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Amide-directed hydrocarbonylation of N-alkenylamides and α-alkenyllactams *

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Abstract

The amide-directed Rh-catalyzed hydroformylation and Pd-catalyzed hydroesterification of *N*-allylamides give the iso-aldehyde and ester, respectively, with good regioselectivity. The Rh- and $Co_2Rh_2(CO)_{12}$-catalyzed reactions of *N*-methallylamide give an 1-acyl-2-formylpyrrolidine through a novel double carbonylation and an 1-acylpyrrolidine through reductive annulation, respectively, with excellent selectivity. A cyclic hemiamidal, *N*-benzoyl-2-hydroxy-4-methylpyrrolidine, the key intermediate for the double carbonylation and the reductive annulation, is obtained selectively in a $Rh_4(CO)_{12}$-catalyzed reaction of *N*-methallylamide. The hydrocarbonylations of this cyclic hemiamidal catalyzed by $RhCl(PPh_3)_3$, $Co_2Rh_2(CO)_{12}$, and $Co_2(CO)_8$ give the corresponding double carbonylation product (2-formylpyrrolidine), reductive annulation product (pyrrolidine), and amidocarbonylation product (proline), respectively, in excellent yield and selectivity. The mechanisms of the novel double carbonylation and the reductive annulation is studied on the basis of deuterium-labeling experiments, and it is found that these reactions proceed via enamide intermediate followed by extremely regioselective metal hydride addition to the enamide.

The Rh-catalyzed hydrocarbonylations of the α-methallyl-γ- and δ-lactams in triethyl orthoformate followed by treatment with TFA give the corresponding 1-azabicyclo[4.*n*.0]alkenones via bicyclic hemiamidals through annulation in excellent overall yields. The $Co_2Rh_2(CO)_{12}$-catalyzed reactions of these α-methallyl lactams give the corresponding 1-azabicyclo[4.*n*.0]alkanones as the sole isolable products in high yields. The $RhCl(PPh_3)_3$-catalyzed hydrocarbonylation of 6-allylpiperidin-2-one gives a mixture of 1-azabicyclo[4.4.0] and 1-azabicyclo[4.3.0] products. However, the addition of phosphines to the Rh catalyst remarkably improves the normal selectivity (*n*/iso = 9) to give 1-azabicyclo[4.4.0]dec-2-en-10-one as the predominant product.

Introduction

Chelation-controlled regioselective and stereoselective reactions have been studied extensively in the application of organometallics and homogeneous catalysts for organic synthesis. For example, Krafft et al. [1] developed amine-directed regioselective hydrocarboxylation of alkenylamines, which is promoted by stoichiometric

* Dedicated to the late Professor Piero Pino for his outstanding contribution to homogeneous catalysis, polymer and organometallic chemistry.

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Table 1

Hydrocarbonylation of *N*-allylacetamide [a]

Entry	Catalyst (mol%)	Yield (%) [b]	Products ratio [b]			
			1	2	3	4
1	$[Rh(dppb)(NBD)]ClO_4$ [c] (1.0)	78	71	–	5	24
2	$RhCl(PPh_3)_3$ (1.0)	80	65	–	7	28
3	$RhCl(CO)(PPh_3)_2$ (1.0)	79	66	–	7	27
4	$HRh(CO)(PPh_3)_3$ (1.0)	76	63	11	13	13
5	$Rh_4(CO)_{12}$ (0.25)	78	79	6	6	9
6	$Co_2Rh_2(CO)_{12}$ (0.5)	80	79	–	21	–
7 [d]	$Co_2Rh_2(CO)_{12}$ (1.0)	80	82	–	18	–

[a] All reactions were run with use of a Pyrex reaction vessel (50 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of *N*-allylacetamide in THF (3.6 ml) at 80 °C and 1200 psi (83 bar) ($CO/H_2 = 1$) for 18 h unless otherwise noted. [b] Determined by ^1H NMR and GLC analyses. [c] dppb = 1,4-bis(diphenylphosphino)butane. NBD = norbornadiene. [d] The reaction was carried out with 1.0 mol% of $Co_2Rh_2(CO)_{12}$ at 60 °C.

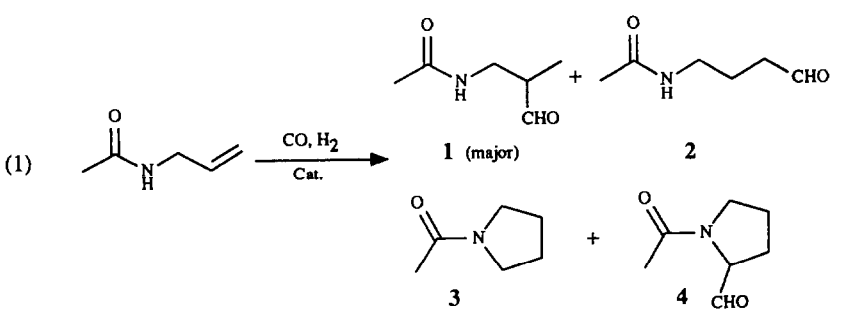
amount of Rh complexes. The asymmetric hydrogenation of dehydroamino acids and dehydropeptides [2], the asymmetric epoxidation of allylic alcohols [3], and the asymmetric isomerization of allylamines [4] are excellent examples of the chelation-controlled methodologies in homogeneous catalysis to attain high stereoselectivity. Burke, Jackson and their coworkers [5,6] reported intramolecular phosphine-directed hydroformylation of alkenes.

In the course of our study on chelation-controlled regio- and stereoselective carbonylations in organic syntheses, we have found that amide functionality can serve as a strong "directing group" in regioselective hydrocarbonylations catalyzed by a variety of group VIII transition-metal complexes [7]. We describe here a full account of our work on amide-directed hydrocarbonylations of *N*-alkenylamides and α-alkenyl lactams.

Results and discussion

Hydrocarbonylation of N-*allylamides*

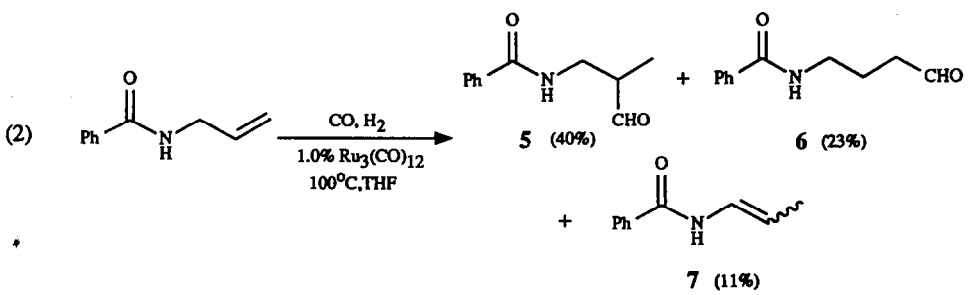
The hydroformylation of *N*-allylacetamide was carried out with a variety of rhodium catalysts i.e., $RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$, $HRh(CO)(PPh_3)_3$, $[Rh(dppb)(NBD)]ClO_4$, $Rh_4(CO)_{12}$, and a Co–Rh mixed metal complex, $Co_2Rh_2(CO)_{12}$ (eq. 1). Typical results are summarized in Table 1.



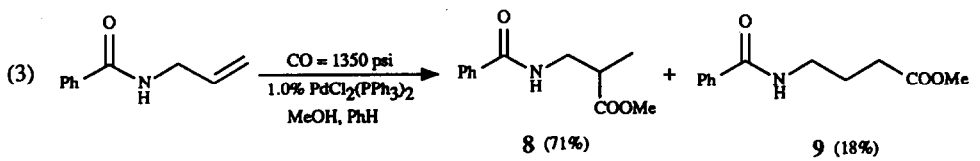
As Table 1 shows, the major product of the reaction is 2-methyl-3-(acetylamino)propanal (**1**: iso-aldehyde) and the minor products are 4-(acetylamino)butanal (**2**: n-aldehyde), 1-acetylpyrrolidine (**3**), and/or 1-acetyl-2-formylpyrrolidine (**4**) which is the product of a novel sequential double carbonylation *.

It is well known that the hydroformylation of 1-alkenes catalyzed by rhodium complexes gives n-aldehydes as the predominant product, and the n-aldehyde selectivity is increased when phosphine ligands are introduced, i.e., the n/iso ratio is in the range of 5–10 for phosphine–rhodium complexes and 1.1–2 for rhodium carbonyls [9]. Accordingly, the good iso-selectivities observed in the present system are *opposite* to those for usual 1-alkenes. It is noteworthy that the Co–Rh mixed metal catalyst, $Co_2Rh_2(CO)_{12}$, brings about substantially better product selectivity than other rhodium complexes, implying the synergistic effects of the mixed metal system **. The observed unique iso-selectivity is best interpreted by taking into account the amide-direct chelation control of regioselectivity.

When $Ru_3(CO)_{12}$ was used as a catalyst for comparison purpose, the reaction gave iso-aldehyde (**5**, 40%), n-aldehyde (**6**, 23%) and an isomerization product (*N*-(1-propenyl)-benzamide (**7**), 11%) (eq. 2). The result clearly indicates that the a similar chelation-control is operative in the Ru-catalyzed reaction as well.

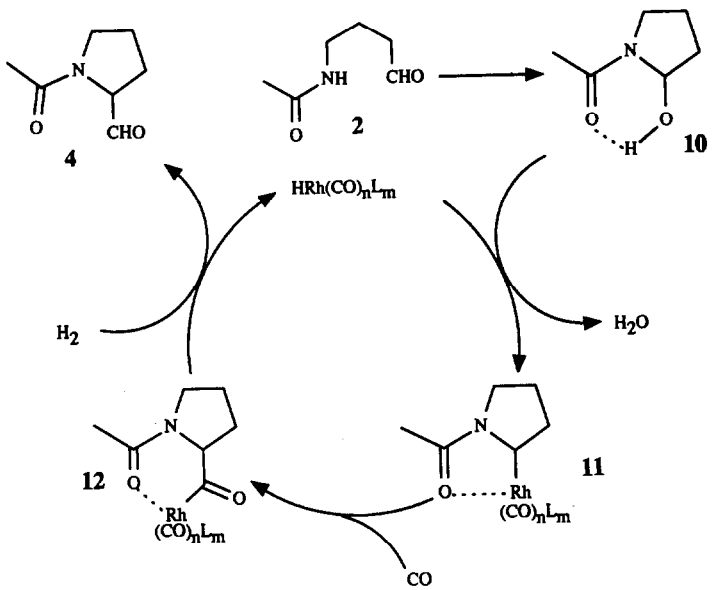


Next, the hydroesterification of *N*-allylbenzamide with methanol catalyzed by $PdCl_2(PPh_3)_2$ was carried out at 80 °C and 1,350 psi (93 bar) of carbon monoxide in benzene (eq. 3). The reaction gave iso-ester **8** (methyl *N*-benzoyl-α-methyl-β-alaninate) and n-ester **9** in 71% and 18% yields, respectively, i.e., iso/n = 4.



* Becker, Eisenstadt, and Stille reported the hydroformylation of *N*-allylacetamide catalyzed by $HRh(CO)(PPh_3)_3$ at 40 °C and 500 psi (34 bar; $CO/H_2 = 1$), which gave the iso-aldehyde (**1**) and *N*-acetyl-2-pyrroline with 54/46 ratio [8]. As Table 1 shows, we observed different selectivities and products under our reaction conditions, viz., the formation of *N*-acetyl-2-pyrroline was not observed at all.

** The $Co_2(CO)_8$-catalyzed hydrocarbonylation was reported to give a mixture of three amino acids instead of amino aldehydes, i.e., 2-(benzoylamino)butanoic acid (45%), 2-methyl-3-(benzoylamino)propanoic acid (8%), and *N*-benzoylproline (21%) [10]. The results of the rhodium complex-catalyzed reaction are not as selective as the $Co_2Rh_2(CO)_{12}$-catalyzed reaction.



Scheme 1. Proposed mechanism for double carbonylation.

The result clearly indicates that an amide-directed chelation control is operative in the palladium complex-catalyzed reaction as well. Since the hydroesterification of 1-alkenes gives n-ester as major products [11], the observed iso-selectivity forms a sharp contrast to the usual 1-alkene case.

N-acetyl-2-formylpyrrolidine (**4**) obtained as a minor product in the rhodium-catalyzed reactions is formed through a new type of amidocarbonylation via the cyclic hemiamidal **10** arising from the n-aldehyde **2** followed by the sequential formation of the alkyl-Rh complex **11** and the acyl-Rh complex **12** as shown in Scheme 1. In the final reductive elimination step, the acyl–Rh bond is selectively cleaved by hydrogen, giving the 2-formylpyrrolidine **4**. This forms a sharp contrast to the Co-catalyzed amidocarbonylation, which gives the corresponding carboxylic acid exclusively [10]. This new type of intramolecular amidocarbonylation reaction provides the first example of rhodium-catalyzed sequential dicarbonylation. Since this novel reaction has high potential as a synthetic method, the reaction has been further studied in order to make it more selective.

Hydrocarbonylation of N-*(2-methyl-2-propenyl)benzamide*

The reaction of *N*-(2-methyl-2-propenyl)benzamide was carried out with $RhCl(PPh_3)_3$. $HRh(CO)(PPh_3)_3$, $[Rh(dppb)(NBD)]ClO_4$, $Rh_4(CO)_{12}$, and a Co–Rh mixed metal complex, $Co_2Rh_2(CO)_{12}$ as the catalysts. Because of the 2-methyl group, initial hydroformylation became highly regioselective, and thus the reaction gave an expected 2-formylpyrrolidine (**13**, 1 : 1 diastereomer mixture) as the predominant product together with a pyrrolidine **14** and a hemiamidal **15** in rhodium-catalyzed reactions (eq. 4). Results are summarized in Table 2.

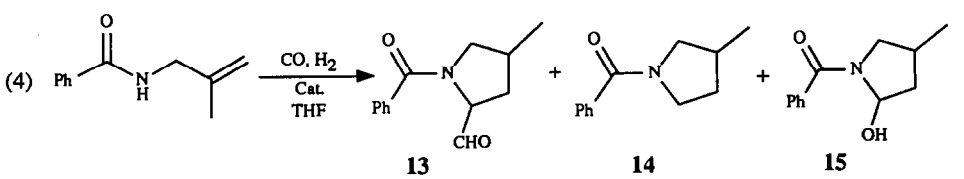


Table 2

Hydrocarbonylation of *N*-(2-methyl-2-propenyl)benzamide [a]

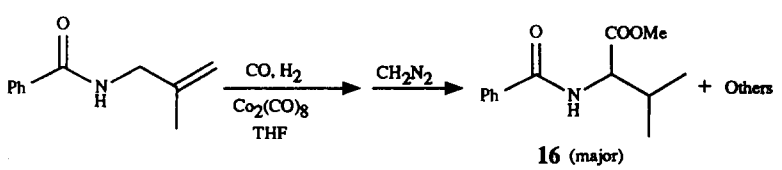
Entry	Catalyst (mol%)	CO (psi)	H_2 (psi)	Yield (%) [b]	Products ratio [b]		
					13	**14**	**15**
1	[Rh(dppb)(NBD)]ClO_4 [c] (1.0)	600	600	94	62	27	11
2		1500	300	90	87	–	13
3 [d]		1700	150	87	*> 99.5*	–	–
4	$RhCl(PPh_3)_3$ (1.0)	600	600	85	54	46	–
5		1500	300	91	82	7	11
6	$HRh(CO)(PPh_3)_3$ (1.0)	600	600	93	48	13	39 [e]
7 [b]	$Rh_4(CO)_{12}$ (0.25)	600	600	95	46	20	34 [f]
8		600	200	87	–	–	*100* [g]
9	$Co_2Rh_2(CO)_{12}$ (0.5)	600	600	83	2	*98*	–
10		300	900	85	0	*100*	–

[a] All reactions were run with use of a Pyrex reaction vessel (50 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of *N*-(2-methyl-2-propenyl)benzamide in THF (3.6 ml) at 100 °C for 18 h unless otherwise noted. [b] Determined by ^1H NMR and GLC analyses. [c] For the abbreviations for dppb and NBD, see the footnote *c* of Table 1. [d] The reaction was run with 2.0 mol% of the catalyst for 71 h. [e] Containing 15% of n-aldehyde. [g] Containing 13% of n-aldehyde.

As Table 2 shows, the product selectivity highly depends on the catalyst used as well as reaction conditions, i.e., the pressure and the ratio of carbon monoxide and hydrogen employed. For example, [Rh(dppb)(NBD)]ClO_4 is the best catalyst for the sequential double carbonylation giving 2-formylpyrrolidine **13** almost exclusively under higher carbon monoxide pressure, e.g., 1700 psi (117 bar) (entry 3). Although $Rh_4(CO)_{12}$ is not a good catalyst for the double carbonylation, the $Rh_4(CO)_{12}$-catalyzed reaction gives the hemiamidal **15** exclusively under certain conditions (entry 8), which is the key intermediate in the sequential double carbonylation giving **13** and in the reductive annulation giving **14** (*vide infra*). The $Co_2Rh_2(CO)_{12}$-catalyzed reaction gives **14** with $\geq$ 98% selectivity (entry 9,10). It is worthy of note that **13**, **14** or **15** can be obtained highly selectively by the proper choice of the catalyst and CO/H_2 pressures.

For comparison purpose, the $Co_2(CO)_8$-catalyzed reaction was carried out under comparable conditions, i.e., $CO/H_2 = 1$; 2000 psi (138 bar), followed by methylation with diazomethane, which gave methyl *N*-benzoylvalinate (**16**) as the major product (45% yield), which is not the product of intramolecular amidocarbonylation, but rather the result of a sequential isomerization–hydrocarboxylation (eq. 5). Accordingly, it is obvious that the highly selective formation of **14** is very unique to the $Co_2Rh_2(CO)_{12}$-catalyzed reaction, which clearly demonstrates the synergistic effects of the mixed metal system.

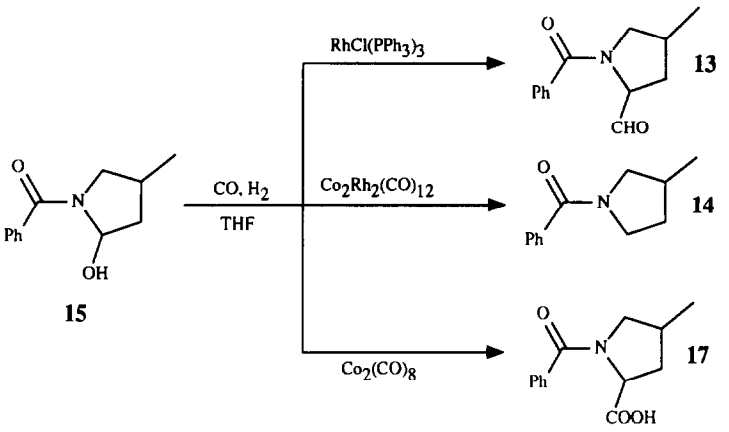
(5)



16 (major)

*Controlled experiments with the hemiamidal **15***

We looked into the mechanisms of these reactions and have found that the

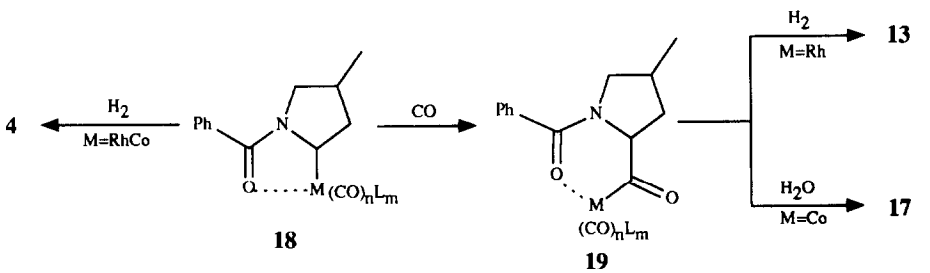


Scheme 2

hemiamidal **15** is the common intermediate to **13** and **14**. Controlled experiments using **15** revealed that (a) **15** was actually converted to **13** (95% yield) in the presence of carbon monoxide and hydrogen (1800 psi; 124 bar) ($CO/H_2 = 5$) and $RhCl(PPh_3)_3$ (1 mol%) at 100 °C for 18 h and, (b) **15** was transformed to **14** (95% yield) in the presence of $Co_2Rh_2(CO)_{12}$ (1 mol%) at 100 °C and 1200 psi (83 bar, $CO/H_2 = 1$) for 18 h (Scheme 2). We also found that the reaction of **15** with $Co_2(CO)_8$ (10 mol%) at 125 °C and 2000 psi (138 bar, $CO/H_2 = 1$) for 20 h gave *N*-benzoyl-4-methylproline (**17**) cleanly in 72% yield (Scheme 2), which was hardly obtained in the direct hydrocarbonylation of *N*-(2-methyl-2-propenyl)benzamide catalyzed by $Co_2(CO)_8$ (see eq. 5).

The formations of **13**, **14** and **17** are rationalized by taking into account the formylation, the hydrogenolysis, and the carboxylation, respectively, of an alkylmetal complex **18** which is generated from **15** (Scheme 3). The three reactions are competing processes: (a) the carbon monoxide insertion is the predominant process for rhodium and cobalt catalysts while the hydrogenolysis is almost exclusive for $Co_2Rh_2(CO)_{12}$; (b) the rhodium catalyst gives the aldehyde **13** through exclusive hydrogenolysis of an acyl-metal complex **19** whereas the cobalt catalyst gives the carboxylic acid **17** through exclusive hydrolysis of **19**.

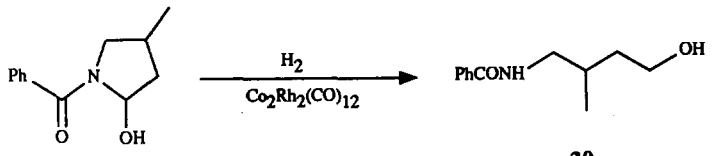
In the hydrogenolysis of the hemiamidal **15** catalyzed by $Co_2Rh_2(CO)_{12}$ giving **14**, we have found that carbon monoxide pressure is necessary to maintain the



Scheme 3

structure of an active catalyst species, which probably is $CoRh(CO)_7$ [12], and prevent from the decomposition of the catalyst to metallic cobalt and rhodium, viz., when only hydrogen was used, the reaction gave an open chain amido-alcohol, 4-benzamido-3-methylbutanol (**20**) as the predominant product in 83% yield (eq. 6).

(6)



15 **20**

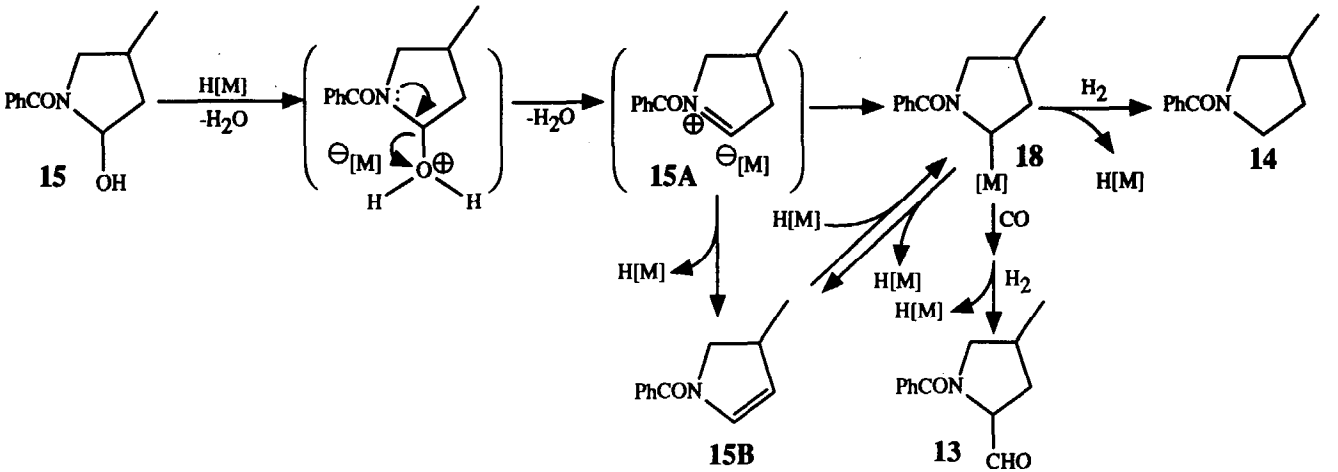
Mechanisms of the double carbonylation and the reductive annulation—labeling experiments

It should be noted that C^2-formyl product **13** was formed exclusively in the sequential double carbonylation of *N*-(2-methyl-2-propenyl)benzamide, i.e., no C^3-formyl product has been detected at all. The sequential double carbonylation should include the initial hydroformylation, annulation giving the hemiamidal **15** and the subsequent formylation of **15**. For the formylation of **15**, two pathways are conceivable, i.e., (a) "direct carbonylation route" which includes the substitution of the hydroxy group by a rhodium complex via an *N*-acyliminium ion **15A**, followed by carbonyl insertion and hydrogenolysis, and (b) "enamide route" which proceeds through the enamide **15B**, followed by regioselective hydroformylation (Scheme 4. Although the formation of **15B** has not been detected at all in the reaction of *N*-(2-methyl-2-propenyl)benzamide, the "enamide route" cannot be excluded. A similar discussion is applicable for the $Co_2Rh_2(CO)_{12}$-catalyzed reaction, in that both (a) "direct hydrogenolysis route" and (b) "enamide route" can be operative (Scheme 4).

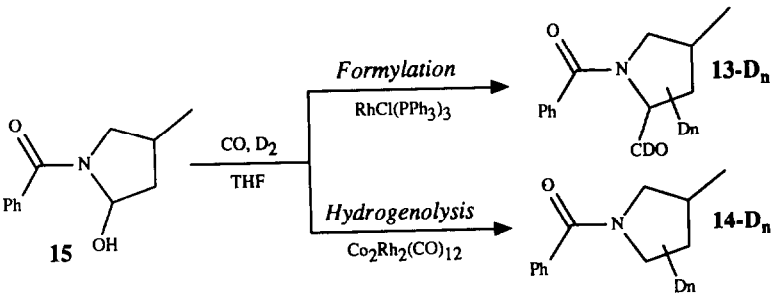
In order to gain an insight into the mechanisms of these two reactions, labeling experiments were performed with the hemiamidal **15** and deuterium gas, i.e., the $RhCl(PPh_3)_3$-catalyzed formylation and the $Co_2Rh_2(CO)_{12}$-catalyzed hydrogenolysis of **15** with deuterium gas were carried out. The $RhCl(PPh_3)_3$-catalyzed reaction gave deuterium labeled 1-benzoyl-2-formylpyrrolidines (**13-D$_n$**) while the $Co_2Rh_2(CO)_{12}$-catalyzed reaction gave deuterium labeled 1-benzoylpyrrolidines (**14-D$_n$**) (Scheme 5). These deuterium-labeled products were analyzed by ^1H NMR, ^2H NMR and mass spectroscopy in comparison with the corresponding non-labeled compounds (**13** and **14**). The protium contents at the C^2 and the C^3 of the labeled products (**13-D$_n$** or **14-D$_n$**) were determined on the basis of ^1H NMR by using the methylene protons at the C^5 as the internal standard. The deuterium contents at the C^2 and the C^3 of the labeled products (**13-D$_n$** or **14-D$_n$**) determined on the basis of the ^2H NMR were in good agreement with the those estimated by the ^1H NMR. The intermolecular deuterium distribution was determined by mass spectroscopy, in which it was assumed that the fragmentation pattern of the deuterium-labeled compounds (**13-D$_n$** and **14-D$_n$**) is essentially the same as that of the protium counterparts (**13** and **14**).

*(a) $RhCl(PPh_3)_3$-catalyzed formylation of the hemiamidal **15** with D_2*

The mass spectral analyses of the products show that the monodeuteriated (on the ring) product (**13-D$_1$**) is the major product (51%) along with dideuteriated


PhCON
15
OH
H[M]
-H2O
PhCON
⊖[M]
O⊕
H
H
-H2O
PhCON
⊕
⊖[M]
15A
PhCON
18
[M]
H2
H[M]
PhCON
14
H[M]
H[M]
CO
H[M]
H2
H[M]
PhCON
15B
PhCON
13
CHO

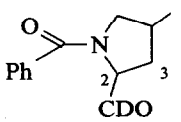
Scheme 4



Scheme 5

(**13-D_2**, 23%), trideuteriated (**13-D_3**, 14%) and non-deuteriated (**13-D_0**, 12%) products (the number does not include deuterium in the formyl group) (see Experimental). The result clearly indicates the occurrence of deuterium scrambling, which should be caused by the β-hydride elimination of the intermediate **18** forming the enamide **15B** (Scheme 4), viz., if the reaction proceeded through the "direct carbonylation route", the deuterioaldehyde **13-D_0** should have been formed exclusively, and if the "enamide route" (**15A** → **15B** → **18** → **13-D_n**) did not include the reverse pathway from **18** to **15B** through β-hydride elimination, the reaction should have yielded **13-D_1** as the single product.

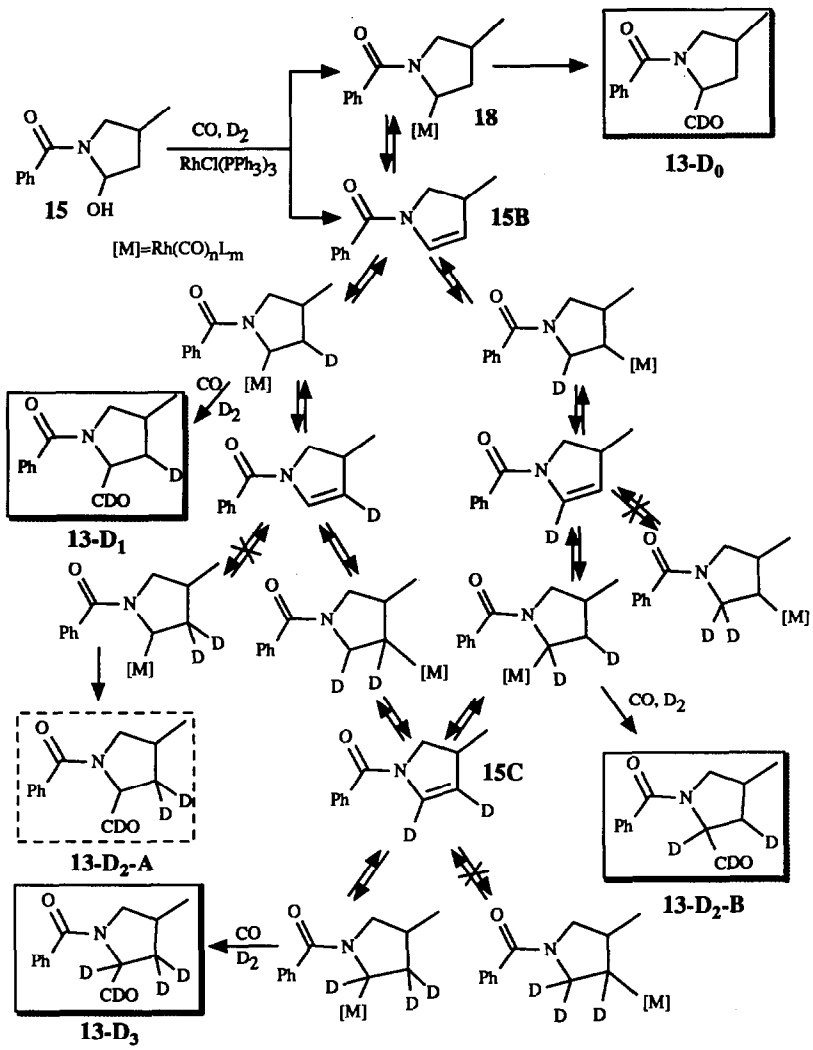
Among the possible deuteriated products, the dideuteriated compounds (**13-D_2**) can have two possible structures, i.e. (C^2-d_2)-**13** (**13-D_2-A**) and (C^2-d, C^3-d)-**13** (**13-D_2-B**), while non-, mono- and trideuteriated compounds have only one possible structure for each (Scheme 6). The ^{1}H NMR analysis shows that the contents of protium are 0.6 at the C^2 and 0.9 at the C^3, respectively, which reflect the average value of the contribution from the differently labeled products (see Experimental). ^{2}H NMR analysis shows that the ratio of the amount of deuterium incorporated at the C^3 to that of the C^2 is 2.75, which is in good agreement with the result of the ^{1}H NMR analysis (see Experimental). Therefore, the average contents of deuterium are 0.4 at the C^2 and 1.1 at C^3, respectively. On the basis of the NMR and the mass spectroscopic analyses described above, **13-D_2-B** is unambiguously assigned to the structure of the dideuteriated product.



13-D_n

Carbon:	C^2	C^3
Protium content:	0.6	0.9
Deuterium content:	0.4	1.1

The results clearly indicate that (a) the formylation of the hemiamidal **15** proceeds predominantly through the "enamide route", and the "direct carbonylation route" may be responsible for 12% of the product, (b) the reaction should involve reversible β-hydride elimination at the alkyl-Rh stage (**18** and its deuteriated counterparts) (see Scheme 6), which is responsible for the observed deuterium scrambling, (c) both the C^2-alkyl-Rh and the C^3-alkyl-Rh complexes are formed in the reaction, but carbonylation does not take place for the C^3-alkyl-Rh complex, (d) there is a pre-equilibrium between the enamide (**15B** and its deuteriated counter-

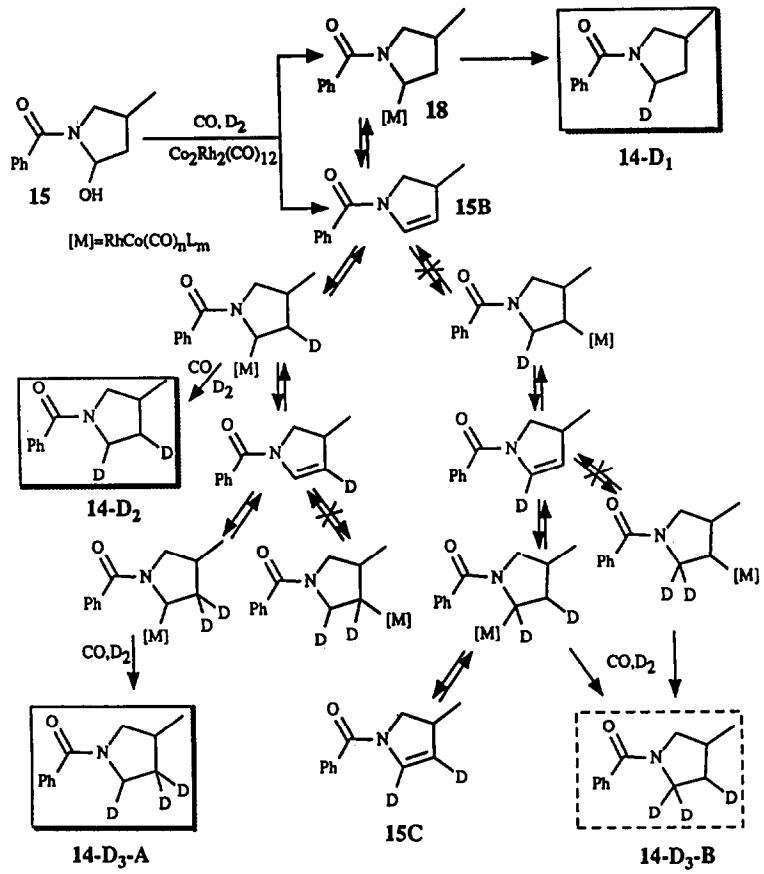


Scheme 6. The possible pathways for the formation of deuterated 2-formylpyrrolidines (**13-D$_n$**).

parts) and the alkyl-Rh intermediate (**18** and its deuteriated counterparts), and (e) the regioselectivity-determining step as well as rate-determining step should be the carbonyl insertion step, which is strongly controlled by the coordination of the amide carbonyl to the Rh metal, giving the C^2-formyl product (**13-D$_n$**) exclusively.

*(b) The $Co_2Rh_2(CO)_{12}$-catalyzed hydrogenolysis of the hemiamidal **15** with D_2*

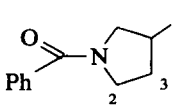
The mass spectral analyses (isotope effect is neglected) of the products indicate that the predominant products are the dideuteriated product (**14-D$_2$**, 39%) and the trideuteriated product (**14-D$_3$**, 51%), and a small amount of the monodeuteriated product (**14-D$_1$**, 10%) is also detected (see Experimental). The existence of trideuteriated product clearly indicates that the reaction involves a pre-equilibrium between **18** and **15B** similar to the one discussed above. Possible pathways for the



Scheme 7. The possible pathways for the formation of deuterated pyrrolidines (**14-D$_n$**).

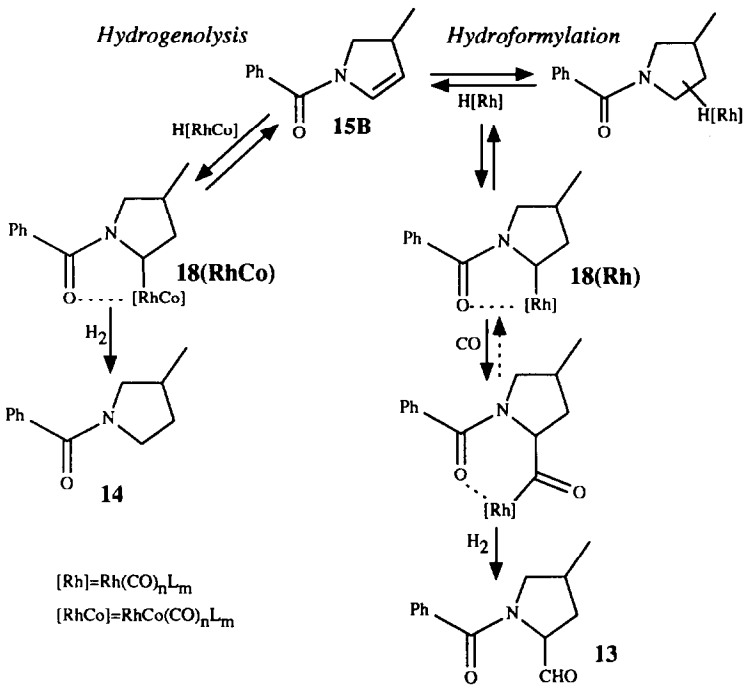
formation of **14-D$_n$** are illustrated in Scheme 7, Among the possible labeled products, only the trideuteriated product (**14-D$_3$**) has two possible structures, i.e., (C^2-*d*, C^3-d_2)-**14** (**14-D$_3$-A**) and (C^2-d_2, C^3-*d*)-**14-D$_3$-B**).

The ^{1}H NMR analysis shows that the protium contents are 1.0 at the C^2 position and 0.55 at the C^3 position, respectively (see Experimental). The ^{2}H NMR analysis indicates that the ratio of deuterium contents at the C^3 to that of the C^2 is 1.45, which is in good agreement with the result of the ^{1}H NMR analysis (see Experimental). Thus, the contents of the incorporated deuterium are 1.0 at the C^2 and 1.45 at the C^3. On the basis of the NMR analyses, it is unambiguously concluded that **14-D$_3$-A** is formed exclusively and the formation of **14-D$_3$-B** can be neglected.



14-D$_n$

Carbon:	C^2	C^3
Protium content:	1.0	0.55
Deuterium content:	1.0	1.45



Scheme 8. Proposed mechanisms for sequential carbonylation and hydrogenolysis.

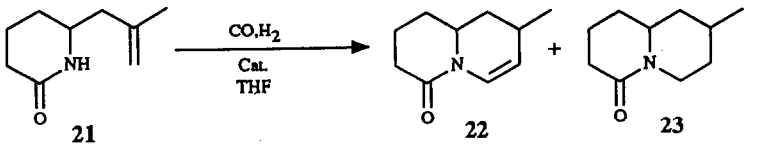
The results clearly indicate that (a) the reaction also goes predominantly through the "enamide route", including the pre-equilibrium between the enamide (**15B** and its deuteriated counterparts) and the alkyl-RhCo intermediate (**18** and its deuteriated counterparts), (b) the reaction includes an extremely regioselective olefin insertion process, which means that only the C^2-alkyl-metal complex can be formed and undergo hydrogenolysis, (c) the rate-determining step should be the final hydrogenolysis step, and (d) the intermediacy of the C^3-alkyl-RhCo complex as well as 2,3-dideuteriated enamide **15-C** can be ignored since these intermediates should give **14-D_3-B** and **14-D_4**, respectively, which are not detected at all.

In conclusion, the labeling experiments have revealed that the formylation and the hydrogenolysis of the hemiamidal **15** predominantly proceed through the enamide **15B**, and extremely strong chelation-control in the carbon monoxide insertion step for hydroformylation and in the reductive cleavage step in the hydrogenolysis. Possible mechanisms which can accommodate all results are depicted in Scheme 8.

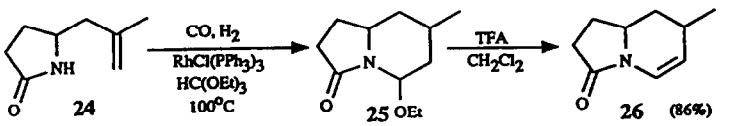
Synthesis of bicyclic nitrogen heterocycles through hydrocarbonylation of α-methallyl and α-allyl lactams

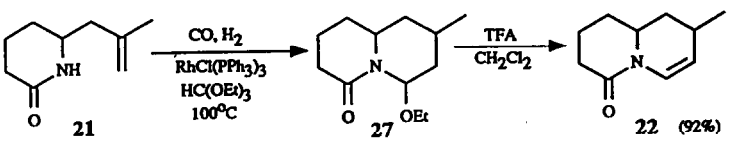
First, the hydrocarbonylation of 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) was carried out using rhodium catalysts, i.e., $RhCl(PPh_3)_3$, $HRh(CO)(PPh_3)_3$ and $Rh_4(CO)_{12}$, at 100 °C and 1200–1700 psi (83–117 bar) ($CO/H_2 = 1–7.7$). The reaction under those conditions gives a mixture of 4-methyl-1-azabicyclo[4.4.0]dec-2-en-10-one (**22**) and 4-methyl-1-azabicyclo[4.4.0]decan-10-one (**23**) (eq. 7). Typical results are listed in Table 3. As Table 3 shows, the increase in the carbon monoxide

pressure as well as the CO/H_2 ratio considerably improves the selectivity for the formation of **22**, but **22** cannot be obtained with high selectivity (entries 3 and 4).

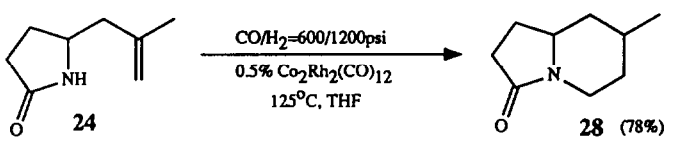
(7) 

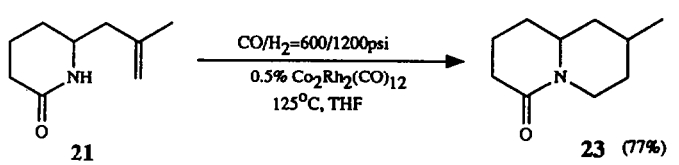
Next, we carried out the reactions of 5-(2-methyl-2-propenyl)-pyrrolidi-2-one (**24**) and **21** in the presence of triethyl orthoformate at 100 °C and 1800 psi (124 bar) ($CO/H_2 = 1$), which gave the corresponding bicyclic *O*-ethyl hemiamidals, **25** and **27**, respectively, in excellent yields (by NMR analyses). The reaction mixture thus obtained was treated with trifluoroacetic acid (TFA) in dichloromethane to give the enamides, **26** and **22**, in 86% and 92% overall yields, respectively (eqs. 8, 9).

(8) 

(9) 

The $Co_2Rh_2(CO)_{12}$-catalyzed reactions of **24** and **21** at 125 °C and 1800 psi (124 bar) ($CO/H_2 = 0.5$) cleanly gave the saturated bicyclic lactams, 4-methyl-1-azabicyclo[4.3.0]nonan-9-one (**28**, 78% yield) and 4-methyl-1-azabicyclo[4.4.0]decan-10-one (**23**, 77% yield), respectively, as the sole isolated products (eqs. 10, 11). The results demonstrate the synergistic effect of the mixed metal catalyst system.

(10) 

(11) 

Next, the reactions of 6-(2-propenyl)piperidin-2-one (**29**) catalyzed by $RhCl(PPh_3)_3$ were carried out at 100 °C and 1800 psi (124 bar) ($CO/H_2 = 1$), which gave a mixture of 1-azabicyclo[4.4.0]dec-2-en-10-one (**30**), 1-azabicyclo[4.4.0]-decan-10-one (**31**), 3-methyl-1-azabicyclo[4.3.0]non-2-en-9-none (**32**), and 2-formyl-3-methyl-1-azabicyclo[4.3.0]nonan-9-one (**33**) (eq. 12). Results are listed in Table 4. As Table 4 shows, almost no regioselectivity is observed for the reaction without phosphine additive (entry 1). However, the addition of 10 equivalents of triphenylphosphine or 5 equivalents of dppb to the Rh catalyst remarkably improves the

Table 3

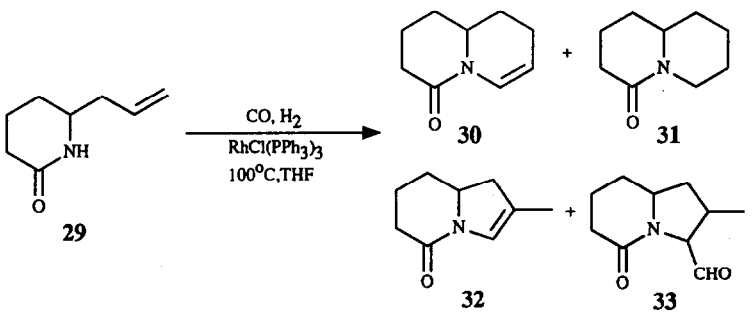
Rh-catalyzed hydrocarbonylation of 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) [a]

Entry	Catalyst (mol%)	CO (psi)	H_2 (psi)	Conversion [b] (%)	Yield (%) [b]	
					22	**23**
1	$Rh_4(CO)_{12}$ (0.25)	600	600	100	49	26
2	$HRh(CO)(PPh_3)_3$ (1.0)	1000	600	100	51	24
3		1500	200	92	62	15
4	$RhCl(PPh_3)_3$ (1.0)	1000	200	86	65	10

[a] All reactions were run with use of a Pyrex vessel (50 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) in THF (3.6 ml) at 100 °C for 18 h. [b] Determined by ^1H NMR and GLC analyses.

normal selectivity (n/iso = 9) to give the enamide (**30**) as the predominant product (entries 2 and 4).

(12)



Consequently, the Rh as well as Rh–Co complex-catalyzed hydrocarbonylation–annulation of α-methallyl and α-allyl lactams provide new and efficient routes to indolizidine and quinolizidine skeletons, which can serve as very useful intermediates for the syntheses of a variety of more complex alkaloids as well as other nitrogen heterocycles.

Table 4

Rh-catalyzed hydrocarbonylation of 6-(2-propenyl)piperidin-2-one (**29**) [a]

Entry	Ligand	Ligand/ Cat.	Yield [b] (%)	Products ratio (%) [b]				n/iso [b]
				30	**31**	**32**	**33**	
1	None	–	93	26	25	–	49	1.0
2	PPh_3	10	92	85	5	4	6	9.0
3	dppb [c]	2	90	52	8	12	28	1.5
4	dppb	5	93	87	3	10	–	9.0

[a] All reactions were run with use of a Pyrex vessel (50 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of 6-(2-propenyl)piperidin-2-one (**29**) and 1.5×10^{-2} mmol of $RhCl(PPh_3)_3$ in THF (3.6 ml) at 100 °C for 18 h. [b] Determined by ^1H NMR and GLC analyses. [c] For the abbreviation for dppb, see the footnote *c* of Table 1.

Experimental

General method

Melting points were measured with a Thomas-Hoover Unimelt and are uncorrected. The ^1H NMR spectra were measured with a Nicolet NT-300, or a GE QE-300 spectrometer with Me_4Si as the internal standard. ^{13}C NMR spectra were measured with a GE QE-300 spectrometer. ^2H NMR spectra were measured with Nicolet NT-300 spectrometer with $CDCl_3$ as the internal standard. The IR spectra were recorded on a Perkin–Elmer Model 1600 FT-IR spectrometer with samples as neat liquid or KBr disks. Analytical gas chromatography was carried out with a Hewlett Packard 5830A, or a Perkin–Elmer 3920 with a Hewlett Packard 3380A integrator gas chromatography using columns packed with Dexsil-300, or OV-17. Mass spectra (GC-MS) were recorded on a Hewlett Packard HP 5980A mass spectrometer equipped with a HP 5710A gas chromatograph and a HP 5933A data system, or a HP 5890 series II gas chromatography with a HP 5971 A mass selective detector (70 eV). 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. Microanalyses were performed at the M-H-W Laboratories, Phoenix, AZ.

Materials

Dicobalt octacarbonyl and 1,4-bis(diphenylphosphino)butane (dppb) were purchased from Strem Chemicals, Inc. and used as obtained. The rhodium complex, $RhCl(PPh_3)_3$, was obtained from Engelhard Industries KK. Other rhodium complexes, $HRh(CO)(PPh_3)_3$ [13], $RhCl(CO)(PPh_3)_2$ [14], $Rh_4(CO)_{12}$ [15], $Co_2Rh_2(CO)_{12}$ [16], $[Rh(NBD)_2]ClO_4$ (NBD = norbornadiene) [17], were prepared by the literature methods. Carbon monoxide, hydrogen and deuterium were purchased from LINDE Specialty Gases. Silica gel used for chromatography, MN-Kieselgel 60 (silica gel 60), was purchased from Brinkmann Instruments, Inc. Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium/benzophenone. *N*-Allylacetamide, *N*-allylbenzamide, *N*-methallylbenzamide, 5-(2-methyl-2-propenyl)pyrrolidin-2-one (**24**) and 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) were prepared by known methods [8,18]. All other chemicals were purchased from Aldrich Chemical Co., Inc.

Hydroformylation of N*-allylacetamide catalyzed by* $RhCl(PPh_3)_3$

To a 25 ml Pyrex reaction vessel containing 1.50 mmol of *N*-allylacetamide and 1.50×10^{-2} mmol of $RhCl(PPh_3)_3$ was added dry THF (3.6 ml) via syringe under argon. The reaction vessel was placed in a 300-ml stainless steel autoclave, and charged with carbon monoxide (900 psi; 62 bar) and hydrogen (900 psi; 62 bar) (initial pressure at 20 °C). The mixture was stirred at 100 °C for 18 h. The autoclave was cooled in an ice-water bath for 30 min, the gases released carefully from the autoclave, and the solvent evaporated to give the crude product, consisting of 2-methyl-3-(acetylamino)propanal (**1**), 1-acetylpyrrolidine (**3**), and 1-acetyl-2-formylpyrrolidine (**4**). The crude product was submitted to GLC and NMR analyses to determine the yield and the product ratio. The products, **1**, **3**, and **4**, were isolated by a column chromatography on silica gel (eluant: hexane/EtOAc = 1).

In a similar manner, the hydroformylations of *N*-allylacetamide catalyzed by $RhCl(CO)(PPh_3)_2$, $HRh(CO)(PPh_3)_3$, $Rh_4(CO)_{12}$ and $Co_2Rh_2(CO)_{12}$ were carried out. Results are summarized in Table 1. In the reaction catalyzed by $HRh(CO)(PPh_3)_3$ or $Rh_4(CO)_{12}$ (entries 4, 5, Table 1), the ^1H NMR spectrum of the reaction mixture showed an aldehyde proton peak at δ 9.74 (t, J 1.0 Hz, 1H), which was assigned to 4-(acetylamino)butanal (**2**).

Hydroformylation of N*-allylacetamide catalyzed by [Rh(dppb)(NBD)]ClO_4*

The catalyst solution was prepared by adding dry THF (3.6 ml) to a mixture of $[Rh(NBD)_2]ClO_4$ (1.50×10^{-2} mmol) and dppb (1.58×10^{-2} mmol) in a 25 ml Schlenk tube via syringe under argon followed by stirring for 20 min at room temperature. The catalyst solution was then transferred into a 50-ml reaction vessel containing 1.50 mmol of *N*-allylacetamide via syringe under argon. The hydroformylation was carried out in a 300-ml stainless steel autoclave under the same reaction conditions as described above and products were analyzed by GLC and NMR analyses.

1: colorless oil; ^1H NMR ($CDCl_3$) δ 1.03 (d, J 7.2 Hz, 3H), 1.85 (s, 3H), 2.60 (m, 1H), 3.33 (m, 2H), 6.74 (bs, 1H), 9.67 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.03, 23.20, 39.44, 170.72, 203.64; IR (neat, cm^{-1}) 3320 (ν(NH)), 1718 (ν(CO)), 1654 (ν(CO)). Anal. Found: C, 56.39; H, 7.64; N, 10.38. $C_6H_{10}NO_2$ calc: C, 56.23; H, 7.87; N, 10.93%.

3 [19]: colorless oil; ^1H NMR ($CDCl_3$) δ 1.37–1.95 (m, 4H), 1.99 (s, 3H), 3.36 (t, J 6.8 Hz, 2H), 3.39 (t, J 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.36, 24.48, 25.99, 45.45, 47.32, 169.19; IR (neat, cm^{-1}) 1631 (ν(CO)).

4: colorless oil; ^1H NMR ($CDCl_3$) δ 2.05 (m, 4H), 2.14 (s, 3H), 3.60 (m, 2H), 4.46 (m, 1H), 9.54 (d, J 1.8 Hz, 1H); IR (neat, cm^{-1}) 2720 (CHO), 1730 (ν(CO)), 1620 (ν(CO)); MS (*m/e*) 141 (M^+, 0.5), 113 (22), 112 (79), 70 (100).

Hydroformylation of N*-allylbenzamide catalyzed by $Ru_3(CO)_{12}$*

In a similar manner, the reaction was carried out with *N*-allylbenzamide (1.81 mmol), $Ru_3(CO)_{12}$ (1.81×10^{-2} mmol) in THF (4.4 ml) at 100 °C and 1,800 psi (124 bar) ($CO/H_2 = 1$) for 18 h. The products were isolated by a column chromatography on silica gel (eluant: hexane/EtOAc = 1) to give 2-methyl-3-benzoylaminopropanal (**5**, 40% yield), 4-(benzoylamino)butanal (**6**, 23% yield), and *N*-(1-propenyl)benzamide (**7**, 11% yield).

5: colorless oil; ^1H NMR ($CDCl_3$) δ 1.22 (d, J 7.5 Hz, 3H), 2.79 (m, 1H), 3.54 (m, 1H), 3.72 (m, 1H). 6.75 (bs, 1H), 7.43 (m, 2H), 7.73 (m, 2H), 9.72 (s, 1H); IR (neat, cm^{-1}) 3140–3680 (ν(NH)), 2720 (CHO), 1720 (ν(CO)), 1640 (ν(CO)); MS (*m/e*) 191 (M^+, 0.8), 163 (9.9), 162 (5.7), 105 (100), 77 (38).

6: colorless oil; ^1H NMR ($CDCl_3$) δ 1.93 (t, J 7.0 Hz, 2H), 2.58 (t, J 7.0 Hz, 2H), 3.46 (m, 2H), 7.40 (m, 3H), 7.77 (m, 2H), 9.78 (s, 1H); MS (*m/e*) 163 (6.0), 162 (5.7), 105 (100), 77 (38).

7 [19]: pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.74 (d, J 6.9 Hz, 3H), 5.33 (m, 1H), 6.96 (m, 1H), 7.42 (m, 3H), 7.81 (m, 2H), 7.75–7.90 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 14.80, 108.81, 123.77, 127.02, 128.58, 131.65.

Hydroesterification of N*-allylbenzamide catalyzed by $PdCl_2(PPh_3)_2$*

A 50-ml reaction vessel containing a solution of $PdCl_2(PPh_3)_2$ (1.50×10^{-2} mmol) and *N*-allylbenzamide (1.50 mmol), methanol (17.8 mmol; 0.72 ml) in

benzene (2.26 ml) under argon was placed in a 300-ml stainless steel autoclave. The autoclave was filled with carbon monoxide (1350 psi; 93 bar) (initial pressure at 20 °C), and the reaction was carried out at 80 °C for 18 h with stirring. After the pressure was released and the solvent removed, the reaction mixture was submitted to GLC and NMR analyses. The reaction mixture was then submitted to a column chromatography on silica gel (eluant: hexane/EtOAc = 1/2) to give methyl *N*-benzoyl-α-methyl-β-alaninate (**8**, 71% yield) and methyl 4-(benzoylamino)butanoate (**9**, 18% yield).

8: colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, *J* 7.3 Hz, 3H), 2.84 (m, 1H), 3.51 (m, 1H), 3.71 (m, 1H), 3.72 (s, 3H), 6.83 (bs, 1H), 7.75 (m, 3H), 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.74, 39.24, 41.95, 51.74, 126.79, 128.33, 131.28, 134.22, 167.45; IR (neat, cm^{-1}) 3326 (ν(NH)), 1735 (ν(CO)), 1644 (ν(CO)); MS (*m/e*) 221 (M^+, 0.7), 190 (1.0), 134 (7.0), 116 (9.0), 105 (100), 77 (27).

9: colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 2H), 2.46 (t, *J* 6.9 Hz, 2H), 3.54 (m, 2H), 3.67 (s, 3H), 6.63 (bs, 1H), 7.75 (m, 3H), 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.35, 31.49, 39.40, 51.52, 126.79, 128.26, 131.15, 134.22, 175.91; IR (neat, cm^{-1}) 3326 (ν(NH)), 1735 (ν(CO)), 1644 (ν(CO)); MS (*m/e*) 221 (M^+, 0.5), 190 (0.5), 148 (4.0), 116 (22), 105 (100), 77 (29).

Hydroformylation of N-*methallylbenzamide*

The hydroformylation of *N*-methallylbenzamide was carried out in a manner similar to that described for that of *N*-allylacetamide. The reaction mixture was submitted to GLC and NMR analyses. The reaction conditions and results are summarized in Table 2. The reaction products, 1-benzoyl-2-formylpyrrolidine (**13**), 1-benzoylpyrrolidine (**14**), and 1-benzoyl-2-hydroxylpyrrolidine (**15**), were isolated by a column chromatography on silica gel (eluant: hexane/EtOAc = 1).

13 (a mixture of two diastereomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ [1.01 (d, *J* 6.5 Hz), 1.06 (d, *J* 6.1 Hz)] (3H), 1.53–2.38 (m, 3H), [3.15 (dd, *J* 7.7, 1.0 Hz), 3.25 (dd, *J* 10.1, 10.1 Hz)] (1H), [3.69 (dd, *J* 7.7, 10.1 Hz), 3.74 (dd, *J* 6.8, 10.1 Hz)] (1H), [4.60 (m), 4.73 (m)] (1H), 7.30–7.61 (m, 5H), [9.65 (d, *J* 2.3 Hz), 9.72 (d, *J* 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (16.52, 17.09), (32.75, 33.94), (33.70, 34.09), (56.56, 57.03), (64.77, 65.45), (127.04, 127.26), 128.12, (130.16, 130.39), (199.12, 199.46); IR (neat, cm^{-1}) 1732 (ν(CO)), 1628 (ν(CO)); Anal. Found: C, 71.60; H, 7.05; N, 6.54. $C_{13}H_{15}NO_2$ calc.: C, 71.86; H, 6.96; N, 6.45%.

14 (a mixture of two diastereomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ [1.01 (d, *J* 6.3 Hz), 1.13 (d, *J* 6.6 Hz)] (3H), 1.53 (m, 1H), 1.97–2.34 (m, 2H), [3.02 (dd, *J* 9.4, 9.4 Hz), 3.17 (dd, *J* 8.5, 12.0 Hz)] (1H), 3.42–3.82 (m, 3H), 7.40 (m, 3H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (17.22, 17.75), (32.25, 34.12), (32.32, 34.20), (45.92, 49.24), (53.19, 56.55), 126.96, 128.11, 129.73; IR (neat, cm^{-1}) 1616 (ν(CO)); MS (*m/e*) 189 (24, M^+), 188 (17), 174 (15), 146 (10), 105 (100), 77 (47); Anal. Found: C, 76.01; H, 7.85; N, 7.36. $C_{12}H_{15}NO$ calc.: C, 76.15; H, 7.99; N, 7.40%.

15 (a mixture of two diastereomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ [1.02 (d, *J* 6.6 Hz), 1.07 (d, *J* 6.6 Hz)] (3H), 1.55–1.66 (m, 1H), 2.01–2.11 (m, 1H), 2.42–2.60 (m, 1H), [3.09 (dd, *J* 10.0, 10.0 Hz), 3.30 (dd, *J* 10.3, 10.3 Hz)] (1H), [3.54 (dd, *J* 6.8, 10.3 Hz), 3.64 (dd, *J* 7.2, 10.0 Hz)] (1H), 4.63 (bs., 1H), 5.81 (d, *J* 5.6 Hz, 1H), 7.37–7.77 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (16.83, 17.05), 31.54, 40.03, (55.74, 56.16), (82.20, 82.73), 127.03, 128.05, 130.25; IR (neat, cm^{-1}) 3348 (ν(OH)), 1638 (ν(CO));

MS (m/e) 205 (1, M^+), 188 (1), 105 (100), 77 (42), 51 (7); Anal. Found: C, 70.38; H, 7.19; N, 6.85. $C_{12}H_{15}NO_2$ calc.: C, 70.22; H, 7.37; N, 6.82%.

Hydrocarbonylation of N*-methallylbenzamide catalyzed by* $Co_2(CO)_8$

The catalyst solution was prepared in a 25-ml Schlenk flask by mixing $Co_2(CO)_8$ (1.5×10^{-2} mmol) and THF (3.8 ml) under argon, followed by stirring for 20 min. To a 50-ml reaction vessel containing *N*-methallylbenzamide (1.50 mmol) was added the catalyst solution via syringe under argon. The reaction vessel was placed in a 300-ml stainless steel autoclave, and charged with carbon monoxide and hydrogen (2000 psi; 138 bar) ($CO/H_2 = 1$). The reaction was carried out at 125 °C for 18 h with stirring. After the pressure was released from the autoclave and the solvent removed, the reaction mixture was dissolved in 10% aqueous sodium carbonate and extracted with ethyl acetate. The two layers were separated and the aqueous layer was acidified with phosphoric acid and extracted with ethyl acetate. The removal of solvent in vacuo from the extract gave the crude product, which was dissolved in chloroform. To this chloroform solution was added an excess amount of diazomethane ether solution at room temperature, and the mixture was stirred overnight at room temperature. The solvent was removed and the resulting crude product was submitted to a column chromatography on silica gel (eluant: hexane/EtOAc = 1/2) to afford methyl *N*-benzoylvalinate (**16**) in 45% yield.

16: m.p. 93–95 °C, ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J 7.0 Hz, 3H), 1.02 (t, J 7.0 Hz, 3H), 2.29 (m, 1H). 3.78 (s, 3H), 4.80 (dd, J 4.9, 8.6 Hz, 1H), 6.68 (d, J 8.6 Hz, 1H), 7.42–7.52 (m, 3H), 7.82 (d, J 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.92, 18.96, 31.59, 52.22, 57.38, 127.00, 128.56, 131.69, 134.083, 167.27, 172.65; IR (KBr, cm^{-1}) 3347 (ν(NH)), 1739 (ν(CO)), 1641 (ν(CO)); MS (m/e) 235 (1.7, M^+), 176 (5.4), 134 (19.6), 105 (100).

Controlled experiments with the cyclic hemiamidal ***15***

Controlled experiments were carried out in a manner similar to those described for the hydrocarbonylation of *N*-allylacetamide and *N*-(2-methyl-2-propenyl)benzamide. The reactions were carried out with the hemiamidal **15** (30.7 mg, 1.50 mmol) in 3.8 ml of THF.

The $RhCl(PPh_3)_3$-catalyzed reaction was carried out with 1.50×10^{-2} mmol of $RhCl(PPh_3)_3$ at 100 °C and 1800 psi (124 bar) ($CO/H_2 = 5$) for 18 h. The $Co_2Rh_2(CO)_{12}$-catalyzed reaction was run with 1.50×10^{-2} mmol of $Co_2Rh_2(CO)_{12}$ at 100 °C and 1200 psi (83 bar) ($CO/H_2 = 1$) for 18 h. For these reactions, the crude reaction mixture was subjected to GLC and NMR analyses. The yields of **13** and **14** were at least 95%.

The $Co_2(CO)_8$-catalyzed reaction was run with 0.15 mmol of $Co_2(CO)_8$ at 125 °C and 2000 psi (138 bar) ($CO/H_2 = 1$). After the solvent was removed, the reaction mixture was dissolved in 10% aqueous sodium carbonate and extracted with ethyl acetate. The aqueous layer was acidified with phosphoric acid and extracted with ethyl acetate. The removal of solvent *in vacuo* gave *N*-benzoyl-4-methylproline (**17**) (25.2 mg, 72% yield), which was converted to the corresponding methyl ester, methyl *N*-benzoyl-4-methylprolinate (**17′**) by reaction with diazomethane in ether in nearly quantitative yield.

17′ (a mixture of two diastereomers): colorless oil; ^{1}H NMR ($CDCl_3$) δ [1.00 (d, J 6.7 Hz), 1.05 (d, J 6.5 Hz)] (3H), 1.51–2.51 (m, 3H), [3.11 (dd, J 7.7, 10.3 Hz),

3.29 (dd, J 10.3, 10.3 Hz)] (1H), 3.58–3.78 (m, 1H), 3.78 (s, 3H), [4.65 (dd, J 7.7, 10.1 Hz), 4.72 (dd, J 3.7, 8.7 Hz)] (1H), 7.42 (m, 3H), 7.58 (m, 2H); IR (neat, cm^{-1}) 1743 (ν(CO)), 1632 (ν(CO)); MS (m/e) 247 (1.1, M^+), 188 (16.1), 105 (100); Anal. Found: C, 67.81; H, 7.05; N, 5.40. $C_{14}H_{17}NO_2$ calc.: C, 67.99; H, 6.93; N, 5.6%.

The $Co_2Rh_2(CO)_{12}$-catalyzed reaction in absence of carbon monoxide was carried out with **15** (73.7 mg, 0.36 mmol) and $Co_2Rh_2(CO)_{12}$ (2.2 mg, 3.6×10^{-3} mmol) in 1.5 ml of THF at 100 °C and 600 psi (41 bar) of hydrogen for 18 h with stirring. The crude product was submitted to a column chromatography on silica gel (eluant: hexane/EtOAc = 1) to give 3-methyl-4-(benzoylamino)butanol (**20**) as a yellow oil (62 mg, 83% yield).

20: ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J 6.8 Hz, 3H), 1.52–1.92 (m, 3H), 3.34 (t, J 6.2 Hz, 2H), 3.75 (m, 2H), 4.15 (bs., 1H), 7.24 (bs., 1H), 7.28–7.49 (m, 3H), 7.77 (d, J 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.36, 30.85, 37.12, 45.77, 60.39, 126.89, 128.40, 131.27, 134.52, 168.0; IR (neat, cm^{-1}) 3321 (ν(OH, NH)), 1713 (ν(CO)), 1643 (ν(CO)); MS (m/e) 207 (M^+, 0.3), 189 (0.8), 134 (12), 122 (13), 105 (100), 77 (24).

Labeling experiments—carbonylation and hydrogenolysis of the hemiamidal ***15***

The $RhCl((PPh_3)_3$-catalyzed deuterioformylation was carried out with $RhCl(PPh_3)_3$ (1.23×10^{-2} mmol) and **15** (1.23 mmol) in THF (3.7 ml) at 100 °C and 1650 psi (114 bar) ($CO/D_2 = 10$) for 18 h. The reaction mixture was subjected to GLC analysis and then submitted to a column chromatography on silica gel (eluant: hexane/EtOAC = 1) to give deuteriated 1-benzoyl-2-formyl-4-methylpyrrolidines (**13-D$_n$**) in 90% yield. The results of mass spectroscopic analysis are shown in Table 5 and the ^{1}H NMR and ^{2}H NMR spectra of **13-D$_n$** are shown in Fig. 1.

In a similar manner, the $Co_2Rh_2(CO)_{12}$-catalyzed reaction was run with **15** (0.51 mmol) and $Co_2Rh_2(CO)_{12}$ (5.1×10^3 mmol) in 1.5 ml of THF at 100 °C and 300 psi (30.5 bar) ($CO/D_2 = 1$) for 18 h. The result of mass spectroscopic analysis is summarized in Table 6 and the ^{1}H NMR and ^{2}H NMR spectra are shown in Fig. 2.

Table 5

MS data for the labeled formylation products (**13-D$_n$**) [a]

m/e	Abundance (%)	Labeled products				Deuterium incorporated [b]
		13-D$_0$	**13-D$_1$**	**13-D$_2$**	**13-D$_3$**	
188	2.6	2.6	–	–	–	0
189	12.6	1.4	11.2	–	–	1
190	11.2	0.2	6.0	5.0	–	2
191	6.6	–	0.8	2.7	3.1	3
192	4.0	–	–	0.4	1.6	
Total %		12	51	23	14	

[a] MS data determined for 1-benzoyl-2-formyl-4-methylpyrrolidine (**13**): 188 ($M^+ - 29$, 49.8), 189 (27.0), 190 (3.6). [b] Deuterium incorporated on the pyrrolidine ring.

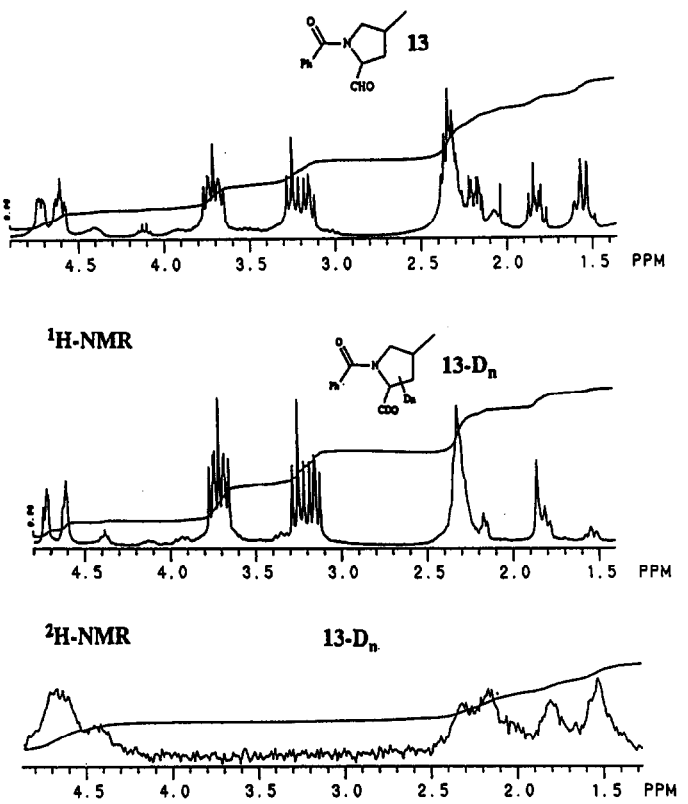


Fig. 1. ^{1}H and ^{2}H NMR spectra of *N*-benzoyl-2-formyl-4-methylpyrrolidines **13** and **13-D$_n$**.

Table 6

MS data for labeled hydrogenolysis products (**14-D$_n$**) [a]

m/e	Abundance (%)	Labeled products			Deuterium incorporated [b]
		14-D$_3$	**14-D$_2$**	**14-D$_1$**	
188	1.2	–	–	0.6	
189	6.3	–	2.0	1.9	
190	12.7	2.6	6.0	4.1	1
191	25.2	7.9	17.0	0.3	2
192	23.9	22.0	1.9	–	3
193	5.7	3.0	–	–	
Total %		51	39	10	

[a] MS data determined for 1-benzoylpyrrolidine (**14**): 188 (21.4), 189 (M^+, 44.5), 190 (6.0), 191 (1.2).
[b] Deuterium incorporated on the pyrrolidine ring.

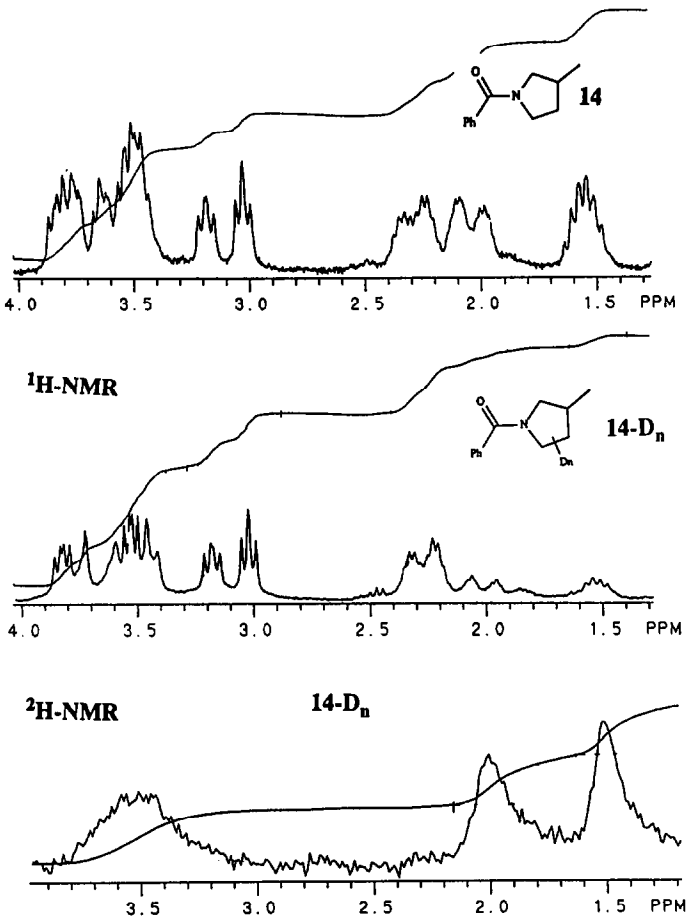


Fig. 2. ^{1}H and ^{2}H NMR spectra of *N*-benzoylpyrrolidines **14** and **14-D$_n$**.

Hydrocarbonylation of 6-(2-methyl-2-propenyl)piperidin-2-one (21)

In a manner similar to that for the $RhCl(PPh_3)_3$-catalyzed hydroformylation of *N*-allylacetamide, the reactions were carried out with 1.50×10^{-2} mmol of a rhodium catalyst and 1.50 mmol of **21** in 3.6 ml of THF at 100 °C and 1200–1700 psi (83–117 bar) ($CO/H_2 = 1$–7.7) for 18 h. The reaction mixture was subjected to GLC and NMR analyses. Results are summarized in Table 3. The authentic samples of 4-methyl-1-azabicyclo[4.4.0]dec-2-en-10-one (**22**) and 4-methyl-1-azabicyclo-[4.4.0]decan-10-one (**23**) were obtained in the highly selective reactions described below.

Synthesis of 4-methyl-1-azabicyclo[4.3.0]non-2-en-9-one (26) and 4-methyl-1-azabicyclo[4.4.0]dec-2-en-10-one (22)

A 50-ml reaction vessel containing 5-(2-methyl-2-propenyl)-pyrrolidin-2-one (**24**) (185 mg, 1.33 mmol) and $Rh_4(CO)_{12}$ (5.0 mg, 6.7×10^{-3} mmol) in triethyl orthoformate (3.3 ml), was placed in a 300-ml stainless steel autoclave. The reaction was carried out at 100 °C and 1800 psi (124 bar; $CO/H_2 = 1$; 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 the solvent removed to give the reaction mixture. The NMR analysis of the reaction mixture showed that the hemiamidal **25** was formed. The reaction mixture was dissolved in 15 ml of dichloromethane, and cooled on an ice-water bath. Several drops of trifluoroacetic acid (TFA) were added to the solution. The progress of the reaction was monitored by GLC analysis every 15 min, and additional TFA was provided until all of the hemiamidal **25** was consumed. The reaction mixture was extracted with dichloromethane (3 × 30 ml), washed with 10% sodium carbonate and brine, dried over anhydrous Na_2SO_4, the solvent removed under reduced pressure to give the crude product. The crude product was purified by bulb-to-bulb distillation to give **26** (172 mg, 86% yield) as a pale yellow oil.

26 (a mixture of two diastereomers): ^{1}H NMR ($CDCl_3$) δ [1.05 (d, J 3.5 Hz) (A), 1.07 (d, J 3.7 Hz) (B)] (3H), 1.54–1.86 (m, 3H), 2.15–2.54 (m, 4H), 3.74 (m, 1H), [4.88 (d, J 8.0 Hz) (A), 5.11 (dd, J 5.5, 8.0 Hz) (B)] (1H), [6.72 (d, J 8.0 Hz) (A), 6.75 (d, J 8.0 Hz) (B)] (1H); ^{13}C NMR ($CDCl_3$) 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 (64.2, M^+), 136 (100). Anal. Found: C, 71.31; H, 8.66; N, 9.09. $C_9H_{15}NO$ calc.: C, 71.49; H, 8.66; N, 9.26%.

Under the same reaction conditions, **22** was obtained as a colorless oil (0.152 g, 92% yield) in the reaction using 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) (153 mg, 1.00 mmol), $Rh_4(CO)_{12}$ (3.7 mg, 5×10^{-3} mmol) and $HC(OEt)_3$ (2.5 ml).

22: ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J 7.2 Hz, 3H), 1.47–1.97 (m, 6H), 2.29–2.50 (m, 3H), 3.45 (m, 1H), 7.20 (d, J 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.74, 21.89, 25.89, 29.94, 32.17, 36.55, 50.17, 115.18, 122.22, 166.99; IR (neat, cm^{-1}) 1722 (ν(NH)), 1714 (ν(NH)), 1651, 1644; MS (m/e) 165 (73.2, M^+), 150 (100). Anal. Found: C, 72.51; H, 9.06; N, 8.53. $C_{10}H_{15}NO$ calc.: C, 72.63; H, 9.15; N, 8.48%.

*Synthesis of 4-methyl-1-azabicyclo[4.3.0]nonan-9-one (**28**) and 4-methyl-1-azabicyclo [4.4.0]decan-10-one (**23**)*

In a manner similar to that described above, the reaction was carried out with 5-(2-methyl-2-propenyl)pyrrolidin-2-one (**24**) (217 mg, 1.56 mmol) and $Co_2Rh_2(CO)_{12}$ (5.0 mg, 1.56×10^{-2} mmol) in THF (3.9 ml) at 1800 psi (124 bar, $CO/H_2 = 0.5$; initial pressure at 20 °C). The mixture was stirred at 125 °C for 18 h. The crude product was purified by bulb-to-bulb distillation to give **28** (186 mg, 78% yield) as a pale yellow oil.

28 [a mixture of two diastereomers (1/1)]: ^{1}H NMR ($CDCl_3$ δ [0.968 (d, J 6.5 Hz), 1.10 (d, J 7.4 Hz)] (3H), 1.30–1.89 (m, 5H), 2.11–2.45 (m, 4H), [2.73 (m), 2.87 (m)] (1H), [3.45 (m), 3.68 (m)] (1H), [3.93 (m), 4.12 (m)] (1H); ^{13}C NMR 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 (73.2, M^+), 152 (100). Anal. Found: C, 70.31; H, 9.73; N, 9.23. $C_9H_{15}NO$ calc.: C, 70.55; H, 9.87; N, 9.14%.

Under the same conditions, **23** was obtained as a colorless oil (208 mg, 77% yield) in the reaction using 6-(2-methyl-2-propenyl)piperidin-2-one (**21**) (248 mg, 1.62 mmol), $Co_2Rh_2(CO)_{12}$ (5.4 mg, 8.1×10^{-3} mmol) and THF (4.1 ml).

23: ^{1}H NMR ($CDCl_3$) δ [0.94 (dd, J 2.1, 6.3 Hz), 1.09 (dd, J 2.1, 6.3 Hz)] (3H), 1.38–2.35 (m, 9H), 2.37–2.74 (m, 1H), [3.23 (m), 3.46 (m)] (1H), [4.53 (m), 4.79 (m)] (1H); ^{13}C NMR ($CDCl_3$) δ 19.05, (21.73, 25.43), (30.21, 30.37), 30.95, (32.81, 33.49), 36.49, 39.50, (41.86, 42.36), (50.67, 56.11), 169.11; IR (neat, cm^{-1}) 1716 (ν(CO));

MS (*m/e*) 167 (49, M^+), 152 (100); HRMS (*m/e*). Found: 167.1309. $C_{10}H_{17}NO$ calc.: 167.1310.

Preparation of 6-(2-propenyl)piperidin-2-one (29)

To a chilled solution of 6-ethoxy-2-piperidinone (1.1 g, 7.4 mmol) and allyltrimethylsilane (2.4 ml, 15.0 mmol) in 50 ml CH_2Cl_2, boron trifluoride etherate (2.97 ml, 8.9 mmol) was added at 0 °C. The mixture was stirred overnight at room temperature. When the reaction was complete by TLC analysis, the reaction mixture was poured into brine. The organic layer was separated and the solvent removed under reduced pressure to give the crude product. The crude product was purified by a column chromatography (hexane/EtOAc = 1) to give **29** as a pale yellow solid (2.01 g, 80% yield).

29 [21]: ^{1}H NMR ($CDCl_3$) δ 1.37–1.44 (m, 1H), 1.67–1.74 (m, 1H), 1.87–1.94 (m, 2H), 2.15–2.44 (m, 4H), 3.42 (m, 1H), 5.15 (m, 2H), 5.72 (m, 1H), 6.59 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.61, 28.16, 31.12, 41.05, 51.98, 118.82, 133.21, 172.28; IR (KBr, cm^{-1}) 3196 (ν(NH)), 1676 (ν(CO)), 1636 (ν(HC=C)).

Hydrocarbonylation of 6-(2-propenyl)piperidin-2-one (29)

In a manner similar to that described above, the reaction was carried out with **29** (1.50 mmol) and a rhodium complex (1.50×10^{-2} mmol) in 3.8 ml of THF at 100 °C and 1800 psi (124 bar; $CO/H_2 = 1$) for 18 h. The products, 1-azabicyclo[4.4.0]dec-2-en-10-one (**30**), 1-azabicyclo[4.4.0]decan-10-one (**31**), 3-methyl-1-azabicyclo[4.3.0]non-2-en-9-one (**32**), and 2-formyl-3-methyl-1-azabicyclo[4.3.0]nonan-9-one (**33**), were separated by a column chromatography on silica gel (eluant: hexane/EtOAc = 1).

30 [22]: ^{1}H NMR ($CDCl_3$) δ 1.48–2.59 (m, 10H), 3.44 (t, *J* 2.2, 11.4 Hz, 1H), 5.13 (m, 1H), 7.24 (d, *J* 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.83, 22.01, 29.98, 30.23, 32.35, 55.22, 109.35, 123.72; IR (neat, cm^{-1}) 1727 (ν(CO)), 1653 (ν(HC=C); MS (*m/e*) 152 (16), 151 (M^+, 100), 150 (8), 138 (7), 123 (12), 122 (10).

31 [23]: ^{1}H NMR ($CDCl_3$) δ 1.24–2.61 (m, 13H), 3.22 (m, 1H), 4.78 (dt, *J* 1.8, 13.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.10, 24.42, 25.29, 30.43, 32.94, 33.97, 42.30, 56.80; IR (neat, cm^{-1}) 1703 (ν(CO)); MS (*m/e*) 154 (10), 153 (M^+, 100), 152 (51), 138 (52), 125 (15), 97 (64), 83 (38), 69 (22), 55 (21).

32: ^{1}H NMR ($CDCl_3$) δ 1.54–2.65 (m, 8H), 1.79 (s, 3H), 4.01 (m, 1H), 6.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.70, 20.61, 28.34, 29.96, 41.33, 59.74, 123.26, 131.85; IR (neat, cm^{-1}) 1728 (ν(CO)), 1673 (ν(HC=C); MS (*m/e*) 151 (M^+, 4), 136 (4), 122 (18), 95 (55), 94 (87), 82 (100).

33: ^{1}H NMR ($CDCl_3$), δ 1.22 (d, *J* 6.4 Hz, 3H), 1.15–1.36 (m, 2H), 1.76–2.51 (m, 7H), 3.66 (m, 1H), 3.94 (dd, *J* 2.7, 9.4 Hz, 1H), 9.56 (d, *J* 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.38, 20.95, 29.14, 30.70, 33.55, 41.86, 60.27, 70.75, 199.32; IR (neat, cm^{-1}) 2873 (CHO), 2720 (CHO), 1729 (ν(CO)), 1609 (ν(CO)); MS (*m/e*) 181 (0.4, M^+), 153 (25), 152 (100), 138 (11), 124 (7).

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