Pergamon

Tetrahedron 58 (2002) 9477–9504

TETRAHEDRON

Tetrahedron report number 624

Tandem cyclization–cycloaddition reactions of rhodium generated carbenoids from α-diazo carbonyl compounds

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Received 16 September 2002

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1. Introduction

The rapid generation of molecular complexity, in a controlled and predictable manner, is a contemporary theme in the practice of modern organic synthesis and finds application in accessing newer entities for the pharmaceutical industry. Efficiency, atom economy, regio-, stereo- and enantiocontrol, ready availability of starting materials and environmentally benign processing are some of the common concerns in any synthetic endeavor. Synthetic brevity is, however, central to the generation of molecular complexity in a resource-effective manner and, in order to attain that objective, two strategic options have been generally explored in recent years, one involving multicomponent reactions and the other involving reactions leading to multiple carbon-carbon bond formation through tandem processes. The latter approach involves recourse to reactions like multiple cycloadditions or cyclization–cycloaddition sequences in which many bonds are formed in a single mode operation and these cascade processes have an inherent advantage in expeditiously assembling polycyclic structures with proper stereochemical control.

Tandem processes[1–7] of a diverse nature, promoted through thermal or photochemical activation or catalysts, have already proven their utility in organic synthesis and found many applications in the acquisition of complexity in the form of functionalized carbo- and heteropolycyclic structures. Cascade reactions involving transition-metal catalysts

Keywords: carbonyl ylides; cyclization; cycloaddition; diazo carbonyl compounds; polycyclic systems; rhodium(II) acetate.
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PII: S0040-4020(02)01187-0

in particular have gained significant importance in recent years.[8–11] Among these, the tandem cyclization–cycloaddition reaction of carbenoids derived from α-diazo carbonyl compounds using rhodium(II) catalysts has been on the ascendancy and attracted the attention of many chemists for diverse synthetic applications and forms the subject matter of this report.[12,13]

Historically, carbenoids derived from α-diazo carbonyl compounds using copper catalysts were mainly employed for cyclopropanation and C–H and X–H insertion reactions. The formation of carbonyl ylides (1,3-dipoles obtained through carbenoid insertion into a carbonyl group) under these conditions was not very efficient and efforts to trap them received only limited attention. The advent of rhodium-based[14] catalysts for generating carbenoids from α-diazo carbonyl compounds was a turning point, however, as it provided efficient access to carbonyl ylides that could be trapped through 1,3-dipolar cycloaddition.[15,16] It is the selectivity and preparative efficiency of the rhodium(II) mediated carbonyl ylide formation from α-diazo carbonyl compounds that has paved the way for many interesting synthetic applications through cascade processes.[12,13] Many methods like thermolysis or photolysis of epoxides (**D**) having electron-withdrawing substituents,[17] the thermal extrusion of nitrogen from 1,3,4-oxadiazolines (**G**),[18] extrusion of carbon dioxide from 1,3-dioxolan-4-ones (**F**)[19] and the photolysis of diazo carbonyl compounds in noble gas matrixes (**E**)[20] are known for the generation of carbonyl ylides (Fig. 1). The easiest route to carbonyl ylides, however, is through the addition of a metallo-carbenoid[12,13] derived from a diazo precursor onto the oxygen atom of a carbonyl group (**A**) (Fig. 1). The carbonyl ylides (**B**) generated can be readily trapped inter- or intramolecularly with π-bonds via a range of 1,3-dipolar cycloaddition reactions[21] to afford oxygen-containing polycyclic systems (**C**), which are amenable to further diverse transformations. This aspect of carbonyl ylide chemistry, particularly when executed in an intramolecular mode, leading to complex oxacyclic systems, has gained importance because highly substituted oxacyclic moieties are conspicuous[22,23] structural units in naturally occurring bioactive molecules like ionophores,[24] macrocyclic antibiotics[25] and a range of marine toxins.[26] In addition, complex oxapolycyclics can be readily maneuvered to furnish carbocyclic compounds and carbonyl ylide cycloadditions have therefore found application in the synthesis of both heterocyclic and carbocyclic systems.

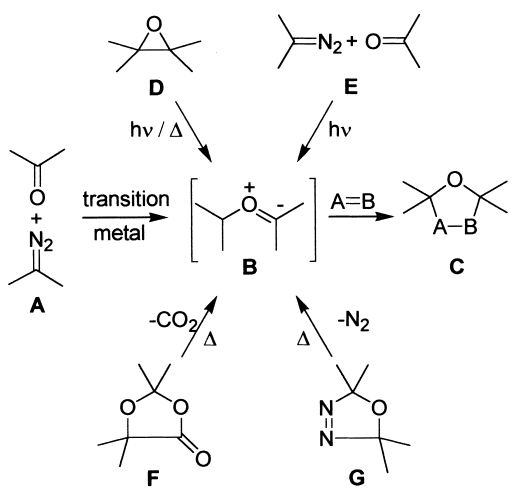


Figure 1.

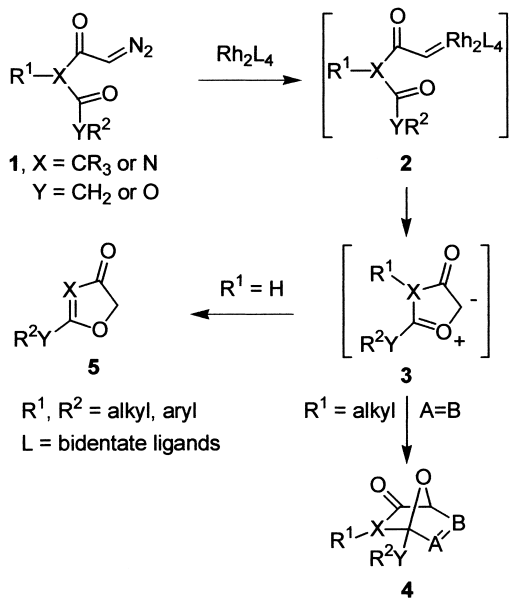
1.1. Scope and organization of the review

As indicated above, access to practical methods for generating carbonyl ylides has resulted in a plethora of activity directed towards the acquisition of complex heterocyclic frameworks and diverse natural products. The generation and trapping of an intramolecular carbonyl ylide methodology were initially demonstrated by Ibata and co-workers[27] and this has culminated in the development of a very versatile methodology for the construction of complex and highly functionalized organic compounds. This review will cover aspects related to the carbonyl ylides derived from the Rh(II)-catalyzed reactions of α-diazo carbonyl compounds and provide an overview of the existing literature with appropriate emphasis on recent examples. For convenient dissemination of the literature, the examples are schematically presented. The fertile area of cascade reactions emanating from carbonyl ylides has been reviewed in 1991[12] and updated[13] in part in 1996 by Padwa, whose group has made pioneering contributions to the field. It is hoped that the present review covering the period of 1991 to mid-2002 will provide a useful reference for those active in this area and stimulate further efforts in this sphere which has much more potential for varied synthetic applications.

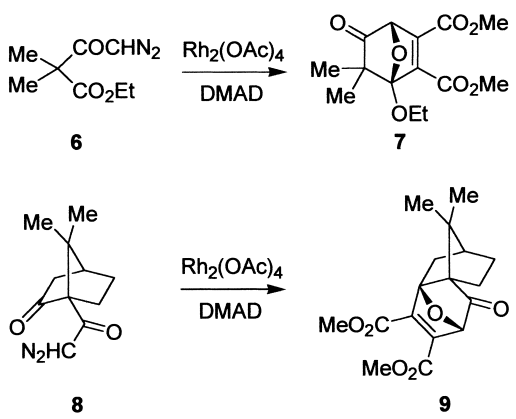
This report is organized on the basis of the intramolecular generation of carbonyl ylide intermediates of various ring sizes, namely five, six and seven-membered rings, and their synthetic applications are delineated in the respective sections. Each of these ring sizes is further sub-classified based on the nature of the carbonyl group, e.g. ketone, ester and amide, primarily involved in the generation of the carbonyl ylide intermediate from the rhodium(II) carbenoid precursor. In general, ketone and amide carbonyl groups are much more reactive towards the formation of carbonyl ylide than the ester carbonyl group. From the synthetic and mechanistic point of view, five- and six-membered intramolecular carbonyl ylide intermediates and their subsequent [3+2]-cycloaddition reactions have received greater attention. Only a very few examples of the formation of seven-membered ring carbonyl ylides have surfaced so far. In Section 5, the intermolecular generation of carbonyl ylides is discussed and these have not yet received as much attention as their intramolecular counterparts.

2. Intramolecular five-membered ring carbonyl ylides

When a diazo functionality located at the γ-position to a carbonyl group of a substrate is exposed to an appropriate transition metal catalyst, an intramolecular five-membered ring carbonyl ylide is formed as a transient species through transannular cyclization onto the neighboring keto carbonyl oxygen. The formation of less strained five-membered ring ylides is generally favored compared to other ring sizes.[28] The generation of intramolecular five-membered ring carbonyl ylide intermediates in the presence of metal



Scheme 1.



Scheme 2.

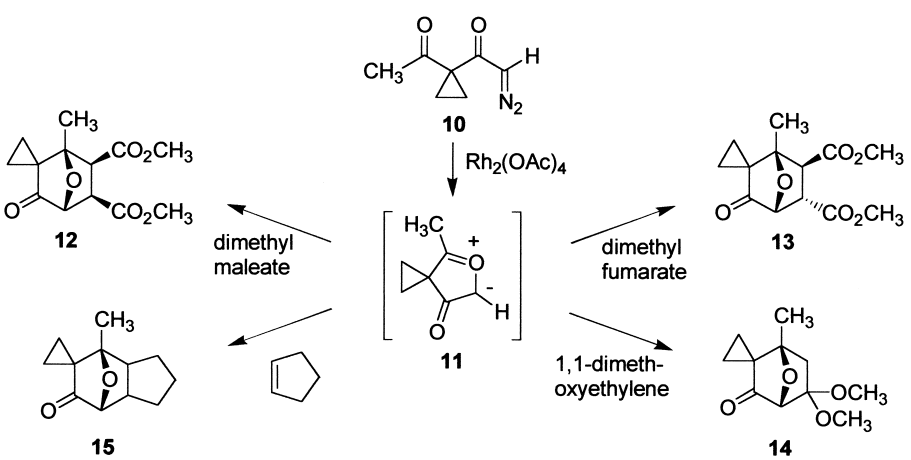
catalyst can be achieved with a variety of carbonyl-bearing precursors such as ketones, esters and amides. The successful trapping of such five-membered ring carbonyl ylides depends on the substrate structure and the absence of competition from alternative intramolecular reaction pathways. As an example, the rhodium(II)-catalyzed reaction of substituted α-diazo ketones **1** generates initially the rhodium-carbenoids **2**, followed by the five-membered ring carbonyl ylides **3**, which can be trapped regio- and stereoselectively using a dipolarophile A=B to form the oxabicyclic compounds **4** (Scheme 1). If R_1 is a hydrogen atom (see Scheme 1), the formation of the corresponding hydrogen migrated product **5** through an intramolecular proton transfer, which is faster than intermolecular 1,3-dipolar cycloaddition, is observed. From a synthetic perspective and to gain efficient access to the cycloaddition products **4**, it is important that competitive reactions like proton transfer and C–H insertion are avoided through a proper choice of the substrate **1**.

2.1. With keto carbonyl groups

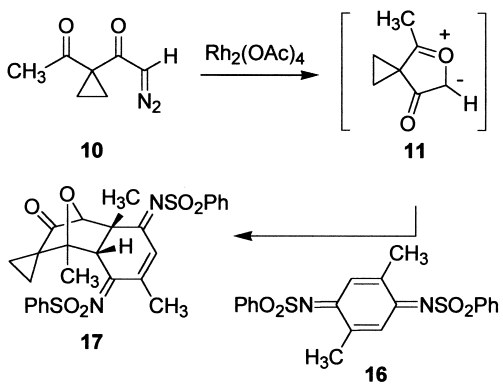
Among the early examples of the successful generation and trapping of the five-membered ring carbonyl ylides emanating from the pioneering efforts of Padwa are the reactions of the readily accessible diazo carbonyl compounds **6** and **8** with rhodium(II) acetate [$Rh_2(OAc)_4$] in the presence of dimethyl acetylenedicarboxylate (DMAD) to furnish the highly functionalized cycloadducts **7** and **9**, respectively (Scheme 2).[29]

The reactions of the cyclopropyl-substituted carbonyl ylide **11** derived from the α-diazo ketone **10** with different dipolarophiles have been investigated by Padwa.[30] The compound **10** undergoes cycloaddition in the presence of $Rh_2(OAc)_4$ with dimethyl maleate, dimethyl fumarate, 1,1-dimethoxyethylene and cyclopentene, furnishing the expected cycloadducts **12**–**15**, respectively (Scheme 3).[30b] The regiochemical outcome of the 1,3-dipolar cycloaddition reactions of the cyclic five-membered ring carbonyl ylide **11**, generated from the α-diazo ketone **10**, with a variety of acyclic and cyclic alkenes having activated or inactivated π-bonds can be rationalized[30] on the basis of frontier molecular orbital considerations, with the HOMO and LUMO of the carbonyl ylides dominating the reactions with electron deficient and electron rich dipolarophiles, respectively.

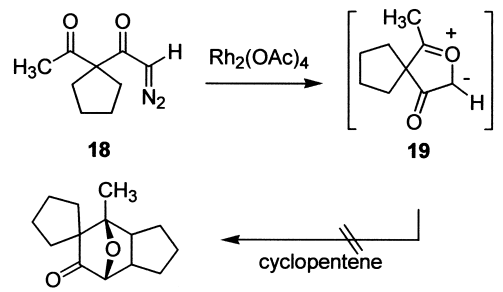
The reactivity of the spirocyclic ylide **11** derived from the α-diazo ketone **10** with *p*-quinoneimides such as **16** has



Scheme 3.



Scheme 4.

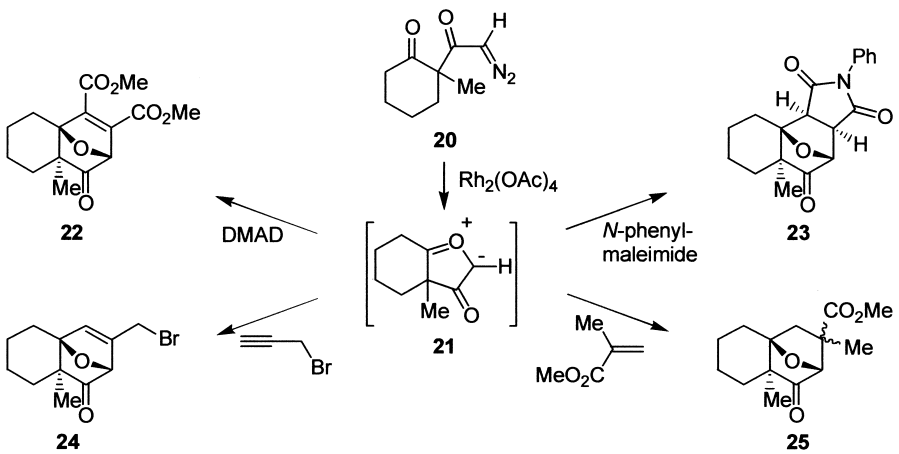


Scheme 5.

energy (early transition state) in the cyclopropyl substrate or greater steric hindrance in the cyclopentyl-substituted system.

Muthusamy and co-workers have reported the reactions of the bicyclic ylide **21** generated from the diazo carbonyl compound **20** with dipolarophiles including DMAD, *N*-phenylmaleimide (NPM), propargyl bromide and methyl methacrylate,[32] exposure of the cyclohexanone-substituted α-diazo carbonyl compound **20** to DMAD and NPM in the presence of $Rh_2(OAc)_4$ as the catalyst furnishing the cycloadducts **22** and **23**, respectively (Scheme 6). These cycloadditions were diastereoselective and, in the case of unsymmetrical dipolarophiles such as propargyl bromide and methyl methacrylate, they were regioselective and furnished **24** and **25**, respectively (Scheme 6).

The same research group has reported the 1,3-dipolar cycloaddition of the bicyclic carbonyl ylide **21** derived from the diazo carbonyl compound **20** with further interesting substrates, namely indoles,[33] fulvenes[34] and norbornenes.[35] In these tandem cyclization–cycloaddition reactions involving indoles, fulvenes and norbornenes, four stereocenters and two new C–C bonds are formed in a single step. Intermolecular cycloaddition of the fused five-membered ring cyclic carbonyl ylide **21** with indole, *N*-methylindole and *N*-benzylindole afforded the decahydrobenzo[*c*]carbazole **26** with a high regioselectivity (Scheme 7).[33] With an



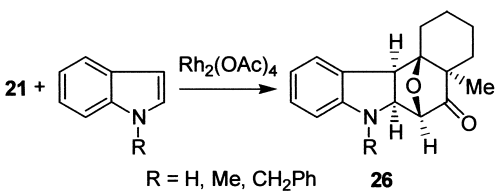
Scheme 6.

been probed by Nair and co-workers to furnish the *endo*-adduct **17** in a chemo- and stereoselective manner (Scheme 4).[31]

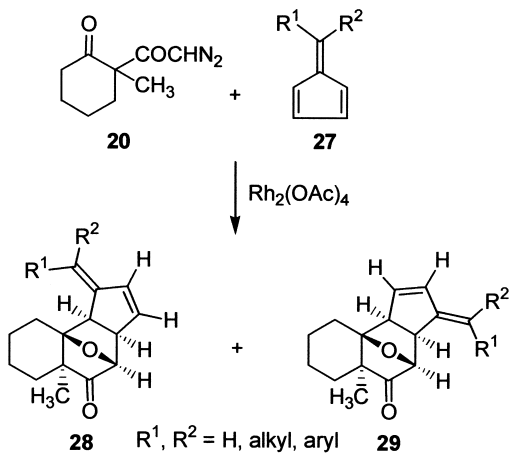
The reactions of the related cyclopentyl-substituted ylide **19** having reduced I-strain, derived from the α-diazo ketone **18**, with different dipolarophiles have also been investigated by Padwa.[30b] As expected, the compound **18** undergoes cycloaddition in the presence of $Rh_2(OAc)_4$ with DMAD, dimethyl maleate and 1,1-dimethoxyethylene and furnished the expected cycloadducts. No cycloaddition was, however, observed between the spirocyclic ylide **19** and unactivated π-bonds (cyclopentene), indicating that the dipole **11** derived from the cyclopropyl-substituted diazo ketone **10** is clearly more reactive (Scheme 5).[30b] This difference in reactivity could be attributed to either a lower activation

electron-withdrawing group on the indole nitrogen, however, regioisomeric decahydrobenzo[*a*]carbazoles are also obtained.

Similarly, the reaction of the carbonyl ylide **21** derived from the α-diazo carbonyl compound **20** with either symmetrical or unsymmetrical pentafulvenes **27** led to the novel



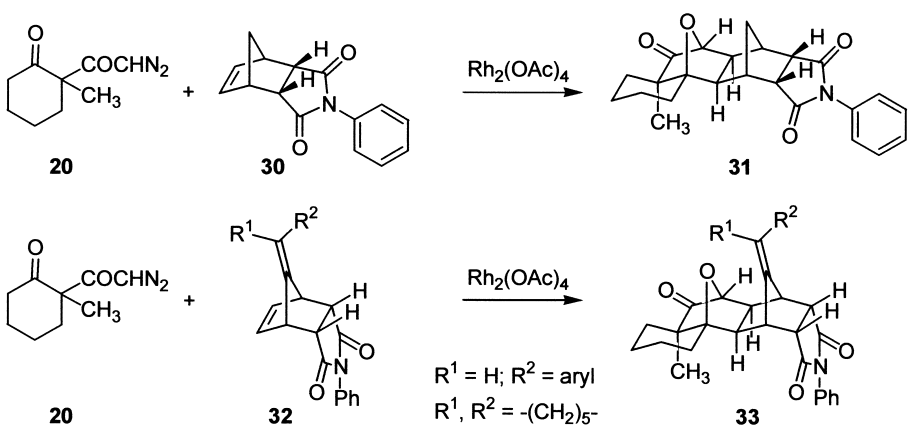
Scheme 7.



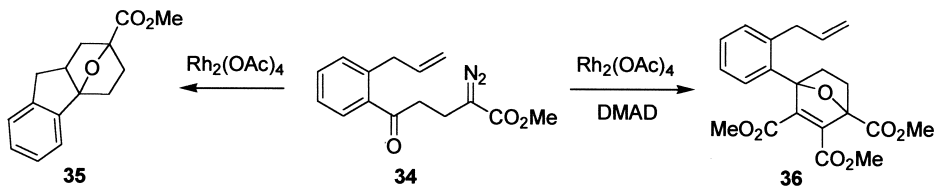
Scheme 8.

Not unexpectedly, an intramolecular variant of the five-membered ring carbonyl ylide cycloaddition has also been explored.[36] When the specially crafted α-diazo ketoester **34** was decomposed in the presence of $Rh_2(OAc)_4$, an intramolecular cycloaddition product **35** was realized in good yield (Scheme 10). On the other hand, if DMAD was present in the reaction mixture, the bimolecular adduct **36** was isolated.

Investigations and stereoselective studies on the tandem rhodium(II)-catalyzed reactions of the carbonyl ylides **21** generated via the α-diazo carbonyl compound **20** with various carbonyl compounds like aromatic aldehydes, α,β-unsaturated aldehydes, furan-2-carboxaldehyde and 2,3,4,5-tetraphenylcyclopenta-2,4-dienone have also been studied to provide the corresponding dioxatricyclic ring systems **37**–**40** with high regio- and chemoselectivity (Scheme 11).[37]



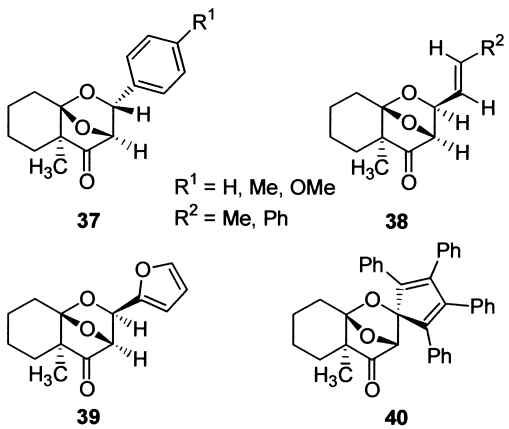
Scheme 9.



Scheme 10.

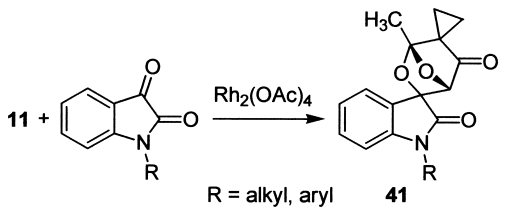
regioisomeric oxatetracyclo[6.5.1.$0^{1,6}$.$0^{9,13}$]tetradecene derivatives **28** and **29** (Scheme 8).[34] It is interesting to note that the regioisomer ratio (**28**/**29**) changed from 1:10 for the symmetrical fulvenes to 1:2 for the unsymmetrical fulvenes.

An efficient protocol for the synthesis of *syn*-facially bridged norbornane frameworks has been developed via the tandem cyclization–cycloaddition reactions of the carbonyl ylide **21** derived from the diazo ketone **20** with norbornene derivatives. The reaction of the diazo ketone **20** with the dipolarophiles **30** and **32** in the presence of $Rh_2(OAc)_4$ furnished[35] the *syn*-facially bridged norbornane frameworks **31** and **33**, respectively, in high yield (Scheme 9). For the norbornene derivative **32** having multiple C=C bonds, the 1,3-dipolar cycloaddition was regioselective.



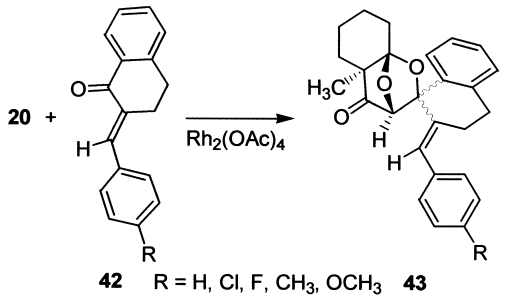
Scheme 11.

The reaction of the spirocyclic ylide **11** derived from the diazo ketone **10** with 1,2-dicarbonyl compounds like *N*-substituted isatins has been studied and exclusively affords the oxygenated spiro-oxindoles **41** through regioselective addition on the C_3 carbonyl group (Scheme 12).[38]



Scheme 12.

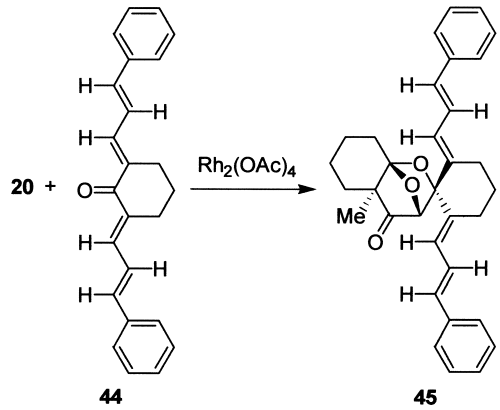
Carbonyl ylides engage α,β-unsaturated carbonyl compounds to furnish a mixture of cycloadducts through both C=C and C=O addition.[39] Examples have been reported where five membered ylides react with α,β-unsaturated carbonyl compounds regioselectively at the C=C bond.[40,41] Chemoselectivity towards C=O cycloaddition can also be achieved, however, in specifically crafted α,β-unsaturated ketones such as arylidenetetralones, bis(arylmethylidene)-ketones and bis(heteroarylmethylidene)ketones. The reaction of the bicyclic carbonyl ylide **21** generated from the α-diazo ketone **20** and arylidenetetralones **42** in the presence of $Rh_2(OAc)_4$, for example, led[42] to the spiro-dioxa ring systems **43** with high regio- and chemoselectivity (Scheme 13). The product **43** is obtained as a diastereomeric mixture (2:3) and no C=C bond addition product was observed.



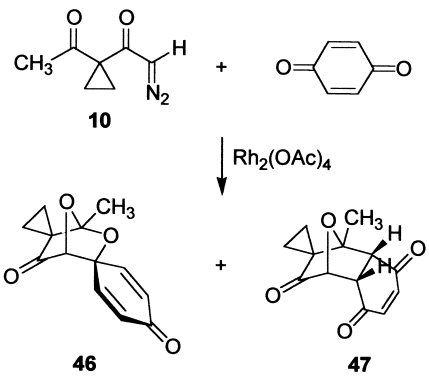
Scheme 13.

Another interesting example of C=O-selective carbonyl ylide cycloaddition is the rhodium(II)-mediated reaction of the α-diazo ketone **20** with the bis(phenylallylidene)cyclohexanone **44** to furnish the spiro-dioxa-bridged ring system **45** with complete regio- and chemoselectivity in good yield (Scheme 14).[43]

Carbonyl ylides engage *p*-quinones, in a manner reminiscent of their reaction with α,β-unsaturated carbonyl compounds. Pirrung has reported[44] the 1,3-dipolar cycloaddition of the five-membered ring carbonyl ylide **11** to *p*-quinones to provide ready access to complex oxa-functionalized networks in a single step through addition at both the C=O and C=C bonds, the reaction of the α-diazo carbonyl compound **10** with *p*-benzoquinone in the presence of $Rh_2(OAc)_4$ leading to a 1:1.7 mixture of the cycloadducts **46** and **47** in moderate yield (Scheme 15). Interestingly, the product ratios are solvent and catalyst-



Scheme 14.

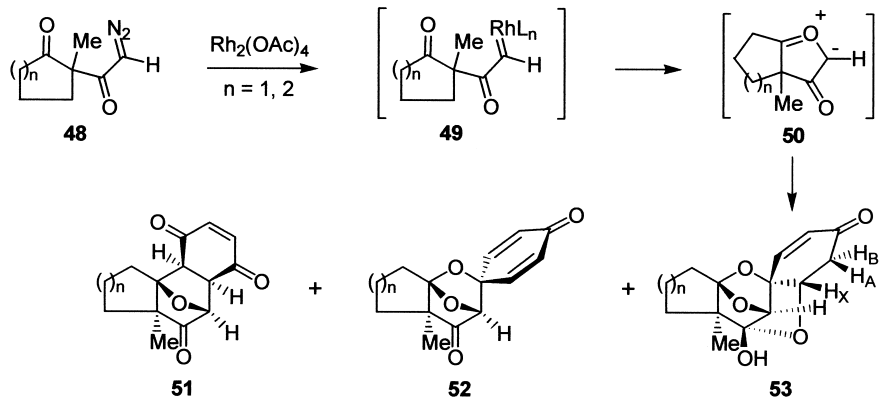


Scheme 15.

dependent and have been optimized to favor the formation of either product.

Muthusamy and co-workers have employed the bicyclic ylide **50** derived from the α-diazo carbonyl compounds **48** via the rhodium carbenoids **49** in the presence of $Rh_2(OAc)_4$ as the catalyst to furnish complex oxapolycyclic systems.[45] The reaction of **48** with *p*-benzoquinone led to the novel oxa-bridged polycyclic systems **51**–**53** through stereoselective C=C and C=O bond addition (Scheme 16). The formation of **53** through tandem intramolecular cyclization–intermolecular cycloaddition and further addition of water and intramolecular Michael addition is quite interesting as four C–O bonds and one C–C bond are formed in a single step.

The intermolecular five-membered ring carbonyl ylide trapping strategy has proved to be remarkably effective in the synthesis of biologically active sesquiterpenoids including illudins, ptaquilosin, pterosins and acylfulvenes. The formation of the illudin skeleton could be readily conceptualized through a cycloaddition between the cyclopropyl-substituted carbonyl ylide **11** and the cyclopentenone derivatives as dipolarophiles. As an application of the tandem cyclization–cycloaddition methodology, (±)-Illudin M (**56**), a toxic sesquiterpene isolated[46] from the jack-o′-lantern mushroom, has been synthesized[47] by Kinder and co-workers via the spirocyclic carbonyl ylide **11** generated from the cyclopropyl-substituted α-diazo ketone **10**. $Rh_2(OAc)_4$-mediated decomposition of the α-diazo ketone **11** in the presence of cyclopentenone **54** afforded the key

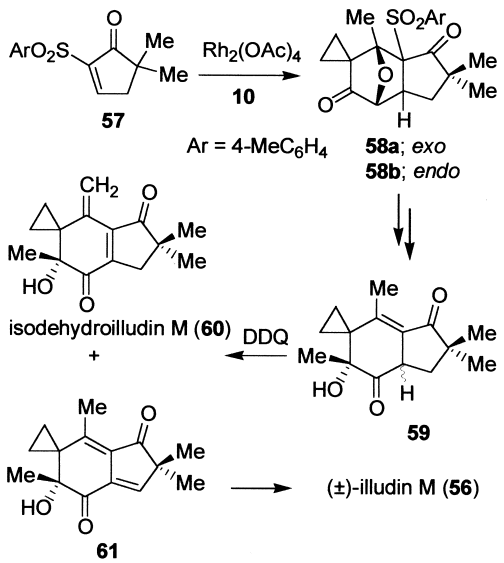


Scheme 16.

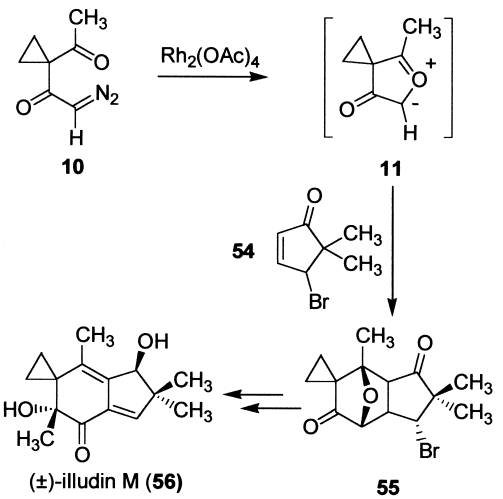
cycloadduct **55** as a single diastereomer, bearing the complete skeleton of the natural product (Scheme 17). Functional group manipulations in the adduct **55** led to a total synthesis of (±)-illudin M (**56**).

An alternative tandem cyclization–cycloaddition approach[40] to (±)-illudin M (**56**) and the closely related isodehydroilludin **60** was executed by Padwa and co-workers employing an arylsulphonyl-substituted cyclopentenone **57** as the dipolarophile. The reaction of the α-diazo ketone **10** with **57** in the presence of $Rh_2(OAc)_4$ as the catalyst afforded a mixture of the *exo* and *endo*-cycloadducts **58** in high yield (Scheme 18). The two diastereomers were elaborated to a common intermediate **59**. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone mediated (DDQ) dehydrogenation of **59** gave the natural product isodehydroilludin **60** and the compound **61**. As **61** has been previously converted to illudin M, a formal synthesis of this natural product was also accomplished.

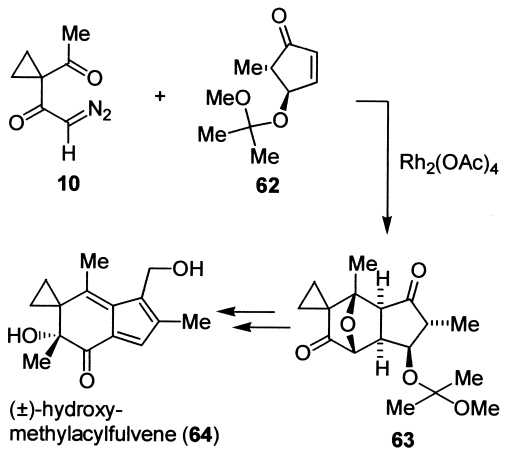
Acylfulvenes represent a new class of potent antitumor compounds derived from the toxic sesquiterpene, illudin S. A synthesis of (±)-hydroxymethylacylfulvene (**64**, HMAF) and related analogues has been accomplished by McMorris and co-workers[41] using tandem cyclization–cycloaddition methodology involving the cyclic five-membered ring carbonyl ylide **11**. The rhodium-mediated decomposition of the diazo ketone **10** in the presence of the acetal **62** led to the cycloadduct **63**. Further manipulation of the functional groups including opening the oxygen bridge afforded (±)-hydroxymethylacylfulvene **64** (Scheme 19). The same research group[48] has also accomplished the total synthesis of two more acylfulvene analogs having promising anti-cancer activity using an adaptation of their tandem carbonyl ylide methodology. The cycloadduct **65** was obtained



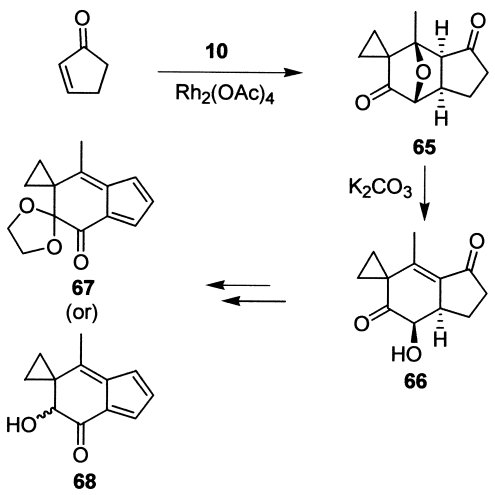
Scheme 18.



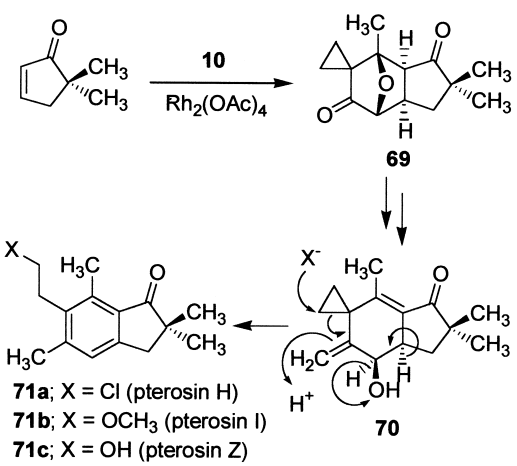
Scheme 17.



Scheme 19.



Scheme 20.



Scheme 21.

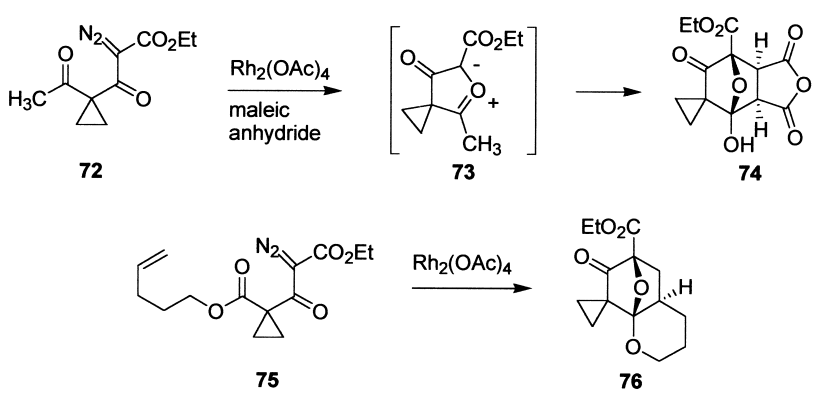
diastereoselectively from the decomposition of the diazo compound **10** and cyclopentenone in the presence of $Rh_2(OAc)_4$ as the catalyst. The selective cleavage of the epoxy-bridge under alkaline conditions afforded **66** (Scheme 20). The functional group maneuvers in **66** furnished the acylfulvene analogs **67** and **68** in good yield, these compounds exhibiting impressive anticancer activity.

The carbonyl ylide cyclization–cycloaddition approach described above has been further extended[49] towards a short synthesis of the pterosin family of sesquiterpenes bearing a hydrindane framework with a penta-substituted aromatic ring. The earlier classical approaches to the synthesis of pterosins relied on electrophilic substitution reactions for the construction of the penta-substituted aromatic ring, wherein the inherent problems of regio-selectivity[50] were a limiting factor. The key concept in the synthesis of pterosins H (**71a**), I (**71b**) and Z (**71c**) was the carbonyl ylide-based stereoselective 1,3-dipolar cyclo-addition reaction to rapidly deliver the functionalized hydrindane framework, followed by cyclopropane ring opening to install the ethyl side arm and concomitant aromatization. The rhodium(II)-catalyzed decomposition of the α-diazo ketone **10** in the presence of 5,5-dimethyl-2-cyclopenten-1-one afforded the cycloadduct **69** in good yield (Scheme 21). A series of transformations on **69** involving Wittig olefination and oxa-bridge opening provided **70** which, on acid-catalyzed cyclopropyl ring opening, afforded the three members of the pterosin sesquiterpenoids **71a–c**.

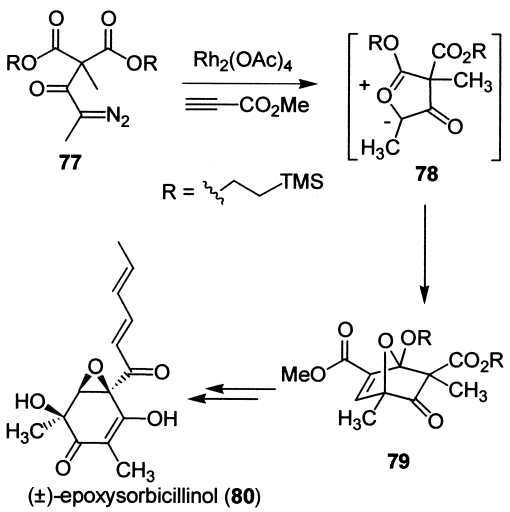
2.2. With ester carbonyl groups

Only a few examples of the formation of five-membered ring carbonyl ylides using ester carbonyl groups have been reported. The reaction of the diazo ester **72** under standard Rh(II)-catalyzed conditions results in the formation of the ylide **73** which undergoes smooth cycloaddition with a variety of dipolarophiles such as DMAD, maleic anhydride, *N*-phenylmaleimide and 1,1-diethoxyethylene to afford the corresponding cycloadducts.[51] The adduct **74** being readily formed from **72** with maleic anhydride (Scheme 22). An intramolecular variation (**75**→**76**) of the ester carbonyl-derived ylide has also been reported[51] (Scheme 22).

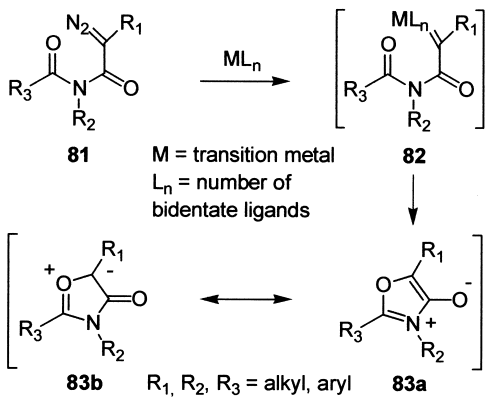
The utility of the ester-derived five-membered ring carbonyl ylide has been demonstrated in the first total synthesis of the biologically active natural product, (±)-epoxysorbicillinol **80**,[52] a novel vertinoid polyketide possessing an epoxide functionality. The rhodium(II)-catalyzed decomposition of the α-diazo ketone **77** in the presence of methyl propiolate furnished the diastereomerically pure oxabicycle **79** via the intermediate ylide **78** in excellent yield (Scheme 23). Following functional group manipulations, a synthesis of the natural product, (±)-epoxysorbicillinol **80**, was accomplished.



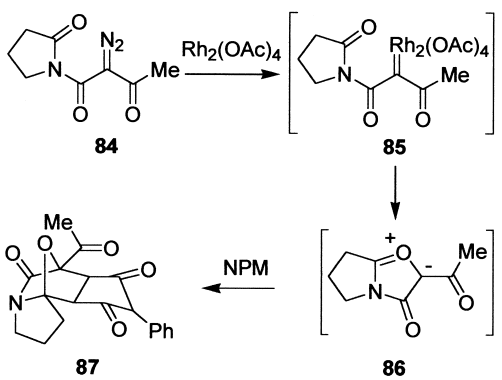
Scheme 22.



Scheme 23.



Scheme 24.



Scheme 25.

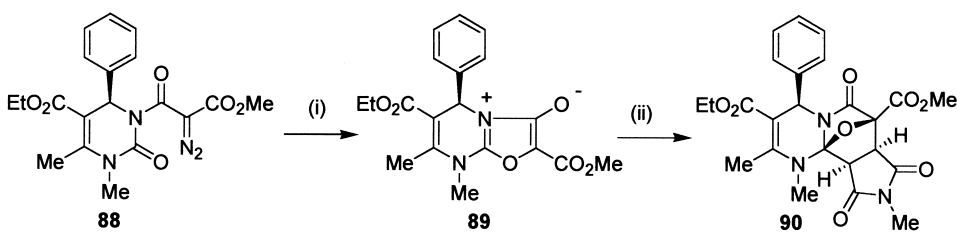
2.3. With amide carbonyl groups (isomünchnones)

The decomposition of suitably tailored diazoimides **81**, in the presence of a transition metal catalyst, affords the metallo-carbenoids **82** that undergo intramolecular cyclization onto the neighboring amide carbonyl oxygen to form the five-membered ring carbonyl ylides (isomünchnones) **83** (Scheme 24). Early examples of inter- and intramolecular 1,3-dipolar cycloaddition of the mesoionic ylides **83** have mainly emanated from the research groups of Ibata,[53] Maier[54] and Padwa.[55] These reactive species (isomünchnones) can be trapped by various electron-rich and electron-deficient dipolarophiles[56] to give the cycloadducts in high yield. Much work has been reported in this area and for the clarity of presentation is described here under various subheadings.

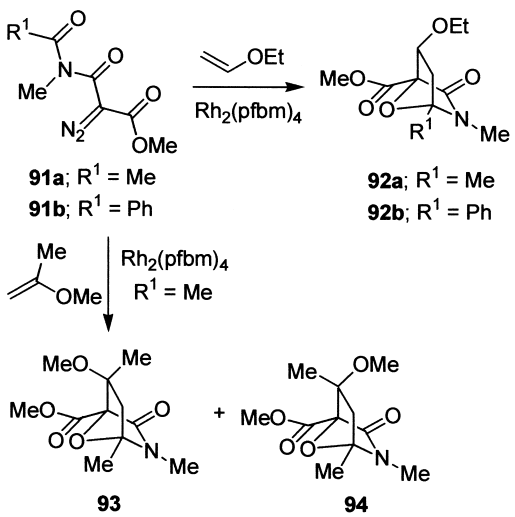
2.3.1. Intermolecular isomünchnone cycloadditions. Initial studies on the rhodium(II)-catalyzed reactions of cyclic diazoimides were investigated in the presence of *N*-phenylmaleimide as a dipolarophile, to find out whether the initial rhodium-carbenoid prefers to form an isomünchnone or to undergo a competitive C–H insertion reaction.[57] Indeed, the diazoimide **84** initially formed the rhodium carbenoid **85**, which cyclized onto the adjacent imide carbonyl group to generate the isomünchnone **86**, which subsequently underwent intermolecular 1,3-dipolar cycloaddition with NPM to furnish **87**, without forming any C–H insertion product (Scheme 25). The regioselective cycloaddition reactions of isomünchnones with unsymmetrical dipolarophiles such as methyl vinyl ketone and diethyl ketene acetal have also been reported.[55a]

Kappe and co-workers have studied the cycloaddition reactions of dihydropyrimidine-fused mesomeric betaines,[58] the reaction of the diazoimide **88** with $Rh_2(OAc)_4$ in the presence of NPM furnishing the cycloadduct **90** in high yield (Scheme 26). Surprisingly, the isomünchnone **89** precipitated from the reaction as a colorless solid when the same reaction was carried out in the absence of a dipolarophile. This carbonyl ylide dipole **89** proved to be remarkably stable and could even be recrystallized from methanol. The reactions of **88** proceed with a high degree of regioselectivity, facial selectivity and *exo*/*endo* diastereoselectivity.

The diastereoselective cycloaddition of a variety of vinyl ethers with isomünchnones has been investigated by Austin and co-workers to explore the reactivity of various unsymmetrical, monoactivated alkenes.[59] The reaction of the α-diazoimides **91a**,**b** with ethyl vinyl ether in the presence of rhodium(II) perfluorobutyramidate



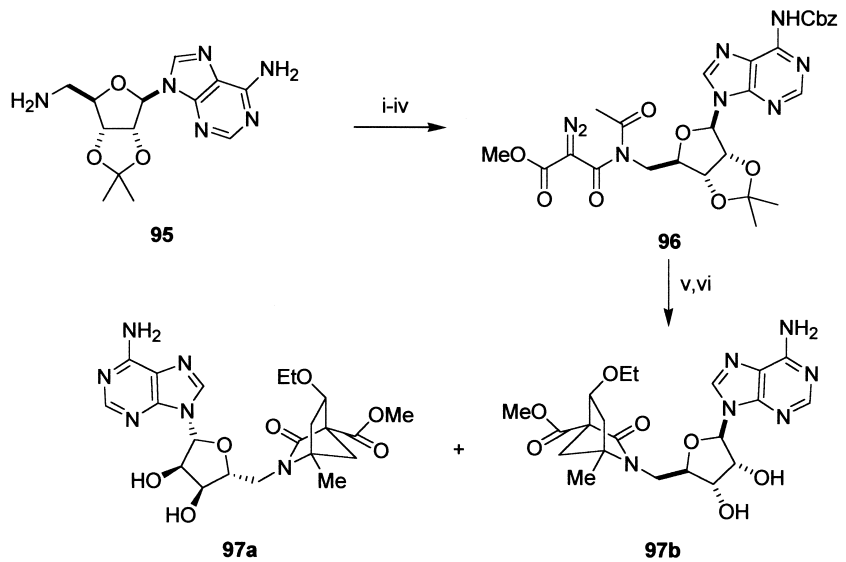
Scheme 26. (i) $Rh_2(OAc)_4$; (ii) *N*-phenylmaleimide.



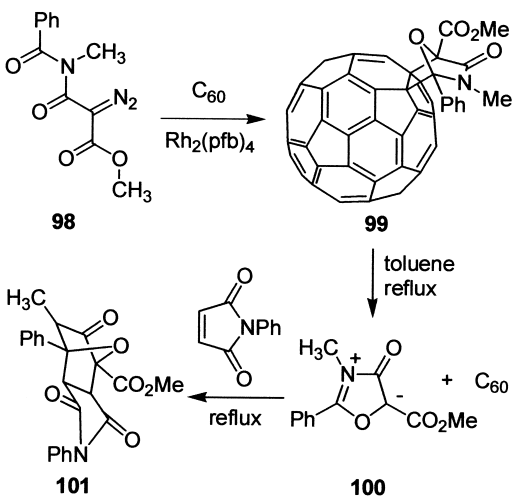
Scheme 27.

[Rh_2(pfbm)$_4$] as the catalyst afforded the cycloadducts **92a**,**b** as single diastereomers (Scheme 27). This reaction was generalized by carrying out the cycloaddition with other enol ethers.[59] Further, the reaction of the diazoimide **91a** with 2-methoxypropene, an *ipso*-substituted vinyl ether, was studied to evaluate whether the above-observed stereoselectivity was steric or electronic in nature. The observation of a 1:3 *exo*/*endo* ratio of the diastereomers **93** and **94** from the reaction at a relatively high temperature (130°C) and a prolonged exposure (8 h) indicated a dramatic decrease in the reaction rate and indicated the existence of a large HOMO–LUMO gap that supported a steric contribution to the diastereoselectivity (Scheme 27).

As isomünchnone-based strategy has also been deployed by the same research group to gain access to a new class of 5-functionalized adenosines. Elaboration of the 5′-aminoadenosine **95** employing amine protection, amide formation with methyl malonyl chloride and the usual diazotransfer reaction led to the α-diazoimide **96**. The Rh_2(pfbm)$_4$-



Scheme 28. (i) $(CH_3CO)_2O$, pyridine; (ii) Rapoport's reagent; (iii) methyl malonyl chloride; (iv) MsN_3, Et_3N; (v) ethyl vinyl ether, Rh_2(pfbm)$_4$; (vi) TFA/H_2O 10:1; Pd/C, EtOH, NH_4CO_2H.

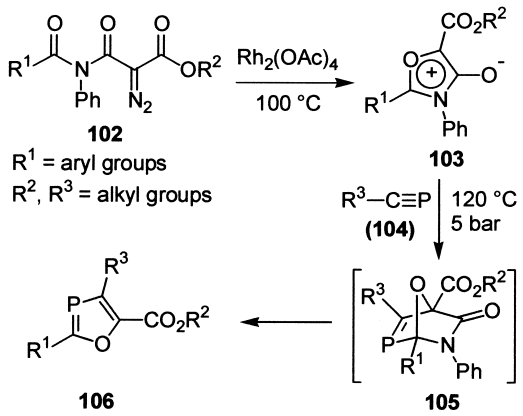


Scheme 29.

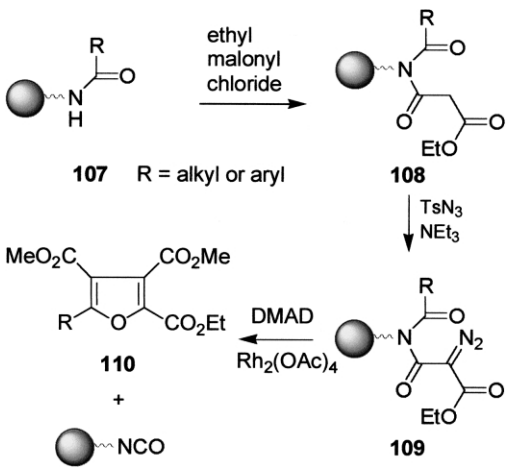
catalyzed reaction of the diazoimide **96** in the presence of ethyl vinyl ether yielded the *endo*-selective cycloadducts **97a** and **b** as a 1:1 mixture of diastereomers with the facial bias imposed by the chiral ribose moiety present in adenosine (Scheme 28).[60]

The 1,3-dipolar cycloaddition reactions of isomünchnone dipoles with buckministerfullerene C_{60} have been studied to furnish [3+2]-cycloadducts which, on thermolysis, regenerate the mesoionic heterocycle in an excellent yield. The reaction of, the diazoimide **98** with C_{60} in the presence of a rhodium(II) perfluorobutyrate [Rh_2(pfb)$_4$] catalyst afforded the cycloadduct **99** in moderate yield (Scheme 29).[61] Further thermal activation of the cycloadduct **99** regenerated the isomünchnone **100**, which could be trapped with *N*-phenylmaleimide to give the adduct **101** in high yield (Scheme 29).

The reaction of isomünchnones with phosphaalkynes has been reported as a novel route to 1,3-oxaphospholes.[62] The



Scheme 30.



Scheme 31.

isomünchnones **103** can be isolated in moderate yields when the diazo carbonyl compounds **102** are exposed to $Rh_2(OAc)_4$ as the catalyst. When the isomünchnones **103** are treated with the phosphaalkynes **104** in a pressure-Schlenk tube under 5 bar pressure, the 1,3-oxaphospholes **106** are obtained regiospecifically in very good yields (Scheme 30). The bicyclic intermediates **105** are presumably formed in the first step of this 1,3-dipolar cycloaddition process and apparently decompose immediately in a retro-Diels–Alder reaction to furnish the 1,3-oxaphospholes **106**. On consideration of the charge distribution in the isomünchnone system and the polarity of the P≡C triple bond, the regiochemistry of this 1,3-dipolar cycloaddition is rather surprising and it is clear that this 1,3-dipolar cycloaddition does not proceed under charge control.

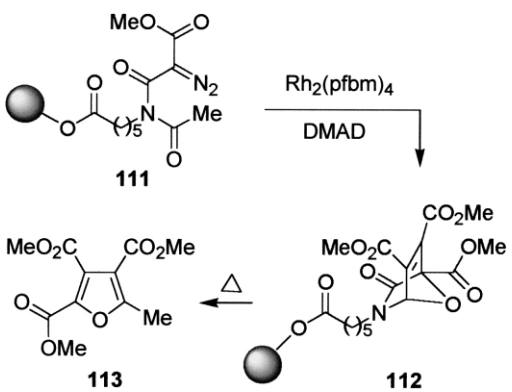
The synthesis of various functionalized furans has been described previously by the cycloaddition of isomünchnones to acetylenic dipolarophiles.[63] The intermolecular 1,3-dipolar cycloaddition of isomünchnones with alkynes is typically followed by extrusion of an alkyl or aryl isocyanate (RN=C=O) moiety to give the substituted furans. In view of the interest in generating furan-based combinatorial libraries, a 'traceless' solid phase version of this reaction has been developed.[64] Towards this end, the amides **107** were obtained by the acylation of TentaGel™-NH_2 resin and treated with ethyl malonyl chloride to obtain the imides **108**. Diazo transfer in **108** led to the diazoimides **109**, which were decomposed with $Rh_2(OAc)_4$ as the catalyst in the presence of DMAD (Scheme 31). Under these reaction conditions, the transient cycloadducts underwent cycloreversion to eject the isocyanate-bound resin. The reactions with other substituted acetylenes afforded a series of substituted furans **110**.

Another variation of the solid phase furan synthesis has surfaced simultaneously.[65] The Wang resin-protected diazo ester **111** on decomposition with $Rh_2(pfbm)_4$ in the presence of DMAD afforded the cycloadduct **112** (Scheme 32) and thermally-induced cycloreversion in **112** provided the furan **113** in >98% purity. This reaction of acetylenes with isomünchnones was presented as a general methodology for the combinatorial formation of a furan-based library.

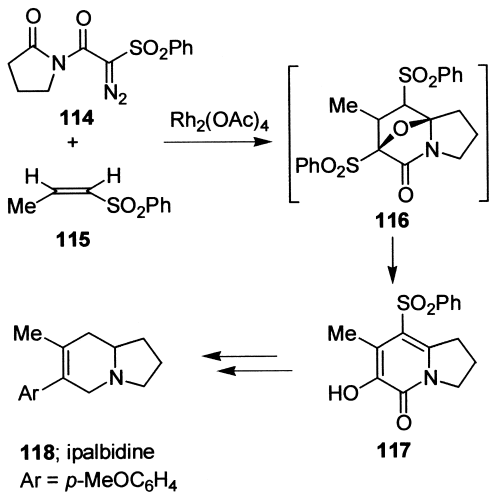
An example of ligand-dependent site selectivity in the Rh(II)-catalyzed decomposition of a glycine-derived diazoacetamide has been reported by Padwa.[66] The results indicate that the reactivity of the transient rhodium carbenoid derived from the α-diazoimide is dependent on the electronic nature of the catalyst with the fluorinated ligands exhibiting a distinct preference for isomünchnone formation. Studies on π-facial diastereoselection in [3+2]-cycloadditions of several isomünchnone dipoles derived from substituted cyclic amides have also been carried out to define the stereochemical issues.[67] High levels of diastereoselectivities were encountered in these cycloadditions, leading to the *exo* products.

As an application of the intermolecular cycloaddition reaction of isomünchnone, a new synthetic route to 2-pyridones was successfully developed and extended to the synthesis[68] of the indolizidine alkaloid, (±)-ipalbidine **118**. The decomposition of the diazoimide **114** was effected using $Rh_2(OAc)_4$ as the atalyst in the presence of *cis*-1-(phenylsulfonyl)-1-propene **115** to afford the cycloadduct **116**. The cycloadduct **116** was not stable and readily underwent ring opening to 3-hydroxy-2(1*H*)-pyridone **117** (Scheme 33). Further elaboration of **117** involving Stille coupling with tributyl(4-methoxyphenyl)tin as the key step led to (±)-ipalbidine **118**.

2.3.1.1. Applications in asymmetric synthesis. Asymmetric versions of the intermolecular cycloaddition of isomünchnones, further enhancing the synthetic appeal of this cycloaddition protocol, have been developed. Austin and co-workers have reported[69a] the optimization of a chiral



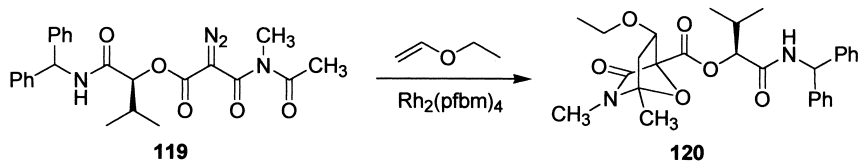
Scheme 32.



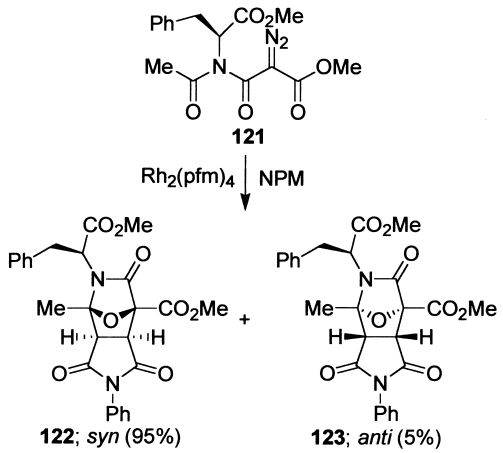
Scheme 33.

auxiliary for the diastereofacially selective 1,3-dipolar cycloaddition of isomünchnones in the presence of a variety of vinyl ethers. The diastereomeric excess (de) obtained with the optimized auxiliary exceeds 95% and the auxiliary is efficiently removed from the cycloadducts through an unusually facile ester aminolysis. Treatment of the α-diazoimide **119** with $Rh_2(pfbm)_4$ as the catalyst in the presence of ethyl vinyl ether, for example, led to the formation of the cycloadduct **120** (95% de) (Scheme 34). The same group has demonstrated the above methodology for solid phase synthesis using a benzhydrylamine (BHA) resin and a novel and chemoselective resin cleavage process has been described.[69b]

Stereocontrolled [3+2]-cycloadditions using various amino acid-derived chiral isomünchnone dipoles provide access to the enantiopure cycloadducts.[70] Decomposition of the amino acid-derived diazoimide **121** with rhodium(II) perfluorobutyroamidate [$Rh_2(pfm)_4$] in the presence of



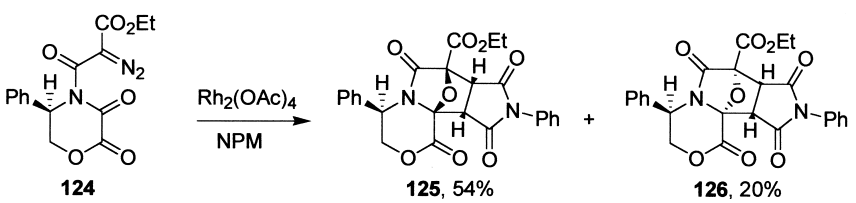
Scheme 34.



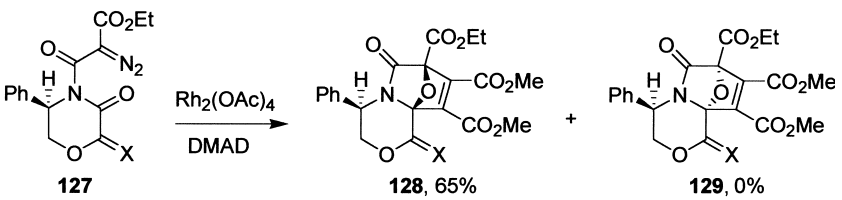
Scheme 35.

NPM resulted in the formation of the cycloadducts **122** and **123** with nearly complete *exo*/*endo* selectivity and high π-facial selectivity (Scheme 35).

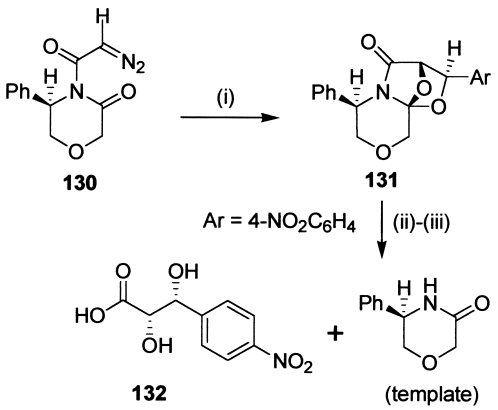
Harwood and co-workers have devised novel chiral templates for isomünchnone cycloadditions,[71] the chiral diazoimide **124** reacting with NPM in the presence of rhodium(II) acetate to furnish the isomünchnone-derived *endo*-adduct **125** (32%) and *exo*-adduct **126** (18%) (Scheme 36). Whereas the formation of the major *endo*-cycloadduct can be explained because of electronic factors, the minor *exo*-cycloadduct is a consequence of the steric hindrance of the C-5 phenyl substituent. The comparatively less flattened diazoimide **127** has also been prepared and subjected to rhodium(II)-catalyzed cycloaddition to DMAD to furnish *endo*-**128** (65%) with high diastereoselectivity and without any observation of *exo*-**129** (Scheme 37).[72]



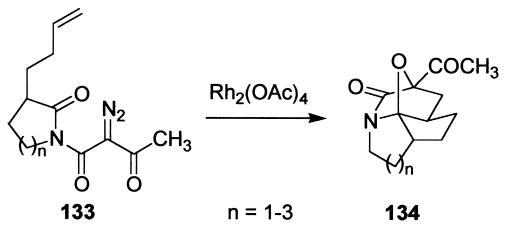
Scheme 36.



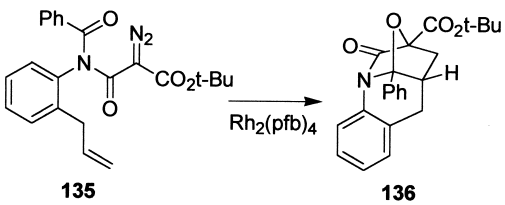
Scheme 37.



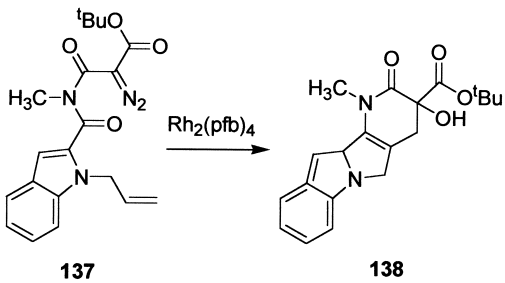
Scheme 38. (i) *p*-Nitrobenzaldehyde, $Rh_2(OAc)_4$ or $Rh_2(tfa)_4$; (ii) H^+, H_2O/THF; (iii) $LiOH/H_2O_2$/THF/H_2O.



Scheme 39.



Scheme 40.



Scheme 41.

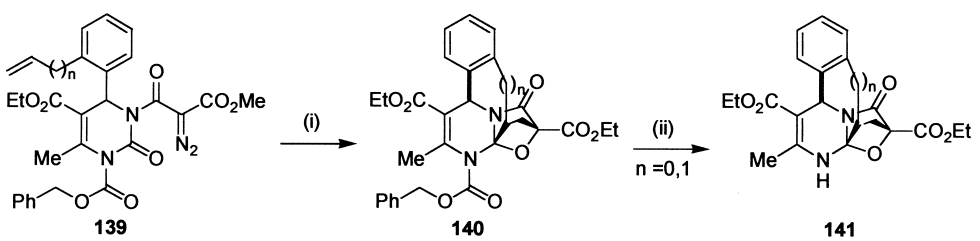
Harwood's group has extended the use of the chiral α-diazoimide **130** to devise a synthesis of enantiopure α,β-dihydroxyacids.[73] Decomposition of the chiral diazoimide **130** in the presence of an achiral aldehyde like *p*-nitrobenzaldehyde employing rhodium(II) acetate or trifluoroacetate as the catalyst afforded the cycloadduct **131** (Scheme 38). These cycloadditions between various chiral diazoimide-derived isomünchnones and aldehydes proceed with high diastereofacial and *exo* selectivity. The observed regioselectivity is in accordance with the literature precedents.[39,74] Access to α,β-dihydroxy acids such as **132** from the cycloadduct **131** was straightforward through the hydrolytic removal of the template (Scheme 38).

2.3.2. Intramolecular isomünchnone cycloadditions. The intramolecular variant of the 1,3-dipolar cycloaddition reaction of the rhodium-generated isomünchnone constitutes a promising route[54] to many complex polycyclic structures as exemplified by the one-step formation of **133** from the diazoimides **134** in a stereoselective manner (Scheme 39).[55]

A related diazoimide system **135** having an alkene tethered to the benzene backbone was exposed to $Rh_2(pfb)_4$ as the catalyst to furnish the diastereospecifically polyheterocyclic system **136** in excellent yield (Scheme 40).[75] The cycloaddition occurs *exo* with respect to the carbonyl ylide dipole and is in full agreement with the lowest energy transition state in both cases.

An intramolecular isomünchnone cycloaddition reaction of the acyclic diazoimide **137** incorporating an indole nucleus has been investigated. Decomposition of the diazoimide **137** in the presence of $Rh_2(pfb)_4$ as the catalyst led exclusively to **138** (Scheme 41).[76] Interestingly, the initially-formed cycloadduct readily underwent a ring-opening reaction followed by proton elimination to generate the enamide **138**.

Kappe and co-workers have extended their intermolecular isomünchnone cycloaddition reaction (see Scheme 26) to an intramolecular version to obtain the conformationally rigid polyheterocycles **141**, which mimic the putative receptor-bound conformation of dihydropyrimidine-type calcium channel modulators.[77] The key step in the synthesis involves the regio- and diastereoselective intramolecular 1,3-dipolar cycloaddition reaction of a dihydropyrimidine-fused isomünchnone dipole. The diazoimides **139** were readily prepared by *N*-malonyl acylation of the corresponding pyrimidones, followed by a standard diazotransfer and CBZ protection reactions. Decomposition of the CBZ-protected diazoimides **139** with a catalytic amount of $Rh_2(OAc)_4$ furnished the pentacyclic dihydropyrimidine systems **140** without the isolation of the initially-generated transient



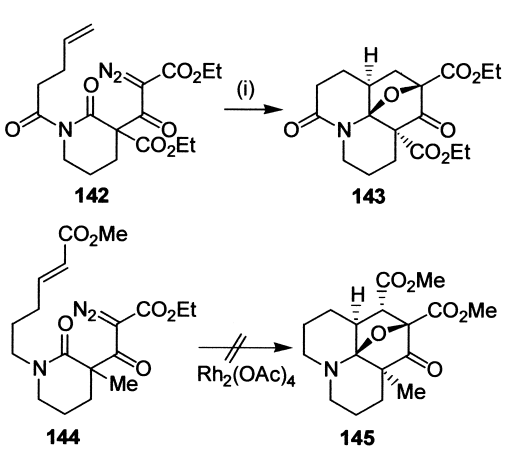
Scheme 42. (i) $Rh_2(OAc)_4$; (ii) H_2, 10% Pd/C, rt, 1 atm.

isomünchnone dipoles (Scheme 42).[78] The removal of the CBZ group by the catalytic hydrogenation method provided the desired conformationally rigid dihydropyrimidine **141** in high yield.

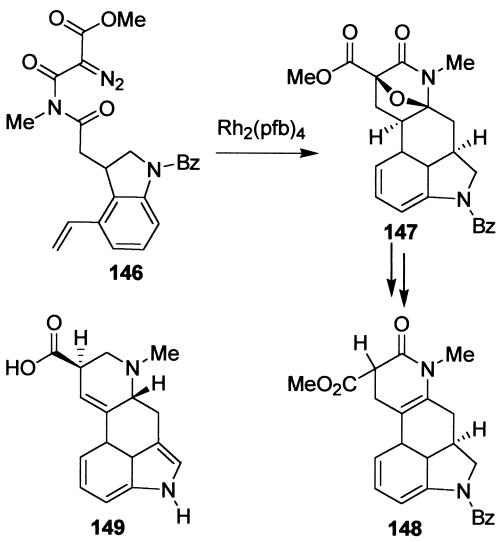
The rhodium-catalyzed formation of carbonyl ylide intermediates from cyclic diazoamides provides tetracycles depending upon the substitution present in the tether. The diazoimide **142** with $Rh_2(OAc)_4$ gave the tetracyclic adduct **143** with complete diastereoselectivity (Scheme 43). But a similar substrate **144** having no carbonyl substituent present on the tether failed to undergo intramolecular cycloaddition to provide the corresponding adduct **145**. It was found,[79] however, that **144** did undergo intermolecular cycloaddition with DMAD to the expected dipolar cycloadduct. The factors that influence the intramolecular cycloaddition and the substituent effect have been probed using ab initio transition state geometry optimizations. The calculations signify that a rigorous cross-ring 1,3-diaxial interaction caused by the bridgehead methyl group in **144** promotes a boat or twist-boat conformation in the piperidine ring fused to the newly-forming ring. Interestingly, the presence of a carbonyl group in the dipolarophile tether assists in the relief of steric hindrance.[79]

A number of approaches to complex alkaloids have been reported in which the intramolecular cycloaddition reactions of a transient isomünchnone dipole feature as the pivotal step for assembling the polycyclic frameworks. Intramolecular reactions of isomünchnone dipoles generated from a series of alkenyl and alkynyl-substituted diazoimides have been exploited to develop an approach to the quinoline ring system (rings C and D) of the ergot alkaloids (e.g. lysergic acid, **149**). In one example, the $Rh_2(pfb)_4$-mediated tandem cyclization–cycloaddition sequence from the diazoimide **146** led to the cycloadduct **147** in very good yield (Scheme 44).[80] The polycyclic adduct **147** was readily elaborated to **148** en route to ergot alkaloids via $BF_3{\cdot}OEt_2$-mediated ether bridge cleavage and a Barton-McCombie deoxygenation sequence (Scheme 44). Further attempts towards lysergic acid (**149**) were, however, thwarted due to the inability to isomerize the tetrasubstituted double bond in **148**.

A formal synthesis of (±)-vallesamidine (**153**) has been achieved[81] based on an intramolecular dipolar cycloaddition



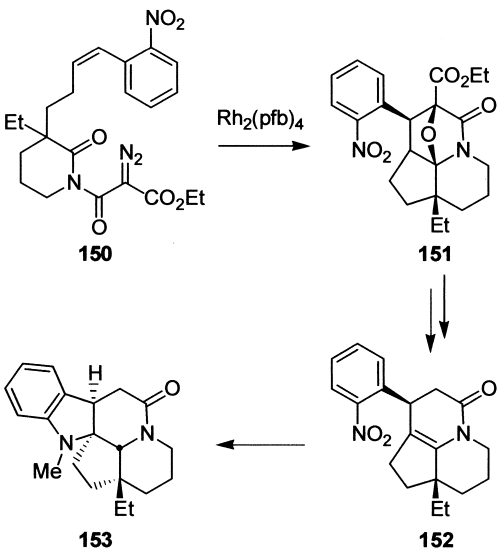
Scheme 43. (i) $Rh_2(OAc)_4$.



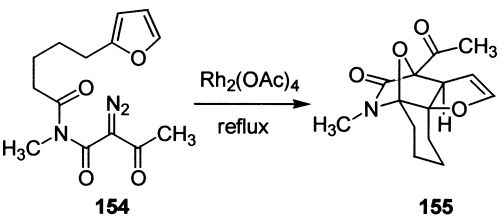
Scheme 44.

reaction of isomünchnone. Following a study of a range of model subtrates, the reaction of the cyclic diazoimide **150** with $Rh_2(pfb)_4$ was carried out to obtain the desired cycloadduct **151** as a single diastereomer (Scheme 45). A series of functional group maneuvers on **151** afforded the enamide **152**, which can be readily elaborated to (±)-vallesamidine (**153**) using a known methodology.[82]

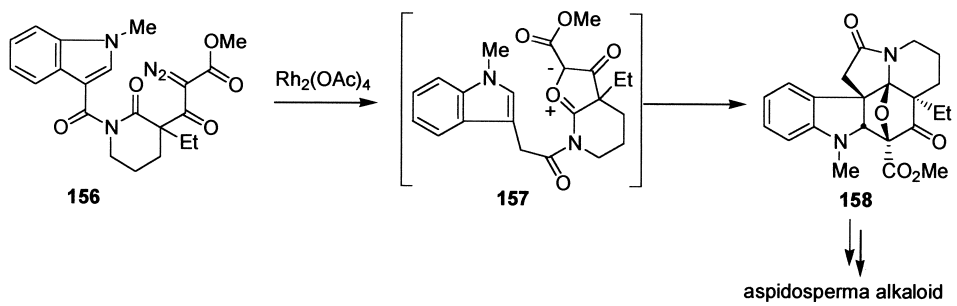
Isomünchnones are known to undergo intramolecular dipolar cycloaddition reactions with tethered heteroaromatic rings,[55b] the diazoimide **154** having a furan ring



Scheme 45.



Scheme 46.



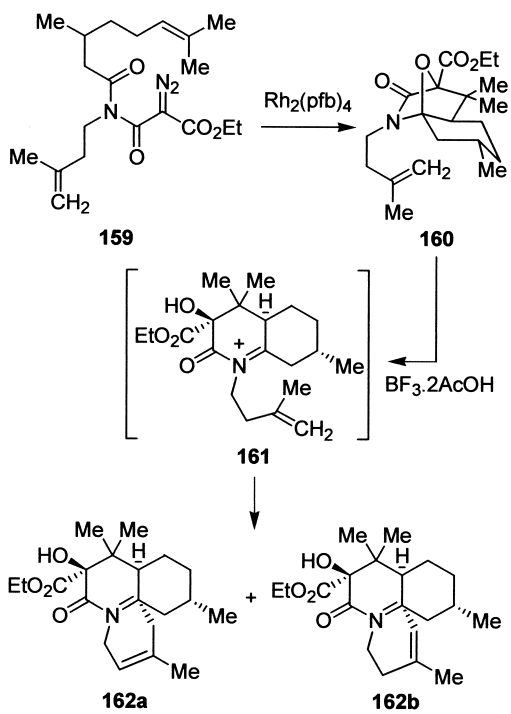
Scheme 47.

in its tether undergoing a smooth intramolecular dipolar cycloaddition to produce the cycloadduct **155** in high yield (Scheme 46).[83]

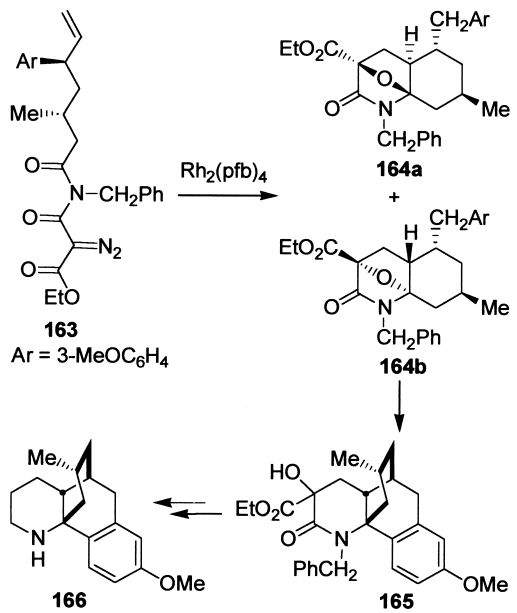
As an extension of the above methodology, the intramolecular cycloaddition of isomünchnone dipoles across an indole double bond has been investigated.[55b] This reaction has been shown to provide a facile entry into the pentacyclic skeleton of the aspidosperma alkaloids.[84] Towards this end, the α-diazoimide **156** was synthesized and subjected to $Rh_2(OAc)_4$ catalysis to obtain the cycloadduct **158** as a single diastereomer (Scheme 47). The *endo* cycloaddition of indole to the dipole **157** occurs exclusively from the side of the ethyl group away from the more sterically encumbered piperidone ring. The tandem cyclization–cycloaddition sequence is attractive as four stereocenters are formed in a single step with a high degree of stereocontrol and further functional group manipulations in the cycloadduct **158** afforded the pentacyclic skeleton of the aspidosperma ring system.

The potential use of the tandem carbenoid cyclization–cycloaddition–Mannich cyclization reaction of diazoimides for the construction of polyheterocyclic ring systems has been demonstrated.[85a] The construction of a more complex nitrogen heterocyclic system, particularly the B-ring homologues of the erythrinane family of alkaloids, can be easily achieved by incorporating an internal nucleophile on the tether. An interesting example of the sequential cycloaddition–π-cyclization process is shown with the diazoimide **159**, obtained from citronellic acid. The reaction of the diazoimide **159** with $Rh_2(pfb)_4$ generated the isomünchnone dipole, which underwent an intramolecular cycloaddition with the tethered alkene to give the cycloadduct **160** in good yield (Scheme 48).[85b] Successive treatment of the cycloadduct **160** with $BF_3{\cdot}2AcOH$ furnished a 4:1 mixture of the tetracyclic lactams **162a**,**b** via the formation of the *N*-acyliminium ion **161**.

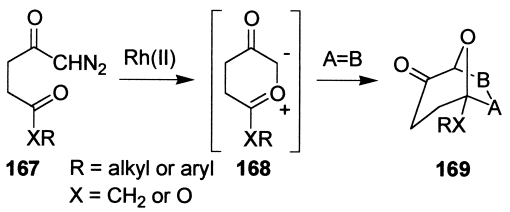
The tandem cycloaddition–cationic π-cyclization protocol has been extended to the formal synthesis of the alkaloid, (±)-lycopodine.[86] Following a study of various model substrates, the reaction of the α-diazoimide **163** with $Rh_2(pfb)_4$ provided the cycloadducts **164a** and **b** as a 3:2 mixture of the *endo*-diastereomers (Scheme 49). The cyclization of both **164a** and **b** using $BF_3{\cdot}2AcOH$ occurs regiospecifically to give **165**, tetracyclic product derived from *para* attack of the anisyl ring. The tetracyclic product **165** has been further evolved to **166**, an advanced intermediate in the synthesis of lycopodine.



Scheme 48.



Scheme 49.



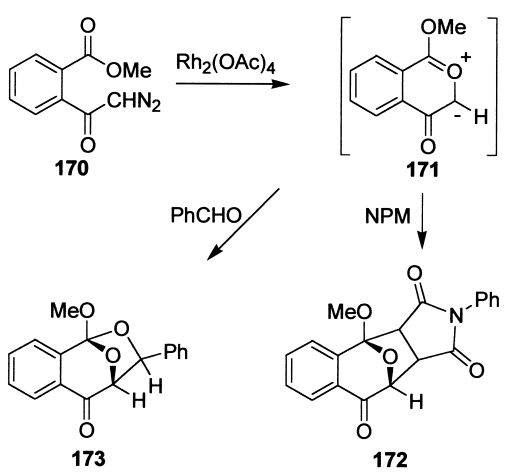
Scheme 50.

3. Intramolecular six-membered ring carbonyl ylides

When a substrate with a diazo functionality at the δ-position to the carbonyl group, e.g. **167**, is reacted with an appropriate transition metal catalyst, an intramolecular six-membered ring carbonyl ylide **168** is formed as a transient species through transannular cyclization onto the neighboring carbonyl oxygen. These transient species **168** readily engage a variety of dipolarophiles in inter- or intramolecular [3+2]-cycloadditions to furnish adducts like **169** (Scheme 50). In general, the six-membered ring carbonyl ylide intermediates **168** in the presence of a transition metal catalyst are generated from a variety of carbonyl-bearing precursors such as ketones, esters and amides. The reactions of ylides derived from each of these carbonyl precursors are discussed below.

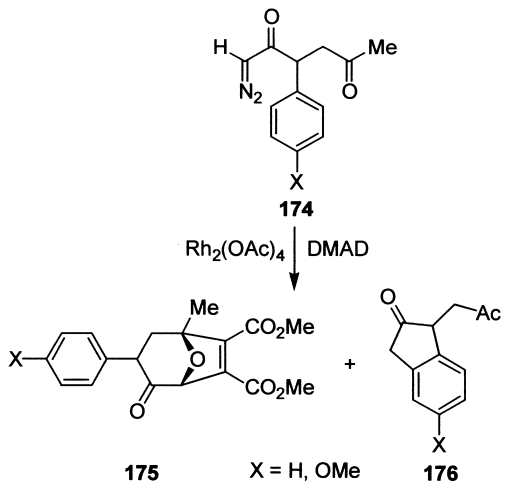
3.1. With keto carbonyl groups

Initially, Ibata and co-workers demonstrated[27] the utility of the ylides derived from the transition metal-catalyzed decomposition of *o*-(alkoxycarbonyl)diazoacetophenones through cycloaddition to various dipolarophiles. Treatment of the diazoacetophenone **170** with $Rh_2(OAc)_4$, for example, generated the carbonyl ylide **171**, which was readily trapped by NPM and benzaldehyde to deliver the cycloadducts **172** and **173**, respectively (Scheme 51). Later, this ability of carbonyl ylides to engage aldehydic π-bonds has been exploited for the total synthesis of brevicomin.[39]



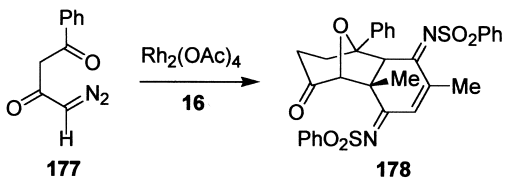
Scheme 51.

A series of diazo carbonyl compounds have been prepared to investigate the chemoselectivity of rhodium carbenoids towards the competitive reactions such as intramolecular aromatic substitution and carbonyl ylide formation,[87] the decomposition of **174** using $Rh_2(OAc)_4$ as the catalyst in the presence of DMAD giving a mixture of the oxabicyclo-octanone **175** (60%) and the 2-indanone **176** (20%) (Scheme 52). Electron-deficient ligands, such as $Rh_2(pfb)_4$, facilitate aromatic C–H insertion whereas donor ligands like rhodium(II) caprolactam [$Rh_2(cap)_4$] preferentially give carbonyl ylide dipoles.



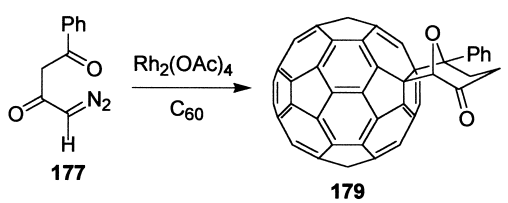
Scheme 52.

In a reactivity profile similar to that of the five-membered carbonyl ylides (see Section 2.1), Nair and co-workers have observed the reaction of the six-membered ring carbonyl ylide generated from the diazo ketone **177** with *p*-quinone-imides such as **16** to afford[31] the bicyclic compound **178** in good yields (Scheme 53).



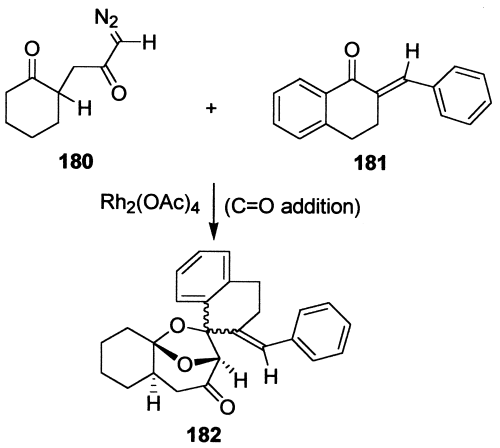
Scheme 53.

Novel C_{60} derivatives of the type **179** have been synthesized through 1,3-dipolar cycloaddition reactions of six-membered carbonyl ylides with [60]-fullerene.[88a] The Rh(II)-catalyzed transformation of the diazo ketone **177** in the presence of C_{60} afforded the cycloadduct **179** (Scheme 54). The reaction has been further generalized.[88b]

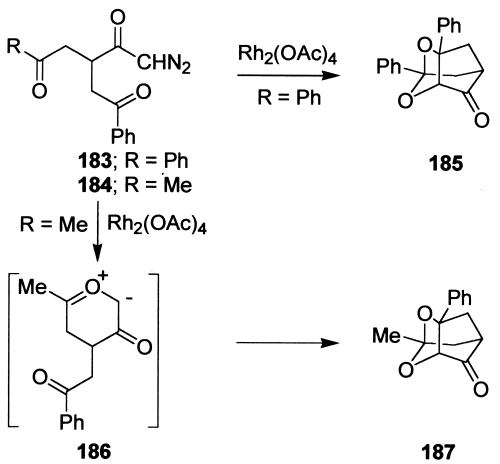


Scheme 54.

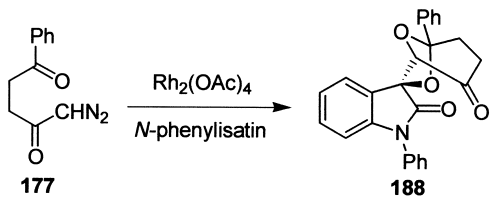
Chemoselective 1,3-dipolar cycloadditions of fused six-membered ring carbonyl ylides with α,β-unsaturated carbonyl compounds have been reported.[42] Treatment of the α-diazo ketone **180** with the arylidenetetralone **181** in the presence of $Rh_2(OAc)_4$ led to the spiro-dioxa ring system **182** through exclusive C=O addition in a manner



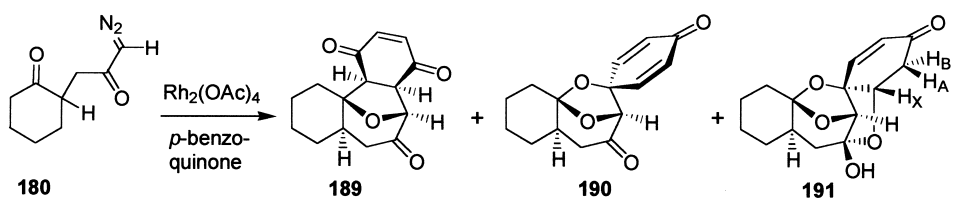
Scheme 55.



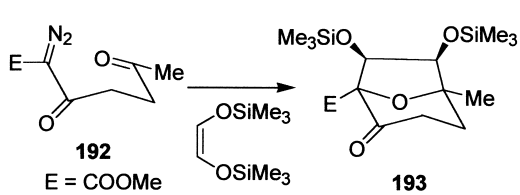
Scheme 56.



Scheme 57.



Scheme 58.



Scheme 59.

analogous to the five-membered ring carbonyl ylides (see Section 2.1) (Scheme 55).

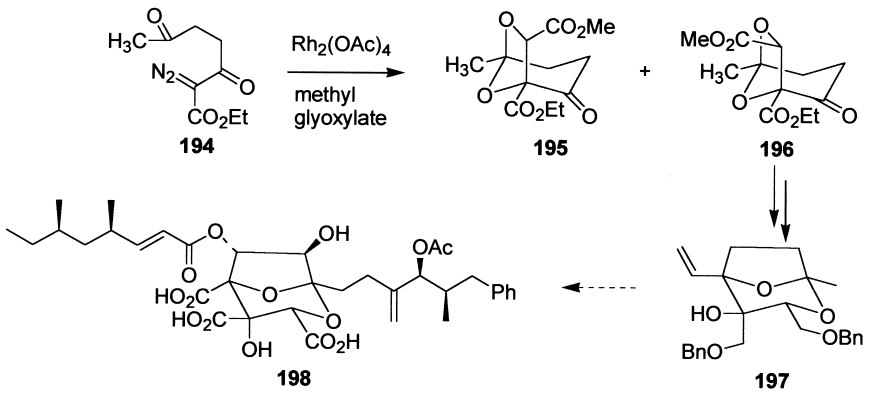
The effect of two different carbonyl groups in the same molecule on ylide formation and subsequent 1,3-dipolar cycloaddition has been probed,[89] the Rh(II)-catalyzed decomposition of the symmetrical dibenzoyl system **183** giving the cycloadduct **185** (Scheme 56). The regiochemical outcome of the reaction is understandable on the basis of electronic and conformational factors. The decomposition of the unsymmetrical α-diazo ketone **184** afforded the cycloadduct **187** exclusively via cycloaddition of the six-membered carbonyl ylide **186** across the benzoyl carbonyl π-bond (Scheme 56). The preference of the acetyl group in **184** to form the carbonyl ylide may be due to its enhanced nucleophilicity relative to the benzoyl group.

Symmetrical and unsymmetrical 1,2-diones exhibit diverse cycloaddition modes in reactions with carbonyl ylides to yield novel and highly oxygenated spiro compounds.[90] Typically, the six-membered ylide generated from the known diazo ketone **177** on reaction with N-phenylisatin afforded the spiro-oxindole derivative **188** (Scheme 57).[38] As anticipated, the ylide reacted exclusively with the more electrophilic carbonyl in the isatin and only the *endo*-adducts were formed in all cases. Similarly, the diazo ketone **177** furnished cycloadducts with substituted 1,2-benzoquinones[91] and acenaphthenequinone.[90,91b]

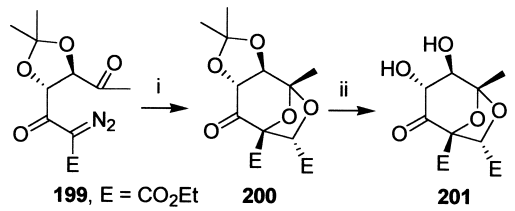
Rhodium-generated bicyclic six-membered ring carbonyl ylides from the diazo ketone **180** with *p*-quinones have been studied to yield interesting oxapolycyclic compounds. In line with the five-membered ring carbonyl ylide reactions (see Section 2.1), the α-diazo carbonyl compound **180** furnished the corresponding carbonyl ylide dipoles, which undergo a facile 1,3-dipolar cycloaddition with *p*-benzoquinone at C=C and C=O sites to furnish the oxa-bridged polycyclic systems **189**–**191** (Scheme 58).[45]

The rhodium(II)-induced tandem cyclization–cycloaddition process involving six-membered ring carbonyl ylides has been exploited for the synthesis of diverse natural products. One of the early applications of six-membered ring carbonyl ylides in natural product synthesis emanated from the groups of Dauben[92] and of McMills[93] and was targeted towards the ring system of tigliane diterpenoids. Wender and co-workers have exploited the intramolecular carbonyl ylide cycloaddition strategy to access the phorbol skeleton.[94]

A carbonyl ylide-based approach towards zaragozic acid A **198** (also known as squalestatins), a potent inhibitor of squalene synthase, has been reported.[74] The rhodium

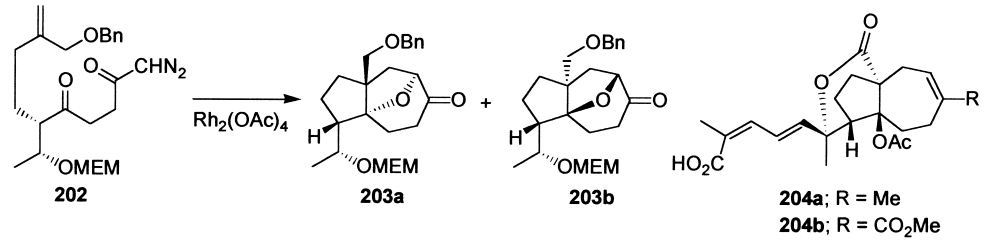


Scheme 60.



Scheme 61. (i) Methyl glyoxylate, $Rh_2(OAc)_4$; (ii) $CDCl_3$, 25°C.

Intramolecular cyclization–cycloaddition cascade reactions of rhodium carbenoids have been deployed to devise an approach towards the cytotoxic diterpenoids, pseudolaric acids **204**.[96] The enantiomerically pure diazo carbonyl compound **202** was assembled via multistep synthesis and its rhodium(II)-mediated decomposition afforded the diastereomeric oxatricyclic products **203a** and **b** (1.25:1) (Scheme 62).



Scheme 62.

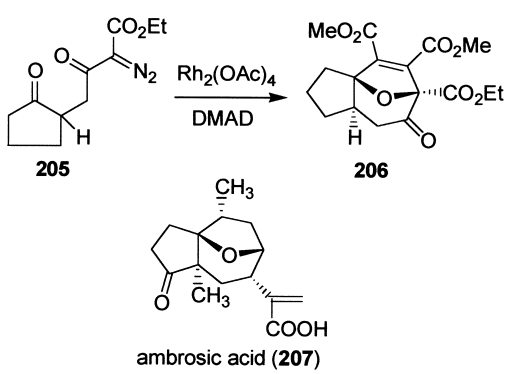
carbenoid cycloaddition approach allows the rapid assemblage of the bicyclic core structure of zaragozic acid in a single step. The rhodium(II)-catalyzed reaction of the diazo ketone **192** in the presence of 1,2-bistrimethylsiloxyethene as a dipolarophile afforded the cycloadduct **193** (Scheme 59). Interestingly, the commonly-employed electron-deficient dipolarophiles such as methyl acrylate or methyl propiolate failed to trap the 1,3-dipole generated from **192**. The order of dipolarophile reactivity switches depending on the presence or absence of an extra carboxyl group on the dipole and can be easily accommodated by FMO theory.

In an alternate approach to the zaragozic acid system using the cycloaddition of six-membered ring carbonyl ylides, the reaction of the diazo diketoester **194** with glyoxalates in the presence of a catalytic amount of $Rh_2(OAc)_4$ was investigated to generate the 6,8-dioxabicyclo[3.2.1]octanes **195** and **196** in good yield (Scheme 60).[95] Elaboration of **196** provided the 2,8-dioxabicyclo[3.2.1]octane skeleton **197** of zaragozic acid A **198**.

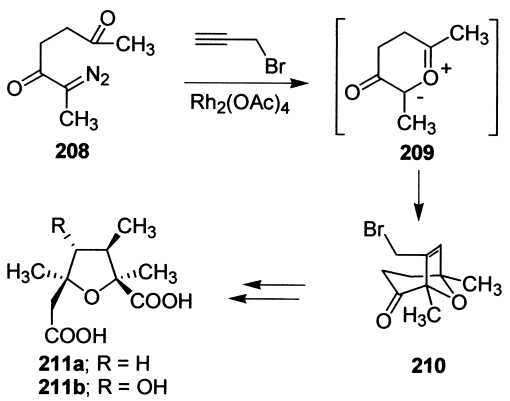
Functionally embellished diazo diketoesters such as **199** also undergo highly regio- and diastereoselective cycloaddition with glyoxylates to give the cycloadduct **200** and, further, **201**, representing the bicyclic core of the zaragozic acids/squalestatins (Scheme 61).[95]

In an approach towards guaianolide sesquiterpenes, their hydroazulenic framework has been constructed through a rhodium(II)-catalyzed reaction of the α-diazo ketone **205** with DMAD to afford the oxatricyclic system **206**, which forms the skeleton of ambrosic acid **207** (Scheme 63).[32]

Hodgson and co-workers[97] have recently reported concise and stereoselective syntheses of *cis*-nemorensic acid (**211a**) and 4-hydroxy-*cis*-nemorensic acid (**211b**) via a tandem carbonyl ylide-cycloaddition protocol. The key step was the regioselective reaction of the carbonyl ylide **209** generated from the α-diazo ketone **208** with $Rh_2(OAc)_4$ in the



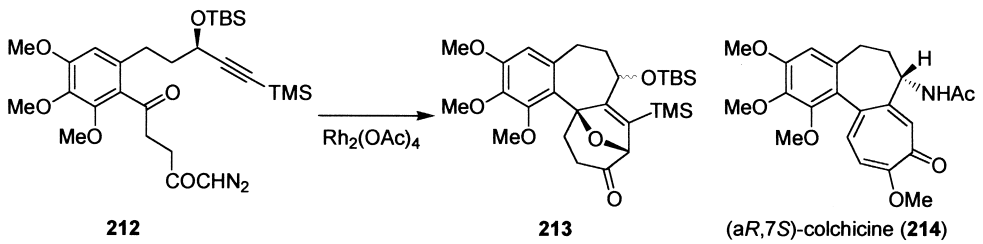
Scheme 63.



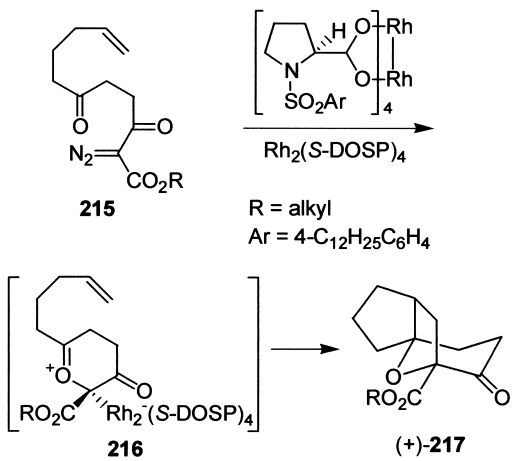
Scheme 64.

α-diazo ketone **212** with a TMS-protected alkyne moiety was employed.

3.1.1. Applications in asymmetric synthesis. An enantioselective version of the tandem six-membered ring carbonyl ylide formation-intramolecular cycloaddition of α-diazo carbonyl compounds using chiral rhodium(II) carboxylates has been demonstrated by Hodgson and co-workers for the first time.[99] It had previously been shown[100] that α-diazo-β-ketoesters **215** undergo intramolecular cycloaddition faster than intermolecular cycloaddition of the ylide with the highly reactive dipolarophile DMAD. The reaction of α-diazo-β-ketoesters **215** using 1 mol% of dirhodium(II) tetrakis[*N*-[(4-dodecylphenyl)sulphonyl]-(*S*)-prolinate], Rh_2(*S*-DOSP)$_4$, as catalyst gave the cycloadducts **217** via



Scheme 65.



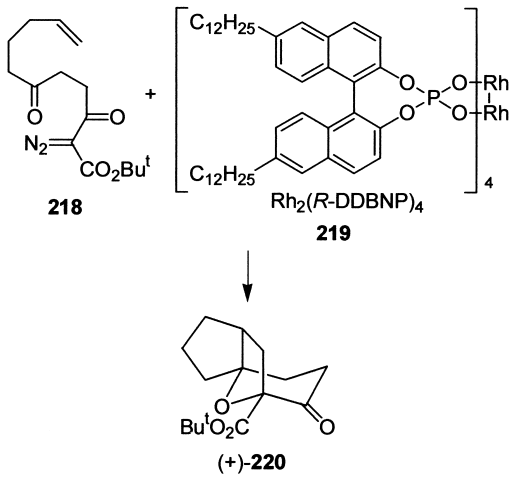
Scheme 66.

presence of propargyl bromide to furnish the cycloadduct **210** in high yield (Scheme 64). Following a number of functional group manipulations on the cycloadduct **210**, a stereoselective synthesis of the nemorensic acids **211** was accomplished.

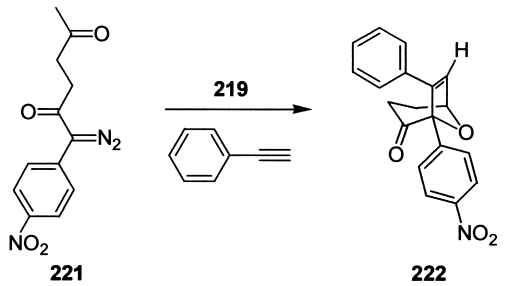
A short and elegant approach towards the cytotoxic alkaloid, colchicine (**214**), known for its remarkable antimitotic activity, has been reported by Schmalz and co-workers employing the intramolecular cyclization–cycloaddition cascade reactions of a carbonyl ylide.[98] Decomposition of the α-diazo ketone **212** in the presence of $Rh_2(OAc)_4$ furnished the cycloadduct **213** in good yield as a mixture of diastereomers (Scheme 65). In order to avoid possible participation of the relatively acidic alkynyl hydrogen atom in the undesired proton transfer, the

the six-membered carbonyl ylides **216** with enantioselectivites of up to 53% ee (Scheme 66). No specific rotation was, however, observed when the reaction was repeated using other catalysts such as $Rh_2(OAc)_4$ and Rh_2(5*R*-MEPY)$_4$.

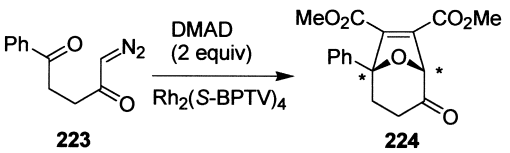
The same research group has also demonstrated a successful catalytic enantioselective tandem carbonyl ylide formation-cycloaddition of the α-diazo-β-keto ester **218** using 0.5 mol% dirhodium tetrakis(1,1′-binaphthyl-2,2′-diyl phosphate), Rh_2(*R*-DDBNP)$_4$ **219**, as catalyst to afford the cycloadduct **220** in good yields and up to 90% ee (Scheme 67).[101a] A detailed study on enantioselective tandem carbonyl ylide formation-cycloaddition of diazo compounds **215** using a series of dirhodium tetrakiscarboxylate and tetrakisbinaphtholphosphate catalysts under different solvent conditions to afford the cycloadducts **217** has been



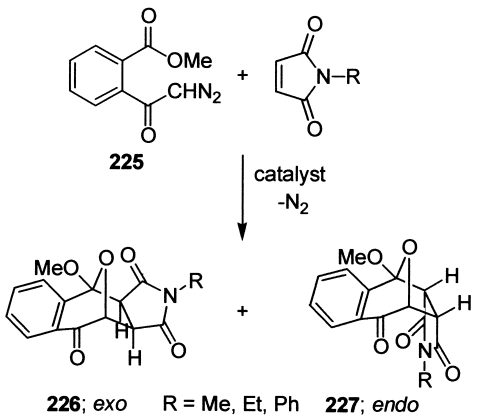
Scheme 67.



Scheme 68.



Scheme 69.



Scheme 70.

described.[101b] These studies indicate that dirhodium tetrakisbinaphtholphosphate catalysts are superior to the more commonly-used carboxylates and carboxamidates in asymmetric transformations.

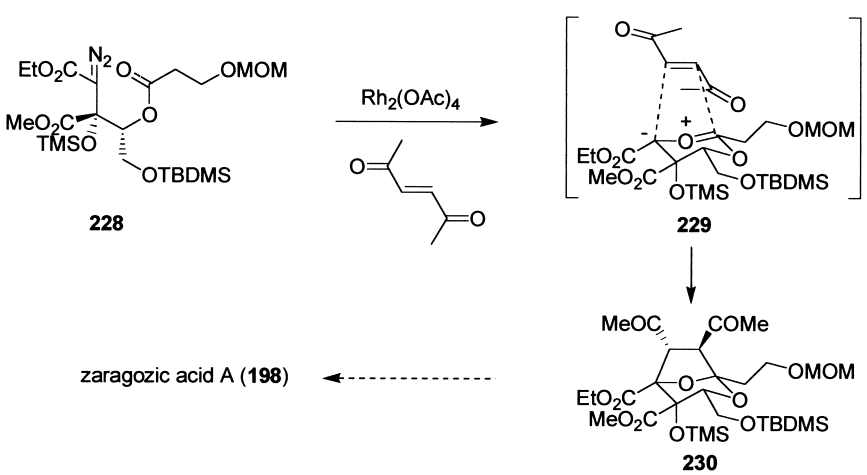
Hodgson and co-workers have further demonstrated[102] that the reaction of α-aryl-α-diazodiones with aryl acetylenes in the presence of chiral rhodium catalysts provided cycloadducts with considerable enantioselectivity. Typically, the reaction of the nitrophenyl-substituted diazodione **221** and phenyl acetylene in the presence of the binaphthyl catalyst **219** at 0°C afforded the cycloadduct **222** with 76% ee (Scheme 68).

Another successful catalytic enantioselective approach based on the tandem carbonyl ylide formation-intermolecular cycloaddition of α-diazo carbonyl compounds using phthaloyl-derived chiral rhodium(II) catalysts has been demonstrated by Hashimoto and co-workers.[103] A six-membered ring carbonyl ylide formation from the α-diazo ketone **223** and subsequent 1,3-cycloaddition with DMAD under the influence of 1 mol% of dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-phenylvaline], Rh_2(*S*-BPTV)$_4$,[104] has been explored to obtain the cycloadduct **224** in up to 92% ee (Scheme 69).

The important factor which could influence asymmetric induction, would be that cycloaddition is faster than catalyst decomplexation from the ylide. Although the precise mechanism remains unclear, the high levels of enantioselection in intermolecular cycloadditions with dipolarophiles provide definite support for the intermediacy of the chiral rhodium(II)-associated carbonyl ylide involved in the cycloaddition step. These examples indicate that metal-catalyzed dipole formation followed by cycloaddition has the potential to be a powerful method for asymmetric synthesis.

3.2. With ester carbonyl groups

The first examples of dramatic changes in stereoselectivity caused by the metal catalyst and Lewis acid in 1,3-dipolar cycloadditions of carbonyl ylides derived from ester carbonyl compounds with *N*-substituted maleimides have been reported.[105] The decomposition of *o*-(methoxycarbonyl)-α-diazoacetophenone **225** in the presence of NPM using a range of typical metal catalysts (5 mol%) for the decomposition of the diazo compound afforded **226** and **227** as the *exo* and *endo* cycloadducts, respectively (Scheme 70). Surprisingly, when metal catalysts having Lewis acidity such as CuOTf (*endo*/*exo*=87:13) and Cu(OTf)$_2$ (*endo*/*exo*=82:18) were used, highly *endo*-selective 1,3-dipolar cycloaddition occurred which is not usually observed in the carbonyl ylide cycloadditions. A high *endo* selectivity

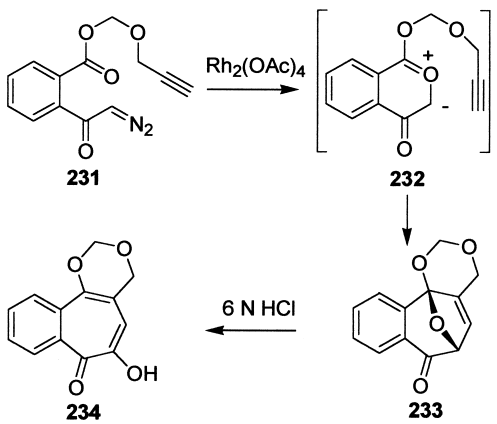


Scheme 71.

(*endo*/*exo*=94:6) was observed by adding 5 mol% of $Yb(OTf)_3$ under 5 mol% of CuCl-catalyzed conditions. On the other hand, the reaction involving the use of $Rh_2(OAc)_4$ showed the highest *exo* selectivity (*exo*/*endo*=11:89). The results indicate that the Lewis acid presumably controls the stereoselectivity in the 1:3-dipolar cycloaddition of carbonyl ylides by coordination to dipolarophiles, as reported[106] for the reactions of nitrones.

A highly efficient alternative construction of the 2,8-bicyclo[3.2.1]octane core structure of zaragozic acids (squalestatins) **198** has been achieved by Hashimoto and co-workers exploiting the sequence of rhodium(II)-mediated intramolecular carbonyl ylide formation from an α-diazo ester and stereocontrolled 1,3-dipolar cycloaddition with (*E*)-3-hexene-2,5-dione.[107] Towards this end, the fully functionalized α-diazo ester **228** was reacted with $Rh_2(OAc)_4$ in the presence of (*E*)-3-hexene-2,5-dione to afford the cycloadduct **230** via the intermediate **229** as a single diastereomer out of the four possible diasteromers (Scheme 71).

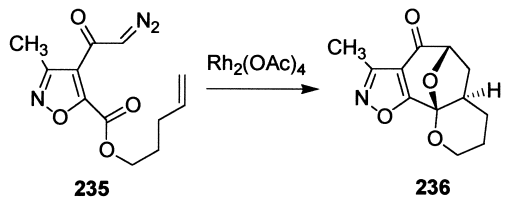
An intramolecular version of these reactions has also been reported. The generation of six-membered carbonyl ylides using ester carbonyl groups and their intramolecular trapping using acetylenic dipolarophile has been well documented in the synthesis of novel annulated benzotropolones[108] and successfully applied to the synthesis of tropolone natural products. Exposure of the α-diazo ketone **231** to $Rh_2(OAc)_4$ resulted in the formation of a reactive metal-carbenoid intermediate which underwent intramolecular carbonyl ylide **232** formation and subsequent 1,3-dipolar cycloaddition to give the tetracyclic compound **233** (Scheme 72).[109] Acid-catalysed ring opening in **233** yielded the tricyclic tropolone **234** with the methylene acetal still in place.



Scheme 72.

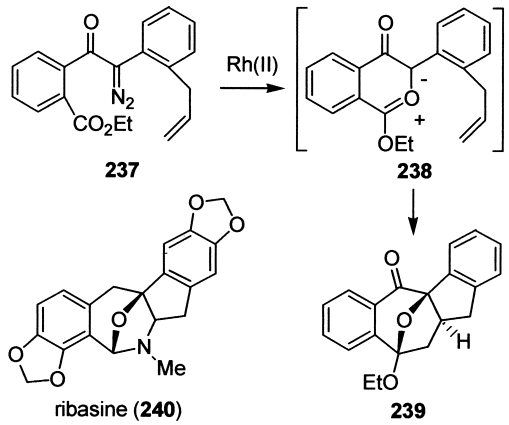
The six-membered ring carbonyl ylides formed using ester carbonyl groups followed by intramolecular trapping have provided facile entry into highly functionalized polycyclic systems,[110] the decomposition of the diazo ketone **235** in the presence of the Rh(II) catalyst affording the cycloadduct **236** (Scheme 73).

A series of α-diazo-β-(*o*-carbomethoxy)-substituted aryl ketones were prepared and employed as model systems for a



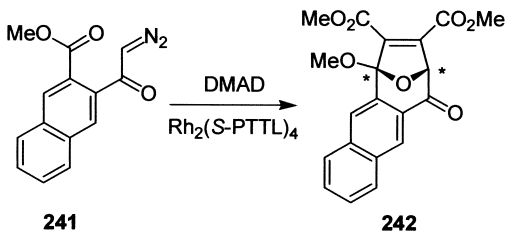
Scheme 73.

synthetic approach towards the alkaloid, ribasine (**240**).[111] This intramolecular cyclization–cycloaddition sequence has been extended as a model route to an alkaloid. The six-membered ring carbonyl ylide dipoles **238** were generated from the *o*-allyl-substituted diazo ketoester **237** and $Rh_2(OAc)_4$ to access the cycloadduct **239** (Scheme 74). This result constitutes a promising model study towards the synthesis of the alkaloid, ribasine (**240**).



Scheme 74.

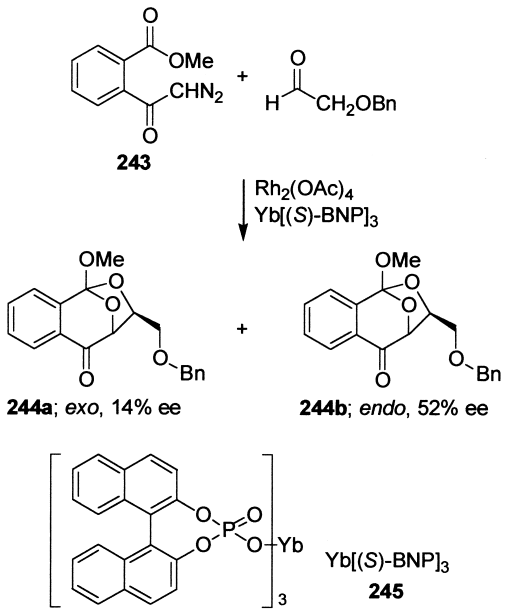
3.2.1. Applications in asymmetric synthesis. Hashimoto and co-workers have shown that the enantioselective 1,3-dipolar cycloaddition of the ester-derived carbonyl ylides can be achieved using chiral dirhodium(II) carboxylates. The ester-derived carbonyl ylide from the α-diazo ketone **241** in the presence (1 mol%) of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] (Rh_2(*S*-PTTL)$_4$) as the catalyst afforded the cycloadduct **242** with 93% ee (Scheme 75).[112]



Scheme 75.

It has been reported that Lewis acids such as $Yb(OTf)_3$ can profoundly affect the stereochemical outcome of the carbonyl ylide cycloadditions.[113] This provided a clue to effect asymmetric carbonyl ylide cycloaddition using a chiral Lewis acid. The first example of asymmetric induction using the chiral lanthanide catalyst, ytterbium tris(*S*)-1,1′-binaphthyl-2,2′-diyl phosphonate (Yb[(*S*)-BNP]$_3$) **245**, for cycloaddition of carbonyl ylides has been reported. The reaction of diazoacetophenone **243** with

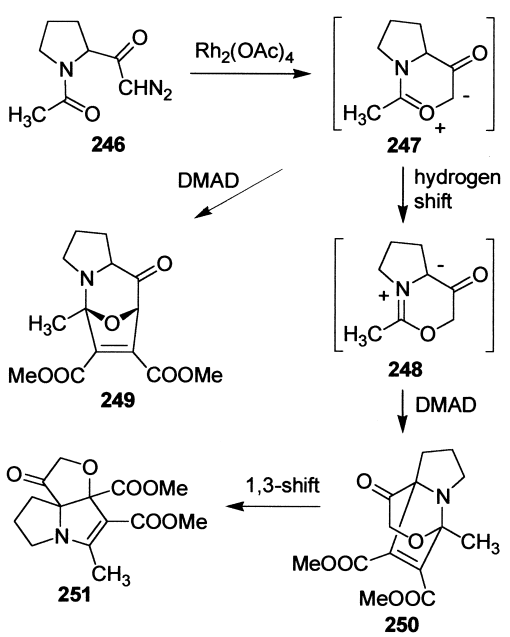
benzyloxyacetaldehyde furnished the cycloadducts **244a** and **b** with moderate enantioselectivity (Scheme 76).



Scheme 76.

3.3. With amide carbonyl groups

The formation of a six-membered cyclic carbonyl ylide with amide functional groups leads to the interconversion of one dipole **247** into another **248**. Less attention, however, has been given to this type of interconversion and not many examples of cycloaddition have been reported (cf. isomunchnones in Section 2.3). This type of interconversion has been termed as 'dipole cascade' and involves three distinct classes of 1,3-dipoles.[114] The cascade can be initiated by a $Rh_2(OAc)_4$-catalyzed cyclization of an α-diazo ketone such as **246** onto a neighboring carbonyl group to generate a carbonyl ylide dipole **247** which undergoes a proton shift to the azomethine ylide **248** (Scheme 77). The corresponding cycloadducts **249** and **250** were obtained in the presence of DMAD. The initially-formed cycloadduct **250** undergoes a subsequent alkoxy 1,3-shift to generate the tricyclic dihydropyrrolizine ring system **251**.

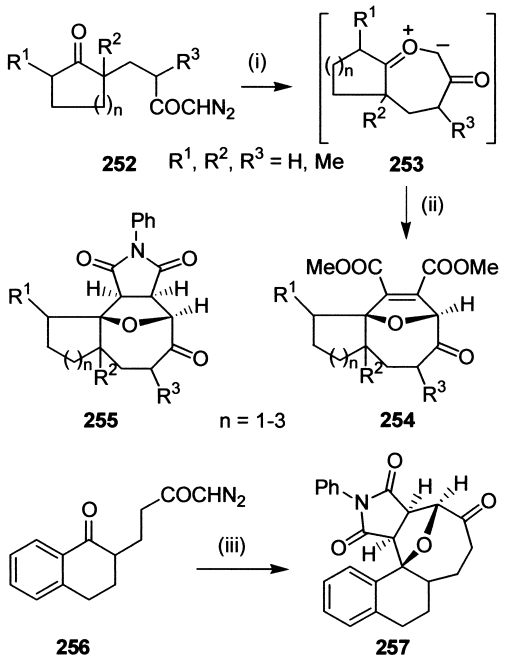


Scheme 77.

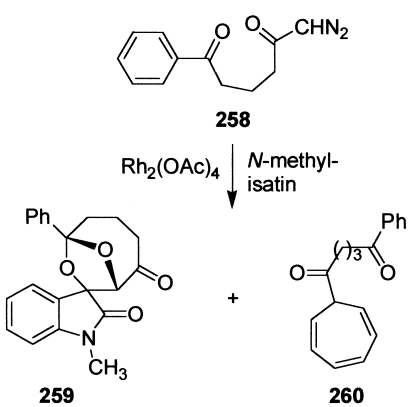
4. Intramolecular seven-membered ring carbonyl ylides

4.1. With keto carbonyl groups

Relatively little research effort has been reported with seven-membered ring carbonyl ylides.[29b,115] In one example, the decomposition of compounds having a tethered diazo carbonyl functionality on the cycloalkanone ring systems **252** in the presence of $Rh_2(OAc)_4$ provided the seven-membered carbonyl ylides **253**. The generation of **253** was demonstrated by trapping experiments using dipolarophiles like DMAD and NPM to provide the cyclooctanoid systems **254** and **255**, respectively (Scheme 78). Similarly, the tetralone-derived diazo



Scheme 78. (i) $Rh_2(OAc)_4$; (ii) DMAD; (iii) $Rh_2(OAc)_4$, NPM.



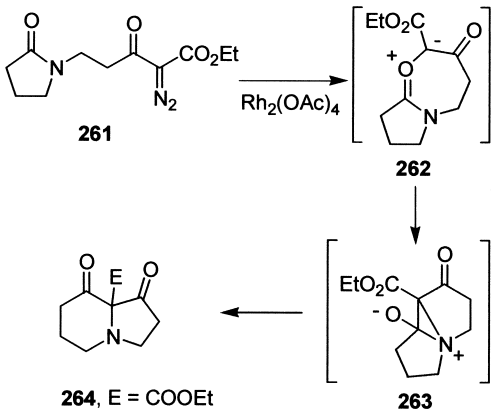
Scheme 79.

carbonyl compound **256** furnished the epoxy-bridged cyclooctanoid ring system **257** in the presence of *N*-phenylmaleimide.

The reaction of a seven-membered ring carbonyl ylide generated by the Rh(II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexadione **258** was studied with *N*-methylisatin.[38] The reaction afforded a cycloadduct **259** in 32% yield along with **260** (8%) resulting from the Büchner reaction of benzene and the carbenoid (Scheme 79).

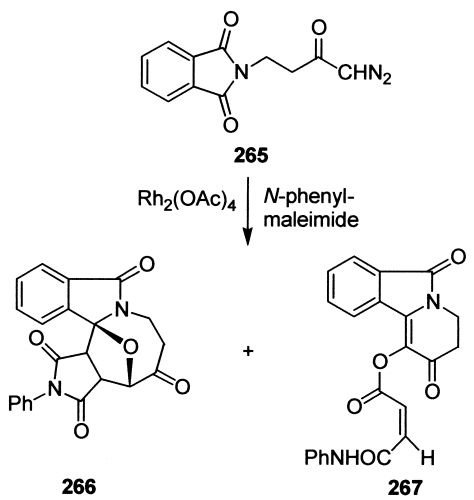
4.2. With amide carbonyl groups

A range of cyclic diazo ketoamides have been studied to generate seven-membered carbonyl ylides. The Rh(II)-catalyzed reaction of the amido diazo ketoester **261** was found to cleanly afford the rearranged indolizidone **264** via the intermediates **262** and **263** (Scheme 80).[116]



Scheme 80.

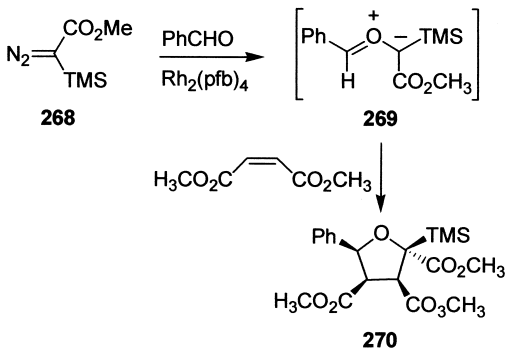
Seven-membered ring carbonyl ylides derived from phthalimides can also participate in these tandem cyclization–cycloaddition reactions, the $Rh_2(OAc)_4$-catalyzed reaction of 1-diazo-4-phthalimidobutanone (**265**) proceeding quite smoothly with DMAD and NPM.[116] When *N*-phenylmaleimide was used as the trapping agent, the cycloadduct **266** (45%) was obtained as the major product (Scheme 81), along with **267**.



Scheme 81.

5. Intermolecular carbonyl ylides

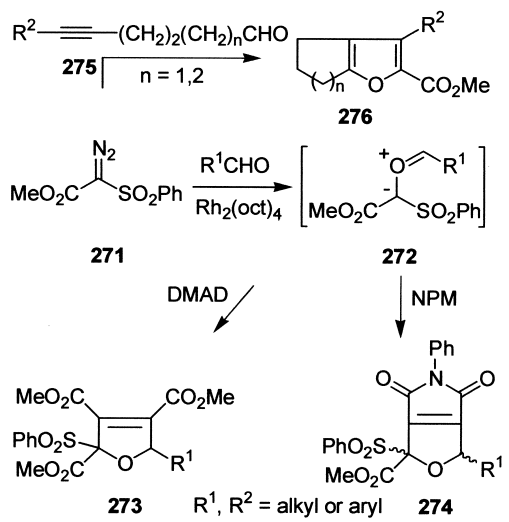
There are only a limited number of examples of the formation of ylides through intermolecular reactions between diazo ester compounds and aldehydes or ketones in the presence of transition metal catalysts. These transient species undergo electrocyclization to oxiranes or 1,3-dipolar cycloaddition with dipolarophiles. The latter process has been utilized for the synthesis of heterocycles.[13,17g,117] The $Rh_2(pfb)_4$-catalysed decomposition of the α-diazo ester **268** in the presence of benzaldehyde, for example, generated the carbonyl ylide **269**, which was trapped with dimethyl maleate to furnish the tetrahydrofuran **270** in moderate yield (Scheme 82).[118]



Scheme 82.

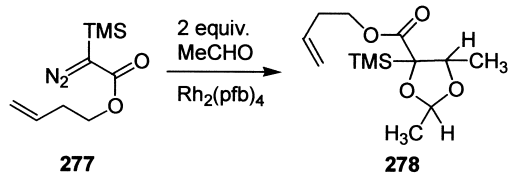
Another example leading to substituted oxygen heterocycles is from the diazo ester **271** which forms an intermolecular carbonyl ylide **272** in the presence of aldehydes.[119] This reactive carbonyl ylide intermediate **272** has been trapped with DMAD and NPM to afford the substituted dihydrofurans **273** and **274**, respectively (Scheme 83). The intramolecular version of this reaction was also investigated in the presence of aldehydes having an alkynyl group, the reaction of equimolar quantities of **271** and the aldehydes **275** in the presence of $Rh_2(oct)_4$ as the catalyst furnishing the annulated furans **276** in moderate yields (Scheme 83).

The reactive carbonyl ylides, generated in an intermolecular manner, have also been trapped by carbonyl compounds,



Scheme 83.

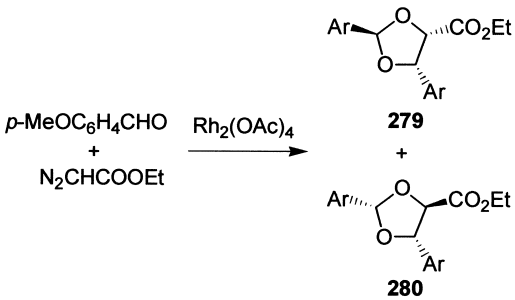
either in an intermolecular process to produce dioxolanes[120] or in an intramolecular 1,3-dipolar cycloaddition to produce[121] 1,3-dioxoles. The unsaturated α-diazo-α-(trimethylsilyl)acetate (**277**) with 2 equiv. of acetaldehyde under the catalytic action of $Rh_2(pfb)_4$ was found to produce the 1,3-dioxolane **278** in good yield (Scheme 84).[122]



277 **278**

Scheme 84.

Early investigations by Huisgen and De March[120] showed that the reaction of dimethyl diazomalonate with benzaldehyde in the presence of $Cu(acac)_2$ or $Rh_2(OAc)_4$ or $Cu(OTf)_2$ furnished two major dioxolane stereoisomers. Treatment of a composite of *p*-anisaldehyde and a catalytic amount of $Rh_2(OAc)_4$ with ethyl diazoacetate resulted in the formation of two carbonyl ylide cycloaddition products, identified as **279** and **280**, out of the four possible diastereomers in <15% yield (Scheme 85).[123] Higher conversions were achieved with catalysis by dirhodium(II) caprolactamate, $Rh_2(cap)_4$ (52%), but the same ratio of **279**/**280** did not change from 52:48. With *p*-nitrobenzaldehyde, all four isomers were obtained with different ratios of products based on the catalyst variations. This strong influence of the catalyst on the product selectivity is unprecedented in carbonyl ylide chemistry[90] and requires association with the ylide during cycloaddition. The results obtained for the catalyst-derived carbonyl ylide formation show that there is a dual pathway to the cycloaddition products. Stereoelectronic factors control 'free' ylide formation and stereoselectivity for cycloaddition is controlled by steric effects.



Scheme 85.

6. Concluding remarks

As can be gleaned from the forgoing examples, interest in the explorations with carbonyl ylides is widespread and on the ascendancy. The possibilities of rapid generation of molecular complexity and diversity with good stereo- and regiocontrol make this rhodium-mediated tandem cyclization–cycloaddition approach an economical, effective and efficient synthetic strategy. This protocol is particularly relevant in the context of the enormous current interest of the pharmaceutical industry in rapidly accessing diverse, small molecule libraries with high levels of functionalization. Indeed, carbonyl ylide-based strategies can be very valuable in this quest. Recent research efforts in the area leading to the crafting of new and selective rhodium-based catalysts and the development of solid phase versions and asymmetric variants has substantially amplified the appeal and scope of this carbonyl ylide based tandem cyclization–cycloaddition strategy. While concise and stereoselective syntheses of many complex natural products, particularly terpenoids and alkaloids, have been accomplished, there are many more targets where the carbonyl ylide-based strategy can be effectively harnessed. Many exciting prospects, particularly with regard to the development of a general, catalytic, asymmetric version of this reaction, are in store and such challenges are going to sustain the ongoing interest in the carbonyl ylide-based tandem cyclization–cycloaddition chemistry.

Acknowledgements

S. M. thanks the Council of Scientific and Industrial Research and the Department of Science and Technology, New Delhi for their financial support for our research work on tandem reactions.

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