Reviews:

Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103.
Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1484.
Crimmins, M. T. *Chem. Rev.* **1988***, 88*, 1453–1473.
Bach, T. *Synthesis* **1998**, 683–703.

Challenges:

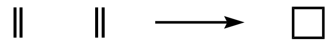
- Cyclobutanes are highly strained:

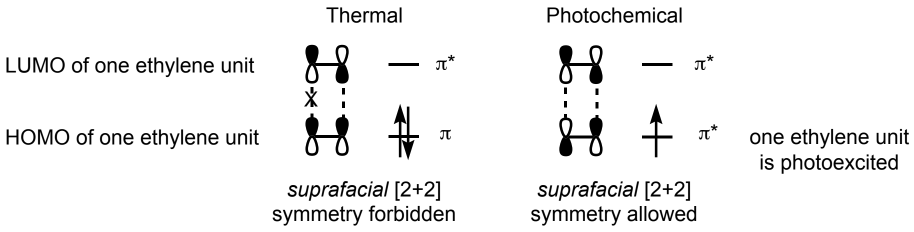
Strain energy in kcal/mol 27.5 26.3 6.2 0.1

Wiberg, K. B. *Angew. Chem. Int. Ed.* **1986**, *25*, 312–322.

Synthetic Methods For the Construction of Cyclobutanes:

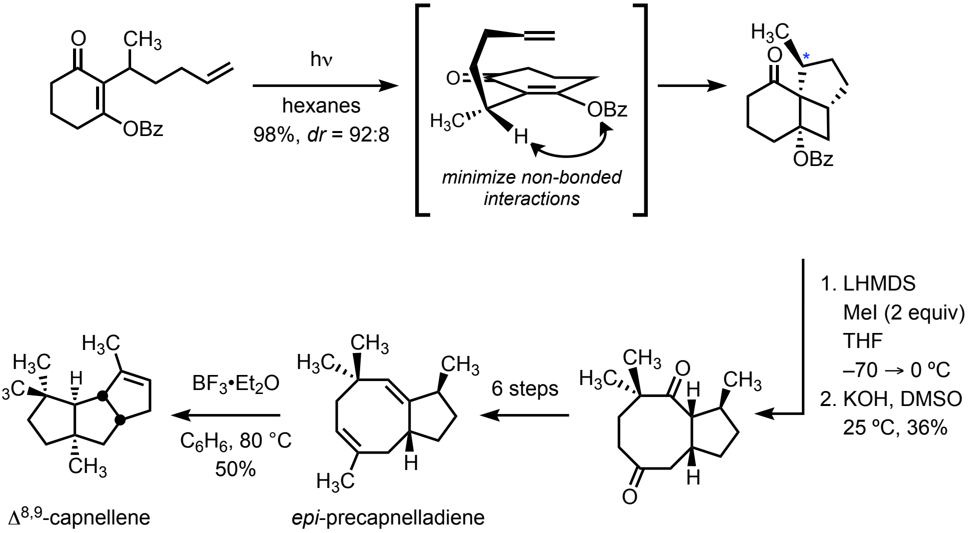
- **[2+2] Cycloadditions:**
- Suprafacial [2+2] cycloadditions are photochemically allowed but thermally forbidden.
- Frontier Molecular Orbital Analysis:





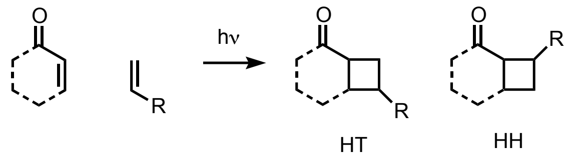
- Enones are generally used as they are more easily photoexcited than isolated olefins.
- Photoexcited enones react via the T1 (triplet excited state).
- Quantum efficiencies are higher in cyclic systems due to rapid intersystem crossing.
- Acyclic and macrocyclic enones are typically not suitable for [2+2] photocycloaddition because upon photoexcitation, they undergo *cis*/*trans* isomerization.

- **Intramolecular [2+2] Cycloadditions:**
- Intramolecular [2+2] cycloadducts are readily formed. Tethers are typically 2 to 4 atom:



Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 1195–1197.
Birch, A. M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1,* **1983**, 1913–1917.

- **Intermolecular [2+2] Cycloadditions**
- Regioselectivity issues: head-to-tail (HT) vs. head-to-head (HH)



- Generally:

HT-isomer favored when R = donor (electron donating)

HH-isomer favored when R = acceptor (electron withdrawing)

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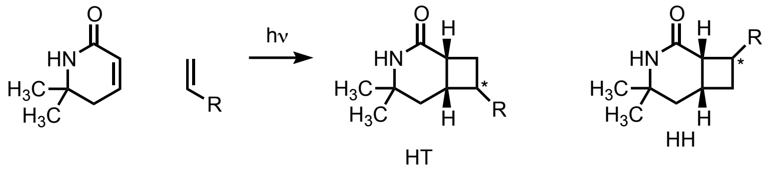
- **An Example of Regioselectivity Governed by Electronics**



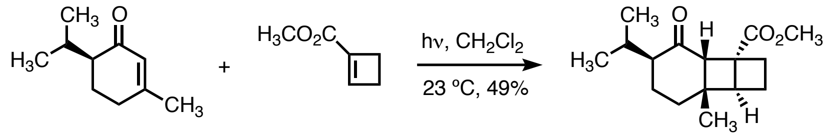
R	*d.r.* (HT : HH)
CN	18 : 82
OEt	95 : 5

- Both HT and HH products were obtained as a mixture of two diastereomers.

Suishu, T.; Shimo, T.; Somekawa, K. *Tetrahedron* **1997,** *53,* 3545–3556.

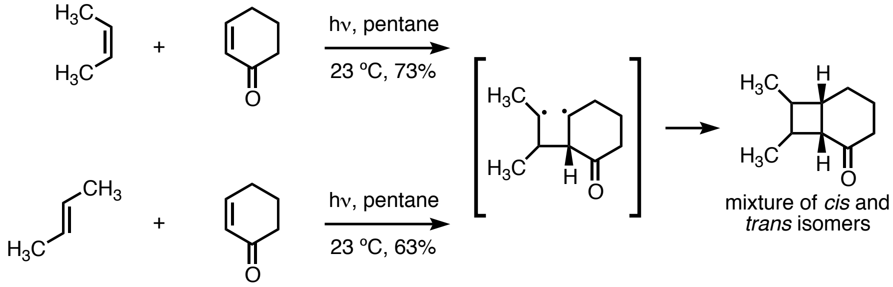
- **Stereoselectivity in Intermolecular [2+2] Cycloadditions**

- The least hindered transition state usually dominates. There is no "*endo*" effect, as in the Diels-Alder Reaction:



Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373–7379.

- When the double bond is not constrained within a rigid ring system, the intermediate triplet state diradical can lead to *cis*/*trans* isomerization of the double bond:



mixture of *cis* and *trans* isomers

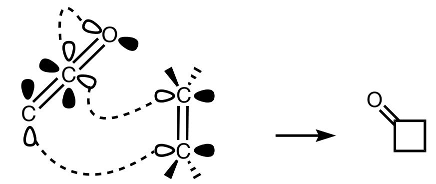
Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570–5583.

- **Ketene [2+2] Cycloadditions**

- Antarafacial [2+2] cycloadditions are thermally allowed but geometrically disfavored for most substrates.

- Ketenes are linear and sterically less encumbered, making them good substrates for thermal [2+2] cycloadditions.

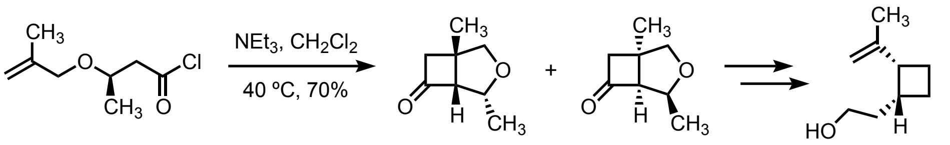
- Frontier Molecular Orbital Analysis:



LUMO of C=C=O — ketene

HOMO of C=C — alkene

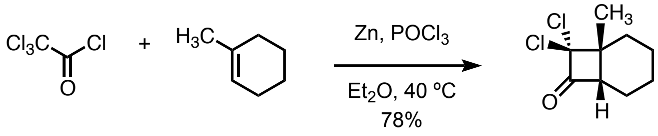
- Ketenes can be generated in situ from acid chlorides:



3.4 : 1 (separable by chromatography)

(+)-grandisol

Mori, K.; Miyake, M. *Tetrahedron* **1987**, *43*, 2229–2239.



Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879–2882.

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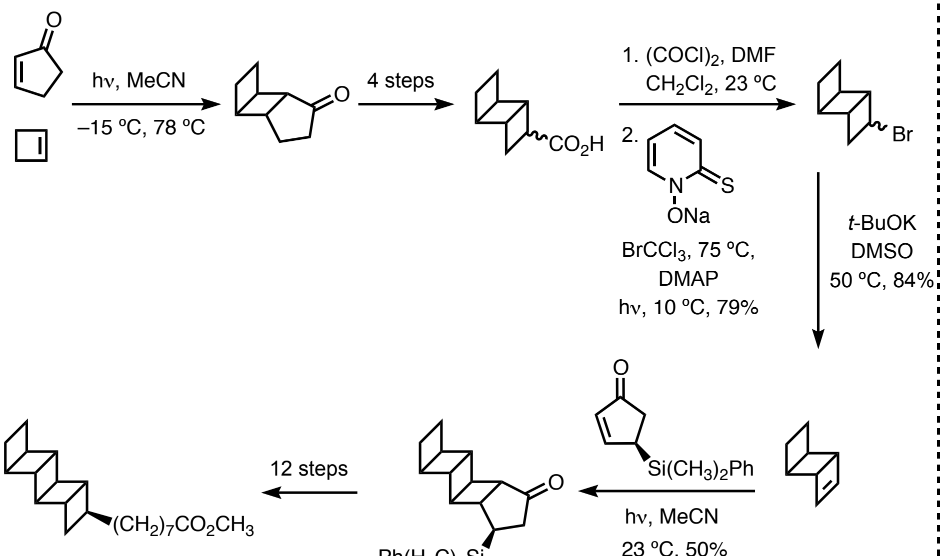
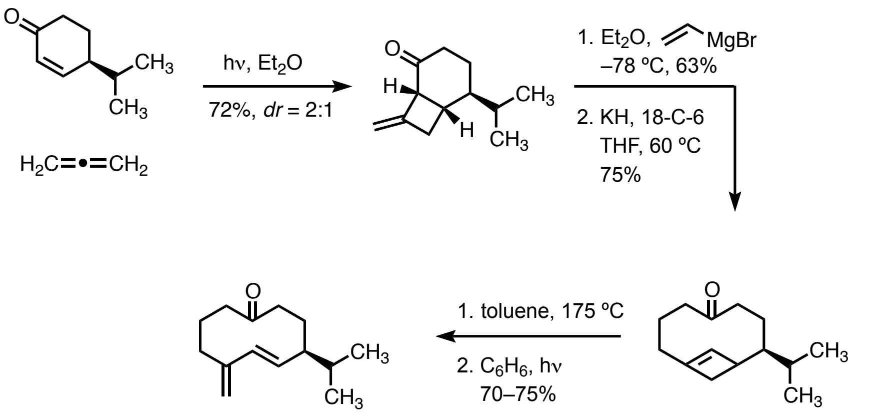
- **Examples of [2+2] Cycloaddition in Synthesis**
- Synthesis of pentacycloanammoxic acid, the principal lipid component of the cell membrane of the anaerobic microbe *Candidatus Brocadia anammoxidans:*



pentacycloanammoxic acid

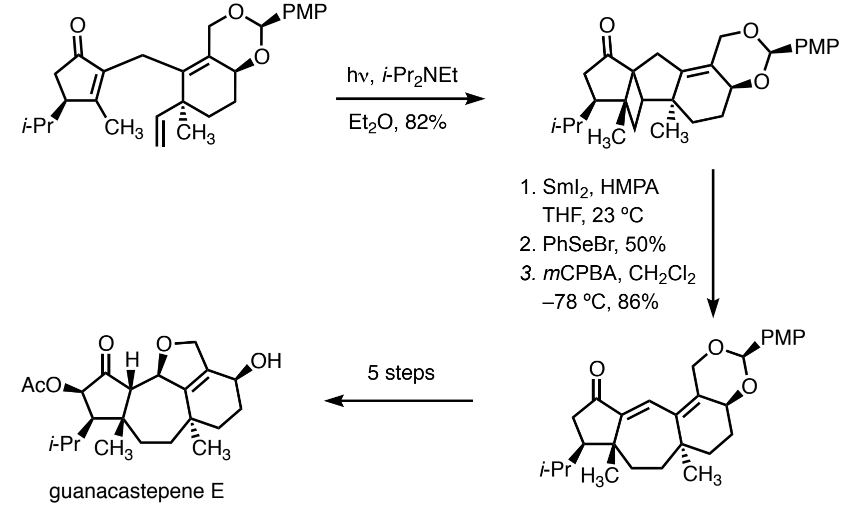
Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118–3119.

- A [2+2] cycloaddition/anionic oxy-Cope/electrocyclic ring opening cascade provided a key intermediate to periplanone B. Note that both diastereomers from the [2+2] cycloaddition step can be converted to the final product:



Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038–4039.

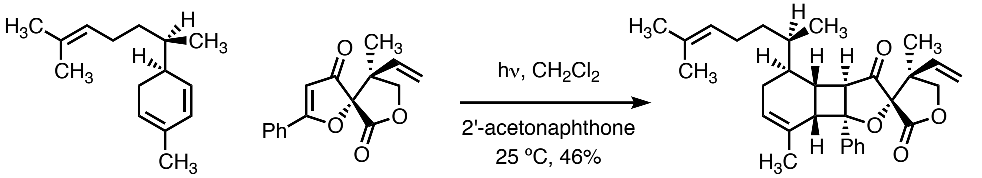
- A [2+2] Cycloaddition followed by radical fragmentation provided a key intermediate to guanacastepene E:



guanacastepene E

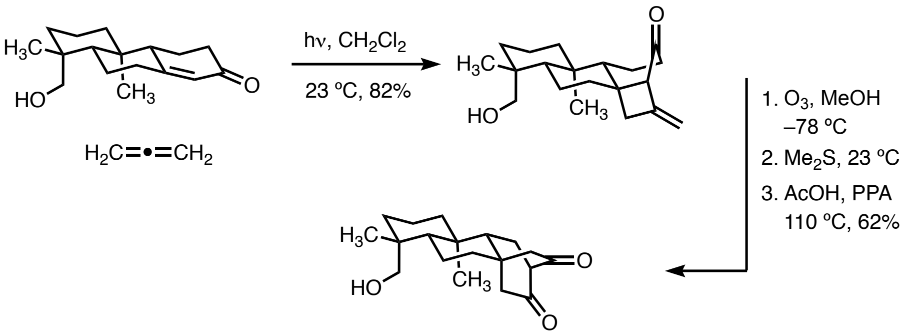
Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.

- A late-stage coupling reaction provided access to biyouyanagin A:



Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4708–4711.

- A [2+2] photocycloaddition followed by acid-catalyzed rearrangement provided a key intermediate to steviol:



Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 9019–9022.

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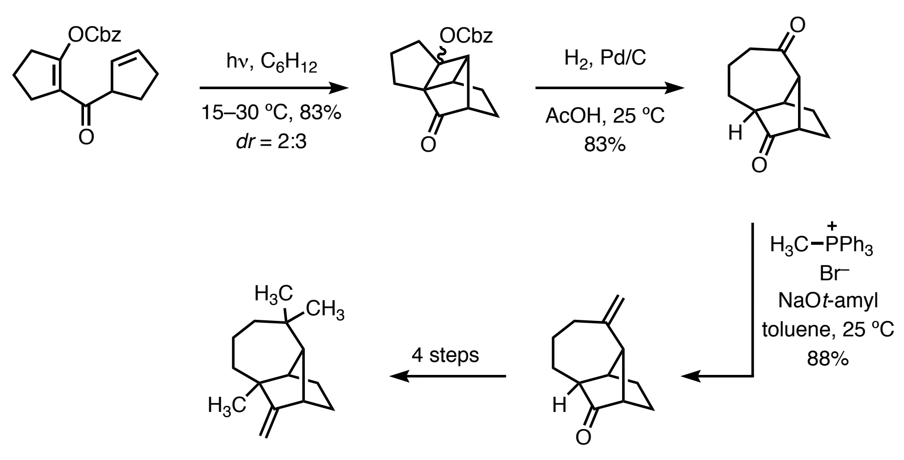
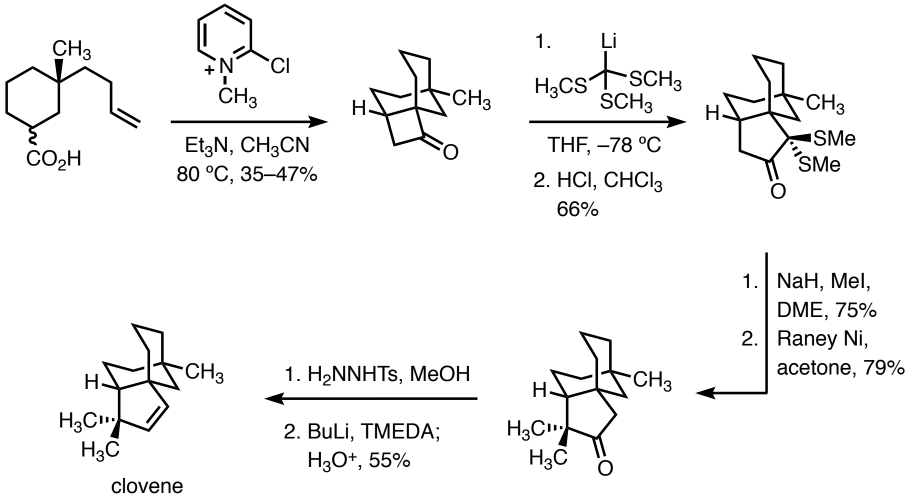
- The synthesis of longifolene was accomplished via a de Mayo reaction — a [2+2] cycloaddition followed by retro-Aldol fragmentation:



Longifolene

Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583–2584.

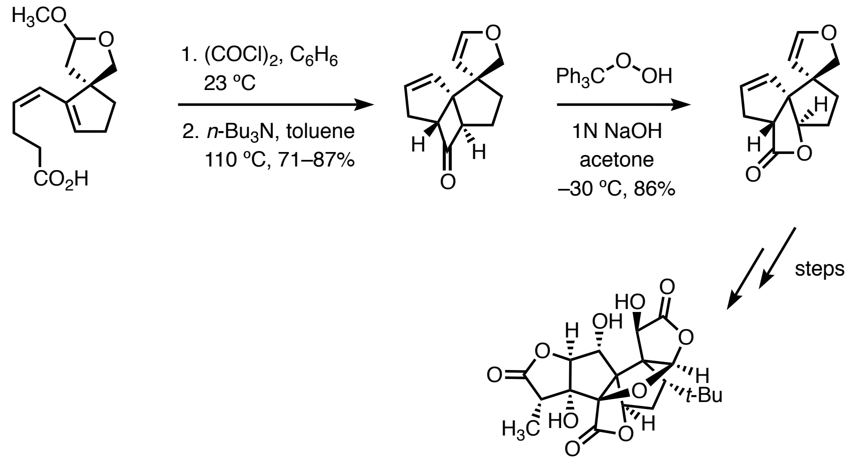
- Synthesis of clovene via a ketene [2+2] thermal cycloaddition:



Bamford-Stevens-Shapiro Reaction

Funk, R. L.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493–1496.

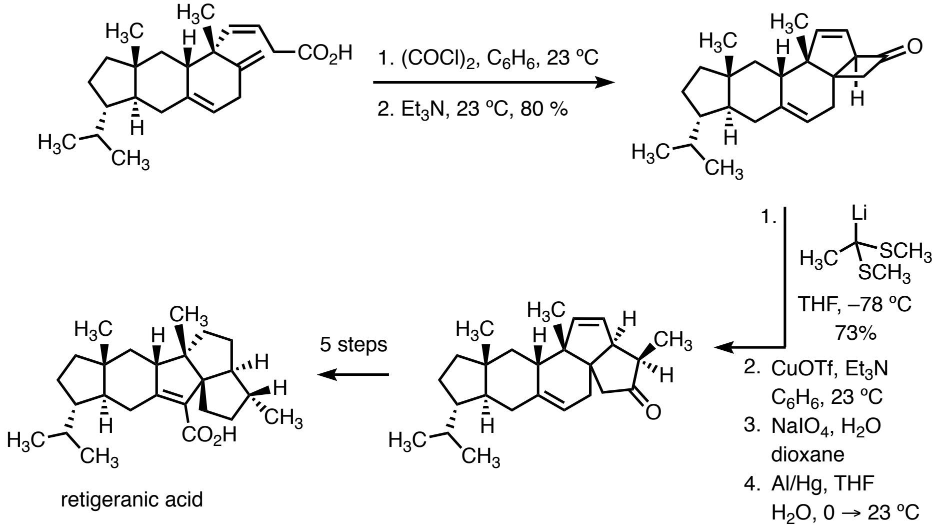
- In the synthesis of ginkgolide B, three contiguous stereogenic centers were established using an intramolecular ketene [2+2] cycloaddition reaction:



Ginkgolide B

Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651.

- Synthesis of retigeranic acid via a ketene [2+2] cycloaddition followed by cyclobutane ring expansion:



Corey, E. J.; Desaid, M.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339–4341.

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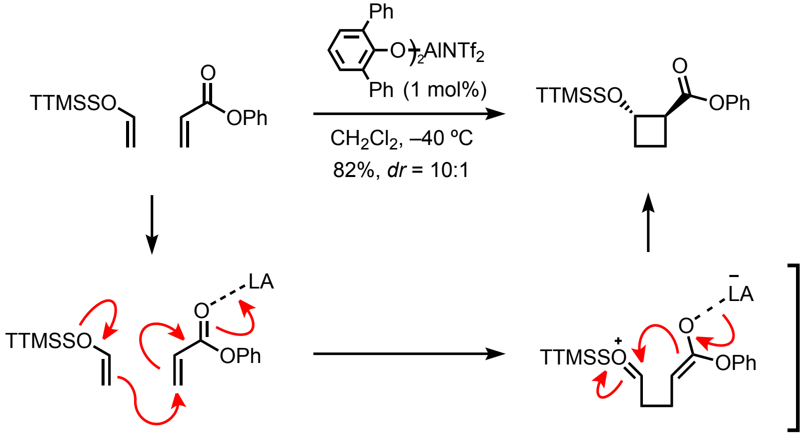
- **Formal [2+2] Cycloadditions: Michael-Aldol Mechanism**

- Silyl enol ethers and α,β-unsaturated compounds form cyclobutanes in a stepwise, Lewis acid-catalyzed process.

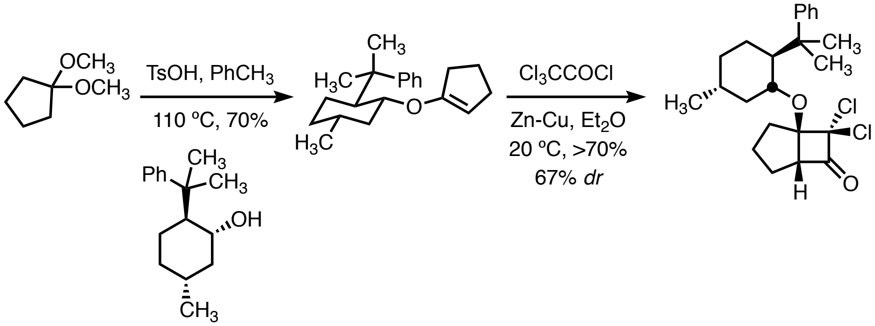
- In the following example, the bulky tris(trimethylsilyl)silyl (TTMSS) protecting group is required to stabilize the cationic intermediate. This and the use of a bulky aluminum catalyst with the triflimide counterion suppress silyl transfer:



Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2008**, *7*, 3127–3129.

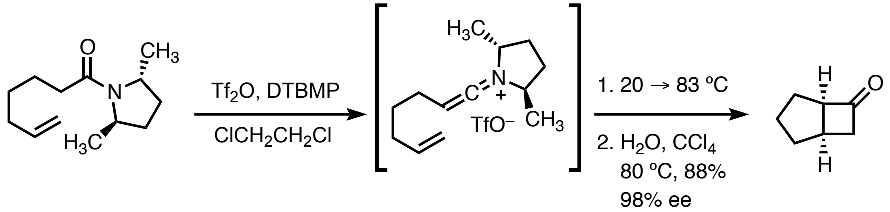
- **Auxiliary-Controlled Stereoselective [2+2] Cycloadditions**

- One of the earliest reports involved the use of (–)-phenylmenthol as a chiral auxiliary to achieve a diastereoselective [2+2] cycloaddition:



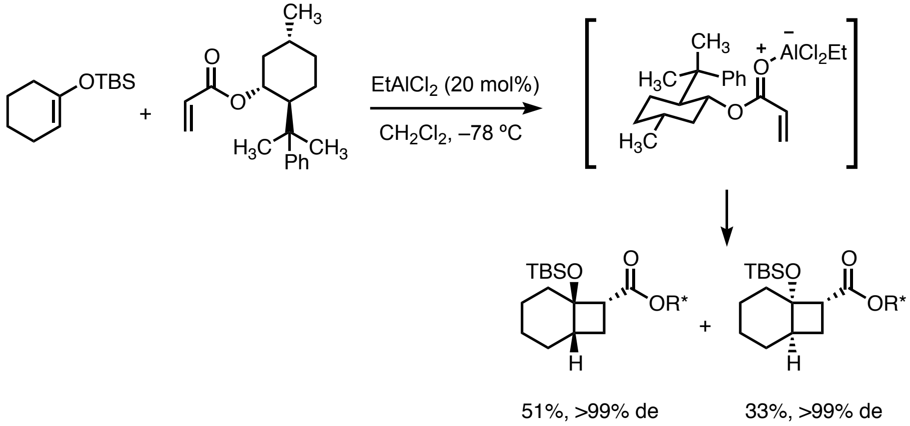
Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525–5528.

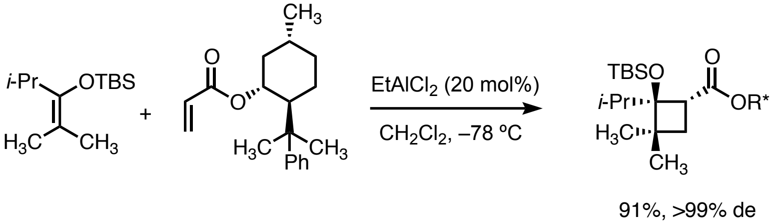
- Upon activation by triflic anhydride, C_2-symmetric chiral pyrrolidine amides form keteniminium salts, which undergo thermal [2+2] cycloadditions with excellent stereoselectivities:



Chen, L.; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467–4470.

- (–)-Phenylmenthol was also found to be an effective chiral auxiliary in formal [2+2] cycloadditions of silyl enol ethers and acrylates:





Takasu, K.; Nagao, S.; Ueno, M.; Ihara, M. *Tetrahedron* **2004**, *60*, 2071–2078.
Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517–521.

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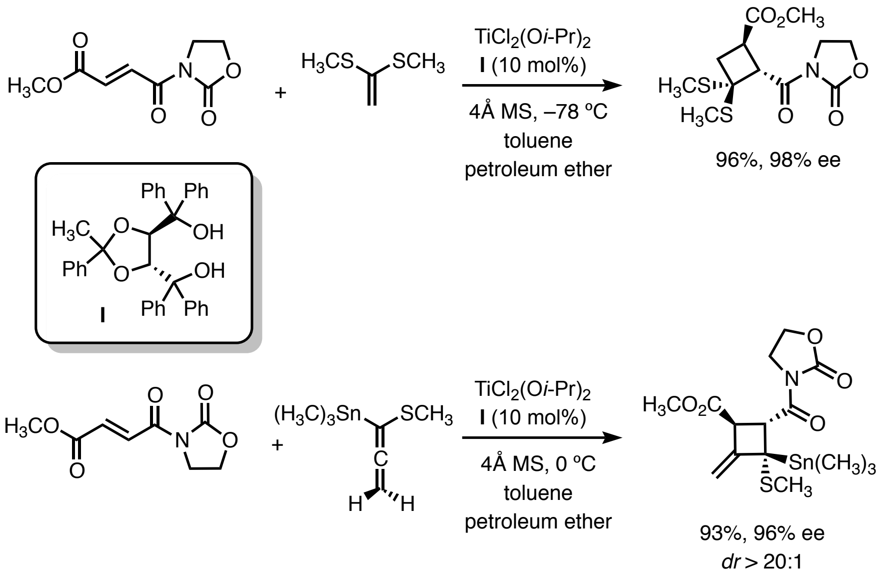
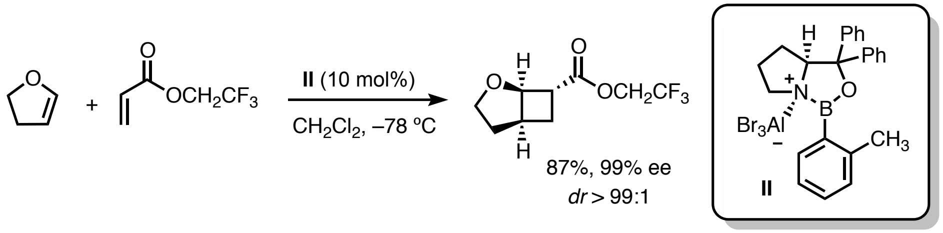
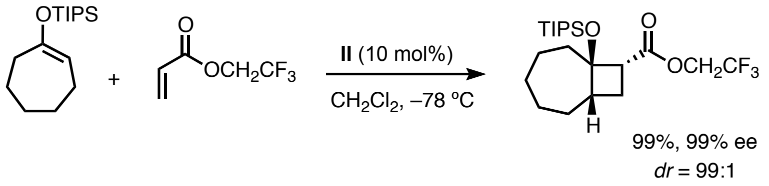
- **Enantioselective [2+2] Cycloadditions with Lewis Acid Catalysts**
- In early reports, taddolates were found to catalyze formal [2+2] cycloadditions:



Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1989**, 793–796.
Hayashi, Y.; Niihata, S.; Narasaka, K. *Chem. Lett.* **1990**, 2091–2094.

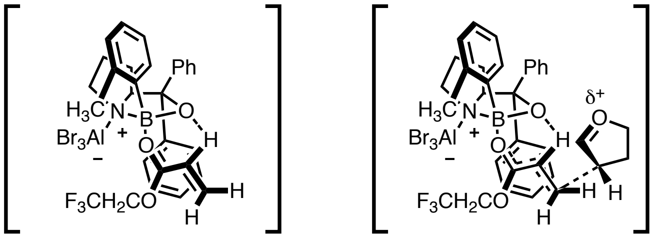
- An aluminum bromide oxazaborolidine complex was found to be a highly efficient catalyst:



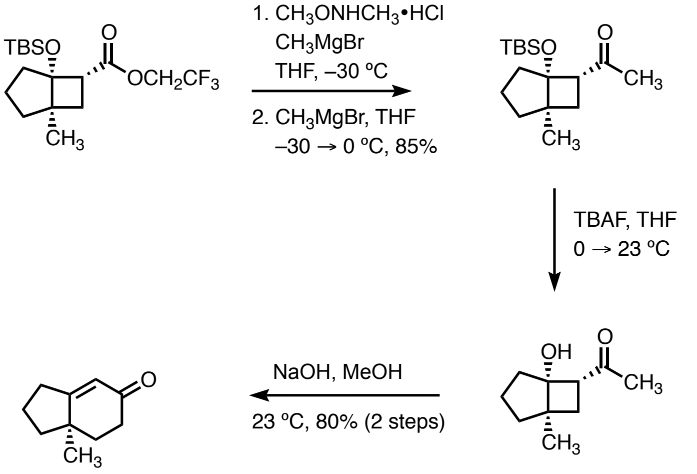


Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686–12687.

- The reaction is proposed to occur by an asynchronous process. The structures shown below were presented to rationalize the stereochemical outcome:



- Transformations of the cyclobutane products:



Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686–12687.

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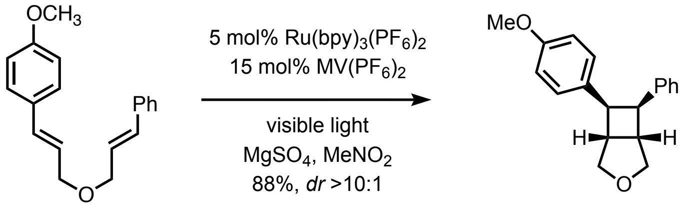
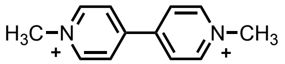
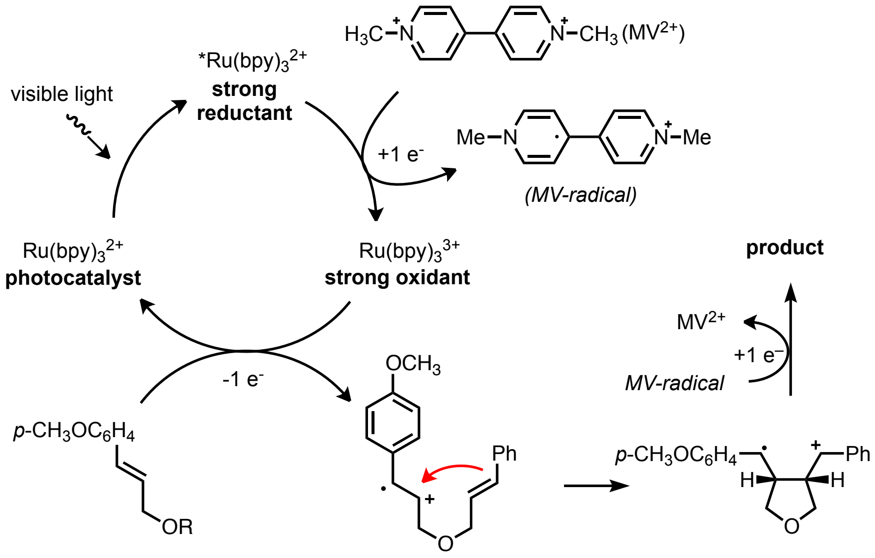
- **Photoredox Catalysis**
- Photoredox catalysts absorb light in the visible region and provide a pathway for cyclization mediated by electron transfer rather than direct photoexcitation of the substrate:



MV^{2+} = methyl viologen (*N,N'*-dimethyl-4,4'-bypyridinium)



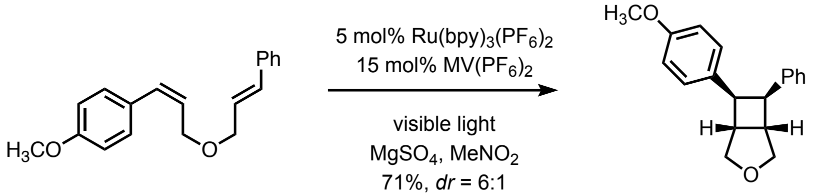
- **Mechanism:**



- Upon photoexcitation, the photocatalyst ($Ru(bpy)_3(PF_6)_2$) acts as a strong reductant, reducing MV by a single electron.
- The resulting Ru(III) species acts as a strong oxidant, which oxidizes the electron-rich styrene to produce a radical cation and regenerates photocatalyst.
- The resulting radical cation undergoes cyclization.

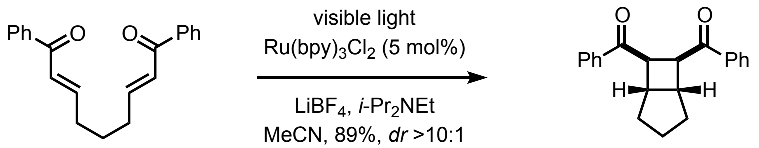
Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572–8574.

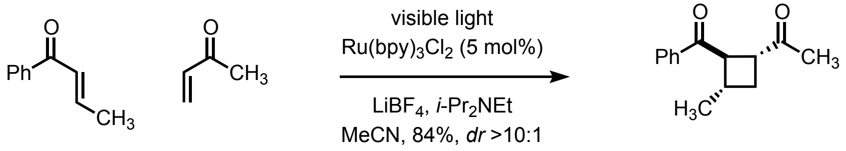
- *Cis*-olefins are isomerized during the course of the reaction:



- Limitation of the method: at least one of the styrenes must bear an electron-donating substituent at the *para* or *ortho* position. Aliphatic olefins are not suitable reaction partners.

- Photoredox catalysis can also be used for [2+2] cycloadditions of enones:





Ischay, M. A.; Anzovino, M.E.; Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.

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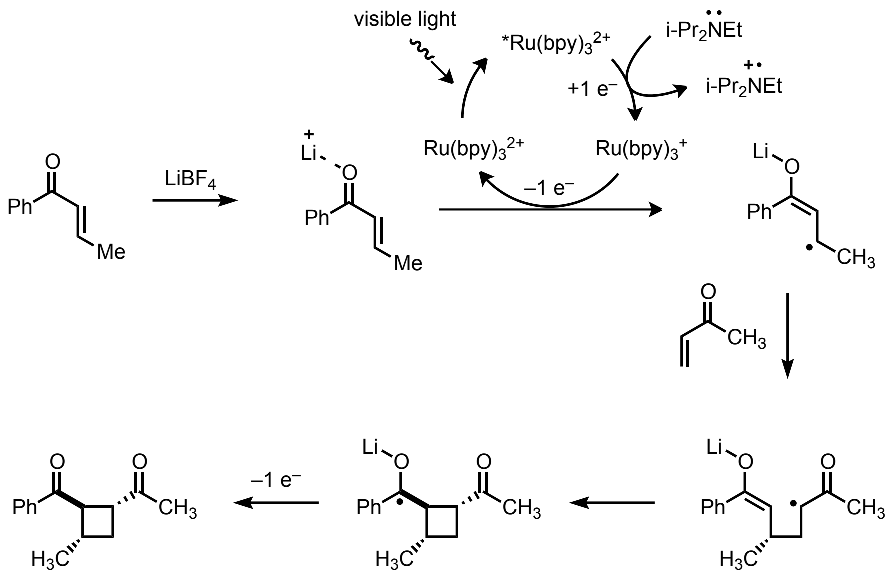
- **Mechanism:**

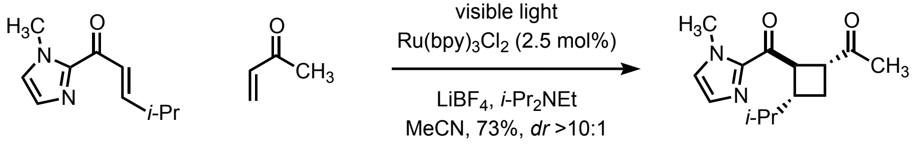


- Lewis acid coordination decreases the reduction potential of the enone, facilitating single electron transfer.

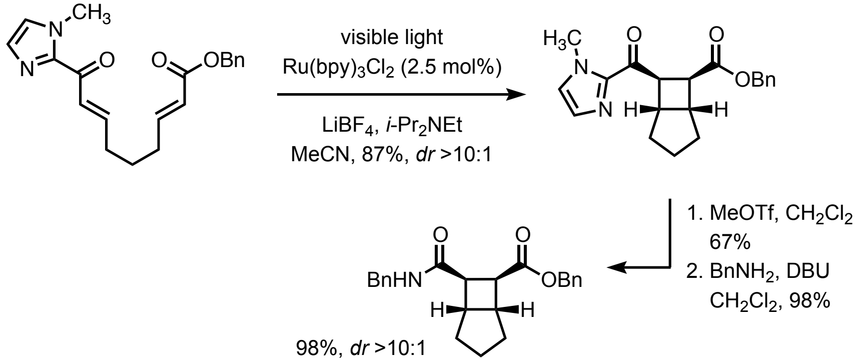
- Limitation of the method: one coupling partner must be an aromatic ketone. Aliphatic ketones and esters do not under go cycloaddition because of their higher reduction potentials.

Ischay, M. A.; Anzovino, M.E.; Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
Du, J.; Yoon, T.P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.

- α,β-Unsaturated 2-imidazolyl ketones also undergo photochemically induced cycloadditions:

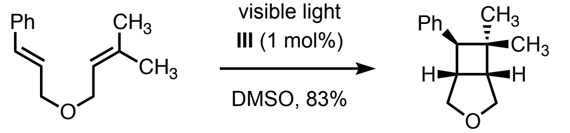


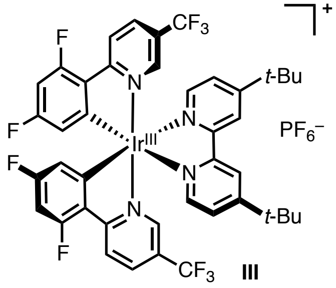
- An intramolecular variant was also developed.
- The product can be converted to acids, esters, thioesters and amides:



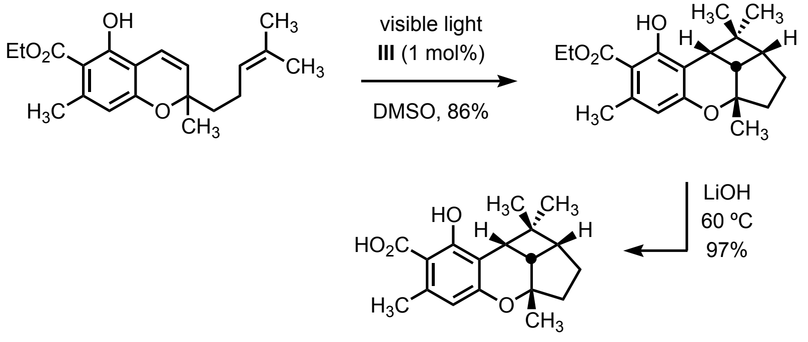
Tyson, E. L.; Farney, E. P.; Yoon, T. P. *Org. Lett.* **2012**, *14*, 1110–1113.

- Styrenes and alkenes undergo [2+2] cycloaddition in the presence of an Ir catalyst (**III**) and light. The catalyst functions as a photosensitizer.





III

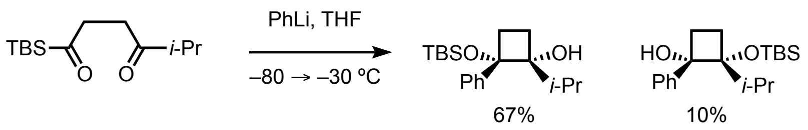


(±)-cannabiorcicyclolic acid

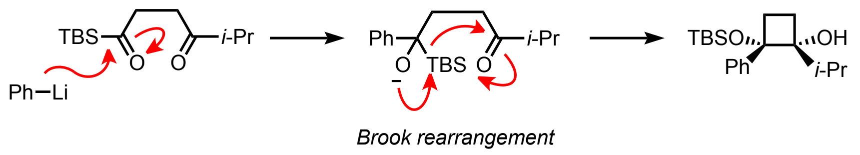
Lu, Z.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 10329–10332

Danica Rankic

- **Other Methods for Cyclobutane Synthesis**
- **Brook Rearrangement of 1,4-Dicarbonyls**
- Treatment of keto acylsilanes with organolithium reagents produces highly functionalized cyclobutanes favoring *cis*-stereochemistry between newly formed alcohols

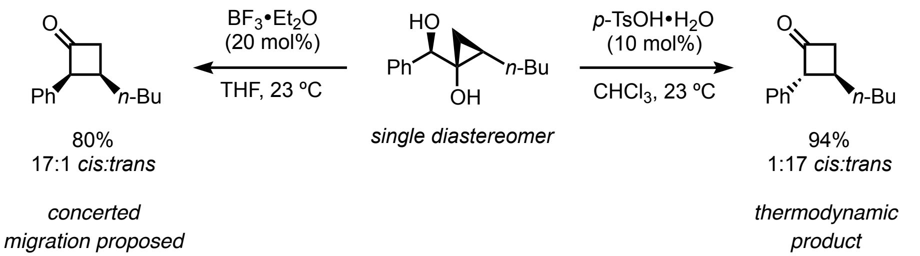


Mechanism:



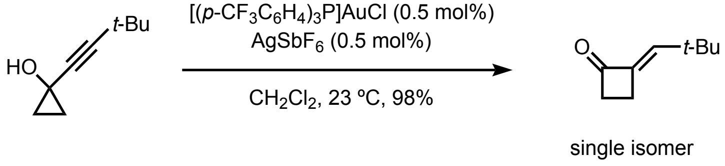
Takeda, K.; Haraguchi, H.; Okamoto, Y. *Org. Lett.* **2003**, *5,* 3705–3707.

- **Ring Expansion of Cyclopropanes via Pinacol-Type Rearrangements**
- Hydroxycyclopropyl carbinols can be ring-expanded by treatment with protic or Lewis acids.
- Either *cis*- or *trans*-substituted cyclobutanones could be produced from a single diastereomer of a an α-hydroxycyclopropyl carbinol:

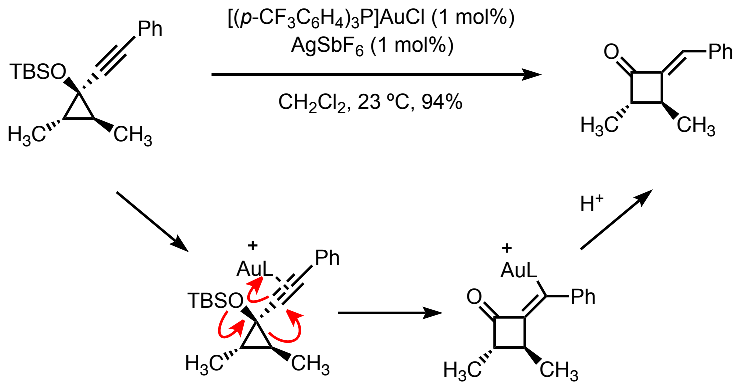


Hussain, M. M.; Li, H.; Hussain, N.; Urena, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516–6524.

- **Gold(I)-Catalyzed Ring Expansion of Cyclopropanes**
- Alkynyl cyclopropanols can undergo ring expansion upon treatment with catalytic Au(I):



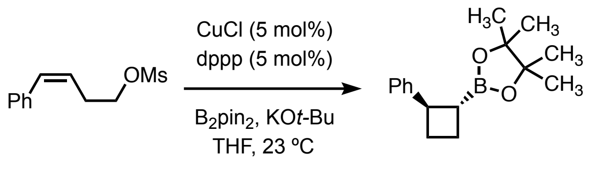
- The mechanism is proposed to involve a stereospecific 1,2-alkyl shift:

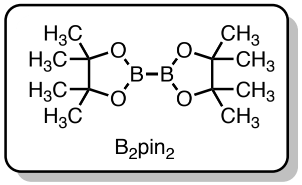


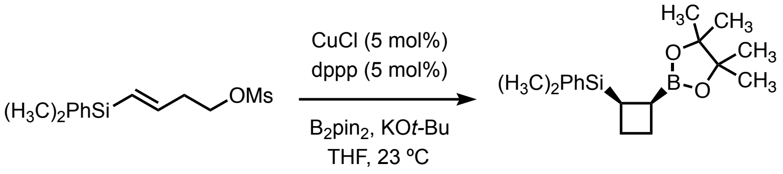
Markham, J. P.; Staben, S. T.; Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709.

Danica Rankic

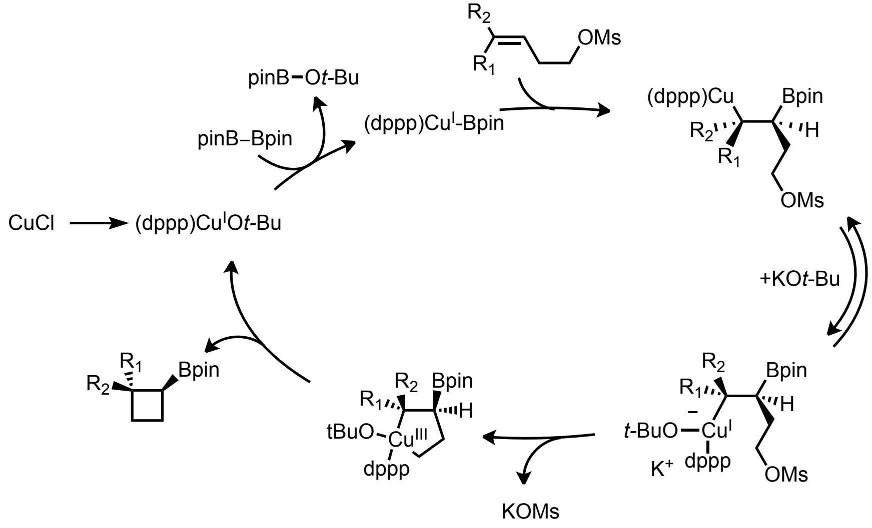
- **Cu-catalyzed 1,4-Ring closure**
- Homoallylic sulfonates can undergo borylation/cyclization using a Cu^I catalyst:







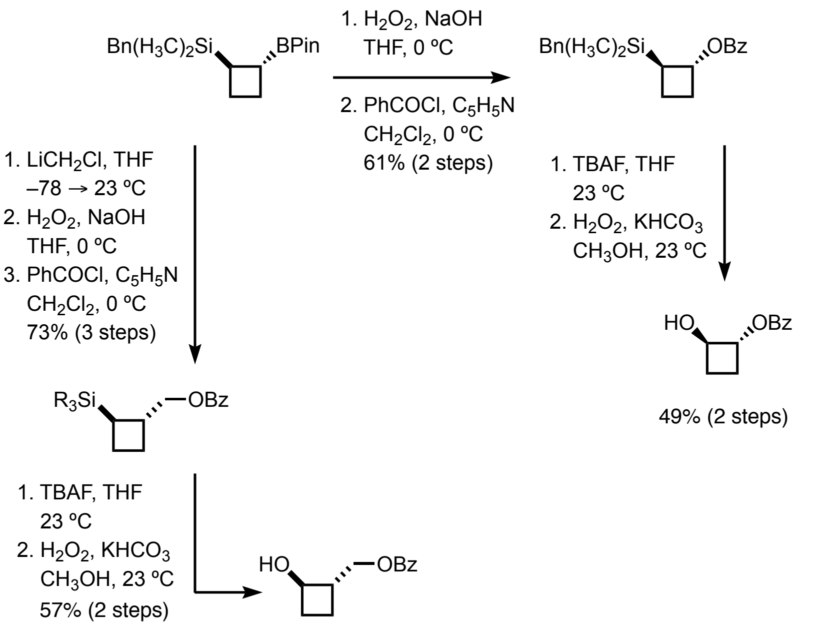
- Mechanism:

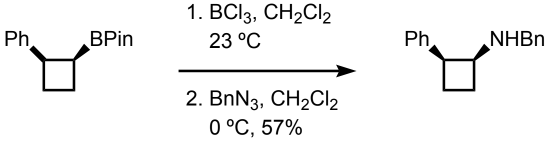


- Limitation of the method: only aryl- or silyl-substituted olefins react; alkyl olefins do not undergo borocupration.

Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990–5992.

- The products can be derivatized:





- Note that in each case the stereochemistry of the starting material is preserved in the product.

Markham, J. P.; Staben, S. T.; Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709.