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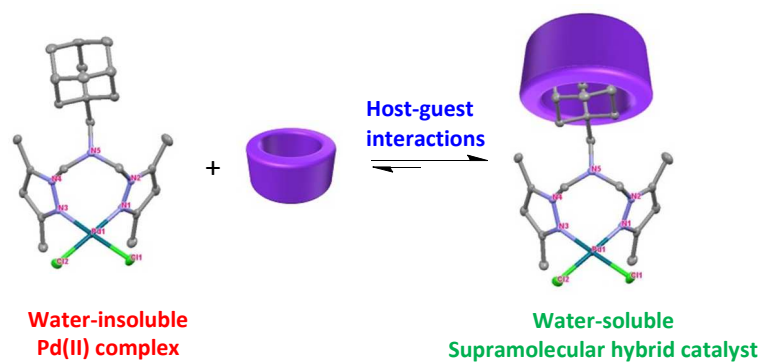
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## TOC



A Pd(II) pyrazolyl complex is solubilized by host-guest inclusion to give an efficient, recyclable catalyst for Suzuki-Miyaura couplings in aqueous-organic solvents.

## ARTICLE

# A Supramolecular Recyclable Catalyst for Aqueous Suzuki-Miyaura Coupling†

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A water-soluble, supramolecular catalytic system has been designed based on inclusion complexation between a hydrophobic palladium(II)-dipyrazole complex bearing an adamantyl (Ad) molecular recognition moiety and a complementary, hydrophilic  $\beta$ -cyclodextrin ( $\beta$ -CD) derivative. The single-crystal molecular structure of the Pd(II) complex was determined and its host-guest inclusion complexation with heptakis(2,6-di-O-methyl)- $\beta$ -CD (dm $\beta$ -CD) in aqueous medium was confirmed by 2D NOESY <sup>1</sup>H NMR spectroscopy. The catalyst showed high activity for Suzuki-Miyaura coupling of hydrophilic aryl bromides with aryl boronic acids in aqueous organic solvents. In the presence of *n*-Bu<sub>4</sub>NBr as stabilizer, the catalyst-containing reaction solution can be recycled and reused multiple times to catalyze the coupling reaction of fresh substrates once the product has been removed by centrifugation. This work demonstrates a supramolecular complex approach, non-covalently modifying a water insoluble metal complex to provide a water-soluble inclusion system to serve as a recyclable catalyst for potential application in green chemical synthesis.

## Introduction

Green chemistry addresses the environmental impact of both chemical products and the processes by which they are produced.<sup>1-4</sup> Water is an ideal green solvent and may offer additional benefits such as improved reactivities, selectivities, simplified workup procedures and recycling of an expensive metal catalyst.<sup>5,6</sup>

The development of novel water soluble catalysts has elicited interest from both industrial and academic researchers.<sup>7, 8</sup> Designing catalytically active metal species to operate in an aqueous phase has primarily focused on ligands with suitable hydrophilic groups in addition to their functionality necessary to support the stability, activity, and selectivity of the metal center. Most commonly, ionic substituents such as sulfonate, carboxylate, phosphonate, or ammonium are employed, but neutral hydrophilic polyols, carbohydrates, and polyethylene glycols have also been successfully used.<sup>9</sup>

We herein present a new approach to the design and preparation of water-soluble metal catalysts by utilizing non-covalent rather than covalent bonding. This strategy makes use of host-guest inclusion complexation to reversibly tether a hydrophilic moiety to the hydrophobic ligand of the metal complex thereby enhancing its solubility in aqueous media.

Cyclodextrins (CDs) are well-known cyclic oligosaccharides formed from the enzymatic degradation of starch.<sup>10</sup> Their partial water solubility, homochirality and ability to form

inclusion complexes makes them among the most studied hosts in supramolecular chemistry,<sup>11-16</sup> with a wide range of applications from drug delivery,<sup>17-19</sup> to resolution of enantiomers<sup>20</sup> and as catalysts.<sup>21-23</sup> The supramolecular structures formed between CDs and polymers have also inspired interesting supramolecular biomaterials. Some of us have recently constructed a series of supramolecular hydrogels, non-covalently connected micelles, nano-capsules and pseudo-block copolymers based on the inclusion complexation between  $\beta$ -CD moieties and adamantyl (Ad) groups.<sup>24-27</sup>

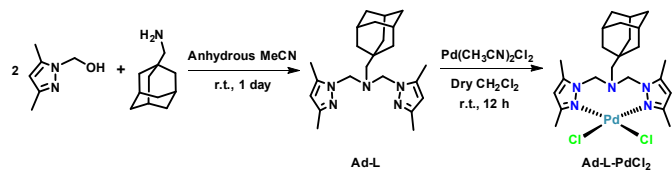
On the basis of this experience with the self-assembling behavior of  $\beta$ -CD/Ad pairs and of transition metal complexes bearing pyrazole-derived ligands,<sup>28</sup> we have now designed a bidentate dipyrazole ligand tethered to an Ad group as the molecular recognition moiety (Ad-L). This ligand then reacted with the Pd(II) precursor PdCl<sub>2</sub>(NCCH<sub>3</sub>)<sub>2</sub> to form an Ad-containing complex (Ad-L-PdCl<sub>2</sub>) that is insoluble in water because of the bulky hydrophobic group. Upon host-guest inclusion complexation of Ad-L-PdCl<sub>2</sub> with heptakis(2,6-di-O-methyl)- $\beta$ -CD (dm $\beta$ -CD) in aqueous media, however, the Pd(II) complex dissolves completely at room temperature to form a water soluble supramolecular assembly (Ad-L-PdCl<sub>2</sub>⊂ $\beta$ -CD) that efficiently catalyzes Suzuki-Miyaura coupling between hydrophilic aryl bromides with aryl boronic acid at room temperature. By comparison, the Pd(II) complex (Ad-L-PdCl<sub>2</sub>),

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that is present heterogeneously in the aqueous reaction mixture exhibits much lower catalytic efficiency under similar conditions.

## Results and discussion

### Synthesis and characterization of Ad-L and Ad-L-PdCl<sub>2</sub>

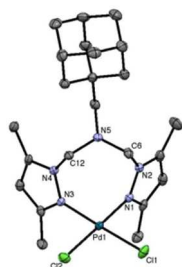


Scheme 1. Synthesis of Ad-L and Ad-L-PdCl<sub>2</sub>.

The ligand Ad-L was synthesized by the nucleophilic substitution reaction of one equivalent of 1-adamantanemethylamine with two equivalents of (3,5-dimethyl-1*H*-pyrazolyl)methanol in anhydrous acetonitrile at room temperature over 24 h (Scheme 1). This facile procedure resulted in good yields with little side products. The central amine and the two pyrazolyl nitrogen atoms of this ligand are potential ligand donors to the metal centre and hence this hybrid molecule can possibly bind to a metal in a  $\kappa^2(N,N)$  or  $\kappa^3(N,N',N)$  fashion depending on the electronic state and steric constraints around the metal.<sup>29</sup> The co-presence of a tertiary amine and pyrazolyl nitrogen donors in proximity also enhances the hemilability which gives it coordinative freedom and conformational freedom to adapt to the coordination and geometry changes of the metal during the catalytic cycle.<sup>30, 31</sup>

The adamantyl-containing Pd(II) complex (Ad-L-PdCl<sub>2</sub>) was quantitatively prepared by reacting Ad-L with an equal amount of PdCl<sub>2</sub>(NCCH<sub>3</sub>)<sub>2</sub> in dry CH<sub>2</sub>Cl<sub>2</sub> at room temperature. The <sup>1</sup>H NMR spectrum of the ligand showed a 0.1–0.4 ppm downfield shift upon coordination. Most affected was the –CH<sub>2</sub>– group bridging the central amine and the pyrazolyl group. From a singlet in the free ligand, this signal became two doublets at 7.11 and 5.23 ppm with a geminal coupling constant of 15 Hz (see Supporting Information, Figure S1).

Single crystals of adamantyl-containing Pd(II) complex suitable for Single-Crystal X-ray Diffraction analysis (Figure 1) were obtained by slow diffusion of diethyl ether into a solution of complex in CH<sub>2</sub>Cl<sub>2</sub> at –20 °C. Selected bond lengths and bond angles are summarized in Table 1.



**Figure 1.** ORTEP diagram of adamantyl-containing Pd(II) complex shown with 50% probability ellipsoids (hydrogen atoms are omitted for clarity).

The Pd(II) centre in Ad-L-PdCl<sub>2</sub> is slightly distorted from the ideal square planar geometry that is typically found in a *d*<sup>8</sup> metal centre. The bidentate chelating ligand binds the Pd(II) centre through the two pyrazolyl nitrogen atoms N3 and N1. The non-coordinating [N5...Pd] distance is 3.683 Å. This

$\kappa^2(N,N)$  coordination gives rise to a puckered 8-membered metallocyclic ring –Pd1–N1–N2–C6–N5–C12–N4–N3– which is best described as a boat-chair like conformation. The Pd–N(pyrazolyl) bond lengths are 2.019(2) Å and 2.024(2) Å which are consistent with literature values<sup>32–34</sup> as are the Pd–Cl distances of 2.2777(6) Å and 2.2858(6) Å.<sup>32–35</sup>

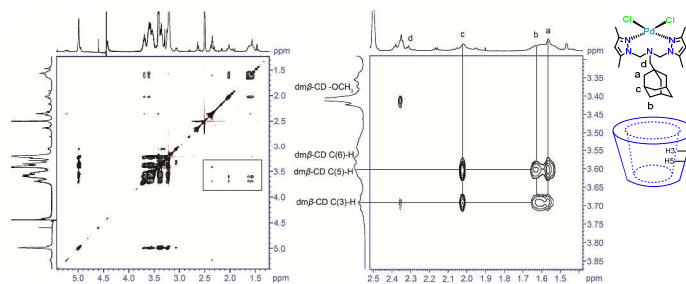
**Table 1.** Selected bond lengths (Å) and bond angles (°)

Bond Length (Å)		Bond Angle (°)	
Pd(1)–N(3)	2.019(2)	N(3)–Pd(1)–N(1)	88.44(8)
Pd(1)–N(1)	2.024(2)	N(3)–Pd(1)–Cl(1)	177.60(6)
Pd(1)–Cl(1)	2.2777(6)	N(1)–Pd(1)–Cl(1)	89.20(6)
Pd(1)–Cl(2)	2.2858(6)	N(3)–Pd(1)–Cl(2)	90.01(6)
		N(1)–Pd(1)–Cl(2)	177.62(6)
		Cl(1)–Pd(1)–Cl(2)	92.33(3)

### Host-guest inclusion complexation between Ad-L-PdCl<sub>2</sub> and $\beta$ -CD derivative

The adamantyl (Ad) group and  $\beta$ -CD moiety is a well-known host-guest pair with a stability constant (log *K*) up to 5 at room temperature.<sup>36–38</sup> To confirm the host-guest inclusion complexation of the adamantyl-containing Pd(II) complex with heptakis(2,6-di-*O*-methyl)- $\beta$ -CD (dm $\beta$ -CD), 2D-NOESY <sup>1</sup>H NMR measurements were made in aqueous DMSO. Dm $\beta$ -CD was chosen for this analysis because of its enhanced solubility in water relative to  $\beta$ -CD.<sup>25</sup>

The sample was prepared by adding a solution of Ad-L-PdCl<sub>2</sub> (guest) in DMSO-*d*<sub>6</sub> into a solution of dm $\beta$ -CD (host) in D<sub>2</sub>O. The final host-guest mixture (molar ratio 1:1) in D<sub>2</sub>O/DMSO-*d*<sub>6</sub> (1:1, v/v) was filtered before measurement. It can be seen in the 2D NOESY spectrum (Figure 2, left) that the peaks of the Pd(II) complex were only present at low intensity compared to the peaks belonging to dm $\beta$ -CD. This is most likely due to longer proton relaxation times and the high hydrophobicity of the former. This is a common phenomenon for amphiphilic materials like copolymers in aqueous solution.<sup>26</sup> The C(3)-*H* and C(5)-*H* of dm $\beta$ -CD (3.6 to 3.7 ppm) point into the hydrophobic cavity of  $\beta$ -CD and exhibit correlation signals with the protons (1.6 to 2.0 ppm) on the guest Ad group (Figure 2, right), indicating that the Ad moiety has inserted into the  $\beta$ -CD cavity. This observation is in agreement with literature reports by us and by other groups.<sup>26, 27, 39</sup>



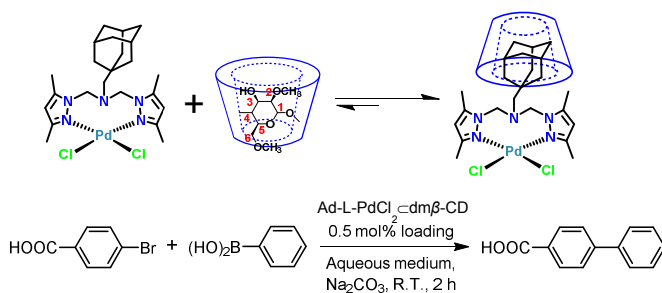
**Figure 2.** (left) 2D NOESY <sup>1</sup>H NMR spectrum of Ad-L-PdCl<sub>2</sub> and dm $\beta$ -CD in D<sub>2</sub>O/DMSO-*d*<sub>6</sub> (1:1, v/v) with water suppression (500 MHz, 25°C); (right) Expanded 2D NOESY <sup>1</sup>H NMR spectrum.

### Suzuki-Miyaura coupling reaction

**Selection of solvent.** The Suzuki-Miyaura coupling reaction is one of the most important synthetic methodologies for the

formation of carbon-carbon bonds.<sup>40, 41</sup> These reactions are generally catalyzed by soluble palladium complexes with various Pd(0) stabilizing ligands in organic media. A number of protocols have also been developed by us<sup>42, 43</sup> and other groups<sup>7, 44-48</sup> using water or aqueous mixed solvents as the reaction media to reduce the negative environmental impact of conducting this reaction on an industrial scale.

In this work, Suzuki-Miyaura cross coupling of 4-bromobenzoic acid and phenylboronic acid was used to evaluate the catalytic performance of our supramolecular catalyst (Ad-L-PdCl<sub>2</sub>⊂dmβ-CD) (Scheme 2) in a series of water-organic solvent mixtures (3/1, v/v). These reactions were carried out in air at room temperature with a 0.5 mol% catalyst loading. The supramolecular pre-catalyst and the substrates dissolved in the water-organic solvent reaction media to form a homogeneous reaction mixture. Product yields after 2 hours are given in Table 2.



Scheme 2. Suzuki-Miyaura coupling reaction of 4-bromobenzoic acid and phenylboronic acid in aqueous media catalyzed by supramolecular inclusion complex catalyst (Ad-L-PdCl<sub>2</sub>⊂dmβ-CD).

**Table 2.** Yield of Suzuki-Miyaura coupling reaction in different aqueous solvent mixtures after 2 hours<sup>[a]</sup>

Entry	Reaction media	Yield (%) <sup>[b]</sup>
1	H <sub>2</sub> O-CH <sub>3</sub> OH	>97
2	H <sub>2</sub> O-DMF	87.7
3	H <sub>2</sub> O-CH <sub>3</sub> CN	31.3
4	H <sub>2</sub> O-Acetone	61.2

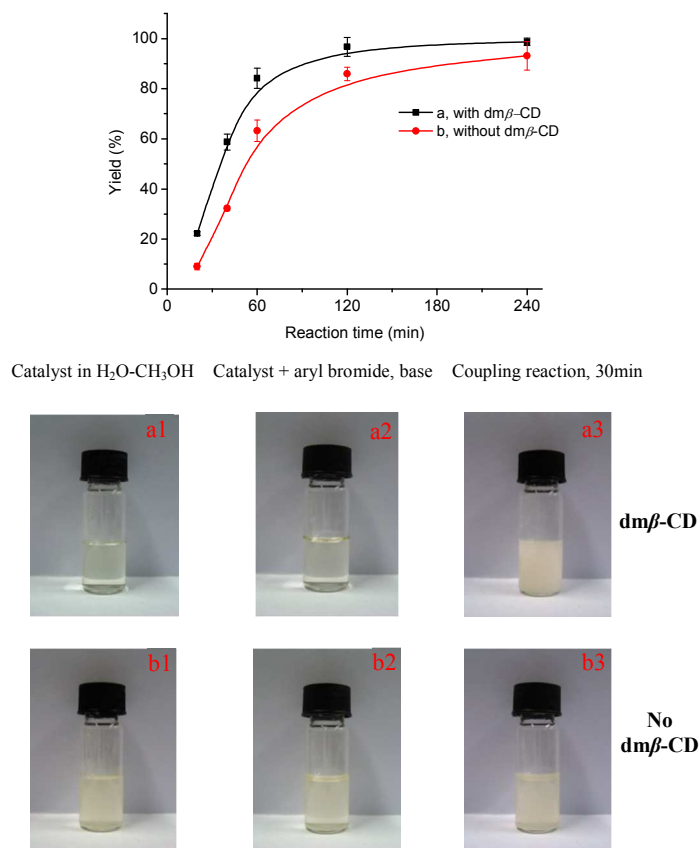
<sup>[a]</sup> Reaction conditions: 0.5 mol% supramolecular catalyst (Ad-L-PdCl<sub>2</sub> complexed with an equal amount of dmβ-CD), 0.5 mmol of 4-bromobenzoic acid, 0.6 mmol of phenylboronic acid, 1.2 mmol of Na<sub>2</sub>CO<sub>3</sub>, 4 mL of water-organic mix solvent (3/1, v/v), room temperature for 2h in air.

<sup>[b]</sup> Yields were determined by <sup>1</sup>H NMR analysis in *d*<sub>6</sub>-acetone using an internal standard (dodecane) and calculated using a product calibration plot with R<sup>2</sup>=0.998 (see Supporting Information).

It can be seen from Table 2 that the yield of the Suzuki-Miyaura coupling product after 2 hours decreased in the order H<sub>2</sub>O-CH<sub>3</sub>OH > H<sub>2</sub>O-DMF > H<sub>2</sub>O-Acetone > H<sub>2</sub>O-CH<sub>3</sub>CN. Fortuitously, the H<sub>2</sub>O-CH<sub>3</sub>OH mixture is also the 'greenest' of these water-organic solvent mixtures.<sup>49</sup>

**Contribution of host-guest inclusion complexation to Suzuki-Miyaura coupling reaction.** Next, the efficacy of host dmβ-CD was evaluated in the optimal solvent (Figure 3). The presence of dmβ-CD resulted in a very high product yield (>98%) after 4 hours. In the absence of dmβ-CD, the reaction proceeded in a slightly reduced yield (ca. 93%) over the same period. Importantly, the reaction was significantly faster over

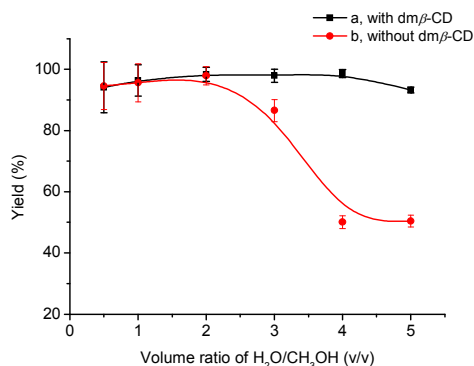
the first two hours in the presence of the solubilizing host (Figure 3, curve a and b). The series of photographs in Figure 3 illustrates the improved solubility of Ad-L-PdCl<sub>2</sub> in the presence of dmβ-CD. The presence of the latter resulted in the Pd(II) complex dissolving completely to result in a clear yellow solution (Figure 3, bottom a1). The solution remained clear on addition of the 4-bromobenzoic acid and the base Na<sub>2</sub>CO<sub>3</sub> (Figure 3, bottom a2). Subsequently, when the water soluble phenylboronic acid was added and the coupling reaction initiated, the reaction mixture became increasingly turbid on the generation of water insoluble product (Figure 3, bottom a3). Without the host dmβ-CD, the Pd(II) complex was not dissolved in the reaction medium H<sub>2</sub>O-CH<sub>3</sub>OH (3/1, v/v) but dispersed in a light yellow suspension. The reaction mixture was also less turbid over the same reaction period suggesting a slower reaction rate (Figure 3, bottom b1-b3).



**Figure 3.** (top) Comparison of Suzuki-Miyaura coupling reactions performed in H<sub>2</sub>O-CH<sub>3</sub>OH (3/1, v/v) with and without dmβ-CD in air at room temperature over 4h. Each point represents the mean value ± SD of 2 runs; (bottom) Photographs comparing the homogeneity of catalyst and catalyst mixed with 4-bromobenzoic acid/Na<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O-CH<sub>3</sub>OH (3/1, v/v), as well as the turbidity of the reaction mixtures after adding phenylboronic acid in 30 min with (a1-a3) and without (b1-b3) the host dmβ-CD, respectively.

The influence of solubility was further investigated by varying the proportion of organic solvent in the presence and absence of the host dmβ-CD (Figure 4). The reactions in the presence of dmβ-CD always afforded the product in higher yields (94% -

99%) over a volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH ranging from 0.5 to 5. The reactions in the absence of dm $\beta$ -CD also afforded the product in good yields (94% - 98%), but only when the volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH was below 3. Interestingly, when the volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH was higher than 3, the yields dropped to around 50% because of poor aqueous solubility of the catalyst. When the volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH was in the range 0.5-2, the Pd(II) complex either dissolved or was well dispersed in the reaction medium, even in the absence of dm $\beta$ -CD. Therefore the yields in both cases (i.e. with and without dm $\beta$ -CD) were similar. When the volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH was 3, the Pd(II) complex was kept soluble in the reaction medium by the dm $\beta$ -CD. However, when dm $\beta$ -CD was absent, the Pd(II) complex dissolved poorly resulting in a lower yield (around 86%) and this was exacerbated by increasing the volume ratio of H<sub>2</sub>O/CH<sub>3</sub>OH to 4 and 5 (yield around 50%).



**Figure 4.** Comparison of Suzuki-Miyaura coupling performed in various proportions of H<sub>2</sub>O and CH<sub>3</sub>OH, with and without dm $\beta$ -CD (conditions: room temperature, 2 h in air). Each point represents the mean value  $\pm$  SD of 2 runs.

### Recycling of the catalyst

High precious metal prices and toxicity make recycling of the Pd catalyst attractive from an economic and environmental perspective. Recycling experiments were performed using the standard Suzuki-Miyaura coupling reaction of 4-bromobenzoic acid and phenylboronic acid in water-MeOH (3:1, v/v). The coupling product was easily isolated by centrifugation. The aqueous filtrate was recovered and investigated for its ability to catalyze the reaction of freshly added substrates (Table 3). It has been reported that pH strongly influences catalyst activity for Suzuki-Miyaura cross coupling reactions conducted in aqueous media<sup>50</sup> and that a pH of around 11 is optimal.<sup>50, 51</sup> In this work, the pH value of the original reaction mixture was measured to be *ca.* 11.0 at the beginning of the coupling reaction. However, by the end of the reaction, the pH value of the recycled filtrate dropped to be *ca.* 10.0 and then *ca.* 9.0 after the second reaction. Therefore, the pH of the reaction mixture was adjusted back to 11.0 with dilute aqueous NaOH before each recycling experiment.

**Table 3.** Catalyst recycling for the Suzuki-Miyaura coupling reaction of 4-bromobenzoic acid and phenylboronic acid with and without stabilizer.<sup>a</sup>

Entry	Stabilizer	Stabilizer/Aryl bromide (mol/mol)	Yield for each recycling step (%) <sup>b</sup>				
			Step 0	Step 1	Step 2	Step 3	Step 4
1	-	-	100	59.4	21.9	15.1	9.0
2	TBAB	0.1	100	62.4	32.8	21.4	18.8
3	TBAB	0.15	83.0	100	77.5	53.0	20.6
4	TBAB	0.20	69.2	92.2	69.7	52.4	15.6
5	TBAB	0.25	69.7	81.1	49.8	35.0	15.5
6	TBAB	1.0	8.4	25.6	15.4	18.7	14.6
7	NaBr	1.0	100	43.0	19.0	11.8	11.5

<sup>a</sup> Reaction conditions: 4-bromobenzoic acid (1.0 equiv., 0.125 mol/L), phenylboronic acid (1.2 equiv.), initial catalyst loading (0.5 mol%, for step 0), pH (11.0, at the beginning of each step), room temperature for 2 h in air in water-MeOH (3:1, v/v).

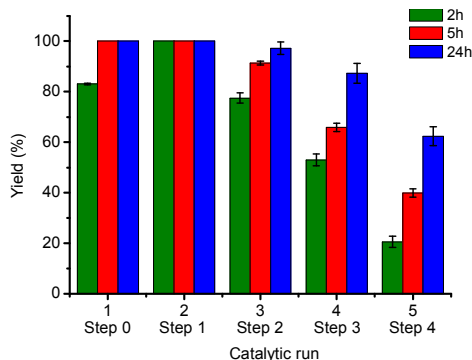
<sup>b</sup> Yields were determined by <sup>1</sup>H NMR analysis in *d*<sub>6</sub>-acetone using an internal standard (dodecane) and calculated using a product calibration plot with R<sup>2</sup> = 0.998 (see Supporting Information).

The Suzuki-Miyaura coupling reaction of 4-bromobenzoic acid and phenylboronic acid in water-MeOH was quantitative after 2 h (Table 3, entry 1). However, this high catalytic activity was not maintained using the recycled catalyst. The yield dropped to *ca.* 60% at the first recycle (i.e. step 1) and was less than 10% by the 4<sup>th</sup> recycling step. Palladium black was observed in these reactions, thus suggesting catalyst decomposition.

Pd(0) intermediates are the catalytically active species in Suzuki-Miyaura cross coupling reactions.<sup>52-54</sup> Catalyst decomposition to form palladium black is also frequently observed. This phenomenon is usually explained by assuming that the oxidative addition step which starts the catalytic cycle is in competition with an ill-defined sequence of reactions leading to palladium nanoparticles (Pd-NPs) that eventually aggregate irreversibly to form larger, catalytically inactive, palladium metal particles (palladium black).<sup>55</sup> Obviously a low conversion will result if the aggregation is faster than the cross coupling. Catalyst decomposition also hampers recycling. A simple and effective approach to prevent the catalyst from losing activity is to use quaternary ammonium salts which stabilize Pd-NPs and slow the aggregation process.<sup>56-58</sup> Stabilization of Pd-NPs can increase the catalytic activity because dispersible Pd-NPs are themselves active catalysts<sup>57</sup> or act as a reservoir of soluble, catalytically active Pd(0).<sup>59, 60</sup> Both the cation and anion of ammonium salt play a combined role in stabilizing Pd-NPs, the anion being coordinated to the electrophilic metal nanoparticles with the cation surrounding the negatively-charged anion-metal sphere.<sup>55</sup>

In our work, a suitable amount of tetrabutylammonium bromide (TBAB) was found to be effective to stabilize the catalyst against decomposition and made recycling feasible. Experiments carried out using different TBAB/4-bromobenzoic acid molar ratios showed that the catalytic performance for each recycling step increased significantly with increasing the stabilizer until a maximum was reached at the TBAB/4-bromobenzoic acid molar ratio of 0.15:1 (Table 3, entries 2-6). When higher amounts of stabilizer were used, the substrate conversion decreased. When TBAB in recycling reaction 1 was increased from 0 to 0.15 equiv., the yield increased from *ca.* 60% (entry 1) to 100% (entry 3). When the TBAB was further increased to 0.25 equiv., the yield decreased from 100% to *ca.* 80% (entry 5) and to *ca.* 25% when 1.0 equivalents of TBAB were employed (entry 6). No catalyst decomposition was observed in these TBAB stabilized reactions. These results indicate that the optimal molar ratio of TBAB to substrate was

0.15 and that high loadings of TBAB actually inhibited the reaction, presumably at the oxidative addition step. By contrast, NaBr did not stabilize the catalyst and slight inhibition was observed (entry 7).



**Figure 5.** Variation of yield with increasing reaction time in catalyst recycling experiments; 4-bromobenzoic acid (1.0 equiv., 0.125 mol/L), phenylboronic acid (1.2 equiv.), initial catalyst loading (0.5 mol%, for step 0), TBAB (0.15 equiv.), pH (11.0, at the beginning of each step), room temperature, air, water-methanol (3:1, v/v). Each point represents the mean value  $\pm$  SD of 2 runs.

Although 0.15 equiv. of TBAB significantly enhanced the catalytic performance in subsequent recycling steps (Table 3, entry 3, step 1-4), this was not the case for the initial run (Table 3, entry 3, step 0). The yield for this step was quantitative without stabilizer and approximately 80% with stabilizer. It is possible that the higher stability gained from the TBAB stabilization leads to longer catalytic induction period. Further, a series of catalytic reactions and recycling experiments was carried out for 5 h and 24 h, and compared with those performed at 2 h in the presence of 0.15 equiv. of TBAB (Figure 5). At a reaction time of 5 h (red bars), the aqueous solution with supramolecular catalyst can be recycled and reused twice before the yield dropped to below 90% and three times for a reaction time of 24 h (blue bars).

## Experimental

### Synthesis of bis[(3,5-dimethyl-1H-pyrazolyl)methyl] [(1-adamantyl)methyl] amine (Ad-L)

The synthesis of Ad-L was modified from a previous report by our group.<sup>28</sup> (3,5-Dimethyl-1H-pyrazolyl)methanol (0.252 g, 2 mmol) was dissolved in anhydrous CH<sub>3</sub>CN (30 mL). 1-Adamantanemethylamine (0.166 g, 1 mmol) was added and the solution stirred in a closed vessel for 24 h at room temperature. The solvent was removed under reduced pressure and the resultant white solid re-dissolved in 10 mL of n-hexane, filtered and the clear solution cooled overnight at 4 °C, yielding white crystals (0.26 g, yield 68%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 1.21 (s, 6H, Ad -CH<sub>2</sub>-), 1.54 (d, 3H, *J* = 16.3 Hz, Ad -CHH'-), 1.61 (d, 3H, *J* = 12.3 Hz, Ad -CHH'-), 1.84 (s, 3H, Ad -CH), 2.19 (s, 6H, Pz-CH<sub>3</sub>), 2.27 (s, 6H, Pz-CH<sub>3</sub>), 2.37 (s, 2H, Ad-CH<sub>2</sub>-N-), 4.91 (s, 4H, Pz-CH<sub>2</sub>-N-), 5.79 (s, 2H, Pz CH). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 12.1 (Pz CH<sub>3</sub>), 14.2 (Pz CH<sub>3</sub>), 29.1 (Ad CH<sub>2</sub>), 35.4 (Ad C), 37.7 (Ad CH<sub>2</sub>), 41.1 (Ad CH), 62.2 (Ad -CH<sub>2</sub>-N-), 69.0 (N-CH<sub>2</sub>-Pz), 106.3 (Pz CH), 140.2 (Pz C), 147.9 (Pz C). ESI-MS (in CH<sub>2</sub>Cl<sub>2</sub>, *m/z*(%)): [M+H]<sup>+</sup> = 381(100),

[2M+Na]<sup>+</sup> = 784(30). Anal. Calcd for C<sub>23</sub>H<sub>35</sub>N<sub>5</sub>: C, 72.40; H, 9.25; N, 18.35. Found: C, 72.35; H, 8.38; N, 18.12.

### Synthesis of adamantyl-containing Pd(II) complex (Ad-L-PdCl<sub>2</sub>)

PdCl<sub>2</sub>(NCCH<sub>3</sub>)<sub>2</sub> was synthesized following a literature procedure.<sup>61</sup> A suspension of PdCl<sub>2</sub> (1.00 g, 5.65 mmol) was heated under reflux in CH<sub>3</sub>CN (50 mL) with vigorous stirring for 10 h under N<sub>2</sub>. The resultant wine-red colored solution was cooled for 16 h at 4 °C and a yellow-orange solid was filtered, washed with Et<sub>2</sub>O and dried *in vacuo* at room temperature. Solutions of PdCl<sub>2</sub>(NCCH<sub>3</sub>)<sub>2</sub> (0.070 g, 0.27 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and Ad-L (0.103 g, 0.27 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were mixed and stirred at room temperature for 12 h<sup>62</sup> and then concentrated under vacuum. Et<sub>2</sub>O (5 mL) was added to induce precipitation. A yellow-orange solid was obtained, washed with Et<sub>2</sub>O, and dried under vacuum. The product was crystallized from a CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O mixture to give bright orange crystals (0.14 g, yield 92%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.64 (s, 6H, Ad -CH<sub>2</sub>-), 1.70 (d, 3H, *J* = 18.9 Hz, Ad -CHH'-), 1.78 (d, 3H, *J* = 11.9 Hz, Ad -CHH'-), 2.07 (s, 3H, Ad -CH), 2.14 (s, 2H, Ad-CH<sub>2</sub>-N-), 2.36 (s, 6H, Pz-CH<sub>3</sub>), 2.78 (s, 6H, Pz-CH<sub>3</sub>), 5.23 (d, 2H, *J* = 15.1 Hz, Pz-CHH'-N-), 5.87 (s, 2H, Pz CH), 7.11 (d, 2H, *J* = 15.7 Hz, Pz-CHH'-N-). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 13.6 (Pz CH<sub>3</sub>), 15.8 (Pz CH<sub>3</sub>), 28.8 (Ad CH<sub>2</sub>), 37.2 (Ad C), 37.4 (Ad CH<sub>2</sub>), 41.8 (Ad CH), 57.6 (Ad -CH<sub>2</sub>-N-), 70.7 (N-CH<sub>2</sub>-Pz), 108.8 (Pz-CH), 143.7 (Pz C), 151.9 (Pz C). ESI-MS (in CH<sub>2</sub>Cl<sub>2</sub>, *m/z*(%)): [M-Cl]<sup>+</sup> = 524(100), [M+Na]<sup>+</sup> = 576(20). Anal. Calcd for C<sub>23</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>5</sub>Pd: C, 49.43; H, 6.31; N, 12.53. Found: C, 48.66; H, 5.71; N, 11.91.

### Measurements and Experimental Methods

#### General procedure for Suzuki-Miyaura coupling reaction.

**(Method 1)** Palladium (II) complex (Ad-L-PdCl<sub>2</sub>) (1.4 mg, 0.0025 mmol) was dissolved in 0.5 mL of MeOH and 0.03 mL of acetone in a clean vial with stirring at 40 °C until a bright yellow solution resulted. The acetone assists complete dissolution of the complex. This solution was then added dropwise to dm $\beta$ -CD (3.5 mg, 0.0025 mmol) in deionized water (1.5 ml) with stirring at room temperature. A clear, bright yellow solution (2 ml) was formed. 4-Bromobenzoic acid (0.101 g, 0.5 mmol), phenylboronic acid (0.073 g, 0.6 mmol), and Na<sub>2</sub>CO<sub>3</sub> (0.127 g, 1.2 mmol) were dissolved in 2 ml of water-methanol (3:1, v/v) with stirring at room temperature until a clear, pale yellow solution was formed. The catalyst solution and substrate solution were mixed together and stirred at room temperature. After the required time had elapsed, the reaction mixture was neutralized with dilute, aqueous HCl. The resulting white precipitate was filtered, washed with water and dried under vacuum at 50 °C. **(Method 2)** Palladium (II) complex (Ad-L-PdCl<sub>2</sub>) (1.4 mg, 0.0025 mmol) was dissolved in 1.0 mL of methanol and 0.03 mL of acetone with stirring at 40 °C until a bright yellow solution resulted. This solution was then added dropwise to dm $\beta$ -CD (3.5 mg, 0.0025 mmol) in deionized water (3.0 ml) with stirring at room temperature. Then 4-bromobenzoic acid (0.101 g, 0.5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (0.127 g, 1.2 mmol) were added with stirring until a clear, pale yellow solution was formed. Phenylboronic acid (0.073 g, 0.6 mmol) was added and the reaction mixture was stirred for the prescribed time at room temperature before being neutralized with dilute aqueous HCl. The white precipitate was separated by filtration, washed with water and dried under vacuum at 50 °C.

**Yield calculation for Suzuki-Miyaura coupling reaction.** Yields were calculated by <sup>1</sup>H NMR spectroscopy based on the 4-bromobenzoic acid used using hexadecane as an internal standard.

After the Suzuki-Miyaura coupling reaction, the reaction mixture was neutralized with dilute aqueous HCl and a measured amount of hexadecane (usually 14 mg) in ethyl acetate (4 mL) was added. The organic phase was separated, and the reaction mixture extracted with fresh ethyl acetate (3×3 mL). The organic extracts were combined, washed twice with water (5 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and a 0.9 mL aliquot was filtered, evaporated at room temperature and re-dissolved in deuterated solvent (acetone-*d*<sub>6</sub>). The yield of the product was calculated from a calibration curve (Figure S2, R<sup>2</sup> = 0.998).

**Catalyst recycling.** After a standard Suzuki-Miyaura coupling reaction of 4-bromobenzoic acid and phenylboronic acid in water-methanol (3:1, v/v), the white coupling product was isolated by centrifugation (6000 rpm, r.t.). The clear filtrate was transferred to a clean vial, and measured amounts of fresh substrate were added with stirring at room temperature. The pH was adjusted to 11.0 using dilute aqueous NaOH. After the required time had elapsed, the white coupling product was isolated by centrifugation, and the clear filtrate was recycled and reused for the next coupling reaction.

## Conclusions

A key catalytic design in this system is the incorporation of an adamantyl tether onto the ligand backbone that does not interfere with the catalytic process but activating its inclusion property to capture a β-cyclodextrin moiety and uses that to solubilise the entire supramolecular hybrid in an aqueous or aqueous-organic mixed media. The main challenge in this design is the chemical and thermal stability of the supramolecular hybrid catalysts and, very importantly, introduction of the inclusion pair (adamantyl and cyclodextrin here) must not infringe with the catalytic site thereby hurting the catalytic efficacy. The crystal and molecular structure of the adamantyl-tethered complex reported herein gives clear evidence that the bulky pendant is pointing away from the metal center and that its introduction does not interfere with the coordination sphere of the Pd(II). It also does not impose undesirable bonding of the amine with the metal, which has been witnessed in other functional hybrid ligand systems.<sup>28</sup> Encouraged by these results, we are actively applying this simple yet powerful design to a range of other metal catalysts and catalytic reactions.

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## Notes and references

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†Electronic Supplementary Information (ESI) available: General measurement and experimental methods; A table of single crystal data and structure refinement parameters for adamantyl-containing Pd(II) complex (Ad-L-PdCl<sub>2</sub>); <sup>1</sup>H NMR spectra of Ad-L and Ad-L-PdCl<sub>2</sub>; Calibration curve based on <sup>1</sup>H NMR analysis for the yield calculation for Suzuki-Miyaura coupling reaction. CCDC Deposition Number (CCDC 1031688). See DOI: 10.1039/b000000x/

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