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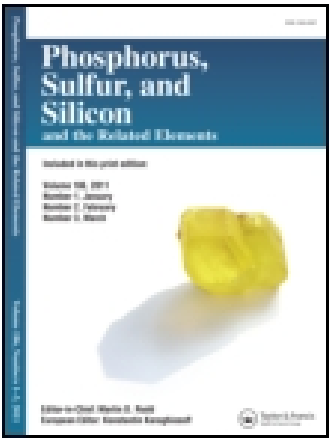

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Regioselectivity of Selenium-Mediated Carbonylation of Organolithium Compounds with Carbon Monoxide

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REGIOSELECTIVITY OF SELENIUM-MEDIATED CARBONYLATION OF ORGANOLITHIUM COMPOUNDS WITH CARBON MONOXIDE

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Regioselectivity of selenium-mediated carbonylation of organolithium compounds with carbon monoxide has been investigated. The reactions of lithium enolates of 2,2-dicyclohexyl aldehyde and 1,1-dicyclohexylpropane-2-one with selenium and carbon monoxide afforded the corresponding selenocarbonates by carbonylation at the enolate oxygen as the main product. Carbonylation of nitrogen-containing heterocycles can give either C- or N-carbonylation product, but diphenyl(4-pyridyno)methane, imidazole, and pyrazole afford only corresponding carbamoselenoates via N-carbonylation.

Keywords Carbamoselenoates; carbon monoxide; organolithium compounds; selenium; selenocarbonates; selenol esters

INTRODUCTION

We have reported selenium-mediated carbonylation of a series of organolithium compounds with carbon monoxide[1] giving rise to the corresponding selenol esters[2–4] and carbamoselenoates[5] after trapping with alkyl halides. The related imidoylation by the use of isocyanides in place of carbon monoxide has also been disclosed.[6] For example, lithium enolates of aldehydes and ketones were carbonylated to afford β-formyl and β-keto selenol esters having 1,3-dioxoalkane units,[3a,7] which are frequently encountered frameworks of organic molecules as versatile and important functionalities in synthetic chemistry. As for the mechanism of carbonylation of lithium enolates, we proposed a unique mechanism composed of *O*-carbonylation and subsequent migration of the SeCO moiety to the α-carbon. As shown in Scheme 1, reaction of enolates **1** with Se affords selenolates **2**,[8] which then react with CO to give lithium selenocarbonates **4** as an initial carbonylation intermediate, probably via formal rearrangement of **3**. The detailed mechanism leading to **4** has not yet been determined, but it may proceed stepwise with elimination of carbonyl selenide (SeCO)

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Dedicated to Professor Naomichi Furukawa on the occasion of his 70th birthday.

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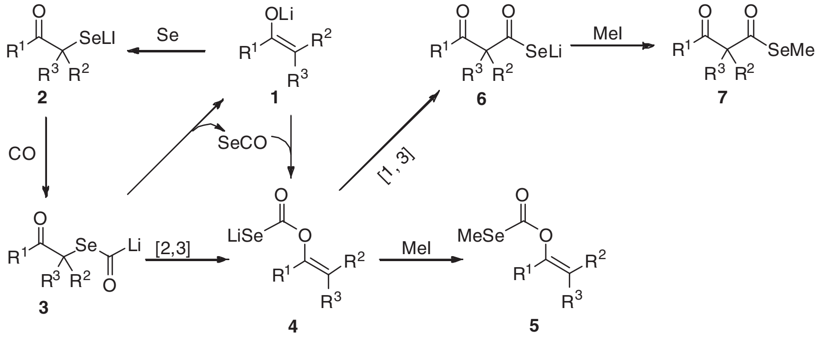


Scheme 1 Plausible mechanism.

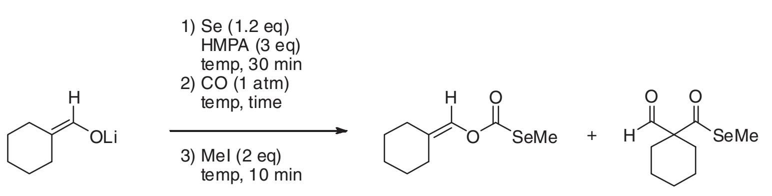
followed by nucleophilic attack of enolate oxygen at the central carbon of SeCO[9–11] or [2,3]-rearrangement. In the cases of enolates of aldehydes, selenocarbonates **5** are obtained by alkylation of **4** at −23°C or below, while **4** undergoes [1,3]-rearrangement at 0°C or above to lithium selenocarboxylates **6** giving *β*-formyl selenol esters **7**. However, none of the *O*-carbonylation products were obtained so far from enolates of ketones and other carbonyl compounds even at −23°C. These results suggest that rearrangement from **4** to **6** is rapid when $R^1 \neq H$, probably due to steric repulsion between R^1 and OC(O)SeLi moiety.[12]

In this work, we examined regioselectivity of carbonylation of lithium enolates carrying bulkier substituents at the *α*-position(s) in order to confirm the proposed *O*-carbonylation mechanism shown in Scheme 1. In addition, regioselectivity of carbonylation of some cyclic nitrogen compounds was also examined.

RESULTS AND DISCUSSION

Carbon vs. Oxygen

We have reported that lithium enolate **1a** of cyclohexanecarboxaldehyde, prepared from the corresponding trimethylsilyl enol ether and MeLi at 20°C, gave selenocarbonate **5a**, *O*-carbonylation product, in 64% yield together with 16% of *β*-formyl selenol ester **7a**, *C*-carbonylation product, when treated with CO at −23°C followed by trapping with MeI. On the contrary, **7a** was obtained selectively at 20°C [Equation (1)].[3a]



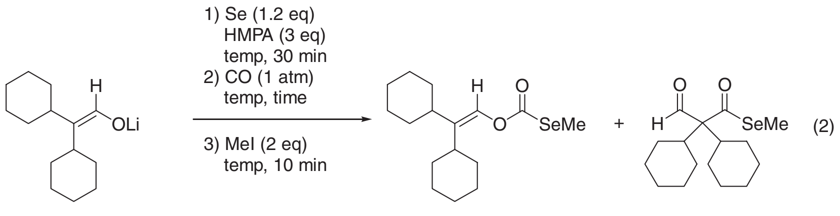
(1)

1a **5a** **7a**

	5a	7a
temp = -23 °C, time = 60 min	64%	16%
temp = 20 °C, time = 20 min	0%	59%

In order to examine the effect of substituents on the regioselectivity, we performed carbonylation of a lithium enolate of more hindered aldehyde. Lithium enolate **1b** of 2,2-dicyclohexyl aldehyde, generated in a similar manner as that of **1a**, was allowed to react with selenium and then with carbon monoxide (1 atm) at −23°C for 30 min.

Selenocarbonate **5b** was obtained exclusively in 93% yield after trapping with MeI and β-formyl selenol ester **7b**, *C*-carbonylation product, was not detected. When carbonylation was conducted at 20°C for 5 h, **5b** and **7b** were obtained in 27% and 18% yields, respectively.[13] These results indicate that bulkier substituents at the α-position retards isomerization of **4b**, *O*-carbonylation intermediate, to *C*-carbonylation intermediate **6b** [Equation (2)].

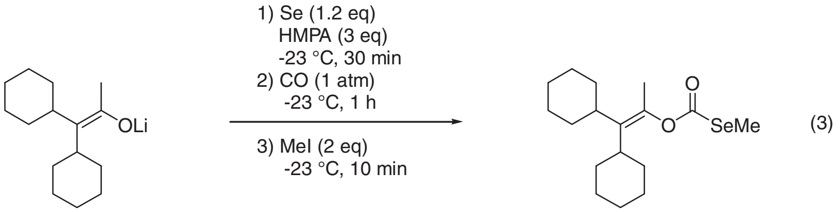


1b **5b** **7b**

temp = -23 °C, time = 30 min 93% 0%

temp = 20 °C, time = 5 h 27% 18%

We then examined carbonylation of the corresponding lithium enolate of ketone **1c** having two cyclohexyl groups at an α-carbon and found that selenocarbonate **5c** was obtained in 42% at -23°C [Equation (3)]. This is the first example of detecting *O*-carbonylation product from ketones rather than aldehydes and would support the *O*-carbonylation mechanism shown in Scheme 1 even for ketones.[14]

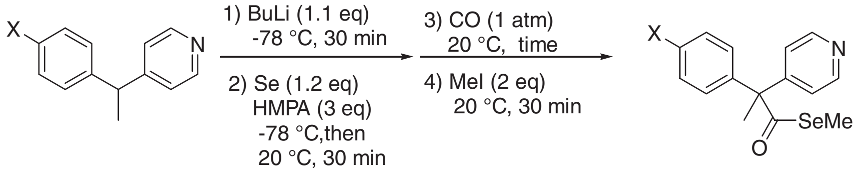


1c **5c**, 42%

Carbon vs. Nitrogen

We have revealed that the lithio derivative of 1-pheny-1-(4-pyridino)ethane **8a** is carbonylated at benzylic carbon.[2a] Introduction of chlorine at the *para* position of the phenyl ring (**8b**), which should have more acidic benzylic protons than **8a**, led to the acceleration of CO uptake and the carbonylation time was drastically shortened; however, the yield of the product **9b** was not improved [Equation (4)].[15]

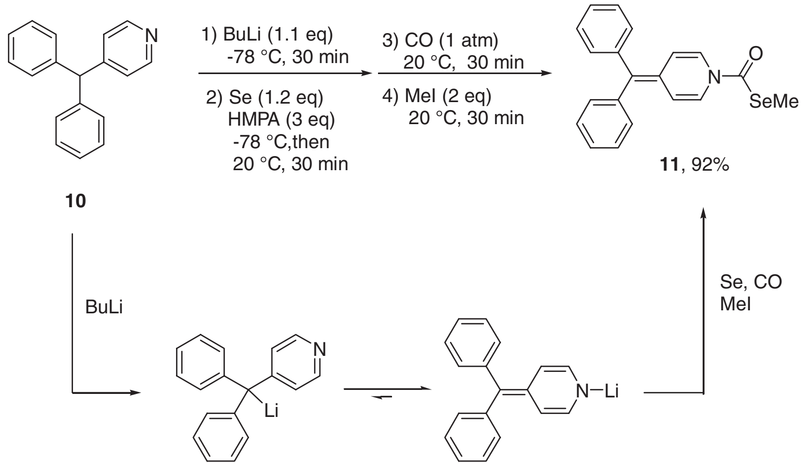
In contrast to the reaction of **8**, diphenyl-4-pyridylmethane **10** was carbonylated at the nitrogen atom to give only carbamoselenoate **11** in 92% yield [Equation (5)] as in the case of imidoylation.[6] The corresponding carbonylation product at the central carbon was not obtained. This regioselectivity can be explained not only by the steric factor but also by the electron density that the anion charge of lithio-4-pyridyldiphenylmethane **12** is localized at the nitrogen atom of the pyridyl ring.[16]



(4)

8a: X = H
8b: X = Cl

9a, 35% (time = 13 h)
9b, 41% (time = 2 h)



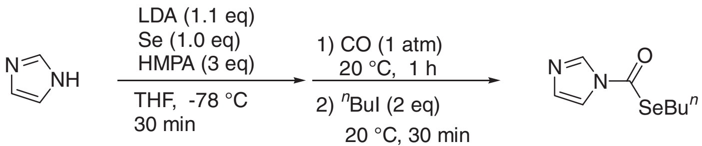
(5)

10

11, 92%

12

Regioselectivity of carbonylation of other nitrogen-containing heterocycles was also examined. Lithio derivatives of imidazole **13**, that would be present in solution as shown in the equilibration in Figure 1, was carbonylated exclusively at nitrogen to afford carbamoselenoates **14** in 61% yield [Equation (6)]. Similarly, pyrazole **15** gave the corresponding carbamoselenoate **16** as the sole product [Equation (7)].



(6)

13

14, 61%

(7)

15

16, 75%

Figure 1 Possible equilibration of lithio derivative of imidazole.

EXPERIMENTAL

Carbonylation of lithium enolate **1b** from 1-trimethylsiloxy-2,2-dicyclohexylethylene: MeLi (1.17 M in Et_2O, 1.0 mL, 1.17 mmol) was added to a THF (15 mL) solution of 1-trimethylsiloxy-2,2-dicyclohexylethylene (1.03 mmol) at 20°C under Ar. After 30 min, the solution was cooled to −23°C, selenium (1.20 mmol) and HMPA (2.96 mmol) were added, and the mixture was kept at the same temperature for 30 min. The reaction vessel was then purged with CO. After CO absorption ceased (30 min), MeI (2.11 mmol) was added at the same temperature, and the mixture was warmed up to room temperature. Aqueous saturated NH_4Cl solution (100 mL) was added, and the mixture was extracted with Et_2O (50 mL). After the organic layer was dried over $MgSO_4$, evaporation of the solvent gave a yellow residue. Purification by PTLC using *n*-hexane-Et_2O (20:1, *v/v*) yielded *Se*-methyl *O*-(2,2-dicyclohexylvinyl)selenocarbonate (**5b**, 93%) as a pale yellow oil; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.00$–1.35 (m, 10 H), 1.35–1.90 (m, 11 H), 2.19 (brs, 1 H), 2.29 (s, 3 H), 6.87 ppm (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 6.5$, 26.1, 26.8, 26.9, 30.7, 33.1, 39.3, 40.7, 131.4, 136.8, 165.4 ppm; IR (neat): = 1722 cm^{-1}; MS (CI), m/*z* (relative intensity,%) 331 ($M^+ + 1$, 62). Anal. Calcd for $C_{16}H_{26}O_2Se$: C, 58.35; H, 7.96. Found: C, 58.42; H, 7.98.

Se-Methyl 2,2-Dicyclohexyl-3-oxo-selenopropionate (7b)

A colorless oil; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.85$–0.97 (m, 4 H), 1.07–1.30 (m, 8 H), 1.55–1.78 (m, 8 H), 2.14 (brs, 1 H), 2.29 (s, 3 H), 9.98 ppm (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 5.1$, 26.4, 26.8, 27.1, 28.0, 28.5, 40.2, 75.0, 203.2, 203.7 ppm; IR (neat): = 1679, 1726 cm^{-1}; MS (CI), m/*z* (relative intensity,%) 331 ($M^+ + 1$, 26). Anal. Calcd for $C_{16}H_{26}O_2Se$: C, 58.35; H, 7.96. Found: C, 58.74; H, 8.12.

Se-Methyl 1-(*p*-Chlorophenyl)-1-(4-pyridyl)ethane-1-selenocarboxylate (9b)

A yellow oil; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3 H), 2.21 (s, 3 H), 7.14 (d, $J = 6.4$ Hz, 2 H), 7.19 (d, $J = 8.8$ Hz, 2 H), 7.32 (d, $J = 8.8$ Hz, 2 H), 8.56 ppm (d, $J = 6.4$ Hz, 2 H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 6.5$, 26.0, 64.3, 123.2, 128.5, 130.2, 134.1, 140.0, 149.9, 152.2, 206.0 ppm; IR (neat): = 1682 cm^{-1}; MS (CI), m/*z* (relative intensity,%) 340 ($M^+ + 1$, 100). HRMS (CI) Calcd for $C_{15}H_{15}ClNOSe$: 340.0008. Found: 340.0008.

Se-Methyl 4-(Diphenylmethylidene)-4*H*-azine-*N*-selenocarbamate (11)

A yellow oil; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.35$ (s, 3 H), 6.16 (d, J = 8.8 Hz, 2 H), 7.15–7.32 pm (m, 12 H); ^{13}C NMR (68 MHz, $CDCl_3$): $\delta = 6.8$, 114.0, 123.6, 126.3, 126.8, 128.2, 129.0, 13.2, 141.8, 162.7 ppm; IR (neat): = 1650 cm^{-1}; MS (CI), m/*z* (relative intensity,%) 367 ($M^+ + 1$, 50). HRMS (EI) Calcd for $C_{20}H_{17}NOSe$: 367.0475. Found: 367.0483.

Se-*n*-Butyl Imidazole-1-carboselenolate (14)

A pale brown oil; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 0.96$ (t, J = 7.3 Hz, 3 H), 1.46 (sext, J = 7.3 Hz, 2 H), 1.80 (quint, J = 7.3 Hz, 2 H), 3.19 (t, J = 7.3 Hz, 2 H), 7.11 (s, 1 h), 7.44 (s, 1 H), 8.17 pm (s, 1 H); ^{13}C NMR (68 MHz, CDCl$_3$): $\delta = 13.4$, 22.9, 27.9, 32.1, 116.0, 131.0, 135.4, 164.4 ppm; IR (neat): = 1689 cm^{-1}; MS (EI), m/z (relative intensity,%) 232 (M$^+$, 10). Anal. Calcd for $C_8H_{12}N_2OSe$: C, 41.56; H, 5.24; N, 12.12. Found: C, 41.29; H, 5.41; N, 11.94.

***Se-n*-Butyl Pyrazole-1-carboselenolate (16)**

A yellow oil; ^{1}H NMR (270 MHz, CDCl$_3$): $\delta = 0.95$ (t, J = 7.3 Hz, 3 H), 1.46 (sext, J = 7.3 Hz, 2 H), 1.76 (quint, J = 7.3 Hz, 2 H), 3.04 (t, J = 7.3 Hz, 2 H), 6.48 (s, 1 h), 7.73 (s, 1 H), 8.14 pm (s, 1 H); ^{13}C NMR (68 MHz, CDCl$_3$): $\delta = 13.5$, 22.9, 25.4, 32.4, 109.8, 126.8, 143.8, 168.7 ppm; IR (neat): = 1692 cm^{-1}; MS (EI), m/z (relative intensity,%) 232 (M$^+$, 17). Anal. Calcd for $C_8H_{12}N_2OSe$: C, 41.56; H, 5.24; N, 12.12. Found: C, 41.69; H, 5.34; N, 11.98.

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