Microreactors

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Accelerating Reactions with Microreactors at Elevated Temperatures and Pressures: Profiling Aminocarbonylation Reactions**

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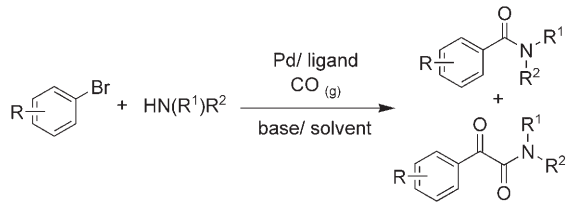
The use of microreactors can greatly accelerate scanning and optimization of reaction conditions because of enhanced heat and mass transfer, reduced reaction volumes, and the ability to run several experiments within a sealed system (minimizing contamination by oxygen and water). These advantages have been demonstrated in several studies over the past decade at conditions typically used in bench-scale synthesis.[1–10] A major advantage of microreactors is the ability to perform reactions under conditions that cannot be easily realized in conventional glassware, such as the use of standard solvents (e.g. toluene) at elevated temperatures and pressures.[4,9] Reactions performed under these conditions is one of the major benefits of microwave synthesis.[11,12] Microreactors offer many of the advantages of microwave reactors and have the additional advantages of continuous flow and that they do not require a microwave generator.

The realization of high pressure in glass-based microreactors is complicated by difficulties in interfacing with fluid inlet and exit tubes. For example, typical compression sealing techniques of glass and silicon devices are cumbersome, and they are typically limited to moderate pressures (ca. 10 bar) to avoid breaking the device. Herein we use a recently developed solder-based sealing technique[5] to construct microreactors capable of reaching pressures exceeding 100 bar[13] and to demonstrate the potential advantages of operating above the boiling point of toluene in Heck aminocarbonylation[14] reactions (Scheme 1). The use of microreactors enables rapid evaluation of the effects of modifications to the reaction conditions on yield and selectivity, as well as the use of experiments with several reagent solutions in rapid succession. The ability to rapidly change reactants and conditions would be a powerful strategy for the high-throughput synthesis of a diverse array of compounds as well as for catalyst screening. Chemical parameters such as functional groups, ligand properties, and base strength could be rapidly varied along with reaction conditions. The continuous operation and scanning of reaction parameters provides information that can lead to improved insight over typical batch- or array-based processes, which are often limited to one-variable-at-a-time experimentation. The case study also illustrates the advantages of a closed system in handling elevated pressures of a toxic gas (carbon monoxide) and air-sensitive Pd catalysts.



Scheme 1. Pd-catalyzed Heck aminocarbonylation.

The microreactor (Figure 1) is formed in silicon by defining the mixer and channel layout by lithography and then etching channels in silicon.[4] Subsequent oxidation of silicon forms a glass layer on the surface so that when the channels are capped by bonding a Pyrex glass wafer to the oxidized silicon device, the reaction channels become functionally equivalent to a glass reaction vessel. Moreover, the top glass layer provides visual access to the reaction medium,

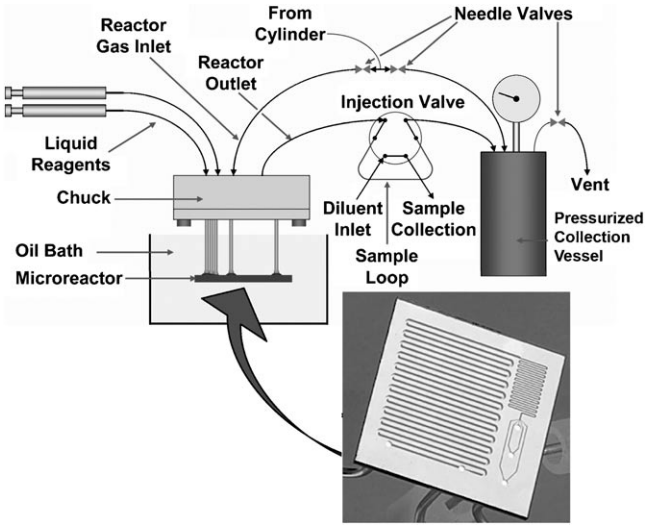


Figure 1. Pressurized microreactor setup.

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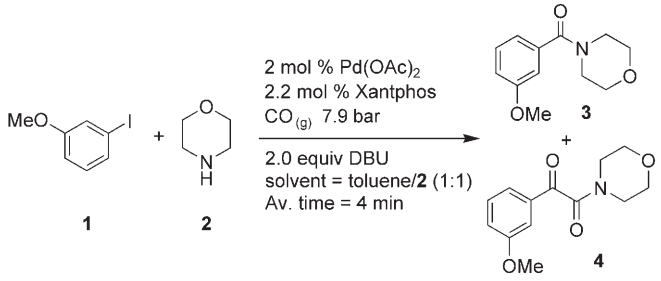
which is particularly useful in monitoring gas–liquid contact and detecting the formation of solid by-products.

In the initial studies with the setup shown in Figure 1, a Xantphos-Pd catalyst[15] was used with a silicon microreactor, which we had previously designed for general organic synthesis[5] [Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene]. Because of the small dimensions of the reactor channels, the generation of precipitates needed to be controlled and their potential to clog the reactor minimized. The solid by-products of chief concern were palladium black, palladium carbonyl complexes,[16] and protonated amine salts. Although some precipitation was observed, the formation of solid materials was minimal and occurred primarily along the reactor walls. The microreactor was rinsed daily with methanol, which was sufficient to avoid any blockage of the flow.

The first Pd-catalyzed aminocarbonylation reaction explored was that of 3-iodoanisole (**1**) and morpholine (**2**) (Scheme 2). The carbonylation was performed by delivering CO with a syringe pump at 7.9 bar. The pulsation of the



Scheme 2. Aminocarbonylation of 3-iodoanisole.

syringe pump induced minor changes in the residence times, but the average reaction times (ca. 4 min) could still be determined from the active reactor volume (78 μL) divided by the averaged volumetric flow rate ($Q_L = 4\ \mu L\,min^{-1}$ per syringe; $Q_G = 12\ \mu L\,min^{-1}$).

In contrast to conventional benchtop reactions at near-atmospheric pressure, aminocarbonylation in the microreactor at elevated CO pressures produced significant quantities of α-ketoamide **4**, in addition to amide **3**.[14] This shift in product distribution is attributed to the superior gas–liquid contact area, the resulting improvement in mass transfer, and the greater amount of CO in solution.[17] Figure 2 shows measured yields of **3** and **4** for samples with greater than 90% conversion of 3-iodoanisole and an average reaction time of four minutes. The yield of amide increases with an increase in temperature. In particular, temperatures above the normal boiling point of the solvent (toluene, 110 °C) produce a significant shift towards amide formation, which underscores the advantage of being able to conduct experiments at elevated pressures. These initial results suggest that in addition to achieving faster reaction rates at elevated temperatures, it could be possible to manipulate the relative yields of amide and α-ketoamide by varying the temperature and pressure. An increase in the temperature favors amide formation whereas elevated CO pressures will enhance α-ketoamide formation.

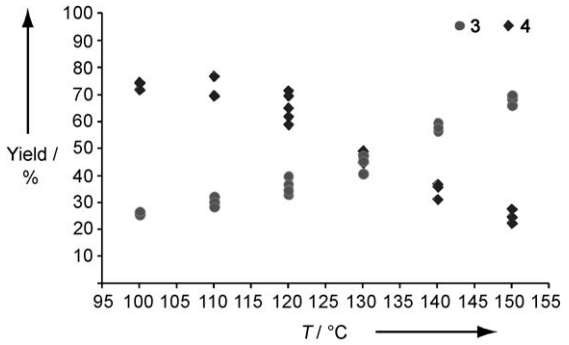
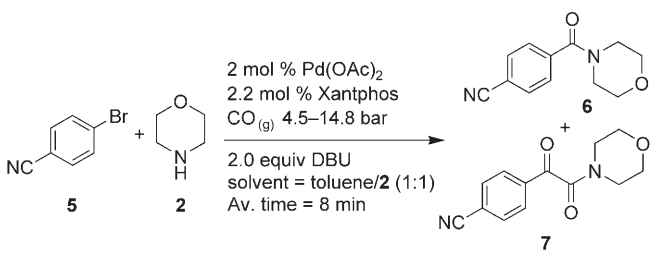


Figure 2. Aminocarbonylation product yields for samples with greater than 90% conversion of 3-iodoanisole. Each data point represents an individual experiment.

To further demonstrate the ability of the microreactor to rapidly scan pressures and temperatures and to explore their effect on α-ketoamide formation, the selectivity of the aminocarbonylation reaction of 4-bromobenzonitrile (**5**) was profiled. Though carbonylation reactions of aryl bromides are more challenging than those of aryl iodides, the greater diversity and the lower cost of commercially available substrates make the aryl bromide reactions more attractive. To accommodate the longer reaction times required when using the less reactive aryl bromides, the selectivity study was performed by using the original microreactor design and a volume extension consisting of a 300-mm length of stainless steel tubing (1.17-mm internal diameter). The volume extension was connected to the reactor through the same solder-bonding technique used for the other connections and it was submerged alongside the reactor into the oil bath, to give a total heated reactor volume of 400 μL. Rather than using the syringe pump with its complicating pulsating flow, carbon monoxide was delivered directly from the tank and controlled by using needle valves (Scheme 3).

Reaction data were collected at temperatures between 98 and 160 °C and carbon monoxide pressures of 4.5, 7.9, and 14.8 bar. For each sample, the overall selectivity for α-ketoamide **7** was calculated as the ratio of α-ketoamide to amide and plotted in Figure 3. The expected increase in selectivity for amide formation with an increase in temperature was observed, along with enhanced selectivity for the production of α-ketoamide with increasing pressure, which corresponds to larger amounts of dissolved carbon monoxide in the solvent.

In addition to using the microreactor to rapidly scan the effect of reaction conditions on yield and selectivity, several reagent solutions could be tested in rapid succession by



Scheme 3. Aminocarbonylation of 4-bromobenzonitrile.

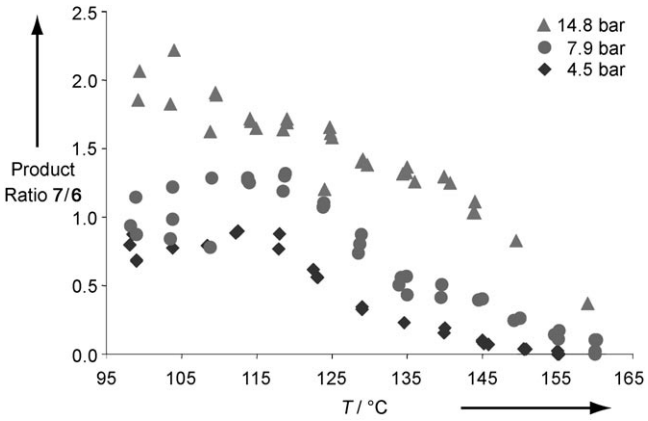


Figure 3. Product ratio of α-ketoamide (**7**) to amide (**6**) for the aminocarbonylation of 4-bromobenzonitrile (**5**). Each data point represents an individual experiment.

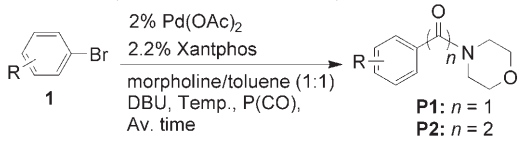
installing injection valves onto the liquid reagent inlet lines. Thus, if one desired to run several combinations of substrates under the same conditions, this could be accomplished by simply varying the solutions loaded into the inlet-sample loops. This ability to rapidly change reactants and conditions is a powerful strategy for fast synthesis of a diverse array of compounds as well as for catalyst screening.

We demonstrated this ability by switching between 4-bromobenzonitrile and 4-bromoanisole without stopping the flow into the reactor. The system was brought to pressure with toluene loaded in each syringe and the sample loops were loaded with reagent stock solutions: $Pd(OAc)_2$, Xantphos, and toluene in one and Ar-Br, DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene), dodecane (internal standard), and morpholine in the other. This system was successfully used to test aminocarbonylation of 4-bromoanisole (Table 1, entry 5).

The use of a pressurized microreactor system greatly expands the range of reaction conditions available to the bench chemist. In this study, pressures from 4.5 to 14.8 bar and temperatures from 98 to 160 °C were examined with greater flexibility, in terms of loading and sampling, than would be possible with traditional high-pressure chemical equipment such as a Parr bomb or autoclave. In addition, the use of injection valves on the inlet lines offers the possibility of using a wide range of substrates to efficiently produce a library of products. Furthermore, with the microreactor system, the reaction conditions themselves are improved. The significantly greater mass-transfer area resulting from segmented gas–liquid flow enables very rapid reaction times from the accelerated mass transfer.[18]

The carbonylation case study demonstrates the considerable potential of continuous-flow, microreactor-based experiments at conditions not easily achieved in conventional benchtop experiments. In particular, the technique provides a useful tool for quickly and safely scanning reaction conditions and reagents. By using this technique, we were able to test multiple aryl halides over a wide range of temperatures and pressures much more rapidly than could be accomplished with batch experiments. For instance, in the study of the effects of pressure and temperature on the aminocarbonylation of 4-bromobenzonitrile (**5**) up to 36 samples were collected and analyzed in a single day. Table 1 summarizes the conditions at which the maximum amide and α-ketoamide yields for each reaction were observed. These results reveal the general trend for an increase in the yield of amide with an increase in temperature and an increase in the selectivity of α-ketoamide at lower temperatures and higher pressures.

Table 1: Maximum yields for various carbonylation reactions.



1	*P* [bar]	*T* [°C]	Av. time [min.]	Conv.	Yield **P1** [%]	Yield **P2** [%]
MeO, I	7.9	146	3.3	100	68	28
	7.9	116	4.2	100	35	65
NC, Br	2.7	160	7.1	100	83	0
	14.8	109	6.6	99	32	57
MeO, Br	2.7	150	12.7	48	35	0

Experimental Section

Aminocarbonylation with carbon monoxide gas delivery directly from gas tank: The system pressure was controlled by three needle valves (Upchurch P-445). The cylinder outlet was split and each branch was connected to a needle valve. One branch was connected to the microreactor gas inlet and the second branch was connected to the pressure bomb (pressurized collection vessel) makeup inlet (Figure 1). The third needle valve was connected to the bomb outlet tubing such that there was a controlled constant leak from the headspace of the pressure bomb.

After the bomb was pressurized, all needle valves were closed. The cylinder delivery pressure was then raised an additional 5% to compensate for pressure drops in the delivery system. The liquid reagent flow rate was next set to the desired reaction conditions, and the reactor gas inlet was partially opened to allow gas flow and begin slug flow equilibration. Additionally, the leak valve was slightly opened to allow the microsystem to come to steady state. During operation, these two valves were used to control the flow rate as observed in the reactor by measuring the speed of the slugs. The overall flow rate was varied between 30 and 150 $\mu L\,min^{-1}$, which corresponds to reaction times of 13–2.5 min, respectively. The bomb inlet valve remained fully closed unless the pressure in the bomb dropped below the desired operating pressure, in which case the valve was opened to allow repressurization.

Sample analysis: The samples were analyzed by gas chromatography with an Agilent 6890 Series gas chromatograph and an FID detector. The samples were injected by an Agilent 7683 automatic liquid sampler into a 10-meter Agilent HP-1 capillary column (internal diameter 200 μm; film thickness 0.11 μm) with a flow rate of nitrogen 1 $mL\,min^{-1}$. The oven temperature was raised from 70 to 240 °C over 6.5 minutes. Sample peak areas were normalized to the response of the internal standard to determine the sample concentrations. Compounds were isolated by chromatography on the residue

resulting from combining several samples from a series of experiments by using the same stock solutions and removing the solvent.

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