Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 7191–7198
Tetrahedron

# Selenium-catalyzed oxidative halogenation

Shelli R. Mellegaard-Waetzig, Chao Wang and Jon A. Tunge*

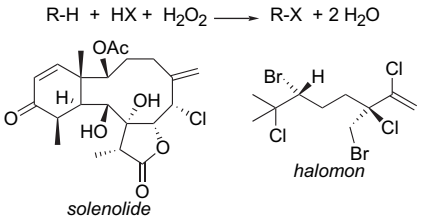
*Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045, USA*

Received 1 December 2005; accepted 5 December 2005
Available online 11 May 2006

**Abstract**—Organoselenides catalyze the oxidation of halides by $H_2O_2$. Furthermore, these selenides catalyze the transfer of oxidized halogens from *N*-halosuccinimides to olefins and ketones. Thus, organoselenides catalyze oxidative halogenation reactions including halolactonization, α-halogenation of ketones, and allylic halogenation. The ability of selenium to undergo reversible $2e^-$ oxidation–reduction chemistry facilitates halogenation through selenium-bound halogen intermediates.


## 1. Introduction

Biological systems use haloperoxidase enzymes to catalyze the halogenation of organic substrates with $H_2O_2/X^-$ (X= Cl, Br, and I; Scheme 1), resulting in a wealth of halogenated natural products.[1–4] While their biological function is often unknown, several halometabolites have been shown to be involved in chemical defense.[5] The properties that make these compounds feed deterrents also lead to antibacterial, antifungal, antiviral, and antitumor activity.[6] Common structural motifs include substituted tetrahydrofurans and tetrahydropyrans, which are apparently derived from halocyclization reactions.[3] Also, products such as the antiviral solenolide[7] and the antitumor agent halomon[8] are seemingly derived from simple additions such as dihalogenation, allylic halogenation, and halohydration of terpenes. The efficient synthesis of such compounds necessitates the selective introduction of carbon–halogen bonds, unfortunately most attempts to selectively halogenate substrates in vitro using haloperoxidase enzymes have failed.[9,10] This failure has been ascribed to the propensity of the enzymes to release freely-diffusing sources of oxidized halogen (HOX and $X_2$).[1] Thus, the development of a synthetic haloperoxidase that halogenates substrates through reagent-bound intermediates remains a significant challenge.




**Scheme 1**.

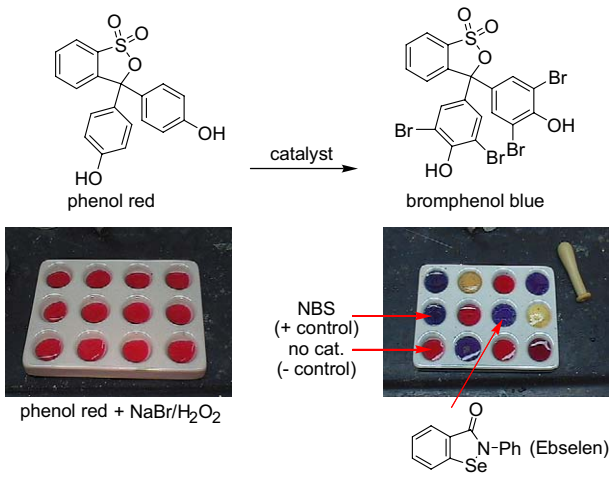
Selenium compounds are of interest for haloperoxidase mimicry due to the biological role of selenium in peroxide activation. In response to oxidative stress, the enzyme glutathione peroxidase utilizes catalytic selenocysteine residues to remove peroxides by oxidation of the sulfide glutathione.[11] Since oxidative stress has been correlated with aging and disease,[12] various synthetic selenium antioxidants have been produced as potential pharmaceuticals.[13] Many of these have been shown to be effective at catalytic reduction of peroxide.[14] In fact, some selenium-containing peroxidase catalysts have been used to catalyze oxidative halogenations,[15] however, these catalysts appear to function only as halide oxidants that produce freely-diffusing electrophilic halogen sources such as $Br_2$. Thus, in pursuit of reagent-controlled selectivity, our goal is to catalyze oxidative halogenation *through catalyst-bound halogen sources*.

Initially, potential catalysts were screened for their ability to catalyze haloperoxidase-like chemistry. The conversion of phenol red to bromophenol blue was used as a qualitative measure of the haloperoxidase activity. Electrophilic halogenation of phenol red produces bromphenol blue, so electrophilic halogenation through oxidized halogen species can be easily probed by color change (Scheme 2).[16] Treatment of a 0.08 M aqueous NaBr solution containing phenol red (0.1 mmol) and PhSeCl (0.02 mmol) with $H_2O_2$ resulted in a steady change in color from red to deep blue over a period of 24 h. The cyclic selenamide Ebselen behaved similarly, although its solubility was significantly lower. The control, which contained no selenium, remained unchanged.

Having identified several potential selenium catalysts for oxidative halogenation, attention was turned to the development of synthetic methods for the introduction of halogen functionality. While the oxidation of phenol red was a useful initial screen, it was unclear from these experiments whether the oxidative halogenation was occurring through

* Corresponding author. E-mail: tunge@ku.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.12.072



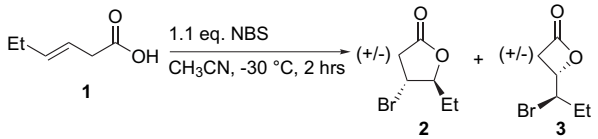

**Scheme 2**. Screening for haloperoxidase-like activity.

freely-diffusing oxidized halogens (i.e., $Br_2$ and HOBr) or through reagent-bound oxidized halogens. With the eventual goal of exploiting catalyst-control of regio- or stereoselectivity, we felt it was crucial that the catalysts halogenate organic substrates through reagent-bound halogen species. Thus, a reagent that can catalytically oxidize $Br^-$ to '$Br^+$' must also be capable of catalyzing $Br^+$ addition to the substrates. Since we know that various selenium catalysts are capable of catalyzing the oxidation of halides, we shifted our focus to catalyzing $X^+$ transfer from 'preoxidized' halogen sources such as *N*-halosuccinimides.

Since haloperoxidase enzymes seemingly control a wide variety of halogenation reactions, we chose to investigate the ability of organoselenium compounds to catalyze a diverse array of oxidative halogenation reactions. These include halolactonization, α-halogenation of ketones, and allylic halogenation.[17]

## 2. Halolactonization

To begin, a variety of selenium catalysts were screened for their ability to control the regioselectivity of bromolactonization with *N*-bromosuccinimide (NBS).[17a] Although it was not tested in our model study using phenol red, diphenyl diselenide turned out to be the most active and selective catalyst for bromolactonization (Scheme 3). While cyclization of *trans*-3-hexenoic acid using NBS in the absence of catalyst exhibited a 2:1 selectivity for the formation of the γ-lactone, performing the same reaction in the presence of 5 mol % diphenyl diselenide led to a useful regioselectivity of

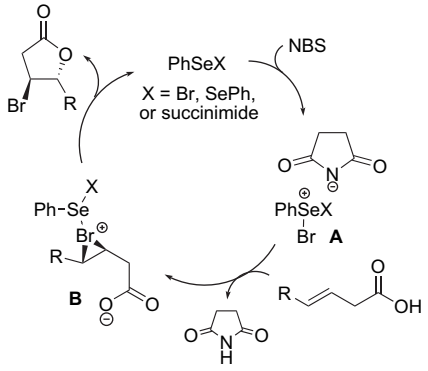



| | 2 | 3 |
|---|---|---|
| **no catalyst** | 2 | 1 |
| **5 mol % PhSeSePh** | 17 | 1 |
| **5 mol % PhSeBr** | 4 | 1 |
| **5 mol % PhSe(pthalimide)** | 2 | 1 |

**Scheme 3**. Selenium-catalyzed halolactonization.

17:1 in favor of the γ-lactone (**2**). Furthermore, the β-lactone (**3**) was not converted to the γ-lactone under the conditions of catalysis, so the observed regioselectivity is the result of kinetic control rather than thermodynamic control.

Careful investigation of this transformation substantiated the catalytic effect of PhSeSePh. Specifically, time-dependent $^1H$ NMR spectroscopic investigation of the reaction mixtures with and without catalyst were performed at −30 °C in $CD_3CN$. At this temperature, hexenoic acid failed to react with NBS in the absence of catalyst, however, NBS rapidly reacted in the presence of 5 mol % PhSeSePh. Furthermore, the fact that free NBS is not observed in solution suggested that the overall rate of the catalytic reaction was dictated by the rate of dissolution of NBS in $CH_3CN$. While conclusive mechanistic studies remain to be done, we propose that the electrophilic NBS is activated via nucleophilic attack by PhSeSePh (Scheme 4). The oxidized selenium halide is then capable of cyclizing the olefin in a manner similar to bromopyridinium reagents, where the pyridine (or selenium) derivative remains coordinated to bromine during lactone ring formation.[18]




**Scheme 4**.

Encouraged by the reactivity of the selenium catalyst, we were able to show multiple examples of halocyclizations of other unsaturated acids, as well as an example of chlorolactonization utilizing NCS and PhSeCl (Fig. 1).

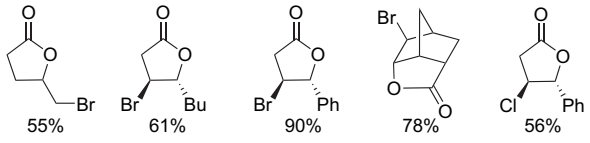


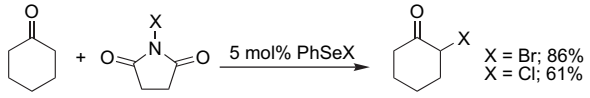

**Figure 1**. Products of selenium-catalyzed halolactonization.

## 3. α-Halogenation

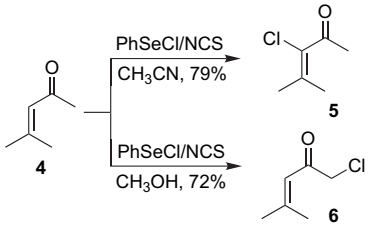
Having demonstrated that organoselenium reagents can activate electrophilic halogen sources toward oxidative halogenation, we turned our attention to α-halogenation of ketones.[17b] In this case, a catalyst screen revealed phenylselenium halides to be more active than other selenium catalysts such as diphenyl diselenide.

Cyclohexanone underwent α-monohalogenation with either NCS or NBS and 5 mol % of the corresponding phenylselenium halide (Scheme 5). No reaction was observed for either

case in the absence of the selenium catalyst. Mesityl oxide (**4**) also underwent clean α-chlorination with a curious solvent-dependent regioselectivity (Scheme 6). In acetonitrile, only the product of vinyl halogenation (**5**) was formed,[19] while in methanol only the product of methyl halogenation (**6**) was observed. This difference in regiochemistry is likely caused by different catalyst speciation in $CH_3OH$ versus $CH_3CN$.

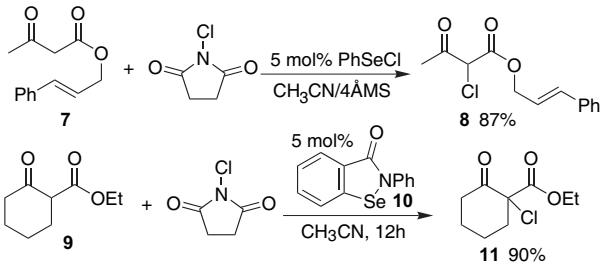



**Scheme 5**.



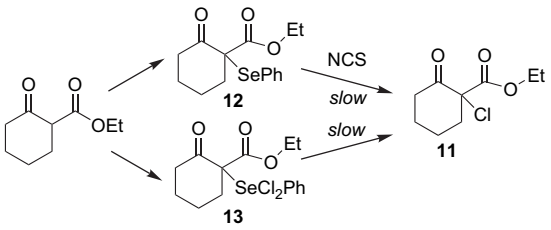

**Scheme 6**.

Halogenation of β-ketoesters was also investigated. Bromination of β-ketoesters was difficult to control, producing mixtures of mono- and α,α-dibrominated products. However, chlorination proceeded smoothly to provide mono-chloro-β-ketoesters in good yield. While a variety of β-ketoesters undergo monochlorination, the ability to monochlorinate the β-ketoester fragment of **7** in the presence of a reactive olefin is particularly noteworthy (Scheme 7). In addition, the pharmaceutical peroxidase Ebselen (**10**) was a competent catalyst, however, the rate of catalysis was slow due to the poor solubility properties of the cyclic selenimide.

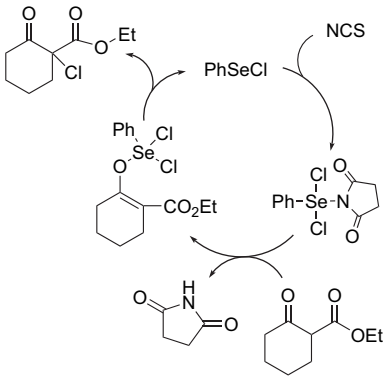



**Scheme 7**.

The mechanism of oxidative chlorination was probed by preparation of several potential intermediates (**12** and **13**, Scheme 8). The fact that formation of chlorinated product from α-selenylated intermediates is not kinetically competent with the observed catalysis strongly suggests that the reaction proceeds by an electrophilic chlorination mechanism rather than electrophilic selenylation. This is important because it indicates that selenium catalysts function by enhancing the electrophilicity of oxidized halogen sources. We speculate that the activation of NCS proceeds by oxidative addition to PhSeCl to form an Se(IV) intermediate (Scheme 9).[20] Deprotonation and halogen transfer would complete the catalytic cycle.




**Scheme 8**.

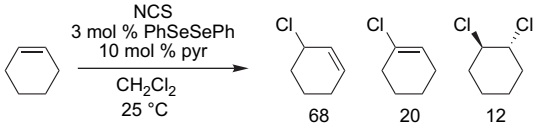



**Scheme 9**.

## 4. Allylic halogenation

While the halolactonization and α-halogenation reactions do not proceed by formation of C–Se bonds, the reaction of Se(II)- and Se(IV)-halogen reagents with alkenes is a well-known method for the stereospecific *anti*-addition of Se–X bonds to olefins.[21] Often times, this stoichiometric addition is followed by oxidative *syn*-elimination of selenium to regenerate an alkene.[22] Thus the selenium addition–elimination sequence is a potentially powerful synthetic tool for creating carbon–halogen bonds without loss of any substrate functionality (i.e., olefins are regenerated).

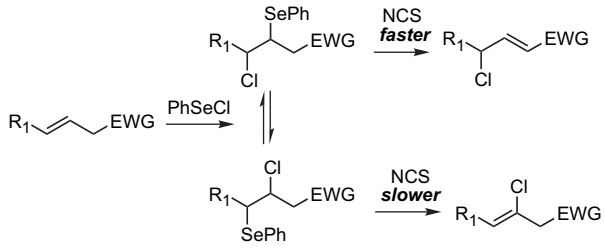
Sharpless initially reported that the addition and elimination steps can be combined in one pot, resulting in allylic halogenation,[20] however, the reaction was complicated by competing formation of regioisomers as well as vinyl halides and dihalides (Scheme 10).




**Scheme 10**.

We felt that a synthetically useful procedure would result if competing formation of vinyl halide was circumvented by providing either an electronic or steric bias for the elimination reaction (Scheme 11). Toward this end, β,γ-unsaturated carboxylic acids, nitriles, and esters were subjected to our modified conditions for selenium-catalyzed allylic halogenation.[17c] In each of these cases, the allylic chlorides are isolated as single regioisomers, and <5% of vinyl chlorides and dichlorides are formed (Fig. 2). Clearly the presence of an

electron-withdrawing group leads to preferred formation of the conjugated products.




**Scheme 11**. Electronic control of the elimination regiochemistry.

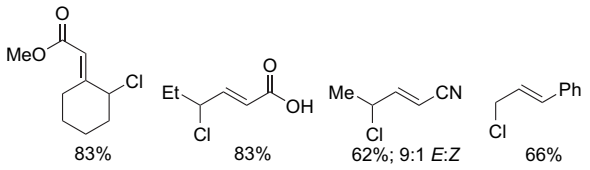
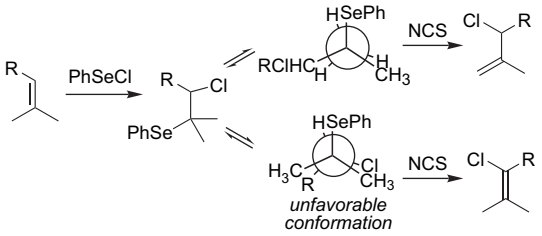



**Figure 2**.

In addition to the electronic bias present in the above substrates, the selectivity of halogenation can also be controlled by sterics. This is most evident in the high selectivity for allylic halogenation exhibited by prenyl olefins (Scheme 12). If we assume that the elimination proceeds by *syn*-elimination of H and Se, as is common for selenium eliminations, then the elimination to form vinyl chloride requires adoption of a high-energy eclipsed conformation. Consistent with this picture, treatment of a variety of prenyl olefins under the conditions for selenocatalytic allylic chlorination produced the terminal olefinic regioisomers with high selectivity (>85%, Fig. 3).




**Scheme 12**.

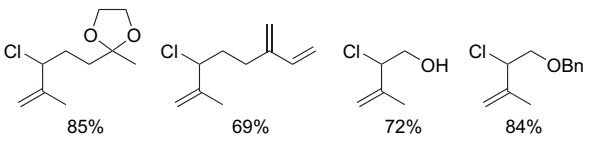
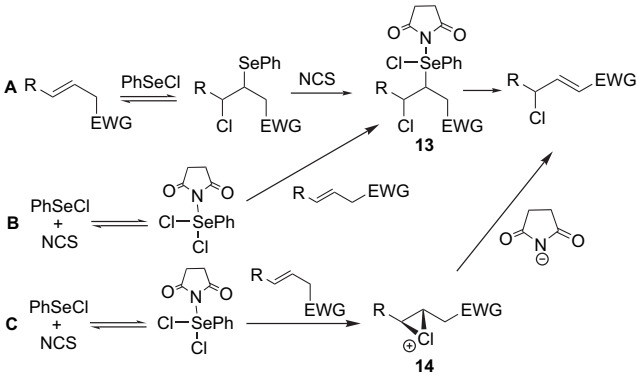



**Figure 3**.

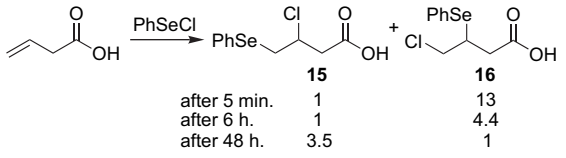
## 5. Mechanism of allylic chlorination

We envisioned that allylic chlorination might occur in one of three ways,[23] designated paths A, B, and C (Scheme 13). Path A is characterized by 1,2-addition of phenylselenium chloride across the olefin. Oxidation of the addition product by NCS would lead to **13**. Finally, elimination of succinimide would produce the allyl halide and regenerate the catalyst. Path B involves oxidative addition of NCS to phenylselenium chloride,[20] forming phenyl(succinimidyl)-selenium dichloride. The selenium(IV) chloride could then add across the olefin, producing **13**, which will follow the same course as in path A. Finally, in mechanism C, an oxidized selenium compound could act as a source of chloronium ions, leading to allyl halide through a pathway similar to that observed for Walling chlorination with ROCl.[24] Ultimately, pathways A and B are distinguished by the oxidation states of selenium in the addition and C is distinguished by the lack of formation of a C–Se bond.




**Scheme 13**.

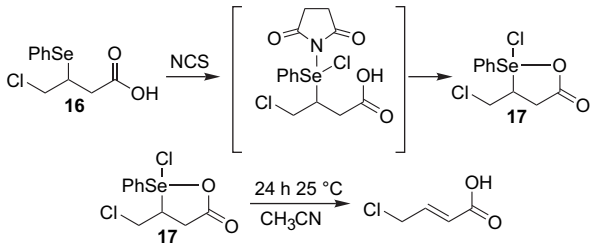
To distinguish between these pathways, experiments were conducted with stoichiometric quantities of PhSeCl in hopes of observing the elementary steps of catalysis. We chose to initiate studies by investigating the elementary steps in the order proposed for mechanism A: addition of PhSeCl to the olefin, oxidation of Se(II) to Se(IV), and subsequent elimination. Thus, we first treated 3-butenoic acid [0.23 M] with 1 equiv PhSeCl in dry $CD_2Cl_2$. After 5 min at ambient temperature, a 1:13 ratio of **15**:**16** exists (Scheme 14).[25] Upon prolonged standing, this mixture equilibrates to a 3.5:1 ratio of **15**:**16**. Thus, **16** is the kinetic product and **15** is the thermodynamic product.




**Scheme 14**.

Next, in order to look at the oxidation step necessary for mechanism A, a solution of kinetic addition products was generated followed by the addition of NCS after 5 min. The oxidation occurred rapidly (<5 min), forming succinimide and a new compound in >90% yield as judged by integration of the $^1$H NMR spectrum. Although the oxidized product was not stable to isolation, it has been tentatively assigned as the selenurane **17** based on NMR spectroscopic characterization and the observed liberation of succinimide (Scheme 15). The formation of this compound can be explained by oxidation of addition product **16** by NCS, followed by elimination of succinimide.[26] Importantly, allowing **17** to stand at room temperature resulted in the clean liberation of allylic halide. Furthermore, the elimination occurred with a concomitant change in the color of the solution

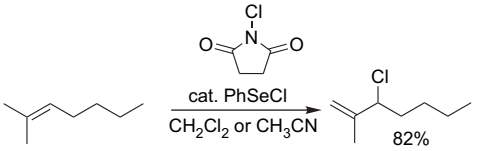
to orange, the color expected if PhSeCl was regenerated. The formation of a relatively stable selenurane is also consistent with the faster reaction of esters (which cannot form selenurane) as compared to carboxylic acids. In fact, no intermediates were observed when the NCS oxidation was performed on the analogous substrate where the carboxylic acid was protected as the methyl ester.




**Scheme 15**.

While we have not ruled out potential mechanism B, the combination of each of the steps observed with stoichiometric selenium represents a closed catalytic cycle for selenocatalytic allylic halogenation through mechanism A.

At this point, one major issue remained unexplained. Qualitatively, these reactions appeared to be inhibited by NCS, with the most dramatic inhibition occurring with β,γ-unsaturated carboxylic acids. Because the halogenation of acids was inhibited by even a small excess of NCS relative to PhSeCl, we chose to conduct kinetic experiments on a more easily studied substrate, 2-methyl-2-heptene (Scheme 16).




**Scheme 16**.

The reaction of 2-methyl-2-heptene with pseudo-first order concentrations of NCS was studied by $^1$H NMR spectroscopy in $CD_2Cl_2$. The control reaction of 2-methyl-2-heptene with NCS in the absence of PhSeCl was slow, providing 5% conversion upon standing for 24 h in $CH_2Cl_2$ at ambient temperature. In contrast, the initial rates of 2-methyl-2-heptene conversion in the presence of 2.5 and 5 mol % PhSeCl and 0.24 M NCS were $3.6(5)\times10^{-4}$ s$^{-1}$ and $6.7(3)\times10^{-4}$ s$^{-1}$ ($t_{1/2}$~17 min), respectively.[27]

Examining the effect of higher NCS concentrations on the rate proved more interesting. The overall rates of product formation decrease with increasing [NCS], confirming that NCS is inhibiting the reaction (Fig. 4). However, close analysis of the data shows that the initial rates of reaction are the same throughout the range of 0.24–0.54 M [NCS] (Fig. 5). In other words, the initial catalysis is zero-order in NCS, but the overall rates and conversions are inhibited by NCS.

Given the observed kinetics, the rate law for selenium-catalyzed allylic halogenation follows the rate law $-$d[2-methyl-heptene]/d$t$=$k$[PhSeCl][olefin] at an early reaction

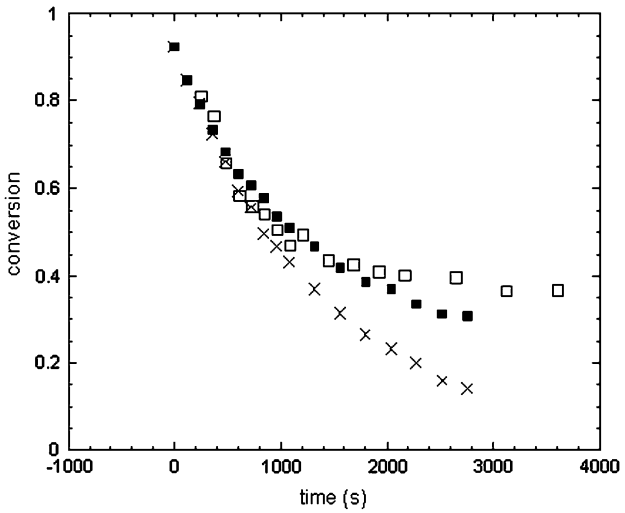



**Figure 4**. Decay of 0.016 M 2-methyl-2-heptene at × 0.24 M, ■ 0.37, and □ 0.55 M NCS in $CD_2Cl_2$.

time. We have conclusively shown that the rate-limiting step for allylic halogenation of β,γ-unsaturated acids is the elimination step. Since the addition of PhSeCl to alkenes and the oxidation of Se(II) to Se(IV) are processes that are known to be rapid,[20] we propose that elimination is rate-limiting for other substrates as well. The zero-order dependence of the initial rate on [NCS] is most easily explained if one assumes that the resting state of the catalyst is PhSe(succinimide)$Cl_2$ (Scheme 17). Under these conditions the compositions of both the resting state and rate-limiting transition state (elimination) include one NCS molecule, thus a zero-order dependence on [NCS] would be expected. Consistent with the hypothesis of PhSe(succinimide)$Cl_2$ as the resting state, the $^{77}$Se resonance for PhSeCl in $CD_2Cl_2$ ($\delta$ 1042 ppm) is immediately replaced by a new species with a resonance at $\delta$ 701 ppm upon addition of 1 equiv of NCS. Furthermore, the inhibition of both rate and conversion at high [NCS] and long reaction times indicates the presence of a process that irreversibly destroys the catalyst. Importantly, over the timescale of typical catalysis (1–3 h), the $^{77}$Se resonance at 701 ppm slowly decays with the appearance of a new species at $\delta$ 905 ppm. While we cannot

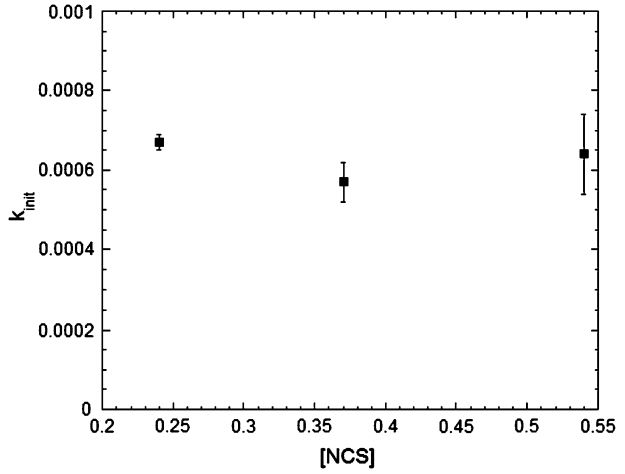
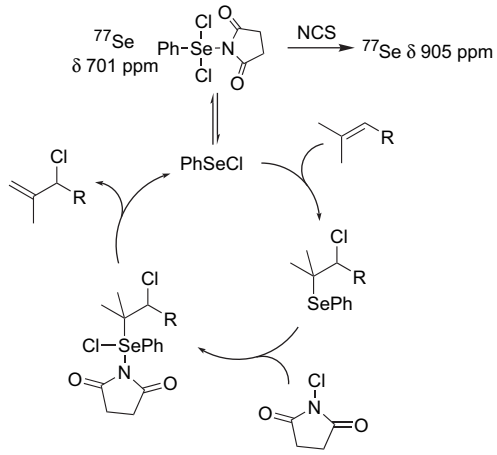


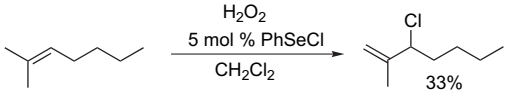

**Figure 5**. Initial rate of 2-methyl-2-heptene decay as a function of [NCS].

comment further on the identity of this selenium complex, it seems likely that it is the product of over-oxidation to a Se(VI) complex.




**Scheme 17**.

Finally, since arylselenides have been established as peroxidase catalysts as well as catalysts for oxidative halogenation, we were interested in the possibility of using simple arylselenides as selective haloperoxidase analogous. Indeed, when phenylselenium chloride (5 mol %) is allowed to react with 2-methyl-2-heptene and sodium chloride in a biphasic $CH_2Cl_2$/30% $H_2O_2$ mixture, allyl halide **8a** is produced in 33% yield after 1 h (Scheme 18). While the conversion is not high, this experiment demonstrates the potential utility of selenium reagents as selective, synthetic haloperoxidases.




**Scheme 18**.

## 6. Conclusions

In conclusion, allylic oxidation of alkenes takes advantage of the facile 1,2-addition and 1,2-elimination reactions afforded by Se(II) and Se(IV), respectively. Ultimately, catalysis of halolactonization, α-halogenation, and allylic chlorination is made possible through the accessibility of selenium-centered $2e^-$ oxidation–reduction cycles. In this way, selenium is analogous to many transition metal catalysts, which operate by similar Tolman cycles.

## 7. Experimental

### 7.1. General

$^1H$ NMR spectra were obtained on a Bruker Avance 400 spectrometer and referenced to residual protio solvent signals. $^{13}C$ and $^{77}Se$ NMR spectra were obtained on a Bruker Avance 500 DRX spectrometer. Structural assignments are based on $^1H$, $^{13}C$, DEPT-135, COSY, and HMQC spectroscopies. Column chromatography was performed with silica gel, (0.06–0.2 mm). Reactions were monitored by thin-layer chromatography on Merck Kieselgel $60F_{254}$.

### 7.2. General procedure for bromolactonization

Diphenyl diselenide (0.05 mmol) was dissolved in 5 mL of $CH_3CN$ (stored over 4 Å MS), which produced a yellow solution. The unsaturated acid (1.00 mmol) was added, and the resulting mixture was cooled to −30 °C. Next, *N*-bromosuccinimide (1.1 mmol) was added with stirring, and the resulting reaction mixture was stirred until reaction went to completion as determined by TLC analysis (1–5 h). The resulting solution was concentrated to <1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with $H_2O$ (2×3 mL). The resulting ether layer was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography (100% methylene chloride).

### 7.3. General procedure for α-halogenation

The ketone (1 mmol) and PhSeCl (0.05 mmol) were dissolved in dry $CH_3CN$ (stored over 4 Å MS). *N*-Chlorosuccinimide (1.1 mmol) was added and the solution was stirred at room temperature. Upon completion as determined by TLC analysis, the reaction was poured into $H_2O$ (5 mL) and extracted with $Et_2O$ (3×10 mL). The resulting ether layer was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography.

### 7.4. General procedure for allylic halogenation of unsaturated acids

Phenylselenium chloride (10 mol %, 0.052 mmol) was dissolved in 3 mL $CH_3CN$ (stored over 4 Å MS), producing an orange solution. To this solution 4 Å MS (four beads, ~0.15 g) was added followed by addition of the β,γ-unsaturated acid (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. A solution of *N*-chlorosuccinimide (0.57 mmol, in 3 mL $CH_3CN$) was prepared and drawn into a 5 mL GASTIGHT syringe equipped with a Teflon needle. The solution of NCS was added via syringe pump at the rate of 0.191 mL/h. After 16 h, completion of the reaction was confirmed by $^1H$ NMR. This solution was concentrated to <1 mL, and 10 mL diethyl ether was added. The ether was decanted from the solid and washed with $H_2O$ (2×3 mL). The resulting ether layer was dried over $MgSO_4$, concentrated and the residue was purified by flash chromatography (95:5 hexane/ethyl acetate).

### 7.5. General procedure for allylic halogenation of prenyl olefins

Phenylselenium chloride (10 mol %, 0.052 mmol) was dissolved in 3 mL $CH_3CN$ (stored over 4 Å MS), producing an orange solution. To this solution, olefin (0.52 mmol) was added. The addition of the olefin resulted in an immediate color change from orange to pale yellow. *N*-chlorosuccinimide (77 mg, 0.57 mmol) was then added to reaction. After 1 h, completion of the reaction was confirmed by $^1H$ NMR. This solution was concentrated to <1 mL, and

10 mL diethyl ether was added. The ether was decanted from the solid and washed with $H_2O$ (2×3 mL). The resulting ether was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography.

### 7.6. In situ generation of 4-chloro-3-(phenylselanyl)-butanoic acid (16)

PhSeCl (20 mg, 0.1 mmol) was dissolved in 600 μL $CD_2Cl_2$ in an NMR tube to produce an orange solution. To this solution, 3-butenoic acid (1 equiv) was added with shaking. The completion of the reaction was noted by a rapid color change to pale yellow. $^1H$ NMR characterization is consistent with the assigned structure:[25] $^1H$ NMR (400 MHz, $CD_2Cl_2$) $\delta$ 2.70 (dd, $J$=8.6, 16.7 Hz, 1H, CH*H*CHSePh), 3.19 (dd, $J$=4.3, 16.9 Hz, 1H, C*H*HCHSePh), 3.61 (m, 1H, CHSePh), 3.67 (app. t, $J$=10.39 Hz, 1H, CH*H*Cl), 3.96 (dd, $J$=3.8, 10.6 Hz, 1H, C*H*HCl), 7.34 (m, 3H, Ar–H), 7.62 (d, $J$=6.8 Hz, 2H, Ar–H), 10.70 (br s, 1H, $CO_2H$). Allowing the solution of **16** to stand at room temperature for 2 d led to complete equilibration to a 1:3.5 mixture of **16** and **3**-chloro-**4**-(phenylselanyl)butanoic acid (**15**): $^1H$ NMR (400 MHz, $CD_2Cl_2$) $\delta$ 2.79 (dd, $J$=9.1, 16.4 Hz, 1H, CH*H*CHCl), 3.22 (m, 1H, CH*H*CHCl), 3.30 (dd, $J$=3.5, 16.3 Hz, 1H, C*H*HSePh), 3.45 (dd, $J$=4.8, 13.1 Hz, 1H, CH*H*SePh), 4.38 (dt, $J$=4.4, 4.4, 9.1, 9.1 Hz, 1H, CHCl), 7.33 (d, $J$=2.5 Hz, 3H, Ar–H), 7.57 (dd, $J$=2.3, 5.8 Hz, 2H, Ar–H), 11.00 (br s, 1H, $CO_2H$).

### 7.7. In situ generation of selenurane (17)

A solution of **16** was generated as described above. After 5 min, NCS (14 mg, 0.1 mmol) was added. Shaking this mixture resulted in the formation of a colorless solution that contains a 1:1 mixture of succinimide and **17**. $^1H$ NMR (400 MHz, $CD_2Cl_2$) $\delta$ 2.87 (dd, $J$=9.1, 17.4 Hz, 1H, CH*H*CHSePh), 3.17 (d, $J$=17.4 Hz, 1H, CH*H*CHSePh), 4.22 (dd, $J$=12.4 Hz, 1H, C*H*HCl), 4.62 (dd, $J$=4.5, 12.4 Hz, 1H, CH*H*Cl), 4.72 (br s, 1H, CHSePhClO), 7.58 (m, 3H, Ar–H), 7.83 (d, $J$=8.0 Hz, 2H, Ar–H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 34.8 (*C*$H_2CO_2$), 43.8 ($CH_2Cl$), 69.6 (CHSe), 129.3 (Ar C–H), 130.5 (Ar C–H), 132.6 (Ar C–H), 134.5 (q Ar–C).

### 7.8. Kinetics

*N*-Chlorosuccinimide (19–43 mg) was dissolved in dry $CD_2Cl_2$ (580 μL). Upon complete dissolution of the NCS, 2-methyl-2-heptene (10 μL of a 0.97 M standard solution in $CD_2Cl_2$) was added. The NMR tube was sealed with a septum and immediately taken to the NMR spectrometer. Next, PhSeCl (10 μL of a 0.05 M standard solution in $CD_2Cl_2$) was injected and the sample was mixed by shaking. The resulting solutions were quickly inserted into the spectrometer for analysis.

## References and notes


1. *Biohalogenation*; Neidleman, S. L., Geigert, J., Eds.; Wiley: New York, NY, 1986.
2. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
3. (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1–6.
4. Winterton, N. *Green Chem.* **2000**, *2*, 173–225.
5. (a) Paul, V. J.; Hay, M. E.; Duffy, J. E.; Fenical, W.; Gustafson, K. *J. Exp. Mar. Bio. Ecol.* **1988**, *114*, 249–260; (b) Cowart, J. D.; Fielman, K. T.; Woodin, S. A.; Lincoln, D. E. *Mar. Biol.* **2000**, *136*, 993–1002.
6. Faulkner, D. J. *Oceanus* **1992**, 29–35.
7. Groweiss, A.; Look, S. A.; Fenical, W. *J. Org. Chem.* **1988**, *53*, 2401–2406.
8. (a) Egorin, M. J.; Rosen, D. M.; Benjamin, S. E.; Callery, P. S.; Sentz, D. L.; Eiseman, J. L. *Cancer Chemother. Pharmacol.* **1997**, *41*, 9–14; (b) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094–7095.
9. Asymmetric oxidation of sulfides to sulfoxides has been successful with a haloperoxidase enzyme. Andersson, M.; Willets, A.; Allenmark, S. *J. Org. Chem.* **1997**, *62*, 8455–8458.
10. (a) Martinez, J. S.; Carroll, G. L.; Tschirret-Guth, R. A.; Altenhoff, G.; Little, R. D.; Butler, A. *J. Am. Chem. Soc.* **2001**, *123*, 3289–3294; (b) Itoh, N.; Hasan, A. K. M. Q.; Izumi, Y.; Yoshikazu, Y.; Yamada, H. *Eur. J. Biochem.* **1988**, *172*, 477–484.
11. (a) Kohrle, J.; Brigelius-Flohe, R.; Bock, A.; Gartner, R.; Meyer, O.; Flohe, L. *Biol. Chem.* **2000**, *381*, 849–864; (b) Gamble, S. C.; Wiseman, A.; Goldfarb, P. S. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 123–134.
12. *Free Radicals in Molecular Biology, Aging and Disease*; Armstrong, D., Sohal, R. S., Cutler, R. G., Slater, T. F., Eds.; Raven: New York, NY, 1984.
13. Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125–2179.
14. (a) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2002**, *124*, 12104–12105; (b) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1994**, *116*, 2557–2561; (c) Mugesh, G.; Panda, A.; Singh, H. B.; Punekar, N. S.; Butcher, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 839–850.
15. (a) Drake, M. D.; Bateman, M. A.; Detty, M. R. *Organometallics* **2003**, *22*, 4158–4162; (b) Higgs, D. E.; Nelen, M. I.; Detty, M. R. *Org. Lett.* **2001**, *3*, 349–352.
16. (a) Stenger, V. A.; Kolthoff, I. M. *J. Am. Chem. Soc.* **1935**, *57*, 831–833; (b) Martinez, J. S.; Carroll, G. L.; Tschirret-Guth, R. A.; Altenhoff, G.; Little, R. D.; Butler, A. *J. Am. Chem. Soc.* **2001**, *123*, 3289–3294.
17. (a) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979–8981; (b) Wang, C.; Tunge, J. A. *Chem. Commun.* **2004**, 2694–2695; (c) Tunge, J. A.; Mellegaard, S. R. *Org. Lett.* **2004**, *6*, 1205–1207.
18. (a) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977–5982; (b) Neverov, A. A.; Feng, H. X.; Hamilton, K.; Brown, R. S. *J. Org. Chem.* **2003**, *68*, 3802–3810.
19. Ley, S. V.; Whittle, A. J. *Tetrahedron Lett.* **1981**, *34*, 3301–3304.
20. (a) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4204–4208; (b) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208–4210.
21. (a) *The Chemistry of Double-bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, NY, 1977; (b) Engman, L. *J. Org. Chem.* **1987**, *52*, 4086–4094.
22. (a) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86–87; (b) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979–1982; (c) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22–30.
23. Radical inhibitors do not inhibit this reaction.

24. Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877–3884.
25. Selenolactonization of butenoic acid only occurs after passage through silica gel: Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, *50*, 4801–4804.
26. For a similar transformation see: Kataoka, T.; Iwamura, T.; Tsutsui, H.; Kato, Y.; Banno, Y.; Aoyama, Y.; Shimizu, H. *Heteroat. Chem.* **2001**, *12*, 317–326.
27. Clean first-order decay of the 2-methyl-2-heptene was observed over >3 half-lives only when [NCS]<0.3 M.