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Bimolecular Cycloaddition Reactions of Isomünchnones Derived from the Rhodium(II) Catalyzed Cyclization of Diazo Pyrrolidinones

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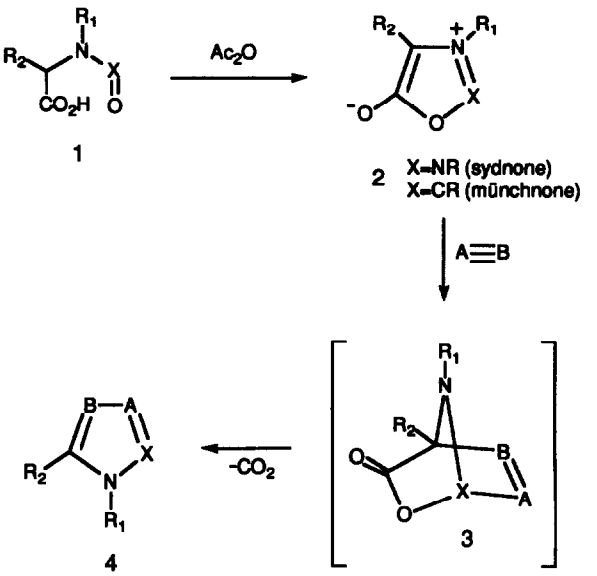
Abstract: Treatment of diazo substituted pyrrolidinones with a catalytic amount of rhodium(II) acetate in refluxing benzene results first in the formation of a rhodium carbenoid which then cyclizes onto the neighboring carbonyl oxygen to produce an isomünchnone ring system. Subsequent cycloaddition across the pi-bond of an added dipolarophile affords 1,3-dipolar cycloadducts in high yield. The isomünchnone derived from 2-diazoacetyl-2-pyrrolidinone reacts readily with both electron-rich (diethyl ketene acetal) and electron deficient (N-phenyl maleimide, methyl vinyl ketone) dipolarophiles. The regiochemical results are in full accord with FMO theory. The frontier orbital coefficients of the isomünchnone were determined by semi-empirical AMAC calculations. When acetylenic dipolaro-philes were used as the trapping agents, the expected dipolar cycloadducts were not isolated, but underwent a 4+2-cycloreversion instead to furnish furanoisocyanates. The isocyanates were characterized as their urethane derivatives by reaction with methanol.

The 1,3-dipolar cycloaddition reaction has long been recognized as a favored strategy for the synthesis of heterocyclic rings, often with a high degree of regio and stereochemical control.[1] Experience indicates a concerted mechanism and frontier molecular orbital theory has successfully explained both the relative rates and regioselectivity of these cycloadditions.[2] During the last decade a new impulse has been given to research in this field when it was found that mesoionic compounds undergo 1,3-dipolar cycloaddition with various dipolarophiles.[3-5] Of the known mesoionic heterocycles, the structure, physical properties, and reactions of münchnones and sydnones have drawn the closest scrutiny.[6-8] Studies with these two mesoionic systems have generated considerable theoretical interest and have resulted in practical, unique syntheses of numerous functionalized monocyclic and ring annulated heterocycles.[9-15]

Whereas the chemistry of 1,3-oxazolium-5-olates (münchnones) has been studied in great detail,[16] much less is known about the isomeric 1,3-oxazolium-4-oxides (isomünchnones).[17-21] This class of mesoionics has been prepared by several different methods.[22-26] Our interest in the chemistry of isomünchnones stems from studies in our laboratory dealing with the rhodium(II) catalyzed reaction of α-diazoketones in the presence of various heteroatoms.[27] In a series of papers we have demonstrated that the rhodium(II) catalyzed reaction of diazodiones proceeds by initial formation of a cyclic carbonyl ylide, followed by a 1,3-dipolar cycloaddition with a suitable dipolarophile (eq 1).[28] However, little was known about the interaction of the metal carbenoid with other carbonyl groups when we started our work in this area.[29] We soon discovered that diazoimides of type 8 readily



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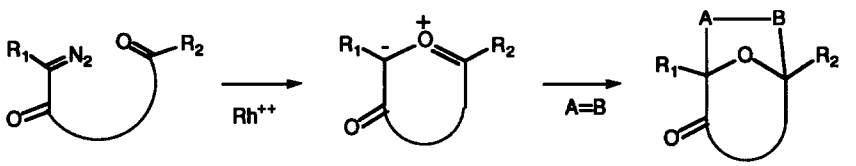
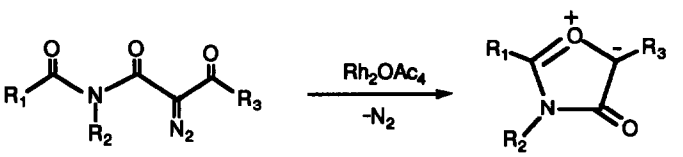
cyclize to produce isomünchnones (*i.e.*, **9**) when treated with catalytic quantities of a Rh(II) carboxylate (eq 2).[21] In this paper we describe the results obtained using 2-pyrrolidinone as a reagent for the preparation of cyclic isomünchnones and the resulting bimolecular cycloaddition chemistry.



5 6 7 eq 1

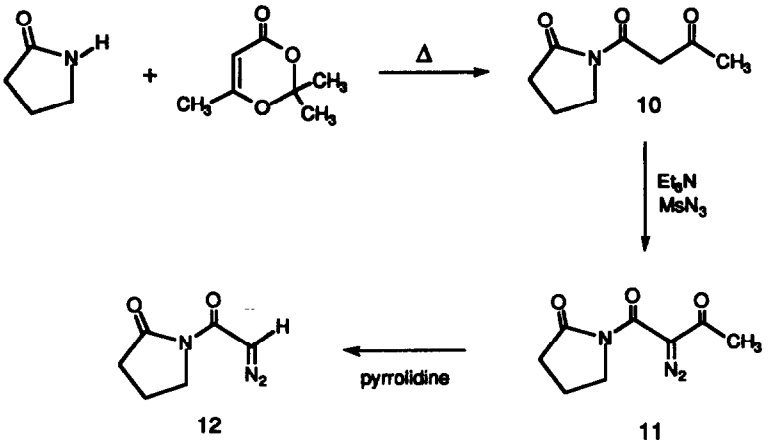


8 9 eq 2

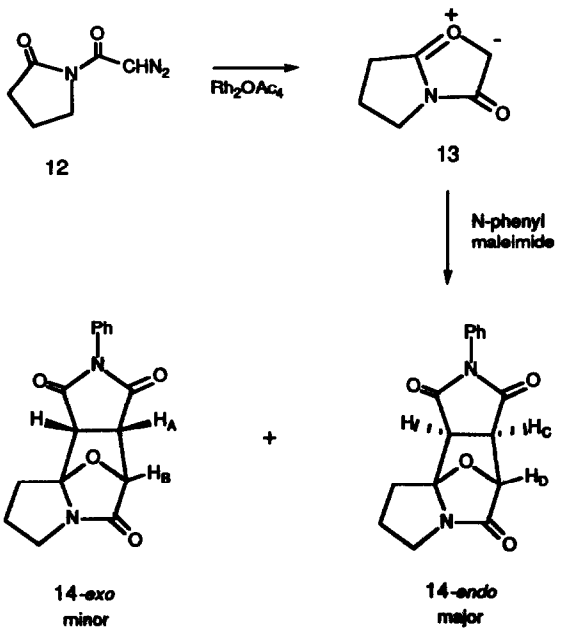
Results and Discussion:

Even though the bimolecular cycloaddition reaction of isomünchnones has been reported in the literature,[17,18] the range of their structural variation has remained somewhat narrow. In virtually every investigation to date, at least one of the substituents of the isomünchnone is an aryl moiety presumably due to electronic stabilization of the dipole to a sufficient degree to allow for its facile generation. In order to broaden the utility of this mesoionic species for organic synthesis, we thought it worthwhile to investigate the possibility of generating transient isomünchnones in which the peripheral substituents were part of a cyclic system. With this in mind, diazoimide **12** seemed to be an

ideal candidate for such a study. The preparation of **12** proved to be quite straightforward and is outlined below. Heating a sample of 2-pyrrolidinone with 2,2,6-trimethyl-4H-1,3-dioxen-4-one[30] in xylene at 140°C was followed by reaction with mesyl azide[31] in the presence of triethylamine to afford diazoimide **11** in high yield. Deacetylation of **11** was accomplished by treatment with excess pyrrolidine[32] at 0°C to give **12** as a crystalline solid, mp 46-47°C, in virtually quantitative yield. Diazoimide **12** is remarkably stable and can be kept for weeks at room temperature without noticeable decomposition.

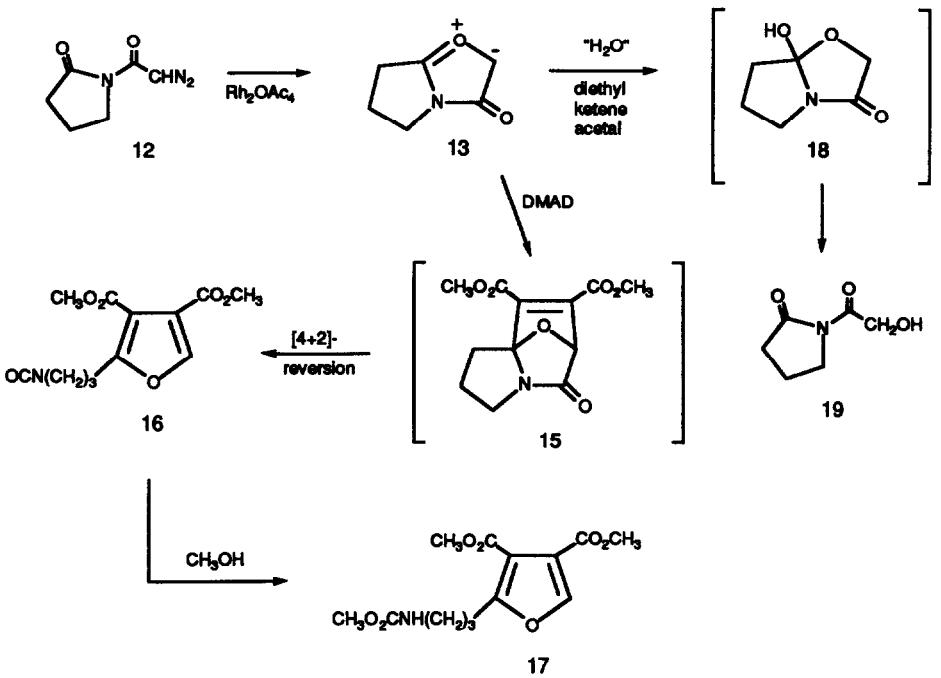


A sample of cyclic diazoimide **12** was allowed to react with rhodium(II) acetate in refluxing benzene and the initially formed rhodium carbenoid cyclized onto the adjacent imide carbonyl group, producing an isomünchnone dipole (**13**). This species readily underwent 1,3-dipolar cycloaddition



with N-phenylmaleimide to afford the expected dipolar cycloadduct **14** as a 2.4:1 mixture of *endo* and *exo* isomers in 86% yield. No products resulting from potential competitive C-H insertion could be detected.[33-35] The assignment of stereochemistry was made upon inspection of the proton NMR coupling constants. A molecular mechanics calculation[36] of the *exo*-cycloadduct shows that the dihedral angle between protons H_A and H_B is approximately 40°. The Karplus relationship predicts a coupling constant of 6.7 Hz while the observed value is 6.4 Hz. The *endo*-cycloadduct possesses a dihedral angle of 77° between H_C and H_D, a value for which the Karplus relationship predicts a coupling constant of 0.3 Hz. This prediction agrees well with the absence of observed coupling between the two protons.

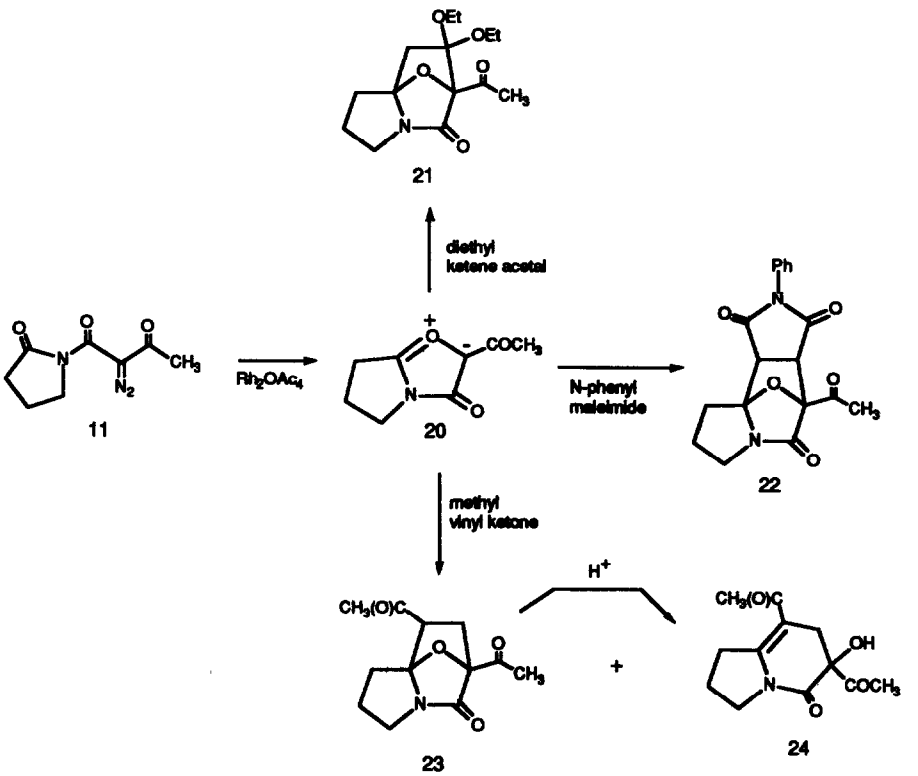
When DMAD was used as the trapping dipolarophile, the expected cycloadduct was not isolated. Instead, furanoisocyanate **16** was initially formed (IR 2280 cm^{-1}) and was subsequently trapped with methanol to give urethane **17**. The formation of **16** is the result of a 4+2-cycloreversion of the initially formed dipolar cycloadduct **15** under the reaction conditions.



Isomünchnones contain a carbonyl ylide dipole within their framework and are therefore willing participants in 1,3-dipolar cycloaddition.[3] Of the three categories described by Sustmann,[37] type II is particularly common for carbonyl ylides since they possess one of the smallest HOMO-LUMO energy gaps of all the common 1,3-dipoles.[38] The HOMO of the dipole is dominant in reactions with electron deficient dipolarophiles whereas the LUMO of the dipole is the controlling molecular orbital in reactions with electron rich dipolarophiles. It was therefore surprising to discover that isomünchnone **13** did not undergo cycloaddition with diethyl ketene acetal or other electron rich dipolarophiles. The only isolable material proved to be hydroxyimide **19** which is formed by the addition of adventitious

water to isomünchnone **13** followed by collapse of the hemiaminal **18** to **19**.[23]

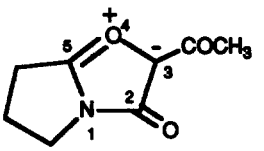
The inability of isomünchnone **13** to undergo cycloaddition with diethyl ketene acetal raised the question as to whether the more electronegatively substituted isomünchnone (*i.e.*, **20**) derived from diazoimide **11** might be able to react with this electron rich dipolarophile. In fact, the Rh(II)-catalyzed reaction of **11** with diethyl ketene acetal in benzene proved to be a remarkably efficient process (92%), especially in light of the unwillingness of **12** to undergo cycloaddition with this dipolarophile. The regiochemistry of cycloadduct **21** is based upon a FMO analysis (see Table I) of the reaction. In this case, the dominant interaction is the LUMO-dipole HOMO-dipolarophile (type III),



which predicts formation of cycloadduct **21**. The frontier orbital coefficients at the reacting centers of isomünchnone **20** were calculated by using the QCPE AMPAC program with the AM1 Hamiltonian. MNDO calculations indicate that the atomic coefficient at the amide carbonyl center (*i.e.*, C_5) is larger (0.69) than the acetyl substituted center (*i.e.*, C_3 (0.30)) in the LUMO. It is well known that the C_β-coefficient of the HOMO of diethyl ketene acetal is larger than the C_α coefficient and consequently cycloadduct **21** is predicted to be the major regioisomer formed.

The high yield of the cycloaddition of diethyl ketene acetal with isomünchnone **20** led us to explore whether cycloaddition would occur preferentially across an electron-rich or electron-deficient dipolarophile if both pathways were available. In order to probe this point, the reaction of diazoimide **11** with Rh(II) acetate in the presence of a 1:1 mixture of N-phenylmaleimide and diethyl ketene

Table I. HOMO and LUMO Energies and Coefficients for Isomünchnone **20**

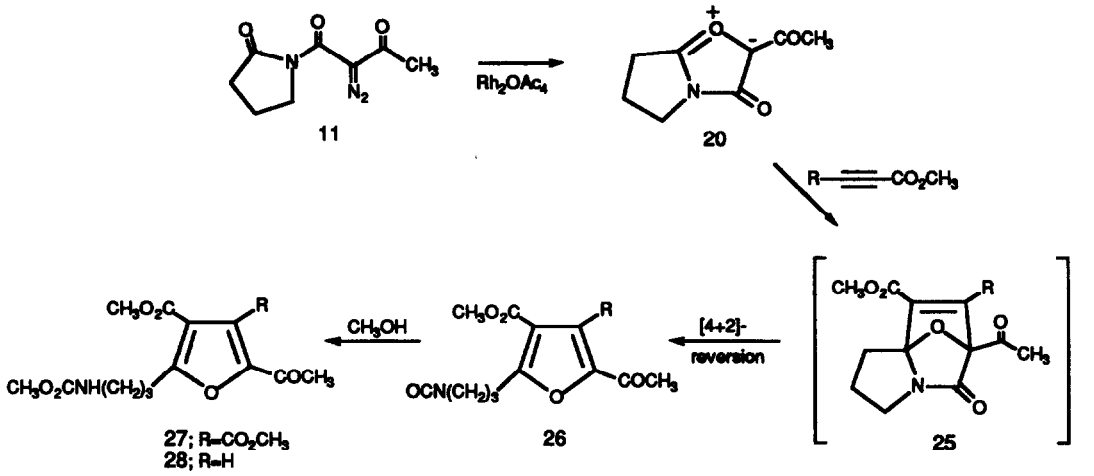


atom no.	C_3	C_5
HOMO coeff	-0.72	+0.31
LUMO coeff	+0.30	+0.69
	energy separation ΔE *eV*	
dipolarophile	*type I*[a]	*type III*[b]
diethyl ketone acetal	9.36	8.69
N-phenylmaleimide	7.05	10.63
methyl vinyl ketone	8.45	9.85
DMAD	8.02	10.94
methyl propiolate	8.65	10.55

[a][HOMO$_{(dipole)}$ - LUMO$_{(dipolarophile)}$]
[b][HOMO$_{(dipolarophile)}$ - LUMO$_{(dipole)}$]

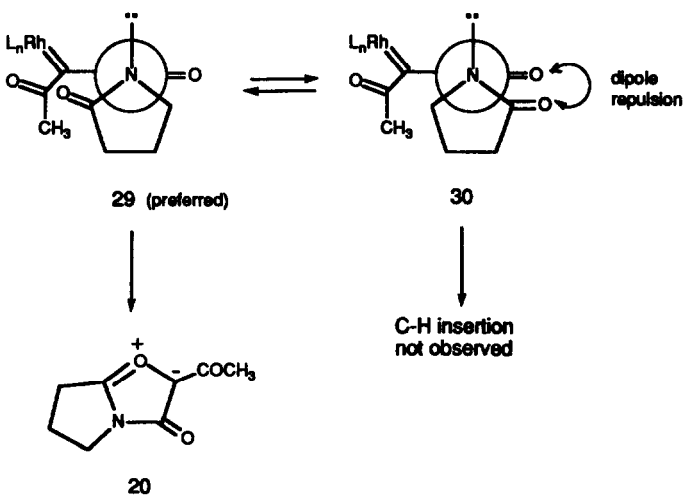
acetal was carried out. The only product isolated from the reaction corresponded to cycloadduct **22** derived from the cycloaddition of **20** with N-phenylmaleimide. MNDO calculations indicate that the smaller energy gap (ΔE = 7.05 eV) corresponds to the type I process and consequently reaction of isomünchnone **20** occurs preferentially with the electron deficient dipolarophile (see Table I). When an unsymmetrical dipolarophile such as methyl vinyl ketone is used, the main interaction is between its LUMO and the HOMO of the dipole (type I) which correlates to the exclusive formation of cycloadduct **23**. In this case the atomic coefficient at the C_3-carbon of the isomünchnone is larger than the C_5-carbon for the HOMO. Cycloadduct **23** readily undergoes C-O bond cleavage when exposed to acidic conditions. The initially formed acyl iminium ion loses a proton to produce **24** in quantitative yield.

The rhodium(II) catalyzed reaction of diazoimide **11** in the presence of acetylenic dipolarophiles also proceeds smoothly. Thus, reaction of **11** with DMAD provided crude isocyanate **26** (2300 cm^{-1}) which on treatment with methanol gave furan carbamate **27** in 90% overall yield. It should be noted that the related reaction of isomünchnone **13** with DMAD proceeded in only 29% yield clearly indicating the importance of the acetyl group in the cycloaddition process. Apparently the presence of an additional electron withdrawing group at the "anionic" terminus helps stabilize the dipole and facilitates the cycloaddition. The difference in reactivity of the isomünchnones derived from diazoimides **11** and **12** is even more pronounced in their reactions with methyl propiolate. While the Rh(II) catalyzed reaction of **12** with methyl propiolate failed to give a cycloadduct, reaction of **11** provided



carbamate **28** in 69% yield. The type I interaction favors regioisomer **28**, exactly as observed.

One final point worth noting is that no detectable quantities of a β-lactam were found in these Rh(II) catalyzed reactions. The initially formed rhodium carbenoid prefers to cyclize onto the adjacent amide carbonyl group rather than undergo intramolecular carbon-hydrogen insertion as was encountered by Doyle with acyclic diazoacetamides.[34,35] More than likely, the preferred rhodium carbenoid (*i.e.*, conformer **29**) is the one which avoids an unfavorable dipole repulsion between the two amido groups (*i.e.*, conformer **30**).



In conclusion, the facility with which the rhodium(II) catalyzed cyclization-cycloaddition reactions of cyclic diazoimides occurs makes these processes particularly attractive for the synthesis of nitrogen containing polycycles. Dipolar repulsion between the carbonyl groups favors that conformation in which the amide carbonyl group two atoms removed from the original diazo carbon is oriented

in close proximity to the electrophilic metal carbene center. We are continuing to explore the scope and mechanistic details of these rhodium catalyzed processes and the use of isomünchnones for heterocyclic synthesis.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390 and a GE QE-300 spectrometer. ^{13}C-NMR spectra were recorded on an GE QE-300 75 MHz spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, Ga. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Preparation of 1-(2-Diazoacetyl)-2-pyrrolidinone (12). A solution containing 2.55 g (30 mmol) of 2-pyrrolidinone and 5.12 g (36 mmol) of 2,2,6-trimethyl-1,3-dioxen-4-one in 30 ml of xylene was heated at reflux under a nitrogen atmosphere for 90 min. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using a 5:1 hexane-ethyl acetate mixture as the eluent to give 4.80 g (94% yield) of 1-(1,3-dioxobutyl)-2-pyrrolidinone (**10**) as a colorless oil; IR (neat) 1750, 1690, 1630, 1585, 1400, 1370, 1330, 1170, and 1025 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.97 (m, 2H), 2.20 (s, 3H), 2.50 (t, 2H, J=8.0 Hz), 3.75 (t, 2H, J=7.0 Hz), and 3.90 (s, 2H).

To a solution containing 4.80 g (28.96 mmol) of the above β-ketoimide and 4.26 g (31.86 mmol) of mesyl azide in 30 mL of acetonitrile was added 4.5 mL (58 mmol) of triethylamine under a nitrogen atmosphere at room temperature. After stirring for 3 h, the solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography using an ethyl acetate-hexane mixture as the eluent. In this manner, 4.96 g (88% yield) of 1-(2-diazo-1,3-dioxobutyl)-2-pyrrolidinone (**11**) was obtained as pale yellow crystals, mp 51-52°C; IR ($CHCl_3$) 2150, 1740, 1655, 1645, 1360, 1320, 1235, and 1190 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.00-2.20 (m, 2H), 2.47 (s, 3H), 2.60 (t, 2H, J=8.0 Hz) and 3.85 (t, 2H, J=8.0 Hz); Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.21 H, 4.65; N, 21.54. Found: C, 49.07, H, 4.55, N, 21.38.

To a solution containing 1.44 g (7.38 mmol) of diazoimide **11** in 17 mL of methylene chloride at 0°C under a nitrogen atmosphere was added 3.1 mL (37mmol) of pyrrolidine over a 3 min period. The solution was stirred for 2 h at 0°C and the solvent was removed under reduced pressure. Subjecting the residue to flash silica gel chromatography using a 67% hexane-ethyl acetate mixture as the eluent gave 1.09 g (92% yield) of 1-(2-diazoacetyl)-2-pyrrolidinone (**12**) as a yellow solid, mp 46-47°C; IR (neat) 3111, 2100, 1730, and 1624 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.99 (quin, 2H, J=8.2 Hz), 2.55 (t, 2H, J=8.2 Hz), 3.83 (t, 2H, J=8.2 Hz), and 6.68 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 16.5, 32.9, 45.0, 49.7, 164.1, and 174.7. Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.61; N, 27.44. Found: C, 46.98; H, 4.61; N, 27.41.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazoacetyl)-2-pyrrolidinone (12) in the Presence of N-Phenylmaleimide. A solution containing 233 mg (1.34 mmol) of N-phenylmaleimide and a catalytic amount of rhodium(II) acetate in 2.5 mL of benzene was heated at 80°C. To the refluxing solution was added a solution containing 187 mg (1.22 mmol) of diazoketoimide **12** in 3.5 mL of benzene over a 20 min period. The solution was heated an additional 2.5 h at reflux and was then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography using a 90% methylene chloride-ethyl acetate mixture as the eluent. The minor fraction contained 90 mg (25% yield) of *exo*-4,9a-epoxy-2,3,3a,4,5,9b-hexahydro-1,3,5-trioxo-2-phenyl-1H-pyrrolo[3,4-g] indolizine (**14-*exo***) as a white solid, mp 166-

167°C, IR (KBr) 2963, 2893, 1716, 1383, and 1190 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.08-2.20 (m, 2H), 2.38 (ddd, 1H, J=14.5, 6.6, and 3.4 Hz), 2.52 (ddd, 1H, J=14.5, 10.7, and 7.9 Hz), 2.97 (ddd, 1H, J=11.1, 9.6, and 7.0 Hz), 3.65 (d, 1H, J=8.5 Hz), 3.72 (ddd, 1H, J=12.2, 6.5, and 4.0 Hz), 3.93 (dd, 1H, J=8.3 and 6.5 Hz), 4.95 (d, 1H, J=6.4 Hz), 7.13 (d, 2H, J=7.1 Hz), and 7.34-7.48 (m, 3H); ^{13}C-NMR δ 25.5, 27.6, 43.3, 46.4, 50.6, 80.5, 104.3, 126.0, 128.4, 128.7, 130.6, 171.1, 171.5, and 171.9; Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.46; H, 4.70; N, 9.38.

The major fraction contained 220 mg (61% yield) of *endo*-4,9a-epoxy-2,3,3a,4,5,9b-hexahydro-1,3,5-trioxo-2-phenyl-1H-pyrrolo[3,4-*g*]indolizine (**14-*endo***) as a white solid, mp 161-162°C, IR (KBr) 2900, 1737, 1713, 1383, and 1190 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.06-2.22 (m, 2H), 2.28 (dt, 1H, J=14.5 and 5.3 Hz), 2.54 (dt, 1H, J=14.5 and 9.3 Hz), 3.12 (dt, 1H, J=11.3 and 8.1 Hz), 3.37 (d, 1H, J=6.7 Hz), 3.53 (d, 1H, J=6.7 Hz), 3.62 (dt, J=11.1 and 5.2 Hz), 4.89 (s, 1H), 7.22 (d, 2H, J=7.5 Hz), and 7.32-7.48 (m, 3H); ^{13}C-NMR δ 25.6, 26.2, 42.7, 45.2, 50.8, 81.7, 105.1, 125.7, 128.4, 128.6, 130.8, 172.3, 172.7, and 173.2; Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.30; H, 4.68; N, 9.31.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazoacetyl)-2-pyrrolidinone (12) with Dimethyl Acetylenedicarboxylate. A solution containing 216 mg (1.52 mmol) of dimethyl acetylene dicarboxylate and a catalytic amount of rhodium(II) acetate in 2.5 mL of benzene was heated at 80°C under a nitrogen atmosphere. To this solution was added 211 mg (1.38 mmol) of diazoketoimide **12** in 2.5 mL of benzene over 25 min. The solution was heated at reflux for 2 h and was then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was dissolved in 8 mL of methanol and heated at reflux for 30 min. The solution was allowed to cool to rt and the solvent was removed under reduced pressure. Purification of the residue by flash silica gel chromatography using a 1:1 hexane-ethyl acetate mixture as the eluent gave 119 mg (29% yield) of dimethyl 4-(3-amino-propyl-N-methylcarboxylate)-3,4-furandicarboxylate (**17**) as a colorless oil; IR (neat) 2954, 1723, 1553, and 1445 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.82 (q, 2H, J=6.8 Hz), 2.87 (t, 2H, J=7.2 Hz), 3.04-3.17 (m, 2H), 3.60 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.33 (bs, 1H), and 7.73 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.1, 27.7, 39.4, 51.8, 51.9, 52.0, 113.3, 118.5, 145.8, 145.9, 157.0, 161.5, 162.3, and 163.8; Anal. Calcd. for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73; N, 4.68. Found: C, 52.14; H, 5.69; N, 4.63.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazoacetyl)-2-pyrrolidinone (12) in the Presence of Diethyl Ketene Acetal. To a solution containing 116 mg (1.10 mmol) of diethyl ketene acetal and a catalytic amount of rhodium(II) acetate in 2.5 mL of benzene heated at reflux was added a solution containing 153 mg (1.00 mmol) of diazoketoimide **12** in 2.5 mL of benzene over a 10 min period. The solution was heated at reflux for 1 h following the addition, and was then allowed to cool to rt. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel chromatography using ethyl acetate as the eluent. The only isolable fraction contained 48 mg (63%) of 1-(2-hydroxyacetyl)-2-pyrrolidinone (**19**) as a colorless solid, mp 65-66°C, NMR ($CDCl_3$, 300 MHz) δ 2.10 (quin, 2H, J=7.5 Hz), 2.56 (t, 2H, J=8.1 Hz), 3.25 (bs, 1H), 3.81 (t, 2H, J=7.5 Hz), and 4.61 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 17.8, 32.8, 44.8, 64.1, 174.2, and 175.3; Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.49; H, 6.35; N, 9.75.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazo-1,3-dioxobutyl)-2-pyrrolidinone (11) with Diethyl Ketene Acetal. To a solution containing 347 mg (1.78 mmol) of dizoamide **11** and 230 mg (1.96 mmol) of diethyl ketene acetal in 5 mL of benzene was added a catalytic amount of rhodium (II) acetate dimer. The solution was immediately placed in an oil bath preheated to 95°C and was heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography using a 50% hexane-ethyl acetate mixture as the eluent.

The major fraction contained 464 mg (92%) of cycloadduct **21** as a colorless oil: IR (neat) 2894, 1730, and 1379 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, 6H, J=7.0 Hz), 1.91-2.14 (m, 4H), 2.24 (s, 3H), 2.20-2.30 (m, 1H), 2.43 (d, 1H, J=11.5 Hz), 3.00-3.15 (m, 1H), 3.35-3.59 (m, 3H), 3.61-3.73 (m, 1H), and 3.85-3.98 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.9, 15.1, 25.7, 28.8, 28.9, 43.6, 45.1, 58.6, 59.6, 97.1, 100.8, 109.4, 170.2, and 199.5; HRMS Calcd. for $C_{14}H_{21}NO_5$: 283.1421. Found: 283.1420.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazo-1,3-dioxobutyl)-2-pyrrolidinone (11) in the Presence of N-Phenylmaleimide. A solution containing 340 mg (1.74 mmol) of diazoimide **11** and 332 mg (1.92 mmol) of N-phenylmaleimide in 15 ml of benzene together with a catalytic amount of rhodium(II) acetate dimer was placed in an oil bath preheated to 95°C. The mixture was allowed to reflux for 25 min and the solvent was removed under reduced pressure. The resulting residue was dissolved in methylene chloride and filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography using a 1% ethyl acetate-hexane mixture as the eluent to give 4-acetyl-4,9a-epoxy-2,3,3a,4,5,9b-hexahydro-1,3,5-trioxo-2-phenyl-1H-pyrrolo[3,4-g] indolizine as a 1:1.2 mixture of *exo* and *endo*-isomers. The minor fraction (35%), mp 182-183°C, was assigned as **22-*exo*** on the basis of its spectral data: IR ($CHCl_3$) 2960, 1790, 1740, 1720, 1600, 1385, and 1195 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.21-2.25 (m, 2H), 2.44-2.62 (m, 2H), 2.65 (s, 3H), 2.98-3.10 (m, 1H), 3.74-3.84 (m, 1H), 3.80 (d, 1H, J=8.5 Hz), 3.86 (d, 1H, J=8.5 Hz), and 7.12-7.50 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.4, 27.1, 27.3, 43.8, 48.3, 51.6, 92.1, 102.0, 125.9, 128.6, 128.7, 130.4, 168.5, 170.2, 170.7, and 197.0; HRMS Calcd. for $C_{18}H_{16}N_2O_5$: 340.1059. Found: 340.1059

The major fraction (44%), mp 186-187°C, was assigned as **22-*endo*** on the basis of its spectral data: IR ($CHCl_3$) 1745, 1600, 1500, 1385, and 1190 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.18-2.29 (m, 2H), 2.38-2.48 (m, 1H), 2.58-2.70 (m, 1H), 2.60 (s, 3H), 3.19-3.29 (m, 1H), 3.92 (d, 1H, J=6.7 Hz), and 7.19-7.49 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.4, 26.0, 27.4, 43.3, 47.4, 52.3, 92.8, 102.6, 125.6, 128.5, 128.6, 130.4, 169.0, 171.1, 171.3 and 196.0; HRMS Calcd. for $C_{18}H_{16}N_2O_5$: 340.2059. Found: 340.1059.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazo-1,3-Dioxobutyl)-2-piperidinone (11) in the Presence of Methyl Vinyl Ketone. A solution containing 202 mg (1.03 mmol) of diazoimide **11**, 80 mg (1.14 mmol) of methyl vinyl ketone, and a catalytic amount of rhodium(II) acetate dimer in 5 mL of benzene was placed in an oil bath preheated to 95°C. The solution was heated at reflux for 6 h and was then allowed to cool to rt. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography using a 60% methylene chloride-ethyl acetate mixture as the eluent. The minor fraction contained 67 mg (27%) of cycloadduct **23** as a white solid, mp 127-128°C, IR (KBr) 2954, 1721, 1391, 1225, and 1175 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.02-2.13 (m, 3H), 2.15 (s, 3H), 2.22 (dd, 1H, J=13.0 and 4.1 Hz), 2.29 (s, 3H), 2.14-2.42 (m, 1H), 2.50 (dd, 1H, J=13.0 and 8.8 Hz), 2.92-3.10 (m, 1H), 3.16 (dd, 1H, J=8.8 and 4.1 Hz), and 3.63 (dt, 1H, J=8.8 and 3.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 26.3, 27.1, 27.8, 28.8, 31.5, 43.1, 57.3, 91.0, 103.4, 172.7, 200.3, and 205.2; Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.66; H, 6.43; N, 5.82.

The major fraction contained 108 mg (44%) of a pale yellow oil identified as **24** on the basis of its spectral properties: IR (neat) 2890, 1715, 1675, 1602, 1370, and 1255 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.05 (quin, 2H), 2.24 (s, 3H), 2.25 (s, 3H), 2.73 (dd, 1H, J=17.4 and 2.2 Hz), 3.07-3.18 (m, 2H), 3.18 (d, 1H, J=17.4 Hz), 3.68-3.90 (m, 2H), and 4.44 (s, 1H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 21.7, 23.9, 29.3, 32.0, 32.4, 46.2, 78.1, 108.0, 151.9, 167.5, 195.6, and 205.2; Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.62; H, 6.38; N, 5.89. It should be noted that

cycloadduct **23** was readily converted to **24** when stirred with a trace of *p*-toluenesulfonic acid in benzene.

Rhodium(II) Acetate Catalyzed Reaction of 1-(2-Diazo-1,3-dioxobutyl)-2-pyrrolidinone (11) with Dimethyl Acetylenedicarboxylate. A solution containing 279 mg (1.43 mmol) of diazoimide **11** and 223 mg (1.57 mmol) of dimethyl acetylenedicarboxylate in 15 ml of benzene together with a catalytic quantity of rhodium(II) acetate dimer was placed in an oil bath preheated to 95°C. The mixture was allowed to reflux for 2.5 h and then the solvent was removed under reduced pressure. The residue was taken up in methylene chloride, filtered through a pad of Celite, and the solvent was removed under reduced pressure. The resulting residue was dissolved in 15 mL of methanol with a single crystal of *p*-toluenesulfonic acid and stirred at rt for 2 h. At the end of this time the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using a 2% ethyl acetate-hexane mixture as the eluent, to afford 439 mg (90% yield) of dimethyl 2-acetyl-4-(3-aminopropyl-N-methylcarboxylate)-3,4-furandicarboxylate (**27**) as a light yellow oil; IR (neat) 2890, 1735, 1730, 1690, 1600, 1555, and 1455 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.85-2.00 (m, 2H), 2.45 (s, 3H), 3.07 (t, 2H, J=7.4 Hz), 3.15-3.25 (m, 2H), 3.68 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H) and 5.00-5.18 (bs, 1H); HRMS Calcd. for $C_{15}H_{19}NO_8$: 341.1111. Found: 341.1109.

Rhodium(II) Catalyzed Reaction of 1-(2-Diazo-1,3-dioxobutyl)-2-pyrrolidinone (11) in the Presence of Methyl Propiolate. To a solution containing 260 mg (1.33 mmol) of diazoimide **11** and 123 mg of methyl propiolate (1.47 mmol) in 5 mL of benzene was added a catalytic amount of rhodium (II) acetate. The solution was immediately placed in an oil bath preheated to 95°C. After being heated to reflux for 1.5 h, the solution was allowed to cool and was then taken up in 5 mL of methanol and stirred at rt for 14 h. At the end of this time the solvent was removed under reduced pressure and the residue was subjected to flash chromatography using a 60% ethyl acetate-hexane mixture as the eluent. The major fraction contained 259 mg (69%) of methyl 2-acetyl-4-(3-aminopropyl-N-methylcarboxylate)-4-furancarboxylate (**27**) as a white solid, mp 85-86°C, IR (KBr) 2958, 1717, 1680, 1586, 1443, and 1245 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.80-1.93 (m, 2H), 2.37, (s, 3H), 3.03 (t, 2H, J=7.3 Hz), 3.05-3.18 (m, 2H), 3.57 (s, 3H), 3.78 (s, 3H), 5.23 (bs, 1H), and 7.31 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.2, 25.2, 27.3, 39.2, 51.2, 51.3, 115.1, 117.5, 149.7, 156.4, 162.7, 165.1, and 185.3; Anal. Calcd. for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.16; H, 6.08; N, 4.88.

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References and Notes

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1. Padwa, A. Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1983; Vols. 1, 2.
2. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
3. Potts, K. T. in *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley, Inc.; New York, 1984; Chapter 8.
4. Gingrich, H. L.; Baum, J-S. in *Oxazoles*; Turchi, I. J., Ed., *The Chemistry of Heterocyclic Compounds*, Weissberger, A.; Taylor, A.; John Wiley, New York, 1986, Vol. 45, pp 731-961.
5. Ollis, W. D.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1.
6. Ohta, M.; Kato, H. in *Nonbenzenoid Aromatics*, Snyder, J. P. Ed., Academic Press, New York, 1969, pp 117-248, and references listed therein.

7. Baker, W.; Ollis, W. D.; *Quart. Rev.* **1957**, *11*, 15.
8. Stewart, F. H. C. *Chem. Rev.* **1964**, *64*, 129.
9. Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2611.
10. Gotthardt, H.; Huisgen, R.; *Chem. Ber.* **1970**, *103*, 2625.
11. Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.*, **1970**, *92*, 4340.
12. Hershenson, F. M. *J. Org. Chem.* **1972**, *37*, 3111; **1975**, *40*, 740.
13. Huisgen, R. *Bull. Soc. Chim. Fr.* **1965**, 3431.
14. Huisgen, R.; Gotthardt, H. *Chem. Ber.*, **1968**, *101*, 1059.
15. Gotthardt, H.; Huisgen, R. *Chem. Ber.*, **1968**, *101*, 552.
16. Padwa, A.; Lim, R.; MacDonald, J. G.; Gingrich, H. L.; Kellar, S. M. *J. Org. Chem.* **1985**, *50*, 3816.
17. Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475.
18. Ibata, T.; Hamaguchi, M.; Kiyohara, H. *Chem. Lett.* **1975**, 21. Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499.
19. Maier, M. E.; Evertz, K. P. *Tetrahedron Lett.* **1988**, 1677. Maier, M. E.; Schoffing, B. *Chem. Ber.* **1989**, *122*, 1081.
20. Doyle, M. P.; Pieters, R. J.; Tauton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
21. Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077. Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731.
22. Hamaguchi, M. *J. Chem. Soc., Chem. Commun.* **1978**, 247.
23. Hamaguchi, M.; Ibata, T. *J. Chem. Soc., Chem. Commun.* **1980**, 230.
24. Potts, K. T.; Marshall, J. L. *J. Org. Chem.* **1979**, *44*, 626.
25. Haddadin, M. J.; Tannus, H. T. *Heterocycles*, **1984**, *22*, 773.
26. Moore, D. R.; Mathias, L. J. *J. Org. Chem.* **1987**, *52*, 1599.
27. Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22.
28. Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2875. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817. Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271.
29. Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.
30. Sato, M.; Kanuma, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 1315.
31. Regitz, M.; Hocker, J.; Leidhergener, A. in *Organic Syntheses*; John Wiley: New York, 1973; Collect. Vol. 5, pp 179-183.
32. Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1985**, *50*, 425.
33. Ponsford, R. J.; Southgate, R. J. *Chem. Soc., Chem. Commun.* **1979**, 846. Smale, T. C. *Tetrahedron Lett.* **1984**, *25*, 2913. Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247.
34. Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.
35. Doyle, M. P.; Tauton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.
36. We gratefully acknowledge Kosta Steliou of the University of Montreal for a copy of the VMS Still-Steliou Model 2.94 program.
37. Sustmann, R. *Tetrahedron Lett.* **1971**, 2717. Sustmann, R.; Trill, H. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 838.
38. Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.