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Phosphine-free Heck reactions in aqueous medium using hydroxypropylated cyclodextrins as supramolecular hosts

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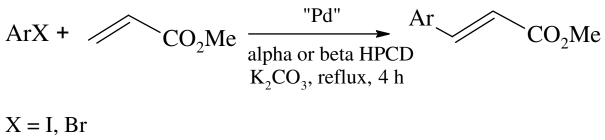
Abstract—It was made possible to carry out Heck reactions in aqueous media using hydroxypropylated cyclodextrins. Best yields were obtained with $Pd/CaCO_3$ as catalyst reservoir. Recycle of the whole system has been made possible up to three times.

Palladium-catalyzed cross-coupling reactions are of major importance in organic chemistry, providing good protocols to the synthesis of elaborated organic compounds from simpler blocks.[1] From ecological and process development perspectives, efforts to produce cheaper and environmentally safe methods have recently been the focus of attention in the scientific community. In this respect, some processes have appeared to be efficiently performed in aqueous environments,[3] including the Heck reaction for certain water-soluble aryl iodides and bromides.[4] In addition, there has been a great search for phosphine-free approaches along with the use of ligand-free palladium.[2a–c] Even though the latter case offers advantages, most of these underligated systems have an inherent instability and the precise control of the parameters that govern the efficiency in aqueous catalytic reactions may be a difficult task. On the other hand, the use of innovative additives, such as water-soluble polymers, dendrimers, membranes and specific ligands, have appeared as interesting alternatives to increase the efficiency and selectivity, acting in the stabilization of Pd nanoclusters.[5]

Cyclodextrins (CDs), cyclic oligosaccharides consisting of 6 (in α), 7 (in β) and 8 (in γ) D-glucopyranose units attached by α-1,4-linkages, have attracted substantial attention in contemporary chemistry.[6a–c] Their hydrophobic internal cavity can include lipophilic molecules, causing significant increase of their solubility in polar solvents, for example, water, which allows better accessibility to aqueous reactions. CDs show catalytic activity in several reactions, including Diels–Alder reactions,[6d] aromatic electrophilic substitution[6e] and hydrolysis of DNA.[6f]

In the field of organometallic chemistry, the ability of CDs is also involved in the formation of host–guest adducts with organometallic complexes, which can be used in technological applications.[7] Indeed, the effect of methylated cyclodextrins in biphasic Suzuki reactions has recently been demonstrated, where their role as mass transfer promoters appeared to be very efficient.[8]

In order to explore the potential of CDs as catalytic promoters in aqueous Heck reactions and from the standpoint of recycling, we report here the palladium-catalyzed cross-coupling of aryl halides with methyl acrylate in the presence of hydrophilic 2-hydroxy-propyl α and β-CDs (α/β-HPCDs, Scheme 1). Our interest in this work has been stimulated by the merging of three



Scheme 1.

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main factors: (i) the practical advantages on the use of aqueous medium in Heck reactions,[9] (ii) our continuous attention in exploring host–guest supramolecular complexes with CDs[10] and (iii) the recently reported ability of CDs to stabilize metal clusters.[11]

Firstly, the use of three different aqueous mixtures was investigated in order to find the most appropriate condition. According to our successful results with the Pd/$CaCO_3$ catalyst,[12b] it was first used as a palladium source. *N*,*N*-Dimethylformamide (DMF), an usual solvent of choice for conventional Heck reactions, was tested in proportions of DMF/H_2O 1:9 and 1:2, respectively. A biphasic medium was tested with CH_2Cl_2, where the performance of hydroxypropylated CDs as mass transfer agents could be evaluated.

As shown in Figure 1, DMF/H_2O ratio affects the catalytic efficiency, probably because the increase in water content reduces the ability of more hydrophilic CDs to perform as mass transfer promoters. In addition, the use of CH_2Cl_2/α or β-HPCD in a biphasic medium does not appear to be a good condition to promote the Heck reaction. Nevertheless, the presence of α or β-HPCD always led to the highest yields, which means CDs significantly enhanced the activity of the cross-coupling reaction. When comparing the efficiency from the viewpoint of CD cavity sizes, α-HPCD best performed to improve the catalytic activity, as noticed by methyl cinnamate yield after 4 h (74%).

To optimize phenyl iodide conversion, the α-HPCD-to-phenyl iodide ratio was varied and its effect in reaction yield was studied. All other reaction parameters were kept constant (temperature, time and catalyst). As observed in Figure 2, as α-HPCD-to-phenyl iodide ratio was lowered from 1.0 to 0.01, the methyl cinnamate yield increased up to 92%. This can be explained by another ratio, inclusion complex to free substrate, that is, the stability constant of the inclusion compound, which is significant for phenyl iodide with α-CDs ($>700\ M^{-1}$).[13] Then, the lowering of CD content frees a part of this reactant from inclusion, which makes them available to react. Although an equivalent amount of α-HPCD contributes to the increase in the efficiency, there seems to exist an optimum cyclodextrin concentration to be used, which does not follow 'the greater, the better' tendency.

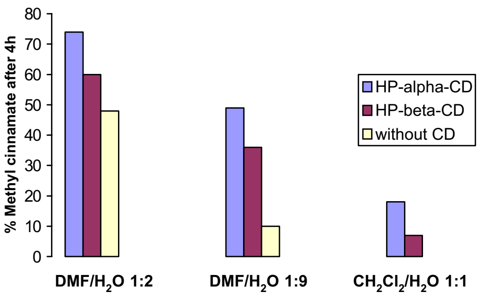

Figure 1. Methyl cinnamate yield (%) after 4 h with α- and β-HPCDs. Reaction conditions: phenyl iodide (1.0 mmol), methyl acrylate (1.3 mmol), K_2CO_3 (2.0 mmol), α- or β-HPCD (1.0 mmol), Pd/$CaCO_3$ (5% w/w, 1 mol % Pd, 70 ppm), 15 mL, under reflux.

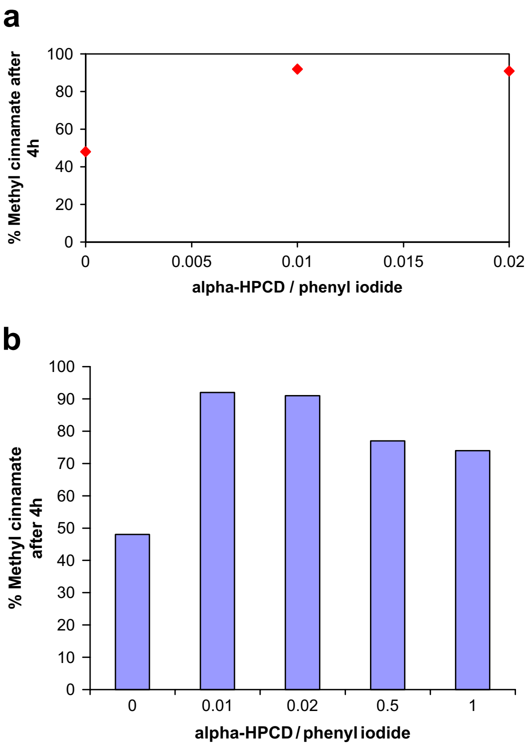

Figure 2. Effect of the α-HPCD/phenyl iodide ratio on the yield of methyl cinnamate after 4 h.

Control experiments with neat DMF in the presence and in the absence of α-HPCD were also carried out. For the latter, a good yield (80%) in a CD free medium was observed, while very low methyl cinnamate yield was noticed from DMF-α-HPCD solution. These results show that in DMF there is no need of the addition of α-HPCD to obtain a reasonable yield, by the contrary, this addition jeopardizes the desired reaction.

The Heck reaction with CDs also proved to be influenced by the palladium source used. Surprisingly, the use of a homogeneous catalyst, $Pd(OAc)_2$, resulted in a low yield of the desired product. In addition, the most classic supported catalyst (Pd/C) showed only a moderate yield under the same conditions (Table 1, entries 1 and 2). Actually, a better dispersion in the aqueous medium was noticed with the Pd/$CaCO_3$ catalyst, which can explain the outstanding increase in activity, compared with Pd/C. This suggests a possible affinity by adsorption of hydrophilic CDs on the surface of the

Table 1. Effect of palladium source on the Heck reaction of phenyl iodide with methyl acrylate in the presence of 1 mol % HPCD

Entry	Source (70 ppm Pd)	Yield[a] (%)
1	$Pd(OAc)_2$	11
2	Pd/C	48
3	Pd/$CaCO_3$	92

[a] Measured by GC–MS.

Pd/$CaCO_3$ catalyst. A similar phenomenon was also verified by Cassez and co-workers when using Pd/C in the presence of methylated-β-CDs.[8]

In an attempt to extend the application of our system under optimized conditions, the coupling of less reactive halides, such as aryl bromide and chloride, with methyl acrylate was carried out. As shown in Table 2, the reactions with phenyl bromide and electron-deficient or electron-rich aryl iodides resulted in moderate to good yields (Table 2, entries 1, 3 and 4) but no appreciable yield was obtained with the less reactive phenyl chloride (entry 2).

Some research groups have previously demonstrated the beneficial effect of CDs in the presence of noble metals. Recently, Luong and co-workers[11d] showed that the presence of unmodified α,β and γ-CDs limited the coalescence of Au nanoparticles, allowing the synthesis of very small (2–4 nm) clusters. Similar findings were reported by Mandler and Willner[14a] and by the Kaifer's group[14b] involving the use of native or perthiolated β-CDs as suitable Pd nanoparticle stabilizers.

As an attempt to confirm the role of α-HPCD as a stabilizer of possible clusters, the preparation of Pd colloids was carried out by reduction of palladium chloride(II) with sodium borohydride in the presence and in the absence of α-HPCD. After refluxing for 24 h, these solutions were cooled to room temperature. At this point, the reagents were added and the reaction mixtures were refluxed for 4 h again. No appreciable yield of methyl cinnamate was observed in the reaction carried out in the absence of α-HPCD. Indeed, the formation of Pd-black was detected in the end of the reaction, as expected in the absence of stabilizing agents. On the other hand, a moderate yield was obtained in the presence of CD (∼50%), suggesting that the effectiveness in the catalytic activity could be a result of CD-stabilized Pd colloids. However, if compared to the results discussed so far, the considerable lower methyl cinnamate yield reveals that the conditions whereby Pd colloids were prepared are not fully appropriate, according to the preparation conditions described by Mandler[14a] for reduction of bicarbonate to formate mediated by Pd-β-CD colloids.

Finally, to evaluate the possibility to recover our catalytic system quantitatively, its reusability was examined by performing three consecutive runs. In this case, we wanted to assure the presence of Pd(0)/Pd(II) soluble species as the true catalysts, according to our previous results.[12] Therefore, after the convenient work-up, the aqueous layer was reloaded and the coupling between phenyl iodide and methyl acrylate was carried out in a Pd/$CaCO_3$ free solution. In all cases, no significant loss of activity was observed between each run (Table 3). Nevertheless, the small decrease in the methyl cinnamate yield could be a consequence of the metal leaching from the aqueous phase to the organic phase, whereas the recovered organic phase was slightly coloured (entry 3).

Table 2. Heck coupling of aryl halides with methyl acrylate using α-HPCD

Entry	Aryl halide	Yield[c] (%)	Reaction time (h)
1	PhBr	60[a] (22)[b]	7
2	PhCl	Traces	24
3	p-$MeOC_6H_4I$	71[a]	4
4	p-$O_2NC_6H_4I$	75[a]	5

[a] Reaction conditions: 1.0 mmol halide, 1.3 mmol methyl acrylate, 2.0 mmol K_2CO_3, 0.01 mmol HPCD, Pd/$CaCO_3$ (0.01 mmol), 15 mL H_2O–DMF (2:1) under reflux.

[b] Without HPCD.

[c] Measured by GC–MS.

In conclusion, the beneficial effect of sub-stoichiometric amounts of α and β-HPCDs in aqueous Heck reactions, using Pd/$CaCO_3$ as catalyst reservoir, between aryl halides and methyl acrylate was shown. In fact, α-HPCD appeared to be the best supramolecular mediator, contributing to a huge enhancement of activity.

The optimum performance of the system studied seems to be a result of combining the cyclodextrin concentration and the choice of palladium source. As discussed, the cyclodextrin to substrate (phenyl iodide) ratio of 0.01 gave the best yield along with the use of Pd/$CaCO_3$ catalyst. In this regard, our results suggest a dual role of α-HPCD whereas it increased the dispersion of the Pd/$CaCO_3$ and seems to stabilize Pd clusters, leached from the support. So far, this is the first example of the use of CDs in Heck reactions. Moreover, the catalytic system can also be recovered and reused with reasonable efficiency, which contributes to its versatility from an industrial viewpoint. Further studies are currently underway in our laboratory in order to better evidence the interaction between α-HPCD and Pd colloids.

General procedure for Heck reactions: In a 100-mL two-necked flask were placed aryl halide (1.0 mmol), methyl acrylate (0.12 mL, 1.3 mmol), α-HPCD (11.8 mg, 0.01 mmol), potassium carbonate (276.4 mg, 2.0 mmol), 5 mL *N*,*N*-dimethylformamide and 10 mL distilled water. After a complete homogeneity, Pd/$CaCO_3$ powder (5% w/w, 1 mol % Pd) was added to the flask and the reaction was heated and stirred for 4 h at 120 °C. Samples were then taken at regular time intervals and analyzed by GC–MS. After centrifugation (5000 rpm), the solid catalyst was recovered and the reaction medium was washed three times with chloroform. The organic phases were dried, evaporated and the isolated products were collected and analyzed by GC–MS.[15] The aqueous phase was stored for reusability.

Table 3. Recycling of the catalytic system[a]

Entry	Cycle	Yield[b] (%)
1	0	92
2	1	85
3	2	77

[a] Reaction conditions: 1.0 mmol phenyl iodide, 1.3 mmol methyl acrylate, 2 mmol K_2CO_3, recovered aqueous phase, 5 mL DMF under reflux.

[b] Measured by GC–MS.

Recycling experiments: The first run was carried out as described above. In a 100 mL flask containing the aqueous phase were poured phenyl iodide (0.11 mL, 1.0 mmol), methyl acrylate (0.12 mL, 1.3 mmol), potassium carbonate (276.4 mg, 2.0 mmol) and 5 mL *N*,*N*-dimethylformamide. The resulting mixture was stirred and heated for 4 h at 120 °C.

(*E*)-*Methyl cinnamate*. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ 7.65 (d, $J = 16.0$ Hz, 1H), 7.57–7.53 (m, 2H), 7.41–7.39 (m, 3H), 6.49 (d, $J = 16$ Hz, 1H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): δ 167.1, 114.7, 134.2, 130.2, 128.8, 128.0, 117.7, 51.5. GC–MS: 162 *m*/*z*, 131 *m*/*z*, 103 *m*/*z*.

(*E*)-*Methyl 4-methoxycinnamate*. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ 7.7 (d, $J = 16.0$ Hz, 1H), 7.47–7.44 (m, 2H), 6.93–6.89 (m, 2H), 6.32 (d, $J = 16$ Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): δ 167.6, 161.5, 144.5, 129.7, 127.2, 115.3, 114.4, 55.4, 51.5. GC–MS: 192 *m*/*z*, 161 *m*/*z*, 133 *m*/*z*.

(*E*)-*Methyl 4-nitrocinnamate*. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ 8.23 (d, $J = 8.7$, 2H), 7.70 (d, $J = 16$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 2H), 6.55 (d, $J = 16$ Hz, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): δ 166.73, 149.2, 142.3, 141.3, 129.4, 124.9, 123.3, 51.6. GC–MS: 207 *m*/*z*, 176 *m*/*z*, 148 *m*/*z*.

Acknowledgements

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15. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 200 and 50 MHz NMR spectrometer in $CDCl_3$. The mass spectra were obtained using a Shidmadzu instrument GC–MS-26542. The chemicals were obtained from commercial sources and used without previous purification.