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.
Funding information

Providing accurate funding information will enable us to help you comply with your funders’ reporting mandates. Clear acknowledgement of funder support is an important consideration in funding evaluation and can increase your chances of securing funding in the future.

We work closely with Crossref to make your research discoverable through the Funding Data search tool (http://search.crossref.org/funding). Funding Data provides a reliable way to track the impact of the work that funders support. Accurate funder information will also help us (i) identify articles that are mandated to be deposited in PubMed Central (PMC) and deposit these on your behalf, and (ii) identify articles funded as part of the CHORUS initiative and display the Accepted Manuscript on our web site after an embargo period of 12 months.

Further information can be found on our webpage (http://rsc.li/funding-info).

What we do with funding information

We have combined the information you gave us on submission with the information in your acknowledgements. This will help ensure the funding information is as complete as possible and matches funders listed in the Crossref Funder Registry. If a funding organisation you included in your acknowledgements or on submission of your article is not currently listed in the registry it will not appear in the table on this page. We can only deposit data if funders are already listed in the Crossref Funder Registry, but we will pass all funding information on to Crossref so that additional funders can be included in future.

Please check your funding information

The table below contains the information we will share with Crossref so that your article can be found via the Funding Data search tool. Please check that the funder names and grant numbers in the table are correct and indicate if any changes are necessary to the Acknowledgements text.

<table>
<thead>
<tr>
<th>Funder name</th>
<th>Funder's main country of origin</th>
<th>Funder ID (for RSC use only)</th>
<th>Award/grant number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Università degli Studi di Ferrara</td>
<td>Italy</td>
<td>501100007109</td>
<td>Unassigned</td>
</tr>
</tbody>
</table>

Researcher information

Please check that the researcher information in the table below is correct, including the spelling and formatting of all author names, and that the authors’ first, middle and last names have been correctly identified. Names will be indexed and cited as shown on the proof, so these must be correct.

If any authors have ORCID or ResearcherID details that are not listed below, please provide these with your proof corrections. Please ensure that the ORCID and ResearcherID details listed below have been assigned to the correct author. Authors should have their own unique ORCID ID and should not use another researcher’s, as errors will delay publication.

Please also update your account on our online manuscript submission system to add your ORCID details, which will then be automatically included in all future submissions. See here for step-by-step instructions and more information on author identifiers.

<table>
<thead>
<tr>
<th>First (given) and middle name(s)</th>
<th>Last (family) name(s)</th>
<th>ResearcherID</th>
<th>ORCID iD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arianna</td>
<td>Brandolese</td>
<td></td>
<td>0000-0003-2423-8008</td>
</tr>
<tr>
<td>Daniele</td>
<td>Ragno</td>
<td>Q-5342-2017</td>
<td>0000-0003-0016-290X</td>
</tr>
<tr>
<td>Graziano</td>
<td>Di Carmine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tatiana</td>
<td>Bernardi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olga</td>
<td>Bortolini</td>
<td>D-8058-2014</td>
<td>0000-0002-8428-2310</td>
</tr>
<tr>
<td>Pier Paolo</td>
<td>Giovannini</td>
<td></td>
<td>0000-0002-7089-5466</td>
</tr>
<tr>
<td>Omar Ginoble</td>
<td>Pandoli</td>
<td>E-8134-2013</td>
<td>0000-0002-2220-7817</td>
</tr>
<tr>
<td>Alessandra</td>
<td>Altomare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Queries for the attention of the authors

Journal: Organic & Biomolecular Chemistry  Paper: c8ob02425a
Title: Aerobic oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid and its derivatives by heterogeneous NHC-catalysis

For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Org. Biomol. Chem., (year), DOI: 10.1039/c8ob02425a.

Editor’s queries are marked like this [Q1], [Q2], and for your convenience line numbers are indicated like this 5, 10, 15, ...

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

<table>
<thead>
<tr>
<th>Query Reference</th>
<th>Query</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Funder details have been incorporated in the funder table using information provided in the article text. Please check that the funder information in the table is correct.</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>Please confirm that the spelling and format of all author names is correct. Names will be indexed and cited as shown on the proof, so these must be correct. No late corrections can be made.</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>Please check that ref. 2 has been displayed correctly.</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>Ref. 20: Please check that the initials for the 3rd author are displayed correctly.</td>
<td></td>
</tr>
<tr>
<td>Q5</td>
<td>Ref. 33: Can this reference be updated? If so, please provide the relevant information such as year, volume and page or article numbers as appropriate.</td>
<td></td>
</tr>
</tbody>
</table>
Aerobic oxidation of 5-hydroxymethylfurfural to 5-hydroxymethyl-2-furancarboxylic acid and its derivatives by heterogeneous NHC-catalysis†

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

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 (Mw = 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 polyesters16 and as a precursor of FDCA.17 Additionally, HMFCa itself displays antitumor activity18 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.7,16–24 Interestingly, Zhang, Deng and their co-workers reported the ability of dioxygenolybdenum(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...
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. 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, 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 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (mol%)</th>
<th>HMFCA (%)</th>
<th>BHMF (%)</th>
<th>Poly-HMFA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Air</td>
<td>35</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Air</td>
<td>38</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>3a</td>
<td>1 (100)</td>
<td>—</td>
<td>—</td>
<td>95</td>
</tr>
<tr>
<td>3b</td>
<td>1 (100)</td>
<td>50</td>
<td>—</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>Air, 2 (20)/3 (5)</td>
<td>5</td>
<td>—</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>Air, 3 (5)</td>
<td>5</td>
<td>—</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Air, FeCl3 (20)</td>
<td>8</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Air, 3 (5)</td>
<td>5</td>
<td>—</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Air, 3 (5)</td>
<td>5</td>
<td>—</td>
<td>91</td>
</tr>
</tbody>
</table>

| 9a    | Air, 3 (5)     | 5          | —         | 91            |

a HMF (1 mmol), THF (4.0 mL), atmospheric air (balloon technique).
b Yield detected by 1H NMR of the crude reaction mixture after aqueous work-up with 1 M HCl (durene as an internal standard).
c THF–H2O (2:1) as the solvent.
d Degassed conditions (Ar).
e Anhydrous Me-THF as the solvent.
f Reaction performed with recycled 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\textsuperscript{38} and Sundén\textsuperscript{39} studies on the utilization of electron transfer mediators in aerobic oxidations, catalytic 1 was generated \textit{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 oxidative 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 $^{13}$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.
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–H2O) 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 ºC), 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 ºC; 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 A3/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.

Scheme 3 One-pot two-step synthesis of HMFCA (“catch and release” technique), ester 4, and amide 5.
imine (entry 3). Actually, there is still an open debate about the mechanism of NHC-catalyzed aldehyde oxidative amidation 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 according the secondary amide 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 in acceptable 48% yield despite the occurrence of competitive ethanethiol oxidation (entry 5). Afterwards, the scope of the disclosed methodology was extended to the synthesis of representative oxidation products of furfural. Furoic acid, which is a promising precursor of FDCA, was readily obtained in 90% yield (entry 6). This result is comparable to that reported with a soluble imidazolium salt promoter, thus confirming the high catalytic activity of the heterogenous pre-catalyst A. As expected, formation of ester, amid and thioester 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, 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, 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 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 for subsequent regeneration and recycle of the oxidant (see the Experimental section).

---

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>NuH</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HMF</td>
<td>MeOH</td>
<td>4 (64%)</td>
</tr>
<tr>
<td>2</td>
<td>HMF</td>
<td>n-BuOH</td>
<td>7 (92%)</td>
</tr>
<tr>
<td>3</td>
<td>HMF</td>
<td>BuNH₂</td>
<td>6 (62%)</td>
</tr>
<tr>
<td>4</td>
<td>HMF</td>
<td></td>
<td>5 (18%)</td>
</tr>
<tr>
<td>5</td>
<td>HMF</td>
<td>EtSH</td>
<td>7 (61%)</td>
</tr>
<tr>
<td>6</td>
<td>FF</td>
<td>H₂O</td>
<td>8 (48%)</td>
</tr>
<tr>
<td>7</td>
<td>FF</td>
<td>n-BuOH</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>8</td>
<td>FF</td>
<td></td>
<td>10 (90%)</td>
</tr>
<tr>
<td>9</td>
<td>FF</td>
<td>EtSH</td>
<td>11 (79%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 (52%)</td>
</tr>
</tbody>
</table>

---

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (conv. [%])</th>
<th>Rate (μL min⁻¹)</th>
<th>P⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 (90)</td>
<td>30</td>
<td>460</td>
</tr>
<tr>
<td>2</td>
<td>7 (92)</td>
<td>30</td>
<td>471</td>
</tr>
<tr>
<td>3</td>
<td>10 (95)</td>
<td>35</td>
<td>591</td>
</tr>
<tr>
<td>4</td>
<td>11 (94)</td>
<td>35</td>
<td>591</td>
</tr>
</tbody>
</table>

---

HMF or FF (1 mmol), Me-THF (4.0 mL), atmospheric air (balloon technique). Isolated yield. THF-H₂O (2 : 1) as the solvent.

---

See the Experimental section for a description of the flow apparatus. Instant conversion in the steady-state regime as established by ¹H NMR analysis. Productivities (P) are measured in mmol(product) h⁻¹ mmol(cat)⁻¹ and calculated on the basis of isolated product (see the Experimental section for details).
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 triazolylienedene 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 F254 with detection by charring with potassium permanganate and/or phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). 1H (300 MHz) and 13C (101 MHz) NMR spectra were recorded in CDCl3 or acetone-d6 solutions at room temperature. The chemical shifts in 1H and 13C NMR spectra were referenced to trimethylsilane (TMS). Peak assignments were aided by 1H-1H 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) set as follows: positive ion mode, spray voltage 5.5 kV, spectrometer (Thermo Scientific Inc., Milan, Italy) set as follows: positive ion mode, spray voltage 5.5 kV, temperature procedure.33 Kharasch oxidant 1, 2,6-di-tert-butylphenol 2, iron(a) phthalocyanine 3, 5-hydroxymethylfurufural (HMF), furfural (FF), and AMBERSEP 900-OH were commercially available and used as received. DBU was freshly distilled before its utilization. 5,5’-Bilhydroxymethyl furil (BHMF), 5-hydroxymethyl-2-furancarboxylic acid (HMFCA),47 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 Na2SO4 and concentrated. Yields of HMFCA, BHMF, and poly-HMFCA were evaluated by 1H NMR analysis of the reaction mixture (durene as the internal standard).

Entries 3 and 4. A 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 Na2SO4, concentrated, and analyzed by 1H 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 Na2SO4, concentrated, and analyzed by 1H 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 Na2SO4, concentrated, and analyzed by 1H NMR.

Entry 7. A mixture of HMF (98 µL, 1.00 mmol), FeCl3 (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 Na₂SO₄, concentrated, and analyzed by ¹H 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 Na₂SO₄, concentrated, and analyzed by ¹H 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 Na₂SO₄ 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.** ¹H NMR (300 MHz, CDCl₃) δ = 7.17 (s, 8H, Ar), 6.58 (s, 8H, Ar), 5.30 (s, 16H, COOCH₂), 4.67 (s, 2H, CH₂), 3.92 (bs, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ = 158.1, 153.8, 119.9, 113.3, 58.4. ESI-MS (886.1 for HMFCA-Me-ester)

**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).

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

**Method B.** A mixture of HMF (98 µL, 1.00 mmol), 3 (28 mg, 0.05 mmol) and pre-catalyst A (156 g, 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 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 of the concentration of the solution afforded crude poly-HMFC (190 mg).

A mixture of the above crude poly-HMFC (190 mg), BuNH₂ (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. ᵃH NMR (300 MHz, CDCl₃) δ = 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, OCH₂), 3.45–3.37 (m, 2H, CH₂(H-1butyl)), 1.81 (bs, 1H, OH), 1.63–1.52 (m, 2H, CH₂(H-2butyl)), 1.45–1.34 (m, 2H, CH₂(H-2butyl)), 0.95 (t, J = 7.3 Hz, 3H, CH₃(butyl)). ᵃC NMR (101 MHz, CDCl₃) δ = 158.4, 155.3, 147.8, 114.6, 110.0, 57.4, 38.9, 31.7, 20.0, 13.7. HRMS (ESI/Q-TOF) calcd for C₁₀H₁₅O₄ ([M + H]+) 199.0968, found: 199.0964.

Butyl furan-2-carboxylate (6). Column chromatography with 2:1 cyclohexane–acetonitrile afforded 6 (156 mg, 90%) as a colorless oil. ᵃH NMR (300 MHz, CDCl₃) δ = 7.14 (d, J = 3.5 Hz, 1H, Ar), 6.44 (d, J = 3.5 Hz, 1H, Ar), 4.69 (s, 2H, OCH₂), 3.06 (q, J = 7.4 Hz, 2H, CH₂(ethyl)), 1.98 (bs, 1H, OH), 1.34 (t, J = 7.4 Hz, 3H, CH₃(ethyl)). ᵃC NMR (101 MHz, CDCl₃) δ = 180.9, 158.4, 150.9, 116.7, 110.1, 58.0, 23.0, 15.2. HRMS (ESI/Q-TOF) calcd for C₅H₁₀O₃ ([M + H]+) 187.0423, found: 187.0420.

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 of the solution, and elution from a column of silica gel with 1:2 cyclohexane–EtOAc afforded 5 (16 mg, 8%).
(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 NaHCO₃ 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 Na₂SO₄ and concentrated to give furoic acid 9 (101 mg, 90%) at least 95% pure as judged by ¹H NMR analysis. Purification by crystallization (EtOH) afforded 9 as a gray solid.⁴⁹ M.p. 129–130 °C (EtOH), lit. 130–132 °C.⁵³ ¹H NMR (300 MHz, CDCl₃) δ = 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); ¹³C NMR (101 MHz, CDCl₃) δ = 163.4, 147.4, 143.9, 120.0, 112.2. HRMS (ESI/Q-TOF) calcd for C₅H₅O₃ [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.

Acknowledgements

We gratefully acknowledge the University of Ferrara (fondi FAR) for financial support. Thanks are also given to Paolo Formaglio for NMR experiments.

Notes and references

20. The classical Cannizzaro reaction has also been described for the synthesis of HMFCA with the limit of the maximum theoretical selectivity (50%) due to the concomitant formation of equimolar 2,3-di(hydroxymethyl)furural (DHMF): S. Subbiah, S. P. Simeonov, J. M. S. S. Esperanca, L. P. N. Rebelo and C. A. M. Afonso, Green Chem., 2013, 15, 2849–2853.
44. This reaction was performed in the dark to prevent the photoinduced oxidation of ethanethiol promoted by phthalocyanine: P. Kumar, G. Singh, D. Tripathi and S. L. Jain, RSC Adv., 2014, 4, 50331–50337.