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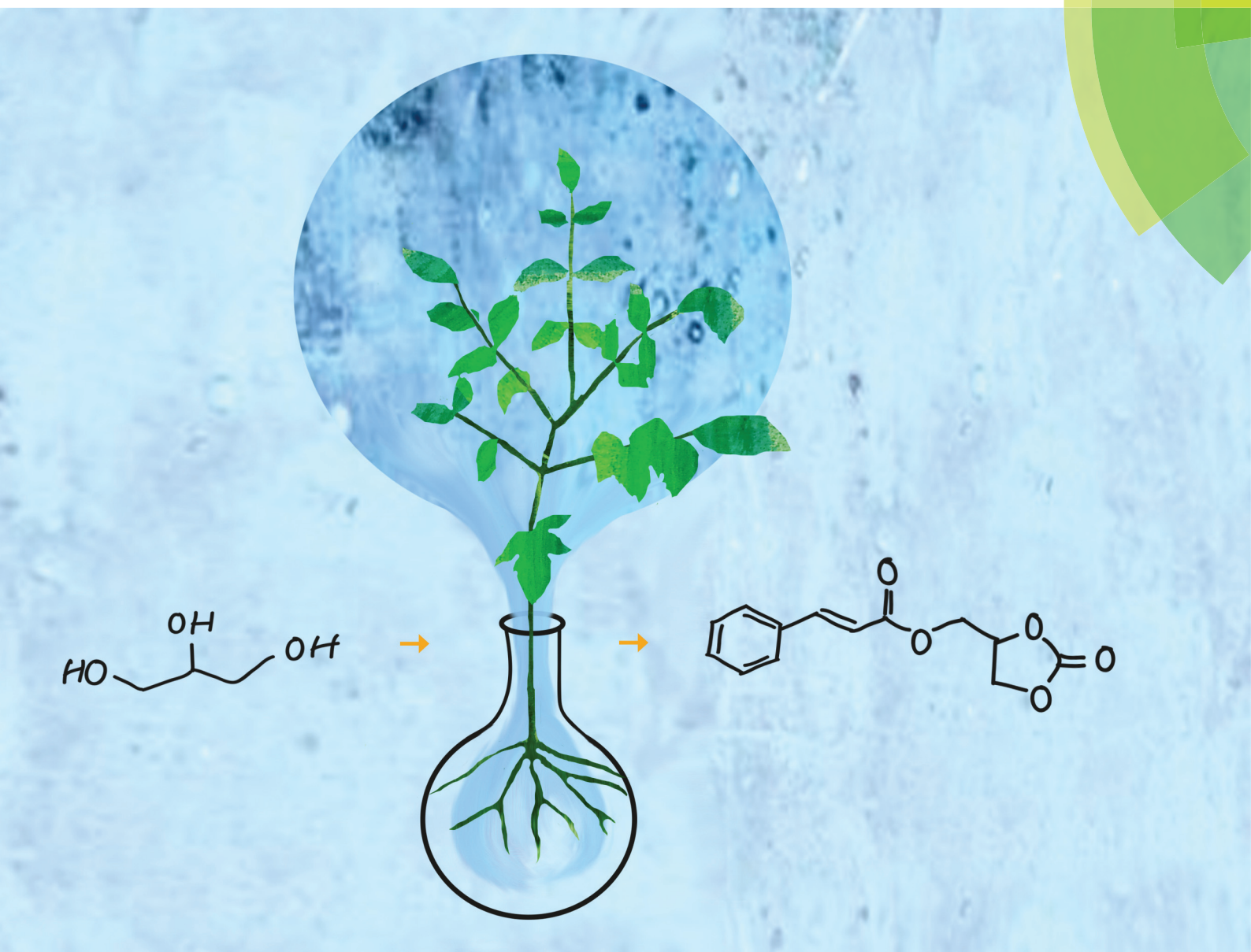

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Organocatalytic valorisation of glycerol *via* a dual NHC-catalysed telescoped reaction†

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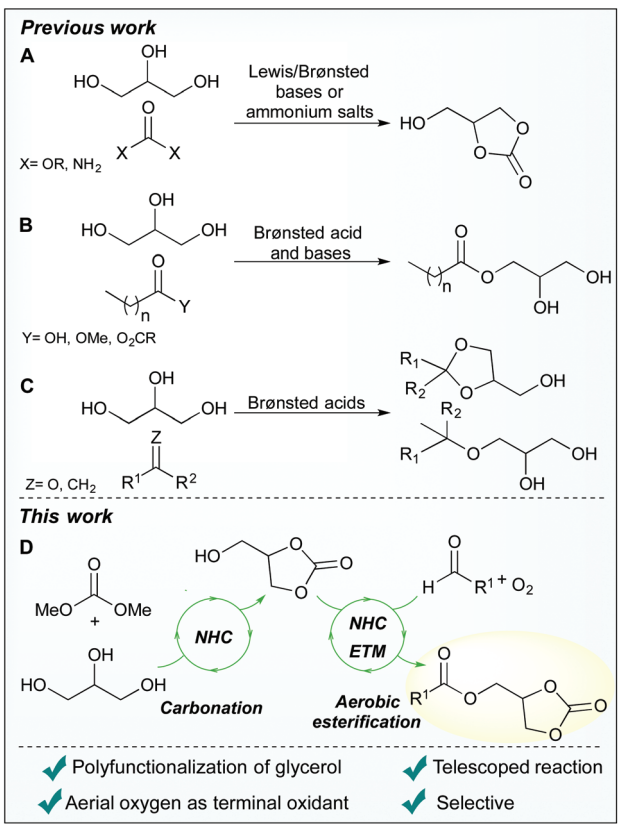
A general telescoped reaction for the NHC-catalysed carbonation and aerobic esterification of glycerol and 2-amino-2-methyl-propane-1,3-diol has been developed. The reaction provides highly functionalised glycerol derivatives in good to excellent yields (up to 95%) using low catalyst loadings and ambient conditions.

Our current dependence on fossil resources represents a major obstacle in the transition towards sustainable development.[1] It is estimated that up to 95% of the carbon-containing molecules needed to sustain daily life are derived from petrochemical sources.[2] Hence, the valorisation of biomass into fuels, bulk and fine chemicals as well as pharmaceuticals, is of utmost importance.[2–4] Moreover, in efforts to circumvent direct competition with food production the use of waste-streams instead of first generation biomass is preferred.[5] For this reason, glycerol is an excellent feedstock since it is obtained as a by-product from the production of biodiesel. Consequently, there is currently a large surplus of glycerol readily available.[6] Conversion of glycerol into commodity and fine chemicals is typically performed using metal catalysts.[7–10] In contrast, organocatalytic functionalisation of glycerol is not commonly utilized. A possible explanation for this is that transition metal catalysts are typically considered to be more reactive than organocatalysts. Nevertheless, organocatalysts have many virtues such as low-cost, low-toxicity and high stability and can thus be considered as competitive alternatives to their metal counterpart. Moreover, the increasingly tough restrictions regarding metal contaminants in consumer-products further favours organocatalysis.[11]

Previous organocatalytic transformations of glycerol have shown that glycerol carbonate can be synthesised from glycerol and dialkyl carbonates or urea using N-heterocyclic carbenes (NHCs), quaternary ammonium salts and Brønsted-Lowry bases (Scheme 1A).[12–16] Additionally, acylation of glycerol is possible by transesterification of fatty methyl esters with either phosphazene- or guanidine-based catalysts, *via* Fisher esterification catalysed by sulfonic acids, and by acetate-catalysed reactions with anhydrides (Scheme 1B).[17–21] Both homogenous and heterogeneous sulfonic acids have also found use in the



Scheme 1 Previous organocatalytic strategies for glycerol valorisation: transcarbonation (A), acylation (B) and acetal or ether formation (C) and the current approach combining carbonation and aerobic esterification in a telescoped reaction (D).

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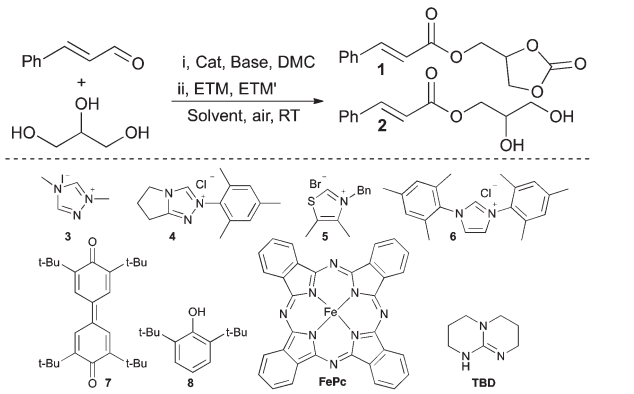
conversion of glycerol into a variety of ethers and acetals (Scheme 1C).[22–24]

While NHC-catalysis offers a multitude of reaction paths[25–28] and has proven compatible with glycerol, to date, the use of NHC-catalysis in glycerol valorisation is limited to carbonation reactions. As our research interest include sustainable NHC-catalysis, we set out to merge oxidative NHC-catalysis[29,30] with glycerol upgrading. Instead of employing conventional methods that require stoichiometric amounts of high molecular weight oxidants, such as the Kharasch oxidant **7**,[31,32] an aerobic approach was envisioned, as previously reported by us and others.[33–40] More precisely, it was hypothesised that aerobic esterification of glycerol would be possible by using a biomimetic strategy comprised of electron transport mediators (ETMs), as pioneered by the Bäckvall group.[41–45] The ETMs work in concert by enabling a low energy path for electrons to flow from the substrate to oxygen (O_2), circumventing the unfavourable reaction kinetics associated with direct O_2-oxidations.[45] Moreover, it was predicted that a dual functionalisation of glycerol, comprising a sequential NHC-catalysed carbonation followed by an aerobic esterification, would be possible by using a telescoped reaction strategy (Scheme 1D). This approach offers several advantages including: direct valorisation of glycerol, high atom economy, improved pot-economy,[46] and the incorporation of the carbonate group as a valuable synthetic handle.[12]

An initial experiment with a telescoped approach that included a one-pot sequential carbonation, using dimethyl carbonate (DMC), and aerobic esterification was successful providing the unsaturated carbonate (**1**) in 89% yield (Table 1, entry 1). It should be noted that dimethyl carbonate is considered a benign reagent as it can be obtained from CO_2, is nontoxic and biodegradable.[47] A survey of different NHC-catalysts showed that the thiazolium based catalyst **5** was inactive (entry 3), while **4** and **6** provided **1** in slightly lower yields compared to when **3** was employed (entries 2 and 4). This is due to increased carboxylic acid formation and incomplete consumption of cinnamaldehyde, respectively. The choice of base also proved important and the use of K_2CO_3 or Et_3N in place of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) resulted in no conversion of starting material (entries 5 and 6). This effect can be rationalised by the fact that the essential *in situ* FePc-catalysed aerobic oxidation of **8** to **7** is also base-catalysed.[31] Thus, by replacing **8** with **7** the loading of TBD can be decreased from 0.5 to 0.2 equivalents with maintained yield (entry 7), albeit with prolonged reaction time (24 h). Moreover, when the reaction is performed under a nitrogen atmosphere **1** is obtained in only 5%, showcasing that aerial oxygen truly is the terminal oxidant (entry 8). Omission of the NHC-precatalyst in the carbonation step results in the incomplete conversion of glycerol with subsequent side product formation, such as, **2**, the secondary- and the diester (14% determined by ^{1}H NMR) suggesting that this step is also NHC-catalyzed. Synthesis of **2** *via* a direct aerobic esterification of glycerol, omitting the carbonation step, was possible and **2** was obtained in 87% yield (entry 9). However, due to the formation of side products (the secondary ester and the diester, *ca.* 10%), it was not possible to obtain the pure product in a satisfactory manner. Regardless of concentration and solvent selection the amount of side products remained around 10%. For example, when acetone was used as the reaction solvent a competing aldol reaction was observed and **2** was obtained in 81% yield (entry 10).

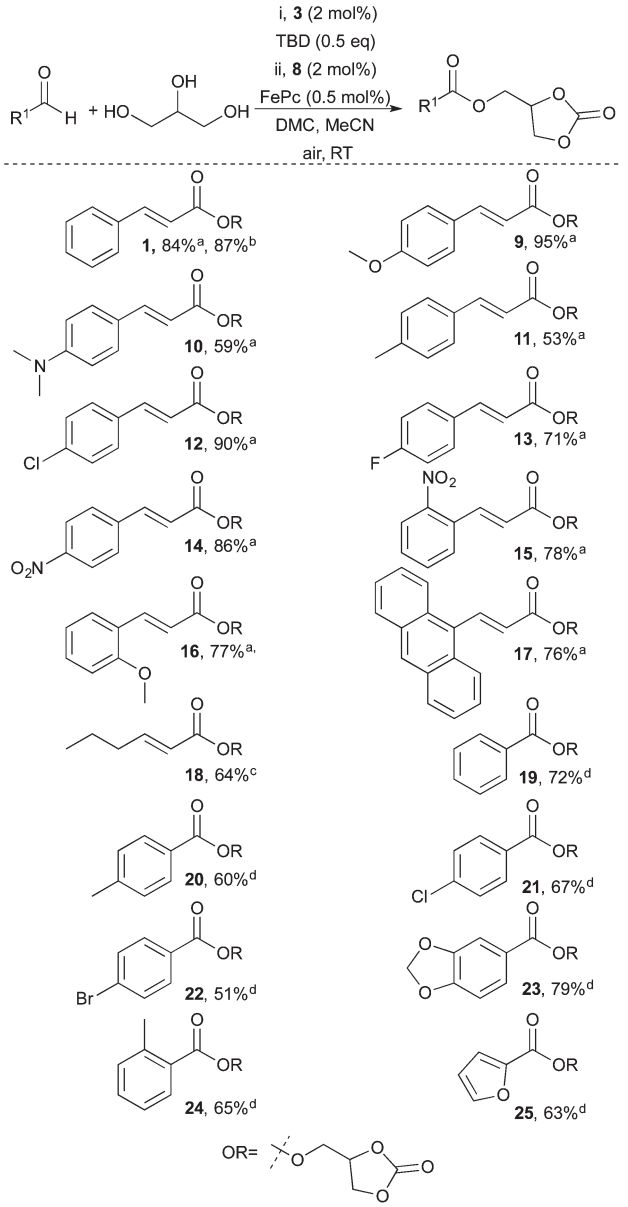
Table 1 Optimization of reaction conditions for the dual functionalisation of glycerol



						Yield[a] (%)	
Entry	Cat	ETM	ETM′	Base	Solvent	**1**	**2**
1[b]	3	8	FePc	TBD	MeCN	89	
2[b]	4	8	FePc	TBD	MeCN	86	
3[b]	5	8	FePc	TBD	MeCN	0	
4[b]	6	8	FePc	TBD	MeCN	81	
5[b]	3	8	FePc	K_2CO_3	MeCN	0	
6[b]	3	8	FePc	Et_3N	MeCN	0	
7[c]	3	7	FePc	TBD	MeCN	88	
8[b,d]	3	8	FePc	TBD	MeCN	5	
9[e]	3	8	FePc	TBD	MeCN		87
10[e]	3	8	FePc	TBD	Acetone		81

[a] Determined by ^{1}H NMR with durene as internal standard. [b] i, Glycerol (1.1 eq.), TBD (0.5 eq.), NHC (2 mol%), solvent/dimethyl carbonate 5 : 2. ii, Cinnamaldehyde (0.5 mmol), FePc (0.5 mol%), **8** (2 mol%). [c] As in footnote b, but with 0.2 eq. TBD and 0.01 eq. of **7**. [d] Last step performed under a nitrogen atmosphere. [e] Glycerol (4 eq.), TBD (0.5 eq.), **3** (2 mol%), cinnamaldehyde (0.5 mmol), FePc (0.5 mol%), **8** (2 mol%).

Having successfully identified mild conditions (Table 1 entry 1) that enabled selective dual functionalisation of glycerol with aerial oxygen as the terminal oxidant, the scope of this transformation was investigated (Scheme 2). The reaction proved general, and both electron-donating (**9–11**, **16**) and electron-withdrawing (**12–15**) substituents were tolerated on the cinnamaldehyde scaffold. Compound **9**, isolated in 95% yield, is worth highlighting since 4-methoxycinnamates are commonly used in sunscreens and the glycerol ester has been investigated as a more benign sunscreen agent.[48] Moreover, polyaromatics were well tolerated and anthracene ester **17** could be obtained in 76% yield. Initial reactions with aliphatic enals were sluggish. However, by using 4 mol% of the more active catalyst **4** 2-hexenal yielded the corresponding ester **18** in 64% yield. Benzaldehydes proved less reactive than



Scheme 2 The scope of the aerobic glycerol functionalisation. [a] (i) Glycerol (1.1 eq.), TBD, **3**, MeCN/DMC 5 : 2. (ii) Aldehyde (0.5 mmol), FePc (0.5 mol%), **8** (2 mol%). [b] 1.6 grams isolated. [c] 4 mol% of catalyst **4** used. [d] 4 mol% of catalyst **3** used.

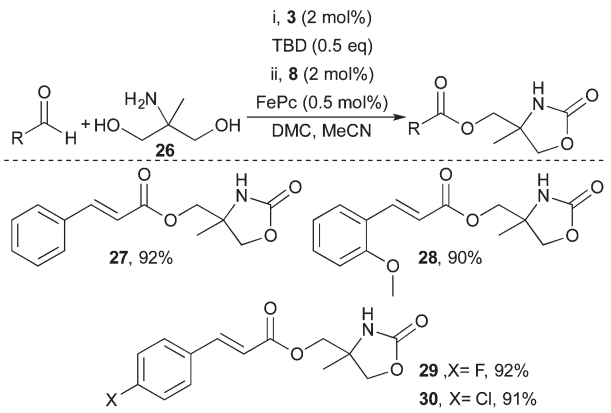
cinnamaldehydes and required 4 mol% (instead of 2 mol%) of catalyst **3** to react efficiently. With the increase in catalyst loading both electron rich and electron poor aromatic as well as heteroaromatic aldehydes worked well, affording the corresponding products (**19–25**) in moderate to good yields (51–79%).

For instance, piperonal derived ester **23** could be obtained in 79% yield. Moreover, this reaction is scalable and α,β-unsaturated ester **1** could be obtained in 87% yield and 1.6 grams.

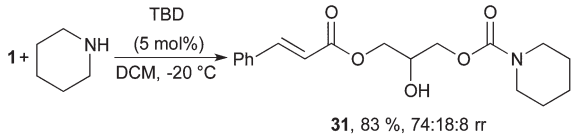
Encouraged by the successful functionalisation of glycerol, the compatibility of the developed system with the amino-alcohol 2-amino-2-methyl-1,3-propanediol (**26**) was investigated (Scheme 3). The approach was successful and both electron rich and electron poor enals could be transformed into the corresponding 2-oxooxazolidine esters in excellent yields. For instance, cinnamaldehyde and 4-chlorocinnamaldehyde both reacted well and provided the corresponding α,β-unsaturated esters in 92% and 91% yield respectively (**27** and **30**).

Ring opening of glycerol carbonate and its derivatives have obtained a lot of attention, for example, in sustainable synthesis of pharmaceuticals and polymers.[9,49,50] Consequently, the herein developed procedure could generate several new glycerol carbonate building blocks for use as green monomers or for further manipulation. With this in mind, the nucleophilic ring opening of the 2-oxo-1,3-dioxolan group with piperidine was investigated (Scheme 4). Inspired by reports from Kleij *et al.*,[51,52] it was possible to selectively activate the less electrophilic carbonate in the presence of the unsaturated ester using 5 mol% of TBD, yielding acyclic carbamate **31** in 83% yield and good regioselectivity (Scheme 4). Usage of higher loadings of TBD or other solvents (MeCN, THF) leads to formation of the amide as a side product.

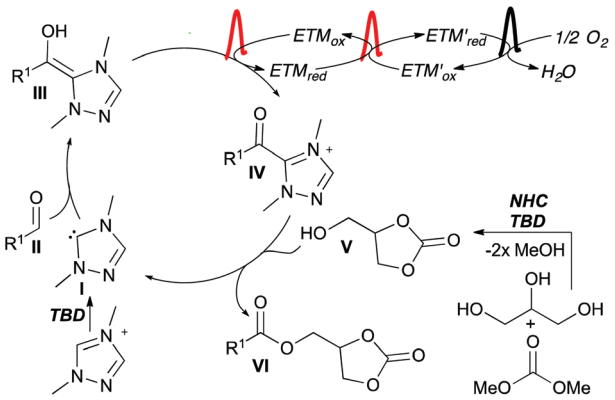
The proposed catalytic cycle starts with addition of the NHC (**I**) to aldehyde **II** forming the Breslow intermediate (**III**) (Scheme 5). Intermediate **III** is oxidized by the coupled system of ETMs to the acyl azolium **IV**. Glycerol carbonate (**V**), formed by NHC/TBD catalysis in the first step of the telescoped reac-



Scheme 3 Selective modification of aminopolyol **26** by telescoped carbamate formation and aerobic esterification. (i) **26** (1.0 eq.), **3**, TBD, MeCN/DMC 5 : 2. (ii) Aldehyde (0.5 mmol), FePc, **8**, isolated yields.



Scheme 4 Organocatalytic ring opening of **1** to form acyclic carbamate **31**. **1** (0.2 mmol), piperidine (1.2 eq.), isolated yield, regioisomeric ratio determined by ^{1}H NMR of crude material, major isomer separable by flash chromatography.



Scheme 5 Proposed catalytic cycle.

tion, adds as a nucleophile to **IV** forming the product (**VI**) and regenerating the NHC.

In summary, a telescoped protocol for the NHC-catalysed carbonation and aerobic esterification of glycerol has been developed. The presented method gives access to highly functionalised glycerol derivatives from sustainable resources such as glycerol, dimethyl carbonate and aerial oxygen. The reaction occurs under ambient conditions, is high yielding, scalable and has a broad scope that tolerates (hetero)aromatic aldehydes, aromatic and aliphatic α,β-unsaturated aldehydes. The method could also be further extended to amino-polyols, affording 2-oxooxazolidine esters in excellent yields. Lastly, chemoselective activation of the less electrophilic carbonate was demonstrated, showcasing the use of the obtained products. These results demonstrate the possibility to extend the role of NHC-catalysis in glycerol valorisation beyond carbonation reactions, enabling access to new sustainable building blocks for chemical synthesis.

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