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Temperature Responsive Polymer-Supported TEMPO: An Efficient and Recoverable Catalyst for the Selective Oxidation of Alcohols

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Graphical Abstract

The advantages of homogeneous catalysis and heterogeneous catalysis were combined by immobilizing TEMPO into a temperature responsive polymer.



Highlights:

- > The advantages of homogeneous catalysis and heterogeneous catalysis were combined.
- > The catalyst system was highly efficient to the selective oxidation of alcohols.
- > Temperature responsive polymer was developed as a TEMPO support.

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Introduction

The selective oxidation of alcohols into the corresponding aldehyde or ketone represents one of the most important transformations in organic synthesis and total synthesis of natural products [1,2]. These reactions are typically achieved with the use of stoichiomeric amounts of high-valence transition-metal salts or organic-based oxidants that generate relatively large amounts of hazardous wastes [3-6]. The development of environmentally friendly procedures for the organic reactions is always an important goal of chemists [7-11]. In this regards, stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was developed as an organic catalyst for the selective oxidation of alcohols, and displayed excellent catalytic performance [12-16]. Although low catalyst loading are required, product isolation and catalyst recovery remain key issues with this system. To overcome these issues, immobilization of TEMPO as heterogeneous catalysts adopting different solid supports such as microporous organic nanotube networks [17], magnetic core-shell nanoparticle [18], silica [19-20], SBA-15 [21], cross-linked polystyrene [22,23], Ionic liquid [24] etc. have been reported. However, the activity and selectivity of the catalysts are often reduced if they are fixed onto insoluble solid or carriers with poor dispersibility [25].

The combination of the advantages of homogeneous and heterogeneous catalysis, so that the catalyst has the characteristics of homogeneous catalyst during the reaction process, and can be recycled as a heterogeneous catalyst after reaction, is of great significance [26]. Consequently, PEG-supported TEMPO catalysts with excellent solubility in reaction media have been developed, which displayed excellent catalytic activities and can be recovered by solvent-induced precipitation [27-30]. Developing new carrier to combine the advantages of **Table 1.** Data of the P(MEO₂MA-co-OEGMA) Polymers

This study aimed to combine the advantages of homogeneous catalysis and heterogeneous catalysis by immobilizing TEMPO into a water-soluble temperature responsive polymer. The supported TEMPO was water soluble and displayed excellent activity in the selective oxidation of alcohols below the LCST and can be easily recovered.

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homogeneous and heterogeneous catalysis for selective oxidation of alcohols is still highly desirable. Temperature responsive polymer, due to the hydrophilic effect of the hydrophilic group and the hydrophobic effect of the alkyl group, exhibits the Lower Critical Solution Temperature (LCST) in water [31]. When the temperature is lower than its LCST, the polymer form hydrogen bonds with water molecules make the polymer water soluble. When the temperature is higher than its LCST, it tends to form intramolecular hydrogen bonds, resulting in phase separation from water $[32^{33}-35]$. The unique characteristic of temperature responsive polymer make it can act an excellent carrier for catalyst immobilization [36-39]. Poly(oligo(ethylene glycol) methacrylate) as a kind of temperature responsive polymer has been widely studied [40,41]. The LCST of copolymer of di(ethylene glycol) methyl ether methacrylate (MEO₂MA) and oligo(ethylene glycol) methyl ether methacrylate (OEGMA) can be tuned by adjusting the ratio of two monomers in the copolymer [42]. Herein, we report the synthesis of temperature P(MEO₂MA-co-OEGMA)-supported responsive polymer TEMPO, its catalytic activity and recovery in the selective oxidation of alcohols.

Activated ester-amine chemistry as a post-polymerization modification method was introduced in functional polymer synthesis even before the advent of click chemistry [43]. In our initial study, we tried to synthesize temperature responsive copolymer with a terminal activated ester group by RAFT polymerization using NHS-CEPA as a RAFT reagent. NHS-CEPA was prepared by slightly modifying the literature method (Scheme 1) [44]. To achieve a carrier with a suitable LCST, we used feeding ratios of MEO₂MA and OEGMA in 3:1, 2:1, 5:3,

Sample	Feeding Ratio	M_n^{a}	${\mathbf M_n}^{\mathrm b}$	PDI	LCST ^c
Sample	(n _{MEO2MA} : n _{OEGMA})				(°C)
NHS-P(MEO ₂ MA ₄₈ -co-OEGMA ₁₄) (1a)	3:1	11900	13595	1.134	43 (40)
NHS-P(MEO ₂ MA ₄₅ -co-OEGMA ₁₉) (1b)	2:1	12400	14530	1.168	47.5
NHS-P(MEO ₂ MA ₄₂ -co-OEGMA ₁₉) (1c)	5:3	11500	13966	1.130	49
NHS-P(MEO ₂ MA ₃₅ -co-OEGMA ₂₇) (1d)	1:1	13000	15048	1.128	55.5 (53)
NHS-P(OEGMA ₆₅) (1e)	0:1	14300	19860	1.217	72.5 (71.5)

^aMeasured by GPC (in THF).

^bMeasured by ¹H NMR (in CDCl₃, Fig. S3)

°Temperature at the maximum of $|\triangle S/\triangle T|$ (Fig. S4), LCST of TEMPO-P(MEO₂MA-*co*-OEGMA in parentheses.

ABSTRACT



Fig. 1. The percent transmittance of copolymer versus temperature (a) copolymers NHS-P(MEO₂MA-co-OEGMA) $1a\sim1e$; (b) copolymers TEMPO-P(MEO₂MA-co-OEGMA) 2a, 2d and 2e (compared with the corresponding copolymers 1a, 1d and 1e).

1:1, and 0:1 to synthesize the copolymers and the samples were marked as $1a \sim 1e$ (Scheme 2).

The molecular weight and MW/Mn (PDI) of the synthesized NHS-P(MEO₂MA-*co*-OEGMA) were measured by Gel Permeation Chromatography (GPC). The detail information of was summarized in Table 1. It can be seen that NHS-P(MEO₂MA-*co*-OEGMA) have uniform distributions (PDI<1.22) and their molecular weights ranged from 11.5 KDa to 14.3 KDa.



Scheme 2 Synthesis of NHS-P(MEO₂MA-co-OEGMA).

The LCSTs of the copolymers were measured using UV-vis spectrometer (Fig. 1). Where, the LCST was defined as the temperature at the derivation absolute value ($|\Delta S/\Delta T|$) of the curve of transmittance versus temperature (Fig. S4). We found that the LCST of NHS-P(MEO₂MA-*co*-OEGMA) gradually decreases as the proportion of MEO₂MA increases, which could be well explained by less hydrogen bond between polymer chain and water formed with the increasing of MEO₂MA segments.

TEMPO was introduced into the terminal of the polymers by the facile reaction of the activated ester of NHS-P(MEO₂MA-*co*-OEGMA) with 4-amino-TEMPO (Scheme 3). We found through its ¹H NMR that the characteristic peak of NHS in NHS-P(MEO₂MA-*co*-OEGMA) in 2.85 ppm disappeared completely after the reaction , and the characteristic triplet signal of TEMPO appeared in Electron Spin Resonance (ESR) spectra (Fig. 2) [45-46].

These observation indicated that TEMPO was successfully loaded into the temperature responsive polymers and NHS group of NHS-P(MEO₂MA-*co*-OEGMA) was completely replaced by TEMPO.



Scheme 3 Synthesis of TEMPO-P(MEO₂MA-co-OEGMA).

Compared to NHS-P(MEO₂MA-*co*-OEGMA), the LCST of TEMPO-P(MEO₂MA-*co*-OEGMA) decreased 1~3 °C owning to

the successful introduction of a relative hydrophobic TEMPO to the end group of the temperature responsive polymers (Fig. 1b), which is consistent with our expectations. Among copolymers 2a, 2d and 2e, the LCST of copolymer 2a was 40 °C, which not only facilitate the homogeneous catalysis at room temperature or lower temperature, but also the catalyst recovery at acceptable high temperature. Therefore, copolymer 2a was the catalyst of choice.

After the successful preparation of the catalyst, we examined its catalytic activity in the selective oxidation of alcohols. The oxidation of benzyl alcohol was selected as a model reaction to optimize the reaction conditions using copolymer 2a as a catalyst. To our delight, 1.0 mol% copolymer 2a could efficient catalyze the reaction in water/DCM biphasic media at 0 °C using a slightly excess of buffered aqueous NaClO (1.25 mol equiv., pH = 9.1) as the terminal oxidant and NaBr (1.25 mol%) as the co-catalyst,

affording nearly complete conversion to benzaldehyde (Table 2, entry 1).

Encouraged by the results, we next investigated the catalyzed selective oxidations of a variety of alcohols under the optimized conditions. The results were summarized in Table 2. Benzyl alcohols containing either electron-withdrawing group (NO₂-, Br-) or electron-donating group (CH₃O-, CH₃-) were readily selective oxidated to the corresponding aldehydes in almost quantitative yields within 1 hour, as found in the case of unsubstituted benzyl alcohol (Table 2, entries 2-5). It is worth noting that the system also has excellent catalytic activities for different types of aromatic alcohols including 1-phenylethanol, 2-phenylethanol, 1naphthalenemethanol and diphenylmethanol. Both primary and secondary alcohols were highly efficiently oxidized to their corresponding carbonyl compounds (Table 2, entries 6-8, 12). In addition, fatty alcohols that are more difficult to selectively oxidize than aromatic alcohols were also efficiently converted. GC-MS yields were consistently high for straight-chain and less steric alcohol (Table 2, entry 9, 10). To our delight, the sterically hindered 2-adamantanol were also oxidized in high yield (Table 2, entry 13), and sulfur-containing benzyl alcohol also could be efficiently selective oxidized to corresponding aldehyde keeping the methylthio group untouched.

Ease of separation and reusability are extremely important for polymer-supported catalyst. The recyclability of TEMPO-P(MEO2MA₄₈-co-OEGMA₁₄) was investigated using benzyl alcohol as substrate under the optimized reaction conditions. After the completion of the reaction, cold diethyl ether was added to extract the product. The remaining aqueous phase appeared as a light-yellow transparent homogeneous solution. Heating the residual aqueous solution to 60 °C (>LCST) resulted in phase separation of the temperature responsive polymer-supported TEMPO from water. Subsequently, the muddy aqueous solution was carefully centrifugated offering the viscous oil in the bottom of the bottle, and then the upper aqueous solution was dumped to





Fig. 2 ESR spectra of TEMPO-P(MEO₂MA-co-OEGMA)

recover the catalyst (Fig. 3). The loss of catalyst weight was around 3.7% (Fig. S5) each run being observed, which may attributed mainly to the mechanical loss during the recovery. The loss of catalyst may be reduced through optimization of the heating/centrifugation method. After thoroughly washing with cold diethyl ether, the recovered catalyst was used in the next run directly without further purification, and almost consistent activity was obtained for 6 consecutive cycles although the catalyst loading decreased to a certain degree (Fig. 4).





^aReaction condition: alcohol (0.8 mmol), TEMPO-P(MEO₂MA-co-OEGMA) (1.0 mol%), NaBr (1.25 mol%) in CH₂Cl₂ (2 mL), aq NaClO (2 mL), at 0 °C, pH = 9.1.

^b GC-MS yields, and isolated yields in parenthesis.



Fig. 3 Before and after heating/centrifugation.

_	entry	alcohol	product	Time	Yield ^b (%)			
	1	OHOH	С—сно	1 h	>99			
	2	O2N-OH	02N-СНО	1 h	>99			
	3	Br-OH	Br-CHO	1 h	>99			
	4	H3CO-	н ₃ со-Сно	30 min	>99			
	5	H3C-	н₃с-∕сно	1 h	>99			
	6	⊘⊢		1 h	>99			
	7	⊘Он	СНО	1 h	>99			
	8	ССС	СНО	1 h	>99			
	9	~~~~он	СНО СНО	30 min	>99			
	10	ОН	Сно	1 h	>99			
	11		С————————————————————————————————————	1 h	>99 (94)			
	12	OH OH		1 h	>99 (96)			
	13	OH	∫ C ⁰	1 h	97 (91)			
	14	99-0H	9 -S-D-HO 92	30 min	>99 (92)			
-	Vield(%)	1 2 3						
Cycle index								



Conclusions

In conclusion, we have successfully immobilized TEMPO on temperature responsive polymer resulting in a high efficient and recyclable catalyst for the selective oxidation of alcohols in biphasic solvent media at 0 °C. Under the optimized reaction conditions, the catalyst system was highly efficient to the selective oxidation of a variety of substrates including the benzyl alcohols with electron-donating or electron-withdrawing group, 1-naphthalenemethanol, diphenylmethanol and sterically hindered fatty alcohols. Importantly, the catalyst can be easily recovered by heating/centrifugation of the polymer aqueous solution, and reused at least six reaction cycles without loss of catalytic activity. Investigation of the developed TEMPO system

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for selective oxidation of alcohols in halogen-free conditions is in progress in our laboratories.

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