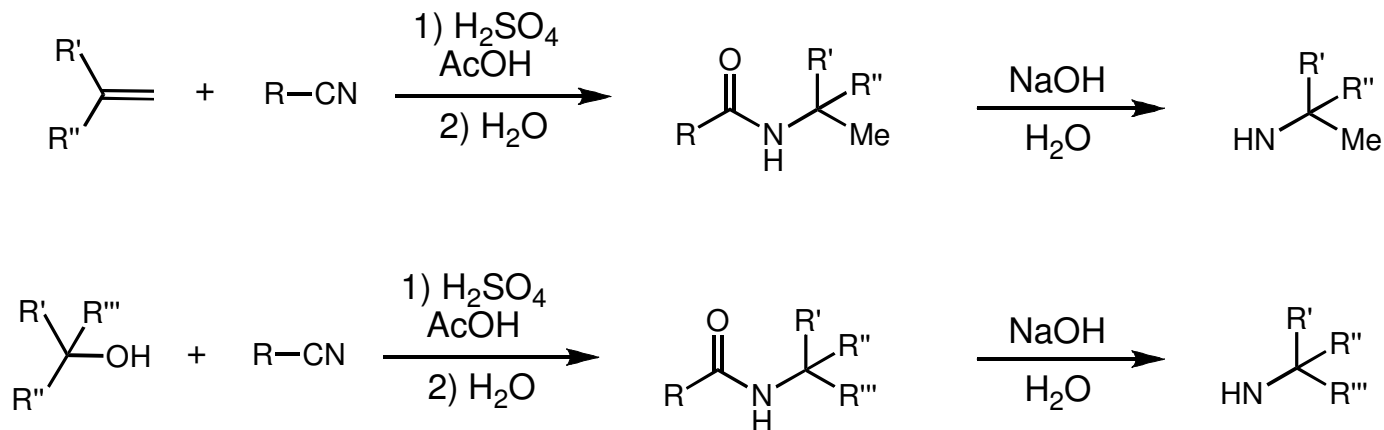


# *Ritter Reaction*

Lisa Marie Ambrosini  
Synthesis Literacy Meeting  
August 8, 2008

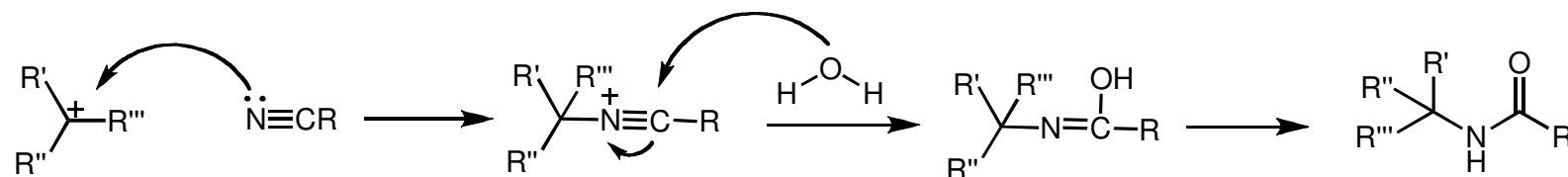
# Seminal Papers

## ■ 1948: Ritter, NYU



Yields: 12-90 %

## ■ Mechanism



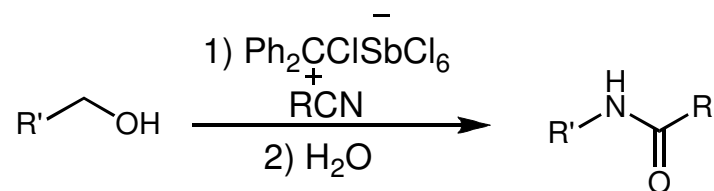
## ■ Limitations:

- Only works for species that can form a stable carbocation
- Very harsh acidic conditions

Ritter, J. J., Minieri, P.P., *J. Am. Chem. Soc.*, **1948**, 70, 4045.  
Ritter, J. J., Kalish, J., *J. Am. Chem. Soc.*, **1948**, 70, 4048.

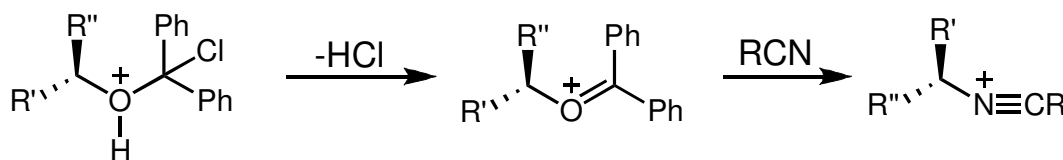
# Activation of Primary and Secondary Alcohols

## ■ Activation by Chlorodiphenylmethylium Hexachloroantimonate



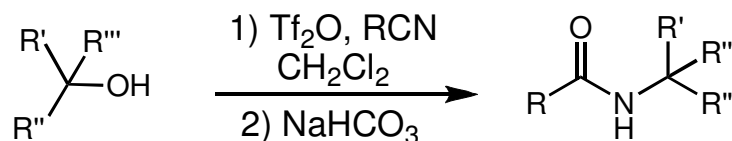
- 12 examples with ranging from 50-86 %

## ■ Mechanism



Barton, D. H. R., *et. al*, *JCS Perkin Trans. 1*, **1974**, 2101.

## ■ Activation by Triflic Anhydride



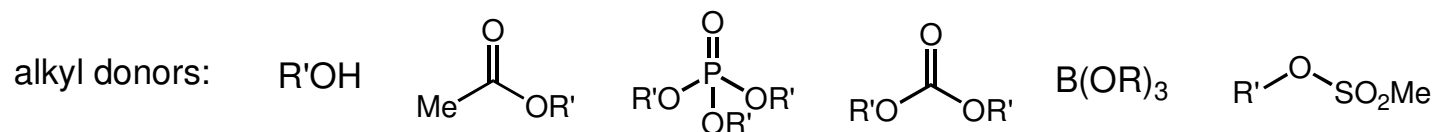
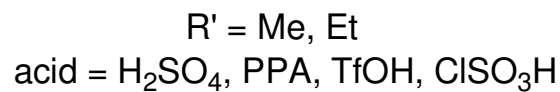
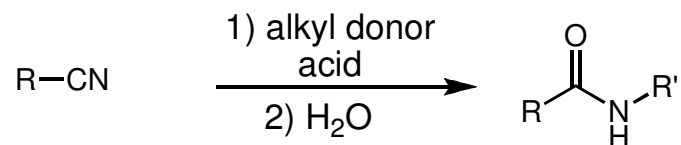
### Yield

Primary 75-90 %  
Secondary 68-75 %  
Tertiary 50 %

Martinez, A. G., *et. al*, *Tet. Lett.*, **1989**, 30, 581.

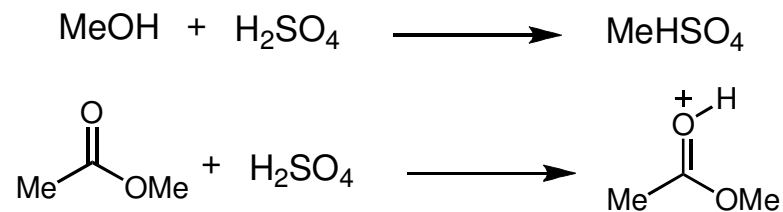
# Modification for Synthesis of N-Primary-alkyl Amides

## ■ Methyl and primary alkyl donors



- yields range from 48-95 %
- temp: 100-140 °C

## ■ Reactive species



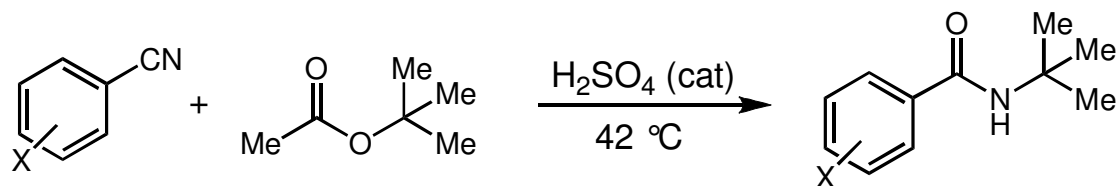
- Offer equivalents of electrophilic methyl

Lebedev, M. Y., *et. al*, *Tet. Lett.*, **2002**, 43, 1397.

## Other Alkyl Donors

---

### ■ *tert*-Butyl Amides from *tert*-Butyl Acetate



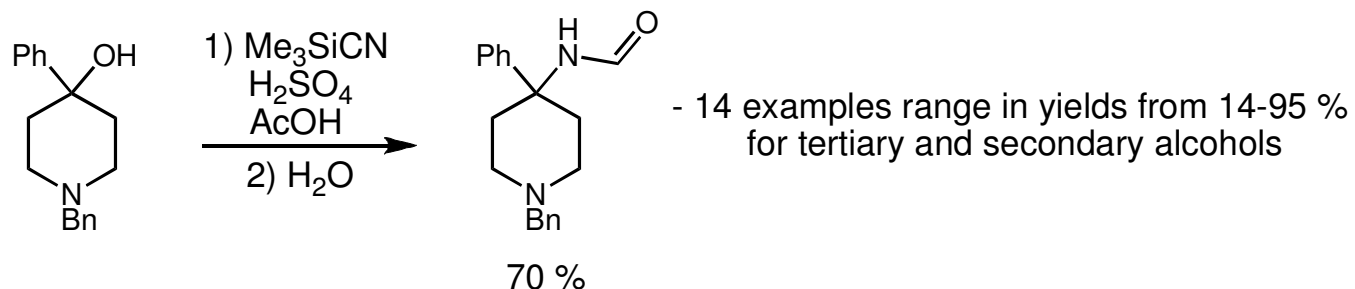
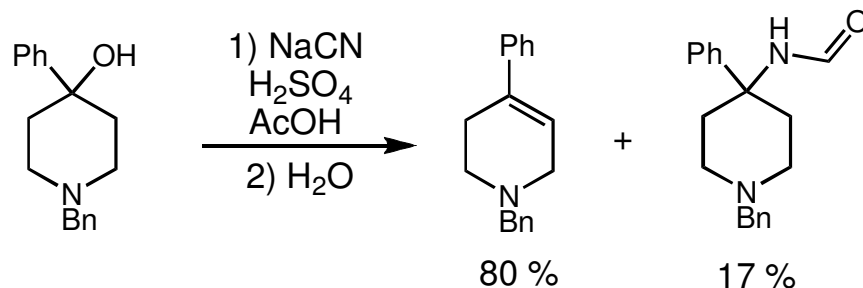
X: H, Me, OH, MeO, CF<sub>3</sub>, CF<sub>3</sub>O, F, Br, SMe  
Ar: phenyl, naphthyl, pyridyl, thiophenyl

- yields 88-95 %
- only requires catalytic acid
- 2-6 hr

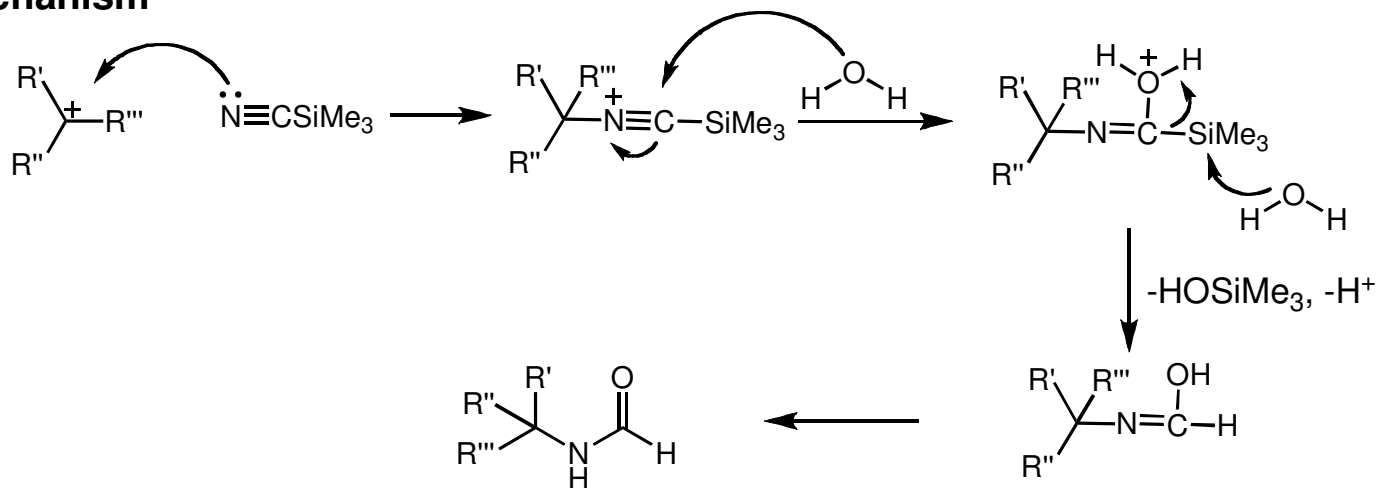
Reddy, K. L., *Tet. Lett.*, **2003**, 44, 1453.

# HCN Equivalent for Synthesis of Formamides

## ■ Intermediate in synthesis of a series of tachykinin NK<sub>3</sub> antagonist analogues

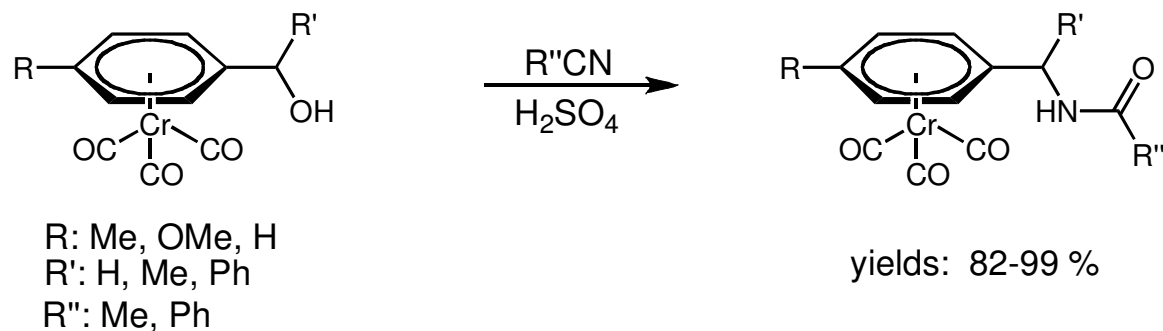


## ■ Mechanism



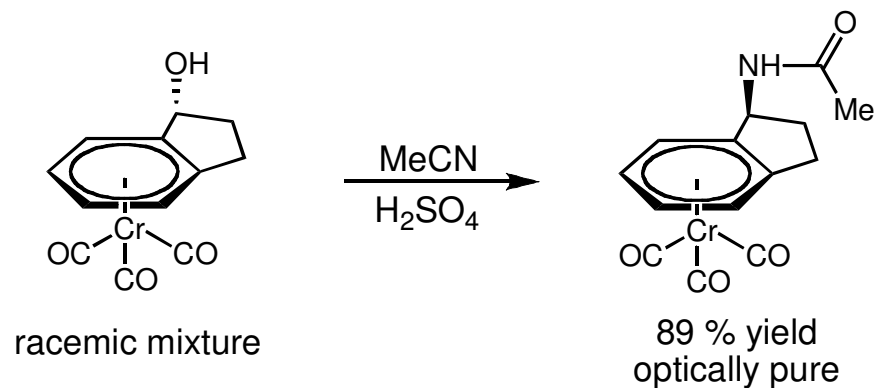
# Transition Metal Activation

## ■ Chromium Tricarbonyl Complexes of Benzyl Alcohol Derivatives



yields: 82-99 %

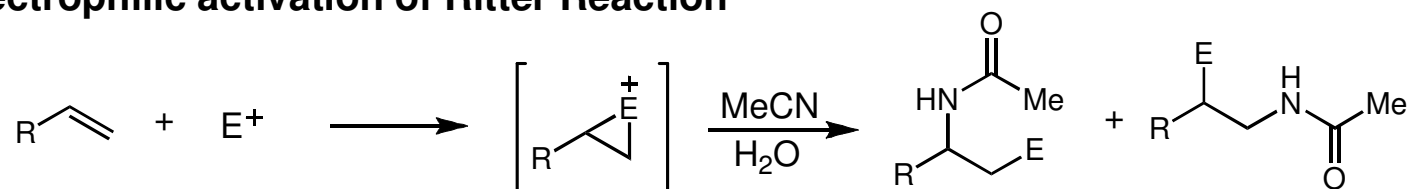
## ■ Complex provides stereochemical control



- asymmetric induction
- complete inversion of configuration

# Electrophilic Activation

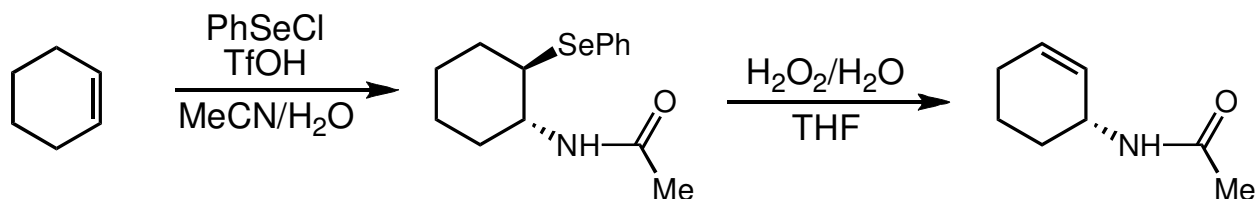
## ■ Electrophilic activation of Ritter Reaction



- Heteroatoms shown to mediate reaction: F, Br, I, N, Se, S

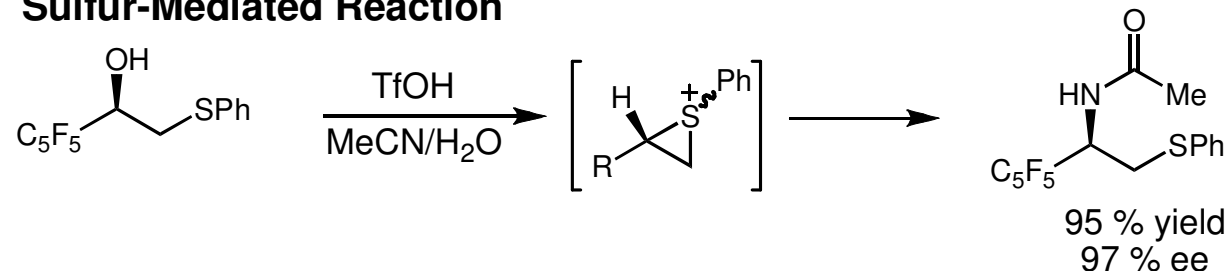
Warren, S., *et. al*, *Synthesis.*, **2002**, 17, 2124 and references therein.

## ■ Selenium-Mediated Reaction



-14 examples range in yields from 36-98 %

## ■ Sulfur-Mediated Reaction

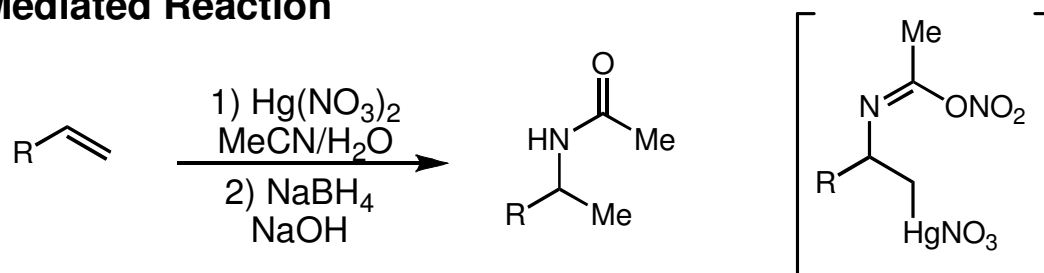


- 8 examples range in yields 68-96 % and ee's of 86-100 %

Toshimitsu, A., *et. al*, *J. Org. Chem.*, **1981**, 46, 4727.  
Toshimitsu, A., *et. al*, *Tet. Lett.*, **1991**, 32, 4317.

# Mercury Activation

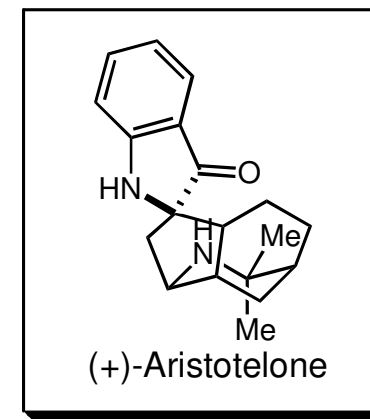
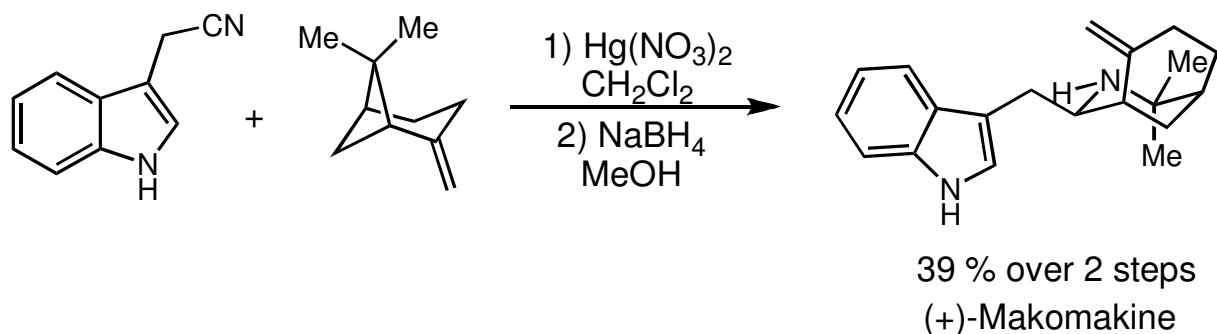
## Mercury-Mediated Reaction



- 6 examples ranging in yields of 50-95 %

Brown, H. C., *et. al*, *J. Am. Chem. Soc.*, **1969**, 5647.

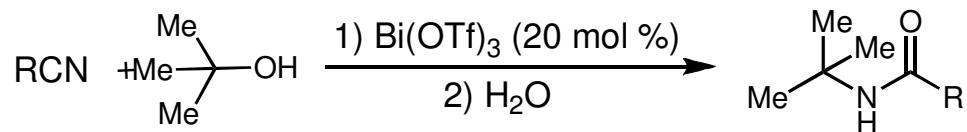
## Heathcock's Total Synthesis of Aristotelone



Heathcock, C. H., Stoermer, D. I. *J. Org. Chem.*, **1993**, 58, 564.

# Lewis Acid Catalyzed Reactions

## ■ Metal Triflate Catalysis

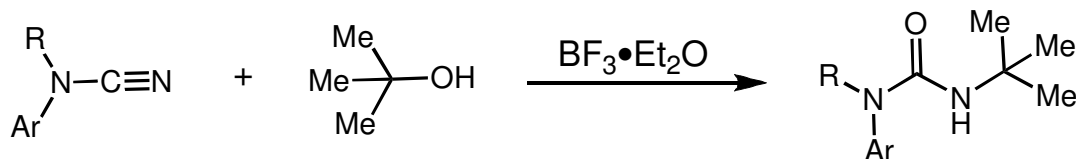


R = alkyl, aryl

- 19 examples ranging in yields from 50-95 %
- only tertiary alcohols

Callens, E., *et. al*, *Tet. Lett.*, **2006**, 8699.

## ■ Synthesis of Ureas, Acylureas, and Sulfonylureas



R = aryl, acyl, sulfonyl

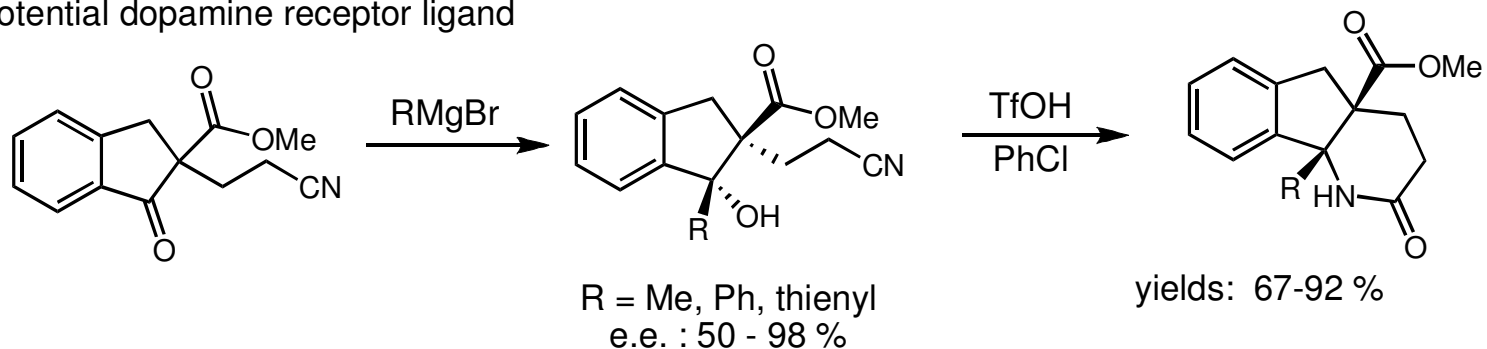
- 18 examples ranging in yields of 37-84 %

Anatol, J., *et. al*, *Synthesis*, **1975**, 111.

# Intramolecular Ritter Reactions

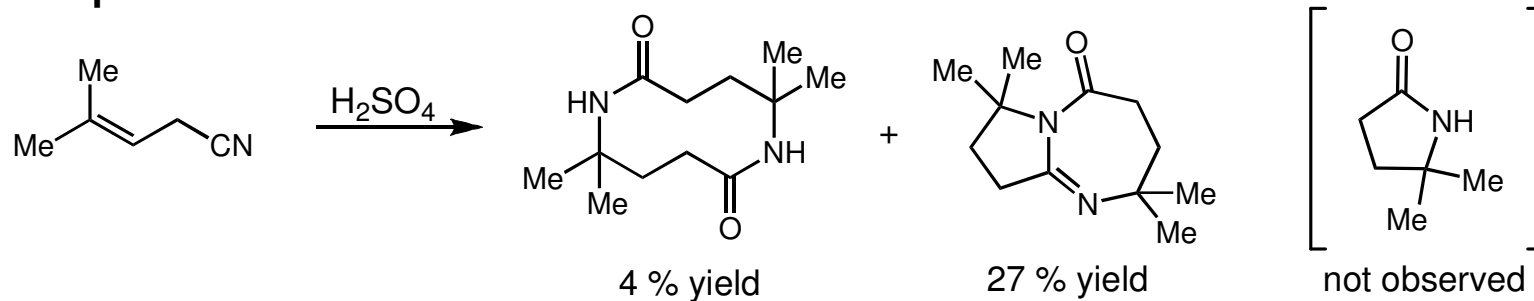
## ■ Diastereoselective Synthesis of NK<sub>1</sub>-antagonists

- potential dopamine receptor ligand



Compernolle, F., *et. al, Org. Lett.*, **2000**, 2, 3083.

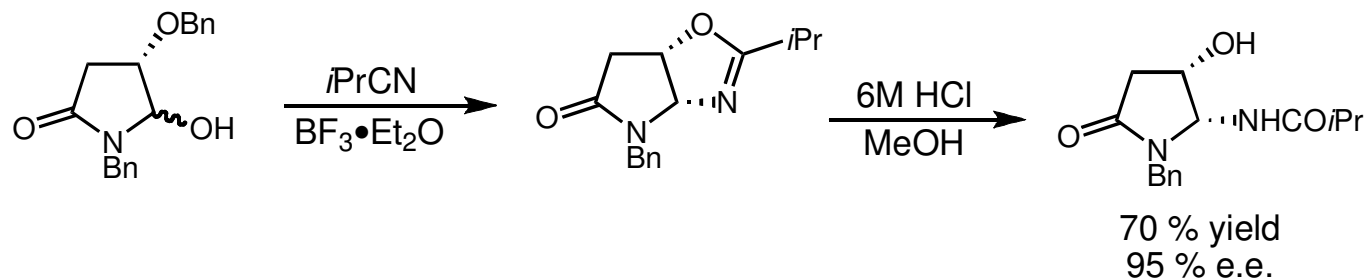
## ■ Unexpected Dimerization



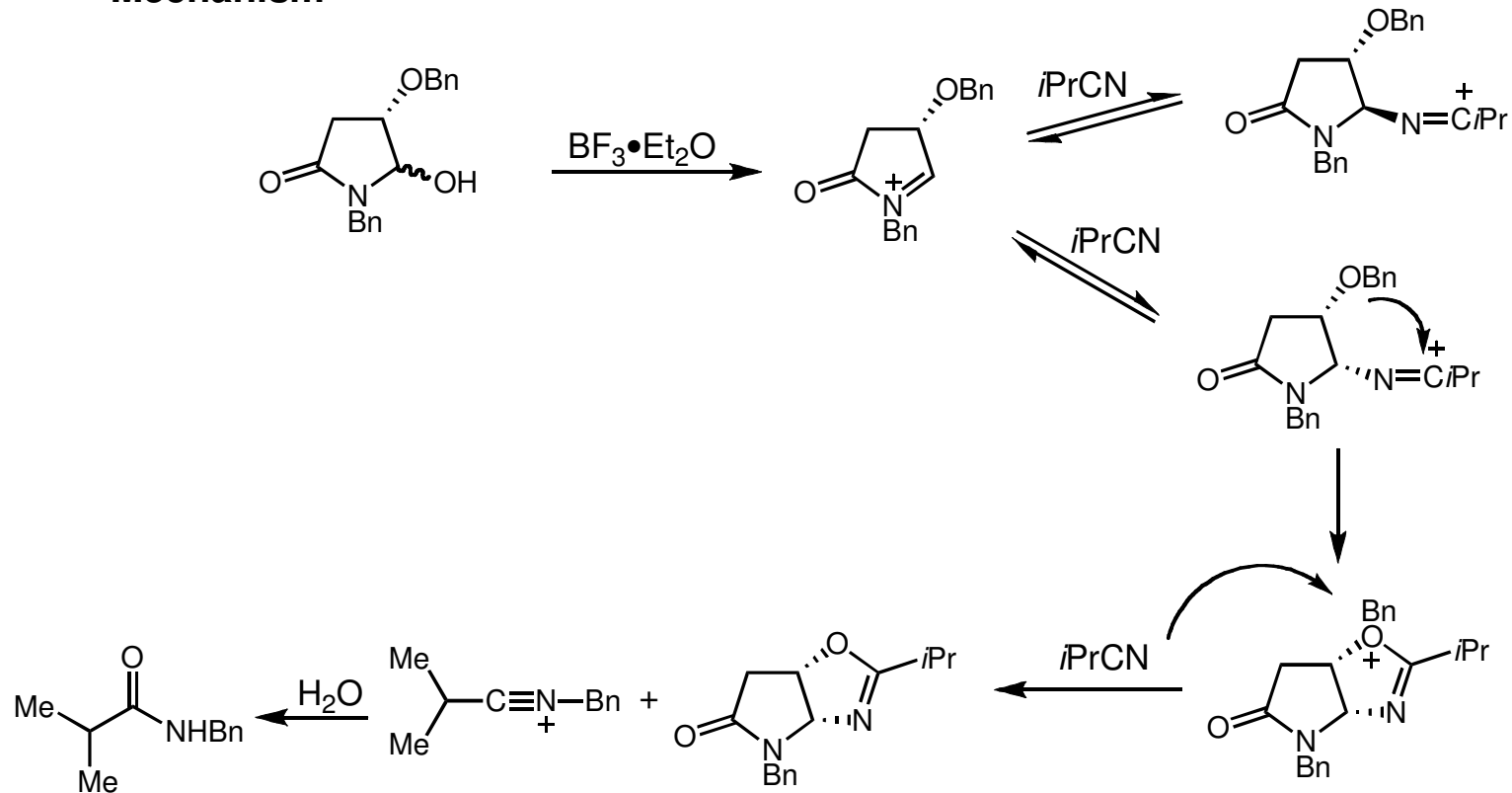
Duckner, J.W., *et. al, Aust. J. Chem.*, **1968**, 21, 2809.

# Diastereoselective Ritter Reactions

## ■ Diastereoselective synthesis of acylaminopyrrolidines



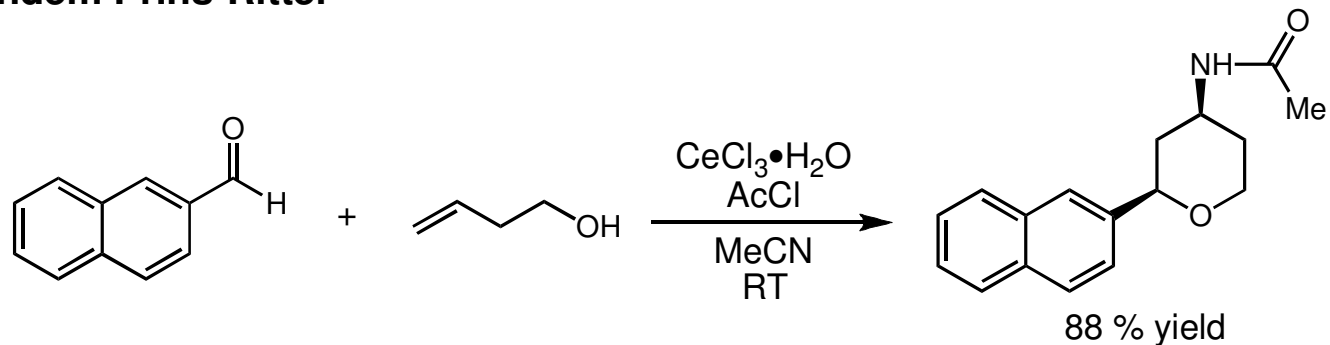
## ■ Mechanism



Morgan, I. R., et. al, *J. Org. Chem.*, **2008**, 73, 2943.

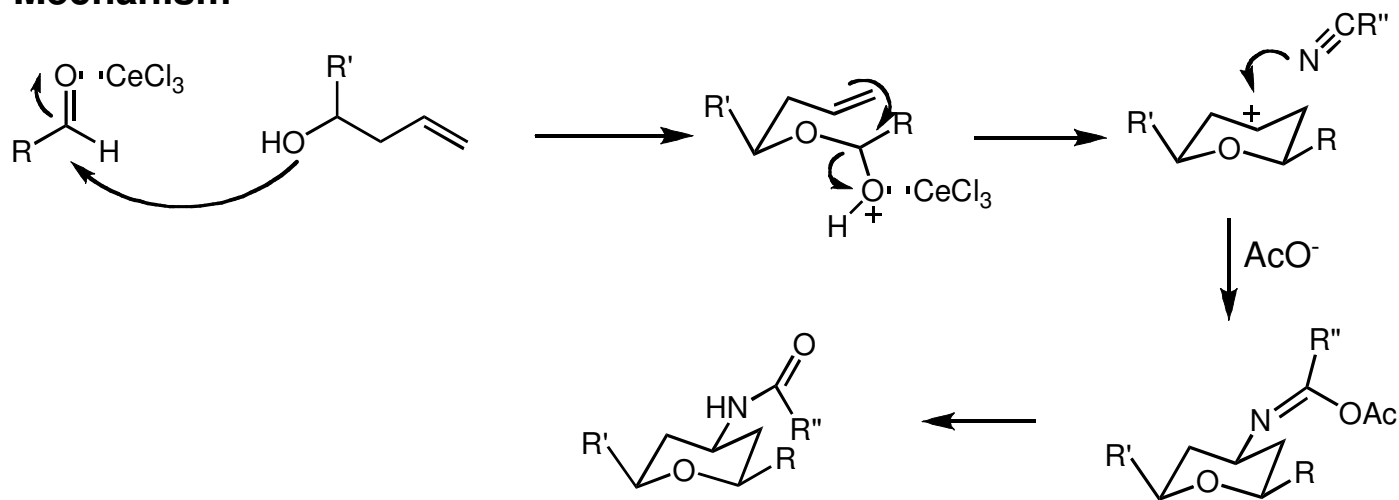
# Tandem Reactions

## ■ Tandem Prins-Ritter



- primary and secondary homoallylic alcohols
- aromatic aldehydes, aliphatic ketones
- yields range from 80-94 %
- complete cis selectivity

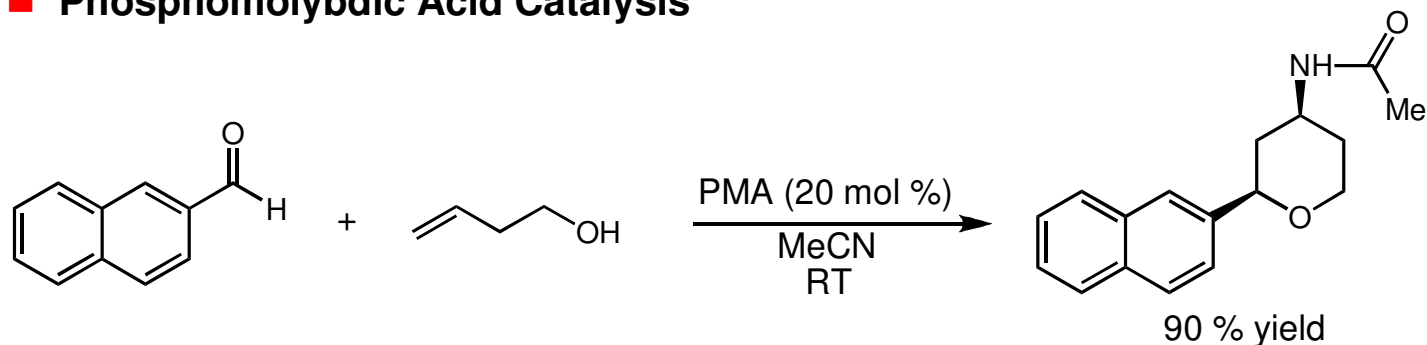
## ■ Mechanism



Yadav, J. S., et. al, *Tet. Lett.*, **2007**, 48, 4903.

# Tandem Reactions

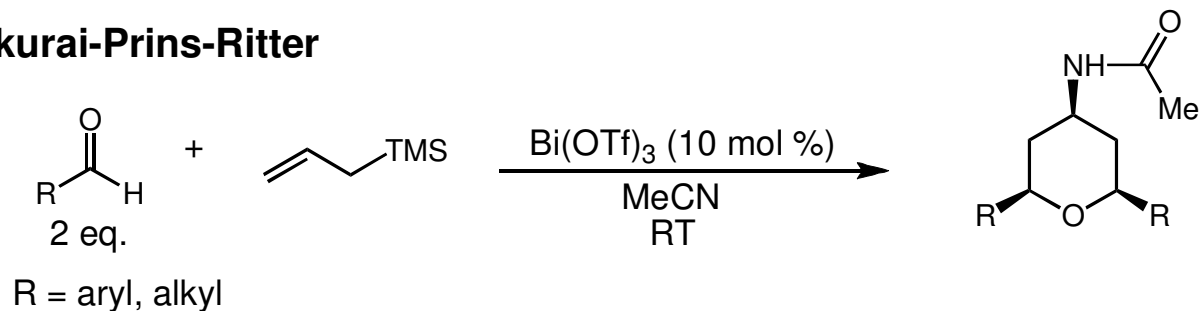
## ■ Phosphomolybdic Acid Catalysis



- essentially same substrate scope, but protic acid instead

Yadav, J. S., *et. al*, *Tetrahedron*, **2008**, *64*, 3025.

## ■ Sakurai-Prins-Ritter

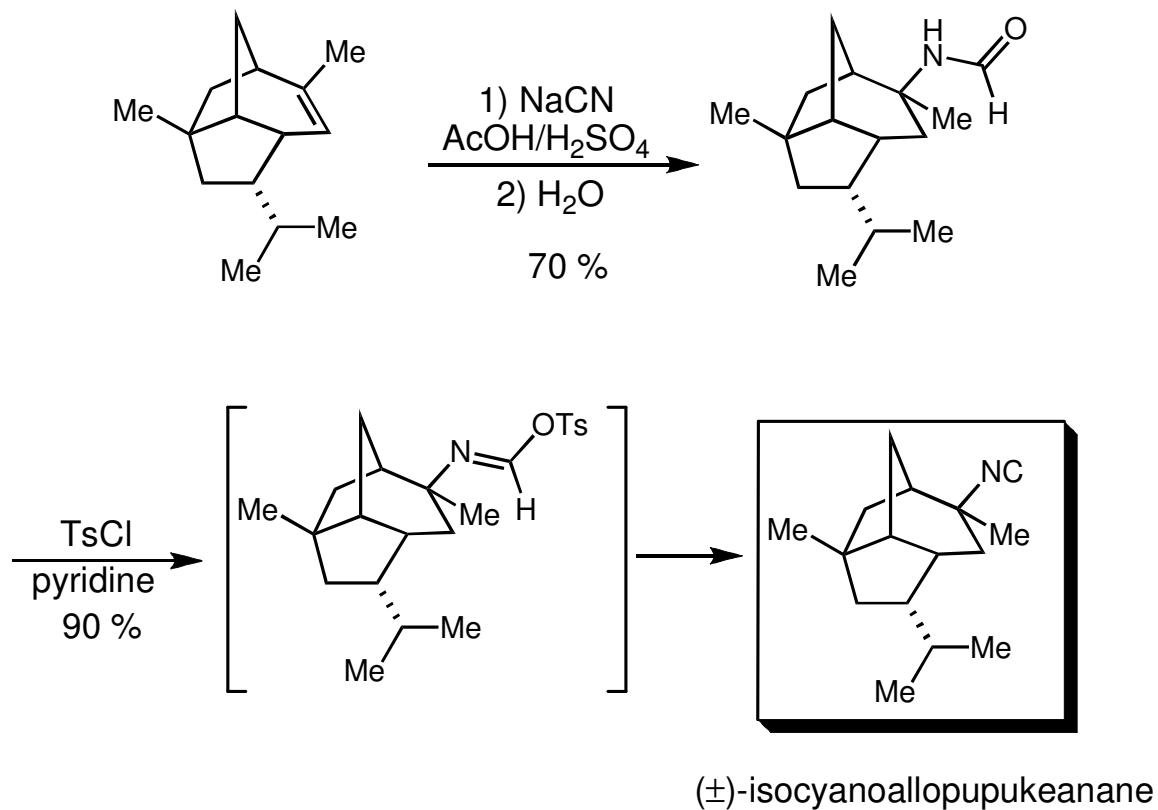


- 11 examples with yields ranging 60-98 %  
-high diastereoselectivity  
-also show other aromatic and aliphatic nitriles

Yadav, J. S., *et. al*, *Tet. Lett.* accepted manuscript.

## Examples from Total Synthesis

### ■ Ho's Total Synthesis of Isocyanoallopupukeanane



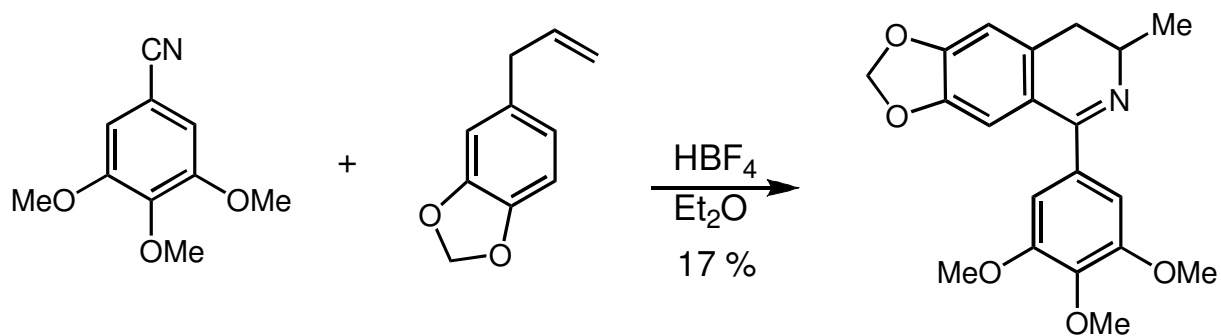
Ho, T. -L., *et. al*, *J. Org. Chem.*, **2000**, *65*, 5774.

## Modified Ritter for Synthesis

---

### ■ Janin's Synthesis of a library of analogues of PK11195

- series of electron-rich carboxyisoquinolines



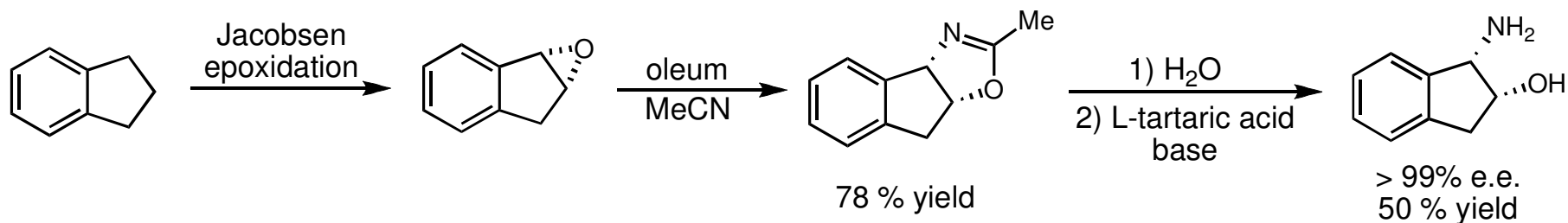
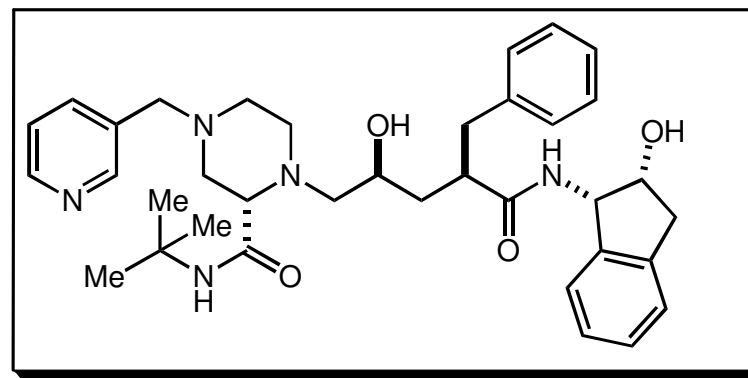
- standard Ritter conditions led to extensive decomposition

Janin, Y. L., *et. al*, *Tetrahedron*, **2004**, *60*, 5481.

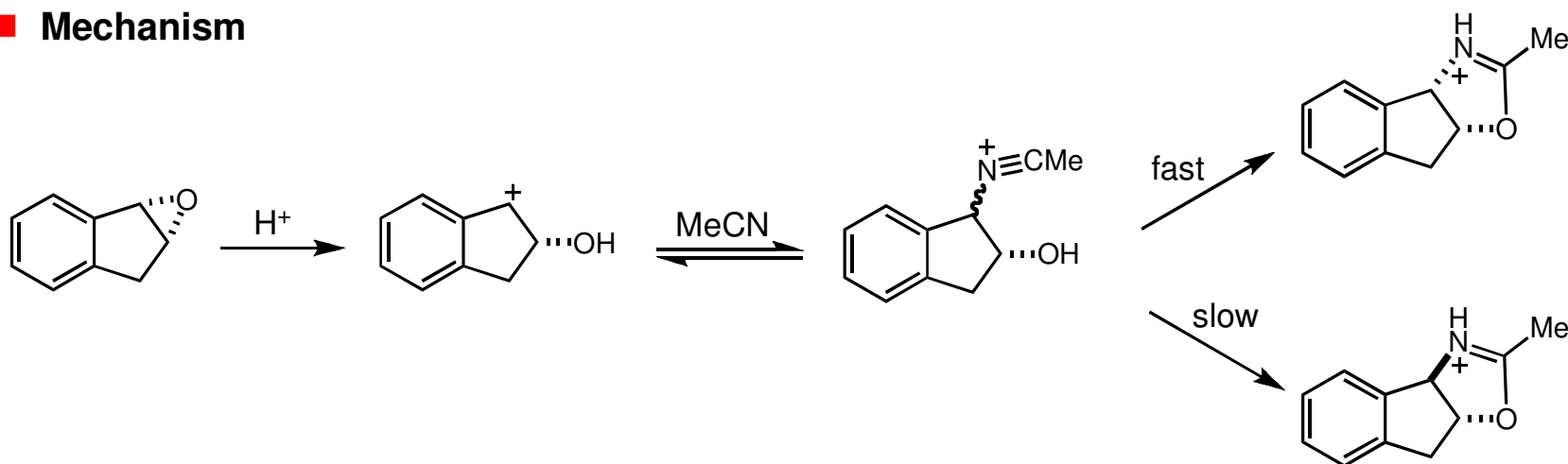
# Ritter Reaction in Pharmaceutical Synthesis

## ■ Indinavir (Crixivan)

-HIV protease inhibitor  
-introduced by Merck in 1996



## ■ Mechanism



Reider, P. J., *et. al*, *Tet. Lett.*, **1995**, 36, 3993.