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The interaction of rhodium carbenoids with carbonyl compounds as a method for the synthesis of tetrahydrofurans

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Abstract

The transition metal catalyzed reaction of α-diazo carbonyl compounds has found numerous applications in organic synthesis, and its use in either heterocyclic or carbocyclic ring formation is well precedented. In contrast to other catalysts that are suitable for carbenoid reactions of diazo compounds, those constructed with the dirhodium(II) framework are most amenable to ligand modification that, in turn, can influence reaction selectivity. The reaction of rhodium carbenoids with carbonyl groups represents a very efficient method for generating carbonyl ylide dipoles. Rhodium-mediated carbenoid–carbonyl cyclization reactions have been extensively utilized as a powerful method for the construction of a variety of novel polycyclic ring systems. This article will emphasize some of the more recent synthetic applications of the tandem *rhodium carbenoid cyclization/cycloaddition cascade* for natural product synthesis. Discussion centers on the chemical behavior of the rhodium metal carbenoid complex that is often affected by the nature of the ligand groups attached to the metal center.
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Keywords: Rhodium(II); Carbenoid; Diazoketone; Carbonyl ylide; 1,3-dipole; Dipolar-cycloaddition; Tetrahydrofuran

1. Introduction

In recent years, a widespread upsurge of activity in the stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans has occurred [1]. Although a variety of methods exist for tetrahydrofuran synthesis [2–4], few of these are based on an annulation strategy [5], and of those that are, single step procedures are uncommon [6]. Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation [7]. One of the simplest routes for the generation of carbonyl ylides involves the addition of a metallo carbenoid onto the oxygen atom of a carbonyl group [8–11]. The study of this cyclization reaction has also stimulated interest in the use of metallo carbenoids as reactive intermediates for the generation of other types of ylides [10].

2. Carbonyl ylide cycloadditions

Many studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a metallo carbenoid with a carbonyl oxygen [12–16]. Reactions of carboalkoxycarbenes with carbonyl compounds were described as early as 1885 [17] and the structures of the dioxolane products were proposed in 1910 [18]. The early investigations by Huisgen and de March [19] with dimethyl diazomalonate (**1**) revealed that in reactions with benzaldehyde, a mixture of isomeric 1,3-dioxolanes (**2**) was formed (Scheme 1) when $Rh_2(OAc)_4$, $Cu(acac)_2$ or CuOTf was used as the catalyst. Since

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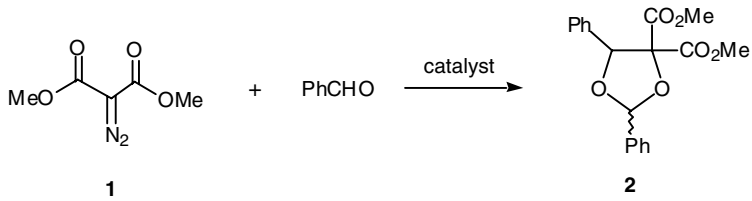
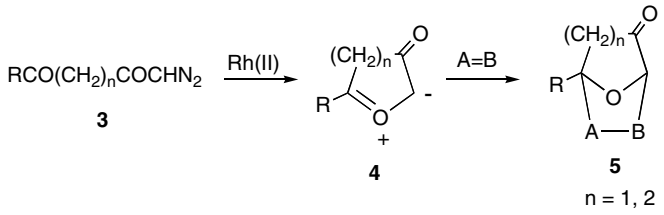


Scheme 1.

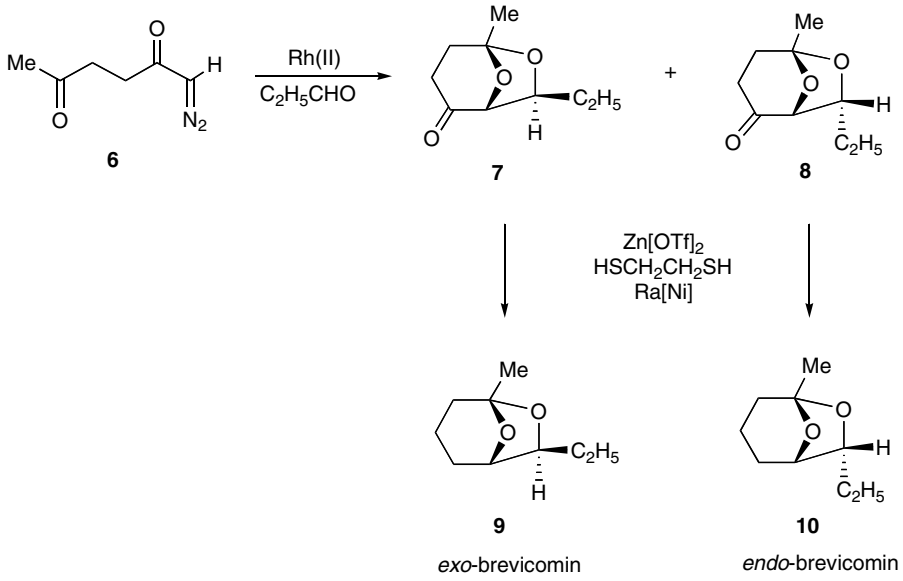
the initial Huisgen report, the catalytic generation of carbonyl ylides from diazo compounds has developed into a powerful reaction for organic synthesis [20–22].

In 1986, our research group at Emory started a program to synthesize bridged hetero-substituted bicycloalkanes from the rhodium(II)-catalyzed cyclization-cascade of 1-diazoalkanediones (**3**) [23]. The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate and subsequent cyclization of the electrophilic carbon onto the distal keto group to generate a cyclic carbonyl ylide, followed by 1,3-dipolar cycloaddition (Scheme 2) [24]. Most of our studies were carried out with five and six-membered ring systems [25]. The resulting cyclic dipole (i.e., **4**) always contained a carbonyl group within the ring. We [9] and others [10] have found that the intramolecular trapping of carbonyl ylide dipoles with tethered alkenes represents an extremely effective method for the synthesis of a variety of natural products.

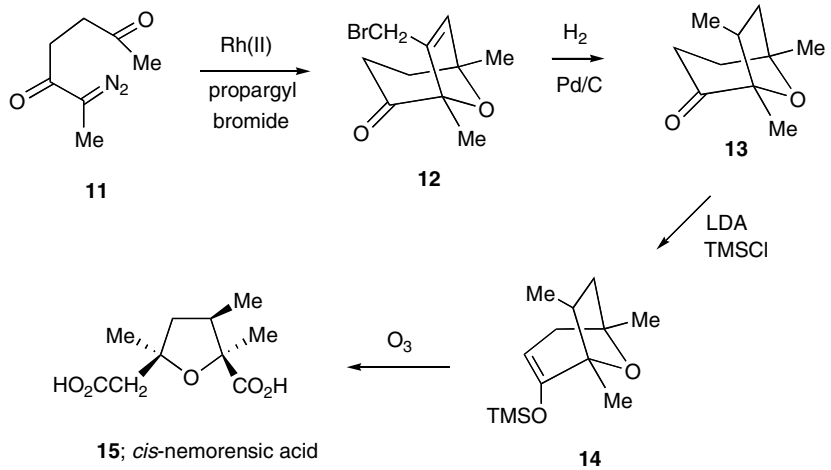
This methodology was initially applied to the synthesis of *exo*- and *endo*-brevicomin [26]. The *exo* and *endo* isomers of brevicomin are exuded by the female Western Pine Beetle and the *exo*-isomer is known to be a key component of the aggregation pheromone of this destructive pest [27]. Cycloaddition of 1-diazo-2,5-hexanedione (**6**) with rhodium(II) acetate in the presence of propionaldehyde afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in 60% isolated yield as a 2:1-mixture of *exo* **7** and *endo* **8** isomers (Scheme 3). The isomers were separated by silica gel chromatography and were subsequently



Scheme 2.



Scheme 3.



Scheme 4.

carried on to *exo*- and *endo*-brevicomin (**9** and **10**) in good yield.

Another example which highlights the versatility of the tandem cascade sequence for the synthesis of structurally complex tetrahydrofurans was recently reported by Hodgson and coworkers [28]. 1,3-Dipolar cycloaddition of propargyl bromide with the carbonyl ylide derived from 6-diazoheptane-2,5-dione (**11**) represents the key step in a concise synthesis of *cis*-nemorensic acid (**15**). Thus, diazo-dione (**11**) underwent $Rh_2(OAc)_4$-catalyzed tandem carbonyl ylide formation-cycloaddition with propargyl bromide to give cycloadduct **12** in good yield (Scheme 4) [28]. Reaction of cycloadduct **12** with H_2–Pd/C in methanol effected both hydrogenolysis of the C–Br bond and *exo* selective alkene hydrogenation to furnish a single saturated ketone **13** with the correct relative stereochemistry at all three stereocenters for *cis*-nemorensic acid synthesis. Formation of the silyl enol ether **14** under standard conditions was followed by oxidative cleavage to give *cis*-nemorensic acid (**15**).

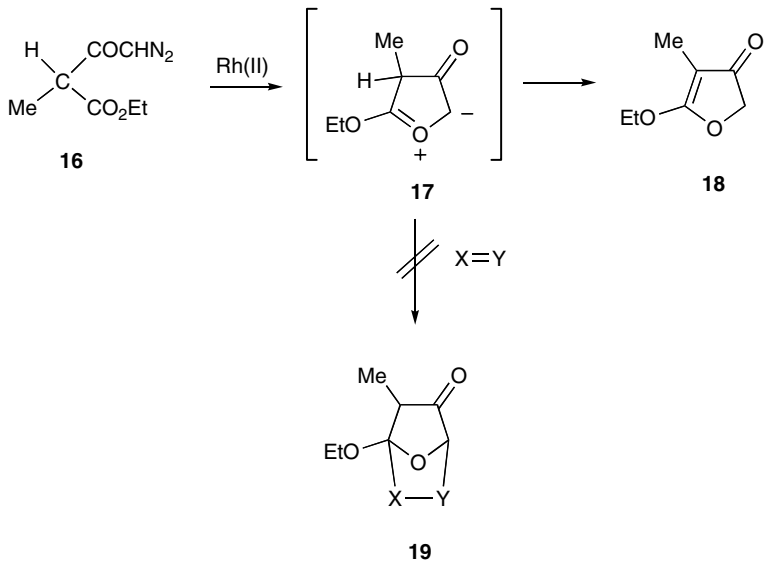
3. Spatial proximity effects

The primary spatial requirement for intramolecular carbonyl ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the carbonyl group and the diazoketone would have on the course of the reaction was studied by varying the length of the methylene tether separating the two functionalities [25]. The majority of systems examined in the literature involved the formation of a six-membered ring carbonyl ylide intermediate. The ease of ring closure as a function of ring size generally increases on going from three- to five-membered rings and then decreases rapidly [29]. This observation is perfectly compatible with the fact that five-membered ring carbonyl ylide formation occurs smoothly upon treatment of 1-diazobutane-2,4-diones with rhodium(II) carboxylates [25]. For example, the reaction of ethyl 4-diazo-2-methyl-3-oxobutyrate (**16**) with the Rh(II) catalyst afforded 5-ethoxy-4-methyl-3-(2*H*)-furanone (**18**) in 90% isolated yield (Scheme 5). The mechanism by which **16** is converted into **18** involves rapid cyclization of the rhodium carbenoid onto the neighboring carbonyl group to give the five-ring carbonyl ylide **17**, which undergoes a subsequent proton transfer [30]. All attempts to trap the suspected 1,3-dipole **17** with a variety of dipolarophiles failed to produce a dipolar cycloadduct **19**. Apparently the highly stabilized dipole **17** transfers a proton at a faster rate than bimolecular cycloaddition. The formation of furanone **18** comes as no real surprise since one of the characteristic reactions of carbonyl ylides derived from the reaction of α-diazoalkanes with ketones consists of an intramolecular proton transfer [30].

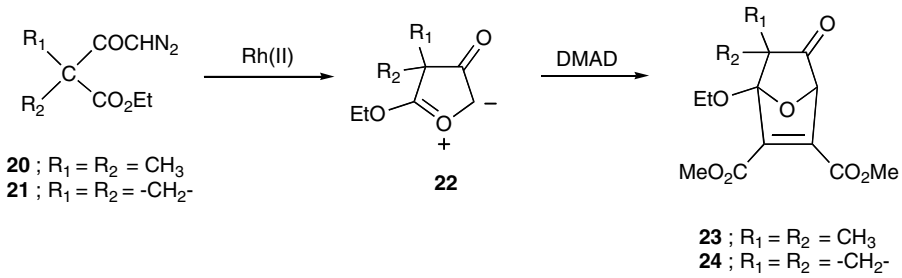
When the α-position of the 1-diazobutanedione skeleton was blocked with two substituent groups (i.e., **20** or **21**), the rhodium-catalyzed cycloaddition with dimethyl acetylenedicarboxylate (DMAD) led to the derived carbonyl ylide cycloadducts **23** (85%) or **24** (55%), respectively (Scheme 6) [25].

4. Illudin family of sesquiterpenes

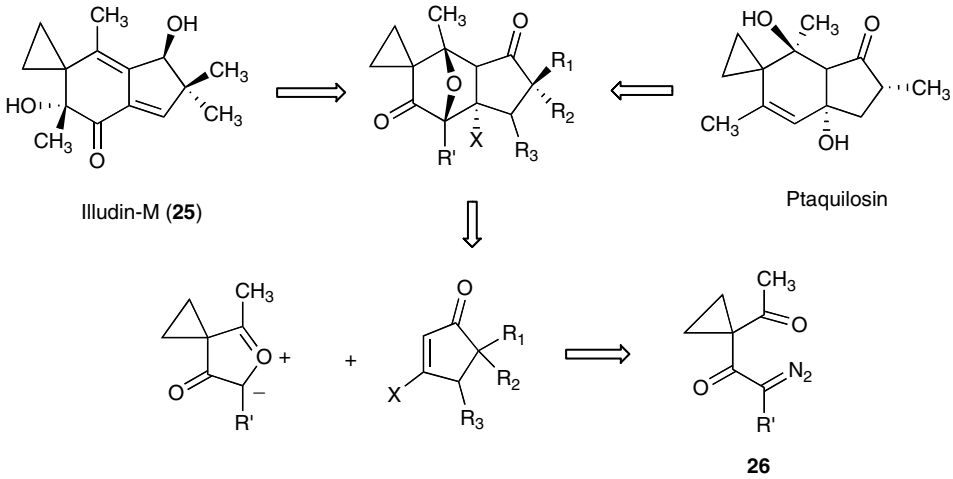
Products of five-ring carbonyl ylide cycloaddition derived from α-diazoketone (**26**) can undergo cleavage of the oxabicyclic ring system to produce the core structure of the illudin (**25**) and ptaquiloxin family of sesquiterpenes [31]. This strategy provides for a rapid assembly of the basic core unit of the target molecules having most of the functionality in place (Scheme 7). Thus,



Scheme 5.



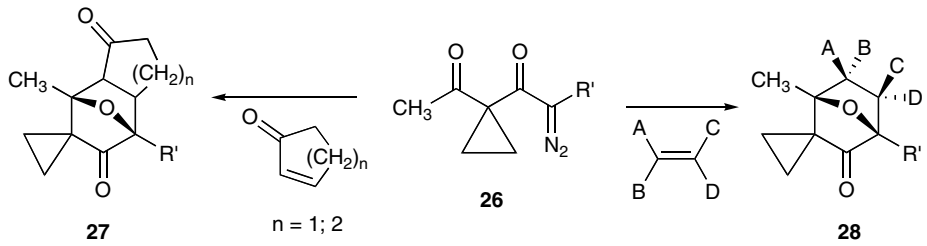
Scheme 6.



Scheme 7.

the Rh(II)-catalyzed cycloaddition reaction of cyclopropyl-substituted α-diazoketones of type **26** with a variety of acyclic and cyclic alkenes gave oxabicyclo-[2.2.1]octanes (**27**) and (**28**). These could be readily cleaved with base or samarium iodide to produce the desired skeleton (Scheme 8).

(±)-Illudin M (**25**), a toxic sesquiterpene isolated from the jack-o'-lantern mushroom, has been synthesized via



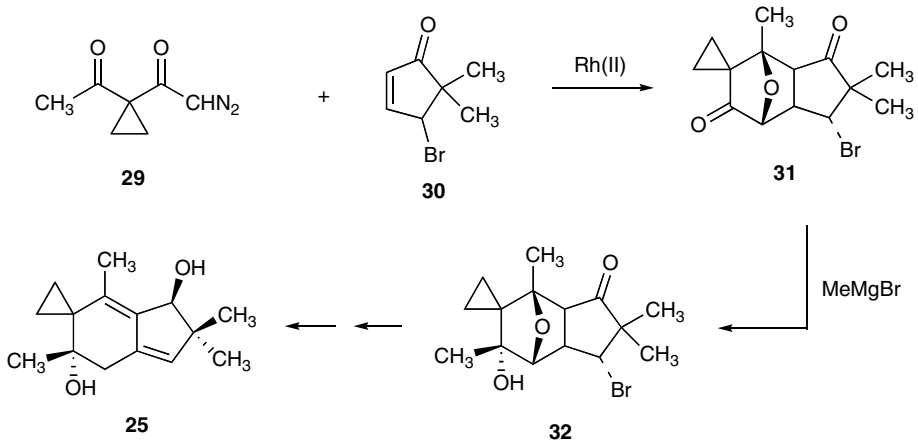
Scheme 8.

the same tandem cyclization–cycloaddition strategy using diazo ketone **29** as the starting substrate. The first and key step of the synthesis consisted of a carbonyl ylide 1,3-dipolar cycloaddition reaction with cyclopentenone **30** to form cycloadduct **31** with high diastereoselectivity. Several functional group manipulations were carried out to eventually give illudin M (**25**) in modest yields (Scheme 9) [32].

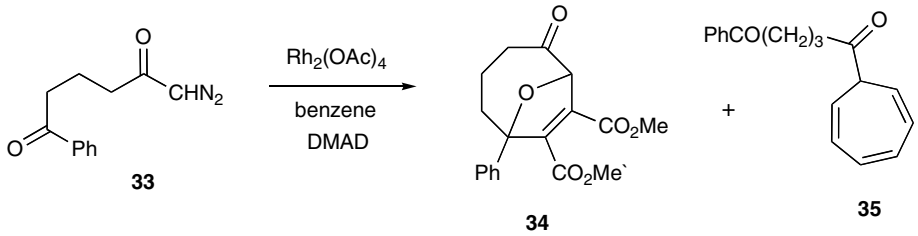
Separating the interacting carbonyl group from the carbenoid center by three methylene units resulted in the formation of a seven membered ring carbonyl ylide intermediate [33]. Thus, the rhodium(II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione (**33**) in benzene using dimethyl acetylenedicarboxylate afforded a 2:1 mixture of cycloadduct **34** (45%) as well as cycloheptatriene **35** (22%) (Scheme 10). It would appear that by extending the tether to three methylene groups, the rate of intramolecular cyclization is sufficiently retarded to allow the bimolecular reaction with benzene to competitively occur.

5. Metal-complexed carbonyl ylides

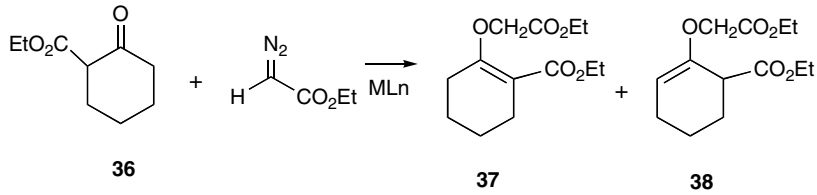
One of the first suggestions that carbonyl ylides derived from metal catalyzed diazo decomposition could proceed via a metal-complexed dipole was made by Landgrebe in 1989 [34]. The Rh(II)-catalyzed reaction of ethyl diazoacetate with β-ketoester **36** afforded a mixture of enol ethers **37** and **38** which are derived from an intermediate carbonyl ylide intermediate (Scheme 11). Most interestingly, the ratio of regioisomeric enol ethers



Scheme 9.



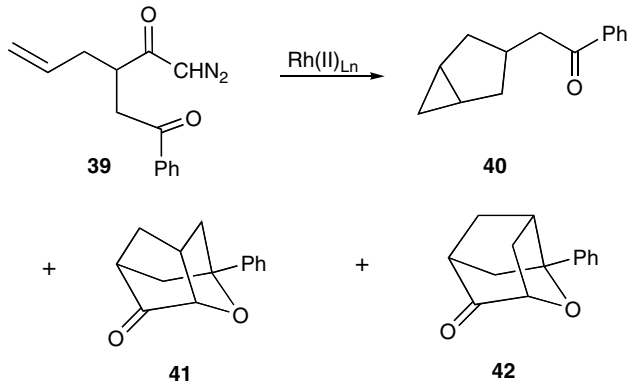
Scheme 10.



Scheme 11.

was found to be catalyst dependent which led Landgrebe to conclude that the catalyst is present during the 1,4-sigmatropic shift of hydrogen [34].

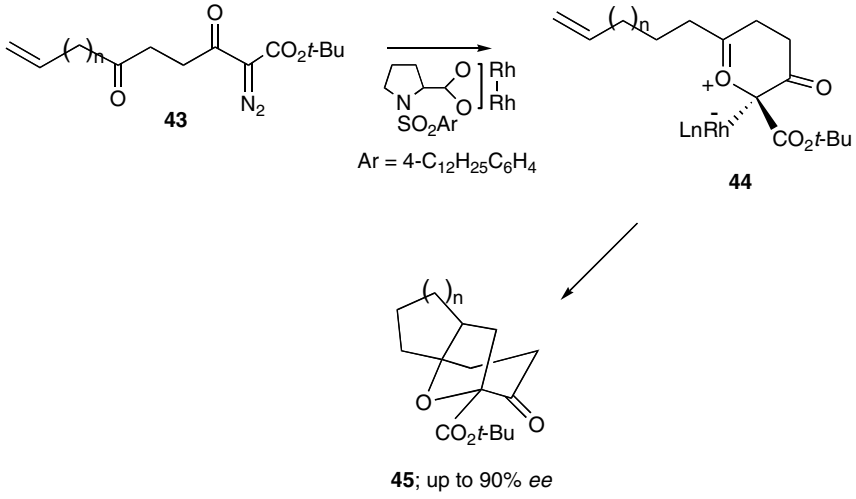
Another study which originated from the author's laboratory provides even more definitive support for the involvement of a metal associated dipole in a diazo catalyzed cycloaddition reaction [35]. A series of competition experiments were carried out using diazoketone **39** (Scheme 12). Although the chemoselectivity profile was found to be insensitive to the catalyst used, a regiochemical crossover in the carbonyl ylide cycloaddition vs. cyclopropanation was observed on changing the catalyst. The major regioisomer formed used $Rh_2(OAc)_4$ or $Rh_2(cap)_4$ (cap = caprolactamate) was found to be **41**. However, cycloadduct **42** was the predominant product formed under $Rh_2(tfa)_4$ (tfa = trifluoroacetate) catalysis. Its formation probably involves coordination of the rhodium catalyst with the carbonyl oxygen, electrophilic addition to the diazo carbon, then dinitrogen loss and ring closure. Intramolecular cyclopropanation (i.e., **40**) 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.



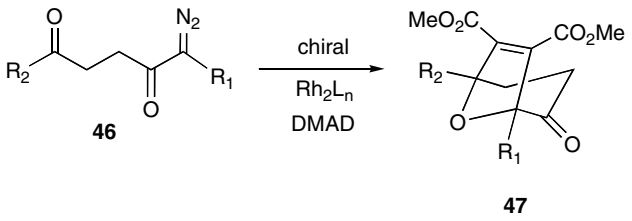
Scheme 12.

6. Asymmetric induction studies

Once the metal complexed carbonyl ylide is formed from the diazo catalyzed reaction, 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 [10]. Hodgson and coworkers [36] reported



Scheme 13.



Scheme 14.

the first examples of enantioselective carbonyl ylide cycloaddition (up to 53% ee) using unsaturated α-diazo-β-ketoesters (Scheme 13). Later work by this same group showed that it was possible to achieve a 90% ee for the cycloaddition reaction [37]. 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 (e.g., **44**).

Enantioselective tandem carbonyl ylide formation–intermolecular cycloadditions have been reported by Doyle and coworker [38], Ibata and coworkers[39], Hashimoto and coworkers [40] and Hodgson et al. [41]. The asymmetric induction in these cycloadditions was generally low (<30% ee), aside from the work of Hashimoto using α-diazoketones with DMAD as the dipolarophile, where ee values up to 92% were reported (Scheme 14) [40]. However, only a small range of dipolarophiles have been examined in asymmetric intermolecular cycloadditions of carbonyl ylides to date and further studies are clearly warranted. More recent studies by Hodgson et al. [36] using α-aryl-α-diazodiones suggest that a complex blend of electronic effects from the dipole and dipolarophile, together with the nature of the catalyst, contribute to the origin of asymmetric induction.

7. Conclusion

Tandem carbonyl ylide generation from the reaction of metallo carbenoids with carbonyl compounds constitutes an important method for the synthesis of complex tetrahydrofurans. Effective carbonyl ylide formation in transition metal catalyzed reactions of diazo compounds depends on the catalyst, the diazo species, the nature of the interacting carbonyl group and competition with other processes. As is the case in all new areas of research using metallo 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 these fascinating and synthetically important processes.

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