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Imidazolium-containing diselenides for catalytic oxidations with hydrogen peroxide and sodium bromide in aqueous solutions

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ABSTRACT

The design and synthesis of imidazolium-containing diselenides **4a**–**c** is described. The introduction of the *N*-methylimidazolium group gives freely soluble compounds in water, unlike the majority of common organic diselenides. Catalytic amounts of **4a**–**c** effectively promote bromination of organic substrates using a safe and inexpensive NaBr/H_2O_2 system in water. Kinetics experiments revealed that the bromination of 4-pentenoic acid has a first-order dependence with respect to both NaBr and H_2O_2 concentrations The rate of reaction was also sensitive to the pH of the solution. Preparative reactions showed that, compared to **4a**, diphenyl diselenide **5** was a poor catalyst and the ionic liquid 1-benzyl-3-methylimidazolium bromide **6** showed no catalytic activity with H_2O_2 indicating synergy from the combined functionality.

1. Introduction

Halogenated compounds are key synthons in organic transformations and frequently exhibit biological activity.[1] However, in most protocols their synthesis involves the use of molecular halogen or other sources of positive halogen, both of which can have adverse impact on health and the environment. Currently there is increased interest in developing new halogenation methods that are efficient, environmentally benign, and non-toxic.[2]

Reactions using H_2O_2/bromide salts to replace bulk Br_2 as a reagent are attractive for organic bromination reaction: (1) H_2O_2 is an inexpensive oxidizing agent, (2) it decomposes to oxygen and water, and (3) bromide is a safe and inexpensive halogen precursor relative to toxic and corrosive Br_2.[2c] However, even though H_2O_2 is a potent oxidizing agent thermodynamically, reactions with H_2O_2 can be sluggish kinetically limiting its application. Organochalcogen compounds have been extensively employed as catalysts/activators of H_2O_2 in many diverse transformations, including epoxidation reactions,[3] Baeyer–Villiger oxidations,[4] and oxidations of thiols and sulfides[5] among others.[6] Organoselenium catalysts have also found synthetic utility for the halogenation of organic compounds in several different ways: bromination via reaction of diorganylselenides with Br_2,[7] halogenation via the combination of a halosuccinimide with PhSeSePh or PhSeCl,[8] and bromination via the activation of H_2O_2 for the oxidation of sodium bromide to 'Br^+' species using selenoxides or aryl seleninic acids as catalysts.[9,10]

As a continuation of our interest in the use of organochalcogen compounds as catalysts for the activation of H_2O_2[11] we describe herein the preparation of new water-soluble diselenides **4a**–**c** (Chart 1). These compounds were evaluated as catalysts to promote bromination reactions with H_2O_2/NaBr in aqueous solutions. The incorporation of the *N*-methylimidazolium group as in **4a**–**c** greatly enhances water solubility. This feature in synergism with the diselenide functionality improves the catalytic activity of **4a**–**c** when compared to diphenyl diselenide **5** or to the ionic liquid 1-benzyl-3-methylimidazolium bromide **6**.

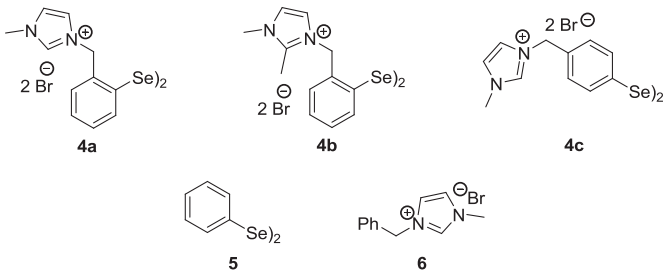

Chart 1. Structures of catalysts used in this study.

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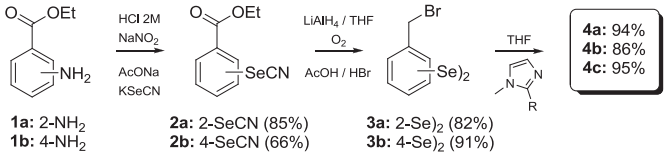
2. Results and discussion

Diselenides **4a**–**c** were prepared by the reaction sequence shown in Scheme 1. Diazotization of ethyl aminobenzoate **1** with $HCl/NaNO_2$, followed by reaction with KSeCN gave selenocyanate **2**.[12] Compound **2** was then reduced with $LiAlH_4$ in THF and converted to the dibromomethylphenyl diselenide **3** by heating in an acetic acid/HBr solution. The final step in the synthetic route was the reaction of bromide **3** with 1-methylimidazole or 1,2-dimethylimidazole in THF to furnish the desired catalysts **4a**–**c** in a range of 86–95% yield. Diselenides **4a**–**c** are stable compounds and completely water soluble at the concentrations that we examined. These compounds were fully characterized by HRMS, ^1H and ^{13}C NMR spectroscopy and showed the characteristic chemical shift for diselenides in their ^{77}Se NMR spectra ($\delta \approx 450$ ppm).



Scheme 1. Synthetic route for the preparation of catalysts **4a**–**c**.

In order to evaluate the ability of diselenides **4a**–**c** to activate H_2O_2 in aqueous solutions, we studied the oxidation of NaBr. The formation of 'Br^+' can be indirectly measured by the appearance of brominated products of 4-pentenoic acid (**7**, Table 1). Bromination of **7** gives a mixture of 4,5-dibromopentanoic acid (**8**) and bromolactone **9** under a variety of conditions. Upon standing at pH 6, dibromide **8** is converted completely to bromolactone **9**. The progress of the reaction can be easily followed by ^1H NMR since **7** and **8**/**9** have distinct ^1H NMR signals for the alkene and bromoalkane regions.[9]

A kinetic study of the NaBr oxidation was performed by ^1H NMR spectroscopy at 298.1±0.1 K with pH 6 phosphate buffer solutions in D_2O, 4-pentenoic acid (**7**, 0.12 M), catalyst **4** (2.5 mol %), H_2O_2 (0.35–1.4 M) and NaBr (0.64–2.58 M). Rate constants (k_{obs}) and relative rates (k_{rel}) presented in Table 1 are the average of duplicate runs obtained under conditions where pseudo-first-order behavior was followed. The ^1H NMR signal of H_2O/HOD was suppressed and propionic acid (0.01 M) was used as an internal standard to assess the conversion of 4-pentenoic acid into products. Diphenyl diselenide **5** was not sufficiently soluble in the aqueous solvent to include in this kinetic study in D_2O. The relative catalytic activity of **5** is described in later experiments using 1,4-dioxane as an organic co-solvent.

The vital role of catalyst **4a** in the oxidation of NaBr is evident by comparison of rates in the catalyst-free reaction with rates using 2.5 mol % of **4a**, entries 1 and 2, respectively (Table 1). The rate using 2.5 mol % of catalyst **4a** is 130-fold faster than the background (catalyst-free) reaction. For comparison purposes, the conditions used in entry 2 were employed as standard conditions. Under pseudo-first-order conditions (excess H_2O_2 and NaBr), bromination of **7** showed first-order dependence for H_2O_2 (Fig. 1a), with k_{obs} in a range of 6.99×10^{-5} s^{-1} to 2.51×10^{-4} s^{-1} (entries 2–4, Table 1). With respect to the NaBr concentration, a similar first-order dependence was observed (Fig. 1b) with k_{obs} in the range of 1.04×10^{-4} s^{-1} to 3.03×10^{-4} s^{-1} (entries 2, 5 and 6, Table 1).

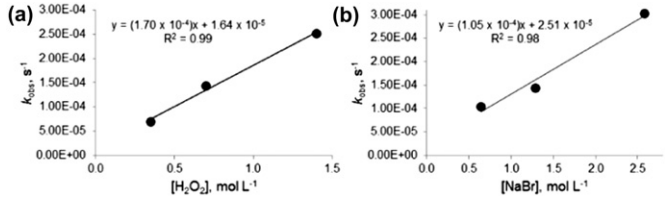
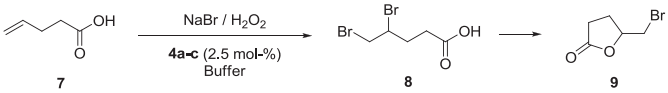


Fig. 1. Reaction rate dependence for the bromination of 4-pentenoic **7** acid using 2.5 mol % of **4a** on: (a) H_2O_2 concentration; (b) NaBr concentration.

Catalysts **4b** with a 2-methyl substituent on the imidazolium ring, and **4c**, with selenium functionality in the *para*-position, were also tested under the standard reaction conditions. Catalyst **4b**, k_{rel}=0.98, displayed essentially the same catalytic activity as **4a** (k_{rel}=1.00), (entries 2 and 7, Table 1). The results with **4b** suggest that neither increased steric interactions from the 2-methyl substituent nor the enhanced acidity of the hydrogen bonded to the 2-position of the imidazolium ring, as in catalyst **4a**, plays a significant role in the catalytic process.[13] However, the position of the imidazolium ring relative to the selenium functionality does impact catalytic activity. The catalytic activity of *ortho*-substituted catalysts **4a** and **4b** is approximately 3-fold higher than that observed for **4c** with selenium functionality in the *para*-position (entries 2, 7 and 8, Table 1).

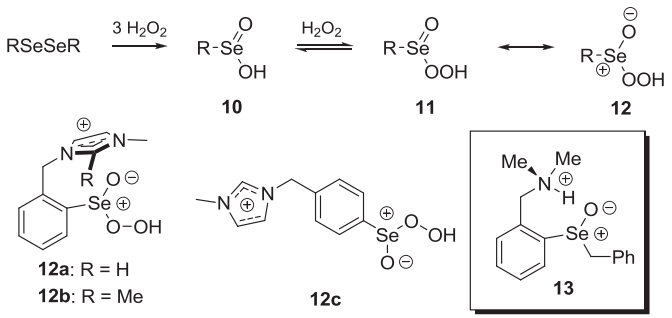
The synthetic utility of diselenides as catalysts in oxidation reactions arises from its combination with H_2O_2 to produce seleninic acids **10** and perseleninic acids **11**/**12** (Scheme 2). The latter are the active species in oxidations promoted by the diselenide/H_2O_2 system.[3,4,6,9d] The question can be asked as to why the imidazolium-containing catalysts are more active than phenylseleninic acid and why the *ortho*-substituted derivatives **12a**,**b** are more active than *para*-substituted derivative **12c**. The positive charge on the *ortho*-substituted imidazolium ring derivatives is positioned to contribute electrostatically to stabilizing negative charge development in the perseleninic intermediate **12a**,**b** from diselenides **4a** and **4b** as shown in Scheme 2. For the *para*-substituted derivative **4c**, similar electrostatic stabilization cannot occur intramolecularly in the seleninic acid/H_2O_2 intermediate **12c** and intermolecular stabilization (dimer formation) would be necessary. A previous study for oxidation of NaBr with H_2O_2 using selenoxide catalysts demonstrated increased catalytic activity for selenoxides bearing chelating amino groups.[9e] Under the conditions of reaction described in Ref. 9e, selenoxide derivative **13** would be protonated and an electrostatic stabilization of the selenoxide oxygen similar to that described for **12a**,**b** for the perseleninic acid intermediate would favor addition of H_2O_2 to **13** and, thus, would increase catalytic activity. The electronic structure of the imidazolium group renders it positive at all times and is consistent with electrostatic contributions to the increased catalytic activity observed with **12a**,**b**.

Table 1
Bromination of 4-pentenoic acid **7** in aqueous solution promoted by **4a**–**c**



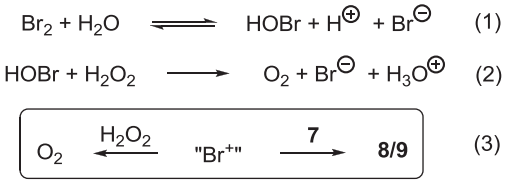
Entry[a]	Cat	pH	$[H_2O_2]$ (mol/L)[b]	[NaBr] (mol/L)[b]	k_{obs} (s^{-1})[c]	k_{rel}
1	—	6.1	0.7	1.29	$(1.07\pm0.55)\times10^{-6}$	0.01
2	**4a**	6.1	0.7	1.29	$(1.44\pm0.02)\times10^{-4}$	1.0
3	**4a**	6.1	0.35	1.29	$(6.99\pm0.15)\times10^{-5}$	0.49
4	**4a**	6.1	1.4	1.29	$(2.51\pm0.03)\times10^{-4}$	1.74
5	**4a**	6.1	0.7	0.64	$(1.04\pm0.02)\times10^{-4}$	0.72
6	**4a**	6.1	0.7	2.58	$(3.03\pm0.04)\times10^{-4}$	2.10
7	**4b**	6.1	0.7	1.29	$(1.41\pm0.03)\times10^{-4}$	0.98
8	**4c**	6.1	0.7	1.29	$(5.27\pm0.10)\times10^{-5}$	0.37
9	**4a**	4.2	0.7	1.29	$(2.49\pm0.03)\times10^{-4}$	1.73
10	—	4.2	0.7	1.29	$(4.30\pm0.12)\times10^{-6}$	0.03

[a] 4-Pentenoic acid=0.12 mol/L (final concentration), catalyst=2.5 mol % (related to 4-pentenoic acid).
[b] Final concentrations.
[c] Average of duplicate runs that agreed within 5% at 298.1±0.1 K.



Scheme 2. Intermediates in seleninic acid-catalyzed reactions with H_2O_2.

The influence of the pH in the reaction course was another parameter considered. Using the same concentrations of reagents, the bromination of 4-pentenoic acid (**7**) carried out at pH 4.2 (NaH_2PO_4 0.5 M) is roughly two times faster than that at pH 6.1 (Table 1, entries 2 and 9). Nevertheless, in the catalyst-free reaction at pH 4.2, negligible bromination of **7** was observed. The catalyzed reaction is approximately 60 times faster than the catalyst-free reaction (Table 1, entries 9 and 10, respectively). The role of pH on the rates of bromination is consistent with the fate of bromine produced in the aqueous solution. In water, bromine is reversibly hydrolyzed to produce hypobromous acid, bromide and 1 equiv of proton, Scheme 3, Eq. (1).[14] Under acidic conditions, the equilibrium is shifted to the formation of bromine. On the other hand, if HOBr is predominant in the equilibrium and H_2O_2 is present, the reaction that can take place is the irreversible disproportionation of H_2O_2, producing singlet oxygen, bromide and a proton, as shown in Eq. (2).[15] In other words, the 'Br^+' produced in the media (HOBr, Br_2 or Br_3^-) can be competitively quenched by H_2O_2 or react with substrate to produce product, as shown in Eq. (3).



Scheme 3. Reaction sequences for the hydrolysis of Br_2 or H_2O_2 disproportionation promoted by HOBr.

We next examined a series of preparative experiments [1.5 mmol of 4-pentenoic acid (**7**)] in order to optimize the formation of the brominated products **8**/**9** using a NaBr/H_2O_2 mixture catalyzed by **4a** (Table 2). Considering that, ideally, the reaction should be acidic and have a lower concentration of H_2O_2 to minimize the unproductive disproportionation of H_2O_2, further experiments were conducted at pH 4.2. Initially the number of equivalents of H_2O_2 required to accomplish the bromination of 4-pentenoic acid (**7**) was evaluated in reactions conducted for 24 h at ambient temperature. The composition of the reaction mixture was analyzed by ^{1}H NMR spectroscopy following extraction of products with ethyl acetate and quenching the remaining peroxide with a sodium bisulfite wash. As indicated in Table 2 the reaction with 3 equiv of H_2O_2 and 2.5 mol % of catalyst **4a** gave the best results, with complete consumption of **7** after 24 h and bromolactone **9** as the only observable product (by ^{1}H NMR spectroscopy), which was recovered in a yield of 61% (entry 2). Reactions carried out with 5 equiv of H_2O_2 produced 51% of the same product, while 1.5 equiv were not sufficient to give complete conversion of 4-pentenoic acid (**7**) to products (Table 2, entries 1 and 3, respectively). Incomplete bromination of **7** was also observed employing 1.0 mol % of catalyst or in a catalyst-free reaction (entries 4 and 5, respectively).

Table 2
Optimization of the yield of bromination products for 4-pentenoic acid with **4a**, NaBr and H_2O_2

#[a]	H_2O_2 (equiv)	Cat (mol %)	Rxn (h)	NaBr (equiv)	Yield[b] (%)		
					7	**8**	**9**
1	5.0	**4a**/2.5	24	20	0	0	51
2	3.0	**4a**/2.5	24	20	0	0	61
3	1.5	**4a**/2.5	24	20	9	2	50
4	3.0	**4a**/1.0	24	20	8	3	54
5	3.0	—	24	20	69	6	7
6	3.0	**4a**/2.5	6	20	0	14	55
7	3.0	**4a**/2.5	6[c]	20	0	8	77
8	3.0	**4a**/2.5	2[c]	20	0	23	55
9	3.0	**4a**/2.5	1[c]	20	11	30	39
10	3.0	**5**/2.5	2[c]	20	59	11	11
11	3.0	**6**/2.5	2[c]	20	73	2	1
12	3.0	**4a**/2.5	2[c]	10	13	14	45
13	3.0	**4a**/2.5	2[c]	5	29	9	41

[a] Reaction at room temperature; solvent=20 mL of aqueous 0.5 M NaH_2PO_4 (pH 4.2); [4-pentenoic acid (**7**)=0.075 mol/L].
[b] Yield determined by ^{1}H NMR spectroscopic analysis of the extracted mass (ethyl acetate, 4×8 mL) followed by addition of 0.5 g of $NaHSO_3$ to the organic layer. The organic phase was then washed with brine (1×10 mL), dried with $MgSO_4$, filtered, and solvent removed.
[c] Solvent=20 mL of a 3/1 mixture of NaH_2PO_4 0.5 M in water (pH 4.2) and 1,4-dioxane.

The apparent inconsistency of the results using different amounts of H_2O_2 was elucidated in another set of experiments. The kinetics experiments showed a linear relationship between the increase of the peroxide concentration and consumption of 4-pentenoic acid over the initial half-life of reaction, where conditions remain pseudo-first-order. The preparative reactions under the conditions of Table 2, while initially pseudo-first-order, will become higher order as H_2O_2 is consumed and rates of reaction will slow. The data in Table 2 also indicate that the use of 3 equiv of H_2O_2 instead of 5 gives a higher yield of brominated products. We reasoned that this discrepancy may be actually due to the hydrolysis of the final product, so an experiment was performed using a shorter reaction time (6 vs 24 h). The amount of isolated brominated products increased by 8%, full consumption of **7** was observed along with 4,5-dibromopentanoic acid **8** (14%) and lactone **9** (55%) (Table 2, entry 2 vs entry 6).

1,4-Dioxane was found to be an effective co-solvent with pH 4.2 phosphate buffer in entries 7–13 of Table 2. The reactions were homogeneous and products could be readily extracted from the 3/1 buffer/dioxane solvent. With catalyst **4a**, the buffer/dioxane solvent increased the yield of brominated products to 85% with bromolactone **9** as the major product (Table 2, entry 7). Shorter reaction times with this solvent system gave different distribution of products, and clearly showed that the full conversion of starting material to the brominated products occurs between 1 h and 2 h of reaction (entries 8 and 9).

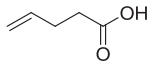
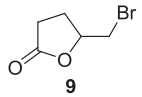
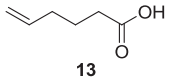
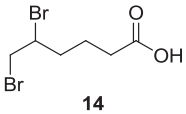
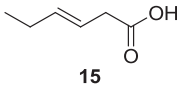
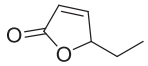
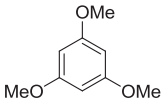
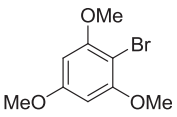
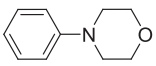
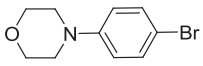
Diphenyl diselenide **5**, which was soluble in the 3/1 buffer/dioxane solvent, was a poorer catalyst compared to the diselenide **4a** under the conditions described in Table 2. While catalyst **4a** promoted complete bromination of **7** within 2 h (≥5 half-lives) with brominated products isolated in 78% yield, PhSeSePh (**5**) gave only 22% bromination of 4-pentenoic acid with 59% 4-pentenoic acid (**7**) remaining (<1 half-life, Table 2, entries 8 and 10, respectively). Brominated products **8** and **9** were observed in only 11% yield by ^{1}H NMR spectroscopy using PhSeSePh (**5**) as catalyst. Ionic liquid **6** lacking the diselenide functionality gave only trace amounts of brominated products **8** and **9** as observed by ^{1}H NMR spectroscopy (entry 11).

Lowering the amount of NaBr also reduced the yield of brominated products **8** and **9** in the **4a**-catalyzed reactions. With 10 and 20 equiv of NaBr, 4-pentenoic acid (**7**) was observed as 13% and 29%

of the reaction mixture, respectively (entries 12 and 13, respectively, Table 2).

The results from a series of preparative bromination reactions (1.5 mmol in substrate) with 4-pentenoic acid, 5-hexenoic acid, *E*-3-hexenoic acid, 1,3,5-trimethoxybenzene, and *N*-phenylmorpholine as substrates are summarized in Table 3. These substrates were chosen primarily due to their commercial availability. The reactions were run using 2.5 mol % of diselenide **4a** as catalyst and 3/1 pH 4.2 phosphate buffer/1,4-dioxane as solvent.

Table 3
Representative substrates brominated using $NaBr/H_2O_2$ with 2.5 mol % of **4a** in a 3/1 mixture of pH 4.2 phosphate buffer/dioxane

#[a]	Substrate	H_2O_2 (equiv)	Time (h)	Product	Yield[b] (%)	Catalyst-free (%)[c]
1	 **7**	3	7	 **9**	82±3	4
2[d]	 **13**	3	2.5	 **14**	68±2	1
3[d]		3	7		65±4	n.d.
4	 **15**	3	7	 **16**	79±2	2
5	 **17**	1.1	4.5	 **18**	94±2	3
6	 **19**	1.1	4.5	 **20**	71	n.d.
7		1.5	4.5		87±4	2

[a] Substrate=1.5 mmol; H_2O_2 (8.8 M) using the amounts indicated in the table; NaBr 30 mmol (20 equiv); catalyst **4a** 2.5 mol % (related to substrate); solvent=20 mL of a 3/1 mixture of NaH_2PO_4 0.5 M in water (pH 4.2) and 1,4-dioxane; room temperature.
[b] Average isolated yields of duplicate reactions.
[c] Yields from ^1H NMR spectroscopy.
[d] Along with approximately 4% of six-membered lactone.

On the 1.5-mmol scale, 4-pentenoic acid **7** gave bromolactone **9** in 82% isolated yield after 7 h of reaction, while only 4% of the same product was observed in the catalyst-free reaction (Table 3, entry 1). Bromination of **7** was also conducted on a 20-mmol scale in pH 4.2 phosphate buffer (200 mL) and 1,4-dioxane (70 mL) using 2.5 mol % of diselenide **4a** as catalyst, 20 equiv of NaBr and 3 equiv of H_2O_2. After 7 h of reaction at ambient temperature, bromolactone **9** was extracted from the aqueous phase with ethyl acetate in 2.65 g (74%) yield. Bromination of 5-hexenoic acid **13** gave 5,6-dibromohexanoic acid (**14**, 68% yield) as the major product after 2.5 h of reaction (Table 3, entry 2). A longer reaction time (7 h) did not improve this result (entry 3). In both cases, approximately 4% of the corresponding six-membered bromolactone was formed. With this substrate, the catalyst-free reaction gave only trace amounts of brominated products ($\leq$1%). Bromination of *E*-3-hexenoic acid **15** followed by elimination of HBr furnished 5-ethyl-2-furanone **16** in 79% yield (entry 4). With this substrate, the uncatalyzed reaction gave $\leq$2% of the same product. The electron rich aromatic compounds 1,3,5-trimethoxybenzene **17** and 4-phenylmorpholine **19** were efficiently brominated using lower quantities (1.1–1.5 equiv) of H_2O_2 under the standard conditions. Negligible product formation was observed in the catalyst-free experiments (entries 5–7).

3. Conclusions

In this study we describe the synthesis of novel, water-soluble diselenides **4a**–**c**, which are efficient catalysts for the oxidation of NaBr with H_2O_2 in aqueous solutions. The *N*-methylimidazolium group in these compounds imparts the water solubility, a characteristic uncommon in ordinary organic diselenides. The formation of 'Br^+' species was monitored by ^1H NMR spectroscopy in D_2O, through the reaction of 'Br^+' with 4-pentenoic acid. Kinetics experiments revealed that the reaction for the oxidation of NaBr with H_2O_2 is first-order dependent in both NaBr and H_2O_2 and is also sensitive to the pH of the reaction medium. The catalytic performance of **4a**–**c** is impacted by the proximity of the imidazole group to the selenium functionality. With **4a** and **4b**, the imidazole group is in the *ortho*-position and these two compounds showed nearly identical catalytic activity. In contrast, **4c** with the imidazole group in the *para*-position relative to the selenium functionality was approximately 3-fold less active. These data suggest that electrostatic interactions are perhaps important in stabilizing the seleninic acid/H_2O_2 intermediate. Diphenyl diselenide was a very poor catalyst for bromination with H_2O_2/NaBr and the ionic liquid 1-benzyl-3-methylimidazolium bromide **6** showed no catalytic activity for the same transformation. An obvious synergy is apparent from the linking of the two different functional groups.

Bromination of organic substrates was observed in all-aqueous solutions using **4a** as a catalyst for H_2O_2 activation. However, improved results were obtained employing 3/1 mixtures of 0.5 M NaH_2PO_4 (pH 4.2) and 1,4-dioxane as an organic co-solvent. The use of 2.5 mol % of **4a** allowed bromination of suitable substrates employing the $NaBr/H_2O_2$ system in high yields as shown in Table 3. In contrast, catalyst-free systems gave negligible formation of products in control experiments. Bromination of 4-pentenoic acid was also successfully performed on a multi-gram scale. Other synthetic applications for the activation of H_2O_2 by **4a**–**c** are currently under investigation.

4. Experimental section

4.1. General

^1H, ^{13}C and ^{77}Se NMR spectra were recorded at 500, 75 and 76 MHz, respectively, with tetramethylsilane as internal standard for ^1H and ^{13}C spectra and diphenylselenide as internal standard for ^{77}Se NMR spectra. All other solvents and chemicals were used as purchased unless otherwise noted.

*4.1.1. Procedure for the synthesis of **2a**–**b**.*[12] A mixture of ethyl aminobenzoate **1a** or **1b** (3.3 g, 20 mmol) and $NaBF_4$ (3.3 g, 30 mmol) was suspended in 2 N HCl (30 mL) at 0 °C. Then a solution of $NaNO_2$ (1.45 g, 21 mmol, dissolved in 20 mL of water) was added dropwise while the mixture was held at 0 °C. After stirring for 1 h, saturated sodium acetate (ca. 40 mL) was added dropwise until the mixture reached pH 6. Then, the mixture was poured in one portion into an aqueous solution of KSeCN (2.88 g, 20 mmol, dissolved in 40 mL of water). The reaction mixture was stirred 1 h at ambient temperature and then extracted with Et_2O (3×30 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated. Purification was performed via column chromatography on flash silica, eluting with a 20/80 (v/v) mixture of ethyl acetate/hexanes.

*4.1.1.1. Ethyl 2-selenocyanatobenzoate (**2a**).* Pale yellow solid, mp 122–124 °C; Yield 85%; ^1H NMR ($CDCl_3$, 500 MHz): δ=8.13 (d, J=8.0 Hz, 1H), 8.06 (d, J=9.0 Hz, 1H), 7.60 (t, J=7.0 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 4.44 (q, J=6.8 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=167.85, 134.48, 131.28, 131.09, 129.93, 127.49, 126.44, 105.81, 62.63, 14.12; HRMS, m/z 254.9804 (calcd for $C_{10}H_9NO_2{}^{80}Se$ 254.9799).

*4.1.1.2. Ethyl 4-selenocyanatobenzoate (**2b**).* Yellow solid, mp 112–114 °C; Yield 66%; ^1H NMR ($CDCl_3$, 500 MHz): δ=8.06 (d, J=8.5 Hz, 2H), 7.67 (d, J=8.5 Hz, 2H), 4.40 (q, J=7.0 Hz, 2H), 1.41 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=165.27, 131.35, 131.22, 131.12, 127.80, 100.39, 61.39, 14.15; HRMS, m/z 254.9796 (calcd for $C_{10}H_9NO_2{}^{80}Se$ 254.9799).

*4.1.2. Procedure for the synthesis of **3a**–**b**.*[12] $LiAlH_4$ (285 mg, 7.5 mmol) was suspended in anhydrous Et_2O (60 mL) under an argon atmosphere and **2a** or **2b** (1.27 g, 5 mmol, dissolved in 40 mL of Et_2O) was slowly added to the mixture. After heating at reflux for 2 h, the reaction mixture was cooled with an ice bath, 2 N HCl (ca. 25 mL) was carefully added and the mixture was stirred under air overnight. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The crude alcohol was dried under vacuum for 2 h and acetic acid (25 mL) was added, followed by the slow addition of 48% hydrobromic acid (17 mL). The resulting mixture was heated at 90 °C for 3.5 h and then cooled to ambient temperature. Aqueous Na_2CO_3 was added to neutralize the reaction mixture, which was then extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered through Celite®, and concentrated. The crude product, **3a** or **3b**, was used in the next reaction without further purification.

*4.1.2.1. 1,2-Bis(2-(bromomethyl)phenyl)diselenide (**3a**).*[12] Brownish-orange solid, mp 71–73 °C; Yield: 82%; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.72 (d, J=8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.26 (t, J=7.5 Hz, 1H), 7.21 (t, J=7.5 Hz, 1H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=139.22, 135.41, 132.47, 130.08, 129.66, 128.98, 33.85, HRMS, m/z 497.7635 (calcd for $C_{14}H_{12}Br_2{}^{80}Se_2$ 497.7636).

*4.1.2.2. 1,2-Bis(4-(bromomethyl)phenyl)diselenide (**3b**).* Yellow solid, mp 84–85 °C; Yield 91%; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.49 (d, J=7.5 Hz, 2H), 7.21 (d, J=8.5 Hz, 2H), 4.38 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=137.35, 131.52, 130.97, 129.80, 32.76; HRMS, m/z 497.7635 (calcd for $C_{14}H_{12}Br_2{}^{80}Se_2$ 497.7636).

*4.1.3. Procedure for the synthesis of **4a**–**c**.* 1-Methylimidazole (0.95 mL, 11 mmol) or 1,2-dimethylimidazole (0.98 mL, 11 mmol) was added to a solution of **3a** or **3b** (2.49 g, 5 mmol) in THF (5 mL) and the resulting solution was stirred at ambient temperature. Within 20 min of the addition of the imidazole, the formation of a yellow solid could be observed. After 4 h, Et_2O (10 mL) was added and the resulting mixture stirred for an additional 10 min. The solids in the reaction mixture were allowed to settle and the organic layer was decanted. Another 10 mL of Et_2O was added, the mixture stirred for 10 min, allowed to settle and decanted. This procedure was repeated a total of three times. Finally, the product (yellow solid) was dried under vacuum overnight and kept under argon.

*4.1.3.1. Diselenide (**4a**).* Yellow solid (hygroscopic), yield 94%; ^1H NMR (D_2O, 500 MHz): δ=8.58 (s, 1H), 7.43–7.38 (m, 3H), 7.31 (s, 1H), 7.27–7.24 (m, 1H), 7.20 (s, 1H); 5.30 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (D_2O, 125 MHz): δ=137.87, 136.11, 135.42, 131.36, 131.04, 130.80, 130.63, 123.70, 122.09, 52.89, 35.86; ^{77}Se NMR (D_2O, 76 MHz): δ=454.87; HRMS, $m/2z$ 252.0160 (calcd for $[C_{14}H_{24}N_4{}^{80}Se_2]^{2+}$ 252.0160).

*4.1.3.2. Diselenide (**4b**).* Yellow solid (hygroscopic), yield 86%; ^1H NMR (D_2O, 500 MHz): δ=7.48 (d, J=7.5 Hz, 1H), 7.36 (t, J=7.0 Hz, 1H), 7.22 (t, J=7.5 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J=7.5 Hz, 1H), 6.87 (s, 1H), 5.11 (s, 2H), 3.63 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (D_2O, 125 MHz): δ=144.51, 137.91, 135.60, 130.84, 130.68, 130.28, 129.74, 122.44, 120.54, 51.63, 34.82, 9.41; ^{77}Se NMR (D_2O, 76 MHz): δ=458.65; HRMS, m/z 610.9822 (calcd for $[C_{24}H_{28}BrN_4{}^{80}Se_2]^+$ 610.9822).

*4.1.3.3. Diselenide (**4c**).* Yield 95%; ^1H NMR (CD_3OD, 500 MHz): δ=8.90 (s, 1H), 7.62 (d, J=8.5 Hz, 2H), 7.55 (s, 1H), 7.54 (s, 1H), 7.32 (d, J=8.5 Hz, 2H), 5.37 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (D_2O, 125 MHz): δ=135.83, 133.38, 131.57, 131.38, 129.57, 123.85, 121.95, 51.99, 35.79; ^{77}Se NMR (D_2O, 76 MHz): δ=451.41; HRMS, m/z 582.9515 (calcd for $[C_{22}H_{24}BrN_4{}^{80}Se_2]^+$ 582.9509).

4.2. Procedure for the synthesis of 1-benzyl-3-methylimidazolium bromide (6).[16]

1-Methylimidazole (1.6 mL, 20 mmol) was added to a solution of benzyl bromide (3.49 g, 20 mmol) dissolved in THF (20 mL). The mixture was stirred at ambient temperature overnight and the solvent removed furnishing a viscous oil. This oil was washed with Et_2O (3×10 mL) and dried under vacuum. The final product is a pale yellow oil, yield 86%; ^1H NMR (CD_3OD, 500 MHz): δ=9.07 (s, 1H), 7.62 (t, J=2.0 Hz, 1H), 7.59 (t, J=2.0 Hz, 1H), 7.46–7.40 (m, 5H), 5.44 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz): δ=135.33, 130.27, 130.20, 129.80, 125.11, 123.45, 53.82, 36.85.

Kinetic studies: all the solutions used for these experiments were prepared in D_2O. The progress of the reaction was monitored by ^1H NMR spectroscopy at 298±0.1 K suppressing the signal corresponding to the H_2O/HOD signal. Different stock solutions were prepared in pH 6.1 phosphate buffer (Na_2HPO_4, 0.25 M) or pH 4.2 (NaH_2PO_4 0.5 M) containing 4-pentenoic acid (**7**, 0.15 M), propionic acid (0.010 M), and NaBr (0.825 M, 1.65 M or 3.3 M). Serial dilution of H_2O_2 was employed to prepare 4.4 M and 2.2 M solutions from commercially available 8.8 M H_2O_2. Catalysts **4a**–**c** were dissolved in D_2O to produce 0.05 M solutions. One milliliter of the stock solution was transferred to a vial (0.15 mmol of **7** along with the corresponding amount of NaBr), followed by the addition of 75 μL of the stock solution of catalyst **4a**–**c** (0.00375 mmol, 2.5 mol %) and 205 μL of the desired H_2O_2 solution. The mixture was quickly transferred to a 5-mm NMR tube and acquisitions were recorded at 300-s intervals with the total time of the experiment being approximately 90 min. The consumption of 4-pentenoic acid was measured comparing the changes between the relative integral values of the internal alkene proton of 4-pentenoic acid (δ=5.8 ppm) and the methylene protons of propionic acid (δ=1.1 ppm). The results were plotted following pseudo-first-order conditions (time in seconds vs ln [4-pentenoic acid]).

4.3. General procedure for bromination of organic substrates

1,4-Dioxane (5 mL) was added to a mixture of substrate (1.5 mmol) and NaBr (3.09 g, 30 mmol). Catalyst **4a**, 2.5 mol % (25 mg, 0.0375 mmol) was dissolved in 15 mL of a pH 4.2 phosphate solution (NaH_2PO_4 0.5 M) and added to the reaction mixture. Then, H_2O_2 (8.8 M) was added (the number of equivalents of H_2O_2 is described in Table 3) and the reaction stirred at room temperature for the amount of time reported in Table 3. The products were extracted with ethyl acetate (4×8 mL), the combined organic extracts were washed with 20 mL of $NaHSO_3$ 0.5 M, 20 mL of brine, dried over $MgSO_4$, and concentrated under vacuum. When required, purification was performed by column chromatography on flash silica.

*4.3.1. 5-(Bromomethyl)dihydrofuran-2(3H)-one (**9**)[9f] (Table 3, entry 1).* Yield 82%; ^1H NMR ($CDCl_3$, 500 MHz): δ=4.78–4.73 (m, 1H), 3.60–3.53 (m, 2H), 2.70–2.54 (m, 2H), 2.49–2.42 (m, 1H), 2.17–2.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=176.10, 77.77, 34.07, 28.27, 26.07.

*4.3.2. 5,6-Dibromohexanoic acid (**14**) (Table 3, entry 2).* Yield 68%; ^1H NMR ($CDCl_3$, 500 MHz): δ=11.68 (br, 1H), 4.19–4.15 (m, 1H), 3.88–3.85 (m, 1H), 3.63 (t, J=10.0 Hz, 1H), 2.48–2.40 (m, 2H), 2.26–2.20 (m, 1H), 2.00–1.92 (m, 1H), 1.89–1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=179.40, 51.91, 35.90, 35.23, 33.12, 22.03; HRMS m/z calcd for $[C_6H_9Br_2O]^+$ 254.9015, found 254.9015.

*4.3.3. 5-Ethylfuran-2(5H)-one (**16**)[17] (Table 3, entry 3).* Yield 79%; ^1H NMR ($CDCl_3$, 500 MHz): δ=7.47 (d, J=5.5 Hz, 1H), 6.12 (d, J=5.5 Hz, 1H), 5.02 (t, J=5.5 Hz, 1H), 1.88–1.83 (m, 1H), 1.77–1.71 (m, 1H), 1.02 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=173.15, 156.08, 121.64, 84.25, 26.22, 8.94.

*4.3.4. 2-Bromo-1,3,5-trimethoxybenzene (**18**)[9f] (Table 3, entry 4).* Yield 94%; ^1H NMR ($CDCl_3$, 500 MHz): δ=6.16 (s, 2H), 3.87 (s, 6H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=160.36, 157.34, 91.83, 91.59, 56.24, 55.42.

*4.3.5. N-(4-Bromophenyl)morpholine (**20**)[9f] (Table 3, entry 5).* Yield 87%; ^1H NMR ($CDCl_3$, 400 MHz): δ=7.34 (d, J=9.0 Hz, 2H), 6.75 (d, J=11.5 Hz, 2H), 3.83 (t, J=6.5 Hz, 4H), 3.10 (t, J=6.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=150.20, 131.84, 117.17, 112.02, 66.65, 49.00.

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