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Poly(ethylene glycol)-Supported TEMPO: An Efficient, Recoverable Metal-Free Catalyst for the Selective Oxidation of Alcohols

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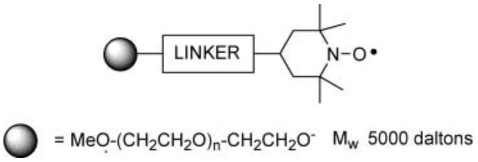
ABSTRACT



Poly(ethylene glycol)-supported TEMPO (PEG-TEMPO) has been prepared, and its catalytic activity in the chemoselective oxidation of alcohols with stoichiometric amounts of organic or inorganic oxidants has been investigated. The new metal-free catalyst exhibits high activity and is easily removed from the reaction mixture by filtration. Recycling experiments showed that PEG-TEMPO can be reused up to six times with no loss of catalytic activity.

An intense research activity has recently been devoted to the development of solid supported catalysts, currently regarded as a viable tool to improve the efficiency of a catalytic process by allowing simple catalyst recovery and recycling.[1] In this context, the use of polymer-supported organic catalysts is attracting increasing attention,[2] the expression "organic catalyst" being used to define an organic compound (of relatively low molecular weight and simple structure and devoid of any metal) capable of promoting a given transformation in substoichiometric quantity.[3] In principle, metal-free catalysts are particularly suitable to anchoring on a support, because they are not affected by the problem of metal leaching that requires catalyst regeneration by metal replenishment before recycling.

The use of metal-free catalysts for selective oxidations of organic substrates is very appealing.[4] One of the most useful synthetic applications of this approach is the chemoselective oxidation of alcohols promoted by oxoammonium salts.[5] These remarkably active species can be conveniently (re)-generated upon the action of terminal oxidants on stable free nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Efficient methods for the conversion of alcohols to aldehydes, ketones, or carboxylic acids under mild conditions have been thus developed, using TEMPO as a catalyst and stoichiometric amounts of inexpensive, safe, and easy to handle oxidants (among which are bleach,[6] [bis-(acetoxy)iodo]benzene (BAIB),[7] trichloroisocyanuric acid

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(1) *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000. (b) An issue of *Chemical Reviews* has recently been devoted to recoverable catalysts and reagents: *Chem. Rev.* **2002**, *102*, 3215−3892. (c) For an early review on supported catalysts, see: Manecke, G.; Storck W. *Angew. Chem., Int. Ed.* **1978**, *17*, 657.

(2) For a recent review on polymer-supported organic catalysts, see: Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.

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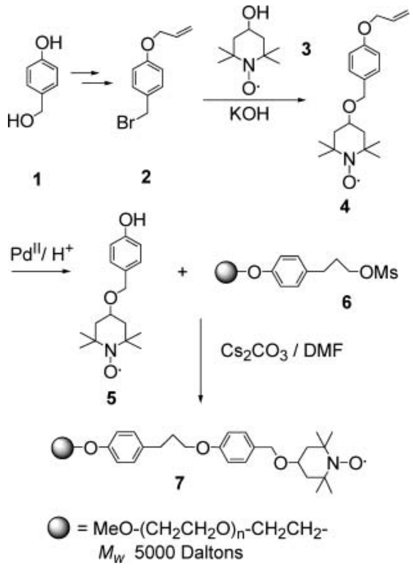
(TCCA),[8] Oxone,[9] or iodine[10]). However, separation of the products from TEMPO could require lengthy workup procedures, especially when reactions are run on large scale.[11] To solve this problem, TEMPO has been immobilized onto both inorganic[12] and organic polymers,[13] affording heterogeneous catalysts, which are readily separated from the reaction mixtures but are usually far less versatile than the homogeneous TEMPO.[14]

Over the past few years we have been interested in the development of both achiral[15] and chiral[16] organic catalysts immobilized on poly(ethylene glycol). Among the different polymeric matrixes employed in solid-phase chemistry, these soluble polymers recently emerged as very convenient supports for the synthesis of a variety of small organic molecules, ligands, and catalysts.[17] Poly(ethylene glycol)s (PEGs) of M_w greater than 2000 Da are readily functionalized, inexpensive polymers that feature convenient solubility properties, being soluble in many organic solvents and insoluble in a few other solvents. Therefore, the choice of proper solvent systems makes it possible to run a reaction under homogeneous catalysis conditions (where the PEG-supported catalyst is expected to perform at its best) and then to recover the catalyst as if it were bound to an insoluble matrix.[18] We wish to report here the synthesis of a PEG-supported TEMPO (2,2,6,6-tetramethypiperidine-1-oxyl) and its use as a highly efficient, recoverable, and recyclable catalyst in oxidation reactions.

On the basis of our previous experience in the field,[19] we decided to connect TEMPO to a properly modified poly(ethylene glycol) through a linker, as depicted in Scheme 1.

Scheme 1. Synthesis of PEG-Supported TEMPO **7**



The *p*-allyloxy benzyl bromide **2**, easily prepared from commercially available *p*-hydroxy benzyl alcohol **1** in two steps in 90% overall yield,[19] was reacted with **3** and NaOH in the presence of tetrabutylammonium bromide to give **4** in 65% yield. After Pd^{II}-catalyzed deprotection of the *O*-allyl protective group (73% yield), the phenol **5** was attached to the modified poly(ethylene glycol) mesylate derivative **6**[19] through reaction with Cs_2CO_3 in *N*,*N*-dimethylformamide to give the PEG-supported TEMPO **7** in 87% yield.[20] As expected, this new compound is soluble in organic solvents such as CH_2Cl_2 and AcOH but insoluble in ethers and hexanes.

PEG-TEMPO **7** proved to be an effective catalyst for the selective oxidation of 1-octanol with various stoichiometric oxidants (Table 1), affording octanal in good yields and short reaction times. The observed activity of the polymer-immobilized catalyst was generally similar to that of TEMPO, as in the case of TCCA (entry 5) when **7** (1 mol %) gave results in full agreement to those obtained under standard reaction conditions. However, a few points are worth noting. When BAIB was used as the terminal oxidant and MTBE as a solvent, the catalyst (5 mol %) was not active (entry 1). Thus, in contrast to other organic polymers,[13] PEG-TEMPO **7** cannot be used as an heterogeneous catalyst. The influence of the solvent system on the oxidation of 1-octanol with BAIB (entries 2−4) was quite unexpected: CH_2Cl_2 gave good results (entry 2), but the use of AcOH (entry 3) did not enhance the oxidation rate, despite the remarkable effect this solvent shows in reactions run with free TEMPO.[7] On the other hand, the reaction proceeded faster upon addition of small amounts of AcOH to the CH_2Cl_2 solution (entry 4). It was under these conditions that recycling of PEG-TEMPO **7** was studied. Indeed, since an incomplete conver-

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Table 1. PEG-TEMPO **7**-Catalyzed Oxidation of 1-Octanol to Octanal Using Various Terminal Oxidants

entry	oxidant	solvent	time	conversion (%)[a]	yield (%)[a]
1	BAIB[b]	MTBE	5 h		
2	BAIB	CH_2Cl_2	1 h	79	77
3	BAIB	AcOH	1 h	64	58
4	BAIB	CH_2Cl_2/AcOH[c]	1 h	93	89
5	TCCA[d]	CH_2Cl_2	15 min	100	96
6	NaOCl[e]	CH_2Cl_2/H_2O	10 min	100	91
7	NaOCl[f]	CH_2Cl_2/H_2O	30 min	98	95

[a] Determined by GC (internal standard method). [b] BAIB = bis(acetoxy)-iodo]benzene (1.1 mol equiv with respect to the substrate; see ref 7). [c] AcOH = 2.5 mol equiv with respect to BAIB. [d] TCCA = trichloroisocyanuric acid (1.05 mol equiv with respect to the substrate; see ref 8b). [e] 1.25 mol equiv with respect to the substrate; cocatalyst = KBr (see ref 5a). [f] 1.25 mol equiv with respect to the substrate, bromide-free conditions.

Table 2. PEG-TEMPO **7**-Catalyzed Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds Using Bromide-Free NaOCl as Terminal Oxidant

entry	alcohol	conversion (%)[a]	yield (%)[b]
1	benzyl alcohol	100	>98 (83)
2	1-phenylethanol	100	>98 (93)
3	benzyl alcohol/1-phenyl ethanol[c]	98/17	96/16
4	4-bromobenzyl alcohol	100	>98 (91)
5	1-undecanol	100	93
6	cinnamyl alcohol	67	28
7	2-undecanol	100	>98
8	2-octanol	96	94
9	cyclohexanol	100	>98
10	cyclooctanol	100	>98 (78)

[a] Determined by GC (internal standard method). Reaction time = 30 min. [b] Determined by GC (internal standard method). Isolated yields in parentheses. [c] Competition experiment (1:1 mixture of alcohols).

sion was observed with the fresh catalyst, any loss of activity would have been easily detected. Constant conversions and yields were obtained in the oxidation of 1-octanol carried out in seven subsequent runs with a reaction time of 60 min, using the catalyst easily recovered by addition of Et_2O to the reaction mixture, followed by filtration and washing of the solid with Et_2O (see Supporting Information). The amount of catalyst recovered after seven subsequent runs was slightly lower than the initial (<10%). Such a weight reduction was possibly due to mechanical losses occurring during the repeated filtration of the precipitated catalyst.

TEMPO-catalyzed oxidation of alcohols to carbonyl compounds with buffered aqueous NaOCl has found broad application, even on large-scale operations. Indeed, this selective methodology involves the use of safe, inexpensive inorganic reagents under mild reaction conditions. When PEG-TEMPO **7** (1 mol %) was employed as a catalyst in combination with KBr (10 mol %) and a slight excess of buffered bleach (pH = 8.6) as the terminal oxidant, partial overoxidation of 1-octanol to octanoic acid was observed (entry 6).[21] This can be avoided either by using a stoichiometric amount of NaOCl or, more conveniently, working under bromide-free conditions (entry 7). Although slightly decreased, the oxidation rate remains high even in the absence of KBr.

We next examined the oxidation of a variety of alcohols with buffered bleach under bromide-free conditions (Table 2). All reactions were carried out at 0 °C in the presence of 1 mol % of catalyst and 1.25 mol equiv of terminal oxidant. Under these conditions, most alcohols were quantitatively oxidized within 30 min, as found in the case of 1-octanol. After this reaction time, the catalyst was precipitated out from the organic layer by addition of Et_2O and eliminated by filtration. GC yields were consistently high for both primary and secondary alcohol and were in good agreement with those obtained in further preparative experiments run on a 3-mmol scale (entries 1, 2, 4, and 10). The quick separation of the polymer-supported catalyst greatly simplified the recovery of the products, which were isolated pure after column chromatography using a short pad of silica gel.

PEG-TEMPO **7** showed a good selectivity in the competitive oxidation of primary and secondary benzylic alcohols (entry 3), in analogy with the behavior of the unsupported parent compound. The strong resemblance of **7** with free TEMPO is further stressed by the outcome of the oxidation of cinnamyl alcohol (entry 6). The scanty aldehyde yield (28%), which is due to the competitive addition of hypohalogenous acids to the double bond, compares to that previously obtained with TEMPO (20%).[5a]

In conclusion, we have successfully immobilized a stable free nitroxyl radical on commercially available poly(ethylene glycol).[22] This readily prepared polymer-supported organic catalyst combines the advantages already demonstrated for heterogenized TEMPO (simplified workup of the reaction mixture, catalyst recycling) with those of the soluble parent compound (versatility, selectivity, and high activity under mild, environmentally safe reaction conditions).

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Supporting Information Available: Synthesis and characterization of polymer-supported compound **7** and general procedures for oxidation reactions and catalyst recycling. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) It should be noted that the oxidation of aldehydes to carboxylic acids is remarkably slow when TEMPO is used as the catalyst under the same conditions (ref 5a). However, the addition of a phase-transfer catalyst leads to reaction completion in a few minutes; the PEG portion of **7** could play a similar role. We are currently investigating this particular behavior of the PEG-immobilized catalyst.

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