Reactions of a Cyclic Rhodium Carbenoid with Aromatic Compounds and Vinyl Ethers[1]

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Further investigation has been made of the reactions between the cyclic diazo compound 2-diazo-1,3-cyclohexanedione and aromatic heterocycles or vinyl ethers, catalyzed by rhodium carboxylates. The extraordinary reactivity of the carbenoid derived from this diazo compound is shown by its ready reaction with solvents such as dichloromethane, dichloroethane, and fluorobenzene. Detailed investigation of its reactions with furans have shown that steric interactions dominate, both in terms of regioselectivity with unsymmetrical substrates and yield. This reaction provides a useful entry to the furo[2,3-*b*]furan ring system found in a number of naturally-occurring compounds and is formally a 1,3-dipolar cycloaddition. Products of net C–H insertion and with reverse regiochemistry (furo[3,2-*b*]furan ring system) were also detected. With pyrroles and thiophenes, cycloadducts were seen in a few cases, but were generally the exception; C–H insertion products dominate these reactions. Vinyl ethers proved reliable reactants in providing dipolar cycloadducts. The results of this study have been interpreted in terms of four pathways: an initial cyclopropanation would produce a spirocyclic dicarbonyl system that on heterolytic cleavage of one of the two cyclopropane bonds would give a zwitterion. The partitioning of such a zwitterion between ring closure and proton transfer would define the ratio of C–H insertion and dipolar cycloaddition products. Both thermodynamic and stereoelectronic arguments have been advanced to explain the observations and were supported by calculations.

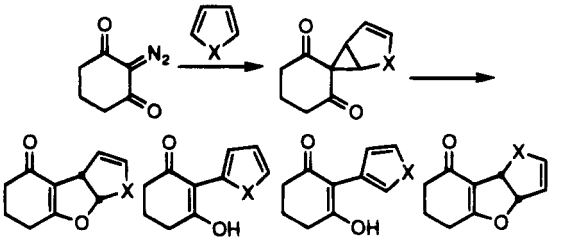
Introduction

We have been interested in the reactions of cyclic diazo compounds with aromatic heterocycles mediated by dinuclear rhodium catalysts because of the power they offer in the synthesis of complex polyheterocyclic frameworks.[4] In order to examine the breadth and generality of the reactions described in our preliminary communications, we have studied a wide variety of furans, thiophenes, and pyrroles in reaction with the carbenoid derived from 2-diazo-1,3-cyclohexanedione. In general, several classes of products have been observed, including formal 1,3-dipolar cycloadducts and C–H insertion products. Our earlier report interpreted the data for cycloaddition with furans in terms of a reaction pathway involving initial cyclopropanation (Scheme 1). In this manuscript, we expand the application of that model to new reactions. In addition, we have examined the application of such cyclic dipolar cycloadditions to vinyl ethers, a class of reactions already known with acyclic diazo compounds.[5]

Results

Reactions with Solvents. Diazotransfer with methanesulfonyl azide[6] was used to prepared the known[7] compound **1**. While many rhodium-catalyzed carbenoid reactions[8] have been conducted in dichloromethane, dichloroethane, benzene, and fluorobenzene solvents, **1** reacts with each of them, producing varying amounts of byproducts, during reactions with the desired substrates to be described below. The reactions with solvents were therefore studied in the absence of aromatic compounds to permit the production of these byproducts in quantity for characterization. We had earlier postulated[4b] that reactions conducted in dichloromethane lead to the product of formal O–H insertion into adventitious water, but now report that this product is actually **2**, the formal HCl abstraction product. To characterize this material, the decomposition of **1** with 1% rhodium acetate was purposely conducted in the absence of any reactants; **2** is readily produced in both dichloroethane (99% yield) and dichloromethane (80%). A reasonable mechanism

Scheme 1



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(4) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987–5990. Pirrung, M. C.; Zhang, J.; McPhail, A. T. *J. Org. Chem.* **1991**, *56*, 6269–6271.
(5) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.
(6) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4078–80. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–64.
(7) Stetter H.; Kriebs, K. *Chem. Ber.* **1965**, *98*, 1181.
(8) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. *Chem Rev.* **1986**, *86*, 919. Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75.

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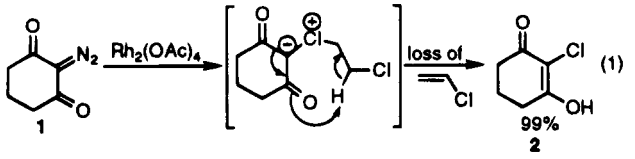
Table 1. Catalyzed Reactions of 1 with Chlorinated Solvents

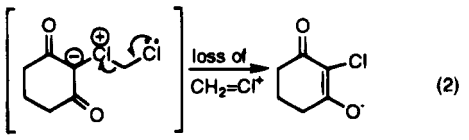
entry	catalyst	solvent	1 (% recovd)	% yield of 2	% yield of 3
a	$Cu(OAc)_2$	CH_2Cl_2	68	0	0
b	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	71	11	0
c	$Zn(OAc)_2$	CH_2Cl_2	92	0	0
d	$Zn(OAc)_2$	$ClCH_2CH_2Cl$	90	0	0
e	$Rh_2(OPiv)_4$	CH_2Cl_2	0	0	80
f	$Rh_2(OPiv)_4$	$ClCH_2CH_2Cl$	0	98	0
g	$Rh_2(OAc)_4$	CH_2Cl_2	0	82	0
h	$Rh_2(OAc)_4$	$ClCH_2CH_2Cl$	0	98	0

involving formation of a chloronium ylide[8b,9] explains the efficient formation of **2** from dichloroethane (eq 1). A



(1)

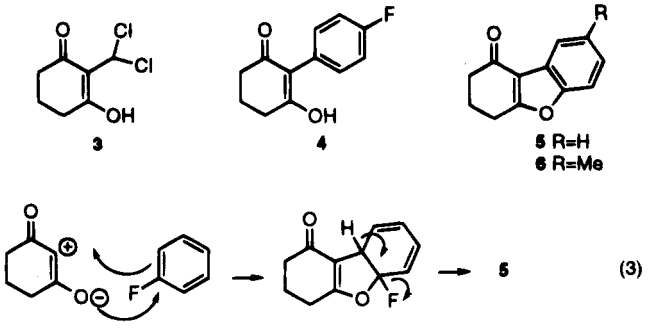
more complicated process must be invoked to explain HCl abstraction from dichloromethane, accounting for the lower isolated yield of **2** (eq 2). The formation of **2** is



(2)

enhanced by pretreating either solvent with neutral and/or basic alumina. The chlorine abstraction reaction appears unique to the *cyclic* diazo dicarbonyl compound, because 3-diazo-2,4-pentanedione provides multicomponent mixtures containing no chlorine abstraction products when treated with either dichloromethane or dichloroethane in the presence of dirhodium tetraacetate. The influence of catalyst (1 mol %) on the reaction with chlorinated solvents was investigated as summarized in Table 1. No products of chlorine abstraction from dichloromethane are seen with zinc or copper acetate (at room temperature). Interestingly, $Rh_2(OPiv)_4$ catalysis affords the "C–H" insertion product **3**, a process that can be explained based on a recent study wherein $Rh_2(OPiv)_4$ gave the greatest selectivity among a number of catalysts based on its superior backbonding.[10] In dichloroethane, copper(II) acetate catalysis affords a small fraction of the chlorine abstraction product in 20 h at ambient temperature, while $Rh_2(OPiv)_4$ catalysis affords a high yield of **2** in less than 5 min. Finally, **1** was treated with only 2 equiv of dichloroethane in fluorobenzene utilizing 1 mol % of $Rh_2(OAc)_4$ to afford **2** in a 96% yield.

Fluorobenzene seems an ideal solvent for rhodium-mediated carbenoid reactions because of its relative inertness, but it too reacts with the carbenoid derived from **1**. After a reaction time of 20 h at room temperature, a 2:1 ratio of **4**:**5** is isolated along with a 10% recovery of unreacted starting material. These compounds were frequently observed as byproducts in reactions conducted in fluorobenzene. These products may result from "C–H" insertion and net dipolar cycloaddition followed by HF elimination (eq 3), though the latter reaction is unprecedented. A brief examination of this



(3)

reaction was made to enhance the yield of the benzofuran product by "blocking" the position para to the fluorine. 4-Fluorotoluene affords cycloadduct **6** in a 45% unoptimized yield after an easy chromatographic isolation.[11] The 2-aryl-1,3-cyclohexanedione major product seen in the reaction of **1** with fluorobenzene is similar to those derived in modest yield by its triplet-sensitized irradiation in aromatic solvents,[12] a process suggested by Wheeler to involve electrophilic attack of the triplet diketocarbene on the electron-rich aromatic system, and reactions between diazo-1,3-indanedione and unsaturated systems reported by Schechter.[13] Wheeler reported strong *ortho* directing effects and an absence of products from reactions with electron-poor aromatics. Schechter reported cyclopropanation, cyclopropenation, and dipolar cycloaddition products with alkenes and alkynes, while "C–H" insertion analogous to that observed here was seen with benzene derivatives.

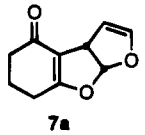
Other solvents briefly evaluated included tetrahydrofuran, dimethoxyethane, nitromethane, and pentane. Low reactant/catalyst solubility, formation of byproducts, and low yields show that these are poor choices for the dipolar cycloaddition reactions of **1**. Because carbenes and carbenoids are reported to be unreactive toward hexafluorobenzene,[14] several cycloaddition reactions were conducted in this solvent. Dirhodium tetraacetate is completely insoluble in hexafluorobenzene at room temperature, so recovery of starting materials was observed, but several of the reactions could be conducted at reflux (80.5 °C).

Furans. We originally described three reactions of **1** with simple furans. In the previous paper we reported that the cycloadduct **7a** was obtained in 54% yield with furan as solvent and the cycloadduct **8** was obtained in 80% yield in neat 2,5-dimethylfuran. These results suggest that the more electron-rich system produces a higher yield. An anomalous result was the claim that a similar reaction in 2-methylfuran afforded a mixture of cycloadduct **9** and dienal **13**, a member of the class of compounds usually observed in additions of carbenes to furans. All of these reports must now be amended.

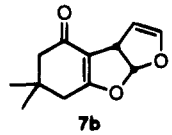
Several experiments were used to study the reactions of symmetrical furans. When a rhodium-mediated reaction of **1a** with furan is performed in fluorobenzene, cycloadduct **7a** is reproducibly obtained in 90% yield.

(9) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263–309.
(10) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991.
(11) In 4-fluoroanisole, two "C–H" insertion products were obtained: the major derived from insertion *ortho* to the methoxy group and the minor product from insertion into the methoxy group. In 4-fluoronitrobenzene, complexation with the catalyst evidently occurred, as the reaction turned brilliant blue-green and the starting material **1** was recovered in 94% yield after 22 h at room temperature.
(12) Wheeler, T. *J. Org. Chem.* **1979**, *44*, 4906.
(13) Rosenfeld, M. J.; Shankar, B. K. R.; Schechter, H. *J. Org. Chem.* **1988**, *53*, 2699.
(14) *Fundamentals of Organic Reaction Mechanisms*; Harris, J. M.; Wamser, C. C., Eds.; John Wiley & Sons: New York, 1976.

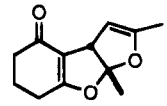
Under the same conditions, however, 2,5-dimethylfuran affords cycloadduct **8** in only 27% yield along with a multicomponent mixture including **4** as a primary byproduct. A higher yield of **8** (36%) is obtained when **1** is treated with neat 2,5-dimethylfuran. These relative reactivities were confirmed by treatment of **1** with a neat equivolume mixture of furan and 2,5-dimethylfuran and 1 mol % of dirhodium tetraacetate to afford a 2:1 ratio of the furan cycloadduct **7a** to the 2,5-dimethylfuran cycloadduct **8** (yields 46 and 23%, respectively). This reaction was repeated in fluorobenzene using 4 equiv each of furan and 2,5-dimethylfuran to afford an enhanced ratio of 4.4:1. One rationalization of these results is simple steric effects (*vide infra*). Two experiments were performed to detect possible intermediates in these transformations. Since the chemical shift of the quaternary methyl groups in starting material, presumed cyclopropane, and cycloadduct **8** should be distinct, the reaction of 2,5-dimethylfuran and **1** was conducted in d_6-benzene in an NMR tube. No signals other than those of starting material or **8** could be observed. Hoping to trap any rhodium–alkyl intermediates involved in this transformation, the cycloaddition of **1** with furan was performed under 1 atm of hydrogen. The production of cycloadduct **7a** was unperturbed. A study of the effect of catalyst showed that the cycloaddition of diazodimedone with furan to give **7b** was more effective when rhodium acetate (56%) was used rather than rhodium pivalate (44%).



7a



7b



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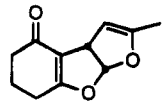

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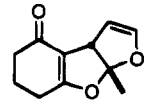

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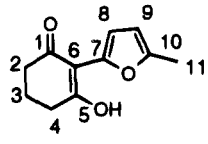

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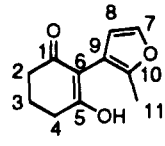

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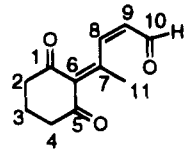
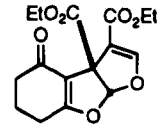


13

The contrast between the behavior of furan and 2,5-dimethylfuran caused us to question our earlier reported results with 2-methylfuran, so the reaction of **1** in neat 2-methylfuran was repeated. A three-component mixture is produced consisting of two inseparable minor compounds **9** and **10** (19% yield each) which are assigned cycloadduct structures. The major component (60%) possesses ^{1}H NMR spectra identical to those reported for the "dienal" product, but the signal we had assigned to the aldehyde proton readily exchanges with D_2O. This material can be readily extracted into aqueous base, acidified, and extracted back into organic solvent as an alternative to purification by column chromatography. By analogy with other products observed in this study (*vide infra*), it was obvious that this compound was derived from net "C–H" insertion, but it was necessary to distinguish between insertion into the 3- and 5-positions of 2-methylfuran. The initial structural assignment as **11** was based on the coupling constant of 3.2 Hz between the furan protons in the ^{1}H NMR spectrum, a value indicative of β,β coupling.[15] Further confirmation of the structure was based on ^{13}C NMR. The diketone–dienal carbons of **13** would exhibit three peaks with shifts greater than 190 ppm, whereas both 3- and 5-position "C–H" insertion products **11** and **12** would have only two peaks greater than 190 ppm. Using the *specinfo*[16] program, the ^{13}C NMR shifts were calculated for all three structures (Table S1 in supplementary material), readily eliminating **13** as a possibility. The ^{13}C NMR spectrum closely correlates to the chemical shift predictions made for **11** and **12**, but the multiplicity of particular resonances should differ. The off-resonance decoupled ^{13}C NMR spectrum shows unambiguously that the product is derived from net "C–H" insertion into the 5-position of 2-methylfuran (compound **11**). Still further support for the structural assignment was obtained from an HMQC spectrum, which evaluates single bond connectivities. The protons in the 6–7 ppm range correlate only to the carbons at 107.42 and 109.96 ppm (and not at 140 ppm).

With these errors corrected, the synthetic scope of the furan cycloaddition reaction was investigated. In each case, 4 equiv of the substituted furan were used in fluorobenzene with 1 mol % dirhodium tetraacetate unless otherwise noted. The reactions were performed at room temperature under N_2 for 15 h. The reaction of **1** with diethyl 3,4-furandicarboxylate affords the cycloadduct **14** in 26% yield along with 11% of **4**. It is interesting that the product distribution in this reaction is virtually identical to that in the reaction with 2,5-dimethylfuran. When this reaction is done neat, a multicomponent mixture with no evidence of **14** results. A competition study was conducted in fluorobenzene to compare the relative reactivities of 2,5-dimethylfuran and diethyl 3,4-furandicarboxylate. The only cycloadduct isolated is **8** in 22% yield along with solvent related byproducts.



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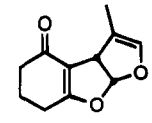


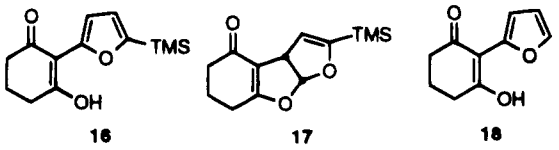
15

With monosubstituted furans, cycloadditions are generally successful. Treatment of **1** under rhodium catalysis in the presence of 3-methylfuran affords cycloaddition product **15** in 72% yield. The only other products are solvent-related. This result is intriguing because our previous results would predict the reaction to occur on the unsubstituted olefin, but would not necessarily predict the exclusion of reaction at the more electron-rich olefin. Substitution at the 3-position of furan appears to have a more dramatic steric effect on the approaching carbenoid.[17] Treatment of **1** with 2-(trimethylsilyl)furan affords a four-component reaction mixture easily separated by column chromatography. Only 10% of the solvent-derived **4** was obtained, and the remaining products **16–18** can be isolated in ~30% yield each.

(15) *Tables of Spectral Data for Structure Determination of Organic Compounds*; Pretsch, Clerc, Seibl, Simon, Eds.; Springer-Verlag: New York, 1989.

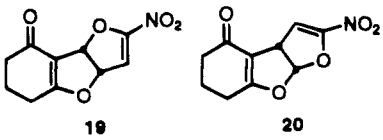
(16) STN Express® *specal* CNMR ALL.

(17) The reaction of **1** with the trisubstituted furan menthofuran produces only solvent-related products.

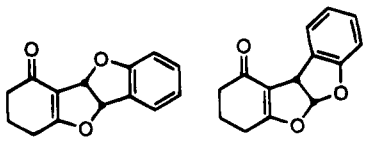


16 17 18

In some instances, "reverse" regiochemistry in the cycloaddition process is observed. Treatment of **1** with 2-nitrofuran affords products of reaction only at the unsubstituted olefin **19** and **20** in 28 and 36% yields, respectively. The former is not stable for any period of time, even under N_2 at 0 °C. We previously reported the reaction of benzofuran with **1** in benzene, which gives a 1:2 ratio of **21** and **22** in a total isolated yield of 58%. In fluorobenzene, the product distribution is 1:3.7 in favor of the "normal" cycloadduct with a total yield of 66% and 12% formation of **4**.



19 20



21 22

Pyrroles. Carbenoid reactions with pyrroles have been fairly well studied.[18] Davies work suggested that protection of the nitrogen with an electron-withdrawing substituent would increase the likelihood of cyclopropanation. Both because we had postulated that cyclopropanation was the initial step of the net cycloaddition process and because the primary enamine that would be derived from cycloaddition to an NH pyrrole would be expected to be unstable, protection of the nitrogen was a high priority. To confirm that it was necessary, reaction of **1** with pyrrole and 2,5-dimethylpyrrole promoted by 1 mol % of dirhodium tetraacetate was attempted under various conditions: neat, in fluorobenzene, in pentane, and at low temperature. All of these reactions resulted in multicomponent mixtures in which no cycloaddition products could be isolated.

We previously reported the cycloadditions of **1** with *N*-(ethoxycarbonyl)pyrrole to produce **23a** in 34% yield, with *N*-acetylpyrrole to produce **23b** in 32% yield, and with *N*-acetylindole to yield **24** in 54% yield. Under the standard cycloaddition conditions in fluorobenzene, **1** affords the cycloadduct in reaction with *N*-acetylindole in 62% yield. Further, as contrasted to the benzofuran case, none of the other regioisomer was observed. We have now determined the structure of **24** by X-ray crystallography,[34] as shown by the ORTEP plot in Figure 1. The crystal structure demonstrates the *cis*-configuration at the 5,5-ring juncture and affirms the regiochemistry. The arrangement of the carbonyl of the acetyl group toward the aromatic ring accounts for the downfield shift observed for the ortho aromatic proton (H @ C2) in the ^{1}H NMR spectrum of **24**. The chemical shift of δ 7.56 observed for this proton in the oxygen analog,

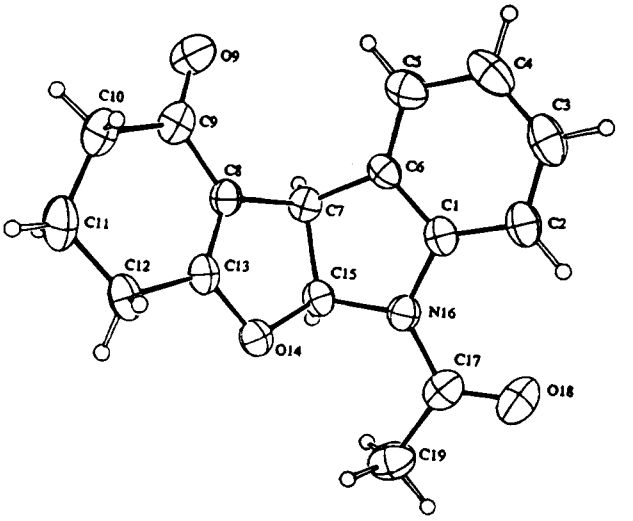
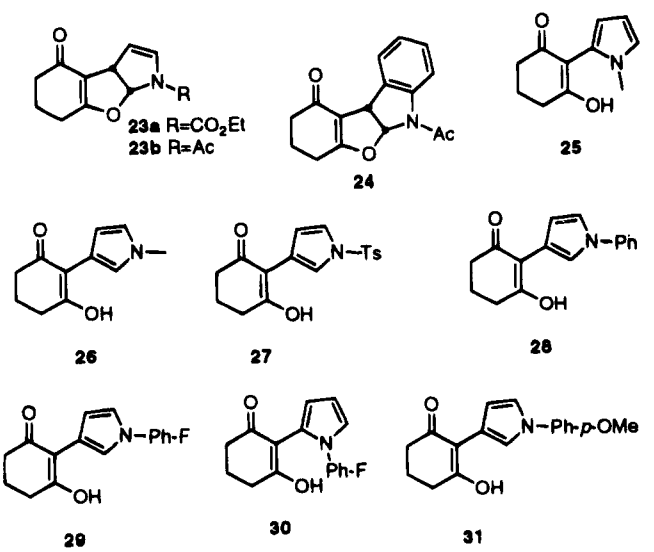


Figure 1. ORTEP view of the molecular structure of **24**.

22, compares with δ 8.19 for **24** and is presumably due to the deshielding effect of the carbonyl.

Rhodium-mediated reactions with novel substituted pyrroles were investigated using 1 mol % catalyst based on **1**. Compound **1** reacts preferentially with the fluorobenzene solvent even when 4 equiv of the pyrrole substrates were used. Switching to the inert solvent hexafluorobenzene, which required refluxing due to the low solubility of the rhodium catalyst, produces pyrrole C−H insertion products as the only compounds isolated. The rhodium-catalyzed reaction of **1** with *N*-methylpyrrole both neat and in fluorobenzene affords only poor yields of the net 3-position "C−H" insertion product **26**, but when this reaction is conducted in hexafluorobenzene at reflux, a 2:1 ratio of the 2- and 3-position regioisomers **25** and **26** is observed. By following this reaction by thin layer chromatography, a single component with $R_f = 0.30$ (1:1 hexane:ethyl acetate) is initially observed, but this material could not be isolated. It is readily converted to the two-component mixture (R_f = 0.32 and R_f = 0.16) representing the 3-position and 2-position substitution isomers. The intermediate may be a cyclopropane in which the selectivity between 2- and 3-position bond cleavage determines the ratio of substitution. For similar reactions, Maryanoff has suggested a nitrogen ylide intermediate.



25 24 26 27 28 29 30 31

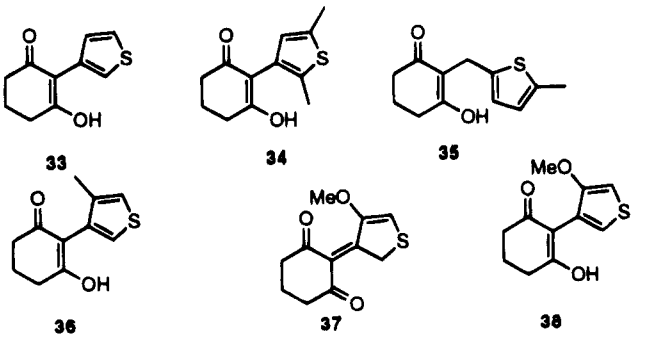
(18) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696−5700. Maryanoff, B. E. *J. Org. Chem.* **1979**, *44*, 4410. Maryanoff, B. E. *J. Org. Chem.* **1982**, *47*, 3000.

Treatment of **1** with *N*-tosylpyrrole in fluorobenzene affords the 3-position "C–H" insertion product **27** in 23% isolated yield with **4** as the major byproduct in 26% yield. In hexafluorobenzene at reflux, only **27** is obtained in a 59% yield. Several *para*-substituted phenyl pyrroles were examined in rhodium-mediated reactions with **1**, and again "C–H" insertion products are observed. In contrast, Maryanoff reported that the *N*-phenylpyrrole system was deactivated and does not react with ethyl diazoacetate using either rhodium or copper catalysts. The reaction of **1** with *N*-phenylpyrrole affords **28** in a 72% yield along with 16% of **4**. With *N*-(4-fluorophenyl)-pyrrole in hexafluorobenzene, the 3-position substitution product **29** is obtained in a 2:1 ratio with the 2-position regioisomer **30**. Treatment of **1** with *N*-(4-methoxyphenyl)pyrrole affords the 3-position net "C–H" insertion product **31** in 66% yield. These results suggest that the electronic effect of the *para*-substituent on the *N*-phenylpyrrole has little consequence for the cycloaddition reaction. Reactions of **1** with 1-(dimethylamino)pyrrole, 2,5-dimethylpyrrole, *N*-(triisopropylsilyl)pyrrole, *N*-(4-nitrophenyl)-2,5-dimethylpyrrole, *N*-(4-acetylphenyl)-2,5-dimethylpyrrole, *N*-(4-nitrophenyl)pyrrole, and *N*-benzyl-2,5-dimethylpyrrole produce only multicomponent mixtures containing solvent-related products.

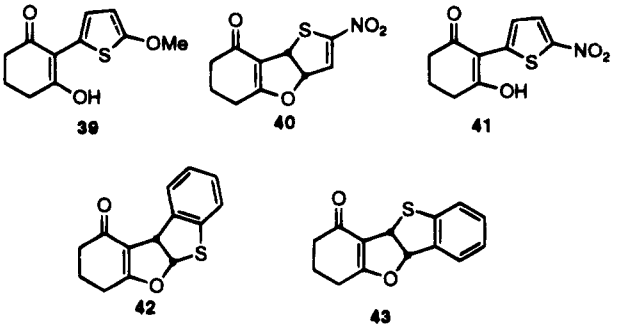
Thiophenes. We had initially reported that reactions performed neat with sulfur-containing substrates failed, probably due to rhodium coordination. For this reason all of the following reactions were conducted in fluorobenzene with a 4-fold excess of the thiophene and 1 mol % of dirhodium tetraacetate at room temperature. Interestingly, little or no solvent related byproducts are observed, and many of the products precipitate directly from the reaction mixture in high isolated yields.

In order to directly compare with the corresponding furans, both thiophene and 2,5-dimethylthiophene were examined. In both cases, "C–H" insertion products are obtained. The former affords **33** in 94% yield, while the latter affords **34** in 66% yield along with a small amount of **35**. Several unsymmetrical thiophenes were examined as well. A reaction of **1** with 3-methylthiophene affords the 3′-substituted product **36** in high yield. This result is consistent with the earlier observation with 3-methylfuran that reaction occurs exclusively on the unsubstituted olefin, but divergent in that the dipolar cycloadduct is not obtained. Treatment of **1** with 3-methoxythiophene under standard conditions affords a 3-alkylidene-2,3-dihydrothiophene (**37**) in 92% yield. As expected, the reaction occurs exclusively at the unsubstituted double bond, but a completely anomalous product is produced. This compound is stable at room temperature in a chloroform solution and remains intact when exposed to silica gel chromatography. However, when just one drop of dimethyl sulfoxide is added, it is completely converted to the net 3-position substitution product **38** in less than 2 h, as observed by ^{1}H NMR. An interesting comparison can be made to the reaction of **1** with 2-methoxythiophene, in which case exclusive reaction on the unsubstituted double bond occurs to afford the 5-substituted product **39**.

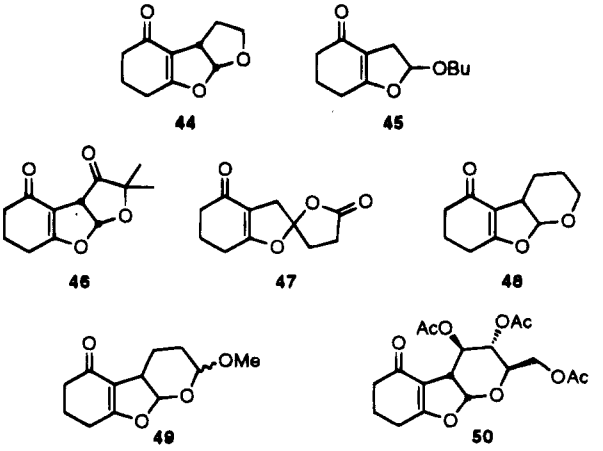
Thus far in this study, thiophene or thiophenes substituted with electron-donating groups have afforded 2- and 3-position net "C–H" insertion products. However, when **1** was treated with the electron-deficient 2-nitrothiophene, cycloadduct **40** with the "reverse" regiochemistry is obtained in 78% yield along with the net 2-position "C–H" insertion product **41**. While **41** appears



reasonably stable, **40** blackens on standing at 5 °C under N_2, like its oxygen analog. Finally, **1** was treated with thianaphthene under the standard conditions to afford cycloadduct **42** and the "reverse" cycloadduct **43** in a ratio of 5:1.



Vinyl Ethers. The reaction of **1** with dihydrofuran served as the prototype for all of the reactions with aromatic heterocycles reported in our preliminary communication and in the preceding sections. The product **44** is obtained in 84% yield when the reaction is conducted neat and in 70% yield in fluorobenzene. On stirring neat butyl vinyl ether with **1** for 24 h at room temperature with rhodium acetate, **45** is produced in 92% yield. 5,5-Dimethyl-2*H*-3-furanone gives the somewhat unstable **46** in 55% yield as a yellow solid. Compound **47**, a member of a class of compounds that has also been prepared by oxidative cyclization of dicarbonyl compounds and vinyl esters,[19] is produced in 63% yield from γ-methylenebutyrolactone in benzene. With neat dihydropyran, compound **48** is obtained in 84% yield as a 7.4:1



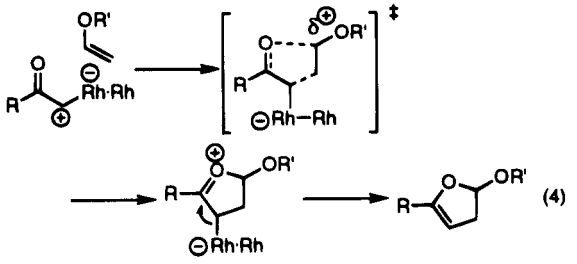
mixture of diastereomers of unassigned stereochemistry.

(19) Mellor, J. M.; Mohammed, S. *Tetrahedron* **1993**, *49*, 7547–7556.

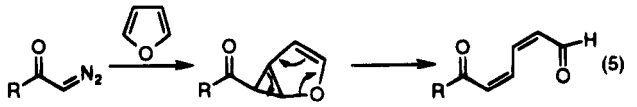
The strict geometric imperative for a *cis* ring fusion that was observed with five-membered ring heterocycles is seemingly relaxed in the pyran series, with the consequence that a mixture of stereoisomeric products is obtained. With neat methoxydihydropyran, **49** is produced in 87% yield. Triacetyl glucal (1 equiv in fluorobenzene) gives the homogeneous **50** in 40% yield. It is reasonable that the stereochemistry at the ring fusion is as shown based on steric approach control, which is supported by a recent study of the additions of cyclic carbenoids to a number of glycals.[20]

Discussion

A mechanism previously proposed by Doyle for the known[21] dipolar cycloaddition of diazocarbonyl compounds with donor-substituted alkenes is shown in eq 4.



It is reasonable that the positive charge character of the carbon α to the carbonyl group dictates the regiochemistry of bond formation through the hypothetical transition state shown and that the oxonium intermediate eliminates dimetal to provide the dihydrofuran product. While this model accommodates most of our results with vinyl ethers, it does not address the loss of stereochemistry with a six-membered ring reactant. A zwitterionic intermediate (*vide infra*) that lives long enough to undergo single bond rotation explains the formation of the *trans*-fused ring junction. For the five-membered ring reactants, the strong thermodynamic preference for *cis*-fused 5-5 ring systems does not allow the stepwise nature of the reaction to be discerned. The Doyle mechanism is also not adequate to explain the formation of dipolar cycloadducts of both regiochemistries and, with some heteroaromatic substrates, 2- and 3-position "C–H" insertion products. We therefore consider alternative mechanisms for these processes. Wenkert had advanced, without support, a mechanistic model for the rhodium-catalyzed reaction between furans and diazocarbonyl compounds involving initial [2 + 2] cycloaddition of the rhodium carbenoid to a furan double bond in both regiochemistries.[22] Rh–C bond cleavage would produce one of two zwitterions that undergoes elimination to produce an alkylidene-2,3-dihydrofuran (analogous to **37**) or a dienal. Wenkert's experimental observations require modification of this scheme, since exo-substituted cyclopropanes were the major products in some of his reactions and, with applied heat or the addition of a Lewis acid, converted to dienals (eq 5). Interestingly, no endo-



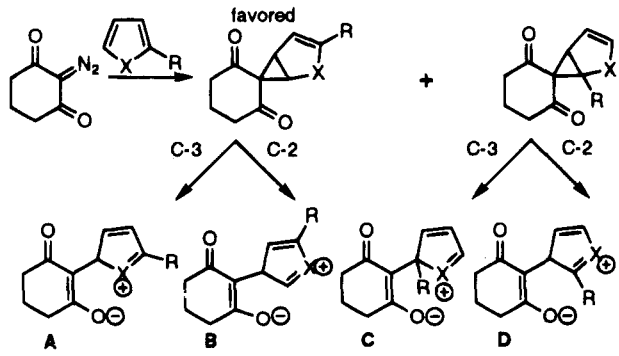
substituted cyclopropanated furans were isolated even though complete stereoselection would not be expected. This result suggested that, if formed, *endo*-cyclopropanes were sufficiently unstable as to be directly converted to the dienal. Wenkert observed selectivity for reaction at the less-substituted alkene in unsymmetrical furans, isolated β-carbon C–H insertion products in some cases, and implied that the latter were derived from isomerization of alkylidene-2,3-dihydrofurans. Alternatively, a pathway involving cyclopropanation followed by electrocyclic ring opening has been used by Padwa to explain the production of dienals in the intramolecular reactions of diazo compounds with furans.[23]

An initial cyclopropanation therefore seemed a reasonable mechanistic hypothesis for the net 1,3-dipolar cycloaddition reaction of **1** to heteroaromatics, but the absence of dienal products required an explanation. That cyclopropane intermediates were never observed was not a serious detriment to this hypothesis, since Wenkert had observed in his rhodium-mediated reactions that cyclopropanes bearing endo carbonyl groups could not be isolated and, if formed, must be unstable under the reaction conditions. Cycloadducts of **1** *must* have an endo carbonyl group. The involvement of a cyclic diazo compound, resulting in a spiro-fused cyclopropane, is not the source of the unique reactivity of **1**, since a diazo β-lactam gives dienal products in a rhodium-catalyzed reaction with furan.[24] A variety of experiments have led to the somewhat phenomenological observation that the carbenoid derived from **1** is far more reactive than many previously-studied carbenoids. For example, the reaction of 3-diazo-2,4-pentanedione with chlorinated solvents catalyzed by rhodium acetate gives a complex product mixture containing no chlorine-abstraction products. Likewise, when 3-diazo-2,4-pentanedione is treated with furan (excess, fluorobenzene, dirhodium tetraacetate), only polymeric materials and no furan-related products are formed. Consequently, the involvement of a diazo dicarbonyl compound, resulting in a doubly-activated cyclopropane, is not the source of the unique reactivity. A reasonable suggestion is the combination of a dicarbonyl with a spiro ring system. The superiority of such a structural array for nucleophilic additions to cyclopropanes has been previously shown by Danishefsky,[25] and it is reasonable to suggest that the formation of a zwitterion from the cyclopropane intermediate is an intramolecular nucleophilic cleavage of the cyclopropane. Explanations for all of the products of reactions between **1** and heteroaromatics can arise from this formalism.

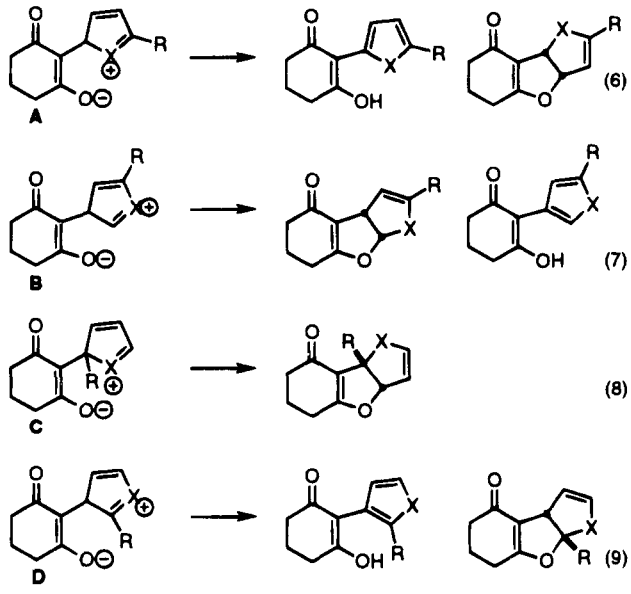
A mechanistic matrix accounting for our observations is shown in Scheme 2. We have rationalized the net dipolar cycloaddition through a cyclopropanation/ring opening pathway. The product distribution is consistent with our earlier competition studies, where initial electrophilic attack at an unsubstituted olefin is faster than at a substituted olefin. This trend is presumably based on steric effects. The cyclopropane intermediates can undergo bond cleavage at the furan 2- or 3-position,

(20) Pirrung, M. C.; Lee, Y. R. *J. Chem. Soc., Chem. Commun.* **1995**, in press.
(21) Alonso, M. E.; Morales, A.; Chitty, A. W. *J. Org. Chem.* **1982**, *47*, 3748. Alonso, M. E.; Jano, P.; Hernandez, M. I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047–3050. Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 4778–47xx. Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.
(22) Wenkert, E.; Guo, M.; Lavilla, R.; Porter, B.; Ramachandran, K.; Sheu, J.-H. *J. Org. Chem.* **1990**, *55*, 6203–6214.
(23) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299–308.
(24) Matlin, S. A.; Chan, L. *Tetrahedron Lett.* **1981**, *22*, 1627.
(25) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–70.

Scheme 2

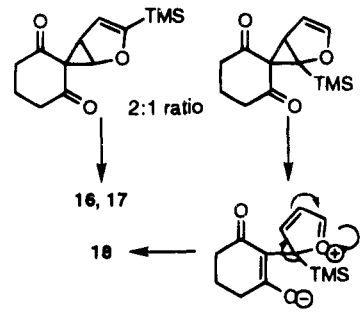


delocalizing the electrons into the β-diketone system. Four possible zwitterions **A**–**D** can be formed, each having proton transfer and C–O bond formation pathways available that account for the observed products (eqs 6–9). Proton transfer from **A** gives 2-position "C–



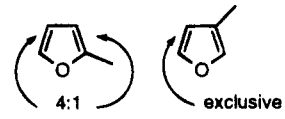
H" insertion, and ring closure gives the furo[3,2-*b*]furan ring system ("inverse" regiochemistry). Proton transfer from **B** or **D** gives 3-position "C–H" insertion, and ring closure gives the furo[2,3-*b*]furan ring system ("normal" dipolar cycloadduct).

All of the products of the pathways in this Scheme have been observed experimentally except ring closure from **C** and proton transfer from **D**. A major pathway with furans is accounted for by intermediates **B**/**D**, though **11**, **16**, **19**, and **21** can be explained as arising via **A**. The product ratio in the reaction of **1** with 2-methylfuran is consistent with 4:1 selectivity in the initial cyclopropanation (**A**+**B**:**C**+**D**). The difference in the major pathway taken by 2-methylfuran and furan (C-3 bond cleavage instead of C-2) can be explained by increased stabilization of **A** by methyl substitution. The partitioning of intermediates **A**,**B**, derived from reaction at the less substituted alkene, into three parts **A** and one part **B** explains the **11**:**9** ratio. Compound **10** is explained by exclusive partitioning of reaction at the more substituted alkene through **D**. It is difficult to explain the formation of **A** as an intermediate toward **19** with nitrofuran, since it requires positive charge to be located through resonance α to an electron-withdrawing nitro group; perhaps here a homolytic ring-opening applies. Formation of the two benzofuran cycloadducts can be rationalized from dipolar species derived via 2-position or 3-position bond cleavage. The production of **21** is easily attributed to the resonance stabilization provided from the aromatic ring within the product of C-3 bond cleavage, which is correctly predicted to be minor due to the loss of aromaticity. The reaction with trimethylsilylfuran can be explained by a 2:1 ratio of reaction at the unsubstituted olefin to the substituted olefin, though the steric bias that had previously been observed makes an intermediate bearing a bulky silyl group on a quaternary center problematic. The generation of **18** can be explained via **C**, wherein desilylation is favored over ring closure. Control experiments dem-



onstrate that it does not arise by desilylation of **16**. The reactions of pyrroles are best accounted for via **B**, with partitioning heavily toward proton transfer. With thiophenes, intermediates **A** and **B** best explain the observed products.

The results presented above suggest that the product distributions from the treatment of **1** with five-membered ring heterocycles are governed by steric interactions. Furan is a superior substrate compared to 2,5-dimethylfuran, and the reaction appears to be affected more by 3-position than 2-position substitution. For example, 2-methylfuran shows a 4:1 ratio of reaction on the unsubstituted 4,5 bond compared to the substituted olefin, whereas 3-methylfuran shows exclusive reaction on the unsubstituted olefin. There is little suggestion of



an electronic effect in the initial attack of the carbenoid. Heterocycles substituted with both electron-withdrawing groups and electron-donating groups afford products in similar yields, though a competition between the formation of **8** and **14** is resolved in favor of the electron-donating substituent.

The regioselectivity resulting from steric effects can be understood using a model for the transition structure for the reaction of cyclohexane-1,3-dione carbene with furan, which was determined using the *ab initio* quantum mechanics package SPARTAN[26] employing the 3-21G* basis set.[27] In this model, the dominant steric interactions are between the approaching carbonyl oxygens and the groups resident on the furan ring. For furans with β-substitution, the model must consider steric interactions with the 3- and 4-positions for attack on the substituted or unsubstituted alkenes, respectively. The

(26) SPARTAN is a product of Wavefunction, Inc.
(27) Giessner-Prettre, C.; Jacob, O. *J. Comput.-Aided Mol. Des.* **1989**, *3*, 23–37.

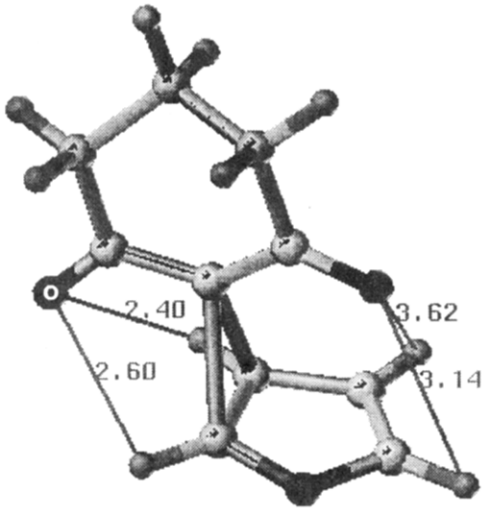
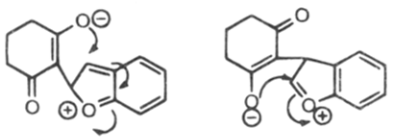


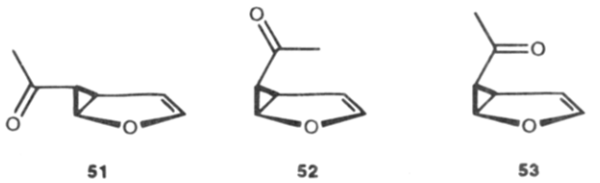
Figure 2. The transition structure model for the parent reaction with furan. The forming bond lengths are constrained to 2.1 Å. The distances shown between the nearest carbonyl group and the furan hydrogens are given in angstroms.

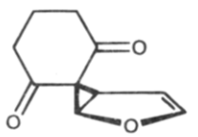
distance between the exo carbonyl and the furan 3-position is 2.40 Å, while the distance between the endo carbonyl and the furan 4-position is 3.62 Å (Figure 2). Therefore, the former should dominate and attack would be favored on the unsubstituted olefin. For furans with α-substitution, the model must consider steric interactions with the 2- and 5-positions for attack on the substituted or unsubstituted alkenes. The distance between the exo carbonyl oxygen and the furan 2-position is 2.60 Å, while the distance between the endo carbonyl and the furan 5-position is 3.14 Å, which is much less difference than with β-substitution. Attack on the more substituted olefin would therefore be limited but not blocked completely, leading to a mixture of products.

The selective generation of furo[2,3-*b*]furan products from furan C-2 bond cleavage with cyclic diazo diketones and butadienal products from furan C-3 bond cleavage with acyclic diazo ketones was also considered through theoretical methods. The issues investigated included the geometry of the cyclopropyl intermediate and the bond cleavage requiring the lowest activation energy in each system. The divergence of reactivity between the



systems was of particular interest, since a simple analysis of orbital geometries suggests that C-2 bond cleavage would be favored in either the cyclic or acyclic systems because one of the lone pairs on the furan oxygen is antiperiplanar to the breaking bond. Semiempirical calculations using AM1 were used to study the two possible bond cleavages in the cyclopropane intermediate in both cyclic and acyclic systems. A model system for the latter was the putative cyclopropane adduct between furan and diazoacetone. The exo product **51** has a ground state energy 3.7 kcal/mol lower than the endo product constrained in either of its two rotamers (**52** and **53**; the carbonyl is twisted to reduce electrostatic repulsion with the furan oxygen) and so was used to investigate the ring opening process. The breaking bond (either C-2 or C-3)





was stretched to 2.5 Å and the system minimized under this constraint. The constraint was removed from the resulting structure, which was further minimized to determine if the bond-stretched model would be transformed to a new compound. When the C-2 bond was stretched, minimization led back to the cyclopropyl intermediate; when the C-3 bond was stretched, minimization led to the dienal, confirming that minimization from a stationary point on the reaction coordinate predicts the correct product. Since C-2 bond cleavage is nonproductive, this could explain the isolation of some cyclopropyl intermediates in these systems. The C-2 bond cleavage does not lead to the furo[2,3-*b*]furan product in the acyclic case because (1) the endo stereoisomer which is proximal on the reaction coordinate to the dipolar cycloadduct is the minor product of the cyclopropanation step and (2) the energetic cost (*vide infra*) to rotate the oxygen from conformation **52** to **53** so that it may attack the oxonium ion is larger than the difference between C-2 and C-3 bond cleavage.

With this background, similar calculations were performed on the putative cyclopropane adduct from furan and the cyclic diketocarbene **54**. This intermediate should be much less stable than in the acyclic system for the following reasons. First, the constraint of the ring forces two oxygens to face one another, imposing severe electrostatic repulsions which could explain why this cyclopropyl intermediate is not observed. Second, as the more labile C-2-spiro carbon bond breaks, the endo carbonyl oxygen can attack C-2. In the substituted furans, C-3 bond cleavage could be favored by resonance stabilization. Theory predicts that this should lead to the dienal product, but in fact products of C−H insertion at C-2 (derived from C-3 bond cleavage and proton transfer) are observed. Thus, a competition between stereoelectronic and thermodynamic effects may govern the regiochemistry in cleavage of the putative cyclopropyl ring.

While our observations of the reaction of cyclic dicarbonyl carbenoids with furans are unique, the results we have obtained with pyrroles are in line with previous reports. Maryanoff found products of "C−H" insertion at the 2-position to be favored, while Fowler isolated an initial ethyl diazoacetate cyclopropanation product of *N*-(methoxycarbonyl)pyrrole that rearranged on heating to the 2-pyrroleacetic acid.[28] Davies interpreted the formation of azabicyclo[3.2.1]octane ring systems in the rhodium-mediated reactions of vinyl diazo compounds

(28) Tanny, S. R.; Grossman, J.; Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 6495.

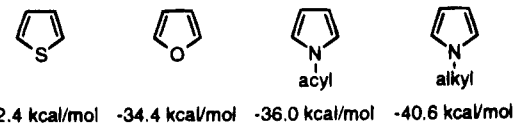


Figure 3. Calculated transition state energies for the reaction of cyclohexane-1,3-dione carbene with aromatic heterocycles.

with pyrroles through the formation of a divinylcyclopropane that undergoes Cope rearrangement. This process must occur faster than the ring opening others observe.

There are a few previous reports of the reactions of diazo compounds with thiophenes. One commonly reported process is the formation of stable sulfonium ylides, including those derived from cyclic diazo dicarbonyls.[29] Padwa has also reported intramolecular cyclopropanation of thiophenes, the products of which rearrange to give formal "C−H" insertion products. Wenkert had also reported the reaction of ethyl diazoacetate with thianapthene, thermally and under copper catalysis.[30] It produces a cyclopropanation product in low yield and the carbene trimer. The rhodium-mediated decomposition of **1** with thiophene or with thiophenes substituted with electron-donating groups affords net 2- or 3-position substitution products in high yields. These reactions yield no solvent related byproducts and in several cases the products precipitate from the reaction medium. The reaction of **1** with a thiophene substituted with an electron-withdrawing group (2-nitrothiophene) affords a cycloadduct with "inverse" regiochemistry. The thianaphthene cycloaddition reaction yields only cycloadducts, but of both regiochemistries.[31]

The theoretical rationale developed above can also explain the thiophene results, since in both cases there is a lone pair antiperiplanar to the breaking bond, but it does not explain the pyrrole results. The *N*-acylpyrrole lone pair is perpendicular to the plane of the ring, and bond cleavage must be dictated by other factors. The regioselectivity of addition and of the cyclopropyl ring opening are explained, but there is no simple rationale for the observed difference in reactions with solvent.

The *ab initio* theoretical study was extended to compare our results with furan to those with thiophene, *N*-alkylpyrroles, and *N*-acylpyrroles. If it is assumed that each of these reactions proceeds through a cyclopropane intermediate, albeit transient, then calculations performed on models for an intermediate along the reaction coordinate for their formation could be a tool to explain the observed relative reactivities. These results do not consider any role that might be exerted by the metal catalyst. The same constraints were applied to the forming bonds of the cyclopropane intermediate of each heterocycle (forming bonds are 2.1 Å) to calculate transition structure energies. The results are shown in Figure 3. The thiophene system is calculated to be the highest in energy, followed by furan, *N*-acylpyrrole, and *N*-alkylpyrrole. The combined yields of products isolated in the rhodium-mediated reactions of **1** with the substituted heterocycles were the highest with substituted thiophenes and lowest in the reactions with *N*-alkylpyrroles, and reaction with fluorobenzene solvent was the primary competing reaction. The calculated free energies of formation for these intermediates would predict a ranking of reactivities exactly opposite to that which is observed: a comparison of the calculated energies of the transition structures with the amount of solvent byproducts isolated reveals an inverse relationship. It is difficult to use these theoretical studies to explain the relative reactivities except to say that reaction with solvent may be controlled by factors other than simple addition.

(29) Gillespie, R. J.; Murray-Rust, J.; Murray-Rust, P.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1978**, 83. Glidewell, C.; Lloyd, D.; Metcalfe, S. *Synthesis* **1988**, 319. Meth-Cohn, O.; Vuorinen, E.; Modro, T. A. *J. Org. Chem.* **1989**, *54*, 4822.

(30) Wenkert E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L. *J. Org. Chem.* **1977**, *42*, 3945.

(31) The acyclic diazo dicarbonyl 3-diazo-2,4-pentanedione afforded the sulfur ylide in quantitative yield.

Conclusion

We have shown that rhodium-mediated reactions of 2-diazo-1,3-cyclohexanedione with substituted furans afford cycloaddition products (furo[2,3-*b*]furan ring systems) and net 2-position "C−H" insertion products. Steric effects are the dominant factor in the overall product distributions of both cycloaddition reactions and "C−H" insertion reactions. A greater than 2:1 ratio of reaction occurring on the unsubstituted olefin of a monosubstituted furan to the substituted olefin was observed. Substituents in the 3-position of furan appear to have a stronger steric effect than those in the 2-position. Modest yields were obtained in reactions with furans substituted both with electron-donating and electron-withdrawing groups. The reaction of **1** with benzofuran and 2-nitrofuran were the only cases wherein the furo[3,2-*b*]furan ring system (opposite regiochemistry) was formed. With other aromatic heterocycles, the parent pyrrole, indole, and thianapthene give cycloadducts, but the remainder provide "C−H" insertion products. Vinyl ethers, however, prove reliable reaction partners for dipolar cycloaddition.

Experimental Section

General. ^{1}H NMR spectra were acquired using a Varian Unity 300 MHz spectrometer in $CDCl_3$ and reported in parts per million (ppm) internally referenced to residual $CHCl_3$ (7.24 ppm) unless otherwise noted. ^{13}C NMR spectra were acquired using a Varian Unity Spectrometer at 75.4 MHz with Waltz composite decoupling in $CDCl_3$ and reported in parts per million (ppm) internally referenced to the solvent peak (77.0 ppm) unless otherwise noted. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Infrared spectra were recorded on a Perkin Elmer FT IR spectrometer. Melting points were taken on Mel-Temp II and are uncorrected. Fast atom bombardment mass spectra (FAB MS) were obtained through Glaxo Research Institute's analytical support group on a JEOL AX505. Chemical ionization mass spectra (CI MS) were also obtained through Glaxo Research Institute's analytical support on a Hewlett Packard HP5988A. High resolution FAB mass spectra were obtained through Analytical Instrument Group, Raleigh, NC. The accuracy of the mass determination was between 1.5−2.0 mmu standard deviation from the mass for averaged data with resolution from 5000−10000. All purchased chemicals were used without purification unless otherwise noted. Aldrich Sure-seal anhydrous solvents were used without further treatment. Chemical suppliers used were Aldrich, Maybridge, and Lancaster. All flash chromatography was done using silica gel 60 (230−400 mesh ASTM). The neutral activated aluminum oxide was Brockmann I, ~150 mesh. The basic activated aluminum oxide was Brockmann I, ~150 mesh. Chromatography analytical analyses were performed on precoated glass TLC silica gel K60F plates. Indicators used: Iodine, anisaldehyde dip (2.0 mL of anisaldehyde, 2.0 mL of H_2SO_4, 0.5 mL of HOAc, 36 mL of EtOH), UV shortwave light, phosphomolybdic acid dip (dissolved in EtOH). All reported R_fs are from TLC in 1:1 hexane:ethyl acetate.

Three diazo dicarbonyl decomposition reaction conditions were used and denoted methods a–c as described below. If any experimental details were varied they are noted for the particular compound. An effort was made to keep the conditions as consistent as possible in order to evaluate the reactivity of 2-diazo-1,3-cyclohexanedione. For this reason, all of the reactions are unoptimized.

Method a. 2,5-Dimethylfuran (2.0 mL) and dirhodium tetraacetate (9.6 mg, 0.0217 mmol) were combined under N_2 at rt. 2-Diazo-1,3-cyclohexanedione (300 mg, 2.17 mmol) was dissolved in 2,5-dimethylfuran (2.0 mL) and added dropwise over 10 min. The reaction was allowed to continue stirring for 15 h and concentrated to half-volume before placing directly onto a silica gel column. The column was eluted with 3:1 hexane:ethyl acetate followed by 1:1 hexane:ethyl acetate. The appropriate fractions were combined, rotary evaporated, and dried under high vacuum to afford a clear colorless oil (163 mg, 36%).

Method b. 2,5-Dimethylfuran (0.93 mL, 8.70 mmol) was dissolved in fluorobenzene (2 mL) under N_2 at rt and dirhodium tetraacetate (9.6 mg, 0.0217 mmol) was added. 2-Diazo-1,3-cyclohexanedione (300 mg, 2.17 mmol) was dissolved in fluorobenzene (3 mL) and added dropwise over 10 min. The reaction was allowed to stir for 15 h and concentrated to half-volume before placing directly onto a silica gel column. The column was eluted with 3:1 hexane:ethyl acetate followed by 1:1 hexane:ethyl acetate. The appropriate fractions were combined, rotary evaporated, and dried under high vacuum to afford a clear colorless oil (120 mg, 27%).

Method c. *N*-Methylpyrrole (0.70 g, 8.70 mmol) was dissolved in hexafluorobenzene (2.0 mL) at rt under N_2. Dirhodium tetraacetate (9.6 mg, 0.0217 mmol) was added. 2-Diazo-1,3-cyclohexanedione (300 mg, 2.17 mmol) was slurried in hexafluorobenzene (3 mL) and added dropwise over 10 min. The reaction was placed in a preheated oil bath set to 85 °C and stirred at reflux for 2.0 h. A dark colored precipitate formed during the reaction, but the reaction mixture remained a clear yellow solution. The hot solution was decanted away from the residue and reduced to half volume under rotary evaporation before placing directly onto a silica gel column. The column was eluted with 1:1 hexane:ethyl acetate. The appropriate fractions were combined to afford compound **33** (2-position substitution, 249 mg, 60%) and compound **32** (3-position substitution, 120 mg, 29%).

2-Chloro-1,3-cyclohexanedione (2).[32] Dichloroethane (2.0 mL) was passed through basic alumina and 1.0 mL was combined with dirhodium tetraacetate (1.6 mg, 1 mol %) catalyst under N_2 at rt. 2-Diazo-1,3-cyclohexanedione (50 mg, 0.36 mmol) was dissolved in the pretreated dichloroethane (1.0 mL) and added dropwise. The reaction was filtered after 5 min, and the solid was dried in vacuo to afford a cream colored solid (53 mg, 99%): mp 208 °C. An identical procedure was followed using dichloromethane which required 4 h to reach completion and gave the identical product in 82% yield. ^{1}H NMR (DMSO-d_6): δ 1.92 (m, 2H), 2.43 (m, 4H), 11.68 (bs, 1H). ^{13}C NMR: δ 19.97, 33.41, 36.80, 107.33, 157.00, 193.29. CI MS 147 (MH^+), 149 (^{37}Cl isotope MH^+). HRMS calcd for $C_6H_8O_2Cl$ (MH^+): 147.0213 (using ^{35}Cl isotope). Found: 147.0213.

2-(4-Fluorophenyl)cyclohexane-1,3-dione (4). This was the byproduct in many of the reactions carried out in fluorobenzene as a solvent. Dirhodium tetraacetate was stirred with fluorobenzene under N_2 while a solution of **1** in fluorobenzene was added dropwise at rt. The reaction mixture was stirred for 20 h and placed directly onto a silica gel column. The first eluent was 1:1 hexane:ethyl acetate to remove the less polar component, followed by ethyl acetate to elute **4**. The volatiles were removed in vacuo to afford the title compound as a pale yellow solid (126 mg, 42%): mp 184 °C. ^{1}H NMR (DMSO-d_6): δ 1.91 (m, 2H); 2.46 (m, 2H); 7.08 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 21.45, 39.5, 114 (J = 21 Hz), 115.39, 130.3 (J = 3 Hz), 132 (J = 8 Hz), 161 (J = 242 Hz), 186.44. FAB MS 207 (MH^+). Anal. Calcd for $C_{12}H_{11}FO_2 \cdot 0.5H_2O$: C, 67.28; H, 5.18. Found: C, 67.57; H, 5.36.

3,4-Dihydro-2*H*-dibenzofuran-1-one (5).[33] Procedure as above. R_f = 0.67, clear colorless oil, 64 mg, 24%. ^{1}H NMR: δ 2.28 (dt, J = 6.6, 6.3 Hz, 2H); 2.61 (t, J = 6.3 Hz, 2H); 3.06 (t, J = 6.6 Hz, 2H); 7.32 (m, 2H); 7.48 (m, 1H); 8.06 (m, 1H). ^{13}C NMR: δ 22.39, 23.73, 37.79, 107.11, 111.03, 121.78, 124.44, 124.96, 127.90, 156.55, 162.34, 195.49. FAB MS 187 (MH^+). FAB HRMS calcd for $C_{12}H_{10}O_2$ (MH^+): 187.0759. Found: 187.0757.

8-Methyl-3,4-dihydro-2*H*-dibenzofuran-1-one (6). Method a: R_f = 0.55, colorless viscous oil, 130 mg, 45%. ^{1}H NMR: δ 2.27 (dt, J = 6.6, 6.3 Hz, 2H); 2.45 (s, 3H); 2.60 (t, J = 6.3 Hz, 2H); 3.02 (t, J = 6.6 Hz, 2H); 7.12 (d, J = 7.5 Hz, 1H); 7.35 (d, J = 7.5 Hz, 1H); 7.88 (s, 1H). CI MS 201 (MH^+). FAB HRMS calcd for $C_{13}H_{12}O_2$ (MH^+): 201.0915. Found: 201.0917.

2-(5-Fluoro-2-methoxyphenyl)cyclohexane-1,3-dione. Method a: R_f = 0.25, white solid, 130 mg, 38%, mp 81 °C. ^{1}H NMR: δ 2.05 (dt, J = 6.6, 6.3 Hz, 2H); 2.49 (t, J = 6.0 Hz, 2H); 2.68 (t, J = 6.0 Hz, 2H); 3.91 (s, 3H); 6.83 (m, 2H, one is exchangeable); 6.94 (m, 2H). ^{13}C NMR: δ 20.21, 27.73, 36.86, 58.02, 115.69 (J = 15), 115.85 (J = 45), 131.20, 154.00, 156.23, 159.40, 162.21 (J = 247), 166.30, 193.23. Electrospray MS 237 (MH^+), 259 (M + Na). FAB HRMS calcd for $C_{11}H_{13}O_3F$ (MH^+): 237.0927. Found: 237.0934.

3a,6,7,8a-Tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (7a). Method b: R_f = 0.25, clear colorless oil, 356 mg, 92%. ^{1}H NMR: δ 2.03 (m, 2H); 2.33 (m, 2H); 2.50 (m, 2H); 4.38 (m, 1H), 5.36 (t, J = 2.7 Hz, 1H); 6.36 (t, J = 2.7 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H). ^{13}C NMR: δ 21.39, 23.28, 36.22, 48.11, 103.51, 112.33, 115.92, 143.99, 176.21, 194.53. FAB MS 179 (MH^+). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.20; H, 5.28.

3a,6,7,8a-Tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (7b). Method b: 56%. ^{1}H NMR: δ 1.07 (s, 3H), 1.11 (s, 3H), 2.21 (d, J = 16.2 Hz, 2H), 2.23 (d, J = 16.2 Hz, 2H), 2.36 (d, J = 1.6 Hz, 2H), 4.31 (d, J = 7.5 Hz, 1H), 5.38 (d, J = 2.7 Hz, 1H), 6.39 (d, J = 2.7 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ 28.4, 28.7, 34.1, 37.4, 47.7, 50.9, 103.4, 112.7, 114.6, 144.2, 174.9, 194.0. IR (neat): 3108, 2932, 1645, 1400, 1361, 1285, 1214, 1040, 977, 927, 723 cm^{-1}. MS (CI) m/e calcd for $C_{10}H_{12}O_3$: 206.0952, found, 206.0946; 206, 178, 169, 150, 122, 94, 79, 66.

2,8a-Dimethyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (8). Method a: R_f = 0.48, pale yellow oil, 163 mg, 36%. ^{1}H NMR: δ 1.67 (s, 3H); 1.82 (s, 3H); 2.03 (m, 2H); 2.31 (m, 2H); 2.47 (m, 2H); 3.91 (d, J = 1.5 Hz, 1H); 4.92 (d, J = 1.5 Hz, 1H). ^{13}C NMR: δ 13.35, 21.48, 23.70, 23.89, 36.64, 52.21, 98.78, 117.01, 122.44, 153.61, 175.53, 193.45. IR (neat): 2930, 1678, 1640, 1390, 1292, 1116, 997, 825 cm^{-1}. MS (CI) 207 (MH^+). MS (EI) m/e calcd for $C_{12}H_{14}O_3$: 206.0945, found 206.0947; 206, 163, 136, 121, 108, 7955.

3-Hydroxy-2-(5-methylfuran-2-yl)cyclohex-2-enone (11). Method a: R_f = 0.44, white solid, 60%, mp 151 °C. ^{1}H NMR: δ 2.00 (m, 2H); 2.34 (s, 3H); 2.47 (t, J = 7.1 Hz, 2H); 2.63 (t, J = 6.3 Hz, 2H); 6.07 (d, J = 3.2 Hz, 1H); 6.93 (d, J = 3.2 Hz, 1H); 9.22 (s, 1H, exchangeable). ^{13}C NMR (off-resonance decoupled): δ 13.29 (q), 20.00 (t), 29.28 (t), 37.30 (t), 107.06 (s),-107.42 (d), 109.96 (d), 147.18 (s), 148.62 (s), 171.41 (s), 195.14 (s). IR ($CHCl_3$): 3402, 3018, 2977, 1645, 1588, 1525, 1410, 1303, 1203 (s), 1011, 755 (s) cm^{-1}. FAB MS 193 (MH^+). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75, H, 6.25. Found: C, 68.53; H, 6.30.

2-Methyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta-[*a*]inden-4-one (9). ^{1}H NMR: δ 1.79 (s, 3H), 1.97 (m, 2H); 2.24 (m, 2H); 2.40 (m, 2H); 4.16 (m, 1H); 6.22 (t, J = 1.8 Hz, 1H); 6.45 (d, J = 7.5 Hz, 1H). **8a-Methyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (10).** ^{1}H

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(33) Kucherova, N. F.; Aksanova, L. A.; Sharkova, L. M.; Zagorevskii, V. A. *Khim. Geterotsikl. Soeden* **1973**, 149–153.

(34) The author has deposited atomic coordinates for this structure 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.

NMR: δ 1.59 (s, 3H), 1.97 (m, 2H); 2.24 (m, 2H); 2.40 (m, 2H); 3.84 (t, J = 1.8 Hz, 1H); 4.87 (m, 1H); 5.22 (t, J = 2.4 Hz, 1H). CI MS m/z 193 (MH^+).

3a,3-Bis(ethoxycarbonyl)-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (14). Method b: R_f = 0.24, clear colorless oil, 181 mg, 26%. ^1H NMR: δ 1.25 (m, 6H); 2.06 (m, 2H); 2.40 (m, 2H); 2.62 (m, 2H); 4.18 (m, 2H); 4.27 (m, 2H); 6.17 (s, 1H); 7.58 (s, 1H). IR ($CHCl_3$) 2975, 1744, 1709, 1642, 1630, 1396, 1360, 1297,1182, 1118, 962 cm^{-1}. FAB MS m/z 323 (MH^+). FAB HRMS calcd for $C_{16}H_{18}O_7$ (MH^+): 323.1134. Found: 323.1131.

3-Methyl-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (15). Method b: R_f = 0.56, clear, colorless oil, 301 mg, 72%. ^1H NMR: δ 1.68 (s, 3H); 2.04 (m, 2H); 2.35 (m, 2H); 2.49 (m, 2H); 4.18 (d, J = 7.2 Hz, 1H); 6.02 (s, 1H); 6.56 (d, J = 7.2 Hz, 1H). ^{13}C NMR: δ 9.85, 21.29, 23.55, 36.51, 51.15, 113.39, 114.38, 115.53, 138.06, 176.75, 194.78. FAB MS m/z 193 (MH^+). IR (neat): 2947, 1716 (w), 1637 (s), 1396, 1282, 1218, 1168, 1019, 926. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.62; H, 6.46.

3-Hydroxy-2-[5-(trimethylsilyl)furan-2-yl]cyclohex-2-enone (16). Method b: R_f = 0.76, white solid, 165 mg, 30%, mp 101−103 °C. ^1H NMR: δ 0.24 (s, 9H); 2.00 (m, 2H); 2.46 (m, 2H); 2.62 (m, 2H); 6.70 (d, J = 3.3 Hz, 1H); 7.05 (d, J = 3.3 Hz, 1H); 9.68 (s, 1H, exchangeable). FAB MS 251 (MH^+). Anal. Calcd for $C_{13}H_{18}O_3Si$: C, 62.40; H, 7.20. Found: C, 62.64; H, 7.07.

3-Hydroxy-2-(furan-2-yl)cyclohex-2-enone (18). Method b: R_f = 0.34, tan solid, 100 mg, 26%, mp 143 °C. ^1H NMR: δ 2.00 (m, 2H); 2.51 (m, 2H); 2.64 (m, 2H); 6.50 (dd, J = 1.8, 3.2 Hz, 1H); 7.07 (d, J = 3.2 Hz, 1H); 7.39 (d, J = 1.8 Hz, 1H); 9.26 (s, 1H, exchangeable). FAB MS 179 (MH^+). FAB HRMS calcd for $C_{10}H_{10}O_3$ (MH^+): 179.0708. Found: 179.0706.

2-(Trimethylsilyl)-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (17). Method b: R_f = 0.62, pale yellow oil, 128 mg, 24%. ^1H NMR: δ 0.15 (s, 9H); 1.98 (m, 2H); 2.32 (m, 2H); 2.45 (m, 2H); 4.23 (dd, J = 7.5, 2.4 Hz, 1H); 5.50 (d, J = 2.4 Hz, 1H), 6.57 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ −2.58, 21.33, 23.50, 36.30, 49.18, 113.72, 114.13, 115.91, 161.53, 175.98, 194.94. CI MS 251 (MH^+). IR ($CHCl_3$): 2947, 1638, 1389,1246,1218,1161, 1018, 983, 833 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3Si$: C, 62.36; H, 7.25. Found: C, 61.85; H, 7.15.

2-Nitro-3a,6,7,8a-tetrahydro-5*H*-3,8-dioxacyclopenta[*a*]inden-4-one (19). Method b: R_f = 0.60, 135 mg, 28%. ^1H NMR: δ 2.04 (m, 2H); 2.40 (m, 2H); 2.52 (m, 2H); 5.72 (d, J = 1.5 Hz, 1H); 6.11 (d, J = 6.0 Hz, 1H); 6.90 (dd, J = 6.0, 1.5 Hz, 1H). ^{13}C NMR: δ 20.45, 27.30, 36.10, 77.76, 152.42, 120.36, 123.26, 141.12, 168.86, 194.06. CI MS 224 (MH^+). FAB HRMS calcd for $C_{10}H_9NO_5$ (MH^+): 224.0559. Found: 224.0557.

2-Nitro-3a,6,7,8a-tetrahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (20). Method b: R_f = 0.38, yellow oil, 176 mg, 36%. (This material changed from a yellow oil to a tacky dark-brown solid. No difference in the ^1H NMR could be determined within 24 h at 0 °C, however the shelf life is questionable.) ^1H NMR: δ 2.18 (dt, J = 6.6, 6.3 Hz, 2H); 2.38 (t, J = 6.3 Hz, 2H); 2.56 (t, J = 6.6 Hz, 2H); 4.61 (dd, J = 7.80, 2.70 Hz, 1H); 6.40 (d, J = 2.70 Hz, 1H); 6.76 (d, J = 7.80 Hz, 1H). ^{13}C NMR: δ 21.58, 23.78, 36.66, 48.87, 104.63, 112.17, 114.51, 162.43, 177.44, 194.50. CI MS 224 (MH^+). FAB HRMS calcd for $C_{10}H_9NO_5$ (MH^+): 224.0559. Found: 223.0566.

3,4,5a,10b-Tetrahydro-2*H*-benzo[*b*]benzo[4,5]furo[3,2-*d*]furan-1-one (22). Method b: R_f = 0.62, pale yellow viscous oil, 86.3 mg, 52%. ^1H NMR: δ 2.0 (m, 2H); 2.32 (m, 2H); 2.49 (m, 2H); 4.82 (d, J = 7.1 Hz, 1H); 6.76 (d, J = 7.1 Hz, 1H); 6.92 (m, 2H); 7.16 (m, 1H); 7.56 (d, J = 7.3 Hz, 1H). IR (neat): 2947, 1637, 1467, 1389, 1204, 1168, 1019, 933, 741 cm^{-1}. FAB MS 229 (MH^+). FAB HRMS calcd for $C_{14}H_{12}O_3$ (MH^+): 229.0865. Found: 229.0859.

2,3,4b,9b-Tetrahydro-1*H*-benzo[*b*]benzo[4,5]furo[2,3-*d*]-furan-4-one (21). Method b: R_f = 0.31, cream colored solid, 23.5 mg, 14%: mp 138 °C. ^1H NMR: δ 2.09 (m, 2H); 2.40 (m, 2H); 2.51 (m, 2H); 6.11 (d, J = 7.4 Hz, 1H); 6.29 (d, J = 7.4 Hz, 1H); 6.85 (m, 2H); 7.30 (m, 1H); 7.45 (d, J = 6.9 Hz, 1H). FAB MS m/z 229 (MH^+). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.63; H, 5.29.

3a,6,7,8a-Tetrahydro-5*H*-1-oxa-8-aza-8-(ethoxycarbonyl)cyclopenta[*a*]inden-4-one (23a). To a solution of *N*-(ethoxycarbonyl)pyrrole (6.10 g, 44.0 mmol) in fluorobenzene (30 mL) in the presence of $Rh_2(OAc)_4$ (49.0 mg) was added a solution of 2-diazocyclohexane-1,3-dione (3.10 g, 22.0 mmol) in fluorobezene (10 mL). The reaction mixture was stirred at room temperature for 24 h. Evaporation of the solvent under reduced pressure and purification of the crude product by chromatography with 33% EtOAc/hexane afforded an oil (1.73 g, 32%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.63 (m, 1H), 6.56 (broad s, 1H), 5.39 (broad s, 1H), 4.43 (broad m, 1H), 4.25 (m, 2H), 2.49 (m, 2H), 2.34 (m, 2H), 2.04 (m, 2H), 1.31 (m, 3H); IR (neat) 3113, 2951, 1776, 1719, 1659, 1402, 1339, 1314, 1238, 1173, 1134, 1021, 1134, 986, 925, 769 cm^{-1}; MS (CI) m/e calcd for $C_{13}H_{15}NO_4 + H^+$: 250.1080, found 250.1085; 250, 234, 206, 178, 162, 136, 100.

3a,6,7,8a-Tetrahydro-5*H*-1-oxa-8-aza-8-acetylcyclopenta[*a*]inden-4-one (23b). The reaction was performed with **1** (0.138 g, 1.0 mmol) and *N*-acetylpyrrole (0.218 g, 2.0 mmol) in PhF (2 mL) in the presence of $Rh_2(OAc)_4$ (8.0 mg). The product was purified with 1/4 EtOAc/hexane, and an oil was isolated (70.4 mg, 34%). ^1H NMR (300 MHz, $CDCl_3$): δ (a pair of rotamers), 6.84 (m, 1H), 6.56 (m, 1H), 5.57 (m, 1H), 4.48 (m, 1H), 2.48 (m, 2H), 2.37 (m, 2H), 2.28 (d, 3H), 2.04 (m, 2H); MS (CI) m/e calcd for $C_{12}H_{13}NO_3$: 219.0895, found 219.0899; 220 $(M + H)^+$, 178, 168, 136, 100.

10-Acetyl-4b,6,7,8,9a,10-hexahydro-9-oxa-10-azaindeno[1,2-*a*]inden-5-one (24). Method b: R_f = 0.34, 302 mg, 62%, mp 146−148, 151−153 °C. ^1H NMR: δ 2.01 (m, 2H); 2.40 (m, 2H), 2.51 (m, 5H); 4.88 (d, J = 8.1 Hz, 1H); 6.71 (d, J = 8.4 Hz, 1H); 7.06 (t, J = 7.5 Hz, 1H); 7.24 (t, J = 7.8 Hz, 1H); 7.61 (d, J = 7.5 Hz, 1H); 8.19 (d, J = 8.1 Hz, 1H). FAB MS m/z 270 (MH^+), 228 (MH^+ − Ac). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 23.6, 23.7, 36.6, 46.7, 98.0, 115.7, 116.6, 124.6, 125.9, 128.2, 130.6, 141.0, 169.6, 176.2, 194.6; IR (neat) 2944, 1681, 1650, 1477, 1388, 1282, 1153, 958, 912, 762 cm^{-1}; MS (CI) m/e 270 (M + 1), 228, 212, 162, 130, 113. Anal. Calcd for $C_{16}H_{15}NO_3 \cdot 0.25H_2O$: C, 70.19; H, 5.71; N, 5.12. Found: C, 70.05; H, 5.67; N, 4.92.

3-Hydroxy-2-(*N*-methylpyrrol-2-yl)cyclohex-2-enone (25). Method c: R_f = 0.22, clear colorless oil, 249 mg, 60%. ^1H NMR: δ 2.10 (m, 2H); 2.49 (m, 2H); 2.64 (m, 2H); 3.41 (s, 3H); 6.06 (dd, J = 1.8, 3.3 Hz, 1H); 6.18 (t, J = 2.7 Hz, 1H); 6.78 (t, J = 1.8 Hz, 1H); 6.97 (s, 1H, exchangeable). ^{13}C NMR: δ 20.37, 27.66, 34.40, 36.88, 108.03, 109.42, 109.83, 124.63, 162.11, 174.31, 196.59. CI MS 192 (MH^+). FAB HRMS calcd for $C_{11}H_{13}NO_2$ (MH^+): 192.1025. Found: 192.1024.

3-Hydroxy-2-(*N*-methylpyrrol-3-yl)cyclohex-2-enone (26). Method c: R_f = 0.42, yellow oil, 120 mg, 29%. ^1H NMR: δ 2.04 (m, 2H); 2.51 (m, 4H); 3.63 (s, 3H); 6.09 (t, J = 2.4 Hz, 1H); 6.64 (t, J = 2.4 Hz, 1H); 6.67 (d, J = 1.8 Hz, 1H); 7.20 (bs, 1H, exchangeable). FAB HRMS calcd for $C_{11}H_{14}NO_2$ (MH^+): 192.1025. Found: 192.1025.

3-Hydroxy-2-[*N*-(toluenesulfonyl)pyrrol-3-yl]cyclohex-2-enone (27). This reaction was performed numerous times. The 3-position substitution has been the major component under most conditions attempted. The cleanest reaction occurred using hexafluorobenzene at reflux with 1 mol % of the dirhodium tetraacetate. No cycloaddition product was observed. R_f = 0.68, cream colored solid, mp 105 °C. ^1H NMR (DMSO-d_6): δ 1.81 (m, 2H); 2.35 (s, 3H); 2.40 (m, 2H); 2.48 (m, 2H); 6.80 (dd, J = 3.3, 1.5 Hz, 1H), 7.18 (dd, J = 3.0, 2.4 Hz, 1H); 7.42 (d, J = 8.1 Hz, 2H); 7.57 (d, J = 2.4 Hz, 1H); 7.79 (d, J = 8.4 Hz, 4H); 11.25 (bs, 1H, exchangeable). ^{13}C NMR (DMSO-d_6): δ 20.00, 21.00, 23.64, 80.76, 107.86, 113.88, 116.30, 118.90, 119.12, 121.12, 126.60, 130.26, 135.52, 145.16, 191.29. FAB MS: 332 (MH^+). HR FAB MS calcd for $C_{17}H_{17}NO_4S$ (MH^+): 332.1876. Found: 332.1881.

3-Hydroxy-2-(*N*-phenylpyrrol-3-yl)cyclohex-2-enone (28). Method b: R_f = 0.45, cream colored solid, 328 mg, 72%, mp 194 °C dec; ^1H NMR (DMSO-d_6): δ 1.89 (m, 2H); 2.47 (m, 4H); 6.65 (dd, J = 3.0, 1.2 Hz, 1H); 7.20 (m, 2H); 7.45 (m, 4H); 7.60 (t, J = 1.8 Hz, 1H), 10.75 (bs, 1H, exchangeable). ^{13}C NMR (DMSO-d_6): δ 21.19, 24.36, 37.77, 109.77, 112.19, 116.85, 117.71, 118.33, 118.94, 124.85, 129.76, 140.11, 164.33, 193.89.

Anal. Calcd for $C_{16}H_{15}NO_2 \cdot H_2O$: C, 70.85; H, 5.75; N, 5.17. Found: C, 71.25; H, 5.75; N, 4.87. FAB MS: 254 (MH^+).

2-[*N*-(4-Fluorophenyl)pyrrol-3-yl]-3-hydroxycyclohex-2-enone (29). Method c: $R_f = 0.45$, cream colored solid, 348 mg, 59%, mp 191 °C. ^1H NMR: δ 2.08 (m, 2H); 2.47 (m, 4H); 3.80 (bs, 1H); 6.33 (t, $J = 2.1$ Hz, 1H); 7.10 (m, 4H); 7.35 (m, 2H). ^{13}C NMR: δ 20.03, 32.21 (b), 111.38, 111.72, 114.04, 116.19, 116.49, 119.71, 120.87, 122.30 ($J = 34$), 136.68, 159.17, 162.10 ($J = 247$), 190.13. FAB MS 272 (MH^+). Anal. Calcd for $C_{16}H_{14}NO_2F \cdot 0.75H_2O$: C, 67.48; H, 5.49; N, 4.92. Found: C, 67.65; H, 5.10; N, 4.78.

2-[*N*-(4-Fluorophenyl)pyrrol-2-yl]-3-hydroxycyclohex-2-enone (30). Method c: $R_f = 0.25$, bright yellow solid, 177 mg, 30%, mp 163 °C. ^1H NMR: δ 2.09 (m, 2H); 2.58 (m, 4H); 6.31 (t, $J = 1.8$ Hz, 1H); 6.35 (t, $J = 2.1$ Hz, 1H); 6.65 (bs, 1H, exchangeable); 7.01 (t, $J = 2.1$ Hz, 1H); 7.10 (m, 2H); 7.34 (dd, $J = 8.7$, 4.5 Hz, 2H). ^{13}C NMR: δ 21.01, 28.01, 36.78, 110.41, 11.40, 116.10, 116.22, 116.50 ($J = 36$), 119.62, 121.01, 122.23 ($J = 6.3$), 122.32 ($J = 6.3$), 160.11, 162.32 ($J = 245$), 193.43. FAB MS 272 (MH^+). HR FAB MS cacld for $C_{16}H_{15}NO_2F$: 272.1087. Found: 272.1076.

3-Hydroxy-2-[*N*-(4-methoxyphenyl)pyrrol-3-yl]cyclohex-2-enone (31). Method b: The product precipitated from the reaction mixture and was collected by filtration, washed with diethyl ether, and placed under vacuum for 10 h. This afforded a cream colored solid, 203 mg, 66%, mp 181 °C dec. ^1H NMR: δ 2.03 (m, 2H); 2.58 (m, 4H); 3.83 (s, 3H); 6.29 (d, $J = 1.8$ Hz, 1H); 6.93 (d, $J = 8.7$ Hz, 2H); 7.05 (t, $J = 2.4$ Hz, 1H); 7.08 (t, $J = 2.4$ Hz, 1H); 7.30 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR: δ 20.34, 28.81, 36.33, 55.89, 110.79, 111.91, 113.41, 114.62, 115.97, 116.23, 119.68, 120.98, 132.59, 133.98, 157.85, 185.66, 193.42. FAB MS 284 (MH^+), 283 ($M^{+\bullet}$) Anal. Calcd for $C_{17}H_{17}NO_3 \cdot 1.25H_2O$: C, 66.76; H, 6.43; N, 4.58. Found: C, 66.60; H, 5.66; N, 4.05.

3-Hydroxy-2-(thien-3-yl)cyclohex-2-enone (33). Method b: $R_f = 0.21$, 396 mg, 94%, cream colored solid, mp 186 °C dec. Reaction time was reduced to 15 min and product was collected by filtration. No column chromatography was necessary for analytically pure material. ^1H NMR ($CDCl_3$ + 1 drop DMSO-d_6): δ 1.80 (m,2H); 2.41 (m, 4H); 6.84 (dd, $J = 5.1$, 3.3 Hz, 1H); 7.05 (dd, $J = 0.9$, 5.1Hz, 1H); 7.38 (dd, $J = 0.9$, 3.3 Hz, 1H); 10.42 (bs, 1H). ^{13}C NMR ($CDCl_3$ + 1 drop DMSO-d_6): δ 20.00, 39.51, 111.13, 126.83, 127.29, 127.60, 131.66, 181.27, 193.11. CI MS 195 (MH^+). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.84; H, 5.21.

2-(2,5-Dimethylthien-3-yl)-3-hydroxycyclohex-2-enone (34). Method b: $R_f = 0.21$, amber oil, 318 mg, 66%. ^1H NMR: δ 2.06 (m, 2H); 2.19 (s, 3H); 2.41 (s, 3H); 2.48 (m, 2H); 2.60 (m, 2H); 6.18 (bs, 1H); 6.42 (s, 1H). Electrospray MS 223 (MH^+). FAB HRMS calcd for $C_{12}H_{14}O_2S$ (MH^+): 223.0793. Found: 223.0795.

3-Hydroxy-2-[(5-methylthien-2-yl)methyl]cyclohex-2-enone (35). Method b: $R_f = 0.57$, pale yellow oil, 62 mg, 13%. ^1H NMR: δ 2.00 (m, 2H), 2.37 (m, 2H); 2.43 (m, 2H); 2.48 (s, 3H); 4.95 (s, 2H); 5.49 (s, 1H, exchangeable); 6.64 (dd, $J = 3.6$, 0.9 Hz, 1H); 6.89 (d, $J = 3.6$ Hz, 1H). ^{13}C NMR: δ 15.32, 21.09, 28.98, 36.67, 65.19, 103.25, 125.05, 128.35, 134.33, 162.14, 178.23, 195.66. HRMS calcd for $C_{12}H_{15}O_2S$: 223.07927. Found: 223.07927.

3-Hydroxy-2-(4-methylthien-2-yl)cyclohex-2-enone (36). Method b: $R_f = 0.60$, cream colored solid, 405 mg, 90%, mp 204–206 °C dec. Product was collected by filtration and column chromatography was not neccessary. ^1H NMR: δ 2.09 (m, 2H); 2.27 (s, 3H); 2.58 (m, 2H); 2.63 (m, 2H); 6.71 (bs, 1H, exchangeable); 6.81 (d, $J = 0.8$ Hz, 1H), 7.02 (d, $J = 0.8$ Hz, 1H). CI MS 209 (MH^+). IR ($CHCl_3$): 2939, 1566, 1360, 1317, 1260, 1175, 954, 841 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2S$: C, 62.75; H, 5.70; S, 15.39. Found: C, 62.75; H, 5.70; S, 14.02. HRMS calcd for $C_{11}H_{13}O_2S$: 209.06354. Found: 209.06353.

2-(4-Methoxythien-3-ylidene)cyclohexane-1,3-dione (37). Method b: $R_f = 0.25$, light purple solid, 448 mg, 92%, mp 114 °C. ^1H NMR: δ 1.96 (m, 2H); 2.59 (m, 4H); 3.73 (s, 2H); 3.96 (s, 3H); 7.84 (s, 1H). ^{13}C NMR: δ 18.76, 37.80, 37.99, 39.55, 59.63, 105.92, 119.18, 182.44, 183.57, 195.89, 197.80. FAB MS m/z 225 (MH^+). Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 59.00; H, 5.41.

3-Hydroxy-2-(4-methoxythien-3-yl)cyclohex-2-enone (38). DMSO-d_6 was added to the NMR tube and allowed to stand at rt for 5 h. Complete conversion was realized and the $CDCl_3$ was removed *in vacuo*. ^1H NMR (DMSO-d_6): δ 1.88 (m, 2H); 2.48 (m, 4H); 3.66 (s, 3H); 6.30 (s, 1H); 7.28 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 19.85, 32.04, 39.21, 56.59, 95.57, 107.46, 109.03, 117.56, 133.51, 156.78, 186.41.

3-Hydroxy-2-(5-methoxythien-2-yl)cyclohex-2-enone (39). Method b (reaction time reduced to 3.5 h): $R_f = 0.21$, cream colored solid, 396 mg, 81%, mp 175 °C. The solid was collected by filtration and needed no further purification. ^1H NMR: δ 2.09 (m, 2H); 2.49 (m, 2H); 2.64 (m, 2H); 3.90 (s, 3H); 6.17 (d, $J = 3.90$ Hz, 1H); 6.63 (d, $J = 3.90$ Hz, 1H); 6.78 (s, 1H, exchangeable). ^{13}C NMR: δ 19.97, 29.88, 36.40, 59.80, 103.62, 110.04, 117.34, 126.00, 162.11, 168.25, 194.86. CI MS 225 (MH^+). Anal. Calcd for $C_{11}H_{12}O_3S \cdot 0.5H_2O$: C, 56.65; H, 5.57; S, 13.73. Found: C, 56.10; H, 5.14; S, 12.51.

2-Nitro-3a,6,7,8a-tetrahydro-5*H*-8-oxa-3-thiacyclopenta[*a*]inden-4-one (40). Method b: $R_f = 0.30$, 405 mg, 78%, yellow oil. This material darkens at room temperature, but ^1H NMR appears unchanged. ^1H NMR: δ 2.08 (m, 2H); 2.34 (m, 2H); 2.52 (m, 2H), 5.37 (d, $J = 10.2$ Hz, 1H); 6.25 (dd, $J = 10.2$, 3.3 Hz, 1H); 6.66 (d, $J = 3.3$ Hz, 1H). ^{13}C NMR: δ 21.01, 23.61, 35.82, 50.86, 92.71, 114.87, 120.38, 158.88, 177.99, 193.97. CI MS 240 (MH^+). FAB HRMS calcd for $C_{10}H_9NO_4S$ (MH^+): 240.0331. Found: 240.0331.

3-Hydroxy-2-(5-nitrothien-2-yl)cyclohex-2-enone (41). Method b: $R_f = 0.54$, tan solid, 102 mg, 19%, mp 106 °C. ^1H NMR: δ 2.11 (quintet, $J = 6.6$ Hz, 2H); 2.39 (t, $J = 7.5$ Hz, 2H); 2.6 (m, 2H); 5.60 (bs, 1H); 5.82 (d, $J = 6.0$ Hz, 1H); 6.96 (d, $J = 6.0$ Hz, 1H). ^{13}C NMR: δ 21.05, 23.23, 36.00, 54.48, 114.47, 115.89, 129.99, 142.01, 175.31, 193.39. CI MS 240 (MH^+). FAB HRMS calcd for $C_{10}H_9NO_4S$: 240.0331. Found: 240.0329.

4b,7,8,9a-Tetrahydro-6*H*-9-oxa-10-thiaindeno[1,2-*a*]inden-5-one (42). Method b: $R_f = 0.34$, white solid, 325 mg, 62%, mp 138 °C. ^1H NMR: δ 2.04 (dt, $J = 6.6$, 6.3 Hz, 2H); 2.38 (t, $J = 6.3$ Hz, 2H); 2.49 (t, $J = 6.6$ Hz, 2H); 5.33 (d, 9.3 Hz, 1H); 6.47 (d, $J = 9.3$ Hz, 1H), 7.12 (t, $J = 7.2$ Hz, 1H); 7.20 (d, $J = 7.5$ Hz, 1H); 7.29 (t, $J = 7.2$ Hz, 2H); 7.44 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR: δ 21.33, 23.90, 36.20, 95.10, 116.32, 122.37, 124.38, 126.84, 131.00, 134.89, 142.22, 177.63, 194.46. FAB MS m/z 245 (MH^+). FAB HRMS calcd for $C_{14}H_{12}O_2S$ (MH^+): 245.0636. Found: 245.0638.

4b,7,8,9b-Tetrahydro-6*H*-5-oxa-10-thiaindeno[2,1-*a*]inden-9-one (43). Method b: $R_f = 0.78$, white solid, 62 mg, 12%, mp 149 °C. ^1H NMR: δ 2.01 (m, 2H); 2.36 (t, $J = 6.3$ Hz, 2H); 2.48 (m, 2H); 5.20 (d, $J = 8.7$ Hz, 1H); 6.69 (d, $J = 8.7$ Hz, 1H); 7.08 (m, 1H); 7.18 (m, 2H); 7.75 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR: δ 21.18, 23.78, 36.71, 54.41, 95.94, 115.80, 121.40, 125.36, 126.75, 128.29, 137.07, 139.68, 177.24, 194.63. CI MS 245 (MH^+). FAB HRMS calcd for $C_{14}H_{12}O_2S$ (MH^+): 245.0636. Found: 245.0636.

2,3,3a,6,7,8a-Hexahydro-5*H*-1,8-dioxacyclopenta[*a*]inden-4-one (44). To a solution of rhodium acetate (13.2 mg, 0.03 mmol) in freshly-distilled dihydrofuran (2 mL) was added a solution of 2-diazo-1,3-cyclohexanedione (0.276 g, 2.0 mmol) in dihydrofuran (2 mL). The reaction mixture was stirred at room temperature for 20 h. Evaporation and purification by chromatography with 25% EtOAc/hexane afforded an oil (0.325g, 90%). ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, $J = 5.9$ Hz, 1H), 4.08 (m, 1H), 3.72 (m, 1H), 3.64 (m, 1H), 2.48 (m, 2H), 2.34 (m, 2H), 2.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 23.7, 30.3, 36.6, 43.8, 67.9, 112.8, 113.6, 177.5, 195.2; IR (neat) 2950, 2882, 1728, 1634, 1410, 1367, 1243, 949, 899, 808 cm^{-1}; MS (CI) m/e calcd for $C_{10}H_{12}O_3$: 180.0786, found 180.0787; 180, 165, 151, 137, 124, 109, 104, 96, 91, 84, 77, 73, 68, 61, 55.

2,3,6,7-Tetrahydro-2-butoxy-5*H*-1-oxainden-4-one (45). The reaction was performed with **1** (0.11 g, 0.79 mmol) and butyl vinyl ether (0.22 g, 1.58 mmol) in PhH (2 mL) in the presence of $Rh_2(OAc)_4$ (8 mg). The product was purified by chromatography with 1/3 EtOAc/hexane and a solid was isolated (58.4 mg, 31%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, $J = 7.6$ Hz, 1H), 7.28 (m, 1H), 7.04 (m, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 5.59 (d, $J = 8.8$ Hz, 1H), 4.35 (dd, $J = 11.0$, 4.9

Hz, 1H), 3.77 (dd, J = 11.0, 8.8 Hz, 1H), 3.62 (m, 1H), 2.47 (m, 2H), 2.36 (t, J = 6.7 Hz, 2H), 2.05 (m, 2H); IR (neat) 2924, 1628, 1488, 1467, 1402, 1376, 1339, 1239, 1181, 1114, 998, 909, 763, 730 cm^{-1}; MS (CI) m/e calcd for $C_{15}H_{14}O_3$: 242.0942, found 242.0937; 242, 214, 199, 186, 158, 118, 89, 77.

2,3,3a,6,7,8a-Hexahydro-5*H*-2,2-dimethyl-1,8-dioxa-3-oxocyclopenta[*a*]inden-4-one (46). To a solution of rhodium acetate (19.8 mg, 0.045 mmol) in 2,2-dimethyl-3(2*H*)-furanone (0.627 g, 6.0 mmol) in PhF (5 mL) was added a solution of **1** (0.414 g, 3.0 mmol) in PhF (2 mL). The reaction mixture was stirred at room temperature for 10 h. Evaporation and filtration through Celite with 25% EtOAc/hexane afforded a viscous oil which upon treatment with ether/hexane gave 359 mg (54%) of gummy solid. ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (d, J = 6.6 Hz, 1H), 3.95 (d, J = 6.6 Hz, 1H), 2.54–2.01 (m, 6H), 1.32 (s, 6H); IR (KBr) 2956, 1740, 1628, 1397, 1330, 1186, 1132, 1100, 915 cm^{-1}.

2,3,4,5,6,7-Hexahydro-4-oxo-1-oxaindene-2-spiro-5′-4′,5′-dihydrofuran-2′(3′*H*)-one (47). To a solution of rhodium acetate (19.8 mg, 0.045 mmol) in γ-methylene-γ-butyrolactone (1.40 g, 15.0 mmol) in PhF (5 mL) was added a solution of **1** (0.414 g, 3.0 mmol) in PhF (2 mL). The reaction mixture was stirred at room temperature for 10 h. Evaporation and purification by chromatography with 30% EtOAc/hexane afforded a white solid (0.431, 69%), mp 101–103 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.13–2.04 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.6, 174.4, 174.1, 116.7, 112.4, 36.1, 35.8, 32.8, 27.8, 23.2, 21.2; IR (KBr) 2963, 2943, 1791, 1642, 1408, 1347, 1294, 1250, 1168, 1135, 1035, 912 cm^{-1}.

2,3,4,4a,7,8-Hexahydro-6*H*-1,9-dioxacyclohexa[*a*]inden-5-one (48). To a solution of rhodium acetate (19.8 mg, 0.045 mmol) in 3,4-dihydro-2*H*-pyran (1.260 g, 15.0 mmol) in PhF (5 mL) was added a solution of **1** (0.414 g, 3.0 mmol) in PhF (2 mL). The reaction mixture was stirred at room temperature for 10 h. Evaporation and purification by chromatography with 30% EtOAc/hexane afforded an oil (0.340 g, 58%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (d, J = 7.7 Hz, 1H), 3.75 (m, 2H), 3.08 (m, 1H), 2.49–1.53 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.9, 176.0, 115.7, 106.3, 60.1, 36.2, 34.5, 23.3, 21.2, 19.9, 18.8; IR (neat) 2940, 1635, 1401, 1232, 1184, 1150, 1115, 1059, 1000, 919 cm^{-1}.

2,3,4,4a,7,8-Hexahydro-6*H*-2-methoxy-1,9-dioxacyclohexa[*a*]inden-5-one (49). To a solution of rhodium acetate (19.8 mg, 0.045 mmol) in 3,4-dihydro-2-methoxy-2*H*-pyran (1.70 g, 15.0 mmol) in PhF (5 mL) was added a solution of **1** (0.414 g, 3.0 mmol) in PhF (2 mL). The reaction mixture was stirred at room temperature for 10 h. Evaporation and purification by chromatography with 30% EtOAc/hexane afforded an oil (0.432 g, 64%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (d, J = 7.2 Hz, 1H), 4.74 (t, J = 5.3 Hz, 1H), 3.46 (s, 3H), 3.14 (m, 1H), 2.51–1.48 (m, 10H); IR (neat) 2939, 1637, 1454, 1403, 1233, 1184, 1118, 1038, 1000, 942 cm^{-1}.

2,3,4,4a,7,8-Hexahydro-6*H*-2-(acetoxymethyl)-3,4-diacetoxy-1,9-dioxacyclohexa[*a*]inden-5-one (50). The reaction was performed with **1** (0.414 g, 3.0 mmol) and D-triacetylglucal (1.630 g, 6.0 mmol) in PhF (5 mL) in the presence of $Rh_2(OAc)_4$ (19.8 mg). The product was purified by chromatography with 50% EtOAc/hexane. A white crystal was obtained (0.389 g, 34%), mp 104–105 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.06 (d, J = 7.8 Hz, 1H), 5.44 (t, J = 4.1 Hz, 1H), 4.93 (dd, J = 8.3, 3.9 Hz, 1H), 4.20 (d, J = 5.4 Hz, 2H), 3.78 (m, 1H), 3.39 (m, 1H), 2.50 (m, 2H), 2.33 (m, 2H), 2.07 (s, 6H), 2.05 (m, 2H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 20.8, 21.0, 23.6, 36.7, 40.1, 63.4, 67.5, 68.9, 69.0, 104.4, 112.8, 169.2, 169.5, 170.6, 176.6, 194.1; IR (neat): 2952, 1744, 1642, 1383, 1235, 1129, 1039, 893 cm^{-1}; MS (CI) m/e calcd for $C_{18}H_{22}O_9 + H^+$: 383.1342, found 383.1343; 400 ($M + NH_4$), 383 ($M + H$), 325, 281, 265, 203, 156, 100.

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Supplementary Material Available: Table of predicted ^{13}C NMR chemical shifts for **11–13**; ^1H NMR spectra of compounds whose elemental compositions were determined by HRMS (26 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.

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