Transition Metal Mediated Carbonylative Ring Expansion of Heterocyclic Compounds

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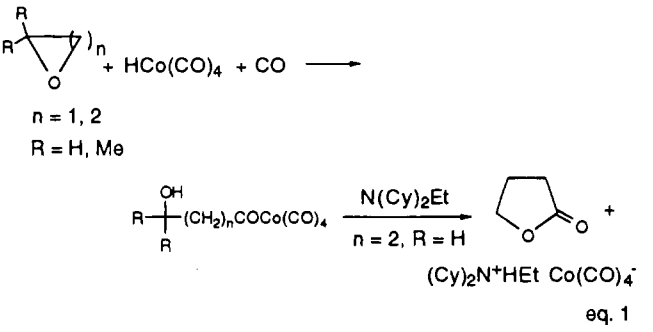
Introduction

Carbonylation chemistry is widely used in organic synthesis both in academia and in industry. Among numerous methods for the introduction of a carbonyl moiety into an organic molecule, the direct functionalization of a substrate using carbon monoxide has attracted a great deal of attention among chemists during the last two decades. As a rule, these transformations require the presence of a transition metal complex functioning as a catalyst or as a stoichiometric reactant. Metal-catalyzed reactions involving carbon monoxide are quite diverse. One of the most interesting and synthetically useful carbonylation reactions is the insertion of CO into a carbon–heteroatom bond of a heterocyclic compound. This reaction comprises a simultaneous ring expansion and functionalization of a heterocyclic substrate.[1-3] The carbonylation reaction provides a very convenient and effective one-step procedure for ring homologation. In many cases the reaction gives rise to heterocyclic derivatives which are not readily accessible or are unavailable through conventional methods. Reactions of this type provide direct access to a large variety of products including lactams, lactones, thiolactones, etc. In this Account, we will discuss recent results of studies on the carbonylation reactions of heterocycles with carbon monoxide gas and related transformations which occur in the presence of transition metal complexes and result in carbonylative ring expansion.

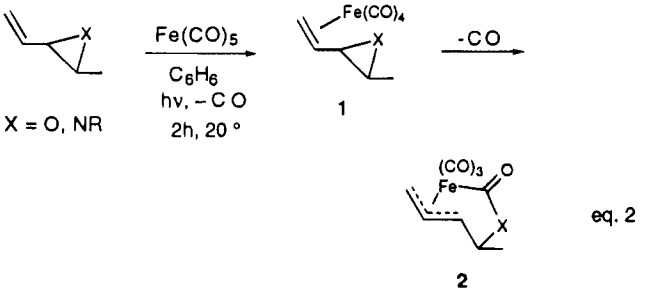
Stoichiometric Reactions

In 1963, Heck reported the ring-opening reaction of oxiranes and oxetane using hydridocobalt tetracarbonyl and cobalt tetracarbonyl anion. In the case of oxetane, the product, (4-hydroxybutyryl)cobalt tetracarbonyl, was treated with a tertiary amine, affording γ-butyrolactone and cobalt carbonyl anion (eq 1).[4]



eq. 1

In 1974, Aumann's group discovered the light-induced reaction of iron pentacarbonyl with 2-vinyloxiranes and 2-vinylaziridines. Initial formation of the π-iron complex **1**, followed by migratory insertion of coordinated CO into the Fe–O or Fe–N σ bonds, affords the corresponding ferralactone or ferralactam **2** in good yield (eq 2).[5] The driving force for the



eq. 2

cleavage of the epoxide is the formation of a π-allyl complex and release of ring strain. In subsequent experiments, it was shown that the carbonylation reaction was applicable to a wide variety of 2-vinyloxiranes **(3)** and the nature of the product was controlled by the nature of the metal complex.[6] For

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Howard Alper received his Ph.D. degree from McGill University in 1967. After one year as a NATO Postdoctoral Fellow at Princeton University, he joined the faculty of the State University of New York at Binghamton. In 1975 he moved to the University of Ottawa, where he became full professor in 1978 and served as department chair during 1982–1985 and 1988–1994. His research program is in metal-catalyzed reactions (oxidation, reduction, cycloaddition, and carbonylation) of potential interest in the areas of pharmaceuticals and petrochemicals. Among the awards and honors which he has received for his research contributions are the E. W. R. Steacie Award of the Canadian Society for Chemistry in 1993, for distinguished contributions to chemistry, and the Commemorative Medal of the Government of Canada for significant contributions to Canada.

(1) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991.
(2) Alper, H. *J. Organomet. Chem.* **1986**, *300*, 1.
(3) Alper, H. *Pure Appl. Chem.* **1988**, *60*, 35.
(4) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 1460.
(5) Aumann, R.; Frohlich, K.; Ring, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 275.
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(7) Annis, G. D.; Ley, S. V.; Sivaramakrishnan, R.; Atkinson, A. M.; Rogers, D.; Williams, D. J. *J. Organomet. Chem.* **1979**, *182*, C11.
(8) Annis, G. D.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1977**, 581.
(9) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270. For the use of $Fe_2(CO)_9$ and ultrasonification, see: Horton, A. M.; Hollinshead, D. M.; Ley, S. V. *Tetrahedron* **1984**, *40*, 1737.
(10) Bates, R. W.; Fernandez-Moro, R.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 2651.
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(12) Horton, A. M.; Ley, S. V. *J. Organomet. Chem.* **1985**, *285*, C17.
(13) Aumann, R.; Ring, H.; Kruger, C.; Goddard, R. *Chem. Ber.* **1979**, *112*, 3644.

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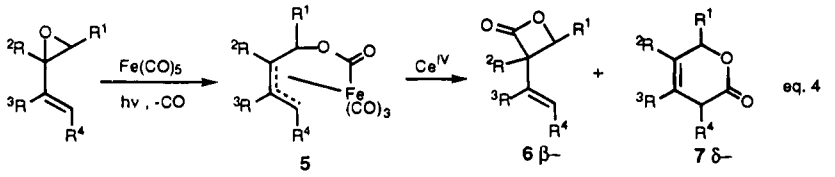


Table 1

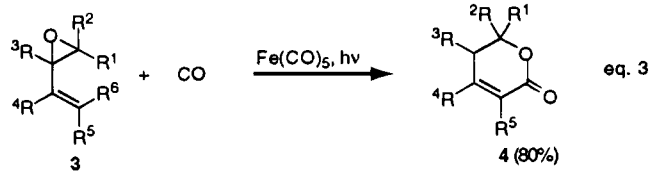
R^1	R^2	R^3	R^4	% yield[a]	% β-[b]	% δ-[b]
H	Me	Me	H	65	42	16
$-CH_2CH_2CH_2-$		H	H	75	51	29
Cholestanyl		H	H	56	12	27
H	H	$-CH_2CH_2CH_2-$		72	100	–
H	$-CH_2CH_2CH_2CH_2-$		H	29	15	55
pentyl	H	H	H	95	68	–
cyclohexyl	H	H	H	49	52	–
H	H	H	cyclohexyl	46	43[c]	–
–	H	H	$R^1, R^4 = CH_2CH_2$	32	86	–

[a] the combined yield of the *syn*- and *anti*-isomers

[b] %β- and %δ- of the oxidation of *syn*-ferralactones. All the *anti*-ferralactones give only δ-isomer

[c] %yield after reduction with lithium aluminium hydride

instance, the α,β-unsaturated lactone **4** is obtained from **3** and $Fe(CO)_5$ (eq 3), whereas the *catalytic* carbonylation of **3** with CO in the presence of $[Rh(COD)Cl]_2$ regiospecifically furnished β,γ-unsaturated lactone in good yield (see eq 9).[6]

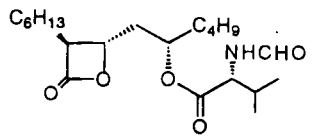


The carbonylation reaction has been shown to occur via a ferralactone complex **5** such as that shown in eq 4. The complexes can be formed in both *syn*- and *anti*-fashion, and both structures were confirmed by X-ray crystallography (see below for an example of *syn*- and *anti*-complexes).[7] The versatility of complex **5** in

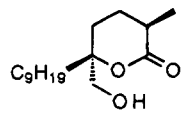
syn-isomer *anti*-isomer

organic synthesis has been amply demonstrated by the elegant work of Ley and his co-workers (Table 1). In the majority of these studies, oxidation of the *syn*-ferralactone complex is carried out with ceric ammonium nitrate (CAN) to form the β-lactone **6** as the major or only product. Alternatively, oxidation of the *anti*-ferralactone gives the δ-lactone **7** as the only product.[8,9]

Using the ferralactone complexes, Ley and coworkers were able to synthesize valilactone (**8**), a β-lactone natural product possessing an esterase-inhibiting activity,[10,11] as well as δ-lactonic natural products such as malyngolide (**9**).[12]



8 Valilactone



9 Malyngolide

A mechanistic study of the formation of the ferralactone complex and its reaction with a variety of nucleophiles has been carried out.[13] The addition of an external nucleophile (e.g., secondary amine) to **10** results in a ferralactam complex **15**. The stereochemical result (inversion of configuration) can be rationalized by the reaction sequence outlined in Scheme 1.

A wide variety of β- and δ-lactams can be prepared using amines as external nucleophiles.[14,15] This strategy has been applied to the synthesis of β-lactam derivatives (**17**), which were subsequently used for the preparation of **18**, the key intermediate leading to nocardicin (eq 5).[16]

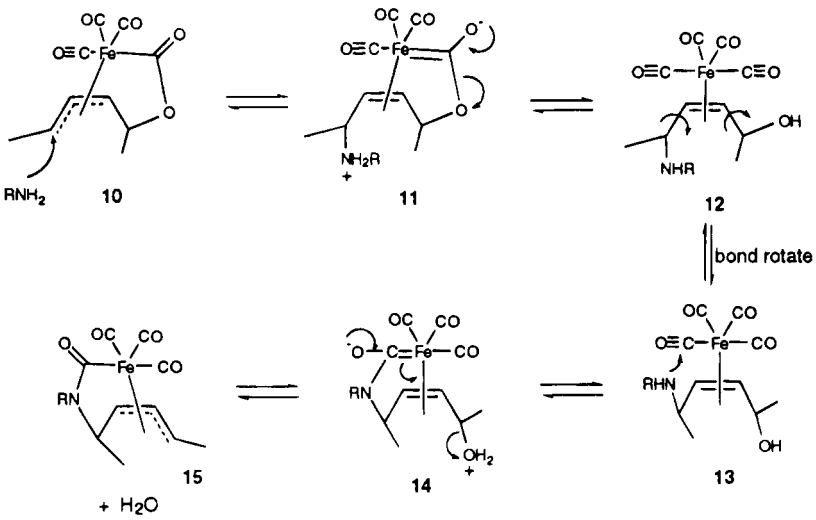
The insertion of carbon monoxide into the less substituted C–N bond of an aziridine ring has been accomplished by Pinhas and Chamchaang.[17,18] By opening aziridines (**19**) with LiI (i.e., via **20**), followed by treatment with an *excess* of $Ni(CO)_4$ as the carbonylating agent under argon, the corresponding β-lac

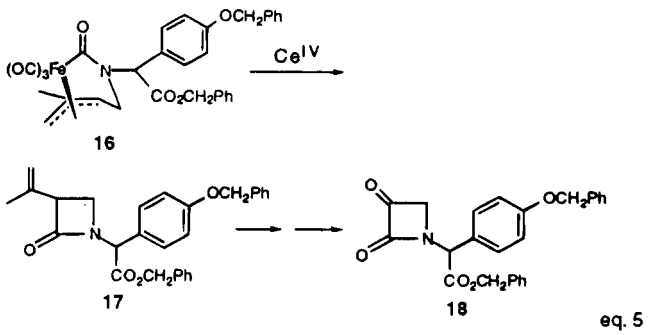
(14) Annis, G. D.; Hebblethwaite, E. M.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1980**, 297.

(15) Annis, G. D.; Hebblethwaite, E. M.; Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2851.

(16) Hodgson, S. T.; Hollinshead, D. M.; Ley, S. V.; Low, C. M. R.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2375.

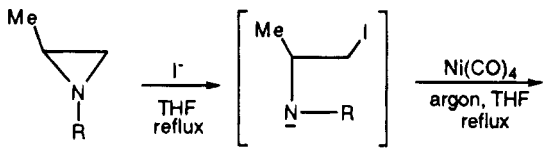
Scheme 1



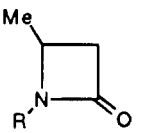


eq. 5

tams, **21**, were obtained in moderate (20–50%) yield (eq 6). In the case of disubstituted aziridines, it was found that the yield could be improved by running the reaction under CO.[18]

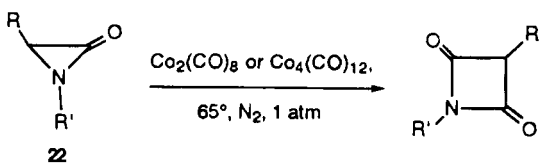


R = CH_2Ph, $CH_2C_6H_4OCH_3$, SO_2CH_3



eq. 6

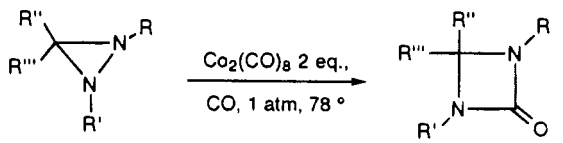
When α-lactams (**22**) were employed as the substrates using $Co_2(CO)_8$ as the carbonylating agent under a nitrogen atmosphere, only the azetidine-2,4-dione **23** was formed. This compound resulted from CO insertion into the C(sp^3)–N bond, which is weaker than the C(sp^2)–N amide bond. This reaction was retarded under a CO atmosphere (eq 7). An identical transformation is also effected by catalytic amounts of Rh(I) (see eq 25).[19]



R, R' = t-Bu, 1-adamantyl

eq. 7

Cobalt carbonyl was also used for the carbonylation of diaziridines (**24**) under a CO atmosphere, affording 1,3-azetidin-2-ones (**25**) in 11–65% yield (eq 8). This carbonylation is only applicable to 3,3-disubstituted diaziridines, since monosubstituted substrates undergo polymerization under such conditions.[20]



R, R' = alkyl
R'', R''' = $-(CH_2)_5-$, $-(CH_2)_4-$

eq. 8

Catalytic Reactions

The metal-mediated ring expansion reactions described above have proven to be synthetically useful. However, since they are *stoichiometric* processes, significant quantities of transition metal compounds are required for these reactions. Moreover, as we have already seen, some reactions need to be conducted in the presence of a large excess of highly toxic metal carbonyls, like $Ni(CO)_4$. It should be emphasized that carbon monoxide is less toxic than $Ni(CO)_4$. Clearly, development of efficient and safe procedures employing only *catalytic* quantities of transition metals and CO is a highly desirable goal.

The first examples of the *catalytic* carbonylative ring expansion of heterocycles were described by Reppe's group,[21] Murahashi and Horiie,[22] and Nienburg and Elschnigg[23] in the 1950s. It was shown that, in the presence of catalytic amounts of cobalt complexes,

(14) Chamchaang, W.; Pinhas, A. R. *J. Chem. Soc., Chem. Commun.* **1988**, 710.
(15) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943.
(16) Roberto, D.; Alper, H. *Organometallics* **1984**, *3*, 1767.
(17) Alper, H.; Delledonne, D.; Kameyama, M.; Roberto, D. *Organometallics* **1990**, *9*, 762.
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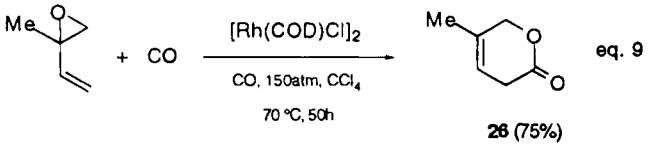
(19) Murahashi, S.; Horiie, S. *J. Am. Chem. Soc.* **1956**, *78*, 4816.
(20) Nienburg, H. J.; Elschnigg, G. Ger. 1,066,572 (Oct 8, 1959); *Chem. Abstr.* **1961**, *55*, 10323h.
(21) Kamiya, Y.; Kawato, K.; Ohta, H. *Chem. Lett.* **1980**, 1549.

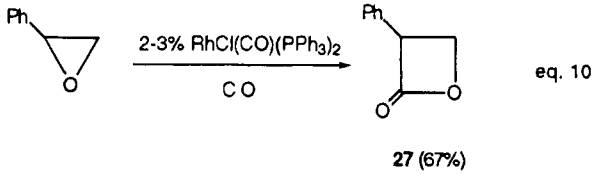
oxolane,[21] indazolone,[22] and oxetane[23] undergo insertion of CO into the C–O bonds under drastic conditions (150–250 atm, 200–230 °C). In the late 1970s and early 1980s, Aumann et al.,[6,13] Kamiya, Kawato and Ohta,[24] and our group[25] reported the first successful examples of catalytic carbonylative ring expansion reactions of three-membered-ring heterocycles. Since then, a number of highly efficient and simple catalytic procedures have been developed for the synthesis of various heterocyclic compounds, following this methodology. The results obtained in this field by our research group and others are described below.

Three-Membered Heterocycles

Oxiranes. As previously mentioned, vinyloxiranes undergo carbonylative ring expansion in the presence of CO and catalytic amounts of $[Rh(COD)Cl]_2$ to give β,γ-unsaturated δ-valerolactones.[6] Isoprene oxide (**3**; $R^1 = R^2 = R^4 = R^5 = R^6 = H$; $R^3 = Me$) was reacted with CO in this manner to yield **26** in 75% yield (eq 9).

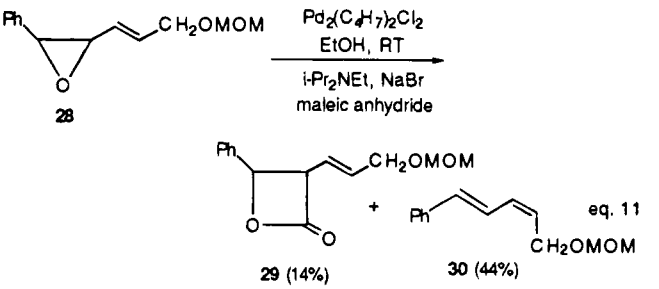


When styrene oxide was treated with catalytic amounts of $RhCl(CO)(PPh_3)_2$ under CO, the β-lactone **27** was obtained in 67% yield (eq 10).[24] Therefore, though the formation of a π-benzylic intermediate (similar to **1**) is conceivable for styrene oxide, its reactivity is completely different. The scope of this method is, however, quite limited. The reaction was only successful for styrene oxide, and even closely related stilbene oxide was unreactive. All aliphatic epoxides examined in this study gave very low yields of the desired β-lactones (ca. 5%). The authors attempted to explain the reactivity of styrene oxide by invoking a cationic intermediate generated by coordination of the epoxide to rhodium in a Lewis acidic manner.[24] In our opinion, the possibility of a π-benzyl intermediate also should be considered.

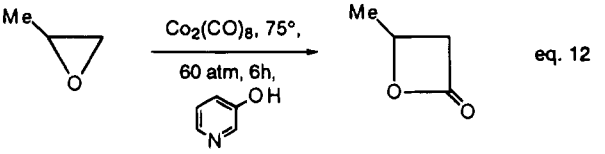


Yamamoto's group has reported the palladium-catalyzed carbonylation of 2-vinyloxiranes.[26] In this reaction, the β-lactone **29** is observed only for 2-alkenyl-3-aryloxiranes with an internal C=C bond in the side chain (**28**). Even for these substrates, the β-lactone **29** is obtained in low yield, with the corresponding diene **30** being the major product (eq 11).[26]

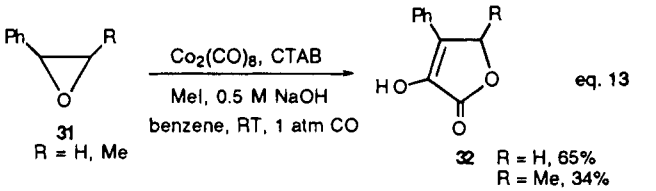
Recently, Drent and Kragtwijk developed this process further using $Co_2(CO)_8$ in the presence of a hydroxy-substituted pyridine ligand. Under these conditions, propylene oxide was transformed to the



corresponding β-lactone in 93% conversion and 90% selectivity (eq 12). The presence of 3-hydroxypyridine appears to be essential, although its function remains unclear.[27] The regiospecificity in this case involves CO insertion into the less substituted C–O bond.

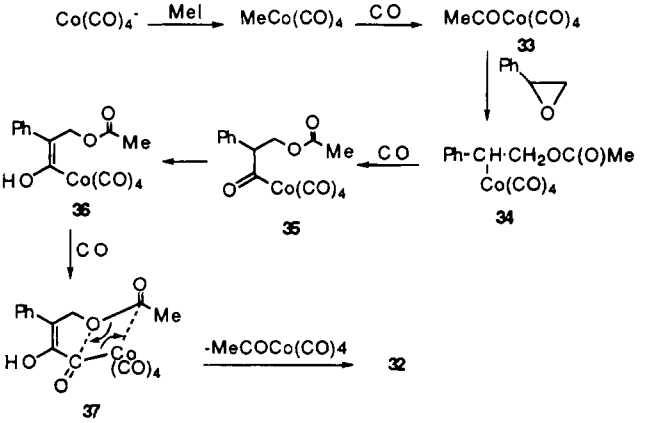


The carbonylative ring expansion reactions were also performed under phase transfer catalysis (PTC) conditions. Using a catalytic amount of $Co_2(CO)_8$, it was found that both styrene oxide and β-methylstyrene oxide were reactive in the presence of MeI and 0.5 N NaOH, under 1 atm of CO, with cetyltrimethylammonium bromide (CTAB) as the phase transfer catalyst. The product of this reaction, 2-hydroxy-3-phenyl-γ-butyrolactone (**32**), results from the incorporation of *two* molecules of carbon monoxide (eq 13).[25]



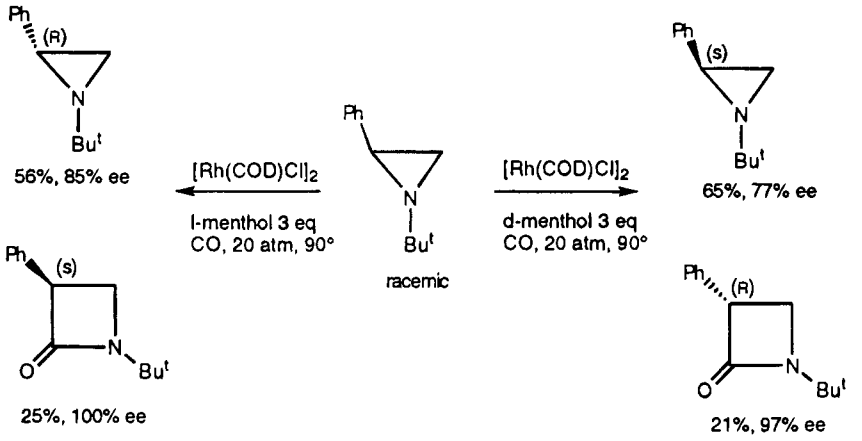
The reaction was proposed to begin with the formation of $MeCOCo(CO)_4$ from methyl iodide and $NaCo(CO)_4$, generated *in situ* by interfacial reaction of dicobalt octacarbonyl and sodium hydroxide. Addition of acetylcobalt tetracarbonyl to the aryloxirane can give intermediate **34**, which undergoes carbonylation to **35** and then enolization to **36**. Insertion of CO in the C–Co bond of **36** gives **37**, the cyclization of which affords product **32** (Scheme 2). While applicable to 1,2-disubstituted oxiranes, this method does not work

Scheme 2



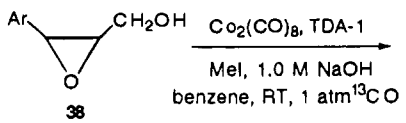
(25) Alper, H.; Arzoumanian, H.; Petrignani, J.-F.; Maldonado, M. S. *J. Chem. Soc., Chem. Commun.* **1985**, 340.
(26) Shimizu, I.; Maruyama, T.; Makuta, T.; Yamamoto, A. *Tetrahedron Lett.* **1993**, *34*, 2135.
(27) Drent, E.; Kragtwijk, E. Eur. Pat. Appl. EP 577,206 (Jan 5, 1994); *Chem. Abstr.* **1994**, *120*, 191517c.

Scheme 3

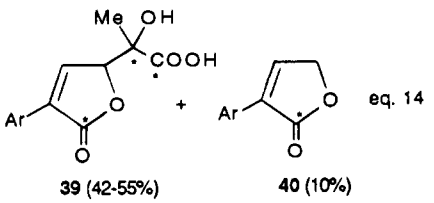


for 1,1-disubstituted substrates. This is probably due to the fact that the second carbonylation takes place only after enolization (i.e., to intermediate **36**), which could not occur in 1,1-disubstituted systems.[25]

When 2-aryl-3-(hydroxymethyl)oxiranes (**38**) were used under PTC conditions (with TDA-1 as the phase transfer agent), highly functionalized *triple* carbonylation products **39** were obtained along with small amounts of the corresponding furanone **40** (eq 14).[28] This remarkable, direct incorporation of three molecules of carbon monoxide in the final product was proven by ^{13}CO labeling experiments.

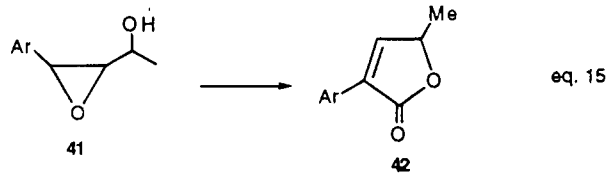


Ar = Ph, p-tolyl, 1-naphthyl



eq. 14

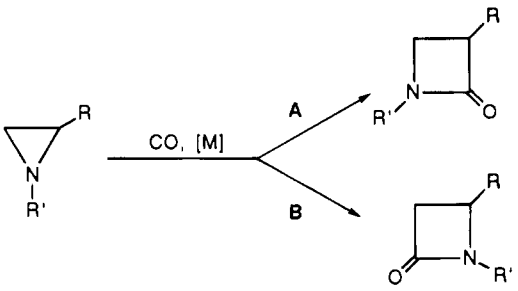
For oxiranes **41**, containing a secondary alcohol functionality in the side chain, monocarbonylation was observed, affording furanone **42** (eq 15).[28]



eq. 15

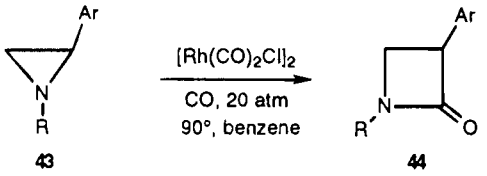
Aziridines and Related Compounds. Depending on the nature of substituents on the aziridine ring, one or the other C–N bond is carbonylated *regiospecifically* (eq 16). Path A is operative when R = aryl or vinyl, and this is probably due to the intermediate formation of π-allyl- or π-benzyl-type complexes.

2-Arylaziridines can be carbonylated in the presence of $[Rh(CO)_2Cl]_2$, affording β-lactams (eq 17).[29] Many aziridines can be employed in this reaction, but the presence of an aryl group α to nitrogen is essential. For these substrates, the corresponding β-lactams can be obtained in quantitative yield. Since the carbonylation occurs regiospecifically at the aryl-substituted-



eq. 16

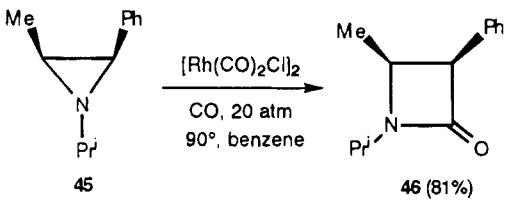
C–N bond, it is conceivable that the aryl group directs the metal insertion via the formation of a π-benzyl intermediate.[29] The trend of this reaction is similar to that described by Ohta et al. for the carbonylation of styrene oxide (eq 10).[24] It was shown that the



eq. 17

R = t-Bu, 1-adamantyl
Ar = Ph, p-PhC$_6$H$_4$, p-BrC$_6$H$_4$

carbonylation reaction of *cis*-**45** furnishes *cis*-**46** and occurs with retention of configuration at both chiral centers (eq 18).[30]

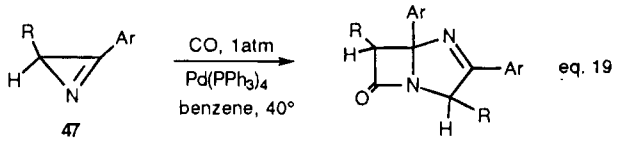


eq. 18

A high degree of asymmetric induction was observed when chiral ligands were used in the reaction.[30] This reaction is useful not only for the synthesis of chiral nonracemic β-lactams but also for the preparation of enantiomerically enriched aziridines. Among the different types of chiral ligands studied, *d*- and *l*-menthol were shown to be the most effective in asymmetric synthesis (Scheme 3).

(28) Alper, H.; Eisenstat, A.; Satyanarayana, N. *J. Am. Chem. Soc.* **1990**, *112*, 7060.
(29) Alper, H.; Urso, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737.
(30) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931.

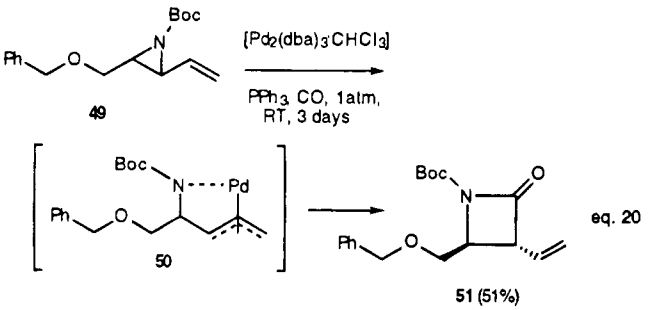
Azirines (**47**) readily react with CO in the presence of $Pd(PPh_3)_4$ under both homogeneous[31] and PTC[32] conditions (eq 19). It was proposed that the reaction involves dimerization followed by carbonylation, both processes being catalyzed by palladium. On the other hand, the reverse reaction sequence (carbonylation with subsequent cycloaddition of another molecule of as yet unreacted azirine) may also be possible. It is likely that, in this case, the carbonylation reaction 19 occurs via an aza (π-allyl)palladium intermediate.[31]



47 R = H, Me; Ar = Ph, p-MeC_6H_4, p-ClC_6H_4, p-BrC_6H_4 — 48 (25-63%)

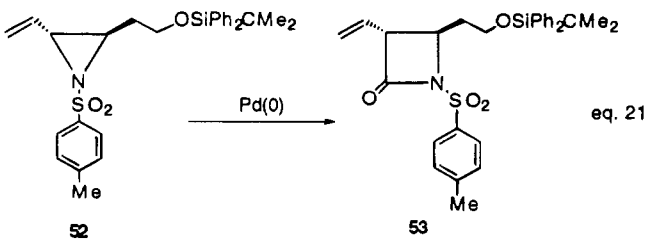
PTC conditions : CO 1atm, $Pd(PPh_3)_4$, benzene, 40-50 °C, K_2CO_3, TEBA

An efficient and straightforward carbonylation of vinylaziridines under mild conditions was observed in the presence of $[Pd_2(dba)_3{\cdot}CHCl_3]$ as the catalyst and PPh_3 as the added ligand (eq 20). The driving force for this transformation may again be the formation of a (π-allyl)palladium complex (**50**). Although the starting aziridine was used as a 3:1 mixture of the *cis* and *trans* isomers, the product was 100% *trans*. The *trans* isomer product likely results from the π-allyl intermediate, but since the total yield of this reaction did not exceed 75%, the possibility that only *trans*-**49** was reactive cannot be ruled out.[33]



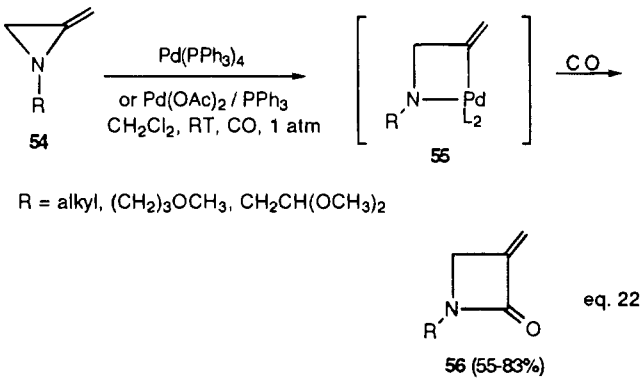
49 — 50 — 51 (51%)

A similar strategy was recently used for the preparation of an optically active β-lactam.[34] When optically pure *trans*-vinylaziridine **52** was used, β-lactam **53** was obtained with retention of configuration (eq 21). This β-lactam (**53**) is the key intermediate for the total synthesis of the carbapenam antibiotics.[34]



52 — 53

Although the formation π-allyl-type palladium complexes seems to be the driving force for reactions 19–21, it certainly was not the case in the carbonylation of methyleneaziridines **54**. The reaction of **54** with CO in the presence of $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ occurred regiospecifically at the $C(sp^2)$–N bond, forming α-methylene β-lactams (**56**) in fair to good yields (eq 22).[35] It was demonstrated that reaction 22 likely proceeds via the generation of the vinylpalladium species, followed by CO insertion and subsequent reductive elimination. It was found that palladium complexes of 1,2-bis(diphenylphosphino)ethane (dppe) or dibenzylideneacetone (dba) did not catalyze this reaction.[35]

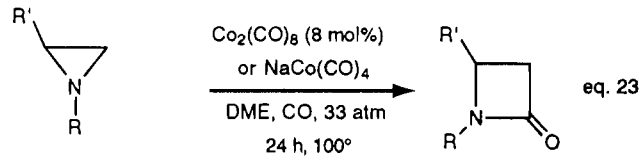


54 — 55

R = alkyl, $(CH_2)_3OCH_3$, $CH_2CH(OCH_3)_2$

56 (55-83%)

When the structure of the three-membered-ring N-heterocycle is unsuitable for the formation of π-allyl or π-benzyl complexes, the carbonylation always follows path B (eq 16), involving cleavage of the less substituted C–N bond. This regiospecificity is similar to the stoichiometric (eq 1)[4] or catalytic reaction (eq 12)[27] with oxiranes employing cobalt complexes. The catalytic carbonylation of 2-alkylaziridines readily occurs in the presence of $Co_2(CO)_8$ or $NaCo(CO)_4$ as catalysts (eq 23).[36] It should also be noted that when

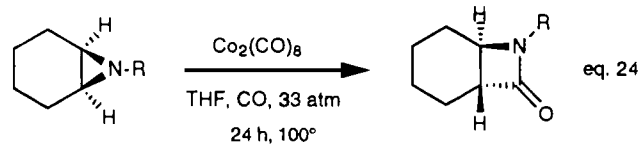


57 — 58 (64-94%)

R = CH_2CH_2Ph, CH_2Ph, i-Pr, C_6H_4OMe

R' = Et, n-Bu, t-Bu;

1,2,3-trisubstituted aziridines were used as the starting materials, the reaction proceeded with inversion of configuration (i.e., *cis*-aziridine yielding the *trans* β-lactam and *trans*-aziridine give the *cis* product) (eq 24).[36] This stereochemical feature, complemented by



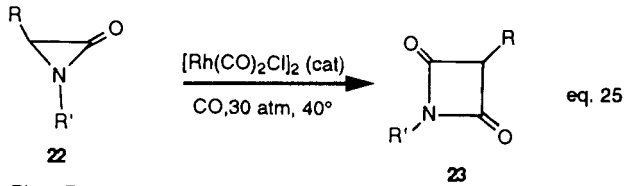
R = adamantyl — 80%

the retention of configuration observed using rhodium catalysts, enables one to prepare a wide range of β-lactams in a completely stereospecific manner.

When α-lactams (**22**) were employed as the substrates using $[Rh(CO)_2Cl]_2$, the carbonylation occurred

(31) Alper, H.; Perera, C. P.; Ahmed, F. R. *J. Am. Chem. Soc.* **1981**, *103*, 1289.
(32) Alper, H.; Mahatantila, C. P. *Heterocycles* **1983**, *20*, 2025.
(33) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91.
(34) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415.
(35) Alper, H.; Hamel, N. *Tetrahedron Lett.* **1987**, *28*, 3237.
(36) Alper, H.; Piotti, M. Unpublished results.

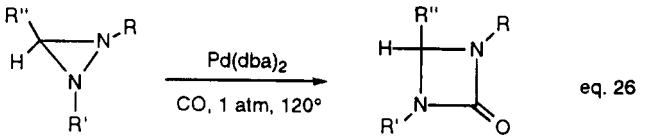
under mild conditions to afford azetidinediones **23** in good to almost quantitative yields (eq 25).[19] The results are similar to those obtained with stoichiometric amounts of cobalt carbonyl (eq 7), but only catalytic quantities of Rh(I) are required. These reaction conditions are milder than those employed for the carbonylation of 2-substituted aziridines (see eq 7).



22 **23** eq. 25

R, R' = t-Bu, 1-adamantyl

The catalytic carbonylative ring expansion was also effected with substrates containing two nitrogen atoms in the same ring. It was found that CO inserted into the N–N bond of diaziridines (**24**) when a catalytic amount of $Pd(dba)_2$ was used at 120 °C (eq 26). The reactivity of the palladium system contrasts with that observed when $Co_2(CO)_8$ was used in stoichiometric amounts (eq 8). The carbonylation of 3,3-disubstituted diaziridines can be effected with cobalt but not palladium complexes, while palladium is effective for monosubstituted diaziridines and cobalt is not (see eq 8).[20]



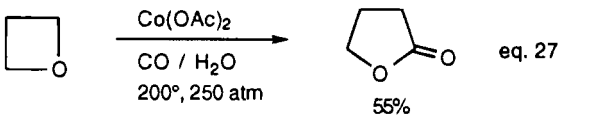
24 **25** (39-66%) eq. 26

R, R', R" = alkyl

Thus, aziridines and related three-membered N-heterocycles are good substrates for the carbonylative ring expansion reaction under various conditions. Depending on the substitution pattern and the metal catalyst, the more or the less substituted C–N bond can be carbonylated in a regio- and stereospecific manner.

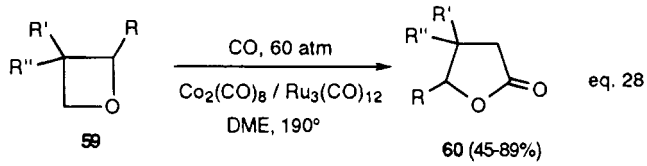
Four-Membered Heterocycles

Oxetanes. In 1959, it was reported that γ-butyrolactone was obtained in fair yield from oxetane using a catalytic amount of $Co(OAc)_2$ under 250 atm of CO in the presence of H_2O at 200 °C (eq 27).[23]



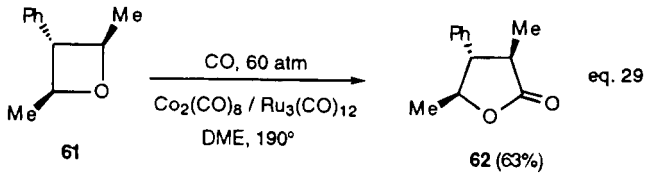
55% eq. 27

Almost 30 years later, it was found that the carbonylation of oxetanes could be accomplished under considerably lower pressure using mixed metal carbonyls.[37] The best results were obtained when a 1:1 mixture of $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ was employed under 60 atm of CO at 165–240 °C. A wide variety of oxetanes were reactive under these conditions, affording the corresponding lactones in good yields (eq 28). It was also found that the carbonylation proceeded with retention of configuration at all the carbon centers of the ring, including that α to the reactive C–O bond (eq 29).



59 **60** (45-89%) eq. 28

R = H, Hexyl
R' = H, Me
R" = H, Me, CH_2OCOMe

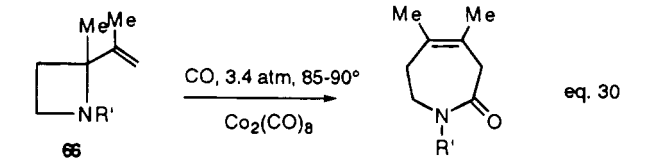


61 **62** (63%) eq. 29

Azetidines. The carbonylation of azetidines is feasible and can be effected under relatively mild conditions. As in the aziridine systems, the regioselectivity of the carbonylation reaction was directed by the substituents at the 2-position on the ring. For example, cobalt carbonyl catalyzed carbonylation of 2-alkylazetidines led to 5-alkylpyrrolidinones (**64**) while 2-arylazetidines form 3-arylpyrrolidinones (**65**) (Scheme 4).[38] It should be noted that the latter reaction, as in the aziridine case, occurred with retention of configuration.

When R = C(O)OMe, the reaction is more facile and can be effectively performed at approximately 40 °C (43 h). The reaction led to a 1:2.6 mixture of **65** and **64**. The formation of **65** in this case can be rationalized by coordination between the cobalt center and the methoxycarbonyl side chain.

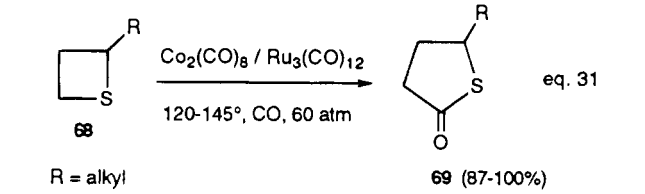
When vinylazetidines (**66**) were used as the starting materials (eq 30), the final products obtained were azepinones (**67**) with the vinyl side chain incorporated into the ring.[38] A similar incorporation of the vinyl group was also observed in the carbonylation of vinyloxiranes (eq 9).



66 **67** (52-93%) eq. 30

R' = H, $(CH_2)_3COCH_3$, $(CH_2)_2COOCH_3$, $(CH_2)_2CN$

Thietanes. Thietanes (**68**) undergo carbonylation with ring expansion to give γ-thiolactones (**69**) in high yield by using the mixed catalytic system of $Co_2(CO)_8$/$Ru_3(CO)_{12}$ (1:1) under conditions similar to those applied for structurally related oxetanes (eq 31). The CO inserted into the less substituted C–S bond.[37] As

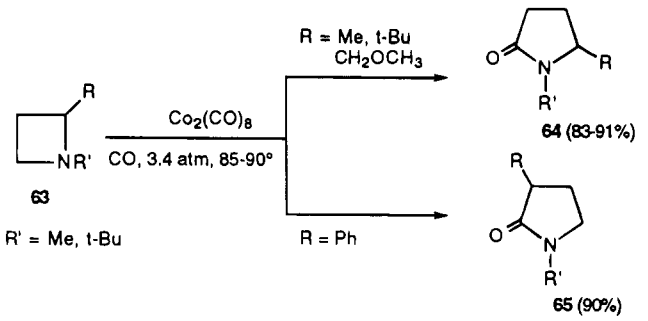


68 **69** (87-100%) eq. 31

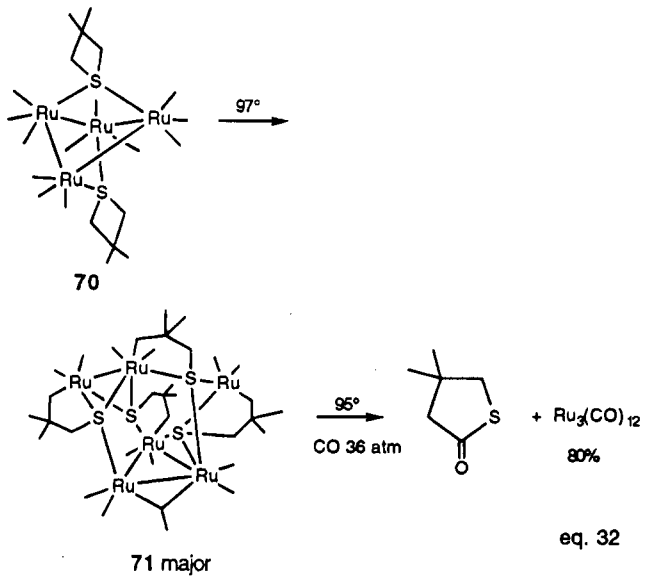
R = alkyl

in the case of oxetanes (see eq 28), the presence of both

Scheme 4

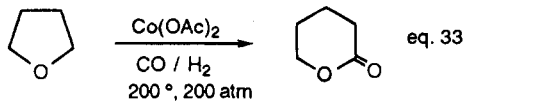


metal carbonyls seems to be essential, although the nature of this synergism has not been established.[37] Note that a thietane ruthenium cluster complex **70** was recently shown to give complex **71** upon heating as a major product.[39] The latter affords γ-thiolactone when treated with carbon monoxide (eq 32). Similar intermediates may be responsible for the carbonylation of thietanes **(68)**.



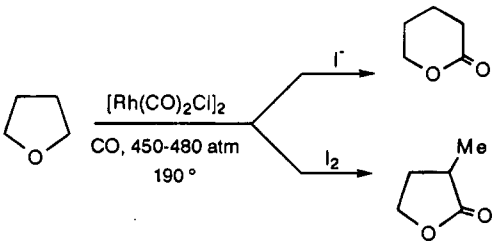
Five-Membered Heterocycles

Oxolanes. In 1953, Reppe and co-workers reported that δ-valerolactone can be obtained in 35–45% yield by carbonylation of tetrahydrofuran, using catalytic amounts of $Co(OAc)_2$ in the presence of CO and H_2 (eq 33).[21]

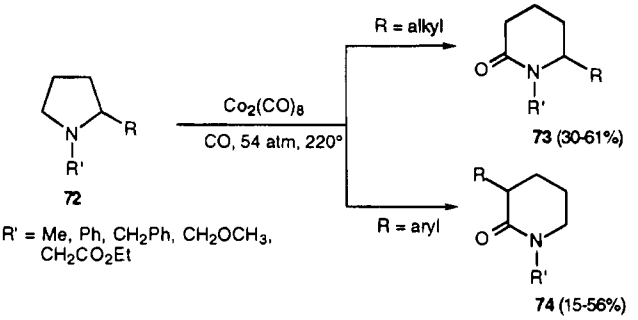


There was also a report of the carbonylation of tetrahydrofuran using $[Rh(CO)_2Cl]_2$ as the catalyst.[40] It was found that different products are formed depending on the promoter (Scheme 5). When iodide ion was used (MeI, LiI, or HI), the major product was the δ-valerolactone. When I_2 was used in the reaction, α-methyl-γ-butyrolactone was the major product. In all cases, however, the yield of the carbonylated

Scheme 5



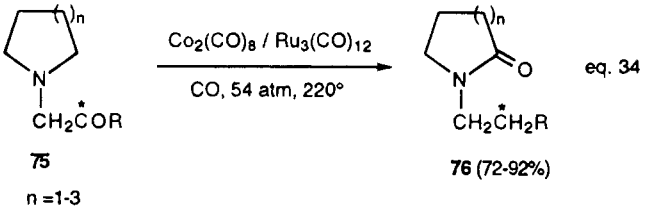
Scheme 6



products did not exceed 15% due to the polymerization of the lactones. It was also found that $Co(OAc)_2 \cdot 4H_2O$ was even less efficient than the rhodium catalyst under these conditions.[40]

Pyrrolidines. The carbonylation of pyrrolidines also required quite drastic conditions, presumably due to the lack of ring strain. Thus, the carbonylation of pyrrolidines can be accomplished using $Co_2(CO)_8$ as the catalyst under 54 atm of CO at 220 °C. The regioselectivity of the CO insertion is dependent on the 2-substituent as described above for azetidines (Scheme 6).[41]

The nature of the side chain played an important role for this system. For example, when the starting pyrrolidine contained a methylene ketone substituent at the nitrogen, a multistep rearrangement occurred instead of the ring expansion, giving rise to the pyrrolidinone in good yield (eq 34). This reaction also takes place for six-, seven-, and eight-membered ring systems. The ^{13}C labeling experiment using ^{13}CO



revealed that no ^{13}C was incorporated into the final product. The role of CO is probably to stabilize one or more key reaction intermediates since there was only a 5% yield of the product when the reaction was run under nitrogen. Furthermore, when the starting material contains ^{13}C at the carbonyl carbon side chain, the labeled carbon converted to the methylene carbon unit in the product. This result provides evidence for the positional exchange of the oxygen and two hydrogen atoms.[41]

Other Five-Membered-Ring Heterocycles. When indazolone **77** was subjected to reaction with carbon monoxide at elevated temperature (230 °C) in the presence of a catalytic amount of $Co_2(CO)_8$, the product

(37) Wang, M. D.; Calet, S.; Alper, H. *J. Org. Chem.* **1989**, *54*, 20.
(38) Roberto, D.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 7539.
(39) Adams, R. D.; Belinski, J. A.; Yamamoto, J. H. *Organometallics* **1992**, *11*, 3422.
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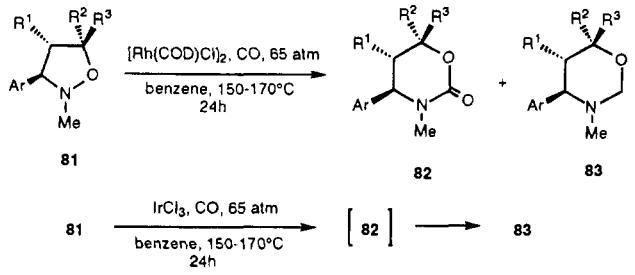
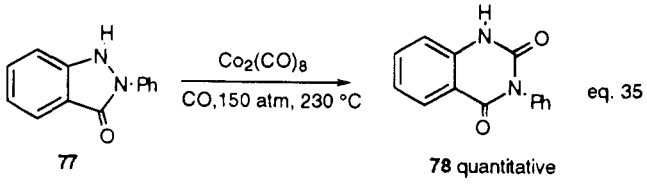
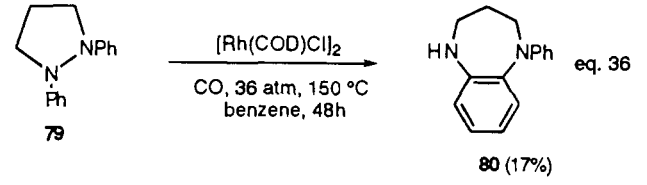
Scheme 7



of carbonylation of the N–N bond, 3-phenyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**78**), was isolated in quantitative yield (eq 35).[22]

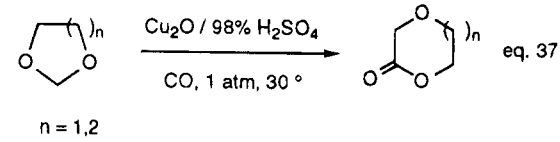


However, CO insertion did not take place with 1,2-diphenylpyrazolidine (**79**). Instead, an unusual rearrangement occurred, affording benzodiazepine **80** in 17% yield, when $[Rh(COD)Cl]_2$ was used as the catalyst (eq 36). No reaction was observed either with $Co_2(CO)_8$ under similar conditions or in the absence of metal complexes.[42]

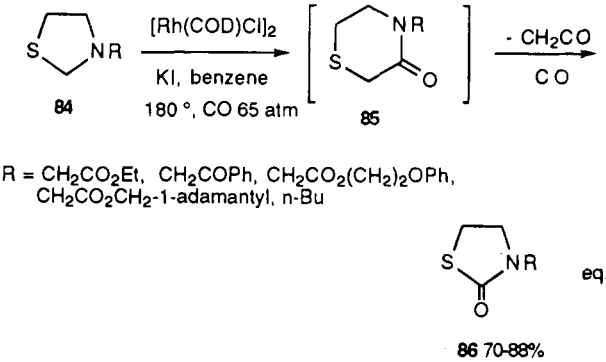


As anticipated, the carbonylation of isoxazolidines proceeded with insertion of CO into the N–O bond, affording tetrahydro-1,3-oxazin-2-ones **82** in 20–82%yield with $[Rh(COD)Cl]_2$ as the catalyst (Scheme 7). However, when iridium trichloride was used as the catalyst, the carbonylation occurred and was followed by hydrogen transfer from another molecule of starting material. This was confirmed by an experiment using a mixture of **81** and **82** bearing different substituents. It was also demonstrated that cyclohexene can be used as an external hydrogen source for the Ir-catalyzed conversion of **81** to **83**.[43]

Carbonylative ring expansion was also studied for heterocycles with two heteroatoms in a 1,3-position. Thus the reaction of 1,3-dioxolane in the presence of Cu_2O and H_2SO_4 was claimed to give 1,4-dioxan-2-one in 90% yield. Also, this method is apparently applicable to the expansion of six- to seven-membered rings (eq 37).[44]



An unusual and unexpected transformation was observed when thiazolidines (**84**) were reacted with CO in the presence of the Rh catalyst (eq 38) affording thiazolidinones (**86**) in excellent yield. It was clearly demonstrated that the reaction involves sequential CO insertion, elimination of ketene from the resulting thiazinone **85**, and finally another carbonylation to give **86** (eq 38).[45] In one case, the intermediate **85** was isolated, characterized, and shown to give the corresponding **86** in quantitative yield upon treatment with CO and the Rh catalyst under standard conditions. Some thiazolidinones (e.g., **86**, R = *n*-Bu) have significant fungicidal activity.[46] The formation of phenylketene in the course of the carbonylation of 2-phenylthiazolidine was unambiguously proven by spectroscopic means and by quenching the reaction with MeOH to give methyl phenylacetate.



Conclusion

A large variety of N-, O-, and S-containing heterocyclic compounds undergo carbonylative ring expansion when exposed to CO in the presence of transition metal complexes. These reactions afford various functionally substituted heterocycles, some of which are difficult or impossible to obtain by other methods. The reactions display, in most cases, excellent regio- and stereochemical control, making this methodology of value for the construction of heterocycles with stereochemically defined substituent groups. One can anticipate the discovery and development of a substantial number of new examples of this class of catalytic reactions.

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(45) Khumtaveeporn, K.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 5662.
(46) Montedison, S.p.A. Jpn. Kokai Tokyo Koho 81 87 574; *Chem. Abstr.* **1981**, *95*, 187236h.