Specific Two-Step Decarboxylation of Copper(I,II) β-Keto Carboxylates. A Novel Type of Regulation of the Decarboxylation of β-Keto Acids[1]

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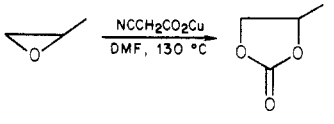
Copper(I,II) β-keto carboxylates undergo a specific two-step decarboxylation. For example, the decarboxylation of copper(I) 1-oxocyclohexane-2-carboxylate (1) evolves CO_2 in a 50% yield in dimethylformamide (DMF) at 70 °C. No further CO_2 evolution beyond this 50% decarboxylation occurs at 70 °C. At a higher temperature of 120 °C, the remaining 50% of the CO_2 is released. This specific two-step decarboxylation of 1 results from the intermediate formation of a dicopper(I) salt of the enol of 1-oxocyclohexane-2-carboxylic acid (**10**) which is stable to decarboxylation at 70 °C. Compound **10** is isolated from the reaction mixture after the 50% decarboxylation. Decarboxylations of copper(I,II) benzoylacetates, copper(I) oxaloacetate, copper(II) 1-oxocyclohexane-2-carboxylate, and copper(II) chloride 1-oxocyclohexane-2-carboxylate also proceed stepwise in DMF. On the other hand, copper(I,II) benzoylcyclopropane-1-carboxylates without an enolizable α-hydrogen atom evolve CO_2 in a usual one-step manner. The present specific two-step decarboxylation of copper(I,II) β-keto carboxylates provides a novel type of regulation of the decarboxylation of β-keto acids and also a method of generating copper(I,II) enolate. The bearing of the two-step decarboxylation of copper(I) β-keto carboxylates on both the Cu(I)-mediated carboxylation of ketones and organic synthesis is also described.

In relation to organocopper chemistry and utilization in organic synthesis, the decarboxylation of copper(I,II) carboxylates has been actively studied.[2] However, the studies have been mainly confined to the decarboxylation of copper(I,II) aromatic carboxylates. The decarboxylation of copper(I,II) aliphatic carboxylates bearing an electron-withdrawing group at the α-position is of interest, because it may produce the organocopper(I,II) intermediates having useful functionalities in organic synthesis.[3] Previously we have investigated the decarboxylation of copper(I,II) cyanoacetates in dimethylformamide (DMF) and have obtained the following interesting results.[4] Copper(I) cyanoacetate undergoes a facile decarboxylation at 50 °C to produce isolable (cyanomethyl)copper(I) (eq 1). Cop-

$$NCCH_2CO_2Cu \xrightarrow{DMF,\ 50\ °C} NCCH_2Cu + CO_2 \quad (1)$$

per(I) cyanoacetate acts as a CO_2 carrier to transfer its CO_2 moiety to propylene oxide[5] (eq 2). On the other hand, the



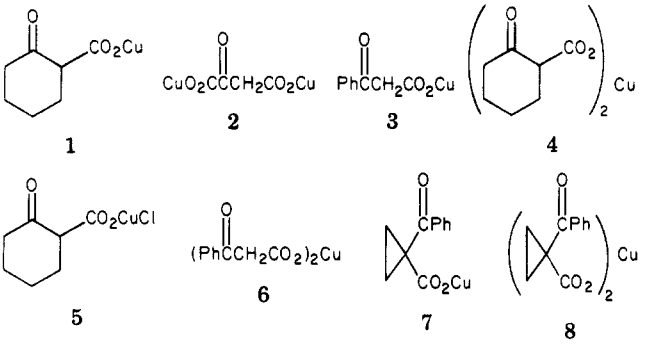
(2)

decarboxylation of copper(II) cyanoacetate reduces the Cu(II) atom to produce (cyanomethyl)copper(I) and succinonitrile (eq 3).[4] In this paper we present a study on

$$(NCCH_2CO_2)_2Cu \xrightarrow{DMF,\ 50\ °C} {}^1/_2NCCH_2CH_2CN + NCCH_2Cu + 2CO_2 \quad (3)$$

the decarboxylation of copper(I,II) carboxylates bearing a β-keto group, i.e., copper(I,II) β-keto carboxylates.

Chart I



1 2 3 4 5 6 7 8

Results and Discussion

Preparation of Copper(I,II) β-Keto Carboxylates. Copper(I) β-keto carboxylates were prepared by acidolysis of copper(I) *tert*-butoxide[6] with an equimolar amount of β-keto acids in benzene or tetrahydrofuran (THF) at −10 to +7 °C. *tert*-Butyl alcohol was quantitatively liberated. Evaporation of *tert*-butyl alcohol and the solvent in vacuo produced solids of copper(I) β-keto carboxylates. For the preparation of copper(II) β-keto carboxylates, copper(II) methoxides[7] were used instead of copper(I) *tert*-butoxide. Since β-keto acids are thermally labile, the facile reaction between copper(I,II) alkoxides and β-keto acids at around 0 °C provides a convenient preparative method of copper(I,II) β-keto carboxylates. The following copper(I,II) β-keto carboxylates were prepared: copper(I) 1-oxocyclohexane-2-carboxylate (**1**), dicopper(I) oxaloacetate (**2**), copper(I) benzoylacetate (**3**), copper(II) bis(1-oxocyclohexane-2-carboxylate) (**4**), copper(II) chloride 1-oxocyclohexane-2-carboxylate (**5**), copper(II) benzoylacetate (**6**), copper(I) benzoylcyclopropane-1-carboxylate (**7**) and copper(II) bis(benzoylcyclopropane-1-carboxylate) (**8**; see Chart I).

Specific Two-Step Decarboxylation of Copper(I) 1-Oxocyclohexane-2-carboxylate (1). Decarboxylation of 1 at 70 °C in DMF rapidly evolved CO_2 in a 50% yield. Further decarboxylation did not occur beyond this 50% decarboxylation (Figure 1). Cyclohexanone was produced

(1) Some of these results were presented at the 26th IUPAC Congress, Tokyo, Japan, Sept 1977; Abstracts, Session I, p 83.

(2) See, for example: (a) Piers, E.; Brown, R. K. *Can. J. Chem.* **1962**, *40*, 559. (b) Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 3187. (c) Nilsson, M.; Ullenius, C. *Acta Chem. Scand.* **1971**, *25*, 2428 and references cited therein. (d) Trost, B. M.; Kinson, P. L. *J. Org. Chem.* **1972**, *37*, 1273. (e) Cohen, T.; Berninger, R. W.; Wood, J. T. *Ibid.* **1978**, *43*, 837 and references cited therein.

(3) See, for example: (a) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (b) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487. (c) Kauffmann, Th. *Angew. Chem.* **1974**, *86*, 321. (d) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (e) Tsuda, T.; Miwa, M.; Saegusa, T. *J. Org. Chem.* **1979**, *44*, 3734.

(4) Tsuda, T.; Nakatsuka, T.; Hirayama, T.; Saegusa T. *J. Chem. Soc., Chem. Commun.* **1974**, 557.

(5) Tsuda, T.; Chujo, Y.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1976**, 415. See also: Bäckvall, J. E.; Karlsson, O.; Ljunggren, S. O. *Tetrahedron Lett.* **1980**, *21*, 4985.

(6) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658.

(7) Brubaker, C. H., Jr.; Wicholas, M. *J. Inorg. Nucl. Chem.* **1965**, *27*, 59.

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Scheme I

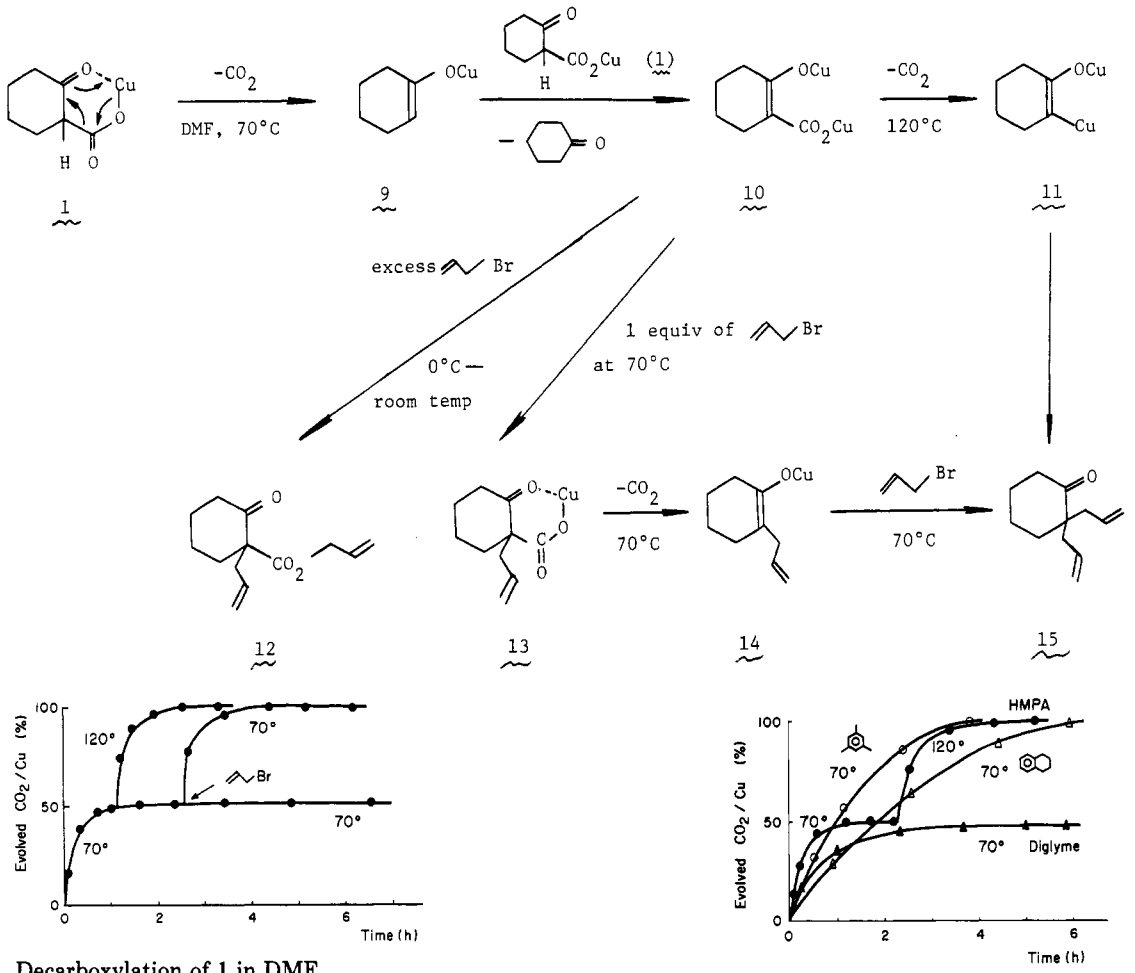


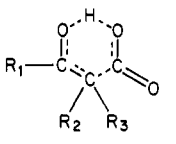
Figure 1. Decarboxylation of 1 in DMF.

Figure 2. Solvent effect upon the decarboxylation of 1.

in a 52% yield at this stage. Raising the reaction temperature to 120 °C evolved the remaining 50% CO_2. Thus, 1 underwent a specific two-step decarboxylation. The solvent effect on the specific two-step decarboxylation is remarkable (Figure 2). The stepwise decarboxylation took place in aprotic polar solvents such as DMF, hexamethylphosphoric triamide (HMPA), and diglyme. On the other hand, ordinary one-step decarboxylation occurred in nonpolar hydrocarbon solvents such as tetralin and mesitylene.

The stepwise decarboxylation suggests an intermediate generation of another species of copper(I) carboxylate which is inert to the decarboxylation at 70 °C. Trials to trap the copper(I) intermediates involved in each stage of the decarboxylation with allyl bromide were made. The results are summarized as follows. (i) Treatment of the resulting reaction mixture after the 50% decarboxylation with allyl bromide at 0 °C to room temperature produced allyl 2-allyl-1-oxocyclohexane-2-carboxylate (**12**) in a 58% yield.[8] (ii) Addition of 1 equiv of allyl bromide at 70 °C to the resulting reaction mixture after the 50% decarboxylation caused a quantitative decarboxylation (Figure 1), and further addition of an excess of allyl bromide at 70 °C produced 2,2-diallylcyclohexanone (**15**) in a 25% yield.[8] (iii) Treatment of the completely decarboxylated reaction mixture at 120 °C with allyl bromide at room temperature produced **15** in a 10% yield.[8] The results obtained suggest a reaction path of the specific two-step decarboxylation of 1, which is shown in Scheme I.

Compound **1** showed IR absorptions of the β-keto and carboxylate groups at 1628 and 1534 cm^{-1}, respectively. Copper(I) acetate absorbs at 1525 cm^{-1}.[9] The absorption of the β-keto group of **1** is decreased to 1630 cm^{-1} in comparison with that of **12** at 1716 cm^{-1}, which suggests the coordination of the β-keto group toward the Cu(I) atom. This coordination facilitates the simultaneous CO_2 release and enolization as shown by arrows in Scheme I. Thus, the presence of the electron-withdrawing, enolizable β-keto group is indispensable for the facile decarboxylation of **1**. The situation is similar to the decarboxylation of free β-keto acids. It is generally accepted that β-keto acids decarboxylate via a six-membered cyclic transition state (**16**).[10] The decarboxylation of **1** in aprotic polar solvents



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takes place easily at 70 °C to produce the Cu(I) enolate of cyclohexanone (**9**). Then, **9** rapidly abstracts an activated α-hydrogen of **1** to form a dicopper(I) salt of the enol of 1-oxocyclohexane-2-carboxylic acid (**10**) with the concomitant formation of cyclohexanone. **10** is stable to the

(8) The yield was based on the dicopper(I) salt of the enol of 1-oxocyclohexane-2-carboxylic acid (**10**).

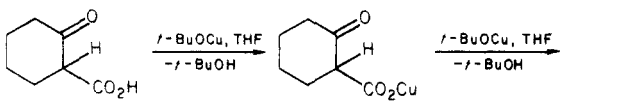
(9) Prepared by acidolysis of copper(I) *tert*-butoxide with an equimolar amount of the carboxylic acid in benzene at ca. 7 °C.

(10) Logue, M. W.; Pollack, R. M.; Vitullo, V. P. *J. Am. Chem. Soc.* **1975**, *97*, 6868.

decarboxylation at 70 °C due to the absence of the β-keto group. Thus, the decarboxylation at 70 °C stops at the stage of the quantitative formation of **10** with CO_2 evolution and the formation of cyclohexanone in 50% yields. The decarboxylation of **10** requires a higher temperature, 120 °C, to give a vinylcopper(I) intermediate **11** which is thermally unstable. Trapping of **11** with allyl bromide gives **15** only in a low yield, because **11** may decompose at the decarboxylation temperature. An equimolar reaction of **10** with allyl bromide forms **13** to regenerate the β-keto group. Thus, the addition of an equimolar amount of allyl bromide at 70 °C to the reaction mixture after the 50% decarboxylation evolves the remaining 50% CO_2 via **13** to give **14**, which reacts with allyl bromide to produce **15**. **10** reacts with an excess of allyl bromide to produce **12** via **13** in a good yield at 0 °C to room temperature where the decarboxylation of **13** does not occur.

The one-step 100% decarboxylation of **1** in nonpolar solvents may be explained by assuming the inability of **9** to abstract the α-hydrogen of **1** in nonpolar solvents. In accord with this explanation, copper(I) *tert*-butoxide can abstract the α-hydrogen of **1** in THF at −10 °C but not in benzene at 7 °C (vide post). The usual one-step decarboxylation of **1** in nonpolar solvents produces the Cu(I) enolate of **9**. The isolation of **9** by the decarboxylation of **1** in mesitylene at 70 °C, however, was unsuccessful. Considerable decomposition of **9** at the decarboxylation temperature may take place. The low yield of **15** in the trapping experiment of **14** with allyl bromide at 70 °C may be similarly explained. In a protic solvent which destroys **9** and **10**, **1** undergoes the usual one-step decarboxylation. Thus, **1** decarboxylated at 70 °C in *tert*-butyl alcohol to evolve CO_2 monotonously and quantitatively in 50 min.

Conclusive evidence for Scheme I is the isolation and characterization of the key intermediate of **10**. The decarboxylation of **1** proceeded heterogeneously. A white suspension of **1** in DMF produced a brown precipitate after the 50% decarboxylation at 70 °C, which was isolated by filtration and was identified as **10**. Its IR absorptions at 1542 and 1483 cm^{-1} are assignable to a $C{=}CCO_2$ structure on the basis of the absorptions of copper(I) acrylate at 1543 and 1490 cm^{-1}.[9] The isolated sample of **10** evolved CO_2 only in a 4% yield in DMF at 70 °C for 2 h but released CO_2 quantitatively at 120 °C. **10** reacted with 5 equiv of allyl bromide at 0 °C to room temperature to give **12** in a good yield. **10** is insoluble in organic solvents and probably has a polymeric structure. **10** was prepared by another independent route. Metalation of 1-oxocyclohexane-2-carboxylic acid with 2 equiv of copper(I) *tert*-butoxide in THF at −10 °C produced **10** quantitatively (eq 4). However, the metalation of the α-methine proton of



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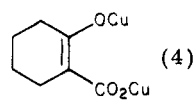


(4)

10

1 did not occur in benzene. Thus, the reaction of 1-oxocyclohexane-2-carboxylic acid with 2 equiv of copper(I) *tert*-butoxide in benzene at 7 °C produced only **1**. One mole of copper(I) *tert*-butoxide remained unreacted. This interesting finding supports the explanation of the solvent effect on the decarboxylation of **1**, i.e., the two-step decarboxylation in polar aprotic solvents and the one-step decarboxylation in nonpolar solvents (vide ante). **10** prepared by the metalation route has the same characteristics as **10** obtained by the decarboxylation, which further supports the participation of **10** in the specific two-step decarboxylation of **1**.

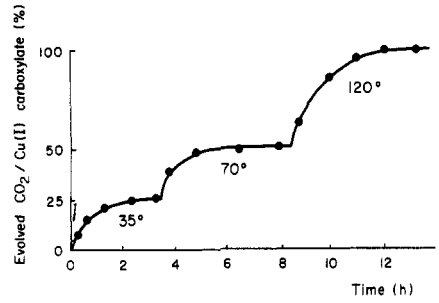


Figure 3. Stepwise decarboxylation of **2**.

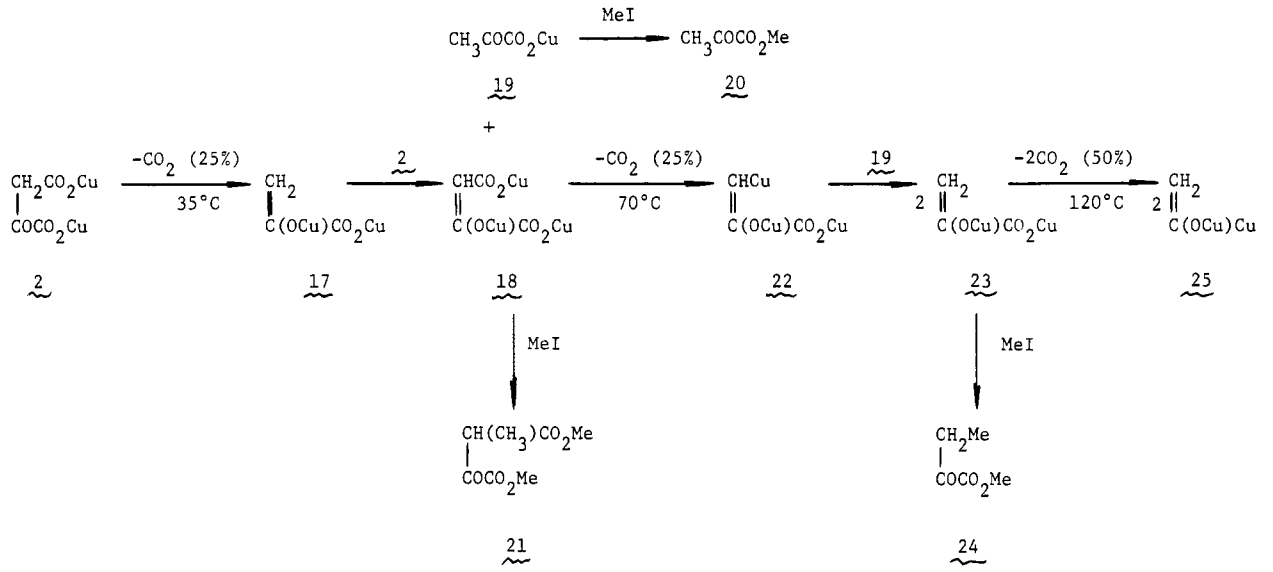
Specific Stepwise Decarboxylation of Copper(I) Oxaloacetate (2) and Copper(I) Benzoylacetate (3). Generality of the Specific Two-Step Decarboxylation of Copper(I) β-Keto Carboxylates. To establish the generality of the specific stepwise decarboxylation of copper(I) β-keto carboxylates, the decarboxylations of copper(I) oxaloacetate (**2**) and copper(I) benzoylacetate (**3**) were investigated. The decarboxylation of oxaloacetic acid is a reaction of biological importance, which is catalyzed by the metal-containing enzymes.[11] Thus, it is interesting to explore the stepwise decarboxylation of **2**.

Interestingly, the decarboxylation of **2** proceeded in three steps under appropriate conditions (Figure 3). The decarboxylation of **2** in DMF stopped at 35 °C after 25% CO_2 evolution. Raising the reaction temperature to 70 °C caused a further 25% CO_2 release. At 120 °C, the remaining 50% CO_2 was evolved. Oxaloacetic acid is considered to be a composite of α-keto and β-keto acids. Our unpublished results show that copper(I) β-keto carboxylate decarboxylates more easily than copper(I) α-keto carboxylate. For example, the quantitative decarboxylation of copper(I) pyruvate in HMPA requires the condition of 120 °C and 5 h.[12] On the basis of this finding and the two-step decarboxylation mechanism of **1** (Scheme I), the three-step decarboxylation of **2** is understandable in terms of the initial two-step decarboxylation of the β-keto carboxylate moiety and the subsequent one-step decarboxylation of the α-keto carboxylate moiety (Scheme II). The intermediates **18**, **19**, and **23** were trapped by MeI in the presence of a n-Bu_3P ligand. Without n-Bu_3P, the yields of the methylated products were low. Thus, addition of n-Bu_3P and MeI to the reaction mixture after the first 25% CO_2 evolution produced methyl pyruvate (**20**) and dimethyl methyloxaloacetate (**21**) in 80% and 30% yields, respectively. Treatment of the reaction mixture resulting from the second 25% decarboxylation with n-Bu_3P an MeI gave methyl α-oxobutyrate (**24**) in a 32% yield.

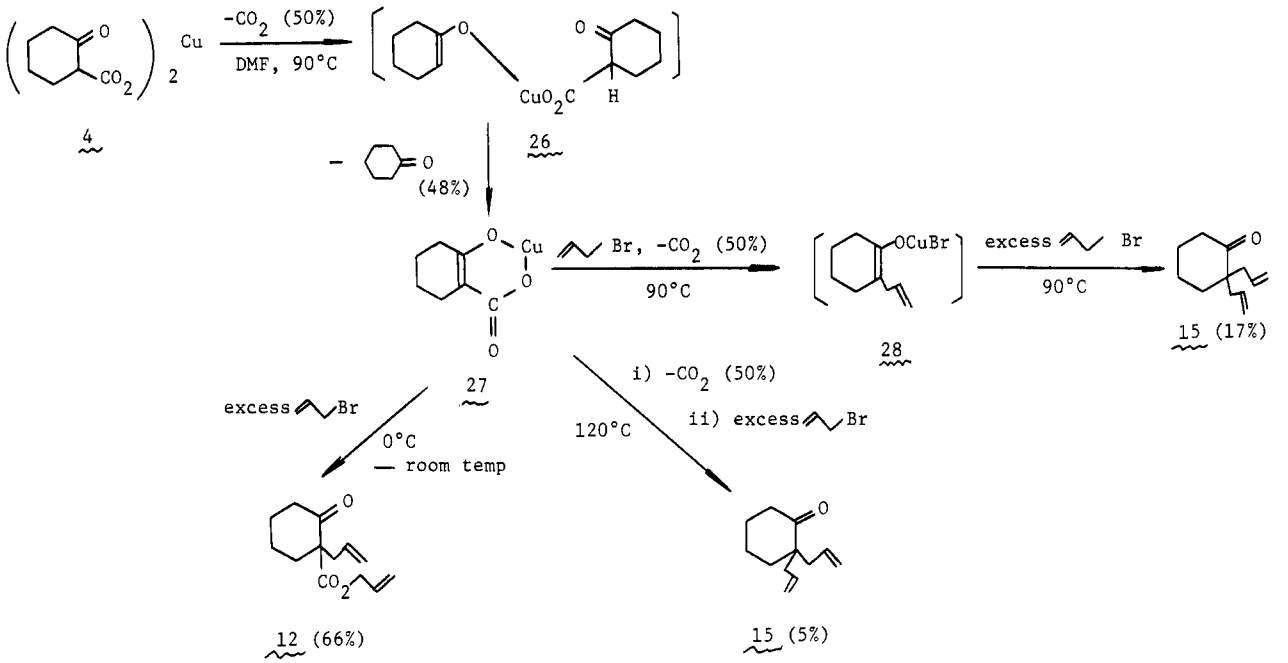
The Cu(II) ion catalyzed biphasic decarboxylation of oxaloacetic acid in buffered aqueous solution has been reported.[13] In this decarboxylation, however, the specificity of the decarboxylation such as in the 25%, 50% and 100% decarboxylations was not observed. **3** also underwent the specific two-step decarboxylation in DMF: the first-step decarboxylation at 35 °C and the second-step decarboxylation at 110 °C. Thus, the decarboxylations of

(11) (a) Krebs, A. *Biochem. J.* **1942**, *36*, 303. (b) Speck, J. *J. Biol. Chem.* **1949**, *178*, 315.
(12) Tsuda, T.; Y. Chujo, Y.; Saegusa, T., unpublished results.
(13) (a) Raghavan, N. V.; Leussing, D. L. *J. Am. Chem. Soc.* **1974**, *96*, 7147. (b) *Ibid.* **1976**, *98*, 723.

Scheme II

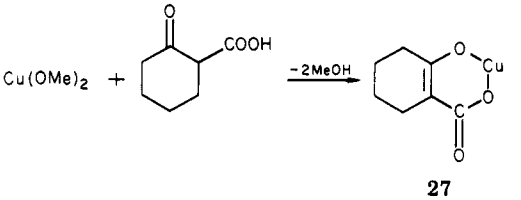


Scheme III



1–3 suggest the generality of the specific stepwise decarboxylation of copper(I) β-keto carboxylates in aprotic polar solvents. Extensive work has been done on the decarboxylation of copper(I,II) carboxylates[2] including the Cu(II) ion catalyzed decarboxylation of oxaloacetic acid in aqueous solution.[13] However, there has been no precedent of the specific two-step decarboxylation. The present stepwise decarboxylation provides a novel type of regulation of the decarboxylation of β-keto acids. It also provides a convenient method to generate copper(I) enolate which may be a useful intermediate in organic synthesis (vide post). To our knowledge, **10** is the first example of the isolation of a copper(I) enolate. **10** is a key intermediate in the Cu(I)-mediated carboxylation of cyclohexanone, which demonstrates a close relationship between the two-step decarboxylation of copper(I) β-keto carboxylates and the Cu(I)-mediated carboxylation of ketones (vide post).

Specific Two-Step Decarboxylation of Copper(II) β-Keto Carboxylates 4–6. Copper(II) bis(1-oxocyclohexane-2-carboxylate) (**4**) also underwent the two-step decarboxylation in DMF: the first-step decarboxylation at 90 °C and the second-step decarboxylation at 120 °C. Detection of cyclohexanone in the first stage of the decarboxylation, the results of trapping experiments with allyl bromide, and the isolation of the Cu(II) salt of the enol of 1-oxocyclohexane-2-carboxylic acid (**27**) for the 50% decarboxylation are taken to suggest the reaction path shown in Scheme III which has common characteristics with Scheme I. The six-membered chelated intermediate **27** is assumed to be formed by the intramolecular transfer of α-methine proton in **26**. **27** was also prepared by the metalation of 1-oxocyclohexane-2-carboxylic acid with 1 equiv of copper(II) dimethoxide in THF at −10 °C (eq 5).



(5)

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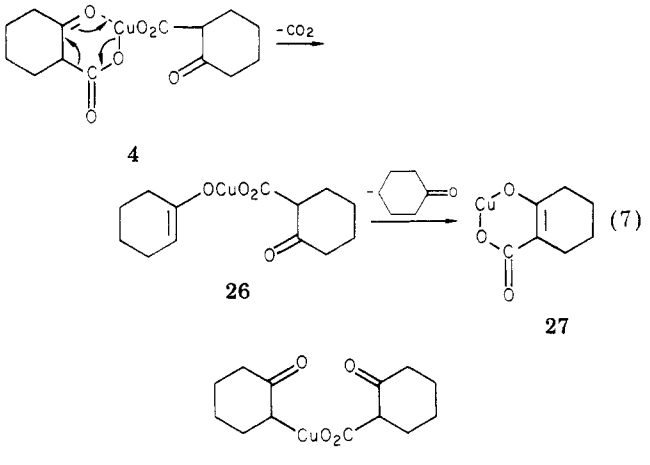
27 is insoluble in organic solvents and probably has a polymeric structure. Copper(II) chloride 1-oxocyclohexane-2-carboxylate (5) and copper(II) benzoylacetate (6) also underwent the stepwise decarboxylation in DMF: for 5 the first-step decarboxylation was at 90 °C and the second step decarboxylation at 120 °C; for 6 the first-step decarboxylation was at 35 °C and the second step decarboxylation at 120 °C. These findings further indicate the generality of the specific two-step decarboxylation of copper(I,II) β-keto carboxylates in aprotic polar solvents.

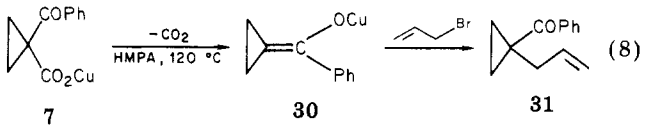
It is generally accepted that the decarboxylation of Cu(I) aromatic carboxylates involves the arylcopper(I) intermediates.[2c] (Pentafluorophenyl)copper(I) has been isolated by the decarboxylation of copper(I) pentafluorobenzoate.[2b] The decarboxylation of copper(I) cyanoacetate produces isolable (cyanomethyl)copper(I).[4] Participation of an organocopper(II) intermediate also has been suggested in the decarboxylation of copper(II) bis(cyanoacetate). The decarboxylation of copper(II) bis(cyanoacetate) in DMF at 50 °C reduces the Cu(II) atom to give (cyanomethyl)copper(I) and succinonitrile.[4] These products are reasonably assumed to arise from the oxidative coupling of the organocopper(II) intermediate $NCCH_2CO_2CuCH_2CN$ (eq 6).

$$(NCCH_2CO_2)_2Cu \xrightarrow{-CO_2} NCCH_2CO_2CuCH_2CN \xrightarrow{-0.5NCCH_2CH_2CN} NCCH_2CO_2Cu \xrightarrow{-CO_2} NCCH_2Cu \quad (6)$$

On the contrary, the first step of the decarboxylation of 4 produced 27 without the reduction of the Cu(II) atom. The formation of 27 may be explained by assuming the coordination and the subsequent bond formation of the oxygen atom of the β-keto group toward the Cu(II) atom without any participation of an organocopper(II) intermediate such as 29 during the process of initial CO_2 cleavage (eq 7).



One-Step Decarboxylation of Copper(I,II) Benzoylcyclopropane-1-carboxylates 7 and 8. The two-step decarboxylation of copper(I,II) β-keto carboxylates requires the presence of an enolizable α-hydrogen atom in the β-keto carboxylate moiety. Copper(I,II) β-keto carboxylates without such α-hydrogens are expected to undergo a usual one-step decarboxylation. To confirm this expectation, we examined the decarboxylations of copper(I,II) benzoylcyclopropane-1-carboxylates 7 and 8. The decarboxylation was carried out in HMPA instead of DMF because the disproportionation of 7 to metallic copper and 8 takes place in DMF. 7 released CO_2 monotonously in HMPA at 120 °C to give a copper(I) enolate intermediate 30, which was trapped with allyl bromide to produce 1-allyl-1-benzoylcyclopropane (31) in a 74% yield (eq 8). 8 also underwent the one-step decarboxylation in HMPA at 130 °C.



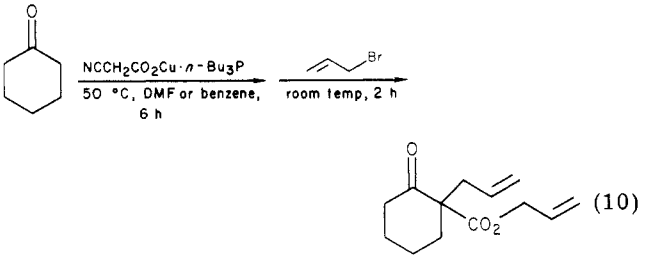
7 30 31

Relation of the Specific Two-Step Decarboxylation of Copper(I) β-Keto Carboxylate to the Cu(I)-Mediated Carboxylation of Ketone. The decarboxylation reaction, which is the reverse of the carboxylation reaction, may be expected to provide useful information on the carboxylation reaction. The two-step decarboxylation of copper(I) β-keto carboxylate is attributable to the formation of the dicopper(I) salt of the enol of β-keto acid, which is more stable to the decarboxylation than the starting copper(I) β-keto carboxylate. This fact suggests that the Cu(I)-mediated carboxylation of ketone to produce copper(I) β-keto carboxylate may be promoted by the formation of such dicopper(I) salt. Very recently we have reported the transcarboxylation to cyclohexanone by a reversible CO_2 carrier of $NCCH_2CO_2Cu{\cdot}n\text{-}Bu_3P$ (32)[14] or $HOCO_2Cu(PEt_3)_3$ (33).[15] In this Cu(I)-mediated carboxylation of cyclohexanone, 10 coordinated with the phosphine ligand plays an important role.

Copper(I) cyanoacetate undergoes quantitative and irreversible decarboxylation at 50 °C in DMF to give isolable (cyanomethyl)copper(I) (eq 1). In the presence of a n-Bu_3P ligand, however, CO_2 insertion into (cyanomethyl)copper(I) took place, and the decarboxylation became reversible (eq 9). 32 acted as a CO_2 carrier to transfer its CO_2 moiety

$$\underset{\mathbf{32}}{NCCH_2CO_2Cu{\cdot}n\text{-}Bu_3P} \rightleftarrows NCCH_2Cu{\cdot}n\text{-}Bu_3P + CO_2 \quad (9)$$

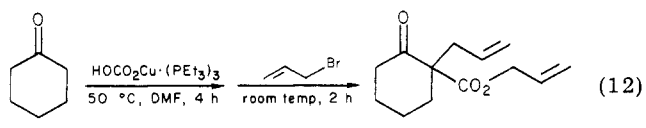
to cyclohexanone (eq 10). The primary transcarboxylation



12, 87% (DMF); 88% (benzene)

product was treated with allyl bromide to give 12. The copper(I) bicarbonate complex 33 behaves similarly. 33 is soluble in both water and common organic solvents including benzene and n-pentane. 33 underwent reversible decarboxylation under mild conditions in both water and DMF (eq 11), and transferred its CO_2 moiety to cyclohexanone in DMF (eq 12).

$$\underset{\mathbf{33}}{HOCO_2Cu{\cdot}(PEt_3)_3} \rightleftarrows HOCu{\cdot}(PEt_3)_3 + CO_2 \quad (11)$$

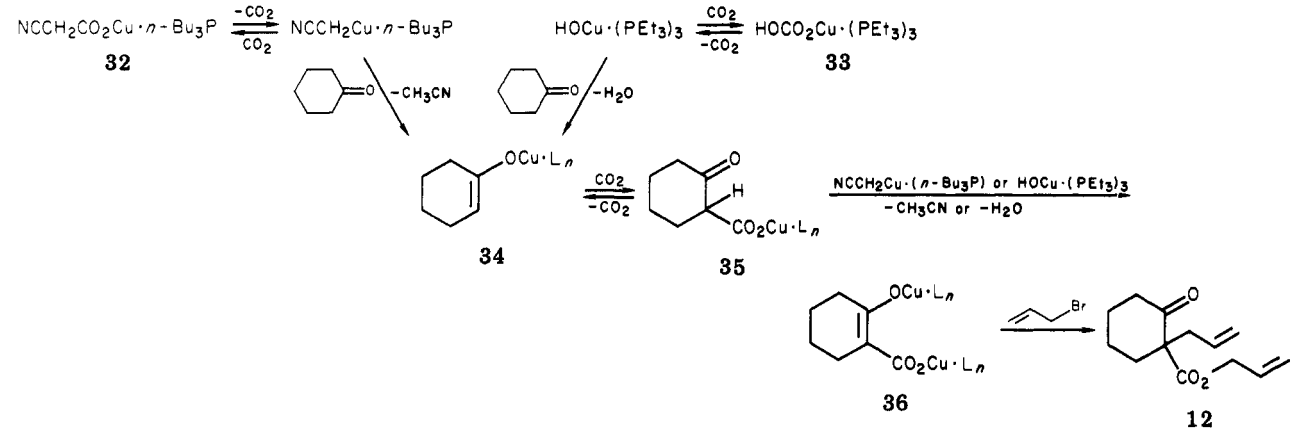


12, 46%

hexanone in DMF (eq 12). A reasonable reaction path for the carboxylation of cyclohexanone by 32 or 33 is shown

(14) Tsuda, T.; Chujo, Y.; Saegusa, T. *J. Am. Chem. Soc.* **1978**, *100*, 630.
(15) Tsuda, T.; Chujo, Y.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 431.

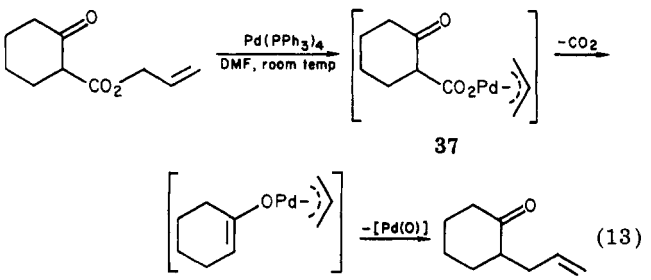
Scheme IV[a]



[a] L = n-Bu_3P or PEt_3.

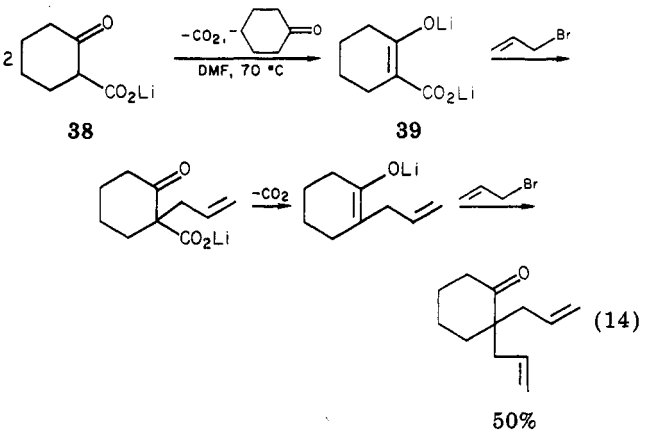
in Scheme IV. The key step in Scheme IV is the formation of a phosphine-coordinated dicopper(I) salt of the enol of 1-oxocyclohexane-2-carboxylic acid **36**. Although the copper(I) 1-oxocyclohexane-2-carboxylate–phosphine complex **35** decarboxylates easily under the reaction conditions of the transcarboxylation, **36** fixes CO_2 firmly due to its inertness toward the decarboxylation. The inertness of **36** to the decarboxylation was evidenced by using **10** isolated by the metalation method. In the presence of 1 equiv of n-Bu_3P, **10** released CO_2 only in a 6% yield in DMF at 70 °C for 3 h while **1** evolved CO_2 in a 41% yield after 2 h. Treatment of **10** with allyl bromide in the presence of 3 equiv of n-Bu_3P produced the transcarboxylation product of **12** in a 73% yield. Thus, the two-step decarboxylation of **1** has been demonstrated to be closely related to the Cu(I)-mediated carboxylation of cyclohexanone. This result suggests that the decarboxylation of metal β-keto carboxylates is useful for the understanding of the carboxylation of ketones induced by metal salts.[16]

Application of the Decarboxylation of Copper(I,II) β-Keto Carboxylates to Other Metal β-Keto Carboxylates. Versatility of the Decarboxylation of Metal β-Keto Carboxylates in Organic Synthesis. Metal enolates are important intermediates in organic syntheses. Application of the present study to other metal β-keto carboxylates may be expected to provide a general and convenient method to produce metal enolates with synthetic versatility. Very recently we have reported the facile generation of a reactive palladium(II) enolate intermediate by the decarboxylation of palladium(II) β-keto carboxylate and its utilization in allylic alkylation. For example, a π-allylpalladium(II)–1-oxocyclohexane-2-carboxylate complex (**37**) underwent a one-step decarboxylation to produce 2-allylcyclohexanone almost quantitatively (eq 13).[17]



(13)

Lithium 1-oxocyclohexane-2-carboxylate (**38**) undergoes a specific 50% decarboxylation to produce an isolable dilithium salt of the enol of 1-oxocyclohexane-2-carboxylic acid (**39**), which is, for example, utilized for the regioselective dialkylation of cyclohexanone (eq 14).[18] These two



(14)

50%

examples demonstrate the versatility of the decarboxylation of metal β-keto carboxylates in organic synthesis. The decarboxylation of other metal salts of β-keto acids may be expected to produce the synthetically useful metal enolate intermediates with distinguishing reactivities.

Experimental Section

Infrared (IR) spectra were determined on a Hitachi EPI-G3 grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded at a Hitachi R-20B spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on a Hitachi R-MS-4 instrument. Gas chromatographic analyses (GLC) were made on Shimadzu 4APT and GC-2C instruments equipped with a thermal-conductivity detector. Quantitative GLC analyses of organic products were made with internal standards, with calibration based upon authentic samples, and by employing a 20% silicone DC 550 on Celite 545 column or a 20% PEG 20M on Celite 545 column. CO_2 gas was analyzed by GLC on a activated charcoal column by using methane as an internal standard. Iodometry of the copper content of Cu(I,II) compounds was made by a conventional method.

All experiments employing Cu(I,II) compounds were conducted under an atmosphere of dry nitrogen. Organic solvents were distilled from calcium hydride under nitrogen. Allyl bromide and methyl iodide were distilled from calcium chloride under nitrogen.

(16) (a) Bottacio, G.; Chiusoli, G. P. *Chem. Commun.* **1966**, 618. (b) Mori, H.; Yamamoto, H.; Kwan, T. *Chem. Pharm. Bull.* **1972**, *20*, 2440. (c) Corey, E. J.; Chen, R. H. K. *J. Org. Chem.* **1973**, *38*, 4086. (d) Ito, T.; Takami, Y. *Chem. Lett.* **1974**, 1035.

(17) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

(18) Tsuda, T.; Chujo, Y.; Saegusa, T., to be submitted for publication.

Commercially available tri-*n*-butylphosphine was used after deoxygenation by a stream of nitrogen. Commercially available triethylphosphine was distilled from calcium sulfate under nitrogen. 1-Oxocyclohexane-2-carboxylic acid,[19] benzoylacetic acid,[19] and 1-benzoylcyclopropanecarboxylic acid[20] were prepared by the reported procedures. Oxaloacetic acid was a commercial reagent and used without further purification. Copper(II) dimethoxide and copper(II) chloride methoxide were prepared by the published method.[7] Copper(I) *tert*-butoxide,[6] copper(I) cyanoacetate,[4] and a copper(I) bicarbonate complex, $HOCO_2Cu\cdot(PEt_3)_3$ (**33**),[15] were prepared by our own methods. A copper(I) cyanoacetate–phosphine complex, $NCCH_2CO_2Cu\cdot n\text{-}Bu_3P$ (**32**), was prepared in situ by equimolar addition of tri-*n*-butylphosphine to copper(I) cyanoacetate in dimethylformamide (DMF) or benzene.[14]

General Experimental Procedure for the Preparation of Copper(I,II) β-Keto Carboxylates 1–8. Preparation of Copper(I) 1-Oxocyclohexane-2-carboxylate (1). To a stirred suspension of copper(I) *tert*-butoxide (0.68 g, 5.01 mmol) in 3 mL of benzene cooled to ca. 7 °C was added 1-oxocyclohexane-2-carboxylic acid (0.71 g, 5.01 mmol) in 5 mL of benzene. The stirring was continued for 3 h at ca. 7 °C to produce a white precipitate. GLC analysis (a silicone DC 550 column, dioxane as an internal standard) of the supernatant benzene solution indicated the formation of *tert*-butyl alcohol in a 99% yield. Evaporation of benzene and *tert*-butyl alcohol by a freeze–drying technique produced a white solid of copper(I) 1-oxocyclohexane-2-carboxylate (**1**): 1.02 g (5.00 mmol, 99.8%); Cu content by iodometry 30.6% (calcd for $C_7H_9O_3Cu$ 31.0%); IR (Nujol) 1628, 1534 cm^{-1}; CO_2 evolution on thermolysis in DMF at 120 °C, 100%. Other copper(I,II) β-keto carboxylates (**4**, **5**, **7**, and **8**) were prepared as described above. Copper(I) oxaloacetate (**2**), copper(I) benzoylacetate (**3**), and copper(II) bis(benzoylacetate) (**6**) were prepared in tetrahydrofuran (THF), because the corresponding β-keto acids are insoluble in benzene.

Due to high oxygen sensitivity, elementary analysis of the copper(I) β-keto carboxylates required special handling not available to us. As an alternative to the usual analytical data, we determined the Cu content of copper(I,II) β-keto carboxylates by iodometry where the sampling can be done on a millimole scale in a drybox under nitrogen.[4,6,15] The determined Cu contents together with IR (Nujol) $\nu_{C=O}$ absorptions are as follows: copper(I) oxaloacetate (**2**), 49.0% (calcd for $C_4H_2O_5Cu_2$ 49.4%) and 1734, 1575 cm^{-1}; copper(I) benzoylacetate (**3**), 27.9% (calcd for $C_9H_7O_3Cu$28.0%) and 1598, 1529 cm^{-1}; copper(II) bis(1-oxocyclohexane-2-carboxylate) (**4**), 18.9% (calcd for $C_{14}H_{18}O_6Cu$ 18.4%) and 1706, 1582 cm^{-1}; copper(II) chloride 1-oxocyclohexane-2-carboxylate (**5**), 27.3% (calcd for $C_7H_9O_3ClCu$ 26.5%) and 1708, 1588 cm^{-1}; copper(II) bis(benzoylacetate) (**6**), 16.9% (calcd for $C_{18}H_{14}O_6Cu$ 16.3%) and 1680, 1540 cm^{-1}. These copper(I,II) β-keto carboxylates evolved CO_2 almost quantitatively on thermolysis in DMF or hexamethylphosphoric triamide (HMPA) as described in the text.

Decarboxylation of Copper(I) 1-Oxocyclohexane-2-carboxylate (1). To a white suspension of 1 (0.18 g, 0.88 mmol) in 5 mL of DMF in a closed 200-mL flask equipped with a rubber septum was added methane (9 mL, 0.40 mmol) as a GLC internal standard through the septum with a hypodermic syringe. The mixture was stirred at 70 °C, and CO_2 evolution was monitored by GLC analysis of a gaseous sample taken out with the hypodermic syringe through the septum. The decarboxylation proceeded rapidly to evolve CO_2 in a 50% yield after 1 h, but no further decarboxylation took place beyond this 50% decarboxylation. At this stage, GLC analysis (a silicone DC 550 column, toluene as an internal standard) of the liquid phase over a brown precipitate indicated the formation of cyclohexanone in a 52% yield based on 1.

In a separate experiment, the reaction mixture after the 50% decarboxylation of 1 (0.21 g, 1.04 mmol) was cooled to 0 °C, and allyl bromide (0.21 mL, 2.53 mmol) was added. The mixture was stirred at room temperature for 3 h. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that allyl 1-oxo-2-allylcyclohexane-2-carboxylate (**12**) was formed in a 58% yield based on **10**. **12** was isolated by GLC and identified: IR (neat) 1745, 1716, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.45–1.90 (m, 6 H), 2.15–2.55 (m, 4 H), 4.50 (d, 2 H), 4.70–5.90 (m, 6 H); mass spectrum, *m/e* 222 (M^+).

In a separate experiment, when allyl bromide (0.044 mL, 0.52 mmol) was added at 70 °C through the septum to the resulting reaction mixture after the 50% decarboxylation of 1 (0.21 g, 1.04 mmol) in 5 mL of DMF, CO_2 was evolved in a 50% yield to complete the decarboxylation of 1. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that 2,2-diallylcyclohexanone (**15**) was formed in a 25% yield based on **10**. **15** was isolated by GLC and identified: IR (neat) 1718, 1649 cm^{-1}; NMR ($CDCl_3$) δ 1.60–1.90 (m, 6 H), 2.10–2.45 (m, 6 H), 4.75–5.85 (m, 6 H); mass spectrum, *m/e* 178 (M^+).

In a separate experiment, after the 50% decarboxylation of 1 (0.20 g, 0.98 mmol) at 70 °C in 5 mL of DMF, the resulting mixture was heated further at 120 °C for 1.5 h to evolve CO_2 in a 50% yield. The mixture was cooled to room temperature, and allyl bromide (0.21 mL, 2.45 mmol) was added. The mixture was stirred at room temperature for 4 h. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that **15** was formed in a 10% yield based on **10**.

The decarboxylation of 1 in hexamethylphosphoric triamide (HMPA), diglyme, mesitylene, tetralin, or *tert*-butyl alcohol was carried out and monitored in a manner similar to that for 1.

Isolation of a Dicopper(I) Salt of the Enol of 1-Oxocyclohexane-2-carboxylic Acid (10). By Decarboxylation. A white suspension of 1 (1.39 g, 6.78 mmol) in 5 mL of DMF was stirred at 70 °C for 2 h in a 50-mL flask equipped with a three-way stopcock to produce a brown precipitate. Evolved CO_2 gas was released outside the flask during the course of the decarboxylatioin through the three-way stopcock under a stream of nitrogen. The precipitate was filtered, washed consecutively with DMF and with THF, and dried in vacuo at room temperature to give a brown solid of **10**: 1.73 g (6.49 mmol, 96%); Cu content by iodometry 46.8% (calcd for $C_7H_8O_3Cu_2$ 47.6%); IR (Nujol) 1542, 1483 cm^{-1}; CO_2 evolution (in DMF) 4.3% (70 °C, 2 h), 98% (120 °C, 3 h); formation of **12** by the treatment with allyl bromide (DMF, 0 °C to room temperature), 68%.

By Metalation. To a stirred suspension of copper(I) *tert*-butoxide (0.67 g, 4.93 mmol) in 3 mL of THF cooled to −10 °C was added dropwise 1-oxocyclohexane-2-carboxylic acid (0.35 g, 2.47 mmol) in 5 mL of THF. The mixture was stirred for 7 h at −10 °C to produce a brown precipitate. The precipitate was filtrated, washed consecutively with DMF and with THF, and dried in vacuo at room temperature to give a brown solid, **10**: 0.62 g (2.33 mmol, 94%); Cu content by iodometry 47.0% (calcd for $C_7H_8O_3Cu_2$ 47.6%); IR (Nujol) 1545, 1484 cm^{-1}; CO_2 evolution (in DMF) 6.7% (70 °C, 2 h), 102% (120 °C, 3 h); formation of **12** by the treatment with allyl bromide (DMF, 0 °C to room temperature), 71%.

Metalation of 1-Oxocyclohexane-2-carboxylic Acid with Copper(I) *tert*-Butoxide in Benzene. To a stirred suspension of copper(I) *tert*-butoxide (0.31 g, 2.27 mmol) in 3 mL of benzene cooled to ca. 7 °C was added 1-oxocyclohexane-2-carboxylic acid (0.16 g, 1.14 mmol) in 5 mL of benzene. The mixture was stirred at ca. 7 °C for 7 h. Evaporation of benzene and *tert*-butyl alcohol by a freeze–drying technique produced a pale brown solid. An IR spectrum of the solid (Nujol) consisted of combined absorptions of 1 and copper(I) *tert*-butoxide without the absorptions of **10**.

Stepwise Decarboxylation of Copper(I) Oxaloacetate (2). To a suspension of **2** (0.21 g, 0.82 mmol) in 5 mL of DMF in a 200-mL closed flask with a rubber septum was added methane (10 mL, 0.45 mmol) as a GLC internal standard with a hypodermic syringe through the septum. The mixture was stirred at 35 °C. The decarboxylation was monitored by GLC analysis of the gaseous phase. After 3.5 h, CO_2 was evolved in a 26% yield (the first 25% decarboxylation), and no further decarboxylation was observed. Raising the reaction temperature to 70 °C resumed the decarboxylation to evolve CO_2 in a 25% yield after 4 h (the second 25% decarboxylation), and the further decarboxylation stopped. Then, the mixture was heated at 120 °C for 6 h to release CO_2 in a 49% yield.

(19) Haruki, E.; Arakawa, M.; Matsumura, N.; Otsuji, Y.; Imoto, E. *Chem. Lett.* **1974**, 427.
(20) Singh, R. K.; Danishefsky, S. *J. Org. Chem.* **1975**, *40*, 2969.

In a separate experiment, the resulting reaction mixture after the first 25% decarboxylation of **2** (0.19 g, 0.74 mmol) was cooled to 0 °C, and methyl iodide (0.23 mL, 3.70 mmol) and tri-*n*-butylphosphine (0.37 mL, 1.48 mmol) were added. The mixture was stirred at room temperature for 2 h. GLC analysis (a silicone DC 550 column, ethylbenzene and acetophenone as internal standards for **20** and **21**, respectively) of the resulting reaction mixture revealed that methyl pyruvate (**20**) and dimethyl methyloxaloacetate (**21**) were formed in an 80% yield based on **19** and in a 30% yield based on **18**, respectively. **20** and **21** were isolated by GLC and identified by the agreement of GLC retention times and IR spectra with those of authentic samples.

In a separate experiment, the resulting reaction mixture after the second 25% decarboxylation of **2** (0.15 g, 0.58 mmol) was reacted with methyl iodide (0.18 mL, 2.90 mmol) and tri-*n*-butylphosphine (0.29 mL, 1.16 mmol) at room temperature for 2 h. GLC analysis (a PEG 20M column, tetralin as an internal standard) of the resulting reaction mixture revealed that methyl α-oxobutyrate (**24**) was formed in a 32% yield based on **23**. **24** isolated by GLC had an identical IR spectrum with that of the authentic sample.

Decarboxylation of Copper(I) Benzoylacetate (3), Copper(II) Bis(1-oxocyclohexane-2-carboxylate) (4), Copper(II) Chloride 1-Oxocyclohexane-2-carboxylate (5), and Copper(II) Bis(benzoylacetate) (6). The two-step decarboxylations of **3–6** were carried out and monitored in a manner analogous to that of **1**. The procedures for the trapping of Cu(II) intermediates (**27** and **28** in Scheme III) were similar to those used in the decarboxylation of **1**.

Isolation of the Cu(II) Salt of the Enol of 1-Oxocyclohexane-2-carboxylic Acid (27). By Decarboxylation. A suspension of **4** (1.05 g, 3.01 mmol) in 5 mL of DMF was stirred at 90 °C for 4 h in a 50-mL flask equipped with a three-way stopcock to produce a precipitate. Evolved CO_2 gas was released outside the flask during the course of the decarboxylation through the three-way stopcock under a stream of nitrogen. The precipitate was filtered, washed consecutively with DMF and with THF, and dried in vacuo at room temperature to give a pale green solid, **27**: 0.59 g (2.89 mmol, 96%); Cu content by iodometry 31.3% (calcd for $C_7H_8O_3Cu$ 31.22%); IR (Nujol) 1547, 1484 cm^{-1}; CO_2 evolution (in DMF) 6.2% (90 °C, 2 h), 99% (120 °C 3 h); formation of **12** by the treatment with allyl bromide (DMF, 0 °C to room temperature), 68%.

By Metalation. To a stirred suspension of copper(II) dimethoxide (0.51 g, 4.06 mmol) in 3 mL of THF cooled to −10 °C was added dropwise 1-oxocyclohexane-2-carboxylic acid (0.58 g, 4.06 mmol) in 5 mL of THF. The mixture was stirred for 7 h at −10 °C. The resulting precipitate was filtered, washed consecutively with DMF and with THF, and dried in vacuo at room temperature to give a pale green solid, **27**: 0.83 g (4.05 mmol, 100%); Cu content by iodometry 31.6% (calcd for $C_7H_8O_3Cu$ 31.2%); IR (Nujol) 1549, 1483 cm^{-1}; CO_2 evolution (in DMF) 8.3% (90 °C, 2 h), 101% (120 °C, 3 h); formation of **12** by the treatment with allyl bromide (DMF, 0 °C to room temperature), 73%.

Decarboxylation of Copper(I) Benzoylcyclopropane-1-carboxylate (7) and Copper(II) Bis(benzoylcyclopropane-1-carboxylate) (8). The reaction mixture of **7** (0.13 g, 0.51 mmol), 5 mL of HMPA, and methane (10 mL, 0.45 mmol) in a closed flask with a rubber septum was stirred at 120 °C. The decarboxylation was monitored by GLC analysis of a gaseous sample taken out through the septum with a hypodermic syringe. After 6 h CO_2 was evolved in a 101% yield. Then, the mixture was cooled to ambient temperature and reacted with allyl bromide (0.22 mL, 2.55 mmol) for 6 h. GLC analysis (a PEG 20M column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that 1-allyl-1-benzoylcyclopropane (**31**) was produced in a 74% yield. **31** was isolated by GLC and identified: IR (neat) 1680, 1639, 1597 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (m, 4 H), 3.38 (d, 2 H), 4.10–5.80 (m, 3 H), 7.00–7.90 (m, 5 H); mass spectrum, *m/e* 186 (M^+). The decarboxylation of **8** was similarly conducted.

Carboxylation of Cyclohexanone by a Copper(I) Cyanoacetate–Phosphine Complex, $NCCH_2CO_2Cu{\cdot}n\text{-}Bu_3P$ (32). To a solution of copper(I) cyanoacetate (0.10 g, 1.02 mmol) and tri-*n*-butylphosphine (0.25 mL, 1.02 mmol) in 5 mL of DMF cooled to 0 °C was added cyclohexanone (0.53 mL, 5.10 mmol). The solution was stirred at 50 °C for 6 h and then cooled to 0 °C followed by the addition of allyl bromide (0.64 mL, 10.2 mmol). The reaction mixture was stirred at room temperature for 2 h. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that allyl 1-oxo-2-allylcyclohexane-2-carboxylate (**12**) was formed in a 87% yield based on **36** (L = n-Bu_3P, n = 1).

In a separate experiment, copper(I) cyanoacetate (3.59 g, 24.3 mmol), tri-*n*-butylphosphine (6.06 mL, 24.3 mmol), cyclohexanone (12.6 mL, 122 mmol), and 120 mL of benzene were placed in a closed 500 mL-flask. The mixture was stirred at 50 °C for 7.5 h and then cooled to 0 °C followed by the addition of allyl bromide (20.6 mL, 243 mmol). The resulting benzene solution was stirred at room temperature for 2 h and treated twice with 30 mL of a saturated aqueous ammonium chloride solution. The aqueous solutions were combined and extracted with 30 mL of benzene. The benzene solutions were combined, washed twice with 30 mL of water, and concentrated in vacuo. The residue was distilled at 100 °C (ca. 0.5 mm) in a Kugelrohr apparatus to provide **12** (1.73 g, 7.79 mmol, 64%).

Carboxylation of Cyclohexanone by a Copper(I) Bicarbonate–Phosphine Complex, $HOCO_2Cu{\cdot}(PEt_3)_3$ (33). To a solution of **33** (0.23 g, 0.49 mmol) in 3 mL of DMF cooled to 0 °C was added cyclohexanone (0.15 mL, 1.47 mmol). The solution was stirred at 50 °C for 4 h and then cooled to 0 °C followed by the addition of allyl bromide (0.21 mL, 2.45 mmol). The mixture was stirred at room temperature for 2 h. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that allyl 1-oxo-2-allylcyclohexane-2-carboxylate (**12**) was formed in a 46% yield based on **36** (L = PEt_3, n = 3).

Decarboxylation of Tri-*n*-butylphosphine Complexes of 1 and 10 (35 and 36). The tri-*n*-butylphosphine complex of **1** (**35**; L = n-Bu_3P, n = 1) was generated in situ by the addition of tri-*n*-butylphosphine (0.13 mL, 0.51 mmol) to **1** (0.10 g, 0.51 mmol) in 5 mL of DMF cooled to 0 °C in a 200-mL flask with a rubber septum. The solution in the closed flask was stirred at 70 °C for 2 h. GLC analysis of the gaseous phase revealed the evolution of CO_2 in a 41% yield.

The tri-*n*-butylphosphine complex of **10** (**36**; L = n-Bu_3P, n = 1) was generated in situ by the addition of tri-*n*-butylphosphine (0.16 mL, 0.64 mmol) to **10** prepared by the metalation method (0.085 g, 0.32 mmol) in 5 mL of DMF cooled to 0 °C. The decarboxylation of the solution at 70 °C for 3 h evolved CO_2 in a 6% yield.

Reaction of 36 with Allyl Bromide. Compound **36** (L = n-Bu_3P, n = 3) was generated in situ by the addition of tri-*n*-butylphosphine (1.57 mL, 6.30 mmol) to **10** prepared by the metalation method (0.28 g, 1.05 mmol) in 3 mL of DMF cooled to 0 °C, and allyl bromide (0.44 mL, 5.25 mmol) was added. The mixture was stirred at room temperature for 2 h. GLC analysis (a silicone DC 550 column, diphenyl ether as an internal standard) of the resulting reaction mixture revealed that allyl 1-oxo-2-allylcyclohexane-2-carboxylate (**12**) was formed in a 73% yield.

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Registry No. 1, 79172-68-2; 2, 79200-84-3; 3, 79172-69-3; 4, 79172-70-6; 5, 79172-71-7; 6, 79172-72-8; 7, 79172-73-9; 8, 79172-97-7; 10, 79200-85-4; 12, 65726-93-4; 15, 5277-36-1; 20, 600-22-6; 21, 63921-06-2; 24, 3952-66-7; 27, 79172-44-4; 31, 79172-45-5; 33, 73233-55-3; 35 (L = n-Bu_3P, n = 1), 79172-98-8; 36 (L = n-Bu_3P, n = 1), 79201-12-0; 36 (L = n-bu_3P, n = 3), 79201-11-9; 1-oxocyclohexane-2-carboxylic acid, 18709-01-8; oxalacetic acid, 328-42-7; benzoylacetic acid, 614-20-0; 1-benzoylcyclopropane-1-carboxylic acid, 79172-43-3.