# Organic & Biomolecular Chemistry

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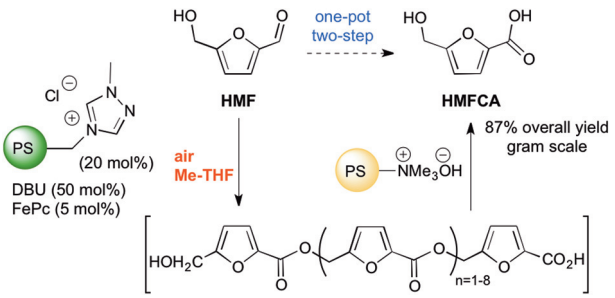
**Aerobic oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid and its derivatives by heterogeneous NHC-catalysis**


Arianna Brandolese, Daniele Ragno, Graziano Di Carmine, Tatiana Bernardi, Olga Bortolini, Pier Paolo Giovannini, Omar Ginoble Pandoli, Alessandra Altomare and Alessandro Massi*


Heterogeneous NHC-catalysis is an effective synthetic platform for the production of bio-based furan derivatives.

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Organic & Biomolecular Chemistry

PAPER

# Aerobic oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid and its derivatives by heterogeneous NHC-catalysis†

Cite this: DOI: 10.1039/c8ob02425a

Arianna Brandolese, [a] Daniele Ragno, [a] Graziano Di Carmine,[a] Tatiana Bernardi,[a] Olga Bortolini, [a] Pier Paolo Giovannini, [a] Omar Ginoble Pandoli, [b] Alessandra Altomare[c] and Alessandro Massi *[a]

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The application of the oxidative system composed of a heterogeneous triazolium pre-catalyst, iron(II) phthalocyanine and air is described for the selective conversion of 5-hydroxymethylfurfural (**HMF**) into the added-value 5-hydroxymethyl-2-furancarboxylic acid (**HMFCA**). The disclosed one-pot two-step procedure involved sequential oxidative esterifications of **HMF** to afford a polyester oligomer having hydroxyl and carboxyl terminal groups ($M_w$ = 389–1258), which in turn was hydrolyzed by a supported base (Ambersep 900 OH) to yield **HMFCA** in 87% overall yield. The same strategy was adopted for the effective synthesis of ester and amide derivatives of **HMFCA** by nucleophilic depolymerization of the oligomeric intermediate with methanol and butylamine, respectively. The utilization of the disclosed oxidative system for the direct conversion of **HMF** and furfural into their corresponding ester, amide, and thioester derivatives is also reported.

## Introduction

In recent years, the biorefinery concept based on the valorization of renewable carbon sources (agroindustrial waste and carbon dioxide) has emerged as a sustainable alternative to petroleum refinery for the production of added-value chemicals, polymers, fuels, and syngas.[1–4] An attracting direction in this area is devoted to the synthesis of biomass-derived furan derivatives, namely furfural (**FF**) and 5-hydroxymethylfurfural (**HMF**), which can be obtained from the dehydration of lignocellulosic sugars at the industrial scale.[5,6] **HMF** is widely recognized as a versatile platform chemical, which can be upgraded into a variety of useful compounds by elaboration of the hydroxyl and formyl functionalities as well as of the furan ring.[7] Indeed, **HMF** belongs to the list of "Top 10 + 4" bio-based chemicals from the U.S. Department of Energy (DOE).[8] Among the possible modifications of **HMF**, oxidation reactions have led to the identification of innovative products for the polymer, pharmaceutical, and agrochemical industries. The selective oxidation of the hydroxyl group affords the furan dialdehyde 2,5-diformylfuran (DFF), which is a valuable intermediate for the synthesis of furan-urea resins,[9,10] fungicides,[11] and functional materials.[12] The full oxidation of **HMF** produces the 2,5-furandicarboxylic acid (FDCA), which is also in the list of platform chemicals indicated by the DOE.[8] FDCA has been mainly applied as a replacement of terephthalic, isophthalic, and adipic acids in manufacturing polyesters, polyamides, and polyurethanes.[13–15] The selective oxidation of the formyl group of **HMF** produces another important bio-based chemical, that is 5-hydroxymethyl-2-furancarboxylic acid (**HMFCA**). This compound is, in fact, utilized as a novel monomer for the synthesis of various polyesters,[16] and as a precursor of FDCA.[17] Additionally, **HMFCA** itself displays anti-tumor activity[18] and is an intermediate in the synthesis of a promising interleukin inhibitor.[19] The potential industrial applications of **HMFCA** have attracted the attention of several groups in the last few years and the synthetic challenge of selectively oxidizing the formyl functionality of **HMF** in the presence of the primary hydroxyl group has been approached by all types of catalysis under both homogeneous and heterogeneous conditions (Scheme 1).[20] Metal catalysts are predominant in **HMFCA** synthesis.[5,7,21–24] Interestingly, Zhang, Deng and their co-workers reported the ability of dioxomolybdenum(VI) complexes immobilized on montmorillonite K-10 clay to activate molecular oxygen and promote the formation of **HMFCA** in good yield and complete selectivity in toluene at

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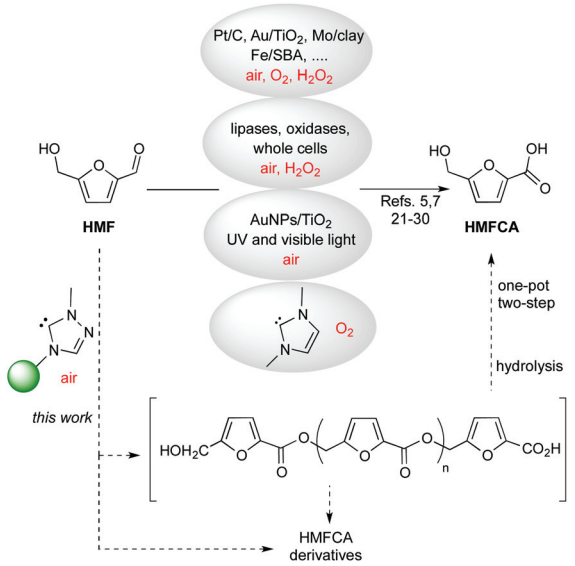
†Electronic supplementary information (ESI) available: MS/MS and NMR spectra. See DOI: 10.1039/c8ob02425a



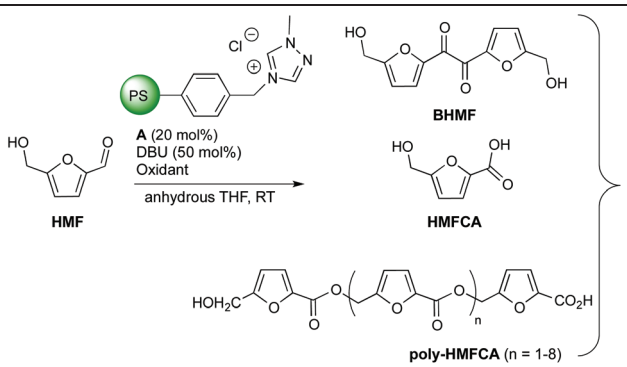

**Scheme 1** Catalytic approaches to the synthesis of **HMFCA**.

elevated temperature.[25] More recently, in an effort to utilize mild oxidation conditions and inexpensive metal promoters, the group of De La Rosa presented a study on the catalytic activity of supported salen complexes of Fe(III) and Cu(II) for the production of **HMFCA** in an aqueous medium with hydrogen peroxide as the oxidizing agent.[26] Environmentally benign biocatalytic methods involved the utilization of lipases,[27] xanthine oxidases,[28] and whole-cell systems,[29,30] and excellent levels of selectivity were reported even with high loadings of **HMF**. Notably, the efficacy of photocatalytic oxidation has been recently demonstrated by the group of Son and Han using Au nanocatalysts supported on $TiO_2$ and atmospheric air under UV and visible light irradiation in basic aqueous solution.[31] During the preparation of this paper, Nakajima and coworkers disclosed the first organocatalytic synthesis of **HMFCA** using a N-heterocyclic carbene (NHC) catalyst (soluble imidazolylidene) and oxygen in DMSO;[32] while the procedure was optimized for furfural oxidation, the presence of the hydroxyl group in **HMF** induced a side reaction that diminished the selectivity and yield of **HMFCA**. Overall, all the reported methods display some advantages but also limitations, thus justifying the continuous search for highly selective, eco-friendly, operationally simple, and effective syntheses of **HMFCA** and eventually derivatives thereof. In this study, we describe a novel procedure for **HMFCA** production that relies on the formation of **HMF**-based oligomers through oxidative esterifications promoted by a heterogeneous NHC catalyst (triazolylidene) and air as the terminal oxidant, followed by oligomer hydrolysis with a basic resin in a one-pot two-step fashion; purification of **HMFCA** was facilitated by the so called "catch and release" technique. The same supported NHC catalyst was applied to the synthesis of ester, thioester, and amide derivatives of **HMFCA** under batch and continuous-flow conditions as well as to furfural oxidation for the production of furoic acid and its derivatives.

## Results and discussion

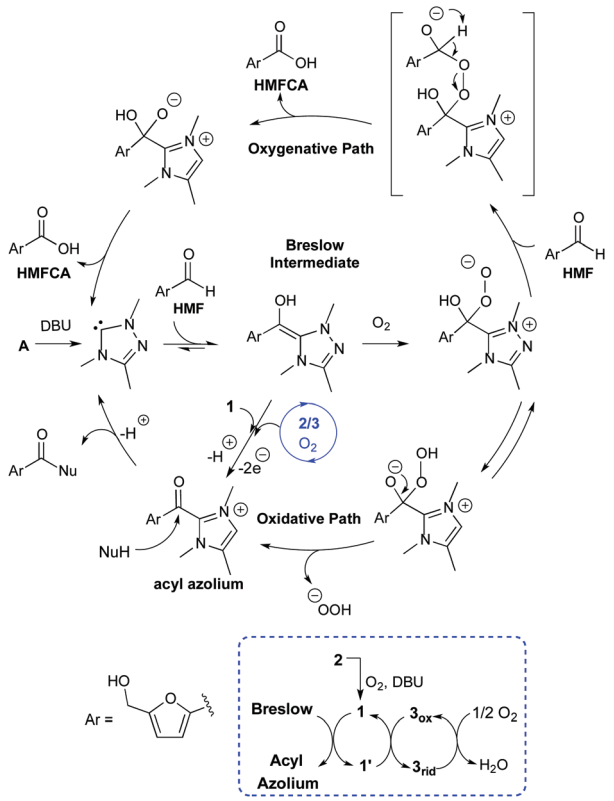
The preliminary investigation of **HMFCA** synthesis by oxidative NHC-catalysis took advantage of our previous findings on glycerol esterification by the same organocatalytic approach.[33] In that study, the polystyrene-supported triazolium pre-catalyst **A** (Table 1), which is readily synthesized in one-step by *N*-alkylation of a commercially available triazole derivative with the Merrifield resin,[33] resulted in the most active pre-catalyst with advantages in terms of ease of the work-up procedure and catalyst recyclability. Accordingly, the heterogeneous promoter **A** (20 mol%) was tested in the selective synthesis of **HMFCA** using DBU (50 mol%) as the optimal base and air as the terminal oxidant in anhydrous THF (Table 1, entry 1). Along with the target acid (35%), which was the expected product of the oxygenative pathway[34–36] of **HMF** oxidation (Scheme 2), 5,5′-bihydroxymethyl furil (**BHMF**) and **HMF**-based polyester oligomers (poly-HMFA; *vide infra* for characterization) were detected in considerable amounts contributing to the almost complete conversion of **HMF**. The former α-diketone product was formed by NHC-catalyzed self-condensation of **HMF**, followed by selective based-promoted oxidation of the hydroxy-ketone functionality of the benzoin intermediate (not shown).[37]

**Table 1** Screening of reaction conditions with supported triazolium pre-catalyst **A** [a]

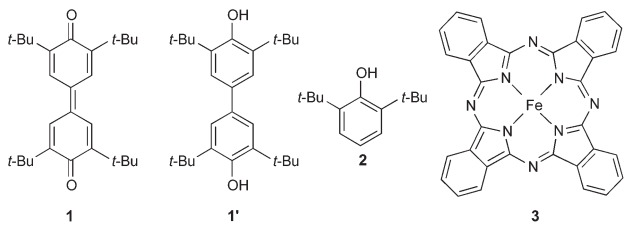



| Entry | Oxidant (mol%) | **HMFCA** [b] (%) | **BHMF** [b] (%) | **Poly-HMFCA** [b] (%) |
|---|---|---|---|---|
| 1 | Air | 35 | 28 | 29 |
| 2[c] | Air | 38 | 25 | 10 |
| 3[d] | **1** (100) | — | — | 95 |
| 4[c,d] | **1** (100) | 50 | — | 42 |
| 5 | Air, **2** (20)/**3** (5) | 5 | — | 92 |
| 6 | Air, **3** (5) | 5 | — | 92 |
| 7 | Air, $FeCl_3$ (20) | 8 | 35 | 5 |
| 8[e] | Air, **3** (5) | 5 | — | 93 |
| 9[e,f] | Air, **3** (5) | 5 | — | 91 |

[a] **HMF** (1 mmol), THF (4.0 mL), atmospheric air (balloon technique). [b] Yield detected by $^1$H NMR of the crude reaction mixture after aqueous work-up with 1 M HCl (durene as an internal standard). [c] THF–$H_2O$ (2 : 1) as the solvent. [d] Degassed conditions (Ar). [e] Anhydrous Me-THF as the solvent. [f] Reaction performed with recycled **A**.




Scheme 2 Proposed mechanisms for selective oxidations of HMF by NHC-catalysis.




The oxidative pathway was, instead, responsible for the formation of **poly-HMFCA** through sequential oxidative esterifications involving the primary hydroxyl group of **HMF** as the nucleophile (NuH, Scheme 2). An attempt to improve HMFA selectivity by the addition of water into the reaction medium (2 : 1 THF–$H_2O$) for triggering the oxidative path of carboxylic acid formation (NuH = $H_2O$) produced unsatisfactory results (entry 2). On the other hand, the use of the Kharasch oxidant **1** (1 equiv.) and degassed (Argon) anhydrous conditions guaranteed the sole generation of **poly-HMFCA**, thus indicating a reaction window for the exclusive activation of the oxidative path (entry 3). Under the same conditions, however, the presence of excess water could not provide the selective production of **HMFCA** (50%), which was formed together with **poly-HMFCA** (42%; entry 4).

At this point, since polycondensation of **HMF** could not be suppressed, we reasoned that **poly-HMFCA** could serve as a suitable precursor of **HMFCA** by subsequent polyester hydrolysis; therefore, our efforts were next directed to the identification of greener catalytic conditions for the synthesis of that **HMF**-based polymer. According to Bäckvall[38] and Sundén[39] studies on the utilization of electron transfer mediators in aerobic oxidations, catalytic **1** was generated *in situ* from the inexpensive precursor **2** (20 mol%) in the presence of iron(II) phthalocyanine **3** (5 mol%) and atmospheric oxygen as the terminal oxidant. After electron transfer from the Breslow intermediate to **1**, the acyl azolium species is formed along with the reduced alcohol **1′**, which in turn is re-oxidized to **1** by phthalocyanine **3** and oxygen (Scheme 2, blue path). Satisfyingly, under these conditions, the target **poly-HMFCA** was produced in high yield (92%) slightly contaminated by **HMFCA** (Table 1, entry 5). Remarkably, the level of reaction efficiency was maintained unaltered in the absence of alcohol **2** as well (entry 6). This result indicates that phthalocyanine **3** ($E$ = +0.74 V *vs.* SCE)[40] is able to mediate the aerobic oxidative esterification of **HMF** with a low energy barrier and it reacts faster than oxygen with the Breslow intermediate (suppression of the oxygenative pathway). In contrast, the previously reported catalytic oxidant $FeCl_3$ [41] was much less reactive and selective in **HMF** oxidation (entry 7). Gratifyingly, the triazolium **A**/**3**/air system worked efficiently with the biomass-derived methyltetrahydrofuran (Me-THF)[42] solvent (entry 8) and using the recycled pre-catalyst **A** (entry 9). Overall, these results together with the possibility of re-use DBU and Me-THF (see the Experimental section) further improved the sustainability of the disclosed aerobic oxidative process.

The **poly-HMFCA** species was duly characterized by NMR and MS analyses before subsequent elaborations. Hence, the reaction mixture of entry 8 was filtered, acidified with 1 M HCl solution, and extracted with ethyl acetate. The concentrated organic phase was then dissolved in dichloromethane and diluted with cold methanol to give the **poly-HMFCA** species as a precipitate. The $^1$H NMR analysis of this solid was diagnostic to establish the formation of linear polyester oligomers with an average number of repeat units ($n$) equal to 7.8, as determined by integration of signals at 5.30 ppm and 4.67 ppm corresponding to the internal and terminal methylene resonances, respectively (Fig. 1a).

In the $^{13}$C NMR spectrum, the carbonyl carbons of the ester linkages clearly resulted at 158.1 ppm, while the signal of the carboxylic acid end-group could not be distinguishable from the background noise (Fig. 1b). Therefore, the structure of **poly-HMFCA** was confirmed by its derivatization with diazomethane and the appearance of the diagnostic resonances of the methyl ester group at 3.80 ppm and 52.1 ppm in the $^1$H and $^{13}$C NMR spectra, respectively (Fig. S1, ESI†). The negative-ion mode ESI mass spectrum of **poly-HMFCA** (Fig. 2a) showed a main series of ions corresponding to deprotonated polyester oligomers ($n$ = 1–8) with a peak-to-peak mass increment of 124 Da (methylfuran-2-carboxylate repeat unit). The calculated spectrum of **poly-HMFCA** (Fig. 2b) and MS/MS analysis of the selected ionic species at $m/z$ 885 (Fig. S2†) further supported our interpretation.

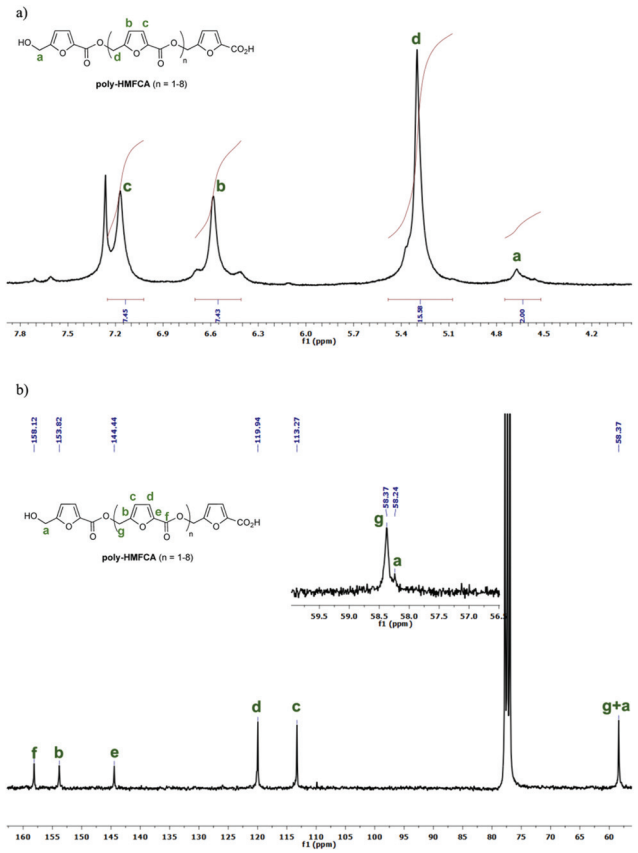



Fig. 1 $^{1}$H NMR (a) and $^{13}$C NMR (b) spectra of **poly-HMFCA** in $CDCl_3$.

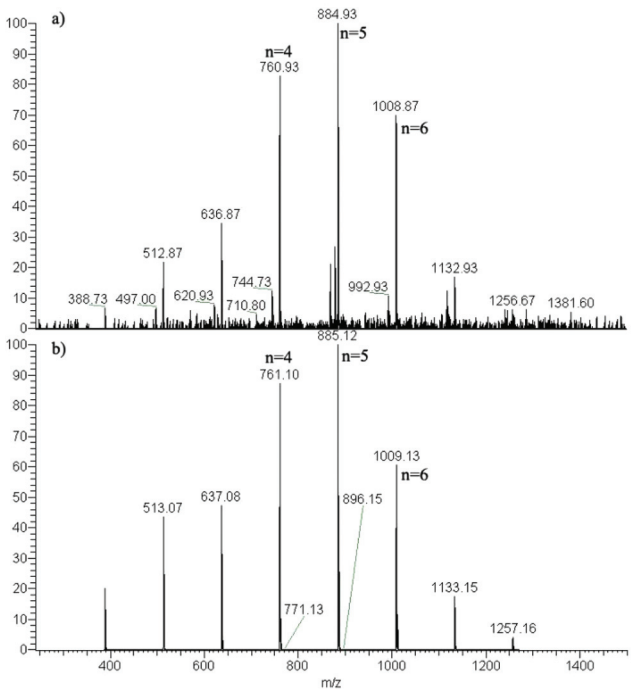
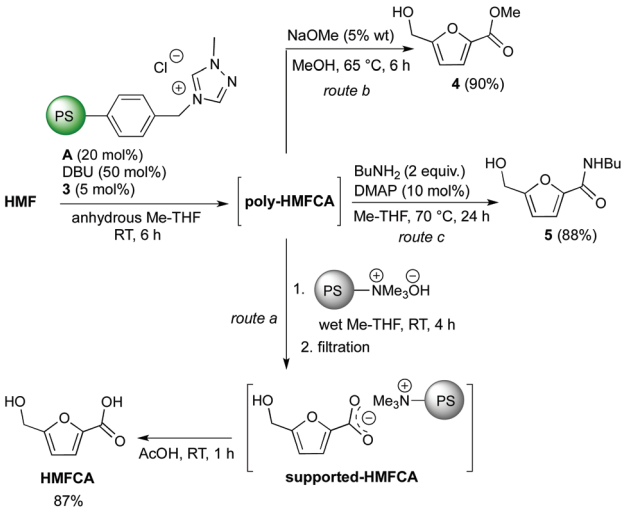



Fig. 2 Experimental (A) and calculated (B) ESI-MS spectra (negative ion mode) of **poly-HMFCA**.




Scheme 3 One-pot two-step synthesis of **HMFCA** ("catch and release" technique), ester **4**, and amide **5**.

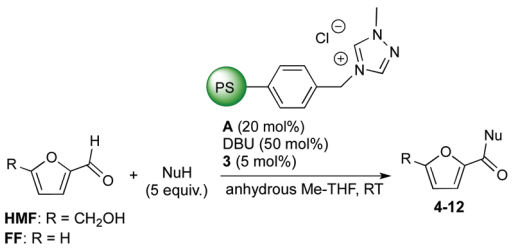
As planned, the **poly-HMFCA** oligomers were subjected to basic hydrolysis for **HMFCA** synthesis (Scheme 3, route a). After a propaedeutic study under homogeneous conditions with aqueous KOH solution, a set of ionic supported bases (Amberlite IRN78, Amberlyst A26 OH form, Ambersep 900 OH) were screened with the aim to selectively catch the carboxylate ion of **HMFCA** on support for impurity removal and subsequently release the acid in solution by protonation ("catch and release" technique). Under optimized conditions, the crude mixture of the oxidative esterification was filtered to recover the pre-catalyst **A**, then diluted with water (20 : 1 Me-THF–$H_2O$) and treated at room temperature with Ambersep 900 OH. After filtration, the resin was suspended in acetic acid for one hour affording the target **HMFCA** in 87% overall yield (one-gram scale).

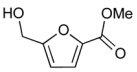
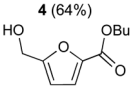
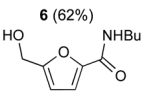
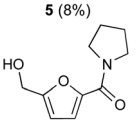
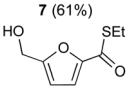
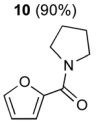
We next envisaged that a similar one-pot two-step procedure could be applied to the synthesis of ester and amide derivatives of **HMFCA**, thus highlighting the synthetic relevance of **poly-HMFCA** oligomers (Scheme 3). Indeed, when crude **poly-HMFCA** was treated with catalytic sodium methoxide (MeOH, 65 °C), the **HMFCA** methyl ester **4** was obtained in 90% overall yield after column chromatography (route b). The primary amide **5** was also prepared by the same strategy (88% yield) with butylamine as the nucleophile (2 equiv.) and catalytic DMAP (Me-THF, 70 °C; route c).

For the sake of comparison, the direct conversion of **HMF** into the corresponding ester, amide, and thioester derivatives was also investigated in a parallel study with the **A**/**3**/air system (Table 2). In general, satisfactory levels of conversion could be achieved only with the use of an excess (5 equiv.) of nucleophile, which was necessary for limiting the side polycondensation of **HMF**. The **HMFCA** methyl ester **4** and its higher homologue **6** were prepared in good yields (entries 1 and 2), while the synthesis of the primary amide **5** (8%) was ineffective by this strategy because of the preferential formation of **HMF**

**Table 2** Reaction scope with the pre-catalyst **A**/**3**/air oxidation system[a]

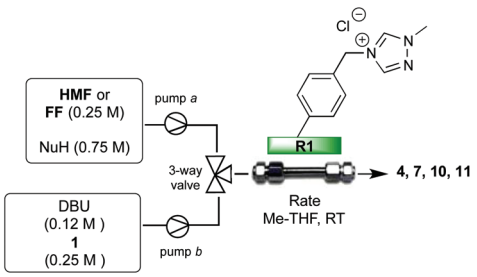



| Entry | Substrate | NuH | Product[b] |
|---|---|---|---|
| 1 | **HMF** | MeOH |  **4** (64%) |
| 2 | **HMF** | *n*-BuOH |  **6** (62%) |
| 3 | **HMF** | $BuNH_2$ |  **5** (8%) |
| 4 | **HMF** |  |  **7** (61%) |
| 5 | **HMF** | EtSH |  **8** (48%) |
| 6 | **FF** | $H_2O$ |  **9** (90%)[c] |
| 7 | **FF** | *n*-BuOH |  **10** (90%) |
| 8 | **FF** |  |  **11** (79%) |
| 9 | **FF** | EtSH |  **12** (52%) |

[a] **HMF** or **FF** (1 mmol), Me-THF (4.0 mL), atmospheric air (balloon technique). [b] Isolated yield. [c] THF–$H_2O$ (2 : 1) as the solvent.

imine (entry 3). Actually, there is still an open debate about the mechanism of NHC-catalyzed aldehyde oxidative amidation[43] that, to the best of our knowledge, has never been applied to **HMF** as the substrate. Pleasantly, the replacement of butylamine with pyrrolidine restored the efficiency of the oxidative process affording the secondary amide **7** in 61% isolated yield (entry 4). The unprecedented synthesis of thioester derivatives of **HMF** was investigated with our oxidative system and the target compound **8** was prepared

**Table 3** Continuous-flow production of selected **HMF** and **FF** oxidation products[a]




| Entry | Product (conv. [%])[b] | Rate (μL $min^{-1}$) | $P^c$ |
|---|---|---|---|
| 1 | **4** (90) | 30 | 460 |
| 2 | **7** (92) | 30 | 471 |
| 3 | **10** (>95) | 35 | 591 |
| 4 | **11** (94) | 35 | 591 |

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

in acceptable 48% yield despite the occurrence of competitive ethanethiol oxidation (entry 5).[44] Afterwards, the scope of the disclosed methodology was extended to the synthesis of representative oxidation products of furfural. Furoic acid **9**, which is a promising precursor of FDCA,[45] was readily obtained in 90% yield (entry 6). This result is comparable to that reported with a soluble imidazolium salt promoter,[32] thus confirming the high catalytic activity of the heterogenous pre-catalyst **A**. As expected, formation of ester **10**, amide **11**, and thioester **12** proceeded with higher efficiency compared to the **HMF**-based analogues because of the lack of the polycondensation side reaction (entries 7–9).

At this stage of the study, we considered the set-up of a flow procedure for the continuous production of selected **HMF** and **FF** oxidation products (Table 3). As previously described by our group,[33] the fixed-bed microreactor **R1** was fabricated by slurry packing the pre-catalyst **A** within a stainless-steel column (length 10 cm, 0.46 cm internal diameter); then, **R1** was fully characterized by pycnometry measurements (see the Experimental section for details). In agreement with our previous observations,[33] the use of the **A**/**3**/air system was made impracticable in the flow regime because of the low concentration of oxygen within the reactor. Hence, the air-recyclable oxidant **1** was employed for the flow experiments, which were optimized by independently pumping inside the pre-activated reactor degassed (Ar) solutions of aldehyde/NuH and DBU/**1** at the concentrations indicated in Table 3. Flow rates were adjusted to achieve high conversions (≥90%) for an easier downstream purification of the target products and the recovery of alcohol **1′** for subsequent regeneration and recycle of the oxidant **1** (see the Experimental section).

## Conclusions

In summary, we have developed a novel catalytic procedure for the synthesis of the valuable bio-based 5-hydroxymethyl-2-furancarboxylic acid (**HMFCA**), which relies on the utilization of polystyrene-supported triazolylidene and iron phthalocyanine catalysts with air as the terminal oxidant and the green solvent Me-THF. The disclosed oxidation system is capable of promoting the sequential oxidative esterification of **HMF** leading to a key oligomeric intermediate, which can be easily elaborated into **HMFCA** and its ester and amide derivatives through a one-pot two-step protocol. The direct conversion under batch and flow conditions of **HMF** and furfural with suitable nucleophiles has been also exploited to expand the set of bio-based chemicals and further demonstrate the potential of heterogeneous oxidative NHC-catalysis in the field of biomass valorization.

## Experimental section

Solvents were dried over a standard drying agent and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 $F_{254}$ with detection by charring with potassium permanganate and/or phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). $^1$H (300 MHz) and $^{13}$C (101 MHz) NMR spectra were recorded in $CDCl_3$ or acetone-$d_6$ solutions at room temperature. The chemical shifts in $^1$H and $^{13}$C NMR spectra were referenced to trimethylsilane (TMS). Peak assignments were aided by $^1$H–$^1$H COSY and gradient-HMQC experiments. For high resolution mass spectrometry (HRMS), the compounds were analyzed using a LTQ-Orbitrap XL mass spectrometer (Thermo Scientific Inc., Milan, Italy) equipped with an electrospray ion source (Thermo Scientific Inc., Milan, Italy) set as follows: positive ion mode, spray voltage 5.5 kV, capillary temperature 275 °C, capillary voltage 16 V, and tube lens offset 120 V. The MS analyzer was externally calibrated with a LTQ ESI Positive Ion Calibration Solution (Thermo Fisher, Milan, Italy) to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 80/20 $H_2O$/ACN 0.1% formic acid into the system at a flow rate of 20 μL min$^{-1}$. Pre-catalyst **A** was synthesized according to a literature procedure.[33] Kharasch oxidant **1**, 2,6-di-*tert*-butylphenol **2**, iron(II) phthalocyanine **3**, 5-hydroxymethylfurfural (**HMF**), furfural (**FF**), and AMBERSEP 900-OH were commercially available and used as received. DBU was freshly distilled before its utilization. 5,5′-Bihydroxymethyl furil (**BHMF**),[46] 5-hydroxymethyl-2-furancarboxylic acid (**HMFCA**),[47] **4**,[48] **9**,[49] **10**,[50] and **11** [43] are known compounds.

### Screening of reaction conditions with pre-catalyst A (Table 1)

**Entries 1 and 2.** A mixture of **HMF** (98 μL, 1.00 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol g$^{-1}$) in the stated solvent (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude reaction mixture. Subsequently, the residue was dissolved in EtOAc (5 mL), acidified with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated. Yields of **HMFCA**, **BHMF**, and **poly-HMFCA** were evaluated by $^1$H NMR analysis of the reaction mixture (durene as the internal standard).

**Entries 3 and 4.** A stirred mixture of **HMF** (98 μL, 1.00 mmol), **1** (408 mg, 1.00 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol g$^{-1}$) in the stated solvent (4.0 mL) was degassed under vacuum, and saturated with argon (by an Ar-filled balloon) three times. Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude mixture of the reaction. Subsequently, the residue was dissolved in EtOAc (5 mL), acidified with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and analyzed by $^1$H NMR.

**Entry 5.** A mixture of **HMF** (98 μL, 1.00 mmol), **2** (41 mg, 0.20 mmol), **3** (28 mg, 0.05 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol g$^{-1}$) in THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude mixture of the reaction. Subsequently, the residue was dissolved in EtOAc (5 mL), acidified with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and analyzed by $^1$H NMR.

**Entry 6.** A mixture of **HMF** (98 μL, 1.00 mmol), **3** (28 mg, 0.05 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol g$^{-1}$) in THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude mixture of the reaction. Subsequently, the residue was dissolved in EtOAc (5 mL), acidified with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and analyzed by $^1$H NMR.

**Entry 7.** A mixture of **HMF** (98 μL, 1.00 mmol), $FeCl_3$ (32 mg, 0.20 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol g$^{-1}$) in THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol), and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude mixture of the reaction. Subsequently, the residue was dissolved in EtOAc (5 mL), acidi-

fied with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and analyzed by $^1$H NMR.

**Entry 8.** A mixture of **HMF** (98 μL, 1.00 mmol), **3** (28 mg, 0.05 mmol), durene (134 mg, 1.00 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded the crude mixture of the reaction. Subsequently, the residue was dissolved in EtOAc (5 mL), acidified with 1 M HCl (5 mL), and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, concentrated, and analyzed by $^1$H NMR.

**Entry 9.** Recycle of the pre-catalyst **A** was performed by simple filtration, washing (MeOH), and drying of the resin. The recycled **A** was used as described in entry 8.

### Poly-HMFCA

A mixture of **HMF** (294 μL, 3.00 mmol), **3** (84 mg, 0.15 mmol) and pre-catalyst **A** (468 mg, 0.60 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (12 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (225 μL, 1.50 mmol) and the reaction mixture was stirred at room temperature for 6 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded crude **poly-HMFCA**. Subsequently, the residue was dissolved in EtOAc (10 mL), acidified with 1 M HCl (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated. Finally, the mixture was dissolved in dichloromethane (8 mL), and diluted with cold methanol (80 mL) to give **poly-HMFCA** (351 mg, 93%) as a precipitate.

**Poly-HMFCA.** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.17 (s, 8H, Ar), 6.58 (s, 8H, Ar), 5.30 (s, 16H, $COOCH_2$), 4.67 (s, 2H, $CH_2$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 158.1, 153.8, 144.44, 119.9, 113.3, 58.4. ESI-MS (886.1 for $n$ = 5): 884.9 $(M - H)^-$.

**DBU recycle.** The above aqueous phase was concentrated under vacuum and the resulting residue was diluted with Me-THF (12 mL) and 1 M NaOH until alkaline pH. The resulting mixture was stirred for 2 h, partially concentrated, and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated to give DBU (195 mg, 1.29 mmol) at least 90% pure as judged by $^1$H NMR analysis.

The structure of **poly-HMFCA** was confirmed by its derivatization with diazomethane to give the corresponding methyl ester. To a cooled (0 °C), stirred solution of **poly-HMFCA** (25 mg) in dichloromethane (1 mL), an ethereal solution of diazomethane was added dropwise. The mixture was stirred for an additional 30 min, warmed to room temperature, and then evaporated by means of a nitrogen stream to give **poly-HMFCA-Me-ester**. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.17 (s, 8H, Ar), 6.58 (s, 8H, Ar), 5.30 (s, 16H, $COOCH_2$), 4.67 (s, 2H, $CH_2$), 3.90 (s, 3H, $COOCH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 157.8, 153.4, 144.1, 119.6, 112.9, 58.0, 52.1.

### 5-(Hydroxymethyl)furan-2-carboxylic acid (HMFCA)

A mixture of **HMF** (784 μL, 8.00 mmol), **3** (224 mg, 0.40 mmol) and pre-catalyst **A** (1.25 g, 1.60 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (30 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (600 μL, 4.00 mmol) and the reaction mixture was stirred at room temperature for 6 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded crude **poly-HMFCA** (1.45 g).

The above crude **poly-HMFCA** (1.45 g) was dissolved in a Me-THF/$H_2O$ mixture (20 mL Me-THF, 1.0 mL $H_2O$) and stirred in the presence of Ambersep 900 OH resin (4.00 g) at room temperature for 4 h. The resin was filtered, thoroughly washed with EtOAc and suspended in acetic acid (10 mL) for 1 h. Subsequently, filtration, washing (EtOAc) of the resin and concentration of the solution afforded crude **HMFCA**. Purification by crystallization (EtOAc) afforded **HMFCA** as a colorless solid (0.98 g, 87%).[47] M.p. 159–161 °C (EtOAc), lit. 163–164 °C;[51] $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ = 7.14 (d, $J$ = 3.4 Hz, 1H, Ar), 6.46 (d, $J$ = 3.4 Hz, 1H, Ar), 4.58 (s, 2H, $CH_2$), 3.92 (bs, 1H, OH); $^{13}$C NMR (101 MHz, acetone-$d_6$) $\delta$ = 160.2, 159.1, 144.8, 118.7, 108.9, 56.8. HRMS (ESI/Q-TOF) calcd for $C_6H_7O_4$ ($[M + H]^+$) 143.0339, found: 143.0336.

### Methyl 5-(hydroxymethyl)furan-2-carboxylate (4)

**Method A.** A mixture of **HMF** (98 μL, 1.00 mmol), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 6 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded crude **poly-HMFCA** (190 mg).

A mixture of the above crude **poly-HMFCA** (190 mg), MeOH (5 mL) and a catalytic amount of sodium methoxide (6 mg, 5 wt%) was stirred at 65 °C for 6 h, then cooled to room temperature, concentrated, and eluted from a column of silica gel with 1 : 1 cyclohexane–EtOAc to afford **4** (140 mg, 90%) as a colorless liquid.[48] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.14 (d, $J$ = 3.4 Hz, 1H, Ar), 6.42 (d, $J$ = 3.4 Hz, 1H, Ar), 4.68 (d, $J$ = 3.4 Hz, 2H, $CH_2$), 3.89 (s, 3H, $OCH_3$), 2.02 (t, $J$ = 3.4 Hz, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 159.5, 158.6, 144.5, 119.2, 109.8, 57.9, 52.3. HRMS (ESI/Q-TOF) calcd for $C_7H_9O_4$ ($[M + H]^+$) 157.0495, found: 157.0491.

**Method B.** A mixture of **HMF** (98 μL, 1.00 mmol), MeOH (202 μL, 5.00 mmol), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol), and the reaction mixture was stirred at room temperature for 16 h. Filtration and washing (EtOAc and MeOH) of the resin, concentration of the solution, and elution from a column of silica gel with 1 : 1 cyclohexane–EtOAc afforded **4** (100 mg, 64%).

***N*-Butyl-5-(hydroxymethyl)furan-2-carboxamide (5)**

**Method A.** A mixture of **HMF** (98 μL, 1.00 mmol), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol) and the reaction mixture was stirred at room temperature for 6 h. Filtration, washing (MeOH) of the resin and concentration of the solution afforded crude **poly-HMFCA** (190 mg).

A mixture of the above crude **poly-HMFCA** (190 mg), $BuNH_2$ (200 μL, 2.00 mmol) and DMAP (12 mg, 0.10 mmol) in Me-THF (4.0 mL) was stirred at 70 °C for 24 h, then cooled to room temperature, concentrated, and eluted from a column of silica gel with 2 : 1 EtOAc–cyclohexane to afford **5** (173 mg, 88%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.02 (d, $J$ = 3.4 Hz, 1H, Ar), 6.37 (d, $J$ = 3.4 Hz, 1H, Ar + bs, 1H, NH), 4.63 (s, 2H, $OCH_2$), 3.45–3.37 (m, 2H, $CH_{2(H\text{-}1butyl)}$), 1.81 (bs, 1H, OH), 1.63–1.52 (m, 2H, $CH_{2(H\text{-}2butyl)}$), 1.45–1.34 (m, 2H, $CH_{2(H\text{-}2butyl)}$), 0.95 (t, $J$ = 7.3 Hz, 3H, $CH_{3(butyl)}$). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 158.4, 155.5, 147.8, 114.6, 110.0, 57.4, 38.9, 31.7, 20.0, 13.7. HRMS (ESI/Q-TOF) calcd for $C_{10}H_{16}NO_3$ ($[M + H]^+$) 198.1125, found: 198.1121.

**Method B.** A mixture of **HMF** (98 μL, 1.00 mmol), $BuNH_2$ (500 μL, 5.00 mmol), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol), and the reaction mixture was stirred at room temperature for 16 h. Filtration and washing (EtOAc and MeOH) of the resin, concentration of the solution, and elution from a column of silica gel with 1 : 2 cyclohexane–EtOAc afforded **5** (16 mg, 8%).

**General procedure for the oxidative esterification, thioesterification, and amidation of HMF or FF (Table 2)**

A mixture of **HMF** (98 μL, 1.00 mmol) or **FF** (83 μL, 1.00 mmol), the stated nucleophile (5 equiv.), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in Me-THF (4.0 mL) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol), and the reaction mixture was stirred at room temperature for 16 h. Filtration and washing (EtOAc and MeOH) of the resin, concentration, and elution of the resulting residue from a column of silica with the suitable elution system afforded the desired product.

**Butyl 5-(hydroxymethyl)furan-2-carboxylate (6).** Column chromatography with 2 : 1 cyclohexane–EtOAc afforded **6** (123 mg, 62%) as a colorless liquid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.12 (d, $J$ = 3.4 Hz, 1H, Ar), 6.41 (d, $J$ = 3.4 Hz, 1H, Ar), 4.68 (d, $J$ = 3.4 Hz, 2H, $OCH_2$), 4.30 (t, $J$ = 6.7 Hz, 2H, $CH_{2(H\text{-}1butyl)}$), 1.98 (t, $J$ = 3.4 Hz, 1H, OH), 1.78–1.66 (m, 2H, $CH_{2(H\text{-}2butyl)}$), 1.51–1.38 ($CH_{2(H\text{-}3butyl)}$), 0.96 (t, $J$ = 7.4 Hz, 3H, $CH_{3(butyl)}$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 159.2, 158.5, 144.82, 118.9, 109.7, 65.2, 58.0, 31.1, 19.5, 14.0. HRMS (ESI/Q-TOF) calcd for $C_{10}H_{15}O_4$ ($[M + H]^+$) 199.0965, found: 199.0961.

**(5-(Hydroxymethyl)furan-2-yl)(pyrrolidin-1-yl)methanone (7).** Column chromatography with 2 : 1 DCM–acetone afforded **7** (119 mg, 61%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 6.96 (d, $J$ = 3.4 Hz, 1H, Ar), 6.37 (d, $J$ = 3.4 Hz, 1H, Ar), 4.65 (s, 2H, $CH_2$), 3.81 (t, $J$ = 6.7 Hz, 2H, $CH_{2(H\text{-}2pyrrolidin)}$), 3.64 (t, $J$ = 6.7 Hz, 2H, $CH_{2(H\text{-}5pyrrolidin)}$), 2.05–1.95 (m, 2H, $CH_{2(H\text{-}3pyrrolidin)}$), 1.95–1.84 (m, 2H, $CH_{2(H\text{-}4pyrrolidin)}$ + bs, 1H, OH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 158.5, 156.3, 148.6, 116.7, 109.4, 58.0, 48.1, 47.3, 26.9, 24.1. HRMS (ESI/Q-TOF) calcd for $C_{10}H_{14}NO_3$ ($[M + H]^+$) 196.0968, found: 196.0964.

***S*-Ethyl 5-(hydroxymethyl)furan-2-carbothioate (8).** The reaction was conducted in the dark.[44] Column chromatography with DCM + 2% acetone afforded **8** (89 mg, 48%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.14 (d, $J$ = 3.5 Hz, 1H, Ar), 6.44 (d, $J$ = 3.5 Hz, 1H, Ar), 4.69 (s, 2H, $OCH_2$), 3.06 (q, $J$ = 7.4 Hz, 2H, $CH_{2(ethyl)}$), 1.98 (bs, 1H, OH), 1.34 (t, $J$ = 7.4 Hz, 3H, $CH_{3(ethyl)}$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 180.9, 158.4, 150.9, 116.7, 110.1, 58.0, 23.0, 15.2. HRMS (ESI/Q-TOF) calcd for $C_8H_{11}O_3S$ ($[M + H]^+$) 187.0423, found: 187.0420.

**Butyl furan-2-carboxylate (10).** Column chromatography with 13 : 1 cyclohexane–EtOAc afforded **10** (152 mg, 90%) as a colorless oil.[50] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.57 (dd, $J$ = 1.7, 0.8 Hz, 1H, Ar), 7.17 (dd, $J$ = 3.5, 0.8 Hz, 1H, Ar), 6.50 (dd, $J$ = 3.5, 1.7 Hz, 1H, Ar), 4.31 (t, $J$ = 6.7 Hz, 2H, H-$1_{butyl}$), 1.78–1.68 (m, 2H, H-$2_{butyl}$), 1.51–1.39 (m, 2H, H-$3_{butyl}$), 0.97 (t, $J$ = 7.4 Hz, 3H, H-$4_{butyl}$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 158.86, 146.13, 144.87, 117.65, 111.74, 64.81, 30.71, 19.12, 13.71. HRMS (ESI/Q-TOF) calcd for $C_9H_{13}O_3$ ($[M + H]^+$) 169.0859, found: 169.0855.

**Furan-2-yl(pyrrolidin-1-yl)methanone (11).** Column chromatography with 8 : 1 cyclohexane–EtOAc afforded **11** (132 mg, 79%) as a yellow oil.[43] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.49 (dd, $J$ = 1.7, 0.8 Hz, 1H, Ar), 7.05 (dd, $J$ = 3.4, 0.8 Hz, 1H, Ar), 6.48 (dd, $J$ = 3.4, 1.7 Hz, 1H, Ar), 3.83 (t, $J$ = 6.7 Hz, 2H, H-$2_{pyrrolidin}$), 3.65 (t, $J$ = 6.7 Hz, 2H, H-$2_{pyrrolidin}$), 2.05–1.93 (m, 2H, H-$3_{pyrrolidin}$), 1.93–1.86 (m, 2H, H-$3_{pyrrolidin}$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 158.11, 148.78, 143.95, 115.69, 111.29, 47.77, 46.99, 26.57, 23.73. HRMS (ESI/Q-TOF) calcd for $C_9H_{12}NO_2$ ($[M + H]^+$) 166.0863, found: 166.0857.

***S*-Ethyl furan-2-carbothioate (12).** The reaction was conducted in the dark.[44] Column chromatography with 3 : 1 cyclohexane–DCM afforded **12** (82 mg, 52%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.56 (dd, $J$ = 1.7, 0.7 Hz, 1H, Ar), 7.17 (dd, $J$ = 3.5, 0.7 Hz, 1H, Ar), 6.52 (dd, $J$ = 3.5, 1.7 Hz, 1H, Ar), 3.05 (q, $J$ = 7.3 Hz, 2H, H-$1_{ethyl}$), 1.34 (t, $J$ = 7.3 Hz, 3H, H-$2_{ethyl}$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 180.7, 151.0, 145.9, 115.2, 112.1, 22.6, 14.8. HRMS (ESI/Q-TOF) calcd for $C_7H_9O_2S$ ($[M + H]^+$) 157.0318, found: 157.0312.

**Furoic acid (9).** A mixture of **FF** (83 μL, 1.00 mmol), **3** (28 mg, 0.05 mmol) and pre-catalyst **A** (156 mg, 0.20 mmol, loading = 1.28 mmol $g^{-1}$) in THF–$H_2O$ (2 : 1 = 2.7 mL THF + 1.3 mL $H_2O$) was stirred under an air atmosphere (by an air-filled balloon). Then, DBU was added (75 μL, 0.50 mmol), and the reaction mixture was stirred at room temperature for 16 h. Filtration, washing (EtOAc) of the resin and concentration of the solution afforded a residue that was diluted with EtOAc

(5 mL) and 1 M HCl (5 mL). The aqueous phase was extracted with fresh portions of EtOAc (2 × 10 mL). The collected organic phases were washed with saturated $NaHCO_3$ solution (5 mL). Subsequently, the aqueous phase was acidified with 1 M HCl and extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated to give furoic acid **9** (101 mg, 90%) at least 95% pure as judged by $^1$H NMR analysis. Purification by crystallization (EtOH) afforded **9** as a gray solid.[49] M.p. 129–130 °C (EtOH), lit. 130–132 °C;[52] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 10.22 (bs, 1H, OH), 7.64 (d, $J$ = 1.6 Hz, 1H, Ar), 7.33 (d, $J$ = 3.4 Hz, 1H, Ar), 6.55 (dd, $J$ = 3.4, 1.6 Hz, 1H, Ar); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ = 163.4, 147.4, 143.9, 120.0, 112.2. HRMS (ESI/Q-TOF) calcd for $C_5H_5O_3$ ($[M + H]^+$) 113.0233, found: 113.0229.

### Continuous-flow production of selected HMF and FF oxidation products (Table 3)

The microreactor **R1** was fabricated by using a 10 × 0.46 cm stainless-steel column as described in ref. 33. 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 **HMF** (0.25 M) [or **FF** (0.25 M)] and the nucleophile (0.75 M) in Me-THF. Channel-B delivered a continuously degassed solution of DBU (0.12 M) and **1** (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 μL min$^{-1}$, 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 **1′** and then give the products **4**, **7**, **10**, and **11**. The quantitative oxidation of **1′** to the Kharasch oxidant **1** was performed with air (1 atm, balloon) and catalytic phthalocyanine **3** (10 mol%, THF, RT).

## Conflicts of interest

There are no conflicts to declare.

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