ORGANIC LETTERS

2013
Vol. 15, No. 21
5508–5511

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

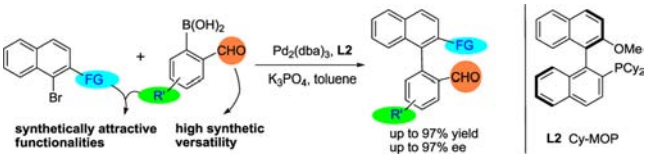
Yougui Zhou,[†] Shouliang Wang,[†] Wenhao Wu,[†] Qing Li,[†] Yuwei He,[†] Yue Zhuang,[†] Lanning Li,[†] Jiyan Pang,[†] Zhongyuan Zhou,[‡] and Liqin Qiu*[,†,§,∥]

School of Chemistry and Chemical Engineering, Guangdong Engineering Research Center of Chiral Drugs, Sun Yat-Sen University, Guangzhou 510275, P. R. China, Huizhou Research Institute of Sun Yat-Sen University, Dayawan, Huizhou, P. R. China, Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, P. R. China, and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China

qiuliqin@mail.sysu.edu.cn

Received September 15, 2013

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 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

[†] Sun Yat-Sen University.
[‡] Huizhou Research Institute of Sun Yat-Sen University.
[§] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.
[∥] The Hong Kong Polytechnic University.

(1) (a) Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581. (b) Bringmann, G.; Price-Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (c) Park, H.; Nandhakumar, R.; Hong, J.; Ham, S.; Chin, J.; Kim, K. M. *Chem.—Eur. J.* **2008**, *14*, 9935. (d) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (e) Furuta, T.; Yamamoto, J.; Kitamura, Y.; Hashimoto, A.; Masu, H.; Azumaya, I.; Kan, T.; Kawabata, T. *J. Org. Chem.* **2010**, *75*, 7010. (f) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563.
(2) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.
(3) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801.
(4) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.
(5) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (c) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059.
(6) For a review, see: Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223.
(7) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

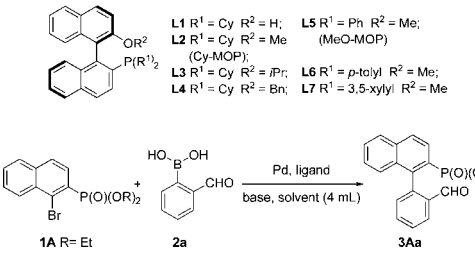
10.1021/ol402666p
Published on Web 10/18/2013

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–Miyaura 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 MOP-type 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-2-naphthylphosphonate (**1A**) with 2-formyl phenylboronic acid (**2a**) was selected as the model reaction (Table 1). **L2** (Cy-MOP) complexed with palladium was found to be the best choice. With the combination of toluene, K_3PO_4, $Pd_2(dba)_3$, 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 *i*PrO (**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]



entry	ligand	Pd	base	yield (%)[b]	ee (%)[c]
1	**L1**	$Pd_2(dba)_3$	K_3PO_4	0	n.d.
2	**L2**	$Pd_2(dba)_3$	K_3PO_4	93	96 (*R*)
3	**L3**	$Pd_2(dba)_3$	K_3PO_4	90	93 (*R*)
4	**L4**	$Pd_2(dba)_3$	K_3PO_4	65	95 (*R*)
5	**L5**	$Pd_2(dba)_3$	K_3PO_4	70	78 (*R*)
6	**L6**	$Pd_2(dba)_3$	K_3PO_4	49	81 (*R*)
7	**L7**	$Pd_2(dba)_3$	K_3PO_4	30	68 (*R*)
8	(*R*)-BINAP	$Pd_2(dba)_3$	K_3PO_4	0	n.d.

[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**-$Pd_2(dba)_3$ as the catalyst,[14] we next explored the substrate scope (Table 2). Using 2-formylphenylboronic acid as the coupling partner, the ee values of products **3Ba** (R = Me), **3Ca** (R = *i*Pr), and **3 Da** (R = Ph) (Table 2, entries 2–4) were comparable to that of **3Aa** (R = Et, Table 2, entry 1). However, the yields of **3Ca** and **3 Da**

(8) For selected references, see: (a) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723. (b) Genov, M.; Almorín, A.; Espinet, P. *Chem.—Eur. J.* **2006**, *12*, 9346. (c) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798. (d) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2078. (e) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278. (f) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8844. (g) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L. *Org. Lett.* **2012**, *14*, 1966. (h) Wu, W.; Wang, S.; Zhou, Y.; He, Y.; Zhuang, Y.; Li, L.; Wan, P.; Wang, L.; Zhou, Z.; Qiu, L. *Adv. Synth. Catal.* **2012**, *354*, 2395. (i) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027. (j) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794. (k) Sun, L.; Dai, W.-M. *Tetrahedron* **2011**, *67*, 9072. (l) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258.

(9) (a) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546. (b) Kamei, T.; Sato, A. H.; Iwasawa, T. *Tetrahedron Lett.* **2011**, *52*, 2638. (c) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 4740.

(10) (a) Zhu, C.; Shi, Y.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1243. (b) Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.; Fernández, I.; Alvarez, E.; Khiar, N. *Org. Lett.* **2009**, *11*, 5130. (c) Chen, W.-W.; Zhao, Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 1072. Axially chiral aromatic aldehydes can also be used in the Betti reaction to prepare potential chiral ligands and complicated compounds: (d) Cardellicchio, C.; Capozzi, M. A. M.; Naso, F. *Tetrahedron: Asymmetry* **2010**, *21*, 507.

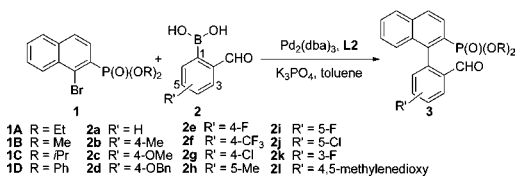
(11) Jumde, V. R.; Iuliano, A. *Tetrahedron: Asymmetry* **2011**, *22*, 2151.

(12) **L1**–**7** were prepared according to literature procedures: Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293.

(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]



entry	ArBr	Ar′B(OH)$_2$	t (°C)	Ar–Ar′	yield (%)[b]	ee (%)[c]
1	**1A**	**2a**	50	**3Aa**	93	96 (*R*)
2	**1B**	**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	**1A**	**2f**	50	**3Af**	53	86 (–)
10[d]	**1A**	**2f**	50	**3Af**	60	86 (–)
11[e]	**1A**	**2f**	50	**3Af**	71	87 (–)
12	**1A**	**2g**	50	**3Ag**	75	94 (–)
13	**1A**	**2h**	50	**3Ah**	53	95 (–)
14	**1A**	**2h**	80	**3Ah**	75	93 (–)
15	**1A**	**2i**	50	**3Ai**	65	92 (–)
16	**1A**	**2i**	80	**3Ai**	87	90 (–)
17	**1A**	**2j**	50	**3Aj**	61	90 (–)
18	**1A**	**2k**	50	**3Ak**	55	92 (–)
19	**1A**	**2k**	80	**3Ak**	79	89 (–)
20[d]	**1A**	**2l**	80	**3Al**	71	94 (–)

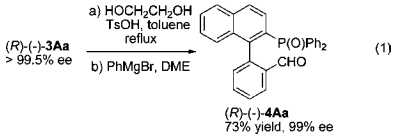
[a] Conditions: **1** (1.0 mmol), **2** (2.0 mmol), K_3PO_4 (3.0 mmol), **L2** (4.8 mol %), $Pd_2(dba)_3$ (2 mol %), toluene (6 mL), 48–72 h. [b] Isolated yield. [c] Determined by HPLC. The absolute configuration of **3Ba**–**3Da** was assigned by analogy with **3Aa**. [d] **L2** (9.6 mol %), $Pd_2(dba)_3$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

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 ≥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 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 (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).

To test the practicality of the protocol, a scaled-up reaction between **1A** (5 mmol) and **2a** (10 mmol) was performed to give **3Aa** without erosion in the enantioselectivity (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 chemistry[16] 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]



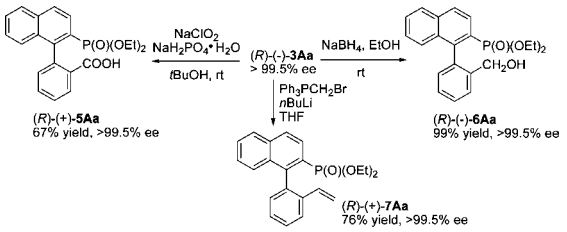
(1)

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 $NaBH_4$ 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

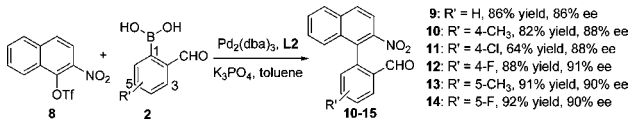
(15) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials* (Vol.1 and 2), 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 12–15.

(16) For reviews, see: (a) Johnson, T. O.; Ermolieff, J.; Jirousek, M. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 696. (b) Nagarajan, R.; Pratt, R. F. *Biochemistry* **2004**, *43*, 9664.

Scheme 1. Transformation of the Formyl Group in **3Aa**



Scheme 2. Asymmetric Suzuki–Miyaura Coupling II[a]



[a] Conditions: sulfonate (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), 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-formylarylboronic 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.

Acknowledgment. We are grateful for financial support from the National Natural Science Foundation of China (NSFC) (20972196, 21272283), Doctoral Fund of Ministry of Education of China (RFDP) (200805580009), Guangdong Provincial Natural Science Foundation (S2011010001305), and Dayawan District Science and Technology Program (201202002). We also wish to thank Prof. Albert S. C. Chan (Hong Kong Baptist University, HK, China) for his valuable discussions.

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.

The authors declare no competing financial interest.