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ARTICLE

Reaction kinetics of a water-soluble palladium-β-cyclodextrin catalyst for a Suzuki-Miyaura cross-coupling in continuous-flow

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In the present study, a capillary microreactor experiment was designed to study the kinetics of a sample Suzuki-Miyaura coupling using a water soluble Pd-β-cyclodextrin (Pd-β-CD) catalyst. A water-ethanol solvent system was explored as a potential reaction medium for the easy separation of organic species and metal catalyst, as well as fluid delivery in continuous microfluidic system. The biphasic, liquid-liquid cross-coupling using the natural product as a ligand was examined for the first time in continuous-flow. Mass transfer limitations were concluded to be negligible by estimation of the Hatta number << 0.02. A catalytic cycle with a third order oxidative addition step was proposed and verified by measurement of the kinetics under different temperatures and residence times. The oxidative addition step was discovered to be the rate determining step, while the activation energy was determined to be 50.1 ± 4.7 kJ/mol, or less than previously reported values of the free energy barrier of the oxidative addition transition state in the range of 60 to 113 kJ/mol. A possible explanation is the dual site catalyst design, which may cooperate to lower the free energy barrier. The use of natural products as ligand for the Suzuki-Miyaura coupling has the potential to advance green chemistry and manufacturing of useful fine chemicals, materials, natural products, and pharmaceuticals.

Introduction

Palladium catalysed Suzuki-Miyaura cross-couplings (SMC) are among the most versatile methods of forming carbon-carbon bonds and to construct heterobiaryl compounds. The reaction is handy for the preparation of fine chemicals, materials, natural products, and pharmaceuticals.[1–4] Thus, understanding the cross-coupling's kinetics with naturally derived catalysts has merit towards sustainable discovery and manufacture.

Water as a co-solvent in organometallic chemistry is attractive since water is nontoxic, inexpensive, and can be easily separated from organic products. The use of water soluble catalysts is promising in offering a way to remove and recycle precious metal catalyst, to reduce metal residues in products, and to ensure inorganic by-products remain soluble.[5–8] Palladium-β-cyclodextrin complexes have been previously reported to catalyse Suzuki-Miyaura hetero-couplings in batch reactors.[7,9] Cyclodextrins (CDs) are natural products that have a cyclic structure with a hydrophilic external rim and a hydrophobic internal cavity. The use of β-CD as a ligand allows competitive yields of cross-couplings in water even at a low catalyst loading (~0.001 mol%) in batch reactors.[6] Natural product ligands, such as CDs, have the potential for application in manufacturing processes, but the reaction kinetics are not well understood.

Continuous-flow synthesis offers advantages such as enhanced heat and mass transfer characteristics and precise control over the reaction conditions. Performing synthetic chemistry in flow can be useful for accurate measurement of the kinetics, along with providing a safer and faster alternative, as compared to traditional batch reactors.[8,10–14] While heterogeneous catalysts in continuous flow come with problems such as palladium leaching or the need to change catalyst cartridges, studying the kinetics of the Suzuki-Miyaura coupling catalysed by Pd-β-CD in continuous-flow is promising, however, the substrates are either insoluble or immiscible in pure water.[15,16] There remains a need to develop the reaction conditions for the coupling of aryl halides and arylboronic acids, and a way to deliver hydrophilic aryl halides in aqueous environments.[17–23]

In the present work, a Suzuki-Miyaura coupling catalysed by Pd-β-CD is studied in flow by oxidative addition, transmetalation, and reductive elimination. In which the transmetalation consists of two steps: the conversion of a palladium halide to a nucleophilic palladium hydroxo complex and its subsequent reaction with a neutral aryl-boron compound.[24,25] Herein, we report for the first time a numerical evaluation of the kinetics of the Pd-β-CD catalyzed Suzuki-Miyaura coupling to verify the possible reaction mechanism. Our experimental results support that two active catalyst sites exist on one Pd-β-CD catalyst.

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Experimental

1. Pd-β-Cyclodextrin synthesis

Pd-β-cyclodextrin was synthesized under air following a previously reported procedure.[6] β-cyclodextrin (0.5 mmol, 0.5675 g) was dissolved in 0.5 M sodium hydroxide (25 mL) solution. Pd $(OAc)_2$ (1.5 mmol, 0.3368 g) was then added to the above clear solution. The resulting suspension was stirred at room temperature for 12 h. Pd-β-cyclodextrin was precipitated by adding ethanol (250 mL) to the mixture. The precipitates were then washed and collected by vacuum filtration. An overall yield of 94% was attained. A ^1H NMR spectrum indicating the formation of Pd-β-cyclodextrin complex is shown as figure 1.

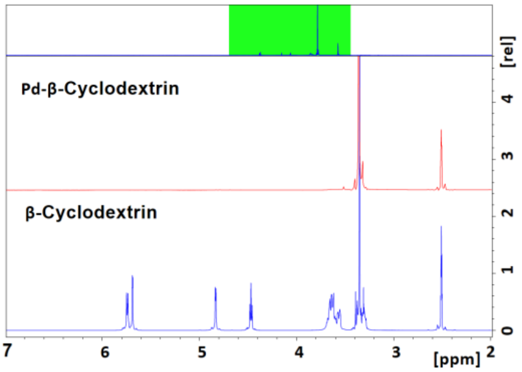


Figure 1. ^1H NMR spectrum (DMSO, 600MHz) of β-cyclodextrin and the palladium-β-cyclodextrin complex.

2. Flow experiments

K_2CO_3 (3 mmol, 1.5 equiv.) was dissolved into 2.3 mL Pd-β-Cyclodextrin (1 mg catalyst in 100 mL DI water) solution. 4-bromoanisole (2 mmol), phenyl boronic acid (2.4 mmol, 1.2 equiv.) was mixed in 2.05 mL of ethanol and ultrasonicated until the solution became clear. The two solutions were then filtered with syringe filters (0.5 µm pore size), and loaded into separate 5 mL Hamilton syringes, respectively.

A Harvard pump was used to deliver reagents into a 50 cm coiled PFA tubing (0.02" ID, 100 µL capacity). For temperatures of 10 °C and 20 °C, the temperature was controlled by using a Cole-Parmer Polystat. For temperatures at 40 °C, 60 °C, and 80 °C, the coiled tube was immersed in a heat insulated oil bath, with an immersion cartridge heater controlled by a PID controller. The fluid at the outlet was collected using a vial filled with 1 M hydrochloric acid to quench the reaction. The mixture was then extracted using hexane. A filter of a pore size of 2 µm was placed downstream of a mixing tee and upstream of the temperature controlled medium to ensure rapid, complete liquid phase mixing. The setup is shown in figure 2. Product was determined by gas chromatograph-mass spectrometry (GC-MS). Species concentrations were estimated by a GC. The reaction progress was evaluated based on the concentrations of 4-bromoanisole and 4-methoxybiphenyl.

3. Chemicals and instruments

β-Cyclodextrin, palladium acetate (98%), phenyl boronic acid (97%), 4-bromoanisole (99%), potassium carbonate (anhydrous, 99%), sodium hydroxide (anhydrous,97%), ethanol (99.5%) were purchased from SigmaAldrich. PFA tubing (0.02" ID, 1/16" OD) were purchased from IDEX Health & Science. Note the compounds used in this study are hazardous chemicals and precautionary measures should be taken, such as use of proper personal protective equipment, as outlined in their respective safety data sheets.

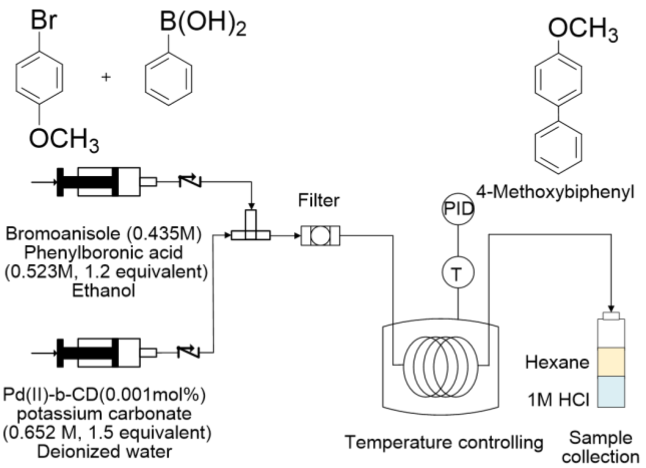
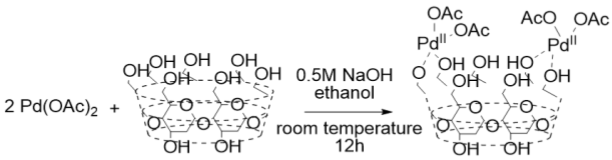


Figure 2. Flow diagram of the experimental set up. Temperatures of 10 °C, 20°C, 40°C, 60°C, and 80°C were tested at different residence times.

1H NMR were performed on a Bruker 600 MHz spectrometer. The coupling products were identified by GC-MS. The reaction progress was monitored by Agilent 7890B Gas Chromatograph. Heating of oil bath and its temperature controlling was achieved by using an immersion cartridge heater and J-KEM Scientific Model 270 controller. Cooling to 10 °C was done by using a Cole-Parmer polystat heat/cool bath. Fluid delivery were performed using a Harvard standard PHD syringe pump. Glass syringes are Hamilton 1000 series. Dynamic light scattering (DLS) was performed on a Zetasizer Nano ZS90 analyzer. The light source for capillary reactor distribution characterization was an Ocean Optics DH-2000-BAL balanced deuterium tungsten source. The Signal was detected by an Ocean Optics flame spectrometer (200 -850 nm). Tracer was injected using Rheodyne microscale injector 8125.

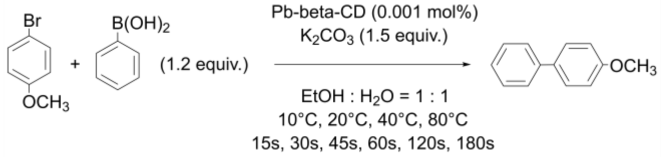


Scheme 1. Synthesis of Pd-β-cyclodextrin

Results and discussion

1. Catalyst synthesis and characterization

Synthesis of palladium-cyclodextrin complex is shown scheme 1. Natural β-cyclodextrin was chosen as the supramolecular host since it is readily available and has been



Scheme 2. Model Suzuki-Miyaura cross-coupling

extensively explored in aqueous environments.[26,27] The Pd-β-CD compound is soluble in water and is thus suitable for catalytic applications in biphasic aqueous-organic media. As can be seen in Figure 1, signal broadening was observed in the ^{1}H NMR spectra of the complex, indicating that palladium bonded to carbons 2, 3 (OH 2 and 3, multiplets centered at 5.70) and 6 (OH 6, multiplets centered at 4.45) on cyclodextrin rims. Once we confirmed the synthesis of the catalyst, we explored its activity.

The synthesized Pd-β-CD catalyst was next tested for the catalyzation of the Suzuki Miyaura cross-coupling in flow. The organic-halide selected for this study was CH_3O-Ph-Br, and the boronic acid was Ph-$B(OH)_2$ (as shown in Scheme 2).

Ethanol was used to dissolve the organic reagents. The reaction which was a solid-liquid-liquid multiphase system in batch, was performed and evaluated in the micro-flow capillary reactor shown in figure 2.

GC-MS results confirmed the formation of product within 2 min of residence time at 40 °C. No side product was observed in the mass spectroscopy shown in figure 3. Additional details on the mass spectroscopy results are reported in the electronic supplementary information (ESI).

In this multiphase flow, 4-Bromoanisole droplets were anticipated downstream of its mixing with the aqueous reagent. The average emulsion droplet size of 484.5 nm was determined by dynamic light scattering (DLS). Note the diameter of the supramolecule β-cyclodextrin is approximately 0.68 nm[28], or three orders of magnitude smaller than the data, confirming the presences of an emulsion. Whether the reaction rate within the thin film was or was not fast enough with respect to the mass transfer rate was evaluate by the Hatta modulus (*Ha*):

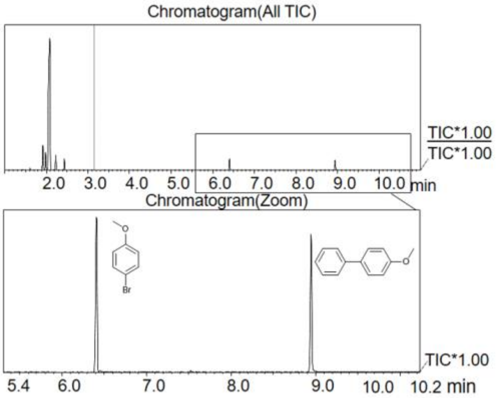


Figure 3. Gas chromatograph mass spectroscopy results of reaction at 40 °C and 2min residence time.

$$Ha = \frac{(D_A k c_A c_B^{bulk})^{1/2}}{k_L} \qquad (1)$$

in which D_A is the diffusivity of reactant A, in our case, 4-bromoanisole, c_A is the concentration of 4-bromoanisole, c_B^{bulk} is the concentration of palladium catalyst, and k the rate constant of oxidative addition step. The liquid phase mass transfer coefficient, k_L, is estimated by:

$$k_L = \frac{D_A}{\delta} \qquad (2)$$

where δ is the film thickness according to thin film theory. In our case, if *Ha* = 0.02, the maximum diameter of droplets should be 3000 nm. Since the droplet diameters measured before and after the reactor at different temperatures were smaller than 1000 nm, *Ha* < 0.02 was always satisfied, indicating an infinitely slow reaction, in which the mass transfer resistance is negligible and rate is determined by chemical kinetics alone.[29] Refer to the ESI for further details on calculation of *Ha* values.

The extent of axial dispersion was evaluated by the Levenspiel number (*lv*) [30]:

$$lv = \frac{uL}{\boldsymbol{D}} \qquad (3)$$

In which $\boldsymbol{D}$ is the axial dispersion coefficient, u is the superficial velocity, and L is the reactor length. Values of Levenspiel number at different flow rates were estimated in the range of 59 to 197 or > 50, indicating a small extent of dispersion.[30] Refer to the ESI for further details on calculation of *lv* values. The impact of dispersion on conversion was therefore considered negligible for the purposes of measuring the kinetics.

Once we had confirmed negligible mass transport limitations, experimental results on various reaction temperatures from 10 °C to 80 °C, and different residence times from 15 s to 3 min, were studied. As shown in figure 4, a trend could be seen that the concentration of 4-bromoanisole decreased, while 4-methoxybiphenyl product increased with increasing reaction temperature or increasing residence time. Similarly, the 4-bromoanisole conversion increased and the 4-methoxybiphenyl yield increased as the reaction temperature increased or the residence time increased (see figure 5). At 80 °C, 90% yield could be reached within 1 min, compared to a residence time of hours required in batch reactions reported by Kaboudin and Kazemi et al.[6] The Pd-CD catalyst remained high activity towards the model Suzuki-Miyaura coupling in the water:ethanol = 1:1 solvent system. The micro-fluidic system had largely expedited the reactions, likely due to enhanced mixing and heat transfer.

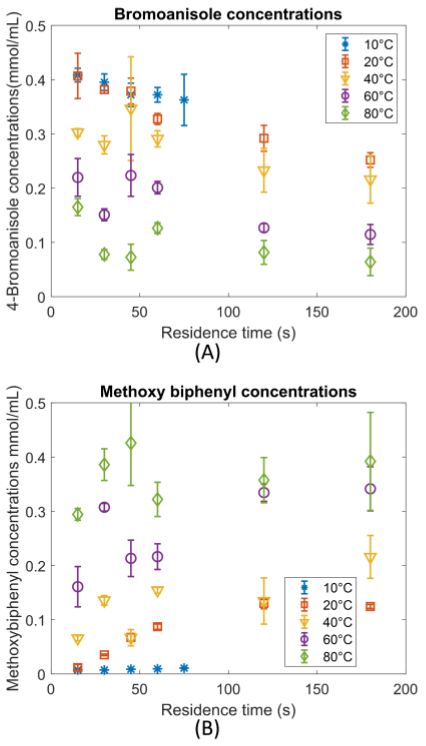


Figure 4. Concentrations of A) 4-Bromoanisole substrate and B) 4-methoxybiphenyl product as measured by GC for different residence times and temperatures in the range of 10°C to 80°C.

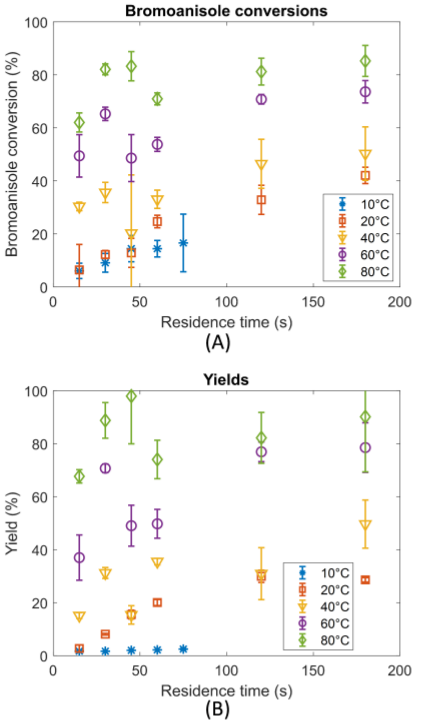


Figure 5. Shown here are the A) 4-bromoanisole conversions and B) 4-methoxy-biphenyl yields at different residence times and temperatures in the range of 10°C to 80°C.

2. Model prediction and activation energy estimation

A general catalytic cycle for Suzuki-Miyaura reaction involves the oxidation addition of an organo-halide to the Pd(0) halide group to aryl group of a Pd(II) intermediate *via* the formation of an [ArPd(OH)Ln] complex with the addition of OH$^-$ ions and then the addition of aryl boronic acid, the reductive elimination step to give the coupling product and the Pd(0) intermediate.[31–33]

In the present work, we propose that the -OAc groups coupled to the Pd centers of Pd(II)-β-cyclodextrin are first eliminated to form an activated catalytic complex Pd(0)-β-CD. This complex then initiates the catalytic cycle. Since there are two active Pd sites per cyclodextrin molecule in the catalyst, the oxidative addition step is a third order reaction. This proposed mechanism is shown schematically as figure 6.

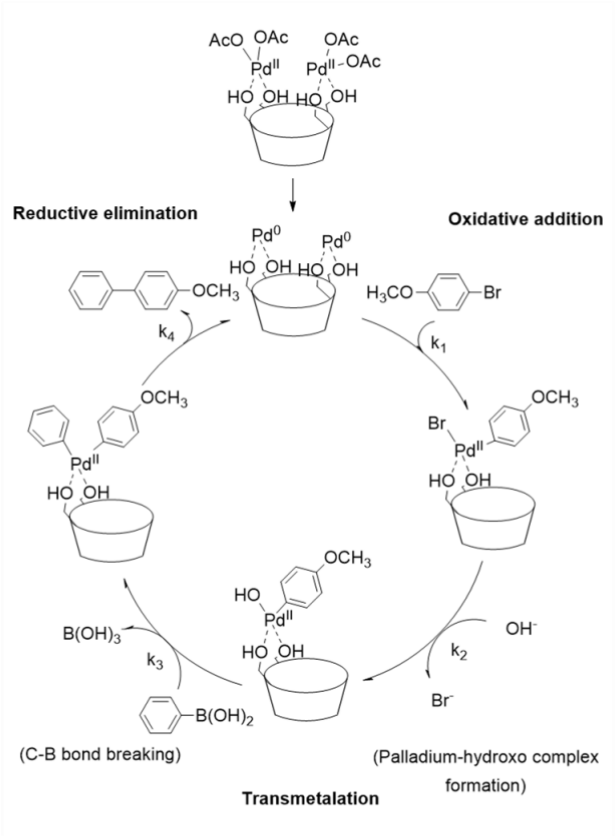


Figure 6. Proposed mechanism for the Pd-β-CD catalyzed model Suzuki-Miyaura cross-coupling.

Experimental data at 20 °C was then fitted and solved numerically in MATLAB using the nlinfit function and by Polymath nonlinear regression into the proposed catalytic cycle to obtain kinetic information. The substrate concentrations were considered far from equilibrium.[34–36] That is, our kinetic analysis considered conditions where significant substrate remained available to react. Deriving a comprehensive rate model (see the ESI), the fitted rate constants of transmetalation and reductive elimination were found to be significantly larger than those of the oxidative addition, with R^2 values = 0.96. The oxidative addition step was thus considered as the rate determining step, which also conformed to the theoretical work of others using phosphine ligands.[37] The experimental 4-bromoanisole concentration and model predictions are shown in figures 7, 8, 9, and 10 at 20, 40, 60, and 80 °C, respectively.

As can be seen in the figures, the residuals indicate excellent agreement between theory and experiment. Thus, the proposed catalytic mechanism with oxidative addition as rate determining accurately describes the synthesis.

Rate constants of oxidative addition at each temperature were then determined using the same method and their values are shown in Table 1. Refer to the ESI for further information on our model and calculations.

Table 1: Fitted rate constants of oxidative addition at different temperatures.

Temperature (K)	Rate constant ($L^2mol^{-2}min^{-1}$)
293.15	1.905×10^4
313.15	4.448×10^4
333.15	1.928×10^5
353.15	5.783×10^5

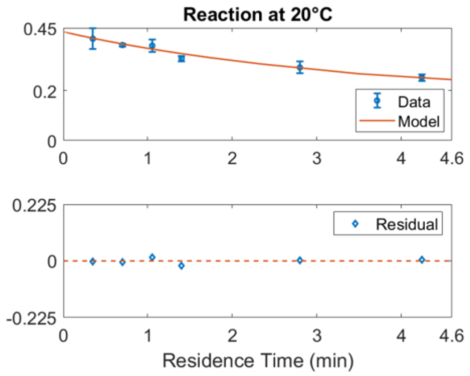


Figure 7. Experimental data, model prediction, and their residuals at 20 °C.

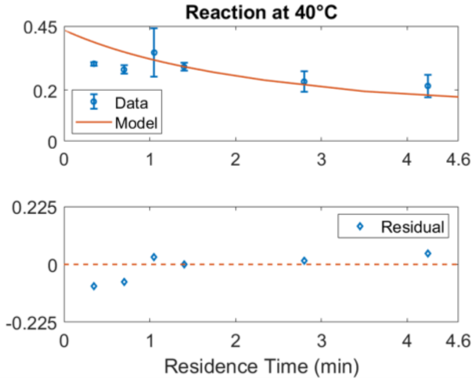


Figure 8. Experimental data, model prediction, and their residuals at 40 °C.

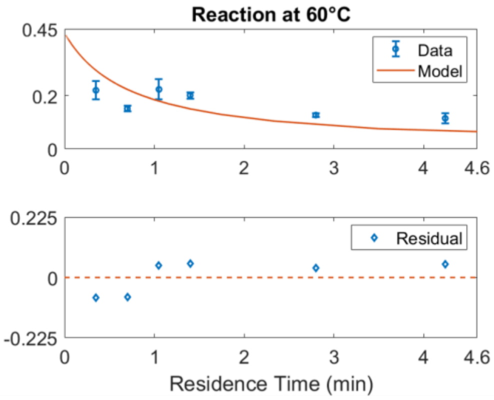


Figure 9. Experimental data, model prediction, and their residuals at 60 °C.

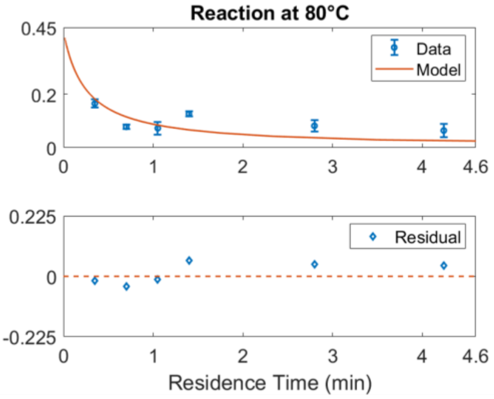


Figure 10. Experimental data, model prediction, and their residuals at 80 °C.

The activation energy of oxidative addition E_a was then determined by linear regression of the Arrhenius expression (see the ESI for more details). The resultant activation energy of oxidative addition step was estimated as E_a = 50.1 ± 4.7 kJ/mol, with an R^2 value of 0.98. Estimation of the error is also reported in the ESI. Compared to literature values, of the Gibbs free energy barrier of the oxidative addition transition state of 60 to 113 kJ/mol of cross-couplings involving phosphine ligands, the Pd-β-CD catalyst appeared to lower the energy barrier of the oxidative addition step.[38–40] A possible explanation for the reduced free energy is the existence of two active catalyst sites per cyclodextrin molecule. Cooperative catalysis of the neighbouring sites could play an important role in our proposed mechanism.

Conclusions

In conclusion, a water-soluble palladium complex (Pd-β-CD) as a catalyst was synthesized, and the kinetics of a model Suzuki-Miyaura cross-coupling evaluated in flow. A water-ethanol solvent system was used for the fluidic delivery of the mixture of organic reagents and water soluble complexes. Evaluation of mass transport resistances using thin film theory confirmed reaction-rate-limited conditions, whereas measurements of the residence time distributions confirmed plug flow for the conditions studied. Organic products were easily extracted and separated from aqueous phase containing metal catalyst by using non-polar organic solvents. The reaction was found to be fast in the above micro-fluidic system with water-ethanol as a solvent, and a higher than 85% yield could be achieved within minutes at 80 °C. Conversion of substrate and the formation of product was observed at even as low as 10 °C. Compared to cyclodextrin-capped palladium nanoparticles, a significantly lower catalyst loading was used.[41] The reaction showed high selectivity and no side products were observed.

A proposed catalytic cycle was verified by derivation of a rate model and its fitting to experimental data by non-linear regression. Estimation of the activation energy supports that oxidative addition is the rate determining step. The estimated activation energy is lower than the state-of-the-art of phosphine-based catalysts, perhaps the lowest free energy ever reported for the Suzuki-Miyaura coupling. A possible explanation is the existence of two active catalyst sites per cyclodextrin molecule, which could promote cooperative catalysis between neighbouring sites.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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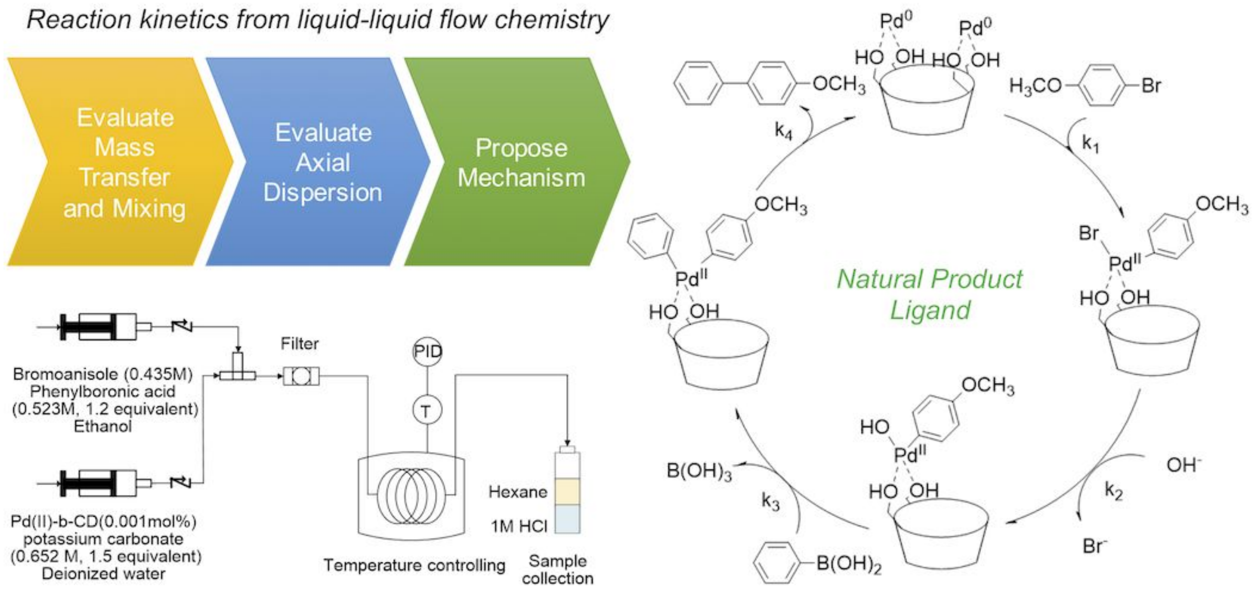

An experimental and theoretical investigation on the reaction kinetics of a Suzuki-Miyaura cross-coupling catalyzed using Pd-β-cyclodextrin ligand in continuous-flow.