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Cu catalyzed oxidation of 5-hydroxymethylfurfural to 2,5-diformylfuran and 2,5-furandicarboxylic acid under benign reaction conditions

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ABSTRACT

The renewable chemical building block 5-hydroxymethylfurfural (HMF) was oxidized to 2,5diformylfuran by an oxidation system consisting of the radical 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) and CuCl. The system was optimized by exploring several reaction conditions and by employing nitrogen containing promoters (NCPs) to obtain excellent yields. In acetonitrile a 95% DFF yield was obtained after 24 h with ambient pressure of dioxygen at room temperature in the presence of different NCPs, which – to our knowledge – is the best result reported thus far for this reaction. The use of NCPs made it further possible to apply various traditional solvents, e.g. acetone, methanol and methyl isobutyl ketone for the reaction. The latter can be used as extraction solvent for HMF synthesis in aqueous media and thus integrate the two processes. Additionally, HMF was oxidized to 2,5-furandicarboxylic acid by a modified oxidation protocol consisting of CuCl and *t*-BuOOH. In all the reactions, mild conditions, including room temperature were employed.

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1. Introduction

Future demand for sustainable technologies has recently initiated profound research efforts in this field [1]. In this context, biomass – as a renewable feedstock – has been suggested to substitute fossil-based transportation fuels [2–4]. A more rational approach is to make value added chemicals from biomass [5], since fuels for the transportation sector can be substituted by alternative carbon free resources whereas carbon containing chemicals cannot [6].

A valuable compound that can be obtained relatively easy from biomass feedstocks is 5-hydroxymethylfurfural (HMF), which is formed by the consecutive dehydration of hexoses, e.g. fructose [7–9]. This compound may function as a bio-based precursor for many industrially valuable chemicals and thus potentially replace numerous chemicals with a fossil origin [5,10]. Accordingly, the production of HMF has received immense attention during the last decade.

Surprisingly, synthesis of the compounds 2,5-diformylfuran (DFF) [11–16] and 2,5-furandicarboxylic acid (FDCA) [17–20], which are derived directly from HMF, has so far received only limited attention despite being recognized as top value added

chemicals obtainable from biomass [21]. DFF is a crystalline stable derivative of HMF that can be used, for example, for production of various poly-Schiff bases as well as a monomer for polyacetylations [22]. So far DFF has primarily been synthesized by using vanadium based catalysts. Carlini et al. oxidized HMF to DFF using a heterogeneous catalyst based on VOPO4.2H2O in dimethylsulfoxide (DMSO) at 150 °C resulting in 97% DFF selectivity at 84% HMF conversion [13]. Navarro et al. obtained 99% DFF selectivity at 77% HMF conversion with vanadium acetylacetonate immobilized on poly(4vinylpyridine) crosslinked with divinylbenzene in trifluorotoluene [14]. Recently, Ma et al. reported a $Cu(NO_3)_2/VOSO_4$ system which was able to form DFF in 99% selectively at 99% HMF conversion in acetonitrile (MeCN) after 48 h [15]. Cottier et al. achieved a 65% DFF yield in MeCN using CuCl and molecular oxygen to oxidize HMF to DFF facilitated by 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) radicals [11]. Finally, DFF has also been synthesized electrochemically in fair yields [23,24]. Among all these reported studies, TEMPO radicals seemed very promising, but further studies are required to entirely optimize the system.

The fully oxidized HMF adduct, FDCA, can potentially replace the monomer terephthalic acid (TPA) which is currently used in very large quantities (ca. 40 Mt/a [25]) in the production of polyesters [26]. One reason for the moderate level of attention to date could be that selective, low-waste synthetic pathways from HMF are hard to accomplish. Traditional oxidation of HMF to FDCA can be achieved by using strong, stoichiometric oxidation reagents such







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Scheme 1. The pathway from hexoses to the oxidized HMF adducts 2,5-furandicarboxylic acid (FDCA) and 2,5-diformylfuran (DFF).

as, e.g. chromate (CrO_4^{2-}), dichromate ($Cr_2O_7^{2-}$) or permanganate (MnO_4^{-}) salts. However, these oxidants are highly toxic and all leave a large amount of undesirable metal waste after use.

In this work, we have investigated the oxidation of HMF to both DFF and FDCA using CuCl and TEMPO radicals as catalyst, and optimized the reaction system to achieve high yields under mild conditions. Motivated by the promising results of Gamez et al. in oxidation of primary alcohols [27], we have included a number of nitrogen containing promoters (NCPs) in the optimization study and investigated the effect of the type and the amount of ligand. Finally, we have examined the catalytic oxidation of HMF to FDCA using a modified oxidation system comprised of CuCl [28] and *tert*-butylhydroperoxide (*t*-BuOOH) as oxidizing agent. Such system has previously revealed good results for the oxidation of primary alcohols to carboxylic acids [29]. Notably, the introduced oxidation protocols are benign and benefit from not using expensive noble metals (e.g. Pt, Pd or Ru), do not require the addition of strong base and do not generate large quantities of toxic metal waste (Scheme 1).

2. Experimental

2.1. Materials

HMF (>99%) was purchased from SAFC, while CuCl (97%), *tert*butyl hydroperoxide (purum, ca. 5.5 M in decane over molecular sieves 4 Å), *m*-chloroperoxybenzoic acid (\leq 77%), hydrogen peroxide solution (puriss, 35% stabilized), acetonitrile (99.9%), acetone (semiconductor grade MOS PURANALTM, Honeywell 17921), ethyl acetate (puriss), pyridine (\geq 99.9%), benzonitrile (99%), methyl isobutyl ketone (\geq 99.0%), methanol (99.6%), 2,2,6,6-tetramethylpiperidin-1-oxyl (98%, TEMPO) and immobilized TEMPO on SiO₂ (1.34%, 39.5 mmol/g) were purchased from Sigma–Aldrich. *N*,*N*-Dimethylaminopyridine (98%), ethylendiamine (\geq 99.0%), bis(2aminoethylamine) (p.a.) and tris(2-aminoethylamine) (p.a.) were purchased from Fluka. 2,2'-Bipyridine (99.5%) was purchased from Merck. All reagents were used without further purification.

2.2. HMF to DFF oxidation procedure

All experiments were carried out in one-necked flasks equipped with a condenser. The condenser was left open in experiments using air as the oxidant and equipped with a balloon containing pure O_2 in experiments using O_2 as the oxidant. In a general procedure, HMF (125 mg, 1 mmol), CuCl (10 mg, 0.1 mmol) and TEMPO (17 mg, 0.1 mmol) were dissolved in solvent (5 mL). The reaction mixture was stirred magnetically (450 rpm) for 24 h and the reaction volume subsequently adjusted. Samples were collected periodically and analyzed via HPLC. More details about the instrument setup and HPLC analysis are found in the Supporting information.

2.3. HMF to FDCA oxidation procedure

The oxidation reactions were conducted in one-necked flasks equipped with a condenser. HMF (125 mg, 1 mmol), and CuCl (10 mg, 0.1 mmol) were dissolved in the solvent (2 mL). Subsequently, *tert*-butylhydroperoxide solution (0.64 g, 1.3 mL, 7.2 mmol) was added slowly via syringe over a period of 15 min under constant magnetic stirring (450 rpm). Upon addition (exothermic) the reaction mixture quickly changed from colorless to dark brown to finally end up as a grass green solution/suspension (see Supporting information, Fig. SI3). The reaction was left for a specified time and samples collected periodically for HPLC analysis.

2.4. Product analysis

Samples of reaction products were diluted in water (DFF) or 1 M NaOH (FDCA) and filtered through a syringe filter (VWR, 0.45 μ m PTFE) prior to analysis by high pressure liquid chromatography (HPLC, Agilent 1200 series, Bio-Rad Aminex HPX-87H, 300 mm × 7.8 mm pre-packed column). A 0.005 M H₂SO₄ mobile phase was employed as eluent at 60 °C with a flow rate of 0.6 mL/min. Concentrations of products were determined from calibration curves obtained with reference samples. The calibration was controlled for drift by applying a standard solution of reference compounds of known concentration prior to every HPLC run. RI and UV detectors were employed. In the case of 5-(hydroxymethyl)furan-2-carboxylic acid (HMFCA), the analyte eluted together with MeCN in the HPLC RI signal so here the UV detector was used.

2.5. Product isolation

DFF was purified by column chromatography (50 mL SiO_2 , 2 cm diameter, eluent: EtOAc/CH₂Cl₂ 1:1), where a colorless band ($R_f = 0.6$) was collected and the solvent removed in vacuo resulting in a white crystalline compound (101.6 mg, 0.82 mmol, isolated yield: 83%, yield by HPLC: 88%).

¹H NMR (300 MHz, CDCl₃): δ /ppm 7.29 (s, 2H), 9.80 (s, 2H); ¹³C NMR (75 MHz, CDCl₃): δ /ppm 119.29 (2C), 154.12 (2C), 179.18 (2C).

3. Results and discussion

3.1. HMF oxidation to DFF

An initial reaction was set up employing the most simple reaction conditions required for the reaction to proceed, i.e. HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), MeCN (5 mL), ambient air pressure and room temperature (RT) (Fig. 1). The reaction was observed to progress with a high selectivity of 97% toward DFF with a HMF conversion of 42% after 24 h. The minor by-product detected in the reaction under these conditions corresponded to oxidation at the aldehyde position, yielding 5-(hydroxymethyl)furan-2-carboxylic acid (HMFCA). Increasing the reaction time to 48 h resulted only in a slightly higher HMF conversion (48%), clearly indicating that the reaction rate decreased significantly at longer reaction time. Full substrate conversion could not be achieved under these conditions pointing to deactivation of the catalytic system, as addressed later. The increase in DFF selectivity over time suggested formation of an intermediate that was converted slower to DFF than the HMF was consumed. Such an intermediate could, however, not be detected by HPLC or GC-MS. It could probably be a complex formed from the HMF and TEMPO that cannot be analyzed with our procedure. Blank experiments



Fig. 1. Oxidation of HMF to DFF by Cu/TEMPO with air as the stoichiometric oxidant as function of time. Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), MeCN (5 mL), 1 bar air, RT.

with TEMPO or CuCl alone, i.e. without catalyst, did not produce any substantial HMF conversion in acetonitrile, verifying that the total activity was relying on both species (Table 1, entries 7 and 8).

The effect of the use of dioxygen as the stoichiometric oxidant was next studied. When the reaction was done in MeCN with dioxygen the DFF yield was enhanced to 67% after 24 h at 75% HMF conversion. Nonetheless, also here the reaction stalled and after 48 h a DFF yield of 58% at 77% HMF conversion was obtained, indicating that DFF degraded at prolonged exposure to oxygen under these conditions, likely due to the formation of other oxidation products. These results correlate fairly well with the results from Cottier et al. who obtained a DFF yield of 65% after 18 h using similar reaction conditions but with twice as high a TEMPO/HMF molar ratio [11].

3.1.1. Effect of the solvent

Substituting the MeCN solvent to acetone (Me_2CO), methyl isobutyl ketone (MIBK), methanol (MeOH) or water (H_2O) under air resulted in a dramatic decrease in the HMF conversion and DFF yield, suggesting the importance of a nitrogen-containing solvent (Table 1, entries 2–5). The lower activity of the copper catalyst system in other solvents than MeCN might be explained by a weaker solvent–Cu interaction, as also suggested by Gamez et al. [27]. Oxidation in MIBK would, however, be particularly attractive as this solvent is preferentially used to extract HMF during dehydration of hexoses, e.g. fructose and glucose [7]. This could possibly eliminate the need to change solvent and integrate the two processes. Of

Table 1

Effect of different solvents on the Cu/TEMPO mediated oxidation of HMF to DFF with air. $^{\rm a}$

Entry	Solvent	DFF yield (%)	DFF selectivity (%)	HMF conversion (%)
1	MeCN	42	97	44
2	Me ₂ CO	14	56	25
3	MIBK	10	62	16
4	MeOH	14	>99	14
5	H ₂ O	10	35	28
6	PhCN	25	93	27
7 ^b	MeCN	<1	10	2
8 ^c	MeCN	<1	4	4

^a Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), solvent (5 mL), 24 h, 1 bar air, RT.

^b Blank experiment in absence of CuCl.

^c Blank experiment in absence of TEMPO.



Fig. 2. Effect of the amount of bipy in the oxidation of HMF to DFF as a function of molar *n*(bipy):*n*(Cu) ratio with Cu/TEMPO in MeCN. Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), 24 h, 1 bar O₂, RT.

the examined solvents, water – which from a sustainability viewpoint would be preferred – was the least suitable for the oxidation with only 10% DFF yield at 28% HMF conversion (Table 1, entry 5). Another nitrogen containing solvent, namely benzonitrile (PhCN), was also investigated as solvent for the oxidation. Here, a high DFF selectivity of 93% was obtained, but only at a rather low HMF conversion of 27% (Table 1, entry 6).

The fact that the oxidation progressed poorly in other solvents than MeCN (Table 1), clearly indicates the importance of the nitrogen containing solvent, ligand or promoter being added. Accordingly, the effect of the presence of NCPs was investigated.

3.1.2. Effect of the addition of NCPs

Several nitrogen containing compounds have previously been reported by Gamez et al. to enhance the activity of the Cu/TEMPO oxidation system in the oxidation of, e.g. benzylalcohol to benzalde-hyde [27]. Especially, 2,2'-bipyridine (bipy) and substituted bipy ligands were found to perform the best; however, no reaction optimization was performed in the study. In our work, we examined the effect of the addition of bipy more thoroughly in the oxidation of HMF to DFF. First, experiments were conducted with different molar ratios of n(bipy):n(CuCl) (ca. 0.25–2) in MeCN at ambient pressure to optimize the amount of NCP necessary. Fig. 2 show the effect obtained applying different amount of bipy to the reaction with dioxygen as oxidizing agent.

The addition of bipy in small amounts was found to increase the HMF conversion and the DFF yield markedly (67% DFF yield to 86% DFF yield without bipy and with 0.25 n(bipy):n(Cu), respectively). However, this was accompanied by a slight decrease in the DFF selectivity. Surprisingly, only bipy amounts corresponding to n(bipy):n(Cu) < 1 were found to have a promoting effect on the oxidation, whereas higher ratios resulted in a drastic decrease in both DFF selectivity and yield. This trend might be a consequence of the chelation of Cu by the ligand, limiting its availability to the substrate.

The effect of other reaction conditions, such as the temperature, was investigated in order to optimize the performance of the system. An augment in temperature from RT to 40 and 50 °C was found to increase the DFF yield and selectivity along with an increased HMF conversion when using air as the oxidant (Table 2, entries 2–4). Thus, at 50 °C a DFF selectivity of 92% was obtained at 97% HMF conversion. These results are exceptionally attractive when compared with the results provided by heterogeneous catalytic systems, in which very high pressures and temperatures are required to reach lower values of conversion [30]. Higher temperatures than

Table 2

Effect of the reaction temperature on the Cu/TEMPO mediated oxidation of HMF to DFF in MeCN with air.^a

Entry	T (°C)	NCP ^b	DFF yield (%)	DFF selectivity (%)	HMF conversion (%)
1	RT	-	42	97	44
2	RT	Bipy	49	79	63
3	40	Bipy	85	91	93
4	50	Bipy	90	92	97

^a Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), 24 h, 1 bar air.

^b 0.03 mmol bipy.



Fig. 3. Oxidation of HMF to DFF by Cu/TEMPO at $50 \,^{\circ}$ C with bipy and air as the stoichiometric oxidant as function of time. Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), MeCN (5 mL), 1 bar air and bipy (0.03 mmol).

60 and 70 °C were found to decrease the HMF conversion significantly (results not shown), probably due to a lower solubility of the oxygen in the solvent at these temperatures.

Since very good results were obtained at 50 °C the kinetic of the reaction was studied in more detail at this temperature by following the oxidation over a 24 h period (Fig. 3). The results showed that 53% of the initial HMF was converted within the first 30 min, where after the rate of the reaction slowed down significantly until 97% HMF conversion was reached after 1440 min. The DFF selectivity increased gradually from 77 to 92% in the 30–1440 min period. This behavior was also observed in the reaction without added bipy (Fig. 1). We speculate that the intermediate can be complex IV or V depicted in Scheme SI1 (Supporting information), which are not detected with our analysis method. Nevertheless, carbon balances were in all reactions higher than ca. 90%.



Fig. 4. Nitrogen containing promoters (NCPs).

Other NCPs than bipy were also applied to study the effect of the addition in the oxidation of HMF to DFF. In the screening, a range of compounds were chosen which incorporated two or more nitrogen atoms and with structural/chemical similarities to bipy. *N*,*N*-Dimethylaminopyridine (DMAP), which is commonly used as a nucleophilic catalyst in organic reactions, contained a pyridine group like bipy as well as a tertiary amino group. The other compounds used; ethylendiamine (EDA), bis(aminoethyl)amine (BAEA) and tris(aminoethyl)amine (TAEA) were amines with different denticity ($\kappa = 2-4$) (Fig. 4).

The initial test reactions were conducted with air as the stoichiometric oxidant in MeCN at RT, and were compared to oxidations without NCP and with bipy, respectively (Fig. 5a). Room temperature was selected to better observe the differences in catalytic activity. The tests showed that the addition of EDA or BAEA resulted in an increased DFF yield. However, bipy provided the highest HMF conversion.

The same NCPs were also tested employing dioxygen as the oxidant with an identical oxidation protocol (Fig. 5b). In these experiments, the differences observed in the catalytic results with the NCPs were greater. EDA, BAEA and DMAP provided superior DFF yields compared to bipy with selectivities higher than 95%. Furthermore, the DFF yields using EDA, BAEA or DMAP all ended at an impressive 95% after 24 h, which to our knowledge is the highest reported DFF yield obtained with this oxidation system. Application of TAEA did not show any effect compared to the reaction without NCPs.

We have also investigated if the presence of catalytic amounts of bipy in the alternative solvents Me₂CO, MIBK, MeOH and H₂O, could compensate for the deficient performance of the Cu/TEMPO system in these solvents (Fig. 6). Effectively, the addition of small amounts of bipy (n(bipy):n(Cu) ca. 0.25) proved to enhance the catalytic performance of the oxidation system in other solvents than MeCN, and the HMF conversion and DFF yield were both increased in Me₂CO, MIBK and MeOH to levels similar to that observed with MeCN with air as oxidant. No enhancement was, however, observed with water



Fig. 5. Screening of NCPs in the oxidation of HMF to DFF in MeCN with (a) air and (b) O₂. Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), MeCN (5 mL), 24 h, 1 bar air/O₂, NCP (0.03 mmol) except PhCN (0.06 mmol), RT.



Fig. 6. Effect of bipy addition in the oxidation of HMF to DFF in different solvents by the Cu/TEMPO catalyst system with/without bipy in air. Reaction conditions: HMF (1 mmol), TEMPO (0.1 mmol), CuCl (0.1 mmol), 24 h, 1 bar air, *n*(bipy):*n*(Cu) ca. 0.25 (when bipy was used), RT.

as the solvent. Hence, in Me₂CO the DFF yield was increased from 14 to 45%, in MIBK from 10 to 49% and in MeOH from 14 to 38%, respectively. The result obtained in MIBK is especially interesting, since oxidation in MIBK may be particularly attractive as this solvent is preferentially used to extract HMF during dehydration of hexoses, e.g. fructose and glucose [7]. This could possibly eliminate the need to change solvent and integrate the two processes. Experiments with bipy under dioxygen atmosphere resulted here in a higher HMF conversion (85%) and DMF yield (75%), proving it is possible to achieve good catalytic results in other solvents when NCPs are used.

3.1.3. Reaction mechanism and catalyst stability

Gamez et al. have proposed a general reaction mechanism for *N*-ligand-Cu/TEMPO catalyzed oxidation of alcohols [27]. In this mechanism, bipy is coordinated to the Cu(I) center, which is subsequently oxidized to Cu(II) by TEMPO. In the reaction with HMF, it would then be coordinated to Cu(II) through the alcohol group under the abstraction of a proton followed by coordination of Cu(II) and TEMPO. Proton/electron rearrangement would form DFF and reform the Cu(I)–bipy complex by a radical mechanism, and TEMPO would finally be regenerated by O_2 oxidation (Scheme SI1 of Supporting information). In the work by Gamez et al. *t*-BuOK was used in catalytic amounts to facilitate the deprotonation of the oxidation efficiency was found when bipy was employed and further a threefold when *t*-BuOK was applied [27].

The oxidation of HMF to DFF in our work was conducted without the addition of t-BuOK, because both HMF and DFF are somewhat labile toward strong basic conditions for extended periods of time. Further, the production of the substrate, HMF, from carbohydrates or a biomass source is usually only facilitated under acidic conditions, which would lead to an undesired change from acidic to alkaline conditions for a combined process from biomass to DFF. Both mono- and bidentate ligands (DMAP or bipy, for instance) showed a remarkable catalytic enhancement of the oxidation system, by coordinatig to the Cu(I)/Cu(II). Further, since the NCPs were present in sub-stoichiometric amounts related to Cu, it is unlikely that the ligand alone accounted for this enhancement. It was more plausible that the NCPs also facilitated the proton transfer from HMF to TEMPO similar to *t*-BuOK in the study by Gamez and co-workers, where a significant increase was also observed in the product yield. Furthermore, the oxidation state of Cu does not



Fig. 7. Oxidation of HMF to FDCA with Cu/t-BuOOH. Reaction conditions: HMF (1 mmol), CuCl (0.1 mmol), MeCN (2 mL), t-BuOOH (3.6 eq), RT.

seem to play an essential role, since similar catalytic results were obtained with $CuCl_2$ as the precursor (results not shown).

Regarding the stability of this catalytic system, Gamez et al. have suggested that TEMPO is deactivated as the substrate is being consumed [27]. Indeed, in order to increase the DFF and HMF conversion after the experiments at 24 and 48 h more TEMPO was required. This fact indicated that deactivation of the TEMPO caused the reaction to stall, as shown in the previous results (Section 3.1).

3.2. Oxidation of HMF to FDCA

The first attempts to oxidize HMF to FDCA were conducted under reaction conditions similar to those employed by Mannam et al. in a general protocol for the oxidation of alcohols, i.e. with MeCN as the solvent of choice, CuCl as the oxidation catalyst and *t*-BuOOH as the stoichiometric oxidant at RT [28]. Contrary to the DFF synthesis, good FDCA yield was obtained without TEMPO in the oxidation with Cu/*t*-BuOOH. Fig. 7 and Table 3 show the results obtained in the oxidation of HMF with different solvents.

As shown in Fig. 7, samples of the reaction solution revealed a mixture of HMFCA and FDCA after short periods. This HMFCA reaction intermediate was slowly converted to form 50% FDCA yield after a period of 48 h (Fig. 7). In all the samples a total conversion of the initial HMF was found and the carbon balance was very low (30–50%), pointing to the formation of undetectable by-products.

MeCN was substituted for other solvents such as Me_2CO (Table 3, entries 1 and 2), ethylacetate (EtOAc) (Table 3, entries 3 and 4) and water (Table 3, entry 5). Again, in all cases the HMF conversion was close to quantitative. Water was, like in the oxidation of HMF to DFF, in particular desired since its use would generate the most benign and eco-friendly reaction system. The use of Me_2CO provoked a diminishing of the FDCA yield from 50 to 33% after 48 h, while EtOAc proved to be a poor solvent in the oxidation of HMF with the reaction conditions employed here. The reaction was also clearly hampered by the presence of water (Table 3, entries 5–7) and HMFCA was usually observed as the main product.

The performance of the CuCl/t-BuOOH catalyst system was also examined in combination with nitrogen containing solvents and NCPs to investigate if such additives had similar promoting characteristics on the FDCA synthesis as found for the DFF synthesis (vide supra). Both systems proved less suited for the oxidation of HMF to FDCA (19 and 5% FDCA yield, Table 3, entries 8 and 9) as compared to the experiments in MeCN (50% FDCA yield, Fig. 7).

The addition of catalytic amounts of halide salts such as, e.g. LiBr (which might be a residue from the dehydration reaction of

Table 3

Cu-catalyzed oxidation of HMF to FDCA with different solvents, co-catalysts and stoichiometric oxidants.^a

Entry	Time (h)	Solvent	Oxidant	Co-catalyst	FDCA yield ^b (%)
1	24	Me ₂ CO	t-BuOOH	-	23
2	48	Me ₂ CO	t-BuOOH	-	33
3	24	EtOAc	t-BuOOH	-	6
4	48	EtOAc	t-BuOOH	-	8
5	48	H ₂ O	t-BuOOH	-	3
6	48	H ₂ O:MeCN ^c	t-BuOOH	-	12
7	48	H ₂ O:MeCN ^d	t-BuOOH	-	31
8	48	Pyridine	t-BuOOH	-	19
9	48	MeCN	t-BuOOH	Bipy ^e	5
10	4	MeCN	t-BuOOH	LiBr ^f	26
11	24	MeCN	t-BuOOH	LiBr ^f	36
12	48	MeCN	t-BuOOH	LiBr ^f	43
13	24	MeCN	H_2O_2	-	<1
14	2 ^g	MeCN	mCPBA	-	1
15 ^h	48	MeCN	t-BuOOH	-	45

^a Reaction conditions: HMF (1 mmol), CuCl (0.1 mmol), MeCN (2 mL), oxidant (3.6 eq) unless otherwise mentioned, RT.

^b No HMF was detected in the products, conversion was 100% in all the cases.

^c H₂O:MeCN = 1:1.

^d $H_2O:MeCN = 1:3.$

^e 0.2 mmol.

^f ca. 5 mg, i.e. catalytic amounts.

⁸ Reaction time where the highest FDCA yield was observed. FDCA was degraded at longer reaction times.

^h Reaction employing CuCl₂ as catalyst.

hexoses to HMF if using salting-out systems [30,31]) were found to increase the rate of HMF conversion during the first 6 h of reaction. Also LiCl, NaBr and CaCl₂ were utilized and showed the same effect on the oxidation reaction (results not shown). After 48 h the reaction yields of FDCA in presence of LiBr were, however, slightly lower than those obtained without added salts (Table 3, entries 10–12). This effect was found for both catalytic and stoichiometric amounts of added salts. Other peroxides such as hydrogenperoxide (H₂O₂) and *m*-chloroperoxybenzoic acid (*m*CPBA) were not found useful in the CuCl-catalyzed oxidation of HMF to FDCA (Table 3, entries 13 and 14) as only traces of FDCA were formed. Increasing the reaction temperature to 35 or 40 °C resulted in an increased reaction rate, as expected, but did not result in improved reaction yields of FDCA compared to the corresponding experiment performed at RT (results not shown).

The active oxidation metal specie was probably Cu(II) resulting from the oxidation of Cu(I) by *t*-BuOOH followed by homolytic cleavage of the hydroperoxide, as also suggested by Mannam et al. [28]. Thus, the oxidation of Cu(I) to Cu(II) should not hamper the catalytic performance. In order to confirm this an experiment using CuCl₂ was also conducted in MeCN. As in the previous case of the oxidation to DFF, CuCl₂ showed to be almost as efficient an oxidation catalyst as CuCl and resulted in 45% FDCA after 48 h of reaction (Table 3, entry 15, vs 50% with CuCl; Fig. 7).

In summary, the oxidation of HMF to FDCA seemed significantly more difficult to achieve than the oxidation to DFF under the examined reaction conditions, which might be associated with a low solubility of FDCA in MeCN [32]. Hence, it is likely that product saturation resulted in FDCA precipitation onto the Cu catalyst, or formation of a FDCA–Cu salt (similar to reported for FDCA–Mg and FDCA–Ni [33,34]), which could account for the observed inhibition.

4. Conclusions

In this study, we have investigated the Cu catalyzed oxidation of HMF with air/O₂ (with TEMPO) or *t*-BuOOH as the stoichiometric oxidants, respectively, in different solvents and with nitrogen containing promoters (NCPs). Oxidation of HMF with CuCl/TEMPO catalyst system in MeCN showed a high selectivity to DFF (97%) at moderate conversions (44%). Using dioxygen as the oxidant under identical reaction conditions increased the HMF conversion and DFF yield. Reactions proceeded generally poorly in other solvents than MeCN. Nevertheless, an enhancement in both substrate conversion and DFF selectivity was observed when several NCPs were added. 90–95% DFF yields were obtained after 24 h in MeCN at RT with O₂ as the oxidant. The use of NCPs, bipy in particular, improved considerably the catalytic activity in other solvents than MeCN, allowing application of MIBK, for instance. MIBK is interesting since it is commonly used as solvent to extract HMF from the aqueous phase in the synthesis from fructose, thus it could prove particular interesting to develop an efficient oxidation protocol with this solvent.

In addition to the synthesis of DFF by oxidation of HMF, we have also demonstrated for the first time (as far as we are aware), that oxidation of HMF into the renewable terephthalic acid substitute FDCA can be achieved in fair to good yields (50%) by using the oxidation pair CuCl/*t*-BuOOH in MeCN. Since FDCA is scarcely soluble in the reaction media, such an oxidation approach might facilitate effective separation of the product by simple filtration. This feature will most likely be of significant importance for future implementation of a HMF oxidation protocol into an integrated process, where carbohydrates (e.g. glucose) are converted via HMF into the renewable plastic monomer FDCA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcata. 2013.01.042.

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