

Continuous Flow Hydrogenation Using an On-Demand Gas Delivery Reactor

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Supporting Information

ABSTRACT: A continuous-flow approach to the hydrogenation of alkenes utilizing Wilkinson's catalyst is reported. The approach relies on a newly developed coil design in which it is possible to load gas and heat the reaction mixture simultaneously. The hydrogenation of various substrates has been performed successfully on small scale and can be scaled up substantially.

INTRODUCTION

Micro- and mesofluidic flow devices have proven to be powerful enabling technologies in organic synthesis. Inherent in these devices are aspects of enhanced safety, ease of scale-up, and efficient mixing of reagents.^{1,2} One area of flow chemistry that is currently of considerable interest is interfacing reactive gases with a stream of liquid reagents. One approach is to use mechanical mixing of the two phases, which is employed by instruments such as the H-cube (for hydrogenation),³ O-cube (for ozonolysis),⁴ and X-cube (for carbonylation).⁵ Alternatively, a semipermeable membrane can be used to introduce gas into the reagent stream, a technique pioneered by Ley and co-workers.^{6–9} In their “tube-in-tube” design, a liquid reagent stream flows within a gas-permeable Teflon AF-2400 membrane and is housed in a PTFE outer tubing filled with a gaseous reagent. This allows for diffusion-mediated gas transfer into the liquid stream. It has been used for hydrogenation,⁶ carbonylation,⁷ and ozonolysis⁸ as well as reactions involving other gases.⁹

One of the drawbacks of these current designs is the inability to load gas and heat the reaction mixture simultaneously. Current approaches rely on saturation of either the reagent or solvent flow prior to heating. This often necessitates running reactions at low concentrations or performing multiple passes through the entire system, thus limiting throughput. Recently, we have had access to a prototype “tube-in-tube” reactor in which it is possible to load gas and heat simultaneously. In a proof-of-concept study we have used this for palladium-catalyzed alkoxycarbonylation reactions.¹⁰ Here we report an extension of the application of this reactor to catalytic homogeneous hydrogenation. The reactor design incorporates a modified “tube-in-tube” model where the inner tube contains the gaseous reagent, while the liquid reaction flows around it contained in an outer stainless steel reactor coil. The inner diffusion membrane is constructed from PTFE-type fluoropolymer, offering excellent chemical compatibility, combined with good high-temperature performance. The stainless steel outer tube, as well as being robust, eliminates loss of dissolved gas. As the liquid is in contact with this thin-walled stainless steel outer tube, excellent heat transfer and therefore temperature control are possible. The gas reactor is shown schematically in Figure 1

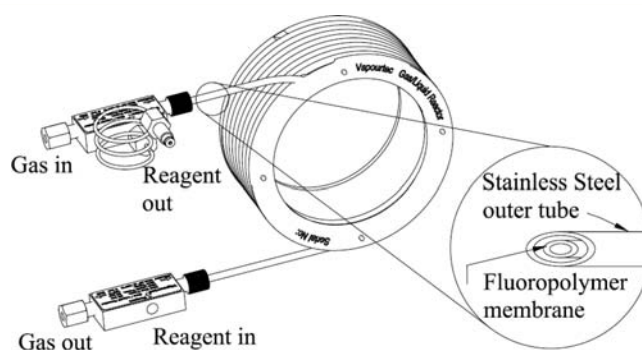


Figure 1. Schematic of the gas reactor unit used.

and, when two are interfaced with the flow unit, pictorially in Figure 2.

RESULTS AND DISCUSSION

Our initial objective was to optimize the reaction conditions for catalytic homogeneous hydrogenation using the on-demand gas reactor. To achieve this, we chose to use anethole (*p*-methoxyphenylpropene, **1**) as a test substrate and $\text{RhCl}(\text{PPh}_3)_3$ (Wilkinson's catalyst¹¹) as the catalyst for hydrogenation. Compound **1** was chosen judiciously as it would be much more difficult to hydrogenate than terminal or electron-deficient alkenes and therefore, would provide optimal conditions for most substrates. Our optimization data are presented in Table 1. We decided to employ the same configuration as used for our alkoxycarbonylation methodology, namely two gas coils in series, both heated to the desired reaction temperature and both individually fed with gas.¹² A schematic representation of the setup is shown in Figure 3. Working on a 5 mmol scale, using 1 mL dichloromethane and employing a catalyst loading of 0.5 mol %, we passed the reaction mixture at a flow rate of 0.5 mL/min through the two gas coils heated to 70 °C and obtained a 28% conversion to **1a** (Table 1, entry 1). Doubling the catalyst loading to 1 mol % almost doubled the conversion

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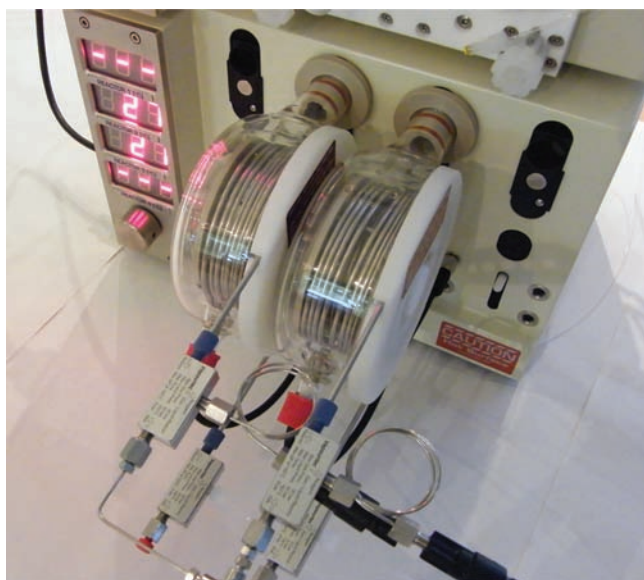


Figure 2. Gas reactor interfaced with the flow apparatus.

Table 1. Optimization of reaction conditions for the continuous-flow hydrogenation of anethole^a

entry	flow rate (mL/min)	temp. (°C)	catalyst loading (mol %)	conversion (%)
1 ^b	0.5	70	0.5	28
2 ^b	0.5	70	1.0	50
3 ^b	0.5	100	1.0	70
4 ^b	0.5	125	1.0	92
5 ^c	0.5	125	1.0	72
6 ^c	0.5	125	1.2	89
7 ^c	0.25	125	1.2	97

^aReaction conducted on a 5 mmol scale using 1 mL dichloromethane as solvent in each case. ^bUsing a first-generation coil design. ^cUsing the second-generation coil design.

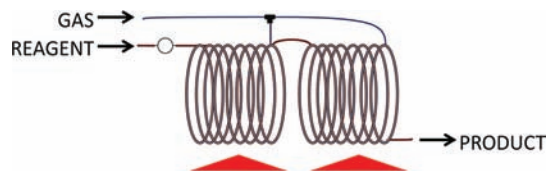


Figure 3. Schematic of the flow configuration used for the hydrogenation of alkenes.

(Table 1, entry 2). By increasing the temperature to 100 °C, the conversion increased to 70% (Table 1, entry 3). Performing the reaction using 5 mmol of anethole in just 1 mL dichloromethane, while simultaneously increasing the temperature slightly to 125 °C, led to a 92% conversion (Table 1, entry 4).

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 significantly lower than the first-generation coil. This was reflected by a decrease in conversion when compared to an identical run in the first-generation coils (Table 1, entry 5). To overcome this drop in conversion we increased the catalyst loading to 1.2 mol % (Table 1, entry 6) and then reduced the flow rate to 0.25 mL/min, leading to a 97% conversion (Table 1, entry 7). When operating at this lower flow rate, we observed the formation of small quantities of an insoluble precipitate which we envisaged could lead to blockage of the back-pressure regulator located at the end of the heated zone. We believe that the precipitate is formed as a result of the formation of $\text{HRhCl}_2(\text{PPh}_3)_2$ (due to the reaction being performed in a chlorinated solvent) or due to dimerization of the catalyst over the now extended reaction time.¹³ While insoluble in dichloromethane, the precipitate readily dissolves in acetone. To avoid blockage of the back-pressure regulator we used an approach previously reported by us.¹⁴ We intercept the product stream with a flow of a suitable organic solvent upon exiting the heated zone, thus solubilizing the product and allowing it to pass through the back-pressure regulator unimpeded. In this case, when we intercepted the product stream with a flow of acetone just before it enters the back-pressure regulator, we were able to perform the hydrogenation reaction without any blockage issues.

With the optimized conditions and coil configuration in hand, we moved on to screening a variety of substrates (Table 2). We were pleased to find that, in all but one case, near quantitative conversions were obtained. The alkane derived from **1** was obtained in excellent isolated yield under the optimized conditions (entry 1). We next examined two styrene derivatives, knowing that Wilkinson's catalyst is very effective in hydrogenating terminal phenyl-substituted alkenes (Table 2, entries 2–3).¹³ The slightly lower isolated yield of the alkane derived from **2** can be attributed to the volatility of the resulting product, whereas we see a marked increase in yield with the alkane from the less volatile benzodioxole, **3** (Table 1, entry 3). We next explored the reduction of two representative electron-deficient alkenes (Table 2, entries 4 and 5), which afforded excellent yields of their corresponding alkanes. Less conjugated alkene systems, namely 1-dodecene, **6**, and eugenol, **7**, were also screened (Table 2, entries 6 and 7), and both furnished the desired product in excellent yield. The alkane derived from (allyloxy)benzene, **8**, was isolated in slightly lower yield, likely for the same rationale as that in the case of **2**. Knowing that terminal alkenes are more susceptible to hydrogenation than internal or other more substituted alkenes, we decided to screen dihydrocarvone, **9**, and diethyl fumarate, **10** (Table 2, entries 9 and 10). Both substrates could be hydrogenated effectively and in high yield.

Not all substrates are compatible with our optimized reaction conditions. While most were tolerated, several functionalities proved problematic (Table 2, entries 11–14). Both the diacetate and alcohol likely failed to undergo complete hydrogenation due to competitive side reactions, causing subsequent catalyst deactivation (Table 2, entries 11 and 12). We believe that, in the case of the alcohol, a chelated metal complex is formed, evidenced by the change in color (green) and the broadening of peaks in the ¹H NMR. In the case of the diacetate, we observed a Tsuji–Trost type reaction (elimination of one acetate moiety) followed by polymerization. The high temperatures of our optimized conditions likely led to competitive polymerization of *N*-vinylpyrrolidinone (Table 2, entry 13). Also, Wilkinson's catalyst is known to react with

Table 2. Continuous-flow hydrogenation of alkenes using the on-demand gas delivery reactor^a

Entry	Alkene	Isolated yield (%) ^{a,b}
1		89
2		77
3		86
4		97
5		98
6		92
7		95
8		80
9		95
10		98
11		-
12		-
13		-
14		-
15		99 ^c

^aReactions conditions unless otherwise indicated: 5 mmol substrate scale, 1 mL CH₂Cl₂, 1.2 mol % catalyst loading, 125 °C coil temperature, 0.25 mL/min flow rate. ^bA quantitative conversion obtained for all reactions except entry 5 (93% conversion by ¹H NMR analysis). ^cReaction performed on a 90 mmol scale using 30 mL of CH₂Cl₂.

aldehydes to give the decarbonylated product, which indeed was the case with *trans*-2-undecenal, **14** (Table 2, entry 14).¹⁵

The final objective of our study was to assess the scalability of our methodology. We previously observed during our

alkoxycarbonylation work that when small portions of reagents were passed through the coils, there is considerable dispersion in the length of the two reactors.¹⁰ We therefore decided to process materials using a 3 M concentration, corresponding to a throughput of 45 mmol h⁻¹ under continuous operation. We selected *trans*-chalcone, **4**, as the representative alkene for scale-up. We obtained a quantitative conversion and 99% isolated yield of the desired alkane (Table 2, entry 15).

EXPERIMENTAL SECTION

Description of the Apparatus. Experiments were performed on a Vapourtec R series.¹⁶ The system was equipped with two gas-loading reactor coils. The “reagent out” port on the first reactor coil was connected to the “reagent in” port on second reactor coil using a 32 mm length of tubing. The “reagent out” port of the second reactor was linked into a T-piece which allowed a flow of acetone to mix with the reaction mixture departing the second reactor coil. The T-piece was finally equipped with a 250 psi back-pressure regulator after which was a length of tubing leading to a waste or collection flask.

The system was initially primed using the equipment manufacturer's suggested startup sequence. **CAUTION:** Make sure the “gas out” apertures vent into a fumehood since hydrogen is highly flammable. After priming the unit, the reactor coils were each heated to 125 °C. Once at temperature, the system was ready for loading the reagent solution.

General Procedure for Small-Scale Hydrogenation Reactions (Hydrogenation of Anethole). A 10 mL tube was charged with Wilkinson's catalyst (0.0555 g, 0.060 mmol 1.2 mol %), anethole, **1** (0.741 g, 5 mmol), and 1 mL of dichloromethane. The solution was thoroughly mixed using sonication until it became a completely homogeneous clear, dark-red solution. The flow reactor was readied using the equipment manufacturer's suggested start-up sequence followed by heating the reactor coils to 125 °C. The reaction mixture was then loaded into the reactor. Product collection was commenced immediately after this switch. After the reaction mixture had been completely loaded into the reactor, the reactor pump was set back to pumping dichloromethane. After the product had been fully discharged from the reactor coils, the resulting clear-yellow solution could then be purified.

Dichloromethane and acetone were removed using rotary evaporation, leaving the crude product. The crude product was dissolved in a small amount of the elution solution (9:1 hexane/EtOAc) and loaded onto a plug of silica. The plug was rinsed thoroughly with eluting solution, and the solvent was stripped in vacuo in a room temperature water bath.¹⁷ This process was repeated until constant weight was obtained. Pure 1-methoxy-4-propylbenzene,¹⁸ **1a**, was obtained as a clear, colorless oil (0.668 g, 89%). ¹H NMR (CDCl₃, 500 MHz) δ 0.99 (t, *J* = 7.25 Hz, 3 H) 1.67 (sxt, *J* = 7.60 Hz, 2 H) 2.58 (t, *J* = 7.60 Hz, 2 H) 3.83 (s, 3 H) 6.88 (d, *J* = 8.83 Hz, 2 H) 7.14 (d, *J* = 8.20 Hz, 2H) ¹³C NMR (CDCl₃, 125 MHz) δ 14.02 (CH₃), 25.06 (CH₂), 37.41 (CH₂), 55.44 (CH₃), 113.88 (CH), 128.53(CH), 135.02 (C), 157.91 (C) GC-MS (EI) 151 ([M + 1]⁺, 5%), 150 ([M]⁺, 44%), 122 (18%), 121 (100%), 91 (16%), 78 (16%), 77 (17%), 65 (6%).

General Procedure for Larger-Scale Hydrogenation Reactions (Hydrogenation of *trans*-Chalcone). A 50 mL conical flask was charged with Wilkinson's catalyst (1.000 g, 1.08 mmol 1.2 mol %), *trans*-chalcone, **5** (19.33 g, 92.8 mmol), and dichloromethane (30 mL). The solution was thoroughly

mixed using a stir bar until it became a completely homogeneous, clear, dark-red solution. The flow reactor was readied using the equipment manufacturer's suggested start-up sequence, followed by heating the reactor coils to 125 °C. The reaction mixture was then loaded into the reactor. Product collection was commenced immediately after this switch. After the reaction mixture had been completely loaded into the reactor, the reactor pump was set back to pumping dichloromethane. After the product had been fully discharged from the reactor coils, the resulting clear-yellow solution could then be purified.

CH₂Cl₂ and acetone were removed using rotary evaporation, leaving the crude product. The crude product was dissolved in a small amount of the elution solution (8:2 hexane/EtOAc) and loaded onto a plug of silica. The plug was rinsed thoroughly with eluting solution, and the solvent was stripped in vacuo in a 50 °C water bath. This process was repeated until constant weight was obtained. Pure **5a**, was obtained as an off-white powdery solid (18.910 g, 99%). ¹H NMR (CDCl₃, 500 MHz) δ 0.99 (t, *J* = 7.25 Hz, 3 H) 1.67 (sxt, *J* = 7.60 Hz, 2 H) 2.58 (t, *J* = 7.60 Hz, 2 H) 3.83 (s, 3 H) 6.88 (d, *J* = 8.83 Hz, 2 H) 7.14 (d, *J* = 8.20 Hz, 2H) ¹³C NMR (CDCl₃, 125 MHz) δ 14.02 (CH₃), 25.06 (CH₂), 37.41 (CH₂), 55.44 (CH₃), 113.88 (CH), 128.53(CH), 135.02 (C), 157.91 (C) GC-MS (EI) 151 ([M + 1]⁺, 5%), 150 ([M]⁺, 44%), 122 (18%), 121 (100%), 91 (16%), 78 (16%), 77 (17%), 65 (6%).

CONCLUSION

In summary, we report a continuous flow approach to the homogeneous catalytic hydrogenation of alkenes, utilizing Wilkinson's catalyst. The new reactor coil employed in this methodology enabled the continuous input of gas while simultaneously allowing for heating of the reaction mixture. A range of alkenes was hydrogenated using this approach. The methodology was amenable to significant scale-up; we processed approximately 0.1 mol of material over the period of 2 h. This would correspond to production of around 2 mol of product per day. A number of flow units running in parallel could increase this throughput further. Comparison of our approach with that of others using continuous-flow processing shows that our system is able to process reaction mixtures at significantly higher substrate concentrations and hence throughput. This is important when considering the current drive towards process intensification. Work is underway to use this apparatus for other reactions using gaseous reagents.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra of the compounds. 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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(12) A screen using only one coil gave a conversion of 36% under the conditions shown in Table 1, entry 1. Adding a second coil allowed for a longer reaction time, and the drop in conversion to 28% (Table 1, entry 1) before further optimization is due to the overall dilution of the reaction mixture (via dispersion) as it proceeded through the length of the reactor.

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