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Cycloaddition Reactions of Pyridinium and Related Azomethine Ylides

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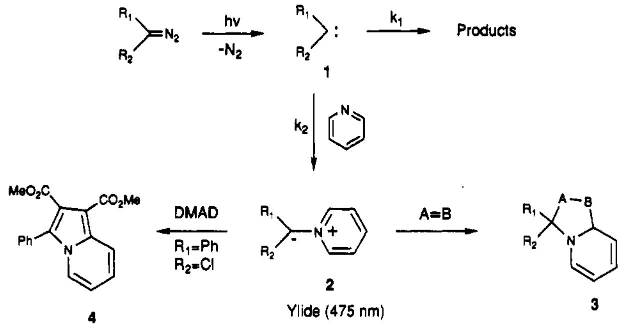
The Rh(II)-catalyzed reaction of α-diazoacetophenone in the presence of 2-(methylthio)pyridine and dimethyl acetylenedicarboxylate gave 3-benzoyl-1,2-dicarbomethoxy-3,5-dihydro-5-(methylthio)-indolizine. The formation of the cycloadduct proceeds via a pyridinium ylide formed by attack of the nitrogen lone pair on the electrophilic keto carbenoid. A related cyclization occurred using 1-diazo-3-[(2-pyridyl)thio]-2-propanone. The Rh(II)-catalyzed reaction of 1-(3′-diazoacetonyl)-2-pyridone with DMAD was also found to give cycloadducts derived from an azomethine ylide. The initial reaction involves generation of the expected carbonyl ylide dipole by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. A subsequent proton exchange generates the thermodynamically more stable azomethine ylide which is trapped by DMAD. Azomethine ylide cycloadducts derived from keto carbenoid cyclization onto a thiobenzoxazole are also formed. When 1-diazo-3-[(2-benzoxazolyl)thio]-2-propanone was used, the initially formed cycloadduct underwent a subsequent 1,3-sigmatropic thio shift. An analogous cyclization occurred using 2-(4-diazo-3-oxobutyl)benzoxazole. In addition to undergoing dipolar cycloaddition, the highly stabilized dipole formed from this benzoxazole loses a proton to produce a cyclic ketene *N*,*O*-acetal. This compound reacts further with DMAD to eventually produce a novel phenolic lactam whose structure was established by an X-ray crystal structure analysis.

Pyridine is an excellent trap of singlet carbenes.[1-5] The trapping reaction gives pyridinium ylides 2, some of which are sufficiently stable to be isolated.[6] Since their introduction in 1960,[1] pyridinium ylides have become increasingly popular probes for the study of the dynamics of carbenes which lack chromophores.[7] The combination of high reactivity, favorable spectroscopic properties, and long ylide lifetime has allowed the study of the dynamics of a variety of "*invisible*" carbenes.[8] The technique has found use in the study of aryl, arylhalo, alkyl, alkylalkoxy, alkylhalo, arylsiloxy, and dialkyl carbenes.[9-12] In a typical experiment, a diazoalkane (or diazirine) is subjected to laser flash photolysis in the presence of pyridine. This results in the formation of the pyridinium ylide 2 which possesses an intense transient absorption at ca. 475 nm.[9] The rate of formation of the ylide is recorded thereby allowing for measurement of the absolute rate constants for reactions of *invisible* carbenes.[8]



Surprisingly, with all of this recent activity, there have been only a few reports describing the 1,3-dipolar cycloaddition chemistry of the pyridinium ylide with various dipolarophiles. Platz and co-workers reported that the photolysis of phenylchlorodiazirine in the presence of both pyridine and DMAD produced cycloadduct 4 in 30% yield by dipolar cycloaddition of DMAD to the ylide followed by loss of HCl.[13] Thermal decomposition of ethyl diazoacetate in the presence of isoquinoline resulted in the formation of a related *N*-ylide which was trapped with DMAD.[14] Our long-standing interest in the application of 1,3-dipolar cycloaddition for the synthesis of complex

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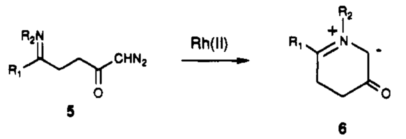
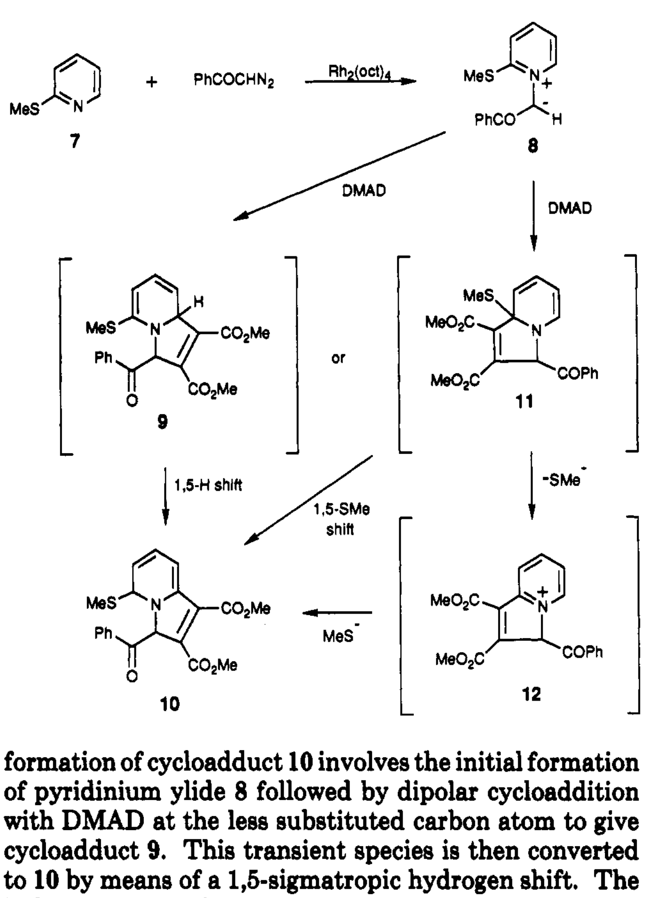
heterocycles led us to study the rhodium(II)-catalyzed reaction of a series of α-diazo ketones in the presence of various heteroatoms.[15,16] An earlier report from our laboratory demonstrated that imine derivatives of type **5**



are able to undergo a rhodium(II)-induced cyclization to generate cyclic azomethine ylides.[17] Since pyridinium ylides are a special subclass of azomethine ylides,[18] we became interested in studying their formation from rhodium carbenoids derived from α-diazo ketones.[19] We were particularly interested in establishing whether the decreased nucleophilicity of the N-lone pair on pyridine and related heterocycles would significantly affect the efficiency of ylide formation relative to "*nonaromatic*" imines. The results of this study are described herein.

Results and Discussion

The transition metal catalyzed reactions of α-diazocarbonyl compounds with aromatic molecules has received much attention in recent years.[20] The decomposition of α-diazo ketones with rhodium(II) acetate produces an α-keto carbenoid which adds to the benzene ring to give a norcaradiene which subsequently tautomerizes to a cycloheptatriene, both inter- and intramolecular examples being known.[21,22] Polyaromatic and π-excessive heteroaromatics containing oxygen or sulfur atoms generally undergo cyclopropanation followed by σ-bond cleavage.[23-25] In contrast, the transition metal catalyzed reaction of α-diazo ketones with N-containing heteroaromatics has not been extensively studied.[26] We initiated our investigations in this area by studying the reaction of α-diazoacetophenone with pyridine in the presence of various trapping agents. Unlike the smooth cyclopropanation reaction which occurred with benzene, the above process led to a complex mixture of products which was extremely difficult to purify. The only compound which could be identified from the mixture corresponded to 1,2,3-tribenzoylcyclopropane. After repeated attempts to trap a pyridinium ylide, our efforts focused on the reaction of 2-(methylthio)pyridine (**7**) with α-diazoacetophenone in the presence of catalytic rhodium(II) octanoate. We reasoned that placement of a thiomethyl group on the pyridine ring would enhance the nucleophilicity of the pyridine nitrogen and thereby promote attack on the electrophilic carbenoid. Indeed, the reaction of α-diazoacetophenone with 2-(methylthio)pyridine (**7**) in the presence of 1.2 equiv of DMAD gave 3-benzoyl-1,2-dicarbomethoxy-3,5-dihydro-5-(methylthio)indolizine (**10**) in 60% yield. The simplest mechanism to account for the formation of cycloadduct **10** involves the initial formation of pyridinium ylide **8** followed by dipolar cycloaddition with DMAD at the less substituted carbon atom to give cycloadduct **9**. This transient species is then converted to **10** by means of a 1,5-sigmatropic hydrogen shift. The isolation of **10** is also consistent with the formation of the regioisomeric cycloadduct **11** which undergoes a 1,5-methylthio shift perhaps via the tight ion pair **12**.



Intramolecular cyclizations have been of considerable synthetic and mechanistic interest,[27] and our long-standing involvement with the tandem intramolecular cyclization–cycloaddition reaction of α-diazocarbonyl compounds[16] prompted us to examine the rhodium(II)-catalyzed behavior of 1-diazo-3-[(2-pyridyl)thio]-2-propanone (**13**). This compound was conveniently prepared from 2-mercaptopyridine and 1-bromo-3-diazo-2-propanone. The rhodium(II) acetate catalyzed reaction of α-diazo ketone **13** in the presence of DMAD afforded a mixture of indolizines **16** (65%) and **17** (15%). The initial reaction involves generation of the expected pyridinium ylide **14** by intramolecular cyclization of the keto carbenoid onto the nitrogen atom of the pyridine ring. Dipolar cycloaddition of **14** with DMAD affords cycloadduct **15** which is readily oxidized to **16**. The formation of indolizine **17** probably involves a 1,5-hydrogen shift of **15** to give **18**, which subsequently undergoes fragmentation in a manner analogous to that encountered with *N*-acyl-2-(1-diazoacetyl)pyrrolidines.[28]

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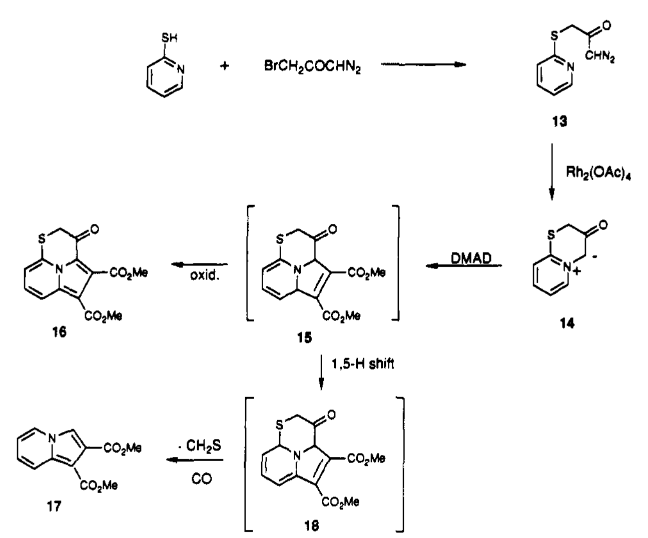
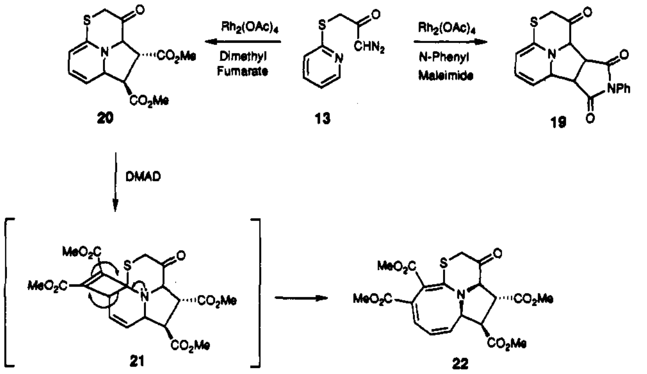
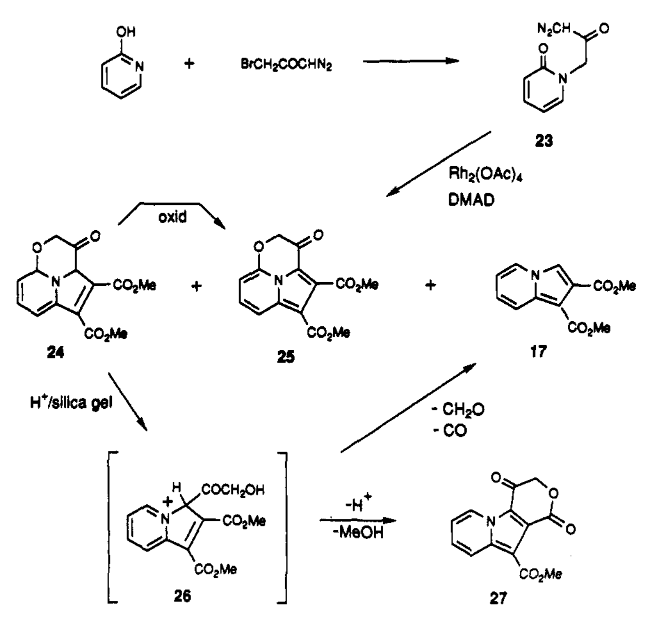


We also studied the cyclization–cycloaddition chemistry of α-diazo ketone **13** with *N*-phenylmaleimide and dimethyl fumarate and found that cycloadducts **19** and **20** were formed in 90% yield, respectively. Both cycloadducts contain a reactive ketene *N,S*-acetal moiety and proved to be difficult to isolate in pure form. When cycloadduct **20** was allowed to react with 1 equiv of DMAD at room temperature, it was converted to azocin-3-one **22** in 70% yield. The structural assignment of compound **22** was unequivocally established by an X-ray crystal analysis. More than likely the formation of **22** proceeds via an initial 2 + 2-cycloaddition of **20** with DMAD to give **21**, followed by an electrocyclic ring opening reaction.



The success achieved with the Rh(II)-catalyzed transformations of diazo ketone **13** prompted us to examine the reaction of the corresponding oxa analogue. An attempt to produce this oxa analogue from reaction of 2-hydroxypyridine with 1-bromo-3-diazo-2-propanone, however, gave 1-(3′-diazoacetonyl)-2-pyridone (**23**) as the exclusive product. Having this material on hand, we decided to examine its transition metal catalyzed behavior. Treatment of **23** with DMAD in the presence of $Rh_2(OAc)_4$ afforded a mixture of three products whose structures were established as **24** (32%), **25** (10%), and **17** (24%) on the basis of their spectroscopic properties (see Experimental Section). Silica gel purification of **24** resulted in a novel acid-catalyzed rearrangement producing indolizine-1,4-dione **27**. This same product was also obtained (50%) by stirring a sample of **24** in benzene in the presence of *p*-toluenesulfonic acid. Under these conditions a significant amount (35%) of indolizine **17** was also formed, in addition to lesser quantities (15%) of **25**. The amount of **25** increased considerably when the reaction of **24** was carried out in the presence of oxygen. This observation suggests that the formation of **25** in the Rh(II)-catalyzed reaction of **23** is the result of a subsequent oxidation of cycloadduct **24**. Formation of compounds **17** and **27** from the acid catalyzed reaction of **24** undoubtedly involves initial C–O bond cleavage to produce pyridinium ion **26**. This transient species can lose a proton and lactonize to **27** or else undergo fragmentation to give formaldehyde, carbon monoxide, and indolizine **17**.



A mechanism that explains the formation of cycloadduct **24** is outlined in Scheme I. The initial reaction involves generation of the expected carbonyl ylide dipole **28** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. In an earlier report from our laboratory,[28,29] we introduced a new strategy for azomethine ylide formation[30,31] in which the key step involved a dipole rearrangement. This reaction, which we have termed a "*dipole cascade*" involves two distinct classes of 1,3-dipoles. It is initiated by a rhodium(II)-catalyzed diazo ketone cyclization onto a neighboring carbonyl group to generate a carbonyl ylide dipole which then undergoes a subsequent proton shift (e.g., **23** → **28** → **29**). Semiempirical molecular orbital calculations have indicated that the heat of formation of cyclic carbonyl ylides of type **28** are generally 10–15 kcal/mol higher in energy than the corresponding azomethine ylides of type **29**.[32] Some of this energy difference is presumably responsible for the facility with which the dipole reorganization of **28** to **29** occurs. Dipolar cycloaddition of **29** with DMAD produces **30** as a transient which undergoes a subsequent 1,5-sigmatropic hydrogen shift to give indolizin-3-one **24**. The fact that we were able to isolate **24** as the major product in this reaction also provides good support for the suggested intermediacy of structure **18** in the thio system (i.e., **13** → **18** → **17**).

In order to further evaluate the ability of the pyridine ring to participate in azomethine ylide formation, we

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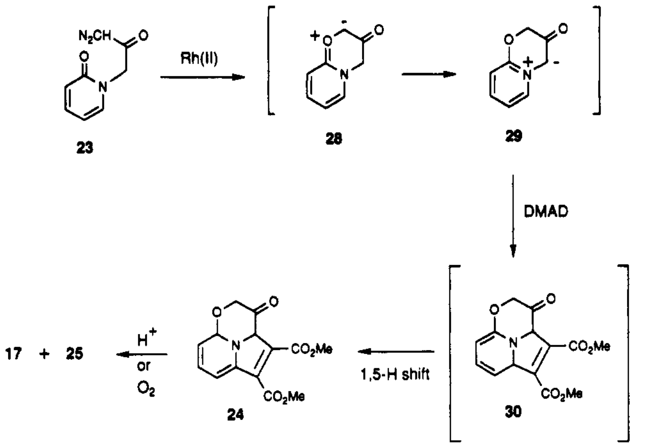
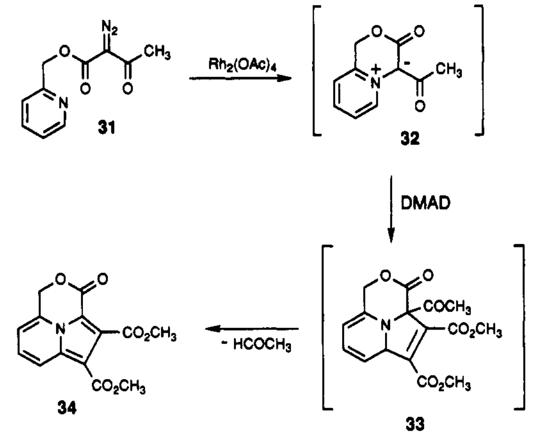
Scheme I

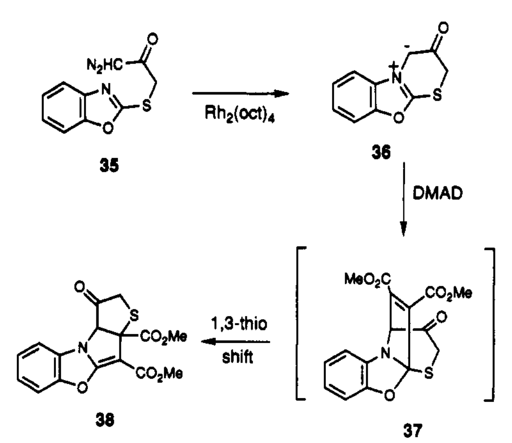


decided to study the rhodium(II)-catalyzed reaction of the related 2-pyridyl methyl 2-diazo-3-oxobutanoate system (31). The cyclization-cycloaddition reaction of 31 with

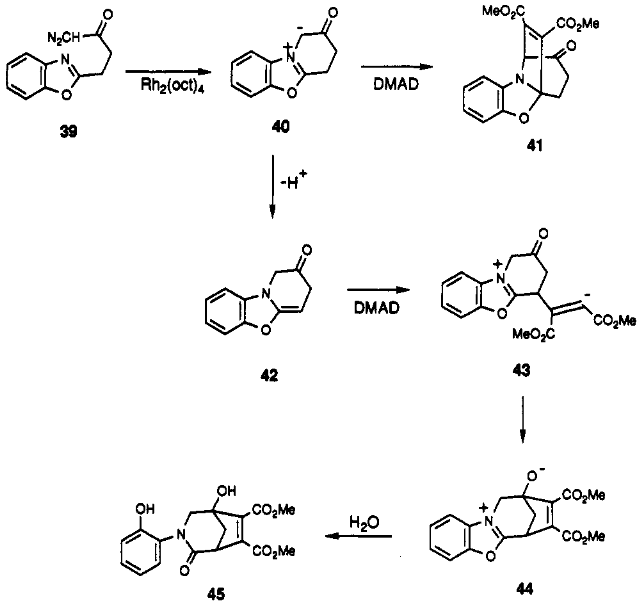


DMAD produced oxoindolizine **34** as the only isolable product in 62% yield. The formation of **34** is consistent with the involvement of an azomethine ylide intermediate (i.e., **32**) which undergoes rapid 1,3-dipolar cycloaddition with DMAD. The initially formed 1:1-cycloadduct **33** is ultimately converted to **34** by deacetylation and subsequent oxidation.

As part of our continuing involvement with the chemistry of azomethine ylides,[17] we became interested in examining the cyclization of several other α-diazo-substituted N-containing heteroaromatic systems as a method for ylide generation. Aside from some examples using simple imines,[33-38] pyridines,[1-7] isoquinolines,[14] and isoxazolidines,[17] little is known about the diazo cyclization process with N-heteroaromatic systems. This led us to explore the potential of α-diazo benzoxazole cyclization as a method for producing novel and synthetically useful dipoles. Interestingly, treatment of 1-diazo-3-[(2-benzoxazolyl)thio]-2-propanone (**35**) with DMAD in the presence of a catalytic quantity of Rh(II) octanoate at 25 °C afforded the rearranged cycloadduct **38**. The structure of **38** was assigned on the basis of its characteristic spectral data and firmly established by an X-ray single-crystal structure analysis. The formation of **38** involves generation of the expected azomethine ylide dipole **36** followed by dipolar cycloaddition with DMAD. The initially formed cycloadduct **37** undergoes a subsequent 1,3-sigmatropic thio shift to give the thermodynamically more stable product **38**. Good analogy exists in the literature for the suggested 1,3-sigmatropic shift.[39]



In an effort to further advance our understanding of the facility with which diazo-substituted benzoxazoles undergo to Rh(II)-induced cyclization, we prepared 2-(4-diazo-3-oxobutyl)benzoxazole (**39**). With this system, dipolar cycloadduct **41** should be stable toward further rearrangement. The 1,3-sigmatropic shift encountered with **37** would be much less likely to occur with **41** since an unfavorable C–C bond cleavage is required. Indeed, treatment of **39** with Rh(II) octanoate at 25 °C in the presence of DMAD gave cycloadduct **41** in 20% yield. The major product isolated (52%), however, corresponded to the novel phenolic lactam **45**, whose structure was unequivocally established by an X-ray crystal structure analysis. The highest yields of **45** were obtained when the solvent (benzene) was not thoroughly dried. A reasonable mechanism which rationalizes the formation of **45** involves generation of the expected azomethine ylide dipole **40** by intramolecular cyclization of the keto carbenoid onto the



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nitrogen atom of the benzoxazole ring. In addition to undergoing dipolar cycloaddition to give **41**, the highly stabilized dipole loses a proton to produce the cyclic ketene *N,O*-acetal **42**. We believe that this compound reacts further with the activated π-bond of the dipolarophile to give zwitterion **43**. The anionic portion of **43** then adds to the adjacent carbonyl group, affording a new zwitterionic intermediate **44**. If there is some water present, this species is converted to the phenolic lactam **45**. In conclusion, diazo-substituted nitrogen-containing heteroaromatics have been observed to undergo cyclization to produce azomethine ylides when treated with Rh(II) carboxylates. Cycloaddition of these dipoles with dimethyl acetylenedicarboxylate affords dipolar cycloadducts in good yield. In certain cases, the initially formed adducts undergo novel rearrangements. We are continuing to explore the scope of the tandem methodology using a variety of heteroaromatic systems and will report additional findings at a later date.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of extra dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate–hexane mixture as the eluent unless specified otherwise.

Rhodium(II)-Catalyzed Cycloaddition of α-Diazoacetophenone with 2-(Methylthio)pyridine (7) in the Presence of Dimethyl Acetylenedicarboxylate. A sample of α-diazoacetophenone was prepared by treating 2.85 g (20 mmol) of benzoyl chloride with 45 mmol of diazomethane in 200 mL of ether. The desired diazo compound was isolated in 95% yield as a yellow crystalline solid: mp 46–47 °C (lit.[40] mp 51 °C); IR (neat) 2115, 1615, 1580, 1400, 1245, and 709 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1 H), 7.44 (t, 2 H, *J* = 7.8 Hz), 7.52 (d, 1 H, *J* = 7.8 Hz), and 7.76 (t, 2 H, *J* = 7.8 Hz).

A solution containing 300 mg (2.0 mmol) of α-diazoacetophenone, 500 mg (4.0 mmol) of 2-(methylthio)pyridine[41] (**7**) and 0.3 mL (2.4 mmol) of DMAD in 5 mL of chloroform was treated with 2 mg of rhodium(II) octanoate at 25 °C for 2 h until no more nitrogen had evolved. Removal of the solvent under reduced pressure was followed by silica gel chromatography of the crude residue. The major fraction (60%) isolated was assigned as 3-benzoyl-1,2-dicarbomethoxy-3,5-dihydro-5-(methylthio)indolizine (**10**); IR (neat) 1730, 1700, 1543, 1245, 1203, and 1170 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.30 (s, 3 H), 3.64 (s, 3 H), 3.75 (s, 3 H), 6.00 (s, 1 H), 7.24–7.36 (m, 4 H), 7.46 (d, 2 H, *J* = 7.5 Hz), 7.78 (dd, 1 H, *J* = 8.1 and 7.6 Hz), 8.17 (d, 1 H, *J* = 8.1 Hz), and 8.58 (d, 1 H, *J* = 4.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.6, 50.8, 51.9, 68.7, 111.7, 121.7, 123.4, 127.2, 127.5, 129.1, 137.3, 141.4, 148.1, 149.0, 153.5, 166.5, 168.7, and 184.5; HRMS calcd for $C_{19}H_{16}NO_5$ ($M^+ - CH_3S$) 338.1028, found 338.1022. Upon standing at room temperature for several hours, indolizine **10** was slowly converted to 3-benzoyl-1,2-dicarbomethoxy-3,5-dihydro-5-hydroxyindolizine: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3 H), 3.58 (s, 3 H), 4.73 (s, 1 H), 5.21 (bs, 1 H), 7.25–8.00 (m, 8 H), and 8.62 (d, 1 H, *J* = 4.5 Hz). All attempts to isolate a pure sample of this material failed. The minor product (ca. 10%) present in the crude reaction mixture was separated by silica gel chromatography and identified as dimethyl methylthiofumarate:[42] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 3.72 (s, 3 H), 3.90 (s, 3 H), and 5.67 (s, 1 H).

Preparation and Rhodium-Catalyzed Cycloaddition Reactions of 2-[(3′-Diazoacetonyl)thio]pyridine (13). A procedure similar to that used by Katznellenbogen and co-workers[43] was employed to prepare 1-bromo-3-diazo-2-propanone. A 2.2-mL (25 mmol) sample of bromoacetyl bromide in 8 mL of ether was added dropwise to a 3-fold excess of an ethereal diazomethane solution at 0 °C. The mixture was stirred in ice overnight, and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 3.6 g (88%) of 1-bromo-3-diazo-2-propanone as a bright yellow oil: IR ($CHCl_3$) 2120, 1640, and 1370 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 3.77 (s, 2 H), and 5.75 (s, 1 H).

To a solution containing 3.3 g (21 mmol) of the above α-diazo ketone in 40 mL of THF was added a suspension containing 1.2 g (21 mmol) of sodium methoxide and 2.3 g (21 mmol) of 2-mercaptopyridine in 20 mL of THF. The reaction mixture was heated at reflux for 30 min. Filtration followed by removal of the solvent under reduced pressure and then silica gel column chromatography gave 3.2 g (83%) of 2-[(3′-diazoacetonyl)thio]pyridine (**13**) as a yellow solid, mp 64–65 °C: IR (neat) 2105, 1640, 1585, 1565, 1460, 1420, 1360, 1130, and 770 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 2 H), 5.79 (s, 1 H), 7.03 (dd, 1 H, *J* = 7.6 and 4.8 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 7.51 (dd, 1 H, *J* = 8.0 and 7.6 Hz), and 8.42 (d, 1 H, *J* = 4.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.5, 53.7, 119.5, 121.3, 135.7, 148.8, 155.8 and 190.4. Anal. Calcd for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75. Found: C, 49.65; H, 3.65; N, 21.67.

To a mixture containing 400 mg (1.8 mmol) of **13** and 0.3 mL (2.2 mmol) of DMAD in 10 mL of chloroform was added 2 mg of rhodium(II) acetate. The reaction mixture was stirred at room temperature for 1 h. Removal of the solvent under reduced pressure left a dark brown oil which was subjected to silica gel chromatography. The minor fraction (15%) isolated from the column was identified as 1,2-dicarbomethoxyindolizine (**17**); mp 90–91 °C (lit.[44] mp 90–91 °C); IR (neat) 1740, 1700, 1520, 1455, 1285, 1226, and 1070 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3 H), 3.92 (s, 3 H), 6.75 (dd, 1 H, *J* = 7.1 and 6.6 Hz), 7.06 (dd, 1 H, *J* = 9.2 and 6.6 Hz), 7.63 (s, 1 H), 7.93 (d, 1 H, *J* = 7.1 Hz), and 8.13 (d, 1 H, *J* = 9.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 50.7, 51.5, 113.0, 116.3, 119.9, 120.9, 122.6, 125.2, 135.5, 163.6, and 164.5. The major product (65%) was assigned as 4,5-dicarbomethoxy-2,3-dihydro[1,3]thiazino[4,3,2-*c,d*]indolizin-3-one (**16**), mp 241–242 °C: IR (KBr) 1735, 1695, 1640, 1512, 1490, 1482, 1448, 1372, 1316, 1244, and 1200 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 2 H), 3.91 (s, 3 H), 4.05 (s, 3 H), 7.15 (d, 1 H, *J* = 7.3 Hz), 7.37 (dd, 1 H, *J* = 8.8 and 7.3 Hz), and 8.21 (d, 1 H, *J* = 8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.8, 51.3, 52.6, 105.0, 113.9, 116.9, 118.8, 126.7, 128.8, 129.3, 137.0, 162.3, 164.8, and 175.2. Anal. Calcd for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.02; H, 3.62; N, 4.55.

To a mixture containing 50 mg (0.23 mmol) of α-diazo ketone **13** and 48 mg (0.28 mmol) of *N*-phenylmaleimide in 0.6 mL of chloroform was added 2 mg of rhodium(II) acetate dimer. The reaction was stirred at room temperature for 30 min giving rise to a single product (90%) whose structure was assigned as (3aα,3bα,6aα,6bα)-2,3,3a,3b,4,5,6a,6b-octahydro-5-phenyl[1,3]thiazino[4,3,2-*d,e*]pyrrolo[3,4-*a*]indolizine-3,4,6-trione (**19**): NMR (300 MHz, $CDCl_3$) δ 3.36 (d, 1 H, *J* = 14.0 Hz), 3.45 (dd, 1 H, *J* = 7.8 and 7.4 Hz), 3.56 (d, 1 H, *J* = 14.0 Hz), 3.75–3.87 (m, 2 H), 4.54 (d, 1 H, *J* = 8.1 Hz), 5.17 (d, 1 H, *J* = 5.9 Hz), 5.64 (dd, 1 H, *J* = 9.5 and 2.0 Hz), 6.03 (ddd, 1 H, *J* = 9.5, 5.9, and 1.4 Hz), and 7.20–7.58 (m, 5 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 36.4, 45.5, 47.1, 62.1, 65.4, 98.8, 111.1, 124.5, 125.5, 128.2, 128.6, 130.9, 134.6, 173.4, 173.9, and 194.3. Anal. Calcd for $C_{18}H_{14}NO_3S$: C, 66.65; H, 4.35; N, 4.32. Found: C, 66.39; H, 4.22; N, 4.14.

To a mixture containing 50 mg (0.23 mmol) of α-diazo ketone **13** and 40 mg (0.28 mmol) of dimethyl fumarate in 0.6 mL of chloroform was added 2 mg of rhodium(II) acetate. The reaction was complete in 30 min affording a major product (90%) whose structure was assigned as (±)-(3aα,4α,5β,5aα)-4,5-dicarbomethoxy-2,3,3a,4,5,5a-hexahydro[1,3]thiazino[4,3,2-*c,d*]indolizin-3-one (**20**): NMR (300 MHz, $CDCl_3$) δ 3.32 (dd, 1 H, *J* = 6.1 and 2.3 Hz), 3.41 (d, 1 H, *J* = 15.6 Hz), 3.47 (dd, 1 H, *J* = 5.7 and 2.3 Hz), 3.59 (d, 1 H, *J* = 15.6 Hz), 3.69 (s, 3 H), 3.76 (s, 3 H), 4.27 (d, 1

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H, $J = 5.7$ Hz), 4.82 (m, 1 H), 4.95 (d, 1 H, $J = 5.9$ Hz), 5.20 (dd, 1 H, $J = 9.8$ and 2.4 Hz), and 5.90 (ddd, 1 H, $J = 9.8$, 5.9, and 1.5 Hz). All attempts to isolate a pure sample of compound **20** failed. This compound readily reacted with 1 equiv of DMAD as described below to give the novel cycloadduct **22**.

To a mixture containing 200 mg (0.92 mmol) of α-diazo ketone **13** and 146 mg (1.01 mmol) of dimethyl fumarate in 5 mL of chloroform was added 2 mg of rhodium(II) acetate. The reaction mixture was allowed to stir at 25 °C for 1 h until no more nitrogen had evolved, and then 0.12 mL (1.01 mmol) of DMAD was added. The resulting mixture was stirred for 3 h at room temperature. Removal of the solvent under reduced pressure followed by silica gel chromatography of the residue afforded a yellow crystalline solid in 70% yield. The structure of this material was identified as (±)-(3aα,4α,-5β,5aα)-2,3,3a,4,5,5a-hexahydro-4,5,9,10-tetracarbomethoxy-1*H*-[1,3]thiazino[4,3,2-*c*,*d*]pyrrolo[1,2-*a*]azocin-3-one (**22**) on the basis of its spectral properties as well as an X-ray crystal structure analysis,[45] mp 180–181 °C: IR (neat) 1740, 1695, 1538, 1440, 1258, 1230, 1210, and 1118 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 3.12 (d, 1 H, $J = 15.0$ Hz), 3.39 (d, 1 H, $J = 6.4$ Hz), 3.52 (d, 1 H, $J = 1.7$ Hz), 3.61 (s, 3 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 3.99 (d, 1 H, $J = 15.0$ Hz), 4.57 (d, 1 H, $J = 1.7$ Hz), 5.10 (dd, 1 H, $J = 7.6$ and 6.4 Hz), 5.75 (dd, 1 H, $J = 10.3$ and 7.6 Hz), 6.72 (dd, 1 H, $J = 10.3$ and 2.9 Hz), and 7.25 (d, 1 H, $J = 2.9$ Hz); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 37.7, 46.5, 47.7, 51.0, 51.7, 51.8, 52.6, 60.6, 67.8, 101.1, 127.9, 132.4, 136.0, 138.8, 155.8, 166.5, 167.0, 170.6, 171.3, and 204.6. Anal. Calcd for $C_{20}H_{21}NO_9S$: C, 53.21; H, 4.69; N, 3.10; S, 7.10. Found: C, 53.30; H, 4.66; N, 3.12; S, 7.06.

Preparation and Rhodium(II)-Catalyzed Reaction of 1-(3′-Diazoacetonyl)-2-pyridone (23) with DMAD. A suspension containing 1.0 g (11 mmol) of 2-hydroxypyridine and 0.8 g (15 mmol) of sodium methoxide in 40 mL of THF was allowed to stir at 25 °C for 30 min, and then 1.65 g (15 mmol) of 1-bromo-3-diazo-2-propanone was added. The resulting mixture was heated at reflux for 5 h. Removal of the solvent under reduced pressure followed by silica gel chromatography of the residue gave 1-(3′-diazoacetonyl)-2-pyridone (**23**) as a yellow crystalline solid, mp 126–127 °C: IR (neat) 2105, 1640, 1590, 1415, 1335, 1150, and 775 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 4.62 (s, 2 H), 5.50 (s, 1 H), 6.23 (td, 1 H, $J = 6.6$ and 1.0 Hz), 6.59 (dd, 1 H, $J = 9.0$ and 1.0 Hz), 7.28 (dd, 1 H, $J = 6.6$ and 2.0 Hz), and 7.39 (ddd, 1 H, $J = 9.0$, 6.6, and 2.0 Hz); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 54.1, 54.7, 105.7, 120.2, 137.5, 139.8, 161.6, and 187.2. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.39; H, 4.06; N, 23.59.

A mixture containing 360 mg (1.8 mmol) of α-diazo ketone **23** and 0.26 mL (2.2 mmol) of DMAD in 10 mL of chloroform was allowed to react with 2 mg of rhodium(II) acetate. The reaction mixture was stirred at room temperature for 1 h until no more nitrogen had evolved. Removal of the solvent under reduced pressure was followed by silica gel chromatography. The first fraction (24%) isolated from column was identified as 1,2-dicarbomethoxyindolizine (**17**).[44] The second fraction (10%) contained a clear oil whose structure was assigned as 4,5-dicarbomethoxy-2,3-dihydro[1,3]oxazino[4,3,2-*c*,*d*]indolizin-3-one (**25**) on the basis of its NMR properties: NMR (300 MHz, CDCl$_3$) δ 3.91 (s, 3 H), 4.04 (s, 3 H), 4.96 (s, 2 H), 6.58 (d, 1 H, $J = 7.7$ Hz), 7.52 (dd, 1 H, $J = 8.8$ and 7.7 Hz), and 7.84 (d, 1 H, $J = 8.8$ Hz). The major fraction isolated from the column (32%) was assigned as (±)-(3aα,8aα)-4,5-dicarbomethoxy-2,3,-3a,8a-tetrahydro[1,3]oxazino[4,3,2-*c*,*d*]indolizin-3-one (**24**) on the basis of its spectroscopic properties, mp 141–142 °C: IR (neat) 1740, 1710, 1650, 1510, 1455, 1320, 1225, and 800 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 3.64 (s, 1 H), 3.93 (s, 3 H), 4.07 (s, 3 H), 4.63 (s, 2 H), 7.17 (dd, 1 H, $J = 7.3$ and 6.5 Hz), 7.50 (dd, 1 H, $J = 8.7$ and 6.5 Hz), 8.38 (d, 1 H, $J = 8.7$ Hz), and 9.98 (d, 1 H, $J = 7.3$ Hz); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 51.3, 53.0, 64.1, 97.8, 104.0, 116.2, 119.3, 128.2, 128.6, 130.6, 137.6, 162.3, 165.9, and 187.1. Anal. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.82; H, 4.47; N, 4.76.

Another fraction (18%) that was also isolated from the silica gel column was identified as 10-carbomethoxy-3,4-dihydro-2*H*-pyrano[3,4-*b*]indolizine-1,4-dione (**27**). This compound was not present in the crude NMR spectrum but rather was formed by a silica-induced reaction of indolizinone **24**. A sample of **24** was also transformed (50%) to **27** by stirring in benzene in the presence of *p*-toluenesulfonic acid. Compound **27**: mp 216–217 °C; IR (neat) 1740, 1662, 1506, 1405, 1320, 1077, and 757 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 4.02 (s, 3 H), 5.09 (s, 2 H), 7.25 (dd, 1 H, $J = 6.8$ and 6.6 Hz), 7.56 (dd, 1 H, $J = 9.0$ and 6.8 Hz), 8.39 (d, 1 H, $J = 9.0$ Hz), and 9.53 (d, 1 H, $J = 6.6$ Hz); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 51.6, 73.1, 117.1, 120.2, 121.9, 127.2, 128.6, 139.3, 156.9, and 179.3. Anal. Calcd for $C_{13}H_9NO_5$: C, 60.23, H, 3.50, N, 5.40. Found: C, 60.12; H, 3.51; N, 5.40.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-Pyridylmethyl 2-Diazo-3-oxobutanoate (31). A 1.0-mL sample of diketene (10.4 mmol) was added in one portion to a stirred solution containing 1.0 mL (12.5 mmol) of 2-pyridinemethanol at room temperature. After the solution was stirred for 3 h, 1.5 g (12.5 mmol) of mesyl azide and 2.9 mL (20.8 mmol) of triethylamine were added and the reaction mixture was stirred an additional 12 h. The mixture was concentrated to a thick yellow oil and subjected to flash silica gel chromatography to give 2.1 g (91%) of 2-pyridylmethyl 2-diazo-3-oxobutanoate (**31**) as a pale yellow solid: mp 43–45 °C; IR (CHCl$_3$) 2135, 1715, 1650, 1315, and 1160 cm^{-1}; NMR (90 MHz, CDCl$_3$) δ 2.49 (s, 3 H), 5.45 (s, 2 H), 7.30 (m, 2 H), 7.75 (td, 1 H, $J = 7$ and 2 Hz), 8.65 (dd, 1 H, $J = 7$ and 2 Hz).

To a stirred solution containing 1.4 g (6.4 mmol) of **31** and 2.4 mL (19.2 mmol) of DMAD in 100 mL of benzene was added 2 mg of rhodium(II) acetate. The reaction mixture was stirred at reflux for 12 h and then concentrated to a dark red oil which was subjected to flash silica gel chromatography to give 1.2 g (62%) of dimethyl 6*H*,8*H*-8-oxoindolizino[3,4,5-*c*,*d*][1,4]oxazine-1,2-dicarboxylate (**34**) as a white crystalline solid, mp 210–211 °C: IR (CHCl$_3$) 1733, 1528, 1432, 1265, and 1227 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 3.89 (s, 3 H), 4.04 (s, 3 H), 5.61 (s, 2 H), 6.92 (d, 1 H, $J = 9$ Hz), 7.41 (dd, 1 H, $J = 9$ and 9 Hz), and 8.19 (d, 1 H, $J = 9$ Hz). Anal. Calcd for $C_{14}H_{11}NO_6$: C, 58.13; H, 3.83; N, 4.84. Found: C, 56.92; H, 3.73, N, 4.66.

Preparation and Rhodium(II)-Catalyzed Reaction of 1-Diazo-3-[(2-benzoxazolyl)thio]-2-propanone (35). A solution containing 2.0 g (13 mmol) of 2-mercaptobenzoxazole in 60 mL of ether was added to a solution containing 2.2 g (13 mmol) of potassium carbonate in 30 mL of water. The reaction mixture was stirred at 25 °C for 15 min, and then a solution containing 2.3 g of 1-bromo-3-diazo-2-propanone in 20 mL of ether was added dropwise. The solution was stirred for 2 h, poured into water, and extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 2.39 g (78%) of 1-diazo-3-[(2-benzoxazolyl)thio]-2-propanone (**35**) as an orange solid, mp 60–61 °C: IR (CHCl$_3$) 3020, 2120, 1640, 1505, 1455, 1365, 1220, and 1140 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 4.05 (s, 2 H), 5.81 (bs, 1 H), 7.22–7.28 (m, 2 H), 7.42–7.45 (m, 1 H), and 7.57–7.60 (m, 1 H); ^{13}C-NMR (300 MHz, CDCl$_3$) δ 38.6, 54.9, 109.6, 118.1, 123.8, 124.1, 141.1, 151.6, 162.9, and 187.7; HRMS calcd for $C_{10}H_7N_3O_2S$ 233.0258, found 233.0254.

A solution containing 328 mg (1.4 mmol) of α-diazo ketone **35** and 0.25 mL (2.0 mmol) of DMAD in 10 mL of benzene was treated with 2 mg of rhodium(II) octanoate. Nitrogen evolution was observed over a period of 15 min. The reaction was stirred at room temperature for an additional 45 min, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 280 mg (57%) of a compound whose structure was assigned as 3a,4-dicarbomethoxy-1-oxo-1,2,-3a,10a-tetrahydrothieno[4′,5′,4,5]pyrrolo[2,1-*b*]benzoxazole (**38**) on the basis of its spectral properties and an X-ray crystal structure analysis,[45] mp 204–205 °C: IR (CHCl$_3$) 1750, 1685, 1645, 1610, 1480, 1445, 1410, and 1140 cm^{-1}; NMR (300 MHz, CDCl$_3$) δ 3.32 (d, 1 H, $J = 15.6$ Hz), 3.72 (d, 1 H, $J = 15.6$ Hz), 3.76 (s, 3 H), 3.81 (s, 3 H), 4.99 (s, 1 H), and 7.01–7.27 (m, 4 H); ^{13}C-NMR (300 MHz, CDCl$_3$) δ 37.0, 50.9, 53.7, 64.8, 65.8, 75.5, 109.9, 111.1, 122.3, 125.4, 128.6, 151.7, 161.1, 163.2, 170.9, and 201.6. Anal.

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(45) The authors have deposited atomic coordinates for structures **22**, **38**, and **45** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Calcd for $C_{16}H_{13}NO_6S$: C, 55.31; H, 3.77; N, 4.03; S, 9.23. Found: C, 54.10; H, 3.80; N, 3.95; S, 8.91.

Preparation and Rhodium(II)-Catalyzed Reaction of 2-(4-Diazo-3-oxobutyl)benzoxazole (39). A solution containing 2.3 mL (17 mmol) of diisopropylamine in 40 mL of dry THF was cooled to 0 °C under a nitrogen atmosphere. To this solution was added 10.4 mL (17 mmol) of a 1.6 M solution of *n*-butyllithium in hexane dropwise. The mixture was stirred at 0 °C for an additional 15 min and then cooled to −78 °C. To the above solution was added 1.8 mL (15 mmol) of 2-methylbenzoxazole dropwise, and the reaction mixture was stirred for 20 min at −78 °C. A solution containing 2.6 mL (17 mmol) of *tert*-butyl bromoacetate in 20 mL of dry THF was then added dropwise over a period of 10 min. After being stirred at −78 °C for an additional hour, the reaction mixture was quenched with 70 mL of a saturated ammonium chloride solution and was allowed to warm to room temperature. The resulting mixture was poured into water and extracted with dichloromethane. The combined organic extracts were washed twice with a saturated sodium bicarbonate solution, washed once with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.53 g (41%) of *tert*-butyl 2-benzoxazolylpropanoate as a pale yellow-green oil: IR ($CHCl_3$) 1725, 1620, 1575, 1455, 1370, 1240, and 1145 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 2.83 (t, 2 H, $J = 7.4$ Hz), 3.19 (t, 2 H, $J = 7.4$ Hz), 7.25 (m, 2 H), 7.45 (m, 1 H), and 7.64 (m, 1 H); HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1200.

To a solution containing 1.2 g (4.9 mmol) of the above ester in 25 mL of methanol was added a solution of 1.2 g (30 mmol) of sodium hydroxide in 5 mL of water. The reaction mixture was heated at reflux for 0.5 h, poured into water, and extracted with ether. The aqueous layer was acidified to pH 3 using concentrated hydrochloric acid and then extracted with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was recrystallized from dichloromethane to give 0.60 g (65%) of 2-benzoxazolyl propanoic acid as a pale yellow solid, mp 125–126 °C: IR (KBr) 3600–2400, 1705, 1615, 1575, 1465, 1435, 1250, and 1160 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.00 (t, 2 H, $J = 6.8$ Hz), 3.27 (t, 2 H, $J = 6.8$ Hz), 7.29 (m, 2 H), 7.46 (m, 1 H), 7.67 (m, 1 H), and 8.00 (bs, 1 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.6, 30.4, 110.4, 119.6, 124.3, 124.8, 140.7, 150.7, 165.5, and 176.0. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.81; H, 4.75; N, 7.33. Found: C, 62.63; H, 4.79; N, 7.26.

A solution containing 170 mg (0.9 mmol) of the above acid in 5 mL of dry dichloromethane was cooled to 0 °C under a nitrogen atmosphere and treated with 0.10 mL (1.1 mmol) of methyl chloroformate, followed by 0.12 mL (0.9 mmol) of triethylamine. The solution was stirred at room temperature for 2 h, and then 10 mL of dry ether was added and the mixture was filtered through a pad of Celite. The filtrate was cooled to 0 °C and allowed to react with 7 mmol of ethereal diazomethane for 12 h. The solvent was removed under reduced pressure, and the resulting residue was subjected to flash silica gel chromatography using a 70% ether–hexane mixture as the eluent to give 157 mg (82%) of 2-(4-diazo-3-oxobutyl)benzoxazole (**39**) as a bright yellow oil that solidified on standing, mp 44–45 °C: IR ($CHCl_3$) 2120, 1650, 1580, 1460, 1380, and 1150 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.93 (m, 2 H), 3.25 (t, 2 H, $J = 7.3$ Hz), 5.35 (bs, 1 H), 7.26 (m, 2 H), 7.45 (m, 1 H), and 7.63 (m, 1 H); HRMS calcd for $C_{11}H_9NO_2$ ($M^+ - N_2$) 187.0633, found 187.0630.

A solution containing 420 mg (2.0 mmol) of α-diazo ketone **39** in 5 mL of dry benzene was added dropwise to a mixture containing 0.26 mL (2.2 mmol) of DMAD and 2 mg of rhodium(II) octanoate in 15 mL of dry benzene at 80 °C. The reaction mixture was heated at reflux for 5 min and cooled, and the solvent was removed under reduced pressure. The crude residue was subjected to silica gel chromatography. The first fraction isolated contained 124 mg (20%) of a pale yellow solid which was identified as 11,12-dicarbomethoxy-1,4a-etheno-2-oxo-2,3,4,4a-tetrahydro-1*H*-pyrido[2,1-*b*]benzoxazole (**41**), mp 102–103 °C: IR ($CHCl_3$) 1735, 1655, 1480, 1440, 1330–1220, 1120, and 745 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.50 (m, 1 H), 2.57 (m, 2 H), 2.72 (m, 1 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 4.84 (s, 1 H), 6.68 (m, 1 H), and 6.83 (m, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.6, 32.2, 52.8, 74.1, 109.8, 110.1, 111.6, 122.8, 123.6, 134.8, 135.0, 145.7, 150.6, 161.5, 163.3, and 195.1. Anal. Calcd for $C_{17}H_{15}NO_6$: C, 61.99; H, 4.59; N, 4.26. Found: C, 61.93; H, 4.63; N, 4.23.

The second fraction isolated contained 335 mg (52%) and was identified as 6,7-dicarbomethoxy-1-hydroxy-3-(2-hydroxyphenyl)-4-oxo-3-azabicyclo[3.2.1]oct-6-ene (**45**) on the basis of an X-ray crystal structure[45] as well as its spectral properties. Recrystallization from an ether–THF–hexane mixture afforded transparent orange crystals, mp 95–96 °C; IR (KBr) 3360, 1730, 1645, 1600, 1455, 1270, and 1145 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.53 (m, 2 H), 3.60 (m, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.92 (d, 1 H, $J = 11.7$ Hz), 6.95 (m, 2 H), and 7.15 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 43.9, 48.1, 52.8, 52.9, 57.3, 78.7, 118.9, 121.1, 126.4, 129.1, 129.2, 163.3, 164.2, and 169.0. Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.80; H, 4.93; N, 4.03. Found: C, 58.71; H, 4.98; N, 4.01.

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Supplementary Material Available: ^{1}H-NMR and ^{13}C-NMR spectra (75 MHz) of new compounds lacking analyses and experimental data for the X-ray diffraction studies of compounds **22**, **38**, and **45** as well as ORTEP drawings (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.