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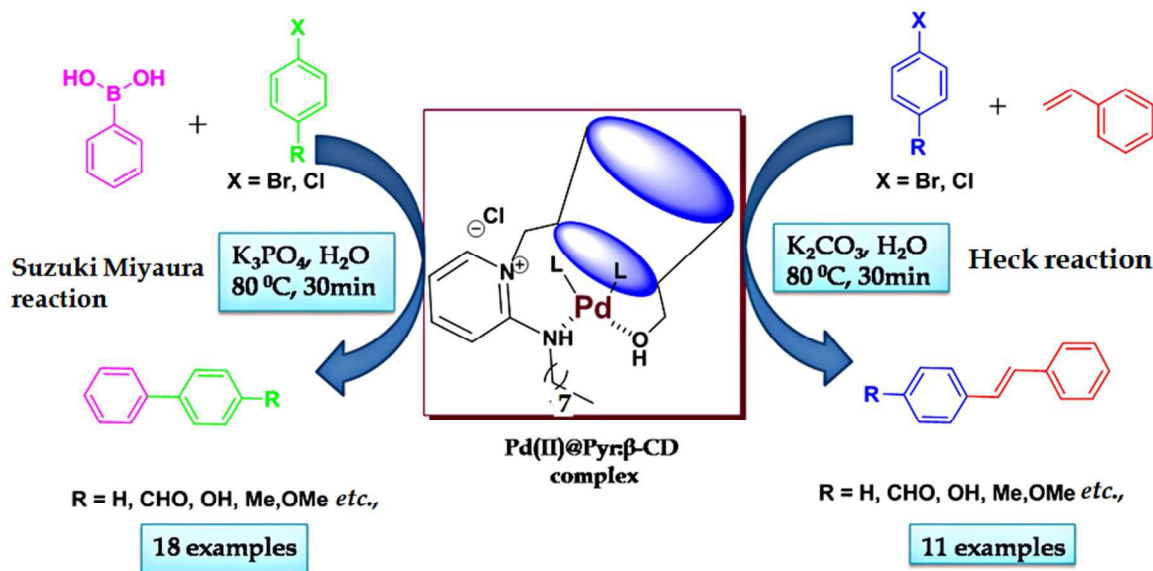
Pyridinium Modified β -Cyclodextrin: An Ionic Supramolecular Ligand for Palladium acetate in C-C Coupling Reactions in Water

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Abstract: An ionic Pd(II) complex stabilized by water soluble pyridinium modified β -cyclodextrin was prepared and characterized by NMR, Mass spectrometry, FT-IR spectroscopy, UV-Visible spectroscopy and DLS (dynamic light scattering). The resulting Pd(II)@Pyr: β -CD complex showed very good catalytic activity in Suzuki- Miyaura and Heck C-C coupling reactions in an environmentally benign water medium. Good to excellent yields were obtained for the coupling of various aryl halides including chlorides with phenylboronic acid/styrene using a catalytic amount of Pd(II)@Pyr: β -CD. This homogeneous catalyst can be reused and recycled more than six times with only marginal loss in its catalytic activity.



Introduction:

Designing green protocols in chemistry offers lots of scope and challenges for chemists in industry and research¹ to develop new products and processes² towards societal, environmental and economic benefits.³ This requires a paradigm shift in approach to reduce the materials and energy requirements of chemical processes and products, diminish or eliminate the dispersion of harmful chemicals in the environment,⁴⁻⁵ exploit the use of renewable wealth and extend the

robustness and recyclability of products in a way which increases the industrial competitiveness.⁶⁻⁷

Suzuki-Miyaura cross-coupling and Heck reactions are the most widely used protocols for the formation of carbon-carbon bonds⁸ and have become significant methods in the synthesis of biaryl and arylolefinic compounds,⁹ resulting in a wide range of pharmaceuticals and natural products. The reagents phenyl-boronic acids and styrene are readily available, fairly stable and form C-C bonds¹⁰⁻¹¹ readily and this is one of the key reasons for the keen interest, wide scope and impressive development of these reactions. Among the various sustainable media, water is an attractive solvent for chemical reactions due to its low cost, non-flammability, non-toxicity, and environmental friendliness.¹²⁻¹⁶

Palladium catalyzed cross-coupling reactions for the formation of carbon-carbon bonds are widely used¹⁸ in synthetic and medicinal chemistry for the preparation of new derivatives with wide ranging therapeutic potentials¹⁹. Generally, phosphine ligands are used to complex and activate the palladium species.²⁰ However, they are sensitive to air and moisture, restricting the reuse of the catalyst and also lead to undesirable residues under aqueous reaction conditions, which place significant limitation on their synthetic applications.²¹⁻²⁵ Therefore, the development of phosphine-free catalytic systems to overcome the above difficulties is considered as one of the most challenging and demanding areas in organic synthesis.²⁶⁻²⁸ In this direction, many homogeneous catalytic systems have been developed.²⁹⁻³⁰

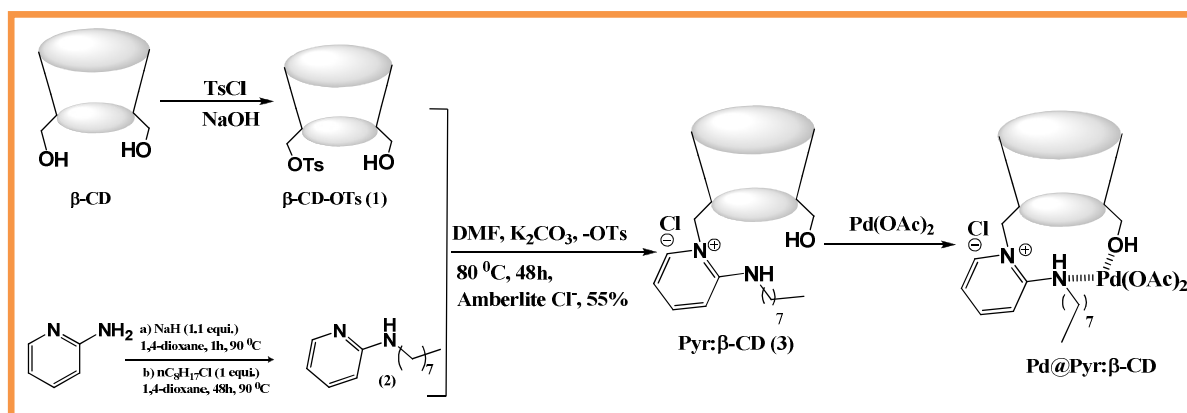
Supramolecular chemistry, an emerging area of chemistry, contributes to the development of numerous innovative concepts. Among the many host systems developed, cyclodextrins (CDs) as simple naturally occurring macrocyclic oligosaccharides, possess a hydrophobic cavity that selectively binds substrates and catalyze chemical reactions through formation of host-guest complexes *via* noncovalent interactions.^{31,32} Modification of cyclodextrins offers enormous opportunities and challenges for chemists,³³⁻³⁵ ranging from achieving solubility in a desired solvent to selective and specific catalysis. Highly water soluble cyclodextrins are desirable in applications such as drug formulation, controlled release studies *etc.*,³⁶⁻³⁸ For example, a random conversion of hydroxyl groups to sulfate groups can be easily achieved and the product has the desired solubility in water.³⁹⁻⁴¹ Recently per-6-amino- β -

cyclodextrin and imidazolium β -cyclodextrin are used in Pd-catalyzed C-C coupling reactions^{42,43}.

These unique features of cyclodextrins prompted us to report the synthesis, characterization and catalytic applications of a novel, ionic, pyridinium modified β -cyclodextrin (Pyr: β -CD), wherein an octyl chain is linked to the pyridinium moiety attached to the primary face of a β -CD. The synthesized Pyr: β -CD (**3**) is soluble in water and exhibits excellent catalytic activity in Suzuki–Miyaura and Heck reactions in the presence of palladium acetate. The observed results are discussed below.

Results and Discussion:

The synthetic pathway to obtain Pyr: β -CD (**3**) is shown in Scheme 1. Mono-6-tosyl- β -cyclodextrin (**1**) was prepared *via* tosylation from commercially available β -CD. Subsequent reaction with *N*-octyl-pyridine-2-amine (**2**) followed by anion-exchange on amberlite Cl⁻ resin afforded the desired amphiphilic pyr: β -CD (**3**) as a pale yellow solid, which was stable towards oxygen and moisture. The synthesis of (**3**) was achieved in a single step straight-forward synthesis with 12% yield. The structures of *N*-octyl-pyridine-2-amine (**2**) and Pyr: β -CD (**3**) were confirmed from FT-IR, ¹H-NMR, ¹³C-NMR, Mass spectra and Elemental analyses (Figures S1-S7, See supporting information).



Scheme 1: Synthesis of pyridinium modified β -cyclodextrin (Pyr: β -CD).

In FT-IR spectrum (Figure S9), the presence of a band at 3346 cm^{-1} is due to the hydroxyl groups of β -cyclodextrin and Pyr: β -CD (**3**) shows two bands at 3346 cm^{-1} and 3537 cm^{-1} with the latter corresponding to secondary N-H stretching frequency. A band at 1142 cm^{-1} corresponds to

the C-N stretching frequency of Pyr:β-CD (**3**). The synthesis of Pyr:β-CD (**3**) was also confirmed from ESI-MS spectra (Figure 1a) which shows an m/z peak at 1323.60 corresponding to $[M+1]$ adduct]. In the complexation of Pyr:β-CD (**3**) with Pd(OAc)₂, the peak at 1323.60 disappeared and a new peak appeared (Figure. 1b) at 1579.62 (m/z), which corresponds to the adduct of pyr:β-CD(**3**) with Pd (cal: m/z = 1580.43 and obs: m/z = 1579.62 for $[M+Pd(OAc)_2+Cl^-]$). Formation of Pd(II)@Pyr:β-CD is also supported by XRF analysis (Figure S10) and downfield shift of its pyridyl protons in ¹H-NMR (spectrum Figure S11).

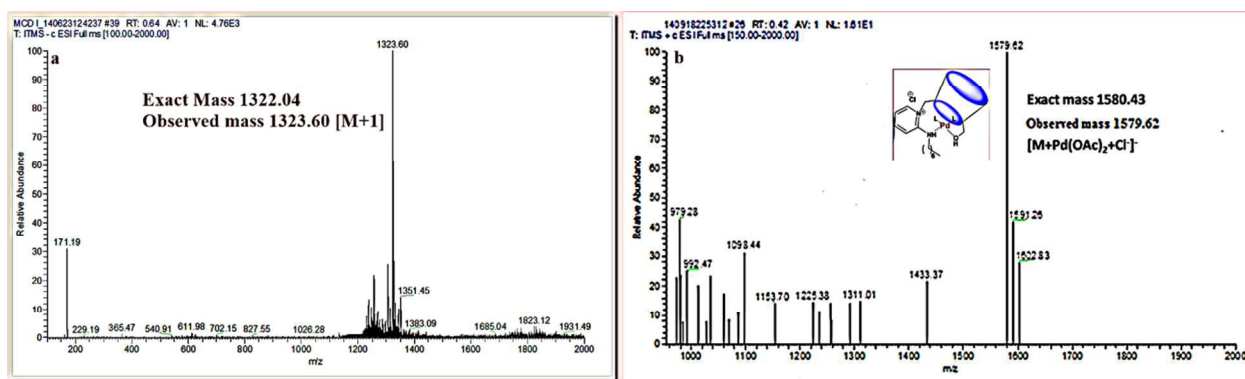
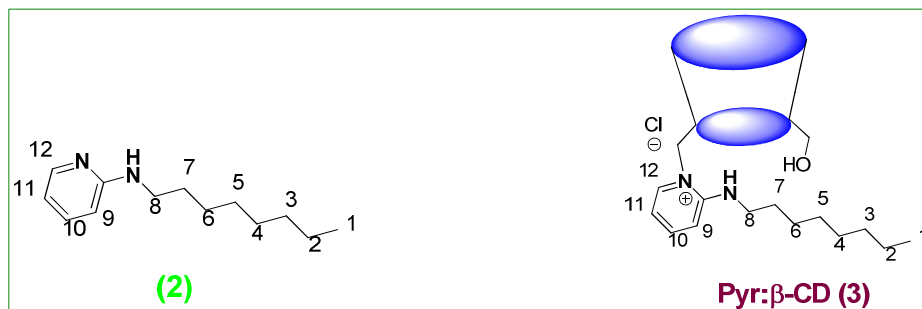


Figure 1 ESI-MS of a) Pyr:β-CD (**3**) and b) Pd(II)@Pyr:β-CD complex.

To gain further evidence for the formation Pyr:β-CD (**3**), ¹H-NMR spectra of Pyr:β-CD (**3**), was recorded in DMSO-d₆ and of *N*-octyl-pyridine-2-amine (**2**) in CDCl₃. (Figures S1 and S4). The chemical shifts were assigned by analogy with the chemical shifts of cyclodextrin protons reported previously⁴⁷ in DMSO-d₆. Details of the chemical shifts values are given in Table 1. From Figure S4, and Table 1, it is clear that there is considerable downfield shifts for the alkyl protons (C1 to C7) of *N*-octyl-pyridine-2-amine (**2**) when it is modified with cyclodextrin. On the other hand, the chemical shift values of C8 protons undergo an upfield shift. Similarly the chemical shift of pyridyl protons also undergoes considerable variations. The ¹³C-NMR chemical shifts of **3** also undergo significant shifts (Table 1) lending support for binding of β-CD to (**2**) to form (**3**). A two-dimensional NOESY-NMR experiment was also carried out, with the aim of examining the potential spatial proximities among the different protons of Pyr:β-CD (**3**) (Figure S7). Absence of cross-contours, in 2D-NOESY spectra, correlating the aromatic protons of pyridine, aliphatic protons of octyl group and the cyclodextrin protons, indicate that

the pyridine moiety and the octyl side chain were not included into the hydrophobic cavity of β -CD.

Table 1. Chemical shifts of *N*-octyl-pyridine-2-amine (2) and Pyr: β -CD (3).



Position	¹ H-NMR			¹³ C-NMR		
	in (2)	in (3)	$\Delta\delta$ (3-2)	in (2)	in (3)	$\Delta\delta$ (3-2)
1	0.9	2.07	+1.17	13.80	13.14	-0.66
2	1.25	2.50	+1.25	22.44	18.32	-4.12
3	1.25	2.50	+1.25	26.72	21.69	-5.03
4	1.25	2.50	+1.25	28.69	25.46	-3.23
5	1.25	2.50	+1.25	28.97	32.21	+3.24
6	1.25	2.50	+1.25	31.59	32.21	+0.62
7	1.82	2.71	+0.89	32.50	34.51	+2.01
8	3.56	2.87	-0.69	44.71	35.10	-9.61
9	6.46	6.55	+0.09	108.26	125.71	+17.47
10	6.59	6.69	+0.10	137.38	140.52	+3.14
11	7.38	7.50	+0.12	141.02	145.57	+4.54
12	7.98	8.07	+0.09	147.76	160.71	+12.95

Compared to native β -cyclodextrin, water solubility of pyr: β -CD (3) is very high. Figure S8 shows the solubility of pyr: β -CD (3) and a 1:1 mixture of β -CD and (2) and the results clearly indicate the vastly increased solubility of pyr: β -CD (3) in water.

Energy minimization studies (Figs. S13 to S18, SI) were carried out using Insight II molecular modeling studies to gain an idea about the possible inclusion of octyl side chain of pyr: β -CD (**3**) in the β -CD cavity. From the results shown in Table 2, it is clear that mode A in which octyl group is present outside the Pyr: β -CD (**3**) cavity is more favored than that of inclusion of octyl group inside the Pyr: β -CD (**3**) cavity (Mode B).

Table 2: Molecular modeling studies of pyridinium modified β -cyclodextrin

Mode of Inclusion	ΔE^a (Kcal.M ⁻¹)
Octyl group outside the pyr: β -CD cavity (Mode A)	-64.8600
Octyl group inside the pyr: β -CD cavity. (Mode B)	-50.8292

^aBinding energy calculation of modified β -cyclodextrin .

The synthesized Pd(II)@Pyr: β -CD acts as an efficient catalyst in C-C coupling reaction of different aryl halides/alkenes in Suzuki Miyaura and Heck coupling reactions and the observed results are discussed below.

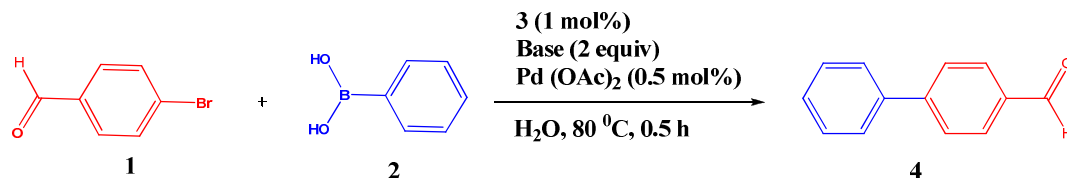
i) Pd(II)@Pyr: β -CD catalyzed Suzuki Miyaura coupling reaction in water

The catalytic activity of Pd@Pyr: β -CD was evaluated in Suzuki Miyaura coupling reaction in water. As boronic acids are water soluble,²⁴ the efficiency of Suzuki Miyaura reaction in water was hampered by a side reaction of phenylboronic acids, namely homocoupling. However, the Pyr: β -CD (**3**) supported palladium catalyst with its ionic character, provides good interaction between water soluble phenylboronic acids and hydrophobic aryl halides, thus improving the efficiency of Suzuki Miyuara cross-coupling reaction in water.

The coupling between 4-bromobenzaldehyde and phenylboronic acid was chosen as a model reaction and the results were summarized in Table 3. Without Pd and β -CD there is no reaction (Table 3, entry 1). However, with only Pd or β -CD, the yield was very low (entries 2 and 3). Among the different solvents examined, water acted as a good solvent at 80 °C to yield the desired products in good yield. Use of various bases were also studied and except K₃PO₄, Cs₂CO₃ and K₂CO₃ all other bases gave desired coupling products in only moderate yield (entries 9-16). K₃PO₄ gave excellent yield compared to Cs₂CO₃ and K₂CO₃. Catalyst loading was also

optimized and in the absence of Pyr:β-CD (**3**), there was no reaction and product formation was effective at low loading level of Pd(OAc)₂ (0.2 mol%) and Pyr:β-CD (**3**) (0.2 mol%).

Table 3. Optimization of reaction conditions.^{a,b}

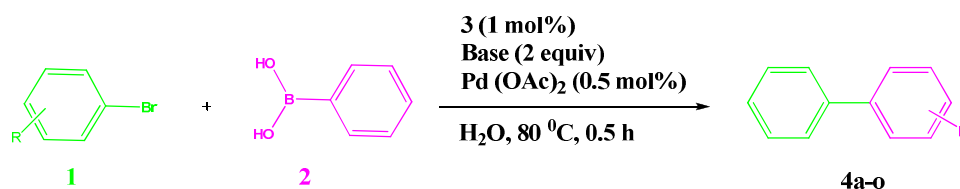


Entry	Ligand	Catalyst	Base	Solvent	Time (h)	Temp(°C)	Yield (%) ^b
1	-	-	K ₂ CO ₃	DMF	14h	110	NR
2	-	Pd(OAc) ₂	K ₂ CO ₃	DMF	14h	110	11
3	β-CD	Pd(OAc) ₂	K ₂ CO ₃	DMF	14h	110	19
4	Pyr	Pd(OAc) ₂	K ₂ CO ₃	DMF	14h	110	26
5	Pyr- β CD	Pd(OAc) ₂	K ₂ CO ₃	DMF	14h	110	49
6	Pyr- β CD	Pd(OAc) ₂	K ₂ CO ₃	DMSO	14h	110	46
7	Pyr- β CD	Pd(OAc) ₂	K ₂ CO ₃	Toluene	14h	80	33
8	Pyr- β CD	Pd(OAc) ₂	K ₂ CO ₃	Water	14h	80	86
9	Pyr- β CD	Pd(OAc) ₂	NaOH	Water	14h	80	46
10	Pyr- β CD	Pd(OAc) ₂	Na ₂ CO ₃	Water	14h	80	50
11	Pyr- β CD	Pd(OAc) ₂	Na ₂ SO ₄	Water	14h	80	56
12	Pyr- β CD	Pd(OAc) ₂	Et ₃ N	Water	14h	80	56
13	Pyr- β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	14h	80	95
14	Pyr- β CD	Pd(OAc) ₂	Cs ₂ CO ₃	Water	14h	80	94
15	Pyr- β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	14,6,1, 0.5 h	80	95, 95, 91, 90
16 ^c	Pyr-β CD	Pd(OAc)₂	K₃PO₄	Water	0.5 h	80	95, 95, 92, 88
17 ^d	Pyr- β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	0.5 h	80	95, 68, NR
18 ^e	Pyr-β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	0.5 h	80	10, 95, 95, 95, 95, 95

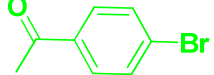
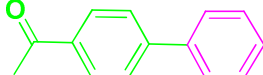
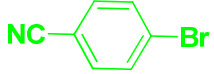
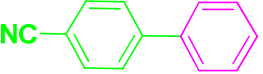
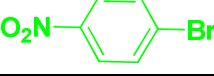
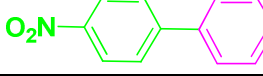
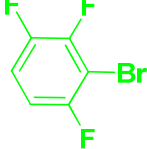
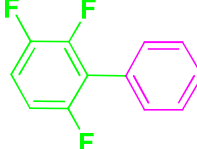
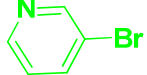
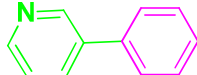
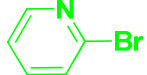
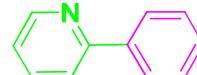
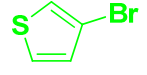
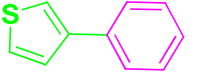

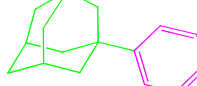
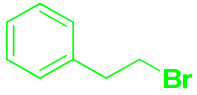
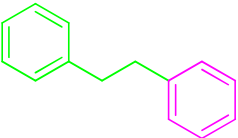
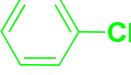
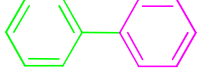
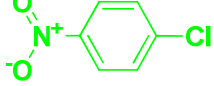
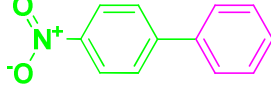
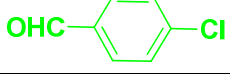
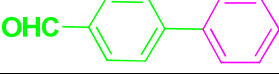
Reaction conditions: Aryl halides (1 mmol, 1 equiv.), phenylboronic acid (1.2 mmol, 1.2 equiv.), base (2 mmol, 2 equiv.), solvent (2 mL), catalyst (0.2 mol %), Ligand (**3**) (0.2 mol %), 80 °C, 0.5 h. ^bGC yield. ^cYield of the reactions carried out with 50, 40, 30 and 20 mgs of Pd/pyr-CD respectively. ^dYield of the reactions carried out with 100, 50 and 0 mol% of base respectively. ^eYield of the reactions carried out with 0 (0.5), 1 (0.5), 1 (0.3), 1 (0.2), 0.5 (0.2) and 0.2 (0.2) mol % of ligand (catalyst) respectively.

The substrate scope of the catalytic system was explored further with a series of aryl halides and phenylboronic acid under the optimized conditions (0.5 mol % Pd(OAc)₂ at 80 °C in 2 mL H₂O respectively). Different 4-substituted aryl bromides containing both electron-donating or electron-withdrawing groups such as methyl, methoxy, amine, cyano, acetyl and fluoride groups (Table 4, entries 1-10) yielded the analogous products in very good yields in short reaction time except nitro-group substitution (Table 4, entry 9). Heterocyclic bromides like 2- and 3-pyridyl bromide and 3-bromothiophene gave moderate yields (Table 4, entries 11-13). Non-aromatic as well as aryl bromides containing aliphatic chains also gave good yields (entries 14 and 15). Encouraged by these results, we next turned our attention to aryl chlorides such as chlorobenzene, 4-chloronitrobenzene and 4-chlorobenzaldehyde. The reactions were facile and very good yields were observed in 2h (Table 4, entries 16-18).

Table 4. Suzuki Miyuara reaction of different aryl halides with phenylboronic acid catalyzed by the pyridinium modified cyclodextrin/Pd(OAc)₂ complex (3).



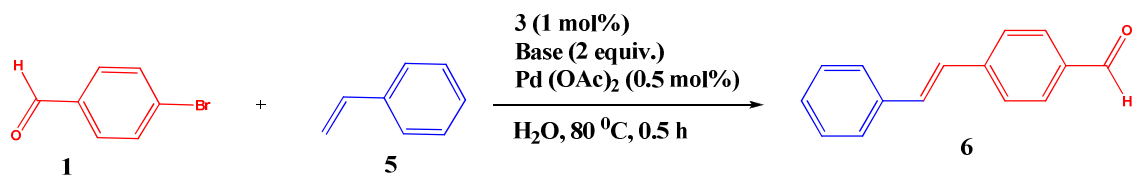
Entry	Aryl halide	Product	(Code)	Yield(%) ^b
1			4a	95
2			4b	80
3			4c	72
4			4d	90
5			4e	90
6			4f	91

7			4g	93
8			4h	90
9			4i	74
10			4j	92
11			4k	90
12			4l	84
13			4m	89
14			4n	93
15			4o	84
16			4a	88 ^c
17			4i	90 ^c
18			4f	87 ^c
Aryl/alkyl halide (1 mmol), phenyl boronic acid (1.2 mmol, 1.2 equiv.), K ₃ PO ₄ (2 mmol), water (2 mL), Pd(OAc) ₂ (0.2 mol%), ligand (3) (0.2 mol%), 80 °C, unless otherwise noted. ^[b] GC yield; ^[c] Reaction time 2h.				

Pd(II)@Pyr:β-CD catalyzed Heck coupling reaction in water

Pd(II)@Pyr:β-CD was also found to be a highly active and efficient catalyst in Heck reaction of a wide variety of aryl bromides, containing substituents such as nitro, chloro *etc.*, to couple with styrene resulting in very high conversion and yield at 80 °C. The reaction was optimized and the observed results are given in Table 5. The reaction carried out without any ligand afforded only 10% of desired product (entry 1). The reaction yield increased to 35% when carried out with β-CD as the ligand in DMF (entry 2). Interestingly, when carried out with *N*-octylpyridine-2-amine (2) in DMF, the reaction yield increased to 42% (entry 3). The reaction when carried out with Pyr:β-CD (**3**) as a ligand in DMF became faster (entry 4). The reaction failed in the absence of a base (entry 5). Among the different inorganic bases used for this coupling reaction (entries 6, 7 and 8), K₂CO₃ gave the best results. Using various solvents such as DMSO, MeOH, CH₃CN and water, only moderate yields (entries 9-12) were obtained.

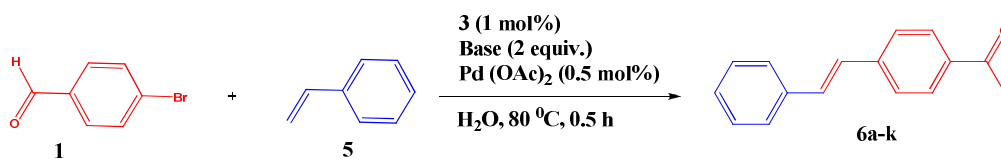
The efficiency of catalyst Pd(II)@Pyr:β-CD was also checked in coupling of various substituted aryl halides with styrene. The results (Table 6) showed that different 4-substituted aryl bromides containing either electron-donating or electron-withdrawing groups such as methyl, methoxy, nitro, cyano, aldehyde or acetyl group gave their analogous products in good yields at short reaction times (Table 6, entries 1-8). We further investigated the Heck reaction of heterocyclic bromides like 5-bromopyridin-2-amine, 1-(5-bromothiophen-2-yl)ethanone and 2-bromopyridine with styrene (entries 9-11) and all the compounds gave the desired products in good yields, though, the yields were lesser compared to aryl halides with electron-donating and electron-withdrawing group substitutions. Heck coupling was also studied with two aryl chlorides (Table 6, entries 12 and 13). The reactions, however, were slower and required longer time.

Table 5 Optimization of reaction conditions in Heck reaction

Entry	Ligand	Catalyst	Base	Solvent	Time (h)	Temp (°C)	Yield (%) ^b
1	-	Pd(OAc) ₂	K ₂ CO ₃	DMF	12	110	12
2	β-CD	Pd(OAc) ₂	K ₂ CO ₃	DMF	12	110	34
3	Pyr	Pd(OAc) ₂	K ₂ CO ₃	DMF	12	110	37
4	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	DMF	12	110	51
5	Pyr-β CD	Pd(OAc) ₂	-	DMF	12	110	3
6	Pyr-β CD	Pd(OAc) ₂	CS ₂ CO ₃	DMF	12	110	72
7	Pyr-β CD	Pd(OAc) ₂	K ₃ PO ₄	DMF	12	110	81
8	Pyr-β CD	Pd(OAc) ₂	Na ₂ CO ₃	DMF	12	110	79
9	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	DMSO	12	110	87
10	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	MeOH	12	110	71
11	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	MeCN	12	110	76
12	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	Water	12	110	95
13	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	Water	12	80	95
14	Pyr-β CD	Pd(OAc) ₂	K ₂ CO ₃	Water	12, 6, 1, 0.5	80	95, 95, 95, 95
15^c	Pyr-β CD	Pd(OAc)₂	K₂CO₃	Water	0.5	80	95, 95, 94, 89
16 ^d	Pyr-β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	0.5	80	95, 68, NR
17 ^e	Pyr-β CD	Pd(OAc) ₂	K ₃ PO ₄	Water	0.5	80	10, 95, 95, 95, 95, 95

Reaction conditions: 4-Bromobenzaldehyde (1 mmol, 1 equiv.), styrene (1.2 mmol, 1.2 equiv.), base (2 mmol, 2 equiv.), solvent (2 mL), catalyst (0.2 mol %), Ligand (**3**) (0.2 mol%), 80 °C, 30 min. ^b GC yield. ^c Yield of the reaction carried out with 50, 40, 30 and 20 mg of Pd/py-CD respectively. ^d Yield of the reaction carried out with 100, 50 and 0 mol% of base respectively. ^e Yield of the reaction carried out with 0 (0.5), 1 (0.5), 1 (0.3), 1 (0.2), 0.5 (0.5) and 0.2 (0.2) mol% of ligand (catalyst) respectively.

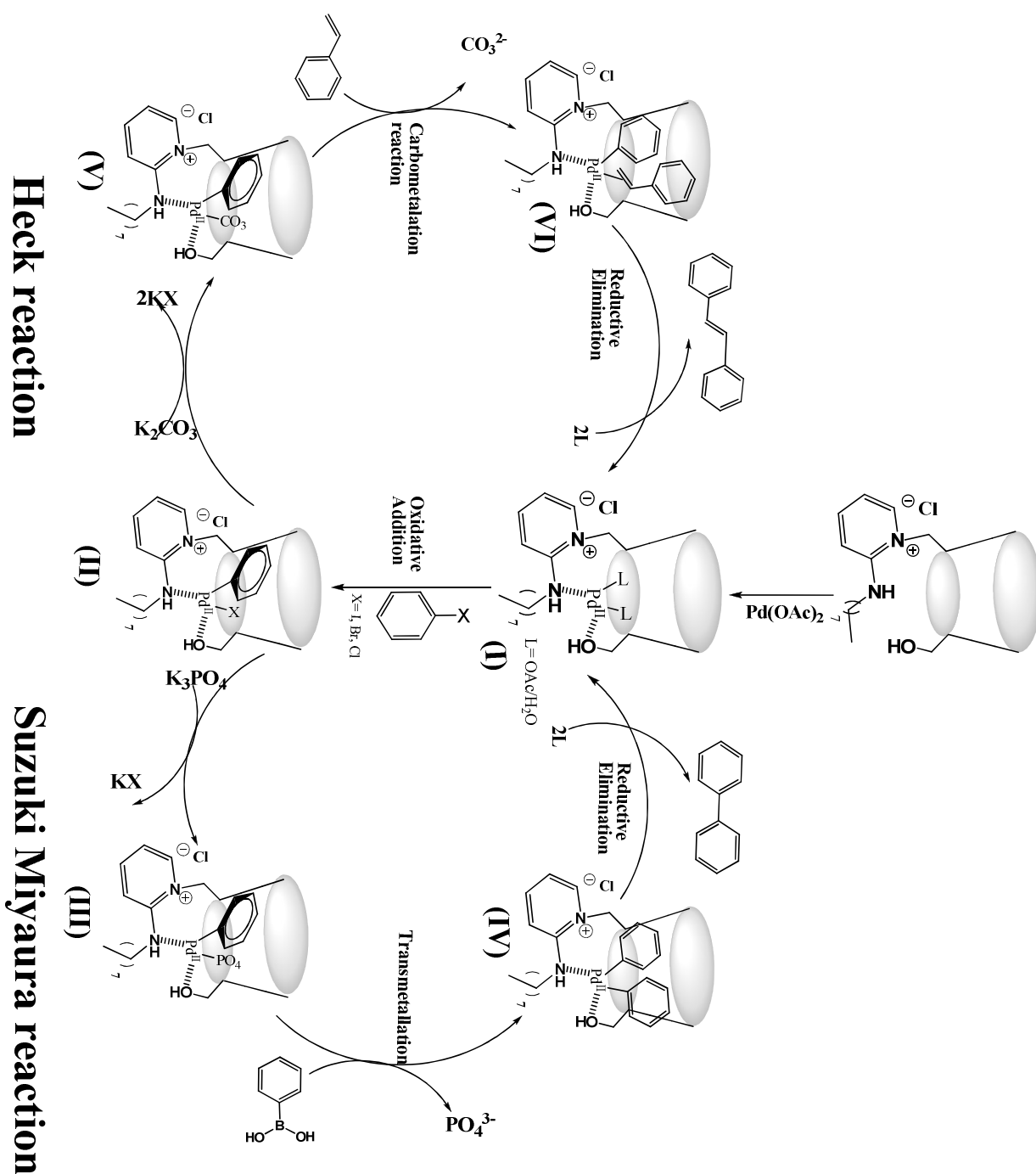
Table 6: Heck coupling reaction of different aryl halides with styrene



Entry	Aryl halide	Product (Code)	Yield (%) ^b
1		6d	96
2		6e	95
3		6g	94
4		6k	96
5		6f	95
6		6a	96
7		6b	95
8		6c	96
9		6h	90
10		6i	88
11		6j	93
12		6f	78 ^c
13		6a	80 ^c

Reaction conditions: Aryl halides (1 mmol, 1 equiv.), styrene (1.2 mmol, 1.2 equiv.), base (2 mmol, 2 equiv.), solvent (2 mL), catalyst (0.2 mol %), Ligand (**3**) (0.2 mol %), 80 °C, 30 min. ^b GC yield, ^c Reaction time 2h.

On the basis of the above results, and also in accordance with previous literature reports,³¹ a plausible mechanism as shown in Scheme 2 is proposed.



Scheme 2 Plausible mechanism for the Pd(II)@Pyr:β-CD catalyzed C-C coupling reactions in water

The Pd(II)@Pyr:β-CD complex is formed *in situ* through the addition of Pd(OAc)₂ to Pyr:β-CD (**3**), *via* coordination between the –OH groups of β-CD, –NH group of *N*-octylpyridine-2-amine (**2**) and Pd(OAc)₂. This is supported by the observation of a strong peak at 1579.02 for ([M+Pd(OAc)₂+Cl]⁺) (Figure. 1), which corresponds to the complex between Pyr-β-CD (**3**) and Pd(OAc)₂. Oxidative addition of aryl halides/styrene leads to a Pd-chelated complex, generating intermediate (II) which undergoes dissociation of halides through the formation of cationic complex (III) and (V). Next, the insertion of phenyl from phenylboronic acid through the transmetallation reaction, and also the syn-insertion of the alkene through the carbometallation reaction, providing (IV) and (VI), which undergoes reductive elimination to give rise to Suzuki Miyaura/Heck coupling products and simultaneously the catalytic active Pd⁰ complex is regenerated *in situ* from a hydridopalladium complex after reductive elimination by base.

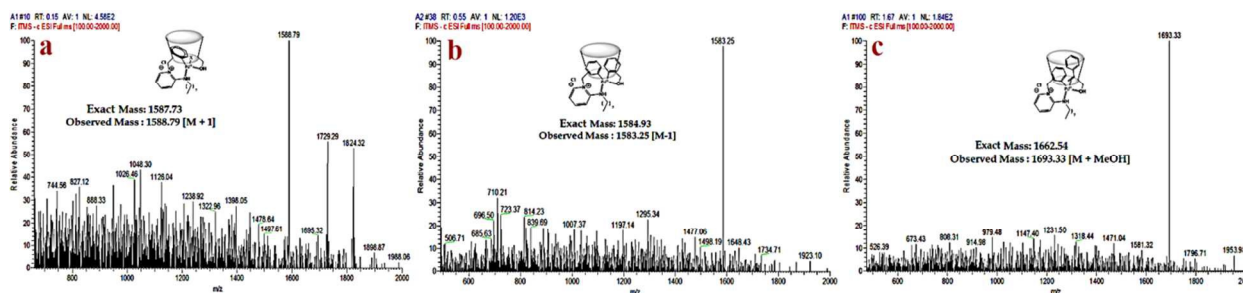


Figure 2 ESI-MS spectra of intermediates (II), (IV) and (VI), discussed in scheme 2.

Control experiments to identify the intermediates and hence to lend support to the proposed mechanism, were also carried out. The reaction mixture, after the addition of successive reagents to the catalyst, was analysed by ESI-MS. Observation of characteristic ESI-MS spectra (Figure 2) for intermediates (II), (IV for Suzuki) and (VI for Heck) provides strong experimental evidence for the proposed mechanism. To the best of our knowledge, similar ESI-MS data for the proposed intermediates (II), (IV) and (VI) were not reported so far in Suzuki Miyaura and Heck reactions.

Control experiments were also carried out in Suzuki Miyaura reaction with Pd(OAc)₂ or *N*-octylpyridine-2-amine (**2**) as the catalysts and the results (Table 7) showed that Suzuki Miyaura coupling reactions were slow with both Pd(OAc)₂, or *N*-octylpyridine-2-amine (**2**) alone. When the reaction were carried out with Pd(II)@Pyr:β-CD good yields were obtained in short reaction time. We believe that the differences in catalytic efficiency among unsupported

palladium and Pd(II)@Pyr:β-CD may be due to the presence of β-CD into the catalytic system, which functioned as an excellent phase-transfer-catalyst to accelerate the present aqueous organic transformation.

Table 7. Control experiments of Suzuki Miyaura coupling reactions in water.^a

Entry	Pd(OAc) ₂		<i>N</i> -octyl-pyridine-2-amine (2)		Pd(II)@Pyr:β-CD	
	Time (h)	Yield (%) ^b	Time (h)	Yield (%) ^b	Time (h)	Yield (%) ^b
1	0.5	12	0.5	10	0.5	95
2	1	28	1	10	1	95
3	3	30	3	25	3	91
4	6	40	6	35	6	90

^aThe reaction were carried out in water (2 mL) in the presence of aryl bromides (1 mmol, 1 equiv.), phenylboronic acid or styrene (1.2 mmol, 1.2 equiv.), base (2 mmol, 2 equiv.), Pd(OAc)₂ (0.2 mol %), Pyr:β-CD (3) (0.2 mol%), 80 °C. ^bGC yield.

From the green chemistry point of view, recycling is one of the major concerns in metal catalysis.²⁹ In contrast to traditional water soluble M-L complexes, recycling of the Pd(II)@Pyr:β-CD species was efficient. The recyclability of the presence of Pd@Pyr:β-CD (3) catalytic system (Figure 3), in Suzuki Miyaura C-C coupling reaction of aryl halides and phenylboronic acid showed that more than six catalytic cycles can be performed without any significant loss of its catalytic activity.

Recycling of homogenous catalyst of Pd(II)@Pyr:β-CD.

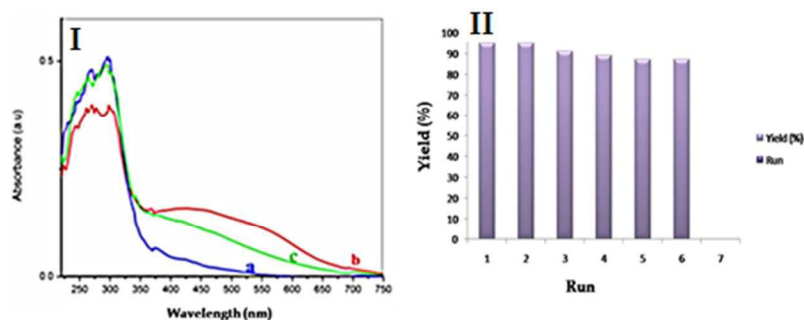


Figure 3. I) Representative UV-DRS spectra for *N*-octyl-pyridine-2-amine (2) (a), Pd(II)@Pyr:β-CD (b), reusability for Pd(II)@Pyr:β-CD in 6th run (c): II) Dependence of yield on the amount of catalyst for Suzuki Miyaura reactions.

The recycling of catalyst Pd(II)@Pyr:β-CD was carried out as follows: After the completion of the reaction, the catalyst Pd(II)@Pyr:β-CD was recovered easily from the filtrate by washing with ethyl acetate followed by evaporation of the aqueous phase *in vacuo*. A detailed schematic representation is given in figure 4.

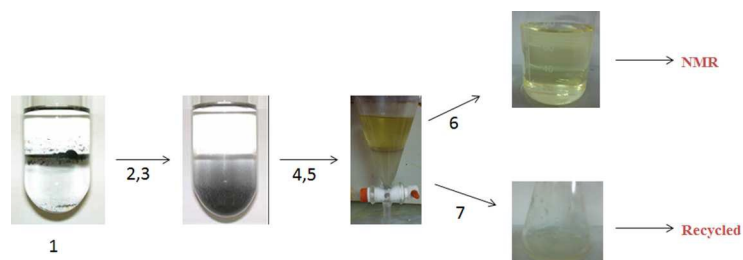


Figure 4. Recycling procedure of the Pd(II)@Pyr:β-CD catalytic system: (1) *in situ* formation of the catalytic species. (2) Addition of phenylboronic acid/styrene and aryl bromide. (3) Stirring for 30 min. at 80 °C. (4) Cooling down to 23 °C. (5) Extraction with Et₂O. (6) Evaporation of the solvent. (7) Reuse of the aqueous phase containing Pd(II)@Pyr:β-CD in subsequent catalytic runs.

Table 8 Comparison table for catalyst performance of different supported catalysts in the C-C coupling reactions.

S.No	Catalyst (mol%)	Solvent	Temp °C	Time (h)	Yield (%)	Ref.
Suzuki-Miyuara coupling						
1	Pd-HP-α-CD ^a (0.5-0.01)	H ₂ O	60	24	100	45
2	PdNPs/bis-Triazolylferrocenyl-CD (0.5)	EtOH:H ₂ O	25	24	98	56
3	bis-MIC CD:Pd ^b (0.5)	EtOH	90	16	99	56
4	β-CD:Pd NPs (0.05)	Water	85	2	95	32
5	α-Cytop-CD:Pd ^c (3×10 ⁻⁹)	Xylene	120	1	95	43
6	β-CD-imidazolium salt:Pd(2.22×10 ⁻²)	Diaxone	50	6	99	38
7	PdLn@β-CD ^d (1×10 ⁻⁷)	Water	50	4	98	36
8	CD-capped PdNPs (0.6)	Water	Reflux	2	98	44
9	Pd-βCD-GNS ^e (0.2)	Water	90	24	90	41
10	PdNPs/Ps ^f (0.5)	H ₂ O/DMF	100	12	100	46
11	PdNPs/Chitosan ^g (4.4×10 ⁻⁴)	Xylene	130	4	71	47
12	Pd(II) complex ^h (0.6)	DMF	80	0.5	50	48
13	PdNPs/TMC ⁱ	H ₂ O	80	14	81	11
14	Pd-basiczeolites (0.3)	EtOH/H ₂ O	50	24	85	49
15	Pd(II)@Pyr-β-CD (0.2)	Water	80	0.5	95	Present work
Heck coupling						
16	PdNPs-β-CD (1.2)	Water	90	2	98	50
17	Pd-αHpCD (0.5)	Water	80	24	96	51
18	PS-PdONPs ^j (1)	Water	80	20	14	52
19	RAME-β-CDmodified Pd/C (0.5)	Water	100	24	29	53

20	Pd-MPTA-1 (10)	Water	Reflux	6	92	54
21	Pd(OAc) ₂ , PABCD ^k (10)	H ₂ O:DMF	80	14	98	55
22	Pd(II)@Pyr-β-CD (0.2)	Water	80	0.5	95	Present work
23	RAME-β-CD, Na ₂ PdCl ₄ (0.02)	Water: hexane	100	5	99	57
24	Pd-[Salen-Py][Br] ₂ (1)	DMF	110	4	98	58

^aPd-Hp-α-CD hydroxyl propyl-α-CD capped palladium. ^bBis-MIC-CD: Pd bis-mesoionic carbine cyclodextrin capped palladium. ^cα-Cytop-CD: Pd cavity supported tetra-phosphine in cyclodextrin with Pd. ^dPdLn@β-CD complex with functionalized β-cyclodextrin. ^ePdβ-CD-GNSPdNPs on β-cyclodextrin functionalized graphene nanosheets. ^fPdNPs/Ps dispersed on cross linked polystyrene polymer. ^gPdNPs/ChitosanPdNPs stabilized on amino modified chitosan-Schiff base ligand. ^hPd(II) complex PdNPs stabilized by dendrimers. ⁱPdNPs/TMCPdNPs supported in thiourea modified chitosan. ^jPdONPs polymer supported palladium nano particles. ^kPABCD per amine modified β-cyclodextrin.

The reaction conditions, activity and effectiveness of the various other catalysts employed earlier for the C-C coupling reactions of phenylboronic acids/styrene and aryl/alkyl halides are given in Table 8. Comparison of the results indicates that our catalytic system (entry 16) exhibits better catalytic activity. The reported systems require organic solvents (entries 1-6, 11, 13 and 15), higher reaction temperature (entries 5 and 10-12) and higher reaction time (entries 1-12, 14 and 15).

Experimental section

General Methods

All reactions were carried out under aerobic conditions. All chemicals were used as commercially available without further purification unless otherwise noted. NMR spectra were recorded at 300 MHz on a Bruker spectrometer. All ¹H NMR and ¹³C NMR spectra were measured in DMSO-d₆ and CDCl₃ with TMS as the internal standard. FT-IR spectral analyses were performed using a JASCO FT/IR-410 instrument by the KBr pellet technique in the range of 4000–500 cm⁻¹. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded in LCQ Fleet, Thermo Fisher Instruments Limited, US. ESI-MS was performed in negative ion mode. XRF analyses were recorded in Horiba Scientific, XGT-5200, X-ray analytical microscope.

General procedure for synthesis of *N*-octyl-pyridine-2-amine (2)

A solution of NaH (29.3 mmol) in 1,4-dioxane (8mL) was added dropwise to a solution of 2-aminopyridine (14.7 mmol) in 1,4-dioxane (8mL). The reaction medium was then heated at 90 °C for 1h. A grey color was observed afterwards, a solution of 1-Cl-Octane (14.7 mmol) in 1,4-dioxane (10mL) is added and the reaction medium was heated at 90 °C for 48h. Color of the mixture changed from grey to pale yellow. 1,4-Dioxane is then removed in vacuum and 125 mL

water is added. The product was extracted with 3×25mL of ethyl acetate, yellow color liquid was observed which was analyzed by NMR spectroscopy (300 MHz, CDCl₃, T=300 K, TMS=0 ppm) and ESI-MS.

Synthesis of Pyridinium Modified β -Cyclodextrin (**3**)

N-octyl-pyridine-2-amine **2** (0.66 mmol) was added to a solution of dried mono-tosyl- β -CD (0.22 mmol) in 1 mL DMF. The reaction medium was heated at 90 °C for 48 h. the reaction mixture was then cooled to room temperature and the product was precipitated with acetone (4 mL). The solid was collected by filtration and washed with acetone (2 x 2 mL). Pure product is obtained via acetone diffusion in DMF. The solid was then dissolved in deionised water (12 mL) and anion exchange from tosylate to chloride was performed using an Amberlite IRA-410 Cl⁻ resin to yield **3** as a light yellow solid (0.12 mmol, 55 %), which was analyzed by NMR spectroscopy (300 MHz, CDCl₃, T=300 K, TMS=0 ppm), FT-IR and ESI-MS. Melting point 210 °C. [Elemental Analysis: for C₅₅H₁₉ClN₂O₃₄: calculated values C, 48.58; H, 6.75; N, 2.06, Found: C, 49.32; H, 7.01; N, 2.12, (Figure S8)].

General procedure for Suzuki cross coupling reaction between aryl halides and phenylboronic acid (4a-q)

A reaction tube equipped with a magnetic stirring bar was charged with pyridinium modified β -cyclodextrin (**3**) (0.003 mmol, 3 mol%) and Pd(OAc)₂ (0.003 mmol, 3 mol%) dispersed in water (2 mL) for 15 min. The phenylboronic acid (1.3 mmol) was added to the in situ formed Pd(OAc)₂ complex with constant stirring. Aryl bromide/iodide (1 mmol) was added and the mixture was allowed to stir at 80°C under aerobic conditions for 30 min. After completion of the reaction, the product was extracted with ethyl acetate, filtered, dried with sodium sulphate, and concentrated under reduced pressure. The resulting crude product was purified by passing it through a column of silica gel 60–120 mesh using petroleum ether/ethyl acetate (9:1 ratio) as the eluent, affording coupling product 4a–q, which was analyzed by NMR spectroscopy (300 MHz, CDCl₃, T=300 K, TMS=0 ppm), FT-IR and ESI-MS. After extraction of the product, the pyridinium modified β -cyclodextrin (**3**) was present in the water layer, which was subsequently reused.

General procedure for Heck cross coupling reaction between aryl halides and styrene (6a-k)

A reaction tube equipped with a magnetic stirring bar was charged with pyridinium modified β -cyclodextrin (**3**) (0.003 mmol, 3 mol%) and Pd(OAc)₂ (0.003 mmol, 3 mol%) dispersed in water (2 mL) for 15 min. The aryl halides (1 mmol) was added to the in situ formed pyr: β -CD/Pd(OAc)₂ complex with constant stirring and continued for 30 min (to complete complexation) and then olefins (1.3 mmol) was added and the mixture was allowed to stir at 80 °C at 30 min. After completion of the reaction, the product was extracted with ethyl acetate, filtered, dried with sodium sulphate, and concentrated under reduced pressure. The resulting crude product was purified by passing it through a column of silica gel 60–120 mesh using petroleum ether/ethyl acetate (9:1 ratio) as the eluent, affording coupling product 4a–q, which was analyzed by NMR spectroscopy (300 MHz, CDCl₃, T=300 K, TMS=0 ppm), FT-IR and ESI-MS. After extraction of the product, the pyridinium modified β -cyclodextrin (**3**) was present in the water layer, which was subsequently reused.

Procedure for recording ESI-MS for intermediates (II), (IV) and (VI)

A reaction tube equipped with a magnetic stirring bar was charged with pyridinium modified β -cyclodextrin (**3**) (0.003 mmol, 3 mol%) and Pd(OAc)₂ (0.003 mmol, 3 mol%) dispersed in water (2 mL) for 15 min. The aryl halides (1 mmol) was added and the mixture was allowed to stir at 80 °C at 30 min. The reaction mixture was separated and its ESI-MS was recorded immediately for intermediate (II). The phenylboronic acid (1.3 mmol) and olefins (1.3 mmol) were added separately to the reaction mixture, allowed to stir for another 30 min. The reaction mixture was separated and its ESI-MS was recorded immediately for intermediates (IV) and (VI).

Conclusions

A novel cyclodextrin derivative, Pyr: β -CD (**3**) bearing *N*-octyl-pyridine-2-amine backbone is developed. This Pyr: β -CD(**3**) functions as an efficient supramolecular ligand for Pd(II) ion and the prepared catalyst, was characterized by NMR, Mass spectrometry, FT-IR spectroscopy, UV-Visible spectroscopy and DLS (Dynamic Light Scattering). Using this Pd(II)@Pyr: β -CD as a homogenous catalyst, an useful and improved aqueous protocol is developed for Suzuki-Miyaura and Heck cross coupling reactions of a wide range of aryl halides

(X= I, Cl, Br) and phenylboronic acid/styrene in water, and it can be used for six runs without significant loss in its activity. The use of environmentally benign water medium, good and excellent yields, easy and rapid recycling protocol, makes this reaction a valid candidate towards the desired objectives of green chemistry. Consequently this catalyst system would open up novel challenging designs of new water soluble catalyst systems with potential industrial applications as well as synthetic utility.

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