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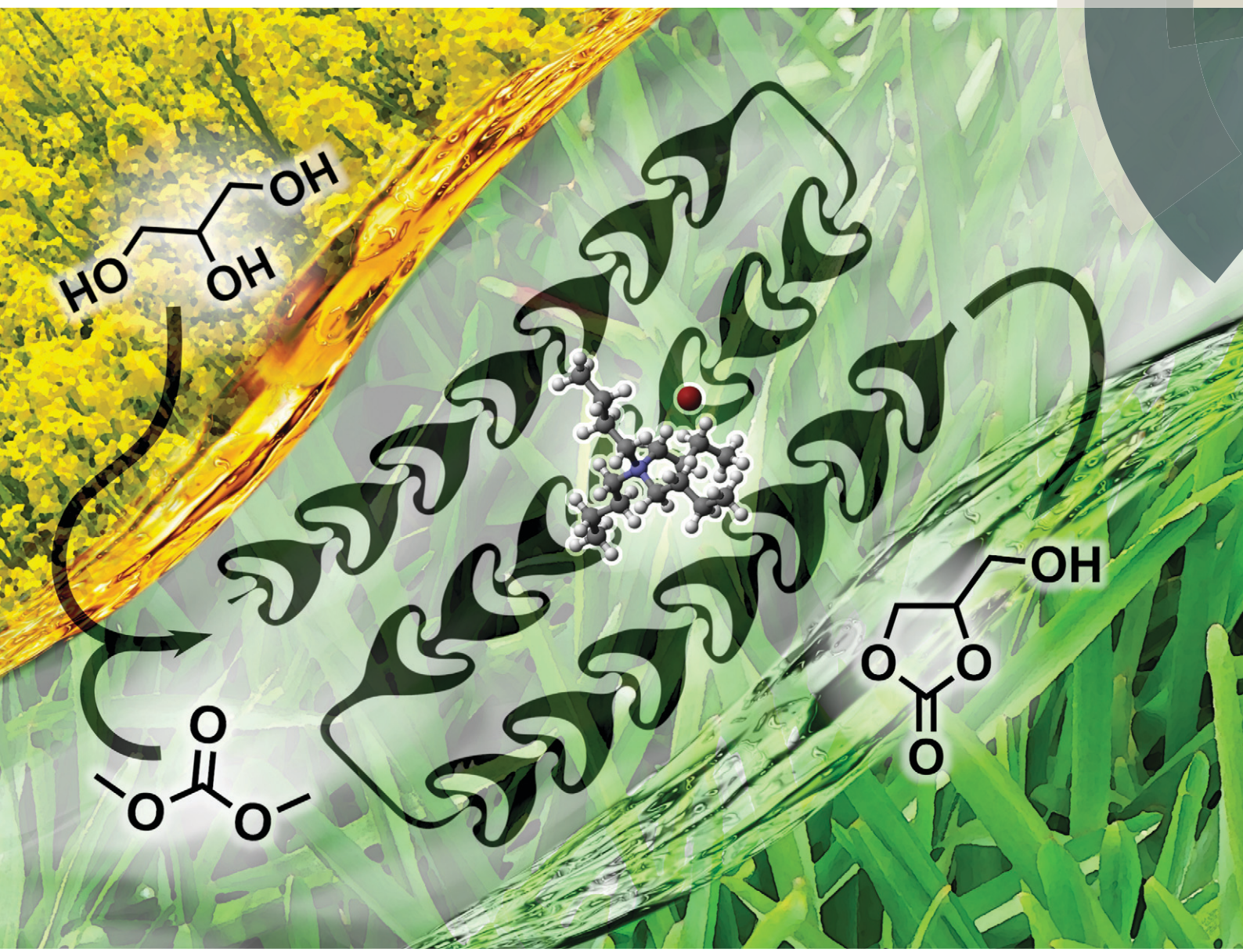

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Versatile and scalable synthesis of cyclic organic carbonates under organocatalytic continuous flow conditions†

Romaric Gérardy,[a] Julien Estager,[b] Patricia Luis,[c] Damien P. Debecker[d] and Jean-Christophe M. Monbaliu*[a]

The benchmark route for the preparation of cyclic organic carbonates starts from toxic, volatile and unstable epoxides. In this work, cyclic organic carbonates are prepared according to alternative sustainable and intensified continuous flow conditions from the corresponding 1,2-diols. The process utilizes dimethyl carbonate (DMC) as a low toxicity carbonation reagent and relies on the organocatalytic activity of widely available and cheap organic ammonium and phosphonium salts. Glycerol is selected as a model substrate for preliminary optimization with a library of homogeneous ammonium and phosphonium salts. The nature of the anion dramatically influences the catalytic activity, while the nature of the cation does not impact the reaction. Upon optimization, glycerol carbonate is obtained in 95% conversion and 79% selectivity within 3 min residence time at 180 °C (11 bar) with 3.5 mol% of tetrabutylammonium bromide as the organocatalyst. A straightforward liquid–liquid extraction procedure enables both the purification of glycerol carbonate and the recycling of the homogeneous catalyst. The conditions are amenable to refined and crude bio-based glycerol, although conversions are lower in the latter case. Control experiments suggest that water present in the crude samples induces significant hydrolysis of glycerol carbonate. The reaction conditions are then successfully applied on a wide variety of substrates, affording the corresponding cyclic carbonates in overall good to excellent yields (20 examples, 45–95%). The substrate scope notably encompasses bio-based starting materials such as glycerol ethers and erythritol-derived diols. In-line NMR is featured as a qualitative analytical tool for real-time reaction monitoring. The scalability of this carbonation procedure on glycerol is assessed in a commercial pilot-scale silicon carbide continuous flow reactor of 60 mL internal volume. Glycerol carbonate is obtained in 76% yield, corresponding to a productivity of 13.6 kg per day.

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Introduction

Cyclic organic carbonates, or 1,3-dioxolan-2-ones (**1**), are biodegradable and non-toxic compounds with a low vapor pressure. A broad range of industrial applications for cyclic organic carbonates have been reported, including their use as solvents, as electrolyte carriers in batteries, and as building blocks for the preparation of various chemicals and polymers.[1–6] Two main strategies are typically reported for their preparation: (a) the carbonation of 1,2-diols (**2**) and (b) the carboxylation of epoxides (**3**) (Fig. 1). The latter is the benchmark route for the preparation of functionalized cyclic organic carbonates and appears to be the most sustainable

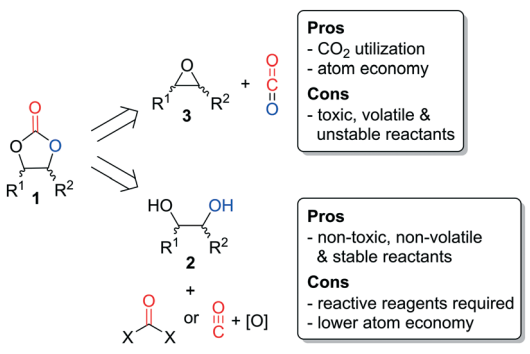

Fig. 1 Main strategies for the preparation of cyclic organic carbonates. R^1, R^2 = alkyl, aryl.

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since it directly utilizes CO_2 as a C_1 platform.[7,8] However, epoxides are in general toxic, volatile and unstable.[9] By contrast, 1,2-diols have a low toxicity profile, a low vapor pressure and are generally stable. Direct carboxylation of 1,2-diols with CO_2 is currently not synthetically viable since it typically requires harsh conditions, elaborate catalysts and toxic additives to attain poor yields.[10,11]

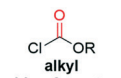
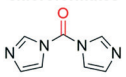
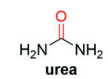
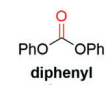
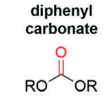
Reactive carbonation reagents are required to convert 1,2-diols into cyclic carbonates (Table 1); typical examples include enthalpy-activated reagents such as phosgene,[12] alkyl chloroformates[13] and carbonyldiimidazole (CDI).[14] The utilization of phosgene on the industrial scale raises safety concerns. Alkyl chloroformates and CDI are far less toxic, but are typically derived from phosgene, expensive and water-sensitive.[15,16] Other reagents such as carbon monoxide in combination with an oxidant,[17,18] urea,[19] diphenyl carbonate,[20] and dialkyl carbonates[21–24] are reported as well; yet, these strategies suffer from some drawbacks (Table 1).

In contrast to higher carbonates, dimethyl and diethyl carbonates (DMC and DEC, respectively) have attracted considerable attention as a class of "green" solvents and reagents for organic transformations. DMC and DEC are widely available, non-toxic liquids, and they are not sourced from phosgene.[25–27] The carbonation of 1,2-diols with DMC or DEC releases 2 molar equivalents of methanol or ethanol, respectively, *i.e.* non-corrosive by-products that can be easily recycled and utilized as solvents, reagents or fuels.

One of the most privileged substrates for carbonation with DMC/DEC is glycerol (**4a**)[28–33] and the methodology was scarcely extended to other functionalized 1,2-diol substrates.[21–24] Numerous homogeneous and heterogeneous catalysts are described for the carbonation of glycerol with DMC/DEC,[28–33] including organocatalysts. Organocatalysts have a bright forecast for the sustainable upgrading of bio-based chemicals.[34] Typical organocatalysts described for the carbonation of **4a** with DMC/DEC include amines, amidines, guanidines, N-heterocyclic carbenes, phosphazenes, enzymes, organic salts and ionic liquids.[21,28–33] However, one of the main drawbacks precluding the utilization of organocatalysts for the upgrading of low-cost, high-volume chemicals, such as **4a**, is their elevated cost.

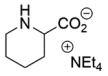
Despite the many assets of continuous flow processes for the manufacturing of commodities and fine chemicals,[35,36] only a few reports described the continuous flow carbonation of **4a** with DMC/DEC (Table 2).[21,37–42] De Souza and coworkers described a process involving 1.5 mol% of diazabicyclo(5.4.0)undec-7-ene (DBU) as a catalyst, 3 equiv. of DMC and solvent-free conditions. Glycerol carbonate (**1a**) was obtained with 80% conversion and 82% selectivity within 8 min at 120 °C.[38] Selva *et al.* reported a catalyst-free procedure for **1a** under high pressure and temperature conditions (230–250 °C, 50 bar) using methanol as a solvent. 10 equiv. of DMC and 15 min of residence within the reactor were necessary to reach conversion in the 78–94% range and 83–92% selectivity. The methodology was also successfully extended to ethylene and propylene glycol (**2b**, **2c**).[40] Baxendale and coworkers described a process using 3 wt% of tetraethylammonium pipecolinate and 3.5 equiv. of DMC for the synthesis of carbonate **1a**. Ethanol was used as the solvent and 30 min of residence at 140 °C was required to obtain **1a** with 90% conversion and 85% selectivity.[41] Monbaliu and coworkers reported a solvent-free procedure

Table 1 Comparison of common reagents utilized for the carbonation of 1,2-diols

Classification	Reagent	Pros	Cons	Ref.
Activated, phosgene-sourced	 phosgene	No catalyst required	Extremely toxic Gaseous	12
	 alkyl chloroformates		Toxic Water-sensitive	13
	 CDI		Water-sensitive Expensive	14
Non activated		Atom economy Cheap and widely available	Extremely toxic Gaseous Pd catalyst + oxidant required	17, 18
	 urea	CO_2-Sourced Cheap and widely available Widely available	Corrosive and gaseous by-product (NH_3) Catalyst required Solvent required for flow processing Toxic by-product (PhOH)	19
Activated, non phosgene-sourced	 diphenyl carbonate	No catalyst required	Solvent required for flow processing	20
	 dialkyl carbonates	Widely available Low toxicity by-products (ROH)	Catalyst required	21–24

CDI = carbonyldiimidazole. R = Me or Et.

Table 2 Homogeneous continuous flow processes from the prior Art for the carbonation of glycerol (**4a**) into glycerol carbonate (**1a**) with DMC

	Solvent	DMC	Catalyst	Conditions	Conv. (%)	Selec. (%)	Scale-up	1,2-Diol substrate scope
De Souza (2015)[38]	Neat	3 equiv.	 (1.5 mol%)	120 °C, 8 min	80	82	None	None
Selva (2016)[40]	MeOH	10 equiv.	None	230–250 °C, 15 min	78–94	83–92	None	3 substrates
Baxendale (2018)[41]	EtOH	3.5 equiv.	 (3 wt%)	140 °C, 30 min	90	85	2.1 kg per day	None
Monbaliu (2019)[21]	Neat	3 equiv.	 (1 mol%)	135 °C, 2 min	94	87	8.1 kg per day	9 substrates
This work	Neat	2.25 equiv.	NBu_4Br (3.5 mol%)	180 °C, 3 min	95	79	13.6 kg per day	20 substrates

utilizing 1 mol% of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine and 3 equiv. of DMC. Glycerol carbonate (**1a**) was obtained within 2 min at 135 °C with 87% selectivity and 94% conversion. The methodology was also successfully extended to 8 other simple substrates upon minor adjustment of the conditions.[21] However, these studies did not demonstrate the applicability of the method for the preparation of functionalized carbonates and relied on expensive organocatalysts or extreme conditions.

Our involvement in scalable, intensified and organocatalyzed carbonation processes led us to consider cheap, widely available and low-toxicity[43] homogeneous organic salts from the ammonium and phosphonium types. The related prior Art contains one patent filed in 1992, where the carbonation of glycerol was effected in batch at 120 °C in the presence of DMC and tetrabutylammonium bromide. Glycerol carbonate (**1a**) was obtained with 92% conversion and 92% selectivity after 6 h under these conditions. The methodology was also extended to ethylene (**2b**) and propylene (**2c**) glycol.[44] In 2014, Selva reported carbonate phosphonium salts as efficient catalysts for the carbonation of **2b** and **2c**, which was conducted in batch at 90 °C.[45]

In this work, we report an efficient organocatalytic process for the preparation of cyclic organic carbonates. The procedure is unique since (a) it involves intensified continuous-flow conditions (*i.e.* solvent-free or highly concentrated media, short reaction times, low catalytic loadings and low excess of DMC), (b) it utilizes cheap, air-stable and benign organic salts of the ammonium and phosphonium-type as catalysts, and (c) it is extended to a wide range of functionalized diols (20 examples). A straightforward liquid–liquid extraction procedure for the isolation of glycerol carbonate and for the recycling of the homogeneous catalyst is proposed. Refined and crude bio-based glycerol samples are evaluated as well, giving promising results. The process also features low-field in-line NMR analysis for qualitative real-time reaction monitoring, and scalability is assessed in a pilot-scale continuous flow reactor.

Experimental section

Chemicals

Ethanediol, 1,2-propanediol, 1,2,3-propanetriol, 3-methoxy-1,2-propanediol, 3-*tert*-butoxy-1,2-propanediol, 3-allyloxy-1,2-propanediol, 3-(*o*-tolyloxy)-1,2-propanediol, 3-(dimethylamino)-1,2-propanediol, 3-morpholino-1,2-propanediol, 1,2-butanediol, 2,3-butanediol, 3-butene-1,2-diol, 1,4-anhydroerythritol, *cis*-1,2-cyclohexanediol, *trans*-1,2-cyclohexanediol, 1,2-octanediol, tetramethylammonium bromide, tetraethylammonium bromide, tetrabutylammonium bromide, tetra-*n*-octylammonium bromide, tetramethylphosphonium bromide, tetrabutylphosphonium bromide, tetraphenylphosphonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, tetrabutylammonium acetate, tetrabutylammonium 2-hydroxybenzoate, tetrabutylammonium trifluoromethanesulfonate, tetrabutylammonium tetrafluoroborate, tetrabutylammonium hexafluorophosphate, dimethyl carbonate, 2,3-epoxy-1-propanol and dimethyl sulfoxide were obtained from commercial sources and used as received. Refined and crude bio-based glycerol samples were provided by Cargill™ and Valtris Champlor SAS. Methyl ((2-oxo-1,3-dioxolan-4-yl)methyl) carbonate, 3-propargyloxy-1,2-propanediol, 3-furfuryloxy-1,2-propanediol, 3,3′-(butane-1,4-diylbis(oxy))bis(propane-1,2-diol) and 3,3′-((furan-2,5-diylbis(methylene))bis(oxy))bis(propane-1,2-diol) were prepared following literature procedures (ESI†).

Experimental setup (microscale)

Microfluidic continuous flow reactors consisted of stainless steel (SS) coils (1.58 mm o.d. × 500 μm i.d.) equipped with SS nuts, ferrules and unions (VALCO). In experiments involving crude glycerol, the reactor consisted of a SS coil (3 mm o.d. × 2.1 mm i.d.) equipped with reducing unions (1/8″ to 1/16″, Swagelok). The reactors were thermoregulated with a Heidolph™ MR Hei-Tec® oil bath equipped with a Pt-1000 temperature sensor. Sections of the reactors that were not subjected to high temperatures were constructed from PEEK

or PFA tubing (1.58 mm o.d. × 750 μm i.d.) equipped with PEEK/ETFE connectors and ferrules (IDEX/Upchurch Scientific). Feed solutions were handled with high force Chemyx Fusion 6000 syringe pumps equipped with SS syringes and Dupont Kalrez O-rings or with Knauer Azura P 4.1S HPLC pumps. Downstream pressure was regulated using a dome-type back pressure regulator (Zaiput Flow Technologies BPR-10) connected to a nitrogen cylinder to set the working pressure (11 bar). In-line NMR reaction monitoring was carried out using a 43 MHz Spinsolve™ carbon NMR spectrometer from Magritek®.

Experimental setup (pilot-scale)

Mesofluidic experiments were carried out in a Corning® Advanced-Flow™ G1 SiC reactor featuring 6 fluidic modules (FMs) connected in series (10 mL per FM). Feed and collection lines consisted of PFA tubing (1/4″ o.d., 0.047 inch wall thickness) equipped with PFA or SS Swagelok connectors and ferrules. Feed solutions were handled with Corning dosing lines (HMP gear pumps). The reactor was thermoregulated with a LAUDA Integral XT 280 thermostat using LAUDA Therm 180 silicone oil. A temperature probe was positioned at a critical position along the thermofluid flow path for temperature monitoring. Downstream pressure was regulated using a dome-type back pressure regulator (Zaiput Flow Technologies BPR-1000) connected to a nitrogen cylinder to set the working pressure (11 bar).

Analytical methods

Conversion and yield were determined by gas chromatography coupled with flame ionization detection (GC/FID) using a Shimadzu GC-2014 gas chromatograph. Selectivity is defined as the ratio between the yield and the conversion. Where specified, yields were determined by high field ^{1}H NMR spectroscopy using mesitylene as the internal standard. Structural identity was confirmed by ^{1}H and ^{13}C NMR spectroscopy conducted on a high field (400 MHz) Bruker Avance spectrometer in $CDCl_3$ or d_4-MeOD (ESI†). The chemical shifts are reported in ppm relative to TMS as the internal standard or to the solvent residual peak. GC conversions were determined using external calibration curves established with commercial standards of ethanediol, 1,2-propanediol, 1,2,3-propanetriol, 3-methoxy-1,2-propanediol, 1,2-butanediol, and 3-butene-1,2-diol. GC yields were determined using external calibration curves established with commercial standards of 1,3-dioxolan-2-one, 4-methyl-1,3-dioxolan-2-one, 4-hydroxymethyl-1,3-dioxolan-2-one, 4-methoxymethyl-1,3-dioxolan-2-one, 4-ethyl-1,3-dioxolan-2-one, 4-vinyl-1,3-dioxolan-2-one, 2,3-epoxy-1-propanol and a synthesized sample of methyl ((2-oxo-1,3-dioxolan-4-yl)methyl) carbonate. 4-Hexyl-1,3-dioxolan-2-one, 4-(*tert*-butoxymethyl)-1,3-dioxolan-2-one, 4-((allyloxy)methyl)-1,3-dioxolan-2-one, 4-((prop-2-yn-1-yloxy)methyl)-1,3-dioxolan-2-one, 4-((furan-2-ylmethoxy)methyl)-1,3-dioxolan-2-one, 4-((*o*-tolyloxy)methyl)-1,3-dioxolan-2-one, 4-((dimethylamino)methyl)-1,3-dioxolan-2-one, 4-(morpholinomethyl)-1,3-dioxolan-2-one, 4,5-dimethyl-1,3-dioxolan-2-one, *cis*-hexahydro-1,3-benzodioxol-2-one, 2-hydroxycyclohexyl methyl carbonate, tetrahydrofuro[3,4-*d*][1,3]dioxol-2-one, 4,4′-((butane-1,4-diylbis(oxy))bis(methylene))bis(1,3-dioxolan-2-one) and 4,4′-(((furan-2,5-diylbis(methylene))bis(oxy))-bis(methylene))bis(1,3-dioxolan-2-one) yields were determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

Typical run 1: microscale synthesis of glycerol carbonate (1a) from commercial glycerol

The syringe pump used to deliver the solution of glycerol (**4a**) containing 3.5 mol% of NBu_4Br was set to 67.2 μL min^{-1} (1 equiv. of **4a**) and the syringe pump used to deliver neat DMC was set to 154 μL min^{-1} (2.25 equiv.). Both streams were mixed through a PEEK T-mixer, and the biphasic mixture entered a 1/16″ o.d. SS coil (0.67 mL, 3 min of residence) heated at 180 °C. The outlet of the reactor was connected to a dome-type back pressure regulator set at 11 bar (Fig. 5). After equilibration, the reactor effluent was collected, diluted with EtOH, and analyzed by GC/FID (**4a** conv. = 95%, **1a** yield = 75%, see Fig. 5).

Typical run 2: microscale synthesis of glycerol carbonate (1a) from crude bio-based glycerol

Crude bio-based glycerol was filtered prior to use. The syringe pump used to deliver the solution of crude bio-based glycerol (**4a**) containing 3.5 mol% of NBu_4Br was set to 212 μL min^{-1} (1 equiv. of **4a**) and the syringe pump used to deliver neat DMC was set to 411 μL min^{-1} (2.25 equiv.). Both streams were mixed through a PEEK T-mixer, and the biphasic mixture entered a 1/8″ o.d. SS coil (1.87 mL, 3 min of residence) heated at 180 °C. The outlet of the reactor was connected to a dome-type back pressure regulator set at 11 bar. After equilibration, the reactor effluent was collected, diluted with EtOH, and analyzed by GC/FID (**4a** conv. = 30%, **1a** yield = 29%, see Table 5, entry 3).

Typical run 3: microscale synthesis of 4-((*o*-tolyloxy)methyl)-1,3-dioxolan-2-one (1l)

The HPLC pump used to deliver the feed solution of mephesin (**2l**, 3 M) and NBu_4Br (0.105 M) in DMSO was set to 222 μL min^{-1} (1 equiv. of **2l**). The HPLC pump used to deliver neat DMC was set to 168 μL min^{-1} (3 equiv.). Both streams were mixed through a PEEK T-mixer, and the mixture entered a 1/16″ o.d. SS coil (1.17 mL, 3 min of residence) heated at 180 °C. The outlet of the reactor was connected to a dome-type back pressure regulator set at 11 bar (Fig. 5). After equilibration, the reactor effluent was collected and analyzed by ^{1}H NMR with mesitylene as the internal standard (**1l** yield = 86%, see Fig. 5).

Typical run 4: pilot-scale synthesis of glycerol carbonate (1a)

The pump used to deliver the preheated (60 °C) feedstock solution of glycerol (**4a**) containing 3.5 mol% of NBu4Br was

set to 10.9 g min^{-1} (1 equiv. of **4a**), and the pump used to deliver the feedstock solution of DMC was set to 21.4 g min^{-1} (2.25 equiv.). Both streams came into contact in the first FM of the Corning® Advanced-Flow™ G1 SiC reactor operated at 180 °C, and further reacted in the 5 other FMs, also operated at 180 °C (2 min residence time, 60 mL total internal volume, see Fig. 7). The outlet of the reactor consisted of a 1/4″ o.d. PFA cooling loop immersed in a water bath and connected to a dome-type back pressure regulator set at 11 bar. After equilibration, the reactor effluent was collected, diluted with EtOH and analyzed by GC/FID (**4a** conv. = 95%, **1a** yield = 76%).

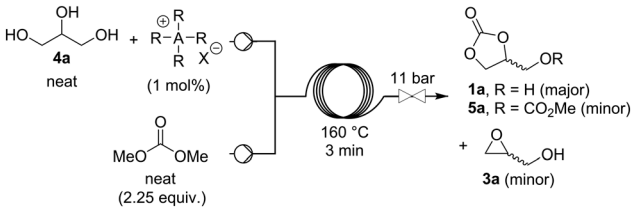


Fig. 2 Schematic continuous flow setup for the carbonation of glycerol (**4a**) with dimethyl carbonate.

Results and discussion

Screening of organic salts as catalysts

The investigation began by screening different organic salts for the model carbonation of neat glycerol (**4a**) with DMC under continuous flow conditions. Several complex and expensive ionic liquids/organic salts are already described as efficient catalysts for this reaction in batch[46–51] and flow.[41] Only cheap and commercially available catalytic materials were considered in the present work (Table 3). Organic salts featuring a hydroxide anion are in general air-sensitive, and were thus not considered. For solubility reasons, the catalysts were typically loaded within the glycerol feedstock solution. Neat DMC was handled as a separate feed since it forms a heterogeneous mixture with **4a**. Both liquid feeds were mixed through a T-mixer and reacted in a heated stainless-steel (SS) capillary coil (Fig. 2). A back pressure regulator (BPR) was inserted downstream the SS coil to maintain the reactor under a counterpressure of 11 bar. Quantitative analyses were carried out by off-line GC/FID analysis of the crude reactor effluent (ESI,† section S2.2). Under these conditions, glycerol carbonate (**1a**) was the major product, although the reaction mixture also contained minor side-products including glycidol (**3a**) and methyl ((2-oxo-1,3-dioxolan-4-yl)methyl) carbonate (**5a**). Although **5a** has no commercial application, **3a** is a high-value added building block, and several reports studied the upgrading of glycerol into glycidol using glycerol carbonate as the reaction intermediate.[47,52–54]

Table 3 Evaluation of organic salts as catalysts for the conversion of glycerol (**4a**) into glycerol carbonate (**1a**)

Entry[a]	Catalyst	**4a** conv.[b] (%)	**1a** selec.[b] (%)
1	—	5	87
2	**NBu_4Br**	**63**	**95**
3	NMe_4Br	56	92
4	NEt_4Br	61	90
5	PMe_4Br	59	91
6	PBu_4Br	59	87
7	PPh_4Br	58	88
8	NBu_4Cl	59	89
9	$NBu_4(OAc)$	58	88
10[c]	$NBu_4(OTf)$	0	—
11[c]	NBu_4BF_4	0	—
12[c]	NBu_4PF_6	5	99

[a] Process conditions are described in Fig. 2. [b] Conversion and yield were determined by GC/FID. [c] The catalyst is insoluble in glycerol and was dissolved in the DMC feedstock solution.

Initial conditions involved a residence time of 3 min, a reactor temperature of 160 °C, 2.25 equiv. of DMC, and 1 mol% of organic salt catalyst. A control experiment without a catalyst yielded a mere 5% glycerol conversion (Table 3, entry 1). Tetrabutylammonium bromide served as a reference catalyst,[44] and afforded glycerol carbonate (**1a**) with 63% conversion and 95% selectivity (entry 2). Within the ammonium bromides, short or long alkyl chains gave overall similar results in terms of conversion (56–63%) and selectivity (90–95%, entries 2–4). Tetraoctylammonium bromide was insoluble in both feeds and could not be assessed. Similarly, phosphonium bromides of various bulkiness gave glycerol conversion in the 58–59% range and a selectivity varying between 87 and 91% (entries 5–7).

The nature of the anion impacted significantly the catalytic activity. Changing the anion from bromide to chloride had only a minor effect on both conversion (59%) and selectivity (89%, entry 8). Tetrabutylammonium iodide and tetrabutylammonium 2-hydroxybenzoate were insoluble in both feeds and could not be assessed.

Tetrabutylammonium acetate [$NBu_4(OAc)$] gave results similar to those of NBu_4Br, with 58% conversion and 88% selectivity (entry 9). On the other hand, non-coordinating anions such as triflate ($CF_3SO_3^-$, OTf), tetrafluoroborate (BF_4^-) and hexafluorophosphate (PF_6^-) were barely active as catalysts (entries 10–12). Similar observations were reported by Sairi *et al.* in relation to the catalytic efficiency of various ionic liquids for the conversion of **4a** into **1a** with DEC. Increasing the hydrogen-bonding ability of the anion improved the activity of the catalyst. For instance, the authors reported that 1-butyl-3-methylimidazolium tetrafluoroborate gave a mere <5% glycerol conversion, while 1-ethyl-3-methylimidazolium acetate gave 94% conversion under the same conditions (120 °C, 2 h, 0.5 mol% of catalyst, and 2 equiv. of DEC).[48] Gu and coworkers reported that the catalytic activity of hydroxypropyl-tripentylammonium hydroxide and halides for the conversion of **4a** into **1a** increased with the basicity of the anion. The yield of **1a** as a function of the anion nature followed the order: OH^- (83%) > Cl^- (21%) = Br^- (21%) > I^- (11%), under identical reaction conditions (80 °C, 90 min, 0.9 mol% of catalyst, and 2 equiv. of DMC).[49] Reports by Kelkar and Selva on the carbonation of alcohols with DMC catalyzed by ionic liquids suggested that both the nature of the anion and of the cation dictate the catalytic activity. A

nucleophilic and electrophilic activation was proposed, where the anion and the cation activate the alcohol and carbonyl moieties, respectively.[53,55] By contrast, Gu and coworkers showed by FTIR the absence of interaction between a propyl-tripentylammonium cation and the carbonyl moiety of DMC.[49] Among the organic salts evaluated in the present work, the nature of the anion dramatically influenced the catalytic activity, while the nature of the cation did not significantly influence the outcome of the reaction. The highest yield of **1a** (60%) was obtained with tetrabutylammonium bromide.

Process optimization

The parameters influencing the carbonation of glycerol (**4a**) with DMC were next evaluated. The optimization concerned the residence time, the temperature and the loading of NBu_4Br, using different molar ratios between DMC and **4a**.

Preliminary trials were carried out at 160 °C with a residence time of 3 min and an increasing DMC/**4a** ratio (1.4, 1.7 or 2.25). The effect of the catalytic loading (1, 2, 3.5 or 5 mol%) on the reaction was investigated. This parameter affected both conversion and selectivity (Fig. 3). Increasing the molar amount of NBu_4Br in the glycerol feed from 1 to 5 mol% raised the conversion from 45 to 68% (with 1.4 equiv. of DMC), from 50 to 74% (with 1.7 equiv. of DMC), and from 63 to 85% (with 2.25 equiv. of DMC). Although it had a positive impact on the conversion, the increase in NBu_4Br loading decreased the selectivity for glycerol carbonate (**1a**). It declined from 93 to 84% (with 1.4 equiv. of DMC), from 92 to 82% (with 1.7 equiv. of DMC), and from 95 to 80% (with 2.25 equiv. of DMC). The decrease in selectivity for **1a** indicates the increasing formation of other side-products. The formation of glycidol (**3a**) increased with larger catalytic loadings. The selectivity for **3a** evolved with the catalytic loading from 1.8 to 7.4% (with 1.4 equiv. of DMC), from 2.9 to 8.5% (with 1.7 equiv. of DMC), and from 1.1 to 7.8% (with 2.25 equiv. of DMC). A similar impact of the catalytic loading on the selectivity for **1a** and **3a** was observed by others using various ionic liquids as catalysts for the reaction between glycerol and DMC/DEC.[47,48,52–54] The carbonation of glycerol with DMC/DEC toward **1a** and the decarboxylation of **1a** into glycidol are consecutive reactions that are both catalyzed by compounds with hydrogen bonding ability or basic sites. It is therefore expected that an increase in the catalytic loading leads to an increase in selectivity for side-product **3a**. The selectivity for methyl ((2-oxo-1,3-dioxolan-4-yl)methyl) carbonate (**5a**) remained low (in the 0.1–1.2% range), regardless of the conditions utilized. While slightly higher yields were obtained with a 5 mol% loading of NBu_4Br, 3.5 mol% gave a good balance between conversion, selectivity and cost-efficiency, and it was defined as the optimized value for further optimization.

Next, the influence of the residence time on the reaction was investigated (ESI,† section S2.3.1). An increase from 3 to 5 min merely improved the conversion of glycerol (**4a**), irrespective of the DMC/**4a** molar ratio. Similarly, the selectivity for **1a** was not affected by the residence time or the excess of DMC. The selectivity for glycidol (**3a**) decreased with the increase in residence time, which might be rationalized by degradation reactions of **3a**, such as oligomerization.[56] The selectivity for compound **5a** followed an opposite trend, slightly increasing with the residence time.[21] A residence time of 3 min was selected as the optimized value, giving the highest productivity for **1a** (0.78 mol per day with 2.25 equiv. of DMC).

The influence of the temperature (150–180 °C) was also evaluated (ESI,† section S2.3.2). Increasing the temperature improved the conversion of glycerol (**4a**), but had no significant effect on the selectivity for glycerol carbonate (**1a**) and for glycidol (**3a**).[52,54] By contrast, the selectivity for side-product **5a** slightly increased with the temperature.[21]

To sum up this round of optimizations, the highest productivity for glycerol carbonate (95% conversion, 79% selectivity, 0.85 mol per day) was obtained at 180 °C within 3 min of residence in the presence of 3.5 mol% of NBu_4Br and 2.25 equiv. of DMC.

Purification

Although glycerol carbonate can be purified by vacuum distillation, the low volatility of **1a** (b.p. = 145–148 °C at 0.2 mmHg (ref. 41)) makes the procedure energy-intensive. In our hands, vacuum distillation of a crude reactor effluent yielded only glycidol (**3a**) through NBu_4Br-catalyzed decarboxylation of **1a**.[47,52–54] An alternative purification procedure was sought and a liquid–liquid extraction procedure was devised[57] to

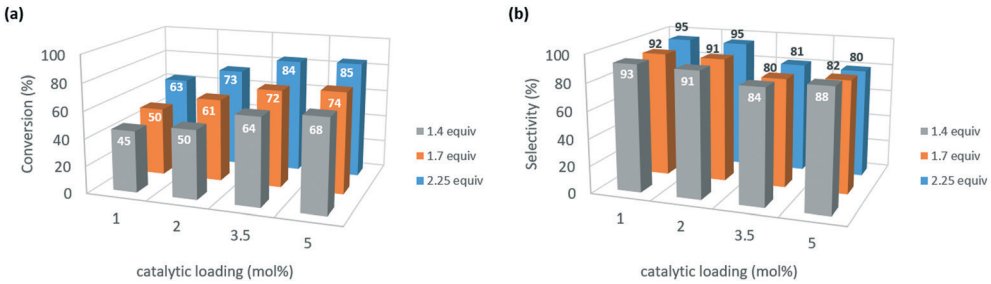


Fig. 3 Evolution of (a) glycerol conversion and (b) glycerol carbonate selectivity as a function of the NBu_4Br loading and the excess of dimethyl carbonate. Conditions: T = 160 °C, residence time = 3 min, P = 11 bar.

Table 4 Optimization of the purification of glycerol carbonate (**1a**) by liquid–liquid extraction

Entry[a]	Organic solvent	Aqueous phase[b]	Volume of organic solvent	Amount of compound extracted in the organic solvent (%)				
				1a	**3a**	**4a**	**5a**	NBu_4Br
1	MIBK	NaCl 1 wt%	3 × 5 mL	90	85	11	>99.9	98
2	AcOPr	H_2O	3 × 5 mL	79	76	0	95	59
3	AcOBu	H_2O	3 × 5 mL	47	—[c]	0	>99.9	16
4	AcOBu	NaCl 1 wt%	3 × 5 mL	60	—[c]	0	>99.9	28
5	CH_2Cl_2	H_2O	3 × 5 mL	53	71	0	>99.9	98.7
6	$CHCl_3$	H_2O	3 × 5 mL	34	42	0	>99.9	94
7	**$CHCl_3$**	**H_2O**	**1 × 3 mL**	**20**	**43**	**0**	**81**	**83**
8	Et_2O	H_2O	3 × 5 mL	15	37	0	40	8
9	MTBE	H_2O	3 × 5 mL	29	51	0	68	5
10	Toluene	H_2O	3 × 5 mL	8	11	0	50	1.6

AcOBu = *n*-butyl acetate, AcOPr = *n*-propyl acetate, Et_2O = diethyl ether, MIBK = methyl isobutyl ketone, MTBE = methyl *tert*-butyl ether. [a] See ESI, section S2.4 for the detailed procedure. [b] Volume = 1 mL. [c] Not determined.

separate unconverted **4a**, side-products **3a** and **5a**, and NBu_4Br from the target compound **1a**. A model solution containing the above-mentioned compounds was prepared, and several extraction solvents were screened (Table 4 and ESI,† section S2.4). Glycerol (**4a**) was quantitatively retained in the aqueous phase, irrespective of the organic solvent utilized. Only MIBK was able to extract a small fraction (11%) of **4a** from the aqueous phase (entry 1). By contrast, side-product **5a** was efficiently extracted (68–99.9%) by most solvents (entries 1–7, 9) except for diethyl ether and toluene (40% and 50% extracted, entries 8 and 10, respectively). In general, oxygenated solvents, such as *n*-propyl acetate, *n*-butyl acetate, diethyl ether and MTBE, were slightly more efficient for the extraction of glycerol carbonate (**1a**) and glycidol (**3a**) than that of NBu_4Br (entries 2–4, 8–9). Chlorinated solvents gave the most interesting results, as they were able to selectively extract NBu_4Br, while retaining most of **1a** in the aqueous phase (entries 5–7). Upon optimization of the extraction volumes, chloroform enabled extraction of 83% of tetrabutylammonium bromide, while retaining 80% of **1a** in the aqueous phase (entry 7).

Based on these results, we applied the methodology on a crude reactor effluent (ESI,† section S2.5). At first, excess DMC and by-product MeOH were removed under reduced pressure. Then, the crude was diluted with water and washed with $CHCl_3$ to remove side-product **5a** as well as NBu_4Br. The chloroform phase could be further processed to recycle the catalyst. The aqueous phase was then loaded with 1 wt% of NaCl, and glycerol carbonate was extracted with MIBK, enabling its separation from unconverted **4a**. Eventually, **1a** was obtained in 60% yield (based on glycerol) after removal of MIBK under reduced pressure. The target compound was contaminated with traces of **3a** (3.1 mol% with respect to **1a**), **4a** (2.7 mol% with respect to **1a**), **5a** (0.6 mol% with respect to **1a**) and NBu_4Br (1.9 mol% with respect to **1a**).

Overall, our methodology not only enabled the purification of glycerol carbonate without vacuum distillation or column chromatography, but was also amenable to the partial recycling and purification of the homogeneous catalyst.

Extension to refined and crude bio-based glycerol

Glycerol is a by-product from the soap, fatty acid and biodiesel industries, and there is a significant difference in price between crude and refined glycerol. In 2013–2014, prices of crude and refined glycerol were about 240 USD per ton and 900–965 USD per ton, respectively.[31] Refined glycerol remains the privileged substrate in the primary literature, but there is considerable economic interest in the direct upgrading of crude **4a**. In this context, we assessed our conditions on samples of refined and crude bio-based glycerol (Table 5). As expected, the sample of refined bio-based glycerol afforded conversion (96%) and selectivity (78%) similar to those of the commercial sample utilized for the process optimization (entries 1–2). Samples of crude **4a** containing various amounts of water, methanol, salts and organic matter (ESI,† Tables S4 and S5) yielded the target compound **1a** with a significantly lower conversion (30 and 44%, entries 3 and 4). On the other hand, the selectivity for glycerol carbonate (**1a**) was excellent

Table 5 Assessment of bio-based glycerol samples for the preparation of glycerol carbonate (**1a**)

Entry[a]	Glycerol supplier	Glycerol grade (purity)	**4a** conv.[b] (%)	**1a** selec.[b] (%)
1	Honeywell	Commercial	95	79
2	Cargill	Refined bio-based (99.5%)	96	78
3	Cargill	Crude bio-based (85%)	30	98
4	Valtris Champlor SAS	Crude bio-based (84%)	44	71

[a] Process conditions: temperature = 180 °C, residence time = 3 min, 3.5 mol% of NBu_4Br, 2.25 equiv. of DMC, P = 11 bar. [b] Conversion and yield were determined by GC/FID.

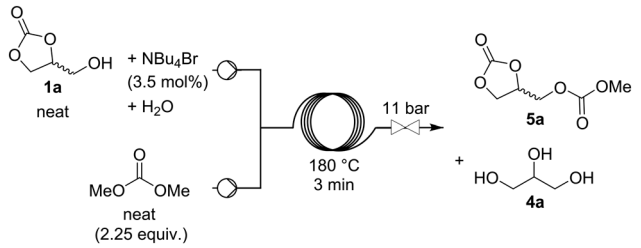


Fig. 4 Continuous flow setup for the assessment of the stability of glycerol carbonate (**1a**) in the presence of water.

with the sample from Cargill (98%, entry 3) and good with the sample from Valtris Champlor SAS (71%, entry 4). In the latter case, the lower selectivity could not be ascribed to the formation of volatile side-products, since only **4a** and **1a** were detected by GC/FID.

Water is present in significant amounts in the crude samples of glycerol and most likely influences the reaction in a negative way. It probably (a) competes with the alcohol moieties of **4a** in binding with the anion of the catalyst, (b) hampers the mass transfer between glycerol and the dimethyl carbonate phase (especially in the presence of salts), and (c) hydrolyses glycerol carbonate (**1a**) back into glycerol (**4a**). A consequence of the hydrolysis of **1a** is the formation of CO_2 as a gaseous by-product, decreasing the residence time of the liquid phase within the reactor. An important evolution of gas was indeed released after the back pressure regulator. Methanol is present in low amounts in the samples of crude glycerol assessed and likely does not influence the equilibrium of the reaction significantly. The detrimental effect of water on the conversion of glycerol into glycerol carbonate was also reported by other authors.[41,52,58,59] To evaluate the significance of **1a** hydrolysis on the outcome of the reaction, several control experiments were performed under the optimized conditions with glycerol carbonate as the substrate in the presence of increasing amounts of water (Fig. 4 and Table 6). Reacting **1a** with DMC in the absence of water yielded methyl ((2-oxo-1,3-dioxolan-4-yl)methyl) carbonate (**5a**) as the main product (21% yield, entry 1). Increasing the amount of water in the feedstock solution of **1a** from 2.5 to 10 wt% decreased the yield of **5a** from 12% to 0% (entries 2–4).

By contrast, increasing the water content from 2.5 wt% to 20 wt% triggered the hydrolysis of **1a** into glycerol up to 43% (entries 2–5). These results suggest that the hydrolysis of **1a** significantly contributes to decreasing the conversion with crude glycerol. Overall, the process would require some re-optimization to attain high conversion of **4a**, but is viable for the upgrading of crude bio-based glycerol.

Table 6 Assessment of the stability of glycerol carbonate (**1a**) in the presence of dimethyl carbonate and an increasing amount of water

Entry[a]	Water content[b] (wt%)	**1a** conv.[c] (%)	**5a** yield[c] (%)	**4a** yield[c] (%)
1	0	28	21	0
2	2.5	14	12	0
3	5	4.6	1.2	2.5
4	10	9	0	9
5	20	43	0	43

[a] Process conditions are described in Fig. 4. [b] Relative to glycerol carbonate. [c] Conversion and yield were determined by GC/FID.

Substrate scope

With the best conditions and catalyst in hand, the scope of the reaction was extended to a large variety of 1,2-diols (ESI,† Table S6). Simple 1,3-dioxolan-2-ones, such as propylene (**1c**) and 1,2-butylene (**1d**) carbonates, were obtained with unsatisfactory conversion of the starting material (77 and 79%, respectively). The process conditions were thus slightly adapted. Increasing the DMC/diol molar ratio from 2.25 to 3 gave excellent results on diol **2c** (conv. = 95%, selec. = 98%) and **2d** (conv. = 98%, selec. = 92%). These adapted conditions were next applied to a wide range of 1,2-diols **2b–t** (Fig. 5). Liquid diols **2b–d**, **2f–k**, **2m–o** and **2r**, **s** were processed under neat conditions, while feed solutions of solid diols **2e**, **2l**, **2p**, **2q** and **2t** were prepared in DMSO (1–4 M) to ensure continuous operation.

Very high to excellent yields (82–93%) were obtained for the preparation of 1,3-dioxolan-2-ones of types **1b–e** with increasing carbon chain length. 3-Butene-1,2-diol (**2f**), which can be sourced from bio-based erythritol,[60] was somehow less reactive and gave vinyl ethylene carbonate (**1f**) in 68% yield. A two-fold increase in the residence time merely improved the yield (71%). The scope also encompassed a wide range of glycerol ethers **2g–l**, which have a promising forecast as versatile renewable building blocks.[56] Methyl (**1g**, 91%), *tert*-butyl (**1h**, 86%), allyl (**1i**, 95%), propargyl (**1j**, 78%), furfuryl[61] (**1k**, 85%) and *o*-tolyl (**1l**, 86%) ethers of glycerol carbonate were obtained in high to excellent yields. The preparation of furfuryl ether **1k** in high yield required a longer residence (9 min). Introduction of a dimethylamino or morpholino group vicinal of the 1,2-diol pattern did not alter its reactivity, and carbonates **1m** and **1n** were obtained in 82% and 92% yields, respectively. A previous report utilizing urea as a carbonation reagent reported only 15% yield for carbonate **1m**,[19] while another study described the synthesis of compound **1n** in 99% yield upon utilization of DMC as the reagent.[24] 2,3-Butanediol (**2o**) was found to be less reactive than the parent 1,2-butanediol (**2d**) under these conditions, and 4,5-dimethyl-1,3-dioxolan-2-one (**1o**) was obtained in 45% yield.[21] A further increase of the residence time to 6 min slightly increased the yield to 51%. The presence of two secondary alcohols that are not cycle-strained in a relative *cis*-configuration (see below) most likely accounted for the lower reactivity of diol **2o** toward DMC.[55] *cis*-Cyclohexanediol (**2p**) was converted into the target cyclic carbonate **1p** in good yield (73%). On the other hand, a control experiment on *trans*-cyclohexanediol (**2q**) yielded methyl carbonate **1q** as the main product in 46%, emphasizing that a relative *cis*-configuration is required for the reaction to proceed on cycle-strained diols. An analogous observation was made by Beller *et al.* upon reacting *trans*-cyclopentanediol with urea, which

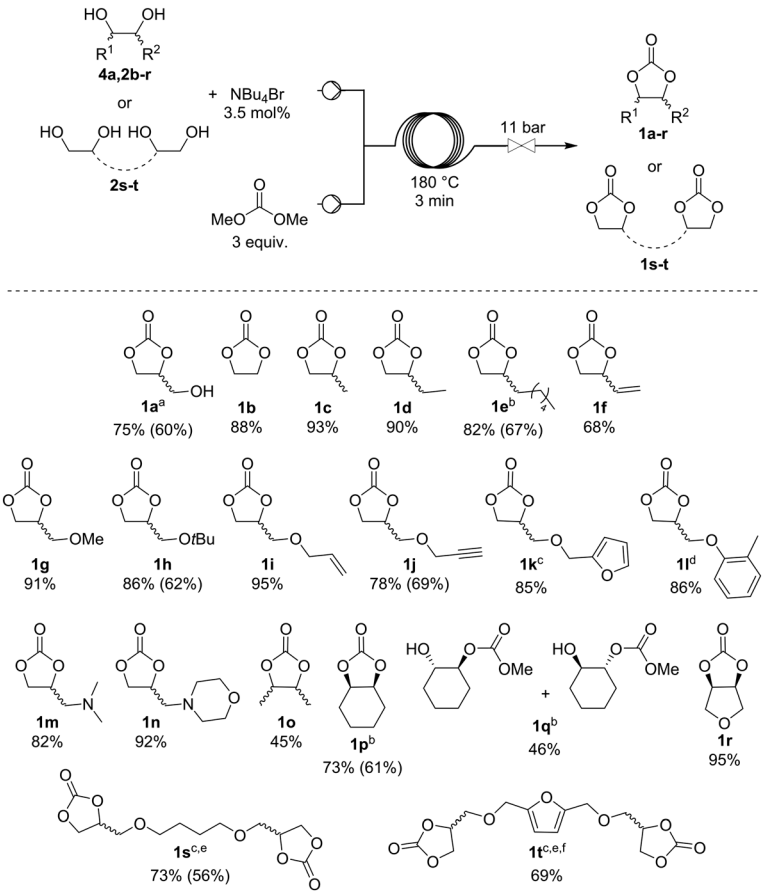


Fig. 5 Substrate scope for the carbonation of 1,2-diols **4a**, **2b**–**t** toward cyclic carbonates **1a**–**t**. Unless otherwise specified, the diol + catalyst feedstock solution was pumped neat. Yields were determined by GC/FID or by ^{1}H NMR with mesitylene as the internal standard (isolated yields are indicated in parentheses). [a] 2.25 equiv. of DMC. [b] The diol was pumped as a 4 M solution in DMSO. [c] Residence time = 9 min. [d] **2l** was pumped as a 3 M solution in DMSO. [e] 3.5 mol% of NBu_4Br and 3 equiv. of DMC per 1,2-diol functional group. [f] **2t** was pumped as a 1 M solution in DMSO.

yielded the corresponding carbamate as the main product.[19] Bio-based anhydroerythritol (**2r**), bearing also a vicinal diol in a relative *cis* configuration, was carbonated into the corresponding bicyclic 1,3-dioxolan-2-one **1r** in excellent 95% yield. Lastly, we considered the preparation of dicarbonates **1s** and **1t** that are potential bio-based monomers for polyurethanes.[3–5,8] Preliminary experiments (ESI,† Table S6) on diol **2s** evidenced that a residence time of 9 min was necessary to afford dicarbonate **1s** in good yield (73%). Applying the same conditions to **2t** yielded the hydroxymethylfurfural-derived dicarbonate **1t** in 69%.

In-line NMR monitoring

Real-time analysis for pollution prevention is one of the twelve principles of green chemistry.[62] In-line NMR has recently emerged as a versatile tool for real-time analytical monitoring of continuous processes.[21,63] In this context, a low-field in-line benchtop NMR spectrometer was inserted downstream the reactor, and the temperature of the reactor was progressively decreased from 180 to 100 °C. These control experiments were implemented to mimic a possible process failure, and thus evaluate the potential for real-time qualitative process monitoring. The spectra acquired during the carbonation of **2c** into propylene carbonate (**1c**) are depicted in Fig. 6. The doublet at 0.8 ppm was used as a probe of the concentration of **2c**, while the doublet at 1.2 ppm and the multiplet at 3.7–4.8 ppm enabled the monitoring of carbonate **1c**. GC/FID was utilized as a complementary tool to obtain

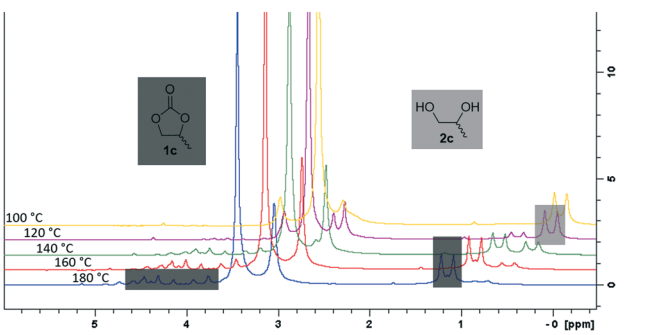


Fig. 6 Representative low-field in-line NMR spectra obtained during the carbonation of **2c** into **1c** in the 100–180 °C range. The doublet at 0.8 ppm was used to monitor the variation of **2c** concentration (light grey). The doublet at 1.2 ppm and the multiplet at 3.7–4.8 ppm were used to monitor the variation of **1c** concentration (dark grey). Conditions: residence time = 3 min, P = 11 bar, 3.5 mol% of NBu_4Br, 3 equiv. of DMC.

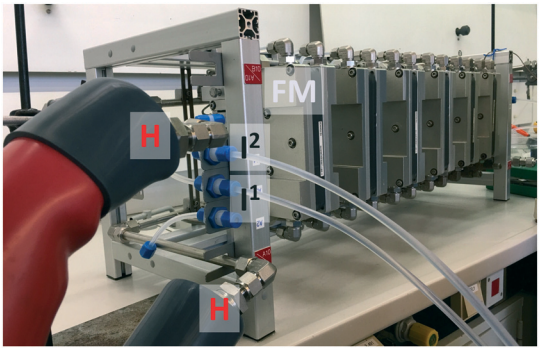


Fig. 7 Photograph of the Corning® Advanced Flow™ G1 SiC reactor. Key: H = inlet and outlet for the heat exchanging fluid; I^1 = inlet for DMC; I^2 = inlet for preheated glycerol and NBu_4Br; FM = fluidic module.

quantitative results (ESI,† Table S6) and similar trends were observed. However, sample preparation and a prolonged analysis time were required for GC/FID, while in-line NMR analysis provided real-time qualitative monitoring of the carbonation procedure. This approach was also extended to the carbonation of diols **2b** and **2d** (ESI,† Fig. S8 and S9).

Scale-up

The scalability of this procedure was assessed in a commercial pilot-scale continuous flow reactor (Corning® Advanced Flow™ G1 SiC reactor, Fig. 7) of 60 mL internal volume. The reactor featured 6 silicon carbide (SiC) fluidic modules (FMs) of 10 mL internal volume each, connected in series and integrated with heat exchangers. Glycerol (**4a**) was selected as the model substrate, since **1a** is the most industrially relevant target. The same process conditions as those on the microscale (180 °C, 3 min, 3.5 mol% of NBu_4Br, and 2.25 equiv. of DMC) were initially applied, and similar results (**4a** conversion = 98%, **1a** selectivity = 74%) were obtained, corresponding to a 9.0 kg per day (76.4 mol per day) productivity for glycerol carbonate (**1a**). In order to further increase the productivity, the residence time was lowered to 2 min, and excellent results were obtained as well (**4a** conversion = 95%, **1a** selectivity = 80%). This data point corresponds to a daily productivity of 115 mol (13.6 kg) in carbonate **1a**, demonstrating the potential application to the industrial scale.

Conclusion

This work reports a robust and low-footprint continuous flow procedure for the carbonation of various 1,2-diols toward 5-membered cyclic organic carbonates (1,3-dioxolan-2-ones). Dimethyl carbonate is utilized as a low-toxicity reagent, and tetrabutylammonium bromide as a cheap and widely available homogeneous catalyst. The conditions feature a low catalytic loading (3.5 mol%), short reaction times (3–9 min) and solvent-free or highly concentrated media. The reaction conditions were optimized on the model synthesis of glycerol carbonate, affording the target compound in 79% selectivity with 95% conversion. Glycerol carbonate was purified and the homogeneous catalyst was partially recovered by a straightforward liquid–liquid extraction protocol. Refined and crude bio-based glycerol were also evaluated as substrates, and promising results were obtained. Control experiments on glycerol carbonate suggested that hydrolysis of glycerol carbonate becomes significant when water is present in the medium at a high level. By contrast to the prior Art, the methodology was extended to a wide palette of substrates (20 examples, broad molecular diversity) that were converted in overall good to excellent yields (45–95%). The efficiency of low-field in-line NMR for real-time analytical monitoring of the process was exemplified. The scalability of the procedure for the carbonation of glycerol was next documented in a pilot-scale continuous flow reactor of 60 mL internal volume, and similar results to those on the microscale were obtained. The pilot-scale reactor yielded a daily productivity of 115 mol (13.6 kg) of glycerol carbonate.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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