# Chiral Diene as the Ligand for the Synthesis of Axially Chiral Compounds via Palladium-Catalyzed Suzuki−Miyaura Coupling Reaction

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**ABSTRACT**
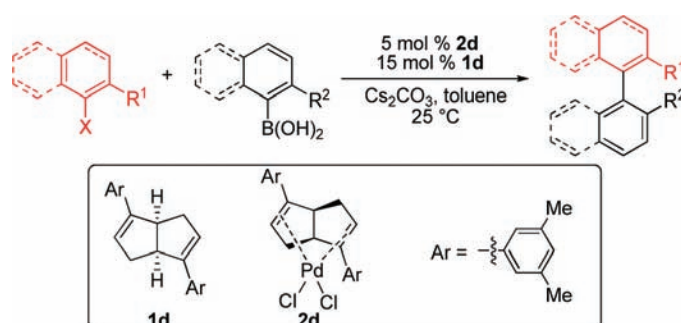


The first palladium−diene-catalyzed asymmetric Suzuki−Miyaura coupling reaction has been achieved. A number of functionalized biaryls were obtained in high yields and in moderate to high enantioselectivities. The existence of an *ortho*-formyl group greatly improves the catalyst efficiency and permits further synthetic elaborations.

Since the seminal works by Hayashi and Carreira,[1] a number of chiral dienes have been designed as novel and efficient ligands for transition-metal-catalyzed asymmetric reactions.[2,3] In several cases, chiral diene ligands outperformed conventional ligands by delivering excellent catalytic activities and enantioselectivities.[2] However, the metals that so far have been employed are only limited to rhodium and iridium. To expand the application scope of chiral diene ligands, employing other metals is in high demand.[2a,c]

Among the transition-metal-catalyzed reactions, palladium is found to be one of the most versatile catalysts.[4] However, a successful example using chiral diene as the ligand in palladium-catalyzed asymmetric transformation remains elusive. Trauner[5] designed a chiral diene−palladium complex and tested it with enyne cyclization reaction, which generated the desired product in a racemic form with low yield (35%). Palladium-catalyzed reactions often involve alterations of the metal valence state ($Pd^0-Pd^{II}-Pd^0$) along the catalytic cycle, which is in sharp contrast to the reactions catalyzed by rhodium-based catalysts where the metal valence state usually keeps constant in the catalytic cycle.[2,3] In addition, the $\pi$-interaction between the double bond and the metal in the

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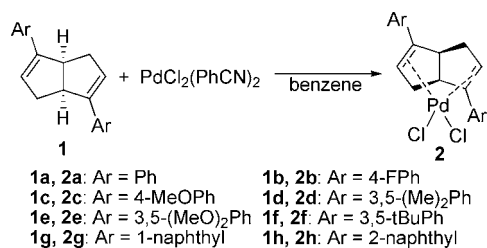‡ Shanghai Institute of Materia Medica.
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olefin−palladium complex is usually weaker than that in the olefin−rhodium complex.[6] It is probably due to these reasons that palladium blacking out is generally observed in palladium-catalyzed reactions, which considerably erodes the catalytic efficiency and might constitute the obstruction to the success of diene−palladium-catalyzed asymmetric reactions.

In recent years, our group introduced a family of diene ligands bearing a [3.3.0]bicyclic backbone and successfully applied them in rhodium-catalyzed reactions.[3a,h,n,7] As an extension, we launched a project to explore the application of these diene ligands in palladium-catalyzed asymmetric reactions. First, we attempted to prepare the chiral diene−palladium catalysts. After several experiments, to our delight, ligand **1a** was found to coordinate with palladium by a ligand exchange from bis(benzonitrile)palladium(II) chloride to furnish the corresponding complex **2a**, which is stable for months in air at room temperature (Scheme 1).[8] Under the

The Suzuki−Miyaura coupling reaction, which is one of the most efficient methods to form axially chiral biaryls,[9] was selected to evaluate the catalytic ability of these complexes. Thus, the coupling reaction between aryl bromide **3a** and aryl boronic acid **4** was first examined.[8] When the reaction was carried out in DME−$H_2O$ at 60 °C with 5 mol % of **2a** as the catalyst and KOH as the base, the desired coupling product **5a** was obtained in 22% yield and 14% ee with observation of palladium black formation. After various solvents and bases were screened, it turned out that toluene and $Cs_2CO_3$[10] were the optimal combination which delivered the coupling product in 52% yield and 60% ee (entry 1, Table 1). More catalysts were then evaluated (entries 2−8, Table

**Table 1.** Screening Ligands and Optimization Experiments[a]
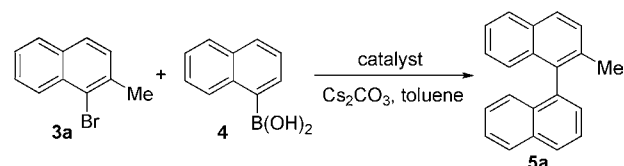


| entry | Pd(II)−diene (mol %) | ligand (mol %) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **2a** (5) | - | 52 | 60 |
| 2 | **2b** (5) | - | 55 | 30 |
| 3 | **2c** (5) | - | 62 | 52 |
| 4 | **2d** (5) | - | 65 | 75 |
| 5 | **2e** (5) | - | 47 | 55 |
| 6 | **2f** (5) | - | 40 | 12 |
| 7 | **2g** (5) | - | 42 | 0 |
| 8 | **2h** (5) | - | 64 | 51 |
| 9 | **2a** (5) | *ent*-**1a** (5) | 45 | 0 |
| 10 | **2d** (5) | **1d** (5) | 67 | 79 |
| 11 | **2d** (5) | **1d** (15) | 70 | 81 |
| 12 | **2d** (5) | **1d** (25) | 70 | 82 |
| 13 | **2d** (3) | **1d** (9) | 62 | 80 |
| 14[d] | **2d** (5) | **1d** (15) | 78 | 90 |

[a] The reaction was carried out with **3** (0.4 mmol, 1 equiv), **4** (0.6 mmol, 1.5 equiv), and $Cs_2CO_3$ (1 mmol, 2.5 equiv) in dry toluene under nitrogen at 80 °C for 0.5 h unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC on a Chiralcel OJ-H Column. [d] The reaction was carried out at 25 °C for 48 h.

**Scheme 1.** Preparation of the Pd(II)−Diene Complex[a]



**1a, 2a**: Ar = Ph    **1b, 2b**: Ar = 4-FPh
**1c, 2c**: Ar = 4-MeOPh    **1d, 2d**: Ar = 3,5-(Me)₂Ph
**1e, 2e**: Ar = 3,5-(MeO)₂Ph    **1f, 2f**: Ar = 3,5-tBuPh
**1g, 2g**: Ar = 1-naphthyl    **1h, 2h**: Ar = 2-naphthyl

[a] Reaction was carried out with diene ligand (0.5 mmol, 1 equiv) and PdCl₂(PhCN)₂ (0.5 mmol, 1 equiv) in benzene (10 mL) at rt overnight.

same conditions, the complexes **2b−h** were also successfully obtained from **1b−h**, respectively.

1). It was found that all the tested catalysts with chiral diene ligands bearing either electron-rich or electron-deficient substituents could catalyze the reaction with similar efficiency, while **2d** gave the best yield as well as ee value (entry 4 in Table 1).

Interestingly, when 5 mol % of catalyst **2a** along with 5 mol % of the corresponding antipode ligand, (*R,R*)-**1a**, was

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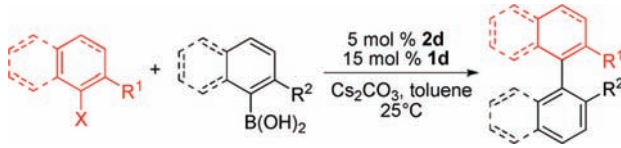(10) Bermejo, A.; Ros, A.; Fernandez, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798.
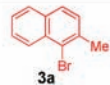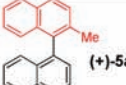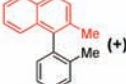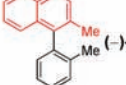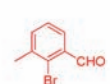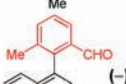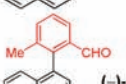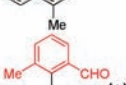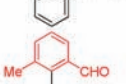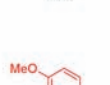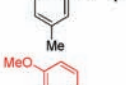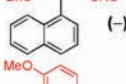
added to the reaction mixture, the racemic product **5a** was obtained (entry 9, Table 1), which indicated that a fast ligand-exchange reaction occurred. It wa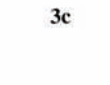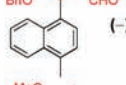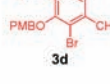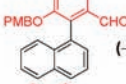s envisioned that the existence of additional free ligand in the reaction system would be favorable for maintaining the catalyst turnover and the enantioselective induction. Thus, various amounts of additional ligands were subsequently evaluated (entries 10−12). We were gratified to find that, with an additional 5 mol % of ligand **1d**, both the yield and ee value were increased (entry 10 vs entry 4). The yields and ee values were further improved with more additional **1d**, and the highest ee reached 82% when 25 mol % of **1d** was added (entry 12). Using 3 mol % of catalyst **2d** with an additional 9 mol % of ligand **1d**, the same level of enantioselectivity (80% ee) could be obtained albeit with diminished isolated yield (entry 13). Gratifyingly, by lowering the temperature from 80 to 25 °C, both the yield and enantioselectivity were enhanced significantly with 78% yield and 90% ee being obtained (entry 14, Table 1).

With the optimal conditions in hand, we next explored the substrate scope. As shown in Table 2, the coupling reaction of arylboronic acids with **3a** gave the corresponding axially chiral biaryls **5b** and **5c** with similar satisfactory results (entries 2 and 3, Table 2). Interestingly, when aryl bromides bearing an *ortho*-formyl group such as **3b−d**, which were used in our previous work on the first nickel-catalyzed Ullmann-type coupling of bisortho-susbtituted arylhalides,[11] were used as substrates, the reactions exhibited excellent isolated yields and good enantioselectivities (entries 4−10). Moreover, palladium blacking out was not observed throughout the whole process. The *para*-methyl group on the aryl boronic acid showed an acceleration effect, and the reaction finished in a shorter time (entries 4 vs 5, 6 vs 7, and 8 vs 9, respectively). Taking advantage of this effect, the reaction proceeded smoothly even at 0 °C without the deterioration of yields and enantioselectivities (12−48 h, entries 3, 5, and 7). It is worth noting that when alkenyl triflate **4e** was used as the substrate, the axially chiral aryl−alkenyl compound **5k** was formed in 72% yield and 48% ee (entry 11).

To gain insight into the nature of the effect of the *ortho*-formyl group and the active catalyst in the reaction, we carried out a spectroscopic investigation that includes in situ IR and X-ray diffraction. We first tried to isolate the oxidative−addition complex of **3b** with **2d** for the X-ray crystallographic studies but did not succeed. Then, the reaction of **3b** with **4** in the presence of a stoichiometric amount of catalyst **2d** was monitored by the in situ IR technique (Figure 1). The kinetic profiles revealed clearly the consumption of **3b** at 1703 cm$^{-1}$ and the formation of **5d** at 1690 cm$^{-1}$. An intermediate species **6** characterized by peak 1666 cm$^{-1}$ (br) disappeared quickly after 1 equiv of **4** was added. This information suggests that the new species **6** is probably the oxidative addition complex of **2b**, and the red-shift of the absorption band (1666 cm$^{-1}$) of the

carbonyl group might be due to a weak interaction of the palladium center with the oxygen atom of the *ortho*-formyl

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**Table 2.** Asymmetric Suzuki−Miyaura Coupling[a]



| | ArX | product | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | 3a | (+)-5a | 48 | 78 | 90 |
| 2 | 3a | (+)-5b | 36 | 90[d] | 84 |
| 3 | 3a | (−)-5c | 48[e] | 77[d] | 87 |
| 4 | 3b | (−)-5d | 12 | 90 | 73 |
| 5 | 3b | (−)-5e | 2 / 12[e] | 99 / 80 | 70 / 81 |
| 6 | 3b | (+)-5f | 12 | 90 | 58 |
| 7 | 3b | (+)-5g | 1.5 / 16[e] | 99 / 97 | 59 / 65 |
| 8 | 3c | (−)-5h | 12 | 93 | 65 |
| 9 | 3c | (−)-5i | 3 | 97 | 69 |
| 10 | 3d | (−)-5j | 24 | 83 | 65 |
| 11 | 3e | (−)-5k | 24 | 72 | 48 |

[a] Conditions: arylbromide (or aryltriflate) (0.2−0.3 mmol, 1.0 equiv), boronic acid (0.3−0.45 mmol, 1.5 equiv), Cs$_2$CO$_3$ (0.5−0.75 mmol, 2.5 equiv), and toluene (1.0−1.5 mL). [b] Isolated yield. [c] Determined by HPLC on chiral stationary phases; see Supporting Information for details. [d] Contains a small amount of impurities (<5%, judged by HPLC and NMR analysis). [e] Reaction was run at 0 °C.
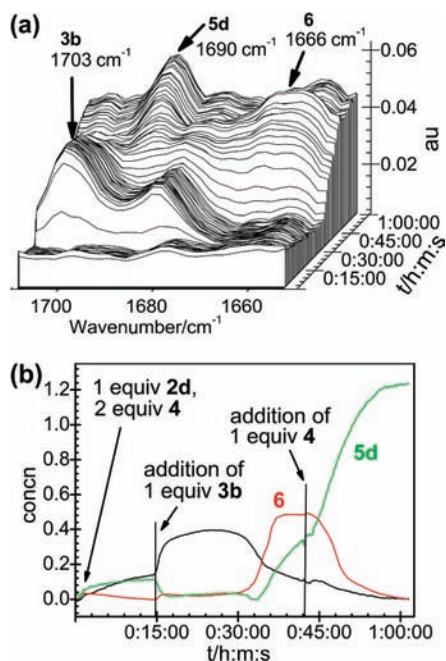
**Figure 1.** (a) 3D-FTIR profiles of the reaction of **3b** with **4** in the presence of stoichiometric amounts of **2d** by stepwise addition. (b) Component profiles for the reaction produced by the iC IR Software.

group.[12] Furthermore, this hypothesis is in agreement with a similar Pd−O interaction in Buchwald's recent publication.[13]

Single-crystal X-ray diffractions of **1a**, **2a**, **2d**, and [RhCl(**1a**)]₂ were conducted, and selected crystal data are shown in Table 3.[14] X-ray analysis of **2a** and **2d** confirms that, similar to [RhCl(**1a**)]₂, two chlorides and two olefin units of the diene ligand are coordinated to the palladium center in a slightly distorted square planar geometry. The bite angles of the bidentate ligands are 86.2° in **2a**, 85.3° in **2d**, and 87.5° in [RhCl(**1a**)]₂, ranging in quite similar level. However, the dihedral angle C6−C5−C1−C2 in [RhCl(**1a**)]₂ is 79.8°, twisted by 27.2° compared with the corresponding value observed in the crystal of free ligand **2a** (107.0°). The dihedral angle in **2a** is 90.8°, twisted by 16.2°. Furthermore, the coordination results in a change in bond length of the C=C bond within the bicyclo[3.3.0]octadiene unit, which lengthened to 1.37 Å and 1.40 Å in **2a** and [RhCl(**1a**)]₂ respectively, compared to 1.32 Å in **1a**. This indicates the metal−olefin bond of palladium−**1a** is weaker than that of

**Table 3.** Selected Crystal Data of **1a**, [RhCl(**1a**)]₂, **2a**, and **2d**
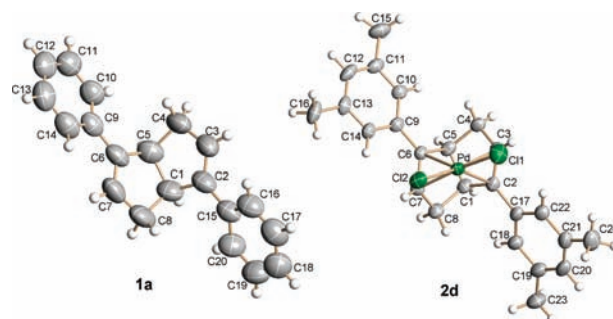


| sample | **1a** | [RhCl(**1a**)]₂ | **2a** | **2d** |
|---|---|---|---|---|
| bite angle[a] | - | 87.5° | 86.2° | 85.3° |
| dihedral angle[b] | 107.0° | 79.8° | 90.8° | 87.6° |
| C=C bond length[c] | 1.32 Å | 1.40 Å | 1.37 Å | 1.38 Å |

[a] Referred to olefin midpoint−M−olefin midpoint angle, M = Pd or Rh. [b] The carbon atom serial number of diene in [RhCl(**1a**)]₂, **2a**, is similar to **1a**. [c] Bond length of the C=C bond within the bicyclo[3.3.0]octadiene units.

rhodium−**1a**.[2b] When the applied ligand **1a** was replaced by **1d**, the observed dihedral angle in the case of **2d** shrank to 87.6°, twisted by 19.4°. Indicating the increased chelating affinity of palladium affords a more favorable conformational complex **2d**.

In conclusion, we have developed an efficient catalytic asymmetric Suzuki−Miyaura coupling reaction to form axially chiral biaryls at room temperature. The excellent yields and good enantioselectivities of chiral biaryls have been obtained through the first atroposelective reaction catalyzed by the palladium−chiral diene complex. The current approach opens a new avenue for the application of chiral diene ligands in palladium-catalyzed asymmetric synthesis.

**Supporting Information Available:** Experimental procedures, characterization data, copies of HPLC and NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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