

Review

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Development of methodologies for reactions involving gases as reagents: microwave heating and conventionally-heated continuous-flow processing as examples

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Abstract: Microwave (MW) heating and conventionally-heated continuous-flow processing have emerged as viable alternatives to the traditional methods of preparing organic compounds. These tools enable the chemist to circumvent some of the issues associated with conventional processing, while improving the efficiency of chemical transformations. Recently, several strategies have been developed to perform reactions using gaseous reagents, employing MW heating or conventionally-heated micro- and meso-flow technologies. This perspective describes some of these strategies by means of a discussion of work performed in our laboratory, focused around alkoxycarbonylation and hydrogenation reactions.

Keywords: carbonylation; flow chemistry; gases; hydrogenation; microwave heating.

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1 Introduction

With the recent trend of making chemistry “greener”, chemists are seeking more sustainable ways of making their target compounds. Advancements in laboratory technology have opened up avenues to do this; improving the efficiency of, and reducing waste produced by synthetic routes. The objective of this perspective is to discuss how two such technologies, microwave (MW) heating and

conventionally-heated continuous-flow processing, have been used to facilitate more environmentally friendly and efficient metal-catalyzed reactions involving gaseous reagents. Attention is focused primarily on the palladium-catalyzed carbonylative coupling of aryl halides, which has been studied extensively by our laboratory. The homogeneous hydrogenation of alkenes using Wilkinson’s catalyst, $\text{RhCl}(\text{PPh}_3)_3$, is also discussed.

1.1 Use of MW heating in preparative chemistry

MW irradiation is a viable alternative to conventional heating (e.g., using hotplates or jacketed reactors). MW heating is based upon the ability of substances to absorb MW energy and convert the electromagnetic energy effectively to heat. Since most reaction mixtures contain at least one MW absorbing component, be that a reagent, a catalyst or the solvent, the use of MW irradiation to heat reactions has been employed widely by organic chemists, both in academia and in industry [1–3]. Certainly, the most useful attribute of the scientific MW is its ability to aid the user when developing new chemistry. Due to the ease of which reactions can be performed under sealed vessel (autoclave) conditions, MW heating opens access to a process window, that is otherwise difficult to access (though not impossible). For instance, a stubborn reaction may traditionally be carried out in refluxing xylenes (b.p. 137–140°C), 1,2-dichlorobenzene (b.p. 178–180°C), or possibly *N*-methyl pyrrolidinone (NMP, b.p. 202°C). The very reason to choose these solvents (namely a high b.p.) is the same attribute that can make them difficult to remove upon workup, especially as scale increases. However, under sealed vessel conditions, nearly any solvent the bench chemist selects becomes a viable option. Ethanol or acetonitrile can replace NMP, ethyl acetate or methyl ethyl ketone can serve as an alternative to xylenes, and

even dichloromethane (b.p. 40°C at 1 atm) can be heated to 160°C, within the typical pressure limitations of most commercially-available scientific MW units. The use of MW heating is not limited to organic synthesis [1]. It has found application in materials [4] and polymer chemistry [5], the preparation of organometallic compounds [6, 7], as well as in peptide synthesis and the biosciences [8–10].

1.2 Use of conventionally-heated continuous-flow processing in preparative chemistry

Industrial chemists have used continuous-flow processing on production scales for many years. However, over the last decade, there has been an increasing interest in miniaturizing this process for the laboratory setting. Recently, this has become practical via a wide range of companies producing equipment for both micro- and meso-fluidic flow chemistry [11, 12]. Inherent in these devices are aspects of enhanced safety, ease of scale-up, and efficient mixing of reagents [13–16]. As such, they have proven valuable for performing chemistry that would traditionally be difficult to conduct in batch. For example, processes that are highly exothermic, require the use of highly reactive reagents, require very high temperatures or pressures, or generate unstable intermediates [17]. Additionally, reactions developed using a bench-sized flow unit, could feasibly be transferred to large-scale production either by using a larger flow reactor or by running multiple, smaller flow reactors in parallel.

A wide temperature window is available using micro- and meso-flow reactors [18]. Reactions requiring cryogenic temperatures, such as those involving organolithium reagents, can be conducted in flow and sometimes with considerably more ease from a synthetic standpoint [19–21]. At the other extreme, flow chemistry can be performed at temperatures in excess of 300°C, allowing synthetic chemists to scale-up reactions typically carried out using flash vacuum pyrolysis protocols [22]. The use of supported reagents and/or catalysts has also been very successful [23–25]. They have the potential to deliver compounds of high purity, without the need for product work-up or chromatography. However, the scalability of the chemistry when using supported reagents can be challenging.

There are some limits to the use of a continuous-flow approach to synthetic chemistry. If the reaction is very slow, it will not benefit from flow processing, because the overall throughput would be too low. Additionally, heterogeneous reactions are not trivial to conduct in current commercially available reactors. Particulates can clog the

narrow-gauge tubing and the back-pressure regulator, or interfere with the operation of the pumps. Some solutions to the problems facing heterogeneous reactions in flow are becoming available, including the interception of reactant streams with a co-solvent [26] or the application of ultrasound [27, 28].

There is a clear parallel between MW irradiation and continuous-flow processing. Both technologies offer the ability to heat reaction mixtures rapidly, safely and (in most cases) easily. Moreover, synthetic methodologies developed on small scale in batch using MW heating can be scaled-up using conventionally-heated flow reactors [29]. The combination of MW heating and flow processing has also found applications [30–35].

2 Alkoxycarbonylation reactions

2.1 Use of batch MW heating for alkoxycarbonylation reactions

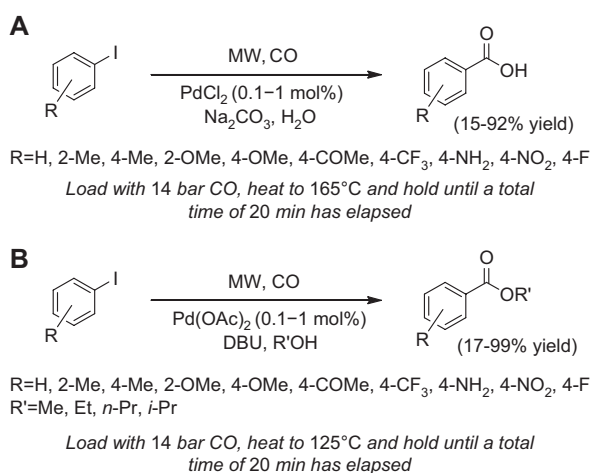
Although popular in large-scale commodity chemicals production, reactions involving gases are less commonly used in more small scale organic syntheses. This is likely because of the requisite high-pressure equipment involved, although a number of protocols have been developed using atmospheric to slightly greater pressures (<5 bar) of gas [36]. Scientific MW units, which are becoming common laboratory equipment, are designed to perform reactions at a variety of pressures (generally up to 30 bar). Therefore, they are ideal gas-loading systems, capable of introducing a gaseous reagent to the MW vessel at a variety of pressures [37]. Hydrogen gas has been the most widely used gaseous reagent in MW-assisted reactions, examples including hydrogenation of olefins [38, 39], hydrodechlorination [40, 41], debenzylation [42, 43], reductive aminations [44], azide reductions [43], and dearomatization of pyridine derivatives to form saturated piperidines [43]. Molecular oxygen [45, 46], 1-propyne [47], and ethene [48, 49] have also seen use as reagents in reactions using MW heating. Palladium-catalyzed carbonylation chemistry using CO has also been employed extensively in MW vessels [43, 44, 50–53]. Using aryl halides as starting materials, carboxylic acids and esters can be prepared.

Prior to the development of gas-loading accessories, a number of approaches had been developed to circumvent the problem of working with gaseous CO [54]. The most widely used method was to use Mo(CO)_6 as a CO source [55–60]. Advantages of using Mo(CO)_6 as a replacement for gaseous CO include the fact that it is a solid and is easily

used on a small scale in commercially available MW apparatus, with no modification required. However, $\text{Mo}(\text{CO})_6$ is toxic, and its use results in metal waste; this being a particular problem if the reaction is to be scaled up. Our work using CO gas started by employing a gas-loading accessory on a MW unit, in which multiple vessels are processed in a carousel (Figure 1A). Each tube in the eight-vessel carousel was individually loaded with gas directly from a cylinder, via a bayonet fitting (Figure 1B). Preloading reaction vessels to 14 bar with CO, we performed a range of hydroxycarbonylation [61] and alkoxycarbonylation [62] reactions, converting aryl iodides to the corresponding carboxylic acids or esters (Scheme 1). $\text{Pd}(\text{OAc})_2$ and PdCl_2 are active catalysts for the reaction and require no additional ligands. Both primary (e.g., ethanol) and secondary alcohols (e.g., 2-propanol) are tolerated under these conditions. Both primary (e.g., ethanol) and secondary alcohols (e.g., 2-propanol) are tolerated under these conditions and gave comparable yields, but yields were slightly diminished when using *ortho*-substituted aryl iodide substrates with secondary alcohols. Moving to a tertiary alcohol (e.g., *t*-butanol), the reaction was unsuccessful, presumably due to steric bulk.

The apparatus had two drawbacks: 1) the maximum scale at which the carbonylation reactions could be performed was 4 mmol per vessel. Beyond this scale, the reaction becomes gas starved, since there is not a constant feed of CO and the parameters of the apparatus allow only a 14 bar initial gas load and 2) the bayonet fitting prevented the complete loading of gas. The pressure measurement device for the carousel read the pressure of the vessel with the highest pressure. Because of these drawbacks, our attention thus turned to alternative MW apparatus in which we could use a single, sealed vessel.

Our key objectives when pursuing the alkoxycarbonylation reaction further, were to scale-up the reaction significantly and minimize the excess of CO required [63]. There are a number of disadvantages to using a significant



Scheme 1 (A) Pd-catalyzed hydroxycarbonylation and (B) alkoxycarbonylation.

excess of CO. From a practical standpoint, the highly toxic nature of CO gas requires the use of extreme care when venting a vessel at the end of the reaction. In addition, efficient Pd catalysis in the presence of a large excess of CO can prove difficult [64]. An atmosphere of CO leads to the formation of so-called “palladium-black”, a catalytically inactive Pd species.

Our results are summarized in Scheme 2. By employing a gas-loading accessory that we could interface with an 80 ml reaction vessel (Figure 2), we were able to reduce the loading of CO to a 1.3 M equivalence. We did find that the key to the success of the reaction was an additional load of nitrogen gas, likely due to enhanced solubility of CO at higher system pressures. Thus, on the 2 mmol scale, reactions were performed after loading the vessel with 1 bar of CO and then filling to a total pressure of 10 bar with nitrogen. Under these conditions, we were able to prepare a range of ethyl esters from aryl iodide starting materials.

When scaling up the reaction, we turned to a MW unit comprised of a 350 ml capacity Teflon reaction vessel with the capability of loading the reaction vessel with gas. Deciding to perform the reaction on the 100 mmol scale, we loaded the vessel with 1.1 equivalents of CO gas. Running the ethoxycarbonylation reaction on this scale, using iodobenzene, resulted in >95% conversion and 86% isolated yield after column chromatography. We could not increase the scale of the reaction any further, because doing so would exceed the pressure limits of the apparatus. Moving to a larger MW unit, we were able access the requisite higher pressures needed for larger-scale reactions [65]. This unit has a reaction chamber volume of 3.5 l and was capable of operating at temperatures up to 200°C and pressures of up to 200 bar. The ethoxycarbonylation of iodobenzene could be performed on the 1 mol

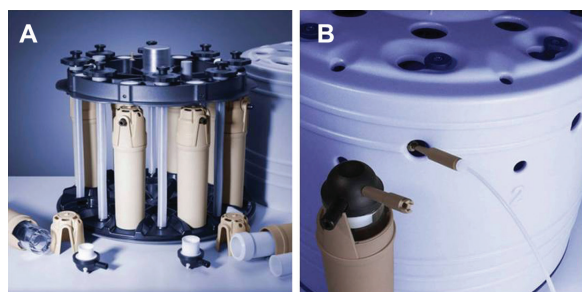
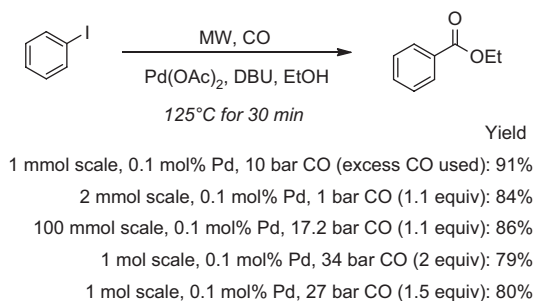


Figure 1 (A) Eight-vessel carousel and (B) gas-loading configuration for performing initial hydroxy- and alkoxycarbonylation reactions. (Reproduced with kind permission from Anton Paar USA, Ashland, VA, USA.)



Scheme 2 Scale-up of the Pd-catalyzed ethoxycarbonylation of iodobenzene.

scale using this device. The desired ester was obtained in a comparable yield (80% isolated yield) [64, 66]. We calculated that 1.1 equivalents of CO equated to a required loading of 27 bar. We first loaded the vessel with 11 bar of nitrogen before loading the CO, followed by a further 12 bar of nitrogen, giving a total initial pressure of 50 bar. This sequence was important, since the internal pressure forms the seal between the vessel and the lid of the unit. For safety reasons, it was critical to have a tight seal before loading the CO into the reactor and so we pre-pressurized to greater than the sealing limit with nitrogen first.

2.2 Use of continuous-flow processing for alkoxycarbonylation reactions

Unfortunately, to proceed to even larger scales, a single sealed vessel approach was not feasible using the MW apparatus at our disposal and also posed increasing safety risks. We therefore decided to turn to continuous-flow processing, where a smaller amount of gas would be in the reactor at any point in time. The use of reactive gases as reagents in flow processing has been widely studied.

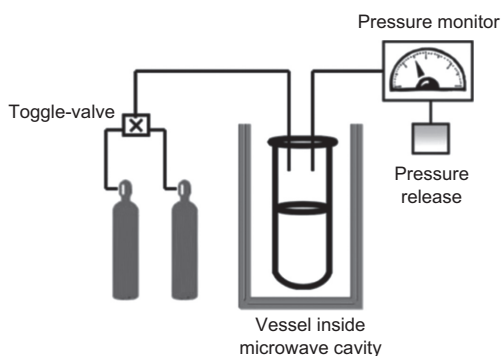


Figure 2 Gas-loading accessory interfaced with a single 80 ml reaction vessel.

Hydrogenation reactions can be performed using the now ubiquitous H-cube system [67]. Gases such as oxygen [68–71], ozone [68, 72], and fluorine [73, 74] have also been used in flow. The use of CO in flow is not unprecedented, aminocarbonylation reactions receiving particular attention [75–77]. Much of the literature precedent involves the application of gases in flow using micro-scale equipment. Our interest lay in performing chemistry on the meso-scale, allowing us to process larger quantities of material per unit time. Our first objective was to modify our commercially available flow reactor, so that we could reliably and reproducibly input gas (Figure 3). Gas was introduced through a back-pressure regulator and at an angle of 90° to the liquid flow. The gas/liquid flow was then heated *via* a polytetrafluoroethylene (PTFE) coil mounted on an aluminum mandrel. We observed the bubbles of CO, indicating that gas was successfully being introduced to the system.

When performing the alkoxycarbonylation [78] reaction, we could not simply take our optimized batch conditions straight to flow mode and hence a complete re-optimization was required. Obtaining consistent bubble flow was challenging in itself and resulted in the requirement of an excess of CO. The size and regularity of the gas bubbles also fluctuated with changes in temperature and solution viscosity. In addition, the carbonylation reaction was relatively slow at catalyst loadings <0.5 mol%. However, above this threshold a significant quantity of palladium black was observed and blockage of the back-pressure regulator ultimately occurred. Despite these initial hurdles, we were able to convert a range of aryl iodides to either ethyl or propyl esters and product conversions were on par with those obtained using the analogous batch approach in microwave (Scheme 3).

A way to alleviate some of the operational issues with performing reactions involving gaseous reagents was reported by Ley and co-workers in 2010. Their approach

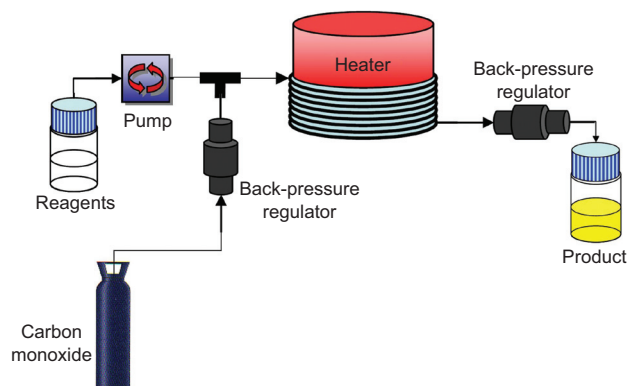
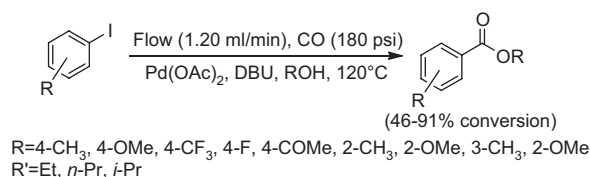


Figure 3 Modified flow reactor for introduction of CO gas.



Scheme 3 Pd-catalyzed alkoxy carbonylation of aryl halides in plug flow.

employs a “tube-in-tube” design, which comprises of an outer PTFE tube and a gas-permeable Teflon inner tube. The reagent stream flows within the inner membrane tubing, while the gas fills the PTFE outer tubing. Diffusion through the inner tube membrane allows for the transfer of gas into the reagent stream. This approach has been successful for numerous reactions, including the ozonolysis of alkenes [79], carboxylation of Grignard reagents with CO₂ [80], Heck reactions using ethene [81], pyrrole and thiourea formation using ammonia [82, 83], and both homogeneous and heterogeneous hydrogenation reactions [84, 85]. This tube-in-tube design, while excellent for ambient reactions, is not amenable to operation at elevated temperatures. This is because, firstly, the liquid runs through the inner tube and so is difficult to heat externally. Secondly, the gas-permeable Teflon tube is not particularly robust. The reaction is thereby limited by the quantity of gas that can be loaded into the solution in the tube-in-tube unit prior to entering the heated zone (Figure 4A). This necessitates running reactions at more dilute concentrations, to match the concentration of the

reagent and gas, or performing multiple passes through the entire system to ensure complete consumption of starting materials.

We have had access to an alternative design for a tube-in-tube reactor in which gas influx and heating can occur simultaneously (Figures 4B and 5). We have used this “on-demand” gas delivery device to perform Pd-catalyzed alkoxy carbonylation reactions. The reactor comprises a coil of stainless steel tubing, through which liquid flows on the outside of a gas-permeable inner membrane. The reactor has a working liquid volume of approximately 15 ml when the inner gas tube is inflated.

On a 5 mmol scale and working at a reagent concentration of 1 M, aryl iodides could be converted to the corresponding ethyl esters (Scheme 4) [86]. To obtain >90% conversion, we found it necessary to use two of the reactors in series to lengthen the residence time in the system. This proved more effective as compared to using just one coil, but a lower flow rate. As we were passing relatively small portions of reagents through the coils, we believed that there may be some considerable dispersion in the length of the two reactors. Therefore, although we were passing reagents into the flow reactor at a concentration of 1 M, it may be that steady state is not achieved and that the concentration of the reaction mixture decreases as it passes through the length of the two coils. This was confirmed to be the case when we increased the scale of the reaction to 25 mmol. Midway through the run, we saw no gas bubbles emerging beyond the back-pressure regulator, suggesting that the reaction had become gas limited.

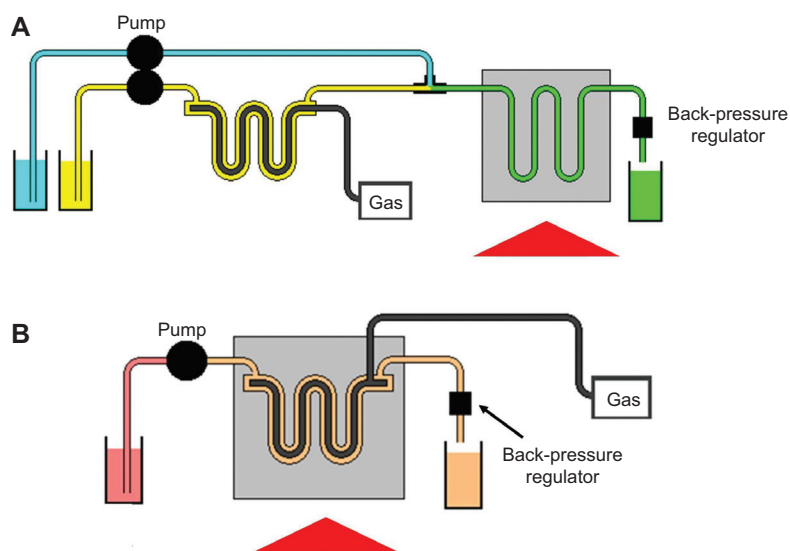


Figure 4 (A) “Tube-in-tube” and (B) “on-demand” approaches to performing reactions involving gaseous reagents. (Modified from an original figure with kind permission from Vapourtec Ltd, Bury St. Edmunds, Suffolk, UK.)

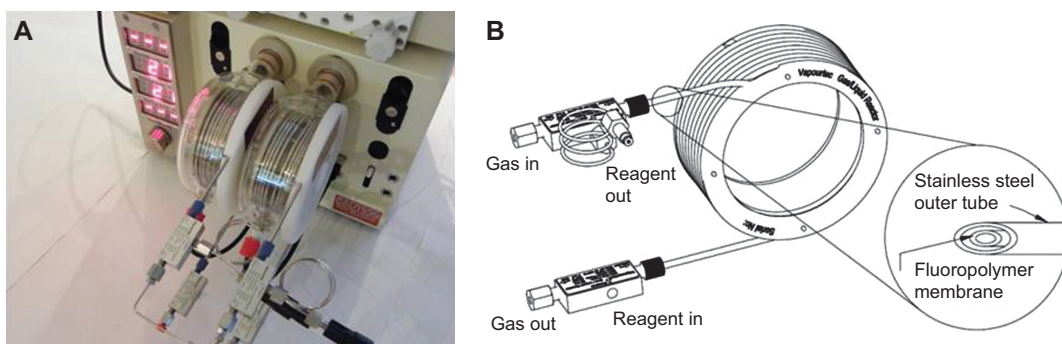


Figure 5 (A) “On-demand” gas reactors interfaced with the flow apparatus and (B) schematic of tube-in-tube gas reactor coil. (Reproduced with kind permission from Vapourtec Ltd, Bury St. Edmunds, Suffolk, UK.)

This postulate was confirmed by analysis of representative fractions from the product stream. Reducing the substrate concentration to 0.5 M led to near-quantitative conversion throughout the run.

The methodology using the heated tube-in-tube reactor was operationally far superior to our original plug-flow approach. Such benefits include: 1) no need to painstakingly optimize bubble size, 2) smaller excess of CO gas used and 3) no formation of Pd black was formed during the course of the reaction.

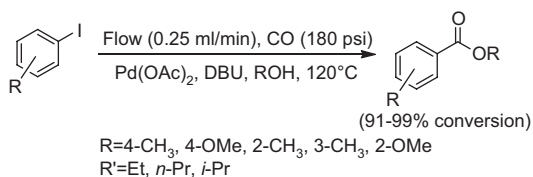
Koos and co-workers have subsequently reported the methoxycarbonylation of a range of aryl halides using their tube-in-tube design [87]. They were able to employ aryl, heteroaromatic and vinyl iodides and an aryl bromide as substrates. They also used *in situ* infrared spectroscopy to measure solution concentrations of carbon monoxide.

3 Homogeneous hydrogenation reactions

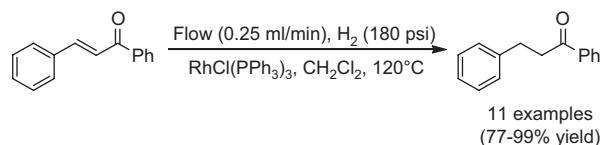
Following the success in alkoxycarbonylation chemistry, we have subsequently used the “on-demand” reactor to perform catalytic homogeneous hydrogenation reactions. The same configuration used for our alkoxycarbonylation

methodology, namely two gas coils in series, both heated to the desired reaction temperature and both individually fed with gas, was employed. In order to achieve satisfactory conversion to the reduced product in a timely fashion, elevated temperatures (>100°C) had to be employed. However, due to the stress of operating at high temperatures for prolonged periods of time, we became concerned about the integrity of the inner gas membrane. We therefore transitioned from the prototype reactor to a newer, more durable production version of the reactor. As a consequence of this switch, we found that the gas permeability of the second-generation coil was somewhat lower than the first-generation coil and some re-optimization was necessary. With optimized conditions and coil configuration in hand, we moved on to screening a variety of alkene substrates (Scheme 5).

A range of alkenes could be hydrogenated using Wilkinson’s catalyst, $\text{RhCl}(\text{PPh}_3)_3$ [88]. Again, while small-scale reactions could be performed at high substrate concentrations, the methodology required minor optimization upon scale-up. The reaction concentration needed to be reduced in order to achieve complete conversion. Under these conditions, a throughput of 45 mmol/h was accomplished. Comparison of our approach, with that of other approaches, using continuous-flow processing, shows that our system is able to process reaction mixtures at significantly higher substrate concentrations and hence higher overall throughput. This is important



Scheme 4 Pd-catalyzed alkoxycarbonylation of aryl halides using “on-demand” gas delivery device.



Scheme 5 Catalytic homogeneous hydrogenation using Wilkinson’s catalyst.

when considering the current drive towards process intensification.

4 Conclusion

As chemistry moves towards “greener” and more sustainable practices, we will see an increased use of new, enabling technologies in the laboratory setting. Both MW heating and continuous-flow processing have proven to be valuable tools for reactions using gases as reagents. When using a batch MW heating approach and looking at scale up, using multiple vessels processed in a carousel, reactions can often be scaled without the need for any re-optimization of conditions, but the loading, sealing, opening and emptying of the vessels can be time consuming. This can be overcome using a single, larger, sealed vessel and we have demonstrated this to the mole scale. Beyond this scale, it may be that continuous processing could be more useful. In doing so on small scale and employing conventional

heating, recent developments in reactor design allowing for “on-demand” delivery of the gas to a reaction mixture while flowing through a heated zone, have opened up the field considerably. It is likely that we will continue to see further applications of these strategies in the near future.

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