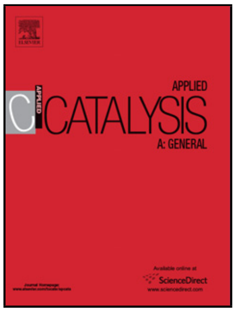

Title: Multifunctional cyclodextrin-based *N,N*-bidentate ligands for aqueous Heck arylation

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Highlights

Two new RAME-β-CD-based N,N-bidentate ligands have been synthesized by click chemistry.

Their palladium complexes have been synthesized and characterized. One of the phosphane displayed a hemilabile coordination mode.

High selectivities were measured in Pd-catalyzed Heck reaction of aryl iodides.

The RAME-β-CD-based N,N-bidentate ligands act as multifunctional ligands as they combined several properties in a single material.

Multifunctional cyclodextrin-based *N,N*-bidentate ligands for aqueous Heck arylation

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Abstract: Novel Pd(II) complexes coordinated by *N,N*-bidentate ligands derived from cyclodextrins have been synthesized by copper-catalyzed azide alkyne 1,3-cycloaddition (CuAAC). Depending on the nature of the *N,N*-bidentate ligand, fast or slow equilibriums between the free *N,N*-bidentate ligand and the Pd-species were detected by NMR measurements. The new Pd(II) complexes acted as efficient water soluble catalysts for the Heck reaction of aryl iodides in aqueous medium. The reaction could tolerate aerobic conditions and affords the coupling products in good yields. Once the reaction was complete, the product and the catalyst could be recovered separately by simple decantation.

Keywords: cyclodextrins – palladium – aqueous catalysis – Heck reaction

1. Introduction

The Pd-catalyzed C-C coupling reaction involving alkenyl or aryl halides and alkenes (Heck reaction) is currently among the most attractive and powerful tools in modern organic synthesis [1-4]. The ease of preparation of a wide range of coupling products, the tolerance of a wide variety of sensitive functionalities and the mild reaction conditions greatly contribute to the spread of the Heck reaction [5,6,7]. The explanation of such an infatuation mainly lies in the efficacy of the numerous catalytic systems that have been developed with time. Both homogeneous and heterogeneous catalysts proved to be suitable candidates [8,9]. Although the true nature of the Pd-catalyst was questioned [10], the efficacy of these catalysts has been clearly demonstrated and very high turnover numbers (TON) could be reached in organic solvents [11]. Efficient catalytic systems have also been developed in non-conventional media [12] such as ionic liquids [13, 14]. Tumas and co-workers [15] and Holmes and Carroll [16] independently reported the application of fluorinated phosphanes coupled with a palladium source in Heck and Suzuki couplings in $scCO_2$. Arai and co-workers reported the use of water-soluble palladium complexes bearing sulfonated phosphanes in $scCO_2$ with an added polar cosolvent for Heck reactions [17]. Water is also a very attractive solvent for Heck reactions [18,19,20,21] as it is cheap, environmental-friendly and available in large quantities. Heck reactions in aqueous media have especially been developed using catalytic systems based on a simple Pd sources [$Pd(OAc)_2$, $PdCl_2$, etc.] without any ligand [22]. Palladium acetate immobilized on reversed phase amorphous silica gel with the aid of an ionic liquid, $[bmim]PF_6$, was highly efficient in the promotion of the Mizoroki-Heck reaction in pure water without any ligand up to the sixth re-use, in 95% average yield [23]. In some cases, biphasic systems were used in combination with palladium salts and water-soluble phosphanes with the specific aim of aiding catalyst recovery as exemplified in the Heck coupling reactions studied by Arai et al. [24]. Shaughnessy and co-workers utilized both sterically demanding water-soluble triaryl-phosphanes in Heck/Suzuki couplings of aryl bromides [25]. Amphiphiles also proved to be effective for Heck reactions in aqueous media [26,27].

In numerous aqueous catalytic systems reported in the literature, the use of ligands was often required to stabilize Pd catalytic species and avoid the formation of Pd black. To this end, phosphanes have been mainly considered as ligands to coordinate the metal [28-30]. The utilization of the resulting phosphane-coordinated Pd-catalysts covered a wide range of coupling partners [31,32]. Nonetheless, although they still attract much attention nowadays due to their catalytic performances [33], phosphanes did not constitute a completely satisfactory solution to stabilize the metal as they are toxic, air-sensitive, expensive, and subject to P-C bond degradation at elevated temperature [34,35]. Accordingly, oxygen-free experimental conditions are required thus limiting the scope of their use. Recently, there has been an increased emphasis on the use of ligands with other donor atoms [36]. Nitrogen-containing ligands have emerged as promising candidates [37-45]. These ligands are moisture and air-stable and economically inexpensive. A few years ago, we developed the use of modified cyclodextrins (CDs) as effective additives to promote the conversion of organic substrates in water. Modified CDs can act as mass transfer promoters for partially hydrophilic substrates and as interfacial receptors for hydrophobic substrates [46]. Among modified CDs, randomly methylated β-CDs (RAME-β-CDs) [47] proved to be especially appropriate in various biphasic catalytic systems due to their ability to adsorb at the aqueous/organic interface [46,48,49]. Herein, we detail the synthesis of two new RAME-β-CD-based *N*,*N*-bidentate ligands and their Pd-complexes. The idea is to combine on a unique molecular platform the coordinating properties of a robust bidentate ligand with the adsorbing properties of RAME-β-CD. The catalytic performances of the resulting multifunctional Pd-complexes have been examined in an aqueous C-C coupling reaction between aryl halides and vinyl derivatives (methyl acrylate or styrene).

2. Experimental

2.1. General procedures

All chemicals were purchased from Acros and Aldrich Chemicals in their highest purity. All solvents were used as-supplied without further purification. Distilled water was used in all experiments. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-backed silica gel (Silica Gel F254). Reactions were carried out on a Mars microwave model (CEM Corporation) that delivered 800 W output at a 2450 MHz frequency. Teflon microwave-transparent XP-1500 vessels (with control temperature conditions inside sample vessels by RTP-300 Plus temperature sensor) were used. The system regulated the microwave power output to maintain a selected temperature parameter. Compounds were identified using UV fluorescence and/or staining with a solution of phosphomolybdic acid in aqueous sulfuric acid and ethanol. NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei. $CDCl_3$ (99.50% isotopic purity), DMSO-d_6 (99.80% isotopic purity) and D_2O (99.92% isotopic purity) were purchased from Euriso-Top. ^{1}H NMR data are reported as chemical shift, multiplicity (s, singlet; d, doublet; m, multiplet), relative integral, coupling constant (J in Hertz). Absorption spectra were recorded on a Lambda 19 (Perkin Elmer) dual-beam spectrophotometer (1 cm path cuvette) using the method of standard additions. In a vessel containing 3.5 mL of an aqueous solution of modified RAME-β-CD (10^{-4} mol.L^{-1}) were added successive aliquots (0.1 equiv.) of an aqueous solution of Na_2PdCl_4 (20 μL, 1.75 x 10^{-3} mol.L^{-1}). Mass spectra were recorded on a MALDI-TOF–TOF Bruker Daltonics Ultraflex II in positive reflectron mode with 2,5-DHB as matrix. Surface tension measurements have been carried out using an Attension Force Tensiometer Sigma 701 with a Wilhelmy plate and two Titronic dispenses. Gas chromatographic analyses of the organic phase were carried out on a Shimadzu GC-17 A 500 gas chromatograph equipped with a polydimethylsiloxane capillary column (30 m×0.32 mm) coupled with a Shimadzu QP-5000 mass spectrometer (GC:MS). Conversions were determined by GC using undecane as an internal standard and comparison with references. Conversions were defined from consumption of aryl halide with time. ICP-AES measurements have been performed using a ICP-AES Vista-Pro VARIAN spectrometer.

2.2. General procedure for the synthesis of randomly methylated mono substituted-β-CDs (1 and 2)

Randomly methylated mono-6-azido-6A-deoxy-β-D-cyclodextrin (1.8 mmol) and hydrated copper sulfate (2.1 mmol) were added to a solution of alkynyl precursor (2.1 mmol alkynyl function) in DMF (90 mL). After subsequent dropwise addition of a freshly prepared solution of sodium ascorbate (5.2 mmol) dissolved in water (10 mL), the mixture was subjected to microwave irradiations under vigorously stirring at 60 °C for 2 h. After solvent evaporation, the crude product was dissolved in an ammoniac solution (10 weight%) and stirred overnight before being purified by column chromatography on silica gel with water as eluent to give the product as a pale yellow powder.

2.3. Randomly Methylated 1-(6A-Deoxy-β-D-cyclodextrin)-4-[(dimethylamino)methyl]-1,2,3-triazole (1)

Yield 83%. ^{1}H NMR (300 MHz, D_2O): δ 8.27 (s, 1 H), 5.19 (m, 4.9 H), 4.98 (m, 50H), 4.44 (m, 2.1 H), 4.13 (m, 3.1 H), 3.98–3.88 (m, 13.1 H), 3.68–3.53 (m, 43.9 H), 3.47–3.29 (m, 17.9 H), 2.82 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 137.4, 135.2, 112.8, 101.4–99.8, 99.0–97.4, 82.7–81.6, 78.5, 73.4, 73.3, 73.1, 72.6, 72.3, 72.2, 70.9, 70.3, 64.4–59.4, 42.4, 30.2, 20.2, 19.7 ppm. MS: m/z (%) = 1433.51 (11.6) (calcd. 1433.57 for $[C_{59}H_{102}N_4O_{34} + Na]^+$), 1447.53 (69.9) (calcd.1447.58 for $[C_{60}H_{104}N_4O_{34} + Na]^+$), 1461.55 (16.1) (calcd. 1461.59 for $[C_{61}H_{106}N_4O_{34} + Na]^+$), 1477.05 (2.3) (calcd. 1475.6 for $[C_{62}H_{108}N_4O_{34} + Na]^+$).

2.4. Randomly Methylated 1-(6A-Deoxy-β-D-cyclodextrin)-4-(2-pyridinyl)-1,2,3-triazole (2)

Yield 68%. ^{1}H NMR (300MHz, D_20): δ 8.60 (2H,m), 8.07 (2H, m), 7.53 (1H, m), 5.48-4.99 (m, overlapped with D_2O), 4.74-4.61 (1H, br. s), 4.40-4.22 (1H, br. s), 4.18-2.93 (68.4H, m) ppm ^{13}C NMR (75.5MHz, D_2O): δ 152.0, 148.4, 146.9, 136.8, 129.3, 127.8, 126.3, 104.6, 102.3, 85.5, 84.0, 81.4, 76.4, 74.7, 73.5, 70.5, 62.7, 61.7, 55.0 ppm. MS : m/z (%) = 1425.18 (0.9) (calcd. 1425.14 for $[C_{59}H_{94}N_4O_{34} + Na^+]$), 1439.19 (4.0) (calcd. 1439.15 for $[C_{60}H_{96}N_4O_{34} + Na^+]$), 1453.21 (19.0) (calcd. 1453.16 for $[C_{61}H_{98}N_4O_{34} + Na^+]$), 1467.24 (57.9) (calcd. 1467.17 for $[C_{62}H_{100}N_4O_{34} + Na^+]$), 1481.26 (14.7) (calcd. 1481.18 for $[C_{63}H_{102}N_4O_{34} + Na^+]$), 1497.26 (2.2) (calcd. 1495.20 for $[C_{64}H_{104}N_4O_{34} + Na^+]$), 1507.20 (1.4) (calcd. 1509.20 for $[C_{65}H_{106}N_4O_{34} + Na^+]$).

2.5. Typical procedure for the Heck reaction

To a stirred solution of aryl halide (1 mmol) in 2.5 mL heptane were added the alkene (1.5 mmol) and the internal standard (undecane, 0.3 mmol). An aqueous solution (2.5 ml) containing ligand **1** or **2** (0.1 mmol), Na_2PdCl_4 (0.005 mmol) and $NaHCO_3$ (1.5 mmol) was then added. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was cooled to room temperature. Once the organic phase has been recovered, the aqueous phase was washed twice with diethyl ether (2 × 2 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and heptane was removed under vacuum. The residue was purified by chromatography over a silica gel column. Elution with 10% ethyl acetate - heptane gave the expected bisaryl products as colorless oils.

Conversions were calculated on the basis of disappearance of aryl halides, with no visible side reactions occurring. Conversions were calculated using the following equation,

$$conversion(t) = ([aryl\ halide]_0 – [aryl\ halide]_t)/[aryl\ halide]_0 \times 100\%$$

where ([aryl halide]$_0$ is initial aryl halide concentration and [aryl halide]$_t$ is the aryl halide concentration at time t during the reaction.

Turnover number (TON) was calculated using the following formula,

$$TON = (moles\ [aryl\ halide]\ converted/mole\ Pd) \times 100.$$

Turnover frequency (TOF) was calculated as the ratio of,

$$TON\ /\ time\ required\ to\ achieve\ TON\ (\mathrm{TON.h^{-1}}).$$

2.6. Reusability of the catalytic system

The reusability of the catalytic system has been carried out as follows. Once the organic phase of the first run has been removed, fresh reactants and the internal standard (undecane) were added into the catalyst-containing flask and the reaction was heated at 100 °C for 3 h. The same work-up as described in the above typical procedure (**2.5.**) was then applied.

3. Results and discussion

3.1. Synthesis and characterization of CD-based *N,N*-bidentate ligands

Ligands **1** and **2** (Scheme 1) were synthesized by copper-catalyzed azide alkyne 1,3-cycloaddition (CuAAC) as follows. The alkynyl precursor (1.3 equiv 3-dimethylamino-1-propyne or 2-ethynylpyridine, respectively) were mixed in DMF with randomly methylated mono-6-azido-β-CD [50] (1.0 equiv) and $CuSO_4.5H_2O$ (0.1 equiv). After addition of sodium ascorbate (0.2 equiv.) at room temperature, the blue solution gradually changed to orange, color characteristic of the presence of cuprous acetylide [51]. The mixture was then subjected to microwave irradiations under vigorously stirring at 60 °C for 2 h. After DMF evaporation, the crude products were submitted to purification. Addition of an ammoniac solution (10 weight%) entrapped the Cu-ions in the form of tetraamminecopper(II) sulfate which was removed by chromatography on a silica column using water as eluent. The deep blue Cu-complex remained at the top of the column whereas the CD-based products migrated to give **1** or **2** in 83 and 68% yields, respectively.

As described below, the availability of the CD cavity was crucial in our catalytic system to promote the conversion of the substrate. Indeed, examples from the literature usually described a CD platform substituted by hydrophobic substituents capable of interacting with the CD cavity [52]. **1** and **2** behaved very differently. As clearly shown in their 2D T-ROESY spectra realized in D_2O at 25 °C (ESI), no correlation could be observed between the protons of the CD-substituent (*N,N*-dimethylaminotriazolyl or pyridyltriazolyl) and the inner CD protons (H3 and H5). The molecular recognition of a guest molecule by the CD cavity thus remained possible. To complete the analysis of **1** and **2**, surface tension measurements have been carried out in water. The regular decrease in surface tension γ was indicative of their interfacial adsorption in the 10^{-5}–1 mM concentration range (Fig. 1). **1** and **2** were more surface active than RAME-β-CD, thus demonstrating their higher ability to interact with the air–water interface. Note that no critical micellar concentration could be observed in the studied concentration range. **1** and **2** could be considered hydrotropic. Their water-solubility was similar to that measured for RAME-β-CD (>500 g/L).

3.2. Synthesis and characterization of Pd-complexes.

The complexing properties of **1** and **2** towards Na_2PdCl_4 were assessed at room temperature in D_2O by NMR spectroscopy. The stoichiometry of the obtained Pd-complexes was determined using a continuous variation method (Job plot) [53]. Two mother solutions of equal concentration were prepared, one containing the free ligand (**1** or **2**) and the other one containing Na_2PdCl_4. Aliquots of each solution were added in a NMR tube so that the total concentrations [Na_2PdCl_4 + ligand] remained constant while the concentration of each compound was varied. Chemical shifts variations ($\Delta\delta$) were recorded for each sample in the ^{1}H NMR spectra. Using **1** as a ligand, average NMR signals (ESI) were detected, illustrative of a fast equilibrium between the free ligand and the Pd-species. In that case, the chemical shifts variations observed for the triazolyl proton and the methylene group attached to the amino group were translated into a Job plot which revealed a maximum around 0.66 characteristic of a 2:1 stoichiometry (two ligands **1** for one Pd). The resulting Pd-complex (**3**) was described in Fig. 2. Conversely, distinct resonances were observed for the free ligand **2** and two different Pd-complexes depending on the concentrations (Figure 3). With ligand **2** in excess, the metal was stabilized by two ligands **2**, resulting in the formation of the Pd-complex **4** containing tetradentate-nitrogen donor ligands, as already observed in the literature [54,55]. However, a fluxional coordination behavior (equilibrium between **4** and a Pd-center coordinated by three nitrogens and one chloride) could not be ruled out at this stage. Conversely, when ligand **2** is in default, only one ligand **2** could then coordinate the metal resulting in the formation of Pd-complex **5**. Note that the observation of three sets of resonances in the ^{1}H spectra revealed a slow equilibrium between the free ligand **2** and the Pd-complexes **4** and **5** (at least on the NMR time scale). The difference in behavior between **1** and **2** resulted from the hemilability of the amino group of **1**. Indeed, it has previously been shown that $-NR_2$ exhibited a strong hemilabile character [56]. Thus, average NMR signals were observed for mixtures of **1** and Na_2PdCl_4 while distinct NMR resonances were observed for mixtures of **2** and Na_2PdCl_4. No cross-peaks could be detected in 2D T-ROESY spectra of mixtures containing **1** or **2** and Na_2PdCl_4. Accordingly, the CD cavities of Pd-complexes **3**, **4** and **5** remained available for the molecular recognition of appropriate substrates (ESI). Indeed, 2D T-ROESY experiments realized using mixtures of **1** (or **2**), Na_2PdCl_4 and phenyl iodide (chosen as a model substrate) clearly showed that cross-peaks were detected between the aromatic protons of the substrate and the CD protons, indicative of the inclusion of phenyl iodide within the CD cavity, even after coordination of the nitrogens onto the Pd center (ESI).

UV/vis spectra were also recorded to characterize the Pd-complexes (ESI). When the absorbance vs wavelength curves related to mixtures of **1** (or **2**) and Na_2PdCl_4 were translated into a plot representing the absorbance vs the amount of Na_2PdCl_4, the ruptures in the slope at 0.5 equiv. confirmed the 2:1 stoichiometry of complexes **3** (two ligands **1** for one Pd) and **4** (two ligands **2** for one Pd).

3.3 Catalytic results

Heck reactions involving aryl halides and methyl acrylate were performed at 100 °C in a water/heptane mixture (2.5 mL each) using Na_2PdCl_4 (0.005 mmol%) as a Pd precursor. Blank runs were carried out using the randomly methylated β-CD (RAME-β-CD), one of the best additive so far in aqueous organometallic catalysis (Table 1).[47] Only very small fractions of aryl iodide (<1%) could be converted in that case (Table 1, entry 1) due to the instability of the active monomeric Pd(0) species. Indeed, the catalytic system rapidly evolved to Pd black. In fact, whatever the amount, RAME-β-CD was not able to stabilize the palladium species in water. Ligand coordination was then required to sustain monomeric Pd(0) in water. As expected, the chelation effect inherent in **1** and **2** ensured the stability of the Pd-species in water. Excess ligand (at least 10 equiv.) was added to Na_2PdCl_4 in water to favor the in situ formation of Pd-complexes **3** or **4**. As usually observed for the Heck reaction, aryl iodides were more readily converted than aryl bromides (Table 1, entries 2-7). No conversion could be measured with aryl chlorides. With aryl iodides (Table 1, entries 6-25), low turnover frequencies (TOF) were measured (up to 39.6 h^{-1}). It should be noted that in all cases only the *trans* products could be selectively obtained as confirmed by ^1H and ^{13}C NMR (ESI). Complex **3** (Pd coordinated by **1**) proved to be a more effective catalyst than complex **4** (Pd coordinated by **2**) presumably because of the hemilabile character of **1** (as revealed by the fast equilibrium in the NMR spectra, see above). Indeed, the amino group of **1** being partially coordinated onto the metal, the oxidative addition of aryl halide was favored leading to an enhanced catalytic activity. Conversely, ligand **2** was more strongly coordinated to the Pd center (as revealed by the slow equilibrium in the NMR spectra). The stability of Pd-species coordinated by ligand **2** then slowed down the oxidative addition of aryl halides, thus decreasing the catalytic activity.

Both aryl iodides bearing electron-donating or electron-withdrawing groups could be converted into coupling products with conversions ranging from poor to excellent (up to 99%). No correlation could be found when comparing the substrates water solubility (W) and the catalytic activity. For example, phenyl iodide (W = 70 mg/L) gave higher TOFs (entries 6 and 7) than *p*-iodophenol (W = 428 mg/L, entries 10 and 11). Similarly, 4-iodobenzonitrile (W = 82 mg/L) gave comparable TOFs (entries 8 and 9) than 3,4-dimethylphenyl iodide (W = 7 mg/L, entries 18 and 19). Interestingly, a recognition process between the CD cavity and the substrate greatly contributed to the catalytic efficacy. Indeed, as already observed for RAME-β-CD,[27] **1** and **2** were capable of adsorbing at the aqueous/organic interface as confirmed by surface tension measurements (Fig. 1). Consequently, the CD cavity of **1** or **2** could interact with the organic phase to promote the conversion of a substrate molecule into a product. Moderate to poor conversions were achieved with hindered aryl iodides (2-methylphenyl iodide and 3,4-dimethylphenyl iodide). While the bad results obtained with 2-methylphenyl iodide (Table 1, entries 22 and 23) could be explained by a lower oxidative addition of the substrate on the Pd-center (hindered coordination sphere), the results obtained with the 3,4-dimethylphenyl iodide were clearly related to a complicated recognition process with the CD cavity. Due to the bulkiness of the methyl substituents, 3,4-dimethylphenyl iodide was unable to enter the CD cavity as clearly shown by the absence of correlations in the 2D T-ROESY spectrum (ESI). Less hindered substrates such as *p*-methoxyphenyl iodide, *p*-tolyl iodide or *m*-tolyl iodide led to higher conversions (Table 1, entries 12, 13, 16, 17, 20 and 21) due to a better inclusion of the substrate in the CD cavity as exemplified by the presence of intense cross-peaks in the 2D T-ROESY spectrum of a stoichiometric mixture of **1** and *p*-methoxyphenyl iodide (Figure 4). Thus, through both Pd-coordination and molecular recognition, **1** and **2** confined the catalyst and the substrate in a restricted volume resulting in enhanced capacity to maximize the C-C coupling reaction. Additionally, whatever the substrates, no by-products could be detected indicative of a very selective catalytic process. Also note that no variation in the catalytic performance could be noticed when the reaction proceeded under anaerobic conditions thus highlighting the robustness of the studied catalytic system.

The catalytic results obtained with methyl acrylate were confirmed with styrene as a substrate (Table 2). The superiority of **3** over **4** was even more marked as the conversions were always better using **1** as a ligand. Here again, the water solubility of the substrate could not be incriminated to explain the catalytic results. The catalytic performance was dependent on the recognition process between the substrates and the CD cavity. As expected, the linear *p*-tolyl iodide, which was well recognized by the β-CD cavity, led to better TOF than the hindered 2-methylphenyl iodide, 3-methylphenyl iodide and 3,4-dimethylphenyl iodide (Table 2, compare entries 6, 7 with 8-13). We believe that, in that case, the catalytic activity was influenced by both the inclusion of aryl iodide within the CD cavity and by the recognition of styrene within another CD cavity. A kinetic monitoring realized with phenyl iodide and styrene as substrates and **1** as a ligand showed that the conversions levelled off after 5 h (Figure 5). This observation probably resulted from the increasing amount of C-C coupling products in the solution. Indeed, the proportion of product included within the CD cavity regularly increased with time, thus limiting the supramolecular recognition of remaining substrate. However, poisoning of the CD cavity by the reaction product could be excluded as the catalytic system could be recycled (Table 2, runs 16). Thus, once the reaction was complete, a rapid decantation took place and the organic phase was recovered by cannula. The aqueous catalyst-containing solution recovered from run 2 was filtered at 80 °C on Celite to remove any heterogeneous Pd-catalysts (such as Pd-particles). Fresh phenyl iodide and styrene were then added into the catalyst-containing flask and the Heck reaction then proceeded under the same experimental conditions as described above. The equilibriums were then displaced to the formation of CD/substrate complexes and the residual product was excluded from the CD cavity. For the second run, 68% phenyl iodide were converted within 5 h vs 74% for the first run. The slight decrease in conversion observed between the first and the second run was likely a consequence of the increasing amounts of salts (NaI) in the aqueous compartment. Indeed, addition of NaI (1 equiv. regarding the substrate) in the reaction mixture at the beginning of the reaction led to a comparable conversion in C-C coupling product (66% after 5 h). As such, the advantage of the present catalytic system lies more in the easy separation of the coupling product and the Pd-catalyst once the reaction was complete than in its reusability. Finally, the recovered organic phases were analyzed by ICP-AES. No trace of metal could be detected (< 0.2 ppm) thus highlighting the efficacy of the current process. Indeed, although the catalytic steps at Pd proceeded smoothly, the multidentate character of the CD-based ligand led to higher coordination states. As such, the Pd(0) intermediates were never underligated during the catalytic cycle. Accordingly, **1** and **2** acted as stabilizing ligands of Pd-species in water, thus avoiding aggregation of Pd into inactive clusters.

4. Conclusions

In summary, RAME-β-CD was used as a platform to access *N*,*N*-bidentate ligands **1** and **2** by click chemistry (CuAAC). **1** and **2** were successfully used as ligands to stabilize Pd(0)-species in water. The latter were effective in phosphane-free Heck reaction of a wide range of aryl iodides (and to a less extent aryl bromides) bearing electron-donating or electron-withdrawing groups with moderate activity and good stability in aerial atmosphere. The *N*,*N*-

dimethylaminotriazolyl-substituted β-CD (**1**) was a better ligand than the *N*,*N*-pyridyltriazolyl-substituted β-CD (**2**) because of the hemilabile character of the *N,N*-dimethylamino group towards the palladium center. **1** and **2** acted as multifunctional ligands as they combined several properties in a single material: i) they stabilized the reactive metal center in water during the course of the Heck reaction (easy separation of the product and the catalyst once the reaction is complete), ii) they allowed for a significant increase of the substrate concentration in water or at the aqueous/organic interface, iii) they increased the local concentrations of substrate and catalyst in a confined environment. Thus, **1** and **2** could be considered as versatile catalysts for aqueous organometallic catalysis. Actually, both hydrophobic and partially hydrophilic aryl halides and alkenes could be readily converted into substituted alkenes. This study is a new illustration of the efficacy of CD-based supramolecular edifices for the transformation of organic substrates in aqueous media.

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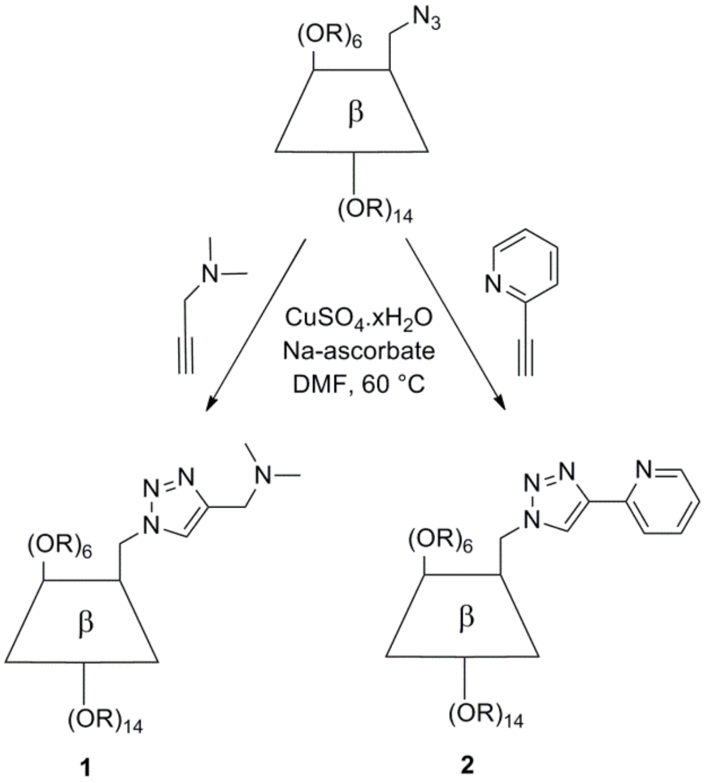


Scheme 1 Synthesis of RAME-β-CD-based *N*,*N*-bidentate ligands **1** and **2**. R = H or CH_3 (substitution degree = 1.8 per glucopyranose unit).

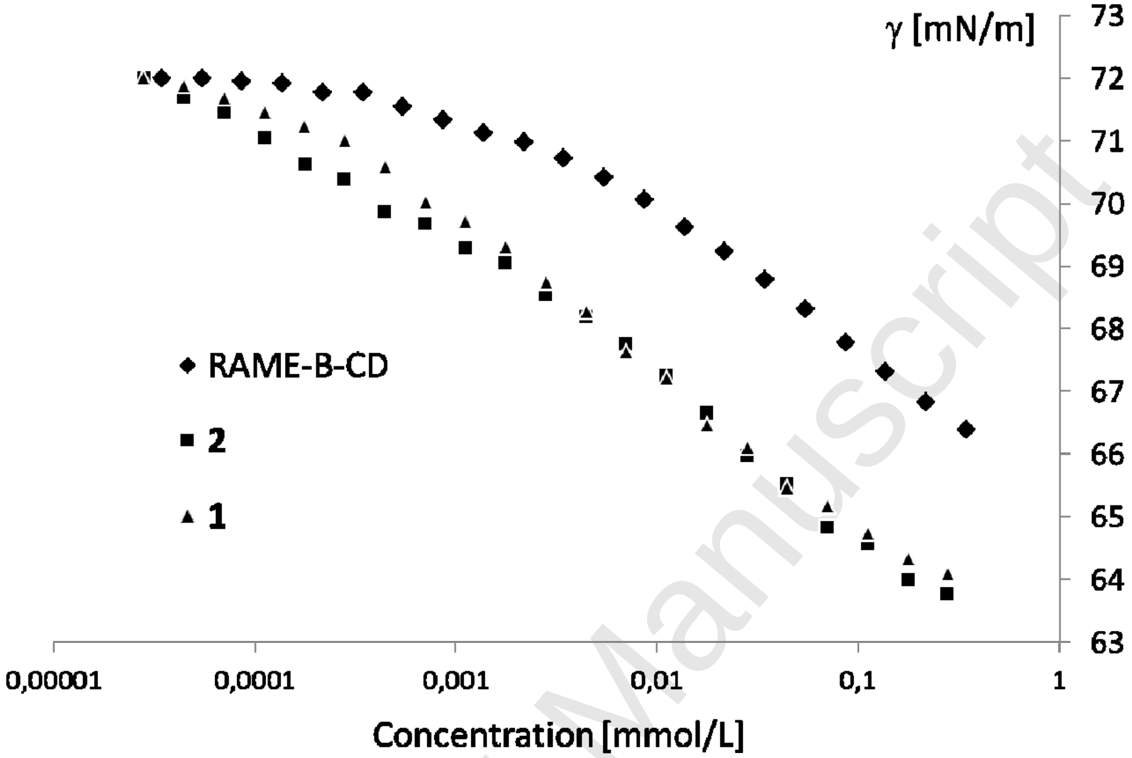


Fig. 1 Surface tension measurements of RAME-β-CD, **1** and **2** as a function of their concentration in water at room temperature.

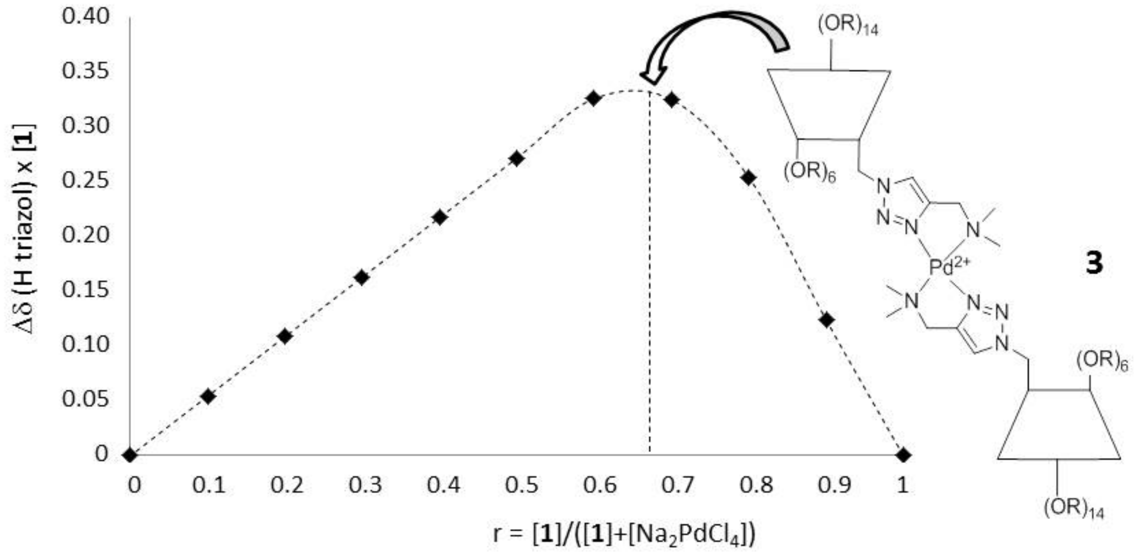


Fig. 2 Continuous variation plot (Job's plot) derived from chemical shift variations of the triazolyl proton of ligand **1**.

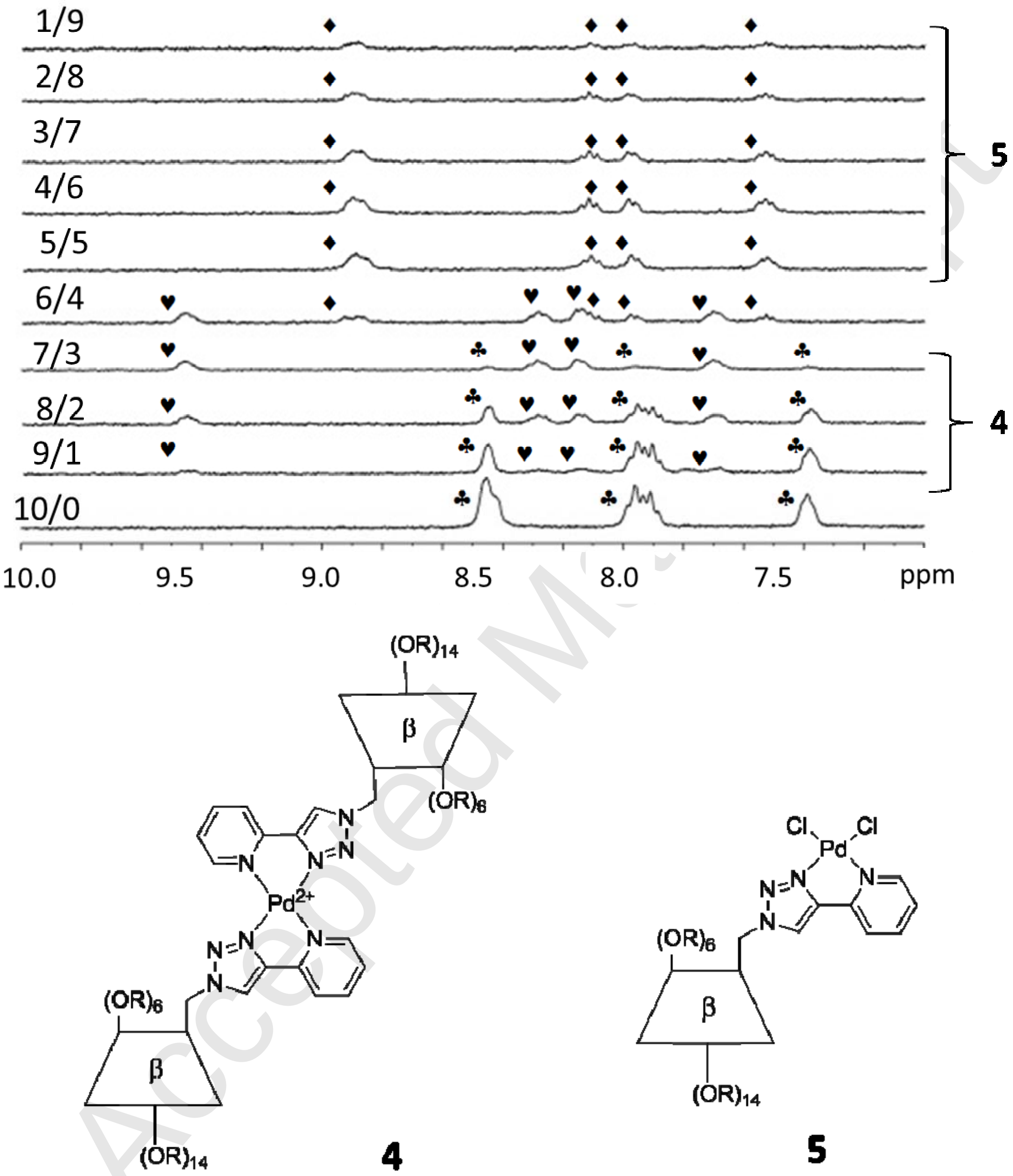


Fig. 3 Partial 300 MHz ^{1}H NMR spectra (triazolyl and aromatic region) of **2**/Na_2PdCl_4 mixtures in D_2O at 25 °C. The total concentration of species is 10 mM. The **2**/Na_2PdCl_4 ratios are given on each spectrum. ♣ free ligand **2**. ♥Pd-complex **4**. ♦Pd-complex **5**.

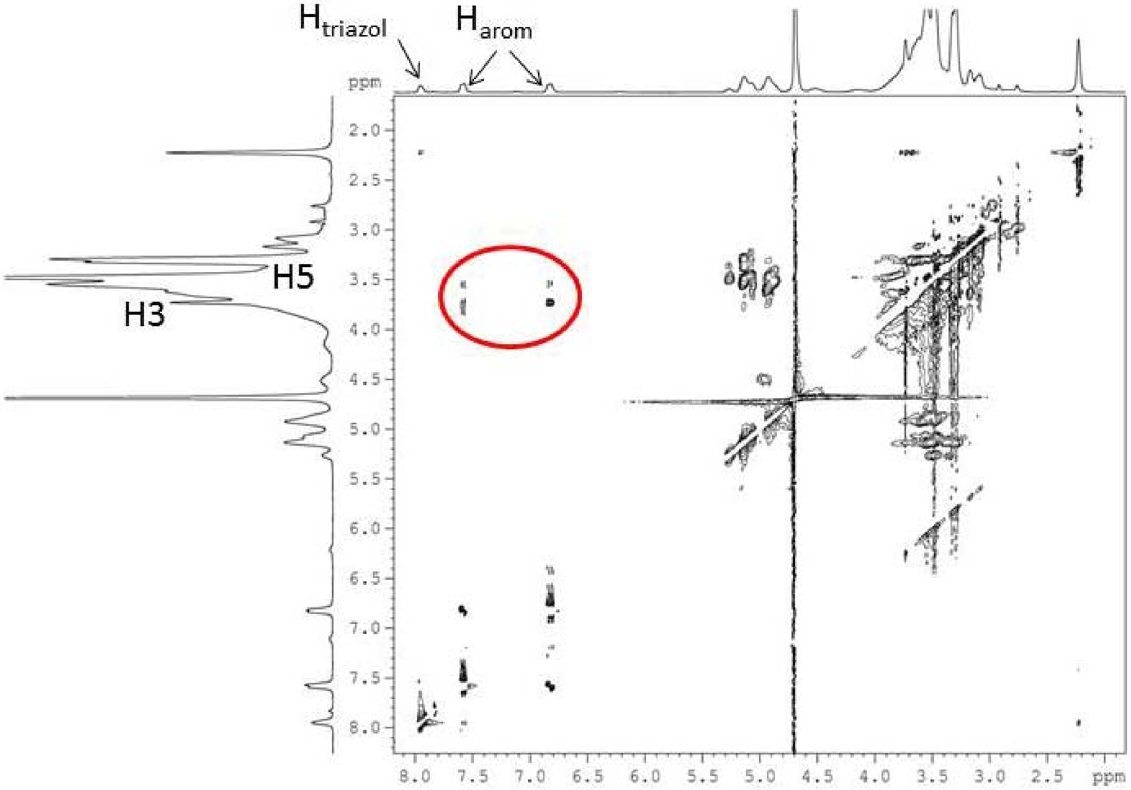


Fig. 4 2D T-ROESY spectrum of a stoichiometric mixture of **1** and *p*-methoxyphenyl iodide (5 M^{-1} each) in D_2O at 25 °C.

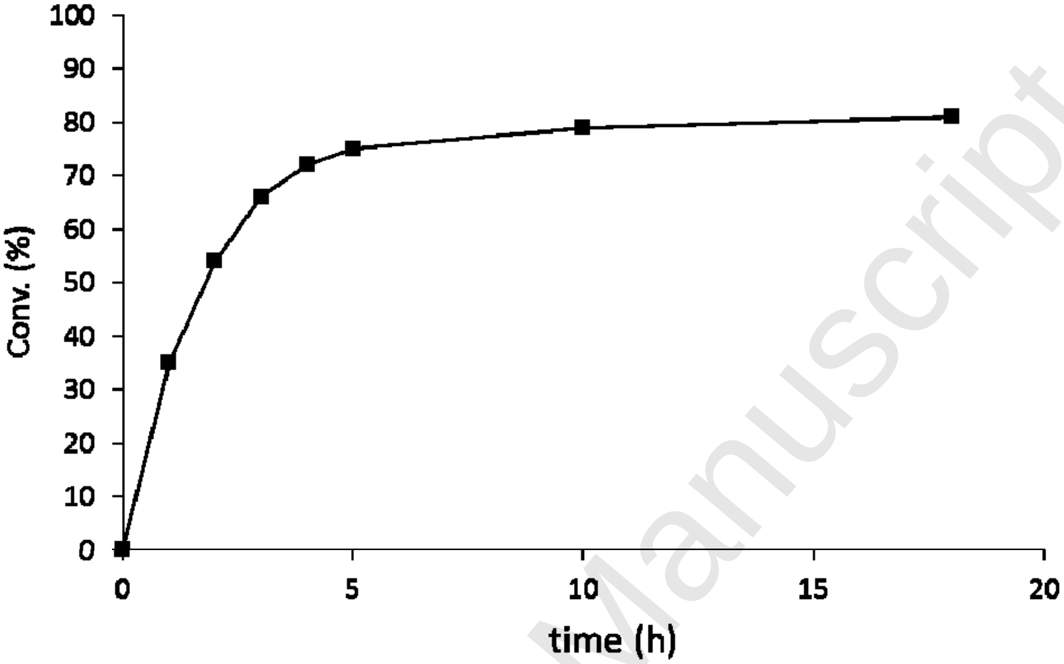
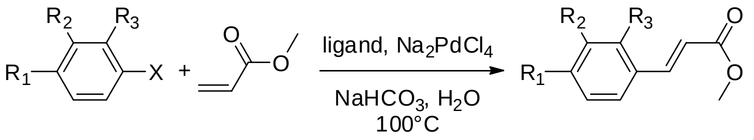


Fig. 5 Kinetic monitoring of the Heck reaction using phenyl iodide and styrene as substrates. Reaction conditions: phenyl iodide (1.0 mmol), styrene (1.5 mmol), ligand **1** (0.1 mmol), Na_2PdCl_4 (0.005 mmol), $NaHCO_3$ (1.5 mmol), water (2.5 mL), heptane (2.5 mL), 100 °C. Conversions were determined by GC-MS analysis.

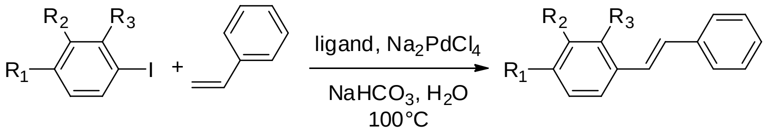
Table 1 Scope of the Heck reaction between aryl halides and methyl acrylate using **1** or **2** as a water-soluble ligand.[a]



Entry	Additive	X	R^1	R^2	R^3	W (mg/L)[b]	Conv(%)[c]	TOF[d]	TON[e]
1	RAME-β-CD	I	H	H	H	70	<1	-	-
2	**1**	Cl	H	H	H	400	0	0	0
3	**2**	Cl	H	H	H	400	0	0	0
4	**1**	Br	H	H	H	197	3	1.2	6
5	**2**	Br	H	H	H	197	2	0.8	4
6	**1**	I	H	H	H	70	57	22.8	114
7	**2**	I	H	H	H	70	30	12	60
8	**1**	I	CN	H	H	82	5	2	10
9	**2**	I	CN	H	H	82	4	1.6	8
10	**1**	I	OH	H	H	428	51	20.4	102
11	**2**	I	OH	H	H	428	16	6.4	32
12	**1**	I	OCH_3	H	H	49	65	26	130
13	**2**	I	OCH_3	H	H	49	26	10.4	52
14	**1**	I	NO_2	H	H	28	32	12.8	64
15	**2**	I	NO_2	H	H	28	20	8	40
16	**1**	I	CH_3	H	H	24	37	14.8	74
17	**2**	I	CH_3	H	H	24	16	6.4	32
18	**1**	I	CH_3	CH_3	H	7	8	3.2	16
19	**2**	I	CH_3	CH_3	H	7	4	1.6	8
20	**1**	I	H	CH_3	H	24	36	14.4	72
21	**2**	I	H	CH_3	H	24	14	5.6	28
22	**1**	I	H	H	CH_3	24	4	1.6	8
23	**2**	I	H	H	CH_3	24	2	0.8	4
24	**1**	I	H	NH_2	H	126	99	39.6	198
25	**2**	I	H	NH_2	H	126	53	21.2	106

[a]Reaction conditions: aryl halide (1.0 mmol), methyl acrylate (1.5 mmol), ligand (0.1 mmol), Na_2PdCl_4 (0.005 mmol), $NaHCO_3$ (1.5 mmol), water (2.5 mL), heptane (2.5 mL), 100 °C, 5 h. [b]Estimated water solubility at 25 °C (from Log K_{ow} using the WsKow v1.41 software). [c]Conversions were determined by GC-MS analysis. [d]TOF = turnover frequency (number of molecules of substrate converted per catalytic site and per hour). [e]TON = turnover number (number of molecules of substrate converted per catalytic site).

Table 2 Scope of the Heck reaction between aryl halides and styrene using **1** or **2** as a water-soluble ligand.[a]



Entry	Additive	R^1	R^2	R^3	W (mg/L)[b]	Conv(%)[c]	TOF[d]	TON[e]
1	RAME-β-CD	H	H	H	70	<1	-	-
2	**1**	H	H	H	70	74	29.6	148
3	**2**	H	H	H	70	16	6.4	32
4	**1**	OCH_3	H	H	49	60	24	120
5	**2**	OCH_3	H	H	49	55	22	110
6	**1**	CH_3	H	H	24	87	34.8	174
7	**2**	CH_3	H	H	24	42	16.8	84
8	**1**	CH_3	CH_3	H	7	14	5.6	28
9	**2**	CH_3	CH_3	H	7	12	4.8	24
10	**1**	H	CH_3	H	24	64	25.6	128
11	**2**	H	CH_3	H	24	17	6.8	34
12	**1**	H	H	CH_3	24	44	17.6	88
13	**2**	H	H	CH_3	24	24	9.6	48
14	**1**	H	NH_2	H	126	28	11.2	56
15	**2**	H	NH_2	H	126	9	3.6	18
16[f]	**1**	H	H	H	70	68	27.2	136
17[g]	**1**	H	H	H	70	66	26.4	132

[a]Reaction conditions: aryl halide (1.0 mmol), styrene (1.5 mmol), ligand (0.1 mmol), Na_2PdCl_4 (0.005 mmol), $NaHCO_3$ (1.5 mmol), water (2.5 mL), heptane (2.5 mL), 100 °C, 5 h. [b]Estimated water solubility (W) at 25 °C (from Log K_{ow} using the WsKow v1.41 software). [c]Conversions were determined by GC-MS analysis. [d]TOF = turnover frequency (number of molecules of substrate converted per catalytic site and per hour). [e]TON = turnover number (number of molecules of substrate converted per catalytic site). [f]performed using the aqueous catalytic phase recovered from run 2 after filtration on Celite. [g]Addition of NaI (1 mmol).

***Graphical Abstract (for review)**