair electrons of the formyl oxygen atom would be repelled by the electron-occupied $4dz^2$ orbital of the Pd atom. Furthermore, NBO population analysis shows that the palladium(II) center has been partial reduced (the NPA charge on Pd is 0.13), which decreases the electrostatic interaction with the electronegative oxygen atom in formyl group.

To conclude, the distorted octahedron configuration of the transition state, that is, the bidentate ligand, the significant transition metal hydrogen bond between H atom of formyl group and palladium(II), as well as the weak interaction between Pd center and the phosphoryl oxygen atom, together make the transition state TS2 the most stable, giving rise to product with *R* stereochemistry.This theoretical study well explains our experimental finding that the formyl group is crucial for high enantioselectivity.

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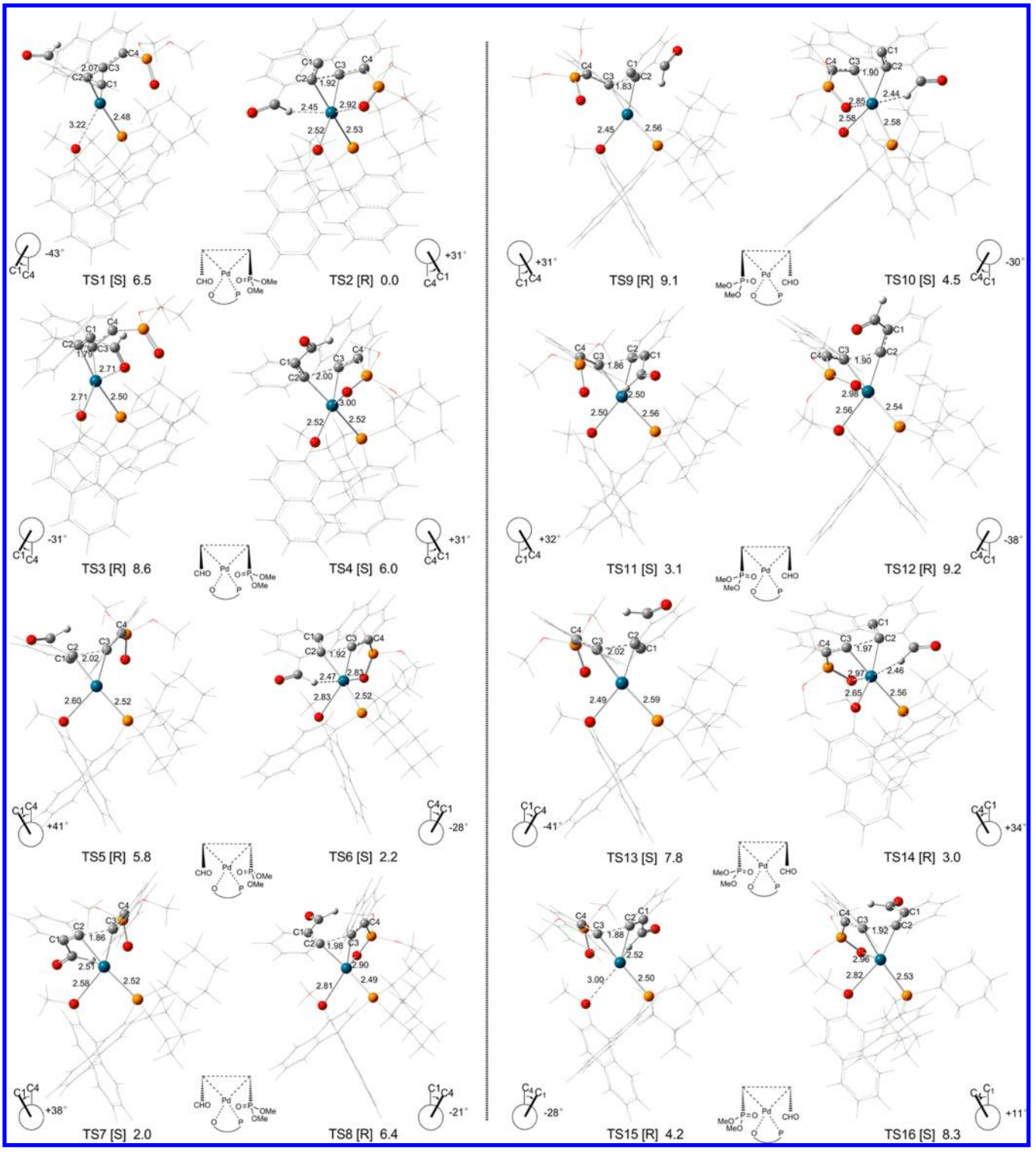

Figure 3. Transition states and corresponding data for reductive elimination of biaryls from Pd−(Cy-MOP) complexes formed after transmetalation. The stereochemistry of the product followed by the reductive elimination is denoted in brackets. The relative free energies are shown just following the brackets (kcal/mol). The distances are in Å.

CONCLUSION

In summary, direct asymmetric Suzuki coupling reaction of arylboronic acids with 2-diarylphosphinyl-1-naphthyl bromide was successfully developed for the first time, affording a variety of axially chiral 2-functionalized-2′-diarylphosphinyl-1,1′-biaryls with up to 94% ee using Pd-chiral bridged biphenyl monophosphine **L1** or Pd−(Cy-MOP) as the catalyst. This methodology provides a highly efficient and practical strategy for the synthesis of novel axially chiral biaryl monophosphine oxides and the corresponding phosphines. Computational studies show that the origin of high enantioselectivity come from the feature of the distorted octahedron configuration of the reductive elimination transition state. In this transition state, the significant transition metal hydrogen bond between H

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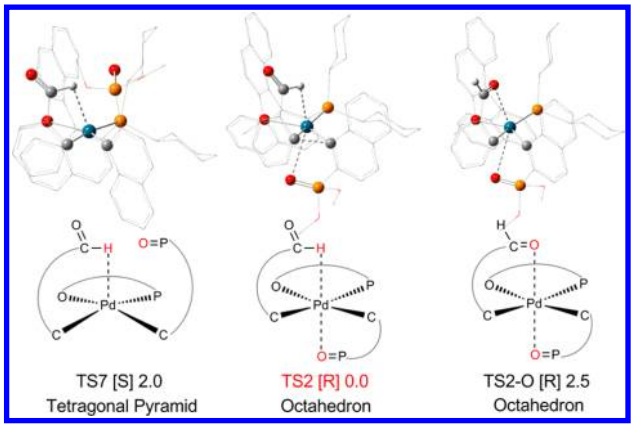

Figure 4. Comparison between TS2 and TS7 transition structures. The stereochemistry of the product followed by the reductive elimination is denoted in brackets. The relative free energies are shown just following the brackets (kcal/mol). In TS2-O, the Pd atom is bound to O atom in the formyl group.

atom of the formyl group and palladium(II) and the weak interaction between Pd center and the phosphoryl oxygen atom play important roles in stabilizing the *R* type transition state TS2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and compound characterization data. Energies and Cartesian coordinates of stationary points from B3LYP calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qiuliqin@mail.sysu.edu.cn.
*E-mail: kezhf3@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

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