RHODIUM-CATALYZED CARBONYL YLIDE CYCLOADDITIONS

Reported by Nathan W. Duncan-Gould November 7, 2005

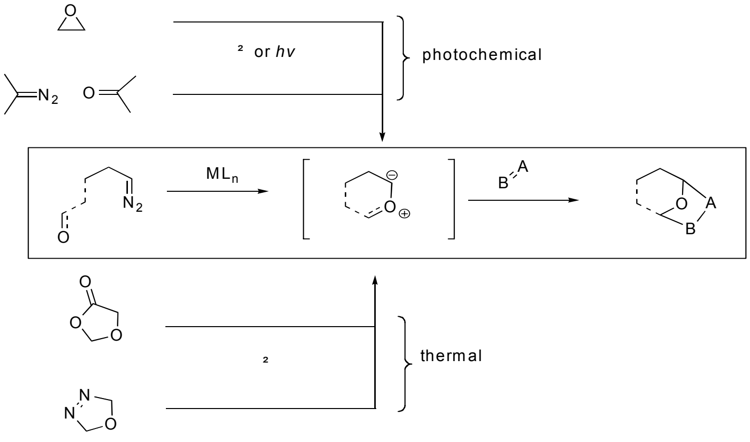
INTRODUCTION

The abundance of furan rings in natural products has stimulated the development of a [3+2]-dipolar cycloaddition method for their construction.[1] Many methods to generate the requisite dipole intermediate have been developed, but most require high temperatures and/or light (Scheme 1).[2] A route involving the decomposition of a α-diazo carbonyl compound by a transition metal takes place under milder conditions (often rt or below).[3] Originally discovered by using copper,[4] rhodium has been found to be a superior catalyst for this process.[5] With the first synthesis of an α-diazo carbonyl by Curtius[6,7] dating back to 1883 and the origins of 1,3 dipolar cycloaddition with Huisgen being in the early 1960's,[8] both aspects of the Rh-catalyzed carbonyl ylide cycloaddition hold a position at the heart of synthetic organic chemistry. The last twenty years has experienced a literal explosion of developments at the interface of these two chemistries, ranging from mechanism to total synthesis. The combination of empirical optimization and an ever-growing mechanistic understanding has rendered this reaction synthetically useful. This review will discuss the mechanistic implications of using a transition metal catalyst for carbonyl ylide cycloaddition, advances in enantioselective versions, and application to synthesis.

MECHANISM

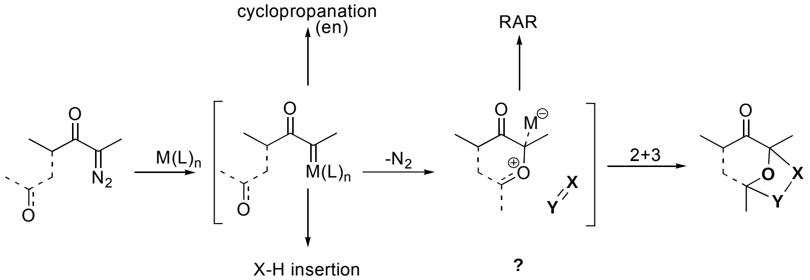
General

Scheme 1. Methods to generate carbonyl ylides

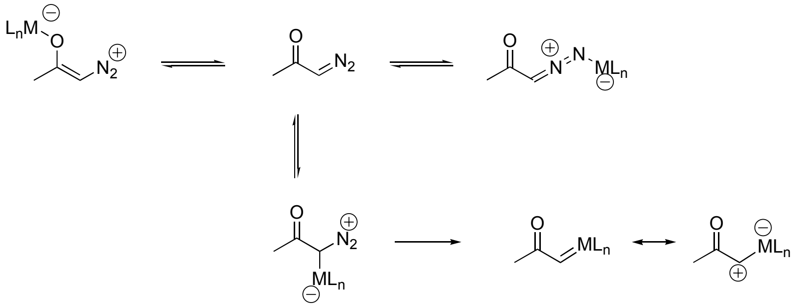


While employing a metallic catalyst to generate the carbonyl-ylide component can be done under synthetically useful conditions, there are a number of competing side reactions (Scheme 2).[9] The currently proposed mechanism involves diazo compound decomposition to generate a α-metallated intermediate, followed by addition of a carbonyl to generate an ylide, which may undergo cycloaddition. The structure, reactivity, and even existence of a metallated intermediate has stimulated continuous debate and speculation for the past 20 years,[3] and numerous methods—from computation to crystallography—have been applied to probe for this elusive species. One complicating factor is that metal-bound intermediates of this type have mostly been studied in the context of other reactions (i.e., cyclopropanations and insertion); so, the fact that the catalytically productive intermediates are the same is assumed (vide infra). Nevertheless, though not definitive, the proposed mechanism does provide a starting point that can be tested.[10] As drawn, the interaction of the metal in a Lewis acidic fashion with the alpha carbon should be the only catalytically productive interaction. As this model predicts, the more basic the diazo compound, the more reactive it is. Furthermore, only coordinative unsaturated metals (Lewis acidic, e.g. copper, cobalt, iron, palladium, rhodium, and ruthenium) catalyze diazo compound decomposition.

Scheme 2. Intermediate(s) and Competing Reactions



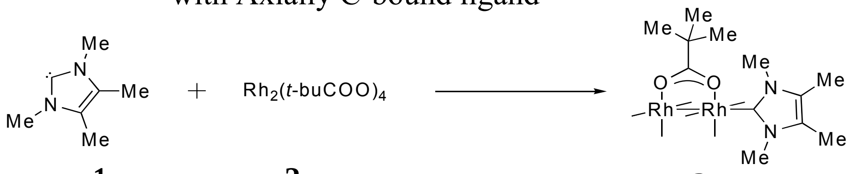
Scheme 3. Currently Accepted Mode of Lewis Acid Activation



Evidence for Intermediates

Two spectroscopic reports indicate the existence of a carbon-bound Rh(II) intermediate, one in the context of cyclopropanations and the other, C-H insertion. Padwa et al.[11] synthesized the N-heterocyclic carbene **3** (Figure 1, X-ray structure) in 73% yield by mixing N-heterocyclic carbene **1** and Rh(II) pivaloate **2**. This species was catalytically competent in both C-H insertion and alkyne cyclization.

Scheme 4. Synthesis of Dimeric Rhodium with Axially C-bound ligand



1 **2** **3**

Perhaps the most convincing evidence was provided by Kodadek,[12] who used low-temperature IR and NMR to detect both the diazo and iodinated monomeric intermediates (Figure 1) at -40 ºC. Upon warming, cyclopropanated products were obtained.

Through kinetic studies, Pirrung provided further support for the proposed mechanism. He found that the rate of C-H insertion with an asymmetric catalyst was ~1/2 that with an achiral catalyst, which can be rationalized by there being ½ the number of approach vectors (i.e.: D_2 vs. D_4). The last piece of evidence that rhodium is bound while the ylide is intact is that asymmetry is induced when a chiral non-racemic catalyst is used. This implies that the stereochemical information contained on the rhodium center is in intimate contact with the dipole during approach of the dipolarophile. Early studies with chiral auxiliaries focused on the isomunchnone series, using chiral vinyl ethers with a directing group. The ease with which Lewis basic functional groups can be interconverted on the dimeric rhodium center was soon realized. Thus, many amino acids, carboxamides, and a phosphonates have been incorporated into these species (Figure 3). Thanks to the work of Hodgson, Davies, and Hashimoto, the carbonyl-ylide cycloaddition can now be done in a catalytic and enantioselective manner[13-17]

Figure 1. Evidence for monomeric Rh-C intermediate

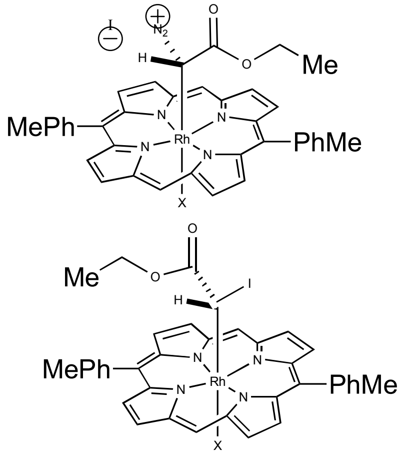
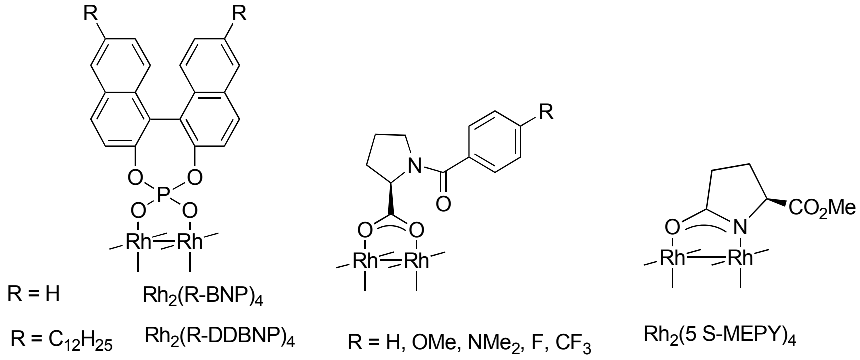


Figure 2. Representative Chiral Dimeric Rhodium Catalysts



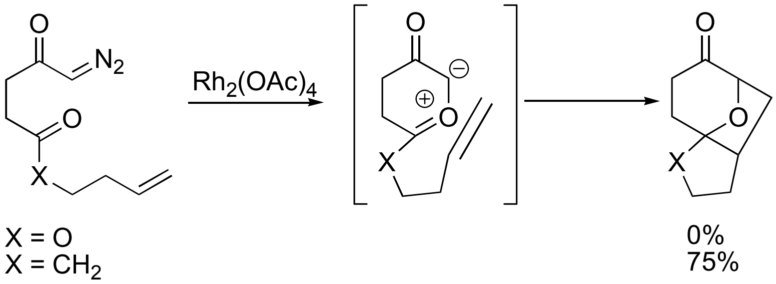
SCOPE

Initial investigations found great success with both aromatic and aliphatic tethers, and ketone carbonyl groups. Oddly, attempts to generate ylides from esters did not afford any identifiable products (Scheme 5). However, high yields of C-H inserted and 2,3-sigmatropic rearrangement products could be isolated when the tether contained an ether.[18] Empirically, it is found that ketones and amides both are the most reliable dipole precursors.[19]

Chemoselectivity

Increasing the complexity of the starting α-diazo carbonyl compound leads to a concomitant increase in the competing rate and probability of side reactions, such as cyclopropanations, insertion, aromatic cyloaddition and

Scheme 5. Initial Studies

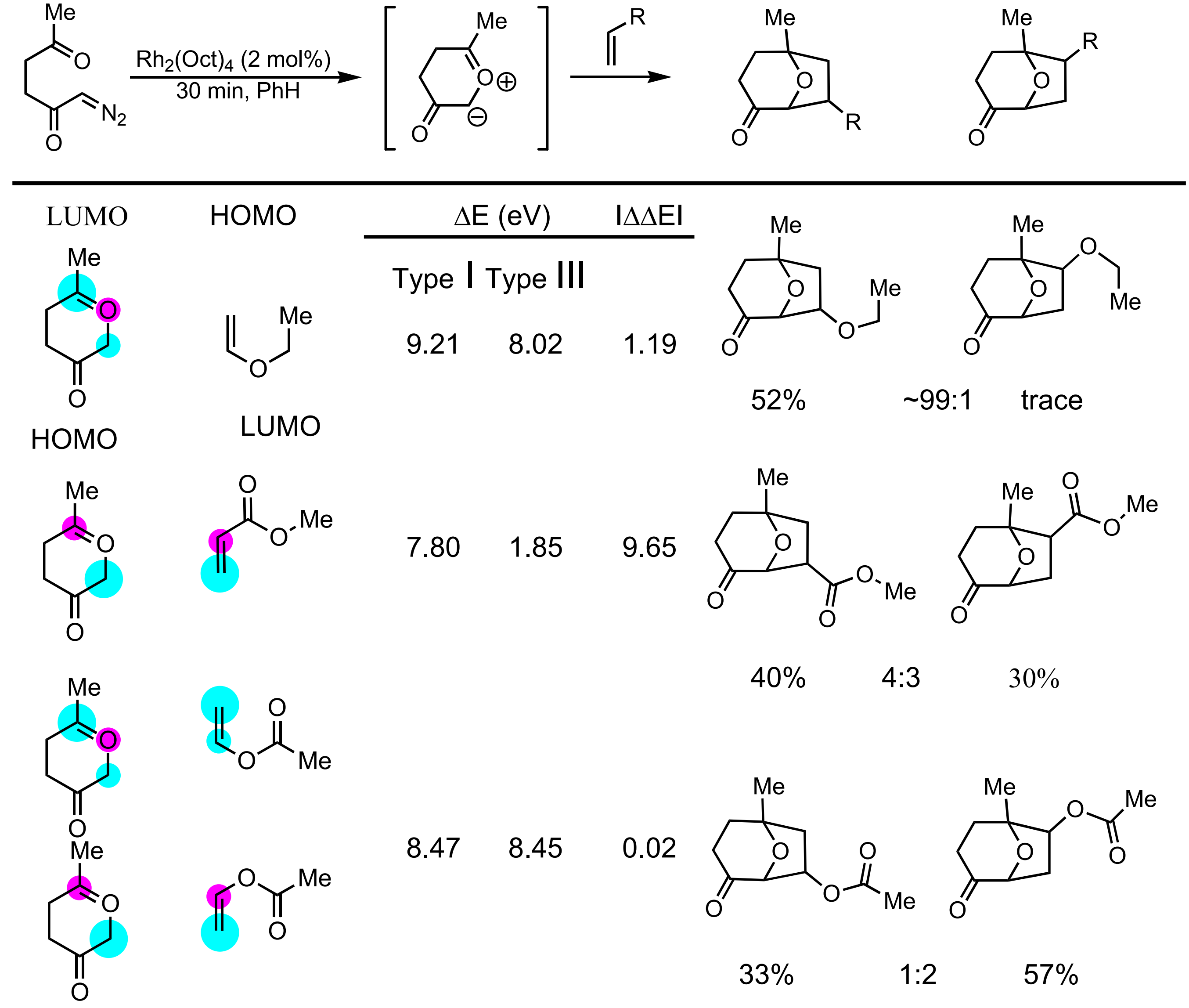


rearrangements. In general, five-membered carbonyl ylides are formed at the greatest rate, as expected. However, they often require that the α-position of the carbonyl be fully substituted, because the rate of 1,3-proton transfer is rapid. Six-membered carbonyl ylides suffer less from depletion due to this pathway, but in most cases the α-position is doubly substituted. Seven-membered carbonyl ylides have been shown to be synthetically useful and are long lived enough to participate in dipolar cycloadditions. All attempts to conduct a cycloaddition with an eight-membered carbonyl ylide has failed. Thus, it seems, at least for the time being, that the tether length is limited to four methylenes.[19,20]

Regioselectivity, Diasterioselectivity and Facial selectivity

Carbonyl ylide cycloadditions are controlled by the relative ratios of the coefficients of the frontier molecular orbitals[21,22] (Scheme 6). They are extremely forgiving electronically and will react

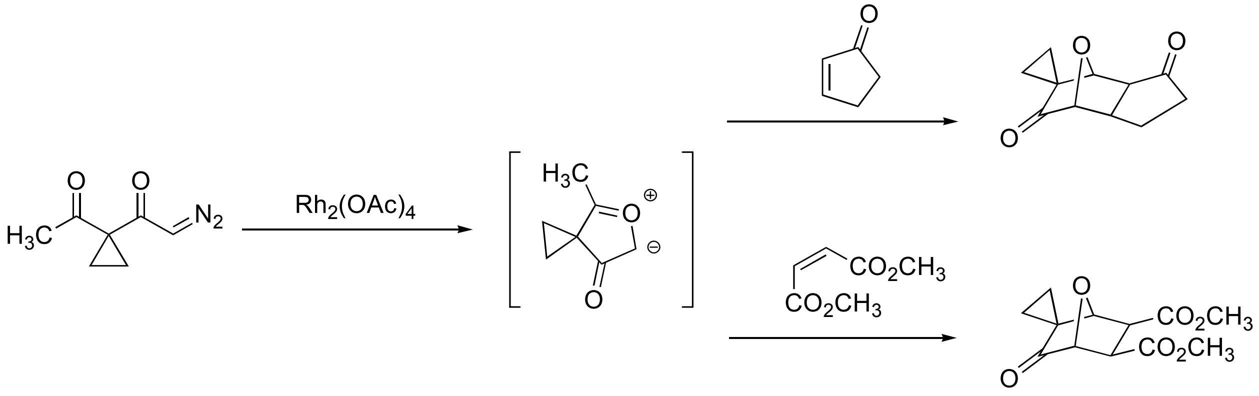
Scheme 6. Analysis of Regioselectivity



readily with both electron-rich and electron-poor dipolarophiles. Generally, the important interactions for electron-poor dipolarophiles are between the dipole HOMO and the dipolarophile LUMO (type III), while with electron rich dipolarophiles these roles are reversed (type I). The regioselectivity of the carbonyl ylide cycloaddition was examined systematically by Padwa and coworkers. They calculated the frontier molecular orbital coefficients on one particular carbonyl ylide and subjecting it to cycloaddition conditions with electron-rich and poor dipolarophiles. Both steric and conformational effects, can override the intrinsic selectivity dictated by the frontier molecular orbitals (entry 2).

While exo/endo selectivity (diastereoselectivity) is highly variable and substrate dependent, reactions are generally exo selective. Substitution of the alpha position of a diazo compound with a cyclopropyl ring typically results in high exo/endo ratios (Scheme 7). Control over exo/endo selectivity has been achieved by using chiral auxiliaries and catalysts.[5]

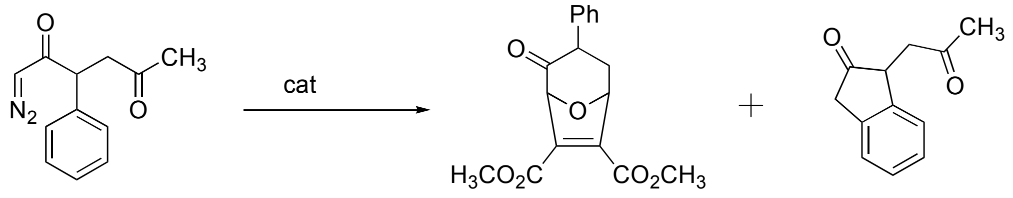
Scheme 7. Highly Diastereoselective Dipolar Dycloadditions



Competing Side Reations

Aromatic C-H vs. Ylide Formation – Changing the ligand can control the extent to which C-H insertions compete with cycloaddition. As can be seen in the competition between aromatic CH insertion and carbonyl ylide cycloaddition (Scheme 8), there is a drastic change in the product ratio depending on the rhodium ligand. The electron-withdrawing perfluorobutyrate gives exclusively CH insertion,

Scheme 8. C-H insertion vs. Ylide Formation

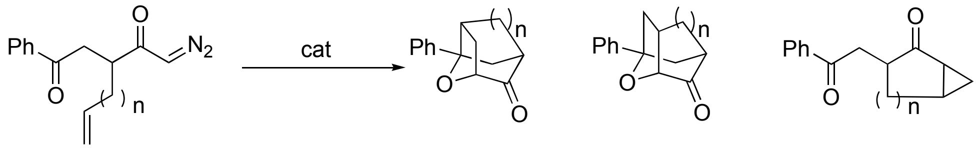


$Rh_2(OAc)_4$	60%	20%
$Rh_2(cap)_4$	90%	0%
$Rh_2(pfb)_4$	0%	85%

while the electron-donating cap gives exclusively cycloaddition product, the electronically intermediate rhodium acetate giving a 3:1 ratio favoring the cycloaddition product.

Cyclopropanation vs. Ylide Formation – Of course, attempts to trap the carbonyl ylide via an intramolecular dipolar cycloaddition encounter cyclopropanations as a major competing reaction. In practice, cyclopropanation dominates always a major pathway when the product is a [3.1.0] bicyclic system (n = 1) but does not compete as much when the product is a bicyclic [4.1.0] system (n = 2), (Scheme 9).[22]

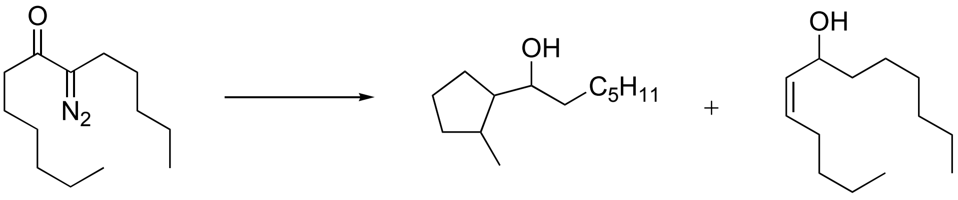
Scheme 9. Cyclopropanation *vs.* Ylide Formation



	n = 1	n = 2	n = 1	n = 2	n = 1	n = 2
$Rh_2(OAc)_4$	10%	60%	47%	11%	37%	13%
$Rh_2(tfa)_4$	34%	67%	12%	0%	30%	0%
$Rh_2(cap)_4$	12%	70%	52%	11%	32%	17%

ß-Hydride elimination vs. Ylide Formation – The third most commonly encountered side reaction is simply ß-hydride elimination. The rate of elimination is greatly enhanced by strongly electron-withdrawing ligands. The opposite is true for CH insertion, and it is sometimes possible to isolate aliphatic CH insertion products when strongly electron-donating ligands are used (Scheme 10).[5]

Scheme 10. ß-Hydride elimination vs. Ylide Formation

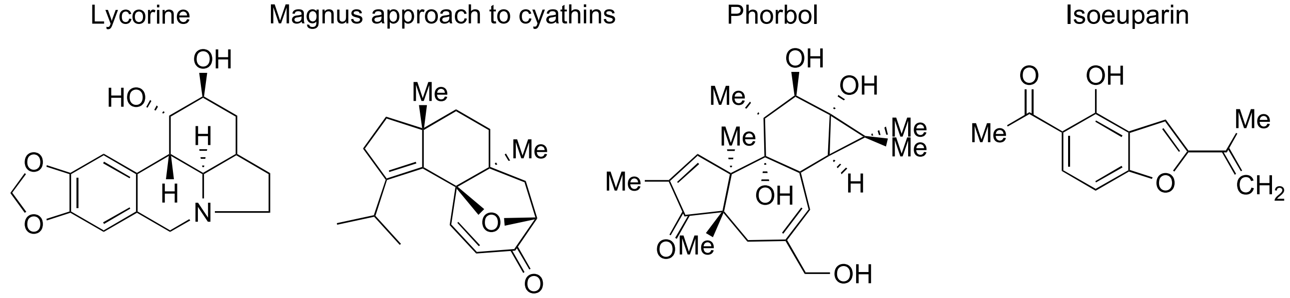


$Rh_2(OAc)_4$	70:30
$Rh_2(OBz)_4$	60:40
$Rh_2(O_2C\text{-}p\text{-}ClC_6H_4)_4$	40:60
$Rh_2(OAc)_4$	38:62

NATURAL PRODUCT SYNTHESIS

Despite the numerous possible and competing reactions, the rhodium-catalyzed cycloaddition of carbonyl ylides has been implemented in many natural product syntheses, and the overall utility of this method is displayed by the rapid construction of many naturally occurring skeletal systems (Figure 4).[5] Many alkaloid core structures have been constructed by use of an imide of amide carbonyl donator allowing rapid entry into the isomunchnone class of dipoles or by incorporating an nitrogen containing functional group in the tether. Also, rapid construction of tropolones and 7-membered allylic alcohols is realized by opening of the furan ring after cycloaddition.

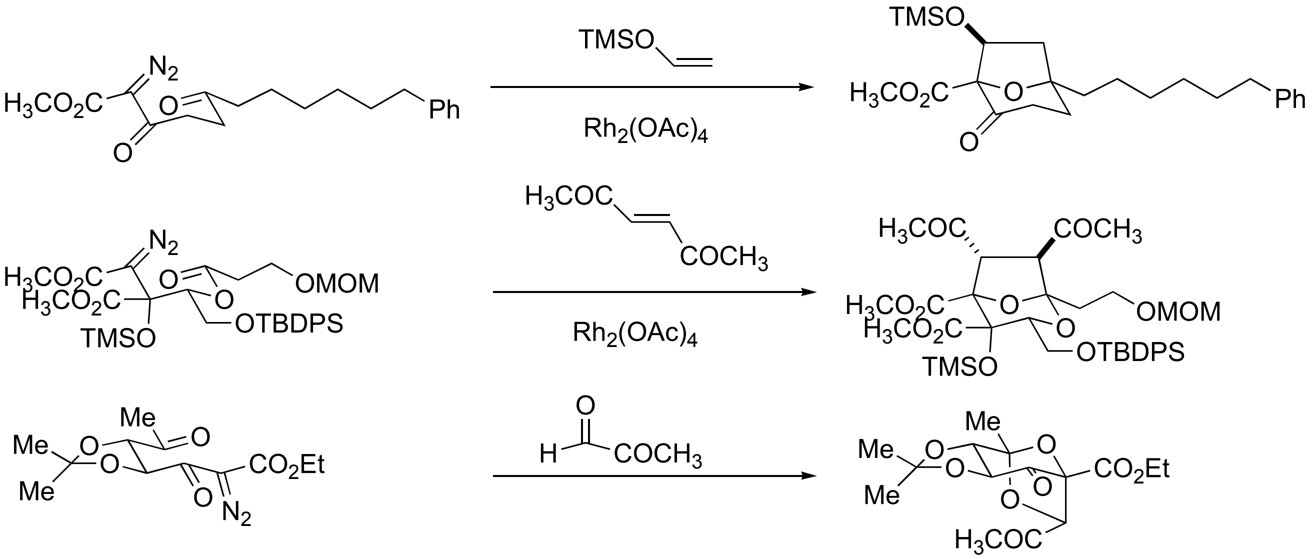
Figure 3. Representative Natural Product Cores Synthesized by Carbonyl Ylide Cycloaddition



Zaragozic Acid

The laboratories of Koyama[23], Hashimoto[24] and Hodgson[25] all have independently described carbonyl ylide-cycloaddition strategies for the construction of the heterocyclic core of Zaragozic Acid A (Scheme 11). Koyama's approach used a vinyl ether to insert the requisite two-carbon bridge and C6 hydroxyl group. The Hashimoto approach utilized a similar cycloaddition strategy but with the inverse electron demand. Further elaboration of the bridging 1,4 diketone functionality to a diol has not yet been reported. Hodgson reports a cycloaddition strategy in which the diol functionality is already intact and the cycloaddition was used to install an anomeric oxygen and bridging carbon concurrently by using methyl glyoxylate as the heterodipolarophiles. Each of the approaches demonstrates the ease with which complex heterocyclic ring systems can be constructed.

Scheme 11. Syntheses of the Core of Zaragozic Acid



CONCLUSIONS

Thanks to the pioneering work of Huisgen, the construction of complex heterocycles by the [3+2] dipolar cycloaddition has become a practical and useful method. Furans have emerged as a recent addition to this class of reactions with the discovery that carbonyl ylides can be generated under mild conditions with dimeric rhodium catalysts. The method has been developed extensively over the past 20 years, with many variations of intra and intermolecular dipolarophiles and different carbonyl group donors. The cycloaddition has an immense scope, as carbonyl-ylide dipoles undergo cycloaddition with a wide range of dipolarophiles, from extremely electron rich and poor, to heterodipolarophiles. Furthermore, regiochemistry can usually be rationalized by a first order FMO analysis, so that the requisite dipolarophile can be rationally designed to give the desired product. Through recent work by Hodgson, this reaction can be added to the catalytic enantioselective toolbox of synthetic organic chemists . Finally, the ease with which the ligands on a rhodium dimer can be interchanged allows for fine-tuning of reaction conditions. The carbonyl-ylide cycloaddtion will certainly continue to experience active development in the arena of natural product chemistry in the years to come.

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