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Syntheses of nitrogen heterocycles by means of amine-directed carbonylation and hydrocarbonylation *,**

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Abstract

Amine-directed carbonylation of 2-allylpiperidine (**5**) gives 8-methyl-1-azabicyclo[4.3.0]nonan-9-one (**7**) with extremely high regio- and stereoselectivity, which is promoted by a stoichiometric amount of $[RhCl(CO)_2]_2$ in the presence of hydrogen chloride. A catalytic version of this process is developed, which converts 5-benzylamino-1-pentene (**9**) to 1-benzyl-3-methyl-2-piperidinone (**10**) selectively. Novel aminocarbocyclization of **9** gives 1-benzyl-3-methylpiperidine (**12**) or 1-benzylazepane (**13**) exclusively by employing appropriate hydrocarbonylation conditions. The scope and limitation of these new processes are discussed.

1. Introduction

Chelation-controlled regioselective and stereoselective reactions have been studied extensively in the application of organometallics and homogeneous catalysts for organic synthesis. Burke, Jackson and their co-workers reported intramolecular phosphine-directed hydroformylation of alkenes [1,2]. We have found that the amide functionality can serve as an effective "directing group" in regioselective hydrocarbonylations catalyzed by a variety of Group VIII transition-metal complexes [3], and a series of mono- and bicyclic nitrogen heterocycles have been synthesized from *N*-alkenylamides, alkenamides and α-allyllactams by using this method. On the other hand, Krafft *et al.* have developed amine-directed regioselective "hydrocarboxylation" of homoallylic amines forming lactams, which is promoted by stoichiometric amounts of Rh complexes in the presence of hydrogen chloride [4]. Knifton, Jackson, Alper and their co-workers reported syntheses of monocyclic nitrogen heterocycles by rhodium complex-catalyzed cyclizations of unsaturated amines [5–7].

In the course of our study on chelation-controlled regio- and stereoselective carbonylations for organic syntheses [3], we have investigated the syntheses of

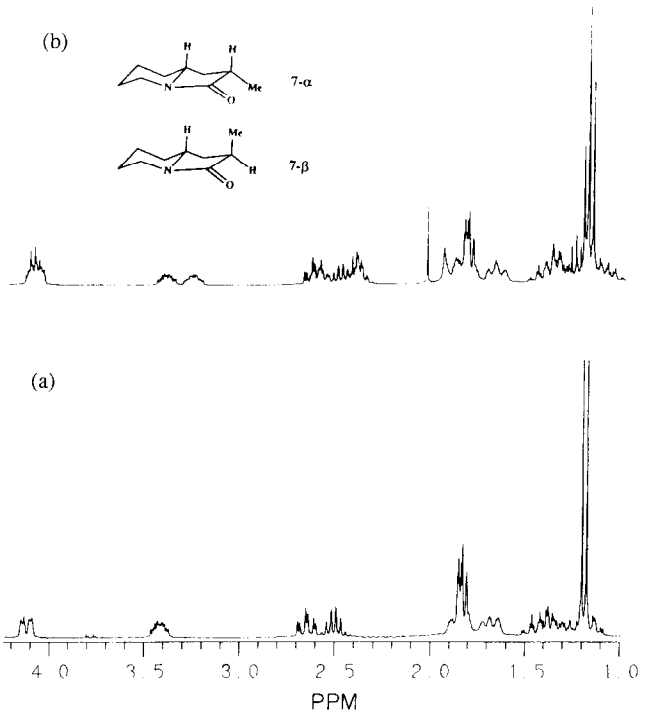

Fig. 1. ^1H NMR spectra of **7**: (a) one diastereomer tentatively assigned as **7**-α; (b) a mixture of two diastereomers.

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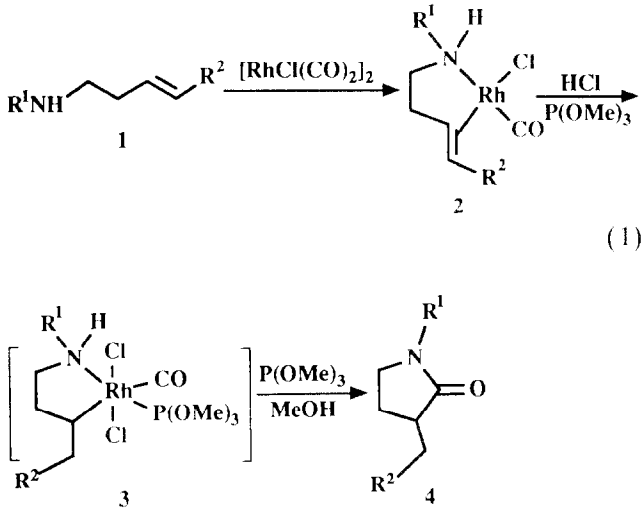
nitrogen heterocycles through amine-directed carbonylations. We describe here our study on the rhodium complex-promoted regio- and stereoselective carbonylation of 2-allylpiperidine (**5**) and 5-benzylamino-1-pentene (**9**) in the presence of hydrogen chloride, and the rhodium complex-catalyzed carbonylation and hydrocarbonylation of **5** and **9**, which give the corresponding homologated cyclic amines and lactams with high selectivities.

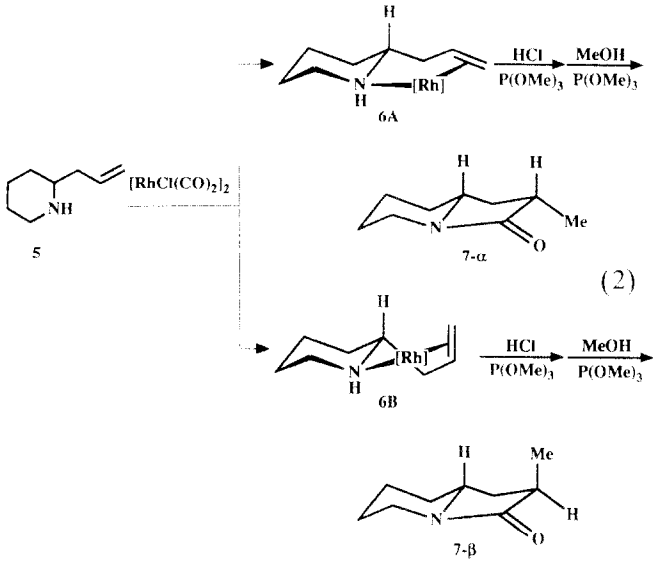
2. Results and discussion

2.1. Highly stereoselective synthesis of a bicyclic lactam through cyclocarbonylation of 2-allylpiperidine (5)

Krafft *et al.* [4] reported that in a rhodium complex-mediated regioselective "hydrocarboxylation", a homoallylic amine (**1**) was converted to an alkyl-Rh^{III} complex (**3**) via a chelated Rh^{I} complex (**2**) in the presence of hydrogen chloride and trimethylphosphite, followed by carbon monoxide insertion and methanolysis to yield a pyrrolidin-2-one (**4**) (eqn. (1)).



We applied this reaction to the diastereoselective annulation of 2-allylpiperidine (**5**) which should give a bicyclic lactam, 3-methyl-1-azabicyclo[4.3.0]nonan-9-one (**7**) (eqn. (2)). It was assumed that the stereodetermining step of the reaction would be the formation of a chelated alkyl-Rh complex (**6A** or **6B**) and diasteroface selection at the chelated-Rh complex forming step might give one diastereomer selectively.

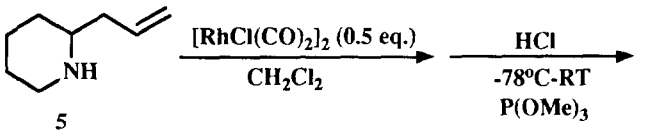


Indeed, this reaction gave **7** as the sole product in 43% isolated yield (eqn. (3)), and some starting material was recovered. The NMR analysis of the crude product indicated the formation of only one diastereomer (see Fig. 1(a)). Accordingly, this chelation-controlled reaction is not only regioselective but also diastereoselective. The stereochemistry of **7** thus obtained was tentatively assigned as 3-α-methyl isomer on the basis of NMR analyses.

TABLE 1. Cyclocarbonylation of 5-benzylamino-1-pentene (**9**) [a]

Run	Catalyst (mol%)	Temperature (°C)	HCl (mol%)	CO [b] (bar)	Conversion [c] (%)	Yield [c] (%)	Product ratio [c]	
							10	**11**
1	$[Rh(dppb)(MeOH)_2]^+ClO_4^-$ (5) [d,e]	100	10	69	92	58	84	16
2	$[Rh(BPPM)(MeOH)_2]^+ClO_4^-$ (5) [d,e]	100	10	69	100	86	92	8
3	$[Rh(BPPM)(THF)_2]^+ClO_4^-$ (5) [f]	100	10	69	89	77	82	18
4	$[Rh(BPPM)(MeOH)_2]^+ClO_4^-$ (2) [e]	100	4	69	97	84	85	15
5	$[Rh(BPPM)(MeOH)_2]^+BF_4^-$ (5) [e]	80	10	35	67	59	95	5
6	$[RhCl(CO)_2]_2$ (5) [f]	100	10	69	100	87	57	43
7	$[RhCl(CO)_2]_2$ (5) [f]	100	5	35	95	79	78	22
8	$[Rh(acac)(CO)_2]$ (5) [d,f]	100	5	35	95	75	75	25

[a] All reactions were run with the use of a Pyrex vessel (25 ml) in a stainless steel autoclave (300 ml) with 0.70–1.00 mmol of **9** in MeOH or THF (3.0–5.0 ml) for 40 h. [b] 69 bar = 1000 psi; 35 bar = 500 psi. [c] Determined by GLC analyses. [d] acac = acetylacetonate; dppb = 1,4-bis(diphenylphosphino)butane; (−)-BPPM = (2*S*, 4*S*)-*N*-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine. [e] Reaction was run in MeOH. [f] Reaction was run in THF.



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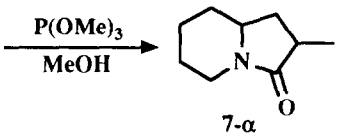
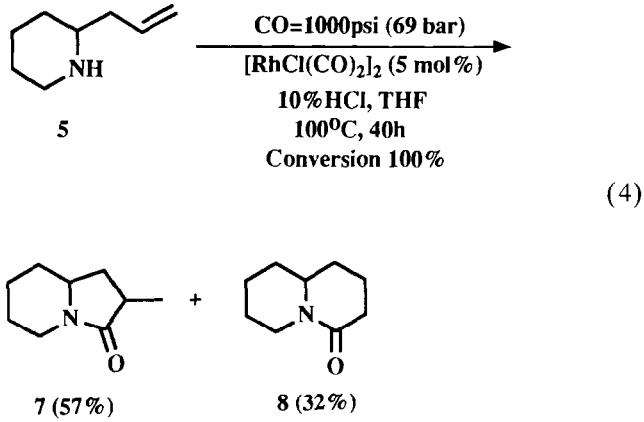


2.2. Catalytic cyclocarbonylation of 2-allylpiperidine (5) and 5-benzylamino-1-pentene (9) in the presence of hydrogen chloride

Since the process using a stoichiometric amount of a rhodium complex is not practical as a synthetic method, a catalytic version of this cyclocarbonylation was investigated. In fact, the catalytic reaction of **5** proceeded smoothly in the presence of a catalytic amount of $[RhCl(CO)_2]_2$ (5 mol%) as the catalyst as well as hydrogen chloride (10 mol%) to yield **7** (57% yield) and 1-azabicyclo[4.4.0]decan-2-one (**8**, 32% yield) (eqn. (4)), *i.e.* this catalytic reaction has only marginal regioselectivity. The NMR analyses of **7** and **8** indicated that **7** thus obtained consisted of a 1:1 mixture of two diastereomers (see Fig. 1(b)), *i.e.* this process is not diastereoselective.



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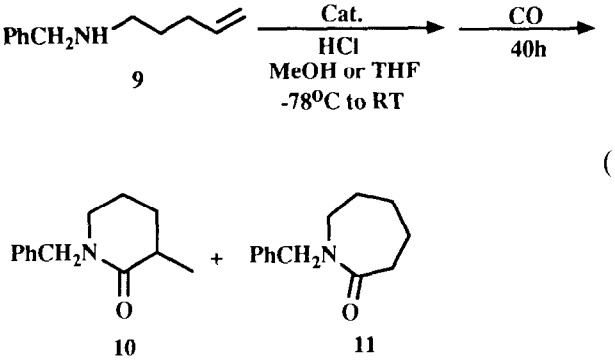
We examined catalytic and regioselective cyclocarbonylation of **9** extensively by using a variety of rhodium complexes in the presence of hydrogen chloride (eqn. (5)). Results are summarized in Table 1. The reactions catalyzed by a cationic diphosphine–Rh complex give 1-benzyl-3-methyl-2-piperidinone (**10**) and 1-benzylazepan-2-one (**11**) in ratios from 82:18 to 95:5 (entries 1–5). The results clearly indicate that the amine-directed chelation control is effectively operative in these catalytic conditions as well. The chiral ligand (−)-BPPM was used in an attempt to synthesize the chiral non-racemic products. However, the enantiomeric purity of the isolated product **10** was only *ca.* 8% ee on the basis of HPLC analysis using a chiral column, Daicel Chiracel OD. The reactions using $[RhCl(CO)_2]_2$ and $[Rh(CO)_2(acac)]$ as the catalysts under the similar conditions (entries 6 and 7) are less regioselective than those catalyzed by the cationic diphosphine–Rh complexes.



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2.3. Catalytic cyclocarbonylation of 5-benzylamino-1-pentene (9) in the absence of hydrogen chloride

Although the results shown in Table 1 seem to imply that the amount of hydrogen chloride used and the ratio of the catalyst and hydrogen chloride have some influence on the selectivity of the reaction, we have examined the possibility of running the same type of reaction in the absence of hydrogen chloride, *i.e.* the process including direct activation of amine functionality by rhodium catalysts. Indeed, this investigation has

TABLE 2. Cyclocbonylation of 5-benzylamino-1-pentene (**9**) in the absence of hydrogen chloride [a]

Run	Catalyst (mol%)	Temperature (°C)	CO [b] (bar)	Conversion [c] (%)	Product ratio [c]	
					10	**11**
1	$[RhCl(CO)_2]_2$ (5)	100	69	87	90	10
2	$[Rh(acac)(CO)_2]$ (5) [d]	100	35	59	78	22
3	$[Rh(dppb)(THF)_2]^+BF_4^-$ (2) [d]	100	35	53	92	8
4	$RhCl(PPh_3)_3$ (2.5)	100	35	88	86	14
5	$HRh(CO)(PPh_3)_3$ (2)	100	35	73	98	2
6	$Co_2Rh_2(CO)_{12}$ (2.5)	100	35	80	98	2
7	$Co_2(CO)_8$ (10)	125	69	0	–	–

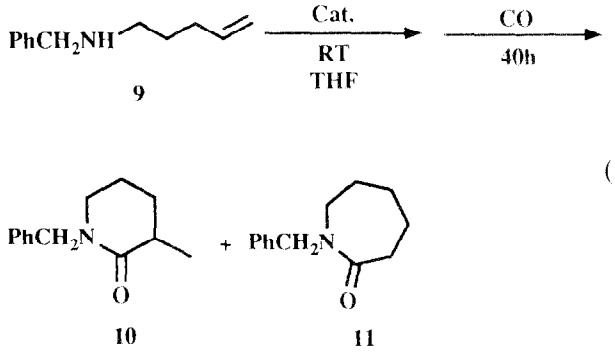
[a] All reactions were run with the use of a Pyrex vessel (25 ml) in a stainless steel autoclave (300 ml) with 1.00 mmol of **9** in THF (5.0 ml) for 40 h. [b] 69 bar = 1000 psi; 35 bar = 500 psi. [c] Determined by GLC analyses. [d] For the abbreviations acac and dppb, see footnote d of Table 1.

TABLE 3. Hydrocyclocarbonylation of 5-benzylaminopentene (**9**) [a]

Entry	Catalyst (mol%)	Ligand	Temperature (°C)	CO [b] (bar)	H_2 [b] (bar)	Yield [c] (%)	Product ratio [c]	
							12	**13**
1	$RhCl(PPh_3)_3$ (1.0)	–	100	62	62	75	87	13
2	$HRh(CO)(PPh_3)_3$ (1.0)	–	100	62	62	85	**95**	5
3	$HRh(CO)(PPh_3)_3$ (1.0)	+ 5 PPh_3	100	62	62	83	25	75
4	$HRh(CO)(PPh_3)_3$ (1.0)	+ 20 PPh_3	100	62	62	81	9	91
5	$HRh(CO)(PPh_3)_3$ (1.0)	+ 5 $P(C_5H_{11})_3$	100	62	62	83	2	**98**
6	$Co_2Rh_2(CO)_{12}$ (0.5)	–	125	41	83	65	51	49
7	$Co_2(CO)_8$ (10.0)	–	125	69	69	0	–	–

[a] All reactions were run with the use of a Pyrex vessel (25 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of **9** in THF (3.0 ml) for 18 h. [b] 41 bar = 600 psi; 62 bar = 900 psi; 69 bar = 1000 psi; 83 bar = 1200 psi. [c] Determined by GLC analyses.

shown that hydrogen chloride is not necessary for the catalytic lactam forming reaction (eqn. (6)). Results of catalytic cyclocarbonylation of **9** in the absence of hydrochloric acid catalyzed by rhodium complexes as well as $Co_2Rh_2(CO)_{12}$ are listed in Table 2. These reactions give slightly lower conversions, but very good to excellent regioselectivities. The best regioselectivity (**10**/**11** = 98/2) is achieved by using $HRh(CO)(PPh_3)_3$ or $Co_2Rh_2(CO)_{12}$ (entries 5 and 6). The results clearly indicate that the amine-directed chelation control is operating in favor of the formation of six-membered ring product **10**. A cobalt complex, $Co_2(CO)_8$, is ineffective under similar conditions (entry 7).



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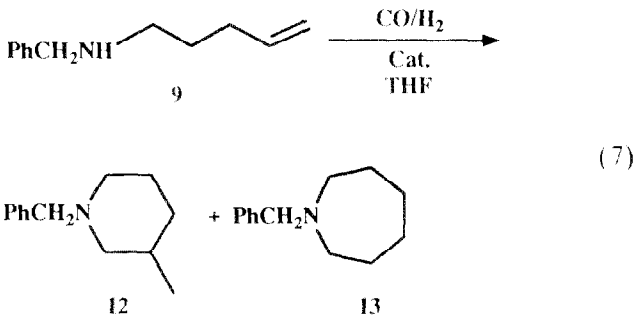
2.4. Catalytic hydrocarbonylations of 2-allylpiperidine (5) and 5-benzylamino-1-pentene (9)

The hydrocyclocarbonylations of **9** in the presence of hydrogen and carbon monoxide were carried out by using $RhCl(PPh_3)_3$, $HRh(CO)(PPh_3)_3$ and $Co_2Rh_2(CO)_{12}$ as the catalysts (eqn. (7)). An attempted reaction with $Co_2(CO)_8$ as the catalyst under typical hydroformylation conditions for this catalyst (125°C, 138 bar, $CO/H_2 = 1$) resulted in the complete recovery of the starting material **9**. Results are summarized in Table 3.



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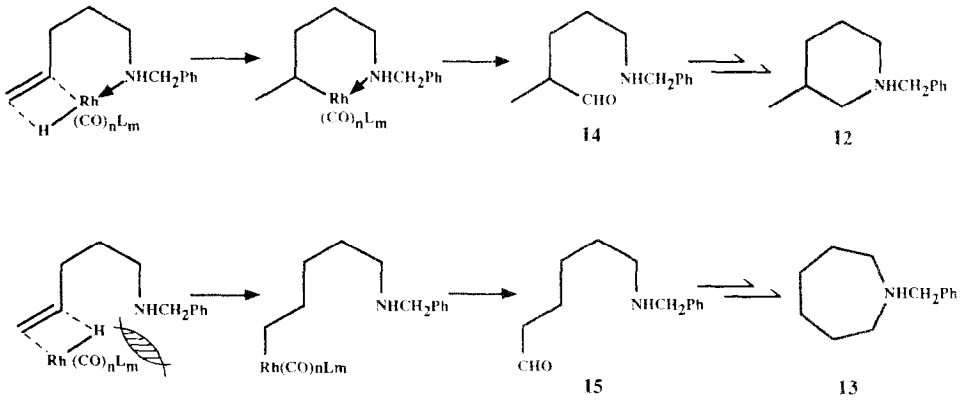
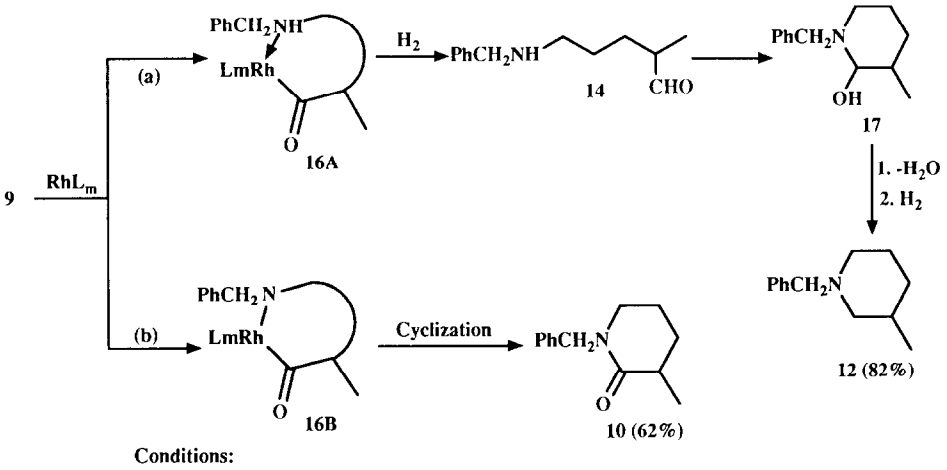
As Table 3 shows, a six-membered ring amine (**12**) or a seven-membered ring amine (**13**) can be obtained



Scheme 1.



Scheme 2.

through novel "aminocarbocyclization" process by choosing appropriate conditions. A $HRh(CO)(PPh_3)_3$-catalyzed reaction gives 1-benzyl-3-methylpiperidine (**12**) almost exclusively (entry 2). The fact that the regioselectivity observed in the present system is opposite to that for usual 1-alkenes [8] indicates that the amine-directed "chelation-control" is effectively operative, thereby favoring the formation of iso-aldehyde in the initial hydroformylation step (Scheme 1). For this reaction, $Co_2(CO)_8$ does not show any catalytic activity at all under the typical hydroformylation conditions (entry 7). The reaction catalyzed by $Co_2Rh_2(CO)_{12}$ gives a 1:1 mixture of **12** and 1-benzylazepane (**13**) in 65% yield, in which an azepane should be formed through a n-aldehyde (Scheme 1). Since the construction of the azepane skeleton is of interest in organic synthesis, the reaction has been investigated further to make it more regioselective by adding bulky phosphine ligands. As Table 3 shows, the addition of 5 equiv. of tricyclohexylphosphine or 20 equiv. of triphenylphosphine to $HRh(CO)(PPh_3)_3$ dramatically reverses the regioselectivity in favor of the formation of azepane **13** (entries 4 and 5). It is clear that $P(C_6H_{11})_3$ is an excellent ligand for this purpose. The observed remarkable reversal of regioselectivity by the addition of bulky phosphines is accommodated by taking into account an effective blocking of the amine-directed chelation control at the regio-determining step as depicted in Scheme 1.

It should also be noted that the reaction of **9** under the same reaction conditions except for a low hydrogen pressure (CO = 62 bar; H_2 = 7 bar) gave **10** selectively in 62% isolated yield. The result clearly indicates that the two types of reactions are competing processes: (a) at a high hydrogen pressure the oxidative addition of H_2 to an acyl–Rh complex (**16A**) is almost exclusive, which is followed sequentially by formation of iso-aldehyde (**14**), formation of hemiaminal (**17**), dehydration and hydrogenation to yield **12**; (b) however, at a lower hydrogen pressure the cyclization becomes pre-

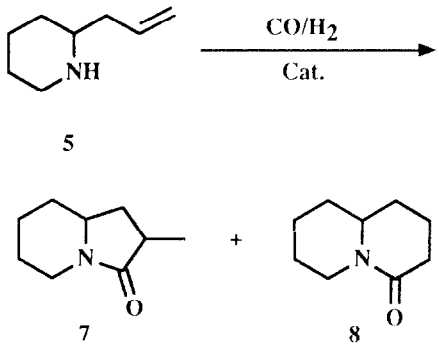
TABLE 4. Hydrocyclocarbonylation of 2-allylpiperidine (**5**) [a]

Run	Catalyst (mol%)	Temperature (°C)	CO [b] (bar)	H_2 [b] (bar)	Solvent or additive (%)	Conversion [c] (%)	Product ratio	
							7	8
1	$RhCl(PPh_3)_3$ (1.0)	100	41	41	THF	100	43	57
2	$HRh(CO)(PPh_3)_3$ (1.0)	100	62	62	$HC(OEt)_3$	100	40	60
3	$HRh(CO)(PPh_3)_3$ (1.0)	100	62	62	THF/PPh_3 (10)	100	35	65
4	$HRh(CO)(PPh_3)_3$ (1.0)	100	62	62	$THF/P(C_6H_{11})_3$ (5)	100	42	58
5	$Co_2Rh_2(CO)_{12}$ (0.5)	125	41	83	THF	100	52	48

[a] All reactions were run with the use of a Pyrex vessel (25 ml) in a stainless steel autoclave (300 ml) with 1.50 mmol of **5** in THF or $HC(OEt)_3$ (3.8 ml) for 18 h. [b] 41 bar = 600 psi; 62 bar = 900 psi; 83 bar = 1200 psi. [c] Determined by GLC analyses.

dominant, which formally does not require a hydrogen source other than amine hydrogen, to give **10** selectively.

In the same manner, hydrocyclocarbonylation of **5** was carried out by using the same set of rhodium and rhodium–cobalt mixed metal complexes as the catalysts (eqn. (8)). The results are listed in Table 4. The observed regioselectivities are much lower than those for the reactions of **9** under similar conditions. The results strongly suggest that regiocontrol for the formations of five- *vs.* six-membered rings is substantially more difficult than that for six- *vs.* seven-membered rings.



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3. Experimental details

3.1. General method

^{1}H NMR spectra were measured with a Bruker AC-250 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 liquid. HPLC analysis was recorded on a Waters 600 E multisolvent delivery system equipped with a chiral column-Daicel Chiracel OD (J.T. Baker) using n-hexane/2-propanol. 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. 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.

3.2. 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. The rhodium complex, $[Rh(acac)(CO)_2]$, was a gift from Mitsubishi Kasei Corp. and used as obtained. Other rhodium complexes, $[RhCl(CO)_2]_2$ [9], $HRh(CO)(PPh_3)_3$ [10], $Co_2Rh_2(CO)_{12}$ [11], $[Rh(NBD)_2]ClO_4$ (NBD = norbornadiene) [12] and $[Rh(NBD)_2]BF_4$ [12] were prepared by the literature methods. Methanol, dichloromethane and trimethylphosphite were distilled under nitrogen prior to use. Tetrahydrofuran (THF) was dried over sodium and distilled under nitrogen from sodium/benzophenone. 5-Allyl-2-pyrrolidinone [3e], 6-allyl-2-piperidinone [3e], *N*-benzyl-4-pentenamide [3e] and (−)-BPPM [13] were prepared by the literature methods. Silica gel (MN-Kieselgel 60) for chromatography was purchased from Brinkmann Instruments, Inc. All other chemicals were purchased from Aldrich Chemical Co., Inc.

3.3. Preparation of 2-allylpiperidine (5)

In a 250 ml dry reaction flask was placed $LiAlH_4$ (2.78 g, 0.073 mol) and the reaction flask was flushed with dry nitrogen gas, and cooled with an ice-water bath. Dry ether (200 ml) was carefully added to the reaction flask with stirring. 3-Allyl-2-piperidinone (5.07 g, 0.037 mol) was added slowly to this suspension. The mixture was refluxed for 3 h and stirred at room temperature overnight. The reaction mixture was then cooled in an ice-water bath and quenched with water. The reaction mixture was extracted with ether (30 ml × 4) and the combined extracts were dried over anhydrous Na_2SO_4 overnight. After the drying reagent was filtered, the solvent was removed under reduced pressure and the product was purified by Kugelrohr distillation to give **5** as a colorless oil (2.74 g, 60.3% yield). ^{1}H NMR ($CDCl_3$): δ 1.04–1.75 (m, 6H); 1.95–2.16 (m, 2H); 2.40–2.60 (m, 2H); 2.99 (d, J = 1.5 Hz, 1H); 3.57–3.65 (m, 1H); 4.99–5.08 (m, 2H); 5.65–5.78 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.78, 26.19, 32.63, 41.75, 47.01, 55.95, 117.14, 135.49. IR (neat): 3292b, 3075m, 1640m, 1440m cm^{-1}. Anal. Found: C, 76.57; H, 12.19; N, 11.01. $C_8H_{15}N$ calc.: C, 76.74; H, 12.07; N, 11.19%.

3.4. Preparation of 5-benzylamino-1-pentene (9)

In a similar manner, **9** was obtained as a colorless oil (3.88 g, 92% yield) through the reduction of *N*-benzyl-4-pentenamide (4.61 g, 0.024 mol) with $LiAlH_4$ (1.85 g, 0.049 mol) in ether (150 ml).

9: ^{1}H NMR ($CDCl_3$): δ 1.61 (quintet, J = 7.4 Hz, 2 H); 2.09 (q, J = 7.1 Hz, 2 H); 2.63 (t, J = 7.3 Hz, 2 H); 3.40 (bs, 1 H); 3.77 (s, 2 H); 4.93–5.05 (m, 2 H); 5.73–5.87 (m, 1 H); 7.25–7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 29.14, 31.41, 48.75, 53.91, 114.46, 126.71, 127.93, 128.22, 138.33. IR (neat): 3310 (vNH), 3062m, 1439m cm^{-1}. Anal. Found: C, 82.28; H, 9.57; N, 8.12. $C_{12}H_{17}N$ calc.: C, 82.23; H, 9.78; N, 7.99%.

3.5. Stereoselective cyclocarbonylation of 2-allylpiperidine (5) in the presence of hydrogen chloride

To a solution of $[RhCl(CO)_2]_2$ (169 mg, 0.44 mmol) in 1.5 ml of dichloromethane at room temperature was added **5** (109 mg, 0.87 mmol) in 1.5 ml of dichloromethane. The resulting yellow solution was stirred for 10 min at room temperature and cooled to −78°C. Then, a cold, ethereal solution of anhydrous HCl (0.16 ml of a 1 M solution) was slowly added down the side of the reaction flask. After stirring for 10 min at −78°C, a solution of $P(OMe)_3$ (0.67 ml) in 2.3 ml of dichloromethane was added down the side of the reaction flask (to prevent warming). Stirring was continued for another 8 h as the orange-yellow solution slowly warmed to ambient temperature. The solvent was removed *in vacuo* and the resulting orange oil of Rh^{III} alkyl complex was dissolved in 5.6 ml of methanol and 5.6 ml of chloroform and then 0.28 ml of $P(OMe)_3$ was added. After stirring for 24 h at room temperature, removal of the solvent followed by flash chromatography (eluant 100% EtOAc) gave 8-methyl-1-azabicyclo[4.3.0]nonan-9-one (**7**, 53 mg, 43% yield) as a colorless oil (one diastereomer; tentatively assigned as **7**-α). ^1H NMR ($CDCl_3$): δ 1.11–1.42 (m, 3.5 H); 1.15 (d, $J = 7.3$ Hz, 3 H); 1.64 (m, 0.5 H); 1.77–1.85 (m, 4 H); 2.47 (m, 1 H); 2.61 (dt, $J = 13.5$, 12.9 Hz, 1 H); 3.38 (m, 1 H); 4.09 (dd, $J = 4.8$, 13.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.83, 23.72, 24.40, 32.88, 33.38, 35.64, 40.24, 55.32, 175.84. The ^1H NMR spectrum is shown in Fig. 1(a), which suggests that this diastereomer is the 3-α-methyl isomer **7**-α based on the comparison with the other diastereomer (see Fig. 1(b)) in terms of the chemical shifts of the 3-methyls as well as the 5-methine protons. Attempted 1D difference NOE and NOESY measurements were not conclusive due to unfortunate overlap of key peaks.

3.6. Cyclocarbonylation of 5 catalyzed by $[RhCl(CO)_2]_2$

In a typical run, $[RhCl(CO)_2]_2$ (29.6 mg, 7.6×10^{-2} mmol) and 2-allylpiperidine (**5**, 191 mg, 1.52 mmol) were placed in a 50 ml reaction vessel under argon. To the reaction vessel was added THF (5.0 ml) via syringe. The resulting mixture was stirred for 10 min and then cooled to −78°C. Then, a cold, ethereal solution of anhydrous HCl (0.15 ml of a 1 M solution) was slowly added down the side of the reaction vessel. After stirring for 10 min at −78°C, the mixture was allowed to warm to room temperature. The reaction vessel was placed in a 300 ml stainless steel autoclave. The autoclave, which was equipped with a magnetic stirrer and immersed in a thermostatted oil bath, was charged with 69 bar (1000 psi) of carbon monoxide. The reaction mixture in the autoclave was heated at 100°C for 40 h with stirring. Then, pressure was carefully released and the reaction mixture was chromatographed on a silica gel column (eluant EtOAc) to give 8-methyl-1-azabicyclo[4.3.0]nonan-9-one (**7**, 133 mg, 57% yield) and 1-azabicyclo[4.4.0]decan-2-one (**8**, 74 mg, 32% yield).

7 (a 1:1 mixture of two diastereomers): ^1H NMR ($CDCl_3$): δ 1.03–1.45 (m, 3.5 H); [1.19 (d, $J = 7.0$ Hz), 1.15 (d, $J = 7.3$ Hz)] (3 H); 1.61–1.94 (m, 4.5 H); 2.37–2.67 (m, 2 H); [3.24–3.25 (m), 3.38–3.42 (m)] (1 H); 4.04–4.12 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ (16.32, 16.83), (23.54, 23.72), (24.26, 24.40), (32.88, 33.78), (33.38, 35.31), (35.64, 36.18), (40.03, 40.24), (54.95, 55.32), 175.84. IR (neat) 1682 ($^{\nu}CO$) cm^{-1}. MS: (*m/e*) 153.1 (72.3, M^+), 152.1 (100), 138.1 (29), 124 (25.8), 83.0 (41.7), 82.0 (32.8). Anal. Found: C, 70.61; H, 9.72; N, 9.00. $C_9H_{15}NO$ calc.: C, 70.55; H, 9.87; N, 9.14. The ^1H NMR spectrum is shown in Fig. 1(b).

8 [14]: ^1H NMR ($CDCl_3$): δ 1.24–2.61 (m, 13 H); 3.22 (m, 1 H); 4.78 (dt, $J = 1.8$, 13.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 19.10, 24.42, 25.29, 30.43, 32.94, 33.97, 42.30, 56.80, 169.00. IR (neat): 1703 ($^{\nu}CO$) cm^{-1}. MS: (*m/e*) 153.1 (69.4, M^+), 152.1 (41.8), 138.1 (57.1), 97.0 (100), 83.9 (54.1).

3.7. Cyclocarbonylation of 5-benzylamino-1-pentene (9) catalyzed by $[RhCl(CO)_2]_2$ or $[Rh(CO)_2(acac)]$

In a manner similar to that described above, the reactions were carried out with 0.05 mmol of $[RhCl(CO)_2]_2$ or $[Rh(acac)(CO)_2]$ and 1.0 mmol of **9** in 5.0 ml of THF at 100°C and 35–69 bar (500–1000 psi) of CO for 40 h. The reaction mixture was chromatographed on a silica gel column (eluant EtOAc) to give 1-benzyl-3-methyl-2-piperidinone (**10**) and 1-benzylazepan-2-one (**11**). The reaction mixture was subjected to GLC and/or NMR analyses.

10: ^1H NMR ($CDCl_3$): δ 1.29 (d, $J = 7.2$ Hz, 3 H); 1.51–1.97 (m, 4 H); 2.46–2.49 (m, 1 H); 3.20 (dd, $J = 5.1$, 7.2 Hz, 2 H); 4.58 (dd, $J = 14.6$, 48.7 Hz, 2 H); 7.23–7.34 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 18.00, 21.56, 29.48, 36.62, 47.49, 50.11, 127.13, 127.88, 128.43, 137.47, 173.19. IR (neat): 1636 ($^{\nu}CO$) cm^{-1}. MS: (*m/e*) 203 (86.9, M^+), 188 (18.8), 112 (83.6), 99 (27.0), 92 (37.7), 91 (100.0). Anal. Found: C, 76.63; H, 8.26; N, 6.89. $C_{13}H_{17}NO$ calc.: C, 76.81; H, 8.43; N, 6.89%.

11: ^1H NMR ($CDCl_3$): δ 1.42–1.46 (m, 2 H); 1.63–1.65 (m, 4 H); 2.53–2.56 (m, 2 H); 3.21–3.24 (m, 2 H); 4.53 (s, 2 H); 7.18–7.25 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 23.44, 28.16, 29.93, 37.17, 48.91, 51.17, 127.25, 128.18, 128.50, 138.00. IR (neat): 1636 ($^{\nu}CO$) cm^{-1}. MS: (*m/e*) 203 (79.7, M^+), 160 (25.1), 106 (50.9), 91 (100.0). Anal. Found: C, 76.60; H, 8.21; N, 7.09. $C_{13}H_{17}NO$ calc.: C, 76.81; H, 8.43; N, 6.89%.

3.8. Cyclocarboxylation of 5-benzylamino-1-pentene (9) catalyzed by cationic rhodium complexes

In a typical run, to a solution of $[Rh(NBD)_2]ClO_4$ (13.5 mg, 3.5×10^{-2} mmol) in 3.0 ml of methanol

under argon was added (−)-BPPM (20.3 mg, 3.6×10^{-2} mmol). The mixture was stirred for 1 h under hydrogen at room temperature, and then the catalyst solution was ready to use. To a solution of **9** (123 mg, 0.70 mmol) in a 50 ml reaction vessel was added the catalyst solution via syringe. The resulting mixture was stirred for 10 min and then cooled to −78°C. Then, a cold, ethereal solution of anhydrous HCl (0.07 ml of a 1 M solution) was slowly added down the side of the reaction vessel. The reaction vessel was placed in a 300 ml stainless steel autoclave. The autoclave, which was equipped with a magnetic stirrer and immersed in a thermostated oil bath, was charged with 69 bar (1000 psi) of carbon monoxide. The mixture in the autoclave was heated at 100°C for 40 h with stirring. Then, pressure was carefully released and the reaction mixture was subjected to GLC and/or NMR analyses.

3.9. Cyclocarbonylation of 5-benzylamino-1-pentene (9) in the absence of hydrogen chloride

In a typical run, the catalyst (0.02–0.05 mmol) and **9** (1.00 mmol) were placed in a 25 ml reaction vessel under argon. To the reaction vessel was added THF (5.0 ml) via syringe. The resulting mixture was stirred for 10 min. The reaction vessel was placed in a 300 ml stainless steel autoclave. The autoclave, which was equipped with a magnetic stirrer and immersed in a thermostatted oil bath, was charged with 35–69 bar (500–1000 psi) of carbon monoxide. The mixture in the autoclave was heated at 100°C for 40 h with stirring. Then, pressure was carefully released and the reaction mixture was submitted to GLC and/or NMR analyses.

3.10. Hydrocyclocarbonylation of 5-benzylamino-1-pentene (9) catalyzed by rhodium complexes

In a typical run, tricyclohexylphosphine (22.6 mg, 7.80×10^{-2} mmol) was placed to a 25 ml Pyrex flask in a glove box under nitrogen. (When triphenylphosphine is used, this phosphine can be added directly to the reaction flask without using a glove box.) Freshly distilled THF (3.0 ml) was added under argon via syringe, and the mixture was stirred for 5 min. To a 50 ml Pyrex reaction vessel with a magnetic stirring bar were added **9** (1.56 mmol, 273 mg) and $HRh(CO)(PPh_3)_3$ (1.56×10^{-2} mmol, 14.3 mg). The Pyrex reaction vessel was pumped into vacuum and filled with argon, which was repeated twice, and then the phosphine solution was transferred into the Pyrex reaction vessel via syringe under argon. The reaction vessel was placed in a stainless steel autoclave (300 ml). The autoclave was flushed with carbon monoxide twice and then filled with carbon monoxide (62 bar = 900 psi) and hydrogen (62 bar = 900 psi) (initial pressures at 20°C). The mixture was stirred at 100°C for 18 h. After the autoclave was cooled in ice-water bath for 30 min, the pressure was released from the autoclave and the solvent was removed. The reaction mixture was submitted to GLC and NMR analyses. The GLC analysis revealed that 1-benzylazepane (**13**) and 1-benzyl-3-methylpiperidine (**12**) were formed in 85% yield in 95:5 ratio. The products were separated by silica gel column chromatography (eluant hexane/EtOAc, 2:1) to give **13** (236 mg, 80% yield) as a colorless oil.

In the same manner, the reaction with $HRh(CO)(PPh_3)_3$ gave **12** in 75% isolated yield as a colorless oil.

12 [15]: ^{1}H NMR ($CDCl_3$): δ 0.83 (d, $J = 5.7$ Hz, 3 H); 1.53–1.87 (m, 5 H); 2.62–2.84 (m, 4 H); 3.49 (s, 2 H); 7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 19.69, 25.45, 31.03, 32.98, 53.90, 61.84, 63.52, 126.85, 128.09, 129.22. IR (neat): 3026w, 2925s, 1642w, 1453m, 1027m cm^{-1}. MS: (*m/e*) 189 (18, M^+), 188 (25.3), 112 (39), 91 (100), 65 (11).

13 [16]: ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 4 H); 1.66 (m, 4 H); 2.70 (t, $J = 5.1$ Hz, 4 H); 3.71 (s, 2 H); 7.25–7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 26.98, 26.98, 55.28, 62.37, 127.36, 128.33, 129.25. IR (neat): 3060w, 3025w, 2926s, 1678w, 1453m cm^{-1}. MS: (*m/e*) 189 (13, M^+), 188 (13), 112 (20), 98 (30), 91 (100), 42 (27).

3.11. Hydrocyclocarbonylation of 2-allylpiperidine (5) catalyzed by rhodium complexes

In a manner similar to that described above, the reactions were carried out with **5** (1.50 mmol) and a catalyst (1.50×10^{-2} mmol) in 3.8 ml of THF or $HC(OEt)_3$ at 100 or 125°C and 83–124 bar (1200–1800 psi; $CO/H_2 = 1$ or 0.5) for 18 h. The reaction mixture was submitted to GLC and/or NMR analyses.

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