Gas–Liquid Flow Chemistry

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The Continuous-Flow Synthesis of Carboxylic Acids using CO_2 in a Tube-In-Tube Gas Permeable Membrane Reactor**

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The use of flow chemistry methods,[1] and immobilized reagents and scavengers[2] is leading to recognizable advances in the praxis of molecular assembly. The operation of these processes can bring wide-ranging benefits, not the least of which releases human resources so necessary for the intellectual design and planning of the synthesis pathways. The increasingly competitive climate of chemical research in industrial and academic programs has necessitated a shift from the previous inefficient downstream chemical processing methods towards more sustainable approaches that better reflect the challenges of the discovery process. To address these issues, we have advocated the use of tools and techniques that facilitate more of a "machine-assisted" approach, of which flow chemistry has been particularly useful for conducting efficient, multistep sequences leading directly to a drug molecule[3] or even natural products.[4] When these methods are coupled with the use of immobilized reagents, scavengers, catch and release, and phase switching methods, our group has shown that flow chemistry can lead to demonstrable improvements particularly as they relate to reaction work-ups by avoiding conventional methods of chromatography, crystallization, distillation and aqueous extractions or pH adjustments.[5] Furthermore, flow chemistry methods can accommodate improved safety through incorporation of appropriate monitoring and remote control methods.[6]

The use of reactive gases in organic synthesis provides advantages in terms of cost efficiency and work-up. Reactive gases can often be used in excess and are readily removed from the reaction mixture, affording cleaner synthesis processes. However, there is a general reluctance to use reactive gases in research laboratories largely owing to problems related to the containment of pressurized gases, associated safety factors, and the high capital costs and infrastructure requirements of large scale gas-liquid reactors.

Flow chemical methods may overcome some of the obstacles to their adoption in useful synthetic transformations. The introduction of gases into flow streams can be achieved through plug-flow techniques,[7] microreactors,[8] or mechanical mixing[9] of gas-liquid phases, however, the resulting ambient pressures or low throughput can restrict these approaches. We have previously reported upon the use of gas permeable membrane tubing (Teflon AF-2400) as a particularly effective method of delivering gas to a liquid flow stream in a controlled manner.[10] Teflon AF-2400 is a chemically inert copolymer of tetrafluoroethylene (TFE) and 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole (Figure 1).[11] The resulting polymer is an extensively microporous, amorphous material with high gas permeability.[12]

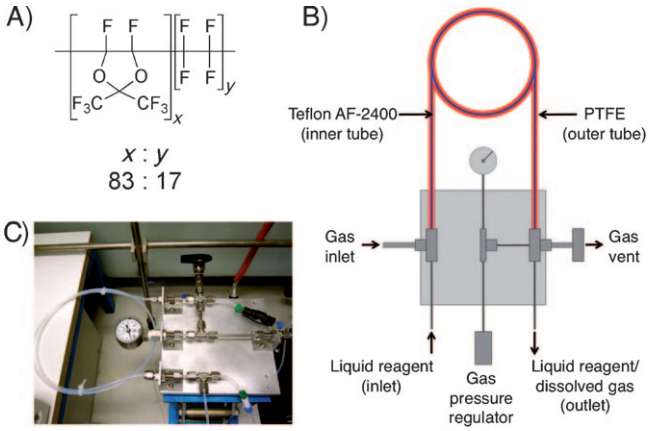

Figure 1. The tube-in-tube flow reactor: A) structure of Teflon AF-2400. B) Schematic of the tube-in-tube reactor configuration (Teflon AF-2400 and PTFE = poly(tetrafluoroethylen)). C) Reactor assembly.

Here we extend our original concept of using gas permeable tubing[13] to deliver gas to a substrate stream in a continuous fashion using a new, cost-effective prototype reactor based upon a tube-in-tube configuration. In this arrangement the Teflon AF-2400 tubing is positioned within a larger diameter PTFE tube containing the reactive gaseous input stream (Figure 1). The reactor operates at pressures of up to 10 bar (although higher pressures are achievable) and accommodates the high flow rates generated from commercially available pumping units. To demonstrate the potential advantages and generality of this technology for gas–liquid flow synthesis, we investigated the carboxylation of Grignard reagents[14] to produce a collection of carboxylic acids. This important carbon–carbon bond-forming transformation is particularly useful in consideration of the ubiquity of

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carboxylic acids (and their derivatives) in medicinally relevant compounds and in fine chemicals.[15] Moreover, there is an increasing need to develop synthetic processes which utilize CO_2 as a renewable feedstock.[16]

The gas–liquid flow reactor is shown in Figure 1. A key feature of the design is the tube-in-tube configuration, in which the Teflon AF-2400 tubing is placed within the 1/8″ (outer diameter) PTFE tube. This configuration allows the flow of a substrate stream within the membrane tubing whilst the gas fills the PTFE outer tubing and diffusion transfers the reactive gas into the substrate stream. The Teflon AF-2400 (1.0 m, 0.28 mL) and the outer PTFE tubing are separated by stainless steel T-pieces, thus allowing the substrate and gas streams to be independently introduced to the reactor with precise control of the flow rate and pressure for each input. For the purposes of safety, the gas pressure regulator for this prototype was set to depressurize the reactor if the 10 bar limit was exceeded. It should also be noted that the total volume available for the gas to occupy in the PTFE tubing is 1.5 mL and this represents an added safety feature in that only a small volume of pressurized gas occupies the reactor at any given time.

Initially, we examined the synthesis of 3,5-dimethoxybenzoic acid (**1b**) from **1a** to allow rapid optimization of conditions in terms of the flow rate and pressure of CO_2. A schematic of the flow configuration for this series of reactions is shown in Figure 2. A Vapourtec R2+ unit[17] was used to

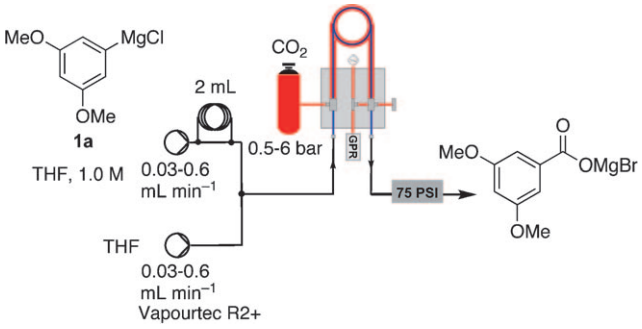


Figure 2. Flow reactor configuration for the carboxylation of Grignard reagent **1a**.

pump the Grignard reagent to the gas-liquid reactor through a 2 mL PEEK sample loop, however, any other commercial pumping device can be used. A second stream of THF (under argon) was used to dilute the Grignard reagent stream and preclude blocking of the reactor by precipitation of magnesium salts formed during the carboxylation step. The two flow streams were united at a T-piece and the combined streams directed into the reactor, which was pressurized with CO_2. A liquid back-pressure regulator was installed after the exiting T-piece to pressurize the solvent and prevent out-gassing of the dissolved CO_2 in the flow stream.

Conversion of **1a** into the carboxylic acid **1b** at 1 bar of CO_2 was quantitative at low flow rates (see the Supporting Information). However, a near linear decrease in conversion was observed with an increasing flow rate. This decrease can be attributed to the reduced effective concentration of CO_2 in the reaction stream. Consequently, increasing the pressure of CO_2 for higher flow rates improved conversion with a plateau being observed at pressures above 3 bar. Beyond a pressure of 3 bar the Grignard reagent becomes limiting and almost quantitative conversions are observed up to 6 bar of CO_2, even at a relatively high reagent-stream flow rate (800 μL min^{-1}). Since the reactions proceeded rapidly at room temperature, it was not necessary to perform a temperature screen.

From these optimization experiments, we concluded that a flow rate of 400 μL min^{-1} with a CO_2 pressure of 4 bar provided a general set of conditions to achieve high conversions with a short residence time (42 s). The scope of these conditions was examined using the flow configuration shown in Figure 3. Although the Vapourtec R2+ remained identi-

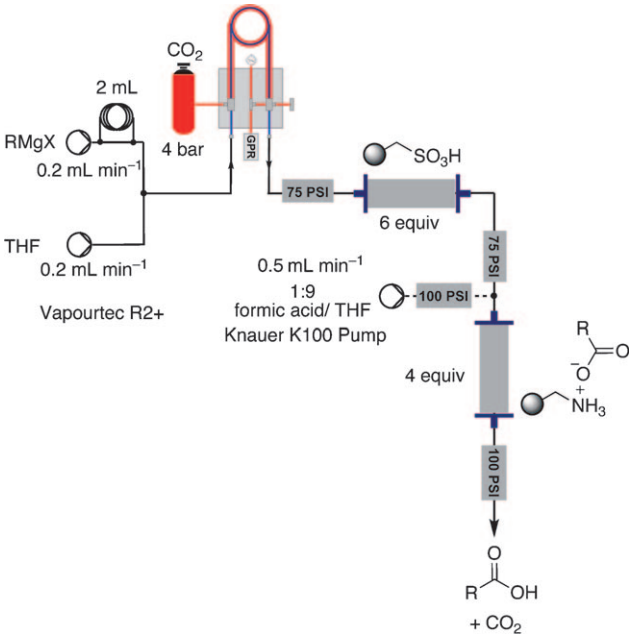


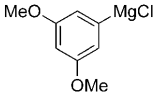
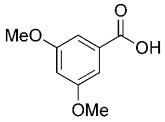
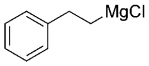
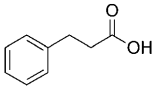
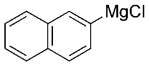
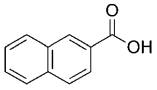
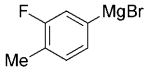
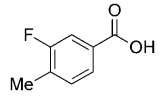
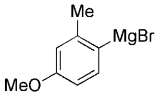
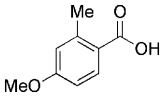
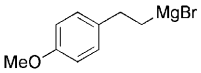
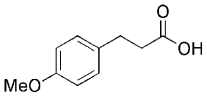
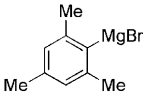
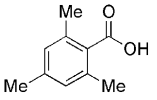
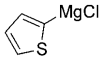
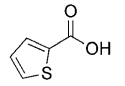
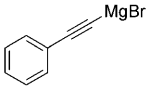
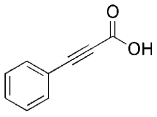
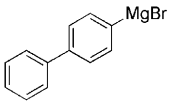
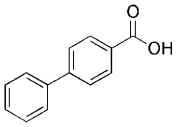
Figure 3. Flow reactor configuration for the carboxylation of Grignard reagents **1a**–**10a**.

cally configured to the optimization experiments, polymer-supported reagents were introduced to permit in-line work-up and purification. The exiting stream from the reactor was first directed through a glass cartridge[18] packed with polymer-supported sulfonic acid (QP-SA) to effect removal of the magnesium salts and concomitant protonation of the carboxylate to form the corresponding acid. Product clean-up was achieved by then directing the stream through a second cartridge containing polymer-supported ammonium hydroxide (A-900) to trap the acid in a "catch-and-release" protocol. Following a washing step with THF to remove any unwanted impurities, a third stream was introduced through an external pump to release the carboxylic acid from the A-900 resin. A solution of formic acid/THF (1:9) was sufficient to promote the complete "release" of the acid from resin. The inclusion of back-pressure regulators before the second T-piece (located in between the cartridges) was necessary to ensure unidirec-

tional flow through the A-900 resin cartridge when the acid stream was introduced and also to allow the complete pressurization of the system to prevent out-gassing of the dissolved CO_2. Similarly, the placement of a back-pressure regulator after the final cartridge was necessary to prevent CO_2 out-gassing within the cartridges.

To examine the scope and limitations of these conditions, the carboxylation of a series of Grignard reagents was investigated. Table 1 shows the yields of carboxylic acids

Table 1: Carboxylic acids[a] prepared under continuous-flow conditions with CO_2.

	Substrate		Product	
1		**1a**		**1b**: 93%
2		**2a**		**2b**: 87%
3		**3a**		**3b**: 86%
4		**4a**		**4b**: 100%
5		**5a**		**5b**: 98%
6		**6a**		**6b**: 86%
7		**7a**		**7b**: 100%, 98%[b]
8		**8a**		**8b**: 95%
9		**9a**		**9b**: 75%
10		**10a**		**10b**: 100%

[a] 1 mmol scale, yields of isolated, analytically pure products are reported. [b] Yield of isolated product at 20 mmol scale.

that were obtained from the flow arrangement shown in Figure 3. Aryl, alkyl and alkynyl Grignard reagents were well tolerated along with electron-donating and electron-withdrawing substituents, and the conversion into the carboxylic acids proceeded smoothly with good to excellent yields.

Furthermore the mesityl derivative (**7a**) gave an excellent yield despite the hindered reactive center. By using ^{1}H NMR analysis, product purity exceeded 97% in all cases. This highlights the advantage of using a reactive input gas stream and the efficiency of the "catch-and-release" strategy, using polymer-supported reagents.

To examine the scalability of the prototype reactor and the process in general, we scaled the synthesis of acid **7b** to 20 mmol. The larger volumes of Grignard reagent **7a** required the Vapourtec R2+ unit to be fitted with a 20 mL sample loop, along with large Supelco VersaFlash plastic cartridges to accommodate the increased masses of QP-SA and A-900 polymer-supported reagents. The total flow rate was adjusted to 1.0 mL min^{-1} to achieve total residence times similar to the smaller scale reactions and the CO_2 pressure increased to 7 bar. Compound **7b** was readily scaled to 3 g and the yield of the pure isolated product closely matched the yield of the smaller-scale reaction, highlighting the straightforward scalability of the flow process.

The prototype reactor reported here expands the synthesis chemist's ability to perform gas-liquid reactions in a safe, scalable, and controlled fashion. The hazards, risks, and precautionary measures associated with the use of traditional high-pressure batch equipment are circumvented, as the volume of gas occupying the reactor at any given instance does not exceed 1–2 mL. The gas–liquid flow reactor proved to be effective at delivering CO_2 into a flow stream enabling the generation of a series of carboxylic acids, which were isolated in high yields and purity through the incorporation of polymer-supported reagents in a "catch-and-release" regime. Moreover, we have briefly demonstrated the straightforward scale-up of gas-liquid reactions without significant modification to reactor configuration, where carboxylic acid **7b** was prepared on a multigram scale. We envisage that these methods can be readily extended to other synthetically important but potentially hazardous gases such as CO, H_2, ammonia, ethylene, SO_2, and NO. The simple tube-in-tube configuration, along with the use of cost-effective and commercially available hardware, allows all synthesis laboratories to access this technology without the need for the specialized fabrication techniques usually required for alternative technologies.

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[17] The Vapourtec R2 + /R4 flow apparatus is commercially available from Vapourtec Ltd. http://www.vapourtec.co.uk/.

[18] Omnifit glass columns are commercially available from Kinesis. http://www.kinesis.co.uk/.

