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A Microfluidic System for Continuous Recycling of Unmodified Homogeneous Palladium Catalysts via Liquid-Liquid Phase Separation**

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With their highly tunable nature and the resulting high activity and selectivity in promoting transformations, homogeneous catalysts have dramatically shaped modern organic chemistry.^[1] Industrial applications are limited, however, by the difficulties associated with catalyst recovery and recycling.^[1b,c] As a result, many strategies have been devised to overcome those challenges,^[2] including immobilizing the catalysts onto solid or liquid supports by structural modifications,^[3-7] enlarging the catalysts for ultra- or nanofiltration,^[8] and using controlled solubility variations.^[9,10] Although leaching of catalyst has remained a general challenge, some of these methods have proved successful. However, the approaches can fall short for demanding reactions, such as palladium-catalyzed cross-coupling reactions often involving strong bases and high temperatures^[11,12] and requiring deliberately designed ligands. Therefore, it would be preferable to recycle the unmodified (“native”) catalyst directly under the best performing conditions.

There are both chemical and technical hurdles associated with catalyst recycling of unmodified systems. First, highly active catalysts could deactivate when out of the reaction environment and/or during the recycling processes. Second, convenient and efficient catalyst isolation is non-trivial and sometimes impossible. Third, manual operations of sensitive catalysts must be carefully implemented, and the process can be very time-consuming.

Our labs have been developing continuous microflow processes of palladium-catalyzed cross-coupling reactions.^[13] Owing to the high surface-volume ratio of the liquids in microchannels, heat- and mass-transfer are very efficient, enabling easy and precise control of process parameters.^[14] Along with other merits, such as producing less waste, reducing footprint, and ready scale-up, continuous-flow reactions have been regarded as one of the key green processes.^[15]

and received considerable attention.^[16,17] Ryu and coworkers reported a continuous-flow process for recycling of an ionic liquid-supported palladium catalyst in Mizoroki-Heck reaction.^[12a] The ligand and the ionic liquid used in this reaction shared the same structural framework. Theberge and Huck designed an aqueous/fluorous biphasic microflow setup and used it for continuous recycling of a fluorous guanidine-ligated palladium catalyst for Suzuki-Miyaura coupling.^[12b] In both examples, static vials were used for passive liquid-liquid phase separation of the pooled multiphase mixtures. Furthermore, a “release-trap” strategy using coordinative polymers has been reported for continuously reuse of catalysts.^[12c,d] However, there have been no precedents about continuous recycling of *unmodified* palladium catalysts based on advanced ligands.^[5a,18] In this communication, we describe a microfluidic system for continuous catalyst recycling in palladium-catalyzed hydroxylation of aryl bromides. A highly-active bulky phosphine was used as the supporting ligand and a microfluidic device for liquid-liquid phase separation.

Palladium-catalyzed selective hydroxylation of aryl halides using biaryl phosphine ligands, first reported by Buchwald in 2006,^[19] is a general method to prepare various phenols from readily available aryl halides.^[20] Later, Beller developed N-aryl imidazole-based phosphine ligands for this reaction^[20b,21] and interesting cationic ligands for catalyst recycling.^[11a] This represented a rare example of recycling palladium catalysts in complex coupling reactions. However, the moisture-sensitive reaction conditions and using product-saturated 1,4-dioxane as the solvent for product separation limited the practicality. We felt that if an immiscible organic/water mixture could work for this reaction, the water-soluble phenolate could be efficiently separated from the catalyst-containing organic phase. Moreover, we have previously developed liquid-liquid biphasic systems for palladium-catalyzed reactions under continuous-flow conditions.^[13] Consequently, we commenced our study by searching for an efficient biphasic catalytic system using 3-bromoanisole as a model substrate. Previously, two phosphines **L1** and **L2** were shown effective as supporting ligands for this reaction in 1,4-dioxane, with **L2** performing better in most cases.^[19a] With these ligands, we found that in a mixture of toluene and water, the reaction also proceeded well, but only when a phase-transfer catalyst (tetrabutylammonium bromide, TBAB) was added as a promoter. Further optimizations under batch conditions were conducted and selected results are shown in Table 1.

Under the otherwise same conditions ($\text{Pd}_2(\text{dba})_3$ 0.5 mol%, ligand 2 mol%, 100 °C, 120 min), the reaction was complete using ligand **L2**, while **L1** led to 60% conversion (entry 2 vs. entry 1). For an efficient flow reaction, a faster reaction would be desirable. When the reaction time was decreased to 10 minutes, however, even 1 mol% $\text{Pd}_2(\text{dba})_3$ and 4 mol% of **L2** gave an incomplete conversion (92%, entry 3). At this point, a more electron-rich ligand **L3**^[22] was tested and proved more effective. With only 0.5 mol% of $\text{Pd}_2(\text{dba})_3$ and 2 mol% of **L3**, the product was quantitatively formed (entry 4).

Very recently, **L3** has been successfully utilized in several challenging coupling reactions;^[23] here we extend its usefulness to

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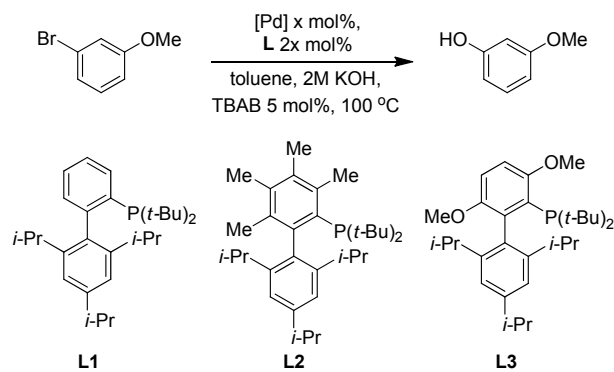
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selective hydroxylation of aryl halides. Because Pd₂(dba)₃ is only slightly soluble in toluene at room temperature, which may not be suitable for studying under flow conditions, allylpalladium chloride dimer was selected as a readily soluble palladium source and proved similarly effective (entry 5). However, we observed that palladium black was formed immediately after reaching full conversion, which was in contrast to the case of Pd₂(dba)₃, where no palladium black was observed. Further decrease in reaction time led to incomplete conversion and the reaction using allylpalladium chloride dimer was slightly faster than the one using Pd₂(dba)₃ (entry 6 and 7), and both reactions did not form significant amounts of palladium black.

Table 1. Optimizations in batch.^[a]

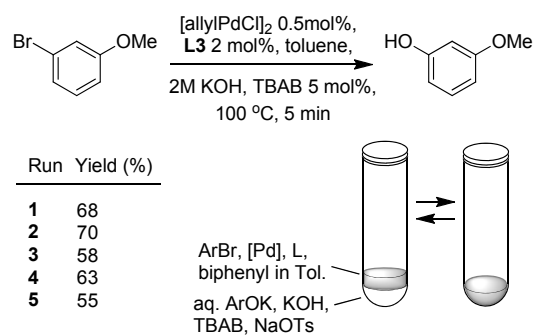


Entr Y	Ligand	Pd source	t (min)	Conversion/ Yield (%) ^[b]
1	L1 (2 mol%)	Pd ₂ (dba) ₃ (0.5 mol%)	120	60/58
2	L2 (2 mol%)	Pd ₂ (dba) ₃ (0.5 mol%)	120	100/95
3	L2 (4 mol%)	Pd ₂ (dba) ₃ (1 mol%)	10	92/85
4	L3 (2 mol%)	Pd ₂ (dba) ₃ (0.5 mol%)	10	100/98
5	L3 (2 mol%)	[allylPdCl] ₂ (0.5 mol%)	10	100/98
6	L3 (2 mol%)	[allylPdCl] ₂ (0.5 mol%)	5	63/57
7	L3 (2 mol%)	Pd ₂ (dba) ₃ (0.5 mol%)	5	44/39

[a] Reaction conditions: 3-bromoanisole (1.0 mmol), L (20–40 μmol), Pd₂(dba)₃ or [allylPdCl]₂ (5–10 μmol), TBAB (50 μmol), biphenyl (internal standard, 0.25 mmol), toluene (1.0 mL), 2 M KOH (2.0 mL), 100 °C, 5–120 min. [b] Conversions and yields based on UHPLC (Ultra-High Pressure Liquid Chromatography) analyses.

Based on these results and the generally accepted mechanism of cross-coupling reactions involving a Pd⁰/Pd²⁺ catalytic cycle,^[24] we postulated that if the aryl halide was kept in excess (i.e., controlled incomplete conversion, CIC), so that Pd⁰ species could be fully trapped into relatively stable Pd²⁺ form(s), thus avoiding palladium black formation, a successful catalyst recycling might be possible. We then tried the catalyst recycling process in a batch fashion to test this possibility (Scheme 1). In a septum-sealed tube, a solution of 3-bromoanisole, allylpalladium chloride dimer, **L3**, and biphenyl (internal standard) in toluene and an aqueous solution of TBAB, potassium hydroxide, and a water

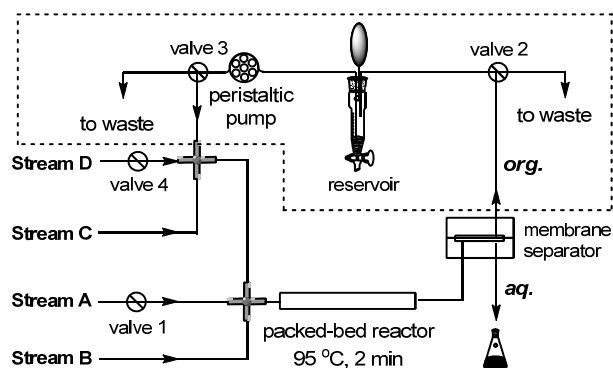
soluble standard sodium tosylate were heated at 100 °C for 5 minutes. After the mixture was cooled down to room temperature, the aqueous phase containing the phenolate was carefully removed using a syringe. The yield was based on UHPLC analysis of the aqueous phase taking sodium tosylate as the internal standard. 3-Bromoanisole (100 mol%) and the aqueous solution (same as the first run) were added to the reaction tube via syringes, and the resulting mixture was again heated at 100 °C for 5 minutes, followed by cooling down and phase separation. This procedure was repeated up to a total five runs. The results in Scheme 1 did show that the catalyst was recyclable under CIC conditions. However, the yields fluctuated significantly, apparently due to the difficulties associated with precise control of the reaction times and temperatures and possible errors during manual operations.



Scheme 1. Catalyst recycling in batch conditions.

In order to obtain reaction profiles in a flow setting, we assembled a continuous-flow setup using syringe pumps, PFA tubing, tee and cross junctions, and a packed-bed reactor. (see SI). Tubular reactors, filled with stainless steel spheres (60–120 μm diameter), have been used in continuous-flow reactions to efficiently enhance biphasic mass- and heat-transfer processes.^[13b,e,g] Initially, a stock solution of allylpalladium chloride dimer in 1,4-dioxane was used as one of the streams and was pumped into the reaction. We found that the reaction results were not reproducible, probably because the catalyst (Pd⁰L) formation process was not effective. A premixing method^[25] in flow was also tested by merging a stream of allylpalladium chloride dimer in 1,4-dioxane and a stream of **L3** in toluene for a few minutes before entering the reactor. This method did improve the reproducibility, but resulted in a more complex setup. Moreover, a stock solution of allylpalladium chloride dimer and **L3** in toluene or 1,4-dioxane was shown to decompose within a few hours, leading to decreased catalytic activity. Finally, we found that using cinnamylpalladium chloride dimer as the palladium source offered a satisfactory solution. Firstly, cinnamylpalladium chloride dimer showed comparable efficiency in the reaction. Secondly, a solution of cinnamylpalladium chloride dimer, **L3**, 2-bromoanisole, and biphenyl in toluene could be stored for a few hours without significant decomposition, dramatically simplifying the flow setup.

Based on the preliminary studies and further optimizations, we assembled a flow setup (Figure 1), for continuous hydroxylation of aryl halides, and a catalyst recycling loop (in the dotted line) was devised using readily available materials. The setup had a packed-bed reactor for efficient mixing in a biphasic reaction, a membrane separator for liquid-liquid phase separation,^[27,28] a reservoir with an argon balloon, and a peristaltic pump for recycling of the organic phase.



Stream A: [cinnamylPdCl]₂, L3, 2-bromoanisole, biphenyl in toluene;
Stream B: 2.0 M KOH, NaOTs, NaCl in water;
Stream C: 0.5 M TBAB in water; **Stream D:** neat 3-bromoanisole

Figure 1. A flow setup for continuous catalyst recycling in palladium-catalyzed hydroxylation of aryl halides.

For a continuous-flow experiment, four stock solutions were prepared and loaded into syringes and introduced into the system by four syringe pumps. Stream A was a solution of cinnamylpalladium chloride dimer, L3, 2-bromoanisole, and biphenyl in toluene. Stream B was an aqueous solution of potassium hydroxide and sodium tosylate, saturated with sodium chloride to facilitate the phase separation. Stream C was a 1.0 M solution of TBAB in water and stream D was neat 3-bromoanisole. To begin the experiment, streams A, B, and C were infused into the packed-bed reactor via a cross-mixer in such a rate that the calculated residence time of the mixture in the reactor was 2 minutes. The reactor was kept in an oil bath at 95 °C. The reaction time and temperature were well controlled so that a stable conversion (80%) was secured. In this system, significant fluctuation of conversion was not acceptable because lower conversion led to accumulation of the starting materials and higher conversion could lead to palladium black formation. Upon exiting the reactor, the biphasic reaction mixture, as slug flow, was introduced into a microfluidic device, where the two phases were separated by a thin porous fluoropolymer membrane. Selective wetting of the membrane by the organic phase and the associated capillary force form the mechanism of separation.^[26] As a result, the aqueous phase containing phenolate product, sodium tosylate, and other water-soluble chemicals flowed out the device and was collected for yield analysis by UHPLC; and the organic phase, containing the 20% of unreacted 3-bromoanisole and palladium species, passed through the membrane and was collected in the reservoir. Before reaching a steady state, the organic phase was passed to waste by switching valve 2. To reuse the palladium catalyst for the next run, a peristaltic pump was employed to deliver the organic mixture in reservoir back to the packed-bed reactor. Again, valve 3 was installed for flushing the system before a steady state was reached. To start the catalyst recycling, valve 1 was switched off to discontinue the infusion of stream A, and valve 4 on, so stream D was infused into the system in a rate to add 80% of neat 3-bromoanisole, mixed with stream C and the recycled organic mixture in a cross junction, and further mixed with stream B in the next cross junction. The resultant mixture flowed through the reactor in a residence time of 2 minutes and then into the separator device for phase separation.

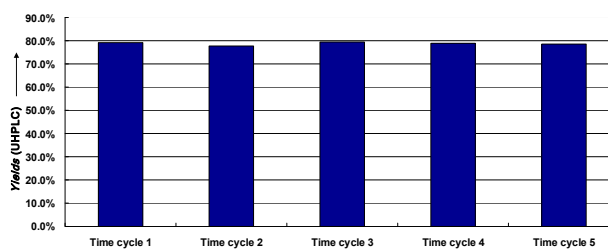


Figure 2. Results of continuous catalyst recycling. A time cycle is the time required for one complete organic phase recycle.

Using this setup, experiments were performed to optimize the conditions for efficient catalyst recycling. The final results are shown in Figure 2. At 95 °C, the reaction under continuous-flow conditions was controlled to have a conversion of 80% in a residence time of 2 minutes, and at the steady state before catalyst recycling (i.e. the first time cycle), the yield was 79% (UHPLC). The catalyst recycling loop was then started according to the above procedure. As expected, under continuous microflow conditions, the reaction parameters could be well controlled so that the conversion was kept stable (with fluctuations less than 2%). No palladium black was observed over the experiment. The organic phase containing the palladium catalyst and ligand L3 could be reused for another four time cycles without significant decrease of activity (yields 78%, 79%, 79%, and 79% respectively). Further recyclings were also possible, albeit leading to slowly decreasing yields. However, due to gradual loss of the organic phase during repeated phase separations, it was difficult to handle the ever smaller amount of organic mixture in the reservoir. Nevertheless, these results have clearly demonstrated the viability of continuous recycling of a highly active, unmodified homogeneous palladium catalyst in a complex cross-coupling reaction.

In conclusion, a prototype microflow system for continuous recycling of homogeneous catalysts via liquid-liquid phase separation has been developed, and its effectiveness has been demonstrated with a challenging palladium-catalyzed hydroxylation reaction. Keys to successful continuous recycle include: 1) the use of L3 as the ligand for a rapid reaction, 2) a toluene/water biphasic mixture for ease of the product isolation, 3) well-controlled reaction parameters for a controlled incomplete conversion which avoids palladium black formation, and 4) a microfluidic device for efficient phase separation. Different from known methods, which often resort to heterogenization of the ligands, we were able to continuously recycle the “native” catalyst under “native” reaction conditions by using a combination of chemical and engineering methods. The catalyst recycling strategy could potentially be amenable to many biphasic catalysis systems given that the product(s) and the catalyst reside in different liquid phases. The methods developed in this report, including controlled incomplete conversion, the phase separation process, and the reservoir, could be useful in other challenging recycling systems as well. Lastly, since the gradual loss of catalytic activity and materials are ultimately unavoidable, for a long-duration continuous-flow system, continuous compensations of catalysts and other materials will be necessary.

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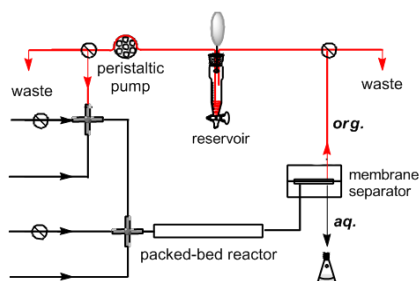
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Entry for the Table of Contents

Continuous Recycling

Pengfei Li, Jason S. Moore, Klavs F. Jensen _____ **Page – Page**

A Microfluidic System for Continuous Recycling of Unmodified Homogeneous Palladium Catalysis via Liquid-Liquid Phase Separation



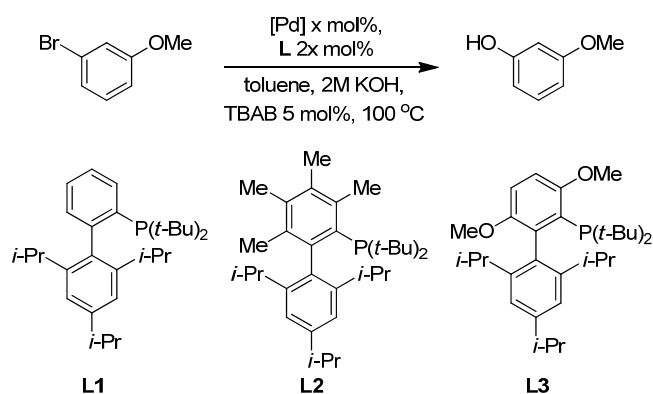
Recycling “native” catalysts

A prototype microflow system for continuous recycling of homogeneous catalysts via liquid-liquid phase separation is developed, and its effectiveness is demonstrated with a challenging palladium-catalyzed hydroxylation reaction. The unmodified catalyst is recycled under standard reaction conditions by using a combination of chemical and engineering methods.

Supporting Information

1. Materials

Packed-beds were prepared according to the literature from standard 1/4 inch HPLC columns.^[S1] Sintered stainless steel (SS) frits (0.189" diameter, 20 µm pore size) were purchased from IDEX Health and Science, formerly Upchurch Scientific. Nuts and ferrule sets (stainless steel, 1/4 inch) were purchased from Swagelok. The tubing (stainless steel, 1/4 inch OD and various IDs) was purchased in different lengths (5 cm, 10 cm, and 15 cm) from McMaster Carr or cut to length with a standard tubing cutter. Stainless steel beads (60 – 125 µm) were purchased from Duke Scientific, a subsidiary of Thermo Fisher. Microfluidic connections were made with standard Upchurch fittings (IDEX Health and Science), either 10-32 coned fittings or 1/4-28 flat-bottomed fittings for 1/16 inch OD tubing. All reactions were carried out using reagent grade solvents, and all solutions were prepared under argon atmosphere. Phosphine ligands were prepared according to literature procedures.^[S2]



Scheme S1. Reaction scheme and phosphine ligands.

^[S1] J. N. Naber, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2010**, *49*, 9469-9474.

^[S2] a) C. H. Burgos, T. F. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 4321-4326;
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2. Analytical Information

All liquid chromatography analyses were performed on an Agilent 1200 series UHPLC. UHPLC column type was Agilent Eclipse Plus C18 (1.8 μm , 4.6 \times 100 mm). HPLC grade water and methanol were purchased from Mallinckrodt Chemicals.

3. Experimental Setup

The experimental setup for the continuous catalyst recycling was assembled in-house as shown in Figure S1. Four Harvard Apparatus PHD2000 syringe pumps were used to deliver reagents from Normject plastic syringes or Harvard Apparatus stainless steel syringes to the reactor. The stainless steel packed-bed reactor had a volume of 635 μL (10 cm length, 5.2 mm ID) and was submerged in an oil bath. The bath temperature was monitored via a thermocouple and maintained with a Waage immersion heater controlled by a J-KEM Scientific Gemini PID controller. The phase separation device is shown in Figure S2 and explained in following section. The reservoir was custom-made glassware (volume 5 mL) with a valve at the bottom and capped with a septum connected to an argon balloon. The organic phase in the reservoir was pumped back to the reactor by a peristaltic pump (Masterflex[®] EW-07523-80 from Cole-Parmer) using a Tygon[®] MHL two-stopper tubing (0.03 inch ID, 39 cm length). The tubing was purchased from IDEX Health & Science (Oak Harbor, WA). The flow rate with this peristaltic pump and the tubing was calibrated before every experiment.

Method of calibration of the peristaltic pump: Certain amount of toluene was contained in a flask which was put in the place of the reservoir. Set the flow rate of the peristaltic pump close to the one used for the experiment (e.g. 105 $\mu\text{L}/\text{min}$ if the actual flow rate will be 100.4 $\mu\text{L}/\text{min}$). After complete flushing the system, the exiting toluene was collected in a vial which was put in the place of the waste out of valve 2. The collecting time (e.g. 100 min) and the volume of the collected toluene were measured. So, the sign and the greatness of the error were obtained. By conducting this test for a few times, the exactly needed flow rate was achieved.

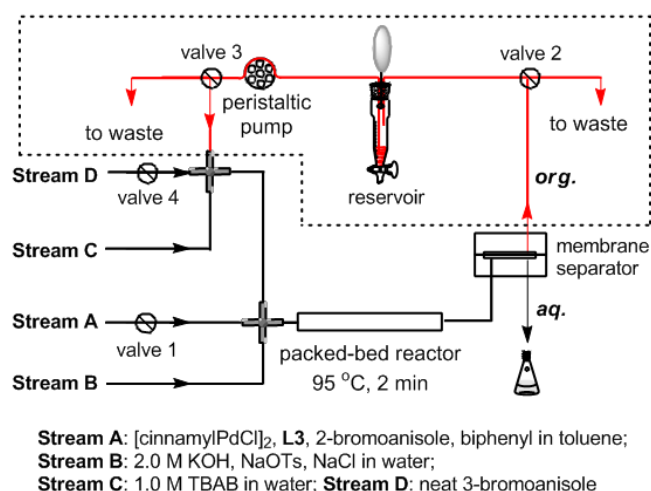


Figure S1. Setup for the continuous recycling experiment.

The phase separation device^[S3] consists of two stainless steel chucks compressed using ten 1/16 inch cap screws. In each stainless steel piece, a $0.5 \times 0.5 \times 20$ mm channel is fabricated using standard machining tools. The microfluidic connection is provided by 1/16 inch Teflon tubing and 1/4-28 screws (Upchurch Scientific) with the inlet and outlet holes of 0.5 mm directly drilled into the channels. A piece of Zefluor membrane (7×30 mm from a 46 mm disk, VWR) was placed between the two pieces to separate the channels.

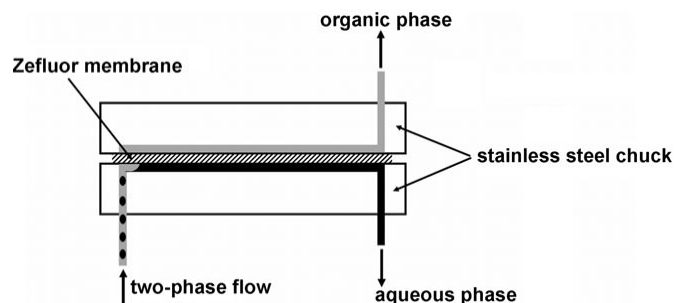


Figure S2. The membrane phase separation device.

^[S3] J. G. Kralj, H. R. Sahoo, K. F. Jensen, *Lab Chip* **2007**, *7*, 256-263.

4. Experimental Procedures

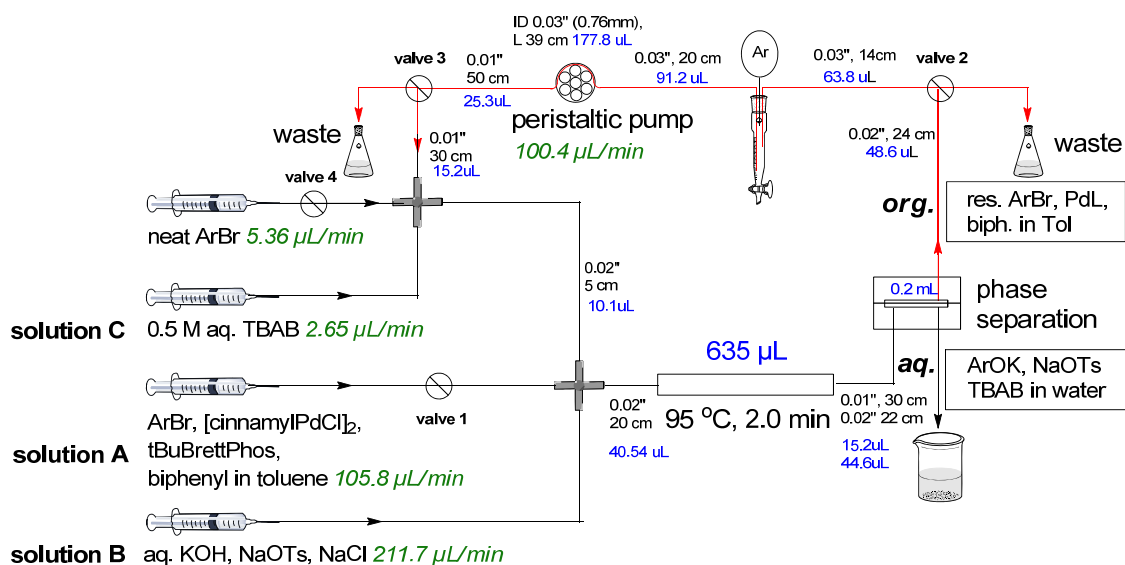


Figure S3. The parameters of the experiments.

Preparation of Solution A: An oven-dried, screw-capped volumetric flask (10.00 mL) was charged with **L3** (tBuBrettPhos 72.8 mg, 0.15 mmol), biphenyl (192.8 mg, 1.25 mmol), and cinnamyl palladium chloride dimer (13.0 mg, 0.025 mmol), then capped with a teflon screw-cap septum. The vessel was evacuated and back-filled with argon (this process was carried out a total of 3 times). 3-Bromoanisole (634 μL , 5.0 mmol) was added by a syringe, toluene was added to dissolve the solids, and finally filled up to volume (10.0 mL).

Preparation of Solution B: A second volumetric flask (25.00 mL), equipped in the same manner, was charged with sodium chloride (5.00 g) and sodium tosylate (607.8 mg, 3.13 mmol), then evacuated and back-filled with argon (this process was carried out a total of 3 times). Degassed aqueous 2.0 M KOH was used to make the solution up to volume.

Preparation of Solution C: Similarly, a volumetric flask (10.00 mL) was charged with tetrabutylammonium bromide (3.224 g, 10 mmol), evacuated, and back-filled with argon three times, followed by addition of a degassed aqueous 2.0 M KOH solution up to volume.

The whole flow system was thoroughly washed with methanol, followed by degassed toluene before experiments. All three solutions and neat 3-bromoanisole were loaded into plastic syringes and fitted to syringe pumps. Stream D was initially switched off using valve 4. To begin the experiment, streams A, B, and C were infused into the packed-bed reactor via a cross mixer in such a rate that the calculated residence time of the mixture in the reactor was 2 minutes (flow rates are shown in Figure S3, $635/(105.8+211.7+2.65) = 1.98 \approx 2$). The reactor was kept in an oil bath of 95 °C. Upon exiting the reactor,

the biphasic reaction mixture, as slug flow, was introduced into the phase separation device. To successfully operate the separation device the combined fluidic resistance from the separated organic stream needs to be less than the separated aqueous stream. In addition, the pressure difference between the organic and the aqueous side across the membrane needs to be less than the capillary pressure difference. Since the recycling loop involves tubings, valves and related parts with an associated increase in pressure drop, the aforementioned two criteria were met by adding backpressure to the aqueous side of the separator. The quality of phase separation was good since a visibly clear aqueous phase was obtained and further phase separation was not observed even when the collected aqueous phase stood for hours. The reaction mixture (four folds of the reactor volume) was directed to waste (using valve 2 for organic phase) until a steady state was achieved, as determined by UHPLC analysis. The organic phase was then directed to reservoir and collected up to 1.0 mL. During this period, the tubing before and after the peristaltic pump were flushed with this organic phase with around 3 folds of their volumes and the mixture was directed to waste by using valve 3. When the organic phase in the reservoir was accumulated up to 1.0 mL, valve 3 was switched so that the organic phase was directed back to the reactor in the indicated flow rate, valve 1 was switched off to discontinue the infusion of stream A, and valve 4 was switched on so that stream D was infused into the system in a rate to add 0.8 equivalent of neat 3-bromoanisole. Samples of the aqueous phase were collected every 2 minutes and analyzed by UHPLC.