Mechanism of Amidocarbonylation: A Stereochemical Approach†

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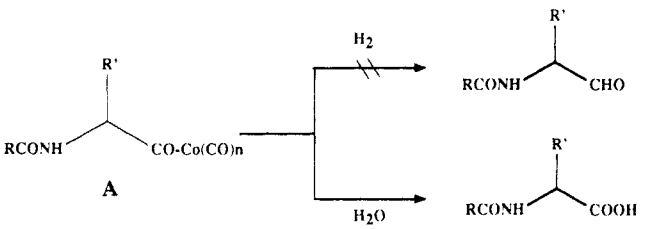
The mechanism of $Co_2(CO)_8$-catalyzed amidocarbonylation of aldehyde is studied on the basis of a stereochemical approach. This study is focused on the distinction of the "azlactone pathway", which has been proposed for some time, and the "direct hydrolysis of an acylcobalt species pathway" in order to account for the selective formation of carboxylic acid instead of aldehyde under a high pressure of hydrogen. Three α-methallyllactams, 4-(2-methyl-2-propenyl)azetidin-2-one (**1**), 5-(2-methyl-2-propenyl)pyrrolidin-2-one (**2**), and 6-(2-methyl-2-propenyl)piperidin-2-one (**3**), have been chosen as the substrates for the study. The MMX calculations of the key intermediates, bicyclic (α-amidoalkanoyl)cobalt species, reveal that (i) if the azlactone formation were the requisite, only **3** (or its hemiamidal intermediate **6**) would give the amidocarbonylation product, the bicyclic *N*-acyl amino acid (**15**), (ii) if the coordination of amide carbonyl to the cobalt metal center were the essential factor, both **3** and **2** (or their hemiamidal intermediates, **6** and **5**) would give the corresponding bicyclic α-acylamino acids (**15** and **14**), and (iii) as far as either the azlactone formation or the coordination of amide carbonyl to the cobalt metal center is indispensable, **1** (or its hemiamidal intermediate **4**) would not give any bicyclic α-acyl amino acid (**13**). In fact, the attempted amidocarbonylation of **1** and its *O*-ethyl hemiamidal (**19**) obtained in the $RhCl(PPh_3)_3$-catalyzed hydrocarbonylation does not give any acid or ester product (**13** or **13**-OEt) but affords a bicyclic enamide (**16**). In sharp contrast to this, the reactions of **2** and **3** and their *O*-ethyl hemiamidals (**20**, **21**) afford the corresponding bicyclic α-acyl amino acids and their esters (**14**, **15**; **14**-OEt, **15**-OEt). The results clearly indicate that the direct hydrolysis of acylcobalt species pathway is the actual mechanism of amidocarbonylation, and thus, the coordination of the amide carbonyl to the cobalt metal center bearing a water molecule as an aquo ligand is crucial for the suppression of hydrogenolysis and promotes the unique hydrolysis even under a high pressure of hydrogen.

Introduction

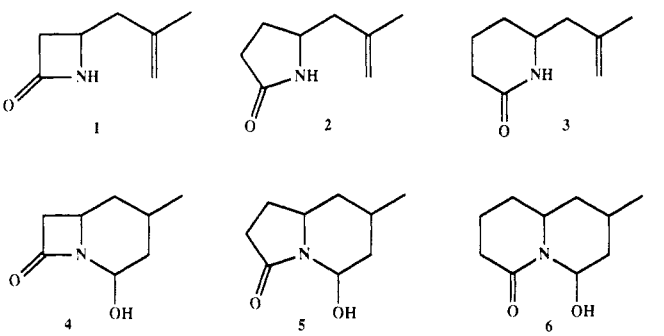
The cobalt-catalyzed amidocarbonylation of aldehydes was discovered in 1971 by Wakamatsu et al. and developed by Ajinomoto's research group as an industrial process for α-amino acid synthesis.[1] Further applications of this reaction, e.g., to the synthesis of heterocyclic compounds, have been developed by Izawa et al.[2] We also have demonstrated successful applications to the isomerization–amidocarbonylation of allylic alcohols and oxiranes[3] and hydroformylation–amidocarbonylation of fluoro olefins[3,4] for the synthesis of the corresponding *N*-acyl α-amino acids using mixed bimetallic catalyst systems. In the last few years, there has been an increasing significance and attention to those hydrocarbonylations involving amidocarbonylation as the key step in the practical synthesis of a variety of amino acid related intermediates and biologically active compounds.[5,6]

One of the most curious aspects of the amidocarbonylation is that the acyl–cobalt bond is not cleaved reductively by hydrogen but is hydrolyzed by water generated in situ in the catalytic cycle. This fact is amazing, since the (α-amidoalkanoyl)cobalt species does not give aldehyde at all in the presence of a large excess of hydrogen (1000–3000 psi) under the typical $Co_2(CO)_8$-catalyzed hydroformylation conditions.



†This paper is dedicated to the late Professor John K. Stille for his outstanding achievement and contribution to the advancement of homogeneous catalysis and its application to organic synthesis and polymer science.

Chart I



A couple of possible mechanisms have been proposed by Wakamatsu,[1b] Pino,[7] Izawa,[2] and Magnus[8] and their coworkers, but no unambiguous evidence has been presented, and thus, it is still controversial. Therefore, it is very

(1) (a) Wakamatsu, H., Uda, J.; Yamakami, N. *J. Chem. Soc. D* **1971**, 1540. (b) Wakamatsu, H. *Sekiyu Gakkaishi* **1974**, *17*, 105.
(2) (a) Izawa, K.; Nishi, S.; Asada, S. *J. Mol. Catal.* **1987**, *41*, 135. (b) Izawa, K. *Yuki Gosei Kagaku Kyokaishi* **1988**, *46*, 218.
(3) (a) Ojima, I.; Hirai, K.; Fuchikami, T. *J. Organomet. Chem.* **1985**, *279*, 203. (b) Ojima, I. *J. Mol. Catal.* **1986**, *37*, 25.
(4) (a) Ojima, I.; Okabe, M.; Kato, K.; Kwon, H. B.; Horváth, I. T. *J. Am. Chem. Soc.* **1988**, *110*, 150. (b) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011. (c) Ojima, I. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp 51–97.
(5) (a) Lin, J.; Knifton, J. F. New Science in Homogeneous Transition Metal Catalyzed Reactions. *Abstracts of Papers*, 199th American Chemical Society National Meeting, April 22–27, 1990, Boston, MA; American Chemical Society: Washington, DC, 1990; CATAL 40. (b) Haggin, J. *Chem. Eng. News* **1990**, *68* (May 21), 32.
(6) (a) Ojima, I.; Zhang, Z. *J. Org. Chem.* **1988**, *53*, 4422. (b) Ojima, I.; Korda, A. *Tetrahedron Lett.* **1989**, *30*, 6283. (c) Ojima, I. In *Future Opportunities in Catalytic and Separation Technology*; Misono, M., Moro-oka, Y., Kimura, S., Eds.; Studies in Surface Science and Catalysis 54; Elsevier: Amsterdam, 1990; Chapter IV.1., pp 301–321. (d) For application to the synthesis of isotope-labeled amino acids, see: Yuan, S.-S.; Ajami, A. M. *J. Chin. Chem. Soc. (Taipei)* **1989**, 36, 479 and references cited therein.
(7) Parnaud, J.; Campari, G.; Pino, P. *J. Mol. Catal.* **1979**, *6*, 341.
(8) Magnus, P.; Slater, M. *Tetrahedron Lett.* **1987**, *28*, 2829.

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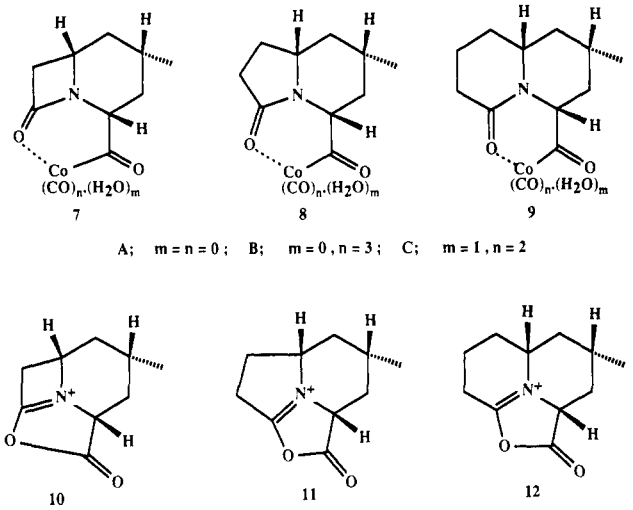
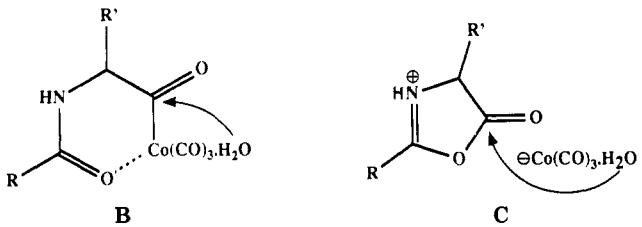
Chart II



important to clarify this historical mystery in the mechanism of the amidocarbonylation.

We planned to elucidate the mechanism by focusing on the following two points. (i) Is the coordination of the amide carbonyl to the acylcobalt the most significant factor in promoting the hydrolysis? (This coordination may prevent the oxidative addition of molecular hydrogen.)[9] (ii) Is the azlactone formation the most significant factor in preventing the hydrogenolysis and promoting the hydrolysis?



Results and Discussion

Three cyclic amides having methallyl side chains (**1–3**) were chosen as the substrates for this mechanistic study by stereochemical approach. According to the widely accepted mechanism of the amidocarbonylation of an aldehyde, the first step is to form a hemiamidal, which is followed by the nucleophilic substitution of a hydroxy group by $[Co(CO)_4]^-$ and a carbonyl insertion to give an (α-amidoalkanoyl)cobalt intermediate, which then gives an *N*-acyl α-amino acid by direct hydrolysis or via an azlactone intermediate followed by hydrolysis.[1-3,7] If the cyclic hemiamidals **4–6**, which are supposed to be formed after the initial hydroformylation followed by cyclization, undergo the above-mentioned process, the corresponding bicyclic (α-amidoalkanoyl)cobalt complexes **7–9** should be formed.

We carried out molecular mechanics energy calculation for **7–9** (A–C) using the MMX program.[10] Results are summarized in Table I. We also performed the MMX energy calculation for the corresponding azlactones **10–12**. Results are also summarized in Table I. Chart II illustrates the stereochemistry of the lowest energy isomers for **7–12**. As Table I shows, the MMX energies (E_{rel}) for **7** and **8** relative to that for **9** for three different cobalt metal moieties (A–C) are +32.08–32.57 and +1.11–1.45 kcal/mol, respectively, and the MMX energies (E_{rel}) for **10** and **11** relative to that for **12** are +50.07 and +12.16 kcal/mol, respectively. Thus, it is anticipated that (i) the formation of **7** is highly unlikely while the chelated intermediate **8** can be formed and (ii) the formation of **10** is virtually impossible and that of **11** is very difficult. Since there is no significant strain in the structures of **9** and **12**, those intermediates can be formed without any difficulty.

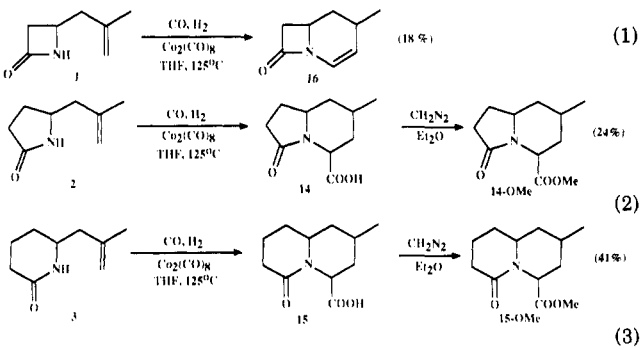
Table I. MMX Energies for Bicyclic (α-Amidoalkanoyl)cobalt Complexes 7–9 and Azlactones 10–12[a]

	7A[b]	8A[b]	9A[b]	7B[c]	8B[c]	9B[c]
MMX energy, kcal/mol	33.36	2.96	1.77	35.98	4.86	3.41
rel MMX energy, kcal/mol	+31.59	+1.19	0	+32.57	+1.45	0
	7C[d]	**8C[d]**	**9C[d]**	**10**	**11**	**12**
MMX energy, kcal/mol	34.98	4.01	2.90	54.29	16.38	4.22
rel MMX energy, kcal/mol	+32.08	+1.11	0	+50.07	+12.16	0

[a] The MMX energy minimization was carried out with all possible diastereomers, and this table shows energies only for the most stable diastereomer in every case. [b] Energy calculations were run with a hypothetical coordinatively saturated cobalt metal (18e) without any ligands other than the bicyclic α-amidoalkanoyl moiety. [c] Energy calculations were run with a trigonal-bipyramidal coordinatively saturated cobalt metal bearing three carbon monoxide ligands. [d] Energy calculations were run with a trigonal-bipyramidal coordinatively saturated cobalt metal with two carbon monoxide ligands and one aquo ligand. Calculations were performed for all possible stereoisomers with regard to the position of the aquo ligand, and it has turned out that the isomer bearing an apical aquo ligand (water molecule and the amide moiety occupy two apical positions) is the most stable. Thus, this table shows the energy only for the most stable isomer.

Accordingly, it is reasonable to assume that (i) **1** would not give the corresponding amidocarbonylation product 4-methyl-8-oxo-1-azabicyclo[4.2.0]octane-2-carboxylic acid (**13**), if either the azlactone formation or the coordination of amide carbonyl to the cobalt were indispensable for the reaction, (ii) **2** may give the amidocarbonylation product 4-methyl-9-oxo-1-azabicyclo[4.3.0]nonane-2-carboxylic acid (**14**), if only the coordination of amide carbonyl to the cobalt were the requisite for the reaction, but **2** would not give **14** if the azlactone formation were essential, and (iii) **3** would give the amidocarbonylation product 4-methyl-10-oxo-1-azabicyclo[4.4.0]decane-2-carboxylic acid (**15**), since this ring system fulfills both requisites for the reaction.

In order to examine our hypothesis, we carried out the hydroformylation–amidocarbonylation of **1–3** catalyzed by $Co_2(CO)_8$ under the standard conditions, i.e., at 125 °C and 2000 psi (CO/H_2 = 1) in the presence of 10 mol % of the catalyst. After the reaction and usual workup, the reaction mixture was treated with diazomethane for GLC analysis and isolation. As eqs 1–3 show, the reactions of **2** and **3**

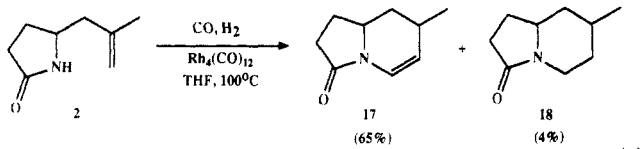


(9) This possibility was pointed out together with the azlactone pathway by Izawa without conclusive supporting evidence.[2b]

(10) The MMX program, developed by Gajewski and Gilbert, was obtained from Serena Software, Bloomington, IN.

gave the corresponding bicyclic amino acid methyl esters **14**-OMe and **15**-OMe, in 24% and 41% isolated yields (27% and 43% GLC yields), respectively. The only moderate isolated yields for **14**-OMe and **15**-OMe can mainly be ascribed to the inefficiency of the hydroformylation of disubstituted olefins with the cobalt catalyst under the given conditions. The attempted amidocarbonylation of **1** under the standard conditions resulted in the formation of 4-methyl-1-azabicyclo[4.2.0]oct-2-en-8-one (**16**) as the sole carbonylation product;[11] i.e., any **13** or **13**-OMe (after diazomethane treatment) was not detected at all, and a substantial amount of the starting material (**1**) was recovered.

Since hemiamidal has been considered as a key intermediate for amidocarbonylation,[1-8] we tried to isolate this intermediate by using rhodium catalysts. In fact, in a previous paper,[6] we reported the selective synthesis of a five-membered monocyclic hemiamidal by a $Rh_4(CO)_{12}$-catalyzed hydroformylation of 2-methyl-2-propenylbenzamide. However, the attempted synthesis of a hemiamidal (**6**) through a rhodium complex catalyzed reaction of **2** at 100 °C and 1200 psi (CO/H_2 = 5) resulted in the formation of a mixture of 4-methyl-1-azabicyclo[4.3.0]non-2-en-9-one (**17**; 94%) and 4-methyl-1-azabicyclo[4.3.0]nonan-2-one (**18**; 6%) in 69% overall yield (eq 4). In contrast with this,



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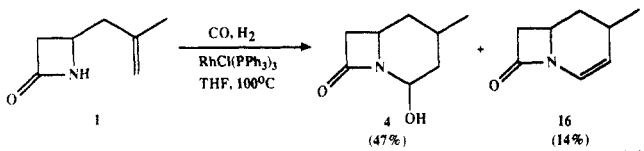
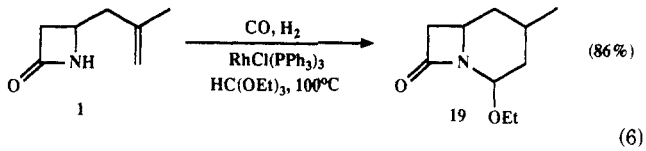


(5)

the reaction of **1** under similar conditions, i.e., at 100 °C and 1800 psi (CO/H_2 = 1), gave the desired bicyclic hemiamidal (**4**) as the predominant product (77%) accompanied by a small amount of 4-methyl-1-azabicyclo[4.2.0]-oct-2-en-8-one (**16**; 23%) in 61% overall yield (eq 5). The attempted carboxylation of **4** with $Co_2(CO)_8$ as the catalyst under the standard amidocarbonylation conditions, i.e., at 125 °C and 2000 psi (CO/H_2 = 1) in THF, did not give the corresponding bicyclic amino acid (**13**) or its methyl ester (**13a**) after diazomethane treatment of the reaction mixture. The reaction was not clean, but **16** was detected as a major product.

When the reactions of **1**–**3** were carried out with ethyl orthoformate as the solvent[12] at 100 °C and 1800 psi (CO/H_2 = 1), the corresponding bicyclic *O*-ethyl hemiamidals **19**–**21** were successfully obtained in good yields (eqs 6–8), which were supposed to serve as key intermediates for amidocarbonylation, giving *N*-acyl α-amino acid esters.

The reactions of the bicyclic *O*-ethyl hemiamidals **20** and **21** at 125 °C and 2000 psi (CO/H_2 = 1) catalyzed by $Co_2(CO)_8$ gave the corresponding bicyclic amino acid ethyl esters **14**-OEt and **15**-OEt, in 50% and 70% yields, respectively (eqs 9 and 10). On the other hand, the reaction of **19** did not give **13**-OEt but afforded **16** and its saturated counterpart **16a** as major products (eq 11).



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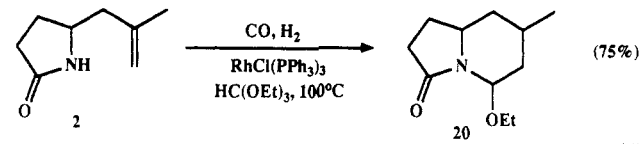

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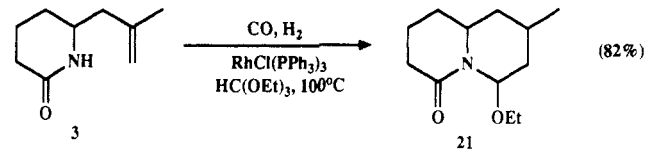

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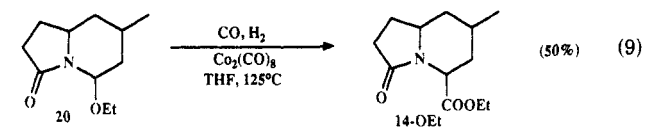

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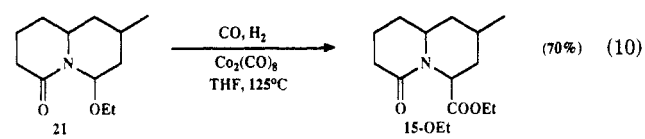

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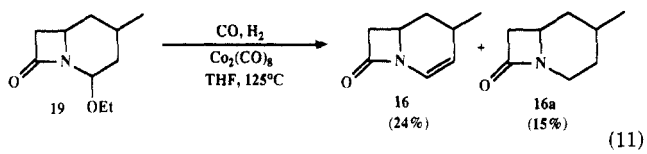

(11)

Although Magnus et al.[8] proposed that a carboxylic acid moiety is introduced by the hydrolysis of an azlactone formed *at workup*, our results, shown in eqs 9 and 10, clearly demonstrate that the amidocarbonylation products **14**-OEt and **15**-OEt are formed prior to workup since the ethyl esters **14**-OEt and **15**-OEt were obtained as the sole amidocarbonylation products in spite of the usual workup, including alkaline treatment in order to remove cobalt species followed by acidification.[13] Therefore, the mechanism proposed by Magnus et al.[8] is ruled out.

On the basis of the observed clear difference in the reaction pattern between **1** and **2** or **3** as well as **19** and **20** or **21**, we can conclude that the coordination of the amide carbonyl to the cobalt metal center and/or the azlactone formation is indeed essential for amidocarbonylation, giving *N*-acyl α-amino acids or their esters. According to our hypothesis on the basis of a molecular modeling study (vide supra), the fact that **2** and **20** give the amidocarbonylation products clearly indicates that (i) the coordination of the amide carbonyl to the cobalt metal center is essential for amidocarbonylation and (ii) azlactone formation is *not* necessary.

Consequently, it is concluded that the coordination of the amide oxygen to the acylcobalt species (vide supra) prevents the central cobalt from the oxidative addition of molecular hydrogen so that the very unique hydrolysis (or alcoholysis) of the acyl–cobalt bond by the in situ gener-

(11) A similar reaction with 4-allylazetidin-2-one (**1a**) was reported by Izawa et al. to give 1-azabicyclo[4.2.0]oct-2-en-8-one (**16a**) as the only product, without details, in the following meeting abstracts: (a) Izawa, K.; Nishi, S.; Asada, S. *32nd Symposium on Organometallic Chemistry*, Osaka, Japan, Nov 5–6, 1985; Kinki Chemical Society: Osaka, Japan, 1985; Abstract B114, p 116. (b) Izawa, K.; Nishi, S. 52nd Chemical Society of Japan Annual Meeting, Kyoto, Japan, April 1–4, 1986; The Chemical Society of Japan: Tokyo, Japan, 1986; Abstracts 3W41, p 1450.

(12) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122.

(13) Izawa has also demonstrated that monocyclic *O*-methyl amidal gives the corresponding methyl ester in the $Co_2(CO)_8$-catalyzed reaction.[2]

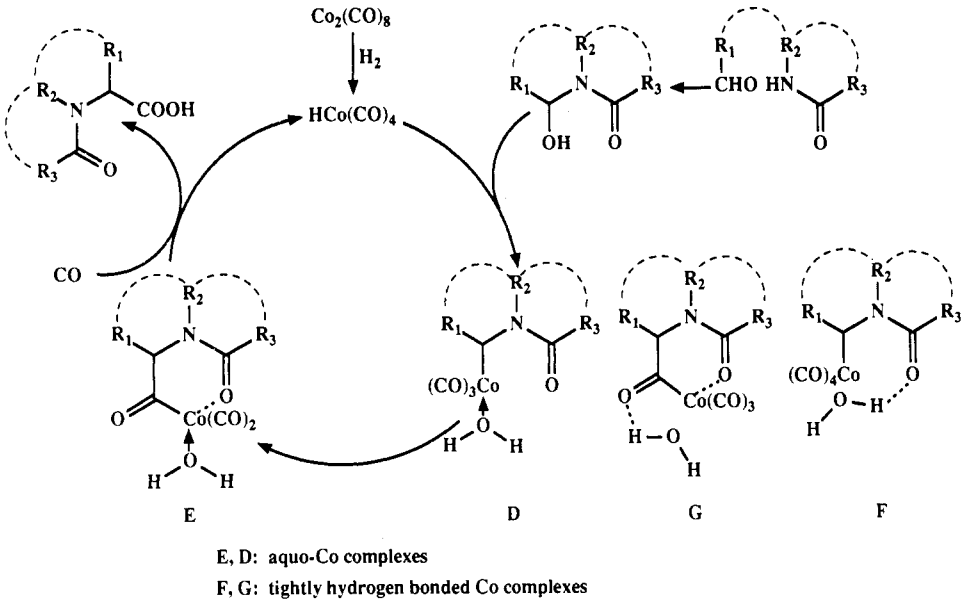

Figure 1. Proposed mechanism of amidocarbonylation.

ated water (or alcohol) takes place even under a high pressure of hydrogen.

It should be noted that the cobalt catalyst is unique in amidocarbonylation; i.e., no other metals have been found to promote the reaction as well as cobalt so far. The fact that cobalt can form stable aquated complexes may account for this uniqueness.[14] Since no additional water (or alcohols) is necessary for the reaction to give carboxylic acid (or ester), the in situ generated water (or alcohol) molecule should be in the proximity of the acyl–cobalt bond to cleave it efficiently, as exemplified in the structures of D and E. Another possibility is the formation of tightly hydrogen-bonded aquated complexes F and G. A proposed general mechanism of amidocarbonylation taking into account these aquated complexes is depicted in Figure 1.

Experimental Section

General Method. Melting points were measured with a Thomas-Hoover Unimelt apparatus and are uncorrected. The ^{1}H NMR spectra were measured with a Nicolet NT-300 or a General Electric QE-300 spectrometer with tetramethylsilane as the internal standard. ^{13}C NMR spectra were measured with a General Electric QE-300 spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 1600 FT-IR spectrophotometer with samples as neat liquids or KBr disks. Mass spectra (GCMS) were recorded on a Hewlett-Packard HP 5980A mass spectrometer equipped with a HP 5710A gas chromatograph and a HP 5933A data system. High-resolution mass spectra (HRMS) were measured with a Kratos MS-890 mass spectrometer equipped with a Carlo Erba gas chromatograph and a Kratos DS-90 data station. Analytical gas chromatography was carried out with a Hewlett-Packard 5890A gas chromatograph with a Hewlett-Packard HP 3396A integrator or a Perkin-Elmer 3920 gas chromatograph with a Hewlett-Packard HP 3393A integrator using columns packed with Dexsil-300 or OV-17. Elemental analyses were performed at the M-H-W Laboratories, Phoenix, AZ.

Materials. Dicobalt octacarbonyl was purchased from Strem Chemicals, Inc., and used as purchased. Tetrarhodium dodecacarbonyl,[15] methallyltrimethylsilane,[16] 5-ethoxy-2-pyrrolidinone,[17] and 6-ethoxy-2-piperidone[17] were prepared by the literature methods. Silica gel used for chromatography, MN-Kieselgel 60 (silica gel 60), was purchased from Brinkmann Instruments, Inc. All other chemicals were purchased from Aldrich Chemical Co., Inc.

Preparation of 4-(2-Methyl-2-propenyl)azetidin-2-one (1). To a solution of 4-acetoxy-2-azetidinone (0.961 g, 7.45 mmol) and methallyltrimethylsilane (15.1 mmol) in 60 mL of CH_2Cl_2 was added 1.27 g (8.93 mmol) of boron trifluoride etherate at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture was poured into brine when TLC indicated completion of the reaction. The organic layer was separated, and the solvent was removed by distillation under reduced pressure. The reaction mixture was purified by column chromatography on silica gel (EtOAc/hexane = 1) to give 1 as a pale yellow oil (0.588 g, 63% yield): ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3 H), 2.32 (d, J = 6.8 Hz, 2 H), 3.10 (m, 1 H), 4.71 (s, 1 H), 4.83 (s, 1 H), 6.42 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.68, 43.58, 46.47, 72.89, 112.32, 141.84, 168.59; IR (neat, cm^{-1}) 3260 (ν_{NH}), 1755 (ν_{CO}). Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.99; H, 8.66; N, 11.16.

Preparation of 5-(2-Methyl-2-propenyl)pyrrolidin-2-one (2). To a solution of 5-ethoxy-2-pyrrolidinone (0.487 g, 3.77 mmol) and methallyltrimethylsilane (7.5 mmol) in 50 mL of CH_2Cl_2 was added 0.54 g (3.80 mmol) of boron trifluoride etherate at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture poured into brine when TLC indicated completion of the reaction. The organic layer was separated, and the solvent was removed by distillation under reduced pressure. The reaction mixture was purified by column chromatography on silica gel (eluant: EtOAc/hexane = 1) to give 0.318 g (60.7% yield) of 2 as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.68–1.73 (m, 1 H), 1.75 (s, 3 H), 2.20–2.38 (m, 5 H), 3.81 (m, 1 H), 4.75 (s, 1 H), 4.85 (s, 1 H), 6.77 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.33, 26.87, 30.04, 44.86, 52.16, 112.84, 141.55, 177.82; IR (neat, cm^{-1}) 3236 (ν_{NH}), 1694 (ν_{CO}). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.16; H, 9.27; N, 9.94.

Preparation of 6-(2-Methyl-2-propenyl)piperidin-2-one (3). In a similar manner, 6-methallyl-2-piperidone (3) was obtained as a white solid (1.26 g, 50.0% yield) by using 6-ethoxy-2-piperidone (2.12 g, 14.8 mmol), methallyltrimethylsilane (4.34 g, 22.2 mmol), and boron trifluoride etherate (2.10 g, 14.8 mmol): mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 1 H), 1.66–1.77 (m, 2 H), 1.73 (s, 3 H), 1.91 (m, 1 H), 2.37–2.14 (m, 4 H), 3.51 (m, 1 H), 4.79 (s, 1 H), 4.90 (s, 1 H), 6.48 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.68, 21.80, 28.65, 31.05, 45.08, 49.83, 114.17, 140.49, 172.03; IR (KBr, cm^{-1}) 3194 (ν_{NH}), 1654 (ν_{CO}). Anal. Calcd for $C_9H_{15}NO$:

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C, 70.55; H, 9.87; N, 9.14. Found: C, 70.50; H, 9.82; N, 8.96.

Hydroformylation–Amidocarbonylation of α-Methallyllactams (2 and 3) Catalyzed by $Co_2(CO)_8$. A 50-mL round-bottomed flask with a septum was charged with $Co_2(CO)_8$ (0.30 mmol) and THF (4.5 mL) under argon, and the catalyst solution was stirred for 20 min. The catalyst solution was transferred by a syringe to a 50-mL reaction vessel containing the substrate (**2** or **3**; 3.0 mmol), and the reaction vessel was placed in a 300-mL stainless steel autoclave. The reaction was run at 125 °C and 2000 psi (CO/H_2 = 1) for 18 h (standard amidocarbonylation conditions in this study). After the pressure was released from the autoclave, the solvent was removed. The reaction mixture was dissolved in 10% aqueous sodium carbonate and the solution extracted with ethyl acetate. Two layers were separated. The aqueous layer was then acidified with phosphoric acid and extracted with ethyl acetate. The removal of the solvent in vacuo from the extract gave the products (carboxylic acids), which were dissolved in chloroform, and then a excess amount of a solution of diazomethane in ether was added. The mixture was stirred overnight at room temperature. The solvent was removed to afford the corresponding methyl ester (**14**-OMe or **15**-OMe). The esters were submitted to GLC and NMR analyses and then purified by column chromatography on silica gel with CH_2Cl_2/MeOH (30/1) as the eluant.

2-Carbomethoxy-4-methyl-1-azabicyclo[4.3.0]nonan-9-one (14-OMe) (a mixture of two diastereomers (1:1)): 24% yield; colorless oil; ^1H NMR ($CDCl_3$) δ [0.93 (d, J = 6.8 Hz), 1.05 (d, J = 6.8 Hz)] (3 H), 1.20–2.60 (m, 9 H), 3.40 (m, 1 H), 3.68 (s, 3 H), 4.09 (m, 1 H); IR (neat, cm^{-1}) 1732 (ν_{CO}), 1694, 1682 (ν_{CO}); MS (m/e) 211 (2, M^+), 152 (100), 110 (36), 84 (18), 41 (21); HRMS (m/e) calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1194.

2-Carbomethoxy-4-methyl-1-azabicyclo[4.4.0]decan-10-one (15-OMe) (a mixture of two diastereomers (1:1)): 41% yield; colorless oil; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.6 Hz, 3 H), 1.33–2.18 (m, 7 H), 2.34–2.46 (m, 3 H), 3.53 (m, 1 H), [3.67 (s), 3.73 (s)] (3 H), 4.15 (m, 1 H), 4.64 (m, 1 H); IR (neat, cm^{-1}) 1738 (ν_{CO}), 1644 (ν_{CO}); MS (m/e) 225 (6, M^+), 166 (100); HRMS (m/e) calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1344.

Attempted Hydroformylation–Amidocarbonylation of 4-Methallyl-β-lactam (1) Catalyzed by $Co_2(CO)_8$. In the same manner as described above, the reaction of **1** (269 mg, 2.15 mmol) was carried out under the standard conditions followed by the standard workup and methylation with diazomethane. The GLC analysis of the reaction mixture thus obtained did not show any formation of 2-carbomethoxy-4-methyl-1-azabicyclo[4.2.0]octan-8-one (**13**-OMe). Instead, 4-methyl-1-azabicyclo[4.2.0]oct-2-en-8-one (**16**) was obtained from the initial ethyl acetate extract of the organic layer formed on adding 10% sodium carbonate to the reaction mixture (vide supra). The GLC analysis of the reaction mixture showed that unreacted **1** was recovered in 65% yield. **16**: 18% yield; colorless oil; ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 7.3 Hz, 3 H), 1.52 (m, 1 H), 1.96 (m, 1 H), 2.43 (m, 1 H), 2.74 (dd, J = 2.4, 15.2 Hz, 1 H), 3.23 (dd, J = 4.7, 15.2 Hz, 1 H), 3.63 (m, 1 H), 5.19 (t, J = 7.5 Hz, 1 H), 6.51 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.39, (26.92, 27.95), (32.49, 35.20), 42.40, (43.40, 43.77), (116.23, 119.86), (128.25, 131.80); IR (neat, cm^{-1}) 1743 (ν_{CO}), 1673 (ν_{CO}); HRMS (m/e) calcd for $C_8H_{11}NO$ 137.0841; found 137.0846.

Attempted Synthesis of 2-Hydroxy-4-methyl-1-azabicyclo[4.3.0]nonan-9-one (5). A 50-mL Pyrex reaction vessel charged with **3** (3.75×10^{-3} mmol) and $Rh_4(CO)_{12}$ (4.5 mmol) in THF (9.3 mL) was placed in a stainless steel autoclave (300 mL). The reaction was run at 100 °C and 1200 psi (CO/H_2 = 5) for 18 h with stirring. After the autoclave was cooled in a ice-water bath for 30 min, the pressure was released and then the solvent was removed to give crude product. The crude product was submitted to column chromatography on silica gel (eluant EtOAc/hexane) to give 4-methyl-1-azabicyclo[4.3.0]non-2-en-9-one (**17**; 65%) and 4-methyl-1-azabicyclo[4.3.0]nonan-9-one (**18**; 4%). **17** (a mixture of two diastereomers): pale yellow oil; ^1H NMR ($CDCl_3$) δ [1.05 (d, J = 3.5 Hz) (A), 1.07 (d, J = 3.7 Hz) (B)] (3 H), 1.54–1.86 (m, 3 H), 2.15–2.54 (m, 4 H), 3.74 (m, 1 H), [4.88 (d, J = 8.0 Hz) (A), 5.11 (dd, J = 5.3, 8.0 Hz) (B)] (1 H), [6.72 (d, J = 8.0 Hz) (A), 6.75 (d, J = 8.0 Hz) (B)] (1 H); ^{13}C NMR ($CDCl_3$) δ 20.53, (21.76, 21.88), (25.97, 26.66), (28.20, 30.58), (35.20, 37.68), (50.56, 55.24), (114.18, 115.07), 119.50, 170.85; IR (neat, cm^{-1}) 1682 (ν_{CO}); MS (m/e) 151 (64, M^+), 136 (100). Anal. Calcd for $C_9H_{15}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.31; H, 8.66; N, 9.09. **18** (a mixture of two diastereomers (1:1)): pale yellow oil; ^1H NMR ($CDCl_3$) δ [0.968 (d, J = 6.5 Hz), 1.10 (d, J = 7.4 Hz)] (3 H), 1.30–1.89 (m, 5 H), 2.11–2.45 (m, 4 H), [2.73 (m), 2.87 (m)] (1 H), [3.45 (m), 3.68 (m)] (1 H), [3.93 (m), 4.12 (m)] (1 H); ^{13}C NMR ($CDCl_3$) δ (16.07, 16.17), 21.78, (25.28, 25.63), (29.43, 30.23), 32.59, 34.75), 38.83, (39.48, 41.80), (51.27, 56.78), 173.30; IR (neat, cm^{-1}) 1694, 1682 (ν_{CO}); MS (m/e) 153 (73, M^+), 152 (100). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.31; H, 9.73; N, 9.23.

Synthesis of 2-Hydroxy-4-methyl-1-azabicyclo[4.2.0]octan-8-one (4). In a similar manner, the reaction of **1** (244 mg, 1.95 mmol) was carried out in THF (4.5 mL) in the presence of $HRh(CO)(PPh_3)_3$ (8.95 mg, 9.75×10^{-3} mmol) at 100 °C and 1200 psi (CO/H_2 = 1; initial pressure at 20 °C) for 18 h. After the usual workup and purification on a silica gel column (eluant EtOAc/hexane = 1), **4** was obtained as a white solid (142 mg, 47% yield), which was a 1:1 mixture of two diastereomers. **4** (diastereomer A): ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7.0 Hz, 3 H), 1.48–1.63 (m, 2 H), 1.73–1.92 (m, 3 H), 2.59 (dd, J = 2.1, 15.1 Hz, 1 H), 3.13 (dd, J = 4.8, 15.1 Hz, 1 H), 3.33 (bs, 1 H), 3.82 (m, 1 H), 5.36 (m, 1 H); ^{13}C NMR δ 22.07, 24.25, 38.81, 39.28, 43.98, 45.54, 70.10, 165.50. **4** (diastereomer B): ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.5 Hz, 3 H), 1.17–1.21 (m, 2 H), 1.81–2.04 (m, 3 H), 2.36 (bs, 1 H), 2.59 (dd, J = 2.0, 14.9 Hz, 1 H), 3.06 (dd, J = 4.7, 14.9 Hz), 3.64 (m, 1 H), 5.43 (m, 1 H); ^{13}C NMR δ 22.07, 24.25, 38.81, 39.28, 43.98, 45.54, 70.10, 165.50. IR (KBr, cm^{-1}): 3350 (ν_{OH}), 1700 (ν_{CO}). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.86; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.24; N, 8.79 (as a mixture of two diastereomers).

Synthesis of 4-Methyl-2-ethoxy-1-azabicyclo[4.2.0]octan-8-one (19), 2-Ethoxy-1-azabicyclo[4.3.0]nonan-9-one (20), and 2-Ethoxy-1-azabicyclo[4.4.0]decan-10-one (21). A 50-mL Pyrex reaction vessel charged with **2** (209 mg, 1.50 mmol) and $RhCl(PPh_3)_3$ (13.9 mg, 1.5×10^{-2} mmol) in triethyl orthoformate (4.5 mL) was placed in a stainless steel autoclave (300 mL). The reaction was carried out at 100 °C and 1800 psi (CO/H_2 = 1, initial pressure at 20 °C) for 18 h with stirring. After the autoclave was cooled in a ice-water bath for 30 min, the gases were released and then solvent was removed to give a crude product. The NMR analysis of the crude product showed that the hemiamidal **20** was formed in 75% yield. Attempted purification of this material by column chromatography on silica gel and bulb-to-bulb distillation resulted in the partial formation of dealcoholation product **18**. Accordingly, this material was used for the next carbonylation reaction without purification. **20** (a mixture of two diastereomers): ^1H NMR ($CDCl_3$) δ [0.93 (d, J = 6.6 Hz), 1.17 (d, J = 6.9 Hz)] (3 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.39–2.50 (m, 9 H), 3.43 (q, J = 7.0 Hz, 2 H), [3.72 (m), 3.90 (m)] (1 H), 5.34 (m, 1 H); IR (neat, cm^{-1}) 1697 (ν_{CO}); MS (m/e) 168 (9, M^+ – 29), 153 (48), 152 (100), 110 (30), 84 (40), 72 (37), 55 (15), 41 (24).

In the same manner, the syntheses of **19** and **21** were carried out. The *O*-ethyl hemiamidals **19** and **21** were formed in 86% and 82% yields, respectively, on the basis of the NMR analysis of the crude products, which were used for the next carbonylation without further purification. Since **19** turned out to be stable, the crude material was submitted to chromatography on silica gel (eluant CH_2Cl_2/MeOH = 30) to give pure **19**. **19** (a mixture of two diastereomers (1:1)): ^1H NMR δ [0.96 (d, J = 6.5 Hz), 1.12 (d, J = 7.0 Hz)] (3 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.40–1.90 (m, 5 H), 2.61 (dd, J = 2.0, 14.9 Hz, 1 H), [3.08 (dd, J = 3.7, 14.9 Hz), 3.16 (dd, J = 4.7 Hz, 14.9 Hz)] (1 H), 3.41–3.73 (m, 3 H), 4.93 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.80, (19.26, 21.93), (24.64, 25.10), (34.96, 35.54), (38.36, 38.53), (42.57, 45.42), (43.76, 44.31), (62.73, 62.93), (75.80, 76.76), (166.47, 167.91); IR (neat, cm^{-1}) 1755 (ν_{CO}). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.72; H, 9.26; N, 7.43. **21** (a mixture of two diastereomers): ^1H NMR ($CDCl_3$) δ [0.91 (d, J = 6.6 Hz), 1.19 (d, J = 6.9 Hz)] (3 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.43–2.08 (m, 9 H), 2.29–2.50 (m, 2 H), 3.41 (q, J = 7.0 Hz, 2 H), [3.55 (m), 3.78 (m)] (1 H), [5.96 (m), 6.03 (m)], (1 H); IR (neat, cm^{-1}) 1650 (ν_{CO}); MS (m/e) 182 (100, M^+ – 29), 166 (64), 150 (54), 138 (23), 122 (50), 98 (28), 55 (47), 41 (40).

Carbonylation of *O*-Ethyl Hemiamidals (20 and 21) Catalyzed by $Co_2(CO)_8$. A 50-mL round-bottomed flask was charged with $Co_2(CO)_8$ (51.3 mg, 0.15 mmol) and THF (4.5 mL) under argon, and the catalyst solution was stirred for 20 min. The

catalyst solution was transferred via syringe into a 50-mL Pyrex reaction vessel containing **20** (296 mg, 1.50 mmol), and the reaction vessel was placed in a 300-mL stainless steel autoclave. The reaction was run at 125 °C and 2000 psi (CO/H_2 = 1) for 18 h with stirring. After the pressure was released from the autoclave, the solvent was removed. The reaction mixture was dissolved in 10% aqueous sodium carbonate and the solution extracted with ethyl acetate. Two layers were separated. The organic layer was dried over anhydrous $MgSO_4$, and then ethyl acetate was removed to give the crude product. The crude product was submitted to GLC and NMR analyses and then purified by column chromatography on silica gel (eluant CH_2Cl_2/methanol = 20) to give 2-carbethoxy-1-azabicyclo[4.3.0]nonan-9-one (**14**-OEt) as a colorless oil (169 mg, 50% yield). **14**-OEt (a mixture of diastereomers): ^1H NMR ($CDCl_3$) δ [1.01 (d, J = 6.9 Hz), 1.04 (d, J = 6.9 Hz)] (3 H), [1.28 (t, J = 6.9 Hz), 1.30 (d, J = 6.9 Hz)] (3 H), 1.4–2.6 (m, 5 H), 3.3–3.9 (m, 4 H), 3.94 (m, 1 H), 4.0–4.28 (m, 3 H); IR (neat, cm^{-1}) 1732 (ν_{CO}), 1698 (ν_{CO}); MS (m/e) 225 (1, M^+), 152 (100); HRMS (m/e) Calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1355.

In the same manner, the reaction of **21** was carried out to give 2-carbethoxy-1-azabicyclo[4.4.0]decan-10-one (**15**-OEt) in 70% yield. **15**-OEt (a mixture of two diastereomers (1:1)): ^1H NMR ($CDCl_3$) δ [0.97 (d, J = 6.5 Hz), 1.00 (d, J = 6.7 Hz)] (3 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.31–2.04 (m, 7 H), 2.34–2.46 (m, 2 H), 3.20–3.80 (m, 2 H), 3.52 (m, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.62 (m, 1 H); IR (neat, cm^{-1}) 1734 (ν_{CO}) 1641 (ν_{CO}); MS (m/e) 239 (1, M^+), 166 (100); HRMS (m/e) calcd for $C_{13}H_{21}NO_3$ 239.1512, found 239.1522.

Carbonylation of Bicyclic Hemiamidal 4 and its *O*-Ethyl Derivative 19 Catalyzed by $Co_2(CO)_8$. A 50-mL reaction vessel containing **4** (142 mg, 0.94 mmol) and $Co_2(CO)_8$ (32.1 mg, 0.094 mmol) in THF (2.4 mL) was placed in a 300-mL stainless steel autoclave. The reaction was run at 125 °C and 2000 psi (CO/H_2 = 1) for 18 h stirring. After the standard workup for amidocarbonylation (vide supra), the organic layer (ethyl acetate extract) was dried and concentrated in vacuo to the crude product. The GLC analysis of the crude product showed the formation of **16** in 31% yield. The aqueous layer was acidified and extracted with ethyl acetate and the extract dried, concentrated in vacuo, and dissolved in chloroform. The chloroform solution was treated with diazomethane in ether. The GLC analysis of the reaction mixture showed many peaks, but no trace of **13**-OMe was detected.

In a similar manner, the reaction of **19** was carried out under the same conditions as those used for the reaction of **4**. The GLC analysis of the reaction mixture showed the formation of **16** (24% yield) and its saturated derivative **16a** (15% yield) as the products. No trace of **13**-OEt was detected. **16a** (a mixture of two diastereomers): colorless oil; ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3 H), 1.10–2.20 (m, 6 H), [2.58 (dd, J = 1.6, 14.5 Hz), 2.63 (dd, J = 1.6, 15.5 Hz)] (1 H), [3.08 (dd, J = 5.3, 14.5 Hz), 3.11 (dd, J = 5.0, 15.5 Hz)] (1 H), 3.71 (m, 1 H), 4.83 (m, 1 H); IR (neat, cm^{-1}) 1754 (ν_{CO}); HRMS (m/e) calcd for $C_8H_{13}NO$ 139.0997, found 139.0993.

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Hydrosilylation of 1-Hexyne Catalyzed by Rhodium and Cobalt–Rhodium Mixed-Metal Complexes. Mechanism of Apparent Trans Addition†

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Hydrosilylation of 1-hexyne with triethylsilane catalyzed by $Rh_4(CO)_{12}$, $Co_2Rh_2(CO)_{12}$, $Co_3Rh(CO)_{12}$, and $RhCl(PPh_3)_3$ gives a mixture of *cis*-1-(triethylsilyl)-1-hexene (**1a**, major), its trans isomer (**2a**, minor), and its α-isomer (**3a**, minor) in excellent yield. Under optimum conditions, the yield of **1a** increases to 96%. The cis/trans ratio depends on the concentration of catalyst as well as the substituents of hydrosilane used. It is found that the lower catalyst concentration, the higher cis/trans ratio. Triethylsilane, dimethylphenylsilane, diethylmethylsilane, and ethyldimethylsilane give thermodynamically unfavorable cis isomers as the major products, whereas chlorodimethylsilane, dichloromethylsilane, and trimethoxysilane do not give cis isomers (**1**) at all under the usual conditions. A mechanism is proposed to accomodate the observed unique stereoselectivity. The proposed mechanism includes first a silicon shift to the acetylenic bond and the carbene-type zwitterionic rhodium complex as the key intermediate, which undergoes isomerization from a higher energy form (Z complex) to a lower energy form (E complex) followed by reductive elimination to give the cis isomer (**1**) as the kinetic product.

Introduction

Hydrosilylation of carbon–carbon multiple bonds has been one of the most important laboratory and industrial methods of forming silicon–carbon bonds. The reaction of alkenes has especially been studied extensively for decades, but less attention has been drawn to that of alkynes. Nevertheless, the reaction of alkynes provides the most convenient and direct route to vinylsilanes, which are very useful intermediates for cross-linked silicones as well as reagents in organic syntheses.[3] The hydrosilylation

† This paper is dedicated to late Professor John K. Stille for his outstanding achievement and contribution to the advancement of homogeneous catalysis and its application to organic synthesis and polymer science.

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