Palladium-Catalyzed Double and Single Carbonylations of β-Amino Alcohols. Selective Synthesis of Morpholine-2,3-diones and Oxazolidin-2-ones and Applications for Synthesis of α-Oxo Carboxylic Acids

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Catalytic cross double carbonylation of secondary amines and alcohols proceeds in the presence of $[PdCl_2(MeCN)_2]$ and CuI under carbon monoxide (80 atm) and oxygen (5 atm). Catalytic intramolecular double carbonylation of β-amino alcohols gives morpholine-2,3-diones, which are excellent protecting compounds of amino alcohols and important precursors for biologically active nitrogen compounds. In contrast, catalytic single carbonylation of β-amino alcohols under a mixture (1 : 1) of carbon monoxide and oxygen (1.0 atm) proceeds to give oxazolidin-2-ones selectively. The reaction can be explained by assuming a mechanism which includes intramolecular nucleophilic attack of the hydroxy group of (hydroxyethyl)aminocarbonyl ligands on the CO ligand of the carbamoylpalladium(II) complexes, followed by reductive elimination to give morpholine-2,3-diones. In contrast, direct nucleophilic attack of the hydroxy group to the carbamoyl group affords oxazolidin-2-ones. As a common intermediate for the double and single carbonylations, carbamoylpalladium(II) complex has been isolated by the reaction of $[PdCl_2(PMe_3)_2]$ with β-amino alcohol under CO.

The present double carbonylation of amino alcohols provides a novel and convenient method for synthesis of α-oxo carboxylic acids. Thus, the morpholine-2,3-diones obtained undergo reaction with Grignard reagents chemoselectively at the ester positions to give 2-substituted 2-hydroxymorpholin-3-ones, which undergo acid hydrolysis to give α-oxo carboxylic acids.

Carbonylation reactions promoted by transition metal catalysts are widely utilized for synthesis of carbonyl compounds such as carboxylic acids, esters, amides, aldehydes, and ketones.[1] Generally, one carbon monoxide molecule is introduced into an organic substrate. In contrast, two carbon monoxide molecules can be introduced in a single step to give two carbonyl groups in adjacent positions.[2] These double carbonylations are of importance in view of mechanistic and synthetic aspects. Palladium-catalyzed double carbonylations of aryl, benzyl, and alkenyl halides with amines, alcohols, and water give the corresponding α-keto acids and their derivatives (Eq. 1).[3,4] Similar cobalt-[5] and nickel-[6] catalyzed double carbonylations proceed under phase transfer conditions. Under similar reaction conditions, styrene oxides undergo cobalt-catalyzed double carbonylation.[7] Secondary amines undergo palladium-catalyzed double carbonylation to give the corresponding oxamides, where two carbon monoxide units are incorporated between two molecules of amines.[8] Alcohols also undergo catalytic double carbonylation to give oxalates by oxidative carbonylations with palladium–copper,[9a] palladium–cobalt,[9b] palladium–iron,[9c] and copper[9d] catalysts (Eq. 2).

$$RX + YH + CO \xrightarrow[\text{base}]{\text{M cat.}} R\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{O}{\|}}{C}\text{-}Y$$

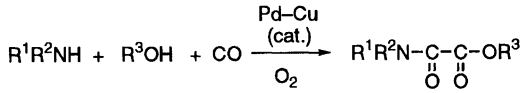
$YH = R^1R^2NH, R^1OH, H_2O$ (1)

$$YH + CO \xrightarrow[\text{base}]{\text{M cat.}} Y\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{O}{\|}}{C}\text{-}Y$$

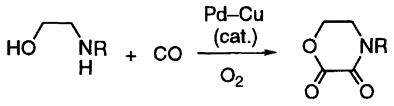
$YH = R^1R^2NH, R^1OH$ (2)

During the course of the systematic study on the activation of secondary amines with transition metal catalysts,[10] we have found that palladium(II) complexes react with secondary amines and alcohols in the presence of CO and base such as triethylamine to give the corresponding oxamates efficiently. The cross double carbonylation of amines and alcohols can be performed catalytically under CO pressure (80 atm) using O_2 (5 atm) and copper salt as an oxidant and a co-catalyst, respectively (Eq. 3). Furthermore, β-amino alcohols undergo palladium-catalyzed double carbonylation highly efficiently to give cyclic oxamates (Eq. 4).[11] In contrast, single carbonylation of β-amino alcohols can be performed selectively to give cyclic carbamates under an atmospheric pressure of a 1 : 1 mixture of CO and O_2 (Eq. 5). Finally, a convenient method for synthesis of α-oxo carboxylic acids is performed upon treatment of morpholine-2,3-dione with Grignard reagents followed by hydrolysis. We

report here full details of the palladium-catalyzed cross double and single carbonylations of amines and alcohols with respect to scope, limitation, mechanism, and application.



(3)



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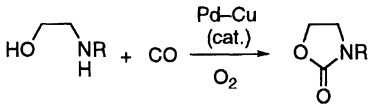
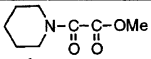
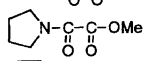
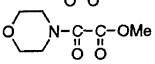
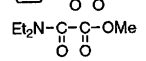
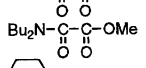
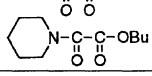


(5)

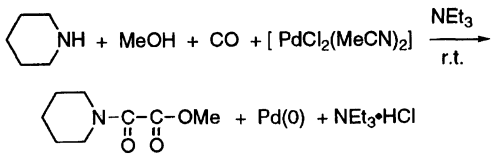
Results and Discussion

Intermolecular Double Carbonylations. The cross double carbonylation of secondary amines and alcohols proceeds selectively in the presence of a stoichiometric amount of palladium(II) complex and excess base under CO (1 atm) at room temperature. When a mixture of piperidine, $[PdCl_2(MeCN)_2]$ (1 molar amount), triethylamine (10 molar amounts), and excess methanol was stirred under CO (1 atm) at room temperature, 1-methoxalylpiperidine (**1**) was obtained in 90% yield along with palladium black (Eq. 6). No cross single carbonylation product, such as carbamate, or homo double carbonylation product, such as oxamide and oxalate, could be detected among the products. $[PdCl_2(MeCN)_2]$ is the best palladium(II) complex among those examined: for example $PdCl_2$, $Pd(OAc)_2$, and $[PdCl_2(PEt_3)_2]$. Representative results for the palladium-promoted cross double carbonylation of secondary amines and alcohols are summarized in Table 1.

Table 1. Carbonylation of Amines and Alcohols Promoted by Palladium(II) Complex[a)]

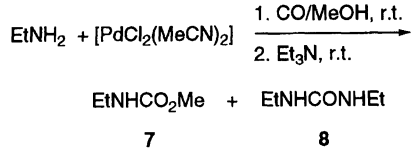
Entry	Amine	Alcohol	Oxamate	Yield/%
1		MeOH		90
2		MeOH		83
3		MeOH		59
4[b)]	Et_2NH	MeOH		69
5	Bu_2NH	MeOH		47
6		BuOH		77

a) The reaction was carried out by stirring a mixture of $[PdCl_2(MeCN)_2]$ (1.0 mmol), amine (1.0 mmol), and alcohol (100 mmol) under CO (1 atm) at room temperature for 1 h, addition of NEt_3 (10 mmol), and further stirring at room temperature for 20 h. b) A mixture of $[PdCl_2(MeCN)_2]$, amine, NEt_3, and alcohol was stirred under CO (1 atm) at 0 °C for 5 h and then at room temperature for 15 h.



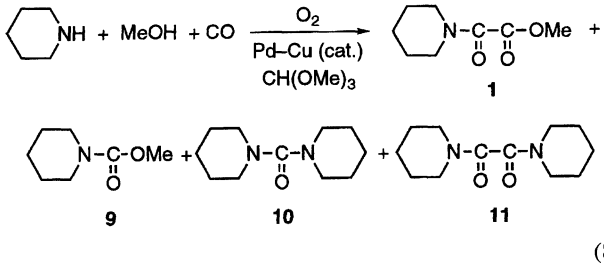
(6)

Primary amines undergo single carbonylation selectively under similar reaction conditions to give a mixture of carbamates and ureas. Typically, the reaction of ethylamine with $[PdCl_2(MeCN)_2]$ in methanol under the conditions described above gave methyl *N*-ethylcarbamate (**7**) and 1,3-diethylurea (**8**) in 37 and 18% yield, respectively (Eq. 7). These results are quite different from those of secondary amines, which afford oxamates selectively. The reaction of primary amines can be explained by assuming formation of an intermediate either amino carbonyl complex or isocyanate, which can be derived by palladium-promoted carbonylation.[12] Palladium-catalyzed single carbonylations of primary amines have also been reported to give carbamates selectively using Pd-black/KI/O_2[13] and $PdCl_2/CuCl_2/HCl/(t\text{-}BuO)_2$ systems.[14]



(7)

Next, we examined catalytic double carbonylation of piperidine and methanol using molecular oxygen and copper halide as an oxidant and a co-catalyst, respectively (Eq. 8). The carbonylation of piperidine in the presence of $[PdCl_2(MeCN)_2]$ (0.05 molar amount), CuCl (0.15 molar amount), and $CH(OMe)_3$ (2.0 molar amounts) in methanol under a mixture (1 : 1) of CO and O_2 (1 atm) gave 1-methoxycarbonylpiperidine (**9**) (28%) and 1,1′-carbonyldipiperidine (**10**) (25%) exclusively. The addition of $CH(OMe)_3$ is essential as dehydrating reagent.



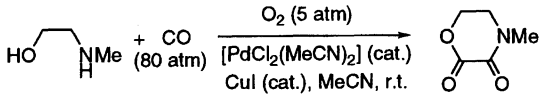
(8)

The higher pressure of CO causes an improvement in the selectivity for the double carbonylation. Thus, when the same mixture was reacted under a mixture of CO (80 atm) and O_2 (5 atm), oxamate **1** (34%) and 1,1′-oxalyldipiperidine (**11**) (38%) were obtained along with carbamate **9** (10%) and urea **10** (5%).[13] When a less basic palladium catalyst such as PdI_2 and $[PdCl_2(MeCN)_2]$ were used, a higher selectivity of **1** was obtained in comparison with $Pd(OAc)_2$ and $Pd(acac)_2$. As a co-catalyst, copper(I) halides such as CuI gave higher selectivity. The use of excess alcohol increases the

amount of cross double carbonylation product **1** rather than that of oxamide **11**. Typically, when a mixture of piperidine, $[PdCl_2(MeCN)_2]$ (0.05 molar amount), and CuI (0.15 molar amount) in methanol was stirred in the presence of a dehydrating reagent $CH(OMe)_3$ (2.0 molar amounts) under CO (80 atm) and O_2 (5 atm), a mixture of oxamate **1** (43%) and oxamide **11** (39%) were obtained along with a small amount of carbamate **9** (2%) and urea **10** (2%).

Double carbonylation of amines and alcohols has also been investigated; the reaction of piperidine and methanol with CO (1 atm) using $PdCl_2$ and $CuCl_2$ as catalysts and di-*t*-butyl peroxide as an oxidant in the presence of HCl gave oxamate **1** and carbamate **9** in 16 and 64% yields, respectively.[14]

Catalytic Intramolecular Double Carbonylations. Intramolecular double carbonylation of β-amino alcohols proceeds catalytically with high efficiency to give cyclic oxamates. The influence of the reaction parameters was examined for the transformation of 2-(methylamino)ethanol (**12**) to 4-methylmorpholine-2,3-dione (**13**). In this catalytic reaction, the addition of dehydrating reagent $CH(OMe)_3$ is not necessary. A system of $[PdCl_2(MeCN)_2]$ and CuI catalysts gave the best results again, and **13** was obtained exclusively. The yield of **13** is dependent on the polarity of the solvent, and acetonitrile is a good solvent. The reaction did not proceed in 1,2-dimethyoxyethane and benzene. Typically, the reaction of β-amino alcohol **12** in the presence of $[PdCl_2(MeCN)_2]$ (0.05 molar amount) and CuI (0.25 molar amount) in acetonitrile under CO (80 atm) and O_2 (5 atm) gave morpholine-2,3-dione **13** in 95% yield (Eq. 9). The stoichiometric double carbonylation of amino alcohol **12** has been reported by a Du Pont group with $PdCl_2$ and NaOAc to give **13** in 57% yield.[15]



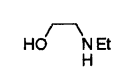
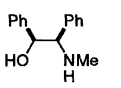
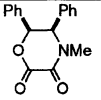
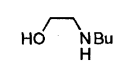
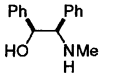
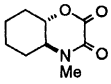
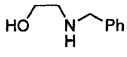
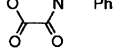
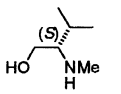
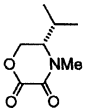
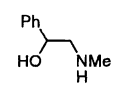
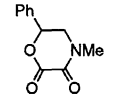
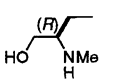
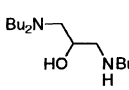
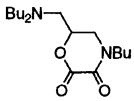
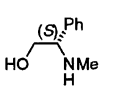
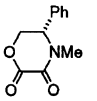
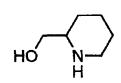
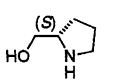
(9)

The representative results of the intramolecular double carbonylation of β-amino alcohols are summarized in Table 2. Cyclic oxamates are excellent protecting compounds of β-amino alcohols and important precursors for biologically active compounds, particularly β-adrenergic blocking agents.[16] Furthermore, some cyclic oxamates have physiological properties such as antiinflamatory[17] and anticonvulsant[18] activities. Pharmacological activities of various 4-alkyl-6-(dialkylamino)methylmorpholine-2,3-diones such as **18** have been examined, and some of them showed local anesthetic, antispasmodic, and analgesic activities and had lower toxicity than amino alcohols themselves.[19]

The carbonylation of optically active β-amino alcohols gave the corresponding cyclic oxamates without loss of chirality (Entries 9—12). These optically active cyclic oxamates are potential precursors for asymmetric induction. Optically active β-amino alcohols are readily prepared by either reduction of chiral amino acids.[20] ring opening of chiral epoxides,[21] enantioselective ring opening of epoxides,[22] and chemoenzymatic reduction of α-azido ketones.[23]

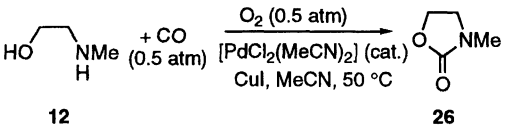
It is noteworthy that the carbonylation of amino alcohol **12** gives double carbonylation product, cyclic oxamate **13**, and/or single carbonylation product, 3-methyloxazolidin-2-one (**26**), depending on the CO pressure employed. As ex-

Table 2. Double Carbonylation of Amino Alcohols Catalyzed by Palladium(II) Complex[a]

Entry	Amino alcohol	Oxamate	Yield/%	Entry	Amino alcohol	Oxamate	Yield/%
1			86	7			33
2			86	8			91
3			85	9			47
4			82	10			85
5			84	11			83
6			76	12			67

a) The reaction was carried out by stirring a mixture of amino alcohol (1.0 mmol), $[PdCl_2(MeCN)_2]$ (0.05 mmol), and CuI (0.25 mmol) in acetonitrile (2 mL) under CO (80 atm) and O_2 (5 atm) at room temperature for 20 h.

pected, the reaction of amino alcohol **12** under a mixture (1 : 1) of CO and O_2 (1 atm) gave carbamate **26** exclusively in 77% yield, while the carbonylation using same catalyst system under 80 atm of CO gave double carbonylation product **13** as the sole product. The single carbonylation of **12** proceeds more efficiently using an equimolar amount of CuI at 50 °C, affording carbamate **26** in 83% yield (Eq. 10).

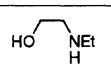
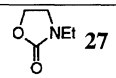
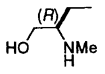
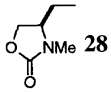
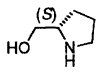
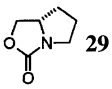
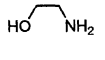
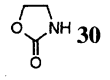
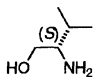
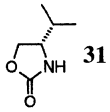
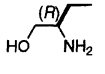
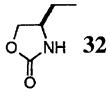
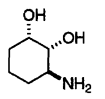
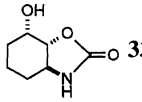


12 **26** (10)

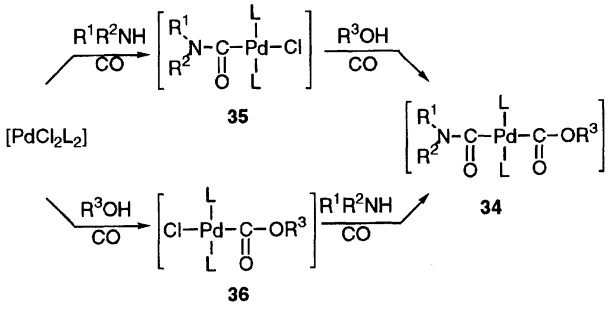
Oxazolidinones are an important class of heterocyclic compounds which have many biological uses; however, these compounds have been prepared using dangerous phosgene or phosgene-based reagents.[24] The present reaction provides an attractive and alternative route to oxazolidinones using CO. The representative results for the single carbonylation of β-amino alcohols are summarized in Table 3.

Amino alcohols having a primary amino group undergo single carbonylation to give oxazolidinones exclusively even under higher pressure of CO. Chiral oxazolidinones such as **31** and **32**, which are used as chiral auxiliaries for asymmetric syntheses,[25] can be prepared from optically active amino

Table 3. Single Carbonylation of Amino Alcohols Catalyzed by Palladium(II) Complex[a]

Entry	Amino alcohol	Carbamate	Yield/%
1		 **27**	76
2		 **28**	64
3		 **29**	90
4[b]		 **30**	65
5[b]		 **31**	72
6[b]		 **32**	75
7[b]		 **33**	93

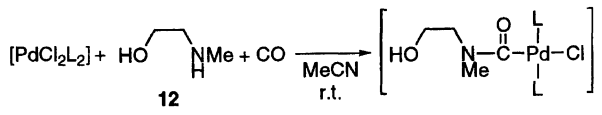
a) The reaction was carried out by stirring a mixture of amino alcohol (1.0 mmol), $[PdCl_2(MeCN)_2]$ (0.05 mmol), and CuI (1.0 mmol) in acetonitrile (2 mL) under CO and O_2 (1 atm) at 50 °C for 20 h. b) The reaction was carried out by stirring a mixture of amino alcohol (1.0 mmol), $[PdCl_2(MeCN)_2]$ (0.05 mmol), and CuI (0.25 mmol) in acetonitrile (2 mL) under CO (80 atm) and O_2 (5 atm) at room temperature for 6 h.



Scheme 1.

alcohols. It is noteworthy that the carbonylation of 3-aminocyclohexane-1,2-diol occurred at amino alcohol function selectively to give bicyclic oxazolidin-2-one **33** (Entry 7).

Mechanistic Aspects. Oxamate synthesis from CO and alcohols catalyzed by palladium complex has been suggested to involve a bis(alkoxycarbonyl)palladium intermediate.[26] The formation of oxamates most likely involves reductive elimination of (carbamoyl)(alkoxycarbonyl)palladium complexes (**34**) formed by nucleophilic attack of amines and alcohols on the coordinated CO ligands.[27] However, one can consider two pathways to form the complex **34**: carbonylation of carbamoylpalladium complexes (**35**) or that of alkoxycarbonylpalladium complexes (**36**), as shown in Scheme 1. In order to clarify this point, $[PdCl_2(PEt_3)_2]$ was allowed to react with amino alcohol **12** under CO (80 atm) at room temperature. Carbamoylpalladium(II) complex **37** was obtained in 38% yield, although the similar reaction under 1 atm of CO did not afford complex **37**. When $[PdCl_2(PMe_3)_2]$ bearing a basic and more compact phosphine ligand was allowed to react with **12** under 1 atm of CO at room temperature, carbamoylpalladium complex **38** was obtained in 95% yield as colorless crystals (Eq. 11). On the other hand, the reaction of the other palladium complexes having PPh_3 and $PMePh_2$ ligands did not afford the corresponding carbamoyl- or alkoxycarbonylpalladium complexes even under 80 atm of CO. The IR spectra of complexes **37** and **38** exhibited strong absorption at 1558 and 1548 cm^{-1}, respectively, assignable to the carbamoyl C=O stretching.[27]



37; L = PEt_3

38; L = PMe_3

(11)

The structure of complex **38** was verified by a single-crystal X-ray structure determination. The ORTEP drawing of **38** in Fig. 1 confirms that the four ligands around the Pd(II) metal are disposed in a square-planar geometry. The chloro ligand and the carbamoyl group are in a trans arrangement with ∠Cl–Pd–C(1)=178.8 (2)°. The hydroxy group of **38** has no direct interaction with the palladium, the oxygen atom (O(2)) being 5.26 Å distant from Pd(II) metal.

Treatment of the complex **38** with CuI under a mixture

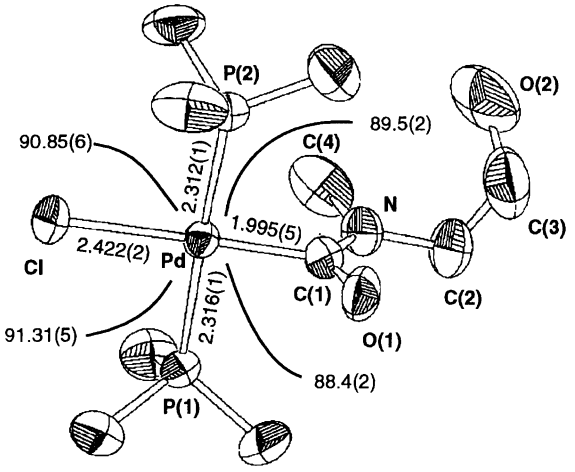
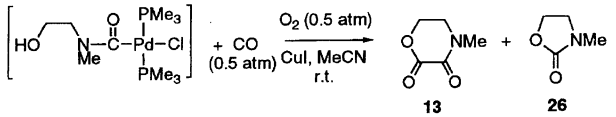
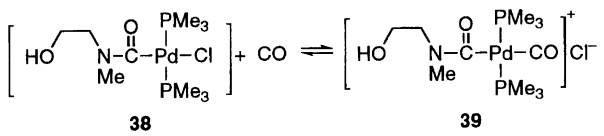


Fig. 1. The ORTEP drawing of *trans*-[PdCl(CONMeCH$_2$CH$_2$OH)(PMe$_3$)$_2$] (**38**).

(1 : 1) of CO and O_2 (1 atm) gave a mixture of the oxamate **13** and the carbamate **26** in 41 and 48% yields, respectively (Eq. 12), although similar treatment of **38** without CuI resulted in no reaction. These results reveal that the carbamoylpalladium complex **38** is a common intermediate for both double and single carbonylations of amino alcohol **12**. On the other hand, when a solution of the complex **38** in $CDCl_3$ was treated with CO (80 atm) at room temperature for 3 d, a red-brown solution was obtained, and neither oxamate **13** nor carbamate **26** was detected. TLC analysis of the solution showed consumption of the complex **38** and formation of a new compound; however, an attempt to isolate the compound failed because of its instability in the absence of CO pressure. The solution changed from red-brown to colorless after standing overnight under nitrogen. The TLC analysis of the resulting colorless solution showed the reappearance of **38** as a sole product. Palladium-catalyzed double carbonylation of aryl halides to produce α-keto amides has been well studied,[28] and an equilibrium between neutral acylpalladium complex and cationic (acyl)(carbonyl)palladium complex has been reported.[28b] Similar equilibrium between neutral carbamoylpalladium complex **38** and CO-coordinated cationic carbamoylpalladium species **39** can be considered in the present reaction (Eq. 13). Recently, it was reported that the use of iodide ion induced high selectivity to the palladium(II)-catalyzed carbonylations of secondary amines to form oxamides.[8b] The intermediacy of carbonylpalladium iodide similar to **39** can be considered to shift the equilibrium in Eq. 13 to the right-hand side in the presence of iodide ion. Therefore, CuI plays the role of an iodide ion source in addition to the re-oxidation of palladium(0) to generate palladium(II).



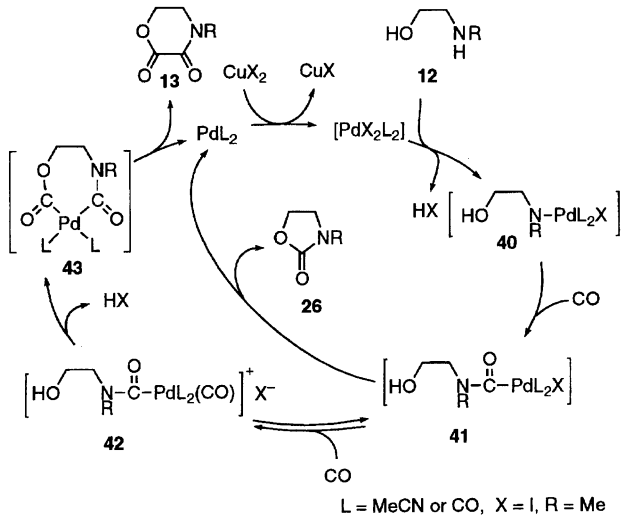
(12)



(13)

The present palladium-catalyzed double and single carbonylation reactions of the amino alcohol **12** can be reasonably accounted for by the catalytic cycle shown in Scheme 2, where the carbonylation occurs mainly at a palladium center. The catalytic cycle is composed of: (i) displacement of one of the halide ligands by amine to give amino palladium complex **40**, (ii) coordination of CO, followed by migration of amino ligand on a coordinated CO ligand to give carbamoylpalladium halide complex **41**, (iii) further CO coordination to the complex **41** to give cationic (carbamoyl)(carbonyl)palladium complex **42**, (iv) nucleophilic attack of the hydroxy group on a coordinated CO ligand to form (carbamoyl)(alkoxycarbonyl)palladium complex **43**, (v) reductive elimination to release the cyclic oxamate **13** with generation of the Pd(0) species, and (vi) re-oxidation of the Pd(0) species to the Pd(II) species by the action of copper to complete the catalytic cycle. Direct nucleophilic attack on the carbamoyl group of **41** affords the cyclic carbamate **26** with generation of Pd(0) species. An alternative mechanism which involves nucleophilic attack of the hydroxy group onto palladium center followed by reductive elimination could not be ruled out. In the case of primary amines, β-hydride elimination from carbamoyl complex **41** (R=H) may afford isocyanate to give carbamate **26** selectively. The selective formation of the oxamate **13** at higher CO pressure suggests that the equilibrium between **41** and **42** lies to the formation of **42** under high pressure of CO to form complex **43**.

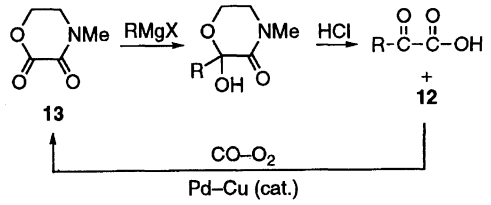
Synthetic Applications. Morpholine-2,3-diones can serve as useful building blocks, since they have two different carbonyl groups in adjacent positions. First, we want to show a convenient and general method for the preparation of α-oxo carboxylic acids[29] starting from the cyclic oxamate



Scheme 2.

13. The morpholine-2,3-dione **13** undergoes reactions with Grignard reagents chemoselectively at the C-2 position to give the corresponding 2-hydroxymorpholin-3-ones, which undergo facile acid hydrolysis to give α-oxo carboxylic acids (Scheme 3). Recovered 2-(methylamino)ethanol (**12**) can be used again as a substrate for the double carbonylation.

The representative results for the two step synthesis of α-oxo carboxylic acids are summarized in Table 4. Typically, the reaction of **13** with phenylmagnesium bromide in THF gave 2-hydroxy-4-methyl-2-phenylmorpholin-3-one (**44**) in 89% yield. Hydrolysis of **44** was performed upon treatment with a 2 M hydrochloric acid solution (1 M=1 mol dm^{-3}) at 100 °C to give phenylglyoxalic acid (**51**) in 94% yield. α-Oxo carboxylic acids can be used for synthesis of various useful organic compounds such as α-amino acids, α-hydroxy acids, and others. One of the most important applications of α-oxo carboxylic acids is the preparation of α-amino acids by enzymatic transamination reactions.[30] However, convenient and general routes for synthesis of α-oxo carboxylic acids are limited. Using the present methodology, α-oxo carboxylic acids having wide range of substituents can be prepared highly efficiently, because R groups of Grignard reagents can be transferred into α-oxo carboxylic acids. Furthermore, fluorine-containing α-oxo carboxylic acids, such as **55**, **56**, and **57**, which are synthons for biologically active fluorine-containing α-amino acids[31] are obtained readily in good yields.

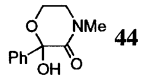
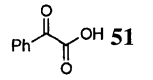
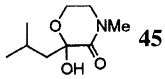
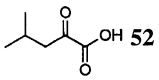
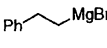
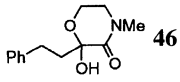
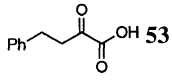
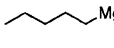
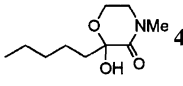
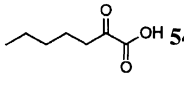
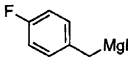
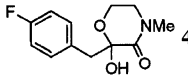
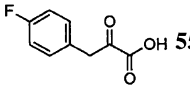
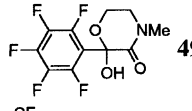
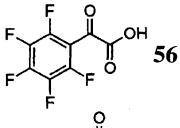
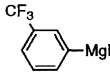
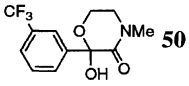
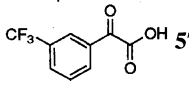


Scheme 3.

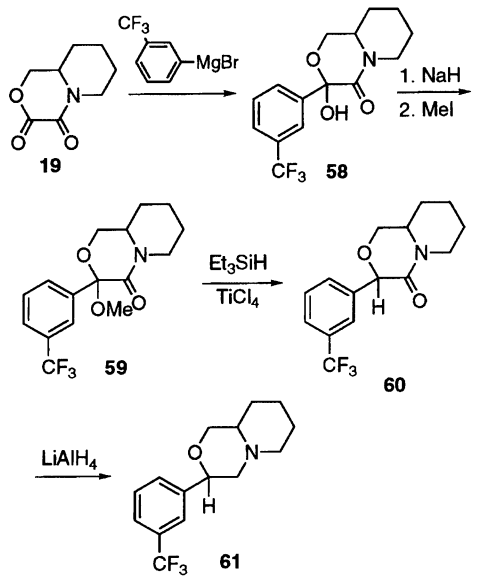
Next, we prepared 3-(3-trifluoromethylphenyl)octahydropyrido[2,1-*c*][1,4]oxazine (**61**) as shown in Scheme 4. Central nervous system pharmacological activity of a series of 3-aryloctahydropyrido[2,1-*c*][1,4]oxazines has been studied, and some of them are known to have anticonvulsant and appetite suppressant activities.[32] In particular, **61** bearing 3-trifluoromethylphenyl group showed the highest activity. The reaction of **19** with 3-trifluoromethylphenylmagnesium bromide afforded hemiketal **58**, in which a hydroxy group was converted into methoxy group to give ketal **59**. Removal of the methoxy group of the ketal **59** was performed by $TiCl_4$-mediated reduction with Et_3SiH (−78 °C) to afford **60**. Reduction of the carbonyl group of **60** with $LiAlH_4$ gave **61** selectively (61% starting from **19**). This methodology provides a general route to prepare various types of morpholines.

In conclusion, cross double carbonylation of secondary amines and alcohols has been found to proceed smoothly in the presence of stoichiometric amounts of $[PdCl_2(MeCN)_2]$ under an atmosphere of CO at room temperature to give the corresponding oxamates in good to moderate yields. Catalytic intramolecular double and single carbonylations of β-amino alcohols proceed smoothly by using $[PdCl_2(MeCN)_2]$

Table 4. Reaction of **13** with Grignard Reagent[a] and Synthesis of α-Oxo Carboxylic Acids[b]

Entry	Grignard reagent	Hemiketal	Yield/%	α-Oxo carboxylic acid	Yield/%
1	PhMgBr	 **44**	89	 **51**	94
2		 **45**	75	 **52**	87
3		 **46**	74	 **53**	99
4		 **47**	87	 **54**	97
5		 **48**	93	 **55**	89
6		 **49**	97	 **56**	95[c]
7		 **50**	83	 **57**	96

a) The reaction was carried out by stirring a mixture of **13** (5 mmol) and Grignard reagent (6 mmol) in THF at 0 °C for 1 h and at room temperature for 3 h. b) The hydrolysis was performed by stirring hemiketal (2 mmol) in 2 M HCl at 100 °C for 2 h. c) 12 M HCl was used.



Scheme 4.

catalyst, CuI co-catalyst, and O_2, giving morpholine-2,3-diones and oxazolidin-2-ones, respectively, depending on CO pressure. Carbamoylpalladium(II) complex, a common intermediate for both double and single carbonylations of β-amino alcohols, has been isolated from the reaction of β-amino alcohol with $[PdCl_2(PMe_3)_2]$ under CO. Furthermore, morpholine-2,3-diones can be used as useful intermediates for synthesis of α-oxo carboxylic acids and morpholines.

Experimental

Materials. NMR spectra were measured in $CDCl_3$ at 35 °C unless otherwise noted. Dichlorobis(acetonitrile)palladium(II) $[PdCl_2(MeCN)_2]$,[33] palladium iodide (PdI_2),[34] and dichlorobis(trimethylphosphine)palladium(II) $[PdCl_2(PMe_3)_2]$,[35] were prepared according to the reported procedures. Carbon monoxide was purchased from Sumitomo Seika and used without further purification.

Double-Carbonylation of Secondary Amines and Alcohols Promoted by Stoichiometric Amounts of Palladium(II) Complex. Procedure A. As a typical example, preparation of 1-methoxalylpiperidine (**1**) will be described. A mixture of $[PdCl_2(MeCN)_2]$ (0.259 g, 1.00 mmol) and piperidine (0.085 g, 1.00 mmol) in MeOH (4.0 mL) was stirred under CO (1 atm) at room temperature for 1 h. To the mixture was added Et_3N (1.40 mL, 10.0 mmol) dropwise over a period of 2 min, and the mixture was stirred for an additional 20 h at room temperature. Palladium metal which precipitated was filtered off and the filtrate was evaporated. To the residue was added aqueous saturated $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation gave oxamate **1** (0.154 g, 90%): Bp 132—135 °C (2.0 mmHg, Kugelrohr, 1 mmHg=133.322 Pa); IR (neat) 1746 (C=O), 1660 (C=O), 1212 cm^{-1}; ^1H NMR (270 MHz) δ=1.65—1.85 (m, 6 H), 3.34 (t, J=5.4 Hz, 2 H), 3.56 (t, J=5.4 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (68 MHz) δ=24.1, 24.9, 26.0, 42.0, 47.0, 52.2, 159.8 (CO_2), 163.4 (CON). Found: C, 55.88; H, 7.70; N, 8.22%. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18%. An authentic sample was prepared from dimethyl oxalate and piperidine.[36]

Procedure B. A mixture of $[PdCl_2(MeCN)_2]$ (1.00 mmol), Et_2NH (1.00 mmol), and Et_3N (10.0 mmol) in MeOH (4.0 mL) was stirred at 0 °C for 5 h, then at room temperature for 15 h. Usual work-up followed by Kugelrohr distillation gave methyl *N*,*N*-diethyloxamate (**4**): Bp 113—116 °C (7.5 mmHg, Kugelrohr); IR (neat) 2987, 1748 (C=O), 1658 (C=O), 1234, 1128 cm^{-1}; ^1H NMR (270 MHz) δ=1.18 (t, J=7.1 Hz, 3 H), 1.22 (t, J=7.1 Hz, 3 H), 3.29 (q, J=7.1 Hz, 2 H), 3.43 (q, J=7.1 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (68 MHz) δ=12.2, 13.9, 38.8, 42.3, 52.1 (OCH_3), 161.0 (CO_2), 163.3 (CON). Found: C, 52.41; H, 8.23; N, 8.68%. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80%. An authentic sample was prepared from dimethyl oxalate and Et_2NH.[36]

1-Methoxalylpyrrolidine (2): Bp 118—122 °C (1.6 mmHg, Kugelrohr); IR (neat) 2963, 1741 (C=O), 1658 (C=O), 1248 cm^{-1}; ^1H NMR (270 MHz) δ=1.85—2.01 (m, 4 H), 3.53 (t, J=6.6 Hz, 2 H), 3.64 (t, J=6.6 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (68 MHz) δ=23.7, 25.8, 45.9, 47.2, 52.3 (OCH_3), 158.1 (CO_2), 162.4 (CON). Found: C, 53.43; H, 7.12; N, 8.94%. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91%.

4-Methoxalylmorpholine (3): Bp 130—135 °C (2.2 mmHg, Kugelrohr); IR (neat) 2865, 1744 (C=O), 1663 (C=O), 1273 cm^{-1}; ^1H NMR (270 MHz) δ=3.47 (t, J=4.9 Hz, 2 H), 3.60—3.75 (m, 6 H), 3.88 (s, 3 H); ^{13}C NMR (68 MHz) δ=41.7, 46.3, 52.5, 66.2, 66.5, 159.7 (CO_2), 162.5 (CON). Found: C, 48.63; H, 6.44; N, 8.19%. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09%.

Methyl *N*,*N*-Dibutyloxamate (5): Bp 121—124 °C (1.0 mmHg, Kugelrohr); IR (neat) 1748 (C=O), 1661 (C=O) cm^{-1}; ^1H NMR (270 MHz) δ=0.92 (t, J=7.3 Hz, 3 H), 0.94 (t, J=7.3 Hz, 3 H), 1.23—1.42 (m, 4 H), 1.50—1.64 (m, 4 H), 3.21 (t, J=7.6 Hz, 2 H), 3.36 (t, J=7.6 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (68 MHz) δ=13.5, 13.7, 19.7, 20.0, 29.2, 30.7, 44.2, 47.7, 52.2, 161.6 (CO_2), 163.6 (CON). Found: C, 61.39; H, 9.84; N, 6.60%. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51%.

1-Butoxalylpiperidine (6): Bp 167—171 °C (2.2 mmHg, Kugelrohr); IR (neat) 2950, 1744 (C=O), 1660 (C=O), 1197 cm^{-1}; ^1H NMR (270 MHz) δ=0.94 (t, J=7.3 Hz, 3 H), 1.42 (dq, J=7.3, 7.3 Hz, 2 H), 1.57—1.75 (m, 8 H), 3.33 (t, J=5.1 Hz, 2 H), 3.56 (t, J=5.1 Hz, 2 H), 4.28 (t, J=6.6 Hz, 2 H); ^{13}C NMR (68 MHz) δ=13.5, 19.0, 24.3, 25.1, 26.2, 30.4, 42.1, 47.2, 65.6, 160.3, 163.4. Found: C, 61.47; H, 8.94; N, 6.44%. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57%.

Carbonylation of Ethylamine and Methanol Promoted by Stoichiometric Amount of Palladium(II) Complex. A mixture of $[PdCl_2(MeCN)_2]$ (0.483 g, 1.86 mmol) and $EtNH_2$ (0.084 g, 1.86 mmol) in MeOH (6.0 mL) was stirred under CO (1 atm) for 1 h at room temperature. To the mixture was added Et_3N (2.60 mL, 19.0 mmol) dropwise over a period of 2 min, and the resulting black suspension was stirred at room temperature for an additional 4 h. Usual work-up followed by Kugelrohr distillation gave methyl *N*-ethylcarbamate (**7**) (0.071 g, 37%) and 1,3-diethylurea (**8**) (0.019 g, 18%).

7: Bp 80—85 °C (16.5 mmHg, Kugelrohr); IR (neat) 3325 (N–H), 2985, 1713 (C=O), 1539, 1460, 1262, 1032 (m), 781 cm^{-1} (m); ^1H NMR (270 MHz) δ=1.13 (t, J=7.1 Hz, 3 H), 3.21 (dq, J=6.6, 7.1 Hz, 2 H), 3.66 (s, 3 H), 4.95 (br, 1 H, NH); ^{13}C NMR (68 MHz) δ=15.1, 35.7 (NCH_2), 51.7 (OCH_3), 156.9 (CO); MS *m/z* 103 (M^+), 88 ($-CH_3$), 72 ($-OCH_3$), 59 ($-NHC_2H_5$), 44 ($-CO_2CH_3$). Found: C, 46.32; H, 8.79; N, 13.70%. Calcd for $C_4H_8NO_2$: C, 46.59; H, 8.80; N, 13.58%. An authentic sample was prepared from methyl chloroformate and $EtNH_2$.[37]

8: Bp 120—125 °C (5 mmHg, Kugelrohr); mp 88.5—89.0 °C (hexane); IR (Nujol) 3338 (N–H), 1631 cm^{-1} (C=O); ^1H NMR (270 MHz) δ=1.15 (t, J=7.1 Hz, 6 H), 1.9 (br, 2 H, NH), 3.22 (q, J=7.1 Hz, 4 H, NCH_2). Found: C, 51.79; H, 10.33; N, 23.99%.

Calcd for $C_5H_{12}N_2O$: C, 51.70; H, 10.41; N, 24.12%.

Catalytic Carbonylation of Piperidine and Methanol under an Atmospheric Pressure of CO and O_2 (1 : 1). A mixture of $[PdCl_2(MeCN)_2]$ (0.013 g, 0.05 mmol), CuCl (0.015 g, 0.15 mmol), piperidine (0.085 g, 1.00 mmol), and $CH(OMe)_3$ (0.213 g, 2.00 mmol) in MeOH (2.0 mL) was stirred under 1 : 1 mixed gas of CO and O_2 (1 atm) at room temperature for 20 h. The dark yellow suspension was filtered, and the filtrate was subjected to GLC analysis using dibenzyl as an internal standard. GLC analysis revealed that 1-methoxycarbonylpiperidine (**9**) and 1,1′-carbonyldipiperidine (**10**) were formed in 28 and 25% yield, respectively.

Catalytic Carbonylation of Piperidine and Methanol under the Pressure of CO and O_2. In a 10-mL autoclave were placed Pd complex (0.05 mmol) and Cu salt (0.15 mmol). To the mixture were added MeOH (2.0 mL), piperidine (0.085 g, 1.00 mmol) and $HC(OMe)_3$ (0.213 g, 2.00 mmol), successively. The autoclave was charged with 80 atm of CO and 5 atm of O_2, and the mixture was stirred at room temperature for 20 h. The resulting dark yellow suspension was filtered, and the filtrate was subjected to GLC analysis using dibenzyl as an internal standard. The yields of oxamate **1**, 1,1′-oxalyldipiperidine (**11**), carbamate **9**, and urea **10** obtained are as follows: $[PdCl_2(MeCN)_2]$–$CuCl_2$ (24, 13, 21, and 5%), $Pd(OAc)_2$–$CuCl_2$ (20, 24, 14, and 2%), $Pd(acac)_2$–$CuCl_2$ (20, 24, 17, and 3%), $[PdCl_2(MeCN)_2]$–CuCl (34, 38, 10, and 5%), $[PdCl_2(MeCN)_2]$–CuI (in 4.0 mL of MeOH) (43, 39, 2, and 2%).

1-Methoxycarbonylpiperidine (9): Bp 95—99 °C (6.8 mmHg, Kugelrohr); IR (neat) 2930, 1705 (C=O), 1266 cm^{-1}; ^1H NMR (270 MHz) δ = 1.45—1.64 (m, 6 H), 3.36—3.45 (m, 4 H), 3.68 (s, 3 H, OCH_3); ^{13}C NMR (68 MHz) δ = 24.3, 25.6, 44.7, 52.2 (OCH_3), 155.9 (CO); MS *m/z* 143 (M^+), 128 ($-CH_3$), 84 ($-CO_2CH_3$), 59 ($-C_5H_{10}N$). Found: C, 58.71; H, 9.31; N, 9.81%. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78%.

1,1′-Carbonyldipiperidine (10): Preparative TLC (SiO_2, benzene–ether=7 : 3, R_f=0.33); IR (neat) 2940, 1647 (C=O), 1254 cm^{-1} (C–O); ^1H NMR (270 MHz) δ = 1.55—1.65 (m, 12 H), 3.10—3.20 (m, 8 H); ^{13}C NMR (68 MHz) δ = 24.8, 25.8, 47.9, 164.7 (CO). Found: C, 67.06; H, 10.08; N, 14.28%. Calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27%. An authentic sample was prepared by carbonylation of piperidine.[38]

1,1′-Oxalyldipiperidine (11): Preparative TLC (SiO_2, benzene–ether=7 : 3, R_f=0.19); mp 91—92 °C (hexane); IR (KBr) 1632 cm^{-1} (C=O); ^1H NMR (270 MHz) δ = 1.56—1.76 (m, 12 H), 3.34 (t, *J*=5.4 Hz, 4 H), 3.57 (t, *J*=5.4 Hz, 4 H); ^{13}C NMR (68 MHz) δ = 24.4, 25.3, 26.4, 41.7, 163.5 (CO). Found: C, 64.13; H, 8.99; N, 12.52%. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49%. An authentic sample was prepared by the reaction of oxalyl chloride with piperidine.[39]

General Procedure for Palladium(II)-Catalyzed Double Carbonylation of Amino Alcohols. In a 10-mL autoclave containing $[PdCl_2(MeCN)_2]$ (0.013 g, 0.05 mmol) and CuI (0.048 g, 0.25 mmol) was added a solution of amino alcohol (1.00 mmol) in MeCN (2.0 mL). Into the autoclave was introduced a mixed gas of CO (80 atm) and O_2 (5 atm). After the mixture was stirred at room temperature for 20 h, the pressure was released. Filtration and Kugelrohr distillation gave morpholine-2,3-diones.

4-Methylmorpholine-2,3-dione (13): Bp 145—150 °C (0.06 mmHg, Kugelrohr); mp 98.0 °C (benzene); IR (KBr) 1750 (C=O), 1686 (C=O), 1352, 1190, 1056 cm^{-1}; ^1H NMR (270 MHz) δ = 3.14 (s, 3 H), 3.71 (br-t, *J*=5 Hz, 2 H), 4.54 (br-t, *J*=5 Hz, 2 H); ^{13}C NMR (68 MHz) δ = 34.8, 46.9, 64.1, 153.9, 156.6. Found: C, 46.40; H, 5.43; N, 10.88%. Calcd for $C_5H_7NO_3$: C, 46.51; H, 5.47; N, 10.85%.

4-Ethylmorpholine-2,3-dione (14): Mp 70.0—70.5 °C (ether); IR (KBr) 1754 (C=O), 1682 (C=O), 1488, 1368, 1178, 1058 cm^{-1}; ^1H NMR (270 MHz) δ = 1.24 (t, *J*=7.3 Hz, 3 H), 3.58 (q, *J*=7.3 Hz, 2 H), 3.66 (br-t, *J*=5 Hz, 2 H), 4.51 (br-t, *J*=5 Hz, 2 H); ^{13}C NMR (68 MHz) δ = 12.1, 42.4, 44.4, 65.3, 153.3, 156.8. Found: C, 50.34; H, 6.39; N, 9.60%. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79%.

4-Butylmorpholine-2,3-dione (15): Mp 62.5—63.0 °C (ether); IR (KBr) 1754 (C=O), 1682 cm^{-1} (C=O); ^1H NMR (270 MHz) δ = 0.95 (t, *J*=7.2 Hz, 3 H), 1.36 (tq, *J*=7.2, 7.2 Hz, 2 H), 1.55—1.66 (m, 2 H), 3.52 (t, *J*=7.4 Hz, 2 H), 3.67 (t, *J*=5.4 Hz, 2 H), 4.52 (t, *J*=5.4 Hz, 2 H); ^{13}C NMR (68 MHz) δ = 13.6, 19.9, 29.0, 45.0, 47.3, 65.4, 153.6, 156.9. Found: C, 56.02; H, 7.69; N, 8.16%. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18%.

4-Benzylmorpholine-2,3-dione (16): Mp 97.0—98.0 °C (benzene); IR (Nujol) 1748 (C=O), 1674 (C=O), 1194, 1052 cm^{-1}; ^1H NMR (270 MHz) δ = 3.55 (br-t, *J*=5.2 Hz, 2 H), 4.43 (br-t, *J*=5.2 Hz, 2 H), 4.71 (s, 2 H), 7.26—7.40 (m, 5 H); ^{13}C NMR (68 MHz) δ = 44.0, 50.6, 65.4, 128.48, 128.51, 129.1, 134.6 (*ipso*), 153.8 (CO), 156.7 (CO).

4-Methyl-6-phenylmorpholine-2,3-dione (17): Mp 134.5—135.0 °C (benzene); IR (KBr) 1742 (C=O), 1680 (C=O) 1192 cm^{-1}; ^1H NMR (270 MHz) δ = 3.16 (s, 3 H), 3.56 (dd, *J*=2.9, 13.9 Hz, 1 H), 3.97 (dd, *J*=10.5, 13.9 Hz, 1 H), 5.72 (dd, *J*=2.9, 10.5 Hz, 1 H), 7.43 (s, 5 H); ^{13}C NMR (68 MHz) δ = 35.0, 53.3, 77.6, 126.0, 129.0, 129.6, 134.1 (*ipso*), 153.7, 156.4. Found: C, 64.40; H, 5.34; N, 6.76%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%.

4-Butyl-6-(dibutylaminomethyl)morpholine-2,3-dione (18):[19] IR (neat) 2960, 1768 (C=O), 1694 cm^{-1} (C=O); ^1H NMR (60 MHz) δ = 0.58—1.92 (m, 21 H), 2.11—3.03 (m, 6 H), 3.03—3.92 (m, 4 H), 4.60 (m, 1 H).

Octahydropyrido[2,1-*c*][1,4]oxazine-3,4-dione (19): Mp 68—69 °C (benzene–ether); IR (KBr) 1760 (OC=O), 1686 cm^{-1} (NC=O); ^1H NMR (60 MHz) δ = 1.16—2.17 (m, 6 H), 2.50—3.07 (m, 1 H), 3.43—3.99 (m, 1 H), 4.01—4.67 (m, 3 H); ^{13}C NMR (68 MHz) δ = 21.9, 23.8, 27.2, 42.7, 52.5, 69.0, 162.3, 162.6; MASS *m/z* 169 (M^+), 141 ($M^+ - CO$), 125 ($M^+ - CO_2$).

4-Methyl-5,6-diphenylmorpholine-2,3-dione (20): IR (KBr) 1762 (OC=O), 1688 cm^{-1} (NC=O); ^1H NMR (270 MHz) δ = 3.11 (s, 3 H), 4.61 (d, *J*=3.2 Hz, 1 H), 6.10 (d, *J*=3.2 Hz, 1 H), 6.69 (br-d, *J*=8 Hz, 2 H), 6.98 (br-d, *J*=8 Hz, 2 H), 7.16—7.33 (m, 6 H).

(4a*R,8a*R**)-4-Methyloctahydro-2*H*-1,4-benzoxazine-2,3-dione (21):** Mp 109.0—110.0 °C (hexane–benzene); IR (KBr) 1770 (C=O), 1688 cm^{-1} (C=O); ^1H NMR (270 MHz) δ = 1.30—1.60 (m, 4 H), 1.75—1.85 (m, 2 H), 2.01—2.30 (m, 2 H), 2.98 (s, 3 H), 3.42—3.56 (m, 1 H), 4.21 (dt, *J*=4.4, 11.2 Hz, 1 H); ^{13}C NMR (68 MHz) δ = 23.0, 23.1, 28.0, 28.8, 29.5, 58.2, 39.7, 154.8, 156.7. Found: C, 59.28; H, 7.23; N, 7.66%. Calcd for $C_5H_7NO_3$: C, 59.00; H, 7.15; N, 7.65%.

(*S*)-5-Isopropyl-4-methylmorpholine-2,3-dione (22): Mp 78.7—79.0 °C; $[\alpha]_D^{22}$ −72.4° (*c* 0.513, EtOH); IR (KBr) 1754 (C=O), 1676 cm^{-1} (C=O); ^1H NMR (270 MHz) δ = 1.05 (d, *J*=6.8 Hz, 3 H), 1.11 (d, *J*=6.8 Hz, 3 H), 2.19 (dh, *J*=6.8, 6.8 Hz, 1 H), 3.17 (s, 3 H), 3.18 (ddd, *J*=1.5, 3.4, 6.8 Hz, 1 H), 4.49 (dd, *J*=1.5, 12.0 Hz, 1 H), 4.60 (dd, *J*=3.4, 12.0 Hz, 1 H); ^{13}C NMR (68 MHz) δ = 19.0, 19.7, 30.3, 35.7, 63.3, 66.2, 153.9, 156.6. Found: C, 56.01; H, 7.65; N, 8.12%. Calcd for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18%.

(*R*)-5-Ethyl-4-methylmorpholine-2,3-dione (23): Mp 86—87 °C; $[\alpha]_D^{21}$ +5.9° (*c* 0.371, EtOH); IR (KBr) 1756 (C=O), 1688 cm^{-1} (C=O); ^1H NMR (270 MHz) δ = 1.06 (t, *J*=6.0 Hz, 3 H), 1.70—1.98 (m, 2 H), 3.14 (s, 3 H), 3.37 (dddd, *J*=1.8, 3.2, 5.2, 9.0 Hz, 1 H), 4.39 (dd, *J*=1.8, 12 Hz, 1 H), 4.63 (ddd, *J*=0.8, 3.2, 12

Hz, 1 H); ^{13}C NMR (68 MHz) δ=10.5, 23.5, 33.8, 58.8, 66.8, 153.5 (CO), 156.5 (CO). Found: C, 53.23; H, 6.90; N, 8.87%. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91%.

(*S*)-4-Methyl-5-phenylmorpholine-2,3-dione (24): Mp 131.0 °C (Et_2O–MeOH); $[\alpha]_D^{18}$ −51.4° (*c* 0.755, EtOH); IR (KBr) 1760 (C=O), 1690 (C=O), 1180 cm^{-1}; ^{1}H NMR (270 MHz) δ=3.04 (s, 3H), 4.48 (dd, *J*=3.9, 11.5 Hz, 1 H), 4.74 (dd, *J*=3.4, 3.9 Hz, 1 H), 4.80 (dd, *J*=3.4, 11.5 Hz, 1 H), 7.20—7.28 (m, 2 H), 7.40—7.48 (m, 3 H); ^{13}C NMR (68 MHz) δ=33.7, 61.0, 70.0, 126.7, 129.4, 129.6, 134.1 (*ipso*), 154.3, 156.2.

(*S*)-Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxadine-3,4-dione (25): Mp 135—137 °C (benzene–hexane); $[\alpha]_D^{28}$ +152.5° (*c* 1.00, $CHCl_3$); IR (KBr) 1756 (C=O), 1688 (C=O), 1450, 1192 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.64 (dddd, *J*=7.3, 9.8, 11.7, 12.2 Hz, 1 H, H-7$_{ax}$), 1.92—2.10 (m, 1 H, H-6$_{eq}$), 2.10—2.28 (m, 2 H, H-6$_{ax}$, H-7$_{eq}$), 3.59—3.78 (m, 2 H, H-5), 4.08—4.22 (m, 1 H, H-7a), 4.26 (dd, *J*=10.7, 11.2, 1 H, H-1), 4.56 (dd, *J*=2.9, 10.7 Hz, 1 H, H-1); ^{13}C NMR (68 MHz) δ=23.6 (C-6), 28.5 (C-7), 45.5 (C-5), 55.8 (C-7a), 70.7 (C-1), 151.9 (C-4), 157.4 (C-3); MASS *m/z* 155 (M^+), 111 ($M^+ - CO_2$). Found: C, 54.11; H, 5.89; N, 8.94%. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03%.

General Procedure for Palladium(II)-Catalyzed Single Carbonylation of Amino Alcohols under an Atmospheric Pressure of CO and O_2. A mixture of $[PdCl_2(MeCN)_2]$ (0.013 g, 0.05 mmol), CuI (0.190 g, 1.00 mmol), and amino alcohol **12** (0.075 g, 1.00 mmol) in MeCN (2.0 mL) was stirred under 1 : 1 mixture of CO and O_2 (1 atm) at 50 °C for 20 h. Usual work-up gave 3-methyloxazolidin-2-one (**26**) (83%): IR (neat) 2925, 1728 cm^{-1} (C=O); ^{1}H NMR (270 MHz) δ=2.89 (s, 3 H), 3.58 (br-t, *J*=8 Hz, 2 H), 4.31 (br-t, *J*=8 Hz, 2 H); ^{13}C NMR (68 MHz) δ=30.8, 46.6, 61.3, 158.6.

3-Ethyloxazolidin-2-one (27): IR (neat) 1738 (C=O), 1262 cm^{-1}; ^{1}H NMR (60 MHz) δ=1.17 (t, *J*=7.4 Hz, 3 H), 3.30 (q, *J*=7.4 Hz, 2 H), 3.53 (t, *J*=7.5 Hz, 2 H), 4.33 (t, *J*=7.5 Hz, 2 H). Found: C, 52.12; H, 7.75; N, 11.96%. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.12%.

(*R*)-4-Ethyl-3-methyloxazolidin-2-one (28): Bp 56 °C (10 mmHg, Kugelrohr); $[\alpha]_D^{21}$ −21.7° (*c* 0.405, EtOH); IR (neat) 2980, 1750 cm^{-1} (C=O); ^{1}H NMR (60 MHz) δ=0.90 (t, *J*=7.0 Hz, 3 H), 1.47—2.00 (m, 2 H), 2.83 (s, 3 H), 3.40—4.00 (m, 1 H), 3.90 (dd, *J*=9.0, 9.4 Hz, 1 H), 4.35 (dd, *J*=9.0, 9.0 Hz, 1 H).

(*S*)-Tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (29): Bp 115—120 °C (3.5 mmHg); IR (neat) 2980, 1750 (C=O), 1390, 770 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.48 (dddd, *J*=8.1, 9.8, 9.8, 12.5 Hz, 1 H), 1.84—1.99 (m, 1 H), 2.01—2.14 (m, 2 H), 3.17 (ddd, *J*=4.4, 9.0, 11.2 Hz, 1 H), 3.64 (ddd, *J*=7.1, 8.1, 11.2 Hz, 1 H), 3.90 (dddd, *J*=3.7, 5.4, 7.8, 9.8 Hz, 1 H), 4.16 (dd, *J*=3.7, 9.0 Hz, 1 H), 4.51 (dd, *J*=7.8, 9.0 Hz, 1 H); ^{13}C NMR (68 MHz) δ=25.6, 30.6, 45.7, 59.4, 67.7, 161.6. Found: C, 56.40; H, 7.14; N, 10.99%. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02%.

General Procedure for the Palladium(II)-Catalyzed Single Carbonylation of Primary Amino Alcohols. A mixture of $[PdCl_2(MeCN)_2]$ (0.013 g, 0.05 mmol), CuI (0.048 g, 0.25 mmol), and 2-amino ethanol (0.061 g, 1.00 mmol) in MeCN (2.0 mL) was stirred under CO (80 atm) and O_2 (5 atm) at room temperature for 6 h. Usual work-up afforded oxazolidin-2-one (**30**) (90%): Mp 88—89°C; IR (KBr) 3270 (N–H), 1728 (C=O), 1258, 1084 cm^{-1}; ^{1}H NMR (270 MHz) δ=3.64 (t, *J*=8.1 Hz, 2 H), 4.45 (t, *J*=8.1 Hz, 2 H), 6.0 (br, 1 H); ^{13}C NMR (68 MHz) δ=40.6, 64.9, 160.6. Found: C, 41.32; H, 5.76; N, 16.16%. Calcd for $C_3H_5NO_2$: C, 41.38; H, 5.79; N, 16.09%.

4-Isopropyloxazolidin-2-one (31): IR (KBr) 3350, 2950, 1648 cm^{-1} (C=O); ^{1}H NMR (270 MHz) δ=0.90 (d, *J*=6.8 Hz, 3 H), 0.96 (d, *J*=6.7 Hz, 3 H), 1.73 (dh, *J*=6.8, 6.8 Hz, 1 H), 3.56—3.65 (m, 1 H), 4.10 (dd, *J*=6.4, 8.6 Hz, 1 H), 4.44 (dd, *J*=8.6, 8.6 Hz, 1 H), 6.34 (br, 1 H); ^{13}C NMR (68 MHz) δ=17.6, 18.0, 32.6, 58.3, 68.6, 160.2. Found: C, 55.71; H, 8.39; N; 10.81%. Calcd for $C_6H_{11}NO_2$: C, 55.81; H, 8.58; N, 10.84%.

(*R*)-4-Ethyloxazolidin-2-one (32): Bp 112—118 °C (4 mmHg, Kugelrohr); $[\alpha]_D^{24}$ +3.01° (*c* 1.364, EtOH); IR (neat) 3326, 1746 (C=O), 1408, 1235, 1053 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.95 (d, *J*=7.3 Hz, 3 H), 1.60 (dq, *J*=7.3, 7.3 Hz, 2 H), 3.81 (ddd, *J*=6.1, 7.3, 8.5 Hz, 1 H), 4.02 (dd, *J*=6.1, 8.5 Hz, 1 H), 4.47 (dd, *J*=8.5, 8.5 Hz, 1 H), 7.0 (br, 1 H); ^{13}C NMR (68 MHz) δ=9.0, 28.0, 53.7, 69.8, 160.3.

(3a*R, 7*R**, 7a*S**)- 7- Hydroxyoctahydrobenzoxazol- 2- one (33):** Mp 164 °C; IR (KBr) 3370 (OH), 1735 cm^{-1} (C=O); ^{1}H NMR (CD_3OD, 500 MHz) δ=1.26—1.34 (m, 1 H), 1.44—1.57 (m, 3 H), 1.66—1.70 (m, 1 H), 1.86—1.92 (m, 1 H), 3.71 (dt, *J*=3.6, 11.5 Hz, 1 H), 3.80 (dd, *J*=2.0, 11.5 Hz, 1 H), 4.18 (s, 1 H), 5.05 (s, 1 H), 7.36 (s, 1 H). Found: C, 53.21; H, 6.86; N, 8.82%. Calcd for $C_7H_{11}NO_3$: C, 53.47; H, 7.05; N, 8.91%.

Stoichiometric Reaction of Dichlorobis(trialkylphosphine)-palladium(II) with Amino Alcohol. The reaction of $[PdCl_2(PMe_3)_2]$ with 2-(methylamino)ethanol (**12**) will be described as a typical procedure. To a suspension of $[PdCl_2(PMe_3)_2]$ (0.165 g, 0.50 mmol) in MeCN (4.0 mL), **12** (0.075 g, 1.00 mmol) was added. After the mixture was stirred under CO (1 atm) at room temperature for 1 h, column chromatography on SiO_2 (5 g, eluent: EtOAc–MeOH) gave chloro[*N*-(2-hydroxyethyl)-*N*-methylcarbamoyl]bis(trimethylphosphine)palladium(II) (**38**) (0.189 g, 95%): Colorless prism; R_f=0.40 (SiO_2, EtOAc–MeOH=4 : 1); IR (KBr) 3250 (OH), 1548 (C=O), 1280, 1078, 952 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.43 (dd, *J*=3.7, 3.7, 18 H), 3.42 (s, 3 H), 3.48 (br, 1 H), 3.49 (t, *J*=4.8 Hz, 2 H), 3.70 (dt, *J*=4.6, 4.8 Hz, 2 H); ^{13}C NMR (68 MHz) δ=14.1 (t), 37.3 (t), 50.5, 61.9, 190.1 (t). Found: C, 30.25; H, 6.39; N, 3.62; Cl, 9.24%. Calcd for $C_{10}H_{26}NO_2ClP_2Pd$: C, 30.40; H, 6.63; N, 3.54; Cl, 8.97%.

X-Ray Crystallographical Study of Complex 38. A colorless prismatic crystal of $C_{10}H_{26}O_2ClNP_2Pd$ was mounted on a glass fiber, and all measurements were made on a Rigaku AFC7R diffractometor with graphite monochromated Mo $K\alpha$ radiation and a 12 kW rotating anode generator. Cell constants and an orientation matrix for data, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range of $49.43° < 2\theta < 50.09°$ corresponded to a primitive monoclinic cell. For Z=4 and F_w=396.12, the calculated density is 1.54 g cm^{-3}. The space group was determined to be $P2_1/c$. The data were collected at 20 °C using the ω–2θ scan technique to a maximum 2θ value of 55.1°, and the data were corrected for Lorentz polarization effects. The structure was solved by heavy-atom Patterson methods. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 3081 observed reflections ($I > 4.00\sigma(I)$) and 155 variable parameters. All calculations were performed using the teXsan crystallographic software package of Molecular Corporation. The crystal data and details of data collection are listed in Table 5. Selected bond distances and angles are listed in Table 6. Tables of atomic coordinates, anisotropic displacement parameters, bond lengths, bond angles, non bonded contacts, and complete $F_c - F_o$ data are deposited as Document No. 69040 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Chloro[*N*-(2-hydroxyethyl)-*N*-methylcarbamoyl]bis(triethylphosphine)palladium(II) (37): Pale green paste; IR (neat)

Table 5. Crystal Data for *trans*-[PdCl(CONMeCH$_2$CH$_2$OH)(PMe$_3$)$_2$] (**38**)

Formula	$C_{10}H_{26}O_2ClNP_2Pd$
FW	396.12
Habit	Prismatic
Temp/K	293
Cryst system	Monoclinic
Space group	$P2_1/c$
a/Å	15.567(2)
b/Å	10.049(2)
c/Å	11.563(2)
β/deg	109.18(1)
V/Å^3	1708.3(10)
Z	4
d_{calcd}/g cm^{-3}	1.54
Cryst size/mm	0.5×0.2×0.3
μ(Mo $K\alpha$)/cm^{-1}	14.23
Radiation	Mo $K\alpha$ (λ=0.71069 Å)
Diffractomator	Rigaku AFC7R
Monochromator	Graphite
Scan type	ω–2θ
$2\theta_{max}$/deg	55.1
Scan speed/deg min^{-1}	16.0
No. of unique reflns	4140
No. of reflns used	3081 ($F_o \geq 4\sigma(F_o)$)
No. of variables	155
R	0.042
R_w	0.065

Table 6. Selected Bond Distances (Å) and Angles (deg) for *trans*-[PdCl(CONMeCH$_2$CH$_2$OH)(PMe$_3$)$_2$] (**38**)

	(a) Bond distances		
Pd–Cl	2.422(2)	N–C(1)	1.387(7)
Pd–P(1)	2.316(1)	N–C(2)	1.449(9)
Pd–P(2)	2.312(1)	N–C(4)	1.398(10)
Pd–C(1)	1.995(5)	C(2)–C(3)	1.43(1)
O(1)–C(1)	1.214(7)	O(2)–C(3)	1.45(1)
	(b) Bond angles		
Cl–Pd–P(1)	91.31(5)	Pd–C(1)–N(1)	117.4(4)
Cl–Pd–P(2)	90.85(6)	O(1)–C(1)–N(1)	123.2(5)
Cl–Pd–C(1)	178.8(2)	C(1)–N(1)–C(2)	119.9(6)
P(1)–Pd–P(2)	177.75(5)	C(1)–N(1)–C(4)	124.1(5)
P(1)–Pd–C(1)	88.4(2)	C(2)–N(1)–C(4)	116.0(6)
P(2)–Pd–C(1)	89.5(2)	N(1)–C(2)–C(3)	114.4(7)
Pd–C(1)–O(1)	119.3(4)	O(2)–C(3)–C(2)	114.7(8)

3415 (OH), 2980, 1588 (C=O), 1560, 1040, 770 cm^{-1}; ^{1}H NMR (60 MHz) δ=1.17 (dt, J_{H-H}=7.8 Hz, J_{P-H}=15.7 Hz, 12 H), 1.47—2.05 (m, 12 H), 3.20—3.76 (m, 5 H), 3.39 (s, 3 H).

Stoichiometric Reaction of [PdCl$_2$(PMe$_3$)$_2$] with Amino Alcohol 12 under CO (80 atm). To a suspension of [PdCl$_2$(PMe$_3$)$_2$] (0.82 g, 0.25 mmol) in CDCl$_3$ (2.0 mL), **12** (0.037 g, 0.50 mmol) was added. After the mixture was stirred under CO (1 atm) at room temperature for 1 h, a TLC spot due to complex **12** was observed at R_f=0.40 (SiO$_2$, EtOAc–MeOH=4 : 1). Then the solution was transferred into an autoclave, CO was introduced up to 80 atm, and the mixture was stirred at room temperature for 3 d. The TLC showed a new spot at R_f=0.70 (SiO$_2$, EtOAc–MeOH=4 : 1). The TLC spot at R_f=0.70 disappeared completely and a spot corresponding to complex **38** reappeared at R_f=0.40 after standing overnight under nitrogen.

Reaction of Carbamoylpalladium Complex 38 with CuI under CO–O$_2$ (1 atm). A mixture of complex **38** (0.027 g, 0.07 mmol) and CuI (0.067 g, 0.35 mmol) in MeCN (5.0 mL) was stirred at room temperature under 1 : 1 mixture of CO and O$_2$ (1 atm) for 20 h. The yields of the oxamate **13** and carbamate **26** were determined to be 41 and 48% yields, respectively, on the basis of GLC analysis by using biphenyl as an internal standard.

Reaction of 4-Methylmorpholine-2,3-dione (13) with Grignard Reagents. As a typical example, the preparation of 2-hydroxy-4-methyl-2-phenylmorpholin-3-one (**44**) will be described. To a solution of **13** (0.646 g, 5.00 mmol) in THF (25 mL), a solution of PhMgBr (1.66 M, 3.10 mL, 5.10 mmol) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. After addition of 2 M HCl, THF was removed under reduced pressure. Extraction with CH$_2$Cl$_2$, drying (Na$_2$SO$_4$), and evaporation gave **44** as a pale yellow solid (0.927 g, 89%), which was recrystallized from CH$_2$Cl$_2$–hexane to give an analytically pure sample as colorless fine particles: Mp 103—105 °C; IR (KBr) 3310 (O–H), 2910, 1638 cm^{-1} (NC=O); ^{1}H NMR (60 MHz) δ=2.48—4.56 (m, 5 H), 2.88 (s, 2.2 H), 3.03 (s, 0.8 H), 7.1—8.0 (m, 5 H). Found: C, 63.80; H, 6.33; N, 6.74%. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.72%.

2-Hydroxy-2-isobutyl-4-methylmorpholin-3-one (45): Mp 64.5—65.0 °C; IR (KBr) 3260 (OH), 2955, 1642 (C=O), 1514 cm^{-1}; ^{1}H NMR (270 MHz) δ=0.85 (d, J=6.6 Hz, 3 H), 0.95 (d, J=6.6 Hz, 3 H), 1.68 (dd, J=6.1, 13.2 Hz, 1 H), 1.79 (dh, J=6.1, 6.6 Hz, 1 H), 1.99 (dd, J=6.1, 13.2 Hz, 1 H), 2.97 (s, 3 H), 3.08 (ddd, J=1.0, 3.4, 12.0 Hz, 1 H), 3.68 (dt, J=4.4, 12.0 Hz, 1 H), 3.78 (ddd, J=1.0, 4.4, 12.0 Hz, 1 H), 4.28 (dt, J=3.4, 12.0 Hz, 1 H); ^{13}C NMR (68 MHz) δ=23.0, 23.78, 23.86, 34.7 (NMe), 47.5, 49.1 (C-5), 57.7 (C-6), 97.6 (C-2), 168.8 (C-3).

2-Hydroxy-4-methyl-2-phenethylmorpholin-3-one (46): Mp 106—110 °C; IR (KBr) 3240 (OH), 1638 cm^{-1} (N–C=O); ^{1}H NMR (270 MHz) δ=2.0—3.5 (br, 1 H, OH), 2.10 (ddd, J=5.1, 11.7, 13.4 Hz, 1 H), 2.33 (ddd, J=5.4, 11.5, 13.4 Hz, 1 H), 2.58 (ddd, J=5.4, 11.7, 13.6 Hz, 1 H), 2.79 (ddd, J=5.1, 11.5, 13.6 Hz, 1 H), 2.95 (s, 3 H), 3.08 (ddd, J=1.0, 3.2, 12.2 Hz, 1 H), 3.68 (ddd, J=4.4, 12.0, 12.2 Hz, 1 H), 3.82 (ddd, J=1.0, 4.4, 12.0 Hz, 1 H), 4.29 (dt, J=3.2, 12.0 Hz, 1 H), 7.12—7.28 (m, 5 H); ^{13}C NMR (68 MHz) δ=29.6 (C-2′), 34.6 (NMe), 40.9 (C-1′), 49.1 (C-5), 58.0 (C-6), 97.2 (C-2), 125.9 (*para*), 128.3, 128.4, 141.3 (*ipso*), 168.4 (C-3). Found: C, 66.86; H, 7.21; N, 5.60%. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%.

2-Hydroxy-4-methyl-2-pentylmorpholin-3-one (47): Mp 36.5—37.5 °C; IR (neat) 3320 (OH), 2925, 2870, 1640 cm^{-1} (N–C=O); ^{1}H NMR (270 MHz) δ=0.87 (t, J=6.8 Hz, 3 H), 1.2—1.5 (m, 6 H), 1.7—1.8 (m, 1 H), 1.9—2.1 (m, 1 H), 1.8—3.6 (br, 1 H, OH), 2.99 (s, 3 H), 3.09 (ddd, J=1.2, 3.4, 12.0 Hz, 1 H), 3.67 (dt, J=4.4, 12.0 Hz, 1 H), 3.78 (ddd, J=1.2, 4.4, 12.0 Hz, 1 H), 4.28 (dt, J=3.4, 12.0 Hz, 1 H); ^{13}C NMR (68 MHz) δ=13.9 (C-5′), 22.4 (C-2′), 22.8 (C-4′), 31.6 (C-3′), 34.5 (NMe), 39.3 (C-1′), 49.1 (C-5), 57.8 (C-6), 97.6 (C-2), 168.7 (C-3).

2-(4-Fluorobenzyl)-2-hydroxy-4-methylmorpholin-3-one (48): Mp 64—66 °C; IR (KBr) 3330 (OH), 1640 (N–C=O), 1512, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ=2.5—3.7 (br, 1 H, OH), 2.84 (s, 3 H), 2.92 (ddd, J=1.2, 3.2, 12.0 Hz, 1 H), 3.09 (d, J=13.2 Hz, 1 H), 3.22 (d, J=13.2 Hz, 1 H), 3.24 (dt, J=4.4, 12.0 Hz, 1 H), 3.75 (ddd, J=1.2, 4.4, 12.0 Hz, 1 H), 4.18 (dt, J=3.2, 12.0 Hz, 1 H), 6.95 (t, J=8.8 Hz, 2 H), 7.22—7.27 (m, 2 H); ^{13}C NMR (68 MHz) δ=34.4 (NMe), 44.6 (C-1′), 48.9 (C-5), 58.3 (C-6), 97.5 (C-

2), 114.7 (d, J=22 Hz, *meta*), 130.4 (d, J=13 Hz, *ortho*), 132.2 (d, J=8 Hz, *ipso*), 162.0 (d, J=245 Hz, *para*), 168.0 (C-3).

2-Hydroxy-4-methyl-2-(pentafluorophenyl)morpholin-3-one (49): Mp 128—131 °C; IR (KBr) 3220 (OH), 1648 (N–C=O), 1530, 1496 cm^{-1}; ^1H NMR (DMSO-d_6, 270 MHz) δ=2.91 (s, 3 H), 3.28—3.34 (m, 1 H), 3.63 (dt, J=4.4, 12.0 Hz, 1 H), 3.83 (dd, J=4.4, 12.0 Hz, 1 H), 4.29 (dt, J=3.4, 12.0 Hz, 1 H), 7.89 (br, 1 H, OH); ^{13}C NMR (DMSO-d_6, 68 MHz) δ=33.9 (NMe), 47.9 (C-5), 57.2 (C-6), 95.6 (C-2), 116.6 (br-t, J=13 Hz, *ipso*), 137.0 (br-dt, J=249, 13 Hz, *meta*), 140.2 (br-d, J=251 Hz, *para*), 144.8 (br-d J=251 Hz, *ortho*).

2-Hydroxy-4-methyl-2-(3-trifluoromethylphenyl)morpholin-3-one (50): Mp 127—128 °C; IR (KBr) 3374 (OH), 1638 (N–C=O), 1337, 1171, 1132, 1111 cm^{-1}; ^1H NMR (DMSO-d_6, 270 MHz) δ=2.85 (s, 3 H), 3.27 (dd, J=3.4, 12.0 Hz, 1 H), 3.79 (dt, J=4.4, 12.0 Hz, 1 H), 3.90 (dd, J=4.4, 12.0 Hz, 1 H), 4.33 (dt, J=3.4, 12.0 Hz, 1 H), 7.48 (s, 1 H), 7.57 (t, J=7.6 Hz, 1 H), 7.68 (t, J=7.6 Hz, 1 H), 7.84 (t, J=7.6 Hz, 1 H), 7.86 (s, 1 H); ^{13}C NMR (DMSO-d_6, 68 MHz) δ=34.0 (NMe), 48.5 (C-5), 57.2 (C-6), 95.6 (C-2), 123.3 (q, J=4 Hz), 124.3 (q, J=272 Hz, CF_3), 124.7 (q, J=4 Hz), 128.2 (q, J=31 Hz), 128.4, 130.9, 143.3, 165.9 (C-3). Found: C, 52.36; H, 4.38; N, 5.12%. Calcd for $C_{12}H_{12}NO_3F_3$: C, 52.36; H, 4.40; N, 5.09%.

Synthesis of α-Oxo Carboxylic Acids. As a typical example, hydrolysis of hemiketal **44** to give phenylglyoxylic acid (**51**) was described. A mixture of hemiketal **44** (0.415 g, 2.0 mmol) and 2 M HCl (4 mL) was refluxed for 2 h. After cooling to room temperature, the reaction mixture was extracted with CH_2Cl_2. The combined extracts were washed with an aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to give **51** (0.281 g, 94%)[29] as a pale yellow solid: IR (KBr) 3000 (OH), 1742 (C=O), 1661 (C=O), 1595, 1453, 1204 cm^{-1}; ^1H NMR (60 MHz) δ=7.2—7.7 (m, 3 H), 7.9—8.2 (m, 2 H, *ortho*), 9.63 (br-s, 1 H, OH).

4-Methyl-2-oxopentanoic Acid (52):[29] IR (neat) 3100 (OH), 1728 (COCO), 1474 cm^{-1}; ^1H NMR (60 MHz) δ=0.98 (d, J=6.0 Hz, 6 H), 1.8—2.6 (m, 1 H), 2.80 (d, J=6.4 Hz, 2 H), 8.89 (br-s, 1 H, OH).

2-Oxo-4-phenylbutanoic Acid (53):[29] IR neat 3200 (OH), 3031, 1730 (COCO), 1605, 700 cm^{-1} (s); ^1H NMR (60 MHz) δ=2.7—3.3 (m, 4 H), 7.14 (s, 5 H), 8.23 (br-s, 1 H, OH).

2-Oxoheptanoic Acid (54):[29] IR (melt) 3100 (OH), 2950, 2870, 1730 cm^{-1} (COCO); ^1H NMR (60 MHz) δ=0.7—3.1 (m, 11 H), 8.37 (br-s, 1 H, OH).

3-(4-Fluorophenyl)-2-oxopropanoic Acid (55):[29] Mp 136—139 °C; IR (KBr) 3480, 3150 (OH), 1700 (C=O), 1624 (C=O), 1246, 1196 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz), δ=6.39 (s, 2 H), 6.9—7.3 (m, 2 H, *meta*), 7.6—7.9 (m, 2 H, *ortho*), 7—10 (br, 1 H, OH); ^{13}C NMR (DMSO-d_6, 68 MHz), δ=108.4 (C-3), 115.1 (d, J=21 Hz, *meta*), 131.1 (d, J=8 Hz, *ortho*), 141.5 (d, J=3 Hz, *ipso*), 161.0 (d, J=245 Hz, *para*), 160.2, 192.0.

Pentafluorophenylglyoxylic Acid (56): IR (KBr) 3000 (OH), 1724 (COCO), 1650, 1524, 1502, 1324, 1156, 988 cm^{-1}; ^1H NMR (60 MHz) δ=9.4 (br, OH); ^{13}C NMR (68 MHz) δ=110.0 (dd, J=4, 16 Hz, *ipso*), 137.8 (ddt, J=16, 254, 14 Hz, *meta*), 144.8 (dtt, J=262, 5, 13 Hz, *para*), 145.9 (dddt, J=4, 6, 260, 14 Hz, *ortho*).

3-Trifluoromethylphenylglyoxylic Acid (57): Mp 91.5—92.0 °C; IR (KBr) 3100 (OH), 1730 (C=O), 1698 (C=O), 1613, 1333, 1198, 1173, 693, 673 cm^{-1}; ^1H NMR (270 MHz) δ=7.70 (t, J=7.8 Hz, 1 H), 7.8 (br, 1 H), 7.95 (d, J=7.8 Hz, 1 H), 8.50 (d, J=7.8 Hz, 1 H), 8.54 (s, 1 H); ^{13}C NMR (68 MHz) δ=127.3 (q, J=275 Hz, CF_3), 127.8 (q, J=4 Hz, C-4), 129.7, 131.7 (q, J=4 Hz, C-2), 131.7 (q, J=33 Hz, C-3), 132.4, 134.2, 161.9, 183.6.

Preparation of 3-Hydroxy-3-(3-trifluoromethylphenyl)octahydropyrido[2,1-*c*][1,4]oxazin-4-one (58). The reaction of octahydropyrido[2,1-*c*][1,4]oxazine-3,4-dione (**19**) (1.02 g, 6.02 mmol) with *m*-$CF_3C_6H_4MgBr$ (7.3 mmol) according to the procedure described above gave hemiketal **58** (1.82 g, 96%) as pale yellow crystals, which was recrystallized from CH_2Cl_2–hexane to give colorless prisms (1.56 g): Mp 129—130 °C; IR (KBr) 3220 (OH), 1630 (C=O), 1333, 1113 cm^{-1}; ^1H NMR (60 MHz) δ=0.4—2.2 (m, 6 H), 2.2—2.9 (m, 1 H), 2.9—4.8 (m, 4 H), 4.8—5.8 (br, 1 H, OH), 6.9—8.5 (m, 4 H).

Preparation of 3-Methoxy-3-(3-trifluoromethylphenyl)octahydropyrido[2,1-*c*][1,4]oxazin-4-one (59). To a suspension of NaH (0.14 g, 60% w/w dispersion in oil, 3.5 mmol, washed twice with dry *n*-pentane) in THF (5 mL) was added a solution of **58** (0.732 g, 2.32 mmol) and MeI (0.22 g, 3.5 mmol) in THF (5 mL) dropwise over a period of 10 min. After the mixture was stirred at 50 °C for 1 h, water (5 mL) was added dropwise. Evaporation of THF, extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation gave **59** (0.688 g, 90%) as a pale yellow solid.

Preparation of 3- (3- Trifluoromethylphenyl)octahydropyrido[2,1-*c*][1,4]oxazin-4-one (60). To a solution of **59** (0.674 g, 2.05 mmol) in CH_2Cl_2 (3 mL) were added dropwise $TiCl_4$ (1.27 g, 11.6 mmol) and a solution of Et_3SiH (0.92 g, 5.8 mmol) in CH_2Cl_2 (3 mL) successively at −78 °C under argon. After the suspension was stirred at −78 °C for 3 h and at room temperature for 30 min, water (5 mL) was added dropwise. Extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation gave a colorless oil, which was chromatographed (SiO_2 13 g, $CHCl_3$–hexane=4 : 1 as eluent) to give **60** (0.525 g, 86%) as a colorless oil: IR (neat) 2940, 1654 (C=O), 1444, 1324, 1264, 1158, 1118 cm^{-1}; ^1H NMR (60 MHz) δ=1.1—2.2 (m, 6 H), 2.2—2.9 (m, 1 H), 3.2—4.3 (m, 3 H), 4.3—4.9 (m, 1 H), 5.07 (s, 1 H), 7.2—7.9 (m, 4 H, ArH).

Preparation of 3- (3- Trifluoromethylphenyl)octahydropyrido[2,1-*c*][1,4]oxazine (61).[32] To a suspension of $LiAlH_4$ (0.067 g, 1.77 mmol) in THF (2 mL) was added a solution of **60** (0.525 g, 1.75 mmol) in THF (2.5 mL) dropwise at room temperature. After the suspension was refluxed for 15 h, water (5 mL) was added dropwise. Extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation gave **61** (0.408 g, 82%) as a pale yellow oil: IR (neat) 2940, 2855, 1122, 800, 700 cm^{-1}; ^1H NMR (270 MHz) δ=1.08—1.42 (m, 2 H), 1.52 (dd, J=2.7, 12.5 Hz, 1 H), 1.60—1.71 (m, 2 H), 1.82 (br-d, J=13 Hz, 1 H), 2.05—2.15 (m, 2H), 2.17 (dd, J=10.5, 11.5 Hz, 1 H), 2.77—2.85 (m, 1 H), 2.86 (dd, J=2.2, 11.5 Hz, 1 H), 3.46 (dd, J=10.5, 11.2 Hz, 1 H), 3.87 (dd, J=3.2, 11.2 Hz, 1 H), 4.72 (dd, J=2.2, 10.5 Hz, 1 H), 7.40 (t, J=7.8 Hz, 1 H), 7.51 (d, J=7.8 Hz, 2 H), 7.63 (s, 1 H); ^{13}C NMR (68 MHz) δ=23.8, 25.4, 27.0, 55.4, 60.8, 61.8, 72.2, 77.6, 122.8 (q, J=3 Hz), 124.0 (q, J=271 Hz, CF_3), 124.3 (q, J=3 Hz), 124.3 (q, J=40 Hz), 128.6, 129.4, 141.4.

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