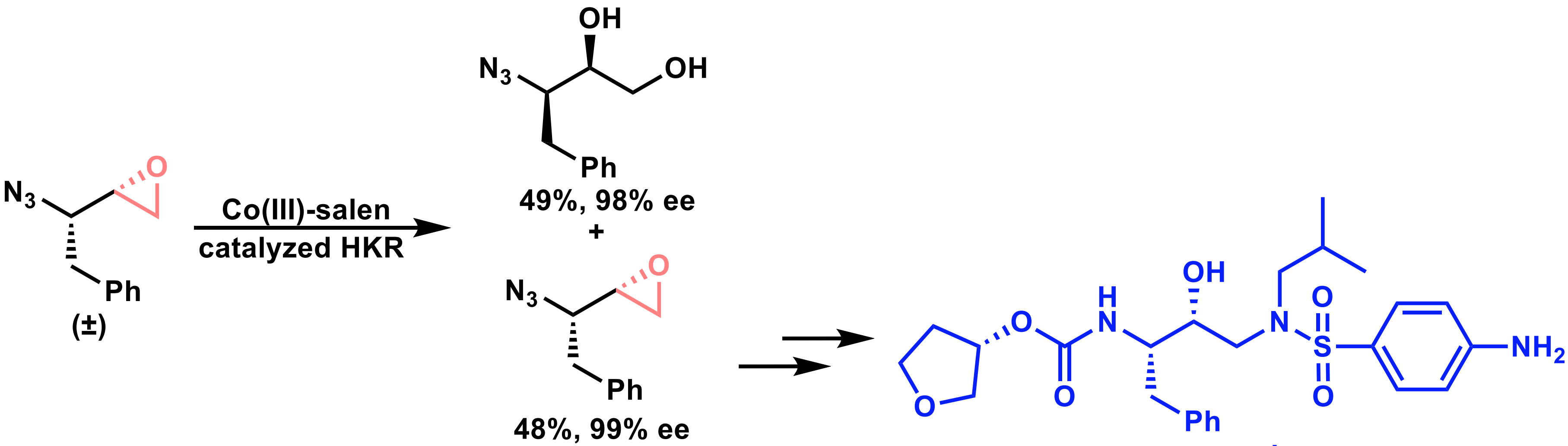
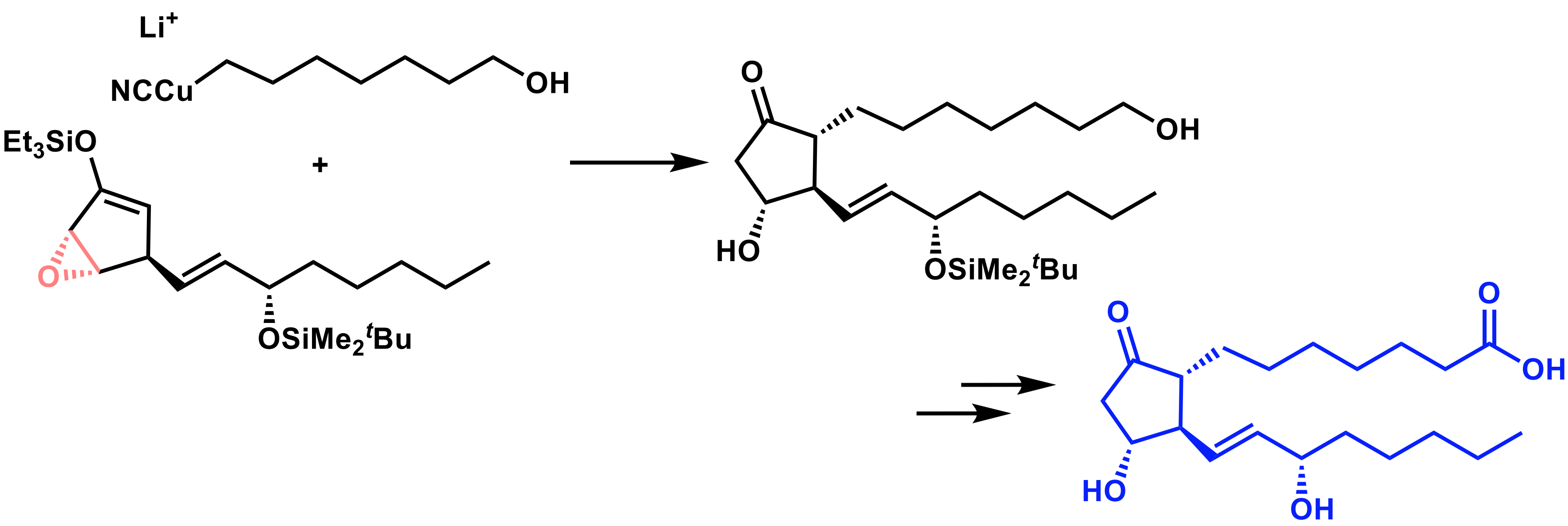
Epoxide in Organic Synthesis

M1 Yuki Hirao

Introduction



amprenavir

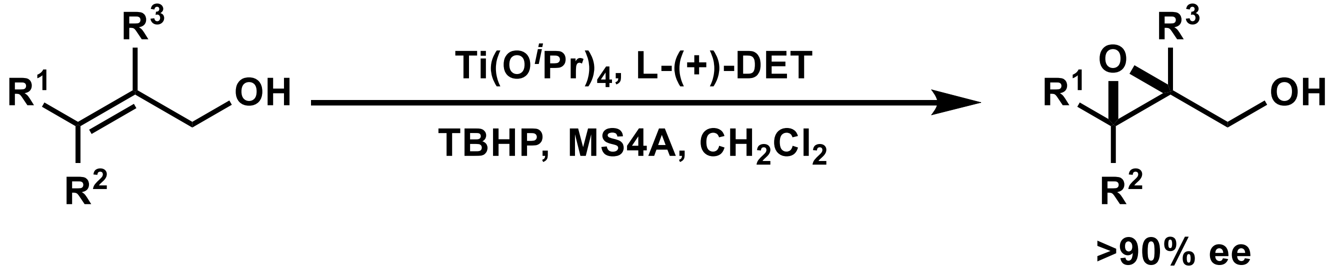


PGE_1

Epoxides are important intermediates in total synthesis.

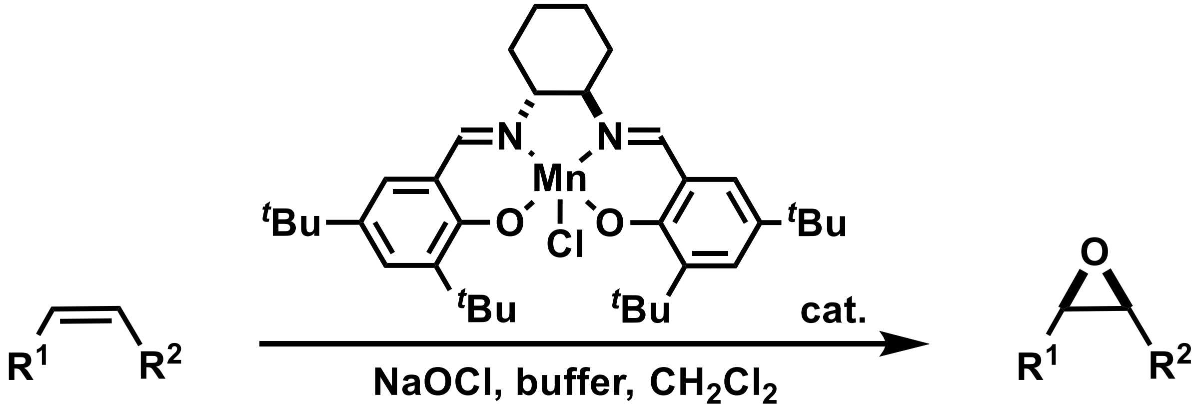
Asymmetric Epoxidation

Sharpless-Katsuki Epoxidation



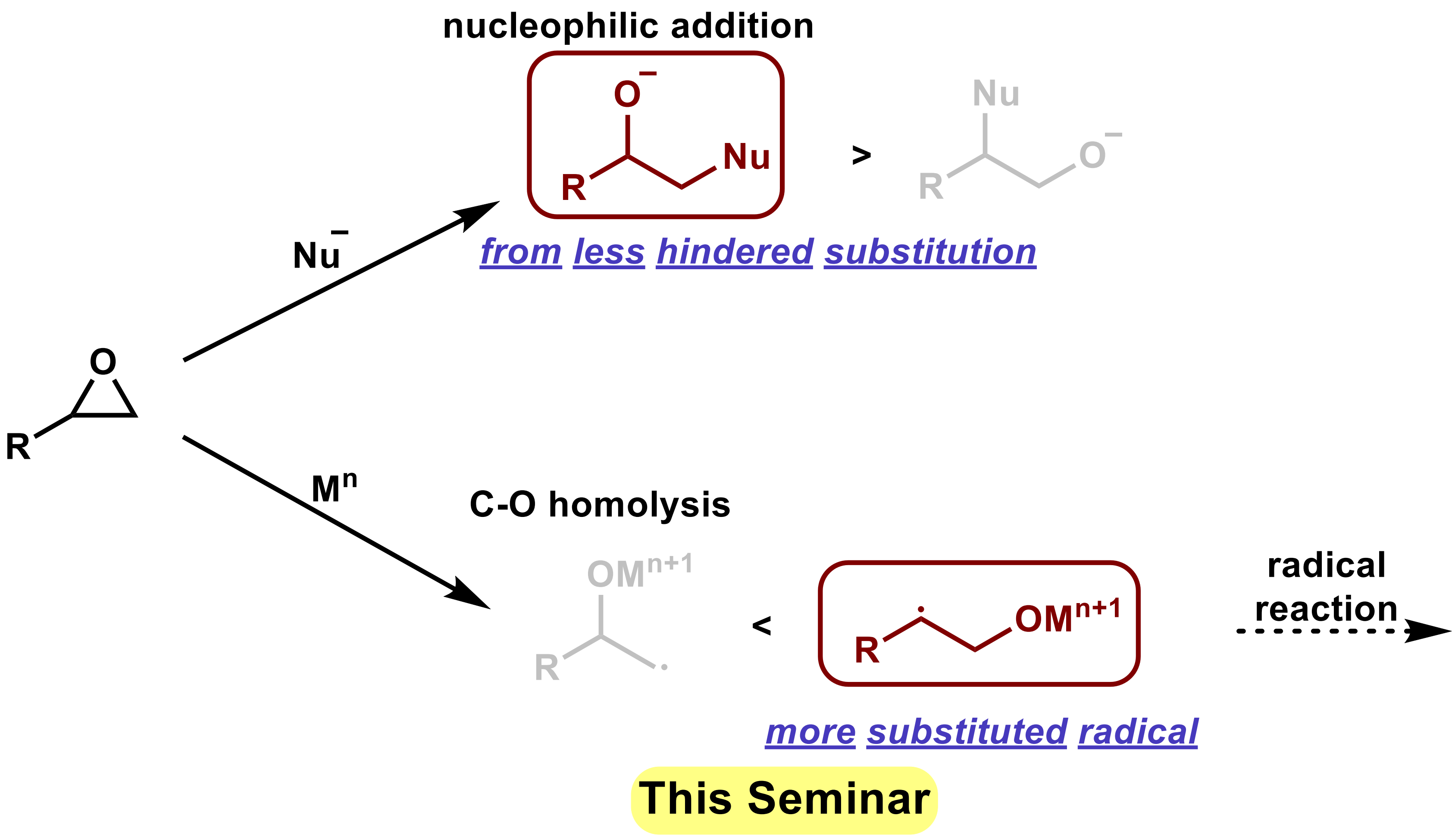
The Nobel Prize
in Chemistry 2001

Jacobsen-Katsuki Epoxidation



Contents

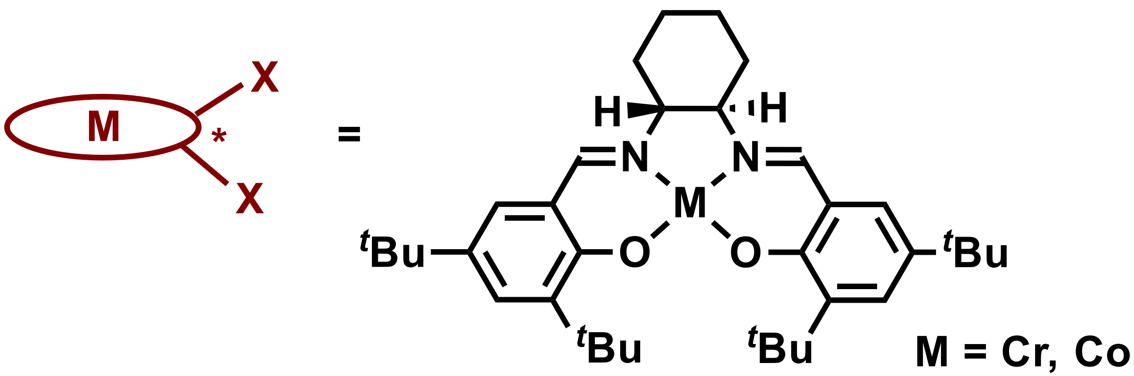
Ring-Opening of Epoxide



Nucleophilic addition

Lewis acid
activation of epoxide

asymmetric ring-opening



Metal-Salen complex

Nu^- = N_3^-, ^-OH, ^-OBz

- **high yield** and **high enantioselectivity** with *meso*-epoxide
- **kinetic resolution** of terminal epoxide

Jacobsen, E, N. *et al. J. Org. Chem.* **1997**, *62*, 4197.
Jacobsen, E, N. *et al. Tetrahedron Lett.* **1997,** *38*, 773.
Jacobsen, E, N. *et al. Science*. **1997**, *277*, 936.

Reductive-opening by SET

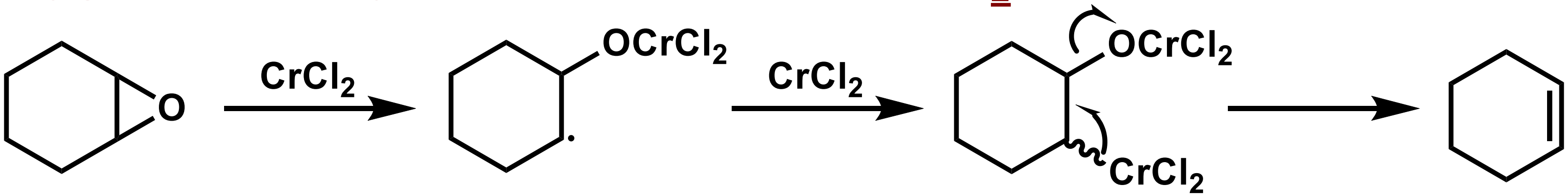
General Ideas

Opening of epoxides with low-valent metal complexes

analogue of the opening of cyclopropylcarbinyl radicals

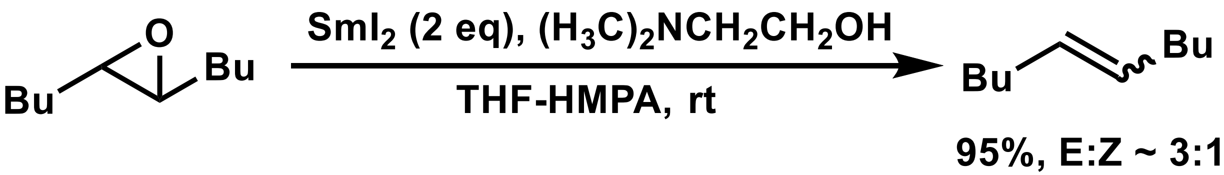
Reductive-opening by SET

Deoxygenation of cyclohexene oxide with $CrCl_2$



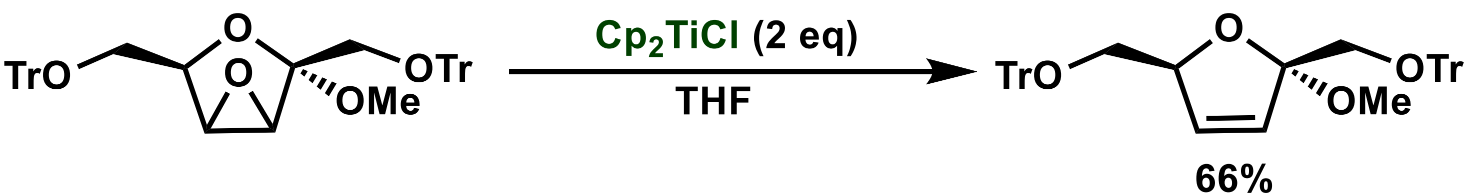
J. K. Kochi, D. M. Singleton, L. J. Andrews, *Tetrahedron*. **1968**, *24*, 3503.

Deoxygenation of epoxides with SmI_2

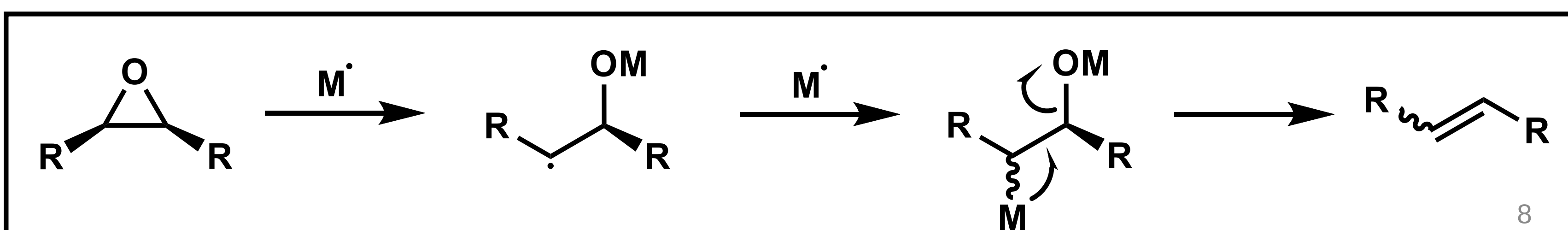


M. Matsukawa, T. Tabuchi, J. Inanaga, M. Yamaguchi, *Chem. Lett*. **1987**, 2101.

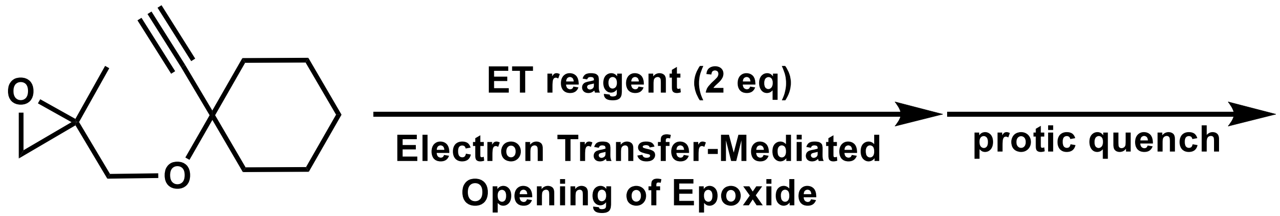
Deoxygenation of epoxides with Cp_2TiCl

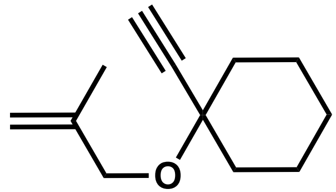
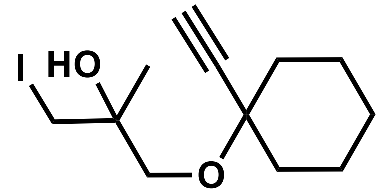
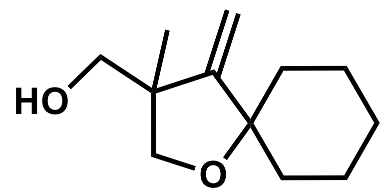
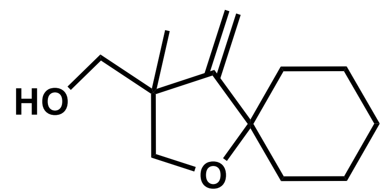


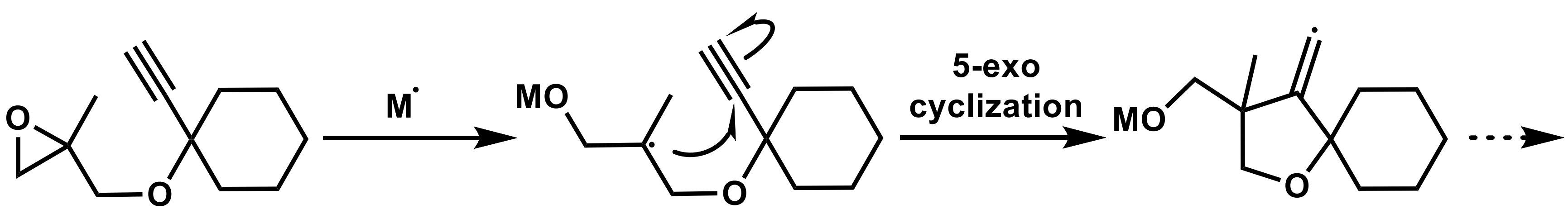
T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc*. **1994**, *116*, 986.



Reductive-opening by SET



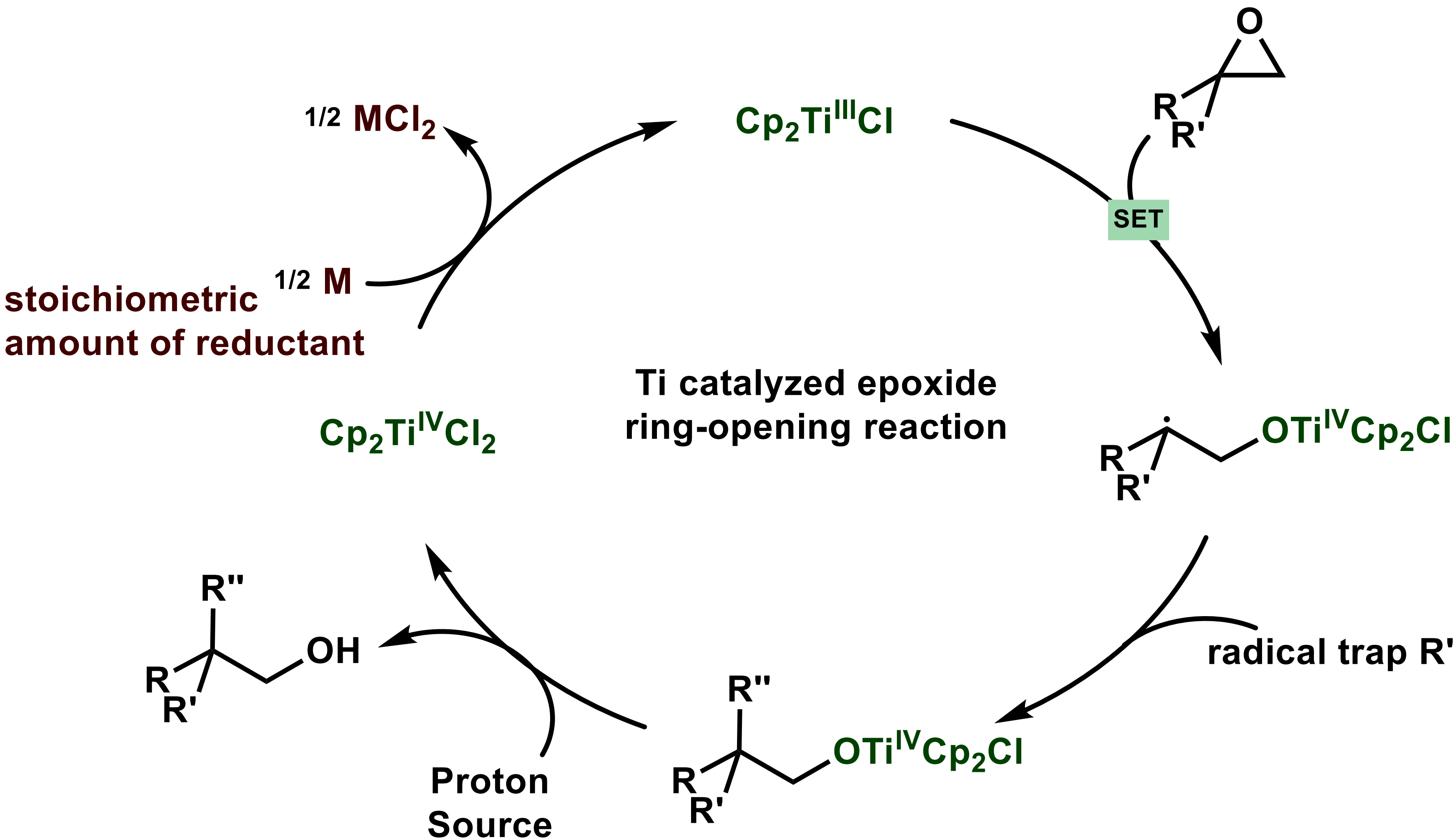
Entry	ET-reagent	Product	Yield (%)
1	SmI_2	 36 	45
2	$CrCl_2$		38
3	Cp_2TiCl		82



A. Gansäuer, B. Rinker, *Tetrahedron*. **2002**, *58*, 7017.

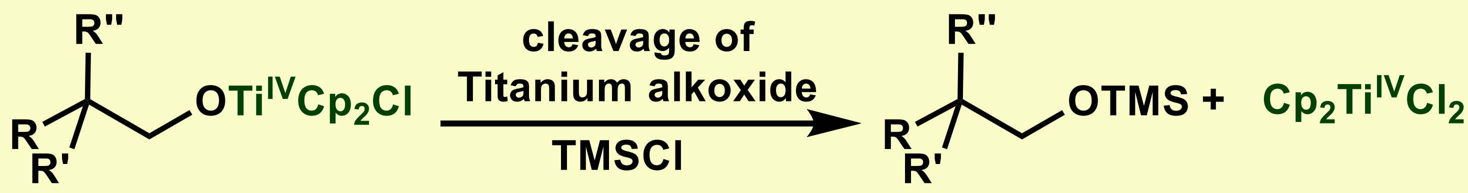
Contents

Titanocene-catalyzed Epoxide Opening



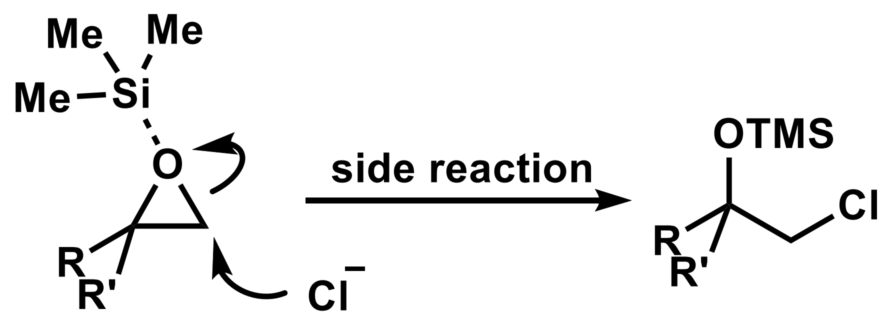
Titanocene-catalyzed Epoxide Opening

➢ **For a catalytic reaction, the regeneration of the redox active species (Cp_2TiCl_2) is needed.**



cf.) McMurry couplings, NHK reactions, pinacol couplings

- **TMSCl instead of proton source**

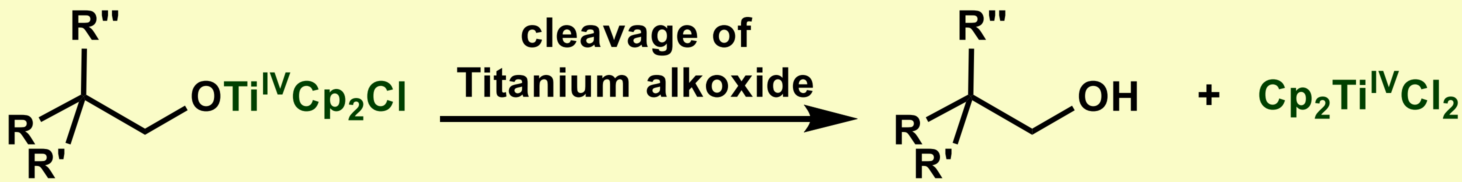


→ **due to the Lewis Acidity of TMSCl**

Fürstner, A. *et al. J. Am. Chem. Soc.* **1995**, *117*, 4468.
Fürstner, *A. et al. J. Am. Chem. Soc*. **1996,** *118*, 2533.
Ikeda, I. *et al. J. Org. Chem*. **1996**, *61*, 366.

Titanocene-catalyzed Epoxide Opening

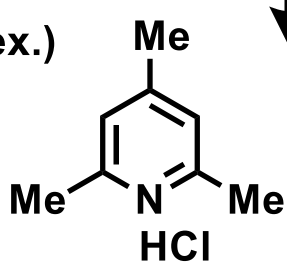
- **For a catalytic reaction, the regeneration of the redox active species (Cp_2TiCl_2) is needed.**



✓ **characteristics of proton source**

1) **must not be strong enough to open epoxides via S_N1 or S_N2 reactions.**
2) **must be strong enough to protonate alkoxides to enable turn over. The pKa of typical alcohols in water are range of 15 - 18.**
3) **must not oxidize the reductant or the titanocene(III) complex.**
4) **must not complex and deactivate any titanium species in the proposed catalytic cycle.**

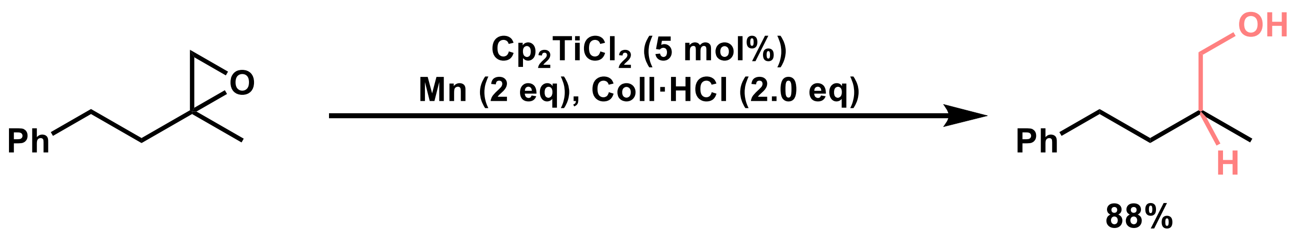
ex.)

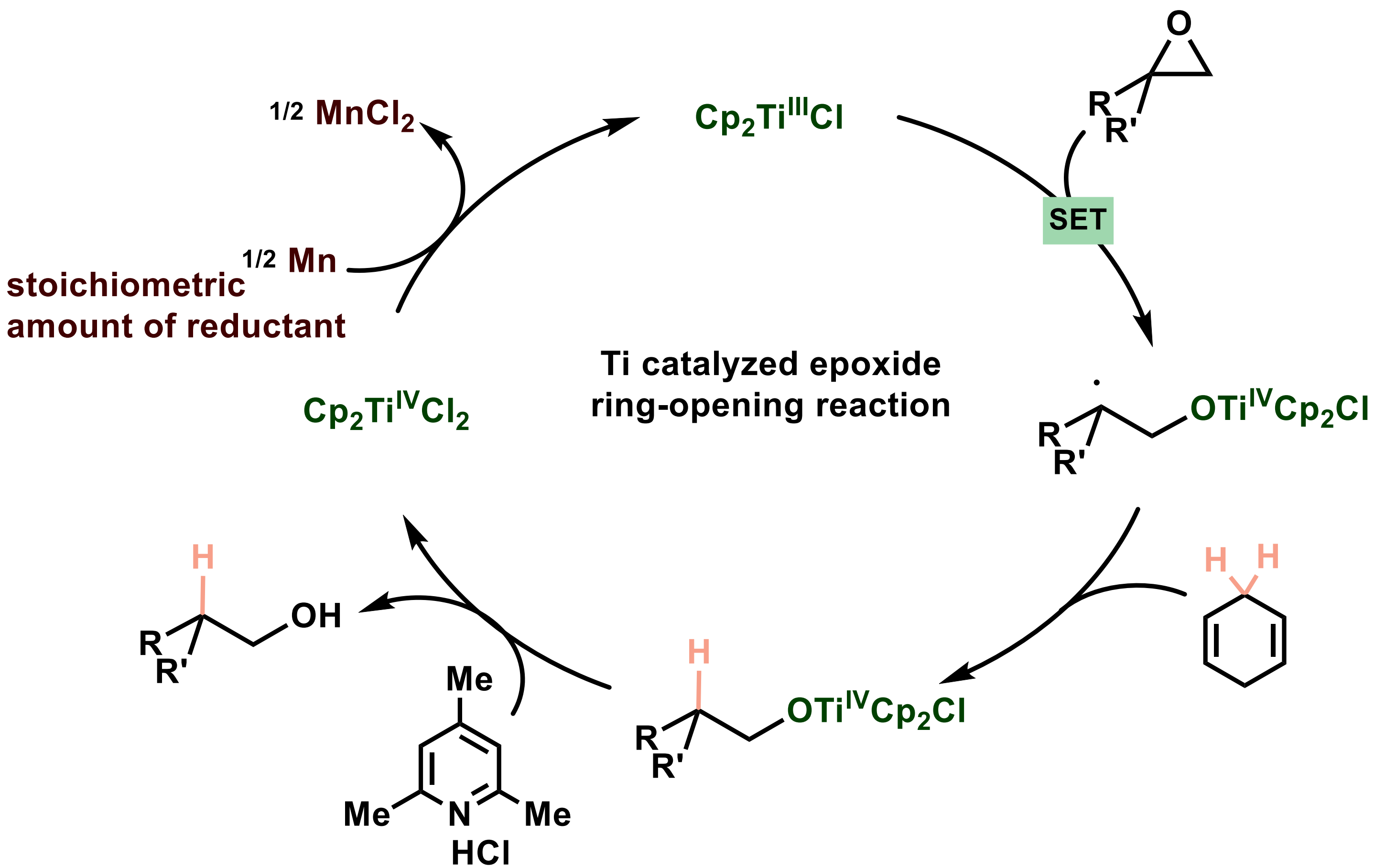


amine hydrochlorides
pKa 6 - 12 in water

A. Gansäuer. *et al. J. Org. Chem*. **1998**, *66*, 2070.
A. Gansäuer. *et al. Eur. J. Org. Chem*. **1998**, 2673.

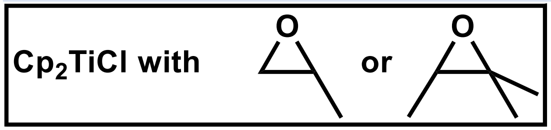
Titanocene-catalyzed Epoxide Opening



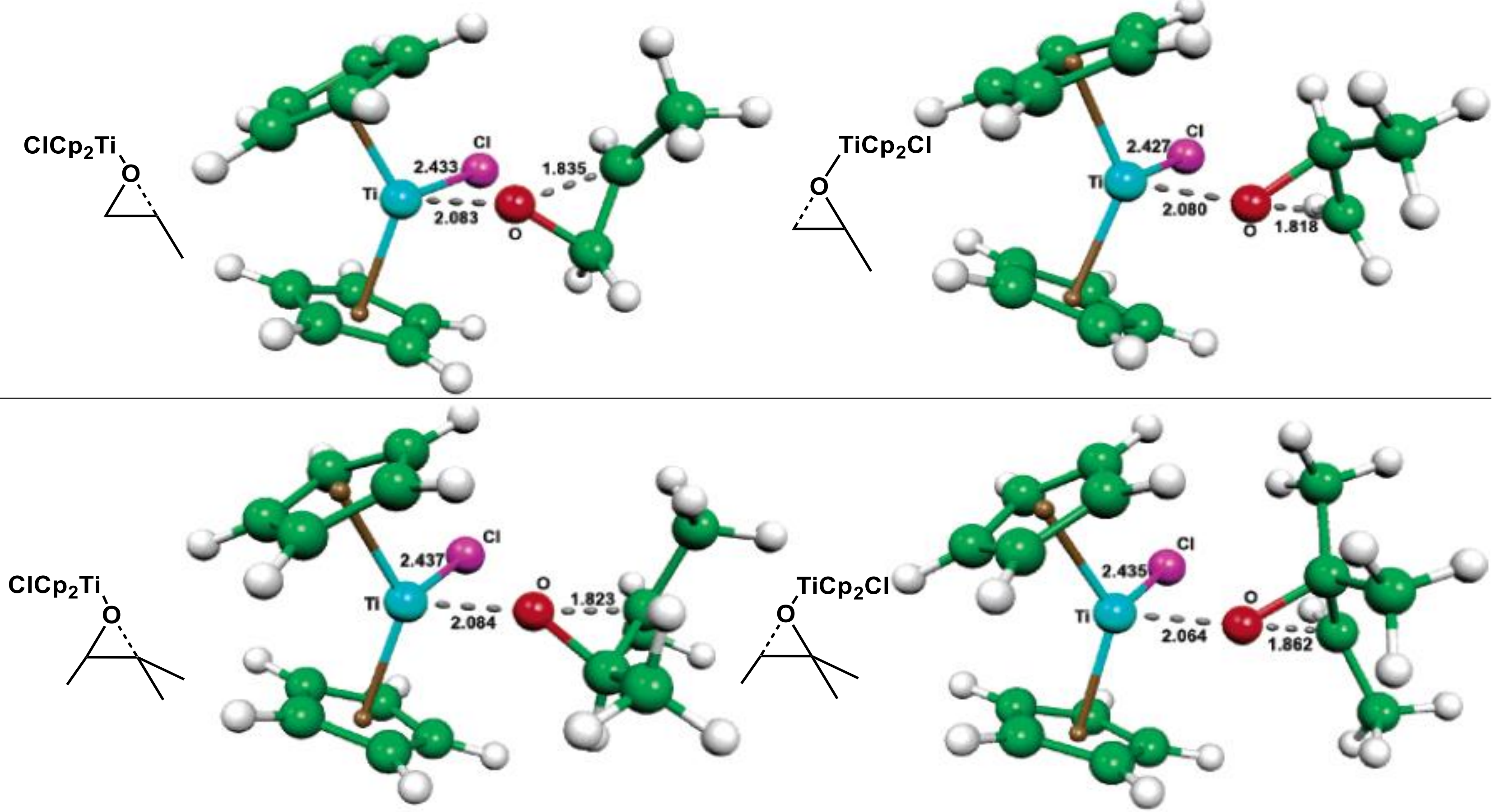


Computational Studies

DFT calculations (BP86/TZVP)



Favored   Disfavored

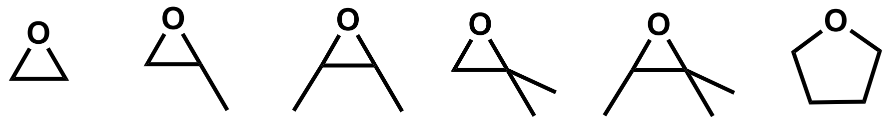


In disfavored transition state, the larger CH3 group gets into closer contact with Cp ligand.

A. Gansäuer. *et al. J. Am. Chem. Soc*. **2007**, *129,* 1359.

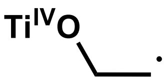
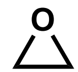
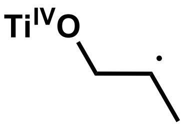
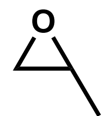
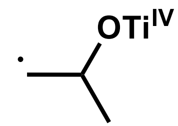
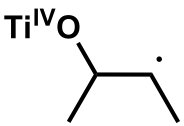
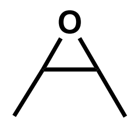
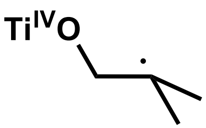
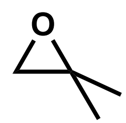
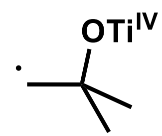
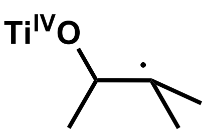
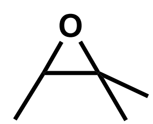
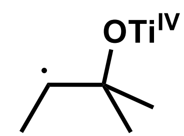
Computational Studies DFT calculations (BP86/TZVP)

Complexation Energies by Cp_2TiCl Relative to Those of THF



---

activation and reaction energies of the epoxide complexes (kcal/mol)

product (a)	ΔE	ΔE‡	substrate	ΔE‡	ΔE	product (b)
	-4.1	8.7		-	-	-
	-4.0	8.2		9.4	-1.8	
	-1.8	8.8		-	-	-
	-8.5	7.0		9.0	-1.3	
	-4.9	8.7		10.3	+0.7	

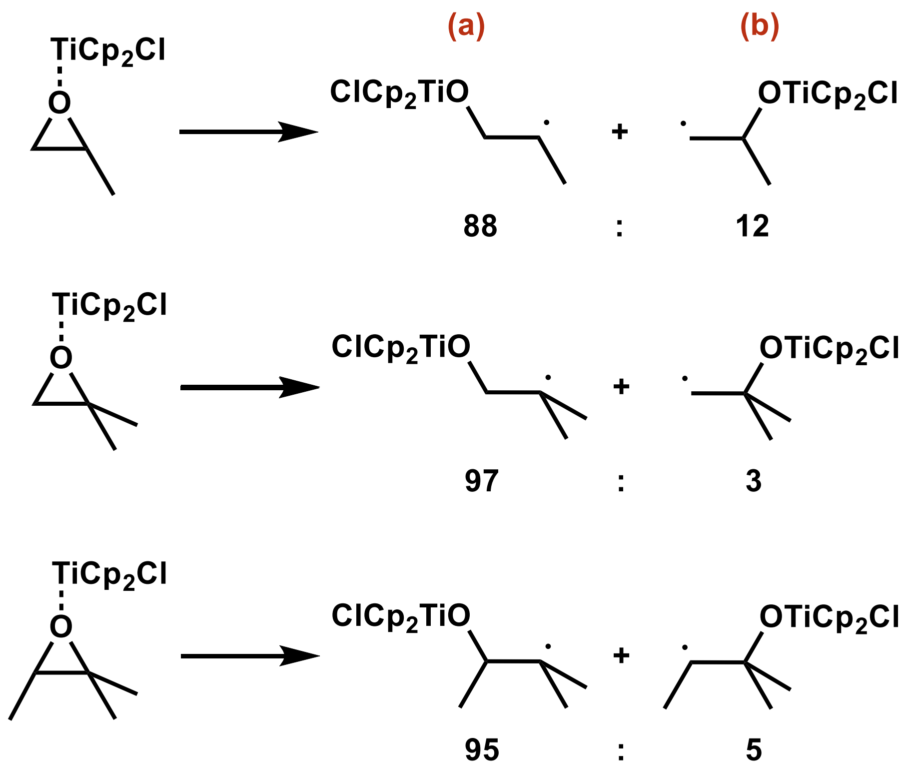
✓Epoxide opening is exothermic.

✓ The formation of the higher substituted radicals is thermodynamically favored.

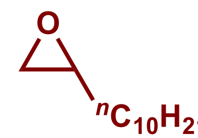
A. Gansäuer. *et al. J. Am. Chem. Soc*. **2007**, *129,* 1359.

Computational Studies

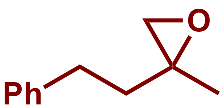
Computed



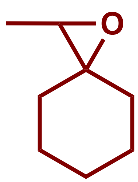
Found



(a):(b) = 88:12

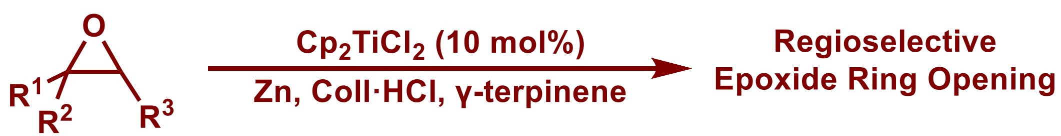


(a):(b) = >97:3

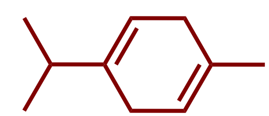


(a):(b) = >97:3

Synthetic Studies



γ-terpinene



Hydrogen Atom Donor

A. Gansäuer. *et al. J. Am. Chem. Soc*. **1998**, *120*, 12849.
A. Gansäuer. *et al. J. Am. Chem. Soc*. **2007**, *129*, 1359.

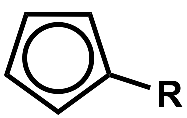
Titanocene-catalyzed Epoxide Opening

manipulating the redox properties

the introduction of substituents to Cp ligands and variation of the inorganic ligands alter the redox potential and electronic properties of the titanocene complexes.

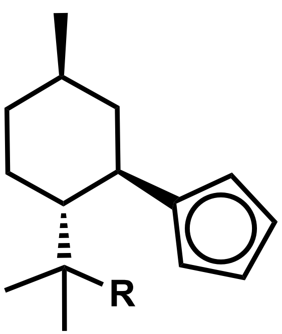
→ these catalysts display high activity, stability, and functional group tolerance.

1. cyclopentadienyl ligand (Cp)

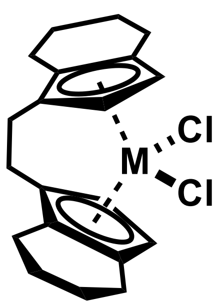


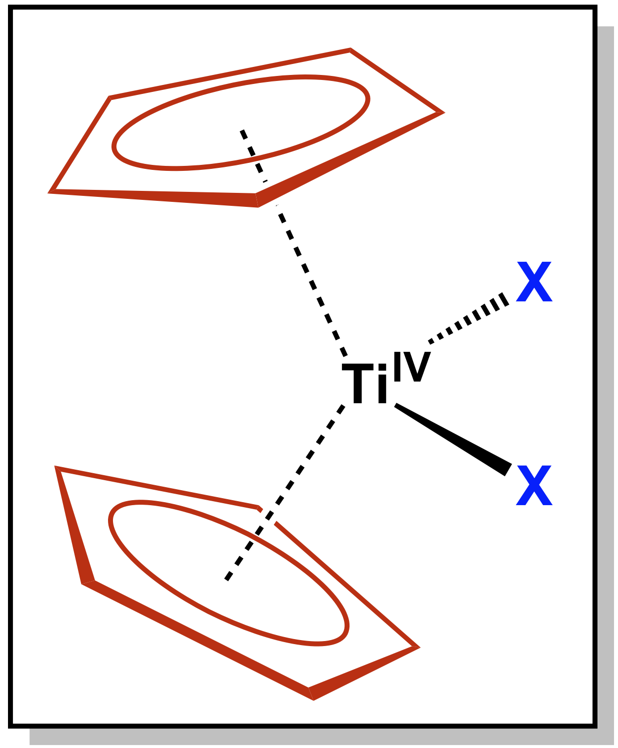
R = Me, ^{t}Bu, Cl, EWG, EDG...

for asymmetric reaction



R = H, Ph



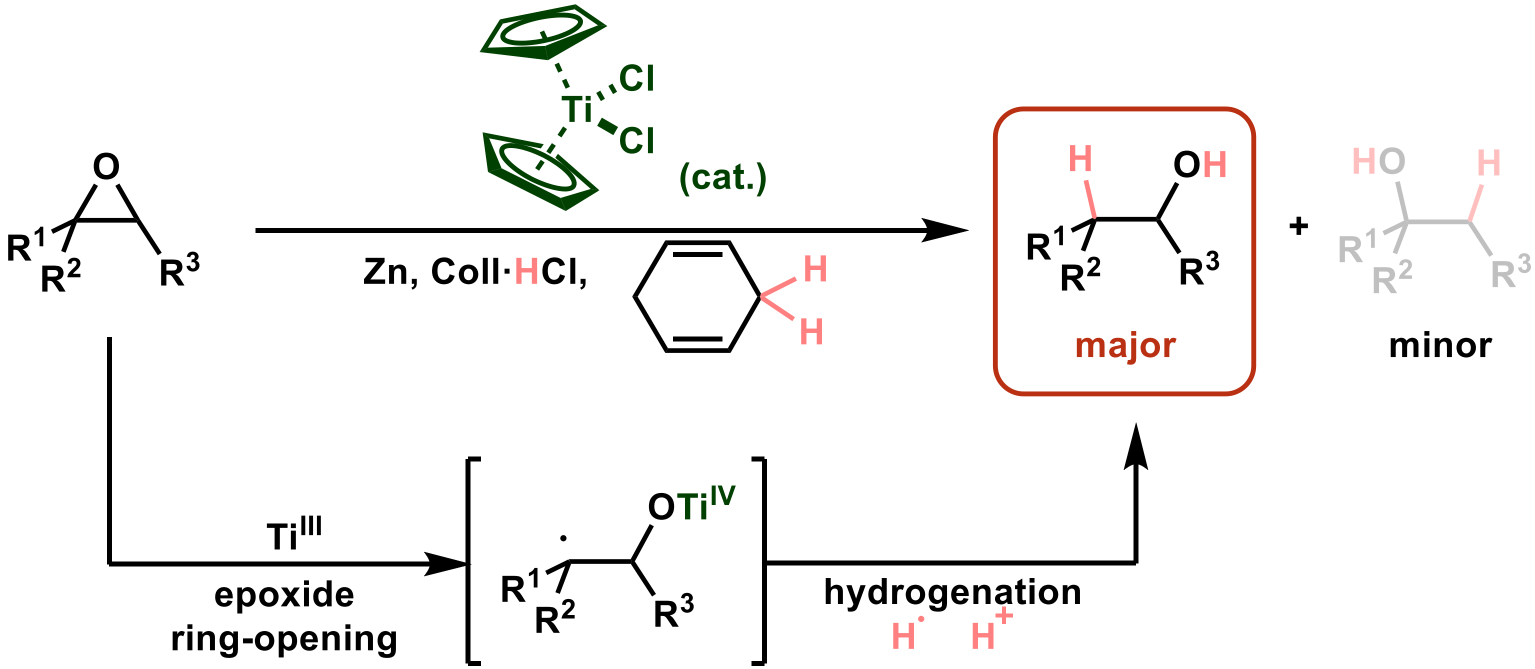


2. inorganic ligands (X)

X = Cl, Br, I, OTf, OTs, OMs, TFA, CSA ...

A. Gansäuer. *et al. J. Am. Chem. Soc.* **2014,** *136,* 1663.
A. Gansäuer. *et al. Chem. Eur.J.* **2018,** *24*, 6371.

Short Summary



Reductive Opening of Epoxides by SET

- ✧**Radical Stability**
- ✧**Steric Interactions between R¹, R² and Cp ligand**

more highly substituted radical

opposed to S_N2 Reaction (from less substituted carbon)

Contents

4. Recent Achievements

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Cite This: *J. Am. Chem. Soc.* 2019, 141, 9548–9554

pubs.acs.org/JACS

Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols

Ke-Yin Ye,[†,‡,§] Terry McCallum,[‡,§] and Song Lin*[,‡]

[†]College of Chemistry, Fuzhou University, Fuzhou, 350116, P.R. China

[‡]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States

RESEARCH

Science

ORGANIC CHEMISTRY

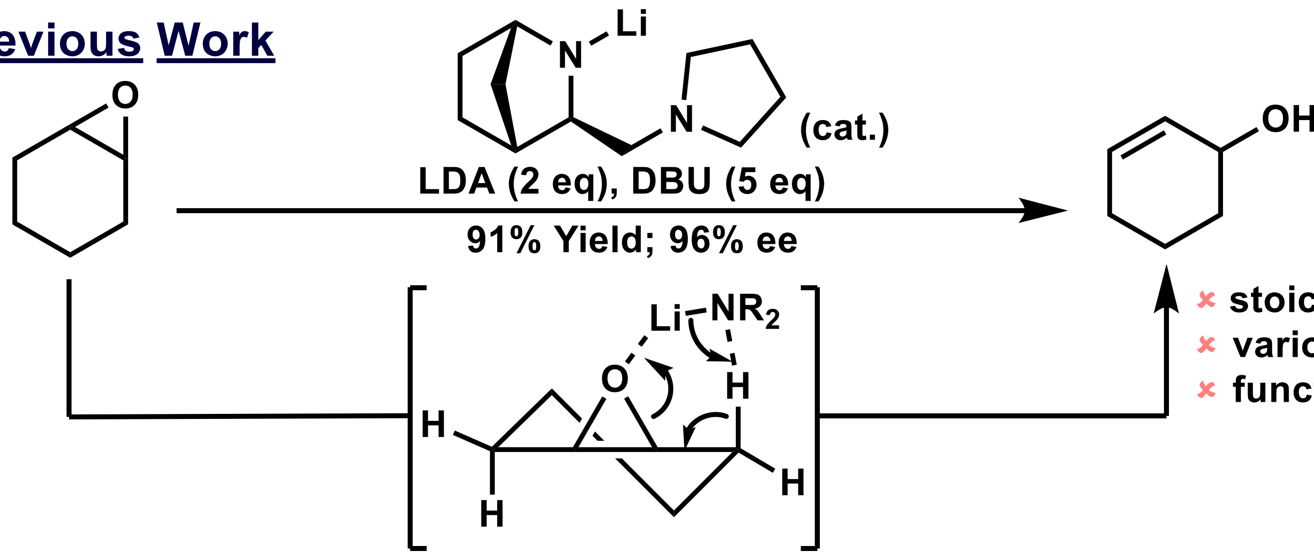
Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis

Chengbo Yao[1], Tobias Dahmen[2], Andreas Gansäuer[3]*, Jack Norton[1]*

Science **364** (6442), 764-767.
DOI: 10.1126/science.aaw3913

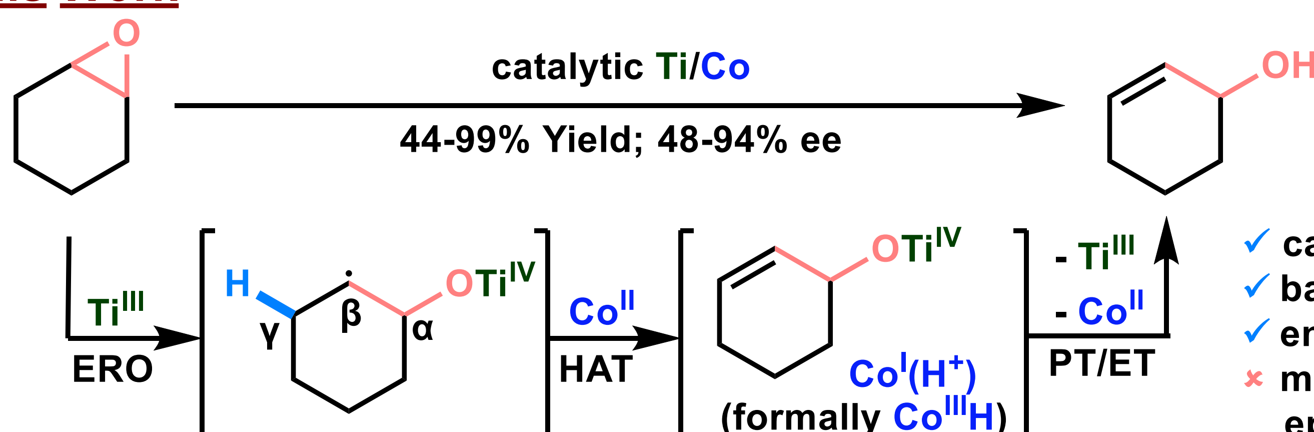
Purpose

Previous Work



- × stoichiometric strong base
- × various side reactions
- × functional-group compatibility

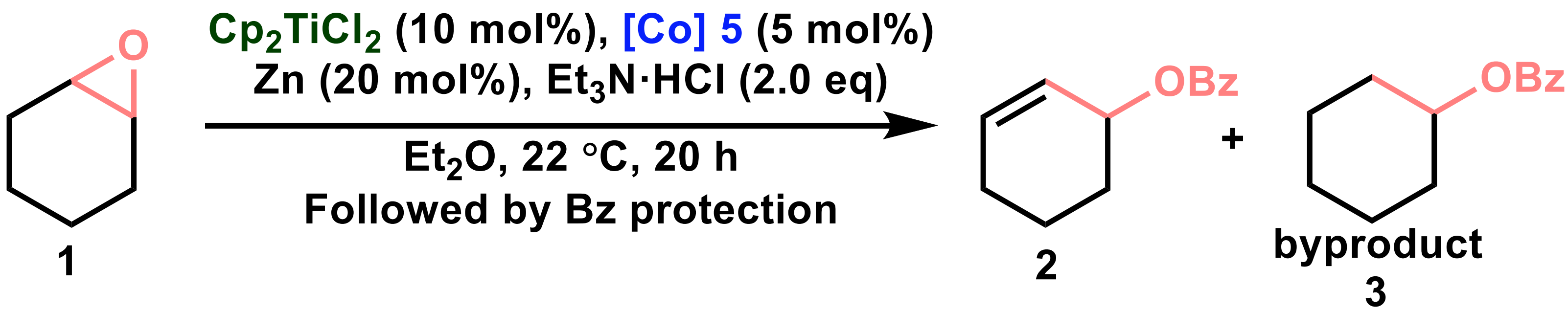
This Work



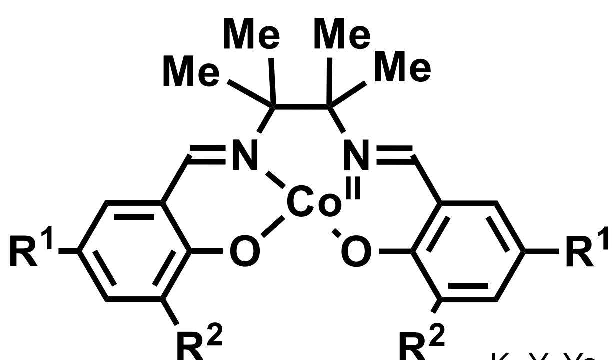
- ✓ catalytic reductants
- ✓ base-free
- ✓ enantioselectivity
- × mono and tetrasubstituted epoxides

J. Andersson. *et al. J. Am. Chem. Soc.* **2000**, *122*, 6610.
K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc.* **2019**, *141*, 9548.

Optimization



Entry	Conditions	2	3
1	[Co] 4	65%	11%
2	[Co] 5	99%	-
3	No Co catalyst (Zn 40 mol%)	-	25%
4	No Ti catalyst	-	-
5	No Zn catalyst	-	-
6	No $Et_3N·HCl$	-	-
7	$Et_3N·HCl$ (0.5 eq)	40%	-

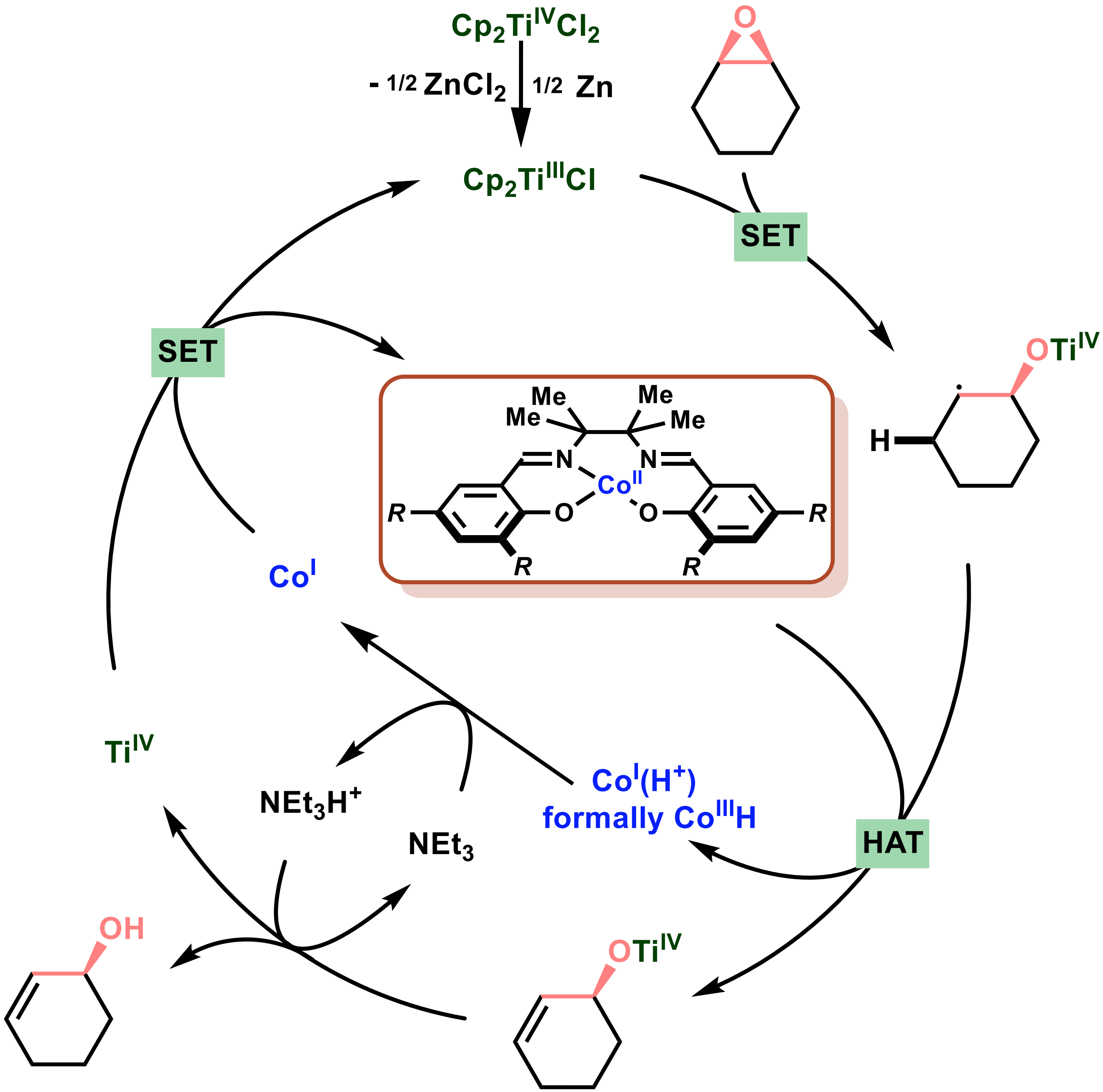


[Co] 4, $R^1 = R^2 = Me$

[Co] 5, $R^1 = CF_3$, $R^2 = {}^tBu$

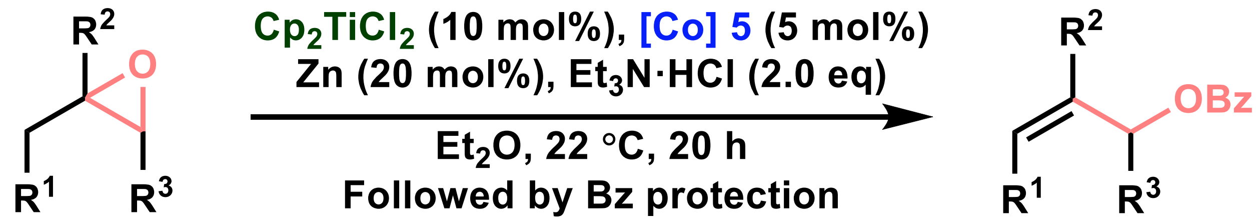
K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

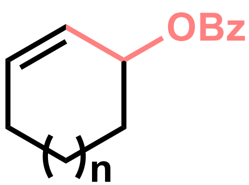
Proposed Catalytic Cycle



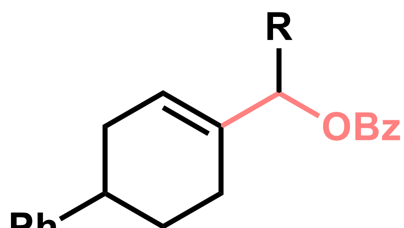
K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

Substrate Scope

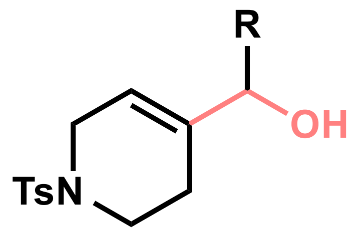




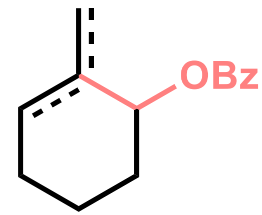
n = 0, 84%
n = 2, 85%
n = 3, 90%



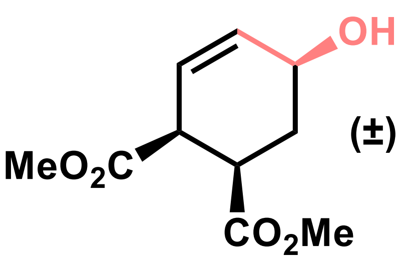
R = H, 70%
R = Me, 69%



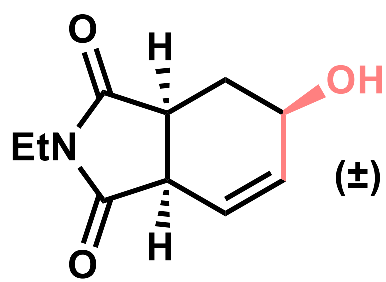
R = H, 95%
R = Me, 90%



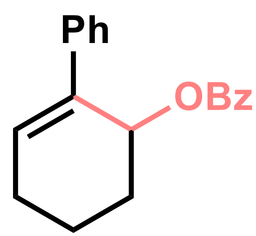
with [Co] 4; 88%
(71:29 *endo/exo*)
with [Co] 5; 73%
(39:61 *endo/exo*)



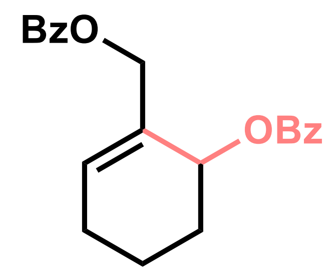
92%
no epimerization



98%
no epimerization



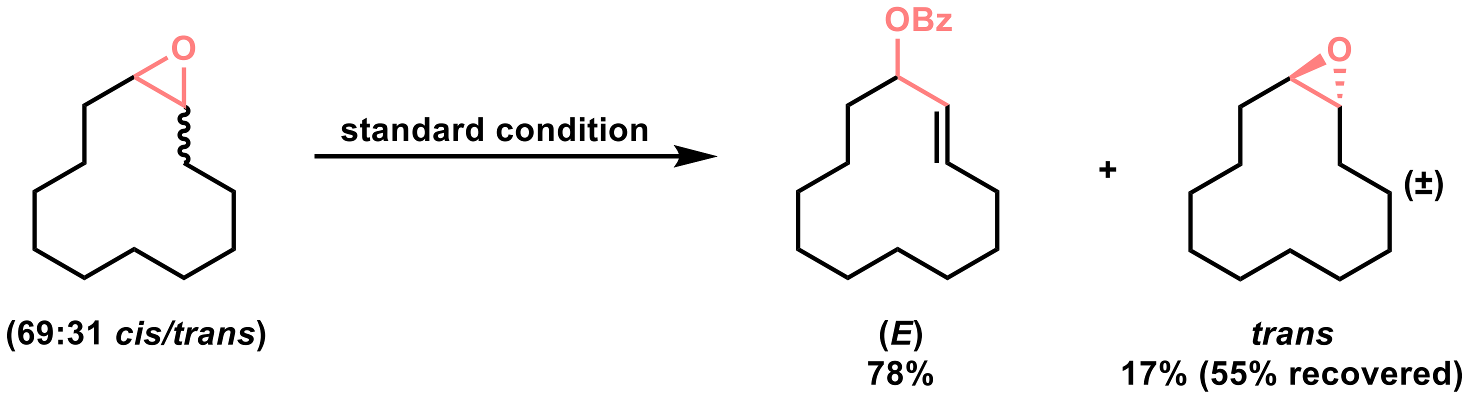
48%, 94% ee
(from 94% ee epoxide)

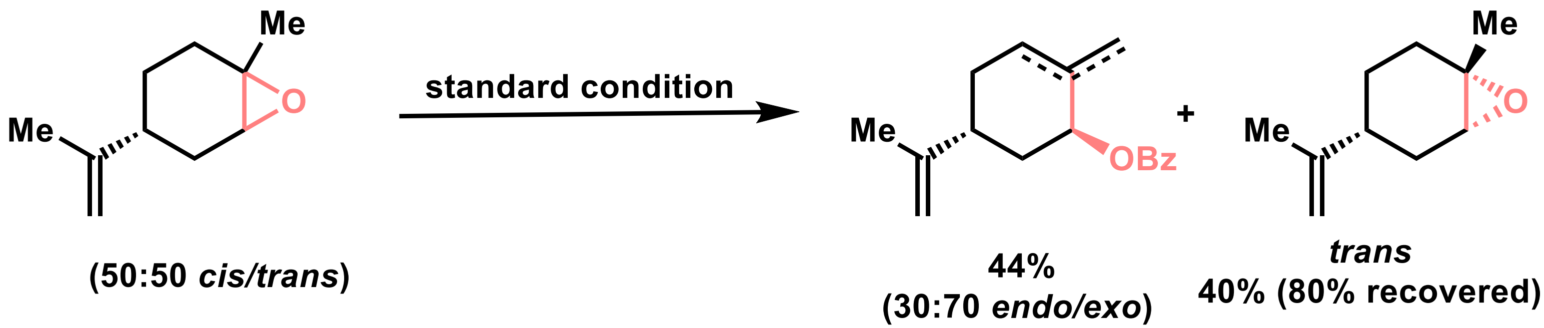


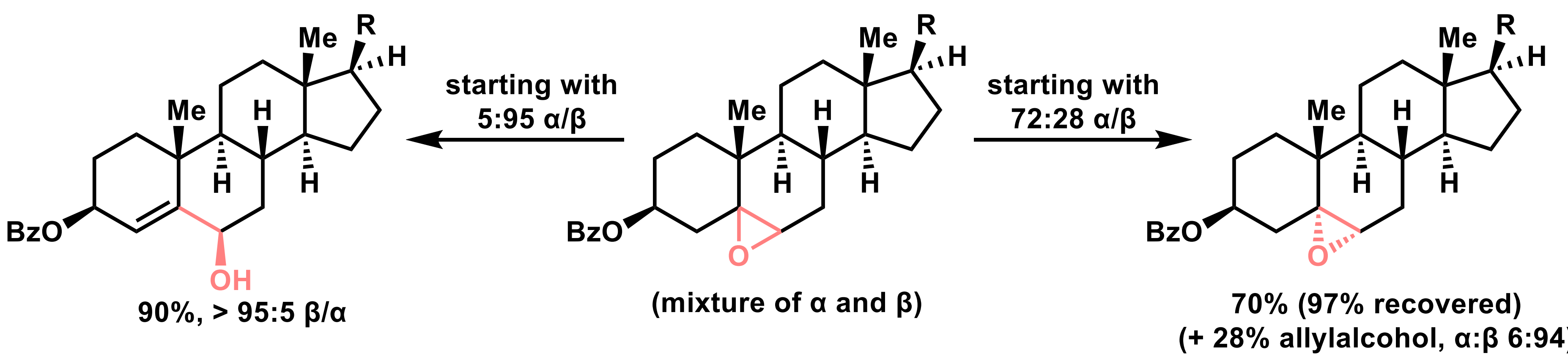
67%, 95% ee
(from 94% ee epoxide)

K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

Kinetic Resolution

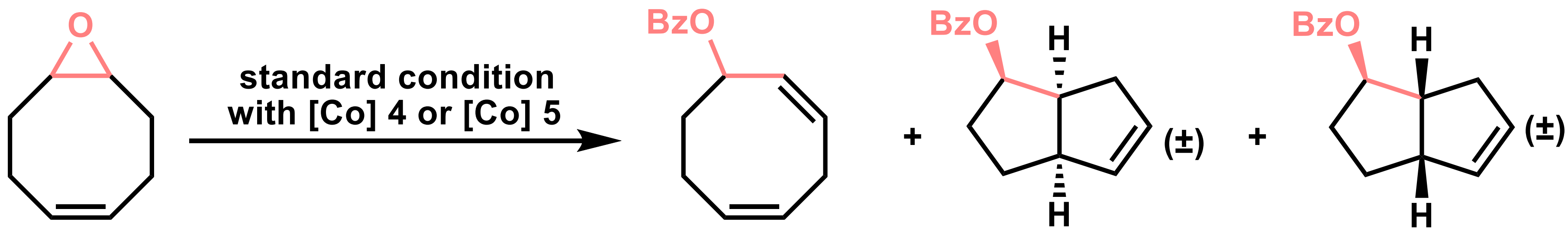




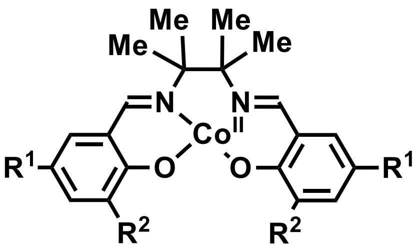


K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

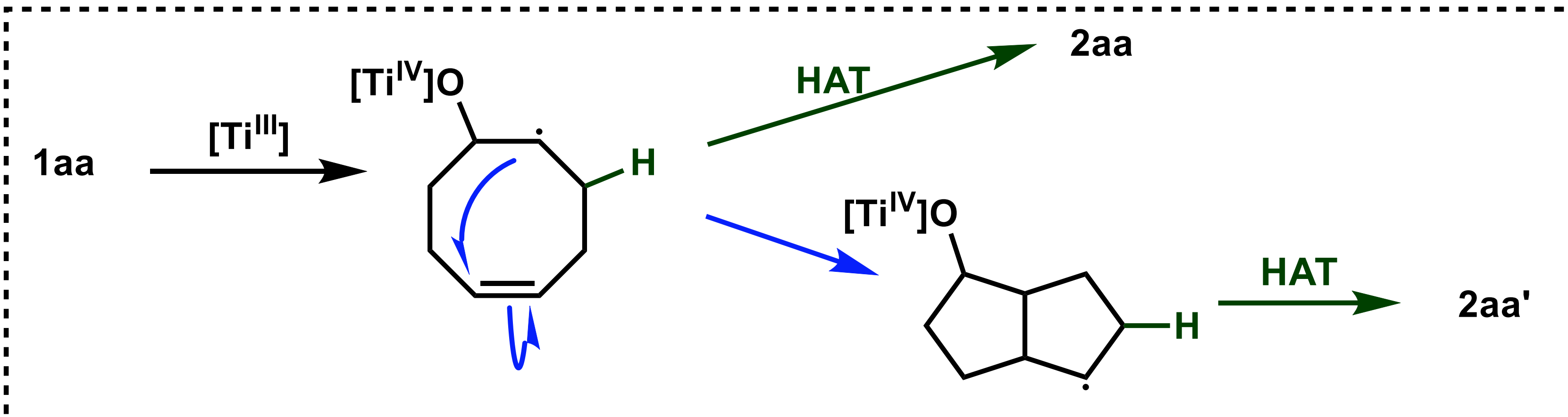
Radical Rearrangement



[Co]	Yield	2aa:2aa'
4 (5 mol%)	71%	57:43
5 (5 mol%)	78%	80:20
5 (10 mol%)	75%	> 95:5

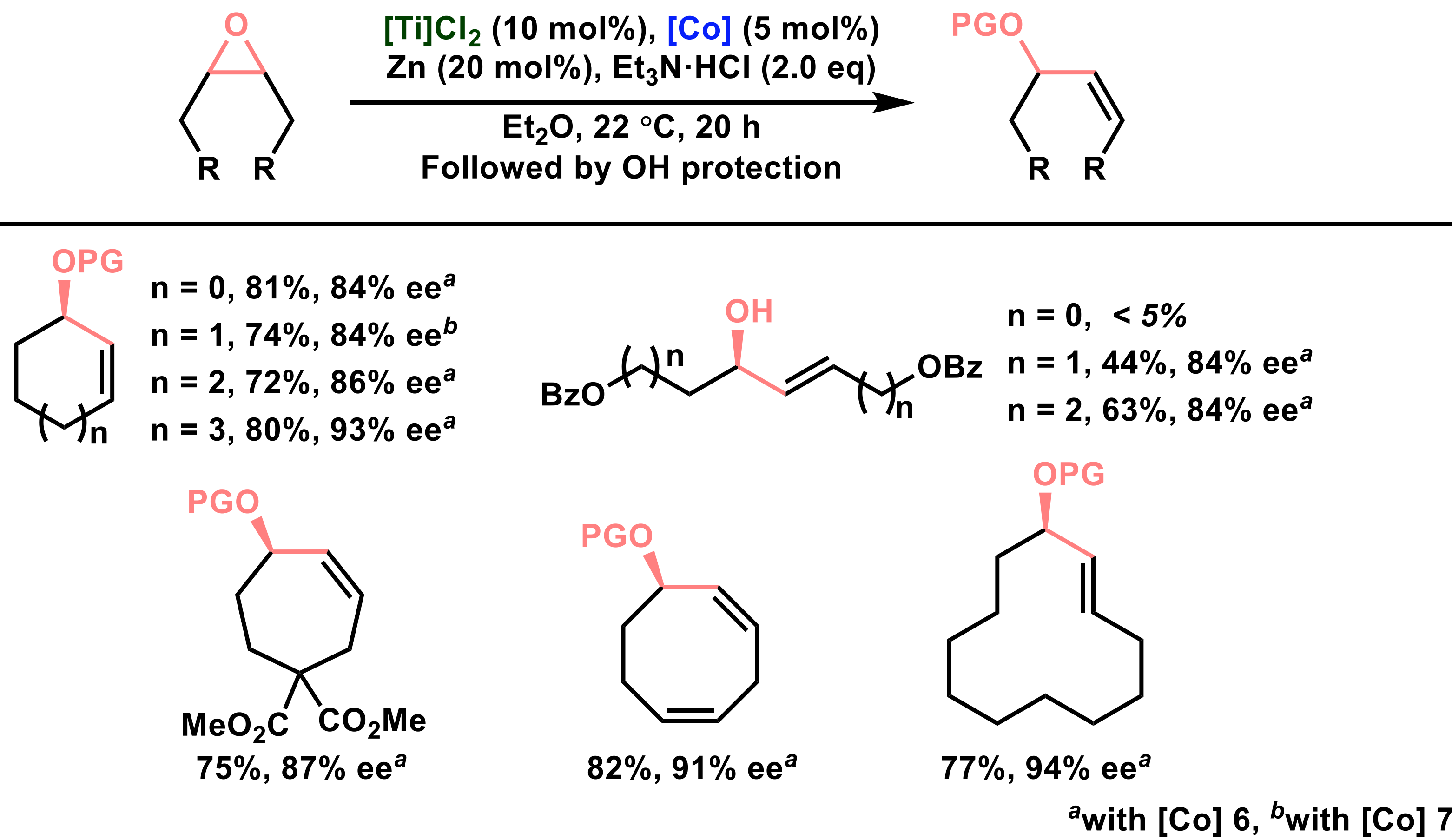


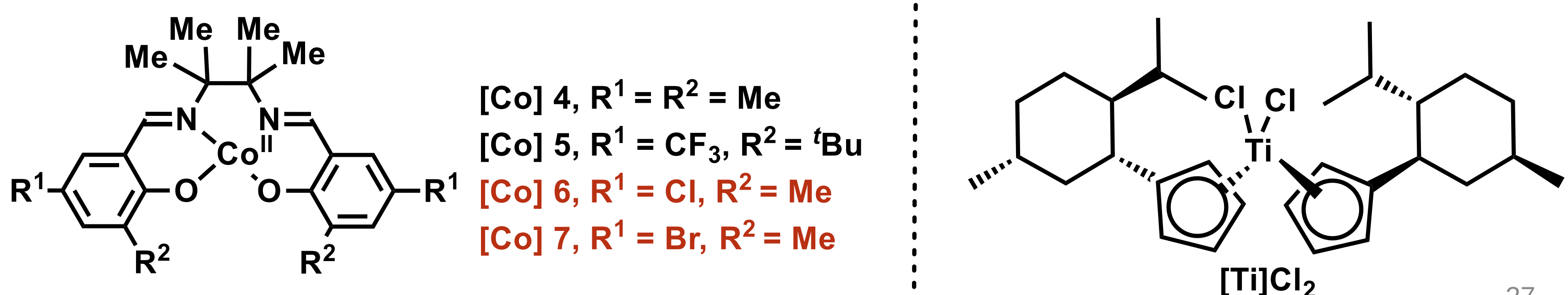
[Co] 4, $R^1 = R^2 = Me$
[Co] 5, $R^1 = CF_3$, $R^2 = {}^tBu$



K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

Asymmetric Reaction





K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

Contents

4. Recent Achievements

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: *J. Am. Chem. Soc.* 2019, 141, 9548−9554
pubs.acs.org/JACS

Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols

Ke-Yin Ye,[†,‡,§] Terry McCallum,[‡,§] and Song Lin*[‡]

[†]College of Chemistry, Fuzhou University, Fuzhou, 350116, P.R. China
[‡]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States

RESEARCH
Science

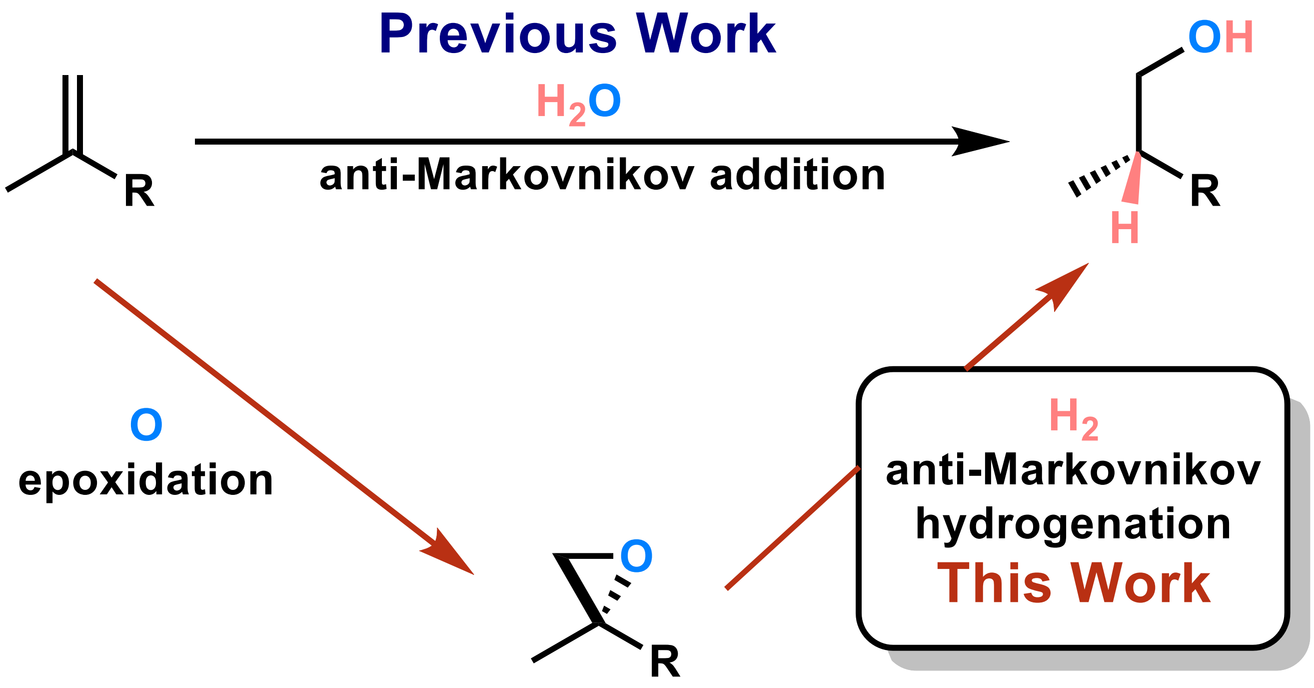
ORGANIC CHEMISTRY

Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis

Chengbo Yao[1], Tobias Dahmen[2], Andreas Gansäuer[3]*, Jack Norton[1]*

Science **364** (6442), 764-767.
DOI: 10.1126/science.aaw3913

Anti-Markovnikov alcohols



C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

Previous Work

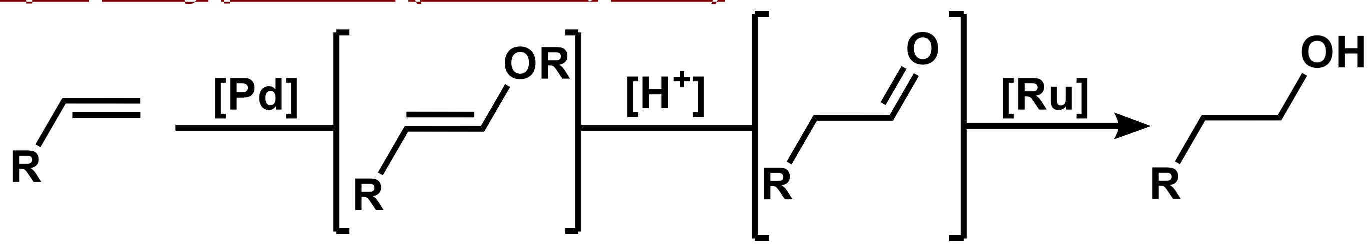
anti-Markovnikov H_2O addition

1. hydroboration and oxidation

- × stoichiometric reactions

K. Burgess, M. J. Ohlmeyer. *Chem. Rev.* **1991,** *91,* 1179.

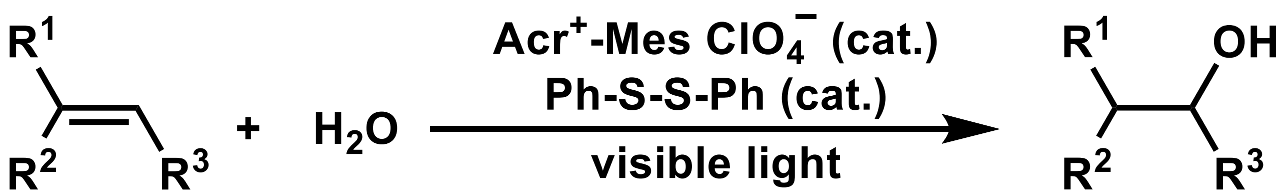
2. triple relay process (Grubbs, 2011)



- × only monosubstituted styrenes

R. H. Grubbs. *et al. Science.* **2011,** *333,* 1609.

3. visible-light-mediated anti-Markovnikov hydration (Lei, 2017)

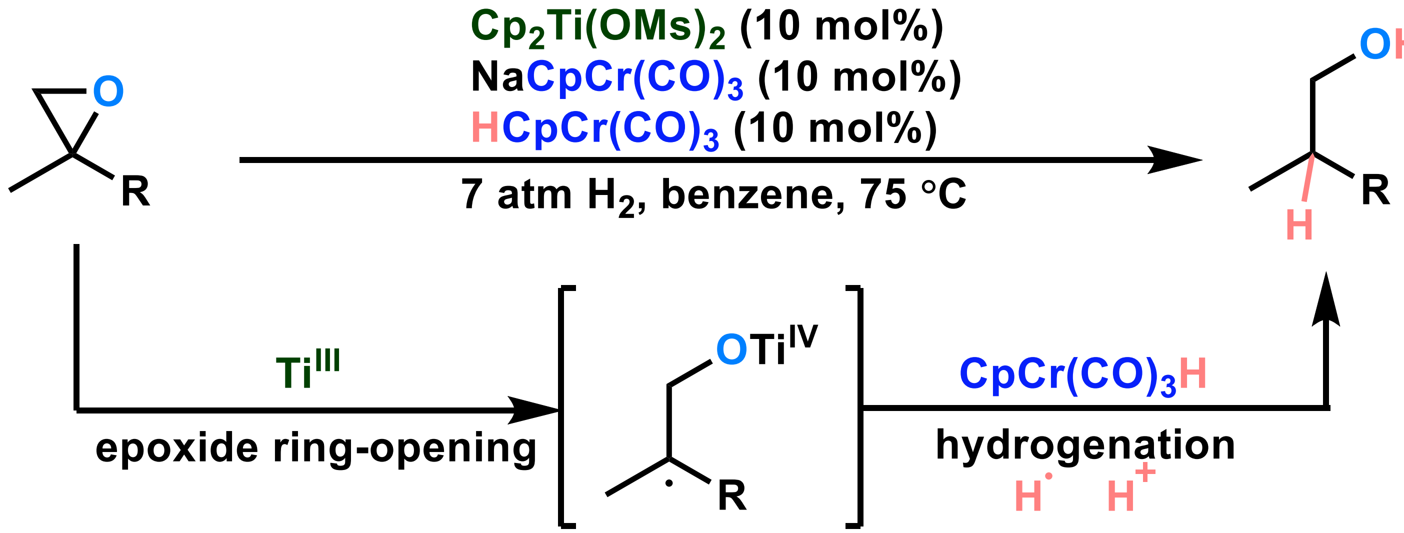


- ✓ metal-free reaction
- × only styrene derivatives

D. A. Nicewicz. *et al. Nat, Chem.* **2014,** *6,* 720.
A. Lei. *et al. ACS Catal.* **2017,** *7,* 1432.

This Work

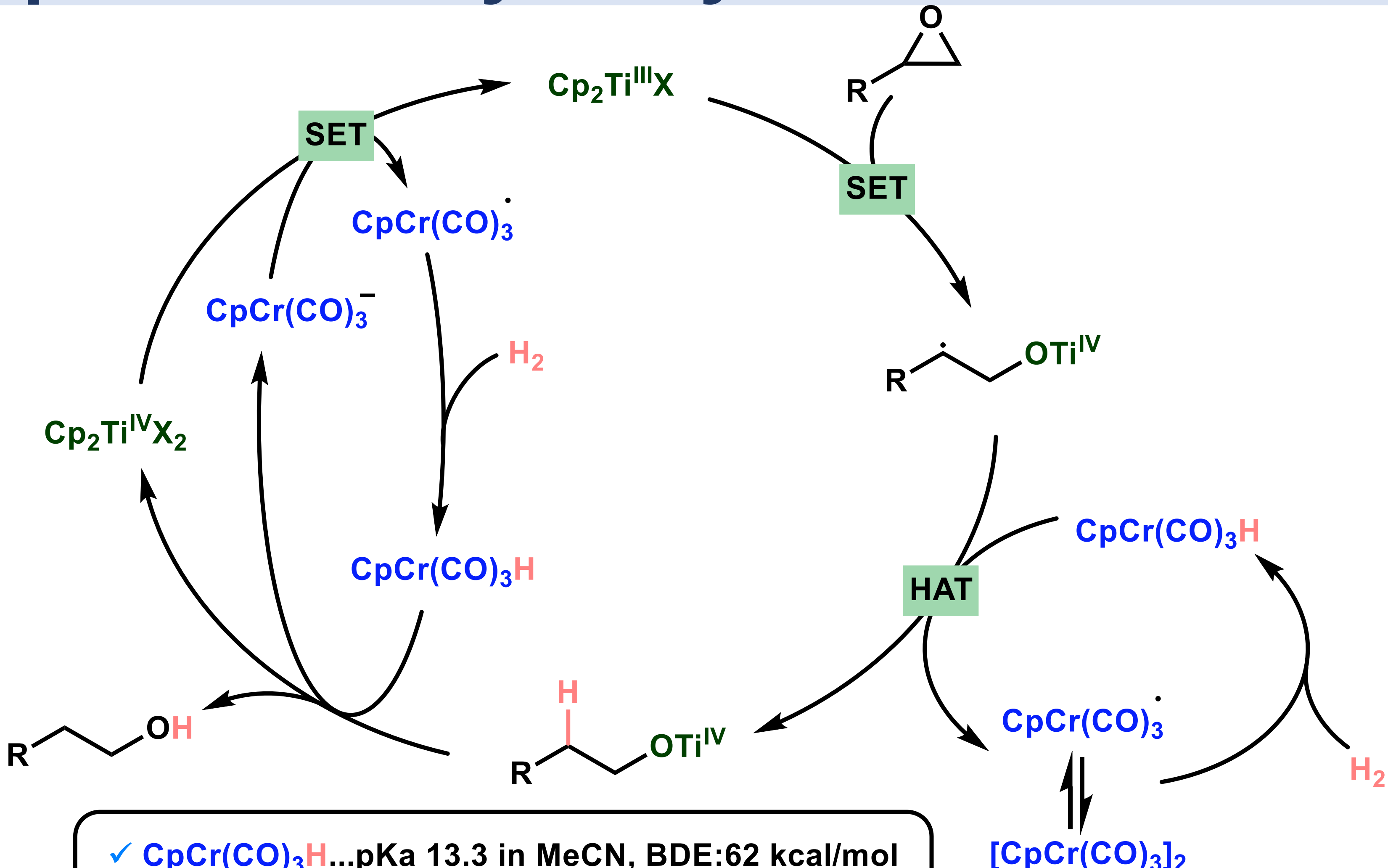
anti-Markovnikov alcohols via epoxide hydrogenation



Entry	Conditions	Time	Yield
1	standard condition	24 h	58%
2		72 h	95%
3	No Ti catalyst	24 h	7%
4		72 h	29%
5	No Cr catalyst	72 h	0%
6	5 mol% instead of 10 mol% for all catalysts	72 h	81%

C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

Proposed Catalytic Cycle

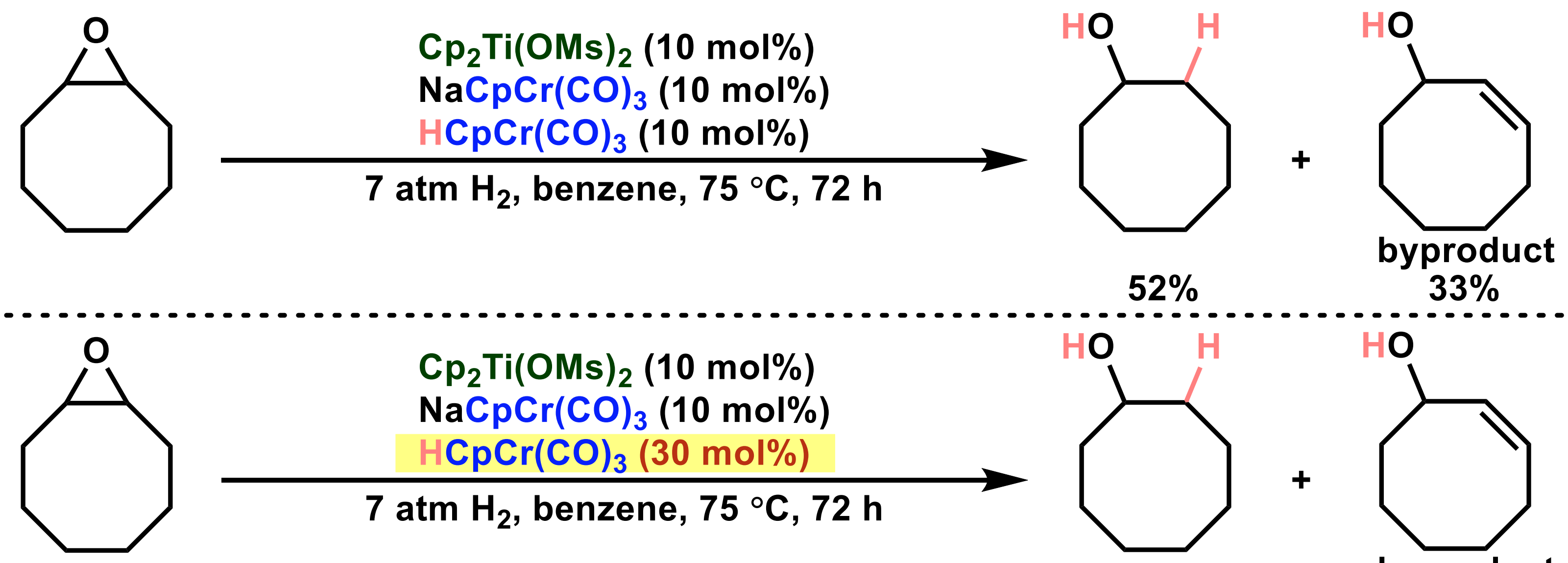


✓ $CpCr(CO)_3H$...pKa 13.3 in MeCN, BDE:62 kcal/mol cleaving the Ti^{IV} alkoxide by protonolysis

✓ $CpCr(CO)_3^-$ ...good one-electron reducing agent -0.67 V (vs Fc/Fc^+ in MeCN)

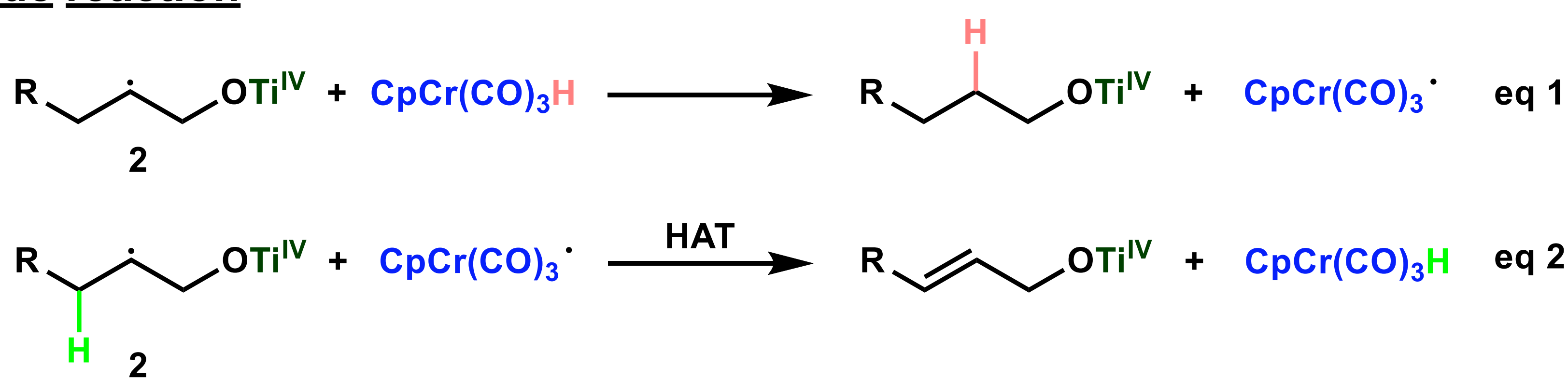
C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

Side Reaction



✓ Allyl alcohol byproduct is suppressed.

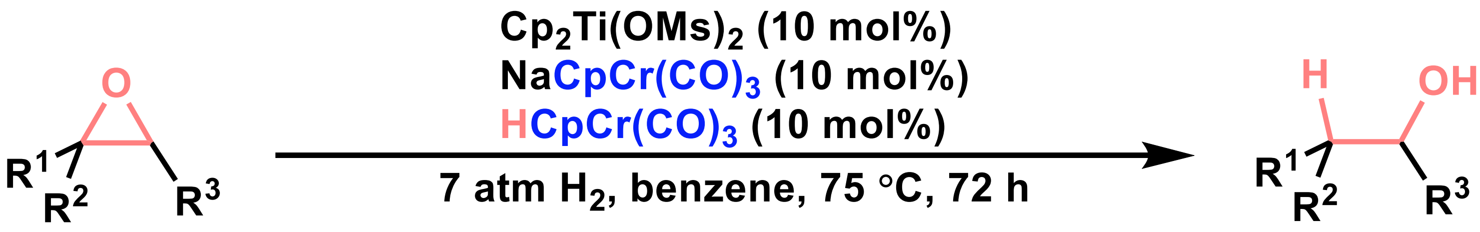
side reaction

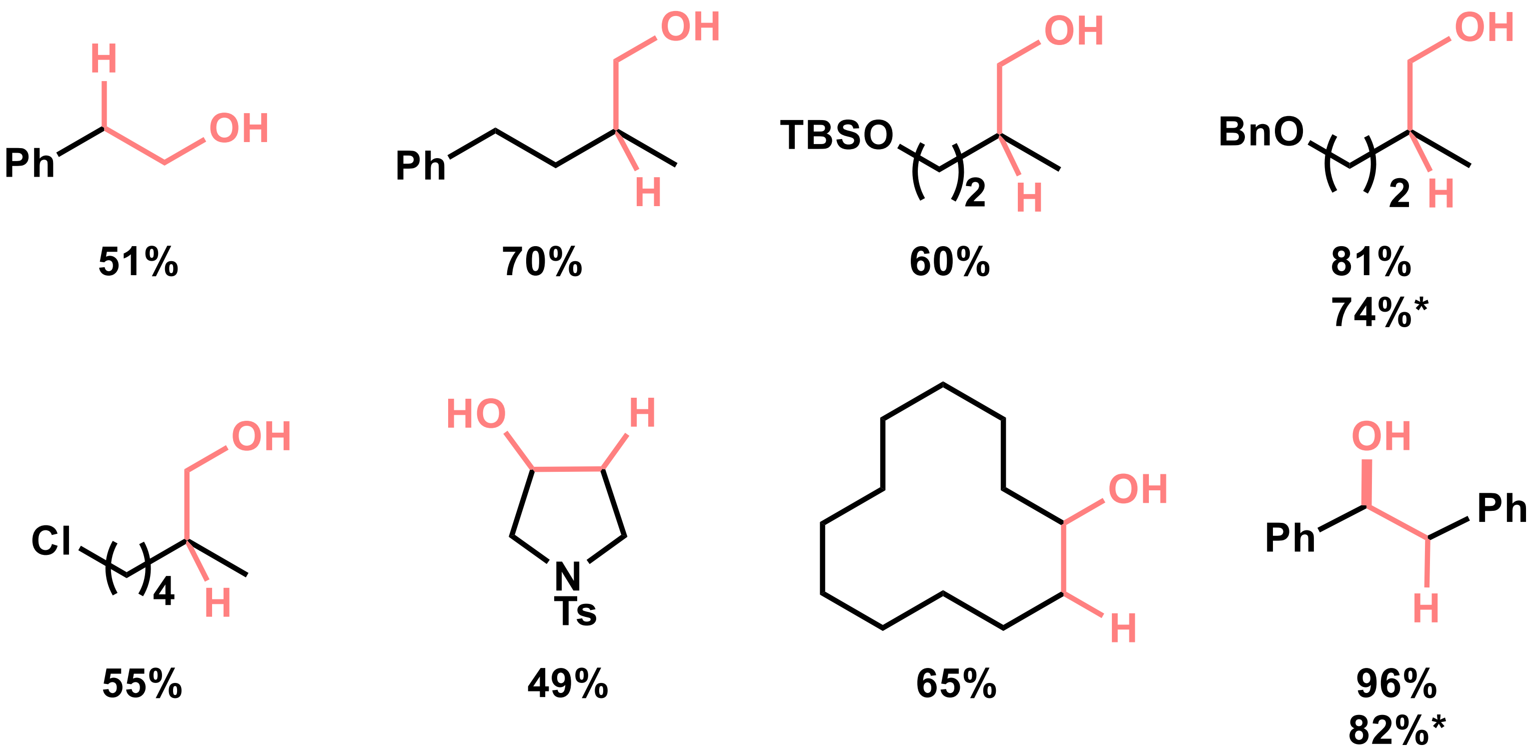


➢ The addition of extra $CpCr(CO)_3H$ gives an elevated rate of H· transfer to 2 (eq 1) and competes effectively for 2 with H· abstraction by $CpCr(CO)_3^{\bullet}$ (eq 2).

C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

Substrate Scope

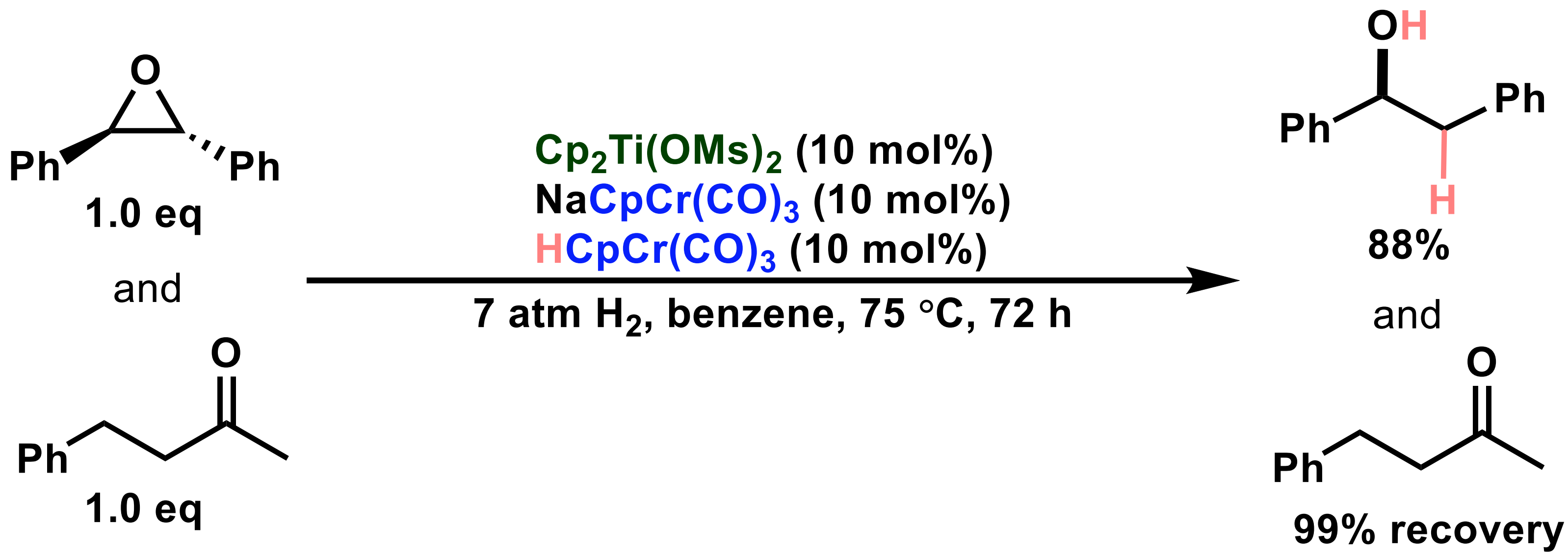


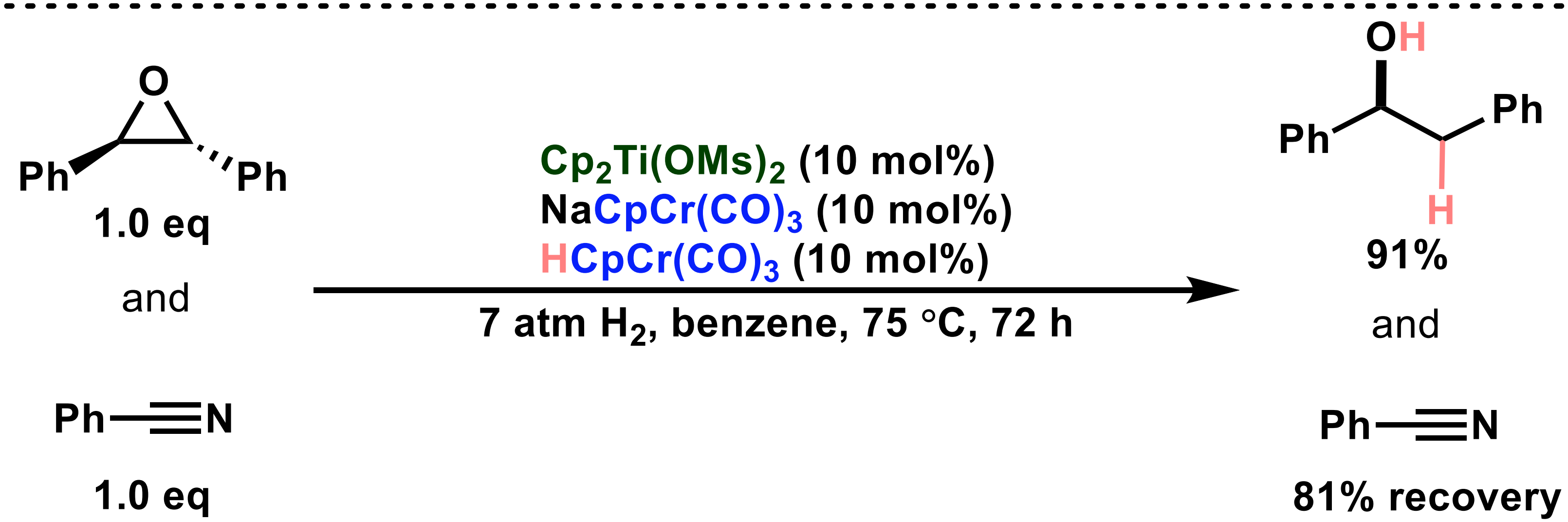


*gram-scale reaction

C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

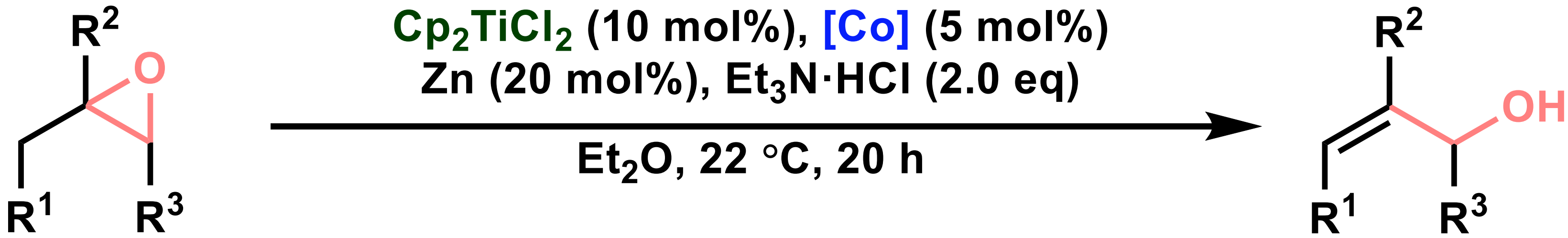
Substrate Scope





C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

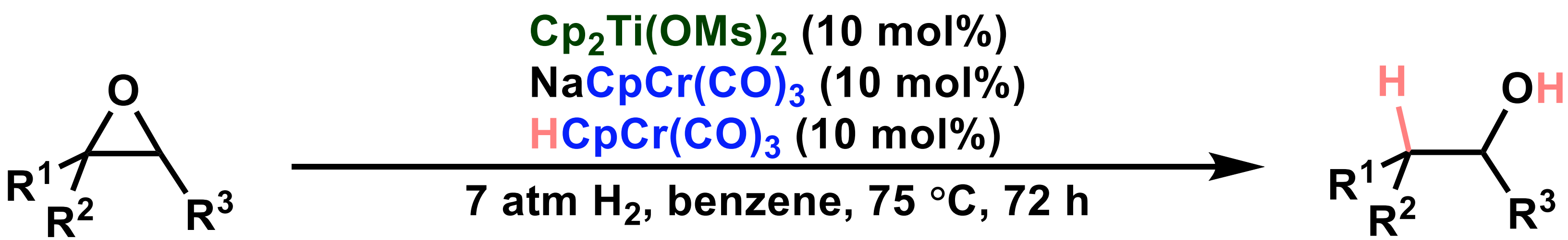
Summary



30 examples
48-99% yield

13 examples
44-85% yield
48-94% ee

- ✓ no stoichiometric reductant
- ✓ strong base-free
- ✓ enantioselectivity

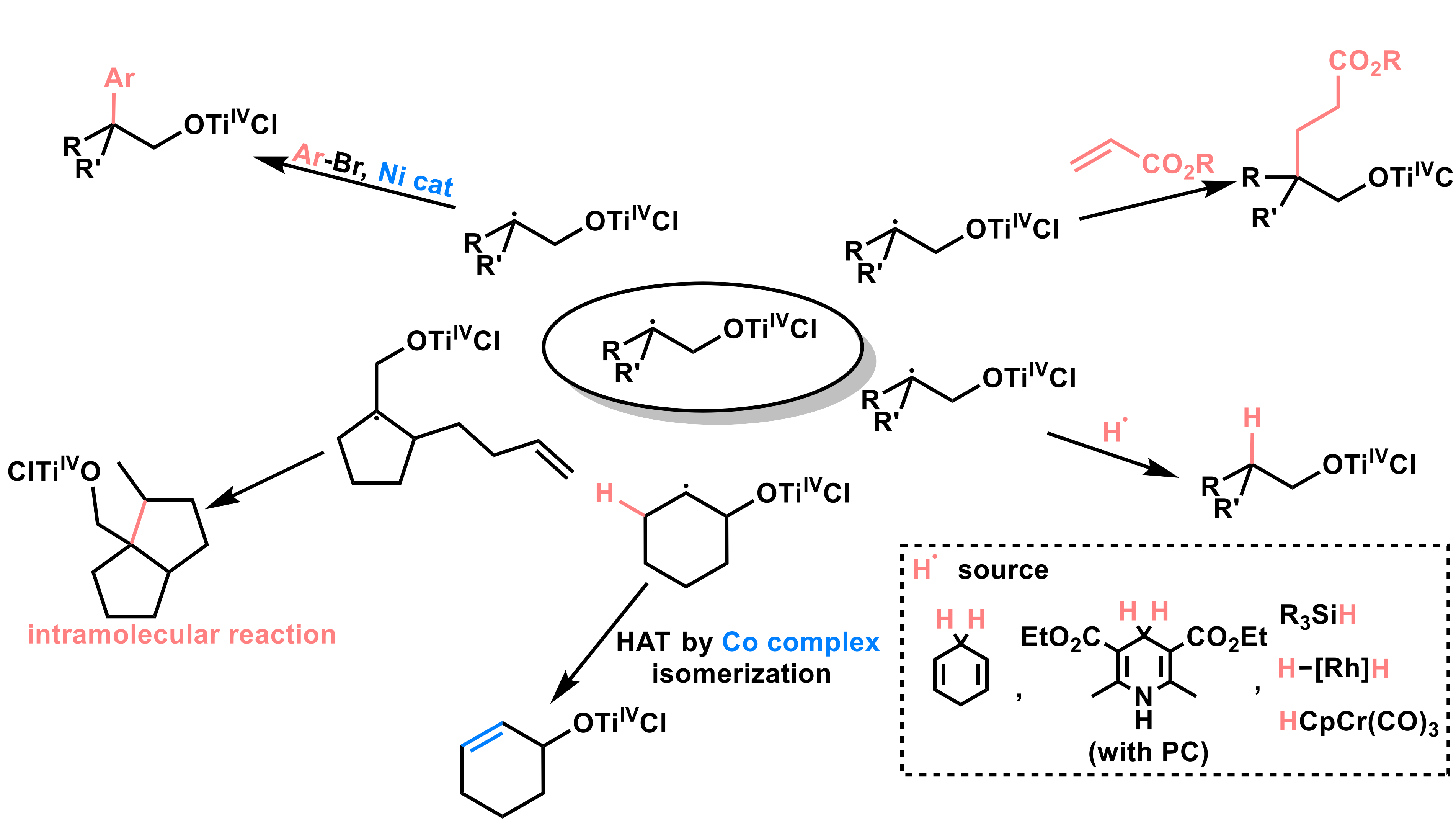


14 examples
48-95% yield

- ✓ no stoichiometric metal reductant
- ✓ anti-Markovnikov regioselectivity
- ✓ excellent atom economy

Appendix

Titanocene-catalyzed Epoxide Opening

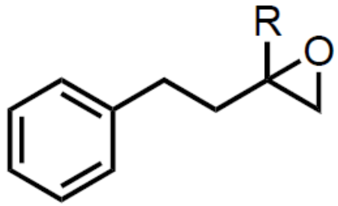


Unsuccessful Substrates

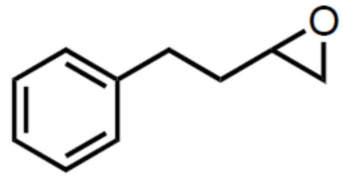
Isomerization of epoxides to Allylic Alcohols

R = H, OBz

S1



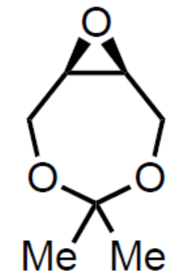
S2



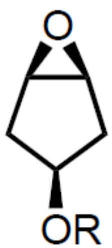
S3

S4

(X = O, NTs, NBoc)

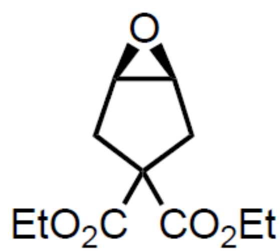


S5

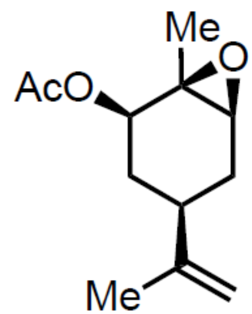


S6

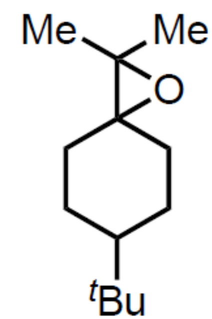
(R = Ac, TBS, Bz)



S7

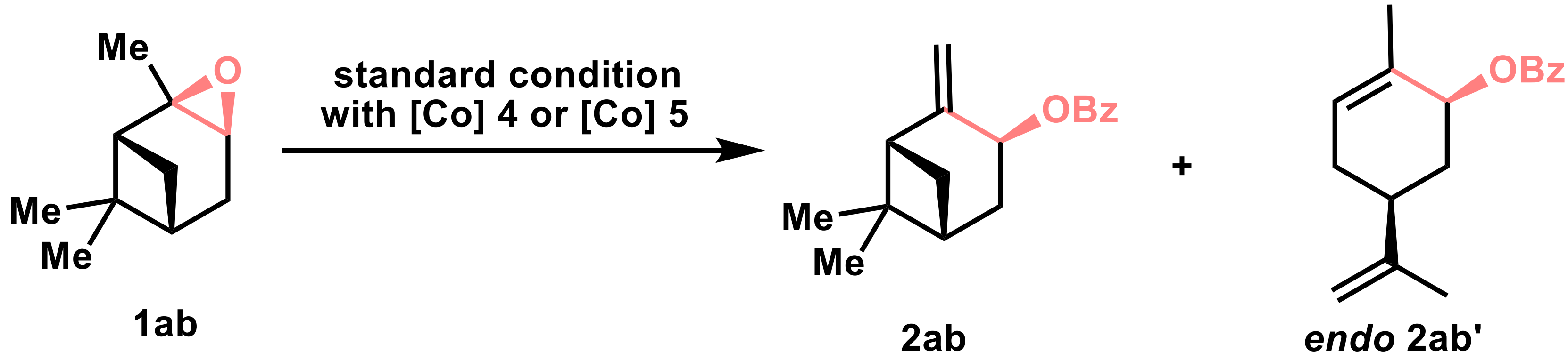


S8

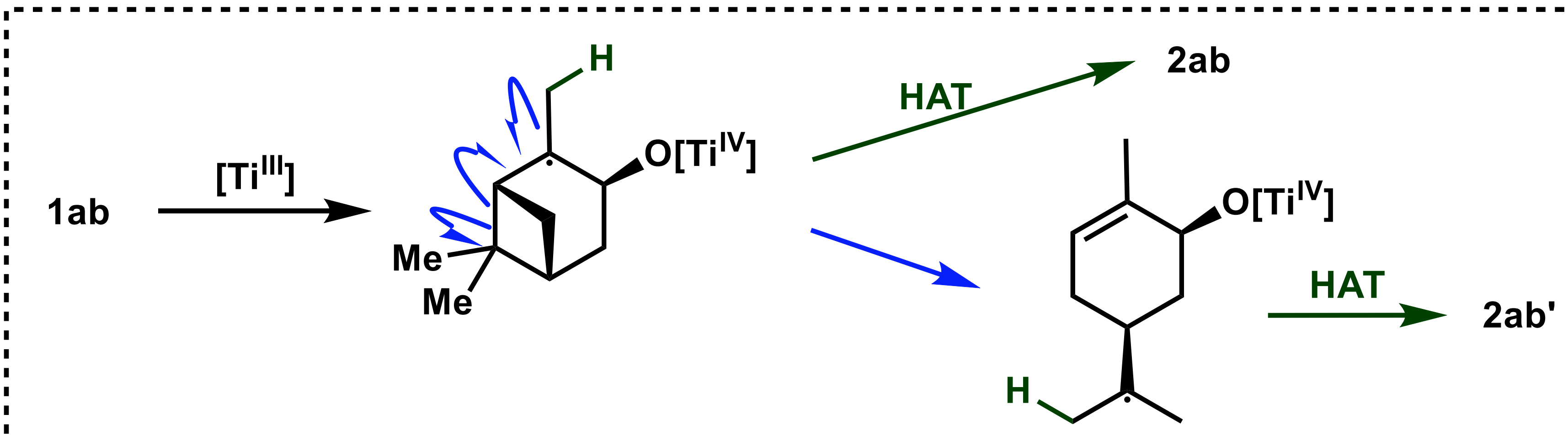


S9

Radical Rearrangement



[Co]	Yield	2ab:2ab'
4 (5 mol%)	88%	33:67
5 (5 mol%)	82%	64:36



K. Y. Ye, T. M. Callum, S. Lin. *J. Am. Chem. Soc*. **2019**, *141*, 9548.

Cyclic Voltammetry Studies

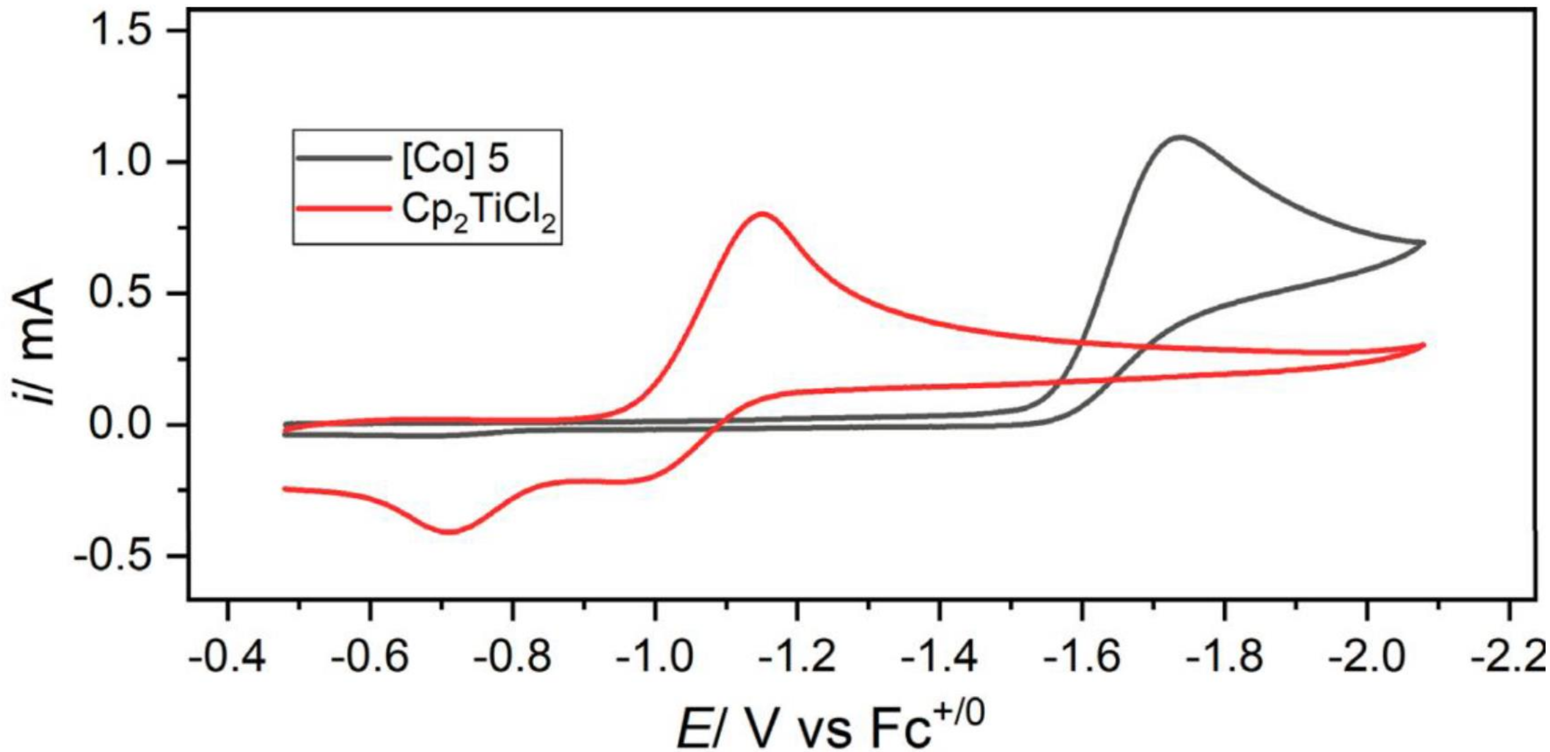
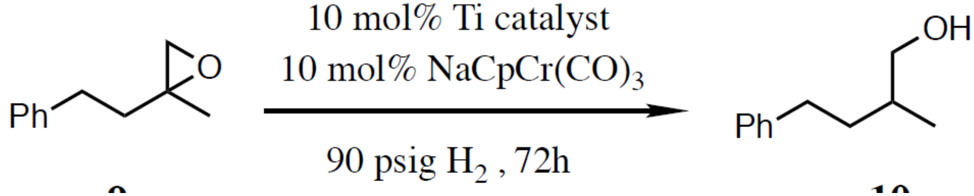


Figure S1. Cyclic voltammogram of [Co] **5** and Cp_2TiCl_2. Conditions: $TBAPF_6$ (0.20 M in MeCN) with (a) [Co] **5** (2.0 mM), $E_{p/2}(Co^{II/I}) = -1.65$ V vs $Fc^{+/0}$ for [Co] **5**; (b) Cp_2TiCl_2 (2.0 mM), $E_{p/2}(Ti^{IV/III}) = -1.06$ V vs $Fc^{+/0}$ for [Co] **5**. Scan rate: 100 mV/s. The two oxidative waves for the Cp_2TiCl_2 complex are likely due to MeCN coordination or loss of Cl^- ligand.

Optimization of anti-Markovnikov hydrogenation



entry	Ti Catalyst	$CpCr(CO)_3H$/mol %	Temp/°C	Solvent	% Yield†
1	Cp_2TiCl_2	0	55	THF	41
2	Cp_2TiCl_2	0	75	benzene	65
3	Cp_2TiCl_2	0	75	CH_3CN	38
4	Cp_2TiCl_2	0	55	$CDCl_3$	0
5	$Cp^*{}_2TiCl_2$	0	75	benzene	38
6	$(C_5H_4Me)_2TiCl_2$	0	75	benzene	56
7	Cp^*TiCl_3	0	75	benzene	15
8	$Cp_2Ti(OTf)_2$	0	75	benzene	0
9	$Cp_2Ti(TFA)_2$	0	75	benzene	75
10	$Cp_2Ti(TFA)_2$	10	75	benzene	80
11	$Cp_2Ti(OMs)_2$	10	75	benzene	95
12	$Cp_2Ti(OMs)_2$	10	75	toluene	92

NMR Studies

protonolysis of $Cp_2TiX(OR)$ → $Cp_2TiCl(OEt)$ as the model compound

$Cp_2TiCl(OEt)$ (1 eq) + $CpCr(CO)_3H$ (1 eq) —(CD_3CN, 48 h)→ ^1H NMR analysis

observation of free EtOH

electron transfer from $NaCpCr(CO)_3$ to Cp_2TiX_2

$Cp_2Ti(TFA)_2$ (1 eq) + $NaCpCr(CO)_3$ (1 eq) —(d_8-THF, H_2, 18 h)→ ^1H NMR analysis

observation of $CpCr(CO)_3H$

C. Yao, T, Dahmen, A. Gansäuer, J. Norton. *Science.* **2019**, *364*, 764.

NMR Studies

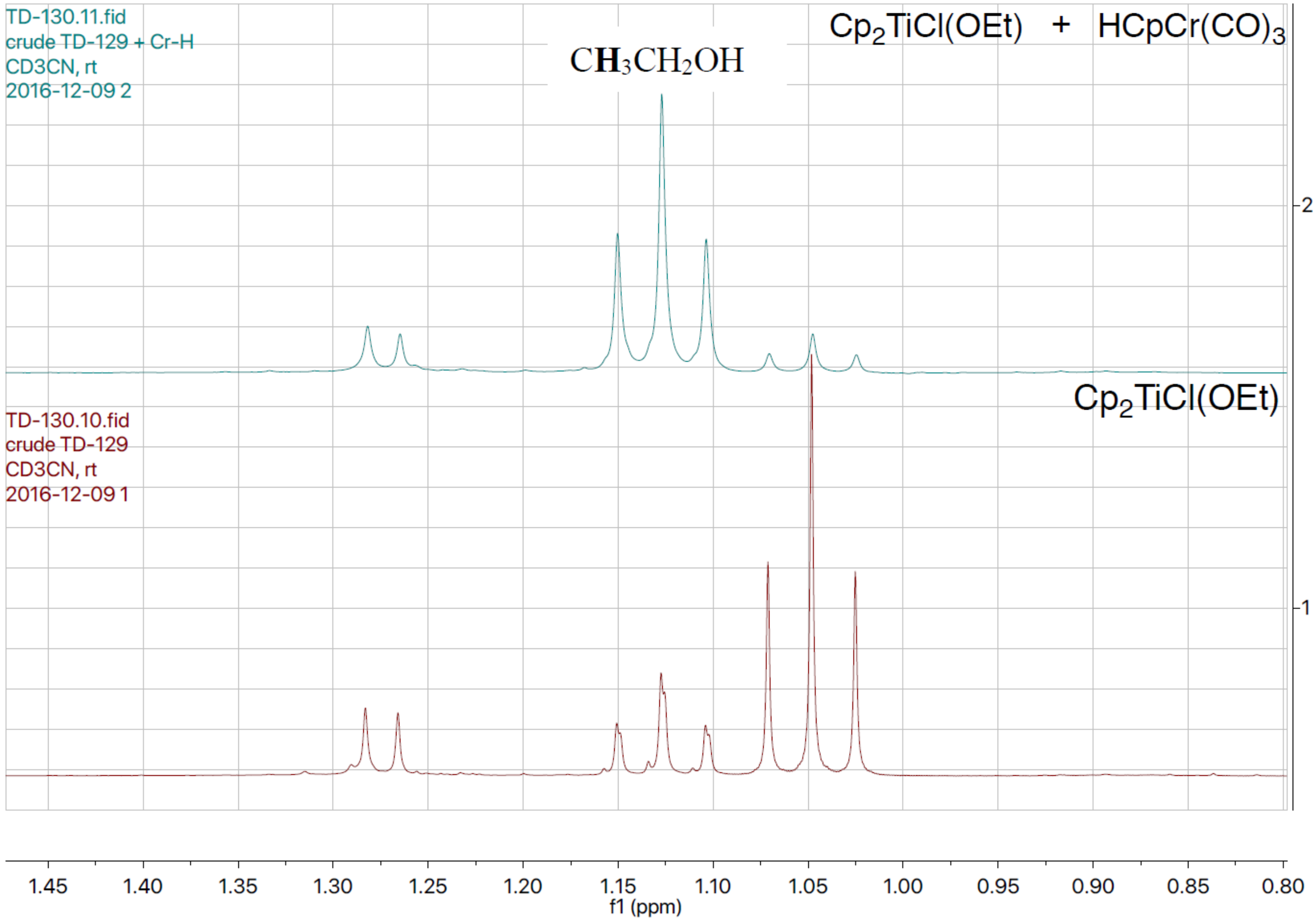


Fig. S2.
Zoom in ^{1}H-NMR of $Cp_2TiCl(OEt)$ (bottom) and the mixture of $Cp_2TiCl(OEt)$ and $CpCr(CO)_3H$ after 48h (top).

NMR Studies

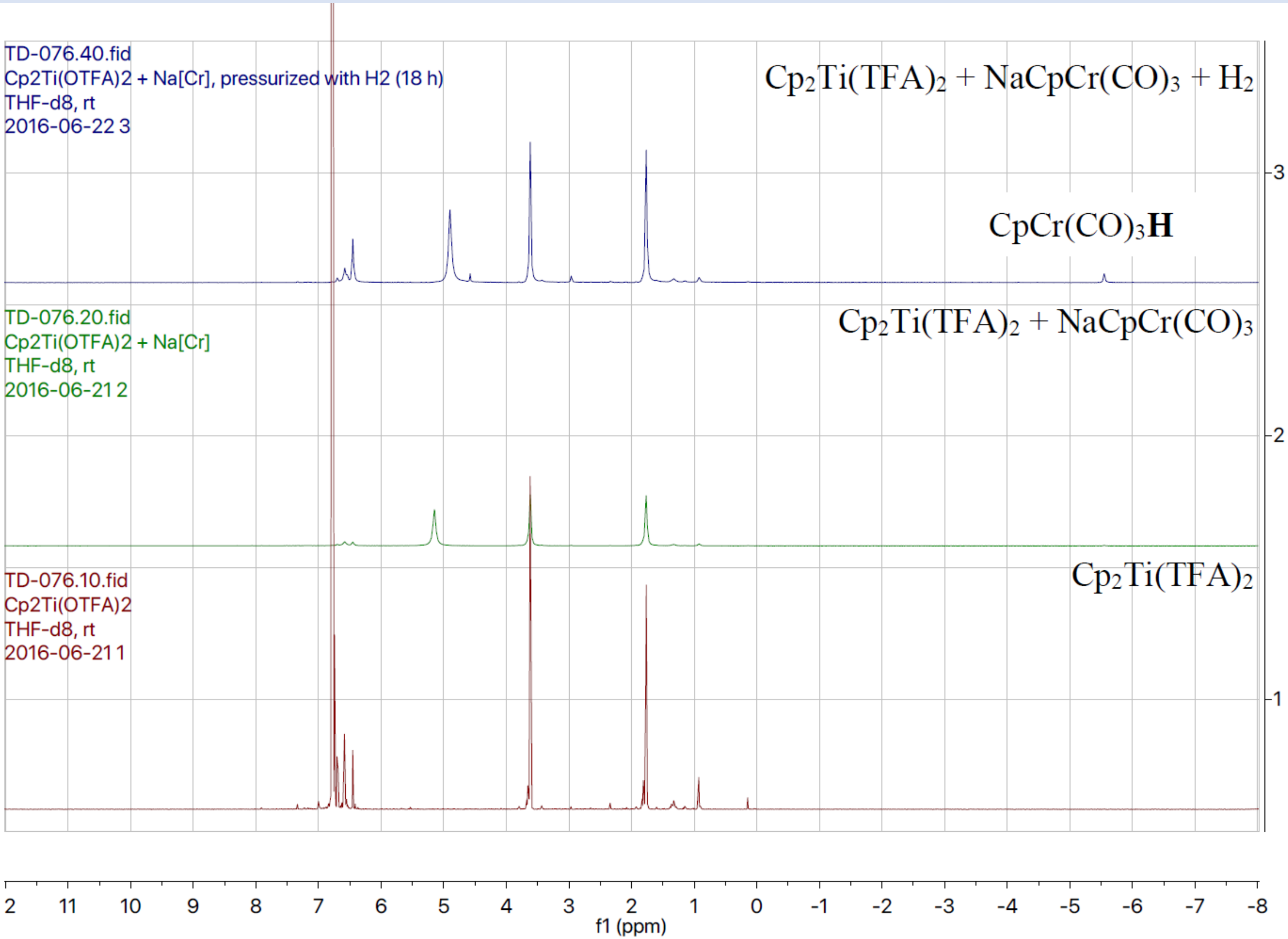


Fig. S3.
[1]H-NMR of $Cp_2Ti(TFA)_2$ (bottom), mixture of $Cp_2Ti(TFA)_2$ + $NaCpCr(CO)_3$ (middle), mixture after 18h pressurization with H_2 (top).

Cyclic Voltammetry Studies

Table 1. CV data for the reduction of Cp_2TiX_2 (**1–6**) in THF in terms of peak potentials for the cathodic wave ($E_{p,c}$) and the two anodic waves ($E_{p,a1}$ and $E_{p,a2}$) recorded at a glassy carbon disk electrode in 0.2 M Bu_4NPF_6/THF at a sweep rate of 0.2 $V{\cdot}s^{-1}$.[a]

Complex	$E_{p,c}$ [V]	$E_{p,a1}$ [V]	$E_{p,a2}$ [V]
1, X=Cl	−1.37[b]	−1.23[b]	–[b]
2, X=OTf	−1.05	−0.31	–
3, X=OTs	−0.96	−0.81	−0.70
4, X=OMs	−1.03	−0.92	−0.62[c]
5, X=TFA	−1.08	−0.98	−0.58
6, X=CSA	−1.05	−0.93	−0.64

[a] All potentials are given in units of V vs. Fc^+/Fc and can be converted to V vs. saturate calomel electrode (SCE) by adding 0.52 V. [b] Not visible at the sweep rates used here.[12] [c] Recorded at a sweep rate of 0.5 $V{\cdot}s^{-1}$.

Table 1. CV Data for the Reduction of Titanocene Dichlorides 1−9 in THF in Terms of Peak Potentials for the Cathodic Wave ($E_{p,c}$) and the Two Anodic Waves ($E_{p,a1}$ and $E_{p,a2}$) Along with the Determined Standard Potential (E_1°)[a]

compound	$E_{p,c}$ [b]	$E_{p,a1}$ [b]	$E_{p,a2}$ [b]	E_1° [c]
Kagan's complex (**1**)[18]	−1.44	−1.32		−1.37[13f]
$(C_5H_4tBu)CpTiCl_2$ (**2**)[20]	−1.39	−1.27		−1.36
$(C_5H_4tBu)_2TiCl_2$ (**3**)[21]	−1.36	−1.25		−1.34[13f]
Cp_2TiCl_2 (**4**)	−1.36	−1.24		−1.27[13b]
$(C_5H_4Cl)CpTiCl_2$ (**5**)[22]	−1.26	−1.15		−1.20
$(C_5H_4COOMe)CpTiCl_2$ (**6**)[23]	−1.20	−1.09	−0.85	−1.15
$(C_5H_4Cl)_2TiCl_2$ (**7**)[22,24]	−1.18	−1.08		−1.12
$(C_5H_4COOMe)_2TiCl_2$ (**8**)[25]	−1.08	−0.92	−0.74	−1.01
$(C_5H_4CN)CpTiCl_2$ (**9**)[10]	−1.06		−0.85	−1.00

[a]All potentials are given in units of V vs Fc^+/Fc and can be converted to V vs SCE by adding 0.52 V.[13b,26] [b]Recorded at a glassy carbon disk electrode with ν = 0.1 V s^{-1} in 0.2 M Bu_4NPF_6/THF. [c]Determined by digital simulation (see the Supporting Information).