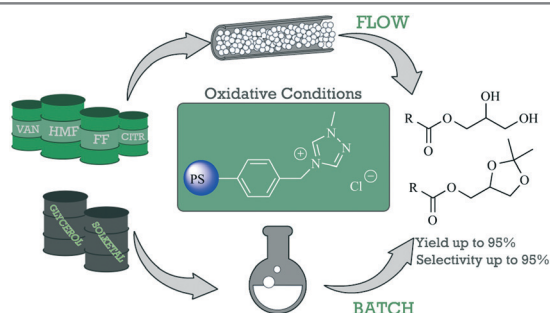


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### Esterification of glycerol and solketal by oxidative NHC-catalysis under heterogeneous batch and flow conditions

Daniele Ragno, Arianna Brandolese, Daniele Urbani, Graziano Di Carmine, Carmela De Risi, Olga Bortolini, Pier Paolo Giovannini and Alessandro Massi\*

Heterogeneous NHC-catalysis in batch and flow modes is an effective synthetic platform for the production of monoacylglycerols.

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Daniele	Ragno	Q-5342-2017	0000-0003-0016-290X
Arianna	Brandolese		0000-0003-2423-8008
Daniele	Urbani		
Graziano	Di Carmine	O-9889-2017	0000-0002-2591-9633
Carmela	De Risi		0000-0001-8162-6782
Olga	Bortolini	D-8058-2014	0000-0002-8428-2310

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## PAPER

# Esterification of glycerol and solketal by oxidative NHC-catalysis under heterogeneous batch and flow conditions†

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Daniele Ragno,  Arianna Brandolise,  Daniele Urbani, Graziano Di Carmine,   
Carmela De Risi,  Olga Bortolini,   
Pier Paolo Giovannini  and Alessandro Massi \*

The design and synthesis of a set of supported azolium salt pre-catalysts is presented along with their utilization in the production of monoesters of glycerol and solketal by oxidative N-heterocyclic carbene (NHC)-catalysis through batch and continuous-flow approaches. After a propaedeutic study with soluble NHCs, the heterogeneous analogues (silica and polystyrene supports) were tested in a model mono-esterification of glycerol using either the Kharasch oxidant or air (in the presence of electron transfer mediators) as the terminal oxidants. The best performing polystyrene-supported triazolium salt pre-catalyst afforded monoacylglycerols (MAGs) in high yields (up to 95%) and almost complete selectivity (monoester/diester >95:5) using air and the green solvent Me-THF. The synthesis of fully bio-based MAGs from furfural, 5-hydroxymethylfurfural (HMF), citronellal, and vanillin is also reported. Continuous-flow experiments have been finally performed by fabricating the corresponding packed-bed microreactor, which could be operated for ca. 120 hours with maintenance of conversion efficiency and selectivity.

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## Introduction

Umpolung (polarity reversal) catalysis mediated by N-heterocyclic carbene (NHC) organocatalysts is a mature synthetic methodology with applications in different areas of chemistry ranging from medicinal to material chemistry fields.<sup>1,2</sup> In recent years, the efficacy of this rapidly evolving catalytic strategy has been further validated by the utilization of NHCs as robust, environmentally benign, and highly selective catalysts for upgrading biomass-derived building blocks into high added-value chemicals.<sup>3,4</sup> In particular, the sugar-derived furfural (FF) and 5-hydroxymethylfurfural (HMF) have been widely exploited as platform chemicals for the production of useful biofuels, polymeric materials, and pharmaceutical intermediates through NHC-catalyzed oxidation, C–C, C–N bond forming reactions, and chain-extension couplings.<sup>3,5</sup> Valorization of glycerol, which is inexpensively available in large amounts as a by-product of biodiesel production,<sup>6</sup> has also been investigated by NHC-catalysis in a few synthetic programs mainly addressed to the production of glycerol carbonate.<sup>7,8</sup> Very recently, the group of Sundén reported the first acylation of glycerol as a part of a telescoped protocol, which

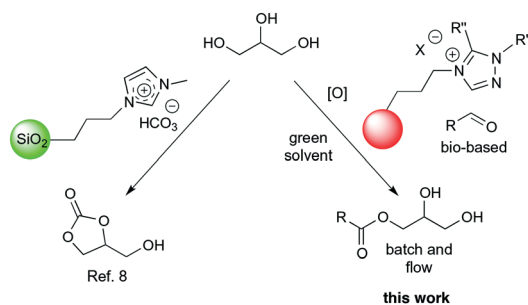
took advantage of oxidative NHC-catalysis<sup>9</sup> with aldehydes as the coupling substrates and air as the terminal oxidant.<sup>7</sup>

The typical poor stability to air and moisture of soluble NHCs may, however, preclude their utilization in the effective production of bio-based new chemicals at the industrial scale. Organocatalyst immobilization and the operation of flow reactors at the laboratory scale<sup>10,11</sup> represent fundamental pillars of process intensification with advantages in terms of catalyst stability, productivity, scalability, and sustainability of the whole synthetic protocol.<sup>12</sup> Indeed, different strategies have been developed for the fixation of NHC organocatalysts on soluble and heterogeneous supports.<sup>13</sup> In the field of biomass valorization, glycerol carbonate has been synthesized by Bruijninx and co-workers in a batch approach by means of a silica-supported hydrogen carbonated-masked imidazolium pre-catalyst, which could be recycled if properly reactivated by anion-exchange procedure (Fig. 1).<sup>8</sup> In general, the implementation of umpolung catalysis in flow reactors is a scarcely investigated synthetic platform<sup>14</sup> that, to the best of our knowledge, has not yet found applications in renewable chemical manufacturing.

Herein, we describe the design and synthesis of a set of triazolium salt pre-catalysts immobilized on silica and polystyrene supports, followed by their utilization in the oxidative monoesterification of glycerol and its derivative solketal under batch and continuous-flow conditions using aldehyde substrates and eco-friendly solvents (Fig. 1). Monoacylglycerols

Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via L. Borsari, 46, I-44121 Ferrara, Italy. E-mail: alessandro.massi@unife.it

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**Fig. 1** Glycerol valorization by heterogeneous NHC-catalysis.

(MAGs) are attractive bio-based derivatives, which find wide applications in energy, polymer, pharmaceutical, and cosmetic fields;<sup>15,16</sup> heterogeneous organocatalytic approaches have been proposed for the selective production of MAGs employing

strong supported Brønsted base and acid catalysts.<sup>17</sup> Besides the use of immobilized NHC Lewis base catalysts in batch and flow mode operations, peculiarity of the present study is also the synthesis of fully bio-based MAGs starting from the biomass-derived aldehydes FF and HMF, and from the bio-genic aldehydes citronellal and vanillin.

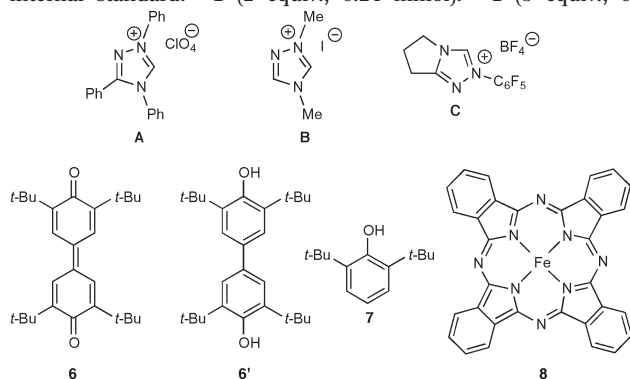
## Results and discussion

A preliminary investigation of the model monoesterification of glycerol **1** with 1-naphthaldehyde **2a** was performed under oxidative homogeneous conditions with the aim to select the optimal class of azolium salt pre-catalysts for their subsequent fixation on supports (Table 1). In agreement with the results of the study by Sundén and co-workers,<sup>7</sup> imidazolyli-dene, imidazolinyli-dene, and thiazolyli-dene carbenes proved

**Table 1** Screening of reaction conditions with soluble triazolium pre-catalysts A–C<sup>a</sup>

Entry	Pre-catalyst (mol%)	Base (mol%)	Time (h)	3a + 4a <sup>b</sup> (%)	3a : 4a <sup>b</sup>	5a <sup>b</sup> (%)	Oxidant (mol%)
1	A (10)	DBU (20)	24	22	88 : 12	—	6 (100)
2	B (10)	DBU (20)	24	82	71 : 29	—	6 (100)
3	C (10)	DBU (20)	1	>95%	66 : 34	—	6 (100)
4	C (10)	KHMDS (20)	1	>95%	63 : 37	—	6 (100)
5	C (10)	DIPEA (20)	1	>95%	67 : 33	—	6 (100)
6	C (10)	NEt <sub>3</sub> (20)	1	>95%	73 : 27	—	6 (100)
7	C (2.5)	NEt <sub>3</sub> (2.5)	1	>95%	71 : 29	—	6 (100)
8 <sup>c</sup>	C (2.5)	NEt <sub>3</sub> (2.5)	1	>95%	84 : 16	—	6 (100)
9 <sup>d</sup>	C (2.5)	NEt <sub>3</sub> (2.5)	1	>95%	91 : 9	—	6 (100)
10	C (2.5)	NEt <sub>3</sub> (2.5)	4	39	>95 : 5	—	TEMPO (150)
11	C (2.5)	NEt <sub>3</sub> (50)	24	59	82 : 18	—	MnO <sub>2</sub> (500)
12	C (2.5)	NEt <sub>3</sub> (5)	24	10	>95 : 5	59	O <sub>2</sub>
13 <sup>e</sup>	C (2.5)	NEt <sub>3</sub> (50)	24	81	80 : 20	10	Air, 7/8
14 <sup>d,e</sup>	C (2.5)	NEt <sub>3</sub> (50)	24	95	90 : 10	5	Air, 7/8
15 <sup>d,e,f</sup>	C (2.5)	NEt <sub>3</sub> (50)	24	67	94 : 6	19	Air, 7/8

<sup>a</sup> **1** (0.12 mmol), **2a** (0.12 mmol), THF (1.0 mL). <sup>b</sup> Yield and selectivity detected by <sup>1</sup>H NMR of the crude reaction mixture with durene as an internal standard. <sup>c</sup> **1** (2 equiv., 0.24 mmol). <sup>d</sup> **1** (3 equiv., 0.36 mmol). <sup>e</sup> ETM/ETM' system: **7** (20 mol%), **8** (5 mol%). <sup>f</sup> *T* = 50 °C.

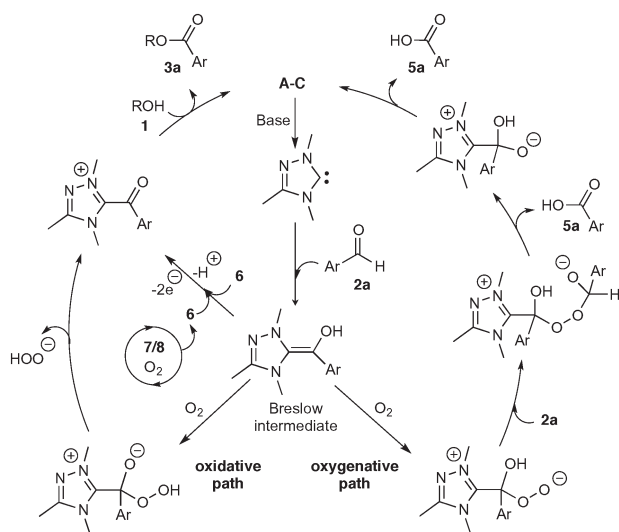


to be less effective compared to the triazolylidene counterparts in the 1/2a coupling under different reaction conditions (experiments not shown). Hence, our attention focused on the screening of the triazolium salts A–C using DBU as the base (20 mol%) and an equimolar amount of the Kharasch oxidant 6 in THF under degassed conditions (entries 1–3). The most effective bicyclic pentafluorophenyl pre-catalyst C provided a 66:34 mixture of MAG 3a and diacylglycerol (DAG) 4a with almost full conversion of stoichiometric 1–2a in one hour at room temperature without any evidence of formation of the by-product 1-naphtic acid 5a (entry 3). This latter compound could be produced by a side oxygenative pathway promoted by C in the presence of residual oxygen (Scheme 1).<sup>9,18,19</sup> Keeping in mind the subsequent development of a flow process, different soluble organic bases were tested (entries 4–6); NEt<sub>3</sub> afforded the best result with a mono/diester ratio of 73:27 (entry 6). Lowering the catalyst amount to 2.5 mol% left almost unchanged the reaction outcome (entry 7), thus highlighting the high catalytic activity of C. Better selectivities were observed using an excess of glycerol (entries 8–9) detecting the highest value (3a:4a = 91:9) with 3 equivalents of 1 (entry 9). Next, alternatives to the Kharasch oxidant 6 were considered (entries 10–13); the stable radical TEMPO gave a low conversion of glycerol (entry 10), while MnO<sub>2</sub> determined a substantial increase of the reaction time (entry 11). The direct use of oxygen (balloon technique, 1 bar) produced a modest level of conversion in 3a with preferential formation of 5a (59%; entry 12), thus indicating a favorable reaction kinetics associated to the oxygenative pathway<sup>9,18,19</sup> for the conversion of the Breslow intermediate (Scheme 1). According to the Sundén studies,<sup>7,20</sup> application of the biomimetic system of electron transfer mediators (ETMs) developed by the Bäckvall group<sup>21</sup> represented a major step forward allowing for the use of air as the terminal oxidant in our model esterification. In details, a catalytic

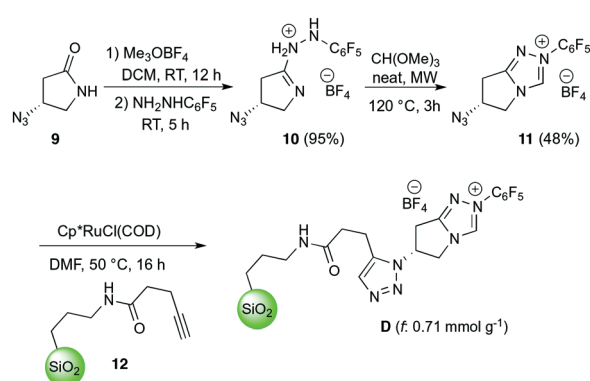
amount of oxidant 6 could be generated *in situ* from the inexpensive precursor 7 under basic conditions affording, after electron transfer with the Breslow intermediate, the acylazolium species and the reduced alcohol 6'. This latter could be re-oxidized to 6 in the presence of catalytic iron(II) phthalocyanine 8 (ETM') and atmospheric oxygen as the terminal oxidant (Scheme 1). Indeed, equimolar 1 and 2a reacted in THF in the presence of C (2.5 mol%), NEt<sub>3</sub> (50 mol%), 7 (20 mol%) and ETM' 8 (5 mol%) affording 3a–4a in 81% yield and 80:20 ratio after 24 hours (entry 13). An increase of selectivity (3a:4a = 90:10) and reduction of acid 5a formation (5%) was achieved with an excess of glycerol (3 equiv.; entry 14). The effect of temperature was finally verified with no success observing a lower reaction conversion and the production of a higher amount (19%) of acid 5a (entry 15).

The immobilization of the most promising pre-catalysts B–C was next considered to set-up an efficient heterogeneous procedure for the synthesis of MAG derivatives of type 3. Driven by our experience<sup>22</sup> on organocatalyst fixation by click reactions<sup>23,24</sup> and the seminal studies of the Rovis group on the synthesis of soluble bicyclic triazolium pre-catalysts,<sup>2,25</sup> the preparation of the silica-supported version of most active triazolium salt C was attempted starting from the readily available 4-azidopyrrolidin-2-one 9<sup>26</sup> (Scheme 2).

Standard amidate formation with the Meerwein's salt, followed by treatment with pentafluorophenyl hydrazine afforded the crude hydrazinium tetrafluoroborate salt 10 in 95% overall yield. The subsequent cyclization reaction represented a crucial step of our synthetic strategy as the typical thermal ring closure in presence of triethyl orthoformate and chlorobenzene at 120 °C afforded a very complex reaction mixture. After a long experimentation, it was found that the utilization of neat trimethyl orthoformate and microwave heating (120 °C, 3 h) resulted in the full conversion of 10 with formation of a cleaner reaction mixture, from which the azido tetrafluoroborate triazolium salt 11 could be recovered in 48% yield after crystallization. In parallel, the alkyne-functionalized silica 12 was readily prepared from 3-aminopropyl-silica and 4-pentynoic acid according to a known procedure.<sup>27</sup> The ruthenium-catalyzed azide alkyne cycloaddition (RuAAC)<sup>28</sup> of 11 and 12 was envisaged as the



**Scheme 1** Proposed mechanisms for the esterification of glycerol 1 with 1-naphtaldehyde 2a.



**Scheme 2** Synthesis of triazolium-functionalized silica D.

immobilization strategy. This coupling reaction leads to 1,5-disubstituted triazole derivatives under almost neutral conditions, thus permitting to avoid the basic medium typically required for the complementary Cu-catalyzed procedure,<sup>23,24</sup> which could be detrimental for triazolium salt **11** stability. Indeed, the **11/12** coupling proceeded smoothly in DMF at 50 °C in the presence of the Cp\*RuCl(COD) catalyst (10 mol%) affording the target silica-supported triazolium salt **D** with good conversion efficiency as determined by elemental analysis ( $f$ : 0.71 mmol g<sup>-1</sup>).

The silica-supported analogue of the triazolium salt **B** was efficiently prepared by *N*-alkylation of the commercially available 1-methyl-1*H*-1,2,4-triazole **13** with 3-chloropropyl silica gel **14**<sup>29</sup> (CH<sub>3</sub>CN, 90 °C, 16 h); by this straightforward approach, the heterogeneous pre-catalyst **E** was obtained with the satisfactory loading of 0.66 mmol g<sup>-1</sup> (Scheme 3, eqn. a). As we were aware of the influence of the support hydrophilicity on the catalytic performance (activity and selectivity) of solid promoters in glycerol esterifications,<sup>17</sup> the polystyrene-supported version **F** was also synthesized from the Merrifield resin **15** with a comparable level of efficiency (Scheme 3, eqn. b).

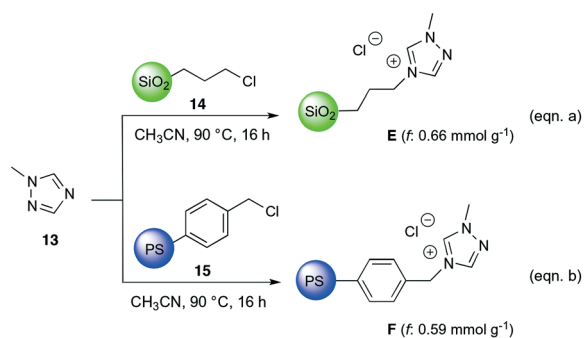
Subsequently, the catalytic activity and recyclability of the newly synthesized heterogeneous triazolium salts **D–F** were deeply investigated (Table 2). For a direct comparison, the pre-catalyst **D** was initially tested under the conditions previously optimized for its homogeneous counterpart **C** (Table 1, entry 14). Disappointingly, the aerobic esterification of glycerol **1** (3 equiv.) with **2a** promoted by **D** (10 mol%) in the presence of NEt<sub>3</sub> (50 mol%) and ETMs in THF resulted in a substantial decrease of reaction conversion (41% vs. 95%; entry 1). We hypothesized that the residual acidity of the silica support could be responsible for this unsatisfactory result. Indeed, the efficiency of the process could be almost restored by replacing triethylamine with the stronger base DBU (**3a** + **4a** = 82%, **3a**:**4a** = 91:9; entry 2). As expected, the presence of the remote stereocenter in the pyrrolidine framework of pre-catalyst **D** had little effect on the enantioselectivity of the monoesterification process (**3a**: 21% ee, see the ESI†). Moreover, the reaction outcome could not be improved by the brief solvent screening with DCM and Toluene (entries 3–4). While a modest activity was detected for the silica-supported pre-catalyst **E** under a number of different reaction condi-

tions (entry 5, selected example), the polystyrene-supported analogue **F** worked properly yielding the target MAG **3a** with almost the same level of efficiency as **D** (entry 6). Due to the simple preparation of **F** in one-step from readily available starting materials, the optimization of the heterogeneous monoesterification procedure was next carried with this catalyst. Hence, a set of environmentally benign solvents were tested to improve the sustainability of the process (entries 7–11). With the hope to take advantage of favorable hydrophobic interactions between the catalytic sites and the polystyrene support of **F**,<sup>30</sup> the use of a 1:1 THF-H<sub>2</sub>O mixture was attempted but with little success because of the preferential formation of acid **5a** (entry 7). Rewardingly, the use of biomass-derived 2-methyltetrahydrofuran (Me-THF)<sup>31</sup> provided a substantial improvement of the reaction output in terms of both conversion (**3a** + **4a** = 92%) and selectivity (**3a**:**4a** > 95:5; entry 8). Ethyl lactate and  $\gamma$ -valerolactone were less effective solvents (entries 9–10), whereas the deep eutectic mixture of glycerol and choline chloride<sup>32</sup> totally inhibited the catalytic process (entry 11). Reducing the excess of glycerol to 2 equivalents (Me-THF as the solvent) led to a partial drop of conversion (70–73%) at room temperature and 50 °C, but still an excellent MAG/DAG selectivity was detected (>95:5; entries 12–13). A verification that no leaching of the active triazolium salt occurred during the catalytic process was carried out by filtering **F** at 40% conversion and letting the filtrate to react under the optimal conditions of entry 8; no further conversion of glycerol took place, thus excluding the activity of any soluble species in the esterification process (entry 14). Also, the catalytic activity of heterogeneous **F** was evaluated under degassed conditions in the presence of the Kharasch oxidant **6** detecting a bit lower conversion compared to the experiment conducted with air and the mediators (84%, entry 15). Finally, catalyst recyclability was investigated over five and ten recycles using both air (entries 16–17) and **6** (entries 18–19) as the terminal oxidants. Gratifyingly, only a moderate decrease (*ca.* 5%) of conversion efficiency with maintenance of selectivity (**3a**:**4a** > 95:5) was observed after each recycle, which consisted in the simple filtration, washing, and drying of the resin.

Overall, these results confirmed the high stability of catalyst **F**, which showed an accumulated turnover number (TON) of 66 and 56 with air and the Kharasch oxidant **6**, respectively. It is important to point out that the simplicity of catalyst recycle compared to previously reported procedures,<sup>8,17</sup> the utilization of air as the terminal oxidant, and the possibility of re-use the biomass-derived Me-THF and excess of glycerol considerably diminish the environmental impact of the monoesterification process.

With the optimized heterogeneous procedure in hand (Table 2, entry 8), the scope of the monoesterification of glycerol **1** with representative classes of aldehydes **2** was next examined (Table 3).

As expected on the basis of our previous observations,<sup>18</sup> the electron poor 4-bromobenzaldehyde **2b** gave the corresponding ester **3b** in lower isolated yield (60%) compared to



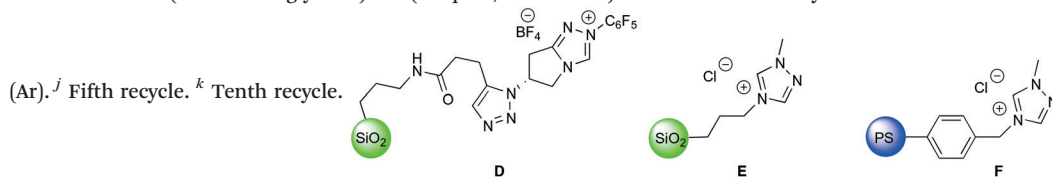
**Scheme 3** Synthesis of silica- and polystyrene-supported pre-catalysts **E** and **F**.



**Table 2** Screening of reaction conditions with supported triazolium pre-catalysts D–F<sup>a</sup>

Entry	Pre-catalyst (mol%)	Solvent	Base (mol%)	Time (h)	3a + 4a <sup>b</sup> (%)	3a : 4a <sup>b</sup>	5a <sup>b</sup> (%)	Oxidant (mol%)
1 <sup>c</sup>	D (10)	THF	NEt <sub>3</sub> (50)	24	41	>95 : 5	—	Air, 7/8
2 <sup>c</sup>	D (10)	THF	DBU (50)	24	82 <sup>d</sup>	91 : 9	—	Air, 7/8
3 <sup>c</sup>	D (10)	DCM	DBU (50)	24	22	>95 : 5	8	Air, 7/8
4 <sup>c</sup>	D (10)	Toluene	DBU (50)	24	33	91 : 8	11	Air, 7/8
5 <sup>c</sup>	E (10)	THF	DBU (50)	24	48	>95 : 5	8	Air, 7/8
6 <sup>c</sup>	F (10)	THF	DBU (50)	24	83	92 : 8	—	Air, 7/8
7 <sup>c</sup>	F (10)	THF/H <sub>2</sub> O (1 : 1)	DBU (50)	24	16	>95 : 5	34	Air, 7/8
8 <sup>c</sup>	F (10)	Me-THF	DBU (50)	24	92	>95 : 5	—	Air, 7/8
9 <sup>c</sup>	F (10)	Ethyl lactate	DBU (50)	24	34	>95 : 5	—	Air, 7/8
10 <sup>c</sup>	F (10)	γ-Valerolactone	DBU (50)	24	35	>95 : 5	12	Air, 7/8
11 <sup>c</sup>	F (10)	Ch-Cl : Gly <sup>e</sup>	DBU (50)	24	—	—	—	Air, 7/8
12 <sup>c,f</sup>	F (10)	Me-THF	DBU (50)	24	73	>95 : 5	5	Air, 7/8
13 <sup>c,f,g</sup>	F (10)	Me-THF	DBU (50)	24	70	>95 : 5	7	Air, 7/8
14 <sup>c,h</sup>	F (10)	Me-THF	DBU (50)	24	40	>95 : 5	—	Air, 7/8
15 <sup>i</sup>	F (10)	Me-THF	DBU (20)	24	84	>95 : 5	—	6 (100)
16 <sup>c,j</sup>	F (10)	Me-THF	DBU (50)	24	68	>95 : 5	—	Air, 7/8
17 <sup>c,k</sup>	F (10)	Me-THF	DBU (50)	24	41	>95 : 5	—	Air, 7/8
18 <sup>i,j</sup>	F (10)	Me-THF	DBU (20)	24	55	>95 : 5	—	6 (100)
19 <sup>i,k</sup>	F (10)	Me-THF	DBU (20)	24	37	>95 : 5	—	6 (100)

<sup>a</sup> 1 (0.36 mmol), 2a (0.12 mmol), solvent (1.0 mL). <sup>b</sup> Yields and selectivity detected by <sup>1</sup>H NMR on the crude reaction mixture with durenene as an internal standard. <sup>c</sup> ETM/ETM' system: 7 (20 mol%), 8 (5 mol%). <sup>d</sup> 3a: 21% ee as determined by chiral HPLC (see the ESI). <sup>e</sup> 1 : 2 molar ratio eutectic mixture (choline Cl : glycerol). <sup>f</sup> 1 (2 equiv., 0.25 mmol). <sup>g</sup> T = 50 °C. <sup>h</sup> Catalyst F filtered off at 40% conversion. <sup>i</sup> Degassed conditions



1-naphthaldehyde 2a (entry 1) due to the occurrence of the competitive homo-benzoin reaction (entry 2). The  $\alpha,\beta$ -unsaturated cinnamaldehyde 2c reacted efficiently affording the MAG 3c in good yield (83%, entry 3). The long chain aliphatic aldehydes 2d and 2e proved to be suitable substrates as well giving the corresponding esters 3d–e in satisfactory yields (entries 4–5).

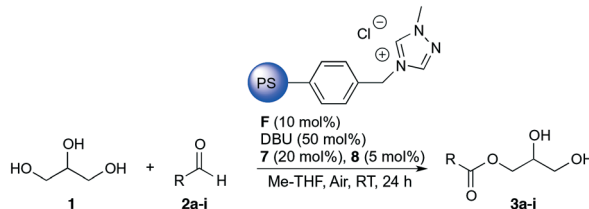
As anticipated, the substrate scope study was also extended to a range of bio-mass derived and biogenic aldehydes to approach a new class of fully bio-based MAGs (entries 6–9). Accordingly, citronellal 2f and vanillin 2g furnished the corresponding monoesters 3f and 2g in reasonable yields without any evidence of formation of DAG derivatives (entries 6–7). Furfural 2h was among the most active substrates (3h, 91%; entry 8), while HMF 2i produced the notable diester 3i in almost quantitative yield (entry 9). Reasonably, compound 3i was formed by monoesterification of glycerol with a first molecule of unprotected HMF 2i, followed by subsequent esterification of the resulting primary alcohol intermediate (not shown) with a second molecule of 2i.

Encouraged by the above results, the heterogenous batch procedure was also applied to the esterification of solketal (1,2-isopropylidenglycerol)<sup>33</sup> 16 (Table 4). In this study, a

lower excess (1.5 equiv.) of alcohol 16 was required because of the absence of selectivity issues. Under these conditions, solketal 16 was effectively converted into the target esters 17a–i in good yields (52–92%) starting from the corresponding aldehydes 2a–i (entries 1–9). Of note, differently from what observed with glycerol, the coupling of solketal with HMF produced the monoester derivative 17i as the sole isolable product (79%; entry 9).

At this stage of the study, the set-up of an effective flow procedure based on the active polystyrene-supported triazolium salt pre-catalyst F was addressed by fabricating the corresponding packed-bed microreactor R1 (Table 5). Accordingly, a pressure-resistant stainless-steel column (length 10 cm, 0.46 cm internal diameter) was filled with the Me-THF swelled resin F by the slurry packing technique. Pycnometry measurements allowed to determine the hold-up (dead) volume ( $V_0$ ) and the total porosity ( $\epsilon_{tot}$ ) of R1 for calculation of the residence time at different flow rates.

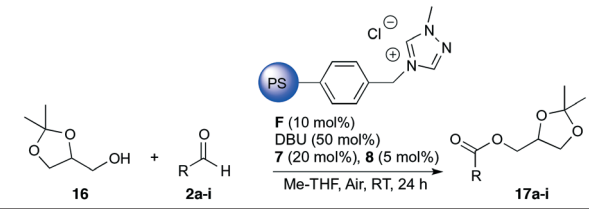
Continuous-flow experiments were conducted with the two-pump, three-way valve apparatus depicted in Scheme 4 using the esterification of glycerol 1 with 1-naphthaldehyde 2a as the benchmark. Unfortunately, it was immediately realized that utilization of ETMs 7/8 and air as the terminal

**Table 3** Reaction scope with **F** and glycerol **1** under batch conditions<sup>a</sup>


Entry	Aldehyde	Product	Yield <sup>b</sup> (%)
1			90
2			60
3			83
4			57
5			63
6			61
7			63
8			91
9			95

<sup>a</sup> **1** (0.75 mmol), aldehyde **2** (0.25 mmol), **F** (0.025 mmol), DBU (0.13 mmol), **7** (0.05 mmol), **8** (0.012 mmol) Me-THF (2.0 mL). <sup>b</sup> Isolated yields.

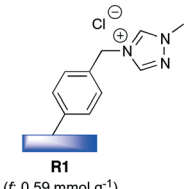
oxidant was precluded with our experimental set-up. Indeed, poor levels of conversion in MAG **3a** (*ca.* 15%) were detected by <sup>1</sup>H NMR analysis of the outlet stream, probably because of the low oxygen concentration present in the liquid phase in-

**Table 4** Reaction scope with **F** and solketal **16** under batch conditions<sup>a</sup>


Entry	Aldehyde	Product	Yield <sup>b</sup> (%)
1			92
2			71
3			55
4			68
5			52
6			91
7			80
8			89
9			79

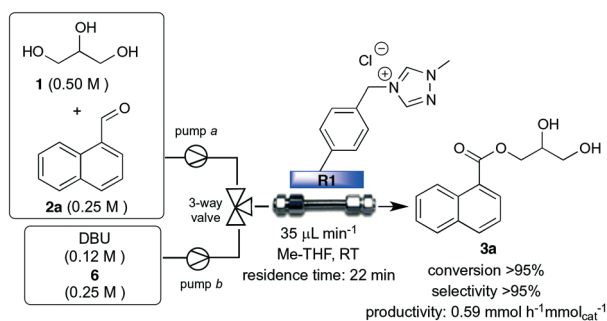
<sup>a</sup> **16** (0.38 mmol), aldehyde **2** (0.25 mmol), catalyst **F** (0.025 mmol), DBU (0.013 mmol), **7** (0.05 mmol), **8** (0.012 mmol) Me-THF (2.0 mL). <sup>b</sup> Isolated yields.

side the reactor. Although a convenient control of the gas flow by means of a mass flow controller (MFC)<sup>34</sup> has not

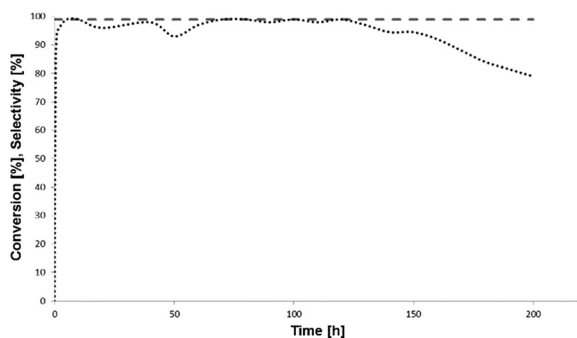
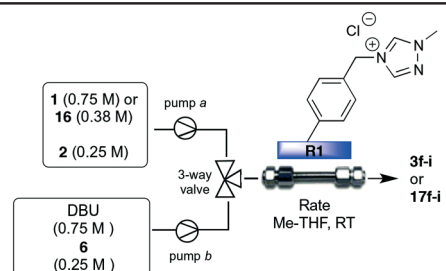
**Table 5** Main features of packed-bed microreactor R1


Loaded F <sup>a</sup> [g]	V <sub>G</sub> <sup>b</sup> [mL]	V <sub>0</sub> <sup>c</sup> [mL]	Total porosity <sup>d</sup>	Time <sup>e</sup> [min]	Pressure <sup>f</sup> [bar]
0.75	1.66	0.78	0.47	39	2

<sup>a</sup> Calculated by difference with catalyst amount in the residual slurry solution. <sup>b</sup> Geometric volume (V<sub>G</sub>) of the stainless-steel column. <sup>c</sup> Void volume (V<sub>0</sub>) determined by pycnometry. <sup>d</sup> Total porosity  $\epsilon_{\text{tot}} = V_0/V_G$ . <sup>e</sup> Residence time calculated at 20  $\mu\text{L min}^{-1}$ . <sup>f</sup> Backpressure measured at 20  $\mu\text{L min}^{-1}$  (RT, Me-THF).

**Scheme 4** Set-up for the continuous-flow experiments.

been explored in study, a practical and effective flow procedure was optimized with our flow system using the air-recyclable oxidant 6.<sup>35</sup> Hence, the pre-activated microreactor R1 was independently fed at 35  $\mu\text{L min}^{-1}$  with continuously degassed mixtures of glycerol (0.50 M)/2a (0.25 M) and DBU (0.12 M)/6 (0.25 M). Under these optimized conditions, the steady-state regime was achieved after 1 hour yielding the ester 3a with full conversion and complete selectivity. Satisfyingly, this output was maintained unaltered for *ca.* 120 hours on stream (TON = 71), while a moderate but progressive loss of conversion efficiency was detected after that time (Fig. 2). Recycle of the packed pre-catalyst F (200 h operation) and

**Fig. 2** Long-term stability of the packed-bed microreactor R1 in the flow synthesis of 3a. Conversion [%], dotted line; selectivity [%], dashed line.**Table 6** Continuous-flow production of selected monoesters 3 and 17 with microreactor R1<sup>a</sup>


Entry	MAG <sup>b</sup> (conv. [%])	Rate ( $\mu\text{L min}^{-1}$ )	P <sup>c</sup>
1	3f (90)	35	537
2	3g (92)	35	549
3	3h (>95)	35	591
4	3i (94)	35	591
5	17f (>95)	30	506
6	17g (92)	30	470
7	17h (94)	30	481
8	17i (91)	30	465

<sup>a</sup> See the Experimental section for a description of the flow apparatus. <sup>b</sup> Instant conversion in the steady-state regime as established by <sup>1</sup>H NMR analysis. <sup>c</sup> Productivities (P) are measured in mmol (product) h<sup>-1</sup> mmol (cat)<sup>-1</sup> × 10<sup>3</sup> and calculated on the basis of isolated product (see the Experimental section for details).

test in the model batch experiment (Table 2, entry 15) confirmed a partial erosion of catalytic activity in terms of conversion with preservation of selectivity (3a: 45%). Disappointingly, the efficiency of the packing material of R1 could not be restored even after treatment with 37% HCl for the conversion of the *in situ* generated carbene into the azolium salt precursor F.<sup>35</sup> Nevertheless, as observed in our previous studies on continuous-flow NHC-catalysis,<sup>14,30</sup> the transition from batch to flow conditions resulted in a substantial increase of process productivity because of the continuous exclusion of trace impurities and moisture from the active carbene species. An additional advantage of the flow regime was the possibility to avoid the over esterification of 3a using a lower excess (2 equiv. vs. 3 equiv.) of glycerol compared to the batch process, thanks to the suitable choice of the residence time (22 min) of the reactants within the reactor.

Finally, the continuous production of the selected bio-based esters 3f-i and 17f-i was performed by suitably adjusting the flow rates with the aim to reach high conversions (>90%) for the simple downstream purification of the products and recovery of the reduced alcohol 6'.<sup>36</sup> Overall, the target MAGs 3 and 17 were obtained with good productivities (*ca.* 0.5 mmol h<sup>-1</sup> mmol<sub>cat</sub><sup>-1</sup>) and complete selectivity (Table 6).

## Conclusions

In summary, we have provided a deep insight into the oxidative esterification of glycerol with aldehydes catalyzed by soluble NHCs in the presence of different oxidation systems. The optimization study under homogenous conditions has driven us to select the most active triazolium pre-catalysts (including

the popular achiral Rovis pre-catalyst) for their immobilization on silica and polystyrene supports. Then, the investigation of a model glycerol esterification has permitted the identification of the best performing polystyrene-supported triazolium pre-catalyst F. This promoter has been able to catalyze the environmentally benign synthesis of a novel class of MAG derivatives starting from bio-based aldehydes (furfural, hydroxymethylfurfural, citronellal, vanillin) with high conversions and selectivities in batch and flow mode approaches using the green solvent Me-THF. Parallely, the same study has been extended to the oxidative esterification of solketal with a comparable level of efficiency. To the best of our knowledge, this work represents the first example of continuous-flow NHC-catalysis applied to the valorization of renewable chemicals, thus further demonstrating the potential of this synthetic platform in the field of green chemistry.

## Experimental section

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over a standard drying agent and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 F<sub>254</sub> with detection by charring with potassium permanganate and/or phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). <sup>1</sup>H (300 MHz), <sup>13</sup>C (101 MHz) and <sup>19</sup>F (376 MHz) NMR spectra were recorded in CDCl<sub>3</sub> or acetone-*d*<sub>6</sub> solutions at room temperature. The chemical shifts in <sup>1</sup>H and <sup>13</sup>C NMR spectra were referenced to trimethylsilane (TMS). The chemical shifts in <sup>19</sup>F NMR spectra were referenced to CFCl<sub>3</sub>. Peak assignments were aided by <sup>1</sup>H-<sup>1</sup>H COSY and gradient-HMQC experiments. Optical rotations were measured at 25 ± 2 °C in the stated solvent; [α]<sub>D</sub> values are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup> (concentration *c* given as g/100 mL). FT-IR analyses were performed using the Bruker Instrument Vertex 70. For high resolution mass spectrometry (HRMS) the compounds were analyzed in positive ion mode using an Agilent 6520 HPLC-Chip Q/TOF-MS (nanospray) with a quadrupole, a hexapole, and a time of flight unit to produce the spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L min<sup>-1</sup>, respectively. The MS analyzer was externally calibrated with ESI-L low concentration tuning mix from *m/z* 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H<sub>2</sub>O/ACN 0.1% TFA into the system at a flow rate of 0.4 μL min<sup>-1</sup>. Elemental analyses were performed using a FLASH 2000 Series CHNS/O analyzer (ThermoFisher Scientific). Catalyst A was synthesized according to a literature procedure.<sup>37</sup> Catalysts B and C, Kharasch oxidant 6, alcohol 7, iron(II) phthalocyanine 8, Cp\*RuCl(COD), glycerol 1, solketal 16 and aldehydes 2a–i (apart from 2d) were purchased from Sigma-Aldrich and used as received. 1-Methyl-1*H*-1,2,4-triazole 13 was purchased from TCI. Aldehyde 2d was synthesized from the corresponding alcohol *via* PCC oxidation. (*R*)-4-Azidopyrrolidin-2-one 9,<sup>26</sup> the alkyne-

functionalized silica 12,<sup>27</sup> and 3-chloropropyl silica gel 14<sup>29</sup> were prepared as described. Liquid aldehydes and bases (DBU, TEA) were freshly distilled before their utilization.

### (*R*)-6-Azido-2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (11)

(*R*)-4-Azidopyrrolidin-2-one 9<sup>26</sup> (0.50 g, 3.96 mmol) was loaded into a flame-dried 100 mL flask equipped with a magnetic stirrer. Next, anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added (40 mL) and the flask was then evacuated and back-filled with Ar; to this solution, trimethyloxonium tetrafluoroborate (0.59 g, 3.96 mmol) was added in a single portion and the reaction mixture was then stirred under Ar atmosphere (by means of an Ar filled balloon) at room temperature for 16 h. After this period, pentafluorophenyl hydrazine (0.78 g, 3.96 mmol) was added and the solution was then stirred for additional 5 h at room temperature, providing hydrazinium tetrafluoroborate 10 in 95% yield. The solvent was evaporated under reduced pressure and the crude mixture was transferred into a 20 mL microwave vial, where trimethyl orthoformate (10 mL) and methanol (2.5 mL) were added; the mixture was then heated under microwave irradiation at 120 °C for 3 h, followed by removal of the solvents under reduced pressure. <sup>1</sup>H NMR analysis of the crude mixture displayed the complete conversion of the starting 10. Purification of the product was performed by crystallization (MeOH/Et<sub>2</sub>O) obtaining the triazolium salt 11 as brown amorphous solid (0.77 g, 48%). [α]<sub>D</sub><sup>25</sup> = -3.6 (*c* = 0.5, acetone). <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>) δ = 10.45 (s, 1H, CH<sub>(3)</sub>), 5.63–5.45 (m, 1H, CH<sub>(6)</sub>), 5.16 (dd, *J* = 13.4, 6.4 Hz, 1H, CH<sub>2(5)</sub>), 4.81 (dd, *J* = 13.4, 3.0 Hz, 1H, CH<sub>2(5)</sub>), 3.98 (dd, *J* = 18.0, 7.2 Hz, 1H, CH<sub>2(7)</sub>), 3.54 (dd, *J* = 18.0, 3.1 Hz, 1H, CH<sub>2(7)</sub>); <sup>13</sup>C NMR (101 MHz, acetone-*d*<sub>6</sub>) δ = 161.8, 143.8, 141.9, 141.5, 138.9 (2 C), 136.4 (2 C), 62.1, 54.0, 29.2. <sup>19</sup>F NMR (376 MHz, acetone-*d*<sub>6</sub>) δ = -147.1 (m, 2F), -149.9 (m, 1F), -152.0 (s, 4F), -162.0 (m, 2F). HRMS (ESI/Q-TOF) calcd for C<sub>11</sub>H<sub>6</sub>F<sub>5</sub>N<sub>6</sub> ([M - BF<sub>4</sub>]<sup>+</sup>) 317.0569, found: 317.0603.

### Synthesis of pre-catalyst D

Triazolium salt 11 (0.30 g, 0.74 mmol) and silica 12<sup>27</sup> (320 mg, 0.37 mmol, loading = 1.16 mmol g<sup>-1</sup>, 230–400 mesh) were loaded into a 5 mL vial and suspended in dry DMF (3.0 mL). The stirred solution was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Cp\*RuCl(COD) (14 mg, 0.037 mmol) was next added in one portion, followed by heating at 50 °C for 16 h. After cooling to room temperature, the mixture was centrifuged with fresh portions of Et<sub>2</sub>O (2 × 8 mL) and acetone (2 × 8 mL). The resulting silica-supported triazolium salt D was finally dried (0.1 mbar, 40 °C, 6 h). Elemental analysis (%) found: N 5.9 (loading = 0.71 mmol g<sup>-1</sup>). FT-IR (KBr): ν 3656, 2980, 1876, 1691, 1528, 1412, 1097 cm<sup>-1</sup>.

### Synthesis of pre-catalyst E

1-Methyl-1*H*-1,2,4-triazole 13 (0.18 mL, 2.40 mmol) and 3-chloropropyl silica gel 14<sup>29</sup> (1.00 g, 0.80 mmol, loading Cl =

0.8 mmol g<sup>-1</sup>, 230–400 mesh) were loaded into a 10 mL vial and dissolved in dry CH<sub>3</sub>CN (4.0 mL) under argon atmosphere; the reaction mixture was next heated at 90 °C for 16 h. After cooling to room temperature, the mixture was centrifuged with fresh portions of CH<sub>3</sub>CN (2 × 8 mL) and Et<sub>2</sub>O (2 × 8 mL). The resulting silica-supported triazolium salt E was finally dried (0.1 mbar, 40 °C, 6 h). Elemental analysis (%) found: N 2.8 (loading = 0.66 mmol g<sup>-1</sup>). FT-IR (KBr):  $\nu$  3654, 2962, 1992, 1873, 1659, 1523, 1446, 1100 cm<sup>-1</sup>.

### Synthesis of pre-catalyst F

1-Methyl-1*H*-1,2,4-triazole 13 (0.46 mL, 6.10 mmol) and the Merrifield resin 15 (5.0 g, 17.5 mmol, loading Cl = 3.5 mmol g<sup>-1</sup>, 200–400 mesh) were loaded into a 20 mL vial and dissolved in dry CH<sub>3</sub>CN (10.0 mL) under argon atmosphere; the reaction mixture was next heated at 90 °C for 16 h. After cooling to room temperature, the mixture was centrifuged with fresh portions of CH<sub>3</sub>CN (2 × 10 mL) and Et<sub>2</sub>O (2 × 10 mL). The resulting silica-supported triazolium salt F was finally dried (0.1 mbar, 40 °C, 6 h). Elemental analysis (%) found: N 2.5 (loading = 0.59 mmol g<sup>-1</sup>). FT-IR (KBr):  $\nu$  3646, 3002, 2915, 2817, 1908, 1874, 1671, 1512, 1587 cm<sup>-1</sup>.

### General procedure for the synthesis of monoacylglycerols 3a–i with pre-catalyst F

A stirred mixture of glycerol 1 (69 mg, 0.75 mmol), aldehyde 2a–i (0.25 mmol), 7 (10.2 mg, 0.05 mmol), 8 (6.8 mg, 0.012 mmol) and pre-catalyst F (40 mg, 0.025 mmol, loading = 0.59 mmol g<sup>-1</sup>) in Me-THF (2.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (19.5  $\mu$ L, 0.13 mmol), and the reaction was stirred at room temperature for 24 h. Filtration and washing (EtOAc) of the catalyst, concentration, and elution of the resulting crude mixture from a column of silica with the suitable elution system afforded the target product 3a–i.

### General procedure for the synthesis of solketal derivatives 17a–i with pre-catalyst F

A stirred mixture of solketal 16 (34 mg, 0.38 mmol), aldehyde 2a–i (0.25 mmol), 7 (10.2 mg, 0.05 mmol), 8 (6.8 mg, 0.012 mmol) and pre-catalyst F (40 mg, 0.025 mmol, loading = 0.59 mmol g<sup>-1</sup>) in Me-THF (2.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (19.5  $\mu$ L, 0.13 mmol), and the reaction was stirred at room temperature for 24 h. Filtration and washing (EtOAc) of the catalyst, concentration, and elution of the resulting crude mixture from a column of silica with the suitable elution system afforded the target product 17a–i.

### Fabrication of microreactor R1

The microreactor R1 was fabricated by using a 10 × 0.46 cm stainless-steel column, which was filled with the swelled resin F. Slurry was prepared by suspending excess in weight of F in Me-THF. Slurry-packing was performed under constant pres-

sure (300 bars, 30 min, Me-THF as solvent) by using an air driven liquid pump (by Haskel). Microreactor void volume ( $V_o$ ) was determined by pycnometry.<sup>38</sup> This method consists in filling the microreactor successively with two different solvents (solvent 1: water; solvent 2: *n*-hexane) and weighing the filled microreactors accurately. Simple math shows that:

$$V_o = (w_1 - w_2)/(\delta_1 - \delta_2),$$

where  $w_1$  and  $w_2$  are the weights of the microreactor filled with solvents 1 and 2 and  $\delta_1$  and  $\delta_2$  the densities of the solvents.

### Experimental set-up for the flow synthesis of esters 3f–i and 17f–i

The continuous flow apparatus setup was made of two binary pumps (Agilent 1100 and Agilent 1100 micro series). Channel-A was used to deliver a continuously degassed solution of 1 (0.50 M) [or 16 (0.38 M)] and 2f–i (0.25 M) in Me-THF. Channel-B delivered a continuously degassed solution of DBU (0.12 M) and 6 (0.25 M) in Me-THF. The feed solutions were pumped at the stated flow rate through the 3-way valve. Microreactor R1 was initially activated by pumping (channel B, 50  $\mu$ L min<sup>-1</sup>, 20 min) a degassed solution of DBU (0.75 M). The microreactor was operated for 6 h under steady-state conditions, then the collected solution was concentrated, and eluted from a column of silica gel with the suitable elution system to recover first the alcohol 6' and then give the product 3f–i [or 17f–i]. The quantitative oxidation of 6' to the Kharasch oxidant 6 was performed with air (1 atm, balloon) and catalytic phthalocyanine 8 (10 mol%, THF, RT).

### Long-term stability study

The long-term stability experiment was performed with the same flow setup using aldehyde 2a (0.25 M); microreactor R1 was operated at 25 °C with a flow rate of 35  $\mu$ L min<sup>-1</sup> for ca. 200 h. After the achievement of the steady-state regime (ca. 1 h), >95% conversion of 2a was maintained for 120 h, while a progressive loss of catalytic activity was observed after that time (TON = 71).

## Conflicts of interest

There are no conflicts to declare.

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