Substituent Effects in Arylseleninic Acid-Catalyzed Bromination of Organic Substrates with Sodium Bromide and Hydrogen Peroxide

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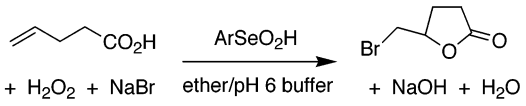
Arylseleninic acids were found to be catalysts for the oxidation of bromide with hydrogen peroxide in a two-phase mixture of ether and pH 6 phosphate buffer. Benzeneseleninic acid (**3**) and 4-methoxyphenylseleninic acid (**4**) were more efficient catalysts than 3,5-bis(trifluoromethyl)phenylseleninic acid (**1**), 4-nitrophenylseleninic acid (**2**), 4-dimethylaminophenylseleninic acid (**5**), and 2,4,6-trimethylphenylseleninic acid (**6**). A variety of organic substrates were efficiently brominated under these conditions using 5−10 mol % of commercially available benzeneseleninic acid (**3**).

Within the family of organic chalcogen-containing compounds, seleninic acids have been efficient catalysts for the activation of H_2O_2. Epoxidation reactions,[1] oxidation of sulfides[1] to sulfoxides and sulfones, Baeyer−Villiger oxidations,[2] oxidation of aldehydes to carboxylic acids,[2c] and oxidation of thiols to disulfides[3] with H_2O_2 have all been catalyzed with seleninic acids. Selinate esters have also been effective catalysts for the oxidation of thiols to disulfides.[4] In reactions where substituent effects have been evaluated, arylseleninic acids bearing electron-withdrawing groups have been reportedly the most efficient catalysts.[1b,2b,c]

One reaction where arylseleninic acids have not been used as catalysts is the oxidation of halide salts with H_2O_2 to give the corresponding positive halogen/hypohalous acid. Although thermodynamically powerful, H_2O_2 is kinetically a slow oxidant for the halide salts,[5] and halogenations must typically be catalyzed for halogenation reactions to occur on a useful time scale. The haloperoxidase enzymes have been used as catalysts in a variety of halogenation reactions,[6] and other catalysts have been designed to mimic the haloperoxidases.[7] Our own work has utilized various diorganochalcogenides as catalysts for the halogenation of organic substrates.[8−10] The development of catalysts for use with H_2O_2 and halide salts is important with respect to the numerous advantages for environmental and safety concerns (i.e., H_2O_2 degrades to O_2 and H_2O)[11] relative to using elemental halogens.[12]

Scheme 1



We report that arylseleninic acids are catalysts for the oxidation of NaBr with H_2O_2 and that stereoelectronic effects are important in the catalyst choice. Preferred catalysts in this reaction have different stereoelectronic demands than those of other arylseleninic acid-catalyzed reactions.[1b,2b,c] The arylseleninic acid-catalyzed reaction is useful for the bromination of organic substrates with NaBr and H_2O_2 in two-phase systems of ether and pH 6 phosphate buffer.

Results and Discussion

Mechanistic Studies. The bromination of 4-pentenoic acid with NaBr and H_2O_2 as shown in Scheme 1 was chosen as a model reaction to evaluate the catalytic activity of arylseleninic acids. In the absence of a

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(3) Back, T. G.; Dyck, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 2079−2080.

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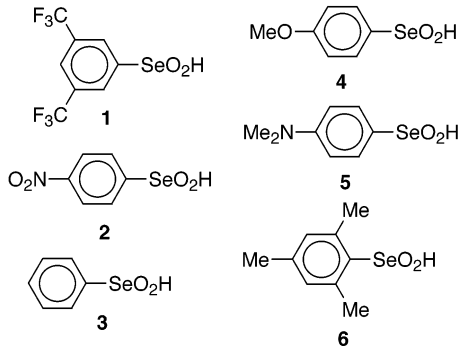
Chart 1



catalyst, the half-life of bromination of 4-pentenoic acid with 1.0 M NaBr and 1.0 M H_2O_2 in a two-phase mixture of ether and pH 6 phosphate buffer was >72 h at 296 K.

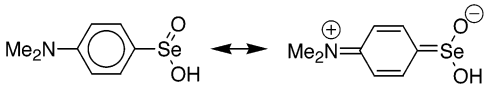
The arylseleninic acids of Chart 1 were prepared from oxidation of the corresponding diselenide with H_2O_2.[3] Identical results were obtained from arylseleninic acids that were isolated following oxidation of the diselenide and from those generated in situ. For the in situ preparation of catalyst, 100 μL of 30% H_2O_2 was added to an ether solution of the diselenide (5 mol % relative to 4-pentenoic acid), which generated 10 mol % of the arylseleninic acid following oxidation. The pentenoic acid, NaBr, and pH 6 phosphate buffer were then added followed by the addition of the remaining H_2O_2 to give final concentrations of 1.0 M NaBr and 1.0 M H_2O_2. The progress of the reaction at 296 K was monitored by ^{1}H NMR spectroscopy of aliquots to determine the half-life of the reaction.

All of the arylseleninic acids of Chart 1 catalyzed the bromination of 4-pentenoic acid with half-lives, $t_{1/2}$, that covered a range of 15 to 90 min. In earlier studies,[1b,2b,3c] 3,5-bis(trifluoromethyl)phenylseleninic acid[1c] (**1**) was a more effective catalyst than either more electron-rich or electron-deficient aryl groups. In the bromination of 4-pentenoic acid, seleninic acid **1** was the poorest catalyst evaluated with respect to rate of reaction ($t_{1/2}$ of 90 min). 4-Nitrophenylseleninic acid[13] (**2**) was a better catalyst, with a $t_{1/2}$ of 20 min. Benzeneseleninic acid (**3**) and 4-methoxyphenylseleninic acid[14] (**4**) were comparable as catalysts and were the two best catalysts that were examined, each with $t_{1/2}$ of 15 min. 4-Dimethylaminophenylseleninic acid[13] (**5**) was a poorer catalyst ($t_{1/2}$ of 40 min) than **3** and **4**. 2,4,6-Trimethylphenylseleninic acid[15] (**6**, $t_{1/2}$ of 25 min) was comparable as a catalyst to **3** and **4**.

Mechanistically, few details are known for seleninic acids as catalysts for H_2O_2. The results from the six catalysts examined here offer some insight into the catalytic cycle. It is known that arylseleninic acids are converted reversibly to the corresponding peroxyseleninic acids with H_2O_2.[16] Logically, the reaction with bromide might be presumed to follow the initial reaction with H_2O_2. Substituent effects can impact catalysis either through the initial equilibrium/reaction with H_2O_2 or through subsequent reaction with bromide. The 4-nitro- (**2**), 4-methoxy- (**4**), and 2,4,6-trimethylphenylseleninic (**6**) acids have rates of catalysis ($t_{1/2}$ of 15−25 min) similar to that of benezeneseleninic acid (**3**, $t_{1/2}$ of 15 min), even though the electronic demands of their substituents are different. While **2**, with a 4-nitro substituent, is slightly slower than **4**, with a 4-methoxy substituent, on net, substituent effects have little impact on the observed rate of catalysis, which suggests that there is little buildup of charge near the aromatic ring in the rate-determining step of the catalytic cycle. Furthermore, catalysis with the mesityl derivative **6** ($t_{1/2}$ of 25 min) suggests that steric demands at Se must also be small in the rate-determining step of the catalytic cycle.

The 3,5-bis(trifluoromethyl)phenyl substituent of **1** is more electron-withdrawing than the 4-nitrophenyl substituent of **2** based on Hammett substituent constants.[17] While $t_{1/2}$ for **2** is only slightly longer than $t_{1/2}$ for **3** and **4**, $t_{1/2}$ for **1** is a factor of 6 slower than for **3** or **4**. The data for **1** and **2** suggest that electron-withdrawing groups slow the rate of catalysis.

4-Dimethylaminophenylseleninic acid (**5**, $t_{1/2}$ of 40 min) has the most electron-donating substituent among acids **1**−**6**, yet catalysis with **5** is slower than catalysis with either **2**, bearing an electron-withdrawing group, or **4**, bearing an electron-donating group. The dimethylamino substituent may impact the initial reaction/equilibrium with H_2O_2 via the following resonance contribution:



Either the equilibrium constant could be shifted toward the seleninic acid side relative to the peroxyseleninic acid or the rate of addition of H_2O_2 to **5** might be slowed. In the case of the former, the reaction velocity would be slowed by a lower concentration of the peroxyseleninic acid, while in the case of the latter by the rate of formation of the peroxyseleninic acid.

Two possible mechanistic paths are illustrated in Scheme 2 for the arylseleninic acid-catalyzed oxidation of bromide with H_2O_2. Initial reversible reaction with H_2O_2 gives peroxyseleninic acid (**7**). One can speculate that direct attack of bromide at the −OH oxygen would give HOBr and arylselinate, which would regenerate **7** in pH 6 buffer in the presence of excess H_2O_2. Alternatively, nucleophilic attack at the Se-O oxygen atom of **7** could lead to $ArSeO_2Br$ (**8**), which might function directly as a brominating agent or which might react directly via nucleophilic attack of bromide at the O-Br bromine atom of **8** to produce Br_2.

Nucleophilic attack at either oxygen atom of the peroxy group of the peroxyseleninic acid is one or two atoms removed from the selenium center, which partially explains the small stereoelectronic effects observed in the aryl substituents shown in Chart 1 (a factor of 6

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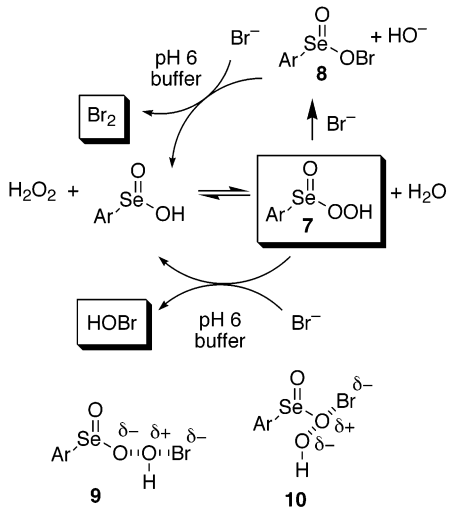
(14) Shimizu, T.; Nakashima, Y.; Watanabe, I.; Hirabayashi, K.; Kamigata, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2151−2155.
(15) Dickson, P. M.; McGowan, M. A. D.; Yearwood, B.; Heeg, M. J.; Oliver, J. P. *J. Organomet. Chem.* **1999**, *588*, 42−50.
(16) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2034. (b) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Ohfune, Y. *J. Chem. Soc., Chem. Commun.* **1977**, 870. (c) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.
(17) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

Scheme 2



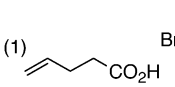
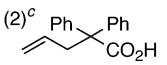
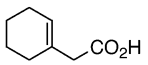
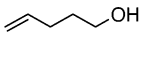
in reactivity). If one assumes that the 4-dimethylaminophenyl substituent is relatively slow due to substituent effects on either the equilibrium constant for the reaction of H_2O_2 with **5** or the rate of addition of H_2O_2 to **5**, then substituent effects in the other arylseleninic acids are consistent with the formation of **8** as the brominating species. The direct attack of bromide at the −OH oxygen of peroxyseleninic **7** would generate HOBr and benzeneselinate via transition state **9**. The partial development of negative charge at the oxygen atom in **9**, while removed from the aromatic ring, would be slightly accelerated via electron-withdrawing substituents. In contrast, nucleophilic attack at the Se-O oxygen atom of **7** would lead to $ArSeO_2Br$ (**8**) via transition state **10**. The partial development of positive charge in **10** would be accelerated via electron-donating substituents. The observation that 3,5-bis(trifluoromethyl)phenylseleninic acid (**1**) and 4-nitrophenylseleninic acid (**2**) are poorer catalysts than benzeneseleninic acid (**3**) and 4-methoxyphenylseleninic acid (**4**) is most consistent with the formation of intermediate **8**.

Preparative Studies. Benzeneseleninic acid (**3**) is commercially available, and the commercial material was used to evaluate the preparative utility of the arylseleninic acid-catalyzed brominations of organic substrates according to the following procedure. The substrate (2.5 mmol) and **3** (5 mol % relative to substrate) were dissolved in a stirred mixture of 20 mL of ether and 20 mL of pH 6 phosphate buffer containing 1.0 M NaBr at ambient temperature. Hydrogen peroxide (30%) was added dropwise over a 1 h period to give a final concentration of H_2O_2 of 1.0 M.

As shown in Table 1, bromolactonization of 4-pentenoic acid gave good yields of a mixture of the 4-bromomethyl γ-lactone (**11**) and some 4,5-dibromopentanoic acid **12** (entry 1). If the mixture of products is stirred an additional 15 h, **11** is isolated as the only product. The same result was obtained using PhSeSePh (2.5 mol %) as a precursor to benzeneseleninic acid (**3**) generated in situ.[2]

The bromolactonization of 2,2-diphenylpentenoic acid[18] gave the γ-lactone **13** as the only product. However, this

Table 1. Bromolactonization of Enoic Acids and 4-Penten-1-ol via Benzeneseleninic Acid (3)-Catalyzed Oxidation of NaBr with H_2O_2

entry[a]	substrate	products	rxn time (h)	% conversion
(1)		**11**	20	Cat. 84 (84)[b] Uncat. <6
		12	20	Cat. 16 (16)[b] Uncat. <6
(2)[c]		**13**	24	Cat. 55 Uncat. 10
(3)		**14**	24	Cat. 29 Uncat. 8
		15	24	Cat. 64 Uncat. 16
(4)		**16**	24	Cat. 48 Uncat. 13
		17	24	Cat. 17 Uncat. 4

[a] Two-phase mixture of 2.5 mmol of substrate in 20 mL of ether and 0.125 mmol (5 mol %) of benzeneselenenic acid (**3**) in 20 mL of pH 6 phosphate buffer containing 1.0 M NaBr and 1.0 M H_2O_2. Conversions are the average of duplicate runs. [b] PhSeSePh (2.5 mol %) used to generate $PhSeO_2H$ (**1**) in situ. [c] 0.25 mmol of **1** in 20 mL of pH 6 phosphate buffer containing 2.0 M NaBr and 2.0 M H_2O_2.

reaction was quite slow at ambient temperature with 5 mol % catalyst (≈10% conversion after 24 h). The use of 10 mol % **3** and 2.0 M NaBr and 2.0 M H_2O_2 for the bromolactonization gave 55% conversion after 24 h (entry 2). The half-life for the uncatalyzed reaction was >120 h under the latter conditions. Bromination of 2-(1-cyclohexenyl)acetic acid[19] (entry 3) gave a 69:31 mixture of the β- and δ-lactones (**14** and **15**, respectively). This ratio remained constant over the course of reaction. For entry 3, the catalyzed reaction had a half-life of 6 h, while the uncatalyzed reaction had a half-life of >48 h. In a related intramolecular cyclization reaction, the bromination of 4-penten-1-ol (entry 4) gave 4,5-dibromopentan-1-ol (**16**) as the major product with small amounts of 2-bromomethyltetrahydrofuran (**17**).

Activated aromatic substrates were also brominated under the two-phase conditions as shown in Table 2. 1,3,5-Trimethoxybenzene at 82% conversion gave 1-bromo-2,4,6-trimethoxybenzene **18** (entry 1) as essentially the only product (>98% by ^1H NMR). At higher conversions, bromination of 1-bromo-2,4,6-trimethoxybenzene became competitive with bromination of the remaining 1,3,5-trimethoxybenzene. The half-life of the catalyzed reaction is roughly 8 h, while the uncatalyzed reaction has a half-life of 60 h.

Bromination of *N*,*N*-dimethylaniline and *N*-phenylmorpholine gave mixtures of 2-bromo and 4-bromo products (entries 2 and 3, respectively, Table 2). The ratio of *ortho*/*para* bromination remained constant over

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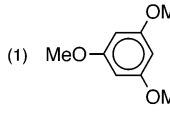
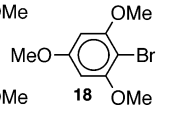
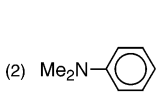
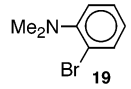
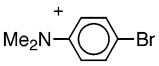
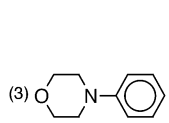
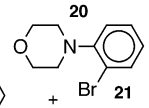
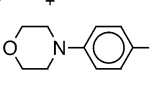
(19) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611−3614.

Table 2. Electrophilic Bromination of Activated Aromatic Substrates via Benzeneseleninic Acid (3)-Catalyzed Oxidation of NaBr with H_2O_2

entry[a]	substrate	products	rxn time (h)	% conversion
(1)		 **18**	24	Cat. 82 Uncat. 21
(2)		 **19**	19	Cat. 47 Uncat. 12
		+  **19**	19	Cat. 39 Uncat. 11
(3)		 **20** +  **21**	24	Cat. 34 Uncat. 12
		22	24	Cat. 52 Uncat. 11

[a] Two-phase mixture of 2.5 mmol of substrate in 20 mL of ether and 0.125 mmol (5 mol %) of benzeneselenenic acid (**1**) in 20 mL of pH 6 phosphate buffer containing 1.0 M NaBr and 1.0 M H_2O_2. Conversions are the average of duplicate runs.

the course of reaction at 55:45 for *N*,*N*-dimethylaniline and 39:61 for *N*-phenylmorpholine.

In summary, arylylseleninic acids are efficient catalysts for brominations of organic substrates with NaBr and H_2O_2. Of the six catalysts examined, benzeneseleninic acid (**3**) and 4-methoxyphenylseleninic acid were the two most active catalysts. Preparative reactions with commercially available benzeneseleninic acid (**3**) demonstrated that the procedure was amenable to a variety of different substrates. The stereoelectronic effects in the series of catalysts **1**−**6** were consistent with the formation of intermediates **8** in Scheme 2.

Experimental Section

The arylseleninic acids were prepared from the corresponding diaryl diselenides. The diselenide precursor to **1** was prepared according to ref 2c. Diselenide precursors to **2** and **5** were prepared according to ref 13. The diselenide precursor to **4** was prepared according to ref 14. The diselenide precursor to **6** was prepared according to ref 15. Benzeneseleninic acid (**3**) was used as commercially received or was prepared by oxidation of commercially available diphenyl diselenide. 2,2-Diphenyl-4-pentenoic acid was prepared according to ref 18. 2-(1-Cyclohexenyl)acetic acid was prepared according to ref 19.

General Procedure for Kinetic Studies of the Bromination of 4-Pentenoic Acid with Hydrogen Peroxide and Sodium Bromide. The appropriate diselenide (0.125 mmol) was dissolved in 20 mL of ether, and 100 μL of 30% H_2O_2 was added with stirring at 296 K. When the yellow solution turned colorless, 20 mL of 0.23 M pH 6.0 phosphate buffer was added followed by NaBr (2.33 g, 22.6 mmol) and 4-pentenoic acid (0.250 g, 2.5 mmol). Hydrogen peroxide (30 wt %, total volume of 2.6 mL, 23 mmol) was added via syringe in one portion. Small aliquots of the reaction mixture were quenched with sodium bisulfite, acidified with 10% HCl, and the progress of bromination was determined by ^{1}H NMR spectroscopy. Half-lives are based on the average of duplicate runs that agreed within 10%.

General Procedure for Preparative Bromination with Hydrogen Peroxide and Sodium Bromide. Preparation of 5-Bromo-γ-valerolactone (11) and 4,5-Dibromopentanoic Acid (12) (entry 1, Table 1). Except as noted, hydrogen peroxide (30%, 2.6 mL, 23 mmol) was added dropwise to a mixture of 2.5 mmol of substrate (4-pentenoic acid, 0.250 g), **3** (0.024 g, 0.125 mmol, 5 mol %), NaBr (2.33 g, 22.6 mmol), 20 mL of ether, and 20 mL of 0.23 M pH 6.0 phosphate buffer. After the indicated time (7 h for pentenoic acid), the reaction mixture was acidified with 10% HCl and the products were extracted with ether. (Continuous extraction with ether for 16 h was used to extract the products of bromination from 4-pentenoic acid.) The ether extracts were dried over $MgSO_4$ and concentrated at reduced pressure. For 4-pentenoic acid, a 74:26 mixture of products was obtained as determined by ^{1}H NMR spectroscopy. The crude product mixture was purified via chromatography on SiO_2 (ether, then ether/CH_2Cl_2, 19:1) followed by Kugelrohr distillation to give **11** (0.300 g, 68%) as a colorless oil and **12** (0.21 g, 24%) as an off-white waxy solid.

For **11**:[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70−4.76 (m, 1 H), 3.49−3.57 (m, 2 H), 2.51−2.69 (m, 2 H), 2.38−2.47 (m, 1 H), 2.06−2.15 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.14, 77.63, 34.28, 28.07, 25.69; IR (film, NaCl) 1775 cm^{-1} (s).

For **12**:[20a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18−4.27 (m, 1 H), 3.85 (dd, J = 4.4, 10 Hz, 1 H), 3.60 (t, J = 10 Hz, 1 H), 2.48−2.72 (m, 3 H), 1.95−2.08 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.79, 51.13, 35.73, 31.55, 31.05; IR (film, NaCl) 3032 cm^{-1} (br), 1692 cm^{-1} (s).

Preparation of 5-Bromomethyl-3,3-diphenyldihydrofuran-2-one (13) (entry 2, Table 1). 2,2-Diphenyl-4-pentenoic acid (0.631 g, 2.50 mmol), **3** (0.047 g, 0.25 mmol, 10 mol %), NaBr (5.33 g, 51.8 mmo), 20 mL of ether, 20 mL of 0.23 M pH 6.0 phosphate buffer, and 30% H_2O_2 (5.9 mL, 52 mmol, 2 M in total aqueous volume) were treated as described above for 24 h. The crude product was purified via chromatography on SiO_2 (CH_2Cl_2/hexanes, 4:1) and then recrystallized from EtOH to give 0.434 g (53%) of **13**[21] as a white solid, mp 87.0−88.5 °C (lit.[21] mp 88−90 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.36 (m, 10 H), 4.51−4.59 (m, 1 H), 3.61 (dd, J = 5, 10 Hz, 1 H), 3.51 (dd, J = 6.6, 10 Hz, 1 H), 3.16 (dd, J = 5, 13.1 Hz, 1 H), 2.81 (dd, J = 10, 13.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.02, 141.34, 139.11, 128.79, 128.24, 127.70, 127.42, 127.17, 127.01; IR (KBr) 1757 cm^{-1} (s).

Preparation of 3a-Bromohexahydrobenzofuran-2-one (14) and 5-Bromo-1-oxa-spiro[3.5]nonan-2-one (15) (entry 3, Table 1). 2-(1-Cyclohexenyl)acetic acid (0.350 g, 2.50 mmol) was treated as described above for 24 h. The product was purified by chromatography on SiO_2 (ether) to give **14** (0.155 g, 29%) and **15** (0.345 g, 64%) as an orange oil.

For **14**:[20b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (t, J = 4.4 Hz, 1 H), 3.04 (d, J = 17.1 Hz, 1 H), 2.91 (d, J = 17.1 Hz, 1 H), 2.16−2.31 (m, 2 H), 1.51−1.99 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.16, 84.24, 59.18, 46.67, 37.06, 25.66, 21.32, 19.53; IR (film, NaCl) 1789 cm^{-1} (s).

For **15**:[20b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31−4.34 (m, 1 H), 3.43 (d, J = 16.5 Hz, 1 H), 3.09 (d, J = 16.5 Hz, 1 H), 2.16−2.31 (m, 2 H), 1.51−1.99 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.75, 78.00, 54.58, 46.36, 32.81, 32.49, 22.20, 22.02; IR (film, NaCl) 1830 cm^{-1} (s).

Preparation of 4,5-Dibromopentan-1-ol (16) (entry 4, Table 1). 4-Penten-1-ol (0.215 g, 2.50 mmol) was treated as described above for 24 h. The 2-(bromomethyl)tetrahydrofuran (**17**) was detected by ^{1}H NMR spectroscopy and co-distilled with unreacted 4-penten-1-ol. The crude product was then purified via chromatography on SiO_2 (EtOAc/hexanes, 3:2) to give **16**[22] (0.293 g, 48%) as an orange oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16−4.21 (m, 1 H), 3.83 (dd, J = 4.3, 10.3 Hz, 1 H), 3.66 (t, J = 6.3 Hz, 2 H), 3.61 (t, J = 10 Hz, 1 H), 2.21−2.28

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(m, 1 H), 2.04 (br s, 1 H), 1.77−1.87 (m, 2 H), 1.61−1.70 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.79, 52.65, 36.19, 32.55, 29.80; IR (film, NaCl) 3359 cm^{-1} (br).

Preparation of 1-Bromo-2,4,6-trimethoxybenzene (18) (entry 1, Table 2). 1,3,5-Trimethoxybenzene (0.421 g, 2.50 mmol) was treated as described for 24 h. The crude product was passed through a short plug of SiO_2 eluted with CH_2Cl_2 and was then recrystallized from hexanes to give **18** (0.485 g, 80%) as a white solid, mp 93.5−95.0 °C (lit.[23] mp 98−99 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 2 H), 3.86 (s, 6 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.43, 157.42, 91.60, 56.30, 55.46.

Preparation of 2-Bromo-*N*,*N*-dimethylaniline (19) and 4-Bromo-*N*,*N*-dimethylaniline (20) (entry 2, Table 2). *N*,*N*-Dimethylaniline (0.303 g, 2.50 mmol) was treated as described above for 19 h. The crude product was purified by chromatography on SiO_2 (CH_2Cl_2) followed by Kugelrohr distillation to give **19** (0.239 g, 47%) as a colorless oil and **20** (0.195 g, 39%) as a white solid, mp 51.5−53.0 °C (lit.[24] mp 53−54 °C).

For **19**:[25] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 1.5, 8 Hz, 1 H), 7.24 (dt, J = 1.5, 7.5 Hz, 1 H), 7.07 (dd, J = 1.5, 8 Hz, 1 H), 6.87 (dt, J = 1.5, 7.5 Hz, 1 H), 2.79 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.79, 133.80, 128.01, 123.82, 120.42, 119.09, 44.13.

For **20**:[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 9 Hz, 2 H), 6.57 (d, J = 9 Hz, 2 H), 2.90 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.40, 131.57, 113.99, 108.35, 40.43.

Preparation of *N*-(2-Bromophenyl)morpholine (21) and *N*-(4-Bromophenyl)morpholine (22) (entry 3, Table 2). *N*-Phenylmorpholine (0.408 g, 2.50 mmol) was treated as described above for 24 h. The crude product was purified by chromatography on SiO_2 (CH_2Cl_2) followed by Kugelrohr distillation to give *N*-(2-bromophenyl)morpholine (0.206 g, 34%) as an orange oil and *N*-(4-bromophenyl)morpholine (0.315 g, 52%) as a white solid, mp 112−115 °C (lit.[26] mp 114.5−115.5 °C).

For **21**:[27] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 1.4, 8.0 Hz, 1 H), 7.27 (dt, J = 1.5, 7.7 Hz, 1 H), 7.03 (dd, J = 1.4, 8.0 Hz, 1 H), 6.91 (dt, J = 1.4, 7.5 Hz, 1 H), 3.86 (t, J = 4.7 Hz, 4 H), 3.02 (t, J = 4.5 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.29, 133.86, 128.27, 124.54, 120.79, 119.81, 67.11, 52.03.

For **22**:[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 9 Hz, 2 H), 6.75 (d, J = 9 Hz, 2 H), 3.83 (t, J = 4.8 Hz, 4 H), 3.10 (t, J = 4.8 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.20, 131.80, 117.14, 111.96, 66.61, 48.98.

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