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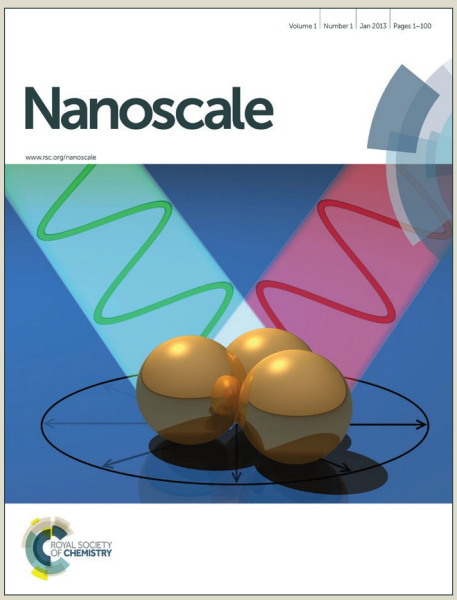

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Space and time-resolved probing of heterogeneous catalysis reactions using lab-on-a-chip

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Probing catalytic reactions on a catalyst surface in real time is a major challenge. Herein, we demonstrate the utility of a continuous flow millifluidic chip reactor coated with nanostructured gold catalyst as an effective platform for *in situ* investigation of kinetics of catalytic reactions by taking 5-(Hydroxymethyl)furural (HMF) to 2,5-Furandicarboxylic acid (FDCA) conversion as a model reaction. The idea conceptualized in this paper can dramatically change the ability to probe time-resolved kinetics of not only heterogeneous catalysis reactions but also for investigating other chemical and biological catalytic processes; thereby making this a broad-based platform for probing reactions as they occur within continuous flow reactors.

Introduction

The probing of liquid phase heterogeneously catalyzed reactions is a challenge due to the difficulty of obtaining *in situ* spatially- and chemically-resolved information on the microscopic scale. Several complicated approaches using batch reactors and liquid cells have been investigated.[1] Unlike the batch reactors, the use of continuous flow reactors for heterogeneous catalytic transformations offer significant advantage due to the ease of catalyst loading, increased heat and mass transfer, uniform mixing and control over the residence time of the fluids.[2-7] Lab-on-a-chip based continuous flow reactors offer the capability to obtain time-resolved mechanistic data of a catalytic reaction with spatial resolution. Among the lab-on-a chip reactors, traditional microfluidics has not been successful to obtain sufficient spectral resolution to carry out in-situ mapping of the catalytic processes.[8] We show here a simple lab-on-a-chip based millifluidic chip reactor as a tool to carry out in-situ real time mapping to understand the mechanistic aspects of a heterogeneous catalytic process. These millifluidic chip reactors are inexpensive to fabricate and their channels can be coated with nanostructured metal catalysts as desired and offer higher signal to noise ratio than traditional microfluidics. In addition, due to millimeter scale channel dimensions,[9] the millifluidic chip reactors provide the ability to integrate variety of spectroscopic tools such as fluorescence, IR, Raman, NMR, and X-ray spectroscopy for detailed kinetic analysis of the catalytic reaction.[10-15]

To demonstrate the underlying concepts, we have followed continuous flow space/time-resolved oxidation of 5-(Hydroxymethyl)furfural (HMF) to 2,5-Furandicarboxylic acid (FDCA) catalyzed by a nanostructured gold catalyst coated within the millifluidic chip reactor channel walls at ambient temperature and pressure (Figure 1). This model reaction is critically important as FDCA has been receiving significant attention as a substitute of petrochemical-derived terephthalic acid in the synthesis of useful polymers.[16] The conversion of HMF to FDCA was characterized at various spatial intervals in the millifluidic chip reactor to analyse the reaction intermediates and to understand the reaction

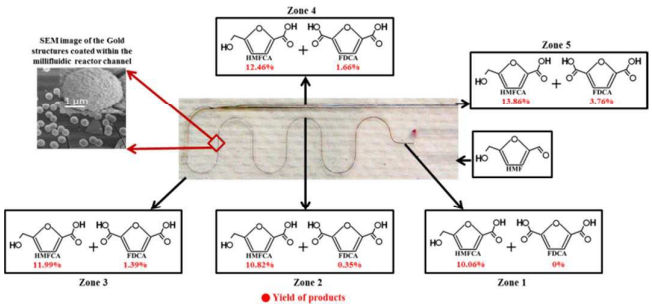

Fig. 1 Nanostructured gold catalyst coated millifluidic chip reactor marked with changes to HMF at different zones (Inset: SEM image of a single hemispherical gold catalyst particle of the catalyst coated within the millifluidic chip reactor channel)

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mechanisms. This is an advanced concept in the development of continuous flow reactors for in-situ probing of heterogeneous catalysis reactions with the ability to convert spatial resolution into time resolution.[17,18] Although there have been several studies on the continuous flow reactors such as microfluidics with embedded and impregnated catalysts[19,20] for chemical conversions with spatial resolution,[8] our method described here differs significantly from the previous reports in that the millifluidic chip reactor is now demonstrated to control the dimension and morphology of the catalyst coated within the reaction channel.[17] In addition, by taking a model biomass conversion reaction as an example, this work showcases the importance in the integration of green chemistry and green engineering into continuous flow catalysis, where multiple value-added products from a range of renewable feed stocks can be produced.

Results and discussion

The catalytic oxidation of HMF was carried out within a millifluidic reactor channel of dimensions 220 mm X 2 mm X 0.15 mm (Length X Width X Height) coated with nanostructured gold catalyst (Figure 1). The millifluidic channel had a combination of serpentine and straight orientation to allow for high channel lengths and increased mixing at the fluid stream interface. The channels had similar inner volume, ensuring comparable residence time of the reaction solutions. The coating of gold catalyst within the millifluidic reactor channel was carried out according to the previously reported protocol by Krishna *et al.*[17] By utilizing the nanostructured gold catalyst coated millifluidic chip, an aqueous mixture of HMF, NaOH and *tert*-butyl hydroperoxide (TBHP) was pumped into the millifluidic reactor channel at 0.1 ml/h at room temperature and pressure. A more detailed experimental protocol is described in the supporting information. At first, an attempt was made for *in situ* probing of the oxidation of HMF at different spatial zones directly on the chip using a fiber optic probe coupled to the UV-Vis spectrophotometer. However, due to the masking of the absorbance of reaction products with the absorbance from polymeric millifluidic chip, no useful UV-Vis absorption data was obtained. We have, therefore, carried out UV-Vis spectroscopy analyses by collecting aliquots of the reaction products in a vial by dissecting the millifluidic chip channel with a scissor[21, 22] at various zones (1 to 4, as shown in Figure 1) with a spatial interval of 44 mm and time resolution of 10 minutes between each zone during the catalytic reaction in order to examine the kinetic evolution of the products of HMF oxidation over the gold catalyst (Figure 2). This longer time resolution is due to the very slow oxidation mechanism of the furan molecules. Ideally, it is possible to collect the same products using a conventional batch or flask-based process for ex-situ analysis; however, the use of continuous flow chip millifluidic reactor offers an advantage in collecting high throughput products with high reproducibility due to its ability to carry out reactions under steady state with less consumption of reagents for optimization.[17] In addition, reactions carried out using batch reactors often result in an inseparable product mixture at any given

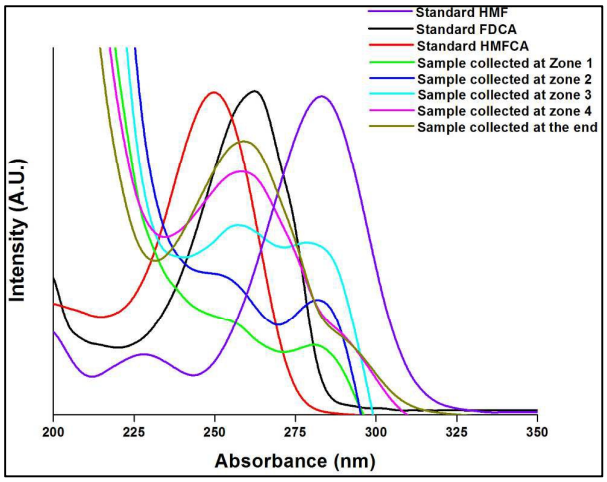

Fig. 2 UV-Vis spectra of the reaction mixtures collected at different zones of the millifluidic reactor channel by dissecting the chip.

point of time; whereas, the utility of lab-on-a-chip based millifluidic technology offers the ability to carry out multistep reactions in sequence, therefore providing an opportunity to obtain the desired product independently at different spatial intervals with time-resolution by changing the residence time of the reactants.[7,8,17]

The UV-Visible absorption spectra (Figure 2) of the reaction mixtures collected with a time resolution of 10 minutes between each zones (1 to 5) at a spatial interval of 44 mm of the millifluidic reactor channel revealed a sequential conversion of HMF to FDCA, where the concentration of the reactant (HMF) decreased with increase in the concentration of the final product (FDCA), as the reactant moved towards the end of the catalyst-coated millifluidic channel. However, differences were noticed in terms of final product (FDCA) selectivity since the product peak at 258 nm for the samples collected at all the zones resulted in a 4 nm shift in the absorbance peak when compared with the absorbance peak of standard FDCA (black-colored spectrum in Figure 2). These results suggested the presence of other products that may have formed during the oxidation of HMF. Therefore, apart from UV-Vis spectroscopy, the same products were also analyzed by high-

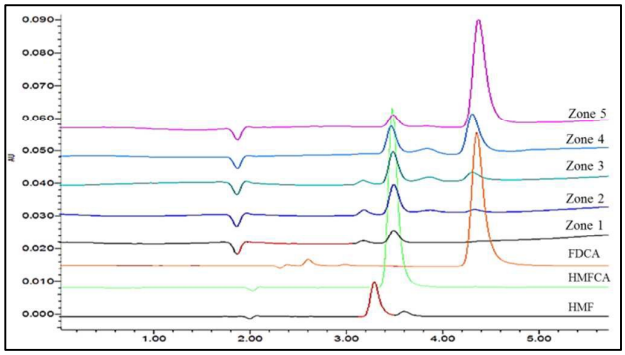

Fig. 3 HPLC analysis of the reaction mixtures collected at different zones of the millifluidic reactor channel

performance liquid chromatography (HPLC) (Figure 3) in order to characterize the intermediates and by-products formed during the oxidation of HMF. The conclusions derived from UV-Vis spectroscopy were supported by the HPLC analysis.

As shown in Figure 3, HPLC of the sample collected at zone 1 revealed a peak corresponding to the primary oxidation product, 5-hydroxy-2-furancarboxylic acid (HMFCA). During this time, no formation of secondary product (FDCA) was observed, suggesting the oxidation of the aldehyde group of HMF. However, a second peak was observed in addition to the primary product peak, indicating the formation of a secondary product (FDCA) for samples collected at subsequent zones (2 to 5). It has been previously reported that the mechanism of HMF oxidation occurs as a result of destabilization of the oxygen bond in TBHP due to the electrons on the gold catalyst surface, resulting in hydroxide ion, which facilitates the dehydrogenation of geminal diol intermediate[23] to produce carboxylic acid in steps 1 and 3 (Figure 4). During the analysis, a maximum peak intensity of primary product (HMFCA) was detected at zones 2 and 3 simultaneously with a gradual decrease at zones 4 to 5. The decrease in the primary reactant (HMFCA) peak intensity at zones 4 to 5 suggested the oxidation of the alcohol group, resulting in the formation of the secondary product, FDCA. This analysis excluded the second possible reaction pathway for oxidation of HMF[24] (Figure S1), where the interaction between the reactants can also lead to formation of 2, 5-Diformylfuran (DFF).

The products were quantified by integrating the HPLC peaks of the reaction solutions as a function of time along the millifluidic reactor channel (Table S1). The HPLC peaks were converted to concentration values (mM) in order to determine the percentage conversion of reactants to products. The percentage of HMFCA detected by HPLC (Table S2) was found to increase gradually at the initial zones (*i.e.* zones 1, 2 and 3) of the millifluidic reactor, thereby demonstrating its pivotal role as an intermediate for the formation of secondary product, FDCA. These results seemed to exclude the competitive reaction between the aldehyde and alcohol groups associated with the HMF furan ring as evidenced from high percentage of FDCA (zones 3, 4 and 5) that cannot be obtained in an aqueous medium without the evolution of the primary product, HMFCA. Therefore, as analysed by UV-Vis spectroscopy and HPLC, it was concluded that the consumption of HMF was followed by the formation of primary product, HMFCA, which further reacted over the coated gold catalyst to form the secondary product, FDCA. Furthermore, the results obtained here highlight that the nanostructured gold catalyst is highly active as suggested by our previous report.[17] In addition to the use of millifluidic reactor, we also performed the catalytic oxidation of HMF using a flask based batch reactor at ambient temperature and pressure in order to compare the reaction kinetics with the continuous flow millifluidic reactor conditions.

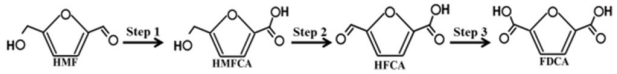

Fig. 4 HMF Oxidation pathway leading to FDCA with HMFCA as the intermediate product

The batch reaction experiments were carried out in a conical flask for 24 h and aliquots from the reaction were collected periodically for HPLC analysis. Table S4 shows the quantification data of FDCA yields under batch reaction conditions calculated by integrating the peaks obtained for HPLC of the reaction aliquots as a function of time. The batch reactor results revealed a 100% HMF conversion within the first 2 h of the reaction with HMFCA as the major product being formed after 60 min (Table S3, entry 2) and its concentration was found to be relatively unchanged even up to 6 h. In addition to HMFCA, lesser concentration of FDCA was also observed in the reactant mixture after 60 min (Table S3, entry 2). The concentration of HMFCA and FDCA suggested the competition between the aldehyde and the alcohol moiety associated with the HMF furan ring during oxidation. The catalysis experiments were continued for different intervals starting from 6 to 24 h, where the percentage of FDCA detected increased from 32.5% to 99%. However, according to the results obtained from the continuous flow oxidation using millifluidic reactor, it can be clearly postulated that the oxidation initially took place at the aldehyde moiety and not at alcohol moiety. It was not surprising that the radical nature of TBHP-based oxidation first oxidized the aldehyde moiety associated with HMF, since aldehyde groups are more prone to oxidation than the alcohol groups. The concentration of HMFCA after 60 minutes did not increase significantly and it appeared that the HMFCA concentration has reached saturation thereby diverting the further oxidation towards the alcohol moiety of HMF resulting in traces of FDCA. The selectivity of HMFCA was nearly constant at all-time intervals (Table S3, entries 2 to 5), which indicated that the reaction pathway was not affected as shown in Figure 4. From these results, it can be understood that the presence of aldehyde moiety decreased the rate of oxidation of the primary alcohol group associated with HMF in aqueous medium, therefore reducing the rate of FDCA production. It should be noted that the oxidation of HMFCA to FDCA proceeded with the formation of another intermediate, Hydroxyfurancarboxylic acid (HFCA, step 2 in figure 4). The presence of HFCA could not be detected in our experiments due to its rapid conversion into FDCA. This rapid conversion is attributed to the freshly formed aldehyde group as a result of the oxidation of the primary alcohol moiety that was present in HMF.

Unlike the previous reports, where the HMF oxidation for FDCA production was carried out at higher temperatures and pressure,[16,25-30] in our experiments, the alcohol oxidation was achieved at room temperature and pressure. Furthermore, there was no by-product formation in all our studies and HMF was completely oxidized to HMFCA and subsequently to FDCA. The HPLC results obtained from the continuous flow millifluidic reactor were used to calculate the rate of formation of products and turnover frequencies (TOF) of the reaction. Although, there are previous reports on the turnover frequencies calculated for the catalytic oxidation of HMF to FDCA using batch reactors,[31,32] the same has not been reported for continuous flow processes. The rate of formation of products and TOF of the reaction using the millifluidic reactor and batch reactor is shown and compared in Table 1.

Table 1. Rate of product formation and turnover frequency of the reaction after 50 minutes using the millifluidic chip at zone 5 and batch reactor

	Millifluidic reactor		Batch reactor	
	HMFCA	**FDCA**	**HMFCA**	**FDCA**
Rate of Formation ($M\ s^{-1}$)	$1.38*10^{-7}$	$3.6*10^{-8}$	$1.43*10^{-8}$	$1.28*10^{-9}$
Turnover Frequency (s^{-1})	$4.10*10^{-26}$	$1.11*10^{-26}$	$1.87*10^{-28}$	$1.26*10^{-29}$

The TOFs for FDCA in our experiments were calculated to be 10^{-26} s^{-1}, which are orders of magnitude less when compared to the TOF calculated by Davis *et al.*[31] and Miao *et al.*[32] for the oxidation of HMF to FDCA using the batch reactor at high pressure. The lower value of TOF in our experiments is likely due to the use of aqueous-phase oxidizing agent (TBHP) which hampered the reaction rate.[33] Moreover, the HPLC quantification of the reaction products indicated 3.76% yield of FDCA at the end of the reaction (Table S2), which is similar to the 3% FDCA outcome reported by Hansen *et al.*[33], while using aqueous phase oxidizing agent (TBHP) with a batch reactor.

The catalytic oxidation of HMF in continuous flow millifluidic reactor as well as in conventional flask-based method required high base concentration for the production of FDCA, similar to Casanova *et al.* experiments.[25] In all the cases, a stable intermediate, HMFCA was produced before sequentially oxidizing to FDCA. Several researchers have also followed the same protocol in order to maintain a high pH to oxidize the alcohol moiety of HMF either at high temperature or high pressure or both.[16,25-30] These stringent reaction conditions have been prone to molecule degradation, especially in the case of HMF. High catalyst loadings were used with these high pH conditions in order to rapidly convert all the HMF molecules to HMFCA,[34] an intermediate product that is very stable in basic environment. In most of the previous reports, researchers have not been completely successful in recycling their catalyst after each oxidation experiment due to problems such as ion leaching, high ratio of base under high temperature and high pressure conditions. Although much of the efforts had been towards increasing the FDCA yield, most of the previous works on HMF oxidation have been focused primarily to increase the efficiency of the catalyst performance. In our experiments, the concentration of NaOH used for the oxidation of HMF was optimized to a NaOH/HMF molar ratio of 4:1, similar to the protocol carried out by Casanova *et al*.[25]

A control experiment was conducted separately without the nanostructured gold catalyst and the samples were analysed using HPLC. The HPLC results revealed that the degradation of HMF molecule occurred as soon as it was mixed with TBHP and NaOH resulting in 1.7 mM concentration of HMF, which is accounted for 43% loss when compared to the initial HMF concentration of 3 mM. The control experiment was continued for 24 h and the HPLC results revealed 1.39 mM concentration of HMF, which is accounted for 53% loss. Another control experiment was carried out with HMFCA as the initial reactant and the samples were analysed using HPLC. The HPLC results revealed 1.44 mM and 1.32 mM concentration of HMFCA at t = 0 and 24 h respectively, which is accounted for 52% and 56% loss due to degradation when compared to the initial concentration of 3 mM. The HPLC results of both the HMF and HMFCA control experiments did not show any conversion of the reactants into FDCA. The results are shown in the Table S5 and S6. Since the emphasis of this research is only to show the capability of millifluidic chip reactor to carry out time-resolved mapping of chemical processes, further experiments to improve the kinetics and mass balances were not considered for the present study.

Conclusions

In conclusion, we have demonstrated the use of a simple millifluidic chip reactor coated with nanostructured gold catalyst for in-situ probing of the kinetics of heterogeneous catalysis reaction (HMF oxidation) with time-resolution. By mapping the sequential transformation of HMF to FDCA at various spatial intervals, a better understanding of the kinetics of the catalytic reaction was obtained. With an option to probe at desired locations, this novel approach of using an easily accessible lab-on-a-chip tool for analysing time-resolved kinetics has the potential to better investigate not only heterogeneous catalysis reactions but also enzymatic catalysis and molecular analysis with implications for broad range of fields from chemistry, biology, spectroscopy and materials science. However, a significant challenge still remains in probing chemical processes by directly integrating this technique for in-situ spectroscopy analysis. Therefore, once the challenge to probe chemical processes without the need for dissecting the chip to collect the analytes is met, this technique will have more potential to investigate both the spatial as well as the temporal complexity of heterogeneous catalytic activity at the nanoscale level.[35]

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Notes and references

1 *Chem. Soc. Rev.* 2010**, 12**, 4541.
2 Y. Song, J. Hormes and C.S.S.R. Kumar, *Small,* 2008, 4(6), 698.
3 A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki and J. Yoshida, *Angew. Chem., Int. Ed.,* 2012, **51**, 3245.
4 E. Gross, J.H.C. Liu, F.D. Toste and G.A. Somorjai, *Nat. Chem.,* 2012, **4**, 947.
5 A. Nagaki, N. Takabayashi, Y. Moriwaki and J. Yoshida, *Chem. Eur. J.,* 2012, **18**, 11871.
6 K.S. Elvira, X.C.I. Solvas, R.C.R. Wootton and A. deMello, *J. Nat. Chem.,* 2013, **5,** 905.

7 C.V. Navin, K.S. Krishna, C.S. Theegala and C.S.S.R. Kumar, *Nanotechnology Reviews,* 2014; **3**(1): 39.
8 E. Gross, X. Shu, S. Alayoglu, H.A. Bechtel, M.C. Martin, F.D. Toste and G.A. Somorjai, *J. Am. Chem. Soc.,* 2014, **136**, 3624.
9 K.S. Krishna, S. Biswas, C.V. Navin, D. Yemane, J.T. Miller and C.S.S.R. Kumar, *JoVE,* 2013, **81**, e50711.
10 B.B. Xu, R. Zhang, X.Q. Liu, H. Wang, Y.L. Zhang, H.B. Jiang, L. Wang, Z.C. Ma, J.F. Ku, F.S. Xiao and H.B. Sun, *Chem. Commun*., 2012, **48**, 1680.
11 I.L.C. Buurmans, and B.M. Weckhuysen, *Nat. Chem.,* 2012, **4**, 873.
12 E. Stavitski and B.M. Weckhuysen, *Chem. Soc. Rev.*, 2010, **39**, 4615.
13 B.M. Weckhuysen, *Angew. Chem., Int. Ed.,* 2009, **48**, 4910.
14 W.L. Xu, J.S. Kong, Y.T.E. Yeh and P. Chen, *Nat. Mater.*, 2008, **7**, 992.
15 J.D. Grunwaldt, S. Hannemann, C.G. Schroer and A. Baiker, *J. Phys. Chem. B*, 2006, **110**, 8674.
16 Z. Zhang, K. Deng, *ACS Catalysis,* 2015, **5(11)**, 6529.
17 K.S. Krishna, C.V. Navin, S. Biswas, V. Singh, K. Ham, G.L. Bovenkamp, C.S. Theegala, J.T. Miller, J.J. Spivey and C.S.S.R. Kumar, *J. Am. Chem. Soc.* 2013**, 135**, 5450.
18 S. Biswas, J.T. Miller, Y. Li, K. Nandakumar and C.S.S.R. Kumar, *Small,* 2012**, 8**(5), 688.
19 H. Amii, A. Nagaki and J. Yoshida, *Beilstein J. Org. Chem.,* 2013, **9,** 2793.
20 J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori and S. Kobayashi, *Science,* 2004, **304**, 1305.
21 Y. Li, A. Sanampudi, V.R. Reddy, S. Biswas, K. Nandakumar, D.G. Yemane, J.S. Goettert and C.S.S.R. Kumar, *Phys. Chem. Phys.* 2012**, 13**(1), 177.
22 C.V. Navin, K.S. Krishna, G.L. Bovenkamp-Langlois, J.T. Miller, S. Chattopadhyay, T. Shibata, Y. Losovyj, V. Singh, C.S. Theegala and C.S.S.R. Kumar, *Chem. Eng. J,* 2015, **218,** 81.
23 S.E. Davis, B.N. Zope and R.J. Davis, *Green Chem.* 2012, **14**, 143.
24 O.C. Navarro, A.C. Canos and S.I. Chornet, *Top Catal.* 2009, **52**, 304.
25 O. Casanova, S. Iborra and A. Corma, *ChemSusChem* 2009**, 2**, 1138.
26 F. Koopman, N. Wierckx, J.H. De Winde and H.J. Ruijssenaars, *Bioresource Technology* 2010**, 101**, 6291.
27 N.K. Gupta, S. Nishimura, A. Takagaki and K. Ebitani, *Green Chem.* 2011**, 13**, 824.
28 S. Albonetti, T. Pasini, A. Lolli, M. Blosi, M. Piccinini, N. Dimitratos, J.A. Lopez-Sanchez, D.J. Morgan, A.F. Carley, G.J. Hutchings and F. Cavani, *Catal Today*. 2012**, 195**, 120.
29 J. Cai, H. Ma, J. Zhang, Q. Song, Z. Du, Y. Huang and Xu, J. *Chem. Eur. J.* 2013**, 19**, 14215.
30 A. Jain, S.C. Jonnalagadda, K.V. Ramanujachary and A. Mugweru, *Catalysis Communications* 2015**, 58**, 179.
31 S.E. Davis, L.R. Houk, E.C. Tamargo, A.K. Datye and R.J. Davis, *Catalysis Today,* 2011**, 160**, 55.
32 Z. Miao, T. Wu, J. Li, T. Yi, Y. Zhang and X. Yang. *RSC Adv.,* 2015**, 5**, 19823.
33 T.S. Hansen, I. Sádaba, E.J. García-Suárez and A. Riisager, *Applied Catalysis A: General*, 2013, **456**, 44.
34 Z. Zhang, B. Liu, K. Lv, J. Sun, K. Deng, *Green Chem.* 2014, **16**, 2762.
35 N.M. Andoy, X. Zhou, E. Choudhary, H. Shen, G. Liu and P. Chen, *J. Am. Chem. Soc.,* 2013**, 135**, 1845.