Inversion of Stereochemistry in the $Co_2(CO)_8$-Catalyzed Carbonylation of Aziridines to β-Lactams. The First Synthesis of Highly Strained *trans*-Bicyclic β-Lactams

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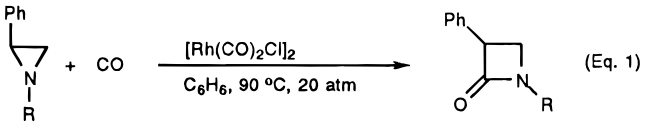
Abstract: β-Lactams were synthesized by the carbonylative ring expansion of aziridines catalyzed by dicobalt octacarbonyl under CO pressure. The active catalyst, cobalt tetracarbonyl anion, induces nucleophilic ring opening of the heterocycle, resulting in inversion of configuration. The regio- and stereospecificity of this reaction resulted in the synthesis of the first highly strained *trans*-7-azabicyclo[4-2-0]octan-8-one derivatives.

Introduction

The use of carbon monoxide for the carbonylation of organic compounds in the presence of transition metal catalysts is an important method for organic synthesis.[1] One facet of this chemistry involves carbonylation with ring expansion of heterocycles, leading to lactams, lactones, or thiolactones.[2] Representative examples include the carbonylation of azirines,[3] azetidines,[4] oxetanes, and thietanes,[5] pyrrolidines,[6] and thiazolidines.[7]

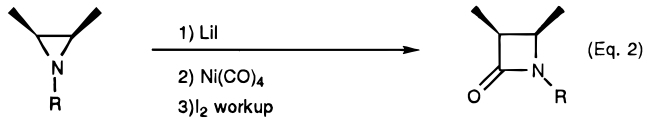
The ring strain present in three-membered ring compounds makes them interesting substrates for carbonylation. The facility to open these rings suggests that carbonylation could take place under relatively mild conditions. Aziridines,[8−10] oxiranes,[11] and thiiranes[12] have been subjected to carbonylation affording different heterocyclic compounds.

There are few examples of the carbonylation and ring expansion of aziridines. The reaction of 2-aryl-1-alkylaziridines[8] with carbon monoxide in the presence of catalytic amounts of $[Rh(CO)_2Cl]_2$ is the most impressive case (eq 1). This reaction, which affords β-lactams in quantitative yields, is regiospecific, with carbonyl insertion occurring exclusively into the aryl bearing carbon−nitrogen bond. The process is stereospecific, proceeding with retention of stereochemistry of the substituents on the carbon atoms of the aziridine ring. When the carbonylation reaction is carried out in the presence of optically pure *d*- or *l*-menthol, kinetic resolution of the aziridine takes place, and the aziridine and the lactam are both obtained in high optical purity. Another interesting example is the carbonylation of vinyl aziridines with $[Pd_2(dba)_3{\cdot}CHCl_3]$, Ph_3P, and CO (1 atm).[9] The carbonyl insertion occurs, as in the above example, at the most substituted ring carbon−nitrogen bond.



(Eq. 1)

The two noted examples are limited to aziridines bearing activating groups in the 2-position (phenyl or vinyl), which likely have a directive effect in the process. Carbonylation of nonactivated aziridines[10] takes place by treating the aziridine first with LiI and then with $Ni(CO)_4$, followed by workup with iodine (eq 2). In this case CO inserts into the less substituted carbon−nitrogen bond with net retention of configuration, affording moderate yields (40−50%) of β-lactams. Unfortunately *excess* quantities of the very toxic nickel tetracarbonyl are required for this reaction.



(Eq. 2)

We now wish to report that nonactivated aziridines can be carbonylated to β-lactams using catalytic amounts of $Co_2(CO)_8$, with CO insertion occurring into the least substituted ring C−N bond. Furthermore, these reactions often proceed in high yields and always with inversion of configuration, complementing the stereochemistry of the rhodium-catalyzed reaction. This methodology also resulted in the isolation of the *trans*-7-azabicyclo-[4.2.0]octan-8-one ring system. This is, to our knowledge, the first synthesis of these highly strained fused β-lactams.

Results and Discussion

Treatment of 1,2-disubstituted aziridines (**1a**−**5a**) with carbon monoxide and dicobalt octacarbonyl in 1,2-dimethoxyethane (DME) for one day at 100 °C and ∼33 atm of CO gave β-lactams in up to 95% yield (Table 1). The ratio of aziridine to $Co_2(CO)_8$ was 12/1. The reaction is regiospecific for **1a**−**4a**, with carbonyl insertion occurring into the less substituted of the two ring carbon−nitrogen bonds. The isolated yields of

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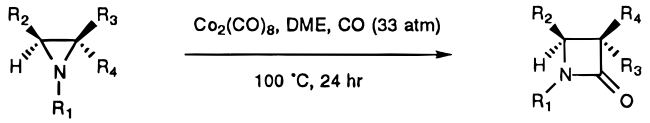
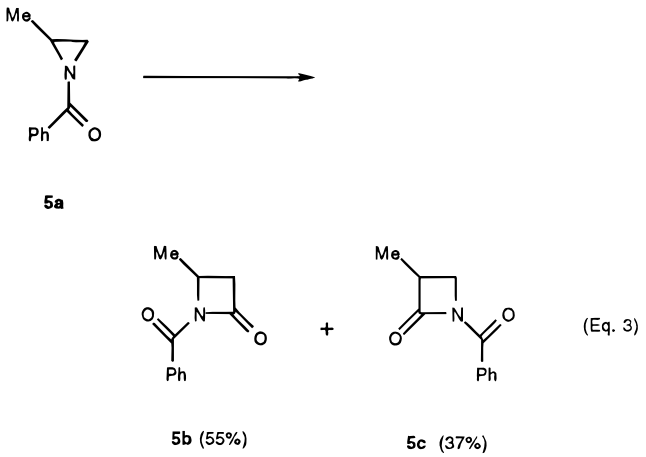
Table 1. Cobalt-Catalyzed Carbonylation of Monocyclic Aziridines



	R_1	R_2	R_3	R_4	product	isolated yield (%)
1a	$PhCH_2CH_2$	Et	H	H	**1b**	94
2a	$PhCH_2CH_2$	*n*-Bu	H	H	**2b**	95
3a	$PhCH_2$	Et	H	H	**3b**	64
4a	*p*-MeOPh	*t*-Bu	H	H	**4b**	50
6a	*i*-Pr	H	Ph	H	**6b**	42
7a	$PhCH_2CH_2$	Me	Me	H	**7b**	95
8a	$PhCH_2CH_2$	Me	H	Me	**8b**	95
9a	*t*-Bu	Ph	Ph	H	**9b**	94
10a	*i*-Pr	Me	Ph	H	**10b**	94

β-lactams are excellent (>90%) for **1b** and **2b**, both of which contain a phenethyl group at nitrogen, but decrease when the nitrogen substituent is changed to benzyl (**3a**) or aryl (**4a**). Nevertheless, as the *p*-methoxyphenyl group can easily be removed by oxidative dearylation using ceric ammonium nitrate[13] to give the unsubstituted 2-azetidinone, this is a useful tool for the preparation of different β-lactam derivatives.

The effect of a benzoyl group in position 1 (**5a**) is significant, since it induces carbonylation of the two C−N bonds, giving a mixture of isomeric products (**5b** and **5c**) in high combined yield (eq 3). The aziridine **5a**, being an amide, is appreciably less basic than **1a**−**4a**.



The nature of the substituent at the 2-position of the aziridine is important. When an alkyl substituent is replaced by a phenyl group (**6a**) the regioselectivity changes completely, giving carbonylation of the phenyl bearing C−N bond in moderate yield.

The results obtained using 1,2,3-trisubstituted aziridines as reactants provide some information regarding the possible mechanism of the reaction. For aziridines containing identical groups in positions 2 and 3 (**7a**−**9a**), carbon monoxide insertion occurs with inversion of configuration at the reacting carbon, i.e. starting from a *cis*-aziridine the product is a *trans*-β-lactam, and the *cis*-β-lactam is formed as the only product by use of a *trans*-aziridine. Reaction of **10a**, which contains two different substituents at positions 2 and 3, with $Co_2(CO)_8$ and CO, affords carbonylation only of the benzylic C−N bond.

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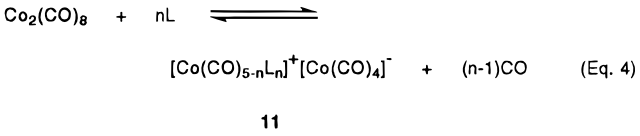
As far as a possible mechanism is concerned, the inversion of configuration resulting from carbonylation indicates that the ring opening of the aziridine may proceed in a S_N2 manner. The reaction of $Co_2(CO)_8$ with N, O, and P donors is known to induce the cleavage of the Co−Co bond and form the ionic pair **11** (eq 4).[14] Tetracarbonylcobaltate is a nucleophile of moderate strength,[15] useful for effecting reactions such as the carbonylation of epoxides with added alcohol to form β-hydroxy esters.[16] It has been proposed that the latter reaction proceeds by anion attack at the less substituted carbon atom of the oxirane ring. A similar sequence of events may occur for an aziridine, which, of course, can be regarded as an N-donor.



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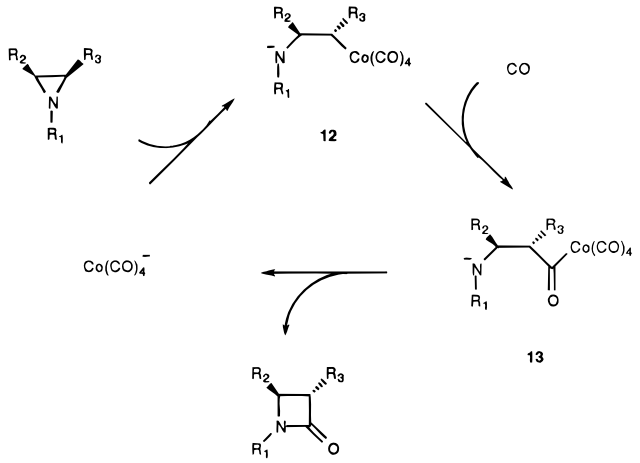
Reaction of an aziridine with $Co_2(CO)_8$ can give $Co(CO)_4^-$, which would be the active catalyst for the reaction (Scheme 1). Nucleophilic ring opening of the aziridine by tetracarbonylcobaltate would occur at the less substituted carbon of the aziridine, with inversion of configuration, to give **12**. Insertion of CO into the C−Co bond of **12** should proceed with retention of configuration to form **13**. Ring closure of the acyl complex **13** gives the β-lactam and regenerates the catalyst.

Scheme 1



The participation of tetracarbonylcobaltate anion in the reaction pathway was confirmed by the use of $Na^+Co(CO)_4^-$ as the catalyst. The β-lactam **2b** was isolated in 92% yield from the aziridine **2a**, although the reaction time is longer than when $Co_2(CO)_8$ was the catalyst. The lower rate of reaction could be due to the lower solvation of the Na^+ counterion, what makes the anion less reactive.

Reaction of 1-benzoyl-2-methylaziridine (**5a**) gives a mixture of two isomers (**5b** and **5c**) in good combined yield. The lower regioselectivity here can be explained by considering some studies done by Stamm *et al.*[17] regarding nucleophilic ring opening of aziridines. Usually this reaction, under neutral or basic conditions, proceeds via an S_N2 like mechanism. However, when there is a moderate activating group attached to the

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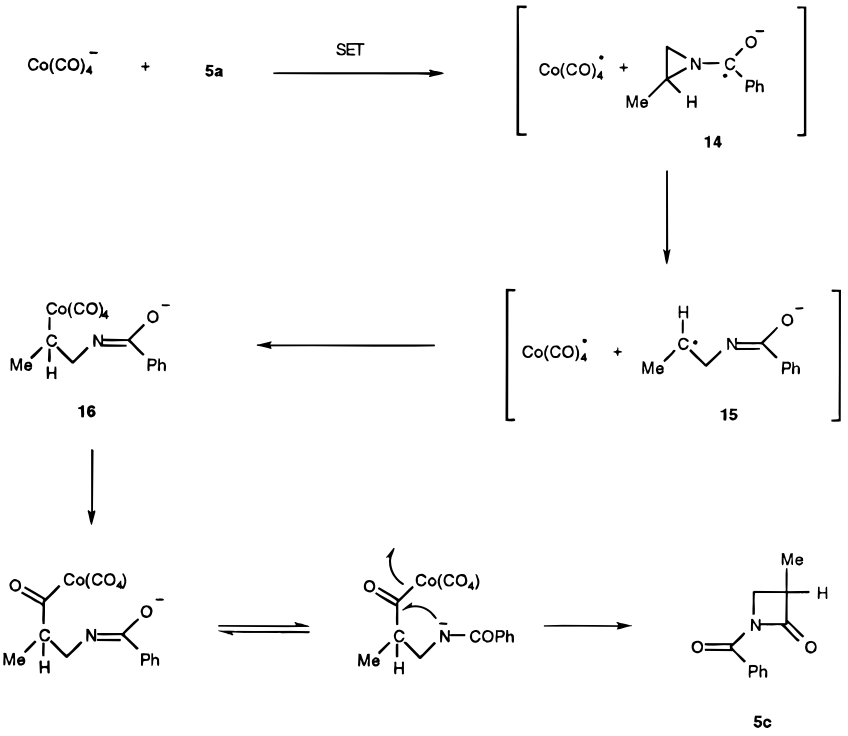
Scheme 2



nitrogen atom, the nucleophile reacts at the most substituted carbon of the aziridine ring with a single electron transfer mechanism proposed for the reaction. It is conceivable that a SET type mechanism (Scheme 2) is competing with the "normal" process (Scheme 1) in the reaction of $Co(CO)_4^-$ with **5a**. A ketyl radical anion (**14**) may be formed, which undergoes ring opening to a secondary radical (**15**). Radical combination with $Co(CO)_4^•$ would afford **16** which is then convertible to **5c**.

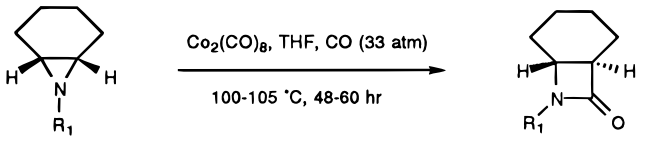
It is well known that benzylic carbons are more reactive toward nucleophiles than alkyl carbons. This is reflected in the carbonylation of **6a**, which takes place at the most substituted carbon to form **6b** in moderate yield. No other carbonylation product was detected in the reaction. The same preference for the benzylic carbon is observed for **10a**, giving **10b** in high yield.

Bicyclic *β*-Lactams. Bicyclic β-lactams are usually prepared by cycloaddition of a cycloalkene and chlorosulfonyl isocyanate[18] (eq 5). The stereochemistry of this reaction is such that one can only obtain the *trans* isomer if a *trans* cycloalkane is used as reactant. The smallest isolable *trans* cycloalkene is *trans*-cyclooctene (**17**), which has been used to prepare the β-lactam **18**[19] (eq 5).

(Eq. 5)

A novel feature of the $Co_2(CO)_8$-catalyzed reaction is the conversion of bicyclic aziridines into highly strained *trans* bicyclic β-lactams. Carbonylation of the *cis*-bicyclic aziridines **19a**−**23a** (7-azabicyclo[4.1.0]heptane derivatives) affords the β-lactams **19b**−**23b**. While the yield of the *trans*-β-lactams is relatively low by using DME as the solvent, it increased significantly when THF was the solvent for the reaction (e.g. 80% yield for **23b** in THF, 35% yield using DME, Table 2). Spectroscopic studies and X-ray analysis of **23b** confirm the *trans* configuration of the product. While *trans*-bicyclic azetidines[20] are known, to our knowledge this is the first example of *trans*-7-azabicyclo[4.2.0]octan-8-ones (β-lactams fused to a six-membered ring in a *trans* fashion). Temperature control is crucial to the success of these reactions, as it must be maintained between 100 and 105 °C. At T < 100 °C the reaction is too slow, and at T > 110 °C the decomposition of the product is faster than its formation, and no lactam can be isolated.

Table 2. Cobalt-Catalyzed Carbonylation of Bicyclic Aziridines



19a-23a 19b-23b

	R_1	product	isolated yield (%)
19a	$PhCH_2CH_2$	**19b**	44
20a	$PhCH_2$	**20b**	28
21a	cyclohexyl	**21b**	69
22a	$(CH_3)_3C$	**22b**	67
23a	1-adamantyl	**23b**	80

The β-lactams **19b** and **21b**−**23b** are white solids while **20b** is a liquid at room temperature. These compounds can be purified by preparative TLC, column chromatography, or recrystallization from hexane. Suitable crystals of **23b** were easily obtained from hexane or mixtures of hexane and ether or methylene chloride and subjected to X-ray analysis. The ORTEP of **23b** (Figure 1) confirms the *trans* configuration for the β-lactam, and pertinent crystallographic data are given in Table 3.

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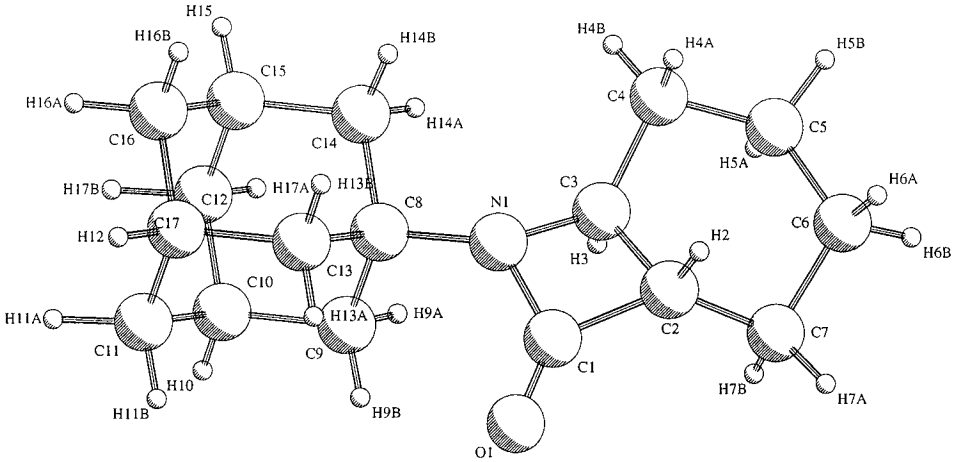

Figure 1. Structure of **23b**, showing the atom-labeling scheme. Selected bond distances (Å): N1−C1, 1.395(4); N1−C3, 1.492(4); N1−C8, 1.456(3); C1−O1, 1.215(4); C1−C2, 1.531(4); C2−C3, 1.524(4). Selected bond angles (deg): C1−N1−C3, 91.25(20); C1−N1−C8, 127.09(23); C3−N1−C8, 127.59(22); N1−C1−C2, 90.62(21); C1−C2−C3, 85.08(20); N1−C1−O1, 131.8(3); C2−C1−O1, 137.6(3).

Table 3. Crystallographic Data for **23b**

formula	$C_{17}H_{25}NO$
fw	259.39
crystal shape	needle
crystal dimensions, mm	0.2 × 0.05 × 0.1
crystal system	monoclinic
lattice parameters	
a, Å	13.904(6)
b, Å	6.385(3)
c, Å	15.793(9)
space group	*P*21/*n*
Z	4
V, Å^3	1401.8(13)
d_{calc}, g/cm^3	1.229
T, K	128
radiation (λ, Å)	Mo Kα (0.70930)
μ, mm^{-1}	0.07
R (R_w), %	5.1 (5.1)

Usually, the four-membered ring in unstrained β-lactams is essentially planar. In addition, the substituent at N lies in the same plane than the ring. These two structural features make possible an optimum amide resonance between the unpaired N electrons and the carbonyl group, resulting in a shorter OC−N bond and a longer C═O bond. This is not the case for **23b**. The X-ray analysis of **23b** shows that the *trans* fusion of the rings adds considerable strain to the system. The N is out of the plane formed by the three carbons in the ring. The distance between the N and the plane is 0.433 Å. In addition the structure shows a pyramidal conformation of N, as reflected by the sum of bond angles about N (345.93°). The N−CO length bond (1.395 Å) is longer than the one present in unstrained systems. All these facts suggest the amide conjugation in the ring is considerably inhibited by the strain of the system. This is a very important property if compared with physiologically active β-lactams.[21a,b] It is known that the activity of β-lactam antibiotics is highly dependent on the deviation of planarity of the four-membered ring. It increases as the tension in the ring is higher, and it is absent when there is not enough strain in the cycle. The acylating power of penicillins and cephalosporins is due mainly to the strain present in the ring, which facilitates the cleavage of the amide bond by lowering the amide resonance.

Table 4. Comparative Structural Parameters of Different Types of β-Lactams

	N−CO bond (Å)	distance between N and plane (Å)	sum of bond angles about N (deg)
23b	1.395	0.433	345.93
penicillins[a]	1.37[b]	0.4[b]	335−343
cephalosporins[a]	1.38[b]	0.2[b]	343−351
unstrained systems[a]	1.347[b]	∼0	∼360

[a] Reference 21b. [b] Average values.

Table 4 shows comparative structural parameters of **23b**, penicillins, cephalosporins, and unstrained systems. The distance from the N to the plane formed by the other three members in the penicillin ring is quite similar to the one observed in **23b**. In addition, the N−CO bond is longer in the latter than the average in penicillins. In the light of these structural similarities it is reasonable to believe that this class of bicyclic β-lactams could find application as acylating agents, and that appropriately substituted derivatives may exhibit significant physiological activity.

In conclusion, a new method has been developed for the synthesis of β-lactams by the carbonylation of a wide range of aziridines, using $Co_2(CO)_8$, an economical catalyst. The yields are often excellent, and the reaction proceeds with inversion of configuration. In most cases the reaction begins by nucleophilic ring opening of the aziridine by in situ-generated tetracarbonylcobaltate anion. A significant result of this research is the preparation of highly strained bicyclic β-lactams containing the *trans*-7-azabicyclo[4.2.0]octan-8-one nucleus. These new compounds present very interesting structural features that resemble those contained in biologically active β-lactams.

Experimental Section

General. Spectral data were obtained by use of the following instruments: Bomem MB-100 (FT-IR), Bruker AMX-500, Varian XL300 or Gemini 200 MHz (NMR), VG 7070E (MS). The carbonylation reactions were run in 45 mL stainless steal autoclaves, containing a glass liner.

Synthesis of Aziridines. Aziridines **1a**−**3a**, **6a**−**8a**, **19a**−**23a** were synthesized by reacting their respective amino alcohols with $Ph_3P{\cdot}Br_2$ and Et_3N in acetonitrile[22] and purified by distillation in vacuo. Aziridine **4a** was prepared by refluxing a toluene solution of *p*-methoxyphenyl azide[23] and 3,3-dimethyl-1-butene for 48 h. The product was purified

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(22) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185.

(23) Mandenhall, G. D.; Smiyh, P. A. S. *Organic Synthesis*; Baumgartner, H. E., Ed.; John Wiley and Sons: New York, 1973; Coll. Vol. 5, p 829.

by column chromatography. Aziridine **5a** was prepared by reacting benzoyl chloride with 2-methylaziridine.[10] Aziridine **9a**[24] was obtained from decyl chloride, and **10a**[25] was prepared from propiophenone, both following known methodology.

Carbonylation of Monocyclic Aziridines. The following is a typical procedure: 0.6 mmol of aziridine **1a**, 10 mL of dry and O_2 free DME, and 0.05 mmol of $Co_2(CO)_8$ (17.4 mg) were placed in a stainless steel autoclave equipped with a stirring bar. The autoclave was purged three times with carbon monoxide and then was charged with 500 psi of carbon monoxide. The reaction was placed in an oil bath at 100 °C and stirred overnight. The autoclave was opened and left in contact with air for a few hours to induce decomposition of the catalyst. Addition of a small amount of ether accelerates the process. A precipitate was formed, the mixture was filtered through a small column packed with silica gel, using ether as the eluant, to give the β-lactam in high purity. For analytically pure β-lactam, the product was further purified by preparative TLC, using hexane/ethyl acetate 65/35 as the developer.

Carbonylation of Bicyclic Aziridines 19a−23a. A 0.6 mmol amount of aziridine, 6 mL of dry and O_2 free THF, and 0.05 mmol of $Co_2(CO)_8$ (17.4 mg) were placed in a stainless steel autoclave equipped with a stirring bar. The autoclave was purged three times with carbon monoxide and then was charged with 500 psi of carbon monoxide. The reaction was placed in an oil bath at 100−105 °C. Conversion of **19a** and **20a** was complete after 60 h. In the case of **21a**−**23a**, 40 h was sufficient for complete reaction. Workup was similar to that described for monocyclic aziridines.

Sodium Tetracarbonylcobaltate. Preparation of sodium tetracarbonylcobaltate was effected from $Co_2(CO)_8$ and NaOH[26] in THF. The catalyst was kept in THF solution. IR of the solution shows characteristic metal carbonyl absorption at 1890 cm^{-1}.

2-Ethyl-1-(2-phenylethyl)aziridine (1a): ^{1}H-NMR (300 MHz) δ 0.99 (tr, 3H, J = 6.7 Hz) 1.22 (m, 2H), 1.38 (q, 2H, J = 6.7 Hz), 1.54 (d, 1H, J = 3.2 Hz), 2.38 (m, 1H), 2.59 (m, 1H), 2.90 (m, 2H), 7.25 (m, 5H). ^{13}C-NMR: δ 12.2, 26.7, 34.3, 37.1, 41.9, 63.8, 126.6, 128.9, 129.3, 140.7. MS: 175 (M^+). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.84; H, 9.79; N, 7.92.

4-Ethyl-1-(2-phenylethyl)-2-azetidinone (1b): ^{1}H-NMR (300 MHz) δ 0.84 (tr, 3H, J = 7.5 Hz), 1.30 (m, 1H), 1.68 (m, 1H), 2.42 (dd, 1H, J = 2.0 and 14.4 Hz), 2.84 (m, 3H), 3.18 (m, 1H), 3.29 (m, 1H), 3.58 (m, 1H), 7.21 (m, 5H). ^{13}C-NMR: δ 9.25, 25.5, 34.5, 41.4, 41.9, 52.9, 126.5, 128.5, 138.6, 167.0. IR (neat): 1743 cm^{-1} (C═O). MS: 203 (M^+). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.84; H, 8.25; N, 7.01.

2-Butyl-1-(2-phenylethyl)aziridine (2a): ^{1}H-NMR (200 MHz) δ 0.90 (tr, 3H, J = 6.9 Hz), 1.18 (d, 1H, J = 6.1 Hz), 1.31 (m, 7H), 1.51 (d, 1H, J = 3.1 Hz), 2.48 (m, 2H), 2.88 (m, 2H), 7.24 (m, 5H). ^{13}C-NMR: δ 14.7, 23.2, 30.3, 33.4, 34.5, 37.1, 40.4, 63.8, 126.6, 128.9, 129.3, 140.7. MS: 203 (M^+). Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.41; H, 10.62; N, 6.80.

4-Butyl-1-(2-phenylethyl)-2-azetidinone (2b): ^{1}H-NMR (200 MHz) δ 0.90 (tr, 3H, J = 6.8 Hz), 1.28 (m, 5H) 1.70 (m, 1H), 2.47 (dd, 1H, J = 2.2 and 14.3 Hz), 2.92 (m, 3H), 3.25 (m, 1H), 3.38 (m, 1H), 3.62 (m, 1H), 7.28 (m, 5H). ^{13}C-NMR: δ 14.6, 23.2, 28.2, 33.1, 35.3, 42.6, 42.7, 52.5, 127.2, 129.2, 139.3, 167.7. IR (neat): 1743 cm^{-1} (C═O). MS: 231 (M^+). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.69; H, 9.39; N, 5.98.

2-Ethyl-1-(phenylmethyl)aziridine (3a):[27] ^{1}H-NMR (200 MHz) δ 0.89 (t, 3H, J = 7.0 Hz), 1.42 (m, 4H), 1.63 (m, 1H), 3.32 (d, 1H, J = 13.2 Hz), 3.53 (d, 1H, J = 13.2 Hz), 7.3 (m, 5H). ^{13}C-NMR: δ 12.1, 26.7, 34.4, 41.9, 65.6, 127.5, 128.7, 128.8, 140.0. MS: 161 (M^+).

4-Ethyl-1-(phenylmethyl)-2-azetidinone (3b):[28] ^{1}H-NMR (200 MHz) δ 0.82 (tr, 3H, J = 7.5 Hz), 1.40 (m, 1H), 1.73 (m, 1H), 2.55 (dd, 1H, J = 14.5 and 2 Hz), 2.98 (dd, 1H, J = 14.5 and 5 Hz), 3.39 (m, 1H), 4.10 (d, 1H, J = 14.5 Hz), 4.60 (d, 1H, J = 14.5 Hz), 7.30 (m, 5H). ^{13}C-NMR: δ 9.2, 25.6, 41.7, 44.6, 52.5, 127.6, 128.1, 128.7, 136.1, 167.2. IR (neat): 1743 cm^{-1} (C═O). MS: 189 (M^+).

2-(1,1-Dimethylethyl)-1-(4-methoxyphenyl)aziridine (4a): ^{1}H-NMR (200 MHz) δ 0.99 (s, 9H), 1.81 (d, 2H, J = 2.3 Hz), 2.15 (t, 1H, J = 2.3 Hz), 3.74 (s, 3H), 6.75 (d, 2H, J = 8.9 Hz), 6.90 (d, 2H, J = 8.9 Hz). ^{13}C-NMR: δ 26.8, 30.3, 30.5, 49.9, 55.5, 114.1, 121.2, 149.1, 154.8. MS: 205 (M^+). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.77; H, 9.01; N, 6.85.

4-(1,1-Dimethylethyl)-1-(4-methoxyphenyl)-2-azetidinone (4b): white solid, mp: 89−90 °C. ^{1}H-NMR (200 MHz) δ 0.93 (s, 9H), 2.74 (dd, 1H, J = 15.2 and 2.5 Hz), 2.95 (dd, 1H, J = 15.2 and 5.5 Hz), 3.76 (s, 3H), 3.97 (dd, 1H, J = 5.5 and 2.5 Hz), 6.85 (d, 2H, J = 9 Hz), 7.23 (d, 2H, J = 9 Hz). ^{13}C-NMR: δ 26.7, 34.6, 38.7, 56.0, 61.4, 114.7, 122.8, 131.6, 157.3, 166.3. IR (KBr): 1730 cm^{-1} (C═O). MS: 233 (M^+). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.43; N, 5.73.

1-Benzoyl-2-methylaziridine (5a):[10] ^{1}H-NMR (200 MHz) δ 1.40 (d, 3H, J = 5.6 Hz), 2.15 (d, 1H, J = 3.1 Hz), 2.57 (m, 2H), 7.49 (m, 3H), 8.04 (m, 2H). ^{13}C-NMR: 17.7, 32.1, 34.5, 128.3, 129.0, 132.6, 133.5, 179.2. IR (neat): 1672 cm^{-1}. MS: 161 (M^+).

1-Benzoyl-4-methyl-2-azetidinone (5b)[29] **and 1-Benzoyl-3-methyl-2-azetidinone (5c)**: ^{1}H-NMR (200 MHz) δ 1.24 (d, 3H, J = 6.9 Hz), 1.31 (d, 3H, J = 6.8 Hz), 2.31 (dd, 1H, J = 16.1 and 9.5 Hz), 2.64 (m, 1H), 2.68 (dd, 1H, J = 16.1 and 5.2 Hz), 3.37 (dd, 1H, J = 16.3 and 12.3 Hz), 3.82 (dd, 1H, J = 16.3 and 7.0 Hz), 3.91 (m, 1H), 7.38 (m, 6H), 7.94 (m, 4H). ^{13}C-NMR: δ 13.0, 22.1, 33.9, 35.8, 49.6, 50.1, 128.1, 128.2, 129.0, 131.0, 132.3, 153.0, 154.5, 166.7, 170.1. IR (neat): 1671 and 1786 cm^{-1} (C═O). MS: 189 (M^+).

1-(1-Methylethyl)-2-phenylaziridine (6a):[30] ^{1}H-NMR (200 MHz) δ 1.85 (d, 6H, J = 6.2 Hz), 1.51 (q, 1H, J = 6.2 Hz), 1.57 (d, 1H, J = 6.6 Hz), 1.79 (d, 1H, J = 3.4 Hz), 2.24 (dd, 1H, J = 6 and 3.4 Hz), 7.2 ppm (m, 5H). ^{13}C-NMR: δ 22.4, 23.0, 37.2, 41.4, 62.5, 127.0, 127.3, 128.8, 141.2. MS: 161 (M^+).

1-(1-Methylethyl)-3-phenyl-2-azetidinone (6b):[31] ^{1}H-NMR (200 MHz) δ 1.13 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 3.12 (dd, 1H, J = 5.3 and 2.5 Hz), 3.54 (t, 1H, J = 5.5 Hz), 3.93 (sept, 1H, J = 6.6 Hz), 4.15 (dd, 1H, J = 5.5 and 2.5 Hz), 7.2 (m, 5H). ^{13}C-NMR: δ 20.9, 21.2, 43.9, 44.8, 53.5, 127.9, 128.0, 129.4, 136.6, 168.1. IR (neat): 1739 cm^{-1} (C═O). MS: 104 (M^+ − 65, PhCH═CH_2).

***cis*-2,3-Dimethyl-1-(2-phenylethyl)aziridine (7a)**: ^{1}H-NMR (200 MHz) δ 1.05 (d, 6H, J = 6.4 Hz), 1.28 (m, 2H), 2.50 (tr, 2H, J = 8.5 Hz), 2.85 (tr, 2H, J = 8.5 Hz), 7.21 (m, 5H). ^{13}C-NMR: δ 13.6, 37.2, 39.3, 63.6, 126.6, 128.9, 129.4, 140.8. MS: 175 (M^+). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.34; H, 9.90; N, 7.98.

***trans*-3,4-Dimethyl-1-(2-phenylethyl)-2-azetidinone (7b)**: ^{1}H-NMR (200 MHz) δ 1.18 (d, 3H, J = 6.1 Hz), 1.20 (d, 3H, J = 7.4 Hz), 2.62 (dq, 1H, J = 7.4 and 2.0 Hz), 2.88 (m, 2H), 3.06 (dq, 1H, J = 6.1 and 2.0 Hz), 3.20 (m, 1H), 3.64 (m, 1H), 7.25 (m, 5H). ^{13}C-NMR: δ 12.8, 17.5, 34.6, 41.2, 51.6, 56.0, 126.6, 128.6, 138.7, 138.7, 170.4. IR (neat): 1738 cm^{-1} (C═O). MS: 203 (M^+). HRMS calcd for $C_{13}H_{17}NO$: 203.1310. Found: 203.1325.

***trans*-2,3-Dimethyl-1-(2-phenylethyl)aziridine (8a)**: ^{1}H-NMR (200 MHz) δ 1.05 (s, 4H), 1.18 (d, 3H, J = 6.4 Hz), 1.72 (dq, 1H, J = 6.4 and 2.2 Hz), 2.55 (m, 1H), 2.85 (m, 3H), 7.22 (m, 5H). ^{13}C-NMR: δ 11.5, 19.0, 38.0, 39.1, 42.4, 54.4, 126.6, 128.9, 129.4, 141.0. MS: 175 (M^+). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.23; H, 9.95; N, 7.90.

***cis*-3,4-Dimethyl-1-(2-phenylethyl)-2-azetidinone (8b)**: ^{1}H-NMR (500 MHz) δ 1.03 (d, 3H, J = 6.4 Hz), 1.09 (d, 3H, J = 7.6 Hz), 2.85 (tr, 2H, J = 7.4 Hz), 3.13 (dq, 1H, J = 7.6 and 5.3 Hz), 3.20 (m, 1H), 3.54 (m, 2H), 7.23 (m, 5H). ^{13}C-NMR: δ 9.3, 14.0, 35.2, 41.9, 47.2, 51.7, 127.1, 129.1, 129.2, 139.4, 171.6. IR (neat): 1739 cm^{-1} (C═O). MS: 203 (M^+). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.44; H, 8.27; N, 7.11.

***cis*-1-(1,1-Dimethylethyl)-2,3-diphenylaziridine (9a)**:[24] White solid, mp: 96.5−97 °C. ^{1}H-NMR (200 MHz) δ 1.21 (s, 9H), 3.20 (s, 2H),

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7.15 (m, 10H). ^{13}C-NMR: δ 27.4, 42.6, 53.9, 126.9, 128.1, 128.6, 138.3. MS: 251 (M^+).

***trans*-1-(1,1-Dimethylethyl)-3,4-diphenyl-2-azetidinone (9b)**:[32] white solid, mp = 91−92 °C. ^{1}H-NMR (200 MHz) δ 1.33 ppm (s, 9H), 3.98 (d, 1H, J = 2.15 Hz), 4.48 (d, 1H, J = 2.15 Hz), 7.35 (m, 10H). ^{13}C-NMR: δ 28.2, 54.7, 63.1, 63.6, 126.3, 127.2, 127.4, 128.3, 128.7, 128.8, 135.5, 140.3, 168.4. IR (KBr): 1745 cm^{-1} (C═O). MS (EI): 180 (M^+ − 99, PhCH═CHPh). MS (CI): 280 (M + 1).

***cis*-3-Methyl-1-(1-methylethyl)-2-phenylaziridine (10a)**:[25] ^{1}H-NMR (200 MHz) δ 0.81 (d, 3H, J = 5.7 Hz), 1.08 (d, 3H, J = 6.2 Hz), 1.09 (d, 3H, J = 6.4 Hz), 1.63 (m, 2H), 2.41 (d, 1H, J = 6.8 Hz), 7.2 (m, 5H). ^{13}C-NMR: δ 13.7, 21.9, 22.1, 40.5, 45.9, 61.3, 126.4, 127.8, 127.9, 138.0. MS: 175 (M^+).

***trans*-4-Methyl-1-(1-methylethyl)-3-phenyl-2-azetidinone (10b)**: ^{1}H-NMR (200 MHz) δ 1.18 (d, 3H, J = 6.8 Hz), 1.22 (d, 3H, J = 6.8 Hz), 1.39 (d, 3H, J = 6 Hz), 3.58 (dd, 1H, J = 6 and 2.1 Hz), 3.66 (d, 1H, J = 2.2 Hz), 3.85 (sept, 1H, J = 6.8 Hz), 7.2 (m, 5H). ^{13}C-NMR: δ 20.8, 21.1, 22.5, 44.5, 56.5, 61.8, 127.9, 129.4, 136.3, 167.6. IR (neat): 1743 cm^{-1} (C═O). MS (EI): 118 (M^+ − 85, PhCH═CH_2-CH_3). MS (CI): 204 (M + 1). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: 76.69; H, 8.52; N, 6.79.

7-(2-Phenylethyl)-7-azabicyclo[4.1.0]heptane (19a):[33] ^{1}H-NMR (200 MHz) δ 1.26 (m, 4H), 1.42 (m, 2H), 1.73 (m, 4H), 2.46 (t, 2H, J = 7.8 Hz), 2.86 (t, 2H, J = 7.8 Hz), 7.24 (m, 5H). ^{13}C-NMR: δ 20.6, 24.5, 36.5, 38.3, 63.2, 125.9, 128.3, 128.8, 140.4. MS: 201 (M^+).

***trans*-7-(2-Phenylethyl)-7-azabicyclo[4.2.0]octan-8-one (19b)**: white solid, mp: 69−70 °C. ^{1}H-NMR (500 MHz) δ 1.33 (m, 3H), 1.78 (m, 5H), 2.55 (m, 1H), 2.80 (m, 2H), 2.86 (m, 1H), 3.19 (m, 1H), 3.60 (m, 1H), 7.23 (m, 5H). ^{13}C-NMR: δ 25.5, 26.0, 26.8, 32.1, 35.9, 44.7, 57.8, 61.0, 126.8, 128.5, 128.8, 139.7, 174.6. IR (KBr): 1742 cm^{-1} (C═O). MS: 229 (M^+). HRMS calcd for $C_{15}H_{19}NO$: 229.1467. Found: 229.1460.

7-(Phenylmethyl)-7-azabicyclo[4.1.0]heptane (20a):[34] ^{1}H-NMR (200 MHz) δ 1.31 (m, 4H), 1.63 (m, 2H), 1.83 (m, 4H), 3.48 (s, 2H), 7.31 (m, 5H). ^{13}C-NMR: δ 20.6, 24.5, 38.5, 64.3, 126.5, 127.4, 128.2, 140.0. MS: 187 (M^+).

***trans*-7-(Phenylmethyl)-7-azabicyclo[4.2.0]octan-8-one (20b)**: ^{1}H-NMR (200 MHz) δ 1.12−1.88 (m, 8H), 2.58 (m, 1H), 2.78 (m, 1H), 4.14 (d, 1H, J = 14.5 Hz), 4.31 (d, 1H, J = 14.5 Hz), 7.20 (m, 5H). ^{13}C-NMR: δ 24.7, 25.5, 26.3, 31.3, 46.9, 57.3, 59.4, 127.4, 128.3, 128.6, 136.7, 174.0. IR (neat): 1752 cm^{-1} (C═O). MS: 215 (M^+). HRMS calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1330.

7-Cyclohexyl-7-azabicyclo[4.1.0]heptane (21a):[35] ^{1}H-NMR (200 MHz) δ 1.25 (m, 13H), 1.72 (m, 8H). ^{13}C-NMR: δ 20.6, 24.8, 25.1, 26.1, 32.3, 36.9, 69.6. MS: 179 (M^+).

***trans*-7-Cyclohexyl-7-azabicyclo[4.2.0]octan-8-one (21b)**: white solid, mp: 43.5−44.5 °C. ^{1}H-NMR (200 MHz) δ 1.0−2.1 (m, 18H), 2.57 (m, 1H), 3.07 (m, 1H), 3.45 (m, 1H). ^{13}C-NMR: δ 24.8, 24.9, 25.0, 25.3, 25.4, 26.4, 30.7, 32.1, 32.5, 51.9, 56.4, 57.1, 173.0. IR (KBr): 1738 cm^{-1} (C═O). MS: 207 (M^+). HRMS calcd for $C_{13}H_{21}NO$: 207.1623. Found: 207.1629.

7-(1,1-Dimethylethyl)-7-azabicyclo[4.1.0]heptane (22a): ^{1}H-NMR (200 MHz) δ 0.91 (s, 9H), 1.18 (m, 2H), 1.35 (m, 2H), 1.65 (m, 6H). ^{13}C-NMR: 20.6, 25.0, 26.6, 30.1, 52.8. MS: 153 (M^+). HRMS calcd for $C_{10}H_{19}N$: 153.1517. Found: 153.1516.

***trans*-7-(1,1-Dimethylethyl)-7-azabicyclo[4.2.0]octan-8-one (22b)**: white solid, mp: 57−58 °C. ^{1}H-NMR (200 MHz) δ 1.29 (s, 9H), 1.30−2.15 (m, 8H), 2.50 (m, 1H), 3.01 (m, 1H). ^{13}C-NMR: δ 25.0, 25.2, 26.5, 27.7, 33.2, 53.8, 55.9, 56.7, 173.0. IR (KBr): 1735 cm^{-1} (C═O). MS: 181 (M^+). HRMS calcd for $C_{11}H_{19}NO$: 181.1467. Found: 181.1464.

7-(1-Adamantyl)-7-azabicyclo[4.1.0]heptane (23a): ^{1}H-NMR (200 MHz) δ 1.13 (m, 2H), 1.36 (m, 2H), 1.48 (m, 6H), 1.62 (m, 10H), 1.87 (m, 2H), 2.02 (m, 3H). ^{13}C-NMR: δ 20.6, 25.3, 28.0, 29.6, 36.9, 40.4, 52.4. MS: 231 (M^+). Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.45; H, 10.61; N, 6.00.

***trans*-7-(1-Adamantyl)-7-azabicyclo[4.2.0]octan-8-one (23b)**: white solid, mp: 122 °C dec. ^{1}H-NMR (200 MHz) δ 1.40−2.40 (m, 23H), 2.48 (m, 1H), 3.07 (m, 1H). ^{13}C-NMR: δ 25.0, 25.3, 26.5, 29.1, 33.5, 36.3, 40.8, 54.7, 55.8, 172.8. IR (KBr): 1732 cm^{-1} (C═O). MS: 259 (M^+). HRMS calcd for $C_{17}H_{25}NO$: 259.1947. Found: 259.1936.

Single Crystal Diffraction Study of 23b. Crystals of **23b** were obtained by layering a concentrated solution of **23b** in ether with hexane. One of the crystals having approximate dimensions of 0.2, 0.05, 0.1 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo Kα radiation. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement using the setting angles of 25 reflections in the range $40 < \theta < 50$ corresponded to a monoclinic cell with dimensions a = 13.904(6) Å, b = 6.385(3) Å, c = 15.793(9) Å, β = 91.43(6). For Z = 4 and FW = 259.39, the calculated density is 1.229 g/cm^3. Based on the systematic absences, the space group was determined to be $P2_1/n$. The data were collected at a temperature of −145 °C using the $\omega-2\theta$ scan technique to a maximum 2θ value of 49.9 degrees.

A total of 2595 reflections was collected. The unique set contains only 2486 reflections. The standards were measured after every 150 reflections. No crystal decay was noticed. The data were corrected for Lorentz and polarization effects.[36] No absorption correction was made.

The structure was solved by direct methods. All the atoms were refined anisotropically except for hydrogen atoms. The hydrogen atoms were found by difference Fourier map. The final cycle of full matrix least-squares refinement was based on 1825 observed reflections ($I > 2.5\sigma(I)$) and 272 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.220 and −0.220 e/a^3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package.[37]

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Supporting Information Available: Experimental details and tables of crystal structure determination data, atomic coordinates, thermal parameters, and bond length and angles for compound **23b** (14 pages); listing of structure factors (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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