

WILEY-VCH

Efficient Mukaiyama-Aldol Reaction with Aqueous Formaldehyde on a Hydrophobic Mesoporous Lewis Acid Polymer

Fang Zhang*, Chao Liang, Zhen Wang, Hexing Li*

Abstract: The design of robust water-compatible solid Lewis acid catalysts in the efficient utilization of aqueous formaldehyde is a challenging task. Herein we described that an ytterbium triflatecontaining ordered mesoporous polymer (Yb(OTf)2-MP) acts as a highly active and selective Lewis acid catalyst for the Mukaiyama-Aldol reaction with aqueous formaldehyde. The unique capacity of hydrophobic surface and ordered mesoporosity was capable of simultaneously stabilizing the hydrophilic and hydrophobic reactants and selectively catalyzing the reaction by minimizing water interference at active sites. Accordingly, it enabled a broad range of silyl enol ethers engaged in this process efficiently to create structurally diverse β -hydroxy carbonyl molecules. Notably, the process can be easily scaled up to achieve gram scale production of the key intermediate of natural product sarkomycin. Also, it is stable in aqueous conditions and can be easily recovered and used repetitively at least six times.

Introduction

The utilization of simple, cheap and abundant C1 molecules as the feedstock in the environmentally benign chemical processes has attracted tremendous interest.1 Formaldehyde is one of the most important single-carbon electrophiles and has been used in many organic reactions and natural product synthesis.² Obviously, formaldehyde gas is carcinogen and not convenient to handle, which causes the environmental and health issues when it is used as the reactant in the chemical transformations. Accordingly, the non-electrophilic oligomers such as paraformaldehyde and trioxaneare are often used as the precursors of formaldehyde. But, they have to convert back to active formaldehyde form by thermal or acid activation. Thermal cracking produces highly toxic, gaseous formaldehyde whereas that rapidly re-polymerizes. Acid treatment inevitably causes the corrosion, a large amount of chemical wastes and difficult operation.3 On the contrary, the ideal reagent is cheap, easily

Prof. Dr. F. Zhang, Mr. C. Liang, Mr. Z. Wang, Prof. Dr. H. Li The Education Ministry Key Laboratory of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials Shanghai Normal University Shanghai, 200234, China Fax: (+)86-21-643222272

E-mail: zhangfang@shnu.edu.cn; HeXing-Li@shnu.edu.cn

Supporting information for this article is given via a link at the end of the document.

handling, and less toxic aqueous solution of formaldehyde (formalin).⁴ Furthermore, a high percentage of water in aqueous formaldehyde increases the environmental advantage for chemical synthesis since it is clean, safe and non-flammable.⁵ However, the consequent challenges are the increased mass transfer resistance and the additional competitive reactions as well as the possible decomposition of active species. Therefore, the successful examples of the utilization of aqueous formaldehyde as C1 feedstock without any additives or organic medium as co-solvent are very rare.⁶

The Mukaiyama-Aldol reaction with formaldehyde provides a useful and straightforward approach to β-hydroxy carbonyl and particularly 1,3-ol homologous unit, a basic repeating functionality featured in numerous biologically important macrolides and polyketides.7 Inspired by the type II Aldolases in Nature, extensive efforts have been devoted to the development of solid Lewis acids to realize this process via the enolate activation mechanism.8 Nonetheless, the aqueous nature tends to reduce the electrophilicity of formaldehyde. Importantly, the traditional Lewis acids such as AICI3 and TiCl4 seriously decompose in the presence of water, thus limiting their applications in the activation of aqueous formaldehyde.9 To address these challenges, Kobayashi, Kim, Gin and our group have come up an elegant solution by developing solid supported lanthanide or scandium triflate and using surfactant-induced micellar Lewis acid catalytic system promoted aqueous formaldehyde-involved Mukaiyama-Aldol reactions.¹⁰ However, these catalytic systems often suffer from the tedious preparation, the relatively expensive catalyst support, the use of toxic organic co-solvent or the unsatisfactory performances. Moreover, the late stage modification of biologically interesting complex molecules with the methodology remain elusive, in part because of the small pore size and the increased diffusion hindrance of the complicated three-phase systems. In this manuscript, we described the synthesis of a novel ytterbium triflate-containing hydrophobic ordered mesoporous polymer by incorporating ytterbium triflate groups in the mesoporous phenol-formaldehyde polymer framework. It can remarkably accelerate the Mukaiyama-Aldol reactions with aqueous formaldehyde without requiring organic solvents as co-solvents or any additives. Notably, this catalyst displayed significantly better catalytic



Scheme 1. Illustration of the preparation of Yb(OTf)2-MP.

performance than homogeneous analogue (Yb(OTf)₃) and Yb(OTf)₂-containing polystyrene counterpart (Yb(OTf)₂-PS). Furthermore, the efficient modification of a variety of bioactive complex structures was achieved. It also realized the gram scale production of bioactive sarkomycin intermediate with high catalytic efficiency. Finally, the robust catalyst can be recycled and reused for six times without significant loss of catalytic activity.

Results and Discussion

Ordered mesoporous phenol-formaldehyde polymer was selected as the support not only because of high surface area and ordered large pores, but also rich hydrophobic and modular phenyl groups in the framework.¹¹ After sulfonation with chlorosulfuric acid, sodium ion exchange and Yb(OTf)₃ coordination treatments (Scheme 1), the phenyl moieties could efficiently transformed to Yb(III) triflate species, resulting in the formation of Lewis acid polymer with ordered mesoporous structure (Yb(OTf)₂-MP). During the preparation process, we carefully investigated the sulfonation parameters (Table S1), Yb(III) triflate amount and the solvents in the post-grafting process (Table S2). Satisfactorily, the optimized catalyst was achieved with 0.366 mmol/g Yb content, as determined by inductively coupled plasma (ICP) analysis, which was the highest reported loading for Yb(OTf)₃-containing heterogeneous catalysts so far.12 This result could be rationalized by the periodically arranged coordinating groups (PhSO₃Na-) in the functionalized mesoporous polymer.

X-ray photoelectron spectroscopy (XPS) measurement of the Yb(OTf)₂-MP showed that the Yb $4d_{5/2}$ and $4d_{3/2}$ binding energies were 187.0 and 200.5 eV, confirming that all Yb

species were present in the trivalent state.¹³ But, Yb 4d_{5/2} and 4d_{3/2} binding energies in the Yb(OTf)₃ compound were 187.6 and 201.1 eV, respectively. Clearly, the binding energies of Yb element in Yb(OTf)2-MP was negatively shifted by 0.6 eV (Figure 1). It was probably explained as the replacement of the CF₃SO₃ligands in Yb(OTf)₃ by the PhSO₃Na- groups in Yb(OTf)₂-MP, thereby making Yb(III) more electron-rich. To further confirm this coordination effect, we compared the S 2p binding energies of Yb(OTf)₃ and Yb(OTf)₂-MP (Figure S1-2). One peak at 169.1 eV corresponding to the OTf-groups could be found in Yb(OTf)3.11 However, for Yb(OTf)₂-MP, the relatively broad peak was observed. The deconvolution result revealed that two peaks at 168.3 eV and 169.4 eV were observed, which were ascribed to the benzenesulfonic acid and the OTf-groups, respectively.¹⁰ As expected, the S 2p binding energy of Yb(OTf)2-MP shifted positively by 0.30 eV in comparison with Yb(OTf)3. Therefore, we concluded that the formation of the Yb(III) Lewis acids in Yb(OTf)₂-MP was through the chemical interaction between the PhSO₃Na- groups in the polymer framework and Yb(OTf)₃ compound, as described in Scheme 1.





10.1002/cctc.201701426

WILEY-VCH



Figure 2. N₂ sorption isotherms (a) and pore size distribution curves (inset of 1a), XRD patterns (b) of MP and Yb(OTf)₂-MP, and TEM images (inset of 1b, c) and EDX analysis (d) of Yb(OTf)₂-MP.

N₂ sorption isotherms (Figure 2a) of both MP and Yb(OTf)₂-MP showed the typical type-IV sorption curves with H₂ hysteresis loops at the relative pressures at 0.4-0.8, indicating the presence of mesopores.14 Their BET surface areas and pore volumes were 343, 319 m²/g and 0.23, 0.20 cm³/g, respectively (Table S3). Particularly, the pore size distribution curves of Yb(OTf)₂-MP and MP were centered at 3.74 and 3.68 nm, respectively (inset of Figure 2a). It is interesting to note that only the slight decreases in surface area, pore volume and pore size of Yb(OTf)₂-MP compared to MP sample indicated that Yb(III) Lewis acid species were homogeneously dispersed in the polymer framework rather than located in the pore channel or pore mouth.¹⁵ Figure 2b showed small angle X-ray diffraction (XRD) patterns of MP and Yb(OTf)₂-MP. Similar to MP sample, Yb(OTf)₂-MP displayed one intense peak at $2\theta = 0.80^{\circ}$ characteristic of (100) reflection, together with one small peak at 20 = 1.39° indicative of (110) reflection. This result demonstrated that the ordered hexagonal structure (p6mm) could be well preserved after transforming the phenyl groups to Yb(III) Lewis acid species.16 TEM images further confirmed that Yb(OTf)2-MP had a two-dimensional (2D) array of one-dimensional channel with uniform pore size (inset of Figure 2c-d). Furthermore, water and toluene vapors were brought to absorb with Yb(OTf)2-MP and their respective absorbed amounts were measured by the weight changes of Yb(OTf)₂-MP (Figure 3a). Interestingly, Yb(OTf)₂-MP only absorbed 4.86 wt.% water while it absorbed 36.3 wt.% toluene. Such surprisingly increase with the hydrophobic molecule indicated that the pore surface of Yb(OTf)₂-MP was highly hydrophobic. On the basis of these results, we can therefore assure that our current approach could effectively avoid the destruction of the original mesostrcture and meanwhile retained the intrinsic hydrophobicity of phenol-formaldehyde polymer. These unique chemical and structural properties may offer unique catalytic features.



Figure 3. Water and toluene vapor adsorption tests (a) and trimethyl(1-phenylprop-1-enyloxy)silane reactant adsorption experiment in water of $Yb(OTf)_2$ -MP.

We focused our initial investigation on the transformation aqueous formaldehyde and trimethyl(1-phenylprop-1of enyloxy)silane as the reactants to explore the catalytic performance of the hydrophobic mesoporous Lewis acid polymer in water. As shown in Table S4, we firstly optimized the catalytic active species by probing different Ln(OTf)2-MP catalysts including La, Ce, Nb, Sm, and Yb and Sc(OTf)2-MP. All these catalysts furnished moderate to good yield with the desired adduct 3-hydroxy-2-methyl-1-phenylpropan-1-one and hydrolyzed byproduct propiophenone. Clearly, Yb(OTf)2-MP exhibited the highest catalytic activity and selectivity under the same reaction conditions. This could be attibuted to its relativley strong Lewis acidity.17 Next, we carefully investigated the reaction conditions of Yb(OTf)2-MP including catalyst loading and the amount of aqueous formaldehyde as well as reaction time and temperature (Figure 3 and S3-5). Gratifyingly, we found that 7.5 mol% Yb(OTf)₂-MP achieved 99% conversion and 96% selectivity at 20°C for 8.0 h with 10 equiv. aqueous formaldehyde (Figure 4). The conditions delivered the highest reported yield by solid Lewis acid in pure water so far (Table S5). Interestingly, the homogenous analog Yb(OTf)3 showed the remarkable decrease in the conversion (54%) and the slight reduction in the selectivity (93%). This result probably reflected the increased mass transfer limitation in the homogeneous

10.1002/cctc.201701426

WILEY-VCH

system, which is composed of water-soluble Yb(OTf)3, hydrophobic substance and hydrophilic aqueous formaldehyde. The interaction between active sites and the reactants was partially restricted and thus afforded the inferior catalytic efficiency. This was confirmed by the plots of conversion against reaction time (Figure 4). Furthermore, the substance adsorption experiments was designed to gain better insight into the unique enhancement of Yb(OTf)₂-MP. As shown in Figure 3b, the silvl enol ether can be quickly adsorbed and the adsorption capacity can reach to 14.3 mg/g within 1.0 h in water, which further confirmed the hydrophobic ordered mesoporous structure of Yb(OTf)₂-MP was crucial for its high catalytic performance. Moreover, the enhanced performance of Yb(OTf)2-MP could be explained based on the proposed reaction mechanism,18 as shown in Figure S6. The aldehyde group in aqueous formaldehyde was activated by Yb(III) via σ bonding coordination and then trimethyl(1-phenylprop-1-enyloxy)silane attacks the activated HCHO to complete the aldol addition reaction. The competing hydrolysis of the silyl enol ether promoted by the Yb(III) Lewis acid occurs simultaneously. Due to the good solubility of homogeneous catalyst Yb(OTf)₃, it exists in the aqueous phase in this Mukaiyama-aldol addition reaction, which impedes the hydrophobic silyl enol ether interaction with the active species, resulting in the low conversion. On the contrary, the unique combination of hydrophobic pore surface and ordered mesopores of the Yb(OTf)2-MP can efficiently adsorb both hydrophobic and hydrophilic reactants and subsequently stablize water sensitive hydrophobic silvl enol ether, and concentrate both reactnants in the active sites. These unique properties delivered the remarkably increased reactivity of Yb(III) compound. Furthermore, the hydrophobic nature of the catalyst surface can also minimize the amount of water molecule around the active sites, leading to the high selectivity.19



Figure 4. Plots of conversion (a) and selectivity (b) against time over $Yb(OTf)_2$ -MP, $Yb(OTf)_3$ and $Yb(OTf)_2$ -PS.

To confirm the above observations, we prepared the control sample Yb(OTf)₂-PS by reacting Yb(OTf)₃ with PhSO₃Nafunctionalzied polystyrene support. TEM image revealed that it didn't have the abundant pores (Figure S7). N2 sorption isotherm verified that BET surface area was only 40 m²/g and the hysteresis loop at P/P₀=0.8 was asigned to the accumulated pores of the particles (Figure S8). Moreover, toulene vapor absorption isotherm showed that the absorbed amount was 13.2 wt.% (Figure S9). As expected, it exhibited the lowest conversion (49.2%) and selectivity (79.8%). The inferior conversion was probably due to the low surface area and small pore size, which could not efficiently adsorb the reactants to interact with Yb(III) active sites. Thus, the reaction was mostly happened on the outer surface. Accordingly, the significant decrease in the selectivity was due to that the Yb(III) active sites on the surface of Yb(OTf)2-PS were easily to interact with water and therefore it caused the serious hydrolysis reaction of the silyl enol ether.



Figure 5. Substrate scope of $Yb(Of)_2$ -MP catalyzed aqueous formaldehydeparticipated reactions with different silyl enol ethers.

Next, we set out to examine the reaction scope by examining a variety of silyl enol ethers. It was found that both electron-rich and -deficient silyl enol ethers were smoothly transformed into the corresponding products in good yield with excellent selectivity. Silyl enol ethers bearing various functional moieties including cyclohexene, naphthalene and indene were

compatible with this protocol, affording the satisfactory yields. Additionally, the molecular structures that are frequently found in biologically active agents, including bicyclo[2.2.1]hept-2-ene and steroid, could be applied with this addition reaction with the moderate conversion and good selectivity, further highlighting the high catalytic activity of our Yb(OTf)₂-MP catalyst (Figure 5).



Figure 6. $Yb(OTf)_2$ -MP catalyzed synthesis of the intermediate of (R)-Sarkomycin.

In addition, this Yb(OTf)₂-MP-catalyzed Mukaiyama-aldol process proved to be scalable under the mild reaction conditions (Figure 6). We were able to perform a 10-mmol-scale (1.82 g) reaction by using 3-ethenyl-1-trimethylsiloxycyclopent-1-ene as the substance with 10 mol% Yb(OTf)₂-MP and 20 equiv. aqueous formaldehyde at 20 °C for 24 h in water to give the corresponding 2-(hydroxymethyl)-3-vinylcyclopentanone (65% yield, d.r. 7:3) for the first time, which is the important intermediate for the synthesis of natural product sarkomycin with antibiotic and anticancer activity.²⁰ The scalability and robustness of this environmentally friendly heterogeneous transformation illustrated its potential application in the manufacture of medicinally useful chemicals on an industrial scale.

To confirm whether the heterogeneous Yb(III) Lewis acid polymer or the leached Yb(III) active species in solution was the real catalyst responsible for this reaction, the following control experiments were carried out.²¹ Yb(OTf)₂-MP catalyst was filtered from the reaction mixture after 4.0 h until conversion exceeded 60%, and the reaction was continued for an additional 10 h under the same reaction conditions. It was found that no obvious change in silyl enol ether conversion or the increased yield of any products was observed. This result ruled out the possible catalytic role of the leaching homogeneous Yb(III) active sites from the polymer framework. This result was consistent with ICP-AES result, which showed that the presence of extremely low amount of Yb element (less than 5.0 ppm) could be detected in the reaction mixture.



Figure 7. Recycle tests of Yb(OTf)₂-MP catalyst in the the Mukaiyama-Aldol reaction between aqueous formaldehyde and trimethyl(1-phenylprop-1-enyloxy)silane.

Furthermore, the reuse and recycle ability of Yb(OTf)2-MP catalyst was investigated in the Mukaiyama-Aldol reaction between aqueous formaldehyde and trimethyl(1-phenylprop-1envloxy)silane. It was demonstrated that Yb(OTf)₂-MP showed very good recyclability (Figure 7). There was no significant activity loss after recycling six times and the yield still remained very high. ICP analysis revealed that Yb content in the reused Yb(OTf)₂-MP after six cycles was almost the same (0.35 mmol/g). Meanwhile, low-angle XRD pattern and TEM image (Figure S10) confirmed that ordered mesoporous structure of the recycled Yb(OTf)₂-MP was well preserved. Moreover, Yb XPS spectrum of the recycled Yb(OTf)2-MP (Figure S11) revealed that the Yb 4d5/2 and 4d3/2 binding energies were 187.0 and 200.5 eV, which were almost the same with the fresh Yb(OTf)2-MP. The result demonstrated that the Yb(III) species in the recycled Yb(OTf)2-MP was stable even after six time reuse. However, Yb(OTf)₂-PS lost its catalytic activity about 30% after only 4 recycles (Figure S12). ICP analysis clearly confirmed that the leaching Yb(III) species in the reaction mixture was about 20% in comparison with the fresh sample. Thus the excellent recyclability of Yb(OTf)2-MP could be attributed to the unique periodically arranged Yb(III) Lewis acids in the polymer skeleton, which effectively stabilized the Yb(III) triflate and inhibited the loss of active species.22

Conclusions

In summary, we have developed a novel Yb(OTf)₂-functinalized hydrophobic ordered mesoporous polymer for the Mukaiyamaaldol reaction with aqueous formaldehyde. It displays remarkable catalytic behavior by the virtue of the unique combination of hydrophobic pore surface and ordered mesopores. The process is applicable for structurally diverse silyl enol ethers to deliver corresponding products in high yield and selectivity. It also can be used to synthesize the important intermediate for synthesis of (R)-sarkomycin in gram scale. Furthermore, the catalyst can be recycled and reused for at least six times without loss of its activity. We anticipate that this strategy will enable the transformation of a broad range of reagents with aqueous formaldehyde to the high value-added fine chemicals in an eco-friendly way.

Experimental Section

Experimental Details. Synthesis of hydrophobic ordered mesoporous Lewis Acid polymer (Yb(OTf)2-MP). Ordered mesoporous phenolformaldehyde polymer (MP) was synthesized by evaporation induced self-assembly (EISA) approach according to the procedure reported elsewhere.¹ After vacuum drying at 105°C for 1.0 h, 1.0 MP sample was introduced into 40 ml CH₂Cl₂ solution at 0°C and subsequently 20 ml chlorosulfonic acid was added dropwise into the mixture with constant stirring. After stirring at 0°C for 12 h, the reaction mixture was refluxed for another 12 h. Then, the mixture was filtered, washed by ethanol for three times and dried in vacuum. The obtained sulfonated mesoporous polymer was re-dispersed in 50 ml NaOH aqueous solution (1.0 mol/l) and then this mixture was heated to 80°C and stirred for 24 h. After that, a certain amount of 1.0 mol/l NaOH aqueous solution was added until the pH value was 7.0, followed by filtering, washing by water and drying in vacuum. The functionalized mesoporous polymer was designated as PhNaSO₃-MP. Furthermore, 0.50 g NaSO₃-MP was added into 15 ml anhydrous ethanol, following by adding 0.224 g ytterbium(III) trifluoromethanesulfonate (Yb(OTf)₃). After stirring for 24 h at 80°C, the solid product was filtered and washed thoroughly with anhydrous tetrahydrofuran and anhydrous ethanol to eliminate un-coordinated Yb(III) salt, followed by vacuum drying at 80°C for 12 h, denoted as Yb(OTf)₂-MP.

Synthesis of Ln(OTf)₂-MP (Ln= La, Ce, Nb and Sm) and Sc(OTf)₂-MP samples. These samples were prepared using the same procedure by using La(OTf)₃, Ce(OTf)₃, Nb(OTf)₃, Sm(OTf)₃, and Sc(OTf)₃ instead of Yb(OTf)₃.

Synthesis of Yb(OTf)₂-PS sample. This sample was synthesized using the same protocol by changing PhNaSO₃-MP to PhNaSO₃-PS support.

Characterization. Lanthanides and scandium contents were measured by inductively coupled plasma optical emission spectrometer (Varian VISTA-MPX). The surface electronic states of ytterbium and sulfur elements were analyzed by X-ray photoelectron spectroscopy (XPS, Perkin-Elmer PHI 5000C ESCA). All the binding energy values were calibrated by using C1s = 284.6 eV as a reference. X-ray powder diffraction (XRD) data were acquired on a Rigaku D/maxr B diffractometer using Cu K\alpha radiation. Nitrogen sorption tests were measured using a Quantachrome NOVA 4000e analyzer. Specific surface areas (S_{BET}) and average pore diameter (D_P) are calculated by using BET and BJH models, respectively. Transmission electron microscopy (TEM) experiments were performed on a JEM-2011 electron microscope. The water and toluene vapour absorption measurements were tested on a Hiden Isochema IGA-002/3 intelligent gravimetric analyzer. A dosed amount of high-purity vapor was directly introduced into the sample chamber and then the weight change was recorded after the stable equilibrium pressure was reached.

Catalytic tests. As a typical run of aqueous formaldehyde participated in Mukaiyama-Aldol reactions, 1.0 mmol trimethyl-(1-phenylprop-1enyloxy)silane, 10 mmol HCHO aqueous solution (37% w/w), a certain amount of Yb(OTf)₂-MP catalyst containing 0.075 mmol Yb(III) and 3.0 ml distilled water were mixed in a three-necked round flask equipped with a condenser and a magnetic stirrer. The reaction was carried out at 20°C for 12 h under mild stirring. The products were analyzed by high performance liquid chromatography analyzer (HPLC, Agilent 6410 series Triple Quad) equipped with Agilent C18 column. The reaction conversion was calculated based on trimethyl(1-phenylprop-1-enyloxy)silane since HCHO was greatly in excess. The reaction selectivity for the target product of 3-hydroxy-2-methyl-1-phenylpropan-1-one was determined based on its ratio to the byproduct propiophenone. The yield of the target product was thus obtained by multiplying the conversion with the selectivity. In all the activity tests, the reproducibility was checked by repeating each result at least three times and was found to be within ±5%

In order to determine Yb(OTf)₂-MP catalyst recyclability, it was allowed to settle down by high speed centrifugation after each run of reactions and the clear supernatant liquid was decanted slowly. The residual Yb(OTf)₂-MP catalyst was reused with a fresh charge of water and reactant for subsequent recycle under the same reaction conditions.

Reactants adsorption test. The adsorption performance of the representative reactant trimethyl-(1-phenylprop-1-enyloxy)silane on Yb(OTf)₂-MP catalyst was determined through the reactant concentration change before and after adsorption of Yb(OTf)₂-MP. In a typical run for adsorption of silicon enolate, 50 mg catalyst was soaked in 50 ml water and oscillated at 25 °C for 12 h, followed by adding 200 ml aqueous solution containing 10 mg/l trimethyl-(1-phenylprop-1-enyloxy)silane. The solution was sampled at given time intervals and the concentration of the left trimethyl-(1-phenylprop-1-enyloxy)silane in solution was determined on a HPLC analyzer (Agilent 6410 series Triple Quad) equipped with Agilent C18 column at the characteristic adsorption wavelength of 218 nm. The adsorption capacity was determined after reaching saturation adsorption.

Acknowledgements

This work is supported by the Natural Science Foundation of China (21677098), PCSIRT (IRT-16R49) and Shanghai Government (TP2016034).

Keywords: C1 feedstock utilization • Aqueous formaldehyde • Mukaiyama-Aldol reaction • Hydrophobic mesoporous polymer • Water-compatible solid Lewis acid

[1] C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark, Green. Chem. 2015, 17, 3111-3121.

[2] M. Onaka, T. Okachi, J. Am. Chem. Soc. 2004, 126, 2306-2307.

[3] S. Meninno, A. Lattanizi, Chem. Rec. 2016, 16, 2016-2030.

[4] (a) S. Mouri, Z. H. Chen, S. Matsunaga, M. Shibasaki, Chem. Commun.

2009, *34*, 5138-5140; (b) P. W. N. M. van Leeuwen, Science of Synthesis: C-1 Building Blocks in Organic Synthesis. *Thieme*, **2014**.

[5] J. Mlynarski, S. Baś, Chem. Soc. Rev. 2014, 43, 577-587.

[6] (a) S. Van de Vyver, C. Odermatt, K. Romero, T. Prasomsri, Y. Román-Leshkov, *ACS Catal.* 2015, *5*, 972-977; (b) F. Zhang, C. Liang, M. Z. Chen, H.
 B. Guo, H. Y. Jiang, H. X. Li, *Green Chem.* 2013, *15*, 2865-2871.

[7] (a) J. Kobayashi, T. Kubota, J. Nat. Prod. 2007, 70, 451-460; (b) B.

Schetter, R. Mahrwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7506-7525; (c) S. B. Jennifer Kan, K. K. H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097-9108.

[8] (a) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* 2008, 37, 1502-1500; (b)
 P. Sreekanth, S. W. Kim, T. Hyeon, B. M. Kim, *Adv. Synth. Catal.* 2003, 345, 936-938; (c) P. Dissanayake, M. J. Allen, *J. Am. Chem. Soc.* 2009, 131, 6342-

6343; (d) S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, *43*, 2519-2521; (e) J. Paradowska, M. Pasternak, B. Gut, B. Gryzło, J. Mlynarski, *J. Org. Chem.* **2012**, *77*, 173-187.

[9] K. Nakajima, Y. Baba, R. Noma, M. Kitano, J. N. Kondo, S. Hayashi, M. Hara, J. Am. Chem. Soc. 2011, 133, 4224-4227.

[10] (a) S. Kobayashi, S. Nagayama, J. Am. Chem. Soc. 1998, 120, 2985-2986; (b) P. Sreekanth, S. W. Kim, T. Hyeon, B. M. Kim, Adv. Synth. Catal.
2003, 345, 936-938; (c) Y. J. Xu, W. Q. Gu, D. L. Gin, J. Am. Chem. Soc. 2004, 126, 1616-1617; (d) Y. L. Gu, C. Ogawa, J. Kobayashi, Y. Mori, S. Kobayashi, Angew. Chem. Int. Ed. 2007, 38, 7217-7220; (e) M. Kokubo, C. Ogawa, S. Kobayashi, Angew. Chem. Int. Ed. 2008, 47, 6909-6911; (f) H. Miyamura, A. Sonoyama, D. Hayrapetyan, S. Kobayashi, Angew. Chem. Int. Ed. 2015, 127, 10705-10709; (g) Y. Liu, K. Mo, Y. Cui, Inorg. Chem. 2013, 52, 10286-20191.
[11] F. Zhang, C. Liang, X. T. Wu, H. X. Li, Angew. Chem. Int. Ed. 2014, 53, 8498-8502.

[12] (a) B. S. Lee, S. Mahajan, K. D. Janda, *Tetrahedron Lett.* **2005**, *46*, 807, 5495-5498; (b) J. J. Li, W. K. Su, J. D. Lin, M. Chen, J. Li, Synth. Commun.

2005, 35, 1929-1937; (c) S. Z. Luo, L. Z. Zhu, A. Talukdar, G. S. Zhang, X. L.
Mi, J. P. Cheng, P. G. Wang, *Mini-Rev. Org. Chem.* 2005, 2, 177-202; (d) W.
B. Yi, C. J. Cai, *Fluorine Chem.* 2008, 129, 524-528; (e) B. Karimi, A. Maleki,
D. Elhamifer, J. H. Clark, A. J. Hunt, *Chem. Commun.* 2010, 46, 6947-6949; (f)
Z. X. Li, F. B. Shi, T. Zhang, H. S. Wu, L. D. Sun, C. H. Yan, *Chem. Commun.* 2011, 47, 8109-8111; (e) S. Hosokawa, S. Iwamoto, M. Inoue, *J. Am. Ceram.* Soc. 2007, 90, 1215-1221.

[13] S. Suga, S. Ogawa, H. Namatame, M. Taniguchi; A. Kakizaki, T. Ishii, A. Fujimori, S. J. Oh, T. Miyahara, A. Ochiai, T. Suzuki, T. Kasuya, *J. Phys. Soc. Jpn.* **1989**, *58*, 4534-4543.

[14] D. Y. Zhao, J. L. Feng, Q. S. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548-552.

[15] S. Inagaki, S. Guan, T. Ohsuna, O. Terasaki, *Nature* 2002, *416*, 304-307.
 [16] A. P. Wight, M. E. Davis, *Chem. Rev.* 2002, *102*, 3589-3614.

[17] (a) S. Kobayashi, I. Hachiya, *Tetrahedron Lett.* **1992**, 33, 1625-1628; (b) K Ohkubo, S. C. Menon, A. Orita, J. Otera, S. Fukuzumi, *J. Org. Chem.* **2003**, 68 4720-4726.

[18] S. Doherty, P. Goodrich, C. Hardacre, V. Pârvulescu, C. Paun, *Adv. Synth Catal.* **2008**, *350*, 295-302.

8578; (d) M. H. Alkordi, R. R. Haikal, Y. S. Hassan, A. Emwas, Y. Belmabkhout, *J. Mater. Chem. A* **2015**, *3*, 22584; (e) M. H. Alkordi, Ł. J.

Weselinński, V. D'Elia, S. Barman, A. Cadiau, M. N. Hedhili, A. J. Cairns, R. G Abdulhalim, J. Basset, M. Eddaoudi, *J. Mater. Chem. A* **2016**, *4*, 7453.

[20] J. Westmeier, S. Kress, C. Pfaff, P. von Zezschwitz, *J. Org. Chem.* 2013, 78, 10718-10723.

[21] R. A. Sheldon, M. I. Wallau, W. C. E. Arends, Schuchardt, U. Acc. Chem. Res. 1998, 31, 485-493.

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

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

An ytterbium triflate-containing hydrophobic mesoporous polymer enables the efficient Mukaiyama-Aldol reaction with aqueous formaldehyde without any additives or organic medium as co-solvent in water. This highly active and selective heterogeneous transformation provides the environmentally friendly way to create a series of structurally diverse β -hydroxy carbonyl molecules. Notably, the process can be easily scaled up to achieve gram scale production. Also, it is very stable in aqueous conditions and can be easily recycled at least six times.



Fang Zhang*, Chao Liang, Zhen Wang, Hexing Li*

Page No. – Page No.

Efficient Mukaiyama-Aldol Reaction with Aqueous Formaldehyde on a Hydrophobic Mesoporous Lewis Ac Polymer