

Master Course
in Organic Chemistry

2018-19

methods and design
in organic synthesis



Pere Romea

THE LORD OF THE RINGS

THE FELLOWSHIP OF THE RING

by John R. R. Tolkien

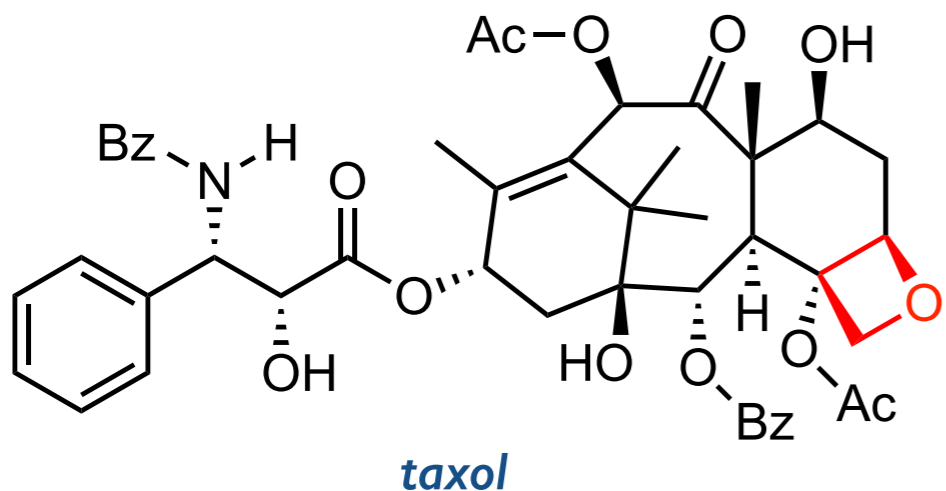


6.4. Making rings (II)

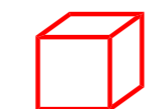
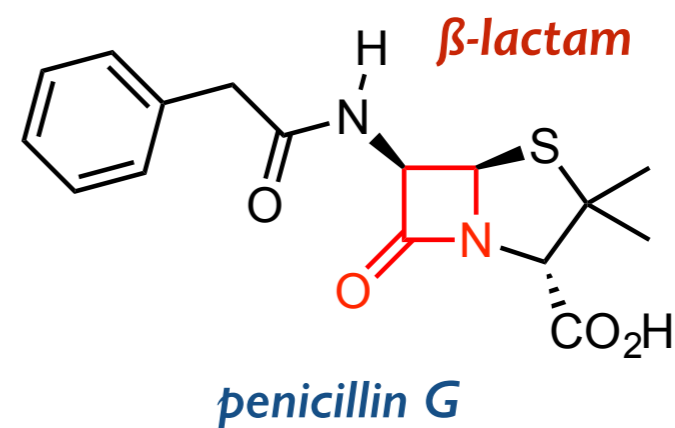
4

4-Membered rings are small and strained cycles

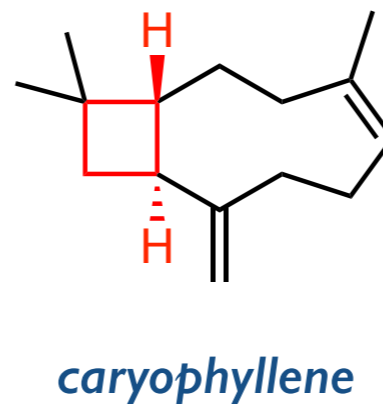
However, they can be found in a variety of natural products ...



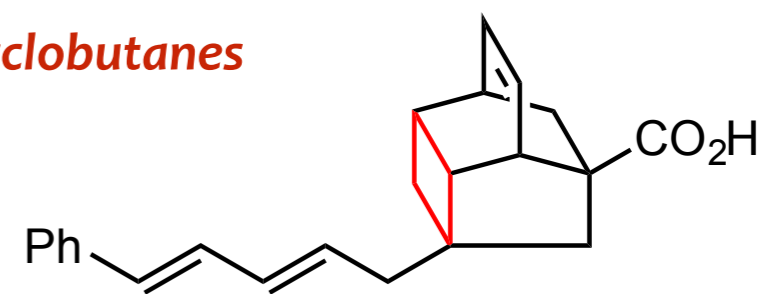
oxetane



cubane



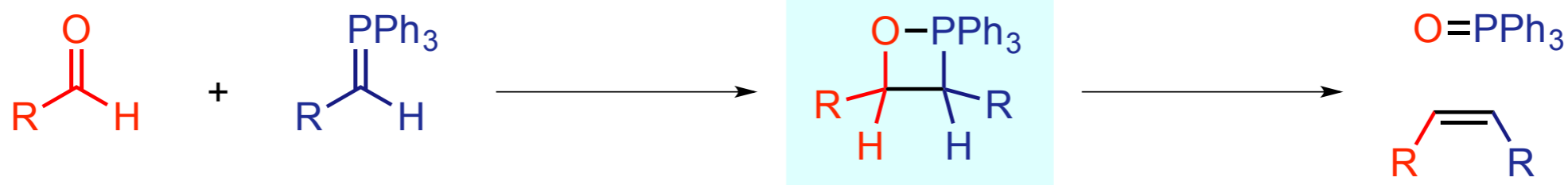
cyclobutanes



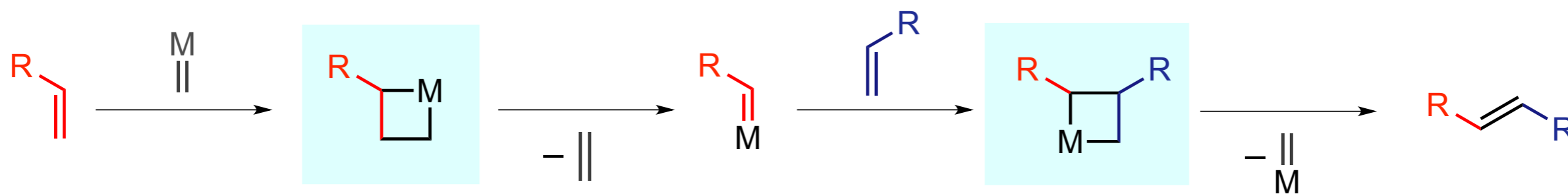
4

4-Membered rings are small and strained cycles

...and also in important intermediates or transition states



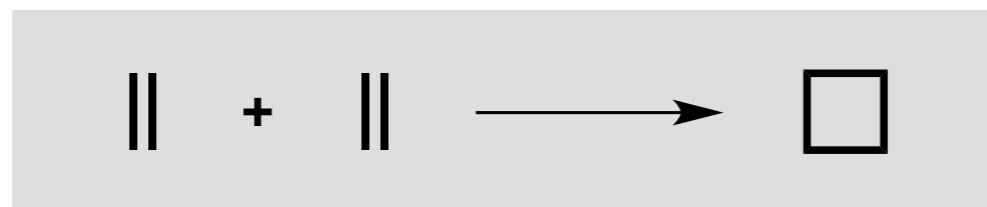
Wittig reaction



Cross metathesis

[2 + 2] Cycloadditions

[2 + 2] Cycloadditions seem the most appropriate approach to cyclobutanes



... but they are not simple processes and the experimental conditions are of paramount importance



The orbital symmetry becomes crucial to understand such a cycloaddition

This process can be considered at different levels

- *FMO approach: just evaluating HOMO-LUMO interactions*
- *Orbital diagram correlation: assessment of full orbital evolution*
- *State diagram correlation: assessment of electronic state evolution*

Orbitals with different symmetries do not mix ■

Only states with the same symmetry mix in configuration interaction ■

States of the same symmetry do not cross ■



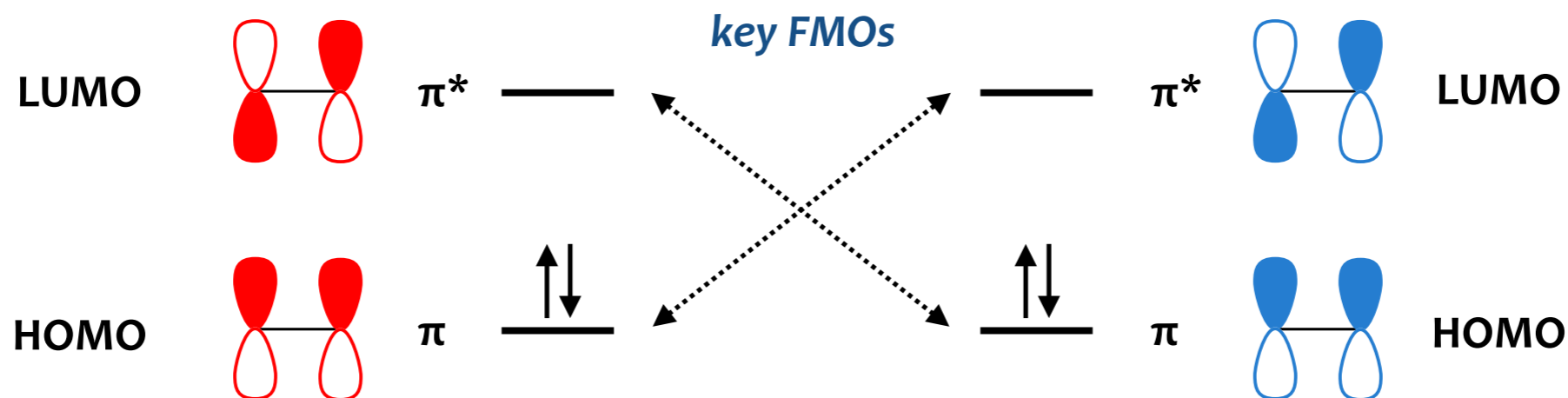


Thermal conditions

refers to reactions in which all the partners are in their electronic ground state

π Molecular orbital of *alkene 1*

π Molecular orbital of *alkene 2*



electronic ground state

electronic ground state

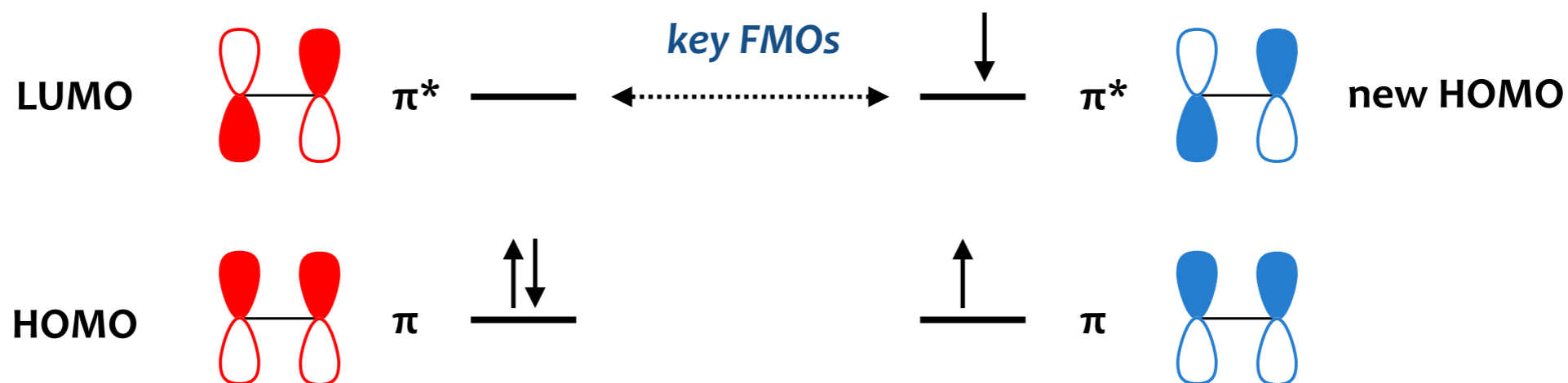


Photochemical conditions

refers to reactions in which one of the partners are is electronically excited

π Molecular orbital of *alkene 1*

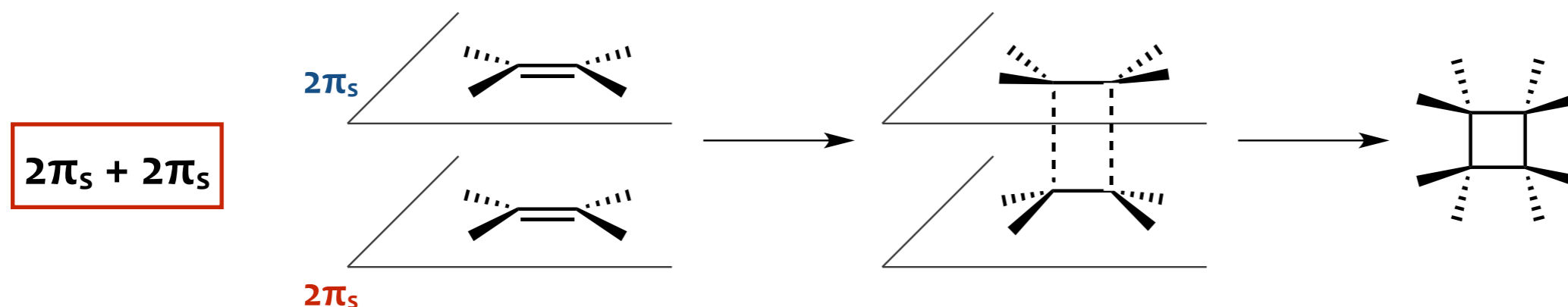
π Molecular orbital of *alkene 2*



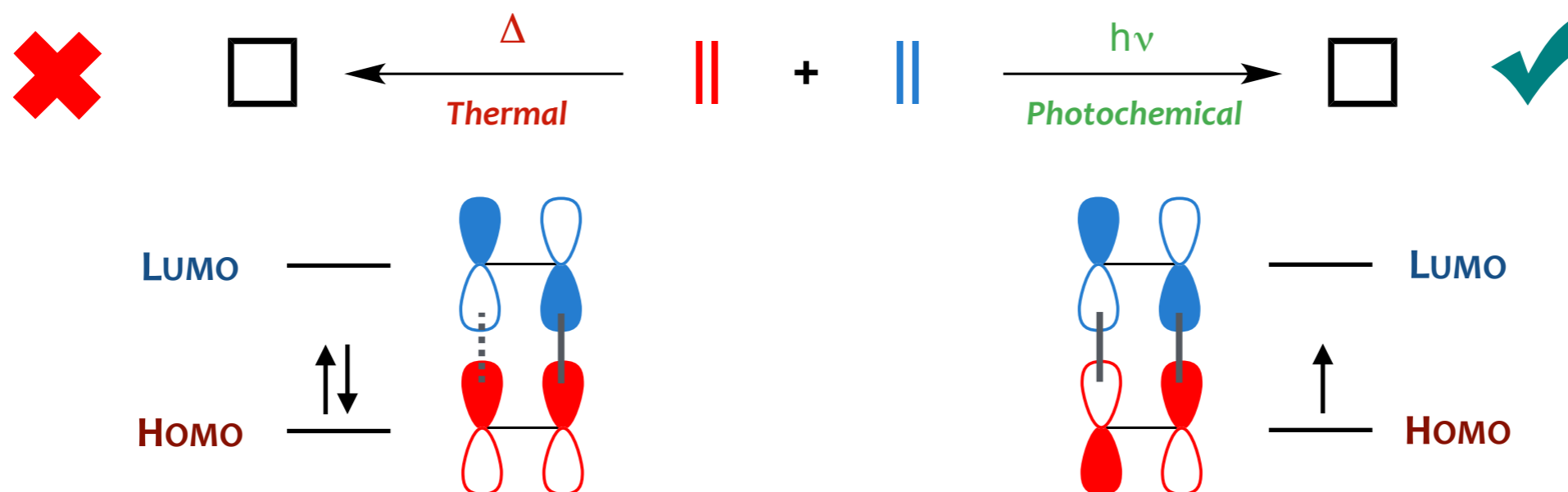
electronic ground state

electronic excited state

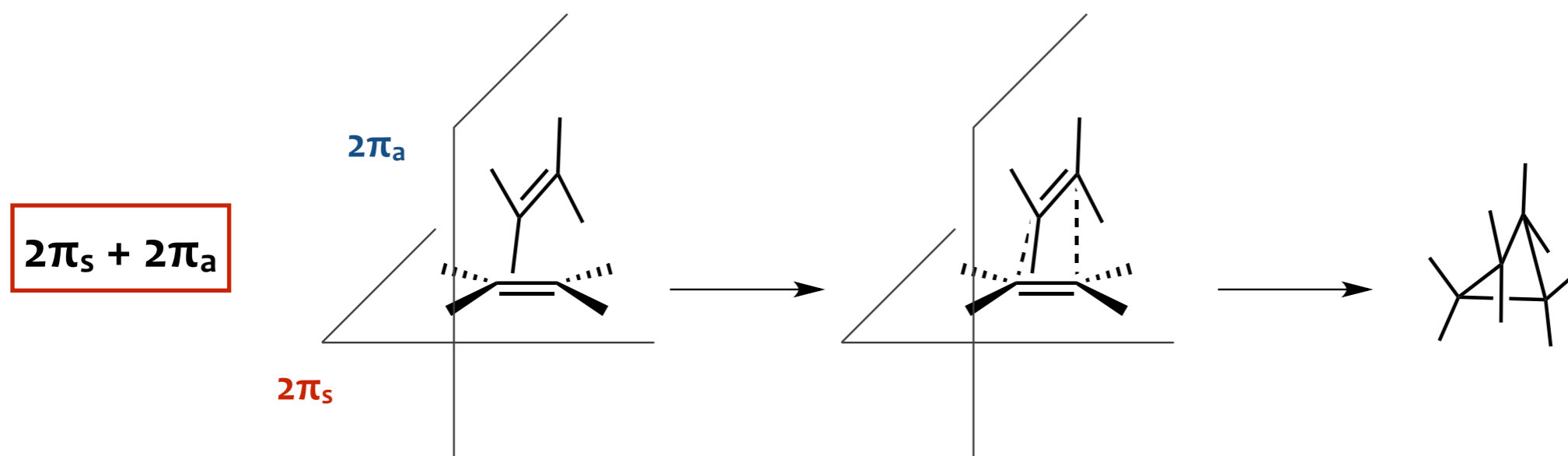
Then, a **suprafacial – suprafacial** approach is the least strained pathway ...



The HOMO of one partner should interact properly with the LUMO of the other partner



But a *suprafacial – antarafacial* approach might be also followed ...



The HOMO of one partner should interact properly with the LUMO of the other partner



... but the geometry is not favorable at all

This process can be considered at different levels

- FMO approach: just evaluating HOMO-LUMO interactions*
- Orbital diagram correlation: assessment of full orbital evolution*
- State diagram correlation: assessment of electronic state evolution*

Orbitals with different symmetries do not mix



Only states with the same symmetry mix in configuration interaction

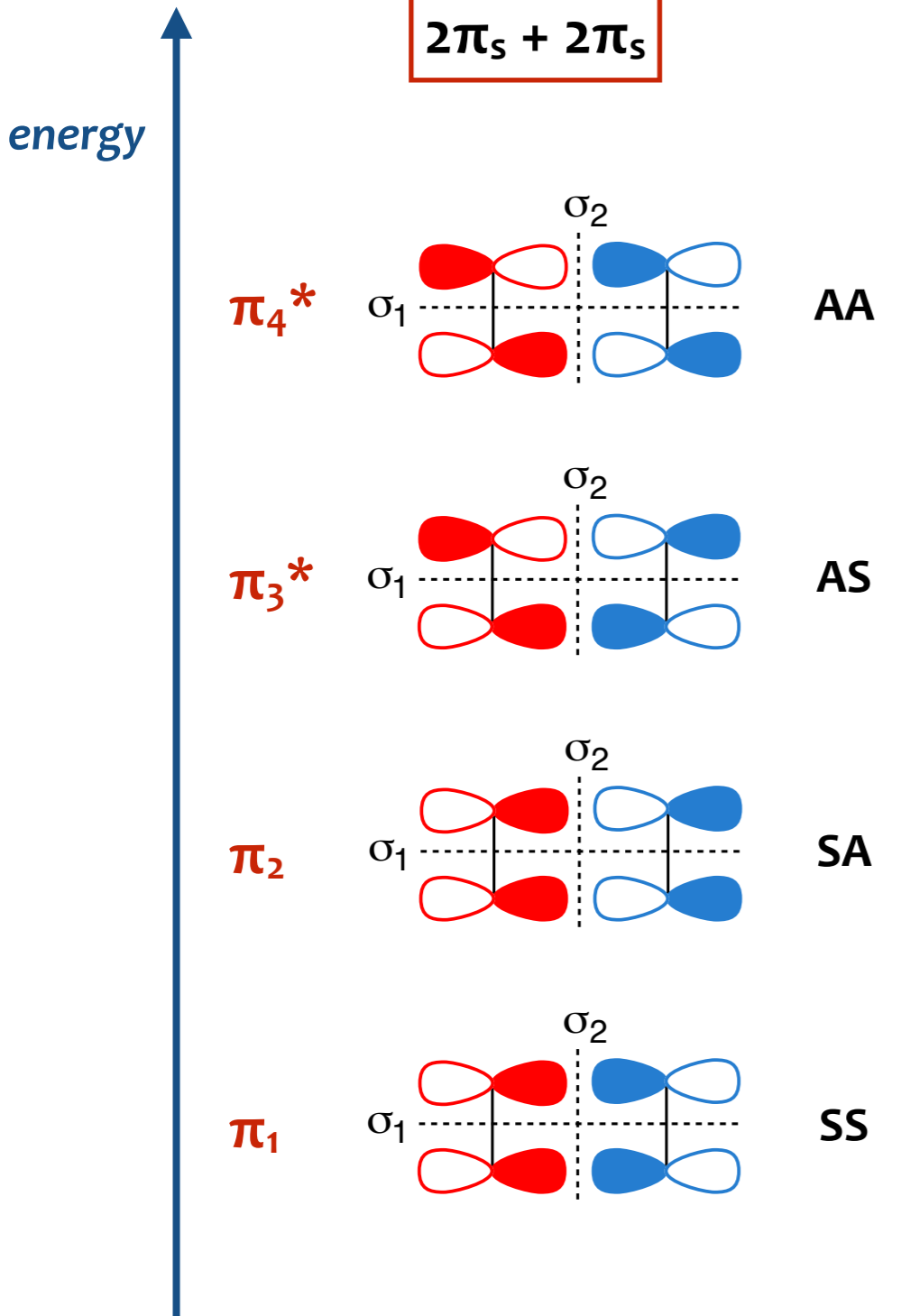


States of the same symmetry do not cross

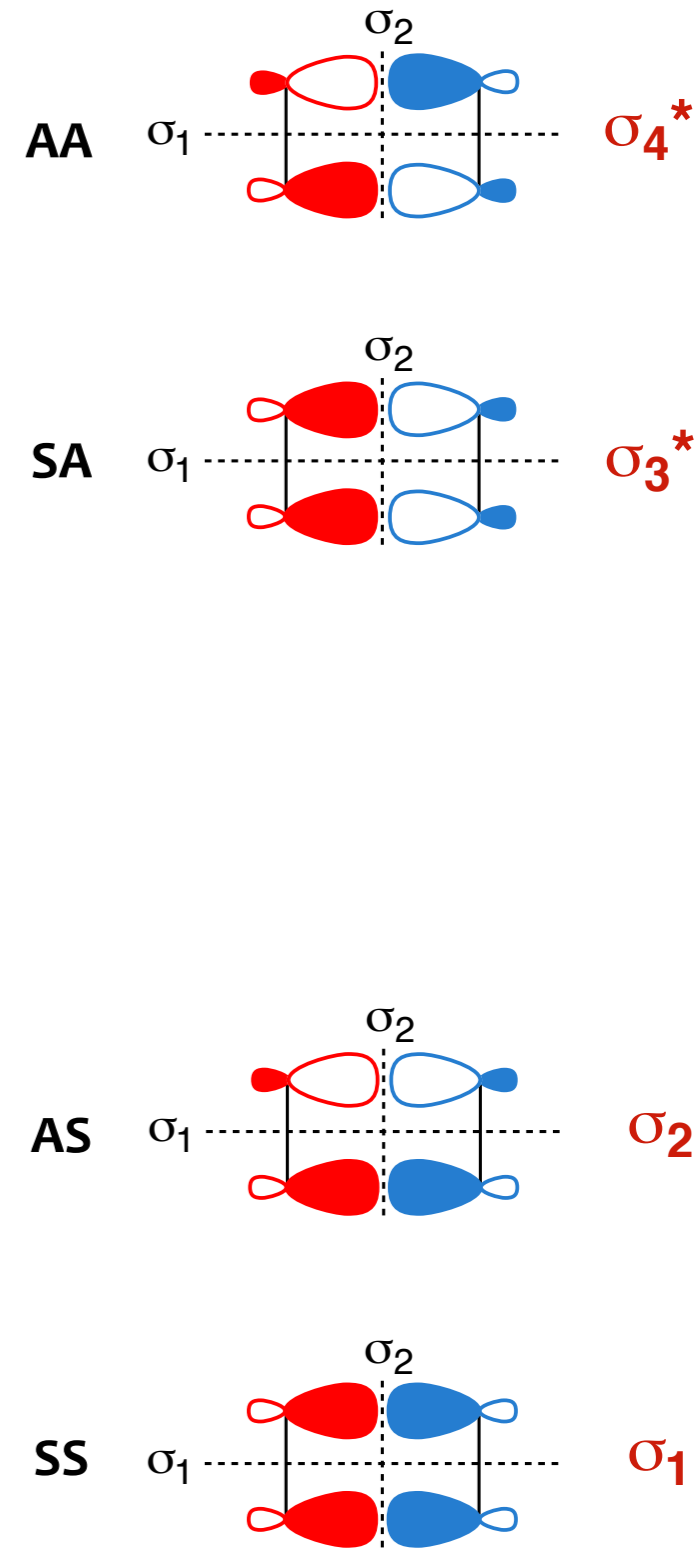


4-Membered Rings

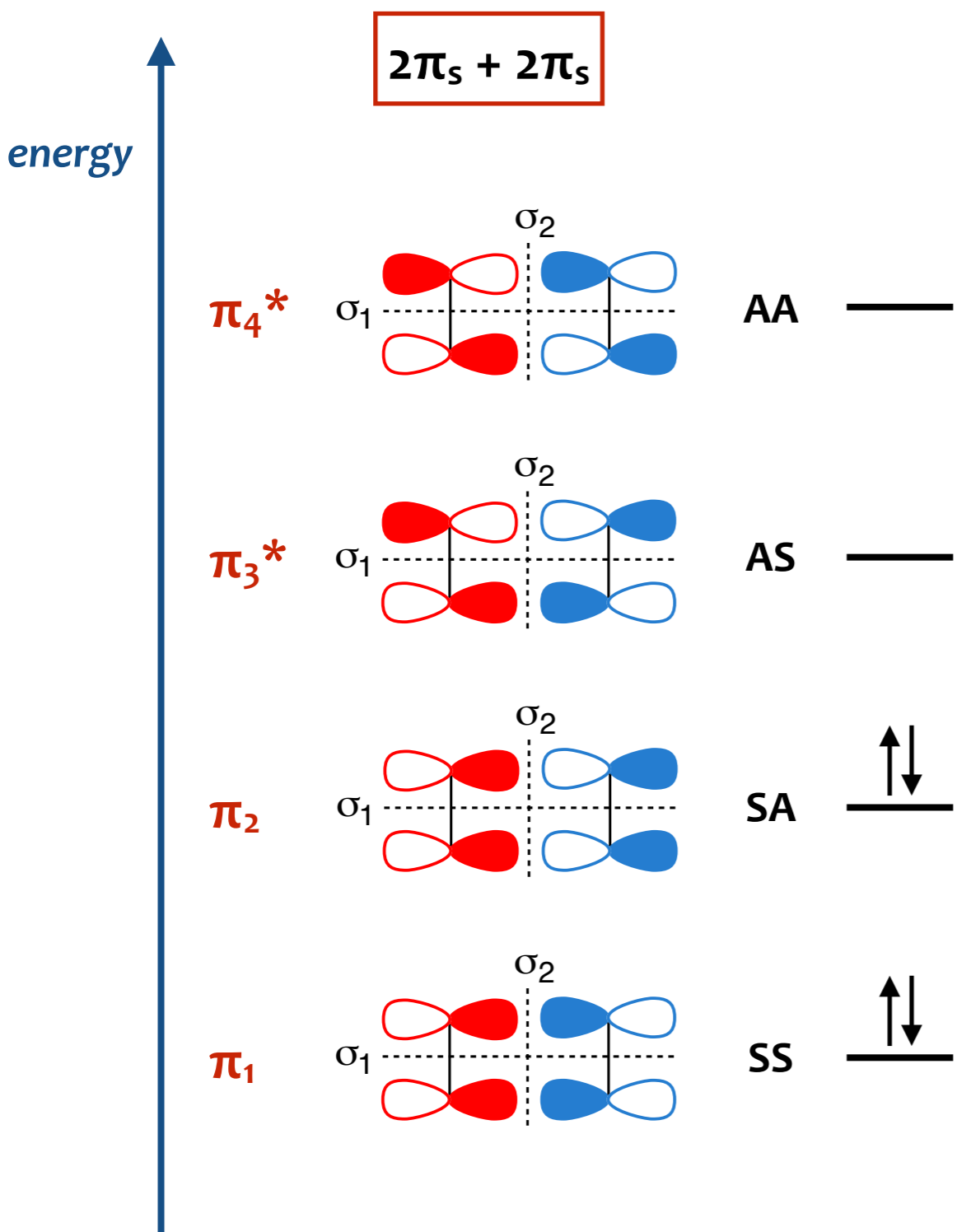
$$2\pi_s + 2\pi_s$$



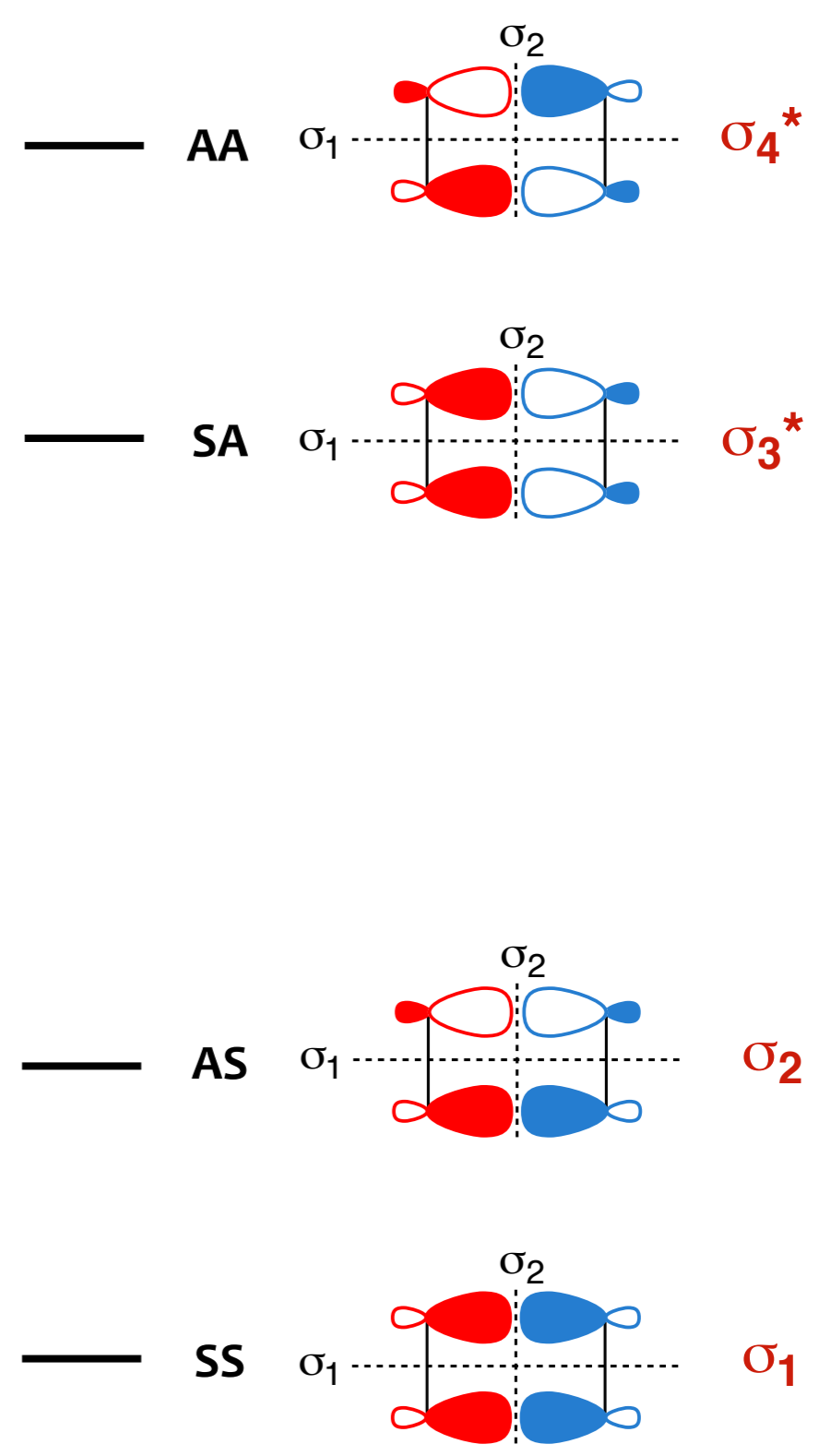
Thermal cycloaddition



4-Membered Rings

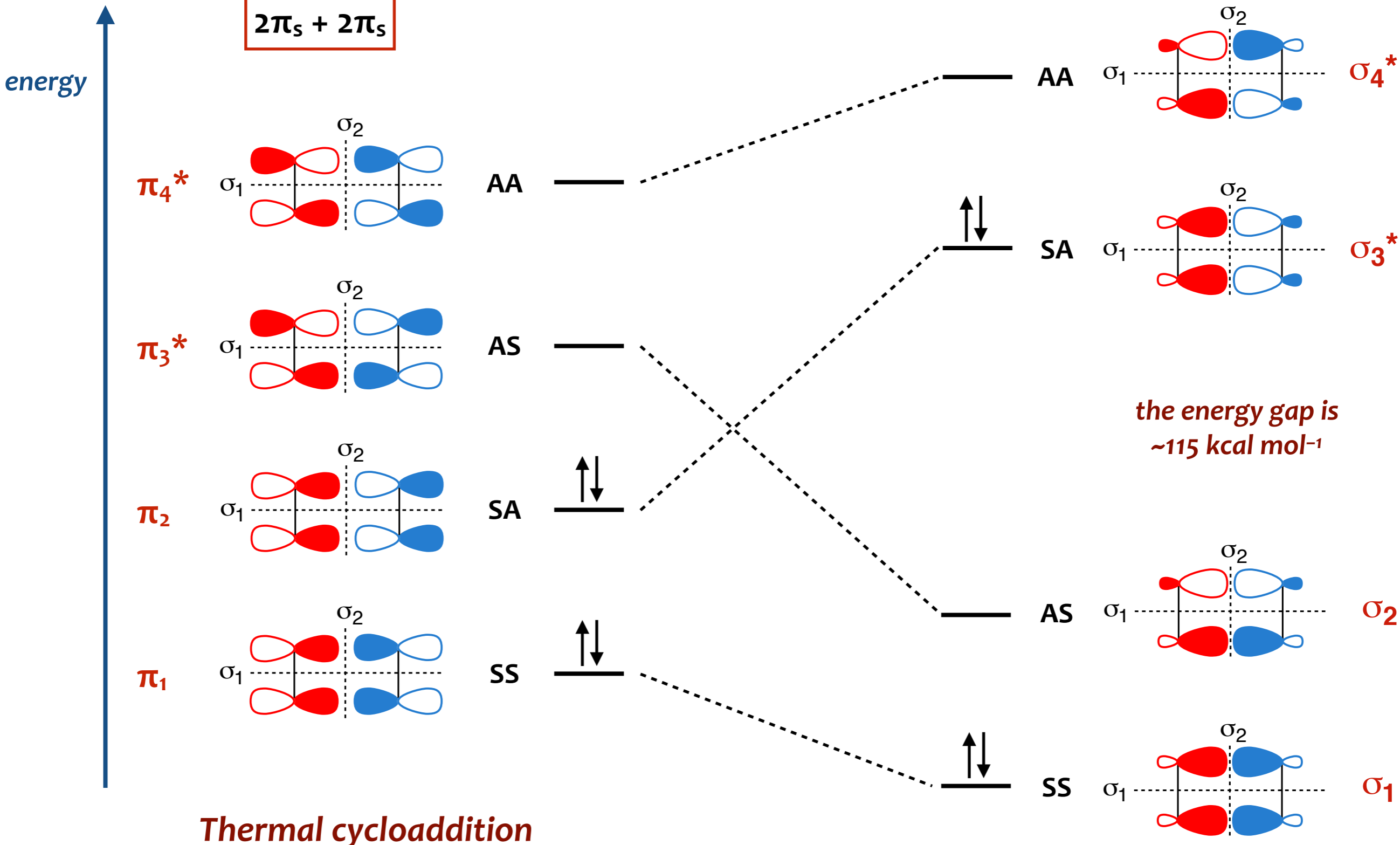


Thermal cycloaddition

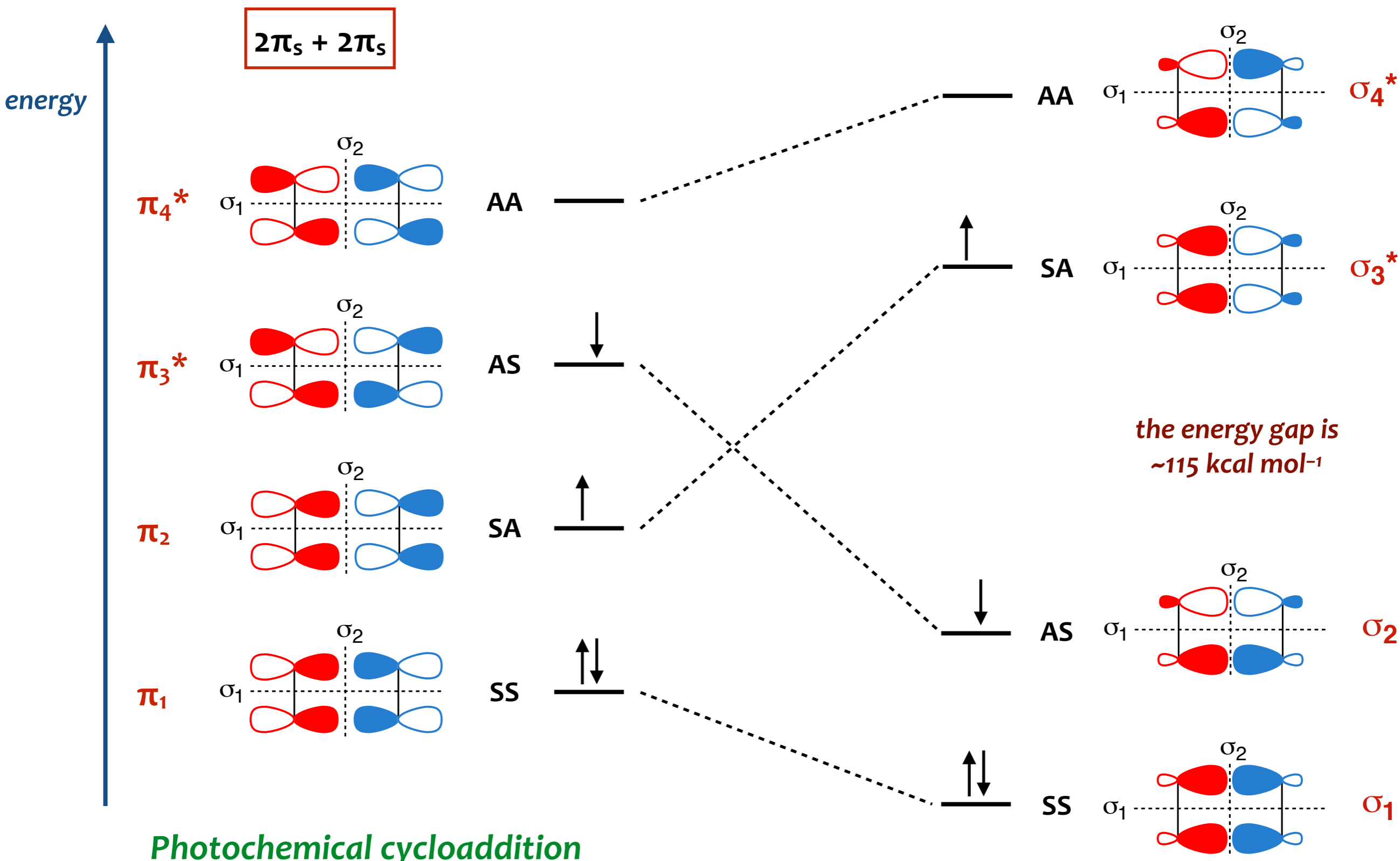


4-Membered Rings

$$2\pi_s + 2\pi_s$$



4-Membered Rings



This process can be considered at different levels

- FMO approach: just evaluating HOMO-LUMO interactions*
- Orbital diagram correlation: assessment of full orbital evolution*
- State diagram correlation: assessment of electronic state evolution*

Orbitals with different symmetries do not mix



Only states with the same symmetry mix in configuration interaction



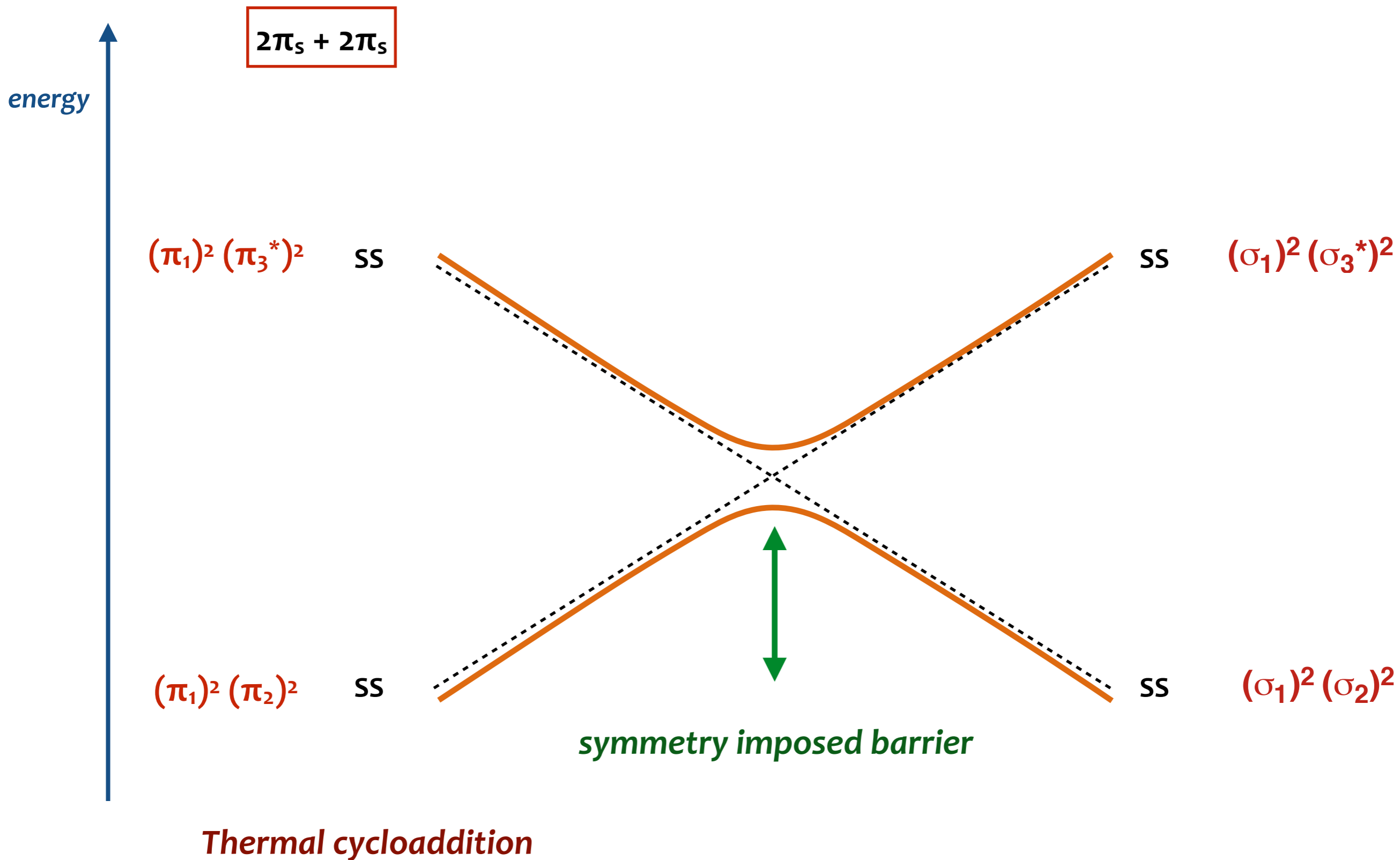
States of the same symmetry do not cross

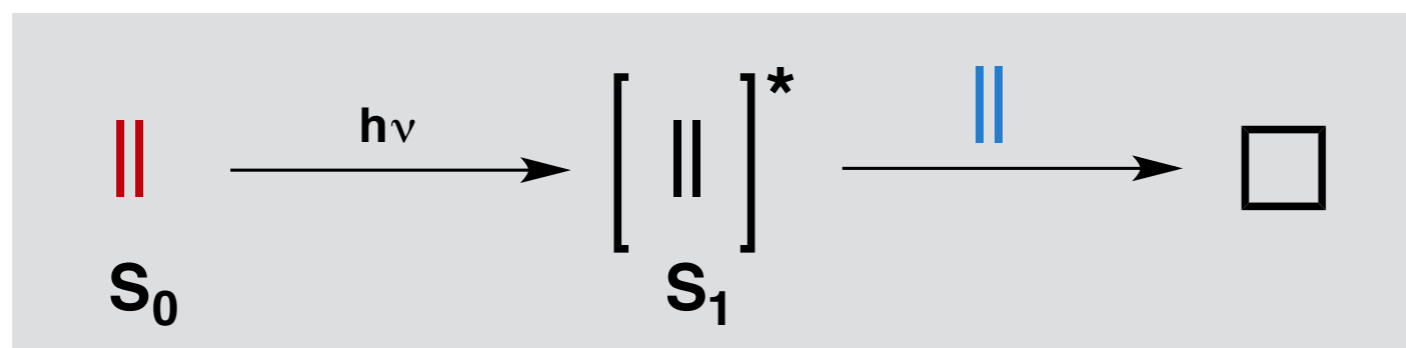


$$2\pi_s + 2\pi_s$$



Thermal cycloaddition





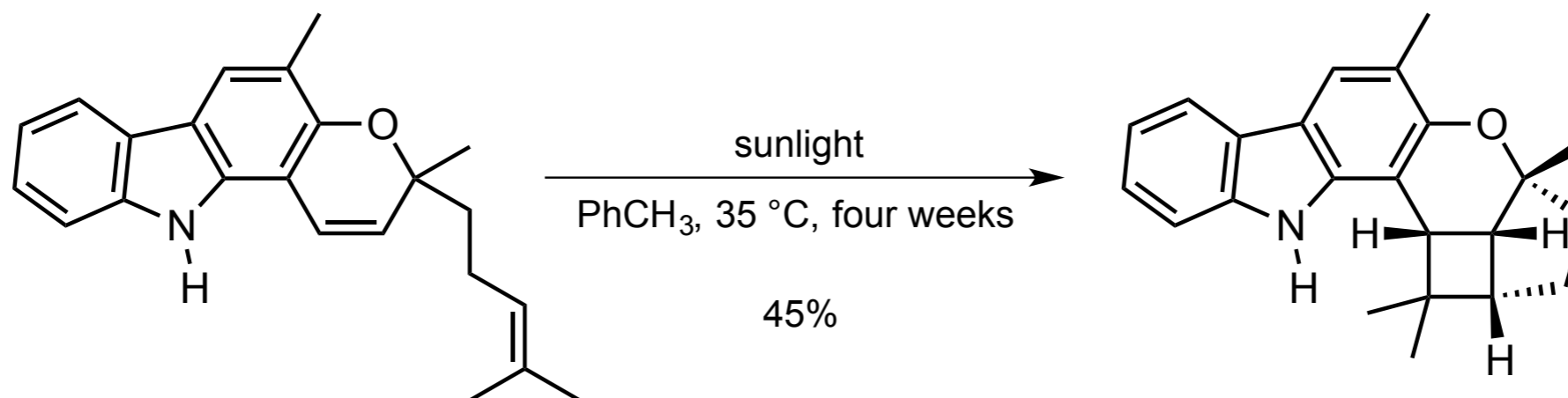
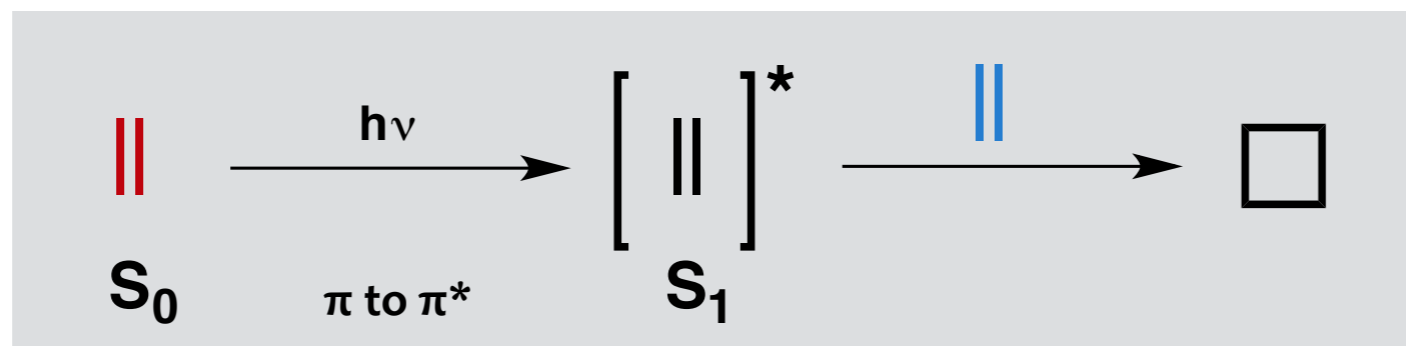
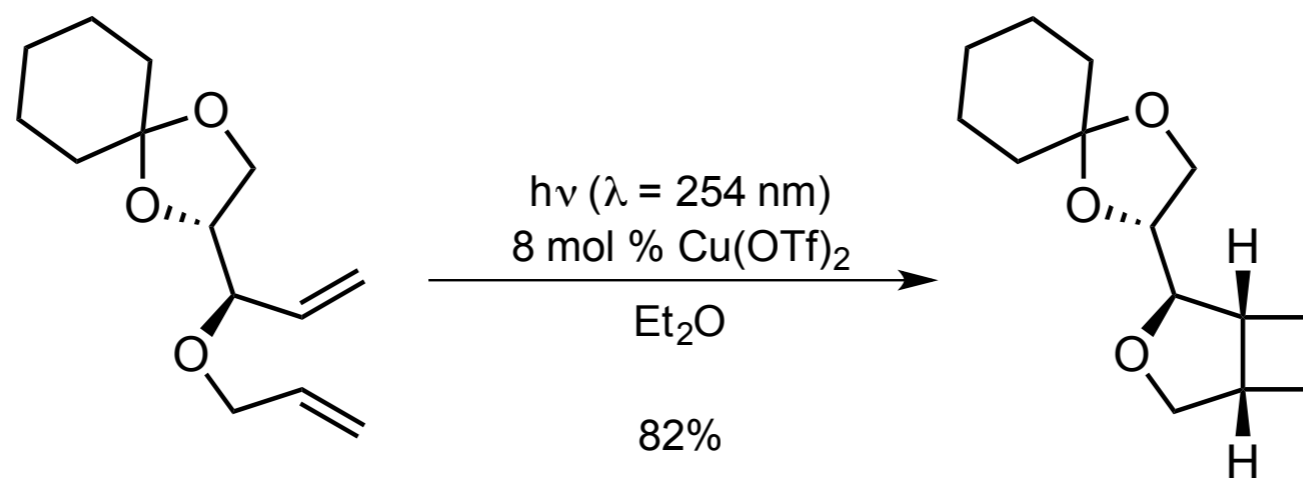
Concerted reaction, stereospecific for both olefins

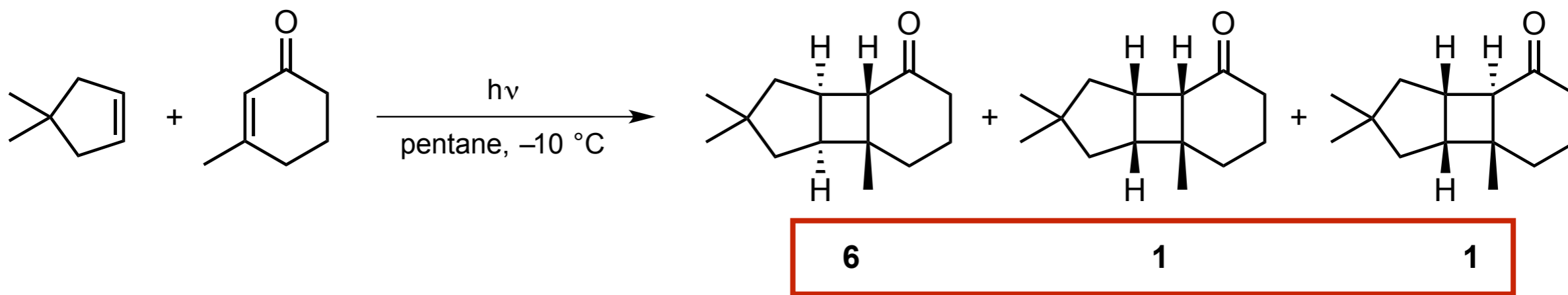
■ **Limitations:** High energy S_1 state for non-conjugated alkenes

Short lived S_1 state

■ **Scope:** Aryl conjugated alkenes

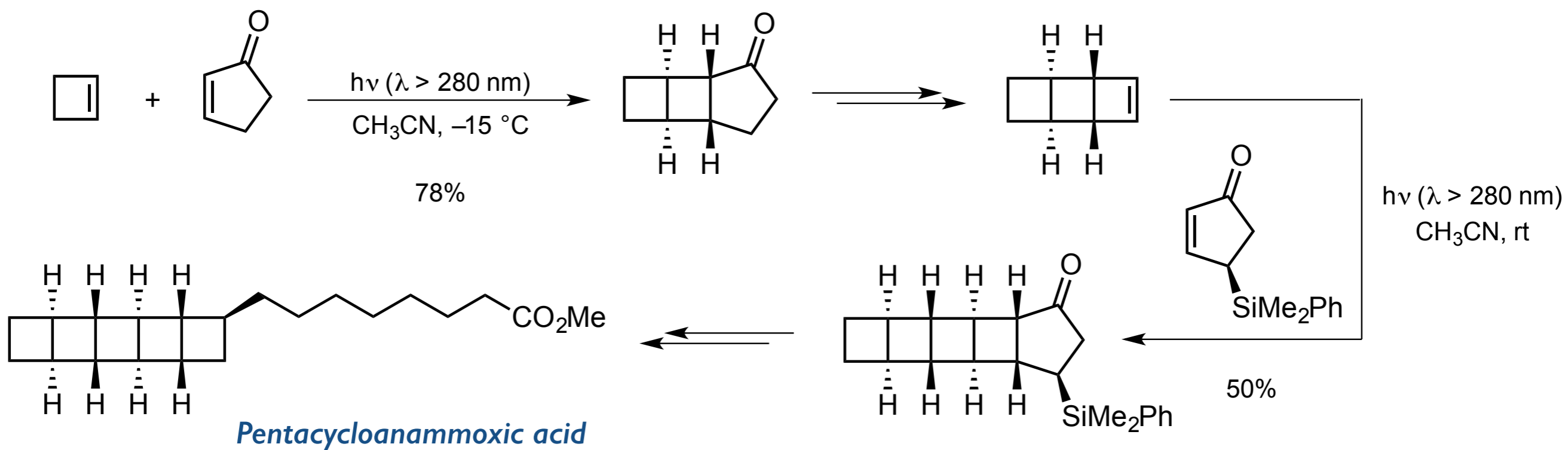
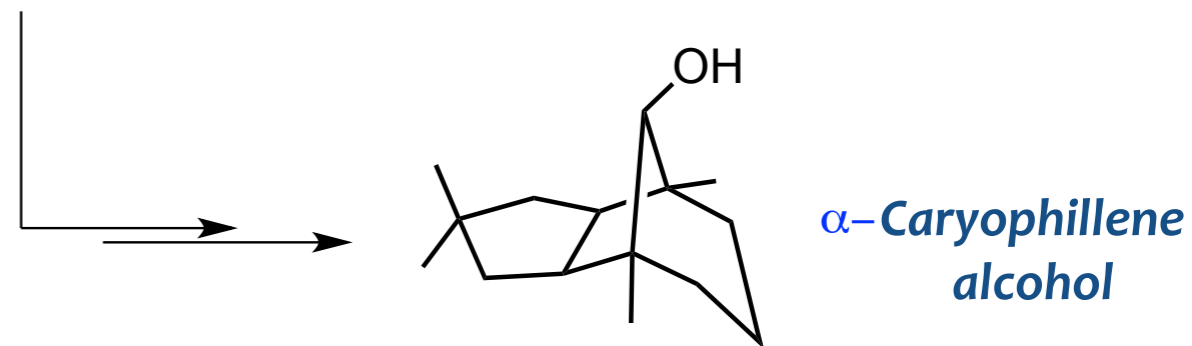
Alkenes through complexation to a transition metal (Cu)

Knölker, H.-J. *CEJ* 2013, 19, 14098Ghosh, S. *OL* 2004, 6, 1903



One of the first photochemical [2+2] cycloadditions

Corey, E. J. JACS 1964, 86, 1652

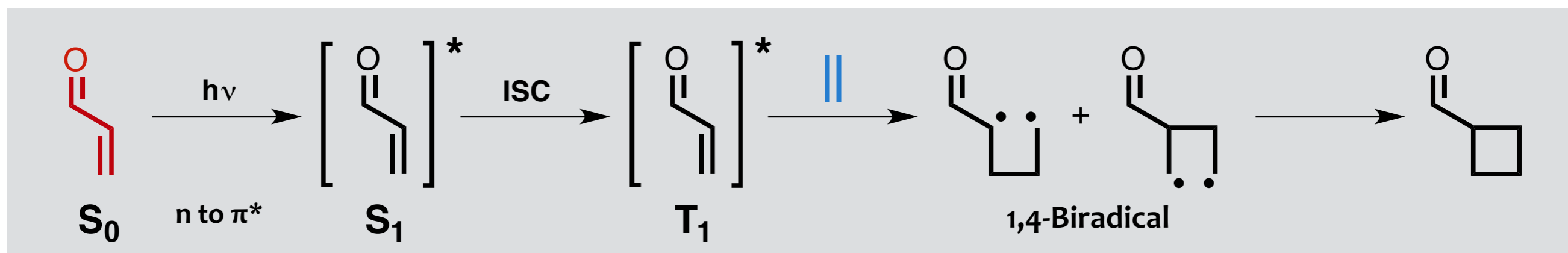


Corey, E. J. JACS 2006, 128, 3118

It is desirable for a successful intermolecular [2+2] photocycloaddition to reach a relatively long-lived excited state, which is available for attack by another olefin

α,β -Unsaturated ketones or esters

The mechanism becomes much more complex ...

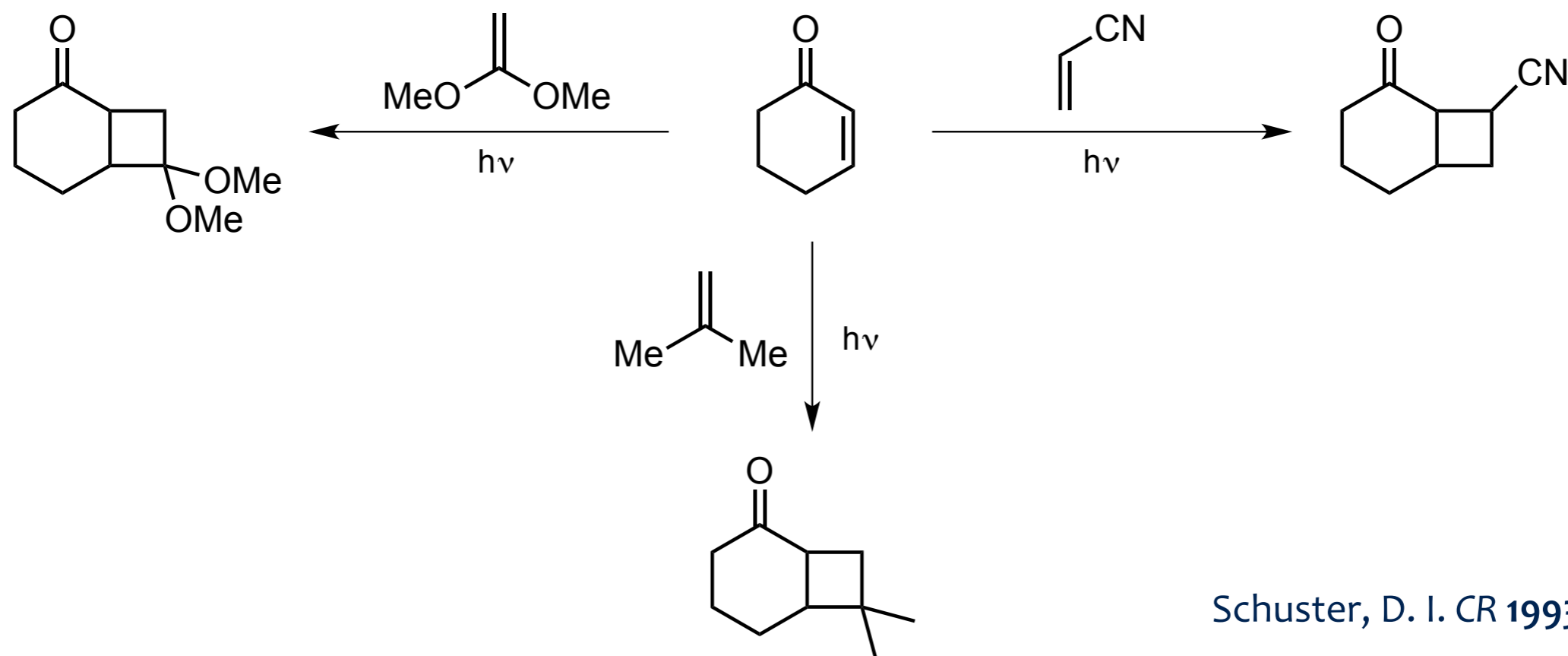
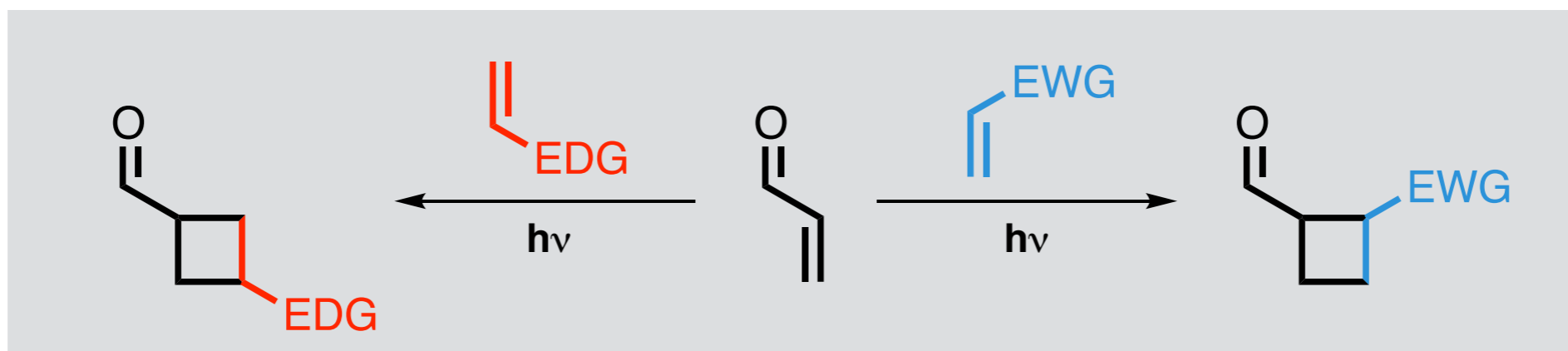


... and the stereocontrol is much more elusive

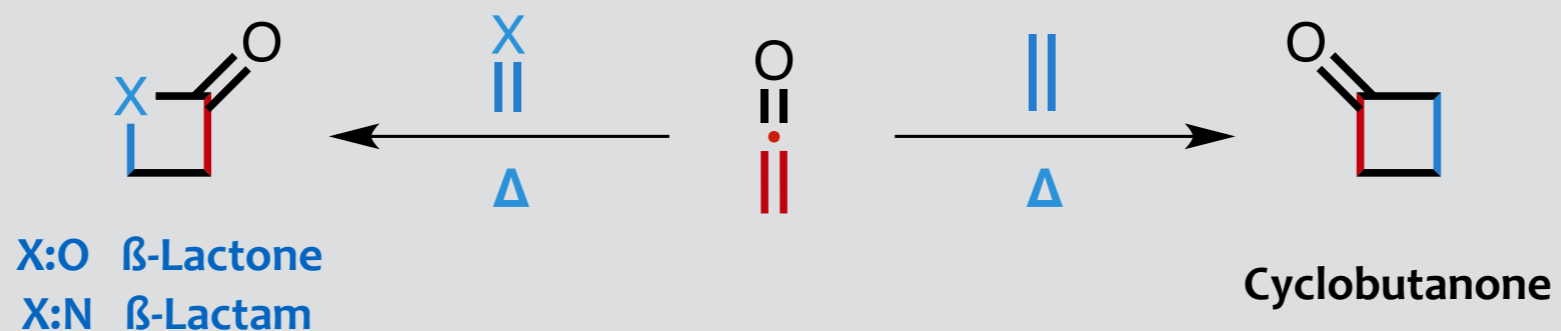
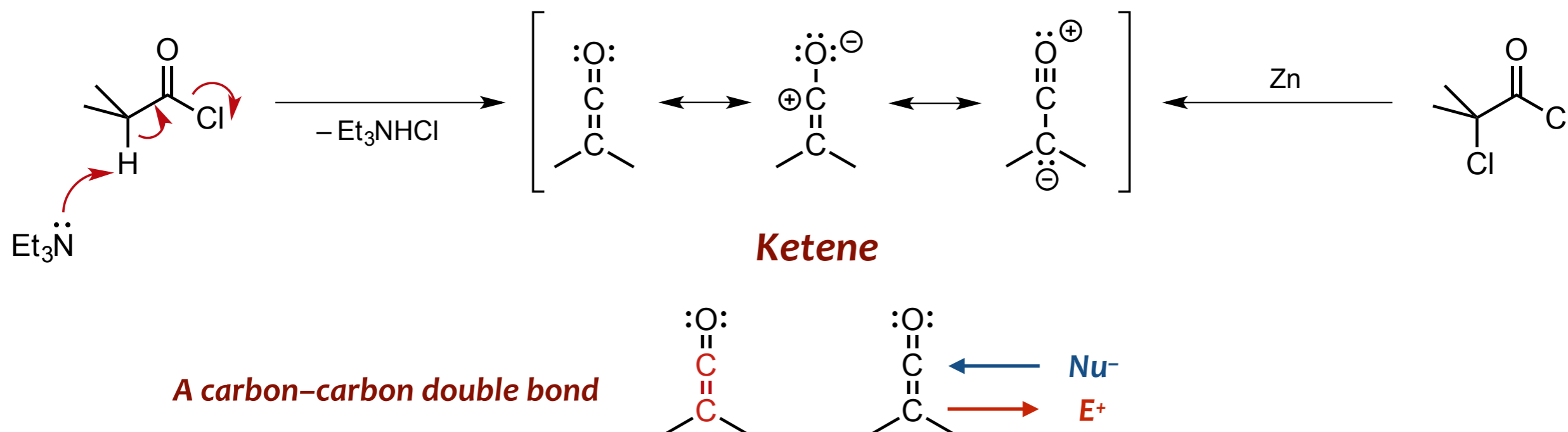
Bach, T. *Synthesis* **1998**, 683; Hoffmann, N. *CR* **2008**, 108, 1052

Bach, T. *ACIE* **2011**, 50, 1000; Bach, T. *CR* **2016**, 116, 9748

Such a [2+2] photocycloaddition is also regioselective

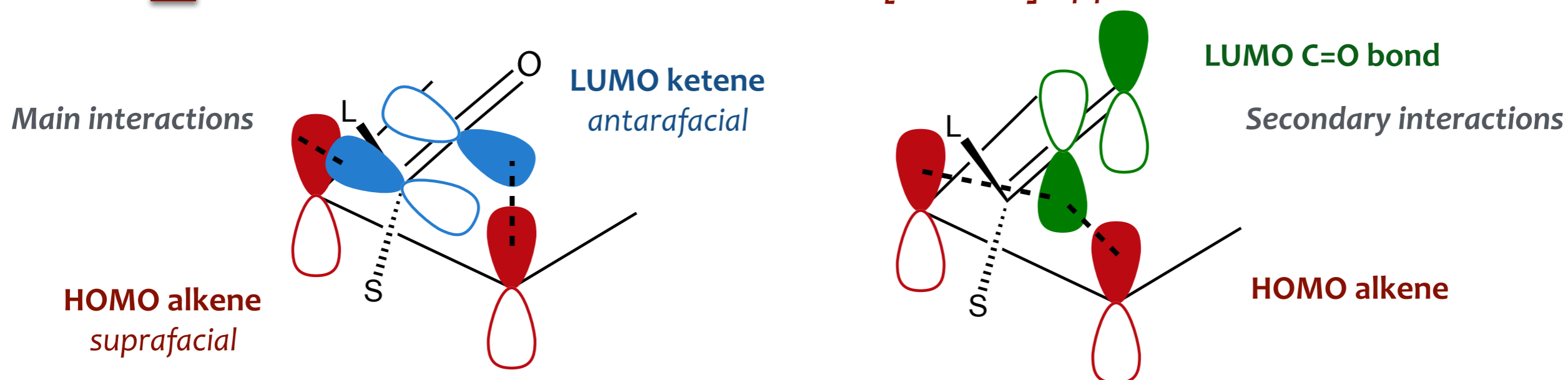


Can [2+2] cycloadditions proceed under thermal conditions?



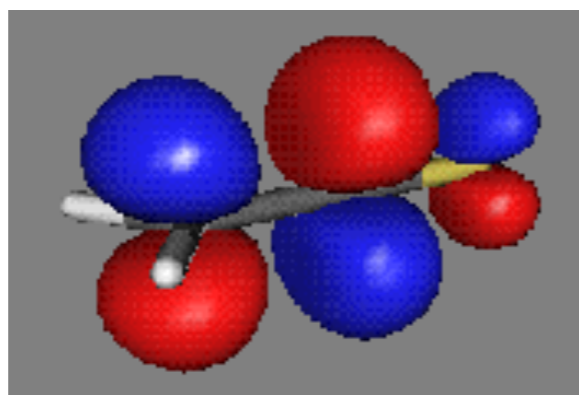
The mechanism is still controversial

■ **Concerted mechanism:** Involves a $[2\pi_s+2\pi_a]$ approach

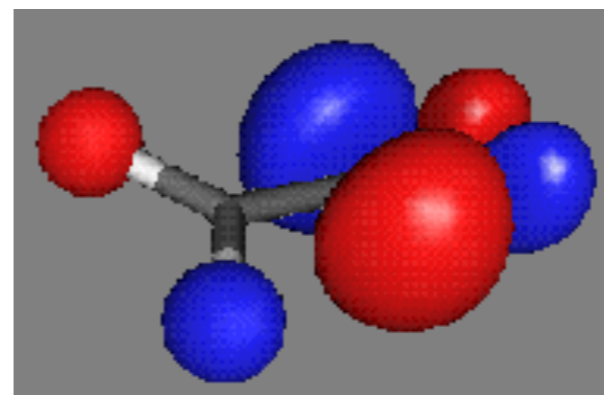


Actually, a close inspection to the orbitals of a ketene reveals that two unoccupied orbitals, close in energy, can play a crucial role in the cycloaddition

LUMO 1



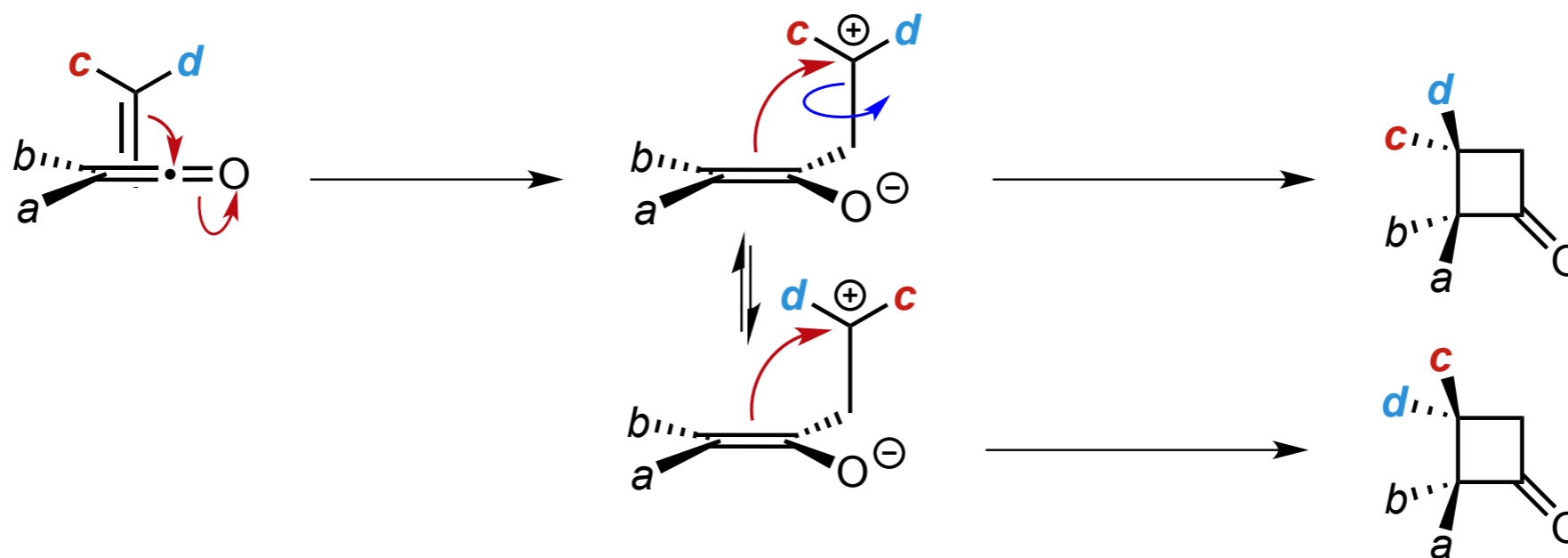
LUMO 2



The mechanism is still controversial

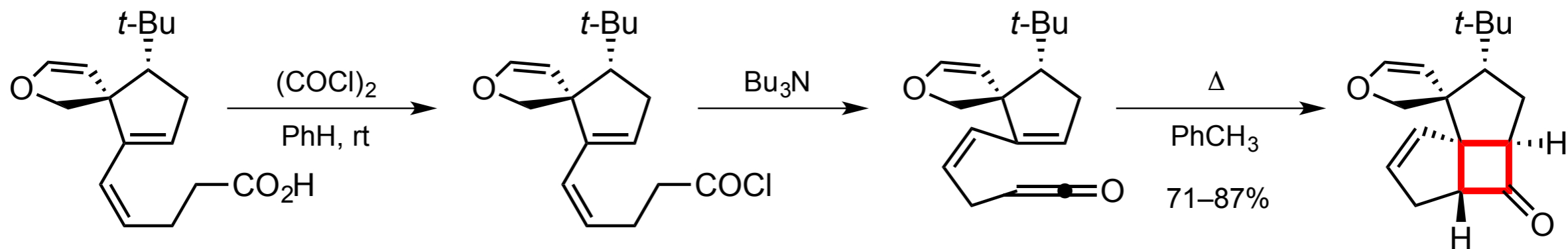
Two-step mechanism:

The cycloaddition can also be explained by means on a two-step process based on the nucleophilic and electrophilic character of an olefin and the ketene respectively

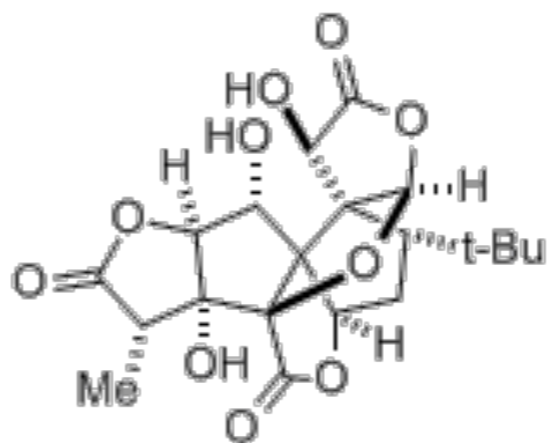


For β -lactams, Cossio, F. P. *JACS* 1993, 115, 995

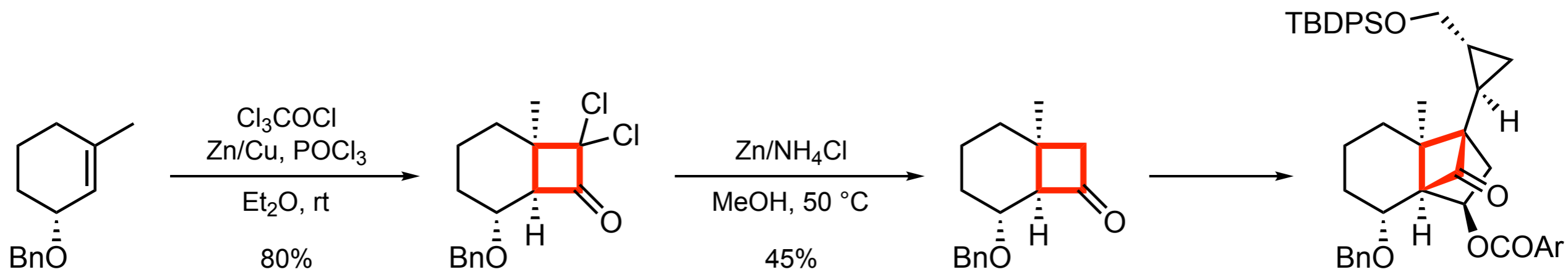
4-Membered Rings



Ginkgolide B



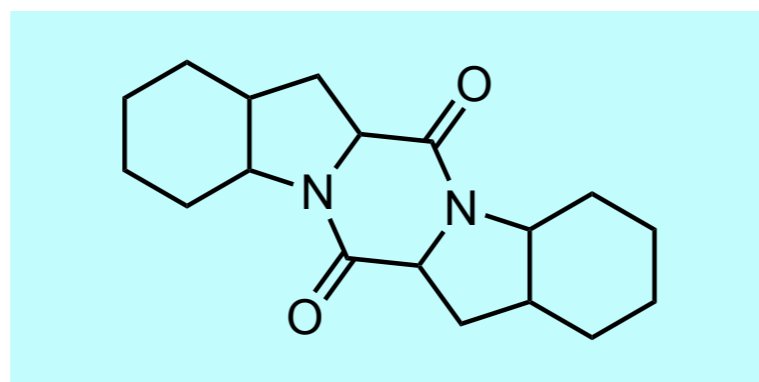
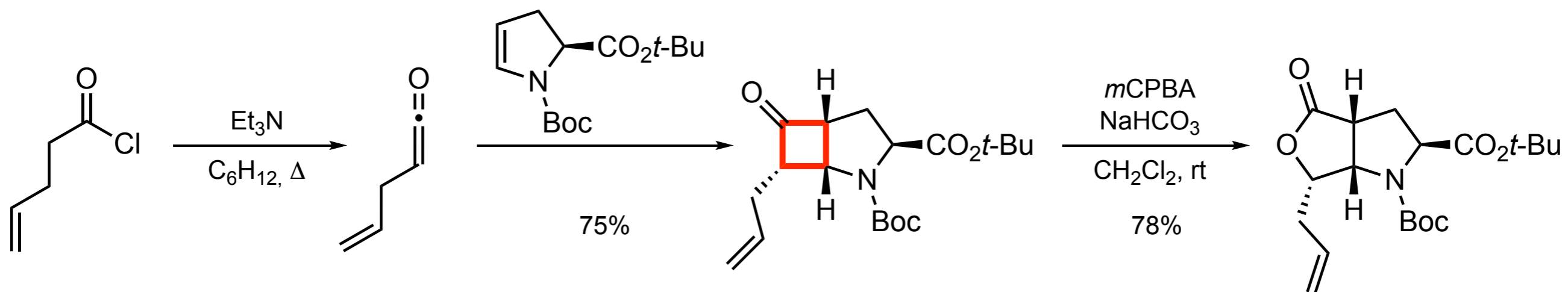
Corey, E. J. *JACS* **1988**, *110*, 649



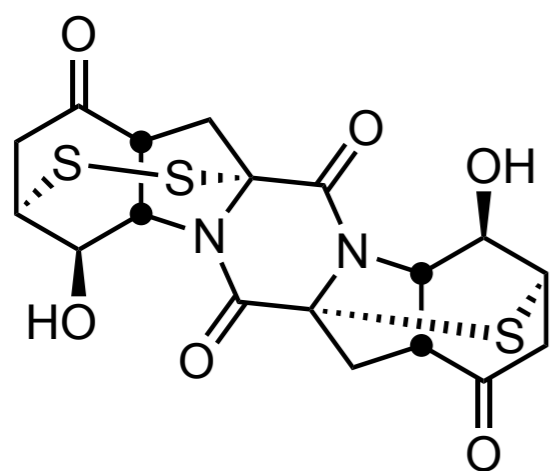
DEFG Rings of solanoeclepin A

Li, W.-D. Z; Qiu, F. G. *OL* **2019**, *21*, xxx

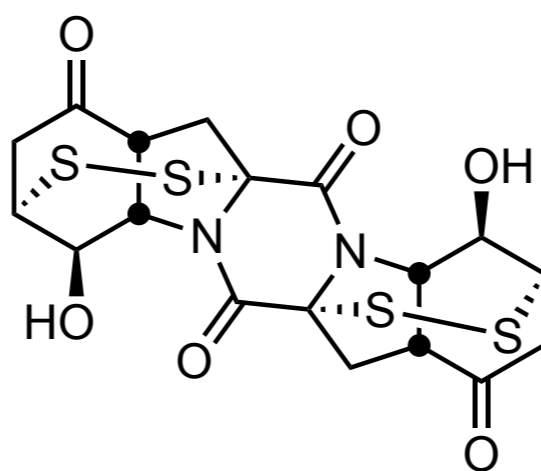
4-Membered Rings



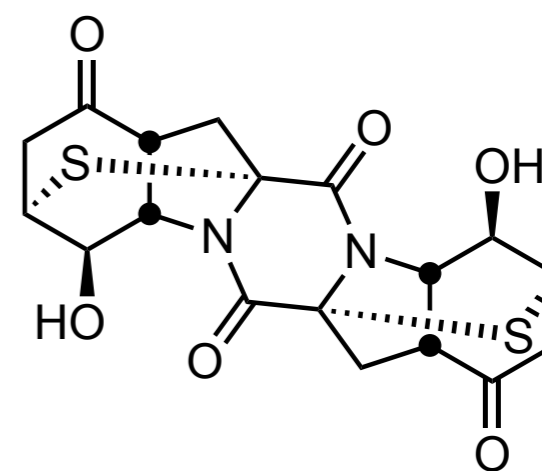
Common intermediate for the synthesis of thiodiketopiperazine mycotoxins



Epicoccin A

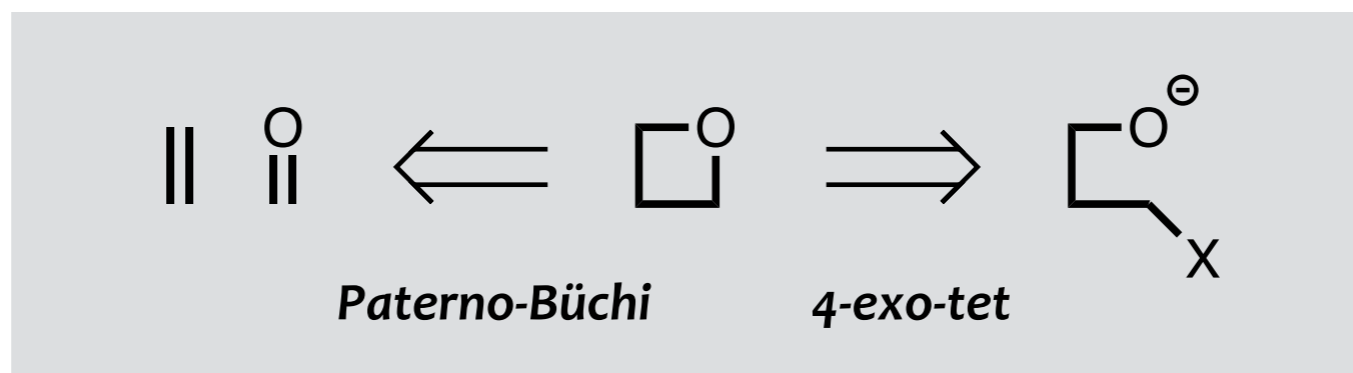


Epicoccin C



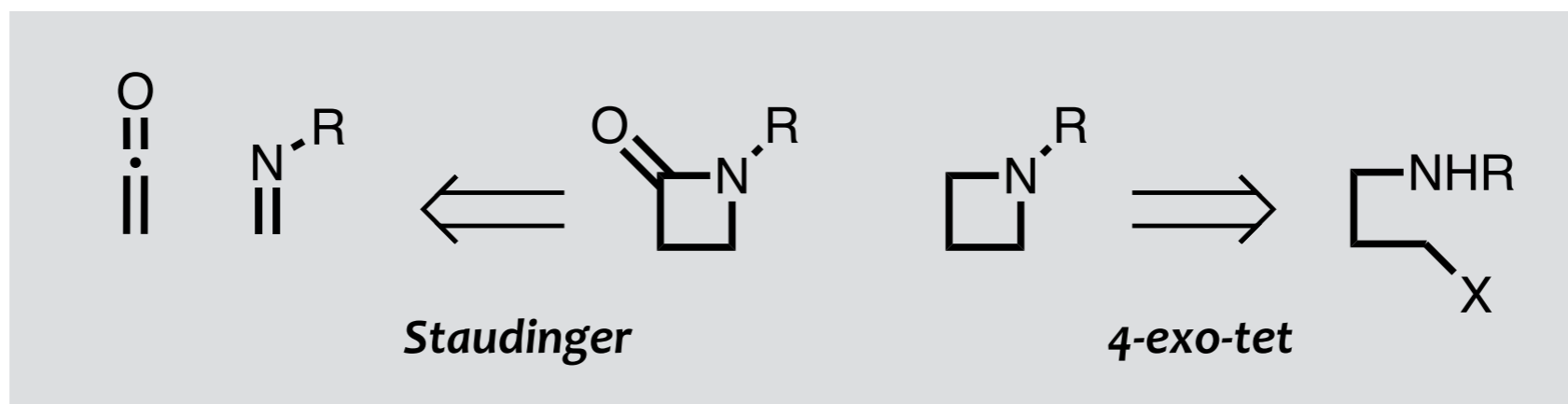
Epicoccin D

Oxetanes can be prepared by intramolecular etherification or formal [2+2] photocycloaddition



Bull, J. A. CR 2016, 116, 12150

Azetidines are usually prepared by cyclization,
while **2-azetidinones** (β -lactams) by addition of imines to ketenes

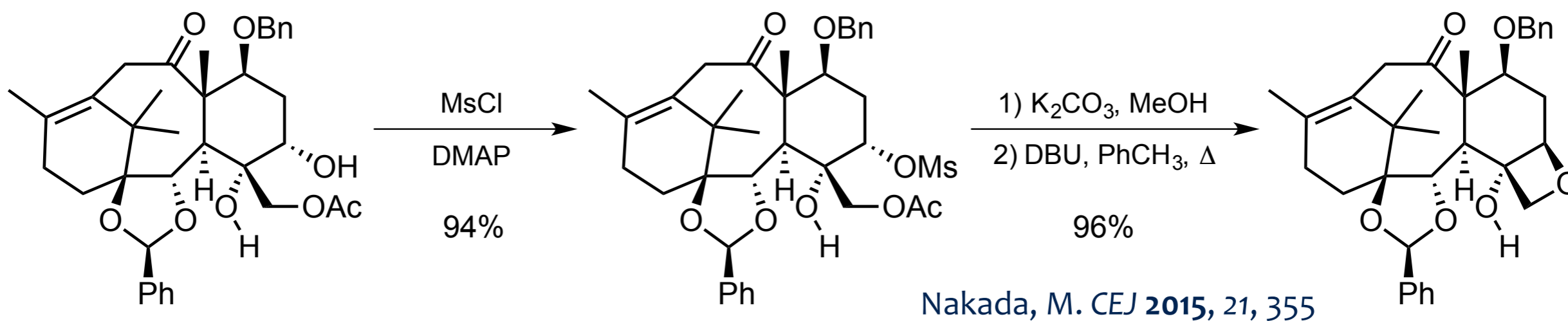


Brandi, A. CR 2008, 108, 3988

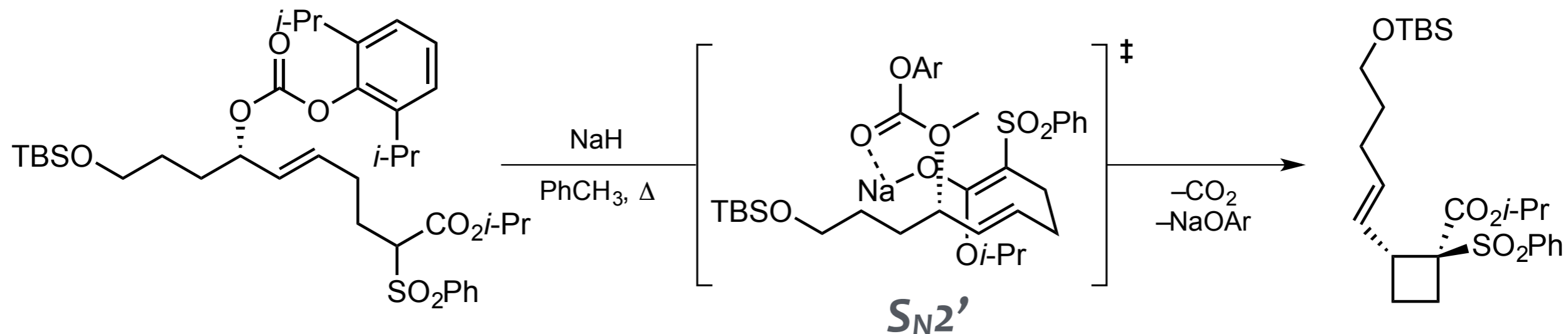
4-Membered Rings

	<i>Exo</i>			<i>Endo</i>		
	<i>Tet</i>	<i>Trig</i>	<i>Dig</i>	<i>Tet</i>	<i>Trig</i>	<i>Dig</i>
3	✓	✓	≈	✗	✗	✗
4	✓	✓	≈	✗	✗	✗
5	✓	✓	✓	✗	✗	≈
6	✓	✓	✓	✗	✓	✓
7	✓	✓	✓	✗	✓	✓

4-exo-tet

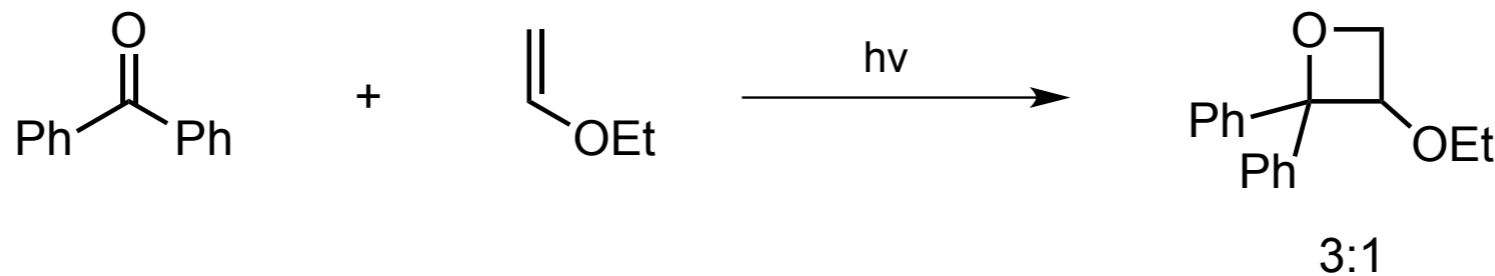
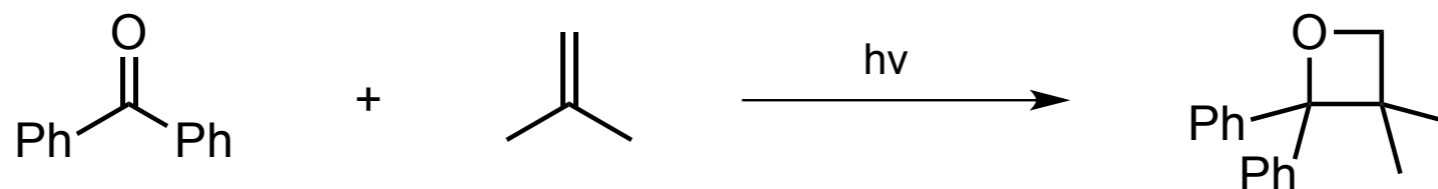
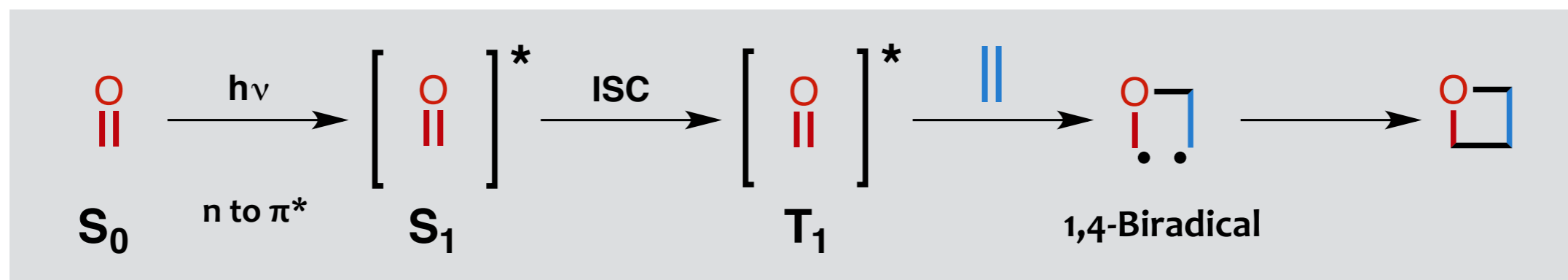


4-exo-trig

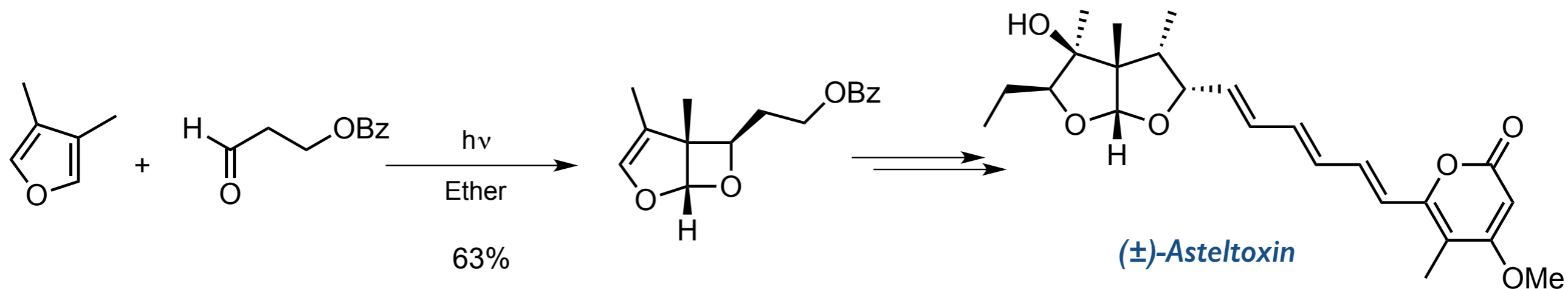
Boeckman, R. K. Jr. *OL* **2016**, *18*, 6136**dr 3:1**

Paterno-Büchi

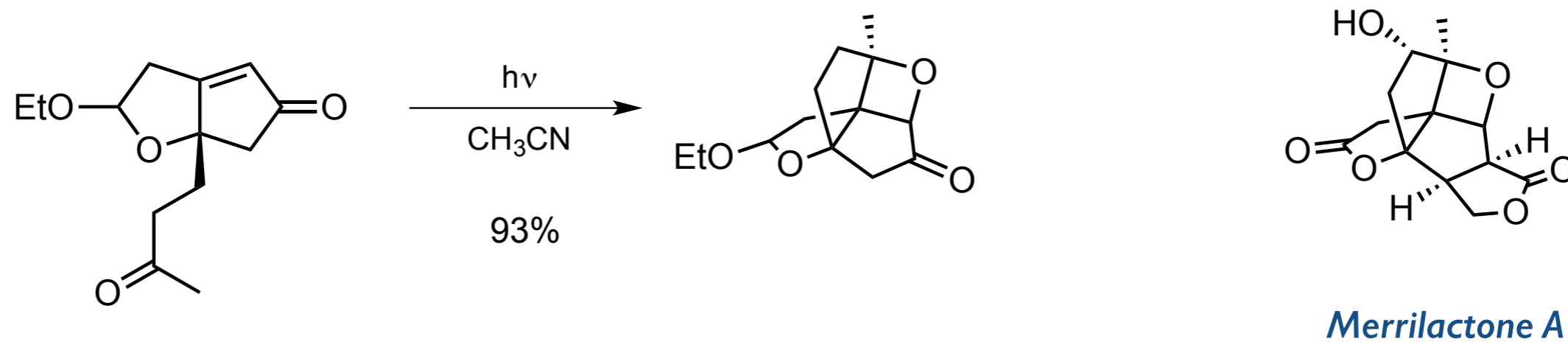
For a recent review, see
D'Auria, M. *Molecules* **2013**, *18*, 11384



The regioselectivity relies on the most stable 1,4-biradical intermediate

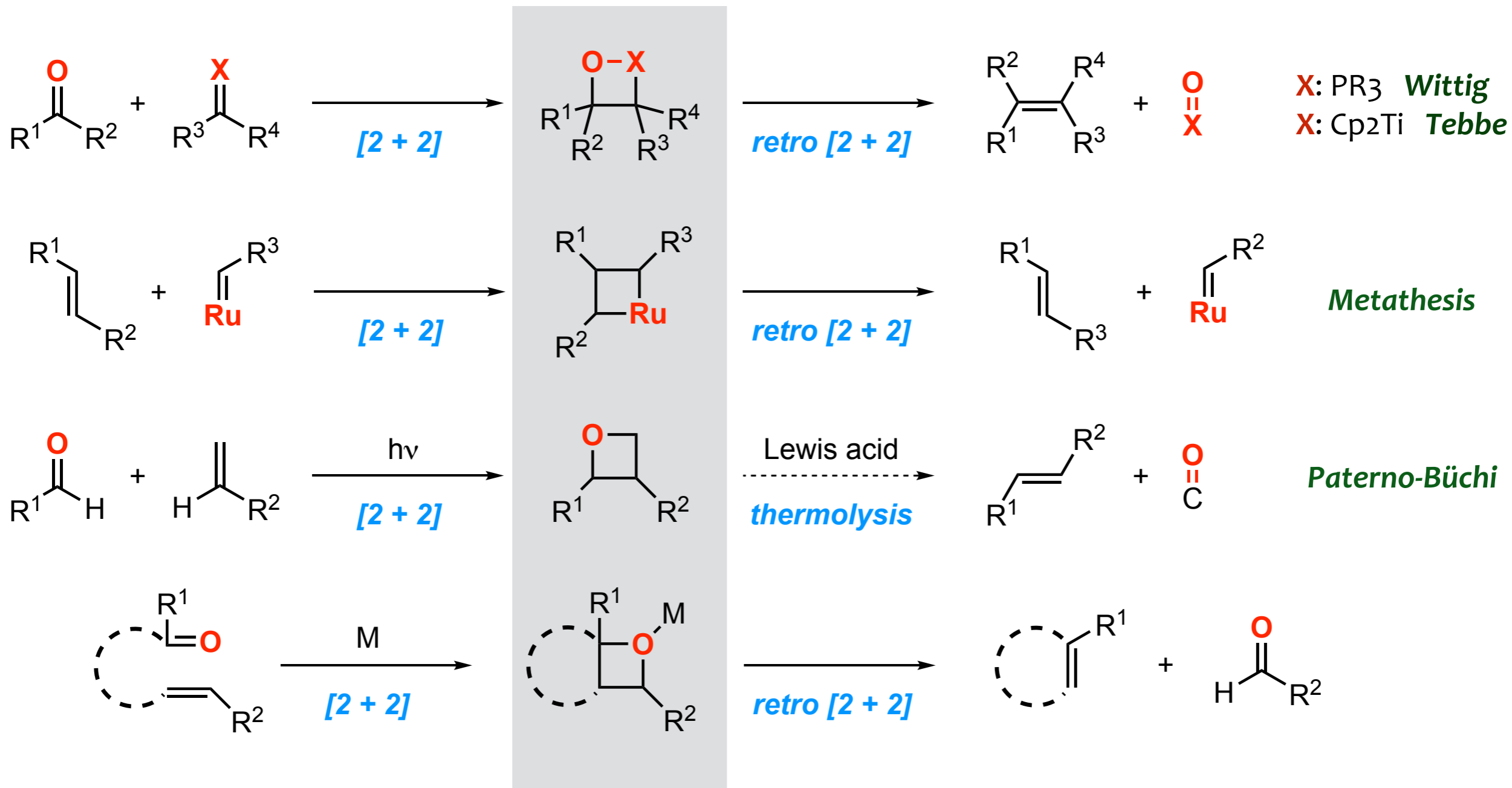


Schreiber, S. L. *JACS* **1984**, *106*, 4186



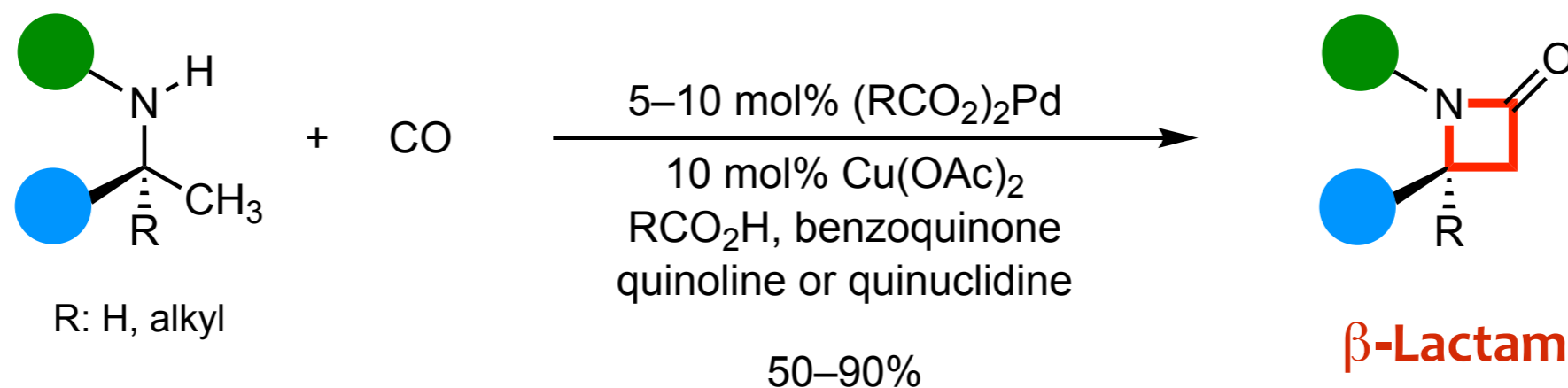
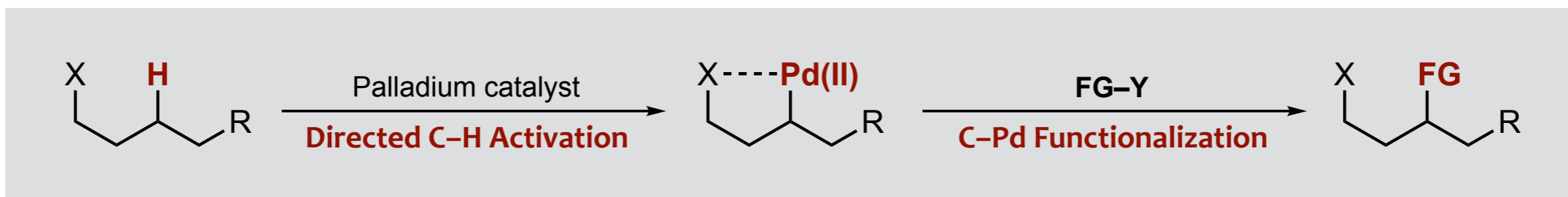
Greaney, M. F. *OL* **2005**, *7*, 3969

Four membered rings play a crucial role in a wide array of transformations



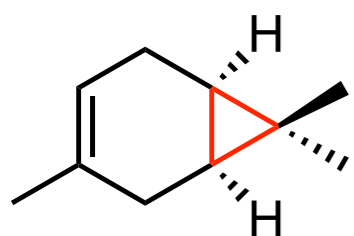
New transformations based on catalytic functionalization of C–H bonds have the potential to simplify the synthesis of complex molecules dramatically

Gaunt, M. J. *Nature* **2014**, 510, 129

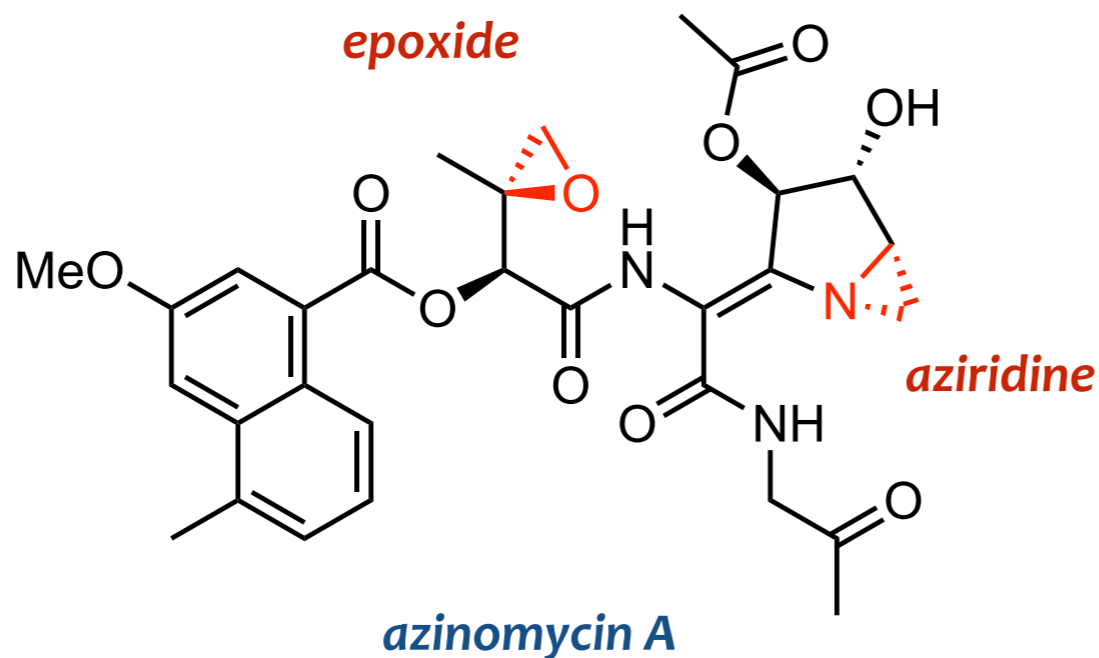


Gaunt, M. J. *Nature* **2014**, 510, 129; *Science* **2016**, 354, 851

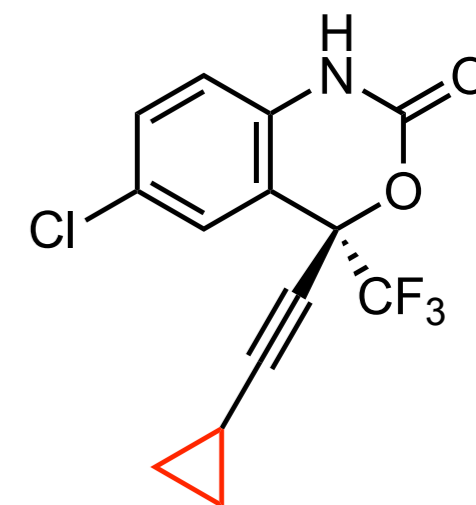
A variety of 3-membered rings are found in natural products and drugs ...



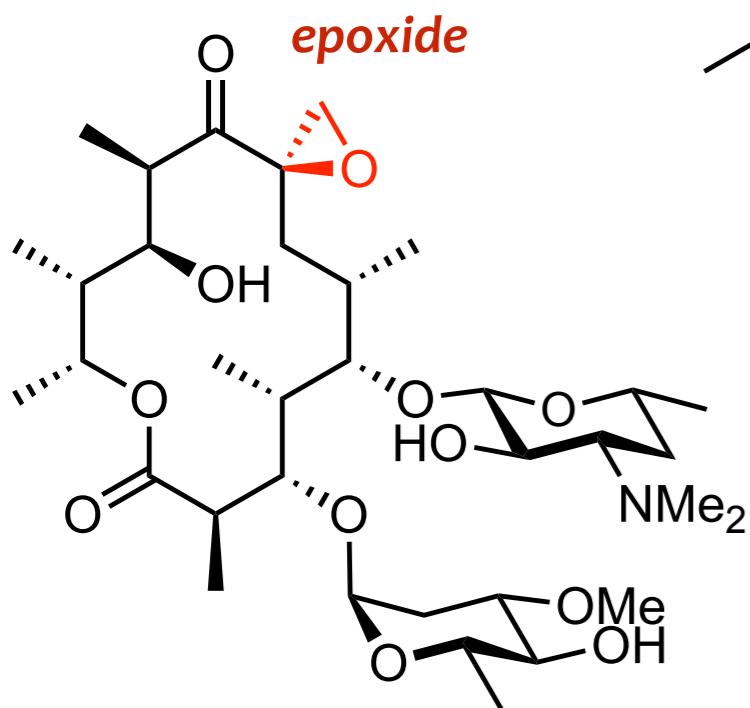
carene



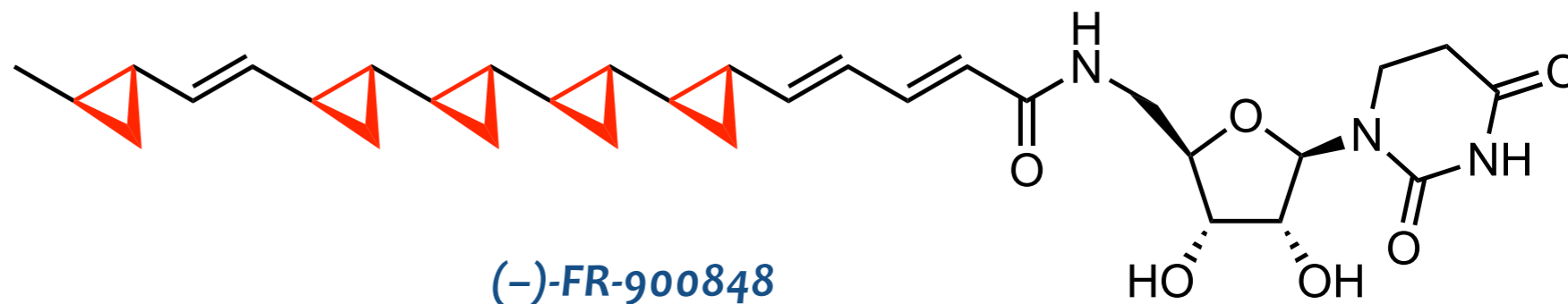
azinomycin A



efavirenz







oleandomycin

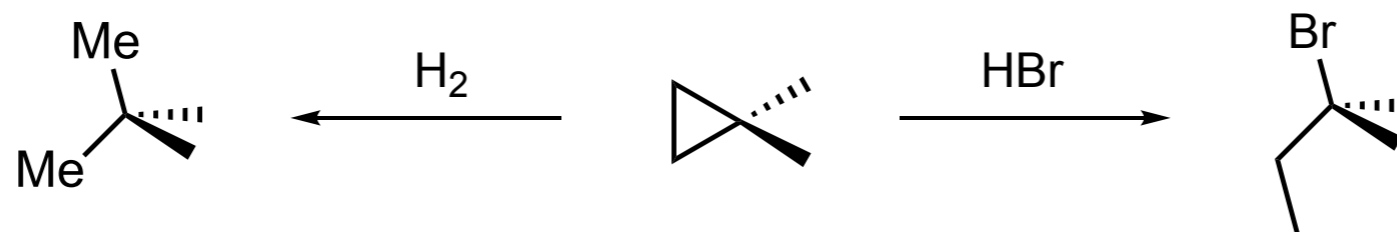
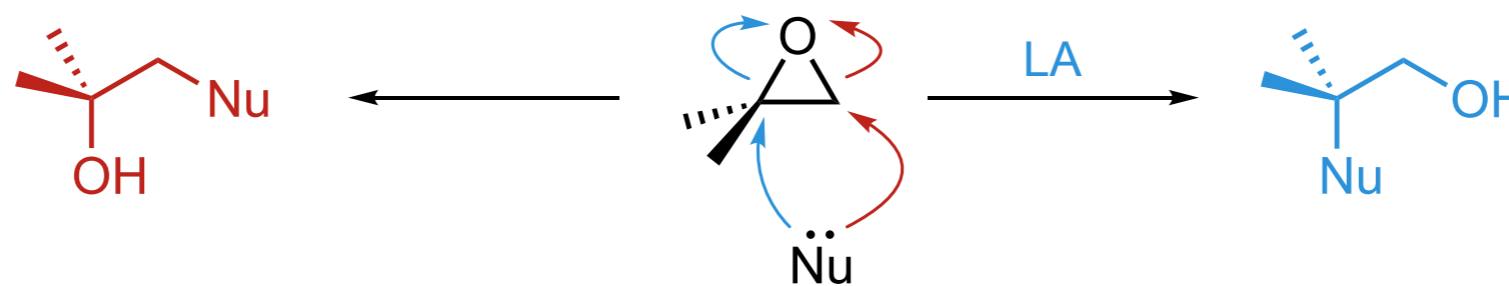


(-)-FR-900848

3-Membered rings are small and very strained cycles

Strain energies (kcal mol ⁻¹)				
	27.5	26.7	26.3	(18.9)

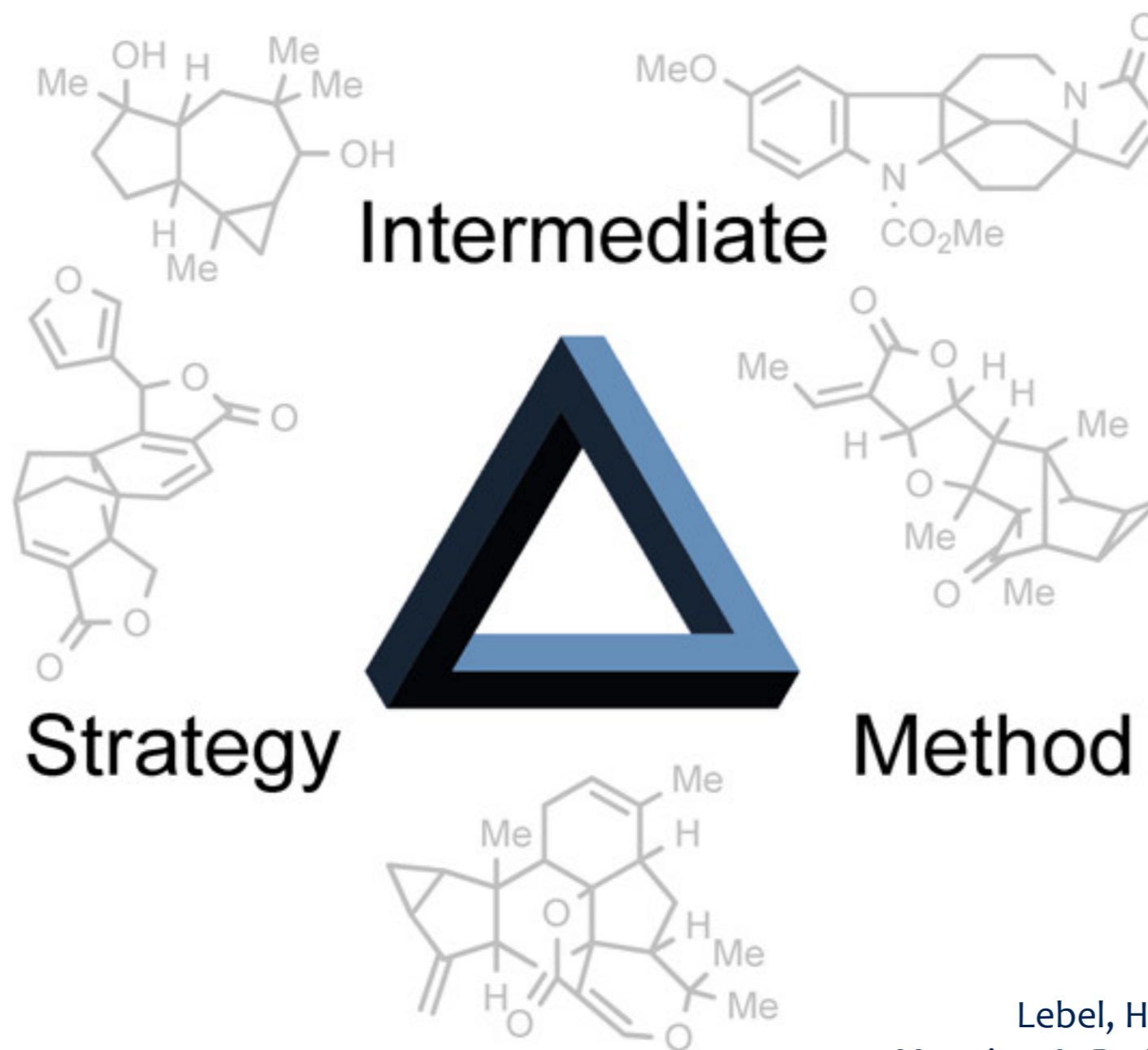
... so they can easily undergo ring opening reactions



Cyclopropanes can react like alkenes in certain cases

Cyclopropanes in Total Synthesis

Carreira, E. M.
CR **2017**, 117, 11651



See also:

Lebel, H.; Charette, A. B. CR **2003**, 103, 977

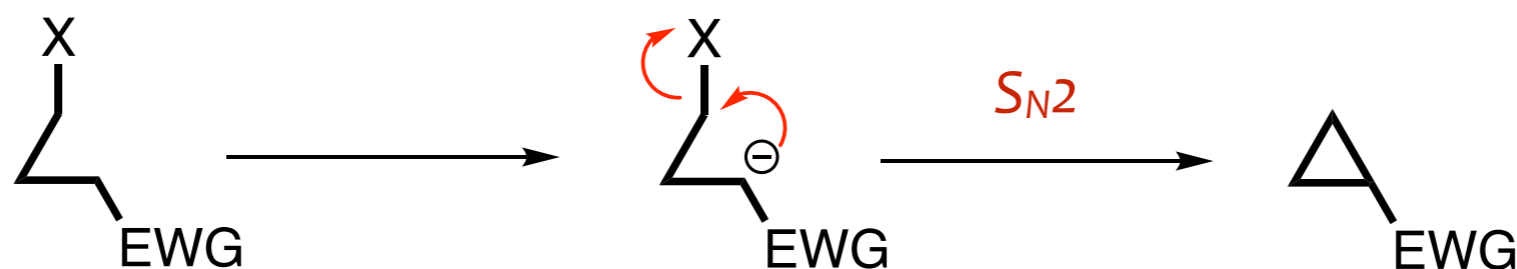
Maguire, A. R.; McKervey, M. A. CR **2015**, 115, 9981

Iwasa, S. ACR **2016**, 49, 2080

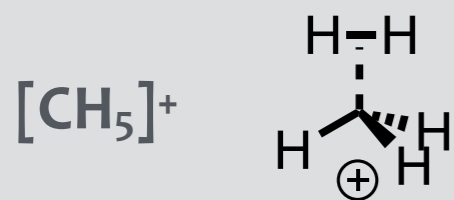
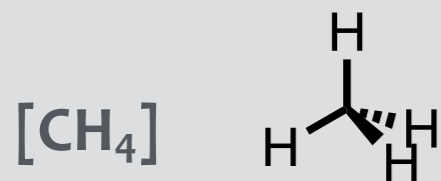
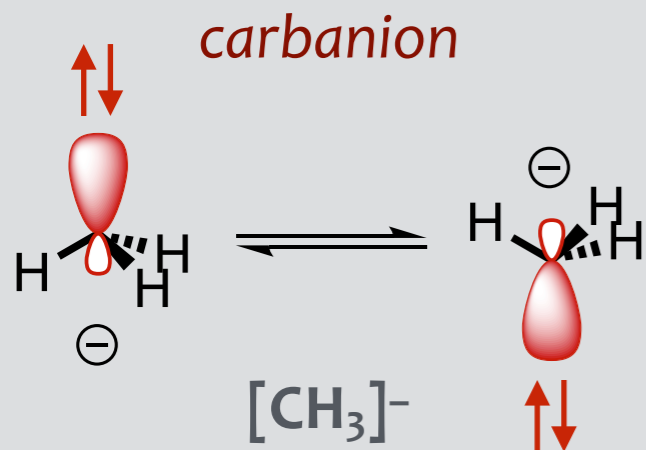
Cyclopropanation of alkenes



Intramolecular nucleophilic cyclopropanation

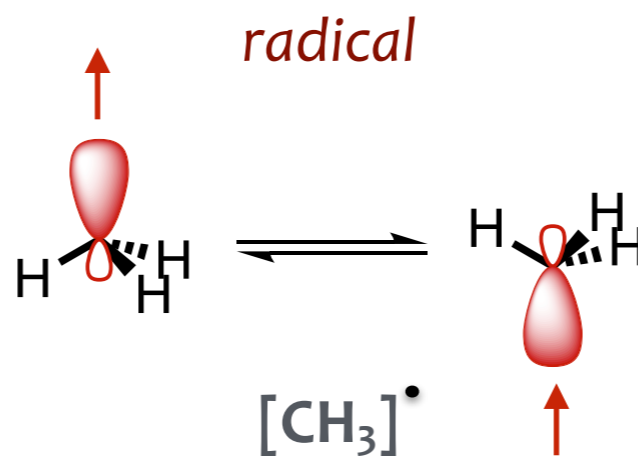


8 e⁻



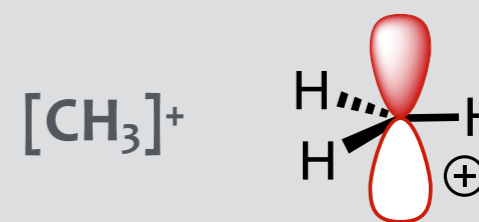
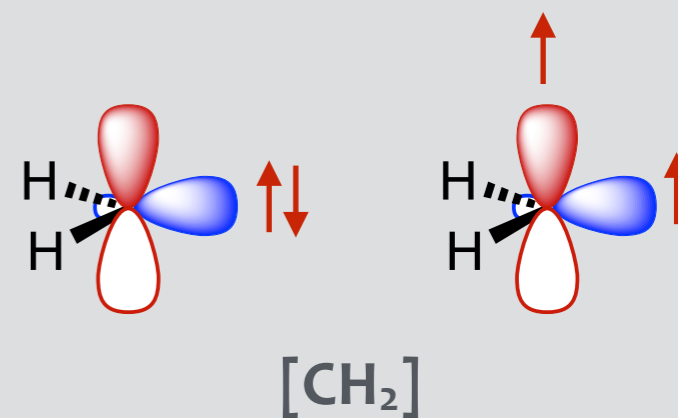
carbonium

7 e⁻



singlet carbene

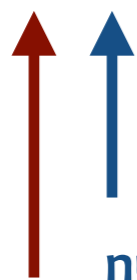
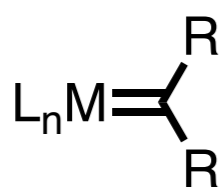
triplet carbene



carbenium

Metal Carbene reactivity depends on the metal (M) and the ligands

Schrock-type

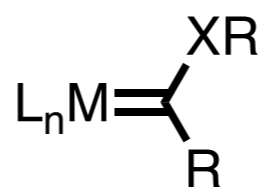


nucleophilic

electrophilic

M: middle transition metal
R: H, alkyl

Fischer-type

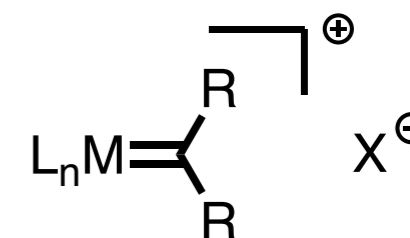
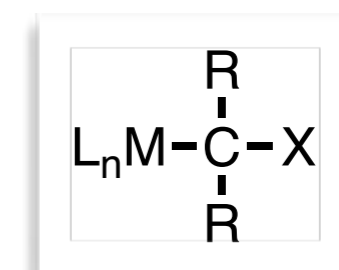


electrophilic

nucleophilic

M: middle or late transition metal
X: NR, O, S

Metal Carbenoid



metal carbene

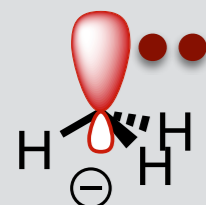
Pérez, P. J. *CEJ* **2017**, *23*, 14389

... they are related by the addition/elimination of an X- group, regardless of the double bond character of the metal-carbon bond in the carbene

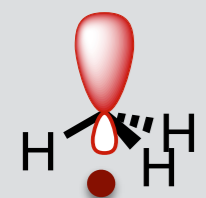
Echavarren, A. M. *CEJ* **2015**, *21*, 7332

A certain attention has recently been paid to a less substituted intermediate

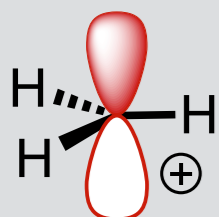
Trisubstituted



carbanion

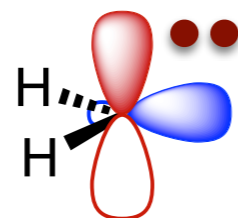


radical



carbenium

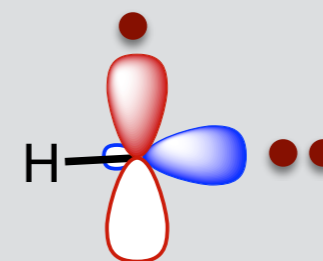
Disubstituted



carbene

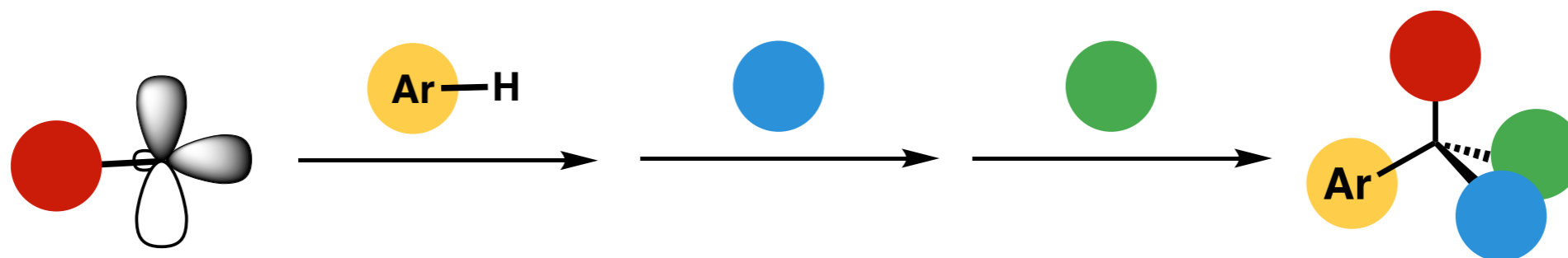
Monosubstituted

$5 e^-$

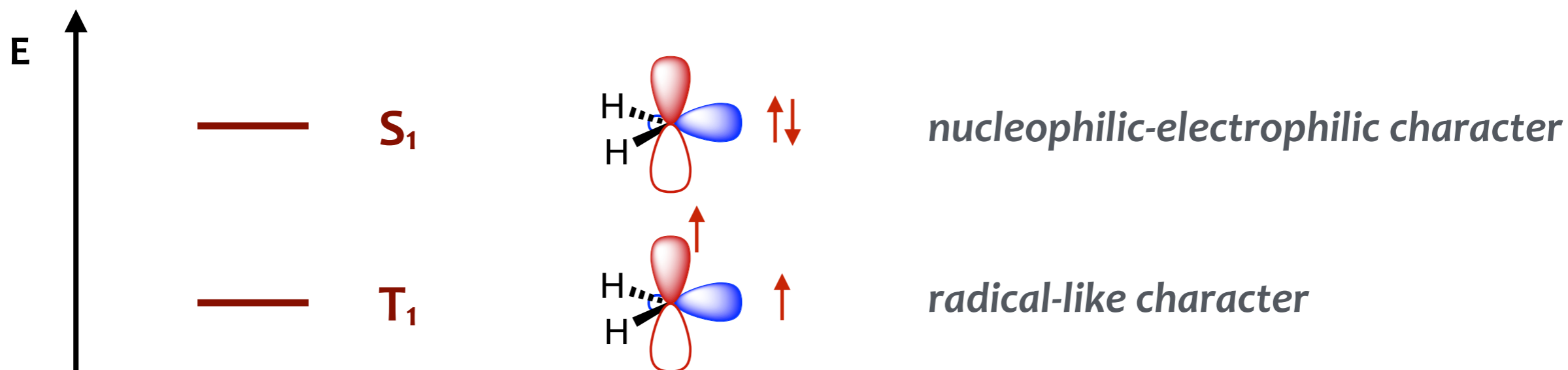


carbyne

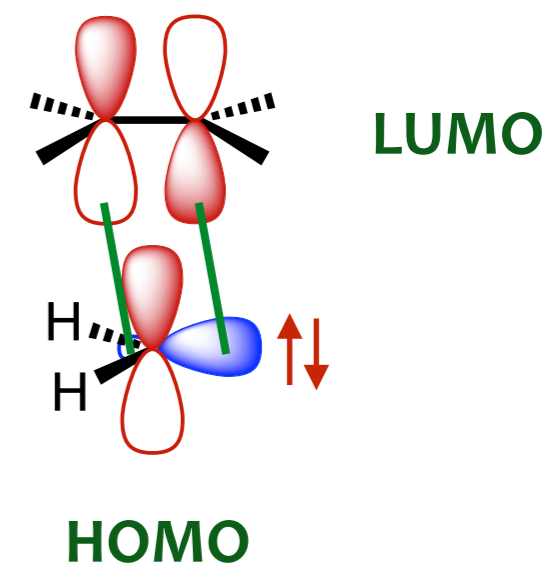
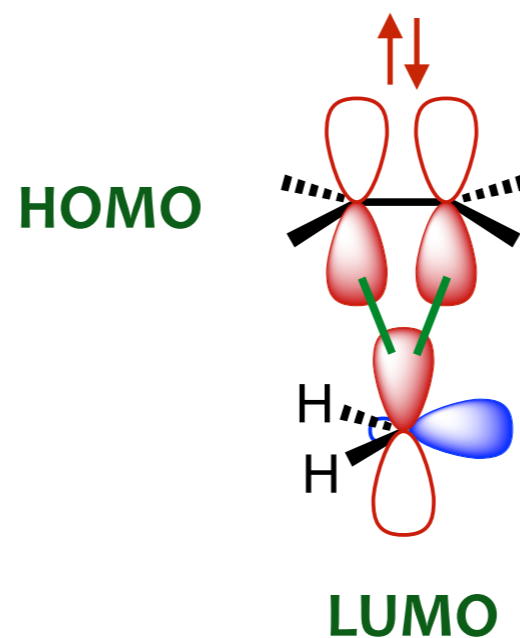
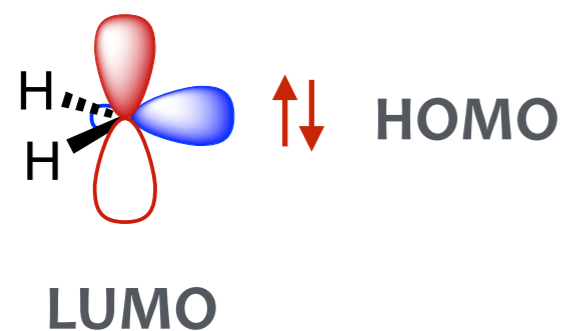
Monovalent carbon
Carbene-radical reactivity

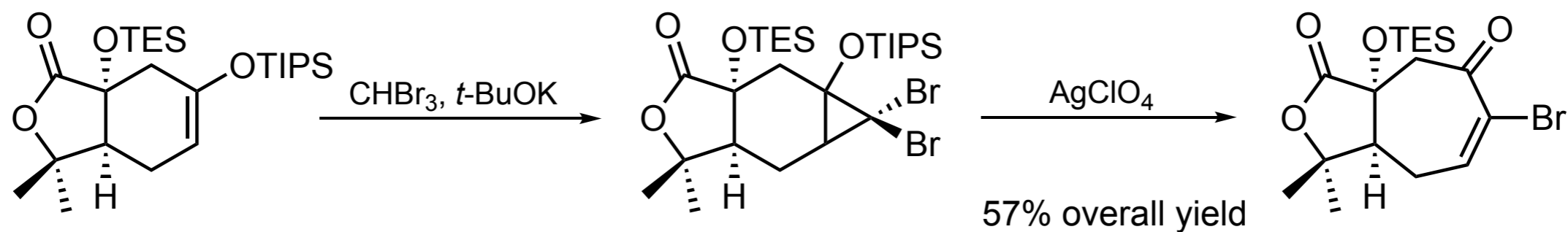
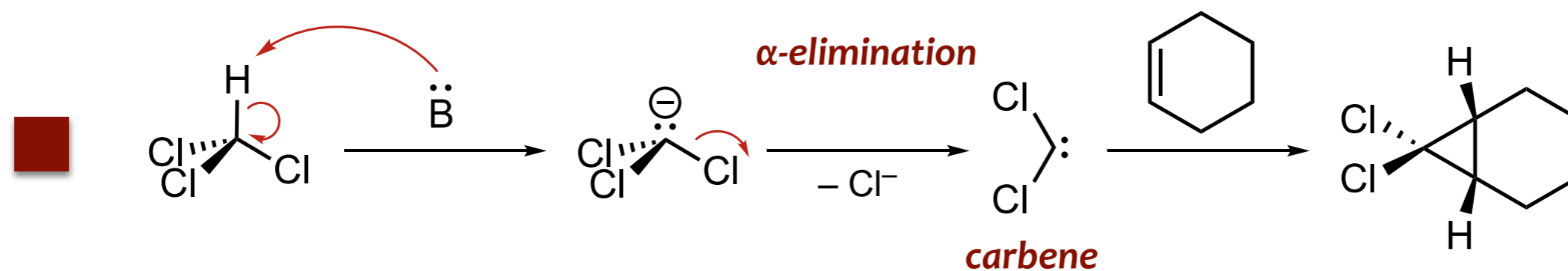
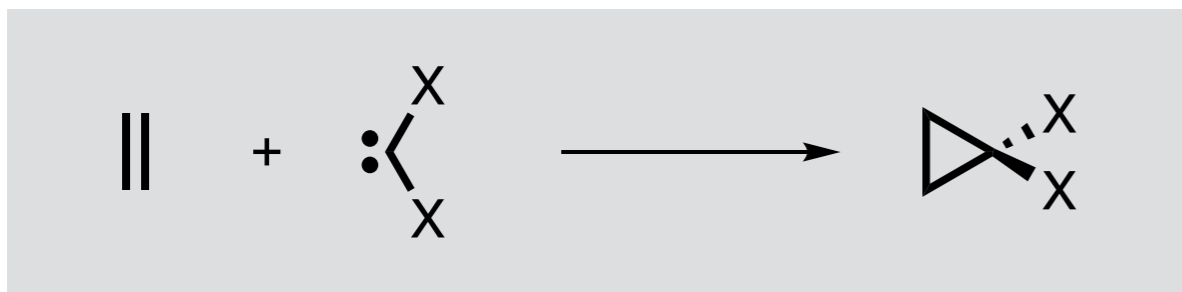


Stereocenter

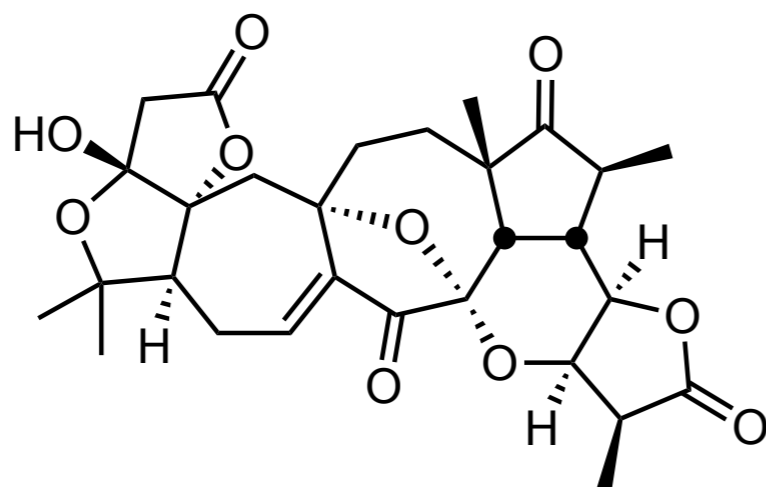


Olefin-carbene cycloaddition

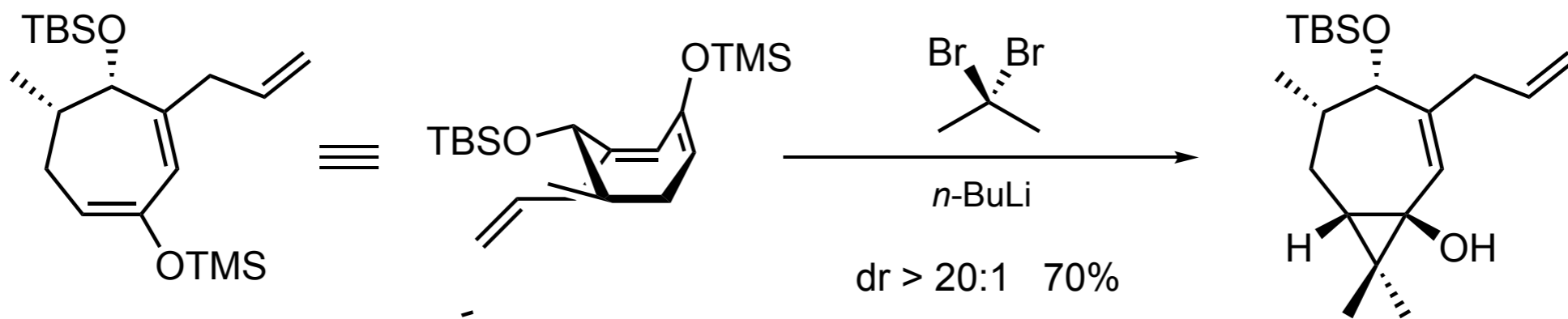
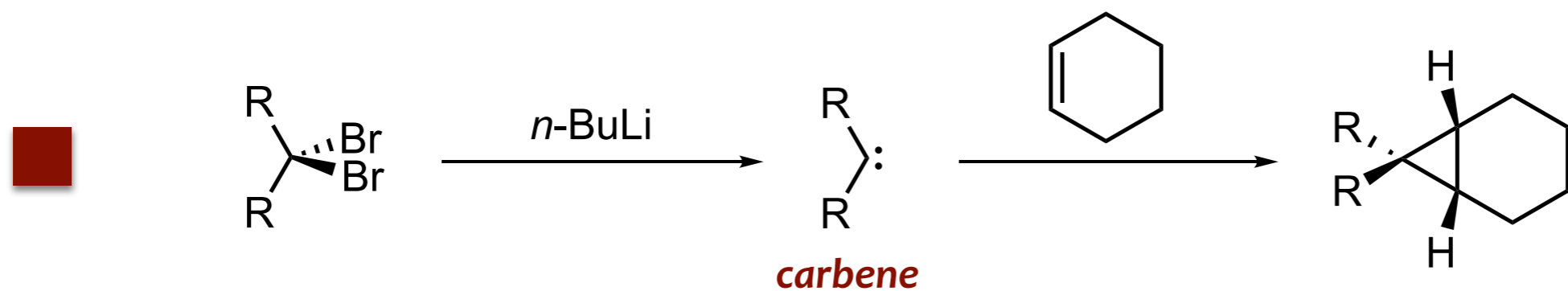
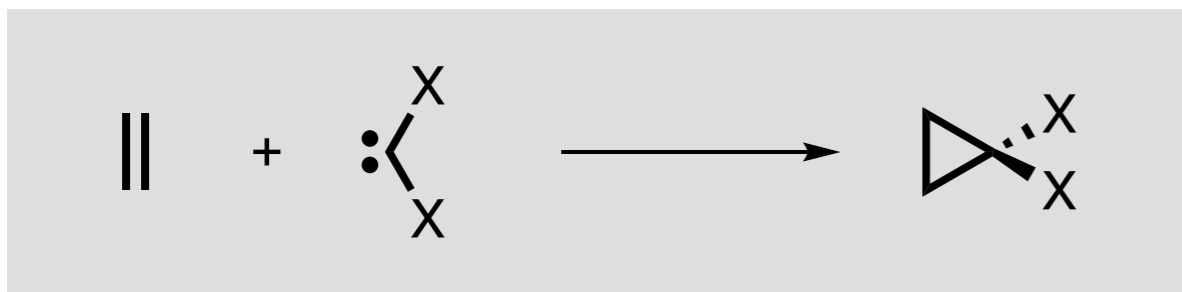




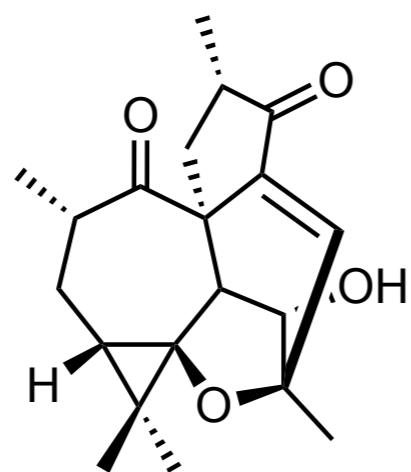
Schindilactone A

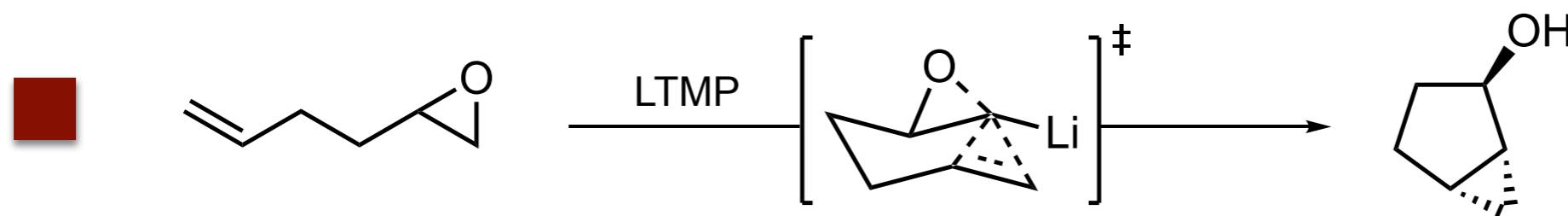
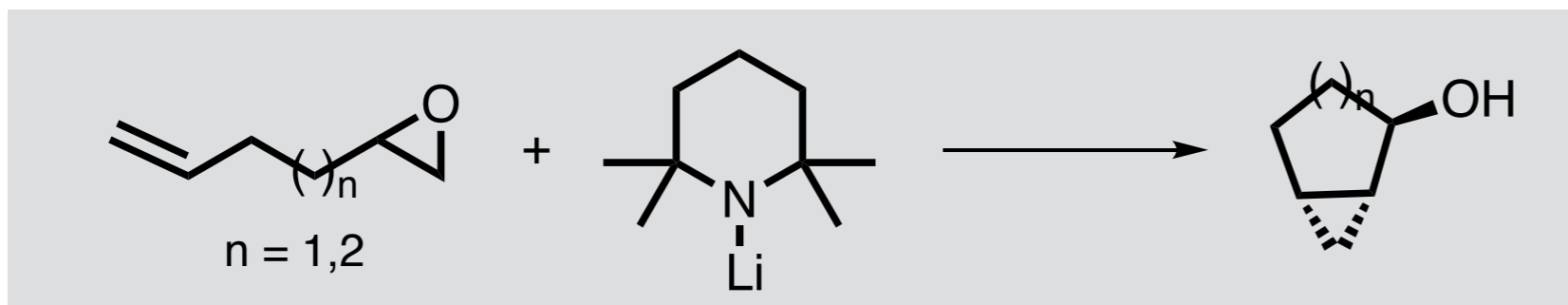


Tang, Y.-F.; Chen, J.-H.; Yang, Z. *ACIE* **2011**, *50*, 7373
See also Yang, Z. *JACS* **2015**, *137*, 10120

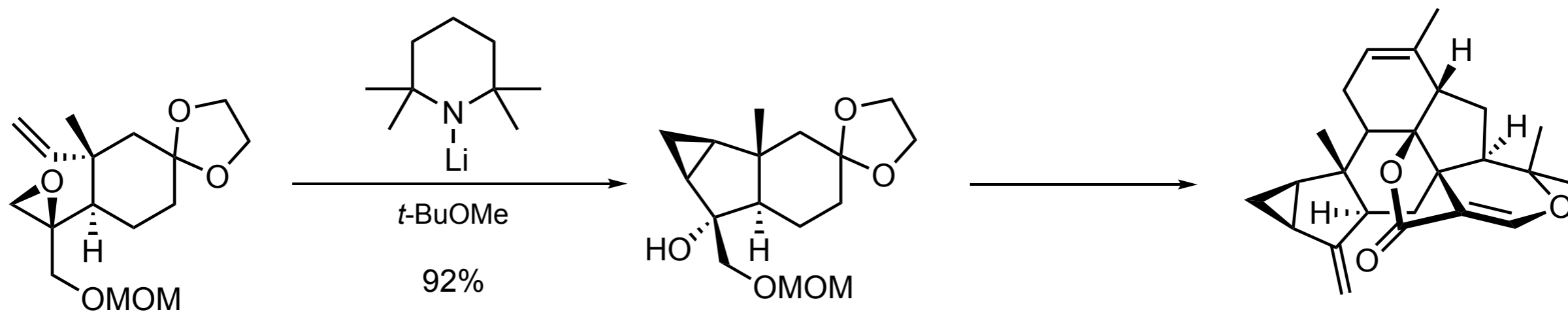


Steenkrotin A





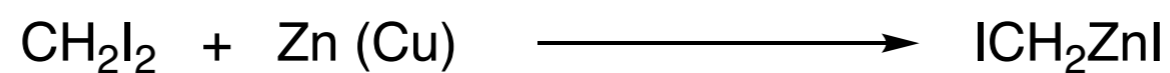
Hogdson, D. M. *JACS* **2004**, 126, 8664; **2007**, 129, 4456



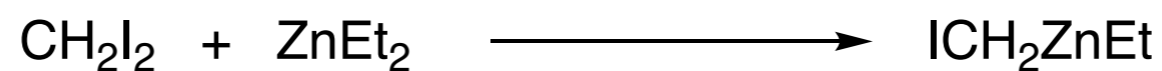
Bolivianine

Liu, B.; Qin, S. *CEJ* **2014**, 20, 2613

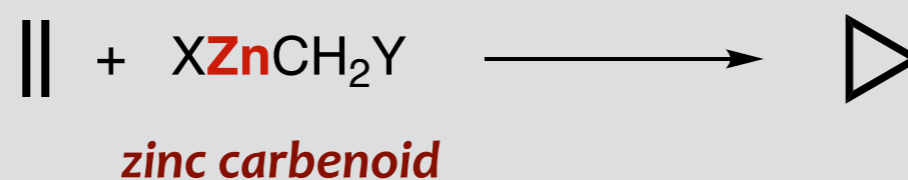
Simmons-Smith



Simmons-Smith

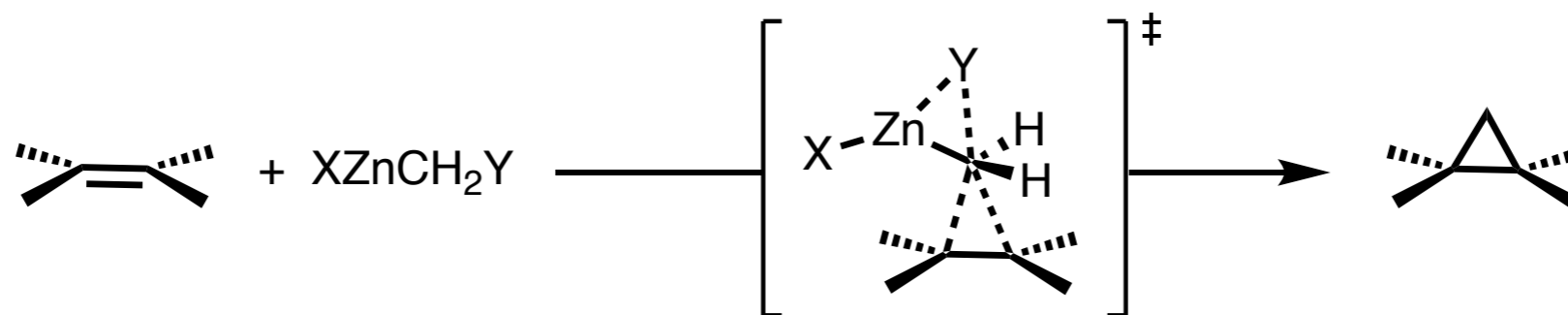


Furukawa



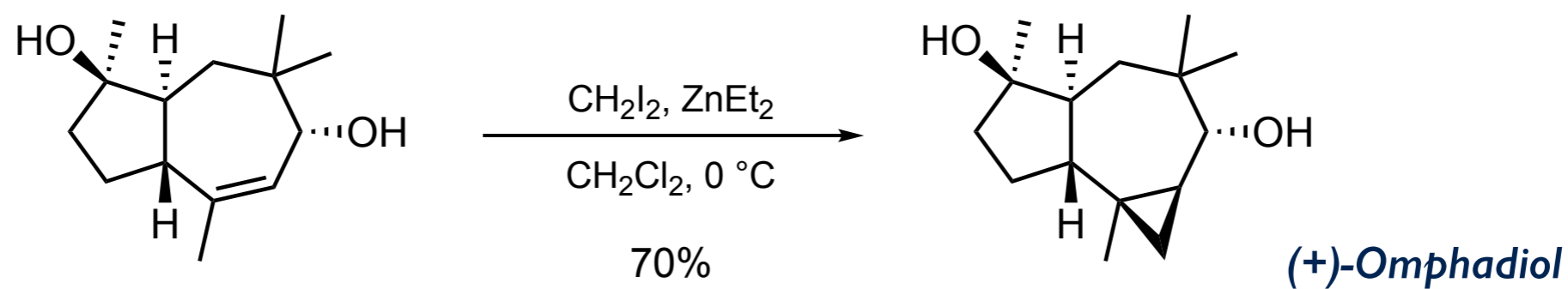
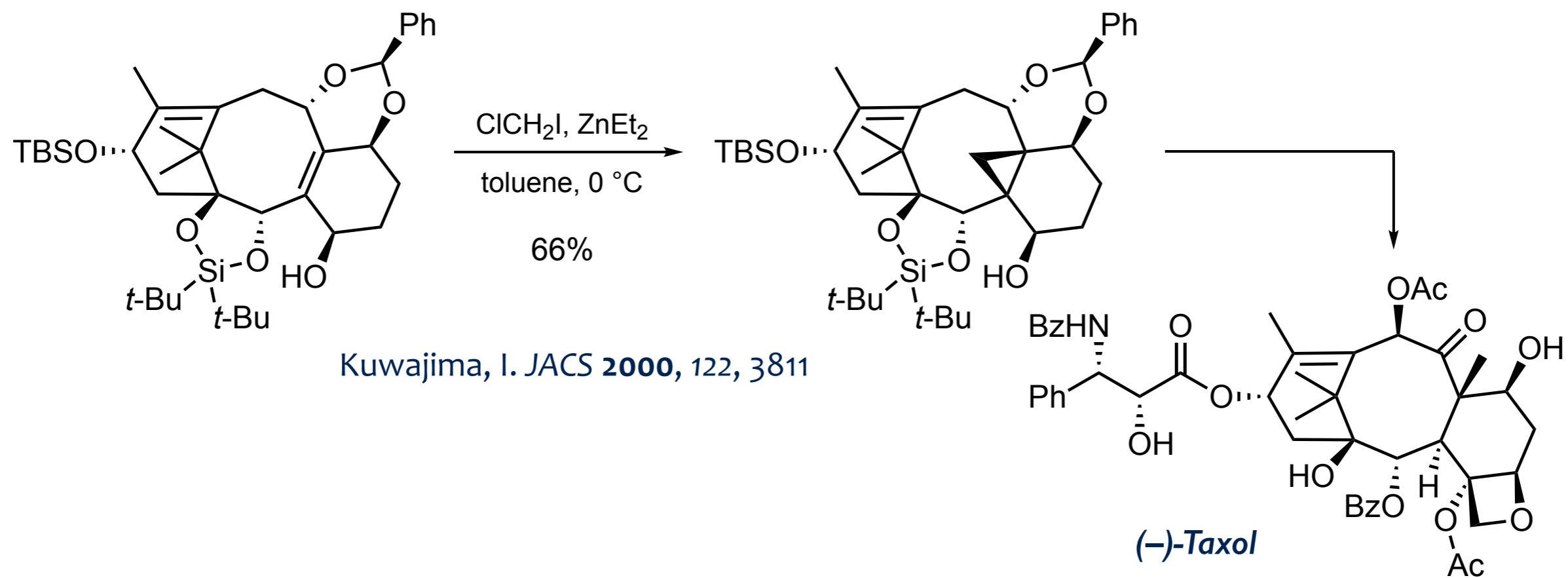
Simmons, H. E.; Smith, R. D. A. *JACS* **1958**, *80*, 5233; **1959**, *81*, 4256

Furukawa, J. *Tet* **1968**, *24*, 53



Nakamura, M.; Nakamura, E. *JACS* **2003**, *125*, 2341

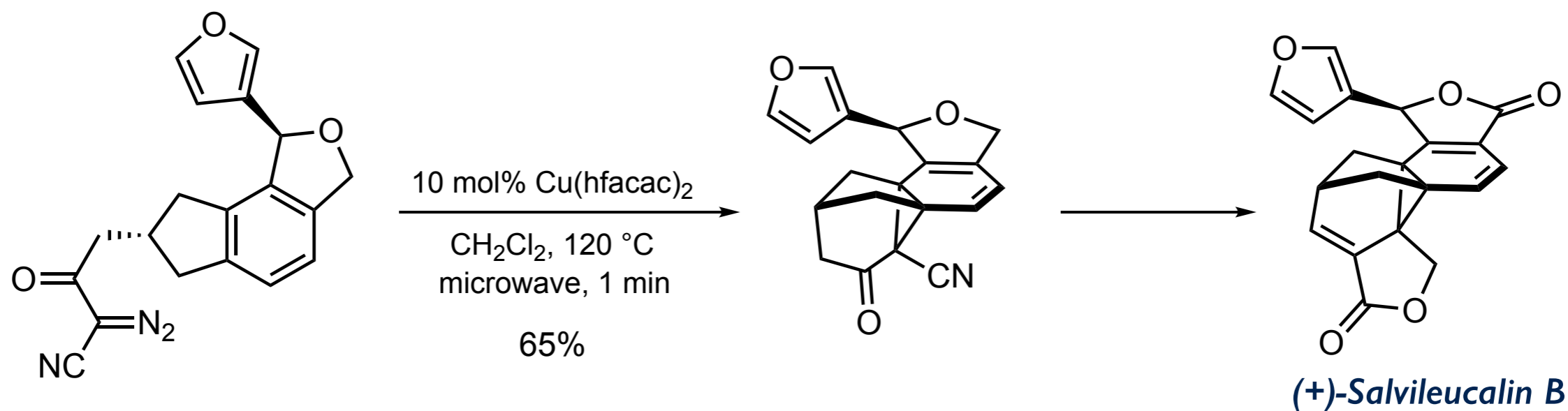
For intramolecular Simmons-Smith reactions, see Charette, A. B. *JACS* **2010**, *132*, 1895



Kalesse, M. *OL* **2016**, *18*, 2320



Padwa, A. *JACS* **1992**, *48*, 5385
 Doyle, M. P. *CR* **1994**, *94*, 1091; *JOC* **2006**, *71*, 9253

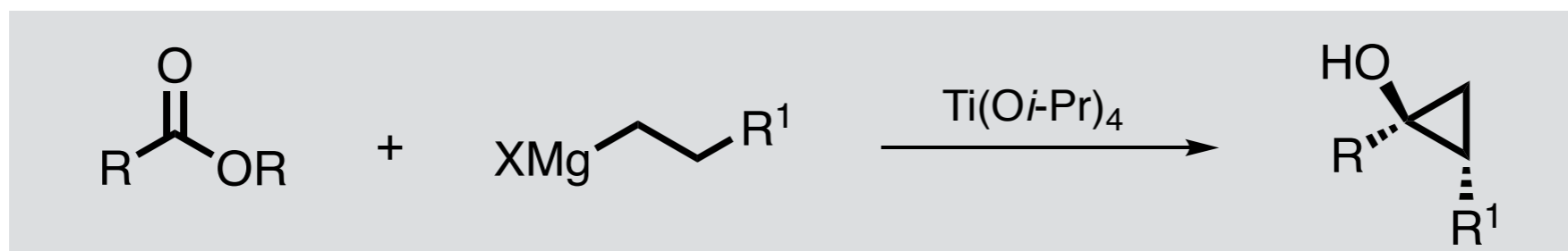


Reisman, S. E. *JACS* **2011**, *133*, 774

Intra better than **inter** cyclopropanation
 Alkyl diazo compounds turn out to be capricious,
 C-H Insertion can sometimes compete with cyclopropanation

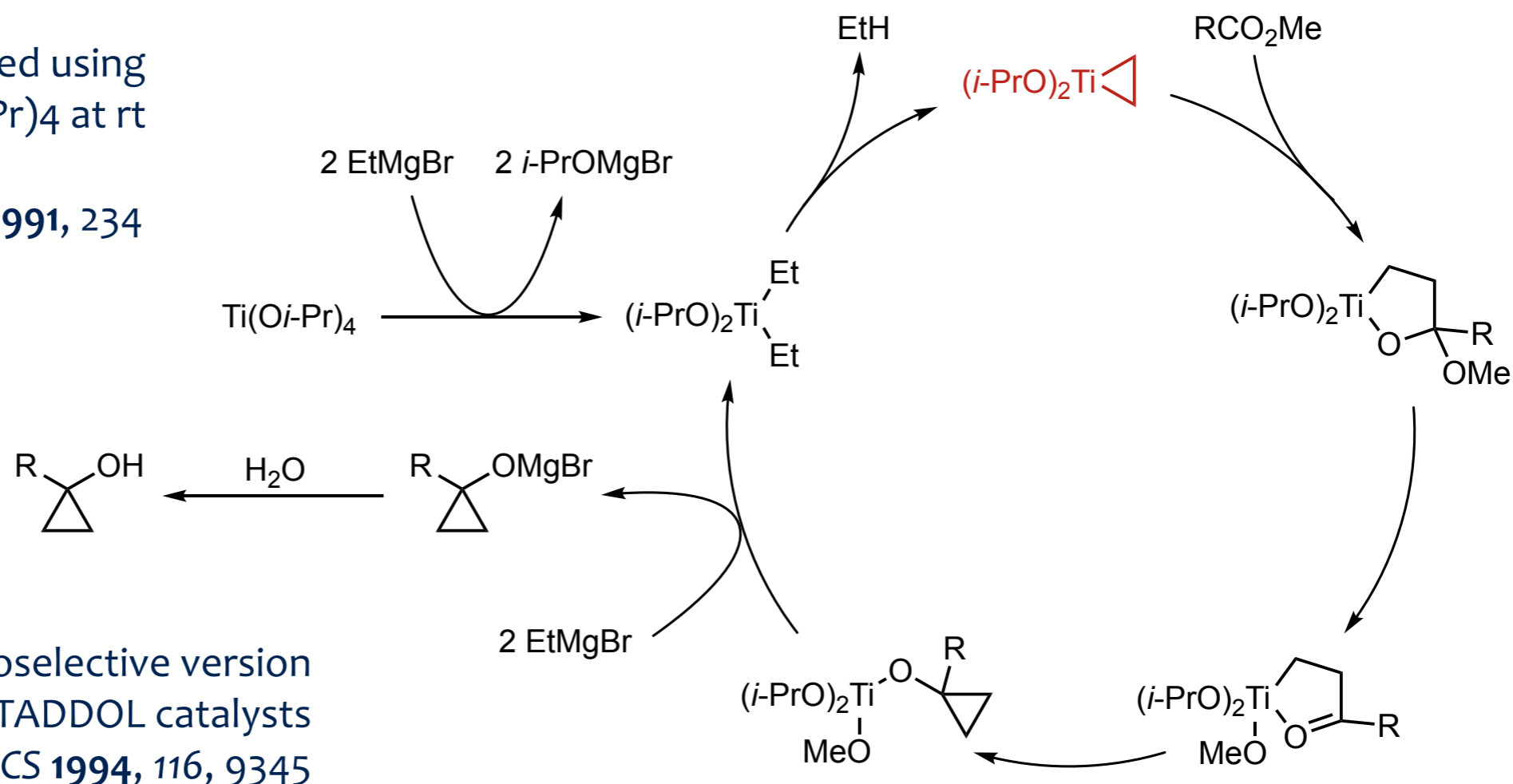
Kulinkovich hydroxycyclopropanation

Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1
 Brimble, M. PA. *OBC* **2012**, *10*, 7649



It can be performed using catalytic amounts of $Ti(Oi-Pr)_4$ at rt

Kulinkovich, O. G. *Synthesis* **1991**, 234



Corey developed an enantioselective version using TADDOL catalysts
 Corey, E. J. *JACS* **1994**, *116*, 9345

Cyclopropanation of esters can be carried out via olefin exchange

