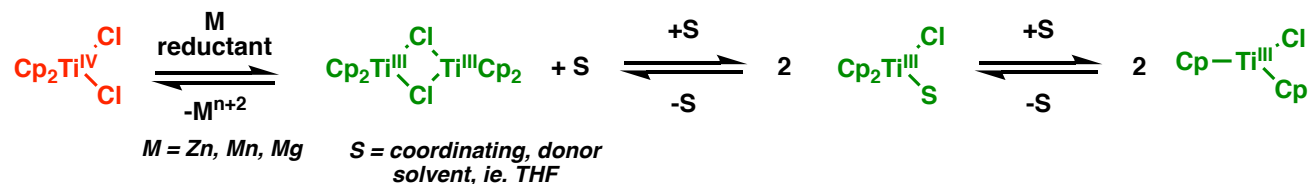


## Nugent-RajanBabu reagent

- $\text{Cp}_2\text{TiCl}$  first reported in 1955 by Wilkinsin
- In situ prep named after W. A. Nugent and T.V. RajanBabu, who found early uses from the preps
- Solvated transition metal centered radical is treated as monomeric  $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$  (in equilibrium)



- isolated  $\text{Cp}_2\text{TiCl}$  can be prepared in this way, if Lewis acidic reductant byproducts are a concern
- $$\text{TiCl}_3 + 2\text{CpTi} \longrightarrow \text{Cp}_2\text{TiCl} + 2\text{TiCl}$$



*Sci. Nat.* 1955, 96  
*JACS* 1988, 8561

## Major Players



Thaliyil V. (Babu) RajanBabu

1969 Kerala University (B.Sc.)  
1971 Indian Institute of Technology (M.Sc.)  
1977 The Ohio State University (Ph.D. w/ H. Shechter)  
1979 Harvard University (Postdoc w/ R. B. Woodward)  
1980-1994 Dupont  
1995 - present Professor, The Ohio State University

William (Bill) A. Nugent

1969 Purdue University (B.S.)  
1976 Indiana University Bloomington (Ph.D.)  
1991-2001 Dupont  
2001-2007 Bristol-Myers Squibb  
2007-2014 Vertex  
2015-?? Consulting and visiting scholar at OSH  
w/RajanBabu

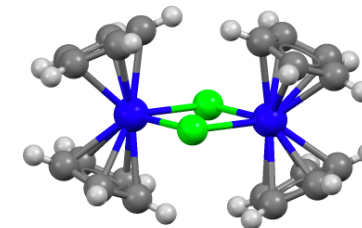


Andreas Gansäuer

1992 University of Bonn/Oxford University (B.S.)  
1994 Max Planck Institute (Ph.D. w/M.T.Reetx)  
1995 Stanford University (Postdoc w/ B.M. Trost)  
1996-2000 University of Göttingen (Habilitation w/ R.Brückner)  
2000-present Professor, University of Bonn

The  $\text{Ti}^{\text{III}}/\text{Ti}^{\text{IV}}$  Redox Couple

- $\text{Ti}^{\text{III}}$  sufficiently Lewis acidic to bind to epoxides
- $\text{Ti}^{\text{III}}$  has soft-electron reducing character (moderate reduction potential,  $E^\circ = -0.8$  vs.  $\text{Fc}^+/\text{Fc}$ ) due to unpaired d electron
- inner-sphere electron transfer with “hard” Lewis bases (ie. epoxides) are possible due to vacant site on Ti
- Chemoselectivity due to this unique combination - engages substrates outside the redox range of the Ti cat.
- $\text{Cp}_2\text{TiCl}$  has been described as the “ideal reagent,” as it is catalytic, chemo- and stereo-selective, abundant, and has low toxicity
- Single electron transfer w/ epoxides driven by strain release and strong  $\text{Ti}^{\text{IV}}\text{-O}$  bond



## Useful Reviews

General Reactivity of  $\text{Cp}_2\text{TiCl}$ :  
*Eur. J. Org. Chem* 2015, 4567

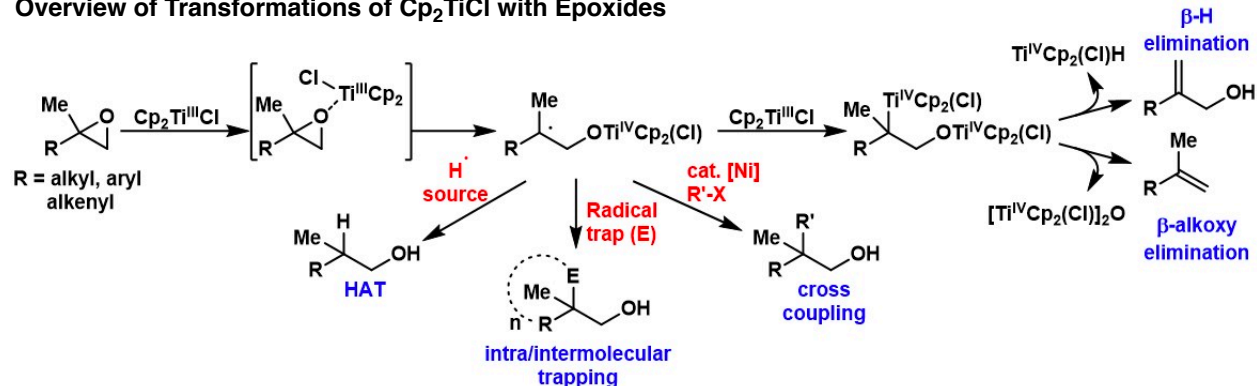
Reactivity of  $\text{Cp}_2\text{TiCl}$  w/Epoxides:  
*Organometallics*, 2018, 4801  
(written by Nugent, RajanBabu, and Gansauer)

$\text{Cp}_2\text{TiCl}$  in Total Synthesis:  
*Org. Chem. Front.* 2014, 15.

$\text{Cp}_2\text{TiCl}$  as a “Green” Reagent:  
*Org. Process Res. Dev.* 2017, 911

$\text{Ti}^{\text{III}}/\text{Ti}^{\text{IV}}$  Redox Couple:  
*J. Org. Chem.* 2019, 14369

Overview of Transformations of Cp<sub>2</sub>TiCl with Epoxides

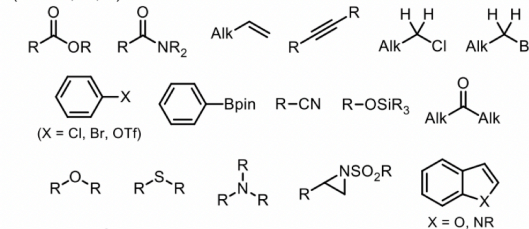


Wikipedia

Ti<sup>III</sup> Functional Group Compatibility

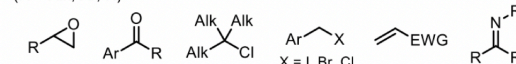
Unreactive functional groups:

(R = Alk, Ar, H)



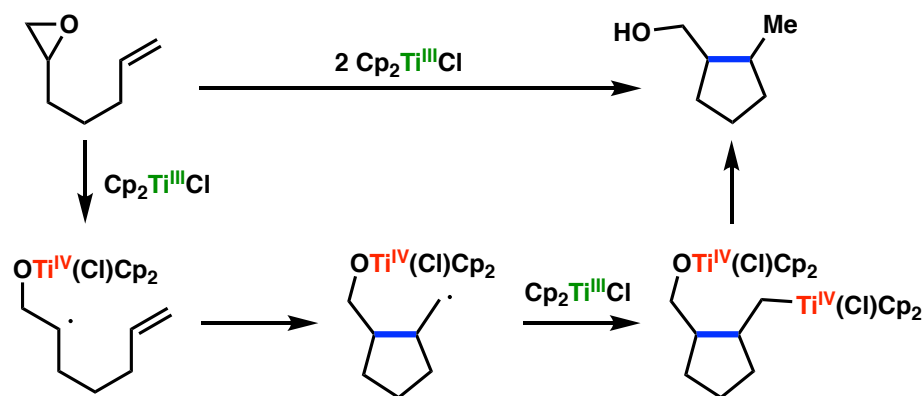
Reactive functional groups:

(R = Alk, Ar, H)

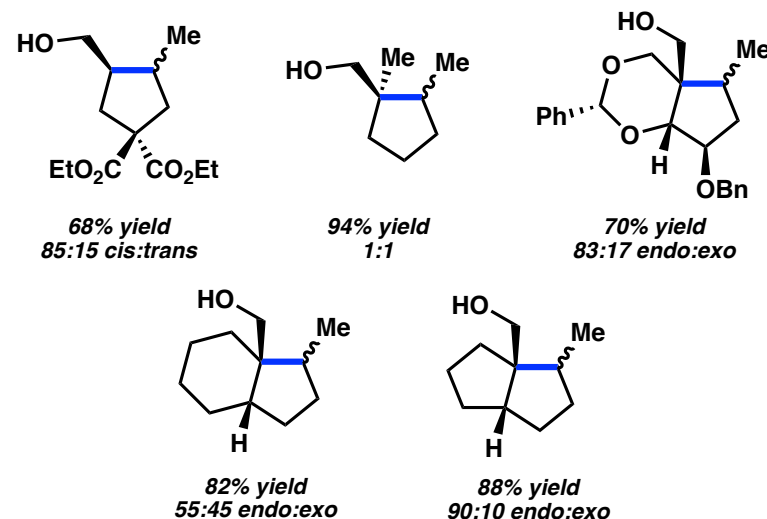


J. Org. Chem. 2019, 14369

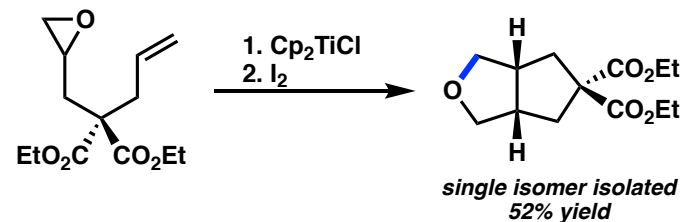
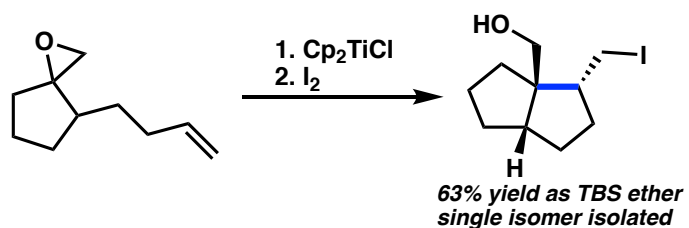
Nugent and RajanBabu's Seminal Report - Intramolecular Cyclization of Epoxyolefins



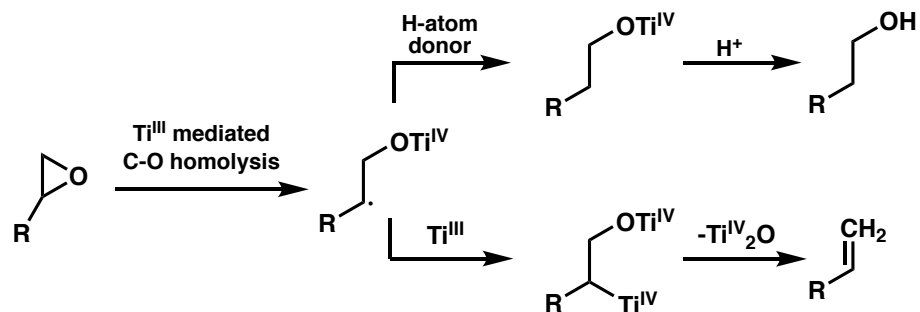
- Instantaneous color change/redox
- Compatible w/ esters, ketone, nitriles
- Incompatible w/ aldehydes, allyl ethers
- Successful at making quaternary centers



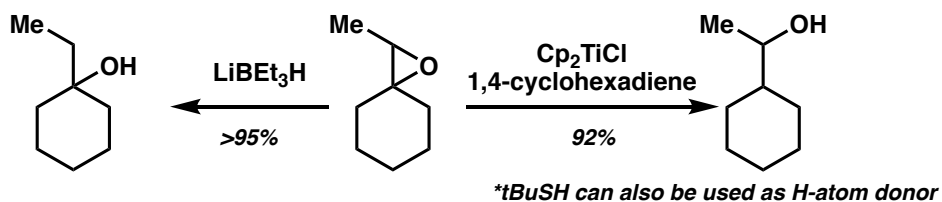
Diversification - Treat Nucleophilic Organotitanium w/ Electrophiles



## Nugent and RajanBabu's Follow Up Reports

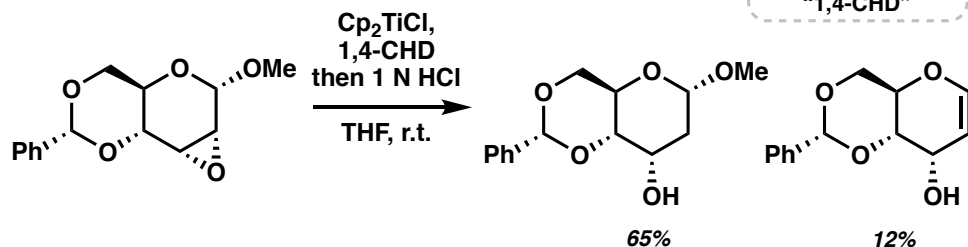
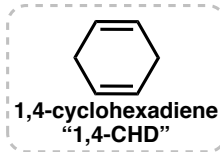


## Epoxide Reduction

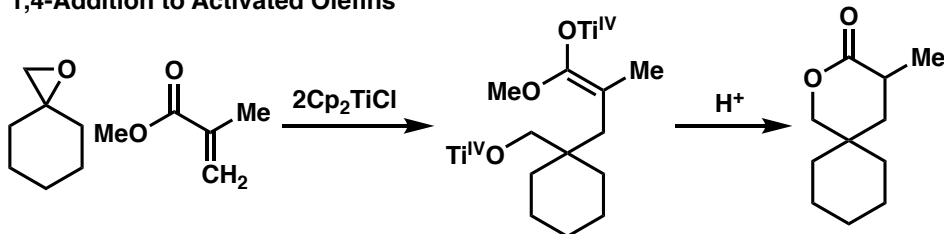


\*tBuSH can also be used as H-atom donor

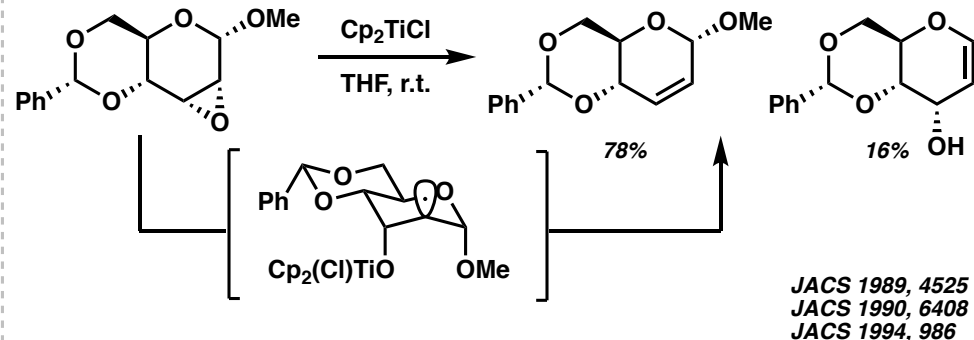
- selectivity depends on substrate (radical stability)
- keep conc. of Ti(III) low to suppress  $\beta\text{-H}$  elimination path
- achieved w/ inverse order of addition, Ti added to epoxide



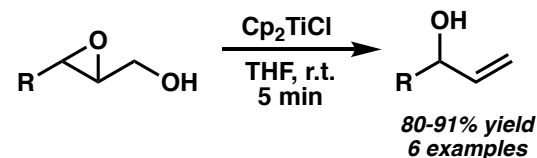
## 1,4-Addition to Activated Olefins



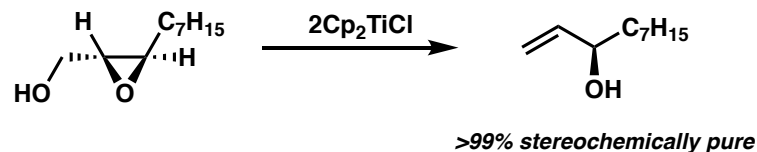
## Deoxygenation of Epoxides



## Deoxygenation of 2,3-Epoxy Alcohols - Synthesis of Allylic Alcohols

*J. Chem. Soc. Chem. Comm. 1990, 843*

## Stereospecific Synthesis of Allylic Alcohols from Sharpless Epoxyalcohols

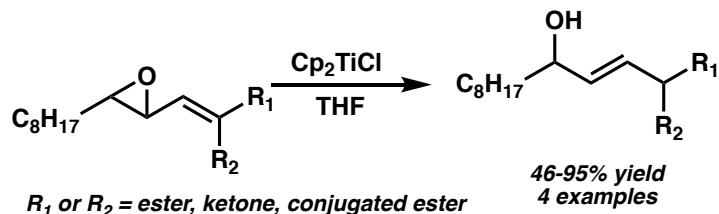


## - O-substitution alters deoxygenation

*JACS 1994, 986*

## Vinyl Epoxides

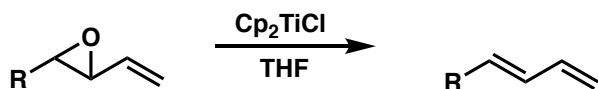
## Regiospecific Reduction of Conjugated Vinyl Epoxides



- Produces only *E*-allylic alcohols
- No *Z*-allylic or homoallylic alcohol side products observed
- For unconjugated systems ( $R_2$  = alkyl), a mix of *E/Z* allylic alcohols is observed
- Kinetic equilibration to the *E* allylic alcohol product cannot occur w/o resonance stabilization of radical by carbonyl

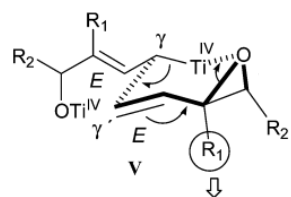
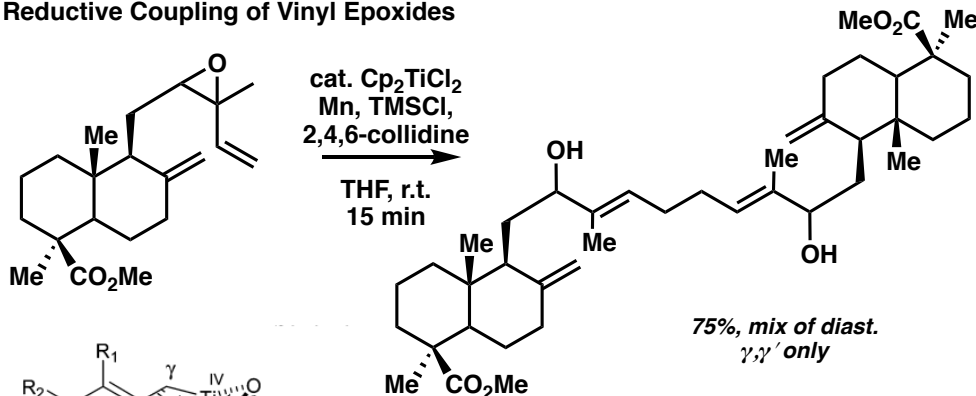
## Exception: terminal vinyl epoxides deoxygenate

- primary radical formation at terminal olefin unfavored/less stable

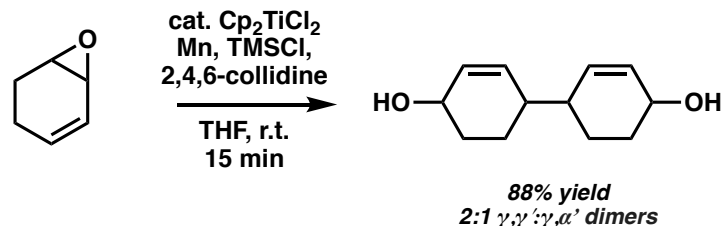
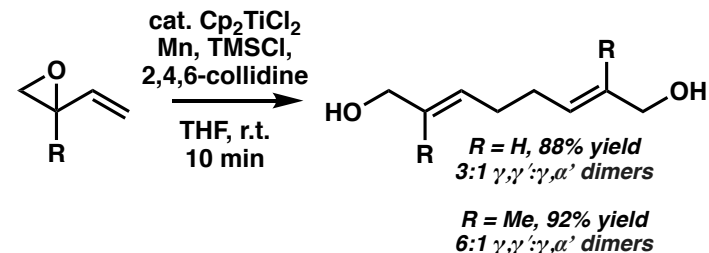


*Tet. Lett.* 1992, 7973

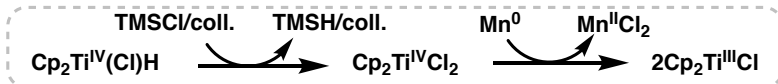
## Reductive Coupling of Vinyl Epoxides



- *E* olefin selectivity a result of steric bulk on epoxide, which favors the *E* di-titanium intermediate
- Observed  $\gamma,\gamma'$  and *E,E* diastereoselectivity proposed explained by transition state shown

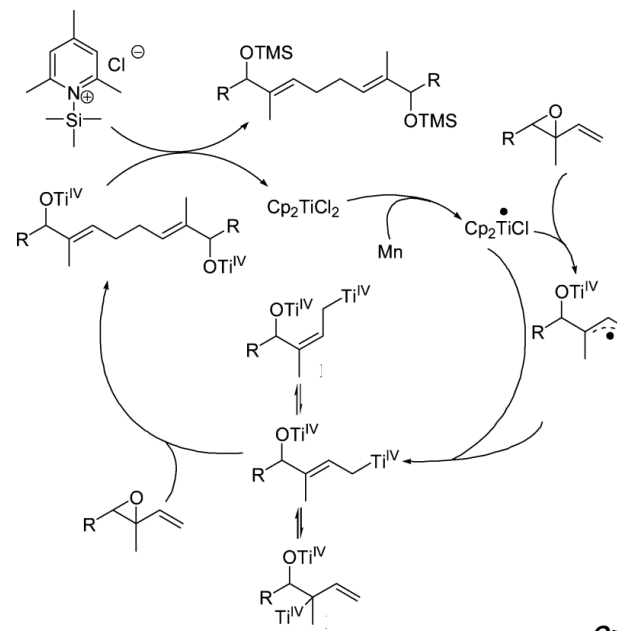


- TMSCl/collidine previously reported by Gansauer to regenerate  $Cp_2Ti^{III}Cl$  from both  $Cp_2Ti^{IV}(Cl)H$  and oxygen-bonded titanium derivatives



Proposed catalytic cycle:

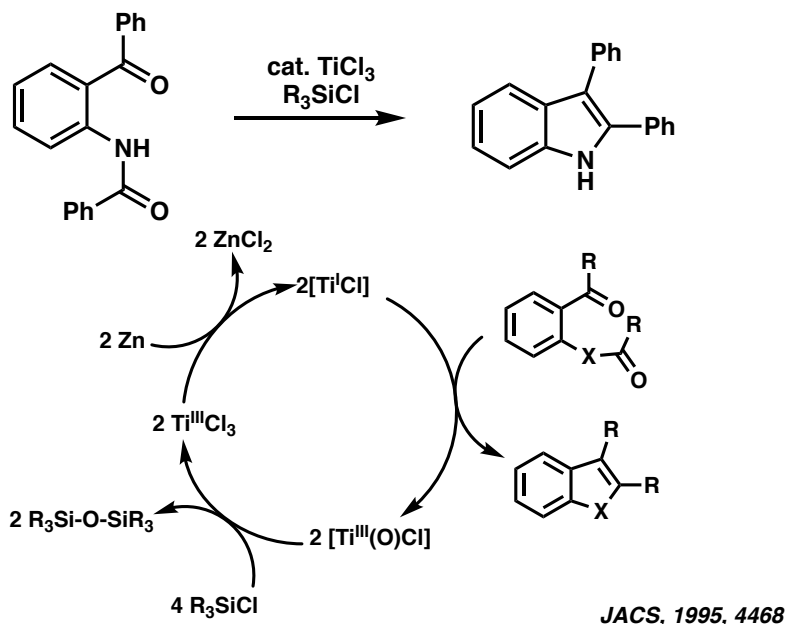
*Chem. Eur. J.* 2004, 1778.



*Org. Lett.* 2006, 669

## Gansauer makes it catalytic...and more!

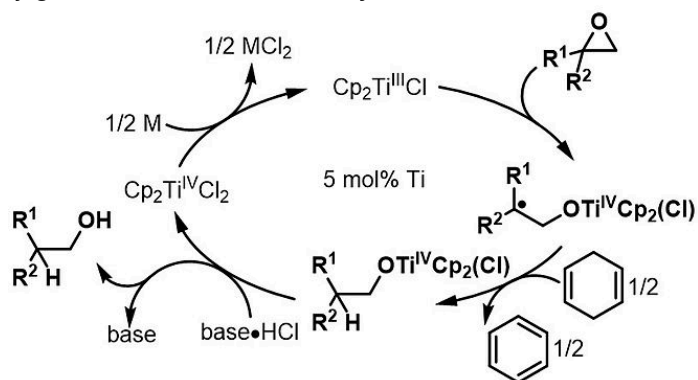
Inspiration: McMurry rxn w/ catalytic Ti by added TMSCl & stoich. Zn reductant



The solution: mildly acidic HCl salt cleaves Ti<sup>IV</sup>-O bond to regenerate Ti<sup>III</sup> cat. w/ stoichiometric reductant

Challenges to consider w/ catalytic modification

- Acid can't be so strong as to open epoxide, only protonate Ti-O and Ti-C bonds
- Acid can't oxidize stoich. reductant
- Conjugate base can't deactivate Ti by coordination



Gansauer proceeds to publish catalytic variants of the transformations previously reported in a stoichiometric fashion by Nugent/RajanBabu.

Reduction:

Cp<sub>2</sub>TiCl<sub>2</sub> (0.05 equiv), Mn (1.5 equiv), collidine-HCl, (1.5 equiv), 1,4-cyclohexadiene (4.3 equiv.), THF, 16 hr

*Angew. Chem.* 1998, 107

Intramolecular Cyclization:

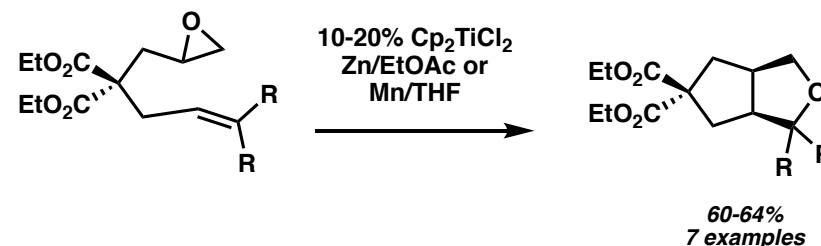
Cp<sub>2</sub>TiCl<sub>2</sub> (0.05 equiv), Mn (1.5 equiv), collidine-HCl, (2.5 equiv), THF, 30 hr

1,4 Addition:

Cp<sub>2</sub>TiCl<sub>2</sub> (0.10 equiv), Zn (4 equiv), ZnCl<sub>2</sub> (2 equiv), collidine-HCl, (6 equiv), acceptor (6 equiv.), THF, 16 hr

*JACS* 1998, 120, 12849  
*Synlett*, 1998, 801

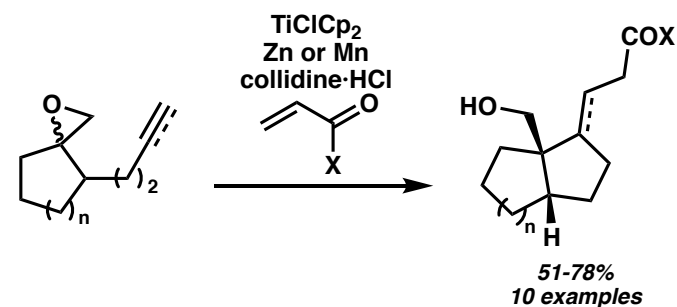
Elaboration of Cyclization - Catalytic Redox Isomerization (Gansauer)



- EtOAc slows down reduction of Ti(IV) w/ Zn
- Low Ti(III) conc. desired for higher yields (minimize reductive trapping of tertiary radical)
- Radical attack on Ti-O bond is downhill by -12.2 to -4.6 kcal/mol (cis vs trans)
- Catalyst regeneration is entropically driven (Ti-O dissociation)

*ACIE*, 2003, 3687

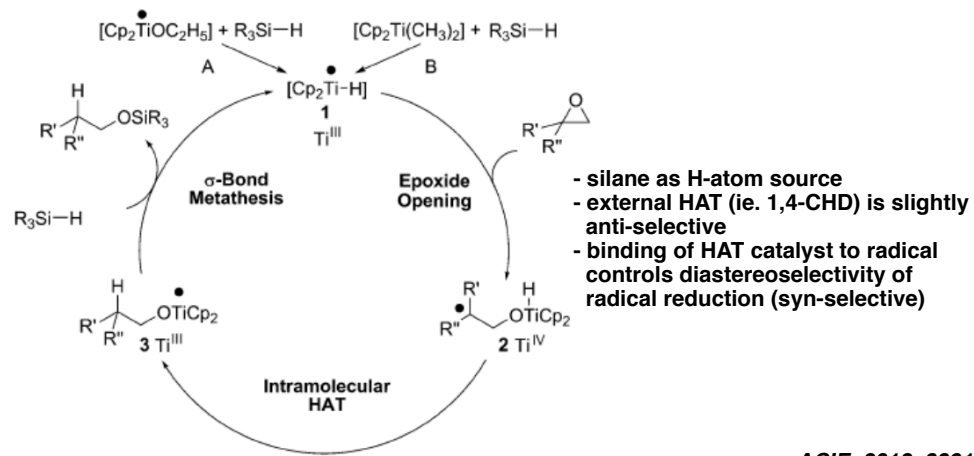
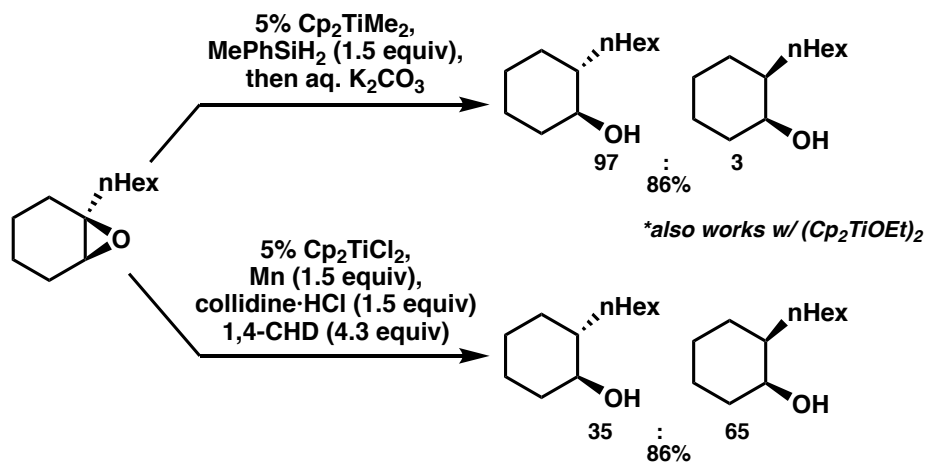
Tandem Cyclization-1,4 Addition (Gansauer)



- E olefins preferred in synthesis of tri-/tetra-substituted olefins, as Ti catalyst coordinated to O blocks face of attack

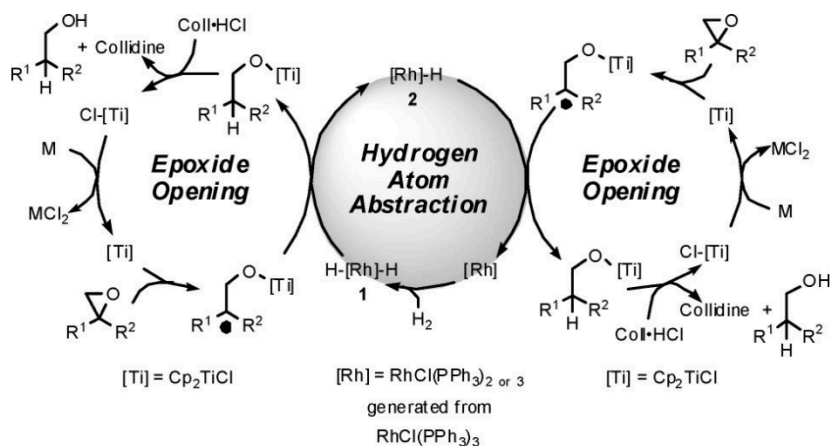
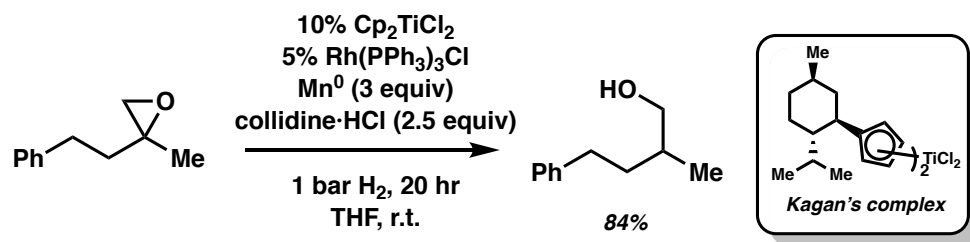
*ACIE*, 2002, 3206

Syn vs Anti-Selective HAT - Gansauer cont.



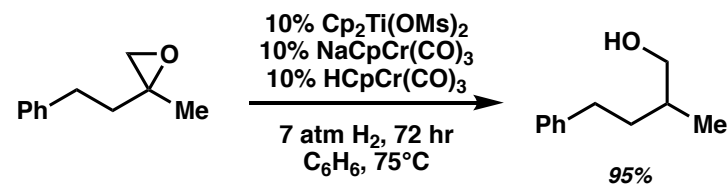
ACIE, 2012, 8891

H<sub>2</sub> as H-atom source - Gansauer cont.

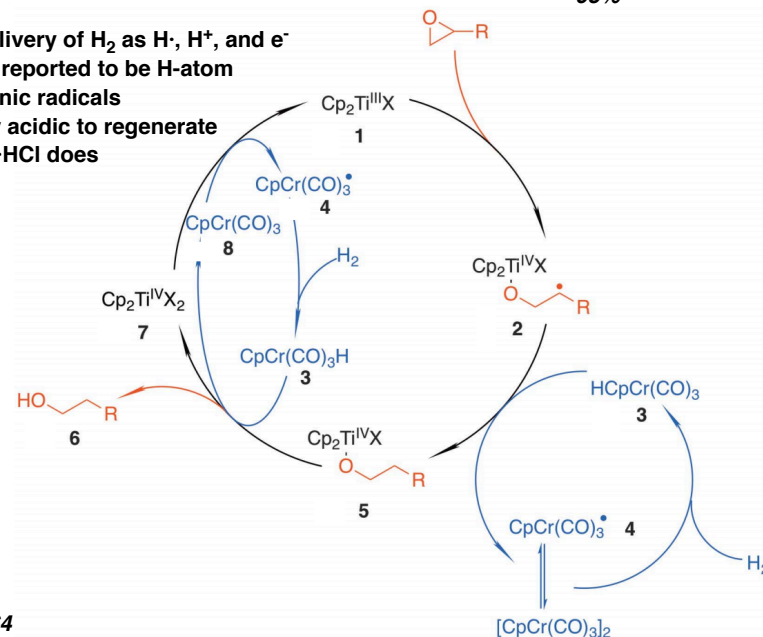


JACS, 2008, 6916

H<sub>2</sub> as H-atom source, but more economic

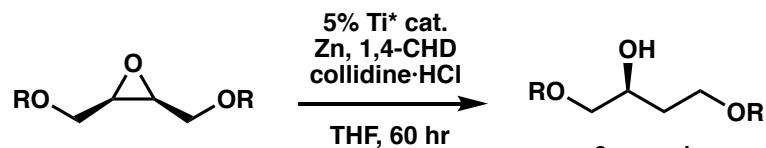


- Cr catalyzes delivery of H<sub>2</sub> as H<sup>-</sup>, H<sup>+</sup>, and e<sup>-</sup>
- CrH previously reported to be H-atom source for organic radicals
- CrH sufficiently acidic to regenerate Ti<sup>III</sup> as collidine-HCl does



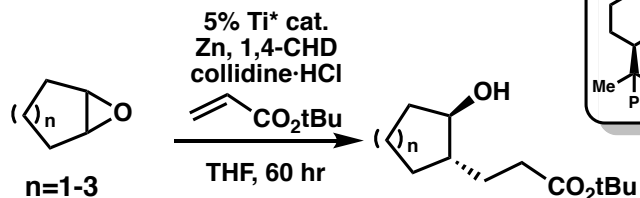
Science, 2019, 764

## Asymmetric Reduction of Meso-Epoxydes (Gansauer)



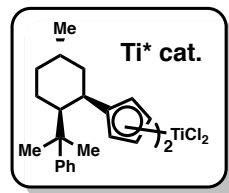
3 examples  
60-65%  
74-93% ee

- first reported example of transition metal catalyzed asymmetric radical formation
- highly selective binding presumed due to  $\pi$  stacking of Ph w/ Cp rings



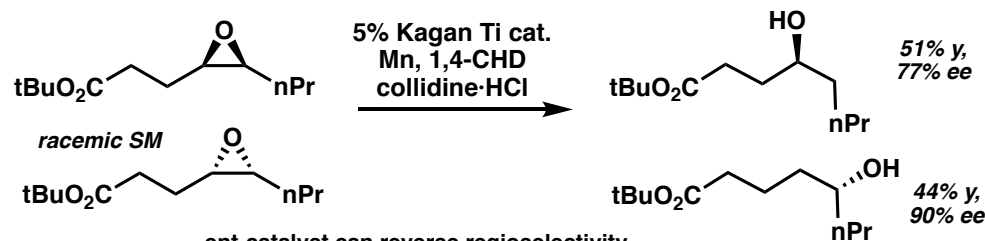
3 examples  
61-68%  
74-93% ee

- larger ring sizes have higher ee



ACIE, 1999, 2909

## Regiodivergent epoxide opening of racemic epoxydes (Gansauer)



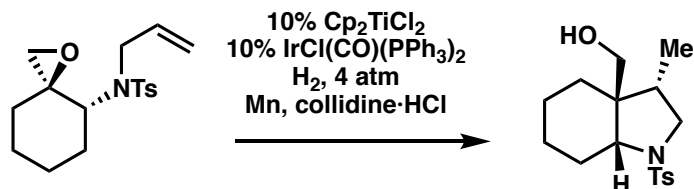
51% y,  
77% ee

44% y,  
90% ee

- ent-catalyst can reverse regioselectivity (observed w/enantiopure epoxide)

JACS, 2007, 3484

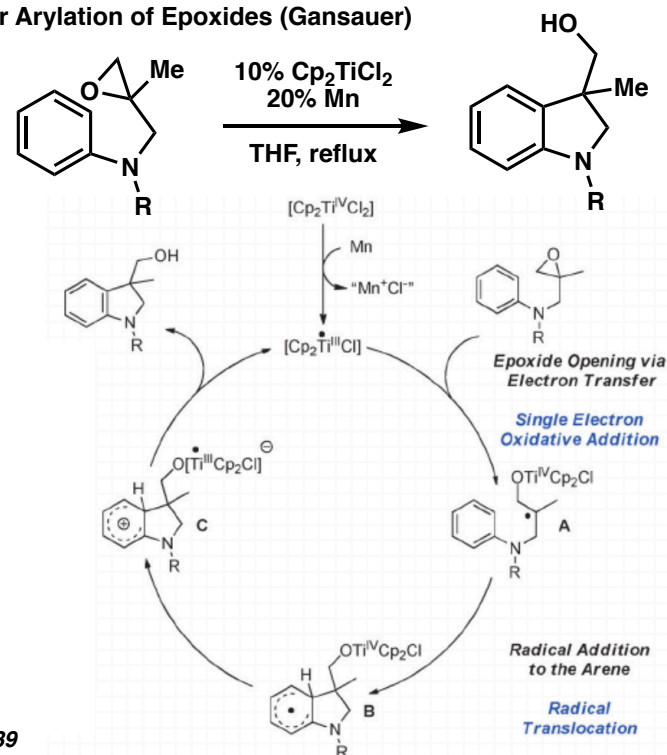
## Cyclization w/ Ir-Catalyzed HAT (Gansauer)



94%  
74:26 d.r.

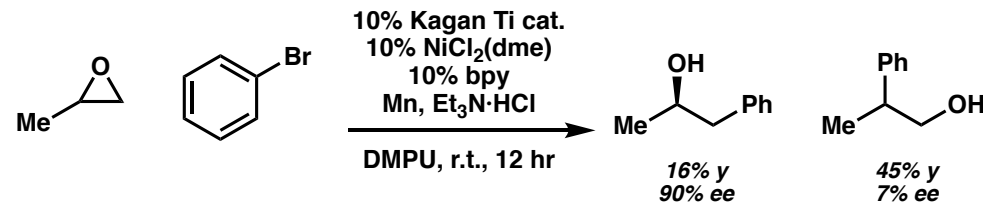
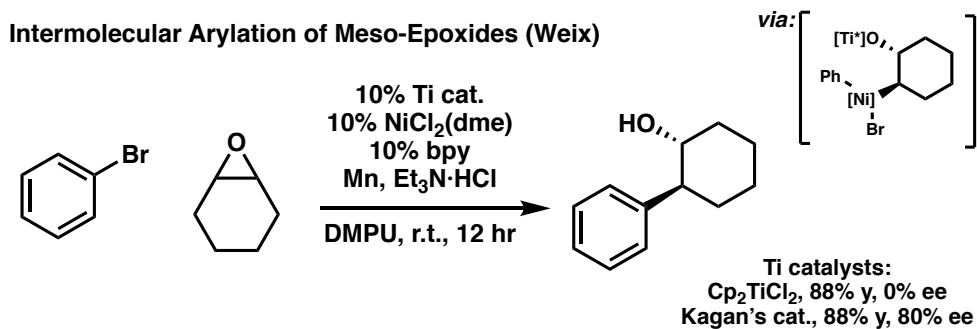
JACS, 2011, 416

## Intramolecular Arylation of Epoxides (Gansauer)



ACIE, 2012, 4739

## Intermolecular Arylation of Meso-Epoxydes (Weix)

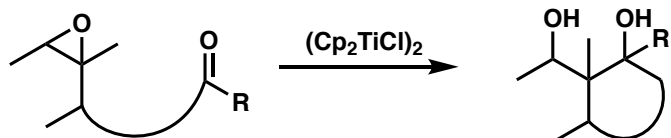


- results of racemic primary epoxide consistent w/ Gansauer's regiodivergent opening
- kinetic resolution of terminal arylation product (high ee)

JACS, 2015, 3237

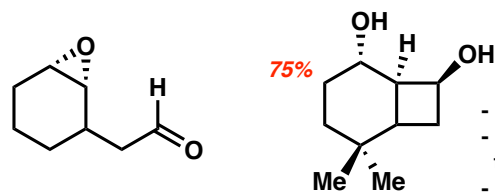
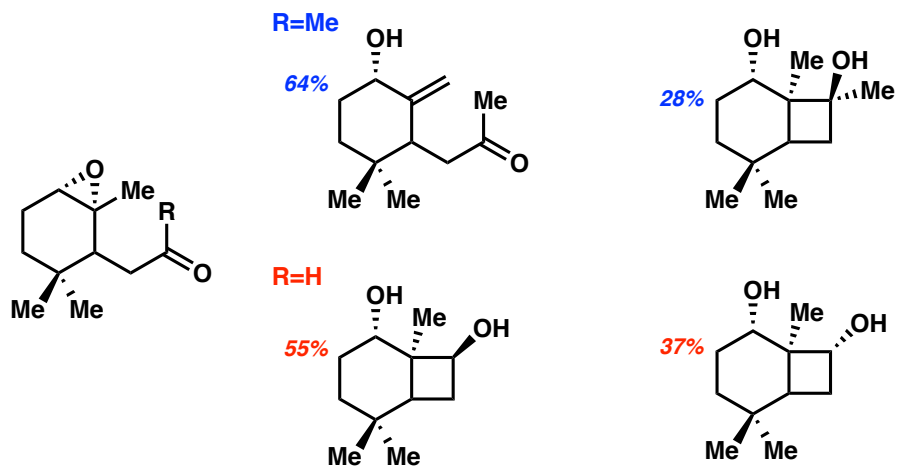
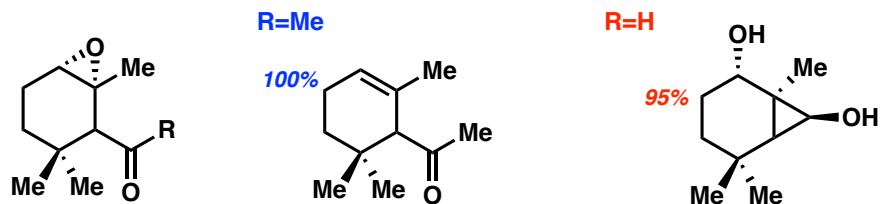


## Intramolecular Addition into Aldehydes/Ketones to give Cycloalkanols



Starting Material

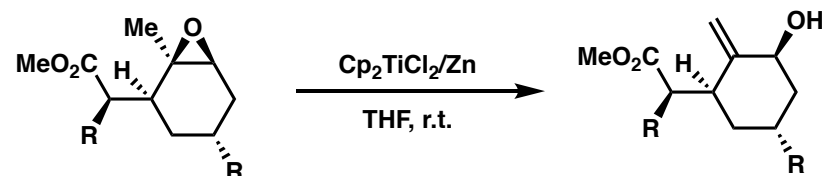
Product(s)



- aldehydes tend to outperform ketones
- di-substituted epoxides higher yielding than tri-substituted
- larger ring sizes possible (cyclopentanol/cyclohexanol) but  $\beta$ -H elimination to exo-methylene allylic alcohols starts to predominate

Org. Lett. 1999, 607

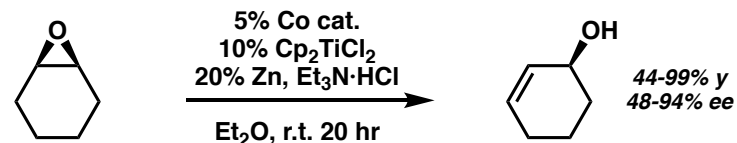
## Isomerization of Trisubstituted Epoxides



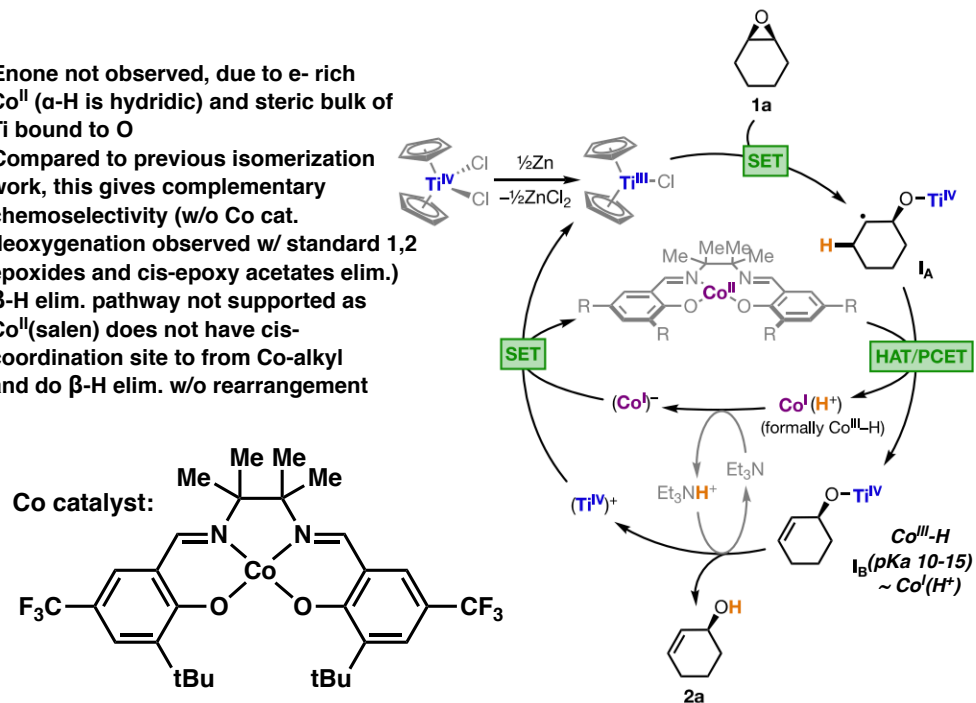
- reduction is major byproduct
- cis-epoxy acetates yield endo-cyclic olefins ( $\beta$ -OAc elimination)
- trans-epoxy acetates yield exo-cyclic olefins ( $\beta$ -hydride elimination)

JOC, 2004, 5275  
More on epoxy-carvone isomerizations, see also:  
Tetrahedron, 2009, 10837  
Tetrahedron, 2013, 1611

## Epoxide Isomerization by Radical Redox-Relay Catalysis (Lin)



- Enone not observed, due to e-rich  $\text{Co}^{\text{II}}$  ( $\alpha$ -H is hydridic) and steric bulk of Ti bound to O
- Compared to previous isomerization work, this gives complementary chemoselectivity (w/o Co cat. deoxygenation observed w/ standard 1,2 epoxides and cis-epoxy acetates elim.)
- $\beta$ -H elim. pathway not supported as  $\text{Co}^{\text{II}}$ (salen) does not have cis-coordination site to from Co-alkyl and do  $\beta$ -H elim. w/o rearrangement

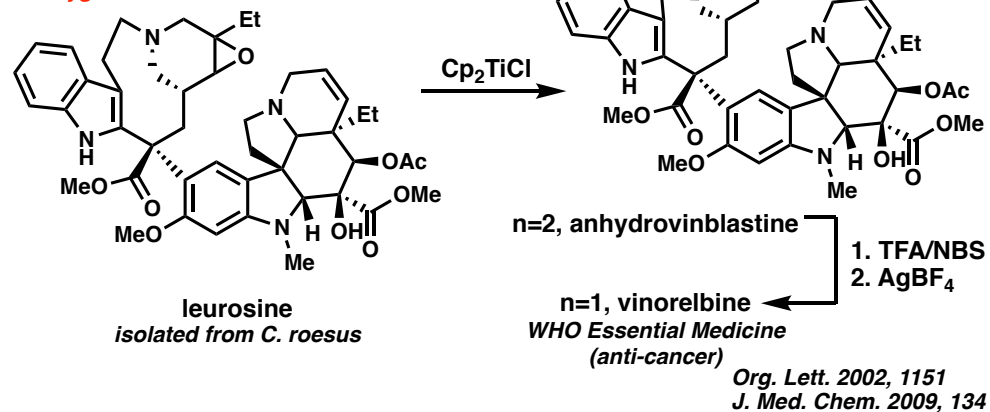


JACS, 2019, 9548



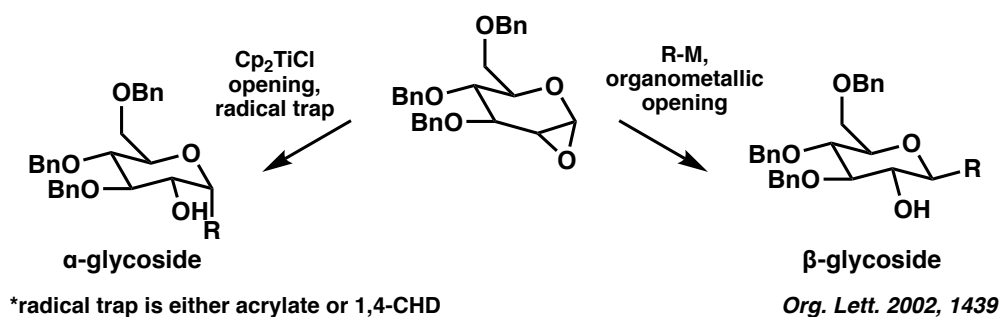
## Selected Examples in Total Synthesis

## Deoxygenation



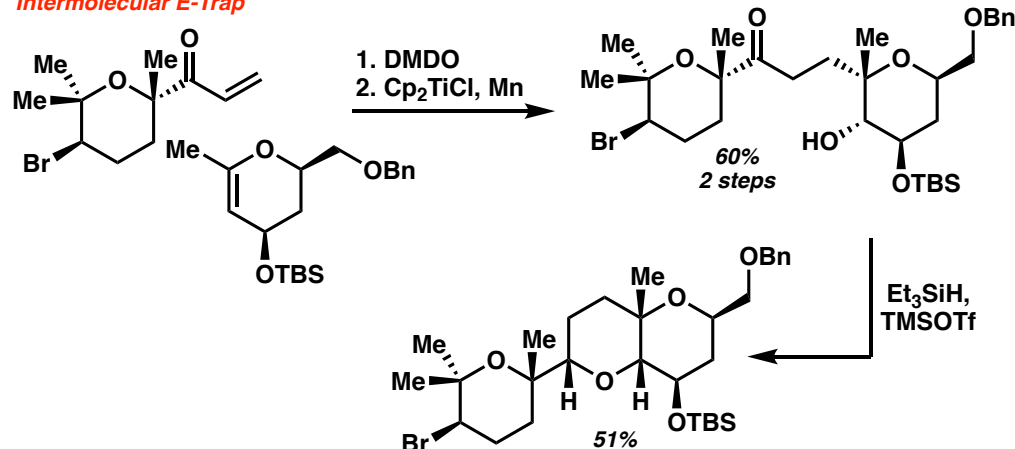
## Stereospecific C-Glycoside Synthesis

## Reduction/Intermolecular E-Trap



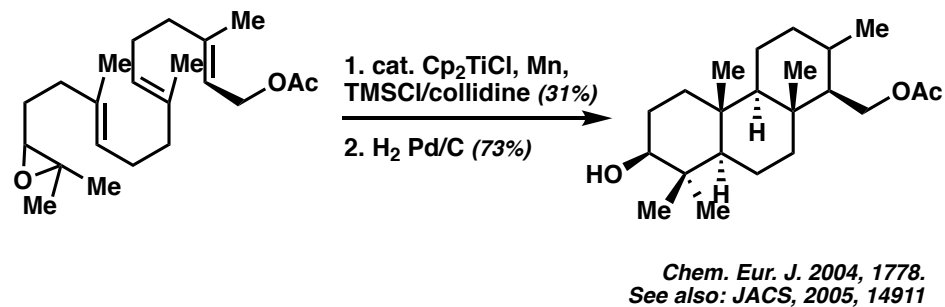
## Accessing Pyranopyrans en Route to Thyrsiferol

## Intermolecular E-Trap



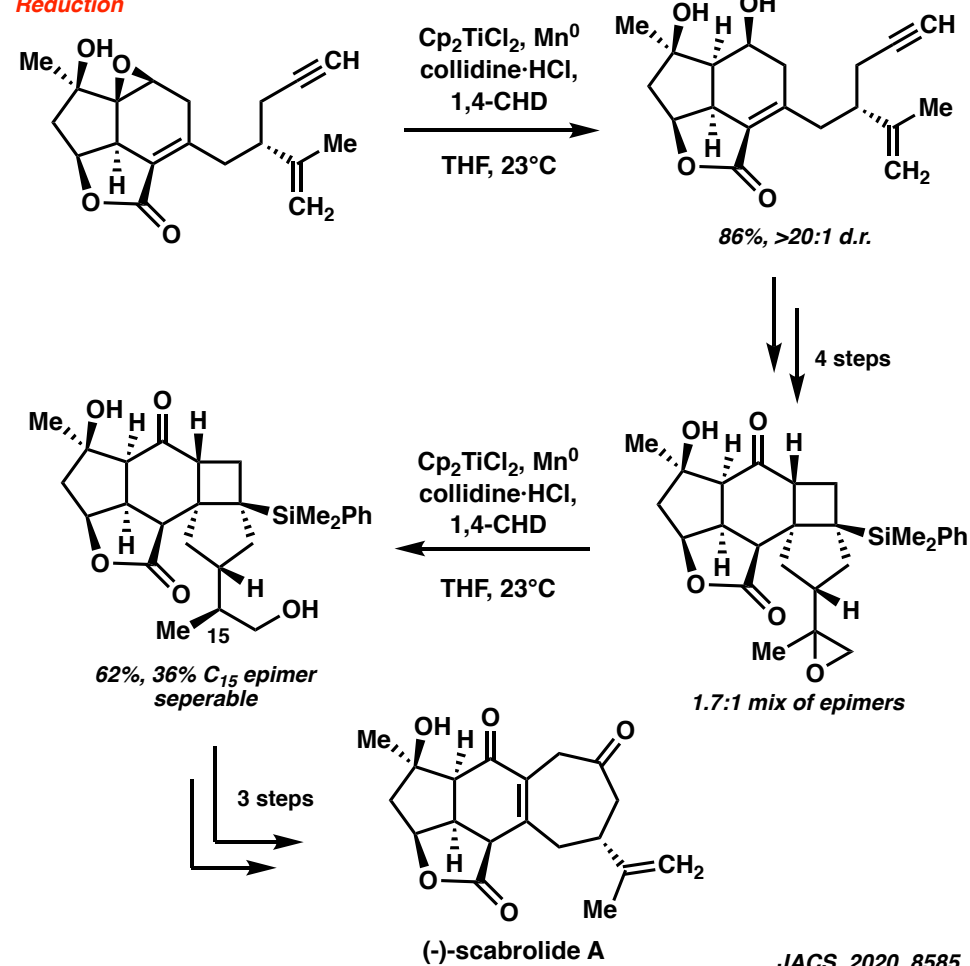
## Terpene Cyclizations

## Intramolecular Trap



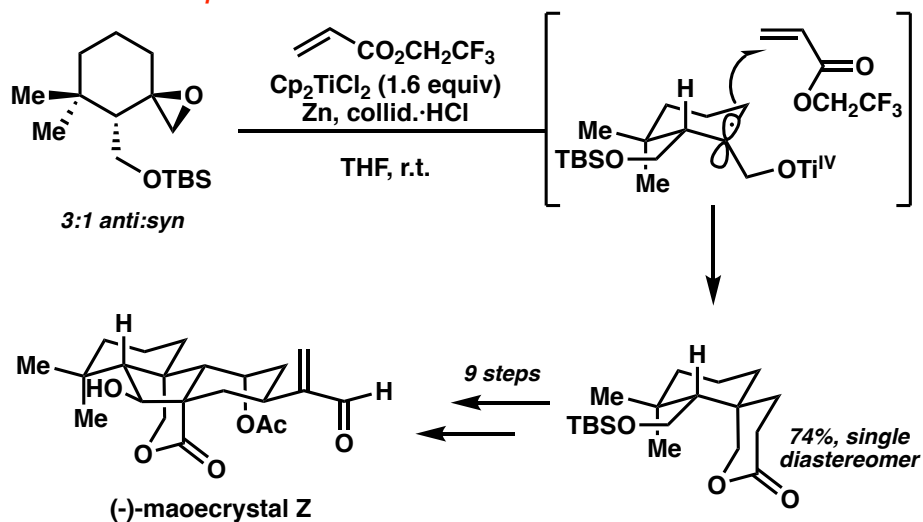
## (-)-Scabrolide A (Stoltz)

## Reduction



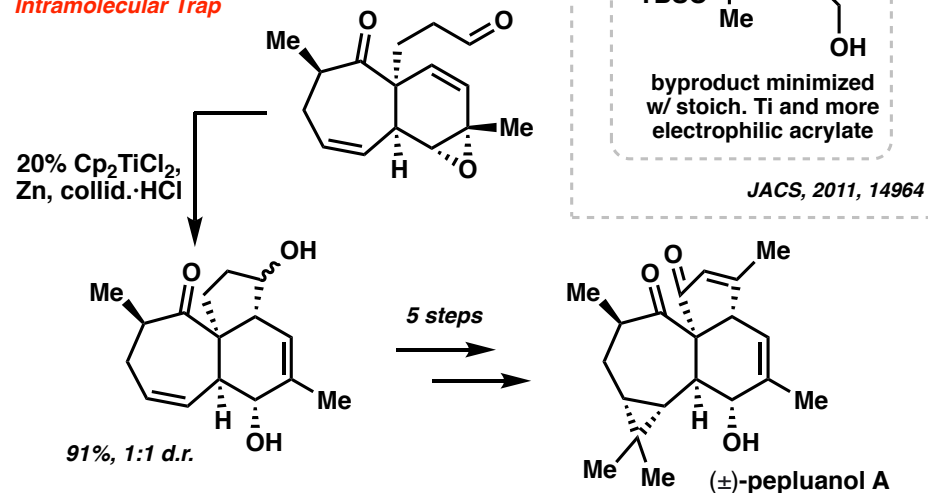
## (-)-Maoecrystal Z (Reisman)

## Intermolecular Trap/Isomerization

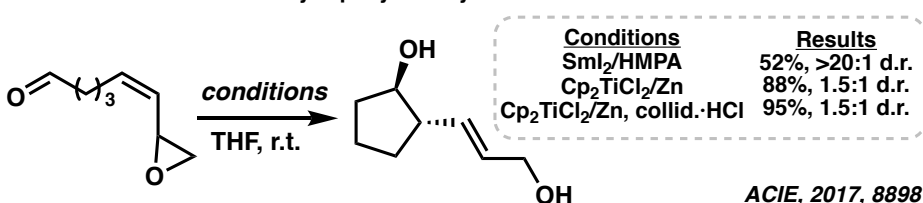


## (±)-Pepluanol A (Ding)

## Intramolecular Trap

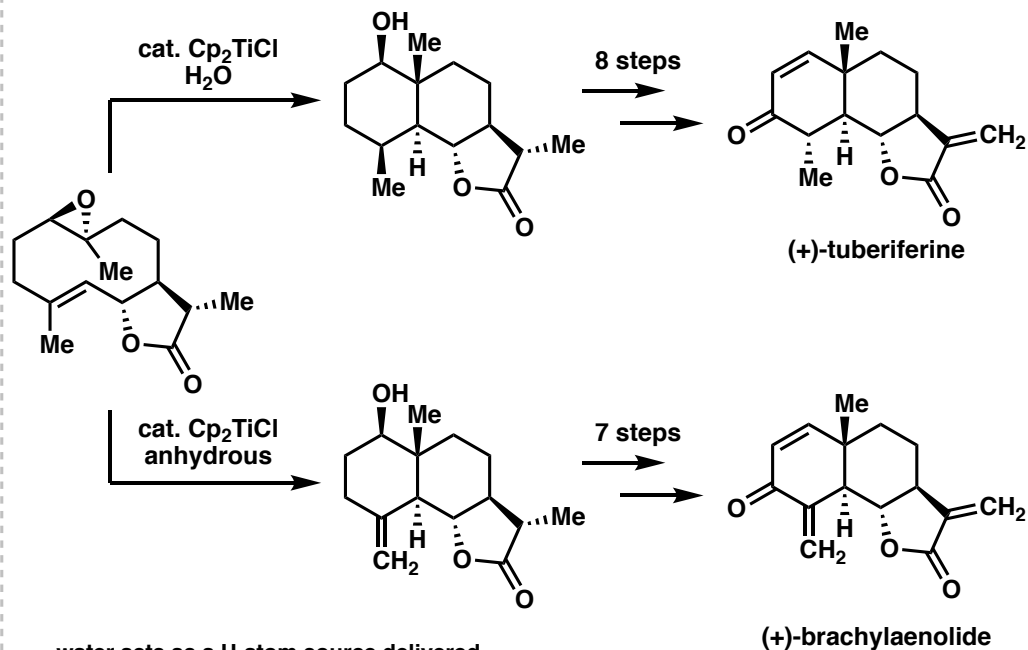


## Reductive Annulation of Vinyl-Epoxy Aldehyde



## Synthesis of Eudesmanolide-Type Compounds (Cuerva/Oltra)

## Reduction/Rearrangement

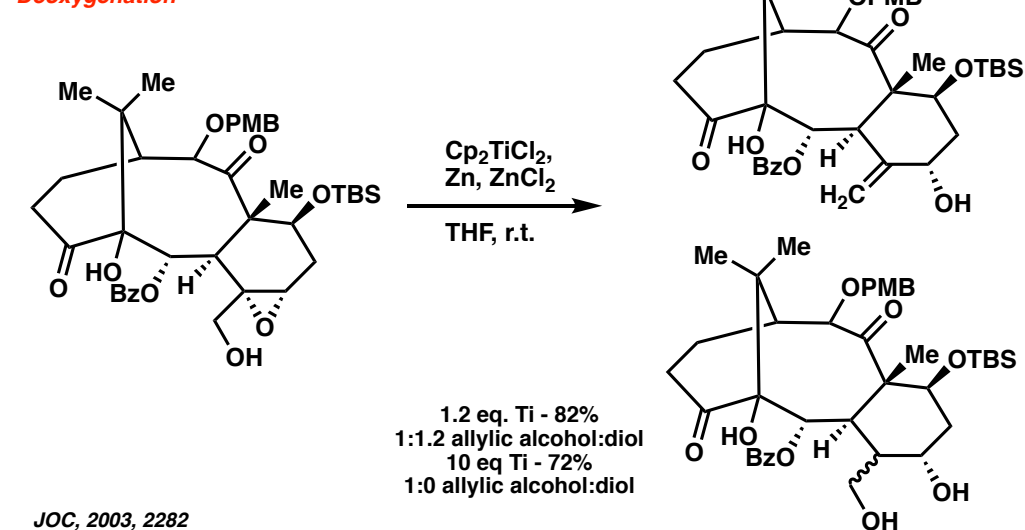


- water acts as a H-atom source delivered via  $\text{Cp}_2\text{Ti}(\text{OH}_2)\text{Cl} \rightarrow \text{Cp}_2\text{Ti}(\text{OH})\text{Cl}$
- standard H-atom abstraction w/o H-atom source

Tetrahedron, 2008, 11938  
See also: JOC 2002 2566

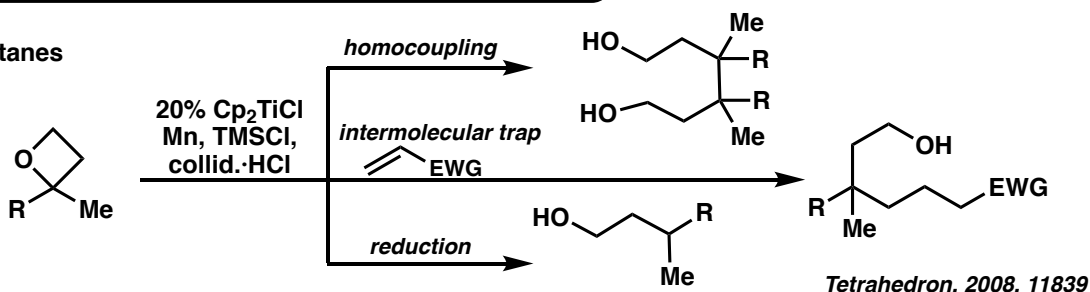
## A Taxane Synthesis (Paquette)

## Deoxygenation

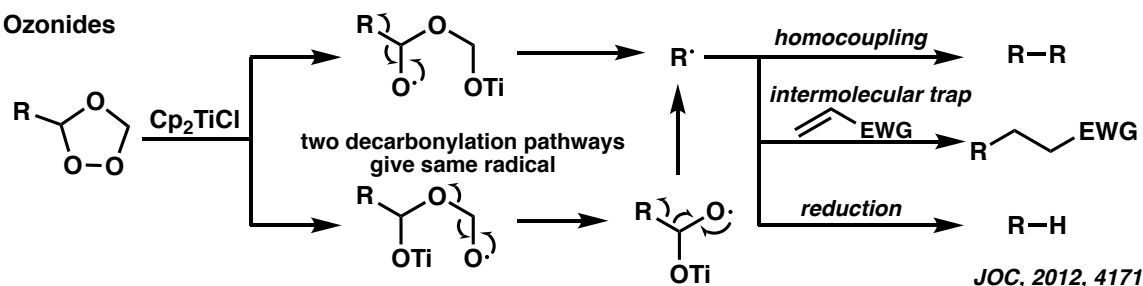


Non-exhaustive overview of other reactions of Cp<sub>2</sub>TiClReview: *Eur. J. Org. Chem.* 2015, 4567

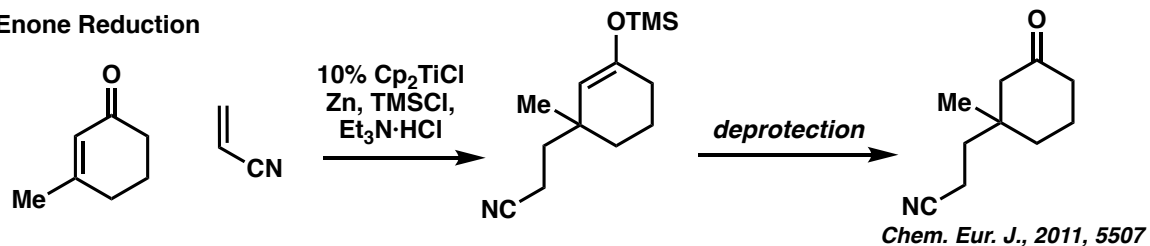
## Oxetanes



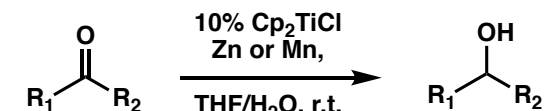
## Ozonides



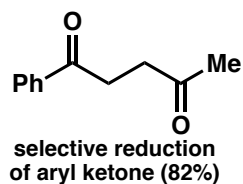
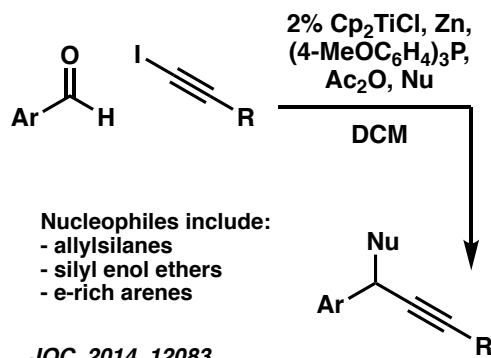
## Enone Reduction



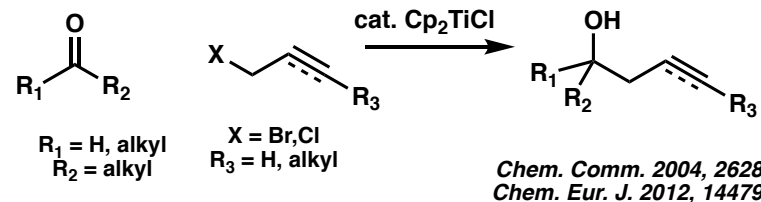
## Ketone Reduction



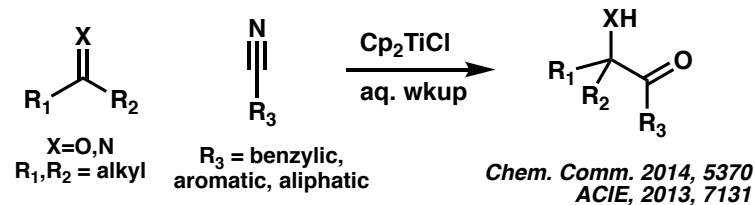
\*limited to cyclic and aryl ketones

potential for catalytic,  
asymmetric reduction w/  
chiral titanocene catalysts*Tet. Lett.* 2003, 1079Three-Component Coupling of  
Acetylides, Aldehydes, and Nucleophiles

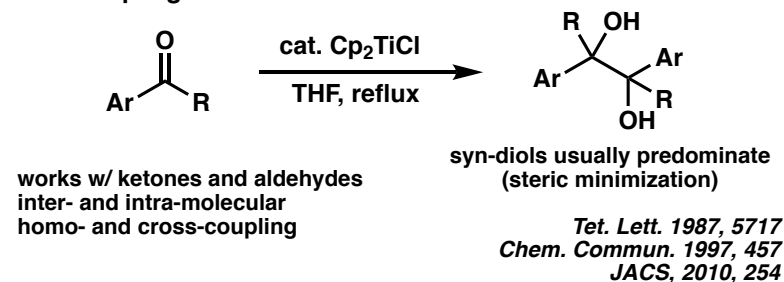
## Barbier-Type



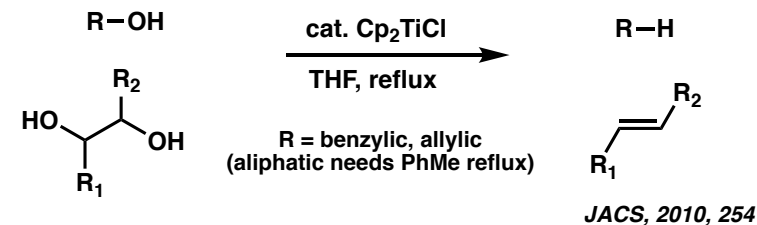
## Cross-Coupling of Ketones/Imines w/Acrylonitriles



## Pinacol Coupling



## Alcohol Deoxygenation



## McMurry Olefination

