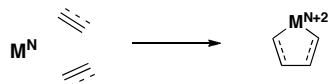
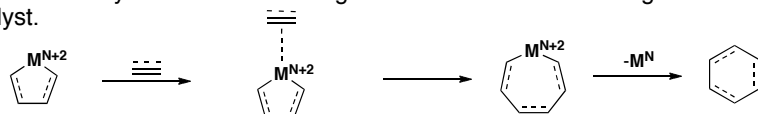


**Notes on Mechanism**

The cyclodimerization of alkenes and alkynes is a fundamental transition metal mediated process. This is the basic step in the mechanism of metal catalyzed or mediated higher order cycloadditions. For a detailed discussion, see Hegedus, L. *Transition Metal in the Synthesis of Complex Organic Molecules*, University Science Books, 1999.



Depending on the nature of the metal, this metallocycle can undergo many different reactions. For the purposes of this presentation, the most relevant are insertion reactions of alkenes, alkynes, and carbon monoxide to form expanded metallocycles. These metallocycles can then undergo reductive elimination to regenerate the active catalyst.



Although the mechanisms of some higher order cycloadditions have not been exhaustively studied, it is believed that cyclization/insertion processes are generally responsible for these reactions.

A further mechanistic point regarding metal mediated reactions is that photolysis is frequently used to aid in the dissociation of carbonyl ligands from metal centers. In metal mediated cycloadditions, irradiation is frequently used for this purpose, rather than to initiate a photochemically allowed concerted cycloaddition.

[2+2], [3+2], and especially [4+2] cycloadditions are well established methods for ring synthesis. By contrast, the synthesis of larger rings through higher order cycloaddition reactions is far less common. Due to the breadth of this topic, this presentation is far from exhaustive and focuses mainly on synthetic applications of higher order cycloadditions.

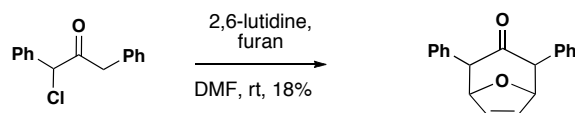
Some general references:

Evans, P.A, ed. *Modern Rhodium-Catalyzed Chemistry*, Wiley-VCH, 2005.  
Yet, L. "Metal-Mediated Synthesis of Medium-Sized Rings" *Chem. Rev.* 2000, 100, 2963-3007.

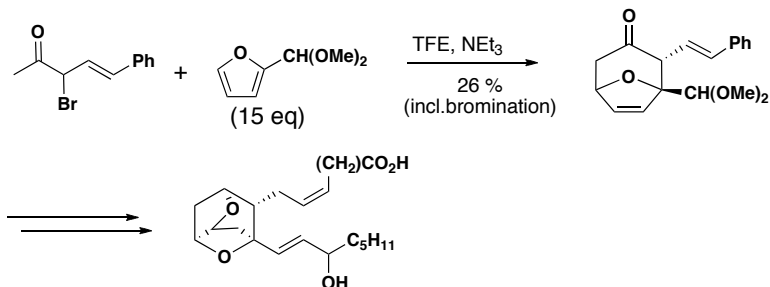
Mehta, G.; Singh, V. "Progress in the Construction of Cyclooctanoid Systems: New Approaches and Applications to Natural Product Synthesis" *Chem. Rev.* 1999, 881-930.

### [4 + 3] Cycloadditions

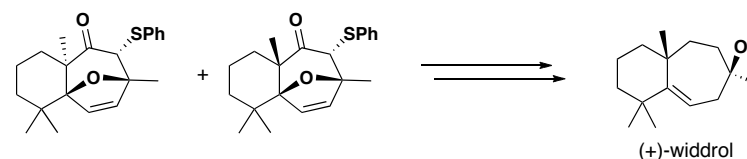
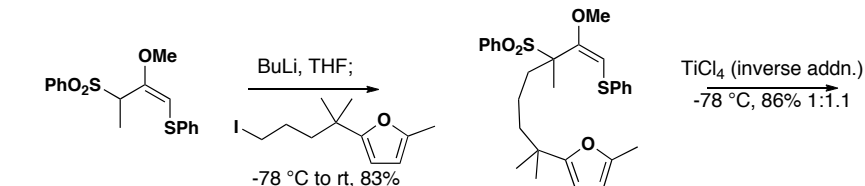
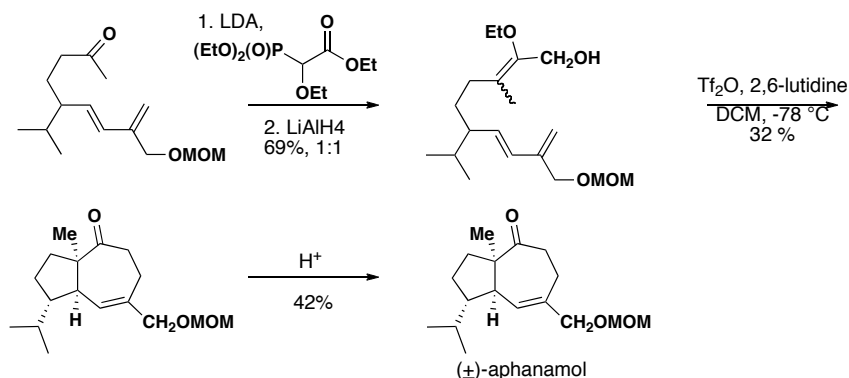
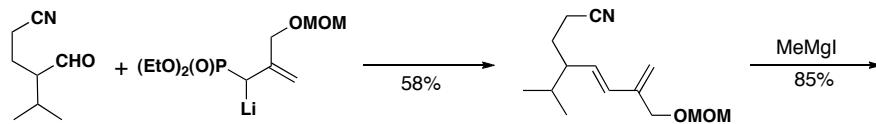
The initial report of a [4+3] cycloaddition came from Fort (*JACS*, 1962, 4979-4981). Furan was used to capture the oxallyl species generated from chlorodibenzyl ketone.



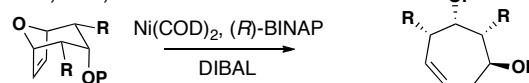
This reaction was adapted for the synthesis of thromboxane analogs. (Bowers and Mann, *Tet. Lett.* 1985, 26(36) 4411-4412.



The intramolecular version of this reaction has been studied extensively with a range of precursors oxallyl species. Harmata *et. al.* *Tet. Lett.* 1997, 38(46), 7985-7988; *Tetrahedron*, 1997, 53(18), 6235-6280; *Acc. Chem. Res.* 2001, 34, 595-605.

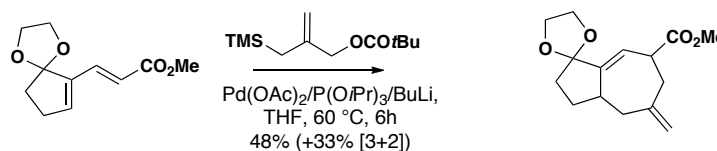


Lautens has demonstrated the enantioselective opening of furan [4+3] adducts. *JACS*, 1997, 119, 11090-1.

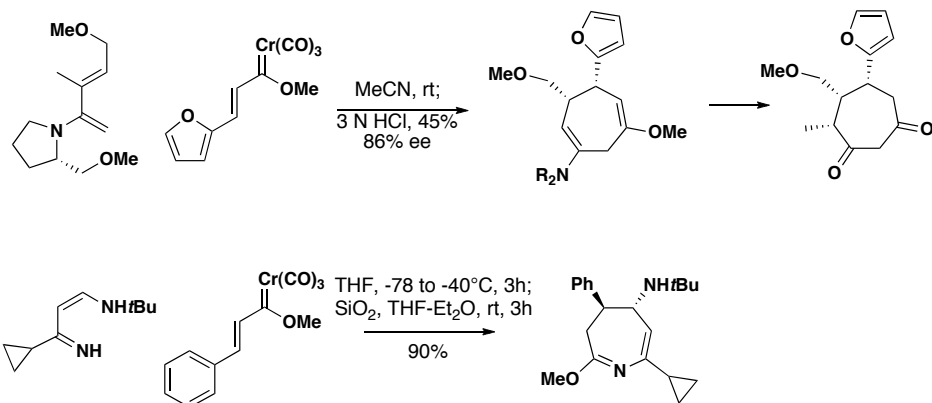


80-100% and >95% ee for multiple substrates, also works for adducts diastereomeric to the one shown.

Trost has shown that trimethylene methane equivalents can undergo [4+3] cyclization with dienes. Due to the stepwise mechanism of this reaction, competing [3+2] reactions can pose a problem. *Chem. Lett.* 1994, 2245-2248.

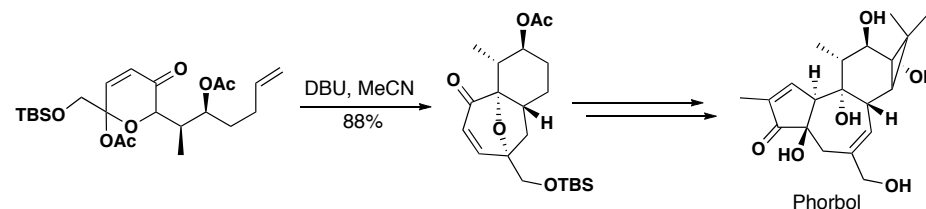
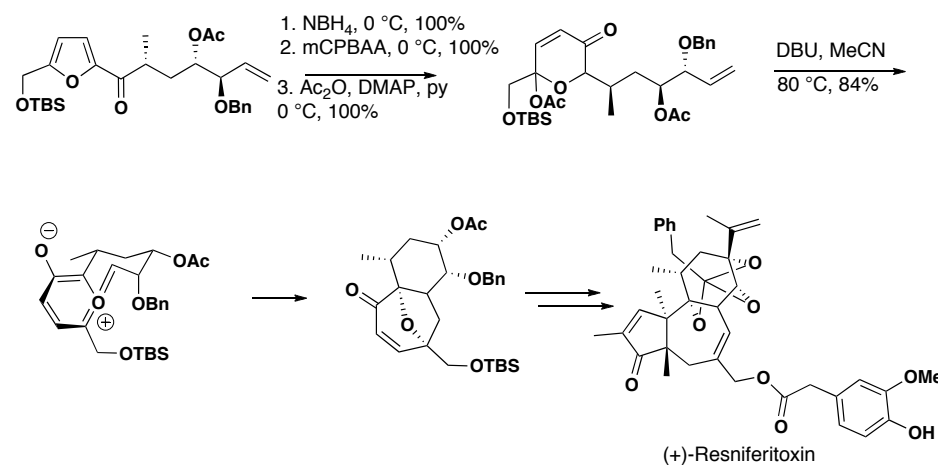


Fischer vinylcarbenes undergo formal [4+3] cycloadditions with a variety of dienes and hetero dienes. It is important to note that these reactions actually proceed via a [2+1] addition followed by Cope rearrangement of the resulting diallyl cyclopropane. This reaction is included here because the Cope rearrangement usually occurs at room temperature and the formal [4+3] adduct is obtained directly (Barlunga *et al.* *JACS*, **1995**, 117(37), 9419-9426; *J. Chem. Soc. Chem. Comm.* **1994**, 321-2).

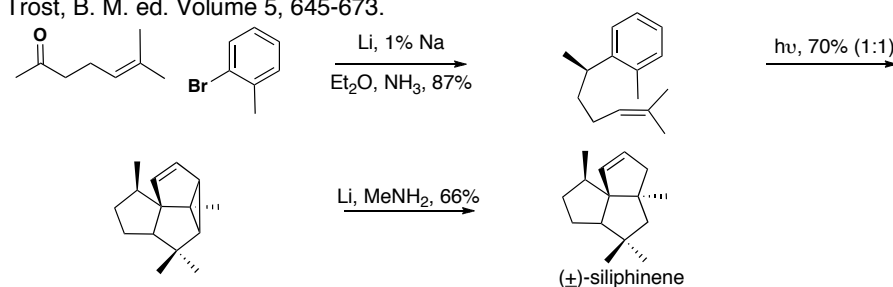


### [5 + 2] Cycloadditions

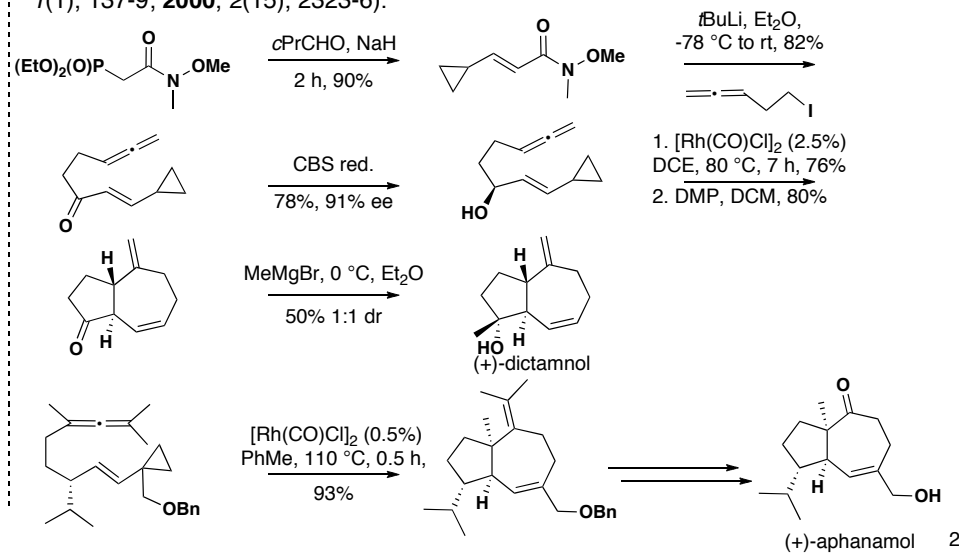
The participation of 3-oxopyrroliums on [5+2] cycloadditions was initially reported in 1962. (Ullman, E. F.; Milks, J. E., *JACS*, **1962**, 84, 1315-6). Wender used an intramolecular version of this reaction in his syntheses of Phorbol and Resniferitoxin (*JACS*, **1997**, 119, 7897-8, 12977-8).



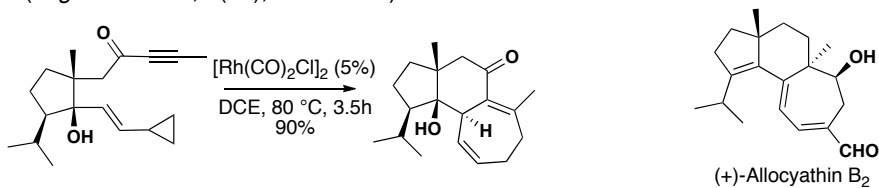
Arenes undergo [5+2] cycloadditions with olefins under photochemical conditions. This served as the basis for Wender's three step synthesis of siliphenine. (*Tet. Lett.* **1985**, 26, 2625). For a more complete treatment of this reaction, see the group meeting presentation "Cyclopentane Synthesis" and Wender, P. A.; Siggel, L.; Nuss, J. M. "[3+2] and [5+2] Arene-Alkene Photocycloadditions" in *Comprehensive Organic Synthesis*, Trost, B. M. ed. Volume 5, 645-673.



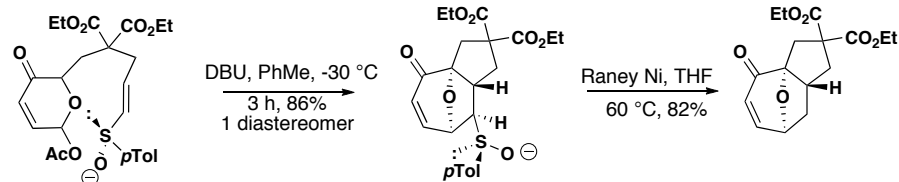
Wender has developed rhodium catalyzed [5+2] cycloadditions of vinylcyclopropanes with a variety of 2 $\pi$  components. Intramolecular cycloaddition with an allene served as the key step in the syntheses of (+)-dictamnol and (+)-aphanamol I. (*Org. Lett.* **1999**, 1(1), 137-9; **2000**, 2(15), 2323-6).



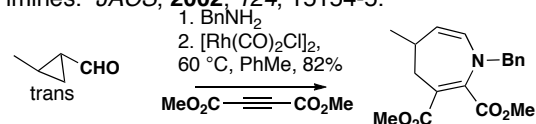
Wender also found that alkynones are viable substrates for intramolecular [5+2] cycloadditions. This reaction was used in the synthesis of the allocyanthin core (*Org. Lett.* **2001**, 3(13), 2105-2108).



Mascarenas has discovered a method using chiral sulfoxides to direct the diastereoselectivity of oxidopyrillium cycloadditions. The diastereoselectivity appears to result from the rotational preference of the sulfoxide (*Org. Lett.*, **2002**, 4(21), 3683-5).

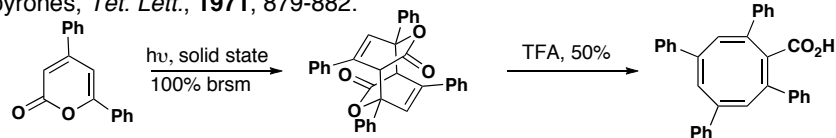


Wender has developed a protocol for hetero [5+2] cycloadditions using cyclopropyl imines. *JACS*, **2002**, 124, 15154-5.

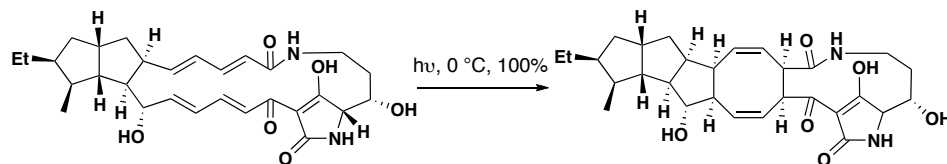


### [4 + 4] Cycloadditions

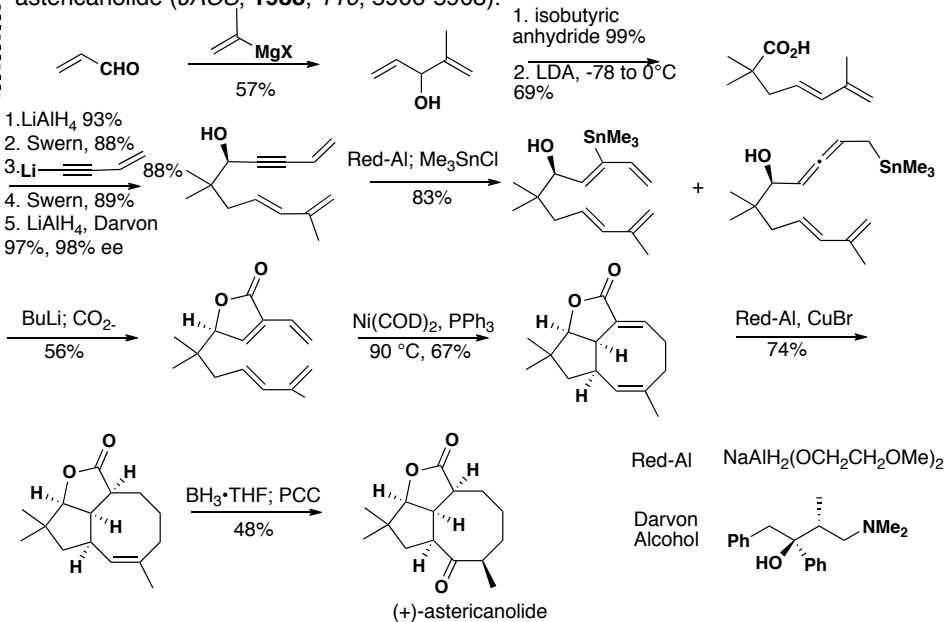
[4+4] cycloadditions are photochemically allowed. However, the substrate range is very limited and the reactions often require harsh conditions (e.g. solid state dimerization of pyrones, *Tet. Lett.*, **1971**, 879-882).



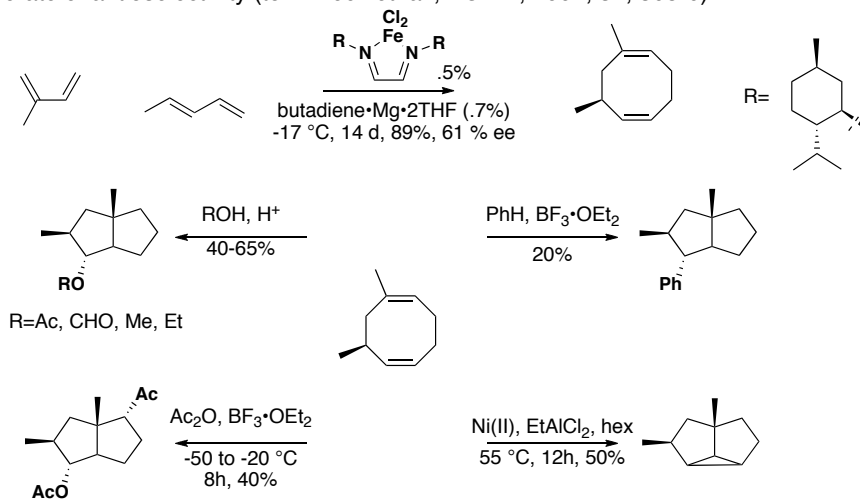
The natural product Alteramide A was observed to undergo an intramolecular [4+4] cycloaddition upon UV irradiation. *JOC*, **1992**, 57(15), 4317-4320.



Wender has developed Ni catalyzed intramolecular [4+4] cycloadditions (*JACS*, **1986**, 108, 4678-9) and applied the methodology to a short total synthesis of (+)-astericanolide (*JACS*, **1988**, 110, 5906-5908).

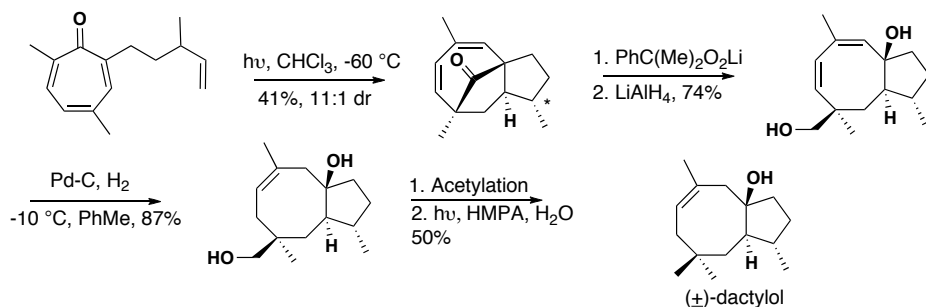


Work on enantioselective intermolecular variations of this reaction has also been done. Although impressive selectivity in heterodimerizations has been achieved, albeit in moderate enantioselectivity (tom Dieck *et. al.*, *ACIEE*, **1992**, 31, 305-6).

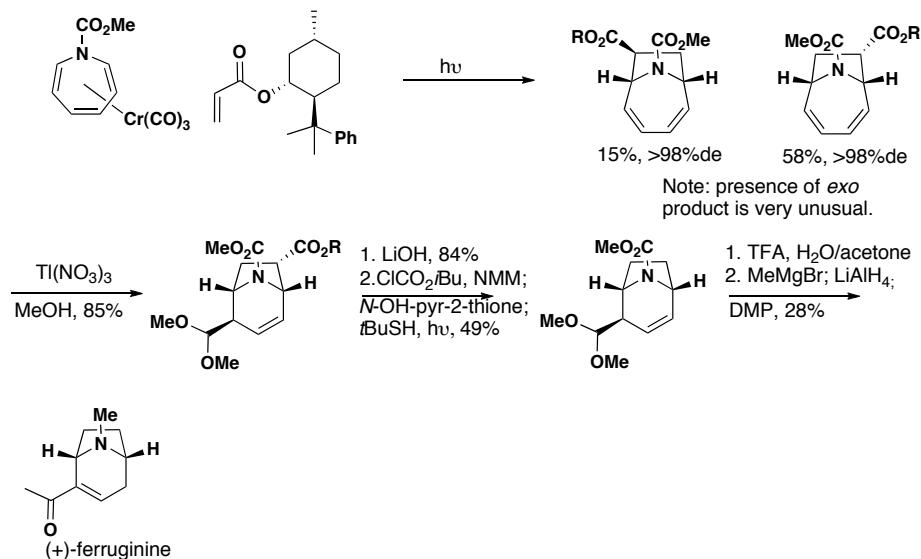


**[6 + 2] Cycloadditions**

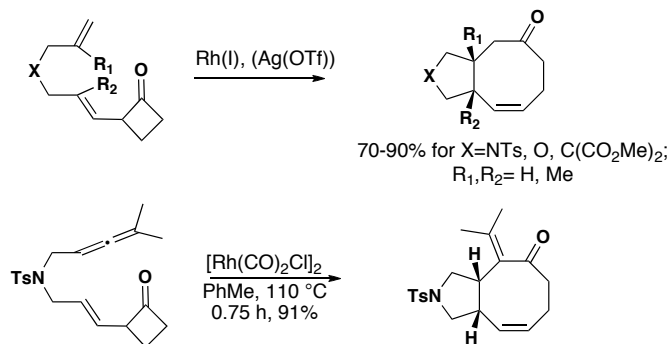
Feldman has studied the photochemical intramolecular cycloadditions of tropones. (*JOC*, **1989**, 54(3), 592-601). This reaction was applied in a synthesis of (±)-dactyol (*JACS*, **1990**, 112(23), 8490-8496).



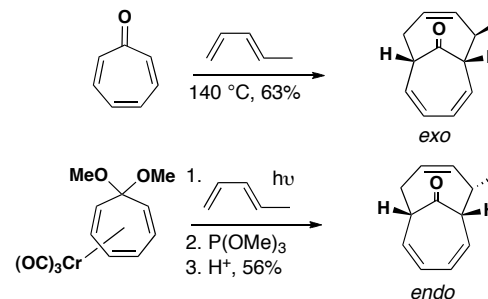
Rigby has developed Cr(0)-mediated [6+2] and hetero-[6+2] additions using Cr coordination complexes. This reaction was used to synthesize (+)-ferruginine (*JOC*, **1995**, 60, 7392-3).



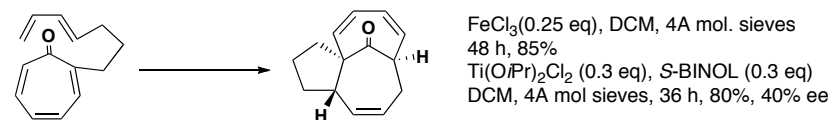
Wender has extended his Rh-catalyzed methodology to vinyl cyclobutanones (*JACS*, **2000**, 122(32), 7815-6).

**[6 + 4] cycloadditions**

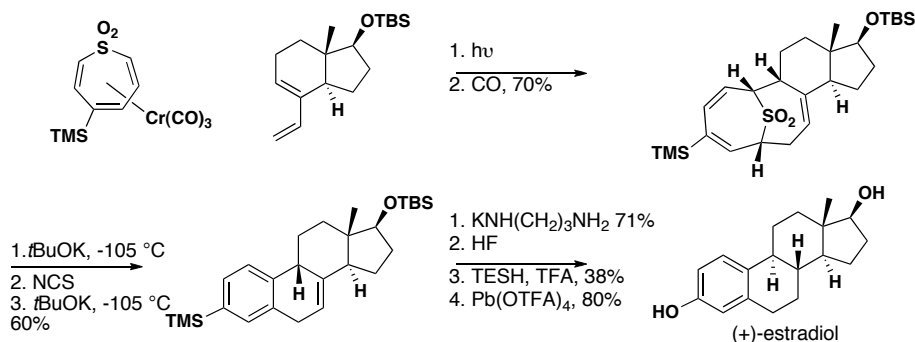
Rigby has extensively studied both thermal and metal-mediated cycloadditions of a variety of partners (*JACS*, **1993**, 115(4), 1382-1396).



Interestingly, the electronic nature of the diene seems to have little effect on the yield of the metal-mediated reaction. Lewis acids appear to catalyze the thermal cycloaddition (*Tet. Lett.* **2002**, 43, 8643-6).

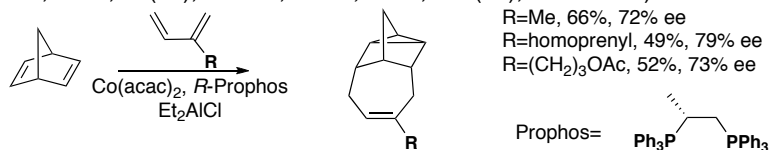


Rigby used the cycloaddition of a sulfone in a synthesis of estradiol (*JACS*, **1999**, 121(36), 8237-8245).

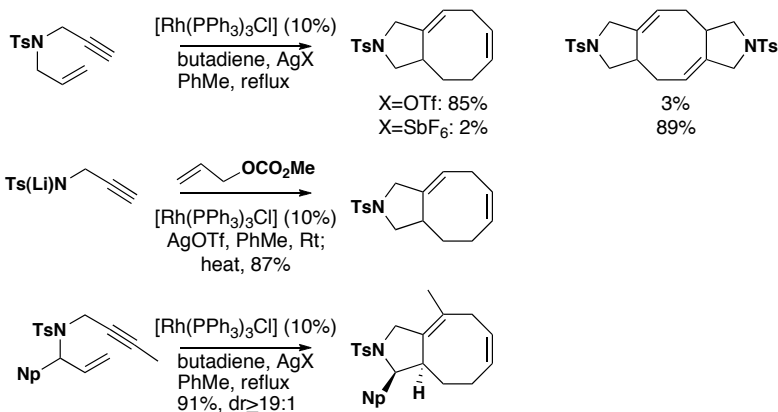


### Multicomponent Cycloadditions

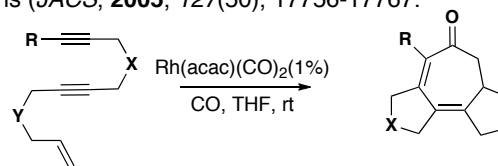
Lautens has reported enantioselective [4+2+2] cycloadditions with norbornadiene (*JOC*, **1993**, 58(17), 4513-5, *JACS*, **1995**, 117(26), 6863-6879).



P. A. Evans, has done extensive work on [4+2+2] cycloadditions (*JACS*, **2002**, 124, 8782-3).

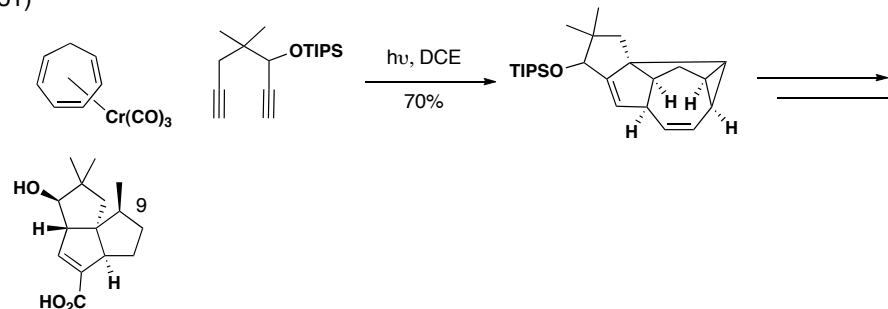


Ojima has discovered a method for intramolecular carbonylative [2+2+2+1] cycloadditions (*JACS*, **2005**, 127(50), 17756-17767).

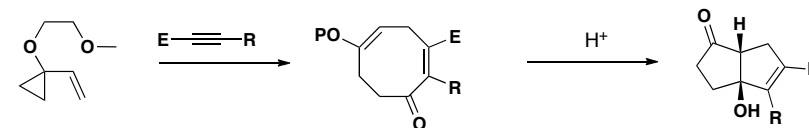


50-90% (usually >80%) for R=H, X, Y=O, NTs, C(CO<sub>2</sub>Et)<sub>2</sub>, C(CH<sub>2</sub>OP)<sub>2</sub>, C(CH<sub>2</sub>OH)<sub>2</sub>  
50-100% for R=Me, Ph, TMS (often includes [2+2+2] product)

Rigby has discovered that Cr complexes can participate in [6+2+2] cycloadditions with alkynes. This process appears to be a [6+2] cycloaddition followed by a [4+2+2] cycloaddition. This was applied to a synthesis of 9-*epi*-pentalenic acid (*JOC*, **2004**, 69, 6751).



Wender has extended his vinylcyclopropane methodology to carbonylative [5+2+1] cycloadditions for the synthesis of bicyclo[3.3.0]octanes (*JACS*, **2002**, 124, 2876-7).



Multiple examples: E=COMe, CONH<sub>2</sub>, CHO, CO<sub>2</sub>Me, R=alkyl, Ph, TMS (CO<sub>2</sub>Me works, but gives 48%)

Ito has reported a carbonylative [4+4+1] dimerization of ene-allenes (*ACIEE*, **1998**, 37(24), 3418-3420).

