Microfluidic Reactors

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Rapid Multiphase Carbonylation Reactions by Using a Microtube Reactor: Applications in Positron Emission Tomography ^{11}C-Radiolabeling**

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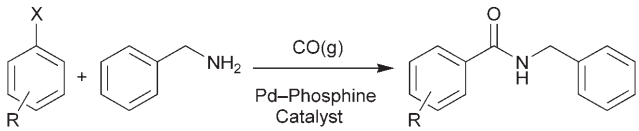
The development of new strategies for the synthesis of positron-emitting radiolabeled compounds is of great current interest owing to the increased use of positron-emission tomography (PET) in medical imaging. Short-lived positron-emitting radionuclides, such as ^{11}C ($t_{1/2} = 20.4$ min), ^{13}N ($t_{1/2} = 9.96$ min), ^{15}O ($t_{1/2} = 2.07$ min), and ^{18}F ($t_{1/2} = 109.7$ min), require specially adapted methods of synthesis owing to their short half-lives and the submicromolar quantities used in reactions. [^{11}C]carbon monoxide is becoming a recognized precursor for ^{11}C labeling[1–5] owing to the potentially wide ranging number of functional groups that can be incorporated into target molecules. However, ^{11}CO labeling is not without its difficulties owing in part to the poor reactivity of carbon monoxide and the problems associated with trapping enough ^{11}CO in organic solvents to perform the reaction. Herein we show that a possible solution to these limitations is to use microfluidic-reactor technology.

Microfluidic-reactor devices are particularly well suited to conducting multiphase gas–liquid or gas–liquid–solid reactions; this is a result of their increased surface-area-to-volume ratio that allows enhanced surface contact between different phases. When compared with conventional laboratory methods, microfluidic reactors have been demonstrated to improve reaction rates, yields, and/or selectivities of a number of gas–liquid[6–10] and gas–liquid–solid reactions.[11–13] These improvements are a direct result of superior heat and mass transfer within the system and controlled mixing of reagent streams. The use of supported reagents[14] and catalysts[15,16] is becoming more attractive to synthetic chemists mainly owing to the ease of purification steps and the cost efficiency of reusable reagents and precious-metal catalysts. We are interested in the palladium-catalyzed carbonylative cross-coupling reactions of aryl halides, which can be used as a route to a number of biologically interesting molecules such as amides, lactams, esters, and lactones. In the typical synthesis of an amide, an amine and an aryl halide are coupled together with a molecule of carbon monoxide in the presence of a palladium catalyst (Scheme 1). However, owing to the poor solubility of carbon monoxide in common organic solvents,[17] carbonylation reactions are usually carried out at elevated pressures. Such methods require high-pressure autoclave reactors that are inherently expensive and require special safety precautions.



Scheme 1. Amide formation through the carbonylative cross-coupling reaction. X = halogen, R = electron-donating or -withdrawing group.

We recently reported the use of a continuous-flow microfluidic reactor[18] for conducting carbonylation reactions that proved to be superior to corresponding batch-reaction methods. Herein, we report a simple, low-cost and effective method for gas–liquid–solid carbonylation reactions employing a reusable silica-supported palladium catalyst packed into standard teflon tubing (see Figure S1 in the Supporting Information). This methodology makes it possible to obtain good yields of the corresponding amides within very short reaction times. These results, in turn, prompted us to employ the microfluidic reactor system for ^{11}C-radiolabeling experiments. More specifically, we present preliminary results on ^{11}CO carbonylative cross-coupling reactions to yield ^{11}C-labeled amides. To prepare the microtube reactor, a teflon tube (45 cm in length and 1 mm in diameter) was packed by injecting a slurry of the supported catalyst (250 mg) in THF and plugged at both ends with cotton filters. The supported catalyst (Scheme 2) was prepared by first synthesizing the palladium–phosphine complex followed by attachment to the silica-support material; this method differs to that previously reported in which the ligand was first attached to a silica support before complexation with Pd^{II}.[19] Two equivalents of bis-diphenylphosphonium chloride were reacted with amino-

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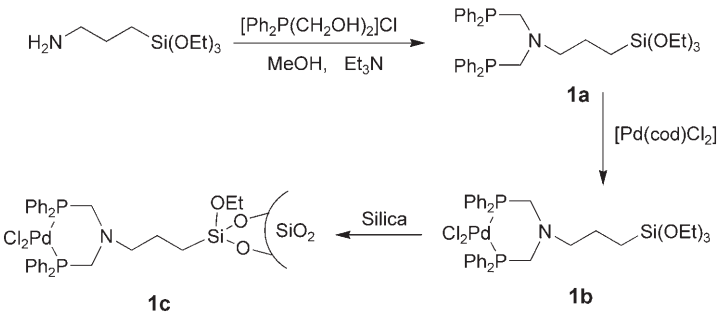


Scheme 2. Synthesis of the silica-supported diphosphine catalyst **1c**.

propyltriethoxysilane to form the chelating ligand **1a**. This was then reacted with one equivalent of $[Pd(cod)Cl_2]$ (cod = 1,5-cyclooctadiene) to form complex **1b**. This compound was then reacted with silica to form the supported catalyst **1c**. Inductively coupled plasma (ICP)-MS analysis of the supported catalyst gave palladium loadings of 1.5%.

The reactor setup (Figure 1) consists of a precision syringe pump to control the infusion rate of the solvents and substrates, an injector port for substrate injection, a mass flow controller to meter the flow of carbon monoxide into the system, and a mixing T piece to mix the gas and liquid reagents and which connects directly to the microtube reactor.

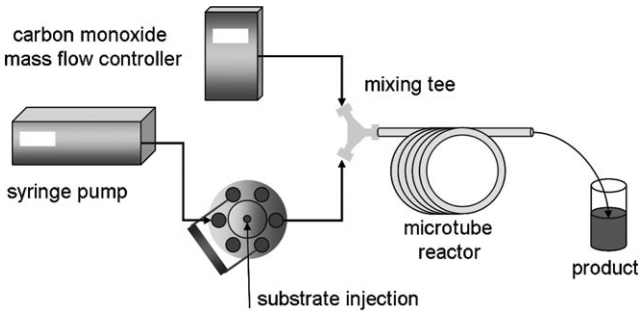
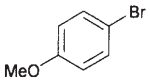
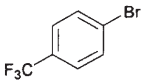
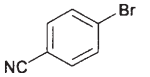


Figure 1. Schematic representation of the carbonylation microtube reactor setup.

In a typical reaction, a 50-μL aliquot of substrate solution (aryl halide and benzylamine) was injected through the injector port into a continuous flow of solvent (THF) where it was mixed with a steady stream of carbon monoxide, passed into the microtube reactor, and then heated to 75 °C. After a 12-minute residence time period in the reactor, the solvent flow was increased, flushing the product from the reactor for collection and analysis. We examined six different arylhalide substrates for the carbonylative cross-coupling reaction with benzylamine; the results of these reactions are displayed in Table 1. Three consecutive runs were carried out for each arylhalide substrate by using the same microtube reactor for all the carbonylation reactions (a total of 18 separate reactions); no loss in catalytic activity was observed between the consecutive runs.

Yields of the carbonylated products from the microtube reactor varied depending on the substrates used in the reaction. Iodobenzene, as expected, gave a higher yield than bromobenzene (Table 1, entries 1 and 2) owing to the more facile oxidative addition of aryliodides to Pd^0 in the catalytic cycle.[20] Product yields were significantly higher over the 12-minute reaction period when the substrates contained electron-withdrawing *p*-trifluoromethyl, *p*-benzonitrile, or 2-pyridyl groups (Table 1, entries 4–6). The yields are significantly less when an electron-donating methoxy group is attached to the *para* position of the aryl ring (Table 1, entry 3). Corresponding batch reactions were carried out by using the same palladium-supported catalyst to compare the microtube reactor with traditional synthetic methods that use standard Schlenk glassware. In all cases, significantly higher yields, over the same 12-minute time period, were obtained by using the microtube reactor method (Table 1).

Table 1: Silica-supported palladium-catalyzed carbonylative cross-coupling reactions using the microtube reactor.

Entry	Substrate	Yield [%][a] (micro reactions)	Yield [%][b] (batch reactions)
1		63	10
2		26	0
3		23	0
4		>99	44
5		>99	27
6		>99	43

[a] Average of three runs based on the aryl halide and calculated by GC with diphenyl ether as the internal standard. [b] Average of two runs based on the aryl halide and calculated by GC with diphenyl ether as the internal standard.

An inherent property of microchannels is the high surface-area-to-volume ratios, ranging from 10000 to 50000 $m^2 m^{-3}$, generated as a consequence of their decreased size. However, when a packing material such as silica is used, surface-area-to-volume ratios can be increased dramatically even when compared with microchannels. The surface-area-to-volume ratio generated within our device was estimated to be 1.1×10^9 $m^2 m^{-3}$, which is approximately 20000 times greater than that generated within a microchannel.[*] We

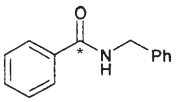
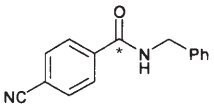
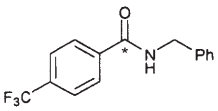
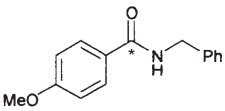
[*] Surface area of silica = 750 $m^2 g^{-1}$, pore volume = 0.68 $cm^3 g^{-1}$. Silica-supported catalyst (0.25 g) was used in the microtube reactor, therefore total pore volume (taken to be the reactor volume) = 0.17 cm^3. Surface-area-to-volume ratio = 187.5 m^2/1.7×10^{-7} $m^3 = 1.1 \times 10^9$ $m^2 m^{-3}$.

believe the improved yields for these flow reactions are due directly to the large surface area provided by the silica-supported catalyst. The silica support provides a microporous structure and an extremely large surface area for the liquid reagents to flow through and spread out. This allows the liquid reagent to coat the surface and therefore enhance the contact with carbon monoxide gas. Furthermore, the silica support should also increase turbulence in the system, enhancing the mixing of the gas and liquid reagents. Once it was demonstrated that the microtube reactor gave good yields of the corresponding amides in short reaction times (under 12 min), it was of interest to investigate its applicability for radiolabeling experiments with ^{11}CO. As indicated before, an important limitation when labeling molecules for PET imaging by using ^{11}CO is the short half-life of ^{11}C ($t_{1/2} = 20.4$ min). A schematic diagram of the experimental setup and experimental details for the radiolabeling experiment is shown in the Supporting Information.

^{11}CO was produced on-line by reduction of cyclotron-generated $^{11}CO_2$ by using a molybdenum catalyst at 850 °C.[21] A stainless-steel loop packed with molecular sieves and cooled by using liquid nitrogen was used to trap and concentrate the ^{11}CO, reaching a maximum radioactivity at approximately 8 min from the end of cyclotron bombardment (EOB). The ^{11}CO was released from the trap by warming to ambient temperatures and forced under a controlled flow of nitrogen into the microtube reactor where the aryl halide and benzylamine reagents had been preloaded and heated to 80 °C. After about 6-min reaction time, under a continuous flow of nitrogen gas, the catalyst loop was lifted out of the oil bath and solvent was pumped through for approximately 5 min, flushing the labeled product into a sample vial. The crude product was filtered and analyzed by using analytical radio HPLC. Four different aryl halides (iodobenzene, 4-bromobenzonitrile, 4-bromobenzotrifluoride, and 4-iodoanisole) were investigated to test the applicability of the microtube reactor system to the ^{11}CO labeling for amide formation. Separate microtube reactors were used for each different substrate and two consecutive runs were carried out for each substrate; the results of these reactions are displayed in Table 2.

The total radioactivity in the system was taken as the sum of the radioactivity measured in the crude product at the end of synthesis, unreacted ^{11}CO that swept through the microtube reactor into a sealed bag, and the radioactivity that was left on the microtube reactor. It was found that typically 10–15% of the total radioactivity remained on the microtube reactor at the end of the synthesis, which may be attributed to traces of labeled products or intermediates sticking to the silica. Good radiochemical yields (>64%) and purities (>93%) of the crude products were obtained for the products shown in Table 2, entries 1 and 2 within about 10 min of ^{11}CO release from the trap, whereas modest radiochemical yields (>33%) and purities (>70%) were obtained for Table 2, entries 3 and 4. Table 2, entry 3 shows lower than expected radiochemical yields even though this substrate is activated by the electron-withdrawing *para*-CF_3 group. The lower radiochemical yields obtained for Table 2, entry 4 may be due to the effect of the deactivating *para*-methoxy group on the aryl halide, which will affect the oxidative addition step of the catalytic cycle. When multiple-labeling reactions, using different substrates, were carried out on the same microtube reactor, mixtures of radiolabeled products were obtained. Even after extensive flushing of the microtube reactor with polar solvent between successive runs, mixtures of labeled products were still obtained. We believe this to be due to traces of either unreacted starting material remaining on the silica or the oxidative addition aryl-Pd species, which remains adhered to the silica and which cannot simply be removed by washing with solvent.

Table 2: ^{11}CO carbonylative cross-coupling reactions using the microtube-reactor system.[a]

Entry	Labeled product		Radiochemical yield [%][b]	Radiochemical purity [%][c]
1		run 1	79	96
		run 2	65	94
2		run 1	67	95
		run 2	70	95
3		run 1	46	70
		run 2	68	90
4		run 1	45	72
		run 2	33	80

[a] * indicates the labeling position. [b] Decay-corrected radiochemical yields, expressed as a percentage of the total radioactivity delivered to the microreactor system, are based on the measured radioactivity trapped in the crude products at the end of synthesis and corrected by their radiochemical purities. [c] Radiochemical purities determined by analytical radio HPLC.

In conclusion, we have provided an effective method for continuous flow carbonylation reactions by using a microtube reactor packed with palladium-supported catalyst, which proved to be reusable for a number of runs. We synthesized a series of amides over a set reaction time and compared this method with batch reaction conditions; the packed microtube reactor method proved superior in all cases and provided excellent yields for three of the substrates in only 12 minutes. We have successfully applied the methodology towards radiolabeling by ^{11}CO carbonylative cross-coupling reactions and gained modest to good radiochemical yields and purities of labeled amides. It is expected that improved synthetic and radiochemical yields may be obtained by increasing the residence time of the substrates within the microtube reactor, and we are currently in the process of optimizing these reactions and applying our setup to other carbonylation reactions.

Experimental Section

General procedure for microtube carbonylation reactions: In a typical reaction, an aliquot (50 μL) of 1M aryl halide solution in

benzylamine was injected into a continuous flow of THF through a Rheodyne 7725 injector port. The substrate mixture was then premixed with a continuous flow of carbon monoxide gas by using a mixing T piece (part no. P-512, Anachem Ltd) before the mixture entered the microtube reactor, and was then heated to 75 °C by using an oil bath. Liquid flow rates were set at 10 $\mu L\,min^{-1}$ and the gas flow rate was metered at 2 sccm by using a Sierra 100 series Smart-Trak mass flow controller. After a residence time period of 12 min from the initial substrate injection, the product was flushed off the microtube reactor by using a higher flow of THF (200 $\mu L\,min^{-1}$). The product was collected, the solvent was evaporated in vacuo, and a standard solution of diphenyl ether was added prior to GC analysis.

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