

Lanthanides in Organic Synthesis

Heathcock / MacMillan Seminar

Feb. 22, 2000

Tristan Lambert

- I. Properties of the lanthanides
- II. Lanthanide metals
- III. Divalent lanthanides
- IV. Trivalent lanthanides
- V. Tetravalent lanthanides
- VI. Enantioselective processes

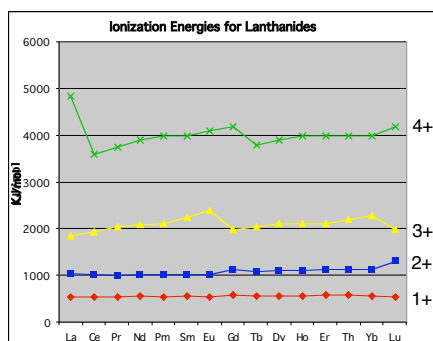
H																	He	
Li	Be											B	C	N	O	F	Ne	
Na	Mg											Al	Si	P	S	Cl	Ar	
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn	
Fr	Ra		Rf	Db	Sg	Bh	Hs	Mt										
		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu		
		Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr		

Reviews: Molander *Chem. Rev.* **1992**, *92*, 29

Imamoto, *Lanthanides in Organic Synthesis*, 1994.

Oxidation States of the Lanthanides

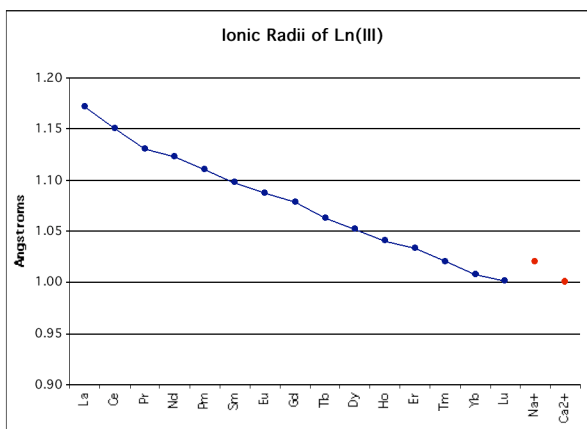
- Most stable oxidation state of the lanthanides is +3
- For dipositive lanthanides Sm^{2+} (f^6 , nearly half-filled), Eu^{2+} (f^7 , half-filled), and Yb^{2+} (f^{14} , filled) are known with relative stability in H_2O being $\text{Eu}^{2+} \gg \text{Yb}^{2+} \gg \text{Sm}^{2+}$
- Ce^{4+} (f^0) is the only tetravalent lanthanide stable in water



- Ionization energies reflect relative energies of the 4f, 5d, 6s orbitals
- 6s electrons are removed first, hence first two ionization energies for all lanthanides are essentially the same
- Third ionization usually results from removal of an electron from the 5d orbital
- Fourth ionization energy reflects successive electron occupation of 4f orbitals

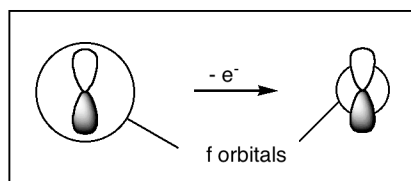
La	$5d^1 6s^2$
Ce	$4f^1 5d^1 6s^2$
Pr	$4f^3 6s^2$
Nd	$4f^4 6s^2$
Pm	$4f^5 6s^2$
Sm	$4f^6 6s^2$
Eu	$4f^7 6s^2$
Gd	$4f^7 5d^1 6s^2$
Tb	$4f^9 6s^2$
Dy	$4f^{10} 6s^2$
Ho	$4f^{11} 6s^2$
Er	$4f^{12} 6s^2$
Tm	$4f^{13} 6s^2$
Yb	$4f^{14} 6s^2$
Lu	$4f^{14} 5d^1 6s^2$

Properties of the Lanthanide Ions



- Lanthanide contraction: ionic radii decrease regularly with increasing atomic number
- Due to ineffective shielding of the 4f electrons \Rightarrow increased effective nuclear charge
- Ionic radii larger than those of d-block elements, can accommodate up to 9 to 12 ligands

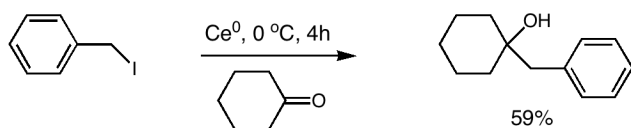
- Upon ionization, f-orbitals are greatly contracted towards the nucleus \Rightarrow effectively eliminates covalent bonding interaction with ligands
- Highly ionic ligand-metal interaction \Rightarrow no need for orbital overlap
- Coordination geometries defined by electrostatic and steric considerations



Organocerium Reagents

Addition to Carbonyls

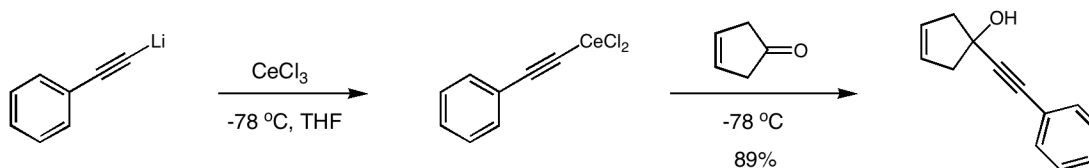
Barbier Reactions



- Ketones and aldehydes react smoothly with organocerium reagents

- Esters and nitriles are unreactive

Imamoto *J. Org. Chem.* **1984**, *49*, 3904.

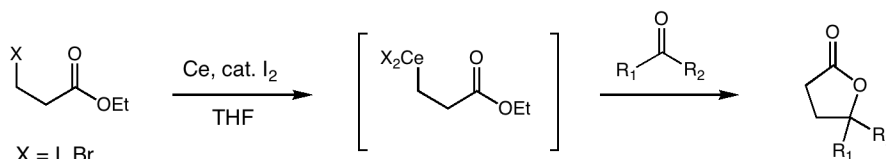


- Even easily enolizable ketones undergo addition in excellent yields

- Organocerium compounds can be prepared from the corresponding organolithium or organomagnesium compounds

Imamoto *Tetrahedron Lett.* **1984**, *25*, 4233.

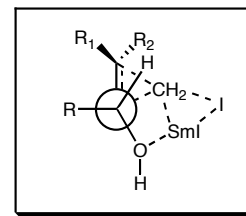
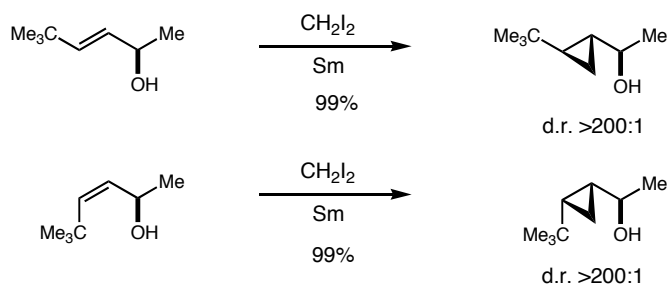
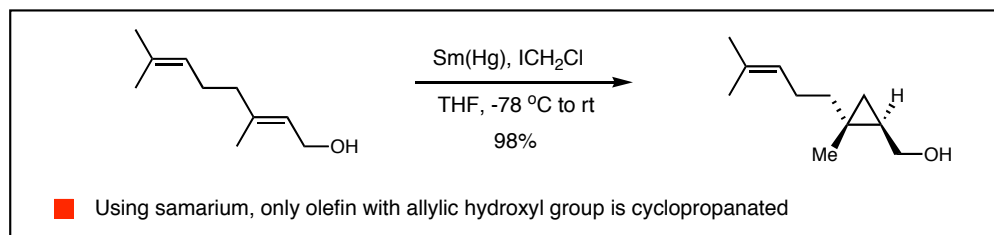
Reformatsky Reactions



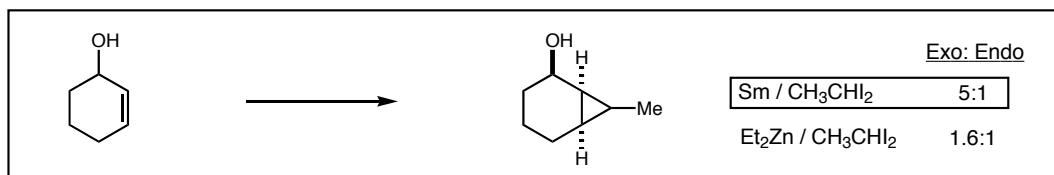
Fukuzawa *J. Org. Chem.* **1990**, *55*, 1628.

Lanthanide Metals: Sm⁰

Cyclopropanation of Allylic Alcohols



Molander *J. Org. Chem.* **1989**, *54*, 3525.

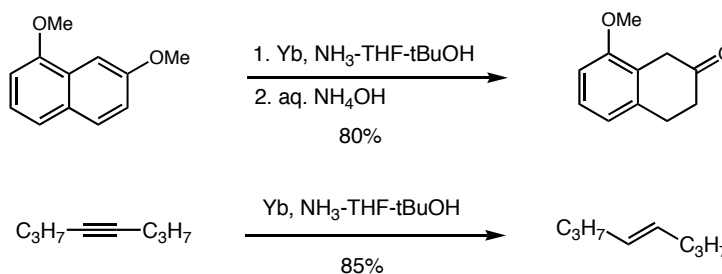


■ Samarium offers enhanced diastereoselectivity over conventional reagents

Evans Chem. Rev. **1993**, *93*, 1307.

Lanthanide Metals: Reductions

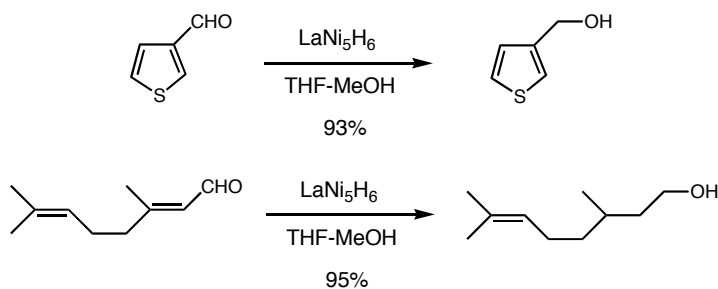
Dissolving Metal Reductions Using Yb



■ Similar to Birch reduction with alkali metal, however avoids strongly basic hydroxide upon workup

White J. Org. Chem. **1978**, *43*, 4555.

Hydrogenation Using Lanthanide Alloys



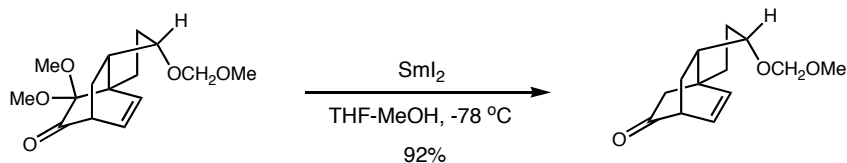
■ Reduces alkynes, alkenes, aldehydes, ketones nitriles, imines, and nitro compounds

■ Not poisoned by amino or halogen containing compounds

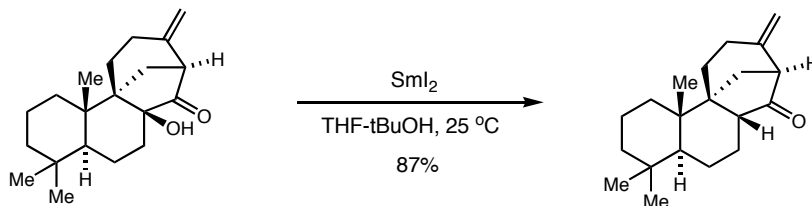
Imamoto J. Org. Chem. **1987**, *52*, 5695.

Divalent Lanthanides: Samarium Iodide

Reduction of α -Substituted Ketones and Esters



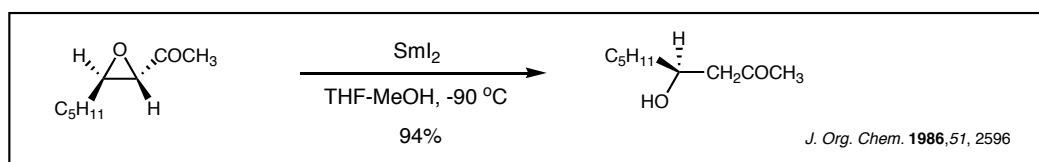
Tetrahedron Lett. 1991,32, 6583



White J. Am. Chem. Soc. 1987, 109, 4424

- α -Halo, sulfoxides, sulfones, and α -oxygenated ketones are reduced
- Primary iodides, esters, and ketones are unaffected

J. Org. Chem. 1986,51, 1135

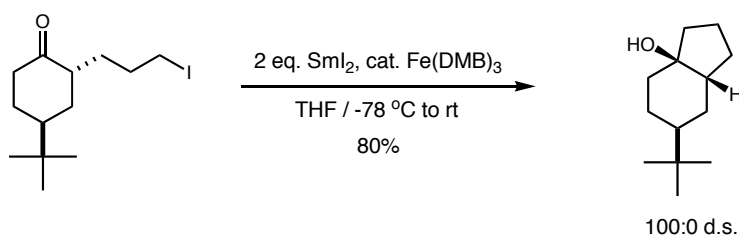


J. Org. Chem. 1986,51, 2596

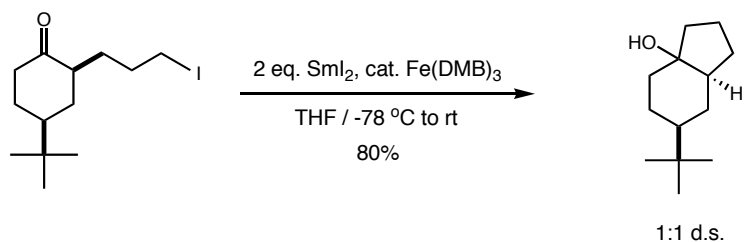
- Reduction of optically active epoxy ketones gives β -hydroxy ketones without loss of optical purity

Divalent Lanthanides: Samarium Iodide

Intramolecular Barbier Reactions

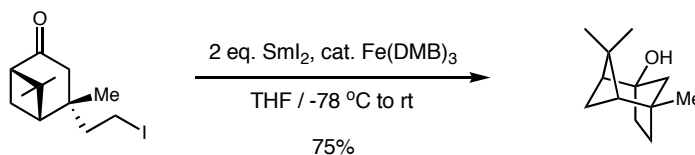


100:0 d.s.



1:1 d.s.

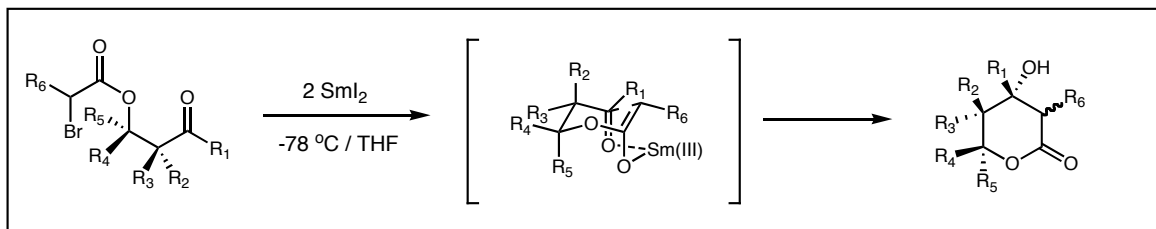
- Method overcomes difficulties associated with using Mg, Li, Na
- Synthetically useful for substrates which allow for control of diastereoselectivity



Molander J. Org. Chem. 1991, 56, 4112.

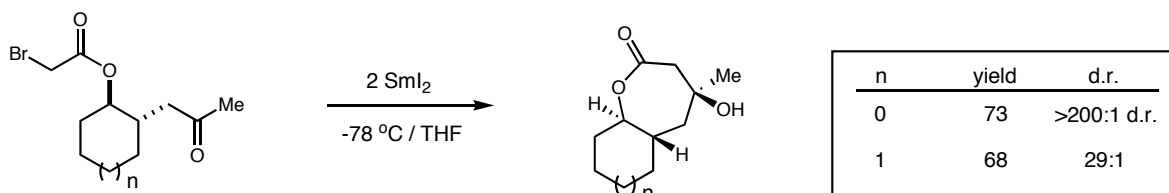
Divalent Lanthanides: Samarium Iodide

Intramolecular Reformatsky Reactions



R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	yield	d.r.
Ph	H	Me	H	H	H	76	>200:1
tBu	H	Me	H	H	H	85	>200:1
Et	H	Me	H	H	H	85	3:1

Large substituent in the R₁ position usually results in high diastereoselectivity



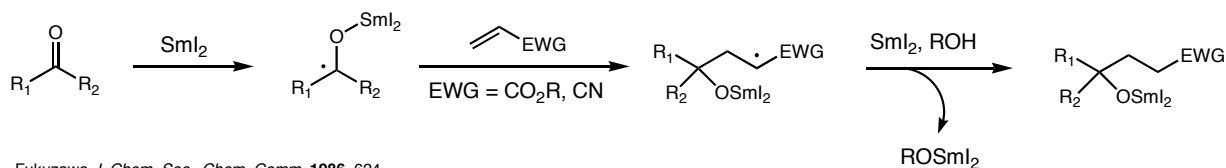
Reactions to form bicyclic systems proceed with very high diastereoselectivities although yields are sometimes moderate to low

Molander *J. Am. Chem. Soc.* **1991**, *113*, 8036.

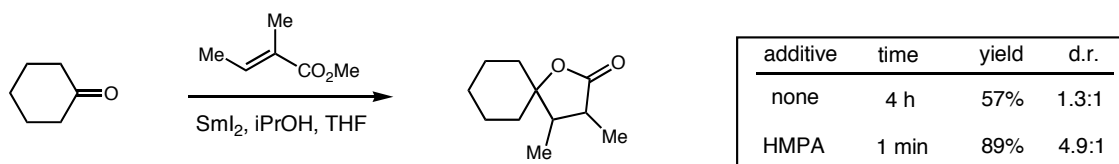
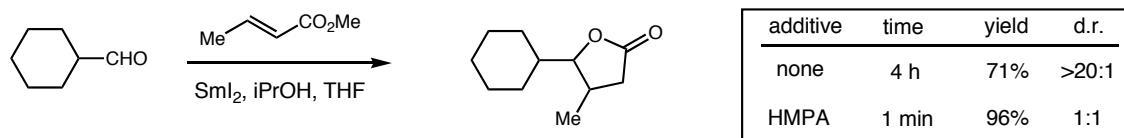
Divalent Lanthanides: Samarium Iodide

Radical Carbonyl-Alkene Couplings

Mechanism



Fukuzawa *J. Chem. Soc., Chem. Comm.* **1986**, 624.



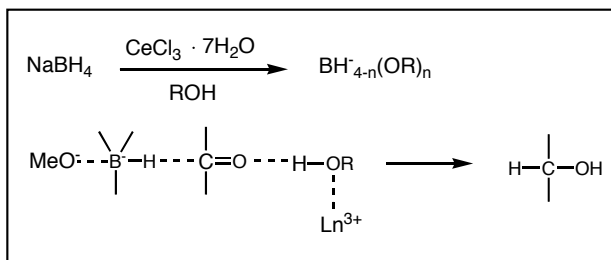
Inanaga *Tetrahedron Lett.* **1986**, *27*, 5763.

- HMPA dramatically improves reaction rate and yield.
- Diastereoselectivity is improved when γ -disubstituted lactones are formed

Trivalent Lanthanides: Luche Reduction

Selective 1,2 Reduction of α -Enones

Mechanism



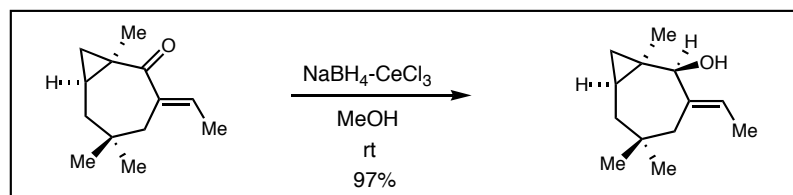
- Sodium borohydride is rapidly converted to an alkoxide species
- Carbonyl is activated through hydrogen bonding by a lanthanide-bound molecule solvent
- Hard borohydride preferentially attacks the hard carbonyl carbon

Luche *J. Am. Chem. Soc.* **1981**, *103*, 5454.



Luche *J. Am. Chem. Soc.* **1978**, *100*, 2226.

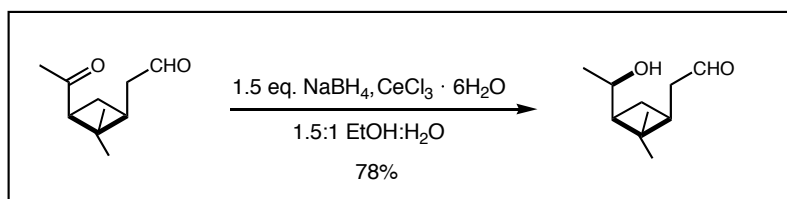
with CeCl_3	97%	3%
without	0%	100%



Paquette *J. Am. Chem. Soc.* **1987**, *109*, 3025.

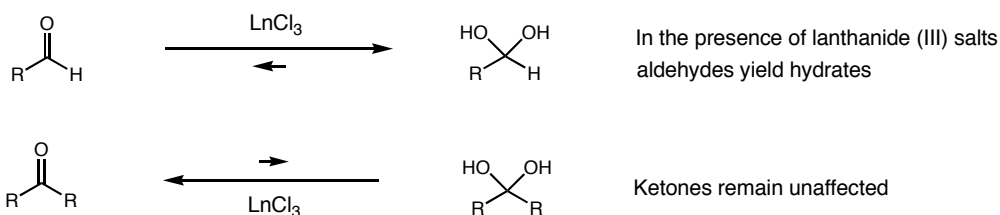
Trivalent Lanthanides: Reduction of Ketones

Selective Reduction of Ketones in the Presence of Aldehydes



- Eliminates need for three step protection-reduction-deprotection scheme

Rationale

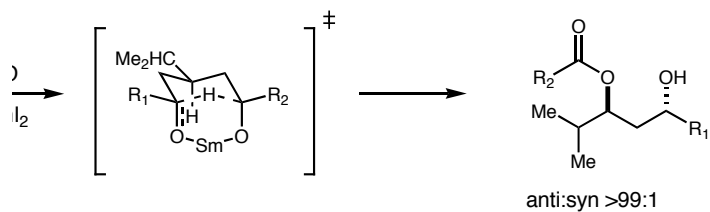


- Hemiketal or Ketal formation is ruled out because similar results (within 5%) were obtained with MeOH and iPrOH

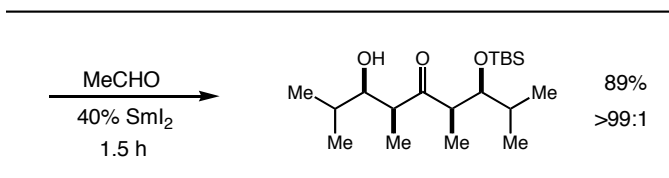
Luche *J. Am. Chem. Soc.* **1979**, *101*, 5848.

anides: Reduction of Ketones

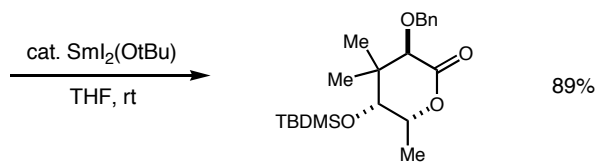
ans-Tischenko Reduction



by β -hydroxy stereocenter dominates α -methyl stereocenter

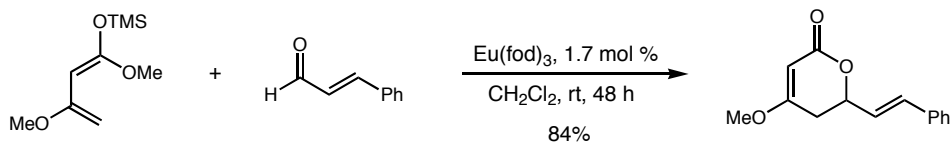


Evans *J. Am. Chem. Soc.*, **1990**, 112, 6447.



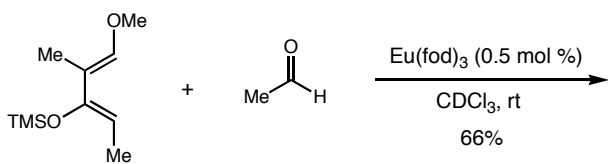
Uenishi *Tetrahedron Lett.*, **1991**, 32, 5097.

Trivalent Lanthanides: Hetero-Diels-Alder



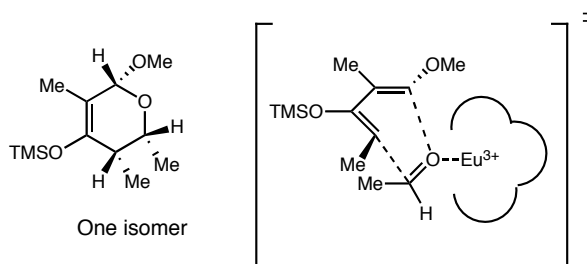
■ Exclusive carbonyl addition

Castellino *Tetrahedron Lett.*, **1984**, 25, 4059.



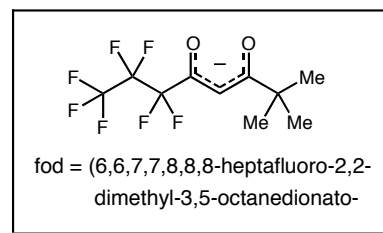
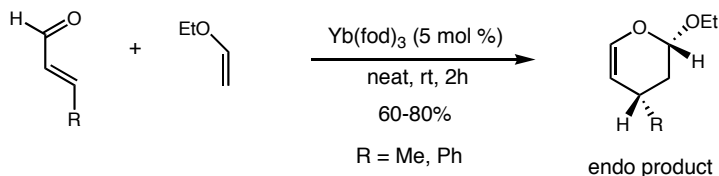
■ Reactions proceed with high endo selectivity

■ Bulky catalyst prefers to occupy exo position



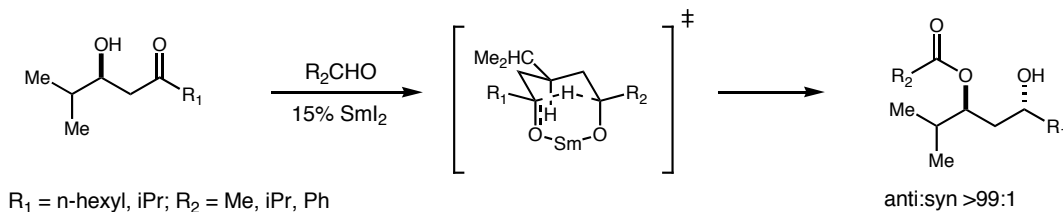
Midland *J. Am. Chem. Soc.*, **1984**, 106, 4294.

Inverse Demand

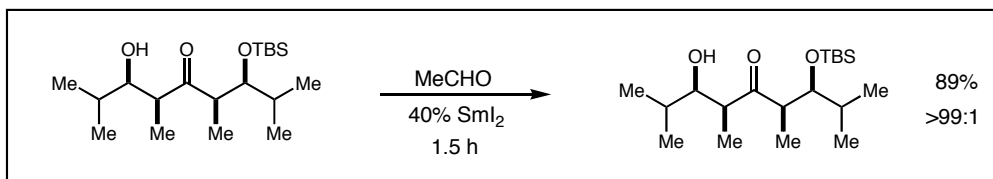


Trivalent Lanthanides: Reduction of Ketones

Evans-Tischenko Reduction

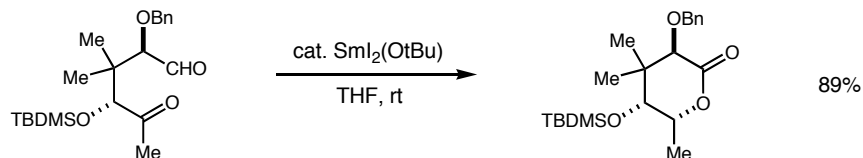


■ Asymmetric induction by β -hydroxy stereocenter dominates α -methyl stereocenter



Evans *J. Am. Chem. Soc.*, **1990**, 112, 6447.

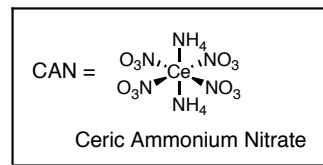
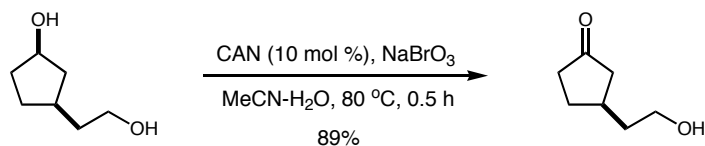
Intramolecular Tischenko Reaction



Uenishi *Tetrahedron Lett.*, **1991**, 32, 5097.

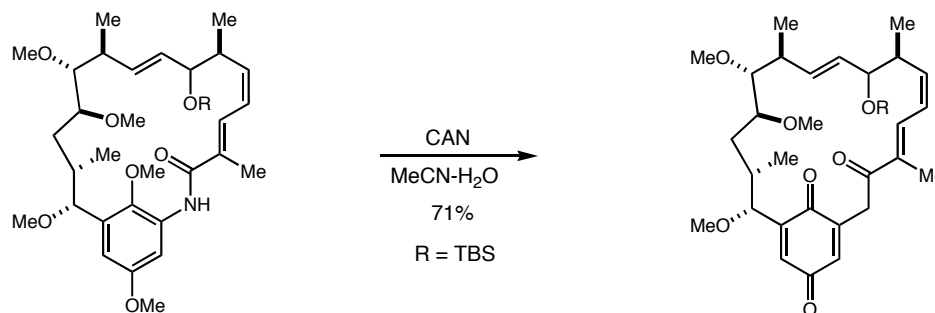
Tetravalent Lanthanides: Oxidations

Selective Secondary Alcohol Oxidation



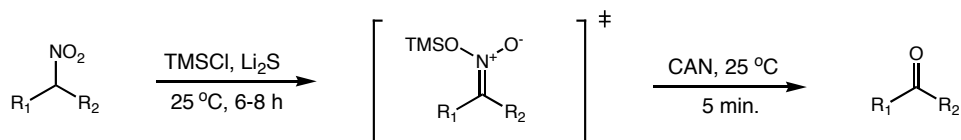
Oshima *Bull. Chem. Soc. Jpn.*, **1986**, 59, 105

Oxidation of Phenol Ethers



Evans *J. Org. Chem.*, **1992**, 57, 1067

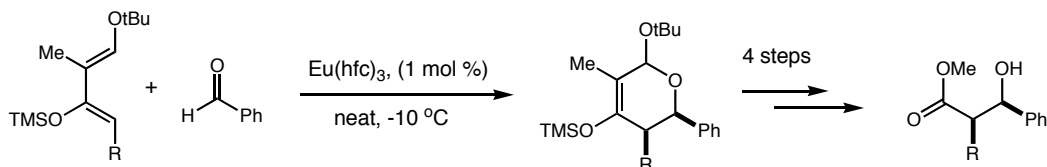
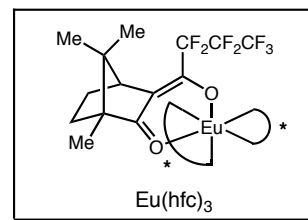
Oxidation of Nitro Compounds to Ketones



Olah *Synthesis*, **1980**, 44

Enantioselective Reactions

Europium(III) Hfc Promoted Hetero-Diels-Alder



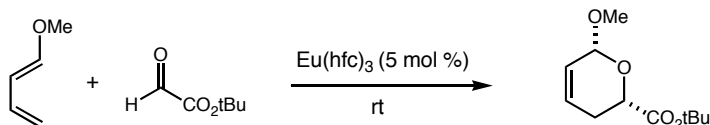
Danishesky, *Tetrahedron Lett.* **1983**, 24, 3451.

Danishesky, *J. Am. Chem. Soc.* **1983**, 105, 3716.

R = H 58% ee

R = Me 55% ee

■ Larger C₁ alkoxy substituents gave increased ee

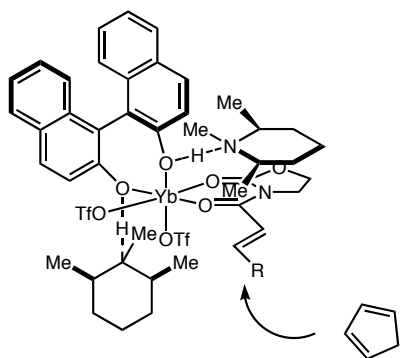
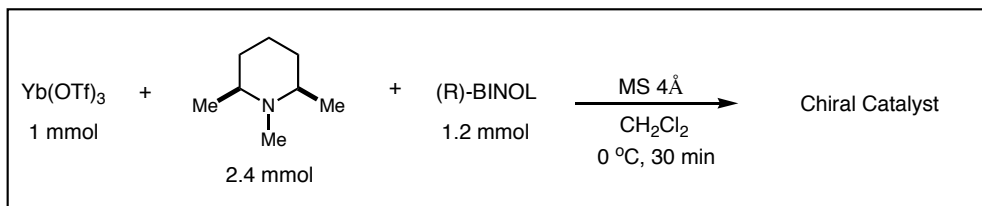
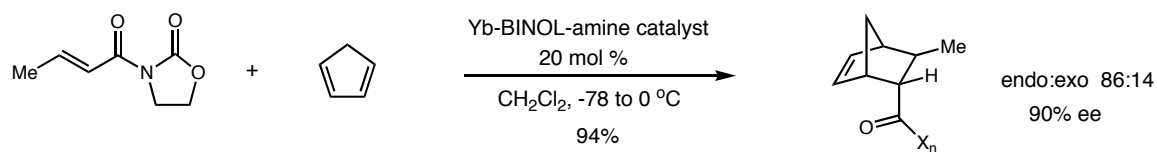


	trans	cis
yield	79	39 %
ee	19	64%

Jankowski, *J. Chem. Soc., Chem. Comm.* **1987**, 676.

Enantioselective Reactions

Yb(III) BINOL Hetero-Diels-Alder



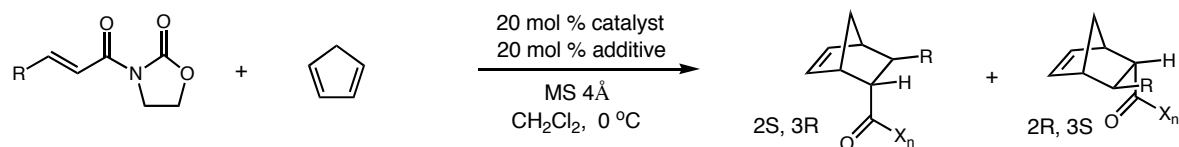
- Reaction proceeds only very slowly without BINOL ⇒ amine not interacting with metal
- Larger amines typically give higher ee
- Spectroscopic evidence for amine-BINOL H-bonding

Kobayashi *Tetrahedron Lett.* **1993**, 34, 4535.

Kobayashi *J. Org. Chem.* **1994**, 59, 3758.

Enantioselective Reactions

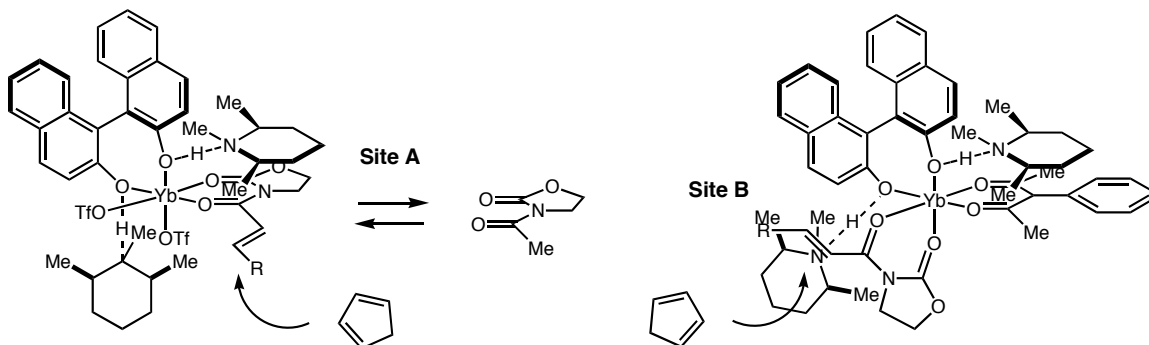
Yb(III) BINOL Hetero-Diels-Alder: Reversal of Enantioselectivity



additive	Me				Ph			
	% yield	endo:exo	2S, 3R	2R, 3S	% yield	endo:exo	2S, 3R	2R, 3S
Me	77	89:11	98	2	83	93:7	9	91
nPr	81	80:20	93	8	81	91:9	10	90

Kobayashi *Tetrahedron Lett.*, **1994**, 35, 6325

Kobayashi *J. Am. Chem. Soc.*, **1994**, 116, 4083

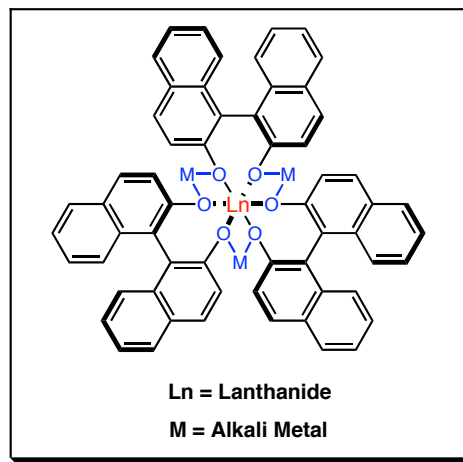
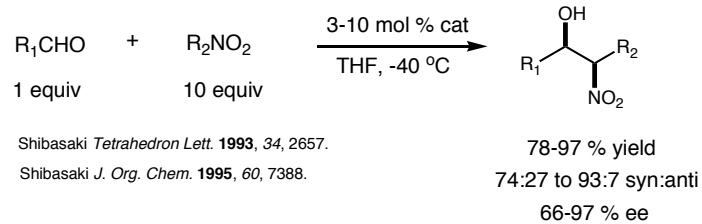


Enantioselective Reactions

Heterobimetallic Catalysis

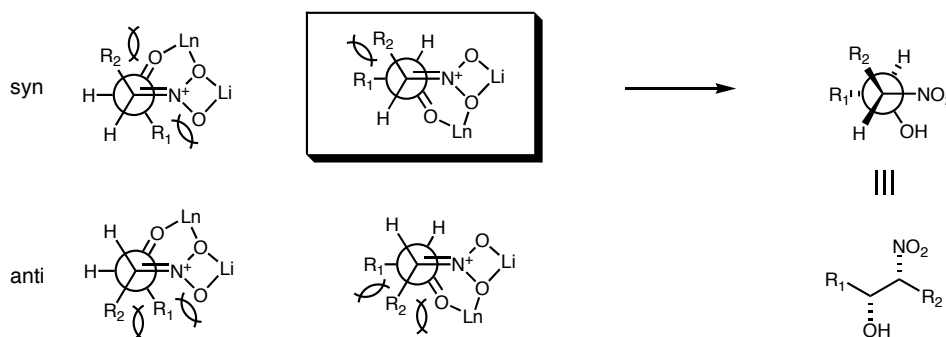
Review: Shibasaki *ACIE*, 1997, 36, 1236.

Nitroaldol



Catalyst acts as **Lewis acid** and **Lewis Base**

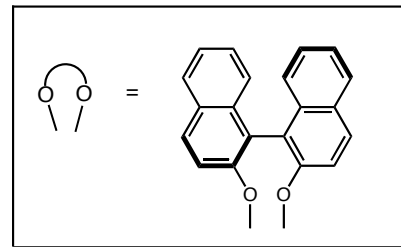
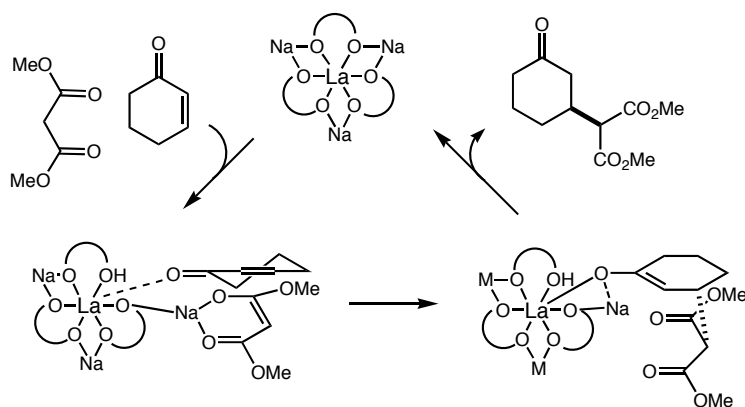
■ Explanation of syn selectivity Shibasaki *J. Org. Chem.* 1995, 60, 7388.



Enantioselective Reactions

Heterobimetallic Catalysis

Michael Reaction



■ Li and K catalysts gave poor ee

■ Metal free La-BINOL complex provides almost no enantioselectivity

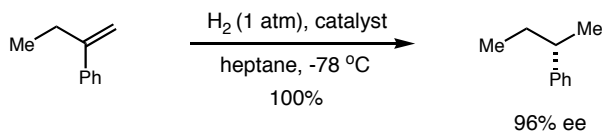
Shibasaki *J. Am. Chem. Soc.*, 1995, 117, 6195

Yield	89	91	98	93
% ee	72	92	83	77

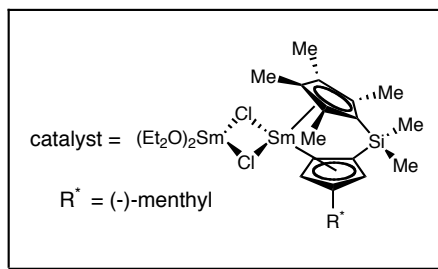
Enantioselective Reactions

Miscellaneous Reactions

Olefin Hydrogenation



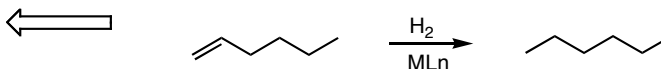
Marks, T. J. *J. Am. Chem. Soc.*, **1992**, *114*, 2761.



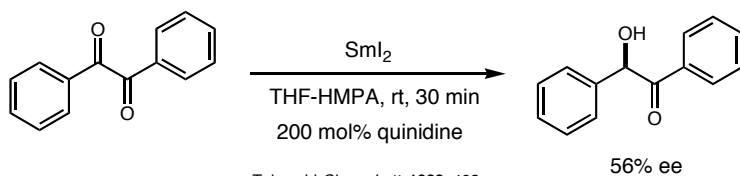
MLn	N_t (turnover number)
$((\text{C}_5\text{Me}_5)_2\text{LuH})_2$	$120,000\text{ h}^{-1}$
$\text{Rh}(\text{PPh}_3)_3\text{Cl}$	650 h^{-1}
$\text{Ru}(\text{H})(\text{Cl})(\text{PPh}_3)_3$	$3,000\text{ h}^{-1}$
$\text{Ru}(\text{COD})(\text{PPh}_3)_2\text{PF}_6$	$4,000\text{ h}^{-1}$

Marks, T. J. *J. Am. Chem. Soc.*, **1985**, *107*, 8111.

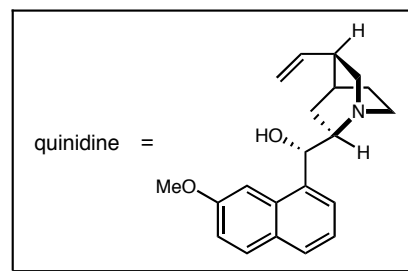
■ Lanthanide hydrogenation catalysts are highly reactive



Ketone Reduction



Takeuchi *Chem. Lett.* **1988**, 403.



Summary

- Lanthanide metals are useful for reduction of functional groups and for carbon-carbon bond forming reactions
- Europium, Samarium, and Ytterbium can form relatively stable divalent states. Europium is stable enough to exist in water. SmI_2 is the most widely employed Ln(II) and is used for one electron reductive reactions
- Trivalent lanthanides are hard Lewis acids with high oxophilicity and as such are employed in several highly selective reactions (Luche reduction, hetero-Diels-Alder)
- f-orbital electrons are imperfect shielders and so Ln(III) have their f-orbitals greatly contracted towards the nucleus. This effectively eliminates covalent bonding interactions with ligands and therefore lanthanide-ligand geometries are largely determined by steric considerations. Asymmetric lanthanide promoted processes are therefore less straightforward than those using main group or d-block elements
- Ce(IV) is the only tetravalent lanthanide which is stable in water and to date is the only synthetically useful Ln(IV) with applications in the oxidation of functional groups such as alcohols and phenol ethers.
- Note: Scandium ($3d^1$) and Yttrium ($4d^1$) have similar properties to those of the lanthanides and are often treated as lanthanides