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Carbonylation of Lithium Enolates with Carbon Monoxide Mediated by Selenium

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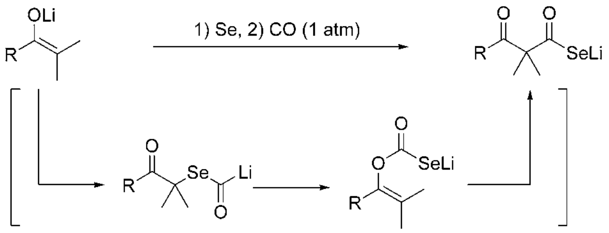
ABSTRACT



Lithium enolates of ketones and aldehydes undergo carbonylation with carbon monoxide with the aid of selenium under mild conditions to yield *β*-keto and *β*-formyl selenol esters after trapping with alkyl iodides. This reaction proceeds via a unique carbonylation mechanism comprised of O-carbonylation and subsequent migration of the SeCO moiety to the α-carbon.

1,3-Dioxoalkane units such as in 1,3-diketones, *β*-keto esters, and malonates are frequently encountered frameworks of organic molecules as versatile and important functionalities in synthetic chemistry. A simple and promising access to these compounds is carbonylation of carbonyl compounds with CO at their α-carbons.[1] As an attractive approach for this transformation, some successful examples of carbonylation of transition metal enolates have been reported using α-halo carbonyl compounds as the substrates. For example, dialkyl malonate synthesis by cobalt(II)-catalyzed carbonylation of alkyl haloacetates has been well studied and applied to industrial production.[2,3] *β*-Keto esters have been prepared by Co(II)-[2f] and Pd(II)-catalyzed[4,5] carbonylation of α-haloketones.[6] However, introduction of CO into non-transition metal enolates has never been attained.

We already disclosed that benzylic and allylic organolithium compounds underwent carbonylation with CO with the aid of Se, yielding selenol esters after trapping with alkyl halides.[7] This successful result prompted us to examine the reaction of CO with lithium enolates, which can easily be generated from parent carbonyl compounds without halogen

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(1) For reviews of carbonylation, see: (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991. (b) Bates, R. W. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds; Pergamon Press: Oxford, 1995; Vol. 12, pp 349−386.

(2) (a) Heck R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 2779−2782. (b) Prang, U.; El-Chahawi, M.; Vogt, W.; Richtzenhain, H. *Ger. Offen.* 2,524,389; *Chem. Abstr.* **1977**, *86*, 105967z. (c) El-Chahawi, M.; Prang, U.; Richtzenhain, H.; Vogt, W. *Ger. Offen.* 2,603,026; *Chem. Abstr.* **1978**, *88*, 190117f. (d) Yamamoto, H.; Shoji, Y. *Jpn. Kokai Tokkyo Koho* 78,112,807; *Chem. Abstr.* **1979**, *90*, 54487r. (e) Onoda, T.; Wada, K. *Jpn. Kokai Tokkyo Koho* 79,112,817 and 79,112,818; *Chem. Abstr.* **1980**, *92*, 22076f and 22077g. (f) Suzuki, T.; Matsuki, T.; Kudo, K.; Sugita, N. *Nippon Kagaku Kaishi* **1983**, 1482−1487; *Chem. Abstr.* **1984**, *100*, 33957d. (g) Yasuda, K.; Shinoda, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 289−291. (h) Theis, C.; Bauer, F.; Latz, W.; Prange, U. Eur. Pat. Appl. 1,127,868, 2001; *Chem. Abstr.* **2001**, *135*, 182386. (i) Bauer, F. *Ger. Offen.* 10,008,899 and 10,008905; *Chem. Abstr.* **2001**, *135*, 210753 and 212591.

(3) Carbonylation using rhodium catalysts supported on activated charcoal: (a) Shinoda, K.; Yasuda, K. *Chem. Lett.* **1985**, 9−10. (b) Gobolos, S.; Talas, E.; Margifalvi, J. *Stud. Surf. Sci. Catal.* **1988**, *41*, 337−344; *Chem. Abstr.* **1989**, *110*, 13442u.

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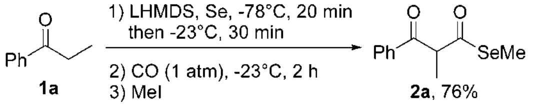
substituents. Here we describe the first example of carbonylation of lithium enolates of ketones and aldehydes with CO mediated by Se, giving rise to 1,3-dioxoalkanes.[8] We also propose here that this reaction proceeds via a unique pathway comprised of O-carbonylation and subsequent migration of the SeCO moiety to the α-carbon.

Propiophenone (**1a**, 2.0 mmol) was added to a black THF suspension of Se (2.4 mmol) and LHMDS (2.4 mmol) at −78 °C under Ar. The mixture was warmed to −23 °C, and then Ar was replaced with CO (1 atm). Within 2 h, a stoichiometric amount of CO was absorbed, and addition of MeI followed by the usual workup gave β-keto selenol ester **2a** in 76% yield (eq 1).[9] The yields of **2a** were not affected by coexistence of additives such as HMPA and DMPU.[10] The use of S in place of Se under the same conditions did not afford the corresponding β-keto thiol ester at all.

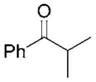
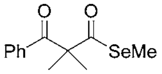
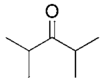
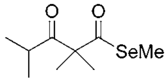
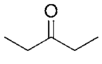
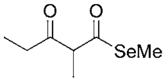
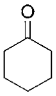
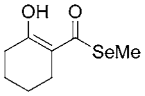
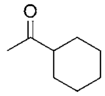
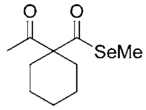


1a **2a**, 76% (1)

The results obtained using several other lithium enolates of ketones are given in Table 1. Symmetric and asymmetric ketones having a secondary alkyl group(s) such as isobutyrophenone (**1b**) and 2,4-dimethyl-3-pentanone (**1c**) can efficiently be carbonylated to give the corresponding selenol esters **2b**,**c** in high yields (runs 1, 2). 3-Pentanone (**1d**) gave **2d** only in 15% yield under similar conditions; however, the yield was improved up to 50% by using 2 equiv of LHMDS (run 3). Similarly, an enolate of cyclohexanone (**1e**) underwent carbonylation, giving **2e** in 41% yield as its enol form (run 4). Carbonylation of a lithium enolate of acetophenone, however, resulted in the recovery (80%) of the ketone.[11]

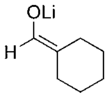
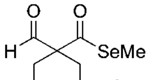
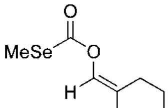
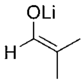
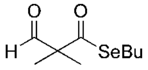
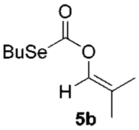
We then investigated the selenium-mediated carbonylation of aldehydes (Table 2). Lithium enolate **3a** of cyclohexanecarboxaldehyde, prepared from the corresponding trimethylsilyl enol ether and MeLi at 20 °C, was allowed to react with Se at −23 °C in the presence of HMPA for 30 min and then with CO (1 atm) at −23 °C for 60 min. Surprisingly, selenocarbonate **5a** was obtained in 64% yield after trapping with MeI at −23 °C in addition to 16% of β-formyl selenol ester **4a** (run 1). A similar result was obtained when the reaction was performed at −45 °C, though prolonged reaction time was needed (run 2). On the contrary, only **4a** was obtained when the reaction was carried out at 0 or 20 °C (runs 3, 4). Similarly, carbonylation of enolate **3b** of isobutylaldehyde afforded a mixture of **4b** and **5b** at −23 °C, while the reaction at 0 °C gave **4b** exclusively (runs 5, 6).

Table 1. Carbonylation of Lithium Enolates of Ketones[a]

run	ketone		product		yield, %[a]
1		**1b**		**2b**	87
2		**1c**		**2c**	85
3[b]		**1d**		**2d**	50
4[b]		**1e**		**2e**	41
5[b]		**1f**		**2f**	63

[a] Reactions were carried out under the same conditions shown in the text unless otherwise specified. [b] Yield of isolated product. [c] LHMDS (4.0 mmol) was used. [d] Lithium enolate of ketone **1f** was generated by the reaction of the corresponding trimethylsilyl enol ether with MeLi at 20 °C.

Table 2. Carbonylation of Lithium Enolates of Aldehydes[a]

run	enolate		temp.,[b] time[c]	products[d]	
		**3a**		 **4a**	 **5a**
1			- 23 °C, 60 min	16%	64%
2			- 45 °C, 90 min	18%	64%
3			0 °C, 40 min	67%	—
4			20 °C, 20 min	59%	—
		**3b**		 **4b**	 **5b**
5			- 23 °C, 40 min	38%	29%
6			0 °C, 20 min	56%	—

[a] Conditions: 3 (2.0 mmol), Se (2.4 mmol, HMPA (6 mmol), 30 min; CO (1 atm), time as indicated above; RI (4.0 mmol), 10 min. For generation of lithium enolates, see Table 1 footnote d. [b] Reaction temperature was maintained throughout the reaction. [c] Carbonylation time. [d] Yields of isolated products.

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(4) (a) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532−534. (b) Choudary, B. M.; Reddy, N. P.; Jamil, M. Z. *Polyhedron* **1986**, *5*, 911−912. (c) Cavinato, G.; Toniolo, L. *J. Mol. Catal. A: Chem.* **1999**, *143*, 325−330. (d) Lapidus, A. L.; Eliseev, O. L.; Bondarenko, T. N.; Sizan, O. E.; Ostapenko, A. G.; Beletskaya, I. P. *Synthesis* **2002**, 317−319.

(5) Stoichiometric reactions of Pd(II) enolates with CO: Ito, Y.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1980**, *21*, 2873−2876.

(6) Formation of acyl nickel complexes was spectroscopically confirmed in the carbonylation of nickel enolate of ethyl acetate: Belderraín, T. R.; Knight, A.; Irvine, D. J.; Paneque, M.; Poveda, M. L.; Carmona, E. *J. Chem. Soc., Dalton Trans.* **1992**, 1491−1495.

(7) Maeda, H.; Fujiwara, S.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1996**, *118*, 8160−8161.

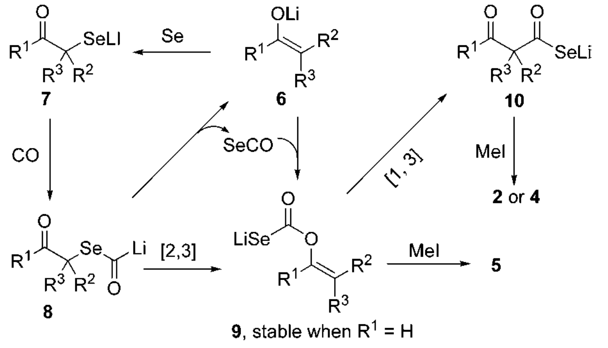
(8) We already reported selenium- (a, b) and sulfur-catalyzed (c) carbonylation of *o*-hydroxy acetophenones to give coumarins at elevated temperature: (a) Ogawa, A.; Kondo, K.; Murai, S.; Sonoda, N. *J. Chem. Soc., Chem. Commun* **1982**, 1283−1284. (b) Ogawa, A.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron* **1985**, *41*, 4813−4819. (c) Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Ogawa, A.; Kambe, N.; Sonoda, N. *Synthesis* **1988**, 257−259.

(9) When LDA was used in place of LHMDS as a base, a significant amount (ca 30%) of aminolysis product, β-keto amide, was formed.

(10) Reaction of lithium enolates of ketones **8** with Se in the presence of additives such as HMPA followed by trapping with alkyl halides resulted in formation of α-alkylselenoketones via alkylation of **9**. The yields were very low without additives: (a) Liotta, D.; Zima, G.; Barnum, C.; Saindane, M. *Tetrahedron Lett.* **1980**, *21*, 3643−3646. (b) Swiss, K.; Choi, W.-B.; Mohan, J.; Barum, C.; Saindane, M.; Zima, G.; Liotta, D. *Heteroatom Chem.* **1990**, *1*, 141−149.

(11) Although a stoichiometric amount of CO was absorbed, the expected product was not obtained at all, probably due to facile decomposition of an intermediate.

Scheme 1. Plausible Reaction Pathways



To probe the reaction mechanism, the following control experiments were performed. First, carbonylation of **3a** was carried out under conditions identical to those in run 1 in Table 2 (at −23 °C for 60 min). The reaction system was then evacuated to remove CO at −78 °C and filled with Ar, and the reaction mixture was warmed to 20 °C. This experiment yielded **4a** in 86% yield without **5a** after trapping with MeI. Second, when the reaction of lithium enolate of cyclohexyl methyl ketone **1f** was carried out at −23 °C starting from the corresponding trimethylsiloxyethylidenecyclohexane, only **2f** was obtained in 63% yield (run 5 in Table 1). From these results and the fact that isolated **5a** did not rearrange to **4a** under the present reaction conditions, we propose reaction pathways as shown in Scheme 1. Reaction of enolates **6** with Se affords selenolates **7**, which then react with CO to give lithium selenocarbonates **9** as an initial carbonylation intermediate, probably via formal rearrangement of **8**. There is still a question of whether the rearrangement **8** → **9** proceeds in a concerted mechanism via [2,3]-sigmatropic rearrangement or stepwise with elimination of carbonyl selenide (SeCO) followed by nucleophilic attack of enolate oxygen at the central carbon of SeCO. In the cases of enolates of aldehydes, selenocarbonates **5** are obtained at −23 °C or below by alkylation of **9**, while **9** undergoes [1,3]-rearrangement[12] at 0 °C or above to lithium selenocarboxylates **10**, giving β-formyl selenol esters **4**. However, none of the O-carbonylation products were obtained from enolates of ketones even at −23 °C. These results suggest that rearrangement from **9** to **10** is rapid when $R^1 \neq H$, probably due to steric repulsion between R^1 and the OC(O)SeLi moiety.

In summary, the present study disclosed that carbonylation of lithium enolates of ketones and aldehydes with CO proceeded under mild conditions in the presence of Se. A unique carbonylation mechanism involving selenocarbonate intermediates has been suggested on the basis of control experiments. In addition, since selenol esters are of potent synthetic importance as versatile intermediates in organic chemistry, the present reaction should attract much attention as a convenient method for the synthesis of β-keto and β-formyl selenol esters.[13]

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Supporting Information Available: Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) An intermolecular acyl transfer process between **9** and **6** is unlikely because crossover products were not obtained when enolate **3b** was added to a solution of **9** derived from enolate **3a**, CO, and Se.

(13) For 1,3-dioxoalkanes involving a selenol ester unit(s): (a) Ziegler, E.; Nölken, E. *Monatsh.* **1958**, *89*, 737−740; *Chem. Abstr.* **1959**, *53*, 12284d. (b) Ruwet, A.; Pourveur, A.; Renson, M. *Bull. Soc. Chim. Belg.* **1970**, *79*, 631−637; *Chem. Abstr.* **1971**, *74*, 53431a. (c) Jansen, B. J. M.; Sengers, H. H. W. J. M.; Bos, H. J. T.; de Groot, A. *J. Org. Chem.* **1988**, *53*, 855−859. (d) Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1335−1336.