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Selenocatalytic α-halogenation†

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Through a 2e- oxidation-reduction cycle, phenylselenides catalytically activate *N*-chlorosuccinimide toward electrophilic reactions with ketones, resulting in α-haloketones.

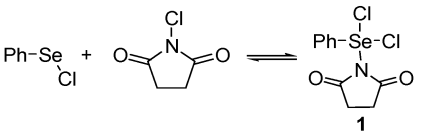
Catalytic α-halogenation of carbonyl compounds has received much attention lately due to the importance of the products as synthetic precursors and pharmaceuticals.[1] The majority of these methods focus on the catalytic activation of the carbonyl substrate by formation of enolates[2] or enamines.[3] Alternatively, the catalytic formation of X_2 (X = Cl, Br, I) from H_2O_2/NaX,[4] or *N*-halosuccinimides has been a successful approach.[5] However, in order to control the selectivity of halogenation, one would like to utilize a catalyst that halogenates ketones through reagent-bound halogens rather than freely diffusing oxidized halogen species.

Recently, we described the use of phenylselenium chloride as a catalyst for allylic halogenation of olefins with *N*-chlorosuccinimide (NCS).[6] In the course of these studies we noted that the reaction was inhibited by NCS. To explain the observed inhibition we postulated that the phenylselenyl chloride catalyst was in equilibrium with the oxidized PhSe(succinimide)Cl_2 (Scheme 1).[6a] While PhSe(succinimide)Cl_2 (**1**) was less active for allylic halogenation, it is known that the related $PhSeCl_3$ α-halogenates ketones.[7] Therefore we thought that **1** might be a useful catalyst for the α-halogenation of ketones with NCS.

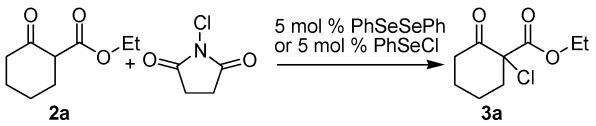
In order to test whether arylselenides can activate NCS toward nucleophilic attack, 2-carboxethoxycyclohexanone (**2a**) was treated with 5 mol% PhSeCl and 1.1 equiv. NCS in CD_3CN (Scheme 2). Analysis of the reaction mixture by ^{1}H NMR spectroscopy after 10 min. at room temperature showed complete conversion to the α-chloro product **3a**. A control reaction run in the absence of PhSeCl showed <1% reaction.

We envisioned several possible mechanisms for product formation (Scheme 3). First, the β-ketoester could be α-selenylated by PhSeCl to afford **4a**.[8] Oxidation of **4a** by NCS would give **5a** which could reductively eliminate the halogenated product (Mechanism A).[9] Alternatively, the β-ketoester can be α-selenylated by the Se(IV) reagent **1**, providing **6a**, which could liberate **3a** upon reductive elimination (Mechanism B). Finally, selenation at oxygen would form **7a**, which could undergo intramolecular nucleophilic attack at the chlorine (Mechanism C).[10] While mechanisms A and B differ by the oxidation state of the selenylating agent, the latter two mechanisms differ only by whether the α-carbon is electrophilically selenylated or chlorinated.

In order to gain some mechanistic insight several reactions utilizing stoichiometric PhSeCl were run. First, **2a** was treated with



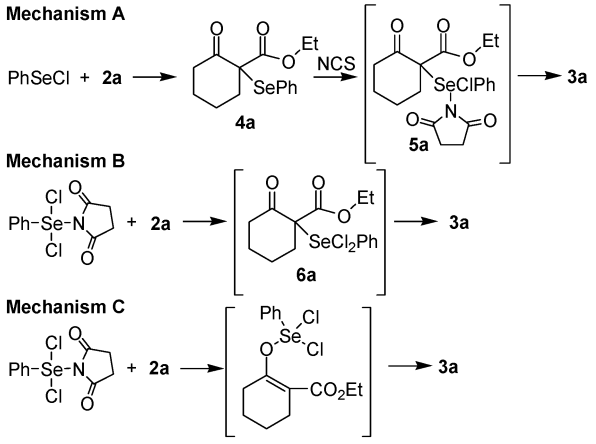
Scheme 1 Oxidative addition of *N*-chlorosuccinimide to PhSeCl.



Scheme 2 Catalytic α-chlorination of a β-ketoester.

PhSeCl in CH_3CN. After stirring overnight, the selenylated product **4a** was isolated and purified by chromatography. Treatment of **4a** with NCS in CD_3CN at room temperature did provide halogenated product **3a**, however after standing 2.5 hours, the reaction was not complete ($t_{1/2}$ ~ 150 min.). Therefore, pathway A is not kinetically competent with the observed catalysis ($t_{1/2}$ < 10 min.). Next, product **4a** was treated with SO_2Cl_2 in CD_3CN, which should provide intermediate **6a**.[7] Doing so led cleanly to one product, tentatively identified as **6a** based on ^{1}H NMR spectroscopy. This compound was stable for several hours at room temperature, but slowly decomposed overnight to give **3a** (67% conversion after 28 h). Once again, this indicates that intermediate **6a** is not a kinetically competent intermediate. Therefore, it appears that the mechanism of catalysis is electrophilic chlorination rather than selenylation. *This is important because it shows that selenium can be used to enhance the electrophilicity of oxidized halogen sources such as NCS.*

With this knowledge in hand, we set out to explore the scope of the catalysis (Table 1). Halogenation of β-ketoesters provided monohalo adducts exclusively. Importantly, the halogenation could be conducted in the presence of olefins (substrate **1e**), without competing allylic halogenation.[5] Consistent with the effects of substituents on the rates of base induce enolization,[11] α-substitution dramatically increases the reaction time. Cyclohexanone was readily α-halogenated, showing that the β-keto activating group is not required. Once again, a qualitative correlation between the rate of the reaction and the rate of enolization is noteworthy (**2a** *vs.* **2h**). Unfortunately, cyclohexanone was not as selective for monochlorination, and a 4 : 1 mixture of α-chlorocyclohexanone:α,α′-dichlorocyclohexane was obtained.



Scheme 3 Three possible mechanisms for catalytic halogenation.

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all compounds. See http://www.rsc.org/suppdata/cc/b4/b410576a/

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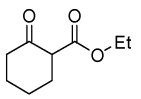
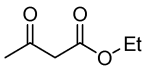
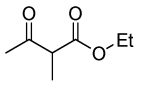
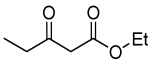
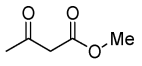
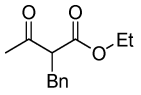
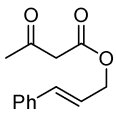
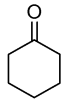
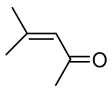
Table 1 PhSeCl catalyzed α-chlorination of ketones in CH_3CN

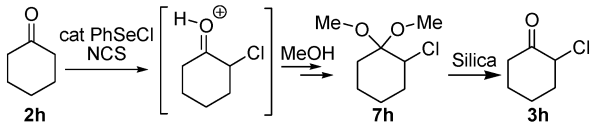
Substrate	Structure	Time	Yield %
2a		10 min	86
2b		10 min	81
2c		18 h	63
2d		30 min	74
2e		10 min	68
2f		48 h	95
2g		16 h	87
2h		18 h	61[a]
2i		7 h	79[b]

[a] Isolated yield of monochlorocyclohexanone. [b] Product is vinyl chloride **8i**.

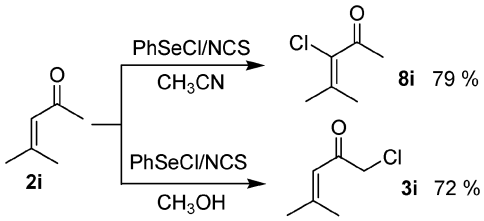
We reasoned that the selectivity for monochlorination could be increased if the monochloro intermediate was trapped by solvent as a hemiacetal or an acetal (Scheme 4). Investigating the reaction in methanol showed that cyclohexanone was chlorinated by NCS in <1 h at room temperature and ^1H and ^{13}C NMR spectroscopies of the crude reaction mixture showed the presence of **7h** with no evidence for dichlorinated product. α-Chlorocyclohexanone was liberated in good yield (72%) upon passage through silica gel. Once again, no reaction occurred in the control without PhSeCl. Aside from the faster reaction kinetics in methanol, the reaction progress was conveniently monitored by the dissolution of the relatively insoluble NCS.

Importantly, cyclohexanone was also α-brominated to provide α-bromocyclohexanone in 86% yield when NBS replaced NCS. No reaction was observed in the absence of PhSeBr.

Finally, we investigated the chlorination of an α,β-unsaturated ketone, mesityl oxide **2i** (Scheme 5). Interestingly, treatment of mesityl oxide with NCS and 5 mol% PhSeCl in CH_3CN provided a good yield of vinyl halide **8i**,[12] however, switching the solvent to MeOH completely reversed the selectivity and only the product of methyl halogenation was observed. While we cannot yet explain



Scheme 4 Trapping monochlorocyclohexanone in methanol.



Scheme 5 Regiochemical solvent effect.

this striking solvent dependent regioselectivity, it is possible that **8i** is not the result of chloronium ion transfer to the olefin. Addition of PhSeCl across the olefin followed by oxidation by NCS and elimination would also provide **8i**.[6a]

In conclusion, we have demonstrated that phenylselenides are efficient and selective catalysts for α-halogenation of ketones. Experiments suggest that the mechanism of the reaction involves oxidative addition of NCS to selenium which activates the "chloronium" toward nucleophilic attack by enols/enolates. This represents the first example of such an activation of oxidized halogen reagents. Exploitation of this principle toward other oxidative halogenations is currently being explored.‡

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Notes and references

‡ General procedure for the selenium-catalyzed α-halogenation of ketones: The ketone (1 mmol) and PhSeCl (0.05 mmol) were dissolved in dry acetonitrile (2 mL). *N*-chlorosuccinimide (1.1 mmol) was added and the solution was stirred at room temperature. Upon completion (TLC), the reaction was poured into H_2O (5 mL) and extracted with Et_2O (3×5 mL). The crude material was purified by chromatography or distillation.

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