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Continuous Recycling of Homogeneous Pd/Cu Catalysts for Cross-Coupling Reactions

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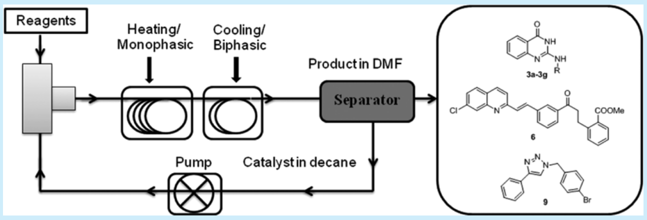
S *Supporting Information*



ABSTRACT: Given the importance of homogeneous catalysts recycling in organic chemistry, we have developed a unique microfluidic loop system for automated continuous recirculation of a soluble polymer supported metal catalyst for novel isocyanide cross-coupling reactions under thermomorphic multicomponent solvent (TMS) conditions. Our system provides an innovative approach for the chemical library synthesis of quinazolinone derivatives as well as an important intermediate of Merck's LTD4 antagonist "Singulair" with efficient continuous homogeneous catalyst recycling.

Environmentally benign catalysis has now become the target of the synthetic chemists. To minimize chemical waste stream and due to a trend toward "green" chemistry in industry, the research community has had to respond to these challenges with innovation and creativity.[1] Today, reuse and recycling of catalysts is receiving new attention as a critical component of emerging chemical technologies due to both environmental concerns and economic benefits.[2] It is not surprising, therefore, that present industrial chemical processes are favoring heterogeneous catalysts which leads to efficient recycling and reuse. However, most heterogeneous systems require a filtration and/or a tedious workup of the final reaction mixture to recover the catalyst.[3] A desirable system is one in which a homogeneous catalyst is used and yet the catalyst is as easily recyclable as a heterogeneous catalyst (Figure 1). One way of satisfying the desire involves use of a thermomorphic multicomponent solvent (TMS).[4] In this TMS system, the catalyst is soluble in one solvent and reactants/products are soluble in another solvent that is immiscible with the catalyst solvent.[5] When supported metal catalysts are air and/or moisture sensitive, it is exigent that practical recycling processes must be carefully executed to avoid deactivation via adventitious oxidation. Hence discontinuous implementation under batch conditions can be very vulnerable.[6] Therefore, we envisage a closed and continuous flow reaction system without air and moisture exposure, which removes the limitation, with an efficient metal catalyst recycling loop.

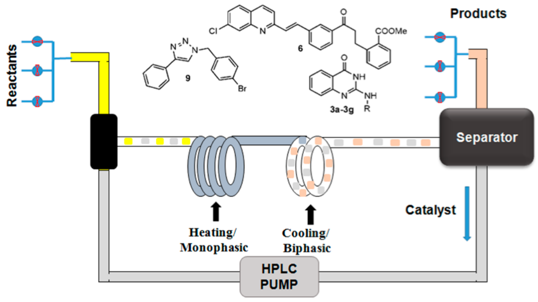


Figure 1. Conceptual scheme for a continuous catalyst recycling microfluidic loop system via TMS separation.

Continuous flow chemistry has now become a significant tool for rapid organic synthesis because of many advantages it offers over traditional batch-based synthetic procedures.[7] Continuous recycling of metal catalysts has recently been reported but most of them were carried out under organic–aqueous biphasic reaction conditions, which are difficult to expand into organic medium reactions, especially when water has to be avoided.[8]

To put the idea into practice, it was necessary to synthesize a series of linear block copolymers for Pd or Cu catalyst support that are compatible with TMS in such a way that the polymer support is soluble in a nonpolar solvent while the products remain in a polar solvent. Recent pioneering work by Bergbreiter has shown that soluble polymers could effect separation of catalysts from products quantitatively.[5a] A series of solvent mixtures have been utilized in liquid/liquid separations under TMS systems.[9] For our purpose, DMF/decane with a large difference in polarity was selected as a model solvent system for in situ recirculation of the catalyst. In this system, the supported polymer catalyst remains in the nonpolar decane solvent and the heterocyclic products mostly go to the highly polar DMF solvent.

To test this premise, poly(*N*-octadecyl-acrylamide-*co*-*N*-acryloxysuccinimide) (PNODAM-PNASI) copolymer was prepared to load the Pd catalyst (Catalysts **I**, **II** in Figure 2; Supporting Information (SI), methods S1–S2).[10] In addition,

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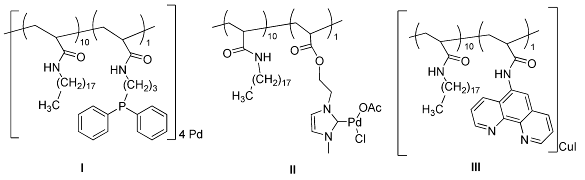


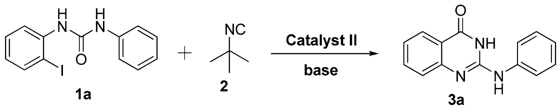
Figure 2. Pd or Cu immobilized random block copolymer catalyst supports for continuous recirculation in a microreactor loop.

the PNODAM-PNASI copolymer was modified with a phenanthroline ligand to immobilize Cu species for a Huisgen 1,3-dipolar cycloaddition reaction (catalyst **III**; SI, method S3). The detailed synthetic routes of block copolymers and the catalyst loading were well described and characterized by various techniques such as ^{1}H NMR, GPC, XPS, EDX, ICP-AES, and TGA (SI, Figures S1−S8). It should be noted that a similar approach may be applicable to the immobilization of a series of metals, such as Ni, Ag, Rh, and Au.[11]

Palladium assisted isocyanide insertion is an attractive approach because of intriguing selectivity and atom economy toward C−C and C−N bond formation.[12] Enlightened by the recent advancement, we have developed a novel isocyanide insertion reaction between urea derivatives and *tert*-butyl isocyanide for the synthesis of 2-amino substituted quinazolinones (**3a**−**3g**) involving continuous catalyst recycling. Interestingly, the synthesis of these molecules conventionally required 5 steps in contrast to our highly concise cascade process (Figure S7).[13]

Our initial efforts were focused on developing stable catalytic activity for the synthesized polymer supported catalysts (**I**, **II**) in the face of repeated use of the catalyst. Synthesis of 2-amino-substituted quinazolinone was performed in a conventional batch system with urea (**1a**) and *tert*-butyl isocyanide (**2**) using DMF and decane (50:50) as a TMS system and DBU as a base with catalyst **II** (for mechanism, see Figure S8). Although the reaction proceeds at 80 °C with catalyst **II** (0.5 mol %), it required a prolonged reaction time (12 h) to achieve an 83% yield. The rate of reaction was enhanced remarkably by increasing the temperature to 110 °C, reaching 85% isolated yield within 6 h. It is important to note here that thermomorphic behavior was not observed below 80 °C but a clear thermomorphic phenomenon occurred above 80 °C in the presence of <1.0 M reagents. Subsequent cooling led to feasible separation of the products and catalyst for repeated use due to the specific solubility of the mixture of unreacted urea and quinazolinone products in DMF and the catalyst in a nonpolar decane. Simply removing the DMF phase after reaction and evaporating the solvent was sufficient for product isolation without using column chromatography (SI, method S4). The catalyst **I** (1.0 mol %) associated with a phosphine ligand revealed a drawback of high leaching, as evidenced by the detection of ~25 ppm of Pd by ICP-AES analysis, and the resulting palladium black with 69% isolated yield of **3a** in 12 h.[14] The catalyst **II** with a *N*-methylimidazole ligand showed higher reliability with no leaching (<1 ppm), which is consistent with the reports that N-heterocyclic carbene (NHC) ligands have excellent stability to load Pd.[15] The NHC-Pd catalyst (**II**) maintained an 80%−88% yield (Scheme 1) during four repeated cross-coupling reactions, and no loss of Pd (<0.1 ppm) was detected in ICP-AES analysis (SI, method S5). After the reaction, catalyst recycling was achieved by adding a fresh DMF solution of the reactants and reheating the system for an additional 6 h. These results confirm the stability of the NHC-Pd system, allowing 4 recycles leading to a turnover number (TON) of 672 and turnover frequency (TOF) of 28 h^{-1}.

Scheme 1. Novel Synthesis of Substituted 2-Aminoquinazolinone (3a) by Typical Batch Recycling Process of NHC-Pd Catalyst under Thermomorphic Conditions



1st reuse: 85% 3rd reuse: 85%
2nd reuse: 88% 4th reuse: 80%

Because the synthesized NHC-Pd catalyst (**II**) and its compatibility with isocyanide insertion fulfilled the requisite condition of high catalytic activity and robustness, we used it in a continuous flow microreactor system. To obtain the reaction time profile in a continuous flow system, a solution of urea (**1a**, 0.1 M), isocyanide (**2**, 0.1 M), and DBU (0.15 M) in DMF and a polymer catalyst (**II**, 0.5 mM) in decane were separately introduced into perfluoroalkoxyalkane (PFA) tubing (total volume = 6.5 mL) through a T-shaped mixer by syringe pumps at 110 °C. We found that 8.2 min was enough to achieve 88% isolated yield for the synthesis of quinazolinone (**3a**). Negligible deviation in yield was observed when the id of the PFA tube was decreased from 800 μm (88%, flow rate = 0.4 mL min^{-1}) to 500 μm (86%), which allowed us to use a larger diameter tube to achieve higher productivity. Instant separation from monophasic to biphasic solvents was observed due to fast heat transfer that is an intrinsic feature of the microreactor. To recover and recirculate the catalyst (**II**), a continuous flow biphase separator for DMF−decane solvents and a microchemical system with an HPLC pump for recycling of the decane phase (Figures 1 and S9) were assembled. In view of the report that a double microchannel separator divided with a hydrophobic PTFE membrane film showed excellent separation efficiency for organic−aqueous mixtures (toluene−water),[16] it was applied for our recirculation. However, the results were not reproducible because of the incomplete separation and recovery of DMF and decane phases via a PTFE membrane separator.

It was found that continuous catalyst recirculation by a reservoir type of collector allowed efficient separation into two layers (SI, method S6). For the continuous flow experiment, a stock solution mixture of urea (0.1 M) (**1**), isocyanide (0.1 M) (**2**), DBU (0.15 M), and NHC-Pd catalyst (0.5 mM, 50 mL) in a reservoir was introduced to the capillary microreactor (total volume = 6.5 mL) with a T-mixer using two HPLC pumps at 110 °C. The flow rates of the DMF and decane solution were kept identical at 0.4 mL min^{-1} for the proper stoichiometry and thermomorphic behavior. Under the steady state for the residence time of 8.2 min, the DMF and decane biphasic mixture was collected, which separated in the reservoir. A pump continuously recirculated the separated catalyst layer from the upper part of decane, whereas the product was continuously collected from the bottom part of DMF.

The novel cross-coupling reaction under these thermomorphic conditions was carried out continuously for 18 h with little or no deviation in product yield of 81.8% in catalyzing 40 mmol of reagent into product **3a** (Figure 3). The total TON has been calculated to be 1308 for the reaction and the TOF to be 73.8 h^{-1}, which is 1.9 times the TON productivity and 2.6 times the

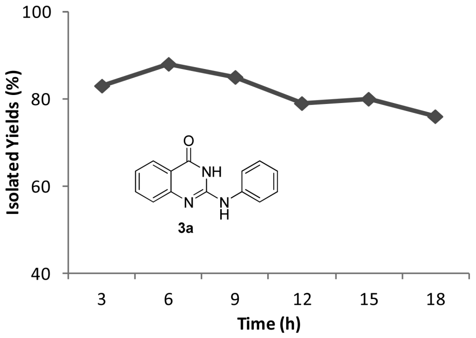
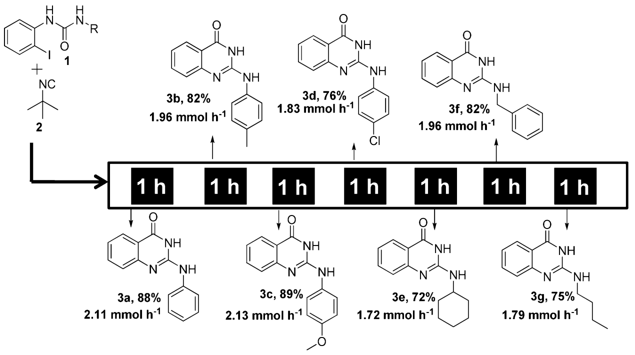


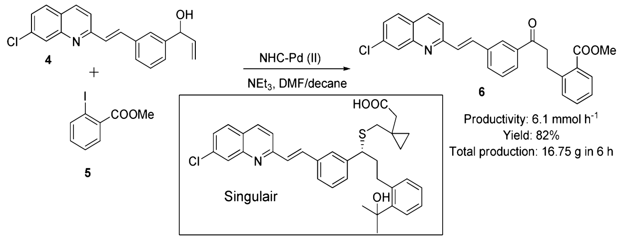
Figure 3. Conversion efficiency of quinazolinone by continuous recovery and recirculation of polymer supported NHC-Pd catalyst (**II**) under TMS conditions for a long period of time. Standard reaction conditions: urea (**1a**) (0.1 M), isocyanide (**2**) (0.1 M), DBU (0.15 M) in DMF, NHC-Pd catalyst (0.5 mM, 50 mL), PFA tubing (total volume = 6.5 mL), flow rate (0.4 mL min^{-1} each), 110 °C, total run (18 h), yield has been calculated after every 3 h. All the yields are isolated.

Scheme 2. Synthesis of Chemical Library of Aminoquinazolinone Derivatives by Serial Reagents Switch in the NHC-Pd Catalyst (II)[a]



[a] Isolated yield has been calculated after every 1 h interval.

Scheme 3. Continuous Flow Syntheis of Drug Intermediate Using Continuous Recovery and Recirculation of Catalyst (II)



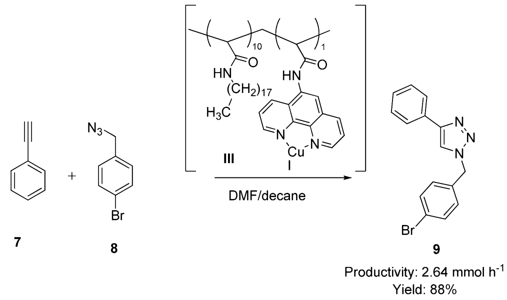
TOF by a batch reactor. The closed loop microreactor system enabled precise control of the reaction time and temperature, hence providing highly reproducible results for the air and/or moisture sensitive metal catalysts being recirculated with no deactivation of the catalytic activity. In contrast, the bulk batch process required laborious Schlenk techniques for each reaction of the sensitive metal catalyst, which is a less reproducible process due to the difficulty of parameter control.

The preliminary success indicated that it was indeed plausible to carry out diverse reactions in the developed system by simply replacing the reagent to generate a well-designed chemical library. These small chemical libraries are of current interest in drug discovery,[17] where milligrams of compounds are generally required for initial *in vitro* and *in vivo* analysis for drug discovery and chemical biology. Accordingly, with a similar setup, seven different urea derivatives with the NHC-Pd catalyst (**II**) were reacted every hour with a flow rate of 0.4 mL min^{-1}. Each product was collected and the system was washed for 15 min with DMF between two consecutive reactions to obtain seven quinazolinone compounds. Delightfully, seven products of 2-substituted aminoquinazolinones (**3a**–**3g**) were obtained with a productivity of 1.72–2.13 mmol h^{-1} within 9 h of the total run (Scheme 2; SI, method S7). These interesting results suggest that this synthetic setup could be employed to generate compound libraries.

The scope of the NHC-Pd catalyst can be extended to Heck reactions at very low catalyst loadings.[18] Therefore, we targeted an important intermediate in the production of Merck's LTD4 antagonist "Singulair" as an antiasthma agent. The key step in the synthesis is the Heck reaction of methyl 2-iodobenzoate (**5**) with allylic alcohol (**4**). For this purpose, the selective solubility of product in DMF was first confirmed. To achieve the final intermediate (**6**), initial precursor **5** was synthesized by the previously reported procedure.[19] A solution of methyl 2-iodobenzoate (**5**) (0.5 M in DMF), allylic alcohol (**4**) (0.5 M in DMF), 1.5 equiv of Et_3N as a base, and the NHC-Pd catalyst (0.5 mM, 50 mL, 0.1 mol % Pd) in a reservoir was then introduced to a PFA capillary (total volume = 6.5 mL) using a T-shape mixer for the reactions to proceed (Scheme 3). A residence time of 13.06 min (0.25 mL min^{-1} each) at 110 °C under thermomorphic conditions was enough to catalyze the reaction. Catalyst **II** was continuously fed into the system via a pump for recirculation. The reaction lasted for 6 h, and up to 16.75 g of product (6.1 mmol h^{-1}) was collected in 82% overall yield (SI, method S8). Under the conditions described the catalyst was exhausted after 6 h.

Finally, to investigate the diverse space in the reaction process, we next turned our attention to a Cu catalyst (**III**) supported on a phenanthroline ligand, which is well established for click chemistry at a low metal loading.[20] The Huisgen 1,3-dipolar cycloaddition reaction as a click reaction was selected, as both the reagents and product are soluble in the DMF layer. A solution of phenylacetylene (**7**) (0.1 M in DMF) and 4-bromobenzyl azide (**8**) (0.1 M in DMF) was then introduced to a PFA capillary (total volume = 6.5 mL) for the reactions to proceed (flow rate = 0.5 mL min^{-1} for DMF and decane each). As seen in Scheme 4, it was observed that a residence time of

Scheme 4. Continuous Flow Click Reaction by Continuous Recovery and Recirculation of Polymer Supported Cu Catalyst (III) under TMS Conditions[a]



[a] Standard reaction conditions.

6.5 min at 120 °C was enough to catalyze the reaction to obtain triazole (**9**). The Cu supported catalyst (**III**) was continuously fed into the system via a pump for recirculation. The reaction time was 10 h with 8.26 g of product (productivity = 2.64 mmol h^{-1}) collected in 88% overall yield. The integrated microfluidic system took only 6.5 min with comparable yields to the conventional batch process without any detectable metal leaching.

In summary, we have developed a microfluidic loop system for continuous recirculation of a polymer supported metal catalyst for novel cross-coupling reactions under thermomorphic multicomponent system conditions. This approach takes full advantage of a homogeneous catalyst system while retaining the advantage a heterogeneous catalyst system offers for easy separation and recirculation of the catalyst. This automated microreactor system successfully demonstrated a novel method for the chemical library synthesis of quinazolinone derivatives as well as an important intermediate of Merck's LTD4 antagonist "Singulair".

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental procedures and characterization of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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