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Multipolymer Reaction System for Selective Aerobic Alcohol Oxidation: Simultaneous Use of Multiple Different Polymer-Supported Ligands

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A multipolymer reaction system has been developed in which a water-soluble polymer-supported 2,2′-bipyridine group and a similarly immobilized TEMPO derivative are used as ligands for copper to effect the mild and selective aerobic oxidation of primary alcohols in acetonitrile−water solvent. In this reaction system, poly(ethylene glycol) monomethyl ether (molecular weight = 5000 Da) was used as the support for both the 2,2′-bipyridine and TEMPO moieties because of its solubility properties. The use of these functionalized polymers simultaneously in catalytic quantities allows for primary alcohols to be oxidized selectively to the corresponding aldehydes in an environmentally friendly manner. This is the first reported example of using two different polymer-supported ligands together to form an organometallic species capable of catalyzing an organic reaction.

Introduction

The use of polymer-supported reagents in organic synthesis has become commonplace, and a wide range of such materials and applications have been reported.[1] Of particular importance in this field is the use of polymer-supported ligands for the metal centers of organometallic catalysts that are capable of effecting organic reactions.[2] While great advances in this area of research have been described, to our knowledge, no examples of reaction systems have been reported in which multiple different polymeric ligands have been used simultaneously to coordinate to a metal center for the generation of a catalytically active species.[3] The development of such methodology should increase the range of reactions in which polymer-supported organometallic catalysts can be applied and facilitate catalyst recycling when multiple different ligands are required.

We have been interested in the development of polymer-supported reagents[4] and their simultaneous use in what are known as multipolymer reactions.[5−8] For example, we have described such reaction systems for the solid-phase synthesis of tertiary amines,[9] the 2,2,6,6-tetramethyl-piperidyl-1-oxy (TEMPO) radical/iodosobenzene diacetate-mediated oxidation of alcohols to aldehydes and ketones,[10] and Mitsunobu reactions.[11] Therefore, we sought to extend this concept to the simultaneous use of two separate polymer-supported ligands, and herein, we describe the first example of such a reaction system.

Recently, Sheldon et al.[12] reported that a copper/2,2′-bipyridine/TEMPO complex is capable of selectively and aerobically oxidizing primary alcohols to the corresponding aldehydes in the presence of a base, such as *t*-BuOK. They proposed that the catalytic species is a complex in which the 2,2′-bipyridine and TEMPO ligands simultaneously coordinate to the copper center, along with the substrate molecule (Figure 1). Since the attachment of both 2,2′-bipyridine and TEMPO groups to various polymers is well established, this reaction seemed attractive to us as a model to determine if it is possible to use two different polymer-supported ligands at the same time.

In recent years, there have been numerous reports describing the synthesis and use of a wide array of supported TEMPO reagents, such as a polyamine-supported TEMPO,[13] a silica-supported TEMPO,[14] a MCM-41-supported TEMPO,[15] a sol−gel TEMPO,[16] a ROMP polymer-supported TEMPO,[17] various cross-linked polystyrene-supported TEMPOs,[10,18,19] a molecularly imprinted polymeric TEMPO,[20] an ionic liquid-supported TEMPO,[21] and various poly(ethylene glycol) (PEG)-supported TEMPOs.[22] On the other hand, while many choices for the TEMPO reagent for our system are available, there are surprisingly few reports of supported 2,2′-bipyridine groups that are applicable to the basic aqueous reaction conditions required for our study. Furthermore, most examples in the literature involving the use of supported bidentate pyridine ligands actually describe dipyridines of various structures,[23,24] rather than the 2,2′-bipyridine itself, although some notable exceptions exist.[25−29]

Results and Discussion

Because the procedure for aerobic primary alcohol oxidation reported by Sheldon et al. requires dissolution of the substrate in an acetonitrile−water solvent mixture, monomethyl ether PEG (MPEG, molecular weight (MW) = ∼5000 Da) was selected as the support for the ligands in the current study because it is soluble in water and can be easily precipitated with diethyl ether or 2-propanol. Thus,

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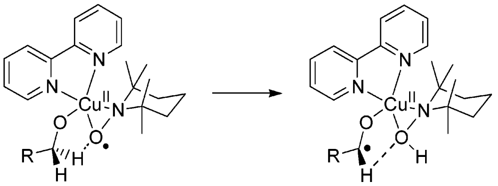


Figure 1.

MPEG-TEMPO (**1**) and MPEG-2,2′-bipyridine (MPEG-Bipy, **2**) were chosen as the ligands. The syntheses of these ligands are outlined in Scheme 1. Ligand **1** was prepared by the literature procedure[22] from 4-hydroxy-TEMPO and MPEG-OMs (**3**), and ligand **2** was prepared starting from 2-acetylpyridine and **3**.

For the synthesis of **2**, pyridinium salt **4** was prepared according to the literature procedure by heating 2-acetylpyridine with iodine in pyridine.[30] This salt was then reacted with methacrolein in formamide in the presence of NH_4OAc to furnish 5-methyl-2,2′-bipyridine **5**.[31] Oxidation of **5** with $KMnO_4$ gave the corresponding carboxylic acid **6**.[32] Esterification of **6** with ethanol in the presence of *p*-TsOH yielded ester **7**, which was reduced by $NaBH_4$ to afford alcohol **8**.[33] Finally, **8** was deprotonated and then alkylated with **3** to form ligand **2**. It should be noted that the esterification/reduction procedure used allowed for a higher yield of **8** to be isolated than did the direct reduction of **6**.

With the polymeric ligands in hand, the aerobic oxidation of primary alcohols was studied. Gratifyingly, our concept of simultaneously using two separate polymer-supported ligands worked from the outset, and various reaction conditions were examined. It was eventually found that for 1 mmol scale reactions, the use of 5 mol % each of $CuBr_2$, **1**, and **2** together with 10 mol % of *t*-BuOK in refluxing acetonitrile−water (2:1) under an atmosphere of oxygen for 18 h was optimal. Thus, a series of primary benzylic, allylic, and aliphatic alcohols (**9a**−**t**) was subjected to these conditions. In all but one case, the corresponding aldehyde (**10a**−**s**) was obtained in good to excellent yield for the benzylic and allylic substrates and moderate yield for aliphatic alcohol **9s** (Table 1). Surprisingly, oxidation of **9t** afforded **10a** as the only aldehyde product, in low yield. We speculate that **10a** was formed from **9t** via a benzylic hydroxylation step followed by oxidative cleavage of the thus formed vicinal diol.[34] The reactions were worked up simply by extraction of the reaction mixture with dichloromethane, precipitation of the polymeric material with diethyl ether, and filtration of the crude product through a plug of silica gel. Generally, the desired aldehyde was the only product formed and was easily separated from any remaining starting material. The identity of the aldehyde products was confirmed by comparison of their ^1H NMR spectra to those of commercially available samples (entries 1−13 and 15−20) and aldehyde **10n** has been previously reported (entry 14).[35] The only substrates that gave modest yields and conversions were the di-ortho-substituted **9l**−**n**, perhaps because of steric reasons, and the aliphatic alcohols **9s** and **9t**. We also tested the use of TEMPO attached to the heterogeneous cross-linked polystyrene support *J*anda*J*el,[36] (*JJ*-TEMPO,[10] **11**) in place of **1**, for the oxidation of **9c**. Interestingly, even this combination of heterogeneous and homogeneous ligands, **2** and **11**, afforded **10c** in a 31% yield using the standard reaction conditions (entry 3).

Next, a series of control experiments was performed to confirm that the presence of both the polymeric ligands was necessary for the alcohol oxidation reactions to proceed efficiently and to thereby support the notion that **1** and **2** simultaneously coordinate to copper to form the oxidation catalyst (Table 2). When only $CuBr_2$ was added to the reaction mixture containing **9c** and *t*-BuOK, no reaction was observed (entry 1). However, when either **1** or **2** was added to a similar reaction, low yields of **10c** were isolated (entries 2 and 3). The addition of **1** and **2** together afforded **10c** in a 13% yield (entry 4), which is essentially the sum of the yields of entries 2 and 3. Furthermore, the addition of $CuBr_2$ to either **1** or **2** did not increase the yield of **10c** (entry 5 vs entry 2 and entry 6 vs entry 3). These results seem to indicate that a contaminant present in both **1** and **2** allows for oxidation to occur on a limited basis and that the simultaneous presence of all 3 components ($CuBr_2$, **1**, and **2**) is indeed necessary for high yields of **10c** to be formed (Table 1, entry 3 vs Table 2).

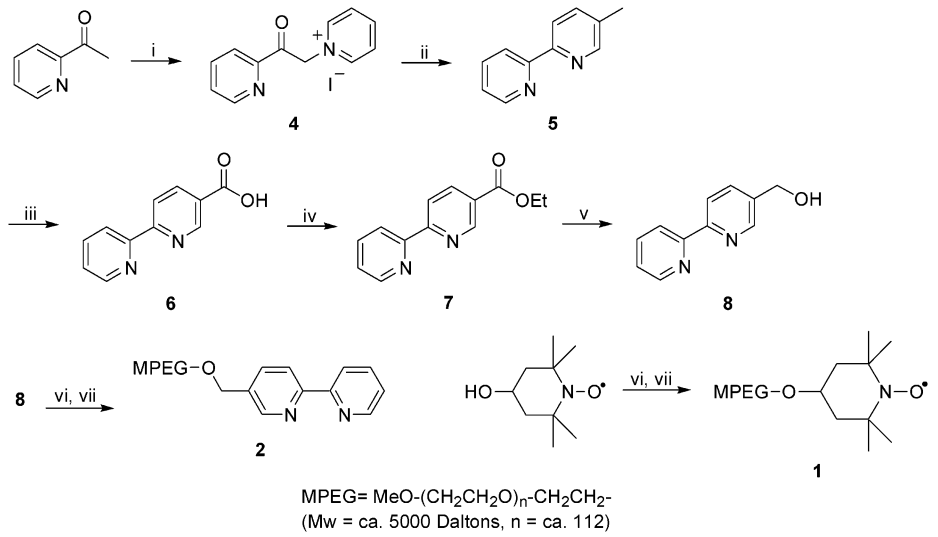
Finally, the recyclability of **1** and **2** was examined (Table 3). Since the copper presumably remains bound to **1** or **2** at the end of the reactions, no additional $CuBr_2$ was added in the subsequent oxidation cycles. Thus, the recovered mixture of **1** and **2** from the oxidation of **9c** was used directly for 4 additional reaction cycles, and the results of these reactions are summarized in column 2. Clearly, there was reduced catalytic activity in each subsequent reaction cycle. We postulated that the reason for this was leaching of the copper from the polymer, and thus conducted a second set of experiments where additional $CuBr_2$ was added prior to the start of each reaction cycle (column 3). Unfortunately, the additional $CuBr_2$ had no noticeable effect on catalytic activity, and thus ligands **1** and **2** are only moderately recyclable.

Some years ago Bergbreiter and Chandran reported the simultaneous use of three *identical* polyethylene-supported phosphine ligands in rhodium(I) hydrogenation catalysts.[3,6c] However, we could find no analogous examples in the literature where *different* polymer-supported ligands were used at the same time in a reaction catalyzed by an organometallic species. Thus, to evaluate the feasibility of this concept, we designed and developed a multipolymer reaction system for selective aerobic oxidation reactions of primary alcohols using MPEG-supported ligands **1** and **2** together. The system developed is efficient for oxidizing benzylic and allylic alcohols. Control reactions indicate that the presence of both ligands is necessary for efficient catalysis, and thus they support the notion that **1** and **2** simultaneously coordinate to the copper center in the catalytically active species. It is expected that this methodology can be extended to many other catalysts that require the simultaneous binding of multiple different ligands to a metal center, and such studies are currently under investigation.

Experimental Section

MPEG-TEMPO (1).[22] Under a nitrogen atmosphere, 4-hydroxy-TEMPO (1.2 g, 7.0 mmol) was added to NaH (0.3 g,

Scheme 1. Synthesis of MPEG-Supported Ligands **1** and **2**[a]



[a] Reaction conditions: (i) I_2, pyridine, 90 °C, 65%; (ii) methacrolein, NH_4OAc, formamide, 80 °C, 98%; (iii) $KMnO_4$, H_2O, 70−90 °C, 80%; (iv) EtOH, *p*-TsOH, room temp, 84%; (v) $NaBH_4$, EtOH, reflux, 90%; (vi) NaH, THF, 0 °C to room temp; (vii) MPEG-OMs (**3**), Bu_4NI, 75 °C, 95% for **1**, 100% for **2**.

7.5 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 2 h at ambient temperature, and then, **3 (**10.0 g, 2.0 mmol) in THF (50 mL) was added via cannula, followed by the addition of Bu_4NI (0.036 g, 0.1 mmol). The mixture was refluxed for 3 days, and then the solvent was removed under reduced pressure. Et_2O (80 mL) was added to the crude residue, and the resulting precipitate was filtered and collected to yield **1** (9.5 g, 95%) as a pink solid. Comparison of the ^1H NMR spectra of the obtained product to that of MPEG-OMs indicated complete disappearance of the methyl sulfonate groups of the starting material and broadening of the peaks resulting from the incorporation of a radical center in the product.

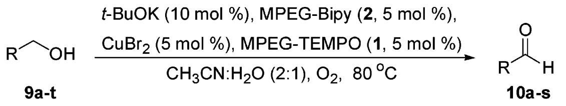
1-(2-Pyridylacetyl)pyridinium iodide (4).[30] A solution of iodine (7.1 g, 28.0 mmol) and 2-acetylpyridine (2.8 mL, 25.0 mmol) in pyridine (30 mL) was prepared in a reaction flask equipped with a condenser and drying tube, and the reaction mixture was stirred for 6 h at 90 °C. At this time, the resulting suspension was filtered, and the residue was refluxed in EtOH (300 mL) with activated charcoal (3.0 g) for 4 h. The suspension was then filtered while hot, and the filtrate was concentrated under reduced pressure to give crude **4**. Recrystallization of the crude product from a saturated EtOH solution was performed to purify **4** (6.3 g, 65%) as a yellow solid. The charcoal treatment and recrystallization operations were repeated as necessary until all of the product was obtained. ^1H NMR (DMSO, 400 MHz): δ 6.50 (2H, s), 7.82−7.85 (1H, m), 8.08 (1H, d, $J = 7.7$ Hz), 8.14 (1H, td, $J = 7.5$, 1.7 Hz), 8.27 (2H, t, $J = 6.2$ Hz), 8.73 (1H, t, $J = 7.8$ Hz), 8.87 (1H, d, $J = 3.7$ Hz), 9.00 (2H, d, $J = 5.5$ Hz). ^{13}C NMR (DMSO, 75 MHz): δ 67.57, 122.96, 128.63, 130.05, 139.07, 147.22, 147.26, 150.48, 151.37, 192.38.

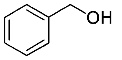
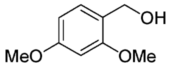
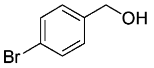
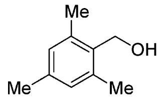
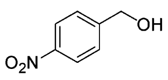
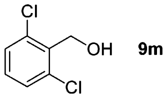
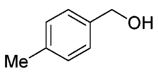
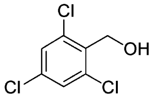
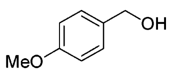
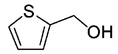
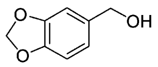
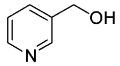
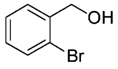
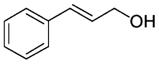
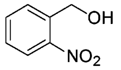
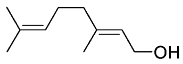
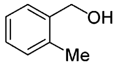
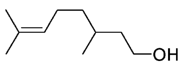
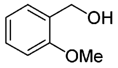
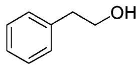
5-Methyl-2,2′-bipyridine (5).[31] Methacrolein (1.8 mL, 22.0 mmol) and H_4NOAc (9.3 g, 120.0 mmol) were sequentially added to the solution of **5** (6.5 g, 20 mmol) in formamide (200 mL). The mixture was stirred at 80 °C for 16 h. At this time, the crude mixture was cooled and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH in CH_2Cl_2) to yield **5** (3.7 g, 98%) as a brown oil. ^1H NMR ($CDCl_{3,}$ 300 MHz): δ 2.31 (3H, s), 7.26−7.30 (1H, m), 7.63 (1H, dd, $J = 8.1$, 2.0 Hz), 7.80 (1H, td, $J = 8.1$, 1.7 Hz), 8.28 (1H, d, $J = 8.1$ Hz), 8.36 (1H, d, $J = 8.4$ Hz), 8.51 (1H, s), 8.67 (1H, d, $J = 4.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.17, 120.46 120.65, 123.22, 133.26, 136.69, 137.29, 148.95, 149.48, 153.48, 156.14. HR EI-MS Calcd for $C_{11}H_{10}N_2$: 170.0844. Found 170.0839.

2,2′-Bipyridinyl-5-carboxylic acid (6).[32] Potassium permanganate (12.3 g, 78 mmol) was added in 7 portions at 1 h intervals to a solution of **5** (3.4 g, 20 mmol) in water (200 mL). The mixture was heated at 70 °C for 3 h and then at 90 °C for 4 h more. The brown mixture was then filtered while hot through celite and washed with hot water (2 × 25 mL). The filtrate was concentrated to approximately 10 mL under reduced pressure, and then 1 M HCl was added slowly until a pH of 4 was obtained. The residue was then filtered and dried to obtain pure **6** (3.2 g, 80%) as a white solid. ^1H NMR (DMSO, 300 MHz): δ 7.48−7.53 (1H, m), 7.99 (1H, t, $J = 7.7$ Hz), 8.38−8.51 (3H, m), 8.73 (1H, d, $J = 4.3$ Hz), 9.16 (1H, d, $J = 1.2$ Hz). ^{13}C NMR (DMSO, 75 MHz): δ 119.64, 120.70, 124.36, 126.63, 136.97, 137.63, 149.01, 149.61, 153.76, 157.64, 165.64. HR EI-MS Calcd for $C_{11}H_8N_2O_2$: 200.0586. Found: 200.0583.

Ethyl 2,2′-Bipyridinyl-5-carboxylate (7). *p*-Toluenesulfonic acid (11.4 g, 60 mmol) was added to a solution of **6** (2.4 g, 12 mmol) in ethanol (50 mL). The reaction mixture was stirred at ambient temperature for 18 h. At this time, the mixture was concentrated under reduced pressure, and a $NaHCO_3$ solution was added to the mixture until a solution pH of 8 was obtained. The crude product was then extracted with ethyl acetate (3 × 100 mL), and the combined organic fractions were washed with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (5% MeOH in CH_2Cl_2) of the crude

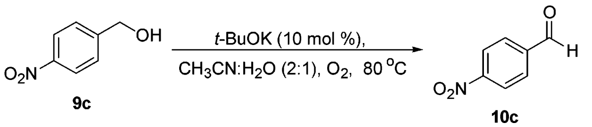
Table 1. Aerobic Oxidation Primary Alcohols



Entry	Alcohol	Yield (%)[a]	Entry	Alcohol	Yield (%)[a]
1	 **9a**	85	11	 **9k**	99
2	 **9b**	94	12	 **9l**	32
3	 **9c**	94 31[b]	13	 **9m**	76
4	 **9d**	92	14	 **9n**	61
5	 **9e**	84	15	 **9o**	85
6	 **9f**	96	16	 **9p**	80
7	 **9g**	90	17	 **9q**	100
8	 **9h**	88	18	 **9r**	92
9	 **9i**	92	19	 **9s**	31
10	 **9j**	100	20	 **9t**	21 of **10a**

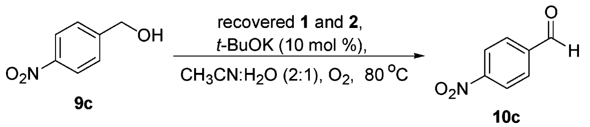
[a] Isolated yields of reaction performed on a 1 mmol scale for 18 h. [b] Isolated yield from a reaction using **11** in place of **1**.

Table 2. Control Experiments



	addition			
entry	$CuBr_2$	**1**	**2**	isolated yield (%)
1	√	×	×	no reaction
2	×	√	×	9
3	×	×	√	5
4	×	√	√	13
5	√	√	×	7
6	√	×	√	16

Table 3. Reactions Using Recycled **1** and **2**



	isolated yield (%)	
cycle	without addition of $CuBr_2$[a]	with addition of 1 mol % $CuBr_2$[a]
1	94	95
2	88	85
3	75	50
4	60	54
5	36	21

[a] Addition made prior to each subsequent reaction cycle.

product yielded **7** (2.3 g, 84%) as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (3H, t, $J = 7.1$ Hz), 4.44 (2H, q, $J = 7.1$ Hz), 7.35−7.38 (1H, m), 7.86 (1H, td, $J = 7.7$, 1.8 Hz), 8.41 (1H, dd, $J = 8.3$, 2.1 Hz), 8.49 (2H, t, $J = 8.1$ Hz), 8.71−8.72 (1H, m), 9.28 (1H, dd, $J = 2.1$, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.31, 61.42, 120.49, 121.90, 124.45, 125.98, 137.06, 137.97, 149.39, 150.53, 155.18, 159.41, 165.38. HR EI-MS Calcd for $C_{13}H_{12}N_2O_2$: 228.0899. Found: 228.0898.

2,2′-Bipyridinyl-5-methanol (8).[33] Sodium borohydride (0.3 g, 35.2 mmol) was added to **7** (1.8 g, 8 mmol) in ethanol (100 mL). The mixture was stirred at ambient temperature for 18 h and then concentrated under reduced pressure. Water (50 mL) was added, and then the crude product was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH in CH_2Cl_2) to obtain pure **8** (1.3 g, 90%) as a brown solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.72 (2H, s), 7.28−7.32 (1H, m), 7.75−7.83 (2H, m), 8.27 (1H, d, $J = 8.1$ Hz), 8.32 (1H, d, $J = 8.0$ Hz), 8.56 (1H, d, $J = 1.4$ Hz), 8.65 (1H, d, $J = 4.4$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 62.20, 121.03, 121.30, 123.73, 135.79, 136.69, 137.11, 147.86, 149.04, 155.08, 155.83. HR EI-MS Calcd for $C_{11}H_{10}N_2O$: 186.0793. Found: 186.0788.

MPEG-bipyridine (2). Under a nitrogen atmosphere, **8** (1.4 g, 7.8 mmol) was added to NaH (0.3 g, 8.0 mmol) in THF (20 mL) at 0 °C. The mixture was stirred for 2 h at ambient temperature, and then **3** (10.0 g, 2.0 mmol) in THF (50 mL) was added via cannula, followed by the addition of Bu_4NI (0.036 g, 0.1 mmol). The reaction mixture was refluxed for 3 days, and then the solvent was removed under reduced pressure. Et_2O (80 mL) was added to the crude residue, and the resulting precipitate was filtered and collected to afford **2** (10.0 g, 100%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 3.38 (3H, s), 3.46−3.81 (514H), 4.65 (2H), 7.31 (1H), 7.81 (2H), 8.39 (2H), 8.64−8.69 (2H).

General Procedure of Aerobic Alcohol Oxidation Reactions. The reagents *t*-BuOK (11.2 mg, 0.1 mmol), $CuBr_2$ (11.2 mg, 0.05 mmol), **2** (0.26 g 0.05 mmol), and **1** (0.26 g, 0.05 mmol) were added sequentially to a solution of the alcohol (1 mmol) in $CH_3CN−H_2O$ (2:1, 4 mL). Oxygen was bubbled through the reaction mixture for 10 min, and then it was then heated at 80 °C for 18 h under an O_2 atmosphere using a balloon. At this time, the crude mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Polymers **1** and **2** were removed by adding Et_2O (20 mL) and filtering off the resulting precipitate. The product-containing filtrate was concentrated under reduced pressure, and the crude product was filtered through a silica plug (10% Et_2O/*n*-pentane) to obtain the pure aldehyde product. In some cases, the recovered polymer was washed and dried for use in the recycling experiments.

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Supporting Information Available. Both ^1H and ^{13}C NMR spectra for compounds **1**−**8** and the characterization data for the aldehydes obtained from aerobic oxidations reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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