# Intensified Continuous Flow Synthesis of Oxazolidones

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**KEYWORDS**

Oxazolidones, Flow chemistry, α-Alkylidene cyclic carbonates (αCCs), Green chemistry, Isocyanate-free synthesis

**ABSTRACT**

Cyclic urethane compounds, known as oxazolidones (Oxas), have historically been synthesized using toxic, phosgene-based isocyanates, prompting the pursuit for greener alternatives. However, those alternatives face obstacles like the use of hazardous reagents and reliance on metal catalysts, leading to scalability limitations. Flow chemistry provides an effective solution, enabling safer, more efficient, and continuous production of Oxas, with enhanced catalyst recovery, reduced reaction times and greater control over reaction conditions. Leveraging these advancements, a novel flow-based method using the aminolysis of $CO_2$-derived α-alkylidene cyclic carbonates (αCCs) was developed, achieving yields of about 99% for aliphatic amines in just 1–5 minutes, with a very high selectivity for Oxas over hydrolysis and uncyclized by-products. This process was further optimized to synthesize oxazolidones in under 1 minute, without solvents and with minimal side reactions. Furthermore, a process utilizing supported catalysts was developed, further improving catalyst recovery and overall reaction efficiency.

## INTRODUCTION

Recent advances have demonstrated the effective use of $CO_2$ as a C1 building block under continuous-flow conditions,[1,2,3,4,5,6] including in the synthesis of ureas,[7] and cyclic carbonates via $CO_2$–epoxide cycloadditions.[2,3,8,9,10] In particular, significant progress has been made in the catalytic conversion of $CO_2$ into exovinylene cyclic carbonates (αCCs), achieved either under

batch conditions[11,12,13,14,15] or through gas–liquid reactions in flow systems.[16] These αCCs can be readily obtained via 100% atom economy the catalytic coupling of $CO_2$ with propargylic alcohols, typically with high yield and selectivity, making them attractive and sustainable $CO_2$-based heterocycles. Unlike conventional 5-membered cyclic carbonates, these heterocycles show remarkable reactivity with *N*-[17,18,19,20,21], *O*-[22,23,24,25] and *S*-nucleophiles[26] allowing their facile post-transformations into a large diversity of (sophisticated) chemicals,[27,28] monomers,[29,30,31] and polymers such as polycarbonates[17,25] or non-isocyanate polyurethanes[17,18,30,31,32,33,34,35,36]. Of particular interest is the reaction of these $CO_2$-based heterocycles with primary amines, affording oxazolidones of potential biological relevance – drug template[37,38,39,40,41] (Figure 1)- and a special class of high performance polyurethanes, i.e. poly(oxazolidone)s, usually only accessible from the conversion of toxic epoxides and isocyanates.[42,43,44,45] However, the aminolysis of αCCs is highly exothermic. While this exothermicity has been an asset in developing $CO_2$ self-blowing non-isocyanate polyurethane foams from room temperature formulations,[46] it poses significant challenges for large-scale synthesis of organic synthons. Flow chemistry is a highly promising tool to mitigate risks associated with handling strongly exothermic reactions. Besides the continuous and highly efficient production of synthons, it allows for better heat transfer, which minimizes exothermic effects, thus preventing unwanted side reactions and simplifying the scaling up of such organic transformations. The precise control over reaction parameters, such as temperature, pressure, and reactant flow rates, further ensures results reproducibility and consistency,[47] making this technology a versatile and reliable method for oxazolidones synthesis.

Herein, we report a rapid and efficient continuous flow process for the synthesis of oxazolidone scaffolds with a broad structural diversity and functional group tolerance through the aminolysis of αCCs. The reactions were carried out at temperatures ranging from 40 to 120 °C with a

(supported) nitrogen superbase (i.e. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)) as the catalyst, achieving remarkable product yields up to 99% for aliphatic amines within 5 minutes. Further optimization allowed the ultrafast and side-product-free preparation of selected compounds in just 1 minute, under solvent- and even catalyst-free conditions. Remarkably, Space-Time Yields (STYs) and productivity were found ~ 20 to 200 folds superior to those reported for other oxazolidones synthetic pathways using flow processes, although these previous reports were not focused on optimizing productivity. They included the photocatalyzed cross-coupling of protected α-amino ester with *N*-bromosuccinimide and the catalytic coupling of $CO_2$ with *N*-aryl epoxy amines (Figure 1).[9,48] Additionally, we present a comprehensive mechanistic study that provides a thorough understanding of the experimental results and offers valuable insights into the reaction pathway.

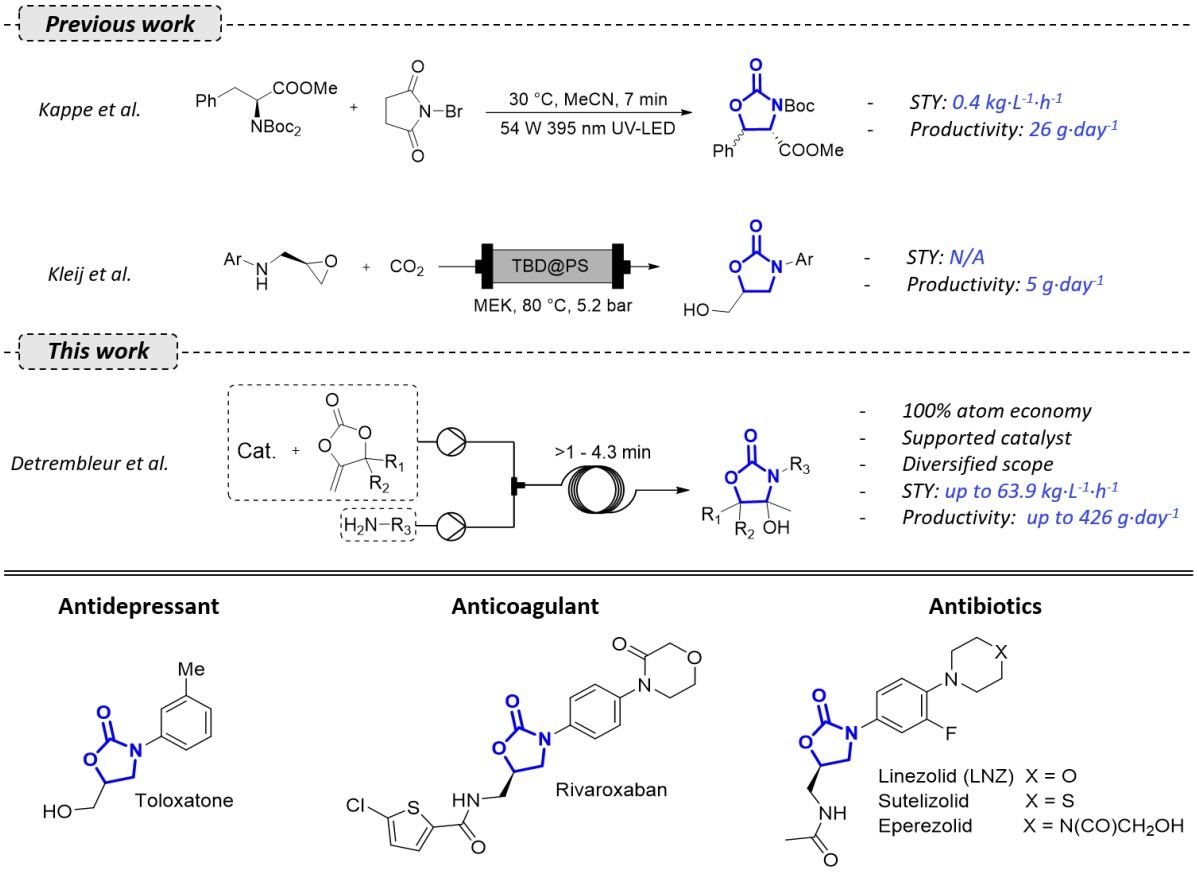


**Figure 1.** Earlier research on the continuous flow synthesis of Oxas, and the current strategy for a continuous flow process for oxazolidones using α-alkylidene cyclic carbonates (αCCs) and primary amines. Below: examples of oxazolidone-bearing drugs.[40]

## EXPERIMENTAL SECTION.

***General information.*** Conversion and selectivity were determined by $^{1}$H NMR spectroscopy, with detailed calculations provided in the ESI (Section 5). Structural identities were confirmed by $^{1}$H and $^{13}$C NMR spectroscopy using a 400 MHz Bruker Avance spectrometer (see ESI, Section 6). All amines were either freshly purchased or purified by distillation prior to use. Dimethyl sulfoxide (DMSO) and acetonitrile (ACN) were dried and stored over 3 Å molecular sieves under an inert atmosphere.

***Microfluidic setup.*** The microfluidic setup was constructed using PFA tubing with an outer diameter of 1.58 mm and an inner diameter of 762 μm. Both the inlet and outlet lines used the same tubing, connected with SuperFlangeless™ PEEK connectors and ferrules from IDEX/Upchurch Scientific. Fluid delivery was controlled by Chemyx Fusion 4000X syringe pumps equipped with stainless steel syringes or alternatively, by B. BRAUN Injekt™ 20 mL Luer Lock syringes. Temperature was regulated using a Heidolph MR Hei-Tec system fitted with a Pt1000 sensor, while downstream pressure was maintained via back pressure regulators from IDEX/Upchurch Scientific (BPR 40 psi). To enhance mixing, the column containing the supported DBU was immersed in a Branson 1510 ultrasonic bath operating at a frequency of 40 kHz and maintained at 70 °C. A thermometer was placed in the bath to monitor the actual temperature of

the system. Comprehensive details and schematic representations are provided in the ESI (Section 2).

***General Procedure for the* synthesis of exovinylene cyclic carbonates (αCC).** In an 80 mL high pressure reactor equipped with a stir bar was added the propargylic alcohol (87 mmol), triphenylphosphine $PPh_3$ (0.46 g, 1.74 mmol, 2 mol%), silver carbonate $Ag_2CO_3$ (0.24 g, 0.87 mmol, 1 mol%) and 10 mL of chloroform. The reaction was realized during 16 h at 50 °C and 100 bar of $CO_2$. During the first hour of reaction, the pressure within the cell was regularly readjusted to 100 bar to compensate the $CO_2$ consumption. After collection, the reaction mixture was purified by vacuum distillation. If necessary, additional purification of the αCCs was performed by silica gel chromatography using petroleum ether (95%) and ethyl acetate (5%) as the eluent. The synthesis was performed following a procedure adapted from literature.[49]

***Continuous flow preparation of hydroxy-oxazolidones.*** A solution of αCC (**1**) in dried DMSO (1.95 M, 5 mol% DBU) and the corresponding pure liquid primary amine were loaded into separate 20 mL syringes. The solutions were introduced into a PFA microreactor (0.9860 mL) via a T-shaped mixer, with the αCC flow rate set at 0.200 $mL \cdot min^{-1}$ and the amine flow adjusted to deliver 1.0 equivalent. Reactions were carried out at 40 °C. After 1.5 × $\tau_r$ (residence time), the output was sampled for $^1H$ NMR analysis. Full experimental details are provided in ESI, section 2. For *p*-anisidine, which is solid at room temperature, a modified protocol using DMSO stock solutions was employed. The αCC (**1a**) (2.60 M) and *p*-anisidine (3.28 M) solutions were delivered at 0.150 and 0.119 $mL \cdot min^{-1}$, respectively. Reaction conditions and analysis followed the general procedure.

***Continuous flow preparation of hydroxy-oxazolidones using supported DBU.*** A stainless-steel column (Waters, 4.6 × 250 mm) with integrated filters was packed with 234.5 mg of polymer-supported DBU (loading: 1.5–2.5 mmol·g$^{-1}$), corresponding to (3.52–5.86) × $10^{-4}$ mol of base. The remaining internal volume was 0.332 mL, representing the solvent-accessible space. At a 1.95 M concentration of **1a** in dry acetonitrile, this corresponds to 0.7–1.2 equivalents of supported DBU relative to the substrate. A solution of αCC (**1a**) in dried ACN (1.95 M) and *n*-heptylamine (**A1**) were loaded into separate 20 mL stainless steel syringes. The solutions were introduced into the stainless-steel column via a T-shaped mixer, with the αCC flow rate set at 0.0173 mL·min$^{-1}$ and the amine flow adjusted to deliver 1.0 equivalent. Reactions were carried out at 70 °C under ultrasound. After 1.5 × $\tau_r$ , the output was sampled for $^1$H NMR analysis.

***Continuous flow preparation of hydroxy-oxazolidones using solvent-free conditions.*** Liquid αCC (**1c** or **1d**) and amine (**A1** or **A9**) solutions were loaded into separate syringes and injected via a T-mixer, with αCC at 0.16 mL·min$^{-1}$ and the amine at an equimolar flow rate. The reaction proceeded in a 0.2773 mL PFA reactor at 120 °C with a residence time of 47–55 seconds. After 1.5 minutes, samples were collected for $^1$H NMR analysis.

**RESULTS AND DISCUSSION.**

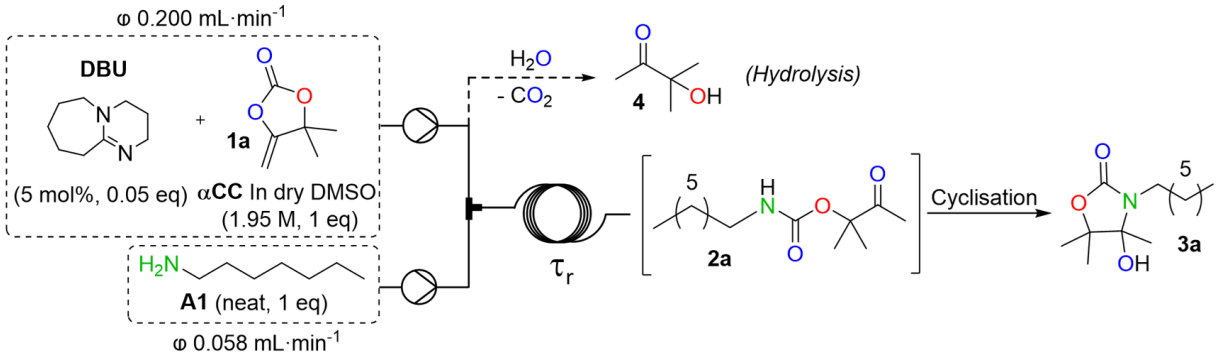
***Process optimization.*** The aminolysis of αCC is highly exothermic in nature. This is exemplified by the DBU-catalyzed reaction in batch conditions of 4,4-dimethyl-5-methylene-1,3-dioxolan-2-one (**1a**) by *n*-heptylamine (**A1**) forming the corresponding oxazolidone. At a high concentration of 3.5 mol·L$^{-1}$ in dimethyl sulfoxide (DMSO) or acetonitrile (ACN), 5 mol% of DBU and an initial

temperature set to 80 °C, the exotherm reaches up to 140 °C in just 15 sec in DMSO despite the small reaction scale (Figure S1). Using diluted conditions (1.95 mol·L$^{-1}$) and a lower bath temperature of 40 °C still induces a temperature overshoot of 35 °C within 30 sec (Figure S1). The rapid temperature rise causes the evaporation of reactants/solvents (ACN) and represents a major challenge for scaling up the reaction. Additionally, high temperatures favor the hydrolysis of αCC by residual water leading to the formation of hydroxyketone side-products. This is supported by the fast hydrolysis of **1a** exposed to 1 equiv. of water at 80 and 140 °C, forming respectively 8 and 35% of hydroxyketone in just 30 seconds (Figure S2). Note that the formed hydroxyketone can in turn act as a nucleophile toward **1a** leading to an additional side-product especially at 140 °C (Figure S2). The oxazolidone can also be thermally dehydrated releasing additional water. In contrast to batch experiments, flow systems offer a significant advantage by effectively managing the exothermicity of the reaction. The continuous flow of reagents allows for a better control of the temperature and the reaction environment creating optimal conditions for selective αCC aminolysis by minimizing the formation of hydrolysis byproducts.

The synthesis of oxazolidones has therefore been transposed and optimized from a batch reactor to a lab-scale continuous flow system using the same model compounds, namely, neat *n*-heptylamine (**A1**) and 4,4-dimethyl-5-methylene-1,3-dioxolan-2-one (**1a**) in solution in dry DMSO. The reaction has been initially performed using a **1a** concentration of 1.95 mol·L$^{-1}$ at 40 °C, adapting conditions from previously reported batch reactions using 5 mol% of DBU (*vs* **1a**).[18] Under these conditions, 83% conversion of **1a** was achieved within 1.3 minutes, with 92% selectivity for the desired product **3a** and 8% selectivity for the oxo-urethane intermediate **2a** (Table 1, entry 1). Notably, no hydrolysis was observed. To explore the effect of temperature, the

reaction temperature was raised from 40 °C to 80 °C, which did not significantly alter the conversion of **1a**, but led to the formation of 5% of hydroxyketone **4** (Table 1, entry 11).

**Table 1.** Optimization of the continuous flow synthesis of oxazolidone **3a** by aminolysis of αCC **1a** and n-heptylamine **A1**.




| *Entry* | *T (°C)* | *[C] (mol·L⁻¹)* | *$\tau_r$ (min)* | *Mixer* | *Conv. 1a (%)[a]* | *2a (%)[b]* | *3a (%)[b]* | *4 (%)[b]* |
|---|---|---|---|---|---|---|---|---|
| ***1*** | 40 | 1.95 | 1.3 | T | 83 | 8 | 92 | 0 |
| ***2*** | 40 | 1.95 | 1.9 | T | 89 | 6 | 94 | 0 |
| ***3*** | 40 | 1.95 | 3.8 | T | 98 | *trace* | 99 | *trace* |
| ***4[c]*** | 40 | 1.95 | 3.8 | T | 98 | 15 | 85 | 0 |
| ***5*** | 40 | 0.67 | 3.8 | T | 82 | 1 | 99 | 0 |
| ***6*** | 40 | 0.67 | 3.8 | Y | 82 | 3 | 97 | 0 |
| ***7*** | 25 | 1.95 | 3.8 | T | 96 | 4 | 96 | 0 |
| ***8[c]*** | 25 | 1.95 | 3.8 | T | 87 | 34 | 66 | 0 |
| ***9*** | 25 | 0.67 | 3.8 | T | 81 | 5 | 95 | 0 |
| ***10*** | 80 | 1.95 | 3.8 | T | 95 | 2 | 95 | 3 |
| ***11*** | 80 | 1.95 | 1.3 | T | 83 | 3 | 92 | 5 |
| ***12[d]*** | 40 | 1.95 | 3.8 | T | 73 | 6 | 94 | 0 |
| ***13[d]*** | 80 | 3.5 | 6.3 | T | 99 | *trace* | 99 | *trace* |

**Conditions:** PFA tubing, internal diameter of 762 µm, internal volume of 0.9860 mL. For $C_{\mathbf{1a}}$ = 1.95 mol·L$^{-1}$ (in dry DMSO), $\varphi_{\mathbf{1a}}$ = 0.2 mL·min$^{-1}$ $\varphi_{\text{n-heptylamine (neat)}}$ = 0.058 mL·min$^{-1}$, DBU (5 mol%), mixed with n-heptylamine. The methodology to calculate flows at other **1a** concentrations is reported in the ESI section. [a] Conversion determined by $^1$H NMR. [b] Composition of product mixture, determined by $^1$H NMR. [c] No catalyst.[d] Carried out in ACN.

Despite the temperature increase, the overall reaction efficiency did not improve, prompting a shift in focus to the residence time. Extending the residence time from 1.3 to 1.9 and 3.8 minutes at 40 °C improved the conversion of **1a** to 89 and 98% respectively, with a 94-99% selective

formation of **3a** (Table 1, entries 2 and 3). Lowering the temperature to 25°C still allowed for quasi-quantitative conversion of **1a** (96%) at a residence time of 3.8 min, with **3a** being the major product (96% *vs* 4% of intermediate **2a**) (Table 1, entry 7). Further optimizations of the reaction are reported in Table 1. As a trend, in the absence of DBU, the conversions of **1a** were 87% (at 25 °C) or 98% (at 40 °C), but the cyclization of intermediate **2a** was significantly slowed down as attested by its high content of 34 to 15% (Table 1, entries 4 and 8). As reported for low **1a** concentration at 40 °C, the T- or Y-shape of the mixer had no impact on the reaction features, as attested by identical conversion of the αCC (82%) and selective formation of **3a** (97-99%) (Table 1, entries 5 and 6). From this study, we defined the optimal conditions as being a residence time of 3.8 minutes, a concentration of **1a** of 1.95 mol·$L^{-1}$ in dry DMSO, using 5 mol% of DBU (*vs* **1a**), and a reaction temperature of 40 °C. These conditions provided a Space Time Yield (STY) of 5.6 kg·$L^{-1}$·$h^{-1}$ and a daily production of **3a** of 133 g. As shown in Table 1 (entries 12 and 13), the reaction was slightly slower in ACN, giving 73% conversion of **1a**. However, optimized conditions were developed to allow the use of this solvent – it is employed to facilitate the purification of the scope of products in the next section. Under these conditions (80 °C, 3.5 mol·$L^{-1}$, 6.3 min residence time), full conversion of **1a** and 99 % selectivity for **3a** were achieved, demonstrating the efficiency of the reaction in ACN. Importantly, while the reaction inherently achieved 100 % Atom Economy (AE), this optimization in ACN enabled further improvements in other green metrics, such as Process Mass Intensity (PMI) and E-factor, which decreased from around 290 to an average of 50, and in some cases even lower than 10. All values were calculated and are summarized in Table S1, highlighting the substantial environmental benefit of this process. Lower metrics might also be obtained by optimizing the purification step, i.e. the solvent volumes used for column chromatography.

***Substrate scope.*** Building on the previous outcomes, the reaction's versatility was evaluated across a wide range of αCCs and (cyclo)aliphatic amines using the optimized conditions ($\tau_r$ = 3.8 min, $C_{\alpha CC}$ = 1.95 mol·L$^{-1}$ in dry DMSO, 40 °C). The conversion and selectivity for each aminolysis reaction were monitored by $^1$H-NMR of the crude mixtures, taking into consideration all the detected products and side-products (Figure S3), while the corresponding isolated yields are reported in ESI (Table S1). Similarly to **A1**, the reaction of **1a** with propylamine **A2** was quasi quantitative (conv. of **1a** 98-96%) and furnished **3b** with a selectivity of 99%. As expected, introducing the sterically congested amine **A3** or the cycloaliphatic amine **A4** hindered the nucleophilic attack of the carbonate ring. This resulted in a decrease of αCC conversion to 82-62% yielding respectively products **3c** and **3d**. Moreover, the product selectivities toward **3c** and **3d** dropped to 70% and 49% with **A3** and **A4**, respectively. Such moderate selectivities arose from the slow cyclization rate of the corresponding **2c-d** intermediates which were the sole observed co-products of the reaction. Replacing **1a** by other αCCs displaying cycloaliphatic (**1b**), isopropyl (**1c**), allylic (**1d**) or aromatic (**1e**) substituents had no impact on the reaction, except in the case of **1c**. For this substrate, when combined with *n*-heptylamine (**A1**), the conversion decreased to 89%, with a selectivity of 93% toward **3f**, while the other oxazolidones **3e**, **3g** and **3h** were quantitatively produced with a selectivity of 99%. Interestingly, our synthetic approach allowed synthesizing oxazolidones with STYs of 1.3-7.8 kg·L$^{-1}$·h$^{-1}$ and daily production of 31-185 g, which was much higher than the values reported in the literature for other synthetic pathways (Table S1). To assess the reaction's functional group tolerance, amines bearing different functional groups were tested (Figure 2, products **3i-p**). With allylamine (**A5**) and propargylamine (**A6**), **1a** was converted at 92-93%, affording both **3i** and **3j** with 99% selectivity. The use of long-chain amine **A7** bearing an

internal olefin led to a conversion of **1a** comparable to the shorter-chain analog **A5** (93-92%). However, despite a similar conversion, the selectivity for **3k** was lowered at 91%, possibly due to increased steric hindrance that hampered the intramolecular cyclization of the oxo-urethane intermediate **2k**. Functional amines with groups such as ether (**A8**), tertiary amine (**A9**), alcohol (**A10**), furan (**A11**) or imidazole (**A12**) also led from good to high αCC conversions (63-99%). With the exception of 3-amino-1-propanol (**A10**), the functional amines furnished the oxazolidones **3l**, **3m**, **3o**, and **3p** with selectivities exceeding 98%. With **A10**, the presence of the alcohol promoted an alternative reaction pathway with the αCC, forming side-products (Figure S4).[25] Indeed, in addition to the desired product **3n**—which constituted 65% of the final crude mixture—a competing ring-closure pathway led to the formation of a six-membered cyclic carbamate, specifically a 1,3-oxazine-2-one (**3'n**) at 32%.[50,51] Furthermore, the hydroxyl group present in the oxazolidone could also react with another αCC, yielding an oxazolidone/oxo-carbonate side product (**3''n**) at 3%. $^{1}$H and $^{13}$C NMR characterisations of **3"n** are given in the ESI section 5. These results confirmed the high versatility of this synthetic method, demonstrating its efficiency across a wide range of amines with functional groups relevant for click chemistry (e.g., furan for Diels–Alder reactions[52,53], alkenes for thiol-ene reactions[54], alkynes for alkyne-azide cycloaddition[55,56]).

Benzylic and related amines **A13** and **A14**, compared to aliphatic amines **A1**, led to slightly reduced **1a** conversion of 81% and 95%, respectively. **It** afforded oxazolidones **3q** and **3r** being produced quasi selectively (96% with **A13**, 97% with **A14**). In contrast, aromatic amines such as aniline (**A15**), exhibited a very low conversion of 5%, with the remaining 95% corresponding to unreacted starting material, without detectable side-products. The introduction in aniline of an ether electron-donating group at the para position (**A16**) slightly improved reactivity, increasing

conversion of **1a** to 24%. For both (substituted) aromatic amines, the oxazolidones **3s** and **3t** were formed with a selectivity >93–99%; in the case of aniline (**A15**) leading to **3s**, no uncyclized intermediate was detected, whereas for p-methoxyaniline (**A16**) affording **3t**, 7% of the corresponding intermediate **2t** was observed. Switching from mild conditions in DMSO to harsher conditions in ACN significantly improved the conversion, as evidenced by an increase to 14% with **A15** and 29% with **A16**. However, this enhancement came at the expense of selectivity for p-methoxyaniline, which decreased to 74%, with the remaining 26% corresponding to intermediate **2t** (Table S1). Extending the residence time in ACN from 6.3 min to 28.3 min at 80 °C did not significantly increase the conversion (31% *vs* 29%), but it substantially improved selectivity for **3t** from 74% to 87%, with the remaining 13% being accounted for intermediate **2t**.

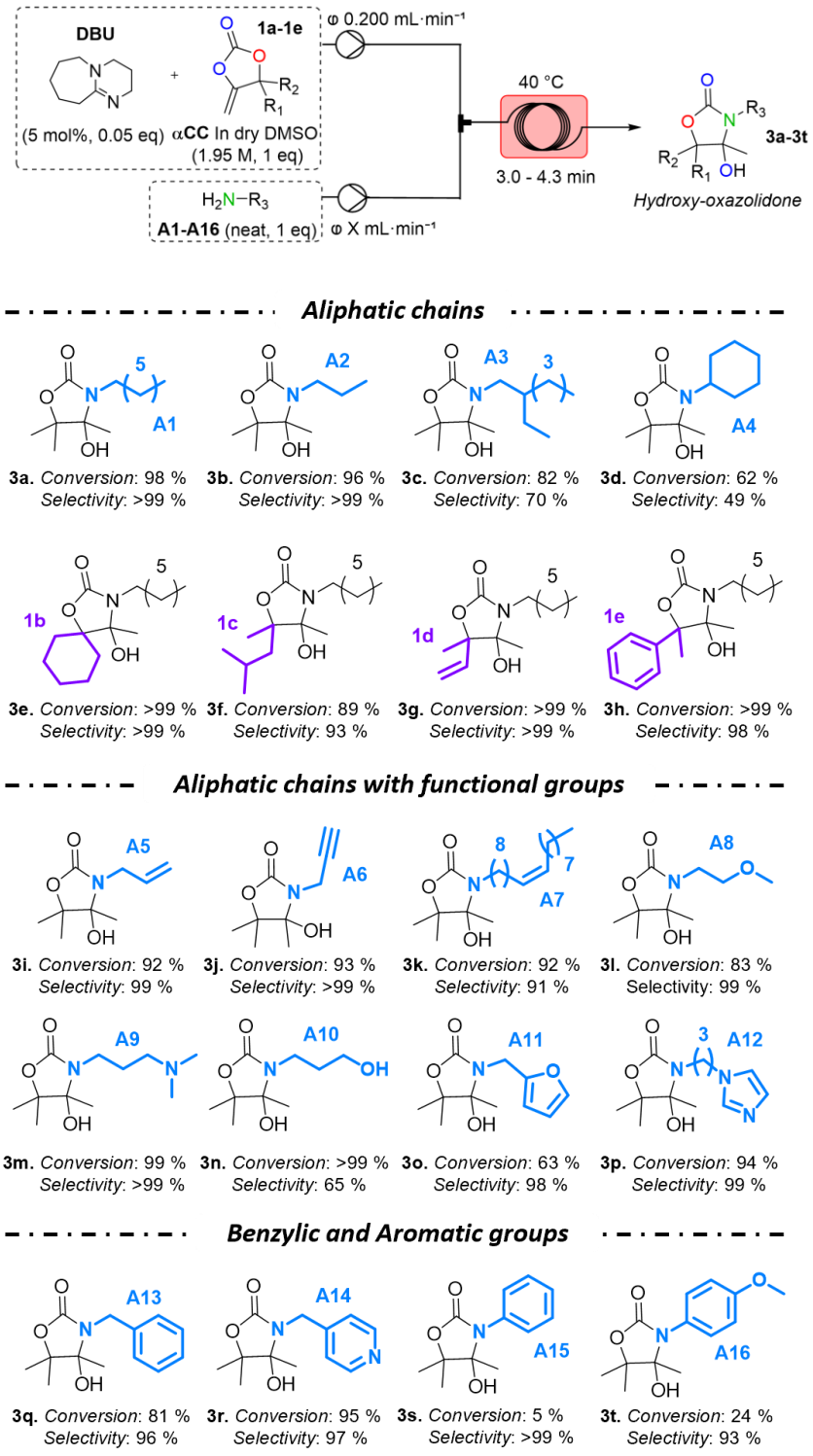



**Figure 2.** Scope of continuous flow synthesized oxazolidones **3** using α-alkylidene cyclic carbonates (αCCs) **1** and primary amines **A**. General reaction conditions: DMSO, 1.95M, 40 °C, $\tau_r$ = 3.0 – 4.3 min, αCC flow rate: 0.2 mL/min. The conversion of **1** and the selectivity were

determined by $^{1}$H NMR by using calculus detailed in ESI. Their space time yield (STY), productivity, isolated yield, process mass intensity (PMI), and E-factor are mentioned in Table S1. Full characterization of the isolated products is found in ESI section 5.

***Mechanism study by DFT.*** To further understand these experimental trends, a detailed DFT investigation was conducted to elucidate the mechanism of DBU-catalyzed aminolysis of αCC and to explain the reactivity differences among various amines. Propylamine (**A2**), cyclohexylamine (**A4**), and aniline (**A15**) were selected as model amines. Calculations were performed using the range-separated hybrid functional ωB97X-D combined with the triple-ζ basis set (6-311++G(d,p)) in acetonitrile, modeled using the conductor-like polarizable continuum model (CPCM). Energy corrections were applied using the GoodVibes module, considering a concentration of 3.5 mol·L$^{-1}$ at 353.15 K (Figure 3). Further details on the calculation methods, transitional steps, and kinetic studies are provided in the ESI (Table S2-3, Figures S5-7). Through DFT calculations, multiple transition states (**TS0–TS6**) and their corresponding intermediates (**int0–int6**) were identified, providing valuable insights into the reaction mechanism. The overall mechanism proceeds in two main stages: (a) **Ring opening**, initiated by the nucleophilic attack of the amine to form a linear oxo-urethane, and (b) **Ring closure**, leading to the formation of the oxazolidone. The mechanisms for the three amines are generally similar, except for aniline (**A15**). For the latter, a distinct **TS0** corresponding to the initial approach of the amine was not identified. Instead, the intrinsic reaction coordinate for **TS1**, which represents bond formation between the amine nitrogen and the carbonyl carbon, showed a loss of inflection, indicating a direct bond formation (Figure S8). For aliphatic amines (propylamine and cyclohexylamine), **TS0** is the rate-determining step, with activation free energies of 17.4–18.6 kcal·mol$^{-1}$. In contrast, for aniline, the rate-determining step corresponds to **TS1**, with a higher Gibbs free energy barrier of 22.8 kcal·mol$^{-1}$. These findings align with

experimental observations (Figure 2 and Figure S9a-c) where propylamine reacts the fastest, followed by cyclohexylamine, while aniline reacts much more slowly. However, by extending the reaction time (from 4 h to 72 h) and the concentration (from 0.5 to 3.5 M) at 25 °C, αCC and aniline were almost fully and selectively converted into the desired oxazolidone (Figure S9d). This experiment suggested that the full transformation of αCC into the desired oxazolidone might be achieved in flow under these conditions, provided that a long residency time could be achieved, which is however not possible with our set-up.

The second stage of the mechanism—cyclization of the oxo-urethane to form the oxazolidone—proceeds through several transition states (**TS4–TS6**). The rate-determining step for cyclization across all amines corresponds to **TS4**, where DBU deprotonates the nitrogen of the urethane intermediate. Aniline shows the lowest Gibbs free energy (12.3 kcal·mol$^{-1}$) due to a less stable oxo-urethane intermediate. Propylamine has a slightly higher barrier to overcome (13.9 kcal·mol$^{-1}$) while the more sterically hindered cyclohexylamine exhibits the highest Gibbs free energy of 16.8 kcal·mol$^{-1}$. As predicted, for aniline, oxo-urethane intermediates are undetectable experimentally even at the earliest stages of the reaction while for propylamine, the intermediate is present at early stage of the reaction and quickly decreases to stay at very low concentrations, whereas for cyclohexylamine, it is more persistent due to a slower cyclization step, making it readily detectable by NMR (Figure S9, a-d).

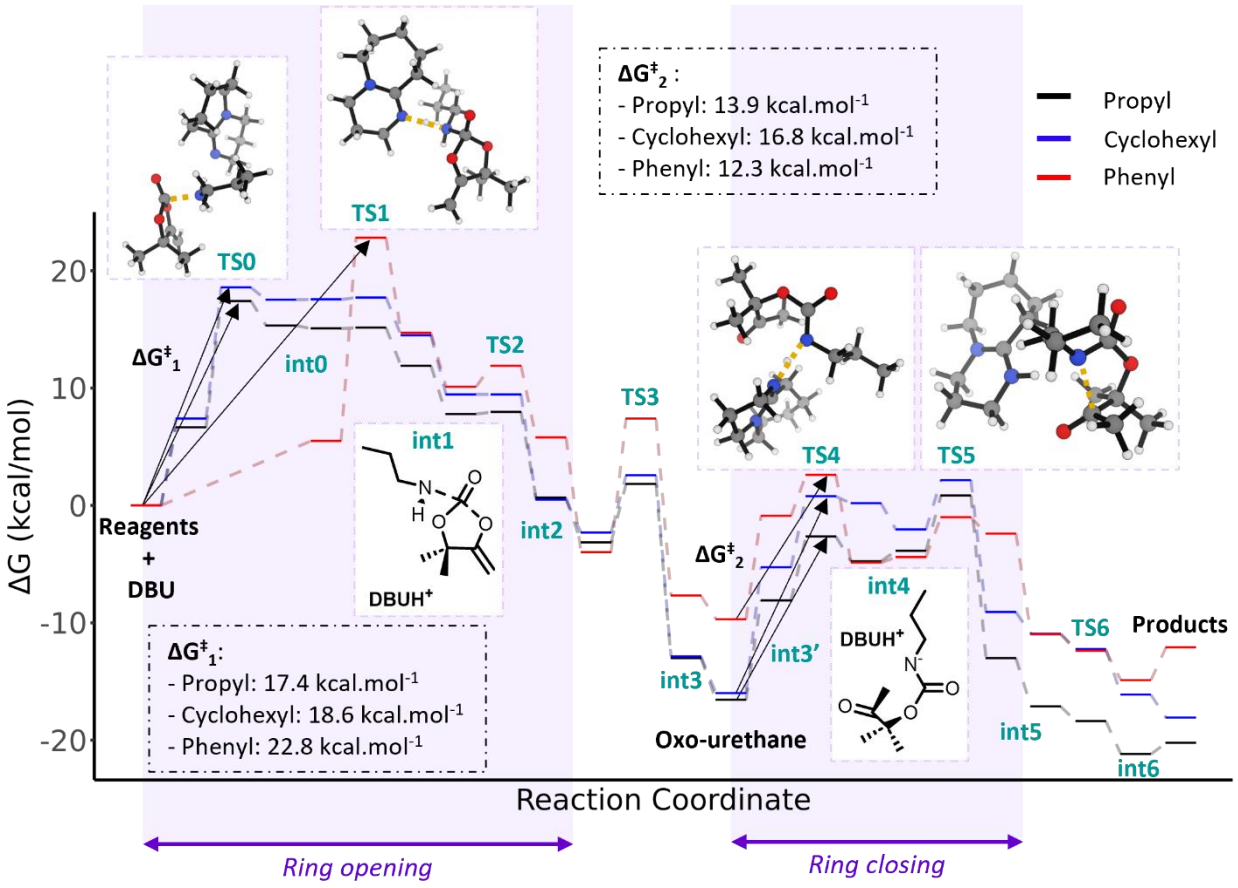



**Figure 3.** Gibbs-Free Energy Profiles of the aminolysis of αCC with different amines. The chemical structures of all transition states and intermediates are depicted in ESI in Figure S6-S7.

***Heterogeneous catalysis.*** Heterogeneous catalysis has been shown to be an effective approach for the synthesis of oxazolidones, facilitating product isolation and process efficiency.[9] Building on this strategy, DBU immobilized onto a resin was tested to further improve the process and streamline purification from the catalyst in the crude reaction product (Figure 4). This is important as this nitrogen superbase typically interacts with the oxazolidones via H-bonding making the product isolation rather difficult. For this test, the experimental set-up was changed. A total of 234.5 mg of polymer-supported DBU (loading: 1.5–2.5 mmol·g$^{-1}$), corresponding to 3.52–5.86 × $10^{-4}$ mol of base, was packed into a packed-bed reactor with a fixed internal volume of 0.332 mL,

corresponding to 0.7–1.2 equivalents of supported DBU relative to the substrate. For the reaction of **1a** with **A1**, the reaction was run at 70 °C to favor the complete cyclization of intermediate **2** into **3a**. The **1a** and **A1** flow rates were adapted to respect stoichiometry, which corresponded to a contact time of 14.9 min. Finally, to facilitate the recovery of **3a**, DMSO was replaced by ACN.

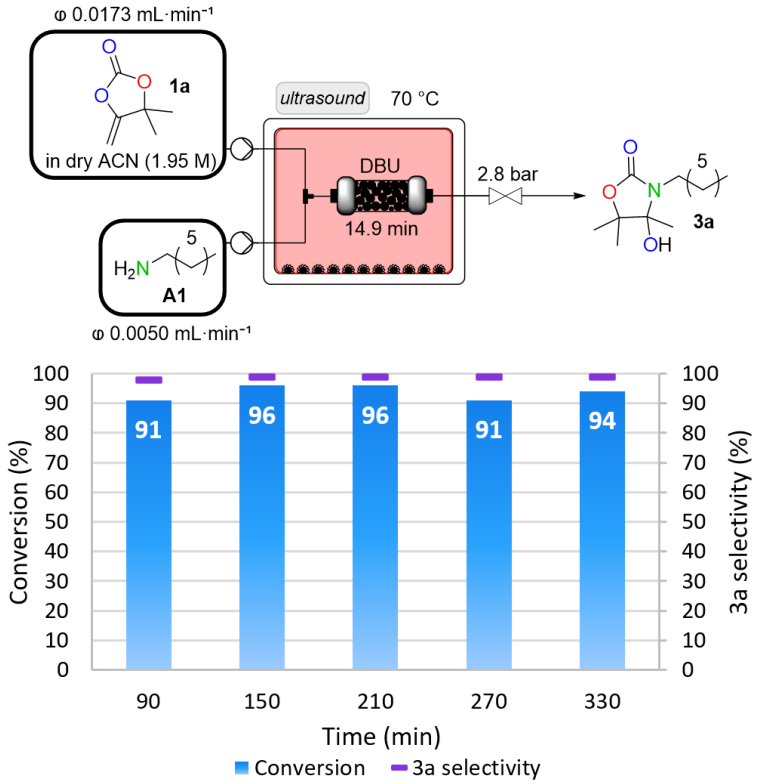



**Figure 4.** Continuous flow synthesis of oxazolidone **3a** by reacting **1a** and n-heptylamine **A1** using supported DBU. Stability study of the heterogeneous catalyst by monitoring **1a** conversion (%) over time.

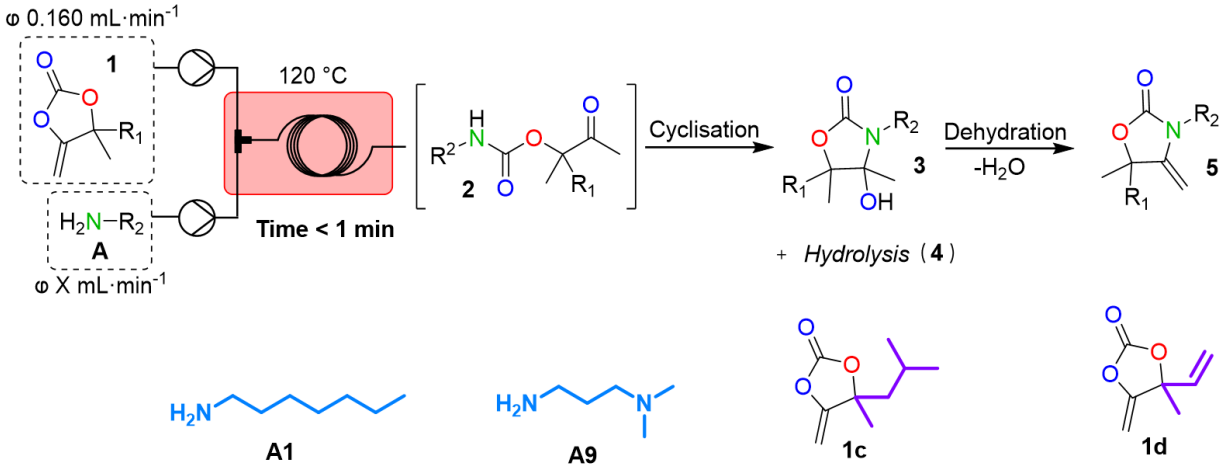
Rather than pushing for complete **1a** consumption, the reaction was deliberately run at the threshold of ~ 95% to validate process stability and better identify a possible catalyst degradation. Overall, the continuous heterogeneous catalytic flow set-up demonstrated remarkable stability and efficiency for at least 5h30. The system maintained consistently high **1a** conversions between 91%

and 96%, with an exclusive formation of **3a** with a selectivity of 98-99%, confirming its robustness. In addition, the productivity of the catalyst was calculated to be in the range of 3.21–5.35 $mmol \cdot h^{-1} \cdot mmol^{-1}_{cat}$, further underlining the efficiency of the process. Notably, no leaching of the supported catalyst (DBU) was detected by $^{1}$H-NMR, which is ascribed to the covalent linkage between the DBU and the polystyrene resin.

***Solvent-free process.*** To further enhance the productivity of the synthesis and target reaction times below 1 min, solvent-free trials at a higher temperature of 120 °C were carried out (Table 2). Under these conditions, running the reaction of **1a** with **A1** in batch was very challenging as illustrated by an exotherm reaching 210 °C in just 10 sec even under catalyst-free conditions (Figure S10). This rapid temperature rise made the process too hazardous for batch synthesis, requiring careful consideration of heat management and control to ensure safe operation on a larger scale. To adapt these operative conditions in flow, **1a** that is solid at r.T, was replaced by liquid **1c** and **1d** to allow continuous injection of αCCs in the set-up. At 120 °C, both αCCs were rapidly transformed into the corresponding oxazolidones **3f** and **3g** using **A1** as model amine. **1c** and **1d** conversions reached up to 90% and 87%, respectively, in 51 and 47 sec (Table 2, entries 1 and 2). However, when using **1c**, some oxo-urethane intermediate **2** was still detected in the crude composition. Hydroxyketone appeared as traces in the crude mixture. When **A9** was combined with **1c**, without the use of solvent or a catalyst, a conversion of 91% was achieved, with an STY of 52.1 $kg \cdot L^{-1} \cdot h^{-1}$ (Table 2, entries 3). Under the same conditions, the reaction involving **1d** reached 99% conversion in just 52 seconds. Notably, 96% of the product was the desired oxazolidone. The remaining 4% were attributed to the dehydration of **3g** into **5**, a well-known

thermally induced side reaction. Despite the formation of this side product, the process still delivered an outstanding STY of 63.9 $kg \cdot L^{-1} \cdot h^{-1}$ (Table 2, entries 4).

**Table 2.** Catalyst- and solvent-free synthesis of oxazolidone under continuous flow conditions**.**




| *Entry* | *αCC* | *A* | *$\tau_r$ (sec)* | *Conv. αCC (%)[a]* | *2 (%)[b]* | *3 (%)[b]* | *4 (%)[b]* | *5 (%)[b]* | *STY ($kg \cdot L^{-1} \cdot h^{-1}$)* |
|---|---|---|---|---|---|---|---|---|---|
| ***1*** | 1c | A1 | 51 | 90 | 8 | 91 | 1 | 0 | 49.2 |
| ***2*** | 1d | A1 | 47 | 87 | 0 | >99 | *trace* | 0 | 60.4 |
| ***3*** | 1c | A9 | 55 | 91 | 0 | >99 | *trace* | 0 | 52.1 |
| ***4*** | 1d | A9 | 52 | >99 | 0 | 96 | 0 | 4 | 63.9 |

**Conditions: 1a** is injected in a PFA tubing at 120 °C at a flow rate of 0.160 $mL \cdot min^{-1}$ and the flow rate of the amine is adapted to have equimolar amount vs αCC. [a] Conversion determined by $^1H$ NMR. [b] Product composition determined by $^1H$ NMR.

This study highlights the adaptability of the methodology and its scalability for industrial application, offering a sustainable and highly efficient pathway to produce oxazolidones in a continuous way. The ability to achieve high conversion in less than one minute, without the need

for solvents nor catalyst, not only makes the process more environmentally sustainable but also enhances efficiency and cost-effectiveness.

## CONCLUSIONS

This work presents a robust and efficient flow chemistry approach that integrates both homogeneous and heterogeneous catalysis for the synthesis of oxazolidones from $CO_2$-derived exovinylene cyclic carbonates and amines. Achieving up to 99% yield, this method demonstrates the reaction's efficiency under mild conditions using DMSO at 40 °C for 3.0–4.3 minutes, while also showcasing its high level of intensification when carried out solvent-free at 120 °C in under 1 minute. The continuous flow setup ensured optimal product yields and high conversion rates, with STY values ranging from 0.25 to 63.9 $kg \cdot L^{-1} \cdot h^{-1}$ and daily outputs spanning from 6 g to 426 g. In the heterogeneous catalysis system using acetonitrile, yields of 95% were achieved, with minimal impurity formation. DFT calculations provided key insights into the reaction mechanism, identifying multiple transition states and intermediates, and revealing amine-specific variations in Gibbs free energy and reaction rates. The process exhibited high versatility, with amine nucleophilicity and steric factors playing pivotal roles in the reaction efficiency. The technology demonstrated to be fast, scalable, and solvent-free, positioning it as a promising solution for the industrial production of oxazolidones.

## ASSOCIATED CONTENT

Supporting information is available free of charge on the ACS Publications website. Material and methods, $^{1}H$, $^{13}C$-NMR, FT-IR spectra, determination of αCC conversion, determination of hydroxy-oxazolidone selectivity, DFT calculation for the formation of the hydroxy-oxazolidone.

DFT-optimized geometries of all molecules, intermediates, and transition states discussed in this study are provided in the accompanying Excel files.

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## Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no conflict of interest.


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## REFERENCES


(1) Darvas, F.; Mezey, P. G.; Dormán, G.; Buchholcz, B.; Janáky, C.; Jones, R. V.; Sipos, G.; Peidl, T.; Mezohegyi, G. Chemistry-Related Innovations in Space, Benefits of Flow Chemistry. In *In-Space Manufacturing and Resources*; John Wiley & Sons, Ltd, **2022**; pp 109–140. https://doi.org/10.1002/9783527830909.ch6.

(2) Luo, H.; Ren, J.; Sun, Y.; Liu, Y.; Zhou, F.; Shi, G.; Zhou, J. Recent Advances in Chemical Fixation of CO2 Based on Flow Chemistry. *Chinese Chemical Letters* **2023**, *34* (5), 107782. https://doi.org/10.1016/j.cclet.2022.107782.

(3) Seo, H.; Nguyen, L. V.; Jamison, T. F. Using Carbon Dioxide as a Building Block in Continuous Flow Synthesis. *Adv Synth Catal* **2019**, *361* (2), 247–264. https://doi.org/10.1002/adsc.201801228.

(4) Wu, J.; Kozak, J. A.; Simeon, F.; Hatton, T. A.; Jamison, T. F. Mechanism-Guided Design of Flow Systems for Multicomponent Reactions: Conversion of CO2 and Olefins to Cyclic Carbonates. *Chem. Sci.* **2014**, *5* (3), 1227–1231. https://doi.org/10.1039/C3SC53422G.

(5) Seo, H.; Liu, A.; Jamison, T. F. Direct β-Selective Hydrocarboxylation of Styrenes with CO2 Enabled by Continuous Flow Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139* (40), 13969–13972. https://doi.org/10.1021/jacs.7b05942.

(6) Seo, H.; Katcher, M. H.; Jamison, T. F. Photoredox Activation of Carbon Dioxide for Amino Acid Synthesis in Continuous Flow. *Nature Chem* **2017**, *9* (5), 453–456. https://doi.org/10.1038/nchem.2690.

(7) Labiche, A.; Norlöff, M.; Feuillastre, S.; Taran, F.; Audisio, D. Continuous Flow Synthesis of Non-Symmetrical Ureas from CO2. *Asian Journal of Organic Chemistry* **2023**, *12* (3), e202200640. https://doi.org/10.1002/ajoc.202200640.

(8) Rehman, A.; Saleem, F.; Javed, F.; Ikhlaq, A.; Ahmad, S. W.; Harvey, A. Recent Advances in the Synthesis of Cyclic Carbonates via CO2 Cycloaddition to Epoxides. *Journal of Environmental Chemical Engineering* **2021**, *9* (2), 105113. https://doi.org/10.1016/j.jece.2021.105113.

(9) Zanda, N.; Zhou, L.; Alza, E.; W. Kleij, A.; À. Pericàs, M. Continuous Organocatalytic Flow Synthesis of 2-Substituted Oxazolidinones Using Carbon Dioxide. *Green Chemistry* **2022**, *24* (11), 4628–4633. https://doi.org/10.1039/D2GC00503D.

(10) Muzyka, C.; Renson, S.; Grignard, B.; Detrembleur, C.; Monbaliu, J.-C. M. Intensified Continuous Flow Process for the Scalable Production of Bio-Based Glycerol Carbonate. *Angewandte Chemie International Edition* **2024**, *63* (10), e202319060. https://doi.org/10.1002/anie.202319060.

(11) Vranješević, F.; Kolympadi Markovic, M.; Matulja, D.; Ambrožić, G.; Sordo, J. Á.; Laclef, S.; Vrček, V.; Marković, D. Recent Advances in the Synthesis of Five-Membered Cyclic Carbonates and Carbamates from Allylic or Propargylic Substrates and CO2. *Catalysts* **2022**, *12* (5), 547. https://doi.org/10.3390/catal12050547.

(12) Li, M.; Abdolmohammadi, S.; Hoseininezhad-Namin, M. S.; Behmagham, F.; Vessally, E. Carboxylative Cyclization of Propargylic Alcohols with Carbon Dioxide: A Facile and Green Route to α-Methylene Cyclic Carbonates. *Journal of CO2 Utilization* **2020**, *38*, 220–231. https://doi.org/10.1016/j.jcou.2020.01.024.

(13) Ngassam Tounzoua, C.; Grignard, B.; Detrembleur, C. Exovinylene Cyclic Carbonates: Multifaceted CO2-Based Building Blocks for Modern Chemistry and Polymer Science. *Angewandte Chemie* **2022**, *134* (22), e202116066. https://doi.org/10.1002/ange.202116066.

(14) Dabral, S.; Schaub, T. The Use of Carbon Dioxide (CO2) as a Building Block in Organic Synthesis from an Industrial Perspective. *Advanced Synthesis & Catalysis* **2019**, *361* (2), 223–246. https://doi.org/10.1002/adsc.201801215.

(15) Johnson, C.; Dabral, S.; Rudolf, P.; Licht, U.; Hashmi, A. S. K.; Schaub, T. Liquid-Liquid-Phase Synthesis of Exo-Vinylene Carbonates from Primary Propargylic Alcohols: Catalyst Design and Recycling. *ChemCatChem* **2021**, *13* (1), 353–361. https://doi.org/10.1002/cctc.202001551.

(16) Stiernet, P.; Verdin, A.; Svanberg Frisinger, M. S.; Grignard, B.; Malherbe, C.; Yuan, J.; Monbaliu, J.-C. M.; Detrembleur, C. Rapid $CO_2$ Coupling to Propargylic Alcohols: Unlocking the Production of α-Alkylidene Cyclic Carbonates *via* Continuous Flow. *Green Chem.* **2025**, *27* (3), 722–730. https://doi.org/10.1039/D4GC05716C.

(17) Gennen, S.; Grignard, B.; Tassaing, T.; Jérôme, C.; Detrembleur, C. CO2-Sourced α-Alkylidene Cyclic Carbonates: A Step Forward in the Quest for Functional Regioregular Poly(Urethane)s and Poly(Carbonate)s. *Angewandte Chemie International Edition* **2017**, *56* (35), 10394–10398. https://doi.org/10.1002/anie.201704467.

(18) Habets, T.; Siragusa, F.; Grignard, B.; Detrembleur, C. Advancing the Synthesis of Isocyanate-Free Poly(Oxazolidones)s: Scope and Limitations. *Macromolecules* **2020**, *53* (15), 6396–6408. https://doi.org/10.1021/acs.macromol.0c01231.

(19) Bruneau, C.; Dixneuf, P. H. Catalytic Incorporation of CO2 into Organic Substrates: Synthesis of Unsaturated Carbamates, Carbonates and Ureas. *Journal of Molecular Catalysis* **1992**, *74* (1), 97–107. https://doi.org/10.1016/0304-5102(92)80227-8.

(20) Shi, M.; Shen, Y.-M.; Chen, Y.-J. Reactions of 5,5-Dimethyl-4-Methylene-1,3-Dioxolan-2-One with Amines in the Presence of Palladium Catalyst. *HETEROCYCLES* **2002**, *57* (2), 245. https://doi.org/10.3987/COM-01-9379.

(21) Titov, I. Yu.; Chernysheva, N. B.; Chudinov, Yu. B.; Bogolyubov, A. A.; Semenov, V. V. 4-Methylenedioxolan-2-Ones as Convenient Synthons for the Preparation of Natural Products of the Berbine and Calycotomine Series. *Russ Chem Bull* **2006**, *55* (3), 569–575. https://doi.org/10.1007/s11172-006-0293-0.

(22) Li, X.; Villar-Yanez, A.; Ngassam Tounzoua, C.; Benet-Buchholz, J.; Grignard, B.; Bo, C.; Detrembleur, C.; Kleij, A. W. Cascade Transformation of Carbon Dioxide and Alkyne-1,n-Diols into Densely Substituted Cyclic Carbonates. *ACS Catal.* **2022**, *12* (5), 2854–2860. https://doi.org/10.1021/acscatal.1c05773.

(23) Shi, W.; Benet-Buchholz, J.; Kleij, A. W. Catalytic Transformation of Carbon Dioxide into Seven-Membered Heterocycles and Their Domino Transformation into Bicyclic Oxazolidinones. *Nat Commun* **2025**, *16* (1), 1372. https://doi.org/10.1038/s41467-025-56681-5.

(24) Joumier, J. M.; Fournier, J.; Bruneau, C.; Dixneuf, P. H. Functional Carbonates: Cyclic α-Methylene and β-Oxopropyl Carbonates from Prop-2-Ynyl Alcohol Derivatives and CO2. *J. Chem. Soc., Perkin Trans. 1* **1991**, No. 12, 3271–3274. https://doi.org/10.1039/P19910003271.

(25) Siragusa, F.; Van Den Broeck, E.; Ocando, C.; Müller, A. J.; De Smet, G.; Maes, B. U. W.; De Winter, J.; Van Speybroeck, V.; Grignard, B.; Detrembleur, C. Access to Biorenewable and CO2-Based Polycarbonates from Exovinylene Cyclic Carbonates. *ACS Sustainable Chem. Eng.* **2021**, *9* (4), 1714–1728. https://doi.org/10.1021/acssuschemeng.0c07683.

(26) Ouhib, F.; Grignard, B.; Van Den Broeck, E.; Luxen, A.; Robeyns, K.; Van Speybroeck, V.; Jerome, C.; Detrembleur, C. A Switchable Domino Process for the Construction of Novel CO2-Sourced Sulfur-Containing Building Blocks and Polymers. *Angewandte Chemie* **2019**, *131* (34), 11894–11899. https://doi.org/10.1002/ange.201905969.

(27) Li, D.; Gong, Y.; Du, M.; Bu, C.; Chen, C.; Chaemcheun, S.; Hu, J.; Zhang, Y.; Yuan, Y.; Verpoort, F. CO2-Promoted Hydration of Propargylic Alcohols: Green Synthesis of α-Hydroxy Ketones by an Efficient and Recyclable AgOAc/Ionic Liquid System. *ACS Sustainable Chem. Eng.* **2020**, *8* (22), 8148–8155. https://doi.org/10.1021/acssuschemeng.9b07546.

(28) Toullec, P.; Carbayo Martin, A.; Gio-Batta, M.; Bruneau, C.; Dixneuf, P. H. Stereoselective Preparation of *Z*-Trisubstituted Alkylidene Cyclic Carbonates via Palladium-Catalyzed Carbon□carbon Bond Formation. *Tetrahedron Letters* **2000**, *41* (29), 5527–5531. https://doi.org/10.1016/S0040-4039(00)00889-3.

(29) Zhang, Y.-F.; Lai, W.-M.; Xie, S.; Zhou, H.; Lu, X.-B. Facile Synthesis, Structure and Properties of CO2-Sourced Poly(Thioether-Co-Carbonate)s Containing Acetyl Pendants via Thio-Ene Click Polymerization. *Polym. Chem.* **2022**, *13* (2), 201–208. https://doi.org/10.1039/D1PY01477C.

(30) Habets, T.; Seychal, G.; Caliari, M.; Raquez, J.-M.; Sardon, H.; Grignard, B.; Detrembleur, C. Covalent Adaptable Networks through Dynamic N,S-Acetal Chemistry: Toward Recyclable CO2-Based Thermosets. *J. Am. Chem. Soc.* **2023**, *145* (46), 25450–25462. https://doi.org/10.1021/jacs.3c10080.

(31) Caliari, M.; Vidal, F.; Mantione, D.; Seychal, G.; Campoy-Quiles, M.; Irusta, L.; Fernandez, M.; de Pariza, X. L.; Habets, T.; Aramburu, N.; Raquez, J.-M.; Grignard, B.; Müller, A. J.; Detrembleur, C.; Sardon, H. Fully Recyclable Pluripotent Networks for 3D Printing Enabled by Dissociative Dynamic Bonds. *Advanced Materials* **2025**, *37* (15), 2417355. https://doi.org/10.1002/adma.202417355.

(32) Siragusa, F.; Crane, L.; Stiernet, P.; Habets, T.; Grignard, B.; Monbaliu, J.-C. M.; Detrembleur, C. Continuous Flow Synthesis of Functional Isocyanate-Free Poly(Oxazolidone)s by Step-Growth Polymerization. *ACS Macro Letters* **2024**. https://doi.org/10.1021/acsmacrolett.4c00203.

(33) Wong, A. R.; Barrera, M.; Pal, A.; Lamb, J. R. Improved Characterization of Polyoxazolidinones by Incorporating Solubilizing Side Chains. *Macromolecules* **2022**, *55* (24), 11006–11012. https://doi.org/10.1021/acs.macromol.2c02104.

(34) Dabral, S.; Licht, U.; Rudolf, P.; Bollmann, G.; Hashmi, A. S. K.; Schaub, T. Synthesis and Polymerisation of α-Alkylidene Cyclic Carbonates from Carbon Dioxide, Epoxides and the Primary Propargylic Alcohol 1,4-Butynediol. *Green Chem.* **2020**, *22* (5), 1553–1558. https://doi.org/10.1039/C9GC04320A.

(35) Habets, T.; Méreau, R.; Siragusa, F.; Grignard, B.; Detrembleur, C. Fast, Regioselective Aminolysis of Tetrasubstituted Cyclic Carbonates and Application to Recyclable Thermoplastics and Thermosets. *ACS Macro Lett.* **2024**, *13* (11), 1425–1432. https://doi.org/10.1021/acsmacrolett.4c00570.

(36) Pal, A.; Wong, A. R.; Lamb, J. R. Chemically Recyclable, High Molar Mass Polyoxazolidinones via Ring-Opening Metathesis Polymerization. *ACS Macro Lett.* **2024**, *13* (5), 502–507. https://doi.org/10.1021/acsmacrolett.4c00147.

(37) Shinabarger, D. Mechanism of Action of the Oxazolidinone Antibacterial Agents. *Expert Opinion on Investigational Drugs* **1999**, *8* (8), 1195–1202. https://doi.org/10.1517/13543784.8.8.1195.

(38) Foti, C.; Piperno, A.; Scala, A.; Giuffrè, O. Oxazolidinone Antibiotics: Chemical, Biological and Analytical Aspects. *Molecules* **2021**, *26* (14), 4280. https://doi.org/10.3390/molecules26144280.

(39) Müller, M.; Schimz, K.-L. Oxazolidinones: A Novel Class of Antibiotics. *CMLS, Cell. Mol. Life Sci.* **1999**, *56* (3), 280–285. https://doi.org/10.1007/s000180050429.

(40) Fernandes, G. F. S.; Scarim, C. B.; Kim, S.-H.; Wu, J.; Castagnolo, D. Oxazolidinones as Versatile Scaffolds in Medicinal Chemistry. *RSC Med. Chem.* **2023**, *14* (5), 823–847. https://doi.org/10.1039/D2MD00415A.

(41) Pathania, S.; Petrova-Szczasiuk, K.; Pentikäinen, O.; Singh, P. K. Oxazolidinones: Are They Only Good for the Discovery of Antibiotics? A Worm's Eye View. *Journal of Molecular Structure* **2023**, *1286*, 135630. https://doi.org/10.1016/j.molstruc.2023.135630.

(42) Sendijarevic, V.; Sendijarevic, A.; Lekovic, H.; Lekovic, H.; Frisch, K. C. Polyoxazolidones for High Temperature Applications. *Journal of Elastomers & Plastics* **1996**, *28* (1), 63–83. https://doi.org/10.1177/009524439602800104.

(43) Azechi, M.; Endo, T. Synthesis and Property of Polyoxazolidone Having Fluorene Moiety by Polyaddition of Diisocyanate and Diepoxide. *Journal of Polymer Science Part A: Polymer Chemistry* **2014**, *52* (12), 1755–1760. https://doi.org/10.1002/pola.27181.

(44) Kitayama, M.; Isda, Y.; Odaka, F.; Anzai, S.; Irako, K. Synthesis and Properties of Polyoxazolidone Elastomers from Diepoxides and Diisocyanates. *Rubber Chemistry and Technology* **1980**, *53* (1), 1–13. https://doi.org/10.5254/1.3535029.

(45) Altmann, H. J.; Clauss, M.; König, S.; Frick-Delaittre, E.; Koopmans, C.; Wolf, A.; Guertler, C.; Naumann, S.; Buchmeiser, M. R. Synthesis of Linear Poly(Oxazolidin-2-One)s by Cooperative Catalysis Based on N-Heterocyclic Carbenes and Simple Lewis Acids. *Macromolecules* **2019**, *52* (2), 487–494. https://doi.org/10.1021/acs.macromol.8b02403.

(46) Makarov, M.; Bourguignon, M.; Grignard, B.; Detrembleur, C. Advancing Non-Isocyanate Polyurethane Foams: Exo-Vinylene Cyclic Carbonate–Amine Chemistry Enabling Room-Temperature Reactivity and Fast Self-Blowing. *Macromolecules* **2025**, *58* (3), 1673–1685. https://doi.org/10.1021/acs.macromol.4c02894.

(47) G. Newman, S.; F. Jensen, K. The Role of Flow in Green Chemistry and Engineering. *Green Chemistry* **2013**, *15* (6), 1456–1472. https://doi.org/10.1039/C3GC40374B.

(48) Chen, Y.; de Frutos, O.; Mateos, C.; Rincon, J. A.; Cantillo, D.; Kappe, C. O. Continuous Flow Photochemical Benzylic Bromination of a Key Intermediate in the Synthesis of a 2-Oxazolidinone. *ChemPhotoChem* **2018**, *2* (10), 906–912. https://doi.org/10.1002/cptc.201800114.

(49) Song, Q.-W.; Chen, W.-Q.; Ma, R.; Yu, A.; Li, Q.-Y.; Chang, Y.; He, L.-N. Bifunctional Silver(I) Complex-Catalyzed CO2 Conversion at Ambient Conditions: Synthesis of α-Methylene Cyclic Carbonates and Derivatives. *ChemSusChem* **2015**, *8* (5), 821–827. https://doi.org/10.1002/cssc.201402921.

(50) Song, Q.-W.; Zhou, Z.-H.; Wang, M.-Y.; Zhang, K.; Liu, P.; Xun, J.-Y.; He, L.-N. Thermodynamically Favorable Synthesis of 2-Oxazolidinones through Silver-Catalyzed Reaction of Propargylic Alcohols, CO2, and 2-Aminoethanols. *ChemSusChem* **2016**, *9* (16), 2054–2058. https://doi.org/10.1002/cssc.201600470.

(51) Aricò, F.; Bravo, S.; Crisma, M.; Tundo, P. 1,3-Oxazinan-2-Ones via Carbonate Chemistry: A Facile, High Yielding Synthetic Approach. *Pure and Applied Chemistry* **2016**, *88* (3), 227–237. https://doi.org/10.1515/pac-2015-1004.

(52) Gandini, A. The Furan/Maleimide Diels–Alder Reaction: A Versatile Click–Unclick Tool in Macromolecular Synthesis. *Progress in Polymer Science* **2013**, *38* (1), 1–29. https://doi.org/10.1016/j.progpolymsci.2012.04.002.

(53) Moreira Grilo, L.; Faoro, S.; Folkersma, R.; Lacerda, T. M.; Mazzocchetti, L.; Loos, K.; Maniar, D. Biobased Networks from Lignin/Cellulose via Diels–Alder Click Chemistry. *ACS Appl. Polym. Mater.* **2024**, *6* (22), 13723–13734. https://doi.org/10.1021/acsapm.4c02434.

(54) Hoyle, C. E.; Bowman, C. N. Thiol–Ene Click Chemistry. *Angewandte Chemie International Edition* **2010**, *49* (9), 1540–1573. https://doi.org/10.1002/anie.200903924.

(55) Haldón, E.; Nicasio, M. C.; Pérez, P. J. Copper-Catalysed Azide–Alkyne Cycloadditions (CuAAC): An Update. *Org. Biomol. Chem.* **2015**, *13* (37), 9528–9550. https://doi.org/10.1039/C5OB01457C.

(56) Pim, S.; Campbell, A. D. G.; Levshov, D.; Herrebout, W.; Durán-Sampedro, G.; Hall, M. J.; Armstrong, R. J.; O'Shea, D. F. Double Click for Chirality: Chiral Dibenzo-Cycloocta-Bis-Triazoles via Strain-Promoted Alkyne-Azide Cycloaddition. *ChemPhotoChem* **2025**, *9* (7), e202500042. https://doi.org/10.1002/cptc.202500042.

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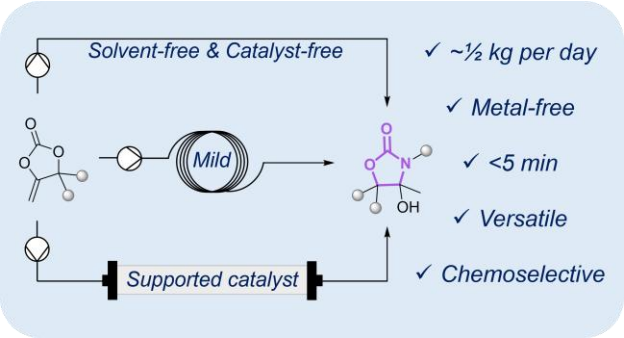


The aminolysis of alkylidene cyclic carbonates in flow rapidly and selectively produces oxazolidones with a high productivity, while minimizing hazardous reagents and wastes.