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Michael Addition of Selenoamides to α,β-Unsaturated Carbonyl Compounds: Stereocontrolled Synthesis of δ-Oxo Selenoamides and Their Reactivity

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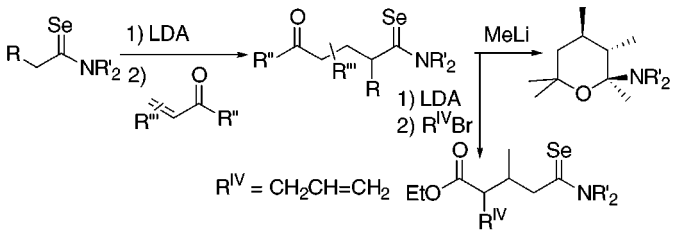
ABSTRACT



Lithium eneselenolates generated from selenoamides underwent Michael addition to α,β-unsaturated esters and ketones with high diastereoselectivity to give δ-oxo selenoamides in moderate to high yields within a few seconds. Further selective transformations of the δ-oxo selenoamides were also achieved.

Although the Michael addition using metal enolates and enethiolates derived from amides[1] and thioamides[1ef,2] has been well studied as synthetically important carbon−carbon bond-forming reactions, a similar reaction using a selenium counterpart of metal enolates, i.e., metal eneselenolates, has not yet been reported. However, the recent development of new synthetic methods for selenocarbonyl compounds[3] and the increasing attention to organoselenium compounds[4] stimulated us to explore the utility of lithium eneselenolates as a carbon nucleophile to Michael acceptors. Very recently, we have established a one-pot synthetic procedure of selenoamides **1**[5] and found that their lithium eneselenolates **2** reacted with aldehydes to afford α,β-unsaturated selenoamides.[6] Herein, we report the stereocontrolled Michael addition of lithium eneselenolates to α,β-unsaturated esters and ketones leading to δ-oxo selenoamides and their reactivity.

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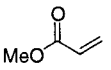
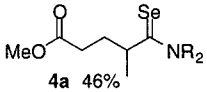
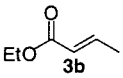
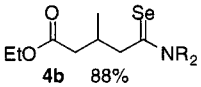
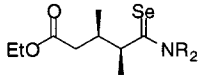
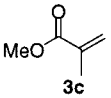
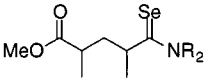
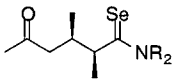
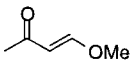
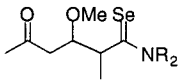
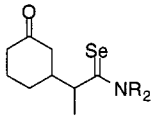
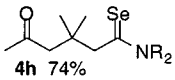
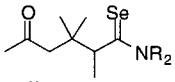
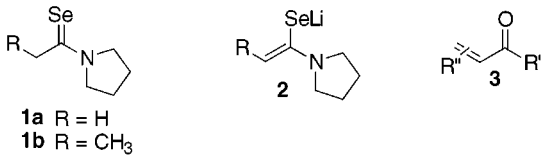
Table 1. Michael Addition of Selenoamides **1** to α,β-Unsaturated Carbonyl Compounds **3**[a]

entry	seleno-amide **1**	α,β-unsaturated carbonyl compound **3**	product[b] yield (%)[c]
1	**1b**	 **3a**	 **4a** 46%
2	**1a**	 **3b**	 **4b** 88%
3	**1b**	**3b**	 **4c** 88% (95 : 5)[d]
4	**1b**	 **3c**	 **4d** 41% (83 : 17)[d]
5	**1b**	 **3d**	 **4e** 73% (75 : 25)[d]
6	**1b**	 **3e**	 **4f** 66% (90 : 10)[d]
7	**1b**	 **3f**	 **4g** 61% (56 : 44)[d]
8[e]	**1a**	 **3g**	 **4h** 74%
9	**1b**	**3g**	 **4i** 69%

[a] The selenoamide **1** (1 mmol) was treated with LDA (1.2 mmol) in THF (5 mL) at 0 °C for 10 min, then to the reaction mixture were added the carbonyl compound **3** (1 mmol) and water (1 mL) successively. [b] NR_2 represents pyrrolidyl. [c] Isolated yield. [d] The ratio of the diastereomers determined by ^{1}H NMR spectra is shown in parentheses. [e] The lithium eneselenolate **2a** was stirred with **3g** for 1 min at 40 °C.

The results of the reaction of lithium eneselenolates **2** with α,β-unsaturated esters and ketones **3** are summarized in Table 1. For example, selenoamide **1b** was treated with LDA at 0 °C for 10 min. Then, to the reaction mixture were added methyl acrylate **3a** and water nearly simultaneously. The purification of the product by column chromatography on silica gel gave δ-oxo selenoamide **4a** in 46% yield (entry 1). In almost all cases, the Michael addition of lithium eneselenolates **2** was complete within a few seconds. Running the reaction for a longer time reduced the yields of the products **4**.

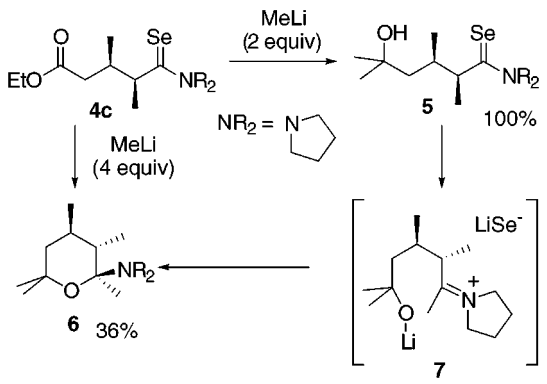
The carbon atom of lithium eneselenolates **2** selectively attacked on the β-carbon atom of Michael acceptor **3**. The



products derived from the addition of the selenium atom of **2** to **3** and from the 1,2-addition of **2** to **3** were not detected. This is in a marked constrast to the reactions of ordinary amides and thioamides which required higher reaction temperatures and reaction time to afford Michael adducts. β,β-Disubstituted α,β-unsaturated ketones are less suceptible to the Michael addition.[1e] Nevetheless, the reaction of lithium eneselenolates **2** with enone **3g** gave 1,4-adducts **4h** and **4i** in good yields (entries 8 and 9). The reaction of lithium eneselenolate **2b** proceeded with high diastereoselectivities (entries 3−6) except for the reaction with cyclohexenone **3f** (entry 7). The stereochemistry of product **4c** was confirmed by converting **4c** to the ordinary amide with m-CPBA oxidation and comparing the NMR spectra of the obtained amide with those in the literature.[1b] The structure of major product **4e** was also estimated on the basis of the similarity of its spectra with those of product **4c**.

The relative reactivity of alkoxycarbonyl and selenocarbamoyl groups toward methyllithium was tested (Scheme 1) since both functional groups are known to be active toward

Scheme 1



organolithium compounds.[8,9] The treatment of δ-oxo selenoamide **4c** with 2 equiv of methyllithium gave quantitatively δ-hydroxy selenoamide **5**. The methyllithium selectively added to the ethoxycarbonyl group, and the selenocarbamoyl group remained intact. In contrast, the use of 4 equiv of

(7) **Experimental Procedure**: To a THF solution (5 mL) of LDA (1 mmol) was added propaneselenoamide **1b** (1 mmol, 0.19 g), and the solution was stirred for 10 min at −78 °C. To the reaction mixture were added ethyl crotonate **3b** (1.2 mmol, 0.15 mL) and water (1 mL) successively. The mixture was washed with saturated aqueous NaCl, and the whole was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified on column chromatography through silica gel using hexane/ether (10/1) as eluent to afford δ-oxo selenoamide **4c** (0.268 g, 0.88 mmol) in 88% yield.

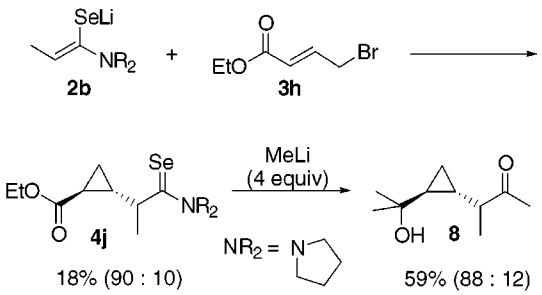
(8) Wakefield, B. J. In *Organolithium Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1988; p 76.

(9) Murai, T.; Ezaka, T.; Kato, S. *Tetrahedron Lett.* **1998**, *39*, 4329.

methyllithium gave the cyclic product **6** in 36% yield.[10,11] Product **6** may be formed via the further addition of methyllithium to product **5** to form iminonium salt **7**, which undergoes stereoselective intramolecular cyclization.

The two-step reaction from lithium eneselenolate **2b** and ethyl 4-bromocrotonate (**3h**) successfully gave *β*-cyclopropylalkyl ketone **8** (Scheme 2). In the first step Michael addition

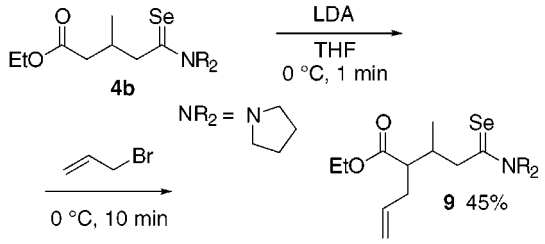
Scheme 2



of **2b** to **3h** may give the ester enolate followed by intramolecular alkylation. Among four possible stereoisomers, two isomers were formed in a ratio of 90:10. The ethoxycarbonyl group was *trans* oriented to the selenocarbamoylethyl group on the cyclopropyl ring. In the second step using 4 equiv of methyllithium, two methyl groups were selectively introduced to the ethoxycarbonyl group and the selenocarbamoyl group of **4j** was selectively converted to an acetyl group.

Finally, the deprotonation of *δ*-oxo selenoamide **4b** was carried out. The treatment of **4b** with LDA at 0 °C for 1 min followed by allylation gave product **9** with high stereoselectivity,[12] although the stereochemistry of the product was not determined. No product derived from deprotonation at the α-carbon atom to the selenocarbonyl group was observed (Scheme 3).

Scheme 3



In summary, we have demonstrated the first Michael addition of lithium eneselenolates **2** to α,*β*-unsaturated carbonyl compounds **3**. The reaction was complete very rapidly and exhibited high selectivity. The selective transformation of the *δ*-oxo selenoamides was also successful. Further applications of the present reactions will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Product **6** was obtained in 80% yield with a purity higher than 90% after the workup. Attempts to purify the crude product through column chromatography failed and gave a complex mixture. Then, product **6** was purified by bulb-to-bulb distillation.

(11) The stereochemistry of product **6** was determined by using a phase sensitive NOESY spectrum.

(12) **Experimental Procedure**. To a THF solution (5 mL) of LDA (0.6 mmol) was added *δ*-oxo selenoamide **4b** (0.5 mmol, 0.145 g), and the solution was stirred for 1 min at 0 °C. To the reaction mixture was added allyl bromide **3b** (0.5 mmol, 0.05 mL), and the solution was stirred for 10 min at 0 °C. The mixture was washed with saturated aqueous NaCl, and the whole was extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified on column chromatography through silica gel using hexane/ether (2/1) as eluent to afford *δ*-oxo selenoamide **9** (0.074 g, 0.23 mmol) in 45% yield.