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Intramolecular cycloaddition of carbonyl ylides as a strategy for natural product synthesis

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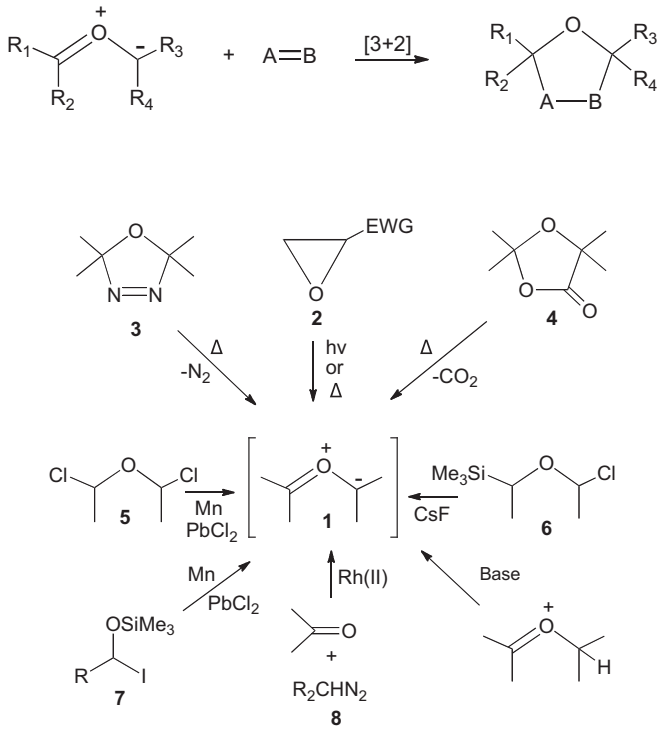
1. Introduction

Due to their common occurrence in nature,[1] oxygen containing heterocycles are frequent and important targets for synthesis either as final products or as useful synthetic intermediates. Of particular importance is the tetrahydrofuran ring[2] since this structural unit is found in many naturally occurring compounds.[3] Although the synthesis of tetrahydrofurans commonly proceeds via C–O bond formation,[3] the application of C–C bond forming reactions to construct this ring has also been used in recent years.[4] Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for the construction of tetrahydrofurans.[5] Common methods for carbonyl ylide generation (Scheme 1) involve the thermolysis or photolysis of epoxides possessing electron-withdrawing substituents,[6–9] the thermal extrusion of nitrogen from 1,3,4-oxadiazolines[10–12] and the loss of carbon dioxide from 1,3-dioxolan-4-ones.[13] Simple carbonyl ylides can be produced by a silicon-based 1,3-elimination under mild and neutral conditions[14] and also be fabricated by treating 1-iodoalkyl trialkylsilyl ethers with both SmI_2[15] and a manganese–$PbCl_2$–Me_3SiCl combination.[16]



Scheme 1. Various methods utilized to generate the carbonyl ylide dipole.

The creation of carbonyl ylides from the reaction of diazo compounds with ketones in the presence of Rh(II) catalysts,[17–19] has significantly broadened their applicability for natural product synthesis.[20–22] The ease of the generating the dipole, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereochemical control of the subsequent [3+2]-cycloaddition, and the fair predictability of its regiochemistry have contributed to the popularity of the reaction.[23] When the reacting components are themselves cyclic or have ring substituents, complex multicyclic arrays, such as those contained in drugs and natural products, can be constructed in a single step.

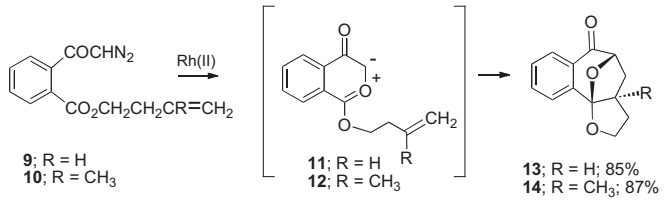
During the past 2 decades, interest in the intramolecular 1,3-dipolar cycloaddition reaction of carbonyl ylides for the synthesis of oxygen as well as nitrogen containing heterocycles has increased exponentially.[24] The primary spatial requirement for the intramolecular 1,3-dipolar cycloaddition is that the distance between the two reacting centers should be sufficiently short so that effective three center overlap of the dipole with the dipolarophile can occur. Moreover, the atoms of the dipolarophile should be arranged in such a way as to allow their π-orbitals to lie in a plane parallel to the plane of the dipole for intramolecular cycloaddition to proceed. An analysis of various transition-state conformers represents a standard method for predicting product outcome and evaluating relative merits of competing reaction pathways. This is particularly true in intramolecular cycloaddition chemistry where issues of regio- and stereochemistry are determined by subtle conformational factors. The relative importance of the two stereochemical pathways, *exo* and *endo*, is often apparent from the ratio of cis and trans fused cycloadducts. The distribution of diastereomeric products obtained from intramolecular 1,3-dipolar cycloaddition reactions of carbonyl ylides can be nicely correlated with stabilities of boat-chair conformers as calculated by molecular mechanics.[25] Converting olefin geometry into the stereochemistry of saturated carbon combined with forming two rings simultaneously from acyclic precursors certainly accounts for the popularity of this approach. The additional intramolecular advantages gained due to entropy, reactivity and diastereoselectivity help explain the explosive growth of this [3+2]-cycloaddition reaction for the synthesis of natural products. In this report, the intramolecular cycloaddition of carbonyl ylides with π-systems as a general method for the formation of natural products is described. While the discussion has been mostly restricted to examples that actually report the synthesis (or formal synthesis) of a specific natural product, also included is some of the methodology development to provide context for the regio- and stereoselectivity of the reactions.

2. Intramolecular cycloadditions of carbocyclic carbonyl ylides

2.1. Model studies

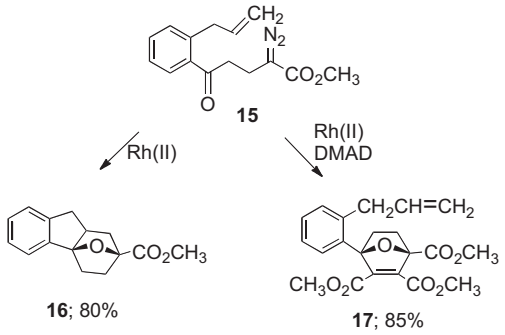
2.1.1. Cyclic six and five-membered ring carbonyl ylides. In 1986, the Padwa group described the first example where a cyclic six-membered ring carbonyl ylide, produced from the Rh(II)-catalyzed reaction of *o*-alkyl-2-enoxy-carbonyl-α-diazoacetophenone **9** (or **10**), underwent intramolecular cycloaddition with a C–C double bond suitably located within the molecule (Scheme 2).[26] The resulting cycloadduct **13** (or **14**) represents a multiply functionalized

rigid bicyclic system, which is capable of subsequent synthetic elaboration.



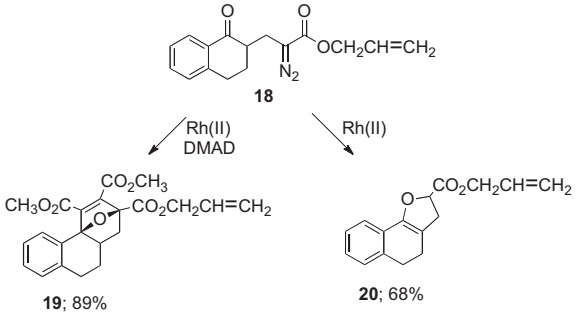
Scheme 2.

The intramolecular trapping of a five-membered ring carbonyl ylide dipole with a tethered alkene was subsequently reported by using α-diazo ketoester **15**.[27] Thus, treatment of **15** with Rh_2OAc_4 at 25 °C furnished cycloadduct **16** in 80% yield. When DMAD was added to the reaction mixture, it was possible to isolate the bimolecular adduct **17** in 85% yield (Scheme 3). Apparently, the intramolecular cycloaddition of the dipole to the unactivated π-bond is sufficiently slow to allow the carbonyl ylide to react exclusively with the more reactive acetylenic π-bond.



Scheme 3.

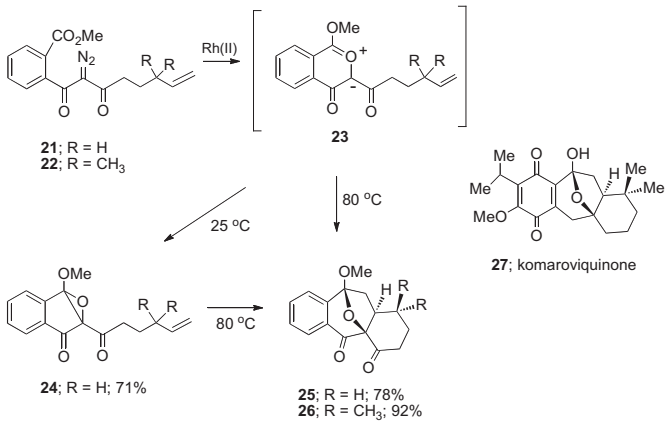
Attempts to carry out a related internal cycloaddition using a system where the tethered alkenyl group resided on the ester portion of the molecule were also carried out.[27] This led to a study the cycloaddition chemistry of diazo ketoester **18**. When the Rh(II)-catalyzed reaction of **18** was performed in the presence of DMAD, cycloadduct **19** was obtained in 89% yield. However, in the absence of any trapping agent, no internal cycloadduct could be detected. Instead, the only identifiable compound obtained from this reaction (68%) corresponded to dihydrofuran **20** (Scheme 4). The formation of **20** is best rationalized by a hydrogen shift of the initially produced dipole.[28,29] More than likely, the failure to trap the dipole is related to conformational factors. It is well recognized that the *Z*-conformers of esters are significantly more stable than the corresponding *E*-conformers.[30] In the *Z*-orientation, intramolecular



Scheme 4.

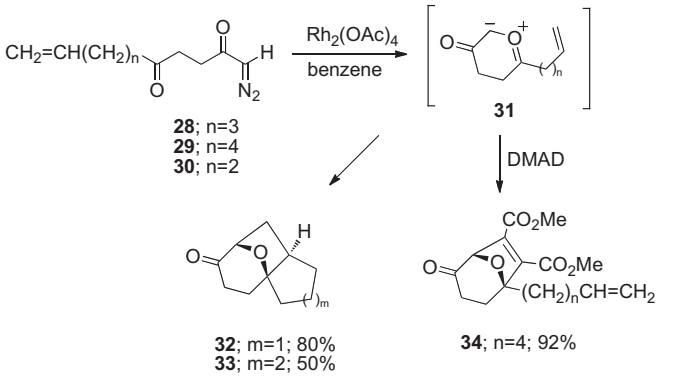
dipolar cycloaddition of the resulting carbonyl ylide cannot occur and instead the dipole collapses by means of a proton transfer to give enol ether **20**.

The rhodium(II)-catalyzed cyclization/cycloaddition cascade of *o*-carbomethoxy aryldiazo dione **21** was also investigated by the Padwa group[31] as a potential route to the oxatricyclo[6.3.1.$0^{0,0}$] dodecane substructure of the icetexane diterpene komaroviquinone **27**.[32] Surprisingly, the initially formed carbonyl ylide dipole **23** prefers to cyclize to give epoxide **24** at 25 °C. Further heating of epoxide **24** at 80 °C in benzene, however, furnished the dipolar cycloadduct **25**. This reaction presumably occurs by thermal C–C bond cleavage of the epoxide ring to regenerate carbonyl ylide **23**, which then undergoes a subsequent intramolecular [3+2]-cycloaddition across the tethered alkene to give **25**. The great majority of literature reports on carbonyl ylides are dominated by 1,3-dipolar cycloaddition reactions[32] rather than cyclization of the dipole to produce the oxirane ring system,[19a,c,33] so the formation of epoxide **24** is rather unusual with this particular system. The Rh(II)-catalyzed reaction of the related dimethyl substituted diazo ester **22** was also studied since this compound contained the appropriate substituent groups needed for a planned synthesis of komaroviquinone **27** (Scheme 5). The rate of an intramolecular reaction is often increased when alkyl groups are placed on a chain between the two reacting centers.[34,35] This is known as the *gem*-dialkyl effect and is often exploited to promote difficult cyclization reactions.[36] Indeed, the reaction of diazo dione **22** with a Rh(II) catalyst only gave cycloadduct **26** in 92% yield thus representing an efficient approach to the core skeleton of komaroviquinone.



Scheme 5.

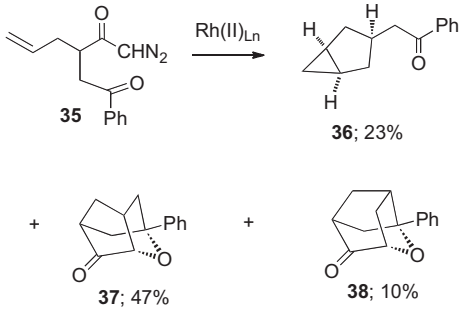
2.1.2. Variation in the tether length. Varying the length of the tether that separates the olefin from the carbonyl ylide dipole also allows for the synthesis of a variety of interesting oxopolycyclic ring systems. α-Diazoketones tethered to the carbonyl group by three methylene units were shown to cyclize most efficiently. For example, treatment of diazoketone **28** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate gave cycloadduct **32** in high yield.[37] In this case, the intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazoketone **29** was also treated with catalytic rhodium(II) acetate in benzene at 25 °C producing cycloadduct **33** in 50% yield. With this system, the carbonyl ylide was readily trapped with the added dipolarophile affording the bimolecular cycloadduct **34** as the exclusive cycloadduct (Scheme 6). Increasing the length of the tether to five methylene units gave no internal cycloadduct. Apparently, the π-bond is not in close enough proximity to the dipole centers to allow the cycloaddition to occur. α-Diazoketone **30**, which contains only two methylene units in the tether, produced none of the internal



Scheme 6.

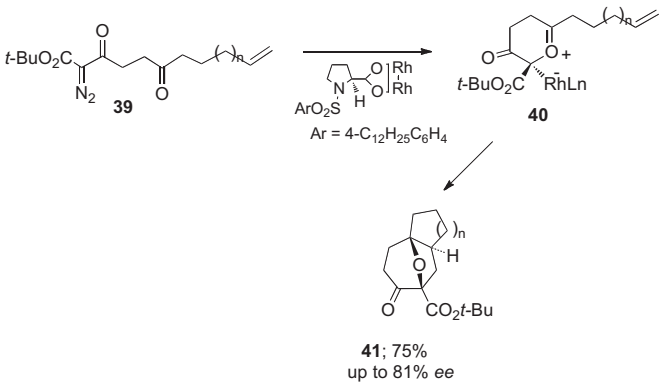
cycloadduct. Clearly the intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four methylene units.

2.1.3. Involvement of a metal associate dipole. Definitive support for the involvement of a metal associated carbonyl ylide dipole in these Rh(II)-catalyzed intramolecular cycloaddition reactions was obtained by carrying out a series of competition experiments using α-diazoketone **35** (Scheme 7).[38] Thus, a regiochemical crossover in the carbonyl ylide internal cycloaddition versus cyclopropanation was observed on changing the catalyst. The major regioisomer formed using $Rh_2(OAc)_4$ or $Rh_2(cap)_4$ (cap=caprolactamate) was found to be **37**. However, cycloadduct **38** was the predominant product formed under $Rh_2(tfa)_4$ (tfa=trifluoroacetate) catalysis. Intramolecular cyclopropanation (i.e., **36**) occurs to a considerable extent with all of the Rh(II) catalysts and is significantly enhanced using $Cu(acac)_2$ or $PdCl_2(PhCN)_2$. These results strongly suggest that the catalyst is coordinated with the dipole and this metal-complexed species is involved in the cycloaddition.



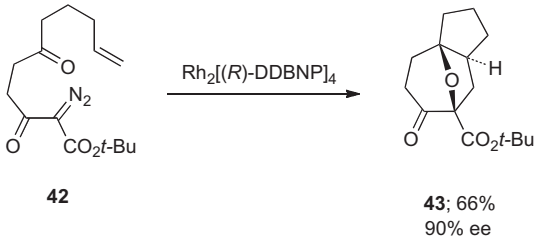
Scheme 7.

Once the metal-complexed carbonyl ylide is formed from the Rh(II)-catalyzed decomposition, there are two possibilities for the subsequent cycloaddition. If the catalyst remains associated with the carbonyl ylide during the [3+2]-reaction, then asymmetric induction may be observed. Alternatively, the catalyst could dissociate and therefore not be involved in the subsequent carbonyl ylide reaction. Recent developments over the past several years have shown that catalytic asymmetric synthesis in a number of carbonyl ylide transformations is possible.[17b,39] Hodgson and co-workers reported the first examples of enantioselective carbonyl ylide cycloaddition (up to 81% ee) using unsaturated α-diazo-β-ketoesters (Scheme 8).[40] Because the catalyst-free carbonyl ylide would be achiral, the observation of enantioselectivity provides unambiguous evidence for an enantioselective ylide transformation taking place via a catalyst-complexed intermediate (i.e., **40**).



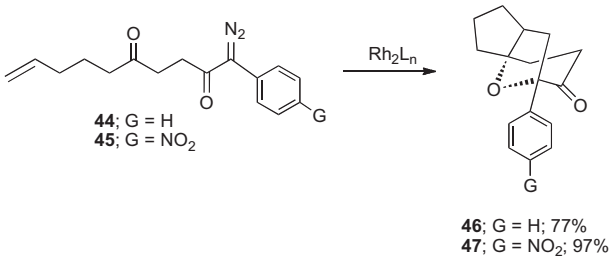
Scheme 8.

2.1.4. Catalytic enantioselective intramolecular cycloaddition. In a later report by this same group, the scope and generality of the catalytic enantioselective intramolecular tandem carbonyl ylide cycloaddition was further evaluated using a series of related unsaturated 2-diazo-3,6-diketoesters.[41] The cycloadditions were found to proceed in moderate to good yields, with a difference in ee exhibited by the electronically different diazo ketoesters used (Scheme 9). Values for ee up to 90% for alkene dipolarophiles and up to 86% for alkyne dipolarophiles were obtained.



Scheme 9.

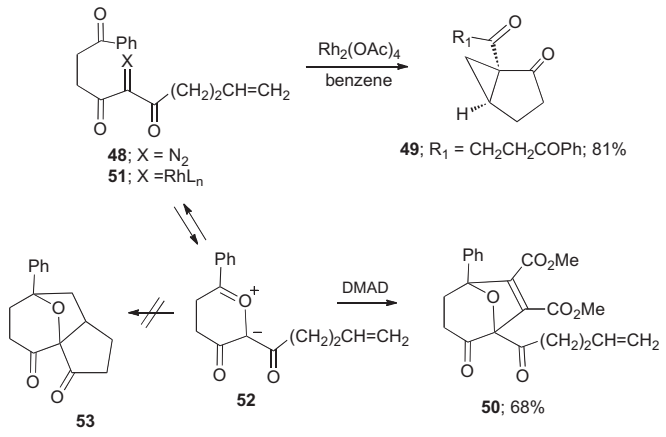
An evaluation of α-aryl-α-diazodiones in tandem intramolecular carbonyl ylide formation-enantioselective [3+2]-cycloaddition was also carried out by the Hodgson group.[42] The substrates were designed to allow investigation of the electronic characteristics of the dipole upon asymmetric induction. Once again, electronic factors were found to play a key role in determining the outcome of the cycloaddition reactions with enantioselectivities of up to 76% ee (Scheme 10).[43]



Scheme 10.

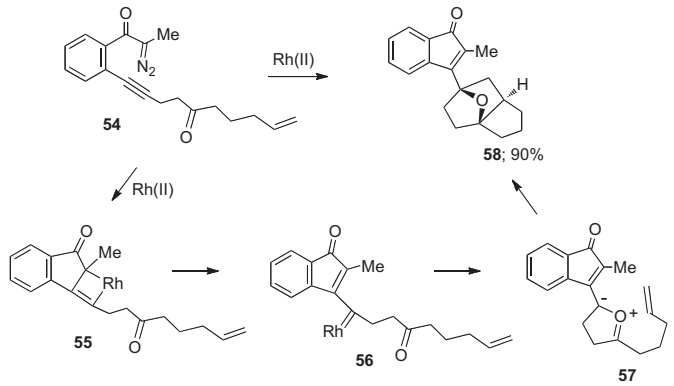
Another interesting result was encountered when α-diazo trione **48** was subjected to the rhodium(II) catalyzed decomposition conditions. The only product that could be isolated corresponded to bicyclo[3.1.0]hexanone **49** in 81% yield.[44] The isolation of **49** suggests that perhaps carbonyl ylide formation was somehow disfavored in this instance, thereby allowing intramolecular cyclopropanation to become competitive. To test this hypothesis, the reaction was carried out in the presence of DMAD. This reaction afforded the bimolecular cycloadduct **50** in 68% yield as well as

a 15% yield of the bicyclohexanone **49** (Scheme 11). Clearly, carbonyl ylide formation is occurring, but intramolecular dipolar cycloaddition to the remote alkene is not competitive with the irreversible cyclopropanation. One possible explanation to account for the failure of carbonyl ylide **52** to undergo intramolecular cycloaddition to give **53** is that the tethered olefin is not able to adopt a conformation in which it is geometrically able to partake in the cycloaddition. The fact that bicyclohexanone **49** is the major product in the absence of DMAD suggests that carbonyl ylide **52** reverts back to the rhodium carbenoid **51**, which then undergoes internal cyclopropanation to produce **49**.



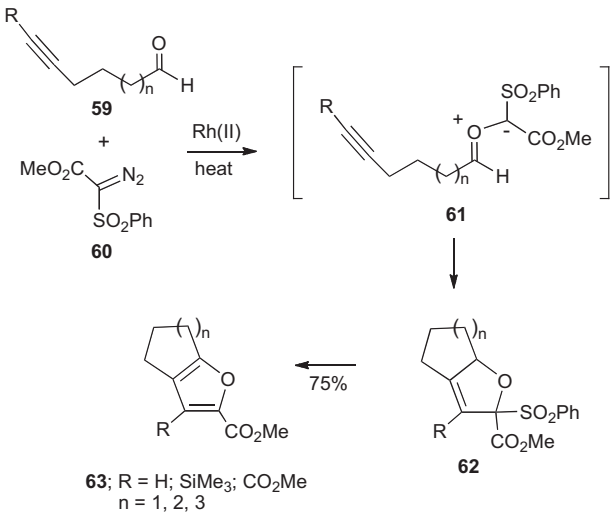
Scheme 11.

2.1.5. Other methods for generating carbonyl ylide dipoles. A novel cascade sequence was observed during a study of the Rh(II) catalyzed behavior of α-diazoketone **54**, which gave the rearranged oxabicyclo **58** in excellent yield when treated with rhodium(II) acetate.[45] The cascade was initiated by migration of the rhodium metal from the original diazo carbon to the alkynyl carbon via a metathesis reaction to produce metallocyclobutene **55**.[46] This intermediate then underwent ring-opening to furnish vinyl carbenoid **56**, which reacted with the adjacent C=O group to form the carbonyl ylide dipole **57**. A subsequent intramolecular [3+2]-cycloaddition leads to the observed product (Scheme 12).



Scheme 12.

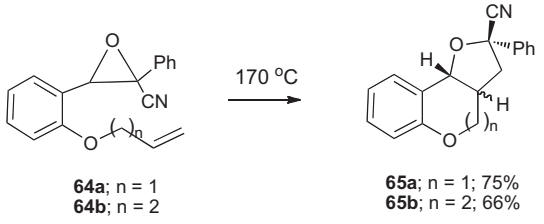
Although the intramolecular carbenoid–carbonyl cyclization sequence is well established as the premier method for generating carbonyl ylide dipoles, it is also possible to utilize a related intermolecular reaction for heterocyclic synthesis. An interesting example of intermolecular generation of carbonyl ylides from aldehydes followed by an intramolecular [3+2]-cycloaddition across a tethered alkyne has been demonstrated by Johnson and coworkers (Scheme 13).[47] Thus, heating equimolar amounts of



Scheme 13.

diazosulfone **60** and a series of alkynyl substituted aldehydes **59** in the presence of 5 mol% rhodium octanoate dimer generated the annulated furans **63** in good yield. The reaction proceeds by the initial formation of a carbonyl ylide dipole **61**, which is trapped intramolecularly by the tethered alkyne. The intermediate dihydrofuran cycloadduct **62** readily aromatizes by elimination of phenylsulfinic acid to yield the substituted furans **63**.

The thermolysis of cyano substituted aryl epoxides has also been used as a method for generating carbonyl ylides, which undergo intramolecular cycloaddition. Thus, heating the trisubstituted epoxide **64a** (n=1) gave rise to a 2:1-mixture of diastereomeric intramolecular cycloadducts **65a** (Scheme 14).[48] Under the same thermal conditions, the homolog **64b** (n=2) only afforded the *trans*-diastereomer **65b**. The formation of these products was attributed to a conrotatory opening of the epoxide ring to generate a carbonyl ylide dipole. Depending on the conformation of the alkenyloxy group, addition to the tethered alkene leads to either the trans or cis-annulated ring system.

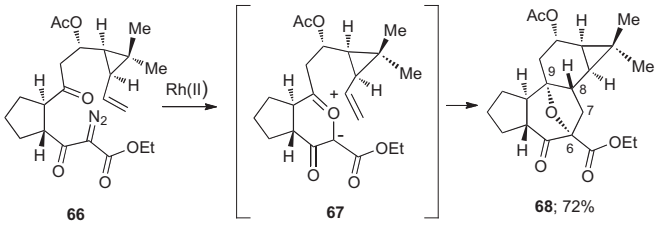


Scheme 14.

3. Application of the method toward the synthesis of complex natural products

3.1. Approach to the tigliane and phorbol systems

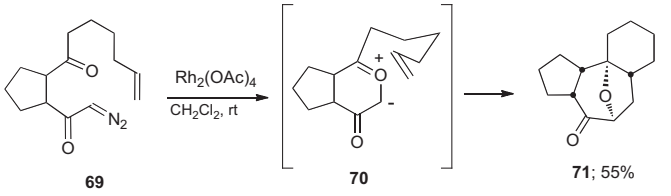
One of the first examples of the intramolecular trapping of a carbonyl ylide dipole with an alkene for natural product synthesis is found as the central step of Dauben's approach to the tigliane ring system (Scheme 15).[21] Carbonyl ylide **67**, generated from the diazocarbonyl **66** in the presence of a catalytic amount of rhodium(II) acetate, underwent an intramolecular addition with the olefin to form the C_6,C_9-oxido-bridged tigliane ring system **68**. The two new stereocenters at C-8 and C-9 were formed with the correct configurations relative to C_{14} and C_{15} presented by the natural tigliane compounds. The high stereospecificity in the ring closure



Scheme 15.

reaction could be related to steric interactions or the introduction of conformational strain in the tether, which disfavors the transition state where the cyclopropane ring and the oxido bridge are on the same side of the molecule.

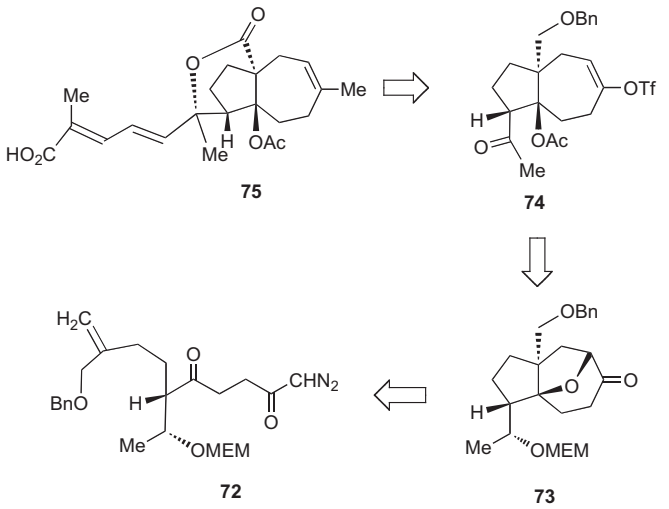
Another successful cyclization of this type was carried out by McMills[49] to produce a simple phorbol analog devoid of most of the oxygenation (Scheme 16). Reaction of diazoketone **69** with $Rh_2(OAc)_4$ produced the transient oxonium ylide **70**, which was trapped by the tethered olefin in a 1,3-dipolar cycloaddition reaction to form tetracyclic ether **71** as a single isomer in 55% yield. An X-ray crystal structure analysis showed the C-8 hydrogen to be located in a *syn*-relationship with the protons, which are cis at the A–B ring fusion. The stereoselectivity of addition of the tethered olefin to the 1,3-dipole was attributed to non-bonded interactions in the transition state where the olefinic side chain adopts a chair-like conformation in the *endo*-mode. This tandem cyclization/cycloaddition strategy represents a particularly efficient approach for the construction of the basic phorbol skeleton.[50]



Scheme 16.

3.2. Synthesis of pseudolaric acids

A further application of the tandem carbenoid cyclization-intramolecular cycloaddition reaction for the synthesis of a complex natural product is found in some work of Chiu and co-workers who used this methodology to prepare advanced intermediates directed toward the synthesis of pseudolaric acids.[51] Pseudolaric acids are a family of diterpenes isolated from the root bark of a tree native to the Zhejiang province in China.[52] These novel compounds show both antimicrobial activity and cytotoxicity against several cancer cell lines. Chiu's retrosynthetic analysis is outlined in Scheme 17 and is related to that previously used by Dauben[21] and McMills.[49] Oxatricyclic ketone **73** was envisioned as the key intermediate that could be constructed by a reaction cascade initiated by the decomposition of an appropriately functionalized acyclic diazoketone **72**. The metal carbenoid was expected to undergo cyclization intramolecularly with the carbonyl group to form a cyclic carbonyl ylide and this would be followed by intramolecular [3+2]-cycloaddition with the 2,2-disubstituted olefin to give the oxatricyclic intermediate. Enol triflate **74** was envisaged as being formed by reductive elimination from the oxatricyclic ketone **73**, in which the tertiary acetate has been masked as an oxygen bridge. Chiu found that substrate controlled diastereoselectivity of the tandem sequence was preferential for the undesired diastereomer,[51] but reagent control through the use of a chiral rhodium catalyst,[17b,39] reversed the selectivity in favor of cycloadduct



Scheme 17.

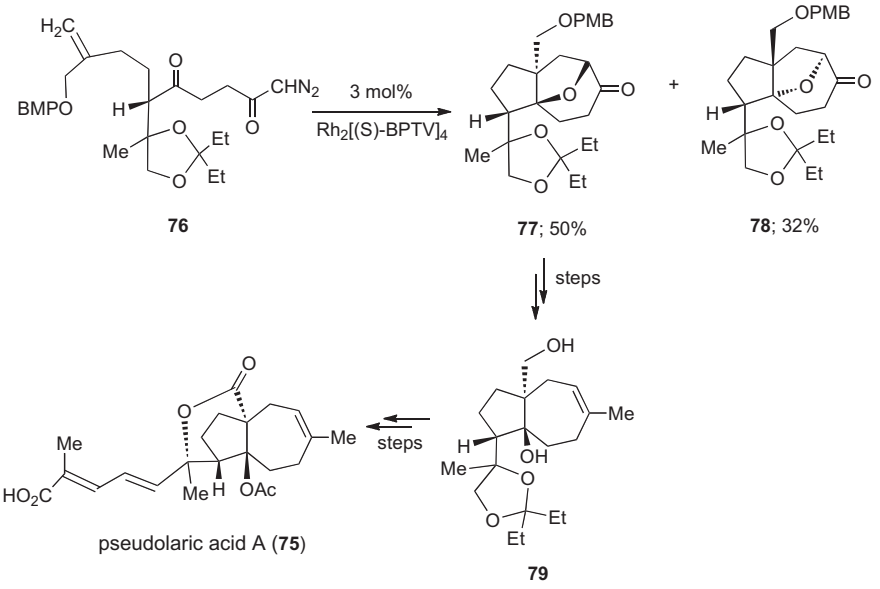
73. Ring opening of the oxabicyclic nucleus to give a hydroxycycloheptene was demonstrated in a model study. More recently,[52] using the related α-diazoketone **76** and employing a chiral catalyst developed by Hashimoto,[53] the preferential formation of the desired diastereomer cycloadduct **77** was obtained as the major product from the intramolecular cycloaddition reaction of **76** (Scheme 18). A reductive elimination protocol was then used to generate perhydroazulene **79** from **77**. At this stage, the central nucleus in pseudolaric acid A bearing the required stereocenters in their correct absolute configurations had been achieved. Subsequent transformations resulted in a completion of the synthesis of pseudolaric acid A (**75**).

3.3. Synthesis of (−)-indicol

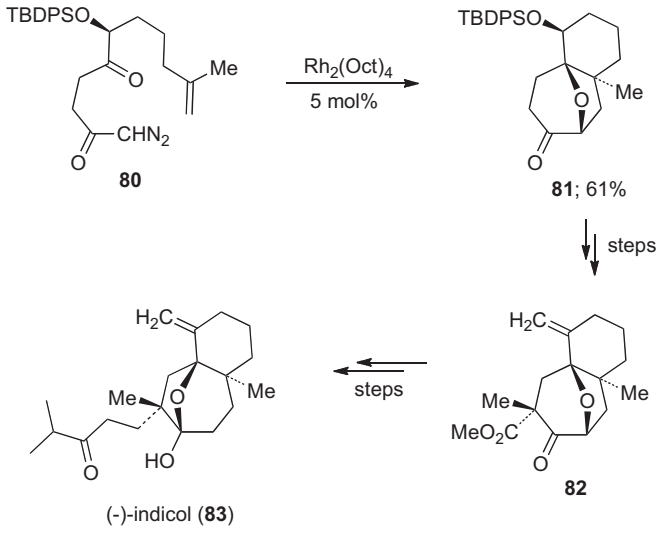
The total synthesis of (−)-indicol (**83**) was also accomplished by Chiu using a related rhodium(II)-mediated carbene cyclization–cycloaddition cascade, by which the core bicyclo[5.4.0] undecane skeleton was assembled in one step.[54] The formation of the major diastereomer proceeded through a transition state in which the tether adopts a chair conformation, with the bulky silyloxy group residing in an equatorial position. This one-pot reaction resulted in the construction of three sigma bonds and three stereocenters in good yield. Moreover, the bicyclic adduct provided the required functional groups and the facial bias to enable the stereoselective dialkylation to create the final stereocenter at C12 of the natural product. Thus, cycloadduct **81** was taken on to compound **82**, which in turn, was transformed into (−)-indicol in several additional steps (Scheme 19).

3.4. Synthesis of polygalolides A and B

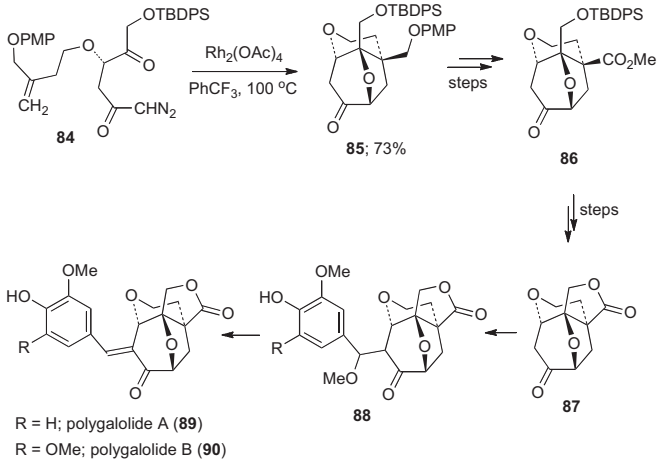
The total synthesis of polygalolides A (**89**) and B (**90**) by the Hashimoto group further illustrates the power of the carbonyl ylide cycloaddition methodology for the rapid assembly of the dioxatricyclic ring system, which is difficult to construct by other means.[55] After some experimentation, it was found that cycloadduct **85** was produced as a single isomer in 73% yield using the rhodium acetate catalyzed reaction of α-diazoketone **84** in trifluorotoluene at 100 °C (Scheme 20). After oxidative removal of the PMP group at C1, two successive oxidations and an esterification with diazomethane gave the methyl ester **86** in 78% yield over three steps. Desilylation and concomitant lactone formation was effected with tetra-butylammonium fluoride in the presence of AcOH to provide the tetracyclic lactone **87**. Ketone **87** was easily converted



Scheme 18.



Scheme 19.



Scheme 20.

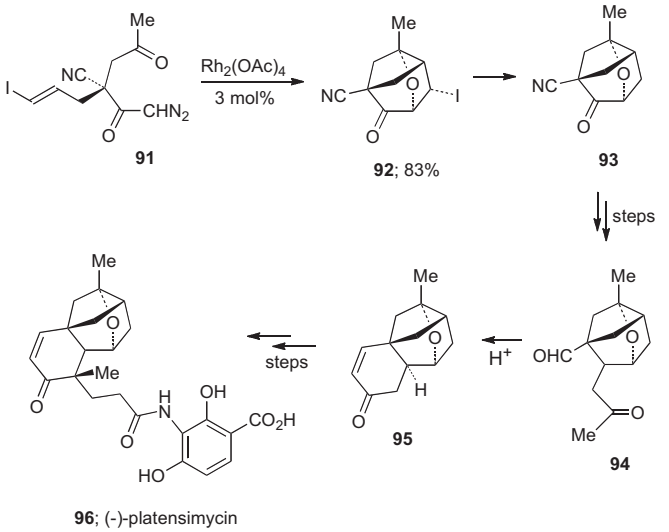
into the corresponding silyl enol ether, which underwent a TMSOTf-promoted coupling with the required dimethoxyacetal to provide the coupling product **88** in 58% yield. The β-methoxyketone **88** was smoothly converted into polygalolide A (**89**) by treatment with DBU, followed by deacetylation. Polygalolide B (**90**) was also synthesized in 41% yield from intermediate **87** following an identical reaction sequence.

3.5. Synthesis of platensimycin

Platensimycin (**96**) is a novel broad-spectrum antibiotic that was isolated from *Streptomyces platensis* by scientists from Merck in 2006.[56] As a result of its biological properties and challenging structure, platensimycin has been the focus of some intense synthetic activity.[57] A formal asymmetric synthesis of (−)-platensimycin was accomplished by the Lee group by synthesizing the tetracyclic enone **95** by way of an intramolecular carbonyl ylide cycloaddition.[58] A chiral synthesis of α-diazoketone **91** was first carried out and this compound was then treated with rhodium acetate to give cycloadduct **92** in 83% yield. Reduction of **92** with hypophosphite afforded tricycle **93** in high yield. An efficient Horner–Emmons reaction gave the expected enone, which was ultimately converted into keto aldehyde **94**. Further transformation of **94** into the tetracyclic intermediate **95** was effected under acidic conditions thereby constituting a formal synthesis of platensimycin (**96**). More recently, the related analog isoplatensimycin was also synthesized by the Lee group using an analogous intramolecular dipolar cycloaddition of a carbonyl ylide as the key step of the synthesis (Scheme 21).[59]

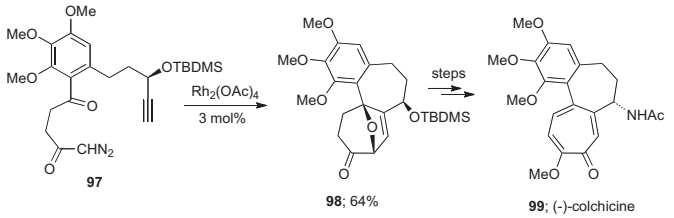
3.6. Synthesis of (−)-colchicine

An efficient 15 step synthesis of the antimitotic alkaloid (−)-colchicine **99** also involved a Rh-catalyzed transformation of α-diazoketone **97** to produce an oxatetracyclic key intermediate **98** through an intramolecular [3+2]-cycloaddition of an in situ generated carbonyl ylide dipole.[60] In this manner both the seven-membered rings B and C are formed in one step with concomitant installation of the oxygen functions in positions C(9) and C(10). Moreover, the intramolecular mode of the cycloaddition step permits the use of an unactivated dipolarophile and thus allows for the



Scheme 21.

installation of the C(7) stereocenter prior to cyclization. The key cycloadduct **98** was obtained in 64% yield with high enantioselectivity (99% ee) and was easily converted to the alkaloid in several additional steps (Scheme 22).

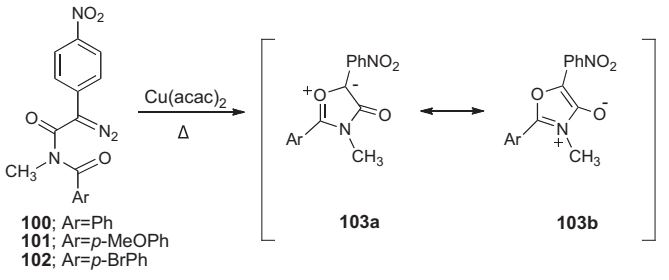


Scheme 22.

4. Intramolecular cycloadditions using isomünchnones as carbonyl ylide dipoles

4.1. Model studies employing isomünchnones as carbonyl ylide dipoles

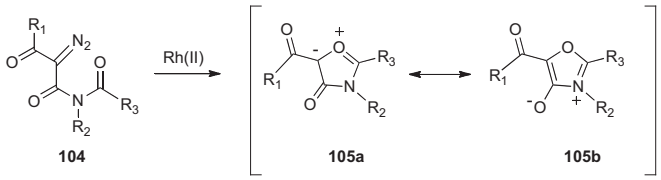
Mesoionic oxazolium ylides (isomünchnones) correspond to the cyclic equivalent of a carbonyl ylide embedded in a heteroaromatic ring and these reactive intermediates readily undergo 1,3-dipolar cycloaddition with suitable dipolarophiles. Isomünchnones are readily obtained through the transition metal catalyzed cyclization of a suitable α-diazoimide precursor.[61] The first successful preparation and isolation of an isomünchnone induced by a transition metal process was described in 1974.[62] Heating a sample of diazoimide **100** in the presence of a catalytic amount of $Cu_2(acac)_2$ afforded a red crystalline material, which precipitated from the reaction mixture (Scheme 23). The red solid was assigned as



Scheme 23.

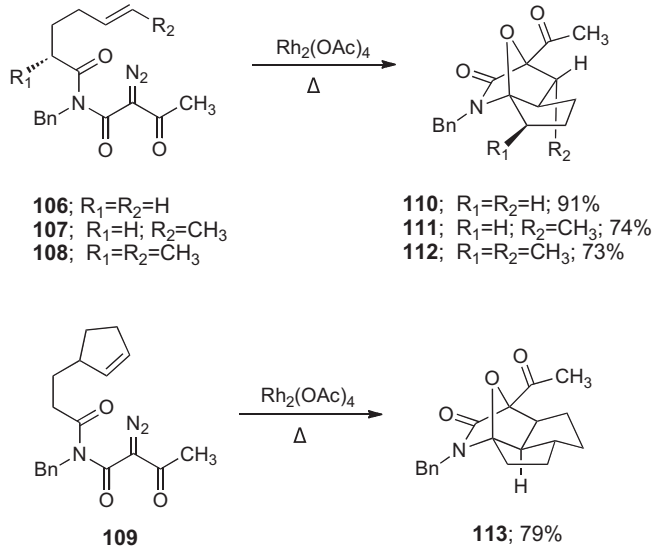
isomünchnone **103** on the basis of its spectral data and elemental analysis. Mesoionic ylide **103** was found to be air stable for several weeks and its overall stability was attributed to its dipolar aromatic resonance structure. Formation of the isomünchnone ring can be rationalized by initial generation of a metallo-carbenoid species, which is then followed by intramolecular cyclization onto the neighboring carbonyl oxygen to form the dipole.[63]

The Padwa[64–66] and Maier[67,68] research groups have further utilized the Rh(II) catalyzed reaction of diazoimides as a method for generating isomünchnones. The starting diazoimides are readily constructed by acetoacylation[69] or malonylacylation[70] of the corresponding amides followed by standard diazo transfer techniques.[71] Intramolecular trapping of the rhodium carbenoid by the lone pair of electrons of the neighboring carbonyl group leads to the desired mesoionic system **105** (Scheme 24). These reactive dipoles can then be trapped with a variety of dipolarophiles to give cycloadducts in high yield.



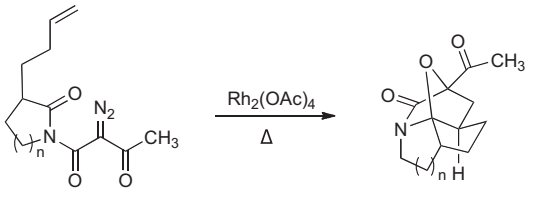
Scheme 24.

Interesting examples of intramolecular 1,3-dipolar cycloadditions of isomünchnones possessing an unactivated alkene have been reported to give rise to complex azapolycyclic compounds in one step.[64,68] The isomünchnones derived from the $Rh_2(OAc)_4$-catalyzed reaction of acyclic diazoimides **106**–**109** were found to undergo facile cycloaddition onto the tethered π-bond to provide polycyclic adducts **110**–**113** (Scheme 25).[67] A notable feature of this cycloaddition is that only one diastereomer is formed. The relative stereochemistry of cycloadduct **113** was determined by X-ray crystallography.[67] This confirmed the fact that addition of the olefin took place *endo* with regard to the isomünchnone dipole.



Scheme 25.

This methodology was further extended, leading to a significant increase in complexity of the resulting polyheterocyclic systems, by employing a series of cyclic diazoimides.[66] Treatment of cyclic diazoimides **114**–**116** with $Rh_2(OAc)_4$ led to good yields of cycloadducts **117**–**119** as single diastereomers (Scheme 26). Once again, the stereochemical outcome is the result of an *endo* cyclization of the



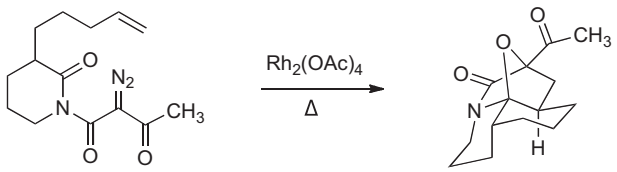
114; n=1
115; n=2
116; n=3

117; n=1 (88%)
118; n=2 (86%)
119; n=3 (83%)

Scheme 26.

π-bond onto the isomünchnone dipole and this was confirmed by an X-ray crystallographic analysis of cycloadduct **117** (Scheme 26).[66]

Lengthening the alkenyl tether by one carbon atom was observed to have no effect on the ability of the isomunchnone to cycloadd across the olefinic π-bond. This was shown in a study of the cycloaddition behavior of diazoimide **120**, which afforded cycloadduct **121** in 86% yield as a single diastereomer (Scheme 27).[66]

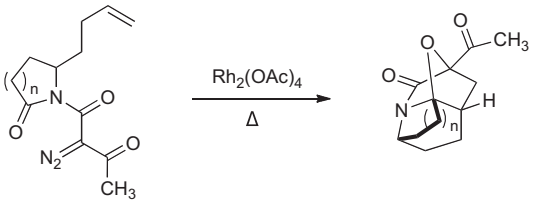


120

121; 86%

Scheme 27.

The generality of the method was further demonstrated by synthesizing cyclic diazoimides **122** and **123** in which the alkenyl tether was placed alpha to the nitrogen atom (Scheme 28). Thus, when these α-diazoimides were treated with a catalytic amount of $Rh_2(OAc)_4$, the tandem cyclization–cycloaddition process gave polycycles **124** and **125** in 69% and 76% yield, respectively. With both of these systems, the length of the alkenyl tether proved to be crucial for the intramolecular cycloaddition reaction across the isomünchnone dipole. Only when the tether was a butenyl group was cycloaddition observed. If the length of the tether was increased or decreased by one methylene unit, no products derived from intramolecular cycloaddition were encountered.[66]

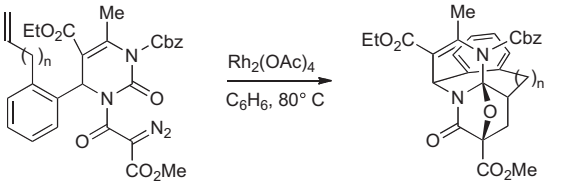


122; n=1
123; n=2

124; n=1 (69%)
125; n=2 (76%)

Scheme 28.

The synthesis of conformationally rigid dihydropyrimidine calcium channel modulators that mimic the proposed bioactive DHP conformation, where two of the three flexible bonds in DHPs/DHPMs are constrained simultaneously, was carried out by Kappe using a rhodium-induced cyclization/cycloaddition cascade protocol.[72] The key step in the synthesis involves the regio- and diastereoselective intramolecular 1,3-dipolar cycloaddition reaction of a dihydropyrimidine-fused isomünchnone dipole. Both analogs of the cycloadduct **127a**,**b** were obtained as single diastereoisomers, which is the result of an extremely favorable transition state alignment of the olefinic tether (n=0,1) relative to the carbonyl ylide dipole embedded into the isomünchnone system (Scheme 29).

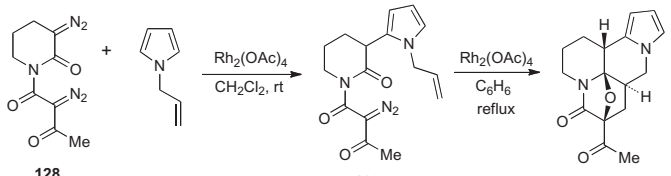


126a; n = 0
126b; n = 1

127a; n = 0; 71%
127b; n = 1; 56%

Scheme 29.

An interesting example of the power of the cascade method for generating complex polycyclic systems from simple starting materials is seen from the Rh(II)-catalyzed reaction of bis-diazoimide **128** with *N*-allylpyrrole in dichloromethane at room temperature.[73] The cyclic diazo group underwent preferential C-alkylation at the 2-position of pyrrole as described in Scheme 30. Further treatment of the resulting diazoimide **129** with the $Rh_2(OAc)_4$-catalyst in benzene under reflux afforded the interesting polycyclic system **130** in 85% yield in a highly diastereoselective manner. Mechanistically, the rhodium(II)-carbenoid derived from diazoimide **129** furnished an isomünchnone dipole as an intermediate, which subsequently underwent the intramolecular 1,3-dipolar cycloaddition to the olefin functionality. These reaction steps could also be performed in a one-pot manner. Thus, diazoimide **129** was allowed to react with *N*-allylpyrrole in the presence of rhodium(II) acetate catalyst in dichloromethane and then the solvent was evaporated. The crude reaction mixture was heated at reflux for 30 min to afford product **130** in a single step via the tandem insertion/cyclization/cycloaddition methodology.



128

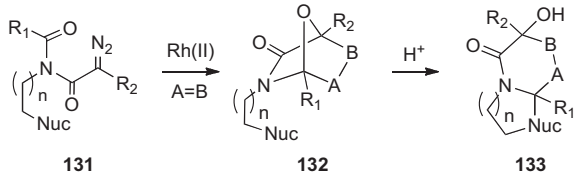
129

130; 85%

Scheme 30.

4.2. Cycloadducts derived from isomünchnones serving as masked *N*-acyliminium ions

The 1,3-dipolar cycloaddition of isomünchnones derived from α-diazoimides of type **131** provides a uniquely functionalized cycloadduct (i.e. **132**) containing a 'masked' *N*-acyliminium ion (Scheme 31). By incorporating an internal nucleophile on the tether, annulation of the original dipolar cycloadduct **132** would allow the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologs of the erythrinane family of alkaloids. By starting from simple acyclic diazoimides **131**, the Padwa group has established a tandem *cyclization cycloaddition cationic*



131

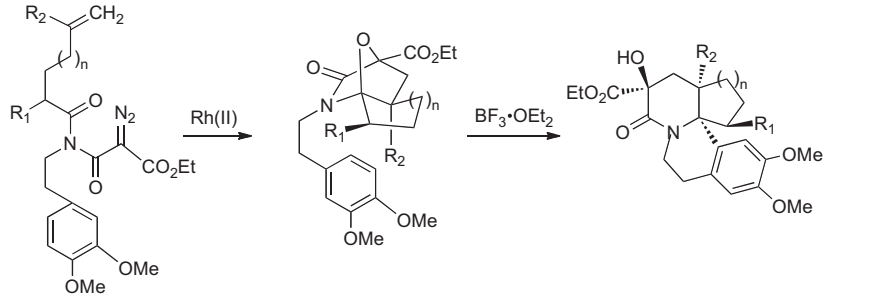
132

133

Scheme 31.

π-*cyclization* protocol as a method for the construction of complex nitrogen polyheterocycles of type **133**.

The first example of such a process involved the treatment of diazoimides **134**, **135**, and **136** with a catalytic amount of rhodium(II) perfluorobutyrate in CH_2Cl_2 at 25 °C, which provided cycloadducts **137** (98%), **138** (95%), and **139** (90%) (Scheme 32). Formation of the *endo*-cycloadduct with respect to the carbonyl ylide dipole in these cycloadditions is in full accord with molecular mechanics calculations, which show a large energy difference between the two diastereomers. When the individual cycloadducts were exposed to $BF_3 \cdot OEt_2$ (2 equiv) in CH_2Cl_2 at 0 °C, the cyclized products **140** (97%), **141** (95%), and **142** (85%) were isolated as single diastereomers. The cis stereochemistry of the A/B-ring junction for **140**–**142** was assigned by analogy to similar erythrinane products obtained via a Mondon-enamide type cyclization[74–78] and was unequivocally verified by an X-ray crystal analysis of all three cycloadducts. In all three cases the *anti* stereochemical relationship is still maintained between the hydroxyl stereocenter (from the oxygen bridge) and the bridgehead proton (R_2=H) or methyl (R_2=CH_3) group.



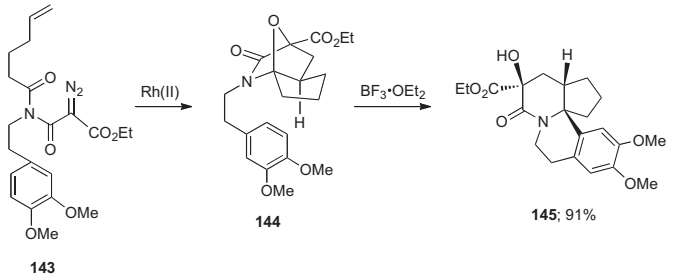
134; R_1=R_2=H; n=2
135; R_1=H; R_2=CH_3; n=1
136; R_1=CH_3; R_2=H; n=1

137; R_1=R_2=H; n=2 (98%)
138; R_1=H; R_2=CH_3; n=1 (95%)
139; R_1=CH_3; R_2=H; n=1 (90%)

140; R_1=R_2=H; n=2 (97%)
141; R_1=H; R_2=CH_3; n=1 (95%)
142; R_1=CH_3; R_2=H; n=1 (85%)

Scheme 32.

When the dipolar cycloadduct **144** derived from the unsubstituted alkenyl diazoimide **143** was exposed to $BF_3 \cdot OEt_2$, the resulting cyclized product **145** (91%) was identified as the all *syn* tetracyclic lactam by an X-ray crystal analysis (Scheme 33). Thus, in contrast to the other three systems, the bridgehead proton of **145** lies *syn* to the hydroxyl stereocenter of the original cycloadduct. It is assumed that the intermediate *N*-acyliminium ions formed from the Lewis acid assisted ring opening of the isomünchnone cycloadducts undergo rapid proton loss to produce tetra-substituted enamides. A subsequent acid induced cyclization then occurs from the least hindered side as has already been established by Mondon and co-workers.[74–76] Cationic cyclizations of this type are known to be governed by steric control.[79] In the case of cycloadduct **138**, the bridgehead proton does not exist and thus deprotonation can only occur in one direction. Apparently the initially formed iminium ion derived from **137** undergoes fast π-cyclization prior to proton loss. In this case, the deprotonation step is significantly slower than in the 6/5 system due to the larger dihedral angle (113°) between the bridgehead proton and the π-system of the *N*-acyliminium ion. The stereochemical outcome in **140** is the result of a stereoelectronic preference for axial attack by the aromatic ring of the *N*-acyliminium ion from the least hindered side.



143

144

145; 91%

Scheme 33.

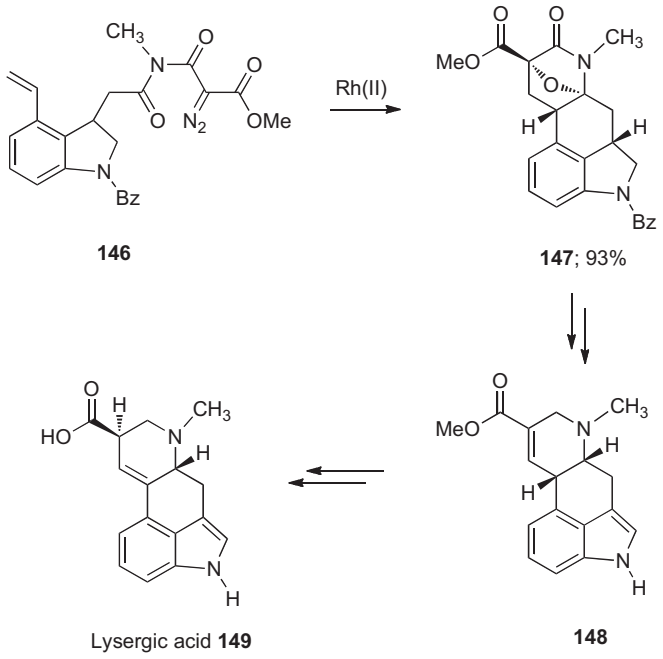
Thus, by incorporating an internal π-nucleophile on the tether, annulation of the original isomünchnone cycloadduct allows for the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologs of the erythrinane family of alkaloids.[80] This reaction sequence represents the first example where a [3+2]-cycloaddition and a *N*-acyliminium ion cyclization have been coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which occurs by a ring opening reaction of the oxabicyclic system. *N*-Acyliminium ions are traditionally generated from the N-acylation of imines, N-protonation and oxidation of amides, electrophilic additions to enamides, and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[81] These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall α-amido alkylation.

4.3. Studies directed toward lysergic acid

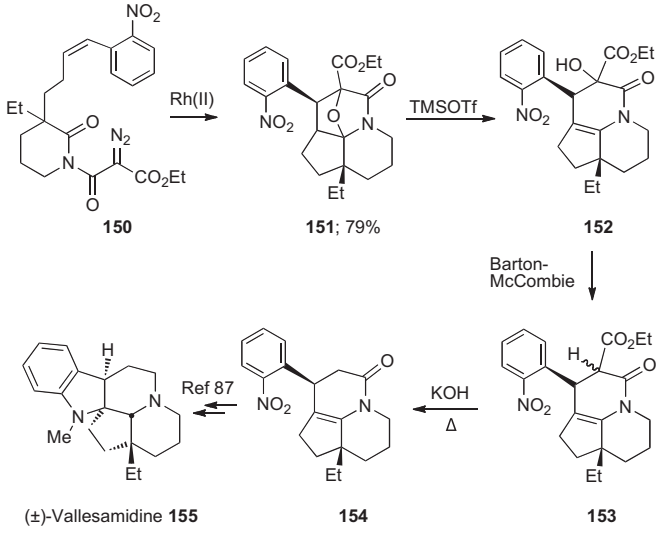
A number of approaches to complex alkaloids have been reported in which the intramolecular cycloaddition reactions of a transient isomünchnone dipole feature as the pivotal step for assembling the polycyclic frameworks. Intramolecular reactions of isomünchnone dipoles generated from a series of alkenyl- and alkynyl-substituted diazoimides have been exploited to develop an approach to the quinoline ring system (rings C and D) of the ergot alkaloids (e.g., lysergic acid, **149**). In one example, the $Rh_2(OAc)_4$-mediated tandem cyclization cycloaddition sequence from the diazoimide **146** led to the cycloadduct **147** in very good yield (Scheme 34).[82] The polycyclic adduct **147** was readily elaborated to **148** en route to ergot alkaloids via $BF_3 \cdot OEt_2$-mediated ether bridge cleavage and a Barton–McCombie deoxygenation sequence. Further attempts toward lysergic acid were, however, thwarted due to the inability to isomerize the trisubstituted double bond in **148**.

4.4. Studies directed toward vallesamidine

Given the success in forming novel azabicyclic systems derived from an intramolecular isomünchnone cycloaddition/*N*-acyliminium ion cyclization sequence, this domino strategy was also used for a formal synthesis of vallesamidine **155**[83] via the key Heathcock intermediate **154** (Scheme 35). Thus, N-malonylacylation of the precursor amide was carried out followed by a standard diazo transfer reaction to produce the requisite α-diazoimide **150**. The reaction of **150** with a Rh(II)-catalyst gave cycloadduct **151**, which underwent a TMSOTf catalyzed ring opening to furnish enamide **152** in 78% yield. With the ring-opened lactam in hand, a Barton-McCombie



Scheme 34.

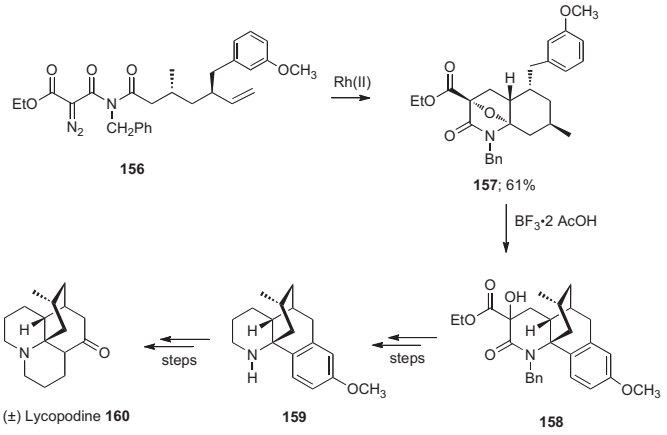


Scheme 35.

deoxygenation reaction[84] delivered **153** in 88% yield. Utilization of the sequential saponification/decarboxylation protocol afforded enamide **154**.[85] This sequence constitutes a formal synthesis of (±)-vallesamidine **155**, based on the successful conversion of **154** into **155** by Heathcock and Dickman.[86]

4.5. Synthesis of lycopodine

Another application of the domino cascade process toward the construction of alkaloids involved the synthesis of (±)-lycopodine **160** (Scheme 36).[87] The isomünchnone cycloadduct **157** was formed from the Rh(II)-catalyzed reaction of diazoimide **156** and was found to be the precursor of the key Stork intermediate **159** (via **158**). Formation of **159** from **158** occurred by way of a Pictet–Spengler cyclization of the *N*-acyliminium ion derived from **157**. Central to this strategy was the expectation that the bicyclic iminium ion originating from **157** would exist in a chair-like conformation.[88,89] Indeed, cyclization of the aromatic ring onto the *N*-acyliminium ion



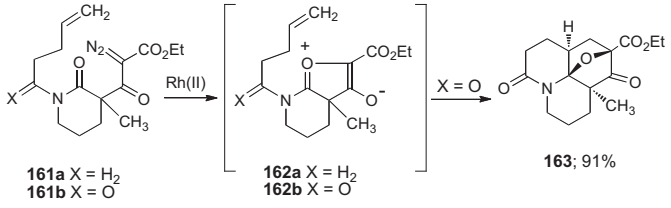
Scheme 36.

center readily occurred from the axial position. The rearranged product **158** was then converted into the key intermediate **159** previously used by Stork for the synthesis of (±)-lycopodine **160**.[88]

5. Intramolecular cycloadditions of *push–pull* carbonyl ylide dipoles

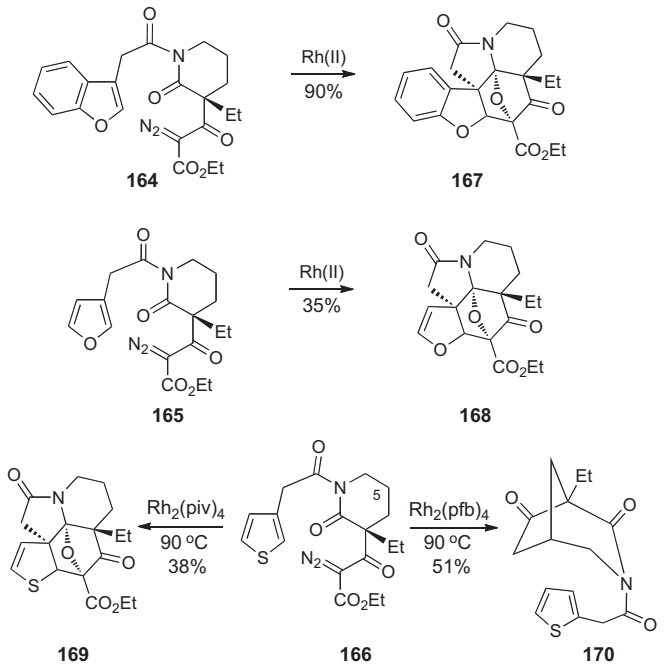
5.1. Model studies employing *push–pull* carbonyl ylide dipoles

The Rh(II)-catalyzed reactions of the related α-diazo ketoamide system **161** have also been examined.[90] In this case, attack of the amido oxygen at the rhodium carbenoid center produces a carbonyl ylide dipole (**162**) that is isomeric with the isomünchnone class of mesoionic betaines. Cycloaddition of this '*push–pull*' dipole furnished tetracycle **163** in good yield, provided that the tether engaged in ring formation carried a carbonyl group (i.e., **161b**, X=O) (Scheme 37). Without the C=O functionality (i.e., **161a**, X=H), only decomposition products were observed. By performing ab initio geometry optimizations with **161a**, it was shown that a severe cross-ring 1,3-diaxial interaction exists in the transition state for the cycloaddition. The presence of a carbonyl group in the tether, on the other hand, helps to relieve the steric congestion by favoring a second boat conformation in the resulting six-membered ring. When the side chain is devoid of a carbonyl group, the calculated reaction barrier is much larger, thereby permitting competing processes to occur. Thus, the reactivity discrepancy between α-diazo amido esters **161a** and **161b** has been attributed to relative differences in steric effects in the respective transition states.[90]



Scheme 37.

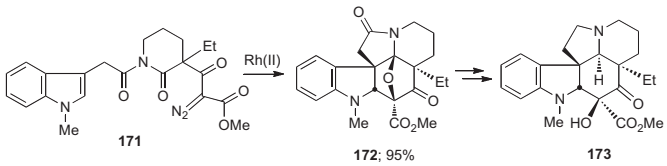
Selective modification of the starting α-diazo amido ester allowed for an application of this methodology for an eventual synthesis of the aspidosperma alkaloid family. In particular, intramolecular [3+2]-cycloaddition of the '*push–pull*' dipole across a tethered heteroaromatic π-bond of several α-diazoimides, such as **164**–**166** proceeded smoothly and provided the novel pentacyclic compounds **167**–**169** in good yield and in a stereocontrolled fashion (Scheme 38).[91] In the case of the thiophenyl-substituted α-diazoimide **166**,



Scheme 38.

changing the ligand group on the rhodium catalyst resulted in a major difference in the overall reaction pathway. Thus, treatment of **166** with Rh(II)-pivalate afforded only cycloadduct **169**. In contrast, the only compound isolated from the rhodium(II) perfluorobutyrate [Rh_2(pfb)$_4$] catalyzed reaction of **166** was lactam **170**. The formation of this compound arose from a formal insertion of the metal carbene into the C–H bond at the C5-position of the lactam ring followed by an unusual ethoxy-decarboxylation reaction. The variation in reactivity reflects the difference in electrophilicity between the various rhodium carbenoid intermediates. Intramolecular C–H insertion is enhanced with the more electrophilic carbene generated using the Rh(II) perfluorobutyrate catalyst.

A related annulation sequence was then used to prepare the required pentacyclic skeleton of the aspidosperma family of alkaloids. Thus, treatment of α-diazoimide **171** with Rh_2(OAc)$_4$ produced the expected '*push–pull*' dipole, which subsequently underwent cycloaddition across the tethered indole π-bond. The resulting cycloadduct **172** is the consequence of *endo* cycloaddition with respect to the dipole and corresponds to the lowest energy transition state. The stereospecific nature of the internal cycloaddition reaction results in the correct relative stereochemistry about the four chiral centers of the C-ring. Cycloadduct **172** was converted in three subsequent steps into desacetoxy-4-oxo-6,7-dihydrovindorosine **173** (Scheme 39).[92]



Scheme 39.

5.2. Synthesis of aspidophytine

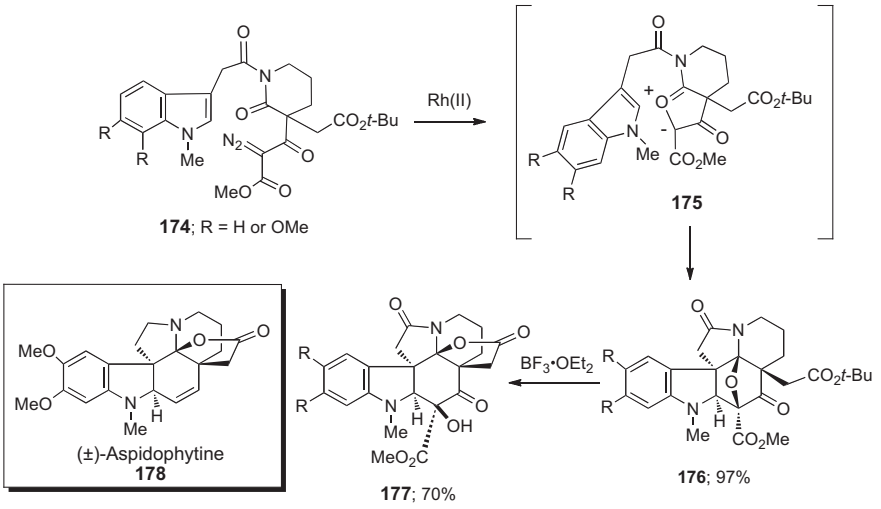
A synthesis of the more complex pentacyclic alkaloid (±)-aspidophytine **178** was then carried out making further use of the domino dipole cascade sequence.[93] The key sequence of reactions involved a 1,3-dipolar cycloaddition of the '*push–pull*' dipole **175** across the indole π-system. In contrast to previous findings,[90–92] the *exo* cycloadduct **176** was the exclusive product isolated from the Rh(II)-catalyzed reaction of **175**. It was assumed that in this case, the bulky *tert*-butyl ester functionality blocks the *endo* approach thereby resulting in cycloaddition taking place from the less-congested exo face. Treatment of the resulting dipolar cycloadduct **176** with $BF_3 \cdot OEt_2$ induces a domino fragmentation cascade. The reaction proceeds by an initial cleavage of the oxabicyclic ring and formation of a transient *N*-acyliminium ion, which reacts further with the adjacent *tert*-butyl ester and sets the required lactone ring present in aspidophytine. A three-step sequence was then used to remove both the ester and OH groups from lactone **177**. Subsequent functional group manipulations allowed for the high-yielding conversion of **177** into (±)-aspidophytine **178** (Scheme 40).

5.3. Synthesis of the kopsifoline alkaloids

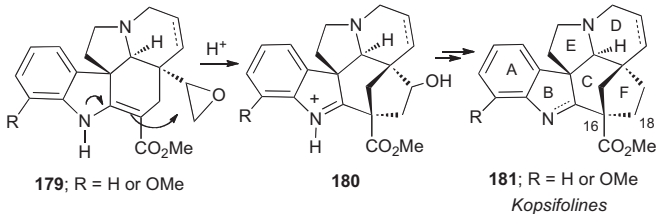
As a further extension of '*push–pull*' dipole cycloaddition chemistry, the Rh(II)-catalyzed cyclization/cycloaddition cascade was applied toward the hexacyclic framework of the kopsifoline alkaloids. The kopsifolines **181** are structurally intriguing compounds, related to and possibly derived from an aspidosperma-type alkaloid precursor **179**. A possible biogenetic pathway to the kopsifolines from **179** could involve an intramolecular epoxide-ring opening followed by loss of H_2O as shown in Scheme 41. The interesting biological activity of these compounds combined with their fascinating and synthetically challenging structure, make them attractive targets for synthesis. Using the metal-catalyzed domino reaction as a key step, the heterocyclic skeleton of the kopsifolines could eventually be built by a 1,3-dipolar cycloaddition of a '*push–pull*' carbonyl ylide dipole derived from α-diazo ketoester **182** across the indole π-bond. The facility and stereoselectivity of the key cycloaddition reaction was investigated in detail using some model substrates. It was found that the heterocyclic skeleton of the kopsifoline alkaloid family **185** could readily be constructed by the proposed sequence of reactions outlined in Scheme 42.[94] The isolation of **183** as a single diastereomer was rationalized by recognizing that the indole moiety approaches the dipole from the least sterically encumbered position. Ring opening of the resulting cycloadduct **183** followed by a reductive dehydroxylation step resulted in the formation of the silyl enol ether **184** necessary for the final F-ring closure of the kopsifoline skeleton (i.e., formation of **185**).

5.4. Asymmetric induction studies directed toward the aspidosperma alkaloids

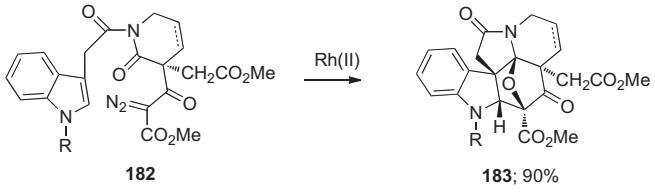
Hashimoto recently described a modified enantioselective protocol that uses chiral dirhodium(II) carboxylates to control the facial selectivity of the cyclization for assembling the pentacyclic ABCDE framework of the aspidosperma alkaloid family.[95] Cycloaddition of the carbonyl ylide derived from indolyl-substituted diazoimides **186a–d** under the influence of Rh_2(*S*-TCPTTL)$_4$ provides cycloadduct **188** in 43% yield and 66% ee with complete *endo* diastereoselectivity (Scheme 43). The undesired bicyclic epoxide **189** was also obtained in 42% as the other major by-product. Attempts to convert **189** into cycloadduct **188** under the same conditions failed, leading the authors to hypothesize that the epoxide does not serve as an intermediate in the reaction. This system represents the first example of asymmetric induction in an intramolecular cycloaddition of a carbonyl ylide dipole across an indolyl π-bond. Efforts by the Hashimoto group directed at improving the enantioselectivity and product yield as well as the synthesis of (–)-vindorosine are currently in progress.

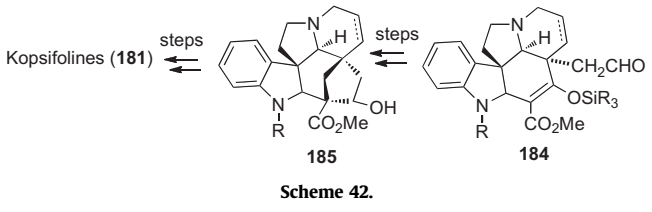


Scheme 40.

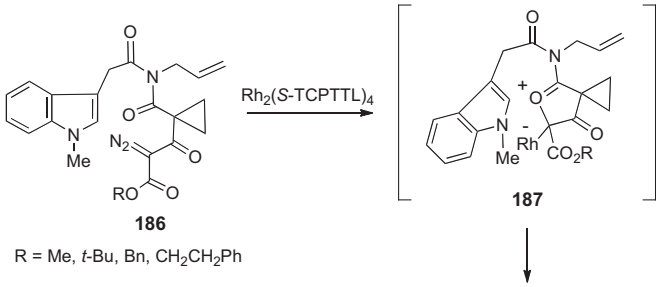


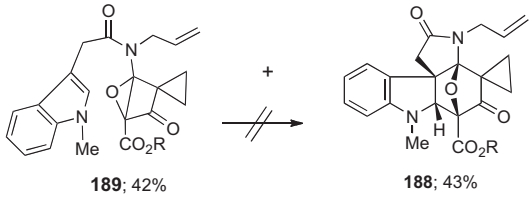
Scheme 41.



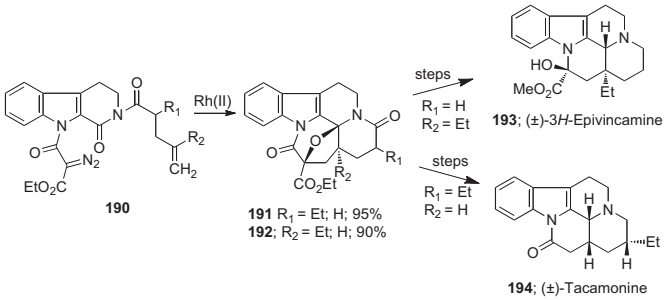


Scheme 42.





Scheme 43.



Scheme 44.

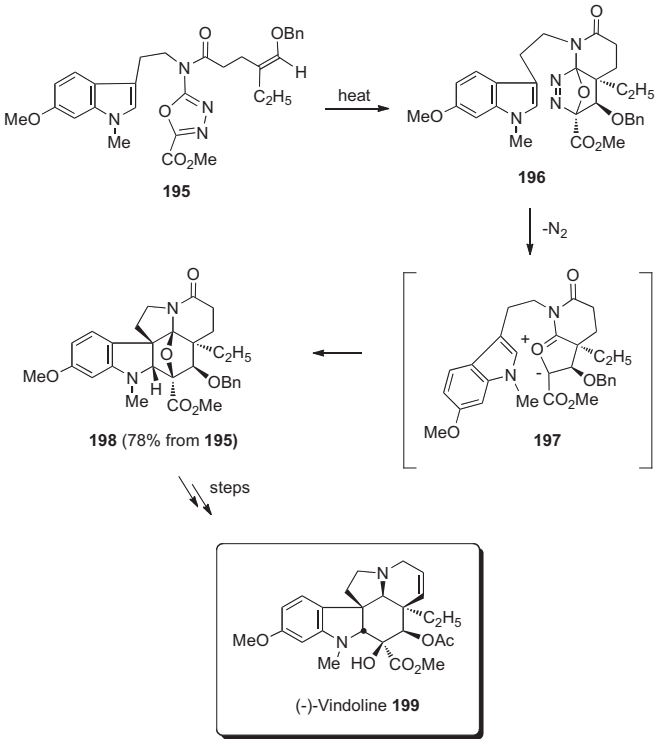
5.5. Synthesis of the *vinca* and *tacaman* class of indole alkaloids

The total synthesis of several members of the *vinca* and *tacaman* class of indole alkaloids has recently been accomplished using '*push–pull*' dipoles in the critical cycloaddition step.[96] The central step in the synthesis consists of an intramolecular [3+2]-cycloaddition reaction of an α-diazo indoloamide (i.e., **190**), which delivers the pentacyclic skeleton of the natural product in excellent yield (Scheme 44). The acid lability of the oxabicyclic structure was exploited to establish the *trans*-D/E-ring fusion of (±)-3*H*-epivincamine **193**. Finally, a base induced ketoamide ring contraction was utilized to generate the E-ring of the natural product. A variation of the cascade sequence of reactions used to synthesize (±)-3*H*-epivincamine **193** was also employed for the synthesis of the *tacaman* alkaloid (±)-tacamonine **194**.

5.6. Thermolysis of 1,3,4-oxadiazoles for the synthesis of vinblastine

In recent years, the Boger group has developed a new synthetic approach to the *vinca* alkaloids based on an intramolecular [4+2]/[3+2] cycloaddition reaction of 1,3,4-oxadiazoles, which proceeds through a '*push–pull*' dipole.[97] This unique domino cascade

assembles the fully functionalized pentacyclic ring system of vindoline **199** in a single step that forms four C–C bonds and three rings while introducing all the requisite functionality and setting all six stereocenters within the central ring including three contiguous and four total quaternary centers. The reaction leading to **198** is initiated by an intramolecular inverse electron demand Diels–Alder cycloaddition of the 1,3,4-oxadiazole **195** with the tethered enol ether. Loss of nitrogen from the initial Diels–Alder cycloadduct **196** provides the '*push–pull*' carbonyl ylide **197**, which then undergoes a subsequent 1,3-dipolar cycloaddition with the tethered indole (Scheme 45). Importantly, the diene and dienophile substituents complement and reinforce the [4+2]-cycloaddition regioselectivity dictated by the linking tether. The relative stereochemistry in the cycloadduct is controlled by a combination of (1) the dienophile geometry and (2) an exclusive *endo* indole [3+2]-cycloaddition sterically directed to the α-face opposite the newly formed fused lactam. This *endo* diastereoselection for the 1,3-dipolar cycloaddition has been attributed to a conformational (strain) preference dictated by the dipolarophile tether.[97] Cycloadduct **198** was eventually transformed into the natural product (−)-vindoline **199** in several additional steps. Extension of these cascade studies by the Boger group eventually provided for a total synthesis of the bisindole alkaloids vinblastine and vincristine.[98]



Scheme 45.

6. Concluding remarks

The application of the intramolecular dipolar cycloaddition of carbonyl ylides for the synthesis of natural products as described in this report spans a broad spectrum of organic chemistry. Carbonyl ylide formation in transition metal catalyzed reactions of diazo compounds is a particularly useful strategy and is dependent on the catalyst employed, the diazo species, the nature of the interacting carbonyl group and competition with other processes. The regio- and stereoselectivity of the internal cycloaddition is now well established, making it an attractive strategic disconnection for synthetic design of various natural products. As is the case in all new areas of research using catalysts, future investigations of the chemistry of these transition metal catalyzed diazo decompositions will be dominated by the search for asymmetric synthesis. From the results already in hand, it seems that efficient catalyst control over enantioselectivity can eventually be developed. Future developments will also depend on gaining a greater understanding of the mechanistic details of this fascinating and synthetically important process.

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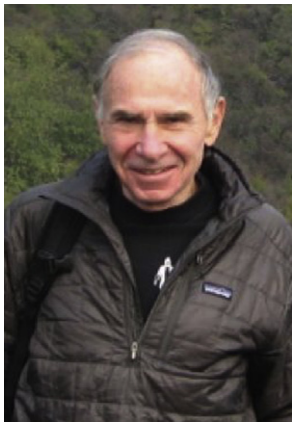
Biographical sketch



Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees from Columbia University. After an NSF postdoctoral position at the University of Wisconsin, he was appointed Assistant Professor of Chemistry at the Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as Associate Professor and was promoted to Professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. He has held visiting positions at University Claude Bernard, France, University of California at Berkeley, the University of Wurzburg, Germany, Imperial College of Chemistry, UK. and Melbourne University in Australia. Professor Padwa has been the recipient of an Alfred P. Sloan Fellowship, John S. Guggenheim Fellowship, Alexander von Humboldt Senior Scientist Award, a Fulbright Hays Scholarship, Senior Award in Heterocyclic Chemistry from the International Society of Heterocyclic Chemists, ACS Arthur C. Cope Scholar Award, an ACS Fellow and is the coauthor of more than 700 publications. He served as the Chairman of the Organic Division of the ACS and as President of the International Society of Heterocyclic Chemistry. He has also served as a member of the editorial boards of the Journal of the American Chemical Society, Journal of Organic Chemistry, Organic Letters, and has been the volume editor of Comprehensive Heterocyclic Chemistry, the Synthesis of Science (Vol. 27) and is currently one of the Associate Editors of the Journal of Organic Chemistry. His research interests include heterocyclic chemistry, dipolar cycloadditions, alkaloid synthesis, tandem transformations, organometallic chemistry, and organic photochemistry. Aside from chemistry, his other passion is mountain climbing in various parts of the world.