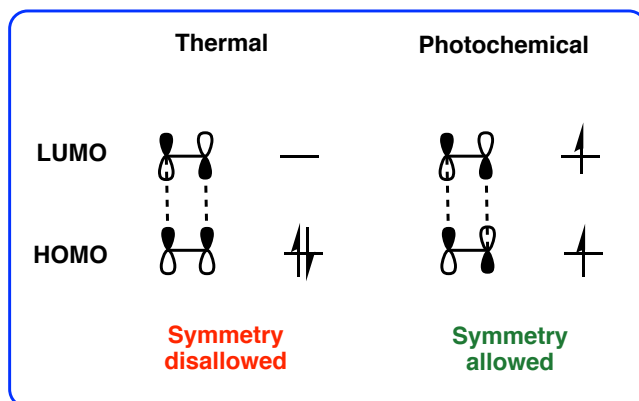
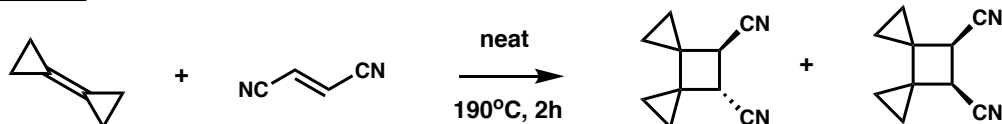


- Cycloadditions are step and atom economic
- Thermal [2+2] cycloadditions have the potential for larger substrate scope than photochemical counterpart
- Concerted thermal [2+2] cycloadditions are forbidden by the Woodward-Hoffman rules but may be induced to proceed by radicals pathways, donor-acceptor complexes and metals among others.

Important references

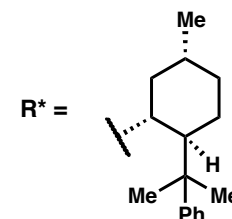
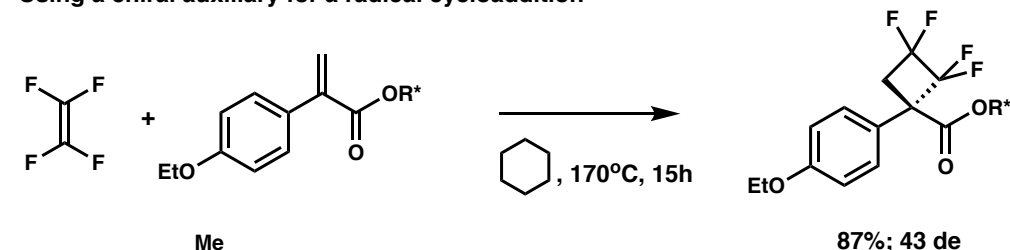
- Allenes:** B. Alcaide, P. Almendros, C. Aragoncillo. *Chem Soc. Rev.* **2010**, 39, 783
- Metal catalyzed:** K. Parthasarathy, C. Cheng. *Comprehensive Organic Synthesis II.* **2014**, 5, 222
- Cyclobutane synthesis:** Z. Rappoport, J. Liebman. **(2005)** *The Chemistry of Cyclobutanes.*

Radical

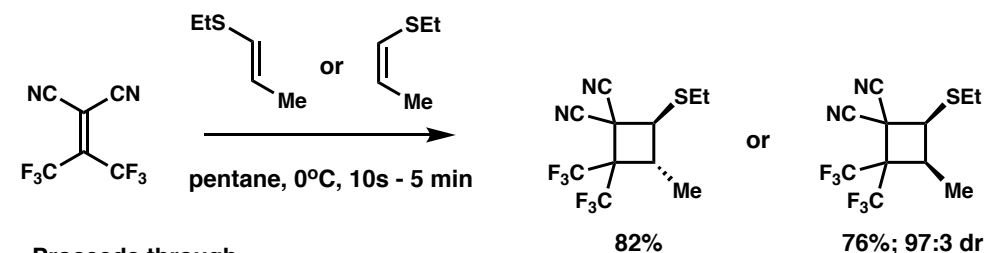
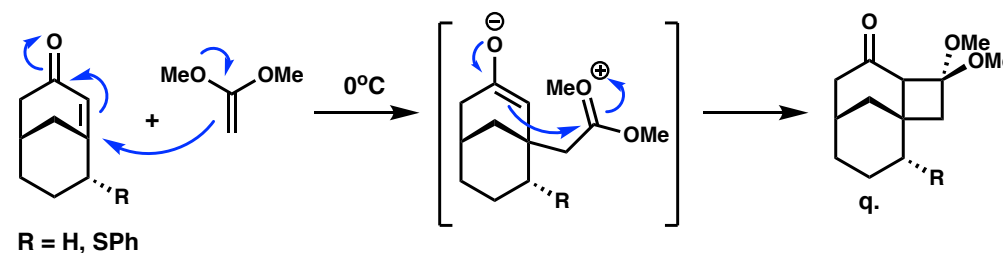
78:22; 57%

- Goes through 1,4 biradical
- High temperatures
 - Poor selectivity

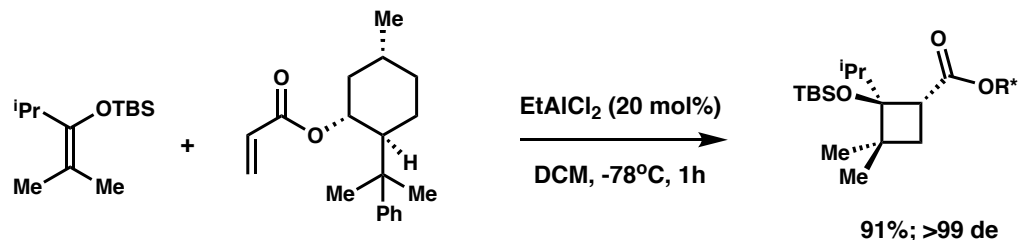
Using a chiral auxiliary for a radical cycloaddition



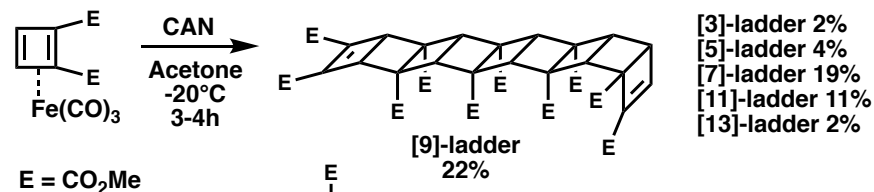
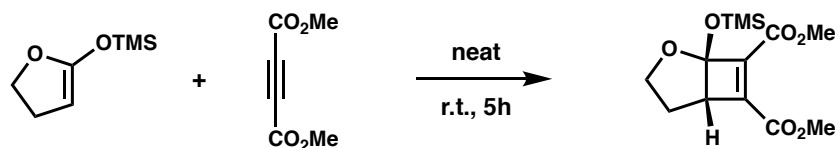
Dictates the facial selectivity of tetrafluoroethylene

Donor-acceptor type

Proceeds through zwitterionic intermediate, yet highly stereoselective



With alkynes

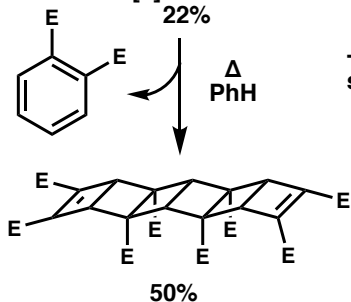


[3]-ladder 2%
 [5]-ladder 4%
 [7]-ladder 19%
 [11]-ladder 11%
 [13]-ladder 2%

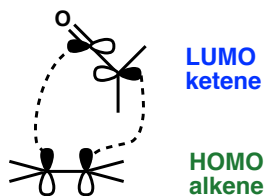
[9]-ladder 22%

-Formally a series of [4+2]s

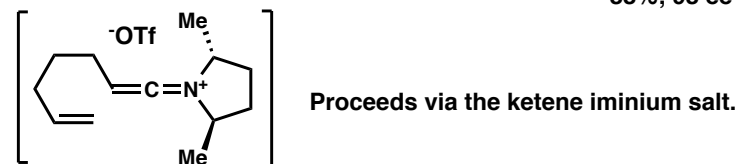
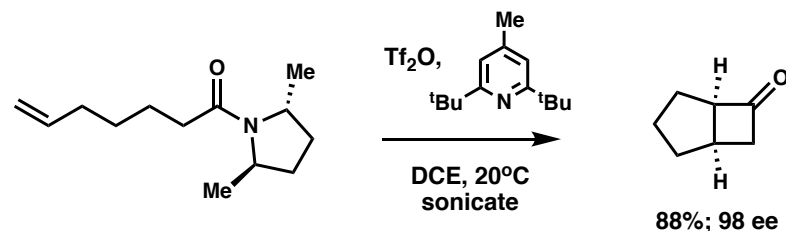
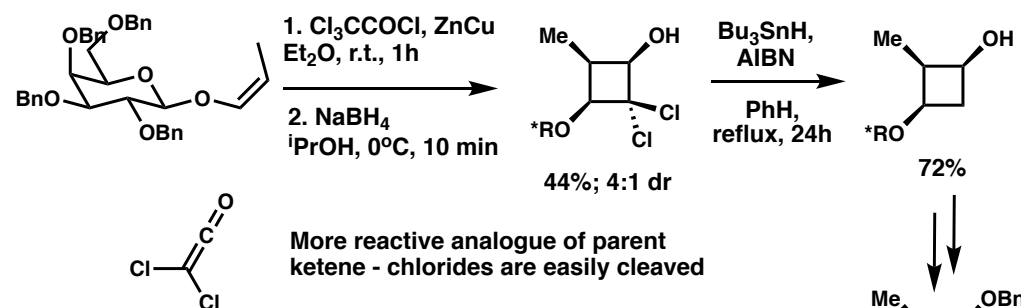
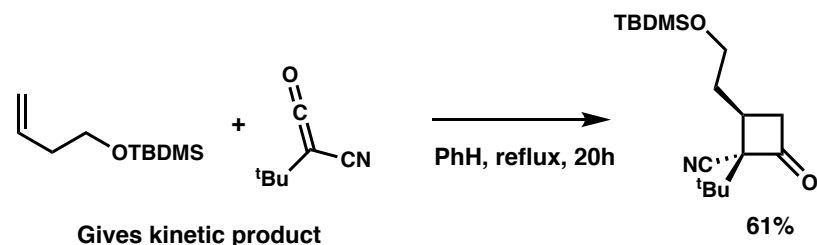
-Does a 4π electrocyclic ring opening followed by retro [2+2] to cleave off phthalate

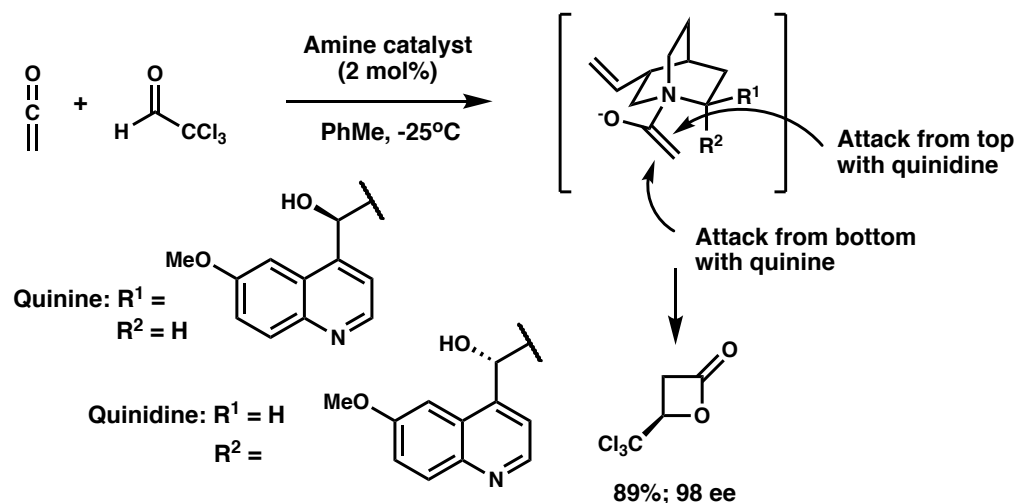


Via ketenes

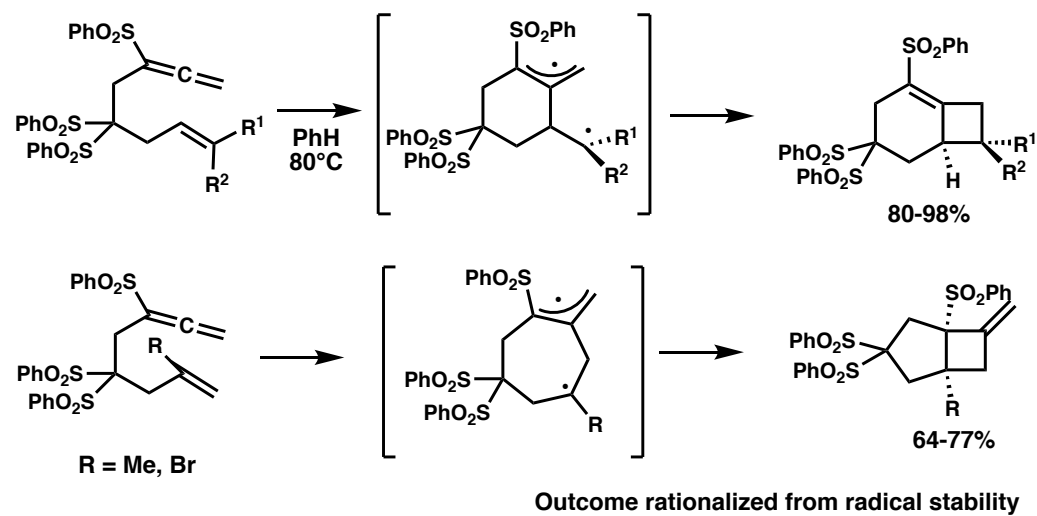
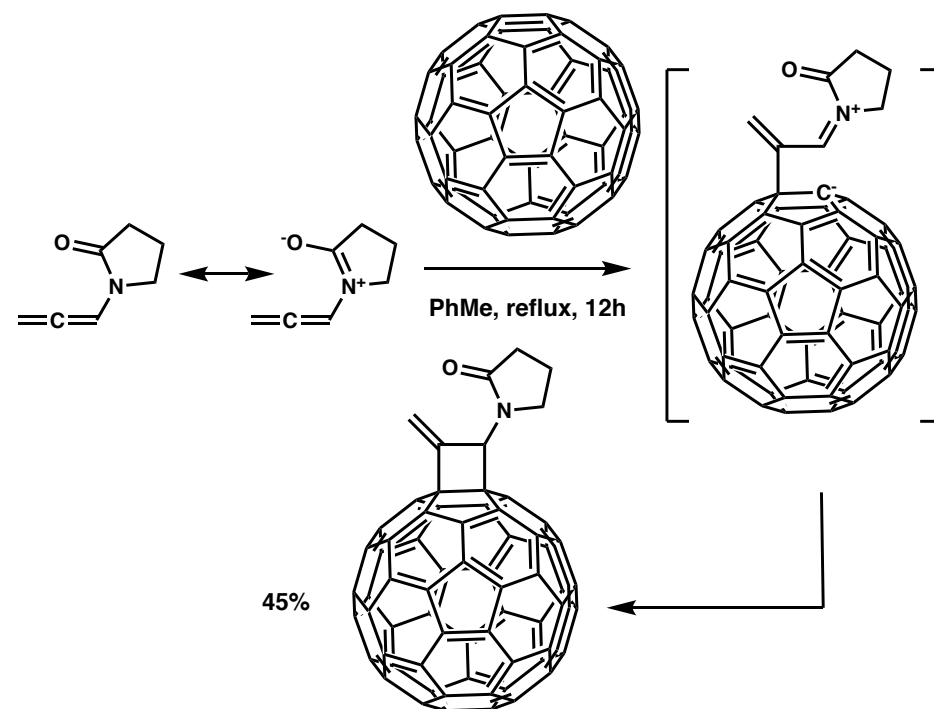
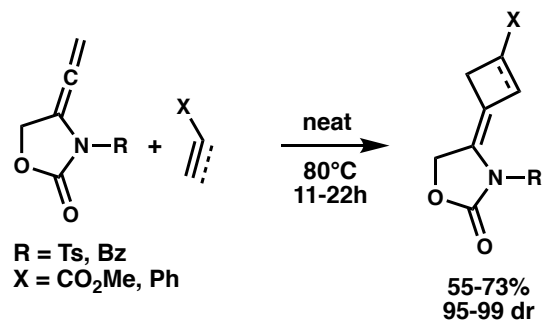
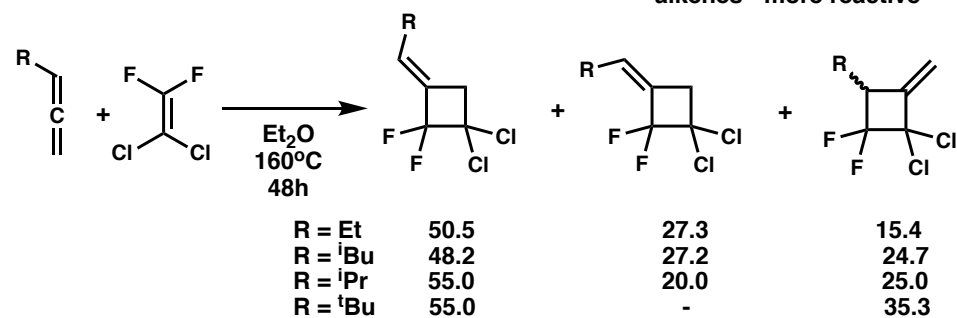


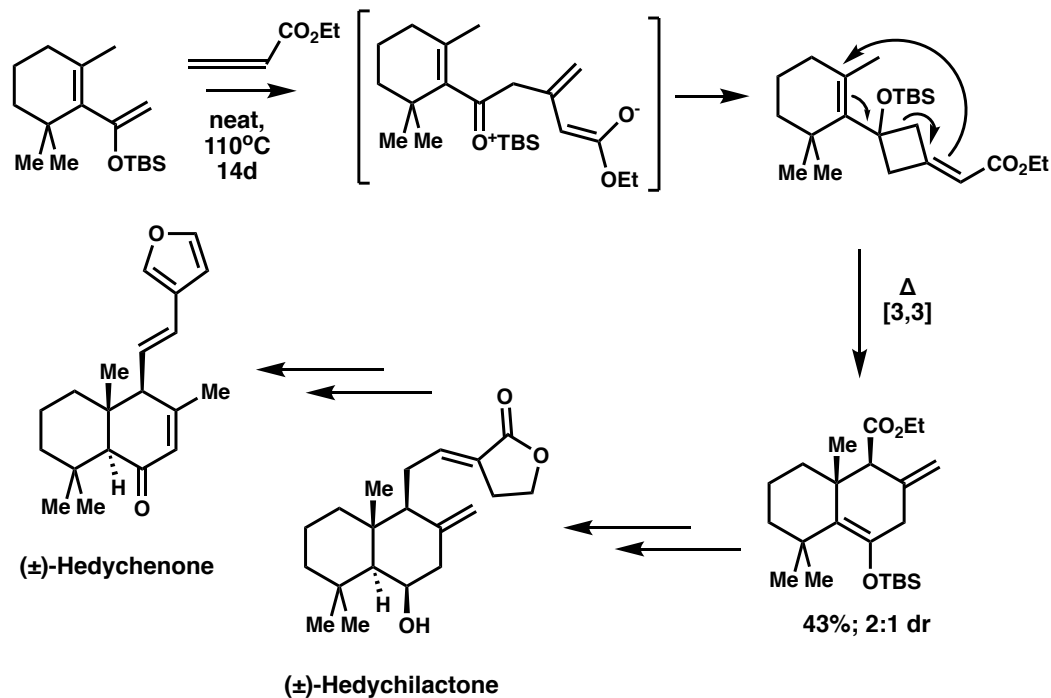
-Can be viewed as a thermally allowed $2\pi_s + 2\pi_a$ process
 -Concerted process predicts stereochemical outcomes well
 -However, believed to be a stepwise mechanism



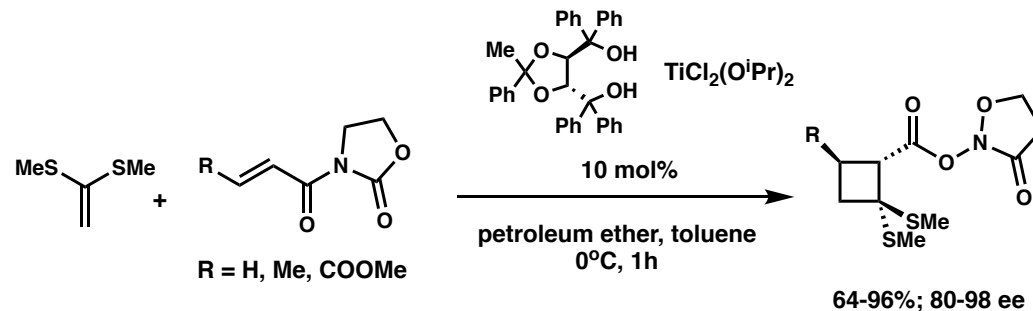
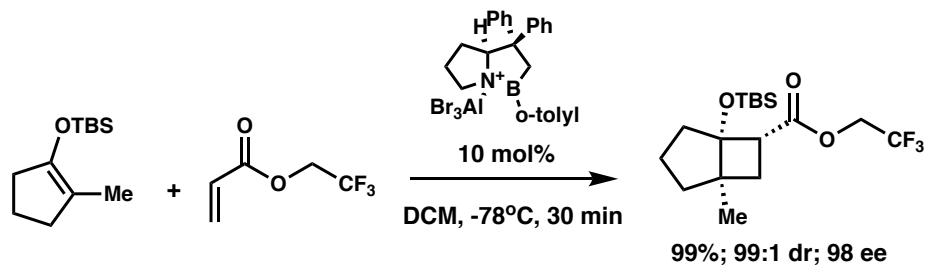
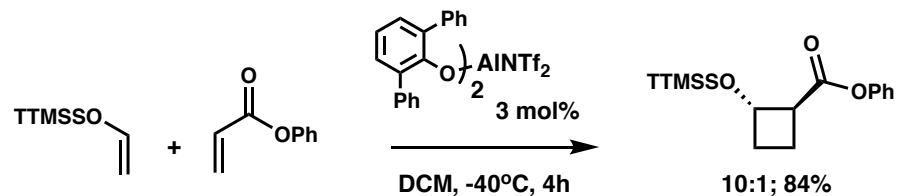


Allenes

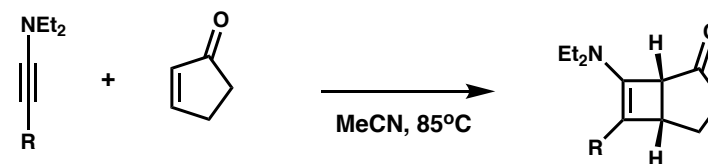




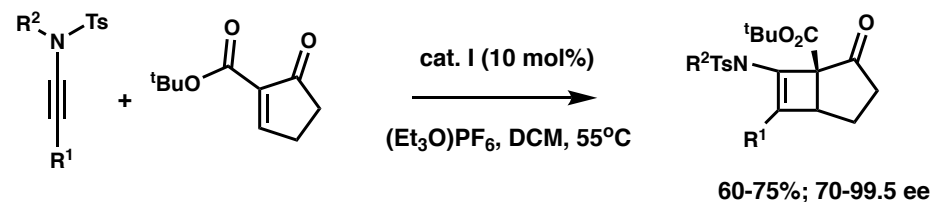
Catalyzed - Lewis acid



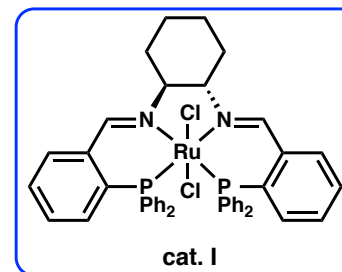
Ficini reaction (non catalyzed)



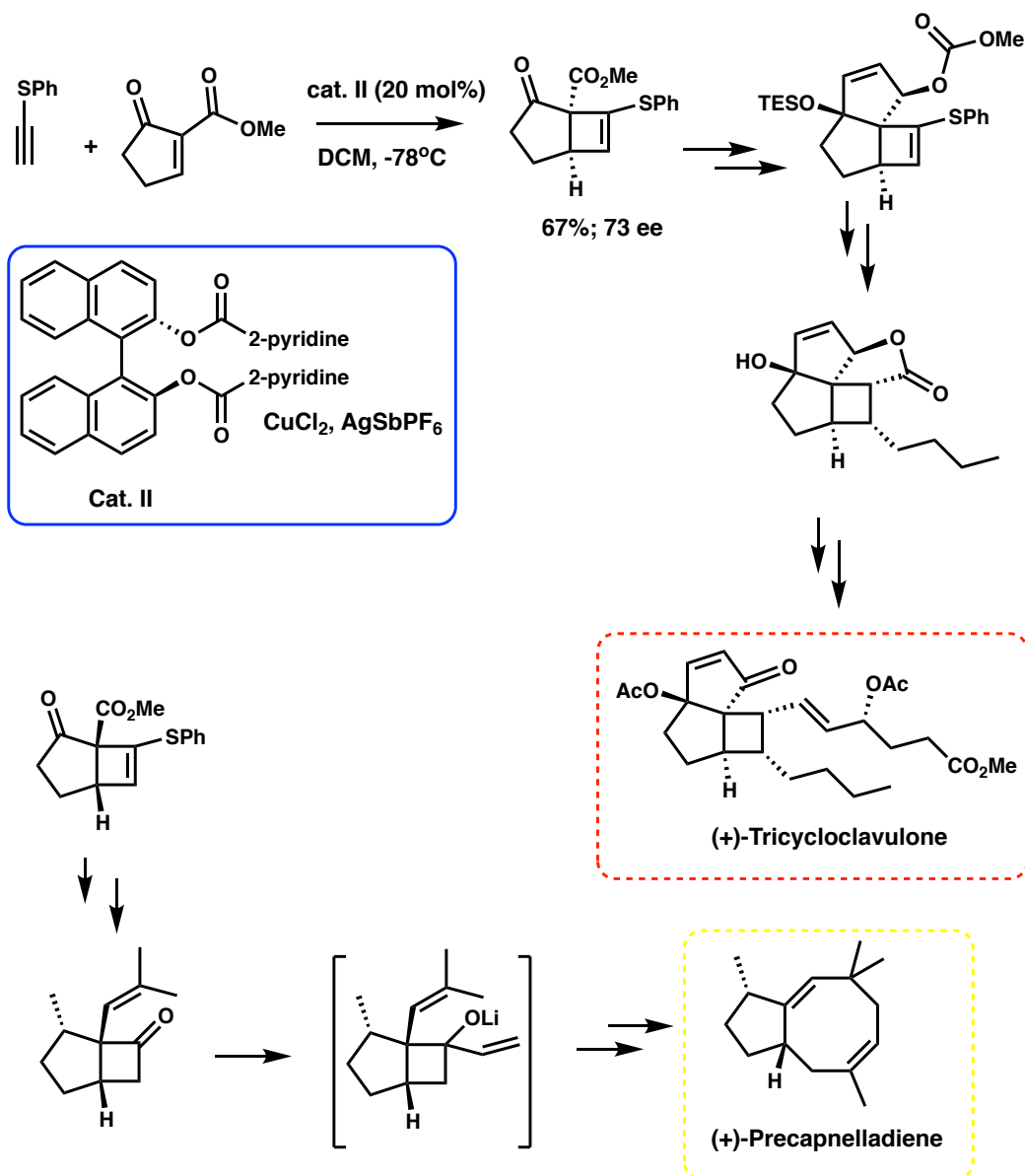
Enantioselective Ficini reaction - proceeds by double carbonyl chelate



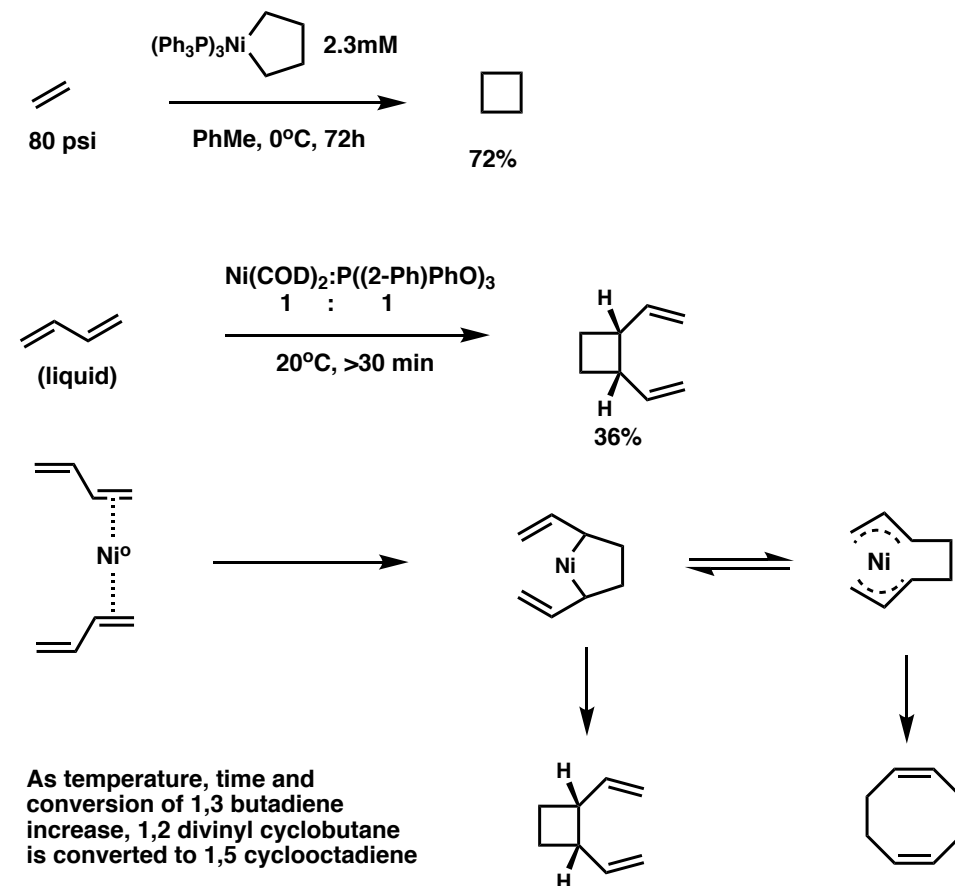
R¹ = Ph, Cy
R² = Bn, Me



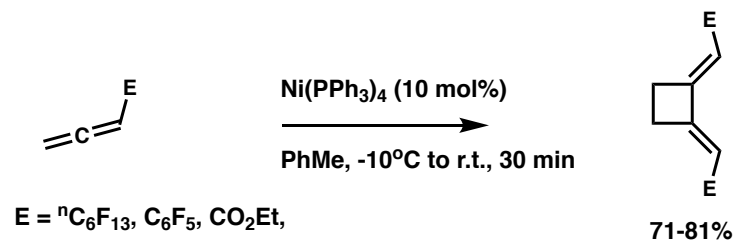
Ficini type Cu reaction has been employed in natural product synthesis



Metallacyclopentanes - Ni



Thermal selectivity problems of allenes can be overcome with Ni catalysts:



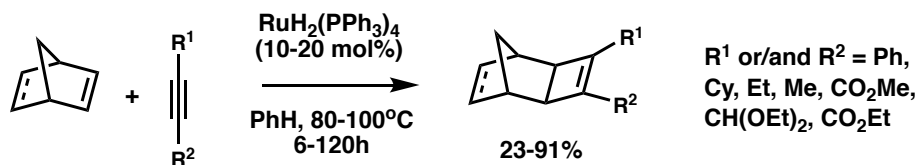
Ruthenium



-Dr. Take-Aki Mitsudo, Kyoto University,
Dept. of Energy and Hydrocarbon Chemistry

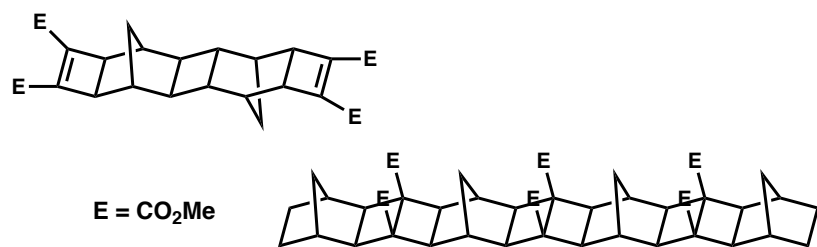
-Big name in early studies on ruthenium
catalysts for [2+2] cycloaddition

Nickel seems to react only with norbornene whereas Ru is not as picky:

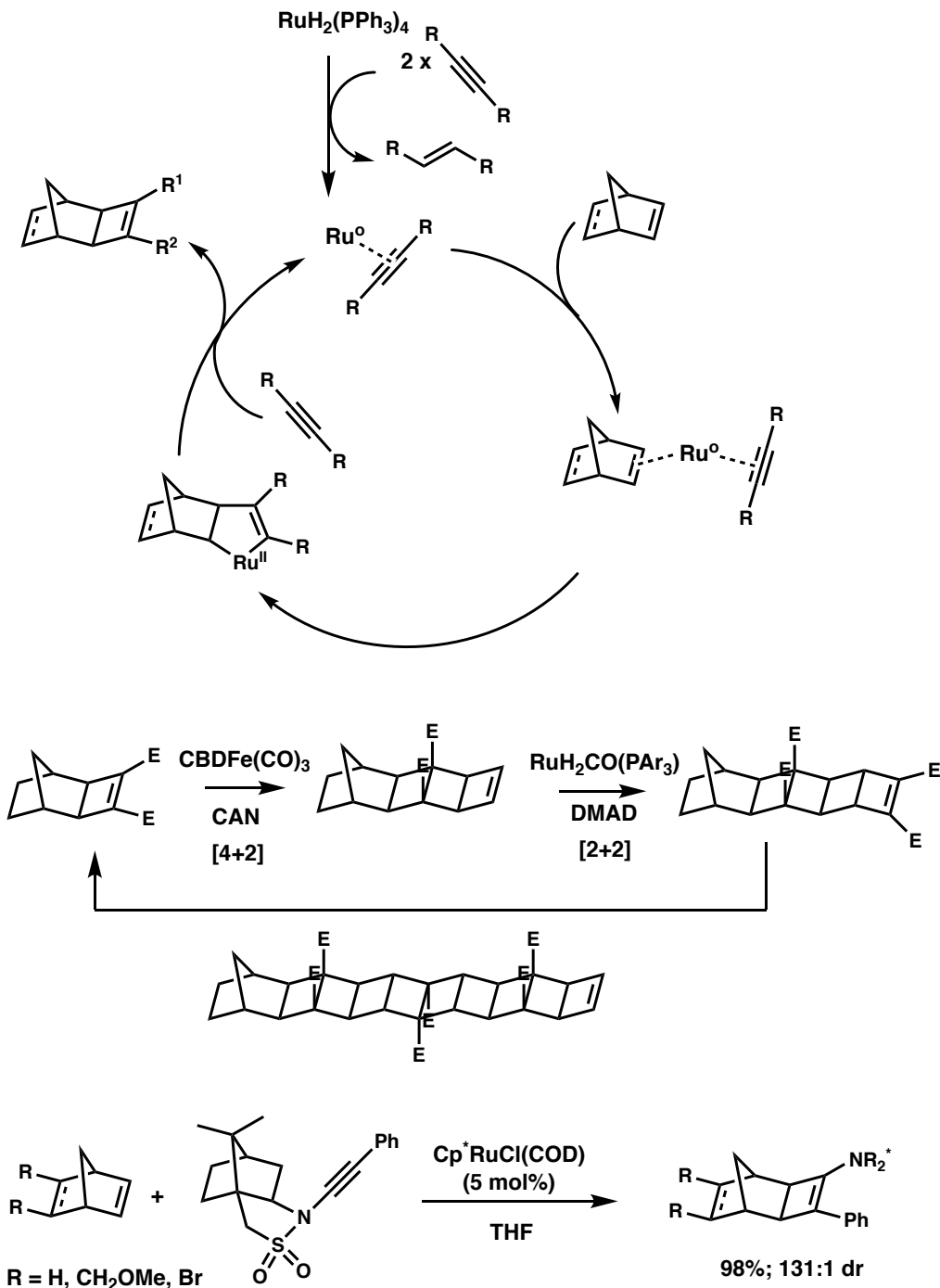


-Large scope of disubstituted acetylenes

-Similar reaction scopes with various other catalysts: $\text{RuH}_2\text{CO}(\text{P}(\text{p-PhF})_3)_3$;
 $\text{RuH}_2\text{CO}(\text{PPh}_3)_3$; $\text{RuCOD}(\text{COT})$

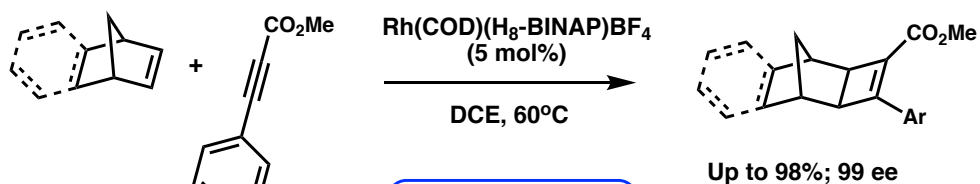


Mitsudo et al. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 580
Mitsudo et al. *J. Org. Chem.* **1987**, 334, 157
Mitsudo et al. *J. Org. Chem.* **1979**, 44, 4492
Mitsudo et al. *JCS. Chem. Comm.* **1976**, 722

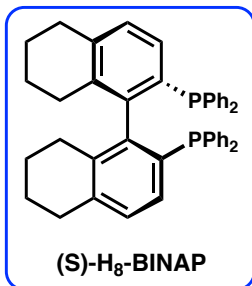


Warrener et al. *J. Am. Chem. Soc.* **1994**, 116, 3645
Villeneuve et al. *Angew. Chem. Int. Ed.* **2004**, 43, 610

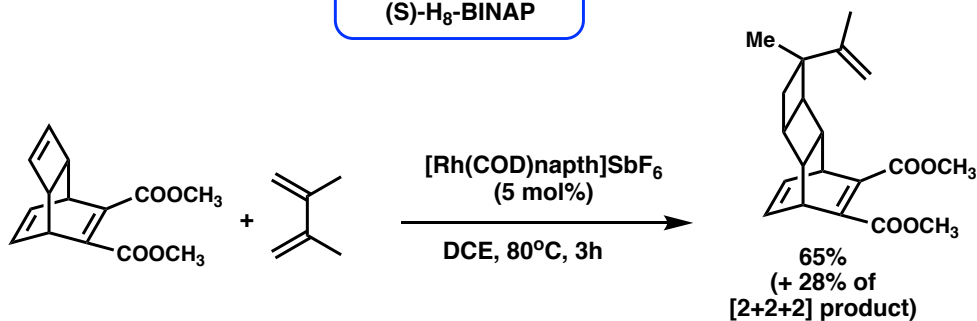
Rhodium



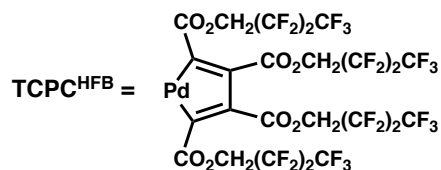
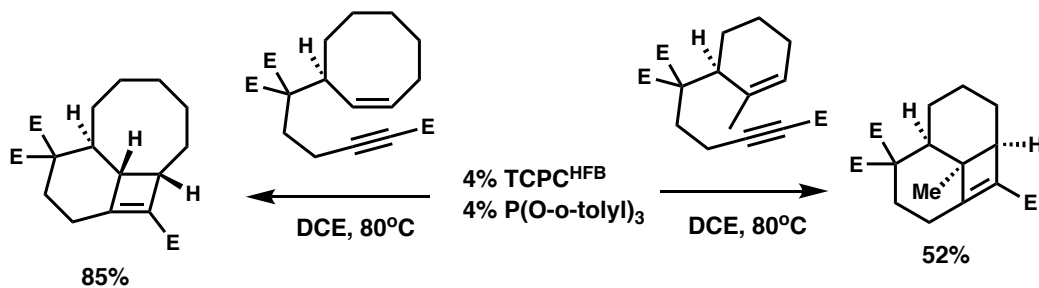
R = both EWG and EDG



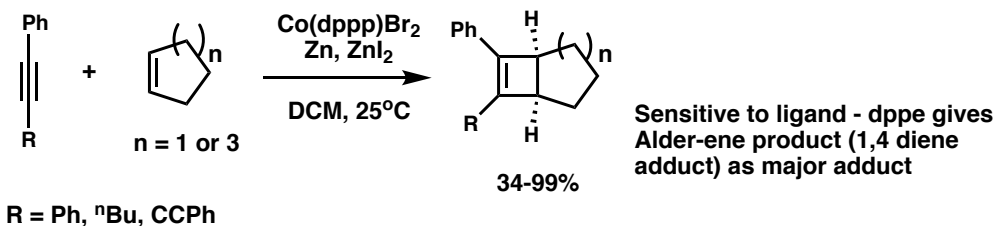
Rh catalyst gives excellent stereoselectivity on the model norbornene system



Palladium

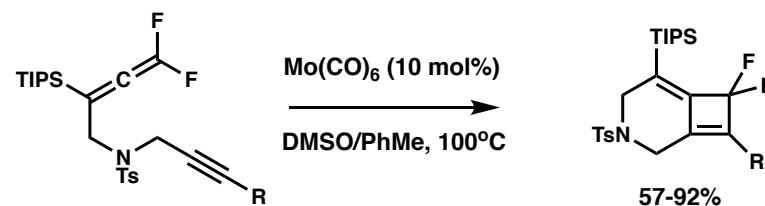


Cobalt

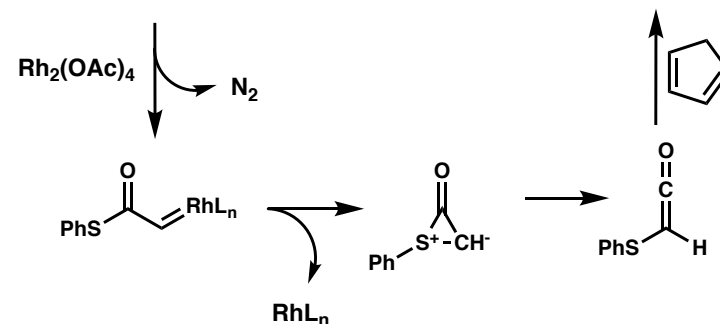
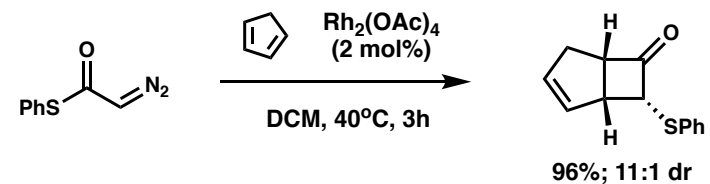


Molybdenum

Rare example of Mo use in a 2+2



Proceeds via Rh catalyzed "thia - Wolff rearrangement"



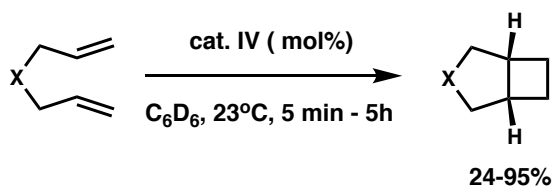
Iron



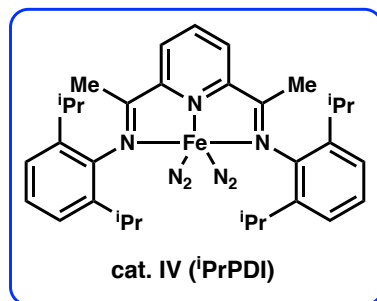
-Professor Paul Chirik, Princeton University

-Advancing the field of [2+2] cycloaddition using the more abundant first row T.Ms - iron in particular

Example of a redox active ligand for the cycloaddition of unactivated alkenes



X = CH₂, C(CO₂Et)₂, NⁱBu, NBn, NBoc

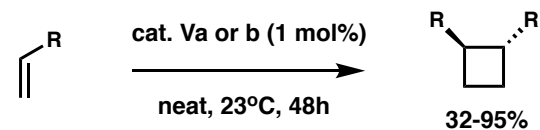


-Original report proposes a ligand metal pair with constant Fe(II) oxidation state: (iPrPDI)²⁻Fe^{II} ↔ (iPrPDI)⁰Fe^{II}

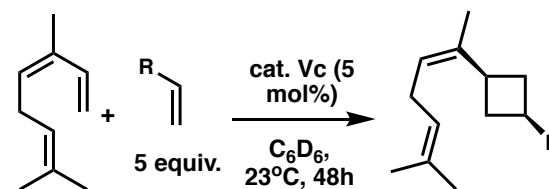
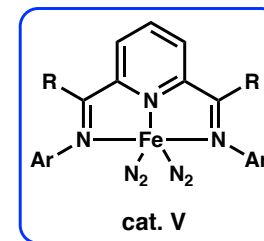
-Follow up studies revises this mechanism to another pair: (iPrPDI)¹⁻Fe^I ↔ (iPrPDI)¹⁻Fe^{III}

The reduced ligand accounts for an Fe^I/Fe^{III} cycle preventing the formation of Fe⁰ and catalyst death

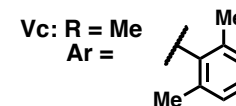
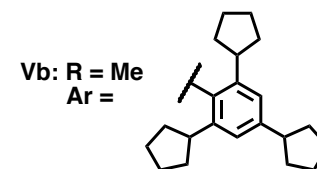
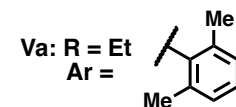
Chirik et al. *J. Am. Chem. Soc. Comm.* **2006**, 128, 13340
Chirik et al. *J. Am. Chem. Soc.* **2013**, 135, 4862



R = Me, ⁿBu, Bn, amyl, ⁱBu, (CH₂)₂Ph, N-methylene-pyrrole



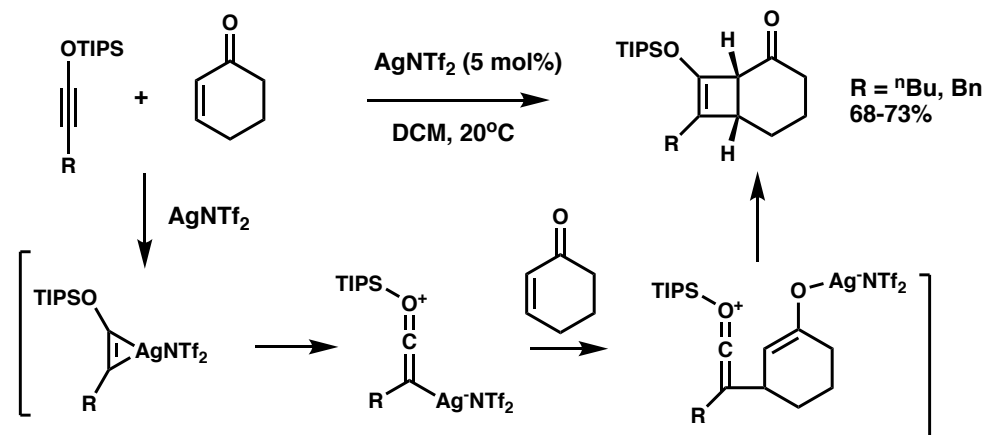
myrcene
(also tested various other 1,3 dienes)



R = ⁿBu, ⁱBu, Bn, (CH₂)₂Ph, CH₂ⁱBu, amyl, cyclohex-3-ene

Silver

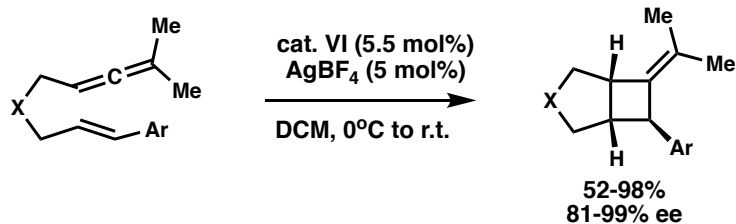
Rearrangement into ketene then 1,4 conjugate addition



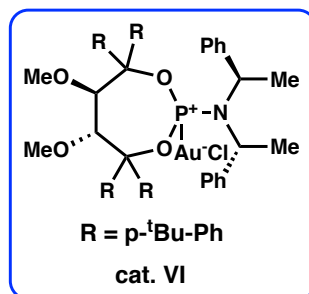
Chirik et al. *Science*, **2015**, 349, 960
Sweiss et al. *J. Am. Chem. Soc.* **2004**, 126, 7442

Gold

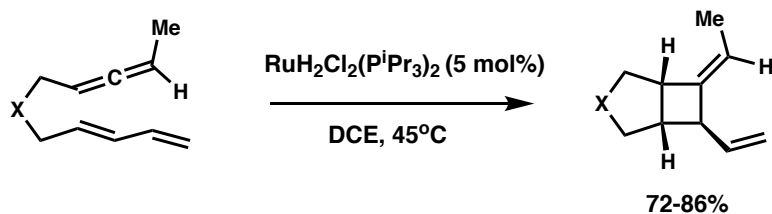
Enantioselective allene-alkene using a gold catalyst



X = C(ester)₂ or C(sulfone)₂ or NTs
Ar = 4-O^tBu-Ph, 4-OMe-Ph, 2-OMe-Ph,
2-naphthyl

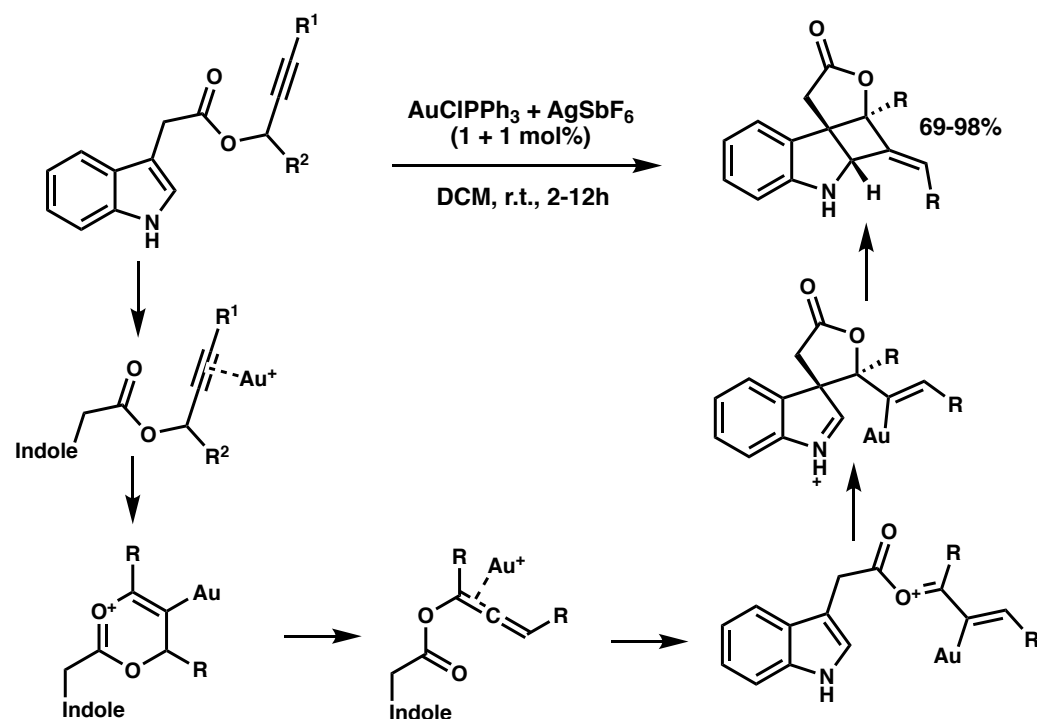


When applied to 1,3 dienes, only the [4+2] product is observed.
The ruthenium catalyst below avoids this.

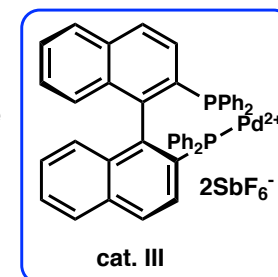
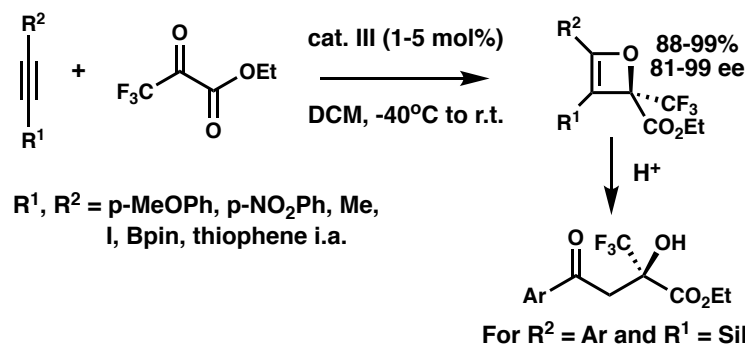


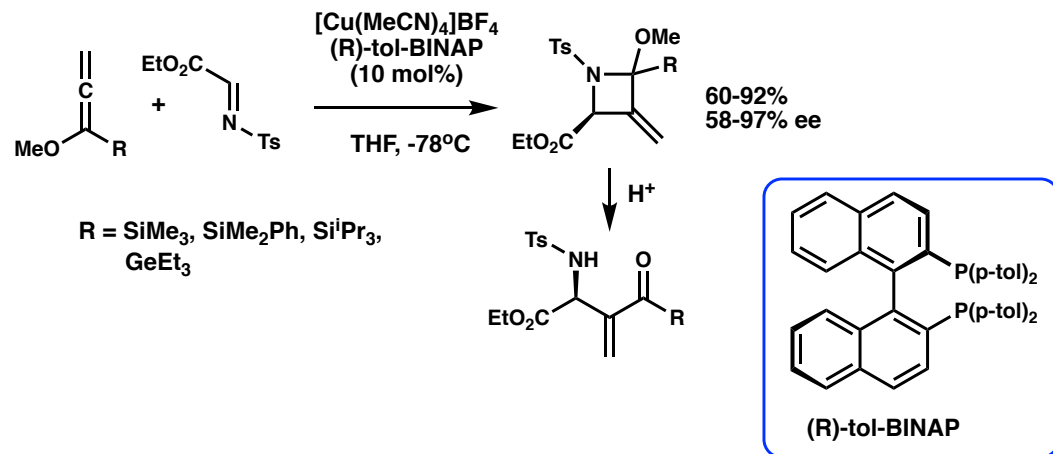
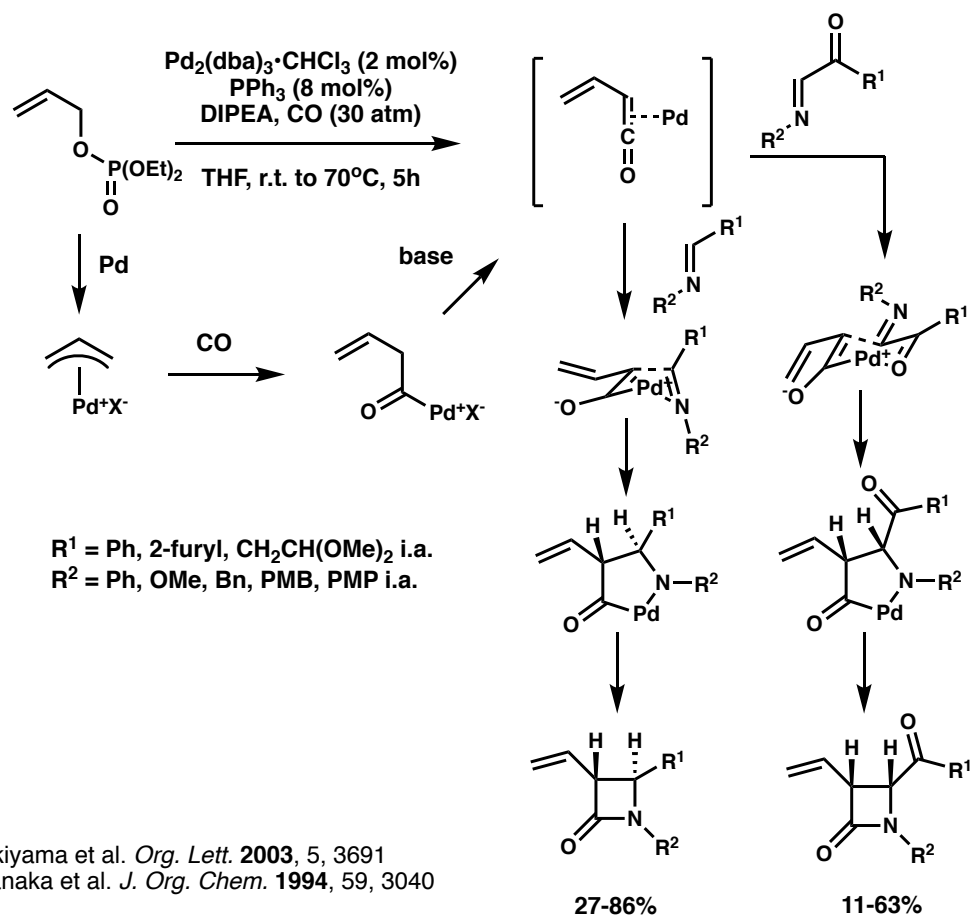
X = C(CO₂Me)₂, NTs, O

Gold effectively catalyzes an indirect [2+2] on indoles



Hetero [2+2]



**β-Lactam synthesis**

END