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Strategies for the Generation of Molecularly Imprinted Polymeric Nitroxide Catalysts

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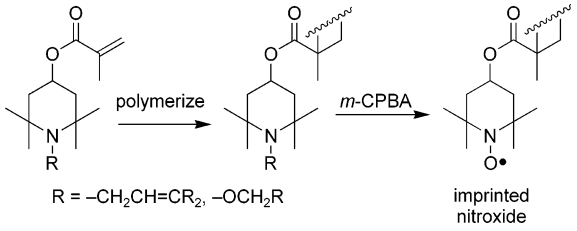
ABSTRACT



Two strategies for preparing catalytically active molecularly imprinted nitroxide-containing polymers are outlined. Both strategies rely upon the thermal rearrangement chemistry of tertiary amine *N*-oxides. To this end, several polymers were prepared and the polymeric nitroxides were revealed by oxidation with *m*-CPBA. All of the resulting polymeric catalysts proved to be competent mediators of the oxidation of alcohols.

Whereas enzymatic processes achieve selectivity by imposing geometric constraints on a given substrate, organic reactions are typically subject to the intrinsic bias of a substrate. One strategy for attaining selectivity by mimicking the geometric constraints imposed by enzymes is the use of molecularly imprinted polymers (MIPs).[1] MIPs are typically highly cross-linked networks with defined and accessible "binding sites". These sites result from the presence of a removable template molecule during the polymerization event. After polymerization, the template can be removed (typically by chemical or physical means) to leave a polymer that retains the shape and complementary polarity of the template molecule (Figure 1). To date, MIPs have been successfully utilized to effect enantioselective hydrolysis,[2] diastereoselective and regioselective reduction,[3] and enantioselective alkylation,[4] among other transformations. Substrate-selective metal-catalyzed oxidation has also been accomplished by the use of MIPs.[5]

Nitroxides, such as TEMPO (**1**), are stable free radicals that are efficient catalysts for the oxidation of alcohols to

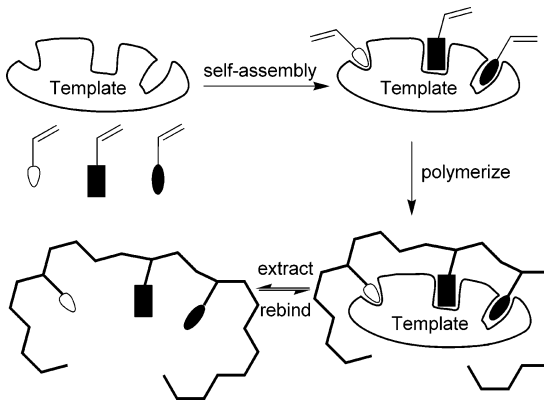


Figure 1. General strategy for the generation of molecularly imprinted polymers.

(1) Wulff, G. *Chem. Rev.* **2002**, *102*, 1−28 and references therein.
(2) (a) Sellergren, B.; Shea, K. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1403−1406. (b) Sellergren, B.; Karmalkar, R. N.; Shea, K. J. *J. Org. Chem.* **2000**, *65*, 4009−4027.
(3) Byström, S. E.; Boerje, A.; Akermark, B. *J. Am. Chem. Soc.* **1993**, *115*, 2081−2083.
(4) (a) Wulff, G.; Vietmeier, J. *Makromol. Chem.* **1989**, *190*, 1717−1726. (b) Wulff, G.; Vietmeier, J. *Makromol. Chem.* **1989**, *190*, 1727−1735.

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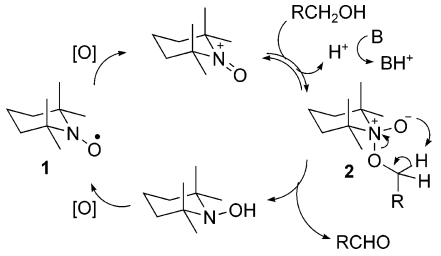


Figure 2. Proposed mechanism of TEMPO-mediated oxidation under alkaline conditions.

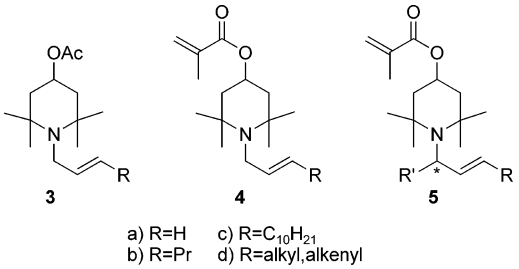


Figure 3. Allylamines.

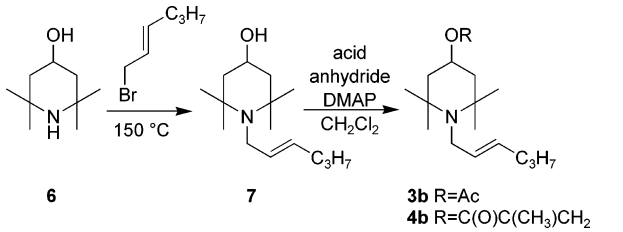
ketones, aldehydes, and carboxylic acids (Figure 2). These catalysts have found widespread use in synthetic chemistry.[6] Several studies have focused on the mechanism of this process, and the currently accepted mechanism under alkaline reaction conditions is depicted in Figure 2.[7] The utility of this organocatalyst has attracted our group and others to investigate the use of chiral nitroxides for the kinetic resolution of secondary alcohols; however, these endeavors have met with limited success.[8]

Our longstanding interest in the chemistry of nitroxides, coupled with the potential of molecularly imprinted polymers for achieving selectivity, led us to initiate a project investigating the interface of these two areas. To this end, we decided to approach the generation of nitroxide polymers from a unique perspective. To date, several immobilized TEMPO moieties have been prepared, including silica-supported TEMPO,[9] MCM-41-supported TEMPO,[10] sol−gel TEMPO,[11] PEG-TEMPO,[12] polynorbornene-derived TEMPO,[13] and polyamine TEMPO.[14] These are all effective catalysts for the oxidation of alcohols to aldehydes and can be removed from reaction mixtures by filtration. However, these catalysts were prepared with monomers incapable of imprinting. In contrast to these methods, we sought to use 2,2,6,6-tetramethylpiperidine derivatives to template the polymer and then selectively remove the *N*-substituent to reveal a catalytically active nitroxide with an imprinted cavity adjacent to the N−O• catalyst site.

One feature of enzymes that is desirable to emulate is the transition-state stabilization imparted by the structure of the active site. As such, our initial plan was to template structures that would effectively mimic *N*-oxide **2**. Unfortunately, it was found that all of the 2,2,6,6-tetramethylpiperidine *N*-oxide derivatives we attempted to synthesize decomposed thermally above 0 °C, precluding the use of such *N*-oxides as templates for the desired MIPs. Thus an alternate strategy of imprinting amine structures, such as allylic amines **4** and *O*-alkyl hydroxylamines **9b**, **16**, and **17**, was adopted. These templates omit the zwitterionic character of the proposed transition structure **2** but maintain an appropriately positioned templating element.

Initially, allylic amines **4a**−**c** were targeted to evaluate the potential of this strategy for the preparation of catalytically active nitroxide polymers (Figure 3). An alkylation approach to these molecules was identified as the most efficient means of attaining the desired structures. 1-Bromo-2-hexene reacted with amine **6** at elevated temperature to provide hydroxy amine **7** in 53% yield, which could be derivatized to acetate **3b** and methacrylate **4b** (Scheme 1).

Scheme 1. Preparation of Tertiary Amine Template **4b**



Allylamine **4a** and allylic amine **4c** were prepared by an analogous sequence. To validate this strategy, **3a** was treated

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(6) Merbouh, N.; Bobbitt, J. M.; Brueckner, C. *Org. Prep. Proced. Int.* **2004**, *36*, 3−31.

(7) (a) Golubev, V. A.; Borislavskii, V. N.; Alexandrov, A. L. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1977**, 1874−1881. (b) Golubev, V. A.; Sen, V. D.; Rozantsev, É. G. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1979**, 1927−1931. (c) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119−1122.

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(9) (a) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795−1796. (b) Fey, T.; Fischer, H.; Bachmann, S.; Albert, K.; Bolm, C. *J. Org. Chem.* **2001**, *66*, 8154−8159.

(10) Brunel, D.; Fajula, F.; Nagy, J. B.; Deroide, B.; Verhoef, M. J.; Veum, L.; Peters, J. A.; van Bekkum, H. *Appl. Catal., A* **2001**, *213*, 73−82.

(11) (a) Ciriminna, R.; Blum, J.; Avnir, D. Pagliaro, M. *Chem. Commun.* **2000**, 1441−1442. (b) Ciriminna, R.; Bolm, C.; Fey, T.; Pagliaro, M. *Adv. Synth. Catal.* **2002**, *344*, 159−163.

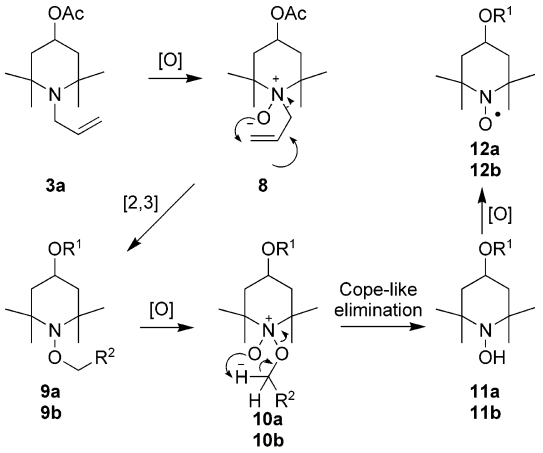
(12) (a) Pozzi, G.; Cavazzini, M.; Quici, S.; Benaglia, M.; Dell′Anna, G. *Org. Lett.* **2004**, *6*, 441−443. (b) Ferreira, P.; Hayes, W.; Phillips, E.; Rippon, D.; Tsang, S. C. *Green Chem.* **2004**, *6*, 310−312.

(13) Tanyeli, C.; Gümüş, A. *Tetrahedron Lett.* **2003**, *44*, 1639−1642.

(14) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **2000**, 271−272.

with *m*-CPBA to provide acetoxy TEMPO **12a** as the only product by GC analysis. This occurs via initial generation of *N*-oxide **8** followed by Meisenheimer [2,3]-rearrangement[15] to provide an *O*-allyl hydroxylamine **9a**, which undergoes oxidation to provide another *N*-oxide, **10a** (Scheme 2). Decomposition by a Cope-like elimination generates a

Scheme 2. Proposed Mechanism of Template Removal



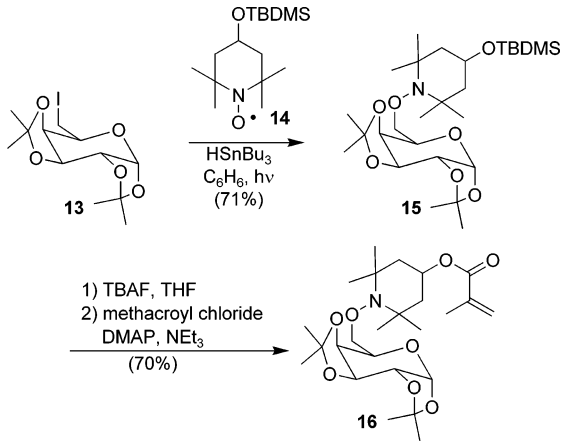
For Series **a**: R^1=Ac, R^2=$CHCH_2$
For Series **b**: R^1=$C(O)CH(CH_3)CH_2$, R^2=C_6H_{13}

hydroxylamine **11a**, which is subsequently oxidized to the nitroxide **12a**. The one limitation of this strategy is the inability to easily access allylic amines **5** in enantiopure form, which would provide entry into chiral templates.

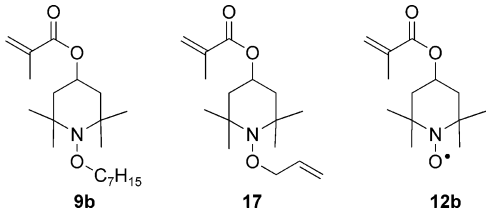
Given the limitation of the allylamine templates, we envisaged that *O*-alkylated hydroxylamines might be suitable templates for MIPs. Additionally, this method would allow direct access into chiral templates. To this end, iodo-galactose **13** was photolyzed in the presence of nitroxide **14** and $HSnBu_3$ to give silyl-protected hydroxylamine **15** in 71% yield.[16] Conversion to a polymerizable methacrylate derivative **16** was achieved in 70% yield over two steps. *O*-Alkyl hydroxylamines **9b** and **17** were prepared by a similar sequence. As a validation of this approach for generating nitroxides, hydroxylamine **16** was treated with *m*-CPBA to give nitroxide **12** in quantitative yield. A proposed mechanism of oxidative removal of the *O*-alkyl hydroxylamine template moiety is illustrated in Scheme 2.

With the desired polymerizable templates in hand, templates **4a**−**c**, **9b**, **16**, and **17** (5 mol % template) were each copolymerized with ethylene glycol dimethacrylate (EGDMA) and methyl methacrylate (MMA) under free-radical conditions using acetonitrile as porogen.[17,18] After crushing

Scheme 3. Synthesis of Diisopropylidene Galactose Template **16**



and washing, the resultant colorless polymers were treated with excess *m*CPBA to reveal the pink-colored imprinted TEMPO catalysts.[19, 20]



After surveying known TEMPO oxidation protocols with the catalyst derived from **4b**, Anelli's procedure (NaOCl, $NaHCO_3$, KBr, H_2O, CH_2Cl_2, 0 °C) emerged as the best method for use with this polymeric catalyst.[21] The oxidations of primary alcohols were rapid (<1 h) with low catalyst loadings (ca. 1 mol % nitroxide), affording good yields of the corresponding aldehydes (Table 1).[22] The rates of these reactions are comparable to other polymeric TEMPO derivatives (20−120 min) and within an order of magnitude of soluble TEMPO oxidations (ca. 10 min).[21] In addition, these catalysts are capable of at least 100 turnovers. Both benzylic and aliphatic alcohols were readily oxidized with this polymeric catalyst and bulk oxidant system. The reactions of secondary alcohols required extended reaction times (2 h). The polymer catalyst was reused three times with no significant loss of activity. Polymeric nitroxides prepared from monomers **4a**, **4c**, **9b**, **16**, and **17** also proved to be

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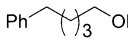
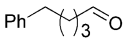
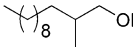
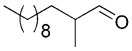
(16) Weigel, T. M.; Liu, H.-w. *Tetrahedron Lett.* **1988**, *29*, 4221−4224.
(17) Spivak, D.; Gilmore, M. A.; Shea, K. J. *J. Am. Chem. Soc.* **1997**, *119*, 4388−4393.
(18) The polymerization mixture was composed of 80 mol % EDGMA, 14 mol % MMA, 5 mol % template, 1 mol % AIBN, and a volume of CH_3CN equal to the four other components.
(19) In addition to becoming pink-colored, the polymers exhibited EPR signals consistent with nitroxides (see Supporting Information). Splitting yield for the MMA/EDGMA/**16** copolymer was 72%.
(20) The allylic groups contained in templates **4a**−**c** and **17** do not undergo polymerization to an appreciable extent. The polymeric nitroxides derived from these templates show catalytic activity similar to that of polymers prepared with nonallylic templates. Unpublished studies have shown that *N*-alkyl-2,2,6,6-tetramethylpiperidine-*N*-oxides, such as those that would arise from polymerization of the allylic moiety, decompose to multiple products, resulting in low yields of nitroxide. Additional support is provided by double integration of the EPR spectra of polymeric nitroxides generated from allylic and nonallylic templates, which shows that the nitroxide loadings are similar.
(21) Anelli, P. L.; Biffi, C.; Montnari, F.; Quici, S. J. *J. Org. Chem.* **1987**, *52*, 2559−2562.

Table 1. Oxidation with EDGMA/MMA/**4b** Copolymer

entry	substrate	product	isolated yield[a]
1			79%
2			76%[b]
3			78%
4			88%
5			55%

[a] Average of two experiments. [b] Reaction maintained at 0 °C for 2 h.

competent catalysts, providing 76−87% isolated yield for the oxidation of 5-phenylpentan-1-ol to 5-phenylpentanal.[23] The range of yields reported for the polymer catalysts described herein are similar to other polymeric nitroxides (70−99% yield (GC)).[9−14]

We anticipated that the polymeric catalyst derived from template **16** would selectively oxidize diisopropylidene galactose **18** in the presence of other oxidizable compounds. To test this hypothesis, 1 equiv of a 1:1 molar mixture of protected galactose **18** and protected glucose **19** was treated with 0.20 equiv of $NaHCO_3$-buffered NaOCl in the presence of 3 mol % of the imprinted polymer derived from **16** and CH_2Cl_2 and KBr. This provided a 4.5:1 mixture of **20**:**21** at 8% conversion of **18** to **20**.[24] Utilization of a nonimprinted polymeric TEMPO catalyst also resulted in a 4.5:1 mixture of **20**:**21** at 13% conversion of **18** to **20**.[25] As a comparison, the reaction was also performed with TEMPO and the ratio of products was 2.8:1 favoring **20** at 23% conversion of **18** to **20**. From these results it is clear that the templating monomer **16** was not effective at altering the chemoselectivity of this oxidation reaction. The lack of selectivity may be due to fact that the current polymers rely solely on hydrophobic and steric interactions to differentiate between substrates. As pointed out by a reviewer, the size and flexibility of the template monomer **16** may be a factor in the lack of selectivity observed with the corresponding imprinted nitroxide polymer. Future generations of polymers will incorporate hydrogen bonding elements in an attempt to increase the bias between substrates.

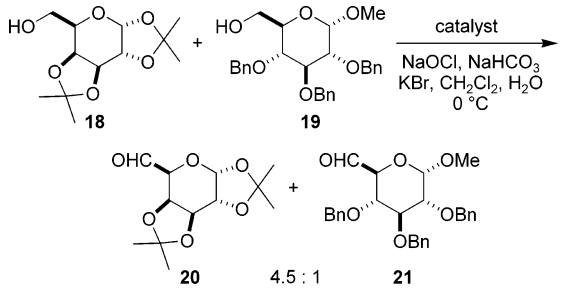


Figure 4. Attempt at realizing selectivity with catalyst derived from monomer **16**.

In summary, two efficient strategies for preparing molecularly imprinted polymeric nitroxide catalysts have been developed. Upon integration into polymer architectures the template molecules can be oxidatively converted to catalytically active nitroxides. These nitroxides are efficient catalysts, providing good turnover (TON ≈ 100) and good yields (55−88%) for a range of oxidation reactions. Although no novel selectivity has been realized to date, the methods reported herein allow access to active catalysts and are amenable to the incorporation of a broad range of templating substrates. The flexibility of these strategies should ultimately result in the identification of selective MIP oxidation catalysts.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) **General Procedure for Alcohol Oxidation with Imprinted Polymeric Catalysts. 5-Phenyl Pentanal.** A 10 mL two-neck flask equipped with an overhead stirrer was charged with 5-phenylpentan-1-ol (100 mg, 0.6 mmol), CH_2Cl_2 (3 mL), polymeric nitroxide derived from **4b** (30 mg, ca. 0.006 mmol), KBr (3.6 mg, 0.03 mmol), and H_2O (50 μL). The mixture was chilled to 0 °C, and then a mixture of 0.35 M NaOCl (2 mL, 0.7 mmol) and $NaHCO_3$ (100 mg, 1.19 mmol) was added with stirring over a period of 25 min. The mixture was stirred for an additional 35 min at 0 °C and then the excess oxidant was quenched by addition of saturated aqueous Na_2SO_3 (2 mL). The polymer catalyst was removed by filtration through glass wool, and the biphasic mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 10:90 ethyl acetate/hexanes) to provide 84 mg (85%) of the 5-phenylpentanal as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, J = 1.7 Hz, 1 H), 7.16−7.30 (m, 5 H), 2.61−2.67 (m, 2 H), 2.43−2.48 (m, 2 H), 1.64−1.71 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 141.9, 128.4, 128.3, 125.8, 43.7, 35.6, 30.9, 21.7; IR (film) 2930, 1724, cm^{-1}. Anal. Calcd for $C_{11}H_{14}O$ C, 81.44; H, 8.70. Found: C, 81.20; H, 8.85. Data are consistent with literature values (see ref 23).

(23) Lewis, F. D.; Reddy, G. D.; Schneider, S.; Gahr, M. *J. Am. Chem. Soc.* **1991**, *113*, 3498−3506.

(24) Determined by ^{1}H NMR integration of diagnostic signals.

(25) The "nonimprinted polymer" is a control polymer prepared by substituting 4-methacryloyl-2,2,6,6-tetramethylpiperidine for the templated monomer in the polymerization reaction. The polymeric nitroxide derived from this polymer is a competent oxidation catalyst.