

**Outline:**

1. Structure and Reactivity
2. Synthesis of MCPs
3. Lewis Acid Catalyzed Ring Expansions
4. Transition Metal Catalyzed Ring Expansions
5. Lewis Acid Catalyzed Cycloadditions
6. Transition Metal Catalyzed Cycloadditions
7. MCPs in Synthesis

**Not Covered:**

- Thermal and Photochemical Reactions of MCPs
- Ring-Opening Polymerization
- Silylated Allylic Acetate TMM Precursors

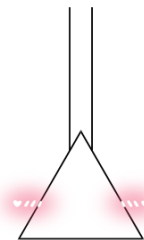
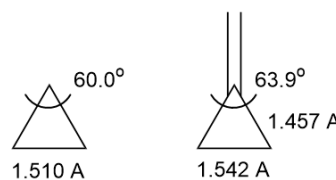
**Reviews and Major References:**

- Binger and Büch, *Topics in Current Chemistry* **1987**, 135, 77  
 Lautens, Klute, and Tam, *Chem. Rev.* **1996**, 96, 49  
 Brandi and Goti, *Chem. Rev.* **1998**, 98, 589  
 Nakamura and Yamamoto, *Adv. Synth. Catal.* **2002**, 344, 111  
 Yamago and Nakamura, *Org. React.* **2002**, 61, 1  
 Rubin et al., *Chem. Rev.* **2007**, 107, 3117  
 Shi et al., *Acc. Chem. Res.* **2012**, 45, 641  
 Yu et al, *Org. Biomol. Chem.* **2015**, 13, 8379  
 Cao et al., *Adv. Synth. Catal.* **2019**

"...very versatile in organic synthesis." - Paul Binger

"...some of the most popular building blocks in synthetic organic chemistry during the past two decades." - Lei Yu

"The attractive feature of these compounds is their surprising stability, accompanied by a high level of strain, conferring on them an otherwise unattainable chemical reactivity." - Alberto Brandi and Andrea Goti

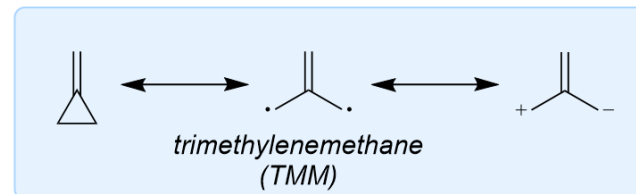
**1. Structure and Reactivity**

Despite significant ring and torsional strain, methylenecyclopropane (MCP) is stable at room temperature

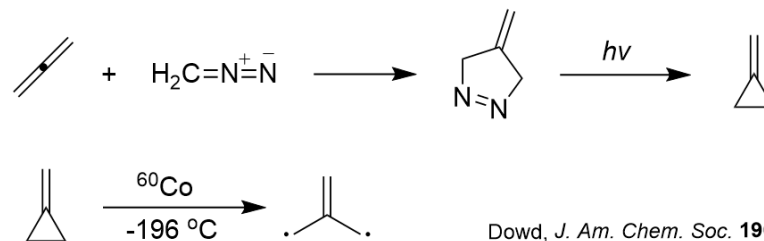
Laurie and Stigliani, *J. Am. Chem. Soc.* **1970**, 92, 1485

Much of the synthetic utility of MCP and its derivatives (collectively referred to as MCPs) arises from the release of ring strain, either due to alkene functionalization or ring cleavage. They function as synthetic equivalents of the diradical trimethylenemethane.

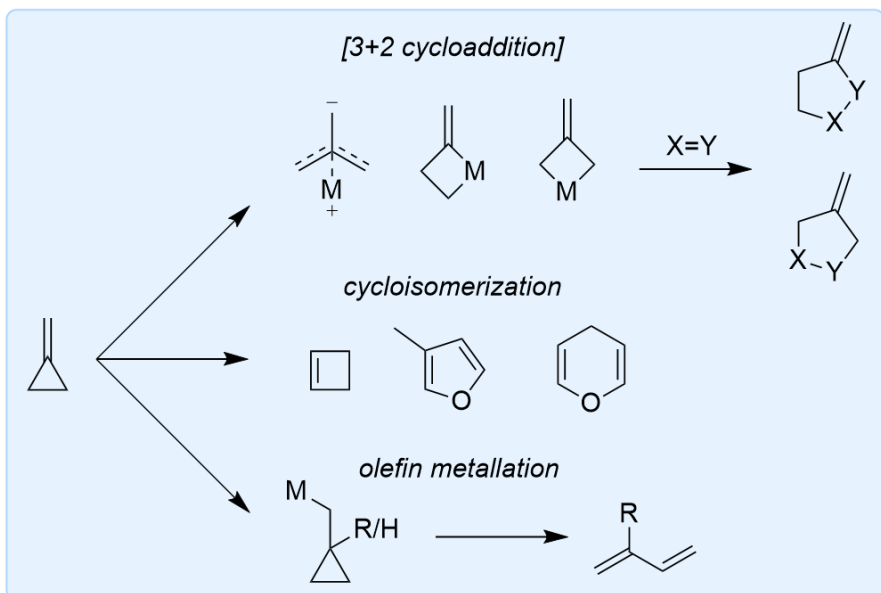
Formally,



Originally a speculative molecule of purely theoretical interest, TMM was first observed spectroscopically by Dowd in 1966. It is only moderately stable at cryogenic temperatures in a solid matrix, so the reactivity of this species needs to be accessed indirectly.

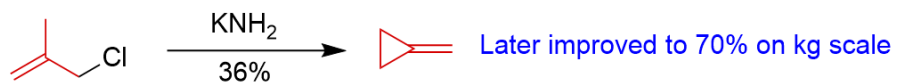


Dowd, *J. Am. Chem. Soc.* **1966**, 88, 2587  
 Dowd and Chow, *Tetrahedron* **1982**, 38, 799

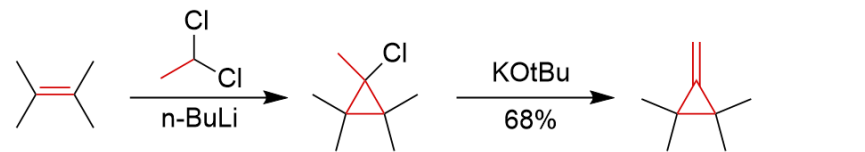
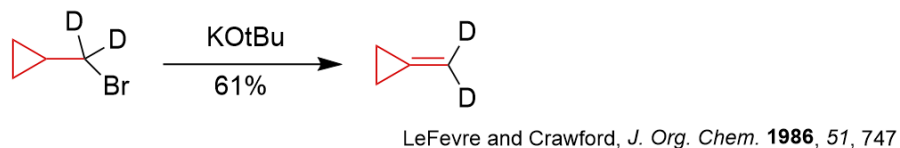
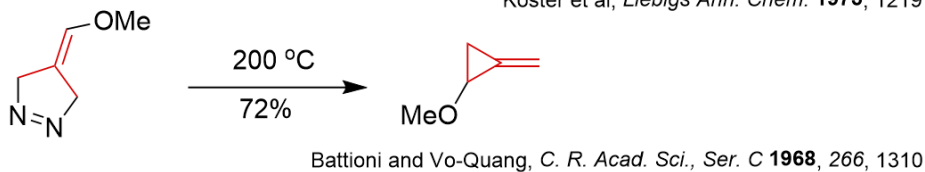


## 2. Synthesis of MCPs

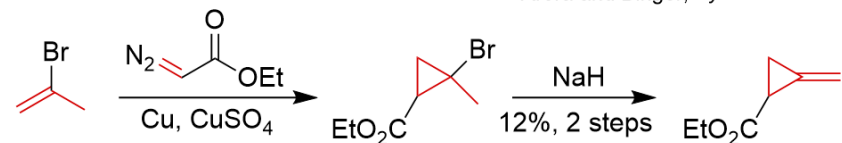
### Eliminations



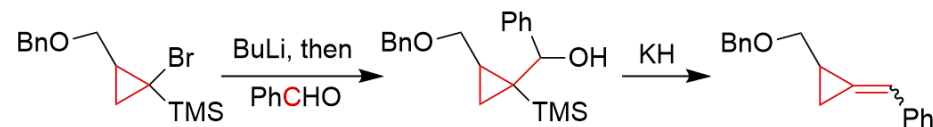
Binger et al., *Angew. Chem., Int. Ed. Engl.* **1969**, 8, 205  
Koster et al., *Liebigs Ann. Chem.* **1973**, 1219



Arora and Binger, *Synthesis* **1974**, 801

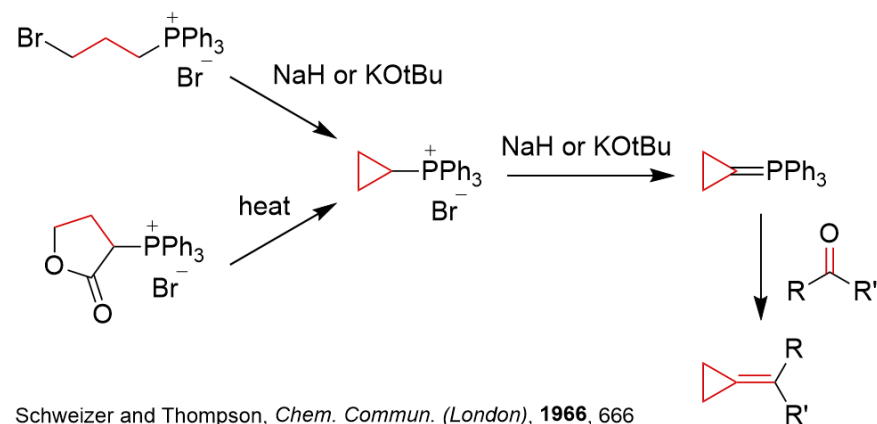


Carbon et al., *J. Am. Chem. Soc.* **1958**, 80, 1002

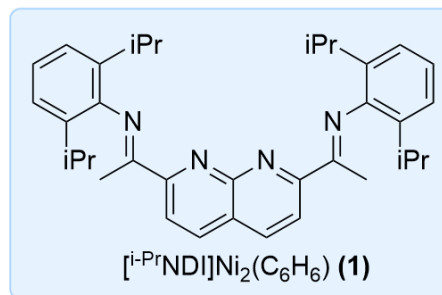
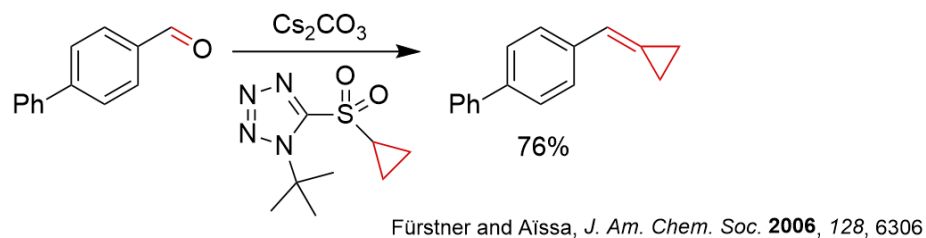
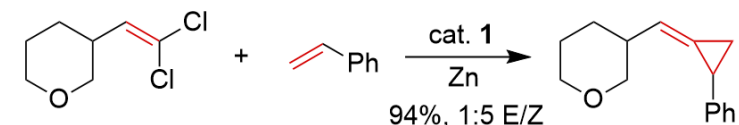
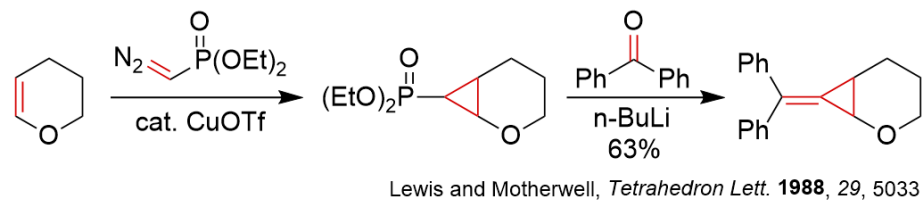
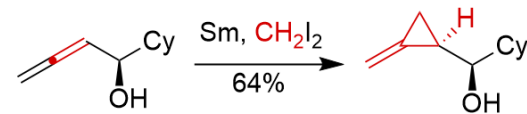
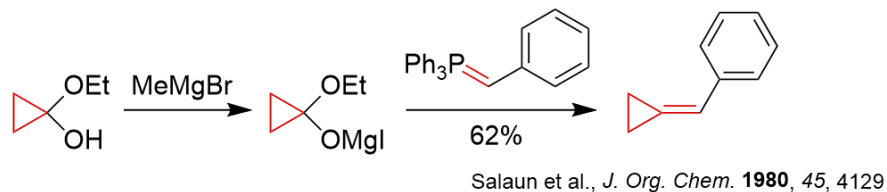


Hiyama et al., *Tetrahedron Lett.* **1982**, 23, 1279

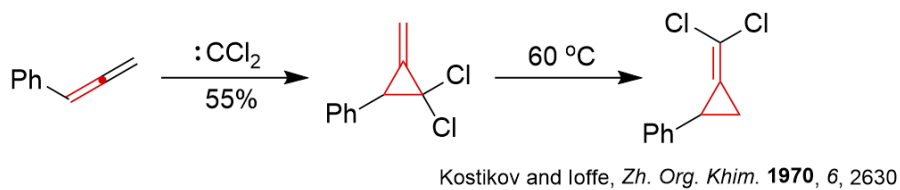
### Wittig and Other Olefinations



Schweizer and Thompson, *Chem. Commun. (London)*, **1966**, 666

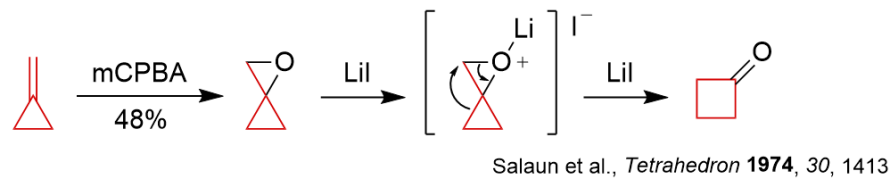
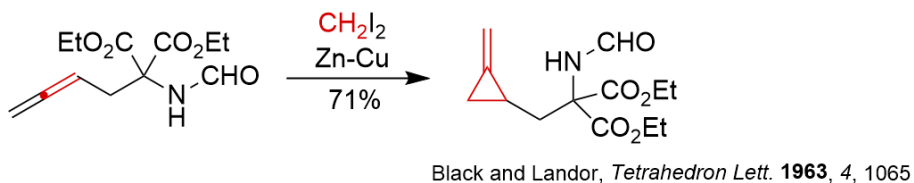


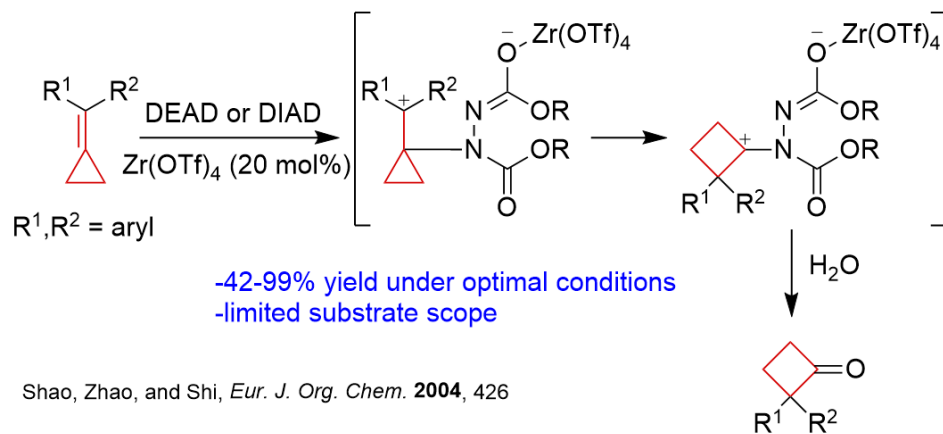
### Carbene / Carbenoid Additions



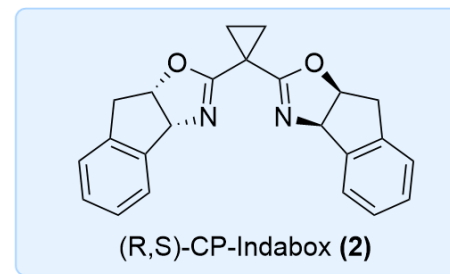
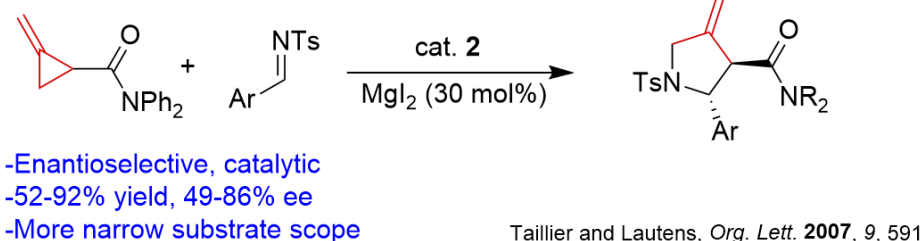
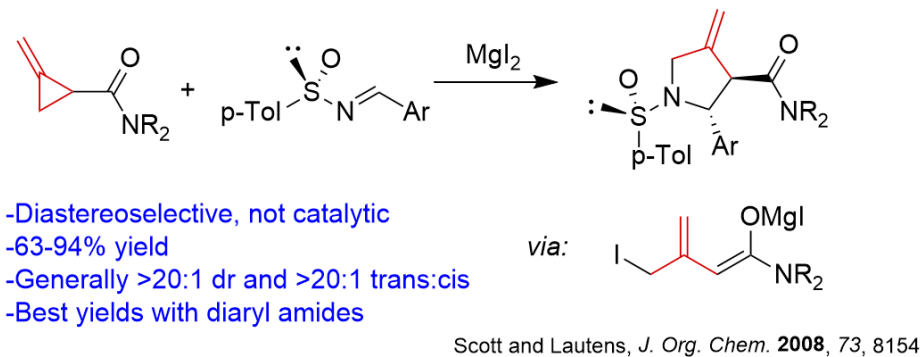
### 3. Lewis Acid Catalyzed Ring Expansions

MCP ring expansion to cyclobutanones mediated by  $Zr(OTf)_4$  complements older method involving mCPBA epoxidation followed by rearrangement.

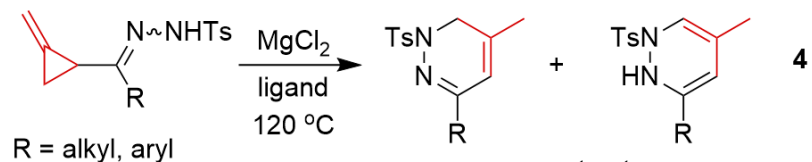




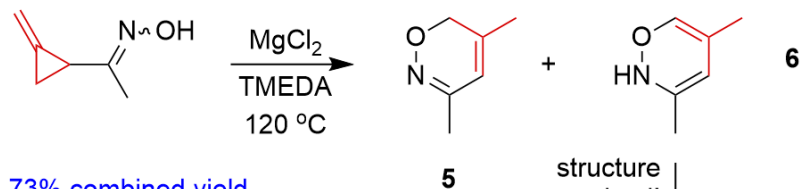
Lautens and coworkers investigated the Lewis Acid mediated ring expansion of methylenecyclopropyl amides to form 2,3-disubstituted pyrrolidines.



Lautens also studied Lewis Acid catalyzed MCP hydrazone ring expansions to form other substituted heterocycles.

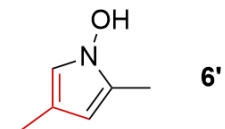


-68-93% yield  
-TMEDA forms **4'** in >20:1 yield  
-N-benzylidene toluenesulfonamide ligand forms **3** in >20:1 yield



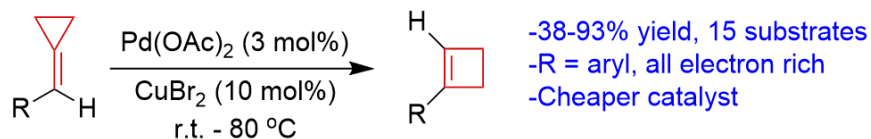
-73% combined yield  
-1:3 selectivity for **5:6'**

Lautens et al., *J. Am. Chem. Soc.* **2007**, 129, 1482  
Lautens et al., *Org. Lett.* **2014**, 16, 3930

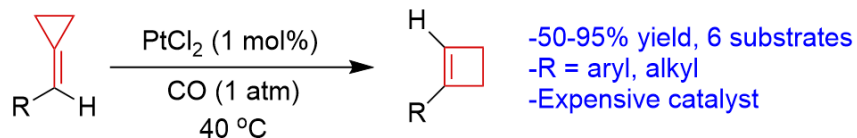


## 4. Transition Metal Catalyzed Ring Expansion

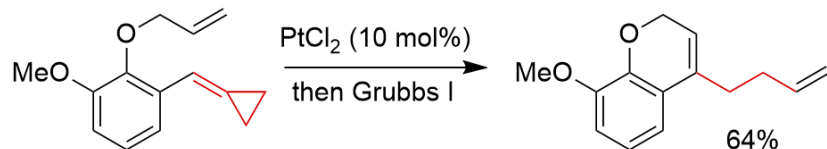
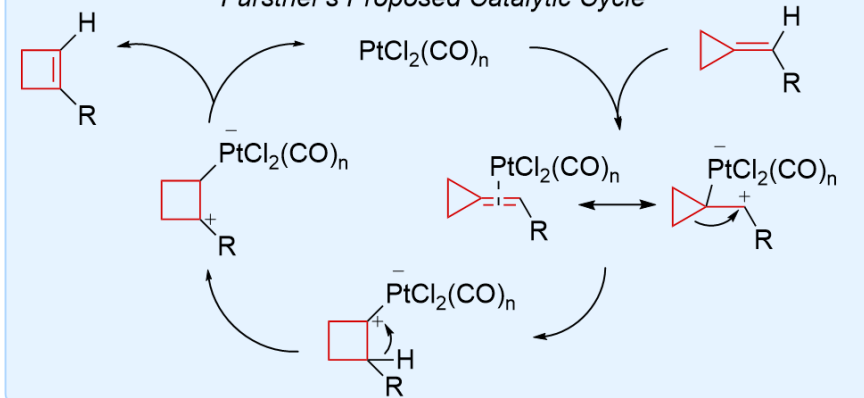
In 2006, Fürstner and Shi independently reported transition metal catalyzed MCP rearrangements to cyclobutenes.



Shi, Liu, and Tang, *J. Am. Chem. Soc.* **2006**, 128, 7430

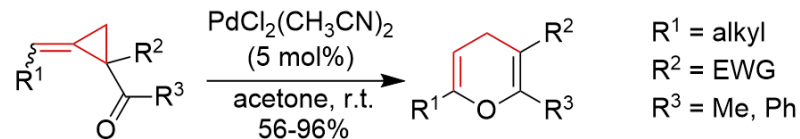


## Fürstner's Proposed Catalytic Cycle

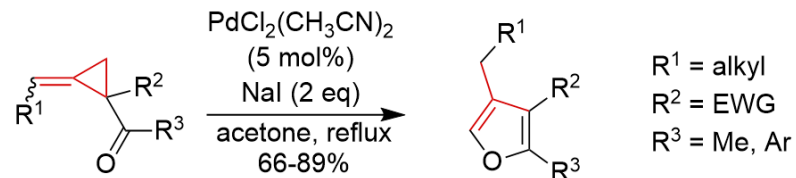
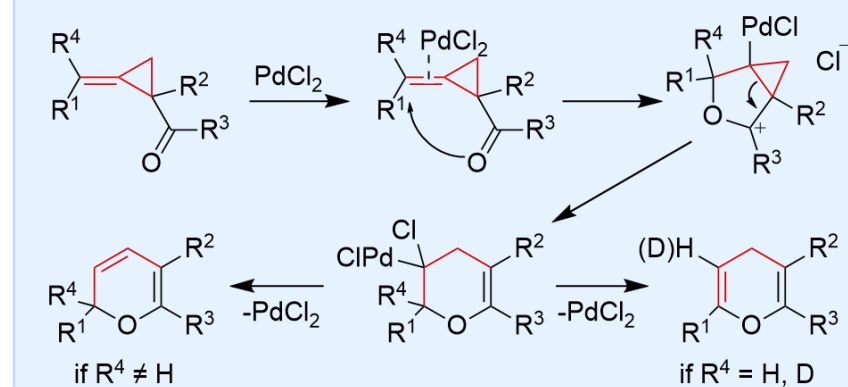


Fürstner and Aïssa, *J. Am. Chem. Soc.* **2006**, 128, 6306

Ma and coworkers studied the palladium catalyzed cycloisomerization of acyl MCPs to either 4H-pyrans or furans, depending on the conditions employed.



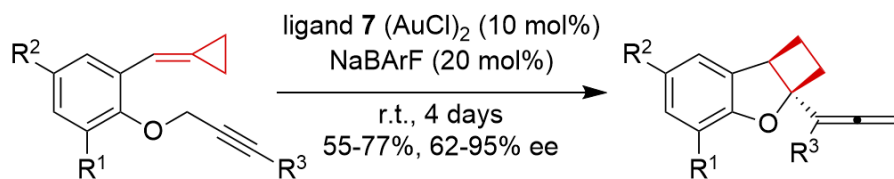
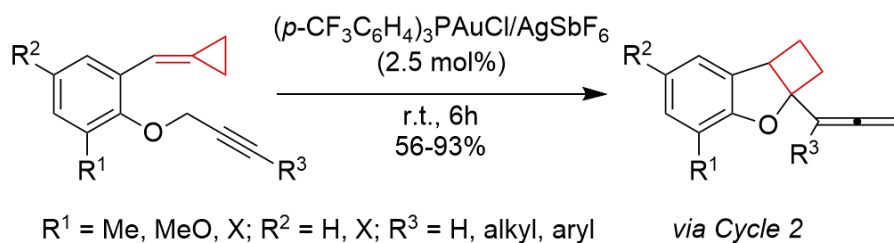
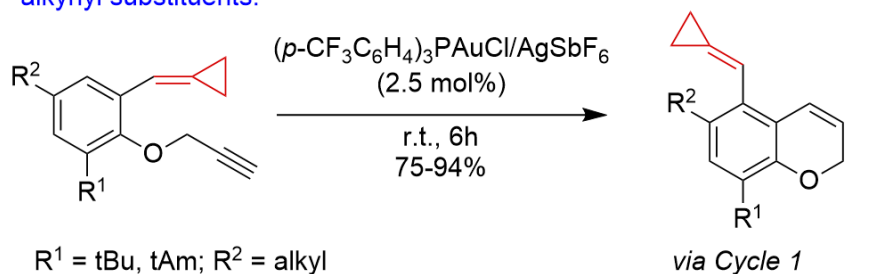
## Ma's Mechanistic Musing



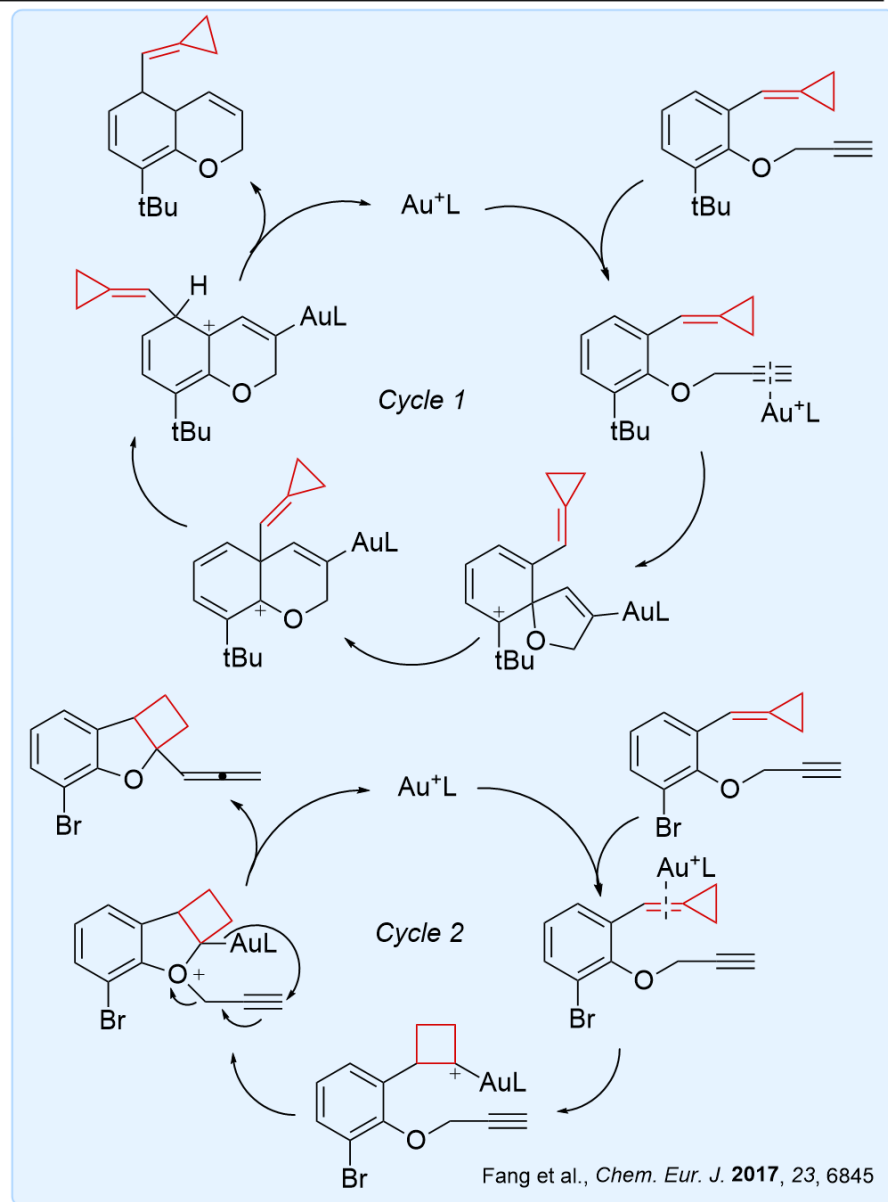
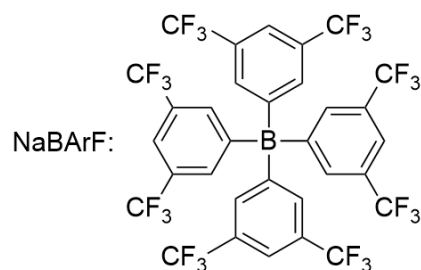
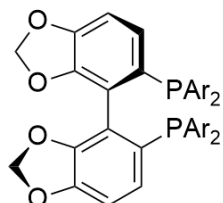
This reaction is analogous to what Lautens observed in his ring expansion of tosyl hydrazone MCPs to pyrroles. In fact, Ma found that this reaction didn't require Pd at all, catalytic NaI was enough.

Ma et al., *J. Am. Chem. Soc.* **2004**, 126, 9645

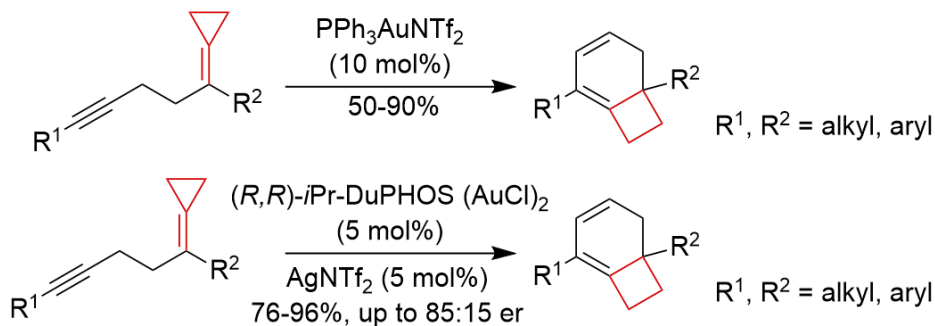
The Shi group observed two different gold catalyzed cycloisomerization pathways of MCPs tethered to aryl propargyl ethers depending on aryl and alkynyl substituents.



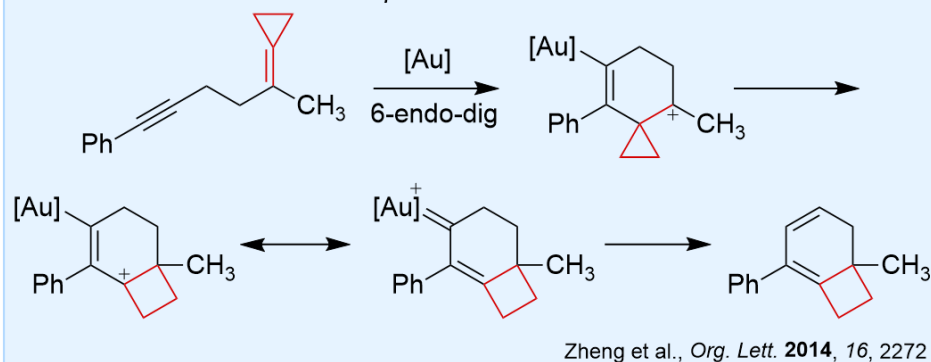
R<sup>1</sup>, R<sup>2</sup> = H, X



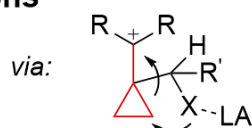
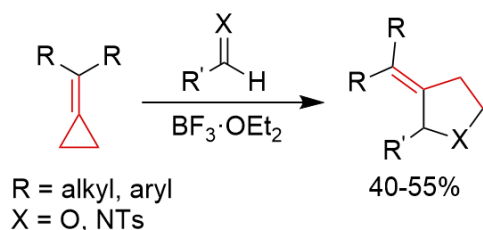
The Gagné group demonstrated that gold-catalyzed enyne cycloisomerization featuring an MCP could access the desirable bicyclo[4.2.0]octane skeleton.



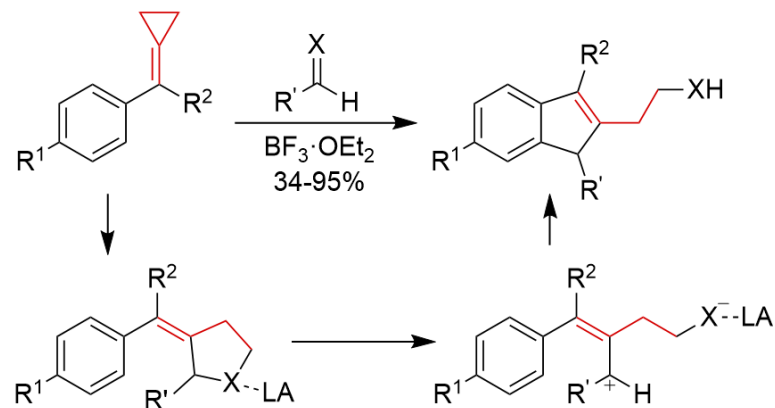
#### Proposed Mechanism



### 5. Lewis Acid Catalyzed Cycloadditions

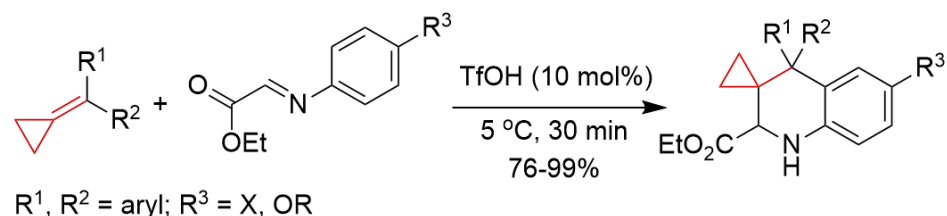
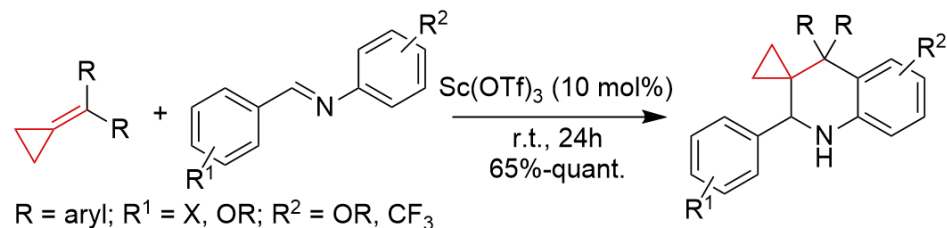


-simple substrates  
-limited scope  
-products unstable under reaction conditions



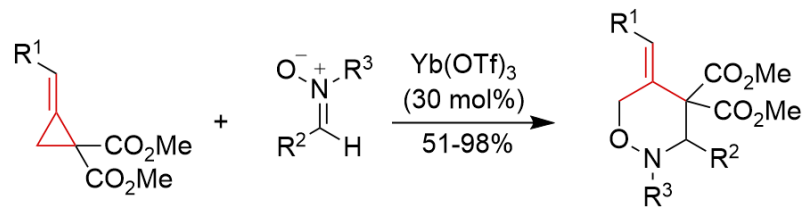
R<sup>1</sup> = H, Me, MeO; R<sup>2</sup>, R' = aryl; X = O, NTs Shi et al., *Org. Lett.* **2004**, *6*, 1175

Lewis Acids can also catalyze the aza-Diels Alder reaction of MCPs with N-aryl imines, although this reactivity has been observed with other olefins.



Shi et al., *Org. Lett.* **2003**, *5*, 579  
Shi et al., *Eur. J. Org. Chem.* **2009**, 2576

Perhaps the most novel Lewis Acid catalyzed cycloaddition, Wang studied a [3+3] cycloaddition involving distal MCP cleavage.

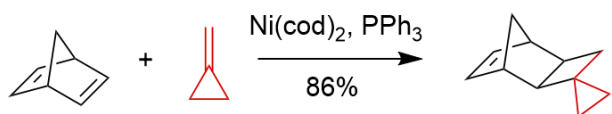


R<sup>1</sup> = aryl, alkyl; R<sup>2</sup> = aryl; R<sup>3</sup> = aryl, Me

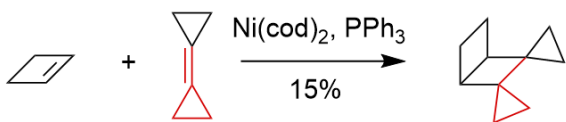
Hu et al., *Chem. Eur. J.* **2009**, 15, 324

## 6. Transition Metal Catalyzed Cycloadditions

Aside from dimerizations which produce synthetically uninteresting mixtures of products, few intermolecular transition metal catalyzed [2+2] cycloadditions of MCPs are known.

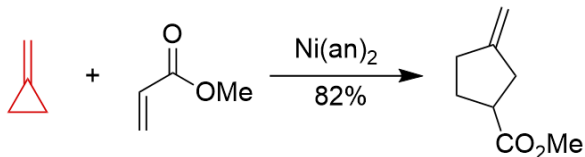


Noyori et al., *J. Am. Chem. Soc.* **1973**, 95, 1674

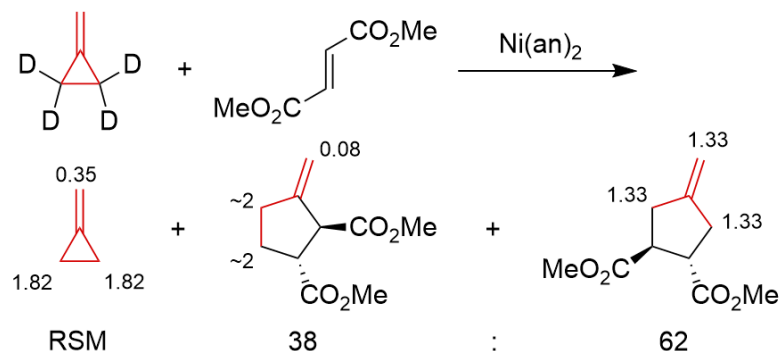


Kaufmann and de Meijere, *Chem. Ber.* **1984**, 117, 3134

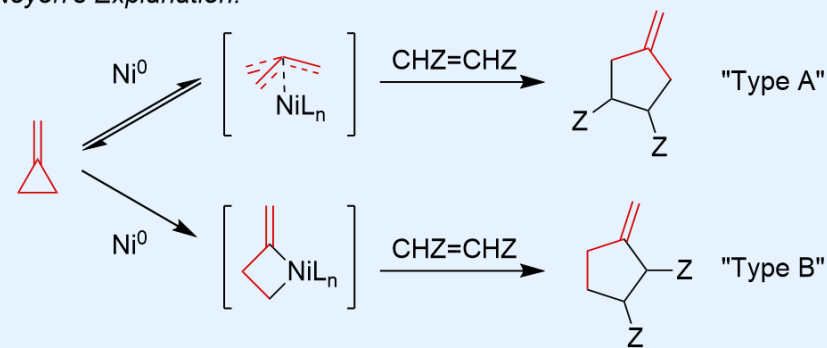
Transition metal catalyzed [3+2] cycloadditions using MCPs are arguably their most well studied and useful transformation. Noyori was the first to explore this chemistry.



Noyori, Odagi, and Takaya, *J. Am. Chem. Soc.* **1970**, 92, 5780

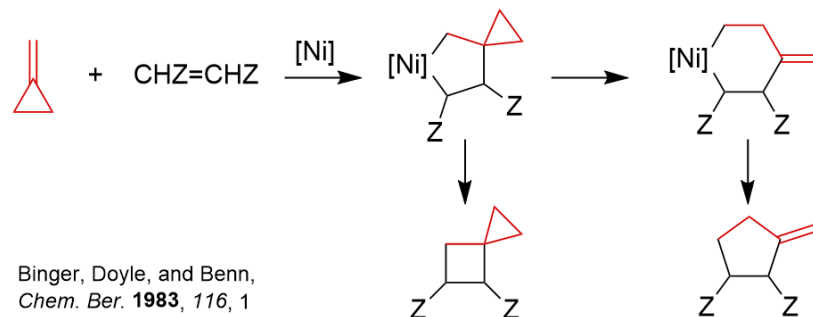


Noyori's Explanation:



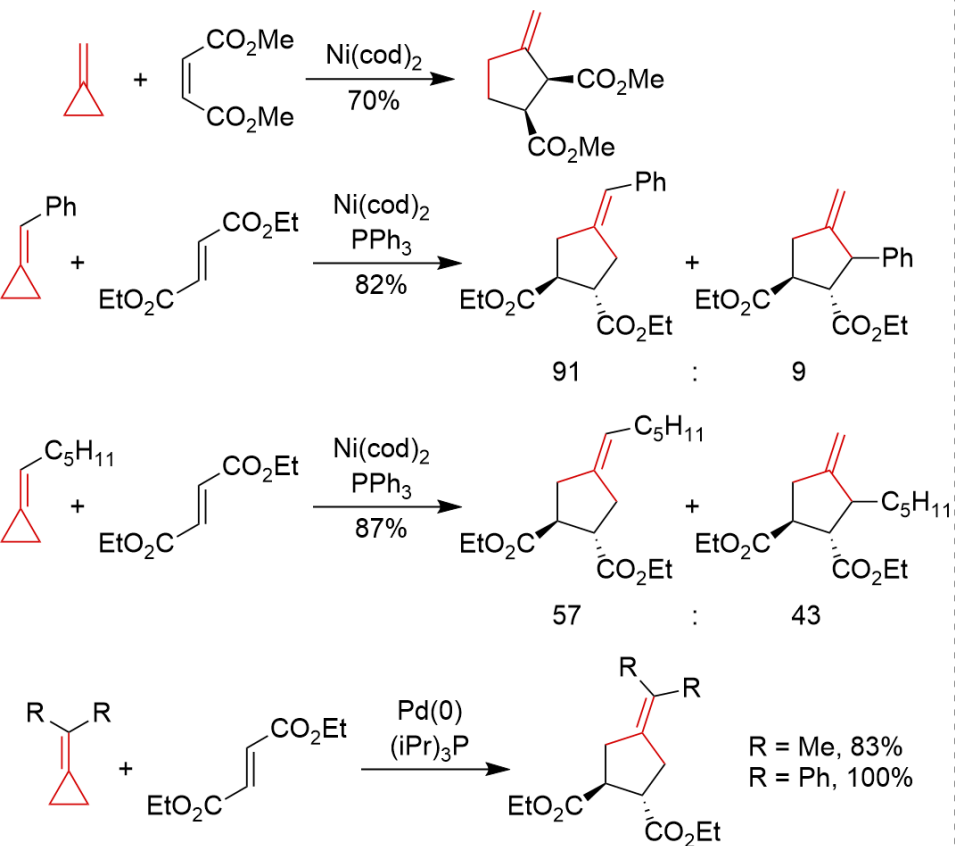
Noyori and Yamakawa, *Tetrahedron Lett.* **1978**, 19, 4823

Binger proposed an alternate route to the Type B product based on observation of a [2+2] side product.



Binger, Doyle, and Benn, *Chem. Ber.* **1983**, 116, 1





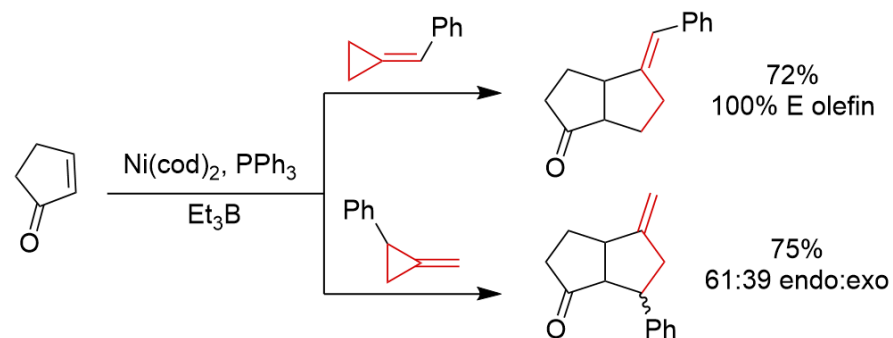
Dozens of additional reactions conducted by the Binger group during the 1980s revealed the following rough trends:

- Ligand-free  $\text{Ni}^0$  catalysis favors Type B products and proximal ring cleavage
- $\text{Ni}^0$  catalysis with phosphine or phosphite ligands generally favors Type A products and distal ring cleavage
- $\text{Pd}^0$  catalysis reliably proceeds by a Type A mechanism
- Type A mechanisms risk substituent migration due to TMM symmetry

Binger and Büch, *Topics in Current Chemistry* **1987**, 135, 77

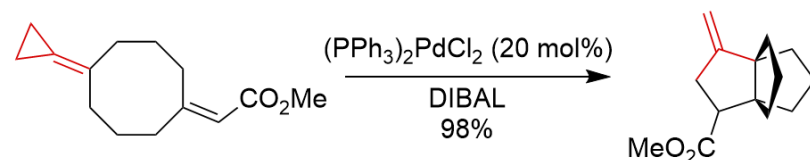
"No clear reason for this trend has emerged." - Mark Lautens

Curiously, Binger reported that the presence of triethylborane in the  $\text{Ni}^0/\text{PPh}_3$  catalytic system restored a preference for Type B products.

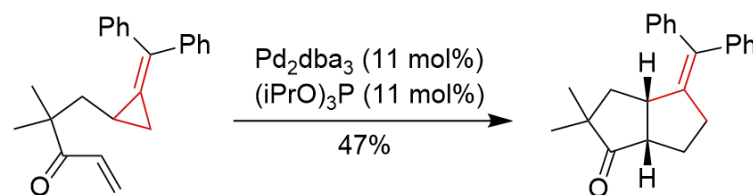


Binger and Schäfer, *Tetrahedron Lett.* **1988**, 29, 4539

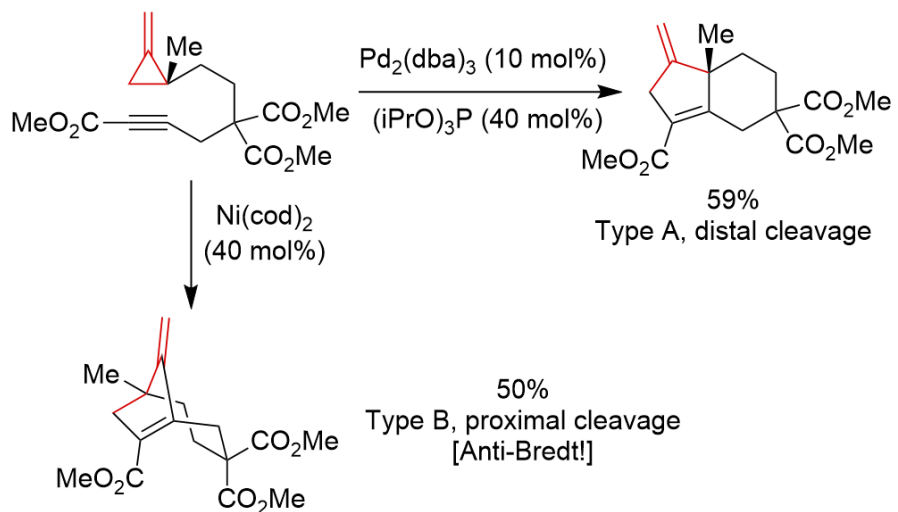
Since these findings, intramolecular MCP cycloadditions under  $\text{Pd}^0$  catalysis have been the most popular due to their more reliable selectivity. Motherwell and Nakamura were among the first to apply this chemistry.



Yamago and Nakamura, *Tetrahedron* **1989**, 45, 3081

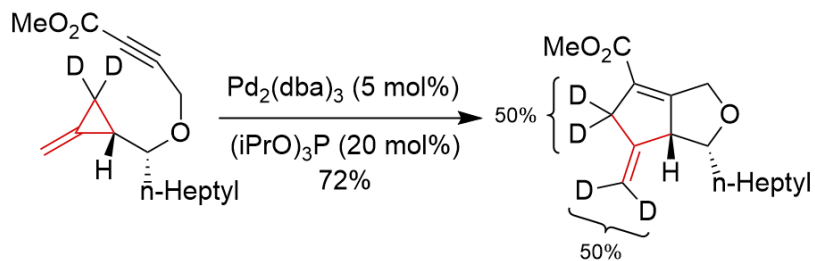


Lewis et al., *Tetrahedron* **1995**, 51, 3289



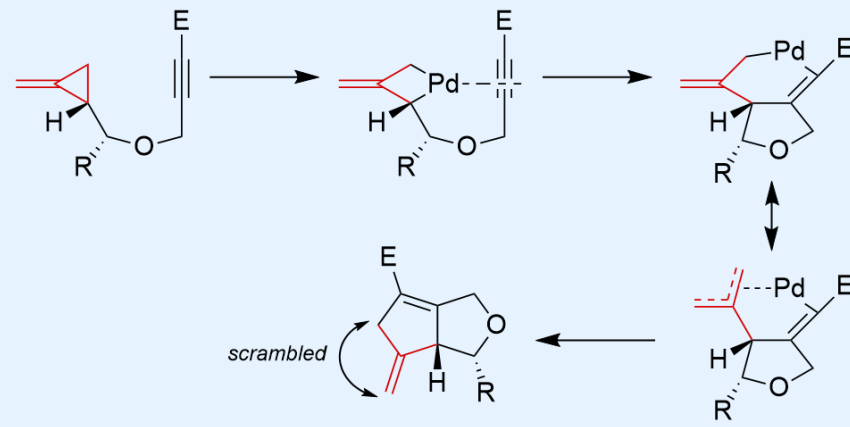
Bapuji, Motherwell, and Shipman, *Tetrahedron Lett.* **1989**, 30, 7107

Lautens and coworkers investigated the stereospecificity of this intramolecular [3+2] cycloaddition.



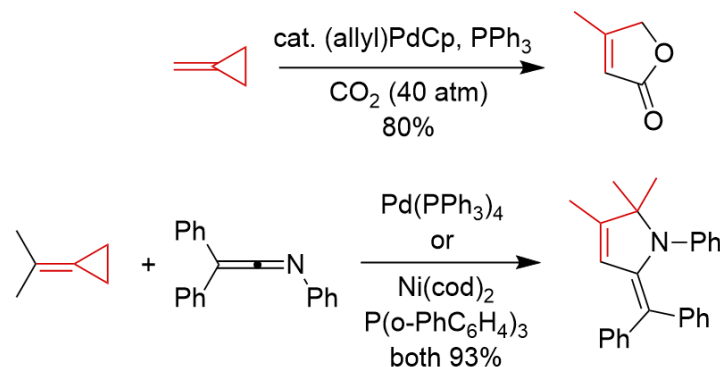
- Stereospecific distal ring cleavage
- Scrambling of deuterium implies symmetrical intermediate
- RSM did not feature scrambling like Noyori's original report, so the insertion must be rate determining

Lautens' Proposed Mechanism (Type A, Intramolecular)

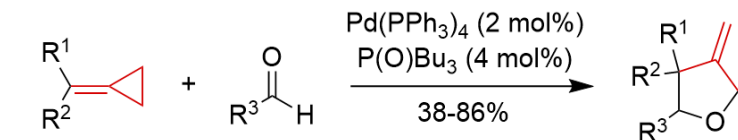


Lautens, Ren, and Delanghe, *J. Am. Chem. Soc.* **1994**, 116, 8821

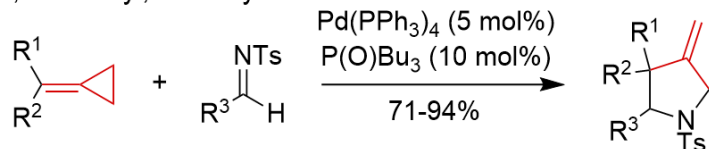
Transition metal catalyzed cycloadditions have been applied to the construction of heterocycles as well.



Binger and Weintz, *Chem. Ber.* **1984**, 117, 654  
 Weintz and Binger, *Tetrahedron Lett.* **1985**, 26, 4075



R<sup>1</sup>, R<sup>2</sup> = alkyl; R<sup>3</sup> = aryl

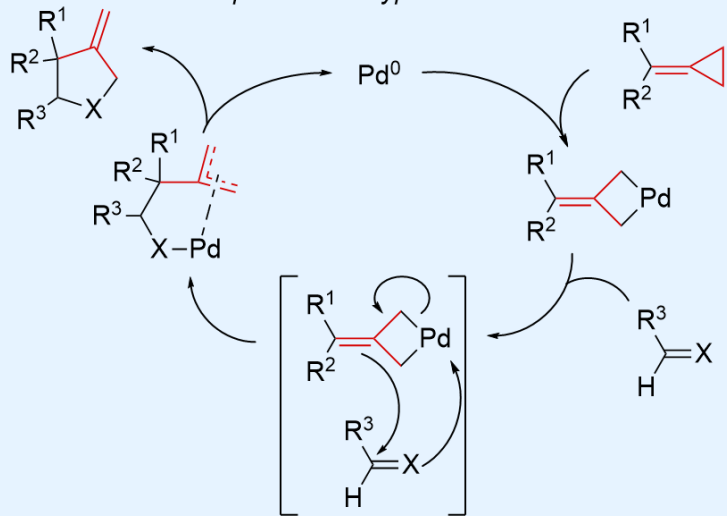


R<sup>1</sup>, R<sup>2</sup> = alkyl; R<sup>3</sup> = aryl

Compare to Shi's Lewis Acid catalyzed methods for the same transformations:

- More broad substrate scope
- Lower catalyst loading
- Complementary MCP cleavage
- Generally better yield
- Higher temperature

#### Proposed Pd<sup>0</sup> Type A Mechanism

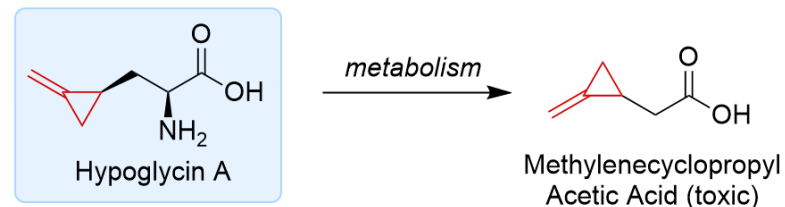


Yamamoto et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 1298

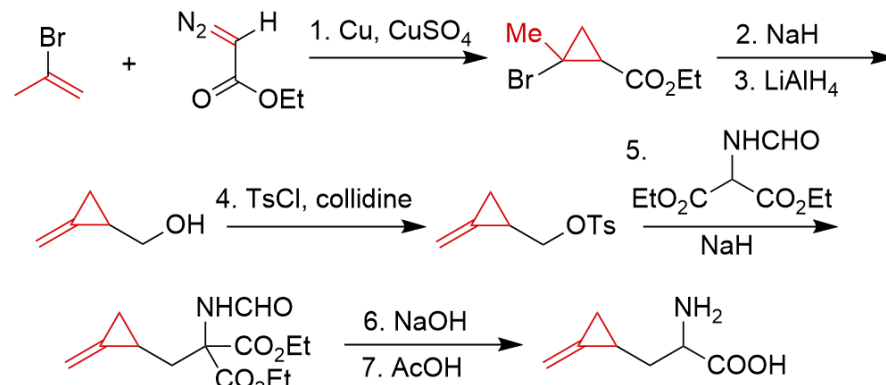
Oh et al., *Tetrahedron Lett.* **2001**, *42*, 6203

## 7. MCPs in Synthesis

The methyleneecyclopropane group is found in nature in Hypoglycin A, an amino acid derivative present in unripe Ackee fruit native to West Africa. This compound is responsible for causing "Jamaican Vomiting Sickness", a life-threatening hypoglycemic illness.

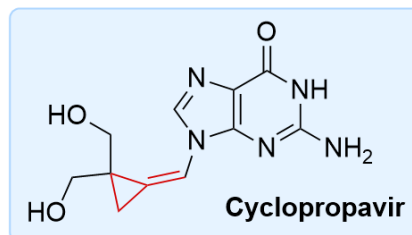


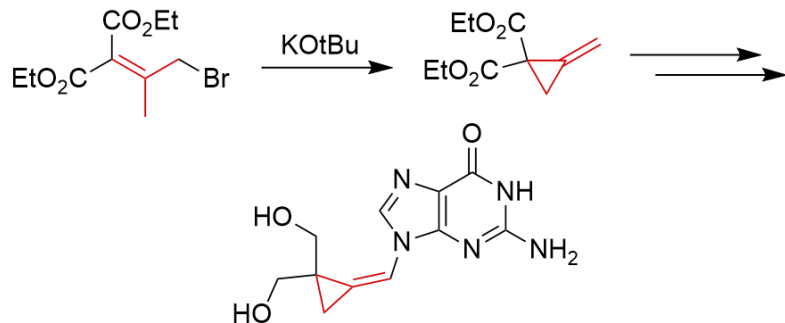
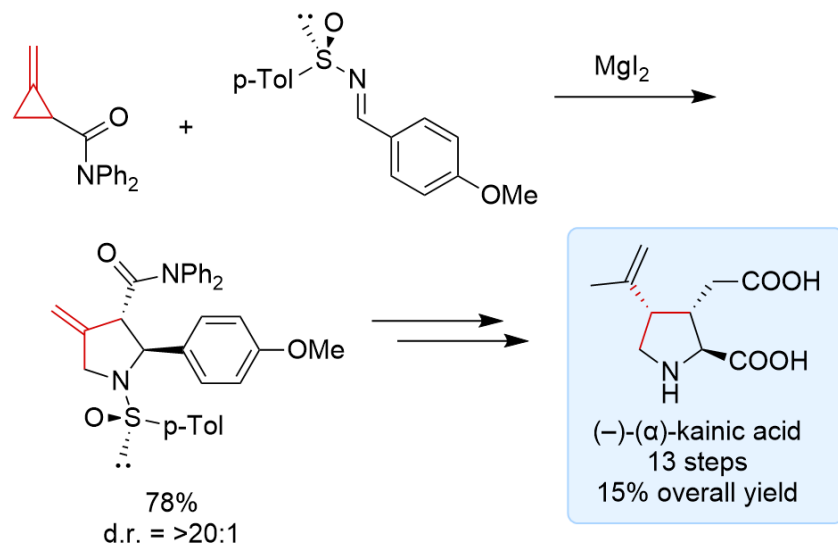
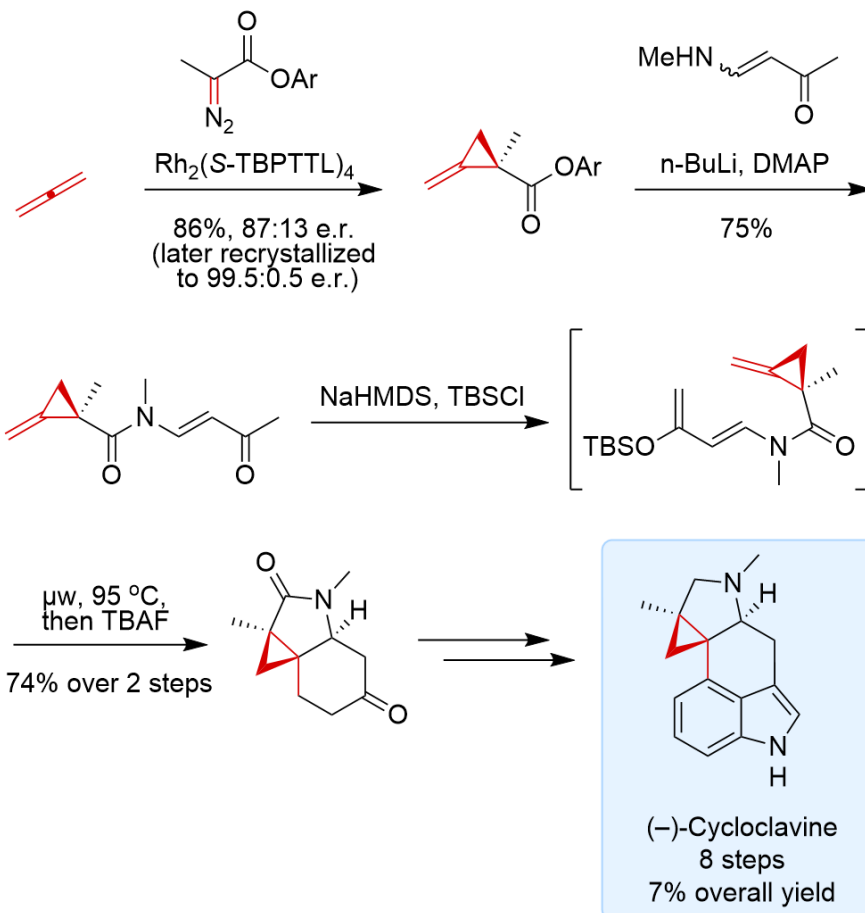
### Carbon's Synthesis of (±)-Hypoglycin A (1958)



Carbon et al., *J. Am. Chem. Soc.* **1958**, *80*, 1002

Cyclopropavir, a small molecule drug with activity against human cytomegalovirus infection, contains an MCP group. It was investigated in Phase 1 FDA clinical trials, but did not proceed further.



Zhou et al., *J. Med. Chem.* **2004**, *47*, 566-575**Scott and Lautens' Total Synthesis of (-)-( $\alpha$ )-Kainic Acid (2005)***Key Step: Lewis Acid Catalyzed MCP Ring Expansion*Scott and Lautens, *Org. Lett.* **2005**, *7*, 3045**McCabe and Wipf's Total Synthesis of (-)-Cycloclavine***Key Step: Intramolecular Strain-Promoted MCP Diels-Alder Reaction*McCabe and Wipf, *Angew. Chem. Int. Ed.* **2017**, *56*, 324