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

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Contents

1. Introduction 9477
   1.1. Scope and organization of the review 9478

2. Intramolecular five-membered ring carbonyl ylides 9478
   2.1. With keto carbonyl groups 9479
   2.2. With ester carbonyl groups 9484
   2.3. With amide carbonyl groups (isomünchnones) 9485
      2.3.1. Intermolecular isomünchnone cycloadditions 9485
         2.3.1.1. Applications in asymmetric synthesis 9487
      2.3.2. Intramolecular isomünchnone cycloadditions 9489

3. Intramolecular six-membered ring carbonyl ylides 9492
   3.1. With keto carbonyl groups 9492
      3.1.1. Applications in asymmetric synthesis 9495
   3.2. With ester carbonyl groups 9496
      3.2.1. Applications in asymmetric synthesis 9497
   3.3. With amide carbonyl groups 9498

4. Intramolecular seven-membered ring carbonyl ylides 9498
   4.1. With keto carbonyl groups 9498
   4.2. With amide carbonyl groups 9499

5. Intermolecular carbonyl ylides 9500

6. Concluding remarks 9500

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\textsuperscript{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

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in particular have gained significant importance in recent years.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{12,13} Many methods like thermolysis or photolysis of epoxides (D) having electron-withdrawing substituents,\textsuperscript{17} the thermal extrusion of nitrogen from 1,3,4-oxadiazolines (G),\textsuperscript{18} extrusion of carbon dioxide from 1,3-dioxolan-4-ones (F)\textsuperscript{19} and the photolysis of diazo carbonyl compounds in noble gas matrices (E)\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{22,23} structural units in naturally occurring bioactive molecules like ionophores,\textsuperscript{24} macroyclic antibiotics,\textsuperscript{25} and a range of marine toxins.\textsuperscript{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.

\subsection*{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\textsuperscript{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\textsuperscript{12} and updated\textsuperscript{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.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{r1}
\caption{Figure 1.}
\end{figure}
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 \( \mathbf{1} \) generates initially the rhodium-carbenoids \( \mathbf{2} \), followed by the five-membered ring carbonyl ylides \( \mathbf{3} \), which can be trapped regio- and stereoselectively using a dipolarophile \( \text{A=B} \) to form the oxabicyclic compounds \( \mathbf{4} \) (Scheme 1). If \( R_1 \) is a hydrogen atom (see Scheme 1), the formation of the corresponding hydrogen migrated product \( \mathbf{5} \) 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 \( \mathbf{4} \), it is important that competitive reactions like proton transfer and C–H insertion are avoided through a proper choice of the substrate \( \mathbf{1} \).

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 \( \mathbf{6} \) and \( \mathbf{8} \) with rhodium(II) acetate \([\text{Rh}_2(\text{OAc})_4]\) in the presence of dimethyl acetylenedicarboxylate (DMAD) to furnish the highly functionalized cycloadducts \( \mathbf{7} \) and \( \mathbf{9} \), respectively (Scheme 2).29

The reactions of the cyclopropyl-substituted carbonyl ylide \( \mathbf{11} \) derived from the α-diazo ketone \( \mathbf{10} \) with different dipolarophiles have been investigated by Padwa.30 The compound \( \mathbf{10} \) undergoes cycloaddition in the presence of \( \text{Rh}_2(\text{OAc})_4 \) with dimethyl maleate, dimethyl fumarate, 1,1-dimethoxyethylene and cyclopentene, furnishing the expected cycloadducts \( \mathbf{12} \)–\( \mathbf{15} \), respectively (Scheme 3).30b

The regiochemical outcome of the 1,3-dipolar cycloaddition reactions of the cyclic five-membered ring carbonyl ylide \( \mathbf{11} \), generated from the α-diazo ketone \( \mathbf{10} \), with a variety of acyclic and cyclic alkenes having activated or inactivated π-bonds can be rationalized30 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 \( \mathbf{11} \) derived from the α-diazo ketone \( \mathbf{10} \) with \( p \)-quinoneimides such as \( \mathbf{16} \) has
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 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 fulvenes34 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 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...
regioisomeric oxatetracyclo[6.5.1.0^1,6.0^9,13]tetradecene derivatives 28 and 29 (Scheme 8). 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 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.

Not unexpectedly, an intramolecular variant of the five-membered ring carbonyl ylide cycloaddition has also been explored. 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-diene have also been studied to provide the corresponding dioxatricyclic ring systems 37–40 with high regio- and chemoselectivity (Scheme 11).
The reaction of the spirocyclic ylide 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 through regioselective addition on the C₅ carbonyl group (Scheme 12).38

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 arylidenediatalanones, bis(aryl methylidene)-ketones and bis(heteroaryl methylidene)ketones. The reaction of the bicyclic carbonyl ylide 21 generated from the α-diazo ketone 20 and arylidenediatalanones 42 in the presence of Rh₂(OAc)₄, for example, led 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.

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

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 Rh₂(OAc)₄ as the catalyst to furnish complex oxapolycyclic systems.45 The reaction of 48 with p-benzoquinone led to the novel oxap-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, (±)-IIludin M (56), a toxic sesquiterpene isolated from the jack-o'-lantern mushroom, has been synthesized by Kinder and co-workers via the spirocyclic carbonyl ylide 11 generated from the cyclopentenone-derivatives mechanism of α-diazo ketone 10. Rh₂(OAc)₄-mediated decomposition of the α-diazo ketone 11 in the presence of cyclopentenone 54 afforded the key
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 \(\alpha\)-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
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 regioselectivity$^{50}$ 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 cycloaddition 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.
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 Maier54 and Padwa.55 These reactive species (isomünchnones) can be trapped by various electron-rich and electron-deficient dipolarophiles56 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 Rh2(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...
[Rh₂(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. Further, the reaction of the diazoimide 91a with 2-methoxypropene, an *ipsos*-substituted vinyl ether, was studied to evaluate whether the above-observed stereoselectivity was steric or electronic in nature. The observation of a 1:3 *exoendo* 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'-amino-adenosine 95 employing amine protection, amide formation with methyl malonyl chloride and the usual diazotransfer reaction led to the α-diazoimide 96. The Rh₂(pfbm)₄-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).

The 1,3-dipolar cycloaddition reactions of isomünchnone dipoles with buckminsterfullerene C₆₀ 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 C₆₀ in the presence of a rhodium(II) perfluorobutyrate [Rh₂(pfb)₄] catalyst afforded the cycloadduct 99 in moderate yield (Scheme 29). 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 phosphalkynes has been reported as a novel route to 1,3-oxaphospholes. The
isomunchnones 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 isomunchnones 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 isomunchnone 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 isomunchnones to acetylenic dipolarophiles. The intermolecular 1,3-dipolar cycloaddition of isomunchnones with alkynes is typically followed by extrusion of an alkyl or aryl isocyanate (RN=CO) 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. Towards this end, the amidites 107 were obtained by the acylation of TentaGel-NH$_2$ resin and treated with ethyl malonyl chloride to obtain the imides 108. Diazio 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 furen synthesis has surfaced simultaneously. 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 isomunchnones was presented as a general methodology for the combinatorial formation of a furen-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. 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 isomunchnone formation. Studies on π-facial diastereoselection in [3+2]-cycloadditions of several isomunchnone dipoles derived from substituted cyclic amidites have also been carried out to define the stereochemical issues. High levels of diastereoselectivities were encountered in these cycloadditions, leading to the exo products.

As an application of the intermolecular cycloaddition reaction of isomunchnone, a new synthetic route to 2-pyridones was successfully developed and extended to the synthesis of the indolizidine alkaloid, (+)-ipalbidine 118. The decomposition of the diazoimide 114 was effected using Rh$_2$(OAc)$_4$ as the catalyst 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(1H)-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 isomunchnones, further enhancing the synthetic appeal of this cycloaddition protocol, have been developed. Austin and co-workers have reported the optimization of a chiral
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 benzhydrylamino (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$_2$(pbfm)$_4$] in the presence of 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
Harwood’s group has extended the use of the chiral α-diazoimide 130 to devise a synthesis of enantiopure α,β-dihydroxyacids. 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. 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 to many complex polycyclic structures as exemplified by the one-step formation of 133 from the diazoimides 134 in a stereoselective manner (Scheme 39). A related diazoimide system 135 having an alkene tethered to the benzene backbone was exposed to Rh₂(pfb)₄ as the catalyst to furnish the diastereospecifically polyheterocyclic system 136 in excellent yield (Scheme 40). 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 Rh₂(pfb)₄ as the catalyst led exclusively to 138 (Scheme 41). 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. 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 Rh₂(OAc)₄ furnished the pentacyclic dihydropyrimidine systems 140 without the isolation of the initially-generated transient.

Scheme 38. (i) p-Nitrobenzaldehyde, Rh₂(OAc)₄ or Rh₂(tfa)₄; (ii) H⁺, H₂O/THF; (iii) LiOH/H₂O₂/THF/H₂O.

Scheme 39.

Scheme 40.

Scheme 41.

Scheme 42. (i) Rh₂(OAc)₄; (ii) H₂, 10% Pd/C, rt, 1 atm.
isomünchnone dipoles (Scheme 42). 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 Rh₂(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, 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.

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 Rh₂(pfb)₄-mediated tandem cyclization—cycloaddition sequence from the diazoimide 146 led to the cycloadduct 147 in very good yield (Scheme 44). The polycyclic adduct 147 was readily elaborated to 148 en route to ergot alkaloids via BF₃·OEt₂-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 tetra-substituted double bond in 148.

A formal synthesis of (±)-vallesamidine (153) has been achieved based on an intramolecular dipolar cycloaddition reaction of isomünchnone. Following a study of a range of model substrates, the reaction of the cyclic diazoimide 150 with Rh₂(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.

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

Scheme 43.

Scheme 44.

Scheme 45.

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

As an extension of the above methodology, the intramolecular cycloaddition of isomünchnone dipoles across an indole double bond has been investigated. This reaction has been shown to provide a facile entry into the pentacyclic skeleton of the aspidosperma alkaloids. Towards this end, the α-diazooimide 156 was synthesized and subjected to Rh₂(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. 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 diazooimide 159, obtained from citronellic acid. The reaction of the diazooimide 159 with Rh₂(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). Successive treatment of the cycloadduct 160 with BF₃·2AcOH 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. Following a study of various model substrates, the reaction of the α-diazooimide 163 with Rh₂(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 BF₃·2AcOH 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.
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 the utility of the ylides derived from the transition metal-catalyzed decomposition of o-(alkoxy carbonyl)diazoacetophenones through cycloaddition to various dipolarophiles. Treatment of the diazoacetophenone 170 with Rh₂(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 aldehydeic π-bonds has been exploited for the total synthesis of brevicomin.

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, the decomposition of 174 using Rh₂(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 Rh₂(pfb)₄, facilitate aromatic C–H insertion whereas donor ligands like rhodium(II) caprolactam [Rh₂(cap)₄] preferentially give carbonyl ylide dipoles.

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 o-quinone-imides such as 16 to afford the bicyclic compound 178 in good yields (Scheme 53).

Novel C₆₀ derivatives of the type 179 have been synthesized through 1,3-dipolar cycloaddition reactions of six-membered carbonyl ylides with [60]-fullerene. The Rh(II)-catalyzed transformation of the diazo ketone 177 in the presence of C₆₀ afforded the cycloadduct 179 (Scheme 54). The reaction has been further generalized.

Chemoselective 1,3-dipolar cycloadditions of fused six-membered ring carbonyl ylides with α,β-unsaturated carbonyl compounds have been reported. Treatment of the α-diazo ketone 180 with the arylidenetetralone 181 in the presence of Rh₂(OAc)₄ led to the spiro-dioxa ring system 182 through exclusive C==O addition in a manner...
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 acenaphthoquinone.\(^{90,91b}\)

Rhodium-generated bicyclic six-membered ring carbonyl ylides from the diazo ketone 180 with 3-quinones have been studied to yield interesting oxapoly cyclic 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 3-quinone 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 syntheyse, has been reported.\(^{74}\) The rhodium

Scheme 55.

Scheme 56.

Scheme 57.

Scheme 58.

Scheme 59.
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-bistrimethylsiloxy-ethene 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 Rh₂(OAc)₄ was investigated to generate the 6,8-dioxabicyclo[3.2.1]octanes 195 and 196 in good yield (Scheme 60). Elaboration of 196 provided the 2,8-dioxabicyclo[3.2.1]octane skeleton of zaragozic acid A 198.

Intramolecular cyclization–cycloaddition cascade reactions of rhodium carbenoids have been deployed to devise an approach towards the cytotoxic diterpenoids, pseudolaric acids 204. 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).

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). Hodgson and co-workers 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 Rh₂(OAc)₄ in the

Scheme 60.

Scheme 61. (i) Methyl glyoxylate, Rh₂(OAc)₄; (ii) CDCl₃, 25°C.

Scheme 62.

Scheme 63.
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 noreoresnic 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. Decomposition of the α-diazo ketone 212 with a TMS-protected alkynyl 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. It had previously been shown 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[1-(4-dodecylphenyl)sulphonyl]-1-(S)-proline, Rh2(S-DOSP)$_4$, as catalyst gave the cycloadducts 217 via the six-membered carbonyl ylides 216 with enantioselectivities 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$_2$(S-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(1,10-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). A detailed study on enantioselective tandem carbonyl ylide formation-cycloaddition of diazo compounds 215 using a series of dirhodium tetrakis(alkoxycarboxylate and tetrakisbinaphtholphosphate catalysts under different solvent conditions to afford the cycloadducts 217 has been accomplished.
described. These studies indicate that dirhodium tetra-
kisbinaphtholphosphate catalysts are superior to the more
commonly-used carboxylates and carboxamidates in asym-
metric transformations.

Hodgson and co-workers have further demonstrated that
the reaction of \( \alpha \)-aryl-\( \alpha \)-diazodiones with aryl acetylenes in
the presence of chiral rhodium catalysts provided cyclo-
adducts 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-inter-
molecular cycloaddition of \( \alpha \)-diazoo carbonyl compounds
using phthaloyl-derived chiral rhodium(II) catalysts has
been demonstrated by Hashimoto and co-workers. A six-
membered ring carbonyl ylide formation from the \( \alpha \)-diazoo
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], \( \text{Rh}_2(S-
BPTV)_4 \), 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 enantio-
selection in intermolecular cycloadditions with dipolaro-
philes 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 stereoelctivity
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. The decomposition of \( o \)-(methoxycar-
bonyl)-\( \alpha \)-diazooacetophenone \( 225 \) 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
ex=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
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 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) 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. Towards this end, the fully functionalized α-diazo ester was reacted with Rh$_2$(OAc)$_4$ in the presence of (E)-3-hexene-2,5-dione to afford the cycloadduct via the intermediate as a single diastereomer out of the four possible diastereomers (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 benzo-tropolones and successfully applied to the synthesis of tropolone natural products. Exposure of the α-diazo ketone to Rh$_2$(OAc)$_4$ resulted in the formation of a reactive metal-carbenoid intermediate which underwent intramolecular carbonyl ylide formation and subsequent 1,3-dipolar cycloaddition to give the tetracyclic compound (Scheme 72).

A series of α-diazo-β-(o-carbomethoxy)-substituted aryl ketones were prepared and employed as model systems for a synthetic approach towards the alkaloid, ribasine (240). This intramolecular cyclization–cycloaddition sequence has been extended as a model route to an alkaloid. The six-membered ring carbonyl ylide dipoles were generated from the o-allyl-substituted diazo ketoester and Rh$_2$(OAc)$_4$ to access the cycloadduct (Scheme 74). This result constitutes a promising model study towards the synthesis of the alkaloid, ribasine (240).

### 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 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 with 93% ee (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. 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)$_3$), for cycloaddition of carbonyl ylides has been reported. The reaction of diazoacetophenone with...
benzyloxyacetaldehyde furnished the cycloadducts 244a and b with moderate enantioselectivity (Scheme 76).

![Scheme 76](image)

**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. The cascade can be initiated by a Rh₂(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 dihydropyrrrolizine ring system 251.

**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. In one example, the decomposition of compounds having a tethered diazo carbonyl functionality on the cycloalkanone ring systems 252 in the presence of Rh₂(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](image)
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 Bünchner 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.](image)

Seven-membered ring carbonyl ylides derived from phthalimides can also participate in these tandem cyclization–cycloaddition reactions, the Rh2(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.](image)

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 Rh2(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.](image)

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 Rh2(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,
either in an intermolecular process to produce dioxolanes\textsuperscript{120} or in an intramolecular 1,3-dipolar cycloaddition to produce\textsuperscript{121} 1,3-dioxolanes. The unsaturated α-diazo-α-(trimethylsilyl)acetate (277) with 2 equiv. of acetaldehyde under the catalytic action of Rb\textsubscript{2}(pfb)\textsubscript{4} was found to produce the 1,3-dioxolane 278 in good yield (Scheme 84).\textsuperscript{122}

![Image 84](image_url_text)

**Scheme 84.** Early investigations by Huisgen and De March\textsuperscript{120} showed that the reaction of dimethyl diazomalonate with benzaldehyde in the presence of Cu(acac)\textsubscript{2} or Rb\textsubscript{2}(OAc)\textsubscript{4} or Cu(OTf)\textsubscript{2} furnished two major dioxolane stereoisomers. Treatment of a composite of p-anisaldehyde and a catalytic amount of Rb\textsubscript{2}(OAc)\textsubscript{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).\textsuperscript{123} Higher conversions were achieved with catalysis by dirhodium(II) caprolactamate, Rb\textsubscript{2}(cap)\textsubscript{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\textsuperscript{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.

![Image 85](image_url_text)

**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.

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### References


Biographical sketch

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