# 19
# Rhodium(II)-Catalyzed 1,3-Dipolar Cycloaddition Reactions

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## 19.1
## Rhodium(II) in 1,3-Dipole Formation

### 19.1.1
### Introduction

The rhodium(II)-catalyzed formation of 1,3-dipoles has played a major role in facilitating the use of the dipolar cycloaddition reaction in modern organic synthesis. This is apparent from the increasing number of applications of this chemistry for the construction of heterocyclic and natural product ring systems. This chapter initially focuses on those aspects of rhodium(II) catalysis that control dipole formation and reactivity, and concludes with a sampling of the myriad examples that exist in the literature today.

As with any modern review of the chemical literature, the subject discussed in this chapter touches upon topics that are the focus of related books and articles. For example, there is a well recognized tome on the 1,3-dipolar cycloaddition reaction that is an excellent introduction to the many varieties of this transformation [1]. More specific reviews involving the use of rhodium(II) in carbonyl ylide cycloadditions [2] and intramolecular 1,3-dipolar cycloaddition reactions have also appeared [3, 4]. The use of rhodium for the creation and reaction of carbenes as electrophilic species [5, 6], their use in intramolecular carbenoid reactions [7], and the formation of ylides *via* the reaction with heteroatoms have also been described [8]. Reviews of rhodium(II) ligand-based chemoselectivity [9], rhodium(II)-mediated macrocyclizations [10], and asymmetric rhodium(II)–carbene transformations [11, 12] detail the multiple aspects of control and applications that make this such a powerful chemical transformation. In addition to these reviews, several books have appeared since around 1998 describing the catalytic reactions of diazo compounds [13], cycloaddition reactions in organic synthesis [14], and synthetic applications of the 1,3-dipolar cycloaddition [15].

### 19.1.2
### The First Examples of Transition Metal-Mediated 1,3-Dipole Formation

The cycloaddition reaction of dipoles has been known since the late eighteenth century; however, before Huisgen's introduction of the concept of a 1,3-dipole, these reactions were considered to proceed *via* a diradical mechanism [16]. One of the earliest examples of metal-catalyzed 1,3-dipole formation involved the controlled decomposition of an $\alpha$-dia-

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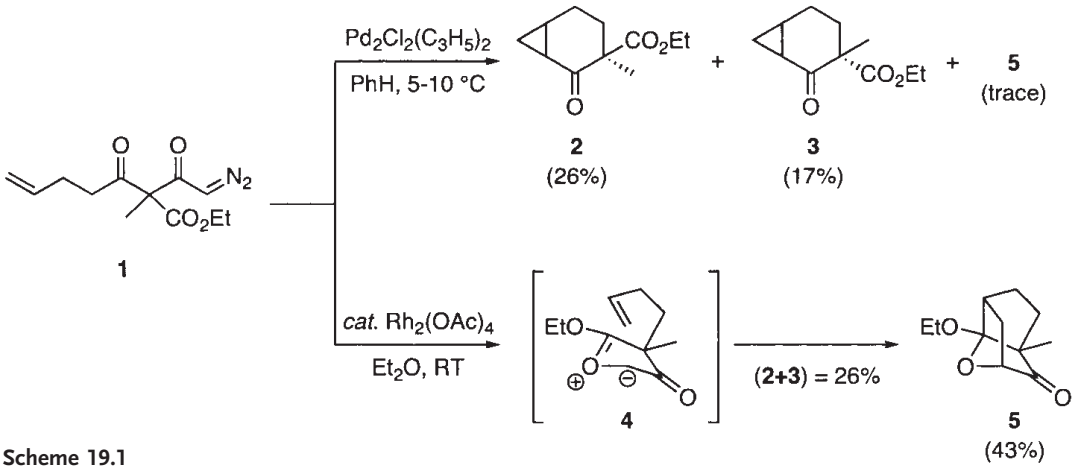
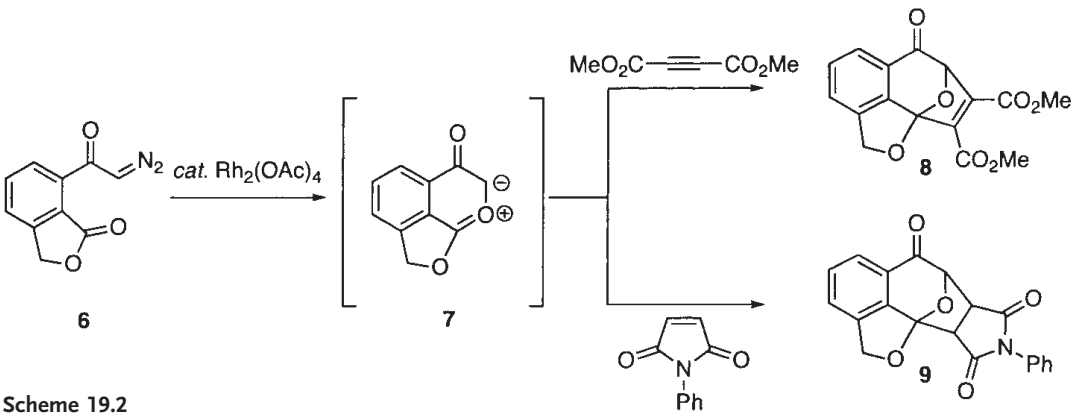
zo ketone in the presence of a catalytic amount of copper(II) acetylacetonate [$Cu(acac)_2$] [17]. It was later established that these α-diazo ketone decomposition products were indeed 1,3-dipoles and could undergo cycloaddition reactions with dipolarophiles [18, 19]. While these early examples utilized copper as the metal species, they set the stage for the evaluation of additional transition metals capable of catalyzing this transformation. The earliest example of a rhodium(II)-catalyzed α-diazo ketone decomposition to form a 1,3-dipole was described by Bien (Scheme 19.1) [20]. In this paper, the authors reported that the cyclopropanation gave **2** and **3** as the major products when palladium was used as the catalyst; however, rhodium catalysis provided cycloaddition adduct **5** as the predominant product. These early issues with selectivity formed the basis for much later work, which in combination with the ability to control product distribution through modification of the ligands within the rhodium(II) complex, ultimately led to the widespread use of this metal over palladium or copper (*vide infra*).




**Scheme 19.1**

Despite this promising beginning, and its growing use for the generation of electrophilic carbenes [5, 6], it was not until many years later that rhodium(II) was used generally for the formation of 1,3-dipoles. Padwa and Stull reported the use of rhodium(II) acetate [$Rh_2(OAc)_4$] in the successful formation of a six-membered ring carbonyl ylide (Scheme 19.2) [21]. This work was quickly followed by the use of rhodium(II) for the generation of




**Scheme 19.2**

furans *via* a [3+2] cycloaddition [22], and the generation of sulfonium and sulfoxonium ylides [23, 24]. The general synthetic utility of these transformations was greatly advanced by the demonstration of dipole formation and cycloaddition in the 1-diazo-2,5-pentanedione system [25], which was later applied to the synthesis of the natural product brevicomin [26]. This sequential cyclization–cycloaddition process, as it has become known, has since been applied to many ring systems [27].

### 19.1.3
### Rhodium(II) Catalysts Used in 1,3-Dipole Formation

Rhodium(II) forms a dimeric complex with a lantern structure composed of four bridging ligands and two axial binding sites. Traditionally rhodium catalysts fall into three main categories: the carboxylates, the perfluorinated carboxylates, and the carboxamides. Of these, the two main bridging frameworks are the carboxylate **10** and carboxamide **11** structures. Despite the similarity in the bridging moiety, the reactivity of the perfluorinated carboxylates is demonstrably different from that of the alkyl or even aryl carboxylates. Solid-phase crystal structures usually have the axial positions of the catalyst occupied by an electron donor, such as an alcohol, ether, amine, or sulfoxide. By far the most widely used rhodium(II) catalyst is rhodium(II) acetate [$Rh_2(OAc)_4$], but almost every variety of rhodium(II) catalyst is commercially available.


**10** **11**

Rhodium(II) carboxylate Rhodium(II) carboxamide

$R_1$ = alkyl, aryl, fluro-alkyl, sulfoxyl
$R_2$ = H, alkyl

Rhodium(II) carbenoids are electrophilic species that have the ability to undergo insertion (C–H, N–H, O–H, and so on), cyclopropanation, cyclopropenation, and dimerization, in addition to dipole formation [5, 6]. By far the largest role that the rhodium metal plays in the formation of 1,3-dipolar cycloadditions is stabilization of the intermediate carbene [5, 6], as a rhodium carbenoid. A second benefit afforded with rhodium catalysts, which makes them preferable to those based on copper or palladium, is the ease with which the bridging ligands may be modified together with the dramatic change in reactivity that is observed from these modifications [9]. Alternatively, carbenes generated by either acidic [28] or photochemical [29] methods suffer from being overly reactive.

One of the most significant additions to the modern rhodium(II) catalyst ligand family was the development of the hybrid catalysts that combined the carboxamide bridging ligands with the enhanced reactivity of perfluoroalkyl substituents. In this series, rhodium(II) trifluoroacetamidate [$Rh_2(tfa)_4$] was the first described [30]. In addi-

tion to having enhanced reactivity, this molecule was initially described as an effective mediator of the O–H insertion reaction. Subsequent studies using $Rh_2(tfa)_4$ and the related rhodium(II) perfluorobutyramidate [$Rh_2(pfbm)_4$] demonstrated an additional propensity for oxindole [31] and indole formation [32] *via* C–H insertion, in addition to the formation of isomünchnones [33]. The enhanced reactivity of the perfluorinated carboxamides was also observed by Doyle *et al*. [34]; however, no increase in enantioselectivity was noted with the chiral variants of these catalysts. The use of rhodium(II) ligand modifications to mediate carbenoid chemoselectivity (Section 19.2.1) [9], as well as the many recent advances in the generation and use of chiral rhodium(II) catalysts [35] (Section 19.2.3), are discussed later in the chapter.

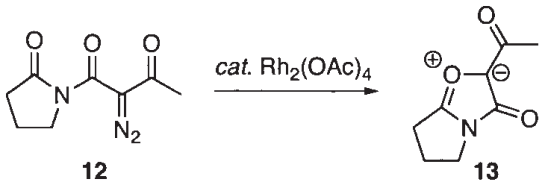
Despite the widespread use of rhodium(II) catalysis, the exact mechanism and nature of the rhodium carbenoid is not completely understood. In an effort to better understand the mechanism of rhodium(II)-mediated carbene reactivity, Pirrung [36] demonstrated that the reaction obeys saturation kinetics, which is consistent with the second step after complexation being rate-determining. This result is analogous with an earlier model for copper-catalyzed diazo decomposition [37]. Pirrung has also reported the ability of these catalysts to be inhibited by Lewis bases, and has further demonstrated their Michaelis–Menten behavior [38]. The first structural insight into the rhodium carbenoid was provided by the isolation and subsequent X-ray crystallographic analysis of a stable metal–carbene complex [39]. The structure showed an increased Rh–Rh bond distance relative to the uncomplexed structure, in addition to a long and presumably weak Rh–C bond, favoring decomplexation as suggested by reactivity.

### 19.1.4
### Dipoles Created Using Rhodium(II) Catalysis

Many different types of 1,3-dipoles have been described [1]; however, those most commonly formed using transition metal catalysis are the carbonyl ylides and associated mesoionic species such as isomünchnones. Additional examples include the thiocarbonyl, azomethine, oxonium, ammonium, and nitrile ylides, which have also been generated using rhodium(II) catalysis [8]. The mechanism of dipole formation most often involves the interaction of an electrophilic metal carbenoid with a heteroatom lone pair. In some cases, however, dipoles can be generated *via* the rearrangement of a reactive species, such as another dipole [40], or the thermolysis of a three-membered heterocyclic ring [41].

Carbonyl ylides were the first, and remain the most prolific, form of 1,3-dipole formed using rhodium(II) catalysis [27]. This is due, in part, to their ease of formation and the utility of the oxygen-containing dipole cycloaddition product (*vide infra*). In addition, by changing the character of the carbonyl group that interacts with the rhodium carbenoid, the nature of the dipole and subsequent product formation can vary widely [42]. Examples include the cycloaddition with aldehydes [43] and their generation from diazo imides [44]. The isomünchnones, which can be considered a subclass of carbonyl ylides, have also been described [45, 46] and widely explored [47]. Specific examples include bimolecular cycloaddition [48], cycloaddition with heteroatomic $\pi$-systems [49], and the formation of polyheterocyclic ring systems [50]. The intramolecular cycloaddition of isomünchnones **13** [51, 52] has yielded a number of complex polyheterocyclic and multibridged ring systems (Eq. 1) [53]. Thiocarbonyl ylides **15** are particularly valuable since

they can be used to form thiol-containing heterocycles (Eq. 2) [54, 55], as well as molecules without sulfur following thermal extrusion [56]. The formation of oxiranes and dihydrofurans utilizing ylides possessing pendant functional groups that enhance reactivity, such as vinylcarbonyl ylides, has also been explored [57].

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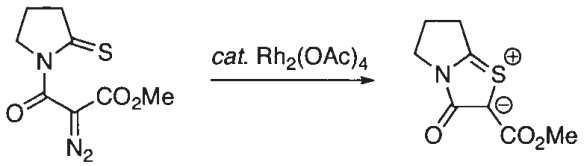
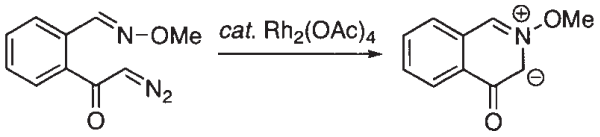



14 15 (2)

In addition to the carbonyl and thiocarbonyl ylides, additional rhodium(II)-generated 1,3-dipoles have been described such as the azomethine ylide **17**, which can generate a rich ensemble of nitrogen-containing hetero- and polyheterocycles (Eq. 3) [58–62]. The oxonium [63] and ammonium ylides **19** [64, 65] have been used to generate a number of heterocyclic ring systems (Eq. 4), and are the subject of a 2002 review [66]. In some cases, the decomposition of an $\alpha$-diazo ketone containing an amide can access either a carbonyl or ammonium ylide [67]. Rhodium(II)-generated nitrile ylides **21**, normally acyl-substituted, can be a convenient source of both pyrroles and oxazoles (Eq. 5) [68, 69].

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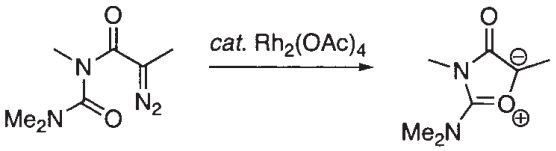


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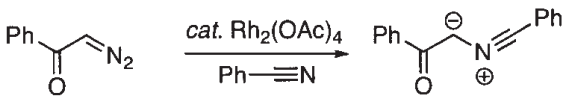



20 21 (5)

1,3-Dipoles can also be generated from rearrangements that take place after the formation of an initial rhodium carbenoid product [40, 70, 71]. One example of this type of transmutation, also known as a dipole cascade process, involves the formation of an azomethine ylide *via* the initial formation of a carbonyl ylide [72]. This process was

successfully applied to other systems such as diazo ketoamides [73, 74], diazo-substituted pyrrolidines [60], and 2-diazo-3-oxobutanoates [59] to form a variety of hetero- and polyheterocyclic systems. Dipoles have also been generated from rearrangement reactions to give aromatic heterocycles [75], *N*-acylium ions [71], and hydroxypyridones [76]. More recently, Doyle has reported the conversion of epoxides and aziridines, formed *via* a rhodium(II)-mediated cyclopropanation, to 1,3-dipoles [41, 77].

## 19.2
## Chemical Aspects of Rhodium-Mediated 1,3-Dipolar Cycloaddition

### 19.2.1
### Aspects of Rhodium(II) Catalysis that Affect Chemoselectivity

The potential for ligand-induced chemoselectivity of rhodium(II)-mediated carbenoid transformations is one of the primary factors in the selection of this catalyst which has resulted in its widespread utilization [9]. A major concern for 1,3-dipolar cycloaddition reactions is that dipole formation takes place over other potential reaction pathways such as insertion or cyclopropanation. Once the dipole has formed, however, the role of the rhodium metal is not clear. Thus the catalyst and reaction conditions employed must be optimized for each molecular system investigated. As described previously, dipoles have the ability to eliminate [19] or rearrange [71] in order to form a more stable species, and the inductive effect of rhodium on the dipole will depend on its tendency to undergo dissociation from this complex. In some cases, suppression of unwanted dipole reactivity, such as elimination, can be avoided by an alternative design of the dipole substituents [78]. Undesired rhodium carbenoid-based reactivity is more difficult to suppress, since this reactivity can occur with a pendant C–H, a group that would not normally be considered reactive under most experimental conditions. Early reports suggested that the tendency toward dipole formation and cycloaddition was dependent on the electrophilicity of the rhodium carbenoid intermediate [79]; however, conformational control of selectivity can dominate product distribution [63, 80]. One of the first investigations of controlled rhodium ligand chemoselectivity demonstrated that, within equal conformational constraints, the perfluorinated acetates, such as rhodium(II) perfluorobyturate [$Rh_2(pfb)_4$], prefer insertion over cyclopropanation and cyclopropanation over carbonyl ylide formation. Alternatively the acetamide catalysts, for example rhodium(II) caprolactam [$Rh_2(cap)_4$], prefer cyclopropanation and carbonyl ylide formation over insertion, while the alkyl acetates, such as rhodium(II) acetate [$Rh_2(OAc)_4$], are capable of forming each of the potential products equally [81, 82].

While the perfluorinated acetates do prefer insertion, they are still capable of forming 1,3-dipoles and have demonstrated interesting effects on the regioselectivity of intramolecular cycloaddition reactions, presumably through Lewis acid-mediated effects on the dipolarophile [83]. Other chemoselectivity effects have been noted in the intramolecular cycloaddition reactions and may or may not be partially induced by conformation and sterics [84]. It was further demonstrated that, when possible, O–H insertion is the predominant outcome over other types of insertion for rhodium(II)–carbenes, independently of the catalyst. However, cycloaddition reactions have been demonstrated to be ligand-dependent [85].

The perfluoroacetamide catalysts, rhodium(II) trifluoroacetamidate [$Rh_2(tfm)_4$] and rhodium(II) perfluorobutyramidate [$Rh_2(pfbm)_4$], are interesting hybrid molecules that combine the features of the amidate and perfluorinated ligands. In early studies, these catalysts were shown to prefer insertion over cycloaddition [30]. They also demonstrated a preference for oxindole formation *via* aromatic C–H insertion [31], even over other potential reactions [86]. In still another example, rhodium(II) perfluorobutyramidate showed a preference for aromatic C–H insertion over pyridinium ylide formation, in the synthesis of an indole nucleus [32]. Despite this demonstrated propensity for aromatic insertion, the perfluorobutyramidate was shown to be an efficient catalyst for the generation of isomünchnones [33]. The chemoselectivity of this catalyst was further demonstrated in the cycloaddition with ethyl vinyl ethers [87] and its application to diversity-oriented synthesis [88]. However, it was demonstrated that while diazo imides do form isomünchnones under these conditions, the selectivity was completely reversed from that observed with rhodium(II) acetate [89, 90].

### 19.2.2
### Aspects of Rhodium(II) Catalysis that Affect Regio- and Diastereoselectivity

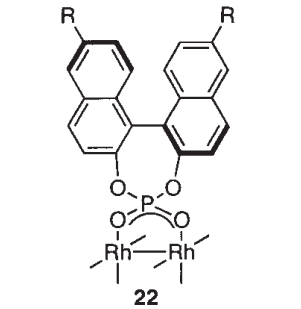
The regioselectivity of 1,3-dipolar cycloaddition reactions is largely controlled by the electronic/orbital nature of the dipole and dipolarophile [1], and is not affected by changes to the rhodium ligands [9]. Diastereoselectivity is achieved by controlling the orientation of the dipolarophile as it approaches the dipole, resulting in either an *exo*- or *endo*-cycloaddition product [47]. In the case of intramolecular cycloadditions, in the absence of electronic effects, the *exo*/*endo* ratio is mainly controlled by steric factors [49, 91, 92]. In the case of intermolecular cycloaddition reactions with electron-deficient dipolarophiles, low selectivities are observed and the *exo*/*endo* ratios are largely case-dependent [47, 87]. Interestingly, the intermolecular cycloaddition of electron-rich dipolarophiles with mesoionic dipoles provides exclusively the *endo*-cycloaddition product [87]. There is little evidence that the rhodium(II) catalyst plays a role in the *exo*/*endo* selectivity; however, it has been reported that addition of 10 mol% ytterbium triflate [$Yb(OTf)_3$] to a rhodium(II)-mediated 1,3-dipolar cycloaddition reaction with *N*-substituted maleimides produced cycloadducts with high *endo*-selectivity [93]. *Exo*/*endo* selectivity does seem to be dipolarophile-dependent, since the same additive led to a high level of *exo*-selectivity with aromatic aldehydes [94]. In both cases no selectivity was observed in the absence of the rare earth metal complex.

### 19.2.3
### Aspects of Rhodium(II) Catalysis that Affect Facial Selectivity

There have been two main approaches to the development of dipolarophile facial selectivity: (1) the use of chiral substrates, templates, and auxiliaries; and (2) the use of chiral rhodium catalysts [35]. In one of the earliest examples of chiral substrate selectivity, Pirrung and Lee reported a selective hydroxy-directed cycloaddition with chiral hydroxy-substituted vinyl ethers [95]. This effort was followed by a number of chiral template approaches to diastereocontrol, including the use of (*R*)- or (*S*)-phenylglycinol to form a cyclic phenyloxazinone for the facially selective cycloaddition of isomünchnones [96, 97]. Padwa and Prein demonstrated acyclic diastereofacial control in the cycloaddi-

tion of isomünchnones, using *N*-substituted *α*-diazo imides based on amino acids [98]. Most recently, Savinov and Austin have reported the modular design of a chiral template that can be easily cleaved, allowing the chiral group to function as an auxiliary for isomünchnone cycloadditions [99] and as a selective cleavage reagent in solid-phase organic synthesis [88].

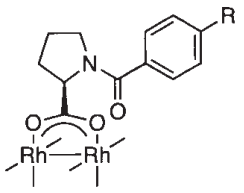
Despite the potential dissociation of the rhodium(II) metal from newly formed dipoles, a number of the chiral rhodium(II) catalysts have been developed that demonstrated the ability to induce enantioselectivity in 1,3-diploar cycloaddition reactions (**22–34**) [11, 35, 100, 101]. One of the earliest examples of a chiral rhodium(II)-induced enantioselective cycloaddition was described by Pirrung and Zhang [102] using a novel bisnaphtholphosphate ligand-containing catalyst **22** in the construction of the dihydrofuro[2,3-*b*]furan ring system. Ishitani and Achiwa later applied chiral *N*-benzoylpyrrolidine carboxylate catalysts **23** to the same transformation, with enantioselectivities ranging from 93 to 98% [103]. Moody described the development of new chiral phthalate ester- and pyrrole-based catalysts, and their application to the formation of oxonium ylides, which subsequently undergo sigmatropic rearrangement [100]. Hodgson [104] applied chiral induction in an intramolecular cycloaddition of a carbonyl ylide using Davies' [105] chiral *N*-arylsulfonyl prolinate rhodium(II) catalyst **24**. Other chiral catalysts were later applied to this [106, 107] and other systems [101, 108–111], with enantioselectivities of up to 92% being achieved. Hashimoto developed the *N*-phthaloyl-(*S*)-amino acid-based chiral dirhodium catalysts **28** and **29**, which have been successfully used in the enantioselective 1,3-dipolar cycloaddition of carbonyl ylides to obtain enantioselectivities of up to 93% [112, 113]. Davies has reported an asymmetric [3+2]-cycloaddition for the formation of cyclopentenes [114].



**22**

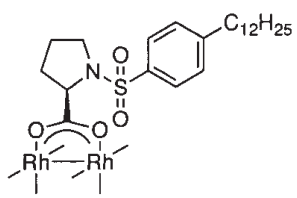
R = H $Rh_2$(*R*-BNP)$_4$

R = $C_{12}H_{25}$ $Rh_2$(*R*-DDBNP)$_4$



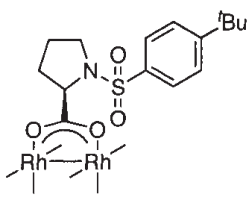
**23**

R = H, OMe, $NMe_2$, F, $CF_3$



**24**

$Rh_2$(*S*-DOSP)$_4$



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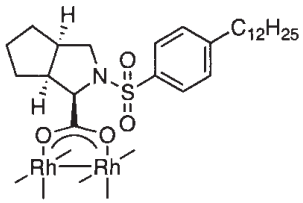
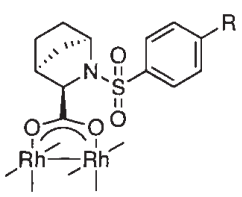
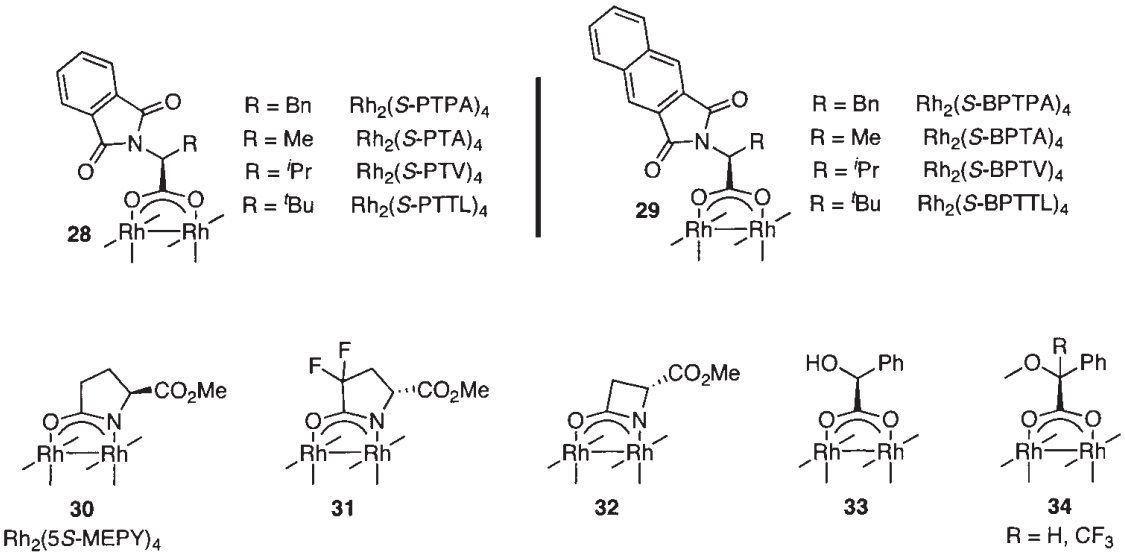


**26**



**27**

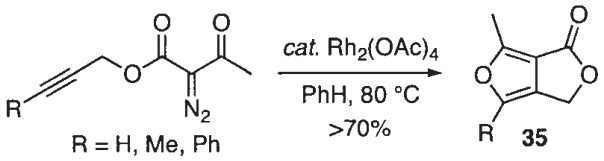
R = $^t$Bu, $C_{12}H_{25}$




## 19.3
## Applications of Rhodium(II)-Mediated 1,3-Dipolar Cycloaddition

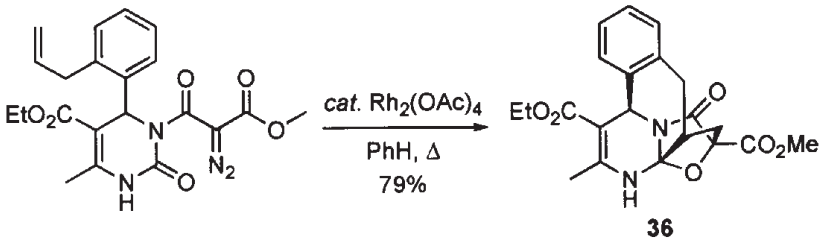
### 19.3.1
### Heterocyclic Synthesis and Novel Ring Systems

One of the earliest uses for rhodium(II)-catalyzed dipoles was demonstrated in Davies' furan synthesis [22]. Isomünchnones were also shown to produce substituted furans [115]. Additional furan syntheses have been described using silylacetates [116], unsaturated esters [117], and fluoroalkyl diazo acetates [118]. The synthesis of furofuranones and indenofuranones **35** from *α*-diazo ketones having pendant alkynes has also been reported (Eq. 6) [119]. Other fused heterocyclic systems include furo[3,4-*c*]furans [120, 121] furo[2,3-*b*]furans [122] as well as thiobenzofurans [123], and benzoxazoles[124] have also been synthesized with this methodology.




(6)

Additional heterocyclic ring systems, such as benzofurans [125], dihydropyrroles and dihydroazepines [41], piperidines and dihydropyrimidines **36** [126], and fused oxazole derivatives [127], have been described (Eq. 7). The formation of epoxides and aziridines, formally emanating from ylides, was recently reported by Doyle *et al.* [77]. Rhodium(II)-catalyzed isomünchnone cycloaddition followed by Lewis acid-mediated ring opening has been used as an entry into the protoberberine azapolycyclic ring structure [128].

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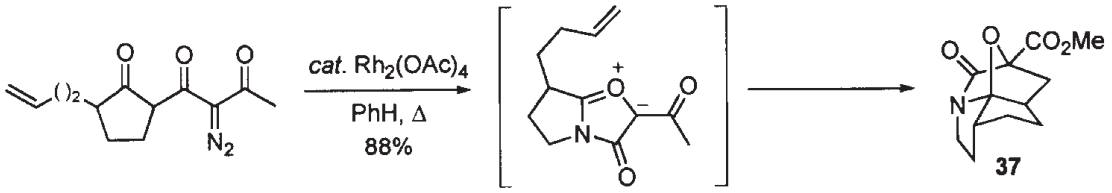


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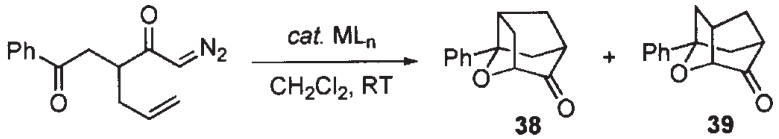
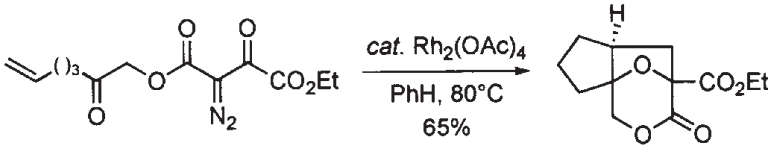



38 39

| $ML_n$ | | | |
|---|---|---|---|
| | $Rh_2(OAc)_4$ | 10% | 47% |
| | $Rh_2(tfa)_4$ | 34% | 12% |
| | $Rh_2(cap)_4$ | 12% | 52% |

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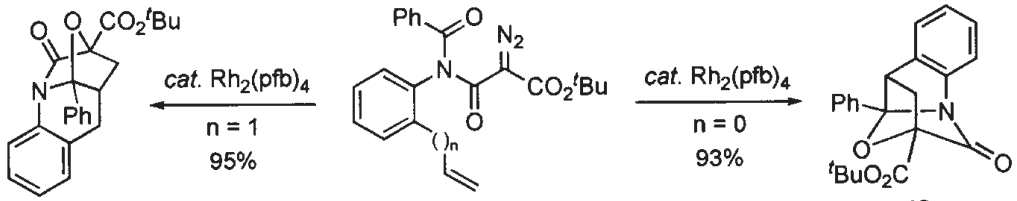
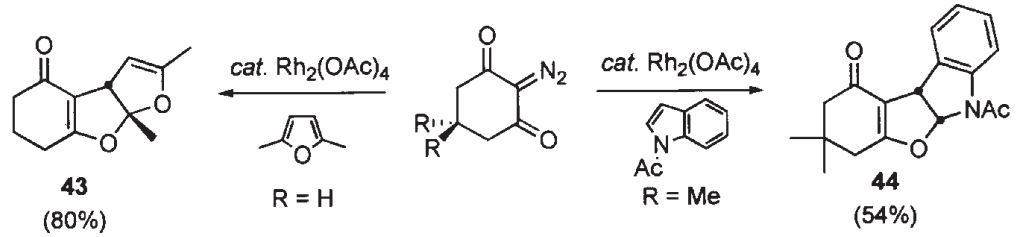



41 42

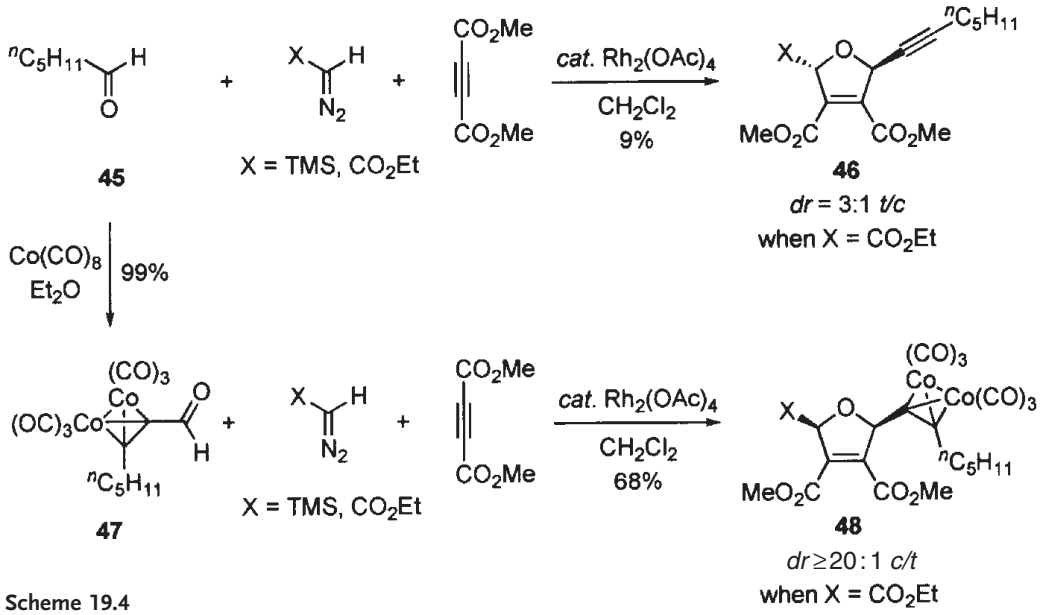



43 (80%) 44 (54%)

Scheme 19.3

A number of bridged heterocyclic compounds have been prepared using the intramolecular cycloaddition of rhodium(II)-generated isomünchnones [51–53, 84, 129], as exemplified by the complex structure **37** [49, 53] and the tricyclic derivatives **38** and **39** (Scheme 19.3) [92]. In addition, several oxabicyclic **40** [43, 67, 79] and azaoxabicyclic systems **41** and **42** [44, 50] have been reported. Other complex ring systems have also been described, such as oxathioles and oxazolones [130], spiro-oxo molecules [129], oxatricyclic compounds [131], and spiroxindole like structures [132–135]. The synthesis of fused ring structures **43** and **44** via the cycloaddition with quinone and quinone-like dipolarophiles was independently described by Pirrung [75, 136, 137], Muthusamy [138, 139], and Nair [140]. Stereoselective studies have generated *syn*-facial bridged norbornane structures [141, 142].

A rhodium-mediated carbonyl ylide approach to di- and tetrahydrofurans (Scheme 19.4) has been reported [143]. Interesting substrate-based selectivity was demonstrated with the dipolarophiles **45** and **47** in the carbonyl ylide cycloaddition to afford **46** and **48**, wherein different selectivities and efficiencies were achieved, based on the presence or absence of the cobalt complex.

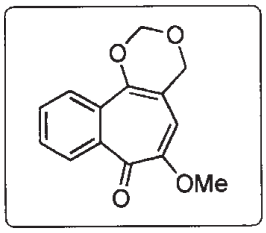



**Scheme 19.4**

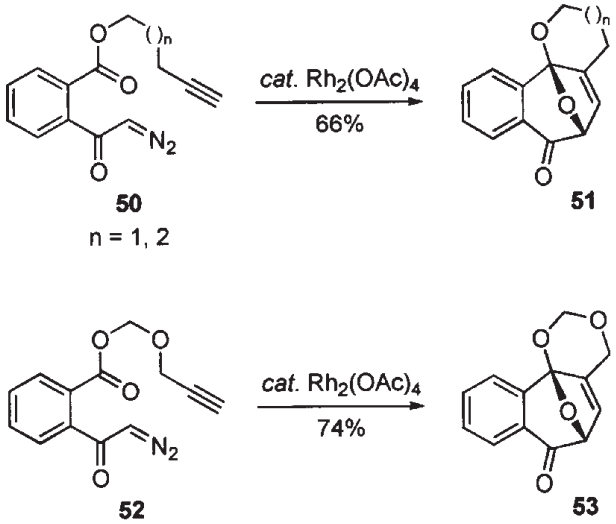
### 19.3.2
### Natural Product Synthesis and Core Structures

Perhaps the most intriguing aspect of rhodium(II)-mediated 1,3-dipolar cycloadditions is the plethora of natural products and natural product core structures that have been accessed using this methodology. A dipolar cycloaddition approach to the fungal metabolite benzotropolone **49** was first put forward by Plüg and Freidrichsen [144] using an intramolecular cycloaddition of a carbonyl ylide containing a terminal alkyne **50** to afford **51** (Scheme 19.5). Baldwin later used this methodology for the construction of the tropolone precursor **53**, in his biomimetic approach to the natural products pycnidione and epolone B [145].

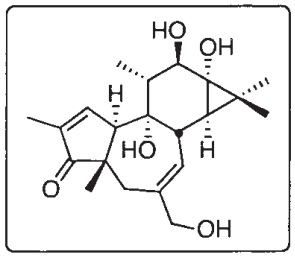
A carbonyl ylide approach to the tigliane natural product phorbol **54** was demonstrated by Dauben, in which a convergent intramolecular cycloaddition was used to



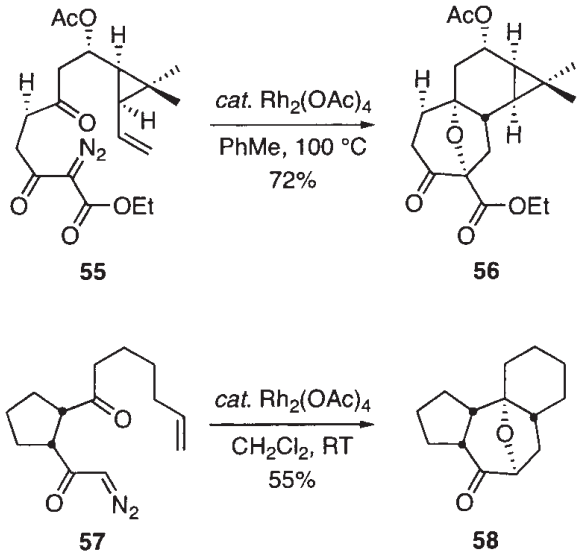

Benzotropolone **49**




Scheme 19.5



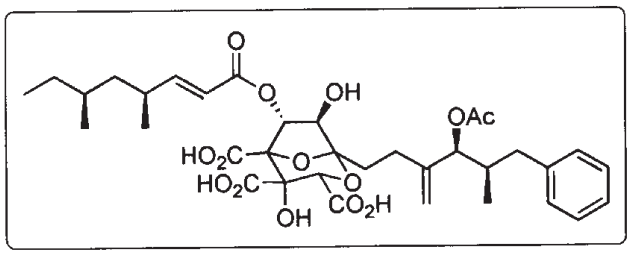

Phorbol **54**



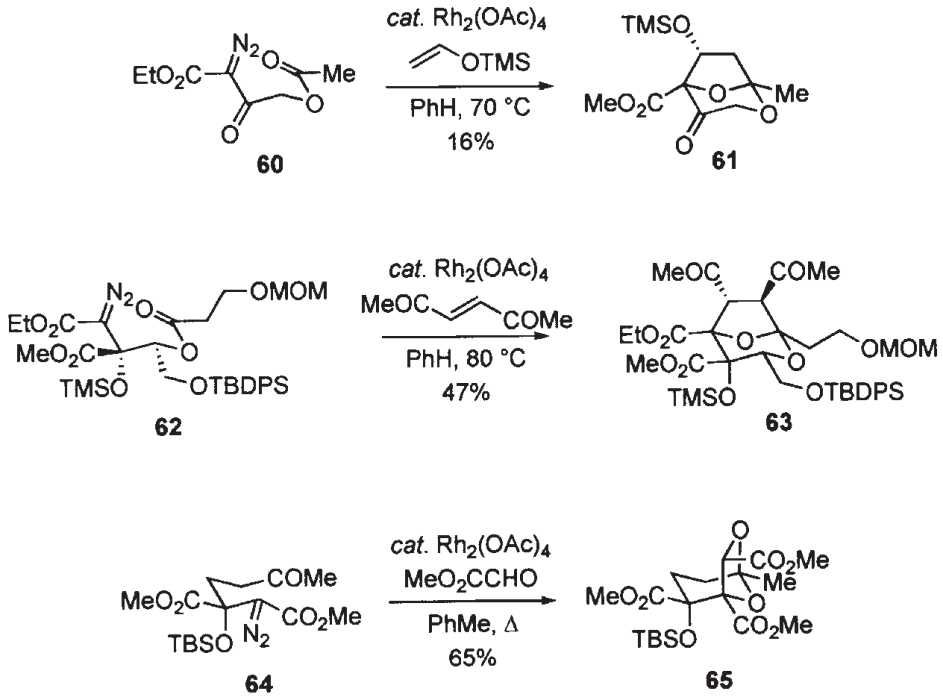

Scheme 19.6

form the oxo-bridged BCD-ring system **56** (Scheme 19.6) [146]. McMills built upon this approach with the construction of the oxo-bridged species **58**, from the diazo ketone **57**, to install the ABC rings of phorbol **54** [147].

Zaragozic acid A **59** is perhaps the most complex ring structure that has been attempted with the 1,3-dipolar cycloaddition reaction (Scheme 19.7). Koyama [148] reported the first approach using **60** with a silyl vinyl ether as the dipolarophile to furnish the requisite skeleton **61**, albeit in low yield. Hashimoto and co-workers [149] used a similar carbonyl ylide route, in which **62** was employed to generate the core **63** in their second-generation approach to this molecule. Hodgson also reported a carbonyl ylide pathway to the zaragozic acids [150], but disconnected the ring system in order to take advantage of its inherent chirality, in the intermolecular reaction of **64** with methyl glyoxalate to furnish **65** [151, 152].

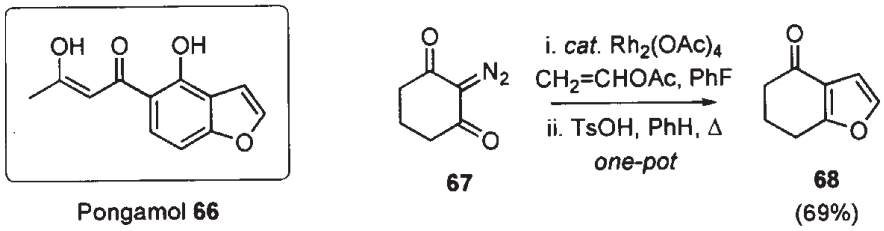


Zaragozic Acid A **59**



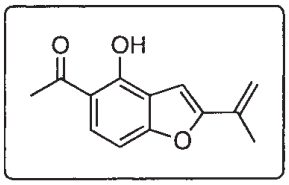

**Scheme 19.7**

Pirrung [153] has described the synthesis of (±)-pongomol **66** via the rhodium(II)-mediated reaction of the diazacyclohexane dione **67**, to afford the fused bicyclic ketone **68** (Scheme 19.8). Moreover, this group [154] also detailed a similar approach in their synthesis of (±)-isoeuparin **69** (Scheme 19.9). Pirrung and Lee [155] expanded their rhodium(II)-mediated dihydrofuran cycloaddition strategy, for the conversion of the

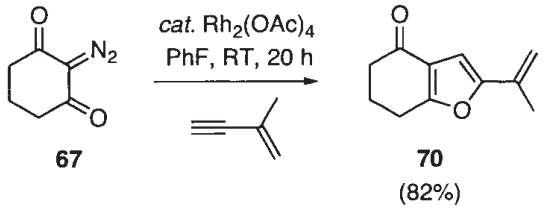



Pongamol **66**

**Scheme 19.8**

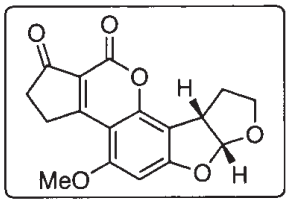


Isoeuparin **69**

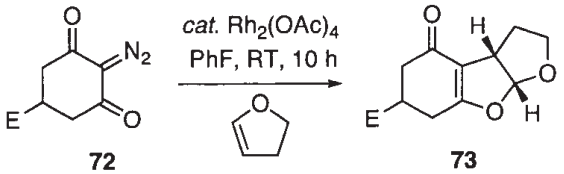



**67** → **70** (82%)

**Scheme 19.9**

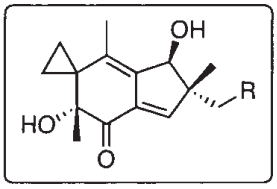


Aflatoxin $B_2$ **71**

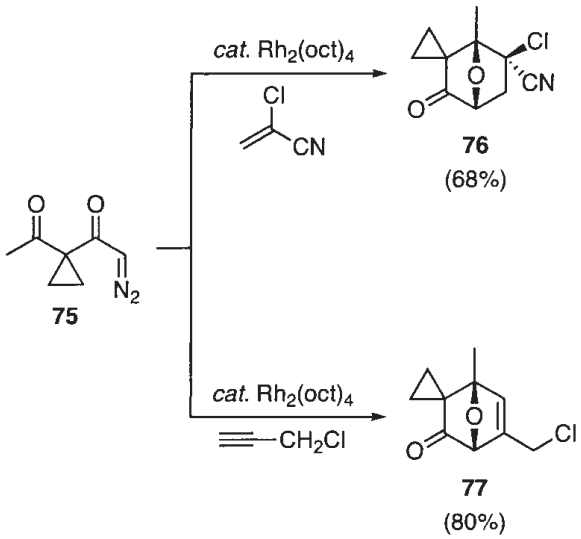



**72** E = $CO_2Me$ → **73** (75%)

**Scheme 19.10**

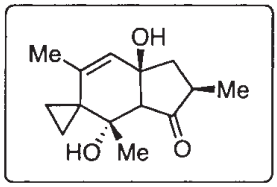


Illudin M (R=H)
Illudin S (R=OH) } **74**

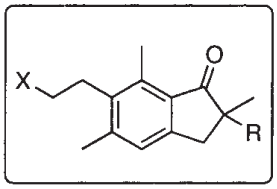



**75** → **76** (68%)

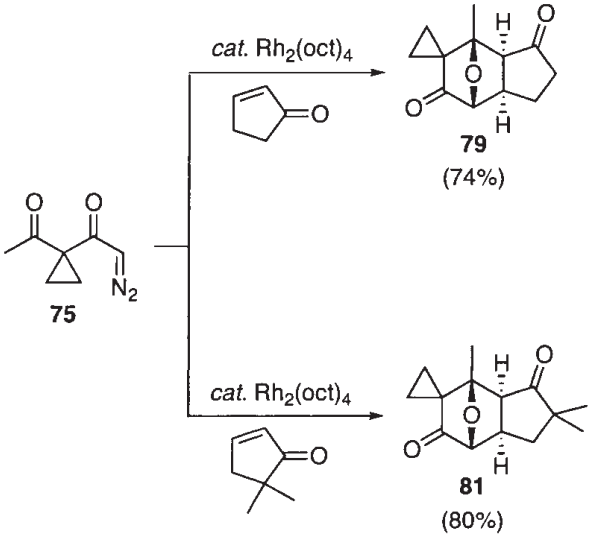
**75** → **77** (80%)



Ptaquilosin **78**



Pterosins **80**
(R=H, Me ; X=OH,OMe,Cl)



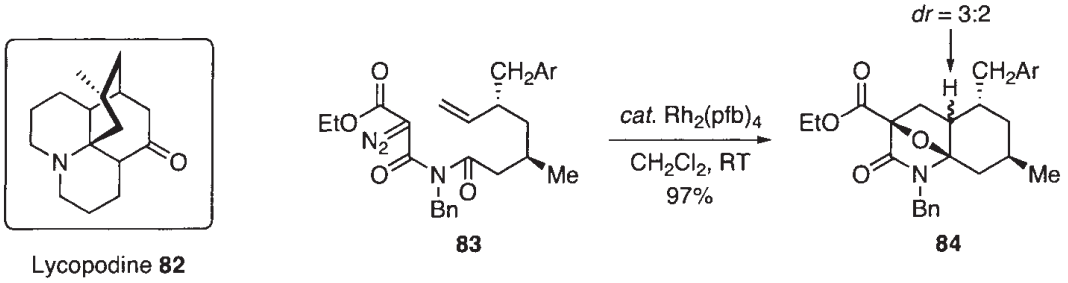

**75** → **79** (74%)

**75** → **81** (80%)

**Scheme 19.11**

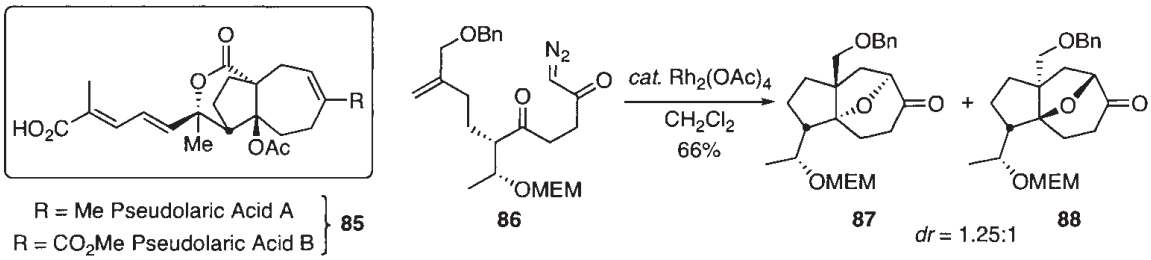
diazo $\beta$-diketone **72** to the tricyclic ketone **73**, for a formal total synthesis of the natural product (±)-aflatoxin $B_2$ **71** (Scheme 19.10).

Padwa has reported a 1,3-dipolar cycloaddition approach to the illudin **74** and ptaquilosin **78** family of natural products (Scheme 19.11) [156]. Shortly thereafter, Kinder and Bair reported the total synthesis of illudin M using a similar approach [157]. Further studies demonstrated the versatility of this approach for the construction of the spirocyclic cores **76** and **77**, applicable to the natural products, from the common diazo ketone **75** [158, 159]. The 1,3-dipolar cycloaddition was also demonstrated for pterosin **80** [160] and the pterosin family [161]. McMorris [162] used this approach to the illudin ring system in order to synthesize a number of acylfulvene derivatives with potential antitumor activity. In addition, Pirrung and Kaliappan demonstrated the cycloaddition with *p*-quinones as an entry into this system [137]. The synthesis of the erythrinane ring system *via* a sequential dipolar cycloaddition of an isomünchnone followed by a Lewis acid-induced Mannich cyclization has been described [163]. An isomünchnone approach to the (±)-lycopodine precursor **84** was also outlined (Scheme 19.12) [164]. Lysergic acid has been the subject of a isomünchnone synthetic approach by Padwa [165], and Moody [166] has described the synthesis of dehydrogliotoxin analogs *via* thioisomünchnone intermediates.



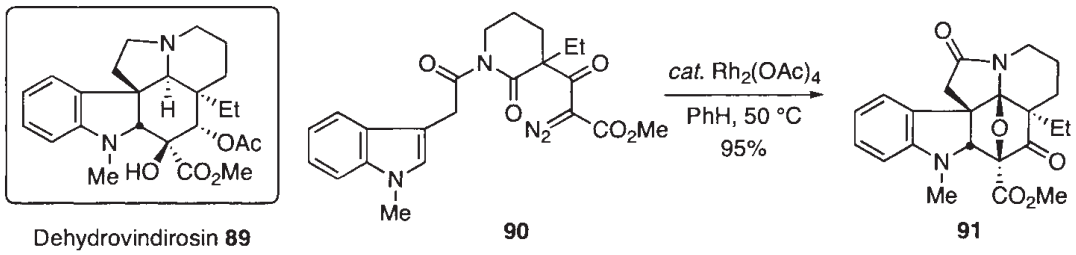

**Scheme 19.12**

In more recent work, Chiu and co-workers [167, 168] have reported an intramolecular 1,3-dipolar cycloaddition approach toward the pseudolaric acids **85**, in which the dipolarophile is an unactivated 1,1-disubstituted alkene. Hence, treatment of the diazo ketone **86** with catalytic $Rh_2(OAc)_4$ furnished a mixture of tricyclic products **87** and **88** in nearly equal proportions (Scheme 19.13). The synthesis of 2-pyridones [169] and their application to the ipalbidine core [170] has been described. The pentacyclic skeleton of the aspidosperma alkaloids was prepared *via* the cycloaddition of a push–pull carbonyl ylide [171]. The dehydrovindorosine alkaloids **89** have also been investigated, in which the $\alpha$-diazo-$\beta$-ketoester **90** undergoes a facile cycloaddition to furnish **91** in



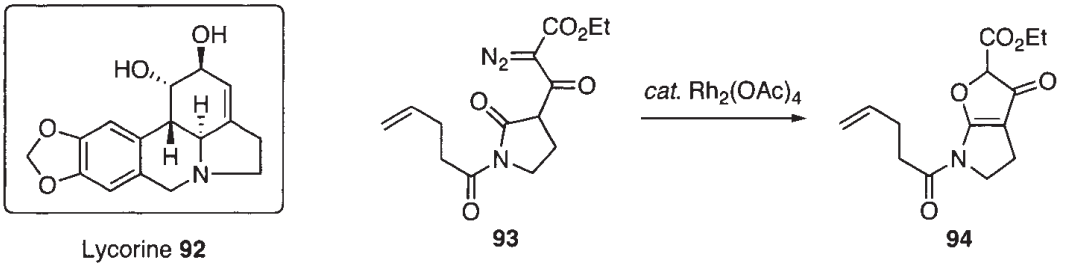

**Scheme 19.13**

95% yield (Scheme 19.14) [172]. Kissel and Padwa [173] have utilized the push–pull carbonyl ylide cycloaddition for the conversion of the $\alpha$-diazo-$\beta$-ketoester **93** to the bicyclic heterocycle **94**, which represents a key intermediate in their approach toward the lycorine ring structure **92** (Scheme 19.15). Angiotensin-converting enzyme (ACE) inhibitor A58365A **95** and related 2-pyridones can be synthesized *via* isomünchnone intermediates, as exemplified by the conversion of **96** to **97** (Scheme 19.16) [169].



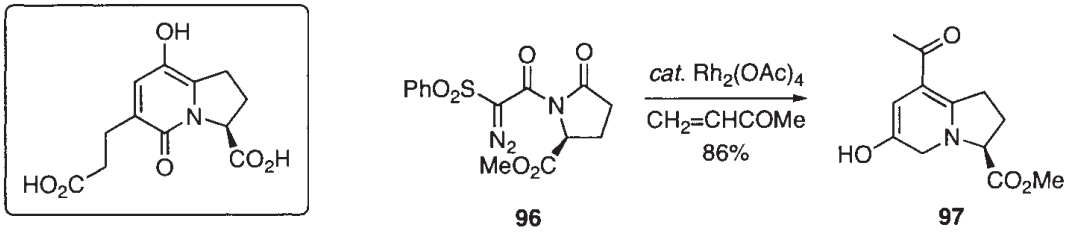

Dehydrovindirosin **89** — **90** — **91**

**Scheme 19.14**



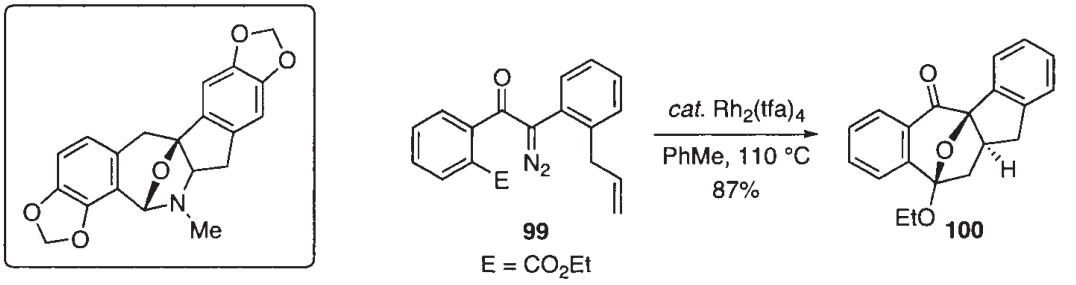

Lycorine **92** — **93** — **94**

**Scheme 19.15**




A58365A **95** — **96** — **97**

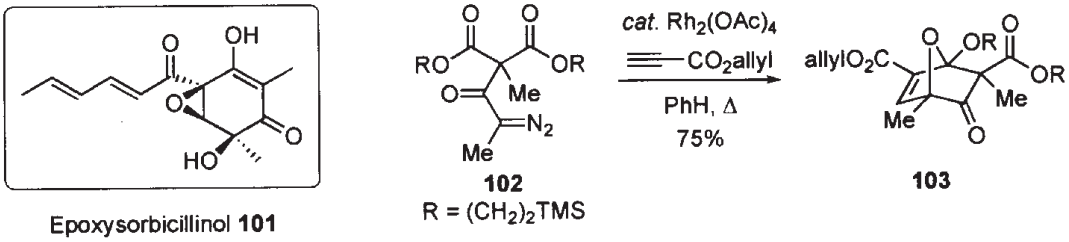
**Scheme 19.16**




Ribasine **98** — **99** — **100**

**Scheme 19.17**

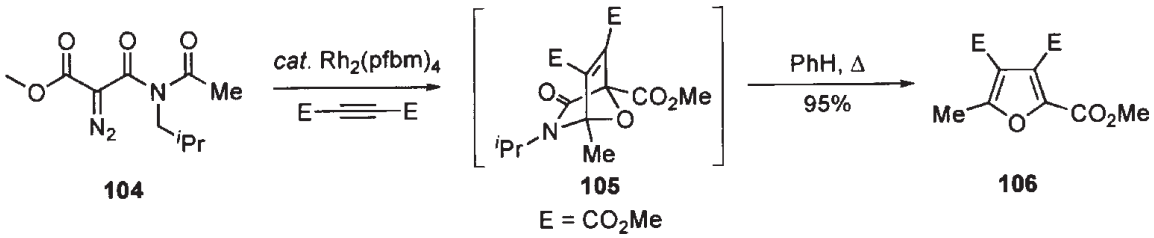
Padwa has reported an approach to the ring system of the ribasine alkaloids **98** [174], using an intramolecular 1,3-dipolar cycloaddition of the $\alpha$-diazo ketone **99** to produce the pentacyclic skeleton **100** (Scheme 19.17). Wood [175] used an intermolecular 1,3-dipolar cycloaddition of a carbonyl ylide for the total synthesis of (±)-epoxysorbicillinol **101** (Scheme 19.18). The key cycloaddition in this approach is the conversion of **102** to the natural product core **103**, which sets the substitution pattern around the entire ring system in a single step.




Scheme 19.18

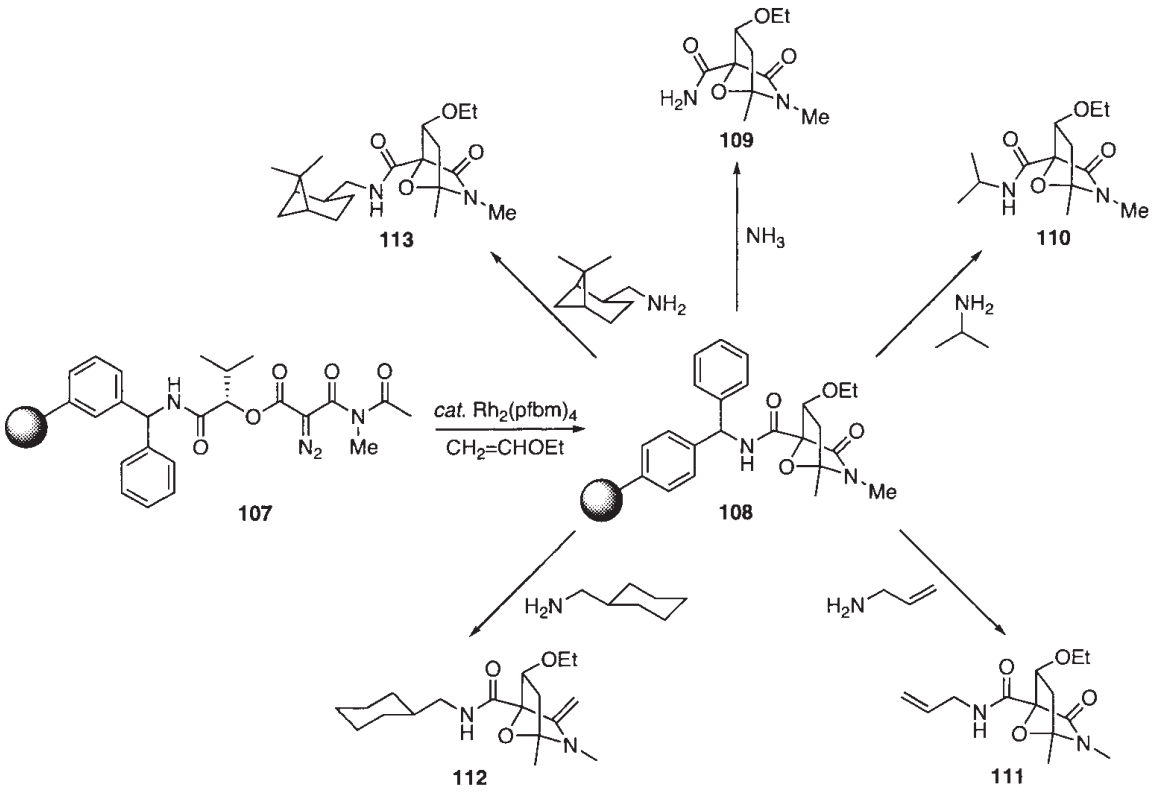
### 19.3.3
### Combinatorial Chemistry and Solid-Phase Organic Synthesis

The isomünchnone cyclization/isocyanate cycloreversion process for substituted furan synthesis has been well studied, as exemplified by the conversion of **104** to **106** (Scheme 19.19). In a solid-phase adaptation of this transformation, two groups independently utilized this reaction to establish a traceless self-cleaving method for the synthesis of substituted furans [176, 177]. Further investigation of the thermal requirements of this cycloreversion led to its application in the split-pool synthesis of a small library of amides [178].




Scheme 19.19

The solid-phase synthesis of bridged bicyclic molecules **109–113**, based on the *endo*-selective cycloaddition of ethyl vinyl ethers with the isomünchnone [87] derived from **107** has also been reported [88]. In addition to good yields and high diastereofacial selectivity imparted through the use of a chiral auxiliary [99], the authors reported the ability to selectively cleave the cycloadduct **108** from the solid support through treatment with nucleophilic amines (Scheme 19.20). This result is based on the lability of the ester linkage between the bicyclic ring and the auxiliary. This dipolar synthetic approach to bicycles was further demonstrated in the construction of a small panel of adenosine mimics [179].




**Scheme 19.20**

## 19.4 Conclusion

The ability to produce 1,3-dipoles, through the rhodium-catalyzed decomposition of diazo carbonyl compounds, provides unique opportunities for the accomplishment of a variety of cycloaddition reactions, in both an intra- and intermolecular sense. These transformations are often highly regio- and diastereoselective, making them extremely powerful tools for synthetic chemistry. This is exemplified in the number of applications of this chemistry to the construction of heterocyclic and natural-product ring systems. Future developments are likely to focus on the enantioselective and combinatorial variants of these reactions.

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