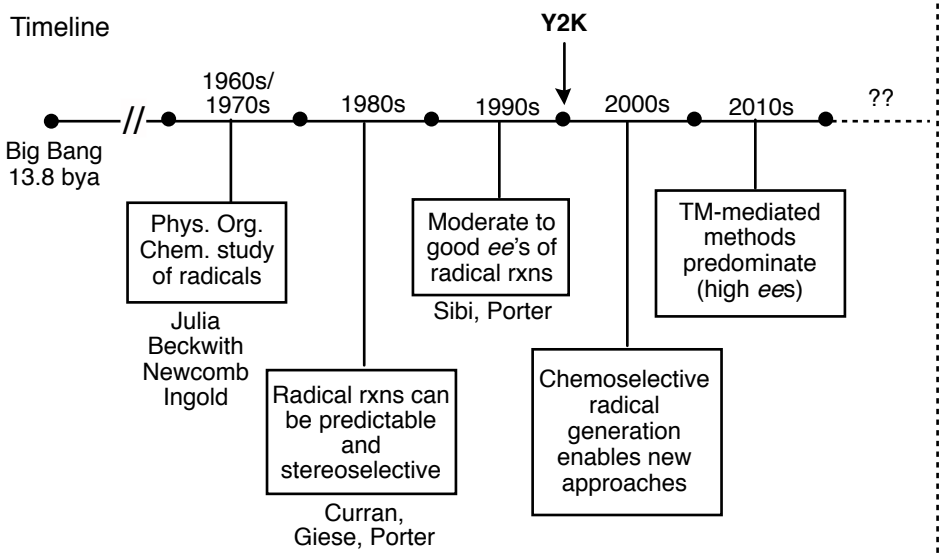
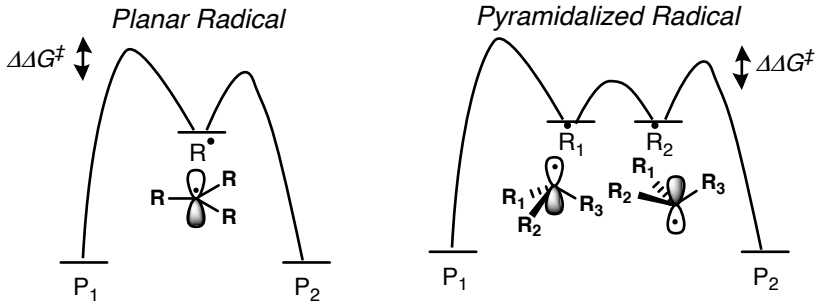
Radical Approaches to Asymmetric Catalysis

Useful Resources:
1) Curran, D.P.; Porter, N.A.; Giese, B. *Stereochemistry of Radical Reactions*: *Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996.
2) Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.*, 2003, *103*, 3263
3) Walsh, P.J.; Kozlowski, M.C. *Fundamentals of Asymmetric Catalysis;* 2009.

Timeline

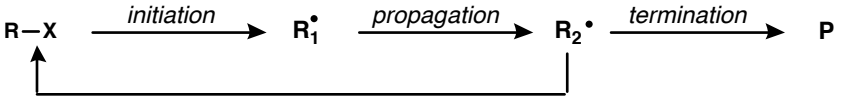


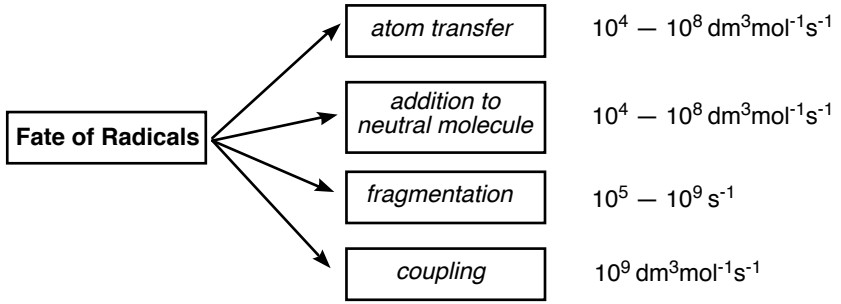
Thermodynamic Considerations for Radical Reactions



If two diastereomeric pathways exist, $\Delta G = RT\ln K$ 1.0 kcal/mol at rt → 69%ee
1.8 kcal/mol at rt → 91%ee
2.2 kcal/mol at rt → 98%ee

Elementary Steps in Radical Chain Process:





When to introduce asymmetry:
- if chiral *initiator* is used, chiral source must remain bound through entire process
- in *propagation* steps:

Chiral Lewis Acid: coordination accelerates chiral pathway (relative to background) *and* influences substrate approach

Chiral Chain Transfer Agent: determines steric approach of atom-transfer step (proton/halogen)

Chiral Catalyst: temporary coordination to both substrate/reacting radical brings about "intramolecular" bond forming step

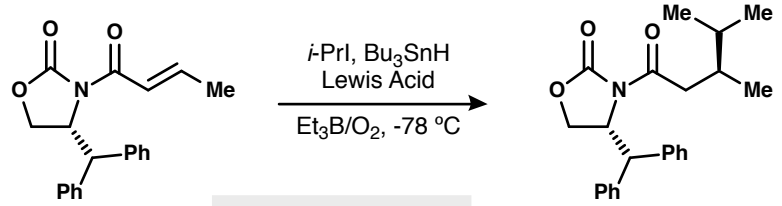
Chiral Memory: inherent chirality of molecule is converted to molecular chirality

Will not discuss today, but see:
Rychnovsky, *JACS*, 2000, *122*, 9386

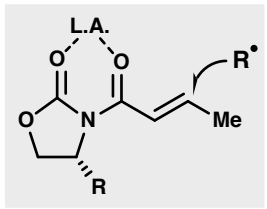
Lewis Acid-Catalyzed Enantioselective Radical Reactions

Prostereogenic Radical Trap —

Sibi, *JACS*, 1995*, 117*, 10779



Radical approaches via Burgi-Dunitz angle (~109º)

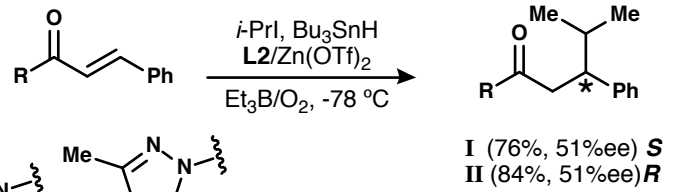


Lewis Acid	yield (d.r.)
none	60 (1.3:1)
$MgBr_2$	90 (6:1)
$Sm(OTf)_3$	90 (18:1)

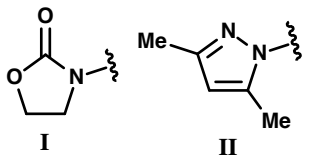
Sibi, *JOC*, 1997, *62*, 3800; *JACS*, 1996*, 117*, 10779

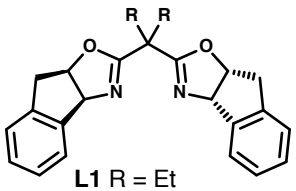
88% (95% ee)

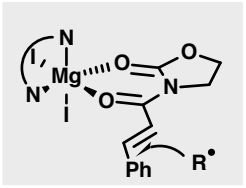
Sibi *TL*, 1997, *38*, 5955



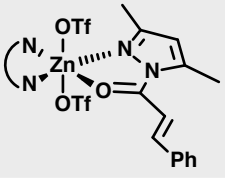
I (76%, 51%ee) ***S***
II (84%, 51%ee)***R***







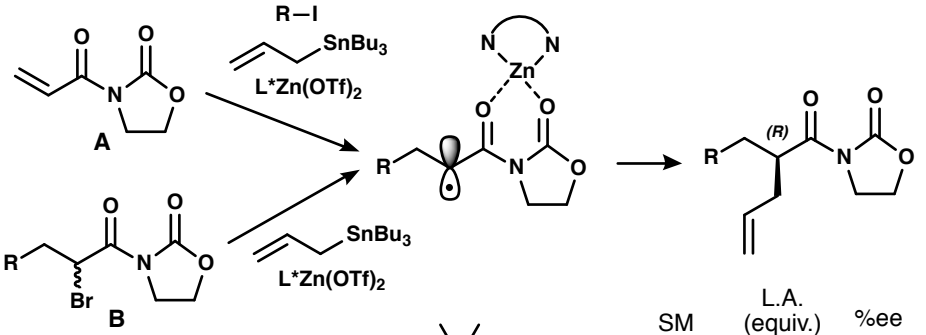
Octahedral geometry accounts for high *ee*



Square planar leads to opp. config. in lower *ee*

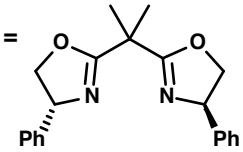
Prostereogenic Radical

Porter, *TL*, 1997, *38*, 2067



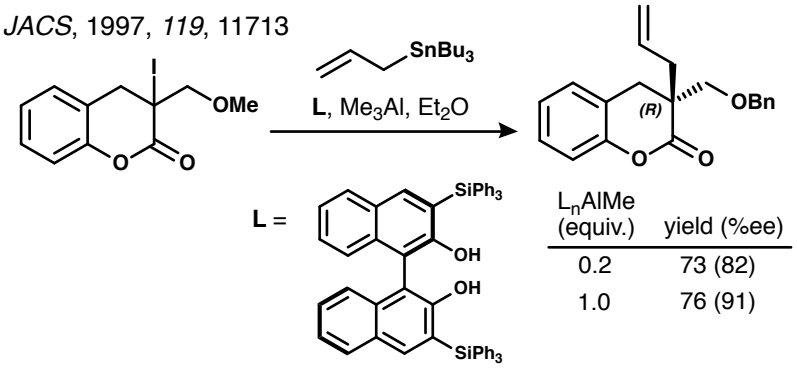
α-radical is planar due to resonance with carbonyl

L* =



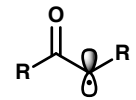
SM	L.A. (equiv.)	%ee
A	0.2	54
A	1.0	90
B	0.2	52
B	1.0	74

JACS, 1997, *119*, 11713

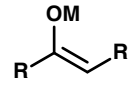


L_nAlMe (equiv.)	yield (%ee)
0.2	73 (82)
1.0	76 (91)

α-carbonyl radicals! They're just like ~~us~~ polar enolate equivalents



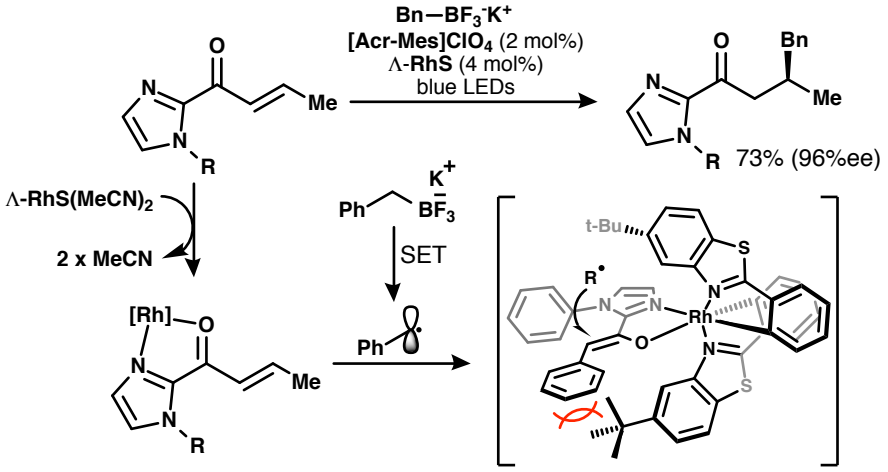
transient species but free from solvent, counteranion, aggregation effects



relatively stable; nature of reactive species not always understood

Recent Approaches Merging Photocatalysis/Lewis Acid Catalysis

Asymmetric Photocatalysis with Bis-cyclometalated Ir/Rh complexes
Meggars, *ACR,* 2019, *52*, 833

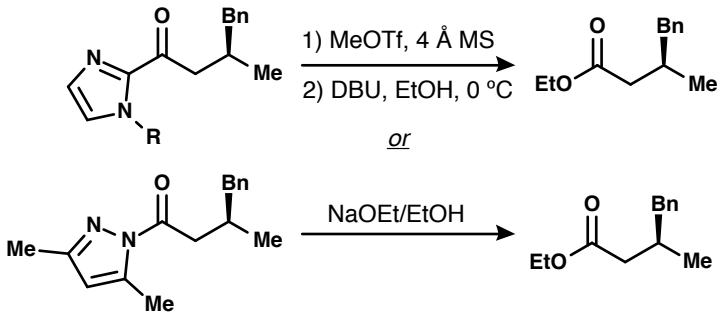


distortion energy responsible for observed *ee*

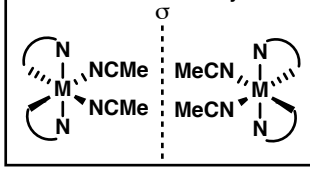
"the substantial energy expenditure required to bend and deform the relatively rigid **Rh** catalyst is responsible for the experimentally observed enantioselectivty" (5.1 kcal/mol)

Houk/Meggars: *JACS*, 2017*, 139,* 17902 Wiest/Meggers: *JACS*, 2017, *139*, 8062

Removal of auxiliary: JACS, 2016, *138*, 6936

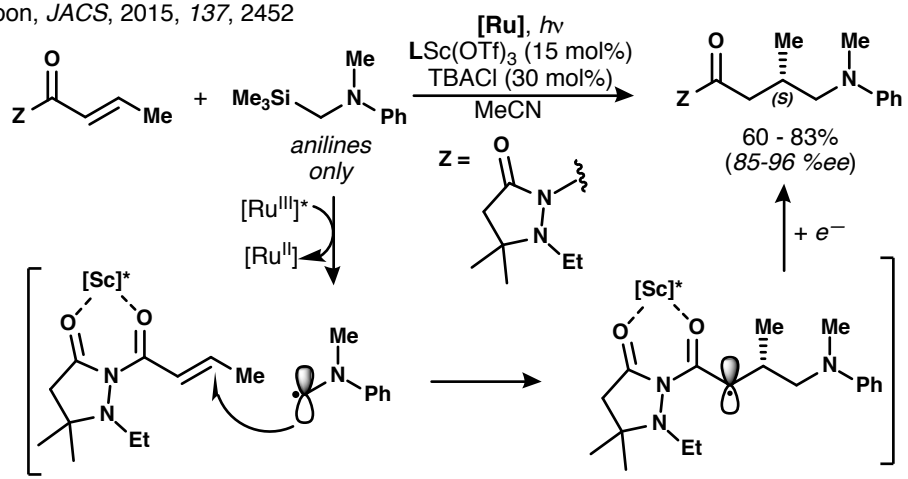


Chiral-at-metal catalysis? *ACR,* 2017*, 50,* 320



- exclusive metal-centered chirality
- activation by metal coordination
- optional activation by visible light

Triplet Sensitized Lewis Acid Catalyzed Radical Additions
Yoon, *JACS*, 2015, *137*, 2452

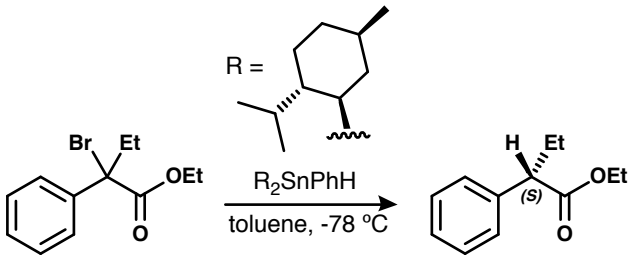


- **[LSc]*** is not excited by photocatalyst (ground state)
- Cl^- anion effects *ee* (by increasing Sc turnover)

Chiral Chain Transfer Reagents

Chiral Stannanes

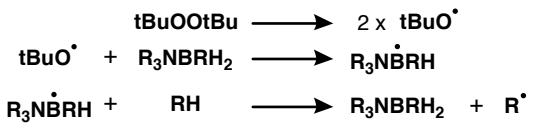
Schiesser *Aust. J. Chem.*, 2001, *54*, 89—91



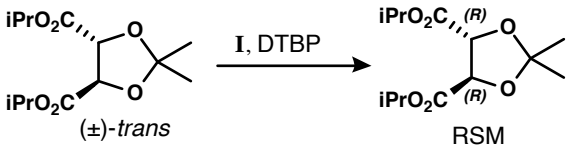
additive	% ee	
none	4	
BF_3	20	
Cp_2ZrCl_2	46	
(*S*,*S*)-Mn(Salen$^{t\text{-Bu},t\text{-Bu}}$)	86	*lead to same enantiomer!*
(*R*,*R*)-Mn(Salen$^{t\text{-Bu},t\text{-Bu}}$)	84	

Other examples of chiral tin hydrides (BINOL) require stoichiometric stannanes and result in only moderate *ee*'s
Nanni and Curran *Tet: Asymm,* 1996, *7,* 2417
Metzger *JOC*, 1998, 177

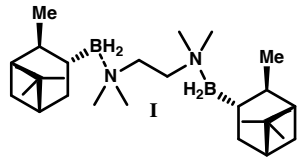
Polarity Reversal Catalysis: Chiral Amino Boranes

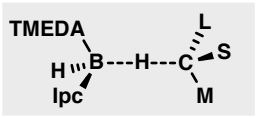


Amino borane is *hydridic* PRC (abtracts H-atom)



+ *(S,S) SM leads to* meso *and dimer products*





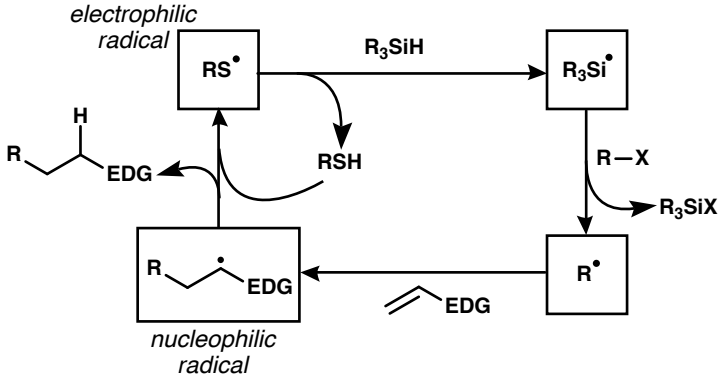
model for lowered TS of more reactive (S,S) enantiomer

Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1993, 665
Roberts, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 1033

Polarity Reversal Catalysis: Chiral Thiols

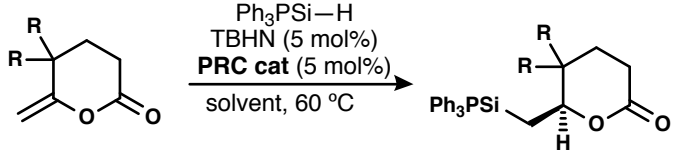
$R_3Si—H$	vs	RS—H
H-atom more *nucleophilic*		H-atom more *electrophlic*
radical chain *initiator*		radical chain *propagator*

Thiol *protic* PRC (donates H-atom)



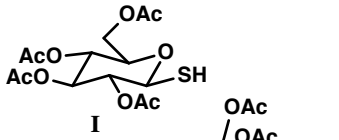
- *Hydrosilanes typically suffer from premature chain termination*
- *Thiol PRC catalyst can be used in substoichiometric quantities*

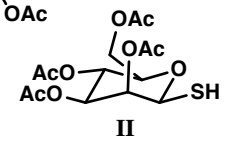
Roberts *J. Chem. Soc.*, *Perkin Trans. 1*, 2002, 1376



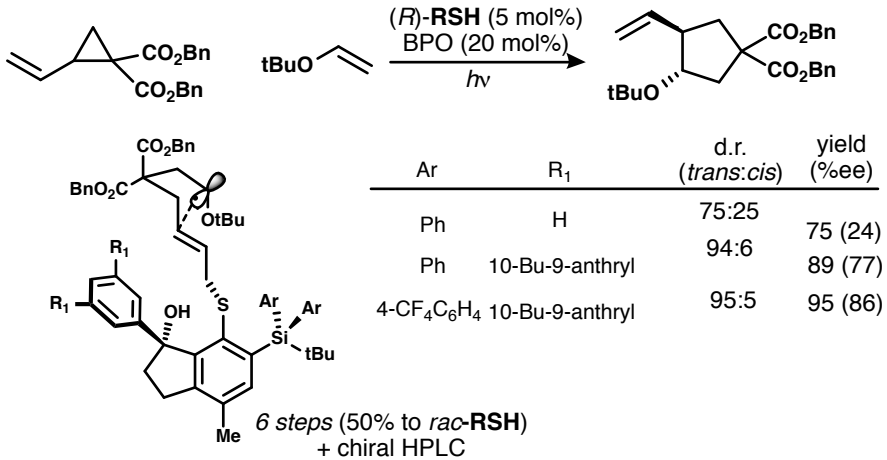
R	PRC cat	solvent	yield (%ee)
Me	**I**	*p*-dioxane	63 (40 %ee)
Ph	**I**	*p*-dioxane	88 (80 %ee)
Ph	**II**	hexane/ *p*-dioxane (5:1)	90 (95 %ee)

PRC catalysts -





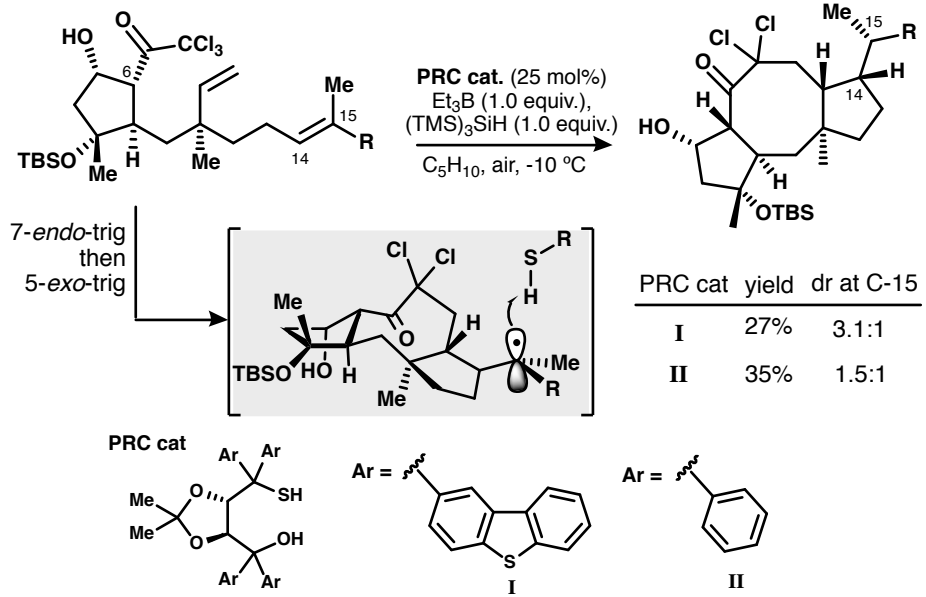
Enantioselective C—C bond formation via radical thiol catalyst
Maruoka, *Nat Chem*, 2014, *6*, 702



Ar	R_1	d.r. (*trans*:*cis*)	yield (%ee)
Ph	H	75:25	75 (24)
Ph	10-Bu-9-anthryl	94:6	89 (77)
4-$CF_4C_6H_4$	10-Bu-9-anthryl	95:5	95 (86)

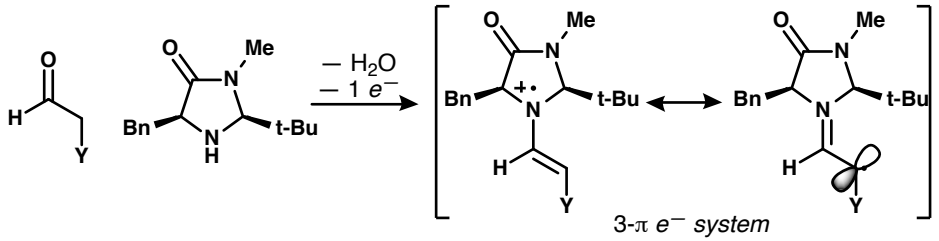
6 steps (50% to *rac*-**RSH**)
+ chiral HPLC

PRC in Total Synthesis: Synthesis of (—)-6-*epi*-ophiobolin N
Maimone *Science*, 2016, *352*, 1078

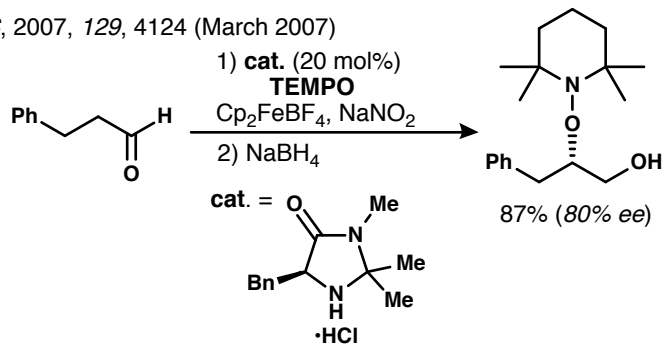


PRC cat	yield	dr at C-15
I	27%	3.1:1
II	35%	1.5:1

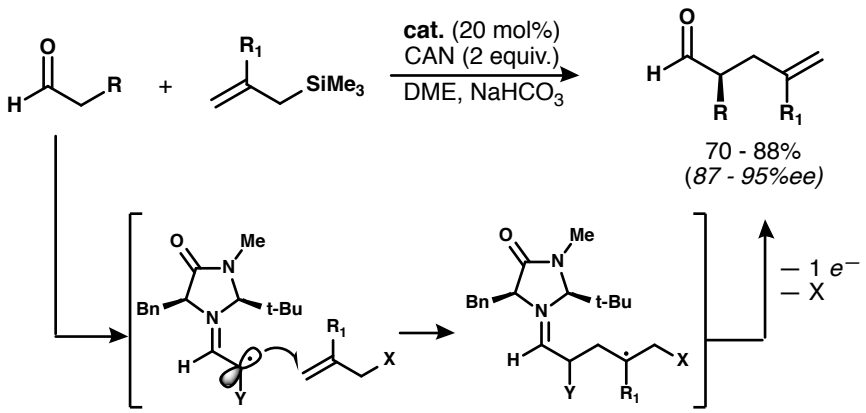
Radical Organocatalysis *via* Enamine Oxidation
First report of oxidation of pyrrolidine enamines with metallic salts leads to carbon centered radicals: *JCS Chem Commun*, 1993, 1218



Sibi, *JACS*, 2007, *129*, 4124 (March 2007)



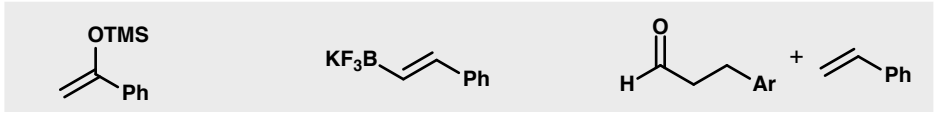
SOMO (singly occupied molecular orbital) catalysis (Macmillan)
Science, 2007, *316*, 582

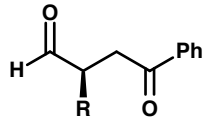


- *Two stepwise oxidation events (2 equiv. of [O] required)*
- *Unsaturated bonds with appropriate leaving group can participate*
- *All methods use inorganic oxidants*

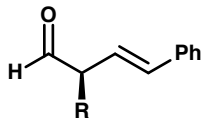
Organocatalytic Approaches

Extension of methodology - 28 subsequent papers

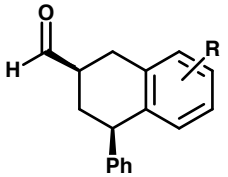




93-96%ee
α-enolation
JACS, 2007, *129*, 7004



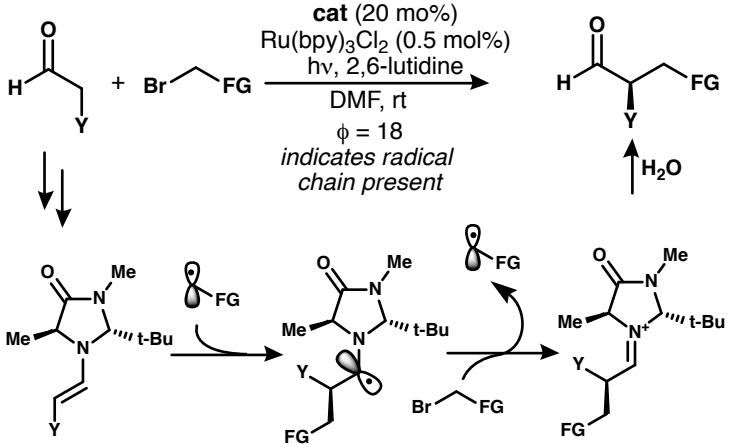
89-95%ee
α-vinylation
JACS, 2008, *130*, 398



good d.r.s
(*88-94%ee*)
cascade cycloadditions
JACS, 2009, *132*, 10015

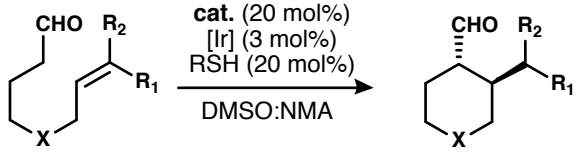
Photoredox/Organocatalytic Dual Catalysis (SOMO-philic enamine)
*strategy is *inverse* of SOMO catalysis above

MacMillan, *Science*, 2008, *322*, 77
Quantum Yield Calc: Yoon, *Chem Sci*, 2015, *6*, 5426



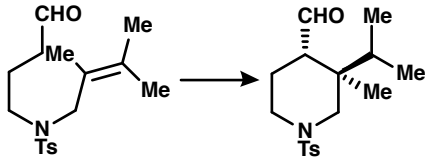
- *Net redox-neutral process*
- *Methods use photoredox catalyst for radical generation*
- *Electrophilic radical generation that adds into electron-rich enamine*
- *Quantum yield reflects chain process*

MacMillan, *Nat. Chem.*, 2017, *9*, 1073

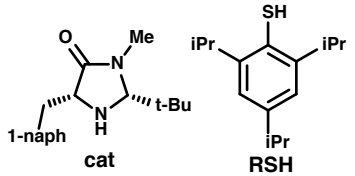


15 examples
62-90% (*84-95%ee*)

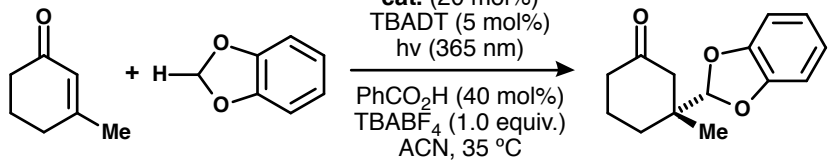
Formation of quat. centers?

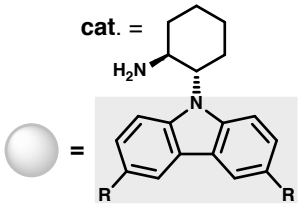


60% >20:1 dr
(*50%ee*)

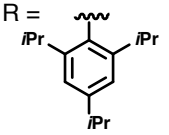


Electron-Relay Radical Conjugate Addition
Melchiorre, *Nature*, 2016, *532*, 218



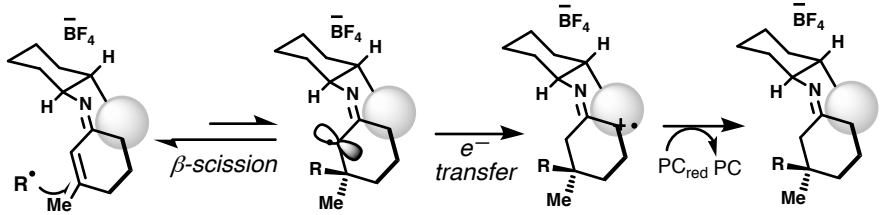


I R = Me
II R =



cat	yield (%ee)
I	33 (0 %ee)
II	46 (93%ee) 48 h
II	75 (93%ee) 84 h

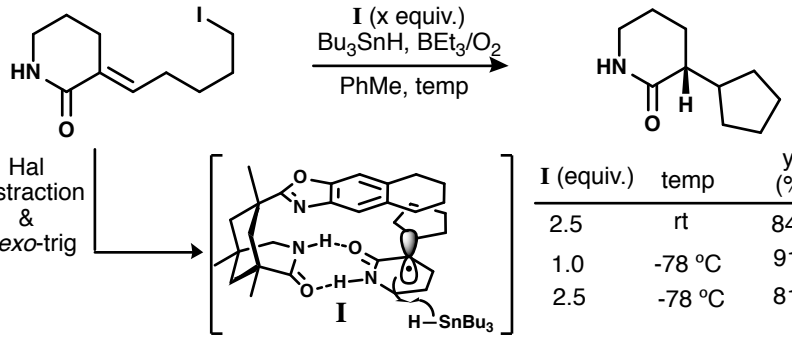
TBADT - tetrabutylammoium decatungstate ($(Bu_4N)_4W_{10}O_{32}$)



- *β-scission is reversible process but electron-relay is irreversible*

Non-Covalent Interactions Enforce Chirality

Bach, *ACIE*, 2004, *43*, 5849

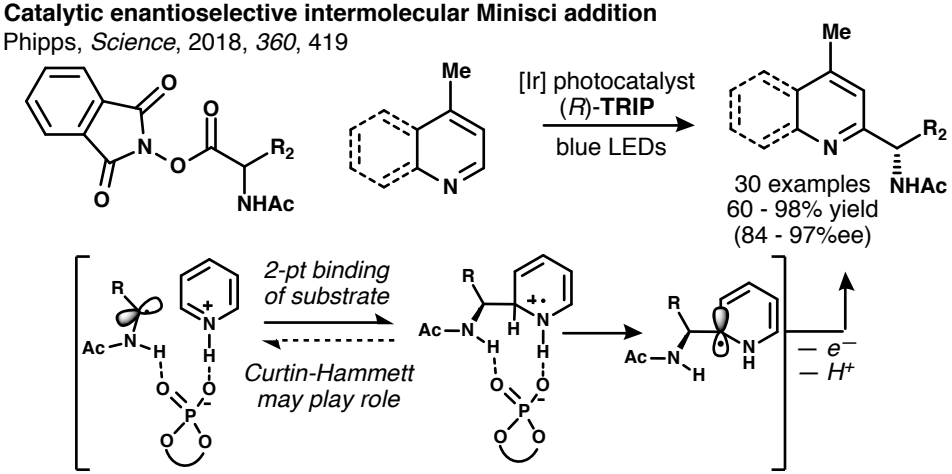


I (equiv.)	temp	yield (%ee)
2.5	rt	84 (38)
1.0	-78 °C	91 (40)
2.5	-78 °C	81 (84)

See also: Bach *OL*, 2006, *8*, 3145

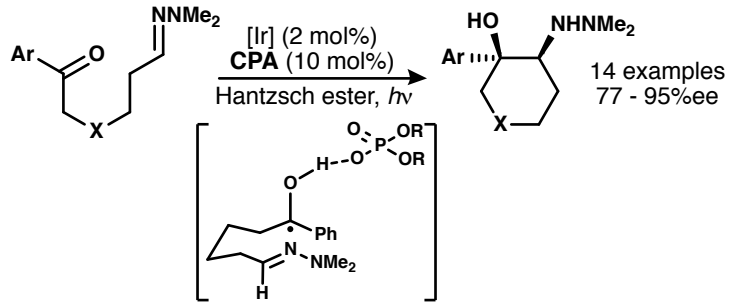
Catalytic enantioselective intermolecular Minisci addition

Phipps, *Science*, 2018, *360*, 419



Enantioselective Aza-Pinacol Cyclization

Knowles, *JACS*, 2013, *135*, 17735

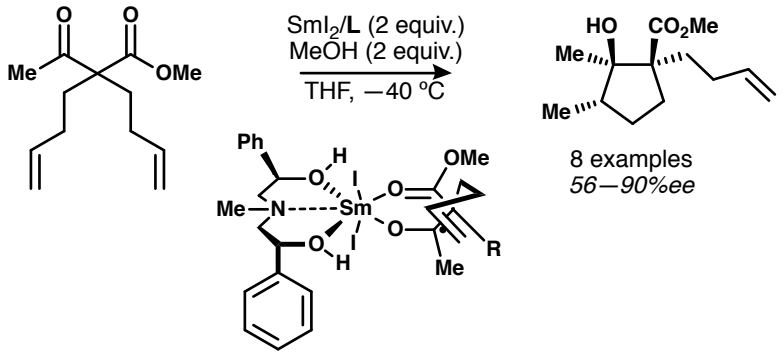


Attempts with **L***SmI_2 had very low *ee*'s: *TL*, 1998, *39*, 4501

Enantioselective, desymmetrizing ketyl cyclization

Proctor *Nat. Chem.*, 2017, *9*, 1198

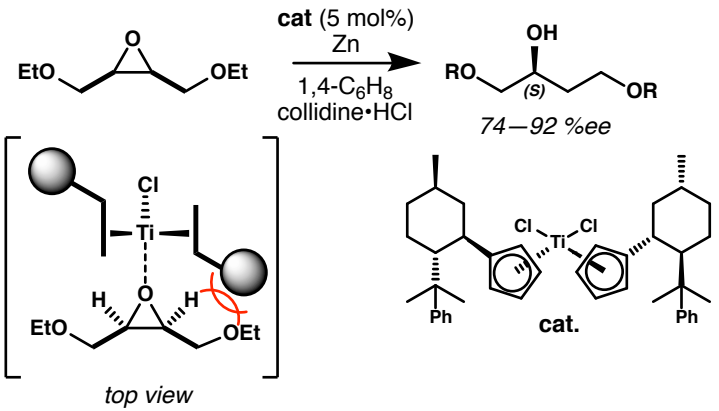
5-exo-trig



Desymmetrizing Ti-catalyzed Epoxide Opening

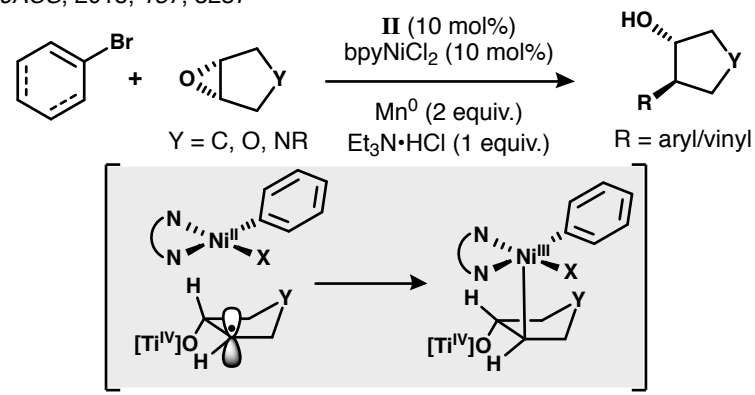
Gansäuer *ACIE*, 1999, *38*, 2909

"the first TM-catalyzed enantioselective formation of radicals"



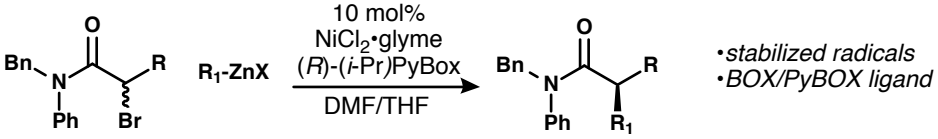
Ni-Mediated Radical Cross Couplings

Weix, *JACS*, 2015, *137*, 3237



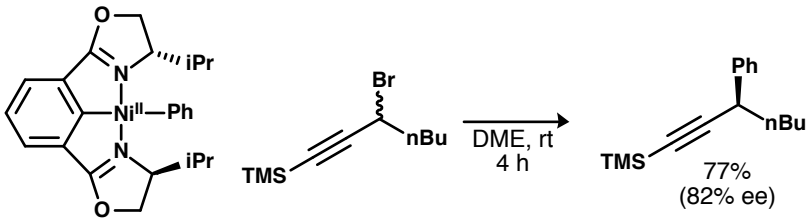
Ni-Catalyzed Enantioconvergent Radical Cross-Couplings

Seminal Publication: Fu *JACS*, 2005, *127*, 4594



- *stabilized radicals*
- *BOX/PyBOX ligand*

Mechanistic work: Fu, *JACS*, 2008, *130*, 12645; *JACS*, 2014, *136*, 16588



Ni^{II}-aryl is catalyst resting state

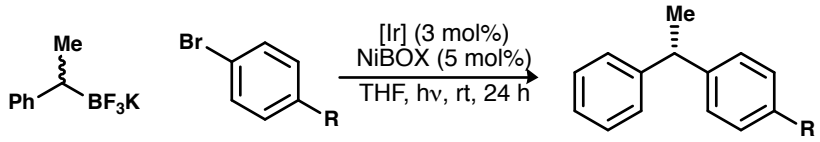
Ni^{I} metalloradical reduces propargylic bromide

Consistent with radical chain mechanism

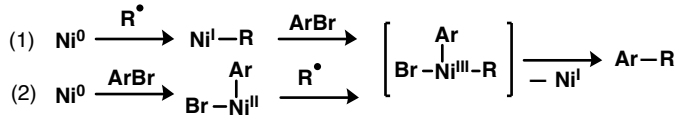
See also:
Enantioselective Synthesis of 1,1-Diarylalkanes
Reisman (*JACS*, 2017, *139*, 5684)
Enantioselective Desymmetrization of Meso Anhydrides
Doyle/Rovis (*ACIE*, 2017, *56,* 3679)

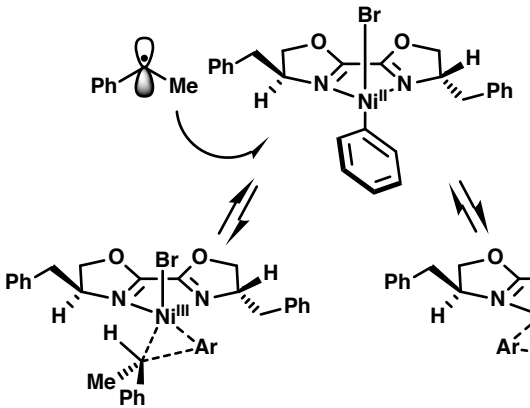
Controlling Enantioselectivity Through the Curtin—Hammet Principle

Molander, *JACS,* 2015, *137*, 4896
See also: Liu, *Organometallics*, 2011*, 30*, 3284



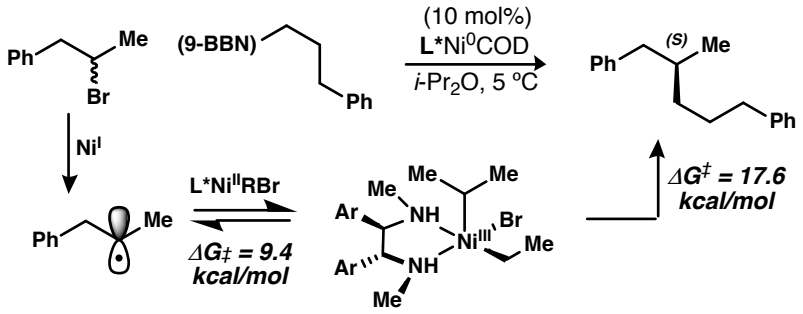
Multiple pathways similar in energy but (1) has lower calculated energy





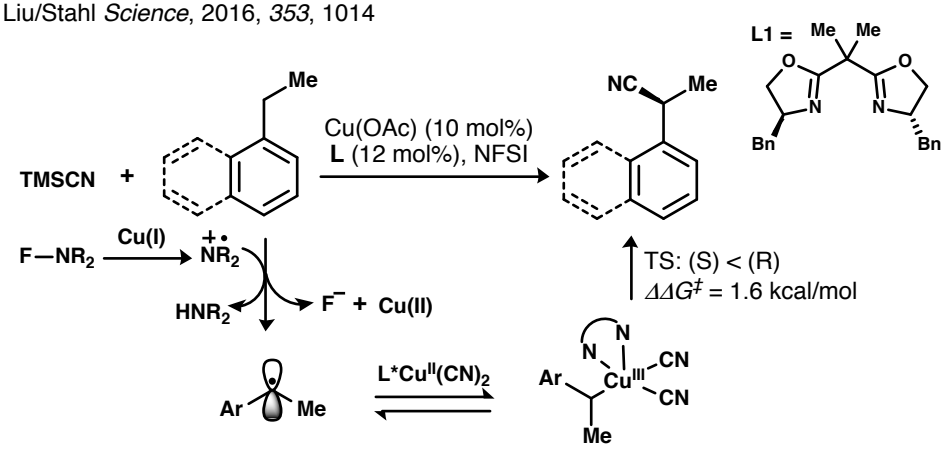
What about *unstabilized* radicals*?*

Enantioconvergent coupling of *unactivated* alkyl bromides
Fu, JACS, 2008, *130*, 6694 (energy calc by Molander (2015))

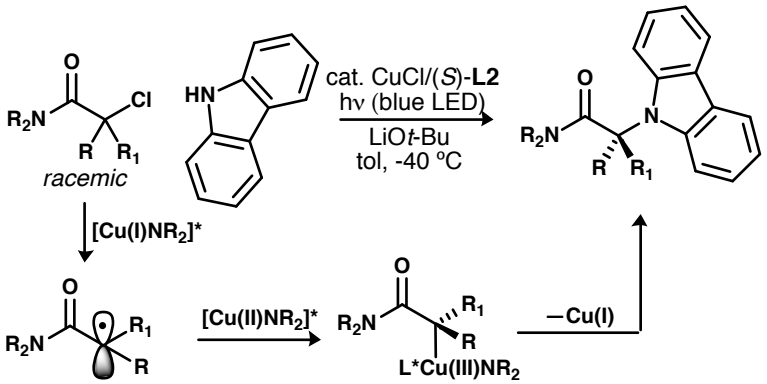


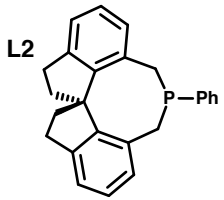
TM-Mediated Radical Cross Couplings

Dynamic kinetic resolution proposed in enantioselective copper "radical relay catalysis"
Liu/Stahl *Science*, 2016, *353*, 1014

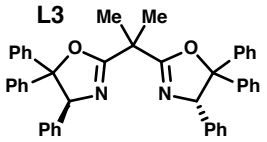


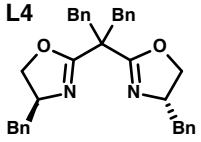
What about *tertiary* radicals?
Enantioconvergent C-N bond coupling
Fu/Peters *Science*, 2016, *351*, 681
JACS, 2017 *139*, 12716



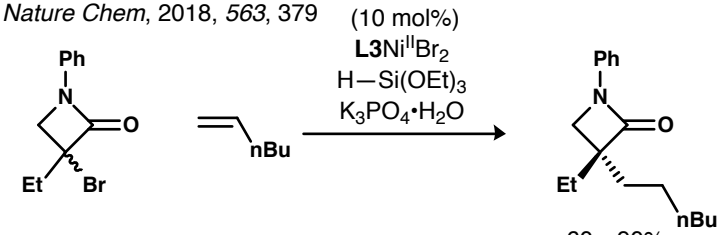


$2.50/mg!!
or 13 steps (+1 chiral separation)

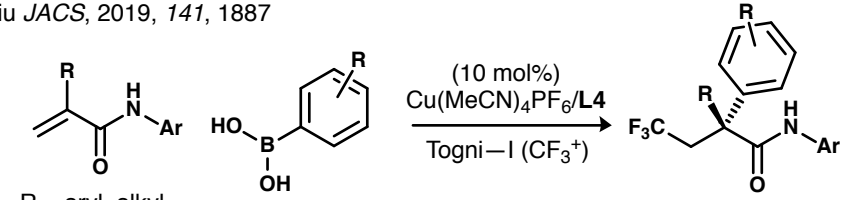




Fu, *Nature Chem*, 2018, *563*, 379



Liu *JACS*, 2019, *141*, 1887

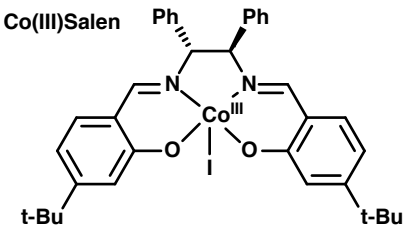


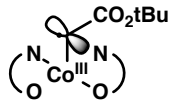
Direct tertiary alkyl radical + nucleophile coupling not precedented
All examples above have -CONR$_2$ group adjacent to 3° radical

Asymmetric Cobalt Catalysis

Cobalt(III) carbene complexes exist as alkyl radical species that can participate in cyclopropanation (Yamada, *JACS*, 2002, *124*, 15152)

Co(III)-Salen Asymmetric Cyclopropanation: Katsuki, *Synlett*, 1995, 825

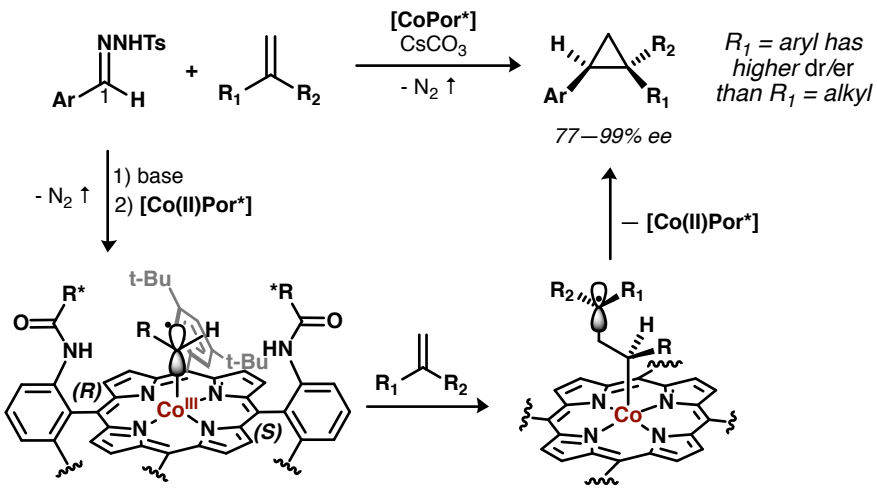




TM-Mediated Radical Cross Couplings

Asymmetric metalloradical catalysis (MRC)

Zhang *JACS*, 2017, *139*, 1049

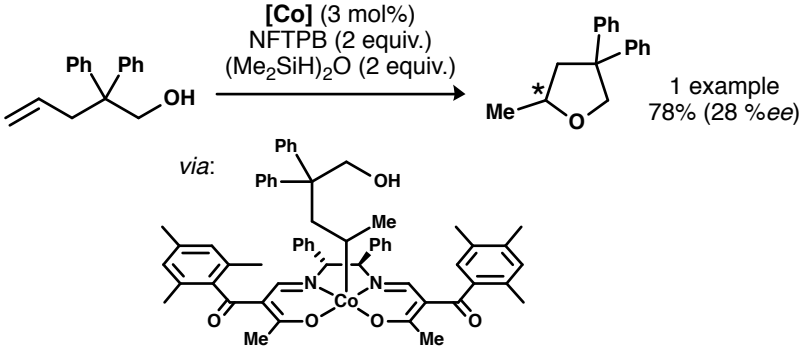


H-bonding between substrate and catalyst enables high ees

Many other radical cyclization strategies established using **MRC** (Zhang)
bridged ligand: *ACIE*, 2019, *58*, 2670
fused cyclopropane: *JACS*, 2017, *139*, 9164
5-membered rings: *JACS,* 2018, *140*, 4792

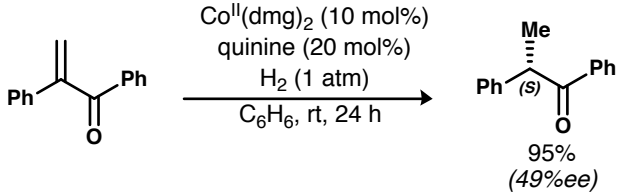
Preliminary evidence for enantioinduction *via* Co—H HAT

Shigehisa *JACS,* 2016,*138,* 10597



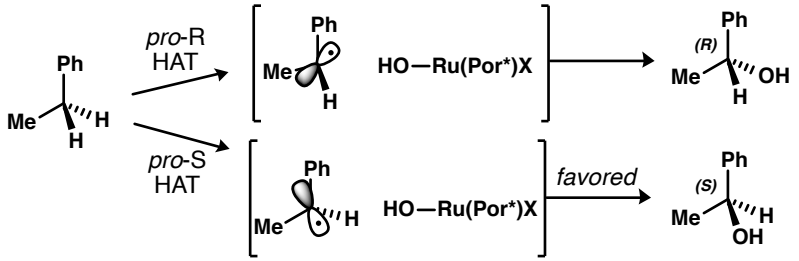
See also **Fe**-catalyzed enantioconvergent Kumada coupling:
JACS, 2015, *137*, 7128

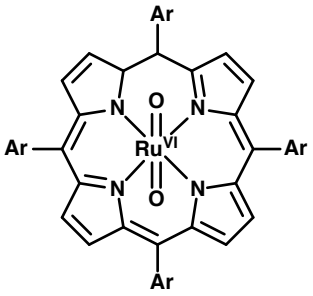
Yoshimura, *Chem Lett*, 1973, 265; *BCSJ*, 1971, 583



Non-Chain Radical Capture *via* Metal-Oxo Complexes

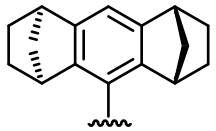
Che *Chem Commun.*, 1999, 1791





D_4-symmetric Ru(VI)

Ar =



See also:
Fe=O: Groves, *JACS*, 1989, *111*, 8537
Mn=O: Katsuki, *TL*, 1996, 37, 4979

So you want to rationally design a catalytic asymmetric radical reaction?

- Consider radical conformation (*planar* vs *pyramidal*). (Unless relying on chiral memory, consider locking into planar conformation.)
- Stereodiscrimination based on *steric approach* is possible, but requires large, synthetically demanding ligands
- Mechanistically investigated TM-catalyzed reactions induce asymmetry through steric bias *plus* distortion-interaction effects and/or Curtin-Hammett principles
- Same principles of enantioinduction for a given transformation can be used with varying means of radical generation