Reductive Epoxide Openings with Low-Valent Ti Reagents

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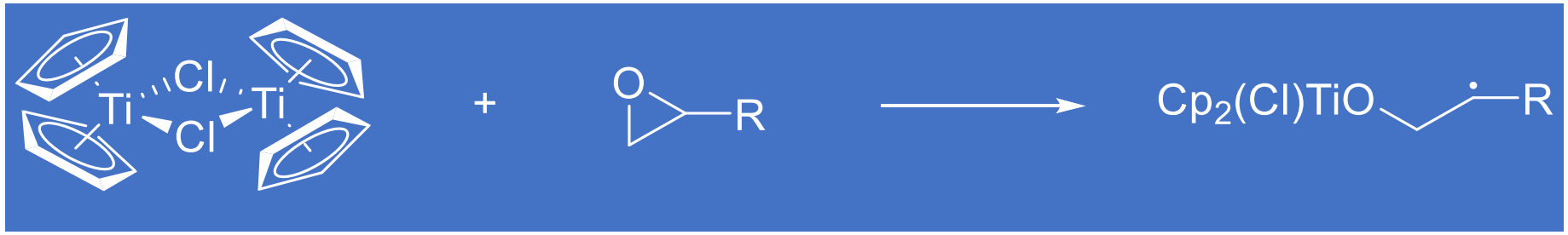
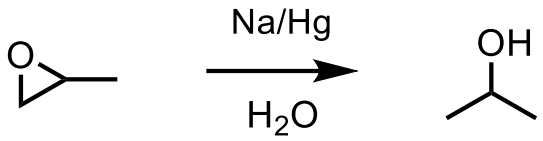
August 10, 2021



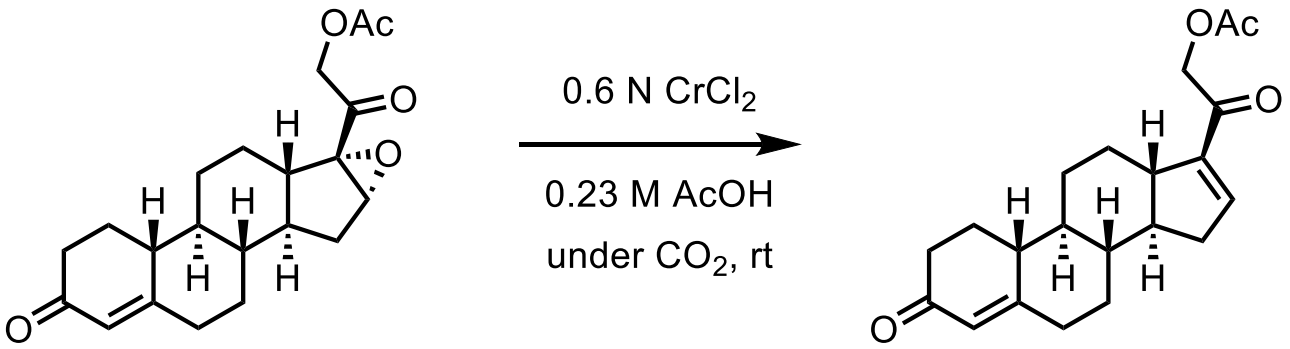
Working Towards Ti(III)

The first report of epoxide cleavage



Propylenoxyd C_3H_6O + H_2 = **Isopropylalkohol** C_3H_8O − H_2 = **Aceton** C_3H_6O.

Julian's work with Cr(II) salts (1954)

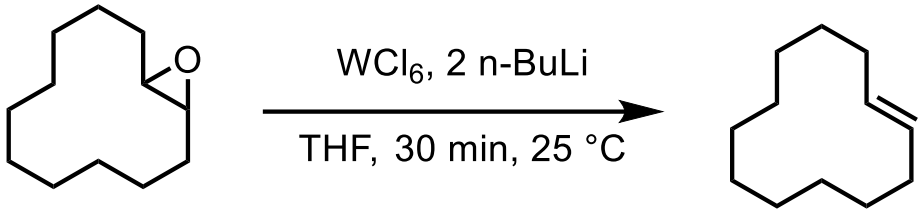


Note: Kochi (1968) postulated this opening occurred via SET to the oxygen based on analogous reactivity and kinetic studies into alkyl halide reduction via Cr(II)en_n

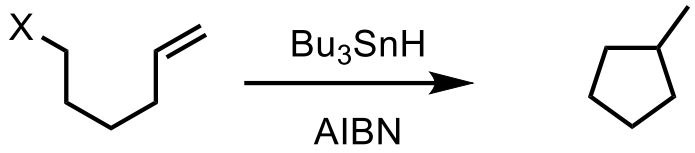
Justus Liebigs Annalen der Chemie **1866**, *140*, 178–179
J. Org. Chem. **1954**, *19* , 131–138.
Tetrahedron **1968**, *24* , 3503–3515

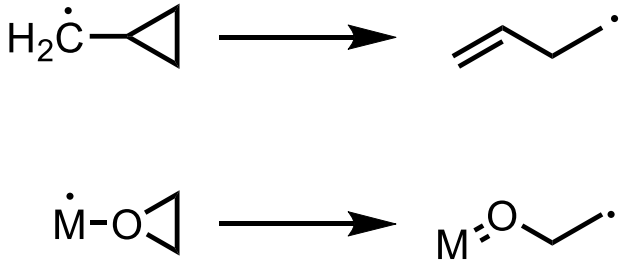
Extending Reactivity to Other Metals and Ti(III)

Sharpless Deoxygenation via Tungsten (1972)



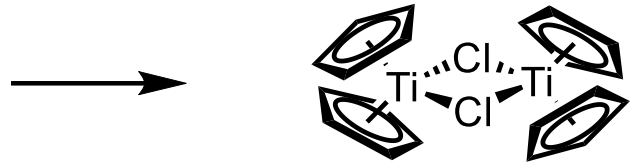
Field-Standard for Cyclizations





Considerations:

- Maintain functionality
- A Low-Valent metal capable of both coordinating to oxygen and promoting homolytic C-O bond cleavage



J. Am. Chem. Soc. **1972**, *94*, 6538–6540

Outline

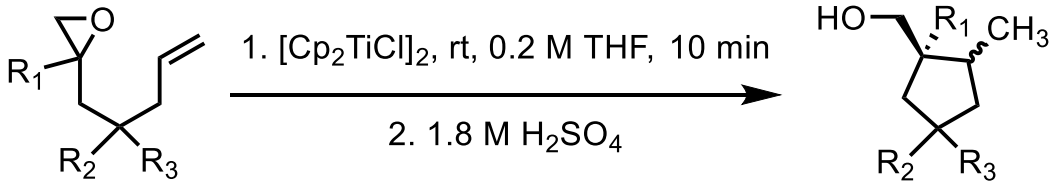
I. Introduction and Mechanism Discussion

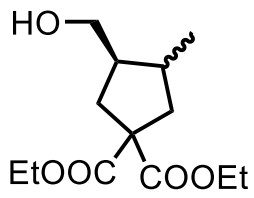
II. Pathways of β-Titanoxy Radicals

III. Cyclizations and Stereoselectivity

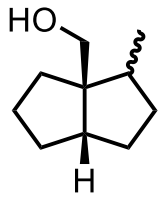
Testing the Hypothesis

Initial Discovery (Rajanbabu/Nugent, 1988)

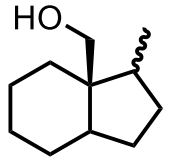




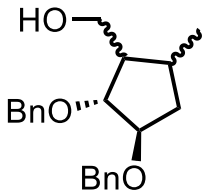
68% yield
85:15 (cis:trans)



88% yield
90:10 (endo:exo)



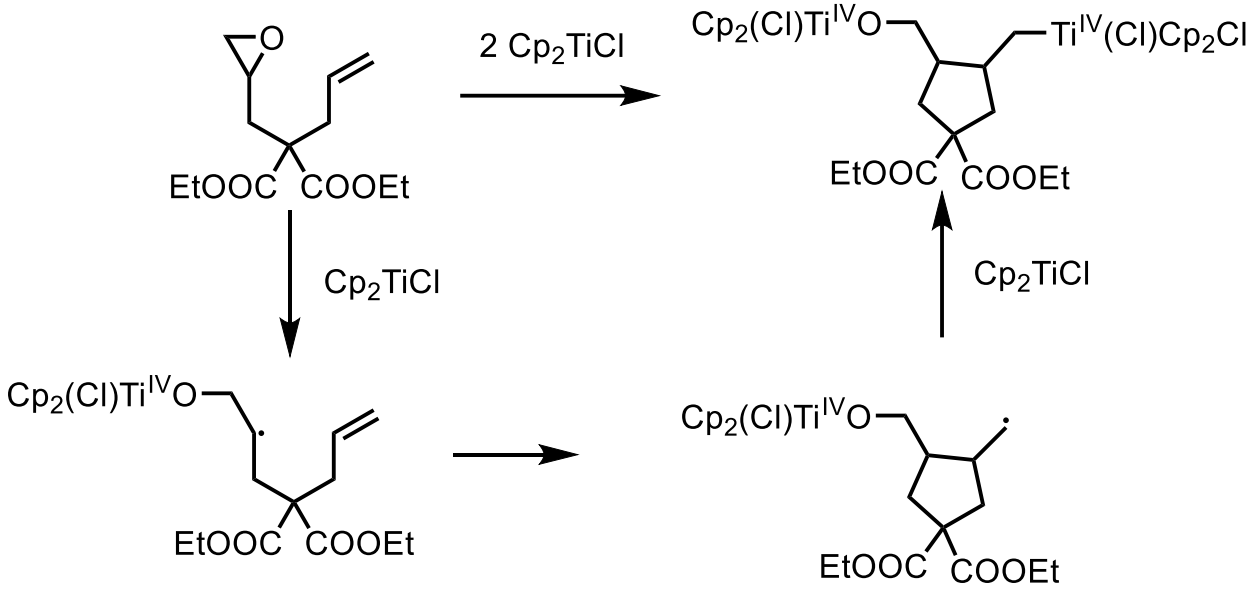
82% yield
55:45 (endo:exo)



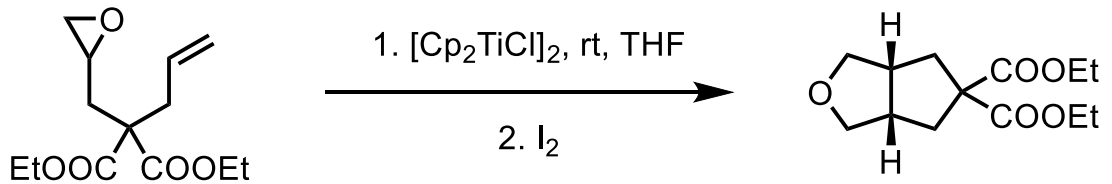
68% yield
45:30:15:10

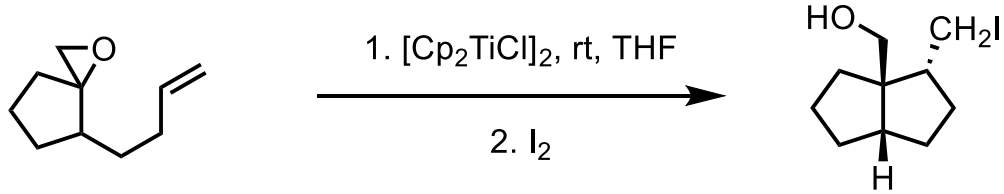
J. Am. Chem. Soc. **1988**, 110, 8561–8562

Postulated Mechanism



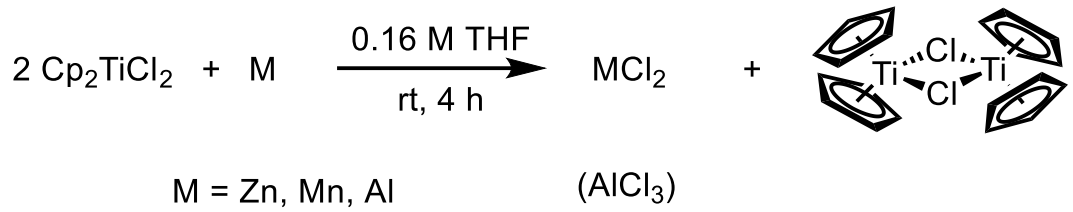
Additional Tests on Nucleophilicity

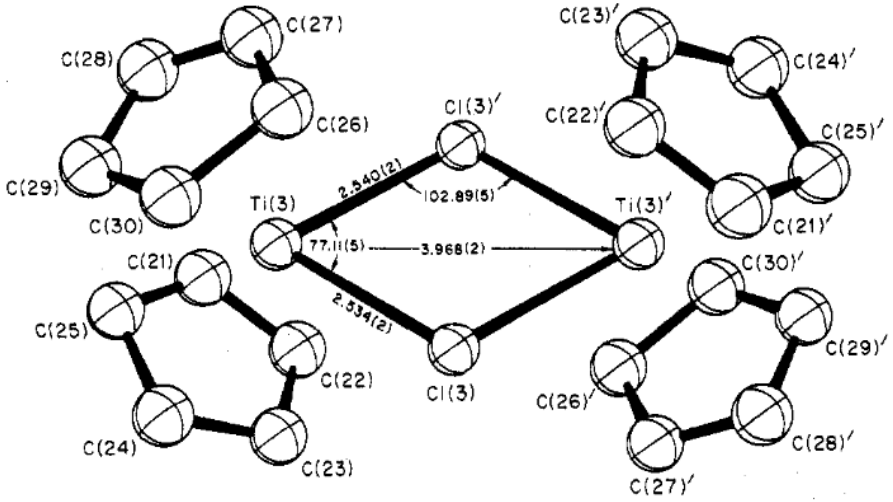




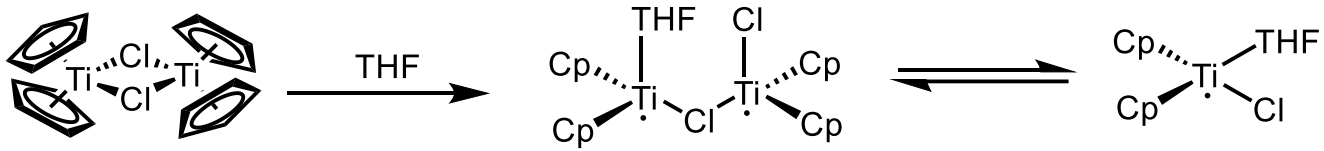
$[Cp_2TiCl]_2$ as a reagent

Standard Method of Generation

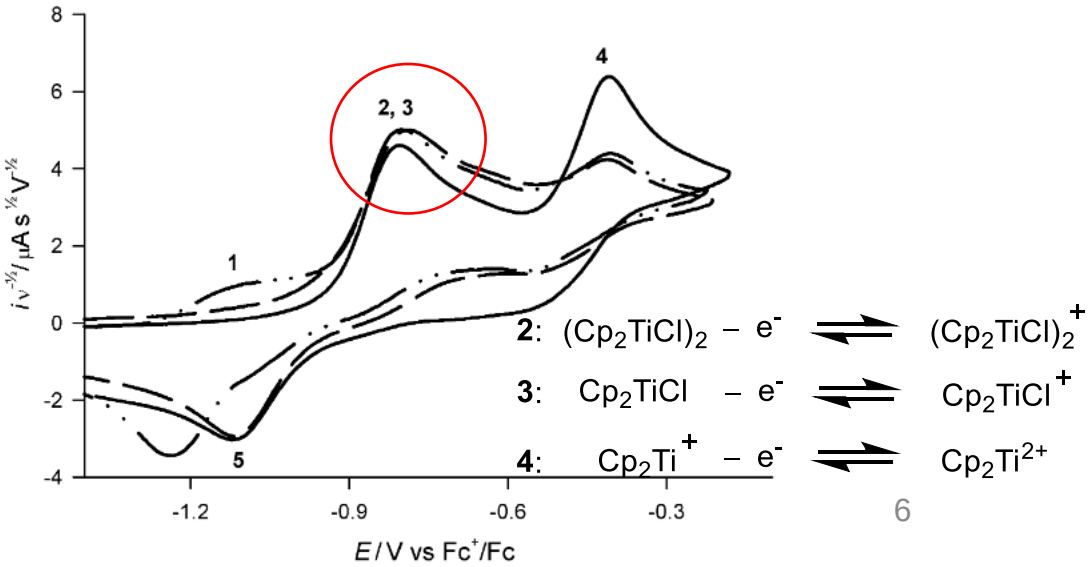




Equilibrium of Titanocene Reagent



CV Showing Redox Potential with Zn, Mn, and Al

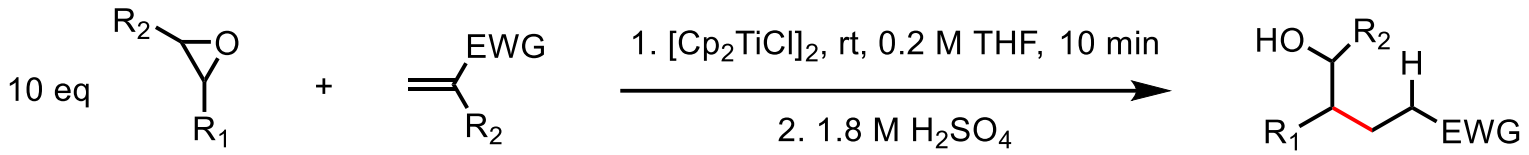


- Changes in sweep rate resulted in disappearance of **4**, implying reaction being electrode-dependent
- Changing Zn concentration broadened **2** and **3**, which implied the presence of an equilibrium

Inorg. Chem. **1977**, *16*, 1645–1655.
J. Am. Chem. Soc. **2004**, *126*, 7853–7864.

Addition to Activated Olefins

Rajanbabu/Nugent (1989): Successfully extended reactivity to intermolecular additions of activated olefins

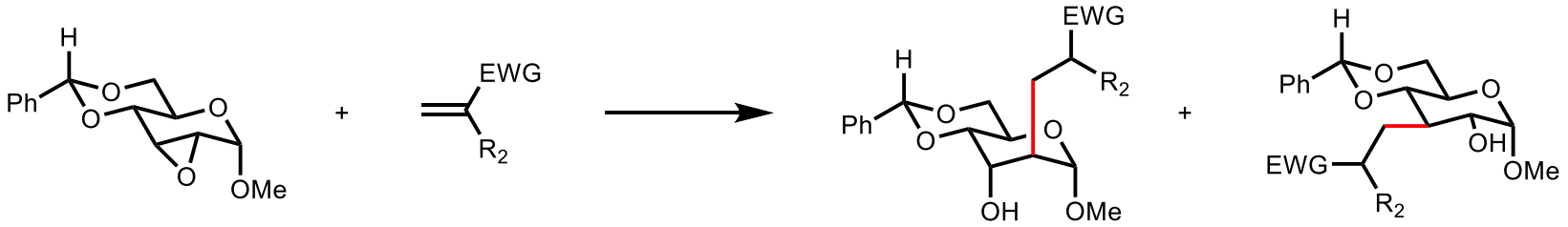


R_1 = alkyl R_3 = H, alkyl

EWG = CN, CO_2Me, COMe

37-82% yield
7 examples

Radicals can be inductively stabilized by substituents



acrylonitrile	32% yield	3% yield
methyl vinyl ketone	45% yield	7% yield
methyl methacrylate	73% yield	11% yield

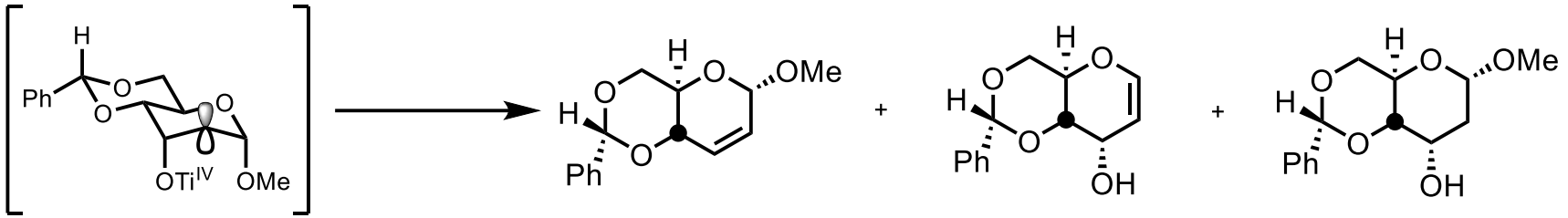
Key Findings:

- There is a slight preference for trans product formation
- Stabilization of the radical can affect site selectivity
- Side reactions are present depending on β-substitution or HAT

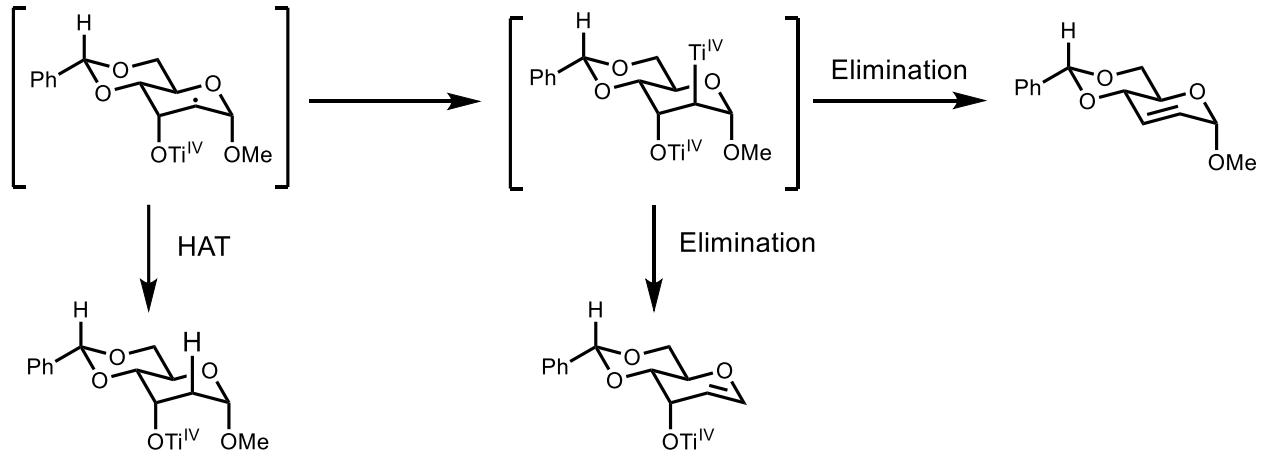
J. Am. Chem. Soc. **1989**, *111*, 4525–4527

Addition to Activated Olefins

Products Observed Without Olefin Present



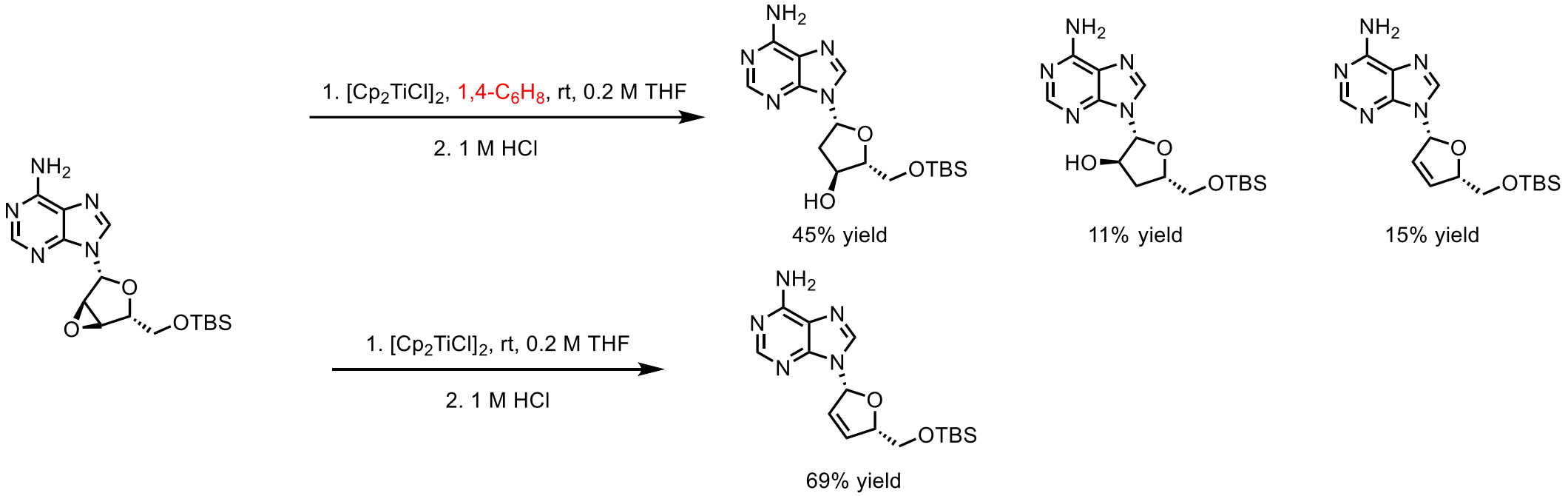
Hypothetical Pathways of Degradation



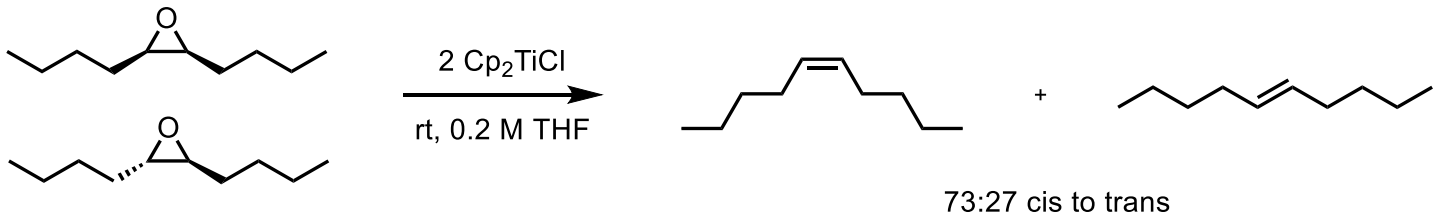
J. Am. Chem. Soc. **1989**, *111*, 4525–4527

Deoxygenation using Ti(III)

Rajanbabu/Nugent (1990): The absence of a HAT reagent can lead to deoxygenation



When reactivity was gauged with 5,6-epoxydecane, both cis and trans epoxides gave the same ratio

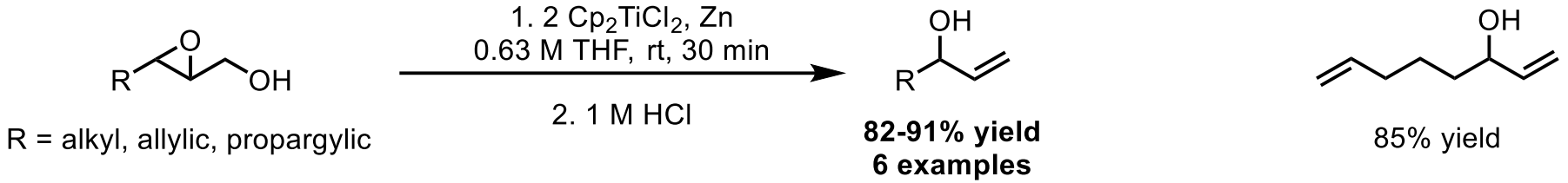


The need for 2 equivalents suggest carbanion-like intermediate, unlike Sharpless's work

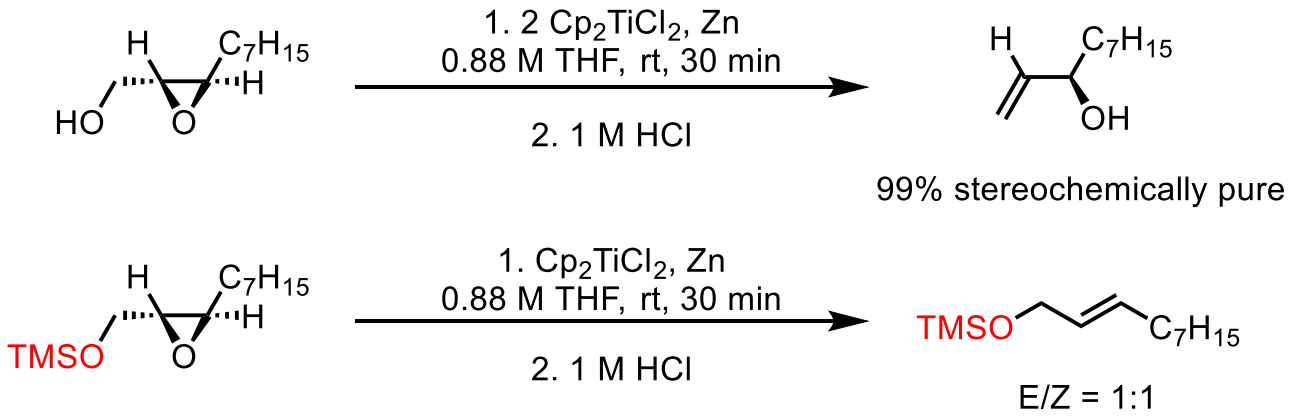
J. Am. Chem. Soc. **1990**, *112*, 6408–6409.

Stereospecific synthesis of Allylic alcohols

Yadav (1990): Showed that allylic alcohols could be formed selectively from 2,3-epoxy alcohols.



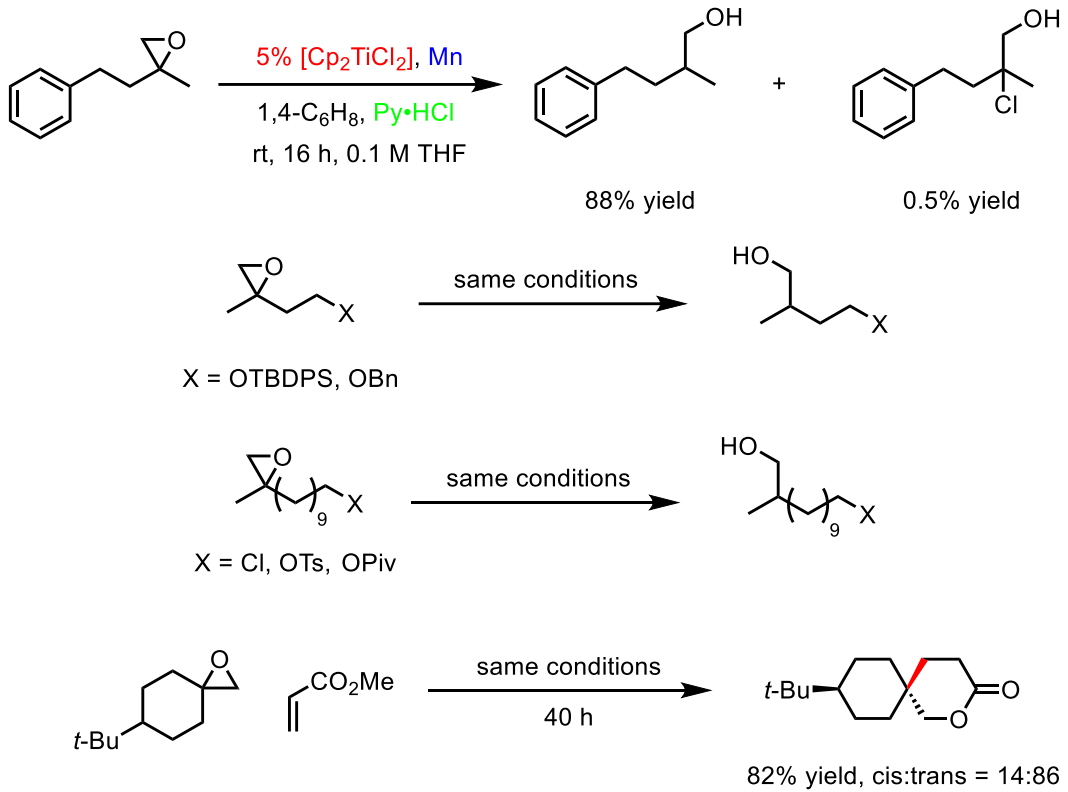
Stereoretentive formation of allylic alcohols suggested formation of radical at β to titanoxy species



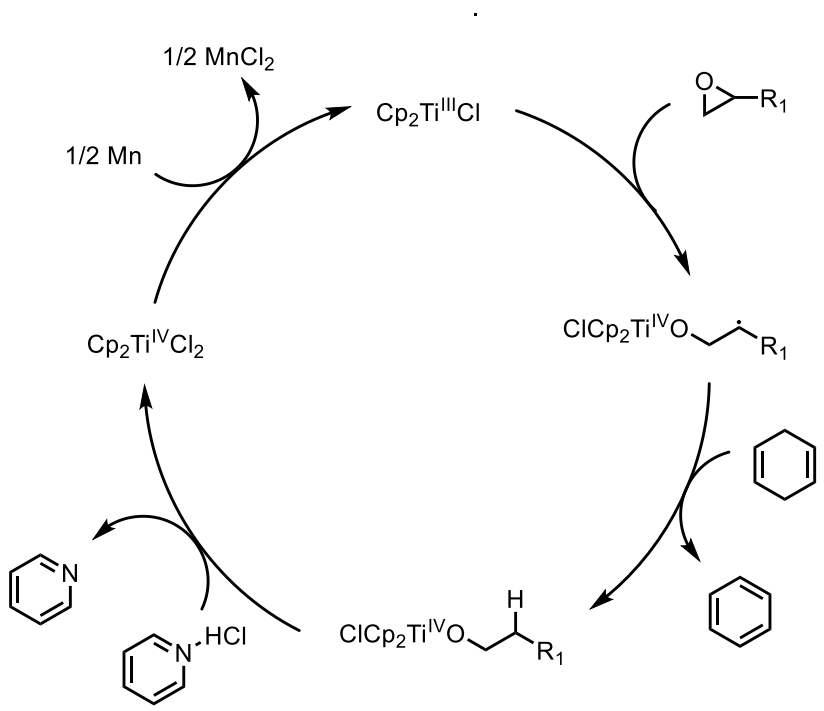
J. Chem. Soc., Chem. Commun. **1990**, 11, 843–844.
J. Am. Chem. Soc. **1994**, *116*, 986–997

Catalytic Version of Reaction

Gansäuer (1998): The first catalytic version of the intra- and intermolecular epoxide ring openings



Proposed Catalytic Cycle

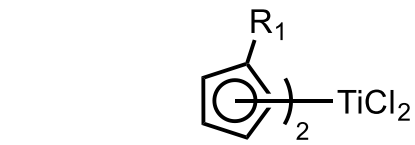


- Note: No deoxygenation is observed, implying the importance of the Ti-C bond in driving deoxygenation in stoichiometric conditions

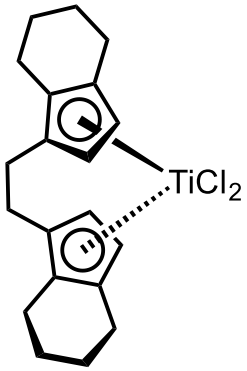
Angew. Chem. Int. Ed **1998**, *37*, 101–103

Controlling Epoxide Opening

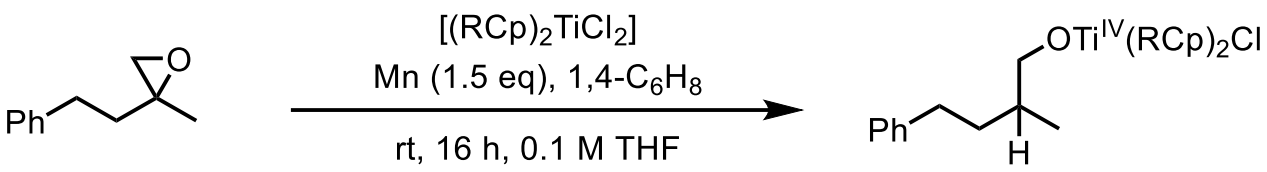
Gansäuer et. al (2007): Published in-depth computational and experimental mechanistic study for epoxide openings

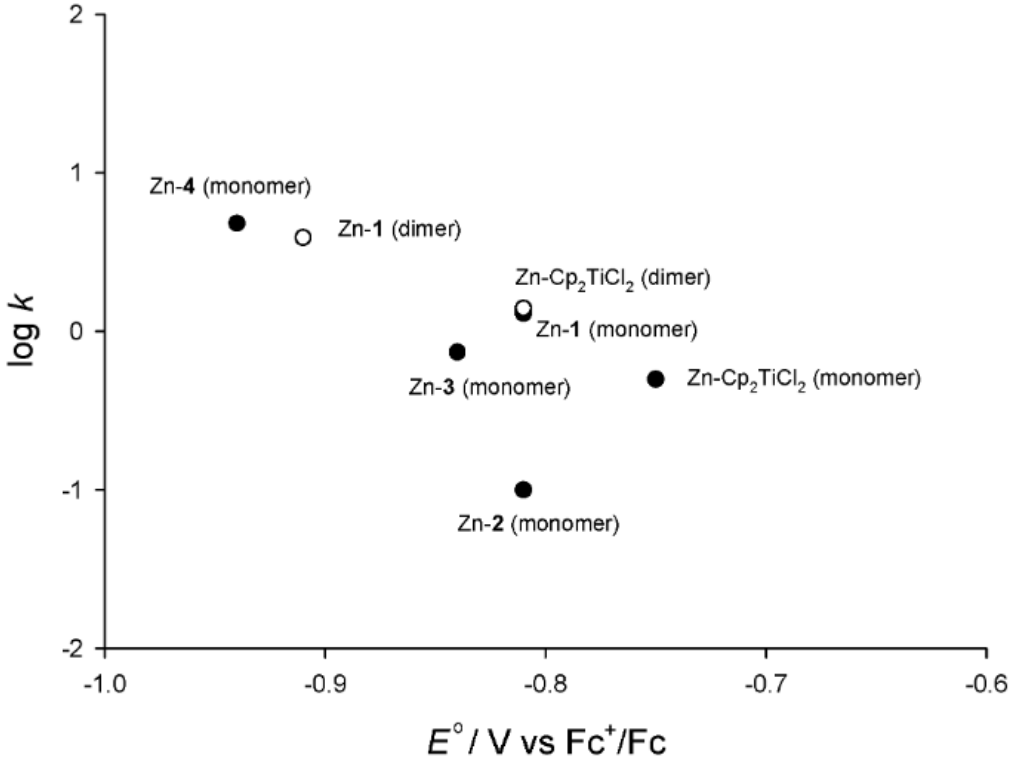


R_1 = Me (**1**), *t*Bu (**2**), (-)menthyl (**3**)



4





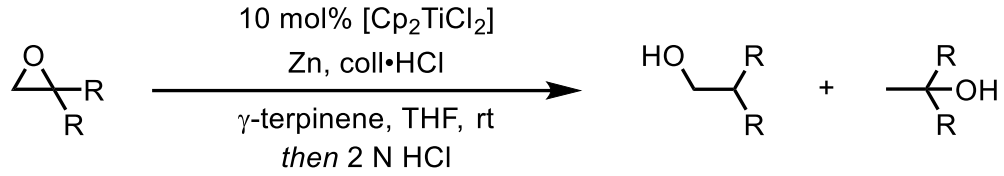
Kinetic Data (monomer):
Indane > Me > menthyl > H >*t*Bu

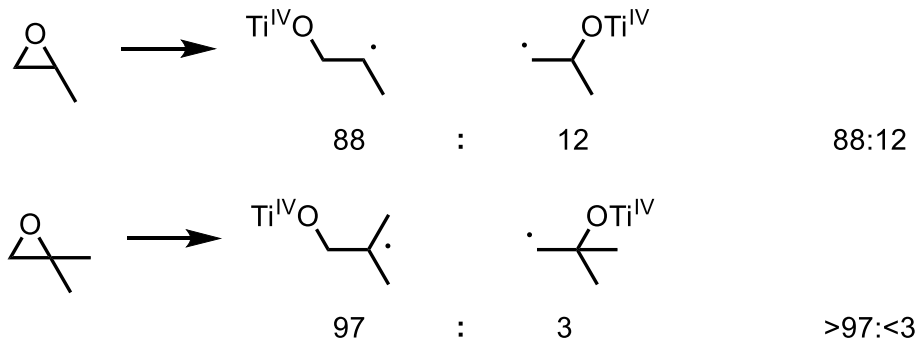
Concentration of 1,4-C_6H_8 doesn't affect the reaction! Electron transfer must be the rate limiting step

J. Am. Chem. Soc. **2007**, 129, 5, 1359–1371.

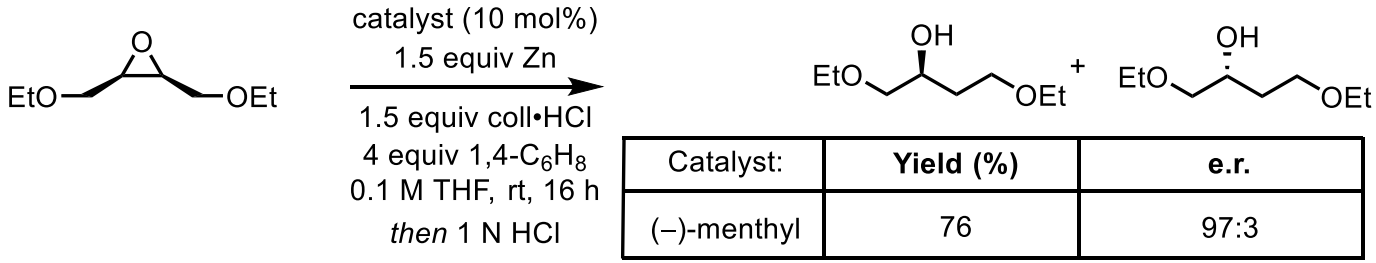
Controlling Epoxide Opening

DFT Comparison to Experimental Data





Enantioselective Opening of Epoxides



Catalyst:	**Yield (%)**	**e.r.**
(–)-menthyl	76	97:3

DFT Study (BP/TZVP)

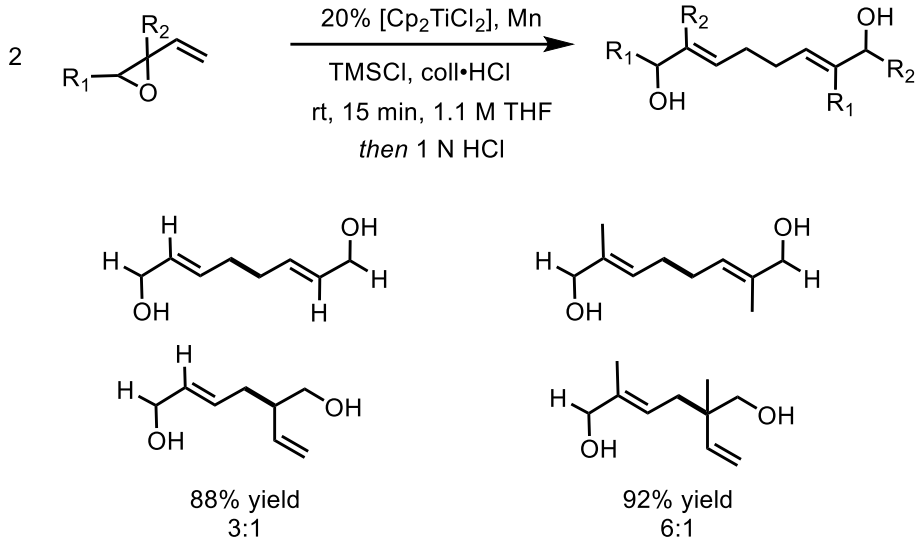
- Epoxide and THF bind reversibly
- Epoxide Opening is Exothermic
- Low barrier between 1° and 2° radical

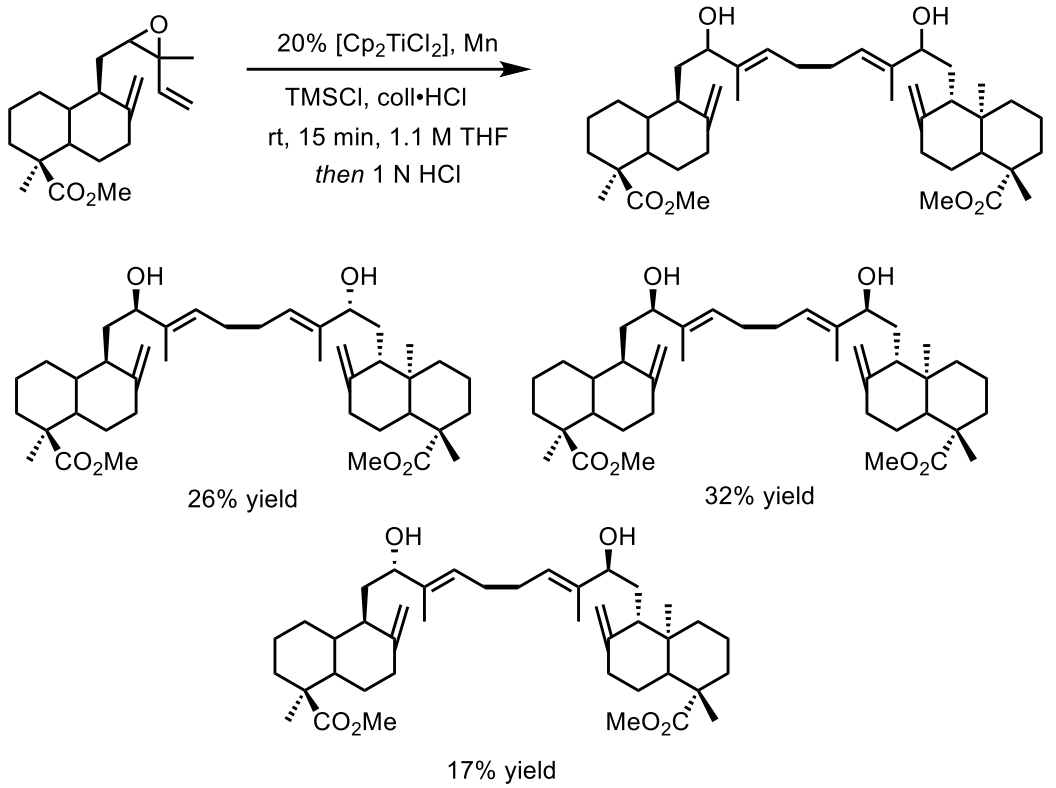
Observation:
Left C-O cleavage causes OEt interaction with the catalyst.

J. Am. Chem. Soc. **2007**, 129, 5, 1359–1371.

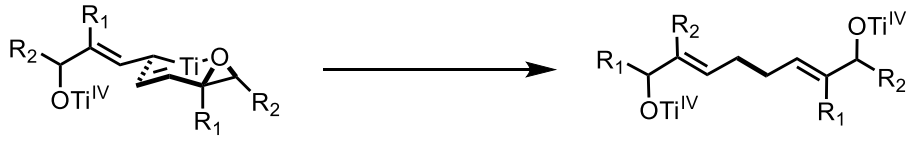
Dimerization of Vinyl/Aryl Epoxides

Barrero (2006): Illustrated Reactivity of Vinyl/Aryl Epooxides





R_1 must be axial for chair transition state!

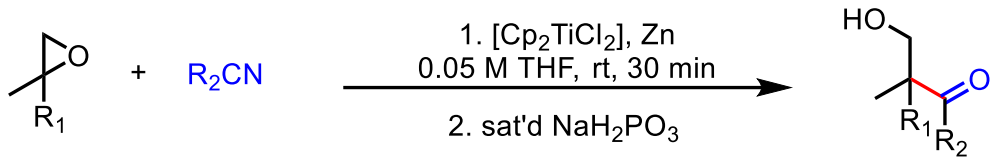


- Reduction of vinyl epoxides can be attributed to allyltitanium intermediates
- They were able to reduce catalyst loading to 0.01 mol % with 8 equivalents of Mn

Org. Lett. **2006**, 8, 669–672

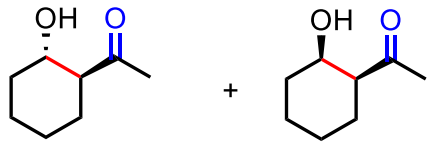
Intermolecular Addition of Epoxides with Nitriles

Fernández-Mateos (2009): “Aldol-Like” reaction of epoxides and nitriles is reported

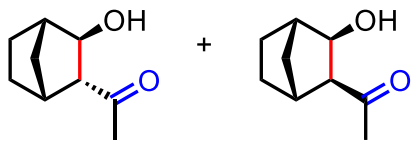


R_2 = Me, Ph

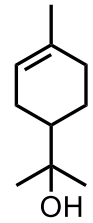
15 examples
36-76% yield



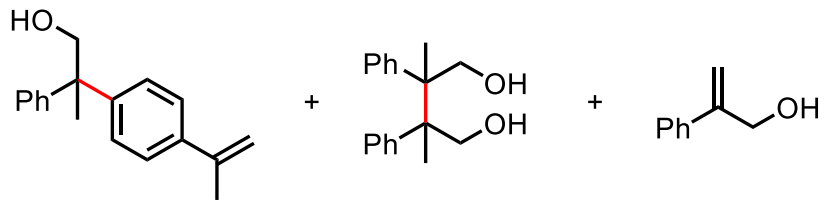
73% yield
77:23 trans:cis



62% yield
54:46



74% yield
no coupling seen for
tetra-substituted epoxide

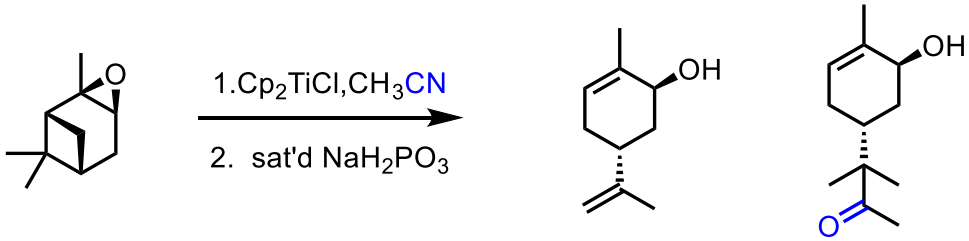


90% yield
18:62:20

Key Findings:

- Epoxides that form tertiary radicals are less likely to do intermolecular addition
- Homo-dimerization is common with vinyl and aryl substituted epoxides
  - When using styrene oxide, the aldol product is formed in 9:50:41 (aldol:homocoupling:deoxyg.)

Pinene Oxide and Acetonitrile Reaction

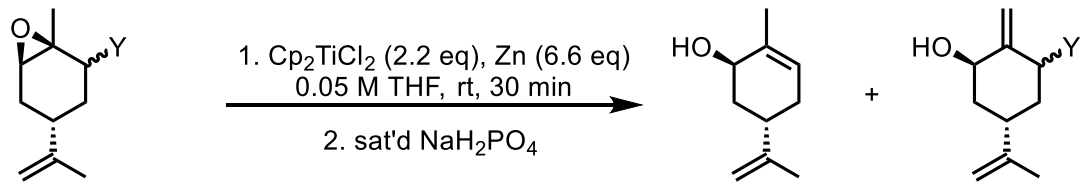


66% yield
40:60

J. Org. Chem. **2009**, *74*, 3913–3918

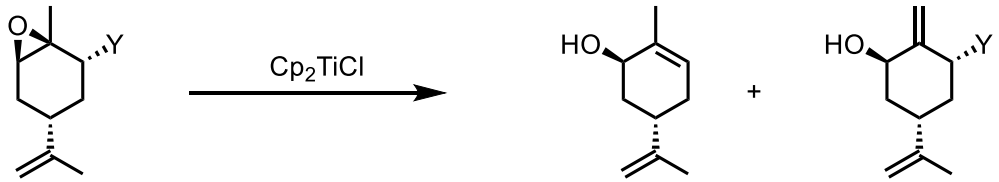
β-hydrogen Elimination

Fernández-Mateos (2013): Investigated the significance of initial stereochemistry in promoting hydrogen-elimination of tri-substituted epoxides

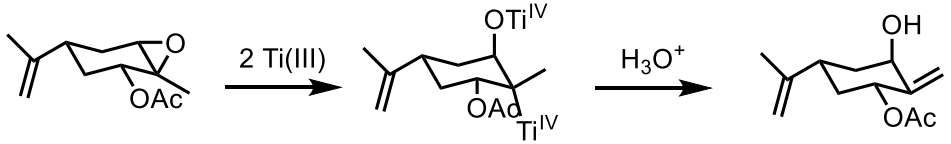


Y = OCH,OAc, OCOPh

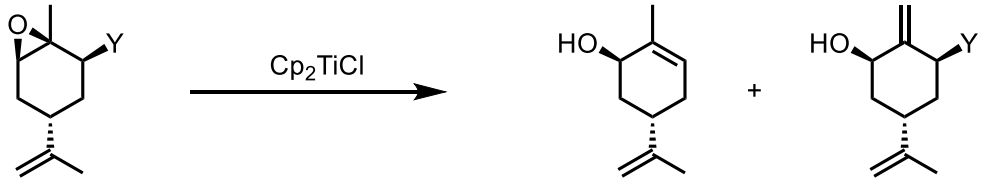
Trans isomer



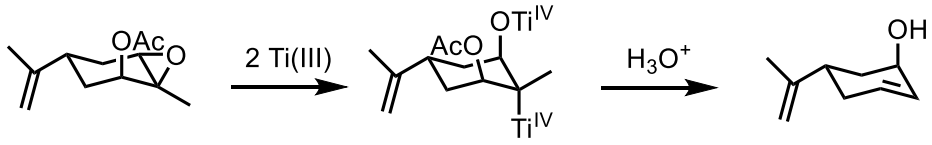
Y:	Y elimination	β-hydrogen
OCH	84	16
OAc	0	100
OCOPh	0	100



Cis isomer



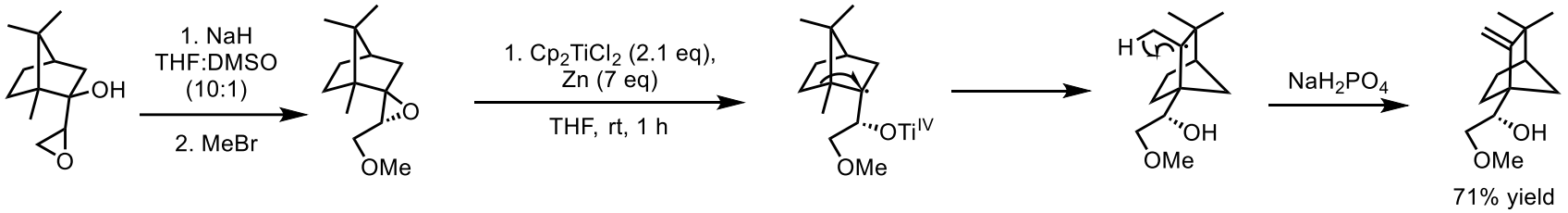
Y:	Y elimination	β-hydrogen
OCH	100	0
OAc	70	30
OCOPh	0	100



Tetrahedron **2013**, *69*, 1611–1616.

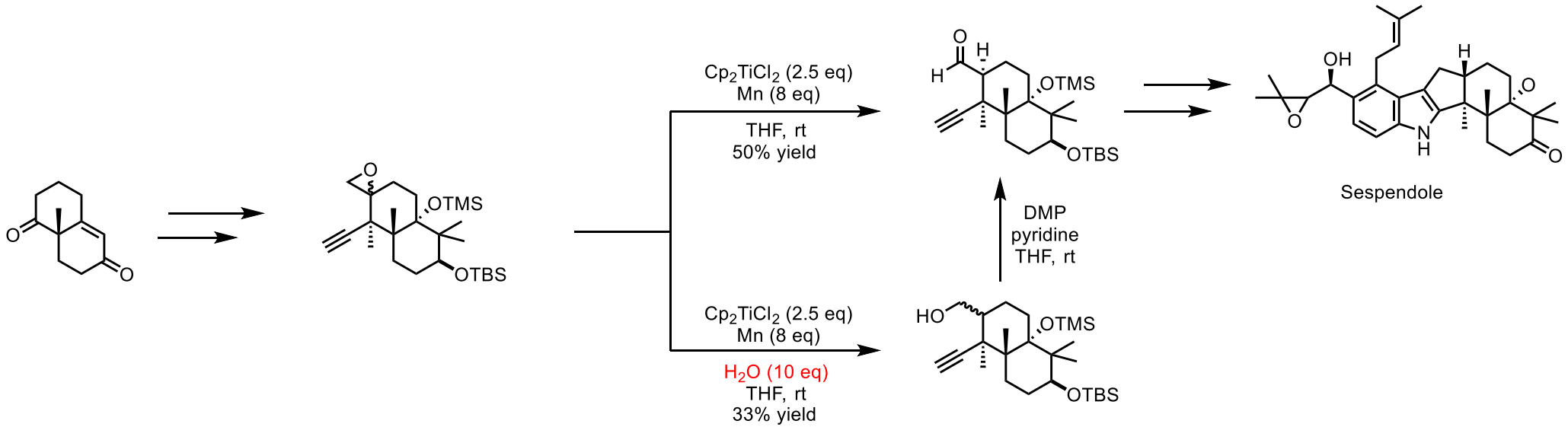
Rearrangement of β-Titanoxy Radicals

Roy (2005): Alkyl-shift observed when using camphor derivatives



- Note: No reaction occurred in the absence of Zn dust, as well as only $ZnCl_2$

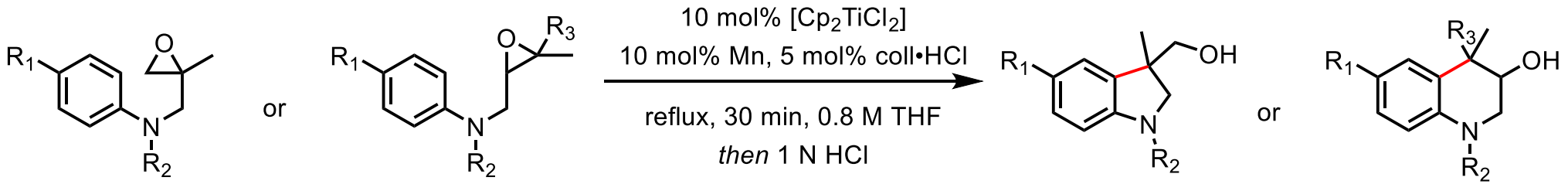
Nishikawa (2011): Discovered that Cp_2TiCl can cause spiro epoxides to rearrange to aldehydes



J. Org. Chem. **2005**, *70*, 8252–8254.
Synlett **2011**, *2011*, 647–650.

Catalytic Arylation of β-Titanoxy Radicals

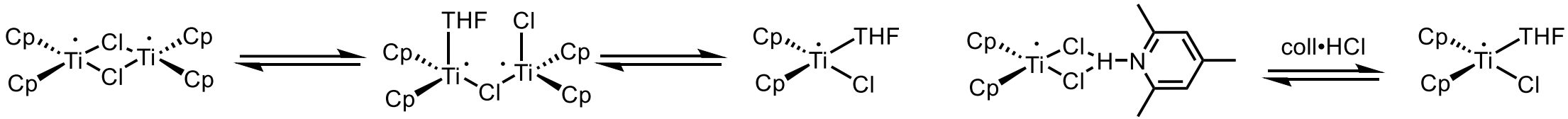
Gansäuer (2012): Publishes catalytic method capable of being done with no stoichiometric reagents



R_1 = H, Me, Br
R_2 = H, Ar

R_3 = H, Me

Gansäuer (2015): Reinvestigates the Mechanism to Provide More Support

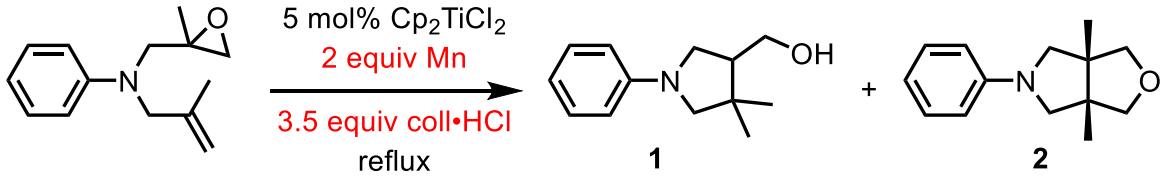


- Dimer and Monomer ratios were monitored via CV to determine the impact of the collidine*HCl salt
  - It showed that the monomer prefers complexation with collidine, acting as a resting state for the catalyst (13:87 dimer:monomer)

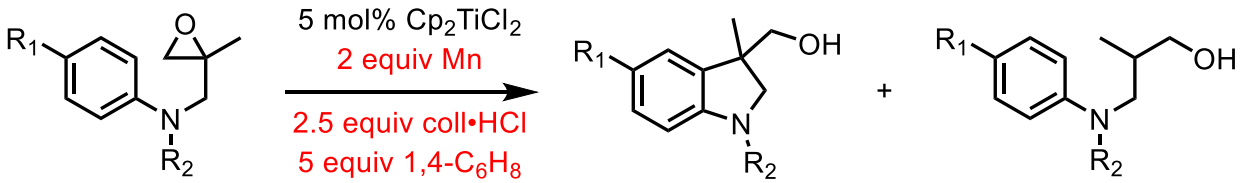
Angewandte Chemie **2012**, *124*, 4819–4823.
Chem. Eur. J. **2015**, *21*, 280 – 289

Competing Pathways of Catalytic Arylation

Radical Arylation vs. 5-*exo* cyclization



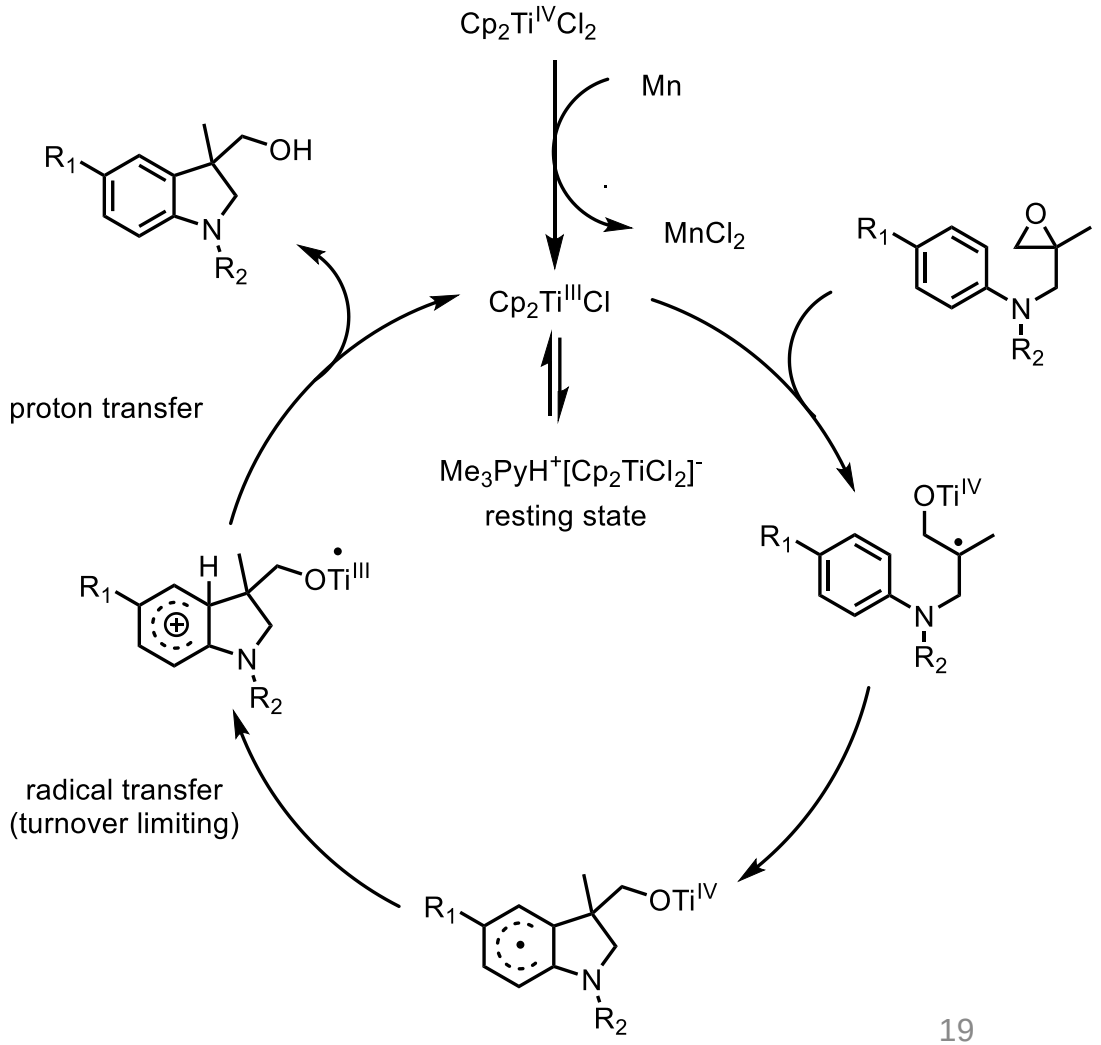
Radical Arylation at High Temp with a HAT reagent



Temp.	3		4
RT:	29	:	71
reflux:	52	:	48

- Cyclization dependent on both higher temperature and removal other pathways

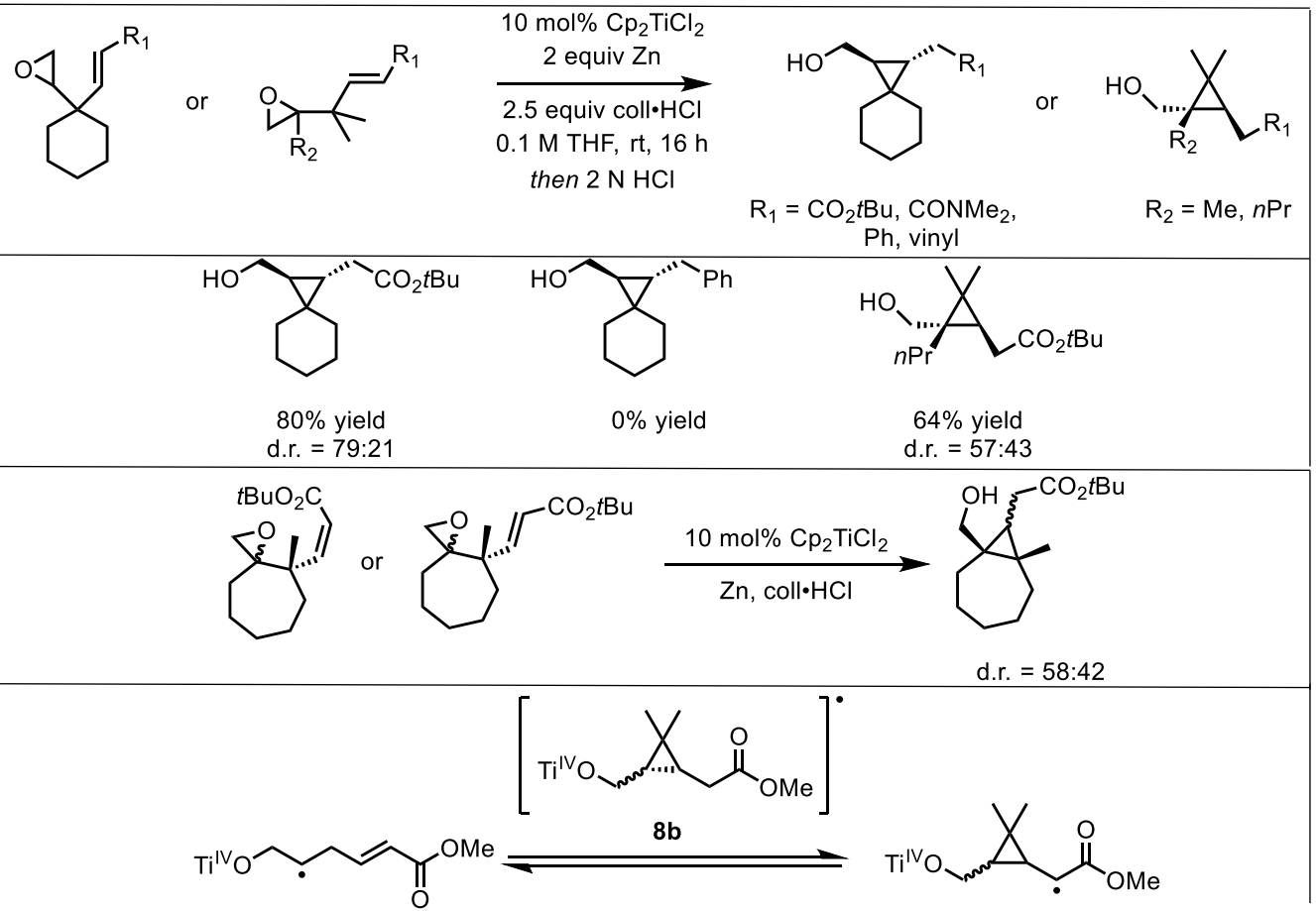
Proposed Cycle of Non-Stoichiometric Reaction



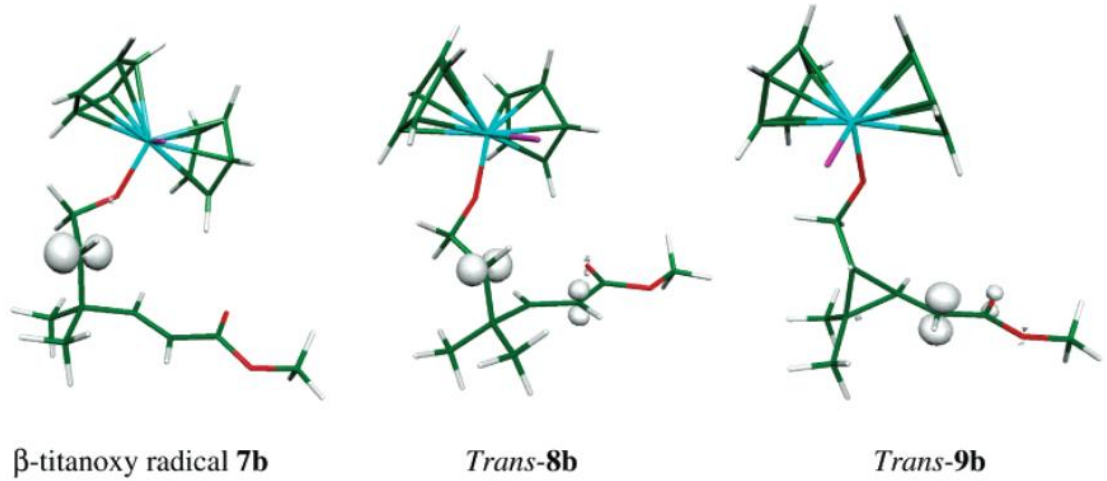
Angew, Chem. **2012**, *124*, 4819–4823.
Chem. Eur. J. **2015**, *21*, 280 – 289

3-*exo*-*trig* cyclization

Friedrich (2005): First Experimental Demonstration and DFT Investigation of Catalytic titanocene 3-exo Cyclization

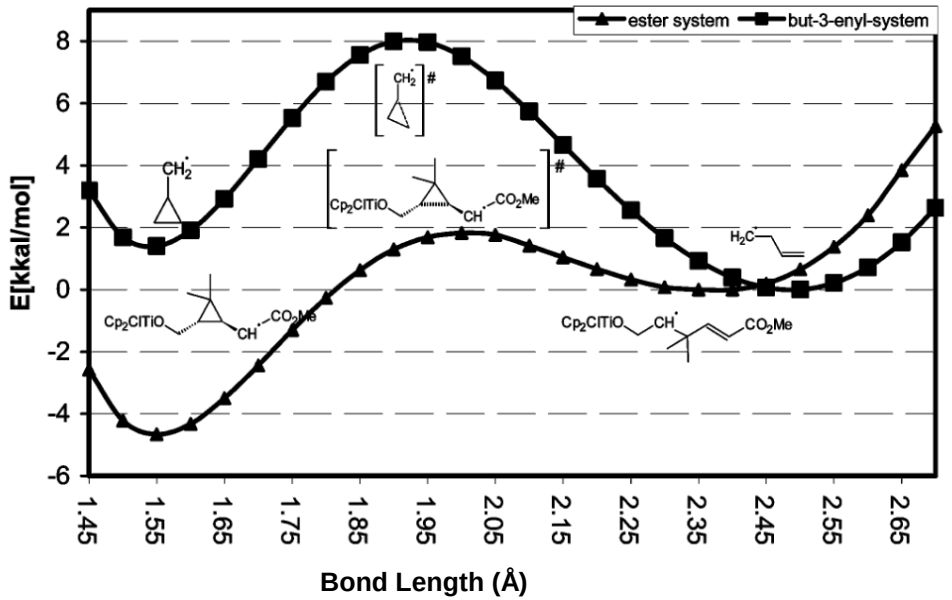


J. Am. Chem. Soc. **2005**, 127, 7071–7077



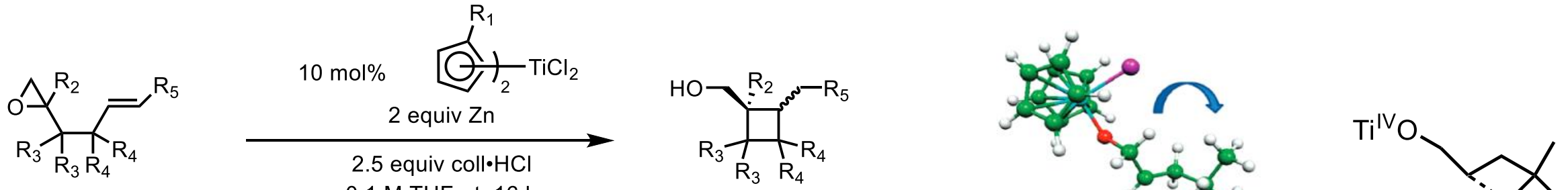
β-titanoxy radical **7b** | *Trans*-**8b** | *Trans*-**9b**

Potential Energy Surface at BP86/TZVPP//BP86/TZVP



4-*exo*-*trig* cyclization

Friedrich (2008): Expansion of Cp_2TiCl to generalize a catalytic approach to cyclobutanes



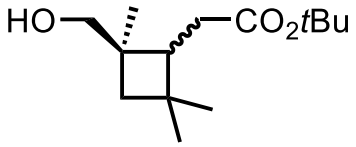
R_1 = H, Cy, *t*Bu
R_2,R_3,R_4 = H, Me
R_5 = CO_2*t*Bu, CO_2NMe_2

21-92% yield
d.r. up to >95:5

cis-TS20

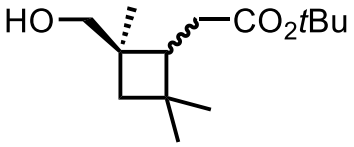
Substrates of Interest

R_1 = H



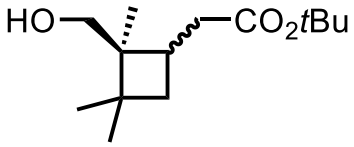
82% yield
67:33 *trans:cis*

R_1 = *t*Bu

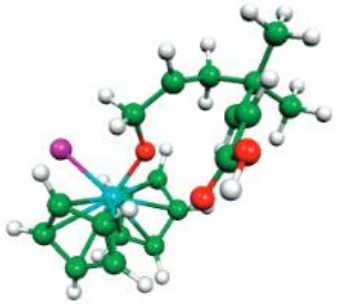


21% yield
77:23 *trans:cis*

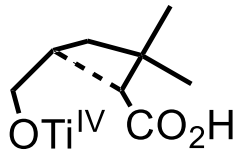
R_1 = H



53% yield
56:44 *trans:cis*



trans-TS20



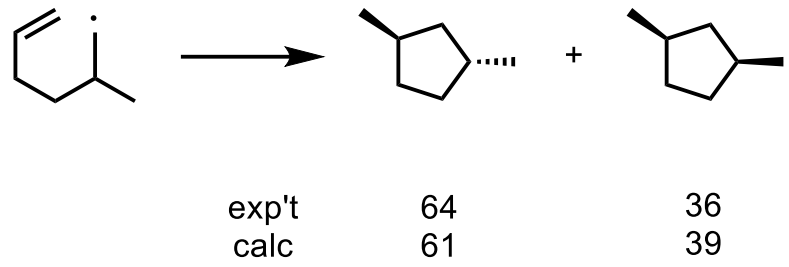
Key Findings

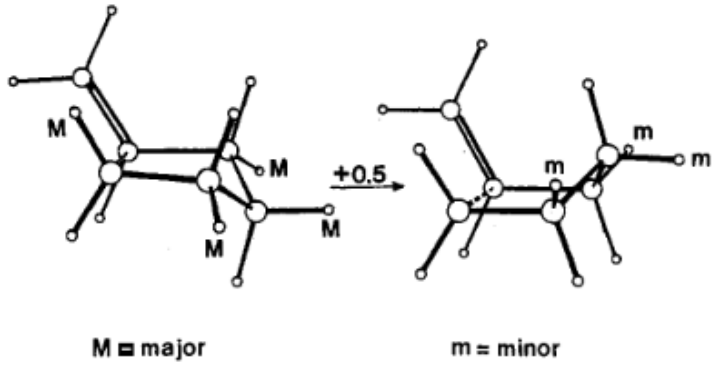
- 4-*exo* cyclization of the pentenyl radical is thermodynamically disfavored computationally and experimentally
- Titanocene steric bulk affects the diastereoselectivity in both catalytic and stoichiometric reactions.
- 1,3 diaxial interactions play a key role in driving selectivity both computationally and experimentally.

J. Am. Chem. Soc. **2008**, 130, 1788–1796

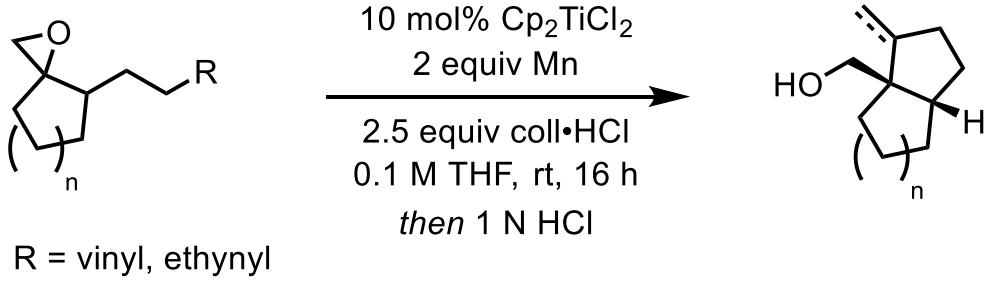
Stereochemistry of 5-*exo* Cyclization

Houk (1987): Publishes an MM2 force-filed model study regarding boat-like and chair-like *exo* transition structures

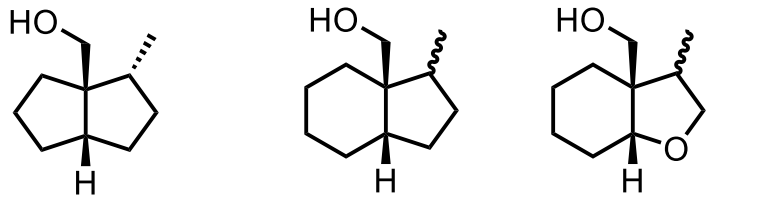


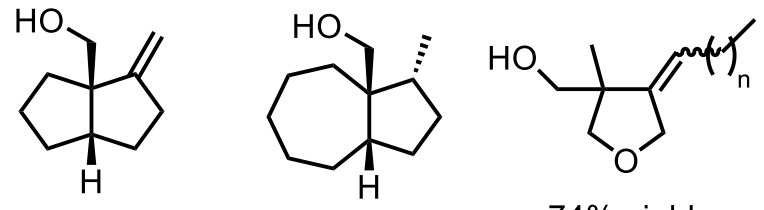


Gansäuer (2000): Publishes demonstration of 5-*exo-trig* and *dig* formation for bicyclic systems



R = vinyl, ethynyl

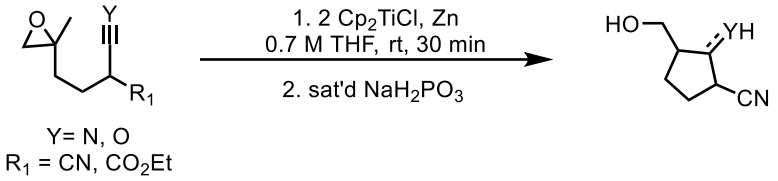




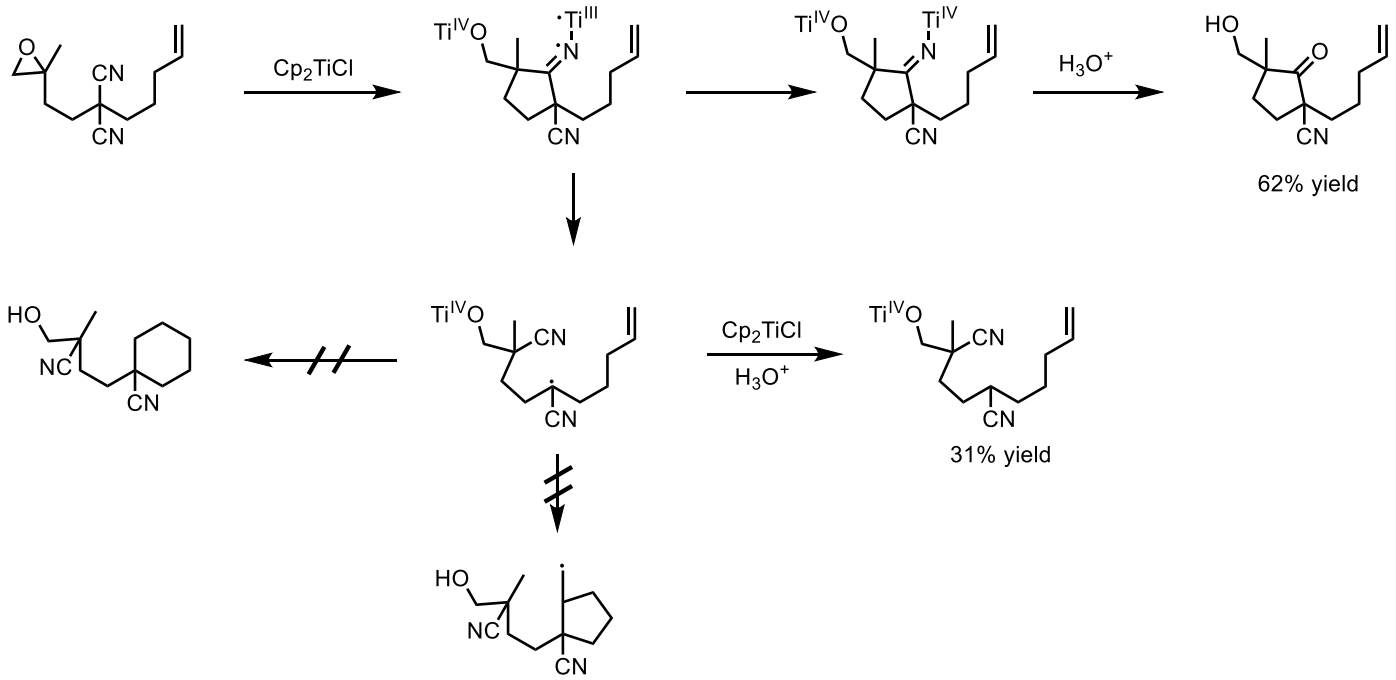
J. Org. Chem. **1987**, *52*, 959–974.
Synlett **2000**, *2000*, 1357–1359.

5-*exo* Cyclization Investigation

Fernández-Mateos (2007): Investigated cyclization of nitriles and ketones

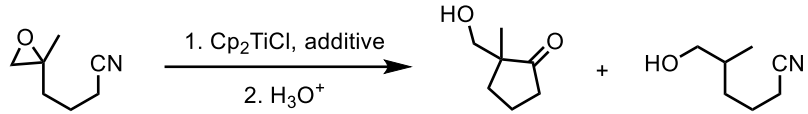


Radical translocation is possible but conditions result in termination of pathway



J. Org. Chem. **2007**, *72*, 9973-9982.

Hydrogen Donor Affects HAT



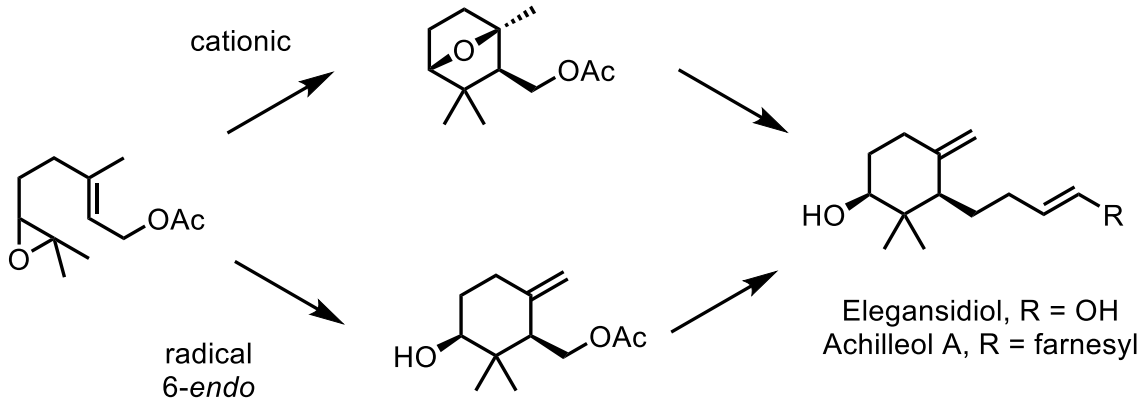
additive:		
Cyclohexadiene	100	0
PhSH	56	44
H_2O	78	22

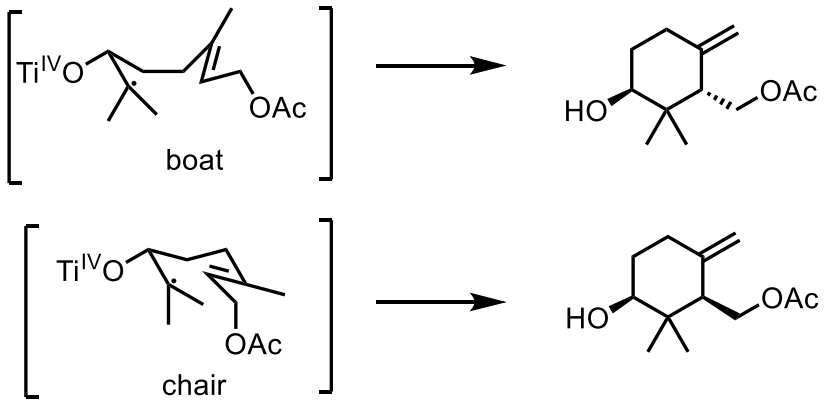
Key Findings:

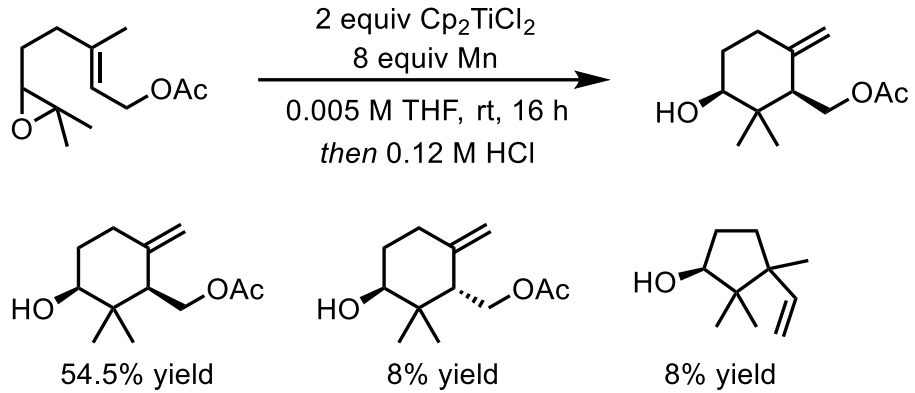
- In non-cyclizations, decyanogenation is 13 times faster than HAT
- Ketones cyclize exclusively with tertiary radicals even with the presence of cyclohexadiene
- THF does not act as H-atom donor as it did not react with benzaldehyde present
- 4-membered cyclizations with dicyano groups result in formation of enaminonitrile.

6-*endo-trig* and 6-*exo-trig* Cyclization

Barrero (2001): Publishes 6-*endo* cyclization inspired by biomimetic Mn(III)/Cu(II) chemistry

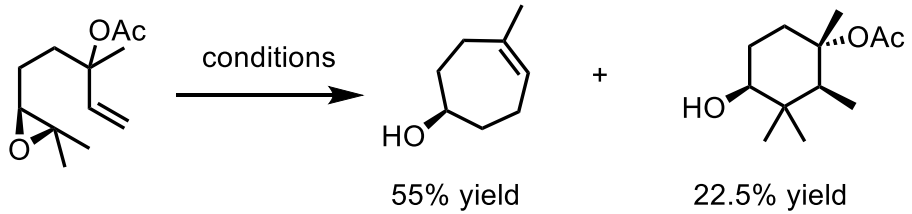






- Takes advantage of sterically unfavored 5-*exo* to promote 6-*endo*
- Elimination of β-Titanoxy radical seen

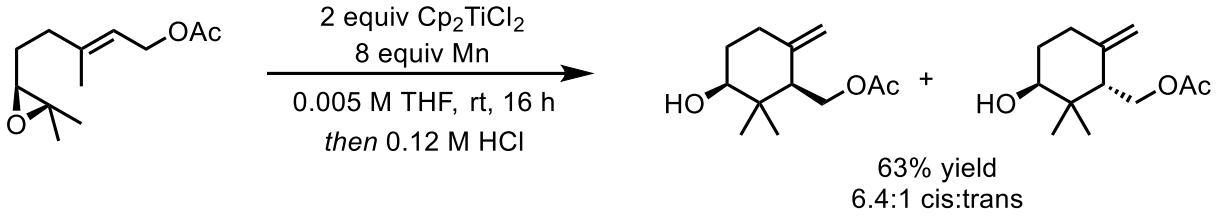
6-*exo* vs. 7-*endo* Cyclization



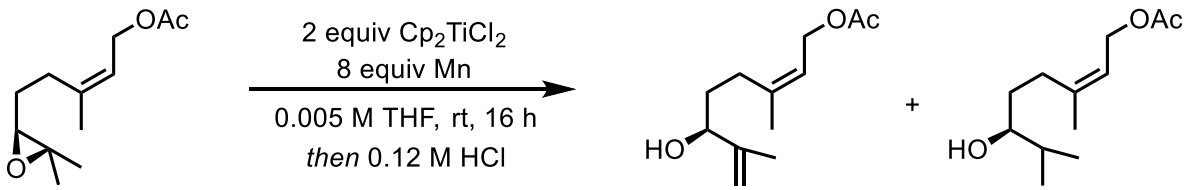
J. Org. Chem. **2001**, *66*, 4074-4078

6-*endo-trig* and 6-*exo-trig* Cyclization

Barrero tested 6-*exo-trig* cyclization with alkene geometry



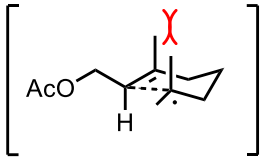
63% yield
6.4:1 cis:trans

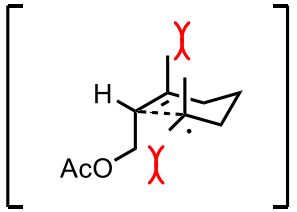


67% yield

7% yield

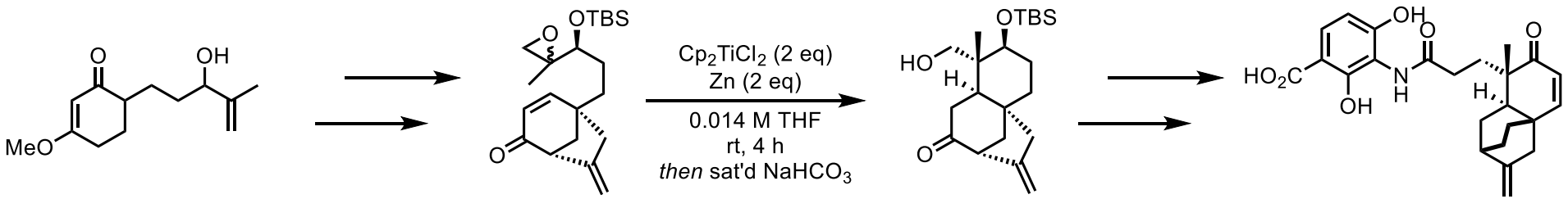
Proposed TS





- Steric Interactions favor (*E*) vs. (*Z*) olefin

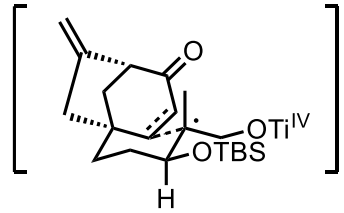
Yoshimitsu (2011): Total Synthesis of (±)-platencin utilizing Cp_2TiCl_2 to give full diastereoselectivity



87% yield
single isomer

(±)-platencin

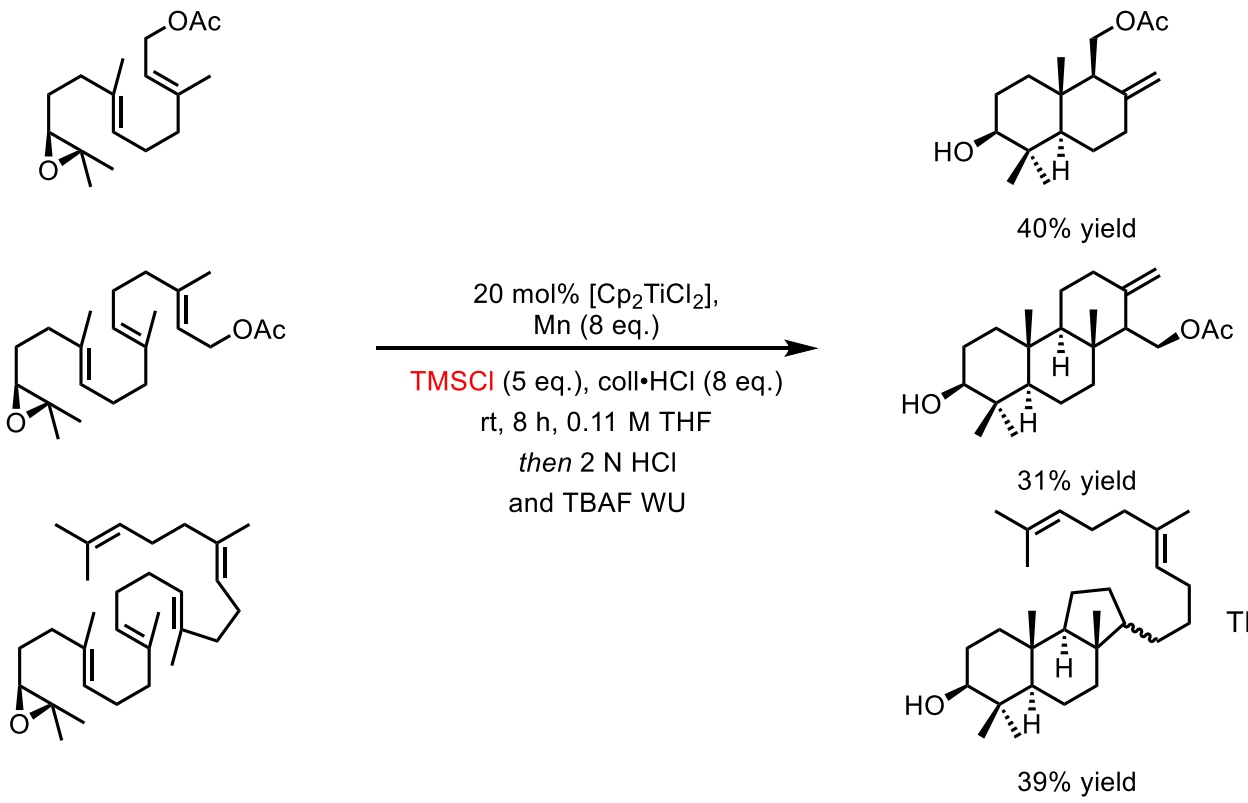
Proposed TS?



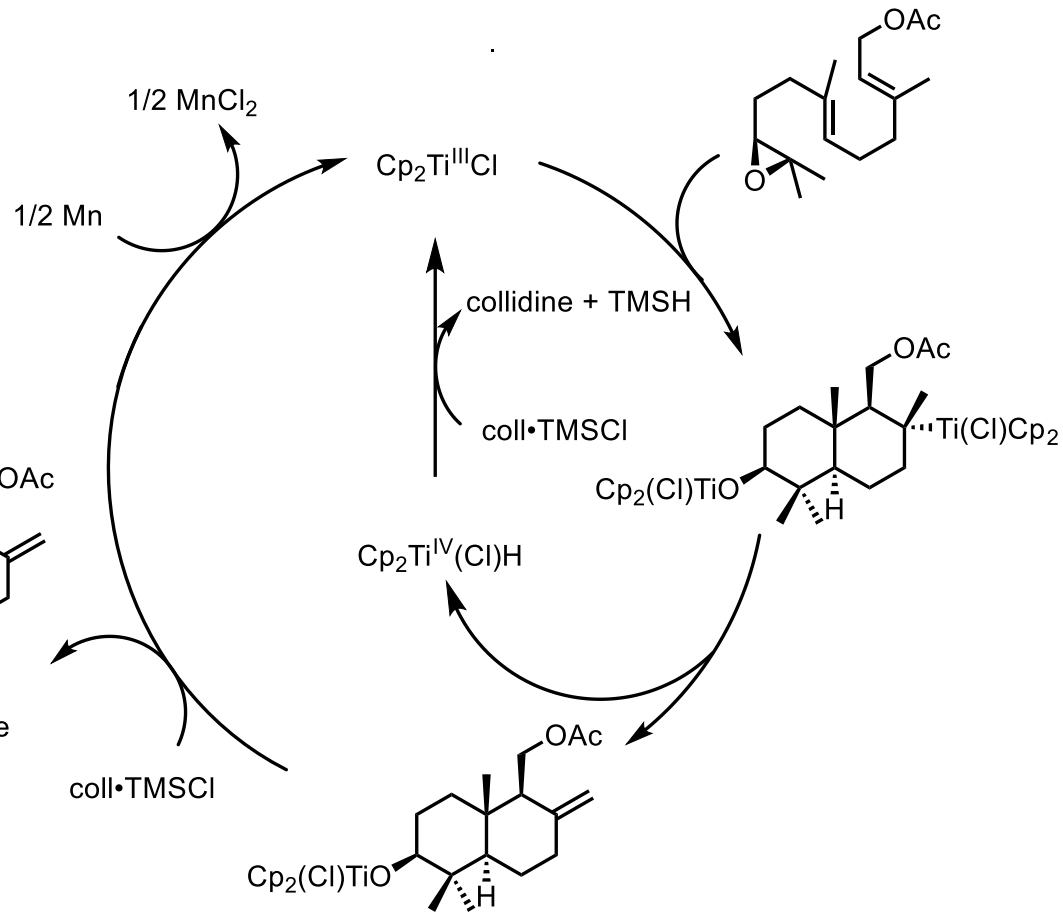
J. Org. Chem. **2001**, *66*, 4074-4078
Org. Lett. **2011**, 13, 3698–3701

Catalytic 6-*endo-trig* Tandem Cyclization

Barrero (2004): Publishes Catalytic Example of 6-*endo-trig* Cyclization



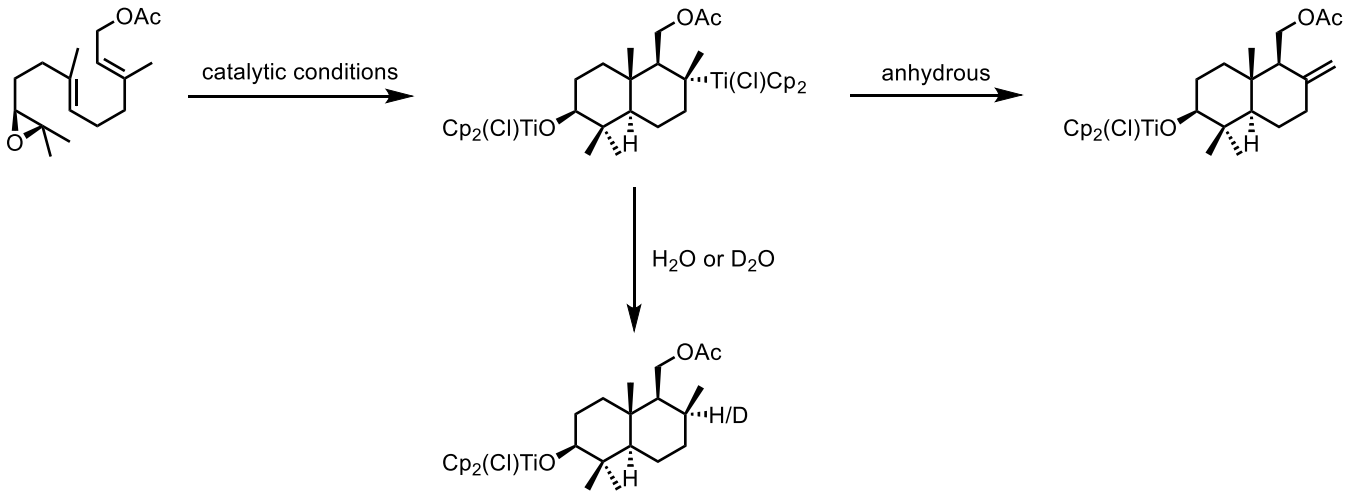
Postulated Catalytic Cycle



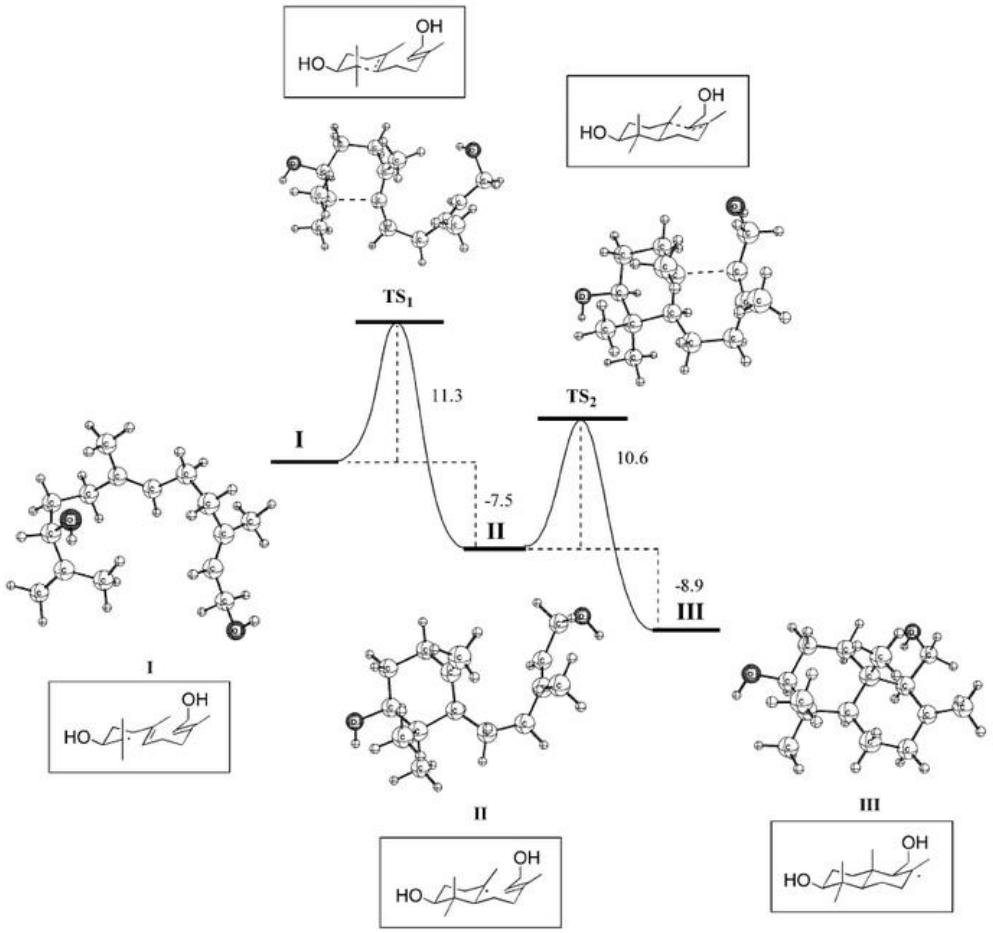
Chem. Eur. J. **2004**, *10*, 1778–1788.

Catalytic 6-*endo-trig* Tandem Cyclization (cont.)

Reactivity of Species In Water



DFT Energy Profile (B3LYP/6-311+G(d,p)//B3LYP/6-31G(d))



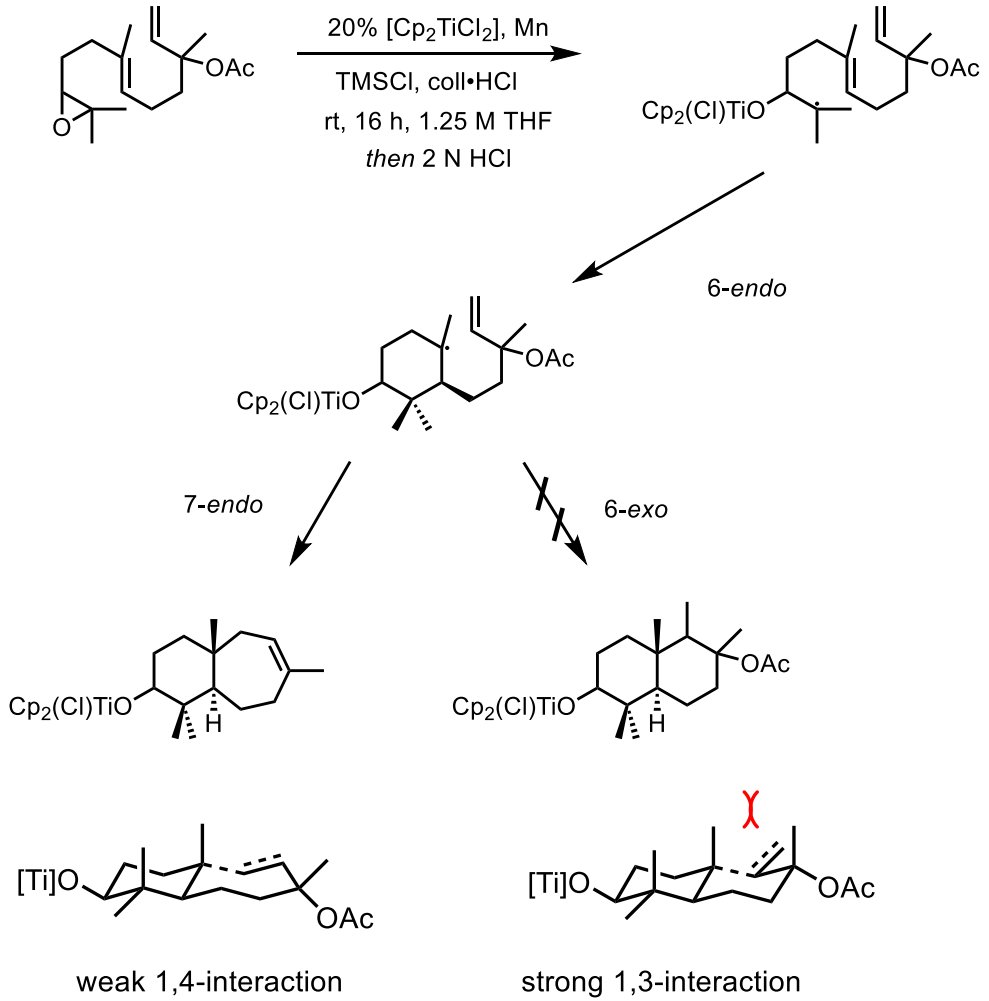
Observation:

- HAT occurs faster than elimination in water
- Implies this may be taking place via step-wise process

Chem. Eur. J. **2004**, *10*, 1778–1788.

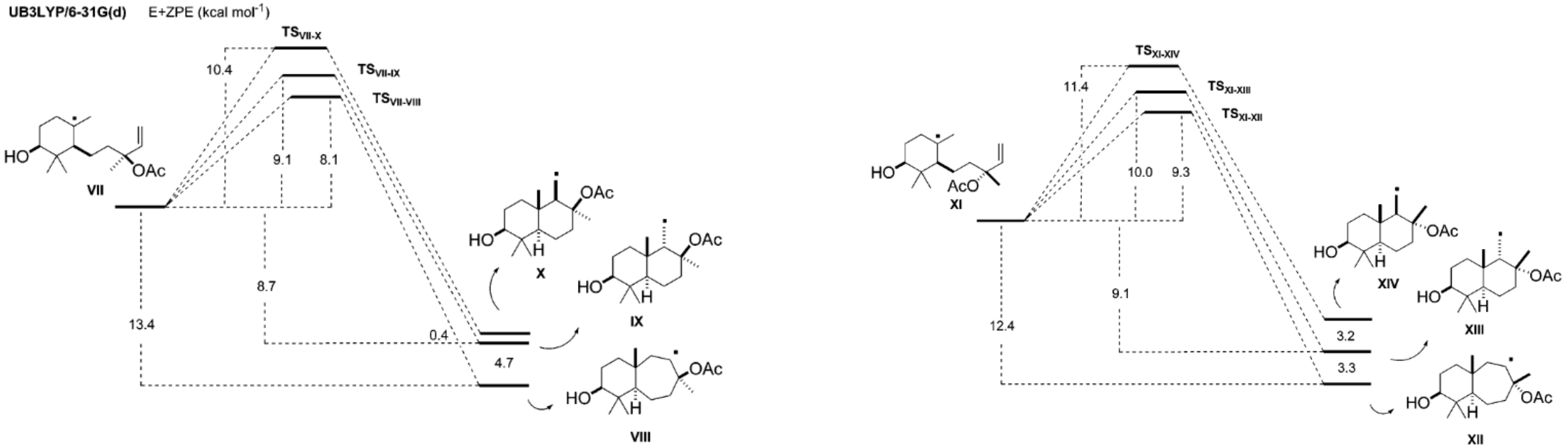
Catalytic 7-*endo*-*trig* Cyclization

Oltra, Cuerva, and Cárdenas (2005): Terpenoid Synthesis



J. Am. Chem. Soc. **2005**, *127* , 14911–14921.

Catalytic 7-*endo-trig* Cyclization



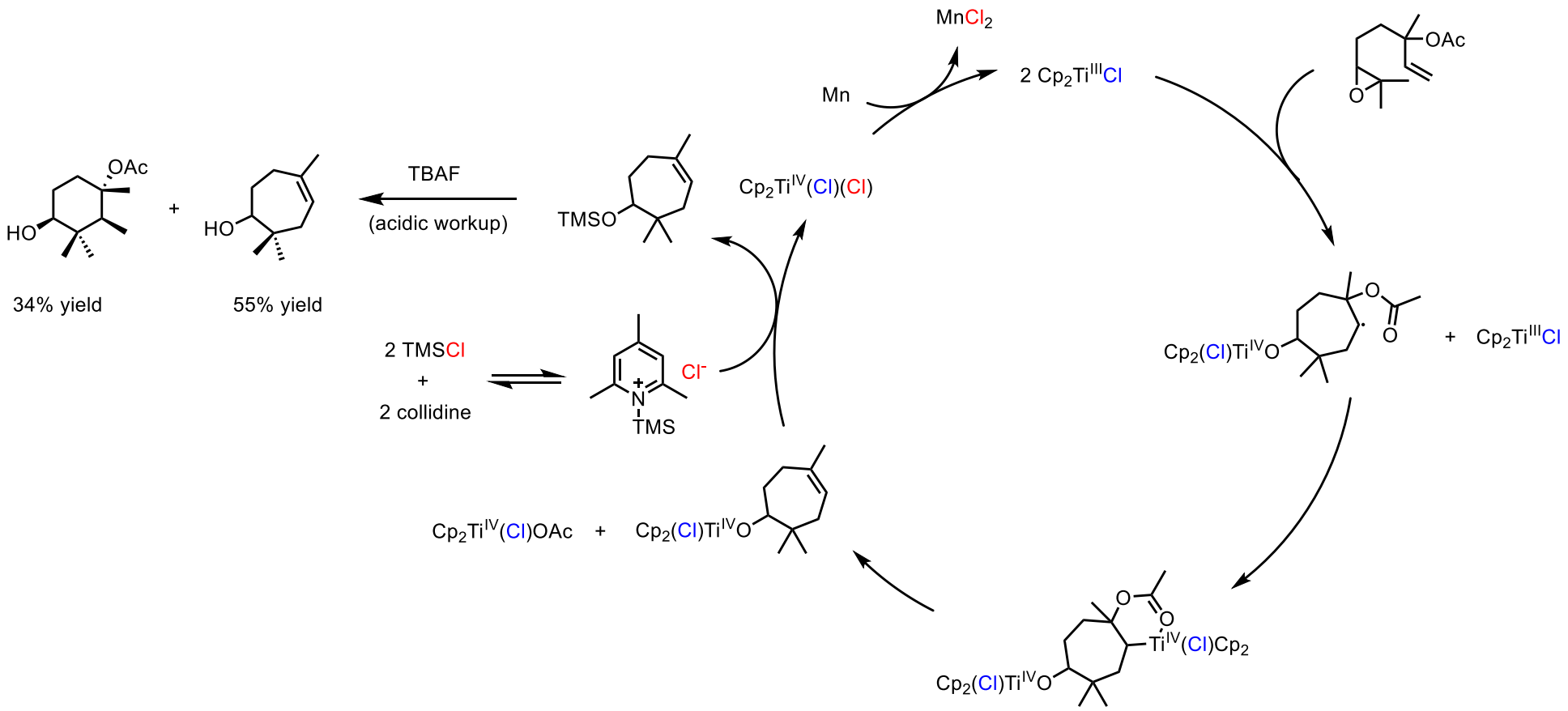
	1,2 cis-6-*exo* (kcal/mol)	1,2 trans-6-*exo* (kcal/mol)	7-*endo* (kcal/mol)
-OAc above ring	10.4	9.1	8.1
-OAc below ring	11.4	10.0	9.3

- 7-*endo* cyclization is always the preferred pathway, regardless of starting diastereomer!
- Low difference in transition states point to potential equilibrium

J. Am. Chem. Soc. **2005**, *127* , 14911–14921.

Cyclization and Aprotic Catalysis (cont.)

Oltra, Cuerva, and Cárdenas propose a mechanism with formation of $Cp_2TiClOAc$

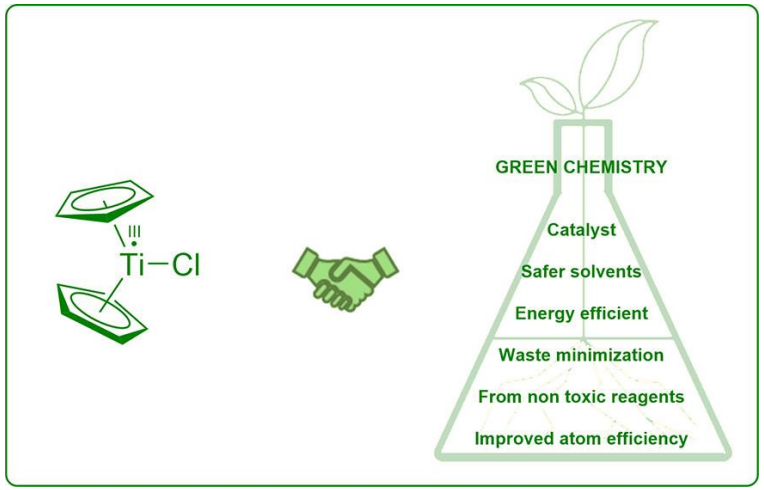


Mechanistic Support

- Strong evidence that Ti(III) can trap carbon-centered radicals.
- The fused ring complex obeys the 18 electron rule
- Formation of Ti-O bond can promote rapid. elimination compared to hydrolysis of Ti-C bond.

J. Am. Chem. Soc. **2005**, *127* , 14911–14921.

Some Final Thoughts



Advantages	Limitations
Very versatile and still widely used reagent for reductive cleavage of epoxides	Non-stereospecific deoxygenation of acyclic epoxides
Considered “Ideal Reagent” for green C-C and C-O bond forming, deoxygenation, and isomerization	Nature of reagent removes stereogenic center enantiopure terminal epoxides
β-Titanoxy radicals are long-lived	Cannot be used with Nitro groups or highly oxidizable functionalities

Org. Process Res. Dev. **2017**, *21*, 911-923.

Reviews Regarding Cp_2TiCl

Castro Rodríguez, M.; Rodríguez García, I.; Rodríguez Maecker, R. N.; Pozo Morales, L.; Oltra, J. E.; Rosales Martínez, A.
Cp2TiCl: An Ideal Reagent for Green Chemistry?
Org. Process Res. Dev. **2017**, *21* , 911–923.

Rosales, A.; Rodríguez-García, I.; Muñoz-Bascón, J.; Roldan-Molina, E.; Padial, N. M.; Morales, L. P.; García-Ocaña, M.; Oltra, J. E. :
The Nugent-Rajanbabu Reagent: A Formidable Tool in Contemporary Radical and Organometallic Chemistry.
European Journal of Organic Chemistry **2015**, *2015* (21), 4567–4591.

Martínez, A. R.; Morales, L. P.; Ojeda, E. D.; Rodríguez, M. C.; Rodríguez-García, I.
The Proven Versatility of Cp2TiCl.
J. Org. Chem. **2021**, *86* (2), 1311–1329.

Questions?