

Lewis Basic Selenium Catalyzed Chloroamidation of Olefins Using Nitriles as the Nucleophiles

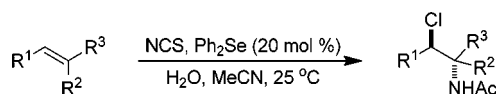
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Received January 28, 2013

ABSTRACT



A Lewis base catalyzed chloroamidation of olefinic substrates was achieved using diphenyl selenide as the catalyst. The reaction conditions are mild and suitable for a wide range of substrates including those which are acid labile.

Haloamidation of an olefin is a useful transformation that produces a vicinal haloamide system, which provides a reactive halogen handle for subsequent manipulation.¹

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In the literature, there are several methods for installing a *trans*-1,2-haloamide/amine functionality directly from an olefin.² A common approach involves the use of a nitrogen nucleophile to open a haliranium ion intermediate derived from an olefin. To achieve the desired products with reasonable reaction efficiency, Lewis acids are usually employed to activate the stoichiometric halogen source in the olefin halogenation process. For example, the use of strongly Lewis acidic catalysts, such as SnCl₄ and BF₃•OEt₂, in the bromoamidation of olefins using *N*-bromosuccinimide (NBS) as the halogen source and acetonitrile as the nitrogen source has been reported.³ Later, the Chandrakanth group reported a similar procedure using InBr₃ as the catalyst in the haloamidation of vinyl arene substrates.⁴ Herein, we disclose a facile, mild, and efficient chloroamidation of olefins using commercially available Lewis basic diphenyl selenide as the catalyst with *N*-chlorosuccinimide (NCS) and acetonitrile as the halogen and nitrogen source, respectively. This method was found to be applicable to a wide range

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of substrates, which makes it suitable for acid-sensitive compounds.

Recently, we have reported the use of Lewis basic sulfur for the activation of halogenating reagents in various bromocyclization processes.^{5–9} We rationalized that a similar Lewis basic system can be used to catalyze the haloamidation process, which can offer mild reaction conditions. Thus, cyclohexene was used in our initial study, and various Lewis basic chalcogen-containing catalysts **3** were examined (Figure 1).

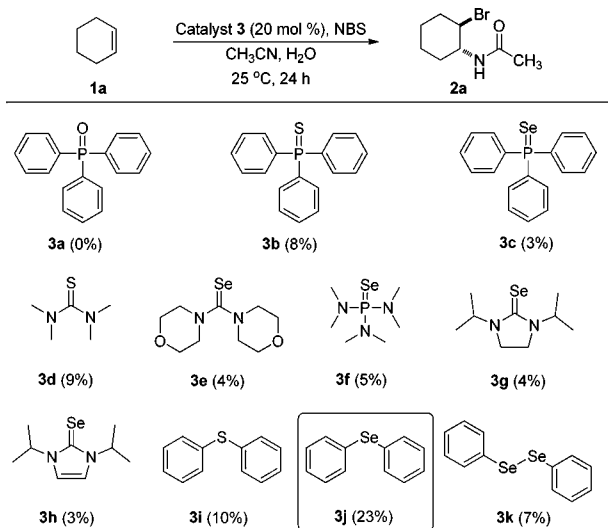


Figure 1. Haloamidation using different Lewis base catalysts. Reactions were carried out with cyclohexene (**1a**) (0.25 mmol), catalyst **3** (0.05 mmol), NBS (0.25 mmol), and water (0.30 mmol) in MeCN (2.5 mL) at 25 °C. The yields indicated in the parentheses were the isolated yields of **2a**.

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Triphenylphosphine oxide was found to be inactive in catalyzing the haloamidation reaction. For the catalysts **3b–h** which contain a C=X or a P=X (X = S, Se) system, very low reaction efficiency was observed. In fact, these catalysts were unstable in the reaction system; elemental sulfur (or selenium) evolved gradually during the reaction, which could be attributed to the hydrolytic decomposition of the catalysts in the presence of water and a halogen source.¹⁰ This result prompted further screening of the diaryl sulfur and selenium catalysts,^{5c,9j} which led to the discovery that diphenyl selenium (**3j**) was exceptionally active in catalyzing this type of reaction.

After identifying a suitable catalyst, other parameters were optimized. The amount of water did not significantly affect the reaction, and the yield was unchanged upon the addition of up to 10 equiv of water (Table 1, entries 1–3). In addition, no haloalcohols were observed to form despite the drastic increase in the amount of water. On the other hand, the concentration did appreciably affect the reaction yield, and the optimum concentration was found to be 0.4 M (Table 1, entries 4–6).

Table 1. Effect of Water and Concentration on the Haloamidation^a

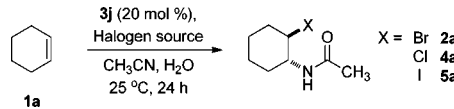
entry	H ₂ O (equiv)	concn (M)	yield (%) ^b
1	1.2	0.1	23
2	3.0	0.1	23
3	10	0.1	24
4	1.2	0.65	30
5	1.2	0.50	35
6	1.2	0.40	36

^a Reactions were carried out with cyclohexene (**1a**) (0.25 mmol), NBS (0.25 mmol), **3j** (0.05 mmol), and water at 25 °C. ^b Yields were calculated based on the ¹H NMR analysis of the crude reaction mixture using hexamethylbenzene as the internal standard.

Various halogenating sources were also investigated. It was found that brominating reagents including *N*-bromophthalimide (NBP), *N*-bromoacetamide (NBA), 2,4,4,6-tetrabromo-2,5-hexadienone (TABCO), and 1,3-dibromo-5,5-dimethylhydantoin (DBH) gave similar yields to that of NBS (Table 2, entries 1–5). Interestingly, a 52% yield of the chlorinated product was obtained when NCS was used (Table 2, entry 7), but *N*-iodosuccinimide (NIS) did not result in any desired product (Table 2, entry 8). It was found that the yields could be further enhanced by increasing the amount of halogenating reagents (Table 2, entries 9–10). The reaction was also found to be readily scalable.

Upon identifying a suitable reaction system, we continued to explore the substrate scope; the results are tabulated

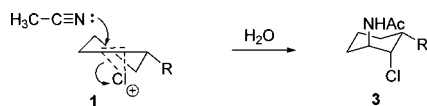
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Table 2. Effect of Halogen Source on Reaction Yield^a


entry	halogen source (equiv)	product	yield (%) ^b
1	NBS (1)	2a	36
2	NBP (1)	2a	35
3	NBA (1)	2a	30
4	TABCO (1)	2a	31
5	DBH (1)	2a	31
6	DCH (1)	4a	34
7	NCS (1)	4a	52
8	NIS (1)	5a	0
9	NBS (2)	2a	56
10 ^{c,d}	NCS (2)	4a	85

^a Reactions were carried out with cyclohexene (**1a**) (0.25 mmol), **3j** (0.05 mmol) in MeCN (0.65 mL) at 25 °C. ^b Yields were calculated based on the ¹H NMR analysis of the crude reaction mixture using hexamethylbenzene as the internal standard. ^c Reactions conducted on 0.25, 1, and 3 mmol scale, and the same yields were obtained. ^d Ca. 10% of desired product was observed when strictly anhydrous conditions were applied.

in Table 3. The haloamidation was found to proceed efficiently with both alkyl olefins and vinyl arenes giving good yields. For the substituted cyclohexenes **1b–1e**, excellent diastereo- and regioselectivity were observed (Table 3, entries 1–4). The high diastereoselectivity could be explained by the stereoelectronic effect of the chairlike transition state that is depicted in Scheme 1. Markovnikov-type products were obtained for aryl olefins **1f–1h** (Table 3, entries 5–7).¹¹ However, anti-Markovnikov product **4i** was achieved (86% yield) when using **1i** as the substrate (Table 3, entry 8). The selectivity can be rationalized by the stabilization effect of the carbocation at the terminal carbon by the Si–C σ -bond.¹²

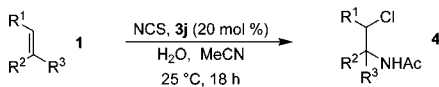
Scheme 1. Possible Transition State of the Chloroamidation

Besides the wide substrate scope, it is also important to note that the reaction can accommodate acid sensitive functional groups. Thus, this Lewis base catalyzed haloamidation can be considered as a complementary method to the corresponding Lewis acid protocols.^{3,4}

Some examples are shown in Table 4. Substrates **1j–1l** gave the desired products smoothly using catalyst **3j** (Table 4, entries 1–3); this was in comparison to the deprotected

(11) *p*-Methoxystyrene was also examined, but only ca. 5% product was obtained.

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Table 3. Haloamidation of Olefins


entry ^a	substrate	product	yield (%) ^b
1	1b	4b	65
2	1c	4c	76
3	1d	4d	55
4	1e	4e	79
5	1f	4f	65
6	1g	4g	89
7	1h	4h	50
8	1i	4i	86

^a Reactions were carried out with olefin **1** (0.25 mmol), NCS (0.50 mmol), and **3j** (0.05 mmol) in MeCN (0.65 mL) at 25 °C for 18 h. ^b Isolated yield.

precursors (Table 4, entries 4 and 6) and the complex mixture obtained (Table 4, entry 5) when the respective Lewis acids were employed as catalysts.

To further illustrate the scope of the reaction, we proceeded to examine a variety of nitriles. As shown in Table 5, both propio- and benzonitrile produced good yields of the corresponding products **7** and **8**, respectively.

During our mechanistic investigation, we initially suspected that the active catalytic species might have been diphenyl selenium oxide (**9**), which can be synthesized by treating diphenyl selenide (**3j**) with NCS and MeOH/H₂O.¹³ We also observed that some diphenyl selenium

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Table 4. Chloroamidation of Acid Labile Substrates^a

entry ^a	R	catalyst	product	yield (%) ^b
1	OBoc	3j		76
2 ^c	OTr	3j		70
3	NHBoc	3j		40
4	OBoc	InBr ₃ or InCl ₃		90
5	OBoc	BF ₃ ·Et ₂ O or SnCl ₄	complex mixture	
6	OTr	BF ₃ ·Et ₂ O or SnCl ₄		90
7	NHBoc	SnCl ₄	no reaction	

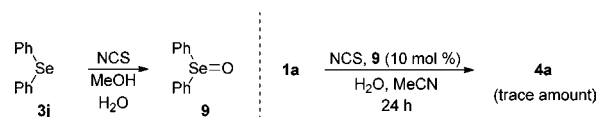
^a Reactions were carried out with olefin **1** (0.25 mmol), NCS (0.50 mmol), and **3j** (0.05 mmol) in MeCN (0.65 mL) at 25 °C for 18 h.
^b Isolated yield. ^c The reaction time was 3 days.

Table 5. Chloroamidation of **1a** with Different Nitrile Partners^a

<div><div><p>1a</p></div><div><p>NCS, 3j (20 mol %) H₂O, RCN 25 °C, 48 h</p></div><div><p>7</p></div></div>				
entry ^a	RCN	product	yield (%) ^b	
1			70	
2			83	

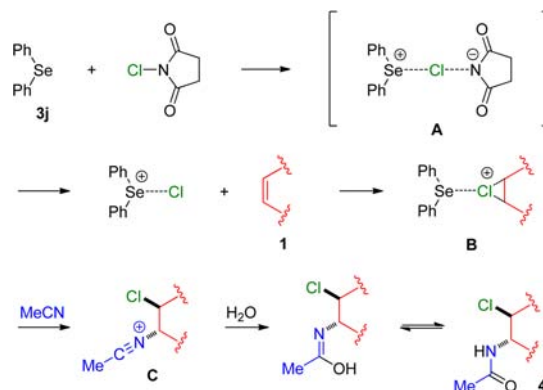
^a Reactions were carried out with cyclohexene (**1a**) (0.25 mmol) and **3j** (0.05 mmol) in RCN (0.65 mL) at 25 °C. ^b Isolated yield.

oxide (**9**) was generated during the chloroamidation reaction, which was elucidated by ¹H NMR experiments of the crude sample. Nonetheless, when we used diphenyl

Scheme 2. Examination of **9** as the Catalyst in the Chloroamidation of **1a**

selenium oxide (**9**) instead of **3j** as the catalyst, the reaction was very sluggish (Scheme 2).

A plausible mechanism for the reaction is described in Scheme 3.^{3,5,9j} The first step is likely to involve the activation of the chlorine atom on NCS via the Lewis basic diphenyl selenide to form intermediate **A**. The electrophilic Cl might then be delivered to olefin **1** to form the haliranium intermediate **B**. At this point, acetonitrile could attack intermediate **B** (i.e., **B**→**C**) which would subsequently be quenched by a molecule of water to form the haloamide product **4**.

Scheme 3. Proposed Mechanism of the Lewis Basic Selenium Catalyzed Chloroamidation

In summary, we have developed a highly efficient Lewis base catalyzed chloroamidation which can be applied to a wide range of substrates including those that are acid labile. Further application of this methodology to other areas is currently being investigated.

Acknowledgment. We thank the financial support from Agency for Science, Technology and Research (A*STAR) (Grant No. 143-000-536-305). D.T. would like to thank A*STAR for sponsoring his PhD scholarship.

Supporting Information Available. Experimental procedures and additional information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.