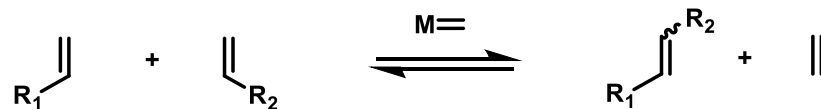


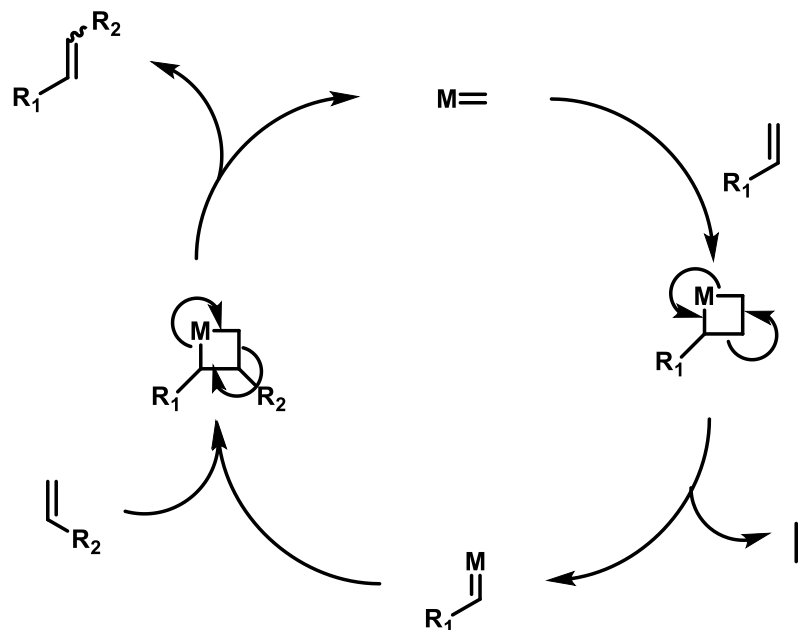
Organic synthesis

Kamil Paruch

Masaryk University, Brno

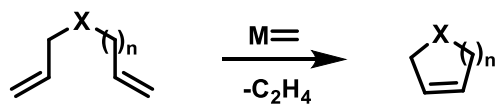


- catalytic amount of Mo or Ru carbene
- mild reaction conditions; various functional groups (OH, COOR, CHO...) tolerated

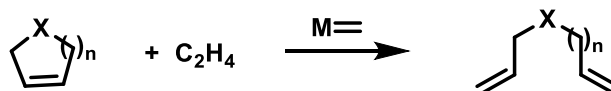


all steps are reversible

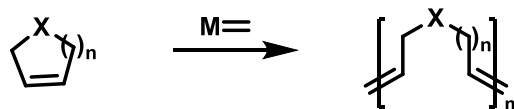
➤ rxn can be pushed to conversion e.g. by removal of ethene



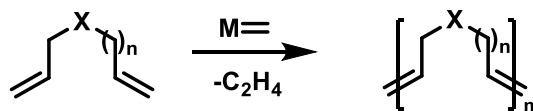
RCM (ring closing metathesis)



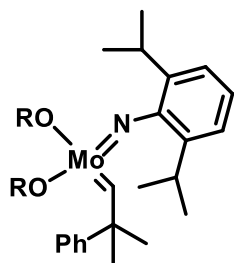
ROM (ring opening metathesis)



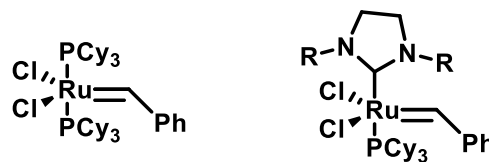
ROMP (ring opening metathesis polymerization)



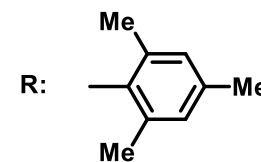
catalysts:

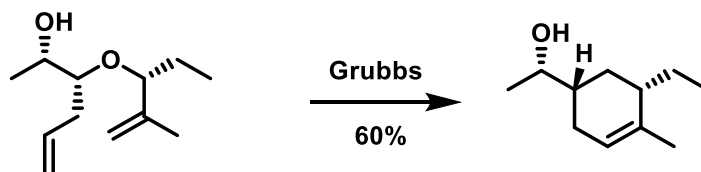


R. R. Schrock

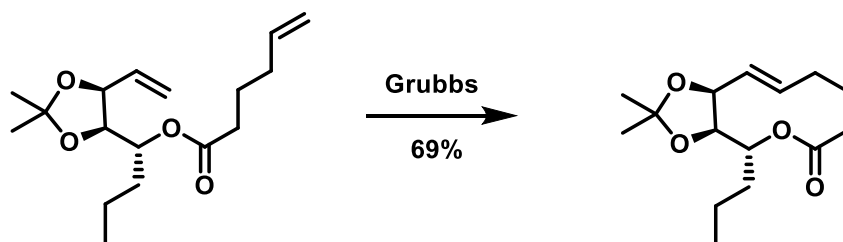


R. H. Grubbs

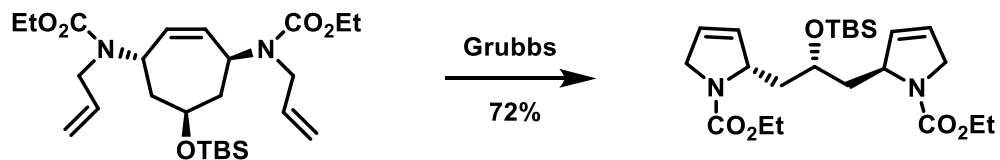




J. Am. Chem. Soc. **2001**, 123, 12432.

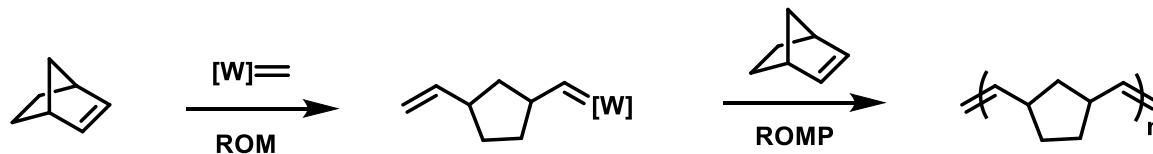


J. Am. Chem. Soc. **2002**, 124, 7061.



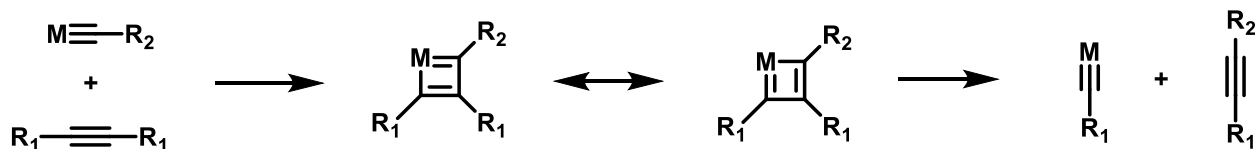
J. Org. Chem. **2002**, 67, 6456.

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

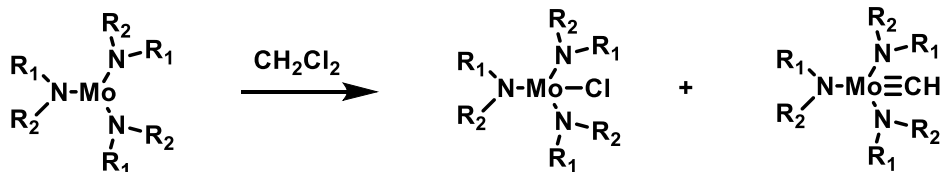
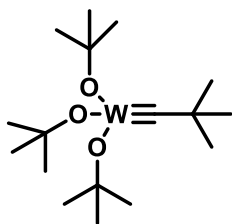


Angew. Chem. Int. Ed. **1997**, 36, 2036.

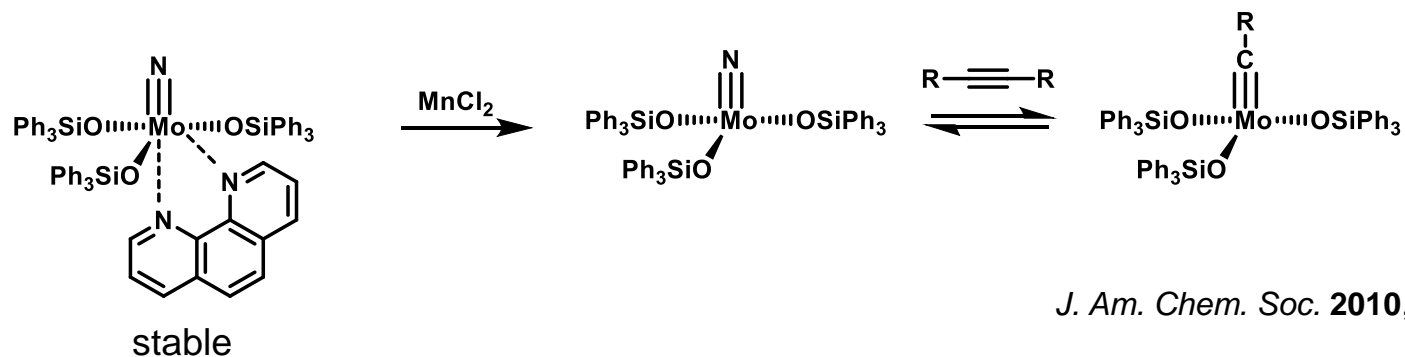
(not terminal)

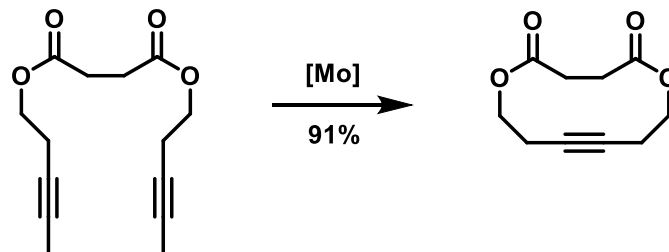


catalysts:

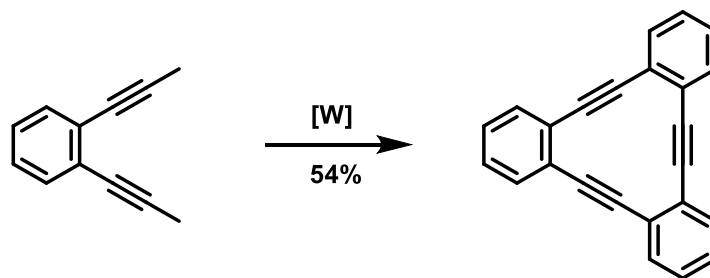


- tolerated: esters, aldehydes, *double bonds*, acetals, nitriles...





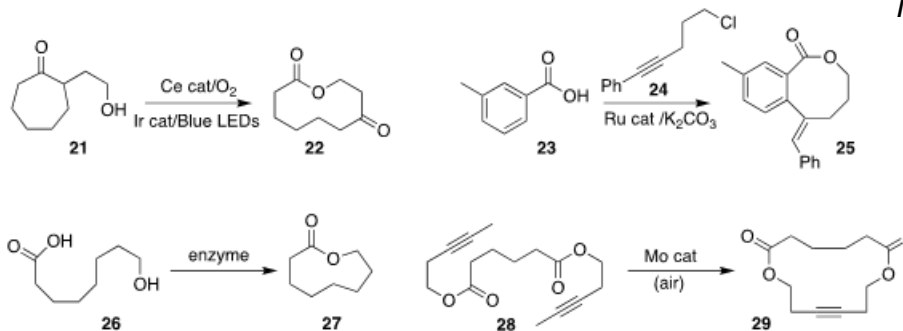
Chem. Eur. J. **2001**, 7, 5299.



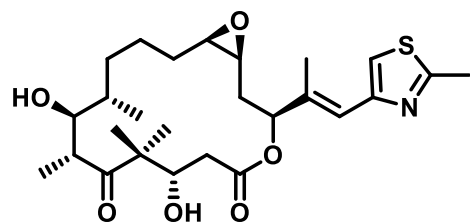
Synthesis **2003**, 2535.

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

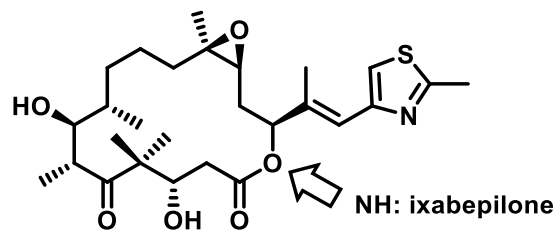
Nature Commun. **2021**, 12, 1136.



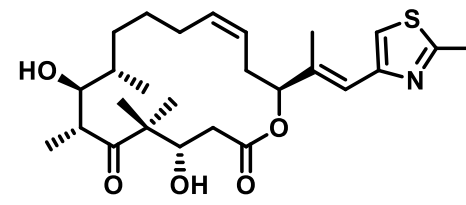
synthesis of epothilones



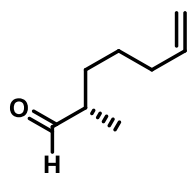
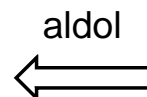
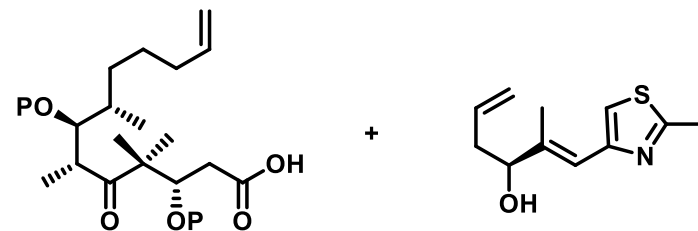
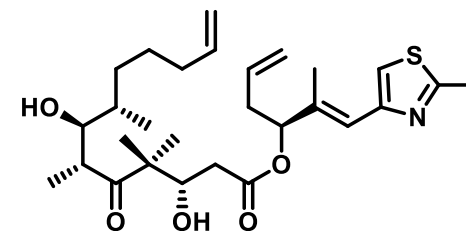
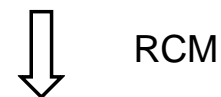
epothilone A



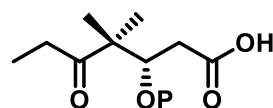
epothilone B



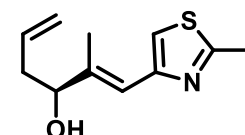
epothilone C



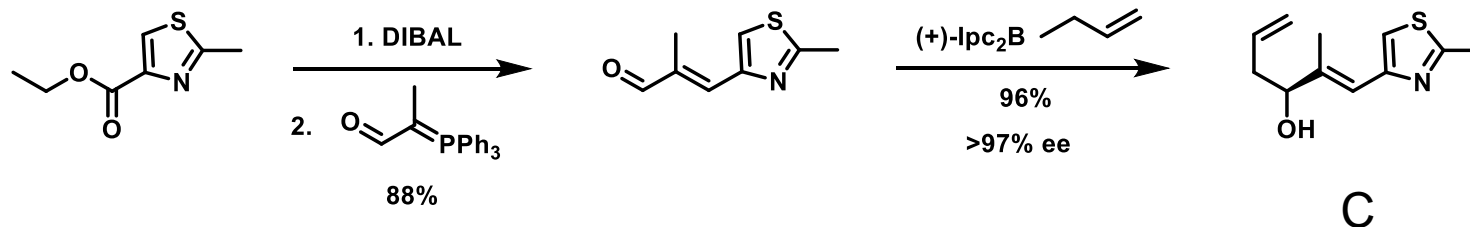
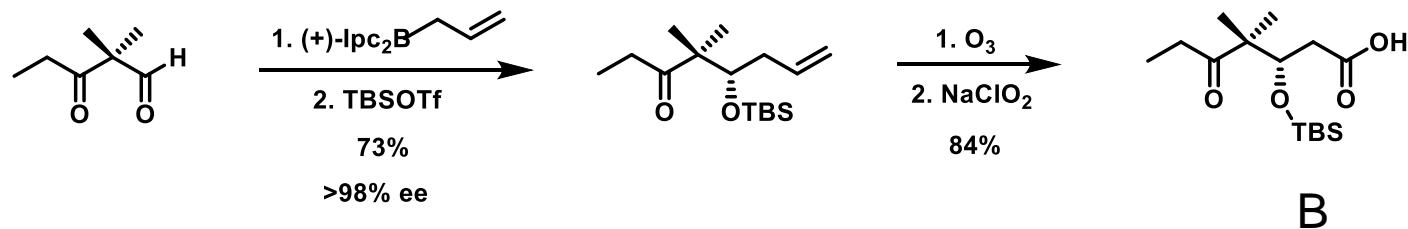
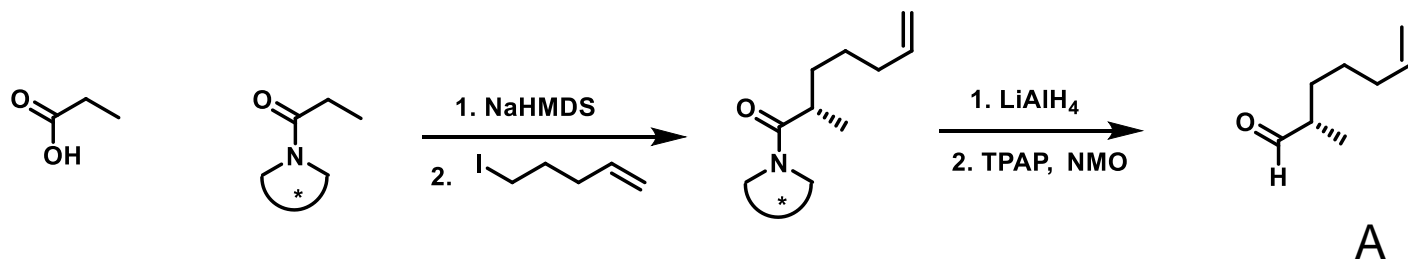
A

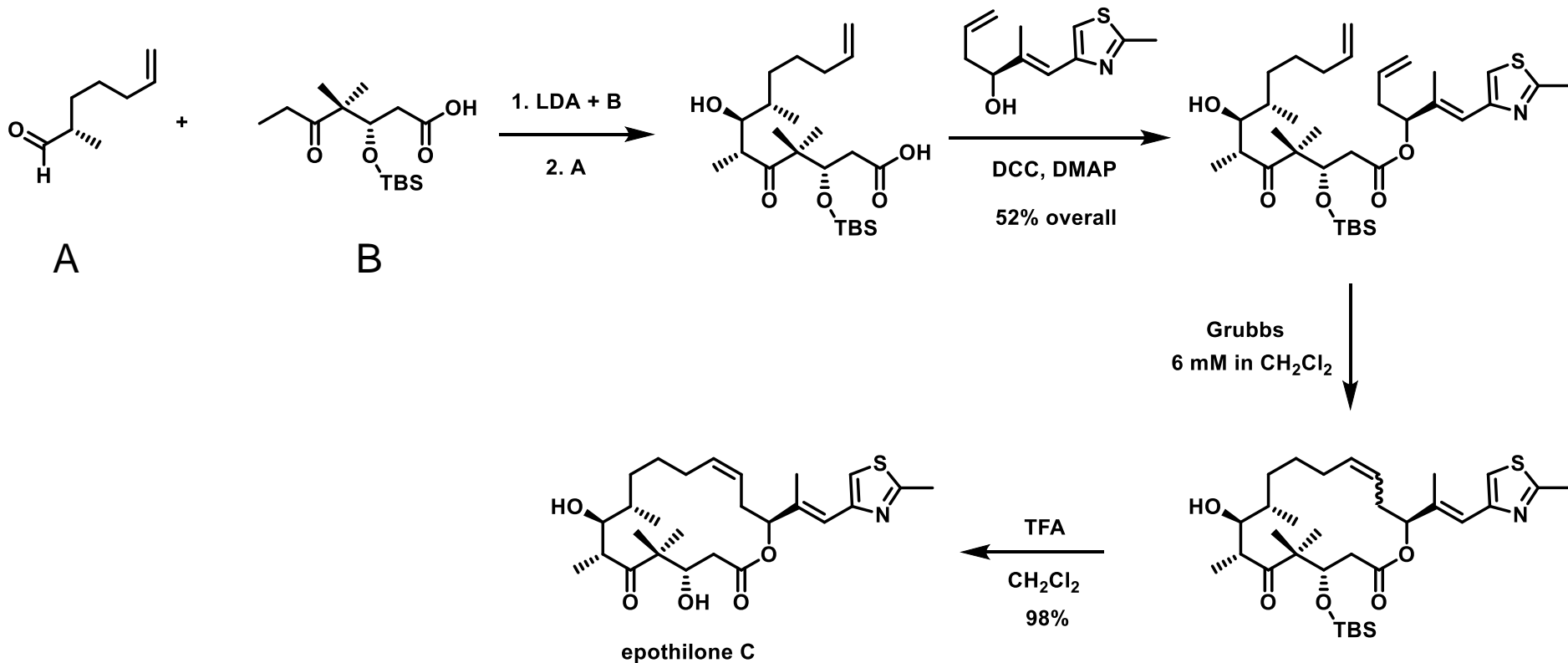


B



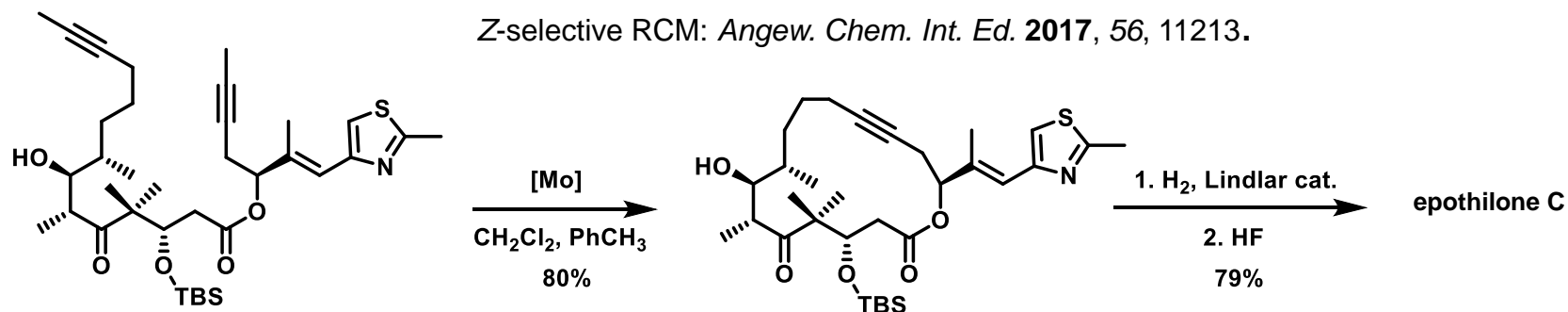
C



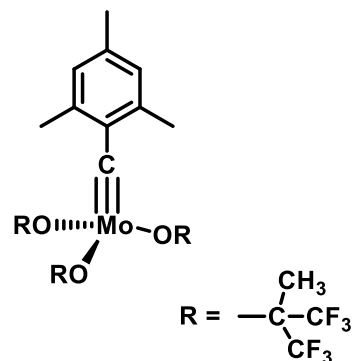


J. Am. Chem. Soc. **1997**, *119*, 7960..

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



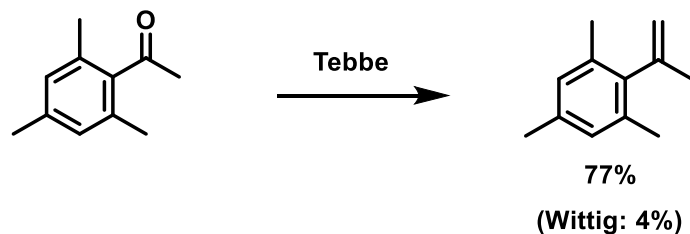
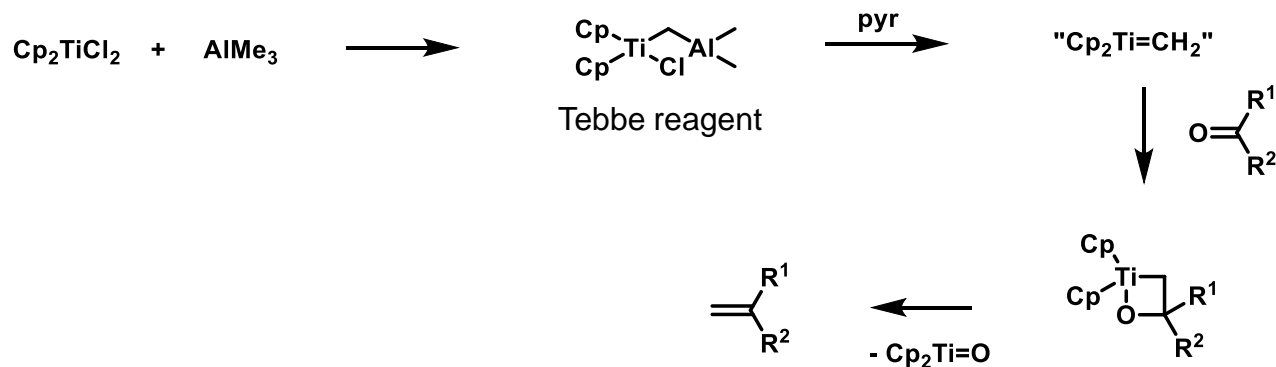
(terminal)



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

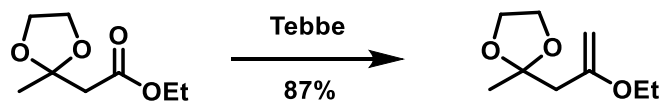
- metathesis of internal and terminal alkynes
- compatible with esters, OMe, SMe

- nucleophilic carbene complex
- methylenation of carbonyl under mild conditions

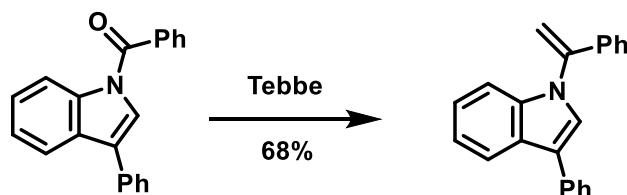


Synthesis **1991**, 165.

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

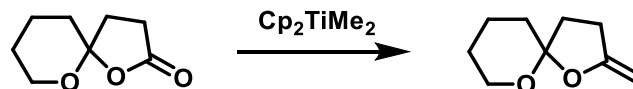
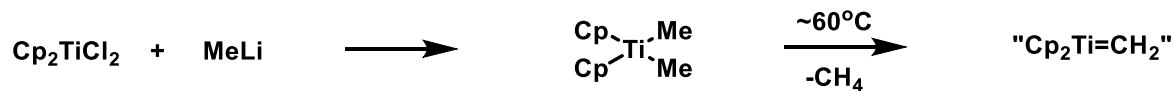


J. Am. Chem. Soc. **1980**, 102, 3270.



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

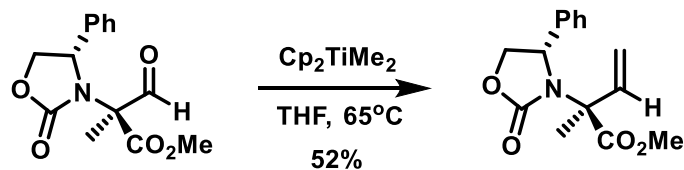
- methylenation of C=O under very mild conditions



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

(Tebbe reagent cleaved the bicyclic system)

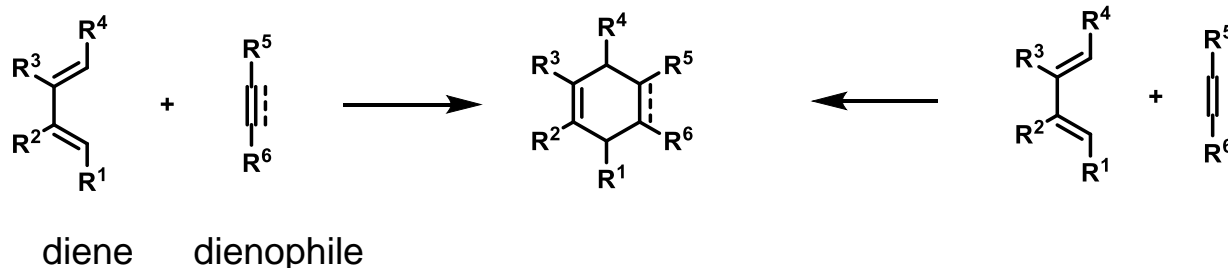
- methylenation of aldehydes and ketones is typically faster than methylenation of esters



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

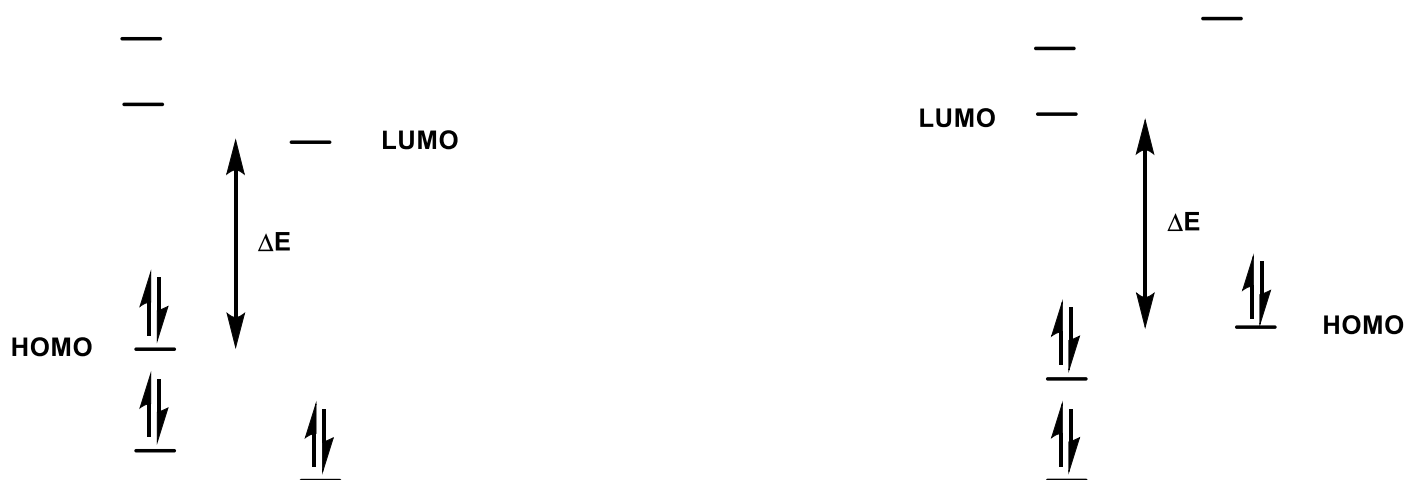
R¹-R⁴: donors (typically OR, OSiR₃, alkyl etc.)

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

inverse electron-demand D-A rxn

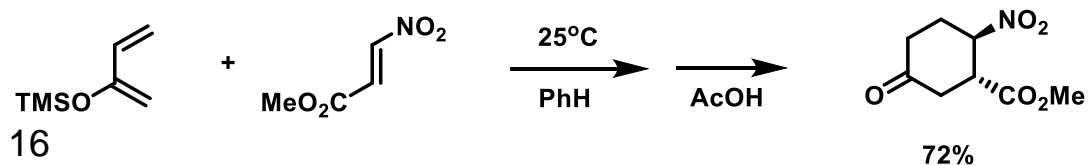
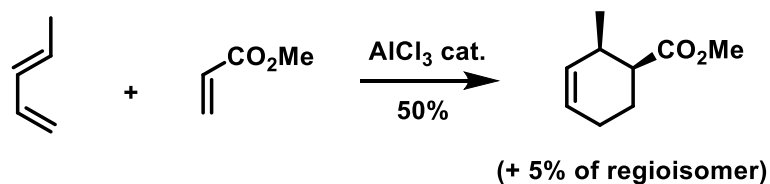
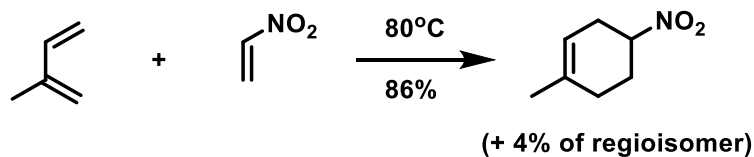
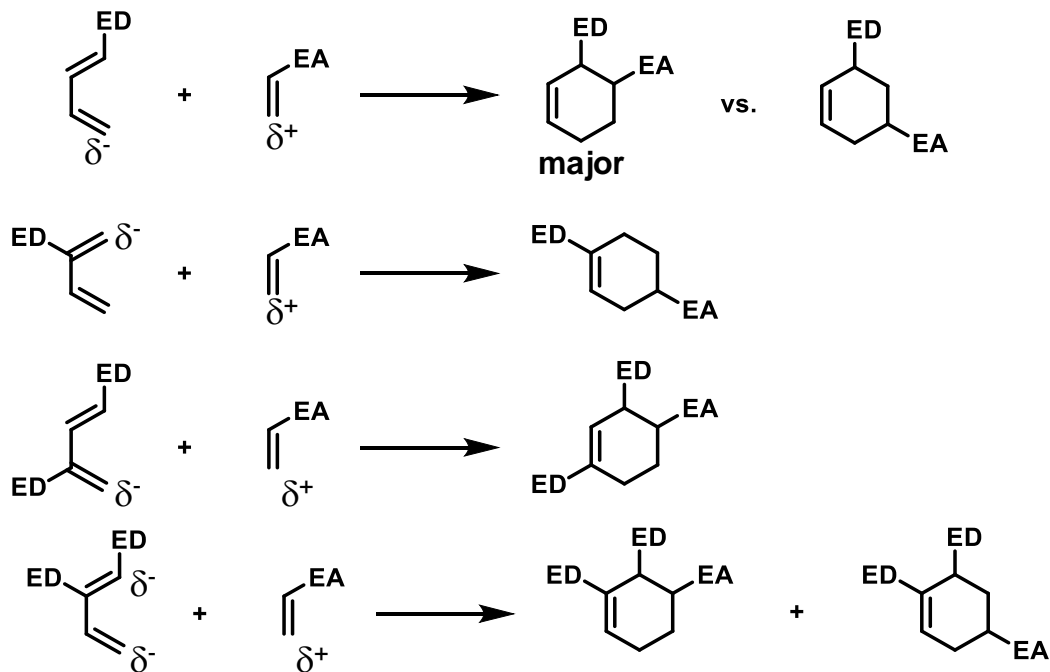
R¹-R⁴: acceptors

R⁵, R⁶: donors

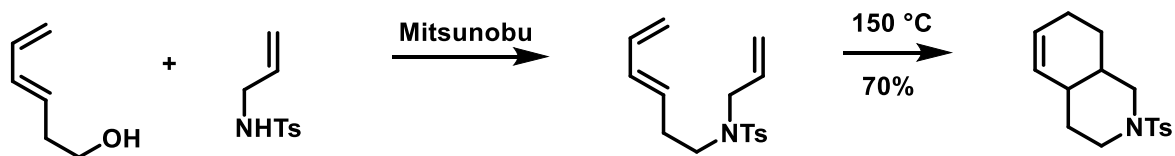


regioselectivity

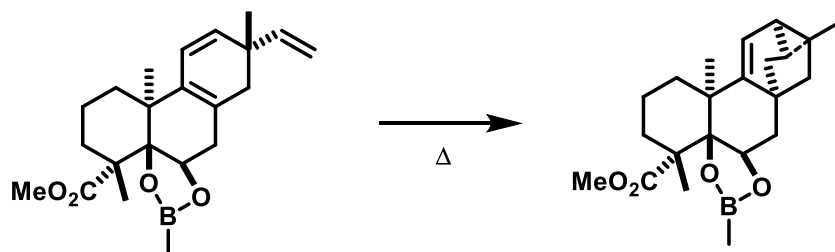
- unsymmetrical/ diene/dienophile



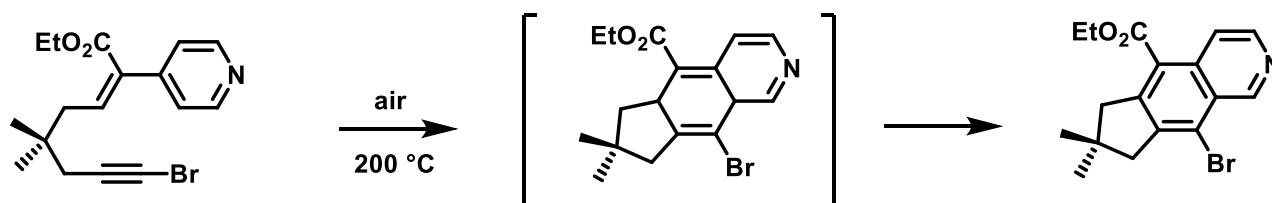
- intramolecular variants can be done with electronically sub-optimal dienes & dienophiles



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

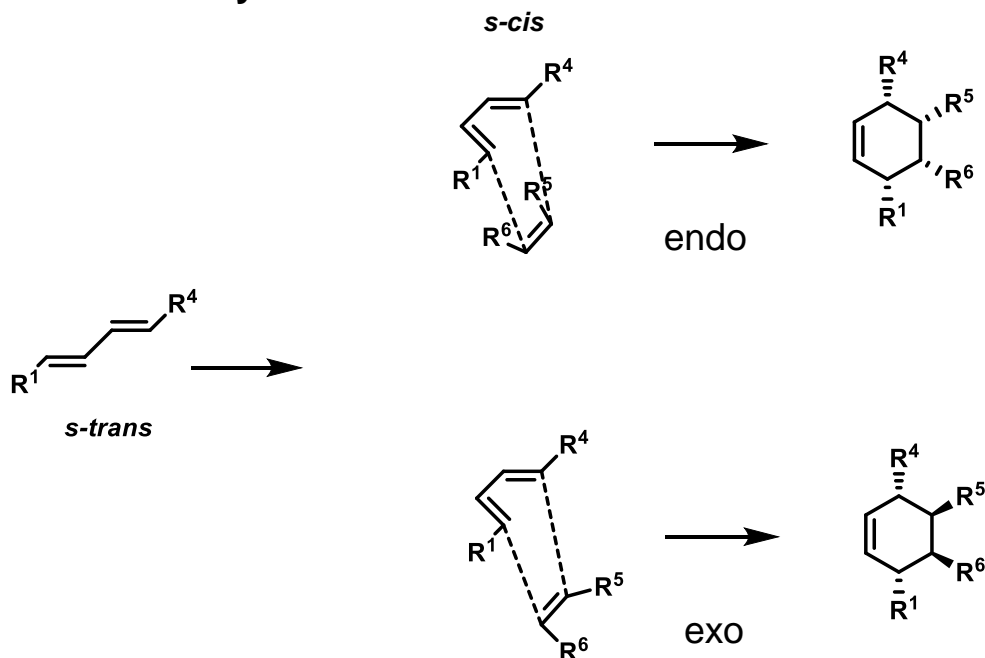


J. Am. Chem. Soc. **2019**, 141, 19589.



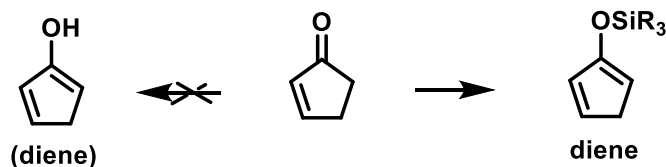
Org. Lett. **2017**, 19, 858.

stereoselectivity

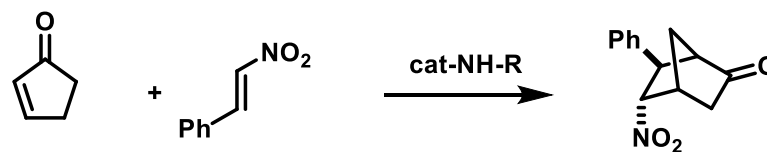


- stereochemistry of the product is dictated by the configuration (*E* vs. *Z*) of the diene and dienophile
- *endo*-diastereomer usually predominates (Alder *endo*-rule)

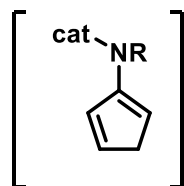
- α,β -unsaturated enones do not react as dienes in their enol form, but can be converted into silyl enol ethers



or enamines (can be done in organocatalysis mode)

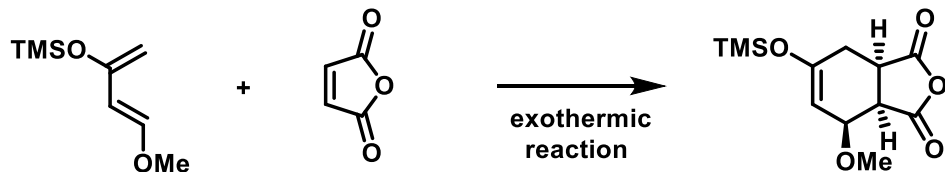
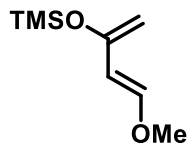


Angew. Chem. Int. Ed. **2015**, *54*, 13630.

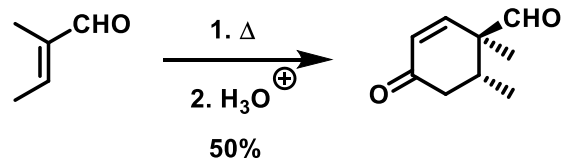
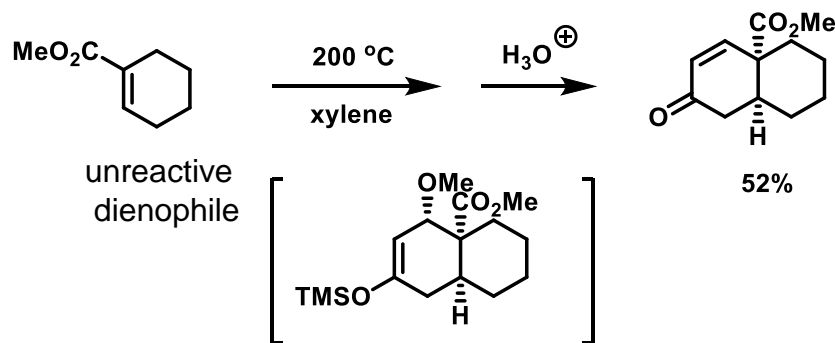


Danishefsky's diene

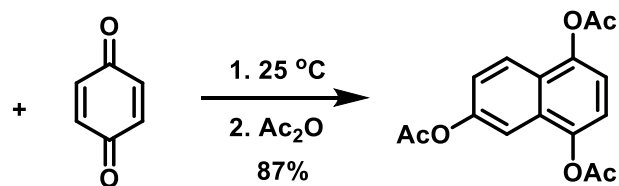
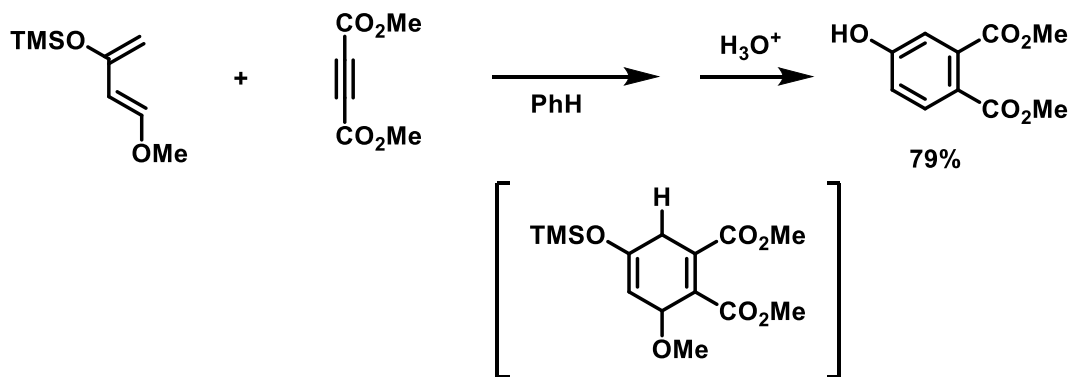
- reactive, universal diene



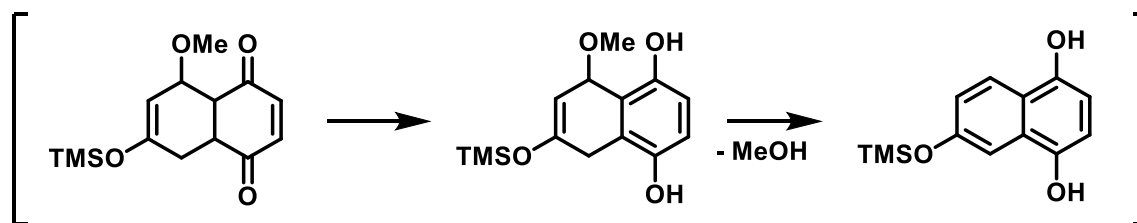
J. Am. Chem. Soc. **1974**, 96, 7807.



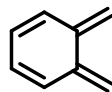
J. Am. Chem. Soc. **1978**, 100, 7098.



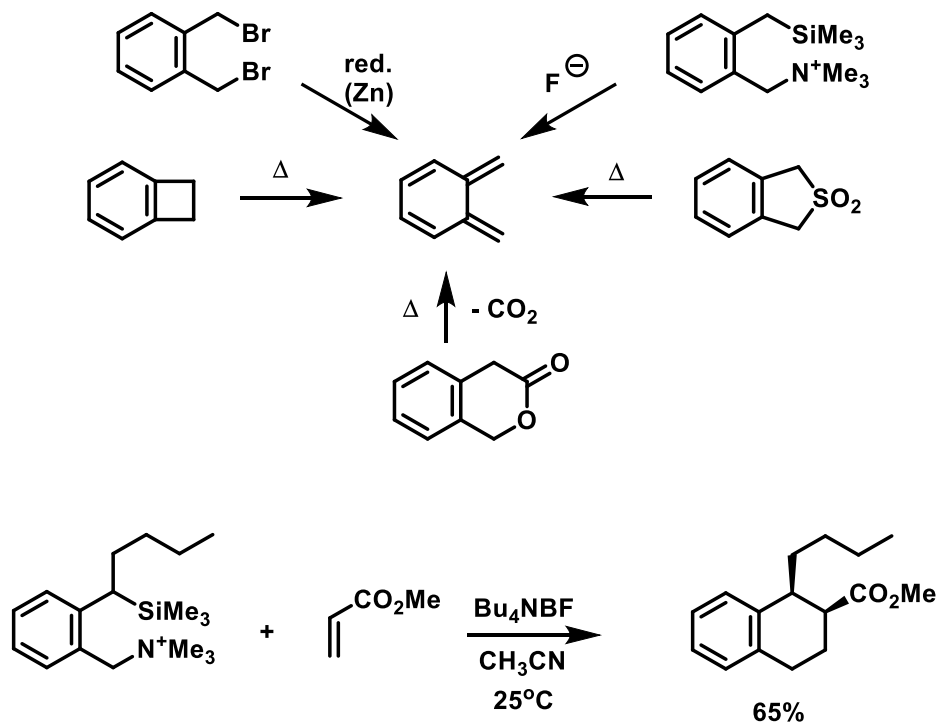
J. Am. Chem. Soc. **1979**, *101*, 6996.



o-quinonedimethane



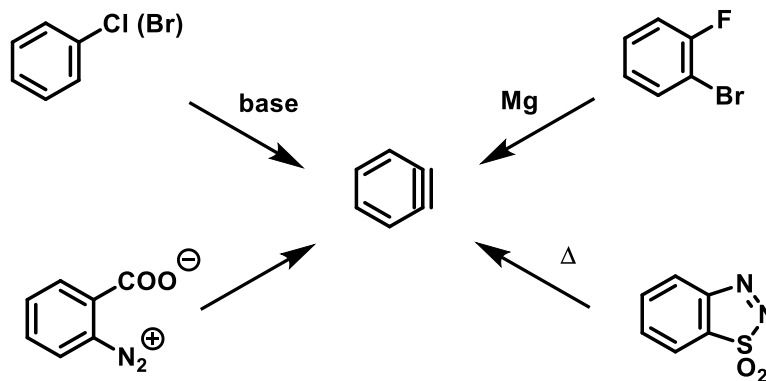
- very reactive diene, prepared *in situ*



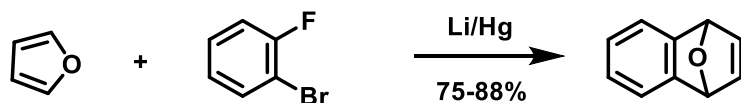
J. Am. Chem. Soc. **1982**, 104, 7609.

benzyne

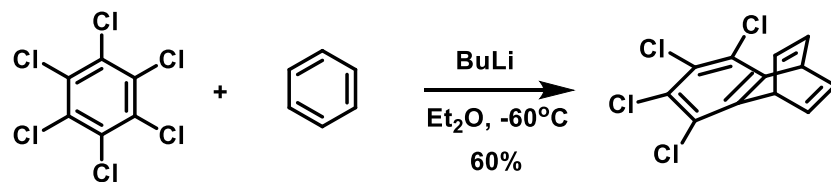
- very reactive dienophile
- generated *in situ*



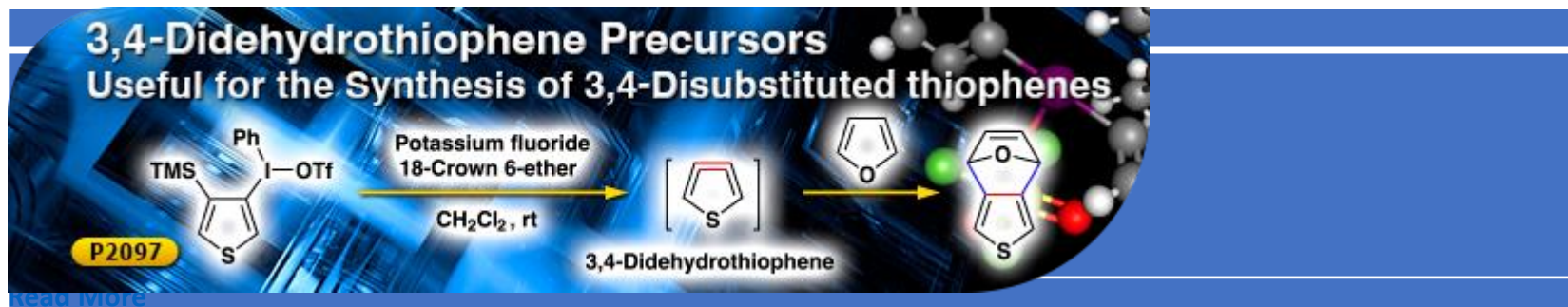
Chem. Ber. **1958**, 91, 895.



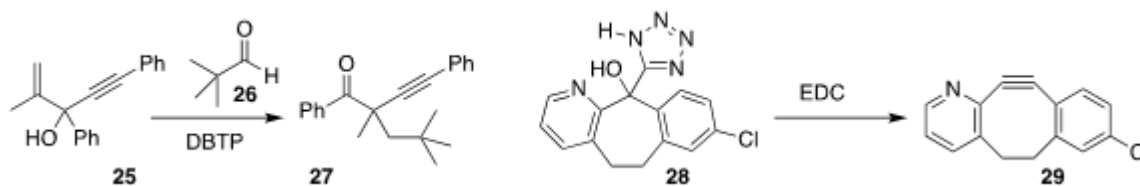
Angew. Chem. **1955**, 67, 348.



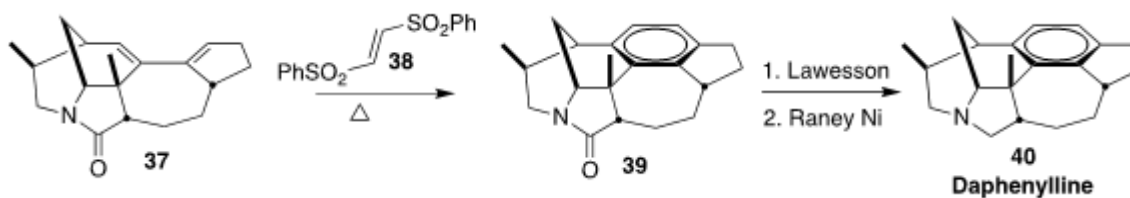
Org. Synth. **1979**, 59, 71.



- preparation of the reactive dibenzocyclooctyne **29** by the carbodiimide-mediated dehydration of the tetrazole **28**
J. Am. Chem. Soc. **2021**, *143*, 9489.

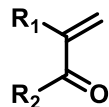


- construction of the central benzene ring in **39** by DA reaction of the diene **37** with the dienophile **38**, leading to **39**
Angew. Chem. Int. Ed. **2021**, *60*, 9439.

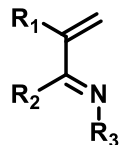


- dienes and dienophiles contain heteroatoms (O, N)
- electron-deficient dienes: inverse electron-demand Diels-Alder reaction (electron-rich dienophile)

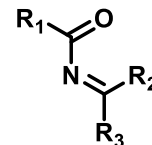
heterodienes:



R_1, R_2 : alkyl, CN, COR

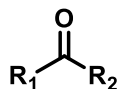


R_3 : NH_2 , SO_2R

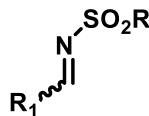


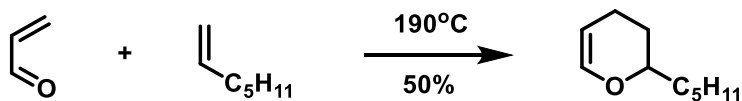
R_1 - R_3 : alkyl, aryl

heterodienophiles:

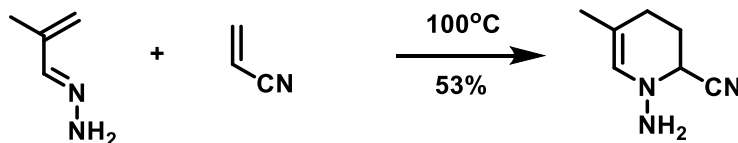


R_1, R_2 : H, alkyl, CO_2R

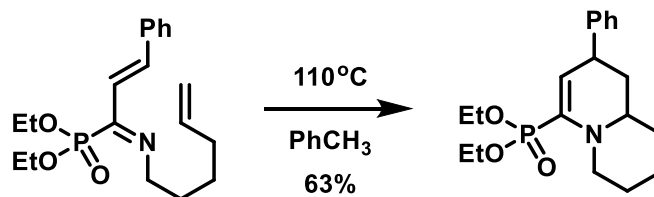




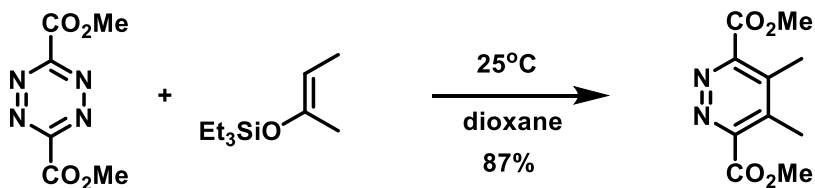
Helv. Chim. Acta **1981**, 64, 1247.



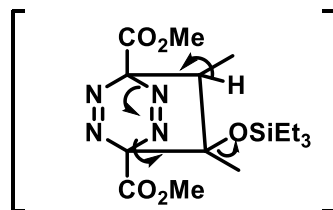
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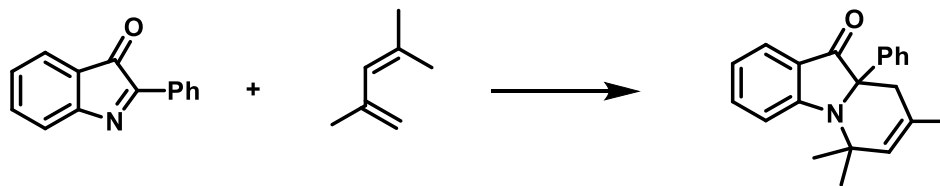


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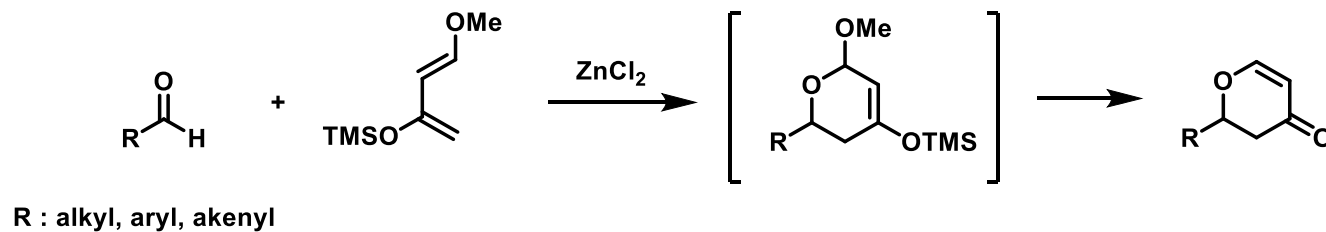


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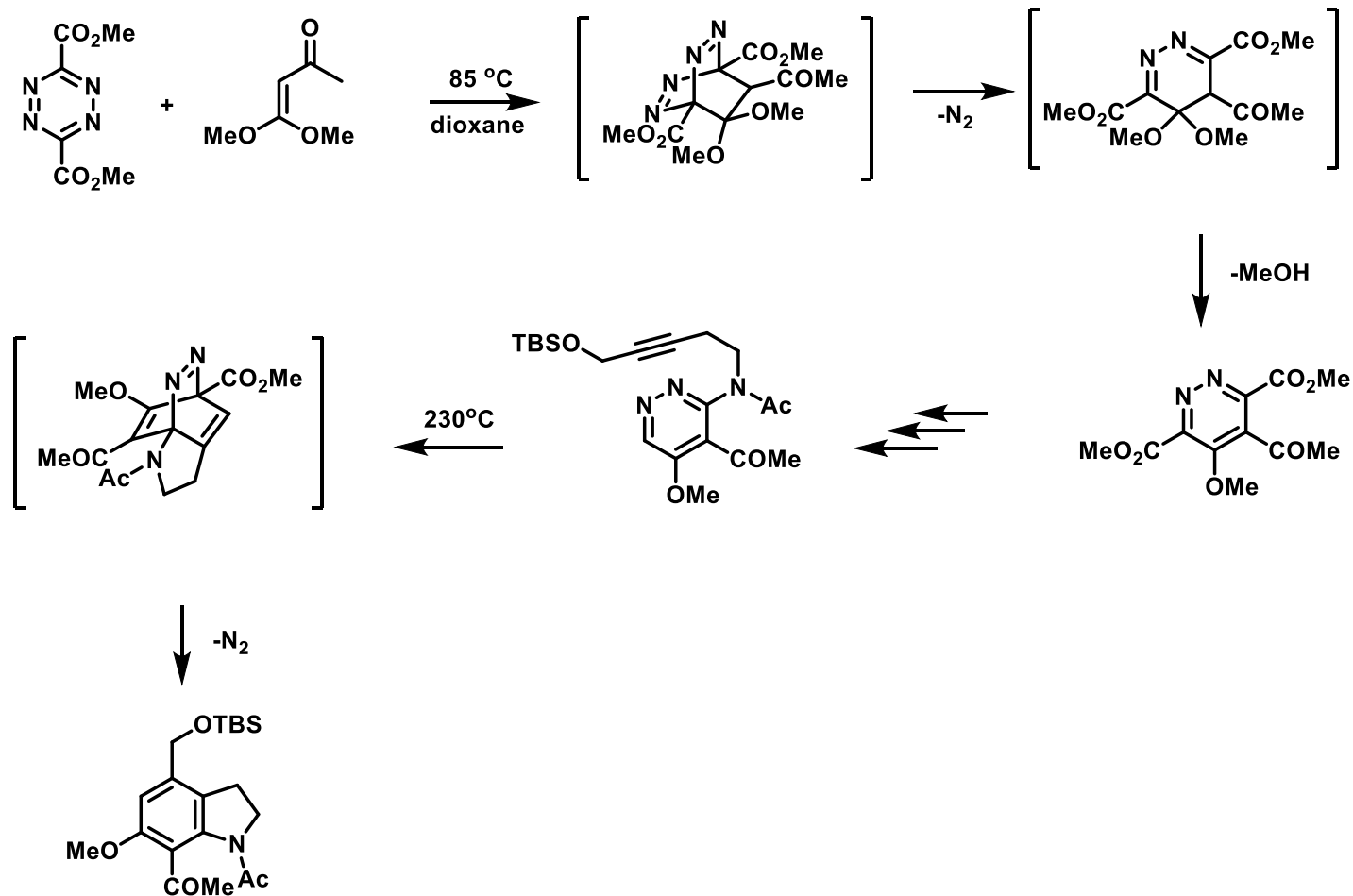




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