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# Heterogeneous Pd/C-catalyzed, ligand free Suzuki–Miyaura coupling reaction furnishes new *p*-terphenyl derivatives

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#### ABSTRACT

A series of new *para*-terphenyls derivatives have been efficiently synthesized by a ligand-free heterogeneous Pd/C-catalyzed two-fold Suzuki–Miyaura coupling reaction. Methyl 5-bromo-2-iodo-benzoate was selected to react with a variety of different aryl boronic acids (**2a-i**). Nine new *p*-terphenyl derivatives (**3a-i**) were prepared and the structures were confirmed by several analytical techniques including infrared, spectroscopy, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, mass spectrometry, and in the case of compound **3 b**, by X-ray diffraction method. The new derivatives were obtained in very good yields (78–91%). This synthetic facile route is envisioned to improve the preparation of *p*-terphenyl-based natural products.

#### **ARTICLE HISTORY**

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#### **KEYWORDS**

Ligand-free catalysis; aryl boronic acids; Suzuki–Miyaura coupling reaction; Pd/C; heterogeneous catalysis



#### 1. Introduction

Terphenyls are aromatic compounds comprising of central benzene ring substituted with two phenyl rings and majority of them are isolated from microorganisms and

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Figure 1. Reported natural terphenyls.

mushrooms (Sawayama et al. 2006). Among natural terphenyls, *p*-terphenyl and *m*-terphenyl analogs were reported in details, while *o*-terphenyls are unknown (Liu 2006). The *p*-terphenyl skeleton has been described as a small molecule  $\alpha$ -helix mimic of proteins (Kazi et al. 2018). The natural and synthetic terphenyl analogs have demonstrated interesting biological properties such as anti-thrombotic, neuro-protective, immuno-suppressant, anti-coagulant, anti-microbial, and neuroprotective (Taylor and Felpin 2007; Kazi et al. 2018). The natural products with the *p*-terphenyl backbone viz., vialinin A and thelephantin O (Figure 1) possess significant cytotoxic effects towards HepG2 and Caco2 cells and non-toxic to normal human cells (Kazi et al. 2018). The *p*-terphenyl compound sarcodonin (Figure 1) has displayed remarkable cytotoxicity towards MCF-7 and SF-268 cells (Calì et al. 2004).

The Suzuki-Miyaura (SM) cross-coupling (Miyaura et al. 1979) has witnessed exceptional attention in the past four decades by academia (Miyaura and Suzuki 1995) and industry (Corbet and Mignani 2006). Initially, palladium complexes along with phosphine ligands were used, but later, highly effective ligands were discovered (Jansa et al. 2017). There are some drawbacks for homogeneous catalysis, such as contamination of the product, sensitivity, cost and sometimes unavailability of the ligands (Taylor and Felpin 2007). Heterogeneous catalysis using Pd/C, without any ligand conditions, is an inexpensive and practical source of palladium, proved to be a perfect alternative method (Yin and Liebscher 2007). The utilization of iterative double-Suzuki-Miyaura coupling reactions (Sinclair and Sherburn 2005; Taylor and Felpin 2007; Beaumard et al. 2009; Salomone et al. 2011; Al-Zoubi et al. 2015; Zhang et al. 2016; Tsypysheva et al. 2019) for a "one pot" preparation of asymmetric *p*-terphenyl



(Target Terphenyl compounds)

Scheme 1. Synthesis of target terphenyl compounds (3a-i). <sup>a</sup>Reaction conditions: (i) 1 (1.0 equiv), 2a-i (2.2 equiv), Pd/C (10 mol %), K<sub>2</sub>CO<sub>3</sub> (6.0 equiv), CH<sub>3</sub>CN, 80 <sup>°</sup>C, 8 h.

compounds is unknown. Recently, Kazi et al. (2018) reported a one pot ligand free preparation of p-terphenyls using a homogeneous palladium, [Pd (OAc)<sub>2</sub>].

In the present study, for the first time, we have investigated the preparation of new *p*-terphenyls using a Pd/C for heterogeneous catalysis. We used ethyl 5-bromo-2-iodobenzoate as starting materials for the synthesis of new *p*-terphenyls. The differences in the reactivity between the C-1 and C-4 positions (iodine and bromine) of 5-bromo-2-iodobenzoate (*ortho* and *meta* to the CO<sub>2</sub>Me group respectively) have been utilized to allow a successive introduction of two aryl groups in a highly convergent and flexible manner.

#### 2. Results and discussion

#### 2.1. Synthesis of terphenyls (3a-i)

Initially, we explored the effect of the reaction temperature on the cross-coupling of methyl 5-bromo-2-iodobenzoate (1) with a simple phenyl boronic acid (**2a**). We found that, at room temperature, the product was not observed even stirring for 12 h (Table S1, entry 10). The optimum reaction condition was acetonitrile, 6 eq. of  $K_2CO_3$  and 10 mol% of Pd/C (Table S1, entry 9). When acetonitrile was replaced with DMF, the yield dropped to 68%. Low yields were obtained (entry 3 and 7) when DMF and DMSO were used as solvents

We investigated a diverse range of combinations including Pd/C/K<sub>2</sub>CO<sub>3</sub>/toluene (Table S1, entry 1), Pd/C/Na<sub>2</sub>CO<sub>3</sub>/THF (Table S1, entry 2), Pd/C/Et<sub>3</sub>N/1,4-dioxane (Table S1, entry 5), Pd/C/K<sub>2</sub>CO<sub>3</sub>/THF (Table S1, entry 4). The results proved to be unsatisfactory (yields  $\leq$  20%). On the other hand, the yields were improved using Pd/C/Na<sub>2</sub>CO<sub>3</sub>/DMSO (yield: 36%; Table S1, entry 3), Pd/C/Et<sub>3</sub>N/CH<sub>3</sub>CN (yield: 36%; Table S1, entry 6), Pd/C/Cs<sub>2</sub>CO<sub>3</sub>/CH<sub>3</sub>CN (yield: 51%; Table S1, entry 8), and Pd/C/KF/CH<sub>3</sub>CN (yield: 38%; Table S1, entry 11). Furthermore, the 5 mol% Pd (OAc)<sub>2</sub> resulted in lower yields (20% (Table S1, entry 13). When Pd (OAc)<sub>2</sub> was increased to 10 mol % in same reaction system, an increase in yield (48%) was observed (Table S1, entry 14).

Very good yields were obtained using the optimised reaction conditions (78-91%) (Scheme 1, Table S2). Both electron donating (-OMe, -Me) and electron withdrawing (-NO<sub>2</sub>, -CF<sub>3</sub>, -F, -Cl) groups attached to the aromatic ring of boronic acid are compatible with the reaction conditions. Interestingly, the electron donating groups in the *ortho* (Table S2, entry 5) and the *para* (Table S2, entries 2 and 3) positions exhibited

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better reactivity when compared to the electron-withdrawing groups (Table S2, entries 4, 6–9). The highest yield (91%) was obtained with an electron donating group viz., methyl at the *para* position (Table S2, entry 2).

The chemical structures of terphenyl compounds (**3a-i**, target compounds) were confirmed by spectroscopic (<sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>19</sup>F NMR, IR and ESI-MS) analysis. The single crystals of **3b** were grown from slow evaporation of  $CH_2CI_2$  solution. The structure of compound **3b** was confirmed by X-ray diffraction method (Figure S1).

# 3. Conclusion

A simple and highly efficient Suzuki–Miyaura double coupling reaction for the synthesis of *p*-terphenyls has been developed, which involves the reactions of methyl 5-bromo-2-iodobenzoate with a variety of aryl boronic acids at 80 °C in the presence of Pd/C catalyst. The present methodology employs a ligand free Pd/C heterogeneous catalyst and an eco-friendly process for the Suzuki–Miyaura double coupling reaction. The operational simplicity, a ligand free protocol and excellent yields are the notable advantages of the present method. Applications of these useful coupling products are under investigation in our laboratory.

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### **Disclosure statement**

No potential conflict of interest was reported by the author(s).

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