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Efficient Chiral Monophosphorus Ligands for Asymmetric Suzuki–Miyaura Coupling Reactions

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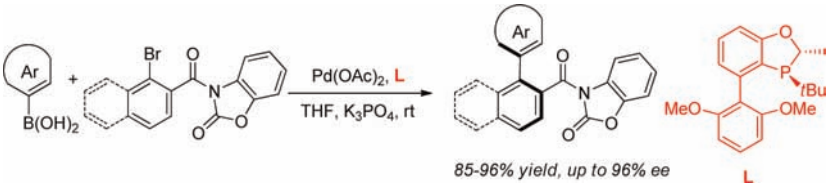
ABSTRACT



A series of novel P-chiral monophosphorus ligands exhibit efficiency in asymmetric Suzuki–Miyaura coupling reactions, enabling the construction of an array of chiral biaryl products in high yields and excellent enantioselectivities (up to 96% ee) under mild conditions. The carbonyl-benzooxazolidinone moiety in these chiral biaryl products allows facile derivatization for further synthetic applications. A computational study has revealed that a $\pi-\pi$ interaction between the two coupling partners can enhance the enantioselectivity of the coupling reaction.

Axially chiral biaryl structures exist in many biologically active natural products[1] as well as serve as privileged frameworks for efficient ligands[2] in the field of asymmetric catalysis. Their syntheses *via* asymmetric cross-coupling reactions remain a challenging and underdeveloped area. Since Hayashi's pioneering work[3] on asymmetric Kumada couplings, efforts toward the development of asymmetric Nigishi[4] or Suzuki–Miyaura couplings[5] have been reported. The asymmetric Suzuki–Miyaura coupling is

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particularly attractive due to its compatibility to a broad range of functionalities. Recent work led by Buchwald,[6] Cammidge,[7] Fernández and Lassaletta,[8] Uozumi,[9] Fujihara,[10] Lin,[11] Espinet,[12] Suginome,[13] and others[14] have shown some progress in this field. However, the current substrate scope of asymmetric Suzuki–Miyaura couplings remains limited. Much less were reported on couplings containing functionalities of synthetic interest. Additionally, high catalyst loadings (> 10 mol %) and prolonged reaction times (> 24 h) were often required in many cases. Thus, the development of novel and efficient catalysts to further expand the scope and utility of asymmetric Suzuki–Miyaura coupling reactions remains of significant interest and challenge.

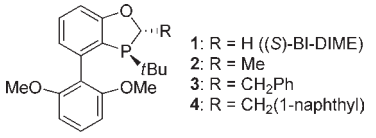
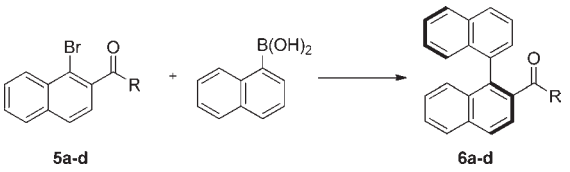


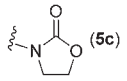
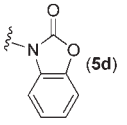
Figure 1. Novel P-chiral monophosphorus biaryl ligands.

The ligand structure dictates the steric and electronic properties of their metal complexes and thus plays an important role in the reactivity and selectivity in metal-catalyzed reactions. One salient structural feature of the biaryl monophosphorus ligands shown in Figure 1 is the rigid framework of the 2,3-dihydrobenzo[*d*][1,3]oxaphosphole structure on the upper aryl ring, which well defines the orientation of the phosphorus atom for metal coordination. Such rigidity limits the ligand to form various conformers when coordinated to a metal.[15] In addition, the facile structural modifications on the upper aryl ring allows for fine-tuning of the overall steric environment. Furthermore, the scalable preparation of their core structure[16] makes them easily accessible. Herein we report the applications of chiral ligands **1**–**4** in asymmetric Suzuki–Miyaura coupling reactions which have led to the preparation of a range of functionalized biaryl compounds in high yields and excellent enantioselectivities.

Our initial study on asymmetric Suzuki–Miyaura coupling reactions with these P-chiral monophosphorus ligands confirmed a chelating functionality on one coupling partner helps achieve good enantioselectivity. This phenomenon boded well with Buchwald's observation on a Pd-KenPhos catalyst,[6] where high enantioselectivities were observed on substrates with chelating phosphonates, phosphine oxides, or amides. Gratifyingly, the P-chiral monophosphorus ligands **1**–**4** also exhibited excellent reactivities on these sterically demanding cross-coupling reactions, allowing most reactions in this study to proceed at rt or a slightly elevated temperature. The mild reaction conditions are crucial for high enantioselectivities of asymmetric Suzuki–Miyaura coupling since the racemization of chiral biaryl products could occur under a higher reaction temperature depending on the substituents on the biaryls.[1d] As shown in Table 1, the coupling between the bromo aldehyde **5a** and 1-naphthylboronic acid in the presence of 5 mol % $Pd(OAc)_2$ and 6 mol % of ligand **2** proceeded smoothly at rt in 4 h to provide the coupling product in an excellent yield albeit with a moderate ee (20%, entry 1). Employment of a bromide **5b** with a dimethylamide functionality led to a significant increase of enantioselectivity (79% ee, entry 2). A further enhancement (87% ee, entry 3) was achieved when a bromide **5c** with a carbonyl-oxazolidinone functionality was employed. Employment of a bromide **5d** with a carbonyl-benzooxazolidinone functionality led to the formation of the binaphthyl compound **6d** in 96% ee (entry 7). For comparison, ligand **1** ((*S*)-BI-DIME) was less reactive and selective for this transformation (entry 4). Ligands **3** and **4** also provided good yields, albeit with slightly low enantioselectivities (entries 5 and 6). To our delight, the reaction also proceeded with a 1 mol % Pd catalyst loading with

Table 1. Ligand and Substrate Screening[a]



entries	R (bromide)	ligand	Pd (mol %)	yield (%)	ee (%)
1	H (**5a**)	**2**	5	90 (**6a**)	20
2	NMe_2 (**5b**)	**2**	5	95 (**6b**)	79
3	 (**5c**)	**2**	5	96 (**6c**)	87
4		**1**	5	50 (**6d**)	45
5	 (**5d**)	**3**	5	92 (**6d**)	90
6		**4**	5	99 (**6d**)	92
7		**2**	5	95 (**6d**)	96
8		**2**	1	95 (**6d**)	96

[a] Reaction conditions: 1.0 equiv of aryl bromide, 2 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 6 mol % of ligand, 3 equiv of K_3PO_4, rt, 4 h under nitrogen, isolated yield. The enantiomeric excesses were determined by chiral HPLC on a chiralcel OD-H column. The *R* absolute configuration of **6d** was determined by converting to its corresponding known alcohol[3a,17] with treatment of $NaBH_4$. The absolute configurations of **6a**–**c** were assigned by analogy.

(15) At least two conformers were found when S-Phos was coordinated with a Pd metal; see: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

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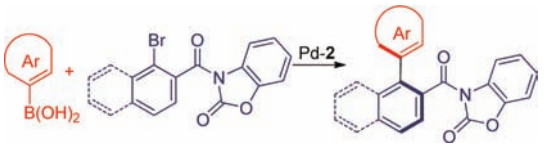
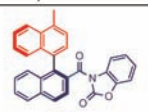
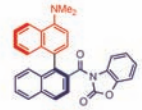
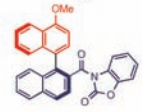
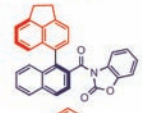
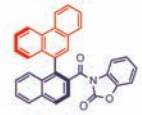
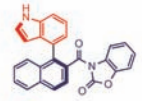
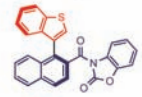
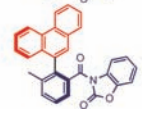
out compromising both the yield and enantioselectivity (entry 8).

Table 2. Asymmetric Suzuki Couplings 1[a]

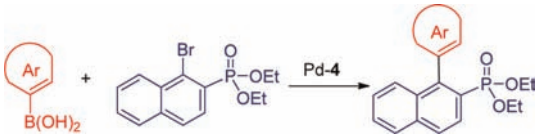


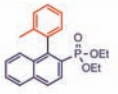
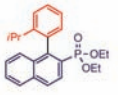
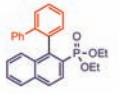
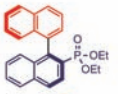
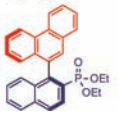
entry	product	temp	time (h)	yield (%)	ee (%)
1		rt	4	95	96
2		rt	4	95	96
3		rt	4	94	94
4		rt	4	96	88
5		rt	4	96	90
6		rt	4	95	90
7		rt	36	95	68
8		rt	4	95	82
9		rt	4	85	70
10		rt	4	90	64

[a] Conditions unless otherwise specified: 1.0 equiv of aryl bromide, 2 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 6 mol % of ligand **2**, 3 equiv of K_3PO_4, rt, 4 h; isolated yield; enantiomeric excesses were determined by chiral HPLC on a chiralcel OD-H or AD-H column. The absolute configurations were assigned by analogy according to optical rotations.

With Pd-**2** as the chiral catalyst, a series of chiral biaryl compounds could be prepared at rt in high yields and in good to excellent enantioselectivities. As shown in Table 2, various arylboronic acids such as substituted 1-naphthaleneboronic acids (entries 1−3), 5-acenaphtheneboronic acid (entry 4), 9-phenanthreneboronic acid (entry 5), and 1-pyreneboronic acid (entry 6) reacted with 3-(1-bromo-2-naphthoyl)benzo[*d*]oxazol-2(3H)-one (**5d**) to provide coupling products in high yields and excellent ee's. Heteroarylboronic acids could also be employed (entries 7−8), and the catalytic system was well tolerable with indole and benzothiophene structures. Substituted phenyl bromides could also react with arylboronic acids to form the corresponding biaryl coupling products in good enantioselectivities (entries 9−10).

Table 3. Asymmetric Suzuki Couplings 2[a]



entry	product	temp (°C)	time (h)	yield (%)	ee (%)
1		rt	12	95	80
2		40	12	75	80
3		40	12	74	96
4[b]		rt	12	88	90
5[c]		rt	12	90	82

[a] Conditions: 1.0 equiv of aryl bromide, 2 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 6 mol % of ligand **4**, 3 equiv of K_3PO_4; isolated yield; enantiomeric excesses were determined by chiral HPLC on a chiralcel OD-H or AD-H column. [b] The *R* absolute configuration of the coupling product was determined by comparing its optical rotation with reported data.[6a,18] [c] The absolute configuration was assigned by analogy according to optical rotation.

High enantioselectivities in asymmetric Suzuki couplings of aryl bromides with phosphonate functionality were reported.[6a,13] It was found that ligand **4** was also effective for these substrates (Scheme 3). For example, with Pd-**4** as the catalytic system, the reaction of diethyl 1-bromonaphthalen-2-ylphosphonate and 2-tolylboronic acid proceeded at rt to provide the coupling product in 95% yield and 80% ee (Table 3, entry 1). 2-Isopropylboronic acid was also applicable (entry 2). Higher enantioselectivities (96% and 90% ee, repectively) were achieved when 2-biphenylboronic acid and 1-naphathaleneboronic acid were employed (entries 3−4). The reaction with 9-phenanthreneboronic acid also provided a high ee (entry 5).

It is important to note that the chiral biaryl products with the carbonyl-benzooxazolidinone functionality can be easily derivatized. For example, **6d** was converted to the corresponding carboxylic acid **7**[19] and alcohol **8** by simple transformations without loss of enantiomeric purities (Scheme 1). The facile derivatization of the carbonyl-benzooxazolidinone moiety demonstrated the versatility of these chiral biaryl coupling products for further synthetic applications.

Scheme 1. Derivatization of **6d**

The dramatic substituent effect observed with bromides **5a**–**d** on the selectivity of asymmetric Suzuki–Miyaura coupling (Scheme 1) deserves further elaboration. Additionally, we observed only ~20% ee of the coupling product from the reaction between bromide **5d** and 2-tolylboronic acid with the Pd-**2** catalyst, suggesting the importance of a large π-aryl system of the boronic acid partner on the enantioselectivity. We performed the DFT calculations on the Pd(II) complex at the reductive elimination step in the reaction of **5d** and 1-naphthylboronic acid with the Pd-**2** catalyst. Based on earlier theoretical studies,[20] the stereochemistry of the coupling product is connected to the conformation of the palladium complex at the reductive elimination step *via* the shortest pathway; hence the chirality of the biaryl product can be determined from the conformation of the Pd(II) intermediate. Using the DFT/B3LYP method with a mixed basis set that takes into account nonbonded van der Waals interactions, our calculation results have shown excellent agreement with the chiral selectivity observed in this system.[21] More specifically, our calculations revealed the presence of a π–π interaction between the two reactants at the lowest energy conformation that has helped guide the orientation of the two aryl groups at the reductive elimination step, resulting in good stereoselection (Figure 2).

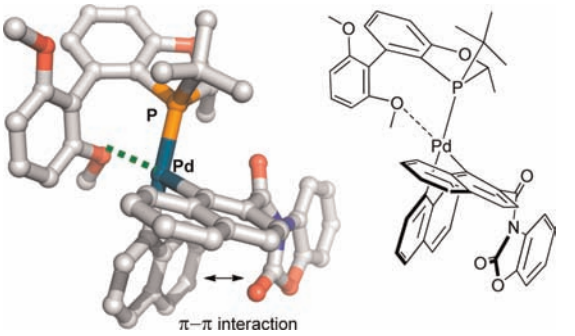


Figure 2. Calculated lowest-energy conformation of the Pd(II) complex at the reductive elimination step (the color codes for the atoms are as follows: carbon, gray; nitrogen, blue; oxygen, red; phosphorus, orange; palladium, teal blue. Hydrogen atoms are omitted for clarity).

In summary, we have developed an array of novel and efficient P-chiral monophosphorus ligands for asymmetric Suzuki–Miyaura coupling reactions which have enabled the construction of a series of chiral biaryl compounds in high yields and excellent enantioselectivities (up to 96% ee). The carbonyl-benzooxazolidinone moiety in these chiral biaryl compounds allows facile derivatization for further synthetic applications. DFT calculations have revealed that a π–π interaction between two coupling partners can enhance the enantioselectivity of the coupling reactions. Efforts in developing a more general method of asymmetric Suzuki–Miyaura couplings and applications to efficient syntheses of complex biaryl natural products are underway.

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Supporting Information Available. Experimental details of chiral ligands, analytical data and spectra of new biaryl products, general procedures of asymmetric Suzuki–Miyaura couplings, and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(19) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(20) Buchwald et al. reported DFT calculations on the coupling of naphthylphosphate bromide and tolylboronic acid with a Pd-KenPhos catalyst and found good agreement with the experimental data; see 6b.

(21) DFT calculations were performed with the Gaussian 03 package. A total of 28 conformations with two different coordination patterns were systematically sampled, and the geometry of each conformation was then optimized by energy minimization with the DFT/B3LYP method. Because this system consists of a bulky aromatic system, nonbonded van der Waals interactions are expected to make a significant contribution to the relative energy of different conformations. We therefore employed the MIDI basis set developed by Truhlar et al. (Zhou, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 10478. Zhou, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2007**, *3*, 289) and supplied by the Gaussian 03 package (MidiX) for the first-row atoms (H, C, N, and O). For phosphorus, the 6-31G(d) basis set was employed; for palladium, the all-electron basis set from optimization of fcc Pd bulk (http://www.chimifm.unito.it/teprica/crystal/crystal.html) was employed. The coordinates of the 24 unique energy-minimized conformations were observed. Three lowest-energy conformations were found with a relative energy of 0, 0.51, and 0.78 kcal/mol, respectively. All other conformations have energies >2 kcal/mol or higher than the lowest-energy state. There are two main interesting observations from the calculation results. First, all three lowest-energy conformations lead to the same chirality in the coupling product that is in agreement with the inferred axial chirality of **6d**. This result suggests that the energetics of the nonbonded π-interaction of the aromatic systems indeed dictate the conformation of the transition state and the chirality of the product. Secondly, the origin of the π-stacking interaction in determining the energetics of this system is most clearly seen in the lowest and 2nd lowest-energy conformations. See Supporting Information for more details.