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Mesoporous Polymeric Catalyst

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A Nanospherical Ordered Mesoporous Lewis Acid Polymer for the Direct Glycosylation of Unprotected and Unactivated Sugars in Water**

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Abstract: *The design of robust solid catalysts which can selectively synthesize highly functionalized carbohydrate derivatives from unprotected and unactivated simple sugars in water is an outstanding challenge. Herein we describe the preparation of a novel nanospherical ordered mesoporous Lewis acid polymer ($Sc(OTf)_2$-NSMP) by functionalizing the mesoporous phenol-formaldehyde polymer framework with scandium triflate groups. In the C-glycosylation reaction between* D*-glucose and dimedone with the $Sc(OTf)_2$-NSMP catalyst, the conversion was 99 % and the yield of xanthone-C-glucoside reached 92 % after 2 days, which exceeded the previous best results. It was shown that other xanthone glycosides can be obtained from various sugars with moderate to good yields. Furthermore, the catalyst can be easily recovered and reused at least seven times without loss of catalytic activity.*

The continuing depletion of fossil resources and increasing environmental consciousness stimulate our society to search for alternative renewable feedstocks for chemical synthesis.[1] A special opportunity to meet this challenge is the utilization of simple sugars, which are abundant, inexpensive, and renewable.[2] Over the past decades, there has been significant development in the synthesis of sugar-containing molecules with key roles in various applications such as drug discovery and sustainable chemical processing.[3] However, the multiple hydroxy groups of sugars cause serious synthetic barriers with regard to their selective functionalization, which usually requires tedious protection–deprotection steps or the strict compliance with special reaction conditions.[4] In addition, the use of toxic organic solvents and expensive noble metal species is detrimental to the environment and the isolation of the final product usually also generates high amounts of hazardous waste.[5] To this end, heterogeneous catalysts are considered to be good candidates for sugar transformation reactions because they are generally associated with lower production of waste, the use of fewer toxic reagents, and easy recycling.[6] Nevertheless, most catalysts reported so far exhibited only poor catalytic activity due to their low surface area and/or small pore size.[7] Fine-particle-based catalysts with very small size offer a high surface area, but their separation from the reaction mixture is inconvenient. Additionally, it is also difficult to maintain their uniform size and morphology in the reaction process due to particle agglomeration. The irregular shape and broad particle size distribution of solid catalysts is believed to impair their catalytic efficiency in sugar transformation reactions, because the diffusion transport process is of practical importance owing to the hydrophilicity and relatively large molecular size of sugars.[8] Therefore, the fabrication of robust solid catalysts which can selectively synthesize highly functionalized carbohydrate derivatives from unprotected and unactivated simple sugars in water still represents a substantial challenge.

Nanospherical ordered mesoporous catalysts have attracted much attention owing to their high surface area and channel lengths on the nanoscale.[9] Recent elegant studies have shown that the catalytic performance of nanospherical mesoporous silica-based catalysts in various chemical transformations is superior to that of traditional mesoporous catalysts with irregular shapes.[10] However, the intrinsic hydrophilicity of silica-based catalysts limited their application in sugar transformations due to the enhanced diffusion resistance in water. To the best of our knowledge, the use of nanospherical ordered mesoporous catalysts for the efficient synthesis of sugar derivatives has not yet been reported. Herein, we describe the preparation of a novel nanospherical ordered mesoporous Lewis acid polymer by functionalizing the mesoporous phenol-formaldehyde polymer framework with scandium triflate. Owing to the homogeneous distribution of acidic sites, the strong hydrophobicity, and short diffusion length, the resulting polymeric framework exhibits high catalytic activity, selectivity, and excellent reusability for the synthesis of xanthone glycosides by direct glycosylation of unprotected and unactivated simple sugars in water.

Scheme 1 briefly illustrates the fabrication of the representative $Sc(OTf)_2$-NSMP catalyst. The nanospherical mesoporous phenol-formaldehyde polymer was synthesized through a low-concentration hydrothermal-assisted Resol-F127 composite assembly protocol. Then, the phenyl sites in the polymer framework were functionalized with sodium benzenesulfonate by a two-step sulfonation and ion-exchange procedure. Subsequently, the sodium benzenesulfonate functionalized support (SO_3Na-NSMP) was used to chelate scandium triflate, giving a nanospherical ordered mesoporous Lewis acid polymer ($Sc(OTf)_2$-NSMP). During the catalyst

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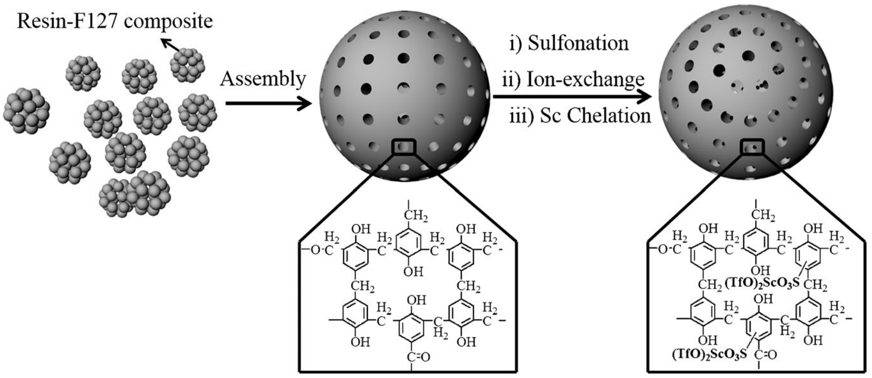


Scheme 1. Synthesis of the nanospherical ordered mesoporous Lewis acid polymer Sc(OTf)$_2$-NSMP.

preparation, we investigated the influence of various parameters such as the sulfonation temperature, Sc(OTf)$_3$ amount, and grafting solvent, on the Sc content of the Sc(OTf)$_2$-NSMP sample (Table S1-2). Satisfactorily, the optimized catalyst was obtained with a Sc^{III} loading of 0.62 mmol g^{-1}, which is the highest reported value for Sc(OTf)$_3$-containing solid catalysts.[11] This result can be attributed to the homogeneous distribution of chelating groups (PhSO$_3^-$) in the mesoporous polymer framework, which provide good stabilization for the active Sc^{III} species.

The FTIR spectrum of Sc(OTf)$_2$-NSMP (Figure S1) displayed two new absorption bands not observed for the original mesoporous phenol-formaldehyde polymer. The bands around 1040 cm^{-1} and 1215 cm^{-1} were attributed to the sulfate stretching vibration absorption and the asymmetric C−F stretching absorption of the CF$_3$ group, respectively.[12] This result demonstrated the successful incorporation of Sc(OTf)$_3$ into the mesoporous phenol-formaldehyde polymer. Furthermore, the XPS spectrum of Sc(OTf)$_2$-NSMP (Figure 1 a) showed that Sc 2p$_{3/2}$ and 2p$_{1/2}$ binding energies were 404.3 and 409.1 eV, indicating that all Sc centers were present in the trivalent state.[13] In comparison with Sc(OTf)$_3$, the Sc^{III} binding energy in Sc(OTf)$_2$-NSMP was negatively shifted by 0.5 eV, which might be due to the replacement of the CF$_3$SO$_3$ ligands by PhSO$_3^-$, thereby making Sc^{III} more electron-rich. This was further confirmed by the XPS analysis of sulfur in the sample. The binding energy of sulfur in the Sc(OTf)$_2$-NSMP sample was positively shifted by 0.4 eV compared with that in Sc(OTf)$_3$ (Figure 1 b). These results confirmed that the formation of the Sc/Lewis acid species occurs through chelation of Sc(OTf)$_3$ with the PhSO$_3^-$ groups in the polymer framework, as shown in Scheme 1.

SEM images of Sc(OTf)$_2$-NSMP displayed uniformly isolated spheres with particle sizes of around 200 nm (Figure 2 a and Figure S2a). Dynamic light scattering measurements (DLS, Figure S2b) showed the presence nanoparticles with an average hydrodynamic diameter of 235 nm and a narrow size distribution. TEM pictures further confirmed its spherical shape and highly ordered mesostructure (Figure 2 b). The XRD measurement of Sc(OTf)$_2$-NSMP (Figure 2 c) showed two well-resolved peaks with interplanar d spacings of 10.42 and 7.55 nm, respectively. These peaks with the d ratio of $1{:}\sqrt{3}$ can be indexed as the (110) and (211) mesostructure reflections of the body-centered 3D cubic space group ($Im3m$).[14a] N$_2$ sorption analysis (Figure 2 d) of Sc(OTf)$_2$-NSMP exhibited a typical type IV isotherm, indicating the presence of uniform mesopores. The pore size distribution was calculated from the adsorption branch of the isotherm and the average pore size was determined to be 2.1 nm. Interestingly, the S_{BET}, D_{P}, and V_{P} values of Sc(OTf)$_2$-NSMP were only slightly lower than those of the nanospherical mesoporous phenol-formaldehyde polymer (Table S3), indicating a homogeneous distribution of the Sc active sites in the polymer framework rather than their accumulation in the pore channels or openings.[15]

Xanthone glycosides have received a lot of attention for their pharmacological activity as well as their importance in chemotaxonomy.[16] Glycosylation is currently believed to be an efficient approach for the synthesis of the biologically interesting xanthone glycosides, because it allows the direct incorporation of carbon chains into the sugar moiety.[17] In this context, we employed the C-glycosylation reaction of D-glucose with dimedone as a model reaction. In control experiments (Table S4), the uncatalyzed reaction did not give any product in water at 100 °C for one day. The NaSO$_3$-NSMP support was also not able to catalyze the conversion of D-glucose. Gratifyingly, we found that D-glucose reacted with dimedone (3.0 equiv) in the presence of 10 mol % of Sc(OTf)$_2$-NSMP catalyst at 100 °C for 2.0 days in water

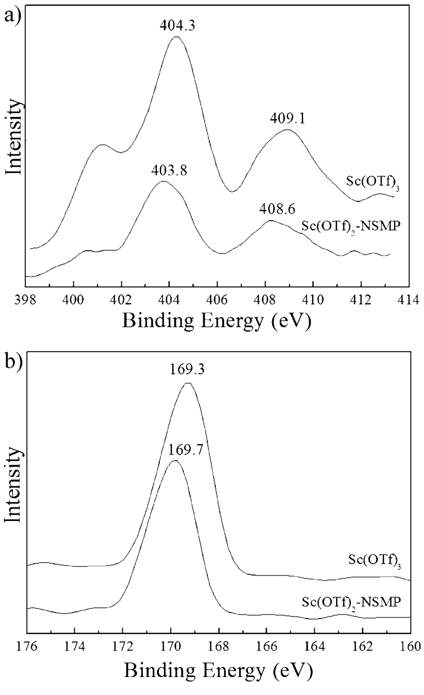


Figure 1. XPS spectra of Sc(OTf)$_3$ and Sc(OTf)$_2$-NSMP. a) Sc 2p; b) S 2p.

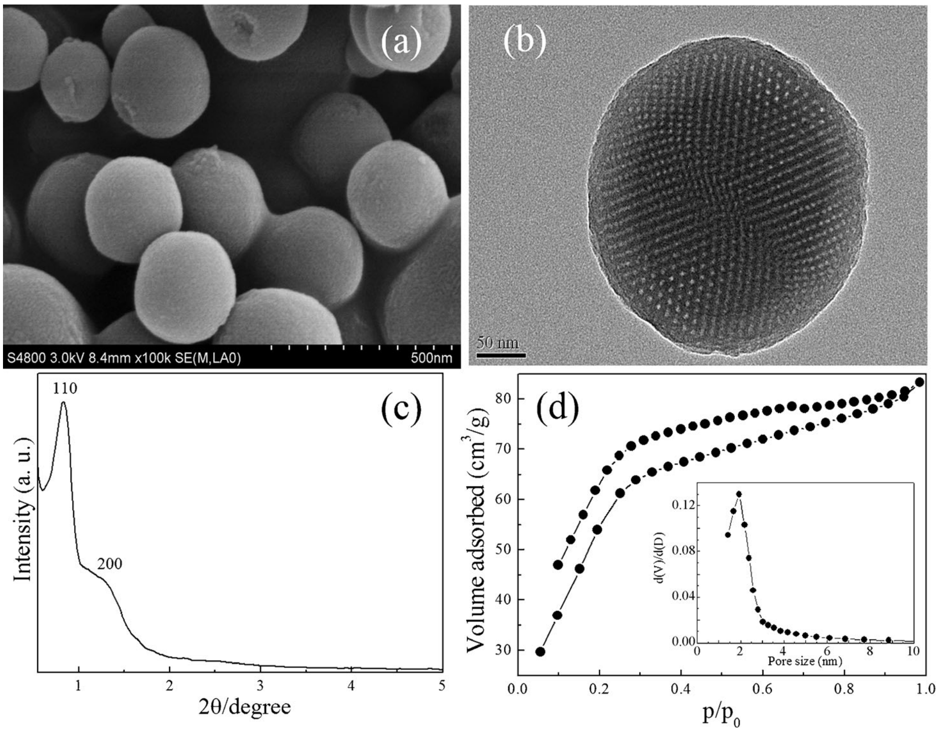


Figure 2. Analysis of $Sc(OTf)_2$-NSMP: a) SEM image, b) TEM image, c) XRD diffraction, and d) N_2 sorption isotherm (inset: pore size distribution).

(3.0 mL), giving a high conversion of 99.0% (Figure 3a). Interestingly, the reaction profile showed that two products, **1** and **2**, were formed in this process. The major product **1** was obtained during the initial 8.0 h, after which a continuing decrease of **1** was correlated to an increasing amount of **2** (Figure 3b). This phenomenon could be explained by considering the reaction mechanism (Figure S3).[18] The carbonyl groups in D-glucose and dimedone first interact with Sc^{3+} active sites through σ bonding coordination, thereby generating the Knoevenagel adduct **1**. The excess dimedone attacks this adduct and a second Knoevenagel condensation gives the final product **2**. According to this mechanism, it was expected that diffusion would determine the final outcome, because the solubility of D-glucose and dimedone in water differs strongly. Clearly, the superior catalytic activity of the $Sc(OTf)_2$-NSMP catalyst could be related to the presence of the mesoporous network, which effectively stabilizes the adduct **1**, thereby allowing the reaction to proceed smoothly to the desired product **2**.[19] Moreover, the intrinsic pore surface hydrophobicity and nanoscale pore channels increase the accessibility of active sites and meanwhile decrease the diffusion limitation of the reactants. To gain better insight into these effects, both toluene and water vapor absorption tests were performed to test the intrinsic hydrophobicity of $Sc(OTf)_2$-NSMP. As shown in Figure S4a, all isotherms showed type V behavior, indicating a weak adsorbent–adsorbate interaction. However, the adsorption capacity of $Sc(OTf)_2$-NSMP for toluene (49.4 wt%) was much higher than that for water (27.7 wt%). This result demonstrated that the surface is rather hydrophobic, resulting in the efficient adsorption of organic reactants. Furthermore, the adsorption of D-glucose (Figure S4b) on $Sc(OTf)_2$-NSMP in water was also measured. The data shows that $Sc(OTf)_2$-NSMP also adsorbs D-glucose quickly and a capacity of 35.8 wt% were reached after 1.0 h. These results demonstrate that $Sc(OTf)_2$-NSMP can efficiently adsorb hydrophilic D-glucose and hydrophobic dimedone, thereby facilitating the interaction between the reactants and the Sc^{III} active sites inside the mesopores, leading to the high catalytic efficiency.

Next, the commercially available solid Lewis acid titanium silicalite-1 (TS-1) was tested under the same reaction conditions (Table S4). However, it achieved only low conversion (30.5%) of D-glucose and low selectivity (33%) for **2**. This was mainly attributed to the small pore size of 0.55 nm, resulting in serious diffusion limitations for medium-sized D-glucose and dimedone.[20] In addition, another control catalyst, $Sc(OTf)_2$-MP, was prepared by constructing the $Sc(OTf)_3$-functionalized polymer framework on mesoporous phenol-formaldehyde polymeric particles with irregular shape and long mesopore channels.[21] The catalyst displayed a very irregular morphology with average particle diameters greater than 2.0 μm and an ordered hexagonal mesoporous structure with an average pore size of 3.6 nm (Figure S5). Nevertheless, the $Sc(OTf)_2$-MP catalyst only achieved 85.3% conversion and 86% selectivity for **2**. This inferior catalytic performance can probably be attributed to the lower Sc^{III} density ($0.462\ mmol\,g^{-1}$) and much longer channel length in comparison with $Sc(OTf)_2$-NSMP catalyst, which caused the enhanced mass transfer resistance.[14b] These results further confirmed the merit of the nanospherical mesoporous structure. Moreover, several homogeneous Lewis acids were also investigated. The results showed that $Ti(OiPr)_4$ did not lead to products owing to its rapid decomposition and $CrCl_3$ afforded only a moderate yield of 61.1%. However, $Sc(OTf)_3$ led to the same high conversion (99.5%) and selectivity (91%) of **2**, which further confirmed that the excellent performance of $Sc(OTf)_2$-NSMP can be attributed to the high catalytic reactivity of $Sc(OTf)_3$.[22]

To verify that polymer-supported rather than leached Sc species are responsible for the catalytic activity, we performed a hot filtration experiment. $Sc(OTf)_2$-NSMP catalyst was filtered from the reaction mixture after 24 h at a D-glucose conversion of 45%. The reaction was continued for additional 2 days under the same conditions. No significant change in the D-glucose conversion or the amount of products was observed. This observation eliminates the possible catalytic involvement of leached homogeneous active Sc species.[23]

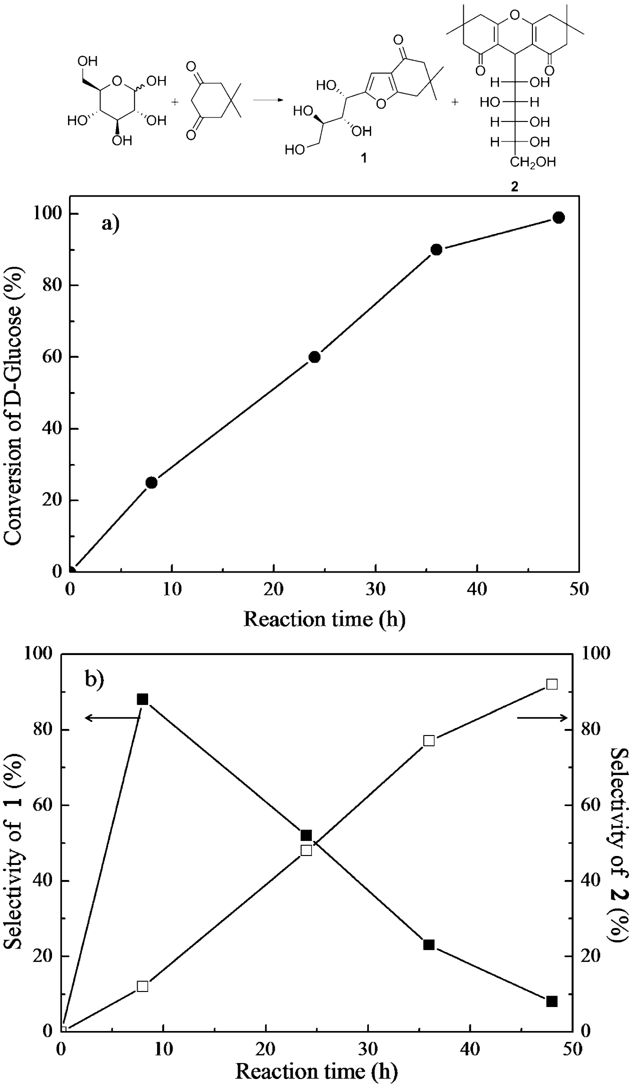
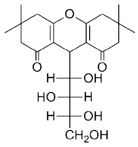
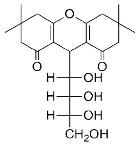
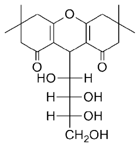
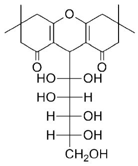
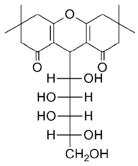
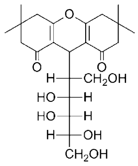


Figure 3. Reaction profiles of the C-glycosylation reaction between D-glucose and dimedone catalyzed by Sc(OTf)$_2$-NSMP in water: a) Conversion and b) selectivity over time.

This result was consistent with ICP-AES analysis, which showed that only a very low amount of Sc (less than 0.15 %) was detected in the reaction mixture.

Furthermore, we examined the substrate scope with various monosaccharides, including D-xylose, D-ribose, D-arabinose, D-fructose, D-galactose, and D-mannose (Table 1). C-glycosylation reactions proceeded with good to excellent conversions for monosaccharides with five-carbon chains. Even unreactive pentoses such as D-arabinose can be transformed by the Sc(OTf)$_2$-NSMP catalyst into the corresponding xanthone-C-glycoside with high yield (81 %). For the monosaccharides with six-carbon chains, we found that the conversion was slightly lower, whereas the selectivity also exhibited similar values, resulting in moderate to good yields of the corresponding xanthone glycosides. This can be attributed to the lower reactivity of the terminal aldehyde in the six-carbon-chain-containing sugars. These results clearly demonstrated the generality of the strategy for the efficient synthesis of xanthone glycosides from various simple sugars.

Table 1: Catalytic performance of Sc(OTf)$_2$-NSMP in the C-glycosylation reaction between various monosaccharides and dimedone.[a]

Sugar	Product	Conv. [%]	Selectivity [%]	Yield [%]
D-Xylose		99	93	92
D-Ribose		89	90	80
D-Arabinose		91	90	81
D-Mannose		75	85	64
D-Galactose		72	82	59
D-Fructose		70	80	56

[a] 1.0 mmol monosaccharide, 3.0 mmol 5,5-dimethyl-1,3-cyclohexanedione, and 0.1 mmol Sc(OTf)$_2$-NSMP catalyst, 3.0 mL H_2O, $T = 100\,°C$, $t = 48$ h.

We also tested the recovery and reuse the Sc(OTf)$_2$-NSMP catalyst in the glycosylation reaction between D-glucose and dimedone.[24] It was found that Sc(OTf)$_2$-NSMP could be reused at least seven times without noticeable loss of catalytic activity and selectivity (Figure S6). The XPS spectrum of the reused Sc(OTf)$_2$-NSMP catalyst exhibited almost the same Sc binding energy as that of the fresh catalyst, proving the intact active species (Figure S7a). ICP analysis revealed that the Sc content of the recycled Sc(OTf)$_2$-NSMP was almost the same (0.60 mmol g^{-1}) than that of the fresh catalyst. This shows that the periodically arranged phenyl sites in the polymer framework can efficiently inhibit Sc leaching even under these harsh reaction conditions.[25] Furthermore, low-angle XRD measurements and TEM images (Figure S7b) confirmed that the nanospherical morphology and ordered mesoporous structure of the Sc(OTf)$_2$-

NSMP was well preserved after recycling, resulting in the excellent durability in the glycosylation reaction in water.

In conclusion, we have developed a novel nanospherical mesoporous Lewis acid polymer by chelating scandium triflate with sodium benzenesulfonate groups attached to ordered mesoporous polymer nanospheres. The unique chemical modification of the phenyl sites in the polymer framework afforded abundant and periodically arranged Sc^{III} active sites, which efficiently catalyze the synthesis of xanthone glycosides through direct glycosylation of simple sugars in water. The excellent performance was attributed to the combined advantages of high acid density, nanoscale pore channels, and strong surface hydrophobicity, which facilitated the diffusion and adsorption of the reactants and the subsequent double Knoevenagel condensation. The catalyst was stable at high temperature in water and could be used repeatedly. The durability was attributed to the periodically arranged phenyl sites in the polymer framework which inhibited the leaching of the active Sc species. The presented synthetic strategy could be further extended to develop more robust mesoporous polymeric catalysts for sustainable carbohydrate transformations.

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[1] J. C. Serrano-Ruiz, J. A. Dumesic, *Energy Environ. Sci.* **2011**, *4*, 83–99.

[2] M. S. Holm, S. Saravanamurugan, E. Taarning, *Science* **2010**, *328*, 602–605.

[3] a) A. C. Weymouth-Wilson, *Nat. Prod. Rep.* **1997**, *14*, 99–110; b) M. Filice, J. M. Palomo, *RSC Adv.* **2012**, *2*, 1729–1742.

[4] C. J. Thibodeaux, C. E. Melançon, H. W. Liu, *Nature* **2007**, *446*, 1008–1016.

[5] a) A. M. Ruppert, K. Weinberg, R. Palkovits, *Angew. Chem.* **2012**, *124*, 2614–2654; *Angew. Chem. Int. Ed.* **2012**, *51*, 2564–2601; b) M. Pfaffe, R. Mahrwald, *Org. Lett.* **2012**, *14*, 792–795.

[6] R. Rinaldi, F. Schüth, *Energy Environ. Sci.* **2009**, *2*, 610–626.

[7] a) S. Sato, Y. Naito, K. Aoki, *Carbohydr. Res.* **2007**, *342*, 913–918; b) N. M. Xavier, S. D. Lucas, A. P. Rauter, *J. Mol. Catal. A* **2009**, *305*, 84–89.

[8] a) A. M. van der Heijden, T. C. Lee, F. van Rantwijk, H. van Bekkum, *Carbohydr. Res.* **2002**, *337*, 1993–1998; b) B. K. Gorityala, J. M. Ma, K. K. Pasunooti, S. T. Cai, X. W. Liu, *Green Chem.* **2011**, *13*, 573–577.

[9] a) J. Schuster, G. He, B. Mandlmeier, T. Yim, K. T. Lee, T. Bein, L. F. Nazar, *Angew. Chem.* **2012**, *124*, 3651–3655; *Angew. Chem. Int. Ed.* **2012**, *51*, 3591–3595; b) F. Zhang, X. S. Yang, F. X. Zhu, J. L. Huang, W. H. He, W. Wang, H. X. Li, *Chem. Sci.* **2012**, *3*, 476–484.

[10] a) S. Huh, H. T. Chen, J. W. Wiench, M. Pruski, V. S. Y. Lin, *J. Am. Chem. Soc.* **2004**, *126*, 1010–1011; b) H. T. Chen, S. Huh, J. W. Wiench, M. Pruski, V. S. Y. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 13305–13311; c) D. J. Mihalcik, W. B. Lin, *Angew. Chem.* **2008**, *120*, 6325–6328; *Angew. Chem. Int. Ed.* **2008**, *47*, 6229–6232; d) D. J. Mihalcik, W. B. Lin, *ChemCatChem* **2009**, *1*, 406–413; e) T. Yokoi, T. Karouji, S. Ohta, J. N. Kondo, T. Tatsumi, *Chem. Mater.* **2010**, *22*, 3900–3908.

[11] a) M. Takeuchi, R. Akiyama, S. Kobayashi, *J. Am. Chem. Soc.* **2005**, *127*, 13096–13097; b) M. T. Reetz, D. Giebel, *Angew. Chem.* **2000**, *112*, 2614–2617; *Angew. Chem. Int. Ed.* **2000**, *39*, 2498–2501; c) Y. L. Gu, C. Ogawa, J. Kobayashi, Y. Mori, S. Kobayashi, *Angew. Chem.* **2006**, *118*, 7375–7378; *Angew. Chem. Int. Ed.* **2006**, *45*, 7217–7220; d) Y. J. Xu, W. Q. Gu, D. L. Gin, *J. Am. Chem. Soc.* **2004**, *126*, 1616–1617.

[12] R. Kumar, J. P. Sharma, S. S. Sekhon, *Eur. Polym. J.* **2005**, *41*, 2718–2725.

[13] T. Kawabata, T. Mizugaki, *J. Am. Chem. Soc.* **2003**, *125*, 10486–10487.

[14] a) Y. Fang, D. Gu, Y. Zou, Z. X. Wu, F. Y. Li, R. C. Che, Y. H. Deng, B. Tu, D. Y. Zhao, *Angew. Chem.* **2010**, *122*, 8159–8163; *Angew. Chem. Int. Ed.* **2010**, *49*, 7987–7991; b) J. Liu, T. Y. Yang, D. W. Wang, G. Q. Lu, D. Y. Zhao, S. Z. Qiao, *Nat. Commun.* **2013**, *4*, 2798–2805.

[15] K. Nakajima, I. Tomita, M. Hara, S. Hayashi, K. Domen, J. N. Kondo, *Adv. Mater.* **2005**, *17*, 1839–1842.

[16] T. Miyase, H. Noguchi, X. M. Che, *J. Nat. Prod.* **1999**, *62*, 993–996.

[17] a) O. Talhi, A. M. S. Silva, *Curr. Org. Chem.* **2012**, *16*, 859–896; b) Y. Tsai, S. Götze, I. Vilotijevic, M. Grube, D. V. Silva, P. H. Seeberger, *Chem. Sci.* **2013**, *4*, 468–481; c) L. X. Wang, B. G. Davis, *Chem. Sci.* **2013**, *4*, 3381–3394.

[18] M. Scherrmann, *Top. Curr. Chem.* **2010**, *295*, 1–18.

[19] R. Gounder, M. E. Davis, *J. Catal.* **2013**, *308*, 176–188.

[20] M. Moliner, *Dalton Trans.* **2014**, *43*, 4197–4208.

[21] Y. Meng, D. Gu, F. Q. Zhang, Y. F. Shi, H. F. Yang, Z. Li, C. Z. Yu, B. Tu, D. Y. Zhao, *Angew. Chem.* **2005**, *117*, 7215–7221; *Angew. Chem. Int. Ed.* **2005**, *44*, 7053–7058.

[22] S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227–2302.

[23] C. D. Wu, A. G. Hu, L. Zhang, W. B. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 8940–8941.

[24] Y. Román-Leshkov, M. E. Davis, *ACS Catal.* **2011**, *1*, 1566–1580.

[25] P. Van Der Voort, D. Esquivel, E. De Canck, F. Goethals, I. Van Driessche, F. J. Romero-Salguero, *Chem. Soc. Rev.* **2013**, *42*, 3913–3955.