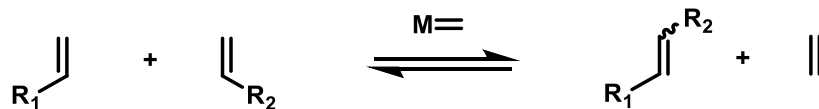


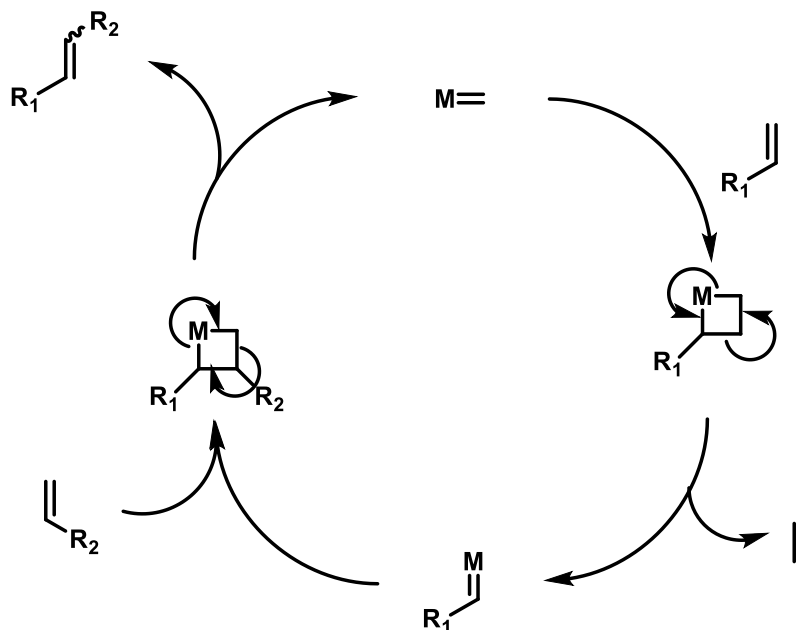
Organic synthesis

Kamil Paruch

Masaryk University, Brno

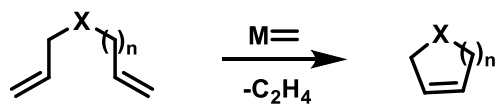


- catalytic amount of Mo or Ru carbene
- mild reaction conditions; various functional groups (OH, COOR, CHO...) tolerated

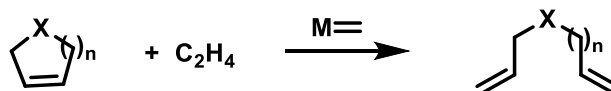


all steps are reversible

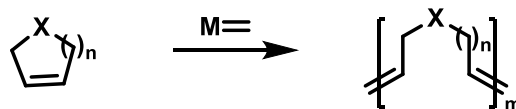
➤ rxn can be pushed to conversion e.g. by removal of ethene



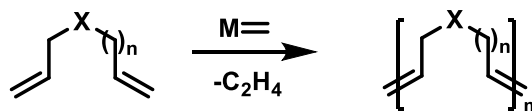
RCM (ring closing metathesis)



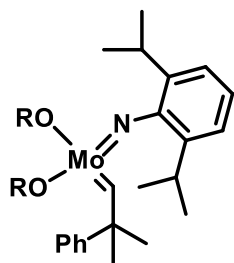
ROM (ring opening metathesis)



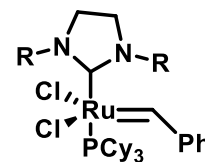
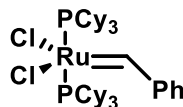
ROMP (ring opening metathesis polymerization)



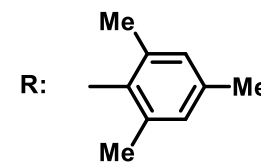
catalysts:

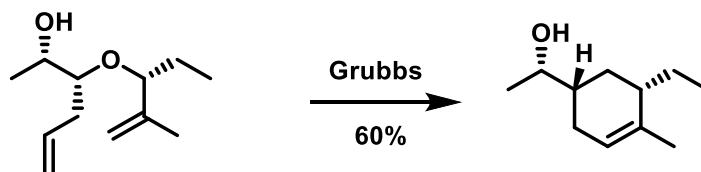


R. R. Schrock

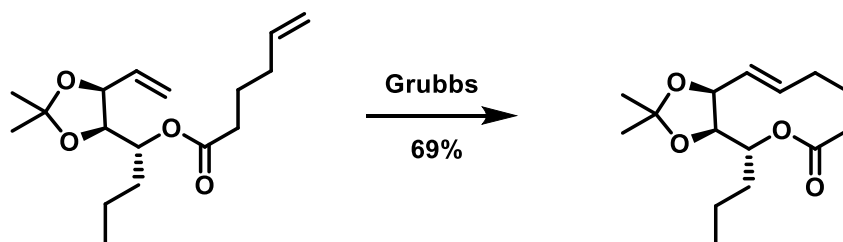


R. H. Grubbs

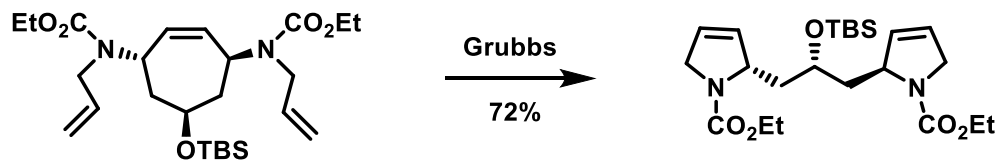




J. Am. Chem. Soc. **2001**, 123, 12432.

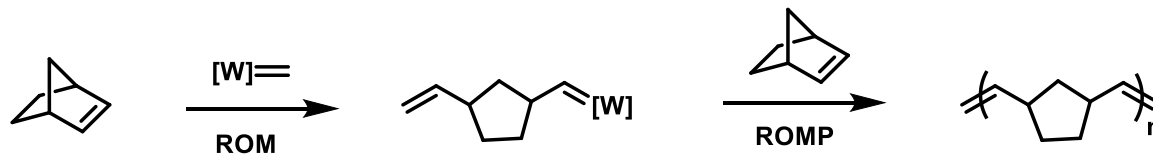


J. Am. Chem. Soc. **2002**, 124, 7061.



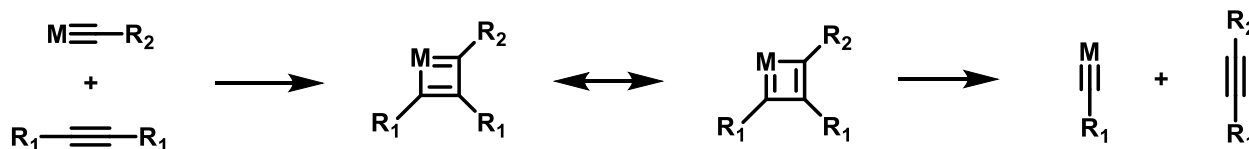
J. Org. Chem. **2002**, 67, 6456.

Norsorex process: polymerization of norbornene (45 000 tons/year)

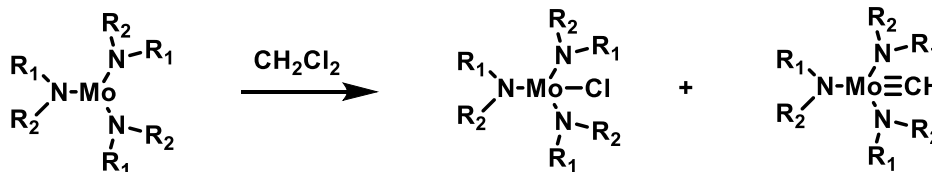
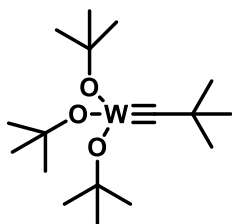


Angew. Chem. Int. Ed. **1997**, 36, 2036.

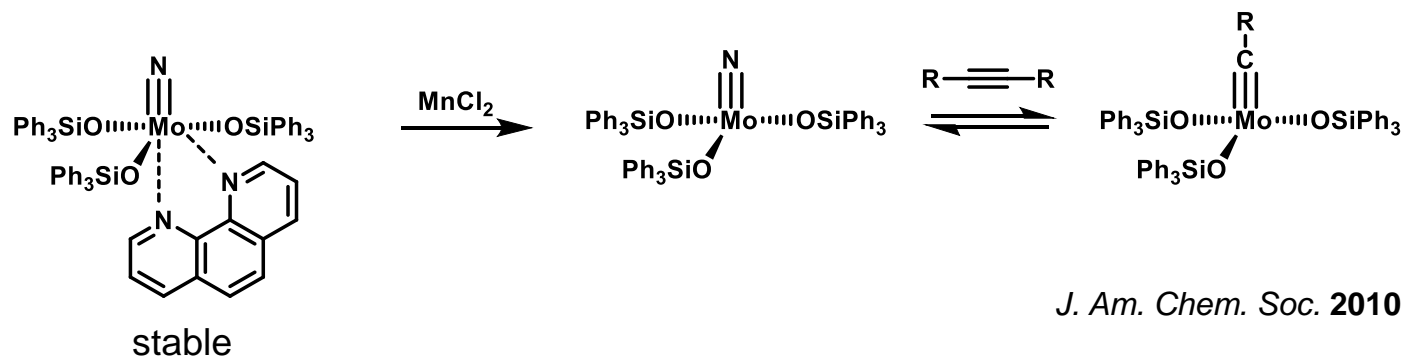
(not terminal)

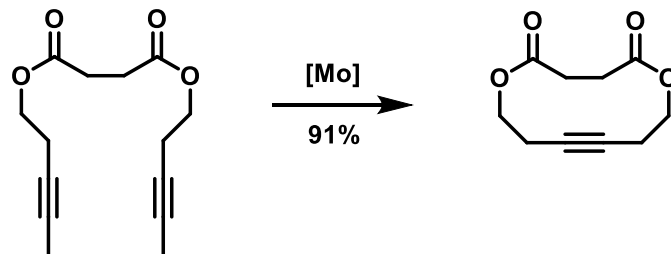


catalysts:

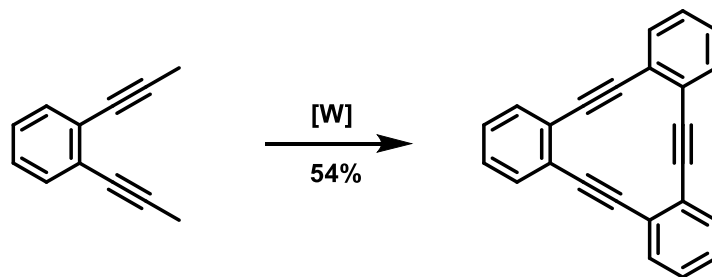


- tolerated: esters, aldehydes, *double bonds*, acetals, nitriles...

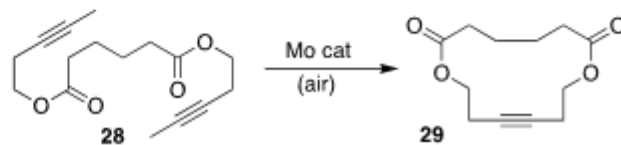




Chem. Eur. J. **2001**, 7, 5299.



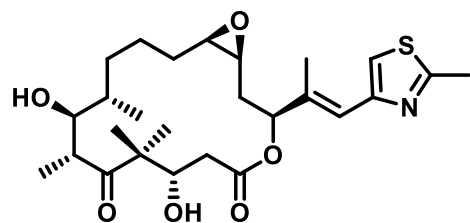
Synthesis **2003**, 2535.



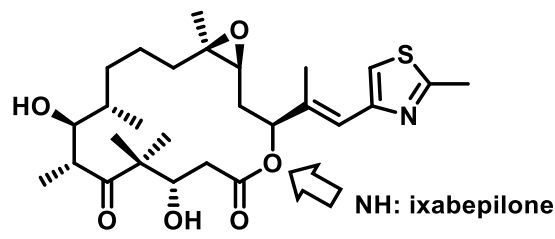
Mo-catalyzed RCM of the diyne **28** to the bis lactone **29** proceeded efficiently even in the presence of air.

Nature Commun. **2021**, 12, 1136.

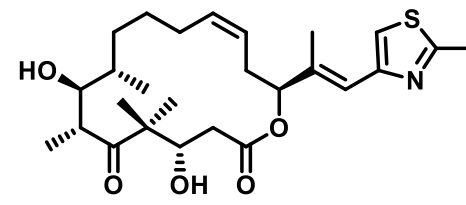
synthesis of epothilones



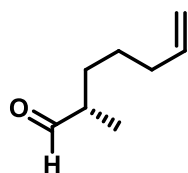
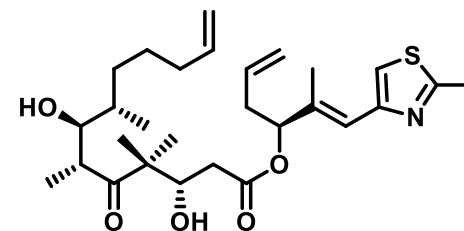
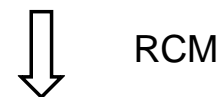
epothilone A



epothilone B

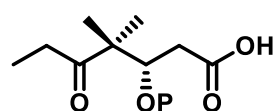


epothilone C

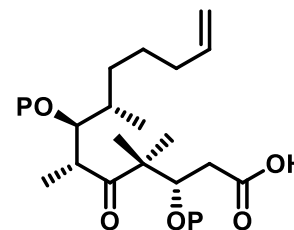
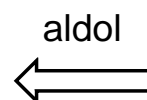


A

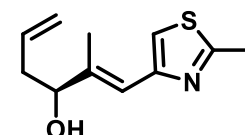
+



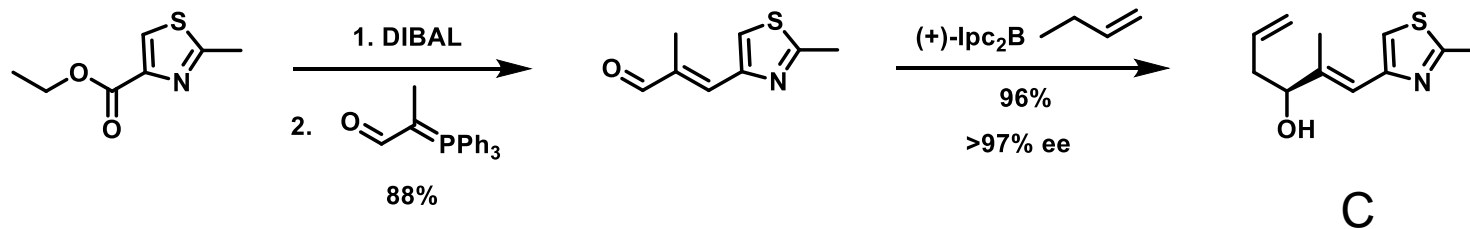
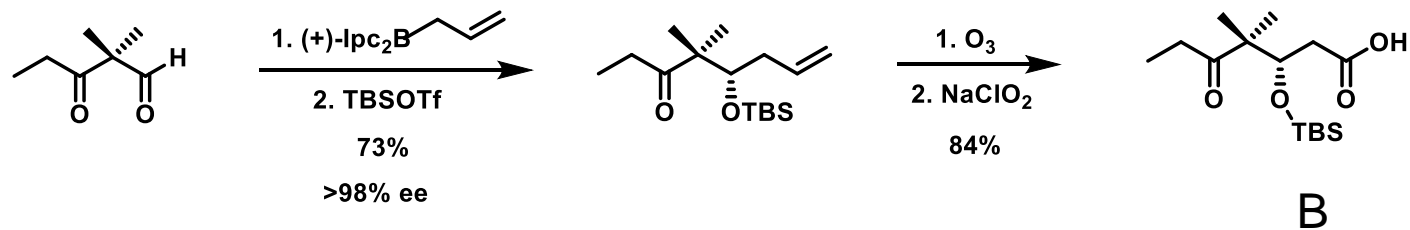
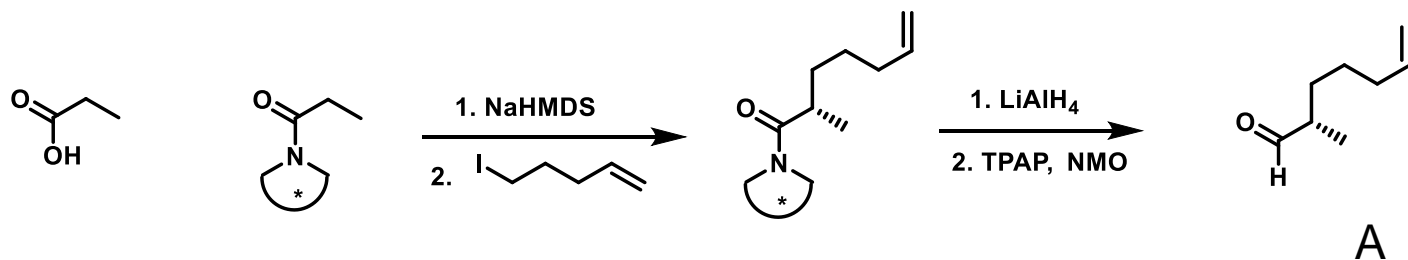
B

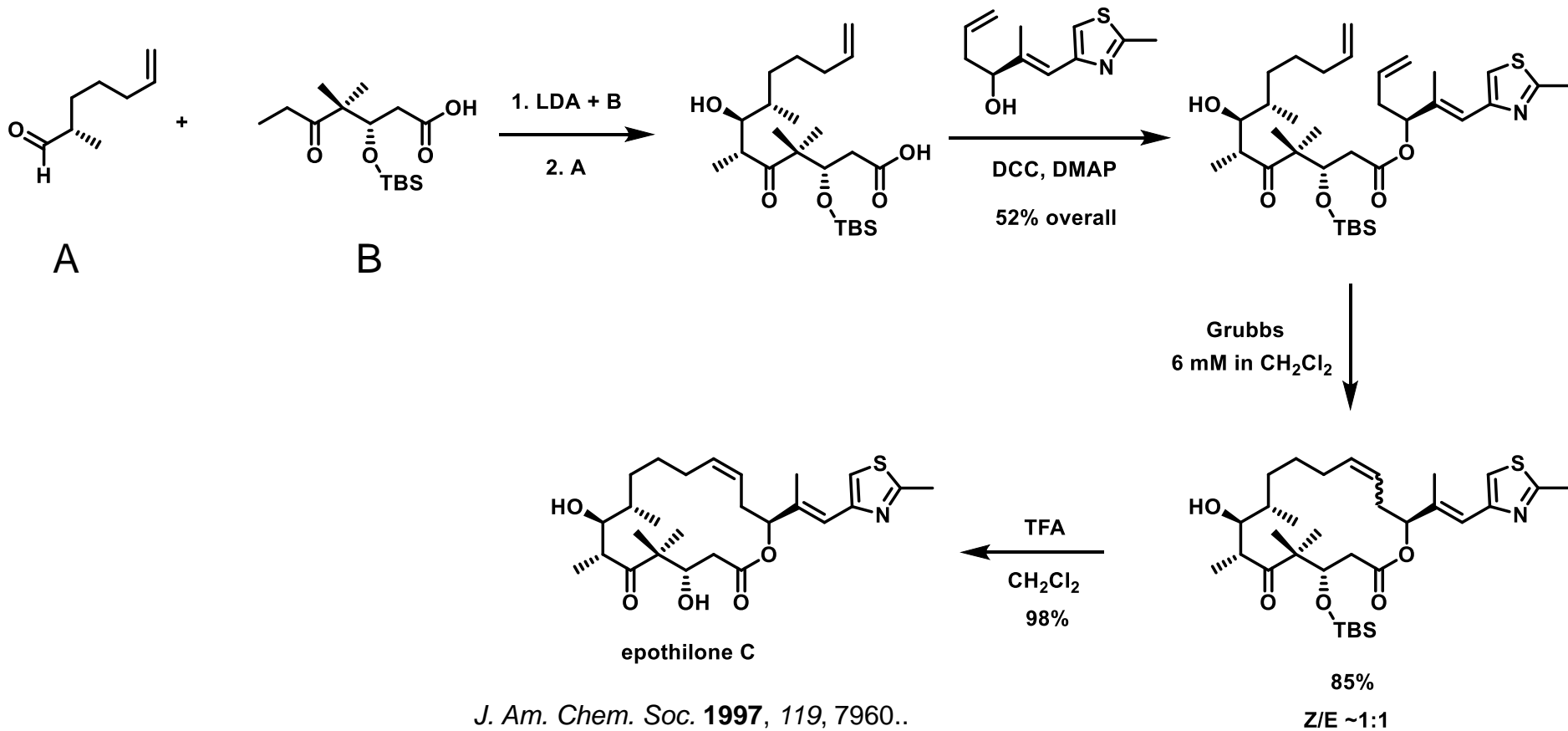


+

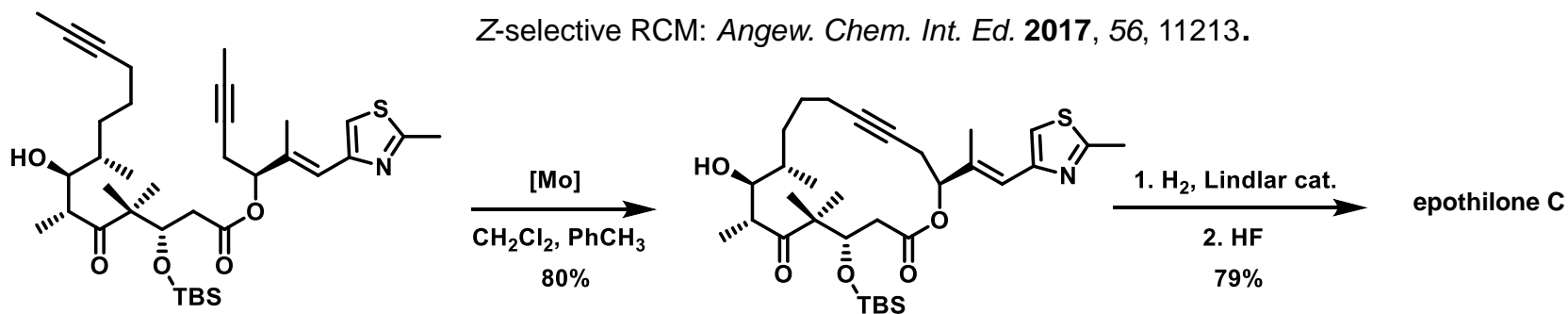


C

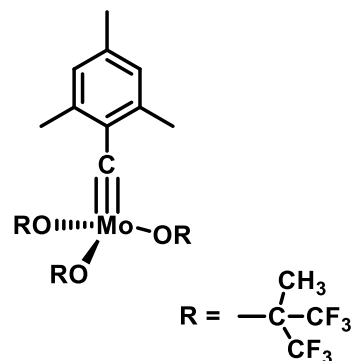




Z-selective RCM: *Angew. Chem. Int. Ed.* **2017**, 56, 11213.



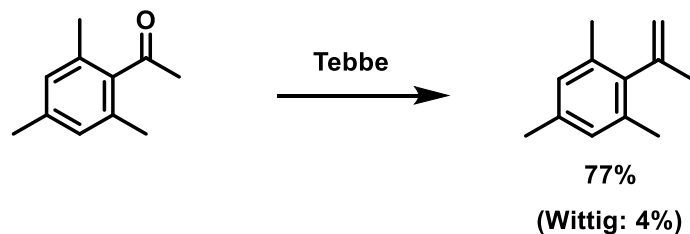
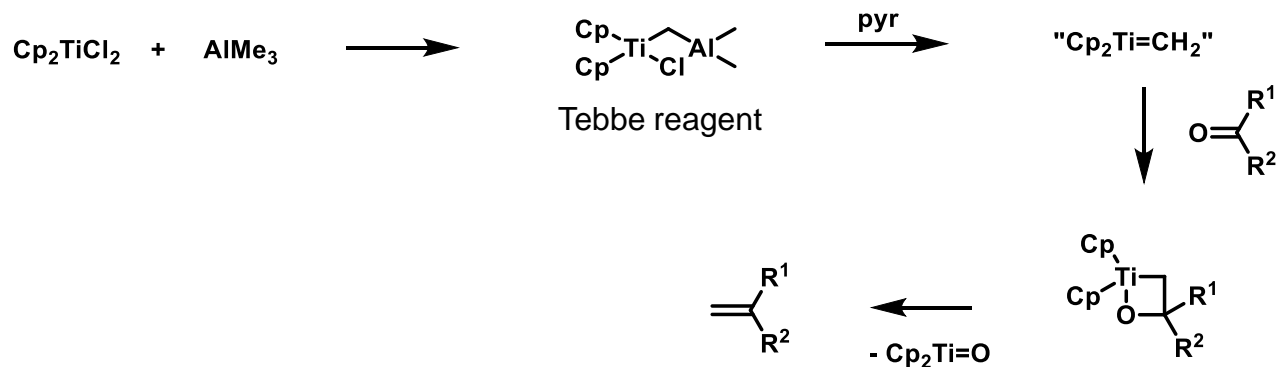
(terminal)



Angew. Chem. Int. Ed. **2012**, 51, 13019.

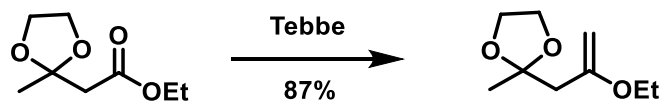
- metathesis of internal and terminal alkynes
- compatible with esters, OMe, SMe

- nucleophilic carbene complex
- methylenation of carbonyl under mild conditions

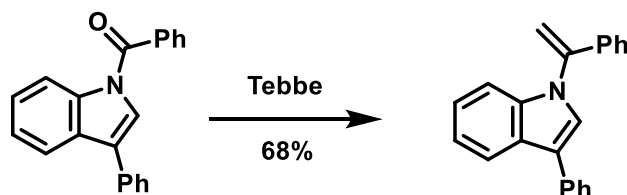


Synthesis **1991**, 165.

- conversion of esters to enol ethers & amides to enamines (in contrast to the Wittig reaction!)

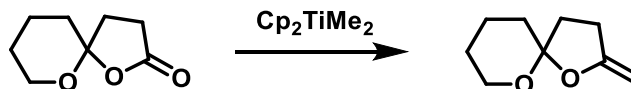
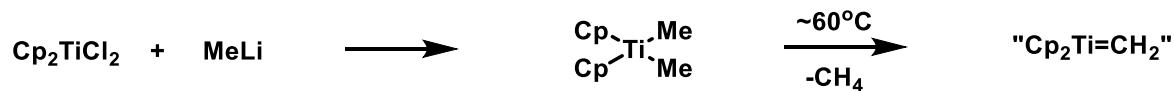


J. Am. Chem. Soc. **1980**, 102, 3270.



J. Org. Chem. **1985**, 50, 1212.

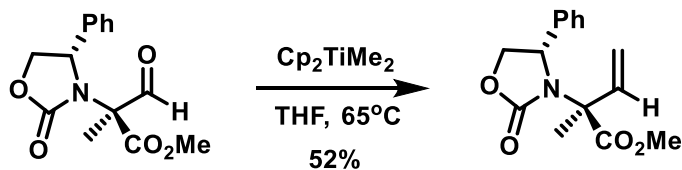
- methylenation of C=O under very mild conditions



J. Org. Chem. **1991**, 56, 3207.

(Tebbe reagent cleaved the bicyclic system)

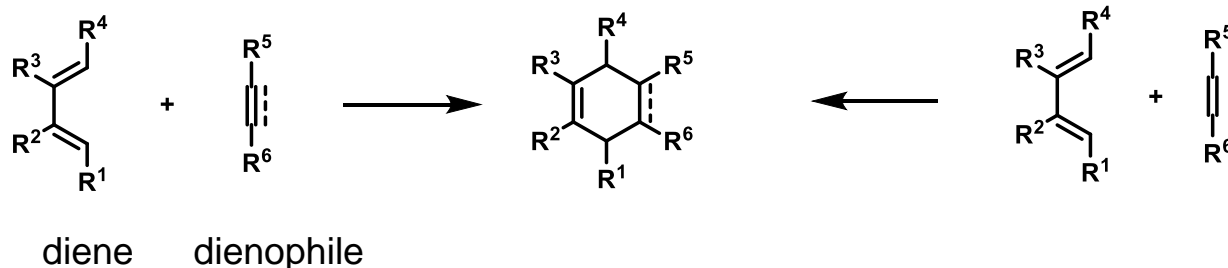
- methylenation of aldehydes and ketones is typically faster than methylenation of esters



J. Org. Chem. **1993**, 58, 5918.

electrons moving in a concerted fashion, cyclic transition state, no intermediates

- cycloadditions (Diels-Alder reaction, dipolar cycloadditions)
- sigmatropic reactions (Claisen, Cope, Wittig rearrangement)
- ene reactions
- cheletropic reactions



- **one of the most important reactions in organic synthesis**
- formation of 2 new C-C (C-N, C-O) bonds & up to 4 new stereogenic centers *in one step*
- stereochemistry of products is determined by the configurations of the diene and dienophile
- can be done in intramolecular fashion -> construction of polycyclic systems
- (enantioselective) catalysis

normal electron-demand D-A rxn

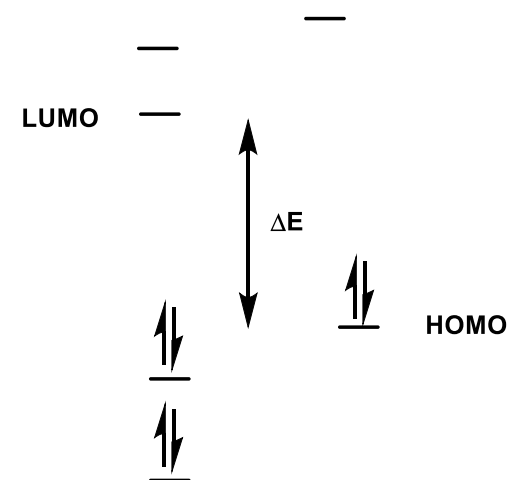
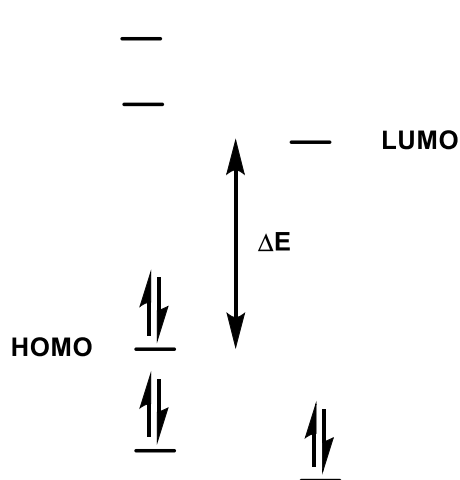
R¹-R⁴: donors (typically OR, OSiR₃, alkyl etc.)

R⁵, R⁶: acceptors (typically NO₂, CN, COR, CO₂R etc.)

inverse electron-demand D-A rxn

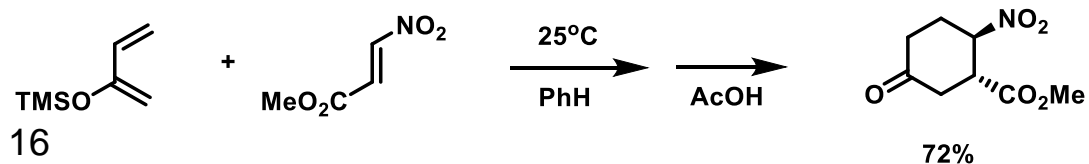
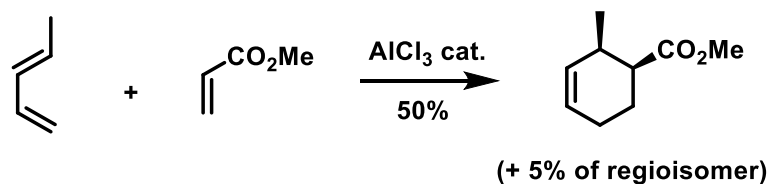
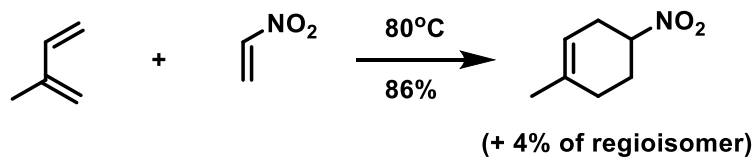
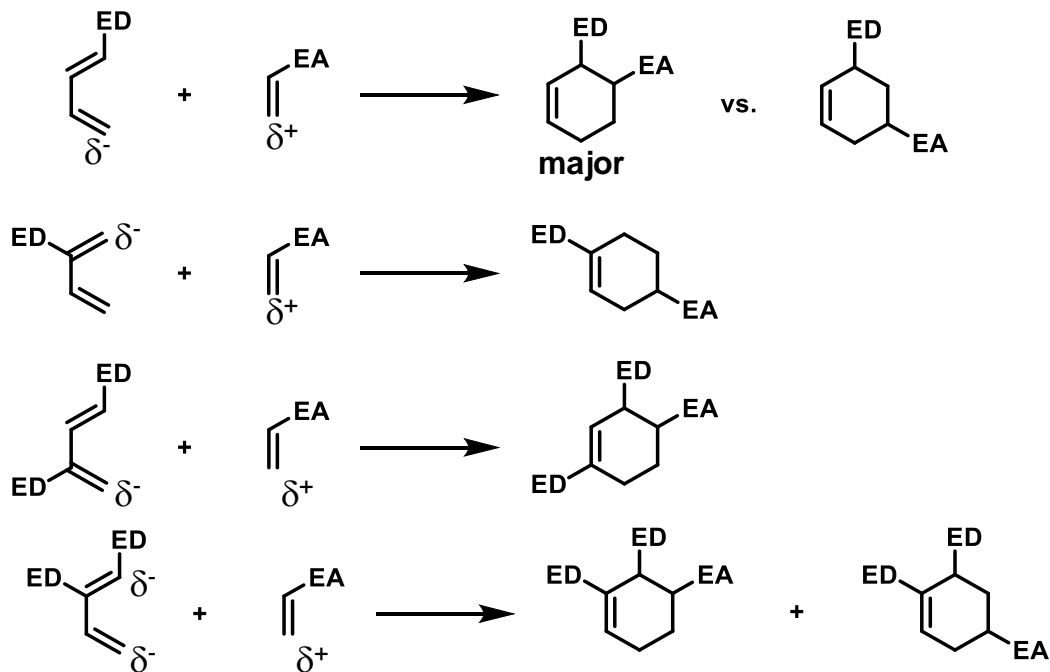
R¹-R⁴: acceptors

R⁵, R⁶: donors

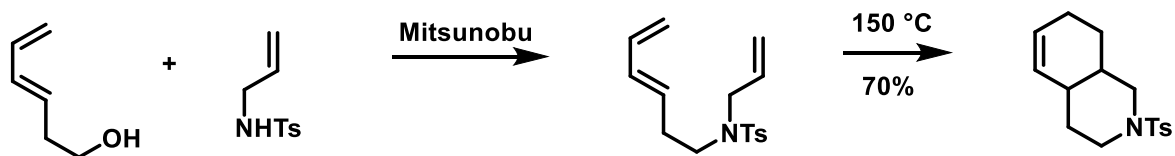


regioselectivity

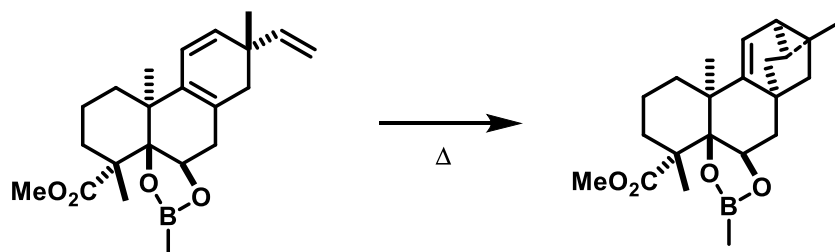
- unsymmetrical/ diene/dienophile



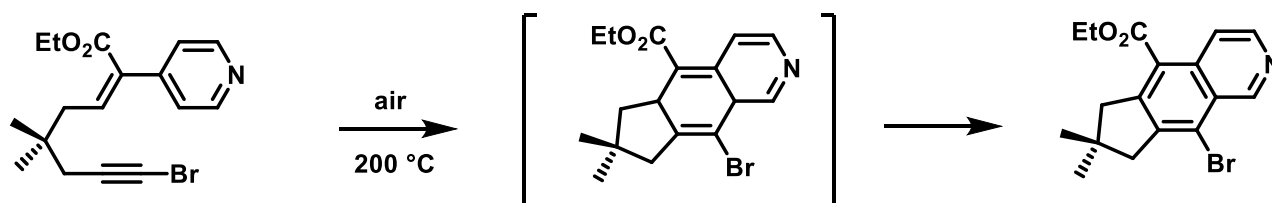
- intramolecular variants can be done with electronically sub-optimal dienes & dienophiles



Angew. Chem. Int. Ed. **2017**, 56, 6280.

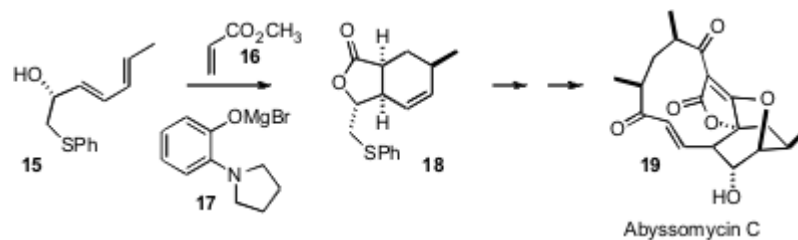


J. Am. Chem. Soc. **2019**, 141, 19589.



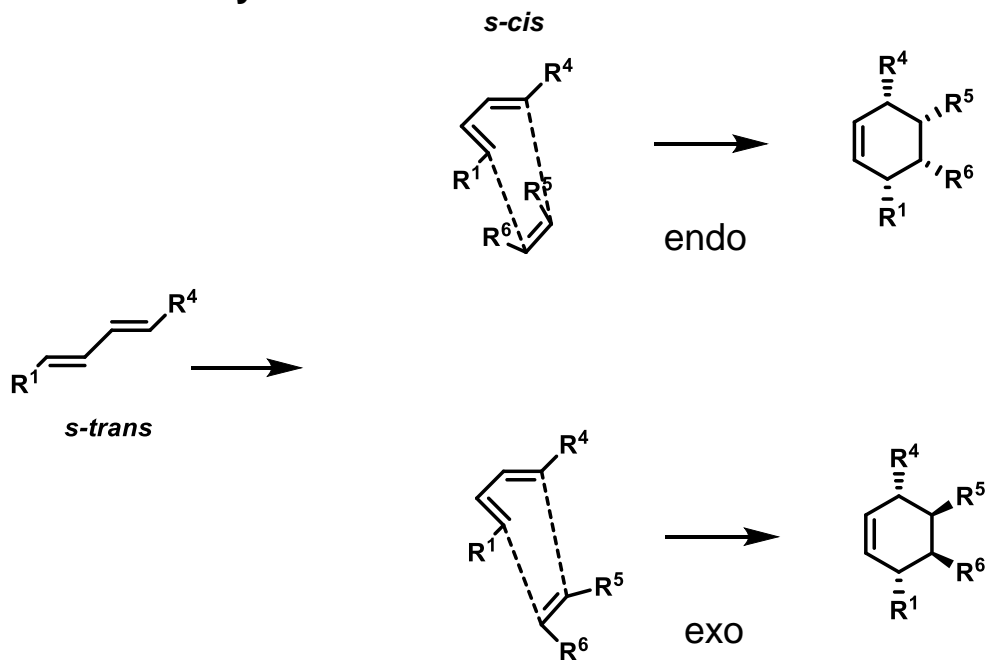
Org. Lett. **2017**, 19, 858.

The dienophile and the diene do not have to be covalently attached for a Diels-Alder reaction to be intramolecular. addition of methyl acrylate **16** to the sorbic acid-derived alcohol **15** proceeded well only in the presence of the magnesium salt **17**, which is presumably serving to complex the diene and the dienophile prior to cycloaddition:



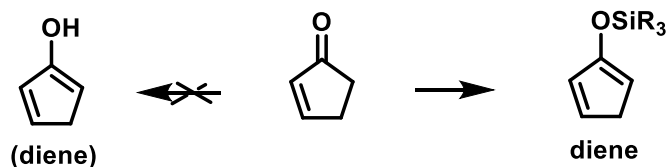
Angew. Chem. Int. Ed. **2006**, *45*, 3256.

stereoselectivity

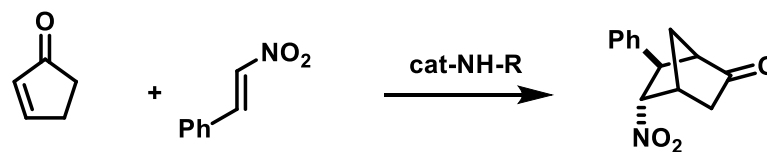


- stereochemistry of the product is dictated by the configuration (*E* vs. *Z*) of the diene and dienophile
- *endo*-diastereomer usually predominates (Alder *endo*-rule)

- α,β -unsaturated enones do not react as dienes in their enol form, but can be converted into silyl enol ethers

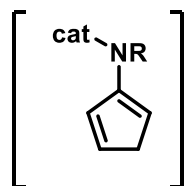


or enamines (can be done in organocatalysis mode)



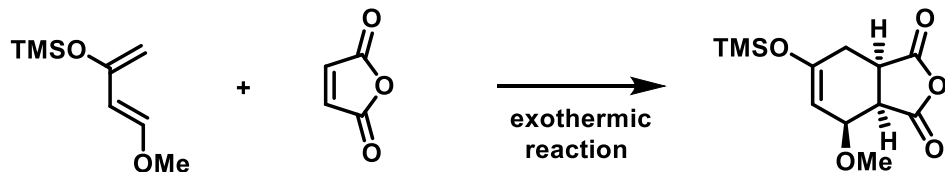
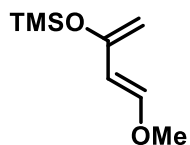
Diels-Alder & hydrolysis

Angew. Chem. Int. Ed. **2015**, *54*, 13630.

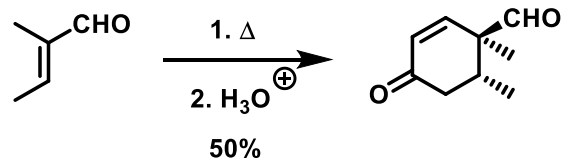
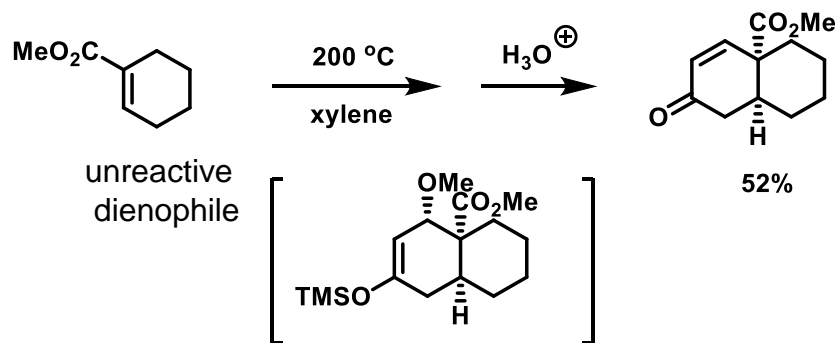


Danishefsky's diene

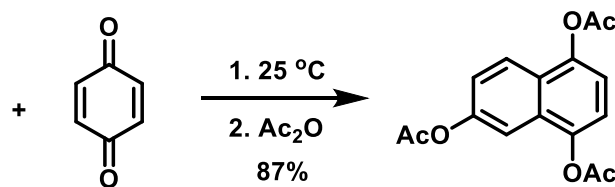
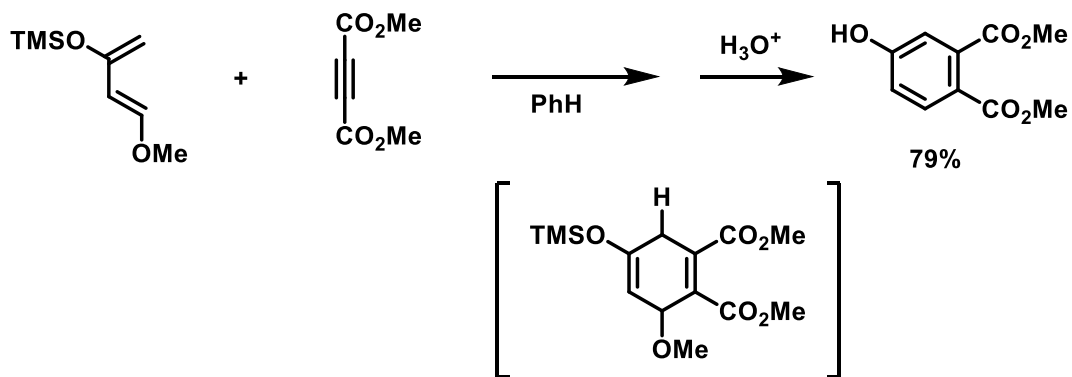
- reactive, universal diene



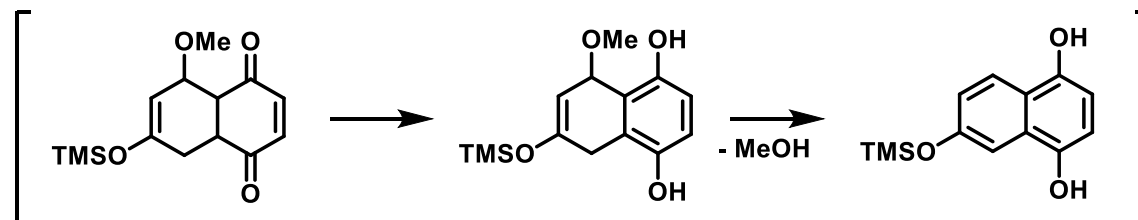
J. Am. Chem. Soc. **1974**, 96, 7807.



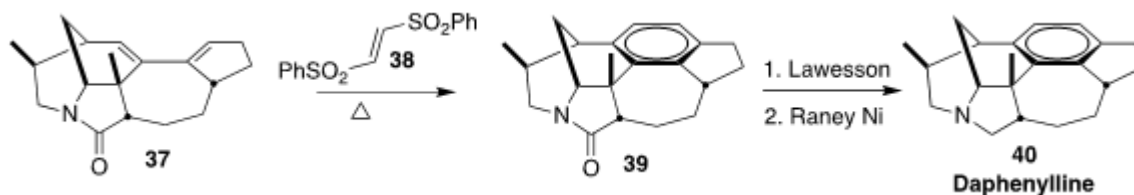
J. Am. Chem. Soc. **1978**, 100, 7098.



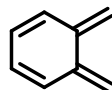
J. Am. Chem. Soc. **1979**, *101*, 6996.



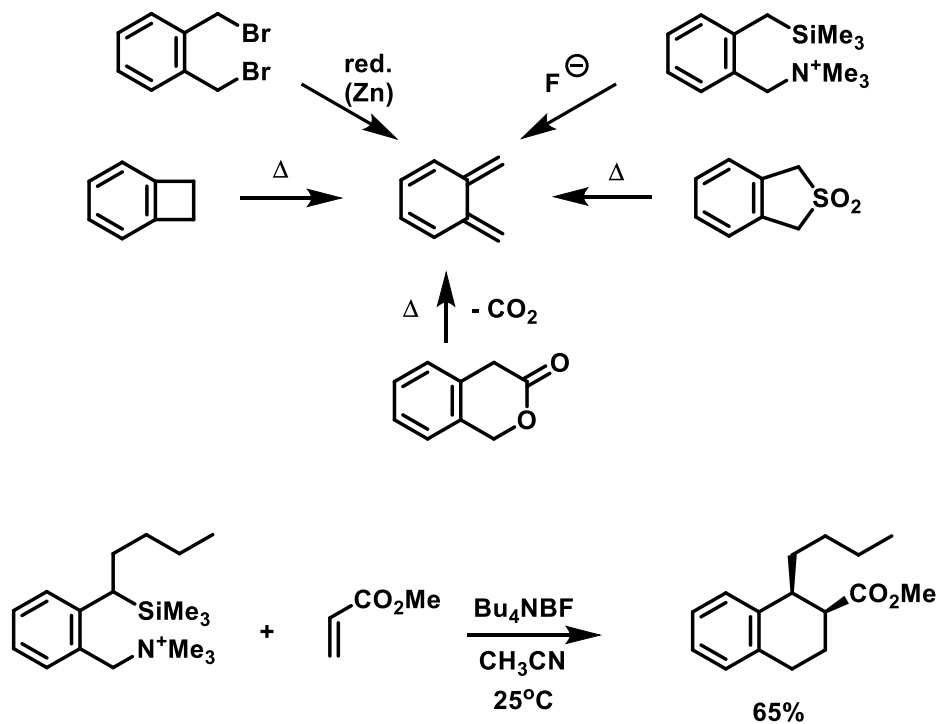
- construction of the central benzene ring in **39** by the D-A reaction of the diene **37** with the dienophile **38**, leading to **39**:



o-quinonedimethane



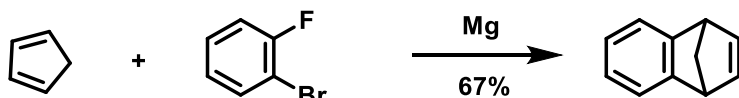
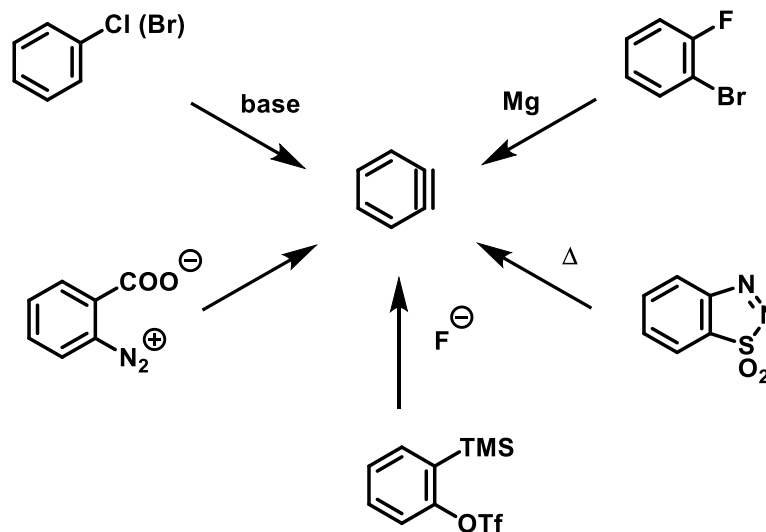
- very reactive diene, prepared *in situ*



J. Am. Chem. Soc. **1982**, 104, 7609.

benzyne

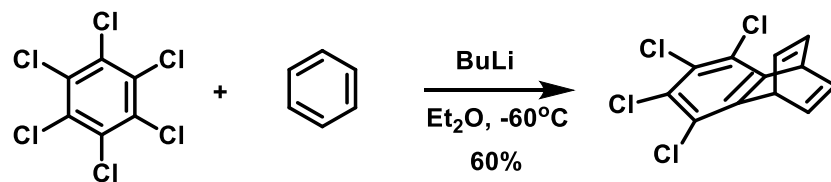
- very reactive dienophile
- generated *in situ*



Chem. Ber. **1958**, 91, 895.



Angew. Chem. **1955**, 67, 348.



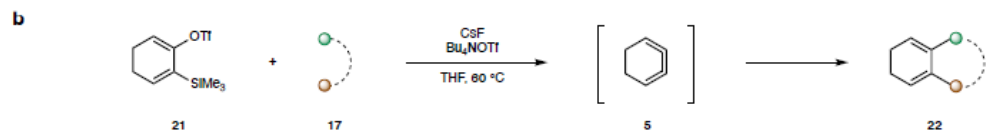
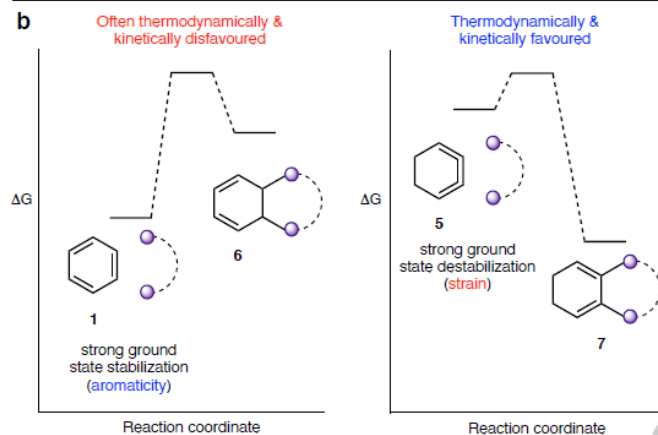
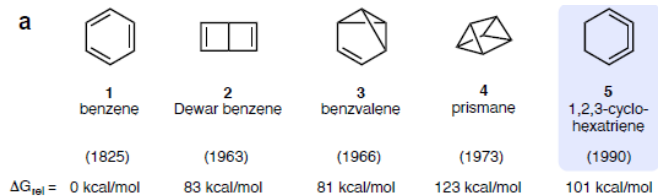
Org. Synth. **1979**, 59, 71.

- preparation of the reactive dibenzocyclooctyne **29** by the carbodiimide-mediated dehydration of the tetrazole **28**



J. Am. Chem. Soc. **2021**, *143*, 9489.

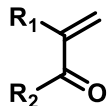
strain-promoted reactions of 1,2,3-cyclohexatriene and its derivatives:



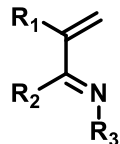
Entry	Trapping Agent	Product	Yield	Entry	Trapping Agent	Product	Yield
1			65%	5			59%
2			62%	6			51%
3			72%	7			44%
4			61%	8 ^f			51%

- dienes and dienophiles contain heteroatoms (O, N)
- electron-deficient dienes: inverse electron-demand Diels-Alder reaction (electron-rich dienophile)

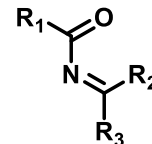
heterodienes:



R_1, R_2 : alkyl, CN, COR

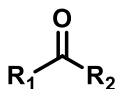


R_3 : NH_2 , SO_2R

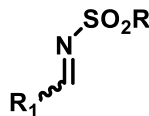


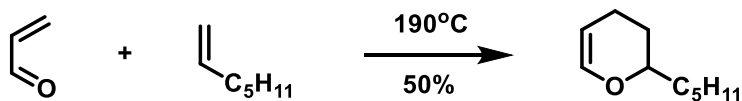
R_1 - R_3 : alkyl, aryl

heterodienophiles:

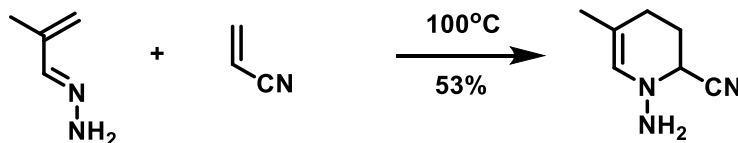


R_1, R_2 : H, alkyl, CO_2R

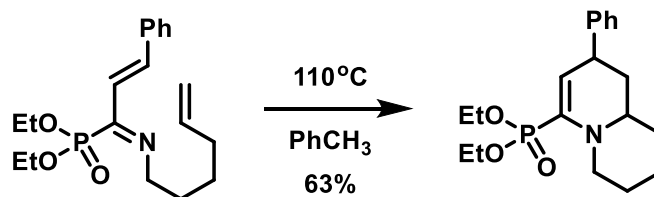




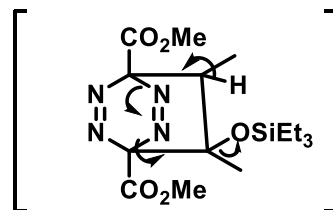
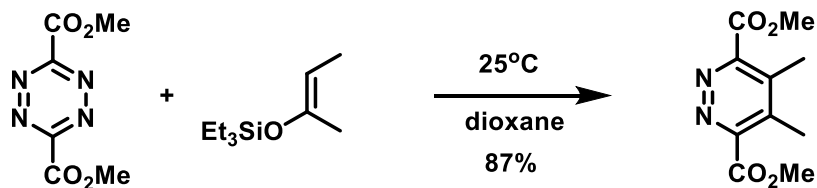
Helv. Chim. Acta **1981**, 64, 1247.



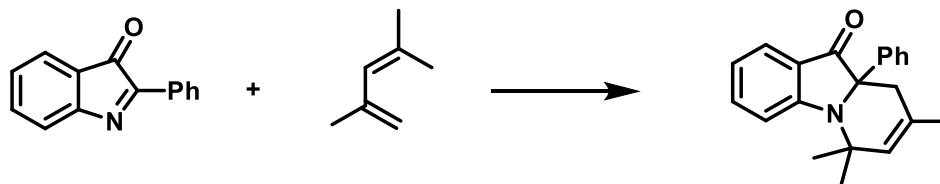
Tetrahedron Lett. **1982**, 23, 3261.



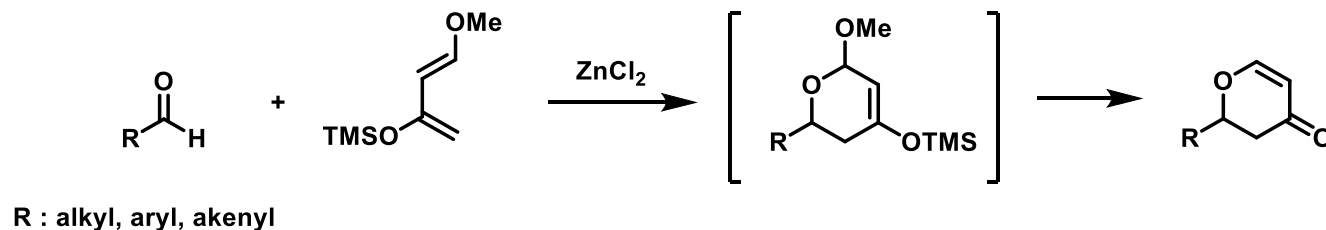
Tetrahedron Lett. **1984**, 25, 2119.



J. Org. Chem. **1985**, 50, 5377.

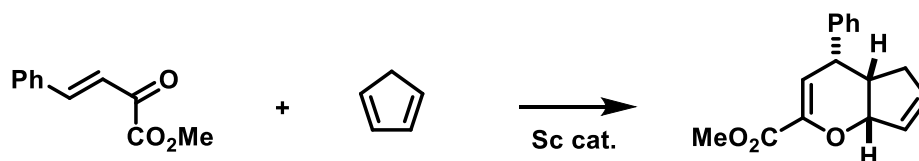


Tetrahedron Lett. **1969**, 1527.

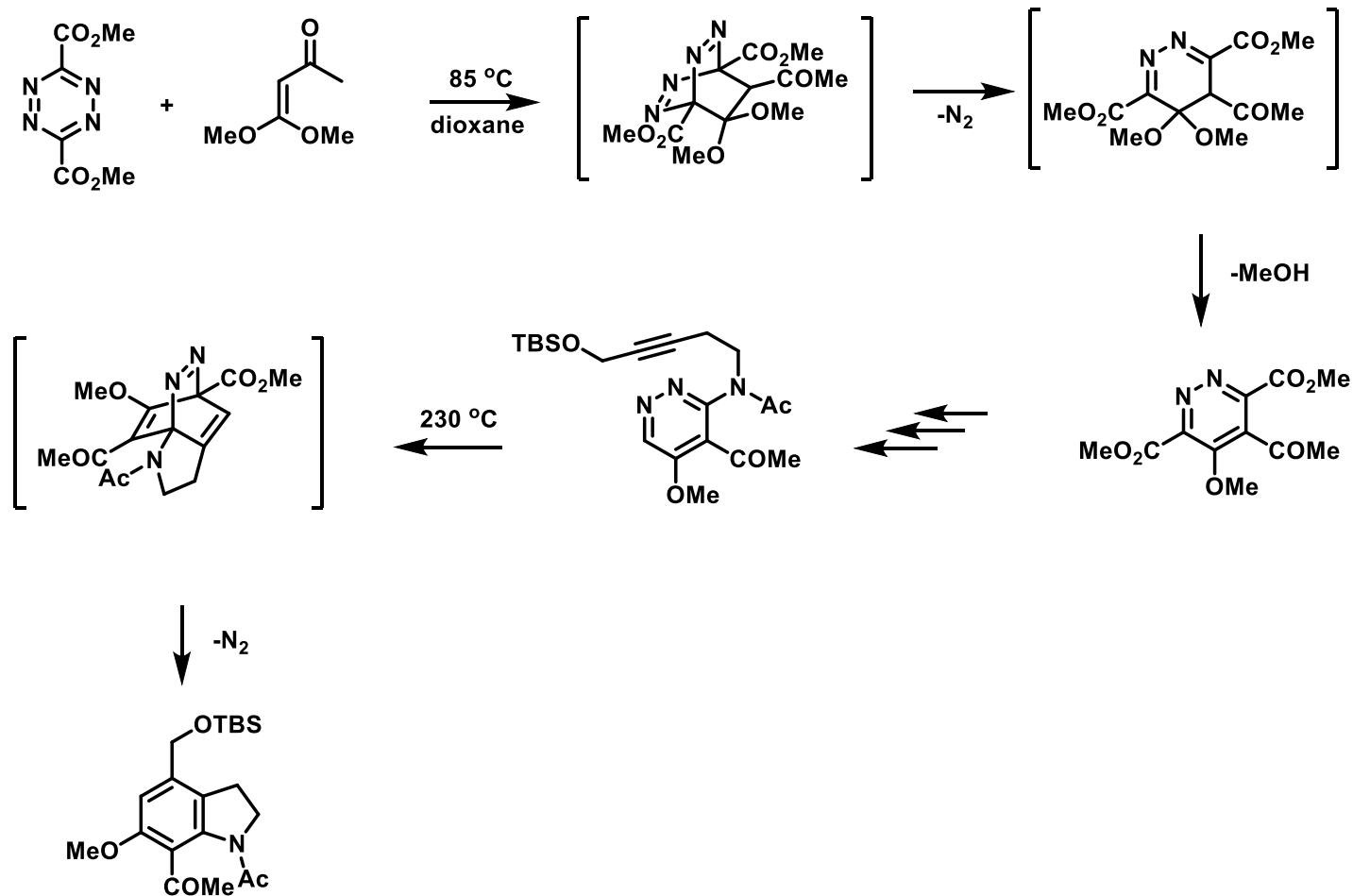


J. Org. Chem. **1984**, 49, 1955.

interesting example of hetero Diels-Alder: cyclopentadiene as *dienophile*



Adv. Synth. Catal. **2022**, 364, 4347.



J. Am. Chem. Soc. **1987**, *109*, 2717.