Seger Van Mileghem[1,2]
Wim M. De Borggraeve[2]
Ian R. Baxendale[1,*]

A Robust and Scalable Continuous Flow Process for Glycerol Carbonate

With glycerol being a bulk waste product, the interest in converting it to other value-added products is steadily increasing. A scalable continuous flow process was developed for the synthesis of glycerol carbonate (2-GLC) from glycerol and dimethyl carbonate on a hydroxide functional resin. High conversion and selectivity were obtained while the residence times were typically shorter than 10 min. Continuous production of 2-GLC was achieved in high throughput and with improved processing metrics, creating the foundations for a production level process.

Keywords: Flow chemistry, Glycerol carbonate, Valorization of glycerol

Received: January 8, 2018; *revised:* July 29, 2018; *accepted:* August 1, 2018

DOI: 10.1002/ceat.201800012

Supporting Information available online

1 Introduction

There has been significant industrial interest in the valorization of glycerol in recent years, mainly due to glycerol being a bulk waste product derived mainly from biodiesel production but increasingly also from oleochemical manufacturing [1, 2]. These industries accounted for over 2247 kt of glycerol in 2013 and the global glycerol market is expected to reach a value of $ 2.52 billion by 2020 [3]. The conversion of glycerol as a waste stream into other value-added products has therefore received considerable attention [4, 5]. Some illustrative examples are hydrogenolysis to 1,2-propanediol [6], dehydration to allyl alcohol [7], transformation to epichlorohydrin [8–10], and gasification to syngas [11].

Glycerol carbonate (2-GLC; 4-(hydroxymethyl)-1,3-dioxolane-2-one; glycerol 1,2-carbonate) is another interesting product derived from glycerol and is considered a renewable building block due to its versatility [12, 13]. Applications of 2-GLC include usage as a curing agent [14], surfactant [15], chemical intermediate for polymer production [16], and electrolyte liquid carrier [17]. 2-GLC is also becoming increasingly popular as a safe bio-based alternative to several traditional organic solvents, possessing a high boiling point (115 °C at 0.1 mbar), low volatility (vapor pressure of 8 mbar at 177 °C), and high dielectric constant ($\varepsilon = 82.7$) [18, 19]. Moreover, 2-GLC is water soluble, nontoxic, readily biodegradable, and non-flammable.

The conversion of glycerol to 2-GLC has been extensively studied (Scheme 1) [12]. Examples include the use of phosgene, carbon monoxide, and carbon dioxide [12]. Other reagents such as organic carbonates and urea have also been used. Carbon dioxide is, of course, the most green reagent of choice for this reaction, but known processes for direct 2-GLC synthesis from CO_2 often include the use of toxic tin reagents and glycerol conversions are low (in the range of 30 %). These processes are therefore less economically feasible for industrial-scale preparation [20]. Dimethyl carbonate (DMC) is widely studied as a carbonyl source to synthesize 2-GLC since it is considered an environmentally benign chemical, and has also been used in industrial settings to synthesize 2-GLC [21–26]. Many catalysts are known for this transesterification, e.g., inorganic bases [27–30], tertiary amines [31–34], lipases [35–37], and *N*-heterocyclic carbenes [38]. However, only a few continuous processes are known for this transformation [39–42] while, in general, continuous processes more often meet the basic criteria for potential industrial feasibility and scale-up. To the best of our knowledge, inorganic bases are the preferred catalysts of use for the industrial preparation of 2-GLC prepared from glycerol and DMC, mainly based upon cost [23–26].

In this paper, we report a robust and scalable continuous flow process transforming glycerol to 2-GLC using DMC as the carbonyl source, by making use of a cheap and easily recyclable polymer-supported catalyst [43–48] in the presence of methanol as a co-solvent. When applying a temperature > 120 °C, high conversions and selectivity are obtained with residence times typically lower than 10 min, thus producing high space-time yields.

2 Experimental

2.1 Materials

All purchased materials were used with further purification unless otherwise noted. Glycerol (glycerin) was purchased from Sigma-Aldrich and DMC was purchased from Fluorochem.

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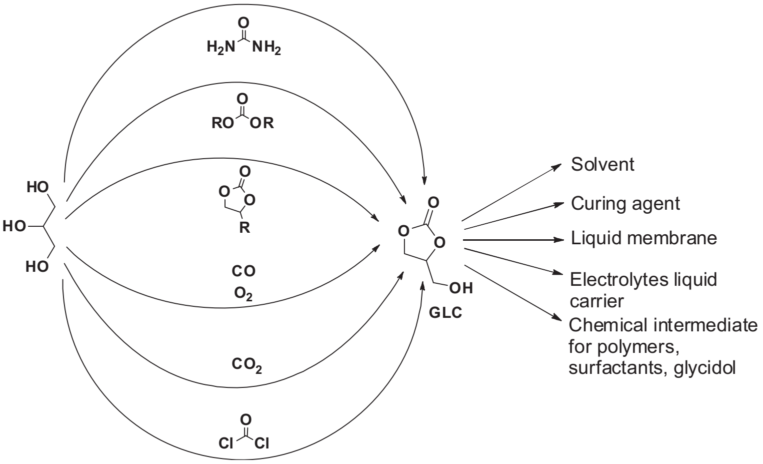
[1] Dr. Seger Van Mileghem, Prof. Ian R. Baxendale
i.r.baxendale@durham.ac.uk
University of Durham, Department of Chemistry, South Road, Durham DH1 3LE, UK.

[2] Dr. Seger Van Mileghem, Prof. Wim M. De Borggraeve
KU Leuven, Division of Molecular Design and Synthesis, Department of Chemistry, Celestijnenlaan 200F, B-3001 Heverlee, Belgium.



Scheme 1. Main routes for the synthesis of glycerol carbonate from glycerol.

Methanol was purchased from Fisher Scientific UK (analytical-reagent grade) and was used as such. Ambersep(R)® 900 hydroxide was purchased from Fluka and rinsed with 1 M solution of aqueous NaOH, deionized water, and dry methanol before use (see below). For column chromatography, silica gel 60 (0.015–0.040 mm) was used (CAS number 7631-86-9, EC number 231-545-4), purchased from Merck Millipore.

2.2 Flow Equipment

A Vapourtec® R2+ R4 unit was used for all flow reactions. An exception to this was when using neat glycerol; then, a Vapourtec E-series system with peristaltic pumps was used. Omnifit® glass columns (10 mm i.d. × 100 mm) were used as reactors for the heterogeneous catalysis experiments.

2.3 CCD Optimization

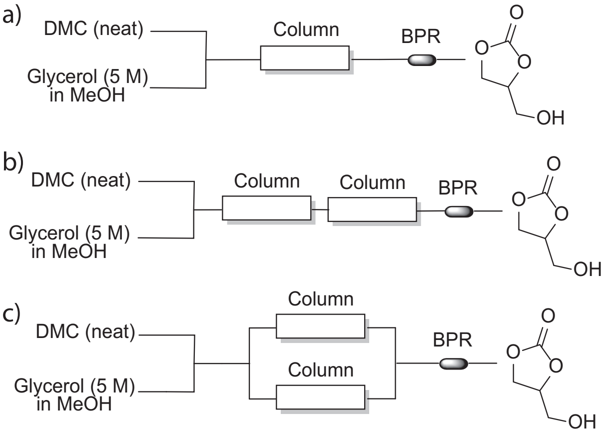
A central composite design (CCD) for optimization of the flow process (flow process 3) was performed using JMP Pro 12.1.0 software optimized for conversion. The predicted test condition sets were derived from a 4-factor 4-level full factorial design and a least-squares fit model (two replicates). Factors addressed were temperature (105, 110, 115, 120 °C), residence time – which equated to a flow rate (5, 7.5, 10, 12.5 min), glycerol concentration (5.8, 6, 6.2, 6.4 M), and stoichiometry (2.0, 2.2, 2.4, 2.6 M), generating surface plots from which the optimized conditions were sampled.

2.4 General Experimental Procedure for Flow Preparative-Scale Synthesis

An Omnifit® glass column (10 mm i.d. × 100 mm) was filled with Ambersep® 900 hydroxide resin beads (4.5 g). The ends of the column were sealed using adjustable polytetrafluoroethylene (PTFE) flow adaptors and the resin was washed by passing an aqueous 1 M solution of NaOH (10 min), water (20 min), and MeOH (40 min) through at a flow rate of 1 mL min^{-1} (a Knauer K120 pump was used for the washing sequence). After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining 10-min period (heating of the column reactors was conducted by placing the Omnifit columns into individual cartridge heaters attached to the Vapourtec® R4 unit). Next, a solution of glycerol (5 M; pump A on the Vapourtec® R2+ system) in MeOH was pumped at 366 μL min^{-1} and combined via a polyether ether ketone (PEEK) T-piece connector with a second stream containing DMC (neat, 4 equivalents; pump B on the Vapourtec® R2+ system) at 634 mL min^{-1}. The combined stream was directed into the reactor column (residence time of approximately 4 min) and finally passed through an in-line backpressure regulator of 17 bar. The output was collected for analysis (calibrated gas chromatography-mass spectrometry (GC-MS); see the Supporting Information (SI) for additional details), and after evaporation of MeOH and DMC (rotary evaporation at 50 °C and 40 mbar), 2-GLC was purified via either vacuum distillation (145–148 °C at 0.2 mmHg) or column chromatography on silica (DCM/MeOH 95:5). 2-GLC: ^{1}H NMR (d_6-DMSO; 400 MHz): 5.26 (t, $J = 5.7$ Hz, 1H), 4.84–4.74 (m, 1H), 4.49 (t, $J = 8.1$ Hz, 1H), 4.28 (dd, $J = 8.1$, 5.7 Hz, 1H), 3.66 (ddd, $J = 12.6$, 5.7, 2.8 Hz, 1H), 3.50 (ddd, $J = 12.6$, 5.7, 3.4 Hz, 1H). ^{13}C NMR (d_6-DMSO; 101 MHz): 155.16 (C), 77.01 (CH), 65.86 (CH_2), 60.59 (CH_2).

2.5 Flow Scale-up Procedure

The different flow setups for processing at different scales are shown in Scheme 2: Single-column reactor (Scheme 2 a, flow process 1), reactors with two sequentially linked columns (Scheme 2 b, flow process 2 and 3), use of packed-bed reactors in parallel (Scheme 2 c, flow process 4 and 5).



Scheme 2. Different flow setups for processing at scale. (a) Single-column reactor, (b) reactors with two sequentially linked columns, (c) use of packed-bed reactors in parallel.

2.5.1 Flow Process 1

A glass column (Omnifit® 10 mm i.d. × 100 mm) was filled with Ambersep® 900 hydroxide resin (4.5 g) and the ends were sealed using adjustable PTFE flow adaptors before being placed into a cartridge heater attached to the Vapourtec® R4 unit. The catalyst bed was washed with aqueous 1 M NaOH (10 min), deionized water (20 min), and MeOH (20 min) pumped through at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C. A stock solution of glycerol in MeOH (5 M; pump A on the Vapourtec® R2+ system) was pumped at 366 μL min^{-1} and combined at a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents; pump B on the Vapourtec® R2+ system) at 634 μL min^{-1}. The combined flow stream (total flow 1 mL min^{-1}) was directed into the column reactor (residence time of approximately 4 min), finally passing through an in-line backpressure regulator of 17 bar resistance. The flow output was collected as a batch and analyzed by calibrated GC-MS (see SI for additional details) and showed a conversion of 96 % and selectivity towards 2-GLC of 82 %. The system was run uninterrupted for 4 h to validate steady-state operation and to test the system for stability.

2.5.2 Flow Process 2

Two Omnifit® glass columns (10 mm i.d. × 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g). Both ends of the columns were sealed using adjustable PTFE flow adaptors and, after linking in series, a 1 M aqueous solution of NaOH (10 min), deionized water (10 min), and then MeOH (20 min) was pumped through at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining 10-min period (heating of the column reactors was conducted by placing the Omnifit columns into individual cartridge heaters attached to the Vapourtec® R4 unit). Next, a solution of glycerol (5 M; pump A on the Vapourtec® R2+ system) in MeOH was pumped at 740 μL min^{-1} and combined via a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents; pump B on the Vapourtec® R2+ system) at 1.25 mL min^{-1}. The combined stream was directed into the two linked columns, finally passing through an in-line backpressure regulator of 17 bar. The flow output was collected and analyzed by calibrated GC-MS (see SI) and showed a conversion of 95 % and a selectivity of 81 %. The process was run uninterrupted for 4 h, processing 82 g of glycerol. Following the evaporation of MeOH and DMC under reduced pressure using a rotary evaporator (50 °C and 40 mbar), the 2-GLC was purified by vacuum distillation in 75 % isolated yield.

2.5.3 Flow Process 3

The setup employed was identical to the sequence described above (flow process 2). The solution of glycerol (5 M; pump A on the Vapourtec® R2+ system) in MeOH was pumped at 1.5 mL min^{-1} and the second stream containing DMC (neat, 4 equivalents; pump B on the Vapourtec® R2+ system) at 2.5 mL min^{-1} (total flow rate of 4 mL min^{-1} and a residence time of 2 min). The flow output was collected and analyzed by calibrated GC-MS (see SI). A standard 4-h run time was used to validate the system stability. The output from the reactor was tested at 30 min, 1 h, 2 h, 3 h, and 4 h, giving 84 ± 1.2 % conversion. Following batch evaporation of the MeOH and DMC under reduced pressure using a rotary evaporator (50 °C and 40 mbar), the 2-GLC was purified by vacuum distillation in 62 % isolated yield.

2.5.4 Flow Process 4

Two Omnifit® glass columns (10 mm i.d. × 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g) and placed in the column heaters of the Vapourtec® R4 unit. The columns were sealed using adjustable PTFE flow adaptors and arranged in-line in a parallel mode using a T-piece connector. The resin beds were washed in sequence with 1 M aqueous solution of NaOH (10 min), water (10 min), and MeOH (20 min) by pumping at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 140 °C over the remaining 10-min period. A stock solution of glycerol (5 M; pump A on the Vapourtec® R2+ system) in MeOH was pumped at 740 μL min^{-1} and combined via a PEEK T-piece connector with a second stream containing DMC (neat, 4 equivalents; pump B on the Vapourtec® R2+ system) at 1.25 mL min^{-1}. The combined stream was directed into the two linked columns before finally passing through an in-line backpressure regulator of 17 bar. The flow output was collected and analyzed by calibrated GC-MS (see SI) and showed a conversion of 97 % and a selectivity towards 2-GLC of 91 %. No further purification was performed on the bulk sample.

2.5.5 Flow Process 5

Two Omnifit® glass columns (10 mm i.d. × 100 mm) were filled with Ambersep® 900 hydroxide resin beads (4.5 g) and placed in the column heaters of the Vapourtec® R4 unit. The columns were sealed using adjustable PTFE flow adaptors and arranged in-line in a parallel mode using a T-piece connector. The resin beds were washed in sequence with 1 M aqueous solution of NaOH (10 min), water (10 min), and MeOH (20 min) by pumping at a flow rate of 1 mL min^{-1}. After the initial 10 min of MeOH washing, the temperature was gradually increased to 115 °C over the remaining 10-min period. A stock solution of glycerol (6.2 M; pump A on the Vapourtec® R2+ system) in MeOH was pumped at 375 μL min^{-1} and combined via a 270-μL Uniqsis mixer chip with a second stream containing DMC (2.45 equivalents; pump B on the Vapourtec® R2+ system) at 410 μL min^{-1}. The combined stream was split via a PEEK T-piece and directed into the two reactor columns before being reunited via a second PEEK T-piece and then passing through an in-line backpressure regulator of 17 bar. The output was connected as the feedline to a rotary evaporator fitted with a 3-L collection flask. The heating bath was at set at 50 °C and the pressure at 40 mbar, facilitating continuous evaporation of volatiles. Vacuum distillation of the crude 2-GLC gave a yield of 80 %.

2.6 Analysis

GC-MS experiments were carried out on a Shimadzu QP2010-Ultra located in CG43. Electron ionization (EI) was carried out at 70 eV and the working mass range was 35–650 u for all experiments. The samples were prepared by dissolving 10 μL of collection volume in 1 mL of methanol. Of this sample, 0.5 μL was split injected (25:1) into the Shimadzu QP2010-Ultra equipped with an Rxi-17Sil MS column using helium as carrier gas (0.41 $\mathrm{mL\,min^{-1}}$). The temperature of the oven was increased from 30 to 300 °C at a rate of 50 $\mathrm{°C\,min^{-1}}$. Finally, the oven was maintained at 300 °C for 5 min. It was found that glycerol and 2-GLC have the same response when plotting the peak area as a function of the concentration (see SI). Therefore, the following terms are defined as follows: conversion as the relative peak area of glycerol with all other peaks, selectivity as the relative peak area excluding the glycerol signal, and GC yield as the relative peak area ratio of 2-GLC with glycerol.

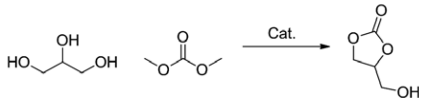
3 Results and Discussion

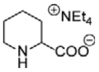
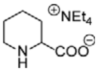
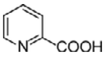
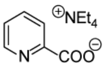
As a starting point for the investigation, neat batch experiments with homogeneous catalysts were performed, in order to derive a better understanding of the transformation (Tab. 1). It quickly became clear that basicity was a crucial parameter. Strong bases gave rise to high yields, which was in accordance with the literature (entries 2, 3, 8, 9) [12, 13].

Increasing the temperature also furnished improved results (Tab. 1, entries 8, 9). Since we were initially also interested in developing a continuous synthesis for glycidol, the recent work of Tao and coworkers [49] seemed of high relevance. Tetraethylammonium amino acid ionic liquids were reported as efficacious catalysts for the one-pot neat synthesis of glycidol, starting from glycerol and DMC under reflux conditions. When replicating their experiments, however, we were unable to achieve selectivity towards glycidol. Instead, a high selectivity towards 2-GLC was obtained (Tab. 1, entries 10, 11). It should be noted that, potentially, glycerol can be derivatized to form different isomers involving either a five- or a six-membered cyclic carbonate. The five-membered derivative is the kinetic product while under alternative reaction conditions the six-membered cyclic glycerol carbonate (3-GLC, 5-hydroxy-1,3-dioxan-2-one, glycerol 1,3-carbonate) can be prepared as the thermodynamic product [50]. Intrigued by the initial results generated by the ammonium catalyst, a selection of related catalysts was also examined for the transformation (Tab. 1, entries 12–14). The low yields obtained in these instances could suggest that both an NH moiety and carboxylate are required for efficient catalysis; entry 12 indicates that acetate alone is not a sufficient catalyst.

Tetraethylammonium pipecolinate was the catalyst of choice for homogeneous catalysis flow experiments, using a Vapourtec® R-series system which was equipped with a fluorinated ethylene propylene (FEP) heated coil reactor. Since DMC and glycerol are immiscible at room temperature, a two-stream setup was used as depicted in Tab. 2. The relative flow rate was adjusted in such a way as to provide 3.5 equivalents of DMC. Initially, we adopted the protocol from the de Souza group [40] using neat glycerol with catalyst, preheated at 70 °C (Tab. 2, entry 1). However, it was immediately apparent that pumping this viscous mixture would not be easily achieved. A solvent that is able to dissolve both glycerol and DMC was desired, e.g., aliphatic alcohols. Therefore, the glycerol and catalyst were dissolved in ethanol for these explorative experiments. It quickly became clear that 2-GLC formation increased with temperature. Applying a temperature of 140 °C yielded 90 % conversion and 85 % selectivity (Tab. 2, entry 4).

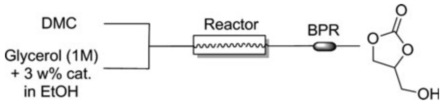
Table 1. Initial batch investigation.[a)]

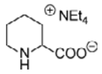
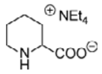
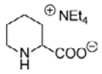
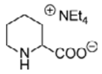
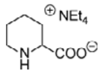
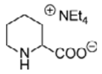
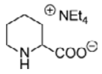


Entry	Catalyst	T [°C]	Duration [h]	GC yield Y [%]
1	none	reflux	12	11
2	KOH	rt	12	79
3	nBuLi	rt	12	93
4	NEt_4I	rt	12	18
5	NEt_4Br	rt	12	16
6	NEt_4Cl	rt	12	19
7	NEt_4OH	rt	12	24
8	tBuOK	rt	12	66
9	tBuOK	60	12	95
10		reflux	2	92
11		reflux	2	91
12	NBu_4OAc	reflux	2	5
13		reflux	2	> 3
14		reflux	2	5

[a)] Conditions: 5 mmol scale, 3.5 equivalents DMC, 5 mol % of the catalyst; CG yield based on calibrated product; rt = room temperature.

Table 2. Homogeneous catalysis flow experiments.[a)]



Entry	Catalyst	T [°C]	t_R [min]	V_R [mL]	C [%]	S [%]
1[b)]		100	30	10	–	–
2		100	30	10	15	71
3		120	30	10	53	84
4		140	30	10	90	85
5	none	140	30	10	< 5	–
6		140	40	20	85	83
7		140	15	10	82	92
8[c)]		140	30	10	10	75

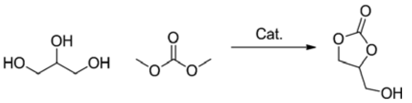
[a)]Conditions: 3.5 equivalents of DMC. BPR = 100 psi; [b)]neat glycerol + catalyst preheated at 70 °C used; [c)]water (1 M) used instead of ethanol.

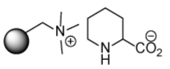
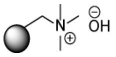
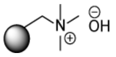
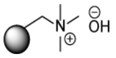
When repeating these conditions in the absence of the pipecolinate catalyst, almost no 2-GLC formation was observed (Tab. 2, entry 5). Variation of the residence time resulted in small conversion differences, while a slight decrease in selectivity was observed with increasing residence time (Tab. 2; cf. entry 6 with entries 4 and 7). It is worth noting that diethyl carbonate formation was observed in small amounts by ^{1}H NMR in these experiments. In a final experiment, water instead of ethanol was used as solvent (note that crude glycerol is often sourced as an aqueous mixture) but only a low conversion of 2-GLC was obtained (Tab. 2, entry 8). This might be due to poor mixing as a biphasic segmented flow was seen while a homogeneous flow was observed when ethanol was used as the solvent.

Easy separation of the catalyst after performing the reaction is one of the key requirements for industrial applicability and it was therefore interesting to see if these results could also be generated when making use of a heterogeneous catalyst system. Therefore, additional batch experiments were carried out, this time using a polymer-supported catalyst (Tab. 3). Pipecolic acid was immobilized by a simple neutralization reaction with Ambersep® 900 hydroxide, a high-performance macroreticular polystyrene resin (Dow Chemical Company; 2.4 mmol g^{-1}; see SI). A nearly quantitative conversion towards 2-GLC was obtained under neat conditions when using the immobilized catalyst (Tab. 3, entry 1). Since one could argue that this result might be due to remaining strongly basic sites on the polymer, a blank experiment was performed using fresh Ambersep® 900 hydroxide as the catalyst (Tab. 3, entry 2). However, a low conversion was obtained and confirmed that the hydroxide anion was replaced by pipecolic acid. Note that this result differs greatly from using potassium hydroxide as catalyst (79 % GC yield; Tab. 1, entry 2), but is in accordance with the result for NEt_4OH (16 % GC yield; Tab. 1, entry 7), with the difference explained due to mass transport limitations. Only a slight increase in yield was observed when methanol was used as co-solvent (Tab. 3, entry 3) or when the reaction was carried out at 120 °C in a microwave reactor (Tab. 3, entry 4). These results strongly suggest that a different mechanism takes place when using weakly basic catalysts of this type rather than strongly basic catalysts (potassium *tert*-butoxide (*t*BuOK), KOH).

When translating this into a continuous flow process, a column reactor was filled with catalyst (see the Experimental section) and heated to the appropriate temperature while the reagents were pumped through. The results are summarized in Tab. 4. (It should be noted that the quoted residence times might be slightly underestimated since the polymer beads have the tendency to contract when heated!) Methanol was the solvent of choice for dissolving glycerol, albeit a more concentrated solution than previously used (Tab. 2), since minimization of the solvent volume is desired for industrial applicability. Moreover, methanol is more easily removed than ethanol and results in less complex mixtures as methanol is generated as a by-product in the reaction. In a first trial, a residence time of 15 min at 100 °C yielded 85 % conversion and 89 % selectivity (Tab. 4, entry 1). Raising the temperature allowed higher conversions with essentially equivalent selectivity (Tab. 4, entries 2, 3). Although

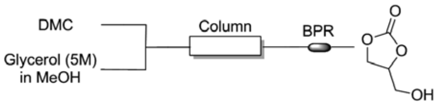
Table 3. Heterogeneous catalysis experiments in batch.[a)]

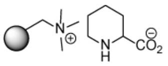
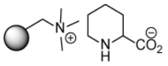
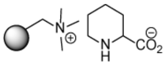
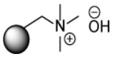
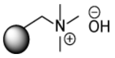
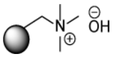
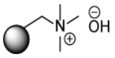
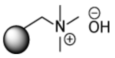
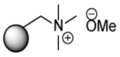
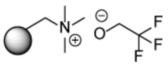


Entry	Catalyst	GC yield [%]
1		95
2		10
3[b)]		27
4[c)]		40

[a)]Conditions: Reflux (2 h), 20 mmol scale, 3.5 equivalents DMC, 1 g polymer (about 1 mol %); [b)]methanol used as co-solvent; [c)]microwave, 1 h, 120 °C.

Table 4. Heterogeneous catalysis flow experiments.



Entry	Catalyst	T [°C]	t_R [min]	C [%]	S [%]
1[a)]		100	15	85	89
2[a)]		110	15	92	91
3[a)]		120	15	100	86
4[a)]		100	15	73	93
5[a)]		120	15	86	94
6[a)]		140	3	94	89
7[b)]		120	5	100	67
8[c)]		120	5	30	90
9[d)]		120	15	87	90
10[e)]		120	15	100	96

[a)] 3.5 equivalents DMC; [b)] 10 equivalents DMC used; [c)] neat glycerol preheated at 70 °C used; [d)] prepared from exchange of Ambersep 900 Cl form and NaOMe; [e)] prepared from exchange of Ambersep 900 Cl form and sodium 2,2,2-trifluoroethanolate; BPR = backpressure regulator (250 psi used at 140 °C, otherwise 100 psi).

showing improved overall conversions, the general trend emulated the results originally obtained using the homogeneous catalyst (Tab. 2, entries 2–4). Of particular interest was that, when repeating the reactions with the strongly basic Ambersep 900 hydroxide catalyst, 73 % conversion and 93 % selectivity were obtained (Tab. 4, entry 4). This is in stark contrast to the results obtained in the batch experiment (Tab. 3, entries 1, 2), where the difference in efficacy between both catalysts was far more pronounced. By comparison in this continuous flow setup, the differences in results are relatively small.

Of note, previously, several polymer-supported basic catalysts have been trialed for the solvent-free batch synthesis of 2-GLC, but interestingly without much success [30]. It was, however, immediately evident that the Ambersep® 900 hydroxide resin is an ideal catalyst for flow scale-up of this process, being a low-cost and commercially available material prepared at a scale for use in water treatment. It was therefore decided to further optimize this process based upon its use.

High conversion and selectivity were obtained when raising the reactor temperature to 120 °C (Tab. 4, entry 5). When further increasing the temperature to 140 °C, the residence time could be lowered to 3 min without significant differences in 2-GLC formation (Tab. 4, entry 6). It was observed that a higher excess of DMC resulted in higher glycerol conversion but decreased the selectivity due to formation of diglycerol tricarbonate, in accordance with the literature (Tab. 4, entry 7) [51]. We also attempted to use neat glycerol by employing peristaltic pumps (Vapourtec E-series system) to deliver the more viscous solution (preheated glycerol at 70 °C; Tab. 4, entry 8), but a conversion of only 30 % was obtained. It appears that methanol as co-solvent enhances the homogeneity of the liquid phase and therefore ensures better mixing and catalyst interaction (less channeling of the viscous solution in the packed bed [52,53]). Ochoa-Gómez et al. [30] have postulated that formation of 2-GLC occurs only if the glyceroxide anion is formed. Therefore, close contact between the catalytic sites and glycerol is required, which is of course enhanced by homogeneity and reduced viscosity. According to Ochoa-Gómez et al. [30], mass transport limitations also explain why their results are poor when using the heterogeneous, strongly basic ion exchange resins, Amberlyst® 26 OH form and Amberjet® 4400 OH, in batch. Likewise, in our hands, we did not manage to achieve high conversion in batch under reflux conditions with our heterogeneous, strongly basic catalyst, Ambersep® 900 hydroxide resin (Tab. 3, entry 2). It was hypothesized that these formerly low conversions were greatly enhanced in our case by (a) using higher temperatures, (b) inducing a homogeneous liquid phase by adding methanol, and (c) performing the reaction in a continuous column reactor, thus inducing more turbulence (convection and diffusion to the catalyst sites) than by conventional batch stirring.

One final question was regarding the speciation of the Ambersep® 900 hydroxide resin specifically if, under the column conditioning or during the reaction, an anion exchange occurred to form a more active catalyst. Considering that the hydroxide resin is potentially capable of exchanging with the methanol co-solvent, a methoxide may be the active species (also accounting for the batch differences with water inhibiting the process). Consequently, an appropriately functional methoxide resin was prepared and tested in the flow process, giving essentially identical results to the formal hydroxide resin (Tab. 4, entries 5 and 9). As the trifluoroethanolate anion had shown a profound counterion enhancement when utilized as part of a guanidinium-based ionic liquid system for 2-GLC synthesis, we elected to also prepare such a resin [54]. When tested, an enhancement in both conversion and selectivity was seen (Tab. 4, entry 10). However, as anticipated, after 35 min of use, the output returned to a composition equivalent to the parent methoxy resin. Despite offering an option of potentially using 2,2,2-trifluoroethanol as a co-solvent, this was not pursued further due to the issue of cost.

Motivated by these findings, it was decided to maintain methanol as the co-solvent. Since conversion and selectivity were quite similar for both homogeneous and heterogeneous flow catalysis, but the residence time was longer for the former, attempts to demonstrate the scalability of the heterogeneous flow setup were performed. As depicted in Scheme 2, the use of single, parallel as well as sequentially sequenced columns was tested to examine different aspects of the scale-up process.

In the first scale-up experiment (flow process 1; Scheme 2 a), a total flow rate of 1 mL min^{-1} was used at 140 °C and employing 4 equivalents of DMC, resulting in a residence time of ~4 min by passage through a single packed column of Ambersep® 900 hydroxide (4.5 g). A satisfying conversion of 96 % and selectivity of 82 % were obtained. To examine the linear scalability, a second equivalent packed-bed column was appended to the flow path (flow process 2, Scheme 2 b) and the flow rate was raised to 2 mL min^{-1}, again maintaining the reactor temperature at 140 °C. A consistent conversion of 95 % and associated selectivity of 81 % were achieved and maintained over 4 h of additional processing without loss of efficiency, consuming 82 g of glycerol. The 2-GLC was isolated in 75 % yield, resulting in a space-time yield of 3.38 kg 2-GLC per liter of the reactor per hour. When repeating this experiment (flow process 3; Scheme 2 b) but lowering the residence time to 2 min (4 mL min^{-1} total flow rate), a slightly reduced 62 % isolated yield of 2-GLC was obtained but resulting in a higher space-time yield of 5.60 kg 2-GLC per liter of the reactor per hour.

Next, we performed the flow process using two parallel reactor cartridges (flow process 4, Scheme 2 c). It should be acknowledged that, although distribution of a flow stream to two parallel linked reactors should theoretically give equal flows and hence equivalent contact times (residence times), in practice this approach can give different results, especially when using heterogeneous in-line reactors. This can be rationalized by the changes in hydrodynamic loading, which affects aspects of mixing, diffusion, and convection through the packed columns [55–59]. This can be particularly problematic at very low flow rates but was not significant in our scenario. Indeed, using a combined flow rate of 2 mL min^{-1} and a reactor temperature setting of 140 °C, a conversion of 97 % and a higher selectivity of 91 % were attained.

To validate the long-term stability of the catalyst, it was used in five consecutive runs of 5 h each performed at 140 °C (with cooling and methanol washing between cycles). A total 10 % decrease in conversion was observed by the fourth usage, which was also associated with a slight browning of the resin bead color from its original ivory shade (Fig. 1).

This decrease in activity could be compensated for by simply decreasing the flow rate as shown in run 5; however, deactivation in further runs was again observed. It appears that the catalyst is robust and air-stable but does suffer from some long-term thermal degradation. This would be expected given the nature of the functionality (benzyltrimethyl ammonium) and the benzylic linker, which may be expected to undergo substitution/elimination reactions at elevated temperature. (Form No. 233-00349-MM-1015X “Product Safety Assessment Dow Water & Process Solution Ion Exchange and Adsorbent Resins”, revised: October 14, 2015. The sheet for Ambersep resins states “DOW resins are stable at storage temperatures of 35 to 122 °F (2 to 50 °C). Exposure to elevated temperatures can cause these products to decompose.” No specific decomposition temperature on the material safety data sheet is provided.) By comparison, an equivalent process run at 120 °C maintained activity even after eight cycles (76–79 % conversion).

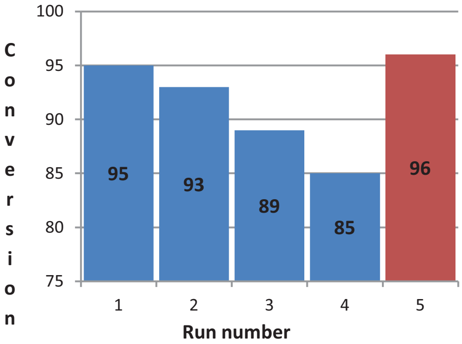


Figure 1. A single packed column of Ambersep® 900 hydroxide (4.5 g) at 140 °C, 1 mL min^{-1} total flow rate and employing 4 equivalents of DMC. Run 5 was performed at a reduced flow rate of 0.75 mL min^{-1}.

Reflecting on the resin stability findings, we set out to create a more sustainable flow process while attempting to decrease the equivalents of DMC and increasing the concentration of glycerol. As the parallel reactor configuration (flow process 4 using the reactor depicted in Scheme 2 c) had shown slightly improved processing characteristics, we continued to employ this setup in our optimization study. The experimental parameters were interrogated through a CCD using JMP Statistical Software (see Experimental for the configuration design). From this profiling, a new reaction concentration of glycerol at 6.2 M was predicted, using 2.45 equivalents of DMC and 115 °C with 10 min of residence time (flow process 5). A stock solution of glycerol (6.2 M in MeOH) was pumped at 375 μL min^{-1} to combine in a 270-μL Uniqsis mixer chip with a flow stream of DMC (410 μL min^{-1}) before being distributed over the two parallel packed-bed reactors distributed using a PEEK T-piece connector. After passing through the heated reactor columns (115 °C), a second T-piece connector was used to recombine the flow streams and the material was then collected after passing a backpressure regulator (250 psi). As an extension to the process, the exiting reaction solution was taken and used as a direct feedline to a rotary evaporator fitted with a 3-L collection flask. The heating bath was set at 50 °C and the pressure fixed at 40 mbar. This enabled a continuous evaporation of the less volatile methanol and DMC which was shown could be recycled. Next, standard vacuum distillation of the residual crude 2-GLC gave an 80 % yield (3.5 h collection) equating to a productivity of 13.2 g h^{-1}, with a reactor space-time yield of 0.84 kg 2-GLC per liter of the reactor per hour.

Although the space-time yield was much lower in this process than previously achieved (flow processes 1–4), we were able to run the system uninterrupted for over 6 days (152 h), producing a consistent output and generating > 2.0 kg of isolated material, equating to a catalyst turnover number (TON) of 981 and turnover frequency (TOF) of 6.46 h^{-1} [60]. It is also worth contrasting the different scale-up processes developed by applying additional processing metrics (i.e. mass intensity (MI) and reaction mass efficiency (RME)), in which case the latter flow process becomes much more competitive in terms of its green credentials (Tab. 5) [61]. Furthermore, taking into account the requirement for reduced heating (115 vs. 140 °C), this makes the latter run even more compelling. In addition, as it was shown that columns can be run in parallel, this would enable a simple numbering-up approach to scaling, especially with having demonstrated the long-term stability of the catalyst. Alternatively, if throughput is critical, it was shown that an automated switching value system could be easily installed to rapidly exchange the catalyst reaction cartridge, for example, on losing activity, without interruption to the flow process [62–65]. This would thus enable the process to be run at a higher temperature and the eventually depleted columns to be replaced, allowing a higher overall throughput albeit with the continual sacrifice of the catalyst, noting in this case its low cost.

Table 5. Comparison of flow experiments.

Proc.	T [°C]	Y [%]	C [%]	S [%]	TP [$\mathrm{g\,h^{-1}}$]	STY [$\mathrm{kg\,L^{-1}h^{-1}}$]	MI [–]	RME [%]
1	140	75	95	81	53.1	3.38	6.3	19.6
2	140	62	96	73	87.9	5.60	7.6	16.2
3	115	80	90	92	13.2	0.84	4.1	30.2

Overall, we feel that this work acts as a powerful proof-of-concept study using a small laboratory setup which could be utilized for further scale-up towards a production level manufacture of 2-GLC using a combination of a simple reactor design and a low-cost catalyst.

4 Conclusions

In summary, a scalable and robust continuous flow process was developed for the synthesis of 2-GLC, starting from two green reagents, glycerol and DMC. The reaction was shown to be efficiently mediated by Ambersep® 900 hydroxide functional resin, a bulk low-cost polymer-supported basic catalyst. High conversion and selectivity were obtained and the residence times were typically short. In a series of scale-up experiments, it was demonstrated that the continuous production of 2-GLC can be achieved in high throughput and with improved processing metrics, creating the foundations for a production level process.

Acknowledgments

We would like to acknowledge the funding and support from the Royal Society UF130576 (to I.R.B.) and KU Leuven project OT/14/067 (to W.D.B. and S.V.M.) that has enabled this work to be undertaken.

The authors have declared no conflict of interest.

Symbols used

C	[%]	conversion
MI	[–]	mass intensity
RME	[%]	reaction mass efficiency.
S	[%]	selectivity.
STY	[$\mathrm{kg\,L^{-1}h^{-1}}$]	space-time yield
T	[°C]	temperature
TP	[$\mathrm{g\,h^{-1}}$]	throughput
t_R	[min]	residence time
VR	[mL]	reactor volume
Y	[%]	yield

Abbreviations

2-GLC	glycerol carbonate
CCD	central composite design
DMC	dimethyl carbonate
FEP	fluorinated ethylene propylene
GC-MS	gas chromatography-mass spectrometry
MI	mass intensity
PEEK	polyether ether ketone
PTFE	polytetrafluoroethylene
RME	reaction mass efficiency
*t*BuOK	potassium *tert*-butoxide

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