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Selective Selenocatalytic Allylic Chlorination

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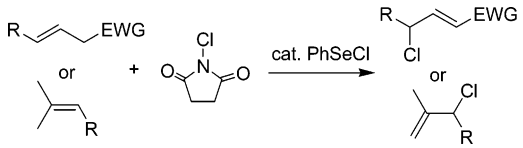
ABSTRACT



Ene-chlorination of olefins by *N*-chlorosuccinimide is catalyzed by phenylselenenyl chloride. This reaction demonstrates the catalytic conversion of C–H bonds into more reactive C–Cl bonds.

The selective conversion of C−H bonds into more reactive functional groups represents a frontier in synthetic organic methodology.[1] We have chosen to focus on the selective catalytic conversion of C−H bonds into carbon−halogen bonds because transformations of the latter play a central role in synthetic chemistry. Recent research has shown that catalytic generation of enolates in the presence of electrophilic halogen sources is a successful strategy toward selective halogenation.[2] In contrast to α-halogenation of carbonyl compounds, allylic halogenation requires substitution of a weakly acidic proton, and selective catalysis of this reaction is not well-studied.[3] This is likely due to the propensity of typical halogenating agents to generate free radicals.[4] Herein we report that selective allylic chlorination can be achieved through selenocatalytic ene-type oxidation of olefins with *N*-chlorosuccinimide.

On the basis of our desire to develop catalysts for oxidative halogenation, we identified two criteria for initial catalyst investigation: (i) the catalyst should be capable of stereospecific addition of halogens to olefins through reagent-bound intermediates so that the addition step might be controlled by changes in the reagent coordination sphere, and (ii) the catalyst should have an accessible 2 e^- oxidation−reduction cycle. These criteria are both met by arylselenium halides.[5,6] In fact, Sharpless communicated that diphenyldiselenide catalyzes the halogenation of olefins with *N*-chlorosuccinimide (NCS); however, the study was limited in scope and the reaction lacked selectivity. Specifically, reaction of simple olefins with NCS in the presence of diselenide catalysts provided mixtures of allyl halides, vinyl halides, and dihalides.[7,8]

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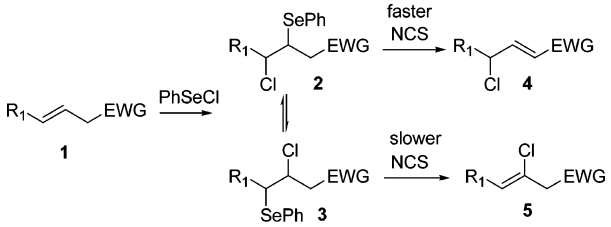
We reasoned that the allyl/vinyl selectivity could be increased by differentiating the acidity of the hydrogens capable of *syn*-elimination from hypothetical selenium addition intermediates **2** and **3** (Scheme 1). Toward this end,

Scheme 1

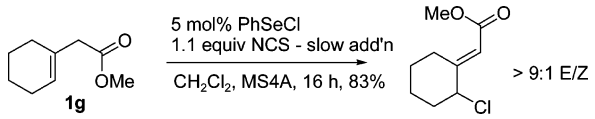


the halogenation of β,γ-unsaturated acids was investigated. Indeed, treatment of vinyl acetic acid (**1a**) with 5 mol % PhSeCl and 1.1 equiv of NCS in CD_2Cl_2 produced the allyl chloride in 70% yield with no evidence for the production of vinyl halides or dihalides. No product was formed in the absence of PhSeCl, demonstrating that PhSeCl is a catalyst or precatalyst for allylic halogenation. Switching the solvent to acetonitrile proved beneficial, and allyl halide was obtained in 82% isolated yield. However, the rates were rather erratic; seemingly identical reactions were complete at varying times (within 1−3 days) at room temperature with some reactions stopping at <60% conversion. Addition of molecular sieves (MS4Å) solved this problem and allowed complete conversion to the allyl halide in 24 h. Qualitatively, it was observed that reactions with higher NCS concentration proceeded more slowly. On the basis of the idea that the reaction was inhibited by NCS, we investigated reactions where the NCS concentration was minimized. It was found that the rates of the reaction could be increased by slow addition of an NCS solution by syringe pump, supporting the idea of some inhibition by NCS. Thus, under optimized conditions vinyl acetic acid was halogenated in 16 h at 25 °C in the presence of 10 mol % PhSeCl, 1.1 equiv NCS, and MS4Å.

The halogenation of substituted allylic acids provided similarly high yields of γ-halo-α,β-unsaturated acids in 16 h at room temperature (Table 1). Importantly, the reactions selectively produced the *E*-isomer as the only isomer within the limits of NMR detection. It is noteworthy that the catalytic production of allyl halides is in contrast to the reaction of β,γ-unsaturated acids with stoichiometric PhSeCl, which results in lactonization.[9]

Protecting the acids as methyl esters substantially reduced the required reaction time. Thus, β,γ-unsaturated esters (**1d**−**g**) provided high yields of chloro-enoates when treated with 5−10 mol % PhSeCl and 1.1 equiv NCS (added by addition funnel or syringe pump) in under 4 h. Disubstituted olefins (**1d**−**f**) produced the *E*-allyl halides exclusively, and the cyclic olefin (**1g**) provided the trisubstituted allyl halide with good *E*/*Z* selectivity (≥9:1, Scheme 2).

Scheme 2



Other electron-withdrawing groups, such as phenyl and cyano, also provided allyl halides selectively. However, allylbenzene and pentenenitrile both required higher catalyst loadings for reasonable rates of conversion to the allyl halide. Furthermore, the *E*/*Z* selectivity for allylic halogenation of 3-pentenenitrile (3:1) was lower than that observed for the corresponding acids and esters but was improved to 9:1 upon chromatographic separation.

Selectivity for allyl halides could also be realized by sterically differentiating the protons capable of elimination. Thus prenyl olefins, where *syn*-elimination to form vinyl chloride requires an unfavorable eclipsed conformation, provide good yields of allyl halides (Scheme 3, Table 2).

Scheme 3

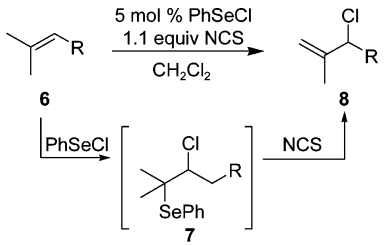


Table 1. Allylic Chlorination of Allylic Acids, Esters, Arenes, and Nitriles

substrate	R1	EWG	time	% yield
1a	H	CO_2H	16 h	82
1b	Et	CO_2H	16 h	83
1c	Bu	CO_2H	16 h	75
1d	Et	CO_2Me	4 h	88
1e	Bu	CO_2Me	4 h	89
1f	Ph	CO_2Me	8 h	77
1h[a]	H	Ph	48 h	66
1i[a]	Me	CN	48 h	62[b]

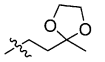
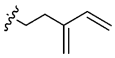
[a] 20 mol % PhSeCl. [b] Isolated as a 9:1 *E*/*Z* mixture

The oxidative halogenation of prenyl olefins was more rapid than the β,γ-unsaturated acids previously described, so slow addition of NCS was not necessary. For example, 2-methyl-2-heptene reacts to give allyl halide in 82% isolated yield in 3 h upon treatment with PhSeCl and NCS in CH_2Cl_2.[10] Prenol (**6c**) reacted much more sluggishly to produce the halohydrin **8c** in 68% yield after 1 day at 35 °C.

(9) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884−3893.

(10) CH_2Cl_2 proved a more convenient solvent for halogenation of prenyl olefins as a result of its volatility and lower water content.

Table 2. Allylic Chlorination of Prenyl Olefins

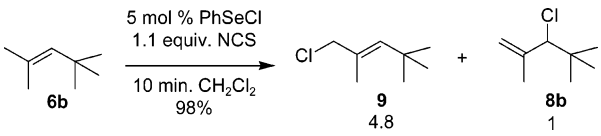
substrate	R	time	% yield
6a	Bu	3 h	82
6b	*tert*-Bu	10 min.	98
6c	CH_2OH	48 h	72
6d	CH_2OBn	3 h	84
6e	CH_2CH_2COMe	4 h	50[a]
6f		4 h	85
6g		24 h	69

[a] Based on ^1H NMR.

The observation that oxidative halogenation is more rapid than alcohol oxidation is interesting in light of the recent report on sulfenamide-catalyzed alcohol oxidation utilizing NCS as the terminal oxidant.[11] As a result of the suspicion that alcohol oxidation may be contributing to the somewhat lower yield, the alcohol was protected as the benzyl ether.[12] This proved successful, reducing the reaction time to 3 h, and pure **8d** was isolated in 84% yield. Reaction of the prenyl ketone **6e** under our standard conditions resulted in the formation of **8e** in low (20−50%) yields along with other products presumably formed by competitive α-selenylation.[13] In line with this assumption, the protected ketone **6f** reacted smoothly to give the allyl halide in 85% yield.

The *tert*-butyl-substituted olefin **6b** did not give the expected product of allylic transposition **8b** as the major product, but rather it reacted to produce a 4.8:1 mix of **9**:**8b** (Scheme 4). Prolonged heating of the product resulted in a

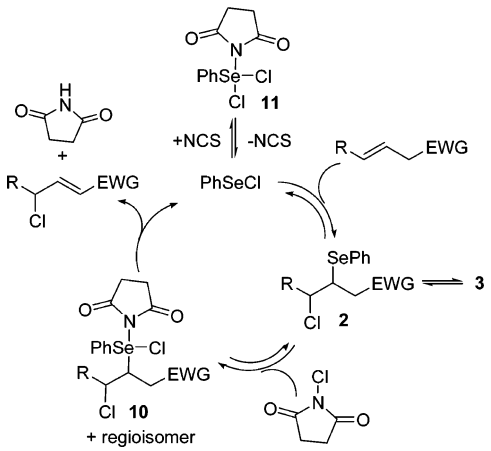
Scheme 4



1:1.2 equilibrium ratio of **9**:**8b**, showing that **9** is the kinetic product of catalytic halogenation. This is the only case where we have observed halogenation without allylic transposition. Interestingly, this substrate was also the most reactive of those studied, with the reaction occurring in <10 min at room temperature. Sharpless noted similar anomalous behavior in the PhSeSePh-catalyzed chlorination of β-pinene; however, in that case PhSeCl was ruled out as the active catalyst.[7b]

The observed catalysis can be adequately described by the catalytic cycle shown in Scheme 5. Phenylselenenyl chloride

Scheme 5



is well-known to undergo 1,2-addition to olefins.[5] This addition is only moderately regioselective for prenyl olefins and β,γ-unsaturated esters[14] but is reversible. Oxidation of the alkylselenide with NCS followed by elimination of succinimide completes the cycle. The observation that a regioisomeric mixture of addition intermediates provides a single product indicates that the oxidation of the alkyl selenides is also reversible. Thus, product allyl halide will result from the regioisomeric intermediate that most rapidly undergoes elimination.

The observed inhibition by NCS can be explained by reversible oxidation of the catalyst, which will sequester some catalyst in an inactive complex **11**. The likely role of the molecular sieves is to protect complexes **10** and **11**, which are expected to be hydrolytically labile.

In conclusion, we have described a practical method for selective allylic halogenation using readily available reagents NCS and PhSeCl. Details concerning the mechanism of this transformation and its extension to asymmetric halogenation will be reported in due course.

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Supporting Information Available: Complete experimental details and characterization of all new compounds prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Mukaiyama, T.; Matsuo, J.-I.; Iida, D.; Kitagawa, H. *Chem. Lett.* **2001**, *30*, 846−847.

(12) A referee correctly pointed out that ether formation could also account for the reduced yield.

(13) (a) Engman, L.; Persson, J.; Tilstam, U. *Tetrahedron Lett.* **1989**, *30*, 2665−2668. (b) Cossy, J.; Furet, N. *Tetrahedron Lett.* **1993**, *34*, 7755−7756.

(14) Reaction of PhSeCl with **1d** gives 3.6:1 ratio of regioisomers after 5 min at 25 °C. Similarly. the regioselectivity with **6a** is 3:1.[7a]