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Poly(ethylene glycol)-Supported Nitroxyls: Branched Catalysts for the Selective Oxidation of Alcohols

Pedro Ferreira,[†] Emyr Phillips,[‡] David Rippon,[‡] Shik Chi Tsang,*[,†] and Wayne Hayes*[,†]

School of Chemistry, The University of Reading, Whiteknights, Reading RG6 6AD, U.K., and
A. H. Marks and Company Ltd., Wyke, Bradford BD12 9EJ, U.K.

w.c.hayes@rdg.ac.uk

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Nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) are highly selective oxidation catalysts for the conversion of primary alcohols into the corresponding aldehydes. In this study, direct tethering of TEMPO units onto linear poly(ethylene glycol) (PEG) has afforded macromolecular catalysts that exhibit solubility in both aqueous and organic solvents. Recovery of the dissolved polymer-supported catalyst has been carried out by precipitation with a suitable solvent such as diethyl ether. The high catalyst activities and selectivities associated traditionally with nitroxyl-mediated oxidations of alcohols are retained by the series of "linker-less" linear PEG-TEMPO catalysts in which the TEMPO moiety is coupled directly to the PEG support. Although the selectivity remains unaltered, upon recycling of the linker-less polymer-supported catalysts, extended reaction times are required to maintain high yields of the desired carbonyl compounds. Alternatively, attachment of two nitroxyl radicals onto each functionalized PEG chain terminus via a 5-hydroxyisophthalic acid linker affords branched polymer-supported catalysts. In stark contrast to the linker-less catalysts, these branched nitroxyls exhibit catalytic activities up to five times greater than 4-methoxy-TEMPO alone under similar conditions. In addition, minimal decrease in catalytic activity is observed upon recycling of these branched macromolecular catalysts via solvent-induced precipitation. The high catalytic activities and preservation of activity upon recycling of these branched systems is attributed to enhanced regeneration of the nitroxyl species as a result of *intra*molecular *syn*-proportionation.

Introduction

The selective oxidation of primary and secondary alcohols into the corresponding aldehydes (or carboxylic acids) or ketones is a key transformation in modern organic synthesis.[1] 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) radicals such as 4-methoxy-TEMPO (**1**) have been used extensively to catalyze the oxidation of a number of alcohol substrates[2] employing co-oxidants including *m*-CPBA,[3] hypochlorite,[4] and molecular oxygen.[5] Alternatively, electrochemical regeneration of nitroxyls has also been described as a suitable oxidative protocol.[6]

The selectivity of TEMPO-mediated oxidations of primary alcohols can be tailored in order to produce the corresponding aldehydes or, if desired, extended to afford the carboxylic acid derivatives by controlling the amount of stoichiometric oxidant used in the process. Furthermore, nitroxyl-mediated oxidations in nonacidic media are highly chemoselective as the rate of oxidation of primary alcohols is several orders of magnitude higher than for secondary alcohols, thereby enabling the direct selective oxidation of primary versus secondary alcohols and obviating the requirement of time-consuming protecting group chemistries.[2]

Several TEMPO catalyst systems have been described that address catalyst recovery and simplification of product isolation. Notable examples of heterogeneous TEMPO catalysts include TEMPO supported on silica,[7] MCM-41,[8] and sol−gel entrapped TEMPO species.[9] However, in recent years, the development of soluble homogeneous polymer supported species[10] has been the focus

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* To whom correspondence should be addressed. Tel: ++44 1183786491. Fax: ++44 118 3786331.

[†] The University of Reading.

[‡] A. H. Marks and Company Ltd.

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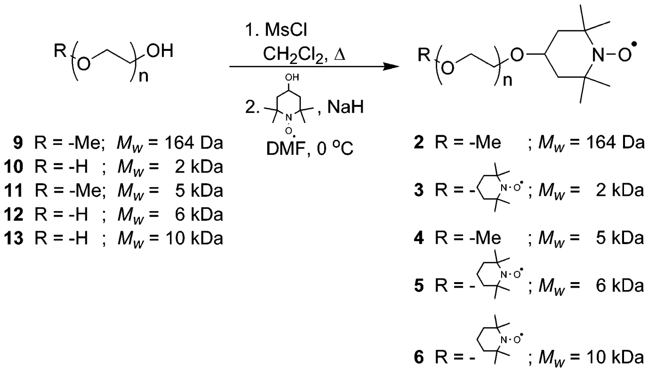
of extensive research in order to provide alternatives to heterogeneous supported reagents and catalysts.[11] Increased solvent compatibility and enhanced rates of reaction are observed frequently in the case of soluble homogeneous supports when compared with heterogeneous analogues.[12] Though the presence of the macromolecular support has, in general, a detrimental effect upon the rates of reaction when compared to unsupported species, this limitation is outweighed generally by the ease of separation associated with macromolecular supports including solvent precipitation followed by simple filtration procedures.[13] Recent examples of soluble polymer-supported TEMPO catalysts for the selective oxidation of alcohols include the polymer-immobilized piperidinyl oxyl (PIPO),[14] polymer-supported TEMPO obtained by ROMP of nitroxyl-functionalized norbornene monomers,[15] and more recently, a PEG-linker-TEMPO[16] system has also been described.

Herein we report two different types of PEG-supported nitroxyl catalysts for the oxidation of alcohols by hypochlorite/bromide under biphasic conditions (water−CH_2Cl_2). PEG is well-suited for this application as a result of the high solubility displayed by the polymer in both solvents required by this type of oxidation protocol. A series of catalysts has been prepared wherein the TEMPO residue is attached directly to the polymer chain terminus via an ether linkage. This group of catalysts was composed of PEG supports of different molecular weights, possessing either one or two hydroxyl functionalities per polymer chain and hereby referred to as the linear "linker-less" PEG-TEMPO systems (**2**−**6**). An alternative group of PEG-supported nitroxyl catalysts, referred to in this paper as "branched" PEG-TEMPO systems (**7** and **8**), features an aromatic hub unit that doubles the loading capacity of the PEG macromolecular support. These macromolecular catalysts were subsequently applied in the selective oxidation of a number of representative alcohols by hypochlorite in biphasic media (water−CH_2Cl_2). In addition, the recyclability of selected catalysts was investigated by means of solvent precipitation, and the results obtained are also reported.

Results and Discussion

Synthesis of PEG-Supported Catalysts. Poly(ethylene glycol) exhibits high solubilities in a range of organic solvents (as well as water), and consequently, a large number of PEG end-group chemistries have been described.[13] Our initial studies involved the synthesis of linear linker-less PEG-supported nitroxyl moieties.[17] These compounds were accessible through a simple two-step synthetic route (Scheme 1), and thus, the terminal hydroxyl functionalities in the PEG chains were converted to the corresponding mesyl esters following methodology described by Janda and co-workers.[18] These macromolecular sulfonyl esters could either be isolated or used in situ upon removal of the excess MsCl. When treated with an excess of the alkoxide of 4-hydroxy-TEMPO, the sulfonyl esters afforded the desired ethers **2**−**6** in high yields (>90% based on polymer recovery).

SCHEME 1



It was observed that reaction of 4-chloro- or 4-methanesulfonyl-TEMPO derivatives with alkyl and 4-substituted phenolic alcohols resulted in elimination of the halogen or methanesulfonic acid moieties with formation of 2,2,6,6-tetramethyl-3,4-dihydropiperidin-1-oxyl as the major product. These observations precluded the use of a route analogous to that reported by Gitsov et al.[19] in which 3,5-dihydroxybenzoic acid was used to construct branched polyesters. Instead, the synthesis of catalysts **7** and **8** bearing two nitroxyl radicals per polymer chain end was investigated via the use of 5-hydroxyisophthalic acid (**14**) as the linker between the polymer chain and the radical residues (Scheme 2). It was observed that attachment of the aromatic hub to the polymer support prior to esterification with the nitroxyl radical moiety simplified the synthesis of these macromolecular catalysts. However, protection of the acid functionalities of 5-hydroxyisophthalic acid as the corresponding methyl esters was required in order to maximize coupling of the hub unit onto the PEG supports. Following the procedure of Mazik and Sicking,[20] the acid chloride derivative of **14** was prepared in situ and addition of cold methanol afforded the methyl ester protected 5-hydroxyisophthalate **15** in excellent yield (>90%). The isophthalate **15** was then dissolved in acetone and reacted with the PEG-supported mesyl esters in the presence of K_2CO_3 to afford the corresponding PEG-supported dimethyl isophthalates **16** and **17**, and the PEG-supported isophthalic acids **18** and **19** were obtained subsequently by in situ alkaline hydrolysis of the methyl esters. Finally, conversion of the

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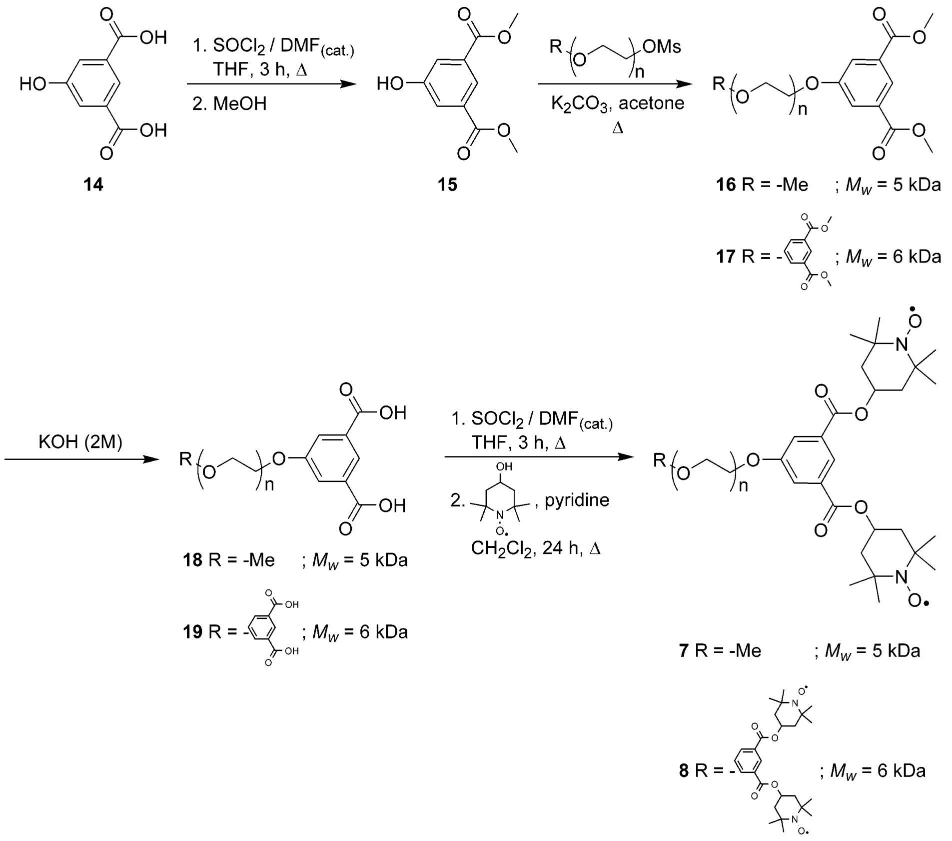
SCHEME 2



carboxylic acids to acid chlorides followed by addition of 4-hydroxy-TEMPO in the presence of pyridine afforded the polymer-supported diradical **7** and tetraradical **8** in yields of 92 and 95%, respectively (based upon polymer recovery).

Although more lengthy, the route involving 5-hydroxyisophthalic acid was preferred to an alternative reported recently by Gitsov and co-workers, regarding the use of 3,5-dihydroxybenzoic acid.

The catalytic activity and recyclability of the polymer supported nitroxyls **2**−**8** in the hypochlorite oxidation of alcohols under biphasic conditions (water−CH_2Cl_2) was then studied. For comparative purposes, 4-methoxy-TEMPO (**1**) was included in our studies. All reactions were performed at constant temperature (0 °C) with a constant nitroxyl concentration (1 mol %) with respect to the alcohol so that any effect of the presence of the polymer support and catalyst architecture could be determined. Thus, the catalyst (0.008 mmol in nitroxyl), alcohol (0.8 mmol), and internal standard (either decane or tetradecane) for GC analysis (0.1 mmol) were added to the organic layer. After the mixture was cooled to 0 °C, the bromide cocatalyst (0.08 mmol) and buffered NaOCl aqueous solution (1.0 mmol, 1.25 equiv with respect to the alcohol substrate) were added. The concentration of the various reagents was such that approximately equal volumes of organic phase (2.00 mL) and aqueous phase (2.16 mL) were utilized. The reaction mixture was then stirred vigorously for 5 min in the case of primary alcohols and 10 min in the case of secondary alcohols, unless otherwise stated.

Catalytic Activity of PEG-Supported TEMPO Catalysts. Nitroxyl radicals have been shown to oxidize alcohols to the corresponding carbonyl compounds in a catalytic manner, and several oxidation procedures have been described that afford the regeneration of the radical (vide supra). The hypochlorite-mediated oxidation of alcohols under biphasic conditions (water−CH_2Cl_2) has, however, been the preferred method for this type of oxidation.[2] Mild conditions (pH = 8−9; T = 0 °C) and high reaction rates have enabled the oxidation of a wide range of alcohols in addition to the demonstration of tolerance toward a wide range of functionalities and protecting groups.[2] The biphasic nature of this highly active oxidative system facilitates removal of the spent inorganic oxidant by simple phase-separation techniques. In addition, efficient product isolation from the catalyst used was desirable, and to this end a number of heterogeneous catalysts which can be separated from the oxidation products by filtration have been described. Furthermore, several catalysts have been reported[14−16] (vide supra) which maintain the ease of separation typically associated with these heterogeneous systems while preserving the nitroxyl solubility during the catalysis.

Linear Linker-less PEG-Supported TEMPO Systems. In our earlier studies,[17] a number of linker-less PEG-supported nitroxyls were developed whereby the active TEMPO residue was attached directly to the terminal alcohol residues of the polymer chain through an ether bond. This methodology afforded a simple synthetic route to PEG-supported nitroxyls that exhibited chemical stabilities similar to that of 4-methoxy-TEMPO (**1**). These catalysts (**2**−**6**) were effective catalysts in the selective oxidation of a number of aliphatic, allylic, and aromatic primary alcohol functionalities (Figure 1).

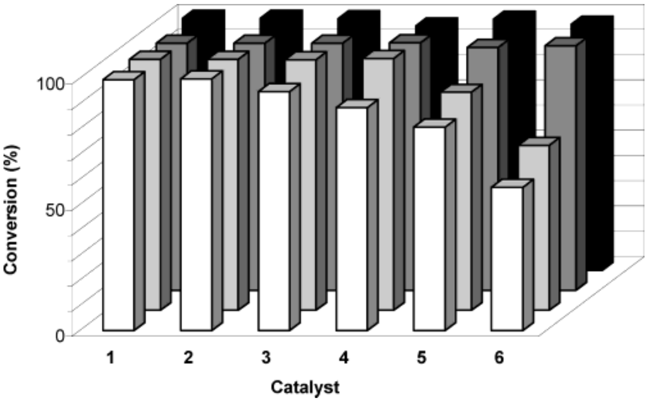


FIGURE 1. Conversion (%) of (black) 1-undecanol, (dark gray) geraniol, (light gray) benzyl alcohol, and (white) cyclohexylmethanol obtained after 5 min of reaction for 4-methoxy-TEMPO (**1**) and the polymer-supported catalysts **2**−**6**. Conversions determined by GC analysis (using an internal standard method).

In agreement with the results obtained for the reference catalyst **1**, the low molecular weight (≤2 kDa) polymeric catalysts **2** and **3** exhibited nearly complete conversion of the alcohol substrates studied to the corresponding aldehydes. However, for the same reaction conditions, higher molecular weight ($5 \leq M_w \leq 10$ kDa) catalysts **4**−**6** afforded complete conversions (>96%) only for unhindered substrates such as 1-undecanol and geraniol, whereas incomplete conversions were obtained for the more sterically demanding substrates benzyl alcohol and cyclohexylmethanol.

Inspection of the catalytic data for **6** ($M_w = 10$ kDa) presented in Figure 1 revealed a significantly lower conversion for benzyl alcohol (66%) when compared to geraniol (97%). Furthermore, comparable yields were obtained in the oxidation of cyclohexylmethanol (57%) and benzyl alcohol as well as 1-undecanol (98%) and geraniol. These data suggested that steric rather than electronic factors limit the rate of oxidation of these substrates, in good agreement with the mechanistic studies reported by Semmelhack and co-workers,[21] where the rate-limiting step in this type of oxidations was attributed to the formation of an intermediate such as **20** (Scheme 3). The formation of such an adduct is consistent with rates of oxidation depending upon steric crowding around the hydroxyl functionality. In the case of the PEG-supported nitroxyls (**2**−**6**) reported, as a result of the absence of a spacer group between the TEMPO residue and the polymer chain, increase in molecular weight had a negative effect upon the rate of oxidation. Thus, an intermediate behavior was observed for catalysts **4** ($M_w = 5$ kDa) and **5** ($M_w = 6$ kDa), whereby a gradual decrease in the rate of oxidation was observed as the molecular weight of the macromolecular support increased. Furthermore, the presence of one (catalysts **2** and **4**) or two nitroxyls per polymer chain (catalysts **3**, **5**, and **6**) had minimal influence upon the total rate of reaction and thus dependence upon the molecular weight of the polymer was the principal phenomenon observed (Figure 1).

TABLE 1. Oxidation of 2-undecanol by Catalysts 1−6

catalyst	substrate	time (min)	yield[a] (%)	TOF[b] (min^{-1})
1	2-undecanol	10	85.7	8.6
2		10	77.5	7.8
3		10	48.5	4.8
4		10	24.0	2.4
5		10	52.4	5.2
6		10	51.3	5.1

[a] Yields of 2-undecanone determined by GC (internal standard method). [b] TOF = turnover frequency.

The oxidation mechanism[21] (Scheme 3) involved conversion of the nitroxyl species **21** to the active oxoammonium ion **22** which in turn oxidizes the alcohol functionality to the corresponding carbonyl functionality via an adduct such as **20** to afford the hydroxylamine **23**. Regeneration of **21** proceeds through a *syn*-proportionation process where **22** and **23** combine to afford two molecules of **20**.

In contrast to the oxidation of primary alcohols, the rate of oxidation of 2-undecanol to the corresponding ketone was lower (Table 1), a result that was consistent with related nitroxyl-mediated oxidations carried out in nonacidic media.[4,21] In a fashion similar to the results obtained for the oxidation of primary alcohols, decreasing

SCHEME 3. Mechanism of the Hypochlorite Oxidation of Alcohols Mediated by Nitroxyl Radicals

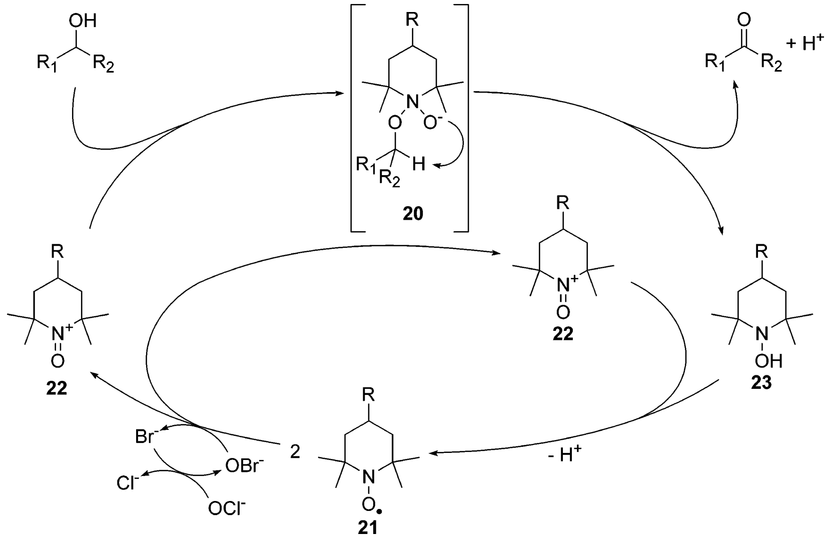


TABLE 2. Recyclability of Catalyst 6 in the Oxidation of Benzyl Alcohol

reaction	substrate	time (min)	yield[a] (%)	TOF (min^{-1})
1	benzyl alcohol	5	81.0	16.2
2		5	34.6	6.9
3		5	26.4	5.3
4		5	30.8	6.2
5		5	26.0	5.2

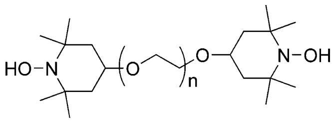
[a] Yields of benzaldehyde determined by GC (using an internal standard method).

yields of 2-undecanone were observed as the molecular weight of the polymeric catalyst increased. Catalysts **1** and **2** afforded high yields of 2-undecanone (86 and 78%, respectively) after a reaction time of 10 min, whereas for higher molecular weight catalysts ($M_w \geq 2$ kDa) lower yields (<55%) of the ketone were obtained under similar reaction conditions (Table 1). Although the concentration in nitroxyl radical was constant in all of the experiments reported in this study (1 mol % with respect to the substrate), similar yields were obtained for catalysts **3** ($M_w = 2$ kDa), **5** ($M_w = 6$ kDa), and **6** ($M_w = 10$ kDa), all bearing two nitroxyl functionalities per polymer chain. Interestingly, the monofunctional catalyst **4** ($M_w = 5$ kDa) afforded a very low yield of 2-undecanone (24%). Unlike the oxidation of primary alcohols whereby a gradual decrease in the yield of hindered primary alcohols was observed as the molecular weight of the polymer support increased (vide supra), in the case of secondary alcohols this effect was less pronounced and catalysts **3**−**6** exhibited similar rates of oxidation.

The recyclability of the linear PEG-TEMPO systems was studied in the oxidation of benzyl alcohol mediated by **6**[4] under standard conditions as described above. In light of the high solubility of PEGs in water and in order to minimize catalyst loss, at the end of the reaction the organic solvent was isolated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were then concentrated, and the catalyst precipitated from solution with diethyl ether. This methodology afforded consistently high recovery yields (≥98%) of the polymeric-supported catalyst. The catalyst could then be reused without further treatment for four subsequent reactions and the results obtained are presented in Table 2.

A noticeable decrease in the rate of oxidation from the first to the second reaction was observed. However, in subsequent reactions (Table 2) the yields remained roughly constant at 29 ± 4% and the catalyst exhibited an average TOF of 5.9 ± 0.8 min^{-1}.

Characterization of the used catalyst at the end of the first reaction by MALDI-TOF mass spectrometry revealed that it retained the average molecular weight and polydispersity of the starting catalyst, and thus catalyst deactivation through detachment of the nitroxyl moiety from the polymer support was not occurring. However, in contrast to the starting catalyst which possessed a pale orange coloration attributable to the presence of the nitroxyl radical, the recovered catalyst was a white solid and IR spectroscopic analysis of this catalyst did not reveal the characteristic stretching frequency associated with the N−O group of nitroxyl moiety (1467 cm^{-1}). Instead, a band of medium intensity was observed at 1372 cm^{-1} which could be attributed to the stretching frequency of the N−O bond in an hydroxylamine, suggesting that the PEG-supported species **6a** was recovered (Figure 2).



6a, M_w = 10 kDa

FIGURE 2. PEG-supported hydroxylamine **6a** obtained by reduction of catalyst **6**.

To improve our understanding of the nature of this drop in catalytic activity, a sample of the catalyst **6** was reduced to **6a** using ascorbic acid in methanol and then isolated via precipitation with diethyl ether. This reduced catalyst was then used under identical biphasic reaction conditions as in the case of the original linker-less PEG-TEMPO catalyst to oxidize selectively benzyl alcohol to benzaldehyde using hypochlorite. The yield and TOF values obtained for the reduced linker-less PEG-TEMPO system (37.5% and 7.5 $min.^{-1}$, respectively) were in good agreement with those recorded previously for reactions 2−5 (Table 2) of catalyst **6**. Furthermore, catalyst **6** was employed in two consecutive reactions under the conditions described above. In the first reaction, benzyl alcohol was converted to benzaldehyde in 81% and a TOF of 16.2 min^{-1} was observed. The catalyst was then isolated by precipitation with diethyl ether and reused without further treatment, but a prolonged reaction time (13 instead of 5 min) was then employed to allow conversion of the alcohol to the desired aldehyde in 87% yield, and a TOF of 6.9 min^{-1} was determined. These data further suggest that the low activity observed for the recycled catalysts is related to the formation of the hydroxylamine and/or occlusion of these chain ends by the polymer backbone during the solvent induced precipitation of the catalyst. Although only moderate conversions were observed for reduced reaction times (5 min), higher yields of aldehyde could be obtained readily upon a small increase in the time of reaction (10−15 min). These results led to the conclusion that regeneration of the hydroxylamine **23** species to the nitroxyl radical **21** via *syn*-proportionation (Scheme 3) was slow in the recovered catalysts, and consequently, a longer induction period might be required in the subsequent reactions employing the recycled catalysts. In a related study of supported TEMPO catalysts, Brunel and co-workers indeed observed[8b] an induction period during the oxidation of α-methyl glucoside mediated by MCM41-supported TEMPO catalysts. This induction period was attributed to the catalyst containing high hydroxylamine contents. Nevertheless, Brunel and co-workers noted that high conversions (>80%) were achieved after a period of 10 min, in good agreement with our observations.

Since the hydroxylamine is involved in the catalytic cycle and high yields of the desired aldehydes were only obtained when fresh catalyst was used, occlusion of the hydroxylamine chain ends within the PEG backbone during catalysis was ruled out. Instead it is suggested that the collapse of the helical structure of PEGs during

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TABLE 3. Oxidation of Alcohols Mediated by Branched PEG-TEMPO Catalysts 7 and 8

		catalyst								
		1			**7**			**8**		
entry	substrate	time[a]	yield[b]	TOF[c]	time[a]	yield[b]	TOF[c]	time[a]	yield[b]	TOF[c]
1	1-undecanol	5	>99.0	19.8	3	97.5	32.5	1	>99.0	99.0
2	*trans*-geraniol	5	98.2	19.6	2	79.3	39.6	0.8	82.7	103.4
3	benzyl alcohol	5	>99.0	19.8	1.5	91.6	61.1	1	>99.0	99.0
4	cyclohexylmethanol	5	>99.0	19.8	2	74.7	37.4	1	90.9	90.9
5	2-undecanol	10	85.7	8.6	5	31.4	6.3	5	47.5	9.5

[a] Time of reaction in minutes. [b] Yields (%) were determined by GC analysis. The aldehydes and ketones were the only products observed in the oxidation of primary and secondary alcohols, respectively. [c] Turnover frequency (min^{-1}) calculated for the total time of reaction indicated.

the precipitation process increases the potential for hydrogen bonding[22] between the terminal hydroxylamine moieties and the PEG backbone. Furthermore, such conformational change could result in occlusion of the terminal hydroxylamine residue from solution upon redissolution of the polymer and consequently sluggish reoxidation of this species to the nitroxyl radical. The formation of hydrogen bonds between terminal moieties and the polymer backbone has been observed previously, where an increase in the nucleophilic character of terminal amino groups of PEG-supported amino acids[13] has been attributed to hydrogen-bonding interactions to the PEG backbone.

Branched PEG-TEMPO Systems. The results obtained for the studies in the linear linker-less PEG-supported TEMPO systems led to the investigation of the use of a branched linker system in order to facilitate catalyst regeneration in situ within the catalyzed oxidation reaction. Rozantsev and co-workers have described the synthesis and characterization of a number of compounds bearing multiple TEMPO units such as tris(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl) trimesate in which intramolecular spin exchange between the nitroxyls was attributed to the close proximity of the multiple radicals.[23] In light of these reports, a branched linker system (5-hydroxyisophthalic acid) located between the active TEMPO species and the PEG supports was investigated. The use of this linker unit presents several advantages as it (i) doubles the loading of any PEG support, (ii) provides a bulky group in the end of the polymer chain, and (iii) brings two nitroxyls into close proximity. An increase in the polymer loading allowed for a decrease in the total mass of macromolecular catalyst required to maintain the content on nitroxyl in the reaction—particularly beneficial for scale-up applications. The introduction of bis(2,2,6,6-tetramethyl-1-oxyl-4-piperidinyl)-5-hydroxyisophthalate provides a bulky end-group reducing the possibility of occlusion of the catalytic centers by the polymer matrix previously proposed for the linker-less systems (vide supra). The close proximity of the nitroxyls in the bis(2,2,6,6-tetramethyl-1-oxyl-4-piperidinyl)-5-hydroxyisophthalate moiety also gives rise to the possibility of catalyst regeneration through *intra*molecular rather than the more spatially restricted *inter*molecular *syn*-proportionation mechanism (vide supra).

Two different PEG polymers of comparable molecular weight were used as supports for these branched catalysts. Whereas the first support (MeO-PEG$_{5000}$-OH) featured only one free hydroxyl functionality, the second support (HO-PEG$_{6000}$-OH) possessed free hydroxyl moieties at both chain ends thus allowing for the synthesis of **7** and **8** (Scheme 2) that featured two and four nitroxyl residues per polymer chain, respectively. These catalysts were then used in the hypochlorite oxidation of alcohols in biphasic media using the experimental conditions identical to those described for the linear linker-less PEG-TEMPO catalytic systems. The results obtained are summarized in Table 3.

With catalysts **7** or **8** (Table 3, entries 1−4), oxidation of primary alcohols reached completion within a shorter time than that required for 4-methoxy-TEMPO (**1**). The end point of the reaction could be determined colorimetrically by the disappearance of the characteristic yellow color (attributed to the presence of the oxoammonium ion) formed upon addition of hypochlorite to the stirred solution of the alcohol and catalyst. Under these conditions the oxidation of primary alcohols proceeded rapidly and high yields of aldehyde were obtained upon addition of the stoichiometric oxidant. Complete conversions of 1-undecanol and benzyl alcohol to the corresponding aldehydes were achieved in 1 min when the reaction was catalyzed by the branched tetraradical **8**. This contrasts with 4-methoxy-TEMPO (**1**), where complete conversion of these substrates required up to 5 min under otherwise identical conditions. Although the biradical **7** was slightly less active than the tetraradical **8**, the typical TOF for the oxidation of primary alcohols mediated by **7** was twice as much than observed for **1**. The differences in activity are even more pronounced when the branched catalysts **7** and **8** are compared with the corresponding linear linker-less analogues **4** and **5**, respectively. In general, a 2-fold increase in the TOFs for the branched catalyst **7** is observed when compared to catalyst **4**. Similarly, the TOFs obtained for **8** are on average five times higher than those calculated for the linker-less catalyst **5**. These results are remarkable since all experiments were performed with an equal content of nitroxyl radical (1 mol % with respect to the alcohol substrate). Thus, the results suggested that the presence of the bis-nitroxyl hub unit has a significant influence in the rate of oxidation of primary alcohols. Surprisingly, the oxidation of 2-undecanol mediated by the branched catalysts **7** and **8** revealed TOFs of the same order of magnitude (Table 3, entry 5) as those observed for **1** and the linear linker-less macromolecular catalysts **2**−**6** (Table 1). The results

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[22] Klok, H.-A.; Joliffe, K. A.; Schauer, C. L.; Prins, L. J.; Spatz, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 7154.

[23] Rozantsev, E. G. *Free Nitroxyl Radicals*; Plenum Press: New York, London, 1970.

TABLE 4. Recyclability of 8 in the Oxidation of Benzyl Alcohol

reaction	substrate	time (min)	yield[a] (%)	TOF (min^{-1})
1	benzyl alcohol	1	>99.0	99.0
2		1	98.6	98.6
3		1	98.1	98.1

[a] Yields of benzaldehyde determined by GC analysis.

obtained for the oxidation of 2-undecanol were, however, in good agreement with the mechanism of oxidation described by Semmelhack and co-workers[21] in which a transition-state was proposed whereby the rate of the intramolecular proton abstraction on the carbon bearing the alcohol functionality by the TEMPO adduct **20** (Scheme 3) could govern the overall rate of reaction. It was noted that for bulky substrates, such as secondary alcohols, this could be the rate-limiting step whereas for less hindered primary alcohols the rate of proton abstraction would be comparable to that of the formation of adduct **20**. In this study, the concentration of nitroxyl was kept constant and, therefore, similar rates of oxidation of 2-undecanol were anticipated for all catalysts in good agreement with the mechanism. The small differences registered could be attributed to the accessibility of the nitroxyl species as a result of the presence of the bulky polymer chain.

The recyclability of the branched systems was investigated in the selective oxidation of benzyl alcohol to benzaldehyde under biphasic conditions by the catalyst **8**. After completion of the reaction, the catalyst was isolated by precipitation with diethyl ether followed by filtration in a fashion similar to the procedure used for catalyst **6**. The catalyst was then reused without further treatment in two subsequent reactions with benzyl alcohol (Table 4).

In contrast to the recyclability results obtained for the linear linker-less PEG-TEMPO catalyst **6**, minimal deactivation was observed in this branched system **8**. Characterization of the recycled catalyst by MALDI-TOF mass spectrometry after the three cycles revealed that the catalyst retained the average molecular weight and polydispersity. The slight decrease in conversion (ca. 2%) after three reactions catalyzed by **8** can be attributed to mechanical losses in recovering small amounts of catalyst. The consistency of yields exhibited by the recycled catalyst **8** contrasts with the low initial activity registered upon recycling of the linear linker-less catalyst **6**. The regeneration of the nitroxyl catalysts has been proposed[2] to proceed through a *syn*-proportionation step (Scheme 3). It is noted that one molecule of hydroxylamine **23** requires one molecule of oxoammonium salt **22** in order to regenerate the nitroxyl radical functionality **21**. This aspect of the mechanism of nitroxyl-mediated hypochlorite oxidation of alcohols in conjunction with Rozantsev's observations on tris(2,2,6,6-tetramethyl-1-oxyl-4-piperidyl) trimesate (vide supra) leads to the conclusion that the high activities of both fresh and recycled branched catalysts arose as a result of enhanced regeneration of the catalytic center. This hypothesis is in good agreement with the higher rate of oxidation of unhindered primary alcohols observed for the branched catalysts **7**-**8** compared to the linear systems **2**-**6** or 4-methoxy-TEMPO **1**. Whereas for linear linker-less systems, regeneration of the hydroxylamine during catalysis involves an *inter*molecular process that is dependent on the successful reaction between one molecule of hydroxylamine and an oxoammonium ion, in the branched catalysts regeneration of the active nitroxyl species can occur in an *intra*molecular fashion, thereby increasing greatly the rate of regeneration of the hydroxylamine resulting in high catalytic activities.

Conclusion

We have described the synthesis and catalytic activity of two types of PEG-supported nitroxyl catalysts. A series of linear linker-less PEG-TEMPO catalysts were prepared via a simple synthetic route and afforded stable catalysts where no leaching of nitroxyl from the polymeric support was observed. These catalysts displayed selectivities and activities similar to those observed typically for low molecular weight TEMPO derivatives such as **1**. Primary alcohols were oxidized selectively to the corresponding aldehydes in high yields. Whereas unhindered alcohols such as 1-undecanol and *trans*-geraniol were oxidized completely in a few minutes, more sterically constrained substrates such as cyclohexylmethanol or benzyl alcohol afforded only partial conversions within the same time of reaction. This selectivity was more pronounced with increase in molecular weight of the polymeric carrier. In contrast the oxidation of secondary alcohols proceeded in a rate comparable to that observed for 4-methoxy-TEMPO (**1**). An induction period was observed upon recycling of the linear systems was observed to slow oxidation of the hydroxylamine form of the catalyst, and constant activities were obtained in subsequent reactions. The branched PEG-TEMPO catalysts possessed several advantages over the linear linker-less systems. The higher polymer loading achieved through the use of the aromatic hub unit enabled the mass of catalyst required to maintain the nitroxyl concentration in the reaction media to be reduced. These branched systems proved to be highly effective catalysts and oxidation of primary alcohols reached completion rapidly for all substrates tested. The presence of two nitroxyl radicals per polymer chain end noticeably increased the rate of oxidation of primary alcohols and activities up to five times higher were observed for the branched catalysts when compared to 4-methoxy-TEMPO (**1**). In a fashion similar to the results obtained for the linear linker-less PEG-TEMPO systems, the oxidation of secondary alcohols by the branched catalysts proceeded at a rate comparable to that of catalyst **1**. The recyclability of the branched PEG-TEMPO systems was also investigated. In contrast to the linear linker-less systems, no induction period was observed upon recycling of the branched PEG-TEMPO catalysts. The presence of the bulky end-groups did not affect catalyst recovery and precipitation of the polymer with diethyl ether afforded high yields of recovery of the catalyst. The high activity of fresh and recycled catalysts was attributed to the fast *intra*molecular regeneration of the catalyst through *syn*-proportionation.

Experimental Section

General Procedure for Preparing the Linear Linker-less PEG-TEMPO Ethers 2−6. To a suspension of NaH (16 mg, 0.2 mmol) in DMF (5 mL) was added 4-hydroxy-TEMPO

(34 mg, 0.2 mmol) and the resulting slurry stirred for 1 h at room temperature under inert atmosphere. PEG mesylate (**12a**, M_w = 6 kDa, 0.63 g, 0.1 mmol) was then added and stirring resumed for 48 h at room temperature. The suspension was then filtered and the filtrate concentrated under reduced pressure. This solution was then added to diethyl ether (100 mL) that was stirred vigorously and the precipitate collected by filtration, washed twice with diethyl ether (2 × 50 mL), and dried under vacuum. The product **5** was obtained as pale orange solid (0.56 g, 89% based on polymer recovery). T_g = 58.7 °C. ^{1}H NMR (DMSO-d_6) δ: 7.36−6.55 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.72 (m, 4H, PEG - α-methylenes), 3.61−3.09 (bm, PEG - methylenes), 1.89−1.82 (m, 4H, TEMPO - methylenes), 1.31−1.19 (m, 4H, TEMPO - methylenes), 1.08 (s, 12 H, TEMPO - axial methyls), 1.05 (s, 12 H, TEMPO - equatorial methyls). ^{13}C NMR (CDCl$_3$) δ: 155−110 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 70.6 (broad), 68.3, 61.7, 44.7, 29.7, 21.0. FTIR (cm^{-1}): 2883, 1467, 1344, 1280, 1242, 1149, 1114. MALDI-TOF MS M_w [**5** + K$^+$]: calcd 6822 Da, found 6817 Da. Calculated nitroxyl loading: 0.29 mmol·g^{-1}.

Ether 2. Isolated by column chromatography as a red oil (63 mg, 65% based on recovery). ^{1}H NMR (DMSO-d_6) δ: 7.39−6.52 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.64−3.41 (bm, 12H, triethylene glycol monomethyl ether - methylenes, m, 1H, TEMPO - methyne), 3.24 (s, 3H, triethylene glycol monomethyl ether - methyl) 1.90−1.83 (m, 2H, TEMPO - methylenes), 1.29−1.19 (m, 2H, TEMPO - methylenes), 1.08 (s, 6 H, axial TEMPO - methyls), 1.05 (s, 6 H, equatorial TEMPO - methyls). ^{13}C NMR (DMSO-d_6) δ: 155−110 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 71.7, 70.7, 70.6, 70.3, 70.2, 70.0, 67.2, 58.4, 58.3, 45.0, 32.9, 20.8. FTIR (cm^{-1}) 2887, 1467, 1344, 1278, 1246, 1149, 1113. MALDI-TOF MS (+20 kV, Reflectron) M [**2** + K$^+$]: calcd 357.19 Da, found 375.00 Da. Calculated nitroxyl loading: 2.67 mmol·g^{-1}.

Ether 3. Isolated as a pale orange solid (0.19 g, 85% based on polymer recovery). T_g = 51.3 °C. ^{1}H NMR (DMSO-d_6) δ: 7.35−6.61 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.74 (m, 4H, PEG - α-methylenes), 3.69−3.12 (bm, PEG - methylenes), 3.32 (s, 3H, PEG - methyl)1.91−1.82 (m, 4H, TEMPO - methylenes), 1.31−1.16 (m, 4H, TEMPO - methylenes), 1.07 (s, 12 H, axial TEMPO - methyls), 1.03 (s, 12 H, equatorial TEMPO - methyls). ^{13}C NMR (CDCl$_3$) δ: 155−110 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine) 70.6 (broad), 67.9, 61.4, 45.0, 29.1, 20.9. FTIR (cm^{-1}): 2883, 1467, 1344, 1280, 1242, 1148, 1114. MALDI-TOF MS M_w [**3** + K$^+$]: calcd 2314 Da, found 2313 Da. Calculated nitroxyl loading: 0.86 mmol·g^{-1}.

Ether 4. Isolated as a pale orange solid (0.49 g, 96% based on polymer recovery). T_g = 59.99 °C. ^{1}H NMR (DMSO-d_6) δ: 7.34−6.58 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.75 (m, 4H, PEG - α-methylenes), 3.68−3.15 (bm, PEG - methylenes), 1.89−1.79 (m, 2H, TEMPO - methylenes), 1.33−1.17 (m, 2H, TEMPO - methylenes), 1.08 (s, 6 H, axial TEMPO - methyls), 1.03 (s, 6 H, equatorial TEMPO - methyls). ^{13}C NMR (CDCl$_3$) δ: 155−110 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 72.0, 70.6 (broad), 68.7, 61.7, 59.1, 44.8, 29.0, 21.5. FTIR (cm^{-1}): 2885, 1467, 1360, 1344, 1280, 1242, 1149, 1109. MALDI-TOF MS M_w [**4** + K$^+$]: calcd 5176 Da, found 5169 Da. Calculated nitroxyl loading: 0.19 mmol·g^{-1}.

Ether 6. Isolated as a pale orange solid (1.01 g, 97% based on polymer recovery). T_g = 53.6 °C. ^{1}H NMR (DMSO-d_6) δ: 7.34−6.58 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.79 (m, 4H, PEG - α-methylenes), 3.70−3.21 (bm, PEG - methylenes), 1.93−1.85 (m, 4H, TEMPO - methylenes), 1.34−1.19 (m, 4H, TEMPO - methylenes), 1.10 (s, 12 H, axial TEMPO - methyls), 1.07 (s, 12 H, equatorial TEMPO - methyls). ^{13}C NMR (CDCl$_3$) δ: 155−110 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 71.5 (broad), 66.4, 60.3, 44.7, 29.1, 21.6. FTIR (cm^{-1}): 2884, 1467, 1343, 1281, 1242, 1148, 1113. MALDI-TOF MS M_w [**6** + K$^+$]: calcd 10365 Da, found 10374 Da. Calculated nitroxyl loading: 0.19 mmol·g^{-1}.

General Procedure for the Preparation of the PEG-Supported Methyl Isophthalate Esters 16 and 17. To a suspension of the bis-mesylate (**12a**, M_w = 6 kDa, 2.46 g, 0.4 mmol) and K$_2$CO$_3$ (0.44 g, 3.2 mmol) in acetone (100 mL) was added the phenol **15** (0.67 g, 3.2 mmol), and the mixture was maintained under reflux for 12 h. Upon filtration of the solids and solvent evaporation, the remaining material was dissolved in CH$_2$Cl$_2$ (5 mL), the solution was added dropwise to diethyl ether (500 mL) that was stirred vigorously, and the resulting suspension was stirred for 30 min. The precipitate was filtered and washed with diethyl ether (2 × 50 mL) to afford the tetraester **17** as a white solid (2.50 g, 97% based on polymer recovery). ^{1}H NMR (CDCl$_3$) δ: 8.26 (t, 2H, J = 1.42 Hz, aryl - methyne), 7.76 (d, 4H, J = 1.42 Hz, aryl - methynes), 4.20 (m, 4H, PEG - α-methylenes), 3.92 (s, 12H, Ar-CO-OCH_3), 3.87 (m, 8H, PEG - methylenes), 3.79−3.25 (bm, PEG - methylenes). ^{13}C NMR (CDCl$_3$) δ: 166.7, 156.6, 131.7, 122.7, 121.1, 70.7 (broad), 52.7. FTIR (cm^{-1}) 2879, 1726, 1351, 1292, 1112. MALDI-TOF MS M_w [**17** + K$^+$]: calcd 6896 Da, found 6879 Da.

Bis-ester 16. Isolated as a white solid (1.93 g, 93% based on polymer recovery). ^{1}H NMR (CDCl$_3$) δ: 8.27 (t, 1H, J = 1.42 Hz, aryl - methyne), 7.76 (d, 2H, J = 1.42 Hz, aryl - methynes), 4.19 (m, 2H, PEG - α-methylenes), 3.91 (s, 6H, Ar-CO-OCH_3), 3.79−3.25 (bm, PEG - methylenes) 3.35 (s, 3H, PEG - methyl). ^{13}C NMR (CDCl$_3$) δ: 166.8, 156.6, 131.6, 122.7, 120.8, 72.0, 70.5 (broad), 58.9, 52.6. FTIR (cm^{-1}): 2881, 1727, 1347, 1289, 1114. MALDI-TOF MS M_w [**16** + K$^+$]: calcd 5214 Da, found 5203 Da.

General Procedure for the Preparation of the PEG-supported Isophthalic Acids 18 and 19. A solution of the tetraester **17** (1.00 g, 0.16 mmol) in 2 M KOH (25 mL) was stirred at room temperature for 18 h. HCl (5% aq) was then added until pH 2, after which time the aqueous layer was extracted with CH$_2$Cl$_2$ (5 × 25 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under vacuum to a small volume (~5 mL). This solution was added dropwise to diethyl ether (250 mL), and the resulting suspension was stirred for 30 min. The precipitate was filtered and washed with diethyl ether (2 × 50 mL) to afford the tetraacid **19** as a white solid (0.90 g, 95% based on polymer recovery). ^{1}H NMR (CDCl$_3$) δ: 8.25 (bs, 2H, J = 1.42 Hz, aryl - methyne), 7.72 (bs, 4H, J = 1.42 Hz, aryl - methynes), 4.16 (m, 4H, PEG - α-methylenes), 3.84 (m, 4H, PEG - β-methylenes), 3.58 (bm, PEG - methylenes). FTIR (cm^{-1}): 2886, 1704, 1607, 1445, 1343, 1279, 1113. MALDI-TOF MS M_w [**19** + K$^+$]: calcd 6836 Da, found 6822 Da.

18. Isolated as a white solid (0.76 g, 92% based on polymer recovery). ^{1}H NMR (CDCl$_3$) δ: 8.25 (bs, 1H, aryl - methyne), 7.71 (bs, 2H, aryl - methynes), 4.14 (m, 2H, PEG - α-methylenes), 3.62 (bm, PEG - methylenes), 3.39 (m, 3H, PEG - methyl). FTIR (cm^{-1}): 2883, 1703, 1601, 1440, 1350, 1283, 1110. MALDI-TOF MS M_w [**18** + Na$^+$]: calcd 5168 Da, found 5163 Da.

General Procedure for the Preparation of the Branched Nitroxyl Catalysts 7 and 8. A solution of tetraacid **19** (100 mg, 0.016 mmol), thionyl chloride (0.5 mL, 0.65 mmol), and DMF (1 drop) in THF (10 mL) was maintained under reflux for 4 h. The solvent was removed in vacuo. The solid was then dissolved in CH$_2$Cl$_2$ (5 mL) and added dropwise to a solution of 4-hydroxy-TEMPO (689 mg, 4 mmol) and pyridine (800 μL, 10 mmol) in CH$_2$Cl$_2$ (10 mL) and the resulting solution stirred at room-temperature overnight. The solution was then maintained under reflux for 5 h, after which time the solution was allowed to cool to room temperature and was filtered. The filtrate was then evaporated to dryness under reduced pressure, and the solids were dissolved in a minimal amount of CH_2Cl_2. This solution was then added dropwise to diethyl ether (100 mL) and the resulting suspension stirred for 30 min. Upon filtration, the tetra-radical **8** was recovered as a pale yellow solid (95 mg; 95%, based on polymer recovery). $T_g = 52.6$ °C. ^{1}H NMR ($CDCl_3$) δ: 7.66 (m, 2H, aryl - methyne), 7.39 (m, 4H, aryl - methynes), 7.36−6.55 (several resonances, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.82 (m, 4H, PEG - α-methylenes), 3.59 (bm, PEG - methylenes), 1.98−0.81 (m, 64H, TEMPO - methylenes and methyls). FTIR (cm^{-1}): 2881, 1721, 1467, 1356, 1109. MALDI-TOF MS M_w [**8** + K$^+$]: calcd 7453 Da, found 7446 Da. Calculated nitroxyl loading: 0.54 mmol·g^{-1}.

Bis-radical 7. Isolated as a pale yellow solid (81 mg; 92%, based on polymer recovery). $T_g = 55.3$ °C. ^{1}H NMR ($CDCl_3$) δ: 7.69 (m, 1H, aryl - methyne), 7.42 (m, 2H, aryl - methynes), 7.36−6.55 (several signals, resulting from the reduction in situ of the nitroxyl radicals with phenylhydrazine), 3.76 (m, 2H, PEG - α−methylenes), 3.61 (bm, PEG - methylenes), 3.21 (s, 3H, PEG - methyl), 2.07−0.79 (m, 32H, TEMPO - methylenes and methyls). FTIR (cm^{-1}): 2886, 1720, 1467, 1359, 1112. MALDI-TOF MS M_w [**7** + K$^+$]: calcd 5494 Da, found 5501 Da. Calculated nitroxyl loading: 0.36 mmol·g^{-1}.

General Procedure for the Oxidation of Alcohols. A jacketed 25 mL round-bottom flask containing the nitroxyl catalyst (1.00 mL of a 0.008 M solution in CH_2Cl_2; 0.01 equiv) and the alcohol substrate (1.00 mL of a 0.8 M solution of the substrate and 0.1 M of the internal standard (either decane or tetradecane) in CH_2Cl_2) was kept at a constant temperature of 0 °C (Haake DC10-K10). At $t = 0$ min, NaOCl (2.00 mL of a 0.5M aqueous solution buffered to pH = 9 by saturation with $NaHCO_3$; 1.25 equiv) and NaBr (0.16 mL of a 0.5 M aqueous solution; 0.1 equiv) were added. The reaction is allowed to proceed using vigorous stirring after which the contents of the reactor were extracted with 50 mL of dichloromethane. The organic phase was separated, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and finally analyzed by GC-FID.

General Procedure for the Recovery of the PEG Catalysts. After completion of the oxidation reaction, CH_2Cl_2 (50 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were added to the organic layer, dried over $MgSO_4$, and concentrated under reduced pressure to a small volume. The resulting concentrated solution was added in a dropwise fashion to diethyl ether (100 mL) which was stirred vigorously and the resulting suspension stirred for 15 min. The precipitate was collected by filtration, washed with diethyl ether (2 × 15 mL), dried, and reused without further treatment.

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Supporting Information Available: General methods used, ^{1}H NMR spectroscopy, MALDI-TOF mass spectrometry, and DSC characterization of compounds **5**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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