

Asymmetric Counterion Directed Catalysis

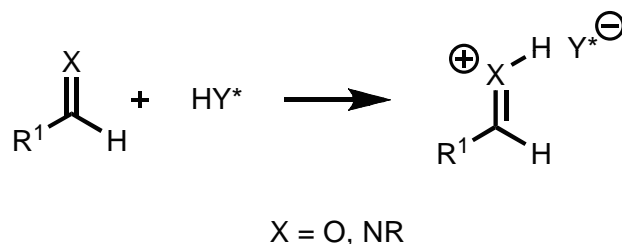


Jason M. Stevens

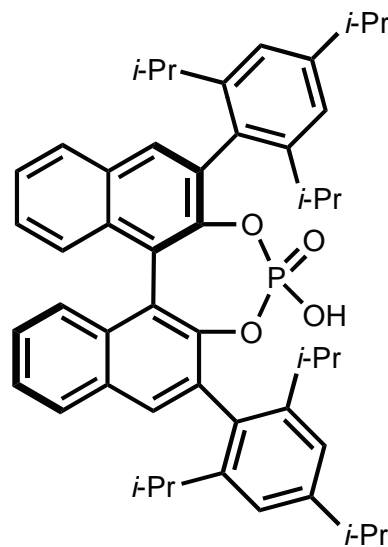
03.05.2008

ACDC: A Brief Overview

- ACDC refers to chiral Brønsted acid catalysis, or specific acid catalysis.
 - The proton is transferred to a lewis basic functionality, thereby activating that functionality for chemical manipulation.
 - The chiral counterion remains in a tight ion pair thus allowing for transfer of chirality to the product.



- ACDC is a term used by List for reactions catalyzed by chiral phosphoric acids.



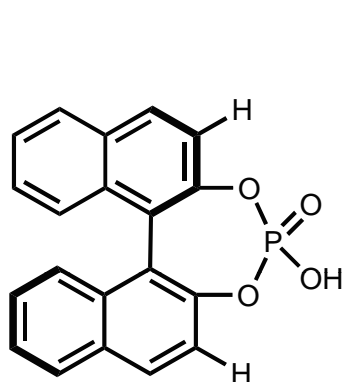
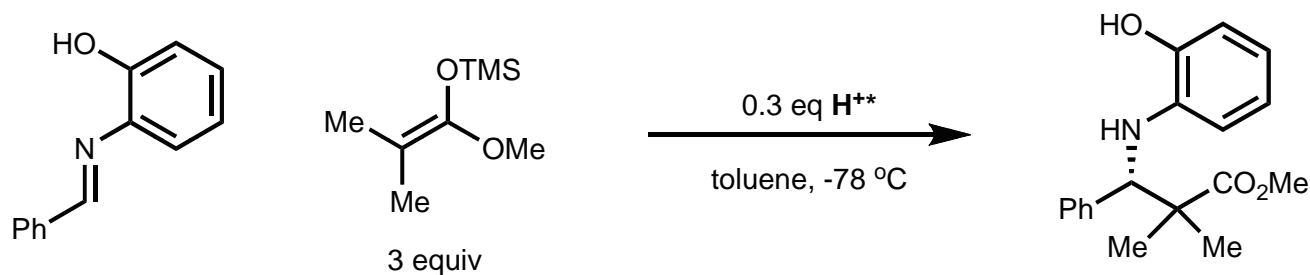
Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, 348, 999 - 1010.

Outline of Today's Discussion

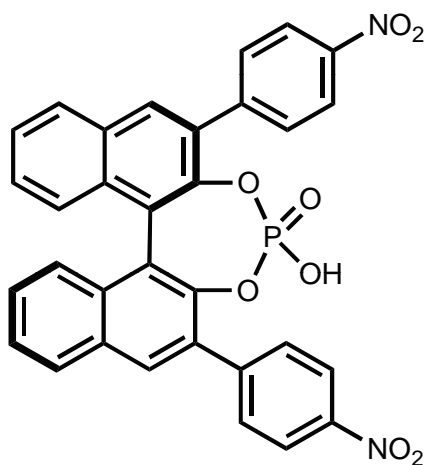
- Asymmetric Mannich/Mannich-Type Reactions
- Reduction of Double Bonds with Hantzsch Esters
- The Emerging Role of ACDC in Transition Metal Catalysis

- Also, pay attention to/think about the following:
 - How substitution on BINOL might transfer stereochemical information to the product.
 - Reaction conditions: temperature, time, solvent.
 - Substrate scope

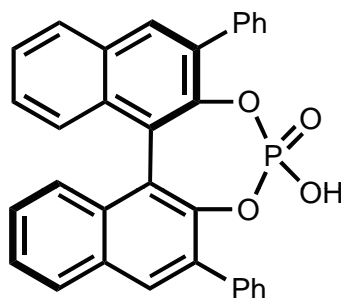
Akiyama's Asymmetric Mannich Reaction



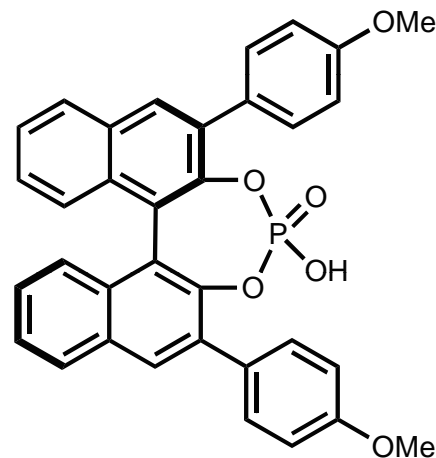
22 h
57%
0% ee



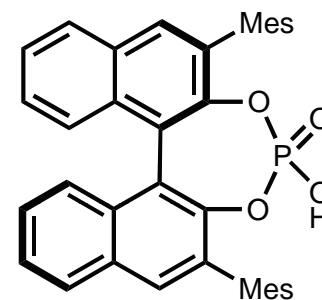
4 h
96%
87% ee



20 h
100%
27% ee

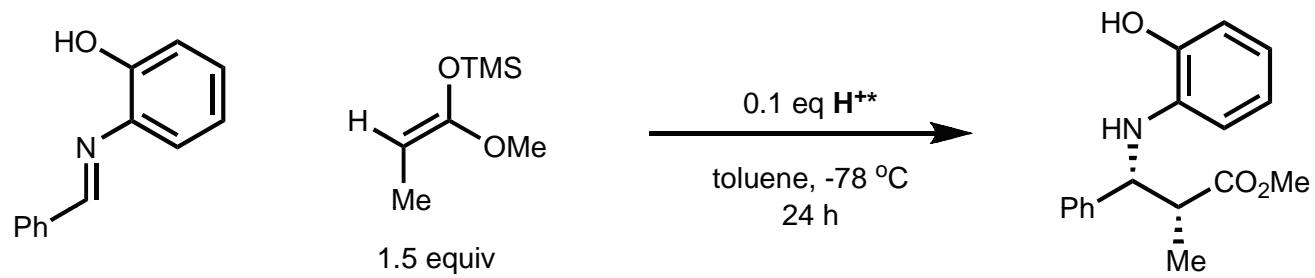


46 h
99%
52% ee

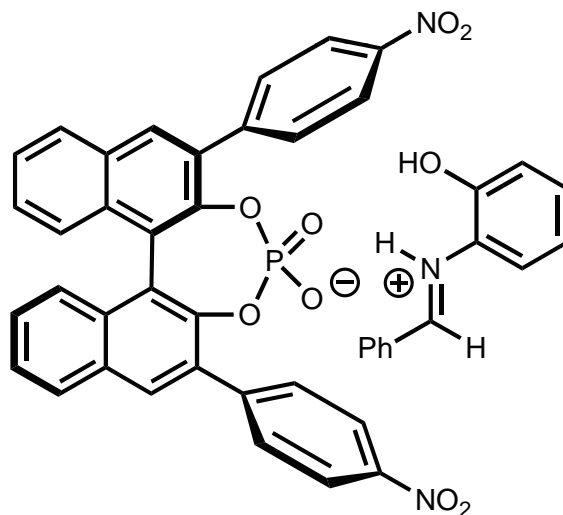
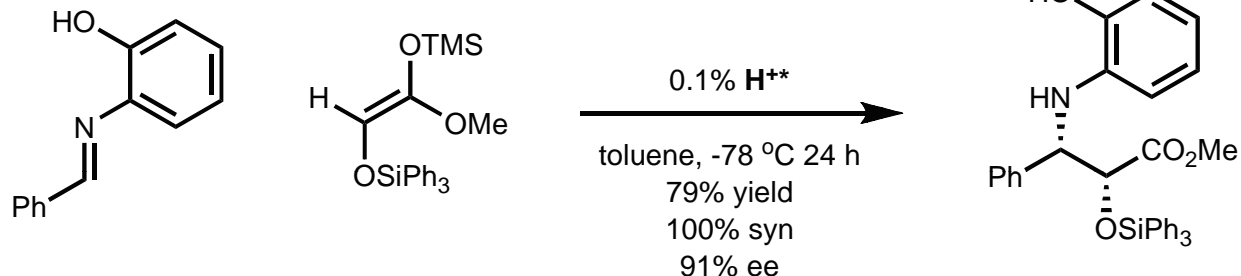


27 h
100%
60% ee

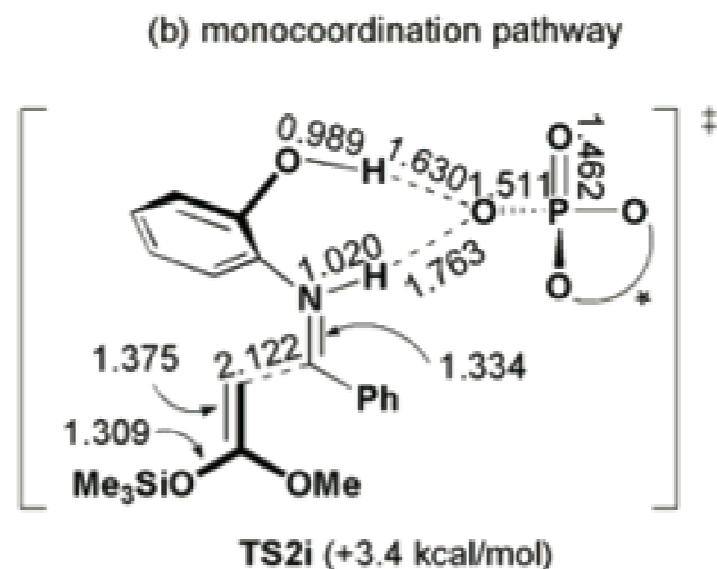
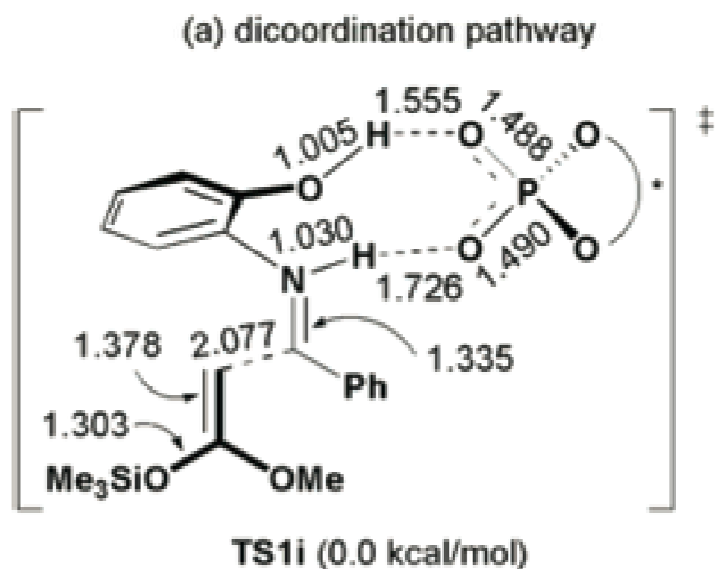
Akiyama's Asymmetric Mannich Reaction



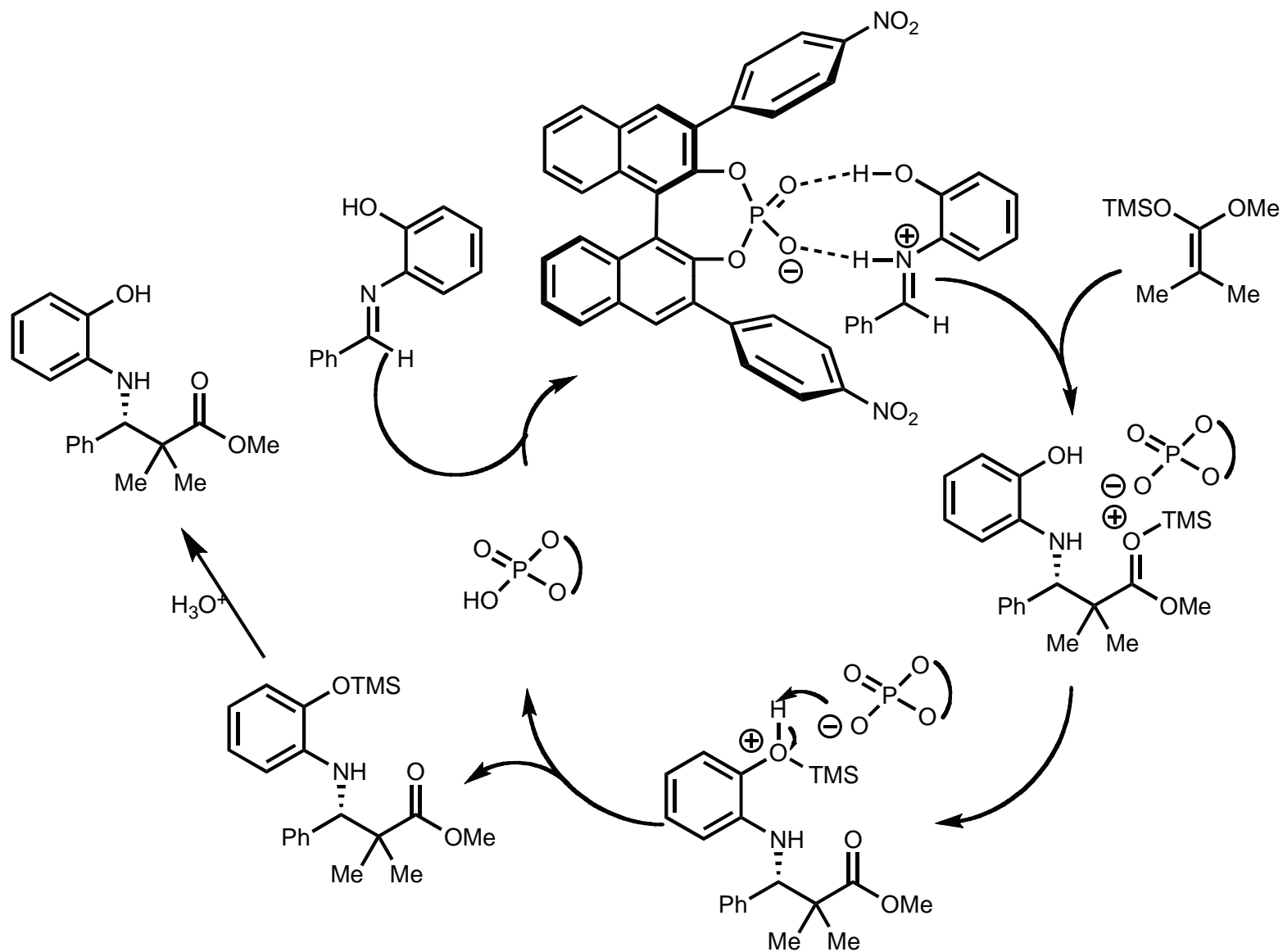
For a variety of Ph derivatives
Typically 100% yield
~ 10:1 syn/anti
~ 85% ee



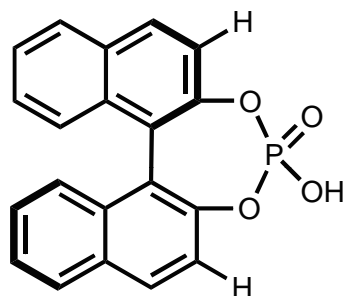
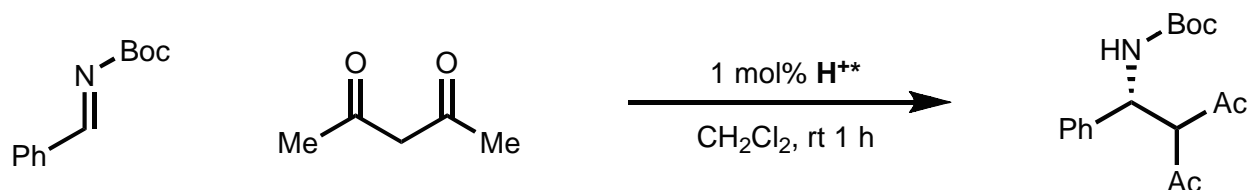
Akiyama's Asymmetric Mannich Reaction DFT Study



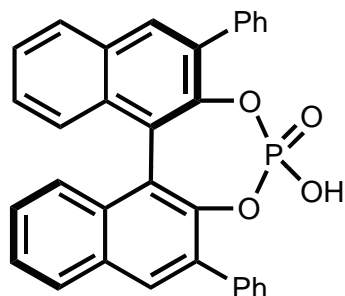
Akiyama's Asymmetric Mannich Reaction Catalytic Cycle



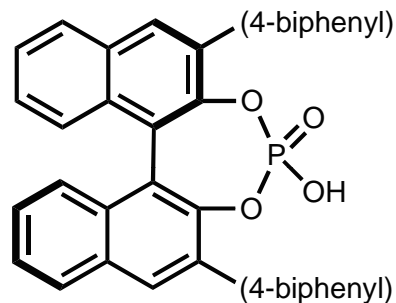
Terada's Asymmetric Mannich Reaction



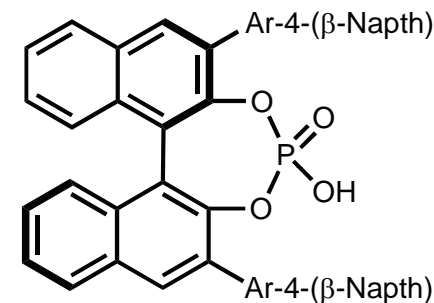
92%
12% ee



95%
56% ee

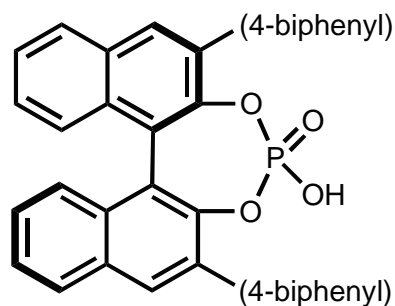
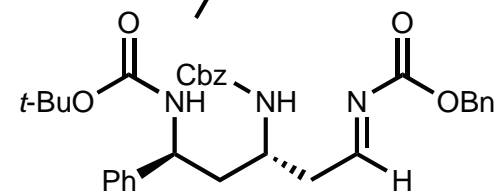
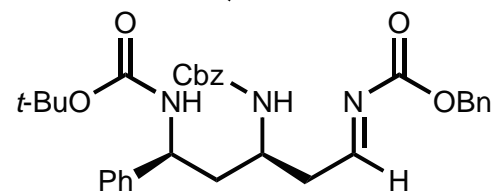
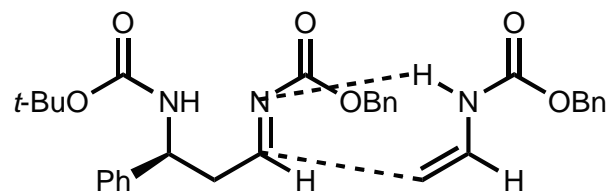
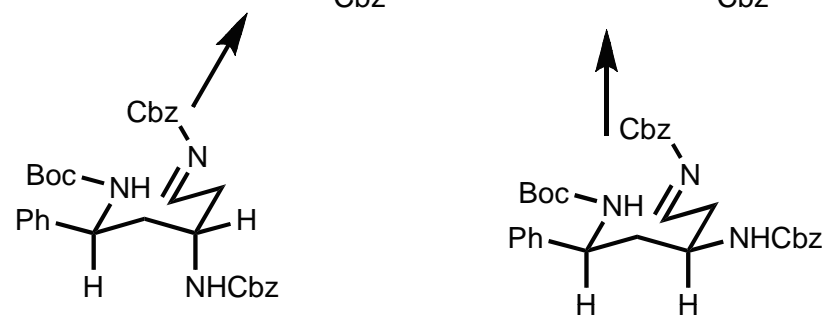
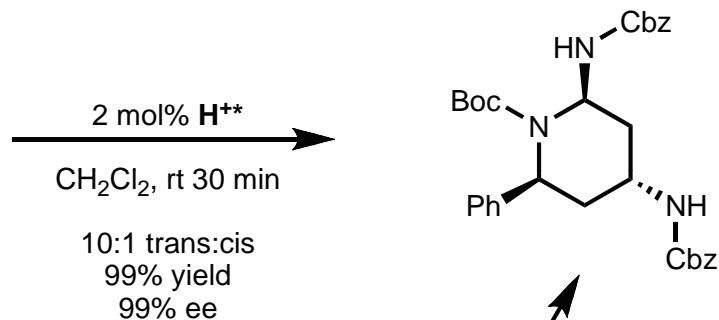
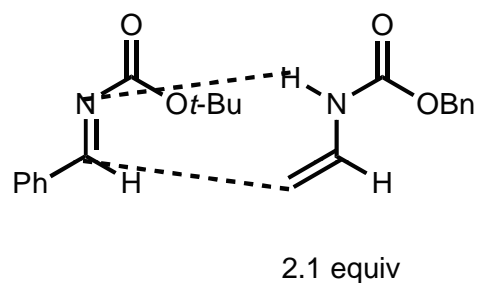


88%
90% ee

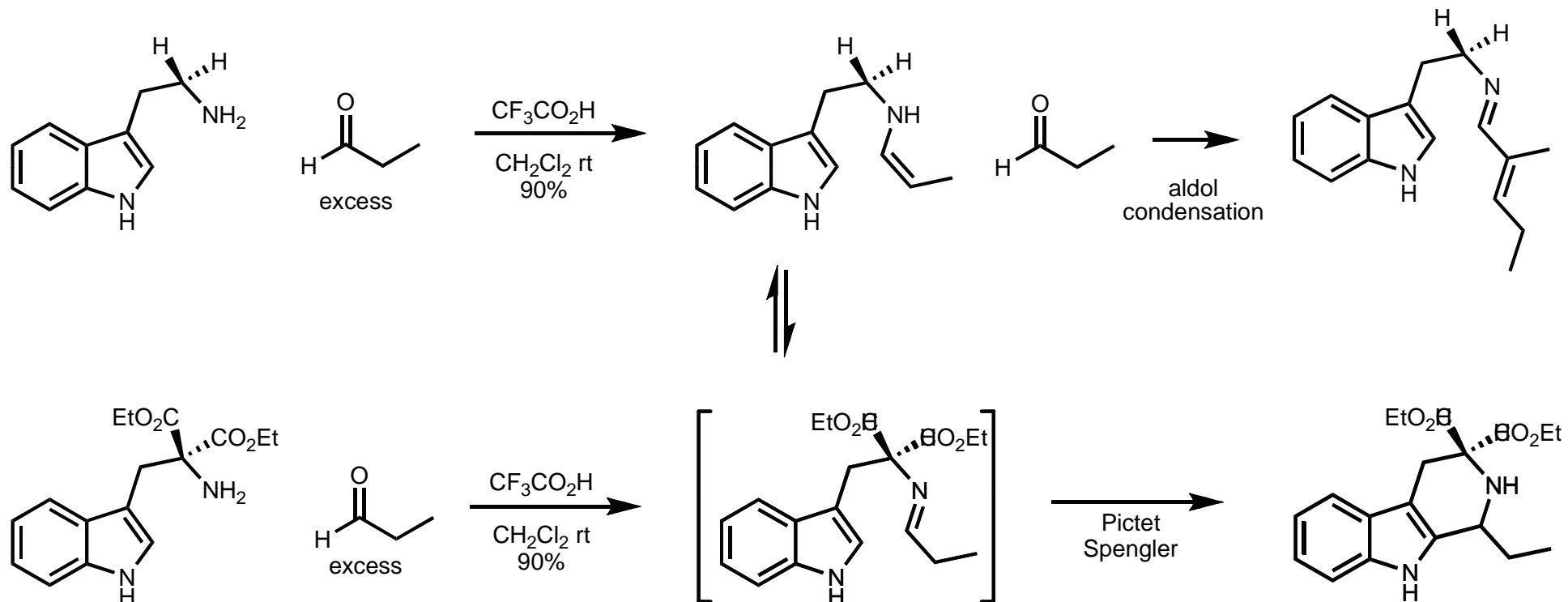


99%
95% ee

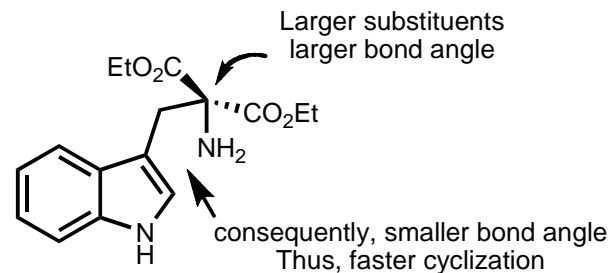
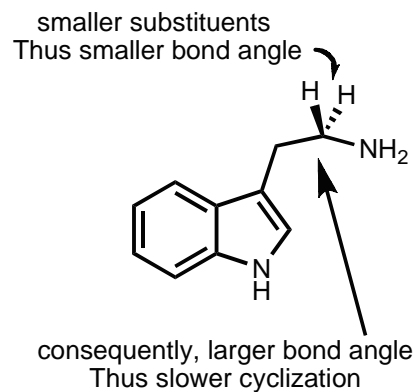
Terada's Asymmetric Piperidine Synthesis



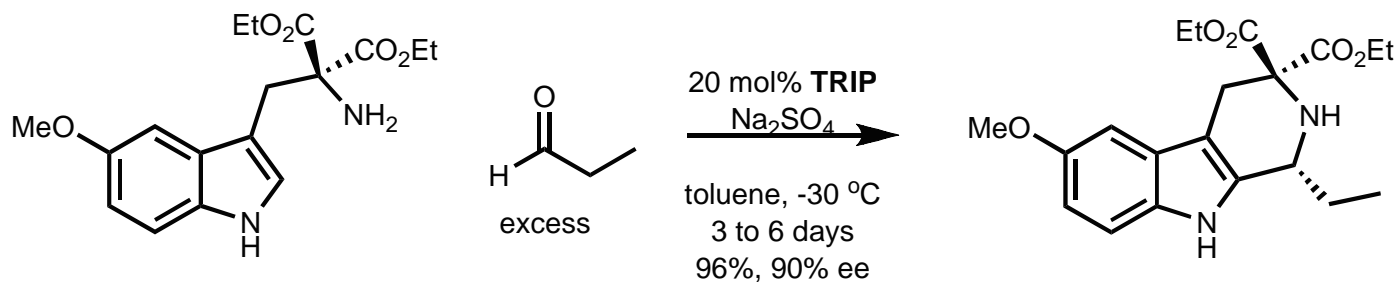
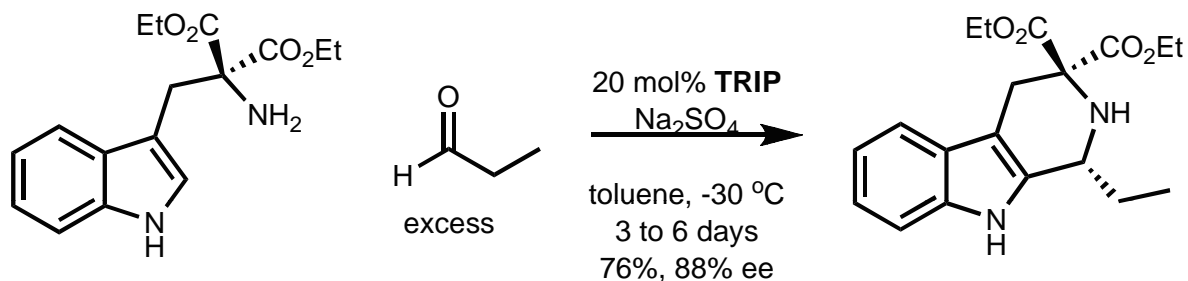
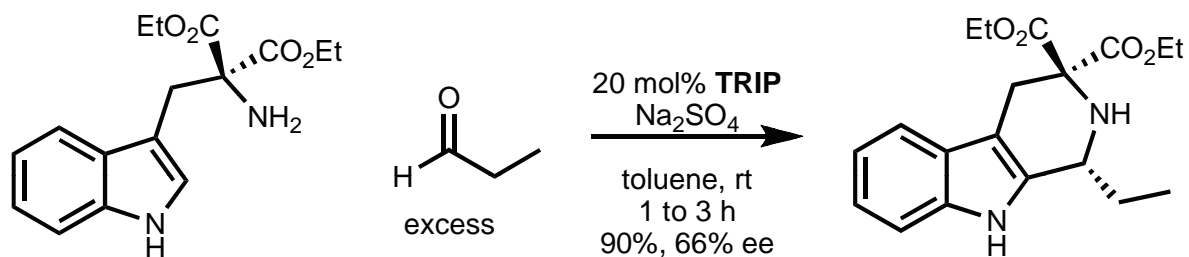
List's Initial Studies Towards an Asymmetric Tryptamine Synthesis



Thorpe-Ingold Effect



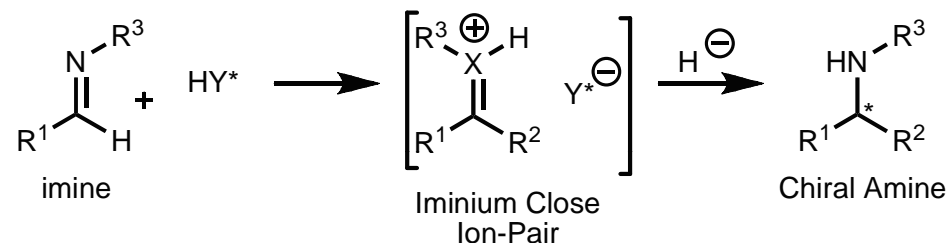
List's Asymmetric Tryptamine Synthesis



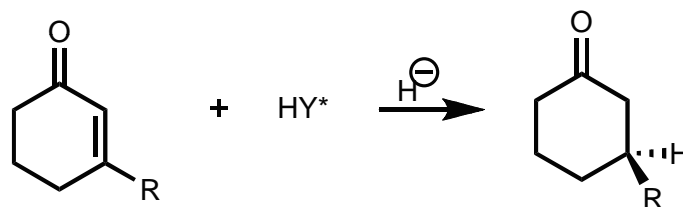
Yield and ee's are best with -OMe substitution and with smaller aldehydes
However a wide range of aldehydes are tolerated

ACDC Reductions

- Reductive Amination:



- Reduction of Enones

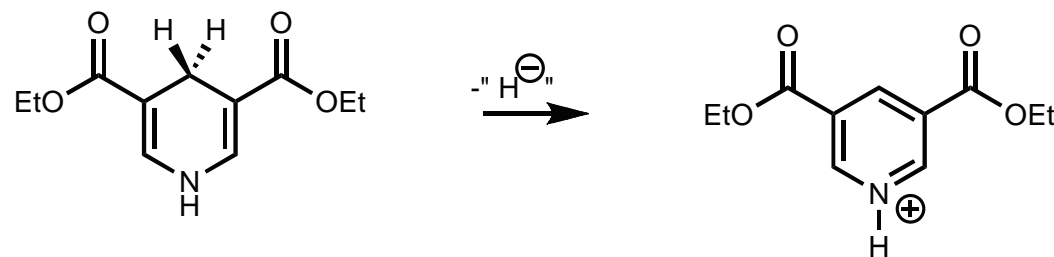


- Hantzsch Ester Reducing Agent

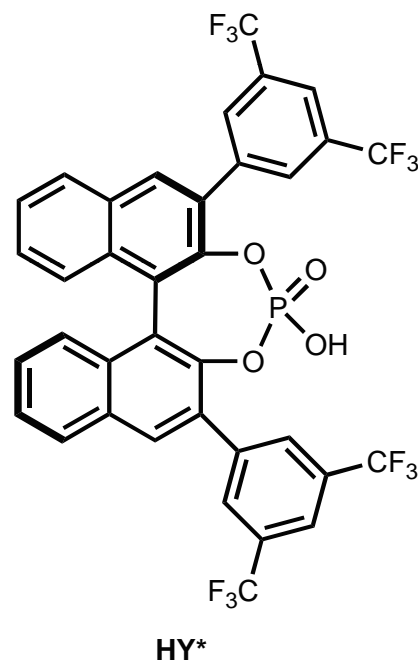
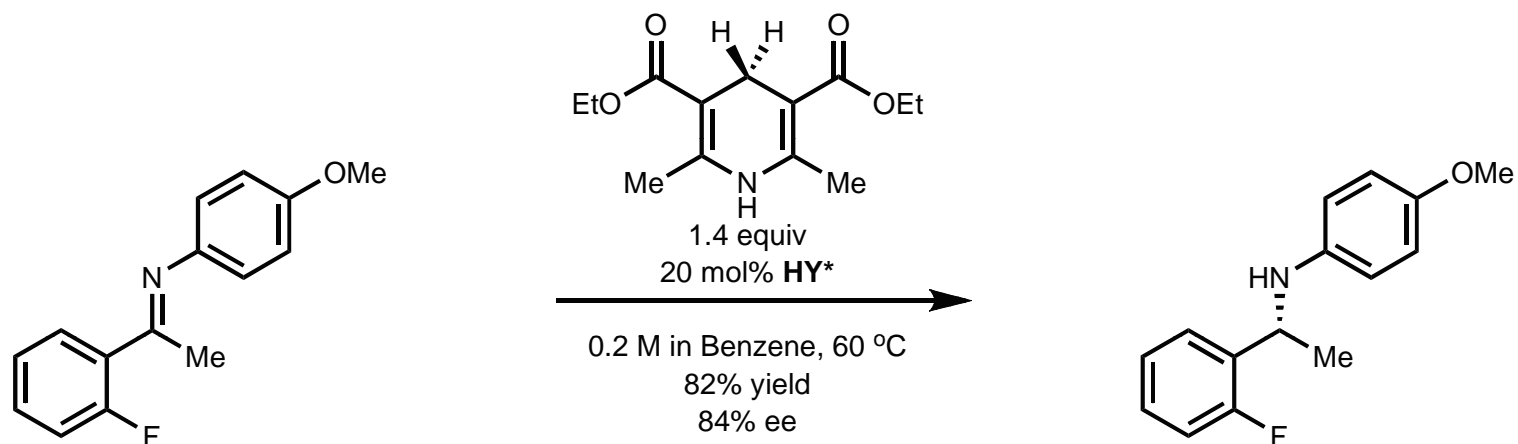
– Reductions are believed to occur by single step hydride transfer but other mechanisms could also be operative in certain cases.

– For more info:

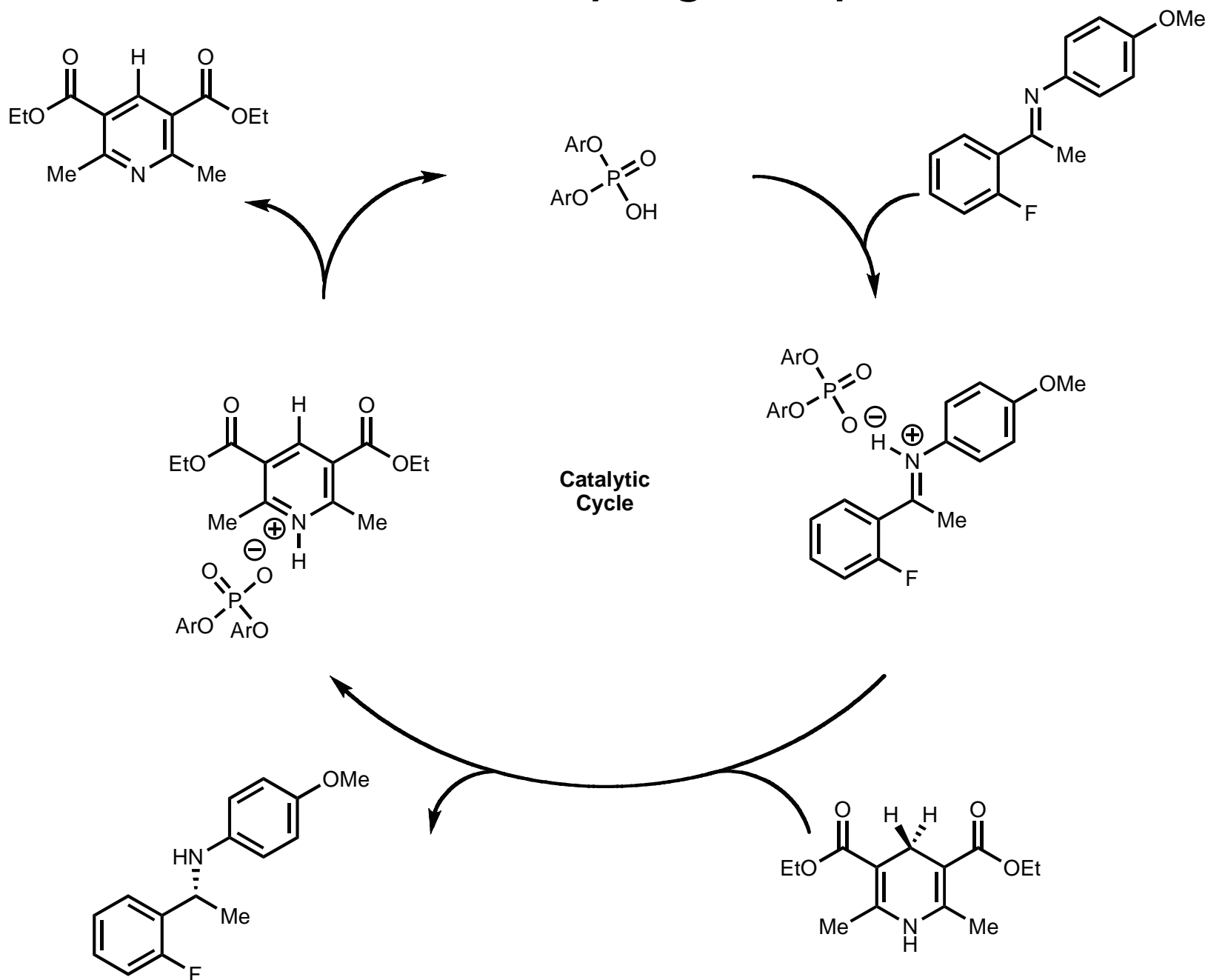
<http://www.princeton.edu/~dmacgr/grpmtgs/2004/JBT%20Hantzsch.pdf>



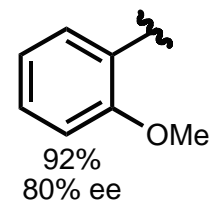
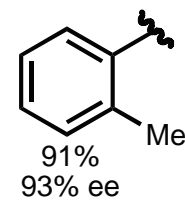
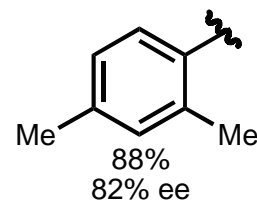
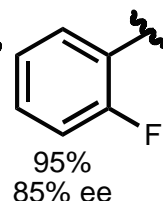
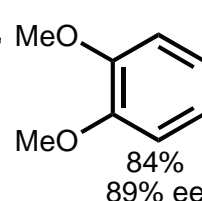
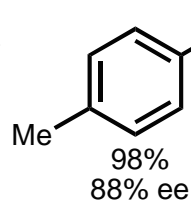
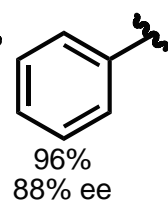
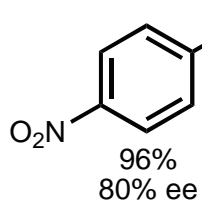
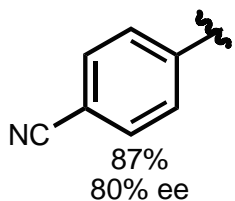
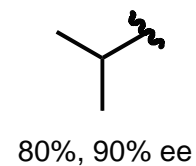
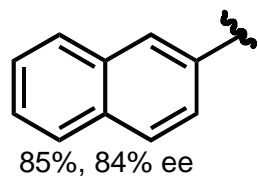
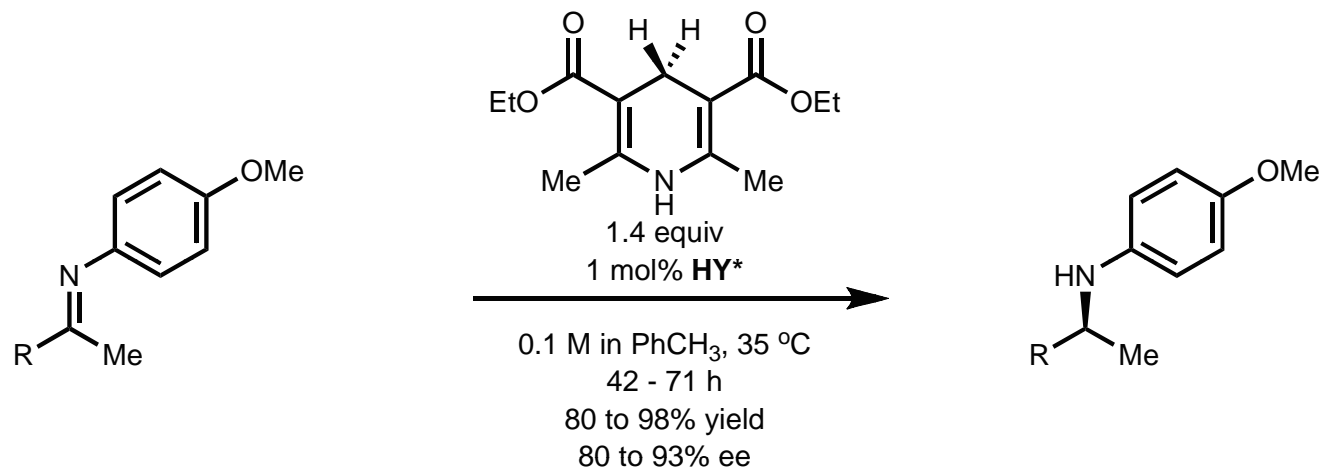
Rueping: First ACDC Reductive Amination



Rueping: Proposed Mechanism

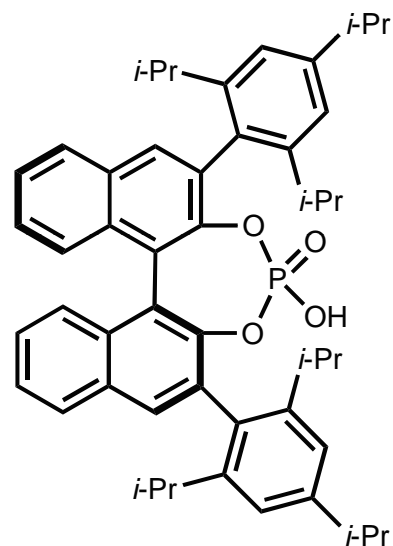
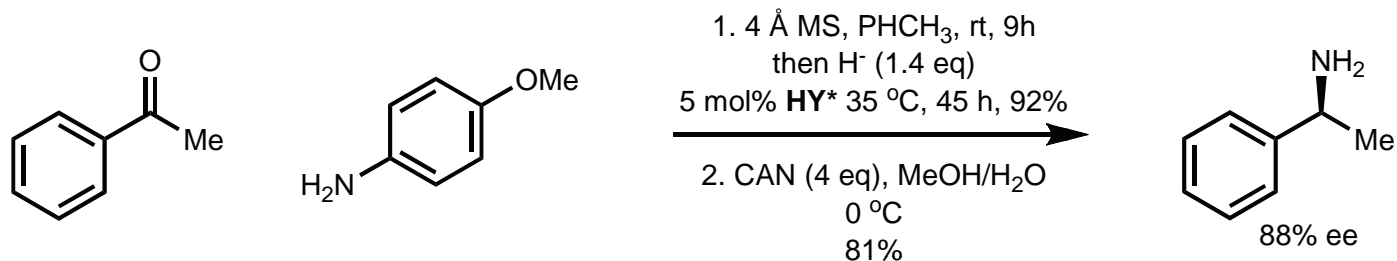


List's ACDC Reductive Amination

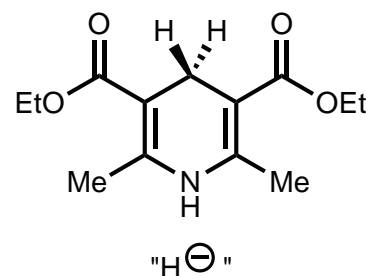


Hoffman, S, Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427.

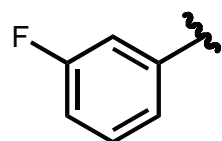
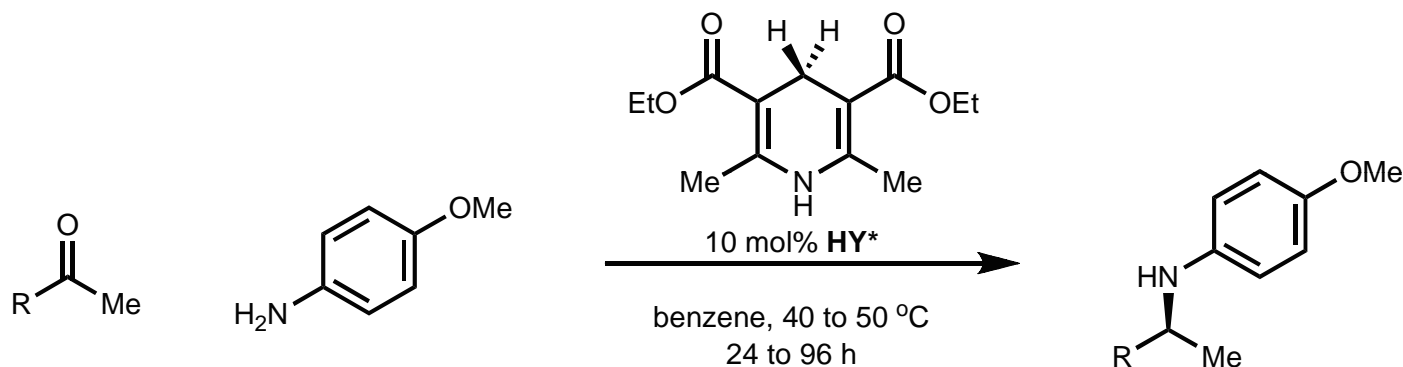
List's Optimized Two Step ACDC Reductive Amination



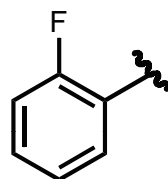
HY*
"TRIP"



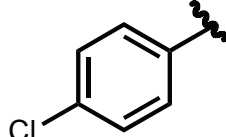
MacMillan's ACDC Reductive Amination: Initial Screen of Catalysts and Substrates



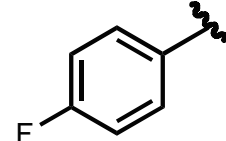
81%, 95% ee



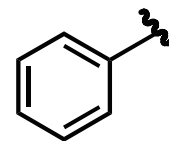
60%, 83% ee



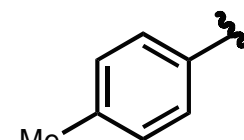
75%, 95% ee



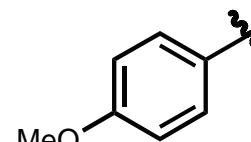
75%, 94% ee



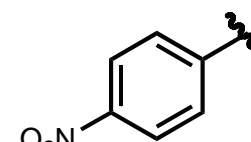
87%, 94% ee



79%, 91% ee



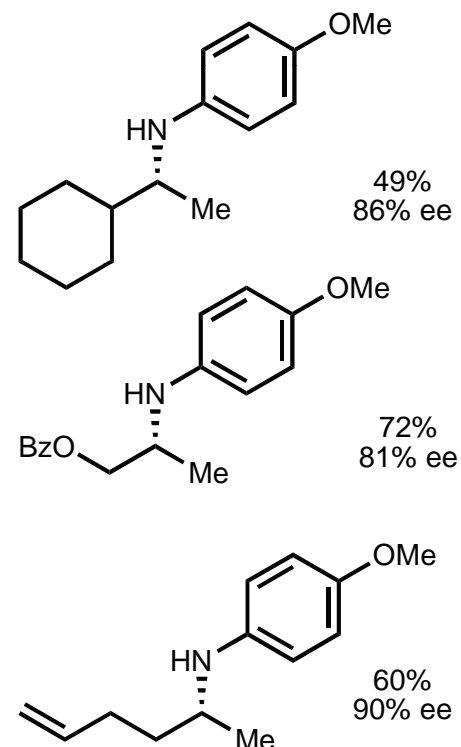
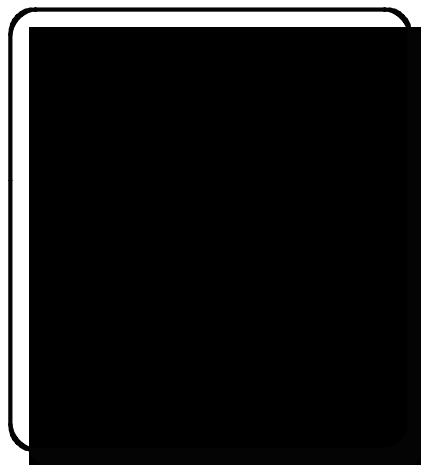
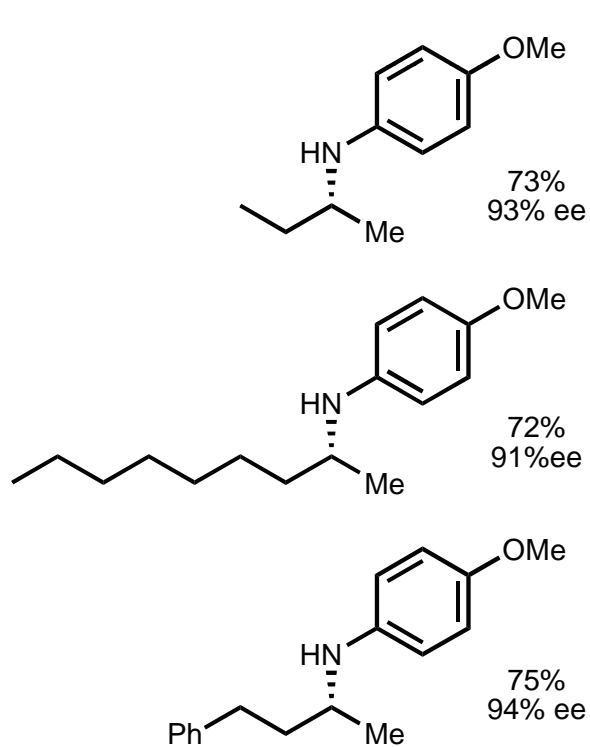
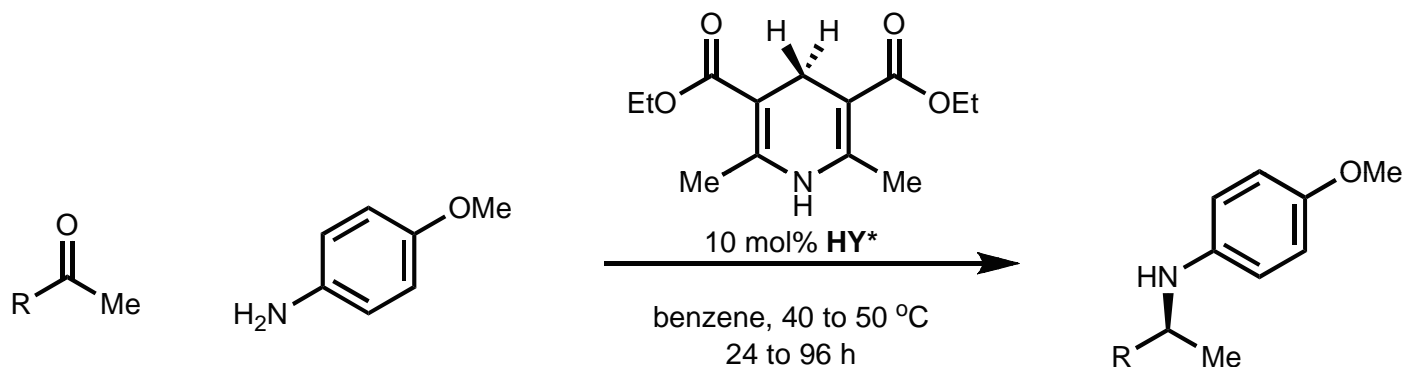
77%, 90% ee



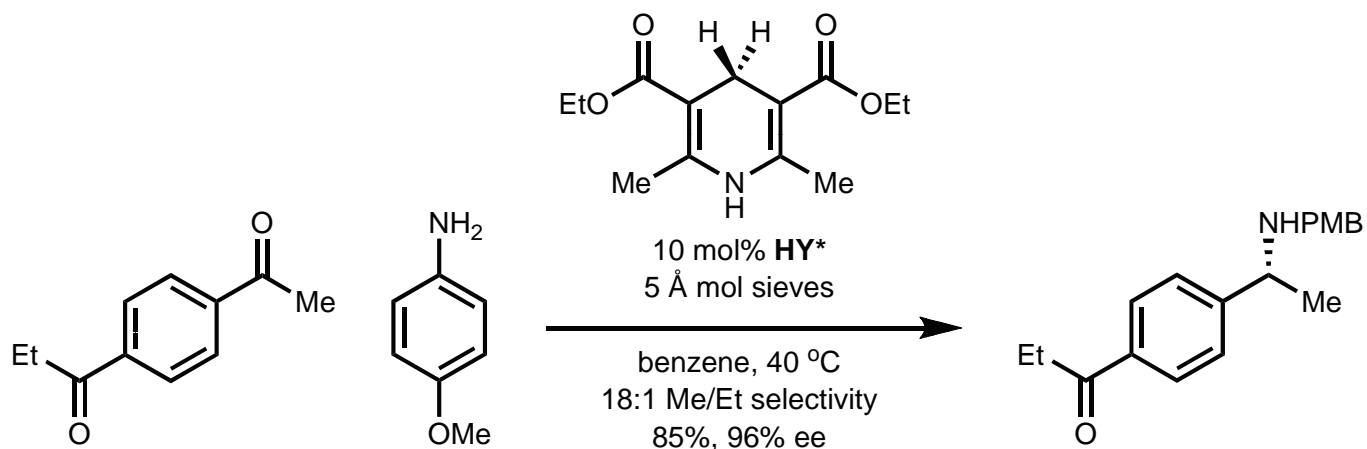
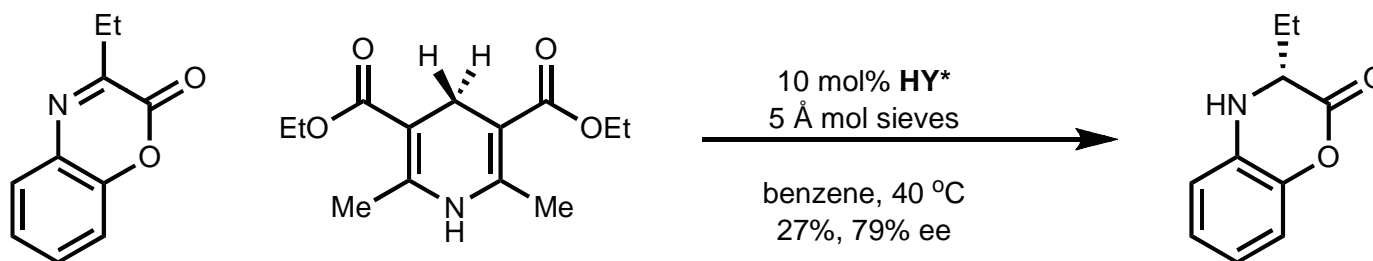
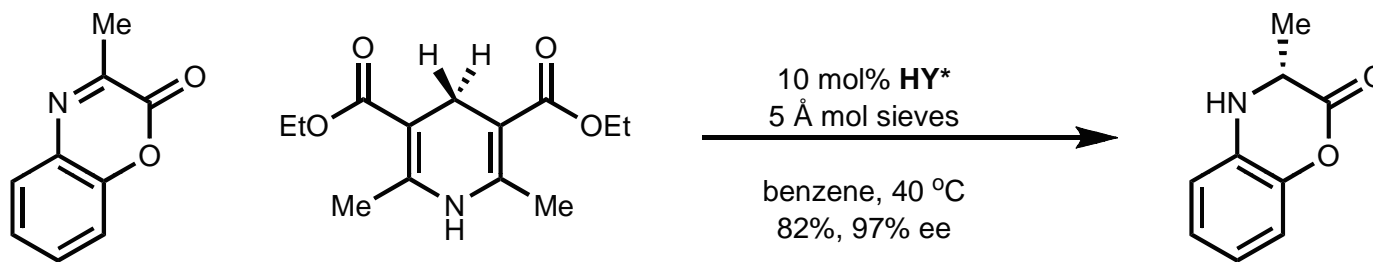
71%, 95% ee

Substituents with ortho substitution have the longest reaction times.

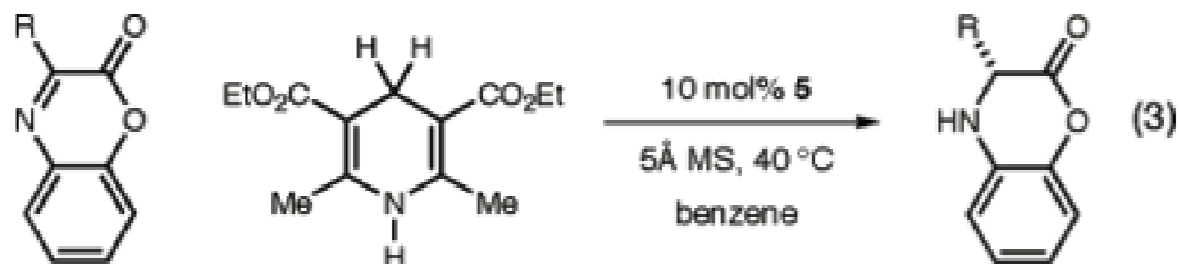
MacMillan's ACDC Reductive Amination: Aliphatic Substrates as Well



MacMillan's ACDC Reductive Amination: Ketone Substitution Studies

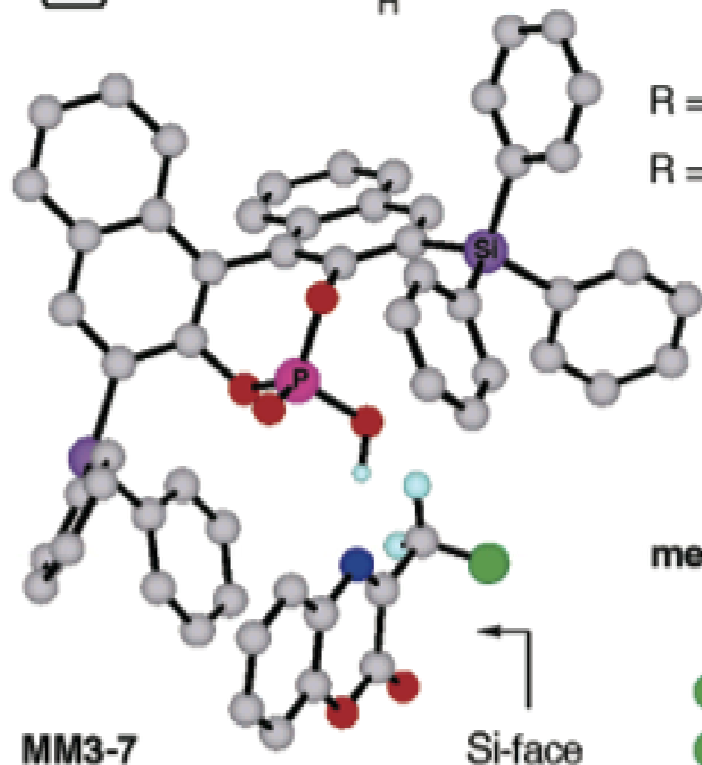


MacMillan's ACDC Reductive Amination: Ketone Substitution Studies

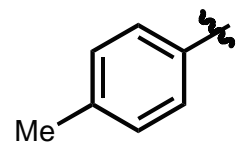
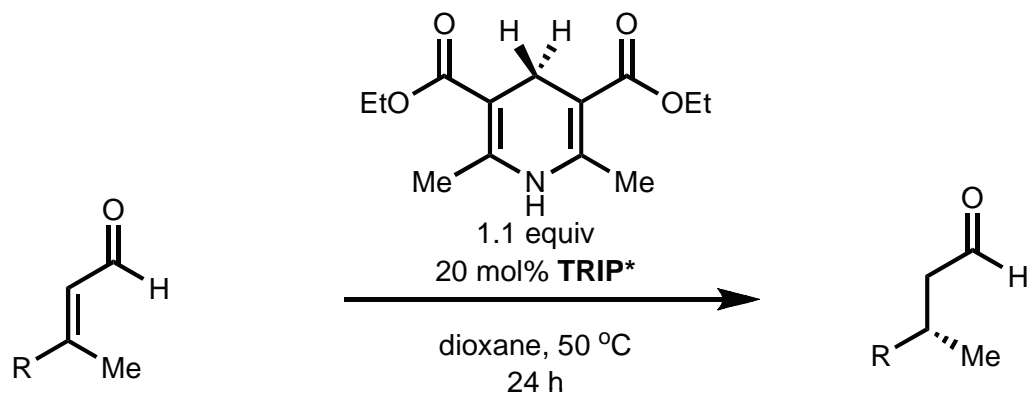


R = Me (**6**), 82% yield, 97% ee

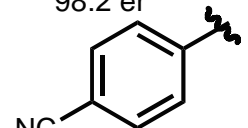
R = Et (**7**), 27% yield, 79% ee



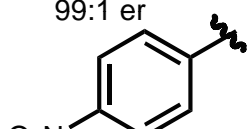
List's Asymmetric Enal Hydrogenation



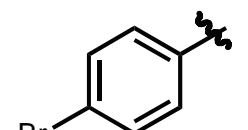
87%
98:2 er



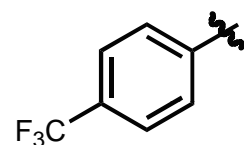
94%
99:1 er



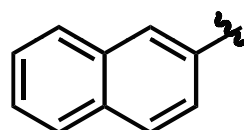
90%
99:1 er



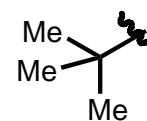
67%
98:2 er



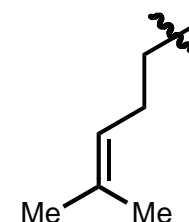
63%
99:1 ee



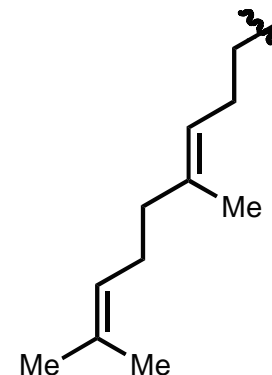
63%, > 99: < 1 er



< 5%, n. d

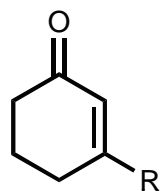
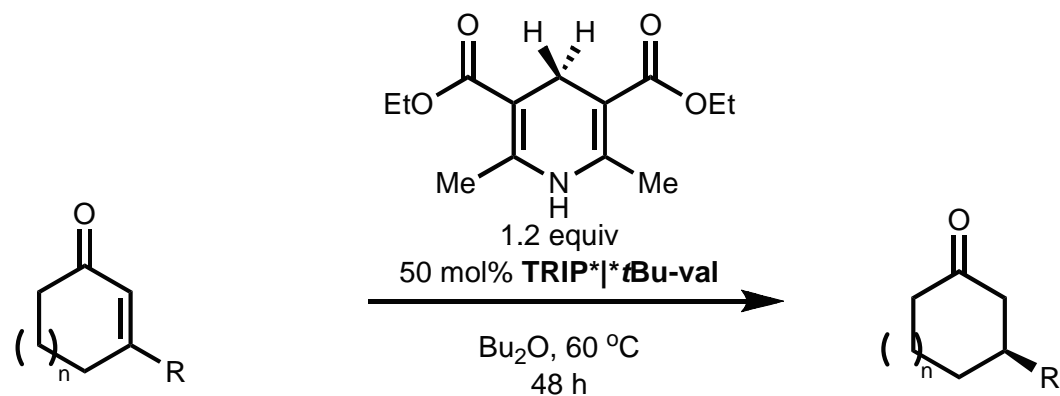


(E)-Citral: gives (R)-Citronellal
71% 95:5 er; rxn @ rt

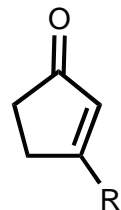


Farnesol: gives (R)-dihydrofarnesal
77% 96:4 er; rxn @ rt, 96 h

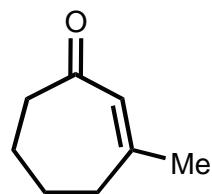
List's Asymmetric Enone Hydrogenation



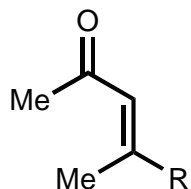
R = Me: 99% 97:3 er
 R = Et: 98% 98:2 er
 R = *i*-Bu: 89% 98:2
 R = *i*-Pr: 94% 99:1 er
 R = CH₂CH₂Ph: 99% 98:2 er
 R = Ph: 99% 92:8 er



R = Me: 78% 99:1 er
 R = Et: 71% 98:2
 R = CH₂CH₂Ph: 68% 98:2



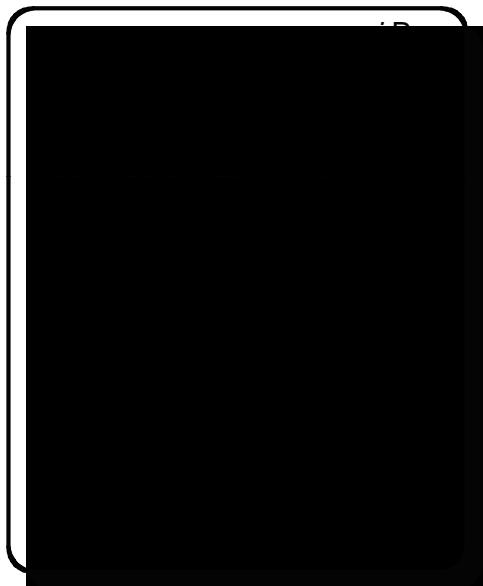
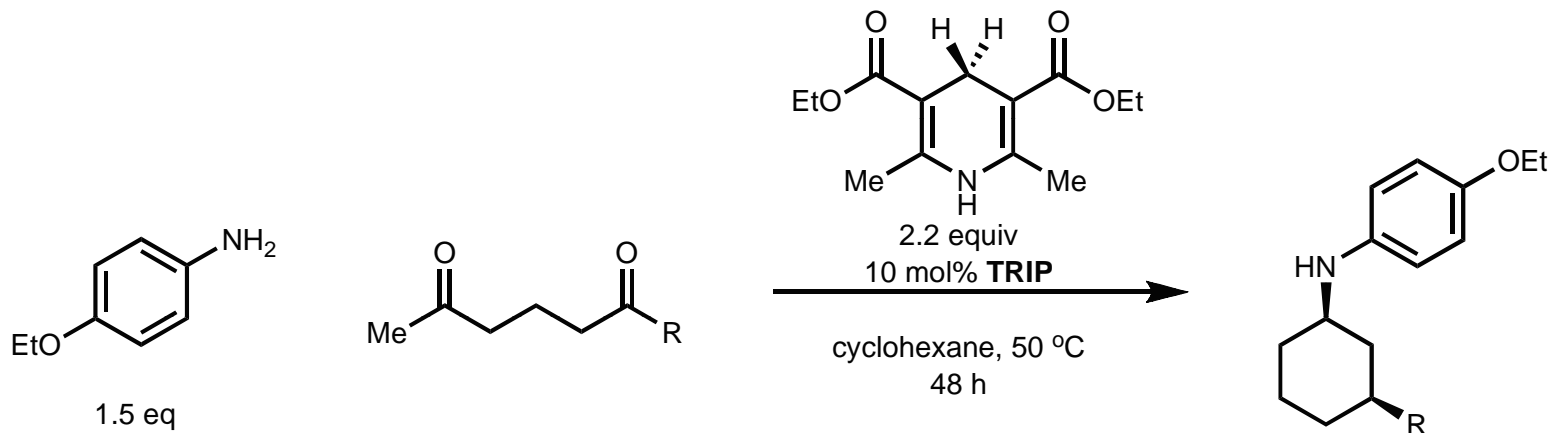
> 99% 98:2



R = CO₂Et: > 99% 92:8 er
 R = Ph: 81% 85:15

R = Me 45% 58:42 er

List's Enantioselective Preparation of Cyclohexylamines



Me	89% 6:1 dr 92:8 er
	75% 10:1 dr 95:5 er
	79% 12:1 dr 98:2 er
	76% 3:1 dr 96:4 er

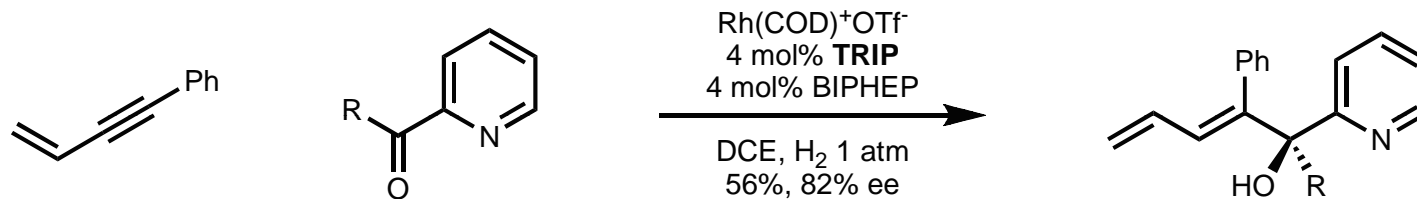
	72% 24:1 dr 98:2 er
	78% 4:1 dr 96:4 er
	89% 19:1 dr 98:2 er

	82% 24:1 dr 98:2 er
	77% 6:1 dr 93:7 er
	73% 2:1 dr 91:9 er

Tandem Transition-Metal/Chiral Phosphoric Acid Catalyzed Reactions

- Allows for asymmetric transition metal catalysis without chiral transition metal catalysts
- The chiral phosphoric acid can activate lewis bases while also acting as ligand
- Could potentially provide a new host of substrates for transition-metal catalysis.

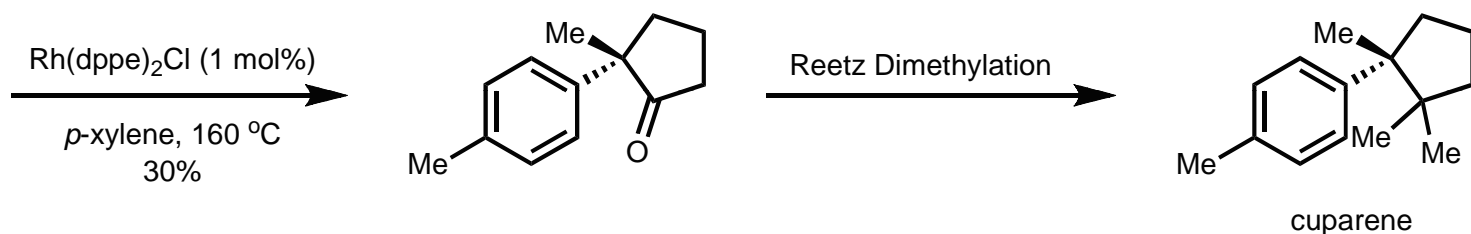
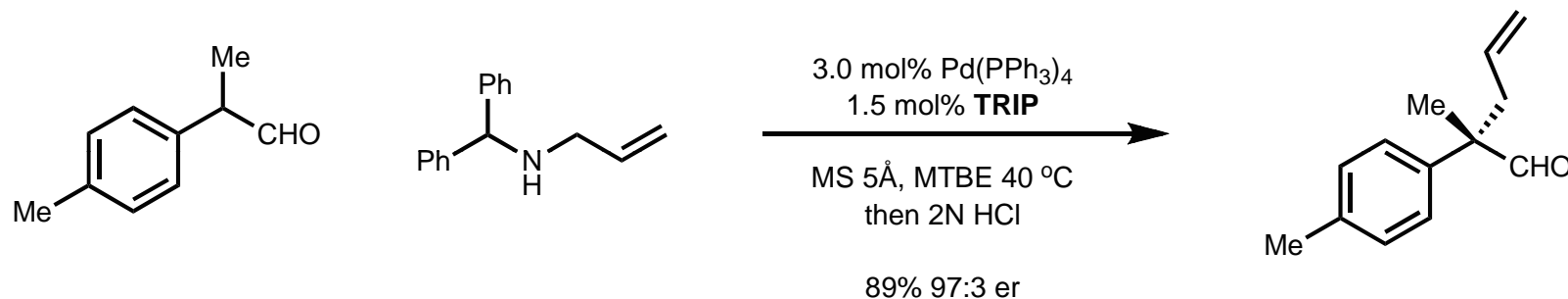
Reductive Coupling of 1,3-Enynes to Heterocyclic Aromatic Aldehydes and Ketones



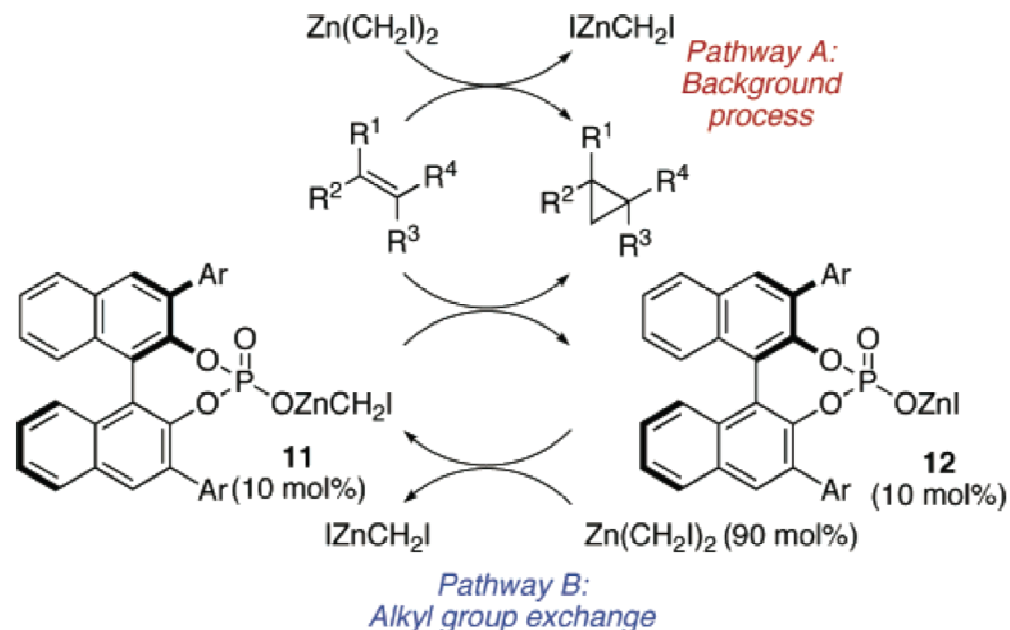
Pd/Brønsted Acid Catalyzed Direct α -Allylation of Aldehydes



Pd/Brønsted Acid Catalyzed Direct α -Allylation of Aldehydes



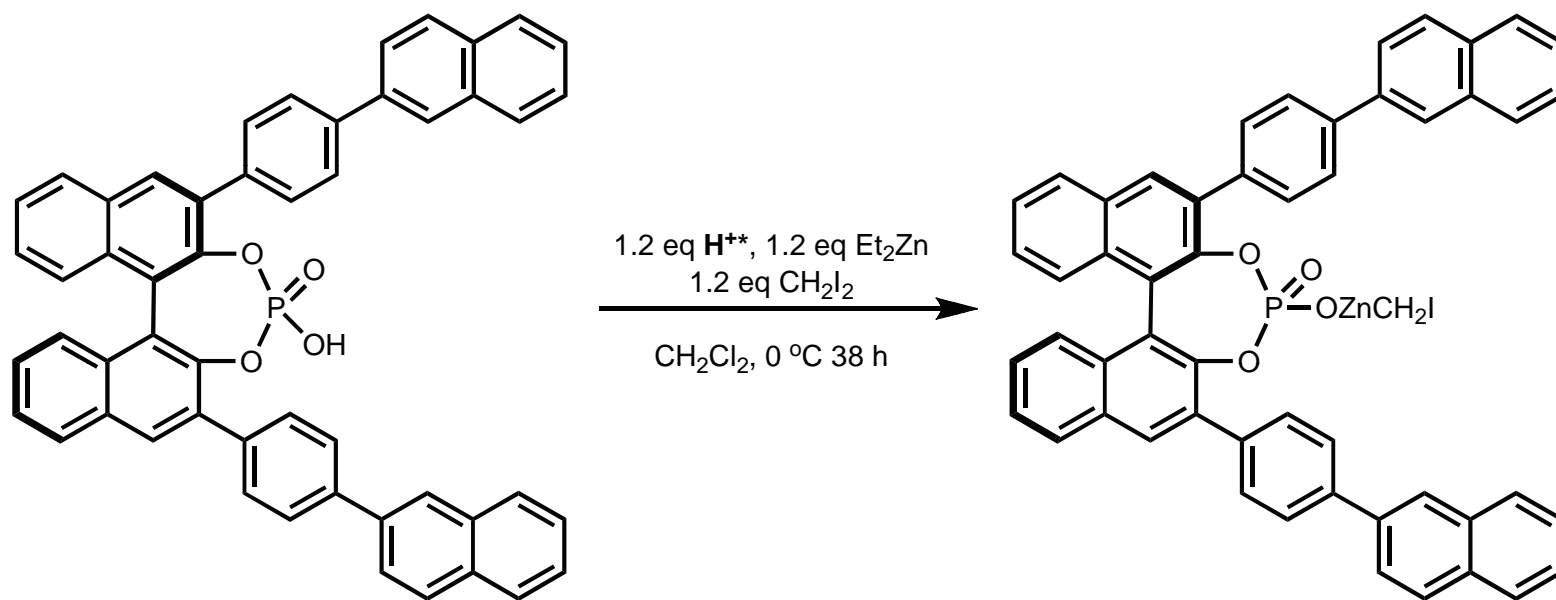
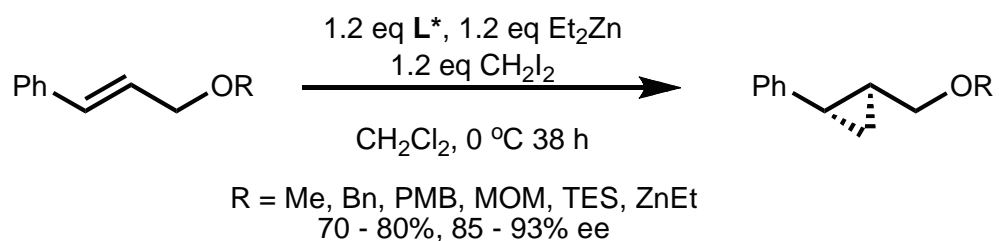
Asymmetric Simmons-Smith Cyclopropanation Catalytic in Chiral Phosphoric Acid



The main problem for catalysis is that the Simmons-Smith reagent is req'd in stoichiometric amounts and is still active when not bound to the chiral source



Asymmetric Simmons-Smith Cyclopropanation



Major drawback was the use of stoichiometric phosphoric acid