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An ordered, nanoporous, TEMPO-based polymer resin formed from lyotropic liquid crystal monomers catalyzes the hetereogeneous oxidation of alcohols with high activity and substrate size selectivity under transition metal-free, aerobic conditions.

The oxidation of alcohols to carbonyl compounds is ubiquitous in organic chemistry and very important in chemical industry. However, most common oxidation reagents suffer from drawbacks that limit their use in the manufacture of pharmaceuticals and fine chemicals, and in other important industrial processes.[1] For example, the heavy metals (e.g., Cr, Mn) used in many oxidation reactions must be removed from the product down to trace amounts, which is cost- and resource-intensive.[1] Also, many oxidizing agents are potentially explosive compounds (e.g., IBX, DMP) and thus dangerous for large-scale use.[2,3] A recent article overviewing the synthetic processes used by three major pharmaceutical companies stated that despite being a common step in many published target-oriented syntheses, alcohol oxidation steps are often designed out of industrial drug syntheses because of these concerns.[1] Therefore, new alcohol oxidation methods, particularly catalytic processes that avoid the problems of current oxidation systems, would be of great value. The ideal alcohol oxidation catalyst should be selective; free of heavy metals; and use an environmentally benign, readily available, and inexpensive oxidant. Moreover, the catalyst should be a solid-state material to allow for facile recovery and reuse.

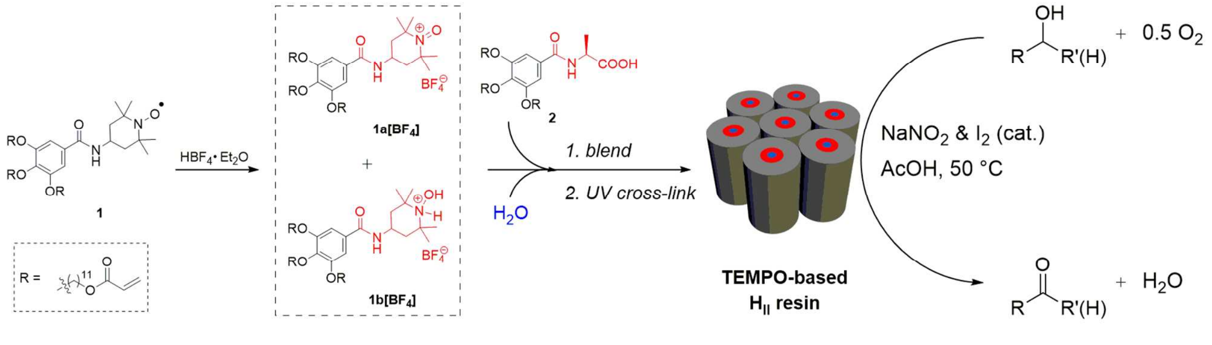

Fig. 1 Structures of TEMPO-based monomers **1** and (**1a[BF$_4$]** + **1b[BF$_4$]**), and non-reactive H$_{II}$-phase-templating co-monomer **2**. Schematic showing H$_{II}$ LLC phase formation and cross-linking of a blend of (**1a[BF$_4$]** + **1b[BF$_4$]**) and **2** and the catalytic activity of the resulting TEMPO-based, ordered, nanoporous polymer resin.

Of the reported materials for heterogeneous catalytic alcohol oxidation, the majority use a transition-metal catalyst supported on a solid.[4–6] These catalysts have the advantages of easy recovery and recyclability but can still introduce metal contamination to the reaction products. In contrast, the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is a well-known, albeit expensive, metal-free organocatalyst for chemoselective alcohol oxidation (i.e., to form aldehydes selectively from 1° alcohols).[7] There has therefore been significant effort to immobilize TEMPO on organic (e.g., polymer[8]) or porous inorganic (e.g., mesoporous silica,[9–12] zeolite[13]) supports. While some of these supported TEMPO-based oxidation catalysts have found industrial use,[14] they still have some drawbacks that limit their practicality. For example, many of them require metal co-catalysts, utilize a

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†Electronic Supplementary Information (ESI) available: Full synthesis procedures and characterization data for monomers **1**, (**1a[BF$_4$]** + **1b[BF$_4$]**), and **2** and the catalytic resins formed by these monomers; data on the setup and monitoring of the catalytic aerobic oxidation reactions and control experiments; details on calculation of the molecular diameters of BA and BTBA. See DOI: 10.1039/x0xx00000x

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stoichiometric amount of an expensive or aggressive oxidant, or they have limited activity.

Herein, we present an ordered, nanoporous, TEMPO-based polymer resin prepared from self-assembled lyotropic liquid crystal (LLC) monomers that catalyzes the oxidation of 1° and 2° alcohol substrates with high activity and molecular size selectivity (Fig. 1). This resin is prepared by the radical cross-linking of a mixture consisting of two new TEMPO-based LLC monomers (**1a[BF$_4$]** + **1b[BF$_4$]**), an LLC co-monomer (**2**), and a small amount of water, which forms an inverted hexagonal (H_{II}) mesophase. The resulting heterogeneous, TEMPO-based H_{II} resin is free of transition metals, uses O_2 as the terminal oxidant, and has a high activity that is comparable to a solution TEMPO catalyst. As expected under water-free reaction conditions,[27] oxidations of 1° alcohol substrates with this catalyst system proceed with complete chemoselectivity for aldehyde formation. The heterogeneous nature of this catalyst also allows for easy recovery from the reaction mixture and catalyst reuse. Finally, the uniform-size nanochannels of the H_{II}-phase resin affords selectivity between alcohols of different molecular size. To our knowledge, a heterogeneous alcohol oxidation catalyst with these features is unprecedented.

Previous reports from our group using nanostructured LLC resins for Lewis acid,[15] Brønsted acid,[16] Brønsted base,[17] and chiral Diels-Alder catalysis[18] have demonstrated the beneficial effects of localizing reactive sites in uniform-size, organic nanopores, such as improved catalyst activity and/or selectivity. Selectivity for molecules of different size has also been observed in these systems, consistent with the presence of ca. 1-nm-diameter pores.[15,19] However, oxidation catalysis has never been developed or demonstrated in such LLC polymer materials.

The new TEMPO-based catalytically active LLC monomers (**1a[BF$_4$]** + **1b[BF$_4$]**) were prepared from TEMPO-containing monomer **1**. Monomer **1** was synthesized by EDC coupling of commercially available 4-amino-TEMPO with a polymerizable gallic acid derivative known to exhibit an H_{II} LLC phase when mixed with polar solvents (see the ESI).[20] **1** is not amphiphilic and thus on its own did not exhibit LLC phase behavior with added polar solvent. However, we hypothesized that the overall wedge shape of **1** would allow formation of an H_{II} phase when blended with an *L*-alanine-based LLC co-monomer (**2**) that has been previously demonstrated to template the formation of H_{II} phases via amide hydrogen bonding with structurally similar monomers.[21] Mixtures of **1**, **2**, and H_2O were found to form H_{II} phases; however, initial attempts to photo-cross-link these LLC mixtures resulted in low degrees of polymerization and a material that did not display catalytic activity. We suspected that the nitroxyl radicals on **1** were quenched by propagating chains during the free radical polymerization. Therefore, we first reacted **1** with $HBF_4{\cdot}Et_2O$ to form a mixture of its oxoammonium (**1a[BF$_4$]**) and hydroxyammonium (**1b[BF$_4$]**) salts,[22,23] which are non-radical species involved in the NO_x-based catalytic oxidation cycle of TEMPO.[24] This salt mixture was isolated as a precipitate from the reaction, characterized, and used without further purification for LLC mixture blending. (See the ESI for characterization data for (**1a[BF$_4$]** + **1b[BF$_4$]**) as well as parent monomer **1**.) Blending this mixture of amphiphilic derivatives of **1** with a four-fold weight excess of LLC co-monomer **2** and 5 wt% H_2O produced a tacky paste that displayed birefringence under polarized optical microscopy (POM). Subsequent photolysis with UV light (365 nm, no added radical photo-initiator) resulted in the formation of a solid resin with retention of the H_{II} nanostructure (see the ESI for full details.)

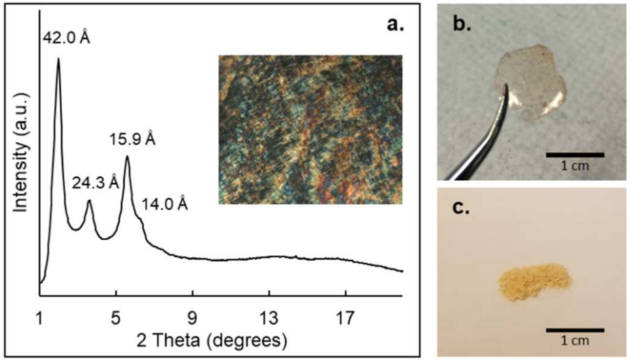

Fig. 2 (a) PXRD spectrum and POM image (inset, 5x mag.) of the TEMPO-based H_{II} resin. (b) Photo of the initially prepared TEMPO-based H_{II} resin as a film. (c) Photo of the TEMPO-based H_{II} resin, powdered and sieved for 75–150 µm particle sizes for catalysis experiments.

The resulting cross-linked TEMPO-based polymer exhibited powder X-ray diffraction (PXRD) peaks with a *d*-spacing ratio of $(1:1/\sqrt{3}:1/\sqrt{7}:1/3)$, indicative of an H_{II} LLC phase (Fig. 2a).[20] These densely cross-linked films were hard, brittle, and completely insoluble in all common solvents (Fig. 2b). These films were powdered and sieved for 75–150 µm particle sizes for catalysis experiments (Fig. 2c). We first tested the TEMPO-based H_{II} resin for the aerobic oxidation of benzyl alcohol (BA). BA was chosen because it has been used as a convenient test substrate for TEMPO-catalyzed alcohol oxidations in the literature,[27] and its relatively small size (calculated diameter: 0.69 nm; see the ESI) should ensure unrestricted entry into the ca. 1-nm nanopores of the H_{II} resin.[19] Many homogeneous (TEMPO/dihalogen/NO_x)-catalyzed alcohol oxidations have been reported in the literature,[24–27] and their mechanisms have been extensively studied.[28–30] We found that using the TEMPO-based H_{II} resin in the presence of catalytic amounts of I_2 and $NaNO_2$ in glacial AcOH under 1 atm of O_2 (conditions reported by Jie et al for chemoselective, homogeneous TEMPO-catalyzed alcohol oxidations)[27] enabled the fastest and most selective conversion of BA to benzaldehyde) (see the ESI Table S3.)

Under these conditions, baseline reactions with no added TEMPO catalyst gave only trace conversion of BA to benzaldehyde in 3 h by NMR analysis (Fig. 3a). Use of 5 mol% of unpolymerized monomer **1** as a solution-phase catalyst afforded oxidation of (99 ± 1)% of the BA to benzaldehyde in 3 h (Fig. 3b). Use of the TEMPO-based H_{II} resin as a heterogeneous catalyst (5 mol% catalytic sites relative to BA based on the composition and mass of the catalyst sample) also resulted in a high BA conversion ((93 ± 3)%) over the same reaction time (Fig. 3c). As with the homogeneous reactions, unreacted BA was the only other organic component detected in the heterogeneous reaction mixture. This result suggests that the uniform, nanoporous nature of the TEMPO-based H_{II} resin affords very good access to the catalytic sites and high activity, exhibiting only a slightly lower oxidation rate ((93 ± 3)% conversion after 3 h)

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than the solution catalysis case ((99 ± 1)% conversion after 3 h). This supposition was supported by catalyst site titration experiments on the LLC resin, which showed ca. 70% site accessibility (see the ESI).

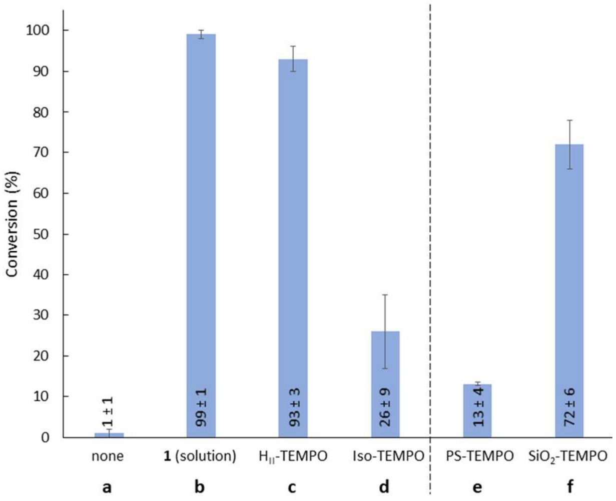

Fig. 3 Conversion of BA over 3 h for various TEMPO-based catalysts. Reaction conditions: 5 mol% catalyst sites relative to BA based on composition and mass of catalyst sample, I_2 & $NaNO_2$ (15 mol%), O_2 (1 atm), glacial AcOH solvent, 50 °C.

The heterogeneous nature of the H_{II} resin catalyst was confirmed by control experiments in which the solid catalyst was removed from the reaction mixture by centrifugation. Upon addition of more BA to the supernatant, no further conversion was detected after an additional 3 h at 50 °C under 1 atm of O_2. Furthermore, the catalyst could be washed multiple times with hot AcOH and reused with only a slight loss in activity after 5 runs, while product chemoselectivity was completely maintained (Fig. 4) (see the ESI for full experimental details). Additionally, we found that this catalyst was active towards a variety of 1° and 2° alcohols and exhibits the same substrate chemoselectivity as homogeneous TEMPO (i.e., 1° and benzylic alcohols react fastest while 2° aliphatic alcohols are the least reactive (see the ESI)).

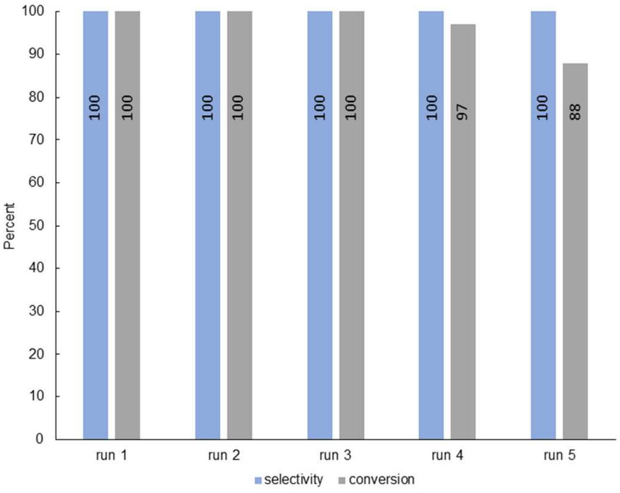

Fig. 4 Percent conversion of BA (gray bars) and percent product selectivity for benzaldehyde (blue bars) after 3 h of reaction for successive recycling experiments using the same TEMPO-based H_{II} resin sample as catalyst. Reaction conditions: 5 mol% available catalyst sites relative to BA with $NaNO_2$ and I_2 (15 mol%) as co-catalysts in glacial AcOH solvent at 50 °C under 1 atm O_2.

Table 1 Comparison of (BA/BTBA) substrate selectivity in the presence of various catalysts. Reaction conditions: 5 mol% catalyst sites relative to alcohol substrate based on composition and mass of catalyst sample, I_2 & $NaNO_2$ (15 mol%), O_2 (1 atm), glacial AcOH solvent, 50 °C, 3 h reaction time.

Entry	Catalyst	BA conversion over 3 h (%)	BTBA conversion over 3 h (%)	Selectivity (BA/BTBA)
A	none	1 ± 1	not detected	n/a
B	**1** (solution)	99 ± 1	96 ± 7	1.03 ± 0.08
C	**H_{II}-TEMPO**	**93 ± 3**	**22 ± 1**	**4.2 ± 0.2**
D	Iso-TEMPO	26 ± 9	23 ± 3	1.1 ± 0.4
E	PS-TEMPO	13 ± 4	not detected	n/a
F	SiO_2-TEMPO	72 ± 6	38 ± 6	1.9 ± 0.3

We hypothesized that in addition to high catalytic activity, the uniform-size nanopores of the TEMPO-based H_{II} resin should impart a degree of physical selectivity for substrates of different molecular size. To test this, we compared the conversion rate of BA with the much larger 3,5-bis(*tert*-butyldiphenylsilyloxy)benzyl alcohol (BTBA, calculated diameter: 1.68 nm, see the ESI). In solution reactions, unpolymerized monomer **1** catalyzed the oxidation of BTBA to its aldehyde at approximately the same rate as for BA, affording a (BA/BTBA) selectivity of (1.03 ± 0.08) (Table 1, entry B). However, in heterogeneous reactions using the TEMPO-based H_{II} resin, oxidation of the larger BTBA was only (22 ± 1)% compared to (93 ± 3)% for the smaller BA over the same 3 h reaction time ((BA/BTBA) selectivity = 4.2 ± 0.2) (Table 1, entry C). This behavior is consistent with the regular nanopores in the H_{II} catalyst resin limiting the access of the larger alcohol substrate to the catalyst sites, a molecular-size-exclusion phenomenon that has been observed in prior work with related LLC polymer systems.[19]

To ensure that these differences in conversion rate and substrate size selectivity were due to the isoporous nanostructure present in the TEMPO-based H_{II} resin, we conducted the same experiments with an amorphous/isotropic resin analog that was prepared by cross-linking the same LLC monomer mixture at 85 °C, above the ca. 75 °C clearing point of the mixture. The absence of nanostructure in the resulting control resin was confirmed by the lack of PXRD peaks and a black texture by POM (see the ESI). Using this TEMPO-based isotropic resin as a catalyst under otherwise identical reaction conditions, we found that BA and BTBA react at approximately the same low rate ((26 ± 9)% and (23 ± 2)% conversion over 3 h, respectively). This corresponds to a very low (BA/BTBA) substrate selectivity of (1.1 ± 0.4) (Table 1, entry D), which is similar to that of the solution-phase TEMPO catalyst **1** (Table 1, entry B). The small activity exhibited by the TEMPO-based isotropic resin is likely explained by the presence of a small amount of surface-accessible catalyst sites, a phenomenon observed in isotropic control resin studies of prior catalytic LLC polymer systems.[16]

The activity and substrate selectivity of the TEMPO-based resin catalysts was also compared to two commercial TEMPO-based solid-state catalysts: microporous silica-supported TEMPO (Siliacat®

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brand, referred to herein as SiO_2-TEMPO) and amorphous polystyrene-supported TEMPO (PS-TEMPO). Under the same reaction conditions (as described previously), the TEMPO-based H_{II} catalyst was more active and more substrate size selective than both commercial solid catalysts (Fig. 3e & f and Table 1 entries E & F). The relatively poor activity of PS-TEMPO is likely due to its amorphous, non-porous/dense nature;[31] whereas the moderate activity and substrate size selectivity of SiO_2-TEMPO are likely attributable to its microporous but weakly ordered nature with non-uniform pores that are reported to be in the 2.5–7.0 nm range[32] (see the ESI for PXRD spectra). These results reinforce the importance of having a regular, nanoporous structure in the design of heterogenous organic catalysts.

In summary, we have developed an ordered LLC-based nanoporous polymer resin for heterogeneous catalytic alcohol oxidation. This TEMPO-based H_{II} resin catalyst is transition-metal-free, uses O_2 as the terminal oxidant, and is active under reaction conditions that provide chemoselectivity for the formation of aldehydes from 1° alcohols. Furthermore, the uniform, nanoporous nature of this new catalyst resin imparts high activity similar to a solution-phase catalyst and selectivity for alcohol substrates of different molecular size. Future work includes determining the physical nanopore size of the TEMPO-based H_{II} resin by electron microscopy imaging and by examining the uptake of different non-reactive probe molecules of increasing molecular size to see when the onset of significant rejection occurs. We expect that determining the pore size of the TEMPO-based H_{II} resin will allow us to test different alcohol substrates of increasing molecular size to fully investigate the extent of catalyst molecular size selectivity. Future work will also focus on utilizing the inherent processability of these materials prior to cross-linking to fabricate aligned H_{II} films[33,34] as a means of generating molecular size-selective, catalytic polymer membranes from this reactive LLC system.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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