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Cycloaddition of oxidopyrylium species in organic synthesis

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1. Introduction

The development of efficient methodology and the discovery of new processes for the rapid creation of molecular complexity in a stereocontrolled manner are some of the important aspects of organic synthesis.[1] Cycloaddition reactions, which allow two new bonds to be formed in one operation in a regio- and stereocontrolled fashion, occupy a central position

Abbreviations: Ac, Acetyl; acac, acetylacetonyl; Bn, benzyl; Bz, benzoyl; COD, cycloocta-1,5-diene; Cp, cyclopentadienyl; *m*-CPBA, *m*-chloroperbenzoic acid; Cy, cyclohexyl; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-dimethylaminopyridine; DME, ethylene glycol dimethyl ether; DMF, *N*,*N*-dimethylformamide; ee, enantiomeric excess; HMPA, hexamethylphoramide; LDA, lithium diisopropylamide; Ms, methanesulfonyl; MOM, methoxymethyl; NBS, *N*-bromosuccinimide; NMO, 4-methyl morpholine *N*-oxide; PCC, pyridinium chlorochromate; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; Py, pyridine; PTC, phase transfer catalyst; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyl dimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TBSOTf, *tert*-butyldimethylsilyltriflate; Tf, trifluoromethanesulfonate; TIPS, triisopropylsilyl; TMP, tetramethylpiperidide; TMS, trimethylsilyl; TMSOTf, trimethylsilyltriflate; *p*-Tol, *p*-tolyl; Ts, *p*-toluenesulfonyl.

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among the available tools of synthetic organic chemistry. Among the various types of cycloadditions, dipolar cycloadditions of oxidopyrylium species of the types I–III (Fig. 1) and the related carbonyl ylides have proved to be a powerful methodology for the synthesis of diverse molecular architectures, which are not readily available otherwise. The intention of this review is to discuss the developments in the chemistry of oxidopyrylium species reported in the literature to date. Previously, there have been a few reviews that have appeared in the literature, but in most cases, these have dealt with different perspectives.[2–5] We wish, in the current survey, to highlight the cycloaddition of oxidopyrylium ylides and their application in organic synthesis. Cycloaddition of the related carbonyl ylides, generated by rhodium-catalyzed addition of diazo ketones, has recently been reviewed[6,7] and hence, only the recent developments are covered here. It is believed that such an overview will give a better understanding of the subject to the reader and will, hopefully, stimulate further investigation.

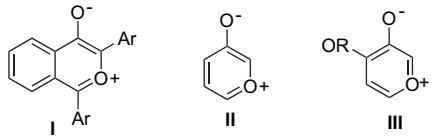


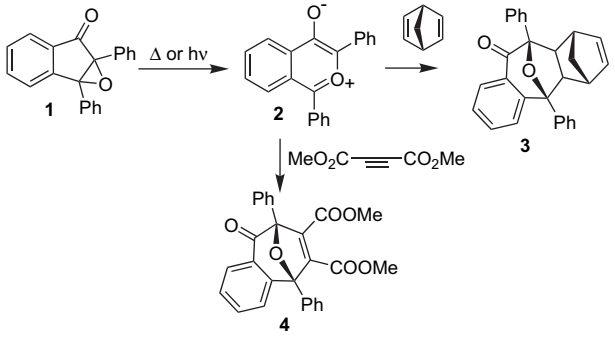
Figure 1. Oxidopyrylium species.

2. Generation and cycloaddition of oxidopyrylium species from epoxyindanones

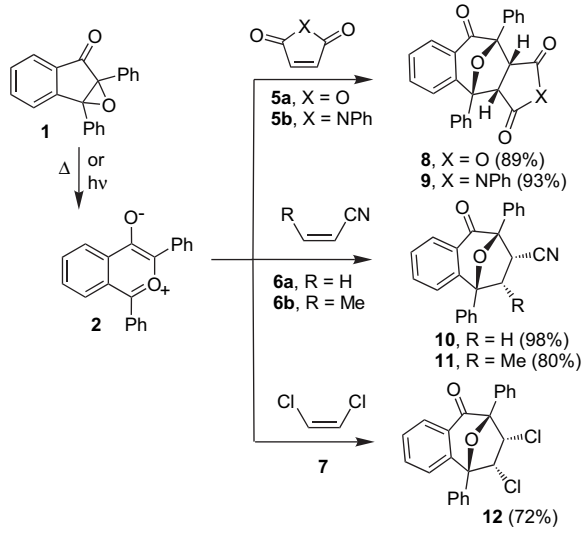
2.1. Intermolecular cycloadditions

Ullman and co-workers have reported that 2,3-diphenylindenone oxide **1**, upon thermolysis or photolysis, produces the red-coloured benzopyrylium oxide **2**.[8] The benzopyrylium oxide **2** behaves as a carbonyl ylide and undergoes cycloadditions with alkenes such as norbornadiene and dimethyl acetylenedicarboxylate to produce the cycloadducts **3** and **4**, respectively (Scheme 1). Irradiation of 2,3-epoxy-2-methyl-3-phenylindanone in the presence of dimethyl acetylenedicarboxylate was also found to give an adduct.[9] Later, Lown and Matsumoto extensively studied the cycloaddition of benzopyrylium oxide **2** with various dipolarophiles.[10] They observed that the cis 2π-addends underwent cycloadditions with the benzopyrylium ion **2** to give a mixture of *endo* and *exo* adducts in which the formation of the *endo* adducts predominated.

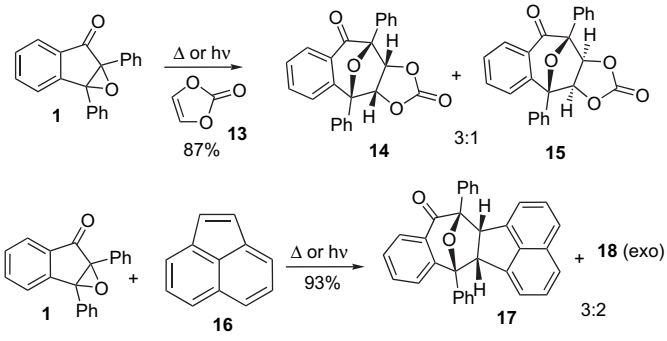
The benzopyrylium ylide **2** reacted with alkenes such as maleic anhydride **5a** and *N*-phenyl maleimide **5b** and provided exclusively the *endo* adducts **8** and **9**, respectively. Similarly, cycloaddition with *cis*-alkenes **6a**,**b** gave the adducts **10** and **11**, respectively, and **7** also resulted in the formation of the *endo* adduct **12** (Scheme 2). The alkenes **13** and **16**, however, gave a mixture of *endo* and *exo* isomers with a preference for the *endo* isomer and furnished the adducts **14**, **15** and **17**, **18**, respectively (Scheme 3).



Scheme 1.

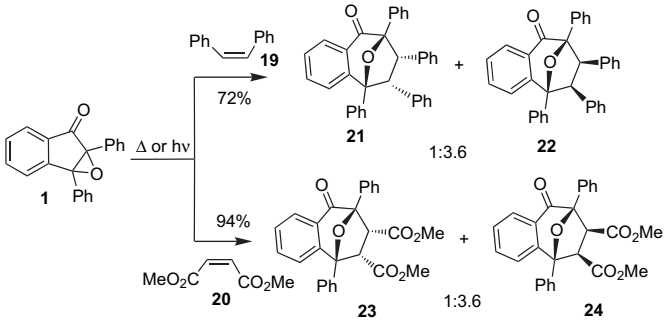


Scheme 2.



Scheme 3.

In contrast to the above observations, the cycloaddition of benzopyrylium oxide **2** with *cis*-stilbene **19** and dimethyl maleate **20** gave a mixture of adducts **21**–**24** having the *exo* adducts as the major products (Scheme 4).

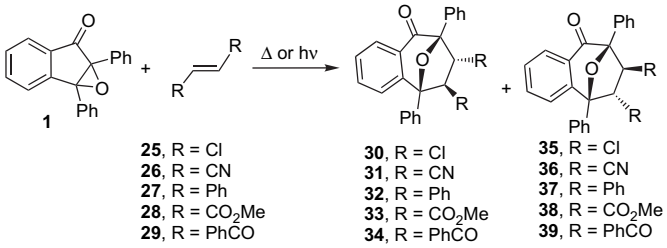


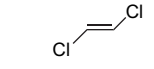
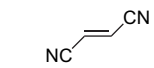
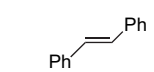
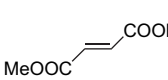
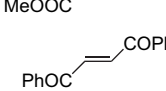
Scheme 4.

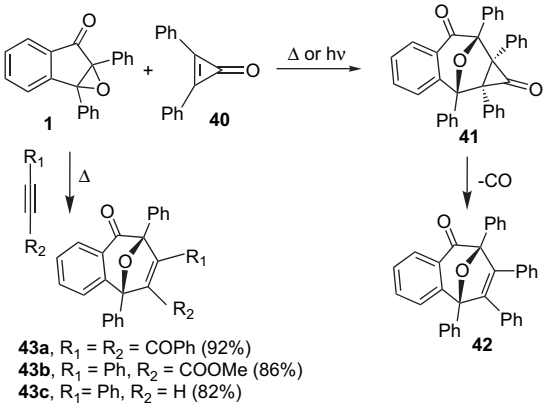
The trans 2π-addends **25**–**29** also gave a mixture of adducts **30**–**39** in which a tendency to form the 2-*exo*-3-*endo* isomer is observed (Table 1). With very bulky substituents such as benzoyl on the addend (entry 5), the exclusive formation of the 2-*exo*-3-*endo* isomer was observed. Diphenylcyclopropenone **40** underwent cycloaddition with **2** to give the cycloadduct **41**, which subsequently loses carbon monoxide to produce the adduct **42**. The adduct **42** was also obtained directly by the addition of diphenylacetylene to the ylide **2** (Scheme 5).[10] George and his associates[11a] also prepared adducts **43a**–**c** by thermal activation of the epoxide **1** in the presence of various acetylenic dienophiles (Scheme 5).

Very recently, Regitz and co-workers reported that unusual dipolarophiles such as the phospha alkyne **44** also underwent regiospecific cycloaddition to provide an oxa-bridged phospha alkene derivative **45** (Scheme 6).[11b]

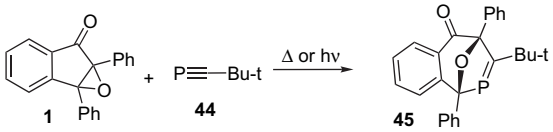
Table 1
Cycloaddition of benzopyrylium species derived from **1** with various dienophiles



Entry	Dipolarophile	Products	Ratio	Yield (%)
1		**30/35**	4:1	69
2		**31/36**	7:1	85
3		**32/37**	5:2	93
4		**33/38**	3:1	92
5		**34/39**	—	88



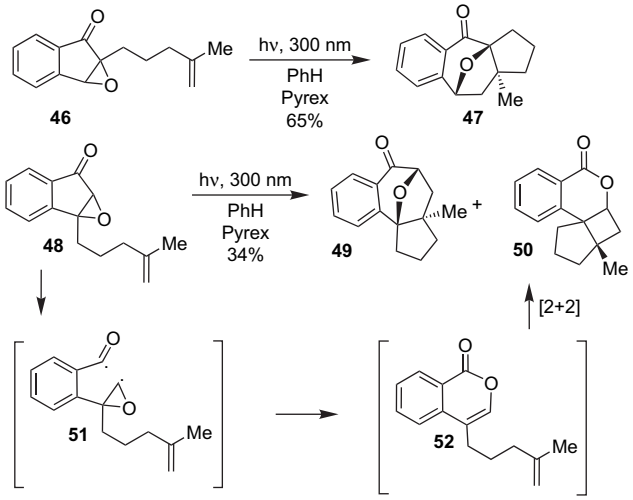
Scheme 5.



Scheme 6.

2.2. Intramolecular cycloadditions

Feldman has reported the intramolecular counterparts of the aforementioned cycloaddition.[12] Irradiation of the monosubstituted epoxyindenones **46** and **48** having olefinic tethers gave the cycloadducts **47** and **49** (Scheme 7). Irradiation of **48** also produced the product **50**, in an equal amount, which is apparently formed via the intermediates **51** and **52**.[12]



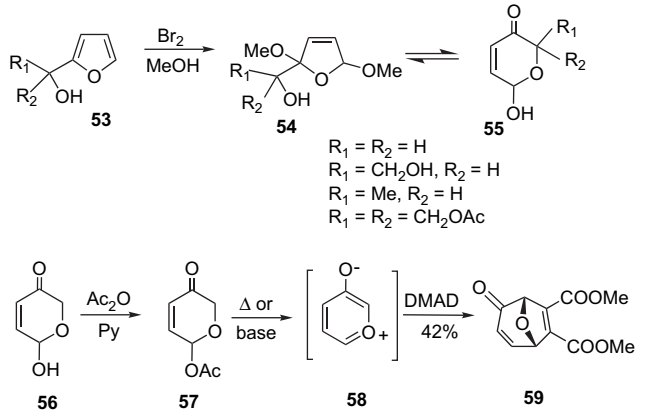
Scheme 7.

3. Generation and cycloaddition of oxidopyrylium species from acetoxypyranones (pyranulose acetates)

3.1. Intermolecular cycloadditions

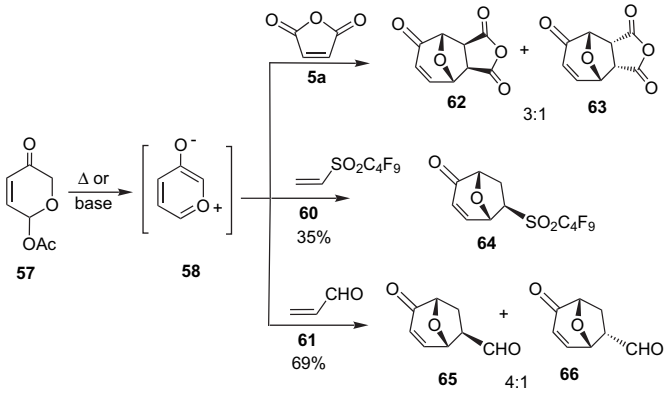
Achamatowicz and co-workers have reported an interesting method for converting furan derivatives into pyranones.

2-Furylcarbinols such as **53** on treatment with bromine in methanol yielded the acetals **54** as a mixture of epimers. Mild acid hydrolysis of **54** produced the hydroxypyranones **55** (Scheme 8).[13] This whole process is now known as the Achamatowicz rearrangement and provides interesting building blocks for the synthesis of a large number of polyoxygenated natural products from simple furan derivatives.[14–16] Hendrickson and Farina reported that the acetoxypyranone **57**, which can be obtained by the acetylation of pyranone **56**, can serve as potentially versatile source of carbonyl ylides. The acetoxypyranone **57** on exposure to either heat or a tertiary base, such as triethylamine, generates the carbonyl ylide **58** formulated as 3-oxidopyrylium. The ylide **58** is a reactive species and can be trapped with suitable dipolarophiles such as DMAD to furnish the corresponding cycloadduct **59**.[17]



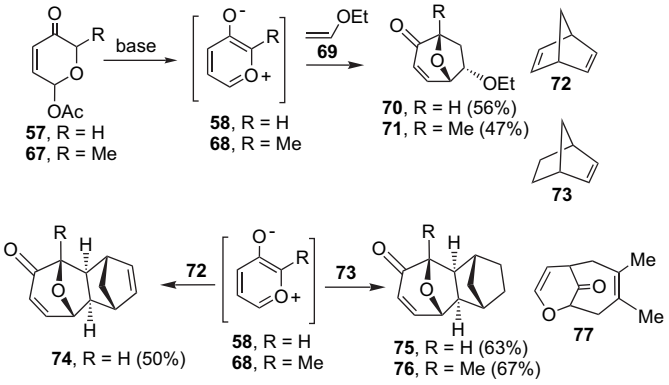
Scheme 8.

Hendrickson and Farina also reported that 3-oxidopyrylium reacted sluggishly with maleic anhydride **5a** and sulfone **60** to give the adducts **62–64**. Acrolein **61** reacted with **58** with greater efficiency and furnished the adducts **65** and **66** (Scheme 9). They also observed that the regioselectivity was as anticipated. The stereoselectivity, however, which favours the formation of the *exo* adduct, is in contrast to Alder's rule.[18]



Scheme 9.

Sammes and co-workers subsequently reported the intermolecular trapping reactions of 3-oxidopyrylium with a range of electron-rich and electron-deficient olefins and thus greatly extended the utility of the 3-oxidopyrylium ylides.[19,20] Thus, ethyl vinyl ether **69**, norbornadiene **72**, and norbornene **73** reacted with 3-oxidopyrylium to produce the corresponding cycloadducts (Scheme 10).[19,20a] The cycloaddition of oxidopyrylium species derived from pyranulose acetates **57** and **67** gave single *endo* adducts **70** and **71**, respectively. In the case of norbornadiene and norbornene, '*exo-syn*' adducts **74–76** were obtained. Interestingly, the reaction of **58** with 2,3-dimethylbutadiene gave the unusual adduct **77**.[19]



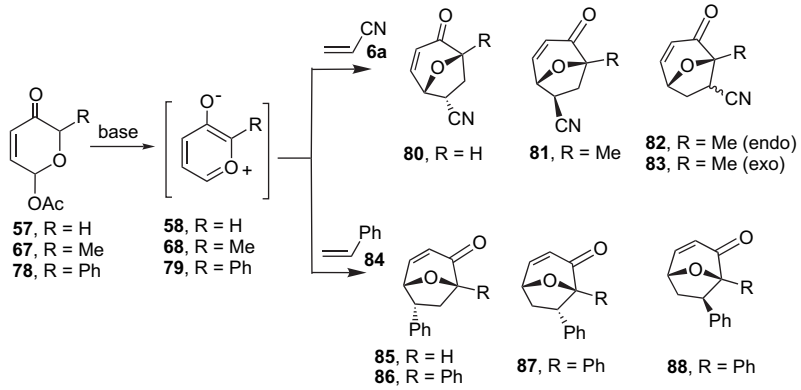
Scheme 10.

Sammes and co-workers reported that 2-substituted pyrylium ions such as 2-methyl-3-oxidopyrylium **68** and 2-phenyl-3-oxidopyrylium **79** on cycloaddition with substituted dipolarophiles furnish the cycloadducts having a reverse regiochemistry from that observed with the unsubstituted 3-oxidopyrylium (Table 2). For instance, the cycloaddition of acrylonitrile with 3-oxidopyrylium **58** gave a single isomer **80** (35%), while the reaction of acrylonitrile with 2-methyl-3-oxidopyrylium **68** gave a mixture of three isomers (**81–83**) in approximately equal amounts. Similarly, the reaction of **58** with styrene gave a single adduct **85** (65%), whereas the oxidopyrylium **79**, derived from **78**, reacted with styrene **84** gave a mixture of three products **86–88** in a 1:6:3 ratio.[20b] Sammes and Street rationalized the formation of reverse regioisomers (i.e., C-7) in the cycloaddition of unsymmetrical dipolarophiles to 3-oxidopyrylium by invoking frontier molecular orbital (FMO) theory.[20b] Table 3 summarizes some additional examples of the adducts **89–109** obtained by cycloaddition of various oxidopyrylium species and a variety of dipolarophiles.

Mascarenas and co-workers reported a highly efficient cycloaddition between the oxidopyrylium derived from **57** and the cyclopropenone acetal **110**, which gave the adduct **111** in excellent yield (Scheme 11).[23a] Further transformation of the adduct was also reported (vide infra). Aggarwal and co-workers[23b] examined the cycloaddition of **112** with the oxidopyrylium species generated from **57**, which gave a mixture of three adducts **113a–c** (Scheme 11).

Recently, Radhakrishnan[24] and co-workers reported a highly interesting and novel dipolar cycloaddition of pentafulvenes with 3-oxidopyrylium betaines, in which the formation of eight-membered ring systems was observed. Thus, the reaction of pyranulose acetates **57** and **67** with a variety

Table 2
Cycloaddition of 2-substituted oxidopyrylium species with acrylonitrile and styrene

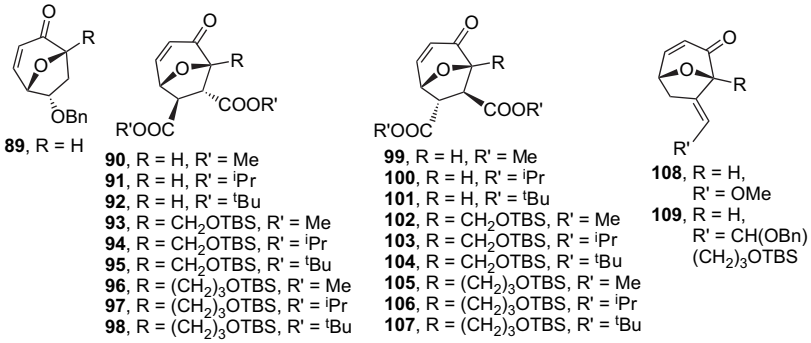


Entry	Dipolarophile	R	Products	Ratio
1	CN	H	**80**	—
		Me	**81/82/83**	1:1:1
2	Ph	H	**85**	—
		Ph	**86/87/88**	1:6:3

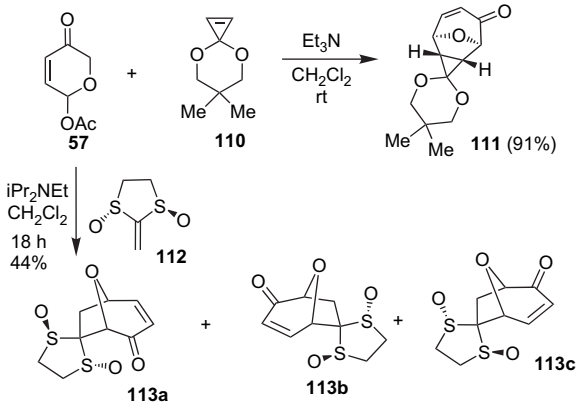
of substituted fulvenes **114** in the presence of base furnished adducts of the type **115b**, presumably via initial formation of the intermediate **115a** followed by a sigmatropic shift.[24a,b] In general, all the cycloadditions gave good-to-excellent yields (57–83%), depending on the nature of the substrates. These workers also examined the scope of this cycloaddition towards the synthesis of 7-5-8-fused oxa-bridged tricyclic systems of type **116**[24c] (Scheme 12). The same authors have reported further studies on the transformation of the adducts of the type **115**, which provide a route to more complex structures.[24d]

Sammes and co-workers have described an alternative route to the generation of the parent 2-benzopyrylium-4-oxide.[25a–c] Cyclohexadiene **117** upon dehydrogenation with palladium on charcoal followed by hydrolysis and acetylation gave the required acetoxypyranone **118** (Scheme 13). Treatment of the acetate **118** with either base or heat generated the reactive intermediate, 4-oxido-2-benzopyrylium **119**, which can be

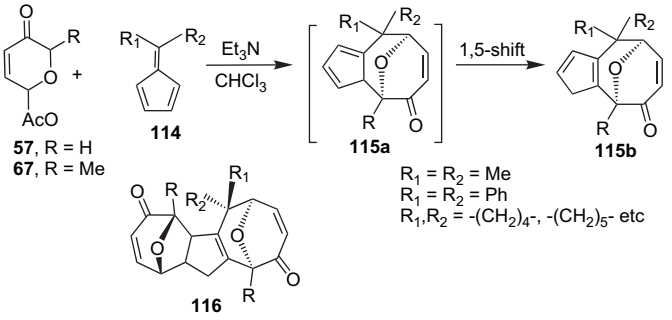
Table 3
Cycloadducts obtained by the reaction of oxidopyrylium species with various dipolarophiles



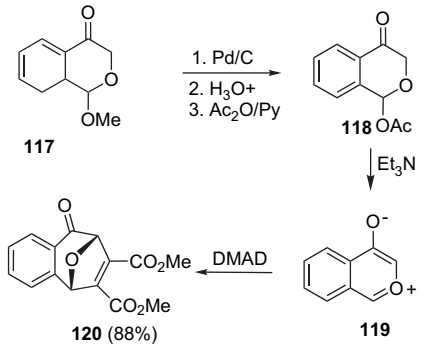
Entry	Dipolarophile	R	Products	Ratio	Ref.
1	OBn	H	**89**	—	20a
	MeO_2C CO_2Me	H	**90/99**	2:1	
2		CH_2OTBS	**93/102**	13:1	21
		$(CH_2)_3OTBS$	**96/105**	4:1	
3	$CO_2{}^iPr$ $CO_2{}^iPr$	H	**91/100**	2:1	
		CH_2OTBS	**94/103**	15:1	21
		$(CH_2)_3OTBS$	**97/106**	7:1	
4	$CO_2{}^tBu$ $CO_2{}^tBu$	H	**92/101**	2:3	
		CH_2OTBS	**95/104**		21
		$(CH_2)_3OTBS$	**98/107**		
5	$CH_2{=}C{=}CHOMe$	H	**108**	—	22
6	$CH_2{=}C{=}CH(OBn)(CH_2)_3OTBS$	H	**109**	—	22



Scheme 11.



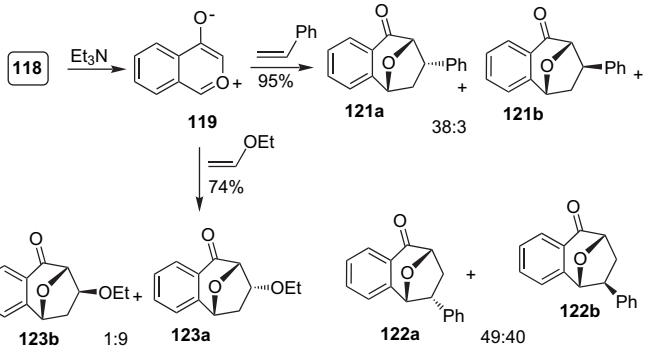
Scheme 12.



Scheme 13.

trapped with a wide range of dipolarophiles (e.g., DMAD) to yield the substituted benzotropone derivative **120**.[25a]

Benzopyrylium **119** on reaction with styrene, a conjugated dipolarophile, yielded a mixture of all four adducts **121a**,**b** and **122a**,**b** (Scheme 14).[25c] The lack of regiocontrol in this case is in accord with simple Hückel molecular orbital calculations, which indicate that the HOMO–LUMO and LUMO–HOMO interactions between the dipole and dipolarophile are approximately equal and predict the opposite regiochemistry. The reaction of **119** with ethyl vinyl ether gave the *endo* adduct **123a** in a major amount, along with the minor adduct **123b**. Here, again, the reverse regioisomer is formed as the major product (in comparison to that observed in the 3-oxidopyrylium series).



Scheme 14.

Even cyclopentene reacted with the ylide **119** to give the *endo* adduct **124** in 70% yield, along with a small amount of the *exo* isomer **125** (8%) (Fig. 2). The preference for the transition state leading to the *endo* adduct is noteworthy, since there are no secondary orbital interactions to consider. Cyclohexene also reacted to give the *endo* adduct **126**, albeit in low yield (10%). Interestingly, cyclohexenone, an electron-deficient dipolarophile that generally does not react with pyrylium-3-olates, added in high yield to the benzo analogue **119** to give three adducts, the *exo* adduct **127**, and the isomeric *exo* and *endo* adducts, **128** and **129**, in the ratio 21:27:51 (Scheme 15). Table 4 summarizes some additional examples of the cycloadditions of oxidopyrylium ylide **119** leading to adducts **130**–**136**.[25c]

3.2. Intramolecular cycloadditions

Having established the scope of the intermolecular cycloadditions, Sammes and co-workers explored the intramolecular cycloadditions of 3-oxidopyrylium. Thus, the acetate **137**, readily prepared from furfural, either on heating or by

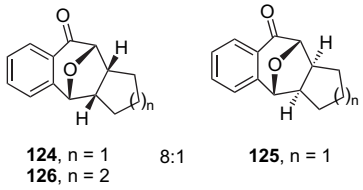
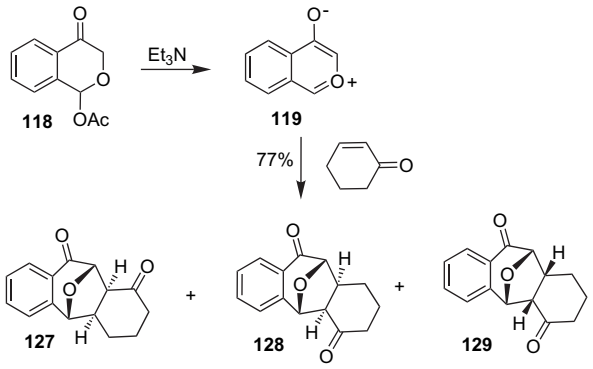
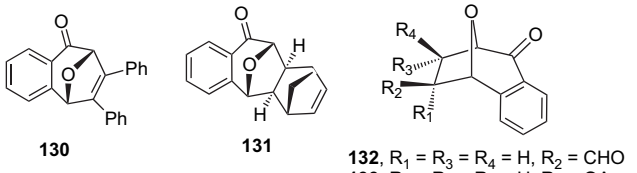


Figure 2. Cycloadducts of **119** with cyclopentene and cyclohexene.

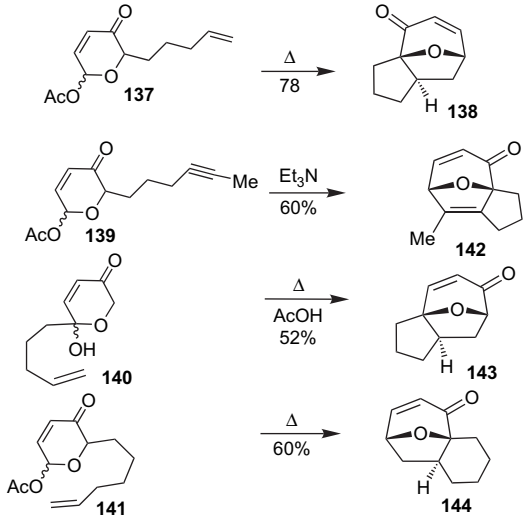


Scheme 15.

Table 4
Adducts obtained by cycloadditions of **119** with various dipolarophiles

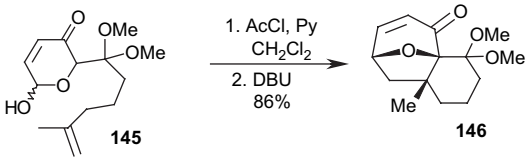


Entry	Dipolarophile	Products (yield, %)	Ratio
1	Ph—≡—Ph	**130**	—
2		**131** (75)	—
3		**132** (45)	—
4		**133/134/135/136** (99)	51:3:36:9

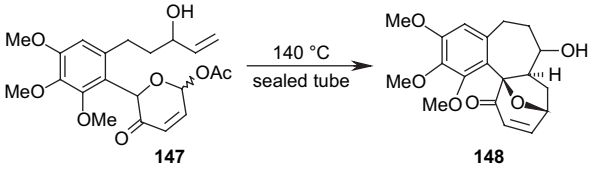


Scheme 16.

treatment with a base, generated the 3-oxidopyrylium, which underwent intramolecular cycloaddition to give the cycloadduct **138** in 78% yield (Scheme 16).[25b] This methodology appeared to be general and, depending on the length of tether, various ring systems could be accessed in a stereocontrolled fashion. The acetates **139–141** gave the cycloadducts **142–144**, respectively, after generation of the corresponding ylides followed by intramolecular cycloaddition.[2,25b] Similarly, the substrates **145** and **147** were also reported to give the cycloadducts **146**[26] and **148**[27] upon appropriate treatment (Eqs. 1 and 2).

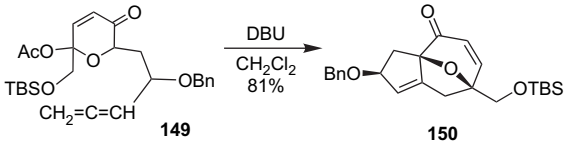


(1)



(2)

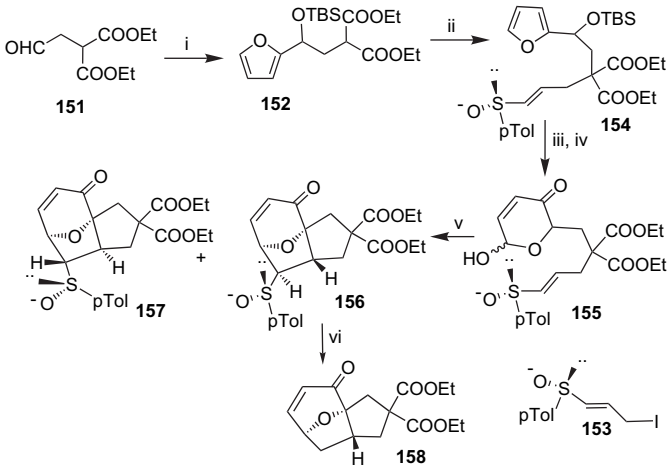
Interestingly, the acetate **149** endowed with a tether having an allenic moiety also underwent a smooth cycloaddition upon treatment with DBU to give the adduct **150** in excellent yield (Eq. 3).[22]



(3)

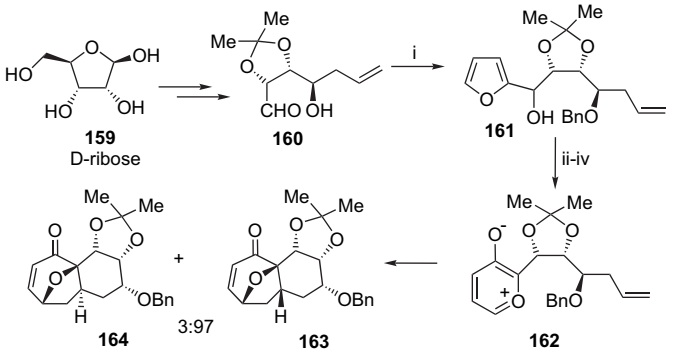
3.3. Asymmetric cycloadditions

One of the most important aspects that have received relatively little attention in [5+2] annulation methods is the asymmetric version of the cycloaddition reaction, despite numerous applications of this class of reactions in organic synthesis. Recently, Mascarenas and co-workers have reported an interesting method for the synthesis of chiral oxabicyclic adducts.[28] The authors envisaged that the introduction of a homochiral *p*-tolylsulfinyl group at the trans-terminal position of the alkene moiety may induce a diastereodifferentiation in the intramolecular cycloaddition. Thus, the 2-substituted furan **152** was prepared from **151**. The reaction of the compound **152** with the enantiopure iodosulfinyl derivative **153** furnished optically active 2-furylcarbinol **154**. Compound **154** was then subsequently transformed into pyrylium ylide precursor **155**, which, upon treatment with DBU in toluene, provided the cycloadducts **156** and **157** having **156** as the major product. The ratio of adducts depends on the solvent and the experimental conditions. Desulfinylation of the cycloadduct **156** with Raney Ni in refluxing THF afforded the oxa-bridged carbocycle (+)-**158** (Scheme 17).

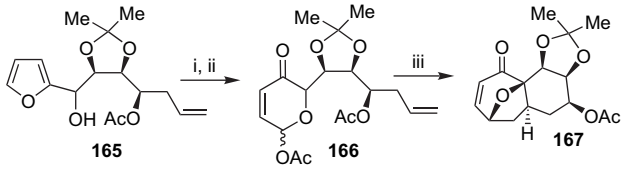


Scheme 17. Reagents/conditions: (i) ^{n}BuLi, furan, THF, −78 °C, after 10 min Et_3N, TMSCl, 83%; (ii) NaH, THF, **153**, 0 °C, 93%; (iii) TBAF, AcOH, THF; (iv) NBS, THF–H_2O, 92% (both steps); (v) acetylation and DBU, toluene, −30 °C, 86%; (vi) Raney Ni, THF, 82%.

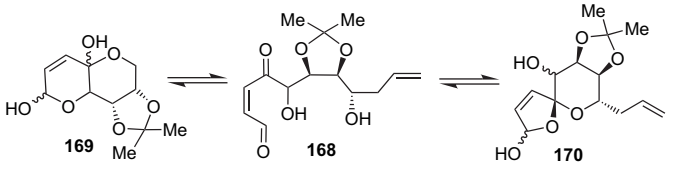
Recently, Trivedi and co-workers demonstrated that the reactions of optically active aldehydes derived from sugar derivatives with 2-lithiofuran provide 2-furylcarbinol intermediates, which led to a convenient and flexible route to optically pure oxabicyclo[*m.n.*0]adducts via intramolecular cycloaddition of oxidopyrylium species.[29,30] Thus, the chiral furylcarbinol **161** was synthesized from the chiral aldehyde **160**, which was prepared from ribose **159**. The furylcarbinol **161** was then converted into the 3-oxidopyrylium zwitterion **162**, which underwent cycloaddition with the tethered olefin to afford the cycloadducts **163** and **164** as an inseparable mixture of diastereomers (93:7) in 65% yield (Scheme 18). Following a similar synthetic strategy and exploitation of the pseudosymmetry of ribose, the same authors synthesized the [5+2] adduct **167** via the carbinol **165** and the acetate **166** (Scheme 19). Efforts to use the hydroxypyranone **168** in the cycloadditions of 3-oxidopyrylium, were, however, reported to be unsuccessful.[30] Based on earlier studies by Bartlett and co-workers,[31] Trivedi and co-workers reasoned that this failure could be a consequence of the existence of the hydroxypyranone **168** predominantly in the form of the hemiketals **169** and/or spiroketals **170** (Scheme 20).



Scheme 18. Reagents/conditions: (i) ^{n}BuLi, furan, THF, −78 °C, 70%; (ii) VO(acac)$_2$, ^{t}BuOOH, CH_2Cl_2; (iii) Ac_2O, Py, DMAP, CH_2Cl_2, 88% (two steps); (iv) Et_3N, MeCN, reflux, 65%.



Scheme 19. Reagents/conditions: (i) VO(acac)$_2$, ^{t}BuOOH, CH_2Cl_2; (ii) Ac_2O, Py, DMAP, CH_2Cl_2, 88% (two steps); (iii) Et_3N, MeCN, reflux, 83%.



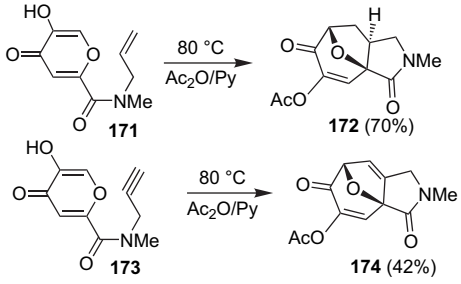
Scheme 20.

4. Oxidopyrylium species from β-hydroxy-γ-pyrones and their cycloadditions

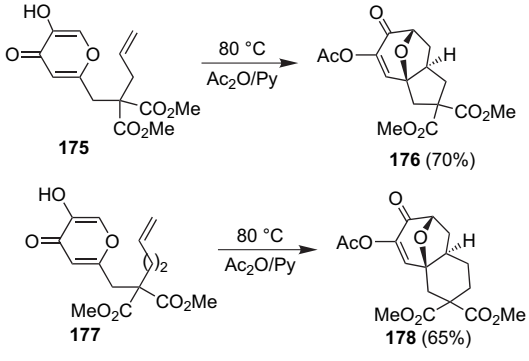
β-Hydroxy-γ-pyrones have also been proved to be a versatile source of oxidopyrylium species and their intra- and intermolecular cycloadditions have led to the development of novel general routes to structurally diverse oxa-bridged molecular frameworks, which are not readily accessible otherwise. Many elegant synthetic applications of the cycloaddition of oxidopyrylium species derived from β-hydroxy-γ-pyrones have been reported and some developments have been delineated below.

4.1. Intramolecular cycloadditions

Garst and co-workers reported that the thermolysis of pyrones derived from kojic acid, such as **171**, promotes an internal [5+2] cycloaddition.[32] This observation provided the first evidence that β-hydroxy-γ-pyrones could serve as an alternative source of the five-carbon component in the cycloaddition. Thus, pyrolysis of amides **171** and **173** in refluxing benzene provided the cycloadducts **172** and **174**, respectively, in moderate yields (Scheme 21). Similarly, the substrates **175** and **177** having three- and four-atom tethers also underwent cycloaddition to give the corresponding adducts **176** and **178**, respectively (Scheme 22).[32]



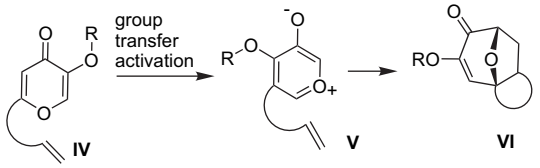
Scheme 21.



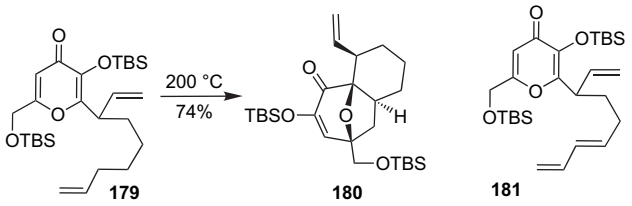
Scheme 22.

The aforementioned cycloadditions apparently proceed through migration of the group (R) from O3 in **IV** to O4 of the carbonyl group, resulting in the formation of an

oxidopyrylium species such as **V** that undergoes subsequent cycloaddition to give the adducts of type **VI**, as shown in Scheme 23.[5b,33,34] It appears that this type of group transfer is rate limiting and it is an important criterion for the reaction to occur and frequently requires high temperatures. For instance, the compound **179** on pyrolysis in toluene at 200 °C gave the cycloadduct **180**, whereas **181** decomposed under these conditions (Scheme 24).[35]



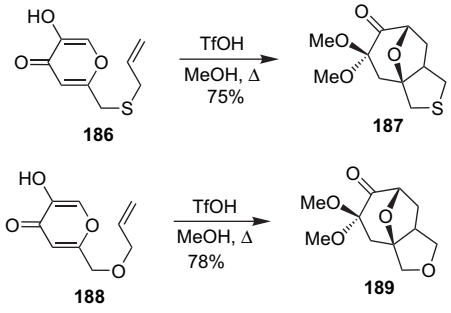
Scheme 23.



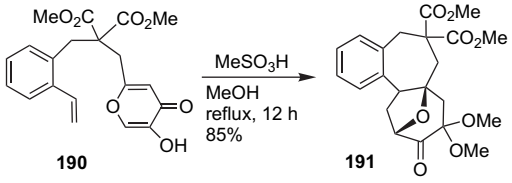
Scheme 24.

In order to avoid the requirement of high temperatures, Wender and co-workers developed an alternative and milder activation process to perform the cycloaddition, even at room temperature. This involves an initial O-4 alkylation, to produce a highly reactive 4-alkoxypyrylium salt, followed by O-3 desilylation to give the desired oxidopyrylium intermediate. Thus, alkylation of **182** with methyl triflate (MeOTf) at 20 °C for 8 h generated the pyrylium salt **184** (Scheme 25). Upon exposure of the salt **184** to anhydrous ceasium fluoride, cycloaddition proceeded smoothly at room temperature to give the cycloadduct **185** as a major product. Interestingly, this protocol permitted the direct use of hydroxypyranones such as **183**. Under these conditions, the intramolecular cycloaddition proceeded in one pot directly from the hydroxypyranone **183** at room temperature to give the cycloadduct **185** as the major product in good yields.[35]

Mascarenas and co-workers have reported the acid-promoted [5+2] cycloadditions of pyrones.[36] These authors reported that pyrones such as **186** and **188** on refluxing in methanol in the presence of trifluoromethanesulfonic acid (TfOH) and trimethyl orthoformate (dehydrating agent) provided the adducts **187** and **189**, respectively (Scheme 26). In fact, Garst and co-workers reported that substrate **190**, which decomposed under thermolysis, did provide the cycloadduct **191** when treated with methanesulfonic acid in refluxing MeOH (Scheme 27).[32]



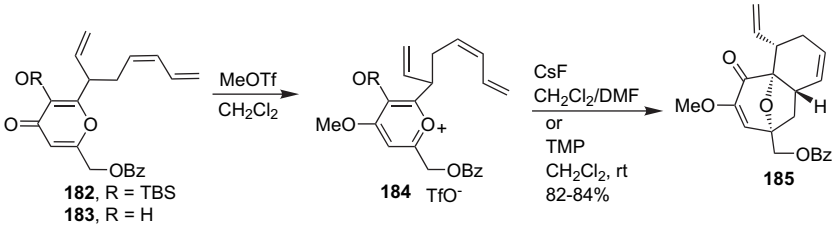
Scheme 26.



Scheme 27.

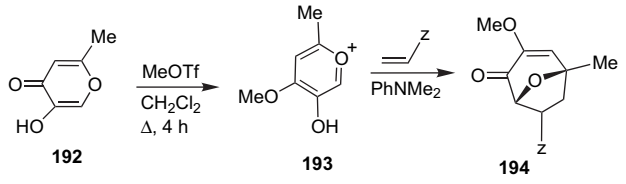
4.2. Intermolecular cycloadditions

There are only a limited number of examples on the intermolecular cycloadditions of β-hydroxy-γ-pyrones. Although the reaction between β-hydroxy-γ-pyrones and alkenes has been shown to proceed efficiently in the intramolecular cycloaddition mode, cycloaddition in the analogous intermolecular variant either fails completely or provides a mixture of stereoisomers. Wender and Mascarenas have reported a few examples of the cycloaddition of highly reactive 4-methoxy-6-methyl-3-oxidopyrylium ylide **193** with various olefinic dipolarophiles.[33] The 3-oxidopyrylium **193** was prepared from α-deoxykojic acid **192**, and intercepted with olefins to give adducts of the type **194**, as shown in Scheme 28. The pyrone **192** was converted into the highly reactive 4-methoxy-3-oxidopyrylium ylide **193** by treatment with *N*,*N*-dimethylaniline. This



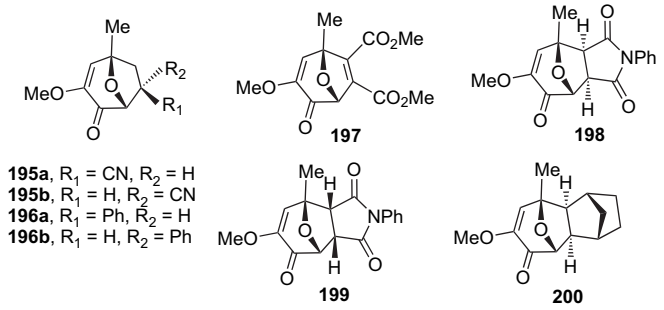
Scheme 25.

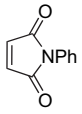
transient species was then trapped with various dipolarophiles to provide the corresponding cycloadducts **195–200** (Table 5).



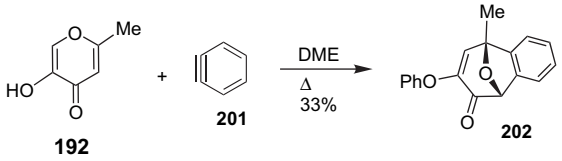
Scheme 28.

Table 5
Cycloadducts derived from **193** and various dipolarophiles



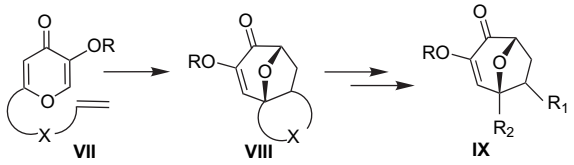
Entry	Dipolarophile	Products (yield, %)	Ratio
1		**195a/195b** (65)	2.3:1
2		**196a/196b** (58)	1:2.2
3	DMAD	**197** (60)	
4		**198/199** (73)	1.8:1
5		**200** (73)	1:0

Guitian and co-workers demonstrated that the generation of benzyne in the presence of α-deoxykojic acid **192** also leads to cycloaddition and gave the benzo-fused adduct **202** in moderate yield (Scheme 29).[37]



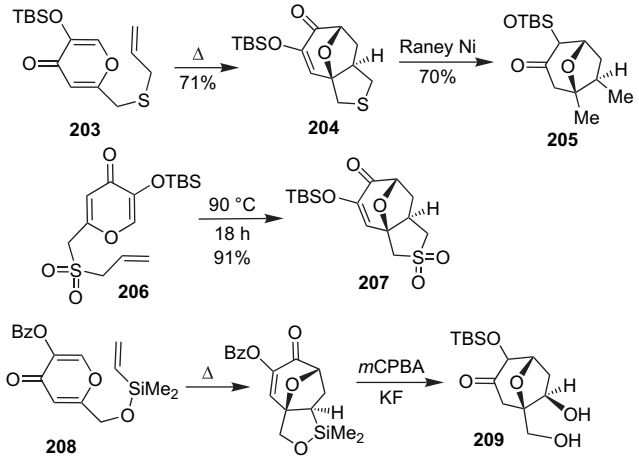
Scheme 29.

The low success rate of intermolecular reactions of the β-hydroxy-γ-pyrones prompted Mascarenas and co-workers to develop an alternate route to the synthesis of oxabicyclo[3.2.1]octane ring systems by employing temporary tethering strategies. The authors envisaged that tethered hydroxypyrones, especially with alkenyl chains containing a heteroatom, such as **VII**, would increase the efficiency of the cycloaddition as well as permit further manipulation of the adducts of the type **VIII** leading to functionalized and substituted oxabicyclo[3.2.1]octanes of the type **IX**, which are not accessible through intermolecular cycloaddition (Scheme 30).



Scheme 30.

Thus, thermolysis of the thioether **203**, which can be prepared by standard procedures, in toluene at 145 °C for 40 h provided a single *exo* adduct **204** in 71% yield.[38] Treatment of the cycloadduct **204** with Raney Ni effected desulfurization and rearrangement to the ketone **205** in 70% yield (Scheme 31). Interestingly, other substrates such as **206** having a sulfone moiety in the tether underwent smooth cycloaddition to give **207** in excellent yield at a considerably lower temperature.[39] Similarly, the substrate **208** readily underwent cycloaddition and the resulting adduct was transformed into the diol **209** that is not readily accessible otherwise (Scheme 31).[38]

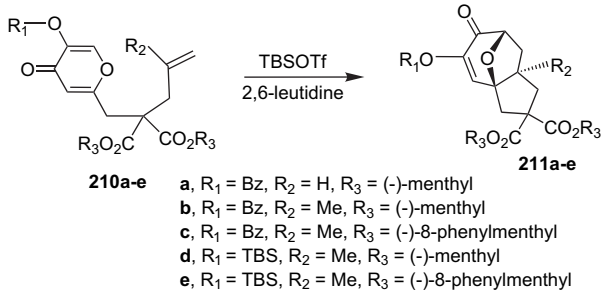


Scheme 31.

4.3. Asymmetric cycloadditions

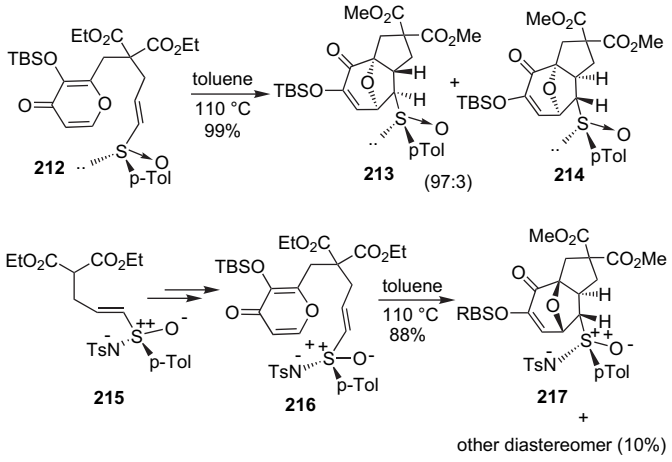
Ohkata and co-workers reported an asymmetric version of the pyranone–alkene cycloaddition by placing chiral auxiliaries in the tether. By using (−)-menthyl and (−)-8-phenylmenthyl as the chiral auxiliaries, moderate levels of diastereoselectivity were observed.[40] Thus, the substrates **210a–e** on reaction with TBSOTf in the presence of 2,6-lutidine underwent cycloaddition at room temperature to give the cycloadducts **211a–e**, respectively (Scheme 32).

Mascarenas and co-workers have reported an ingenious approach for the synthesis of enantiomeric partners of oxabicyclic adducts, by intramolecular cycloadditions of



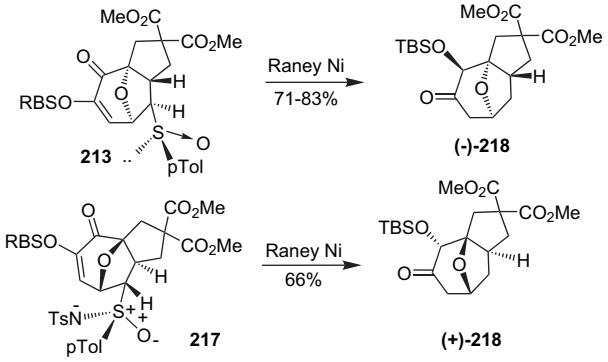
Scheme 32.

β-hydroxy-γ-pyrones having tethers that contain a chiral alkene moiety. Cycloaddition of the pyrone with the tethered olefin having a homochiral *p*-tolylsulfinyl group at the transterminal position led to an excellent level of diastereodifferentiation.[39,41] Thus, the pyrone **212** underwent cycloaddition upon heating to give the adducts **213** and **214** with excellent diastereoselectivity, having **213** as the major product (Scheme 33).[41] Other pyrone derivatives also led to high diastereoselectivity and gave the corresponding adducts in excellent yields.[41]



Scheme 33.

Later, Mascarenas and his associates discovered that transforming the sulfoxide into an appropriate sulfoximine would reverse the diastereofacial selectivity of the cycloaddition. The transformation of sulfoxide into sulfoximine can be readily performed with an aminating agent such as *O*-mesitylsulfonyl-hydroxylamine (MSH) and takes place with retention of configuration.[42–44] Thus, the pyrone **216**, derived from **215**, underwent intramolecular cycloaddition to give the adduct **217** in good diastereomeric excess (Scheme 33).[42] The adducts **213** and **217** were desulfinylated to afford the enantiopure oxabicyclic compounds (−)-**218** and (+)-**218**, respectively (Scheme 34). Thus, both the enantiomeric oxabicyclic adducts can be readily synthesized by an appropriate choice of chiral auxiliary. Recently, Mascarenas and co-workers reported the theoretical rationalization for the difference in the nature of the diastereofacial selectivities, which supported their experimental observations.[45]

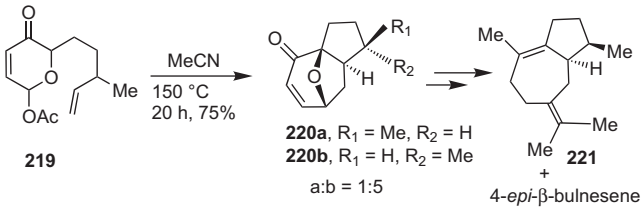


Scheme 34.

5. Cycloaddition of oxidopyrylium species (from acetoxypyranones and/or β-hydroxy-γ-pyranones) in the synthesis of natural products

Cycloaddition reactions of 3-oxidopyrylium species, which can be generated from either the acetoxypyranones or the β-hydroxy-γ-pyranones, with alkenes provide a general, versatile, and stereocontrolled entry into highly functionalized oxa-bridged cycloadducts, which have enormous potential for the synthesis via manipulations of the oxygen bridge and other functionalities. It is evident that such manipulations in the cycloadducts obtained from intermolecular cycloaddition have potential for the synthesis of functionalized seven-membered carbocycles, whereas the adducts derived from an intramolecular reaction may lead to more complex molecular architectures. Therefore, it is not surprising that the cycloaddition (inter- as well as intramolecular) of oxidopyrylium species has been employed as a key strategic element in designing the synthesis of various types of heterocyclic and carbocyclic natural products. Some typical applications are described below.

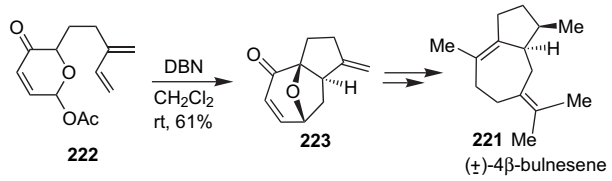
Sammes and co-workers have successfully completed the synthesis of a sesquiterpene, β-bulnesene **221**, employing an intramolecular [5+2] acetoxypyranone–alkene cycloaddition strategy.[46,47] The acetoxypyranone **219** was heated in acetonitrile at 150 °C for 20 h, and the resulting 3-oxidopyrylium underwent intramolecular dipolar cycloaddition to produce the desired isomer **220a** and the unwanted 8-methyl epimer **220b** in a ratio of 1:5 (Scheme 35). The mixture was elaborated into bulnesene **221** and its epimer.[46]



Scheme 35.

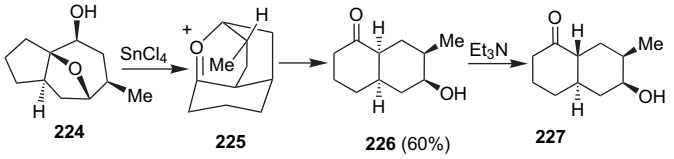
The formation of the incorrect methyl epimer **220b** as the major cycloadduct was probably due to steric repulsions between the methyl group and the aromatic ring in the

3-oxidopyrylium intermediate. This problem was overcome by employing the pyranulose acetate **222** as a precursor. Thus, pyranulose acetate **222** upon heating in acetonitrile at 150 °C or on treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at room temperature furnished the cycloadduct **223** in 61% yield. Hydrogenation over Pd–C/EtOH produced the required epimer, which, on further chemical manipulations, readily provided (±)-4β-bulnesene (Scheme 36).[47]

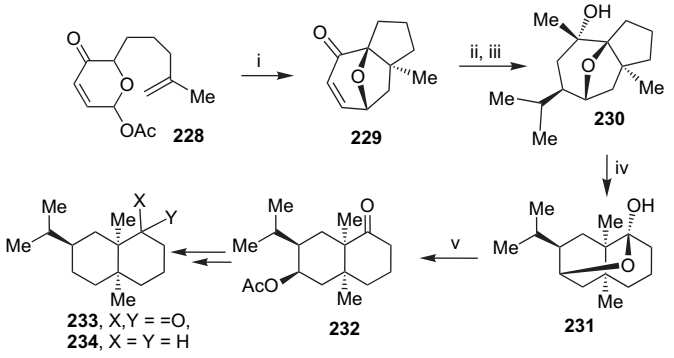


Scheme 36.

Sammes and co-workers reported a Lewis acid-catalyzed rearrangement in compounds of the type **224** to the cis-fused bicyclo[4.4.0]decane **226** via the species **225** (Scheme 37).[46] Treatment of the keto-alcohol **226** with triethylamine readily gave the trans-isomer **227**. This rearrangement was exploited in the synthesis of valerane-type sesquiterpenes. The acetoxypyranone **228** was transformed into the cycloadduct **229** by treatment with Et_3N in acetonitrile. Conjugate addition of the isopropyl group followed by Grignard reaction with methylmagnesium bromide produced the alcohol **230** (Scheme 38). The alcohol **230** on treatment with $TiCl_4$ afforded (±)-cryptofauronol **231**. Treatment of **231** with Ac_2O–NaOAc gave (±)-fauronyl acetate **232**, which was elaborated into valeranone **233** and valerane **234** (Scheme 38).[48] Sammes and his associates have also employed cycloadducts of oxidopyrylium species for the synthesis of other terpenoids.[49]

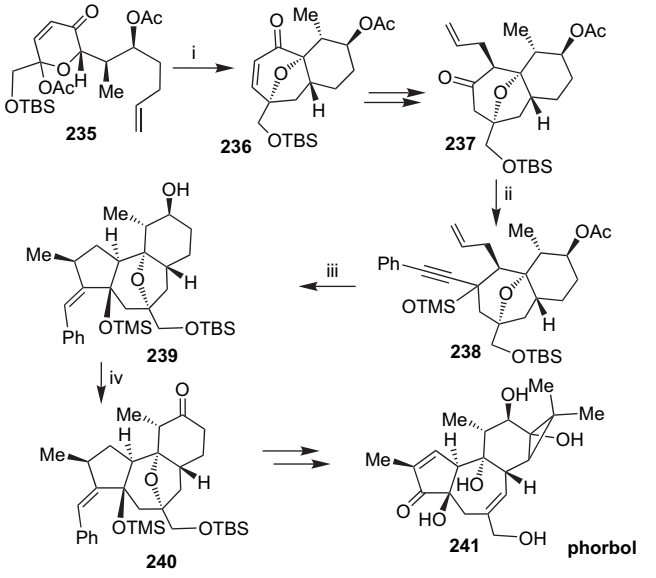


Scheme 37.



Scheme 38. Reagents/conditions: (i) Et_3N, MeCN, 80 °C, 94%; (ii) ^{i}PrMgBr, CuBr, Me_2S, ether, 86%; (iii) MeMgI, ether, 85%; (iv) $TiCl_4$, CH_2Cl_2, 83%; (v) Ac_2O, NaOAc, 82%.

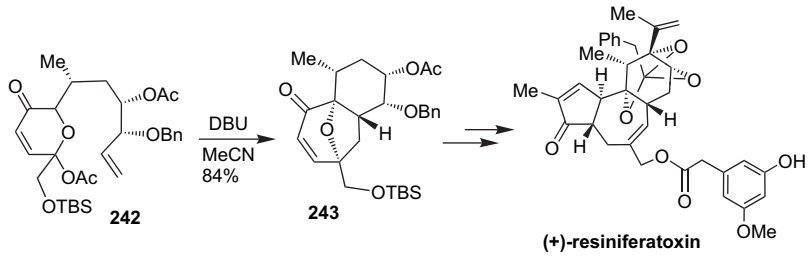
Wender and co-workers have developed elegant applications of the [5+2] cycloaddition of oxidopyrylium species in the synthesis of various types of natural products.[50–54] Earlier, they reported the first synthesis of racemic phorbol[51] and they have recently reported a formal asymmetric synthesis of phorbol.[52] The chiral acetoxypyranone **235** was treated with DBU to give the cycloadduct **236** in a highly stereoselective fashion (Scheme 39).[52] The adduct was elaborated into the compound **237**, which was converted into **238** having a phenylacetylene group, which, upon cyclization with Cp_2ZrCl_2, gave the alcohol **239**. Oxidation of **239** furnished the intermediate **240** in an optically pure form (Scheme 39). In order to demonstrate the utility of **240** as a precursor to phorbol, the authors also developed a route to phorbol **241** from the racemic intermediate **240**. The same workers have developed a synthesis of (+)-resiniferatoxin via the chiral pyranulose acetate **242**, which, on reaction with base, gave the optically pure adduct **243** (Scheme 40). The adduct **243** was elaborated into (+)-resiniferatoxin (an ultrapotent analogue of capsaicin and the most potent irritant known), after a series of transformations.[53]



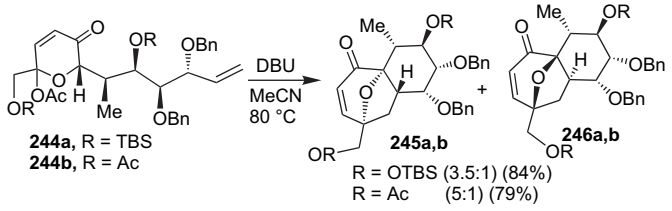
Scheme 39. Reagents/conditions: (i) DBU, MeCN, 79%; (ii) PhCCLi, LiBr, THF, HMPA, TMSCl, 75%; (iii) Cp_2ZrCl_2, ^{n}BuLi, THF, AcOH, 93%; (iv) PCC, NaOAc, CH_2CL_2, 94%.

Wender and his associates have recently reported a number of intramolecular cycloadditions with a view to develop a general route to the BC-ring system of C12-hydroxy daphnetoxins.[54] Thus, the intermediates **244a**,**b** on treatment with DBU in acetonitrile at 80 °C gave two adducts **245a**,**b** and **246a**,**b** in which the isomer **245** was favoured (Scheme 41). Interestingly, the protecting group in the tether was found to control the stereochemistry of the cycloaddition.[54]

Magnus and co-workers have employed an intramolecular [5+2] cycloaddition of an oxidopyrylium species towards their studies on the synthesis of the BC-ring system of taxanes.[55,56] Thus, the acetoxypyranone **247** on treatment with DBU in refluxing toluene gave the cycloadduct **248** as the major product, which was converted into the cyanoenone **249**.

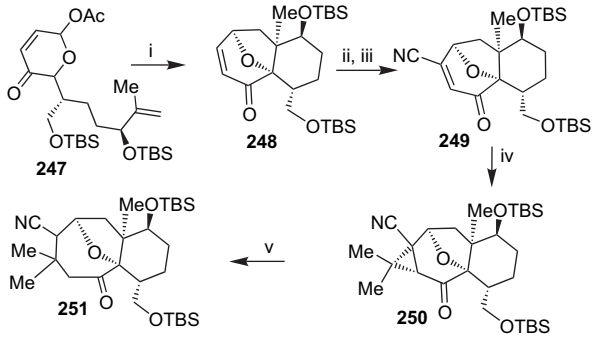


Scheme 40.



Scheme 41.

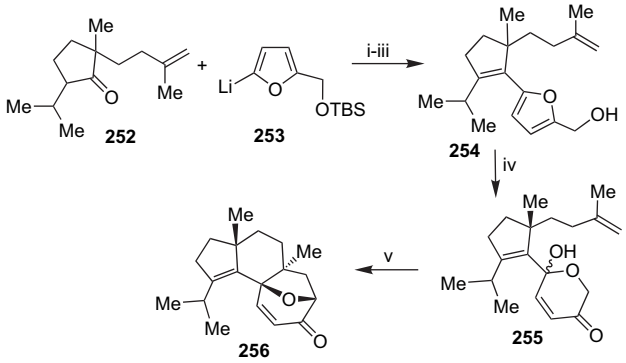
Cyclopropanation in **249** gave the compound **250**, which upon cleavage of the cyclopropane ring furnished the compound **251** having the BC-framework of taxanes (Scheme 42).[55]



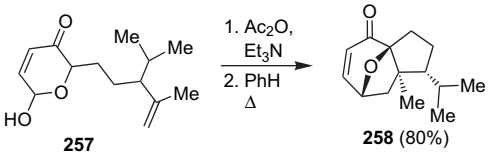
Scheme 42. Reagents/conditions: DBU, toluene, 110 °C, 1.5 h, 77%; (ii) Br_2, Et_3N, 100%; (iii) NaCN, PTC, 96%; (iv) $Me_2C{=}PPh_3$, THF, −78 °C to rt, 95%; (v) sodium naphthalenide, THF, −78 °C, 100%.

Magnus and Shen have also used this dipolar cycloaddition strategy for the synthesis of the cyathin diterpene skeleton (Scheme 43).[57] Thus, addition of furyllithium **253** to the ketone **252** followed by further manipulation of the adduct gave the precursor **254**. Oxidation of **254** with singlet oxygen gave the precursor **255** required for the generation of the oxidopyrylium species. Treatment of pyranulose **255** with trifluoroacetic acid gave the cycloadduct **256** containing the tricyclic network of cyathin (Scheme 43).[57] Similarly, the compound **258** was prepared from the precursor **257** with a view to synthesize the perhydroazulene portion of the diterpene antibiotic, guanacastepene (Scheme 44).[58]

Recently, Pattenden and co-workers[59] reported an elegant biomimetic synthesis of a highly complex natural product, (+)-intricarene. The synthesis involves a transannular dipolar cycloaddition of an oxidopyrylium species (Scheme 45). Thus, the optically pure macrocycle **262** was synthesized from the epoxyalcohol **259**, via **260** and **261**. Oxidative

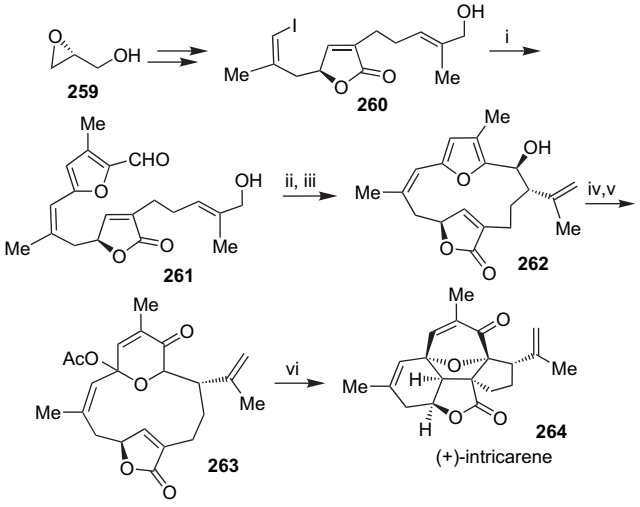


Scheme 43. Reagents/conditions: (i) $CeCl_3$, THF, 90%; (ii) $SOCl_2$, Py, CH_2Cl_2, 94%; (iii) CsF, $^nBu_4NCl$, MeCN, 97%; (iv) O_2, *hν*, CH_2Cl_2, MeOH, Rose Bengal, Me_2S; (v) CF_3COOH, CH_2Cl_2, 62% (both steps).



Scheme 44.

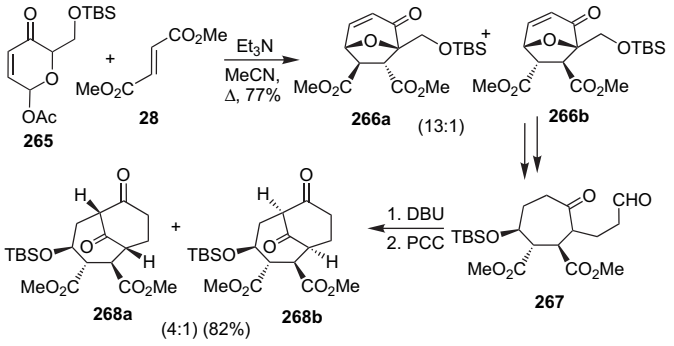
rearrangement in **262** followed by acetylation furnished the macrocyclic pyranulose acetate **263** that, upon treatment with DBU, gave the natural product **264**.



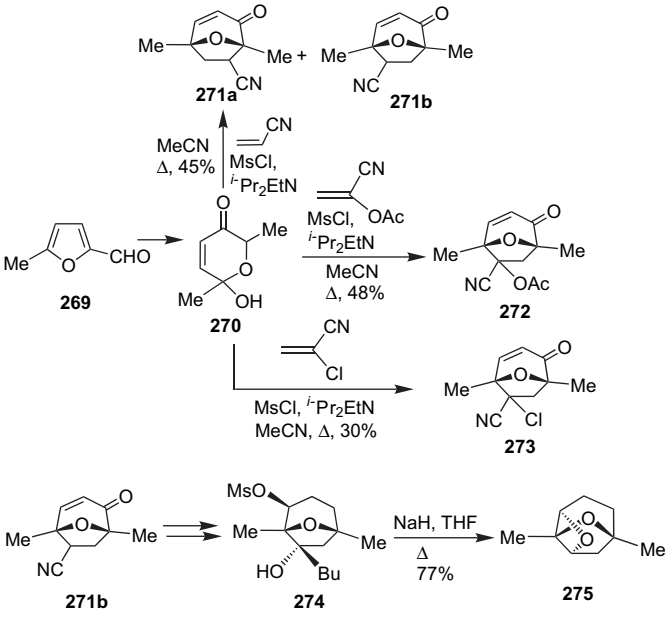
Scheme 45. Reagents/conditions: (i) 3-methyl-6-trimethylstannylfurfural, $Pd(PPh)_4$, CuI, CsF, DMF; (ii) NBS, Ph_3P, 72% for both steps; (iii) $CrCl_2$, 4 Å MS, THF, 70%; (iv) $VO(acac)_2$, ^tBuOOH, CH_2Cl_2, −20 °C; (v) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 30%, two steps; (vi) DBU, MeCN, reflux, 1 h, 10%.

In contrast to the intramolecular versions, there have been relatively few examples of the utilization of intermolecular cycloadditions for the synthesis of natural products. This could be partially attributed to the subtle reactivity of oxidopyrylium zwitterions in the intermolecular versions and a low degree of stereocontrol in these cycloadditions, compared to their intramolecular counterparts.

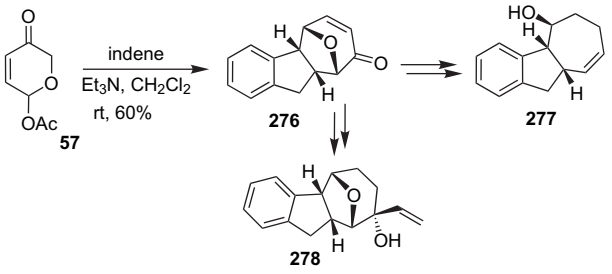
Ohmori reported the synthesis of a bicyclo[4.3.1]decane ring system in his studies towards the synthesis of phomoidride B (CP-263114) via an intermolecular [5+2] oxidopyrylium–alkene cycloaddition as a key step (Scheme 46).[60] Thus, the reaction of the acetate **265** and dimethyl fumarate in the presence of triethylamine gave the adducts **266a**,**b** having **266a** as the major product and **266b** as the minor product. The adduct **266a** was manipulated to give the functionalized cycloheptanone derivative **267**, which, upon intramolecular aldol condensation followed by oxidation, furnished the bridged bicyclic compounds **268a**,**b** containing the bicyclo[4.3.1]-decane ring system of phomoidride B.



Scheme 46.



Scheme 47.



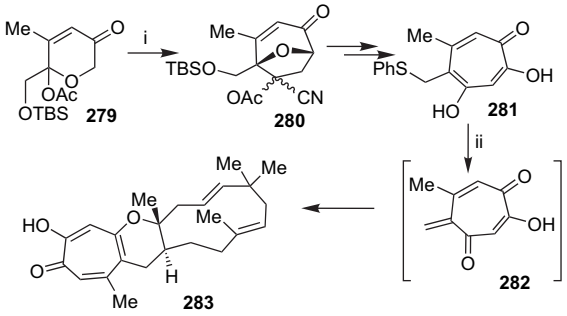
Scheme 48.

Heathcock and co-workers reported the synthesis of 2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane in the context of model studies directed towards the synthesis of dictyoxetane.[61] The hydroxypyranone **270** was prepared from 5-methylfurfural **269**. Mesylation of **270** and thermolysis in the presence of acrylonitrile gave a mixture of adducts containing **271a**,**b**, whereas the reaction of the dipolar species derived from **270** with α-acetoxyacrylonitrile and chloroacrylonitrile gave single adducts **272** and **273**, respectively (Scheme 47). A detailed study of some of these adducts was carried out in order to develop a route towards the synthesis of dictyoxetane. After studying various types of transformations, compound **271b** was elaborated into the hydroxymesylate **274**, which, upon treatment with sodium hydride, furnished the compound **275** having the tricyclic network of dictyoxetane.

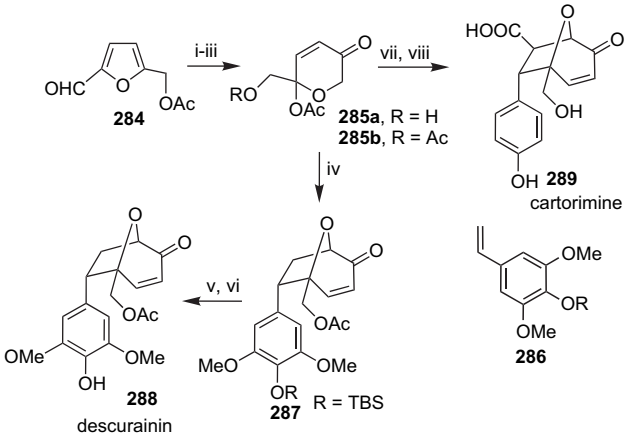
Very recently Trivedi and Murali have reported an expeditious entry into the fused 7-5-6 tricyclic skeleton related to the diterpene natural product, FCRR-Toxin. Their strategy is based on the premise that the intermolecular cycloaddition of 3-oxidopyrylium with indene may result in the formation of the required skeleton with the correct regio- and stereochemistry.[62] Indeed, the reaction of **57** with indene in the presence of base proceeded with exceptional regio- and stereocontrol to provide the single isomer **276**, in good yield, which was elaborated into **277** and **278** (Scheme 48).[62]

Baldwin and co-workers[63] have examined the cycloaddition of oxidopyrylium species in detail and have recently reported[63a,b] an excellent biomimetic approach to tropolone natural products and a synthesis of deoxy epolone B that employs cycloaddition of tropolone *ortho*-quinone methide, which was prepared via dipolar cycloaddition of oxidopyrylium species. The pyranulose acetate **279**, readily available from 3-methyl-methylfuroate, was heated with acetoxyacrylonitrile to give the adduct **280**. This was converted into tropolone **281** in a few steps, which upon thermal activation in the presence of humulene provided deoxy epolone B **283** via the intermediate **282** (Scheme 49).[63a]

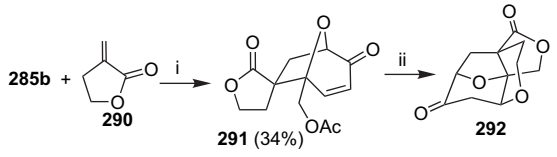
Snider and co-workers[64a,b] designed an efficient synthesis of cartorimine **289** and descurainin **288** that contain an oxabicyclo[3.2.1]octane framework in their molecular structure. The desired pyranulose diacetate **285b** was prepared from 5-acetoxymethylfurfural **284** and subjected to cycloaddition with various styrene derivatives **286** to give the adduct **287**, which was further manipulated to give descurainin **288** (Scheme 50). Similarly, cartorimine **289** was synthesized



Scheme 49. Reagents/conditions: (i) α-acetoxyacrylonitrile, toluene, 120 °C, 6 h, 54%; (ii) humulene, *p*-xylene, sealed tube, 150 °C, 24 h, 22%.



Scheme 50. Reagents/conditions: (i) $NaBH_4$, EtOH, 0 °C; (ii) Br_2, MeOH, H_2O; (iii) Ac_2O, Py, DMAP; (iv) **286**, Et_3N, CH_2Cl_2, 25 °C, 2 d, 31% from **285a**; (v) Py·HF, THF, Py; (vi) KOH, MeOH, H_2O, 87%, both steps; (vii) 4-acetoxymethylcinnamate, MeCN, 175 °C, 2,6-di-*tert*-butylpyridine; (viii) KOH, EtOH, H_2O, △, 13% from **285a**.



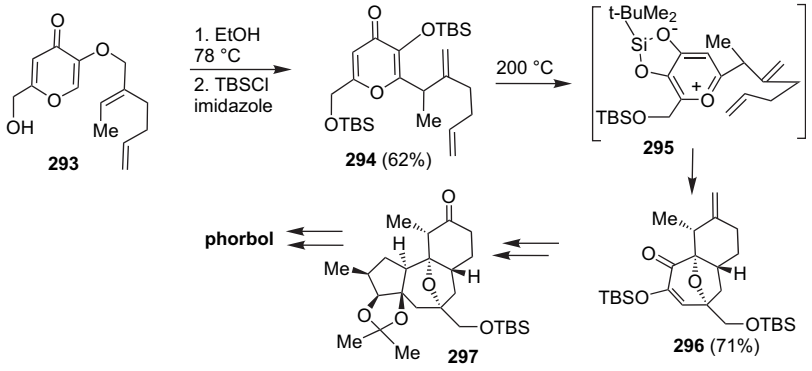
Scheme 51. Reagents/conditions: (i) Et_3N, CH_2Cl_2, 25 °C, 16 h, 34%; (ii) Cs_2CO_3, aq THF, 50 °C, then acidify, pH 1, 57%.

readily, as shown in Scheme 50.[64a,b] Recently, Snider's group has also achieved a formal synthesis of polygalolides A and B employing the cycloaddition of oxidopyrylium species derived from the diacetate **285b**. Thus, the diacetate **285b** was treated with **290** in the presence of triethylamine, which gave the adduct **291** in moderate yield, which upon treatment with ceasium carbonate followed by acidification gave the intermediate **292**, a known precursor for polygalolides A and B (Scheme 51).[64c]

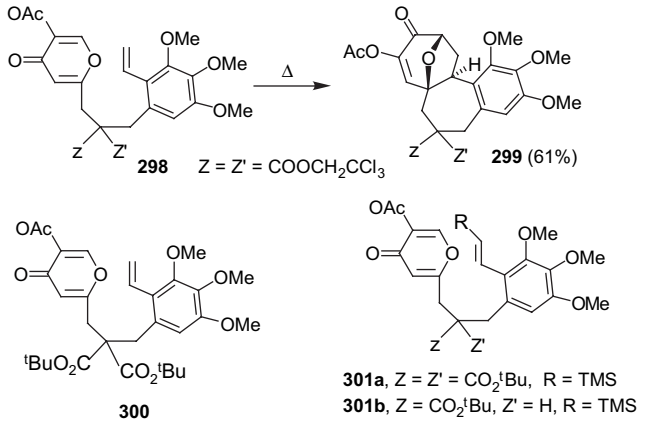
The cycloaddition of oxidopyrylium species derived from hydroxypyrones has also been employed in the synthesis of natural products. In their pioneering work in this area, Wender and his group reported one of the most complex and elegant examples of cycloaddition in their synthesis of phorbol (Scheme 52).[65a] The pyranone **294** was prepared using a Claisen rearrangement in **293** followed by silylation. Heating a solution of the silylated derivative **294** at 200 °C for 48 h leads to the *exo* cycloadduct **296** as a single diastereoisomer via intramolecular cycloaddition in the oxidopyrylium species **295**. This compound was efficiently elaborated into the polycyclic compound **297**, a known precursor of phorbol. Most recently, the intermediate **185** (prepared earlier by Wender's group; see Scheme 25) was elaborated into ABC-ring systems of 1α-alkyl daphnane analogues.[65b]

In the context of a synthesis of colchicine, Garst and McBride examined intramolecular pyrone–alkene cycloaddition in several substrates and transformations on some of the adducts.[66] The precursor **298** underwent cyclization to give **299** under simple thermal activation. The acetoxypyrone **300** gave a mixture of products including the cyclized compound, whereas the precursors **301a**,**b**, bearing a TMS group at the terminal position of the alkene, failed to undergo cycloaddition, probably due to steric reasons (Scheme 53).

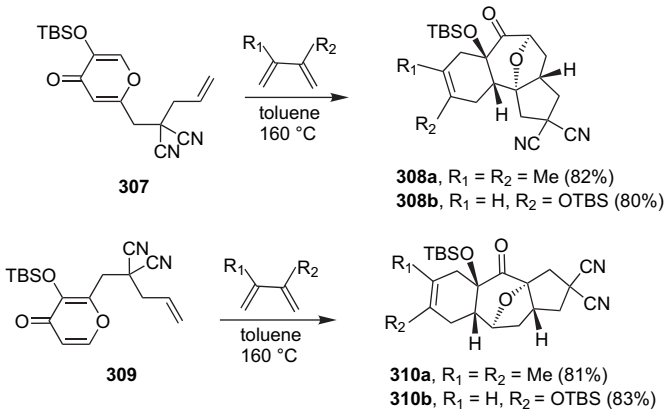
In addition to the construction of seven-membered rings, the adducts obtained by the cycloaddition of oxidopyrylium species also served as useful precursors for the synthesis of tetrahydrofurans.[67] Mascarenas and co-workers have successfully employed the [5+2] cycloadducts in the synthesis of racemic[67a,b] as well as (+)-nemorensic acid **304**,[67c] which is the diacid part of the pyrrolizidine alkaloid, nemorensine. The optically pure compound **303** was synthesized from **302** via cycloaddition and reaction of the major adduct with Raney



Scheme 52.

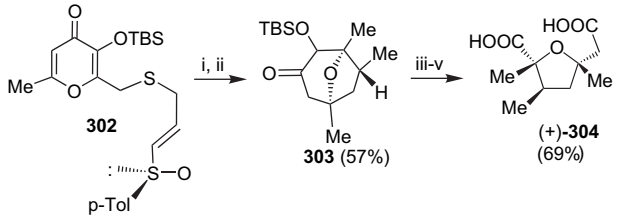


Scheme 53.

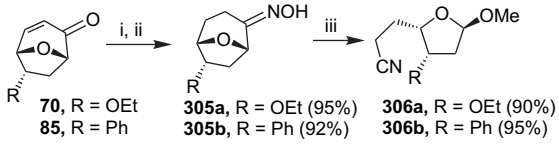


Scheme 56.

Ni. Treatment of **303** with TBAF and subsequent cleavage and oxidation furnished (+)-nemorensic acid (Scheme 54).[67c] In this context, it may be mentioned that Trivedi and his co-workers have also recently reported the transformation of the adducts **70** and **85** into tetrahydrofurans **306a** and **306b**, respectively, via a Beckmann rearrangement in **305a**,**b** (Scheme 55).[68]



Scheme 54. Reagents/conditions: (i) toluene, △; (ii) Raney Ni, THF, △; (iii) TBAF; (iv) $Pb(OAc)_4$, MeOH; (v) CrO_3, H_2SO_4, acetone.



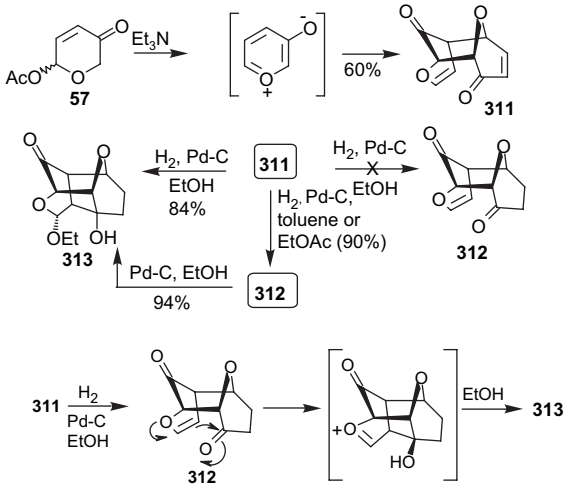
Scheme 55. Reagents/conditions: (i) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH–H_2O; (ii) $NH_2OH \cdot HCl$, NaOAc; (iii) SO_2Cl, MeOH.

6. Tandem [5+2] cycloaddition of oxidopyrylium species and [4+2] cycloadditions

Mascarenas and co-workers have also developed a novel and efficient method for the synthesis of 6,7,5-tricarbocyclic systems having a 1,4-oxa bridge in the seven-membered ring via an intramolecular thermal [5C+2C] pyrone–alkene cycloaddition followed by a Diels–Alder reaction in tandem.[69] Thus, heating the pyranones **307** and **309** in the presence of an appropriate 1,3-diene at 160 °C afforded the carbocycles **308a**,**b** and **310a**,**b** with a well-defined stereochemistry (Scheme 56).[69] The overall sequence constitutes an intramolecular [5+2] pyrone–alkene cycloaddition followed by an intermolecular Diels–Alder reaction.[69,70]

7. Transformation of dimer of 3-oxidopyrylium

In the previous sections, we have presented the cycloadditions of oxidopyrylium with various alkene dipolarophiles and the chemistry of the adducts. In the absence of a suitable dipolarophile, however, these species undergo dimerization. The dimerization reactions of various reactive carbonyl ylides are well documented.[71] Hendrickson and Farina reported that the 3-oxidopyrylium derived from **57** also undergoes self-dimerization in the absence of dipolarophiles to give the dimer **311** (Scheme 57).[72] These authors have suggested that the dimer **311** is a potential precursor for the medium-ring compounds. It is rather surprising that, despite its synthetic potential, the dimer has not received due attention.

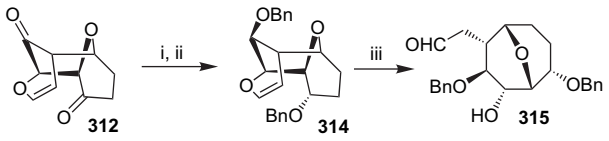


Scheme 57.

Recently, Trivedi and co-workers reported transformations of the dimer **311** to highly functionalized oxa-bridged cyclooctanoids and other interesting carbocyclic systems.[73] Thus, it was observed that hydrogenation of the dimer **311** in ethanol did not give the expected dihydro product **312**, the compound **313** was obtained instead. When the reaction was performed in non-nucleophilic solvents such as ethyl acetate, however, it yielded the expected dihydro product **312** (Scheme 57).

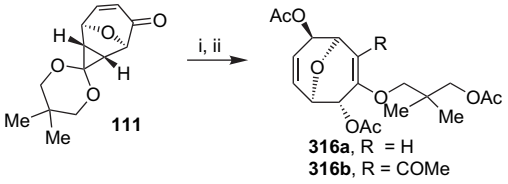
Treatment of **312** with Pd–C in the presence of ethanol also gave the product **313**. Apparently, the product **312** undergoes a transannular reaction, leading to the oxonium ion intermediate that, upon interception with ethanol, gives the compound **313** (Scheme 57).

In order to further explore the synthetic potential, the dihydro product **312** was reduced with sodium borohydride and alkylated with benzyl bromide to give the dibenzyl ether **314**. Hydration of the pyranyl ether **314** in the presence of an acidic resin such as Dowex 50W-X4 gave the aldehyde **315** containing a bridged eight-membered ring (Scheme 58).[73] Thus, the dimerization of 3-oxidopyrylium reported by Hendrickson and Farina[72] and the studies presented herein constitute a potentially useful method of transforming furans into functionalized cyclooctanoids, which are present in many natural products.[74,75]



Scheme 58. Reagents/conditions: (i) $NaBH_4$, MeOH, −10 °C, 68%; (ii) NaH, benzyl bromide, Bu_4NI, THF, 77%; (iii) Dowex 50W-X4, LiBr, aq MeCN, 88%.

In this context, it may be mentioned Mascarenas and co-workers[23a] reported that the adduct **111**, obtained by the cycloaddition of the oxidopyrylium derived from **57** (vide infra; Scheme 11) and cyclopropenone acetal, may be transformed into cyclooctanoids of the type **316**. Thus, the reduction of the carbonyl group and subsequent ring opening of the cyclopropane ring in the presence of Ac_2O–TMSOTf gave the compounds **316a**,**b** (Scheme 59).

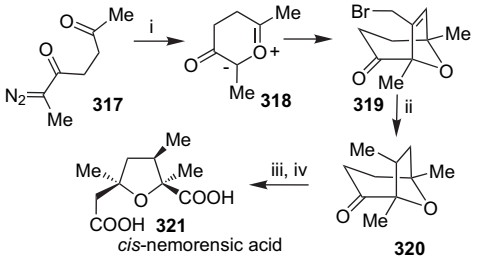


Scheme 59. Reagents/conditions: (i) $NaBH_4$, $CaCl_2$, 93%; (ii) Ac_2O, TMSOTf, **316a** (35%), **316b** (34%).

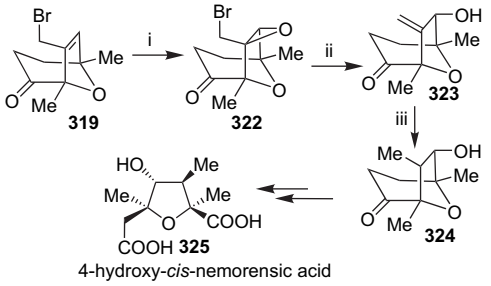
8. Rhodium-catalyzed generation of carbonyl ylides and their cycloadditions

Rhodium-catalyzed generation of carbonyl ylides and their cycloaddition is a vast and rapidly growing field. In view of the recent reviews on this subject,[6,7] we have made attempts to present some of the latest results in this area.

Hodgson and co-workers have extensively examined inter- as well as intramolecular cycloaddition of carbonyl ylides.[76,77] The intermolecular cycloaddition methodology was applied to the synthesis of nemorensic acid and 4-hydroxynemorensic acid (Scheme 60).[76a] Thus, generation of the dipolar species **318** from the diazo ketone **317** and cycloaddition with propargyl bromide gave the adduct **319** in excellent yield. Reduction of **319** gave the ketone **320**, which upon transformation into a silyl enol ether followed by ozonolysis furnished *cis*-nemorensic acid **321** (Scheme 60). Epoxidation of the adduct **319** with dimethyldioxirane gave the epoxide **322**, which was converted into the olefinic alcohol **323**. Further transformation of **323** gave the target 4-hydroxy-*cis*-nemorensic acid **325**, via **324** (Scheme 61).[76a] Hodgson and Le Strat have also reported the synthesis of 3-hydroxy-*cis*-nemorensic acid and nemorensic acid employing the cycloaddition of the carbonyl ylide **318** with allene.[76b] The details of these studies and preliminary results on the enantioselective cycloaddition have appeared recently.[76c]

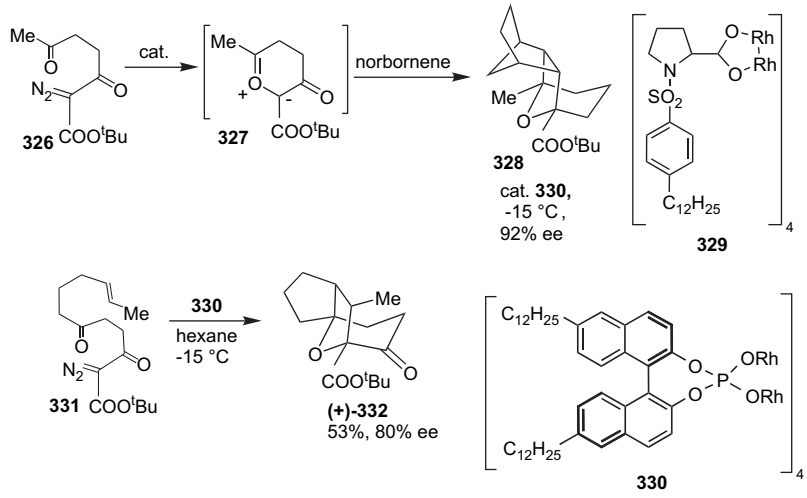


Scheme 60. Reagents/conditions: (i) $Rh_2(OAc)_4$, propargyl bromide, CH_2Cl_2, rt, 84%; (ii) H_2, Pd–C, MeOH, 92%; (iii) LDA, THF, −78 °C, TMSCl, 90%; (iv) O_2/O_3, CH_2Cl_2, −78 °C, then 35% H_2O_2, 88% HCOOH, 100 °C, 97%.



Scheme 61. Reagents/conditions: (i) dimethyldioxirane (0.1 M in acetone), CH_2Cl_2, rt, 94%; (ii) Zn, MeOH, △, 97%; (iii) H_2, $[Ir(cod)py(Pcy_3)]PF_6$, CH_2Cl_2, 93%.

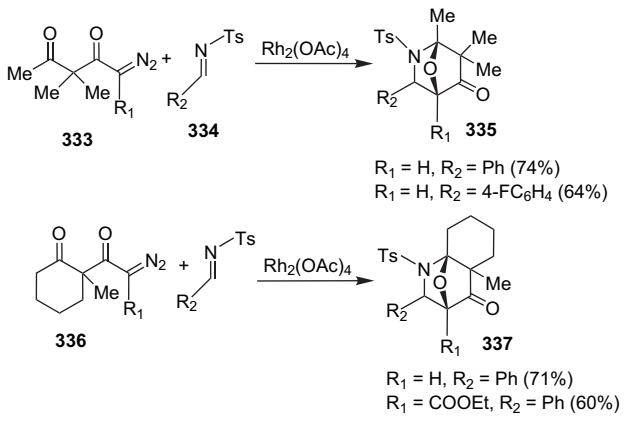
In continuation of their earlier studies on enantioselective cycloaddition, the authors also developed a catalytic enantioselective version of the inter- and intramolecular cycloadditions of carbonyl ylides.[77] Thus, in situ generation of the carbonyl ylide from a precursor of the type **326** in the presence of catalysts **329/330** and cycloaddition of the resulting carbonyl ylide with various alkenes was examined.[77a] The reaction of **326** and norbornene in the presence of the catalyst **330** gave the adduct **328**, via **327**, in maximum enantiomeric excess (92%) (Scheme 62). Norbornadiene also underwent an efficient cycloaddition to give the corresponding adduct in good enantiomeric excess.[77a] Cycloadditions in the presence of **329** as a catalyst generally gave a low enantiomeric excess. Several other catalysts were developed and their efficacy in the enantioselectivity was examined.[77b]



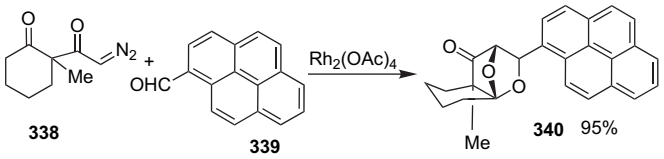
Scheme 62.

Enantioselective intramolecular cycloaddition employing the aforementioned catalysts was also examined.[77c–f] Thus, the in situ generation of the carbonyl ylide from the precursor **331** in the presence of catalyst **330** gave the adduct **332** with good enantiomeric excess (Scheme 62). Cycloadditions of various other analogues of **331** in the presence of both catalysts were examined. In general, the catalyst **330** gave better results.[77c] Most recently, the authors have reported a tandem cross-metathesis/carbonyl ylide generation–cycloaddition, leading to a quick access to various types of polycyclic systems.[77d,e]

Muthusamy and co-workers have reported extensive work on the cycloaddition of various types of carbonyl ylides with a diverse array of dipolarophiles and have developed routes to a number of polycyclic frameworks.[78,79] Recently, the authors have reported the cycloaddition of carbonyl ylides with imines, leading to oxa-bridged piperidinones (Scheme 63).[78a] Thus, the reaction of diazo ketones **333** and **336** with tosylimines **334** in the presence of rhodium acetate furnished the corresponding adducts **335** and **337**, respectively, in good yields (Scheme 63). The same workers have also reported the cycloaddition of carbonyl ylides with carbonyl groups, leading to dioxa-bridged compounds (Scheme 64).[78d]



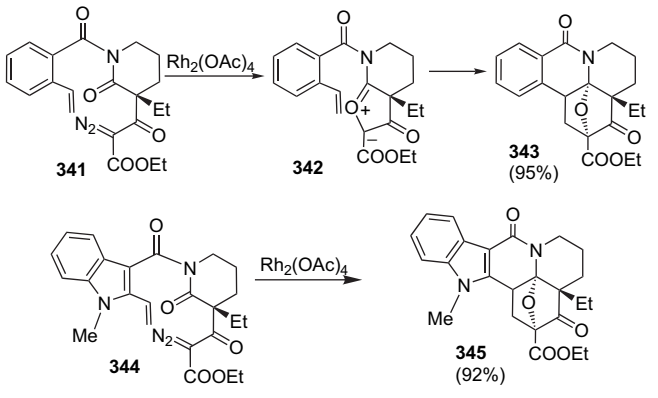
Scheme 63.



Scheme 64.

Treatment of the diazo ketones of the type **338** with rhodium acetate and subsequent reaction with an aromatic aldehyde **339** led to the dioxa-bridged compound **340** in excellent yield. Various aromatic aldehydes were found to undergo efficient cycloaddition to furnish adducts in excellent yields.[78d]

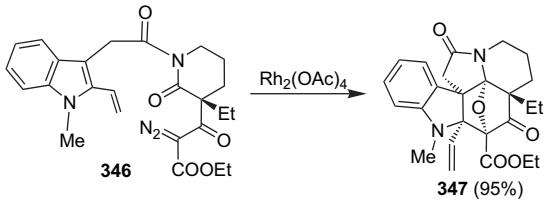
In continuation of their pioneering studies on carbonyl ylide cycloaddition, Padwa and Mejia-Oneto recently reported intramolecular cycloadditions of push–pull diploes that led to complex molecular structures related to alkaloids.[80a] Thus, the reaction of the diazo ester **341** with rhodium(II)acetate gave the pentacyclic compound **343**, via the ylide **342**, in excellent yield (Scheme 65). Similarly, the indolyl analogue **344** gave the compound **345** in excellent yield.



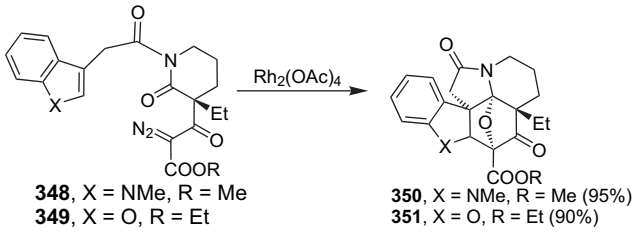
Scheme 65.

Interestingly, in the reaction of the homologue **346**, the resulting carbonyl ylide added to the indole double bond to give

the compound **347** (Scheme 66). In order to check the generality of this cycloaddition across the π-bond of the five-membered ring, the reactions of several other substrates without a vinyl tether were examined. Thus, the precursors **348** and **349** underwent a similar cycloaddition upon treatment with rhodium acetate to give the corresponding adducts **350** and **351**, respectively (Scheme 67).[80a] The ligand effect on such types of cycloaddition was also examined.[80b]

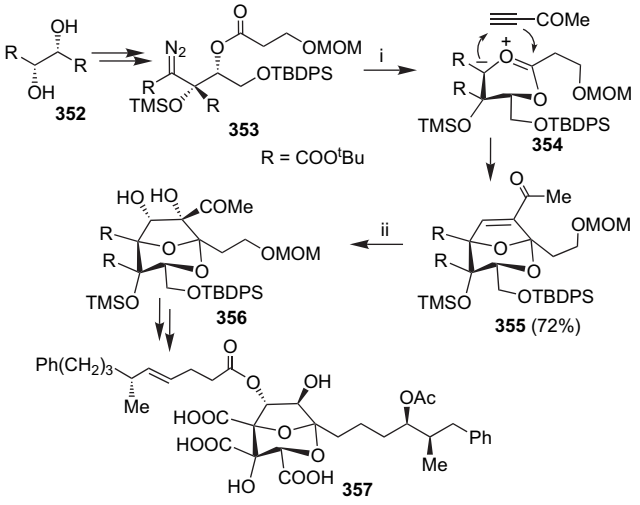


Scheme 66.



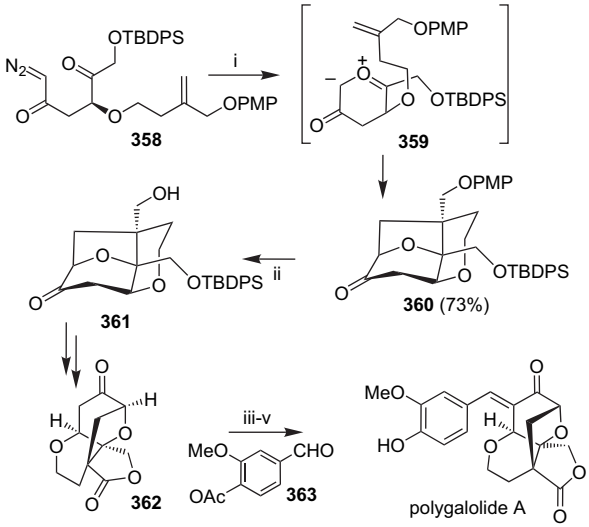
Scheme 67.

Hashimoto and co-workers employed a carbonyl ylide cycloaddition as a key step for the synthesis of zaragozic acid C, a squalene synthase inhibitor.[81] The diazo ester **353** was prepared from the diester **352** in several steps. Treatment of the diazo ester **353** with Rh(II)acetate in the presence of acetylacetylene gave the adduct **355** via cycloaddition of the carbonyl ylide **354** in excellent yield (Scheme 68). Osmylation of the double bond gave the diol **356**, which was elaborated into zaragozic acid C **357** after a series of transformations.[81a]



Scheme 68. Reagents/conditions: (i) $Rh_2(OAc)_4$, PhH, reflux, 72%; (ii) OsO_4, NMO, aq acetone, 88%.

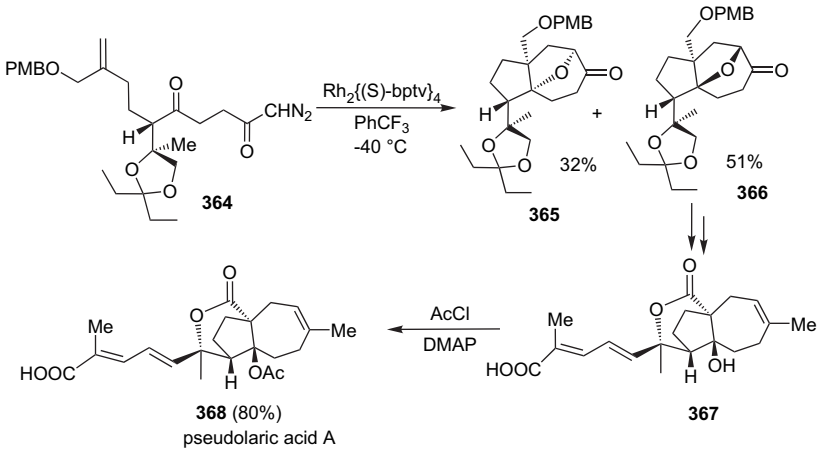
Recently, Hashimoto and co-workers also reported the synthesis of polygalolides in which the carbonyl ylide cycloaddition was used as a key step to create the bridged polycyclic framework.[81b] Thus, the diazo compound **358** upon treatment with Rh(II)acetate generated the carbonyl ylide **359** that underwent intramolecular cycloaddition to give the tricyclic compound **360**, which upon selective removal of the protecting group gave the alcohol **361**. The alcohol **361** was elaborated into **362**, which was subsequently transformed into polygalolide A via reaction with the aromatic aldehyde **363** and creation of the double bond (Scheme 69).[81b]



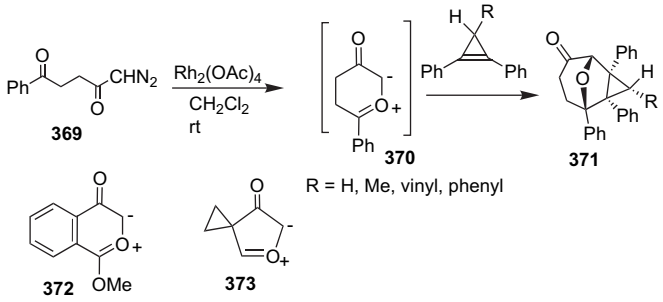
Scheme 69. Reagents/conditions: (i) $Rh_2(OAc)_4$, $PhCF_3$, 100 °C, 73%; (ii) $(NH_4)_2Ce(NO_3)_6$, Py, aq MECN, 91%; (iii) LDA, $ZnCl_2$, THF, −78 °C, **363**, then AC_2O, 0 °C; (iv) SiO_2, CH_2Cl_2; (v) $NaHCO_3$, aq MeOH, 18% (three steps).

Chiu and co-workers developed an intramolecular cycloaddition of a carbonyl ylide with an allene that led to annulated oxa-bridged bicyclo[3.3.1]nonane ring systems[82a] and have also described an enantioselective total synthesis of pseudolaric acid A, a biologically active principle of the Chinese herb *tujinpi* (Scheme 70).[82b] Thus, the diazo ketone **364** upon treatment with a chiral rhodium catalyst gave the adducts **365** and **366** having **366** as the major product. Compound **366** was transformed into the lactone **367**, which upon acetylation furnished pseudolaric acid A **368**.

Molchanov and his group have examined the cycloaddition of carbonyl ylides with cyclopropenes that led to cyclopropane annulated oxa-bridged bicyclic systems.[83a,b] Thus, treatment of diazo ketones of the type **369** with rhodium acetate generated species of the type **370**, which underwent cycloaddition with cyclopropenes to give the corresponding adducts **371** in good yields (up to 84%) (Scheme 71).[83a] They also examined the cycloaddition of carbonyl ylides **372** and **373** and the role of 3-substituents in cyclopropenes on the stereochemistry of cycloaddition and other electronic effects.[83b] Recently, the authors have also reported the cycloaddition of the dipolar species **370** with methylene cyclopropanes and bicyclopropylidene, which gave the corresponding adducts in good yields.[83c]

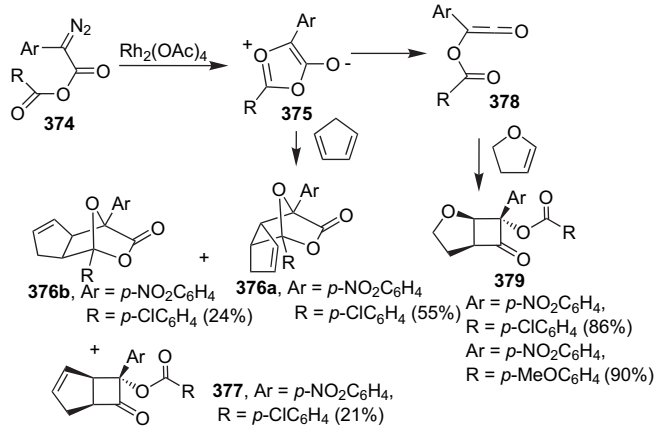


Scheme 70.



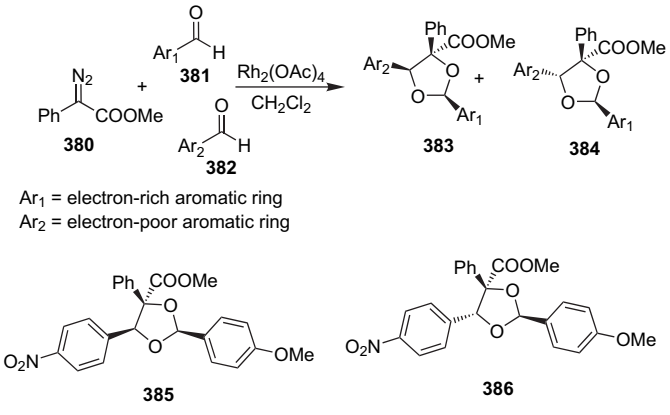
Scheme 71.

Hamaguchi and co-workers[84] have examined the generation of carbonyl ylides (and their conversion into acyloxy ketenes) and their reaction with various π-partners. They observed that mesoionic 1,3-dioxolium-4-olates (generated by a $Rh_2(OAc)_4$-catalyzed decomposition reaction of diazophenylacetic anhydride derivatives) undergo ring opening into acyloxy ketenes that give [2+2] cycloadducts with various ketenophiles. Only in one case, i.e., reaction of **374** in the presence of $Rh_2(OAc)_4$ and cyclopentadiene, did the resulting dipolar species **375** gave the adducts **376a**,**b** as the major products and **377** as the minor product (Scheme 72). Reaction of the dipolar species in the presence of dihydrofuran gave adducts of the type **379** via the intermediate **378** (Scheme 72). Recently, the authors have also reported the generation of 1,3-dioxolium-4-olates from acyloxy ketenes and their reaction with various π-partners.[84b]



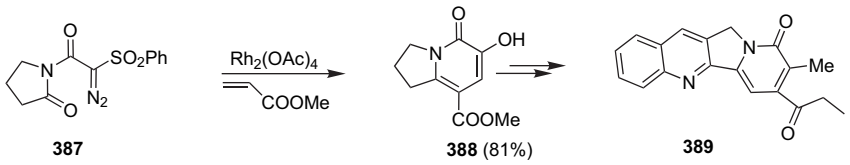
Scheme 72.

Hu and co-workers recently reported a multicomponent Rh(II)acetate catalyzed 1,3-dipolar cycloaddition of methyl phenyldiazoacetate **380** with differentially activated carbonyl groups of aromatic aldehydes **381** and **382** that led to the formation of triaryl-1,3-dioxolanes **383** and **384** in good-to-excellent yields (Scheme 73).[85a] Thus, the decomposition of methyl phenyldiazoacetate in the presence of *p*-anisaldehyde and *p*-nitrobenzaldehyde gave the dioxolanes **385** and **386** (45:55) in 50% yield (Scheme 73), along with minor amounts of the corresponding epoxides derived from the reaction of aldehydes. Interestingly, the electron-rich aldehydes participated in the formation of carbonyl ylides. None of the oxolanes formed from the diazo compound with the same two aldehydes. Application of this methodology for the synthesis of tRNA inhibitor analogues was also reported.[85b]

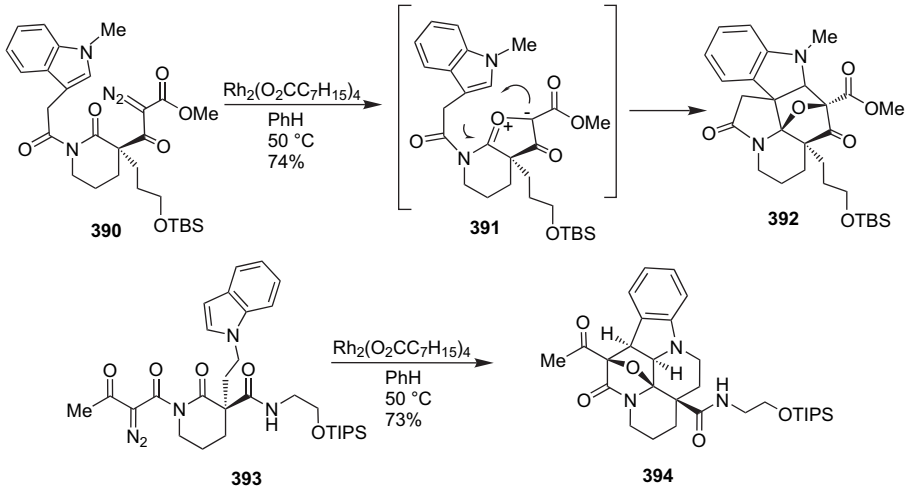


Scheme 73.

Greene and co-workers recently reported the synthesis of many natural products such as mappicine ketone and camptothecinoids that employed annulated hydroxy pyridones as precursors, which were prepared by cycloaddition of carbonyl



Scheme 74.



Scheme 75.

ylides.[86] In one example, the hydroxypyridone **388**, prepared by cycloaddition of the carbonyl ylide derived from **387** with methyl acrylate,[87] was used for the synthesis of mappicine ketone **389** (Scheme 74),[86a] and camptothecin.[86b–d]

Schreiber and Okuri have developed a remarkable strategy involving carbonyl ylide cycloaddition that efficiently leads to complex molecular architectures via a folding pathway.[88] Thus, the diazo ketone **390** on treatment with Rh(II)octanoate gave the compound **392**, via cycloaddition in the species **391**. Similarly, treatment of the diazo ketone **393** with Rh(II)octanoate also furnished the compound **394** in good yield having an alkaloid-like framework (Scheme 75).[88]

9. Concluding remarks

It is evident from the above discussion that cycloaddition of oxidopyrylium species both from pyranulose acetate and from hydroxypyrones has evolved into a powerful methodology for the creation of diverse molecular frameworks having an oxa-bridge that are not readily available otherwise. The presence of an oxa-bridge and other functionalities permits further manipulation of the cycloadducts into various types of functionalized carbocyclic systems related to different classes of natural products. This methodology has led to the total synthesis of complex natural products in regio- and stereoselective fashion. Similarly, the cycloaddition of carbonyl ylides derived from rhodium-catalyzed reactions of diazo ketones provides a more flexible and general methodology for the synthesis of a diverse array of molecular structures and has been employed as a key step in the synthesis of structurally and functionally complex natural products. Moreover, asymmetric versions of the aforementioned cycloadditions provide access to enantiomerically pure/enriched compounds. The cleavage of the oxa-bridge in the cycloadducts is one of the important steps in the manipulation. Although there are some existing methods, the development of an alternative more efficient methodology would further enhance the synthetic potential of cycloadducts. The studies presented in this report provide a deeper insight into mechanistic, and regio- and stereochemical aspects of the cycloadditions, which may enable the design of new precursors for cycloaddition that would generate molecular structures of greater complexity in an efficient manner. Moreover, it would be desirable to develop an organo-catalytic method for the generation of oxidopyrylium/carbonyl ylides and their cycloaddition.

Acknowledgements

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