Transition Metal Catalyzed Higher-Order Cycloadditions – The Direct Formation of Eight-Membered Ring Systems

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INTRODUCTION

Eight-membered rings are notoriously difficult to prepare because of unfavorable entropic and enthalpic effects as well as the propensity for transannular interactions.[1] The impetus for development of methodologies for their construction historically has been limited because few natural products containing such systems were known. However, in the last two decades there has been a rapid increase in the number of natural products containing cyclooctanoid systems, which has helped to drive the development of new methodologies for their construction.[2] [3,3]-Sigmatropic rearrangements from smaller, more accessible rings has recently gained popularity because of the highly predictable stereochemical nature of these reactions. Fragmentation of complex cycles, metal-mediated metathesis, and other acyclic ring closures have also been utilized.[2]

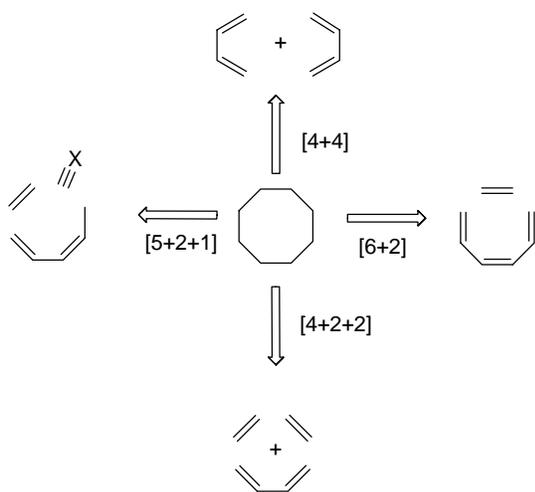Higher order cycloaddition reactions that directly form eight-membered rings have not been extensively utilized toward natural product synthesis because they suffer from a lack of periselectivity and often yield complex mixtures.[3] However, recent advances in this field display many characteristics normally associated with synthetically attractive processes such as a rapid increase in molecular complexity, accommodation of extensive functionality and good control over the creation of new stereocenters. Some recent progress toward the development of these methodologies is presented below.

Figure 1. Synthetically useful ways a cyclooctanoid can be formed from cycloadditions

[6+2] Cycloadditions

Examples of stoichiometric Fe(0) and Cr(0) promoted thermal [6+2] cycloadditions of substituted cycloheptatrienes with 2π partners have been reported by Pettit,[4,5] Grevels,[6] Sheridon,[7] and Rigby.[3] The catalytic version of this transformation was developed by Rigby.[8,9]

Table 1. [6+2] cycloaddition of cycloheptatriene **2** and ethyl acrylate in the presence of catalyst **1**.

catalyst (mol%)	*hv* time (h)	temp(C)	yield %	ratio (**4:5**)
(C$_7$H$_8$)Cr(CO)$_3$ (10%)	none	r.t.	61	1:0
none	none	160	65	0:1
(C$_7$H$_8$)Cr(CO)$_3$ (10%)	2	r.t.	81	1:0

The reaction of cycloheptatriene **2** with ethyl acrylate **3** in the presence of (η^6-naphthalene)tricarbonylchromium(0) **1** and magnesium metal provided cyclooctanoid **4** in a 61% yield; irradiation of the mixture with light increased the yield to 81% (Table 1). Thermolysis of the same mixture without a metal catalyst yielded a mixture of the [4+2] cycloadduct **5** and a trace amount of [6+2] cycloadduct **4** in 65% yield, demonstrating that the presence of the catalyst changes the periselectivity of the cycloaddition. Proper choice of solvent was crucial for maintaining catalytic activity, and sign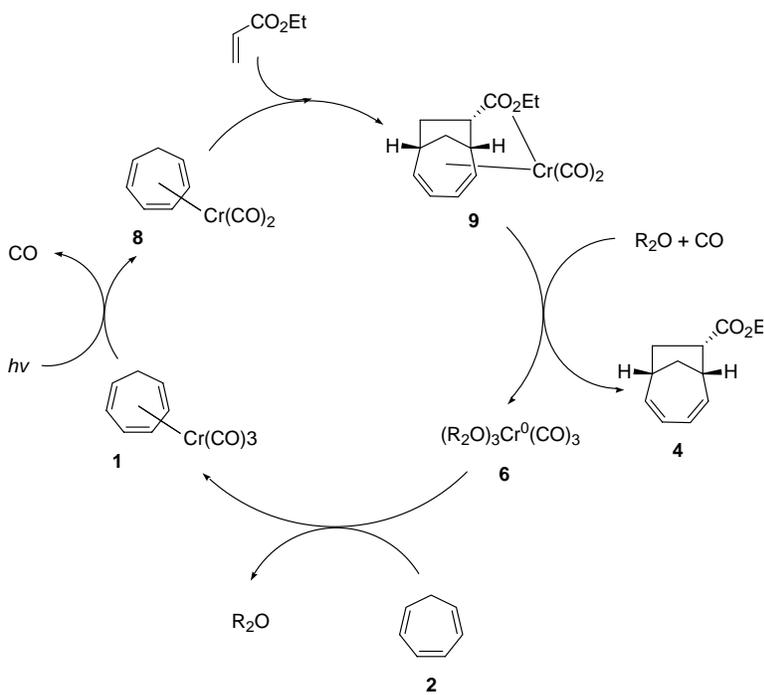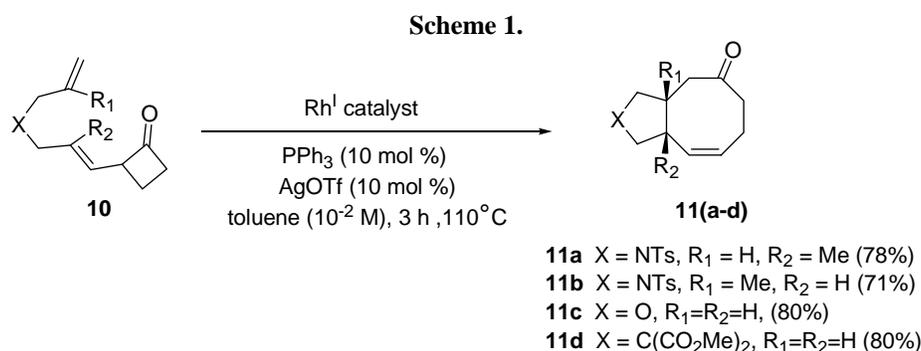ificant catalytic activity was observed in methanol, ethanol and THF. However, water, diethyl ether, DMF and trifluoroethanol all inhibited the cycle. It is necessary to include magnesium powder to obtain good yields as well, presumably to return Cr^{+3} to the active Cr^0 state. The above observations led the authors to propose the catalytic cycle shown in Figure 2. The solvent is believed to play a crucial role in decomplexing intermediate **9** to give the active catalytic complex **6**. Thus the

Figure 2. Proposed mechanism of [6+2] cycloaddition catalyzed by **1.**

solvent must be nucleophilic enough to efficiently decomplex **9**, but should also be capable of being readily displaced by **2**. The role of light is proposed to aid in ligand decomplexation to produce the coordinatively unsaturated chromium species **8**.

The formal [6+2] cyclization of vinylcyclobutanones and alkenes was developed by Wender and coworkers[10] yielding *cis* fused 5-8 ring systems almost exclusively. In the presence

Scheme 1.

11a X = NTs, R_1 = H, R_2 = Me (78%)
11b X = NTs, R_1 = Me, R_2 = H (71%)
11c X = O, R_1=R_2=H, (80%)
11d X = C(CO$_2$Me)$_2$, R_1=R_2=H (80%)

of a rhodium catalyst, silver triflate, and triphenylphosphine, vinylcyclobutanones **10** were found to undergo intramolecular cyclization to yield cyclooctenones **11** in 71-80% yield and as a single diastereomer (Scheme 1). The reaction tolerates methyl substitution of the alkenes to yield quaternary centers, and the 2π component can be alkene or allene, however alkynes provide poor yields.

Mechanistic insight into the catalytic cycle was provided by byproduct **14**, which was
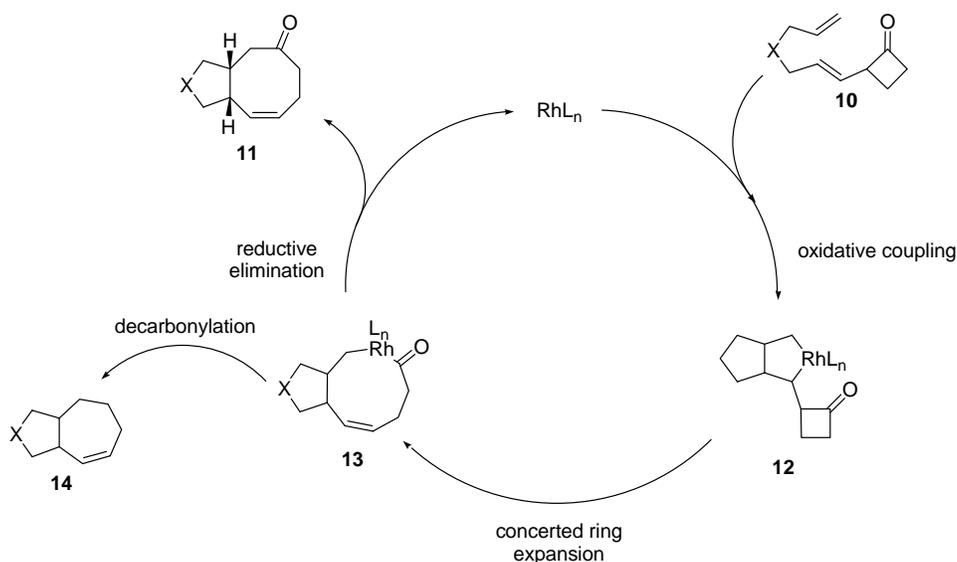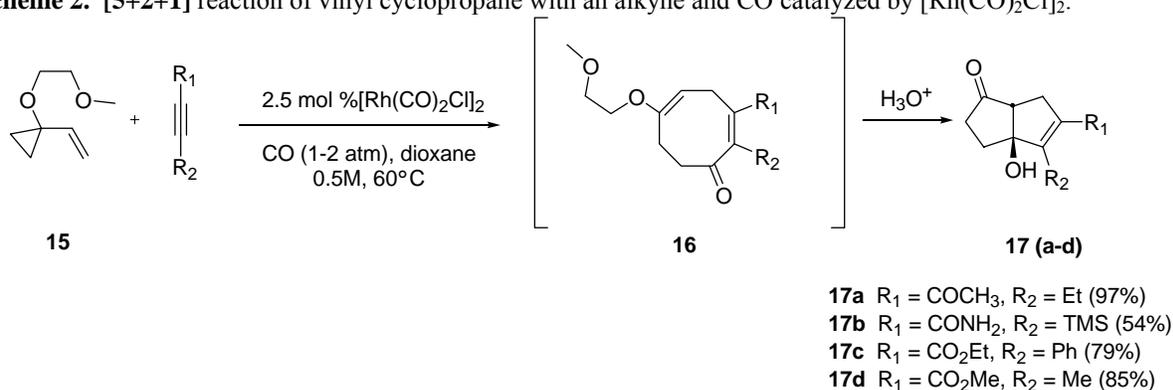

Figure 3. Proposed catalytic cycle of Rh catalyzed [6+2] cycloaddition.

isolated from the reaction mixture in up to 17% yield under certain conditions (Figure 3). It was determined to result from rhodium catalyzed decarbonylation and suggests that the mechanism proceeds through metallocycle **13**; this led to the proposed mechanism. Complexation and oxidative coupling yields metallocyclopentane **12,** which undergoes a concerted ring expansion to metallocycle **13**. Reductive elimination then regenerates the catalyst and product **11**. The formation of byproduct **14** could not be suppressed by conducting the reaction under a CO atmosphere; however, addition of PBu$_3$ was shown to suppress its formation to only 7%.

[5+2+1] Cycloadditions

The observations of byproduct formation described above led to the development of a

Scheme 2. **[5+2+1]** reaction of vinyl cyclopropane with an alkyne and CO catalyzed by [Rh(CO)$_2$Cl]$_2$.

15 **16** **17 (a-d)**

17a R$_1$ = COCH$_3$, R$_2$ = Et (97%)
17b R$_1$ = CONH$_2$, R$_2$ = TMS (54%)
17c R$_1$ = CO$_2$Et, R$_2$ = Ph (79%)
**17d** R$_1$ = CO$_2$Me, R$_2$ = Me (85%)

[5+2+1] cycloaddition. Wender and coworkers reasoned that if intermediate **14**, produced from an appropriate [5+2] pathway, could be intercepted by CO it would yield an eight-membered ring.[11] The reaction proceeded efficiently with vinylcyclopropane **15** and an alkyne in the presence of [Rh(CO)$_2$Cl]$_2$ under an atmosphere of CO (Scheme 2). Only *cis* bicyclo[3.3.0]octenone **17** was isolated, after transannular ring closing of the intermediate cyclooctanoid **16**. Thus, carbonyl activated alkynes give high yields with high or complete regioselectivity where CO insertion occurs distal to the carbonyl functionality on the alkene. Alkyl, aryl, TMS and ester functionalities were demonstrated to work efficiently as substituents on the alkyne, providing quick access to complex building blocks from commercially available starting materials. Although it is proposed that these reactions proceed through the desired cyclooctanoids, conditions leading to their selective isolation were not reported.

[4+4] Cycloadditions

The nickel catalyzed [4+4] dimerization of simple dienes have been explored. High selectivity can be obtained with proper catalyst choice for both regioselectivity and preferential

Scheme 3. [4+4} cycloaddition of a tethered bisdiene catalyzed by Ni(COD)$_2$.

19a n=1 19:1 cis:trans (70%)
19b n=2 all trans (84%)
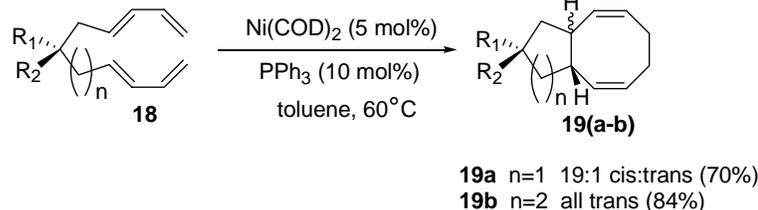
formation of cyclic products over oligomeric products[12] especially if the substituents can chelate to the metal center. However, this reaction is somewhat limited in scope because simultaneous substitution at both termini of the dienes shuts down the reaction pathway. Substitution at other positions along the backbone also causes loss of regioselectivity and substantially decrease the reaction rate. In addition, the reaction gives mixtures of products in cross dimerization. Wender and coworkers demonstrated, however, that the reaction proceeds efficiently when a tether holds the dienes in close proximity (Scheme 3).[13] Five-membered tethers were found to give a 19:1 preference for a *cis* 5-8 ring fusion, while 6-membered tethers exclusively yield *trans* fused rings. The reaction was found to tolerate substitutuion of the dienes with no appreciable decrease in rate, thus the controlled formation of quaternary centers is possible.

High stereoinduction (99:1) was found when a functional group was placed in the allylic position. This drops dramatically to approximately 2:1, however, when the substituent was moved to the homoallylic position. These effects are predominately steric in nature.[14] The small, coordinating cyano group only yields a 1.5:1 stereoinduction, while the bulkier, noncoordinating methyl group gives a 20:1 ratio of products. The acetoxymethyl group, similar in size to a methyl group but still able to coordinate, had a virtually identical effect on stereoinduction to that of the methyl group. This result strongly suggests that stereoinduction is not a result of coordination of substituents to the metal. The carbomethoxy showed the highest level of stereoinduction at >70:1. Using molecular mechanics calculations it has been shown that the relative rate of collapse of diastereomerically related intermediates causes the induction; the

Scheme 4. Construction of the core of Ophiobolin F.


60%

10 steps, 33% from **20**

13
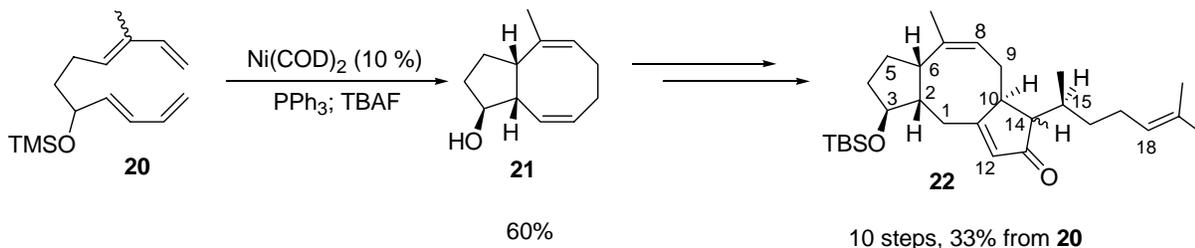
diastereomer which places the substituent in a psudoequitorial position has a higher rate of collapse. This methodology efficiently provides both bridged and fused ring systems and has recently been used to synthesize the core of ophiobolin F (**22**, Scheme 4),[15] in which 5 of the 7 stereocenters are set.

[4+2+2] Cycloadditions

The first metal-catalyzed [4+2+2] cycloaddition between norbornadiene and 1,3-butadiene was reported in 1970 using an iron catalyst and gave a 25% yield.[16] Other catalyst systems were found to improve the yield to between 38-90%,[17] and modest enantiomeric excesses could be obtained using chiral phosphines.[18] Despite being used for the preparation of small, highly strained unnatural products,[19] these reactions were not extensively applied in the synthesis of natural products partially because of its low tolerance for functional groups and limited scope.[19] Several recent advances have shown that the [4+2+2] cycloaddition may be synthetically useful for the preparation of eight-membered rings.

Snyder and coworkers reported the development of a catalytic system for the cycloaddition of butadiene and norbornadiene. This system was tolerant to a broad range of functional groups[18] and the resulting tricyclic cage compounds could be cleaved selectively into bicyclic products suitable for the synthesis of natural products.[20] The cobalt system employed was found to efficiently catalyze the reaction at room temperature and address some of the problems with previous catalytic systems in that little or no butadiene and norbornadiene dimerization was observed and a high level of periselectivity was achieved. A range of functional groups were found to be tolerated and substituents at the 1 and 7 positions of the norbornadiene gave a single regioisomer (Scheme 5). Cleavage of the resulting cycloadducts was accomplished by treatment with Zeise's dimer followed by ozonolysis to yield highly functionalized *cis* fused 5-8 membered ring systems in a stereocontrolled fashion. Substitution at

Scheme 5. [4+2+2] cycloaddition of a norbornadiene and butadiene catalyzed by Co.
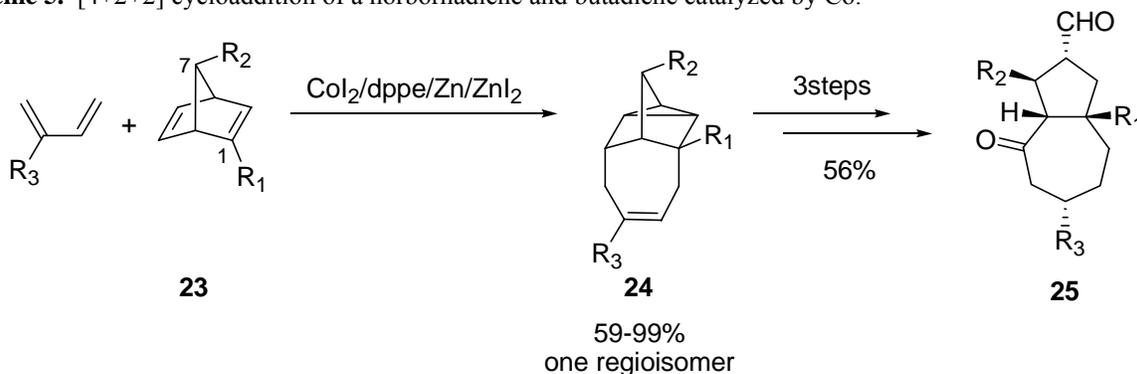
the 1 position of the norbornadiene led to the formation of quaternary centers in good yields. These products form the core of numerous sesquiterpenes, although the full synthetic utility of this approach has yet to be explored.

Rhodium catalyzed cyclization between 1,3-butadiene and an enyne possessing a heteroatom tether has been developed by Evans.[21] Various heteroatom tethers have been shown to proceed in good yields and utilize both terminal and internal alkynes. The enyne can also be assembled *in situ* by a tandem three-component allylic amination/cycloaddition reaction. The lithium salt of N-tosylpropargylamine is coupled with allyl carbonate in the presence of silver triflate – modified Wilkinson's catalyst yielding enyne **26**. After treatment with butadiene, the cycloaddition adduct was isolated in 87% yield as a >19:1 mixture of the desired cycloadduct and the homodimer products. The influence of an allylic directing group was also investigated, and a 19:1 diastereomeric ratio was obtained. The feasibility of sulfone tethers represents a new class of cycloadditions employing the use of these tethers. The proposed mechanistic pathway is shown in Figure 4.

Gilbertson recently reported a rhodium catalyzed [4+2+2] cycloaddition involving a tethered diene and alkyne, and a second external alkyne.[22] Treatment of a solution of [Rh(NBD)Cl]$_2$ with 0.5 equiv or less of silver antimony hexafluoride in the presence of a trialkyl or triaryl phosphine yielded an efficient catalyst. Other catalysts such as [Rh(CO)Cl]$_2$ were found to give [4+2] products predominately, as was the case when the catalyst was prepared with more than 0.5 equiv of AgSbF$_6$. Unfortunately the structure of the active catalyst has yet to be determined.

CONCLUSIONS

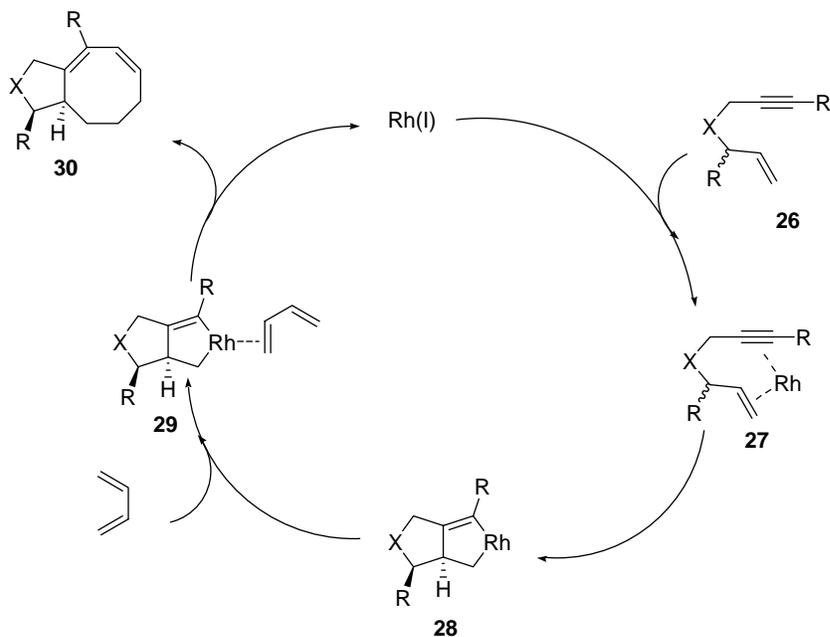Higher-order cycloadditions can be used to

Figure 4. Proposed catalytic cycle for the rhodium catalyzed cycloaddition of enyne **26** and butadiene.

construct eight-membered rings. They are capable of quickly increasing molecular complexity and can be used to form several ring systems in one step. Recent advances continue to improve the scope and tolerance of this approach and increase their potential to be applied in the synthesis of complex natural products. The large variety of components allow retrosynthetic disconnects to be made at positions around the eight-membered ring. However, unlike their counterparts producing smaller rings, higher order cycloadditions still have only been exploited in the synthesis of a limited number of natural products.

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