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Continuous slurry plug flow Fe/ppm Pd nanoparticle-catalyzed Suzuki–Miyaura couplings in water utilizing novel solid handling equipment†

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Herein are reported initial efforts to develop a generally accessible flow process, applying a heterogenous nanocatalyst to aqueous micelle-enabled Suzuki–Miyaura coupling reactions. Also disclosed is a new engineering solution (*i.e.*, a self-draining back pressure regulator), which, when applied, enabled 1.5 hours of continuous operation leading to the production of 20 grams of a pharmaceutical intermediate.

Introduction

The introduction and adaptation of continuous flow technologies to both academic and industrial laboratories has revolutionized the manner by which chemists can synthesize important intermediates, as well as synthetic targets.[1] Indeed, chemistry performed in flow offers many advantages, such as: better universal heat control, improved mass transfer, safer handling of dangerous reagents, automation, generally less waste creation, and reduced reactor footprint for scale-up.[2] However, there are still several hurdles to overcome in this burgeoning area of research, making the transition to fully continuous-based processes difficult, especially from an engineering standpoint. One major problem in this area is use of solids in flow,[3] which can and will result in reactor failure due to clogging of ports, lines, and back-pressure regulators.[4] As a result, flow reactions in constrained systems, where the highest mass-transfer is observed, have been detrimentally limited to homogeneous, organic solvent-based solutions.[5]

Moreover, with the advent of chemistry in recyclable water, use of an aqueous medium for synthesis offers multiple attributes, including abundance and minimal cost, environmental friendliness, and additional safety features (*e.g.*, non-toxic and non-flammable nature).[6] The physical characteristics of water are also appealing for downstream processing, such as direct extraction or filtration of solid products. However, while some reactions can be used occasionally "on water",[7] in most cases the immiscibility of organic substrates and catalysts requires the use of a "soft" organic medium to assist with either partial or complete homogenization of reaction mixtures, where water functions as the global medium rather than as a true solvent.[8] Designer surfactants, such as TPGS-750-M,[9] have been developed for use in water, enabling chemical syntheses by functioning as "nanoreactors", in which organic reactions are facilitated under typically milder conditions than those required in organic solvents.[10]

Research towards applications of chemistry in water to any form of continuous manufacturing had been unknown until recently, where cascading continuous stirred-tank reactors (CSTR) were shown to provide one solution to the intended goal.[11] This technique eliminates clogging issues encountered with insoluble reaction components, such as starting materials, products, and especially heterogeneous reagents used in nanoparticle-catalyzed Suzuki–Miyaura cross couplings. However, wide use of the CSTR platform for chemistry in water in flow is, as yet, challenging due to limited accessibility to commercially fabricated equipment. Chemistry performed in plug flow (PF), however, is significantly more available, as most PF systems require only easily sourced fluorocarbon tubing, commercially available pumps, and potentially a back-pressure regulator. These systems have already been very successfully integrated into fine chemical synthesis.[12] Our goal, therefore, was to further expand chemistry in water into the plugged flow regime by tackling the issues inherent to reaction heterogeneity. Development of this new technology would open the door for further advances in, and applications of, flow technology using water as the reaction medium. This new flow methodology will specifically target a reaction performed

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with a *heterogeneous* catalyst, which is favored over homogeneous catalysis by most of the chemical industry. The nanoparticle (NP) catalyst system used herein, while exemplifying the engineering advancements achieved that otherwise plague use of solids in flow, also offers the benefits associated with a heterogeneous catalyst, such as ease of recovery and simplicity of experimental setup.

Results and discussion

Careful consideration of the best model reaction was given prior to undertaking this study. Thus, we focused on reactions that should benefit from heterogeneous catalysis in water using our recently developed nanoparticles (NPs), which presents the most challenging of situations, with not only the substrates being insoluble in water, but also the catalyst. The selection was further narrowed by excluding reactions that would either require a gas as reaction partner or produce gas as a side-product (*e.g.*, as in NP-catalyzed reduction of nitroarenes using $NaBH_4$).[13] Suzuki–Miyaura couplings catalyzed by NPs, reported previously by us both in batch and CSTR cascade flow, became the prime candidate for this study, given the importance of this Pd-catalyzed process, and one that can be effected at the ppm level of precious metal. It also would allow for direct comparisons to be made with results in hand from such couplings in water performed using the CSTR approach to flow.[14]

Having settled on Suzuki–Miyaura couplings for study,[15] we next examined their viability within a relatively suitable time frame. As reported in the literature, most reactions containing *ca.* 800 ppm of palladium relative to aryl bromide require more than 12 hours at 45 °C, which under flow conditions would lead to unacceptably long retention times and low productivity. Exploring the coupling reaction at higher temperatures, therefore, was considered vital in order to reduce retention times. Previous studies related to TPGS-750-M have indicated that the "cloud-point" in water is *ca.* 70 °C, at which the surfactant will reorganize within the aqueous medium. At 100 °C a solid may form, thereby rendering reactor clogging inevitable. Hence, a temperature limit of 95 °C was set for all couplings in flow. Use of microwave irradiation for initial screening was chosen as a rough guide for, and indication of, coupling reactions to be run under flow conditions.

A model NP-catalyzed Suzuki–Miyaura coupling between 4-bromoanisole and 1-naphthaleneboronic acid was run under microwave conditions at 95 °C for 15 minutes to test the rate of reaction at 0.5 M, using 800 ppm of the palladium NP catalyst. This reaction, known under batch conditions (*vide supra*) to afford a 91% isolated yield of the desired biaryl product, was found to be complete at this elevated temperature within 15 minutes. A simple workup requiring extraction of the product using minimal amounts of recyclable ethyl acetate, followed by passing the crude material through a plug of silica gel led to biaryl **2** in 89% yield. Based on these observations, this protocol was adopted for additional screening of other NP-catalyzed biaryl couplings in flow, using a reaction window of between 2–10 minutes at 95 °C. Importantly, repeating the synthesis of **2**, in this case using a 2-minute reaction time, resulted in identical conversion and yield further highlighting the enhanced rate of the reaction at higher temperatures.

The nature of a reactor for these NP-catalyzed couplings in plug flow was next addressed. Initial studies using freshly prepared catalyst in 2 wt% aqueous TPGS-750-M indicated that these NPs maintain suspension after sonication for >2 hours, while more gentle stirring elongated the duration of suspension indefinitely. Therefore, a simple syringe-driven PFR system should be viable (on small scale) where the NPs are separated from the reaction partners. However, it was also important to concurrently develop a system leading to maximum reaction productivity and throughput, which would require significantly larger volumes than the use of syringes would afford. While other commercial systems were considered, the VapourTec E-Series reactor system was chosen due to its inclusion of peristaltic pumps as the primary mode of delivering reagents together with an internalized, probe-monitored heating well for the reactor coil. This instrument has been reported to accommodate light slurries in suspension,[16] while our examination of this system found that the NPs suspended in an aqueous micellar medium could be easily pumped without clogging. Nonetheless, use of these suspended NPs along with this pump system also raised a few problems, including: (1) a NP stream that reached any "choke" points (where the stream is constrained below 0.03″) or reached a 90° turn in flow would result in filtering of the nanoparticles from the liquid, the consequence being a concomitant pressure drop across the system and removal of the catalyst from the reaction; (2) commercially available back pressure regulators became clogged due to the suspended particles (as well as undissolved reagents/products). Serendipitously, VapourTec had released a software development that would allow for their peristaltic pump to become a back-pressure regulator by reversing the product stream through such a pump, allowing it to act on the associated 1/8″ flexible tubing to hold back pressure. Thus, their E-Series reactor and peristaltic back-pressure regulator were used for all subsequent Suzuki–Miyaura couplings in aqueous flow experiments.

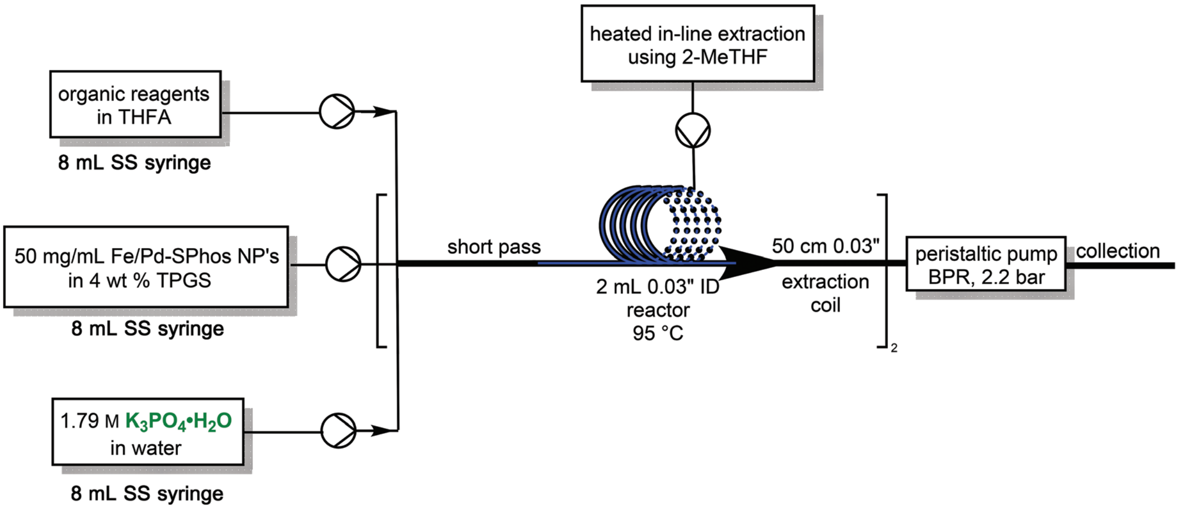
The viability of a ppm Pd NP-catalyzed coupling reaction in flow was then tested by subjecting a batch reaction to flow conditions *via* peristaltic pump delivery of the complete reaction mixture onto a 10 mL, 0.03″ ID coil reactor. The reaction medium was initially tested for "flowability", meaning the ability for the heterogeneous mixture to be evenly pumped out of a reaction vial and through the peristaltic pump, into the reactor. It was quickly found that a batch reaction containing 1-naphthaleneboronic acid, 4-bromoanisole, and potassium tribasic monophosphate for the synthesis of **2** resulted in a mixture containing insoluble agglomerates of starting reagents which, in the composite, was unsuitable for flow. By addition of 20 v/v% of a co-solvent, such as tetrahydrofuran, however, the reaction medium was quickly homogenized into a transportable fluid that could easily be pumped from the vial and into the reactor coil.[17] A 2 mL batch coupling reaction was then prepared for the synthesis of **2** in a vial using an 4 : 1 TPGS-750-M (2 wt% in water)/THF mixture, which was stirred continuously before being injected as a slug into a 10 mL reactor coil delivered at 0.667 mL min^{-1}. This resulted in a 15-minute retention time using fresh aq. surfactant/THF as a mobilizing fluid before and after the reaction materials. After a single retention time, the reactor was flushed with ethyl acetate to recover any starting material and product. Workup and purification of the crude organics from this "batch-to-flow" system resulted in biaryl **2** in 69% isolated yield. A yield incongruent with (and lower than) a batch-facilitated synthesis may be due to reaction dilution on the front end, as well as on the back end of the reaction slug by mixing with additional aq. surfactant/THF, resulting in dilution of a portion of the reagents.

In order to avoid dilution, a similar batch-to-flow reaction was explored using a 4 mL volume scale reaction slug, where the first mL of product stream would be discarded and only the second and third mLs of reaction eluent would be collected and isolated (*i.e.*, only the second and third retention times at a rough steady state are kept). The reaction could be monitored not only by time, but also by observing the orange nanoparticle slug traveling through the reactor coil. Upon collection of the nanoparticle fractions, though, it was found *via* UPLC UV/Vis analysis that neither the reagents nor the products were present in the colored eluent. It was later found that the product had begun to crystallize in the line post reaction at rt prior to reaching the back-pressure regulator, resulting in clogging. It appeared, then, that the product from the reaction did not evenly flow in the reactor coil at the same rate as the NP slug, but could be flowed out of the reactor if maintained at higher temperature.

Observations resulting from the batch-to-flow experiments defined key points associated with development of a fully autonomous plug-flow reactor system. Crystallization of product from the reactor eluent at rt indicated that the reaction needs to be extracted prior to leaving the heated reactor coil. To maintain the overall "greenness" of this process, the organic solvent selected for this heated in-line extraction was easily recoverable 2-methyl-tetrahydrofuran (2-MeTHF). The extraction tee would occur directly after the reaction coil and would be heated to the reaction temperature of 95 °C. It should be noted that the very low solubility of products in the aqueous stream might benefit from direct precipitation upon leaving the reactor, thereby rendering an extraction solvent moot. However, we found it imperative to dissolve the products in the down-stream reaction mixture prior to the BPR in order to avoid clogging, which would certainly occur within the cavity of the BPR at room temperature. The reaction components would also need to be separated such that the reagents and the catalyst would not interact outside the reactor. This issue was solved by separating the NPs into a pre-slurried mixture in aqueous TPGS-750-M at the desired concentration of both the NPs and surfactant. It is important to mention that the nanoparticle catalyst stream "flows" with respect to the entire system, *i.e.*, that there is no fixed bed of solid heterogeneous catalyst, exemplifying the true heterogeneity of this flow system. It was also important to separate the base from the NPs as well, as its pre-mixing either causes NP aggregation or phase separation in the case of organic bases such as triethylamine. For the reactions partners, a major element to the flow system was found to be pre-dissolving the starting materials in a green organic solvent at high concentration (>1 M). Tetrahydrofurfuryl alcohol (THFA) was chosen as the green organic "carrier" solvent, which would comprise less than 20 v/v% of the overall reaction mixture. THFA was chosen as it is considered a green solvent (derived from lignocellulose-based furfural,) it has a high boiling point (178 °C) which would not increase back-pressure requirements, it dissolves the reagents at high concentrations, and is water soluble. It was also found that ethanol can be substituted for THFA as the organic carrier solvent; however, higher reactor pressures were encountered due to its lower boiling point (78 °C) and the reaction temperature (95 °C).

Based on these considerations, a small-scale plug-flow reactor system was constructed for ppm Pd NP-catalyzed Suzuki–Miyaura couplings in flow (Scheme 1). This was achieved by installing a 2 mL coil (PFA, 0.03″ ID tubing) into the VapourTec E-Series heated well as the reactor. A cross-mixing unit was then implemented on the front end of the reactor where the organic, aqueous base, and aqueous nanoparticle streams would mix prior to the reactor. Likewise, a T-mixer was added on to the back end of the reactor. 2-MeTHF would eventually be injected at an equal flow rate at 90° into the product mixture and would act as an in-line extraction system. The entire cross-mixer, reactor, and in-line extraction system was then insulated using aluminum foil in the VapourTec heating well so as to maintain reaction temperature for all components, while minimizing precipitation of either starting material or product. The extraction mixture, on the back end of the reactor, was then plumbed into the VapourTec E-Series back pressure regulator pump to maintain reactor pressure.

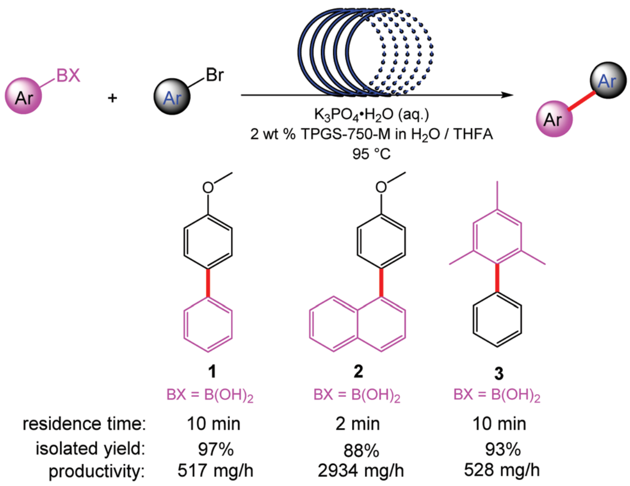
Synthesis of 4-methoxybiphenyl (**1**) was then used as a test case, the coupling found to be complete within 10 minutes under microwave irradiation. This biaryl was considered a first candidate for NP-catalyzed flow synthesis because the reaction temperature should limit problems arising from precipitation of product, as the melting point of the product is *ca.* 90 °C. However, the possibility of precipitation upon cooling leading to clogging would allow for testing of the efficacy of the cross mixer and in-line extraction. The aqueous components were separated such that a 50 mg mL^{-1} solution of the NPs was prepared in 4 wt% TPGS-750-M in water, while the phosphate base was prepared at 1.78 M in water. These two independent components would then be delivered into the reactor at an equal flow rate, thereby resulting in a total 2 wt% solution of aqueous surfactant and basic solution. The reaction partners were also prepared separately by dissolving each in THFA to a 5 mL volume. At this scale, each component was then added to separate stainless steel syringes and Harvard syringe pumps



Scheme 1 Reactor (2 mL) for chemistry in water in flow utilizing aqueous soluble base.

could be used to deliver them individually into the reactor.[18] The overall flow rate of the reaction was adjusted such that the concentration of the NPs present with respect to the starting reagents was akin to that of a batch reaction, where every 1.0 mmol of aryl bromide would be subject to 40 mg of catalyst (or 800 ppm of palladium). Utilizing these newly developed conditions, this biaryl coupling was complete at 95 °C within a 10-minute residence time, resulting in 100% conversion of the bromide. This flow system required no static mixers for maintenance of either the combination of the reagent streams or the in-line extraction unit.

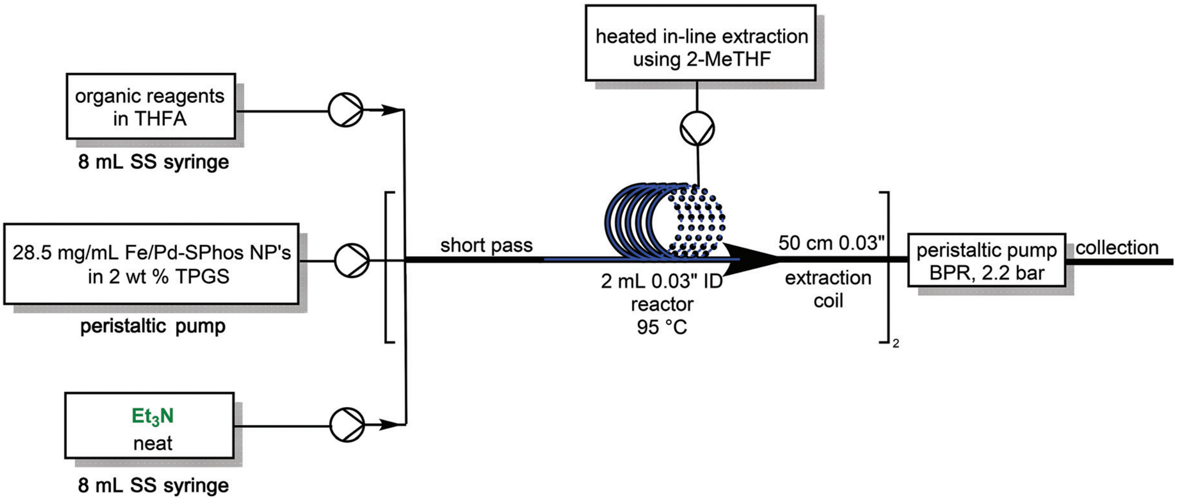
Following this successful run, this same system was used to probe other NP-catalyzed coupling reactions in an autonomous, continuous plug-flow reactor system. The three examples prepared under these conditions are suggestive of the prospects associated with use of this system (Scheme 2).



Scheme 2 Scope of micelle catalyzed biaryl couplings in PF using aqueous soluble base.

Biaryl **2** was realized in yields comparable to those obtained *via* batch mode in the proto-type flow system (*vide infra*) at a combined aqueous/organic flow rate of 1 mL min^{-1} on a 2 mL reactor coil. The high melting point of **2** did not result in reactor clogging due to product precipitation. It appears that the solubilizing capabilities of the aqueous surfactant/THFA mixture were able to overcome phasing out of solid **2** at the reaction temperature. The system was also able to handle high flow rates and relatively rapid synthesis times producing similar yields in comparison to those seen from microwave batch reactions. Complete conversion was also observed *en route* to biaryl **3**, an oil of low viscosity, obtained in high isolated yield.

Notwithstanding the previous alterations in reactor design and the resulting successful couplings, this flow system was not without its problems when products exhibiting high melting points or high crystallinity were encountered. In the case of newly formed biaryl **4** attempts at using longer reaction times led to reactor clogging, not only at the inlet cross-mixing and in-line extraction points, but also within the heated reactor itself. While the melting point and crystallinity of the product most likely contribute heavily to the overall failure of the system to run uninterrupted in a reliable fashion, a control study of the combination of the 4 wt% surfactant solution with the 1.78 M $K_3PO_4 \cdot H_2O$ solution found that the addition of phosphate base will result in an appreciable amount of precipitated gelatinous TPGS-750-M from the water. To avoid these clogging issues, an improved flow system was developed to incorporate triethylamine as base (Scheme 3). Moreover, it was anticipated that the transition from inorganic to organic base would aid in emulsifying highly water-insoluble reaction products. Therefore, a new system was developed that utilized a higher flow rate of NPs in aqueous TPGS-750-M at lower concentrations of both components, 28.5 mg mL^{-1} and 2 wt% respectively, using a peristaltic pump for delivery. This new catalyst stream was then cross-mixed in a similar fashion as with the previous flow system, with organics in THFA being

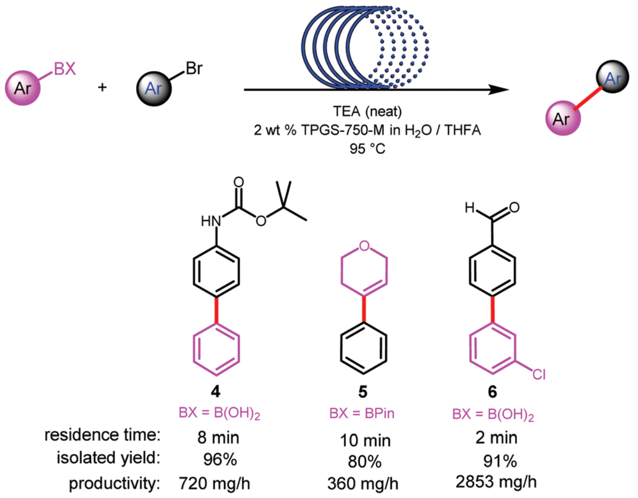


Scheme 3 Reactor (2 mL) for aqueous micellar chemistry in flow utilizing neat organic base.

introduced at the same flow rate as in the inorganic reactor, and with neat triethylamine being added at a significantly lower flow rate to achieve the desired reagent to base ratio (in this case found to be a flow rate of 2 : 1 organic to base rate). An expanded substrate scope was then explored using the improved organic base/NP flow system (Scheme 4).

Product **4** was prepared in flow over the course of five uninterrupted residence times, not including the four residence times required to bring the system to steady state. The product was also easily purified as done for **1** and **2**, only requiring precipitation in water followed by elution through a plug of silica gel. Noteworthy is the observation that a liable protecting group (*N*-Boc) is tolerated, in all likelihood reflecting the reduced reaction time as well as in-line quenching. Product **5** was also prepared in flow in 80% yield, suggesting that a boron ester is stable and yet reactive under the reaction conditions. Biaryl **6**, an intermediate *en route* towards a NEP inhibitor, was also synthesized in high yield. No competitive coupling of the boronic acid to the aryl chloride was detected as a side product. However, a small amount of the tetrahydrofurfuryl acetal of **6** was observed as a minor product which was easily hydrolyzed to the aldehyde in acidic batch workup. While not explored explicitly in this study, it is likely that use of an acidic workup stream would result in a fully integrated process leading to **6** as the sole product (Fig. 1).

Final development of this flow system was demonstration of a prolonged, large scale synthesis of the pharmaceutical intermediate **6**. Ideally, this reactor setup would be developed such that multi-gram quantities of biaryl could be produced and extracted autonomously. Towards this goal, the reactor was adjusted to include a 10 mL reactor coil while maintaining the same 0.03″ internal diameter. Reagents were fed into this reactor coil utilizing the same cross-mixing system used for previous small-scale studies.



Scheme 4 Scope of aqueous micellar catalysis-enabled biaryl couplings in PF using neat organic base.

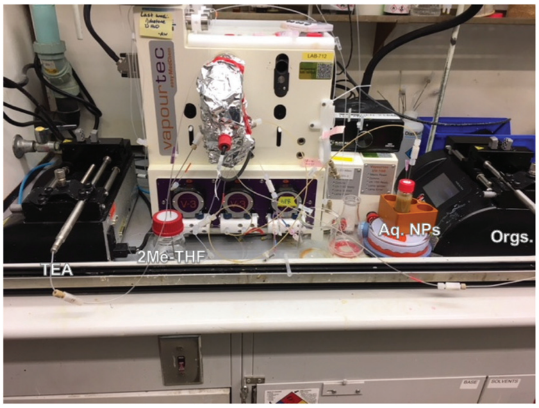


Fig. 1 Assembled reactor system for micellar NP catalyzed Suzuki–Miyaura couplings using neat organic base.

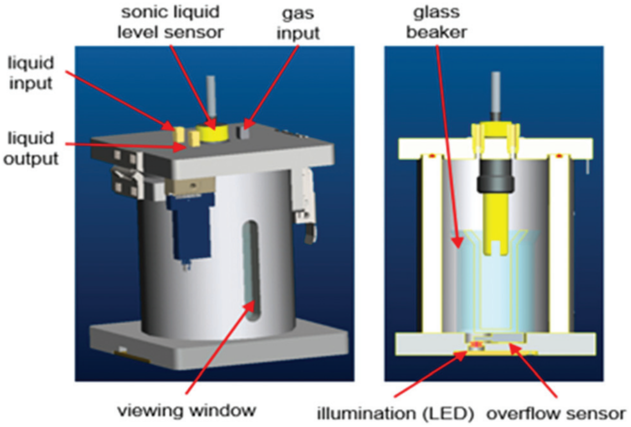


Fig. 2 Drawing of continuous collection and self-draining BPR.

In this case, however, syringes were not satisfactory delivery devices due to limited volumes. Thus, all three VapourTec E-Series peristaltic pumps were utilized to deliver the aqueous catalyst mixture, dissolved reactions partners, and neat triethylamine into the cross-mixer. 2-MeTHF was fed into the T-mixer in a similar manner as with the small-scale extraction unit. The back-pressure regulation (BPR) system was also altered. Scaling the reaction required a back-pressure regulator that could handle large volumes of reactor eluent. Therefore, a pressurized container set to accommodate a back pressure up to 40 PSI both inside of the container as well as inside of the reactor was installed such that the in-line extraction system would be fed directly into the pressurized container.

The newly designed regulator was developed to manage pressurized flow processes on a large scale and is engineered to handle 100 PSI of total back pressure. A metal exterior (185 × 145 × 145 mm) houses a 150 mL glass beaker which collects the reactor effluent from a 1/8″ outer diameter tube directly from the plug flow reactor (Fig. 2). The entire container can then be pressurized using compressed gas, which also includes holding back pressure for the entire PF reactor. The lid of the metal container also features a sonic liquid level detector which connects to a sensor which is suspended inside of the collection beaker. Once the sensor becomes submerged inside of the collecting liquid, a valve is actuated, and the compressed air pressure drains the collected reactor effluent using a second 1/8″ outer diameter tube which is also suspended near the bottom of the collection beaker. In the case of this biaryl scaleup, the BPR drained into a separate glass container. This system allows for continuous back-pressure regulation as well as collection of large volumes of reactor effluent in a separate draining container. Once all components of the PF system have been assembled, the scale associated with the preparation of **6** was increased five times. The calculated productivity of **6** was greater than 13 g h^{-1}. As planned, the system was able to run independently with no interruptions over the course of 90 minutes resulting in 22.8 grams of product (97% yield) (Fig. 3). As in the small-scale synthesis of **6**, this product was obtained after simple acidic workup to hydrolyze any acetal side product. Due to the large volume recovery of the aqueous NP-containing mixture post reaction, a small-scale run was attempted in order to observe recyclability of the nanoparticles. However, it was found that the NPs were no longer effective for use in either flow or batch mode for this coupling reaction, presumably due to separation of the aqueous reaction mixture that contains a significant amount of the needed phosphine ligand. Based on our previous study concerning recyclability of nanoparticles,[19] this problem can be ameliorated by simply adding fresh ligand to the "spent" nanoparticle solution which can then be reactivated for later use.

Conclusions

A plug flow system has been developed and applied to Fe/ppm Pd NP-catalyzed Suzuki–Miyaura couplings using an aqueous micellar medium. This system could be run using

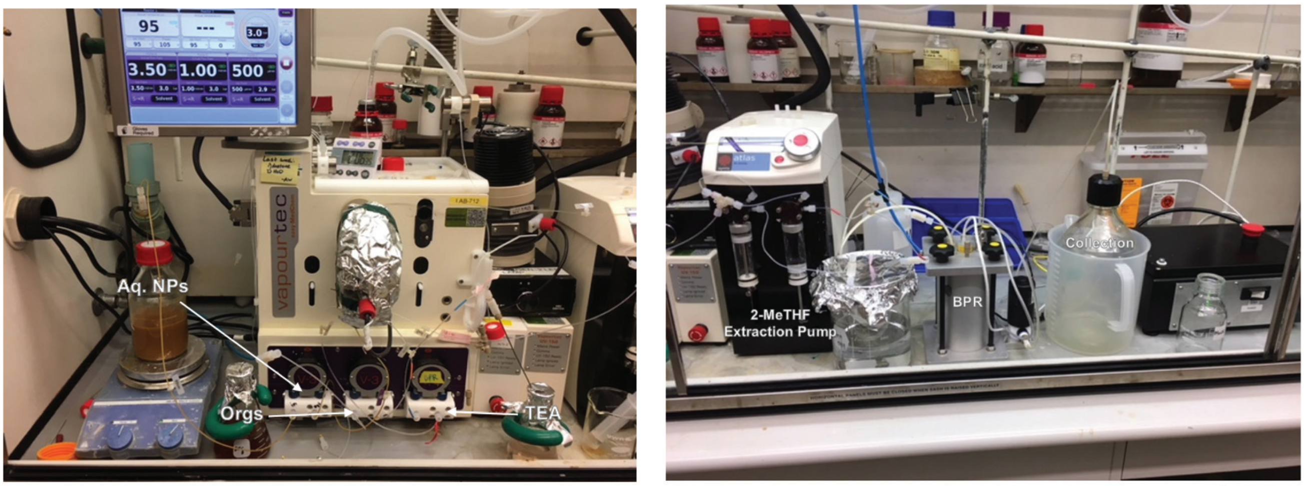


Fig. 3 Pictures of front-end reactor (left) and back-end extraction unit and BPR (right) for scale-up to make **6**.

both traditional syringe pumps, as well as VapourTec E-Series peristaltic pumps for delivering reagents into a heated VapourTec E-Series reactor. Both aqueous-dissolved inorganic base and neat organic base can be accommodated, depending upon the solubility of the biaryl product in the heated surfactant medium. The use of reverse-mode VapourTec E-Series pumps as back-pressure regulators able to handle large volumes of aqueous slurries was also found to be crucial for successful post-reactor product handling, as was a heated in-line organic extraction tee. This PF system could be scaled to produce 20+ grams of product in a 1.5 hours time frame, utilizing a novel back pressure regulator able to collect and drain large volumes of reactor effluent. Further applications to numerous metal- and non-metal-catalyzed reactions of great value to the fine chemical industry are planned and will be the subject of future reports from these laboratories.

Conflicts of interest

The authors declare no conflict of interest.

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