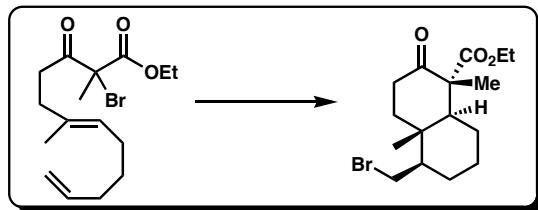
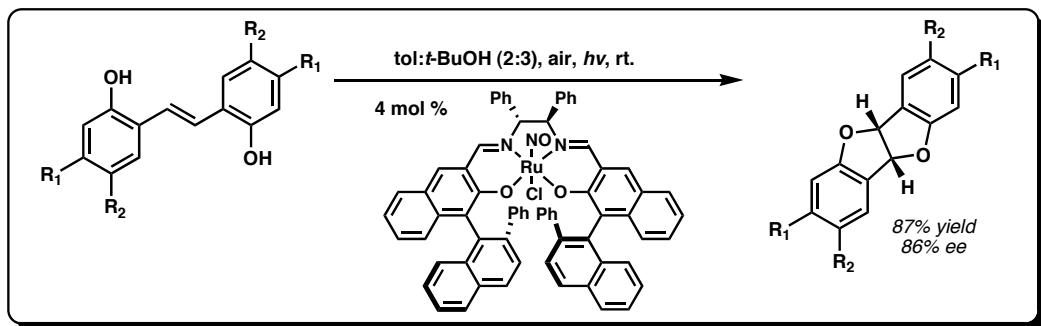


Enantioselective Radical Reactions



Stoltz Group Literature Talk
Monday May 10, 2004
Jeff Bagdanoff



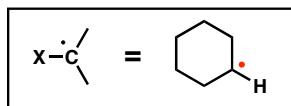
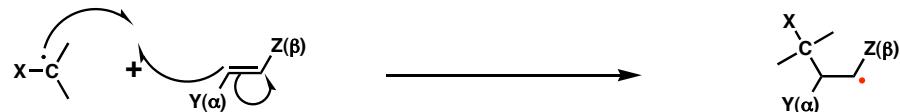
Enantioselective Radical Reactions Contents

1. Introduction to Radical Reactivity
2. Molecular Orbital Interactions
3. Chiral Lewis Acids
 - a. Conjugate Reduction
 - b. Conjugate Addition
 - c. Addition/Trapping
 - d. Cyclizations
4. Halogen Transfer (Rh)
5. Radical Reagents
6. Electron Transfer Reactions (Reduction)
 - a. Homodimerization of Olefins
 - b. Reductive Cyclizations
 - c. Ketyl Radical Addition
 - d. Epoxide Ring Opening
7. Oxidation
 - a. Coupling
 - b. Benzylic and Other Direct Oxidations
 - c. Oxidative Kinetic Resolution

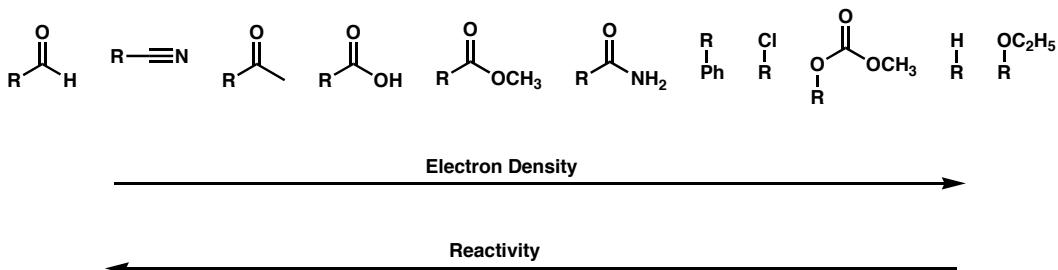
Lead References:

- Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753.
Minisci, F.; Citterio, A. *Adv. Free Radical Chem.* **1980**, *6*.
Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263.
Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 162.
Renaud, P.; Gerster, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2562.

Alkyl Radicals are Nucleophilic: the β effect



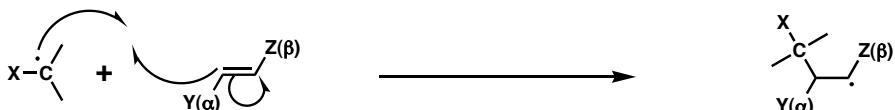
Examining of the nature of Z (when Y = H)



A linear Hammet Plot confirms the dependence of σ -values of Z on reaction rates.

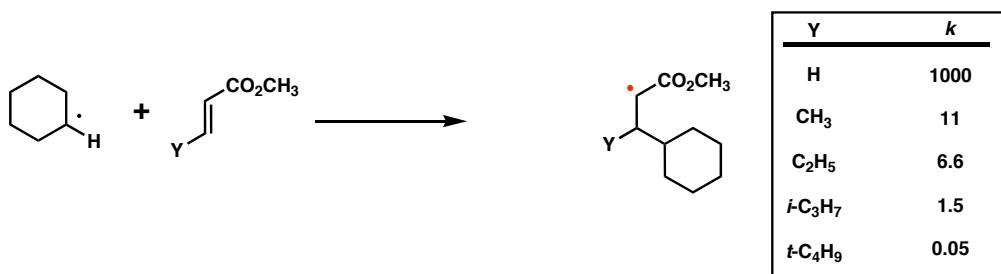
Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 178.

The α - Effect

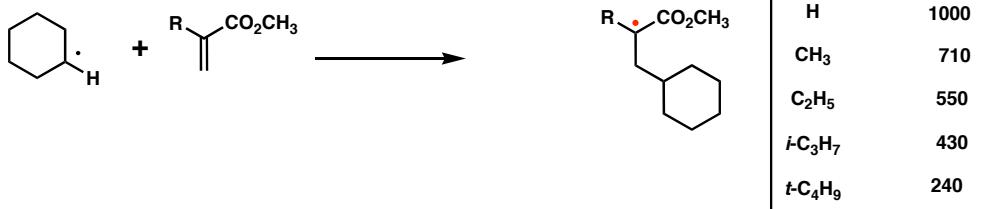


-No Hammet Correlation exists for the reactivity at the carbon bearing Y (α to bond forming center).

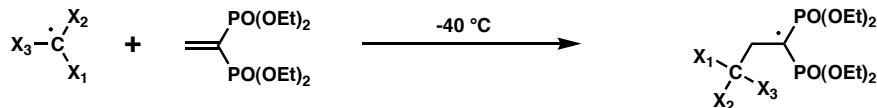
-Principally a steric effect:



- A small steric β - effect is observed.



The Effect of Radical Substituents



X ₁	X ₂	X ₃	k [L·mol ⁻¹ ·s ⁻¹]
H	H	H	2.5·10 ³
CH ₃	H	H	2.6·10 ³
CH ₃	CH ₃	H	1.2·10 ⁴
CH ₃	CH ₃	CH ₃	5.9·10 ⁴

X ₁	X ₂	X ₃	k [L·mol ⁻¹ ·s ⁻¹]
CH ₃	H	H	2.6·10 ³
n-C ₃ H ₇	H	H	5.0·10 ³
CH ₃ O	H	H	6.8·10 ³

Electron releasing substituents increases reactivity.

Increasing substitution on radical substituent increases reactivity with electron deficient alkenes.

t-Bu[·] reacts 24X faster than Me[·]

Remarkable because more substituted radical is more stable and the forming C-C bond is weaker.

[@ 25 °C]

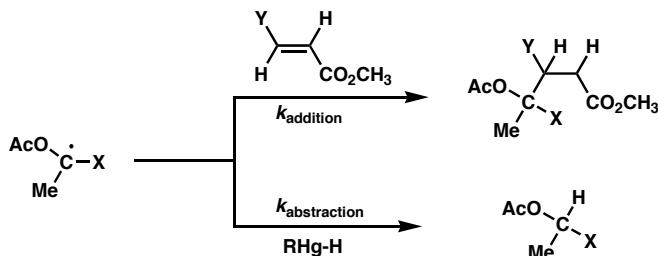
X ₁	X ₂	X ₃	k [L·mol ⁻¹ ·s ⁻¹]
CH ₃	CH ₃	H	4.3·10 ⁶
OAc	CH ₃	H	1.1·10 ⁵
CN	alkyl	H	10 ² ·10 ³

Conversely, electron withdrawing groups decrease reactivity.

Inverse demand radical additions of e⁻ deficient radicals and e⁻ rich olefins are known.

Baban, J. A.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 2* 1981, 161.

Steric Effects on Selectivity of Radicals

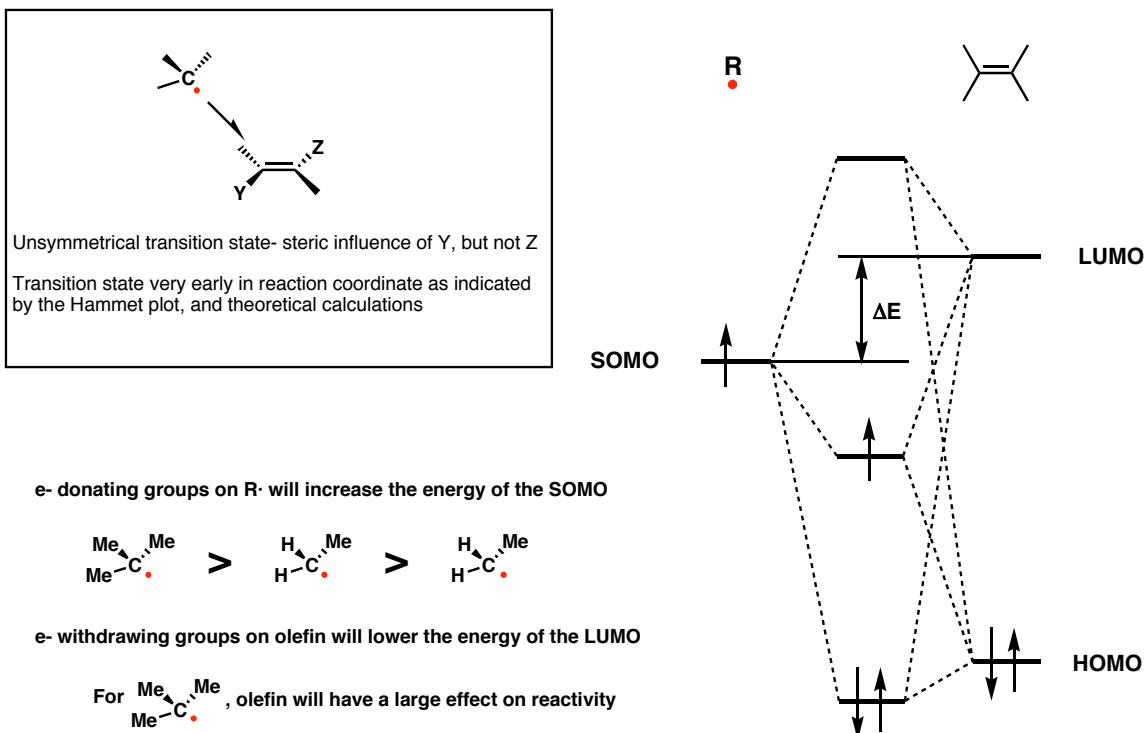


X	Y	$\frac{k_{\text{addition}}}{k_{\text{abstraction}}}$
CH ₃	H	= 1
i-Pr	H	0.25
i-Bu	H	0.05
CH ₃	CO ₂ CH ₃	= 1
i-Pr	CO ₂ CH ₃	0.11
i-Bu	CO ₂ CH ₃	0.0038

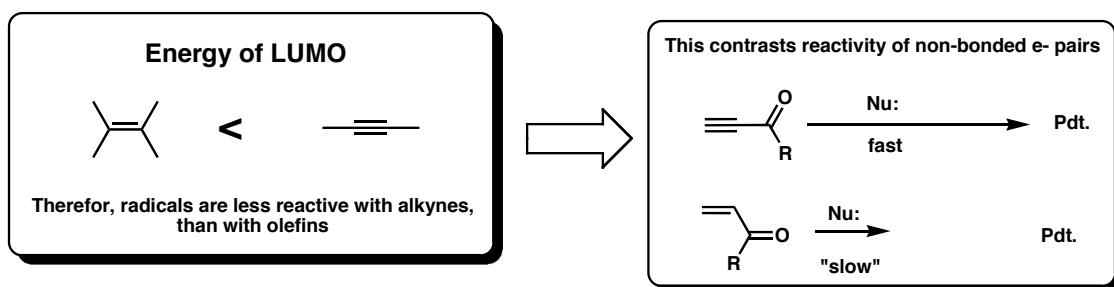
Additions of radicals to olefins are inhibited by increasing steric demand of radical and olefin

Giese, B.; Kretzschmar, G.; Meixner, J. *Chem. Ber.* 1980, 113, 2787.

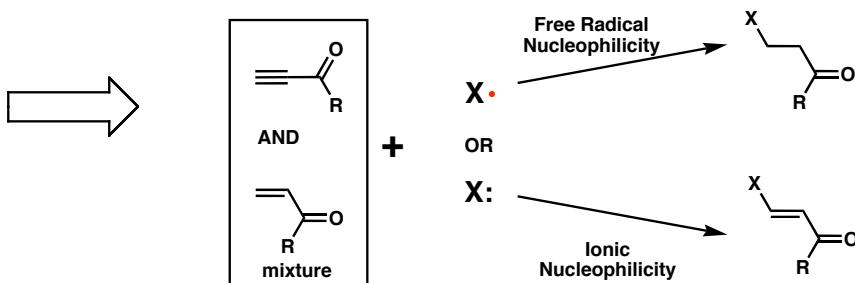
Molecular Orbital Considerations



Divergent Properties

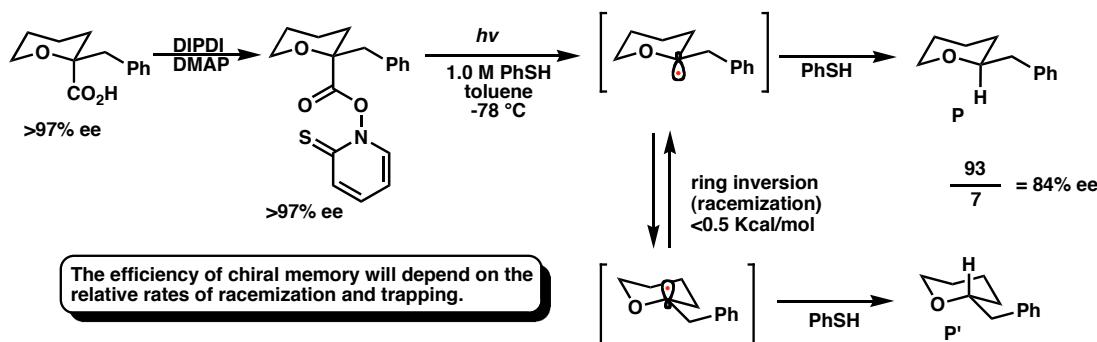


Free Radical Nucleophilicity is governed a very EARLY TS-----> SOMO-HOMO interaction.
Ionic Nucleophilicity proceeds by a very LATE TS-----> rehybridization after bond formation.



This differential reactivity between radicals and anions provides an effective mechanistic probe.

Memory of Chirality with Radical Intermediates
Radical Clock



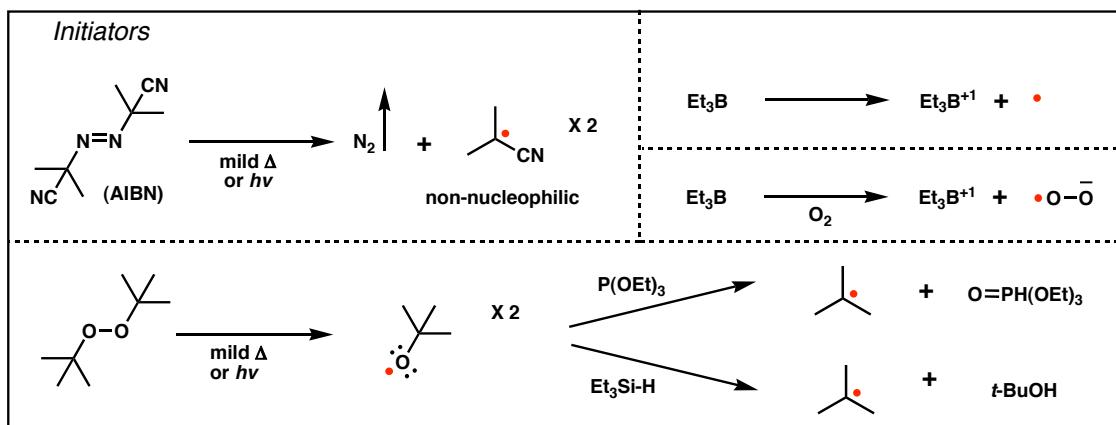
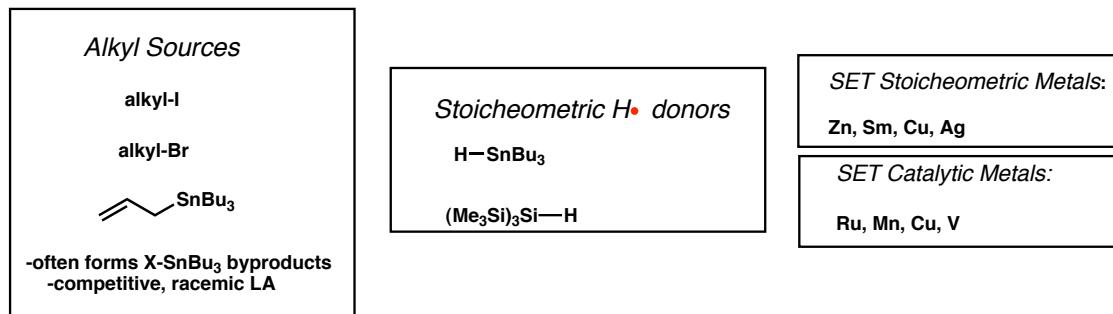
Rate of racemization k_R and rate of H· transfer k_H related by: $k_R = \frac{k_H[\text{PhSH}][\text{P}][\text{P}']}{([\text{P}] - [\text{P}'])}$

- k_H estimated at $1.1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at -78°C from literature values (for $t\text{-BuSH}$)
- k_R is then calculated as $3.9 \times 10^6 \text{ s}^{-1}$ at -78°C
- k_H for several H· sources is then calculated, including PhSH = $2.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$

Bu_3SnH provides 2.6% ee.

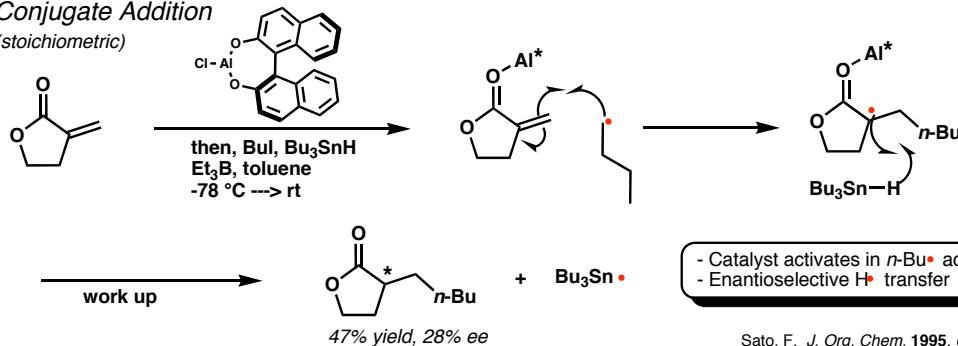
Rychnovsky, S. D. JACS 2000, 122, 9386.

The Usual Players



Stoichiometric Chiral Lewis Acids

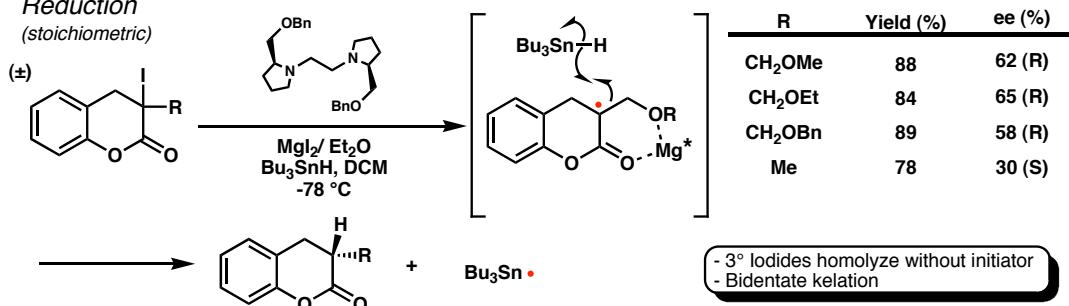
Conjugate Addition (stoichiometric)



Sato, F. *J. Org. Chem.* 1995, 60, 3576.

1st example of asymmetric radical add'n by chiral LA

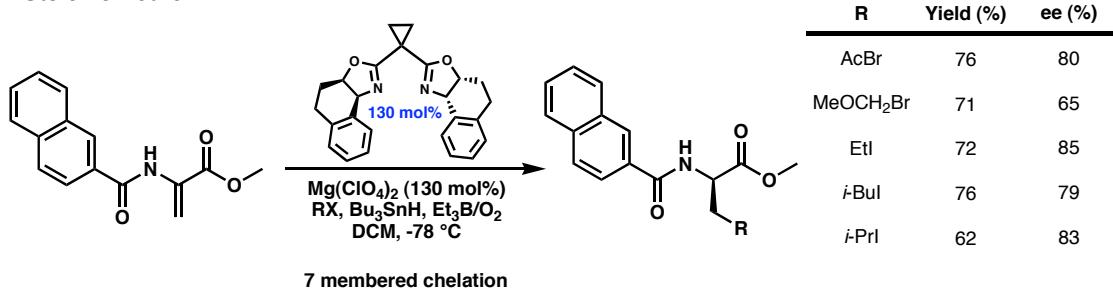
Reduction (stoichiometric)



Murakata, M. *Tetrahedron* 1999, 55, 10295.

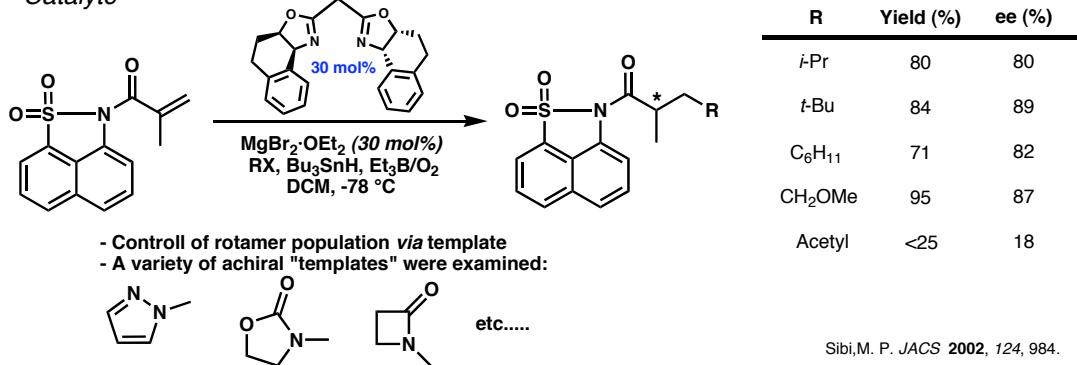
Chiral Lewis Acids

Stoichiometric



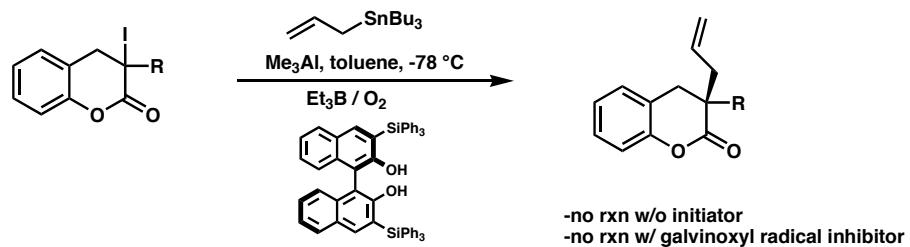
Sibi, M. P. *ACIE* 2001, 40, 1293.

Catalytic

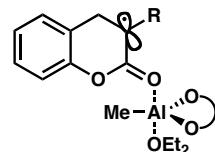


Sibi, M. P. *JACS* 2002, 124, 984.

Quat. Center Formation Allylations



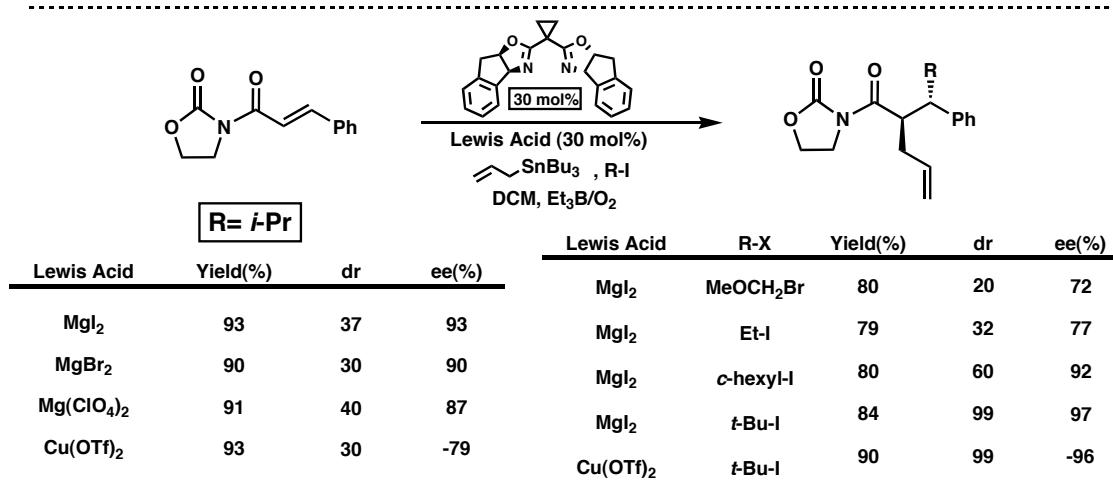
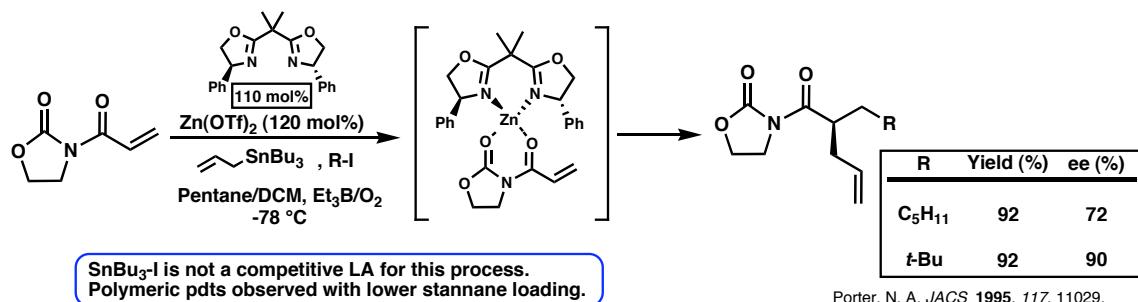
R	LA (equiv.)	Additive	Yield (%)	ee (%)
Me	1.0	none	72	27
Me	1.0	Et ₂ O	84	81
CH ₂ OMe	1.0	none	75	-10
CH ₂ OMe	1.0	Et ₂ O	85	82
CH ₂ OMe	1.0	i-Pr ₂ O	83	43
CH ₂ OBn	1.0	Et ₂ O	76	91
CH ₂ OBn	0.2	Et ₂ O	73	82
CH ₂ OBn	0.1	Et ₂ O	78	71



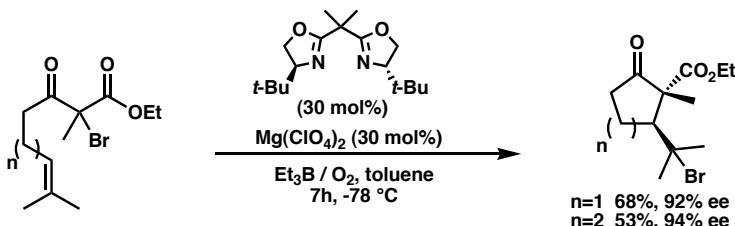
Ether additive influences chiral sphere of catalyst.

Hoshino, O. JACS 1997, 119, 11713.

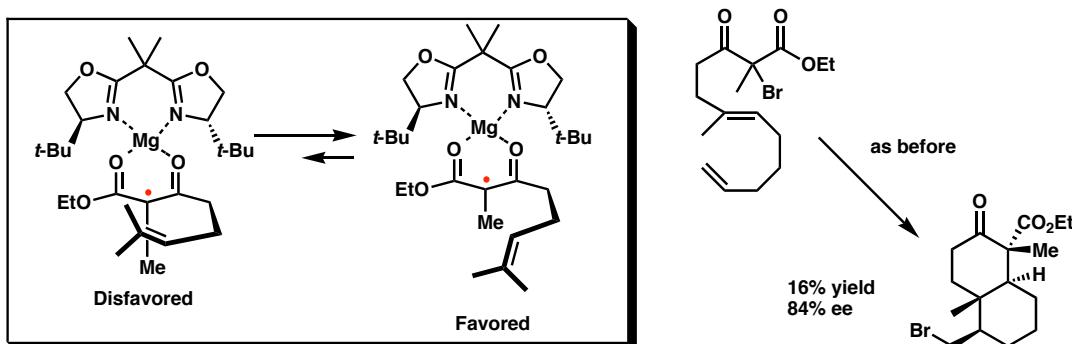
Tandem Reactions: Addition - Trapping



Halogen Transfer with Cyclization

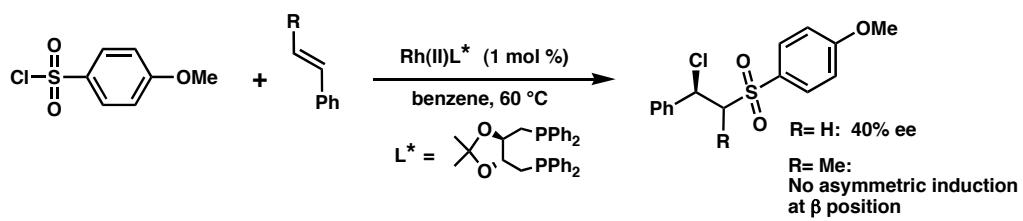


Many other substrates explored. Most require much higher catalyst loadings.

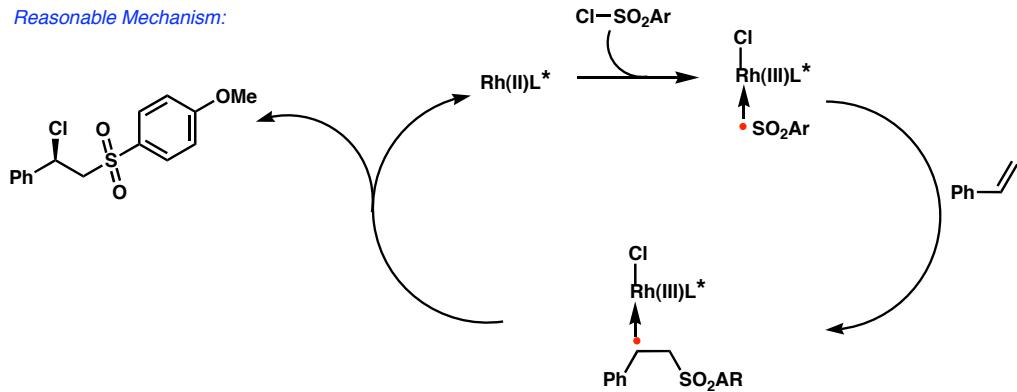


Yang, D. *JACS* 2001, 123, 8612.

Halogen Atom Transfer



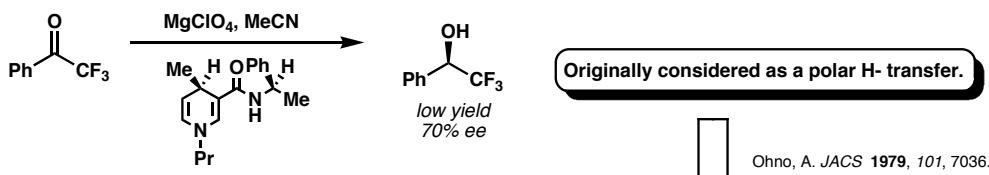
Reasonable Mechanism:



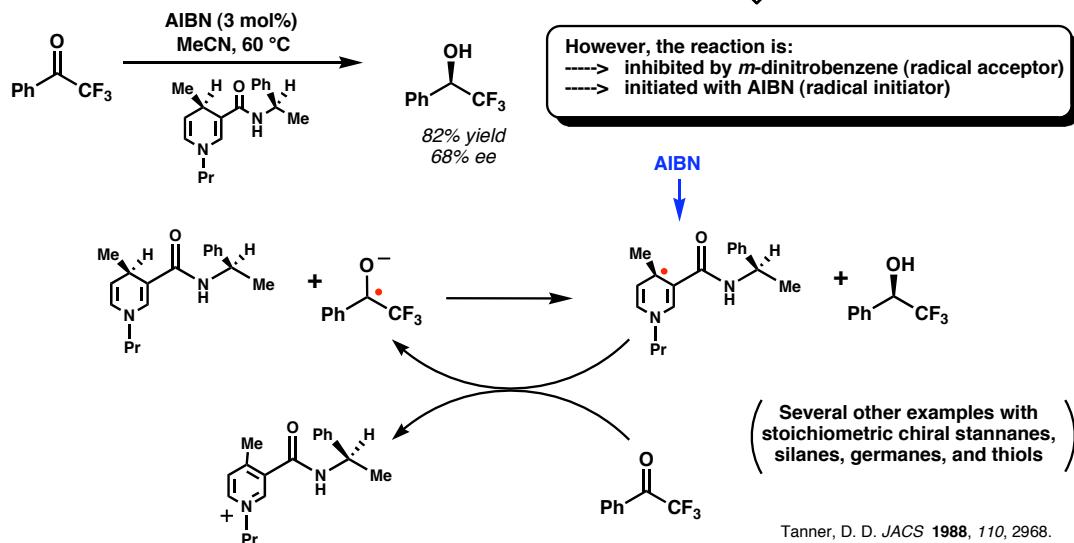
Assumed that "all radicals are restricted within coordination sphere of metal complex". However, no asymmetric induction at β position (?)

Chiral Radical Transfer Reagent

Background:

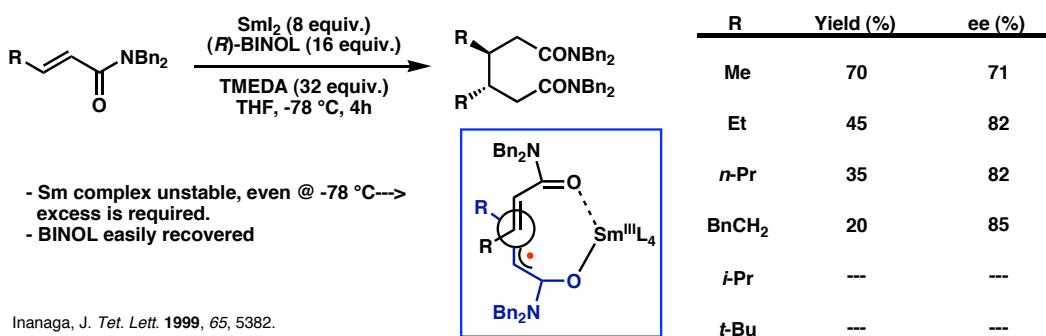


Modified:

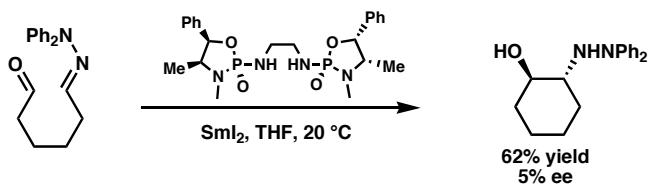


Electron Transfer Reactions: Ketyl Radicals

Homodimerization via Ketyl Radicals

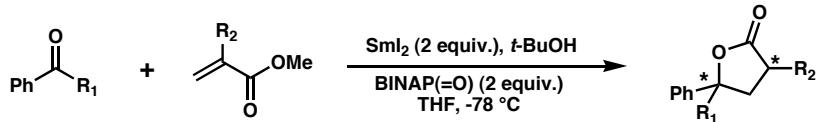


Cyclization: Ketyl Radical Addition to Hydrazone



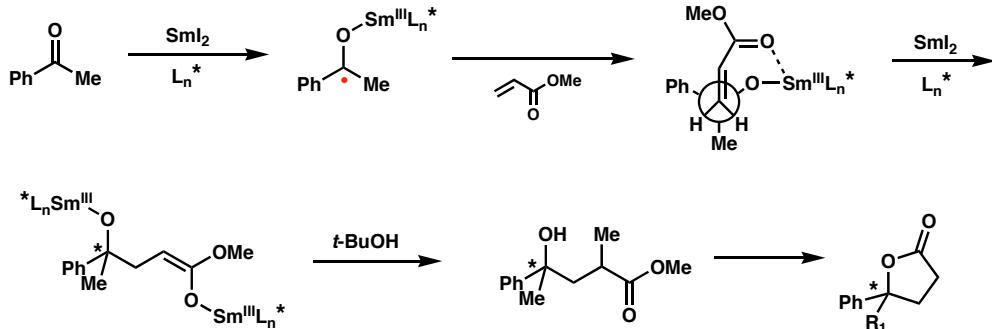
Skrydstrup, T. JOC 2000, 65, 5382.

Electron Transfer Reactions: Ketyl Radical Addition



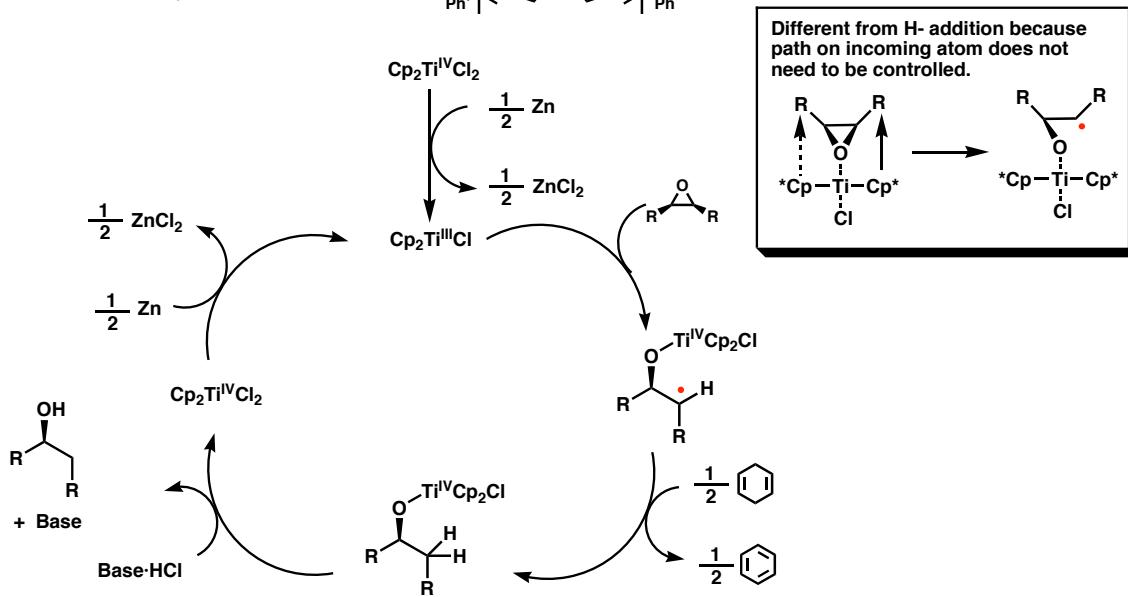
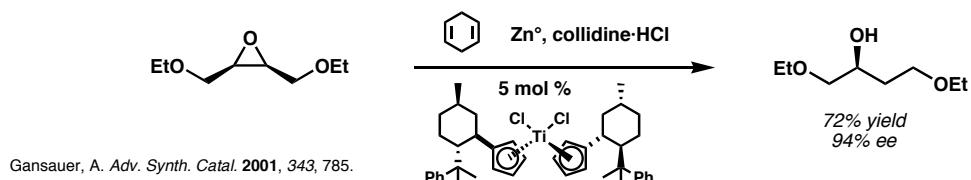
R ₁	R ₂	Yield (%)	cis : trans	ee cis/trans
H	H	46		67
H	Me	42	66:34	95/55
Me	H	18		63

Plausible Mechanism:

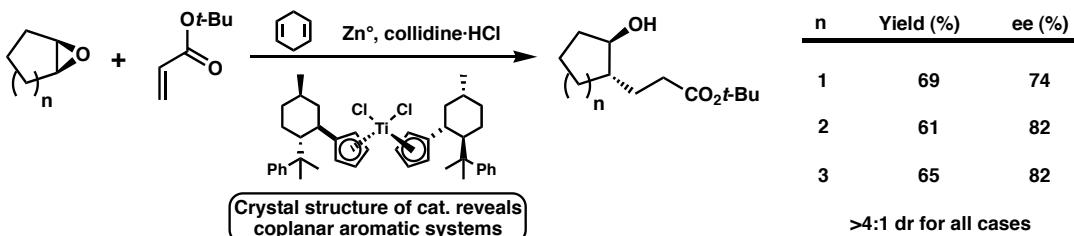


Mikami, K. *TL* 1998, 39, 4501.

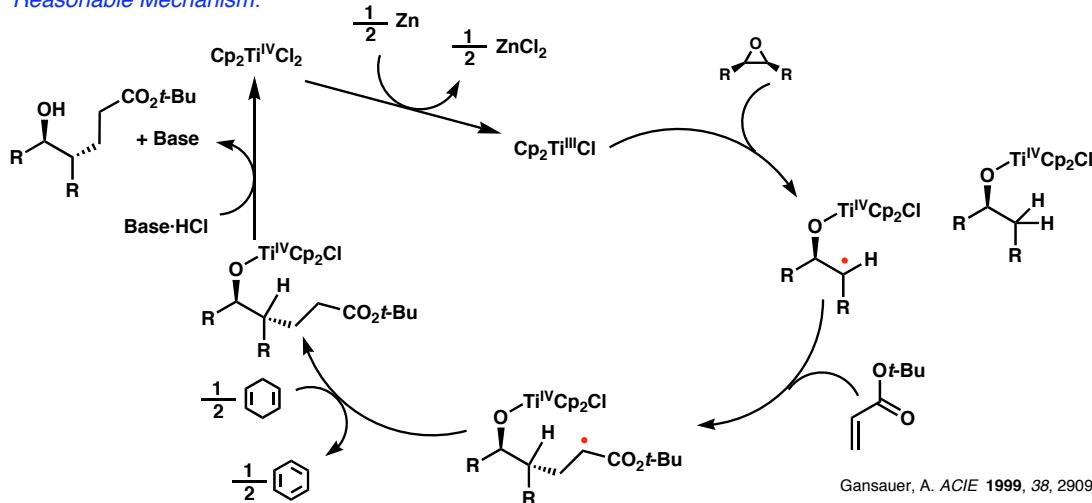
Electron Transfer Reactions: Epoxide Ring Opening



Tandem Electron Transfer Reactions with Epoxides

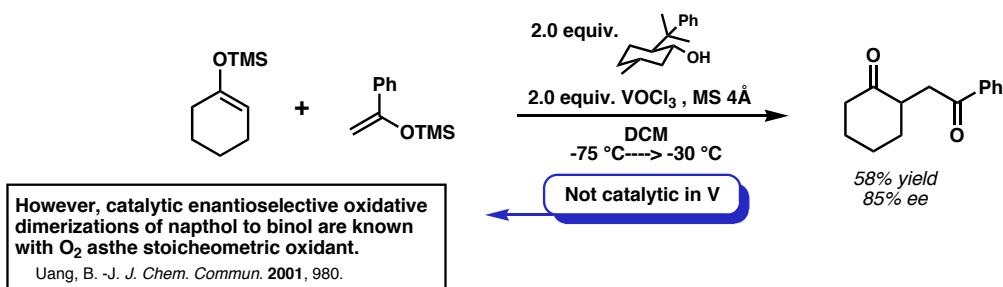


Reasonable Mechanism:



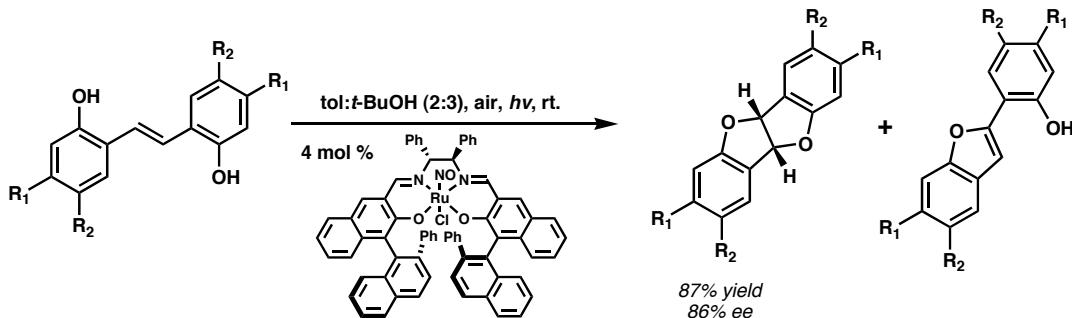
Oxidative Couplings

Oxidative Coupling: Enol Ethers



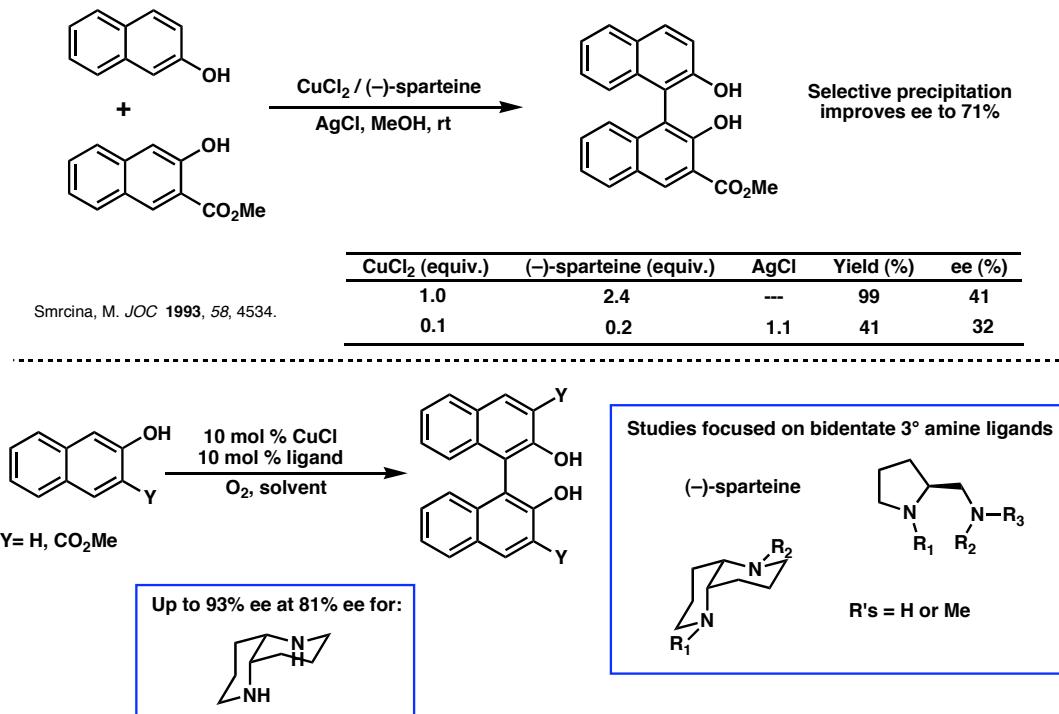
Kurihara, M. Chem. Lett. 2001, 1324.

Oxidative Coupling: Dihydroxystilbene



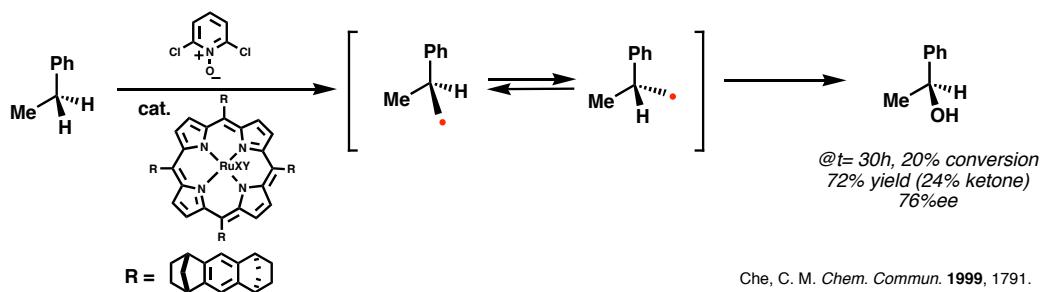
Chen, C. -T. Org. Lett. 2001, 3, 896.

Oxidative Aryl-Aryl Couplings with Cu

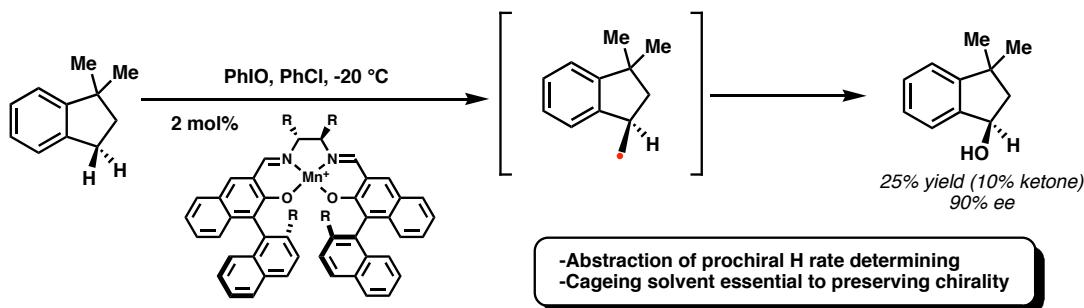


Asymmetric Catalytic Benzylic Oxidation

Chiral Heteroatom Transfer

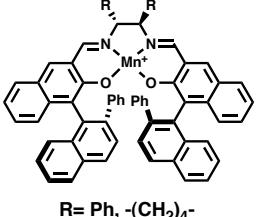
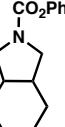
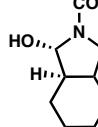
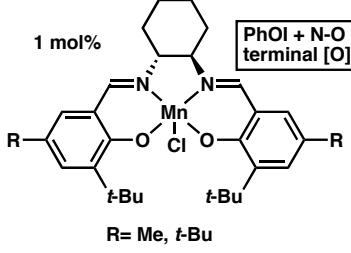
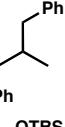
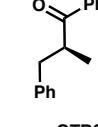
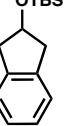
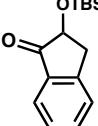


Chiral H Abstraction

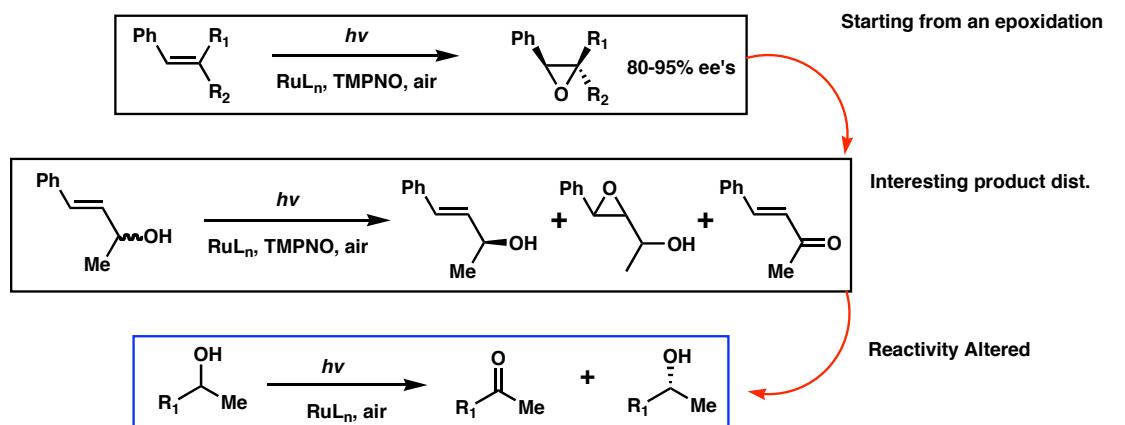


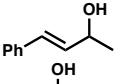
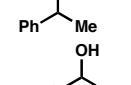
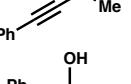
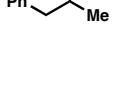
Katsuki, T. TL 1998, 54, 10339. and Synlett 1997, 836.

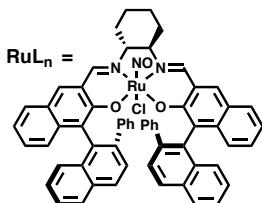
Benzyllic and Beyond

	Substrate	Product	Temp (°C)	Solvent	Yield (%)	ee%
			-40	PhCl	13	48
			-30	PhCl	82	87
Katsuki, T. <i>Tetrahedron</i> 1999, 55, 9439. and <i>TL</i> 1998, 39, 8295.						
			23	PhCl	24	22
			40	PhCl	13	70
Murahashi, S.-I. <i>TL</i> 1998, 39, 7921.						

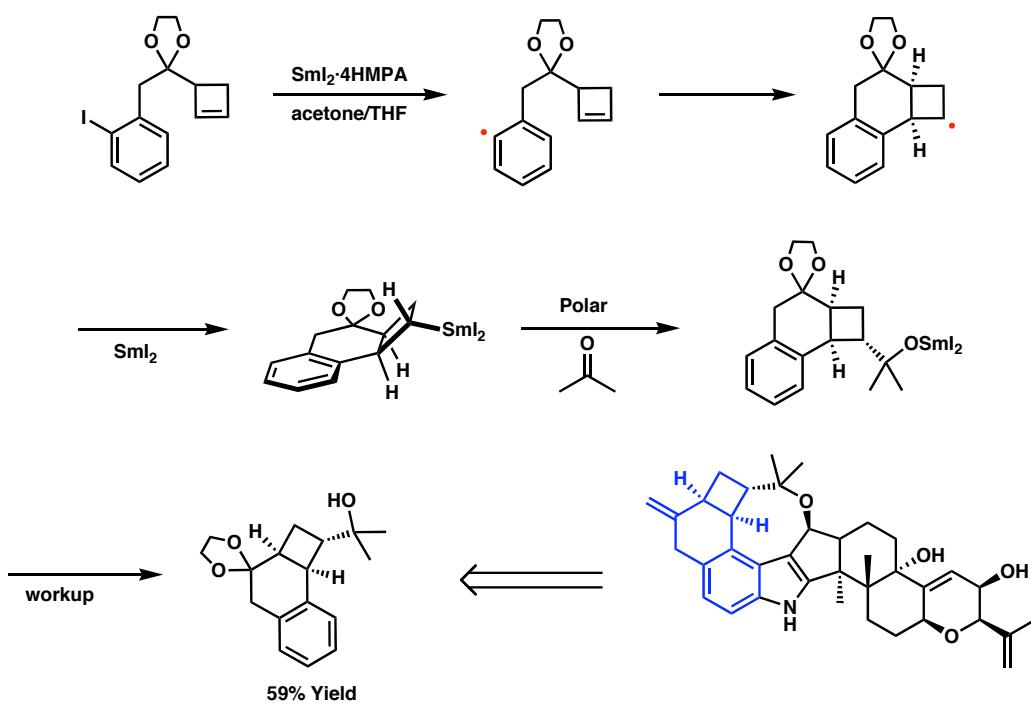
Oxidative Kinetic Resolution



Substrate	Solvent	conversion (%)	ee (%)	s
	Ph-H	76	97	8
	PhCl	65	95	11
	PhCl	65	>99	20
	PhMe	58	82	11



Katsuki, T. *TL* 2000, 41, 5119.



Curran, D. P. *Org. Lett.* **2003**, 5, 419.

In Conclusion.....

Some aspects of radical chemistry mimic polar reaction transformations.

This may lend orthogonal approaches to a given transformation.

Still more transformations evoke the unique characteristics of a radical process.
(i.e. direct enantioselective oxidation of C-H bonds)

Some drawbacks limit the practicality of catalytic asymmetric reactions.

- Many require stoichiometric chiral inducers
- Many require very bulky porphrine or salen ligands
- The impact of these transformations is hampered by poor yields, poor ee's.

The good news is: This stuff mostly works. Many concepts are proven, but not fully developed. Radical/Single electron transformations adopt a different set of rules from polar transformations--- room for exotic reactivity.