

# watthe blo unications

### Synthetic Communications An International Journal for Rapid Communication of Synthetic Organic

Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

# Synthesis of Symmetrical Terphenyl Derivatives by PdCl<sub>2</sub>-Catalyzed Suzuki-Miyaura Reaction of Dibromobenzene Using 3-(Diphenylphosphino)propanoic Acid as a Ligand

Ningning Gu, Yashuai Liu, Ping Liu, Xiaowei Ma & Yan Liu

To cite this article: Ningning Gu, Yashuai Liu, Ping Liu, Xiaowei Ma & Yan Liu (2015): Synthesis of Symmetrical Terphenyl Derivatives by PdCl<sub>2</sub>-Catalyzed Suzuki-Miyaura Reaction of Dibromobenzene Using 3-(Diphenylphosphino)propanoic Acid as a Ligand, Synthetic Communications, DOI: 10.1080/00397911.2015.1126606

To link to this article: http://dx.doi.org/10.1080/00397911.2015.1126606



View supplementary material 🖸

đ	1	ſ	h	
Е			П	
Н	Η	Н	н	
E			Н	

Accepted author version posted online: 02 Dec 2015.



🕼 Submit your article to this journal 🗗

Article views: 4

$\mathbf{O}$

View related articles 🗹



View Crossmark data 🗹

Full Terms & Conditions of access and use can be found at http://www.tandfonline.com/action/journalInformation?journalCode=lsyc20

#### Synthesis of Symmetrical Terphenyl Derivatives by PdCl<sub>2</sub>-Catalyzed Suzuki-Miyaura Reaction of Dibromobenzene Using 3-(diphenylphosphino)propanoic Acid as a Ligand

Ningning Gu<sup>1</sup>, Yashuai Liu<sup>1</sup>, Ping Liu<sup>1</sup>, Xiaowei Ma<sup>1</sup>, Yan Liu<sup>1</sup>

<sup>1</sup>School of Chemistry and Chemical Engineering/Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, P. R. China

Corresponding to Ping Liu, School of Chemistry and Chemical Engineering / Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi 832003, China. E-mail: liuping1979112@aliyun.com

#### Abstract

A simple and efficient catalytic system for PdCl<sub>2</sub> catalyzing the Suzuki-Miyaura reaction

of dibromobenzene and arylboronic acid has been developed by using 3-

(diphenylphosphino)propanoic acid as a ligand in DMSO at 100 °C. Using this method, a

series of symmetrical terphenyl derivatives were obtained with remarkably high yields up

to 93%.



**KEYWORDS:** Terphenyls, Synthesis, P,O ligand, Palladium, Catalysis, Suzuki-Miyaura reaction

#### **INTRODUCTION**

As an important structural motif, terphenyls can be found in a variety of natural products<sup>[1]</sup> or as building blocks in different applications in medicinal chemistry <sup>[2-7]</sup> and materials science <sup>[8-15]</sup>. Most notably, this is due to diverse biological activities and

unique optical and electronic properties <sup>[16, 17]</sup>. Thus, the development of convenient and efficient methods for the synthesis of such compounds has therefore attracted considerable attention. The general methods by which substituted terphenyls have been obtained can be classified into four individual groups: (i) free-radical substitution of an aromatic ring, (ii) Ullmann and related reactions, (iii) additions to dienes, and (iv) condensation reactions of quinones<sup>[18]</sup>. However, this series of synthetic methods offers limited applications due to a narrow substrate range that can be employed, the need for harsh reaction conditions, long reaction times and particularly low yields obtained. Recently, transition metal catalyzed coupling reactions proved to be the most practical and versatile methods for the production of symmetrical and unsymmetrical o-, m- and pterphenyls<sup>[19]</sup>. In particular, the palladium-catalyzed Suzuki–Miyaura reaction has become one of the most important and efficient synthetic technique for the production of polyaryls (biaryls, teraryls, etc.). This is most notably due to the facts that aryl precursors are widely available, easy to handle, and most functional groups can be accommodated by these systems<sup>[20]</sup>. Related to previously published work by our group <sup>[21]</sup>, in this article we describe a simple, yet practical synthesis of symmetrical terphenyls by employing Suzuki-Miyaura reactions. This strategy is believed to provide a much broader range of synthetic applications in academia and industry.

#### **RESULTS AND DISCUSSION**

Our synthetic efforts started with 1,4-dibromobenzene and phenylboronic acid as model substrates for the optimization of reaction conditions, including different palladium sources, bases, solvents and ligands. The results for this are summarized in Table 1.

Several palladium catalysts (2 mol%) such as Pd(OH)<sub>2</sub>, Pd(OAc)<sub>2</sub>, and PdCl<sub>2</sub> were tested by using NaOH as the base in DMSO (2 mL) at 100 °C for 12 h. PdCl<sub>2</sub> was found to be the most promising species (Table 1, Entries 1–3). A variety of different bases have been evaluated and K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O turned out to be the best choice in terms of isolated yields (Table 1, Entries 4–6). Moreover, the use of toluene as well as DMF was found to be superior to other solvents such as 1,4-dioxane and the coupling products were obtained in yields of 87% and 86%, respectively(Table 1, Entries 7–9). Among the ligands used, 3-(diphenylphosphino)propanoic acid (ligand **2**) was found to be the preferred ligand for this catalysis reaction, resulting in the formation of the desired product in 91% isolated yield (Table 1, Entry 11). Remarkably, even when the catalyst loading was decreased from 2 mol% to 1 mol%, the corresponding product was still obtained in 93% yield (Table 1, Entry 12). Finally, the combination of PdCl<sub>2</sub> (1 mol%)/ligand **2** (2 mol%), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (4 equiv.) at 100 °C for 12 h in DMSO (2 ml) was found to be the most efficient reaction conditions.

In general, most of arylboronic acids used readily reacted with 1, 4-dibromobenzene and the desired products were obtained in good to excellent yields (Table 2). The coupling reactions between arylboronic acids containing electron-donating groups such as  $4-C_3H_7$ ,  $4-C_5H_{11}$ , and 1,4-dibromobenzene produced terphenyls in yields of 94% and 90%, respectively (Table 2, Entries 1 and 2). Arylboronic acid species bearing electronwithdrawing moieties reacted with 1,4-dibromobenzene, such as (4-fluorophenyl)boronic acid, (4-(trifluoromethyl)phenyl)boronic acid and (3,4,5-trifluorophenyl)boronic acid. Good yields were obtained for these reactions at similar reaction conditions (Table 2, Entries 3-5). Furthermore, the substrate bearing carbonyl groups, such as (4-

formylphenyl)boronic acid, also resulted in a coupling reaction with 1,4-dibromobenzene to afford the desired product in 75% yield (Table 2, Entry 6). When m-tolylboronic acid was used as the coupling partner, a particularly high yield of 95% was obtained (Table 2, Entry 7). Notably, the sterically demanding ortho substituents, such as o-tolylboronic acid, did not impair the coupling reaction and resulted in the formation of the product in 95% yield (Table 2, Entry 8). To further ascertain the scope of this methodology, 1,2dibromobenzene and 1,3-dibromobenzene were employed. In contrast to 1,4dibromobenzene, when 1,2-dibromobenzene was subjected to react with various arylboronic acids, the target products were obtained in considerably lower yields (Table 2, Entries 9-12). This is most likely due to the steric hindrance of intermediates formed, namely derivatives of 2-bromo-1,1'-biphenyl. Similarly, the reactions of 1,3dibromobenzene with *o*-tolylboronic acid and (4-propylphenyl)boronic acid resulted in the formation of the corresponding products in 76% and 39% yields, respectively (Table 2, Entries 13 and 14).

Moreover, a gram-scale synthesis was performed to substantiate potential practical applications of this catalytic system. Fortunately, the reaction was performed using 5 mmol of 1,4-dibromobenzene and 6 mmol (4-propylphenyl)boronic acid, and proceeded in a remarkably high 95% yield resulting in the production of 1.50 g of the desired product **3b** (**Scheme 1**).

#### **EXPERIMENTAL SECTION**

#### **Materials And Instruments**

Reagents were of analytical grade quality, purchased commercially and used as received. All the reactions were carried out under air using magnetic stirring unless otherwise noted. <sup>1</sup>H NMR spectral data were recorded on a Bruker DPX–400 spectrometer using TMS as internal standard and CDCl<sub>3</sub> as solvent. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model. Column chromatography was performed with silica gel (200-300 mesh) purchased from Qingdao Haiyang Chemical Co., Ltd. Ligands **1** and **2** were synthesized by the literature methods (**Figure 1**).[22]

## General Procedure For The Synthesis Of Symmetrical Terphenyl Derivatives (3a-30)

The Schlenk tube (5 mL) equipped with a stir bar was charged with PdCl<sub>2</sub> (1.0 mol%), Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>2</sub>COOH (2.0 mol%), and K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O (4.0 equiv.), then 1,4-dibromobenzene (0.5 mmol), phenylboronic acid (1.20 mmol), and DMSO (2.0 ml) were added, and the mixture was stirred at 100 °C until the substrate was completely consumed. After cooling to room temperature, the solution was quenched with water and extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtrated and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with PE as the eluent to obtain the desired products.

#### 4,4"-Dipropyl-1,1':3',1"-Terphenyl(30)

white solid ,Isolated yield = 39%, Mp. 69.6-70.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 7.79 (td, J = 1.8, 0.5 Hz, 1H), 7.58–7.52 (m, 6H), 7.45–7.20 (m, 5H), 2.67–2.61

(m, 4H), 1.69 (dt, J = 8.9, 7.5 Hz, 4H), 0.98 (t, J = 7.3 Hz, 6H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) = 141.9, 141.7, 138.6, 129.1, 128.9, 127.1, 125.8, 125.7, 37.7, 24.6, 13.9. HRMS (EI): m/z calcd for C<sub>24</sub>H<sub>26</sub> [M]<sup>+</sup> 314.2035, found 314.2031.

#### CONCLUSION

In summary, we have established a simple, yet efficient catalytic system for 3-(diphenylphosphino)propanoic acid/PdCl<sub>2</sub> catalyzing the Suzuki-Miyaura reaction of dibromobenzene and arylboronic acid for the synthesis of terphenyl compounds in good to excellent yields. Experimental data confirms that a broad range of different functional groups can be used in this type of catalytic reaction. Furthermore, even substrates with sterically hindered groups resulted in sufficient product formation at optimized reaction conditions. The elegant approach presented here, as well as the option for efficient large scale preparation, provide a convenient and more practical approach for a variety of different future applications in academia or industry.

#### **CONFLICT OF INTEREST**

We state that none of the authors have any conflict of interest in the context of this communication.

#### SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

#### ACKNOWLEDGMENT

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (No. 21563025, No. 21463022), the Doctor Foundation of Xinjiang Bingtuan (No. 2012BB010), and Shihezi University Training Programme for Distinguished Youth Scholars (No.2014ZRKXJQ05).

#### REFERENCES

Sawayama, Y.; Tsujimoto, T.; Sugino, K.; Nishikawa, T.; Isobe, M.; Kawagishi, H.
 Syntheses of naturally occurring terphenyls and related compounds. *Biosci. Biotechnol. Biochem.* 2006, 70, 2998.

2. Cali, V.; Spatafora, C.; Tringali, C. Sarcodonins and sarcoviolins, bioactive polyhydroxy-p-terphenyl pyrazinediol dioxide conjugates from fruiting bodies of the basidiomycete Sarcodon leucopus. *Eur. J. Org. Chem.* **2004**, 592.

 Orner, B.P.; Ernst, J.T.; Hamilton, A.D. Toward proteomimetics: Terphenyl derivatives as structural and functional mimics of extended regions of an alpha-helix. *J. Am. Chem. Soc.* 2001, *123*, 5382.

4. Roberti, M.; Pizzirani, D.; Recanatini, M.; Simoni, D.; Grimaudo, S.; Cristina, D.;
Abbadessa, V.; Gebbia, N.; Tolomeo, M. Identification of a terphenyl derivative that
blocks the cell cycle in the G(0)-G(1) phase and induces differentiation in leukemia cells. *J. Med. Chem.* 2006, 49, 3012.

5. Simoni, D.; Giannini, G.; Baraldi, P.G.; Romagnoli, R.; Roberti, M.; Rondanin, R.; Baruchello, R.; Grisolia, G.; Rossi, M.; Mirizzi, D. A convenient synthesis of unsymmetrically substituted terphenyls of biologically active stilbenes via a double Suzuki cross-coupling protocol. *Tetrahedron Lett.* **2003**, *44*, 3005. 6. Simoni, D.; Giannini, G.; Roberti, M.; Rondanin, R.; Baruchello, R.; Rossi, M.;

Grisolia, G.; Invidiata, F.P.; Aiello, S.; Marino, S. Studies on the apoptotic activity of natural and synthetic retinoids: Discovery of a new class of synthetic terphenyls that potently support cell growth and inhibit apoptosis in neuronal and HL-60 cells. *J. Med. Chem.* **2005**, *48*, 4293.

7. Simoni, D.; Rondanin, R.; Baruchello, R.; Rizzi, M.; Grisolia, G.; Eleopra, M.;
Grimaudo, S.; Cristina, A.D.; Pipitone, M.R.; Bongiorno, M.R.; Arico, M.; Invidiata,
F.P.; Tolomeo, M. Novel terphenyls and 3,5-diaryl isoxazole derivatives endowed with growth supporting and antiapoptotic properties. *J. Med. Chem.* 2008, *51*, 4796.

8. Yashima, E.; Maeda, K.; Furusho, Y. Single- and Double-Stranded Helical Polymers: Synthesis, Structures, and Functions. *Acc. Chem. Res.* **2008**, *41*, 1166.

9. Udayakumar, B.; Schuster, G.B. Photoisomerization of 2,2"-ethano-bridged mterphenyl derivatives: ring constraint activates an unreactive chromophore. *J. Org. Chem.***1992**, *57*, 348.

10. Wright, R.S.; Vinod, T.K. Synthesis of m-terphenyl derivatives for potential use as tectons in crystal engineering. *Tetrahedron Lett.* **2003**, *44*, 7129.

11. Liao, H.R.; Lin, Y.J.; Chou, Y.M.; Luo, F.T.; Wang, B.C. Theoretical study of optical and electronic properties of *p*-terphenyls containing cyano substituents as promising light-emitting materials. *J. Lumin.* **2008**, *128*, 1373.

12. Yu, G.; Gao, J.; Hummelen, J.C.; Wudl, F.; Heeger, A.J. Polymer photovoltaic cells-enhanced efficiencies via a network of internal donor-acceptor heterojunctions. *Science*.
1995, 270, 1789.

13. Garnier, F.; Hajlaoui, R.; Yassar, A.; Srivastava, P. All-polymer field-effect transistor realized by printing techniques. *Science*. **1994**, *265*, 1684.

14. Hide, F.; DÍaz-GarcÍa, M.A.; Schwartz, B.J.; Heeger, A.J. New Developments in the Photonic Applications of Conjugated Polymers. *Acc. Chem. Res.* **1997**, *30*, 430.

15. Maya, F.; Tour, J.M. Synthesis of terphenyl oligomers as molecular electronic device candidates. *Tetrahedron.* **2004**, *60*, 81.

16. Todd, M.H.; Balasubramanian, S.; Abell, C. Studies on the Synthesis,
Characterisation and Reactivity of Aromatic Diboronic Acids. *Tetrahedron Lett.* 1997, 38, 6781.

17. Corsico, E.F.; Rossi, R.A. Synthesis of Mono-, Di-, and Tri-phenyl Arenes by
Sequential Photostimulated S<sub>RN</sub>1 and Pd(0)-Catalyzed Cross Coupling Reactions on Aryl
Halides. *ChemInform.* 2000, 31.

 Liu, J.K. Natural Terphenyls: Developments since 1877. *Chem. Rev.* 2006, *106*, 2209.
 Adrio, L.A.; Míguez, J.M.A.; Hii, K.K. Synthesis of Terphenyls. *Org. Prep. Proced. Int.* 2009, *41*, 331.

20. Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457.

21. (a) Liu, Y.; Ma, X.; Xie, J.; Liu, P.; Dai, B.; He, R. Metallomicelles of palladium(II) complexes as efficient catalysts for the Suzuki-Miyaura reaction in neat water. *Appl. Organomet. Chem.* 2013, 27, 494; (b) Ma, X.; Liu, Y.; Liu, P.; Xie, J.; Dai, B.; Liu, Z. Palladium-catalyzed direct arylation of polyfluoroarene and facile synthesis of liquid crystal compounds. *Appl. Organomet. Chem.* 2014, 28, 180; (c) Ma, X.; Liu, Y.; Liu, P.; Xie, J.; Dai, B.; Liu, P.; Xie, J.; Dai, B.; Liu, Z.

vinylbiphenyl derivatives. *Appl. Organomet. Chem.* 2013, 27, 707; (d) Liu, P.; Zhang, W.;
He, R. Preparation and catalytic properties of bis(imino)pyridine palladium(II) complexes as efficient catalysts for Suzuki cross-coupling reaction in water. *Appl. Organomet. Chem.* 2009, 23, 135; (e) Liu, P.; Zhou, L.; Li, X.; He, R. Bis(imino)pyridine palladium(II) complexes: Synthesis, structure and catalytic activity. *J. Organomet. Chem.* 2009, *694*, 2290. (f) P. Liu, M. Yan, R. He. Bis(imino)pyridine palladium(II) complexes as efficient catalysts for the Suzuki-Miyaura reaction in water. *Appl. Organomet. Chem.* 2010, *24*, 131.

22. Liu, Y.S.; Liu, Y.; Ma, X.W.; Liu, P.; Xie, J.W.; Dai, B. 3-

(Diphenylphosphino)propanoic acid: an efficient ligand for the Cu-catalyzed *N*-arylation of imidazoles and 1*H*-pyrazole with aryl halides. *Chin. Chem. Lett.* **2014**, *25*, 775.



	B(OH) <sub>2</sub> + Br	[Pd] catalyst base (4 equiv.)		
	1a 2a	solvent (2 mL) [ 100 °C, 12 h	3a	
Entry	Catalyst	Solvent	Base	Yield/% <sup>b</sup>
1	Pd(OH) <sub>2</sub> (2%)	DMSO	NaOH	trace
2	Pd(OAc) <sub>2</sub> (2%)	DMSO	NaOH	11
3	PdCl <sub>2</sub> (2%)	DMSO	NaOH	82
4	$PdCl_2(2\%)$	DMSO	Cs <sub>2</sub> CO <sub>3</sub>	20
5	PdCl <sub>2</sub> (2%)	DMSO	NEt <sub>3</sub>	trace
6	PdCl <sub>2</sub> (2%)	DMSO	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	87
7	PdCl <sub>2</sub> (2%)	1,4-dioxane	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	33
8	PdCl <sub>2</sub> (2%)	toluene	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	87
9	PdCl <sub>2</sub> (2%)	DMF	$K_3PO_4 \cdot H_2O$	86
10 <sup>c</sup>	PdCl <sub>2</sub> (2%)/Ligand <b>1</b> (4%)	DMSO	$K_3PO_4 \cdot H_2O$	80
11	PdCl <sub>2</sub> (2%)/Ligand <b>2</b> (4%)	DMSO	$K_3PO_4 \cdot H_2O$	91
12	PdCl <sub>2</sub> (1%)/Ligand <b>2</b> (2%)	DMSO	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O	93

<sup>a</sup>Reaction conditions: 1,4-dibromobenzene 0.5 mmol, phenylboronic acid 1.2 mmol, base 2.0 mmol, solvent 2 mL, 100 °C, 12 h.

<sup>b</sup> Isolated yields.

°80 °C.

R B(OH)<sub>2</sub> 1 mol%[Pd] Br base (4 equiv.) DMSO (2 mL) 3 2 100 °C 2a: 1,4-dibromobenzene 2b: 1,2-dibromobenzene 2c: 1,3-dibromobenzene 2 Yield(%) Product Entry **R/1** 94 1  $4 - C_3 H_7 / 1b$ 2a 3b 2  $4 - C_5 H_{11} / 1c$ 2a 3c 90 3 4-F/1d 3d 90 2a 4 4-CF<sub>3</sub>/1e 2a 3e 85 5 3,4,5- trifloro/1f 2a 3f 76 4-CHO/1g 6 2a 3g 75 7 3-CH<sub>3</sub>/1h 2a 3h 95 2-CH<sub>3</sub>/1i 8 3i 95 2a 9 H/**1**a **2**b 3j 43 10 **1e 2**b 3k 60 31 11 1g **2**b 58 12 1d **2**b 3m 57 13 1i **2c** 3n 76 14 1b **2c** 30 39

Table 2. Suzuki-Miyaura reactions of dibromoarenes catalyzed by palladium<sup>a</sup>

<sup>a</sup>Reaction conditions: arylbromide 0.5 mmol, arylboronic acid 1.2 mmol,  $PdCl_2$  1% mol, ligand **2** 2% mol,  $K_3PO_4$ ·H<sub>2</sub>O 2.0 mmol, DMSO 2 mL, 100 °C, 12 h.

<sup>b</sup> Isolated yields





Figure 1. Ligands used in this study

