Published in : Green Chemistry (2025), vol. 27, pp. 722–730
DOI: 10.1039/d4gc05716c
Status : Postprint (Author's version)

RAPID CO2 COUPLING TO PROPARGYLIC ALCOHOLS: UNLOCKING THE PRODUCTION OF A-ALKYLIDENE CYCLIC CARBONATES VIA CONTINUOUS FLOW†

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† Electronic supplementary information (ESI) available: Experimental details, characterizations of catalysts and products, setups details, metrics calculation. See DOI: https://doi.org/10.1039/d4gc05716c

ABSTRACT

α-Alkylidene cyclic carbonates (αCCs) are gaining interest as building blocks in organic and polymer chemistry. To date, their synthesis via the coupling of CO_2 to propargylic alcohols has been restricted to batch processes, with extensive efforts devoted to improving catalytic systems. Herein, utilizing a refined, homogeneous silver–carbene–organobase catalytic system, we optimized batch conditions to achieve, for the first time, complete conversion of tertiary propargylic alcohols within minutes instead of hours. Building on this, we introduce a continuous flow methodology to produce a library of αCCs, achieving the highest space–time yields reported, with quantitative conversions in less than 20 minutes and outputs up to 111 grams per day. This approach reduces CO_2 usage to 1 or 2 equivalents, improves parameter control, and is expected to facilitate scalability. In addition, "plug-and-play" lab-scale continuous flow modules enable seamless integration of subsequent αCC transformations without intermediate purification, as illustrated by the aminolysis of αCCs into oxazolidones with good conversion (91%). Furthermore, supporting the silver–carbene catalyst on a polymer matrix eliminates silver contamination and even suppresses the need for a base co-catalyst. This work advances the scalable synthesis of αCCs via continuous flow, marking a significant step toward greener, CO_2-based cyclic carbonates and derivatives.

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Introduction

In the context of fossil resource depletion, global warming and rising environmental concerns, the use of CO_2 as a local and inexhaustible C1 building block to synthesize commodity chemicals (e.g., methanol, urea, formic acid, and methane) and advanced products with high added value, such as organic carbonates and polymers, is rapidly expanding.[1–6] Several pathways have been developed to valorise CO_2, with one of the most promising being the coupling of CO_2 to propargylic alcohols to afford α-alkylidene cyclic carbonates (αCCs), highly reactive building blocks for organic and polymer chemistries.[4,7] The presence of an exocyclic olefinic bond facilitates the regioselective ring opening of αCCs by primary or secondary amines, alcohols and thiols, yielding the corresponding hydroxy-oxazolidone, oxo-urethane, oxo-carbonate, and oxo-thiocarbonate moieties (Scheme S1†).[8,9] This was recently exploited in macromolecular chemistry to produce poly(hydroxyurethane)s, poly(oxo-urethane)s, poly(oxo-carbon- ate)s, poly(hydroxy-oxazolidone)s, and sulfur-containing polymers under mild operating conditions.[9–15]

Carbon dioxide is well known to be a low-reactivity substrate, and its addition to propargylic alcohols requires catalysis.[4,16,17] While a base activates the alcohol to facilitate the CO_2 fixation and affords the desired αCC by ring closure, this generally requires high temperatures (60–100 °C) and/or high CO_2 pressures (>15 bar) to achieve quantitative conversion within a few hours.[4,16,17] Organocatalysts, particularly ionic liquids and N-heterocyclic carbenes (NHCs) or N-heterocyclic olefins, have been extensively studied for the addition of CO_2 to propargylic alcohols.[18-35] Concomitantly, dual alcohol and alkyne activation has been developed using a base in synergy with a metal cocatalyst.[4] Metals such as cobalt,[36] zinc[37-39] and copper[40-44] have been reported, but silver complexes/salts display generally the best catalytic activities, while being efficient at low CO_2 pressure and temperature with low catalyst loading.[45-65] Notably, tertiary propargyl alcohols are the easiest to convert due to Thorpe–Ingold effect, and the resulting cyclic carbonates are less prone to opening by the initial alcohol substrate or water contaminant.[66,67]

The production of αCCs is currently limited to laboratory-scale batch processes, typically yielding only a few grams per experiment.[4] Scaling up the carbonation of propargylic alcohols presents significant challenges due to the need for pressurized reactors and the laborious process of assembling and disassembling the reactor. To date, no research has leveraged continuous flow chemistry for the fast synthesis of αCCs. This is likely due to the main limitations: (a) homogeneous catalysts are scarce, with minimal research in this area except for Schaub's work suggesting potential catalytic solutions;[51,59] (b) the developed systems are not able to

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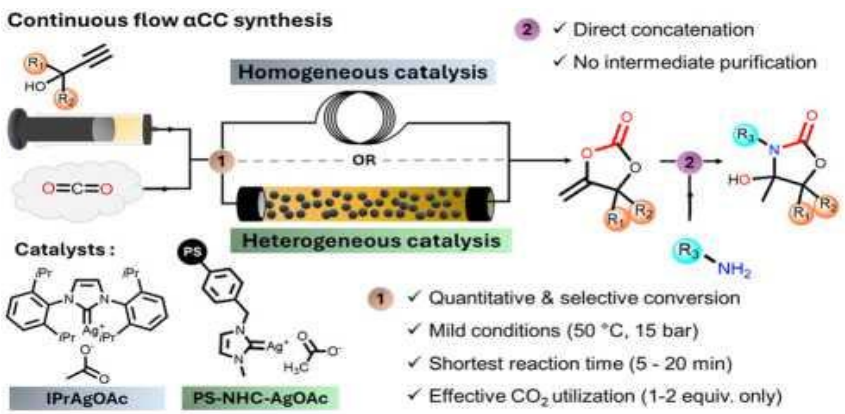
quantitatively convert propargylic alcohols within a short time (ideally a few minutes), a prerequisite for effective continuous flow chemistry; and (c) the difficulty of managing gas–liquid biphasic systems in flow, given the poor solubility of CO_2 in most organic solvents. However, achieving continuous flow production offers numerous advantages. These include (a) the use of only the necessary equimolar amount of CO_2 rather than large excesses as in batch, (b) better control over the reaction exothermicity to minimize side reactions (e.g. hydrolysis or nucleophilic addition by the alcohol precursor), and (c) post-synthesis transformation of the product into advanced compounds via the in-line synthesis of αCCs followed in cascade by its reaction with nucleophiles without intermediates isolation. Recent studies using gaseous CO_2 under continuous flow conditions, notably for the carbonatation of epoxides, served as inspiring guides for the present study.[68–72]

We hereby present the rapid addition of CO_2 to tertiary pro- pargylic alcohols, quantitatively achieved within a few minutes using a homogeneous silver-based catalyst under mild conditions (Fig. 1). This breakthrough enables, to the best of our knowledge, the first production case of αCCs under continuous flow conditions, ultimately reducing the consumption of CO_2 to a stoichiometric amount. Moreover, we demonstrate the transformation of αCCs into hydroxy-oxazolidone heterocycles by cascading the αCCs production with the in-line addition of a primary amine. Last but not least, we consider the immobilization of the silver catalyst on polystyrene beads to achieve silver-free product.

Fig. 1 *Production of αCCs using continuous flow setup with both homogeneous and heterogeneous catalytic strategy.*



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Results and discussion

CATALYST SCREENING FOR THE CARBOXYLATIVE CYCLIZATION OF 2-METHYL- 3-BUTYN-2-OL

The successful implementation of carboxylative cyclization of propargylic alcohols under continuous flow conditions must meet several criteria to optimize microreactor utilization: (1) the reaction should be complete within a much shorter time-frame (about 15 min)[73] than in batch to remain economically viable at larger scales (2) the catalytic system must ensure continuous operation, and (3) the process must ensure effective mass transfer for the gas/liquid system.

In the quest for an efficient catalyst able to promote the flow synthesis of αCCs, we revisited the transformation of tertiary propargylic alcohols into α-alkylidene cyclic carbonates (αCCs) by using a wide range of state-of-the-art silver-based catalysts, regardless of their solubility (Table S1†), yet adopting standard conditions to facilitate the benchmarking of their performances. 2-Methyl-3-butyn-2-ol and acetonitrile were chosen as the model substrate and solvent, respectively. Preliminary experiments were carried out in batch, carefully selecting conditions that would enable successful implementation under continuous flow. Mild operative conditions were selected, including a catalyst loading of 2 mol%, a propargylic alcohol concentration of about 1.67 M in acetonitrile, a temperature of 40 °C, a CO_2 pressure of 5 bar, and a reaction time of 30 minutes. Selected catalytic systems are summarized in Table S1.† The catalytic activity depends primarily on two factors: catalyst solubility and basicity. First, solubility is illustrated by replacing triphenylphosphine with Davephosphine along with silver acetate. This substitution enabled the silver salt to dissolve during the reaction, boosting the conversion rate from 3% to 59% (Table S1, entries 4 and 5†). The second critical factor is the presence of a strong base in the catalytic system. Acetate and carbonate anions (pK_{aH} of acetate in acetonitrile is 23.5,[74] no available data for carbonate) achieved good conversions (59–99%, Table S1, entries 5–8†), while the triflate anion (pK_{aH} in acetonitrile is 2.60),[74] although forming a soluble salt with silver (Table S1, entries 9 and –10†), resulted in an inactive catalyst. These yields were obtained in significantly shorter times compared to what is reported in the literature.[51,62] However, none of the efficient catalytic systems were fully soluble in the reaction mixture preventing their utilization in flow reactors, and the silver carbonate lacked selectivity with the production of hydroxy-ketone and other side products (Fig. S1 and S2†). Eventually, we tested the [1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] silver acetate (IPrAgOAc), reported to efficiently convert primary propargyl alcohol into the corresponding αCC.[51] It afforded a complete conversion of 2-methyl-3-butyn-2-ol into the desired product with a selectivity greater than 99% (Table S1, entry 18†). With this catalyst, the acetate

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but also the carbene might play the role of base.[75] Importantly, IPrAgOAc is soluble in most organic solvents including acetonitrile making it suitable for homogeneous catalysis.

Based on this promising preliminary result, we studied the influence of both the anion of the complex and the N substituent of the N-heterocyclic carbene (ESI, section 4†). Decreasing the anion basicity, notably by changing acetate for more acidic benzoate and chloride anions (pK_{aH}s of 23.5, 21.5 and 10.3 respectively),[74] led to a decrease in the catalytic activity (Table S2, entries 1–3†). This result confirms the active role of the anion as a base in the reaction mechanism. Then, keeping the acetate anion, the substituent of the N-heterocyclic carbene was changed to decrease progressively the bulkiness/ steric hindrance, going from the initial diisopropylphenyl group to benzyl, cyclohexyl and isopropyl group. Despite good solubilities in acetonitrile, all the new complexes precipitated upon addition of 2-methyl-3-butyn-2-ol, leading to a drastic drop in the conversion from 99% for the diisopropylphenyl group to a few percent with the other ones (Table S2, entries 4–6†). The precipitates were likely formed by the coordination of silver acetate with 2-methyl-3-butyn-2-ol with the expulsion of the carbene. However, determining their exact structures is challenging. Liquid NMR analysis is unfeasible due to their insolubility in deuterated solvents, and they quickly turn black when exposed to light or heat, making their isolation difficult.

The reaction solvent influenced the complexes solubility and stability. Switching from acetonitrile to DMSO, DMF and THF allowed the complex with the isopropyl substituent to remain soluble in the presence of the propargylic alcohol. Higher conversions were then achieved, particularly with DMSO and DMF as solvents, though far from being quantitative (about 24 and 31%, respectively) (Table S2, entries 7–9†). Note that IPrAgOAc also starts to precipitate in the presence of 2-methyl-3-butyn-2-ol in acetonitrile after a few hours.

From the above results, IPrAgOAc appears to be the best catalyst, and the operative conditions were optimized to minimize the reaction time (Table S3†). The temperature and pressure were increased to 50 °C and 10 bar to intensify the process and speed up the reaction rate affording 81% conversion in five minutes (Table S3, entry 7†). Eventually, adding 2 mol% of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) in combination with IPrAgOAc led to quantitative conversion (>99%) in an exceptionally short reaction time of about 5 minutes (Table S3, entry 8†). It must be noted that the use of an autoclave introduces significant imprecision when working with short reaction times, as it requires depressurization and opening the reactor to collect the samples. To achieve a more accurate estimate of the reaction kinetics, the reaction was monitored via on-line Raman spectroscopy by utilizing a high- pressure stainless-steel reactor equipped with a sapphire window following a procedure established elsewhere and described in ESI.†[76] Typical stretching of the propargylic alcohol substrate (C≡C) at

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2115 cm^{-1} and of the corresponding αCC at 1830 and 1690 cm^{-1} (CvO and CvC stretching, respectively) are clearly observable in the crude mixture. The molar fractions of the reagent and product are obtained by decomposing the in *situ* kinetic spectra using the t_0 and t_{600} spectra as pure reactant and pure product respectively (ESI section 7†). Fig. 2 shows that a complete conversion of the reactant into the αCC was achieved within 450 seconds (7.5 min).

CATALYSED-CARBOXYLATIVE CYCLIZATION OF A LIBRARY OF PROPARGYLIC ALCOHOLS

The carboxylative cyclization was extended to a library of pro- pargylic alcohols including other tertiary alcohols (1b–1d), primary ones (1e and 1f) and a bispropargylic alcohol (1g) (Fig. 3). The first tests were carried out under mild conditions used for catalyst screening at 5 bar, 40 °C, with no DBU and 30 min of reaction (condition A). The conversion and selectivity were determined by ^{1}H-NMR of the crude mixtures (Fig. S3–S8†).

Fig. 2 *(a) Raman spectra of pure 2-methyl-3-butyn-2-ol (green), 4,4- dimethyl-5-methylene-1,3-dioxolan-2-one (red), acetonitrile and the reaction mixture at t = 0 s and t = 600 s; (b) plots of the calculated molar fractions of both the reagent (left) and the product (right) versus the reaction time. Conditions: 1.94 mL of 2-methyl-3-butyn-2-ol, 10 mL of acetonitrile, 2 mol% of IPrAgOAc (222 mg) and 2 mol% DBU (59.8 µL) at 50 °C and a CO2 pressure of 10 bar.*

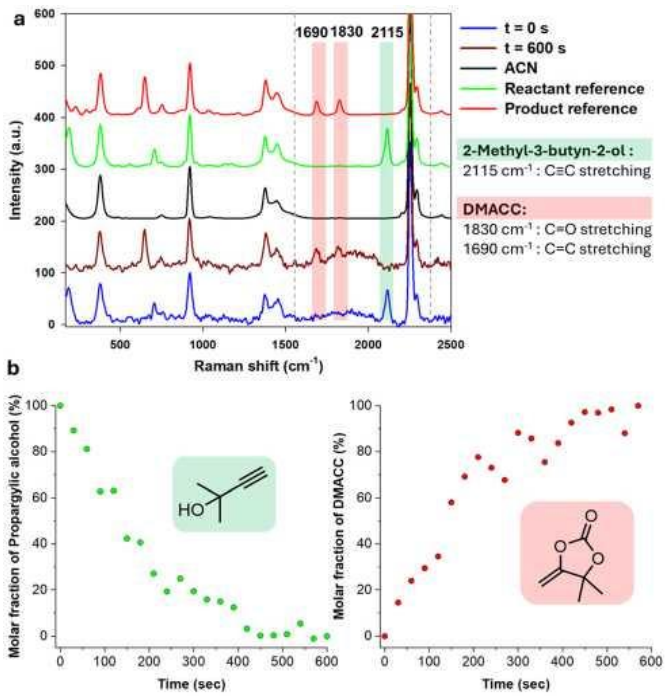

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Fig. 3 *Carboxylative cyclization of various propargylic alcohols with carbon dioxide. The conversion is determined by ^{1}H-NMR of the crude product. The solubility is checked before and after the reaction, precipitations are always observed after the reaction.*

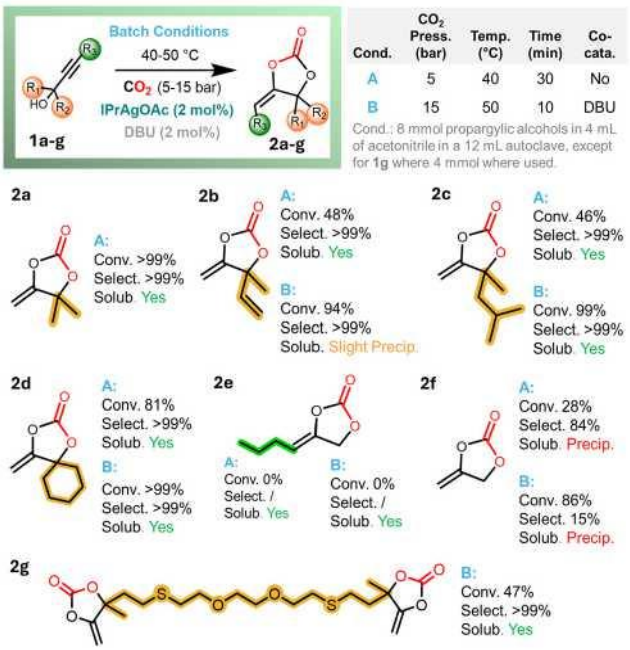
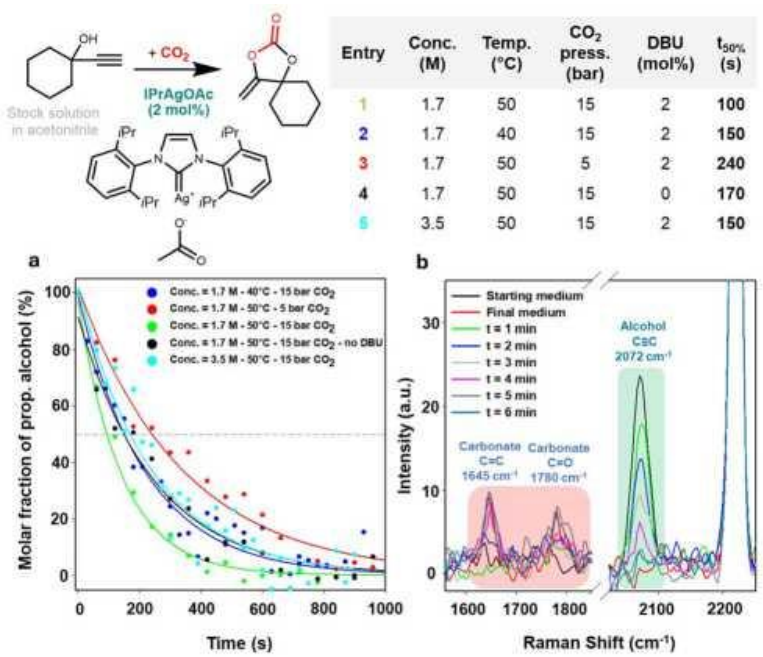


Fig. 4 *(a) Kinetics of carboxylative cyclization of 1d under different conditions followed by Raman spectroscopy and (b) stacking of Raman spectra at different times for condition 1. t50% is the time at 50% conversion.*



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Sterically congested tertiary alcohols with bulkier substituents than two methyl groups (1b–1d) showed a lower conversion compared to 1a reaching about 50% for 1b–c and 81% for 1d, indicating a slower reaction rate under these conditions. Regarding the primary propargylic alcohols, 1e did not react under both conditions, while 1f reached only 28% conversion, forming 2f with a selectivity of 84%. Indeed, 2f is contaminated by an acyclic oxo-carbonate product formed by the ring-opening of the αCC by a second molecule of pro- pargylic alcohol (Fig. S7†). Moreover, precipitation occurred during the reaction. Given these observations, harsher conditions were applied to tentatively achieve higher conversions in shorter reaction times. Conditions B consisted of using 15 bar of CO_2, 50 °C, 2 mol% of DBU and 10 min of reaction. 1b reached a higher conversion rate of 94% but precipitation occurred during the reaction. 1c and 1d were quantitatively converted into the corresponding αCCs. When applying conditions B to 1e, the selectivity dropped to 15% despite a higher conversion (86%). Eventually, we tested the carboxylative cyclization on 1g bearing two propargylic alcohol moieties. The resulting bisαCC is an important monomer used in stepgrowth polymerization with diamines, diols and dithiols.[11,15] Only conditions B were investigated in this case, yielding 47% conversion. This result might be explained by a higher viscosity hampering CO_2 diffusion and solubility.

KINETIC STUDY OF THE CARBOXYLATIVE CYCLISATION OF 2D

Before transposing the reaction from batch to lab-scale continuous flow reactors, we studied the influence of different parameters (CO_2 pressure, temperature, co-catalyst and concentration) on the reaction rate (Fig. 4). Compound 1d and IPrAgOAc were selected as the model substrate and catalyst for this study to monitor the reaction evolution by on-line Raman spectroscopy. Conditions B used previously served as a reference with a temperature of 50 °C, a concentration of 1.7 M, a CO_2 pressure of 15 bar and a catalyst loading of 2 mol% with DBU as a co-catalyst. Under these conditions, a quantitative conversion was achieved within 550 seconds (entry 1, Fig. 4). Expectedly, lowering the temperature or pressure slowed down the envisioned transformation with a drastic influence of the pressure (comparison between entry 1 and entries 2 and 3, Fig. 4). The presence of DBU as a co-catalyst, while not necessary to reach complete conversion, accelerated the reaction (comparison between entries 1 and 4, Fig. 4). Eventually, increasing the concentration from 1.7 to 3.5 M resulted in a decrease in the kinetic rate constant when the reaction curves were tentatively fitted using a pseudo-first-order kinetic model. This observation indicates that the assumption of pseudo-first- order kinetics with respect to the propargylic alcohol concentration is not valid. The actual kinetic behavior appears to be more complex, suggesting that CO_2 concentration may not be constant and instantaneously replenished. It can be rationalized

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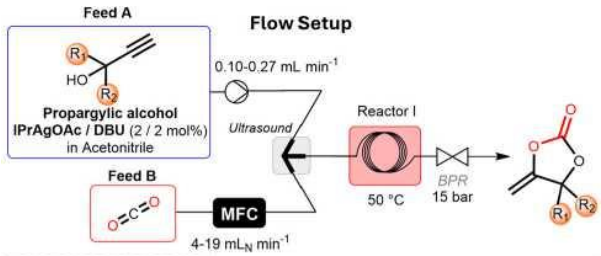
by the mass transfer limitation of the gaseous CO_2. All in all, this study demonstrated that conditions B were the most suitable for achieving a fast and quantitative conversion of tertiary propargylic alcohols (<10 min) and therefore for implementing the continuous flow process.

SYNTHESIS OF ACCS VIA CONTINUOUS FLOW (LAB-SCALE) PROCESS

We next turned our attention to the design of a flow setup using the IPrAgOAc homogeneous catalyst. The schematic setup of the lab-scale continuous flow setup is illustrated in Fig. 5 (see ESI, section 8† for details of the setup). The CO2 was fed with a mass flow controller (MFC) to ensure reproducible and controlled delivery while the solution containing the reagents with the catalysts was fed using conventional high precision syringe pumps. Proper mixing of the gas and the liquid phases was ensured by a high-pressure static micro-mixer (arrowhead-type), immersed in an ultrasonic bath. Ultrasound was applied as active mixing to enhance mass transfer between the gas and liquid segments. The reactor was heated at constant temperature using an oil bath at 50 °C.

Fig. 5 *Continuous flow setup (lab-scale) for the synthesis of a library of cyclic carbonates under different conditions, substrate scope and performance metrics.*



Cond.	Conc. (mol L^{-1})	Feed A (mL min^{-1})	Feed B (mL$_N$ min^{-1})	Reactor volume (mL)
A	1.7	0.11	8	1.70
B	1.7	0.10	4	1.70
C	1.7	0.27	19	4.34
D	3.5	0.104	8	1.70

2a
A: Conv.: >99% Select.: >99% Prod.: 34 g day^{-1} STY: 0.84 kg h^{-1} L^{-1}
B: Conv.: > 99% Select.: > 99% Prod.: 31 g day^{-1} STY: 0.76 kg h^{-1} L^{-1}

2c
A: Conv.: 98% Select.: >99% Prod.: 45 g day^{-1} STY: 1.11 kg h^{-1} L^{-1}
B: Conv.: 99% Select.: >99% Prod.: 41 g day^{-1} STY: 1.01 kg h^{-1} L^{-1}

2d
A: Conv.: >99% Select.: >99% Prod.: 45 g day^{-1} STY: 1.11 kg h^{-1} L^{-1}
B: Conv.: >99% Select.: >99% Prod.: 41 g day^{-1} STY: 1.01 kg h^{-1} L^{-1}
C: Conv.: >99% Select.: >99% Prod.: 111 g day^{-1} STY: 1.06 kg h^{-1} L^{-1}
D: Conv.: 99% Select.: >99% Prod.: 84 g day^{-1} STY: 2.14 kg h^{-1} L^{-1}

2g
A: Conv.: 2% Select.: >99% Prod.: 3 g day^{-1} STY: 0.06 kg h^{-1} L^{-1}
B: Conv.: 9% Select.: >99% Prod.: 11 g day^{-1} STY: 0.26 kg h^{-1} L^{-1}

[a] the concentration is of 0.85 M (1.7 M in propargylic alcohol functionalities)

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The counterpressure was set at 15 bar with a dome-type back pressure regulator. In our batch experiments, the amount of CO_2 is effectively infinite, as any CO_2 consumed is immediately replaced from an open cylinder maintained at a constant pressure. It is very often the case in the literature, or the CO_2 is present in a large excess and its consumption does not change the pressure. In contrast, a flow process provides a finite quantity of CO_2 through a mass flow controller and the consumed gas is not replenished, resulting in a decrease of the reaction rate over time. Moreover, estimating the residence time is challenging because the gas solubility in the liquid phase varies with its amount, the rate of CO_2 solubilization depends on the solvent/reagent mixture, and the CO_2 is consumed over time.

With these challenges in mind, a first set of conditions (conditions A, Fig. 5) was tested with 1a. Experimentally, a solution containing the propargylic alcohol (1.7 M) and the catalysts (IPrAgOAc and DBU, 2 mol% each) was injected with a flow rate of 0.1 mL min^{-1} while the CO_2 was fed at 8 mL_N min^{-1}. This corresponds to 1.91 equivalent of CO_2 compared to the propargyl alcohol. The residence time was estimated at 7.7 minutes. Surprisingly, the gas segments disappeared within a short distance from the mixer meaning that the CO_2 completely dissolved in the liquid phase at an early stage. The conversion was complete with a high selectivity in the desired product (>99%). The space–time yield (STY) of 0.84 kg h^{-1} L^{-1} outperformed the batch conditions (0.14 kg h^{-1} L^{-1}). Under identical conditions, the conversions of the other soluble propargylic alcohols 1c and 1d into the corresponding αCCs were also quantitative with an excellent selectivity (>99%). Remarkably, by decreasing the amount of CO_2 to almost equimolar amount (1.05 equiv., condition B), full conversions for all the propargylic alcohols were also achieved. A higher flow rate in both propargylic alcohol and CO_2 (conditions C, 0.27 mL min^{-1} and 19 mL_N min^{-1}, 1.85 equiv. of CO_2) was considered for 1d to increase the daily production. A bigger reactor was used (4.34 mL) to keep a similar residence time and space–time yield. Complete conversion of 1d was achieved along with a daily production reaching up to 111 g day^{-1}. Finally, a concentration in propargylic alcohols of 3.5 M (conditions D, 1.02 equiv. of CO_2) also afforded 2d in a quantitative yield. These results represent major breakthroughs in the production of α-alkylidene cyclic carbonates, continuous flow allowing the fast and quantitative conversion of tertiary propargylic alcohols using equimolar amount of CO_2 compared to a batch process. Eventually, the bispropargylic alcohol 1g was tested under both conditions A and B, however with little-to- no success (2 and 9% of conversion, respectively). This was ascribed to the low CO_2 solubility in this propargylic alcohol solution in acetonitrile as attested by the gas segments that were still present at the end of the reactor. This low solubility was probably the result of a lower content of acetonitrile (CO_2- philic solvent) needed to prepare the 1.7 M solution of this higher molar mass propargylic alcohol and to perhaps the higher

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viscosity of the solution that hampered an efficient mass transfer.

SYNTHESIS OF HYDROXY-OXAZOLIDONE THROUGH A CONCATENATED CONTINUOUS FLOW SETUP

αCCs can undergo regioselective ring-opening by a primary amine, giving access to hydroxy-oxazolidones that belong to an important family of organic compounds, notably as antibacterial agents.[77,78] Our group recently leveraged this reaction to synthesize poly(hydroxy-oxazolidone)s in continuous flow. For this purpose, bis(αCCs) was first prepared in a batch reactor, purified, and then polymerized with diamines in a flow reactor.[15]

Herein, we explored the direct preparation of hydroxy-oxazo- lidones in a single continuous flow process. In the first module, the αCC was produced by coupling CO_2 to a pro- pargylic alcohol, followed by the concatenation of a second module where a primary amine was delivered to produce the hydroxy-oxazolidone. To avoid the formation of an undesirable carbamate salt by reaction of CO_2 with the primary amine in the second module, the preparation of αCC in the first one had to be carried out under stoichiometric conditions with total CO_2 consumption. This method eliminates the need for intermediate purification, making it an efficient and streamlined process.It is demonstrated for the CO_2 addition to propargylic alcohol 1d followed by the subsequent addition of 1-heptyla- mine to produce the hydroxy-oxazolidone 3d (Fig. 6). Under the optimized conditions previously established, 2d was synthesized in a first reactor using 1 eq. CO_2 (condition D, Fig. 5) at a pressure of 15 bar, achieving a conversion of 99.8% (Fig. S9†). At the reactor outlet, the reaction mixture was combined with 1 eq. of heptylamine containing DBU (3 mol%) through a T-mixer before entering in a second reactor, set at 55 °C and 5.2 bar of counterpressure (BPR cartridge). After a residence time of 11.2 min, 2d was selectively converted to 3d with a conversion rate of 91% resulting in a daily production of 134.8 g day^{-1}. The hydroxy-oxazolidone was purified by recrystallization, and its structure was confirmed by ^{1}H- and ^{13}C-NMR spectroscopy (Fig. S10†). As expected, the precise control of the CO_2 stoichiometry in the first module had the advantage to avoid any carbonation of the primary amine in the second module, allowing its addition to 2d.

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Fig. 6 *Lab-scale continuous flow setup for the synthesis of the cyclic carbonate 2d and its subsequent conversion to the hydroxy-oxazoli- done 3d upon addition of heptylamine.*

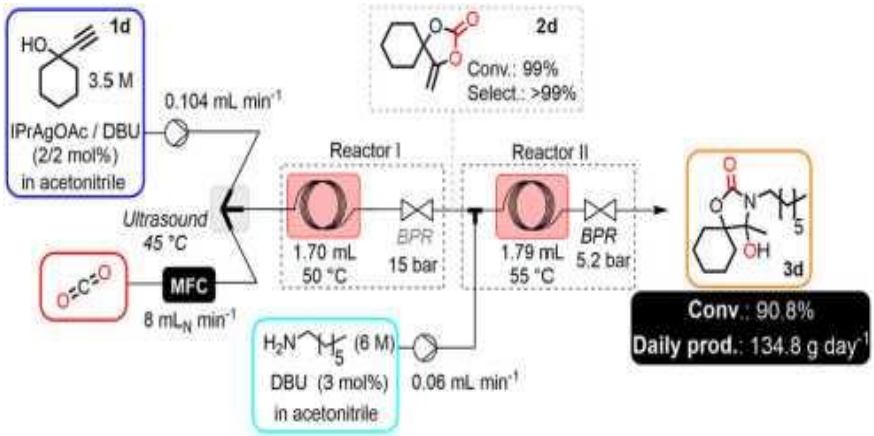
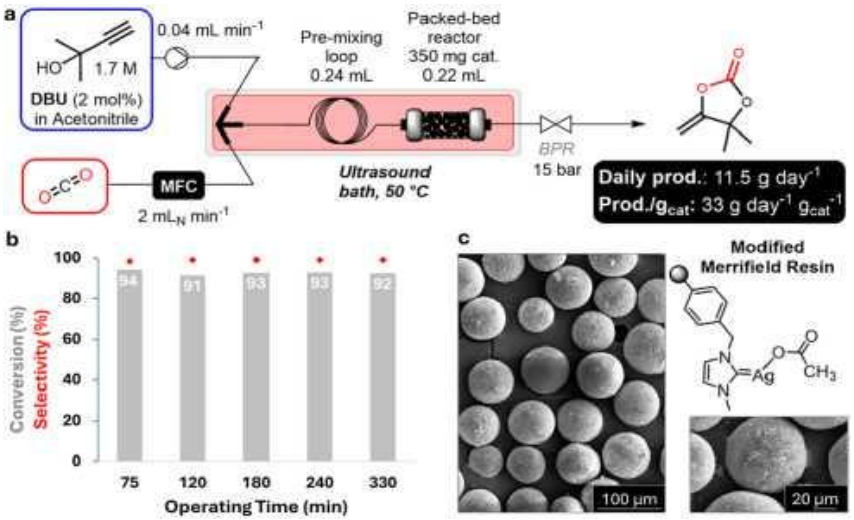


Fig. 7 *(a) Continuous flow setup with a packed-bed reactor consisting of an immobilized N-heterocyclic carbene silver acetate complex on Merrifield resin beads to catalyse the carbonatation of 1a, (b) conversion and selectivity evolution during a 5.5 h run, and (c) SEM images of the Merrifield beads modified by the catalyst.Supported catalyst in packed-bed reactor for CCC synthesis*



An inconvenience of using homogeneous catalyst such as IPrAgOAc is the purification required to remove it from the final product. Although the purification method developed here, consisting in trapping the silver on a thiourea resin, is efficient, it prevents its reutilization. To tackle this issue, we immobilized a N-heterocyclic carbene silver acetate complex on Merrifield resin beads by adapting reported procedures (see ESI, section 5†).[54,57] Briefly, a methyl imidazole was quaternized on the pendent benzyl chloride units of the resin, affording

Published in : Green Chemistry (2025), vol. 27, pp. 722–730
DOI: 10.1039/d4gc05716c
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the corresponding benzyl methyl imidazolium chloride. After exchanging chloride anion for acetate, the carbene silver was obtained through solid–solid phase reaction between the resin beads and silver oxide. The supported catalyst was characterized by elemental analysis to assess the silver content (1.4 $mmol_{Ag}$ g^{-1}, Table S4†) and by N_2 adsorption isotherm to determine its specific surface area (3.8 m^2 g^{-1}). Scanning electron microscopy (Fig. 7 and S11†) revealed an unchanged average diameter of the bead of 74 µm after modification, with a surface slightly contaminated with silver oxide. The beads were packed inside a stainless-steel column with 350 mg of catalyst (0.49 mmol of active site) for an internal volume of 0.22 mL. The continuous flow (lab-scale) setup integrated a pre-mixing loop to ensure the complete dissolution of CO_2 in the liquid phase before it entered the column (Fig. 7A).

The solution of 1a (1.7 M in acetonitrile) containing DBU (2 mol%) was injected with a flow rate of 0.04 mL min^{-1} and mixed with 1.3 eq. CO_2 (2 mL_N min^{-1}). The contact time (T_c) inside the column was approximately 5.5 min with a conversion of 93% in average and a production of 33 g per day per gram of catalyst. The system was run for 5.5 hours (60 T_c) to assess the operational stability of the catalyst, and no decrease of the activity nor selectivity was detected in these conditions (Fig. 7B). Importantly, the sample was collected during 4 h 15 min and purified from residual propargylic alcohol and DBU to afford 70.6% isolated yield. Importantly, no silver was detected by ICP (1 ppm detection threshold). Finally, to get rid of the co-catalyst (DBU), a longer column was packed with 3328 mg of the supported catalyst and ran with a solution of 1d (1.7 M) without DBU at a flow rate of 0.104 mL min^{-1} (T_c of 17.3 min) with 1.01 equiv. of CO_2 (Fig. S12†). 1d was used here as it is more stable than 1a toward precipitation on the column causing clogging. Pure 2d was quantitatively obtained with a productivity of 42.7 g day^{-1}, and no purification was needed after the removal of the solvent under vacuum.

COMPARISON BETWEEN BATCH AND FLOW SETUPS

To date, batch process remained the only way to synthesize αCCs despite the demanding and time-consuming handling of pressurized reactors as well as the waste of CO_2 that is used in a large excess. Moreover, the reactions ran for at least a few hours, limiting the reactor turnover for large-scale production and leading to very low space–time yields (STY) of 0.036 kg h^{-1} L^{-1} (ESI section 9, Table S5†). The development of our optimized catalytic system and conditions enabled us to minimize the reaction time to below 30 minutes, leading to higher STYs (0.14–0.54 kg h^{-1} L^{-1}, Tables S5 and S6†). However, performing such a swift reaction in batch is impractical, as it would require an operator to repeat the load–tighten–pressurize–depressurize–unload process (about 5 minutes) more than 72 times per day. The scaling up in bigger autoclaves would finally lead

Published in : Green Chemistry (2025), vol. 27, pp. 722–730
DOI: 10.1039/d4gc05716c
Status : Postprint (Author's version)

to more handling time than production time.

Our continuous flow setup allows to tackle these difficulties with a daily production of αCC up to 111 g day^{-1} and STYs around 1 kg h^{-1} L^{-1} that go up to 2.1 kg h^{-1} L^{-1} for the optimized conditions using only lab-scale flow reactors (Tables S7 and S8†). The latter are easy to scale up to pilot scale. In addition, flow conditions reduce the reaction time to merely a few minutes (5 to 15 minutes) while handling reduced amounts of CO_2.

Lastly, this continuous flow process meets several core principles of Green Chemistry: (a) use of renewable feedstocks in stochiometric amount (CO_2), (b) catalysis, (c) safer implementation and (d) energy efficiency. The latter both are inherently related to continuous flow technology. The environmental footprint of this carbonatation is quite low as reflected by a E-factor of 3.50 (calculated in batch, ESI section 10†), one of the lowest reported for this reaction as reported elsewhere.[79] It is important to note that the reported E-factors in the seminal works do not account for the materials required for purification, which would result in a higher E-factor if considered.[79]

Conclusions

We developed a homogeneous catalytic system based on silver carbene combined with DBU, achieving a rapid synthesis of α-alkylidene cyclic carbonates in high yield and selectivity. This system enabled, for the first time, the quantitative and selective conversion to be completed within a matter of minutes. This breakthrough allowed us to consider continuous flow chemistry. Several propargylic alcohols have been successfully tested, achieving quantitative and selective conversions as well as daily production rates up to 111 g. The CO_2 consumption was reduced down to an equimolar amount. The quantitative reaction enables the concatenation of αCC synthesis with the further nucleophilic addition of amines affording oxazolidone with a good yield of 91%. Eventually, silver carbenes were effectively immobilized on Merrifield resin yielding cyclic carbonates without silver contamination and even the use of DBU co-catalyst can be avoided. All in all, this work advances the existing batch processes and brings continuous production of cyclic carbonates to the forefront, highlighting all its associated advantages. Future work will focus on improving the stability and performance of supported catalysts. Additionally, the scale-up of αCCs production via mesofluidic technology will be investigated, with special attention devoted to difunctional αCCs and their further in-line polymerization.

Published in : Green Chemistry (2025), vol. 27, pp. 722–730
DOI: 10.1039/d4gc05716c
Status : Postprint (Author's version)

AUTHOR CONTRIBUTIONS

P. S. for conceptualization, investigation, methodology, visualization, writing – original draft; A. V., C. M. and M. S. S. F. for investigation; C. D., J.-C. M. and B. G. for Funding acquisition and Writing – review & editing.

DATA AVAILABILITY

Supplementary data for this article, including characterization methods, ESI tables and figures, experimental protocols, catalyst screening, kinetics monitored by Raman spectroscopy, flow chemistry setup and metrics calculated in this paper have been included in ESI.†

CONFLICTS OF INTEREST

There are no conflicts to declare.

ACKNOWLEDGEMENTS

This research program was funded by the University of Liege and the French Community of Belgium through Concerted Research Action CO2FLUIDICS 21/25-04 (PI: C. D., co-PI: J.-C. M. M.). P. S. is a F.R.S.-FNRS postdoctoral fellow and thanks FNRS for funding the ELITE project. C. D. is F.R.S.- FNRS Research Director and thanks FNRS for funding the CO2Switch project (Grant T.0075.20). J.-C.M.M. and C.D. thank the Region Wallonne for funding the FRFS-WEL-T Advanced Grants (WEL-T-CR-2023 A – 05 "Smart Flow Systems", PI: J.-C. M.M.; and WEL-T-CR-2023 A – 02 "CHEMISTRY", PI: C. D.). J. Y. thanks the European Research Council Consolidator Grant PARIS-101043485 for financial support. P. S. thanks Valérie Collard for having run some experiments.

Published in : Green Chemistry (2025), vol. 27, pp. 722–730
DOI: 10.1039/d4gc05716c
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