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Continuous flow Suzuki–Miyaura couplings in water under micellar conditions in a CSTR cascade catalyzed by Fe/ppm Pd nanoparticles†

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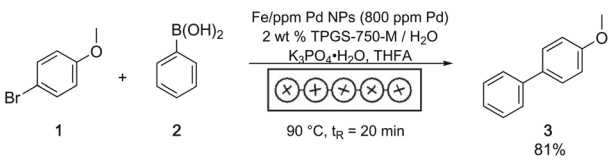
The first demonstration of aqueous surfactant-enabled Suzuki–Miyaura couplings run under flow conditions is described. In addition, use of an even more challenging heterogeneous nanoparticle catalyst, containing only 800 ppm of Pd (*i.e.*, 0.08 mol%) in the form of Fe/ppm Pd nanoparticles, is sufficient using a continuous stirred-tank reactor (CSTR).

In 2018, the Nobel Prize in Chemistry was awarded to acknowledge the fundamental contributions made, in part, in the area of bio-catalysis.[1] And while oftentimes taken for granted, such processes are routinely run in an enzymes' native medium of water.[2] By contrast, chemo-catalysis, or synthetic chemistry using catalysts typically based on transition metals or strictly organic compounds (*i.e.*, organocatalysts), is almost exclusively carried out in organic solvents, notwithstanding the non-sustainable and waste-generating nature of petroleum-based organic solvents. To assist, therefore, with the desired paradigm shift from organic solvents to a nature-driven, truly sustainable, water-based medium for organic synthesis that would constitute an environmentally responsible discipline,[3] we have been developing non-enzymatic-based designer surfactants, such as TPGS-750-M,[4] that spontaneously form nanomicelles in water. These serve much like enzymes with their hydrophobic pockets, or inner cores in which reactions occur, but without the "lock and key" feature that matches one enzyme, natural or otherwise, to a specific reaction. Although this entry to chemistry in water is broadly applicable to a range of valuable bond-forming reactions,[5] it has thus far been limited to "batch" mode usage.[6] The alternative approach to batch reaction processing focuses on continuous flow conditions (*e.g.*, for purposes of eventual manufacturing of pharmaceuticals and other fine chemicals).[7] A flow process is attractive due to its small footprint, and demonstrated benefits from the safety, environmental, and product quality viewpoints.[8] However, the non-homogeneous nature of aqueous micellar catalysis represents a major challenge to typical flow chemistry. Moreover, accommodating the presence of solids in the medium (which can be substrates, products, catalysts, *etc.*) creates distinct hurdles,[9] as these often lead to reactor channel clogging resulting in potential issues in levels of conversion, product quality, and safety.[10]

Numerous reactors and strategies have been explored to mitigate clogging events in the flow process, including the mechanically agitated flow reactor millireactors (Coflore),[11] gas–liquid segmented flow,[12] continuous-oscillatory baffled reactor (COBR),[13] and sonicators.[14] Recently, continuous stirred-tank reactors (CSTRs) have been demonstrated to be a robust and reliable solution for solid-forming reactions, as well as multiphasic reactions in a continuous flow.[15]

Herein we describe not only an application of the recently disclosed CSTR[16] (see ESI†) to Suzuki–Miyaura cross-coupling reactions in water, but also the use of a continuous synthesis platform that can handle Pd-containing iron nanoparticles serving as a heterogeneous catalyst.[17] The coupling of aryl bromide **1** and boronic acid **2** was chosen as the model reaction for the initial flow platform inquiry (Scheme 1).

Slurries of catalyst and reaction mixture were kept suspended by adding a magnetic stir bar inside a syringe, while continuously stirring using an external stirrer. An oscillator was installed at the connecting tube between the syringe and the CSTR in order to enhance transport of solids. The outlet



Scheme 1 Model coupling reaction in a CSTR.

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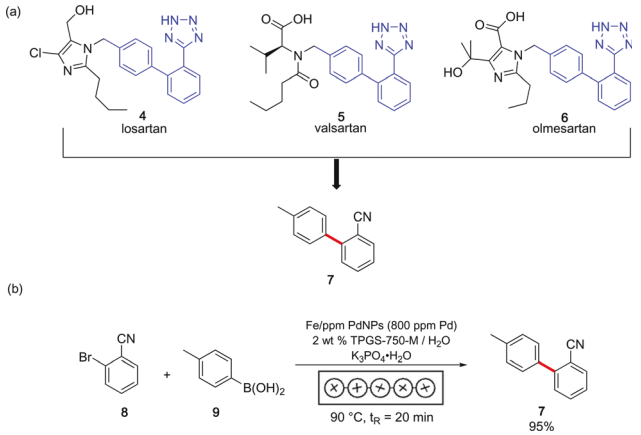
stream was combined with 2-methyltetrahydrofuran (2-MeTHF) using a T-mixer and a positive displacement pump followed by a static mixer to dissolve solids formed during reaction and to prevent clogging of the reactor. The outlet tube between the reactor and T-mixer was insulated to maintain temperature in order to prevent precipitation of the formed product in the aqueous stream. A 30 PSIG back-pressure regulator at the end of tubing chain controlled the system pressure, which was monitored by a pressure controller. During the continuous operation, the CSTR cascade was purged with argon, prefilled with degassed water and then all the reagent syringes were connected. The CSTR cascade was stirred and heated. After achieving the required temperature, the flow rates of all streams were adjusted to achieve the desired concentrations of reagents, nanoparticles, and the aqueous surfactant solution within the CSTR. After reaching steady state (~3 residence times), the product was collected, weighed, and then subjected to analysis (see ESI† for details).

The model biaryl product **3** was synthesized in the CSTR (see ESI† for details). Since aryl bromide **1** is not miscible in H_2O, this coupling partner, along with boronic acid **2**, were dissolved in 10 vol% tetrahydrofurfuryl alcohol (THFA) and introduced into the CSTR as a separate stream. Nanoparticles (Fe/ppm Pd NPs) in aqueous surfactant were found to aggregate in the presence of K_3PO_4. Therefore, aqueous K_3PO_4 was introduced into the CSTR as a separate stream. The continuous flow synthesis leading to product **3** was run, with no observable clogging, at 90 °C [18] with a residence time (t_R) of 20 min for 120 min. Sample collection at the steady state for 50 min afforded product **3** in 81% isolated yield. At this stage, no attempt was made to recycle either the reaction mixture or the Fe/ppm Pd NPs.

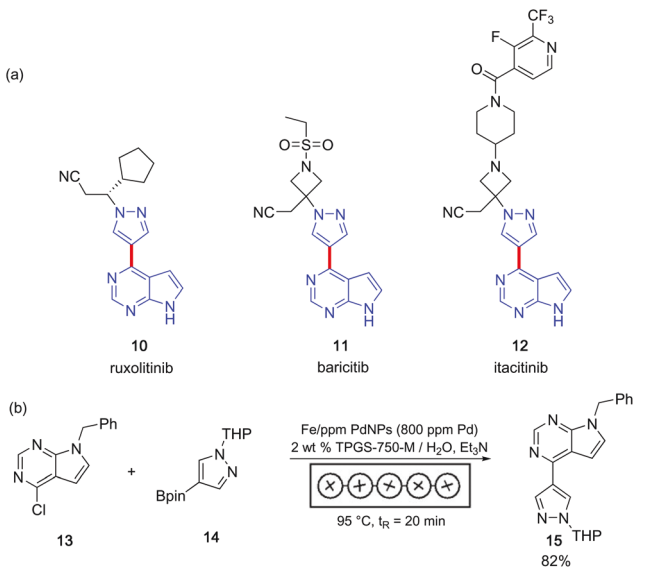
Following the successful demonstration of model biaryl coupling in flow, the newly developed CSTR platform was further applied to coupling reactions involving solid catalyst, substrates, and products, some of which correspond to key pharmaceutical intermediates. For example, sartans (Scheme 2a) remain today as widely used blockbuster drugs for treatment of high blood pressure. It has been more than three decades since the discovery of the first member in this class, losartan (Cozaar®, **4**) by Merck. Five sartan-containing drugs (Entresto® (**5**), Benicar® (**6**), Diovan HCT®, Exforge® and Aprovel®) are on the list of top 200 pharmaceutical products by retail sales in 2018.[19] Most sartans share the methylbiphenyltetrazole skeleton, typically constructed by a Pd-catalyzed Suzuki–Miyaura coupling reaction to install the required biaryl bond (Scheme 2a). The key intermediate **7** was prepared in a CSTR platform (Scheme 2b) by coupling **8** with **9**. Iron nanoparticles containing ligated Pd (800 ppm) suspended in aqueous TPGS-750-M surfactant combined with **8** and **9** was introduced into CSTR as a single stream. The aqueous K_3PO_4 was introduced as a second stream. All the reagents were in the aqueous medium, and no organic solvent was used in any flow synthesis. The solid product **7** formed in a CSTR was dissolved at the outlet using 2-MeTHF introduced *via* a T-junction. The continuous flow synthesis of product **7** was



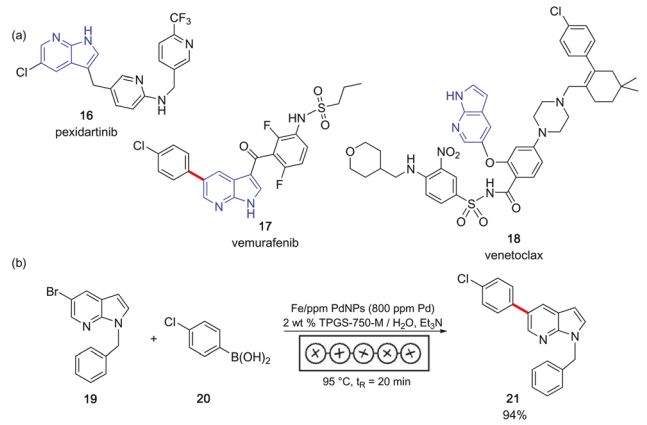
Scheme 2 (a) Structure of various sartans; (b) synthesis of biaryl precursor **7** of sartans in a CSTR platform. See the ESI† for details.

run at 90 °C with t_R of 20 min, and no clogging was observed for 90 min. The steady state sample analyzed after 20 min indicated formation of product **7** in 95% isolated yield.

JAK inhibitors (**10–12**) are among the fastest growing tyrosine kinase inhibitors on the market. Ruxolitinib (Jakafi®, **10**) is the first FDA approved[20] drug for treatment in this category and ranked 140th on the list of top 200 drugs in 2018 by sales.[19] The key C–C bond between the pyrazole ring and pyrrolo(2,3-*d*)pyrimidine can also be formed *via* a Suzuki–Miyaura coupling (Scheme 3). Based on a previous report,[21] this coupling was anticipated using a protected pyrazole pinacolborate and protected 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimi-dine as coupling partners. The former is commercially available as its THP derivative **14**, while the free NH in **13** is easily derivatized using benzyl chloride. Et_3N was introduced into the CSTR as a separate stream, as it aggregates NPs and makes



Scheme 3 (a) JAK inhibitors, and (b) synthesis of heterobiaryl precursor **15** of JAK inhibitors in a CSTR platform.



Scheme 4 (a) BRAF enzyme inhibitors, and (b) synthesis of biaryl precursor **21** of Zelboraf® in a CSTR platform. See ESI† for details.

them unsuitable to flow in a constrained system. The second stream comprised **13**, **14**, and Fe/ppm Pd NPs slurry-suspended in aqueous TPGS-750-M. The flow experiment was run at 95 °C at t_R of 20 min for 90 min. The steady state sample collected for 15 min led to 82% isolated yield of product **15** (Scheme 3b).

Another interesting example is FDA approved BRAF enzyme inhibitor vemurafenib (Zelboraf®, **17**), prescribed for treatment of melanoma, that contains a commonly seen 7-azaindole core, as in the examples shown above that include pexidartnib **16** and venetoclax **18** (Scheme 4a). In the specific case of vemurafenib, the *p*-chlorophenyl residue is accessible *via* a Suzuki–Miyaura biaryl coupling.

In batch mode, coupling between 5-bromo-7-azaindole and **20** did not go to completion. However, upon installation of an *N*-benzyl protecting group to form **19**, the desired product **21** was obtained in (96%) isolated yield. Synthesis of product **21** could also be performed in flow by coupling **19** and **20** (Scheme 4b). Using nanoparticles (Fe/ppm Pd NPs; 800 ppm Pd) as catalyst, together with educts **19** and **20**, were observed to aggregate in a single syringe. Hence, a slurry of NPs in aqueous surfactant, and a slurry of **19** and **20** in H_2O, were introduced into the CSTR as two separate streams. Slurries in both syringes were continuously kept suspended by stirring with an external stir plate and enhanced transport of solids was achieved by installing the oscillators at the connecting tube between the syringe and the CSTR. Continuous synthesis of biaryl precursor **21** of Zelboraf® was carried out for 120 min, with no apparent clogging. The steady state sample collected for 15 min showed product **21** in 94% isolated yield.

Conclusions

In summary, a recently introduced continuous stirred-tank reactor (CSTR) has been used as an effective means of handling slurries/solids not only for substrates and (heterogeneous) catalysts, but also for products formed continuously during especially valuable Pd-catalyzed Suzuki–Miyaura cross-couplings run under aqueous micellar conditions. In addition, this new technology utilizes ppm levels of Pd as part of heterogeneous nanoparticles that serve as the active catalyst for these reactions. Recycling of all reaction components, as well as analyses of the Fe/ppm NPs after a coupling remains for future studies, along with documenting the opportunities for scaling up such reactions. Four examples related to pharmaceutical intermediates associated with potent drugs currently on the market illustrate the potential of this approach as a valuable complement to chemistry in water performed in batch mode.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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18 At 90 °C, it is possible, and perhaps even likely, that the spherical nanoparticles formed by this surfactant, TPGS-750-M,[22] no longer retains its original shape, but reorganizes into a vessicle-like array. While the outcome from its use for this chemistry in flow remains as described, it will be interesting to determine the morphology of such micelles at various temperatures in anticipation of additional uses under these and related conditions.

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