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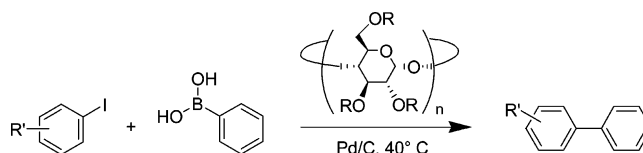
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ABSTRACT



Native and modified cyclodextrins (CDs) have shown polyvalent properties in a biphasic Pd/C-catalyzed Suzuki–Miyaura reaction. In addition to their mass transfer ability, the CDs favored the dispersion of the catalyst in water. With the randomly methylated CDs (RaMe- β -CD), the gains of initial activities were multiplied by factors between 3.8 and 343 depending on the nature of the substrates. The reusability of the system was also demonstrated.

The formation of C–C bonds has long remained a difficult task until the recent development of the Suzuki–Miyaura palladium-catalyzed reaction.¹ A large number of biaryl compounds are now at hand that find applications in many fields including pharmaceuticals, cosmetics, agrochemistry, liquid crystalline materials, and conducting polymers. Experimentally, the coupling reactions between aryl halides and arylboronic derivatives were mainly performed using a phosphine–palladium catalyst in homogeneous,² heterogeneous,³ or biphasic systems.⁴ Though the activities were generally good and the reusability of these systems was often demonstrated, the use of phosphine ligands did not constitute an eco-friendly alternative from an industrial point of view.

In this context, efforts have been made to develop ecological ligandless Pd-catalyzed processes.⁵ Nevertheless, the industrial tonne-scale production is still limited by the low activities (due to the opposite solubilities of both reactants), the severe experimental conditions, and the presence of byproducts resulting from homocoupling reactions.⁶

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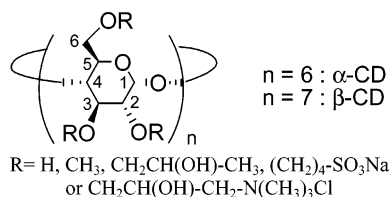
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Our continual exploration of the use of modified α - and β -cyclodextrins (cyclic oligomers made of six or seven glucopyranose units, respectively; Scheme 1) as mass transfer

Scheme 1. Native and Modified β -Cyclodextrins⁷



promoters in biphasic catalytic processes^{4f,8} led us to report here their beneficial contribution to the performances of a Suzuki–Miyaura reaction between aryl iodides and phenylboronic acid in mild experimental conditions using Pd/C as the catalyst. The activity, selectivity, and reusability of the catalyst have been studied, and an unexpected role of cyclodextrins (CDs) was clearly identified.

First, several cyclodextrins have been considered to determine the impact of their structure on the conversion and initial activity of a cross-coupling reaction between phenyl iodide and phenylboronic acid.⁹ When comparing the conversions after 24 h (Figure 1), methylated cyclodextrins (RaMe- α -CD and RaMe- β -CD) appeared to be the most efficient (64 and 62% biphenyl, respectively).

Nevertheless, RaMe- α -CD does not appear to be a valuable mass transfer promoter because a precipitate is observed in the end of the reaction, compromising the reusability of the catalytic system. Indeed, NMR analysis proved that RaMe- α -CD precipitates in a heptan/biphenyl mixture. Interestingly, the efficacy of methylated cyclodextrins strongly depended on their substitution rate. Indeed, the permethylated TriMe- β -CD gave a lower 38% conversion and the partially methylated CrysMe- β -CD led to 30% of biphenyl in the same experimental conditions. The more hydrophilic hydroxypropylated HP- β -CD was slightly less efficient (28% biphenyl), whereas anionic (1-SBE- β -CD) or

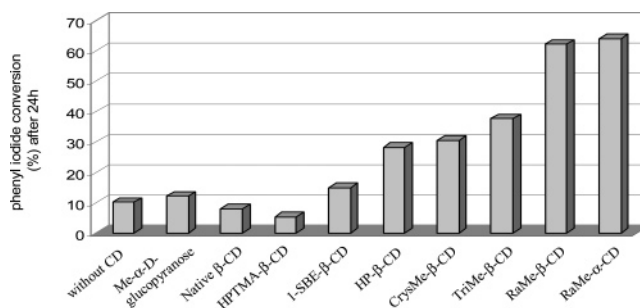


Figure 1. Phenyl iodide conversion (%) after a 24 h reaction with differently shaped CDs. Native β -CD: $R = \text{H}$. RaMe- α -CD and RaMe- β -CD: $R = \text{H}$ or CH_3 (random distribution, 1.8 methyl groups on average per glucopyranose unit). HP- β -CD: $R = \text{H}$ or $\text{CH}_2\text{CH}(\text{OH})\text{-CH}_3$ (5.6 substituents on average per cyclodextrin on the C-2 position). CrysMe- β -CD: $R = \text{H}$ or CH_3 (5 methyl groups on average per cyclodextrin on the C-2 or C-3 position). TriMe- β -CD: $R = \text{CH}_3$. 1-SBE- β -CD: $R = \text{H}$ or $(\text{CH}_2)_4\text{-SO}_3\text{Na}$ (one sulfobutyl group per cyclodextrin on the C-6 position). HPTMA- β -CD: $R = \text{H}$ or $\text{CH}_2\text{CH}(\text{OH})\text{-CH}_2\text{-N}(\text{CH}_3)_3\text{Cl}$ (1.1 substituents on average per cyclodextrin on the C-2). Reaction conditions: $\text{C}_6\text{H}_5\text{I}$ (0.5 mmol), $\text{C}_6\text{H}_5\text{B}(\text{OH})_2$ (0.65 mmol), Na_2CO_3 (1.5 mmol), native or modified cyclodextrins (0 or 0.25 mmol), internal standard $\text{C}_{12}\text{H}_{26}$ (0.3 mmol), Pd/C (5 mg, 9%, 4.2 μmol of Pd) in H_2O (3 g) and heptan (3 g) at 40 $^\circ\text{C}$.

cationic (HPTMA- β -CD) cyclodextrins proved inadequate to improve the performance of the system. Finally, when the reaction was performed with the constitutive building blocks of the CD (methyl- α -D-glucopyranoside), the conversion was only slightly better (12%) than that measured without CD (10%) proving that the CD cavity was responsible for the better performance of the system. In terms of initial activities, it could be noticed that RaMe- β -CD remained the best carrier to promote the Suzuki reaction (44 mol h^{-1}/mol Pd).

To investigate the scope of limitations of the RaMe- β -CDs as supramolecular carriers, the cross-coupling reaction of various monosubstituted phenyl iodide derivatives with phenylboronic acid has been performed. The results are gathered in Table 1.

Whatever the substrate, addition of RaMe- β -CD always improved the catalytic activity, but the relative reaction rate (ratio of the initial activity with RaMe- β -CD to that without RaMe- β -CD) proved sensitive to both the nature and the position of the substituent. For example, though the activity measured for the *p*-acetylphenyl iodide was higher than that measured for the biphenyl iodide (116 vs 24 mol h^{-1}/mol Pd, respectively), the relative reaction rate for the latter was much higher than that obtained for the former (343 vs 6.1, respectively). These results are clearly connected to the water solubility of the substrate.¹⁰ In fact, the more water insoluble the substrate is, the more important the mass transfer promoter contribution is.

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(9) The cross-coupling reaction tests have been performed as follows: in a Schlenk tube, 105 mg of phenyl iodide (0.5 mmol) and 52 mg of dodecane in 3 g of heptan were poured under a N_2 atmosphere on an aqueous solution (3 g) containing cyclodextrin (0.25 mmol), 81 mg of phenylboronic acid (0.65 mmol), 160 mg of sodium carbonate (1.5 mmol), and 5 mg of Pd/C powder (9%, 4.2 μmol of Pd). The reaction was heated at 40 $^\circ\text{C}$ and stirred for 24 h. Conversion in biphenyl was measured by GC and carried out on a Perkin-Elmer Clarus GC500 gas chromatograph equipped with a 5% diphenyl/95% dimethyl silicone capillary column (25 m \times 0.25 mm) and a flame ionization detector. The nature of the products was determined by comparison of their retention times with those of the commercial products.

(10) The water solubility denoted by W (mol L^{-1}) in Table 1 has been evaluated for the different iodide derivatives using an interactive analysis predictor method described in the following paper: Tetko, I. V.; Tanchuk, V. Y.; Kasheva, T. N.; Villa, A. E. P. *J. Chem. Inf. Comput. Sci.* **2001**, 41, 1488–1493.

Table 1. Suzuki–Miyaura Reaction Using Monosubstituted Aryl Iodides (R'C₆H₄I) and Phenyl Boronic Acid as Substrates^g

R'	log ₁₀ (W) ^a	α_i without RaMe- β -CD ^b	α_i with RaMe- β -CD ^b	relative rate ^c	conversion ^d
<i>p</i> -H	-3.07	5.1	47	9.2	65
<i>p</i> -CN	-3.41	18	108	6.0	100 ^e
<i>p</i> -CF ₃	-4.05	0.5	7.8	15.6	86
<i>p</i> -COCH ₃	-2.74	19	116	6.1	100 ^f
<i>p</i> -NH ₂	-2.00	2.2	8.4	3.8	75
<i>p</i> -OCH ₃	-2.12	0.98	34	34.7	49
<i>p</i> -Ph	-5.28	0.07	24	343	31
<i>o</i> -CH ₃	-3.26	0.48	5.6	11.7	15
<i>m</i> -CH ₃	-3.23	0.76	7.0	9.2	26
<i>p</i> -CH ₃	-3.75	0.45	8.2	18.2	37

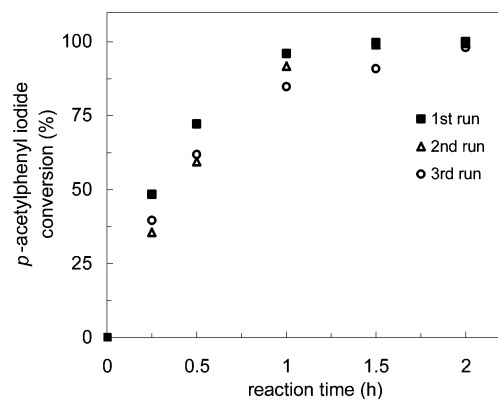
^a Logarithm of calculated water solubility (W) at 20 °C.¹⁰ ^b Initial activities in mol h⁻¹/mol Pd. ^c Defined as the ratio of the initial catalytic activity in the presence of cyclodextrin to the initial catalytic activity without cyclodextrin. ^d Conversion in the presence of RaMe- β -CD (%) after 24 h. ^e Conversion in the presence of RaMe- β -CD (%) after 1.5 h of reaction. ^f Conversion in the presence of RaMe- β -CD (%) after 2 h of reaction. ^g Reaction conditions: R'C₆H₄I (0.5 mmol), C₆H₅B(OH)₂ (0.65 mmol), Na₂CO₃ (1.5 mmol), RaMe- β -CD (0.25 mmol), internal standard C₁₂H₂₆ (0.3 mmol), Pd/C (5 mg, 9%, 4.2 μ mol of Pd) in H₂O (3 g) and *n*-dibutyl ether (3 g) at 40 °C.

In terms of conversion, substrates with an electron-withdrawing substituent (CN, CF₃, or COCH₃) were more rapidly converted than the substrates having an electron-donor group (CH₃, NH₂, OCH₃). For instance, although the water solubility of *p*-trifluoromethylphenyl iodide and *p*-cyanophenyl iodide is close to that of *p*-methylphenyl iodide, the conversions reached 100 and 86% for the substrates with an electron-withdrawing substituent and only 37% for the substrates containing an electron donor group. This reactivity tendency was in line with that generally observed for palladium-catalyzed cross-coupling reactions.¹¹

In terms of chemoselectivity, RaMe- β -CD strongly favored the selective formation of cross-coupling compounds. Thus, the percentage of homocoupling products remained low (1–5%) regardless of the substrate.

Interestingly, it is worth mentioning that RaMe- β -CD was also shape-selective because the three methylphenyl iodide isomers gave different initial activities. The best relative reaction rate was measured for the *p*-methylphenyl iodide (18.2 vs 11.7 for the *o*-methylphenyl iodide and 9.2 for the *m*-methylphenyl iodide) whose structure seemed more appropriate for the inclusion in the CD cavity to occur.

Finally, the reusability of the catalytic system has been evaluated on *p*-acetylphenyl iodide (Figure 2).¹² No ap-

**Figure 2.** Reusability of the catalytic system. Reaction conditions: *p*-CH₃COC₆H₄I (0.5 mmol), C₆H₅B(OH)₂ (1.65 mmol), Na₂CO₃ (1.5 mmol), RaMe- β -CD (0.25 mmol), internal standard C₁₂H₂₆ (0.3 mmol), Pd/C (5 mg, 9%, 4.2 μ mol of Pd) in H₂O (3 g) and *n*-dibutyl ether (3 g) at 40 °C.

preciable loss of activity was observed after three consecutive runs. The initial activities were only slightly decreased (229 vs 187 mol h⁻¹/mol Pd for the first and third runs, respectively), and 98% conversion was still achieved after 2 h in the third experiment.

All the above results have been first rationalized in terms of molecular recognition processes between the aryl iodides and the cyclodextrins. Indeed, it was initially postulated that the beneficial effect of CDs was due to their capacity to transfer organic substrates in the aqueous phase via the formation of inclusion complexes. Nevertheless, the differences in the formation constant values¹³ between phenyl iodide and the CD derivatives are too low to explain the differences in activity and conversion ($K_f(\beta\text{-CD}/\text{C}_6\text{H}_5\text{I}) = 622 \text{ M}^{-1}$; $K_f(\text{HP-}\beta\text{-CD}/\text{C}_6\text{H}_5\text{I}) = 716 \text{ M}^{-1}$; $K_f(\text{RaMe-}\beta\text{-CD}/\text{C}_6\text{H}_5\text{I}) = 785 \text{ M}^{-1}$). Consequently, the recognition process could not constitute the only explanation of the above results.

In fact, we have unexpectedly found that the cyclodextrins can improve the dispersion of the Pd/C catalyst in water. As an example, the triphasic organic/aqueous/catalyst system without CD and with native β -CD or RaMe- β -CD are displayed in Figure 3. Even though the Pd/C catalyst was located at the organic/aqueous interface without CD, a homogeneous distribution of the Pd/C catalyst appeared in the aqueous phase when the CD was added to the medium. Moreover, the homogeneity of the Pd/C catalyst suspension depends on the nature of the CD. Indeed, a much more homogeneous distribution of the Pd/C catalyst in the aqueous phase was obtained with the RaMe- β -CD compared to the native β -CD.

This phenomenon could be explained by assuming an adsorption of the cyclodextrin on the surface of the Pd/C catalyst. Indeed, adsorption of CD increases the hydrophilic

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(12) Catalytic experiments for reusability were carried out as follows: in a Schlenk tube under a nitrogen atmosphere were poured 5 mg of Pd/C (9%, 4.2 μ mol of Pd), 160 mg of Na₂CO₃ (1.5 mmol), 205 mg of phenylboronic acid (1.65 mmol), 327 mg of RaMe- β -CD (0.25 mmol), and 3 g of water. The mixture was kept at 40 °C for 10 min. In another Schlenk tube were dissolved 125 mg of *p*-acetylphenyl iodide (0.5 mmol) and 52 mg of dodecane (0.3 mmol) in *n*-dibutyl ether (3 g). The solution was transferred by cannula into the previous one. The resulting mixture was stirred for 2 h at 40 °C. After decantation, the organic phase was recovered by cannula and the aqueous phase was washed three times with 10 mL of diethyl ether. The aqueous phase was then gently pumped in a vacuum to remove any trace amount of diethyl ether and reloaded with phenylboronic acid, *p*-acetylphenyl iodide, dodecane, and *n*-dibutyl ether as described above.

(13) Formation constants have been determined as described in the following paper: Fourmentin, S.; Outirite, M.; Blach, P.; Landy, D.; Ponchel, A.; Monflier, E.; Surpateanu, G. *J. Hazard. Mater.* **2006**, in press, doi: 10.1016/j.jhazmat.2006.06.090.

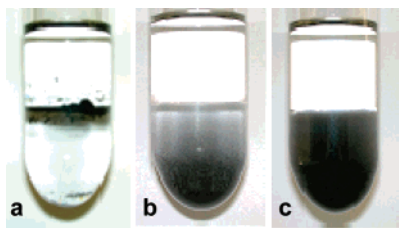


Figure 3. Pd/C distribution in a mixture of water/heptan (10 mg/10 mL/10 mL): (a) without CD; (b) with 57 mg of native β -CD (0.05 mmol); (c) with 66 mg of RaMe- β -CD (0.05 mmol).

character of the support, making its dispersion easier in the aqueous phase. It should be noticed that a previous study has recently shown that cyclodextrins can be adsorbed on activated carbons and that this adsorption is dependent on the number of glucose units of the CD and the size of the carbon pores.¹⁴ In our case, the affinity of the RaMe- β -CD for the Pd/C catalyst has been confirmed by isothermal adsorption studies. Thus, the adsorption isotherm is of Langmuir type and the sorption capacity of the RaMe- β -CD on the Pd/C catalyst reaches $175 \mu\text{mol g}^{-1}$ at the monolayer.

Concurrently to the enhancement of activity due to the CD mass transfer promoter, this dispersing effect of CDs

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on the carbons also widely contributes to the increase in the catalytic activity. The performances of the studied catalytic system are likely a consequence of a combination of two effects: the well-known mass transfer promoter properties of the CDs and their dispersing role on the Pd/C catalyst. Experiments are currently underway to understand how cyclodextrins interact with the Pd/C particles and which of them constitutes the best dispersing agent. Though the interactions between CDs and metallic nanoparticles have already been explored,¹⁵ this is the first example of CD-stabilized Pd/C particles for a catalytic application.

Nowhere else could such a combination of beneficial functional properties be found. As a matter of fact, RaMe- β -CD appeared to be a multifunctional supramolecular entity capable of dispersing and stabilizing Pd/C particles in water, transferring the substrate from the organic to the aqueous phase, recognizing selectively the substrate structure (shape selectivity), and avoiding homocoupling side reactions. Moreover, the advantages of this CD-involving catalytic system also lie in its reusability, the low cost of their constituents, and the low temperature at which it proceeds. All these features give the above triphasic catalytic system a substantial advantage over its main rivals.

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