Generation and Reactions of Selenium Isologues of Enolate Ions

Toshiaki Murai*

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan

Abstract: Characteristic reactions of lithium eneselenolates generated from selenoamides, selenoic acid *O*-esters, and selenothioic acid *S*-esters with carbon electrophiles are described. Reaction and thermodynamic properties of ammonium eneselenolates of selenothioic acid *S*-esters are shown. Generation of eneselenolates from alkenyl and alkynyl metallic species is also introduced.

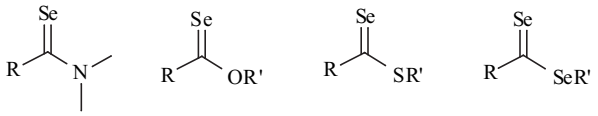
Keywords: Metal eneselenolates, ammonium eneselenolates, selenoamides, selenoic acid *O*-esters, selenothioic acid *S*-esters, seleno-Claisen rearrangement.

INTRODUCTION

Enolate ions are one of the most important species in organic synthesis. Tremendous amounts of derivatives bearing a wide variety of counter cations have been developed, and highly stereoselective reactions with these species have been achieved. On the other hand, much less attention has been paid to selenium isologues of enolate ions, i.e. eneselenolates. This is partly because selenocarbonyl compounds [1], which are the key precursors of eneselenolates, such as selenoaldehdyes and selenoketones, are labile and less accessible compounds. In contrast, the introduction of heteroatom-containing functional groups adjacent to a carbon atom of a selenocarbonyl group enhances the stability of the compounds. Recently, a wide variety of synthetic methods for heteroatom-substituted selenocarbonyl compounds, such as selenoamides and selenoesters, have been developed, and these achievements facilitate the development of chemistry of eneselenolates. In the present review, two types of methods for the generation of eneselenolates are shown. The first procedure involves the deprotonation of heteroatom-substituted selenocarbonyl compounds. The other one is the generation via alkenyl or alkynyl metallic species.

1. GENERATION OF ENESELENOLATES FROM SELENOCARBONYL COMPOUNDS

As heteroatom-substituted selenocarbonyl compounds, selenoamides **I**, selenoic acid *O*-esters **II**, selenothioic acid *S*-esters **III**, and diselenoic acid esters **IV** are known.

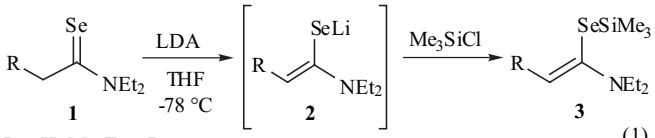


I **II** **III** **IV**

Among them selenoamides **I** [2] and selenoic acid *O*-esters **II** [3] were synthesized more than 30 years ago. In particular, facile new synthetic procedures of **I** were extensively developed, although only a limited number of **II** were reported. In contrast, the first synthetic example of selenothioic acid *S*-esters **III** [4] and diselenoic acid esters **IV** [5] as a stable form was shown in 1993. The stability of these compounds [6] is highly dependent on the substitution patterns. Aliphatic derivatives of **III**, which are good precursors of eneselenolates, can be handled under the air at room temperature, whereas those of **IV** are highly labile. As a result, no example of a eneselenolate derived from **IV** is known.

1.1. From Selenoamides

Similar to ordinary amides, the deprotonation of selenoamides **1** takes place smoothly with a strong base such as LDA [7]. The resulting lithium eneselenolates **2** were trapped with chlorotrimethylsilane to form vinyl selenosilanes **3** in 73 – 85% yields (eq. **1**), although the products **3** were highly labile toward moisture.



1 **2** **3**

R = H, Me, Et, *t*-Bu (1)

In the reaction of eq. **1**, the products **3** were formed as single isomers. This has suggested that eneselenolates **2** derived from selenoamides **1** were also generated as single isomers. These trends are in accordance with those of ordinary amides and thioamides, which form *Z*-isomers of amide or thioamide enolates [8] with high selectivity. Allylation of eneselenolates derived from selenoamides was carried out (eq. **2**, Table **1**) [9].

For example, selenoamide **4a** was treated with LDA for 10 min at 0 °C. Then, to the reaction mixture was added allyl bromide (**5a**) at 0 °C, and stirred for 10 min at this temperature to give the γ,δ-unsaturated selenoamide **6a** in an isolated yield of 84% (entry 1).

The present reaction may proceed through the initial formation of allyl vinyl selenide **7** from lithium eneselenolate **2** and allyl bromide (**5a**). Then, **7** may undergo seleno-Claisen rearrangement to end-up the formation of **6a**.

*Address correspondence to this author at the Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-1193, Japan; E-mail: mtoshi@cc.gifu-u.ac.jp

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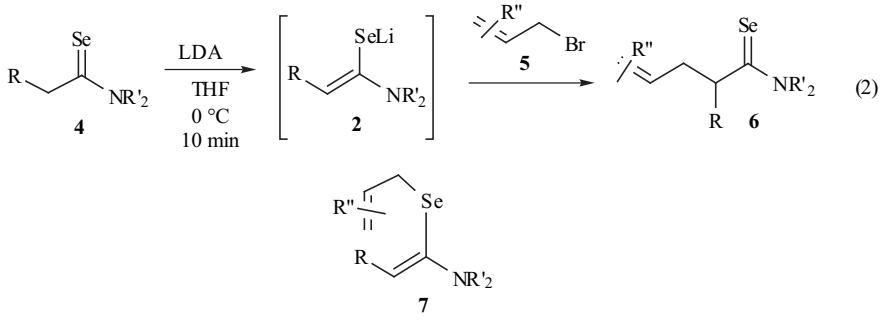
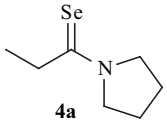
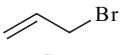
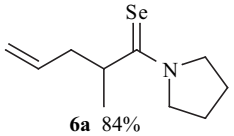
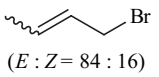
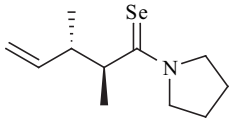
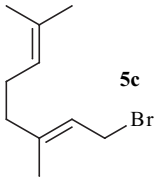
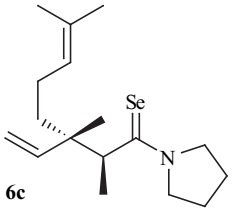
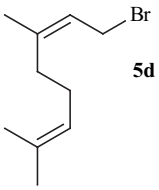
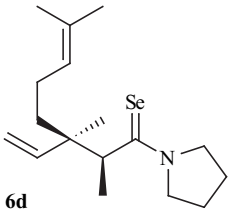
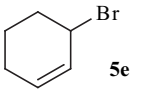
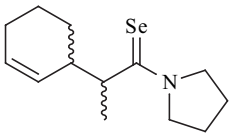


In contrast to thio-Claisen rearrangement [10], the seleno-Claisen rearrangement has not yet been studied in depth [11]. Noteworthy is that the seleno-Claisen rearrangement appears to proceed as quickly as the thio-Claisen rearrangement of allylic vinyl sulfides derived from thioamides, despite the fact that the formation of a reactive carbon-selenium double bond has been believed to be unfavorable compared with that of a carbon-selenium single bond.

The results of the reaction using propaneselenoamide **4a** and allylic bromides **5** are also summarized in Table **1**. In all cases, γ-carbon atom of allylic bromides **5** was selectively introduced to the carbon atom α to the selenocarbonyl group of the starting selenoamide **4a**.

The reaction with **5a** and crotyl bromide (**5b**) was complete at 0 °C within 10 min (entries 1 and 2), whereas

Table 1. Synthesis of α,α-Disubstituted Selenoamides 6 *via* the Seleno-Claisen Rearrangement[a]

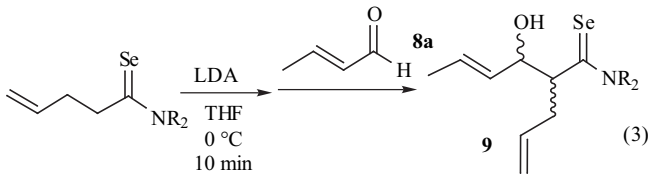
entry	4	allylic bromide 5	temp (°C) time	6 yield[b]
1	 **4a**	 **5a**	0 10 min	 **6a** 84%
2	**4a**	 (*E* : *Z* = 84 : 16) **5b**	0 10 min	 **6b** 88% (83 : 17)[c]
3	**4a**	 **5c**	0 - 67 6 h	 **6c** 87% (97 : 3)[c]
4	**4a**	 **5d**	0 - 67 4 h	 **6d** 97% (92 : 8)[c]
5	**4a**	 **5e**	0 - 67 3 h	 **6e**, 95% (81 : 19)[c]

[a] The reaction was carried out with selenoamide **4a** (1-5 mmol), LDA (1.2 equiv.) and allylic bromide **5** (1.0 - 1.2 equiv.) in THF (5 - 20 mL). [b] Isolated yield. The value in parenthesis represents the ratio of two isomers in $CDCl_3$.

the reaction with geranyl bromide (**5c**), neryl bromide (**5d**), and cyclohexenyl bromide (**5e**) required higher reaction temperatures (entries 3 – 5). Nevertheless, in the reaction with **5c** and **5d** quaternary carbon atoms were constructed at the carbon atom β to the selenocarbonyl group with high efficiency (entries 3 and 4). Furthermore, the ratio of the stereoisomers of bromides **5b** - **5d** retained in the products **6b** – **6d** (entries 2 – 5). These results implied that no isomerization of eneselenolates **2** occurred during the formation of allylic vinyl selenides **7**.

Aldol-type condensation reaction of lithium eneselenolates generated from 4-penteneselenoamides with aldehydes was reported [12]. The diastereoselectivity of the reaction was controlled by the substituents on the nitrogen atom. For example, in the reaction with crotonaldehyde (**8a**) leading to β-hydroxy selenoamide **9a** *N*,*N*-dibenzyl selenoamide **4c** showed better selectivity as in eq. **3**.

Further examples of the reaction with a variety of aldehydes are listed in Table **2**. The use of α,β-unsaturated and aliphatic aldehydes **8b** – **8d** gave the β-hydroxy

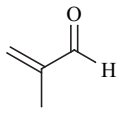
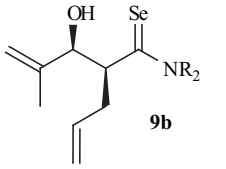
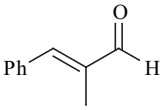
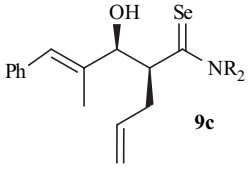
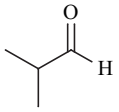
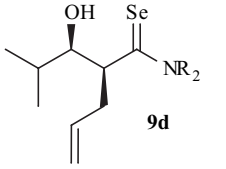
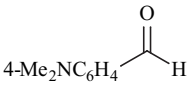
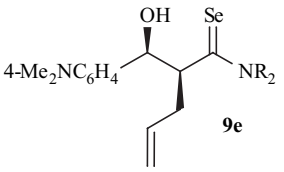
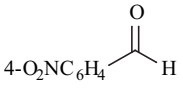
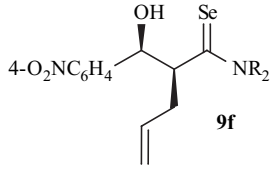


4b R_2 = pyrrolidinyl **9a** R_2 = pyrrolidinyl 70% 55 : 45
4c R_2 = Bn_2 **9b** R_2 = Bn_2 83% 75 : 25

selenoamides **9b** – **9d** in high yields with high diastereoselectivity (entries 1 – 3). In particular, it should be noted that a similar reaction of ordinary amides with aliphatic aldehydes gave the corresponding aldol products only in moderate yields. High diastereoselectivity was also observed for the reaction with aromatic aldehydes **8e** and **8f**, although the yields of the products were low (entries 4 and 5).

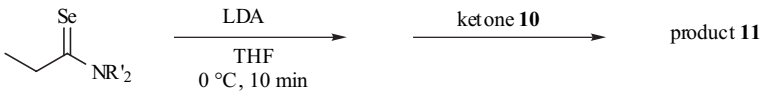
The addition reaction of lithium eneselenolates derived from selenoamides to ketones **10** also took place to form β-hydroxy selenoamides **11** (Table **3**) [13]. The substitution

Table 2. Aldol-Type Condensation Reaction of *N*, *N*-Dibenzyl 4-Pentene Selenoamide 4c with Aldehydes[a]

entry	aldehyde **8**	product **9**[b]	Yield(%)[c,d]
1	 **8b**	 **9b**	81 (93 : 7)
2	 **8c**	 **9c**	81 (71 : 29)
3	 **8d**	 **9d**	87 (94 : 6)
4	 **8e**	 **9e**	27 (>99 : 1)
5	 **8f**	 **9f**	29 (95 : 5)

[a] Selenoamide **4c** (1 mmol) was treated with LDA (1.2 mmol) in Et_2O or THF (5 mL) at 0 °C for 10 min, then to the reaction mixture was added aldehyde **8** (1.2 mmol) at -78 °C and stirred for 10 min at -78 °C. [b] R represents benzyl group. [c] Isolated yield. [d] The ratio in parentheses represents the diastereomeric ratio.

Table 3. Reaction of Selenoamides 4 with Ketones 10[a]



4a NR'_2 = pyrrolidinyl

4d $NR'_2 = NMe_2$

entry	selenoamide **4**	ketone **10**	product **11**	yield (%)[b]
1	**4d**	**10a**	**11a**	57
2	**4d**	**10b**	**11b**	52
3	**4a**	**10c**	**11c**	59 (57 : 43)
4	**4a**	**10d**	**11d**	88 (>99 : 1)
5	**4a**	**10e**	**11e**	81 (100 : 0)
6	**4d**	**10f** Ph	**11f**	58 (91 : 9)
7	**4d**	**10g** 4-$CH_3OC_6H_4$	**11g**	56 (78 : 22)

[a] Selenoamide **4** (1 mmol) was treated with LDA (1.2 mmol) in Et_2O or THF (5 mL) at 0 °C for 10 min, then to the reaction mixture was added ketone **10** (1.2 mmol) at -78 °C and stirred for 10 min at -78 °C. [b] Isolated yield.

patterns of the ketones **10** highly influence the yields of the products and the selectivity of the reaction. For example, the use of methyl ethyl ketone (**10c**) gave the product **11c** with little diastereoselectivity (entry 3), whereas the reaction with isopropyl methyl ketone (**11d**) afforded the product with high selectivity (entry 4).

No reaction took place between **4a** and pinacolone, and the starting selenoamide **4a** was recovered. In the reaction with 4-*tert*-butyl-cyclohexanone (**10e**), the product where the hydroxy and *tert*-butyl groups are located in the *cis*-position was efficiently formed (entry 5). High diastereoselectivity of the reaction was also observed for acetophenone **10f** (entry 6), although the diastereoselectivity decreased in the reaction with 4-methoxyacetophenone **10g** (entry 7).

The lithium eneselenolates of selenoamides **4a** and **4e** undergo Michael addition reactions to α,β-unsaturated ketones and esters **12** (eq. **4**, Table **4**) [14].

The reaction was generally complete within a few seconds at –78 ºC. The reaction for the longer reaction time reduced the yields of the products **13**. In the reaction of selenoacetamide **4e** with α,β-unsaturated ketone **12e** at 0 °C, the 1,2-adduct was also formed, but the reaction at –78 °C selectively gave the 1,4-adduct **13e** (entry 5). Noteworthy is that a similar reaction of ordinary amides and thioamides with **12e** gives 1,4-adducts only in low yields [15]. High diastereoselectivity was observed for the Michael addition of **4a** to **12a** – **12d** (entries 1- 4).

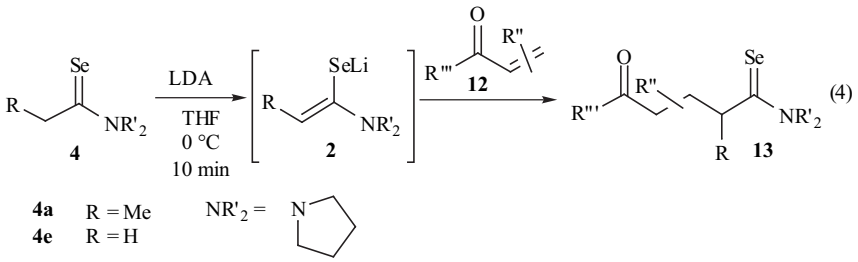
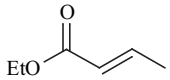
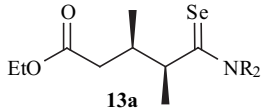
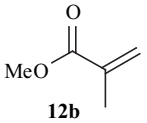
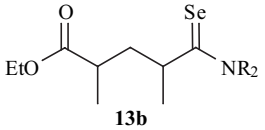
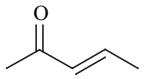
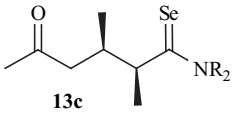
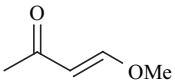
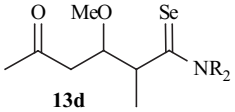
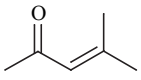
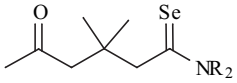


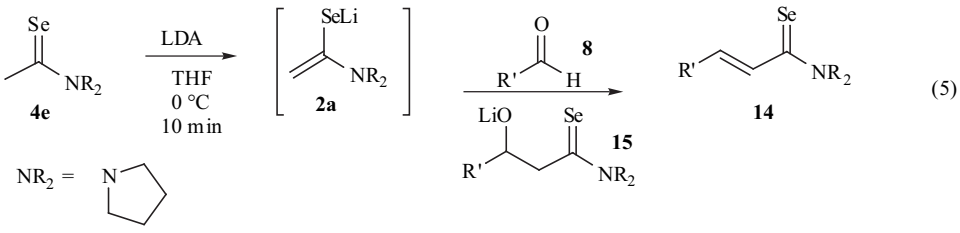
Table 4. Reaction of Selenoamides 4 with α, β-Unsaturated Ketones and Esters 12[a]

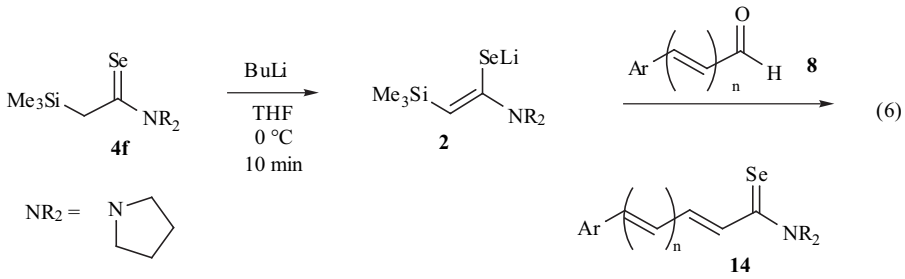
entry	selenoamide **4**	**12**	product **13**[b]	yield (%)[c,d]
1	**4a**	 **12a**	 **13a**	88 (95 : 5)
2	**4a**	 **12b**	 **13b**	41[e] (83 : 17)
3	**4a**	 **12c**	 **13c**	73 (75 : 25)
4	**4a**	 **12d**	 **13d**	66 [e] (90 : 10)
5	**4e**	 **12e**	 **13e**	74

[a] Selenoamide **4** (1 mmol) was treated with LDA (1.2 mmol) in Et_2O or THF (5 mL) at 0 °C for 10 min, then to the reaction mixture was added **12** (1.2 mmol) at -78 °C. [b] NR_2 represents pyrrolidinyl group. [c] Isolated yield. [d] The ratio of diastereomers is shown in parenthesis. [e] The relative stereochemistry of the major isomers was not determined.

The reaction of selenoacetamide **4e** with aldehydes **8** did not give β-hydroxy selenoamides at –78 °C unlike the reaction of α-monosubstituted selenoamides **4a** – **4d**, but the starting selenoacetamide **4e** was recovered quantitatively. When the reaction was performed at 20 °C for 3 h, α,β-unsaturated selenoamides **14** were selectively obtained, and the formation of β-hydroxy selenoamides was not confirmed except for the reaction with acetaldehyde (eq. **5**) [16].

It may be because the equilibrium between the starting **2a**, **8** and β-lithioxy selenoamides **15** lies to **2a** and **8**, and the reaction at higher temperature facilitates the elimination of LiOH from **15**. More highly efficient synthesis of unsaturated selenoamides **14** was achieved by Peterson olefination of α-silyl selenoacetamide **4f** (eq. **6**, Table **5**), which was readily available from (trimethylsilyl)acetylene, selenium, and secondary amines [17].





Butyllithium was efficiently used to generate lithium eneselenolate **2** from **4f**. The reaction with aromatic, α,β-unsaturated and even α,β,γ,δ-unsaturated aldehydes **8** proceeded with high efficiency. The general relationship between the yields of the products **14** and the substituents on the aromatic ring was not observed. Noteworthy is that in all cases *E*-isomers were formed selectively. This is in marked contrast to the reaction of α-silyl thioamide with benzaldehyde, which gave a stereoisomeric mixture of α,β-unsaturated thioamide.

Table 5. Reaction of α-Silyl Selenoacetamide 4f with BuLi and Aldehydes 8[a]

8 Ar	n	product 14 Yield (%)[b]
4-$O_2NC_6H_4$	0	44
	1	63
	2	95
4-BrC_6H_4	1	85
	2	62
4-FC_6H_4	0	83
	1	66
C_6H_5	0	98
	1	82
	2	89
4-MeC_6H_4	0	97
	1	64
4-$MeOC_6H_4$	0	99
	1	95
	2	51

(Table 5)contd.....

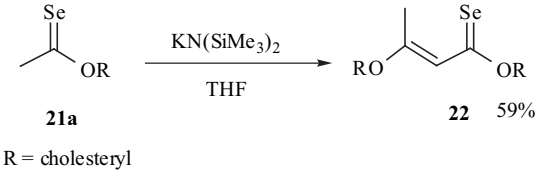
8 Ar	n	product 14 Yield (%)[b]
4-$Me_2NC_6H_4$	0	93
	1	64
	2	36

[a] α-Silyl selenoacetamide **4f** (1 mmol) was treated with BuLi (1.2 mmol) in THF (5 mL) at 0 °C for 10 min, then to the reaction mixture was added aldehyde **8** (1.2 mmol) at 0 °C. [b] Isolated yield.

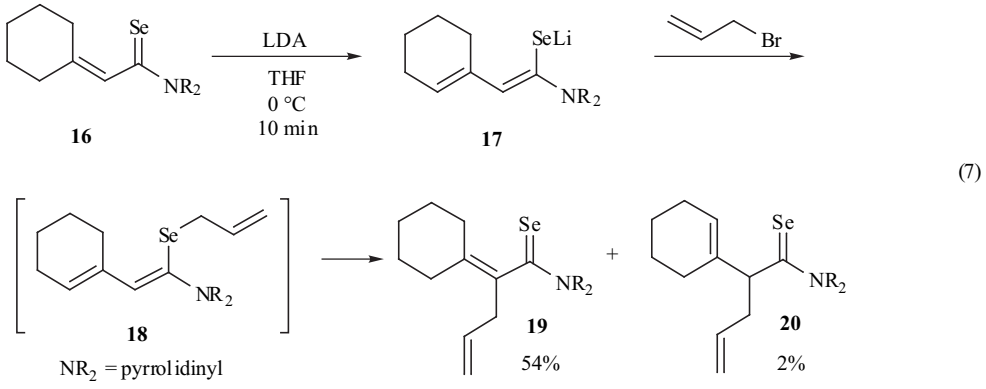
Lithium dieneselenolates were generated from α,β-unsaturated selenoamides [18]. For example, selenoamide **16** was treated with LDA at 0 °C, and allyl bromide was then added (eq. **7**). The product **19** and **20** where allyl group was introduced to the position α to the selenocarbonyl group were obtained in 56% combined yields. In this reaction, allylation may initially take place at the selenium atom of **17** to form allylic vinyl selenide **18**, which then undergoes seleno-Claisen rearrangement to form **20**. The product **20** may be isomerized to **19** under basic reaction conditions.

1.2. From Selenoic Acid *O*-esters

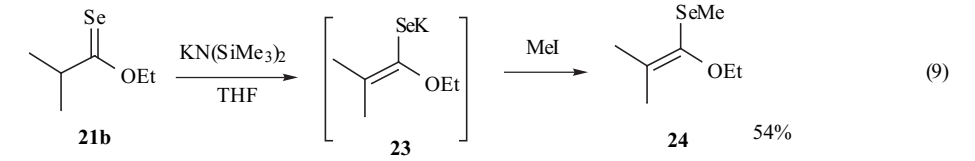
Selenoic acid *O*-esters are less accessible than selenoamides. Thus, only two examples of the generation of lithium eneselenolates from selenoic acid *O*-esters are reported. The self-condensation reaction of selenoacetic acid *O*-cholesteryl ester (**21a**) was carried out with KHMDS as a base (eq. **8**) [19].



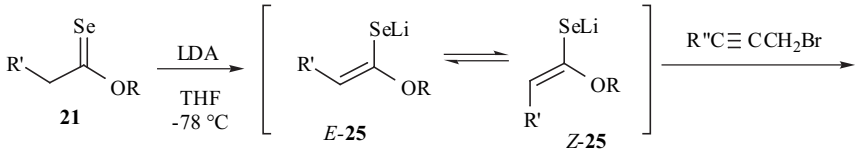
(8)



(7)

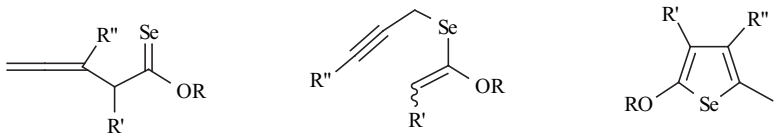


21b **23** **24** 54% (9)



21 *E*-**25** *Z*-**25**

21c R = Et, R' = Ph
21d R = Me, R' = C_6H_4-Cl-4
21e R = Me, R' = Ph
21f R = Pr-*i*, R' = Ph
21g R = Bu, R' = C_6H_4-Cl-4
21h R = Et, R' = Ph (10)



26 **27** **28**

α,β-Unsaturated selenoic acid *O*-ester **22** was formed as a single isomer in 59% yield, although the stereochemistry of **22** was not specified in the literature [19]. In contrast, self-condensation of α-disubstituted selenoic acid *O*-ester **21b** did not take place. When the reaction mixture of **21b** and KHMDS was treated with methyl iodide, ketene selenoacetal **24** was obtained in 54% yield (eq. **9**).

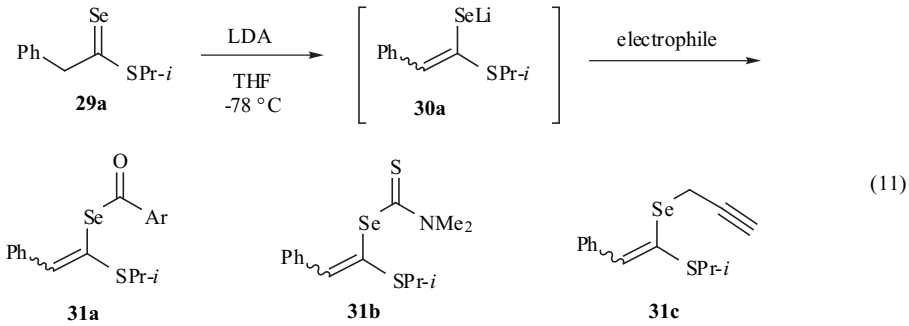
This has implied that potassium eneselenolate **23** was initially formed in the reaction mixture. Lithium eneselenolates **25** were generated from selenoic acid *O*-esters **21c** ~ **21h** and LDA (eq. **10**) [20].

The low temperature NMR spectra of **25** derived from **21e** showed that *E*- and *Z*-isomers of **25** were formed in a ratio of 65 : 35. The propargylation of **25** gave three types of products **26** ~ **28**. The ratio of these products was mainly dependent on the reaction temperature. The allenyl esters **26** were obtained as major products at 0 °C, whereas the reaction at 67 °C gave selenophenes **27** in 43 ~ 62% yields. These results have suggested that allenyl esters **26** undergo intramolecular cyclization to lead to selenophenes **28**.

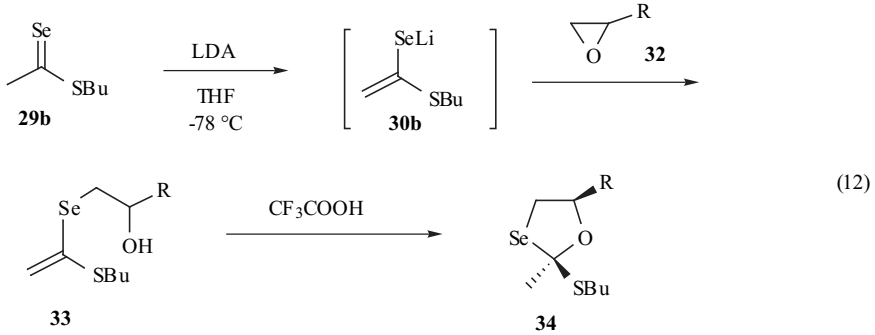
1.3. From Selenothioic Acid *S*-esters

Since a variety of convenient synthetic methods for selenothioic acid *S*-esters have been developed [21], generation of the corresponding eneselenolates have also been studied extensively. α-Phenyl selenothioacetic acid *S*-isopropyl ester (**29a**) was treated with LDA to generate lithium eneselenolate **30a** (eq. **11**) [4].

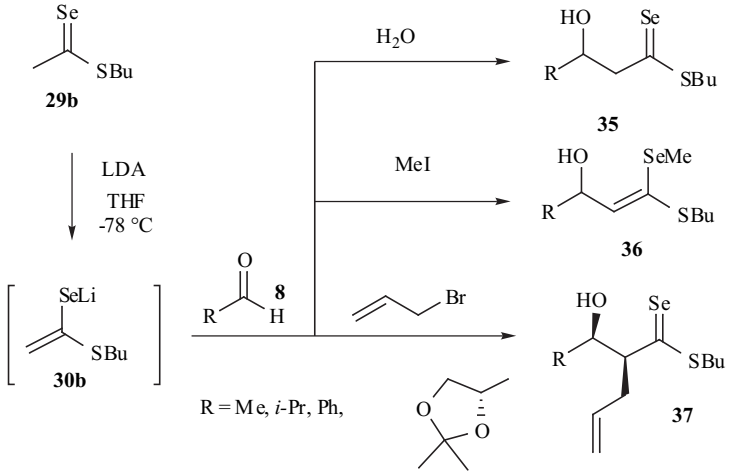
It was then reacted with aroyl chlorides, thiocarbamoyl chloride, and propargyl bromide to form the corresponding



29a **30a** **31a** **31b** **31c** (11)



29b **30b** **32** **33** **34** (12)



(13)

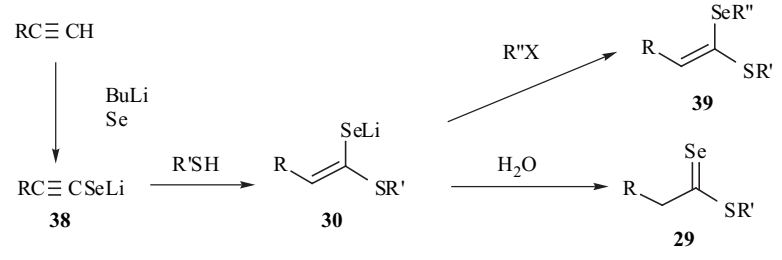
products **31**. In all cases the reaction of **30a** with carbon electrophiles took place at the selenium atom. The ring opening of oxiranes **32** with lithium eneselenolate **30b** gave β-hydroxyethyl vinyl selenides **33**, which have then been converted to 1,3-oxaselenolanes **34** (eq. **12**) [22].

Aldol-type condensation reaction of **29b** with aldehydes **8** was used for the synthesis of β-hydroxy selenothioic acid esters (eq. **13**) [23]. When the reaction mixture of **30b** and aldehydes **8** was further treated with methyl iodide, β-hydroxy ketene selenothioacetals **36** were obtained mainly as *Z*-isomers. Alternatively, addition of allyl bromide gave β–hydroxy α-allyl esters **37**. The reaction showed high *syn*-selectivity except for the reaction with glyceraldehyde.

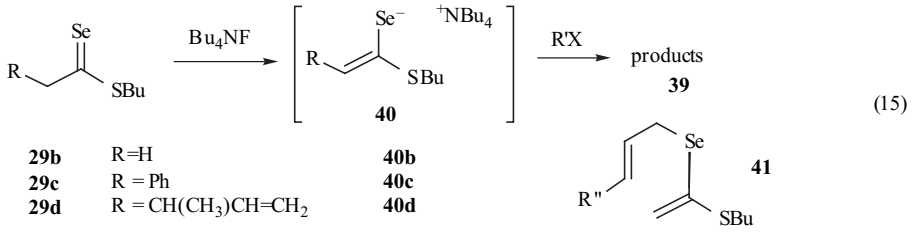
Alternatively, addition of alkanethiols to lithium alkyneselenolates **38** derived from phenylacetylene, 1,3-enynes and aliphatic acetylenes were developed to generate lithium eneselenolates **30** (eq. **14**) [24]. Hydrolysis of **30** generated in this way gave selenothioic acid *S*-esters **29** in moderate yields. The alkylation of **30** gave ketene selenothioacetals **39** in moderate to good yields.

Since selenothioic acid *S*-esters **29** possess acidic α-hydrogen atoms, ammonium fluorides were used as a base (eq. **15**, Table **6**) [25, 26].

Selenothioacetic acid ester **29b** was successively treated with Bu_4NF and allylic bromide in THF to form γ,δ-unsaturated selenothioic acid *S*-esters **29d** ~ **29f**, where more substituted carbon atoms of allylic bromides were introduced to the carbon atom α to the selenocarbonyl group. In the reaction allylic vinyl selenides **41** may be initially formed, then seleno-Claisen rearrangement of **41** takes place (entries 1 – 3) [25]. Methylation and acylation of ammonium eneselenolates **40** in situ generated from esters **29c** and **29d** were carried out (entries 4 – 9) [25,26]. In all cases the reaction proceeded at the selenium atom of **40**. Noteworthy is that the ratio of two stereoisomers is dependent on the reaction time between esters **29** and Bu_4NF (entries 4 – 7) [26]. When ammonium eneselenolate **40c** was generated, and methyl iodide was simultaneously added to the flask, two stereoisomers **39a** were formed in a nearly equal ratio (entry 4). On the other hand, ammonium eneselenolate **40c** was stirred at 0 °C for 30 min followed by the addition of methyl iodide to give predominantly *Z*-isomer of **39a** (entry 7). This may be understood by considering that both isomers of ammonium eneselenolates are kinetically generated, and *E*-isomer of **40** is gradually isomerized to thermodynamically stable *Z*-isomer of **40**. As a matter of fact, *Z*-isomers of **40c** and **40d** were selectively observed in THF-d_8 by ^1H, ^{13}C and ^{77}Se NMR. The electronic properties of these eneselenolates were elucidated on the basis of these data. The *Z*-selective formation of ammonium eneselenolates was specific with selenothioic acid *S*-esters. As for the reaction of α-phenyl selenoic acid ester **42** the *E*-

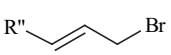
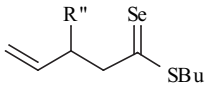
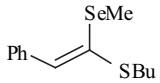
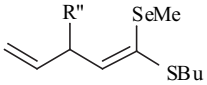
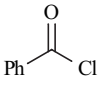
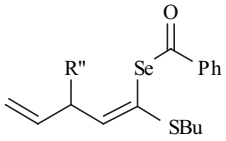


(14)



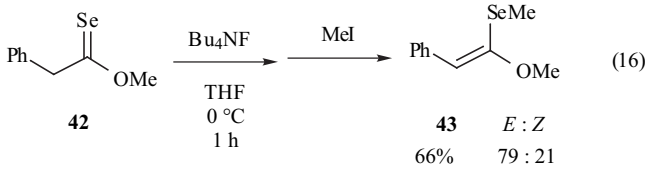
(15)

Table 6. Reaction of Selenothioic Acid *S*-Esters 29 with Bu_4NF and Carbon Electrophiles[a]

entry	ester	R'X	product		yield (%)[b]
1	**29b**			**29d** R" = Me	73
2				**29e** R" = CO_2Et	61
3				**29f** R" = Ph	66
4				1 sec[c]	87(54 : 46)[d]
5	**29c**	MeI		10 min	– (50 : 50)
6				20 min	– (18 : 82)
7			**39a**	30 min	82(12 : 88)
8	**29d**	MeI		**39b**[e]	68(32 : 68)[d]
9	**29d**			**39c**[e]	68(5 : 95)[d]

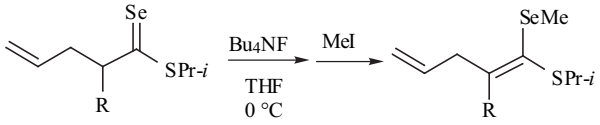
[a]To a THF solution (5 mL) of selenothioic acid *S*-butyl ester **29** (1 mmol) was added Bu_4NF (1.5 mmol) and carbon electrophile (1 mmol) successively at 0 °C unless otherwise noted. [b]Isolated yields. [c]The reaction time between **29c** and Bu_4NF before the addition of MeI. [d]The ratio of E and Z isomers of **39** is shown. [e]The ester was stirred with Bu_4NF for 2 h before the addition of carbon electrophiles.

isomer of ketene selenoacetal **43** was predominantly formed (eq. **16**) [27].



42 **43** *E* : *Z* = 66% 79 : 21 (16)

The deprotonation from α-disubstituted esters **29e** – **29g** with Bu_4NF was complete within 1.5 h (eq. **17**). The methylation of the corresponding ammonium eneselenolates proceeded rapidly to form ketene selenothioacetals **39d** – **39f** with high stereoselectivity.



(17)

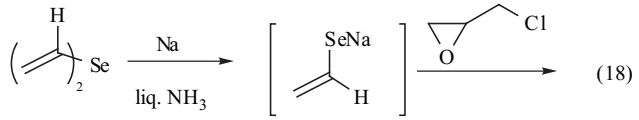
				E : *Z*
29e	R = Ph	**39d**	77%	97 : 3
29f	R = 1-*cyclo*-hexenyl	**39e**	51%	99 : 1
29g	R = Bu	**39f**	80%	62 : 38

2. GENERATION OF ENESELENOLATES VIA ALKENYL OR ALKYNYL METALLIC SPECIES

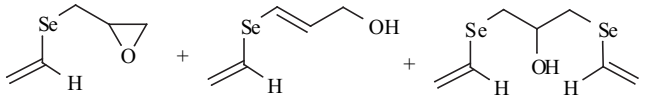
Alternative methods for the generation of metal eneselenolates are the reaction using alkynyl or alkenyl metallic species. These methods often generate metal eneselenolates equivalent to selenoaldehyde enolates.

2.1. Reduction of Divinyl Selenides with Sodium

Sodium eneselenolate **45** was generated from divinyl selenide **44** and sodium metal in liquid NH_3 (eq. **18**) [28,29].

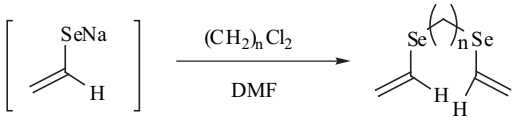


44 **45** (18)



46 **47** **48**

Then, **45** was reacted with epichlorohydrin to give mainly oxiranyl vinyl selenide **46** in 62% yield along with divinyl selenide **47** and alcohol **48**. Dichloromethane and dichloroethane were also added to sodium eneselenolate **45** in DMF to give divinyl diselenoalkanes **49** in good yields (eq. **19**) [30].



45 **49** (19)

n = 1 50%
n = 2 58%

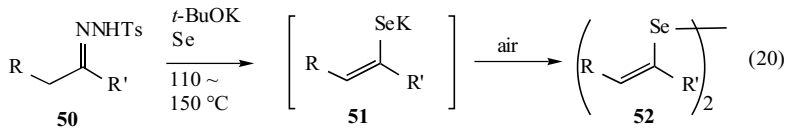
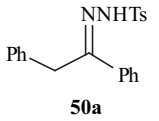
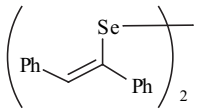
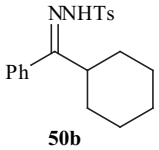
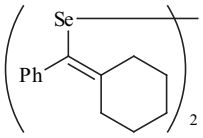
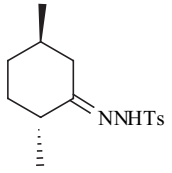
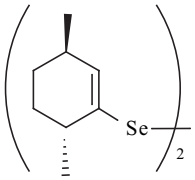
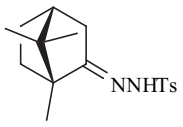
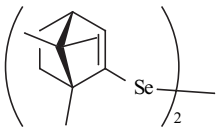


Table 7. Reaction of Ketone *p*-Toluenesulfonyl Hydrazones 50 with *t*-BuOK and Elemental Selenium[a]

entry	hydrazone	temp (°C) time (h)	product 52	yield (%)[b]
1	 **50a**	120 0.5		70
2	 **50b**			52
3	 **50c**			70
4	 **50d**			64

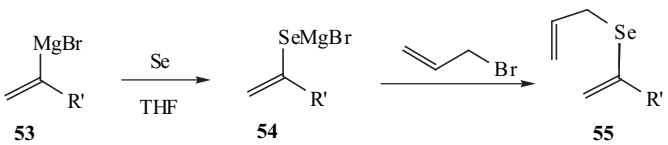
[a]A solution of hydrazone **50** was treated with *t*-BuOK (2.5 mol amt.), Et_2NH (2.5 mol amt.), and elemental selenium (2.5 mol amt.). Then, the reaction mixture was exposed to air for 5 ~ 6 h.

2.2. Insertion Reaction of Elemental Selenium to Alkenyl Metallic Species

The reaction of ketone *p*-toluenesulfonyl hydrazones **50** with *t*-BuOK was utilized for the generation of selenoketone enolates, although potassium eneselenolates **51** were not detected (eq. **20**) [31]. Instead, oxidation of **51** with air was conducted to afford divnyl diselenides **52**. The yields of **52** are summarized in Table **7**.

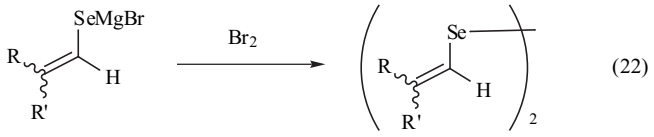
The reaction of ketone *p*-toluenesulfonyl hydrazone derived from acetophenone did not give the corresponding divinyl diselenide, whereas hydrazones **50a** ~ **50d**, which were synthesized from benzophenone, phenyl cyclohexyl ketone, menthone, and camphor, smoothly reacted with *t*-BuOK and elemental selenium to result in the formation of divinyl diselenides **52** in good yields.

The insertion reaction of elemental selenium to Grignard reagents has been well known. The reaction was applied to



the generation of magnesium eneselenolates [32]. For example, the vinyl magnesium bromides **53** were stirred with elemental selenium at 0 °C for 15 min to generate magnesium eneselenolates **54** (eq. **21**) [11].

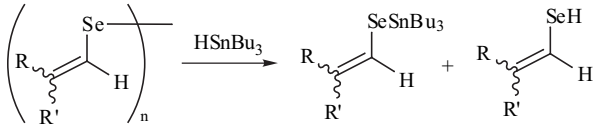
Then, to the reaction mixture was added allyl bromide. Allyl vinyl selenides **55** may initially be formed, but **55** easily underwent a seleno-Claisen rearrangement to form the unstable selenoaldehydes **56**. To confirm the formation of **56**, the reaction mixture was treated with cyclopentadiene at room temperature for 4 days to obtain Diels-Alder adduct **57**. Oxidation of magnesium eneselenolates **54** with bromine was also carried out to afforded divinyl diselenides **52** (eq. **22**) [33].



(22)

54 **52**

The reduction of divinyl diselenides **52** with Bu_3SnH allowed for the first isolation of vinyl selenols **59** (eq. **23**), which had so far only been studied from the theoretical point of view [34].



(23)

52 **58** **59**

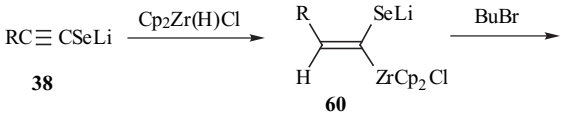
73 ~ 83%

52a R = R' = H
52b R = Me, R' = H
52b' R = H, R' = Me
52c R = R' = Me

The product **59** was collected in a cold finger from the reaction mixture involving vinyl stannyl selenides **58** by vacuum distillation and stored below –50 °C to obtain NMR spectra.

2.3. Reduction of Lithium Alkyneselenolates

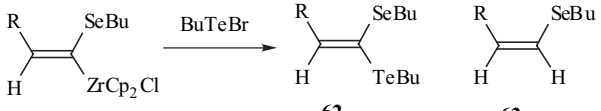
Hydrozirconation of lithium alkyneselenolates **38** was complete within 30 min followed by the addition of butyl bromide and BuTeBr to give ketene telluro(seleno) acetals **62** in good yields (eq. **24**) [35].



38 **60**

R = Pr, Bu, *cyclo*-hexyl
Ph, 1-*cyclo*-hexenyl

(24)



61 **62** **63**

71 ~ 82 %

Hydrozirconation of **38** showed high regio- and stereoselectivity. The zirconium atom was introduced to the carbon atom bearing the LiSe group in **38**. The geometry of the intermediates **61** was confirmed by treating **61** with water, which gave selectively the *Z*-vinyl selenides **63**. A similar treatment of **60** with alkyl halides and sulfenyl chlorides was used for the synthesis of ketene selenothioacetals [36].

In summary, two types of methods for the generation of eneselenolates were demonstrated. Fundamental modes of the reaction of eneselenolates generated from selenoamides, selenoic acid *O*-esters, and selenothioic acid *S*-esters are considerably disclosed. On the basis of this knowledge, eneselenolates can be utilized as good precursors of a wide variety of organoselenium compounds, some of which are of great interest from a synthetic and biological point of view. Eneselenolates via alkenyl and alkynyl metallic species have been studied to a lesser extent, despite their potential availability. Further synthetic application of eneselenolates will be elaborated in the near future.

REFERENCES

[1] Murai T.; Kato, S. In *Topics in Current Chemistry*, Wirth, T., Ed.; Springer-Verlag: Berlin, **2000**, Vol. *208*, p 177.
[2] Dell, C. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds. Pergamon: Oxford, **1995**; Vol. *5*, p 565.
[3] Ishii A.; Nakayama, J. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds. Pergamon: Oxford, **1995**; Vol. *5*, p 505.
[4] Kato, S.; Komuro, T.; Kanda, T.; Ishihara, H.; Murai, T. *J. Am. Chem. Soc.* **1993**, *115*, 3000.
[5] Murai, T.; Mizutani, T.; Kanda, T.; Kato, S. *J. Am. Chem. Soc.* **1993**, *115*, 5823
[6] Murai, T.; Kakami, K.; Hayashi, A.; Komuro, T.; Takada, H.; Fujii, M.; Kanda, T.; Kato, S. *J. Am. Chem. Soc.* **1997**, *119*, 8592.
[7] Sukhai, R. S.; Brandsma, L. *Synthesis* **1979**, 455.
[8] Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806.
[9] Murai, T.; Ezaka, T. unpublished results.
[10] For a review, see: Majumdar, K. C.; Ghosh, S.; Ghosh, M. *Tetrahedron* **2003**, 59, 7251.
[11] Vallée, Y.; Worrell, M. *J. Chem. Soc. Chem. Commun.* **1992**, 1680.
[12] Murai, T.; Suzuki, A.; Kato, S. *J. Chem. Soc. Perkin 1* **2001**, 2711.
[13] Murai, T.; Ishizuka, M.; Suzuki, A.; Kato, S. *Tetrahedron Lett.* **2003**, *44*, 1343.
[14] Murai, T.; Suzuki, A.; Ezaka, T.; Kato S. *Org. Lett.* **2000**, *2*, 311.
[15] Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.
[16] Murai, T.; Ezaka, T.; Ichimiya, T.; Kato, S. *Synlett.* **1997**, 775.
[17] Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. *J. Org. Chem.* **2003**, *68*, 7979.
[18] Murai, T.; Suzuki, A.; Takagi, M.; Kato, S. *Phosphorus, Sulfur and Silicon* **2001**, *172*, 101.
[19] Barton, D. H. R.; Hansen, P.-E.; Picker, K. *J. Chem. Soc. Perkin I* **1977**, 1723.
[20] Kanda, T.; Ezaka, T.; Murai, T.; Kato, S. *Tetrahedron Lett.* **1995**, *36*, 2807.
[21] Murai, T.; Kato, S. *Sulfur Rep.* **1998**, *20*, 368.
[22] Murai, T.; Fujii, M.; Kato, S. *Chem. Lett.* **1997**, 545.
[23] Murai, T.; Endo, H.; Ozaki, M.; Kato, S. *J. Org. Chem.* **1999**, *64*, 2130.
[24] Murai, T.; Kakami, K.; Itoh, N.; Kanda, T.; Kato, S. *Tetrahedron* **1996**, *52*, 2839.
[25] Murai, T.; Hayakawa, S.; Kato, S. *Chem. Lett.* **2000**, 368.
[26] Murai, T.; Hayakawa, S.; Kato, S. *J. Org. Chem.* **2001**, *66*, 8101.
[27] (a) Murai, T.; Hayakawa, S.; Miyazaki, Y.; Kato, S. *Phoshorus, Sulfur and Silicon* **2001**, *172,* 111. (b) Murai, T.; Kondo, T.; Kato S. *Heteroat. Chem.* **2004**, *15,* 187.
[28] Amosova, S. V.; Gostevskaya, V. I.; Gavrileva, G. M.; Afonin, A. V.; Potapov, V. A. *Zhur. Org. Khim.* **1990**, *26*, 1131.

[29] Amosova, S. V.; Gostevskaya, V. I.; Gavrilova, G. M.; Afonin, A. V.; Romanenko, L. S.; Potapov, V. A. *Zhur. Org. Khim.* **1991**, *27*, 1618.
[30] Amosova, S. V.; Gostevskaya, V. I.; Gavrilova, G. M.; Afonin, A. V.; Romanenko, L. S.; Potapov, V. A. *Zhur. Org. Khim.* **1992**, *28*, 306
[31] Shimada, K.; Asahida, M.; Takahashi, K.; Sato, Y.; Aoyagki, S.; Takikawa, Y.; Kabuto, C. *Chem. Lett.* **1998**, 513.
[32] Comasseto, J. V.; Ling, L. W.; Petragnani, N.; Stefani, H. A. *Synthesis* **1997**, 373.
[33] Guillemin, J.-C.; Bouayad, A.; Vijaykumar, D. *Chem. Commun.* **2000**, 1163.
[34] Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2269.
[35] Dabdoub, M. J.; Begnini, M. L.; Guerrero, P. G., Jr.; Baroni, A. C. M. *J. Org. Chem.* **2000**, *65*, 61.
[36] Zhong, P.; Huang, N.-P. *Synth. Commun.* **2001**, *31*, 2423.

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