Universität Konstanz

Metal-catalyzed Cyclization Reactions

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Konstanz, 03.08.22

Content

What is covered today?

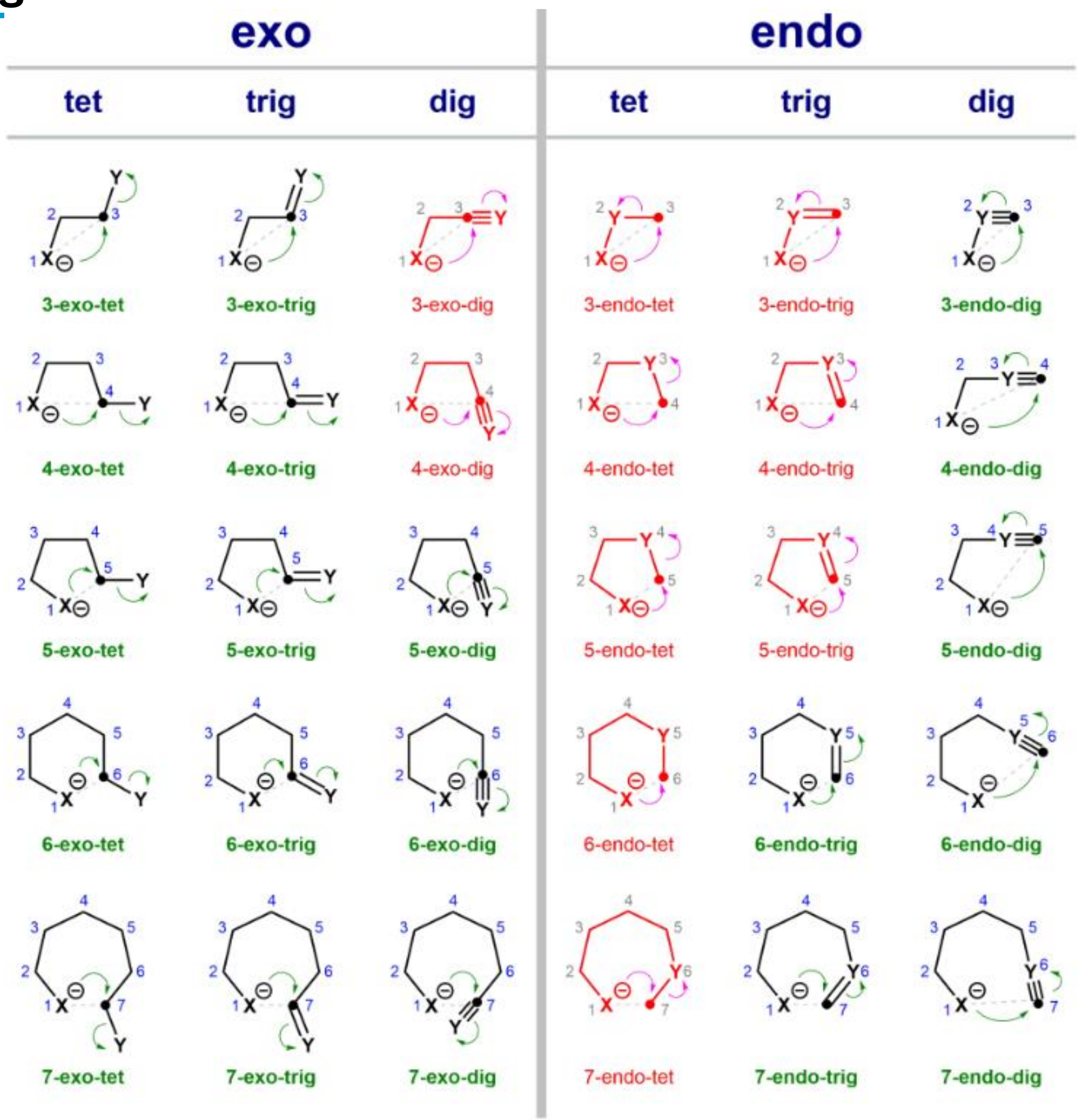
- Content mainly based on structure of the respective Science of Synthesis chapter
- Entry into broad spectrum of different methodologies
- Short introduction into general considerations regarding cyclization reactions
- Cycloadditions / radical processes / allylic substitution reactions / Cycloisomerizations

- Deepening of the underlying mechanisms: shift passive knowledge into active

What not to expect from todays talk:

- Comprehensive overview over one specific topic
- ‚familiar reactions‘ / abundant in Denksport
- Metathesis, Pauson-Khand reaction
- Free-radical cyclizations (Photoredox / Photo / stoichiometric)
- Cyclopropanation, NHK-reaction, Cross-Coupling Reactions
- Not truly catalyzed reactions

Baldwin‘s Guidelines and Beckwith‘s exceptions for intramolecular cyclization reactions



Terminology:

Number: refers to number of atoms in ring
Exo: bond is outside of the newly formed ring
Endo: bond is inside of the newly formed ring
Dig/Tet/Trig: hybridization at the ring closure carbon

Basis:

ideal angle of trajectory + stereo-electronic effects
Tet: 180° - Walden inversion
Trig: 107° - Bürgi-Dunitz
Dig: 120° obtuse angle- Wegner and Baughman

Cheminfographic.wordpress.com – Roman Valiulin
*Baldwin, J.E. Chem.Comm, **1976**, 734, 736*
*WIREs Comput. Mol. Sci. **2016**, 6, 487-514*

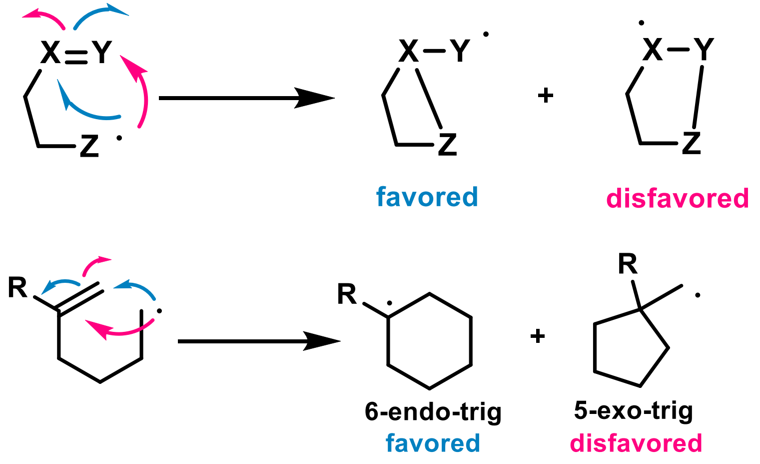
Baldwin‘s Guidelines and Beckwith‘s exceptions for intramolecular cyclization reactions

General exceptions:

- Ring strain of resulting cycle
- Holds true for ‚unbiased‘ systems
- Presence of heteroatoms
- Bond length / angle distortion
- Stepwise vs concerted mechanisms
- Cycloadditions

Beckwith Rules for radical cyclization reactions:

- Intramolecular addition (kinetic control) with n≤5: exo addition preferred
- Substituents disfavor cyclization at substituted position
- Homolytic cleavage favored when respective bond lies close to plane of adjacent filled non-bonding or π-orbital

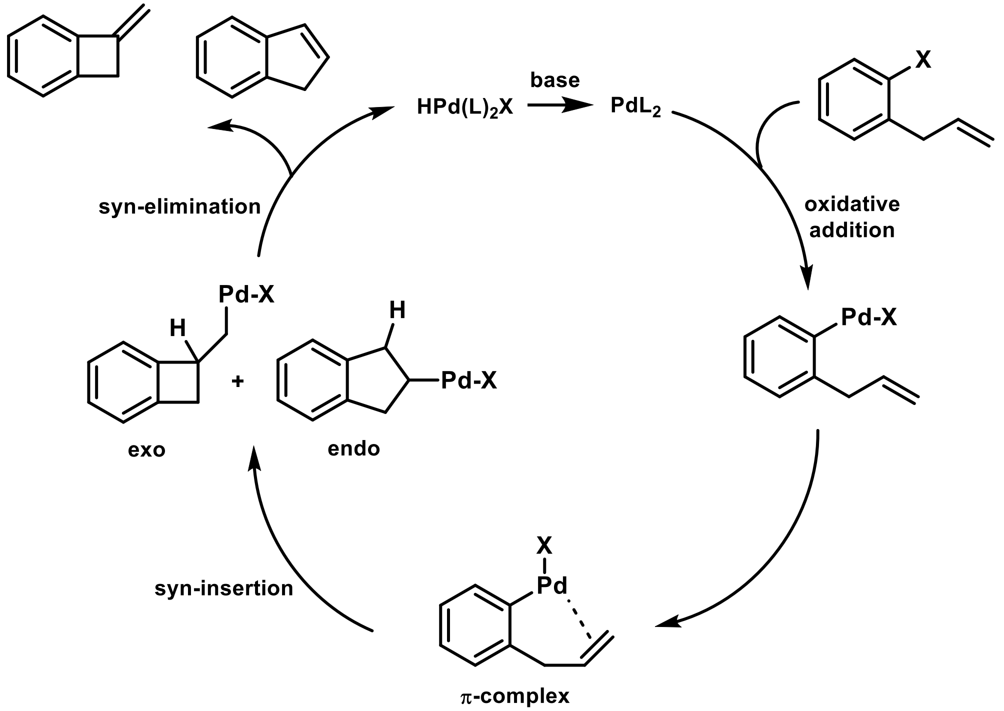


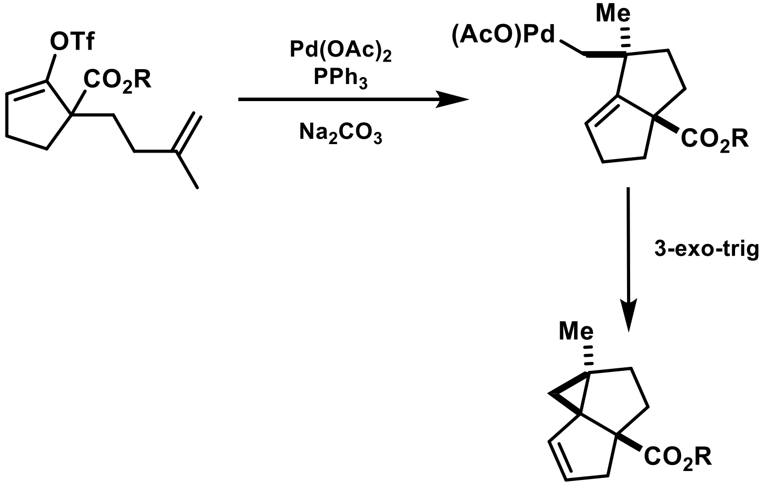
Intramolecular Heck-type cyclization

General:

Vinylation of aryl / vinyl / alkyl (pseudo)halides
Construction of isolated, fused, bridged, spiro rings
Wide application in cascade / domino processes

Mechanism:

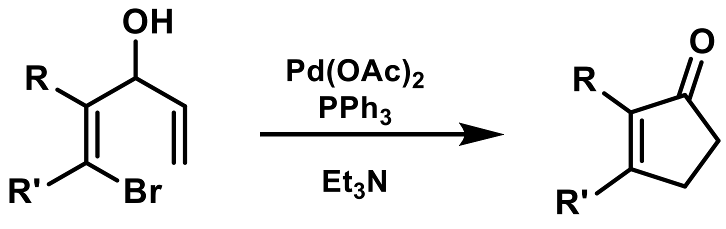


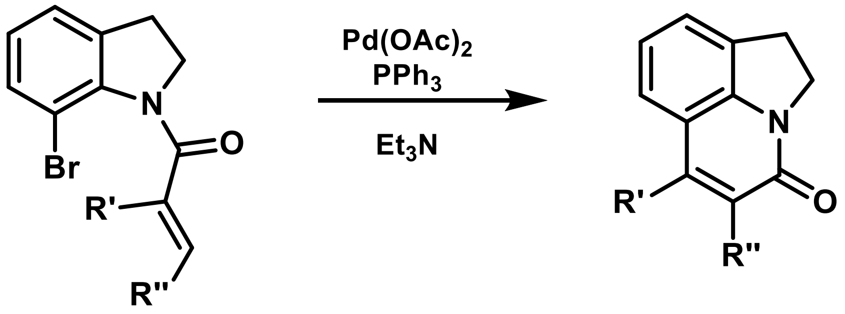


*Heck, R.F. J.Am.Chem.Soc., **1968**, 90, 5518*
*Grigg, R. et al., Tetrahedron, **2006**, 62, 9523*

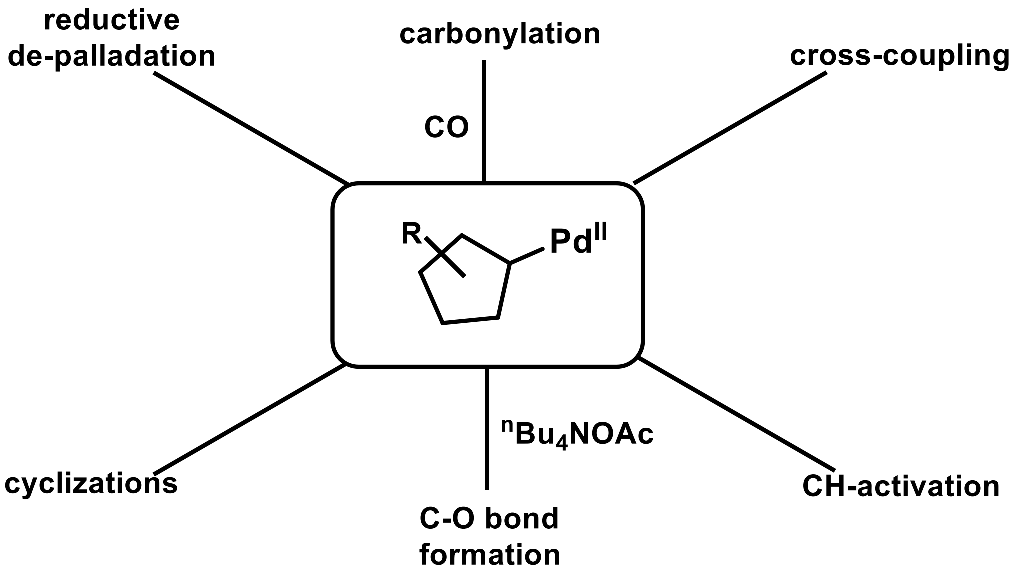
Intramolecular Heck-type cyclizations

Disfavored 5-endo / 6-endo cyclizations:





Tandem-Heck processes:



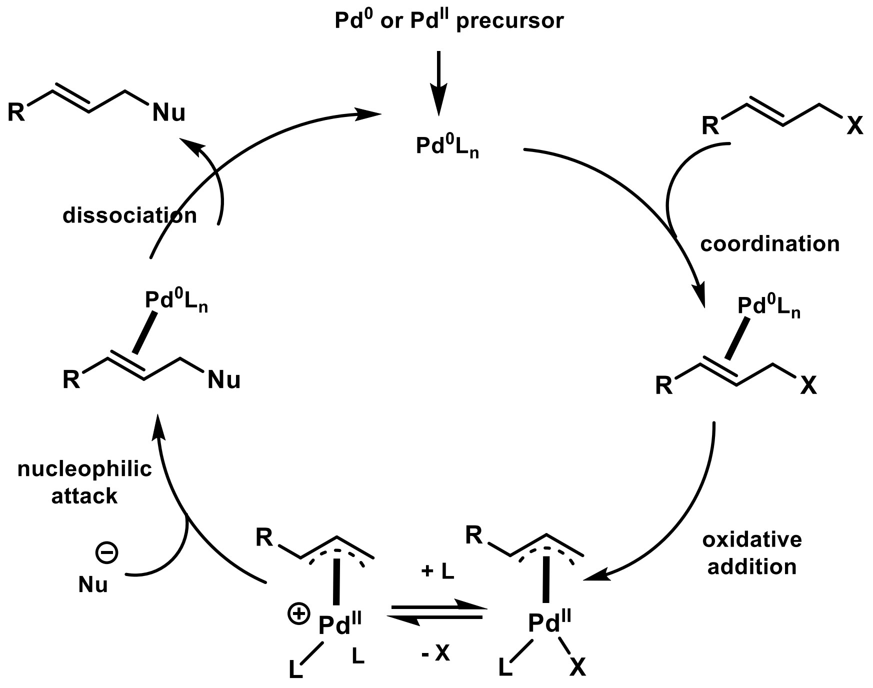
Liu X. et al. Org.Lett., ***2013****, 15, 4814*
Chen B., Synlett, ***2006****, 259*
Dankwardt, J.W., Filippin, L.A., J.Org.Chem., ***1995****, 60, 2312*

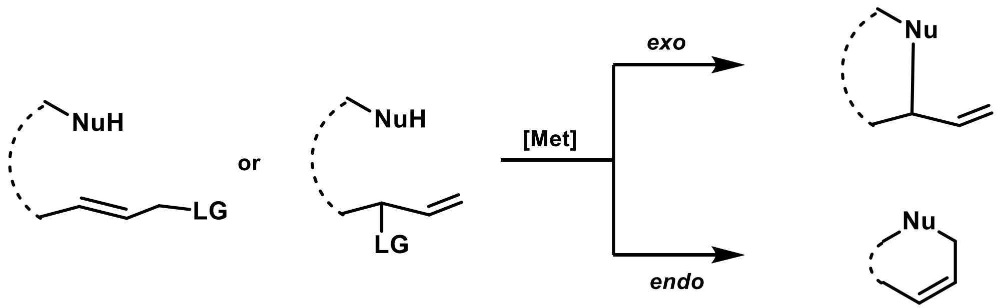
Intramolecular allylic substitution reactions

General:

Seminal work by Trost & Tsuji in 1970
Nucleophilic attack by **soft** carbon- / nitrogen- / oxygen-nucleophiles
π-allyl-Palladium complexes as electrophiles

Modes of action:



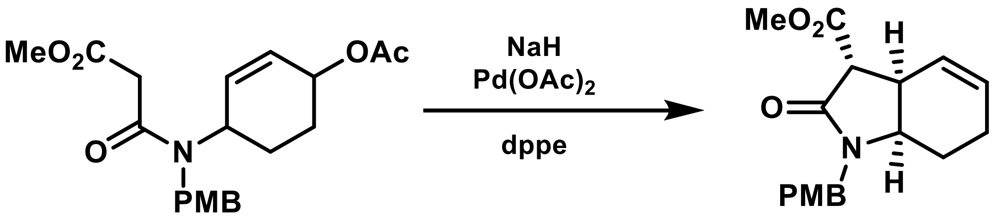


*Trost, B.M., Tetrahedron, **1977**, 33, 2615*

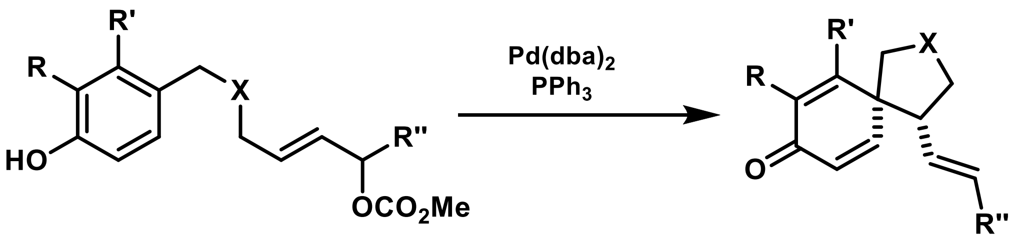
Intramolecular allylic substitution reactions

Carbon Nucleophiles:

5-exo-trig cyclization

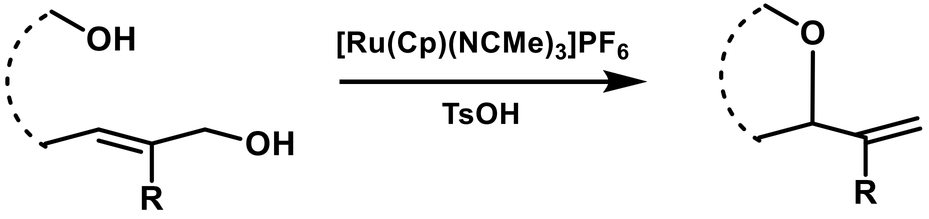


Allylic dearomatization

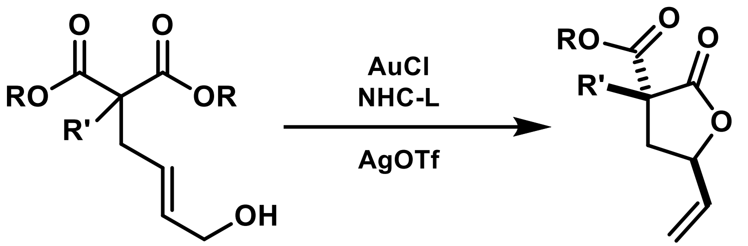


Oxygen Nucleophiles:

Etherification



Esterification



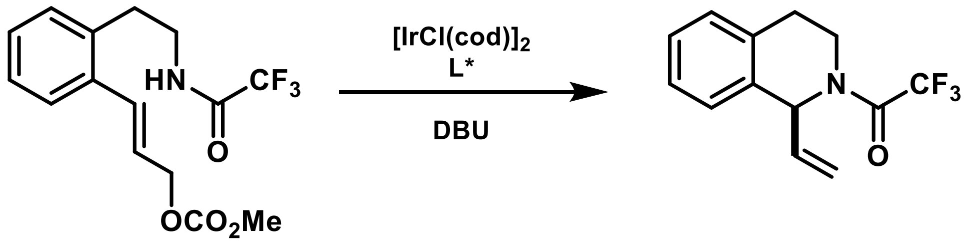
Lemaire, S. et al., Eur.J.Org.Chem., ***2004****, 2840*
Nemoto, T., Org. Lett., ***2010****, 12, 5020*

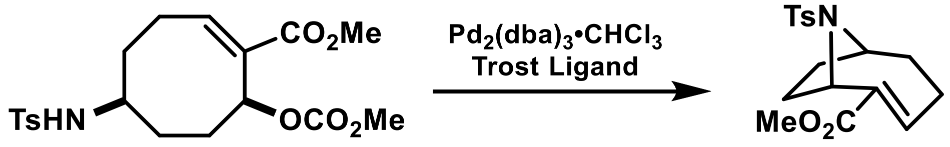
Miyata, K., Angew. Chem., ***2011****, 123, 4745*
Chiarucci, M. et al. Beilstein J. Org. Chem., ***2011****, 7, 1198*

Intramolecular allylic substitution reactions

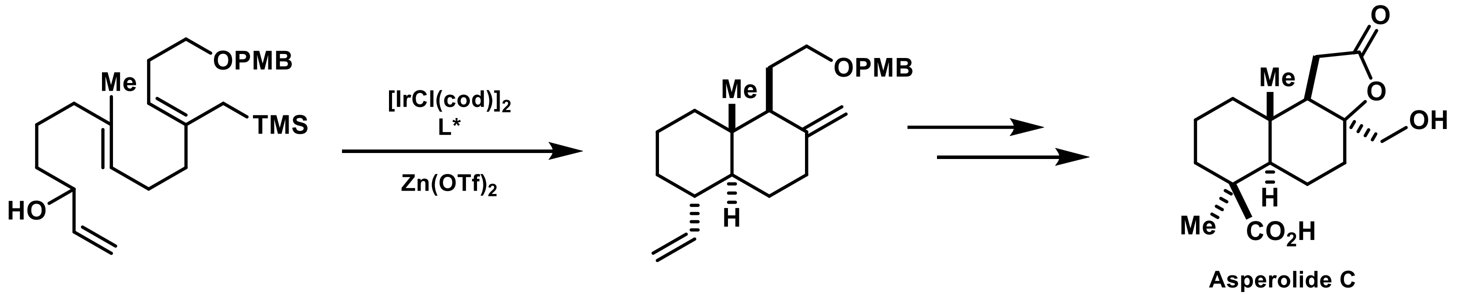
Nitrogen Nucleophiles:

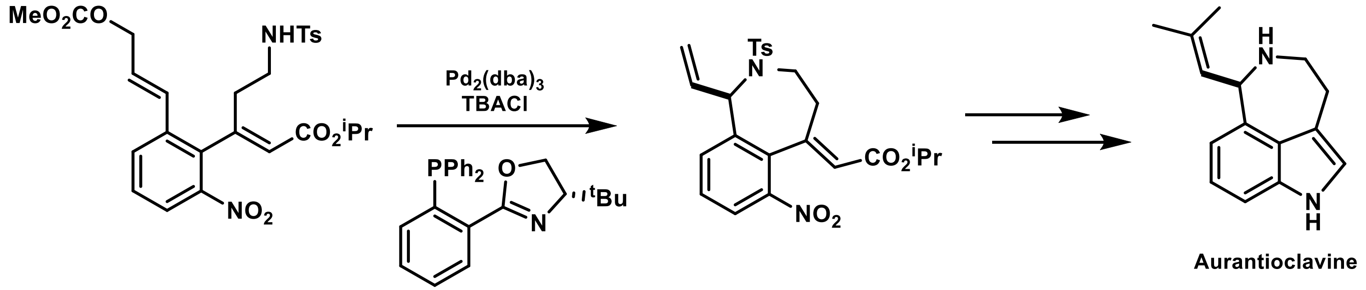
Wide range of reactivity: pyridines, pyrazines, indoles, aniline, amines, amides
Wide range of applicable TM: Pd, Au, Ir, Ru, …





Application in total synthesis:



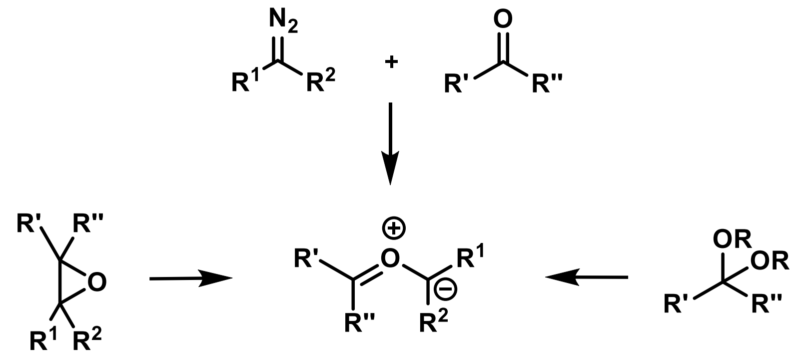


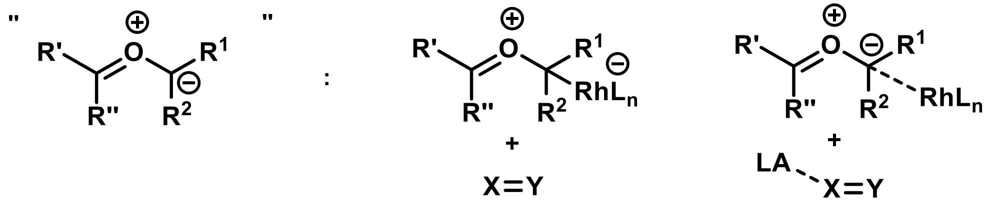
*Trost, B.M., J. Am. Chem. Soc., **1999**, 121, 3057*
*Feringa, B.L., Angew. Chem., **2011**, 123, 714*
*Carreira, E.M., Angew. Chem., **2013**, 125, 12388*
*Takemoto, Y., Org. Lett., **2014**, 16, 996*

1,3-Dipolar Cycloadditions with Carbonyl ylides

- (3+2) CA between carbonyl ylide and π-bond
- Valuable transformation for generation of O- / N-heterocycles

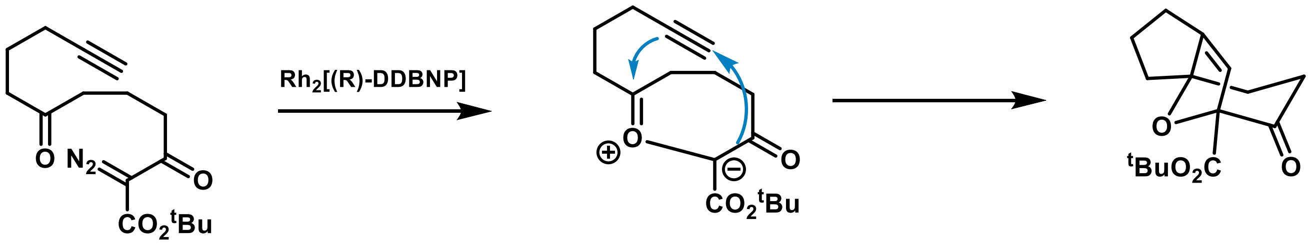
Generation and Complexation:

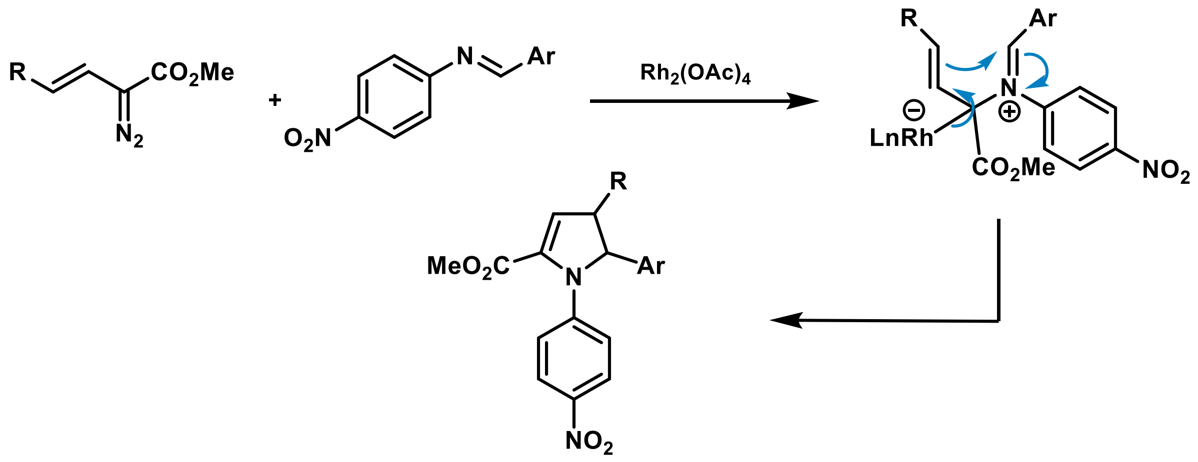




Rh-cat. Controlled or LA-cat. Controlled

Rhodium-catalyzed Cycloadditions:



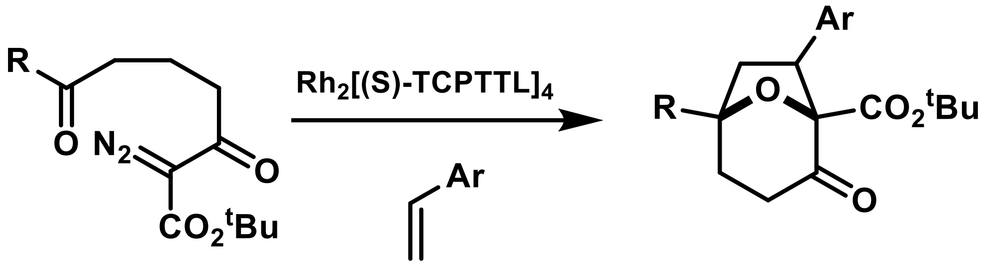


*De Marchm, P., Huisgen, R., J. Am. Chem. Soc., **1982**, 104, 4952*
*Bentabed-Ababsa, G. et al., Org. Biomol. Chem., **2012**, 10, 8434*
*Hodgson, D.M., et al., Tetrahedron: Asymmetry, **2009**, 20, 754*

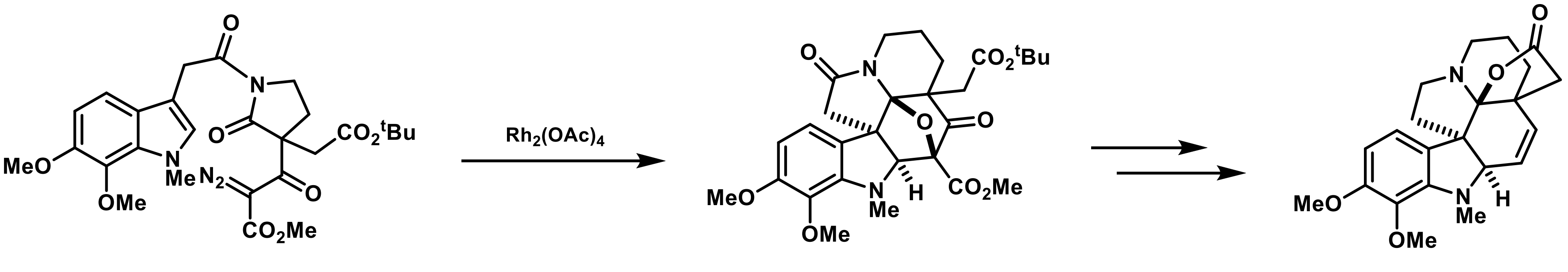
1,3-Dipolar Cycloadditions with Carbonyl ylides

Selectivity:

- Generally, regio- / diastereoselectivity is controlled upon Rh-cat and/or Lewis-acid cat.
- Enantioselective methods well established



Application in total synthesis:



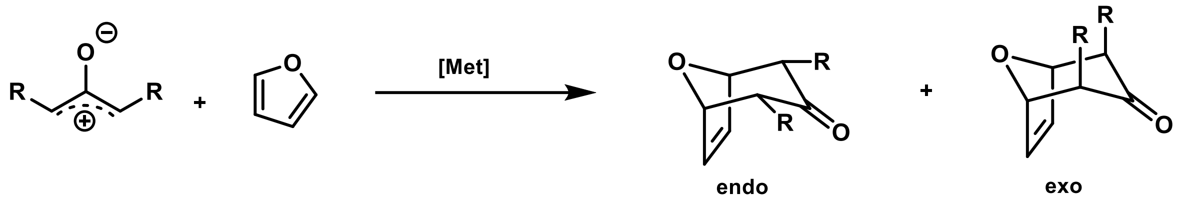
Aspidophytine

Shimada, N. et al., Org. Lett., ***2008***, *10, 3603*
Mejia-Oneto, J.M., Padwa, A., Helv. Chim. Acta, ***2008***, *91, 285*

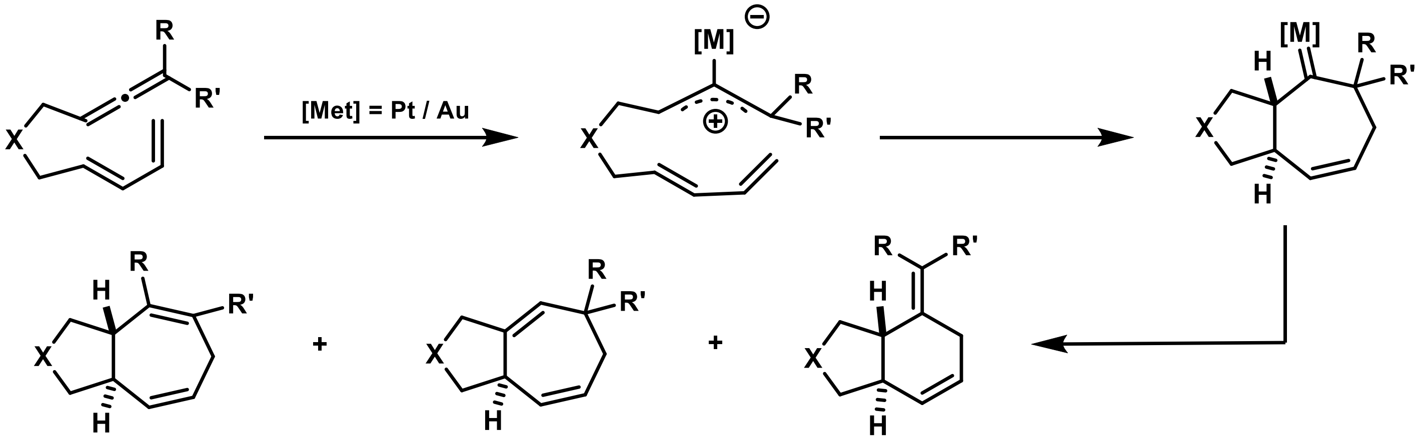
(4+3)-Cycloadditions involving allylic cations

General:

Atom-economical transformation between diene and allylic cation
Resulting in cycloheptenyl cation
Mechanism: continuum between concerted and stepwise process
Only few truly catalyzed examples; rather metal-mediated reactions



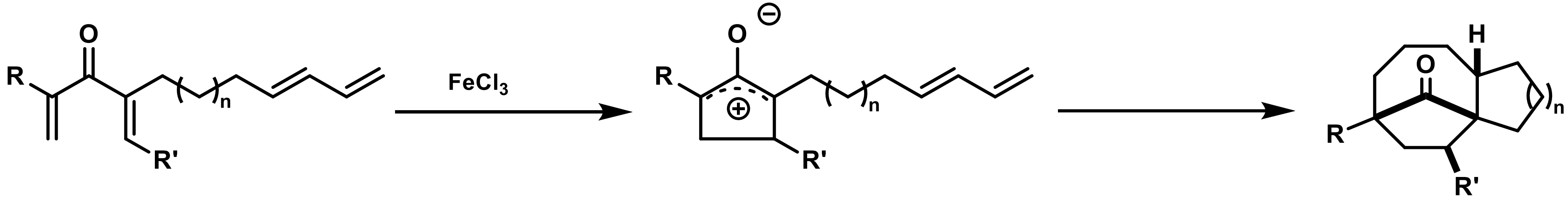
Mode of action (in catalyzed case):



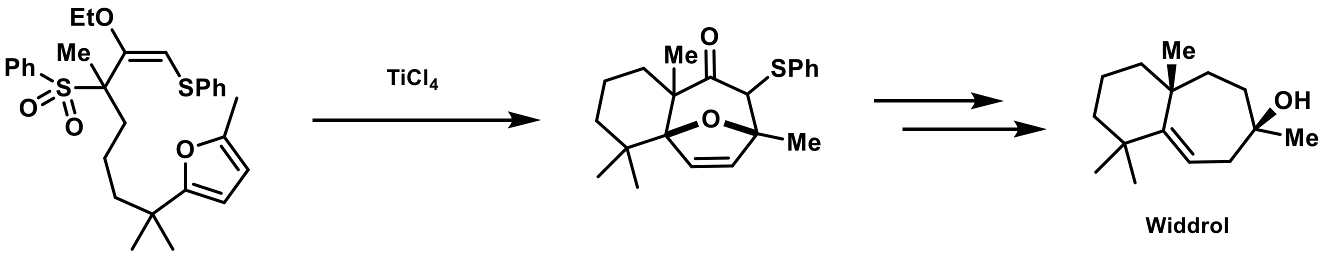
Harmata, M., Chem. Comm. ***2010****, 46, 8904 / 8886*
Mascarenas, J.L., et al., J. Am. Chem. Soc., ***2009****, 131, 13020*

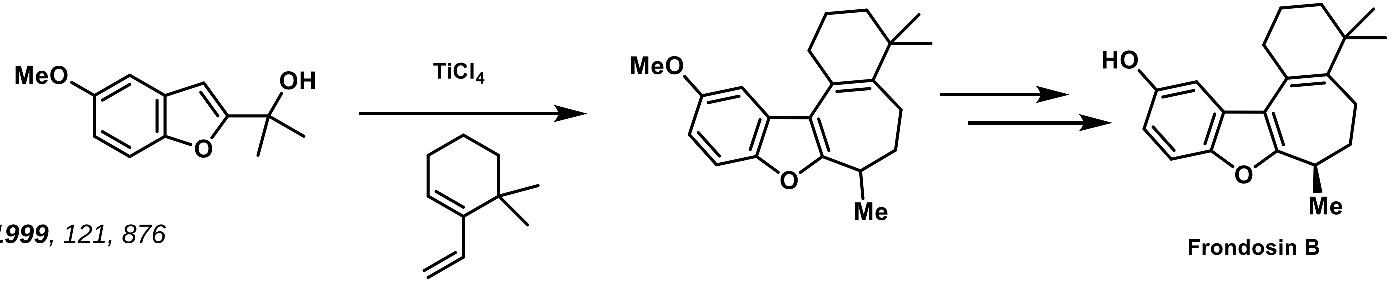
(4+3)-Cycloadditions involving allylic cations

Nazarov-Intermediate as (4+3)-precursor:



Application in total synthesis:





*Wang, Y., Arif, A.M., West, F.G., J. Am. Chem. Soc., **1999**, 121, 876*
*Winne, J.M., Chem-Eur. J., **2014**, 20, 253*
*Harmata, M., et al., Heterocycles, **2004**, 62, 583*

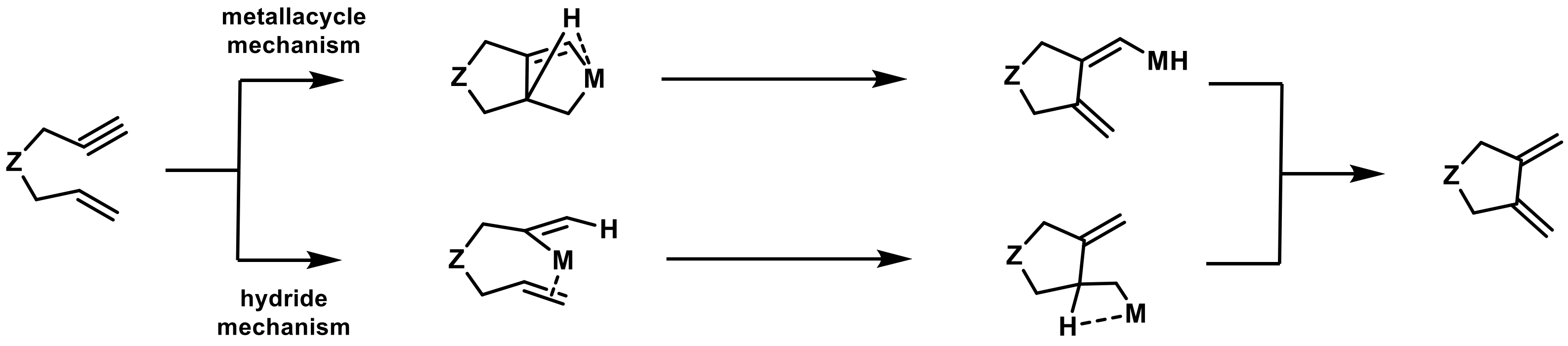
Cycloisomerizations of substrates with multiple unsaturated bonds

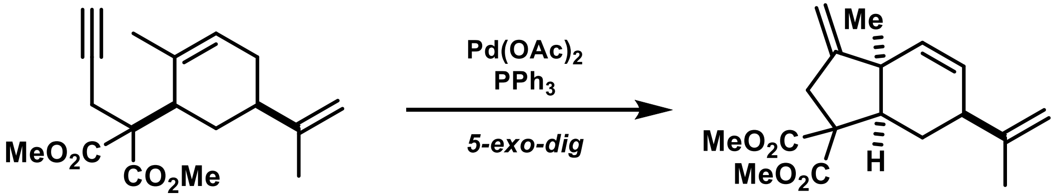
General:

Atom-economical transformations
Produces cyclic frameworks from simple acyclic starting materials
Broad spectrum of TM applied: Pd, Ti, Fe, Ru, Rh, Au, …

Modes of action:

1,6-Enynes:



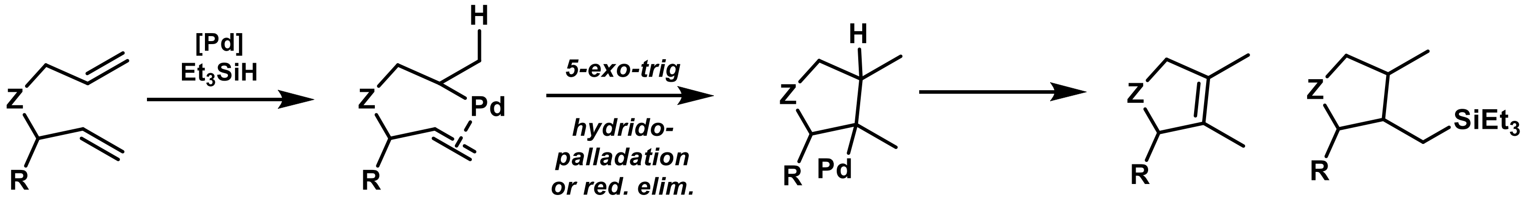


Michelet, V., Toullec, P.Y., Genet, J.P., Angew. Chem., ***2008****, 120, 4268*

Trost, B.M., Lautens, M., Chan, C., J. Am. Chem. Soc., ***1991****, 113, 636*

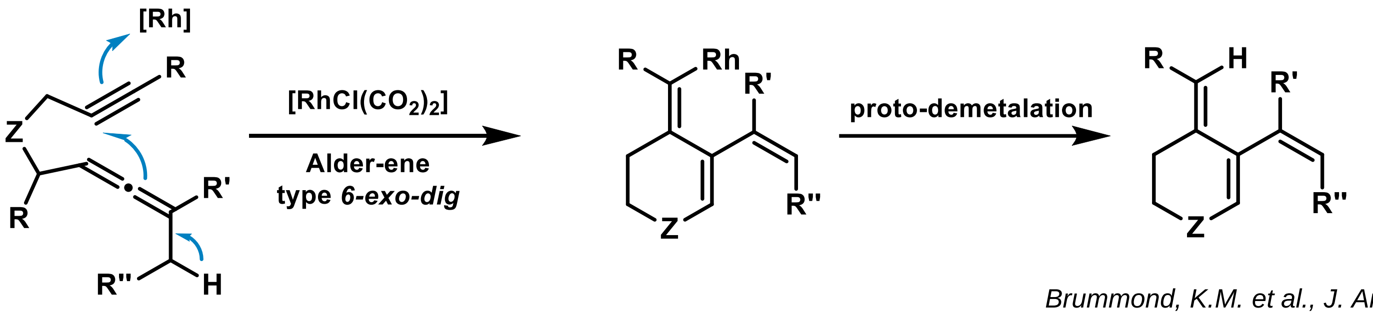
Cycloisomerizations of substrates with multiple unsaturated bonds

1,6-Dienes:



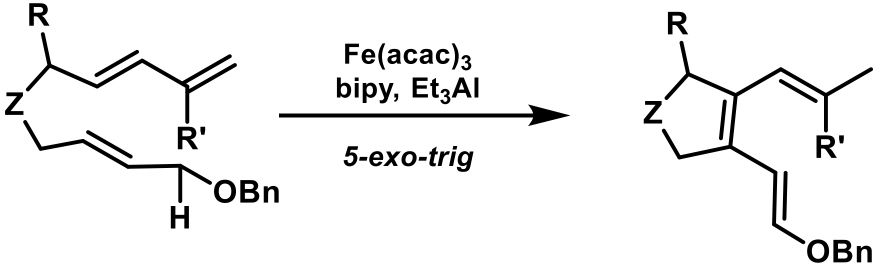
Kisanga, P., Widenhoefer, R.A:., J. Am. Chem. Soc., ***2000***, *122, 10017*

Allenynes:



Brummond, K.M. et al., J. Am. Chem. Soc., ***2002***, *124, 15186*

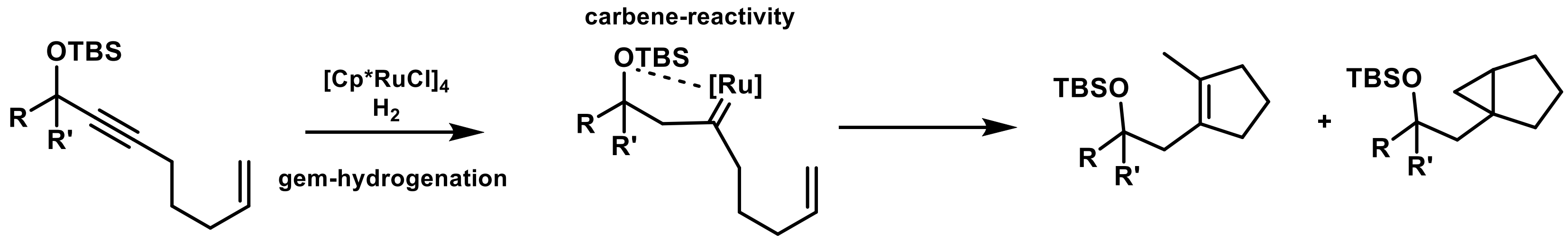
(1,3-Diene)enes:



Takacs, J.M., Anderson, L.G., J. Am. Chem. Soc., ***1987***, *109, 2200*

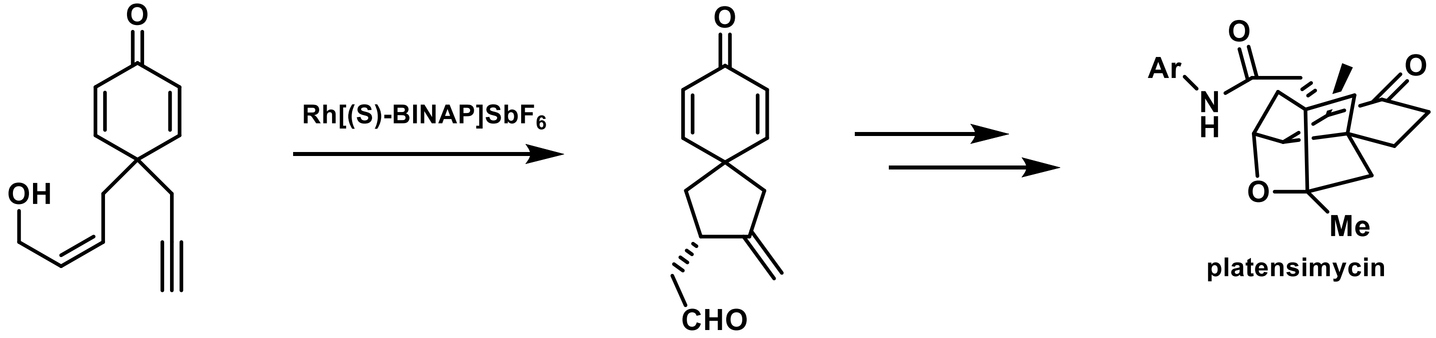
Cycloisomerizations of substrates with multiple unsaturated bonds

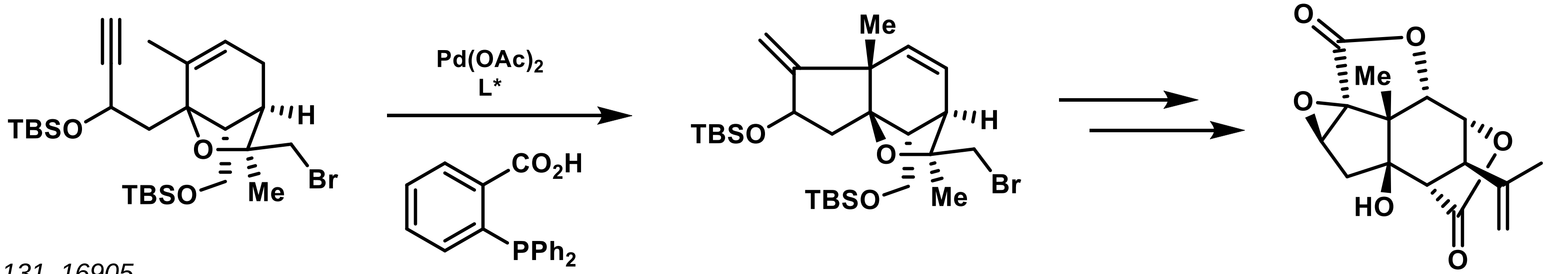
Hydrogenative Cycloisomerization:



Fürstner, A. et al., Angew. Chem., ***2022***, *61. e202113827*

Application in total synthesis:





picrotoxinin

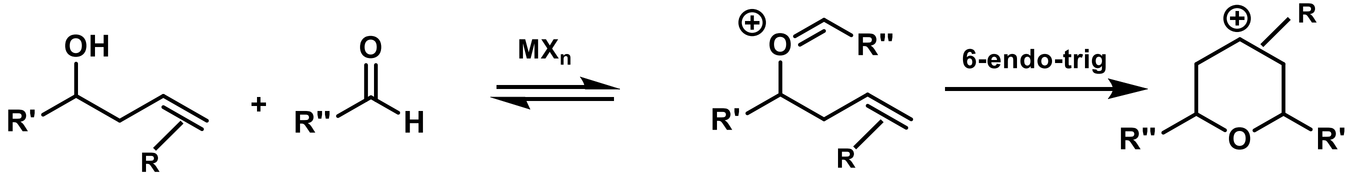
Nicolaou, K.C. et al., J. Am. Chem. Soc., ***2009***, *131, 16905*
Trost, B.M. et al., J. Am. Chem. Soc., 1999, 121, 6183

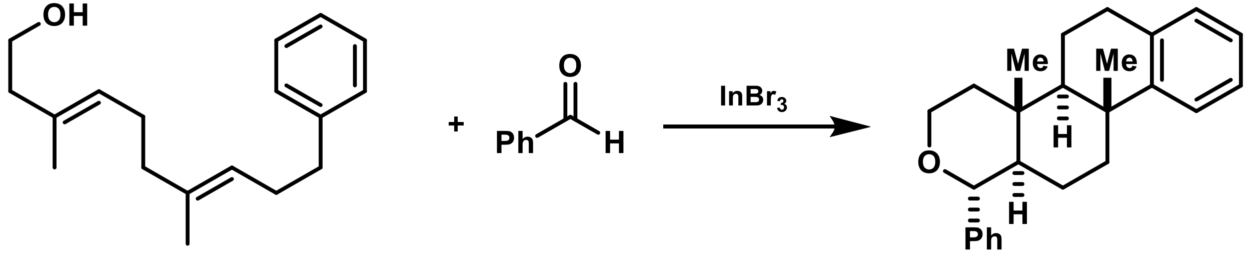
Cyclization reactions of alkenes and alkynes

General:

TM as hard Lewis acids for generation of cationic intermediates
Nucleophilic olefins / alkynes must not (Prins) / must (Ene) react with TM

Prins cyclization: between homoallylic alcohol & aldehydes / aza-variant / alkyne-variant

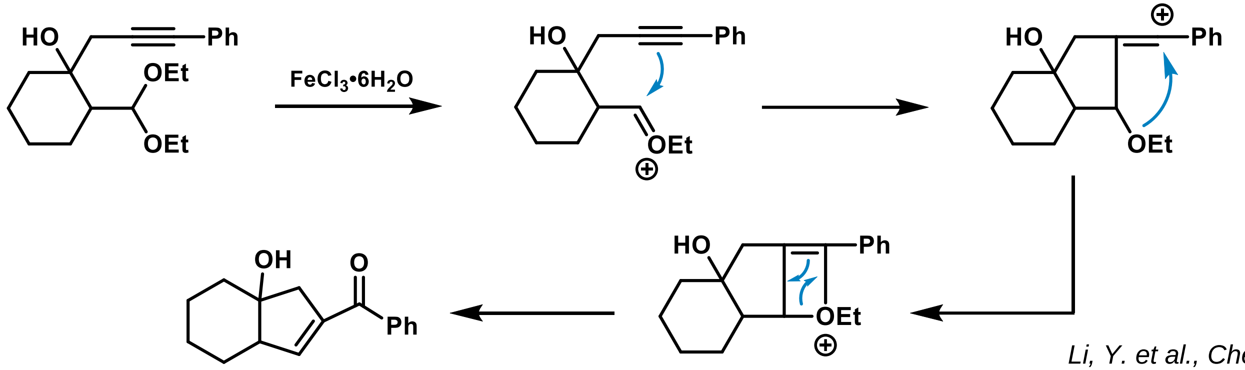




*Trost, B.M., Fleming, I., Eds.; Pergamon: Oxford, **1991**, Vol 2, p527*
*Loh, T.-P. et al., Angew. Chem. Int. Ed., **2012**, 51. 10619*

Cyclization reactions of alkenes and alkynes

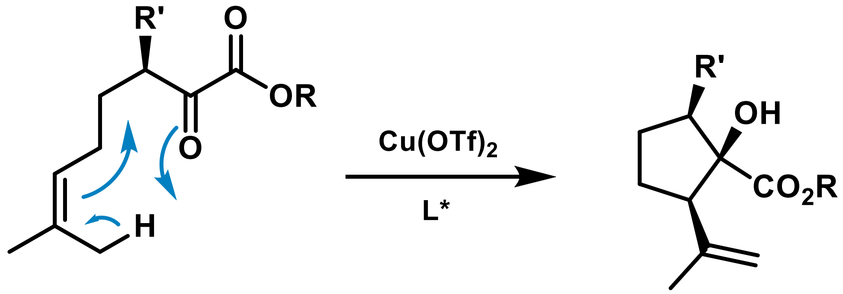
Fe^{III}-cat. Cyclization of Alkynyl-Aldehyde Acetals:



Li, Y. et al., Chem.-Eur. J., ***2010****, 16, 9264*

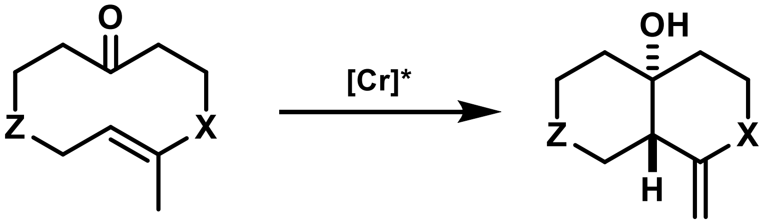
Carbonyl-Ene Reaction:

Enantioselective examples well known:



Yang, D., Yang, M., Zhu, N.-Y., Org. Lett., ***2003****, 5, 3749*

Transannular bond formation:

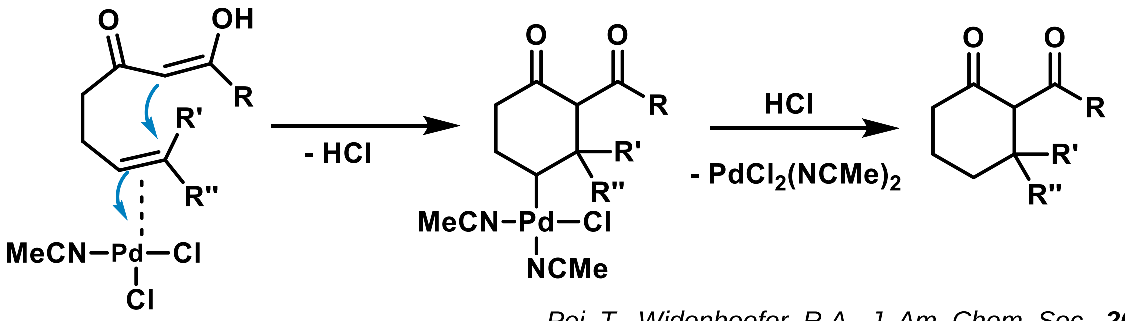


Rajapaksa, N.S., Jacobsen, E.N., Org. Lett., ***2013****, 15, 4238*

Cyclization reactions of alkenes and alkynes

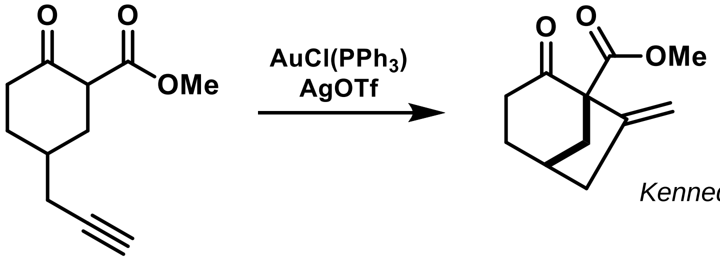
Conia-Ene Reaction:

6-endo-trig cyclization w/o β-hydride elim:



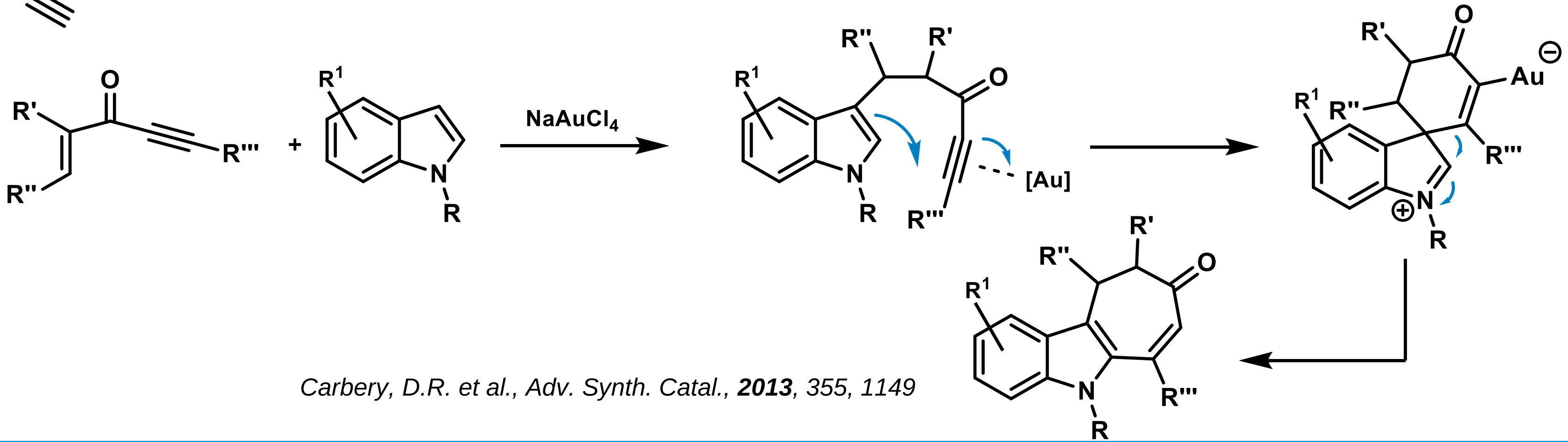
Pei, T., Widenhoefer, R.A., J. Am. Chem. Soc., ***2001****, 123, 11290*

5-exo-dig cyclizations:



Kennedy-Smith, J.J., Staben, S.T., Toste, F.D., J. Am. Chem. Soc., ***2004****, 126, 4526*

Wide applications in heterocycle-chemistry:



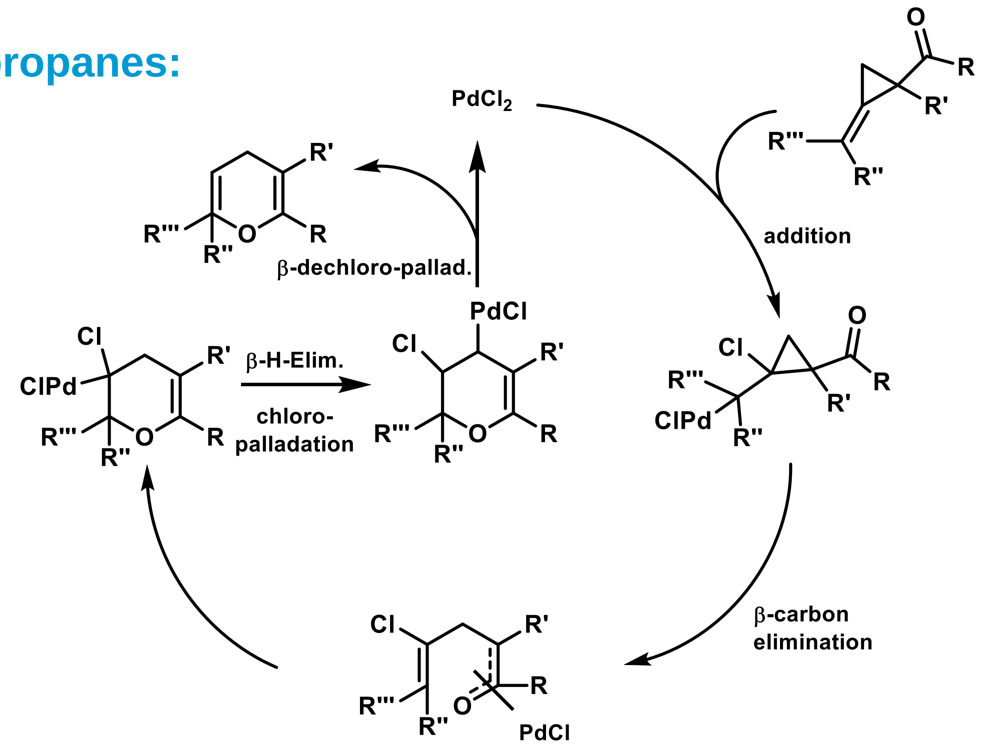
Carbery, D.R. et al., Adv. Synth. Catal., ***2013****, 355, 1149*

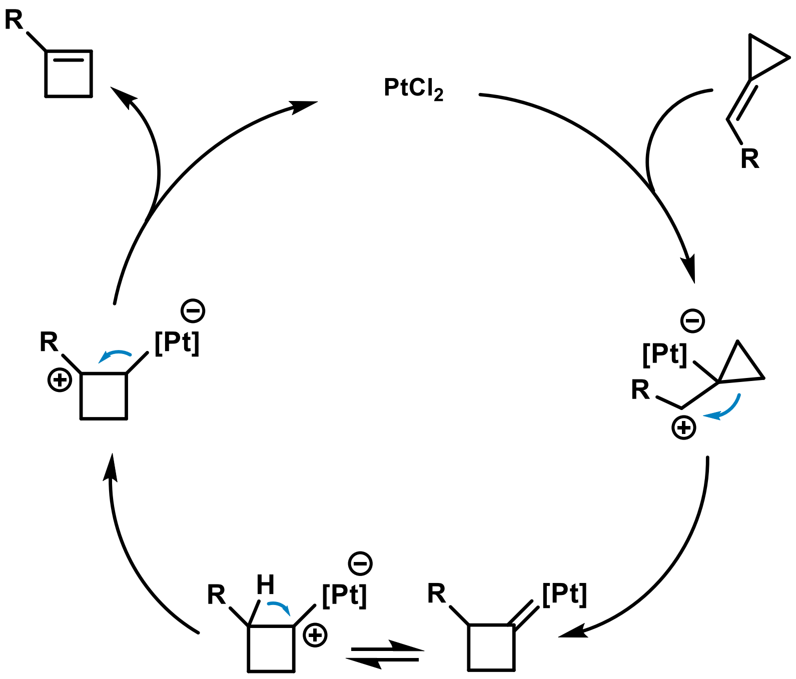
Cyclizations involving Cyclopropane Ring Opening

General:

Ring-Opening process as strong driving force (ring strain)
Smallest carbocycle easily introduced and offers unique properties as functional group

Methylene Cyclopropanes:



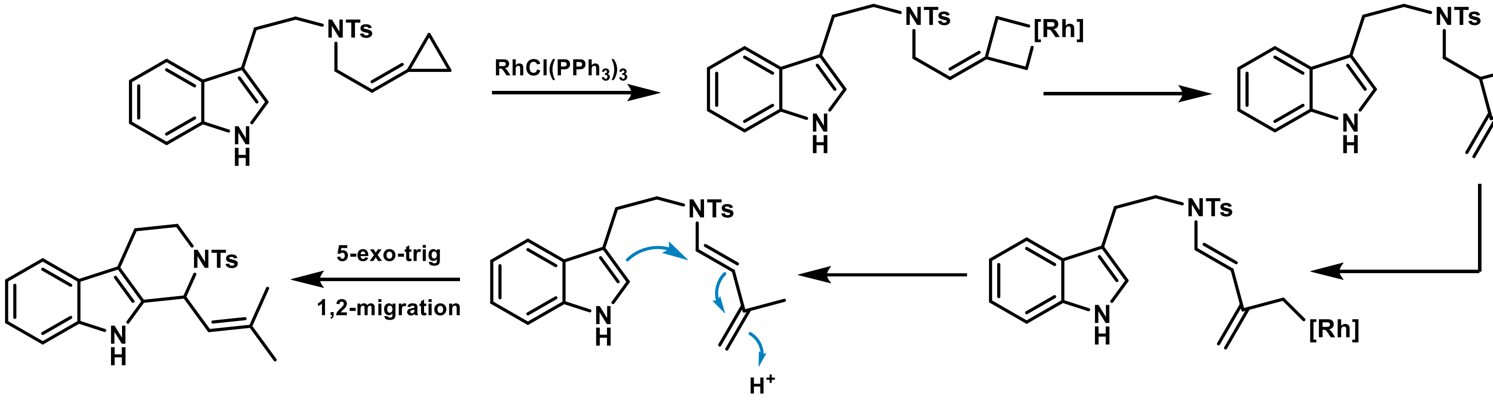


Ma, S., Zhang, J., J. Am. Chem. Soc., ***2004***, *126, 9645*

Fürstner, A., Aissa, C., J. Am. Chem. Soc., ***2006***, *128, 6303*

Cyclizations involving Cyclopropane Ring Opening

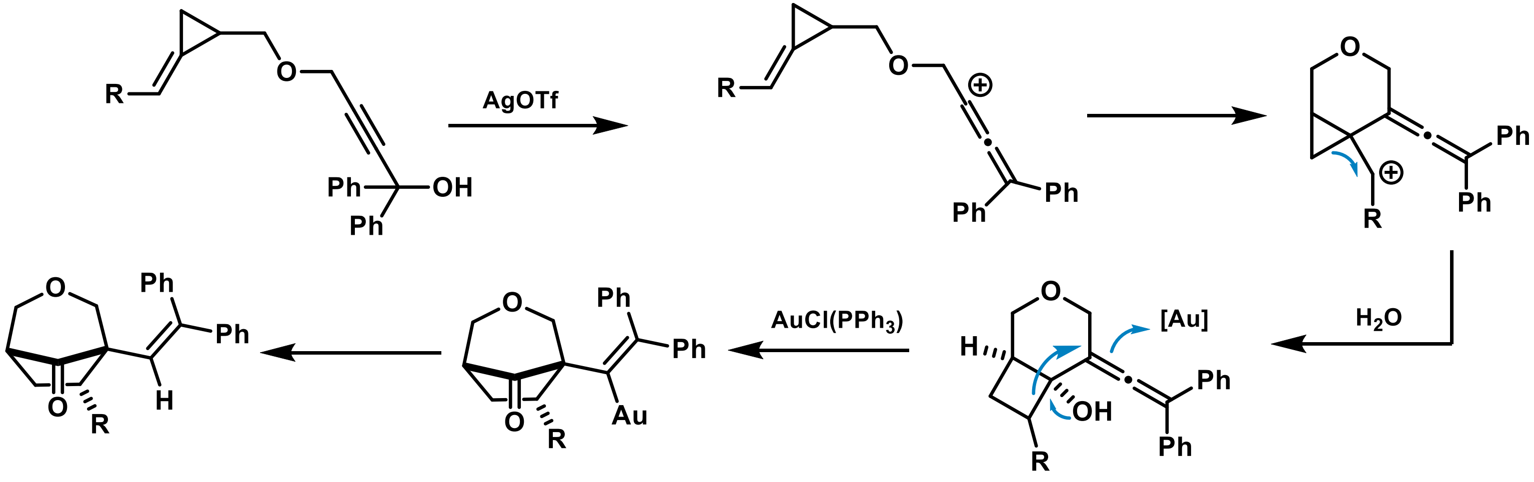
Rh-catalyzed cycloisomerization:



Insertion followed by C-C bond cleavage
Isomerization and β-hydride elimination
Friedel-Crafts-type 5-exo-trig followed by 1,2-migration

*Shi, M. et al., Chem-Eur. J.. **2013**, 19, 13668*

Au-catalyzed Cycloisomerization:

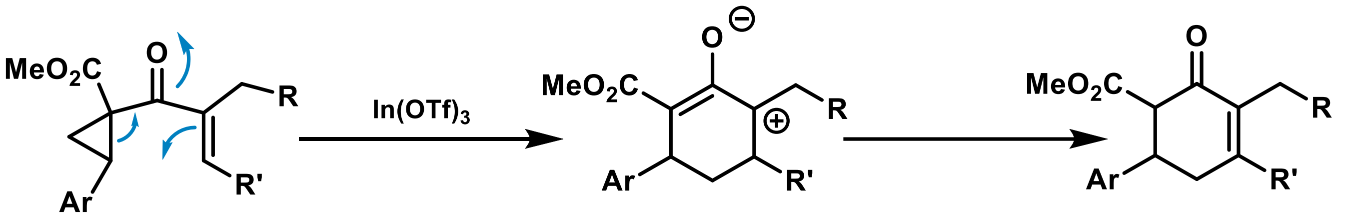


Formation of allenylic cation
Intramolecular attack of methylene followed by ring expansion
Water-quench and Au-cat. Semi-pinacol to activated allene

*Shi, M. et al., Org. Lett., **2009**, 74, 9466*

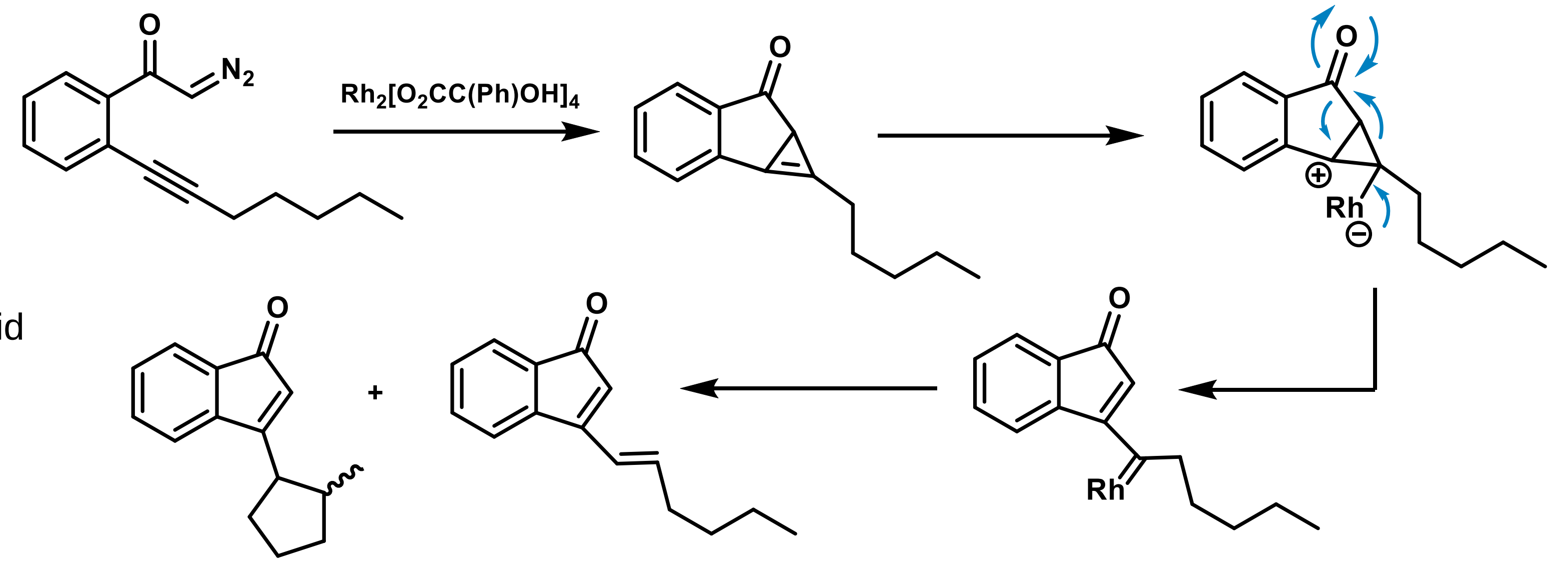
Cyclizations involving Cyclopropane Ring Opening

Homo-Nazarov Cyclization:



*Patil, D., Phun, L.H., France, S., Org. Lett., **2010**, 12, 5684*

Rh-catalyzed Cycloisomerization:



In situ formed cyclopropane followed by
Electrophilic addition of Rh-complex
Ring-opening generates enone + carbenoid

*Schoffstall, A.M. et al., J. Org. Chem., **1990**, 55, 414*

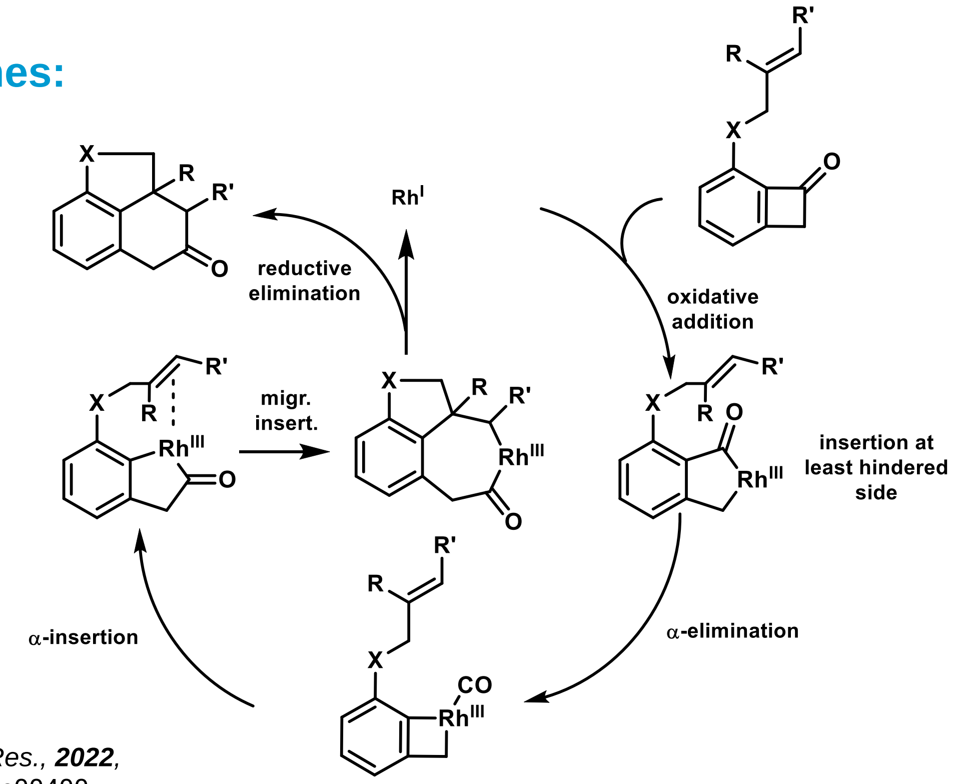
Cyclizations involving Cut & Sew Transformations of Cyclobutanones

General:

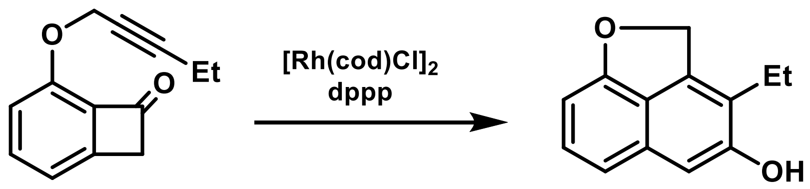
C-C bond activation; between π-bond and cyclobutanone
Utilized for preparation of fused / bridged rings

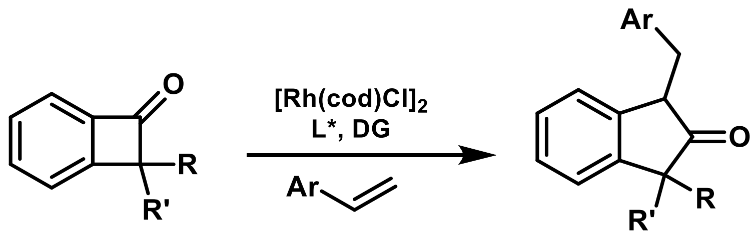
Typical Rh chemistry
Basis: ring strain release + α-carbonyl bond

Benzocyclobutenones:



Olefin equivalent: alkyne, oxime ethers, aldehydes



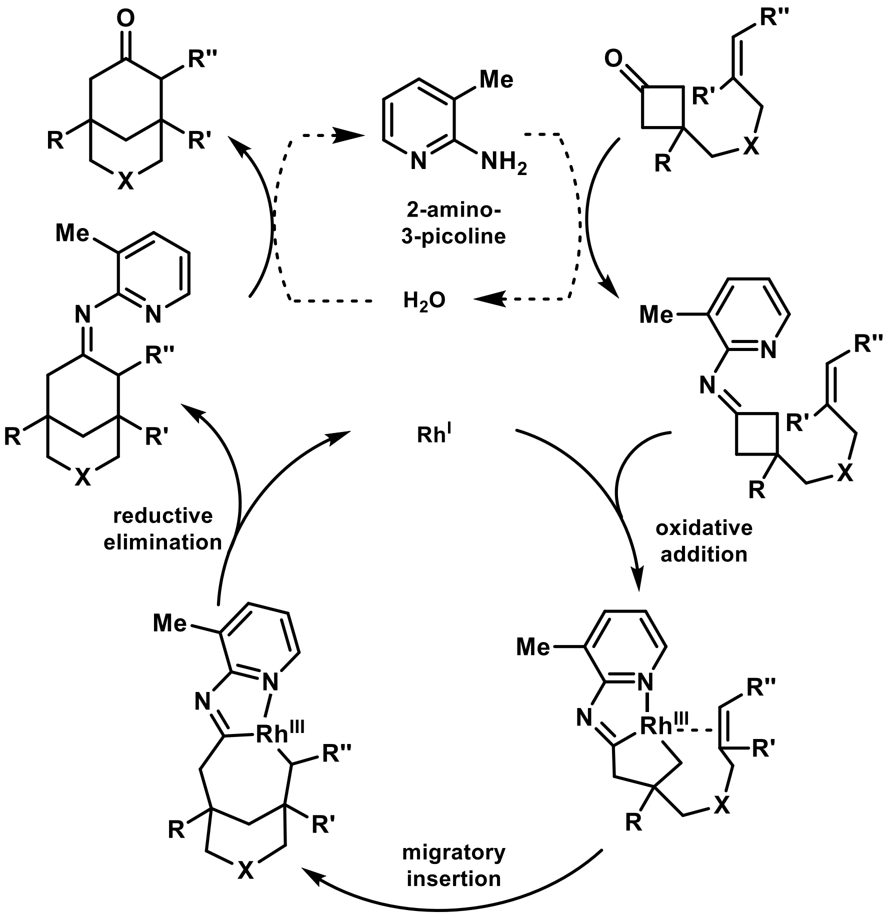


Xue, Y., Dong, G., *Acc. Chem. Res.*, ***2022***, doi.org/10.1021/acs.accounts.2c00400

Dong, G. et al., J. Am. Chem. Soc., ***2012****, 134, 20005 – 20008*
Dong, G. et al., Angew. Chem. Int. Ed., ***2022****, 61,*

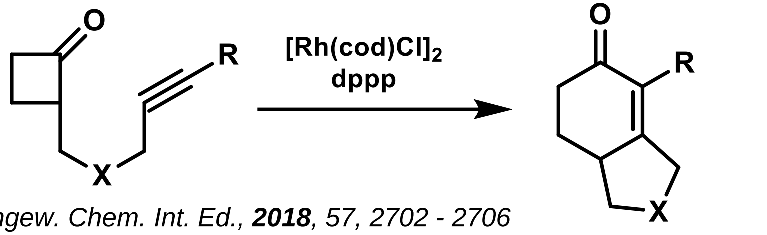
Cyclizations involving Cut & Sew Transformations of Cyclobutanones

Directing-group assisted Cut & Sew:



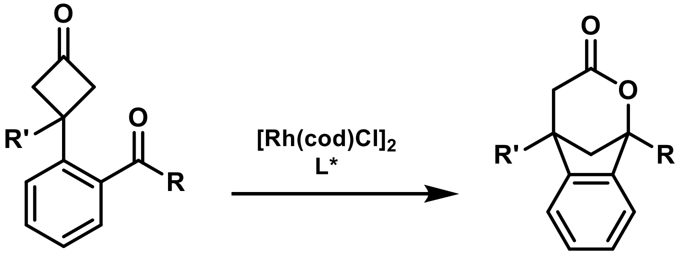
Ko, H.M., Dong, G., *Nat. Chem.*, ***2014***, 6, 739 - 744

α-branched Cut & Sew:



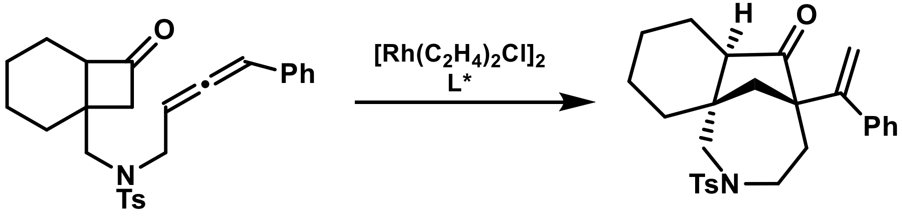
Deng, L., Jin, L., Dong, G., Angew. Chem. Int. Ed., ***2018****, 57, 2702 - 2706*

Carbonyl-Insertion



Cramer, N. et al., Angew. Chem. Int. Ed., ***2014****, 53, 3001 - 3005*

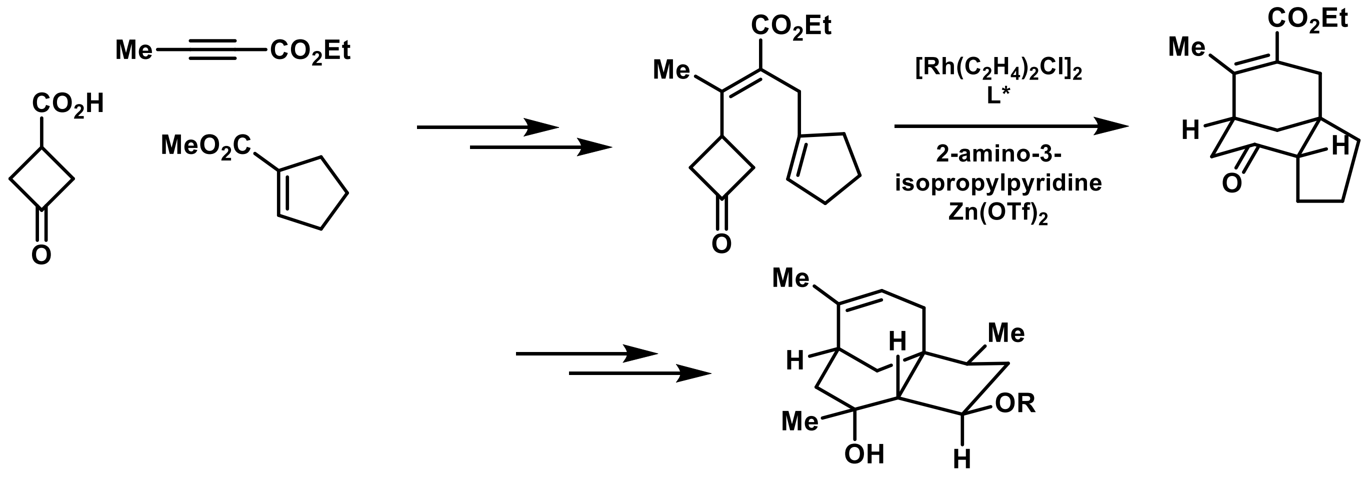
Allene-acceptor:



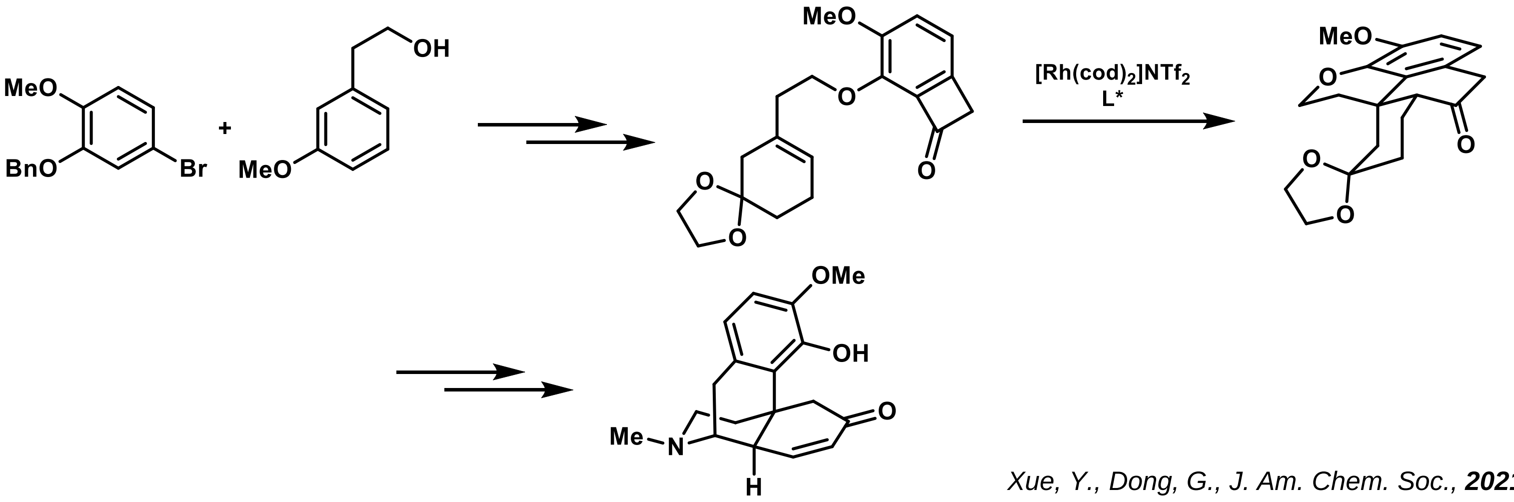
Zhou, X., Dong, G., J. Am. Chem. Soc., ***2015****, 137, 13715 - 13721*

Cyclizations involving Cut & Sew Transformations of Cyclobutanones

Application in total synthesis:



Penicibilaenes A and B



thebainone A

Xue, Y., Dong, G., J. Am. Chem. Soc., ***2021***, *143, 8272 – 8277*
Hou, S-H., Prichina, A.Y., Dong, G., Angew. Chem. Int. Ed., ***2021***, *60, 13057*

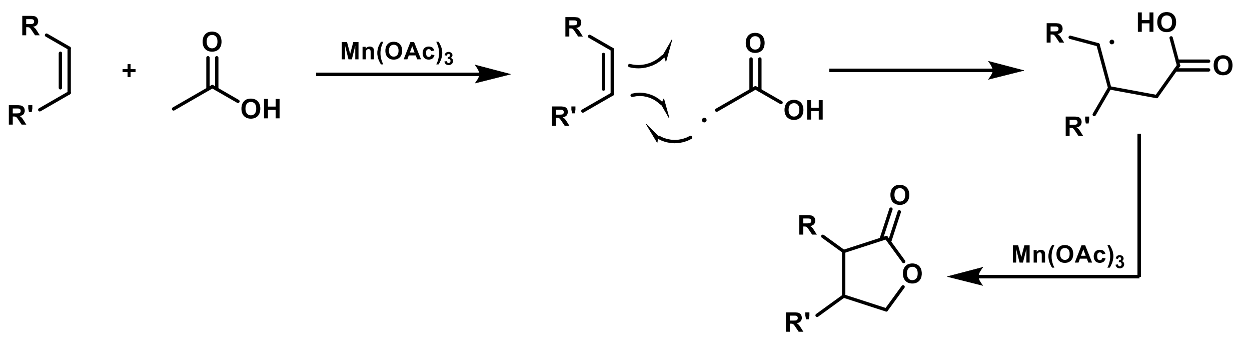
Intramolecular Free-Radical Cyclization Reactions

General:

Powerful tool for mono- / polycylizations through carbon-centered radicals
Typically mild conditions, high functional-group tolerance
Single-electron reduction vs single-electron oxidation
Most prominent: Mn, Cu, Pb, Fe, Co, Ti, Sm, Ce

$Mn(OAc)_3$:

Single-electron oxidant
Oxidation-potential highly dependent on solvent
Not catalytic

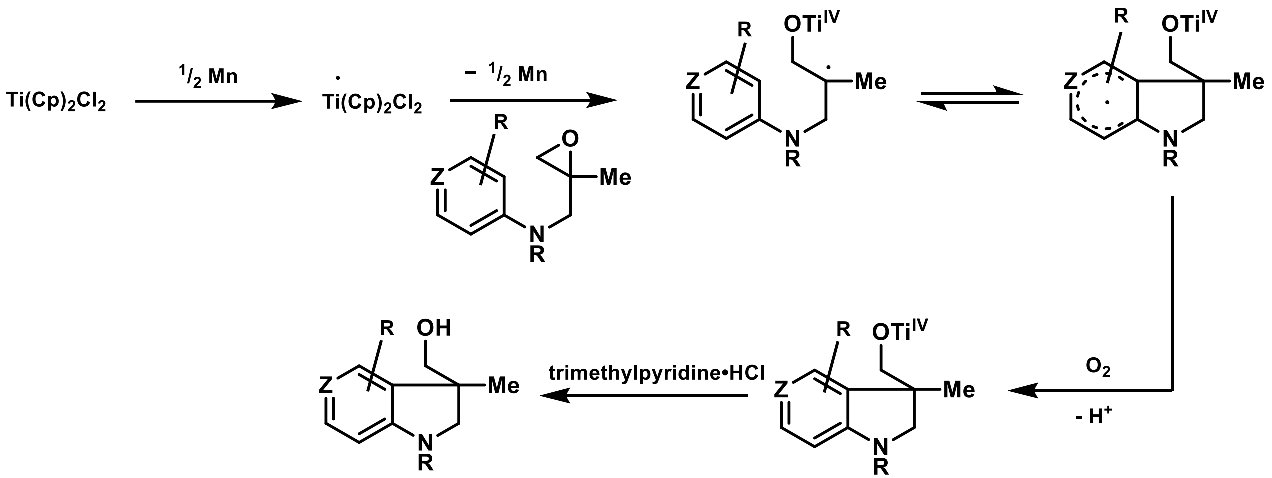


*Bush, J.B., Finkbeiner, H., J. Am. Chem. Soc., **1968**, 90, 5903*

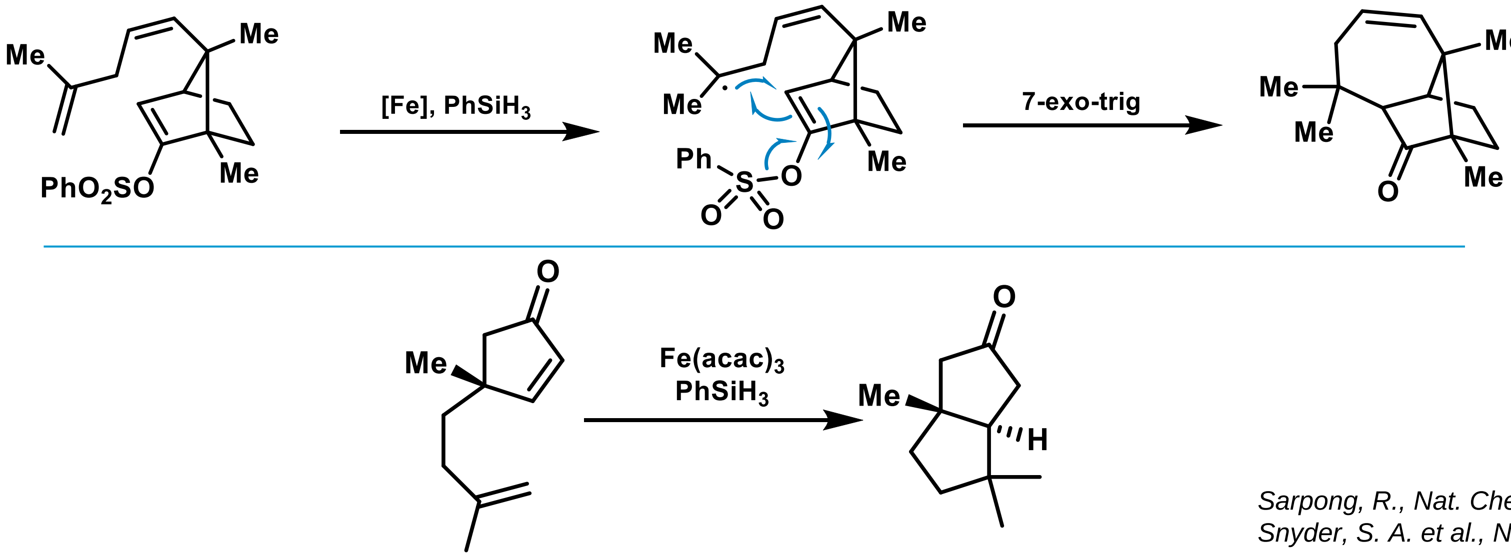
Intramolecular Free-Radical Cyclization Reactions – MHAT processes

Titanocene(III):

Low Lewis acidity, powerful soft reducing agent
Epoxide - / oxetane opening, Wurtz-type reactions
Barbier-type reactions, Pinacol couplings



MHAT-cyclization:



Sarpong, R., Nat. Chem., ***2022****, 14, 450 - 456*
Snyder, S. A. et al., Nature, ***2019****, 569, 703 - 707*

Universität Konstanz

Herzlichen Dank!

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