Enantioselective Synthesis of Axially Chiral Multifunctionalized Biaryls via Asymmetric Suzuki–Miyaura Coupling

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ABSTRACT



Substituted 2-formylarylboronic acids were successfully employed as substrates for asymmetric Suzuki–Miyaura coupling. By virtue of the coupling with dialkoxyphosphinyl substituted naphthyl bromides and 2-nitronaphthalen-1-yl triflouromethanesulfonate, a series of novel multifunctionalized axially chiral biaryls were prepared in 53–97% yields with up to 97% ee using palladium-Cy-MOP as the catalyst. The methodology provides a highly efficient and practical strategy for the synthesis of novel multifunctionalized axially chiral biaryls.

Axially chiral biaryls are important building motifs for the synthesis of natural products, biologically active intermediates, and functional organic materials.¹ Indeed, they are versatile skeletons in many chiral auxiliaries and ligands, particularly the 2,2'-difunctionalized biaryl ligands such as BINOL,² BINAP,³ and MOP-type ligands.⁴ Transition-metal-catalyzed cross-coupling reactions leading to

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biaryl scaffolds have been successful. For instance, the Suzuki–Miyaura coupling reaction is one of the most used protocols for the preparation of achiral biaryls due to its readily available substrates with excellent functional group tolerance.⁵ Nevertheless, efficient chiral catalyst systems for this reaction to acquire axially chiral biaryls are still very limited.⁶ One of the earliest successful examples for the preparation of 2,2'-difunctionalized biaryls via an asymmetric Suzuki–Miyaura coupling reaction was reported by Buchwald in 2000.⁷ Since then, much effort has been devoted toward this challenge, yet only some progress has been achieved in this field.^{8,9} In fact, the organoboron coupling partners were generally limited to 2-alkyl or 2-alkoxy substituted arylboronic acids in these previous works. This severely restricts the application of the coupling

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reaction because the 2-alkyl or 2-alkoxy group in the coupling products hinders further potential functionalizations.

The formyl moiety is a versatile functional group in organic transformation. Synthesis of this type of substrate via asymmetric Suzuki-Mivaura coupling will provide great potential for the development of different kinds of novel functionalized chiral biaryls, which will enrich the synthetic value of this protocol.¹⁰ o-Halogenated aryl aldehydes were first investigated as the substrates for the reaction, but only moderate results were obtained.⁹ Apart from halobenzaldehyde, the nucleophilic 2-formylarylboronic acids can be employed in this reaction. The Iuliano group recently reported an asymmetric coupling of 2-formylphenylboronic acid with 1-bromo-2-methoxynaphthalene, yet only a 33% yield and 27% ee were given.¹¹ Except for this one example, no other literature has been found to adopt such a protocol for the coupling reaction so far. This issue remains significant and challenging in exploring the synthesis of complicated multifunctionalized axially chiral biaryls. Herein we disclose a catalytic system for the preparation of novel axially chiral multifunctionalized biaryls having a phosphonate group or a nitro group and a formyl group at $C_2/C_{2'}$ -positions via a palladium-catalyzed Suzuki-Miyaura reaction. Commercially available 2-formylarylboronic acids, dialkoxyphosphinyl $(P(O)(OR)_2)$ -substituted naphthyl bromides, and trifluoromethanesulfonic acid 2-nitro-napnthalen-1-yl ester were used as the substrates, and electron-rich MOPtype monophosphines L1-7 (Table 1) were employed as the chiral ligands.¹² To the best of our knowledge, this represents the first successful examples for the highly efficient synthesis of these multifunctionalized biaryls.

In order to establish an efficient protocol for the asymmetric Suzuki-Miyaura reaction, we evaluated the efficacy of ligands L1-7. The coupling of diethyl 1-bromo-2naphthylphosphonate (1A) with 2-formyl phenylboronic acid (2a) was selected as the model reaction (Table 1). L2 (Cv-MOP) complexed with palladium was found to be the best choice. With the combination of toluene, K₃PO₄, Pd₂(dba)₃, and L2 (Cy-MOP), the model reaction acquired an astonishing result at 50 °C. The target coupling product **3Aa** was obtained in 93% yield and 96% ee (Table 1, entry 2). In contrast, diphosphine BINAP was virtually ineffective (Table 1, entry 8). When changing the MeO group of L2 into the iPrO (L3) or BnO (L4) group, the corresponding palladium catalysts still showed excellent enantioselectivities, yet the catalytic activities became lower (Table 1, entries 3, 4) and the latter dropped more significantly. No desired product was obtained when L1 was used instead (Table 1, entry 1). These results indicate that the alkoxy groups of these ligands played an important role in the catalytic reaction. While replacing the electron-rich cyclohexyl group linked to the P atom with a phenyl (L5), p-tolyl (L6), or 3,5-xylyl (L7) counterpart, the catalyst activity and enantioselectivity all decreased sharply (Table 1, entries 5-7).

Table 1. Ligand Screening^a



^{*a*} Conditions: **1A** (0.5 mmol), **2a** (1.0 mmol), base (1.5 mmol), ligand (4.8 mol %), Pd (4 mol %), toluene, 50 °C, 72 h. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC. The absolute configuration was determined by X-ray crystallography. ¹³

With L2-Pd₂(dba)₃ as the catalyst,¹⁴ we next explored the substrate scope (Table 2). Using 2-formylphenylboronic acid as the coupling partner, the evalues of products **3Ba** ($\mathbf{R} = \mathbf{M}\mathbf{e}$), **3Ca** ($\mathbf{R} = i\mathbf{P}\mathbf{r}$), and **3 Da** ($\mathbf{R} = \mathbf{P}\mathbf{h}$) (Table 2, entries 2–4) were comparable to that of **3Aa** ($\mathbf{R} = \mathbf{E}\mathbf{t}$, Table 2, entry 1). However, the yields of **3Ca** and **3 Da**

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⁽¹³⁾ For crystal data, see the Supporting Information.

⁽¹⁴⁾ For further optimization experiments of the model reaction, see the Supporting Information.

Table 2. Asymmetric Suzuki–Miyaura Coupling I^a

e

17

18

19

 20^d

1A

1A

1A

1A

2j

2k

2k

21

HO. B'OH HO. B'OH Fr (D)(OR) ₂ 1 2 Fr (CHO Fr (CHO) 1 2 Fr (CHO						
			t		yield	ee
ntry	ArBr	$Ar'B(OH)_2$	(°C)	Ar-Ar'	$(\%)^{b}$	$(\%)^c$
1	1A	2a	50	3Aa	93	96 (R)
2	1 B	2a	50	3Ba	90	95(R)
3	1C	2a	50	3Ca	73	93(R)
4	1D	2a	50	3 Da	77	94(R)
5	1A	2b	50	3Ab	97	97 (-)
6	1A	2c	50	3Ac	96	95(-)
7	1A	2d	50	3Ad	95	96 (-)
8	1A	2e	50	3Ae	91	92(-)
9	1 A	2f	50	3Af	53	86 (-)
10^d	1A	2f	50	3Af	60	86 (-)
11^e	1A	2f	50	3Af	71	87(-)
12	1A	$2\mathbf{g}$	50	3Ag	75	94 (-)
13	1A	2h	50	3Ah	53	95 (-)
14	1 A	2h	80	3Ah	75	93 (-)
15	1 A	2i	50	3Ai	65	92(-)
16	1A	2i	80	3Ai	87	90(-)

^{*a*} Conditions: **1** (1.0 mmol), **2** (2.0 mmol), K_3PO_4 (3.0 mmol), **L2** (4.8 mol %), $Pd_2(dba)_3$ (2 mol %), toluene (6 mL), 48–72 h. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC. The absolute configuration of **3Ba–3Da** was assigned by analogy with **3Aa**. ^{*d*} **L2** (9.6 mol %), $Pd_2(dba)_3$ (4 mol %). ^{*e*} 3 equiv of **2f**, 9.6 mol % of **L2**, and 4 mol % of $Pd_2(dba)_3$ were used.

50

50

80

80

3Aj

3Ak

3Ak

3A1

61

55

79

71

dropped to 73% and 77%, respectively. It demonstrates that the size of the $-P(O)(OR)_2$ groups at the aryl halides influences the catalytic efficiency. The more sterically congested $-P(O)(OR)_2$ group is not favorable for high yields. The Et group as the R group is appropriate for the reaction.

Further experiments showed that different substituted 2-formylphenylboronic acids associating with functional groups reacted with **1A** smoothly, and the corresponding products having complicated multifunctional groups were afforded with 86-97% ee's (most of them $\ge 90\%$ ee) (Table 2, entries 5–20). Coupling of **1A** with 2-formylphenylboronic acids possessing an electron-donating group such as –Me, –OMe, or –OBn at the 4 position provided products **3Ab**, **3Ac**, **3Ad** in excellent yields and ee values (Table 2, entries 5–7, 97\%, 96\%, and 95\% yields; 97\%, 95\%, and 96\% ee's respectively). It indicates that these substitutions positively influenced the catalytic efficiency. For the coupling of 4-F-substituded 2-formylphenylboronic acid **2e** with **1A**, slight decreases in the yield and enantioselectivity were found (Table 2, entry 8, 91% yield

(Table 2, entries 12 and 17). Furthermore, the reaction of 4,5-disubstituted 2-formylphenylboronic acid 2l at 80 °C afforded the coupling product in 71% yield with 94% ee (Table 2, entry 20). 90(-)To test the practicality of the protocol, a scaled-up 92(-)reaction between 1A (5 mmol) and 2a (10 mmol) was 89(-)performed to give 3Aa without erosion in the enantio-94(-)selectivity (96% ee) despite a slight decrease in the yield (90%). By means of single crystallization in hexanes and dichloromethane, crystals of 3Aa were obtained in 80% yield and >99.5% ee.¹³ Functionalized arylphosphonates and their derivatives have been found to possess wide applications in medicinal chemistry¹⁶ and chiral ligands.^{7,8d} The phosphonate group in the coupling products can be easily derivatized to give potential precursors of phosphine ligands. For example, by protecting the formyl group of **3Aa**, followed by a reaction with PhMgBr in DME at 45 °C for 24 h, 4Aa was afforded in 73% overall yield and 99% ee (eq 1).⁷

$$(R)-(-)-3Aa \xrightarrow{P(0)}{P(0)Ph_2} (1)$$

$$> 99.5\% ee \xrightarrow{P(0)Ph_2}{P(0)Ph_2} (1)$$

$$(R)-(-)-4Aa \xrightarrow{R}73\% yield, 99\% ee$$

and 92% ee). Whereas a stronger electron-withdrawing CF_3 was introduced as the substituent at this position (2f),

the yield decreased sharply to 53% due to its easy protodeboronation observed under the alkaline conditions,¹⁵ and the enantioselectivity for the reaction also dropped slightly to 86% (Table 2, entry 9). Through increasing the catalyst loading or the ratio of **2f** vs **1A**, higher yields of **3Af** were obtained successfully (Table 2, entries 10, 11). It is important to note that the reaction of the phenylboronic acids possessing a 5 or 3 substitution pattern with **1A** also afforded the coupling products (**3Ah**, **3Ai**, **3Ak**) in good

enantioselectivites, but only moderate yields were obtained and various amounts of debrominated side products were accompanied at 50 °C (Table 2, entries 13, 15, and 18). When the reaction temperature was increased to 80 °C, delightedly, the target products were afforded in much higher yields with only a slight reduction in ee values (Table 2, entries 14, 16, and 19). The reaction of chloro-substituted 2-formylphenylboronic acids (**2g** and **2j**) with **1A** provided corresponding products (**3Ag** and **3Aj**) with excellent enantioselectivities albeit in relatively lower yields for complicated side reactions

Except for the potential practicability of phosphonate, more important is the versatility of the formyl group in the synthesized chiral biaryls. Further derivation of these compounds provided new types of useful chiral products. For instance (Scheme 1), oxidation of **3Aa** by sodium chlorite afforded **5Aa** in 67% yield. Reduction of **3Aa** by NaBH₄ in EtOH at room temperature gave **6Aa** in nearly quantitative yield. Via a Wittig reaction, **3Aa** was readily converted to **7Aa** in 76% yield. Satisfactorily, no deleterious

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Scheme 1. Transformation of the Formyl Group in 3Aa







^{*a*} Conditions: sulfonate (1.0 mmol), **2** (2.0 mmol), K_3PO_4 (3.0 mmol), **L2** (4.8 mol %), Pd₂(dba)₃ (2 mol %), toluene (6 mL), 50 °C, 48 h. Yields are combined isolated values. Ee values were determined by HPLC.

effect in enantioselectivity was found for all of these transformations.

After successfully preparing the phosphonates and their derivatives, we explored the possibility of replacing the dialkoxyphosphinyl groups in substrate 1. It was found that trifluoromethanesulfonic acid 2-nitro-napnthalen-1-yl ester (8) could also couple with substituted 2-formylaryl-boronic acids efficiently using the same catalyst system (Scheme 2). For example, the reaction of 8 and 2a proceeded at 50 °C to give coupling product 9 in 86% yield and 86% ee. Boronic acids 2b and 2g were also applicable for

this reaction. Higher ee values of the coupling products were achieved when boronic acids **2e**, **2h**, and **2i** were employed (91%, 90%, and 90% ee for **12**, **13**, and **14**, respectively).

In summary, commercially available substituted 2-formylphenylboronic acids were successfully employed as substrates for asymmetric Suzuki–Miyaura coupling. A series of novel multifunctionalized axially chiral biaryls having a phosphonate group or a nitro group and a formyl group at $C_2/C_{2'}$ -positions were successfully prepared in good yields with excellent ee's via the direct coupling reactions catalyzed by the palladium-Cy-MOP complex. This protocol also offers good opportunities to develop other kinds of very important chiral biaryls through further functionalization of the formyl, nitro, and phosphonate groups. Applications of these novel axially chiral biaryls and investigation of a more general procedure for asymmetric Suzuki–Miyaura coupling are currently underway in our laboratory.

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Supporting Information Available. Experimental procedure and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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