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Fast, selective and scalable flow ammonolysis of oxiranes accessible from glycerol toward bio-based amines

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We report a fast, selective, and scalable continuous-flow ammonolysis of oxiranes accessible from glycerol as a sustainable route to amine-functionalized products. Our objective was to upgrade glycidol (**1a**) and epichlorohydrin (**1b**) using aqueous and neat liquid ammonia with rigorous process control and successful pilot-scale translation. For glycidol, we achieve >99% conversion and >98% selectivity to 1-amino-2,3-propanediol (**2a**) in 30 s (120 °C). Mechanistic studies reveal a strong solvent effect, with water promoting epoxide activation and guiding the choice between aqueous and liquid NH₃ regimes based on the inherent reactivity of substrates **1a,b**. Downstream, **2a** is converted to oxazolidinone **3** through an organocatalytic carbonylation using neat dimethyl carbonate, with the assistance of a dedicated in-line methanol-removal module to address equilibrium limitations. For epichlorohydrin (**1b**), the ammonolysis with neat ammonia can be finely tuned to access either 1-amino-3-chloro-2-propanol (**2b**) or 1,3-diamino-2-propanol (**2c**) with high yield and selectivity. The platform delivers strong process metrics (*E*-factor ≤ 6.6, STY up to 166 kg day⁻¹ L⁻¹) and is validated at pilot scale for both ammonia sources on glycidol and epichlorohydrin. Overall, this integrated strategy offers an industrially relevant, safe, and low-waste alternative to classical batch aminolysis for producing bio-based amine derivatives from glycerol.

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1. This work advances green chemistry by enabling a safe, selective, and scalable continuous-flow ammonolysis of glycerol-derived oxiranes using both aqueous and neat liquid ammonia. The developed platform ensures controlled ammonia handling and efficient process intensification toward bio-based amines and oxazolidinones.
2. The process valorizes glycerol, a renewable biodiesel by-product, into high-value nitrogen-functionalized intermediates with excellent sustainability metrics (*E*-factor ≤ 6.6, STY up to 166 kg day⁻¹ L⁻¹) and multi-kilogram productivity. Compared to classical batch ammonolysis, it eliminates sacrificial additives and minimizes solvent use, offering a safe and low-waste route to ammonolysis chemistry.
3. Future efforts will aim to further improve the process through solvent recycling, integration of inline purification, and broader substrate scope exploration. Coupling renewable ammonia production and energy sources will strengthen its contribution to circular, bio-based manufacturing.

Introduction

The production of biodiesel has grown steadily over the past decade,¹ generating approximately 10 wt% of glycerol as a by-product, and creating a surplus that calls for efficient valorization strategies and the development of high-value applications. A vast lineage of higher-value derivatives emerges from gly-

cerol, with a wide array of upgrading opportunities (Fig. 1a).^{2–4} Early in this value chain, two activated oxirane platforms, namely, glycidol (**1a**) and epichlorohydrin (**1b**), stand out. Their versatile applications in polymers,⁵ surfactants,⁶ pharmaceuticals,^{3,7} and fine chemicals^{8,9} make **1a,b** privileged nodes for further upgrading. Further downstream, their corresponding amino-alcohols, 1-amino-2,3-propanediol (**2a**), 1-amino-3-chloro-2-propanol (**2b**) and 1,3-diamino-2-propanol (**2c**), open additional perspectives. Compounds **2a–c** play a role as intermediates for active pharmaceutical ingredients (e.g., non-ionic contrast agent Iodixanol),¹⁰ and as versatile building blocks for high-end applications^{11–14} and functional monomers¹⁵ (Fig. 1a). Selective, efficient, and scalable ammonolysis pathways would broaden the glycerol chain of value, and

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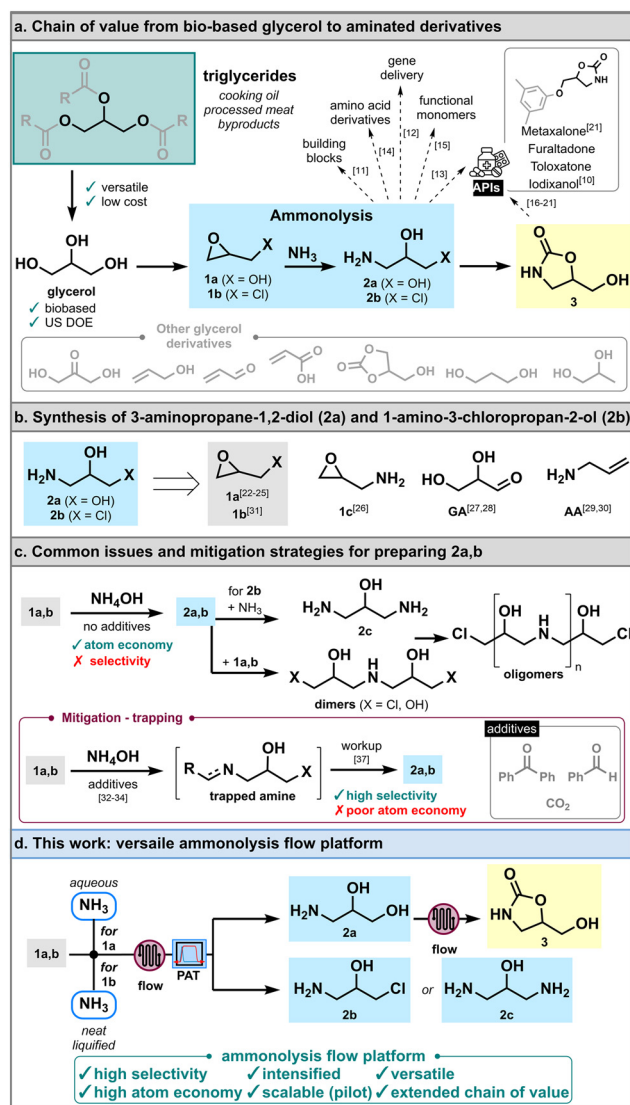


Fig. 1 (a) Value chain from bio-based glycerol to aminated derivatives and their industrial applications. Glycerol, an abundant by-product of biodiesel, can be upgraded into activated intermediates such as glycidol (**1a**) and epichlorohydrin (**1b**). Their selective ammonolysis affords 1-amino-2,3-propanediol (**2a**), 1-amino-3-chloro-2-propanol (**2b**), or 1,3-diaminopropane-2-ol (**2c**) which serve as building blocks for pharmaceuticals (e.g., metaxalone, iodixanol), pharmaceutical building-blocks (e.g., oxazolidinones), functional monomers, and fine chemicals. This roadmap illustrates the progressive valorization of glycerol into high-value molecules. (b) Main route for **2a,b** starting from **1a,b**, as well as alternative routes with limited industrial interest. (c) Side products formed during the synthesis of **2a,b** and strategies to increase selectivity. (d) Continuous flow strategy to produce **2a** from **1a** using aqueous ammonia or to produce **2b** from **1b** using neat ammonia. **2a** can be further derivatized to **3**.

support the transition from a petro- to a bio-based economy. Moreover, **2a** can be further converted into 5-(hydroxymethyl) oxazolidinone (**3**) by reacting with CO₂ surrogates, such as dimethyl carbonate (**DMC**). The oxazolidinone pattern is present in various active pharmaceutical ingredients.^{16–21}

The conventional protocol for the ammonolysis of **1a** relies on aqueous ammonia.^{22–24} Alternative approaches, such as a Gabriel synthesis with phthalimide,²⁵ or the functionalization of alternative building blocks such as **1c**,²⁶ the reduction of glycer-aldehyde (**GA**) using metal catalyst,^{27,28} allylamine (**AA**) dihydroxylation with OsO₄^{29,30} have niche applicability, limited scalability and reduced economic viability (Fig. 1b). On the other hand, the ammonolysis of **1b** is significantly more challenging due to the high reactivity of product **2b**,³¹ and reports of its direct synthesis from ammonia are practically absent in the literature.^{32–34}

For both **1a** and **1b**, dimerization is the main side reaction, as the formed primary amine readily reacts with the substrate (Fig. 1c). To suppress this, additives such as benzaldehyde,³⁵ benzophenone³² or CO₂³⁶ are often employed to temporarily mask the problematic amine functionality as imines or carbamates, followed by release during workup (Fig. 1c).³⁷ While effective, these strategies increase process complexity, purification demands, waste generation, and may require additional steps to recover or recycle the additive.

Continuous operation is known to lead to safer processes, particularly when handling toxic and corrosive compounds such as ammonia, while providing superior mass and heat transfer, and improved selectivity.³⁸ For glycidol (**1a**), a limited number of continuous processes leading to **2a** have been reported. Three patents applied to by Degussa GmbH (now Evonik Degussa) report the ammonolysis of **1a** using liquid ammonia under high pressure.^{39–41} At the time, the processes represented a significant improvement on published methods, increasing the yield from 68% (reported by Baum) to up to 83% while increasing the space-time-yield (STY) by approximately 50-fold.⁴¹ More recently, Vilé *et al.*⁴² reported a gram-scale flow ammonolysis of **1a** using aqueous ammonia (125 °C, 0.2 h); however, the microfluidic process did not outperform existing technologies (Table 1).

In this work, we report an intensified and versatile flow platform for the upgrading of oxiranes accessible from glycerol (Fig. 1d). We explored ammonolysis using both aqueous and neat ammonia, enabling the production of **2a** with an STY exceeding previous reports by more than 50-fold. Furthermore, we report a novel and scalable synthetic route for the direct conversion of **1b** into **2b**. The reported protocols are associated with excellent *E*-factors.

Results and discussion

Microfluidic-scale preliminary optimization

We began our optimization with a preliminary screening of conditions for the aqueous ammonolysis of glycidol (**1a**, Fig. 2a). Previously reported protocols for the batch ammonolysis of **1a** typically require ≥100 equivalents of ammonia for the reaction, affording yields between 44% to 97%.^{22–24,40,43} Subsequent optimization studies reduced the ammonia loading to 14.7 equiv., delivering **2a** in 95% yield after over 9 hours at 15 °C.⁴⁴ The use of this large excess is primarily driven by the need to enhance selectivity and suppress the dimerization by-products.

Table 1 Results obtained from continuous processes for the ammonolysis of **1a** with aqueous ammonia

Parameter	This work	Vil�� ³⁷	US4358615	US4356323	US4360697
Ammonia Source	Aq. NH ₃ (28–30%)	Aq. NH ₃ (14 M)	Aq. NH ₃ (77%)	Neat NH ₃	Neat NH ₃
Solvent	MeOH (4 M)	MeOH (0.1 M)	No	No	Toluene (11.7 M)
Temp. (�C)	110	125	85	85	85
Pressure (bar)	13	10	43	45	43
Res. time (s)	30	720	4608	4146	4146
Conversion Selectivity or Yield (%)	>99% (>98%) ^a	81% ^b	83% ^c	69% ^c	53.5% ^c
Equiv. of ammonia	20	140	17	15	17
<i>E</i> -Factor	5.9 ^d	139.6	3.8	4.2	7.7
STY (kg day ^{−1} L ^{−1})	166	0.4	2.9	3.1	1.9

^a Conversion (selectivity). ^b NMR yield. ^c Isolated yield. ^d *E*-Factor of 4 when using 10 equiv. of ammonia.

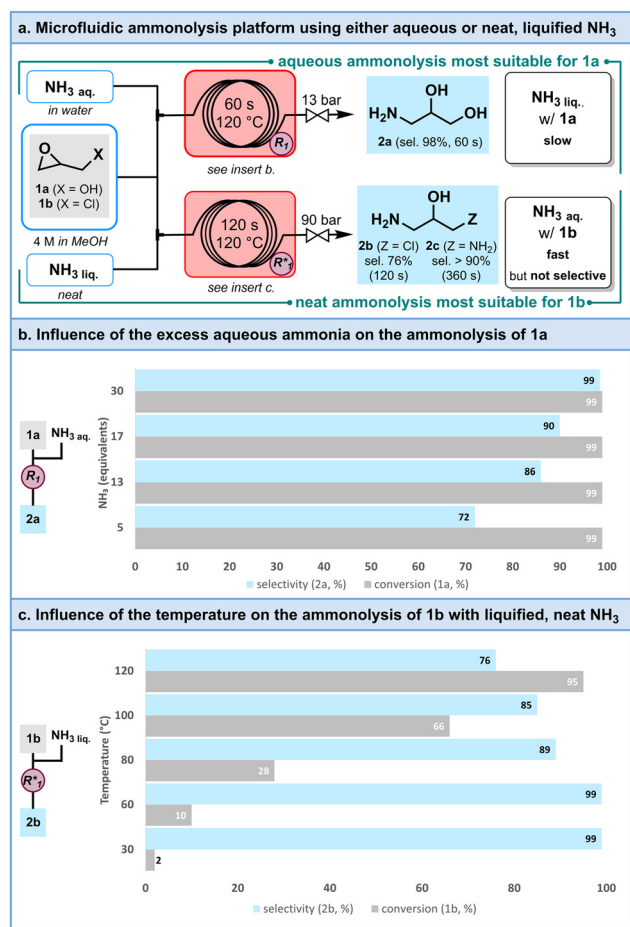


Fig. 2 Microfluidic optimization of the ammonolysis of **1a** with aqueous ammonia and of **1b** with liquefied neat ammonia. (a) Simplified microfluidic setups and conditions. (b) Influence of the excess aqueous ammonia on the ammonolysis of **1a**. Data collected at the microfluidic scale, under 120  C, 13 bar and 1 min of residence time. (c) Influence of the temperature on the ammonolysis of **1b** with liquefied neat NH₃. Data collected at the microfluidic scale with 30 equiv. of NH₃, under 120  C, 90 bar and 2 min of residence time.

In continuous processes, the reported excess is generally between 10 and 20 equiv., with less than 5 equiv. leading to increased dimerization.⁴⁰ In our microfluidic development,

using 17 equiv. of NH₃ led to 90% selectivity, whereas 30 equiv. of NH₃ resulted in the dimer formation being nearly eliminated, affording **2a** with >98% selectivity (120  C, 1 min; Fig. 2b). The concentration of the glycidol feed solution was evaluated over the range of 1 to 4 M. Higher concentrations consistently led to improved selectivity under otherwise identical conditions (data not shown). Concentrations above 4 M were not investigated due to the impractical quantity of material required for experimentation at higher loadings.

The same transformation was tested using neat NH₃. A stainless-steel (SS) microfluidic setup capable of operating at pressures up to 90 bar and elevated temperatures was developed (Fig. 2a). The application of high pressure was required solely to maintain NH₃ in the liquid phase and was not intended to influence the intrinsic reactivity. In-line density monitoring was used to confirm complete liquid-phase behavior of NH₃.

The ammonolysis of **1a** with neat NH₃ was significantly slower, requiring *ca.* 12 min for full conversion with neat NH₃, compared to *ca.* 1 min with aqueous NH₃ (SI, Fig. S11). To rationalize this reactivity difference, a controlled water feed was introduced on the neat NH₃ line (SI, Fig. S12). Systematic variations of water content revealed that the addition of ≥ 10 equivalents of H₂O was necessary to restore the reactivity observed in the aqueous system, which corresponds to an aqueous NH₃ solution of 74% w/w. These results indicate that water is not merely an inert diluent but likely plays an active role in epoxide activation. This rate acceleration may be attributed to hydrogen bonding: H₂O is a strong hydrogen-bond donor (HBD), therefore facilitating epoxide ring-opening, whereas NH₃ itself is a poor HBD.⁴⁵ In aqueous media, the NH₃/NH₄⁺ equilibrium may further contribute, as ammonium species are superior hydrogen-bond donors. Overall, aqueous ammonia proved to be the most efficient and scalable medium for glycidol (**1a**) ammonolysis, combining rapid conversion, high selectivity, and safer handling conditions.

Ammonolysis of epichlorohydrin (**1b**) presents a more complex reaction profile than **1a** due to the labile C–Cl bond. In aqueous NH₃, the primary product, 1-amino-3-chloro-2-propanol (**2b**), readily undergoes a second amination to afford 1,3-diamino-2-propanol (**2c**), plausibly *via* an aziridinium intermediate. The latter was detected in GC-MS, and its relative

abundance correlates with the formation of **2c**. Temperature screening in aqueous NH_3 (30 equiv., 1 min residence time) from room temperature to 120 °C showed that complete conversion of **1b** is reached at 70 °C. However, the selectivity toward **2b** decreased with increasing temperature. The best compromise in aqueous medium was identified at 50–60 °C (*ca.* 53% GC yield of **2b**), whereas higher temperatures favored the double amination to **2c** (SI, Fig. S4).

Similar to our observations with **1a**, ammonolysis of **1b** in neat NH_3 resulted in a slower reaction (Fig. 2a and c). However, in the case of **1b**, this reduced reactivity proved advantageous for selectively accessing **2b**. Within 2 min residence time and a reaction temperature of 120 °C, we obtained near-quantitative epoxide conversion and 70–76% selectivity to **2b**. This behavior is consistent with the solvent effect described earlier for **1a**. Liquid ammonia behaves as a dipolar aprotic medium in nucleophilic substitutions, making Cl^- expulsion less favorable than in water,⁴⁶ and thus mitigating over-amination at short residence times.

The effect of NH_3 equivalents was negligible between 20 to 30 equiv. of NH_3 . Attempts to decrease NH_3 below 20 equiv. led to solid precipitation and reactor clogging, potentially due to oligomerization. Extending the residence time beyond 2 min shifted the system toward **2c**, with >90% selectivity towards the diamine **2c** obtained at a residence time of 6 min. This was accompanied by precipitation of hydrochloride salts in the collection flask (SI, Fig. S16).

Overall, these results indicate a residence-time-dependent divergence in reactivity: neat NH_3 at 120 °C enables direct access to **2b** from epichlorohydrin (**1b**) at short residence times (2 min), whereas longer residence times force the second amination, affording diamine **2c**.

Transposition to pilot scale

The first process to be transferred to pilot scale was the aqueous ammonolysis of **1a** (Fig. 3a). Among the commercial mesofluidic options available in our facility, a Corning® Advanced-Flow™ G1 Silicon Carbide (SiC) Reactor was selected instead of the more conventional glass option due to its chemical compatibility with aqueous ammonia. The reactor configuration comprised two fluidic modules dedicated to pre-heating each reactive feed, followed by three fluidic modules connected in series for the reaction zone (Fig. 3a, 8 mL per fluidic module, 24 mL total volume). Glycidol (**1a**, 4 M in MeOH) was delivered using a dual-piston pump coupled to a Coriolis mass-flow meter; while aqueous NH_3 (28–30 wt%) was fed using a dual-syringe pump. Process stability was monitored through the installation of thermocouples and pressure sensors at critical points along the system, with data managed *via* Hitec Zang LabManager®. No significant increase in temperature or hotspots were detected throughout the course of the reaction. System pressure was controlled using an Equilibar® back-pressure regulator (SI, section 3.1.2).

The results obtained in this reactor surpassed those achieved at the microfluidic scale. Complete conversion was observed even at half the residence time previously required

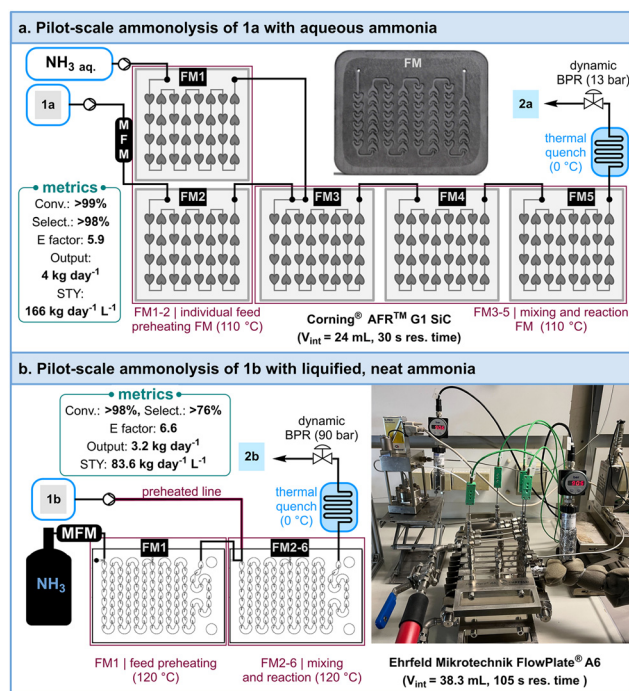


Fig. 3 Pilot scale experiments (FM = fluidic module; BPR = back-pressure regulator; MFM = Coriolis mass flow meter). (a) Simplified continuous flow setup for the ammonolysis of **1a** using aqueous ammonia (Corning® AFR™ G1 SiC). (b) Simplified continuous flow setup for the ammonolysis of **1b** using liquefied neat ammonia (Ehrfeld Mikrotechnik FlowPlate® A6).

(Table 2, entry 3). Further optimization at pilot scale enabled a reduction in temperature (110 °C instead of 120 °C) and a decrease in ammonia excess from 30 to 20 equivalents while maintaining 98% selectivity (Table 2, entry 4), or even 10 equiv. with only a marginal loss in selectivity (97%, Table 2, entry 5; SI, section 3.1.2.2).

The optimized pilot-scale process was run for 20 reactor volumes (10 min), producing 22 g of product. It exhibited excellent sustainability and productivity metrics, including a

Table 2 Pilot scale results for the ammonolysis of glycidol (**1a**) with aqueous ammonia

Entry	Res. time ^a (s)	NH_3 (equiv.)	1a (conv., %)	2a (sel., %)
1	60	30	>99	>99
2	45	30	>99	>99
3	30	30	>99	>99
4	30	20	>99	>99 (98 ^b)
5	30	10	>99	97
6	12	20	94	>99
7	60	30	>99	>99
8	45	30	>99	>99

^a All experiments were carried out in a Corning® AFR™ G1 SiC reactor at 110 °C with 4 M glycidol in MeOH, 28–30 wt% aqueous NH_3 . Samples were analyzed by GC-FID (%area). ^b Selectivity obtained by ¹H NMR.

low *E*-factor (5.9), high productivity (3.98 kg day⁻¹), and a high space-time yield (STY = 166 kg day⁻¹ L⁻¹) (SI, section 3.1.2.3).

Next, a pilot scale continuous flow setup capable of withstanding the high pressure required for the ammonolysis of epichlorohydrin (**1b**) with neat ammonia was developed (Fig. 3b). The reactor consisted of a commercial Hastelloy® (C22) A6 FlowPlate™ mesofluidic reactor from Ehrfeld Mikrotechnik® (38.3 mL internal volume). Both the organic feed (**1b**, 4 M in MeOH) and neat ammonia were delivered using dual-syringe pumps. A Coriolis mass-flow meter was used to monitor the density of the ammonia stream and ensure the liquid-phase state. The ammonia stream was preheated in one 5.6 mL A6 FlowPlate™ fluidic module, whereas epichlorohydrin (**1b**) was preheated in a stainless-steel line. The system pressure was set to 90 bar using an Equilibar® back-pressure regulator. Temperature and pressure sensors were placed at strategic locations, with flow rates, density, pressure and temperature continuously monitored with LabManager®. No significant increase in temperature or hot-spots were detected throughout the course of the reaction (SI, section 3.2.2).

Under these pilot-scale conditions, conversion (>98%) and selectivity towards product **2b** (76%) were comparable to those obtained in the microfluidic prototype (Table 3). These results indicate that, for this reaction, the higher mixing efficiency afforded by commercial reactors including static mixers does not influence the reaction outcome. This is consistent with the assumption that liquid NH₃ is fully miscible with the reaction medium and indicates that the reaction is not mass-transfer limited.

The process using neat ammonia has an *E*-factor of 6.6, comparable to the aqueous route, while benefiting from reduced water usage. The optimized process was run for 6 reactor volumes (10 min) producing around 30 g of **2b**. The productivity (3.2 kg day⁻¹) and space-time yield (STY = 83.6 kg day⁻¹ L⁻¹) further highlight the attractiveness of the process.

Extending the residence time beyond 2 min led to the formation of a white solid in the collection vessel, consistent with downstream formation of the hydrochloride salt of **2c**. However, no attempts to produce **2c** at pilot scale were per-

formed. Finally, a trial performed using the FlowPlate™ reactor with glycidol (**1a**) and neat ammonia (30 equiv.) resulted in only 44% conversion after 2 minutes of residence time (120 °C), confirming the observations made at the microfluidic scale.

Downstream upgrading of aminated glycerol derivatives

As a demonstration of downstream upgrading, we targeted the synthesis of oxazolidinones from 1-amino-2,3-propanediol (**2a**) via carbonylation with dimethyl carbonate (**DMC**). Initial solvent screening showed that only alcohols (MeOH, EtOH or *i*PrOH) could effectively solubilize the system; however, in all cases, significant transesterification side-reactions were observed. Therefore, the reaction was carried out under neat conditions. A range of organic (super)bases was screened as organocatalysts, including amidines (DBU, DBN), guanidines (TBD, MeTBD), phosphazenes (BEMP, P₁-*t*-Bu) and proton sponge (DMAN).^{47,48} Quantitative conversion of **2a** was achieved in all cases, and most organocatalysts provided oxazolidinone **3** with good to excellent selectivity (77–90%). In contrast, DMAN gave only 33% selectivity toward **3** (SI, section 4.1).

DBU was selected for further optimization considering its low cost, availability and efficiency. A design of experiment (DoE) approach was employed to maximize the formation of the desired oxazolidinone **3** while minimizing the formation of intermediates and side-products. The influence of temperature, **DMC** equivalents, and catalyst loading was evaluated (Fig. 4a and SI, section 4.2).

Before optimizing the reaction in flow, efforts were made to elucidate the structure of the main side-product through NMR, IR and GC-MS (SI, sections 4.3 and 4.4). The data converged on 2 plausible structures (**4** and **6**). The first potential structure, oxazolidinone **4** (impurity A in Fig. 4b), bears a linear carbonate moiety and could be formed from the direct reaction of desired product **3** with another equivalent of **DMC**. The second potential structure, compound **6** (impurity B in Fig. 4b), features a cyclic carbonate moiety, potentially deriving from the addition of **DMC** to intermediate *int*-**3**, giving linear carbonate **5**, followed by cyclization to **6**. Alternatively, a possible Payne-type rearrangement⁴⁹ of oxazolidinone **3** into isomeric cyclic carbonate *iso*-**3**, followed by reaction with **DMC** could also lead to the formation of **6**.

To determine the identity of the side product, **4** was synthesized (SI, section 4.3). Comparison of the spectroscopic data confirmed the main side-product to be **4**. Furthermore, to probe the possible Payne-type rearrangement, isomeric carbonate *iso*-**3** was independently synthesized from **2a** in three steps (SI, section 4.4) and subsequently heated in the presence of DBU (5 mol%). No conversion toward **3** was observed, suggesting that ring strain and unfavorable bond angles prevent this Payne-type rearrangement.

Preliminary microfluidic optimization highlighted several challenges associated with the carbonylation of **2a**. The high viscosity of amino diol **2a** required preheating of both the pump and feed lines to ensure smooth delivery (Fig. 4c and SI,

Table 3 Pilot scale results for the ammonolysis of epichlorohydrin (**1b**) with neat ammonia

Entry	Res. time ^a (min)	NH ₃ (equiv.)	1b (conv., %)	2b (sel., %)
1	0.75	30	54	80
2	1	30	66	78
3	1.5	30	87	76
4	1.75	30	93	76
5	2	30	96	Clogging
6	1.5	20	97	76
7	1.75	20	>98	76
8	2	20	>99	Clogging

^a All experiments were carried out at 120 °C with 4 M epichlorohydrin in MeOH. Samples were analyzed by GC-FID (%area). Selectivity was obtained by ¹H NMR.

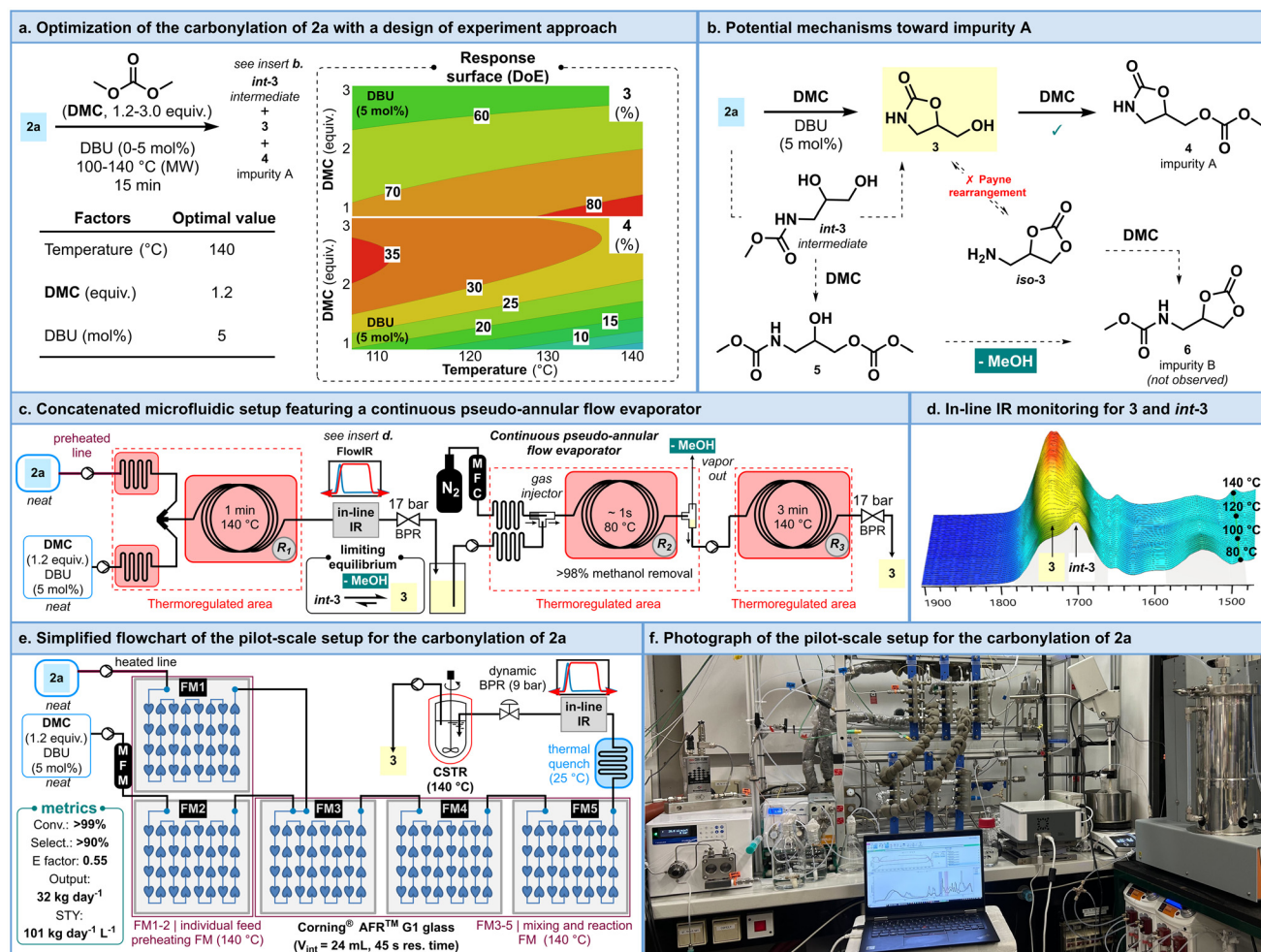


Fig. 4 Downstream upgrading of 1-amino-2,3-propanediol (2a). (a) Optimization of the carbonylation of 2a with dimethyl carbonate (DMC) in the presence of DBU (5 mol%) as organocatalyst following a design of experiment (DoE) approach. (b) Mechanistic study for the identification of potential impurities A (4) and B (6). (c) Concatenated microfluidic setup featuring a continuous pseudo-annular flow evaporator. The flow evaporator enabled the continuous removal of methanol, thus shifting the limiting equilibrium connecting *int-3* and 3 by favoring the intramolecular transesterification. (d) Implementation of PAT for in-line reaction monitoring through IR: details of data acquisition showing the increased conversion of *int-3* ($\nu_{\text{C=O}} = 1699 \text{ cm}^{-1}$, 1540 cm^{-1}) to 3 ($\nu_{\text{C=O}} = 1734 \text{ cm}^{-1}$) at higher temperatures. (e) Simplified flow setup for the transposition of the carbonylation of 2a to pilot scale. The reactor setup features a commercial glass Corning® Advanced-Flow™ G1 mesofluidic reactor. (f) Photograph of the pilot-scale reactor setup.

section 4.5). Moreover, the conversion of linear intermediate *int-3* into oxazolidinone 3 plateaued after 12 minutes, indicating that an equilibrium was reached once the reaction medium became saturated in methanol, limiting further conversion. Continuous removal of methanol was therefore required to drive the reaction to completion.

To overcome this limitation, a custom continuous-flow evaporator module was designed (Fig. 4c and SI, section 4.5.3). In this setup, the hot reaction effluent from the first reactor was mixed with a heated nitrogen stream to induce a pseudo-annular gas–liquid flow regime. The corresponding gas–liquid mixture was directed into an evaporator coil connected to a collection vessel. The hot, methanol-saturated gas exited through the top of the vessel, while the viscous, methanol-depleted liquid was collected at the bottom. This configuration

allowed efficient in-line methanol removal. The resulting concentrated crude was then pumped into a second reactor operated at 140 $^\circ\text{C}$ for a few minutes to complete the cyclization. In-line IR, installed at the outlet of the first reactor, enabled real-time monitoring of linear carbamate intermediate *int-3* and cyclic oxazolidinone 3 (Fig. 4d).

The process was subsequently translated to pilot scale using a commercial glass Corning® Advanced-Flow™ G1 mesofluidic reactor (8 mL per fluidic module, 3 fluidic modules, 24 mL total internal volume) (Fig. 4e and f and SI, section 4.6). Highly viscous neat 2a was delivered using a high-pressure dual-syringe pump through a preheated stainless-steel line, while neat DMC, containing dissolved DBU, was delivered using dual piston-pump coupled with a Coriolis mass-flow meter. Each feed was preheated in one Corning®

Advanced-Flow™ G1 fluidic module (8 mL internal volume). The system pressure was set to 11 bar using an Equilibar® back-pressure regulator.

Under optimized conditions (140 °C, 45 s, 11 bar), complete conversion of **2a** was achieved, yielding a crude mixture containing approximately 26% of *int-3* and 66% of **3**. This stream was fed directly into an open continuous stirred-tank reactor (CSTR) operated at 140 °C, where an additional 10 min residence time afforded **3**, as a highly viscous liquid, in 92% yield. Process stability was monitored through process analytical technology (PAT), including in-line IR reaction monitoring, and multiple pressure and temperature sensors positioned at strategic locations in the setup. The pilot-scale process demonstrated a high degree of sustainability and intensification, with an *E*-factor of 0.55, a productivity of 32 kg day⁻¹, and a STY of 101 kg day⁻¹ L⁻¹ (SI, section 4.6.2.5).

Conclusion

In this work, we developed fast, selective, and scalable flow ammonolysis processes for oxiranes accessible from glycerol, notably introducing an innovative route using neat liquid ammonia. These processes delivered very high conversion (>99%), selectivity (>98%), and process control, outperforming existing literature precedents. The downstream oxazolidinone synthesis was successfully intensified, and the mechanistic studies provided valuable information on side-product formation. Robust scale-up validation confirmed the potential and relevance of the developed flow systems, which combine safety, efficiency, and low waste generation in line with green chemistry principles. Future work will focus on broadening the substrate scope to expand the versatility of the platform and on further process intensification, including integrated purification and continuous solvent recycling. These developments will strengthen the case for implementing sustainable flow-based routes in bio-based amine manufacturing at an industrial scale.

Author contributions

Florian Barbaz: Conceptualization, experimental work, writing – original draft. Hubert Hellwig: Conceptualization, experimental work. Diana V. Silva-Brenes: Project Administration, writing – review & editing. Jean-Christophe M. Monbaliu: Project administration, supervision, funding acquisition, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting the findings of this study are available within the supplementary information (SI) accompanying this article.

Supplementary information: including experimental procedures, analytical data, and full details of equipment and reactor components. See DOI: <https://doi.org/10.1039/d5gc06027c>.

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