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**Picolinamide modified β-cyclodextrin/Pd (II) complex: a supramolecular catalyst for Suzuki-Miyaura coupling of aryl, benzyl and allyl halides with arylboronic acids in water** 

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# Highlights

- A novel series of supramolecular catalysts were prepared and characterized by NMR, FT-IR, TEM, XRD, TGA, and XPS.
- The picolinamide-modified β-cyclodextrin/Pd(II) complex showed very efficient catalytic activity for Suzuki-Miyaura coupling of aryl, benzyl, and allyl halides with arylboronic acids in an environmentally benign aqueous solution.
- A proposed mechanism of the Pd(II)/Pd(IV) catalytic cycle was explored and calculated by *ab initio* QM/MM methods.
- This hydrosoluble catalyst can be reused several times without a significant loss of activity.

#### Abstract

Novel supramolecular catalysts for Suzuki-Miyaura coupling were prepared and characterized by NMR, FT-IR, TEM, XRD, TGA, and XPS. The resulting picolinamide-modified  $\beta$ -cyclodextrin/Pd(II) complex (Pd(II)@PCA- $\beta$ -CD) showed very efficient catalytic activity for Suzuki-Miyaura coupling of aryl, benzyl, and allyl halides with arylboronic acids in an environmentally benign aqueous solution. Various organic halides including chlorides can produce good to excellent yields with phenyl-boronic acid and a catalytic amount of Pd(II)@PCA- $\beta$ -CD. This hydro-soluble catalyst was capable of being reused for at least eight runs with only a slight loss of catalytic activity. A putative mechanism of the Pd(II)/Pd(IV) catalytic cycle was also explored and calculated by *ab initio* QM/MM methods.

**Keywords:** βcyclodextrin/Pd (II) complex; supramolecular catalyst; Suzuki-Miyaura coupling; eco-friendly.

### **1** Introduction

There has been great interest in developing novel water-soluble catalysts for greener synthetic methods and chemical processes (Descorme, Gallezot, Geantet, & George, 2012; La Sorella, Strukul, & Scarso, 2015; Li & Trost, 2008). Cyclodextrins (CDs) have been exploited to elaborate aqueous biphasic catalytic systems that allowed conversion of hydrophobic substrates using water-soluble organometallic catalysts (Floresta et al., 2017; Ghatak, Khan, & Bhar, 2016; Gong, Wang, Ren, Wang, & Chen, 2015; Frédéric Hapiot et al., 2017). With their hydrophobic cavity, cyclodextrins selectively bind substrates and catalyze chemical reactions through the formation of host-guest complexes via noncovalent interactions (Bai, Tian, Zhao, Huang, & Wang, 2017; Hapiot, Bricout, Menuel, Tilloy, & Monflier, 2014). CD-based supramolecular catalysts currently are being widely developed, but only a few palladium complexes with modified CDs as catalysts (Figure 1A) have been reported to be applied in C-C formation in aqueous solution, such as Suzuki-Miyaura, Sonogashira, and Heck cross-coupling reactions (Cintas, Cravotto, Gaudino, Orio, & Boffa, 2012; Kaboudin, Salemi, Mostafalu, Kazemi, & Yokomatsu, 2016; Kairouz & Schmitzer, 2014; Khan & Pitchumani, 2016; Sollogoub, 2013; Zhang et al., 2013). A critical setback for these catalytic systems is difficulty with synthesis or purification, long reaction times, and low recyclability of the catalyst. Thereby, more versatile

CD-based supramolecular catalysts should be developed to achieve efficient metal complexes, allowing for the improvement of catalytic activities.

Palladium-catalyzed Suzuki-Miyaura cross-coupling reactions are currently one of the most important C-C bond-forming processes (Chatterjee & Ward, 2016; Hussain, Capricho, & Yawer, 2016; Kumbhar, 2017; Martina, Manzoli, Gaudino, & Cravotto, 2017). Many types of homogeneous and heterogeneous catalysts have been used for Suzuki-Miyaura coupling reactions, such as homogeneous palladium complexes with phosphine (Hu, Qu, Gerlach, & Shaughnessy, 2017), N-heterocyclic carbene (Guitet et al., 2013; Legrand, Menand, Sollogoub, Tilloy, & Monflier, 2011; Froese, Lombardi, Pompeo, Rucker, & Organ, 2017), quinoline (Cui et al., 2007), oxazolones (Lee, 2006), pyridines (Huang et al., 2012), imidazoles (Deng, Zhang, Zhu, & Tu, 2017), etc., and heterogeneous palladium immobilized on various supports, e.g. carbon (Lee et al., 2017), silica (Shabbir et al., 2017), hydroxyapatites (Indra, Gopinath, Bhaduri, & Kumar Lahiri, 2013). However, there are many shortcomings in these catalytic systems, such as toxicity, high cost, air and thermal sensitivity, high catalyst loadings, and contamination of products, making their application less practical. Therefore, to overcome these problems, Engle and Yu reported a method of ligand design in transition-metal catalysis for Pd(II)-catalyzed C-X (X=halide, C, H) functionalization (Engle & Yu, 2013). The stability and activity of Pd complexes are highly dependent on the characteristics of Pd complexation by ligands, i.e., the proper geometry at the metal center. Hence, it is very important to select the proper ligands for successful catalytic applications of metals.

Recently, picolinamide derivatives as bidentate ligands have been successfully employed in C-C bond formation, such as the alkylation of  $\gamma$ -C(sp<sup>3</sup>)-H bonds catalyzed by a picolinamide was reported by Zhang and Chen for (Zhang et al., 2013). Additionally, Liu and Zhang developed an unprecedented picolinamide-directed coupling of C(sp<sup>2</sup>)-H and C(sp<sup>2</sup>)-H to obtain quinoline and pyridone derivatives (Zhang et al., 2015). Picolinamide complexes with palladium also employed as catalyst for Ullmann-type C-N coupling reactions (Damkaci, Alawaed, & Vik, 2016). According to the literature, the X-ray structure of Pd(II) with picolinamide indicates that it acts as a bidentate chelating ligand and is bound through both the pyridyl-N and amido-O atoms to the Pd(II) center. Further quantum chemical studies suggest that a combination of steric hindrance of the ligand and the electronic effect of metal ions may modulate the coordination preferences (Das et al., 2017). These results indicate that picolinamide-modified CDs complexes with palladium can be used as a novel catalyst for the Suzuki-Miyaura C-C bond-coupling reaction.

Herein, based on the unique features of picolinamide and CDs, in this article we report three novel picolinamide-modified  $\beta$ -cyclodextrins as water-soluble ligands of supramolecular catalyst (**Figure 1B**). We also hypothesize that the proper steric hindrance effect of CDs could enhance the universality and activity of Suzuki-Miyaura coupling reaction in various substrates such as aryl, benzyl and allyl halides. Meanwhile, a possible reaction mechanism involving the Pd(II)/Pd(IV) centers is proposed based on experimental methods and quantum chemical calculation. The synthesized picolinamide-modified cyclodextrin/Pd(II) complexes are

water-soluble and exhibit efficient catalytic activity in Suzuki-Miyaura coupling of aryl, benzyl, and allyl halides with arylboronic acids. Moreover, excellent recyclability of the catalyst makes it potentially applicable in practice. The obtained results are discussed below.



Figure 1. Modified β-cyclodextrins for the Suzuki-Miyaura coupling reaction.

### **2** Experimental section

### 2.1 Reagents and Instrumentation

All chemicals and reagents were of commercial grade, and were used without any further purification unless otherwise noted. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF<sub>254</sub>. Column chromatography was performed with 200-300 mesh silica gel. All yields refer to isolated products after purification unless otherwise noted. The NMR spectra were recorded on a Bruker DRX-400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C: 105 MHz), DRX-500 (<sup>1</sup>H: 500 MHz, <sup>13</sup>C: 125 MHz) and DRX-600 (<sup>1</sup>H: 600 MHz, <sup>13</sup>C: 150 MHz) using CDCl<sub>3</sub>, D<sub>2</sub>O and DMSO-d<sub>6</sub> as solvents. Chemical shifts ( $\delta$ ) are expressed in parts per million (ppm) and J values are given in hertz (Hz). IR spectra were recorded on an FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. HRMS was performed on an Agilent LC/MSD TOF instrument. X-ray powder diffraction (XRD) patterns were examined using Rigaku D/max-2400 X-ray diffractometer (Cu Ka,  $\lambda$ =1.5406 Å, 40 kV, 200 mA). Chemical characterization of the sample surface was recorded with X-ray photoelectron spectroscopy (XPS ULVAC-PHI, Quantera). The charge effect was calibrated using the binding energy of C 1s. The content of TiO<sub>2</sub> nanoparticles in TGH hydrogels were determined by TGA/DSC (Mettler Toledo TGA/DSC 1) in air with a heating rate of 10 °C/min. HRTEM images were obtained with a JEM 2100F field emission gun transmission electron microscope operated at an accelerating voltage of 200 kV.

### **2.2 Preparation of Catalysts**

The detailed preparation for the picolinamide-modified  $\beta$ -cyclodextrin/Pd(II) complex (Pd(II)@PCA- $\beta$ -CD) is illustrated in **Scheme 1**. First, mono-6-tosyl  $\beta$ -cyclodextrin (1,

Tos- $\beta$ -CD) was obtained by the method of Khan etc (Khan & Pitchumani, 2016). Then, Tos- $\beta$ -CD was reacted with NaN<sub>3</sub> to form 6-monodeoxy-6-monoazido- $\beta$ -CD (2,  $N_3$ - $\beta$ -CD), which was further reduced by triphenylphosphine to give a key intermediate: 6-monodeoxy-6-amino- $\beta$ -CD (3). PCA- $\beta$ -CD (4) was prepared by condensation PCA (2-pyridinecarboxylic acid) NH<sub>2</sub>-β-CD of with using N,N'-dicyclohexylcarbo-diimide (DCC) and 1-hydroxy-1H-benzotriazole (HOBt) in N,N'-dimethylformamide (DMF). The synthesis of PCA-(CH<sub>2</sub>)<sub>n</sub>NH- $\beta$ -CD (6) was achieved in two simple steps: nucleophilic substitution (from 1 to 5) and amidation (from 5 to 6). Finally, all the obtained ligands were stirred with  $Pd(OAc)_2$  at room temperature for 24 hours in toluene, and the target complexes Pd(II)@PCA-β-CDs (C1-C3) were obtained as light yellow powders. The water solubility of the 4, 6 ligands and C1, C2, C3 complexes in different temperatures were studied. The results showed the complexes have high solubility in the aqueous solution (see Table 1S in SI).

 $HO \qquad TSO \qquad H_2N_{YH} \stackrel{H}{\longrightarrow} n \qquad d \qquad N \qquad H_{YH} \stackrel{H}{\longrightarrow} n \qquad e \qquad N \qquad H_{YH} \stackrel{H}{\longrightarrow} n \qquad h \qquad H_{YH} \stackrel{H}{\longrightarrow} n \qquad e \qquad N \qquad H_{YH} \stackrel{H}{\longrightarrow} n \qquad H_{YH}$ 

Scheme 1. Synthesis of Pd(II)@PCA- $\beta$ -CDs.

Reaction conditions: (a) TsCl, NaOH, CH<sub>3</sub>CN, H<sub>2</sub>O, rt, 2 h, 15% yield; (b) NaN<sub>3</sub>, DMF, 80 °C, 12 h, 93% yield; (c) PPh<sub>3</sub>, DMF, rt, 10 h, 91% yield; (d) DCC, HOBt, DMF, 4 h at 0 °C, 18 h at rt, 72-83% yield; (e) Pd(OAc)<sub>2</sub>, toluene, rt, 24 h, 60-70% yield; (f) diamine, 80 °C, 12 h, 30% yield.

#### 2.3 General procedure for Suzuki coupling reaction.

Aryl, benzyl or allyl halides (1.0 mmol), arylboronic acid (1.2 mmol),  $K_2CO_3$  (1.5 mmol),  $C_1$  (5 × 10<sup>-6</sup> mol%) and H<sub>2</sub>O (2.0 mL) were added into a sealed tube and the mixture was stirred at 60 °C for a few hours. After the reaction, the aqueous phase was extracted with ethyl acetate for 3 times (3×7 mL). Then the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum and purified by column chromatography.

### 2.4 Computational methods

QM/MM calculations in water as solvent were used to investigate the energetics of our proposed mechanism. The structure of molecules was divided into QM and MM subsystems. For the QM subsystem, including the picolinamide,  $Pd(II)(OAc)_2$ , phenyl-boronic acid and 4-bromo-acetophenone moieties, was treated by the B3LYP functional with 6-31+G(\*) basis set for C, H, N, O, B, Br atoms and LanL2DZ with relativistic effective core potentials for palladium. This B3LYP(SDD, 6-31 G\*) level of QM treatment has been previously tested and employed successfully to describe metal coordination shell. Single point calculations were performed at the M06 level with a mixed basis set of SDD for palladium and 6-311+G(\*) for all other atoms. All calculations were performed with Gaussian 09 program packages. All transition states were confirmed by intrinsic reaction coordinate (IRC) toward a set of pre- and postreaction complexes. Computed structures are displayed with CYLview.

### **3 Results and Discussion**

### **3.1 Characterization of Catalysts**

PCA- $\beta$ -CD (4) and PCA-(CH<sub>2</sub>)<sub>2</sub>NH- $\beta$ -CD (6) were confirmed by <sup>1</sup>H nuclear magnetic resonance (NMR), electrospray ionization-high resolution mass spectrometry (ESI-HRMS), and Fourier transform infrared spectroscopy (FT-IR) (see

SI<sup>†</sup>, **Figure 1S-6S**). Pd(II)@PCA- $\beta$ -CD (C<sub>1</sub> and C<sub>2</sub>) were also characterized by transmission electron microscopy (TEM) and electron-dispersive X-ray spectroscopy (EDS). In addition, thermogravimetric analysis (TGA), X-ray diffraction (XRD), and X-ray photoelectron spectroscopy (XPS) were used to study the presence of palladium in the complex Pd(II)@PCA- $\beta$ -CD.

From the ROESY NMR spectrum (two-dimensional rotating frame overhauser effect spectroscopy) of **C**<sub>1</sub> (**Figure 2**), obvious correlation peaks between the H atoms in the pyridine ring and the H5 in the cavity of the  $\beta$ -CD can be observed. This result confirmed the picolinamide moiety have been linked with  $\beta$ -CD. Additionally, clear nuclear overhauser effect (NOE) interactions between the acetyl protons of the Pd(OAc)<sub>2</sub> and the H5 protons of  $\beta$ -CD were also observed. This illustrated that Pd(II) have been complexed with PCA- $\beta$ -CD. In order to speculate the possible structure of C1, we propused an optimal conformation of C1 by molecular simulation (see ESI, section 1.6).



Figure 2. 2D ROESY NMR spectrum of C<sub>1</sub> in D<sub>2</sub>O (25 °C).

To explore the change from PCA- $\beta$ -CD (**4**) to Pd(II)@PCA- $\beta$ -CD (C<sub>1</sub>), the FT-IR spectra of both of them are shown in **Figure 9S** (see S1<sup>†</sup>). For PCA- $\beta$ -CD (**4**), a broad band centered at 3416 cm<sup>-1</sup> and 2926 cm<sup>-1</sup> was assigned to –OH stretching vibration and –CH<sub>2</sub> asymmetric stretching vibration, respectively. And the bands at 1536 cm<sup>-1</sup> and 1637 cm<sup>-1</sup> can be attributed to the –NH and C=O bending vibrations of –NH–CO–. As for catalyst C<sub>1</sub>, the –OH stretching of the complex, and vibration and –NH–CO– vibration shift to 3397 and 1590 cm<sup>-1</sup>, respectively, indicates that Pd(II) has successfully complexed with ligand (**4**).

The stability of the catalyst Pd(II)@PCA- $\beta$ -CD (C<sub>1</sub>) and ligand PCA- $\beta$ -CD (4) was also investigated by TGA (see S1<sup>†</sup>, **Figure 12S**). For the C<sub>1</sub>, a sharp weight loss of approximately 33% mainly occurred from 260 to 320 °C, which is related to the decomposition of the palladium complex. For the PCA- $\beta$ -CD (4), a weight loss of 45% occurred at approximately 270 °C due to the heat decomposition of grafted CD.

The morphology and distribution of the synthesized catalyst  $C_1$  were further characterized using high-resolution transmission electron microscopy (HRTEM). As shown in **Figure 3a**, we found some metallic aggregate were existed, this might be partial palladium(II) acetate were decomposed to Pd(0) metal clusters when preparing C1. The lattice fringes of Pd were also detected and are shown in **Figure 3b**. The interplanar distance was approximately 0.22 nm, which closely corresponds with the (111) lattice plane of Pd. Then, the mapping image of the C<sub>1</sub> shows that the homogeneous distribution of Pd atoms is clearly observed in the supramolecular

ligand as demonstrated in **Figure 3** (**c**–**d**). Moreover, the EDS spectrum exhibited the presence of carbon, nitrogen, oxygen, and especially palladium in the structure of catalyst **C**<sub>1</sub>, which confirmed that the catalyst was successfully prepared (see S1<sup>†</sup>, **Figure 13S**).



**Figure 3.** HRTEM and Mapping of Pd(II)@PCA-β-CD (C<sub>1</sub>).

In order to obtain further insight into the changes from PCA- $\beta$ -CD (**4**) to the Pd(II)@PCA- $\beta$ -CD (**C**<sub>1</sub>) complex, the XPS spectra of the catalyst and ligand were obtained (**Figure 4**). In the **C**<sub>1</sub>, the binding energy of the doublet peaks at 337 eV and 343 eV was observed in **Figure 4a**, which can be attributed to Pd<sub>3d5/2</sub> and Pd<sub>3d3/2</sub> of Pd<sup>II</sup>, respectively. The sharp N peaks at 400 eV in **Figure 4b** (red curve) reveal the presence of Pd(OAc)<sub>2</sub> in the supramolecular ligand PCA- $\beta$ -CD (**4**). Additionally, the N<sub>1s</sub> binding energy was found to be higher compared to PCA- $\beta$ -CD (**4**), and the corresponding electron density of N-Pd in the **C**<sub>1</sub> obviously increased. These results further indicate that a coordinative conformation was formed between Pd(II) and PCA- $\beta$ -CD (**4**).



**Figure 4.** XPS spectra of PCA- $\beta$ -CD (4) and Pd(II)@PCA- $\beta$ -CD (C<sub>1</sub>). Blue, cyan, green and yellow lines are fitting curves for Pd(0) and Pd(II) peaks, respectively.

### 3.2 The Performance of Catalysts in C-C Coupling

To explore the catalytic activity, picolinamide-modified cyclodextrin/Pd(II) complexes ( $C_1$ - $C_3$ ) were employed for C-C coupling reactions in aqueous solution (see **Table 1a**). Three representative halide compounds, 4-bromo-acetophenone, cinnamyl bromide, and benzyl bromide, as well as 4-methylphenylboronic acid, were chosen to establish a model reaction for the optimization of the reaction conditions. As shown in **Table 1a**, using  $C_1$  gives excellent yields for the three model reactions (entries 1, 4, and 7, **Table 1a**). However, with the length of methylene linker increased, the efficiency of the catalyst ( $C_2$  or  $C_3$ ) was sharply decreased. The reason is probably related to the mismatch between the catalytic metal center and CD's hydrophobic cavity. In addition, compared to the catalyst  $C_1$ , using the native  $\beta$ -CD/Pd(OAc)<sub>2</sub> inclusion complex results in a poor yield (entries 16, 17, and 18, **Table 1a**). Pd(OAc)<sub>2</sub> on its own without the presence of the ligand (entries 19, 20, and 21, **Table 1a**) also leads to a poor yield, highlighting the positive influence of the

picolinamide ligand. Notably, there is no yield obtained with only PCA- $\beta$ -CD as

catalyst (entries 22, Table 1a).

|       | R' R"                            | + HO<br>HO          | Cat (1x10 <sup>-4</sup> -1x10 <sup>-3</sup> mol%<br>K <sub>2</sub> CO <sub>3</sub> (2 eq)<br>H <sub>2</sub> O, r.t 80 °C<br>under air | %)                 | ICH <sub>2</sub> -, -CH <sub>2</sub> - |                           |
|-------|----------------------------------|---------------------|---|--------------------|--|---------------------------|
| Entry | Cat                              | R'                  | R"  | Cat. [%]           | T. [°C]                                | Yield <sup>b</sup><br>[%] |
| 1     | C <sub>1</sub>                   | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | 80                                     | 97                        |
| 2     | C2                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | 80                                     | 55                        |
| 3     | C3                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | 80                                     | 34                        |
| 4     | C <sub>1</sub>                   | Н                   | -CH=CHCH <sub>2</sub> Br  | 1×10 <sup>-3</sup> | 80                                     | 95                        |
| 5     | C <sub>2</sub>                   | Н                   | -CH=CHCH <sub>2</sub> Br  | 1×10 <sup>-3</sup> | 80                                     | 57                        |
| 6     | C3                               | Н                   | -CH=CHCH2Br   | 1×10 <sup>-3</sup> | 80                                     | 32                        |
| 7     | C <sub>1</sub>                   | Н                   | -CH <sub>2</sub> Br   | 1×10 <sup>-3</sup> | 80                                     | 90                        |
| 8     | C <sub>2</sub>                   | Н                   | -CH <sub>2</sub> Br   | 1×10 <sup>-3</sup> | 80                                     | 53                        |
| 9     | C3                               | Н                   | -CH2Br  | 1×10 <sup>-3</sup> | 80                                     | 43                        |
| 10    | C1                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-4</sup> | 80                                     | 96                        |
| 11    | C <sub>2</sub>                   | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-4</sup> | 80                                     | 53                        |
| 12    | C3                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-4</sup> | 80                                     | 30                        |
| 13    | C1                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | r.t                                    | 45                        |
| 14    | C2                               | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | r.t                                    | 12                        |
| 15    | C3                               | 4-COCH <sub>3</sub> | Br  | 1×10-3             | r.t                                    | 11                        |
| 16    | $\beta$ -CD+Pd(OAc) <sub>2</sub> | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | 80                                     | 31                        |
| 17    | $\beta$ -CD+Pd(OAc) <sub>2</sub> | Н                   | -CH=CHCH2Br   | 1×10 <sup>-3</sup> | 80                                     | 27                        |
| 18    | $\beta$ -CD+Pd(OAc) <sub>2</sub> | Н                   | -CH <sub>2</sub> Br   | 1×10 <sup>-3</sup> | 80                                     | 24                        |
| 19    | Pd(OAc) <sub>2</sub>             | 4-COCH <sub>3</sub> | Br  | 1×10 <sup>-3</sup> | 80                                     | 17                        |
| 20    | Pd(OAc) <sub>2</sub>             | Н                   | -CH=CHCH2Br   | 1×10 <sup>-3</sup> | 80                                     | 15                        |
| 21    | Pd(OAc) <sub>2</sub>             | H                   | -CH <sub>2</sub> Br   | 1×10 <sup>-3</sup> | 80                                     | 15                        |
| 22    | PCA-β-CD                         | 4-COCH <sub>3</sub> | Br  | 1×10-3             | 80                                     | 0                         |

Table 1a. Optimization of catalysts in C-C cross-coupling reactions <sup>a,b</sup>

<sup>*a*</sup> Reaction conditions: 4-bromo-acetophenone (0.5 mmol), cinnamyl bromide (0.5 mmol), benzyl bromide (0.5 mmol), 4-methylphenyl-boronic acid (0.6 mmol), base (1.0 mmol), catalyst ( $1 \times 10^{-4} - 1 \times 10^{-3}$  mol%) and H<sub>2</sub>O (1 mL) were stirred under air for 12 h at r.t. or 80 °C, respectively. <sup>*b*</sup> NMR yield.

**1b.** Optimization of the reaction conditions <sup>*a,b*</sup>

|                       | o<br>Br +                       | HO<br>HO                | $\begin{array}{c} \text{Cat } \mathbf{C}_{2}\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $ | 1 (5x10 <sup>-6</sup> mol%)<br>3 (1.5 eq)<br>O, 60 °C<br>nder air | °→-{`>                 |
|-----------------------|---------------------------------|-------------------------|--|---|------------------------|
| Entry                 | Base                            | Base [eq]               | Cat. [%]   | T. [°C]   | Yield <sup>b</sup> [%] |
| 1                     | Na <sub>2</sub> CO <sub>3</sub> | 2                       | 1×10-4   | 80  | 60                     |
| 2                     | КОН                             | 2                       | 1×10-4   | 80  | 5                      |
| 3                     | Et <sub>3</sub> N               | 2                       | 1×10-4   | 80  | 23                     |
| 4                     | K <sub>3</sub> PO <sub>4</sub>  | 2                       | 1×10-4   | 80  | 45                     |
| 5                     | Cs <sub>2</sub> CO <sub>3</sub> | 2                       | 1×10-4   | 80  | 75                     |
| 6 <sup><i>c</i></sup> | K <sub>2</sub> CO <sub>3</sub>  | <b>1.5</b> <sup>c</sup> | 1×10-4   | 80  | 94, <b>97</b> , 97, 90 |
| 7                     | NaHCO <sub>3</sub>              | 2                       | 1×10-4   | 80  | 87                     |
| 8                     | LiOH                            | 2                       | 1×10-4   | 80  | NR                     |

| $9^d$   | K <sub>2</sub> CO <sub>3</sub>   | 1.5                             | 5×10 <sup>-6</sup> d  | 80              | 95, <b>97</b> , 97, 96, 95, 95                               |  |  |  |  |
|---|--|---------------------------------|-----------------------|-----------------|--|--|--|--|--|
| $10^{e}$  | K <sub>2</sub> CO <sub>3</sub>   | 1.5                             | 1×10 <sup>-4</sup>    | 60 <sup>e</sup> | 45, 65, 84, <b>97</b> , 97, 97, 93                           |  |  |  |  |
| <sup>a</sup> Reaction conditions: 4-bromo-acetophenone (0.5 mmol), 4-methylphenyl-boronic acid (0.6 mmol), base (0.75 |  |                                 |                       |                 |  |  |  |  |  |
| mmol),  | , catalyst, C1 (1×1  | 0 <sup>-4</sup> mol%) and H     | 2O (1 mL) were s      | stirred under   | air for 0.5 h at 80 °C. <sup>b</sup> NMR yield. <sup>c</sup> |  |  |  |  |
| Carried   | Carried out with 1.25, 1.5, 1.75, and 2.0 eq of base K <sub>2</sub> CO <sub>3</sub> . <sup><i>d</i></sup> Carried out with $1 \times 10^{-6}$ , $5 \times 10^{-6}$ , $1 \times 10^{-4}$ , $1 \times 10^{-3}$ , |                                 |                       |                 |  |  |  |  |  |
| 5×10-3,   | , and $1 \times 10^{-2}$ mol%  | catalyst C1. <sup>e</sup> Carri | ied out at rt, 40, 50 | ), 60, 70, 80,  | and 100 °C.  |  |  |  |  |

With the best catalyst, **C**<sub>1</sub>, further optimization of the reaction conditions was conducted (see, **Table 1b**). Initially, eight commonly utilized bases were tested with  $1 \times 10^{-4}$  mol% of the catalyst in water at 80 °C for 12 hours (entries 1-8, **Table 1b**). K<sub>2</sub>CO<sub>3</sub> provided the highest coupling yield (entry 6, **Table 1b**), while using other bases gave low to moderate yields for the reaction. Subsequently, we found that a higher yield could still be maintained if the amount of K<sub>2</sub>CO<sub>3</sub> was reduced to 1.5 eq. (entry 6, **Table 1b**). Next, we screened the effect of loading amount of the catalyst on the yield of the reaction. The results showed that even under  $5 \times 10^{-6}$  mol% loading, high catalytic activity was maintained (entry 9, **Table 1b**). Finally, different temperatures were also confirmed, and 60 °C was selected as the most suitable (entry 10, **Table 1b**). Therefore, K<sub>2</sub>CO<sub>3</sub> as a base in water and  $5 \times 10^{-6}$  mol% catalyst C<sub>1</sub> at 60 °C was selected as an optimal reaction condition.

#### 3.3 Application of Pd(II)@PCA-β-CD (C1) catalyzed Suzuki-Miyaura reactions

Initially, we investigated the catalytic activity of C<sub>1</sub> with different aryl halides and arylboronic acids (**Table 2a**). As expected, various substituted aryl halides and arylboronic acids, bearing electron-rich and electron-deficient groups, such as -CH<sub>3</sub>, -OCH<sub>3</sub>, -NO<sub>2</sub>, -CN, -COCH<sub>3</sub>, and F, were found to produce high yields (entries 3, 6, 10, 11, and 13, **Table 2a**). Remarkably, the TONs and TOFs of Pd(II)@PCA- $\beta$ -CD reached up to  $2.0 \times 10^7$  and  $2.0 \times 10^8$ , respectively. The treatment of substituted aryl

iodide with 4-methoxy boronic acid gave the corresponding biaryl with excellent yields (over 90%) in short reaction times (entries 10-13, **Table 2a**), and a high TOF up to  $1.1-2.0 \times 10^8$ . The substituted bromobenzenes also gave satisfactory yields (entries 1-9 and 20-22, **Table 2a**). Meanwhile, most of the substituted chlorobenzenes also generated excellent yields (entries 15-19 and 24-26, **Table 2a**). Heterocyclic thiophene boronic gave a low yield (entry 23, **Table 2a**). ortho-Substituted aryl halides produced the corresponding products in a lower yield for a longer time than meta- or para-positions (entries 1-9, 11-13 and 24-26, **Table 2a**), this may be because increasing the steric hindrance in the aryl halides could decrease the reactivity and make substrates inclusion with catalyst C<sub>1</sub> difficult.

| Table 2a. Suzuki-Miyaura | i coupling reactio | ns between aryl halides | s and arylboronic | acid using | $\mathbf{C}_{1}^{a}$ |
|--------------------------|--------------------|-------------------------|-------------------|------------|----------------------|
|--------------------------|--------------------|-------------------------|-------------------|------------|----------------------|

C<sub>1</sub> (5x10<sup>-6</sup> mol%)

| $R_1 \xrightarrow{HO} X + \frac{HO}{HO} \xrightarrow{R_2} R_2 \xrightarrow{K_2CO_3 (1.5 eq)} R_1 \xrightarrow{R_1} R_2$ |                     |    |                         |      |                        |                     |                           |         |  |
|---|---------------------|----|-------------------------|------|------------------------|---------------------|---------------------------|---------|--|
| Entry   | <b>R</b> 1          | X  | R <sub>2</sub>          | Time | Yield <sup>b</sup> [%] | TON <sup>c</sup>    | TOF $[\mathbf{h}^{-1}]^d$ | Product |  |
| 1   | 2-COCH <sub>3</sub> | Br | 4-CH <sub>3</sub>       | 1.0  | 88                     | $1.8 \times 10^{7}$ | $1.8 \times 10^{7}$       | 1a      |  |
| 2   | 3-COCH <sub>3</sub> | Br | 4-CH <sub>3</sub>       | 1.0  | 93                     | $1.9 \times 10^{7}$ | $1.9 \times 10^{7}$       | 1b      |  |
| 3   | 4-COCH <sub>3</sub> | Br | 4-CH <sub>3</sub>       | 0.5  | 98                     | $2.0 \times 10^{7}$ | $4.0 \times 10^{7}$       | 1c      |  |
| 4   | $2-NO_2$            | Br | 4-CH <sub>3</sub>       | 1.0  | 83                     | $1.7 \times 10^{7}$ | $1.7 \times 10^{7}$       | 1d      |  |
| 5   | 3-NO <sub>2</sub>   | Br | 4-CH <sub>3</sub>       | 1.0  | 88                     | $1.8 \times 10^{7}$ | $1.8 \times 10^{7}$       | 1e      |  |
| 6   | 4-NO <sub>2</sub>   | Br | 4-CH <sub>3</sub>       | 1.0  | 95                     | $1.9 \times 10^{7}$ | $1.9 \times 10^{7}$       | 1f      |  |
| 7   | 2-OCH <sub>3</sub>  | Br | 4-CH <sub>3</sub>       | 1.5  | 81                     | $1.6 \times 10^{7}$ | $1.1 \times 10^{7}$       | 1g      |  |
| 8   | 3-OCH <sub>3</sub>  | Br | 4-CH <sub>3</sub>       | 1.0  | 87                     | $1.7 \times 10^{7}$ | $1.7 \times 10^{7}$       | 1h      |  |
| 9   | 4-OCH <sub>3</sub>  | Br | 4-CH <sub>3</sub>       | 0.5  | 90                     | $1.8 \times 10^{7}$ | 3.6×10 <sup>7</sup>       | 1i      |  |
| 10  | 4-NO <sub>2</sub>   | Ι  | 4-CH <sub>3</sub>       | 0.1  | 96                     | $1.9 \times 10^{7}$ | $1.9 \times 10^{8}$       | 1j      |  |
| 11  | 2-COCH <sub>3</sub> | Ι  | 4-OCH <sub>3</sub>      | 0.1  | 92                     | $1.8 \times 10^{7}$ | $1.8 \times 10^{8}$       | 1k      |  |
| 12  | 3-COCH <sub>3</sub> | Ι  | 4-OCH <sub>3</sub>      | 0.1  | 95                     | $1.9 \times 10^{7}$ | $1.1 \times 10^{8}$       | 11      |  |
| 13  | 4-COCH <sub>3</sub> | Ι  | 4-OCH <sub>3</sub>      | 0.1  | 99                     | $2.0 \times 10^{7}$ | $2.0 \times 10^{8}$       | 1m      |  |
| 14  | 2-CN                | Br | 4-CH <sub>3</sub>       | 1.0  | 83                     | $1.6 \times 10^{7}$ | $1.6 \times 10^{7}$       | 1n      |  |
| 15  | 3-CH3               | Cl | 4-OCH <sub>3</sub>      | 5.0  | 83                     | $1.6 \times 10^{7}$ | $3.3 \times 10^{6}$       | 10      |  |
| 16  | 4-CH <sub>3</sub>   | Cl | 4-OCH <sub>3</sub>      | 3.5  | 87                     | $1.7 \times 10^{7}$ | $5.0 \times 10^{6}$       | 1p      |  |
| 17  | 3-CN                | Cl | 4-OCH <sub>3</sub>      | 4.5  | 81                     | $1.6 \times 10^{7}$ | $3.6 \times 10^{6}$       | 1q      |  |
| 18  | 4-CN                | Cl | 4-OCH <sub>3</sub>      | 3.0  | 85                     | $1.7 \times 10^{7}$ | $5.7 \times 10^{6}$       | 1r      |  |
| 19  | $4-NO_2$            | Cl | 4-OCH <sub>3</sub>      | 3.0  | 82                     | $1.6 \times 10^{7}$ | $5.5 \times 10^{6}$       | 1s      |  |
| 20  | 4-COCH <sub>3</sub> | Br | 3-CH <sub>3</sub>       | 0.5  | 83                     | $1.7 \times 10^{7}$ | $3.3 \times 10^{7}$       | 1t      |  |
| 21  | 4-COCH <sub>3</sub> | Br | 3-F                     | 0.5  | 87                     | $1.7 \times 10^{7}$ | $3.5 \times 10^{7}$       | 1u      |  |
| 22  | 4-COCH <sub>3</sub> | Br | 4-F                     | 0.5  | 86                     | $1.7 \times 10^{7}$ | $3.4 \times 10^{7}$       | 1v      |  |
| 23  | 4-COCH <sub>3</sub> | Br | 3-Thiopheneboronic acid | 3.00 | 74                     | $1.5 \times 10^{7}$ | $4.9 \times 10^{6}$       | 1w      |  |

| 24 | 2-COCH <sub>3</sub> | Cl | 4-OCH <sub>3</sub> | 6.00 | 77 | $1.5 \times 10^{7}$ | $2.6 \times 10^{6}$ | 1x |
|----|---------------------|----|--------------------|------|----|---------------------|---------------------|----|
| 25 | 3-COCH <sub>3</sub> | Cl | 4-OCH <sub>3</sub> | 4.00 | 85 | $1.7 \times 10^{7}$ | $4.3 \times 10^{6}$ | 1y |
| 26 | 4-COCH <sub>3</sub> | Cl | 4-OCH <sub>3</sub> | 3.00 | 89 | $1.8 \times 10^{7}$ | $6.0 \times 10^{6}$ | 1z |
|    |                     |    |                    |      |    |                     |                     |    |

<sup>*a*</sup> Reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.2 mmol), catalyst C<sub>1</sub> ( $5x10^{-6}$  mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol), H<sub>2</sub>O (2 mL), and 60 °C. <sup>*b*</sup> Isolated by column chromatography. <sup>*c*</sup> Turnover number (TON) based on the number of moles of isolated product. <sup>*d*</sup> TOF is defined as mol product molPd<sup>-1</sup> h<sup>-1</sup>.

**2b.**  $C(sp^3)$ - $C(sp^2)$  coupling reactions between cinnamyl halide and arylboronic acid using  $C_1^a$ 

|       | R <sub>3</sub>        |    | + HO HO F             | <b>C</b> <sub>1</sub> (5x10<br>KF (1.5 e<br>R <sub>2</sub> H <sub>2</sub> O, 8<br>under a | <sup>-6</sup> mol%)<br>(q)<br>) °C<br>air | R <sub>3</sub>        | R <sub>2</sub>                    |            |
|-------|-----------------------|----|-----------------------|---|---|-----------------------|-----------------------------------|------------|
| Entry | <b>R</b> <sub>3</sub> | Х  | R <sub>2</sub>        | Time [h]  | Yield<br>[%]                              | b<br>TON <sup>c</sup> | $\operatorname{TOF}_{d} [h^{-1}]$ | Product    |
| 1     | Н                     | Br | 2-OCH3                | 0.5   | 82  | 1.6×10 <sup>7</sup>   | 3.3×10 <sup>7</sup>               | 2a         |
| 2     | Н                     | Br | 3-OCH <sub>3</sub>    | 0.5   | 88  | $1.8 \times 10^{7}$   | 3.5×107                           | 1b         |
| 3     | Н                     | Br | 4-OCH <sub>3</sub>    | 0.5   | 93  | $1.9 \times 10^{7}$   | $3.7 \times 10^{7}$               | 1c         |
| 4     | Н                     | Br | 3-F                   | 0.5   | 83  | $1.7 \times 10^{7}$   | 3.3×10 <sup>7</sup>               | 2d         |
| 5     | Н                     | Br | 4-F                   | 0.5   | 85  | $1.7 \times 10^{7}$   | $3.4 \times 10^{7}$               | 2e         |
| 6     | Н                     | Br | 3-Thienylboronic acid | 0.5   | 82  | $1.6 \times 10^{7}$   | $6.3 \times 10^{7}$               | 2f         |
| 7     | Н                     | Br | 4-CH3                 | 0.5   | 91  | $1.8 \times 10^{7}$   | 3.6×10 <sup>7</sup>               | 2g         |
| 8     | Н                     | Cl | 3-CH3                 | 0.5   | 86  | $1.7 \times 10^{7}$   | $3.4 \times 10^{7}$               | 2h         |
| 9     | Н                     | Cl | 4-CH3                 | 0.5   | 92  | $1.8 \times 10^{7}$   | $3.7 \times 10^{7}$               | 2i         |
| 10    | Н                     | Cl | 4-OCH <sub>3</sub>    | 0.5   | 95  | $1.9 \times 10^{7}$   | $3.8 \times 10^{7}$               | 2j         |
| 11    | Н                     | Cl | 4-F                   | 0.5   | 88  | $1.8 \times 10^{7}$   | $3.5 \times 10^{7}$               | 2k         |
| 12    | Н                     | Cl | 2-OCF <sub>3</sub>    | 0.5   | 83  | $1.7 \times 10^{7}$   | 3.3×10 <sup>7</sup>               | 21         |
| 13    | Н                     | Cl | Н                     | 0.5   | 85  | $1.7 \times 10^{7}$   | $3.4 \times 10^{7}$               | 2m         |
| 14    | $2-NO_2$              | Br | 2-OCH <sub>3</sub>    | 3.0   | 81  | $1.6 \times 10^{7}$   | $5.4 \times 10^{6}$               | 2n         |
| 15    | $2-NO_2$              | Br | 3-OCH <sub>3</sub>    | 2.5   | 86  | $1.7 \times 10^{7}$   | $6.9 \times 10^{6}$               | 20         |
| 16    | $2-NO_2$              | Br | 4-OCH <sub>3</sub>    | 2.5   | 93  | $1.9 \times 10^{7}$   | $7.4 \times 10^{6}$               | 2p         |
| 17    | $2-NO_2$              | Br | 2-CN                  | 2.5   | 80  | $1.6 \times 10^{7}$   | $6.4 \times 10^{6}$               | 2q         |
| 18    | $2-NO_2$              | Br | 3-CN                  | 2.5   | 86  | $1.7 \times 10^{7}$   | $6.8 \times 10^{6}$               | 2r         |
| 19    | $2-NO_2$              | Br | 4-CN                  | 3.0   | 89  | $1.8 \times 10^{7}$   | $5.9 \times 10^{6}$               | 2s         |
| 20    | $2-NO_2$              | Br | 3-Thienylboronic acid | 3.0   | 87  | $1.7 \times 10^{7}$   | $5.8 \times 10^{6}$               | 2t         |
| 21    | $2-NO_2$              | Br | Н                     | 2.0   | 87  | $1.7 \times 10^{7}$   | $8.7 \times 10^{6}$               | 2u         |
| 22    | $2-NO_2$              | Br | 3-CH <sub>3</sub>     | 2.5   | 88  | $1.8 \times 10^{7}$   | $7.0 \times 10^{6}$               | 2 <b>v</b> |
| 23    | $2-NO_2$              | Br | 2,3-CH <sub>3</sub>   | 5.0   | 84  | $1.7 \times 10^{7}$   | $3.4 \times 10^{6}$               | 2w         |

<sup>*a*</sup> Reaction conditions: cinnamyl halide (1.0 mmol), arylboronic acid (1.2 mmol), catalyst C<sub>1</sub> (5x10<sup>-6</sup> mol%), KF (1.5 mmol), H<sub>2</sub>O (2 mL), 60 °C. <sup>*b*</sup> Isolated by column chromatography. <sup>*c*</sup> Turnover number (TON) based on the number of moles of isolated product. <sup>*d*</sup> TOF was defined as mol <sub>product</sub> molPd<sup>-1</sup> h<sup>-1</sup>.

**2c.**  $C(sp^3)$ - $C(sp^2)$  coupling reactions between benzyl halides and arylboronic acid using  $C_1^a$ 

| Ċ     | R                                  | Br +               | НО<br>В<br>НО́ |         | <b>C</b> <sub>1</sub> (5x10 <sup>-6</sup> mol%)<br>K <sub>2</sub> CO <sub>3</sub> (1.5 eq)<br>H <sub>2</sub> O/EtOH, 60 °C<br>under air | R <sub>4</sub>      | R <sub>2</sub>                      |         |
|-------|------------------------------------|--------------------|----------------|---------|---|---------------------|-------------------------------------|---------|
| Entry | $\mathbf{R}_4$                     | $R_2$              |                | Time [h | 1] Yield <sup>b</sup> [%]   | TON <sup>c</sup>    | TOF [h <sup>-1</sup> ] <sup>d</sup> | Product |
| 1     | Н                                  | 2-OCH <sub>3</sub> |                | 0.5     | 79  | $1.6 \times 10^{7}$ | 3.2×10 <sup>7</sup>                 | 3a      |
| 2     | Н                                  | 3-OCH <sub>3</sub> |                | 0.5     | 83  | $1.7 \times 10^{7}$ | 3.3×10 <sup>7</sup>                 | 3b      |
| 3     | Н                                  | 4-OCH <sub>3</sub> |                | 0.5     | 87  | $1.7 \times 10^{7}$ | $3.5 \times 10^{7}$                 | 3c      |
| 4     | 3-CH <sub>3</sub>                  | 4-OCH <sub>3</sub> |                | 0.5     | 89  | $1.8 \times 10^{7}$ | 3.6×10 <sup>7</sup>                 | 3d      |
| 5     | 4-C(CH <sub>3</sub> ) <sub>3</sub> | 4-OCH <sub>3</sub> |                | 1.0     | 88  | $1.8 \times 10^{7}$ | $1.8 \times 10^{7}$                 | 3e      |
| 6     | 3-OCF <sub>3</sub>                 | 2-OCH <sub>3</sub> |                | 1.0     | 81  | $1.6 \times 10^{7}$ | $1.6 \times 10^{7}$                 | 3f      |
| 7     | 3-OCF <sub>3</sub>                 | 4-OCH <sub>3</sub> |                | 0.5     | 86  | $1.7 \times 10^{7}$ | $3.4 \times 10^{7}$                 | 3g      |
| 8     | $4-NO_2$                           | 4-OCH <sub>3</sub> |                | 5.0     | 78  | $1.6 \times 10^{7}$ | $3.1 \times 10^{6}$                 | 3h      |
| 9     | 3-NO <sub>2</sub>                  | 4-CH3              |                | 5.0     | 81  | $1.6 \times 10^{7}$ | $3.2 \times 10^{6}$                 | 3i      |

| 10 | 3-CH <sub>3</sub>                | 3-Thienylboronic acid | 0.5 | 89 | $1.8 \times 10^{7}$ | 3.6×10 <sup>7</sup> | 3j |
|----|----------------------------------|-----------------------|-----|----|---------------------|---------------------|----|
| 11 | 3-NO <sub>2</sub>                | 3-OCH <sub>3</sub>    | 5.0 | 83 | $1.7 \times 10^{7}$ | $3.3 \times 10^{6}$ | 3k |
| 12 | C(CH <sub>3</sub> ) <sub>3</sub> | 3-Thienylboronic acid | 1.5 | 85 | $1.7 \times 10^{7}$ | $1.1 \times 10^{7}$ | 31 |
| 13 | $4-NO_2$                         | 3-Thienylboronic acid | 5.0 | 79 | $1.6 \times 10^{7}$ | $3.2 \times 10^{6}$ | 3m |
| 14 | Н                                | 3-CN                  | 5.0 | 71 | $1.4 \times 10^{7}$ | $2.8 \times 10^{6}$ | 3n |
| 15 | Н                                | 4-CN                  | 5.0 | 73 | $1.5 \times 10^{7}$ | $2.9 \times 10^{6}$ | 30 |

<sup>*a*</sup> Reaction conditions: benzyl halides (1.0 mmol), arylboronic acid (1.2 mmol), catalyst C<sub>1</sub> (5x10<sup>-6</sup> mol%), K<sub>2</sub>CO<sub>3</sub> (1.5 mmol), H<sub>2</sub>O:EtOH = 5:1 (2 mL), 60 °C. <sup>*b*</sup> Isolated by column chromatography. <sup>*c*</sup> Turnover number (TON) based on the number of moles of isolated product. <sup>*d*</sup> TOF is defined as mol <sub>product</sub> molPd<sup>-1</sup> h<sup>-1</sup>.

Next, we explored the performance of catalyst C<sub>1</sub> used with allyl halides and arylboronic acids for C-C coupling (see, **Table 2b**). As shown in **Table 2b**, all substrates reacted smoothly to afford the corresponding cross-coupling products (*E* isomer) in moderate to high yields, and isomerization of the products was not detected in any of the cases. Notably, the reaction of unsubstituted cinnamyl halides (Cl, Br) with most arylboronic acids proceeded with the desired products in excellent yields with high TONs and TOFs (entries 3, 7, 9, and 10, **Table 2b**), while the introduction of a nitro substituent on cinnamyl halides led to an obvious decrease in the reactivity and extended reaction time (entries 14-23, **Table 2b**). When treating 2-substituted and multi-substituted arylboronic acids with cinnamyl halides, satisfactory yields were not obtained (entries 1, 12, 14, 17, and 23, **Table 2b**), which probably was due to the steric hindrance of the substituent group, reinforcement of the carbon-boron bond, and disadvantage in the trans-metallation step.

To further extend the scope of the catalyst system for the  $C(sp^3)-C(sp^2)$  coupling, the reaction of benzyl halides with arylboronic acids was investigated using catalytic amount of  $C_1$  (5×10<sup>-6</sup> mol%), 1.5 mmol K<sub>2</sub>CO<sub>3</sub>, and 2 ml of mixed solvent (H<sub>2</sub>O:EtOH = 5:1) at 60 °C for 0.5-5 hours (see, **Table 2c**). From **Table 2c**,

electron-donating or electron-withdrawing groups of the aromatic ring of benzyl halides did significantly influence the yield of targeted products. For the benzyl halides bearing an electron-donating group, yields up to 89% were obtained in a very short reaction time (entries 4, 5, and 10, **Table 2c**). However, for benzyl halides bearing electron-withdrawing groups, a maximum of 83% yield was obtained after 5 hours (entries 11, **Table 2c**). It is noteworthy that the average yields (75-89%) obtained in this reaction was lower than that of the above-mentioned reactions. In addition, the introduction of a cyano substituent (entries 14 and 15, **Table 2c**) on the phenylboronic acid resulted in a 71-73% yield of the corresponding product.

### 3.4 Putative Mechanism for C1 Catalyzed Suzuki-Miyaura Reactions

In order to establish a chemical reaction mechanism for the  $C_1$  catalyzed Suzuki-Miyaura reaction, firstly, the ROESY NMR of a freeze-dried mixture of 4-bromo-acetophenone (1 mmol), 4-methylphenylboronic acid (1 mmol) and  $C_1$  (0.1 mmol) in D<sub>2</sub>O was recorded (**Figure 5a**). There were obvious NOE interactions between protons of 4-bromo-acetophenone and H5 of  $C_1$ , which indicated that  $C_1$ carried out an adsorption inclusion with 4-bromo-acetophenone in the cavity.

On the other hand, in general, the intrinsic feature of the Pd-catalyzed cross-coupling reactions is the Pd(0)/Pd(II) catalytic cycle. We explored Suzuki-Miyaura C-C coupling reactions catalyzed by Pd(II)(OAc)<sub>2</sub> or Pd(0)(PPh<sub>3</sub>)<sub>4</sub> with PCA- $\beta$ -CD under N<sub>2</sub> (O<sub>2</sub>-free) (see, **Figure 5b**). The former resulted in obtaining the product with an excellent yield of 96%, but the latter only resulted in a trace of the product. This suggests that the reaction may have occurred at the Pd(II)/Pd(IV) center.



**Figure 5. a**). ROESY of the mixture of 4-bromo-acetophenone, (4-Methylphenyl)-boronic acid and  $C_1$  in  $D_2O$ . **b**). Pd(OAc)<sub>2</sub> or Pd(PPh<sub>3</sub>)<sub>4</sub> with PCA- $\beta$ -CD catalyzed Suzuki-Miyaura C-C coupling reactions under N<sub>2</sub> (O<sub>2</sub>-free), respectively.

Indeed, some previous studies (Hickman & Sanford, 2012; Xu, Li, Yang, & Shi, 2010) have reported a C-C bond that formed based on organopalladium(IV). However, the application of the Pd(II)/Pd(IV) catalytic cycle to the Suzuki reaction is very rare. On the basis of the above results, a putative mechanism for the C<sub>1</sub> catalyzed Suzuki-Miyaura reaction is depicted in **Fig. 1B**. Firstly, C<sub>1</sub> conducted an adsorption-inclusion with benzene derivative. The inclusion complexes were advantageous to the oxidative insertion at the Pd(IV) center. In succession, under the attacks of the boron reagent, diaryl/Pd(IV) complex intermediates could be produced

by transmetallation. Lastly, the C-C coupling of aryl-aryl could be formed by reductive elimination, and the product could be dissociated by desorption from the cavity of PCA- $\beta$ -CD. Additionally, it needs to be discussed here, in the real case, aryl boric acid, aryl halide, and even coupling products should be in competition for the inclusion with cyclodextrin C1. The competitive affinity of different substrates will affect the rate and equilibrium constant of the coupling reaction. Meanwhile, the position of palladium can be not only on top of the cavity, but also outside the cavity, the substrate could approach palladium inside or outside the cavity of C1. There is probably a competitive pathway. Taking into account the effects of these factors, more experiments are needed to explore the exact relationship between substrate affinity and reaction mechanism. In Fig. 1B, the above is just a putative mechanism that we assumed.

To explore the possibility of the outlined mechanism, we performed QM/MM and density functional theory (DFT) calculations in water to investigate the energetics of the proposed mechanism (**Figure 6**, detailed methods are in the Supporting Information). We began the calculations from **C**<sub>1</sub>, 1-(4-bromophenyl) ethan-1-one, and p-tolylboronic acid. Firstly, inclusion between substrate and catalyst **C**<sub>1</sub> reduced the energy of the mixture system and produced Pd(II)@PCA- $\beta$ -CD/aryl halide complexes (**Figure 6**, **M2**), which then underwent oxidative addition with a low activation barrier of 4.2 kcal·mol<sup>-1</sup> from **TS1**. Additionally, the free energy of intermediate **M3** is much lower (**Figure 6**), by 37.1 kcal·mol<sup>-1</sup>) than that of **M2**, which makes oxidative addition a very favorable process. Next, the transmetallation

step proceeded with the nucleophilic addition of boron reagent through its coordination and formation of boron-ate adduct. Two stages of the reaction included substitution of the bromine atom, and elimination of boric acid molecules was carried out through the transition states TS2 and TS3. The last reductive elimination stage could take place via the TS4 transition state and required an activation barrier that is equal to 27.3 kcal·mol<sup>-1</sup>. In summary, thermodynamical analysis showed the equilibrium of reaction catalyzed by inclusion complexes C1 was irreversible shift towards the product, as free enthalpy of the system decreased by over 77.4 kcal·mol<sup>-1</sup> as a result of this C-C coupling reaction. Noteworthy, the product of TS4 was calculated again in the vacuum, then the product of TS4 is the included product but not M6, an uphill energy will be encountered to desorb and obtain target product M6. But in the water condition, as the result of solvent, the product of TS4 will be M6. The specific role of solvent may require further study. Moreover, a kinetic experiment was carried out to determine the rate of this catalytic reaction. The results confirmed the reaction following a Michaelis Menten type of kinetics. (see ESI, section 1.10)



Figure 6. Computed free-energy (kcal/mol) profile for the reaction of Suzuki-Miyaura C-C coupling with the catalyst  $C_1$ .

### 3.5 Recyclability of Pd(II)@PCA-\beta-CD (C1) Catalyst

Recently, the assessment of catalyst recycling ability is a serious indicator in practical application (Molnar, 2011; Molnar, etc., 2017). Because of the high price and toxicity of precious metals, recycling of the Pd catalyst is attractive from the economic, environmental, and industrial points of view. The recyclability and reusability of catalyst were investigated using the model reaction of 4-bromo-acetophenone, 4-methylphenylboronic acid and C1. When the reaction completed, the aqueous reaction mixture was extracted by ethyl acetate to remove the product and then the remaining aqueous phase was charged again and another fresh substrate and  $K_2CO_3$  (1.5 eq.) were added to the aqueous phase for the next reaction cycle. A detailed schematic representation is given in **Figure 7a**. In this recycling experiment, there are

steadily decreasing activities from 98% to 90% with 8 runs (**Figure 7b**). Since Pd(II)@PCA- $\beta$ -CD (C1) belongs to homogeneous catalyst and, inevitably, a small amount of C1 remains in the organic phase for each extraction operation, thus we think the reduction of its activity mainly may be attributed to the loss in the extraction process. Additionally, catalytic reaction process needs heating, which may also lead to unstable decomposition of catalyst. These require more experimental data to explain, such as kinetic analysis and TEM images. We will further explore the recycling characteristics of C1 in the application of other reactions.



Figure 7. a). Recycling procedure for  $C_1$  catalyzed C-C coupling reactions. b). Recycling for  $C_1$  in the eight runs.

### **4** Conclusions

In conclusion, we have successfully designed and prepared three novel picolinamide-modified  $\beta$ -cyclodextrin/Pd(II) complexes. The length of linker between picolinamide and CDs affects the catalytic activity of the Suzuki-Miyaura coupling reaction. It may be that the metal ion is far away from the cavity of CDs, resulting in the reduction of catalytic efficiency. Among these catalysts, the supramolecular catalyst C<sub>1</sub> afforded the best catalytic performance and exhibited extremely high TONs and TOFs for the C-C cross-coupling reaction in water. Additionally, it can be easily separated after the reaction and reused several times without a significant loss of activity. Meanwhile, a putative Mechanism for C<sub>1</sub> catalyzed Suzuki-Miyaura coupling was suggested that the reaction may have occurred at the Pd(II)/Pd(IV) center by controlled experiment and quantum chemical calculation. This research addresses a number of sustainability issues within homogeneous catalysis, which further builds bridges between green chemistry and organometallic catalysis.

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