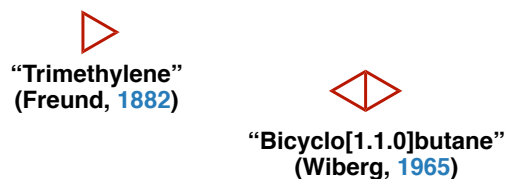


- After proposal that carbons can form rings (Kekulé, 1865) and have tetrahedral geometry (van't Hoff and LeBel, 1874) many think it impossible to form rings smaller than 5 or 6
- August Freund achieves first synthesis of cyclopropane (1882)
- Adolf von Baeyer proposes a strain theory (1885) for which he wins a Nobel prize (1905)

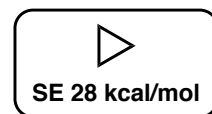
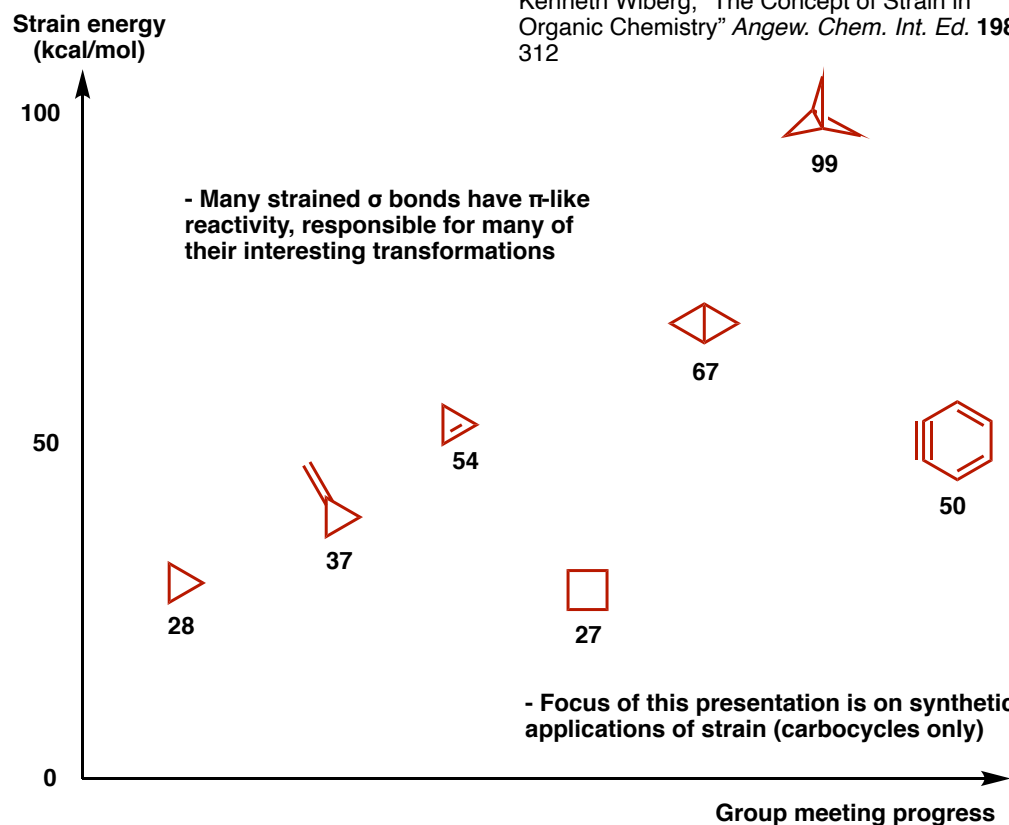


“[G]enerally, the greater the difference in strain energy between a substrate and a product, the greater the driving force for a reaction”  
*Chem. Commun.* 2020, 5718

Contributions to the total strain in a molecule:

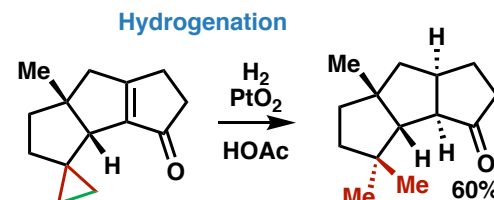
- Bondlength distortion
- Bond angle distortion
- Torsional strain
- Nonbonded interactions
- Energy changes due to rehybridization

Kenneth Wiberg, “The Concept of Strain in Organic Chemistry” *Angew. Chem. Int. Ed.* 1986, 312



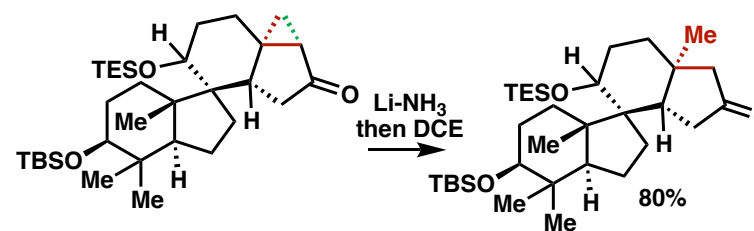
### Cyclopropanes

The many  $\pi$ -like reactions of cyclopropanes



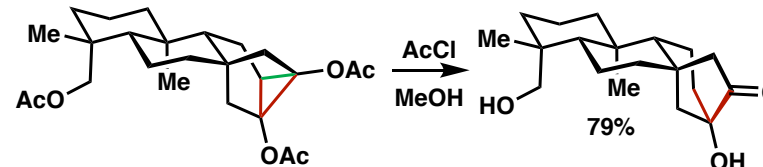
En route to ( $\pm$ )- $\Delta^{9(12)}$ -capnellene

*J. Chem. Soc. Chem. Commun.* 1983, 824



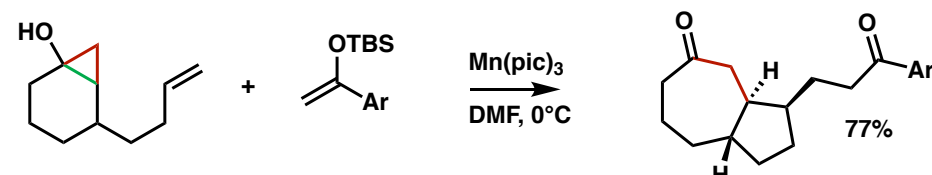
En route to (-)-spirochensilide A

*JACS* 2020, 8116

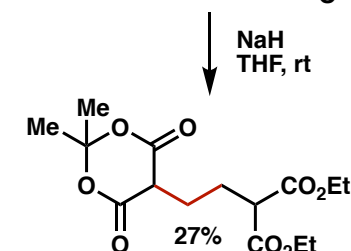
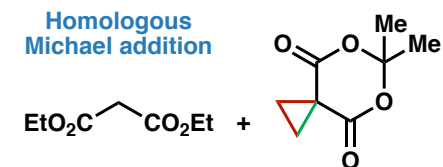


En route to ( $\pm$ )-steviol

*Angew. Chem. Int. Ed.* 2013, 9019

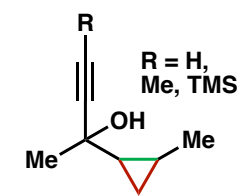


Radical fragmentation

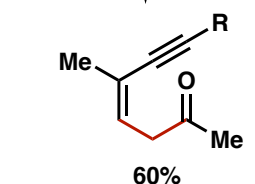


*JACS* 2009, 7214

Cyclopropane Dauben oxidation



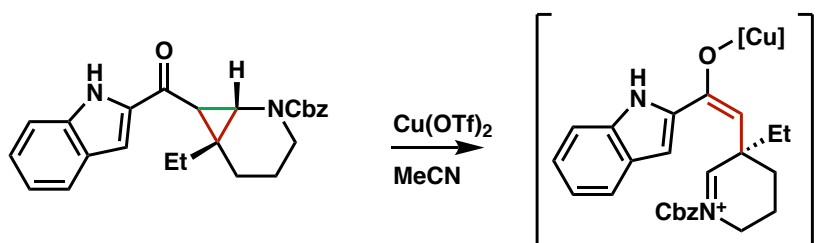
PCC  
DCM, rt



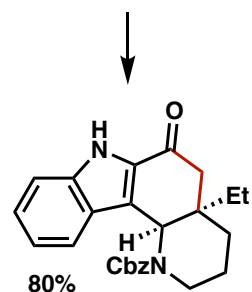
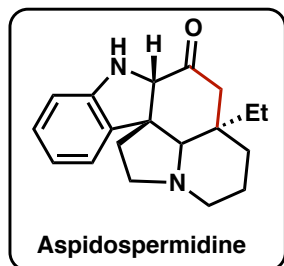
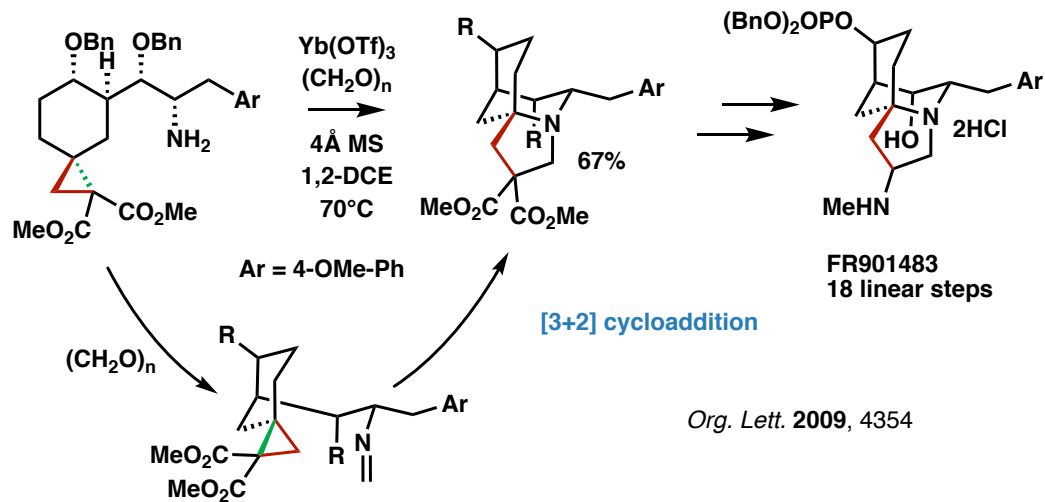
*Chem. Ber.* 1984, 3004

*Chem. Lett.* 1993, 545

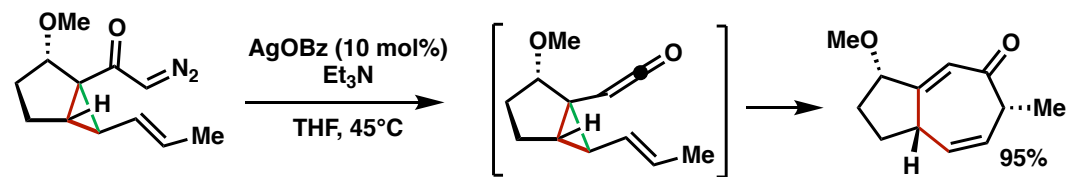
## Donor acceptor cyclopropanes



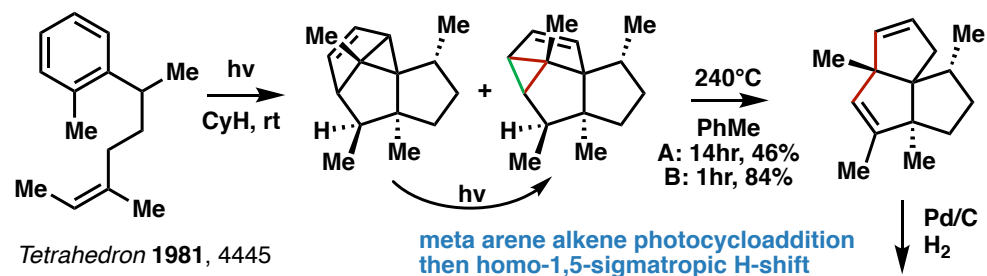
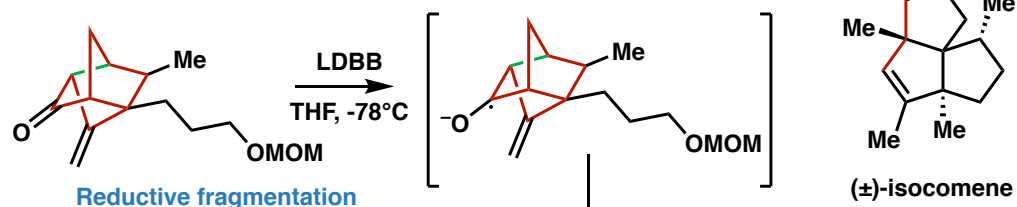
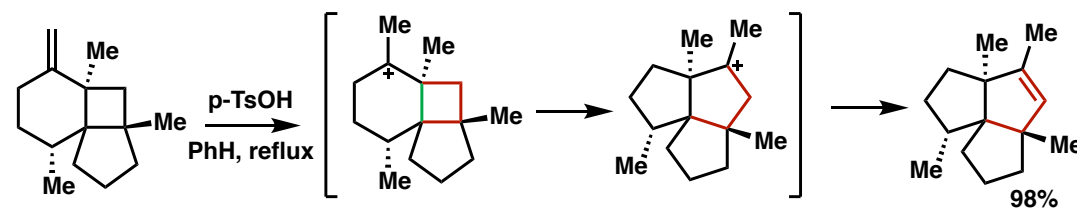
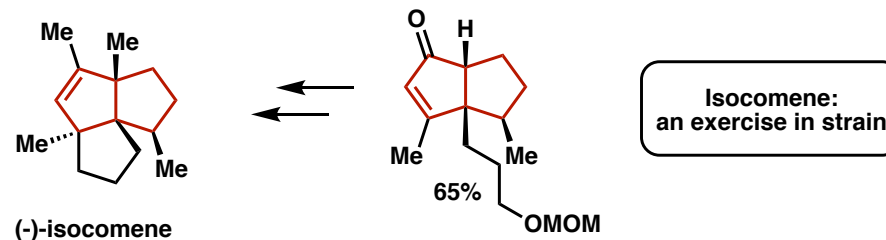
Homo-Nazarov cyclization

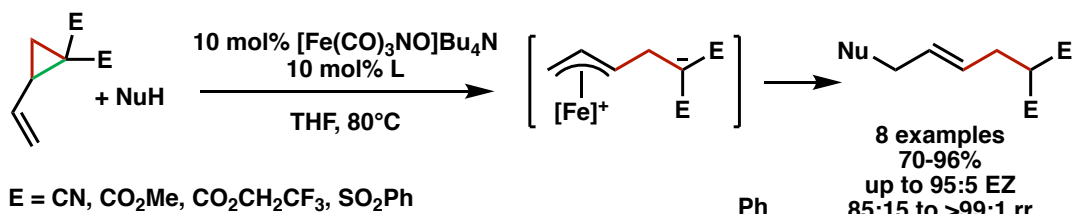
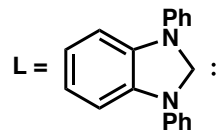
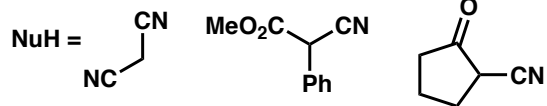
*Angew. Chem. Int. Ed.* 2011, 5767*Org. Lett.* 2009, 4354

## Vinyl cyclopropanes

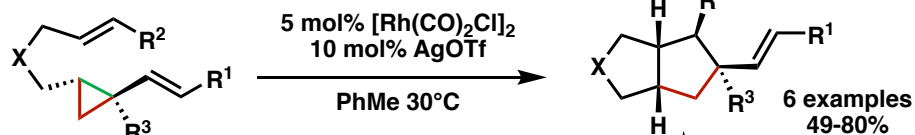
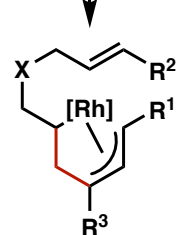
*JACS* 2003, 13624

Strain release Wolff/Cope

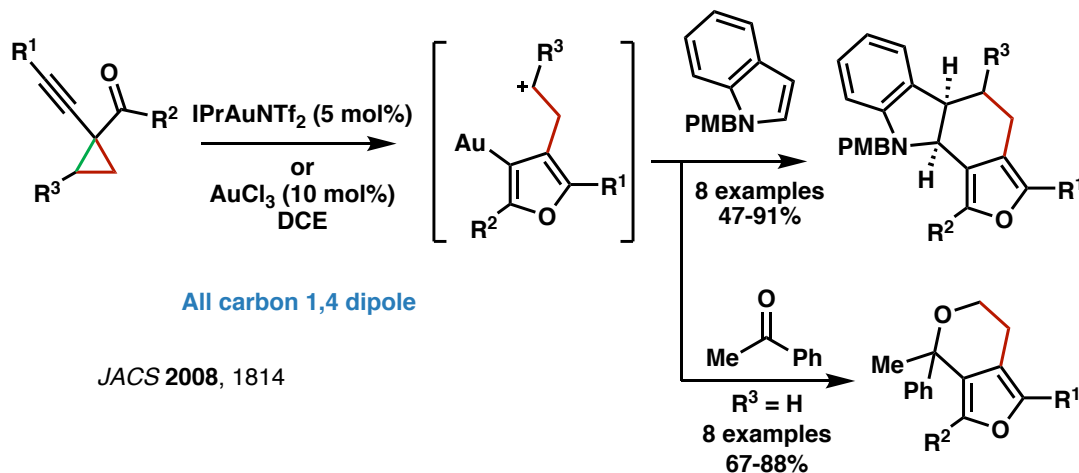
8 examples  
76-98%*Tetrahedron* 1981, 4445*J. Chem. Soc., Chem. Commun.* 1994, 1797*JACS* 1979, 7130

E = CN, CO<sub>2</sub>Me, CO<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>Ph

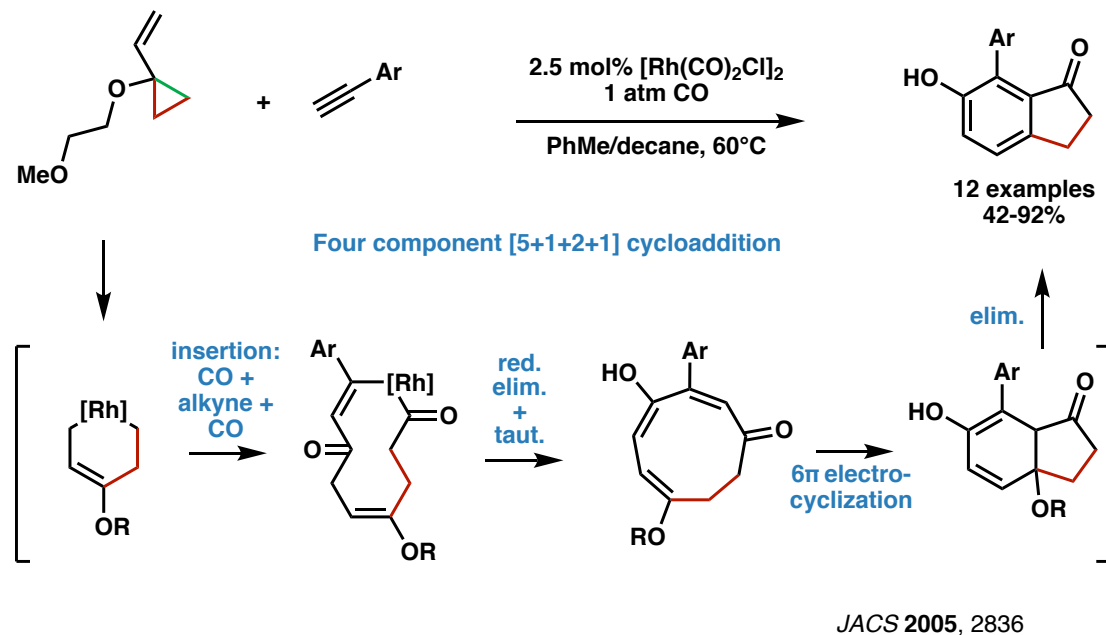
JACS 2012, 5048

X = O, NTs  
R<sup>1</sup> = H, Me, Et, Ph  
R<sup>2</sup>, R<sup>3</sup> = H, Me

JACS 2008, 7178

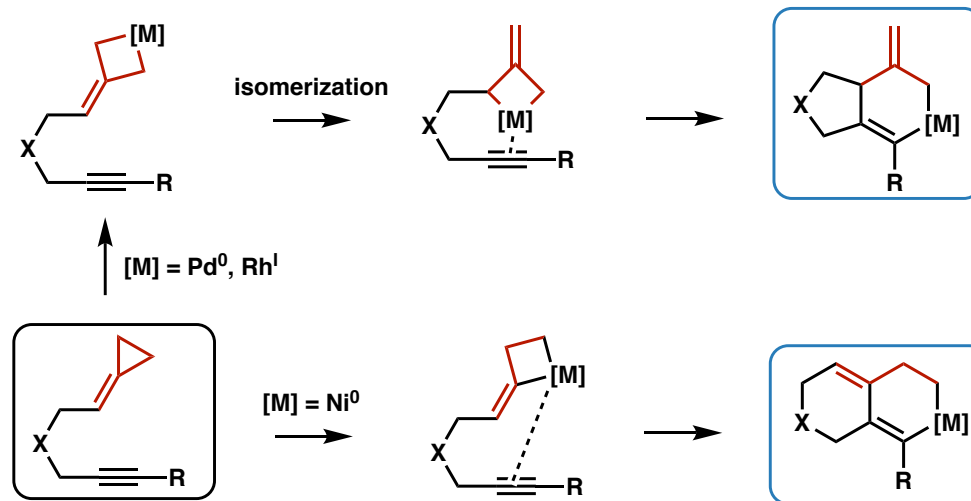
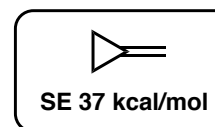


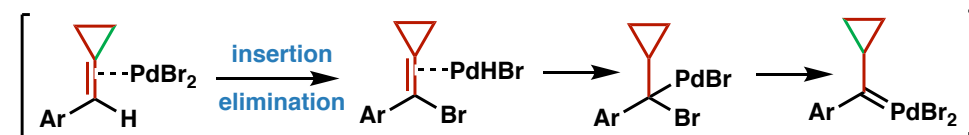
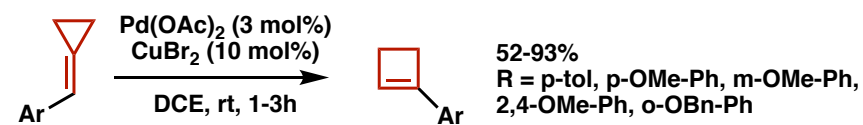
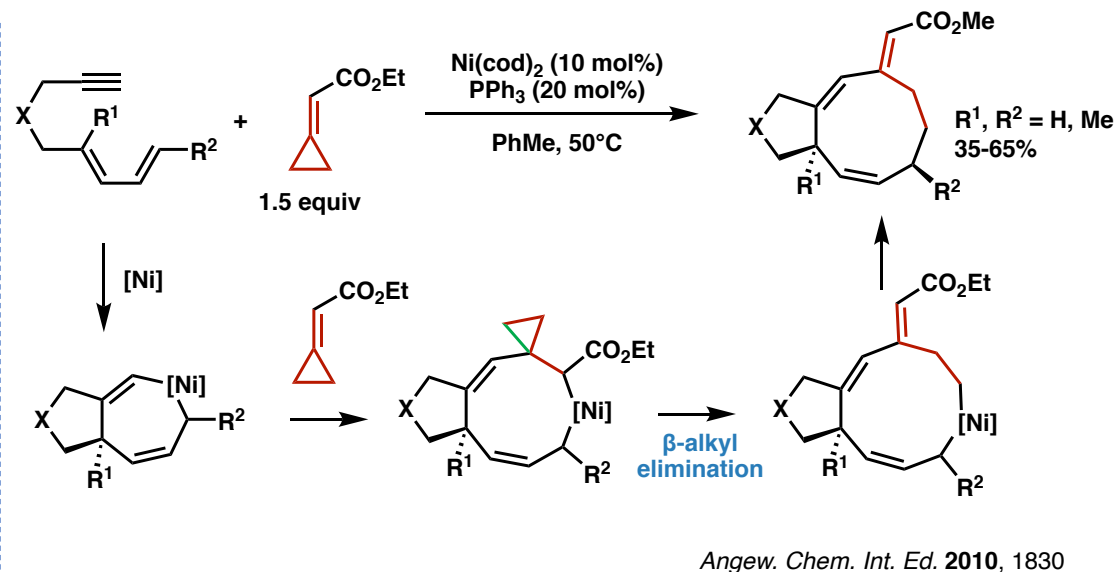
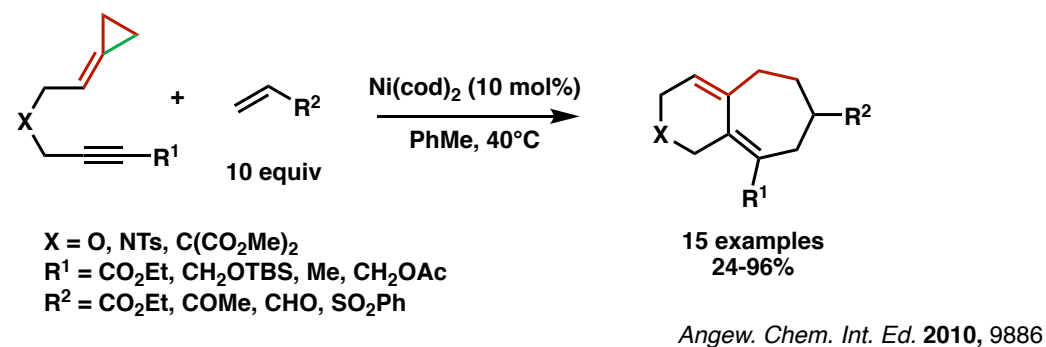
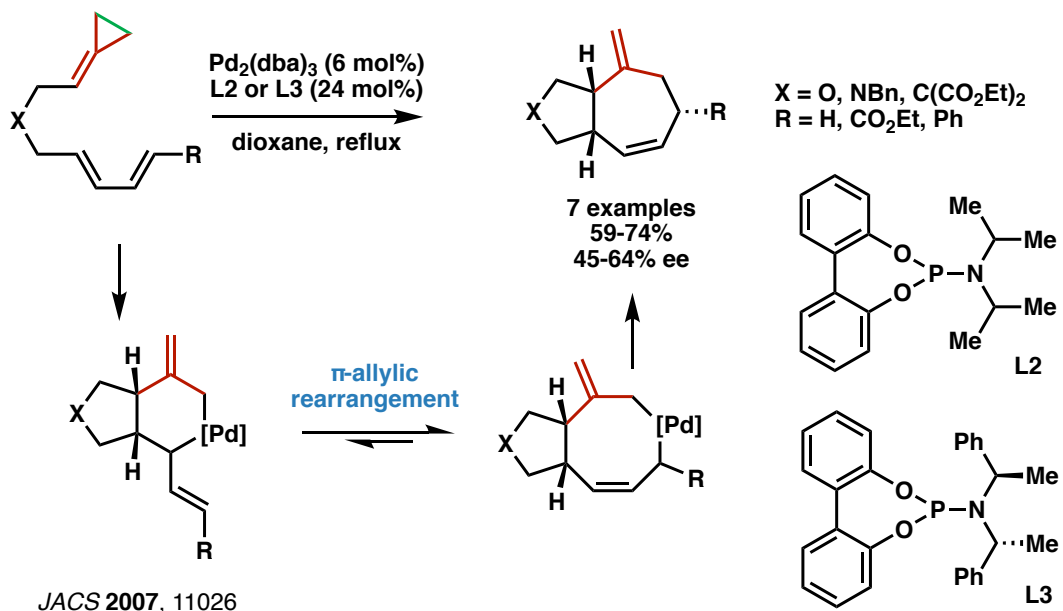
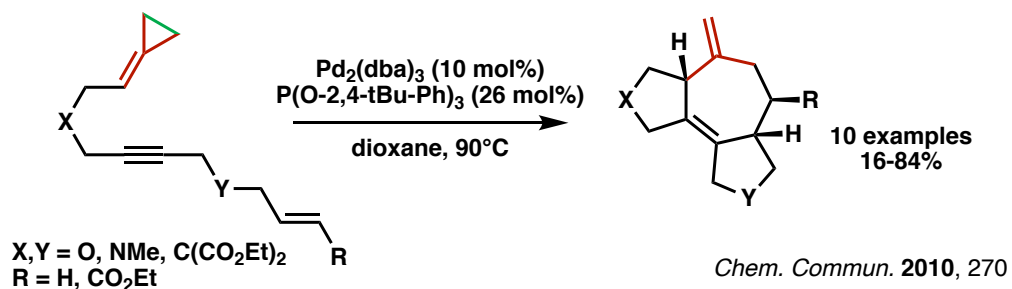
JACS 2008, 1814



JACS 2005, 2836

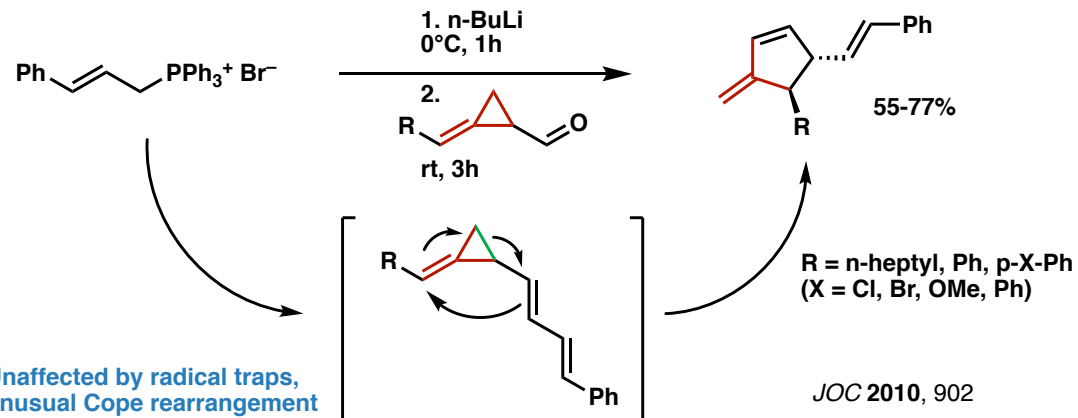
## Alkylidene cyclopropanes

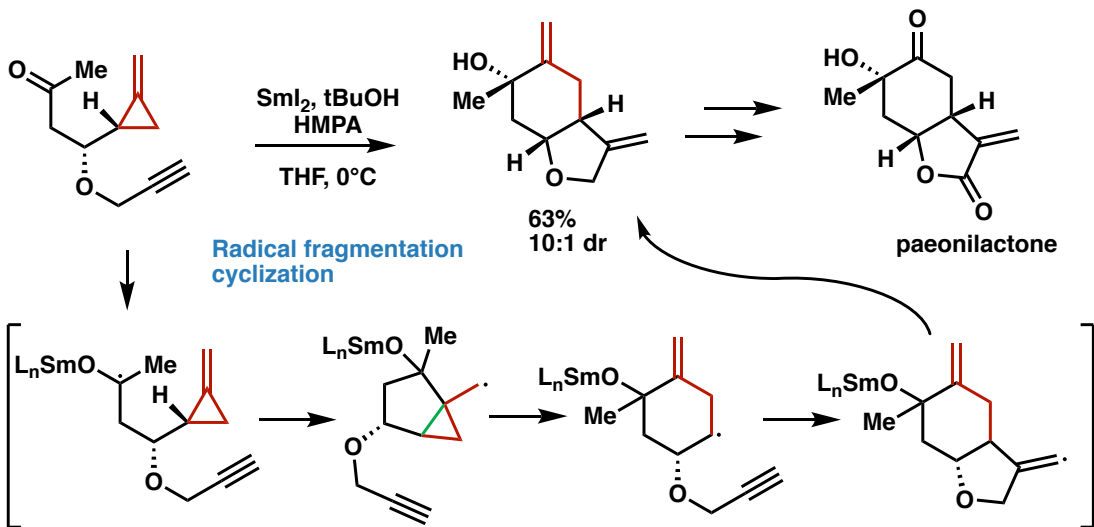
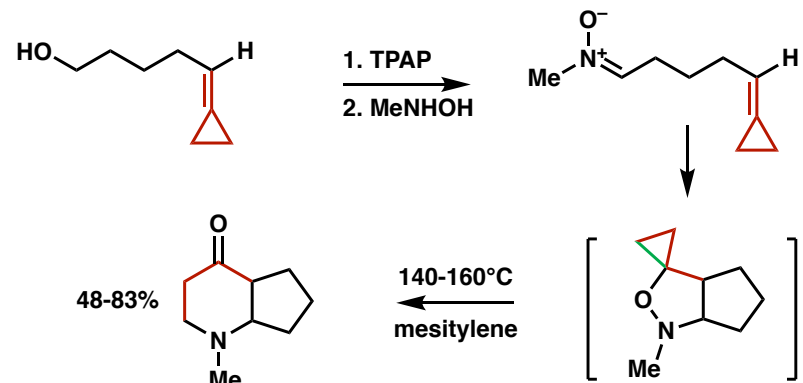
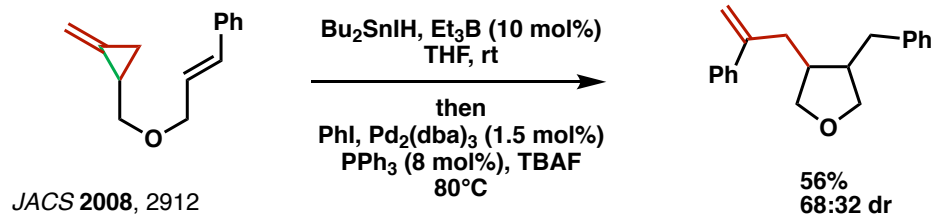




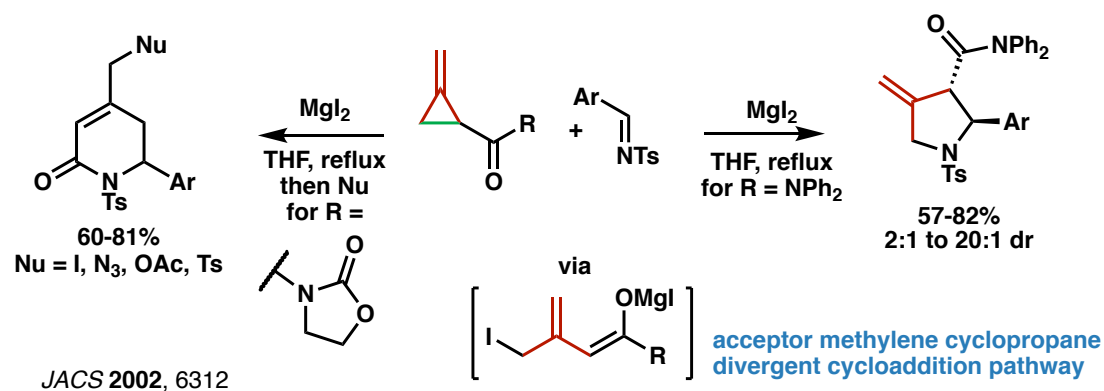
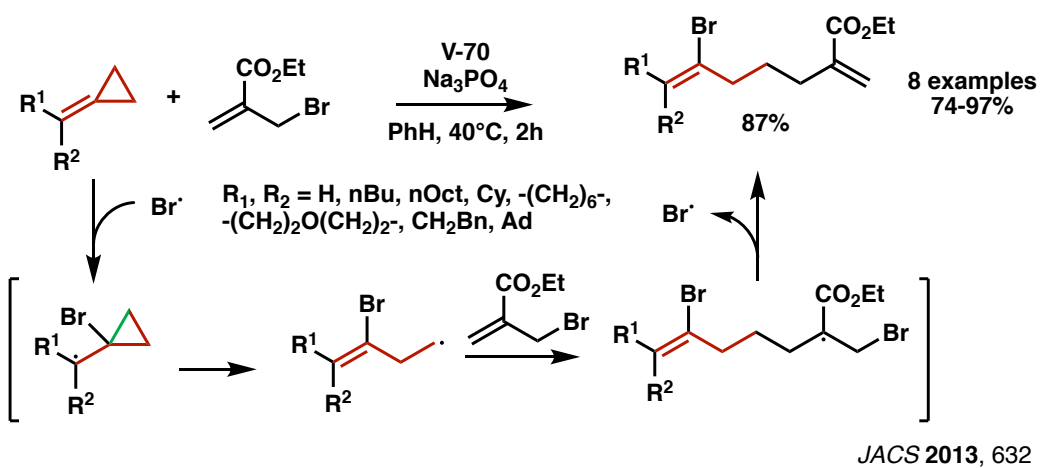
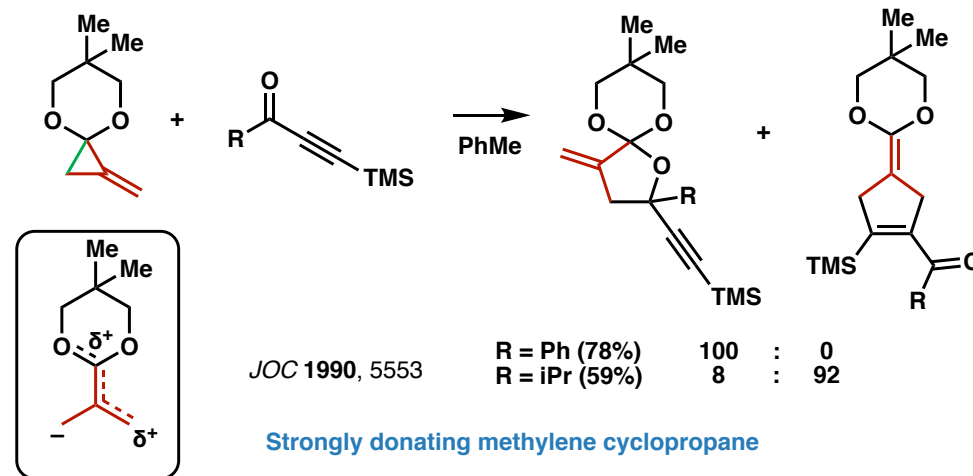
Alkylidene cyclopropanes are common cyclobutene precursors

JACS 2006, 7430

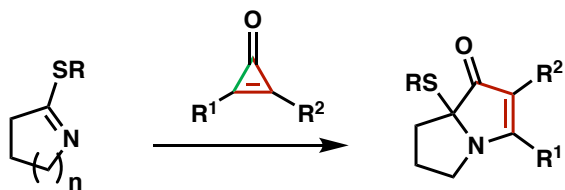




J. Chem. Soc., Chem. Commun. 1998, 1875

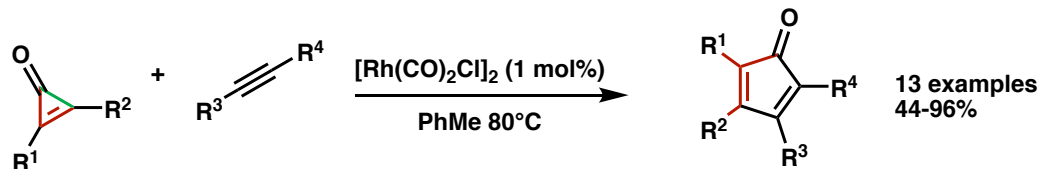


## Cyclopropenes

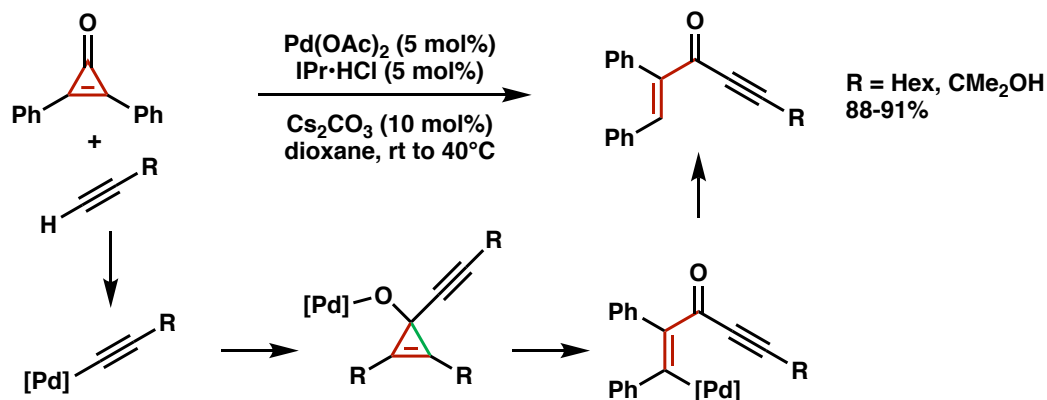


$n = 1, 2, 3$   
 $R^1, R^2 = H, Me, Et, Ph$   
 $R = Me, Et$

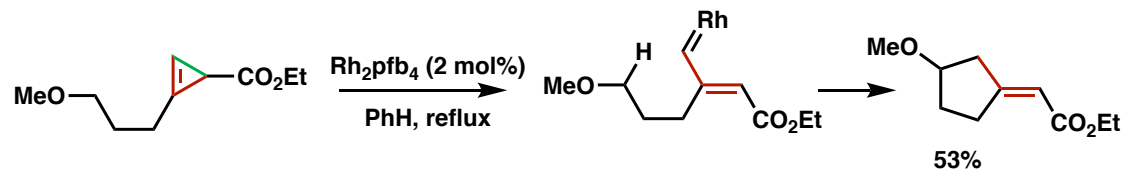
65-85%

*Tetrahedron Lett.* 2008, 6316

$R^1 = Ph$   
 $R^2 = Ph, Me$   
 $R^3 = Alkyl, Ar, OAlkyl, COMe$   
 $R^4 = Ar, HetAr, Alkyl, Alkenyl$

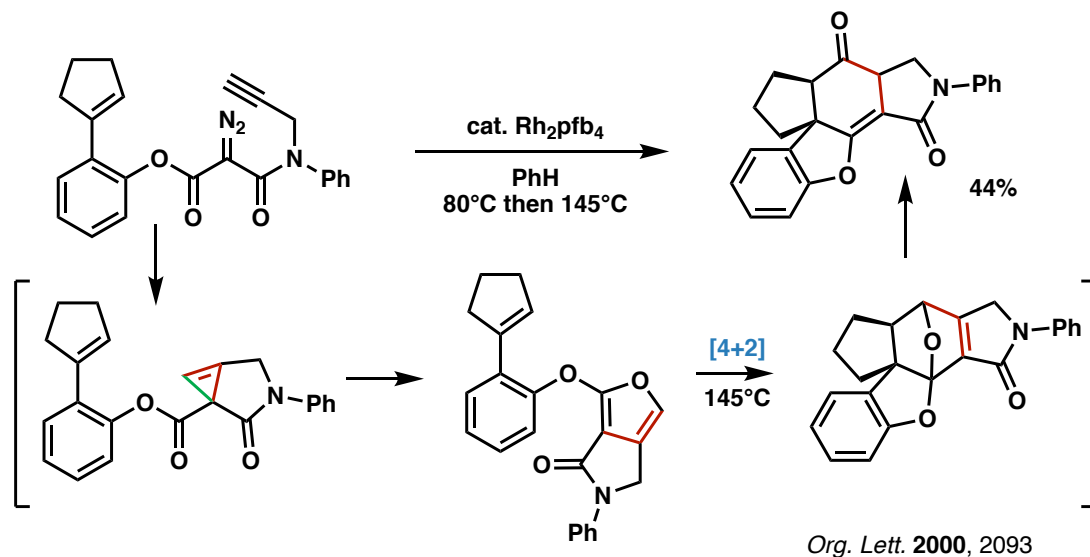
13 examples  
44-96%*JACS* 2006, 14814

$R = Hex, CMe_2OH$   
 88-91%

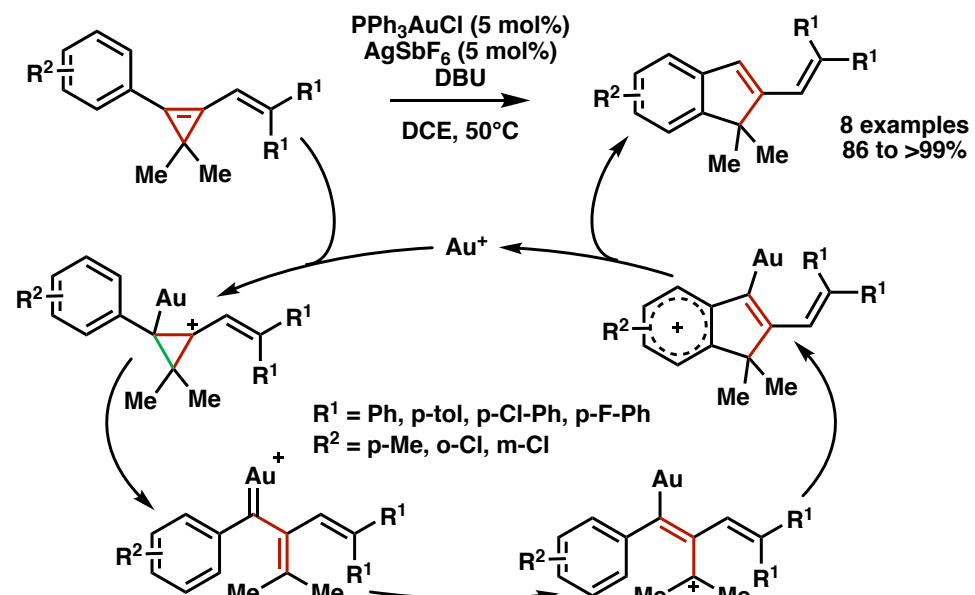
*Eur. J. Org. Chem.* 2013, 4219*Helv. Chim. Acta* 1995, 129

Cyclopropenes as masked vinyl carbenes

53%



44%

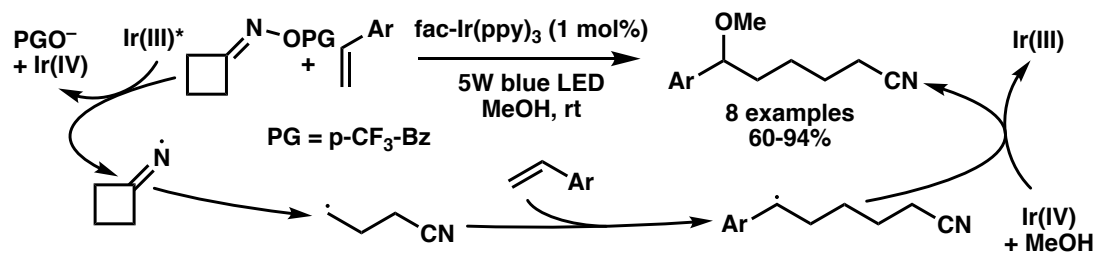
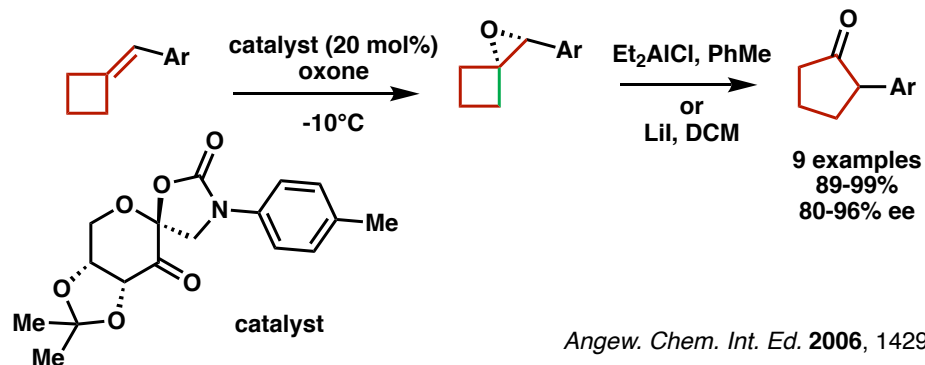
*Org. Lett.* 2000, 20938 examples  
86 to >99%

$R^1 = Ph, p\text{-tol}, p\text{-Cl-Ph}, p\text{-F-Ph}$   
 $R^2 = p\text{-Me}, o\text{-Cl}, m\text{-Cl}$

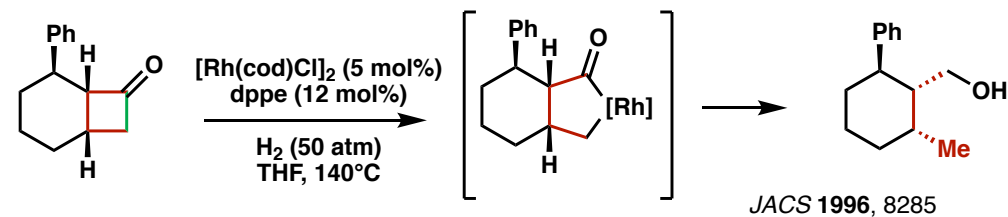
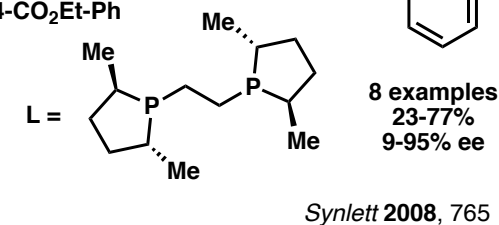
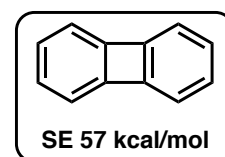
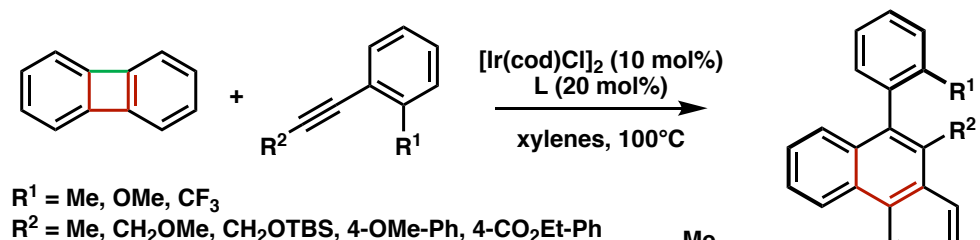
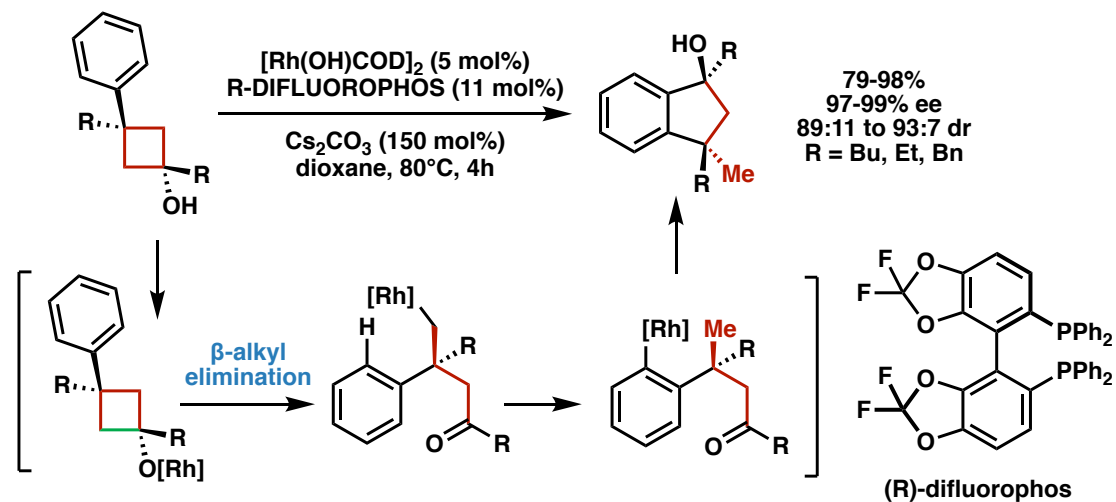
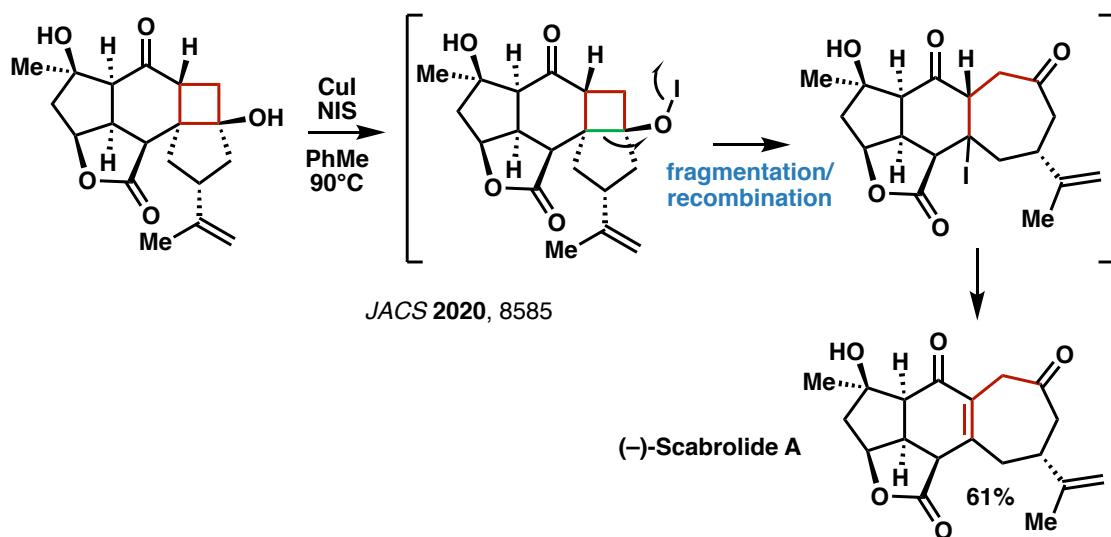
*Chem. Eur. J.* 2008, 10219

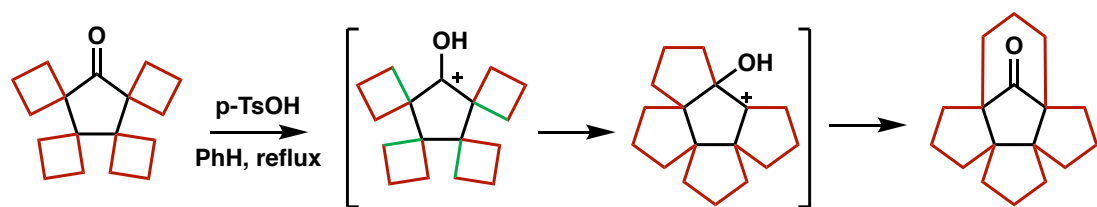
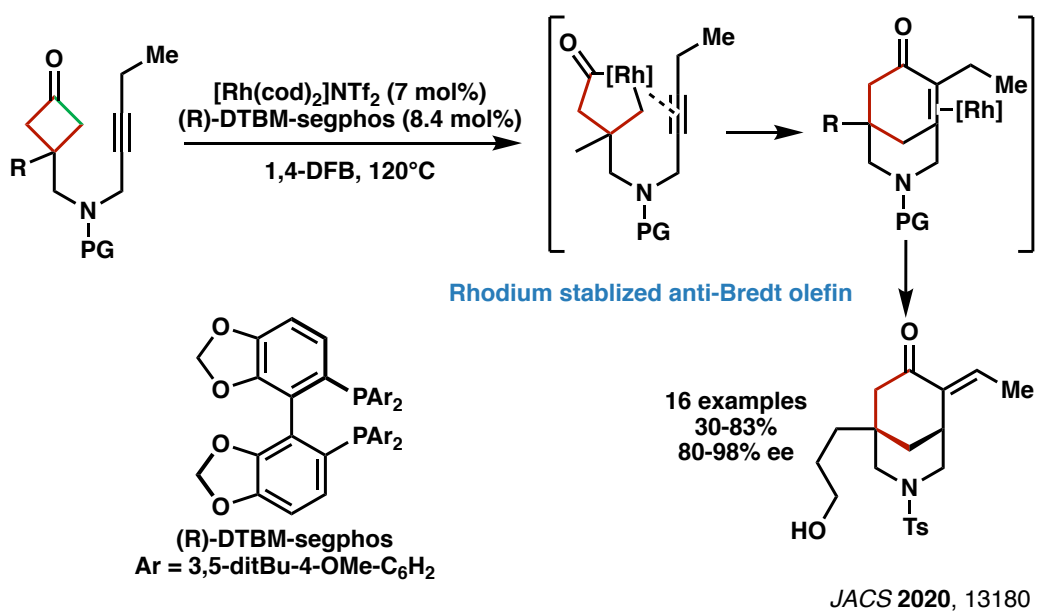
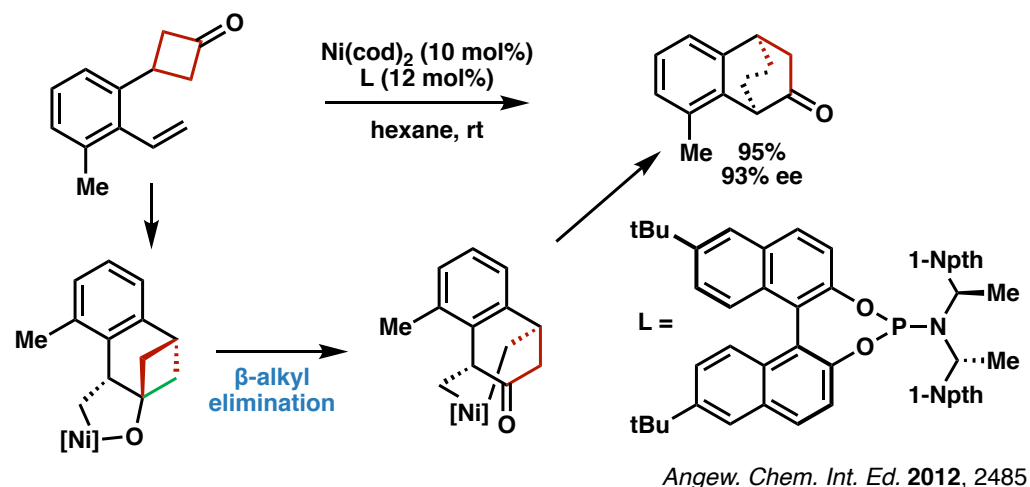
## Cyclobutanes

SE 27 kcal/mol



## Nitrile generating fragmentation

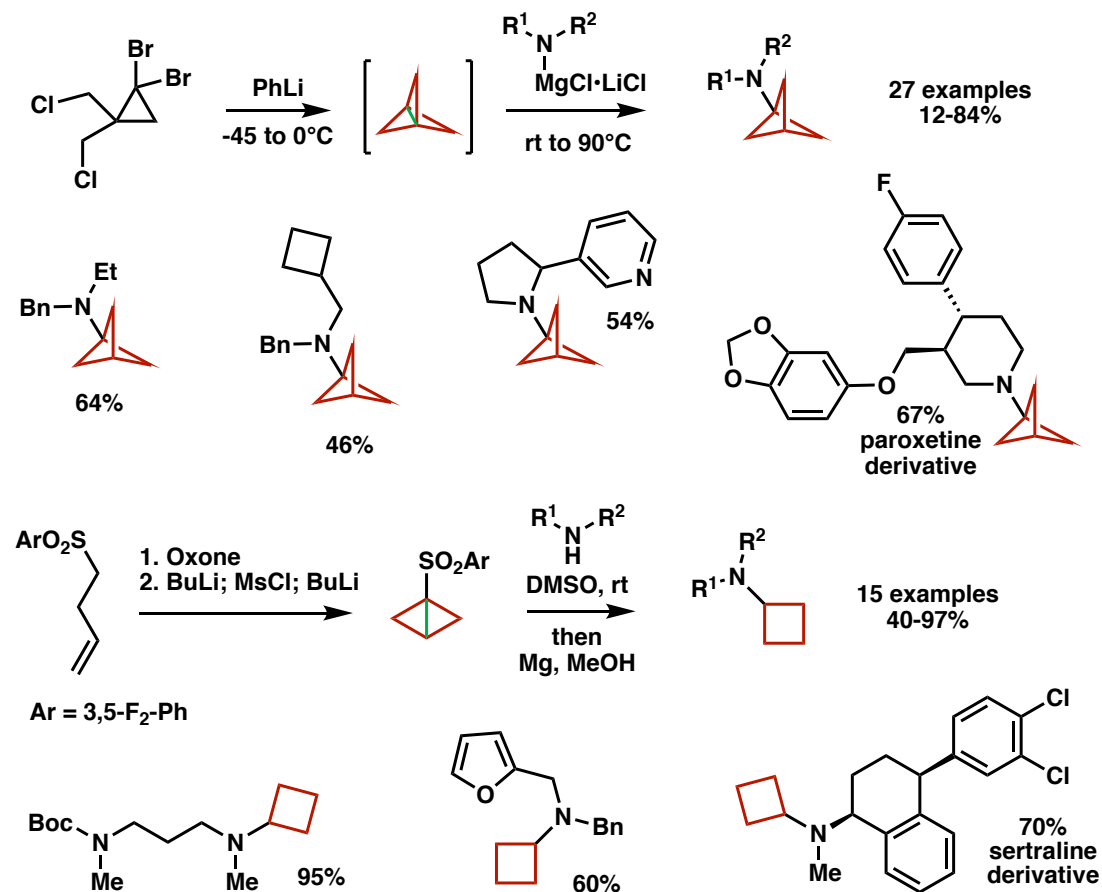
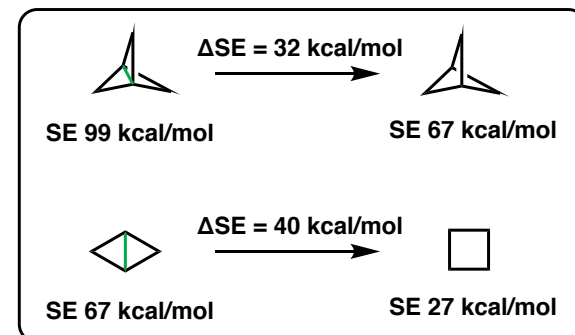




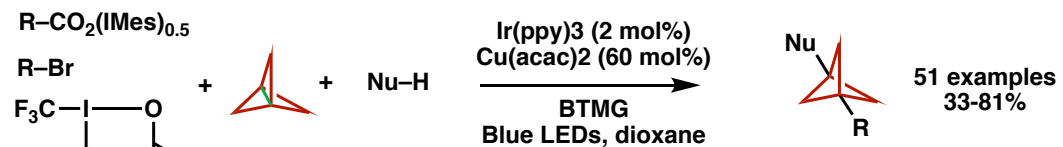
Cascade cyclobutane expansion

*Angew. Chem. Int. Ed.* **1987**, 1023

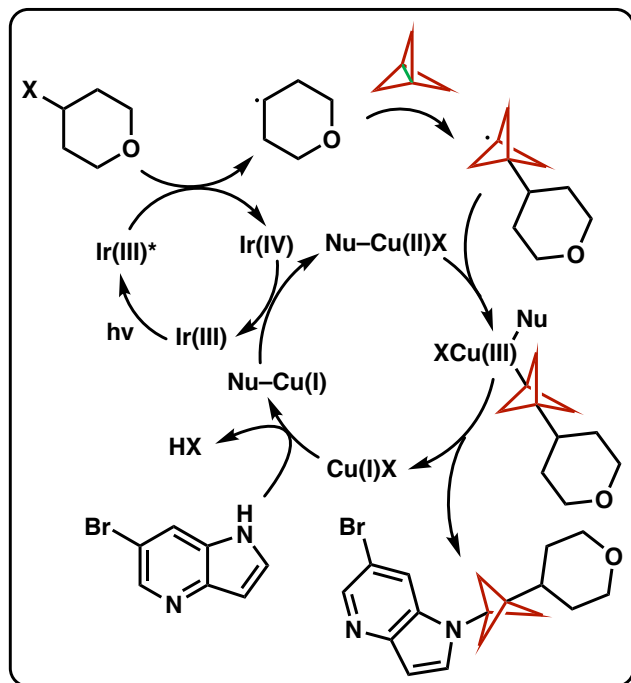
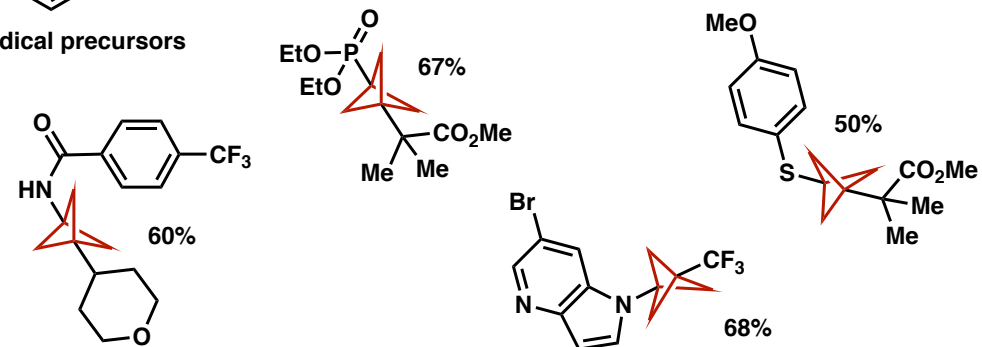
## Polycyclic compounds

*Science* **2016**, 241

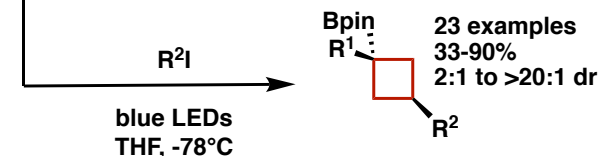
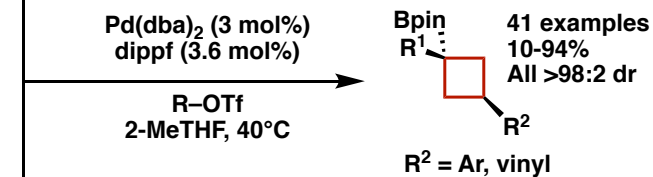
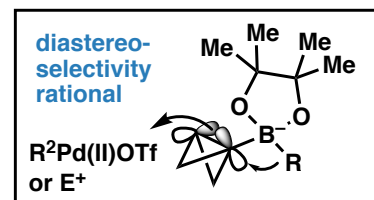
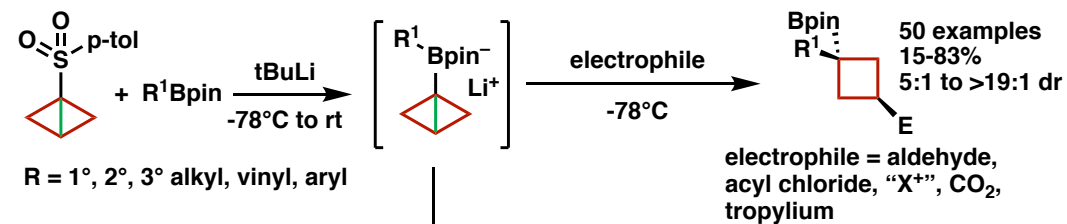




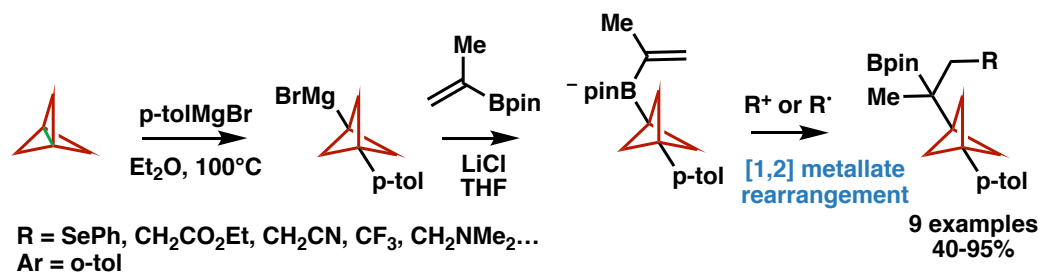
radical precursors



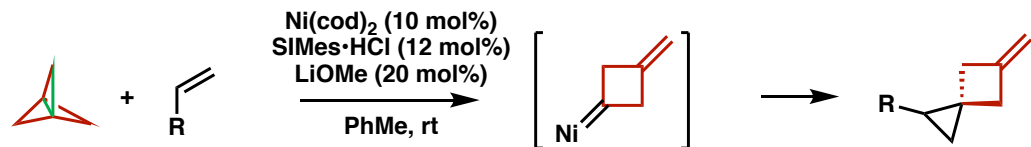
Nature 2020, 220



JACS 2020, 16766  
 Nat. Chem. 2019, 117  
 JACS 2019, 9511



Angew. Chem. Int. Ed. 2020, 3917

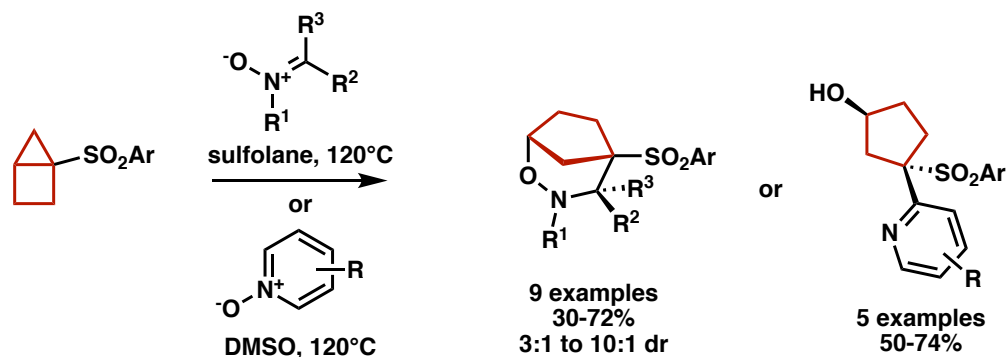


R = alkenyl, alkynyl, Ar

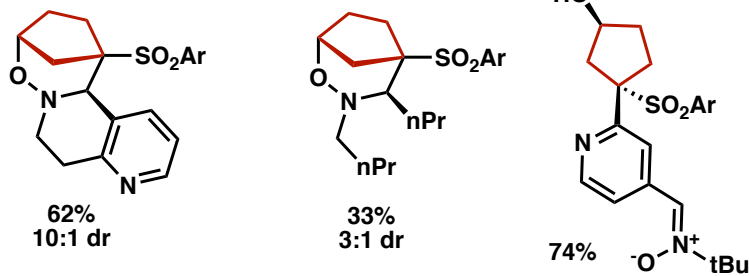
[1.1.1]propellanes as masked methylene cyclobutane carbenes

24 examples  
44-91%

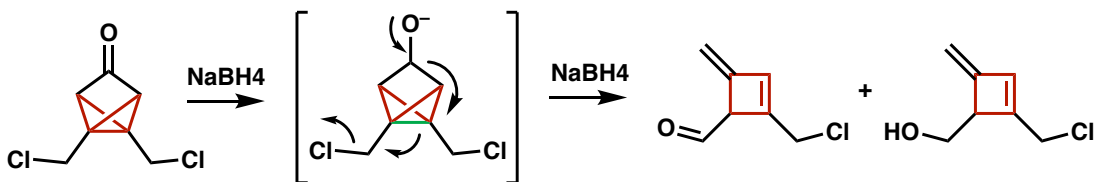
JACS 2019, 20325

9 examples  
30-72%

3:1 to 10:1 dr

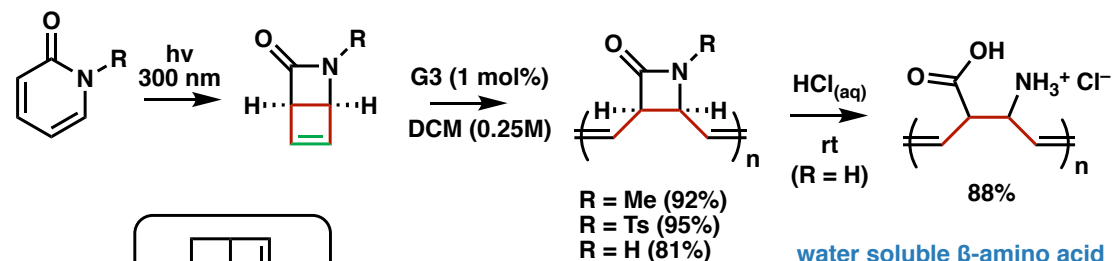
5 examples  
50-74%

Org. Lett. 2019, 4763

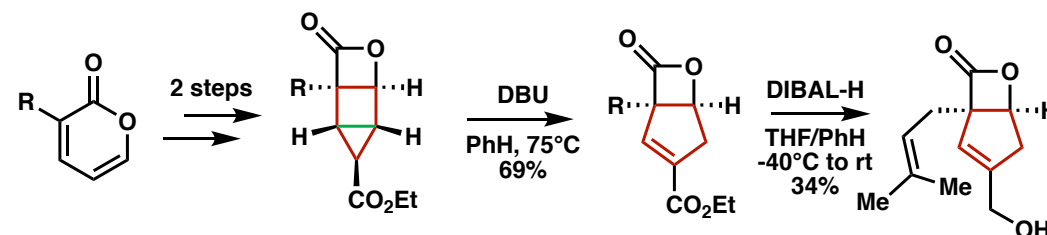
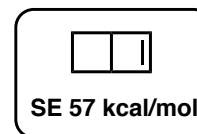


Extended Grob fragmentation - geometric constraints "stretched considerably"

Tetrahedron Lett. 1982, 7

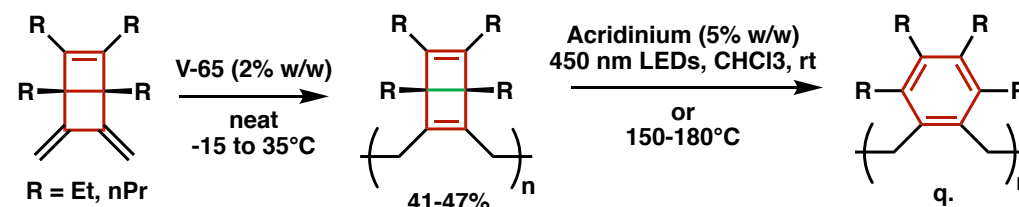
R = Me (92%)  
R = Ts (95%)  
R = H (81%)water soluble  $\beta$ -amino acid  
polymer from dewar pyridone

ACS Macro Lett. 2020, 731

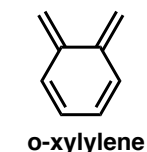


Angew. Chem. Int. Ed. 2019, 1724

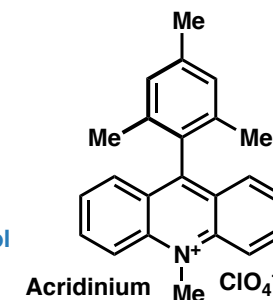
(±)-vibrallactone

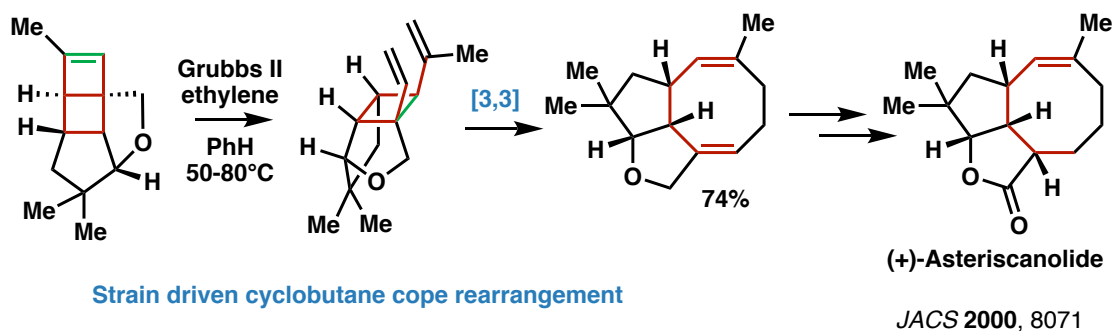


-Poly(o-xylylene) challenging polymer

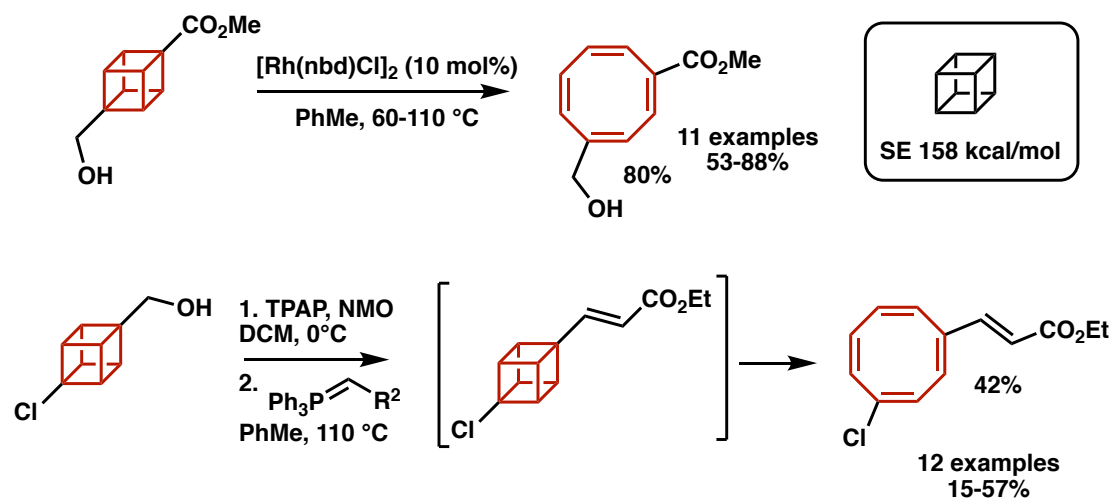
-High M.W. polymers up to 81 kDa  
-Heat of isomerization (dewarbenzene to benzene) -56 kcal/mol  
-Kinetically stable:  $\Delta^\ddagger H$  (hexamethyl dewarbenzene) = 34 kcal/mol

JACS 2018, 5211



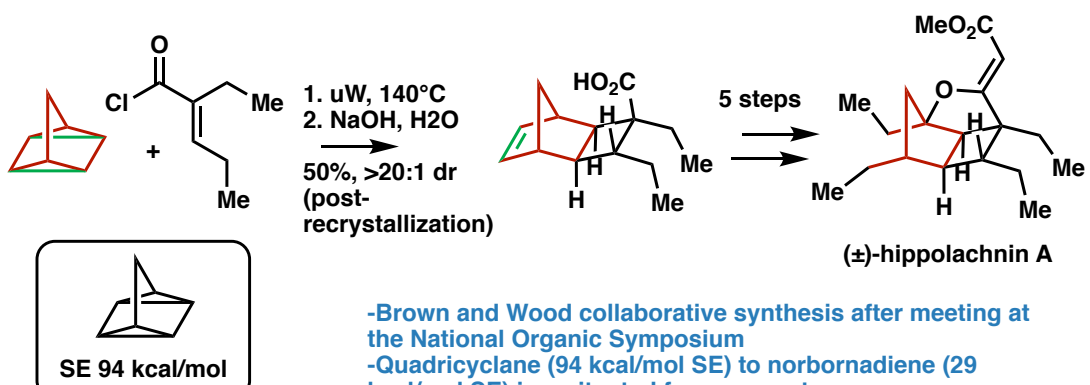


Strain driven cyclobutane cope rearrangement



Vinyllic cyclobutanes are destabilized

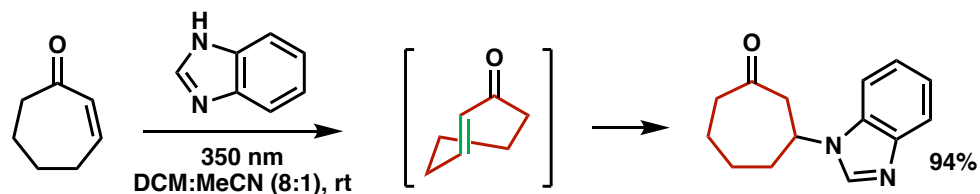
Chem. Eur. J. 2019, 2735



-Brown and Wood collaborative synthesis after meeting at the National Organic Symposium  
-Quadricyclane (94 kcal/mol SE) to norbornadiene (29 kcal/mol SE) investigated for energy storage

JACS 2016, 2437

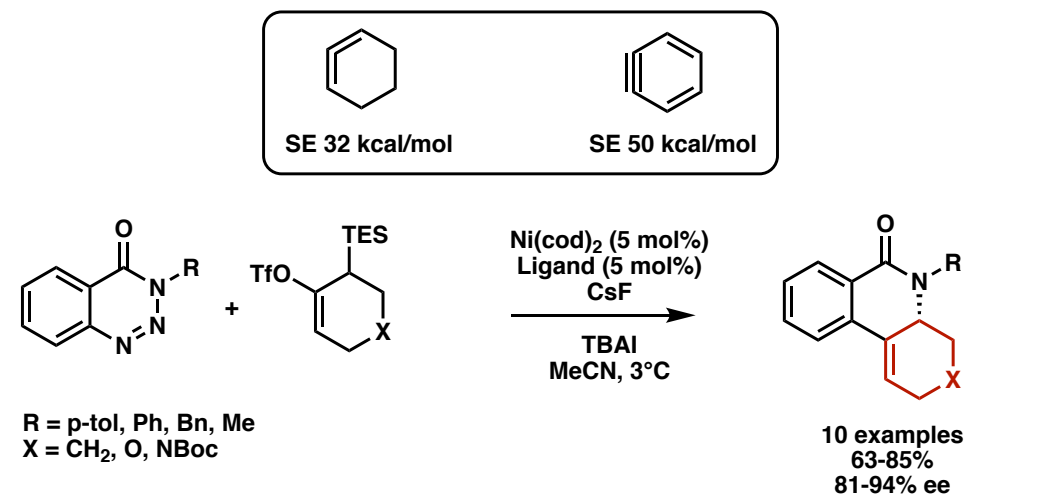
## Strained medium rings



-UV light isomerization to strained olefins  
-Cycloheptenones and cyclooctenones react with nitrogen heterocycles  
-Tolerates broad solvent scope

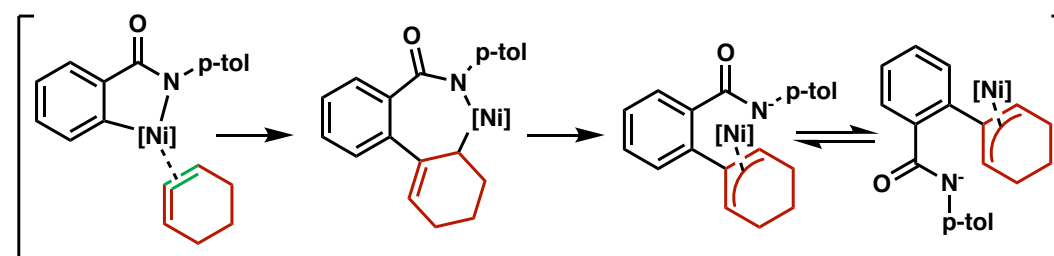
44-99%  
8 examples varying nucleophile  
6 examples varying electrophile

Org. Lett. 2007, 3893

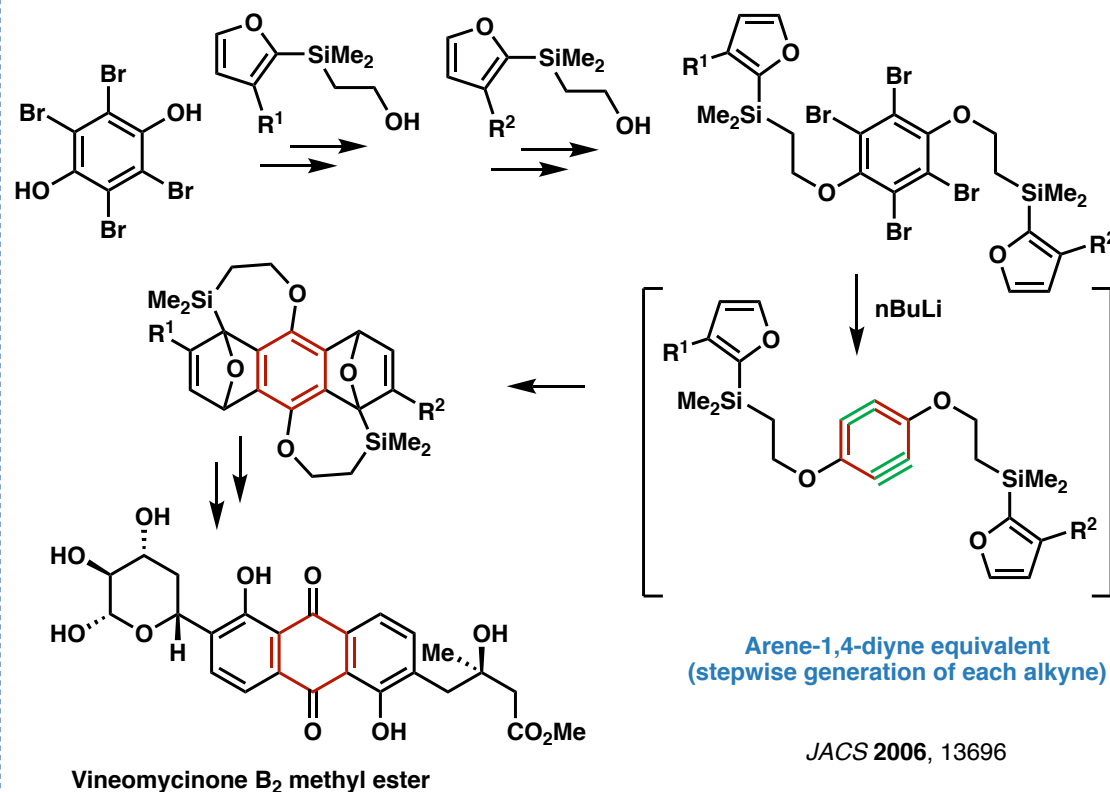
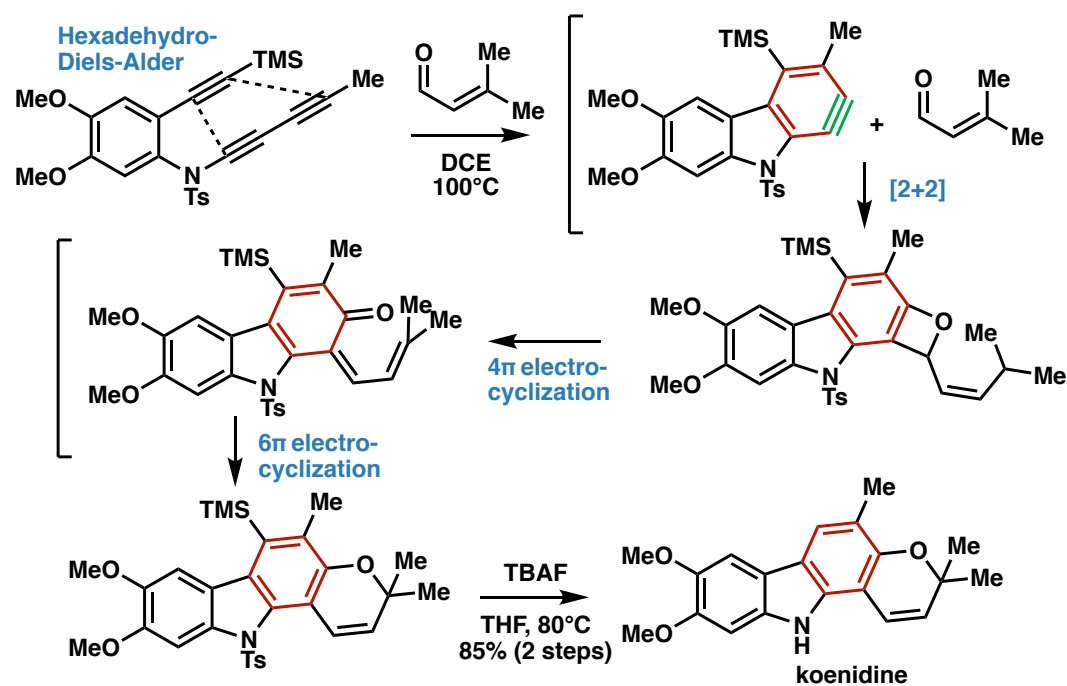
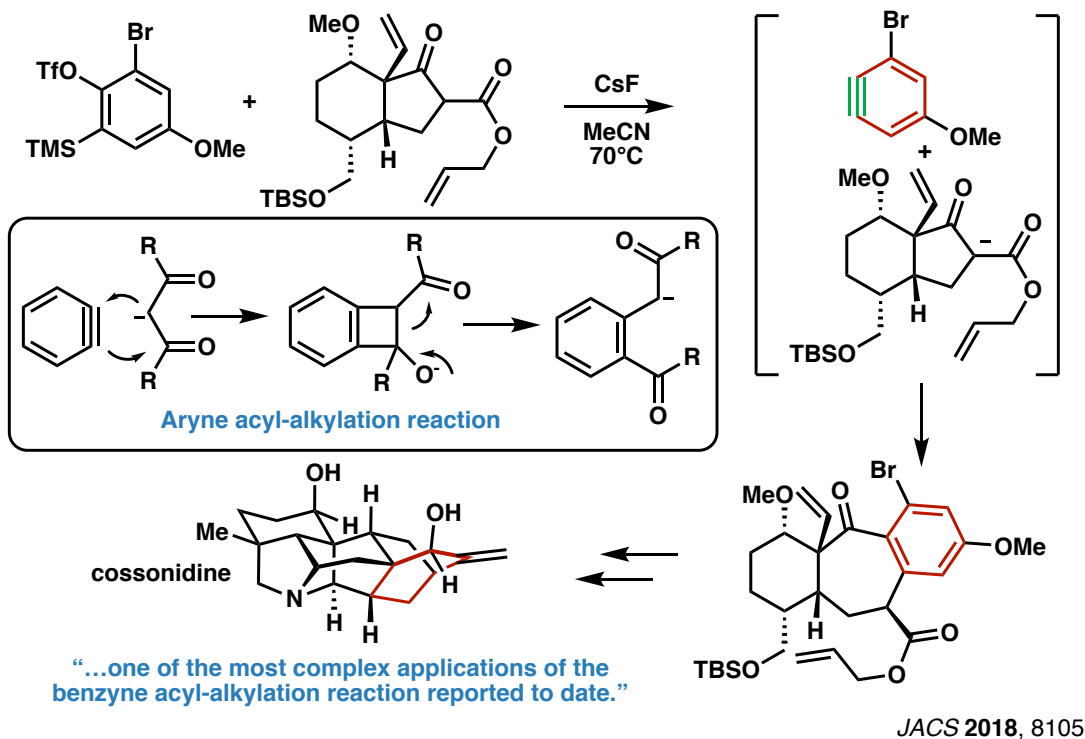


R = p-tol, Ph, Bn, Me  
X = CH<sub>2</sub>, O, NBoc

## First enantioselective trapping of 1,2 cyclohexadiene



Nature 2020, 242



### Key takeaways

- Strain provides a strong thermodynamic driving force for reactions
- Many strained  $\sigma$ -bonds have  $\pi$ -like reactivity
- Strain release can promote irreversibility of a reaction
- Strained motifs can often act as masked functional groups (vinyl carbenes, 1,3 dipoles etc.)
- Strain release can be an efficient method for ring expansion
- The cleaving of strained motifs can effectively promote domino reactivity
- Strain release can be an artistic way to quickly access complex scaffolds