

Sustainable Chemistry

Phase Transfer Catalyst Assisted One-Pot Synthesis of 5-(Chloromethyl)furfural from Biomass-Derived Carbohydrates in a Biphasic Batch Reactor

Sharath Bandibairanahalli Onkarappa and Saikat Dutta^{*[a]}

5-(Chloromethyl)furfural (CMF), a bio-renewable chemical building block, has been produced in good isolated yields from biomass-derived carbohydrates within a closed aqueous HCl-1,2-dichloroethane biphasic reactor in the presence of benzyltributylammonium chloride (BTBAC) as a phase transfer catalyst (PTC). The solvent-economic, one-pot strategy afforded CMF in 73% isolated yield (90 °C, 3 h) from sucrose with a combined yield of 84% for CMF and levulinic acid. The process was optimized on temperature, duration, solvent, type, and loading of PTC. Use of BTBAC led to nearly 10% increase in yield of CMF for all substrates when compared to control reactions.

Introduction

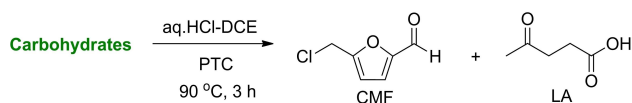
One of the greatest challenges to industrialized societies is to find renewable and greener feedstock for carbon-based fuels, chemicals, and materials.^[1] Carbohydrates are the largest source of renewable carbon and cellulose is the single most abundant and largely under-utilized carbohydrate available in nature. Therefore, terrestrial and algal biomass has received serious attention worldwide as a bio-renewable carbon-based feedstock for transportation fuels and chemicals.^[2] Chemical-catalytic valorizations of biomass are fast, biomass agnostic in nature, do not require live organisms, and relatively less energy intensive.^[3] Acid-catalyzed hydrolysis and dehydration of biomass-derived carbohydrates leads to 5-(hydroxymethyl)furfural (HMF) and is known for more than a century.^[4] HMF retains all the carbon atoms and some of the key functionalities of the parent sugar. During the past two decades, hundreds of publications and patents in the literature have been attributed to the production and/or synthetic upgrading of HMF as a renewable chemical building block for the synthesis of a variety of commodity chemicals including drop-in hydrocarbon fuels, fuel oxygenates, monomers for renewable polymers, plasticizers, solvents, agrochemicals, and pharmaceuticals.^[5] Although high selectivity and yield of HMF have been achieved from

simple sugars such as fructose, similar yields of HMF from more challenging substrates such as starch, cellulose, and untreated cellulosic biomass are relatively rare and often require special reaction conditions.^[6] Being hydrophilic and relatively unstable in aqueous acids, efficient isolation and purification of HMF from the aqueous reaction media is a major challenge in HMF production.^[7] Needless to say, the derivative chemistries of HMF heavily rely on the commercial viability of HMF production. In this regard, congeners of HMF such as 5-(halomethyl)furfural (X = Cl, Br) are also known for over a century.^[8] The first synthesis of 5-(chloromethyl)furfural (CMF, X = Cl) was achieved by treating cotton with ethereal hydrogen chloride.^[9] A literature search showed 218 references on CMF against 13797 references of HMF.^[10] CMF, unlike HMF, is hydrophobic and can conveniently be isolated from the aqueous reaction media by a simple solvent-solvent extraction. CMF is potentially able to participate in all derivative chemistries of HMF.^[11] CMF is a biomass-derived renewable chemical platform and termed as the 'New HMF' with superior properties and reactivity.^[12] Over the past decades, synthesis of CMF from carbohydrates and cellulosic biomasses have been achieved with varying degrees of success.^[13] In 2008, Mascal *et al.* reported the synthesis of CMF from various carbohydrates and cellulosic biomasses within a biphasic batch reactor containing aqueous HCl and 1,2-dichloroethane (DCE).^[14] The reaction was heated at 65 °C by conventional heating and mechanically stirred for 30 h while CMF was continuously extracted from the reaction medium. In a later report, the selectivity and yield of CMF were improved significantly by carrying out the reaction in a glass pressure reactor.^[15] The sealed reactor permitted using higher reaction temperature without evaporative loss of HCl gas during the reaction. In the above processes, levulinic acid (LA) was co-produced in noticeable quantities. LA is a ring-opened product of HMF and CMF that begins with rehydrating the furan ring.^[16] LA is another important bio-renewable chemical building block with huge commercial potential.^[17] CMF has recently been prepared in a biphasic open batch reactor using a mixture of aqueous HCl (35%) and H₃PO₄ (85%) with chloroform as the extracting solvent.^[18] Synthesis of CMF has also been attempted in a continuous flow reactor.^[19] CMF has been prepared in deep eutectic solvents and also catalyzed by metal chlorides.^[20] The yield of CMF is significantly influenced by the efficacy of extracting CMF into the organic phase. The organic solvent plays an important role in the process since it extracts CMF from the aqueous acid as it forms and shields it from

[a] S. B. Onkarappa, Dr. S. Dutta

Department of Chemistry, National Institute of Technology Karnataka (NITK), Surathka, Mangalore-575025, Karnataka, India
E-mail: sdutta@nitk.edu.inSupporting information for this article is available on the WWW under <https://doi.org/10.1002/slct.201901347>

decomposition reactions.^[14] Chlorinated solvents such as chloroform and DCE were found to be most effective in producing CMF. Increasing the ionic strength of the aqueous medium also helps in extracting CMF into the organic phase. The interconversion between HMF and CMF can potentially happen in the interface of the aqueous and organic layer. The relative concentration of HMF and CMF in the aqueous and organic layer depends on their distribution coefficient. The distribution coefficient of CMF is highly favored in most organic solvents due to its hydrophobic nature. However, HMF being hydrophilic, the relative ratio of HMF in aqueous and organic layer depends on the extracting capability of the solvent. Whereas transforming HMF into CMF safeguards it from further decomposition in aqueous acid, the reverse is not true. Hydrolysis of CMF into HMF transports it back into the aqueous layer and exposes it to various degradation pathways. Effect of various surface active agents on the yield of CMF has been studied, but no positive effect was found.^[21] We envisioned that increasing the free chloride ion concentration in the organic layer can potentially slow down the hydrolysis of CMF into HMF. Therefore, a phase transfer catalyst containing chloride counter ion may be used that favors the HMF to CMF transformation both in the aqueous and organic layer. In this work, the effect of various tetraalkylammonium chloride phase transfer catalysts (PTC) on the yield and selectivity of CMF within a biphasic batch reactor is reported (Scheme 1). The



Scheme 1. Production of CMF from carbohydrates using phase transfer catalyst (PTC).

reaction has been optimized on temperature, duration, loading of the substrate, type, and loading of PTC.

Results and Discussion

Initially, a slightly modified literature process of CMF preparation was adopted. Glucose was chosen as the model substrate for process optimization. In a typical reaction, glucose was suspended in aq. HCl (35%)-DCE biphasic reaction mixture taken in a sealed round-bottomed glass pressure reactor fitted with a magnetic stirring rod and Teflon screw top. BTBAC (10 wt% of glucose) was added as a phase transfer catalyst. The reactor was sealed and magnetically stirred in a pre-heated (90 °C) for 3 h. The control reactions were carried out using the same reaction conditions except no BTBAC was added. All the experiments were performed in triplicate, and the average yield is being reported. Intermittent extractions of the DCE layer were avoided to simplify the process and making it a true 'one-pot' process. After the reaction, CMF was isolated from the DCE phase in 64% yield. In addition, LA was isolated from the aqueous layer in 15% yield. When the reaction was conducted under identical conditions without using BTBAC, CMF and LA

were isolated in 47% and 10% yields, respectively. The mass balance is the insoluble humin formation which is significantly more in the control reaction not using BTBAC. The reaction was then optimized on various reaction parameters including temperature, duration, nature of solvent, type, and loading of phase transfer catalyst to maximize the yield of CMF. When the reaction was conducted at 100 °C for 3 h, the yield of CMF decreased to 48% (Figure 1). Lowering the temperature to 80

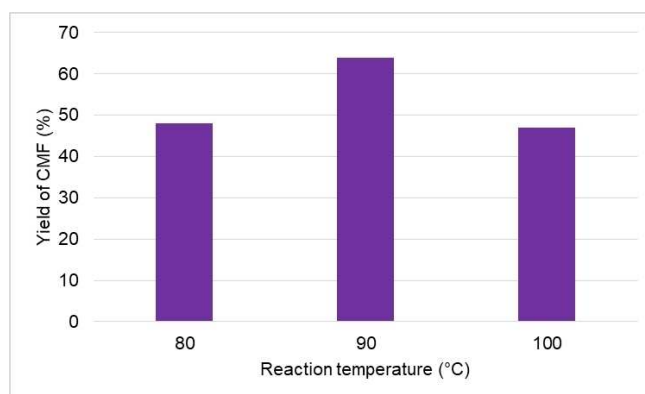


Figure 1. Effect of reaction temperature on the isolated yield of CMF. Reaction conditions: glucose (2 g), HCl (35%, 20 mL), DCE (40 mL), BTBAC (0.2 g, 10 wt%), 3 h.

°C provided 47% yield of CMF. The lower yield of CMF at higher temperature is due to the higher rate decomposition of CMF during reaction whereas a decrease in CMF yield at a lower temperature can be attributed to incomplete reaction. CMF was purified by column chromatography using chloroform as the eluting agent. The BTBAC catalyst was recovered from the silica gel column by eluting with 20% methanol in chloroform where 96% of BTBAC was successfully recovered.

The reaction was then optimized on the duration. When the reaction was conducted at 90 °C for 2 h only, CMF was isolated in only 28% yield (Figure 2).

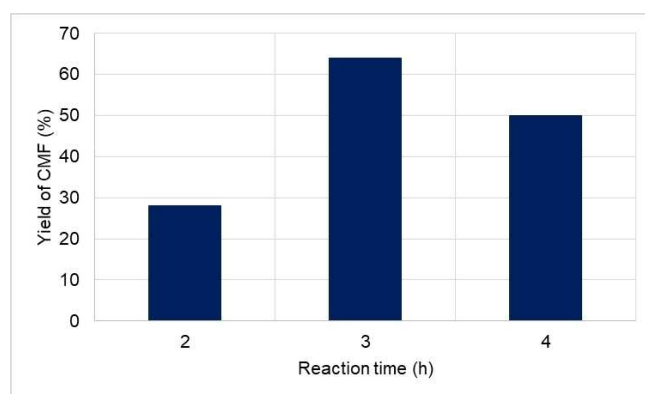


Figure 2. Effect of reaction time on the yield of CMF. Reaction conditions: glucose (2 g), HCl (35%, 20 mL), DCE (40 mL), BTBAC (0.2 g, 10 wt%), 90 °C.

Conducting the reaction for longer than 3 h also lowered the yield of CMF. For example, CMF was isolated in only 50% yield when the reaction was conducted at 90 °C for 4 h. Whereas the lower yield of CMF at 2 h reaction time may be attributed to incomplete conversion of glucose, the lower yield of CMF is due to decomposition of CMF in the reaction mixture.

As mentioned before, the solvent plays a vital role in producing CMF in a biphasic system. When the amount of DCE was doubled in amount (ca. 80 mL), the yield of CMF increased marginally to 68%. The effect of other organic solvents, frequently used in the literature for the synthesis of CMF, has been examined in the present process. Using glucose as the substrate of choice, the effect of toluene, chloroform, and chlorobenzene as extracting solvent was studied and compared with DCE (Figure 3).

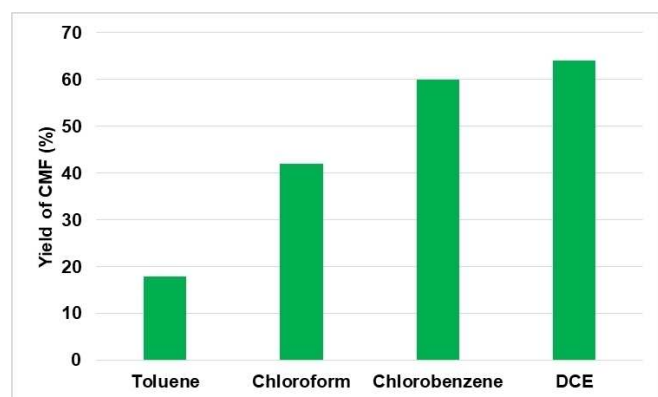


Figure 3. Effect of solvent on the isolated yield of CMF. Reaction conditions: glucose (2 g), HCl (35%, 20 mL), DCE (40 mL), BTBAC (0.2 g, 10 wt%), 90 °C, 3 h.

Toluene performed poorly with less than 20% yield of CMF whereas chloroform as extracting solvent provided CMF in 42% isolated yield. Chlorobenzene was found to be as effective as DCE and provided CMF in 60% yield. The trend can be correlated with increasing dielectric constant of the solvents increasing from toluene to chloroform to chlorobenzene to DCE. A solvent with more dielectric constant extracts HMF and CMF from the aqueous medium into the organic medium more efficiently and shields them from further decomposition in aqueous acid.

In the next step, the effect of various tetraalkylammonium chloride as PTC on the yield of CMF was studied (Figure 4). Glucose was used as the substrate of choice and all the PTA were taken at 5.77 mol% of the glucose amount. Use of tetrabutylammonium chloride (TBAC) as PTC provided CMF in 50% yield against 48% in the control reaction. The effect may be explained by the highly favored distribution coefficient of TBAC towards the aqueous layer that renders it inefficient for slowing down the hydrolysis of CMF into HMF in the organic layer. When choline chloride (ChoCl) was used as PTC, CMF was obtained in 50% yield. Use of hexadecyltrimethylammonium chloride (HDTMAC) as a PTC lowered the yield of CMF even

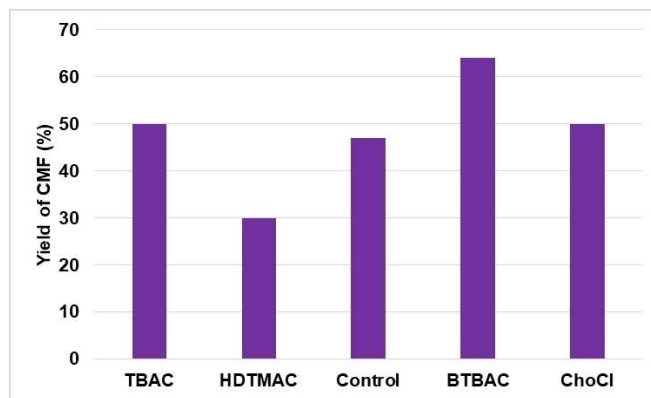


Figure 4. Effect of various tetraalkylammonium chloride as phase transfer catalyst on the yield of CMF. Reaction conditions: glucose (2 g), HCl (35%, 20 mL), DCE (40 mL), PTC (5.77 mol%), 90 °C, 3 h.

below the control reaction and CMF was isolated in only 30% yield. Significantly more humin was isolated in the process. The lower yield of CMF may be explained by the distribution coefficient of HDTMAC which is highly favored towards the aqueous medium. Besides, the surfactant molecule produced lathers in the reaction mixture that possibly accelerated side reactions.

Since BTBAC was found to be the best PTC for the CMF synthesis, the effect of BTBAC loading on the yield of CMF was studied. The loading of BTBAC was varied from 5 wt% to 30 wt% with respect to the weight of glucose used in the reaction (Figure 5). At lower loadings (< 10 wt%) of BTBAC, the increase

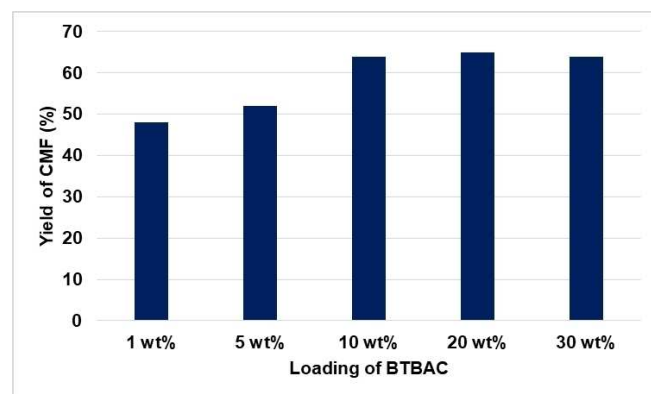


Figure 5. Effect of the loading of BTBAC on the yield of CMF. Reaction conditions: glucose (2 g), HCl (35%, 20 mL), DCE (40 mL), 90 °C, 3 h.

in yield of CMF compared to the control reaction was not pronounced. However, when the loading was increased more than 10 wt% (5.77 mol%), the yield of CMF remained unaltered. Therefore, loading of BTBAC was kept at 10 wt% of the glucose amount.

The optimized reaction was applied to various carbohydrates for the production of CMF. Control reactions were

conducted for each substrate and compared with reaction using BTBAC as PTC. In the presence of 10wt% of BTBAC, glucose provided CMF in 64% isolated yield whereas the control reaction provided only 47% CMF under identical conditions (Figure 6). Fructose provided 62% yield of CMF in

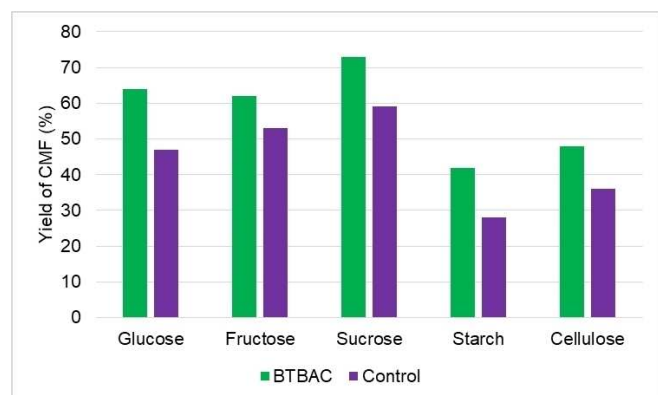


Figure 6. Yields of CMF from various carbohydrates in the presence and absence of BTBAC as the phase transfer catalyst. Reaction conditions: carbohydrate substrate (2 g), HCl (35%, 20 mL), DCE (40 mL), 90 °C, 3 h, BTBAC (0.2 g).

the presence of BTBAC whereas the control reaction provided CMF in 53% isolated yield.^[22] Sucrose provided the best yield of CMF at 73% whereas the control reaction provided 59% yield. Microcrystalline cellulose provided CMF in 48% yield with BTBAC but afforded only 36% yield without the BTBAC additive. CMF was isolated in 42% yield from starch in the presence of 10 wt% BTBAC whereas only 28% CMF was obtained in the control reaction. Therefore, using BTBAC as the PTC, CMF was obtained in 64%, 62%, 73%, 48%, and 42% carbon yield starting from glucose, fructose, sucrose, starch, and cellulose, respectively.

In all the reactions, LA and the insoluble humic matter were isolated from the aqueous layer and quantified. Fructose provided 14% yield of LA (with BTBAC) against 12% of LA in the control reaction (without BTBAC).^[22] When glucose was used as the substrate, LA was isolated in 15% yield whereas the control reaction provided only 10% of LA. The humic matter in the control reaction was also found to be marginally higher than reaction using BTBAC. When sucrose was used as the substrate, LA was isolated in 11% yield whereas the control reaction provided around 8% of LA. Starch and cellulose provided 13% and 15% of LA, respectively. Therefore, in all cases, LA was obtained in marginally higher yields using BTBAC as the PTC. The combined higher yields of CMF and LA using BTBAC was also reflected by less humic matter formation. For example, the humic matter recovered from sucrose using BTBAC was noticeably lower than that obtained from the control reaction (entry 3, table 1).

[a] In an attempt for mass balancing, 0.202 g of soluble humin was found in the aqueous layer. The carbon yield of LA (with BTBAC) from glucose, fructose, sucrose, starch and

Table 1. Formation of LA and humic matter from various carbohydrates with or without using BTBAC.

S/N	Feedstock	With BTBAC		Without BTBAC	
		LA(%)	Humic matter (g)	LA(%)	Humic matter (g)
1	Glucose ^[a]	15	0.170	10	0.183
2	Fructose ^[b]	14	0.182	12	0.200
3	Sucrose	11	0.124	8	0.197
4	Starch	13	0.250	10	0.320
5	Cellulose	15	0.280	9	0.340

[a] In an attempt for mass balancing, 0.202 g of soluble humin was found in the aqueous layer. The carbon yield of LA (with BTBAC) from glucose, fructose, sucrose, starch and cellulose are 12.5%, 11.7%, 9.2%, 10.8%, and 12.5%. [b] Reaction was carried out at 80 °C.

cellulose are 12.5%, 11.7%, 9.2%, 10.8%, and 12.5%. [b] Reaction was carried out at 80 °C.

Lower loading of the substrate provided slightly better yields of CMF. For example, when the loading of glucose was lowered to 5 wt%, the yield of CMF increased to 68%. When higher quantity of DCE was used (ca. 80 mL), CMF was isolated in marginally higher yield. With glucose as the substrate, the use of 80 mL of DCE provided CMF in 69% yield against 64% in presence of 40 mL of DCE. The ¹H and ¹³C NMR spectra of recovered BTBAC shows some (ca. 10%) impurity due to acid-induced decomposition of BTBAC. Use of the recovered BTBAC without further purification provided CMF in 55% yield from glucose.

Conclusions

A one-pot production of CMF has been achieved in a biphasic closed batch reactor consisting of aqueous HCl and DCE in the presence of BTBAC as a phase transfer catalyst. Use of BTBAC afforded CMF in roughly 10% higher yields from all the carbohydrates studied. LA was also isolated in marginally higher yields in reactions using BTBAC compared to the control reactions. Humic matter formed in noticeably lower quantities in reactions using BTBAC.

Supporting Information Summary

The details of the experimental procedure for the isolation of CMF, LA and BTBAC and their spectral characterization are provided as supporting information.

Acknowledgements

The authors thank the Science and Engineering Research Board (SERB), India for funding support under the grant number YSS/2015/001649.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: biomass valorization · carbohydrate · 5-(chloromethyl)furfural · levulinic acid · phase transfer catalyst

- [1] V. Popa and I. Volf, ed. (2018) *Biomass as Renewable Raw Material to Obtain Bioproducts of High-Tech Value*. Amsterdam, NE: Elsevier.
- [2] G. Kumar, S. Shobana, W.-H. Chen, Q.-V. Bach, S.-H. Kim, A. E. Atabani, J.-S. Chang, *Green Chem.* **2017**, *19*, 44-67; D. Ghosh, D. Dasgupta, D. Agrawal, S. Kaul, D. K. Adhikari, A. K. Kurmi, P. K. Arya, D. Bangwal, M. S. Negi, *Energy Fuels* **2015**, *29*, 3149-3157.
- [3] P. Sudarsanam, R. Zhong, S. Van den Bosch, S. M. Coman, V. I. Parvulescu, B. F. Sels *Chem. Soc. Rev.* **2018**, *47*, 8349-8402., R. A. Sheldon *J. Mol. Catal. A: Chem.* **2016**, *422*, 3-12.
- [4] a) G. Dull, *Chem. Ztg.* **1895**, *19*, 216.; b) J. Kiermayer, *Chem. Ztg.* **1895**, *19*, 1003.
- [5] a) R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499-1597.; b) A. A. Rosatella, S. P. Simeonov, R. F. M. Frade, C. A. M. Afonso, *Green Chem.* **2011**, *13*, 754-793.
- [6] F. Menegazzo, E. Ghedini, M. Signoretto, *Molecules* **2018**, *23*, 2201-2218.
- [7] a) Y. Roman-Leshkov, J. N. Chheda, J. A. Dumesic, *Science* **2006**, *312*, 1933-1937.; b) B. Saha, M. M. Abu-Omar, *Green Chem.* **2014**, *16*, 24-38.
- [8] a) H. J. H. Fenton, M. Gostling, *J. Chem. Soc.* **1899**, *75*, 423.; b) H. J. H. Fenton, F. J. Robinson, *J. Chem. Soc.* **1909**, *95*, 1334.
- [9] H. J. H. Fenton, M. Gostling, *J. Chem. Soc. Trans.* **1901**, *79*, 807-816.
- [10] **SciFinder**, web version; Chemical Abstracts Service: Columbus, OH; RN 1623-88-7 and 67-47-0 (accessed March 28, 2019).
- [11] a) M. Mascal, S. Dutta, *Top. Curr. Chem.* **2014**, *353*, 41-83.; b) S. Dutta, M. Mascal, *ChemSusChem* **2014**, *7*, 3028-3030.; c) M. Mascal, S. Dutta, *Green Chem.* **2011**, *13*, 3101-3102.
- [12] a) M. Mascal, *ACS Sustain. Chem. Eng.* **2019**, *7*, 5588-5601.; b) M. Mascal, *ChemSusChem* **2015**, *8*, 3391-3395.
- [13] a) K. Sanda, L. Rigal, M. Delmas, A. Gaset, *Synthesis* **1992**, *6*, 541-542.; b) K. Hamada, H. Yoshihara, G. Suzukamo, *J. Oleo Sci.* **2001**, *50*, 533-536.; c) E. Meller, A. Aviv, Z. Aizenshtat, Y. Sasson, *RSC Adv.* **2016**, *6*, 36069-36076.; d) X. Zhang, N. M. Eren, T. Kreke, N. S. Mosier, A. S. Engelberth, G. Kilaz, *Bioenerg. Res.* **2017**, *10*, 1018-1024.
- [14] a) M. Mascal, E. B. Nikitin, *Angew. Chem.* **2008**, *120*, 8042-8044.; *Angew. Chem., Int. Ed.* **2008**, *47*, 7924-7926; b) M. Mascal, High-yield conversion of cellulosic biomass into furanic biofuels and value-added products 2009, US7829732B2.
- [15] M. Mascal, E. B. Nikitin, *ChemSusChem* **2009**, *2*, 859-861.
- [16] B. Girisuta, L. P. B. M. Janssen, H. J. Heeres, *Green Chem.* **2006**, *8*, 701-709. D. Garcés, E. Díaz, S. Ordóñez, *Ind. Eng. Chem. Res.* **2017**, *56*, 5221-5230.
- [17] a) S. Dutta, L. Wu, M. Mascal, *Green Chem.* **2015**, *17*, 2335-2338.; b) M. Mascal, S. Dutta, I. Gandarias, *Angew. Chem.* **2014**, *126*, 1885-1888.; *Angew. Chem. Int. Ed.* **2014**, *53*, 1854-1857.; c) F. D. Pileidis, M.-M. Titirici, *ChemSusChem* **2016**, *9*, 562-582.; d) C. Antonetti, D. Licursi, S. Fulignati, G. Valentini, A. M. R. Galletti, *Catalysts* **2016**, *6*, 196-224.
- [18] W. Gao, Y. Li, Z. Xiang, K. Chen, R. Yang, D. S. Argyropoulos, *Molecules* **2013**, *18*, 7675-7685.
- [19] a) M. Brasholz, K. von Känel, C. H. Hornung, S. Saubern, J. Tsanaktsidis, *Green Chem.* **2011**, *13*, 1114-1117.; b) T. M. Kohl, B. Bizet, P. Kevan, C. Sellwood, J. Tsanaktsidis, C. H. Hornung, *React. Chem. Eng.* **2017**, *2*, 541-549.
- [20] a) F. Wu, R. Yang, F. Yang, *BioResources* **2015**, *10*, 3293-3301.; b) M. Zuo, Z. Li, Y. Jiang, X. Tang, X. Zeng, Y. Sun, L. Lin, *RSC Adv.* **2016**, *6*, 27004-27007.
- [21] H. H. Szmant, D. D. Chundury, *J. Chem. Tech. Biotechnol.* **1981**, *31*, 205-212.
- [22] The mentioned yields were obtained at the reaction temperature of 80 °C. At 90 °C, the yields of CMF and LA were lowered to 55% and 21%, respectively whereas the control reaction at 90 °C produced 46% CMF and 13% LA.

Submitted: April 12, 2019

Accepted: June 19, 2019