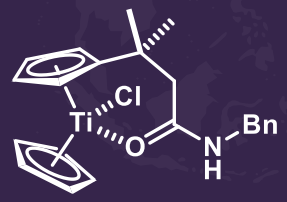
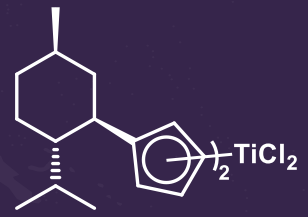
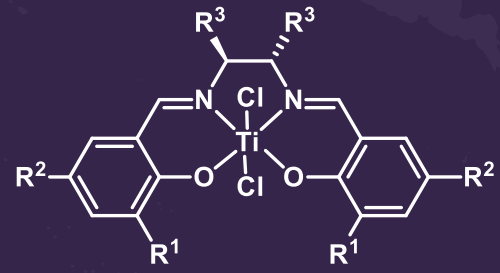
Titanium-Catalyzed Ring-Opening of Three-Membered Rings







Reporter：Shaowei Wang

Supervisor：Prof. Ping Lu

2023.04.28

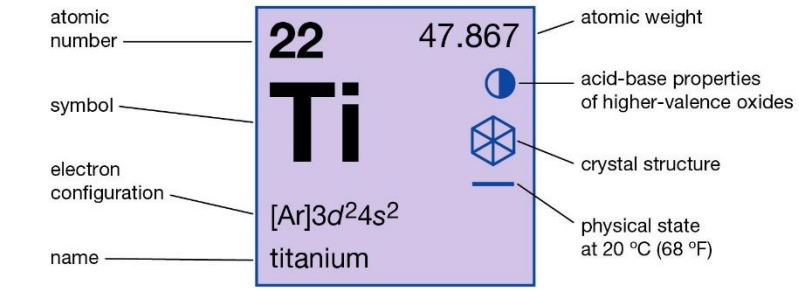
CATALOGUE

PART 1

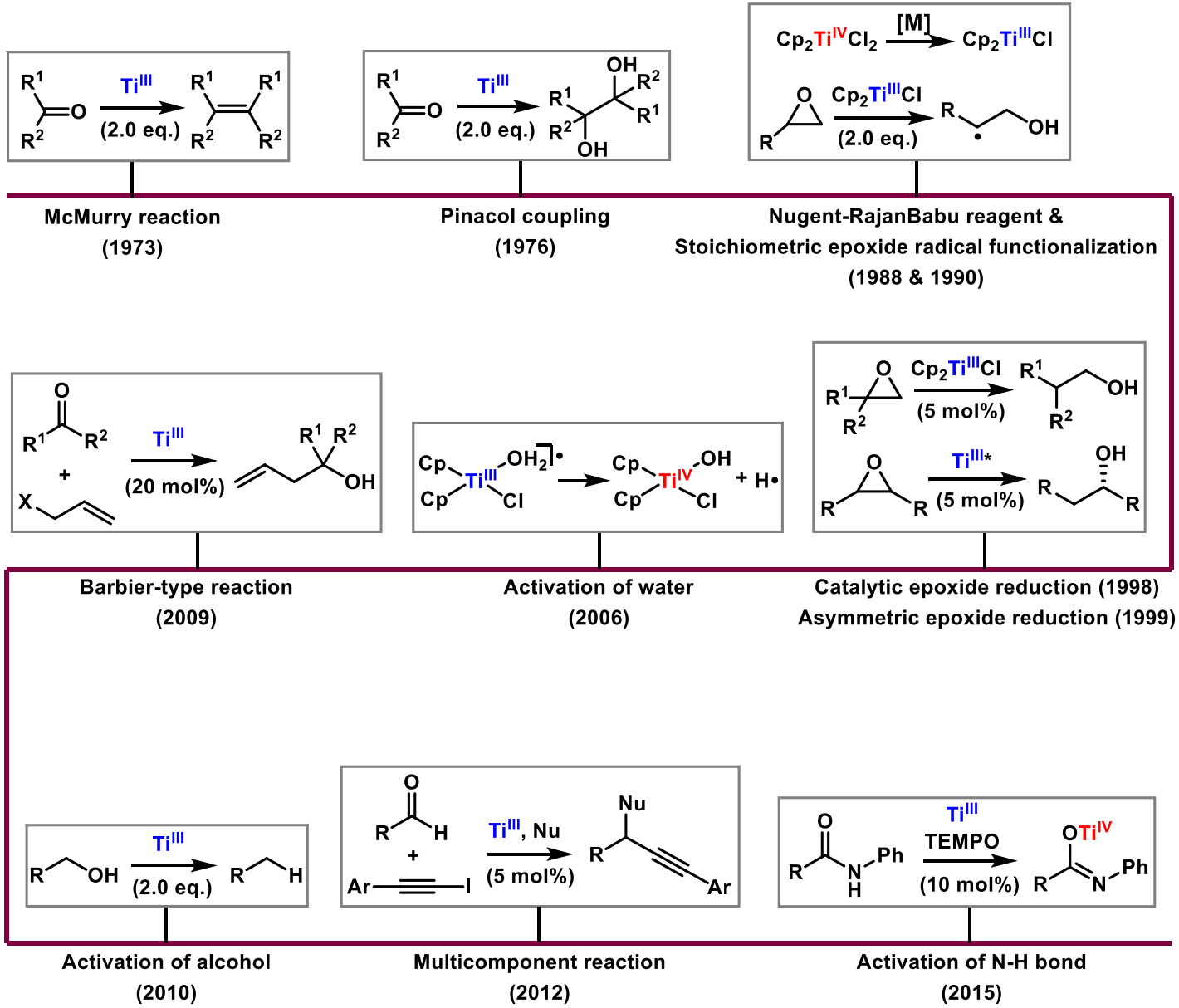
Background

Background

Titanium



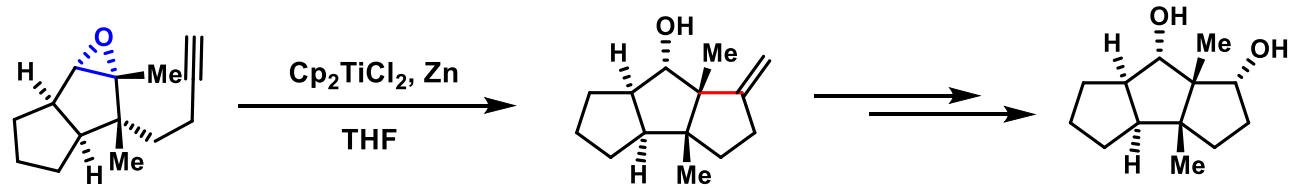
The Development of $Ti^{III/IV}$ Chemistry



Background

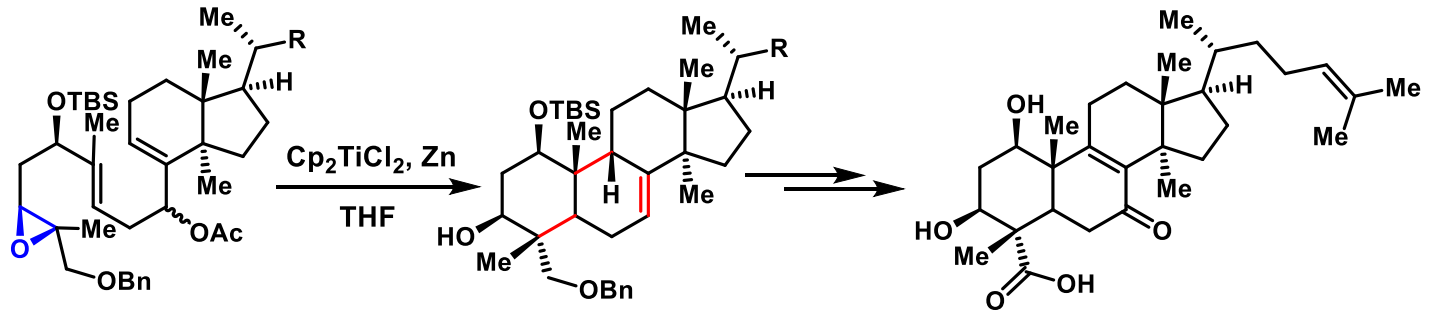
$Ti^{III/IV}$-Mediated Ring-Opening of Epoxides in Total Synthesis

(1)



Ceratopicanol

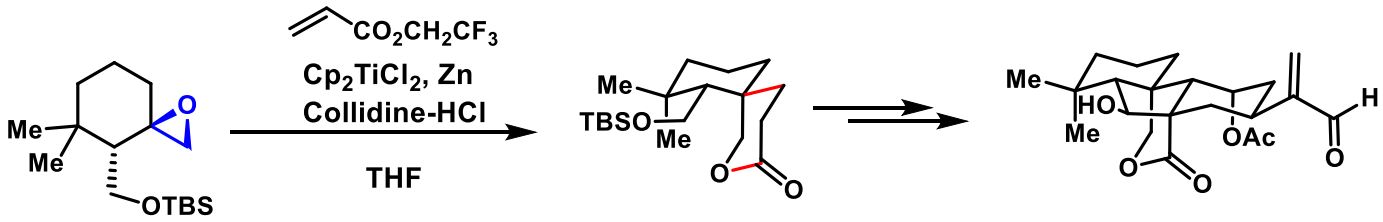
(2)



(R= $CH_2CH_2CH_2OTBS$)

Fomitellic Acid B

(3)



(-)-Maoecrystal Z

Clive, D. L. et al. *Tetrahedron Lett*. **1995**, *36*, 15-18.
Clive, D. L. et al. . *J. Org. Chem*. **1996**, *61*, 2095-2108.
Kobayashi, S. et al. *Tetrahedron Lett*. **2009**, *50*, 6764-6768.
Reisman, S. E. et al. *J. Am. Chem. Soc*. **2011**, *133*, 14964−14967

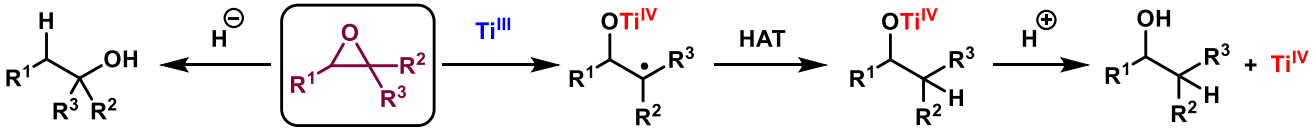
PART 2

Ti-Catalyzed Ring-Opening of 3-Membered Rings

Ti-Catalyzed Ring-Opening of 3-Membered Rings

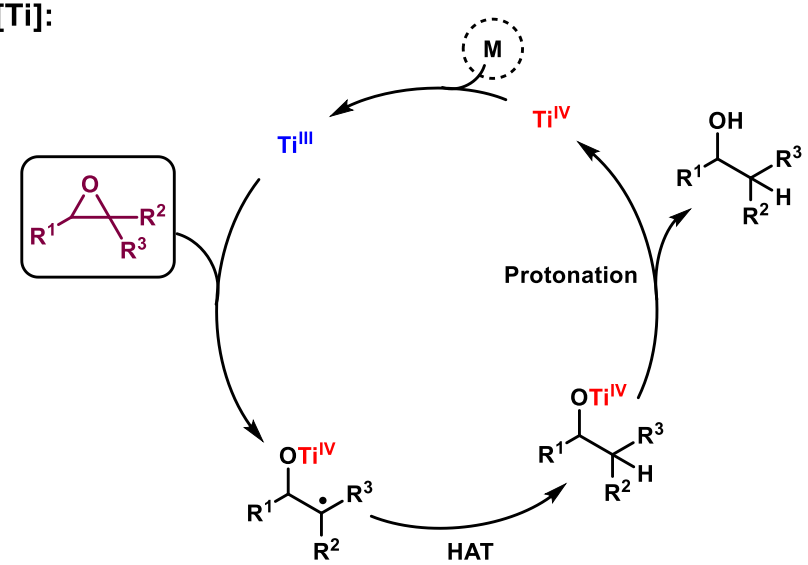
1. Reduction of Epoxides

Stoichiometric [Ti]:

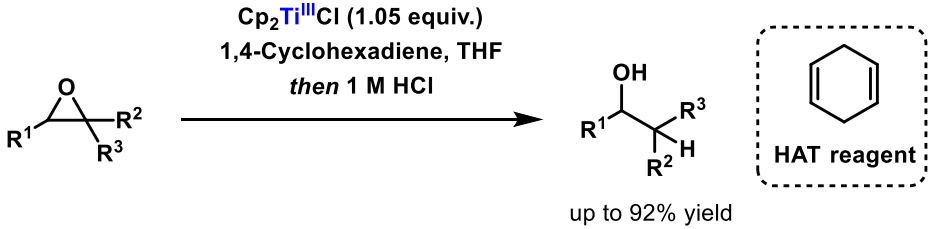


(Anti-Markovnikov Product Formation)

Catalytic [Ti]:

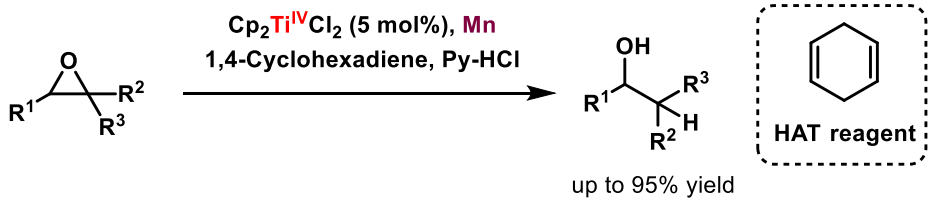


RajanBabu, T. V. et al. (1990):

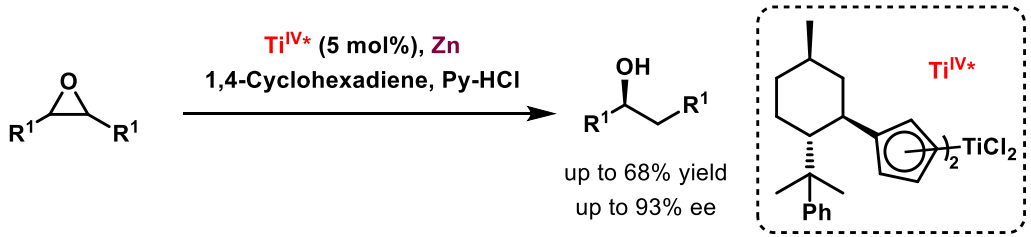


up to 92% yield

Gansäuer, A. et al. (1998 & 1999):



up to 95% yield



up to 68% yield
up to 93% ee

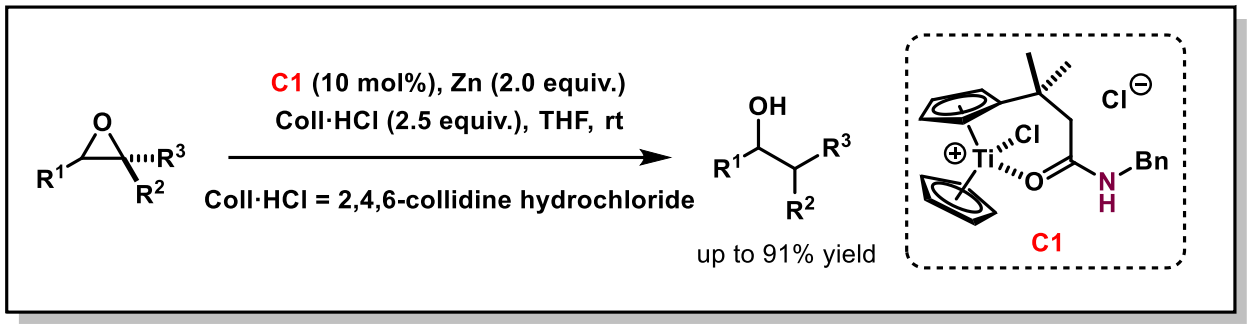
The Development of Epoxides Reduction

i) Novel Hydrogen Atom Transfer (HAT) Process

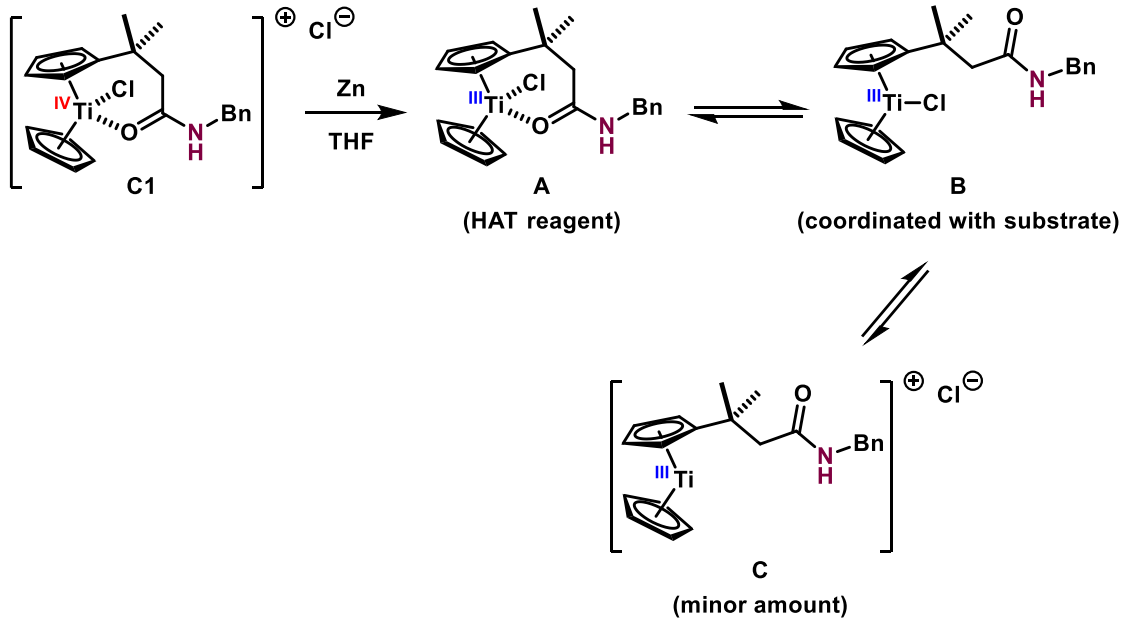
ii) Ti^{IV} **reductive conditions** Ti^{III}

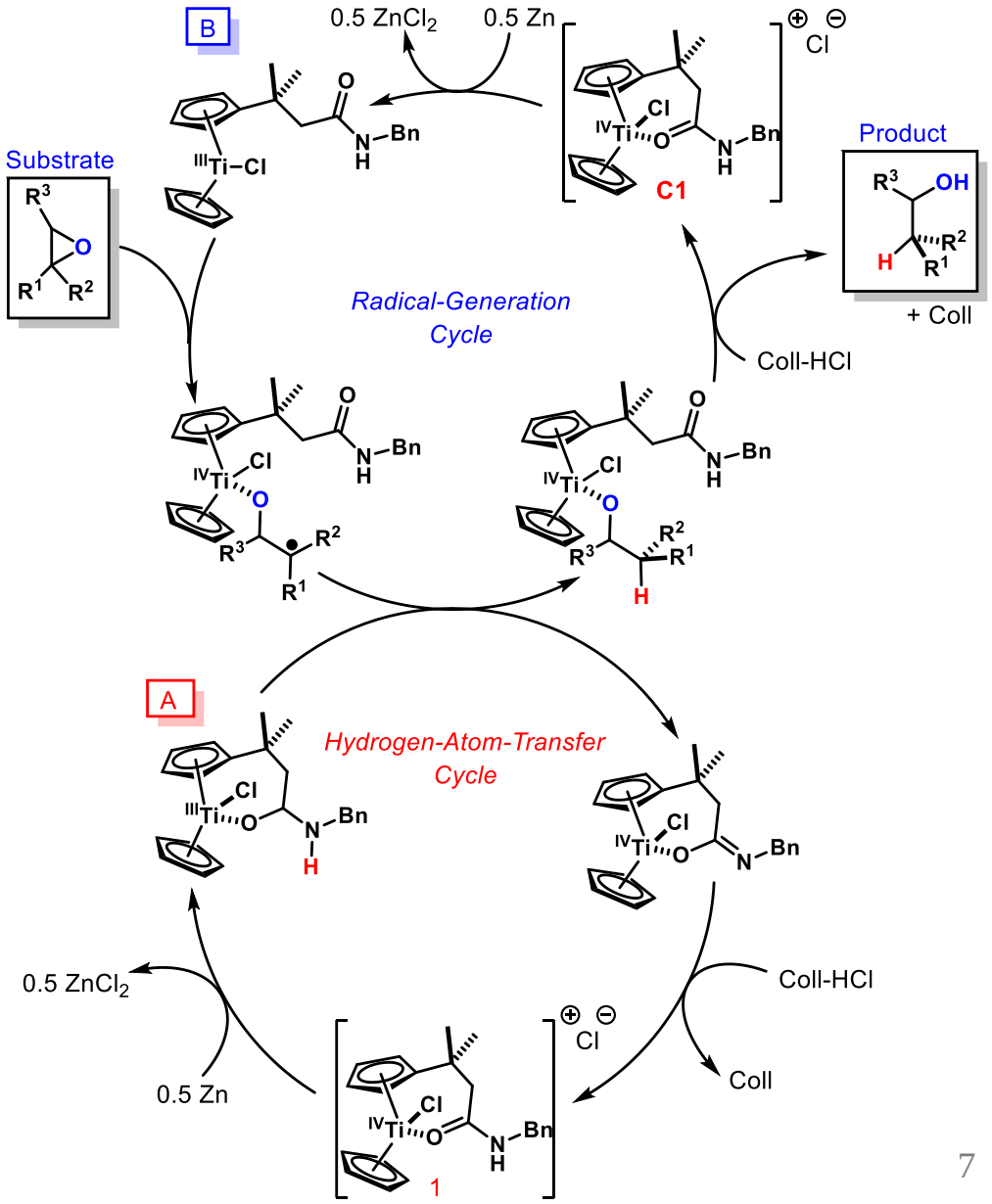
Rajanbabu, T. V. et al. *J. Am. Chem. Soc.* **1990**, *112*, 6408-6409.
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **1998**, *37*, 101-103.
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 2909-2910.

Reduction of Epoxides — HAT (N-H)



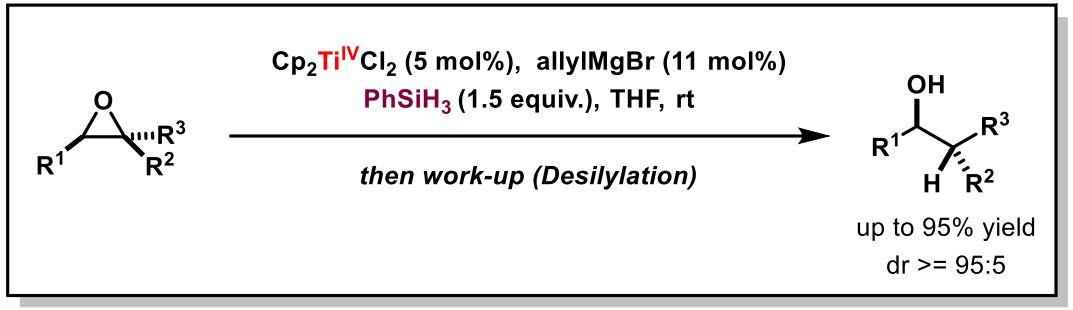
Catalyst & HAT Reagent:



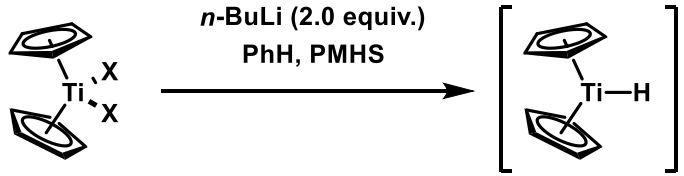


Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 1523 –1526.

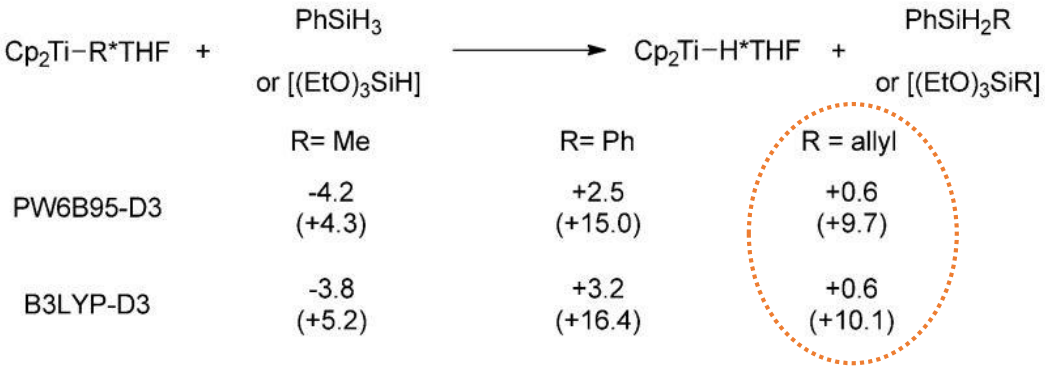
Reduction of Epoxides — HAT (Ti-H)



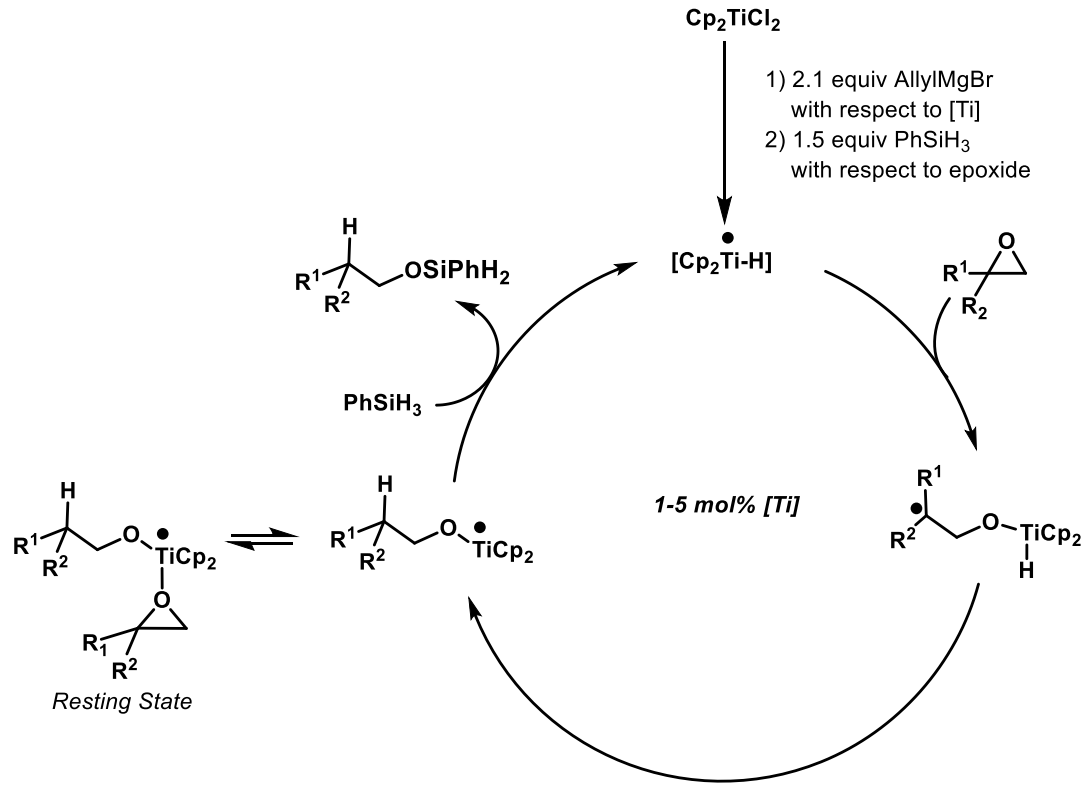
Generation of [Cp_2Ti-H] (1985, 1994):



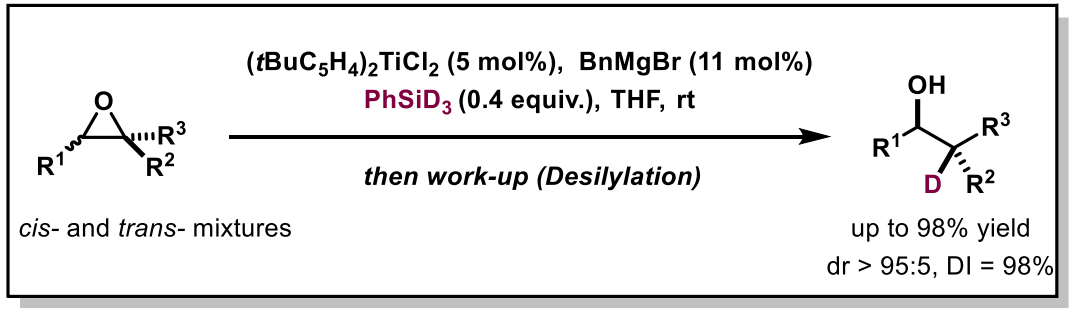
The "Allyl Activation":



Harrod, J. F. et al. *J. Organomet. Chem.* **1985**, *279*, 11-13.
Buchwald, S. L. et al. *J. Am. Chem. Soc.* **1994**, *116*, 11703 – 11714.
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 7671-7675.

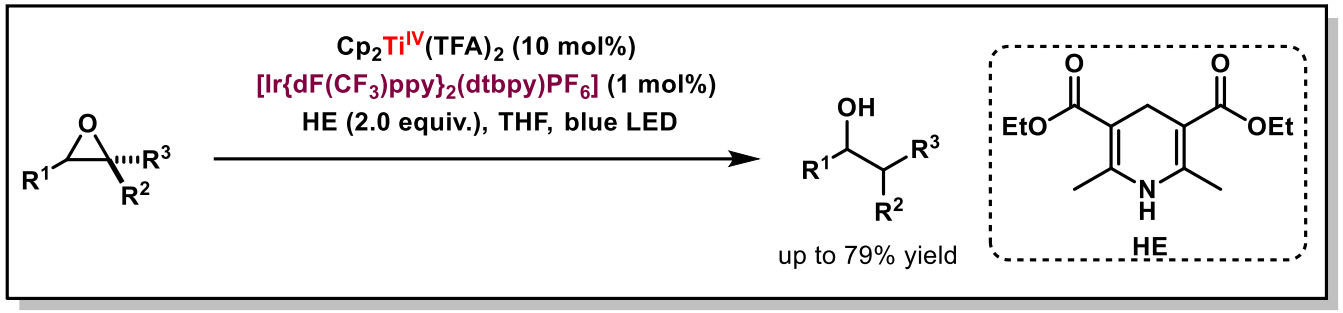


Precision Deuteration (2022):

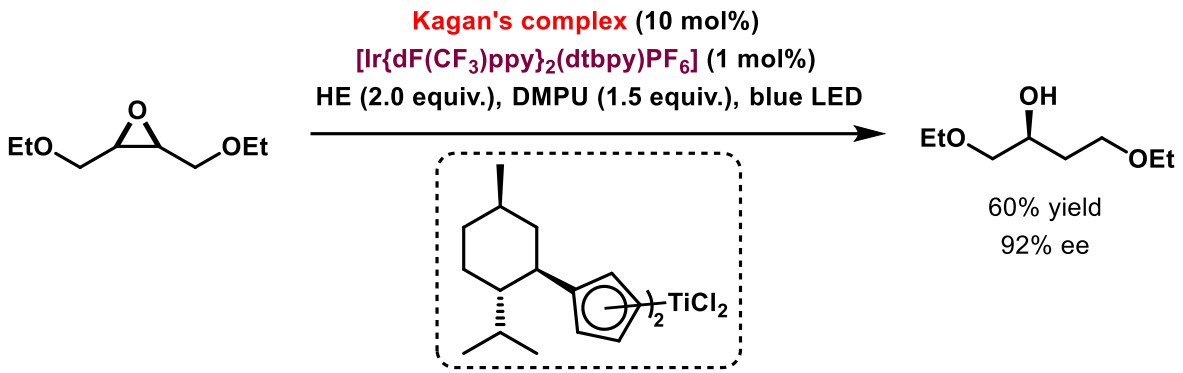


Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114198.

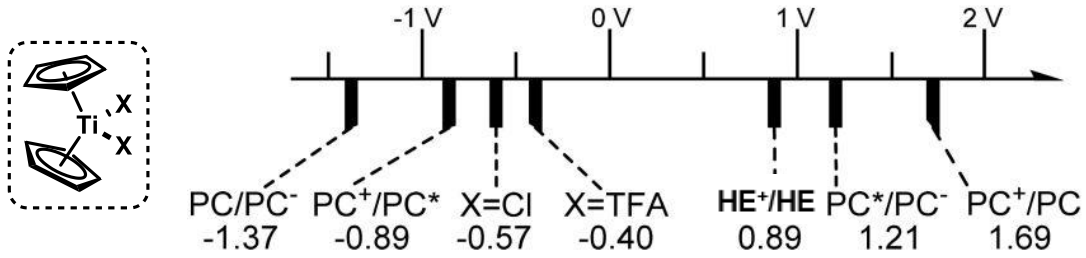
Reduction of Epoxides — Photo-Induced

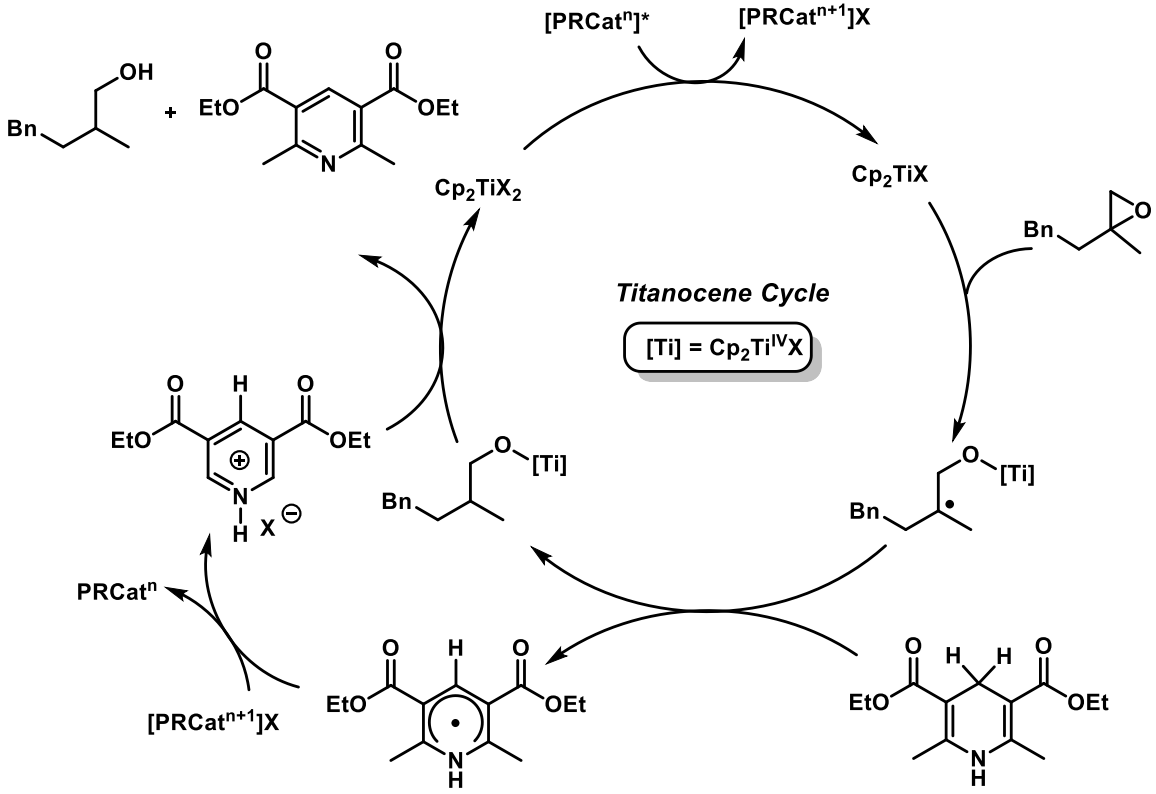


Enantioselective Opening:



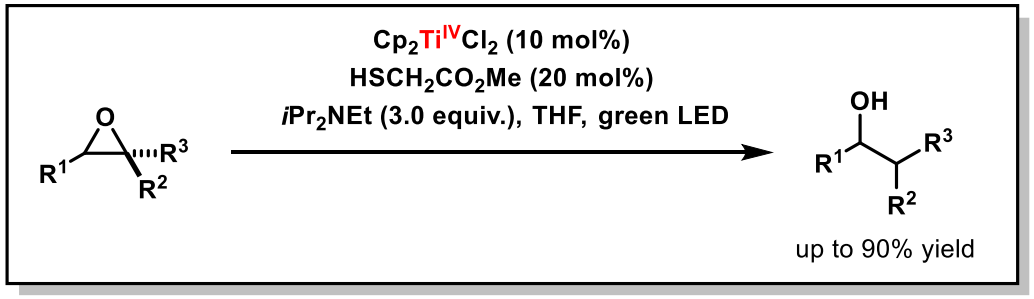
Redox Potentials:

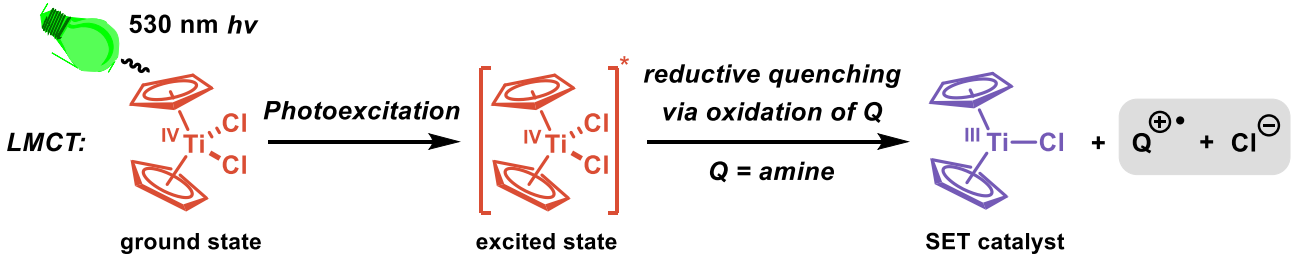


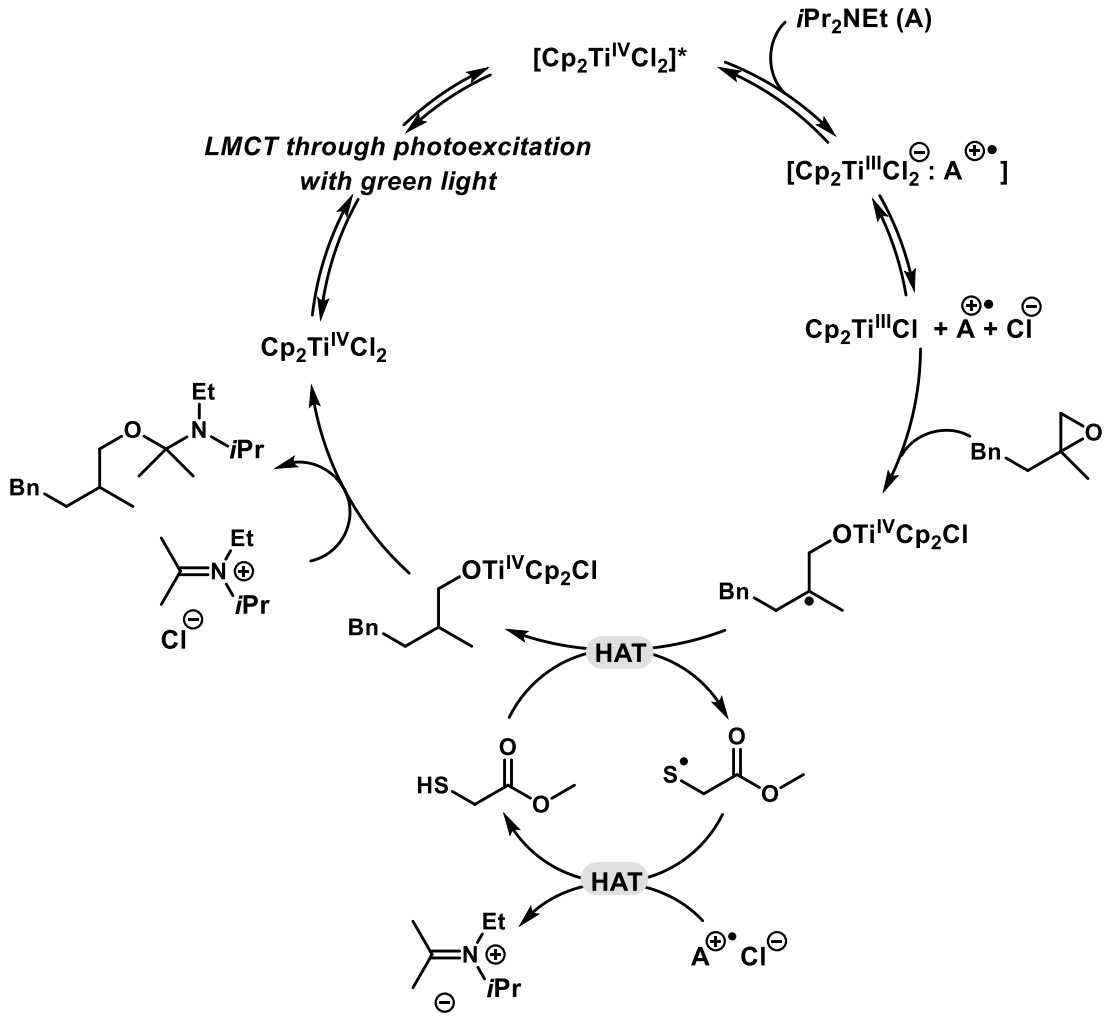


Gansäuer, A. et al. *ACS Catal.* **2019**, *9*, 3208−3212

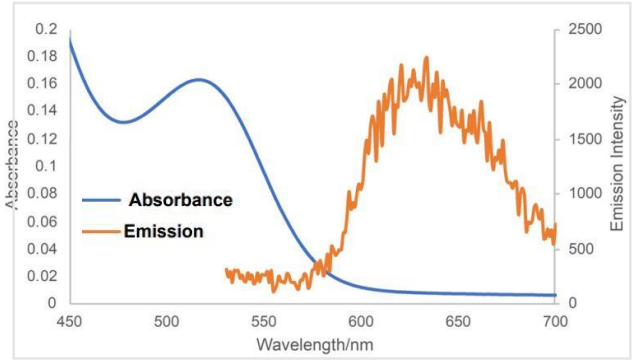
Reduction of Epoxides — Photo-Induced



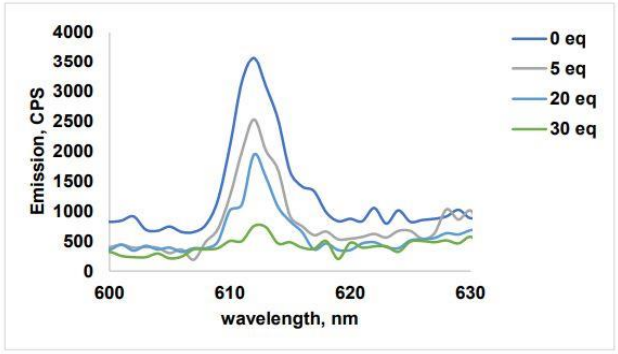




Absorption and Emission Spectra & Stern-Volmer analysis:



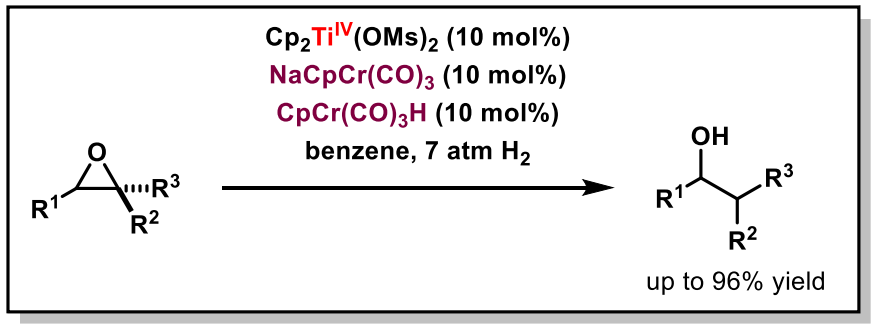
Cp_2TiCl_2 in THF



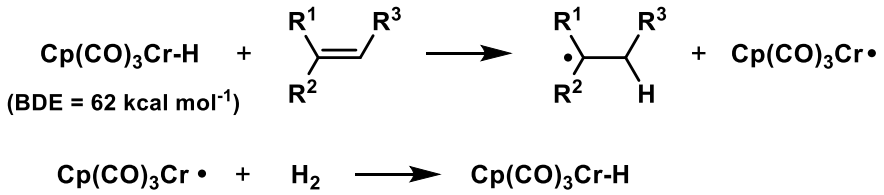
$Cp_2TiCl_2^*$ and DIPEA (quencher, x eq)

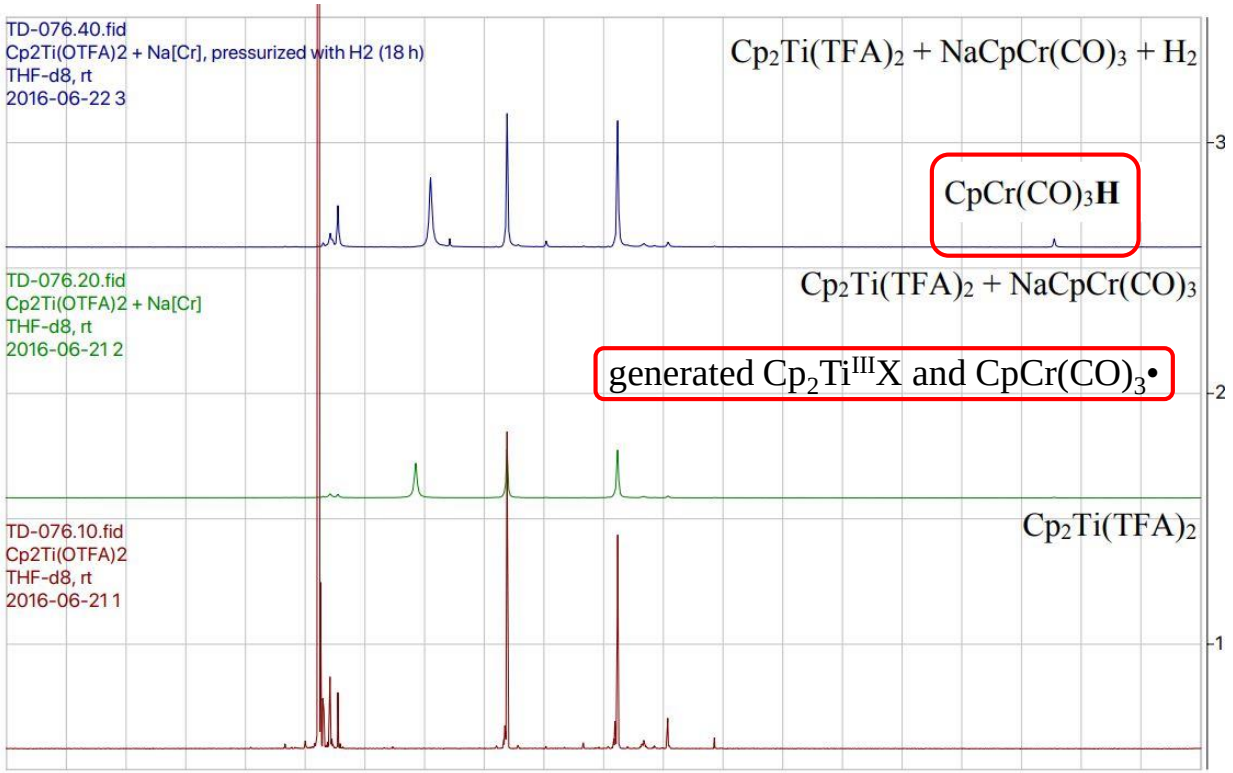
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 9355 –9359.

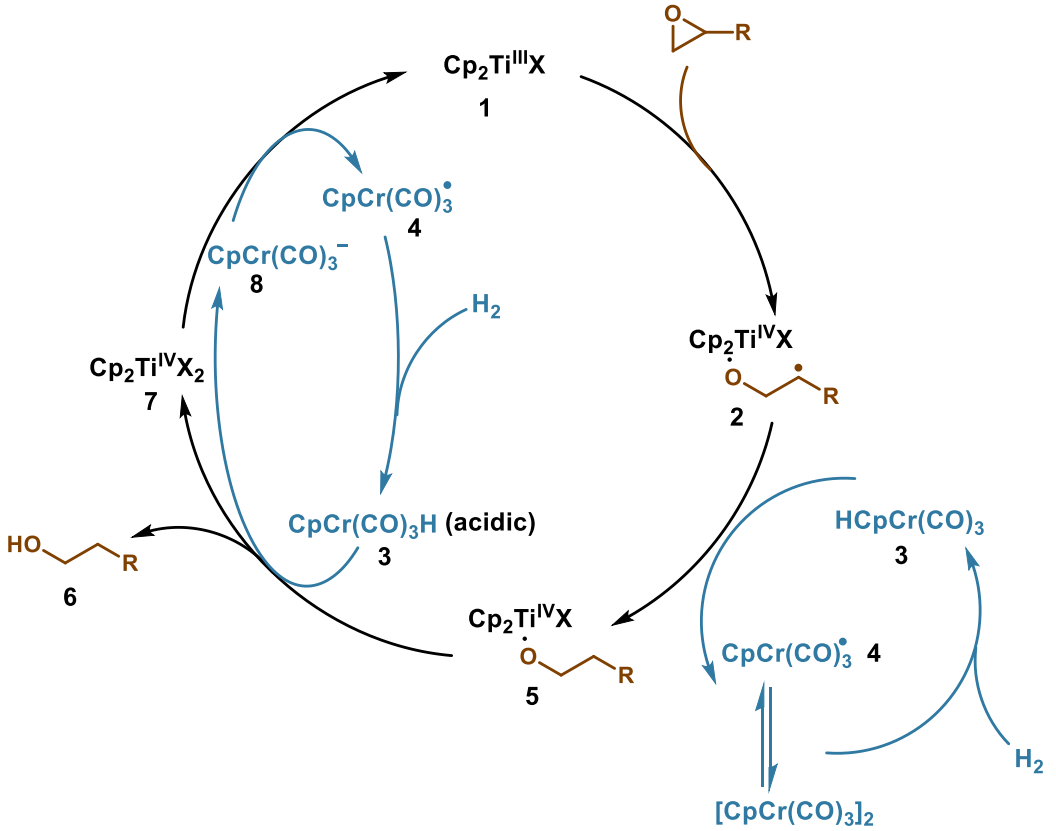
Reduction of Epoxides — Ti/Cr Dual Catalysis



H• Transfer from $CpCr(CO)_3H$ (2007):

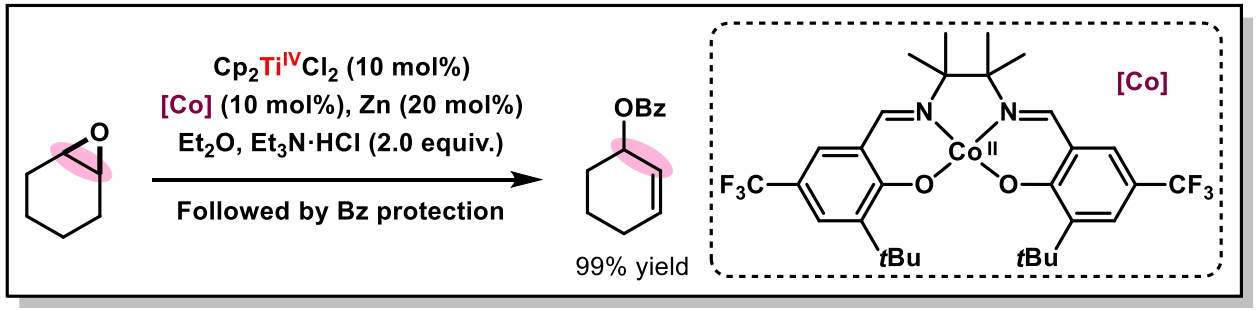




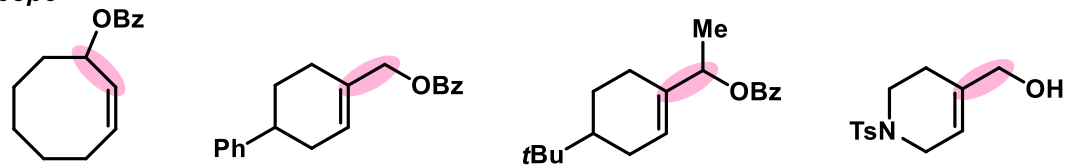


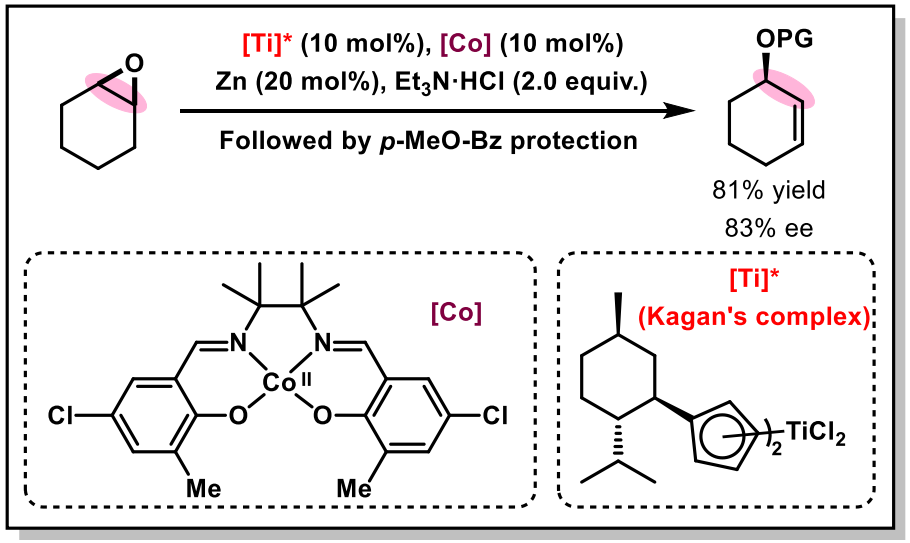
Norton, J. et al. *J. Am. Chem. Soc*. **2007**, *129*, 234-240.
Gansäuer, A, Norton, J. et al. *Science*. **2019**, *364*, 764–767.

Ring-Opening of Epoxides — Ti/Co Dual Catalysis

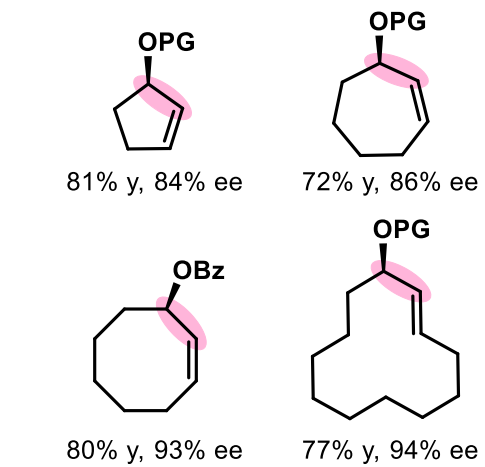


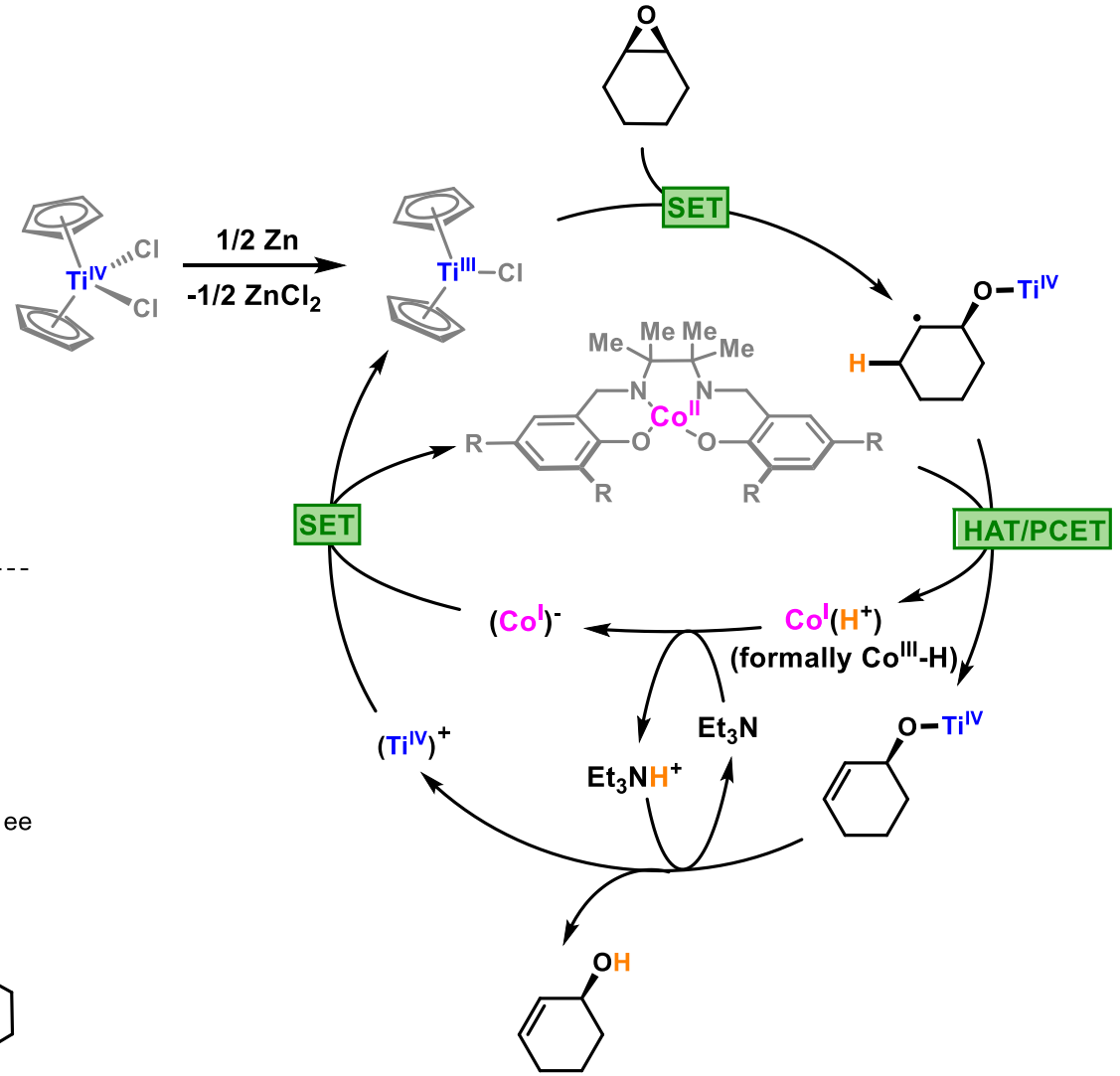
Reaction Scope





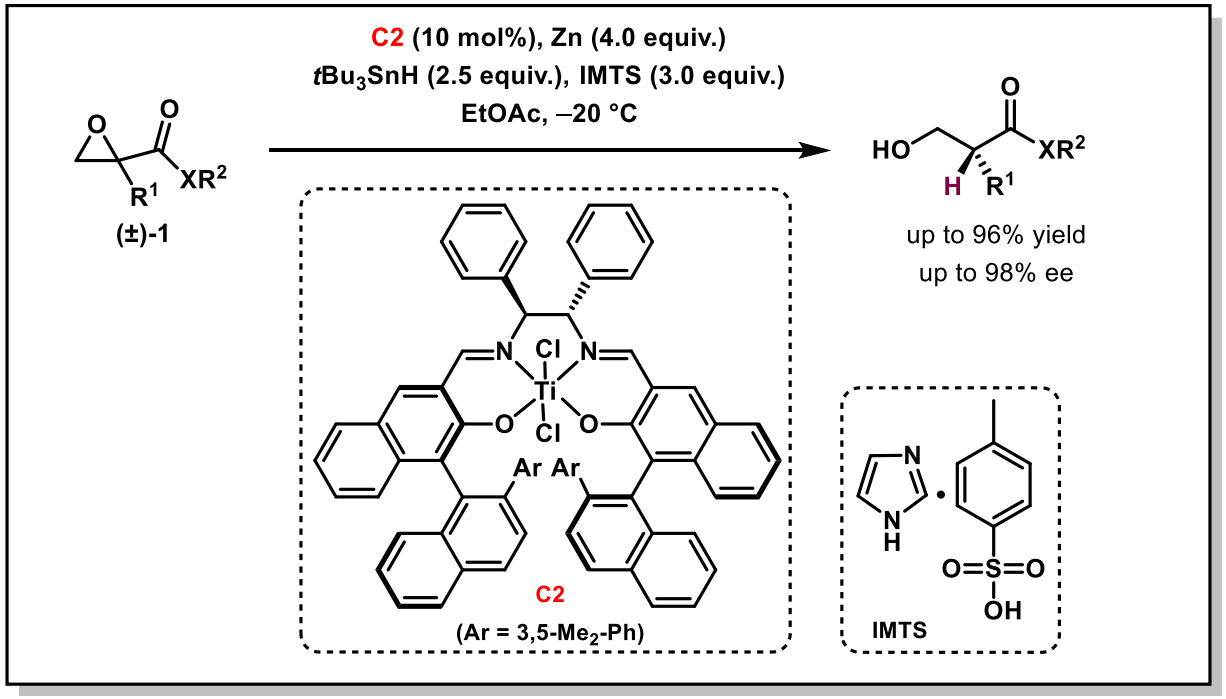
Reaction Scope



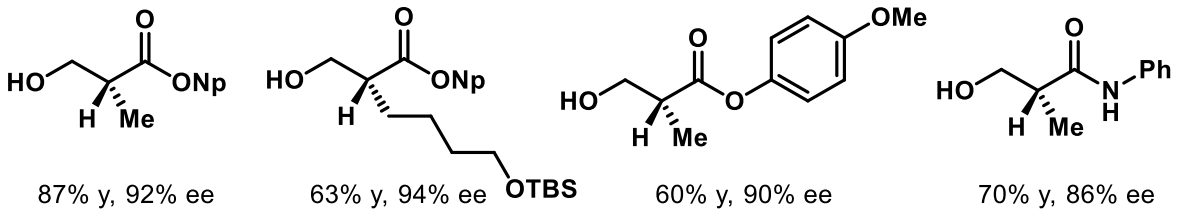


Lin, S. et al. *J. Am. Chem. Soc.* **2019**, *141*, 9548-9554.

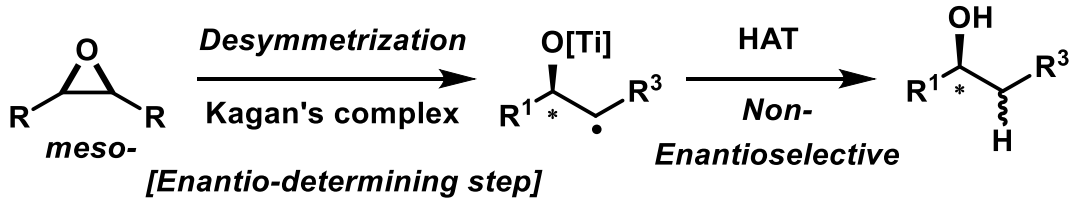
Reduction of Epoxides — Asymmetric HAT



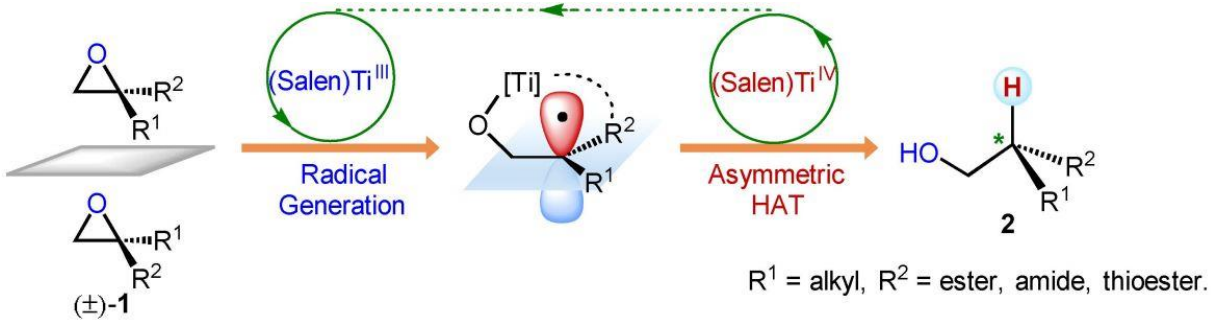
Reaction Scope



Previous work (asymmetric ring-opening):



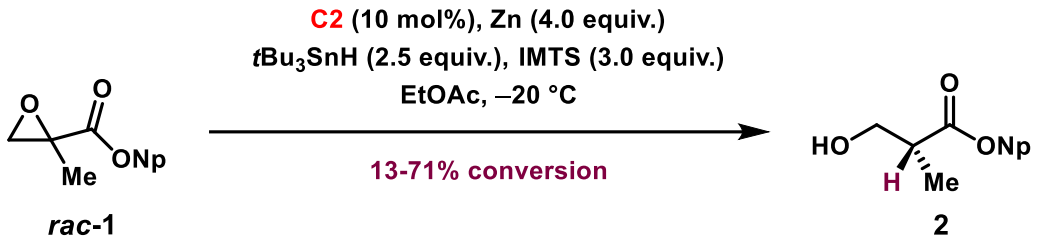
This work (asymmetric HAT):



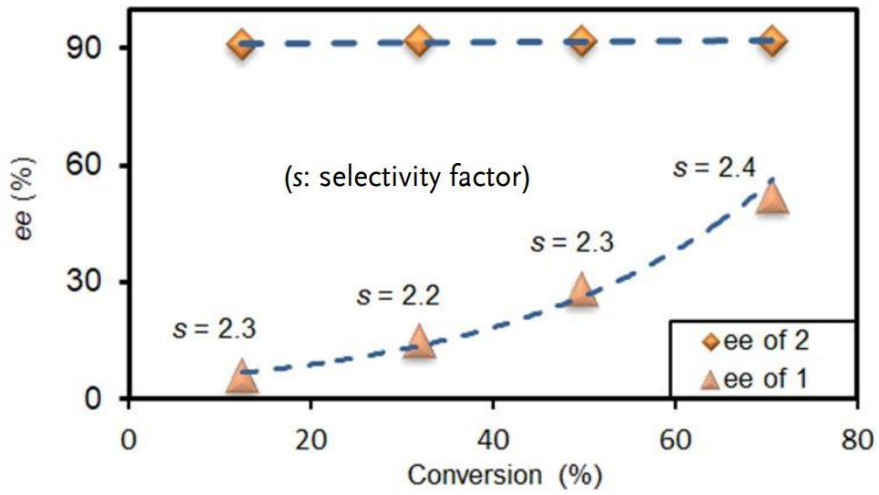
Zhang, Y. Q. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202214111.

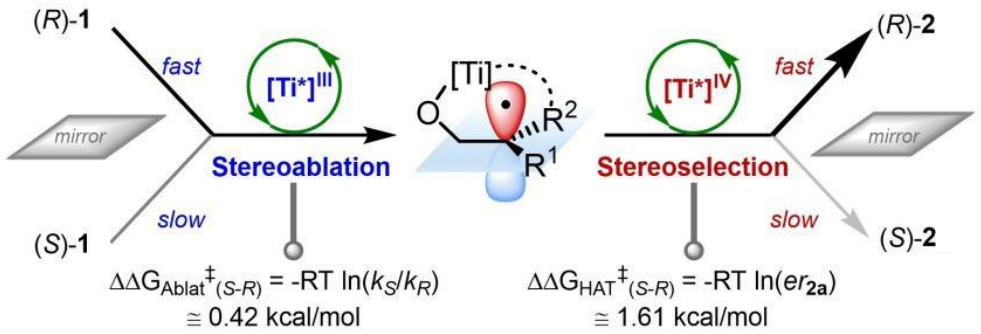
Reduction of Epoxides — Asymmetric HAT

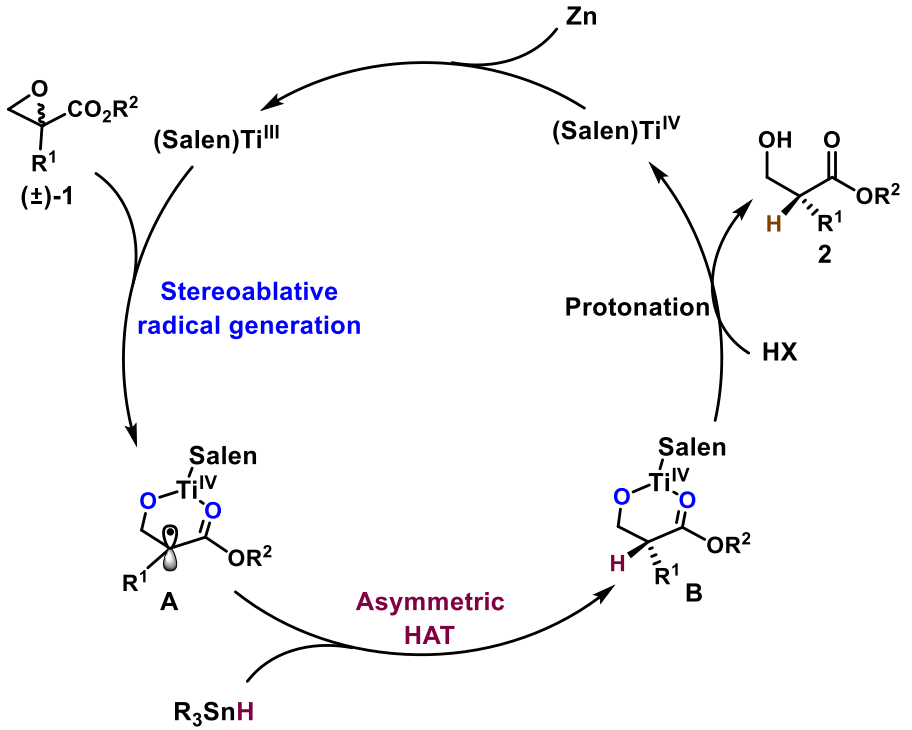
Mechanistic Experiments:



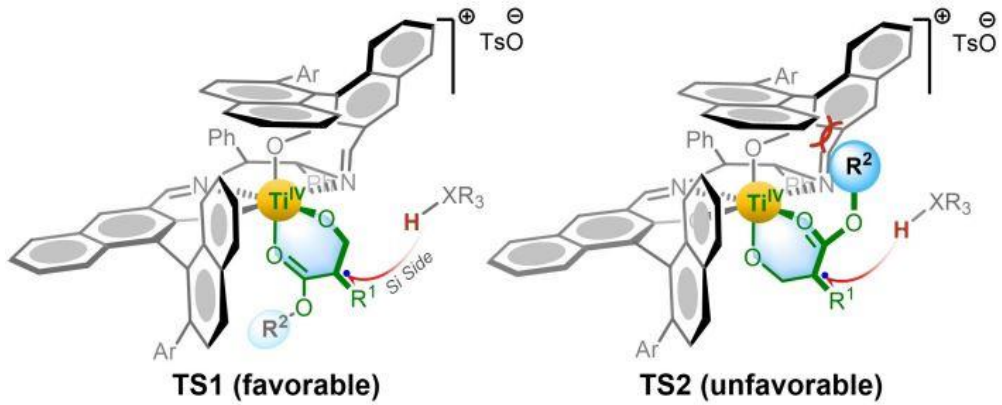
rac-1 2







Transition State Models:

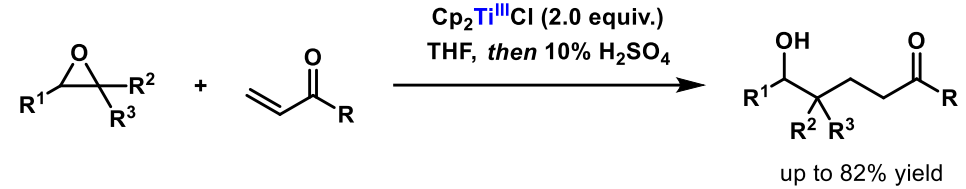


Zhang, Y. Q. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202214111.

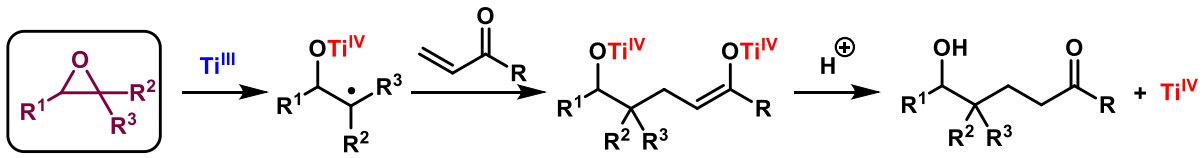
Ti-Catalyzed Ring-Opening of 3-Membered Rings

2. Radical Cascade Reactions

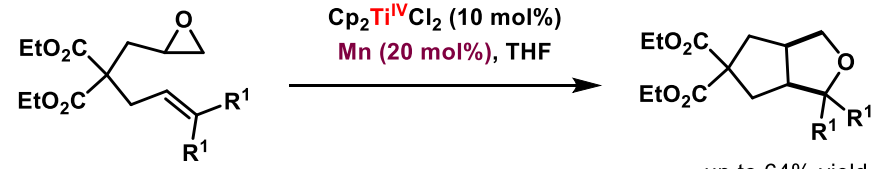
RajanBabu, T. V. et al. (1989):



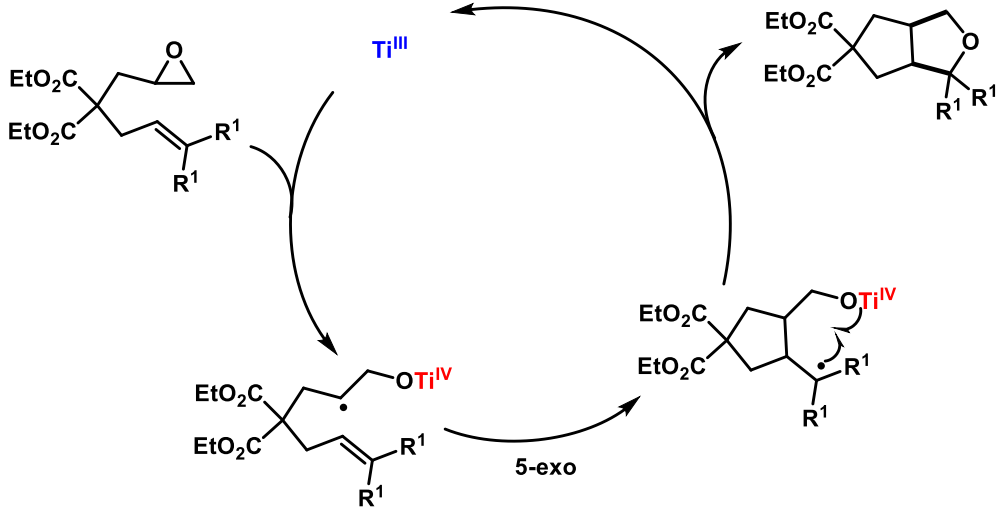
Mechanism:



Gansäuer, A. et al. (2003):



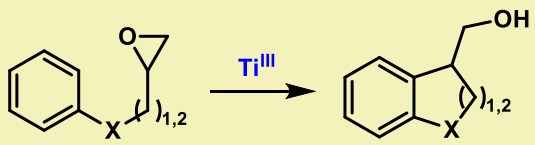
Mechanism:



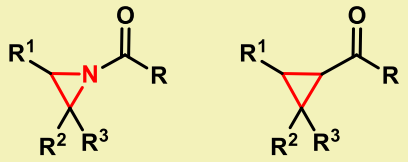
Rajanbabu, T. V. et al. *J. Am. Chem. Soc.* **1989**, *111*, 4525-4527.
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 3687-3690.

The Development of Radical Cascade Reactions

i) Radical Arylation Reactions

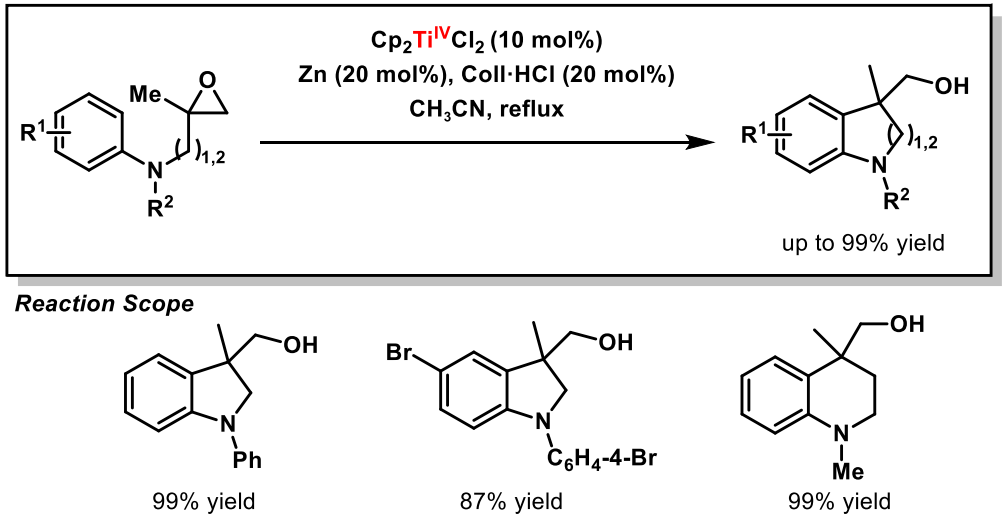


ii) Other Three-Membered Rings

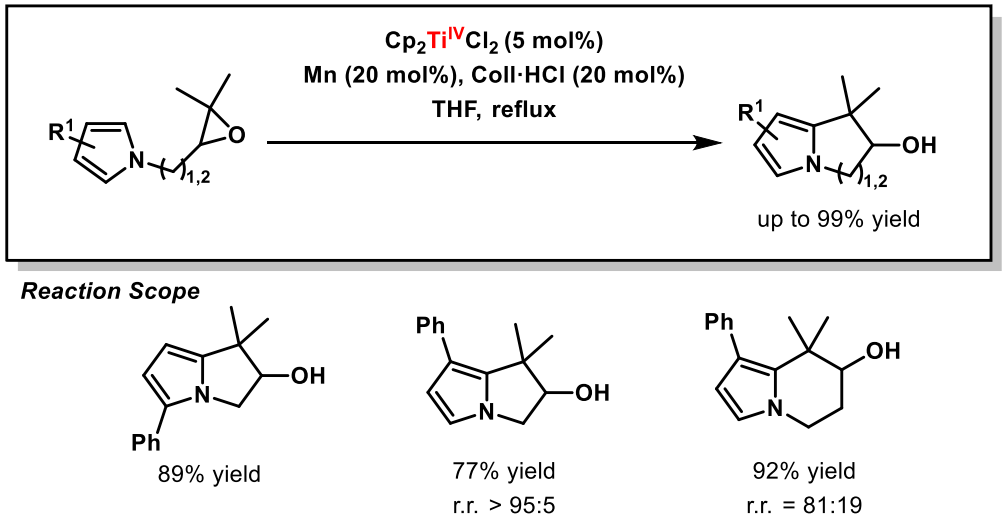


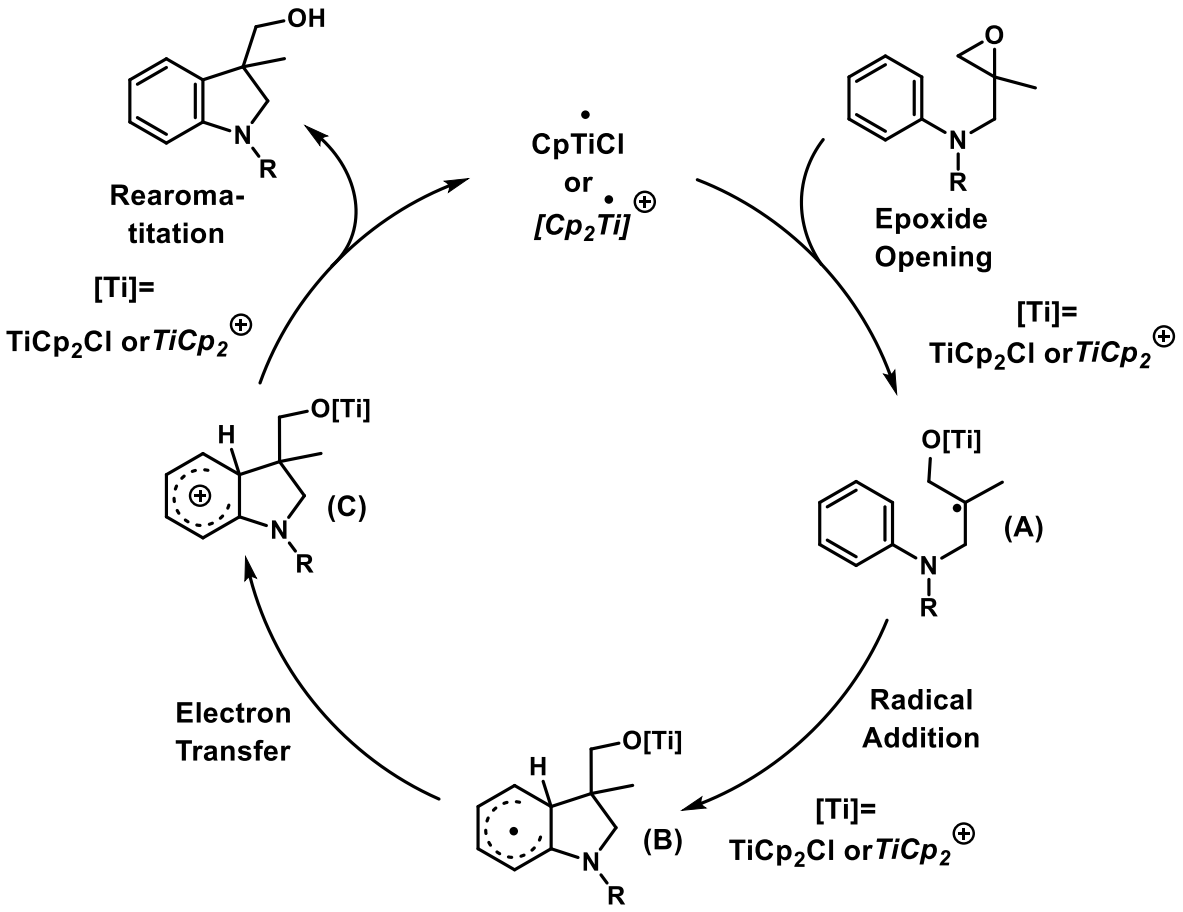
Radical Cascade Reactions — Epoxides

Gansäuer, A. et al. (2015):



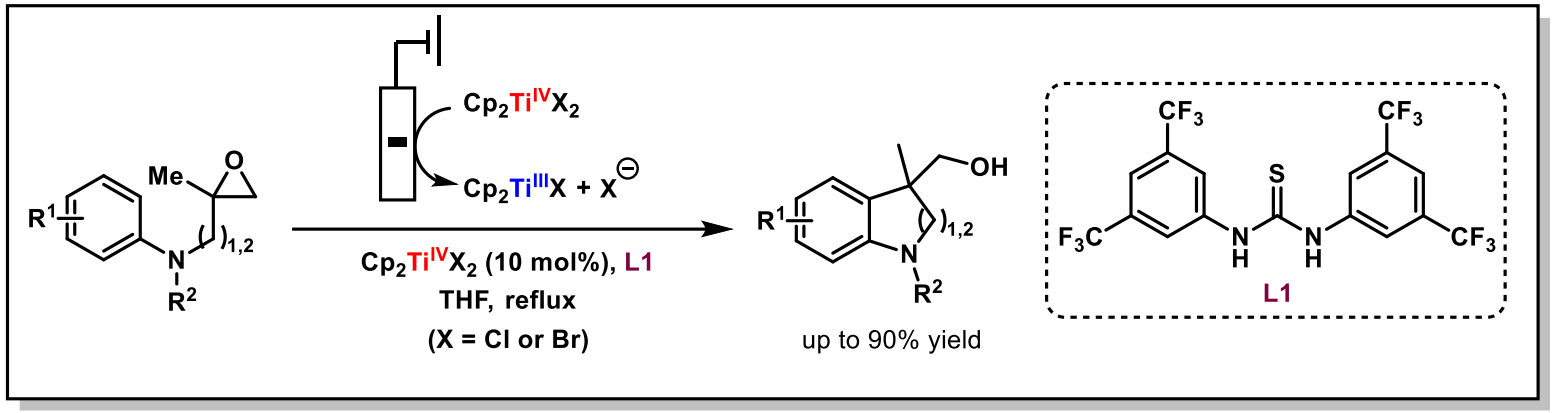
Gansäuer, A. et al. (2016):



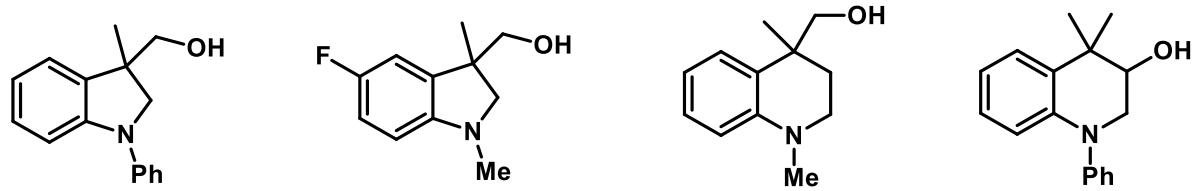


Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 7003-7006.
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 9719-9722.

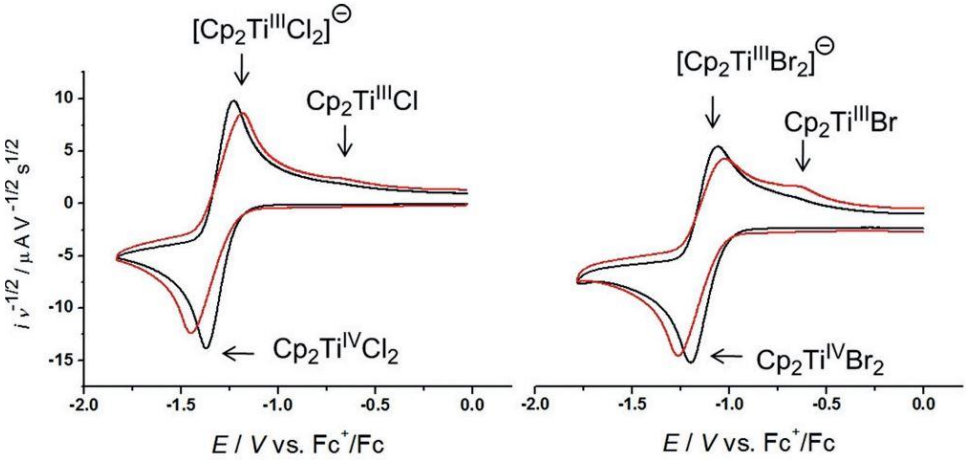
Radical Cascade Reactions — Epoxides

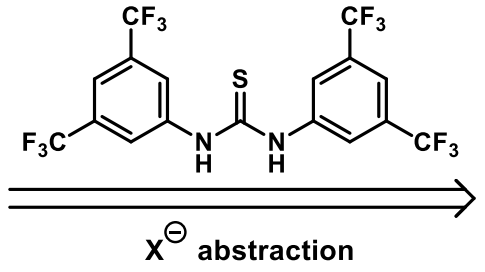


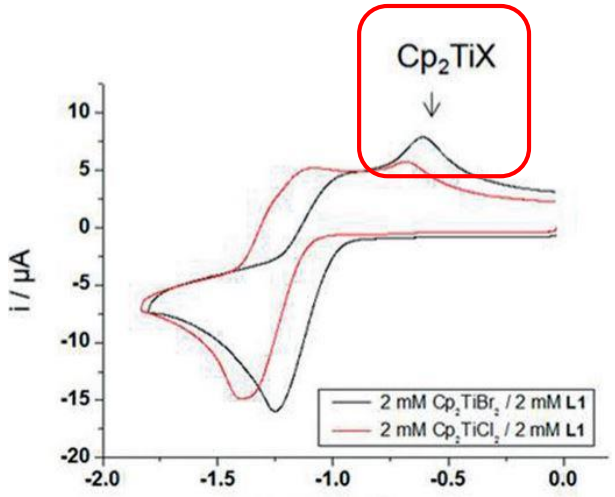
Reaction Scope



Cyclic Voltammograms:

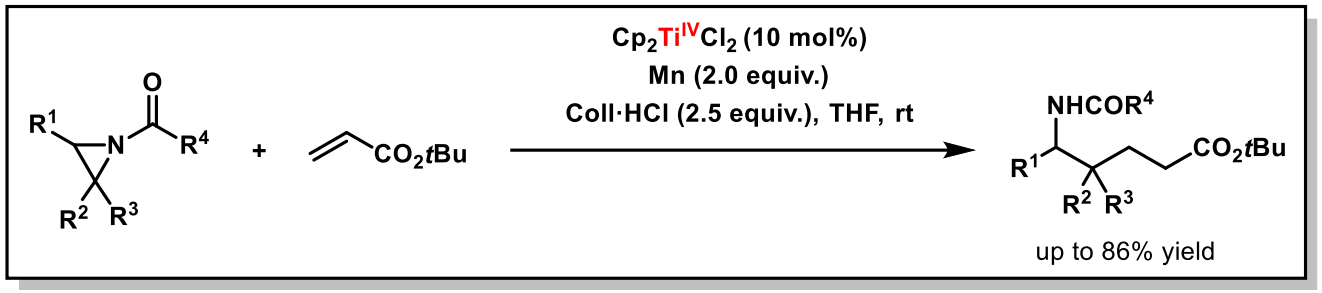




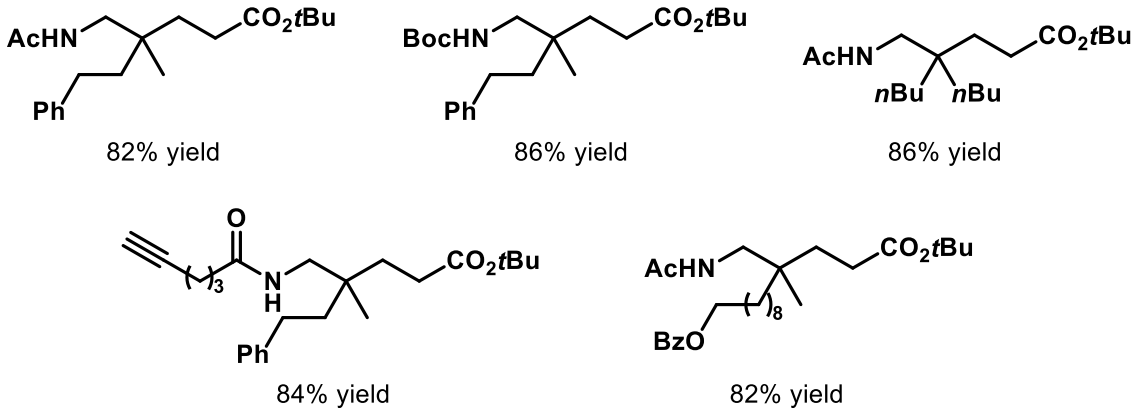


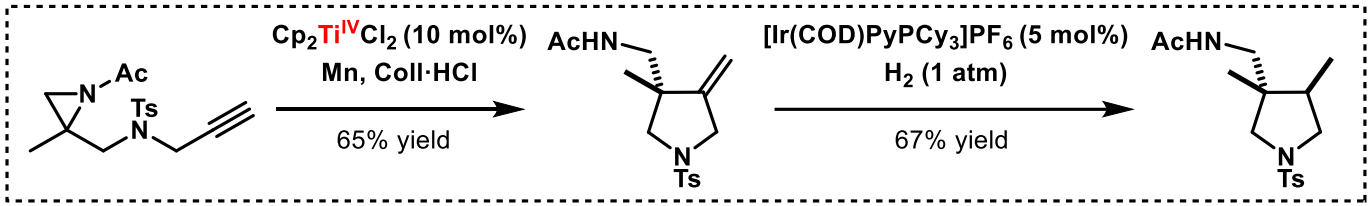
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 5006-5010.

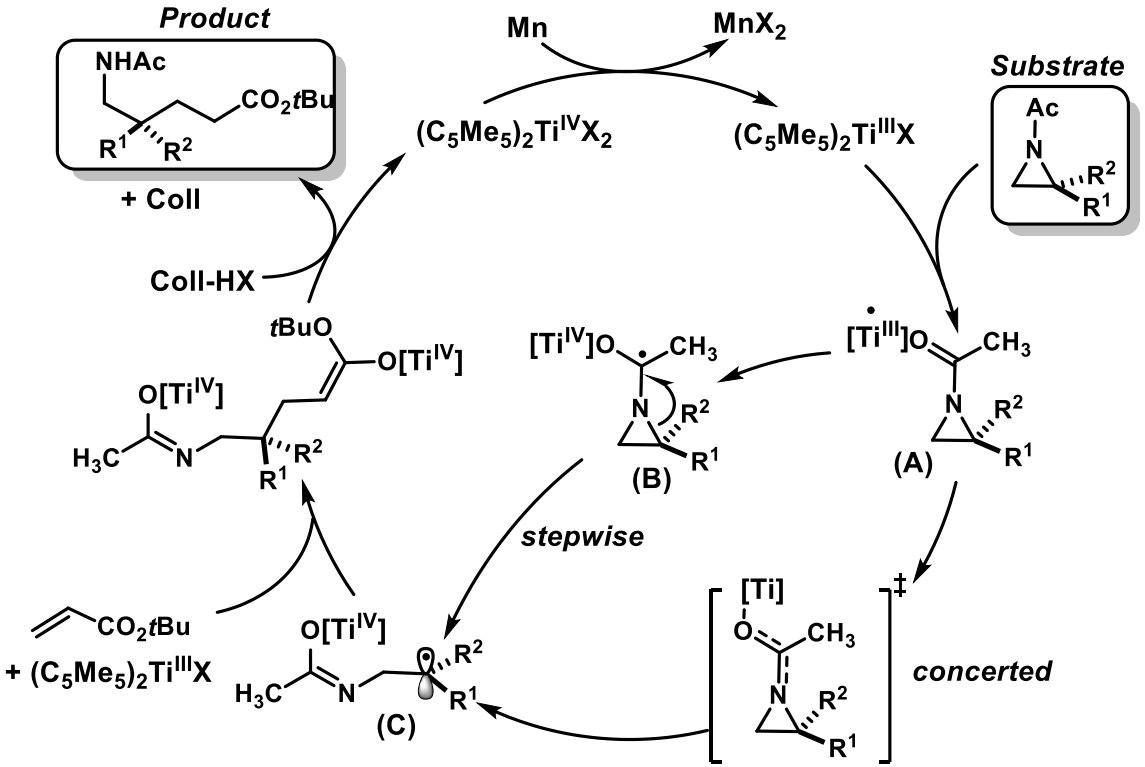
Radical Cascade Reactions — N-Acylated Aziridines



Reaction Scope

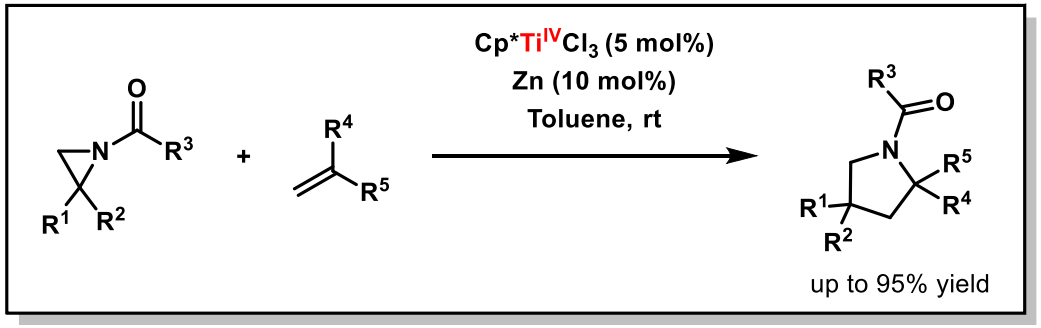




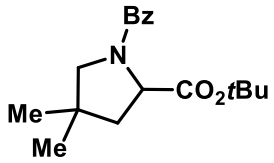


Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 12654-12657.

Radical Cascade Reactions — N-Acylated Aziridines

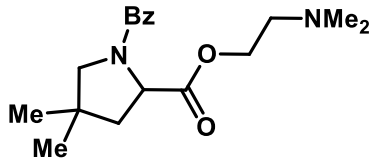


Reaction Scope

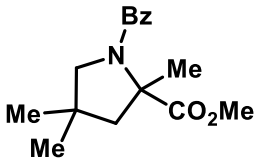


91% yield

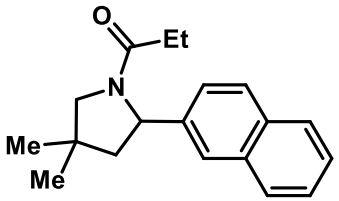
$CpTiCl_3$ instead of Cp^*TiCl_3:	20% yield
Cp_2TiCl_2 instead of Cp^*TiCl_3:	<5% yield
THF instead of Toluene:	<5% yield
(Unreacted starting material observed)	



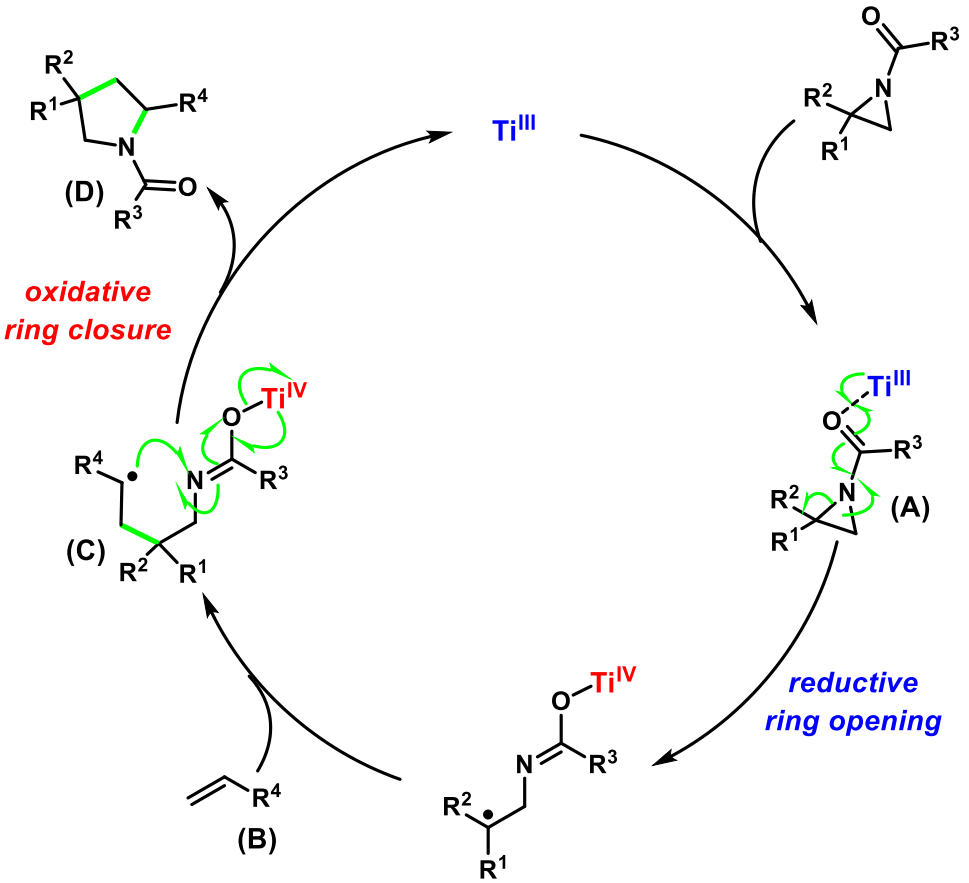
78% yield



78% yield

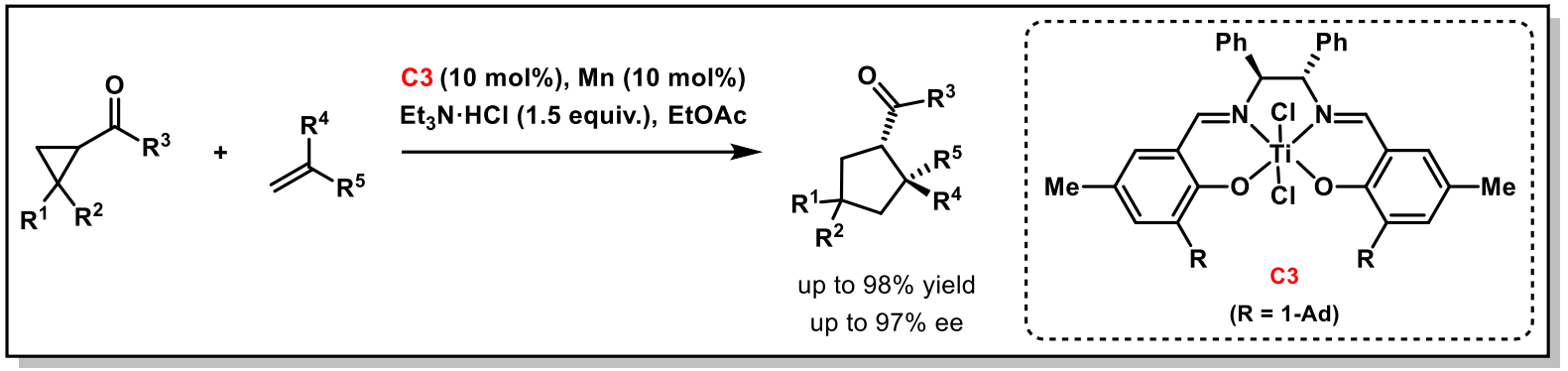


62% yield

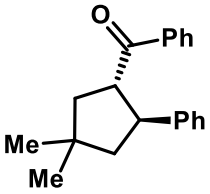


Lin, S. et al. *J. Am. Chem. Soc.* **2017**, *139*, 12141-12144.

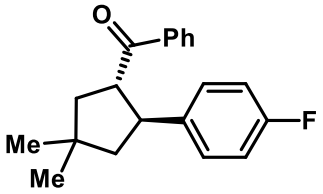
Radical Cascade Reactions — Cyclopropanes



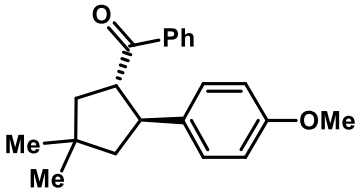
Reaction Scope



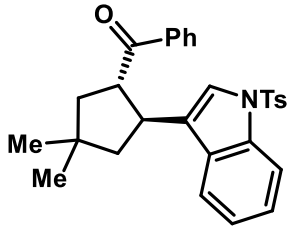
98% y, 97% ee
dr > 19:1



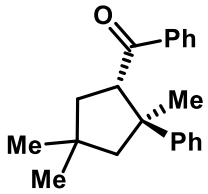
85% y, 94% ee
dr = 12:1



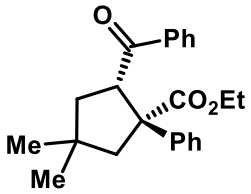
89% y, 96% ee
dr > 19:1



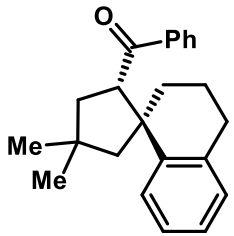
91% y, 98% ee
dr > 19:1



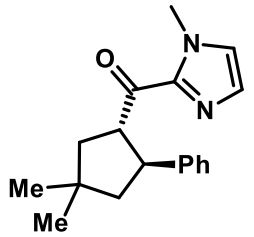
96% y, 96% ee
dr > 19:1



87% y, 80% ee
dr = 9:1



81% y, 90% ee
dr > 19:1

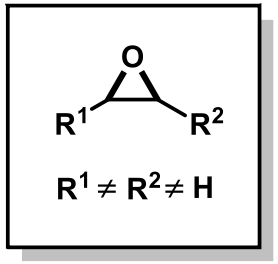


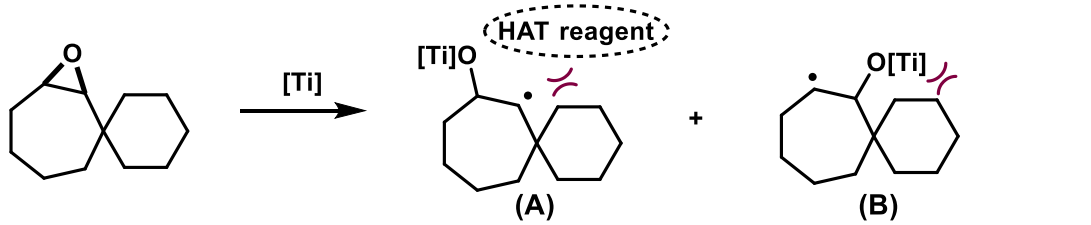
92% y, 88% ee
dr = 6:1

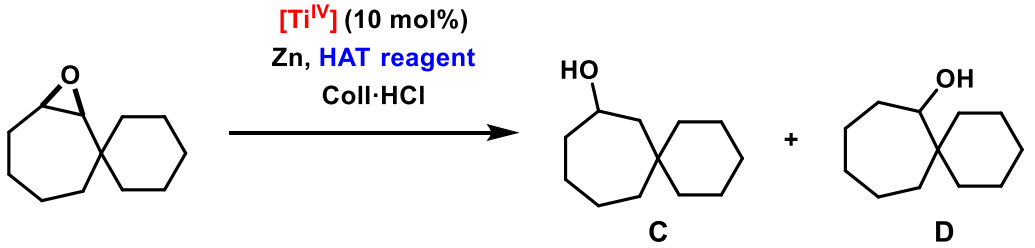
Lin, S. et al. *J. Am. Chem. Soc*. **2018**, *140*, 3514-3517.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

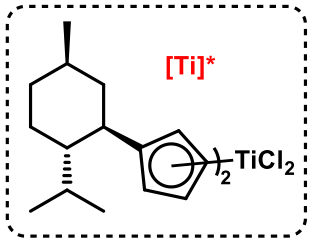
3. Regiodivergent Epoxide Opening (REO)

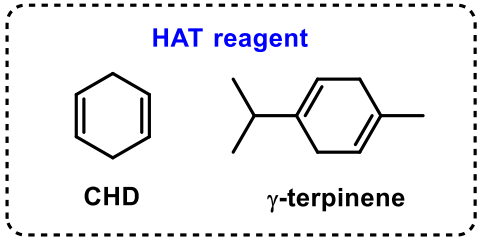






[Ti]	HAT reagent	C (%)	D (%)	
Cp_2TiCl_2	CHD	47	10	⟹ reversible epoxide opening
Cp_2TiCl_2	γ-terpinene	37	23	
[Ti]*	γ-terpinene	82 (ee < 10%)	<1	→ irreversible epoxide opening

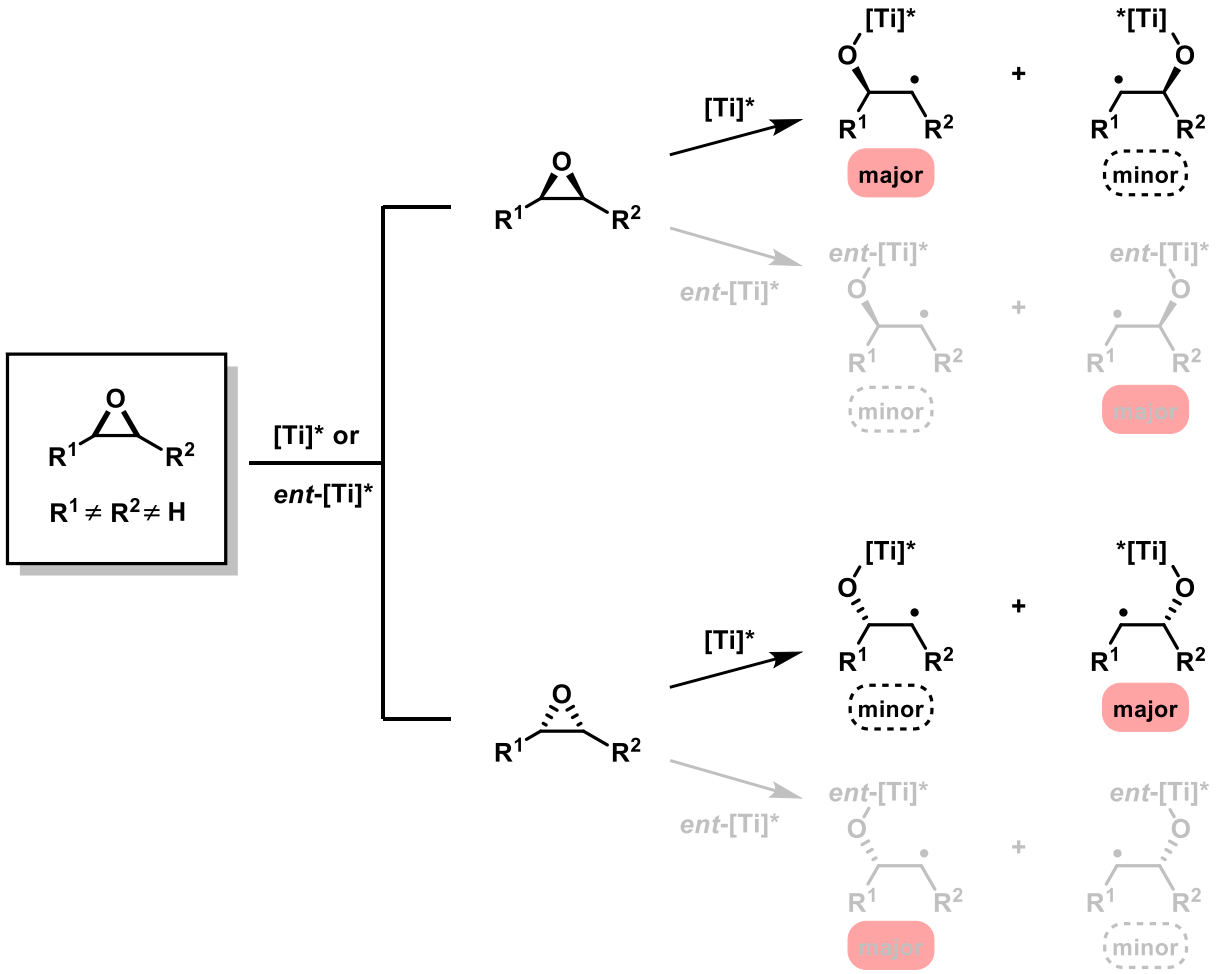


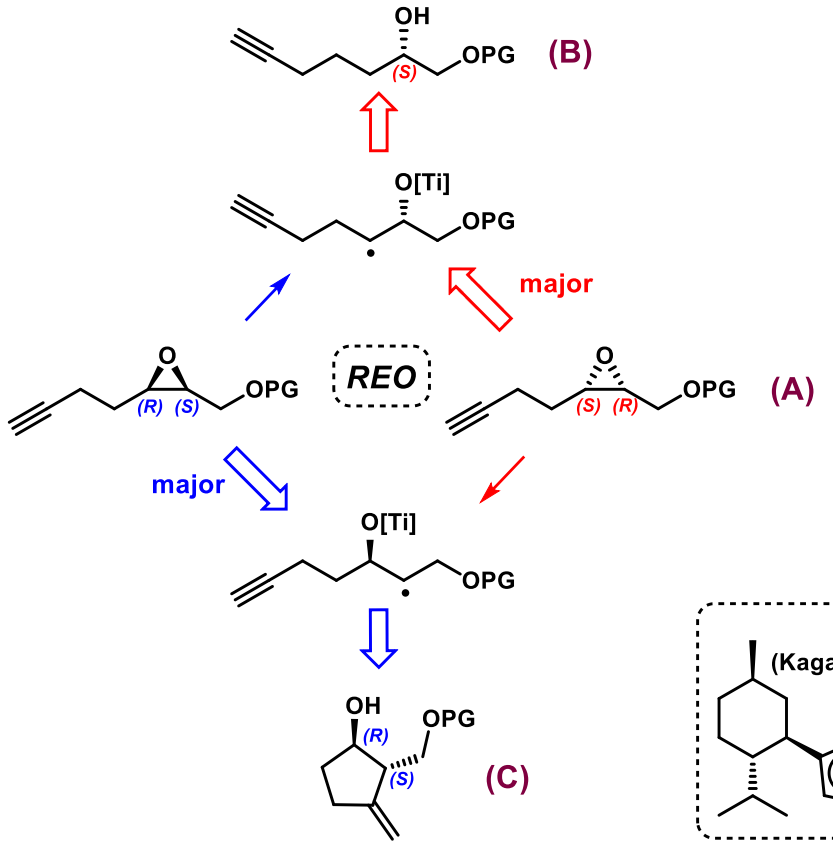


Gansäuer, A. et al. *J. Am. Chem. Soc*. **2007**, *129*, 1360-1371.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

REO & Kinetic Resolution:





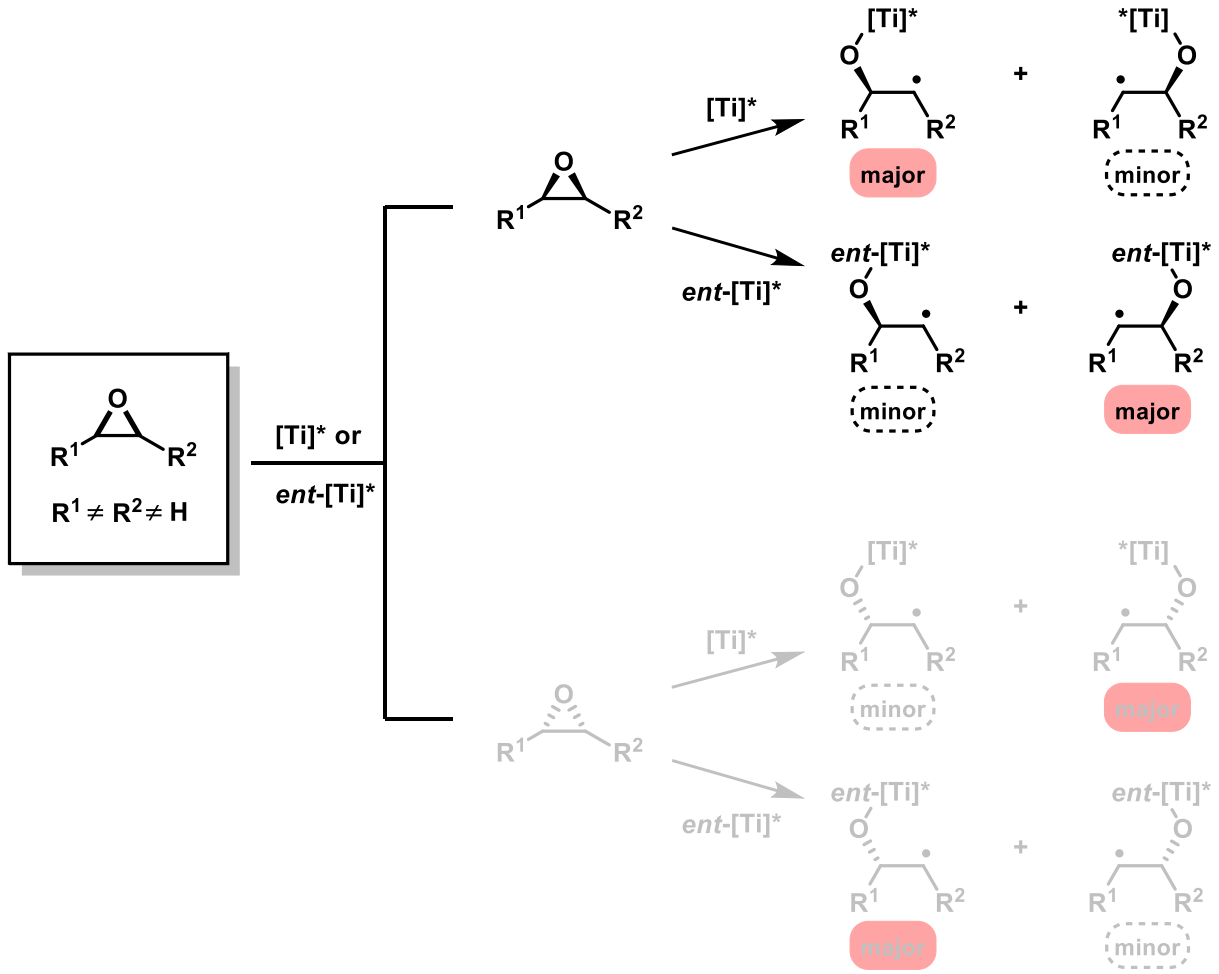
substrate	Ti-catalyst	B (yield, er)	C (yield, *dr*, er)
A (er = 50:50)	Cp_2TiCl_2	31%, **50:50**	9%, *66:34*, **50:50**
A (er = 50:50)	**[Ti]***	36%, **12.5:87.5**	30%, *91:9*, **94:6**
A (er = 93:7)	**[Ti]***	15%, **ND**	68%, *91:9*, **>99:1**
A (er = 93:7)	***ent*-[Ti]***	56%, **>99:1**	2%, *ND*, **ND**

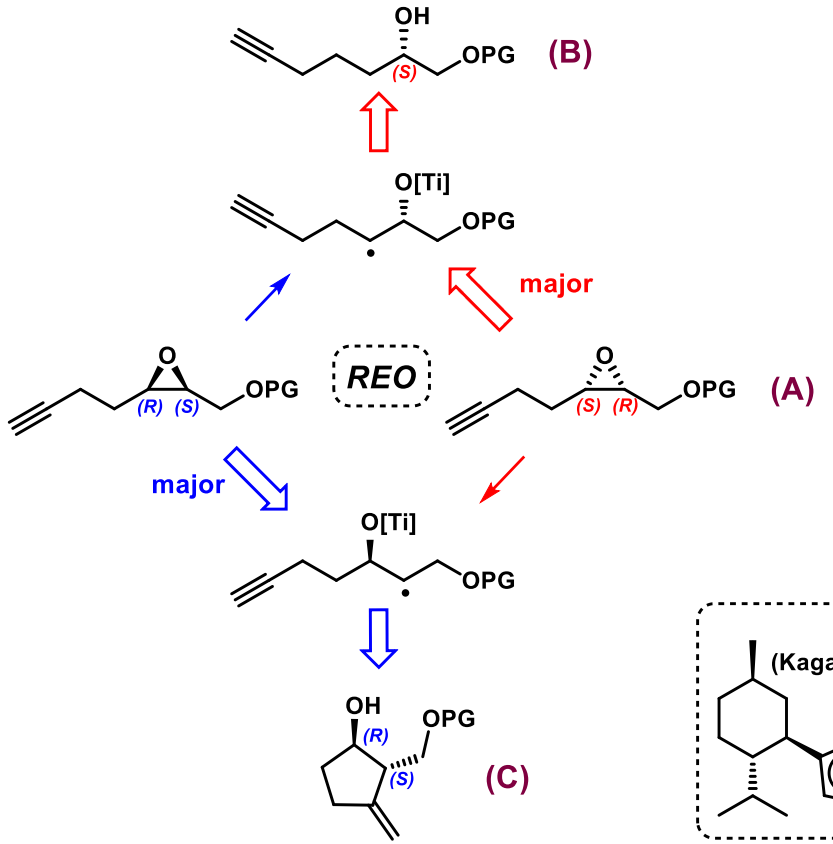
er = (2*S*,3*R*):(2*R*,3*S*)

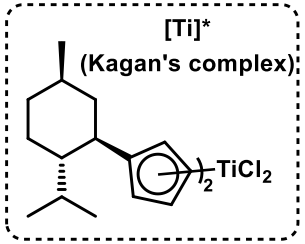
Gansäuer, A. et al. *J. Am. Chem. Soc*. **2010**, *132*, 11858–11859.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

REO & Kinetic Resolution:







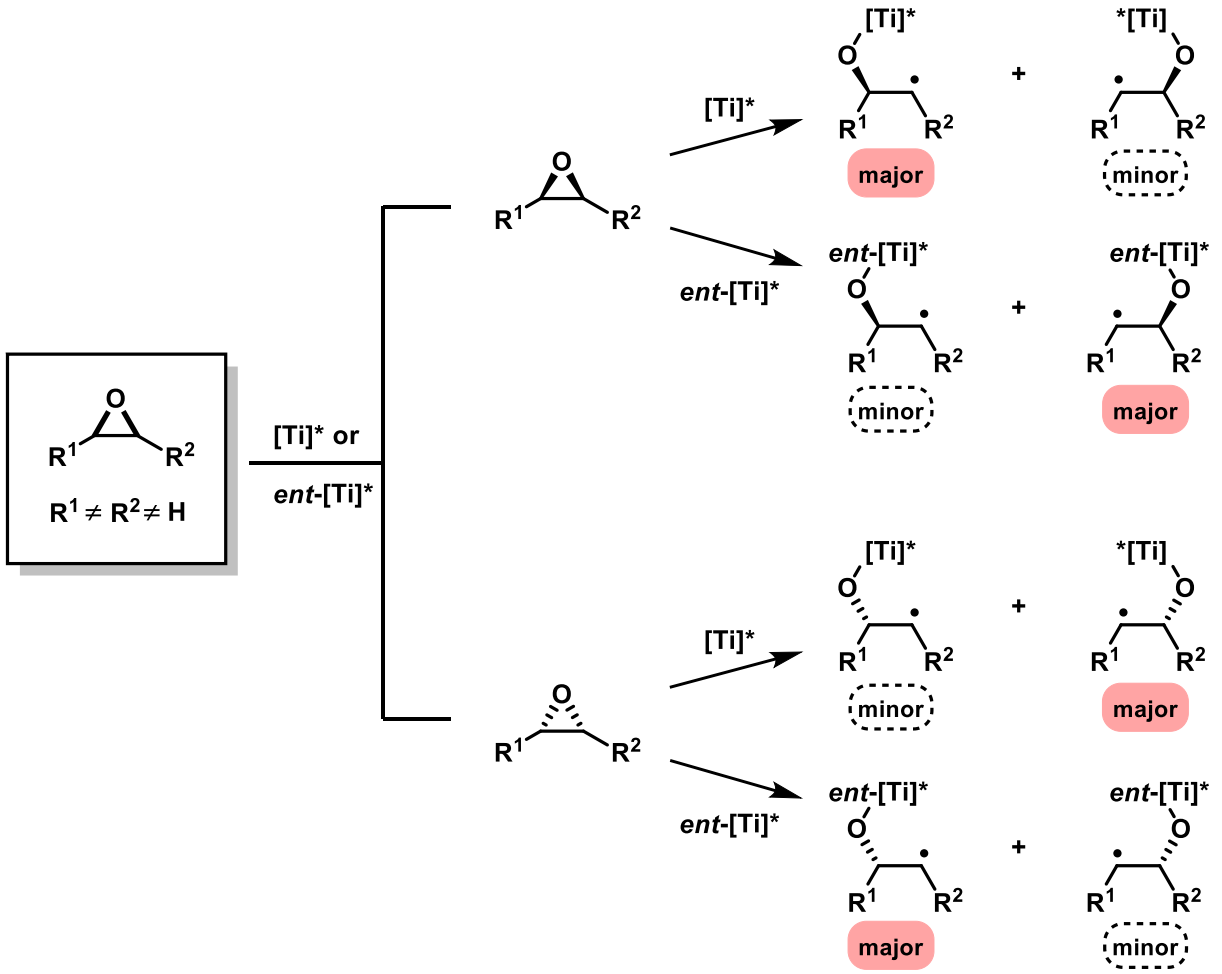
substrate	Ti-catalyst	B (yield, er)	C (yield, *dr*, er)
A (er = 50:50)	Cp_2TiCl_2	31%, **50:50**	9%, *66:34*, **50:50**
A (er = 50:50)	**[Ti]***	36%, **12.5:87.5**	30%, *91:9*, **94:6**
A (er = 93:7)	**[Ti]***	15%, **ND**	68%, *91:9*, **>99:1**
A (er = 93:7)	***ent*-[Ti]***	56%, **>99:1**	2%, *ND*, **ND**

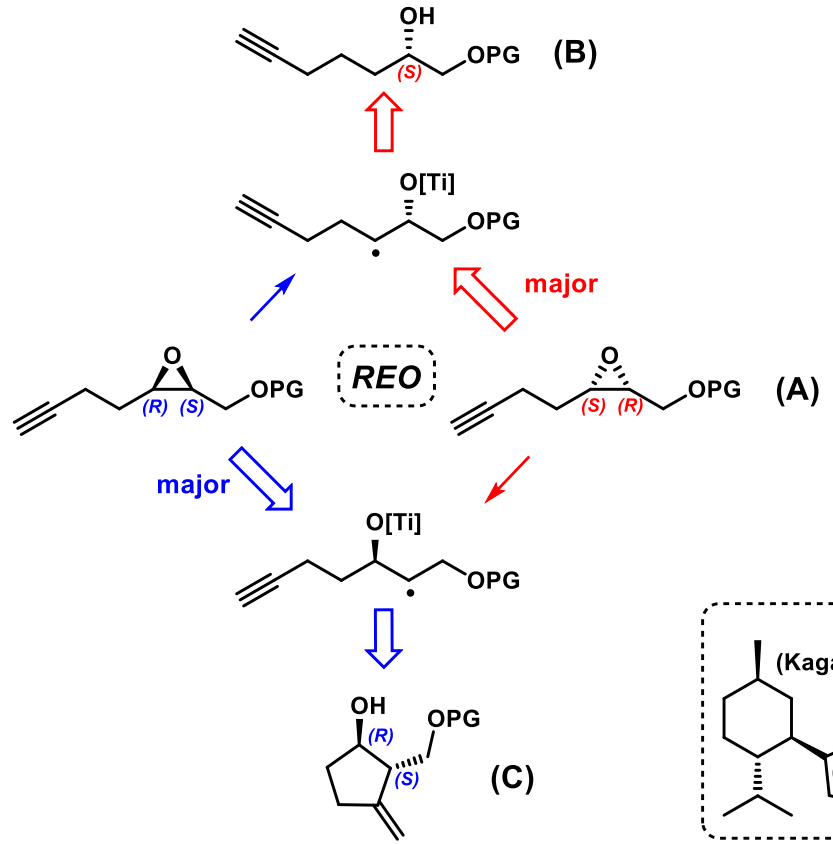
er = (2*S*,3*R*):(2*R*,3*S*)

Gansäuer, A. et al. *J. Am. Chem. Soc*. **2010**, *132*, 11858–11859.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

REO & Kinetic Resolution:



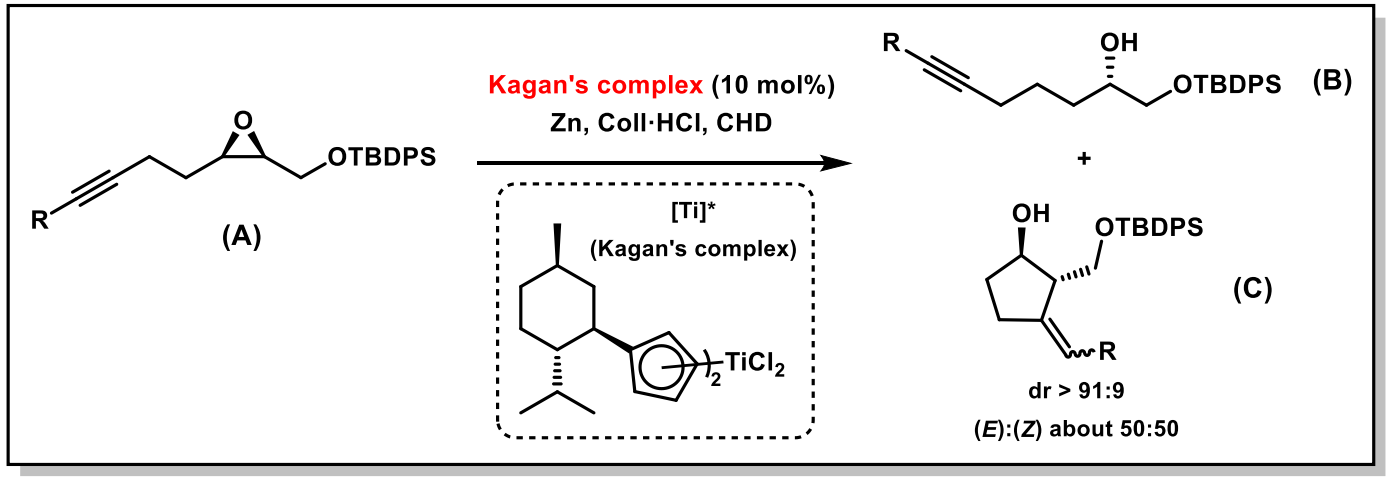


substrate	Ti-catalyst	B (yield, er)	C (yield, *dr*, er)
A (er = **50:50**)	Cp_2TiCl_2	31%, **50:50**	9%, *66:34*, **50:50**
A (er = **50:50**)	**[Ti]***	36%, **12.5:87.5**	30%, *91:9*, **94:6**
A (er = **93:7**)	**[Ti]***	15%, **ND**	68%, *91:9*, **>99:1**
A (er = **93:7**)	***ent*-[Ti]***	56%, **>99:1**	2%, *ND*, **ND**

er = (2*S*,3*R*):(2*R*,3*S*)

Gansäuer, A. et al. *J. Am. Chem. Soc*. **2010**, *132*, 11858–11859.

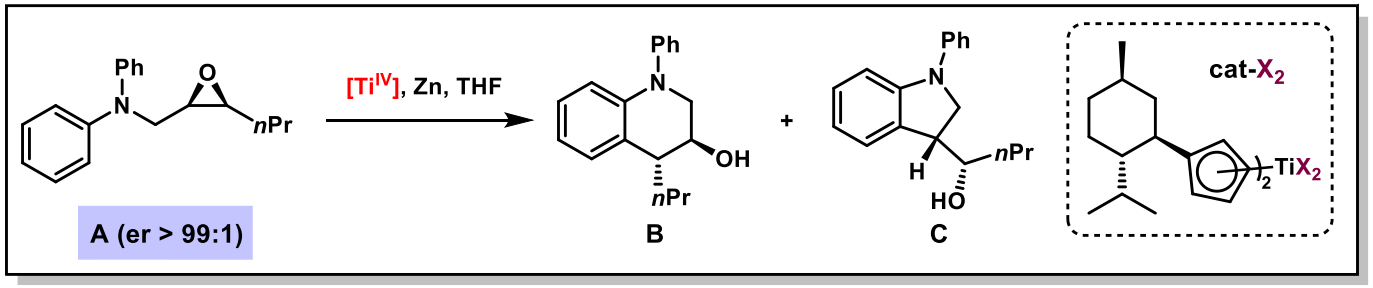
Regiodivergent Epoxide Opening (REO) & Kinetic Resolution



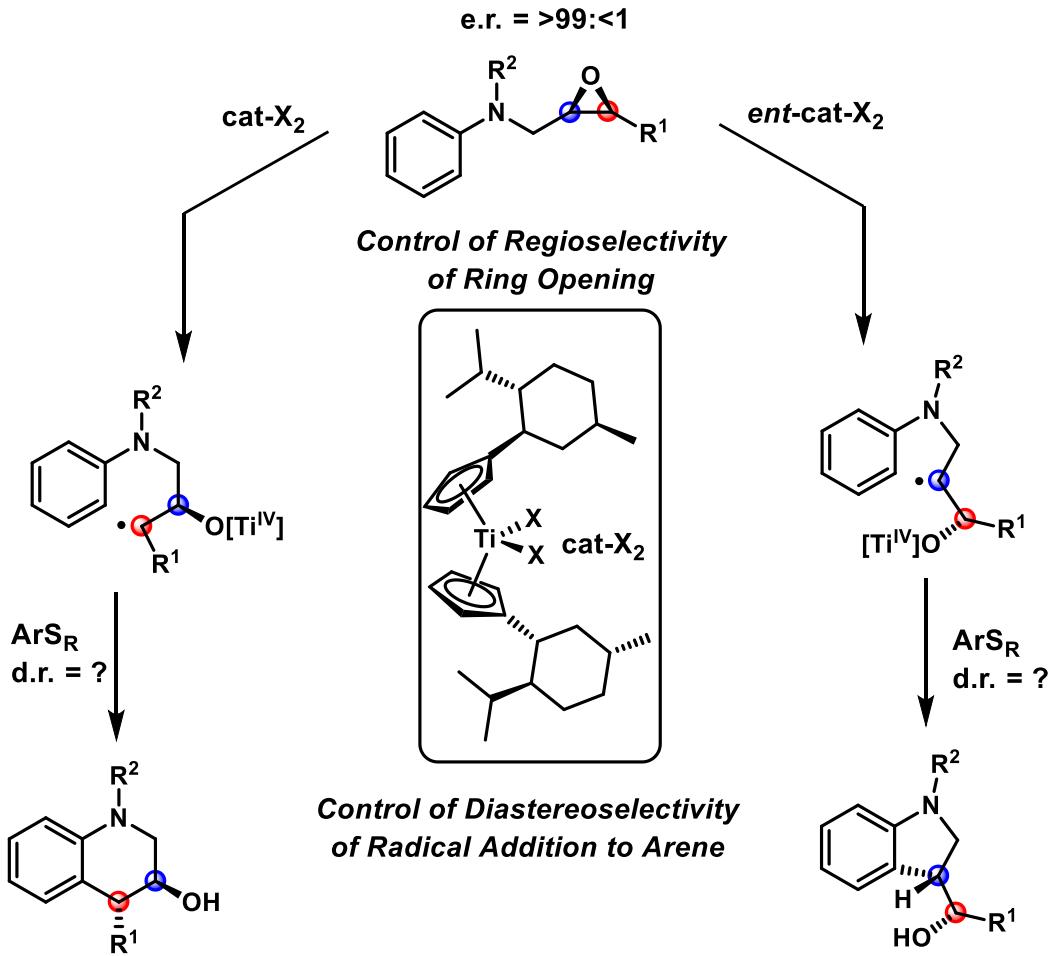
substrate (er)	B (yield, er)	C (yield, er)
R = Et (er = 50:50)	38%, **88.5:11.5**	38%, **97:3**
R = Et (er = 93:7)	14%, **ND**	67%, **>99:1**
R = CO_2Me (er = 50:50)	47%, **85.5:14.5**	33%, **97.5:2.5**
R = CO_2Me (er = 93:7)	31%, **ND**	51%, **98:2**
R = Ph (er = 50:50)	46%, **88:12**	36%, **97.5:2.5**
R = Ph (er = 91:9)	24%, **ND**	56%, **>99:1**

Gansäuer, A. et al. *J. Am. Chem. Soc*. **2010**, *132*, 11858–11859.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution



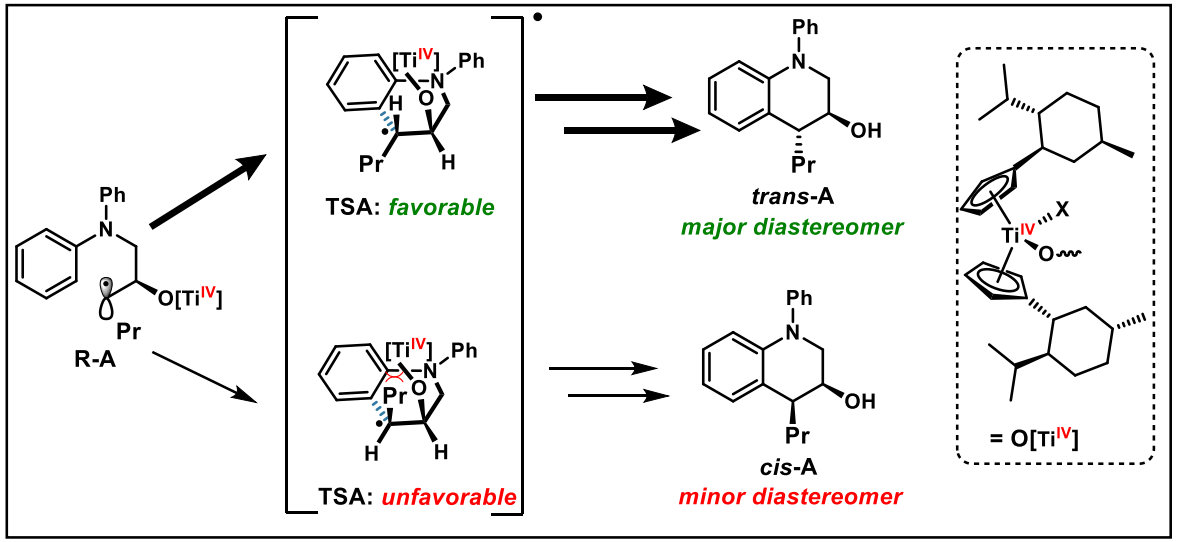
Conditions	B (%, dr)	C (% dr)	
10 mol% Cp_2TiCl_2 30 mol% Zn 30 mol% Lut·HCl	78% dr = 69:31	22% dr = 90:10	
5 mol% *ent*-cat-Cl_2 30 mol% Zn 30 mol% Lut·HCl	10% -	90% dr = 92:8	72% iso y dr > 99:1
10 mol% *ent*-cat-$(OTs)_2$ 30 mol% Zn	16% -	84% dr = 83:17	
10 mol% cat-Cl_2 30 mol% Zn 30 mol% Lut·HCl	93% dr = 67:33	7% -	
10 mol% cat-$(OTs)_2$ 30 mol% Zn	94% dr = 76:24	73% iso y dr = 90:10	6% -

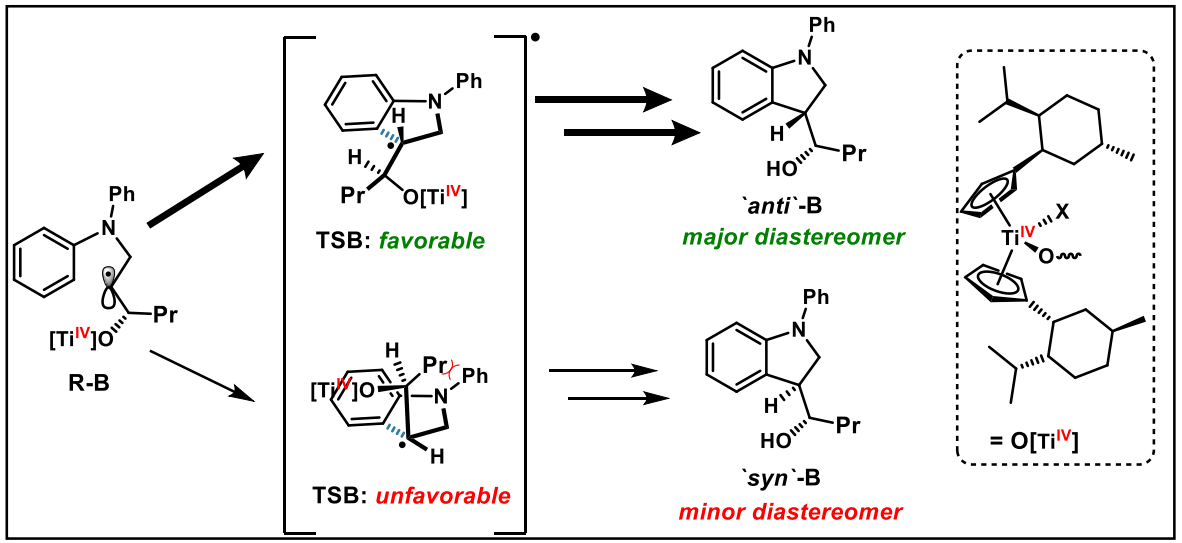


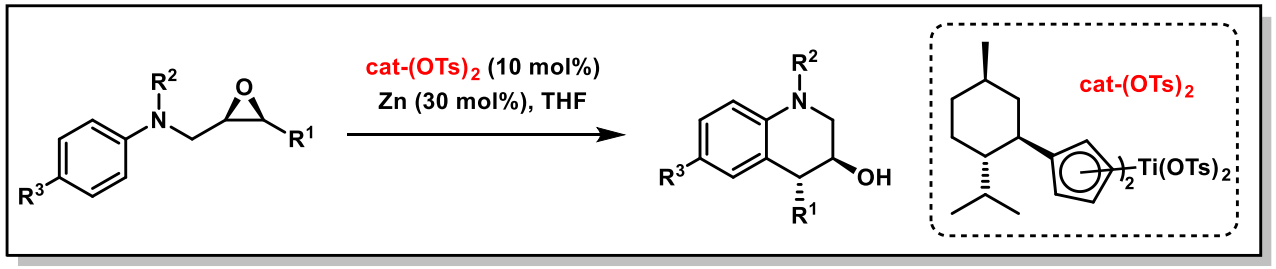
Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 14208 –14212.

Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

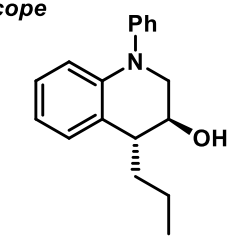
Analysis of Diastereoselectivity:



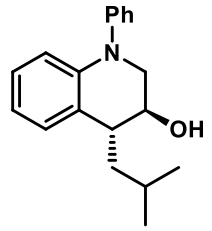




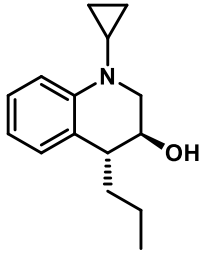
Reaction Scope



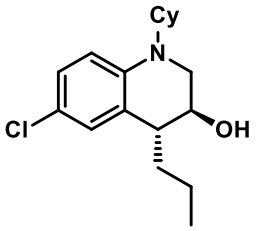
r.r. = 94:6
d.r. crude = 76:24
73% yield



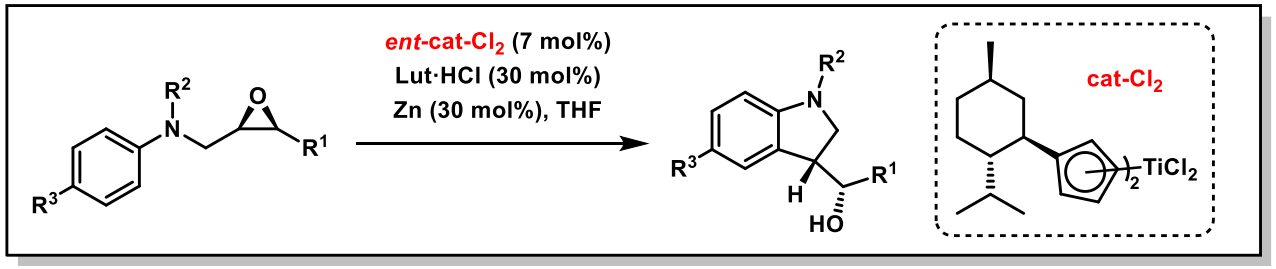
r.r. = 96:4
d.r. crude = 83:17
74% yield



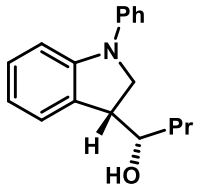
r.r. = 93:7
d.r. crude = 88:12
81% yield



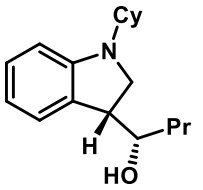
r.r. = 91:9
d.r. crude > 98:2
77% yield



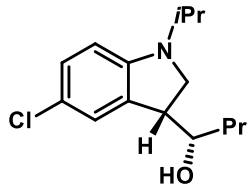
Reaction Scope



r.r. = 90:10
d.r. crude = 92:8
72% yield



r.r. = 91:9
d.r. crude = 86:14
56% yield



r.r. = 91:9
d.r. crude = 85:15
68% yield

Gansäuer, A. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 14208 –14212.

PART 3

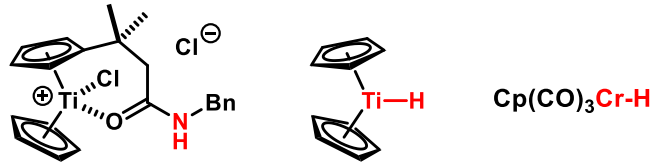
Summary and Outlook

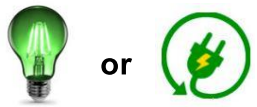
Summary and Outlook

Titanium-Catalyzed Ring-Opening of Three-Membered Rings

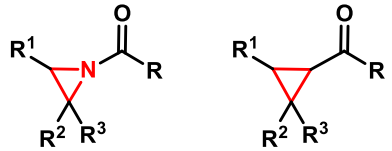
Summary

- Reduction of Epoxides
  - Novel HAT Process:

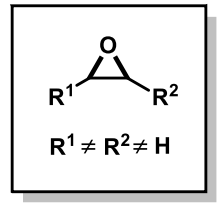


  - Ti^{IV} → Ti^{III} (or )
- Radical Cascade Reactions
  - Radical Arylation Reactions:

  - Other Three-Membered Rings:



- Regiodivergent Epoxide Opening (REO) & Kinetic Resolution

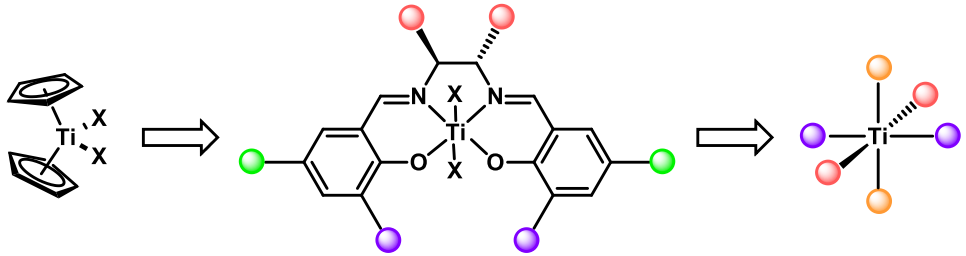


Summary and Outlook

Outlook: Ti-Catalyzed Radical Reaction

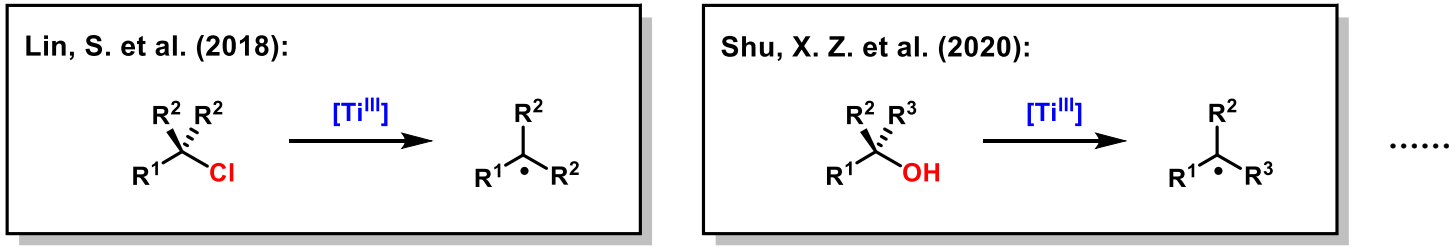
1. Ring-Opening of Three-Membered Rings

1) Development of new reaction mode:  or

2) Development of new [Ti] catalyst: 

3) Development of dual catalytic system: Ti/Ni (Doyle, A. G. et al.), Ti/Cu ……

2. **R-X** as a radical precursor



Lin, S. et al. *J. Am. Chem. Soc*. **2018**, *140*, 14836-14843.
Shu, X. Z. et al. *J. Am. Chem. Soc*. **2020**, *142*, 16787-16794.
Doyle, A. G. et al. *ACS Catal*. **2020**, *10*, 5821-5827.

THANKS