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## Diels-Alder Cycloadditions of 2-Pyrones and 2-Pyridones

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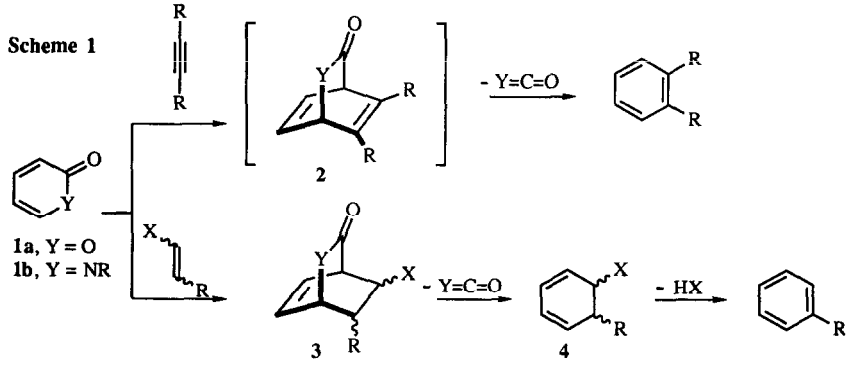
## I. INTRODUCTION

Because 2-pyrone (**1a**) and 2-pyridone (**1b**) dienes have some aromatic character, they undergo Diels-Alder [4+2] cycloadditions less easily than do most cyclic conjugated dienes. Nevertheless, suitable reaction conditions have been developed so that these monoheterocyclic dienes **1a** and **1b** can be used effectively in [4+2] cycloadditions with alkynes and with alkenes. Cycloaddition with alkynes generates initially highly strained bicyclooctadienes that readily undergo extrusion of the 2-atom hetero bridge to form aromatic products (Scheme 1). Cycloaddition with alkenes generates initially more stable and sometimes isolable bicyclooctenes **3** that are structurally and stereochemically rich compounds useful as versatile synthetic intermediates. Extrusion of the 2-atom hetero bridge leads to dihydrobenzenes **4** and often ultimately to aromatic products *via* loss of HX (Scheme 1). Because 2-pyrones are more readily available than 2-pyridones and because 2-pyrones undergo milder Diels-Alder cycloadditions than do 2-pyridones, this review begins with 2-pyrones. Discussion centers on the bicyclic intermediates **2** and **3** in Scheme 1 and on the corresponding aromatic products, with emphasis first on synthetic aspects and then on structure-reactivity relationships in the dienes and dienophiles leading to bicycloadducts **2** and **3**. A separate section is devoted to $^1$H NMR spectroscopic characterization of bicyclooctenes **3**.

**Scheme 1**




## II. SYNTHETIC ASPECTS.

### A. 2-PYRONES.

#### 1. [4+2] Cycloadditions: 2-Pyrones as Dienes.

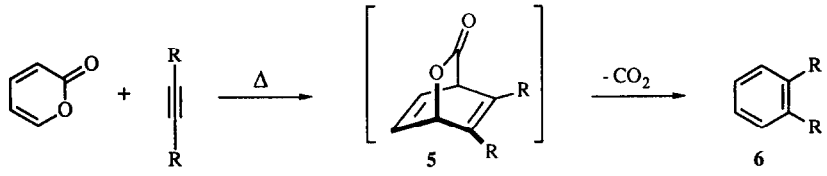
In 1931, three years after they first reported the [4+2] cycloaddition between dienes and dienophiles, Diels and Alder published that 2-pyrones could function as the diene component.[1] After this report, the cycloaddition between 2-pyrone dienes and various dienophiles was occasionally implemented and was the partial subject of a review by Shusherina in 1974.[2] However, during the past two decades, the use of Diels-Alder cycloadditions of 2-pyrones has emerged as a powerful tool in the synthetic chemist's arsenal. Up until the early 1970's, the use of these cycloadditions was restricted almost exclusively to synthesis of aromatic compounds. More recently, it was recognized that the initially formed bicycloadducts (from olefinic dienophiles), if isolable, could serve as a valuable source of opulently functionalized compounds formed with excellent control of relative and absolute stereochemistry. A review of the literature on this topic at this juncture, therefore, is appropriate. Original papers that were discussed in the Shusherina review will be omitted from this article, with only a few exceptions.

##### a. With Alkynes.

###### i. Symmetrically Substituted Alkynes.

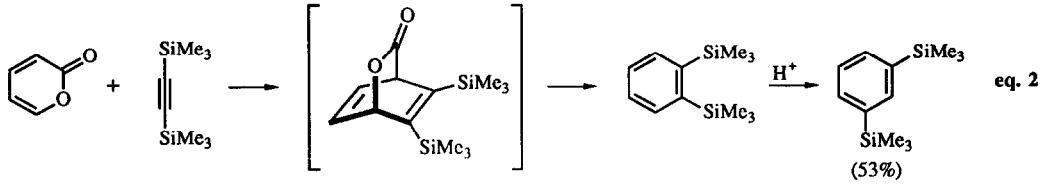
In 1937, Alder and Rickert reported that aromatic products could be obtained from 2-pyrones and acetylenic dienophiles.[3] Under the conditions of cycloaddition, the $CO_2$ bridge was extruded from the initial Diels-Alder adduct **5** to afford readily the corresponding aromatized products **6** (eq. 1). There have not been any reported examples of the isolation of bicyclic dienes of type **5** due to the highly strained nature of such compounds. However, a wide variety

of aromatic compounds have been synthesized by this method. Both stereocenters that are formed in the initial nonisolable bicycloadduct are destroyed en route to the final aromatic product; therefore, the issue of facial selectivity in the cycloaddition will be discussed later in this review. A theoretical, mechanistic study of the cycloaddition between 2-pyrone and acetylene has been reported.[4]



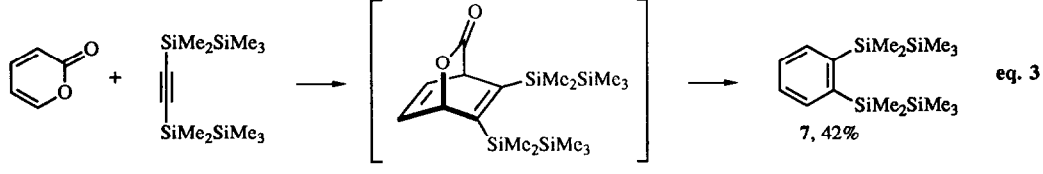

eq. 1

Disubstituted aromatic compounds have been synthesized by the cycloaddition between a 2-pyrone diene and a host of acetylenic dienophiles.[5] It was found that the steric nature of the substituents on the disubstituted acetylene greatly influenced the process outlined in equation 2. Steric interaction in the desired 1,2-disubstituted benzenes can result in rearrangements, leading to changes in the substitution pattern on the aromatic ring. The presence of trace amounts of acid from the reaction solvent (bromobenzene, 150°C) was responsible for the observed isomerizations. The 1,3- and 1,4-disubstituted benzenes were most readily formed when bis(trimethylsilyl)acetylene was used as the dienophile. In all cases, only 1,2-disubstituted aromatic products were isolated when the cycloadditions were conducted in the presence of triethylamine. Moreover, these steric interactions can be severe enough so as to preclude reaction of 2-pyrone and the acetylenic dienophile altogether.



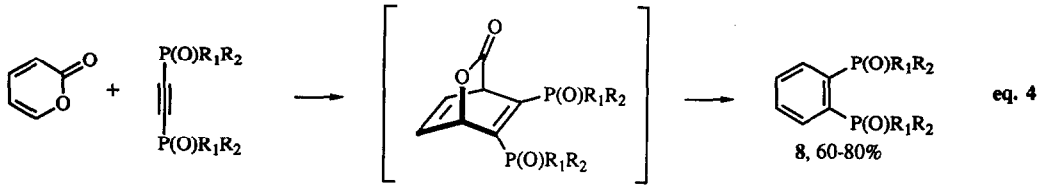

eq. 2

Likewise, a modification of this procedure has been used to prepare 1,2-bis(pentamethyldisilanyl)benzene **7** (eq 3).[6] In this case, the 2-pyrone diene functioned also as the solvent, and under refluxing conditions the desired 1,2-disubstituted benzene was isolated. It was essential to employ extremely pure 2-pyrone as well as bis(pentamethyldisilanyl)acetylene; otherwise, the corresponding 1,3-bis(pentamethyldisilanyl)benzene was formed as a major contaminant.



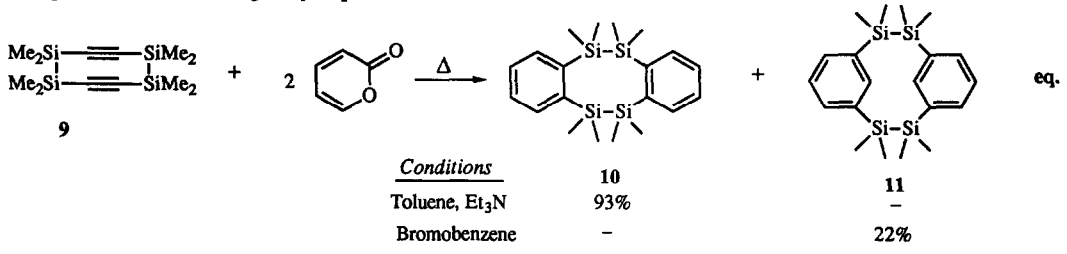

eq. 3

A similar strategy was employed in the synthesis of 1,2-diphosphorylbenzenes **8** (eq. 4).[7] These products resulted from the Diels-Alder cycloaddition between 2-pyrone and diphosphorylacetylenes in 1,2-dichlorobenzene at 180°C for 3-4 hours. Isolated yields ranged from 60-86%; moreover, it appeared that the corresponding 1,3- and 1,4-diphosphorylbenzenes were not formed. This methodology has been expanded by utilizing different mono and disubstituted 2-pyrones.[8] Likewise, the 1,2-diphosphorylbenzenes were isolated in 62-90% yields.



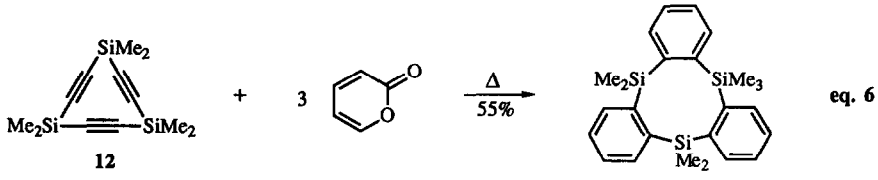

eq. 4

In addition, this protocol has been used in the synthesis of cyclophanes.[9] For example, tetrasilyl diyne dienophile **9** cycloadded with 2 equivalents of 2-pyrone in toluene (containing triethylamine) to afford the [2.2]orthocyclophane **10** (eq. 5). When the reaction was conducted in bromobenzene, [2.2]metacyclophane **11** was isolated. In fact, the [2.2]metacyclophane was formed in 12% yield by prolonged heating of the [2.2]orthocyclophane **10** in bromobenzene at 200°C. The [2.2]paracyclophane was never isolated. Soon thereafter, this methodology was used again to form tris-bridged cyclophane **13**.[10]




| *Conditions* | **10** | **11** |
|---|---|---|
| Toluene, $Et_3N$ | 93% | – |
| Bromobenzene | – | 22% |

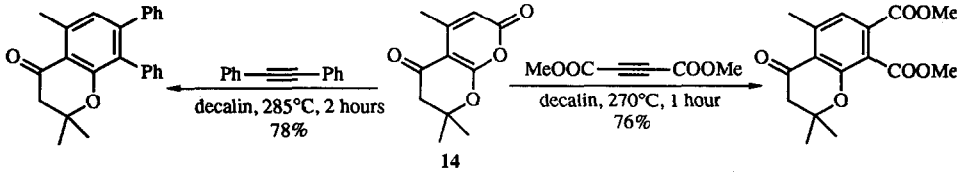
eq. 5




eq. 6

Highly reactive cyclooctynes[11,12] and cyclooctyne equivalents[13] have readily cycloadded also with 2-pyrone to form aromatic compounds after loss of $CO_2$. A rapid entry to 4-chromanones has been developed.[14] The direct precursor to these compounds was pyrone diene **14**, prepared by the base catalyzed dimerization of 6-hydroxy-4-methyl-2-pyrone. Two examples were given in which symmetrical alkynes served as the dienophile component (Scheme 2).

**Scheme 2**

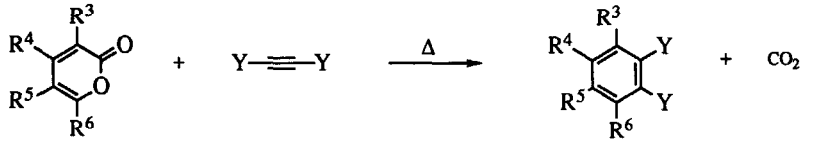



As seen from the previous example, a rapid entry into substituted phthalates could be achieved by cycloaddition of dialkyl acetylenedicarboxylates with 2-pyrone dienes. Indeed, implementation of this protocol has resulted in the synthesis of a host of highly substituted phthalates. A synopsis of this work is given in tabular form (Table 1). Homophthalates are prepared when allene dienophiles are cycloadded with 2-pyrones (see section 1c).

**ii. Unsymmetrically Substituted Alkynes.**

The question of regiochemistry is moot in the [4+2] cycloaddition between symmetrical dienophiles and

**Table 1**



| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Y | Yield | Ref. |
|---|---|---|---|---|---|---|
| H | OMe | H | Me | COOMe | ~ 65% | 16 |
| H | $OPr^i$ | H | Et | COOMe | ~ 65% | 16 |
| H | OMe | H | OMe | COOMe | 70% | 17 |
| H | OTMS | H | OTMS | COOMe | 48% | 17 |
| H | OAc | H | OMe | COOMe | 73% | 17 |
| H | Me | H | OMe | COOMe | 35-95% | 18 |
| H | COOMe | H | OMe | COOMe | | 18 |
| H | $Bu^t$ | H | OMe | COOMe | | 18 |
| H | Ph | H | OMe | COOMe | 95% | 18 |
| Me | Me | H | OMe | COOMe | 35% | 18 |
| H | OH | H | Ph | COOEt | 81% | 19 |
| H | OMe | H | Ph | COOEt | 89% | 19 |
| H | COOMe | H | $CF_3$ | H | 91% | 20 |
| H | COOMe | H | $CF_3$ | COOMe | 67% | 20 |

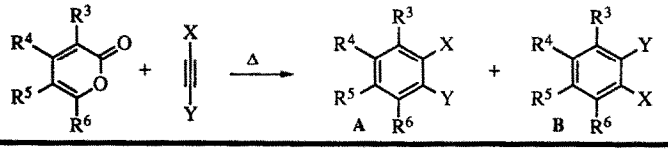
| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Y | Yield | Ref. |
|---|---|---|---|---|---|---|
| H | Me | C(O)Me | OMe | COOMe | 93% | 21, 22 |
| OH | H | H | H | COOMe | 95% | 23, 24 |
| OMe | H | H | H | COOMe | 74% | 25 |
| H | H | H | H | COOMe | 84% | 26 |
| COOMe | H | H | H | COOMe | 92% | 26 |
| H | COOMe | H | H | COOMe | 95% | 26 |
| H | H | COOMe | H | COOMe | 48% | 26 |
| H | H | H | COOMe | COOMe | 73% | 26 |
| H | Me | COOEt | Me | COOEt | 96% | 26 |
| OMe | H | H | H | COOMe | 96% | 26 |
| H | Me | H | OMe | COOMe | 100% | 26 |
| OTMS | H | H | H | COOMe | 95% | 26 |

20 additional examples of substituted 4-hydroxy- and 4-methoxy-2-pyrones cycloadding with dimethyl acetylenedicarboxylate to[26] form the corresponding phthalates; 33 - 97%

pyrone dienes; however, with unsymmetrical dienophiles two different regioisomers can be obtained. The results of a study of the Diels-Alder cycloaddition between a variety of substituted 2-pyrones and four different acetylenic dienophiles is summarized in Table 2, entries 9-16.[15] The resulting regioisomeric aromatic products were not separated from each other, and in each case the chemical yields corresponded to a purified mixture of the two regioisomers. The regioisomeric ratios were determined from integration of appropriate $^1$H NMR resonances.

Dramatic regiocontrol enhancement was observed in the case of entry 16 over both entries 10 and 13. Likewise, a similar advantage was seen for entry 17 over entries 11 and 14. These results led to the conclusion that the superb regiocontrol was due to secondary orbital interactions of the 6-methylthio moiety in the transition state. In addition, the polarization of the pyrone ring, based on calculated charge densities, can be used to predict the same results as FMO. A more detailed analysis of the influence exerted by substituents on the regioselectivity of cycloadditions is presented in Section III.

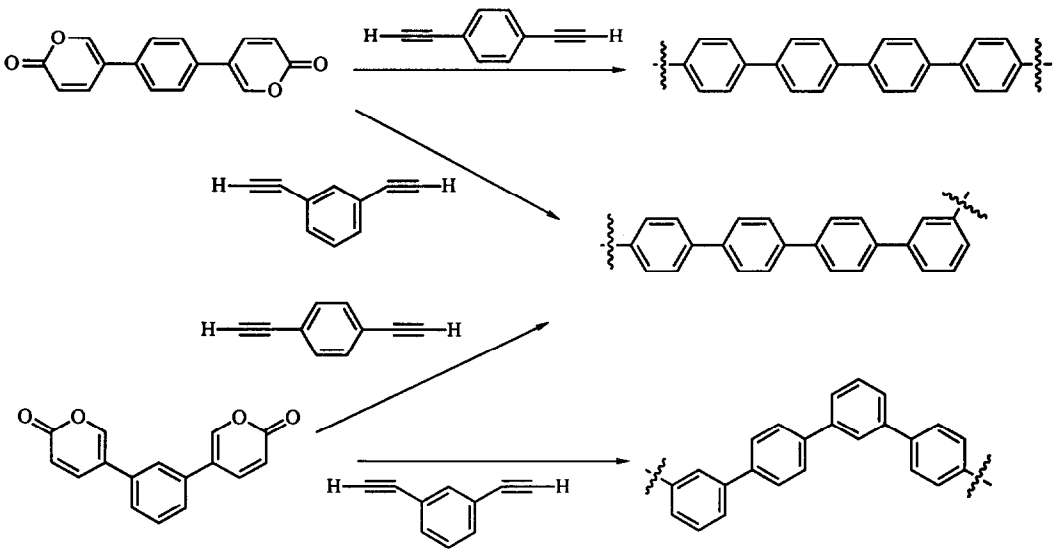
**Table 2**



| entry | $R^3$ | $R^4$ | $R^5$ | $R^6$ | X | Y | A | B | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | Me | H | OMe | H | COOMe | >35% | --- | 18 |
| 2 | H | OMe | H | Ph | H | COOEt | --- | 91% | 19 |
| 3 | H | OMe | H | OMe | H | COOMe | 70% | --- | 17 |
| 4 | H | Me | C(O)Me | OMe | H | COOMe | 56% | 28% | 21, 22 |
| 5 | H | H | alkyl | H | H | C(O)Me | 52% | 43% | 27 |
| 6 | H | Et | Me | Me | H | Ph | 1 : 4 | | 15 |
| 7 | H | Me | COOEt | Me | H | Ph | 1 : 4 | | 28 |
| 8 | H | OMe | C(O)Me | Me | H | COOEt | 50% | 34% | 29 |
| 9 | H | Et | Me | Me | *i*-Pr | COOEt | 85% (90:10) | | 15 |
| 10 | H | Et | Me | Me | H | COOEt | 86% (61:39) | | 15 |
| 11 | H | Et | Me | Me | H | C(O)Me | 95% (52:48) | | 15 |
| 12 | Me | Et | H | Me | *i*-Pr | COOEt | 86% (75:25) | | 15 |
| 13 | H | Et | Me | H | H | COOEt | 72% (52:48) | | 15 |
| 14 | H | Et | Me | H | H | C(O)Me | 61% (80:20) | | 15 |
| 15 | H | Et | Me | SMe | *i*-Pr | COOEt | 83% (94:6) | | 15 |
| 16 | H | Et | Me | SMe | H | C(O)Me | 75% (90:10) | | 20, 30 |
| 17 | H | Et | Me | SMe | H | COOEt | 95% (>95:5) | | 20, 30 |
| 18 | H | COOMe | H | $CF_3$ | H | Ph | 39% (3 : 2) | | 31 |
| 19 | H | COOMe | H | $CF_3$ | Me | $NEt_2$ | ----- | 68% | 32 |
| 20 | H | Me | H | Me | H | COOMe | 77% (4 : 1) | | |
| 21 | H | Ph | H | H | H | Ph | 69% (33: 67) | | |

A similar argument invoking FMO interaction was used to predict correctly the regiochemical outcome of the cycloaddition of phenyl acetylene with various phenyl or carboxyl substituted 2-pyrones.[32] These results were applied in the synthesis of polyphenylenes *via* [4+2] cycloadditions with diethynylbenzenes (Scheme 3).[33]

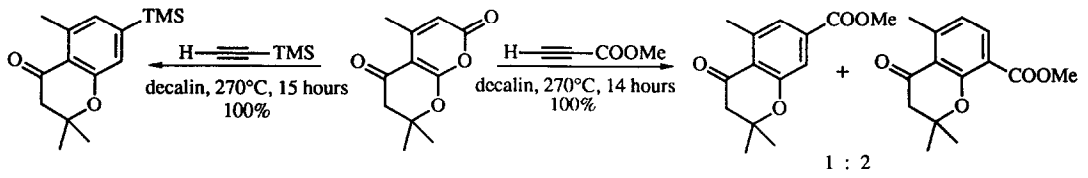
**Scheme 3**



As a general phenomenon, prediction of the regiochemical outcome of such cycloadditions is most accurate when the diene and dienophile components are electronically compatible. In most cases, these dienes cycloadd in a facile manner with complete regiocontrol, barring severe steric factors, whereas the corresponding unsubstituted parent 2-pyrone reacts much more sluggishly and with poorer regiocontrol. Moreover, the examples in the preceding paragraph, in which the regiochemistry could not be predicted in such a manner, utilized pyrone dienes that were not appropriately substituted in terms of electronic compatibility with the dienophile. Indeed, although the pyrones in entries 4, 7, and 8 possessed very electron withdrawing groups in the 5-position, the dienophile counterpart was not electronically compatible (*i.e.* electron rich).

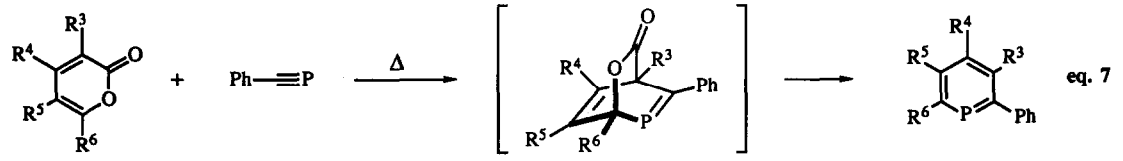
This methodology has been employed widely in the preparation of regiospecifically substituted aromatic compounds. For example, in the synthesis of 4-chromanones (Scheme 4), unsymmetrical alkyne dienophiles were used also.[14] The pyrone diene ring was not optimized in terms of electronic compatibility with the dienophile; therefore, the starting pyrone **14** and methyl propiolate cycloadded with concomitant $CO_2$ extrusion, and a regioisomeric mixture of adducts was obtained. In addition, trimethylsilylacetylene quantitatively formed a single aromatic regioisomer. Steric interaction between the acetylenic dienophile and the *geminal* dimethyl moiety of the pyrone diene was probably responsible for dictating the excellent regiochemical outcome of this cycloaddition process.

**Scheme 4**



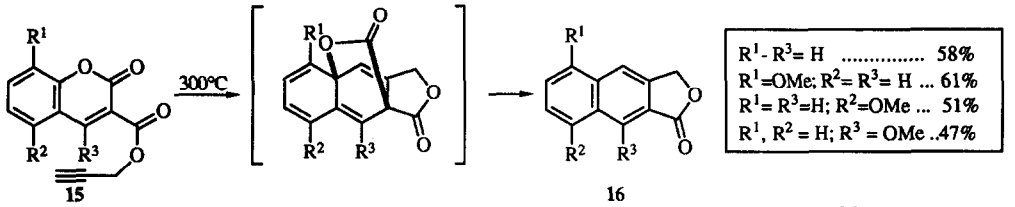

**14**

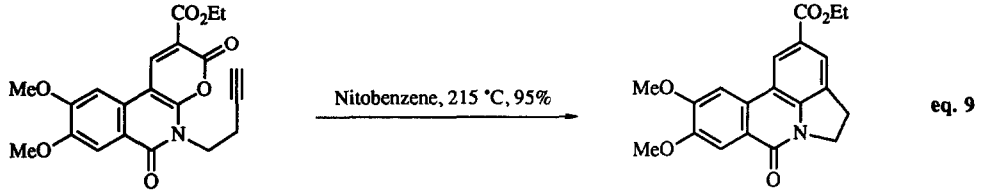
The synthesis of regioisomerically pure phosphabenzenes has been accomplished, albeit in poor yield (9-16%), by the cycloaddition between an *in situ* generated phosphaalkyne and five different hindered phenyl substituted 2-pyrones.[34]




The cycloaddition between methyl coumalate and trichlorosilylacetylene gave a 90% yield of a regioisomeric mixture consisting of two aromatic products.[35] Methyl 4-trichlorosilylbenzoate and methyl 3-trichlorosilylbenzoate were formed in a 45:55 ratio, respectively. As seen with symmetrically substituted disilylacetylene dienophiles (*vide supra*), adventitious acid-promoted migration of the trichlorosilyl group after aromatization could well be the culprit for such poor regioselectivity in this case.

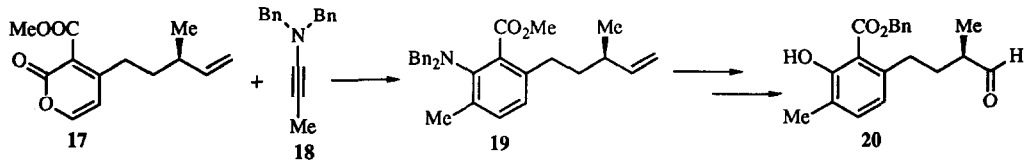
At 300°C, the intramolecular Diels-Alder cycloaddition of coumarin esters **15** provided the corresponding substituted naphthalenes **16** (eq. 8).[36] A similar approach was employed for an entry to Amaryllidaceae alkaloids (eq. 9).[37]

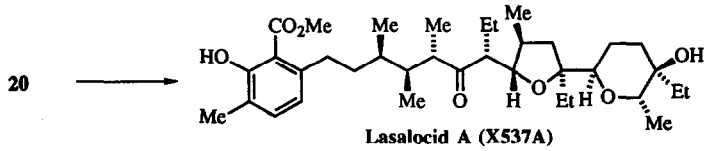



A facile entry to substituted anilines was achieved by [4+2] cycloaddition of an electron poor pyrone diene with an electron rich ynamine.[38] Indeed, this strategy has been used as a key step in the preparation of the left side of Lasalocid A (X537A).[39-41] Electron poor pyrone diene **17** was reacted with amino acetylene **18** in refluxing benzene to give the appropriately substituted aniline **19** as the sole regioisomer in 60-80% yield (Scheme 5). Various functional group manipulations afforded aldehyde **20** in 48% yield which was coupled with the the right side synthon *via* an aldol reaction to produce the desired Lasalocid A (X537A) in 34% yield.

Scheme 5






**Lasalocid A (X537A)**

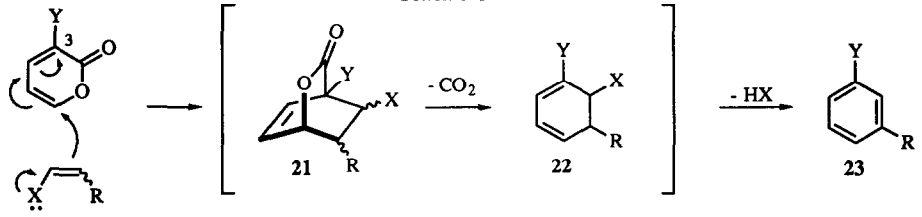
Pyrano[3,4-b]indol-3-ones have been used as pyrone dienes in this type of Diels-Alder reaction. These functioned as indolo-2,3-quinodimethane equivalents. In 1989, this work was the subject of a separate review article.[42] Since that time, the library of pyrone dienes has been expanded to include, for example, pyrano[3,4-*b*]pyrrol-5(1*H*)-ones (80),[43] pyrano[4,3-*b*]indol-3-ones (81),[44,45] pyrano[3,4-*b*]indol-3-ones (82),[46,47] benzothieno [2,3-*c*]-pyran-3-ones (83),[46] benzothieno [3,2-*c*]-pyran-3-ones (84),[48] thieno[2,3-*c*]-pyran-3-ones (85),[49] and thieno[3,2-*c*]-pyran-3-ones (86).[49] Most of the cycloadditions with these pyrone dienes utilized acetylenic dienophiles; however, occasionally olefinic dienophiles were used.

**b. With Alkenes.**

**i. Aromatic Products.**

The bicycloadducts **21** from 2-pyrones and dienophilic alkenes are generally much more stable than the diene cycloadducts formed from alkyne dienophiles. In fact, many examples of isolable regiochemically homogeneous bicycloadducts **21** exist (*vide infra*). However, these bicycloadducts **21** are still thermally labile, although to a lesser extent than diene bicycloadducts, and $CO_2$ extrusion can occur at temperatures as low as 60°C (Scheme 6). After $CO_2$ extrusion has occurred, a second molecule (HX) must also be eliminated from the resulting cyclohexadiene **22** in order to form 1,3-disubstituted aromatic products **23**. Many times this elimination takes place *in situ*; however, base can facilitate the process.

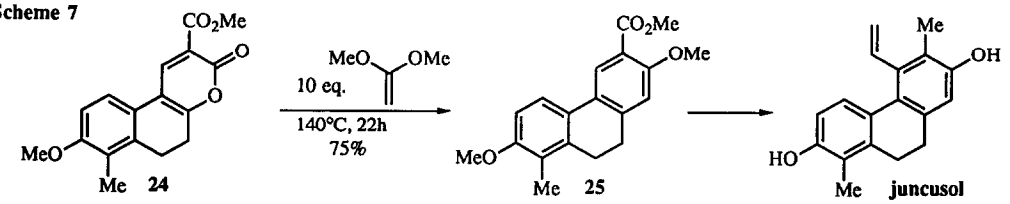
Scheme 6



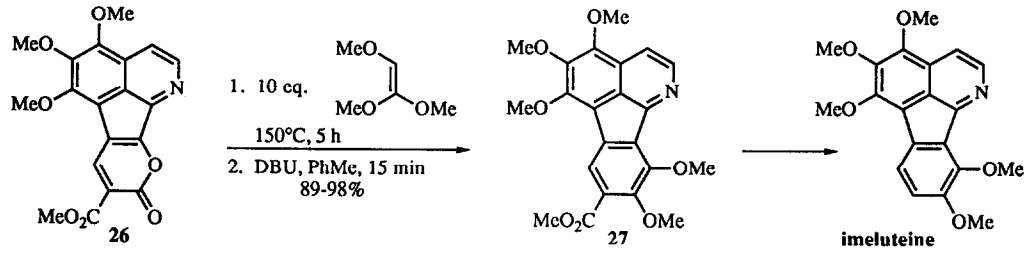

Y=electron withdrawing group
X=electron releasing group

Regioisomeric control for this cycloaddition can be explained in the same manner as that for the similar cycloadditions of 2-pyridones with olefins and acetylenic dienophiles (*vide infra*). Many researchers have also taken advantage of this phenomenon to create highly substituted aromatic products. Boger *et al* have concentrated on the inverse-electron-demand Diels-Alder cycloaddition, and they have incorporated electron rich olefin dienophiles as synthetic equivalents of acetylenic dienophiles.[50,51] They have made prolific contributions in this area as exemplified by the synthesis of sendaverine,[52] 6,7-benzomorphans,[52,53] juncusol (Scheme 7),[54,55] rufescine,[56] and imeluteine[56] (Scheme 8). Substituted pyrone **24** readily cycloadded with 1,1-dimethoxyethylene at 140°C to form the aromatized compound **25** in 75% yield, as the sole regioisomer that was converted into juncusol. Likewise, a similar strategy was utilized in the cycloaddition of pyrone **26** with 1,1,2-trimethoxyethylene to form **27** in excellent yield, which in turn led to imeluteine.

**Scheme 7**

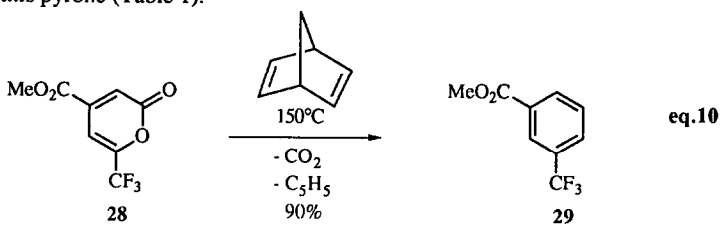



**Scheme 8**



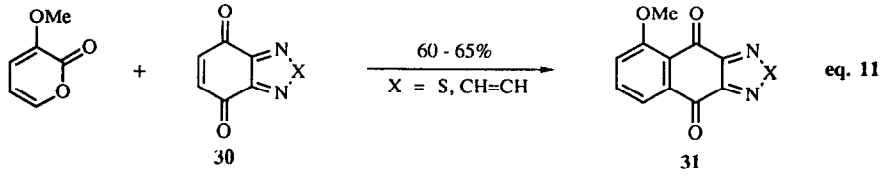

Enamines have been used as nucleophilic dienophiles in the inverse-electron-demand Diels-Alder reaction with substituted coumalates.[28] In all cases, only a single aromatic regioisomer was formed. However, by judicious choice of the starting enamines, the separate formation of both possible regioisomers was possible. Under milder conditions, dihydrobenzenes were also isolated from this reaction (*vide infra*). When the electron deficient dienophile was nitrostyrene, which was not electronically compatible with the electron poor pyrone diene, a regioisomeric mixture of aromatic compounds was obtained.

Pyrone diene **28** reacted also with an acetylene equivalent, norbornadiene, to produce substituted aromatic compound **29** in 90% after elimination of $CO_2$ and cyclopentadiene (eq. 10).[20,30] This complements the reaction of acetylene itself with this pyrone (Table 1).




**eq.10**

The normal-electron-demand [4+2] cycloaddition between 3-methoxy-2-pyrone and quinones **30** afforded anthraquinone analogs **31** in good yields (eq. 11).[57] It is interesting to note that these regiospecific cycloadditions failed when 3-hydroxy-2-pyrone was used as the diene component.

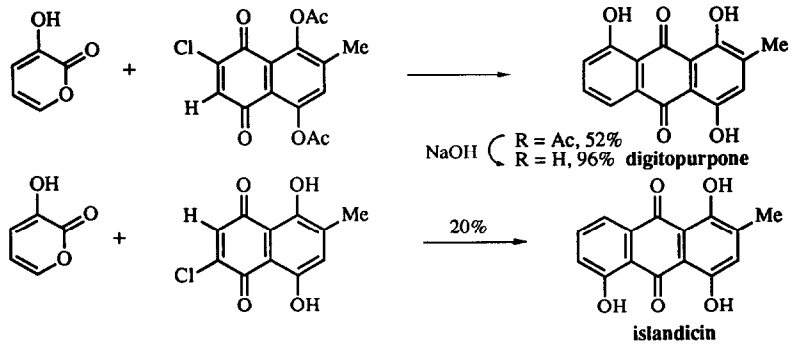



**eq. 11**

On the contrary, it was found that 3-hydroxy-2-pyrone cycloadded with a variety of substituted naphthazarines (*i.e.* quinones), albeit in poor yield.[58] This protocol allowed for the direct formation of the

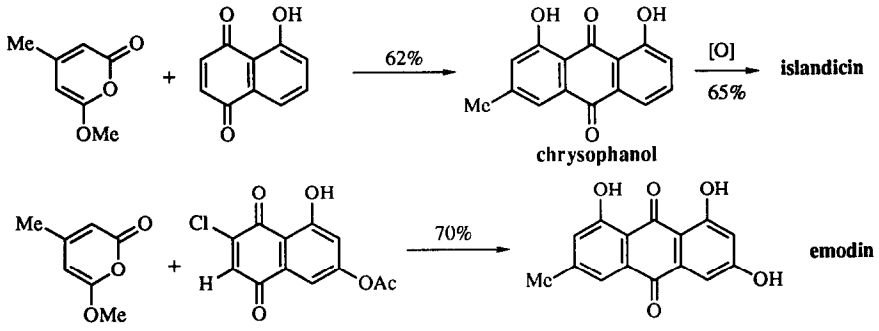
anthraquinones islandicin and digitopurpone (Scheme 9).

Scheme 9



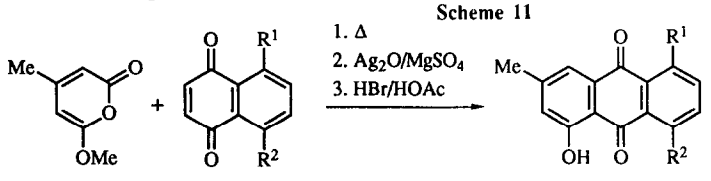

A similar approach was used in the synthesis of the anthraquinones chrysophanol, islandicin, and emodin (Scheme 10).[59] The pyrone diene precursor, 6-methoxy-4-methyl-2-pyrone, was easily prepared in an isotopically labelled fashion (4-$CD_3$ replacement of 4-$CH_3$); hence, the synthesis of these labelled anthraquinones was accomplished.

Scheme 10




This type of chemistry has also been used as a rapid entry to pachybasin, helminthosporin, and chrysophanol (Scheme 11).[22] Other substituted 2-pyrones were used as the diene counterpart with dienophilic quinones as an entry to other natural products.[22]

Scheme 11

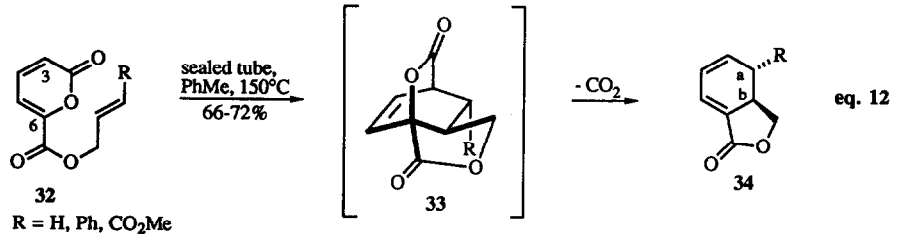



$R^1 = H, R^2 = H$ **pachybasin** 64%
$R^1 = OH, R^2 = OH$ **helminthosporin** 38%
$R^1 = H, R^2 = OH$ **chrysophanol** 62%

### ii. Dihydrobenzene Products.

Typically, olefin dienophiles that are used in this pyrone cycloaddition methodology contain a group that can be eliminated easily . However, if the initial olefin is *geminally* disubstituted with moieties that cannot be eliminated after $CO_2$ extrusion, then aromatization cannot occur. After elimination of $CO_2$ from the initially formed bicycloadduct, the quaternary ring carbon would have neither a proton for abstraction nor a group which could be eliminated. It is not necessary to have the dienophile *geminally* disubstituted in order to form isolable dihydrobenzenes. The olefin simply could be substituted with groups which are unable to eliminate after formation of

the bicycloadduct. Only a handful of examples exist in which the resulting dihydrobenzenes have been isolated. For example, it was found that the 6-substituted pyrone **32** undergoes intramolecular [4+2] cycloaddition in toluene at 150°C (eq. 12).[60] At this temperature, *in situ* $CO_2$ extrusion from the intermediate cycloadduct **33** occurred to afford the substituted cyclohexadiene **34**. In order to aromatize, the elimination of either the a- or b-substituent would need to occur; however, in each of the products **34** neither of the substituents at these two positions was a leaving group. Hence, the cyclohexadienes **34** were isolated in 66-72% yield.



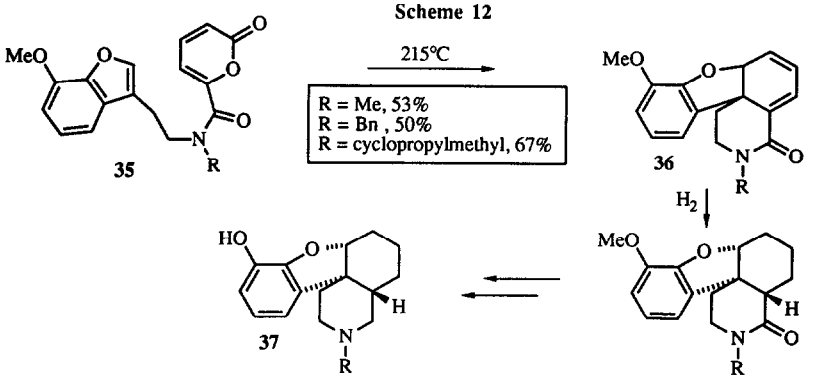

**32**
R = H, Ph, $CO_2Me$

**33**

**34**

Somewhat surprisingly, good yields of cyclohexadienes **36** were isolated from a similar intramolecular reaction in which a tethered vinyl ether on pyrone diene **35** was used as the dienophile (Scheme 12).[61] After cycloaddition and $CO_2$ extrusion, a good leaving group (*i.e.* phenoxide) was attached to the cyclohexadiene skeleton **36**. Indeed, some of the aromatized products were formed after phenoxide elimination; however, the major products were the cyclohexadienes **36**. Reduction of the dihydrobenzene moiety followed by lactam reduction and anisole demethylation afforded new morphine fragments **37**.

**Scheme 12**



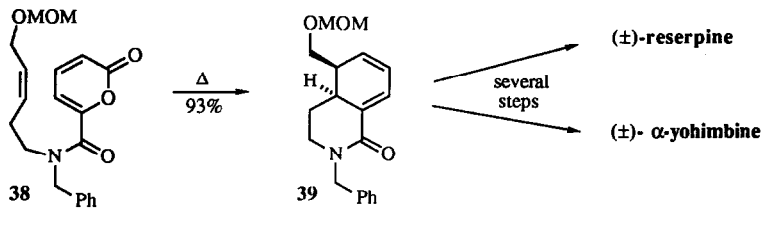

**35**

**36**

**37**

A similar intramolecular Diels-Alder reaction was used to synthesize the D and E ring skeleton of two indole alkaloids.[62] Thus, after refluxing in xylenes for 16 hours, the 6-substituted-2-pyrone **38** underwent a [4+2] cycloaddition followed by immediate extrusion of $CO_2$ to afford the cyclohexadiene **39**. A host of functional group manipulations allowed entry to both (±)-reserpine and (±)-α-yohimbine (Scheme 13).

**Scheme 13**

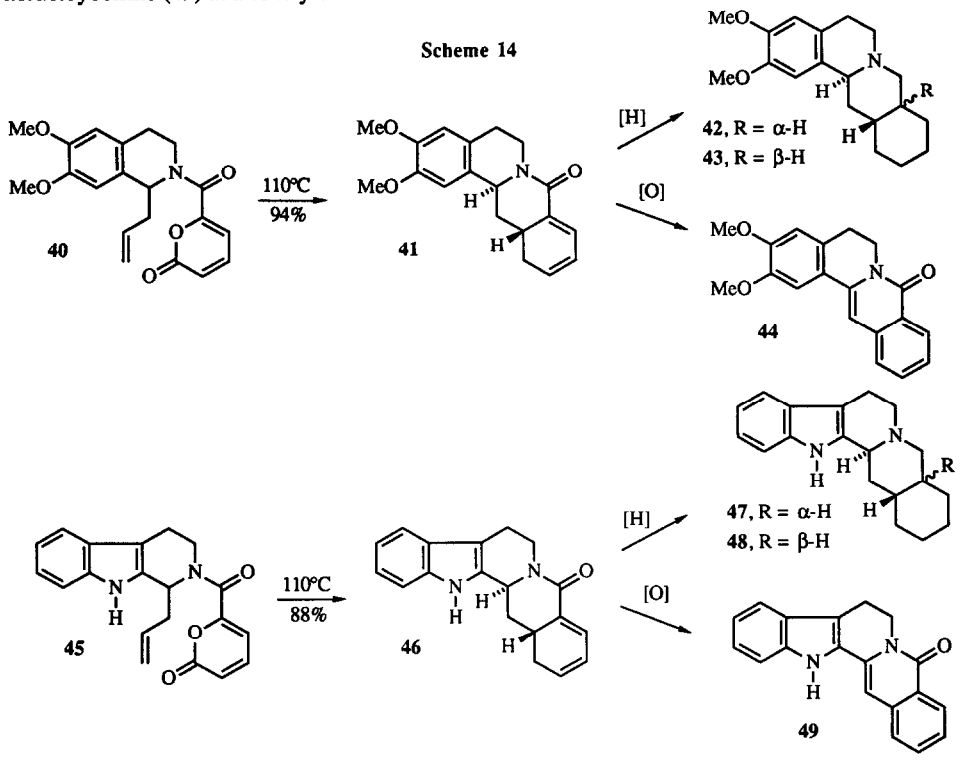



**38**

**39**

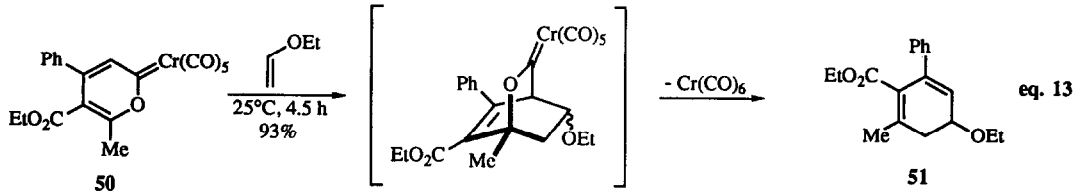
In an analogous fashion, 6-substituted-2-pyrones **40** and **45** were refluxed in toluene to afford the cyclohexadienes **41** and **46** in 94% and 88%, respectively.[63] Reduction of cyclohexadiene **41** gave a 2:1 mixture of (±)-pseudo- and (±)-epiallo-7,8-dimethoxyberbanes (**42** and **43**) in a 62% yield. Oxidation of the cyclohexadiene **41** with DDQ cleanly produced 2,3-dimethoxy-8-oxoprotoberbine (**44**) in a 90% yield. Similar transformations starting with cyclohexadiene **46** resulted in a 62% yield of (±)-pseudo- and (±)-epialloyohimbanes (**47** and **48**) in a 3:1 ratio, and also norketoyobirine (**49**) in a 75% yield.

Scheme 14

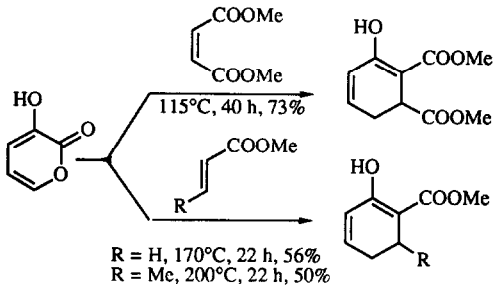



The inverse-electron-demand Diels-Alder reactions of pyranylidine pentacarbonyl complexes **50** of group 6 metals have also been used effectively (eq. 13). These complexes underwent facile (*i.e.* room temperature) reactions with alkyl and silyl enol ethers, enamines and ketene acetals to afford dihydrobenzenes **51** in excellent yields.[64] This transformation was a result of the facile extrusion of a metal carbonyl as compared to the extrusion of $CO_2$. In addition, the reactions of these pyranylidene complexes occurred at room temperature as compared to the elevated temperatures required for similar 2-pyrone cycloadditions. Removing the necessity for a higher temperature also played a key role in the formation of the dihydrobenzenes, since attempted purification by distillation (as well as application to silica gel) led only to the corresponding aromatic products. In comparison, 2-pyrone dienes cycloadded with these dienophiles to afford either the isolated bicycloadduct (see section 1b) or the corresponding aromatic product.

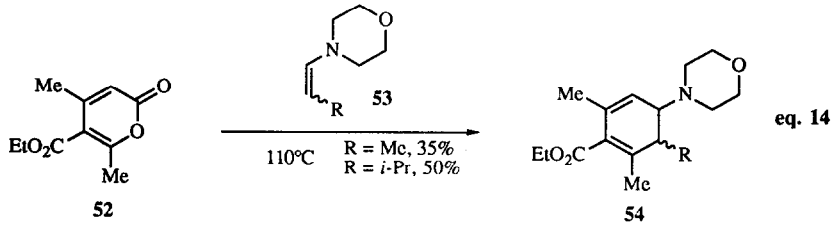
Other dihydrobenzenes have been synthesized in a similar manner.[23] It was found that the normal-electron-demand Diels-Alder cycloaddition of electron rich 3-hydroxy-2-pyrone with dimethyl maleate, methyl acrylate and methyl crotonate, followed by $CO_2$ extrusion, led to dihydrobenzenes in fair to good yields (Scheme 15).




**Scheme 15**



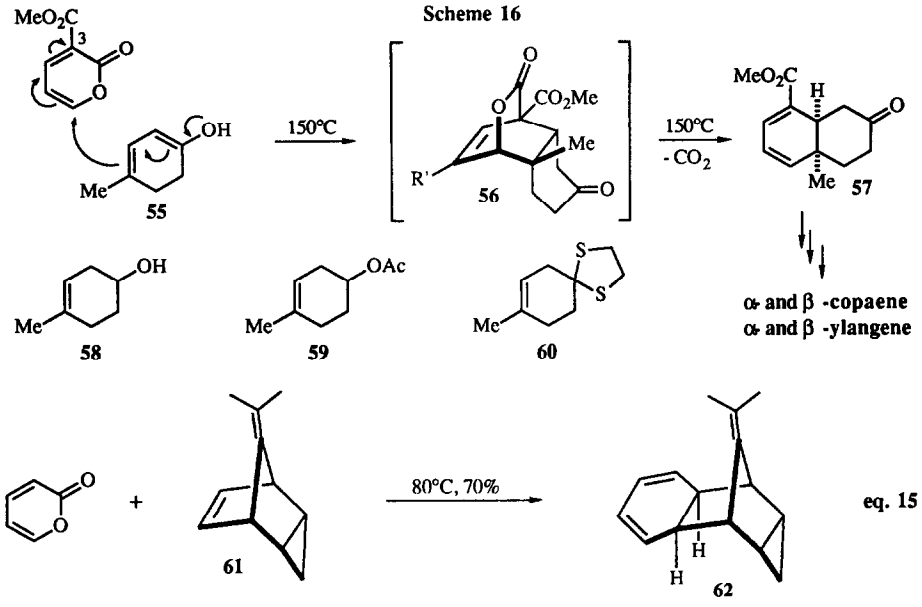

As a complement to this work, it was later reported that dihydrobenzenes could be isolated from inverse-electron-demand Diels-Alder cycloadditions using electron-deficient pyrone dienes. Upon cycloaddition of the substituted coumalate **52** with enamines **53**, in refluxing toluene, the regioisomerically pure dihydrobenzenes **54** were isolated.[28]




3-Carbomethoxy-2-pyrone has been used as a [4+2] cycloaddition partner for 4-methyl-3-cyclohexenone.[65] This ketone acted as a dienophile reacting through the tautomerized vinyl alcohol **55**. At 150°C the cycloaddition occurred; however, the only product formed was the regioisomerically pure dihydrobenzene **57** (Scheme 16). Dihydrobenzene **57** was ultimately transformed into α-and β-copaenes and α- and β-ylangenes. Although bicycloadduct **56** was not isolated under these reaction conditions, this example nicely illustrates the advantage of using an electron-rich dienophile when coupling with an electrophilic pyrone diene. Lending credence to such an argument is the fact that dienophiles **58**, **59**, and **60** failed to cycloadd with 3-carbomethoxy-2-pyrone under similar conditions. These three olefins do not possess the same electron donating ability as the ketone **55**. In addition, only one regioisomer was obtained, consistent with the previously proposed polarized mechanism (Scheme 7).

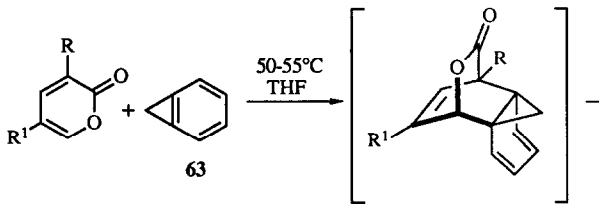
Dihydrobenzene **62** was surprisingly resistant to aromatization (eq. 15).[66] In fact, treatment of the dihydrobenzene with DDQ, chloranil, *o*-chloranil, palladium on charcoal, and sulfur did not result in aromatization. The dihydrobenzene was made as a single cycloadduct in 70% by cycloaddition of 2-pyrone with the endocyclic double bond of tricyclic diene **61**.

Scheme 16




eq. 15

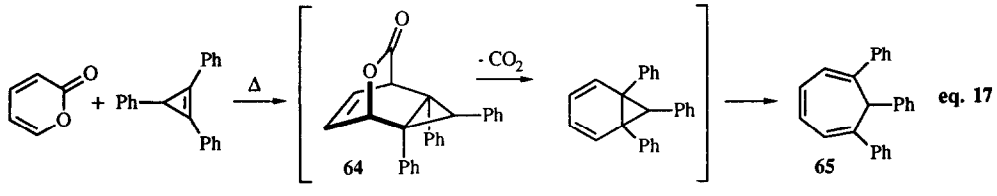
This concept was employed in the synthesis of [10]annulenes. Cycloaddition of various electron-poor pyrone dienes with 1H-cyclopropylbenzene (**63**) afforded highly strained cycloadducts (eq. 16).[67] Temperatures no higher than 55°C were needed to induce cycloaddition. Immediate $CO_2$ extrusion and opening of the 3-membered ring from the initial 1:1 adduct led to the desired [10]annulenes.




| R | $R^1$ | Yield (%) |
|---|---|---|
| H | COOMe | 16 |
| H | COOEt | 18 |
| Br | COOMe | 32 |
| Br | COOEt | 30-35 |
| Cl | COOEt | 34 |
| H | PhCO | 5 |

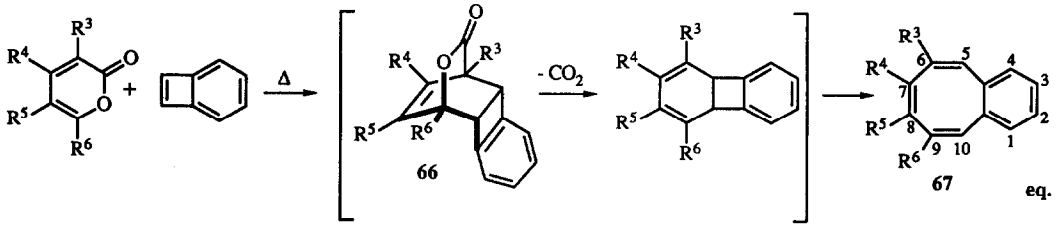
eq. 16

The cycloaddition of 1,2,3-triphenylcyclopropene with 2-pyrone afforded the cycloadduct **64** that immediately extruded carbon dioxide. Spontaneous ring enlargement then produced 1,6,7-triphenyltropilidene (**65**) (eq. 17).[68]




eq. 17

The *in situ* generated benzocyclobutene reacted with various substituted 2-pyrones in refluxing DMF to afford the [4+2] adducts **66**. However, under the reaction conditions, the cycloadducts were not isolable. Extrusion of $CO_2$ followed by ring expansion resulted in the formation of the benzocyclooctenes **67** (eq. 18).[69,70] Successful isolation of cycloadduct **66** was realized in 44% when the reaction temperature was lowered to 95°C.

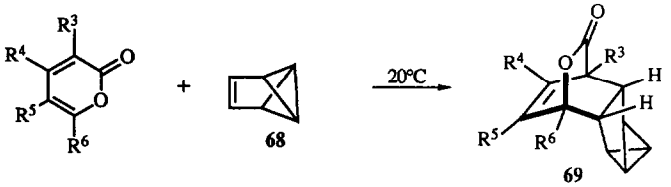



eq. 18

### iii. Isolable Bicycloadducts

The initial bicycloadducts from 2-pyrone dienes and olefin dienophiles can have up to four contiguous stereocenters. Although it is useful to cause $CO_2$ extrusion and further elimination to form regiospecifically substituted aromatic compounds (*vide supra*), it is also, in a sense, a dire process. If isolated, these bicycloadducts could be a rich source for highly-functionalized, stereospecifically-substituted synthetic building blocks. Three general solutions have been developed so that these cycloadditions can occur at lower temperatures, thus avoiding the extrusion of $CO_2$ from the bicycloadduct. The first method has been to make either the pyrone diene or the dienophile highly reactive by imposing geometric constraints on either of these species. The second method has involved strategically substituting the pyrone ring with electron withdrawing groups while simultaneously making the dienophile more electron rich or *vice versa*. The third method has been to use high pressure so as to facilitate cycloaddition.

The first of these three methods is illustrated in the following examples. Bicycloadducts **69** have been isolated from the Diels-Alder cycloaddition of chlorinated 2-pyrones with benzvalene (**68**).[71] The reactivity of the dienophile was attributed to the inherent strain in this ring system.

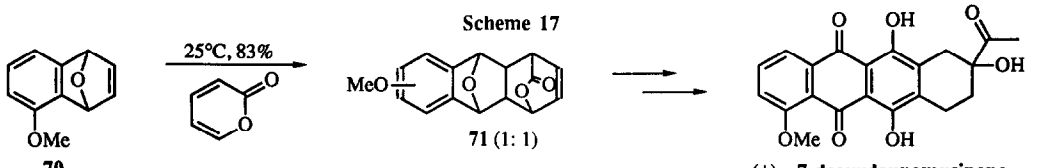



| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Yield |
|---|---|---|---|---|
| Cl | H | Cl | H | 56% |
| Cl | Cl | Cl | H | 95% |
| Cl | Cl | Cl | Cl | 82% |

eq. 19

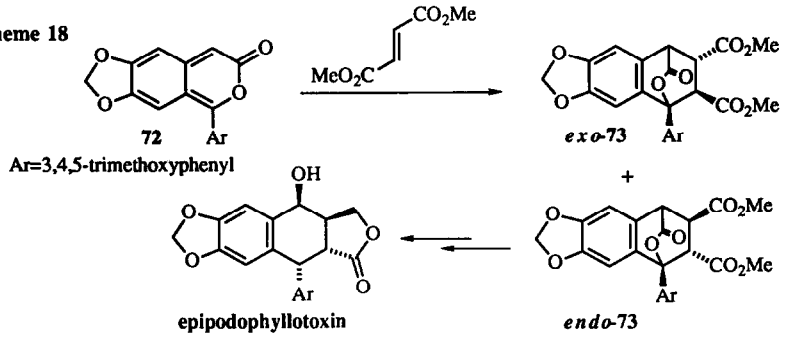
Similarly, utilization of an established protocol [72] resulted in the synthesis of anthracyclines. Thus, 2-pyrone and the reactive 1,4-dihydronaphthalene-1,4-*endo*-oxide **70** formed a 1:1 regioisomeric mixture of Diels-Alder cycloadducts **71**. [73] A few additional transformations resulted in the synthesis of (±)-7-deoxydaunomycinone.

Scheme 17



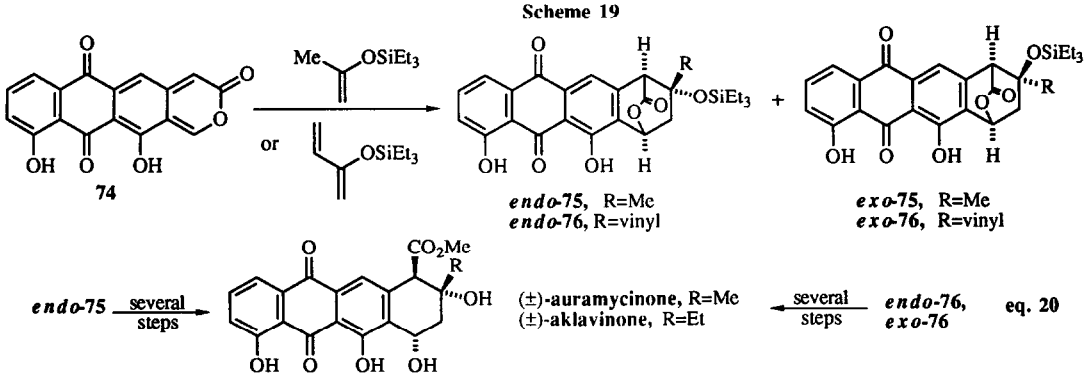

Simultaneous with this work, a similar strategy was used in the synthesis of podophyllum lignans and aromatic steroids.[41-45] Towards podophyllum lignans, *o*-qunionoid pyrone **72** reacted with dimethyl fumarate to give a 5:1 mixture of ***endo*-73** and ***exo*-73**. Cycloadduct ***endo*-73**, isolated in 76% yield, was converted in only a few steps into epipodophyllotoxin (Scheme 18).

Scheme 18



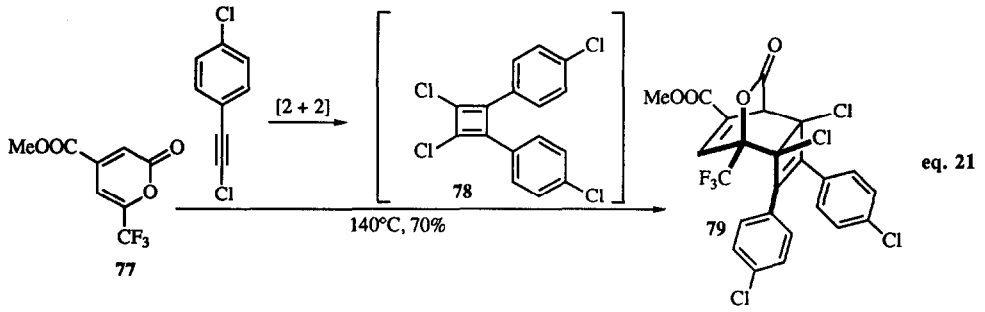

The anthracyclinones (±)-auramycinone and (±)-aklavinone also have been synthesized in this fashion by use of *o*-quinonoid pyrones.[74] Reaction of pyrone **74** with 2-triethylsilyloxypropene afforded 52% of ***endo*-75** and ***exo*-75** in a 2:1 ratio (Scheme 19). After several functional group manipulations, ***endo*-75** was successfully converted into (±)-auramycinone (eq. 20). In identical fashion, 2-triethylsiloxybuta-1,3-diene and *o*-quinonoid pyrone **74** cycloadded to give 75% of ***endo*-76** and ***exo*-76** in a 1:1 ratio (Scheme 19). Both cycloadducts **76** were carried on to (±)-aklavinone (eq. 20). It is interesting to note that the choice of the triethylsilyl group in the dienophile was crucial to the success of the total synthesis. Initial attempts in using alternative silyl groups led to difficulties during subsequent chemical manipulations; however, no comment was made on how the choice of silyl group affected the cycloaddition step. In the cycloaddition of 2-triethylsiloxybuta-1,3-diene, the alkene portion of this dienophile which cycloadded with pyrone **74** was the one activated by the electron releasing siloxy group.

Scheme 19

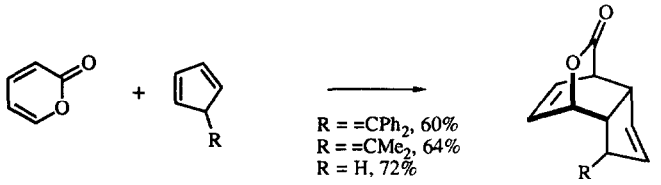



The [4+2] cycloaddition between pyrone **77** and 1-chloro-2-(4'-chlorophenyl)acetylene did not lead to the expected product (eq. 21).[20,30] Apparently, the acetylenic dienophile immediately underwent a head-to-head [2+2] cycloaddition to form a reactive substituted cyclobutene **78**. This cyclobutene then acted as a dienophile through its less hindered double bond. The bicycloadduct **79** was formed in a 70% yield and its structure was confirmed by X-ray analysis.

The bicycloadducts from the [4+2] cycloaddition between 2-pyrone and various dienophilic fulvenes[75] and cyclopentadiene have been reported (eq. 22).[75a] In the cases of diphenylfulvene and dimethylfulvene, only single *endo*-adducts were formed.

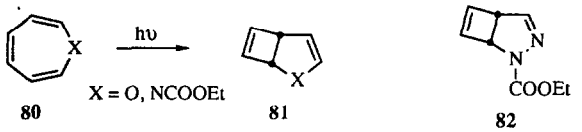



eq. 21

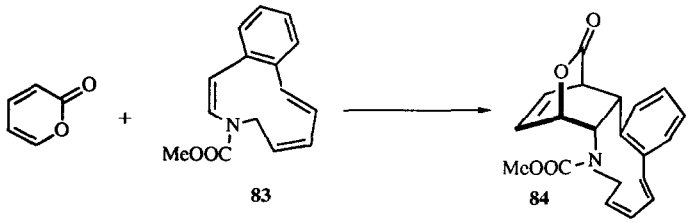



eq. 22

Heterocycles **80** failed to cycloadd with 2-pyrone, even upon prolonged contact at 70-100°C. Therefore, the photoisomers **81** and **82** were utilized as the dienophile component.[76,77] Utilization of these more reactive dienophiles afforded bicycloadducts, albeit with poor chemo- and regioselectivity.




It was found that *trans*-benzazonine **83** formed the 1:1 cycloadduct ***endo*-84** with 2-pyrone at 80°C in a 30% yield. The all *cis*-benzazonine did not form a cycloadduct.[78]

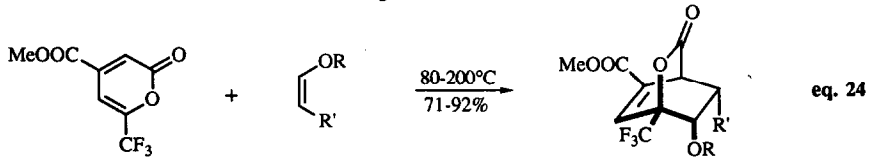


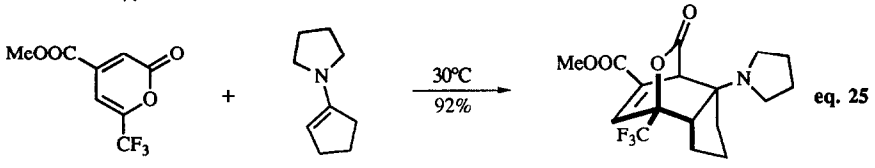

eq. 23

The second general protocol which facilitates cycloaddition and isolation of bicycloadducts is to match the electronics of the pyrone diene and dienophile partner. To accomplish this, the tendency has been to substitute the pyrone at the 3- or 5-position with an electron withdrawing group and use an electron rich dienophile which, by definition, is an inverse-electron-demand Diels-Alder reaction. In a similar vein, substitution of the 2-pyrone at the 3- and 5-positions with electron releasing groups allows the pyrone diene to cycloadd with electron-deficient dienophiles in a normal-electron-demand fashion.

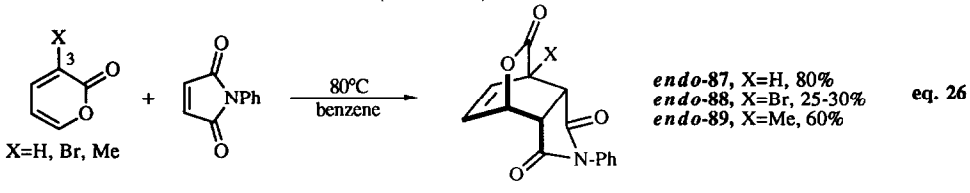
As discussed earlier, an electron withdrawing group at the 3- or 5-position of the pyrone diene governs the regiochemical outcome of the inverse-electron-demand Diels-Alder cycloaddition with a nucleophilic dienophile. However, it seems that substitution of the pyrone diene with such an electron withdrawing group at the 4- or 6-position allows for the formation of bicycloadducts with a reversal in the observed regioselectivity. For example electron-rich dienophiles such as tetramethoxyethylene, 2,5-dihydrofuran, cyclopentene, cyclooctene,

acenaphthylene, and indene led to the desired *endo*-bicycloadducts of type **85** in good yields (eq. 24).[20,30] In terms of regiochemistry, an anomalous result in the cycloaddition between pyrone diene **77** and N-pyrrolidino-1-cyclopentene gave bicycloadduct **86** (eq. 25).[30] The regiochemistry displayed in this adduct was the reverse of that witnessed in other cycloadditions with this pyrone diene and other dienophiles (eq. 24). In addition, the four possible cycloadducts (two *endo* and two *exo)* were observed in the $^1$H NMR spectrum from the reaction of pyrone **77** and vinyl acetate.[30] For discussion of *endo* and *exo* assignments, see section IV.

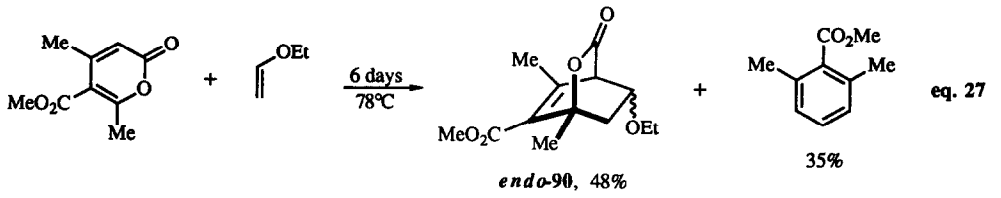



The electronic matching of the dienophile and the diene is not necessary when extremely reactive dienophiles are utilized. For example, in analogy with the original work of Diels and Alder, Shusherina *et al* has used *N*-phenylmaleimide as the dienophile counterpart with the pyrone dienes 2-pyrone, 3-bromo-2-pyrone, and 3-methyl-2-pyrone (eq. 26).[2,79,80] Bicycloadducts ***endo*-87** -**88** and -**89** were formed in refluxing benzene and were isolated as solids in 80%, 25%, and 60% yields, respectively. A discussion of the stereochemical assignment of these bicycloadducts will be made later in this article (section IV).

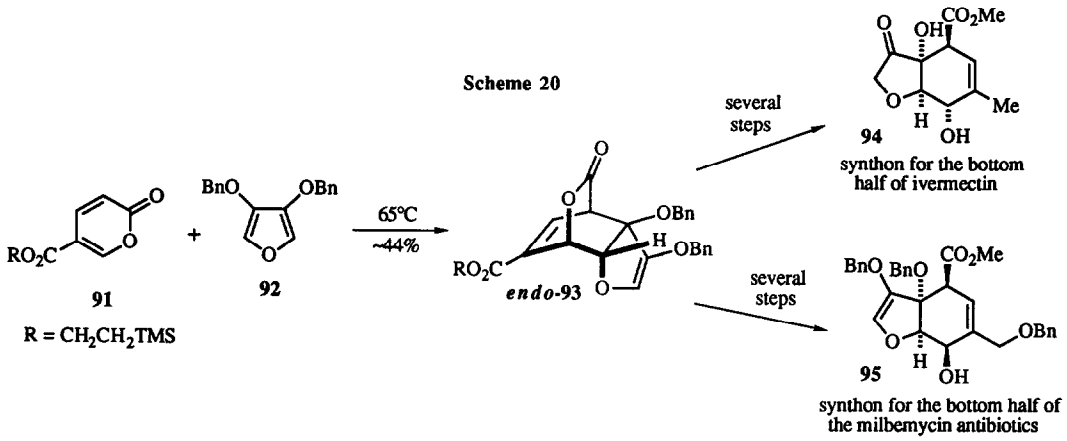



Aklavinone also has been synthesized by several approaches, with the key step in each being the cycloaddition of monocyclic and bicyclic pyrones. This work included inverse-electron-demand cycloadditions of electronically matched electron-poor 4,6-dialkylpyrone-5-carboxylates with electron-rich dienophiles to give bicycloadducts, although substituted benzoates were often formed concomitantly .[81] It has been observed that some substituents at the 4- and 6-position on the pyrone ring facilitate aromatization. As an example, the cycloaddition between 4,6-dimethyl-5-carbomethoxy-2-pyrone and ethyl vinyl ether occurred over 6 days at 78°C to form bicycloadduct ***endo*-90** as a mixture of stereoisomers in 48% yield and 2,6-dimethyl methylbenzoate in 35% yield (eq. 27).[81] Also , the inverse-electron-demand Diels-Alder cycloaddition of electron poor 2-(trimethylsilyl)ethyl coumalate **91** and electron rich 3,4-bis(benzyloxy)furan (**92**, Scheme 20) was successful.[82,83] This cycloaddition afforded an approximately 1:1 ratio of the *endo* and *exo* cycloadducts in 88% yield. The cycloadduct ***endo*-93** was used to synthesize **94**, a key synthon for the bottom halves of the antiparasitic agent ivermectin **94** and the milbemycin antibiotics **95**.[83]

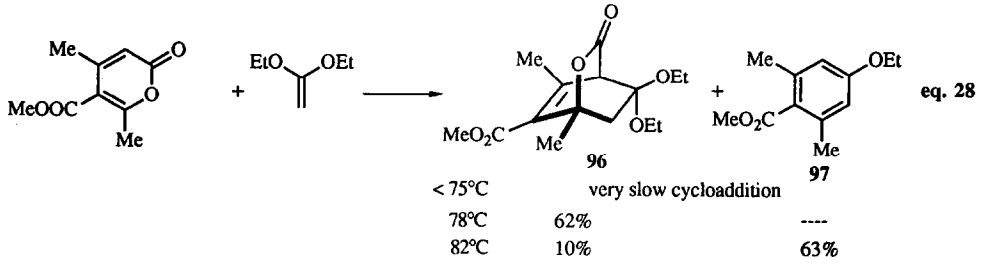



eq. 27

Scheme 20



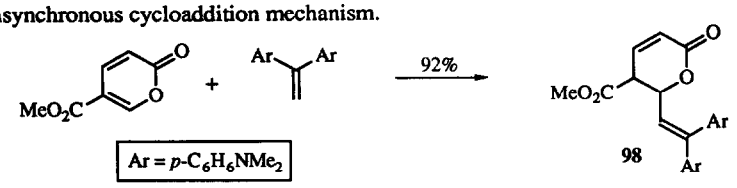

It has been found also that electron-poor 4,6-dimethyl-5-carbomethoxy-2-pyrone readily reacts with 1,1-dimethoxyethylene to form bicycloadduct **96** at 78°C (eq. 28).[84] Raising the reaction temperature to 82°C led to the predominant formation of the aromatized product **97**, while at temperatures lower than 75°C the cycloaddition proceeded very slowly. This cycloaddition perfectly illustrates the somewhat capricious nature of these reactions in which bicycloadducts are isolated. As would be expected, the less nucleophilic ethyl vinyl ether reacted more slowly than the ketene acetal with the pyrone diene. Likewise, the weakly nucleophilic vinyl acetate did not cycloadd with the pyrone diene even after 7 days at reflux.




eq. 28

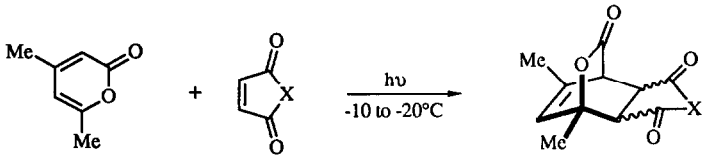
It was found that the electron deficient 5-carbomethoxy-2-pyrone reacted with ketene acetals to form bicycloadducts regiospecifically in 65-94% yields.[85] 5-Carbomethoxy-2-pyrone also cycloadded with a number of other dienophiles to form isolable bicycloadducts.[86] The regiochemistry of this cycloaddition can be explained by the previously proposed mechanism involving a zwitterionic intermediate. Removing the electron withdrawing group from the pyrone diene resulted in a less favorable interaction with the dienophile. In fact, there was not any evidence for [4+2] cycloaddition between 2-pyrone and diethyl ketene acetal even in boiling toluene.[85] Moreover, when a 1,1-diarylethylene was used as the dienophile with the enophilic 5-carbomethoxy-2-pyrone, a bicycloadduct was not

formed.[85] Instead, the substituted dihydropyrone **98** was isolated in 92% yield (eq. 29). This evidence supports a polarized, nonsynchronous cycloaddition mechanism.




eq. 29

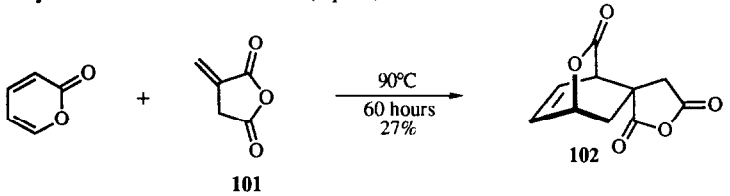
Low temperature photoreactions have been used to obtain bicycloadducts from 2-pyrones.[87] Irradiation of a mixture of 4,6-dimethyl-2-pyrone and maleimide at -10 to -20°C for 2 hours gave the cycloadduct ***endo*-99** in a 60% yield. The cycloaddition between maleic anhydride and 4,6-dimethyl-2-pyrone afforded the bicycloadduct ***exo*-100** in a 52% yield. These cycloadducts were not formed under thermal conditions; in fact, heating ***exo*-99** at 70°C and ***exo*-100** at 40°C caused $CO_2$ extrusion and the corresponding cyclohexadienes were produced.




eq. 30

The third general method to facilitate the isolation of bicycloadducts is the use of high pressure.[88-90] The [4+2] Diels-Alder cycloaddition has a highly negative (-30 to -40 $cm^3$/mol) volume of activation. For systems such as these, the application of pressure accelerates the rate of chemical reaction. Conversely, high pressure retards the rates of chemical reactions which have a positive volume of activation. In other words, pressure tends to drive the equilibrium in favor of the products or reactants that have the lower volume. An example of a reaction with a positive volume of activation is the extrusion of $CO_2$ from a neutral organic compound. Consequently, high pressure is a perfect technique for accelerating the cycloaddition of pyrone dienes with dienophiles while also suppressing extrusion of $CO_2$ from the newly formed bicycloadduct.

Often, successful isolation of bicycloadducts from 2-pyrone is contingent upon the use of high pressure, unless an unusually reactive dienophile is used. For example, the [4+2] cycloaddition of 2-pyrone with a host of electron-poor dienophiles occurred at 5-10 Kbar (occasionally temperatures of up to 80°C were employed along with high pressures).[91] The use of high pressure overrides the low enophile reactivity of this pyrone diene, giving a regioisomeric mixture of cycloadducts. Regioisomeric products have been obtained only when the unactivated parent 2-pyrone is utilized as the diene. On the other hand, under thermal conditions without high pressure, the cycloaddition between 2-pyrone and itaconic anhydride **101** proceeded sluggishly.[92] Even after 67 hours at 90°C, only 27% of the bicycloadduct **102** was formed (eq. 31).

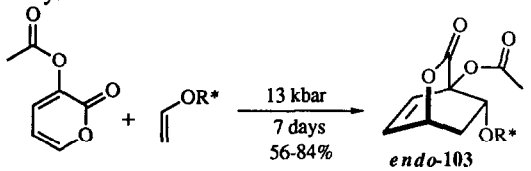



**101** **102**

eq. 31

A similar approach, utilizing very high pressures, has been used to produce bicycloadducts from 2-pyrone with various substituted acrylates and even isolated olefins (e.g. 19 Kbar).[93] Such drastic conditions were not

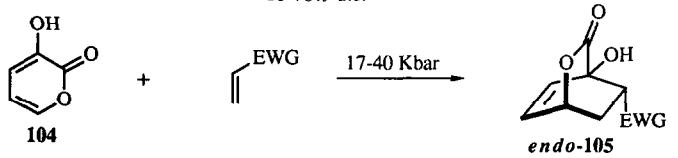
required for the successful cycloaddition between a 5-alkyl-2-pyrone and electron deficient dienophiles.[27] It has been demonstrated that even relatively electron rich carboxylate esters of 3-hydroxy-2-pyrones can cycloadd with electron rich vinyl ethers at a pressure of 13 Kbar for 7 days (eq. 31).[94] It is noteworthy that the same reactions did not proceed under thermal conditions or by use of Lewis acids. Implementation of chiral, non-racemic vinyl ethers led to diastereofacial selectivity of up to 76% d.e. in the cycloadducts ***endo*-103** (56-84% yield). It was found necessary to protect the hydroxyl group of the pyrone; otherwise, under the reaction conditions, aromatization occurred. For example, a quantitative yield of benzene and isomenthol was isolated from the reaction of the 3-acetoxy-2-pyrone diene (eq. 32) and isomenthyl vinyl ether.[94] However, the parent 3-hydroxy-2-pyrone (**104**) has undergone cycloadditions successfully to form bicycloadducts. Pressures of 20-40 Kbar have been employed to obtain the bicycloadducts of the electron rich pyrone diene **104** with acrylate and acrylonitrile derivatives with complete regiocontrol of the cycloaddition (eq. 32).[24] Attempted isolation of these bicyclic lactones **105** led to partial decomposition, probably due to aromatization or a retro aldol reaction. A chiral pyrone diene was prepared by esterification of the hydroxy pyrone **104** with α-methoxyphenylacetic acid. However, cycloaddition of the chiral pyrone diene with either nucleophilic dienophiles[94] or electrophilic dienophiles[95] resulted in poor diastereofacial selectivity.




*endo*-103
10-76% d.e.

R* = acyclic chiral group, camphor-derived chiral group, or cyclohexane-related chiral group

eq. 32




**104**

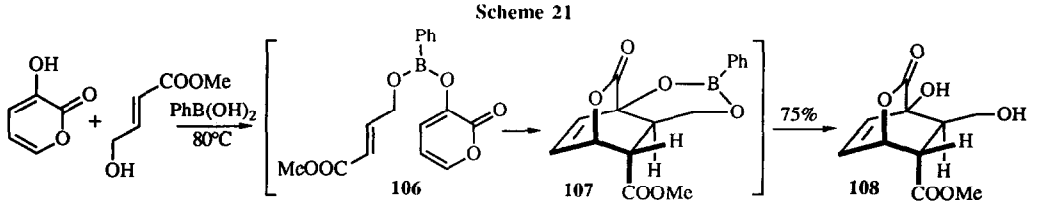
*endo*-105

EWG = electron withdrawing group

eq. 33

In refluxing benzene, a reaction between 3-hydroxy-2-pyrone and 4-hydroxy-2-butenoate did not occur; however, when the cycloaddition was carried out in the presence of phenylboronic acid, single cycloadduct ***endo*-108** was isolated (Scheme 21).[96] The phenylboronic acid functioned as a template to create intermediate boronate **106** that underwent an *intra*molecular Diels-Alder reaction, instead of an *inter*molecular cycloaddition, with the dienophile. In contrast to the cycloadduct that would be formed under high pressure conditions, the regioisomeric cycloadduct **108** was formed *via* Scheme 21. Hydrolysis of the bicyclic boronate **107** led to the bicyclic diol **108** in a 75% yield.

Scheme 21



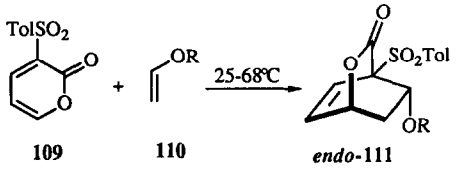

The restricted synthetic utility of strained pyrone dienes or dienophiles is due to the limited availability of such species and to the limited array of cycloadducts that could be obtained by this method. In addition, the general utility of high pressure is precluded by the need for an expensive apparatus. Although the use of high pressure in organic

chemistry is becoming more widespread, many groups still lack the necessary equipment for such a reaction, especially at pressures >10-15 Kbar. For these reasons, our group has focused primarily on manipulating the pyrone diene and dienophile electronically so that they become more compatible with each other.[97] We envisioned that making the pyrone diene system even more electron deficient would facilitate the inverse-electron-demand Diels-Alder cycloaddition with electron rich dienophiles. This general trend had been reported in similar cycloadditions for other electrophilic dienes.[98,99]

Therefore, an even better electron-withdrawing substituent than the often used carbomethoxy moiety was desired. It had been observed, previous to this work, that sulfonyl substituted dienes were extremely electrophilic enophiles in the inverse-electron-demand Diels-Alder reaction.[100] Therefore, 3-(*p*-tolylsulfonyl)-2-pyrone (**109**) was prepared.[101] Gratifyingly, isolable bicycloadducts ***endo*-111** were obtained under thermal conditions when pyrone **109** was treated with various alkyl vinyl ethers.[102] When chiral, non-racemic alkyl vinyl ethers **110** were employed as the dienophile, high levels of diastereoselectivity were observed in the cycloaddition (Scheme 22).[102]

The usefulness of this methodology was displayed in the asymmetric total synthesis of (–)-methyl triacetyl-4-epishikimate.[103] This was accomplished in a total of 14 steps and with an overall yield of 23% from cycloadduct ***endo*-111i** (Scheme 23). Improvement upon the diastereofacial control of this cycloaddition between pyrone **109** and vinyl ether **110i** was realized by conducting the reaction at -45°C in the presence of Yamamoto's aluminum-based "MAD" catalyst.[104] Under these conditions, from vinyl ether (*S*)-**110i**, a 93% yield of cycloadducts ***endo*-111i** (49:1 endo diastereomers) were isolated (eq 34). The synthetic utility of the diasteromerically pure bicycloadduct ***endo*-111i** was exemplified further in the total synthesis of 1α,25-dihydroxyvitamin $D_3$, the most active metabolite of vitamin $D_3$ (Scheme 24).[104]

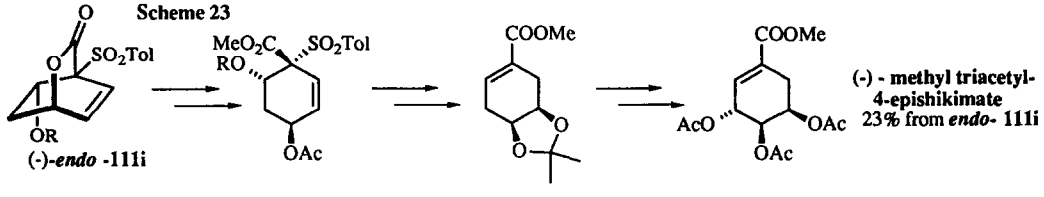
**Scheme 22**

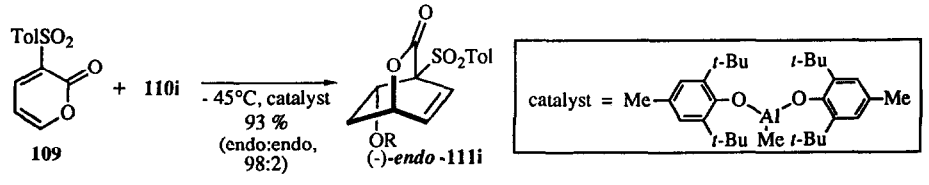



**109** **110** ***endo*-111**

| 111 | R | % yield | % d.e. |
|---|---|---|---|
| a | ethyl | 95 | -- |
| b | 2-octyl | >90 | 0 |
| c | endo-2-bornyl | >90 | 5 |
| d | 8-phenylmenthyl | >90 | 5 |
| e | menthyl | 89 | 54 |
| g | Ph(Me)CH | 75 | 66 |
| i | Ph(*i*-Pr)CH | 94 | 84 |
| j | Ph(*t*-Bu)CH | 90 | |

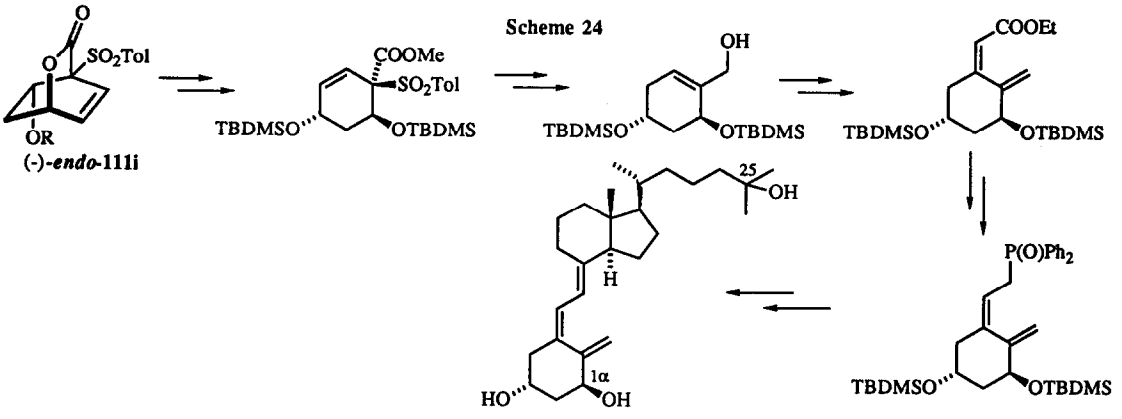
**Scheme 23**



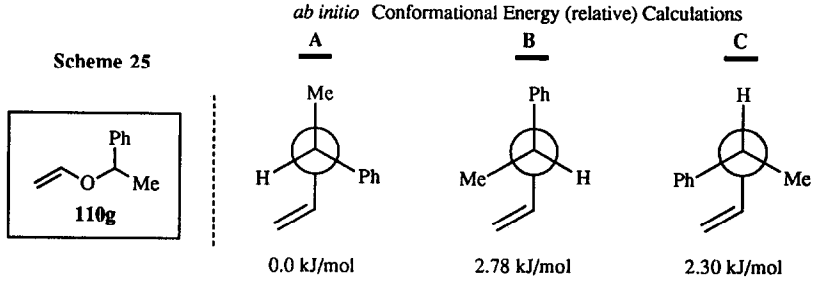

**109** **eq. 34**

Scheme 24



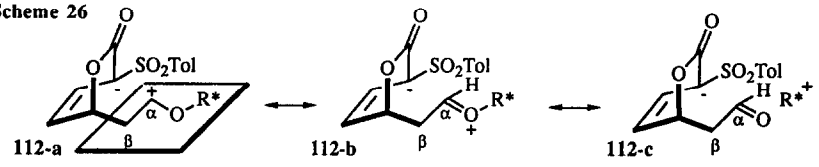

The asymmetric induction of this cycloaddition can be explained by the chiral auxiliary existing, for vinyl ether **110g**, predominantly in the lowest energy conformation, with the facial selectivity arising from the difference in steric bulk of the phenyl and hydrogen substituents (Scheme 25).[105] By increasing the size of the alkyl group, conformation **A** is favored even more over conformations **B** and **C** and, as a result, an increase in facial selectivity should occur. Indeed, experimental observations verified this postulate.[102]

Scheme 25



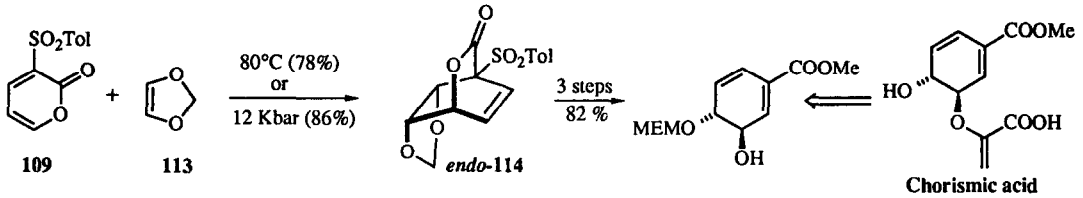

The high stereochemical directing ability of the benzylic chiral auxiliaries in Scheme 22 (e. g. **110g**), in contrast to other often-used but non-benzylic chiral auxiliaries, can be rationalized by considering an extreme zwitterionic intermediate in the cycloaddition represented by resonance contributors **112-a**, **112-b**, and **112-c** (*cf.* Scheme 26). Resonance form **112-c** would be more significant (*i. e.* greater carbocation stability) when R* is benzylic than when R* is non-benzylic. Resonance form **112-b**, consistent with the preferred geometry of Lewis acid-aldehyde complexes in which the Lewis acid resides preferentially *syn* to the aldehyde hydrogen atom, [106] would correspond to the observed *endo* cycloadduct. Resonance form **112-a**, with R*-O-$C_\alpha$-$C_\beta$ coplanar, would result in the transmision of absolute stereochemical information from the vinyl ether to the cycloadduct.[107]

Scheme 26



To broaden the synthetic utility of this type of cycloaddition, electron-rich 1,2-dioxygenated olefin **113** were utilized as the dienophile counterparts to the electron-deficient sulfonyl pyrone diene **109**.[108] Although, for steric reasons, these types of dienophiles were less reactive than simple vinyl ethers (1-alkoxyethylenes), cycloaddition afforded the desired cycloadducts ***endo*-114**. As a complement to earlier work, a formal total synthesis of (±)-chorismic acid was accomplished from bicyclic lactone ***endo*-114** in 3 steps in an 82% overall yield (Scheme 27). It was shown that the cycloaddition of the corresponding pyrone sulfoxide, 3-(*p*-tolylsulfinyl)-2-pyrone (**115**), with electron rich-dienophiles led to isolable bicycloadducts.[109,110] Pyrone sulfoxide **115** was less reactive than the pyrone sulfone **109** as the enophile in inverse-electron-demand Diels-Alder reactions. Although electron-rich 1,1-dimethoxyethylene readily reacted with pyrone sulfoxide **115** at room temperature to form bicyclic lactone ***endo*-116** (d.e. 76%),[109] cycloaddition between pyrone sulfoxide **115** and ethyl vinyl ether required the use of zinc dibromide to expedite product formation. Thus, the desired bicyclic lactone ***endo*-116** was formed in the presence of zinc dibromide (eq.35).[110]

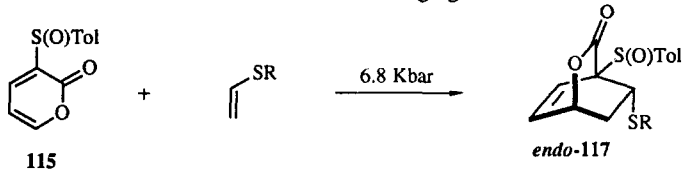
**Scheme 27**





eq. 35

Moreover, vinyl thioethers proved more resistant than the corresponding vinyl ethers to reaction with pyrone sulfoxide **115**. Zinc bromide-assisted cycloaddition failed with thiovinyl ethers; however, successful room temperature cycloaddition occurred at 6.8 Kbar.[110] The diastereoselective Diels-Alder cycloaddition of methyl and phenyl thiovinyl ethers with pyrone sulfoxide **115** afforded the bicyclic lactones ***endo*-117a** and ***endo*-117b**, as the only products (eq. 36). From bicycloadduct ***endo*-117**, a formal total synthesis of (±)-chorismic acid (*i.e.* the synthesis of the same key synthon as shown in Scheme 27) was accomplished in 5 steps in an overall yield of 26%.[110] All attempts to prepare the enantiomerically pure pyrone sulfoxide **115**, so that asymmetry could be induced during the cycloaddition, have this far been discouraging.[110]

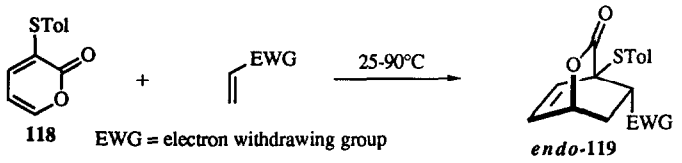



a, R = Me (98%)
b, R = Ph (73%)

eq. 36

In contrast to the inverse-electron-demand cycloadditions of substituted 2-pyrones, little work had been done regarding the normal-electron-demand cycloadditions. It had been demonstrated previously that 3-hydroxy-2-pyrone (**104**) underwent efficient normal-electron-demand Diels-Alder cycloaddition; however, the bicycloadducts were often unstable and decomposed upon attempted isolation (*vide supra*).[24]

We employed 3-(*p*-tolylsulfenyl)-2-pyrone (**118**) as an excellent nucleophilic diene in polar [4+2] cycloadditions with electron-deficient dienophiles. A variety of electrophilic olefins cycloadded with pyrone **118** to form isolable bicycloadducts ***endo*-119** at temperatures <90°C with good to excellent selectivity (eq. 37).[111]



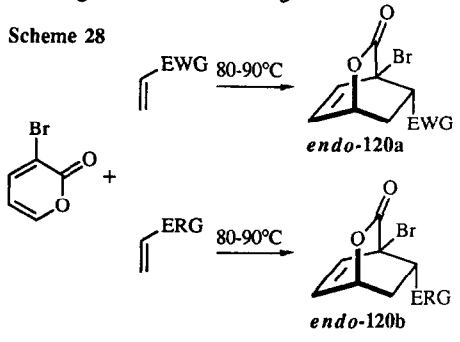

**118** EWG = electron withdrawing group ***endo*-119** eq. 37

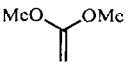
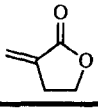
Unfortunately, some more sterically demanding dienophiles (including diethyl ethylidenemalonate, tolyl vinyl sulfone, 1,4-naphthoquinone, 2-butenolide, 2-pentenolide, and 2-cyclohexenone) were resistant to cycloaddtion with pyrone diene **118**, even after prolonged heating. Nevertheless, a good range of cycloadducts were isolated which would not be obtained as efficiently or would be obtained with poor selectivity if the nonsubstituted 2-pyrones were used. The thioether functional group in the bicycloadduct was then reductively cleaved with tributyltin hydride under neutral conditions to form the desulfurized compound. Thus, with relatively unencumbered electrophilic olefins, pyrone **118** is a highly reactive synthetic equivalent of 2-pyrone in thermal (*i. e.* not high pressure) Diels-Alder cycloadditions.

More importantly, we found that 3-bromo-2-pyrone, which is a synthetic precursor to 3-tolylthio-2-pyrone, was an equally useful diene. It underwent slow but very clean cycloaddition reactions under carefully controlled thermal conditions as an electron-deficient diene with electron-rich dienophiles to form the desired bicycloadducts ***endo*-120a** (Scheme 28).[112] Also, in a chameleon-like (ambiphilic) fashion, it served as an electron-rich diene with electron-deficient dienophiles to form isolable bicycloadducts ***endo*-120b** (Scheme 28).[112]

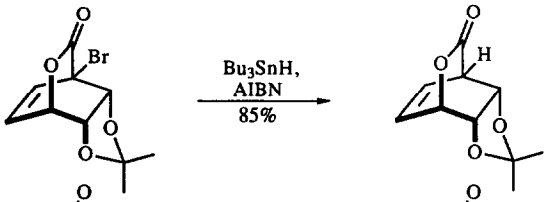
3-Bromo-2-pyrone, like 2-pyrone, is expected to function in both nucleophilic and electrophilic capacity. Unfortunately, 2-pyrone is prone to rapid polymerization under themal conditions, and therefore few examples of its cycloadditions are known. In the reported cycloadditions, regioisomeric bicycloadducts have been formed with little or no selectivity. We found that 3-bromo-2-pyrone, which is not thermally labile, was a slightly more reactive diene than unsubstituted 2-pyrone.[112] For example, 3-bromo-2-pyrone readily reacted with 1,1-dimethoxyethylene while 2-pyrone was resistant to cycloadditions with this dienophile.[85] More interestingly, the products of both types of cycloaddition using 3-bromo-2-pyrone show the same regioselectivity and stereoselectivity. That is, a 5-*endo* bicyclic lactone is formed with total or very high selectivity whether the activating group on the dienophile is electron-withdrawing or electron-releasing.

**Scheme 28**

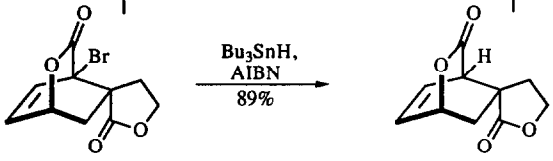



| ERG | Yield (*endo*/*exo*) | EWG | Yield (*endo*/*exo*) |
|---|---|---|---|
|  | 63% (4 : 1) |  | 63% (>98 : 2) |
|  | 60% (- -) |  | 33% (>98 : 2) |
| | |  | 70% (>95 : 5) |

Subsequent reductive substitution of the bridgehead bromine by hydrogen in these isolated bicycoladducts produced the halogen free compounds (eqs. 38, 39)[112] Thus, *via* this sequence of cycloaddition followed by radical reductive debromination, 3-bromo-2-pyrone was the synthetic equivalent of 2-pyrone and required only heat for successful and regiospecific formation of bicycloadducts. Therefore, 3-bromo-2-pyrone offers the important practical advantage over 2-pyrone of not requiring high pressures for successful cycloadditions.



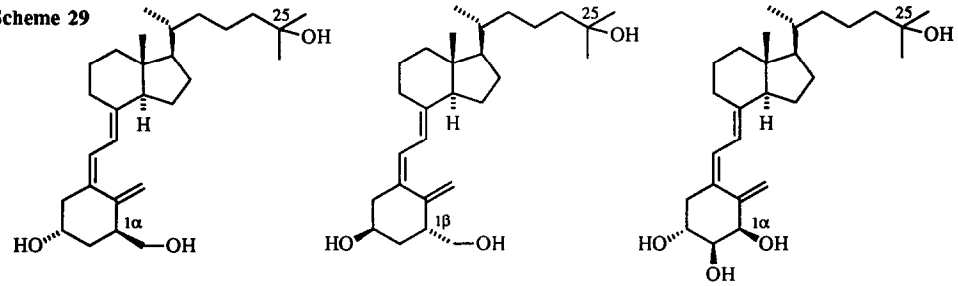

eq. 38



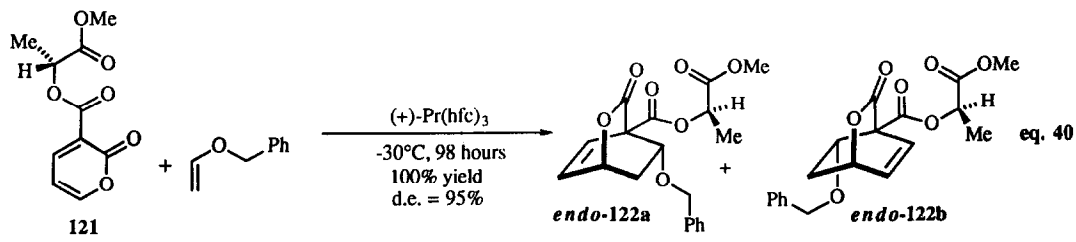

eq. 39

We have used the bicycloadducts formed from the cycloadditions of 3-bromo-2-pyrone in synthesis of some new vitamin $D_3$ analogs (Schene 29).[113] A route similar to the protocol outlined in Scheme 24 was followed.

**Scheme 29**




Asymmetric induction has been achieved during these types of cycloadditions by employing chiral vinyl ethers. To date, our group has been unsuccessful in obtaining very high enantioselectivity in the cycloaddition by using chirally homogeneous catalysts with achiral dienes and dienophiles. However, recently we have been able to transesterify commercially available 3-methylcarboxyl-2-pyrone into enantiomerically pure electron-deficient chiral pyrones esters.[114] These pyrone ester dienes underwent inverse-electron-demand Diels-Alder cycloaddition with electron-rich dienophiles. For example, the enantiomerically pure pyrone ester **121** at -30°C in the presence of a chiral Lewis acid regiospecifically formed bicyclic lactones ***endo*-122** in a quantitative fashion as a 97.5: 2.5 mixture of diastereomers (eq. 40).[114]




**121**

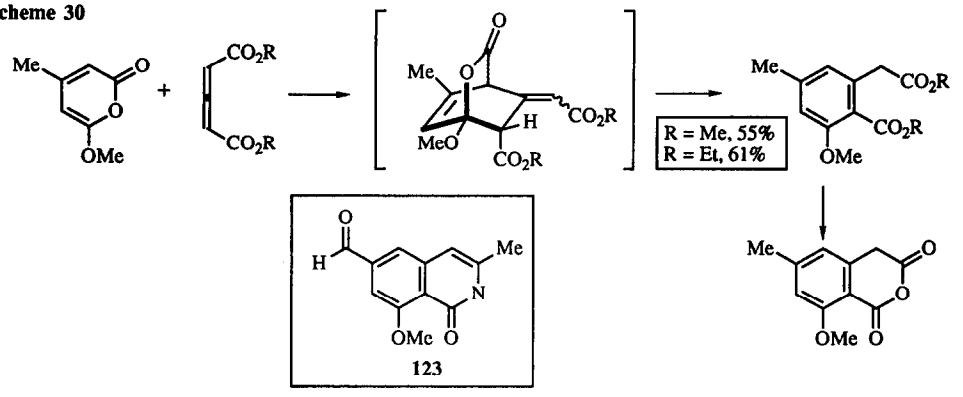
***endo*-122a** + ***endo*-122b**

eq. 40

### c. With Allenes.

Allenes, like alkenes, have reacted with pyrones to form substituted aromatic compounds with good regiospecificity. In these cases, however, the products contained an exocyclic methylene substituent. There have not been any reports of isolated bicycloadducts being obtained from allene dienophiles. A variety of homophthalates have been created using this methodology.[26,115] The carbon skeleton of 8-methoxyhomophthalic anhydride, which is a precursor to anthracyclinones and *peri*-hydroxylated aromatic compounds, has been constructed from the Diels-Alder cycloaddition between 4-methyl-6-methoxypyrone and allene diesters (Scheme 30).[116] A similar strategy has been utilized to synthesize isoquinolone **123**.[117]

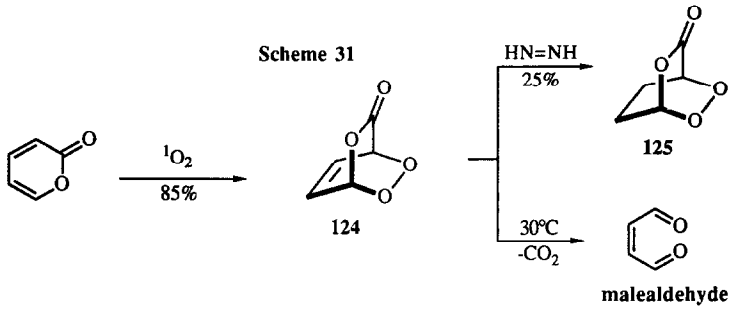
**Scheme 30**




### d. With Other Dienophiles.

The singlet oxygen bicycloadduct **124** of 2-pyrone was produced upon photo-oxygenation of 2-pyrone at 0°C (Scheme 31).[118] This endoperoxide bicycloadduct **124** was isolated by low temperature (-40°C) silica gel chromatography. Upon warming this adduct to 30°C, the spontaneous extrusion of $CO_2$ resulted in the formation of malealdehyde. Diimide reduction of bicycloadduct **124** resulted in the formation of the more stable, saturated bicycloadduct **125**.

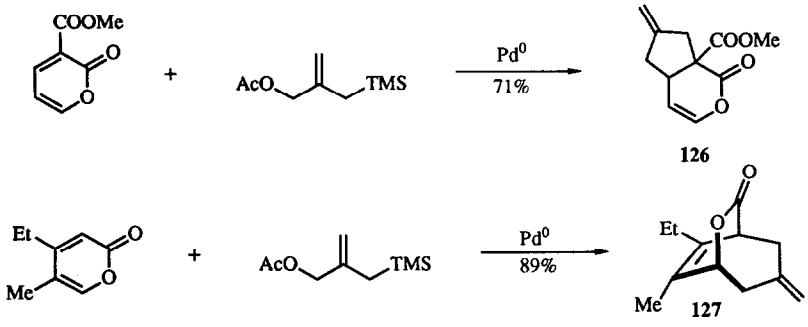
**Scheme 31**



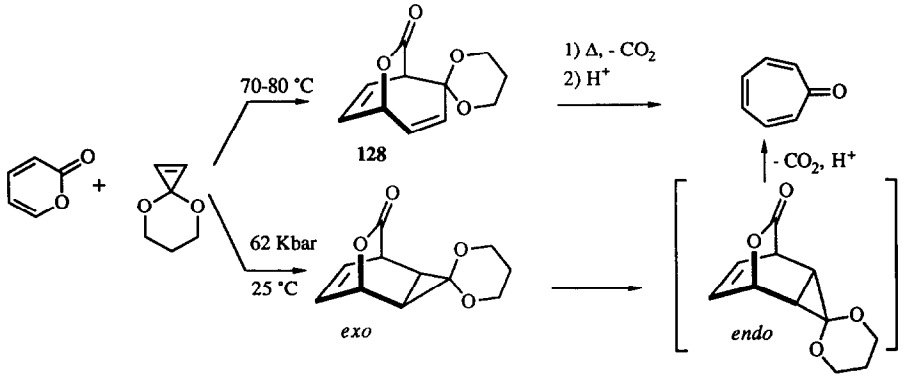

A [2+3] cycloaddition occurred between 3-carbomethoxy-2-pyrone and a trimethylenemethane-Pd[(*i*-PrO)$_3$P]$_2$ complex that resulted in the formation of cycloadduct **126** in 71% (eq.41).[119]

However, when the 3-carbomethoxy group was removed from the pyrone diene, the predominant reaction was a [4+3] cycloaddition.[119] For example, 4-ethyl-5-methyl-2-pyrone reacted with the trimethylenemethane-palladium complex to form the cycloadduct **127** in an 89% yield (eq. 42). The thermal cycloaddition of cyclopropenone ketals and 2-pyrone gives a [4+3] cycloadduct (e.g. **128**). Thus a parallel non-organometallic

approach to 6,5-fused rings was developed.The thermal [4+3] cycloadditions of cyclopropenone ketals should be contrasted to [4+2] cycloadditions obtained under high pressure.[120] This metodology has been used for the synthesis of desacetamido colchicine[121] and as a synthetic approach to gelsemicine.[122]




Scheme 32



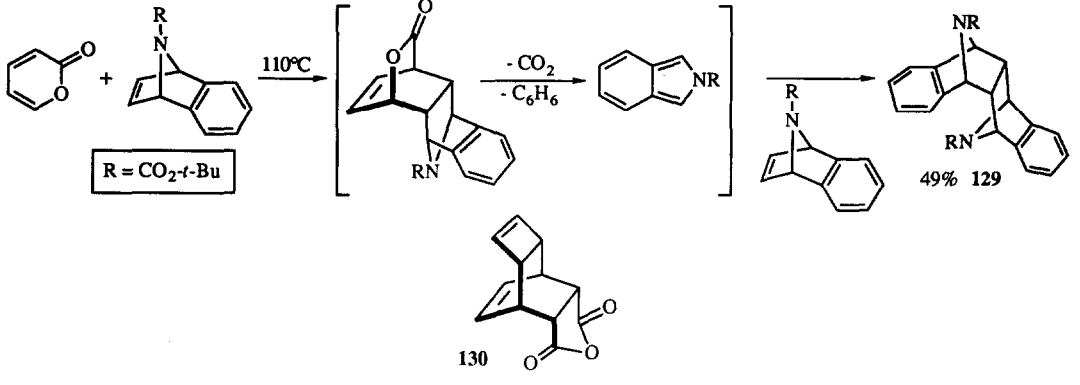

### e. Double Diels-Alder Reactions

By using at least a two-fold excess of the dienophile in the pyrone cycloaddition, double Diels-Alder adducts can be isolated. A criterion for this process is that the reaction must be conducted at high temperatures so as to cause $CO_2$ extrusion from the initially formed bicycloadduct. The resulting cyclohexadiene again can function as a diene by cycloadding with a second equivalent of the dienophile. Most commonly, double Diels-Alder cycloadditions have occurred between a host of substituted-2-pyrones and maleic anhydride or maleimides.[8,17-19,121-124] In order to obtain double Diels-Alder adducts, it is not necessary to carry out both cycloadditions in a single reaction vessel. The bicycloadduct can be formed in the usual manner, and after purification it can be reacted with a second equivalent of dienophile. In this manner, the two dienophile additions occur in separate vessels; therefore, different dienophiles can be used.[60] For example, in refluxing toluene, the initial [4+2] cycloadduct between 2-pyrone and 7-azabenzonorbornadiene spontaneously extruded $CO_2$ and then benzene (Scheme 33).[125] This *in situ* generated diene next reacted with a second equivalent of 7-azabenzonorbornadiene to form adduct **129** as the major product in a 49% yield. The dienophilic cyclobutene **130** has also entered into this protocol by a double Diels-Alder cycloaddition with 2-pyrone.[126]

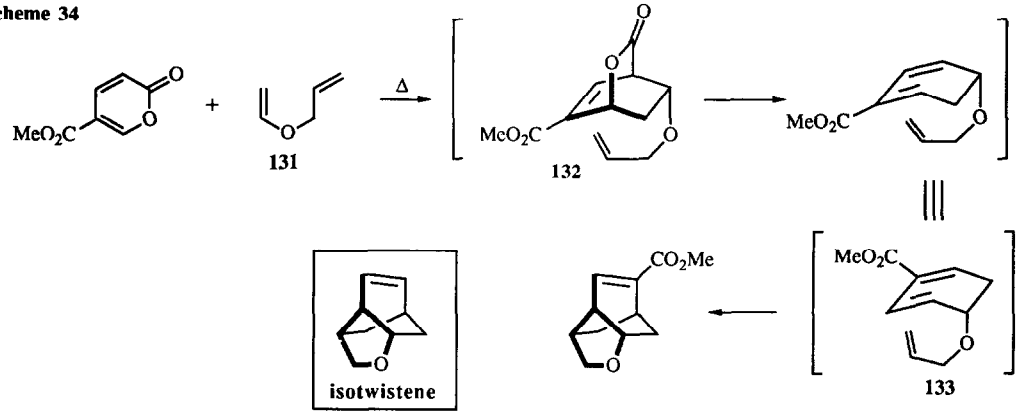
Unactivated symmetrical dienes have also been used as dienophiles in this double Diels-Alder cycloaddition methodology. The initial cycloaddition occurs as normal; however, after $CO_2$ extrusion, the cyclohexadiene

undergoes an intramolecular Diels-Alder reaction with the remaining olefinic moiety of the dienophile.[86,93,127,128] Activated dienophiles that are tethered with an olefin component have also served in such a capacity.[86,129] The activated portion of the dienophile initially regiospecifically reacts with a compatable pyrone diene. After $CO_2$ extrusion, the newly formed cyclohexadiene reacts with the other half of the dienophile. For example, cycloaddition of methyl coumalate and vinyl ether **131** resulted in the initial formation of cycloadduct **132**.[86] However, under the reaction conditions, this cycloadduct immediately lost $CO_2$ and the resulting cyclohexadiene **133** underwent an intramolecular [4+2] cycloaddition with the remaining olefin unit from the dienophile. This sequence allowed for the rapid formation of the isotwistene carbon skeleton.

**Scheme 33**

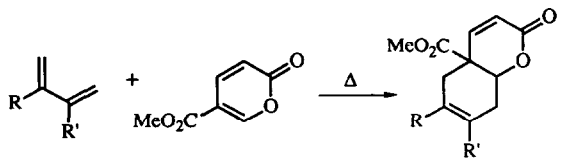



**Scheme 34**




### 2. [2+4] Cycloadditions: 2-Pyrones as Dienophiles

Almost exclusively, when 2-pyrones have participated in the [4+2] Diels-Alder cycloaddition they have functioned as 4π componenets. However, there have been a few examples in which the 2-pyrone ring behaved as a dieneophile. The high pressure and photosensitized dimerization of 2-pyrones has been reported. The dimers were formed by the [4+2] cycloaddition between 2 equivalents of the pyrone.[12] Hence, one equivalent of the 2-pyrone acted as a diene while the second equivalent functioned as a dienophile. In another example of a 2-pyrone reacting as a dienophile, methyl coumalte cycloadded with a variety of acyclic dienes (eq. 39).[73]



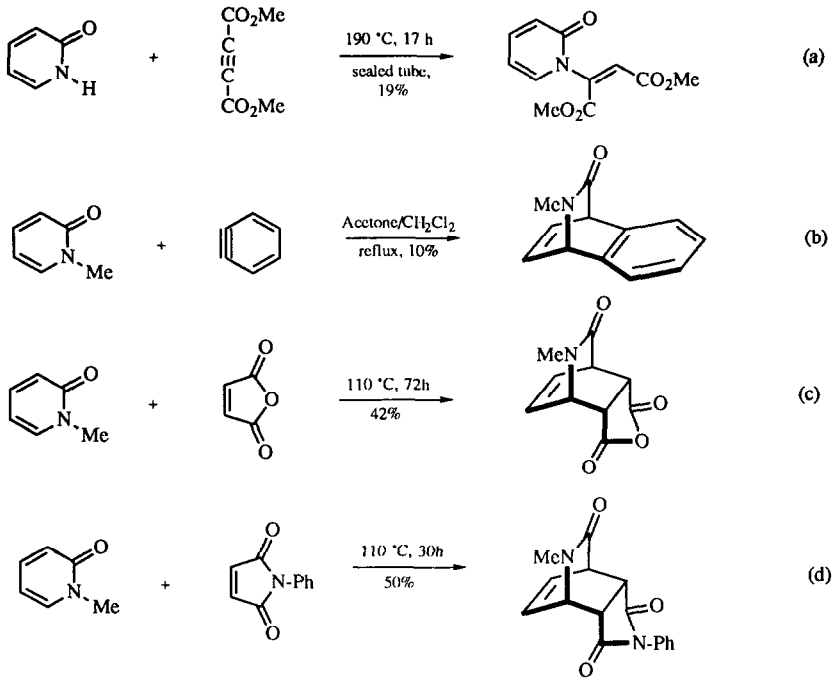

eq. 43

## B. 2-PYRIDONES.

### 1. [4+2] Cycloadditions: 2-Pyridones as Dienes.

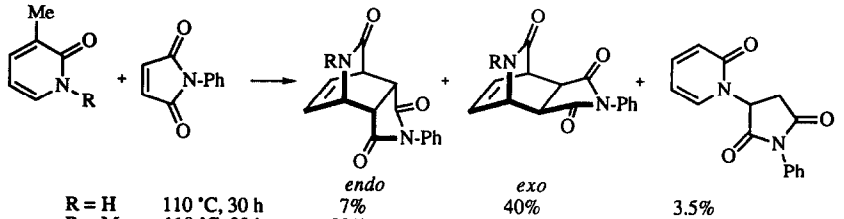
The earliest attempts to obtain cycloaddition between N-unsubstituted 2-pyridone and dienophiles were unsuccessful.[133] Instead, the products were obtained from Micheal type addition of 2-pyridone to the dienophile, commonly through nitrogen and occasionally through oxygen (Scheme 35a). Indeed, nucleophilc addition of 2-pyridones to activated multiple bonds is now a well established route to N-substituted pyridones.[134]

**Scheme 35**




The first successful cycloaddition was reported in 1968 and involved N-methylpyridone and benzyne (Scheme 35b).[135] This was followed soon afterwards by reports of cycloaddition of N-methyl-2-pyridone with maleic anhydride[136,137] (1969) and with N-phenylmaleimide[138] (1973) (Scheme 35c and d respectively). Subsequently, attention has remained focused on the cycloaddition of N-substituted pyridones, though it is now known that the lack of an N-substituent does not neccessarily rule out cycloaddition. For example, Kuzuya has re-examined the cycloaddition to benzyne (eq. b) and has reported cycloaddition of benzyne to N-unsubstituted pyridones, albeit in low yield.[139] Shusherina also has reported cycloaddition between N-unsubstituted pyridones and maleic anhydride or N-arylmaleimide (Scheme 35).[140] In this case, the lack of an N-substituent resulted not only in formation of Michael type adducts as by-products but also in production of more *exo* cycloadduct (eq. 44). The choice of the N-substituent has until recently been restricted to alkyl groups. An acyl group is not recommended

because this group migrates with great facility from nitrogen to oxygen, yielding 2-acyloxypyridines.[141] Although the sulfonyl group also is also prone to such migration, it has found synthetic application since the migration is sufficiently slow at the moderate temperatures required for cycloaddition.[142]



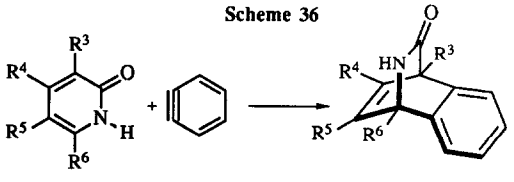
eq. 44

| | | *endo* | *exo* | |
|---|---|---|---|---|
| R = H | 110 °C, 30 h | 7% | 40% | 3.5% |
| R = Me | 110 °C, 32 h | 33% | 0% | 0% |

**a. With Alkynes.**

**Benzyne**: Cycloaddition of N-methyl-2-pyridone to benzyne was first reported by Bauer[135] and has been subsequently studied by Kuzuya and co-workers.[139] Through a study of cycloadditions of diversely substituted 2-pyridones, Kuzuya has shown that on the whole the Diels-Alder reactivity is raised as the number of ring substituents is increased (Scheme 36).[139,143] Furthermore , the 3- and 5-alkyl substituents seem to exert a greater influence than substituents at other positions on the enhancement of reactivity. A 4-phenyl substituent was also found to be very effective in enhancement of reactivity. Calculations of frontier molecular orbital (FMO) interactions between benzyne and 2-pyridone suggest that this reaction is of normal electron demand type, although the calculated HOMO-LUMO energy differences were close. The role of the 3- and 5-alkyl substituents and the 4-phenyl substituent as electron donating groups in enhancement of reactivity by lowering of the LUMO(benzyne)-HOMO(pyridone) energy difference thus was found to be justified. Kuzuya reports that 6-alkoxy substituted pyridones also undergo cycloadditions in good yields, though in every case only the naphthalene product (after the loss of an isocyanate) could be isolated. This suggestion is in contrast to the observations by Sammes regarding the cycloaddition to dimethyl acetylenedicaboxylate[144,145] (see below). No reference to steric factors in promotion of cycloaddition is made by Kuzuya. The replacement of a methyl substitutuent on the pyridone ring by an isosteric bromo substituent does result in lowering of reactivity, though electronic effects cannot be discounted.

Scheme 36

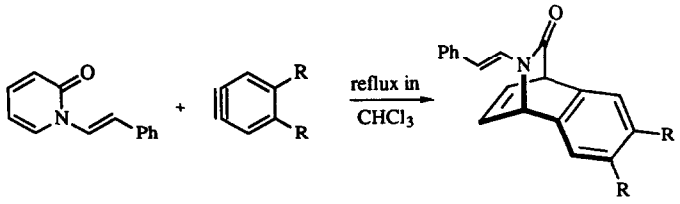


| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Yield[1] (%) |
|---|---|---|---|---|
| H | H | H | H | 7 |
| Me | H | H | H | 4 |
| H | Me | H | H | 12 |
| H | H | Me | H | 17 |
| H | H | H | Me | 4 |
| Me | H | Me | H | 15 |
| Me | H | Br | H | 7[2] |
| Me | Me | Me | Me | 8 |
| Me | Ph | Me | Me | 26 |
| Me | Ph | $-(CH_2)_3-$ | | 30 |

[1] The major product is the 2-pyridylphenyl ether.

[2] Small quantities of the N-phenylpyridone is also formed.

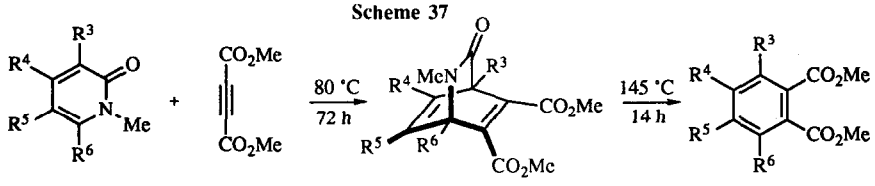
No report of the cycloaddition of unsymmetrically substituted benzynes to pyridones is yet available, although 4,5-dimethoxybenzyne and 4,5-dibenzyloxybenzyne both react with N-styrylpyridones to afford low yields of cycloadducts (eq. 45).[146,147]




eq. 45

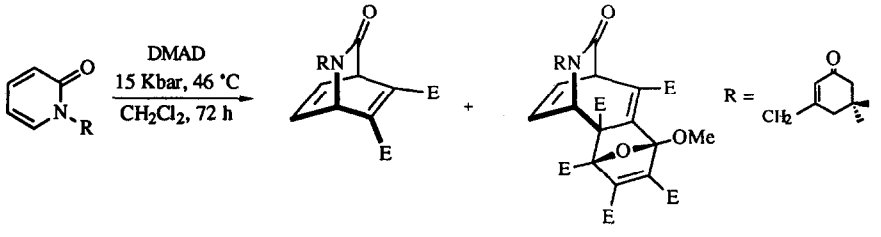
**Dimethyl acetylenedicarboxylate (DMAD)**: Cycloaddition of DMAD to pyridones failed to give any bicyclic adducts in the earliest attempts, though indirect evidence of their formation was presented through isolation of phthalate derivatives formed after loss of the isocyanate bridge.[133] The first bicyclic adduct from this type of cycloaddition was reported by Heep.[148] Although the 2-azabicyclo[2.2.2]octadiene cycloadducts were isolable, their ready fragmentation to methylisocyanate and dimethyl phthalate derivatives was observed. A study of the cycloaddition of the N-methylpyridones and DMAD found, based on unpublished MO calculations by the investigators, that reaction is of normal-electron-demand type, which is in agreement with Kuzuya's previous report.[144,145] However, no cycloadduct could be detected from the reaction of 6-methoxy-N-methylpyridone, whereas the 6-methyl derivative afforded 20% of cycloadduct (Scheme 37). [Comparision of the reactivity of the two molecules is made based on similar reaction conditions and not competition experiments. Also note that, as with Kuzuya's observations (see above), both 6-methoxy-N-methylpyridone and the 1,6-dimethylpyridone afford the corresponding dimethyl phthalate derivatives in similar yields after the loss of methylisocyanate when heated at 145 °C.] The authors conclude that steric as well as electronic factors play a role in this type of cycloaddition. A buttressing effect of the bulkier methyl group was cited for the contrast in reactivity.

Scheme 37



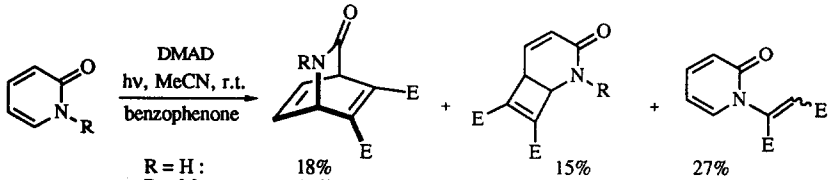

| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Yield (%) | Yield (%) |
|---|---|---|---|---|---|
| H | H | H | Me | 22 | 87 |
| Me | H | H | H | 0 | 21 |
| H | H | Me | Me | 70 | - |
| H | Me | H | Me | 31 | - |
| H | H | H | OMe | 0 | 96 |
| H | Ph | H | H | trace | 75 (after 110h) |
| H | Ph | H | Me | 70 | 89 |

High pressure is reported to aid the cycloaddition of pyridones with DMAD.[149,150] However, it afforded not only the desired 1:1 cycloadduct but also a 1:3 adduct, the structure of which was determined by crystallography (eq. 46).[151]




eq. 46

Photochemical cycloaddition of 2-pyridone and its N-methyl derivative did produce a [4+2] cycloadduct when no other ring substituents were present (eq. 47) (see section 2d).[152]

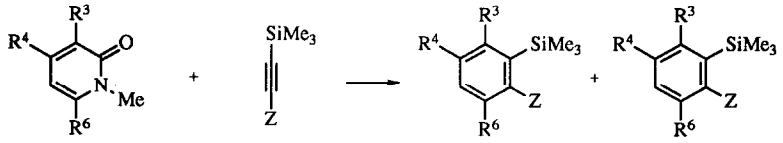



eq. 47

**Other acetylenes:** Addition of trimethylsilylacetylenes to ring-substituted pyridones leads to the formation of substituted biphenyls and benzoates (Scheme 38).[153] A modest regioselectivity is observed which is induced by electronic factors, though it is overpowered by steric factors for 1,3-dimethyl-2-pyridone.

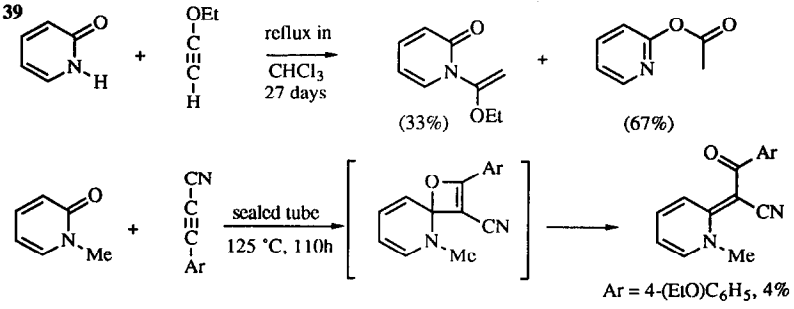
Although this methodology for the synthesis of substituted benzenes is well established for 2-pyrones, 2-pyridones are not commonly sought as starting materials. The reason is that cycloaddition is usually performed under more forcing conditions and can be inefficient. Additionally, it has been noted also that although the 2-aza-3-oxobicyclo[2.2.2]octadienes undergo retro Diels-Alder reaction by loss of an isocyanate group, the 2-aza-3-oxobicyclo[2.2.2]octenes usually revert to the starting pyridone and olefin.[148] The reason for the facile retro Diels-Alder reaction in this case is presumably the comparable aromaticity of the starting pyridone and the final benzene products.

**Scheme 38**



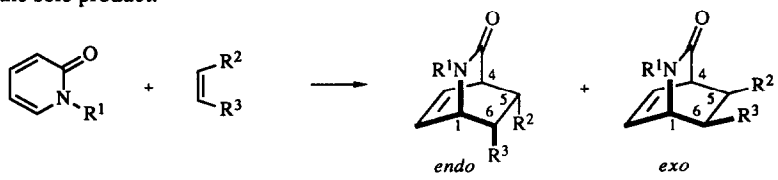

Finally, an attempted inverse-electron-demand cycloaddition between unsubstituted 2-pyridone and ethoxyacetylene failed to give any cycloadduct,[154] though inverse-electron-demand Diels-Alder cycloadditions of pyridones were subsequently successful.[142] Similarly, the adduct of 2-pyridone and a cyanoacetylene was shown not to be bicyclic (Scheme 39).[155]

**Scheme 39**



**b. With Symmetrically Substituted Alkenes.**

Cycloaddition of pyridones to olefins can result in two products of different relative configuration which are commonly refered to as the *endo* and *exo* isomers. Traditionally, in the addition of cyclic dienes to dienophiles, the *endo* cycloadduct is considered the kinetically favored isomer. However, from the earliest investigations, it became clear that the reaction does not always afford the *endo* isomer selectively, and sometimes the *exo* cycloadduct was found to be the sole product.



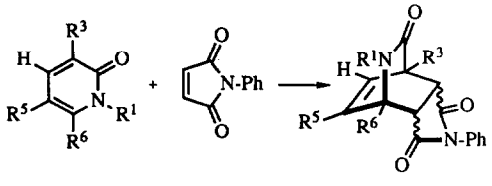

eq. 48

The theoretical basis of the *endo* selectivity was discussed in a review in 1974.[2] We refer the reader to this review for the interpetation of Alder's *endo* rule as applied to pyrones and pyridones. We will emphasize, however, that the assumed role for steric and electronic factors in the *endo* selectivity is valid only for kinetically controlled cycloadditions. In the thermodynamically controlled cycloadditions, these factors are outweighed by those governing relative stabilities of the *endo* and *exo* cycloadducts. Since the *exo* isomer has been shown to be more stable than the *endo* isomer, its formation is favored under thermodynamically controlled reaction conditions.[156]

Regardless of whether the cycloadditions are stereoselective or not, a reliable method for assignment of the relative configuration of cycloadducts is important, and a major part of early investigations was concentrated with this goal. Tomisawa used chemical derivatization to prove the *endo* configuration of the very first cycloadduct that was obtained from N-methyl-2-pyridone and maleic anhydride. As more cycloadducts were isolated, accumulation of their NMR data enabled Shusherina to develop an empirical rule for the assignment of the *endo*/*exo* configuration from the size of proton NMR couplings. This assignment, and its scope and limitations, will be discussed later (see section IV).

**Maleic anhydride, maleates and maleimides**: From a study of cycloadditions of ring substituted N-methylpyridones, it has been concluded that the presence of methyl substituents at the termini of the diene system (positions 3- and 6-) promotes *exo* cycloadduct formation (Scheme 40).[156,157]

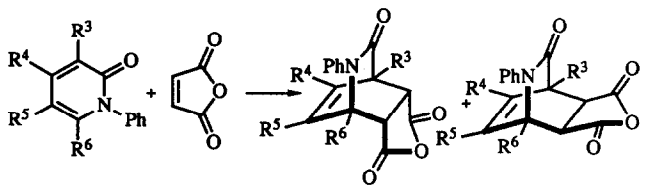
Scheme 40



| $R^1$ | $R^3$ | $R^5$ | $R^6$ | Conditions | Yield *endo* (%) | Yield *exo* (%) |
|---|---|---|---|---|---|---|
| Me | H | H | H | 110 °C, 30h | 50 | 0 |
| Me | Me | H | H | 110 °C, 32h | 33 | 0 |
| Et | Me | H | H | 80 °C, 47h | 13 | 0 |
| H | H | H | H | 110 °C, 30h | 30 | 20 |
| Pr | Me | H | H | 110 °C, 32h | 13 | 13 |
| H | H | -$(CH_2)_4$- | | 110 °C, 30h | 9 | 12 |
| H | Me | H | H | 110 °C, 30h | 7 | 40 |
| H | H | H | Me | 110 °C, 30h | 5 | 41 |
| H | H | Pr | Me | 80 °C, 50h | 1 | 20 |
| Pr | Me | H | H | 160 °C, 38h | 0 | 5 |
| Me | H | Me | Me | r.t., 55 days | 0 | 18 |
| Et | Me | H | H | 140 °C, 24h | 0 | 21 |
| Me | Me | H | H | 140 °C, 30h | 0 | 30 |
| H | H | Me | Me | 80 °C, 70h | 0 | 30 |
| Me | H | Pr | Me | 80 °C, 50h | 0 | 55 |

This trend is confirmed by a recent study regarding the cycloaddition of phenyl substituted N-methylpyridones under normal pressure and high pressure (Scheme 41).[158]

**Scheme 41**

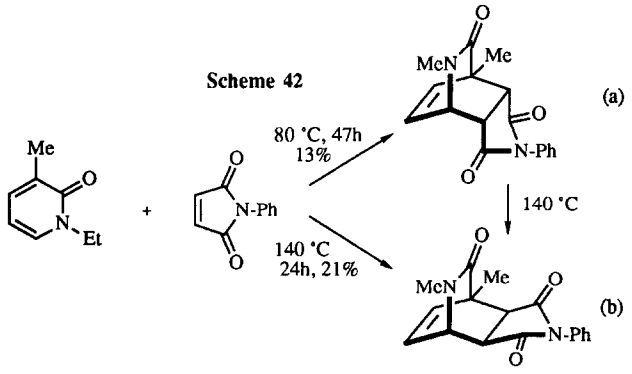


| $R^3$ | $R^4$ | $R^5$ | $R^6$ | Conditions | Yield (%) | *endo* : *exo* |
|---|---|---|---|---|---|---|
| Ph | H | H | H | A | 0 | |
| Ph | H | H | H | B | 76 | 34 : 66 |
| H | Ph | H | H | A | 50 | 100 : 0 |
| H | Ph | H | H | B | 13 | 85 : 15 |
| H | H | Ph | H | A | 90 | 100 : 0 |
| H | H | Ph | H | B | 96 | 81 : 19 |
| H | H | H | Ph | A | 0 | |
| H | H | H | Ph | B | 84 | 90 : 10 |

A : 110 °C, 1 Kbar, 72 h; B : 110 °C, 10 Kbar, 72 h.

Initial observations with N-methylpyridones hinted that the *exo* cycloadduct could not be formed as a result of thermodynamic equlibration since the *exo* cycloadducts were formed under similar or even much milder conditions than for the *endo* cycloadducts.[156,157] However, further studies showed this not to be true for 3-substituted N-alkylpyridones. Shusherina showed that for 1-ethyl-3-methylpyridone the *endo* cycloadduct is formed at lower temperature than the *exo* cycloadduct. Furthermore, the *endo* cycloadduct is transformed into the *exo* cycloadduct when heated at higher temperature (Scheme 42)[159] This observation suggested that the *endo* cycloadduct is the kinetic product and that, since the cycloaddition is believed to be reversible,[148] the *exo* cycloadduct, the thermodynamic product, is formed upon heating at higher temperatures. A similar observation was reported previously by a different group but apparently was not followed up.[160] Our group has found also that, in similar cases, an *endo* isomer can be epimerized into an *exo* isomer under acidic or basic conditions.[161]

**Scheme 42**



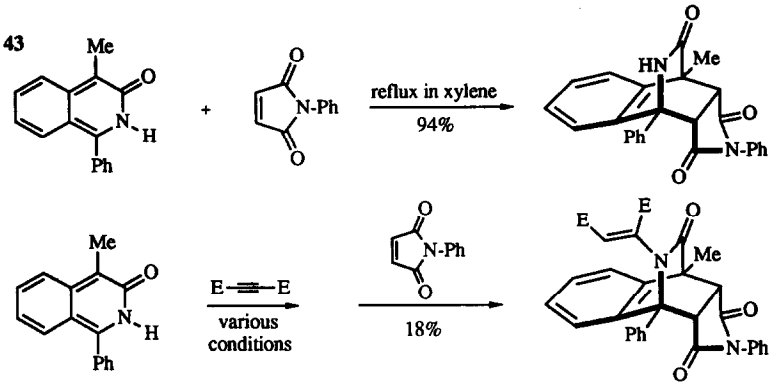
Although the 6-substituent also promotes (in some cases exclusive) *exo* cycloadduct formation,[156,157] no study has yet been performed to see if an *endo* cycloadduct from cycloaddition of such a pyridone would thermally isomerize into the corresponding *exo* cycloadduct.

Interestingly, and in contrast to the established rule that a 3- or 6-substituent promotes *exo* cycloadduct formation, Tomisawa and Hongo reported that cycloaddition of N-methylpyridone bearing an electron withdrawing carbomethoxy group at *any* position on the ring produced *endo* cycloadducts selectively.[162]

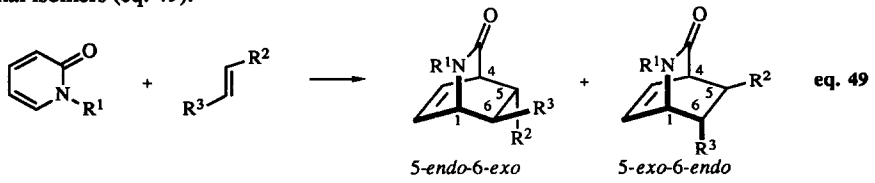
Finally, it has also been shown that the nitrogen substituent of the maleimide dienophile has no effect on the cycloadditions.[163]

3-(2H)isoquinolinones not substituted at nitrogen undergo cycloadditions to maleic anhydride and N-phenyl maleimide to afford the *endo* cycloadduct (assigned based on IR).[164a,b] However, addition to DMAD affords a Michael adduct only which did not undergo cycloaddition itself.[164c]

**Scheme 43**



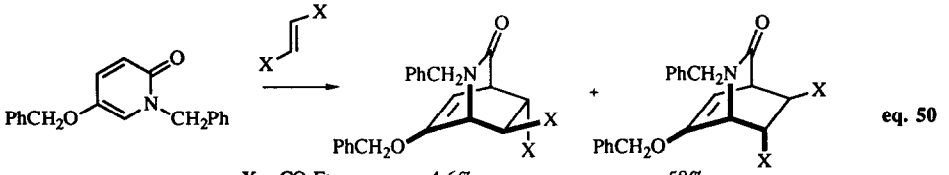

**Fumarates**: Cycloaddition of fumarates and other *trans* olefins to pyridones can afford also two configurational isomers (eq. 49).




*5-endo-6-exo* *5-exo-6-endo* **eq. 49**

The cycloaddition between N-substituted pyridone and dimethyl fumarate or fumaronitrile affords a single product, although the yields are quite low.[165] Extensive NMR studies led to the conclusion that the relative stereochemistry is 5-*endo*-6-*exo*.

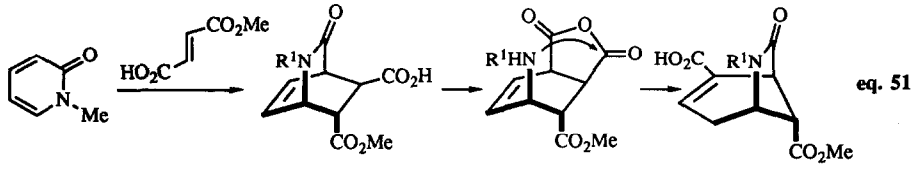
The presence of electron releasing groups at the 3- or 5-position changes the polarity in the expected manner.[162,166-168] The expected regioisomer is obtained also when an electron withdrawing group is present at the 3-position.[142] Interestingly, the major isomer in the cycloaddition of activated 5-benzyloxy-N-benzylpyridone and diethyl fumarate was shown to have the reverse 5-*exo*-6-*endo* configuration (eq. 50), even though the cycloadduct of the same pyridone to *trans*-1,2-(diphenylsulfonyl)ethene had a 5-*exo*-6-*endo* configuration.




**eq. 50**

| | | |
|---|---|---|
| X = $CO_2Et$ | 4.6% | 58% |
| X = $SO_2Ph$ | 87% | 8.3% |

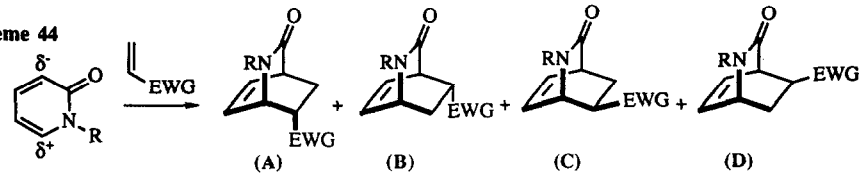
Interestingly, the cycloaddition of fumaric acid and its mono ester affords exclusively a 2-azabicylo[1.2.3]octene ring system. A mechanism for this transformation was proposed by Tomisawa,[169] and the assignment is supported by a deuterium labeling study.[170] Notice that the initial 2-azabicyclo[2.2.2]octene cycloadduct in the proposed mechanism has a 5-*exo*-6-*endo* configuration, in contrast to Tomisawa's own previous assignment of the dimethyl ester cycloadduct (eq. 51).




**c. With Unsymmetrically Substituted Alkenes.**

Addition of 2-pyridones to unsymmetrically substituted olefins can produce not only configurational (*exo*/*endo*) isomers but also regioisomers. The unsubstituted N-alkylpyridone ring is polarized as shown in Scheme 44, affording 6-*endo* cycloadduct (A) as the major product of cycloaddition.[171,172]

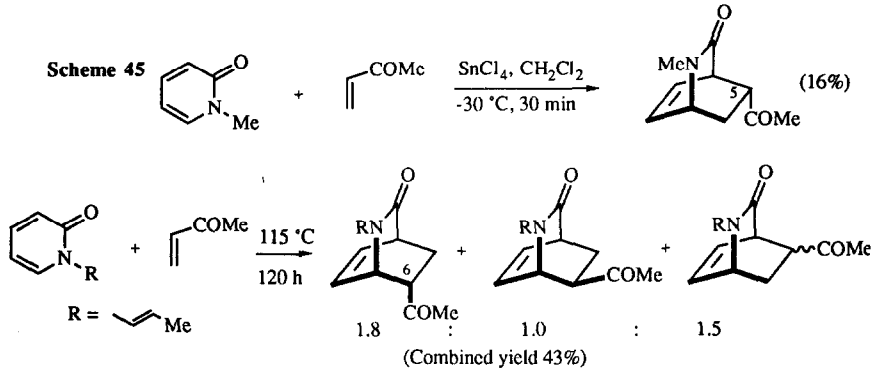
**Scheme 44**




| R | EWG | Conditions | (A) | (B) | (C) | (D) |
|---|---|---|---|---|---|---|
| Me | $CO_2Me$ | 135 °C, 3 days | 17% | 0% | 2% | 2% |
| Me | C≡N | 130 °C, 3 days | 14% | 0% | 7% | 7% |
| $CH_2Ph$ | $CO_2Me$ | 135 °C, 14 days | 17% | 1.4% | 0.8% | 0.4% |

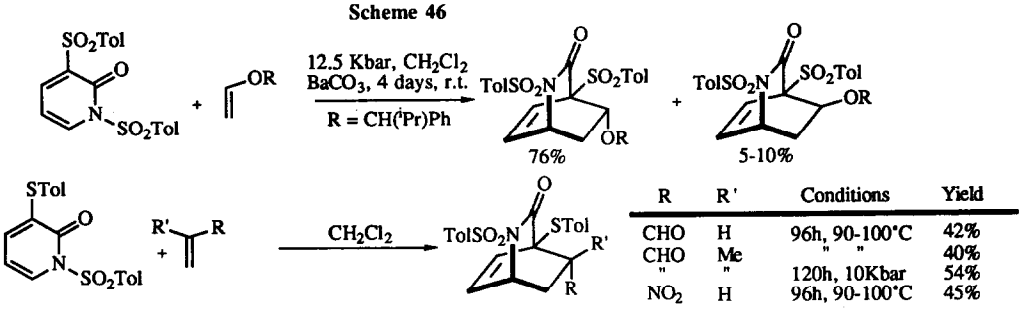
Only one example of the use of Lewis acids for the control of regiochemistry has been reported.[173] In this case, the reverse regioisomer was obtained as the only product, which the authors attributed to coordination of both the pyridone and methyl vinyl ketone carbonyl groups to the Lewis acid. Although there is independent evidence of the aptitude of the oxygen of 2-pyridone to coordinate to Lewis acids,[174] the reported outcome of this cycloaddition cannot be confirmed due to lack of physical data. Notice that cycloaddition of N-styrylpyridone to the same dienophile under thermal conditions is reported to afford the 6-substituted bicyclic lactam.[175]

**Scheme 45**




For the past six years, our group also has been interested in the study of pyridone cycloaddition, and we have made extensive use of N-sulfonylated pyridones. The advantages of N-sulfonylated pyridones over N-alkyl pyridones relate mostly to the greater facility of the cycloaddition and the much improved regiocontrol. The normal-electron-demand reaction was found to be stereospecific, giving only the *endo* cycloadduct. These cycloadditions afford no *exo* cycloadduct within the limits of detection by high field $^1H$ NMR.[164]

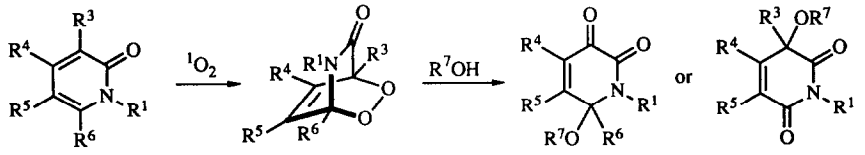
Scheme 46




| R | R' | Conditions | Yield |
|---|---|---|---|
| CHO | H | 96h, 90-100°C | 42% |
| CHO | Me | " " | 40% |
| " | " | 120h, 10Kbar | 54% |
| $NO_2$ | H | 96h, 90-100°C | 45% |

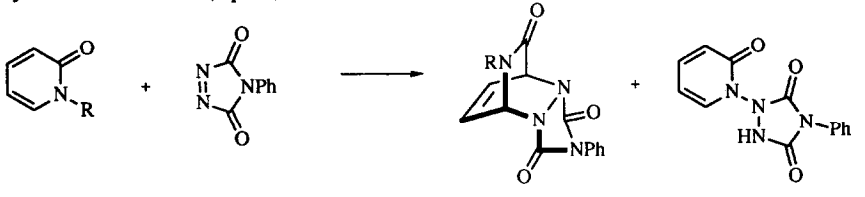
### d. With Other Dienophiles.

N-Substituted pyridones undergo [4+2] cycloaddition to singlet oxygen under photochemical conditions to afford 3,6-dioxygenated pyridones (cycloadducts not isolable or detectable).[176] Such photochemical cycloadditions to pyridones are not rare, though it is rare to obtain [4+2] cycloadducts in this way. More commonly, [2+2] and [4+4] cycloadducts are obtained.[177] The only other example of [4+2] cycloaddition to pyridones under photochemical conditions is that cited above (see eq. 47).




$R^3$ = H, 11-26% $R^6$ = H, 14-65%

Cycloaddition of pyridones to 1-phenyl-1,3,4-triazapenta-2-5-dione also has been reported.[178] Unlike the cycloaddition of 2-pyridone to N-phenyl maleimide (see Scheme 41), in this case the lack of N-substitution afforded *exclusively* a Michael adduct (eq. 53).[179]

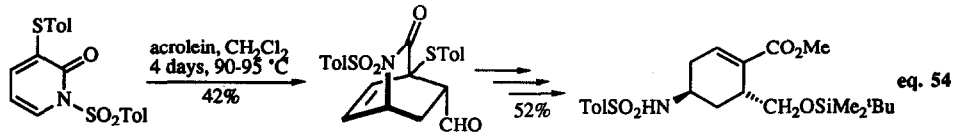



R = Mc 80% 0%
R = H 0% 78%

### e. Synthetic Applications.

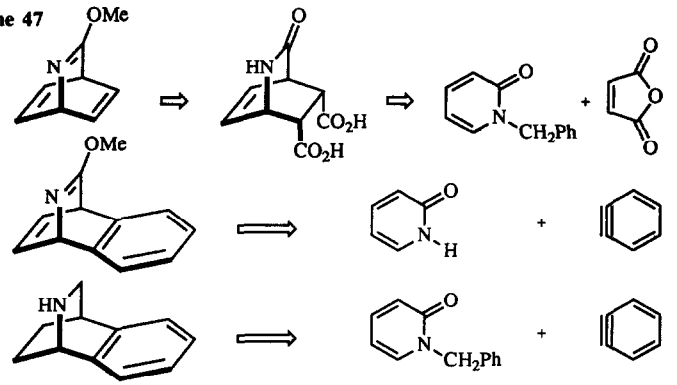
Surprisingly, there has been little use of pyridone cycloadditions for synthesis of natural product targets. The isoquinuclidine skeleton, which is formed by [4+2] cycloaddition of pyridones and alkenes, is found in many natural products. However, ibogamine is the only alkaloid synthesized to date by this methodology. The main reason for this lack of interest presumably arises from the fact that the isoquinuclidine skeleton can be assembled through the Diels-Alder cycloadditions of cyclic azadienes with equal or better efficiency.[180]

An alterative approach, pioneered by our group, has applied this methodology to synthesis of fuctionalized cyclohexenes which can be used as synthetic building blocks for a number of target molecules (e. g. eq. 54).[161]




The cycloaddition of pyridones has been used also for synthesis of other target molecules in addition to natural products. Azabarellane[181] and benzoazabarellane[138] were first synthesised by pyridone cycloadditions (Scheme 47). Two groups have used this methodology for synthesis of rigid analogues of adrenergic agents.[182] Synthesis of biphenyls also has been reported (see Scheme 38).

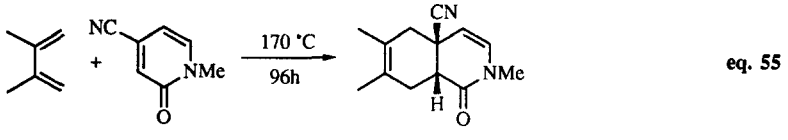
**Scheme 47**



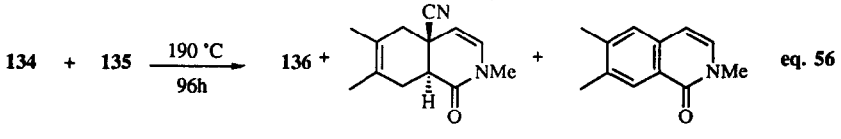

## 2. [2+4] Cycloadditions: 2-Pyridones as Dienophiles

Many references in the literature deal with Diels-Alder reactions of pyridone derivatives used as dienes. However, few references are available concerning reactions of pyridone as **dienophiles.**

The first succesful report cited the reaction of 4-cyano-1-methyl-2-pyridone (**134**) with 2,3-dimethyl-1,3-butadiene (**135**).[183] It is interesting to note that the hydroisoquinoline derivative obtained can be useful as an intermediate for the synthesis of isoquinoline alkaloids. When the reaction was carried out at higher temperature, a mixture of **136, 137** and **138** was obtained.




**135** **134** **136**, 71%

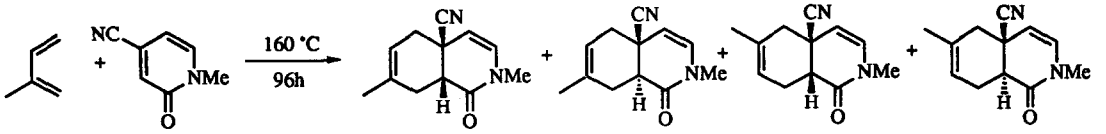



31% 137, 7.5% **138**, 17%

Both compounds **136** and **137** gave isoquinolone **138** upon heating with Pd-asbestos. When *cis*-decalin derivative **136** was heated at 190 °C, *trans*-compound **137** was obtained. However, the same treatment of **137** did not afford **136**; as is known, *trans*-decalin derivatives are in general stereochemically more stable than *cis*-decalin derivatives.

The same authors later extended this methodology by the use of the different butadiene **139**.[184, 185]

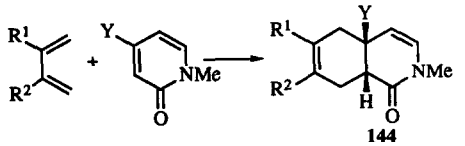
**Scheme 48**




**139** **134** **140**, 6% **141**, 4% **142**, 4% **143**, 1.4%

When the substituent at position 4 in the pyridone is an ester or an acetyl group, the reaction with butadiene produces regioselectively the *cis*-tetrahydroisoquinolones in good yields.

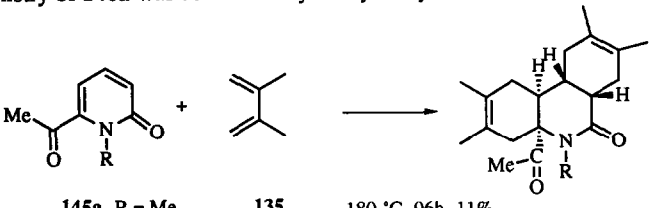
**Scheme 49**




**144**

| Y | $R^1$ | $R^2$ | 144 (%) |
|---|---|---|---|
| COOMe | H | Me | 50 |
| COOMe | Me | Me | 83 |
| COMe | H | Me | 98 |
| COMe | Me | Me | 42 |

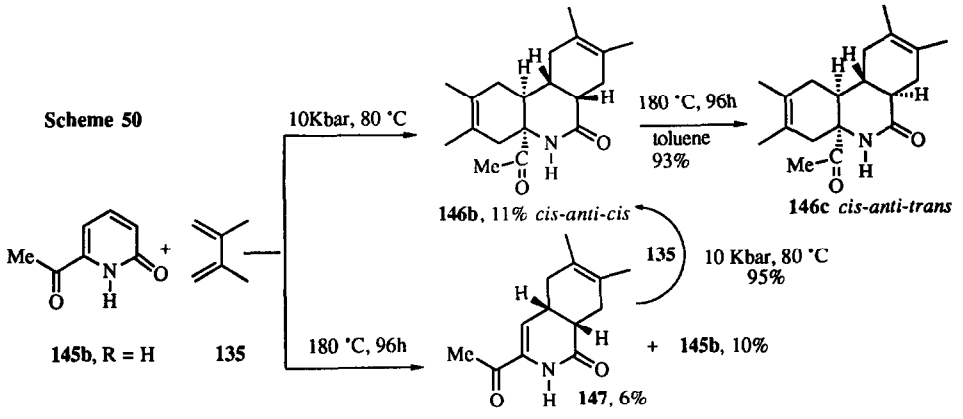
Recently, the first examples of double Diels-Alder cycloadditions of 2-pyridones used as dienophiles under atmospheric and high pressure conditions[186] were reported. Diels-Alder cycloaddition of 6-acetyl-1-methyl-2-pyridone (**145a**) with the diene **135** gave stereoselectively the *cis-anti-cis* adduct **146a** in moderate yield; the *cis-anti-cis* stereochemistry of **146a** was confirmed by X-ray analysis.




**145a**, R = Me **135** 180 °C, 96h, 11% 10Kbar, 80 °C, 19% **146a** eq. 57

When the starting pyridone is not substituted at position 1, the reaction with the diene gave different results under high and atmospheric pressure conditions. Thermal conversion of the *cis-anti-cis* adduct **146b** under the same atmospheric pressure conditions gave the *cis-anti-trans* adduct **146c** in excellent yield.

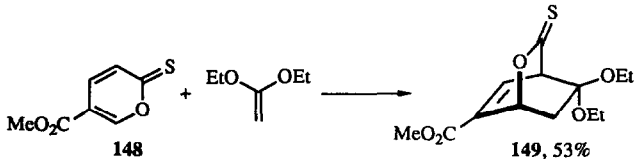
**Scheme 50**




**145b**, R = H **135** **146b**, 11% *cis-anti-cis* **146c** *cis-anti-trans* **147**, 6% + **145b**, 10%

## C. 2-THIOPYRONES AND 2-THIOPYRIDONES.

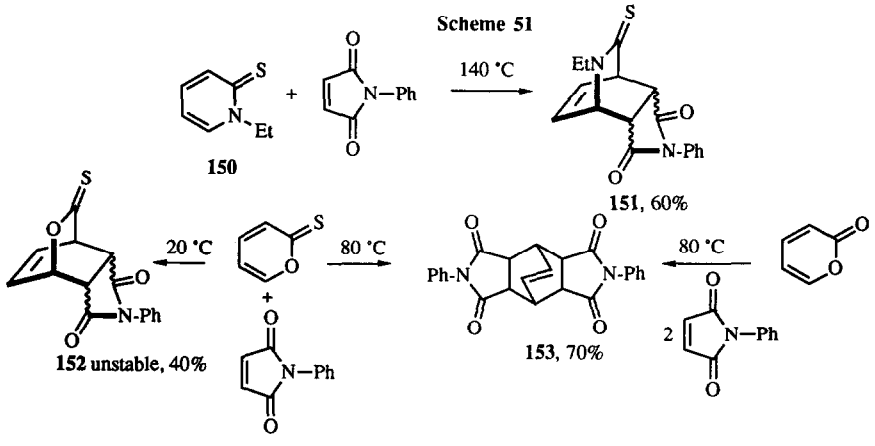
Both pyran-thiones[187] and pyridine-thiones[188] are considered more aromatic than their oxygen analogs. Therefore, they are less likely to react as dienes in a Diels-Alder fashion. That is probably why [4+2] cycloadditions of these thio analogs have not received much attention. The first example reported[85] involves reaction of pyran-thione **148** with a ketene acetal leading to the cycloadduct **149** in moderate yield.



**148** **149**, 53% eq. 58

Later on, the [4+2] cycloadduct **151** was obtained[189] from the reaction of 1-ethyl-2-thiopyridone (**150**) with N-phenylmaleimide; no mention was made about the configuration of the products. The reaction of 2-thiopyridone with N-phenylmaleimide at 18-20 °C led to the production of the unstable adduct **152**. At 80 °C only the bisimide **153**, lacking sulfur and formed as a result of the reaction of 2-thiopyrone by a double diene synthesis, was obtained.[2]

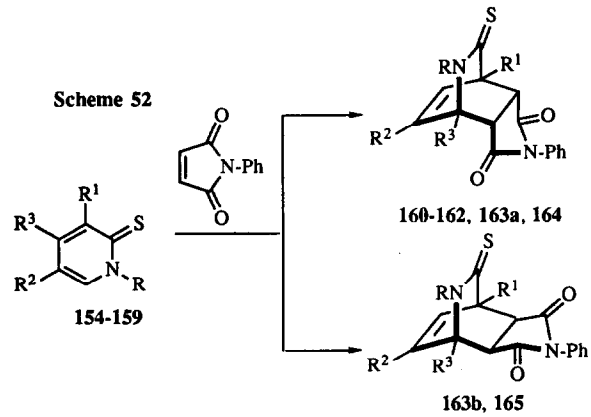
Scheme 51



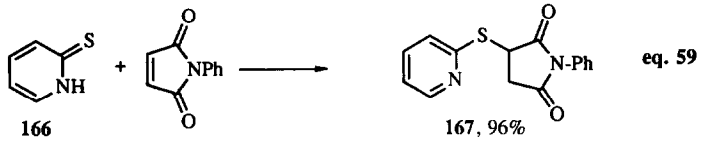
Later on, the study was extended[190] by using 1,3-dimethyl-, 1,5-dimethyl-, and 1,6-dimethyl-5-propyl-2-thiopyridones (**154-159**) in order to trace the effect of the substituents on the stereochemistry of the reaction. 1-Alkyl-2-thiopyridones without substituents at the ends of the conjugated diene system (**154-156, 158**) form 1,4-cycloadducts (**160-162, 164**) with the *endo* configuration, irrespective of the temperature of cycloaddition. In contrast, 1,6-dimethyl-5-propyl-2-thiopyridone (**159**) forms the adduct **165** with the *exo* configuration both at 110 and 140 °C. The reason for this is evidently the *exo*-directing effect of the methyl group at position 6 of the initial thiopyridone **159**[2] This phenomenon is also observed in the [4+2] cycloadditions of 2-pyridone dienes (*vide supra*) and 2-pyrone dienes (*vide supra*). The formation of the *exo*-adduct **163b** at 140 °C from **157** is due to thermal isomerization of the initially formed *endo* adduct **163a**.

In contrast to its oxygen analog, the simple nitrogen unsubstituted-2-thiopyridone **166** does not enter into cycloaddition with N-phenylmaleimide, but it does form the Michael adduct **167**.[191]

Scheme 52




| Thiopyridone | R | $R^1$ | $R^2$ | $R^3$ | Cycloadduct (%) | Temperature (°C) |
|---|---|---|---|---|---|---|
| **154** | $CH_3$ | H | H | H | **160** (63) | 140 |
| **155** | $C_2H_5$ | H | H | H | **161** (60) | 140 |
| **156** | $C_3H_7$ | H | H | H | **162** (69) | 140 |
| **157** | $CH_3$ | $CH_3$ | H | H | **163b** (30) | 140 |
| **158** | $CH_3$ | H | $CH_3$ | H | **164** (53) | 140 |
| **159** | $CH_3$ | H | $C_3H_7$ | $CH_3$ | **165** (61) | 140 |
| **157** | $CH_3$ | $CH_3$ | H | H | **163a** (29) | 110 |



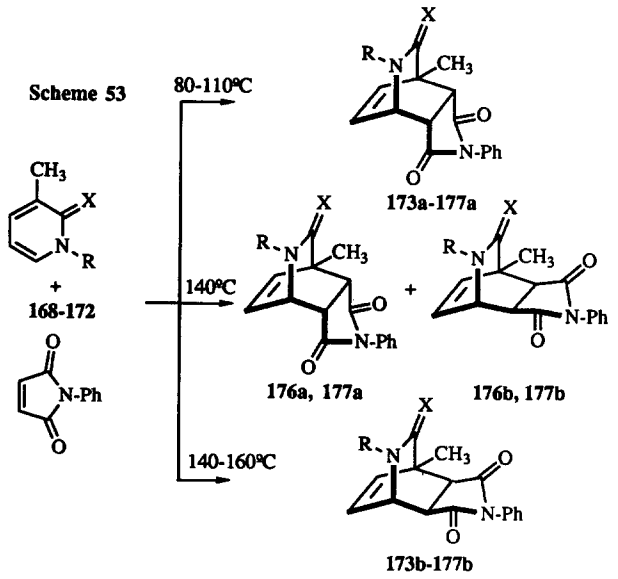

**166** **167**, 96%

eq. 59

The same authors also studied the change in the stereochemistry of the reaction of 1-alkyl-3-methyl-2-pyridones and their thio analogs with N-phenylmaleimide at various temperatures.[159] The *endo* adducts **173a-177a** were obtained from the pyridones at the lowest temperatures at which their reaction with the dienophile occurred (80-110 °C). In the range of temperatures 110-140 °C, mixtures of the *endo* and *exo* isomers **173a-b** and **177a-b** were formed. By increasing the temperature to 140-160 °C, the individual *exo* isomers **173b, 174b, 175b** from the pyridones **168-170** were formed, whereas mixtures of stereoisomers were formed from the corresponding thiopyridones **171** and **172** at 140 °C. Reactions at 160 °C gave only resins. The authors concluded that the formation of the *exo* isomers was due to thermal isomerization of the corresponding *endo* adducts, which were obtained as a result of kinetically controlled reactions. This isomerization was probably due to the presence of the methyl group at position 6.

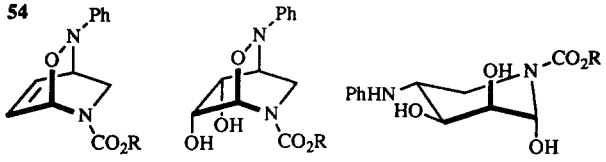
Streith and coworkers[192] described a simple three-step synthesis of racemic diamino-sugars **180** from 1,2-dihydropyridines and nitrosobenzene. The first step was a Diels-Alder cycloaddition that led regiospecifically to bicyclic product **178**. This product was then oxidized to the glycol **179** and then hydrogenolysed to the expected racemic diaminosugar **180**.

**Scheme 53**




| Diene | X | R | Conditions | Cycloadduct (%) |
|---|---|---|---|---|
| 168 | O | $CH_3$ | 80-110 °C | **173a** (33) |
| 168 | O | $CH_3$ | 140-160 °C | **173b** (30) |
| 169 | O | $C_2H_5$ | 80-110 °C | **174a** (13) |
| 169 | O | $C_2H_5$ | 140-160 °C | **174b** (21) |
| 170 | O | $C_3H_7$ | 80-110 °C | **175a** (26) |
| 170 | O | $C_3H_7$ | 140-160 °C | **175b** (50) |
| 171 | S | $C_2H_5$ | 110 °C | **176a**, (22) |
| 171 | S | $C_2H_5$ | 140 °C | **176a /176b** (1/2.3) (16) |
| 172 | S | $C_3H_7$ | 110 °C | **177a** (18) |
| 172 | S | $C_3H_7$ | 140 °C | **177a/177b** (1/1.5) (29) |

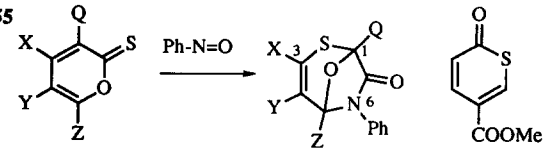
**Scheme 54**



**178** **179** **180**

2-Pyrone is known to react with nitrosobenzene, but the cycloadduct loses $CO_2$ rapidly.[193] The authors prepared the pyran-2-thiones **181a-g** by reacting the corresponding pyrones with Lawesson's reagent.[194] Reaction with nitrosobenzene under mild conditions led then to the adducts **182.**

**Scheme 55**



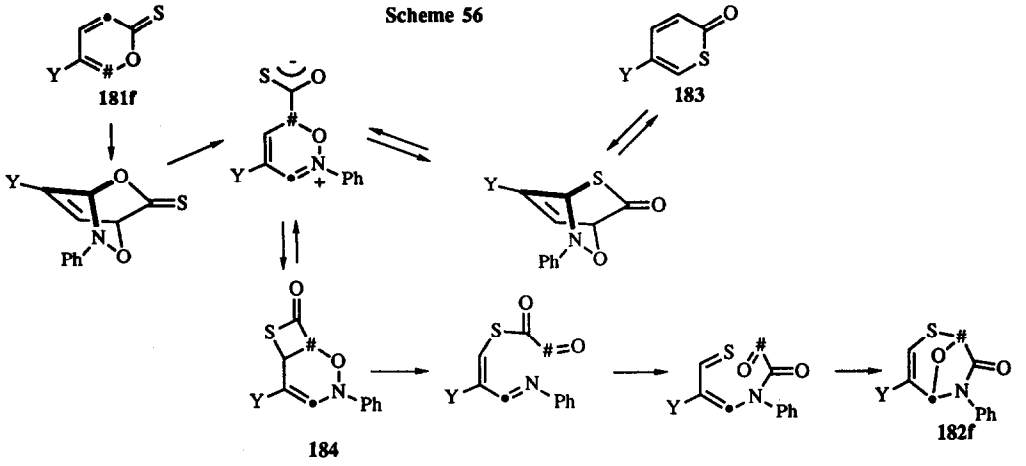

**181a-g** **182a-g** **183**

| | Q | X | Y | Z | Conditions | Yield (%) 182 | 183 |
|---|---|---|---|---|---|---|---|
| **a (b)** | H | H | H | H(D) | 3d, 20 °C | 92 | - |
| **c** | Me | H | H | Me | 10d, 20 °C | 61 | - |
| **d** | H | Me | H | Me | 14d, 20 °C | no reaction | - |
| **e** | H | H | $CF_3$ | H | 1.5d, 40 °C | 93 | - |
| **f** | H | H | $CO_2Me$ | H | <1h, 20 °C | 69 | 20 |
| **g** | H | $CO_2Me$ | H | $CF_3$ | 5d, 40 °C | 34 | - |

At room temperature, 5-substituted thiopyrone **181f** reacted quickly with nitrosobenzene giving the expected adducts **182f** (69%) and **183** (20%). At about -10 °C, the reaction of equimolar amounts of **181f** and nitrosobenzene led quantitatively to an intermediate **184** which disappeared in favour of **182f** and **183** when heated at room

temperature.

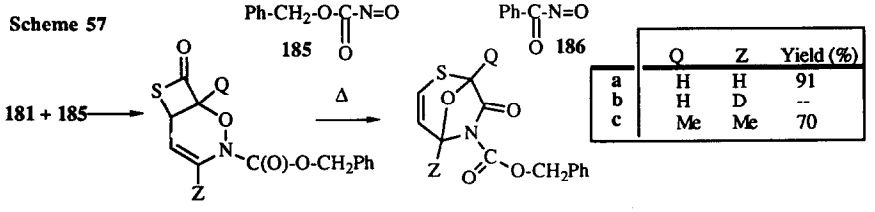
Scheme 56



(For clarity, # and • are used to keep track of carbon atoms in Scheme 56)

The pyran-thiones **181a-c** also reacted with the acylnitroso derivatives **185** and **186** to give the corresponding thieto-oxazines **187a-c** that are stable at room temperature; however, upon heating, these oxazines isomerized quantitatively into the expected bicyclic compounds **188a-c**.

Scheme 57



| | Q | Z | Yield (%) |
|---|---|---|---|
| a | H | H | 91 |
| b | H | D | -- |
| c | Me | Me | 70 |

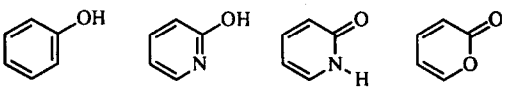
## III. REACTIVITY AND SELECTIVITY ASPECTS.

In this section we will consider the factors that have a role in predicting the **reactivity** of 2-pyrones and 2-pyridones toward cycloaddition and those factors that influence the **selectivity** of cycloadditions.

### A. Aromaticity of Pyrones and Pyridones.

The conventional representations of the 2-pyridones and 2-pyrones emphasize their structures as cyclic dienes. However, since both ring systems are capable of exhibiting aromatic chemistry, such as electrophilic substitution,[195] they have been classed also as aromatic rings. In addition to chemical properties, some of their spectroscopic characteristics (NMR, UV) also support this view.[196] Various studies have indicated that 2-pyrones and 2-pyridones are less aromatic than benzene, though these studies have differed in the degree of aromaticity attributed to each ring system. In general, 2-pyrones and 2-pyridones are considered to possess about 20-40% of the aromatic resonance characteristic of benzene.[187,197] Notice that, strictly speaking, benzene is not the correct point of reference for a comparision of aromaticity since the carbocyclic analogue of both ring systems is phenol.

Scheme 58



The aromatic stablization of pyrones and pyridones has two important influences on the outcome of cycloadditions. First, the activation barrier for cycloaddition is higher than that for non-aromatic dienes, so more activation energy (e.g. higher reaction temperatures) must be supplied for the Diels-Alder reaction. Second, in some cases, the retro Diels-Alder reaction (not to be mistaken with the $CO_2$ or RN=C=O extrusion reaction discribed previously) becomes a possibility, driven by the enthalpy gain. Some cycloaddition reactions, therefore, become reversible, leading ultimately to the thermodynamically more stable *exo* cycloadducts. We have already seen how such retro Diels-Alder reactions affect the *endo*/*exo* selectivity of the cycloaddition of 2-pyridones to maleimides.[159]

In general, the presence of substituents that would impair the delocalization of electrons over the ring system would promote diene character and therefore cycloaddition. In particular, for 2-pyridones where the availability of the nitrogen lone pair for delocalization is crucial, the nitrogen substituent has an important role.

In the case of N-unsubstituted 2-pyridones, a distinct aromatic tautomer exists, in the form of the corresponding 2-pyridinols (Scheme 59). The non-aromatic tautomer, 2-pyridone, is dominant ($K_{eq}$ ca. $10^7$)[198] which should be contrasted with the virtual lack of a non-aromatic keto tautomer for phenol. The pyridinol tautomer does not undergo 4+2-cycloaddition, but it is reactive toward activated olefins and acetylenes. In fact, it undergoes 1,2-addition to activated multiple bonds. Therefore, instead of cycloaddition products from reactions of N-unsubstituted pyridones, 1,2- (Michael-type) adducts to the dienophile are formed. Thus, formation of these 1,2-adducts, which is indicative of the position of equilibrium more in favor of the pyridinol tautomer, is taken to be diagnostic of the lack of enophilicity of pyridones.[199] Little is known about the influence of ring substituents on this tautomeric equilibrium, though theoretical studies suggested that a strong electron withdrawing nitro substituent shifts the equilibrium even more in favour of the pyridone tautomer.[199] The solvent also plays a role in the position of tautomeric equilibrium.[200]

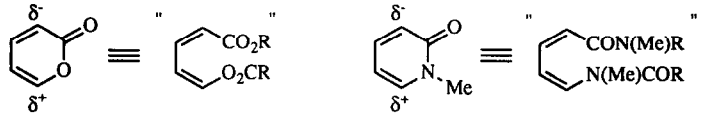
**Scheme 59**


To allow a more detailed scrutiny of the two ring systems, we will discuss electronic and steric features separately and the role that each plays in determination of reactivity or degree of selectivity.

## B. Electronic Features

Regardless of the presence of any substituents that may further influence their electronic nature, 2-pyrones and 2-pyridones are already polarized dienes owing to the carboxyl/carboxamide functional group that joins the termini of the diene system. For simplicity, each of the two may be considered as a non-cyclic diene which bears an electron withdrawing carboxylate or carboxamide at one end and another independent electron releasing acyloxy or acylamino group at the other end (Scheme 60). This crude approximation is useful for a rough analysis of the polarity of the diene component such as applied to the regioselectivity of cycloaddition, as will be demonstrated shortly.

**Scheme 60**




### The Nitrogen Substituent of 2-Pyridones

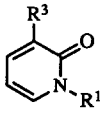
The electronic role of the nitrogen substituent may at first appear to be obscure. On one hand, strong electron withdrawal from nitrogen would help in activation of the 2-pyridone by removing the oppotunity for delocalization of

the nitrogen electron pair. On the other hand, it also weakens the electron push by nitrogen which, as described above, is responsible for the polarization of the diene, hence weakening the enophilic potency. In contrast, an electron-releasing-group on nitrogen would have the opposite effect on both counts.

No reports of cycloaddition of pyridones, substituted at the nitrogen by a strongly electron-releasing-group, to dienophiles exists though N-alkyl-2-pyridones are commonly employed. Our group has pioneered the use of strongly electron-withdrawing sulfonyl substituents at nitrogen.[142,161] We have found that the choice of the electron-withdrawing group is limited. N-Acyl pyridones can be formed only at low temperatures, because at room temperature they rearrange rapidly to O-acyl pyridinols.[201,202] Similarly, N-carbamates cannot be formed at 0 °C, because facile N-O rearrangement affords the corresponding O-carbonates only. We have used N-sulfonylpyridones successfully since the rearrangement to O-sulfonyl pyridinols occurs at high temperatures[203,161] (above 100 °C) and since, at the normal temperature window for the Diels-Alder reaction, these N-O migrations are not significant. The less electron-deficient N-vinyl pyridones, including N-styryl pyridones, also have been successfully employed, though the cycloaddition yields are rather poor.[175]

A closer examination of the spectroscopic properties of N-sulfonyl and N-alkyl pyridones (Scheme 61) reveals how the N-sulfonyl group diminishes ring electron current more significantly than does the N-methyl group. For instance, for an otherwise similarly substituted pyridone, a larger C=O infrared stretching frequency is recorded for the N-sulfonyl compound than for the N-methyl compound. Accordingly, it has been demonstrated also that stronger electron withdrawal of the N-sulfonyl group than the N-methyl group does afford higher cycloaddition yields in inverse-electron-demand type cycloadditions.[161]

**Scheme 61**



| $R^3$ \ $R^1$ | Me | H | -CH=CHMe | $SO_2Tol$ |
|---|---|---|---|---|
| MeO | 1659 | 1660 | not available | 1673 |
| H | 1659 | 1658 | 1668 | 1677 |
| $TolSO_2$ | 1650 | not available | not available | 1685 |

infrared stretching frequency of C=O in $CHCl_3$ solution in $cm^{-1}$

It is expected, based on simple MO theory, that the electron-withdrawing group at nitrogen results in a lowering of HOMO energy levels. This has an adverse effect on normal electron demand cycloaddition since it causes a greater mismatch in the expected orbital interaction. At the same time, it does not help the inverse-electron-demand cycloaddition since it has little effect in lowering of the LUMO. Therefore, such pyridones usually need a further activating group to facilitate the cycloaddition and to improve the regioselectivity and stereoselectivity. Indeed, both strongly electron-releasing[161,166-168] and electron-withdrawing groups[142] fit this role well.

### Other Ring Substituents

In practice, it is found that unsubstituted 2-pyridones and 2-pyrones are nucleophilic dienophiles: they undergo normal-electron-demand type Diels-Alder reactions with electron-deficient dienophiles (see section 2.3). They are found, however, to show poor regioselectivity. Presumably, the directing group is the endocyclic heteroatom, and its weak electron donating power makes the cycloaddition unselective. We will discuss the effect of substituents on the regiochemistry of cycloaddition shortly, but first a short discussion on the reactivity of 2-pyrones and 2-pyridones will be presented.

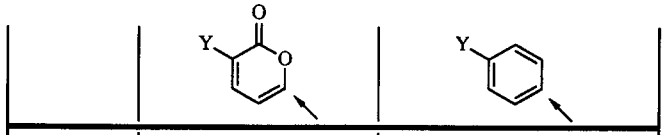
Although the built-in directing power of the ring system is weak, it can be greatly enforced or even reversed by the directing power of any other ring substituent. For instance, 2-pyridones and 2-pyrones bearing highly

electron-withdrawing ring substituents undergo inverse-electron-demand Diels-Alder cycloadditions to electron-rich dienophiles. Furthermore, 2-pyridones and 2-pyrones bearing highly electron-releasing ring substituents undergo normal-electron-demand Diels-Alder cycloadditions to electron-poor dienophiles in better yields and with higher selectivity than the unsubstituted ones.

For 2-pyrones, even if the ring substituent is not highly electronically biased, cylcoaddition is achieved under relatively mild conditions. For instance, 2-pyrones bearing an electron-releasing group as weak as an acetoxyl still undergo normal-electron-demand cycloadditions at moderate temperatures or pressures.[94]

As with 2-pyridones, we have used spectroscopic data to determine the relative apptitude of substituted 2-pyrones towards cycloaddition. We have in particular focused on the chemical shift of C-6 in 3-substituted 2-pyrones (Table 3). To complement this theoretical outlook, we have established a reactivity trend towards vinyl ethers by pyrones bearing electron-withdrawing substituents at the 3-position through competition experiments. By using the chemical shift of C-6, any proximity effects with the 3-substituent would be negligible. For comparison, Table 3 also includes $^{13}C$ NMR data for the *para* position in Y-substituted benzenes. As expected, sulfonyl pyrone **109** was the most electron-deficient pyrone diene. Indeed, competition experiments proved that this pyrone was the most reactive of these pyrone diene under inverse-electron-demand conditions. Also, competition studies showed that the carboxylate pyrone was more reactive than 3-bromo-2-pyrone which in turn was more reactive than 2-pyrone.

**Table 3.** $^{13}C$ NMR Chemical Shift Data



| Y | $^{13}C$ (ppm) | $^{13}C$ (ppm) |
|---|---|---|
| $ArSO_2$- | 157.1[1] | 133.6[2] |
| $MeO_2C$- | 156.5 | 132.8 |
| Br- | 150.9 | 127.0 |
| H- | 151.7 (Δ 4.7) | 128.5 (Δ 1.6) |
| ArS- | 147.0[1] (Δ 9.6) | 126.9[2] (Δ 7.1) |
| $R_3SiO$- | 144.0[3] | 121.4[4] |
| HO- | 142.1 | 121.4 |

[1] Ar=Tol [2] Ar=Ph [3] R=*t*-BuMe$_2$ [4] R=Me$_3$

Other work had previously demonstrated that 3-hydroxy-2-pyrone (**104**) underwent highly efficient normal-electron-demand Diels-Alder cycloaddition; however, the bicycloadducts were often unstable and decomposed upon attempted isolation.[24] From the data in this table (Table 3), we expected that 3-arylthio-2-pyrones would be suitable candidates as nucleophilic dienes in [4+2] cycloadditions with electron-deficient dienophiles. This was indeed the case, and we were able to isolate the *endo* bicyclic adducts after reactions at, or below, 90 °C.[111]

Table 3 indicates that 2-pyrone and 3-bromo-2-pyrone, since their chemical shift values were between the two extremes of the scale, might function in both nucleophilic and electrophilic capacity. Unfortunately, 2-pyrone is prone to rapid polymerization under thermal conditions, and therefore few examples of its cycloadditions are known. In the reported cycloadditions, regioisomeric bicycloadducts have resulted with little or no selectivity.[91] We did find, however, that 3-bromo-2-pyrone, which is not thermally labile, was a slightly more reactive diene than unsubstituted

2-pyrone and underwent regio- and stereoselective cycloaddition reactions with both electron-rich and electron-deficient dienophiles.

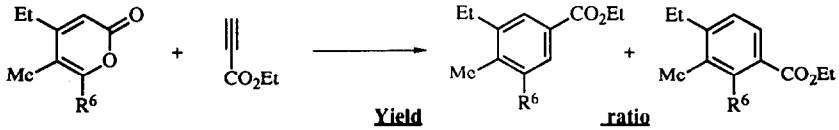
As in electrophilic aromatic substitution reactions in which a bromine substituent inductively deactivates the aromatic ring but *via* resonance directs substitution to the *ortho* and *para* positions, so also the bromine atom in 3-bromo-2-pyrone apparently withdraws or donates electron density to the pyrone diene unit depending on whether an electron-rich or electron-deficient dienophile is encountered. Apparently, the ambiphillic nature of 3-bromo-2-pyrone is not duplicated in the pyridone series. Even though we expected that 3-bromo-1-tosyl-2-pyridone would behave in a similar manner, we were disappointed that it was an unreactive compound.

Kuzuya has demonstrated a good correlation between the relative reactivity of methyl-substituted N-methyl-2-pyridones (measured through competition experiments) to benzyne and the reciprocal of the energy difference between pyridone HOMO and benzyne LUMO. This corelation was expected, as this is a normal-electron-demand cycloaddition, and an increase in the number of Me substituents results in a rise in the pyridone HOMO energy.[139,143]

Of course, fewer examples of cycloadditions are reported for 2-pyridones and therefore it is more difficult to draw general conclusions regarding their reacticity and/or selectivity. However, our investigation of N-sulfonyl-2-pyridones has shown that the ring substituent has to be fairly strongly electron-releasing or electron-withdrawing. 2-Pyridones substituted at the 3- position with mildly electron-releasing or electron-withdrawing groups do not undergo cycloadditions. Thus, 3-substituted tosyloxy, acyloxy or bromo N-toluenesulfonyl-2-pyridones are all unreactive towards both types of dienophiles. N-Toluenesulfonyl-2-pyridone itself does not afford a cycloadduct thermally or at high pressure. However, respective cycloadducts are obtained when the ring is substituted by strongly electron-withdrawing methoxycarbonyl, nitro and sulfonyl groups or by strongly electron-releasing methoxy and sulfenyl groups. In the latter case, a competition experiment has shown as expected that cycloaddition of 3-methoxy-2-pyridone is faster than cycloaddition of the corresponding 3-toluenesulfenyl-2-pyridone. A peculiar cycloaddition was recently reported by Tomisawa in which an electron-deficient pyridone underwent cycloaddition to maleic anhydride.[162]

We have already mentioned that the absence of substituents can result in lack of regiocontrol in cycloadditions of 2-pyrones and 2-pyridones. With both unsubstituted 2-pyrones[91] and N-styryl-2-pyridones,[175] cycloaddition exhibits poor regioselectivity. The presence of ring substituents could alter the regiocontrol in the cycloaddition in two respects. From consideration of the frontier molecular orbital (FMO) interactions, we would expect that cycloaddition of 2-pyrones and 2-pyridones to their respective matched dienophiles would result in predominance of the *endo* cycoadduct. For 3-substituted 2-pyrones, quantitative[15] and qualitative[32] FMO has also been used to rationalize the regiochemistry of cycloadditions to alkynes.[15] The prefered stacking of the 3-substituted 2-pyrone diene and the dienophile so as to allow a secondary molecular orbital interaction between the pyrone's 3-methylthio substituent and the alkyne's ethylcarboxylate was cited for the excellent regioselectivity in the following case.[15]

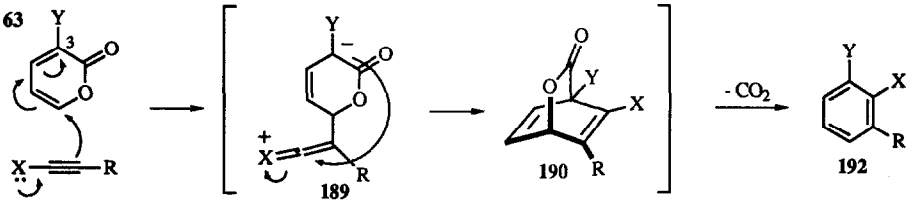
Scheme 62




| | Yield | ratio | |
|---|---|---|---|
| $R^6$ = H | 72% | 48 | : 52 |
| $R^6$ = Me | 86% | 39 | : 61 |
| $R^6$ = SMe | 75% | 10 | : 90 |

The regioselectivity of the cycloadditions could also be predicted from the polarization of the ring. It is expected that any substituent would alter the electronic density on the C-3 and C-6 ring carbons. The electronic effects of any substituents is transmitted through the ring electron current to the carbons it is not directly attached to, though it is only the electronic density at C-3 and C-6, the two bond forming centers, that are of concern to us.

**Scheme 63**

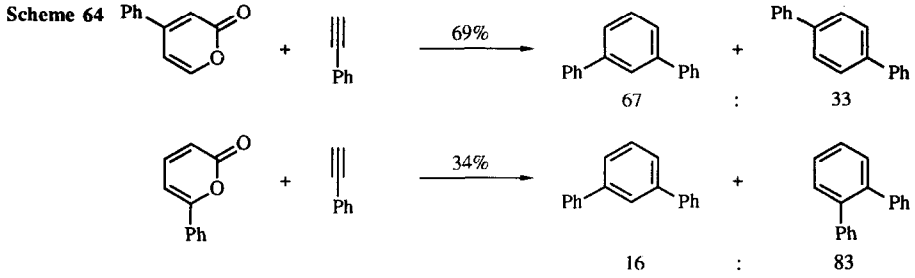



Y=electron withdrawing group
X=electron releasing group

Usually, considering the [4+2] cycloaddition as a nonsynchronous process correctly predicts the observed formation of the prefered regioisomeric adduct. At one extreme, a nonsynchronous process can be defined as a concerted yet slightly polarized mechanism. At the other extreme, a nonsynchronous process can occur in a stepwise fashion. Regardless, the following discussion of regiocontrol holds true. For example, in the inverse-electron-demand cycloaddition, the dienophile reacts by joining its more nucleophilic carbon of the 2π system to the more electrophilic terminal carbon of the 4π diene. The electron withdrawing group on the pyrone/pyridone ring helps to stabilize developing the negative charge as illustrated in the extreme form as zwitterionic intermediate **189**. Formation of the bicycloadduct can be visualized to occur by attack of this newly formed anion on the electrophilic carbon of the dienophile arm of intermediate **189**. A similar argument is made for the normal-electron-demand Diels-Alder reaction; however, now the pyrone diene behaves as the nucleophilic partner.

An exception to using charge densities of the pyrone diene carbons to predict the regiochemical outcome occurred when phenylacetylene cycloadded with various phenyl or carboxyl substituted 2-pyrones.[32] The secondary overlap of frontier molecular orbitals of these 3- and 6-substituted pyrones with phenylacetylene must be used to rationalize the regiochemical outcome of the reaction. For these 3- and 6-substituted pyrones, the role of charge densities was overridden by orbital overlap. However, when the phenyl or carboxyl moiety is at the 4- or 5-position of the pyrone diene, the phenyl group of the dienophile was not juxtaposed for orbital overlap; therefore, charge density correctly predicted the observed regiochemistry of the aromatic products (*meta* substituted phenylene) for these 4- and 5-substituted pyrones (Scheme 64). Another example in which the charge density distribution fails to correctly predict the regioisomeric outcome was shown in eq 19 (Section I).

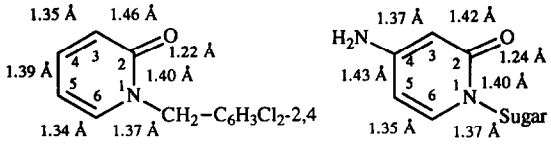
**Scheme 64**



### C. Steric Features.

Unlike cyclohexadiene, 2-pyridones and 2-pyrones do not possess a $C_2$ axis of symmetry. That is to say that, even if there are no ring substituents, the two ends of the diene are sterically unequal. This steric difference arises from ring distortion primarily due to longer bond length by about 0.1 Å at C(2)-C(3) than at C(6)-N/O(1).[204,205]

**Scheme 65**



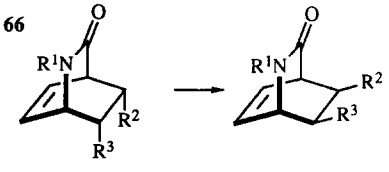

Even though the difference in the steric environment at C-3 and C-6 is small, it leaves the possibility that in 2-pyrones and in 2-pyridones, even with no N-substituent, the C-6 terminus of the diene may be more sterically demanding than the C-3 terminus. But is the difference pronounced enough to have an effect on the reactivity or selectivity of cycloaddition?

To date, no evidence has been presented to suggest that the bulkiness of the ring substituents will retard the cycloadditions. To the contrary, it is postulated that steric bulk at C-6 can actually help some cycloadditions.[144,145] For instance, addition of N-unsubstituted pyridones to benzyne afforded best yields when all other ring positions were substituted. Of course, it could be that in all these cases the electronic influence of the electron-releasing alkyl substituents more than compensates for the steric hindrance.

On the other hand, the size of the 3- and 6-substituents is known to influence the *exo*/*endo* stereoselectivity of cycloadditions. It has been shown that the steric bulkiness of the 3- and 6-substituents increases the proportion of the *exo* cycloadduct. It was further shown that the 3-substituent has a more pronounced effect on *exo* formation than the 6-substituent does. However, it is not clear why these substituents have a role in the *exo* cycloadduct predominance. It appears that the *exo* cycloadduct is thermodynamically more stable than the *endo* cycloadduct, regardless of the substituents at 3- or 6-position of the starting pyridones (positions 1- and 4- on the bicyclic lactam). The reason for this difference is not clear.

Notice that the *endo* cycloadduct is the kinetic product of cycloaddition. This is because of the secondary orbital interaction during the cycloaddition process. We[30] and others[37] have shown that the *endo* cycloadduct can be transformed into the *exo* cycloadduct under thermodynamically controlled reaction conditions. The transformation proceeds not only via a cycloreversion/cycloaddition process (Scheme 2-14) but also by direct epimerization without fragmentation of the bicyclic ring (Scheme 3-9).

**Scheme 66**



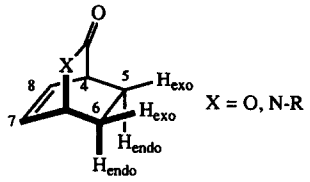

| $R^1$ | $R^2$ | $R^3$ | Conditions |
|---|---|---|---|
| p-Tol-$SO_2$ | $NO_2$ | H | $HCO_2NH_4$/MeOH |
| Me | H | CN | NaH/THF |

It is unclear if the size of the N-substituent has any effect on the selectivity of cycloaddition. Clearly, lack of an N-substituent results in more *exo* cycloadduct formation but, as already mentioned, the formation of the *exo* cycloadduct may be a result of a thermodynamic preference, and therefore a comparision is not possible. Unfortunately, no other studies have yet been performed to elucidate this point.

## IV. SPECTROSCOPIC ASPECTS.

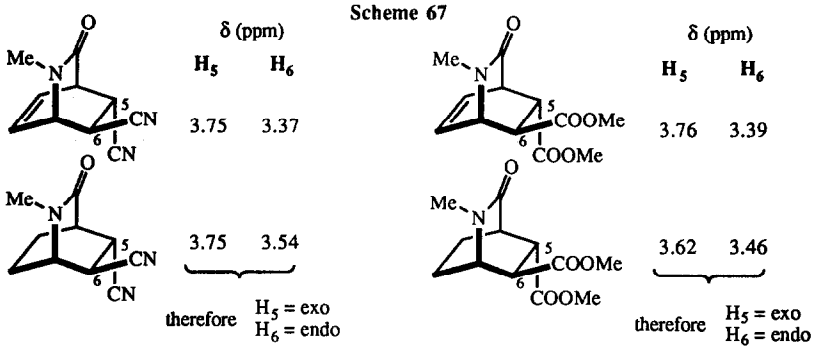
Determination of the relative configuration of cycloadducts (*endo/exo)* was initially performed by chemical manipulations.[136,165,206,172] However, as more cycloadducts were isolated and studied by $^1H$ NMR, it became possible to establish empirical rules relating the NMR spectra and the configuration of the bicyclic lactones and lactams.

Originally, the chemical shifts were used. In bicyclo[2.2.2]octenes, the signals due to *endo* protons at positions 5 and 6 appear at higher magnetic field than those due to the *exo* protons. The differences in chemical shifts are associated with a long range shielding (anisotropic)[207] effect caused by the $C_7$-$C_8$ double bond.[2,86]




The effect of reducing this double bond on the chemical shifts of $C_5$ and $C_6$ methylene protons was used to determine the *exo/endo* configuration of some pyridone cycloadducts.[208] Reduction of the double bond shifts H-*exo* to higher field by approximately 0.14 ppm, and it shifts the signal of H-*endo* to a lower magnetic field by only about 0.05 ppm.

Scheme 67



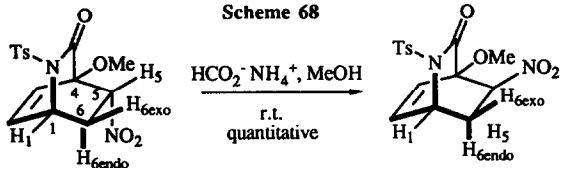

This approach suffers from a major disadvantage in that both the *exo* and *endo* cycloadducts must be available to be analyzed by $^1H$ NMR. A more reliable method is based on the comparison of spin-spin coupling constants between the protons at the bridgehead ($C_1H$ and $C_4H$) and the adjacent positions ($C_6H$ and $C_5H$) in the *endo* and *exo* isomers.

Even though the exact sizes of the coupling constants are different, it has been observed that they fall broadly within two ranges. For 2-azabicyclo[2.2.2]octenes, coupling constants between $H_1$-$H_{6endo}$ are observed in the range 1-1.30 Hz, whereas $J$ $H_1$-$H_{6exo}$ are usually between 2.4 and 4.2 Hz.[157,158,167,168] Therefore, one does not need to obtain both isomers (*exo* and *endo*) from the reaction mixture to be able to elucidate the configuration, but sometimes it is convenient to have a point of reference as can be seen in the following example.

We isolated a single cycloadduct from the Diels-Alder reaction between 3-methoxy-1-tosyl-2-pyridone and nitroethylene; its configuration was assigned to be *endo* on the basis of the coupling constants and confirmed by complete epimerization into the *exo* adduct.[161] Regardless of the configuration at $C_5$ in both compounds, the NMR

signals due to $H_{6endo}$ and $H_{6exo}$ are distinguished from other protons (by their chemical shifts) and from each other (by the size of the coupling to $H_1$). The relative configuration of $H_5$ is then established based on whether it is *syn* to $H_{6endo}$ or to $H_{6exo}$, and this is done by the size of the couplings.

Scheme 68

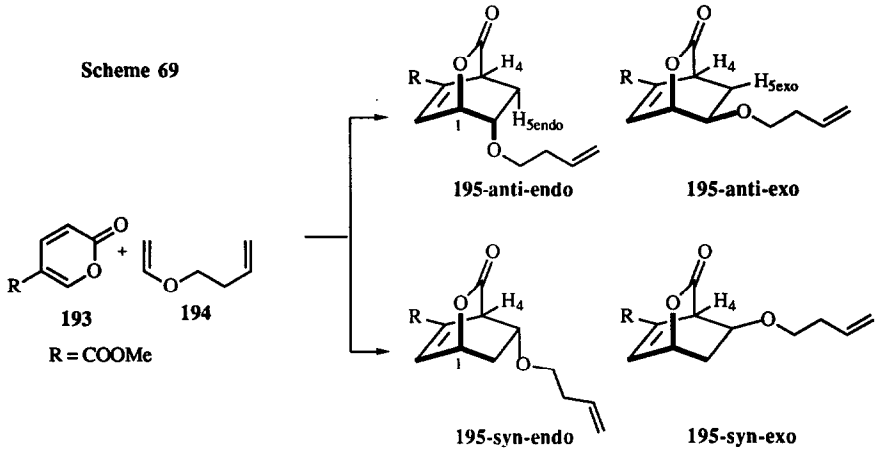



$\left\{ \begin{matrix} J_{1,6exo} = 3.43 \text{ Hz}, J_{1,6endo} = 2.15 \text{ Hz} \\ J_{5,6exo} = 9.25 \text{ Hz}, J_{5,6endo} = 3.80 \text{ Hz} \end{matrix} \right\} \left\{ \begin{matrix} J_{1,6exo} = 3.40 \text{ Hz}, J_{1,6endo} = 2.37 \text{ Hz} \\ J_{5,6exo} = 4.28 \text{ Hz}, J_{5,6endo} = 10.07 \text{ Hz} \end{matrix} \right\}$

In the case of 3-oxo-2-oxabicyclo[2.2.2]oct-7-ene derivatives, these coupling constants have been reported to be in the range 1.1-1.5 Hz for $H_1$-$H_{6endo}$ and 2.0-4.5 Hz for $H_1$-$H_{6exo}$.[71,91,111,210]

For the Diels-Alder reaction between the pyrone **193** and the vinyl ether **194**, four stereoisomers (regioisomers and their *endo*/*exo* isomers ) are possible.[86] In the *syn* adducts with respect to the -COOMe group, the signals of the $H_4$ appeared as a weakly split doublet, whereas those of the *anti* adduct appeared as a multiplet. *Anti* adducts were produced predominantly.

Scheme 69



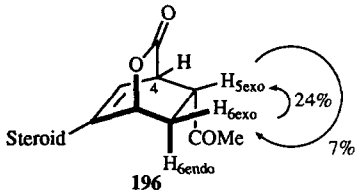

The configuration and the *exo*/*endo* ratios of the cycloadducts were determined on the basis of the $^1H$ NMR signals of $H_4$, $H_{5endo}$, $H_{5exo}$ and $H_6$, using both chemical shifts and coupling constants. The relative stereochemistry of cycloadducts **195**-*anti-endo* and **195**-*anti-exo* was obtained by MM2 calculations (molecular mechanics) followed by MNDO (modified neglect of diatomic overlap) optimization. The calculated coupling constants for the *vicinal* protons according to the Karplus rule[211] and the Williamson-Johnson rule[212] are in good agreement with the observed values. The calculation indicates that the dihedral angles of $H_4$-C-C-$H_{5exo}$ and $H_4$-C-C-$H_{5endo}$ are 56.3º and 60.1º respectively. The calculated coupling constant of $H_4$ with $H_{5exo}$ (2.3 Hz) is slightly larger than that of $H_{5endo}$ (1.8 Hz). However, further rigorous confirmation of the stereochemistry of these cycloadducts by single crystal X-ray analysis has not yet been achieved.

It has become possible, therefore, to determine the configuration at $C_5$ and$C_6$ from the size of the coupling

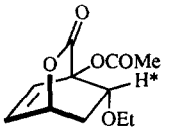
between the protons at those positions to the proton on the adjacent bridgehead position and, as one can see, if a substituent is present at either $C_1$ or $C_4$, it is still possible to determine the configuration at both $C_5$ and $C_6$.

$H_{5endo}$ and $H_{6endo}$ are *syn* as are $H_{5exo}$ and $H_{6exo}$. The size of the coupling between $H_{5endo}$ and $H_{6endo}$ is large (nearly 10 Hz), whereas the size of the coupling between $H_{5endo}$ and $H_{6exo}$ is smaller (up to 5 Hz). The configuration at the adjacent position also can be worked out based on the size of this type of coupling, but, of course, if substituents are present at both $C_1$ and $C_4$ bridgehead carbons, this method cannot be used and alternative means should be looked for.

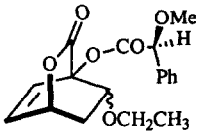
The stereochemical assigment can be corroborated also by difference nuclear Overhauser effect (NOE) studies; in a recent example, it has been observed that irradiation of $H_{6exo}$ in cycloadduct **196** led to 24% enhancement of the proton resonance at $H_{5exo}$, while irradiation of $H_{5exo}$ resulted in 7% enhancement of $H_{6exo}$.[27] A similar method has been used for compound **197**; it has been shown to be *endo* by $^{13}C$-{$^1H$}NOE-difference spectra: irradiation of H* gave 11.6% NOE at the bridge C=O, and the other C=O was identified by irradiation of the acetyl Me protons, giving an NOE at the acetyl C=O. By comparison, this method was employed to assign the structures of *endo* and *exo* isomers **198**.[94]




**196**




**197**




**198**

$^{13}C$-NMR Spectroscopy has been used also for the characterization of cycloadducts obtained from the Diels-Alder reaction of 2-pyrone and 2-pyridones, although a systematic study is not present in the literature. Some examples are given in the Table 4.

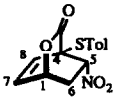
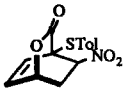
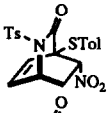
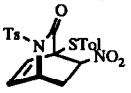
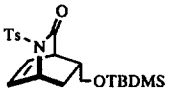
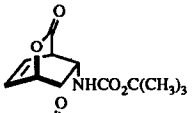
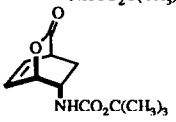
Finally, the infrared (IR) spectra of these cycloadducts commonly show characteristic bands at ca. 1760-1771 $cm^{-1}$ [85,86,111,210] and 1730-1680 $cm^{-1}$ [161,137,213] due to strained six-membered lactone and lactam carbonyl groups, respectively.

## V. CONCLUSIONS.

From a synthetic point of view, cycloadditions of 2-pyrones and 2-pyridones represent a poweful synthetic method for the assembly of complex target molecules as well as structurally diverse synthetic building blocks. For 2-pyrones the versatility of the cycloaddition/$CO_2$ extrusion methodology in the synthesis of substituted benzenes and polyaromatics was demonstrated, though the process is less efficient for 2-pyridones. Similarly, the cycloadditions of 2-pyrones allows access to dihydrobenzenes. Although this methodology is not general, in the sense that restrictions apply to the choice of substituents and/or reaction conditions, it is still useful for the synthesis of these sensitive molecules. In addition, starting from 2-pyrones and 2-pyridones, it is possible to obtain 2-oxa and 2-azabicyclo[2.2.2]octene cycloadducts, respectively. These bridged, bicyclic lactones and lactams are shown to be highly useful for the synthesis of a range of target molecules, in particular richly functionalised cyclohexenes.

We discussed the factors that govern the selectivity in these [4+2] cycloadditions. Desired target molecules thus can be synthesized with predictable and high regiocontrol and stereocontrol. Finally, an overview of the spectroscopic analysis of the cycloadducts was provided as a reliable and important technique for the assignment of the regiochemistry and relative stereochemistry of these compact, richly functionalized molecules. We hope that this review will stimulate further interest in the chemistry of 2-pyrones and 2-pyridones.

Table 4 δ C (ppm)

| | C-1 | C-4 | C-5 | C-6 | C-7 | C-8 | ref. |
|---|---|---|---|---|---|---|---|
|  | 59.50 | 71.90 | 79.30 | 36.10 | 131.15 | 131.0 | 111 |
|  | 58.40 | 71.70 | 83.70 | 34.10 | 134.60 | 132.20 | 111 |
|  | 51.47 | 61.87 | 84.25 | 34.02 | 135.80 | 132.27 | 161 |
|  | 5.11 | 61.87 | 84.62 | 35.00 | 135.41 | 132.72 | 161 |
|  | 53.86 | 47.32 | 30.37 | 35.40 | 133.35 | 129.72 | 161 |
|  | 73.44 | 46.77 | 43.33 | 35.37 | 133.51 | 129.86 | 91 |
|  | 74.38 | 40.86 | 30.05 | 47.63 | 135.00 | 129.73 | 91 |

## VI. ACKNOWLEDGMENTS

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