

# Pinacol Coupling

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Steven Breazzano

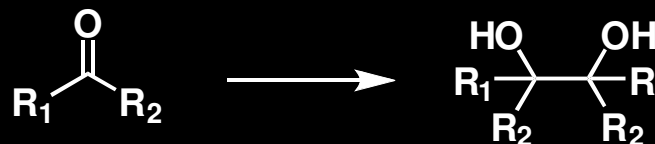
7/25/2008



# Outline

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- Introduction and mechanism
- Diastereoselective coupling
- Enantioselective coupling
- Catalytic conditions
- Other non metal based protocols
- Synthetic Applications



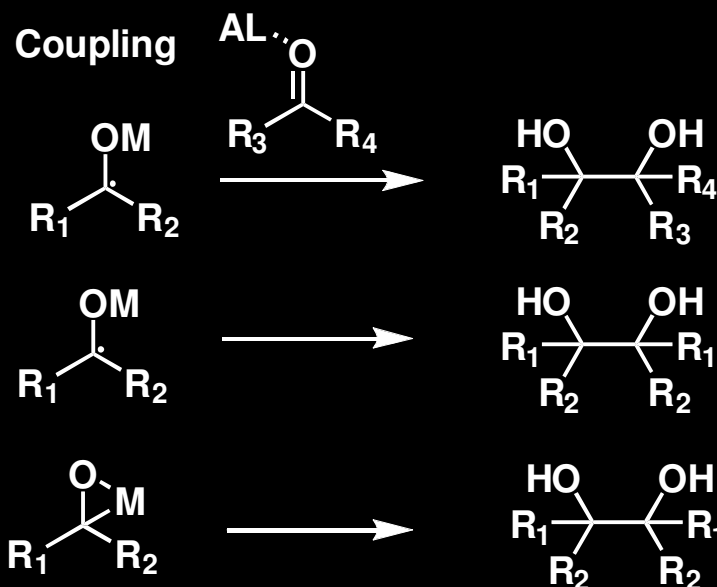
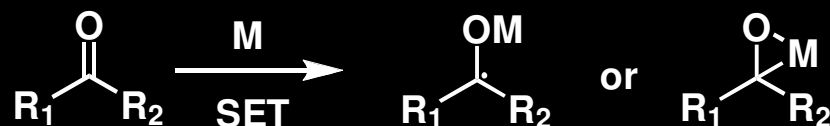
# Introduction

## •Synthetically Useful



## •Mechanism

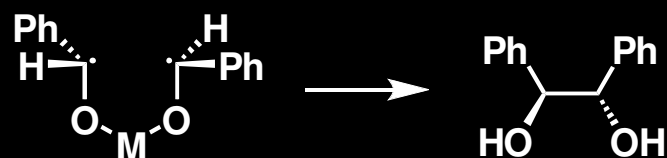
### Generation of Ketyl Radical



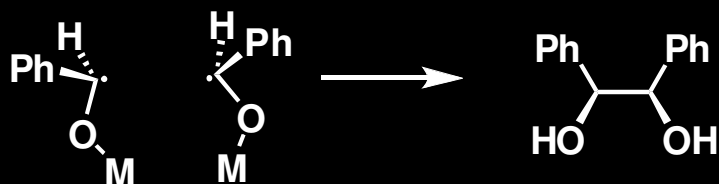
# Diastereoselectivity

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- Bridged Intermediate – dl isomer



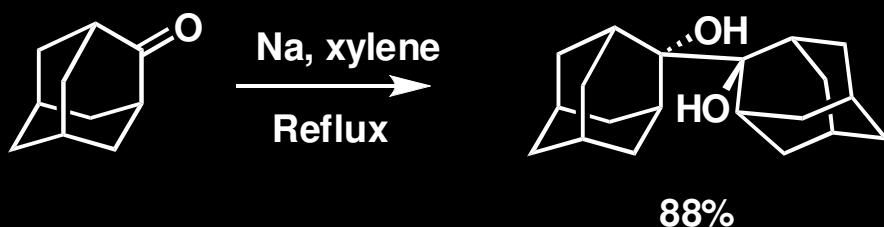
- Acyclic Intermediate – meso compound



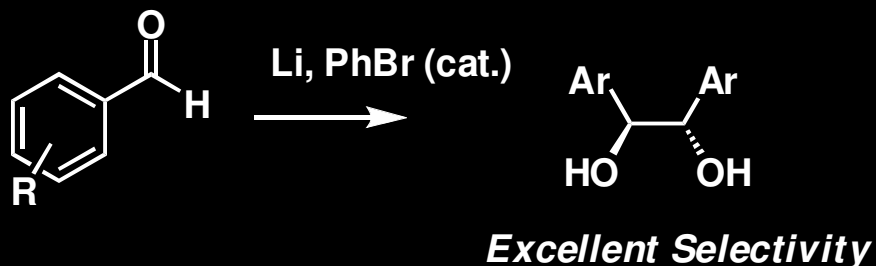
# Commonly Used Reagents

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Alkali and Alkaline Earth Metals – generally poor selectivity  
Exceptions:



New Method from Guo et al. Lithium with Bromobenzene (cat.)  
(neat)



R = various substituents

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Wynberg, H.; Boelema, E.; Wieringa, J. H.; Strating, J. *Tet. Lett.* **1970**, 3613.

Zhao, H.; Li, D.-J.; Deng, L.; Liu, L.; Guo, Q.-X. *Chem. Commun.* **2003**, 506.

# Most Popular Metal: Titanium

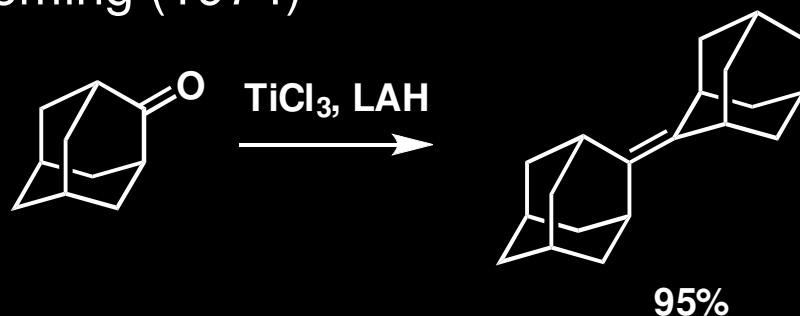
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Low valent Titanium: pioneering work

•Mukaiyama (1973)



•McMurry / Fleming (1974)



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Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, 4708.

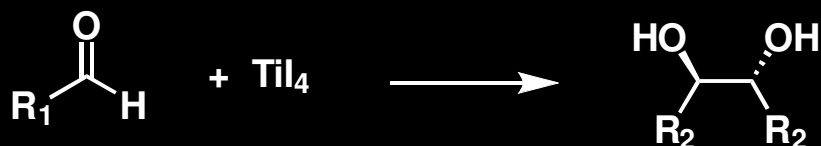
# Other Methods

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Depending on substrate, different conditions are available:

TiCl<sub>3</sub> anhydrous  
Ti(OiPr)<sub>4</sub> / EtMgBr  
TiCl<sub>4</sub> / Zn  
Cp<sub>2</sub>TiCl<sub>2</sub> / Sml<sub>2</sub>  
Cp<sub>2</sub>TiCl<sub>2</sub> / Zn  
Cp<sub>2</sub>TiCl<sub>2</sub> / iPrMgI

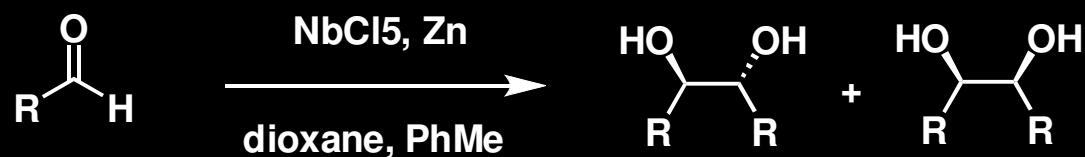
Reducing Agent Free Conditions



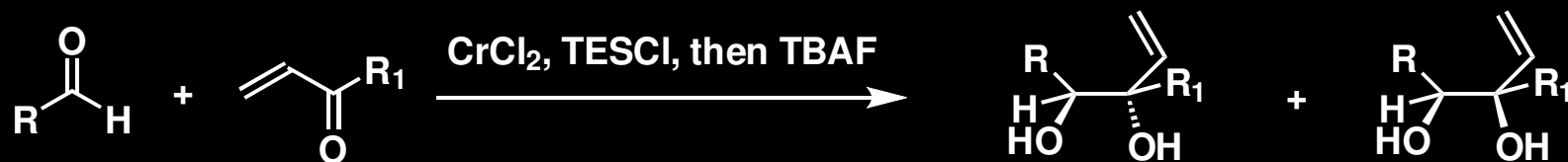
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Chatterjee, N. N. Joshi. *Tetrahedron*. 2006, 12137-12158.  
Hayakawa, R.; Shimizu, M. *Chem. Lett*. 2000, 724.

# Niobium and Chromium



35-87%  
dr up to 99:1



yield 44-99%, dr up to 99:1

Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, 65, 5066.  
Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem., Int. Ed.* **2001**, 40, 1116.

# Lanthanides

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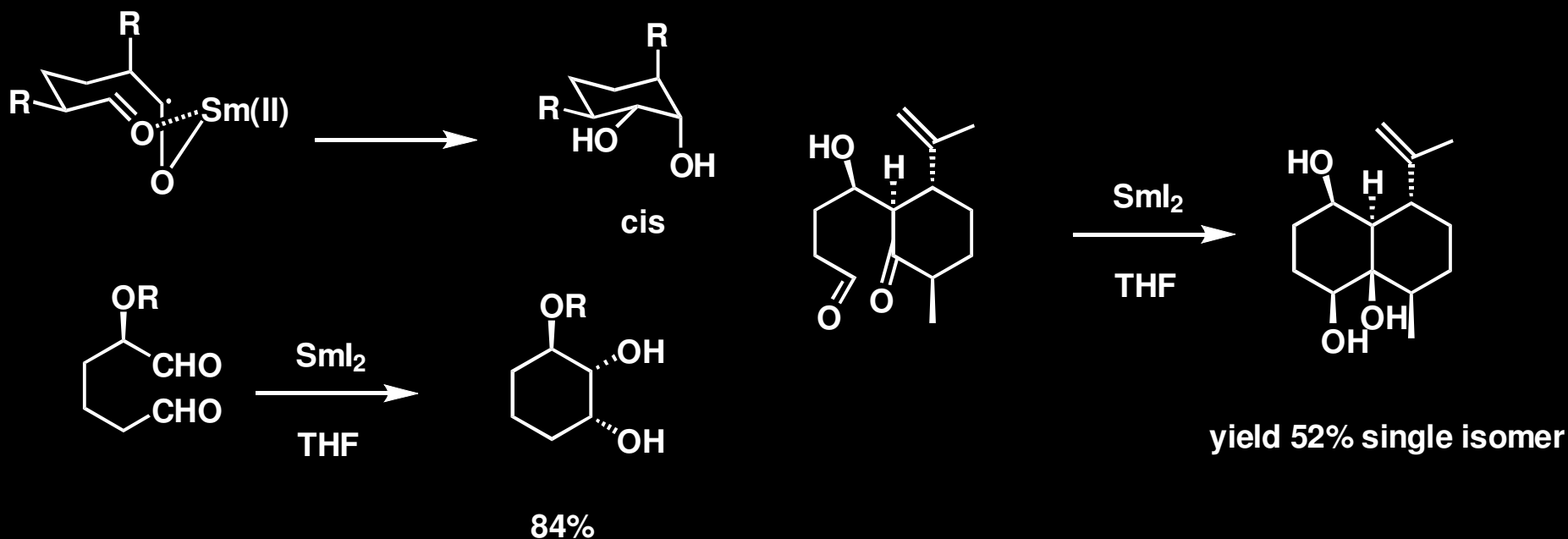
According to Hirao, it is possible to promote pinacol coupling by using almost every lanthanide in the presence of TMSCl under sonication.

Samarium mediated is most popular:



# Samarium

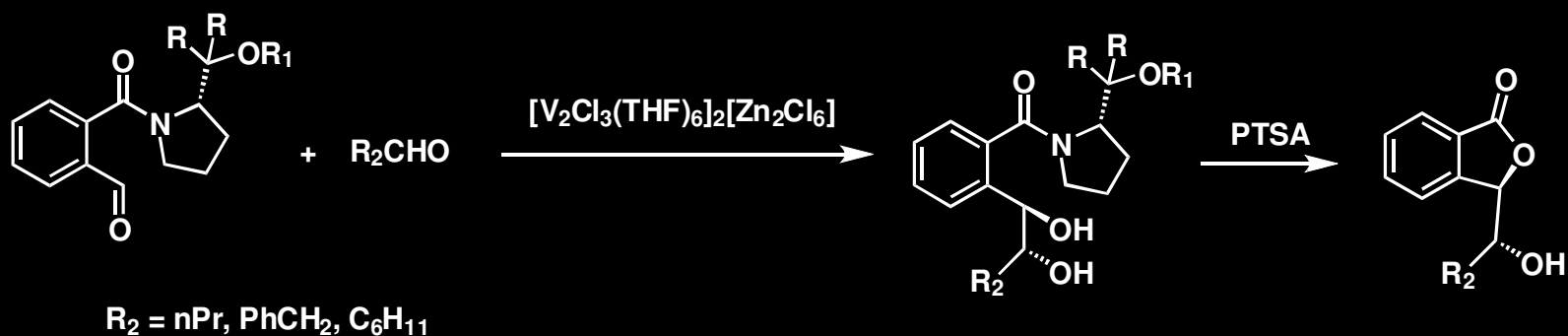
Stereoselectivity governed by substituents and coordinating groups



Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**  
32, 1125.

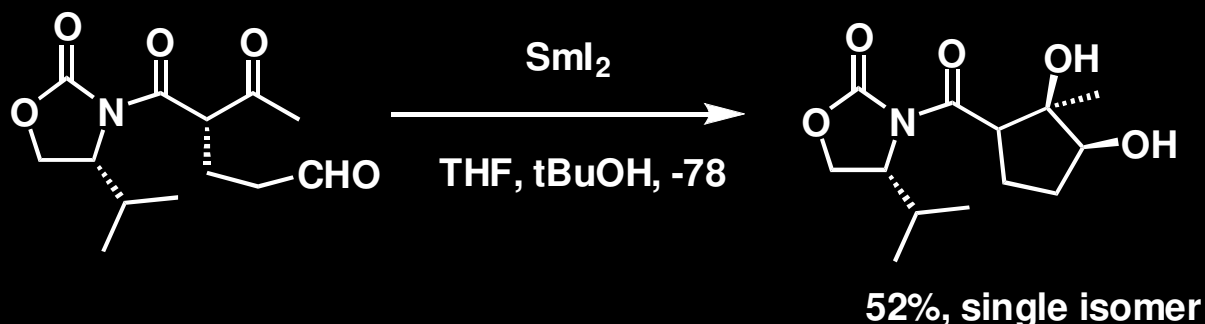
# Enantioselectivity (stoich.)

Vanadium based enantioselective cross coupling



yield 55-83%  
dr up to 93:7  
ee up to 96%

Samarium based

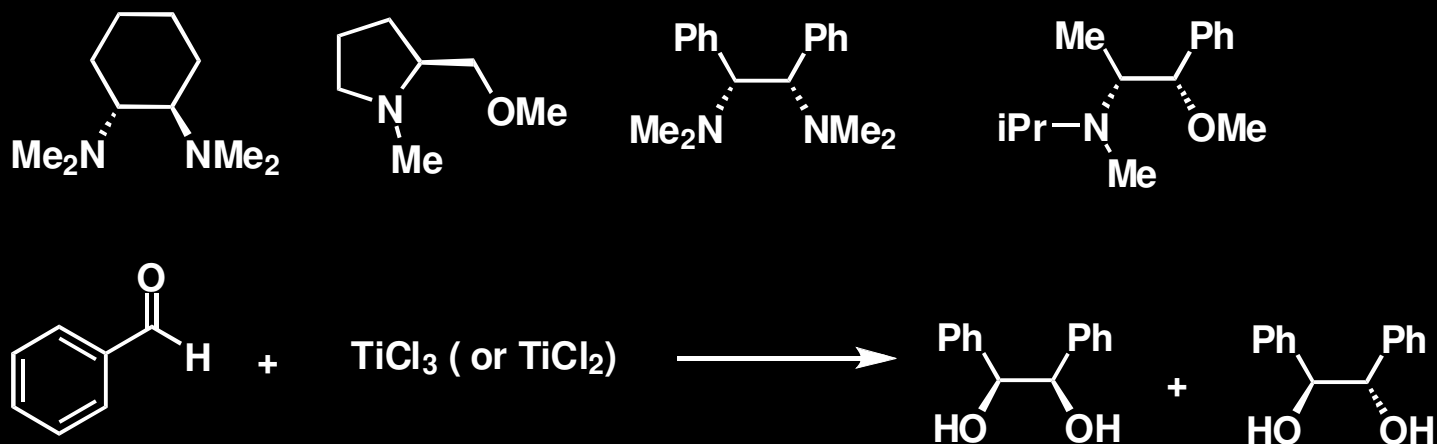


Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992**, *57*, 782.

Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

# Enantioselective

Titanium based with chiral amines

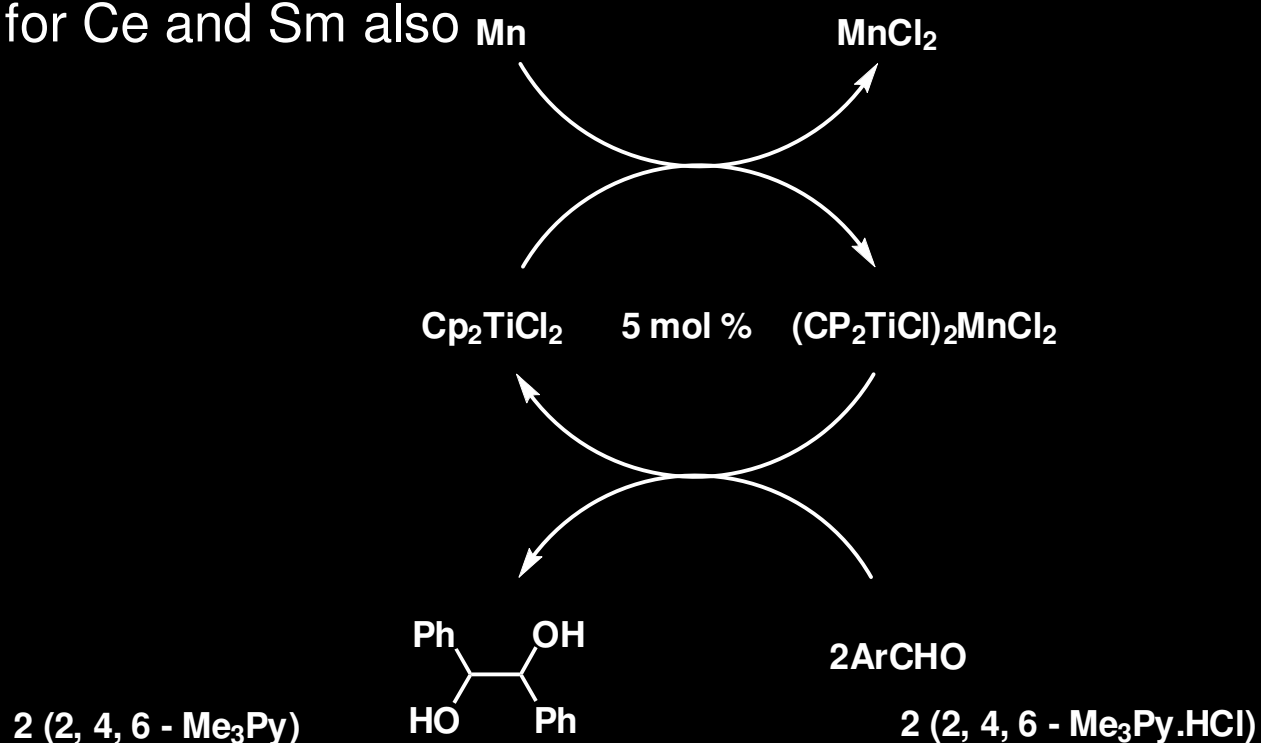


up to 65% ee, good selectivity, but specific substrates

# Catalytic Protocols

Highly desirable for expensive complexes

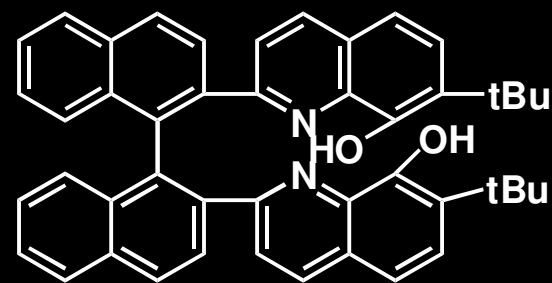
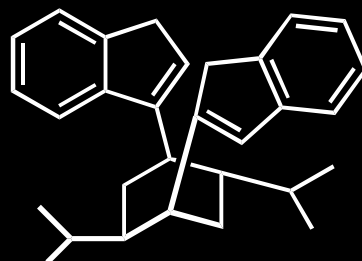
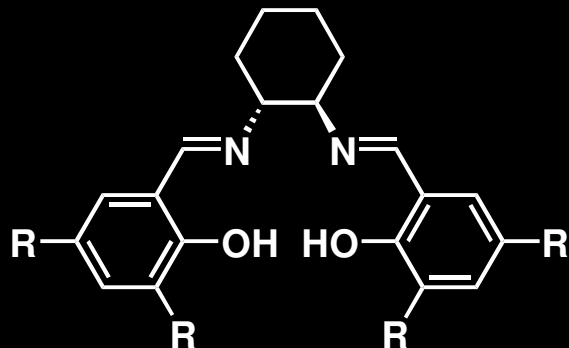
- Simple addition of TMSCl, or in some cases acetic anhydride regenerated catalyst
- New catalytic cycle based on protonolysis.
- Works for Ce and Sm also Mn



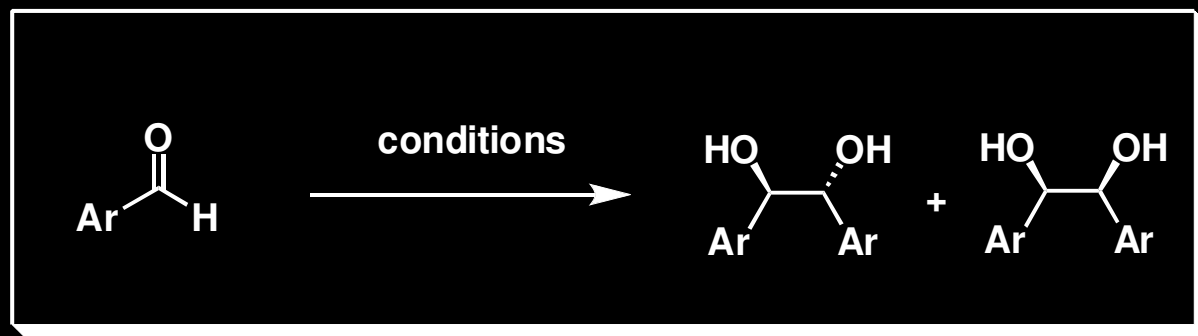
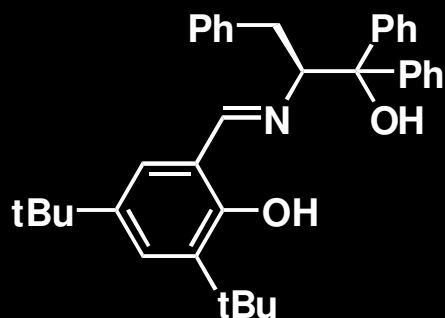
# Catalytic Enantioselective

Conditions: Ti / Zn / TMSCl or Cr- Mn- TESCl

ee : 80-97%



R = tBu or H



Chatterjee, N. N. Joshi. *Tetrahedron*. 2006, 12137-12158.

# Non Metal Based Protocols

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Conditions:

- Sunlight

cheap, but unselective

- Sonication

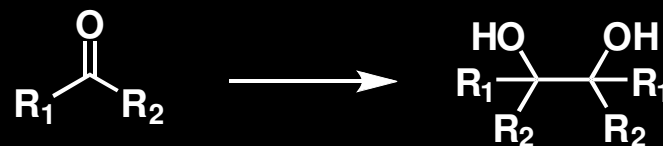
works with Sm and alkali metals. Good selectivities generally

- Electrolysis

some enantioselectivity observed with chiral media, some selectivity based on pH

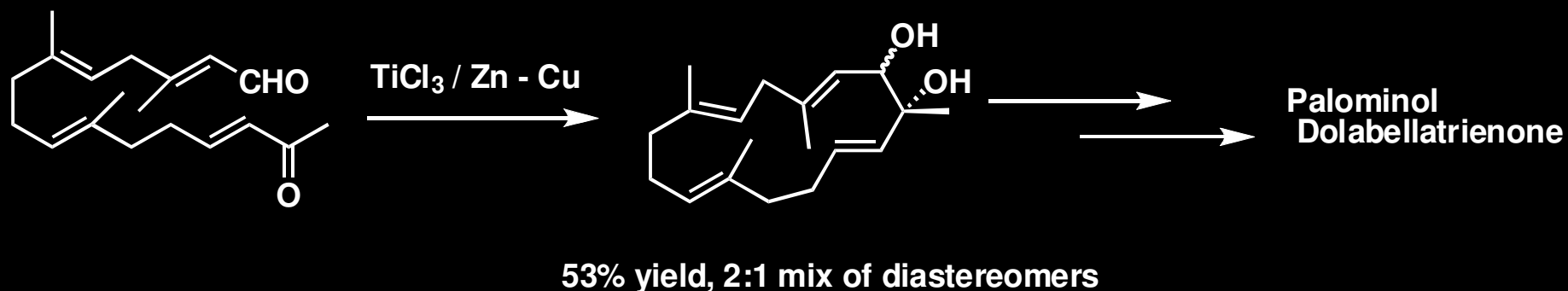
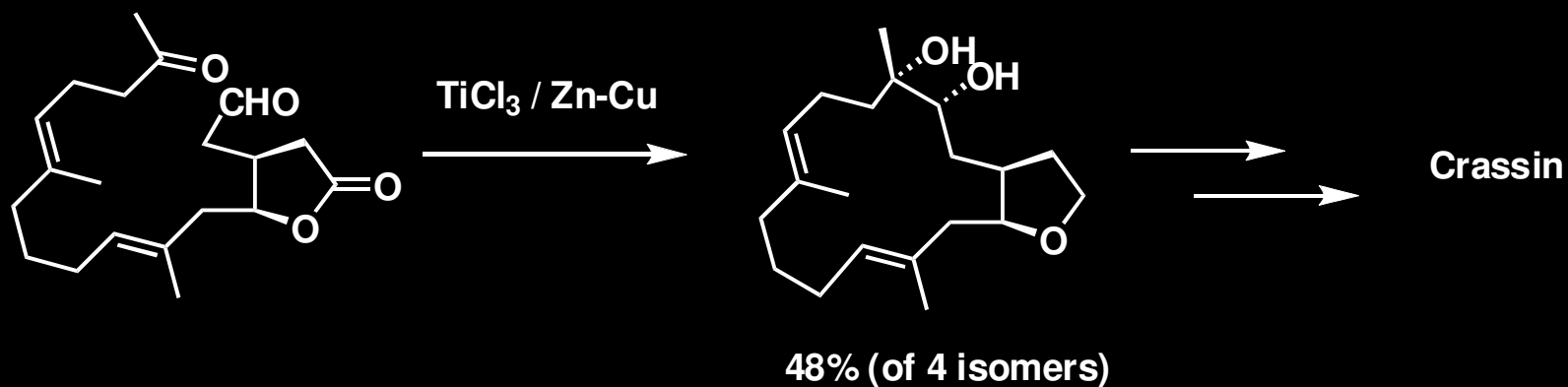
- Aqueous Media

In general selectivity is poor



# Synthetic Applications

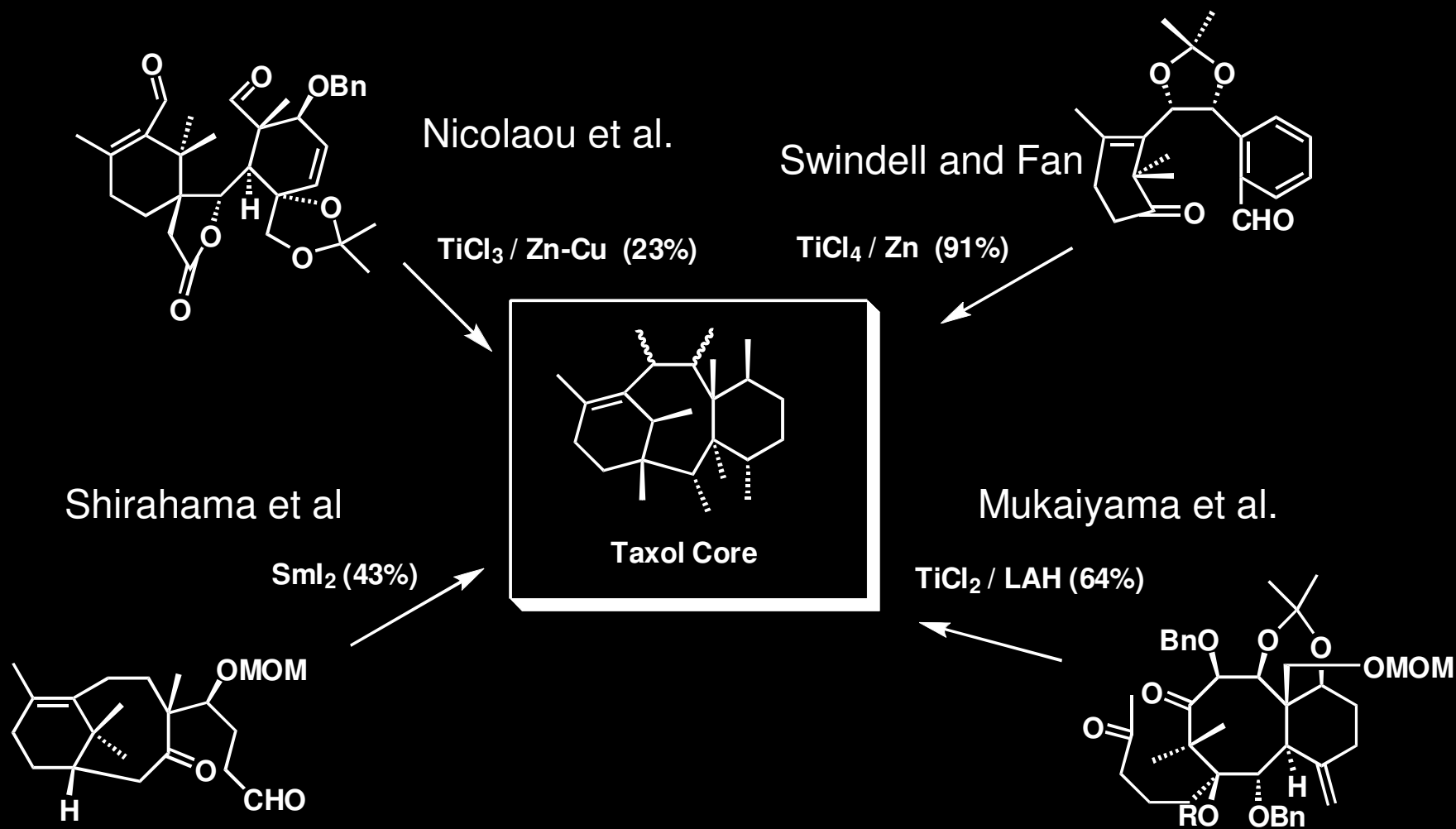
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McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, 111, 8928.  
Corey, E. J.; Kania, R. S. *Tetrahedron Lett.* **1998**, 39, 741.

# Taxol



Chatterjee, N. N. Joshi. *Tetrahedron*. 2006, 12137-12158.