Aspects of Asymmetric Nucleophilic Amine Catalysis: Organocatalyst Design and Implementation

MacMillan Group Meeting
Ian Storer
February 28, 2005

Asymmetric Nucleophilic Catalysis

Outline

- Introduction to *N*-centred nucleophilic catalysts
  - concepts and definitions
  - origins and requirements

- Design, development and application of asymmetric nucleophilic catalysts
  - Natural alkaloid catalysts - Precejus, Wynberg
  - Synthetic alkaloid analogues - Lectka, Hatekeyama, Deng
  - Biomimetic histidine containing peptide catalysts - **Miller**
  - Asymmetric DMAP equivalents - Fuji / **Fu**

Useful Reviews:

- Fance, S.; Guerin, D. J.; Miller, S. J.; Leckta, T., Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis. *Chem Rev.* **2003**, *103*, 2985-3012.
- Miller, S. J. In Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis. Acc. Chem. Res. **2004**, *37*, 601-610.
- Fu, G. C. Asymmetric Catalysis with "Planar-Chiral" Derivatives of DMAP. *Acc. Chem. Res.* **2004**, *37*, 542-547.

Definitions

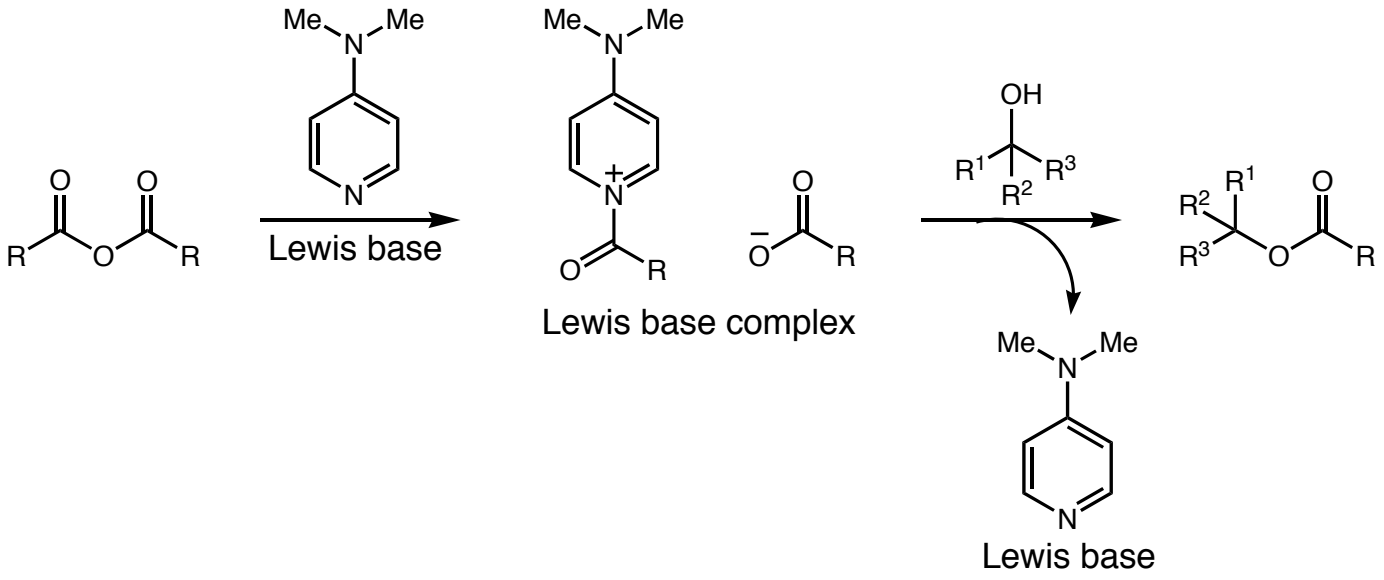
Lewis base

A molecular entity (and the corresponding chemical species) able to provide a pair of electrons and thus capable of coordination to a Lewis acid, thereby producing a Lewis adduct.

Nucleophilic Catalysis

Catalysis by a Lewis base, involving formation of a Lewis adduct as a reaction intermediate. For example, the esterification of anhydrides catalysed by DMAP:

IUPAC Compendium of Chemical Terminology

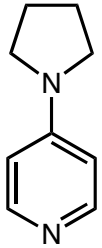


Implication on Choice of catalyst

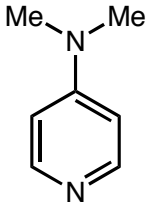
The catalyst has to be a very effective nucleophile and a good leaving group .

Useful Nucleophilic Catalysts

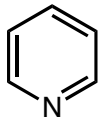
Commonly applied 'everyday' nucleophilic catalysts



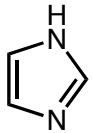
PPY



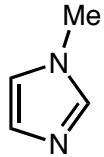
DMAP



Pyridine

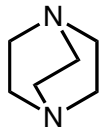


Imidazole



NMI

Nucleophilic Aromatic Amines



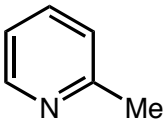
DABCO

nucleophilic teriary amines

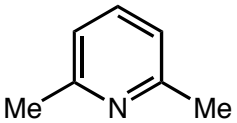
Common applications

- O-acylation - electrophile activation (pyridine, DMAP)
- O-silylation - electrophile activation (imidazole, DMAP)
- Baylis-Hilman reaction - nucleophile activation (DABCO, DMAP)

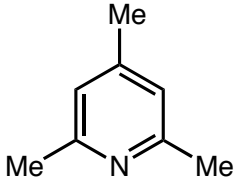
Ineffective bases: Nucleophilicity highly sensitive to steric and electronic factors



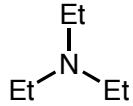
picoline



lutidine



collidine

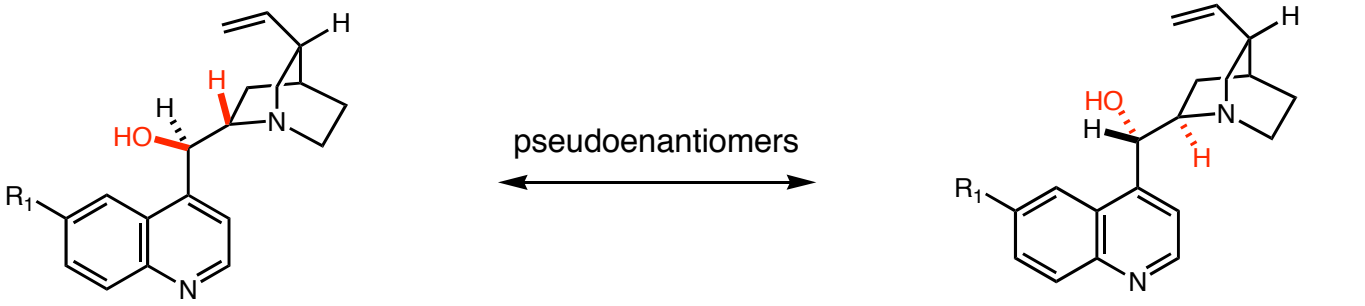


TEA

good Bronsted bases, **poor nucleophilic catalysts**

Cinchona Alkaloids: Earliest Successful Nucleophilic Asymmetric Catalysts

■ First used for a resolution of a racemate in 1853 by Pasteur.



Cinchonidine (**CD**) R^1 = H
Quinine (**QN**) R^1 = OMe

Cinchonine (**CN**) R^1 = H
Quinidine (**QD**) R^1 = OMe

■ Several modes of application

- Asymmetric Bronsted bases
- Asymmetric phase transfer reagents (as salts)
- Asymmetric bifunctional catalysts (acid / base)
- Asymmetric **nucleophilic catalysts**

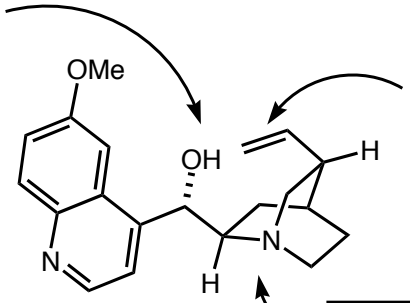
Moncure, R. *MacMillan Group Meeting*, **2003**, web. – contains a more fully discussion of cinchona alkaloids

Alkaloids and Derivatives as Nucleophilic Catalysts

Natural alkaloids

site of modification:
ether/ ester formation

site of inversion of
configuration (epi alkaloids)
-pseudoenantiomers

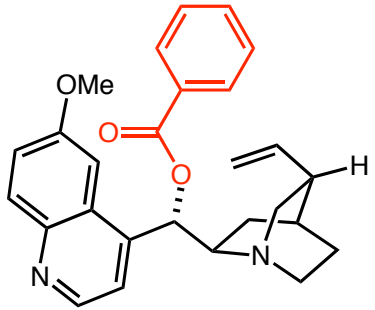


site of modification

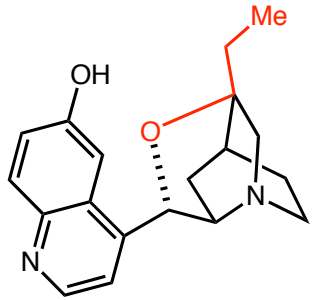
site of quaternary salt formation, **nucleophilic addition** or basicity

Quinidine
Pracejus (1964)
Wynberg (1983)
Simpkins (2001)

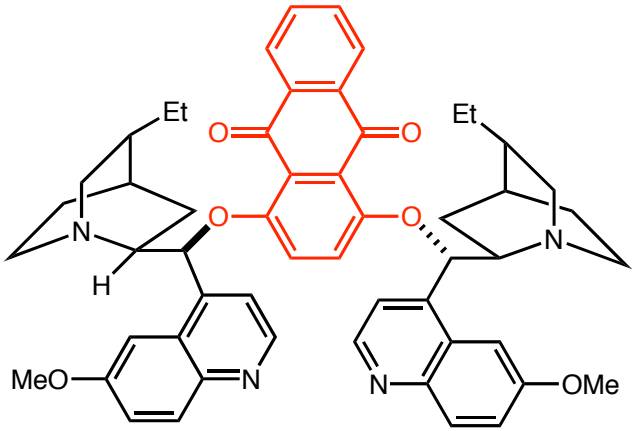
Synthetically modified analogues



benzoylquinine
Lectka (2000)



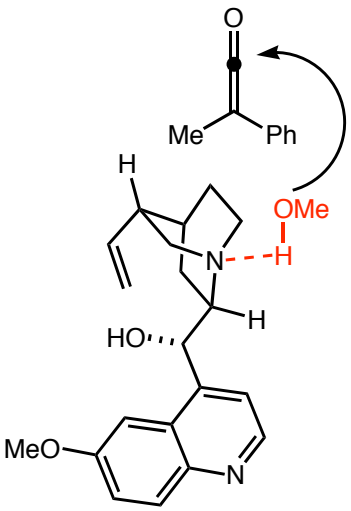
Hatakeyama



$(DHQD)_2AQN$
Deng

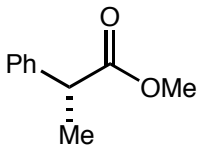
Seminal Findings: Pracejus Methanolysis of Ketenes

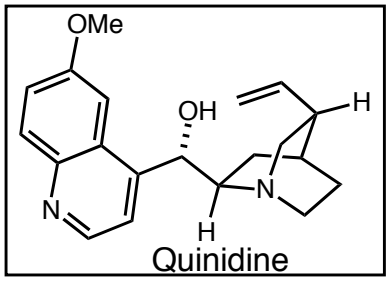
■ Pracejus proposed a mechanism involving QN activation of methanol.



1–2 mol % quinidine

MeOH, –110 °C



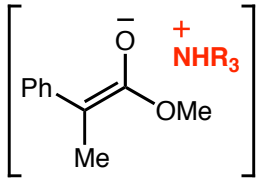


selective protonation

up to 76% ee

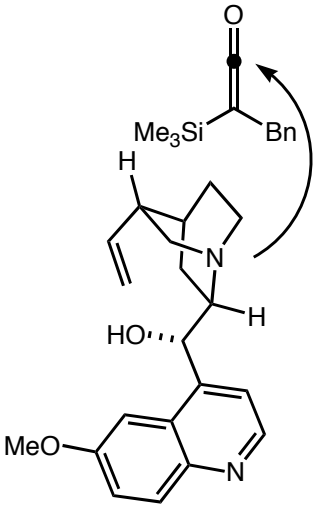
+MeOH

H-bond activation



Precejus, H.; Mätje, H. *J. Prakt. Chem. 4. Reihe.* **1964**, *24*, 195.
Precejus, H.; Santleben, R. *J. Prakt. Chem.* **1972**, *314*, 157.

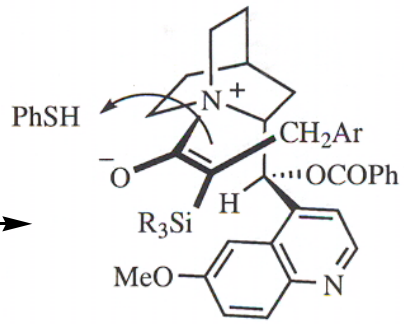
■ Simpkins proposes alternative nucleophilic mechanism



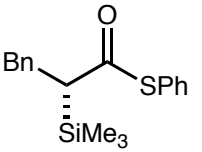
PhSH

10 mol % quinidine

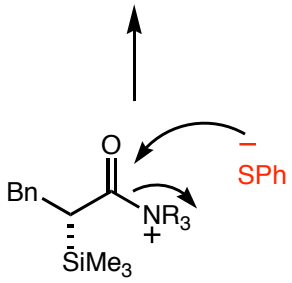
benzene, –78 °C



selective protonation

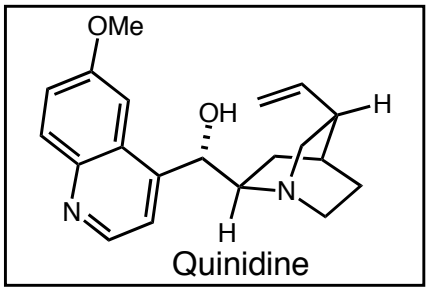


79-93% ee

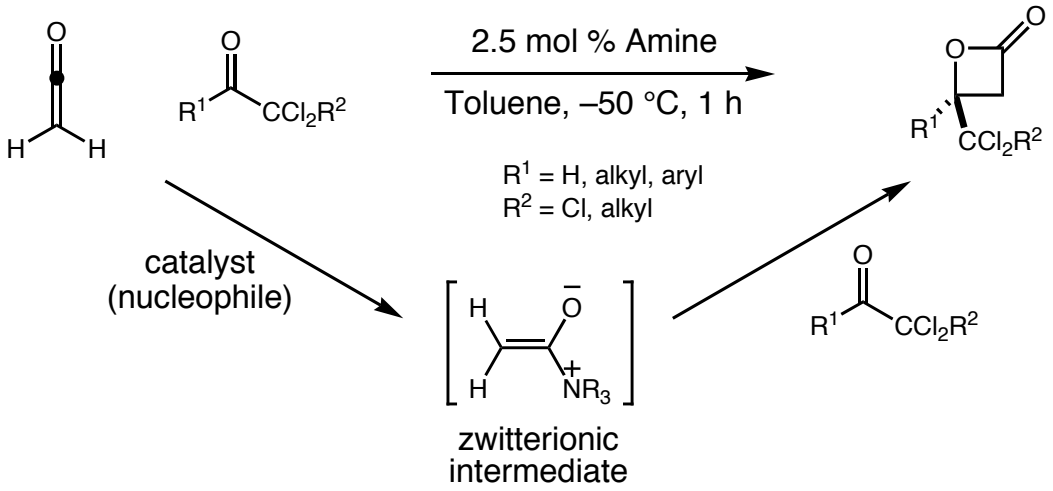


Blake, A. J.; Friend, C. L.; Outram, R. J.; Simpkins, N. S.; Whitehead, A. J. *Tetrahedron Lett.* **2001**, *42*, 2877.

Catalytic Asymmetric Cycloadditions: Synthesis of β–Lactones



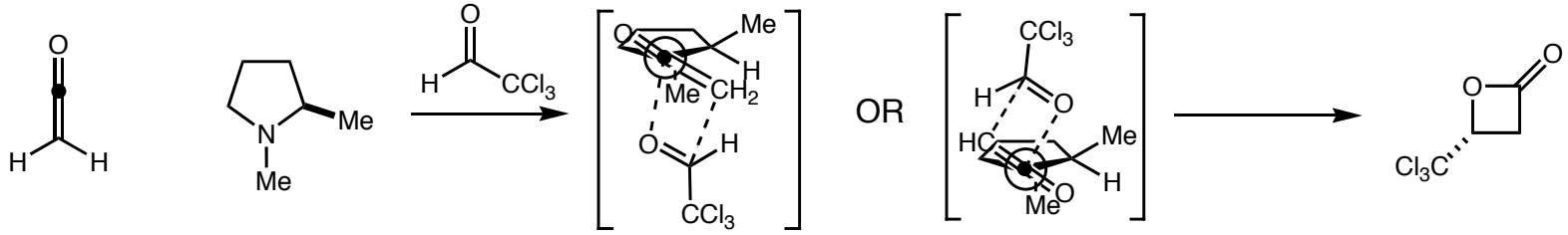
■ An early example of asymmetric nucleophilic catalysis using an alkaloid.



up to 95 % yield
45-98 % ee

- Unprotected quinidine also catalyses its own acylation at OH

■ Wynberg's proposed this stereoselectivity model

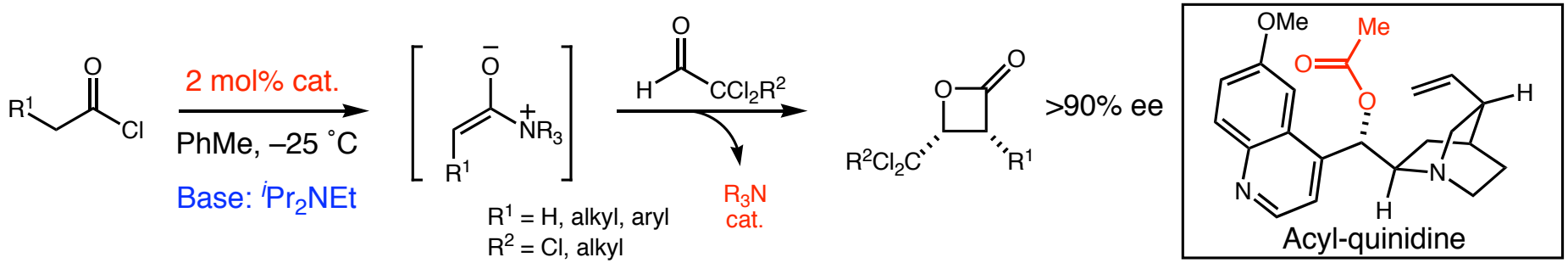


- In the left TS, the ketene oxygen faces the methylene of the catalyst ring .The chloral approaches the catalyst with the trichloromethyl group facing away from the methyl group of the catalyst to avoid steric strain.
- In the bottom TS, the ring is the dominant form of stereocontrol, and the CCl_3 orients itself away from the ring methylene protons.

Wynberg, H. *J. Am. Chem. Soc.* **1982**, *104*, 166.
Wynberg, H. *J. Org. Chem.* **1985**, *50*, 1977.

Development of Functionalised Alkaloid Analogues: Catalytic Asymmetric Cycloadditions

β-lactone synthesis: Romo's expansion of Wynberg's method

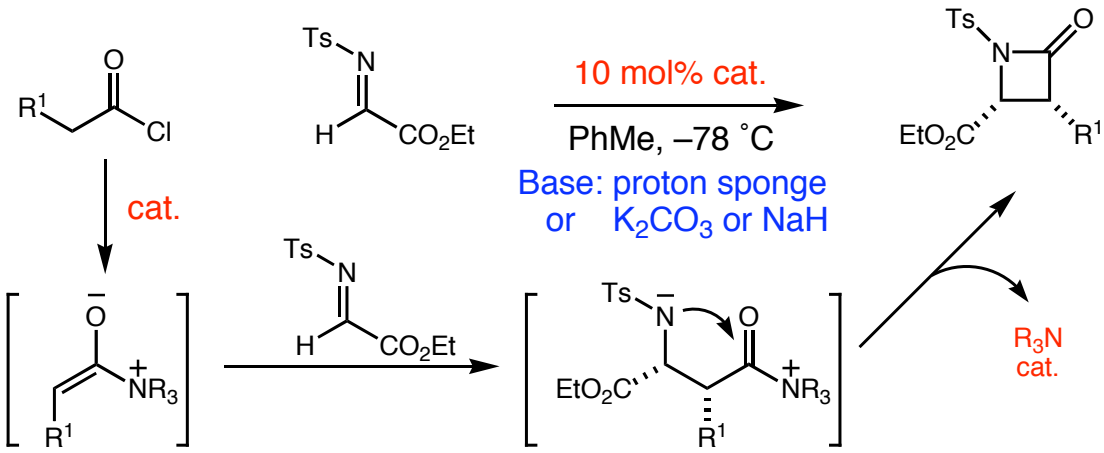


- The use of pre-acylated catalyst stops unwanted acylation of the catalyst during the reaction.
- Applies a stoichiometric, non-nucleophilic base to turn over the catalyst.
- *In situ* ketene generation
- Solubility of the Hunigs salt may be crucial to catalyst turnover.

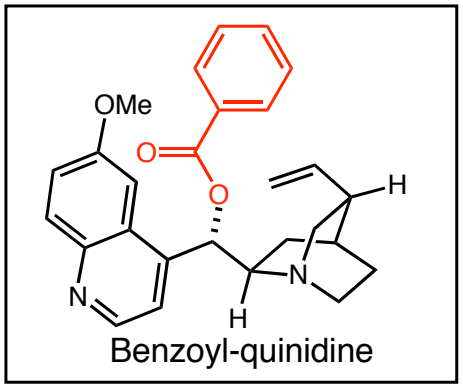
Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248.

Development of Functionalised Alkaloid Analogues: Catalytic Asymmetric Cycloadditions

β-lactam synthesis: Lectka



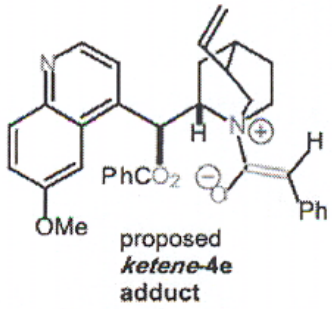
45-65% yield
95-99% ee
25-99:1 dr

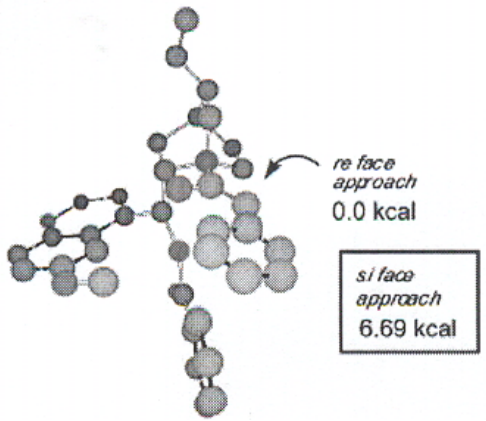


- 'Shuttle deprotonation' using excess of a thermodynamic, non-nucleophilic base.
- Concomitant Lewis acid activation of the imine later provided better yields

Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. J.. *J. Am. Chem. Soc.* **2000**, *122*, 7831.
Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. J.. *J. Am. Chem. Soc.* **2002**, *124*, 6626.

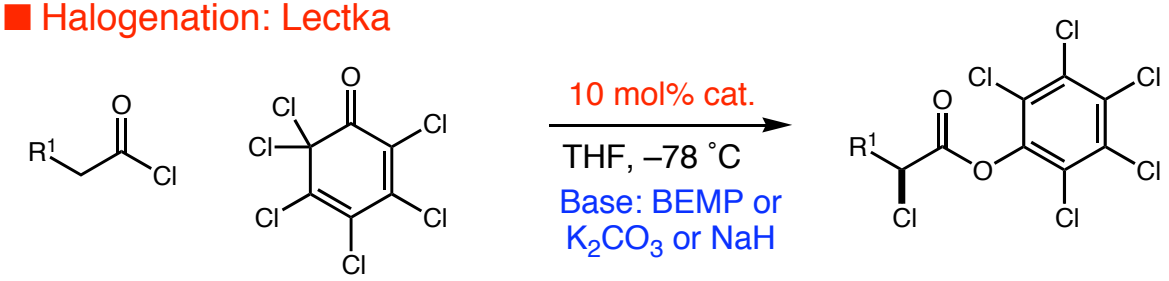
Proposed transition state

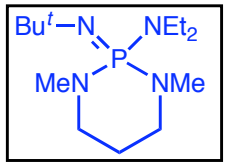


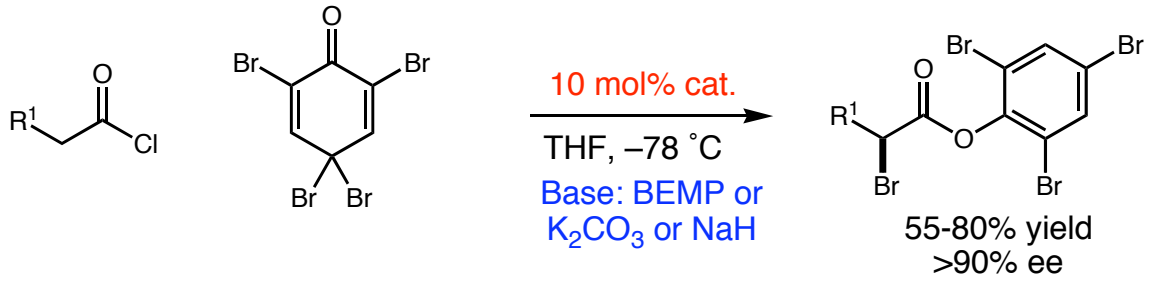


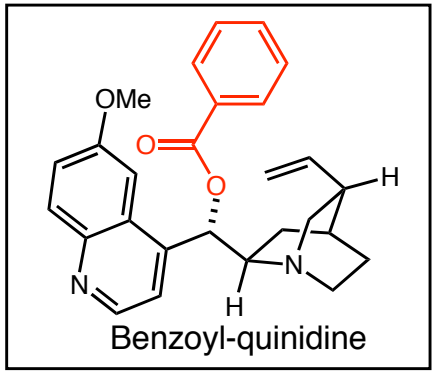
Development of Functionalised Alkaloid Analogues: Catalytic Asymmetric Halogenation

■ Halogenation: Lectka





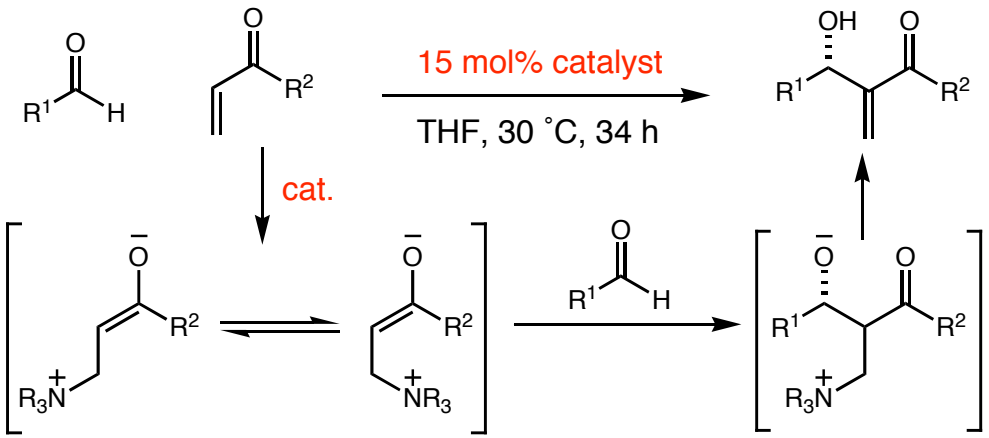


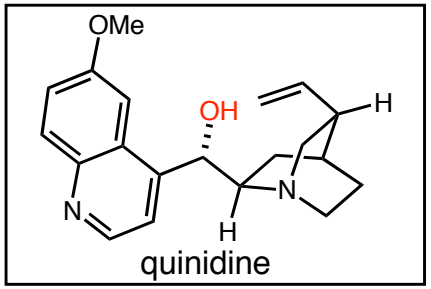


Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 1531.
Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. J. *Org. Lett.* **2001**, *3*, 2049.
Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. J. *Org. Lett.* **2002**, *4*, 627.

Development of Functionalised Alkaloid Analogues: Catalytic Asymmetric Baylis-Hillman Reaction

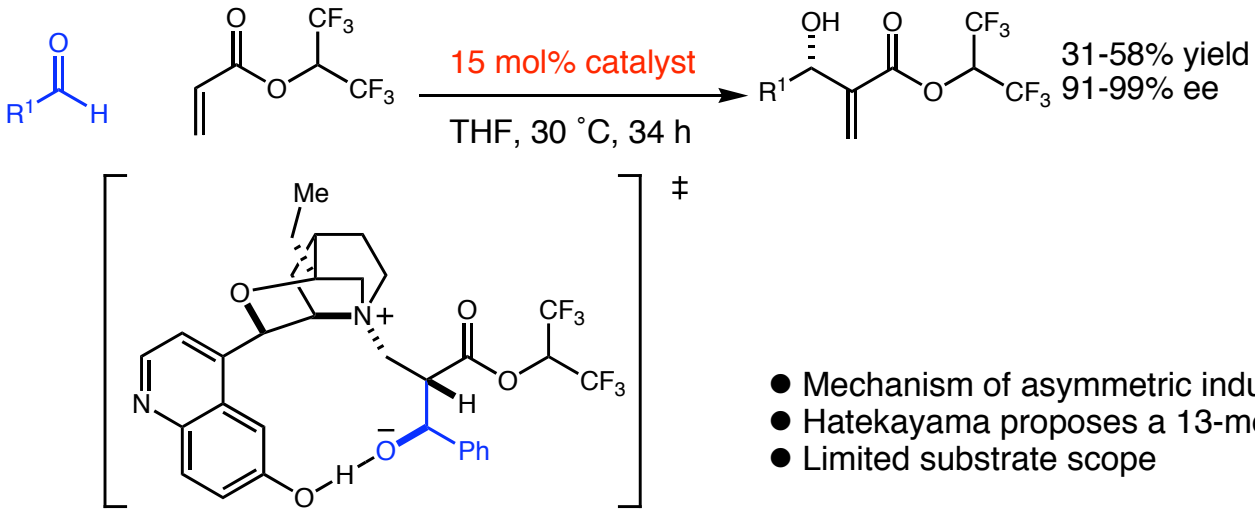
■ Natural alkaloid - poor enantioselectivity

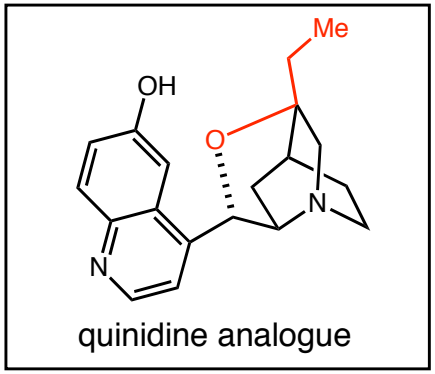




Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.

■ Synthetic analogue - better results

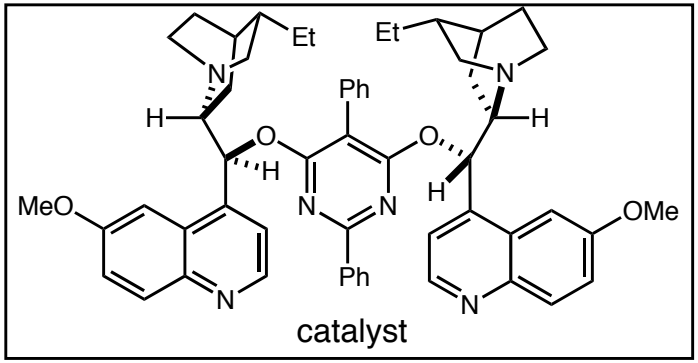




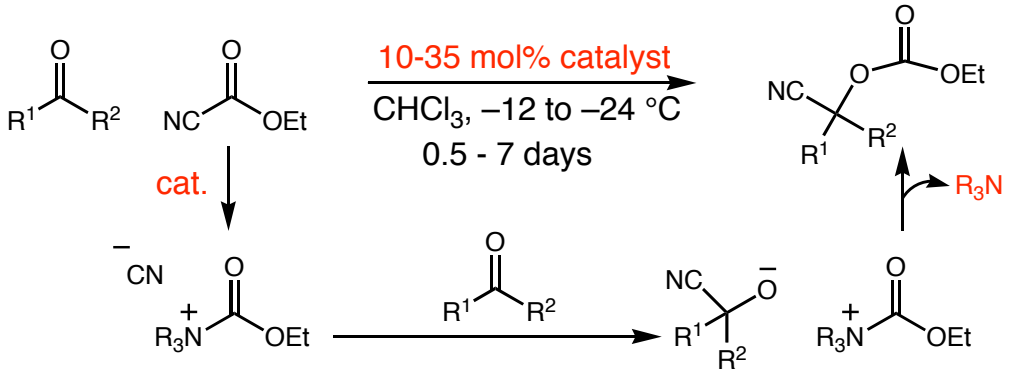
- Mechanism of asymmetric induction not well understood
- Hatekayama proposes a 13-membered ring transistion state
- Limited substrate scope

Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatekeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

Deng's Application of bis-quinuclidines



■ Cyanation

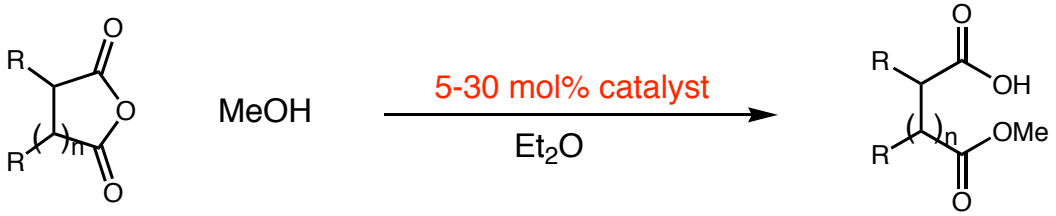


52-78% yield
87-97% ee

- Mechanism of asymmetric induction not well understood

Deng, L. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

■ Desymmmetrization of meso anhydrides



70-99% yield
90-98% ee

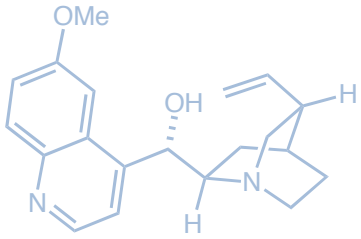
Deng, L. et al. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

Designing Asymmetric Variants of Known Nucleophilic Amine Catalysts

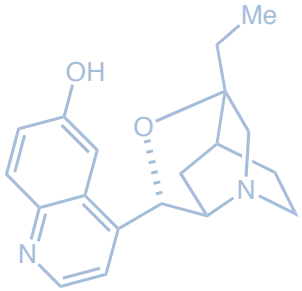
Considerations

- Must be nucleophilc, but maintain good leaving group ability
- Must have a valid chiral pocket to transfer asymmetry to product.

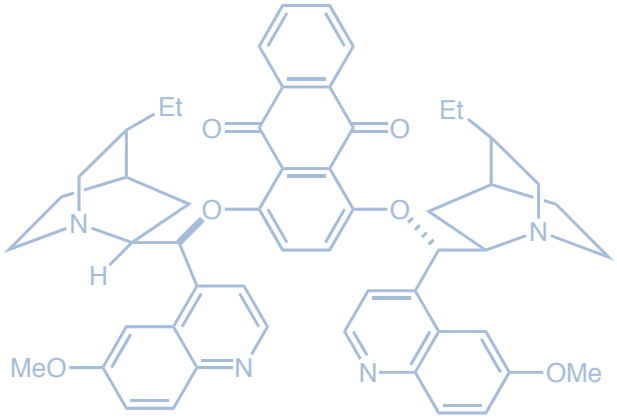
Alkaloids and analogues



Quinine
Wynberg

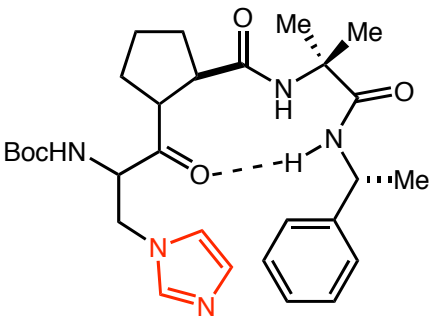


Hatakeyama



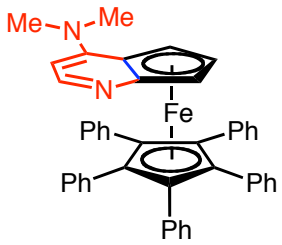
$(DHQD)_2AQN$
Deng

Synthetic chiral analogues of common nucleophilic heterocycles

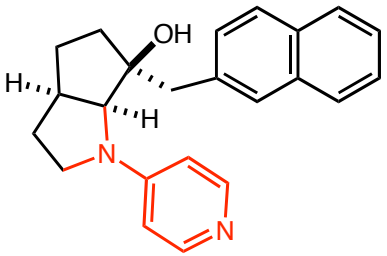


Miller

Synthetic chiral imidazole equivalents



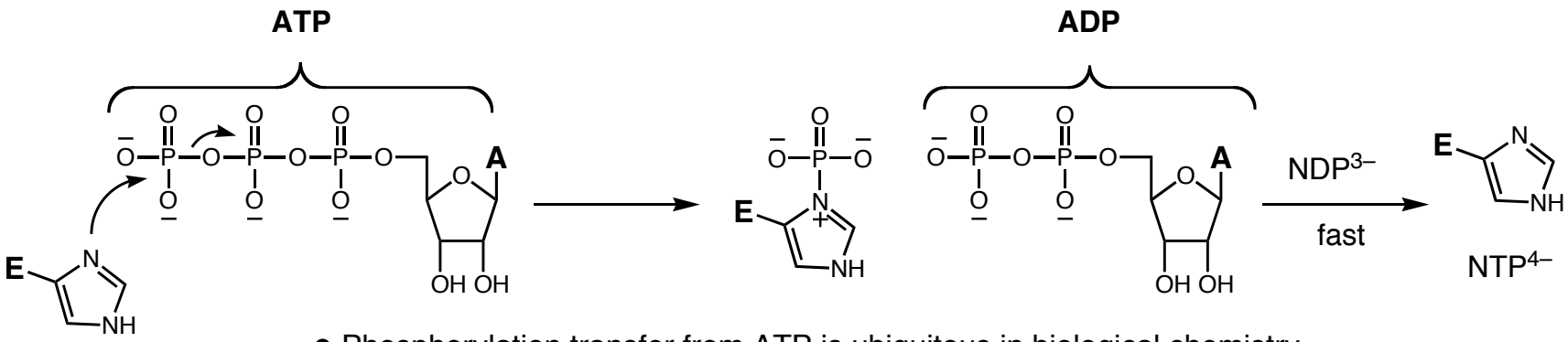
Fu (1998-current)



Synthetic chiral DMAP equivalents

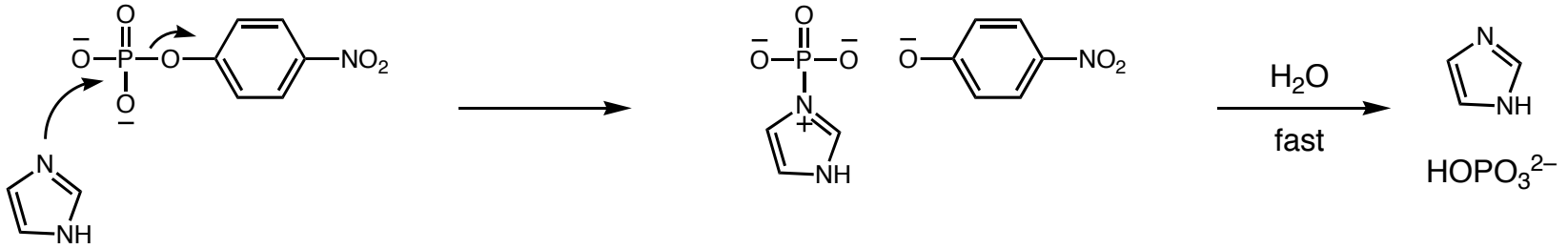
Biological Role of Nucleophilic Catalysis

Mechanism of some kinases - role of histidine



- Phosphorylation transfer from ATP is ubiquitous in biological chemistry.
- Histidine often serves as *in vivo* acceptors of the γ-phosphate of ATP.
- Proposed mechanism of ATPases and nucleoside diphosphate kinase (NDPK).

In vitro phosphorylation of imidazole



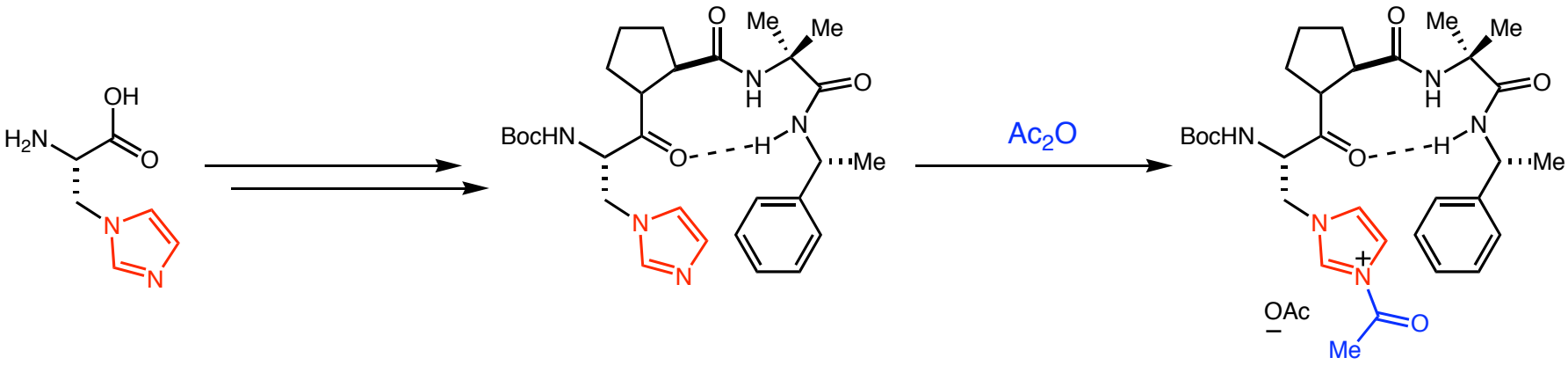
- First *in vitro* example of imidazole participating in phosphoryl transfer from ATP analogues.
- *N*-nucleophiles found to react 30-100 fold faster than *O*-nucleophiles at physiological temperatures.
- Carried out *in vitro* experiments on ATP.
- Supports proposed enzymatic mechanism.

Admiraal, S. J.; Herschlag, D.; *J. Am. Chem. Soc.*, **1999**, *121*, 5837-5845

Miller *N*-Methyl Imidazole-Containing Tripeptide

Synthesis of a nucleophilic tripeptide

- Peptide-substrate interactions are crucial for the fidelity by which an enzyme imparts its selectivity.
- Incorporating an amino acid residue as an analogue of known nucleophilic catalyst N-methyl imidazolium (NMI).
- Work focused on peptides that had propensity to form stable secondary structures (β-turn) in solution.



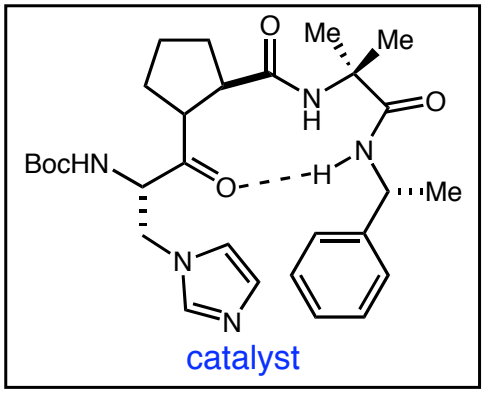
acyl imidazolium

Modularity of peptide-based systems allows for the rapid synthesis and screening of many analogues.

- Initial designs drew heavily from the peptide design literature in order to generate a relatively rigid β-turn structure

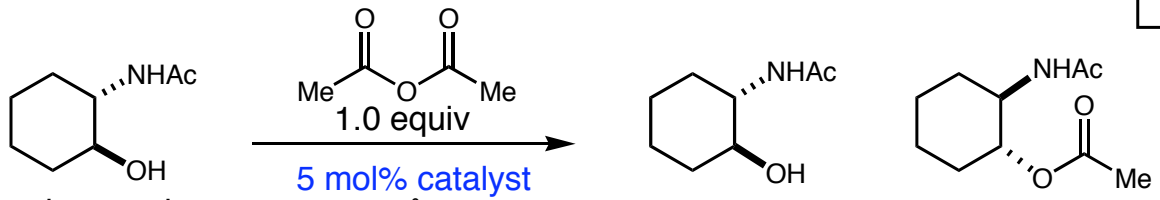
Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630.

Miller Chiral Imidazole Tripeptide: Kinetic Resolution of Alcohols



catalyst

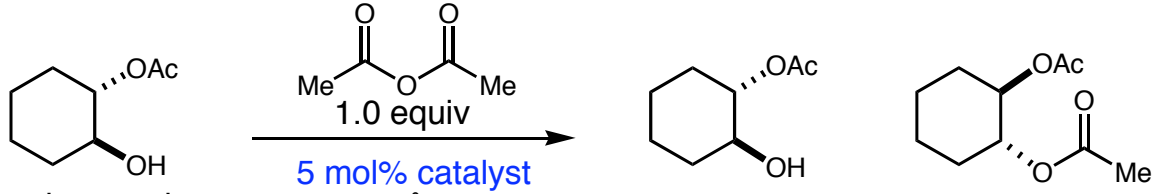
Kinetic resolution of amino-alcohols



anti, racemic
10 equiv

CH_3CN = 12% ee
CH_2Cl_2 = 40% ee
PhMe = 84% ee (S = 12.6)

Kinetic resolution of mono-acylated diols



anti, racemic
10 equiv

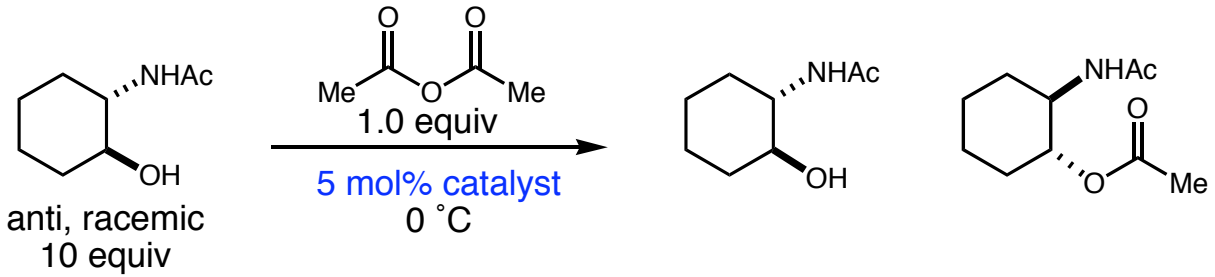
PhMe = 14% ee

- Amide in amino-alcohols necessary for good levels of stereoinduction
- Non-polar solvents which favour H-bonding work best
- Replacement of the amide with an ester provides only poor selectivity

Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630.

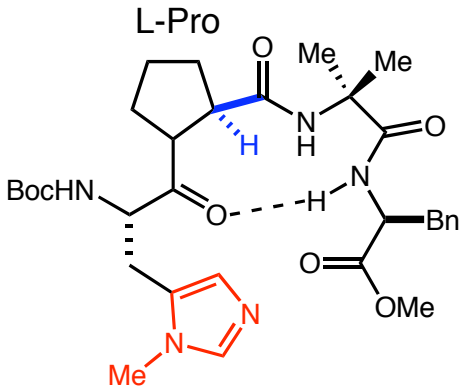
Probing Origins of Selectivity

Test System: Kinetic resolution

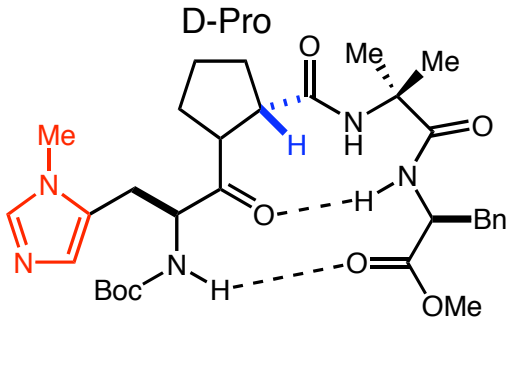


Diastereomeric catalysts display enantiodivergence

- Changing a single stereocentre in the catalyst causes a change in secondary structure.
- Changing a single stereocentre in the catalyst causes a complete switch in enantioselectivity.



S = k_{SS} / k_{RR} = 3.1



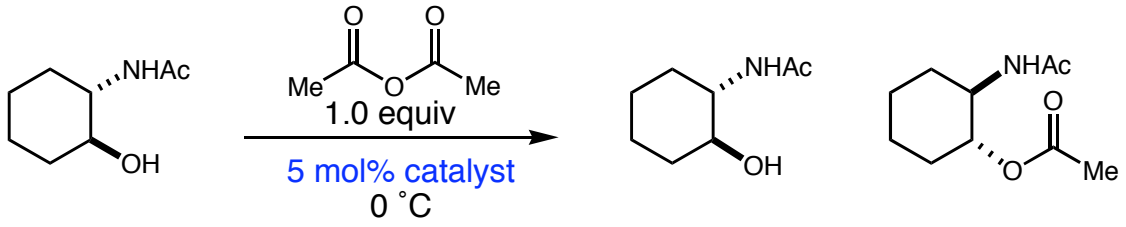
S = k_{RR} / k_{SS} = 28

What is the mechanism of binding and role of the peptide backbone structure?

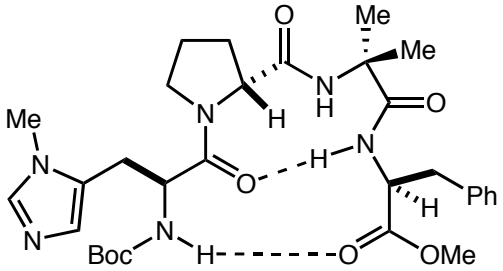
Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306.
Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 11270.

Miller "Biomimetic" Strategy

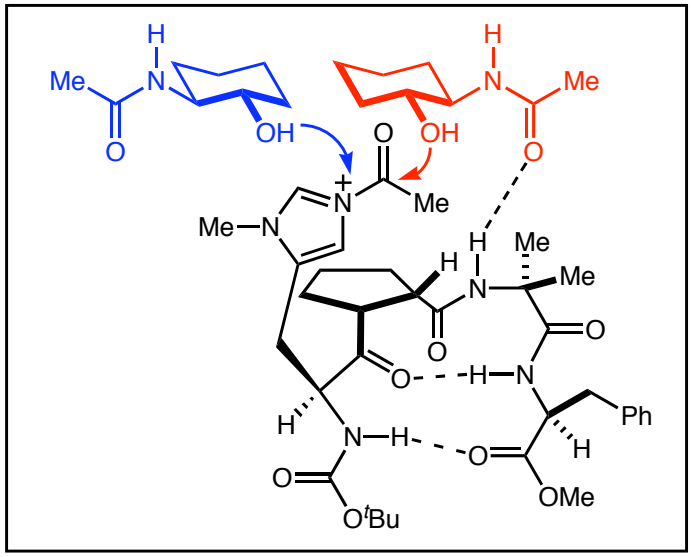
- Kinetic resolution of amino-alcohols

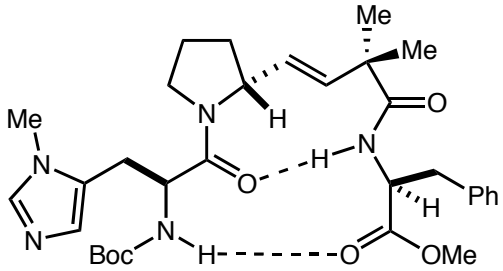


- Mechanistic postulate



k_{rel} = 28





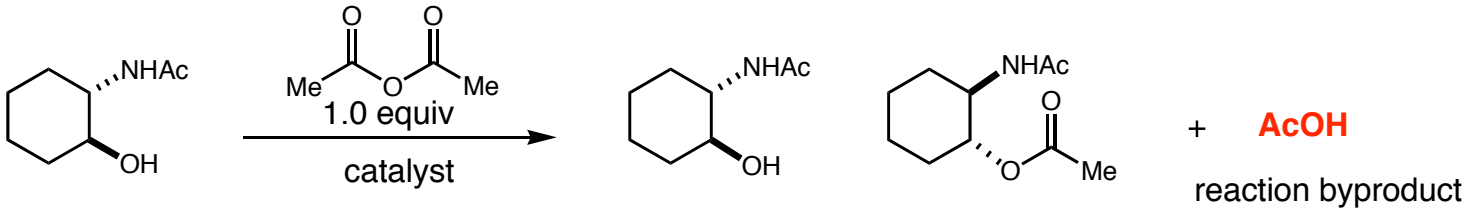
k_{rel} = 1

Larger rate acceleration than using DMAP - NMI is usually less activating?

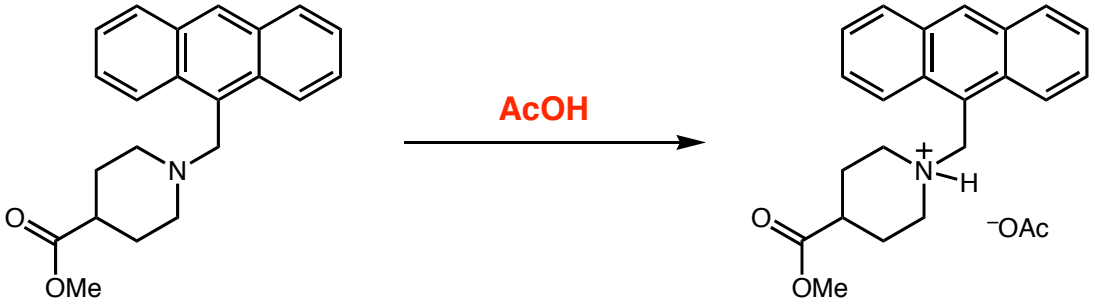
Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 2824-2827.

Miller: Development of a Fluorescence Assay

Kinetic resolution of amino-alcohols



Development of a fluorescence probe for rapid reaction conversion analysis



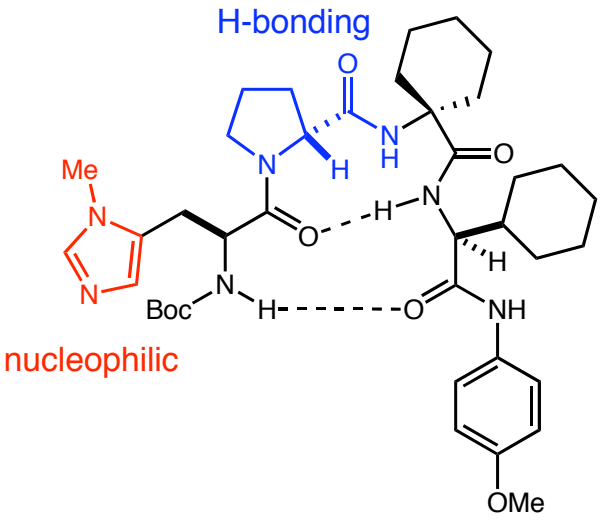
Non-Fluorescent **Fluorescent**

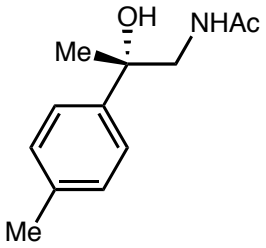
- Fluorescence intensity is a function of acetic acid concentration
- Assisted rapid catalyst discovery.

Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.*. **1999**, *121*, 4306.
Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.*. **2000**, *122*, 11270.

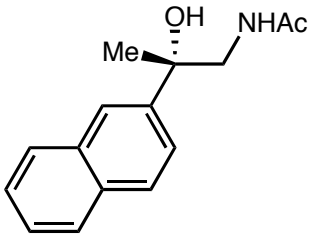
Miller Histidine-Containing Peptide Catalysts

- Catalyst for the kinetic resolution of tertiary alcohols



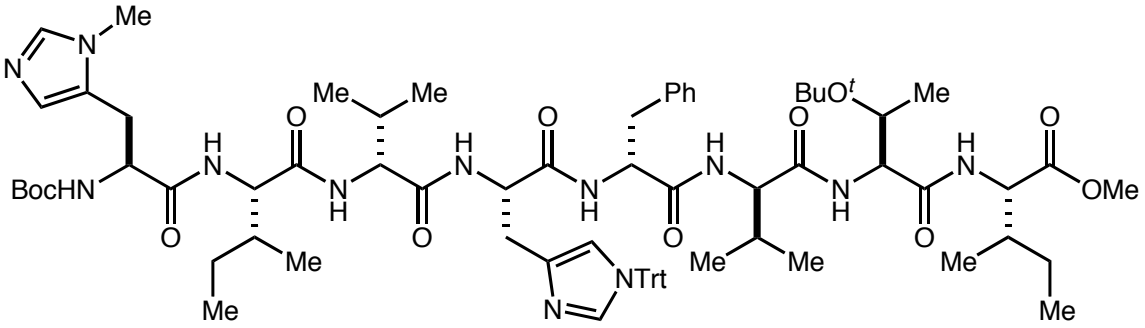


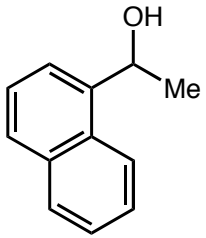
k_{rel} = >50



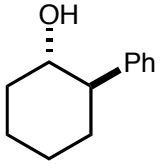
k_{rel} = 40

- Kinetic resolution acetylation of unfunctionalised alcohols





k_{rel} = >50



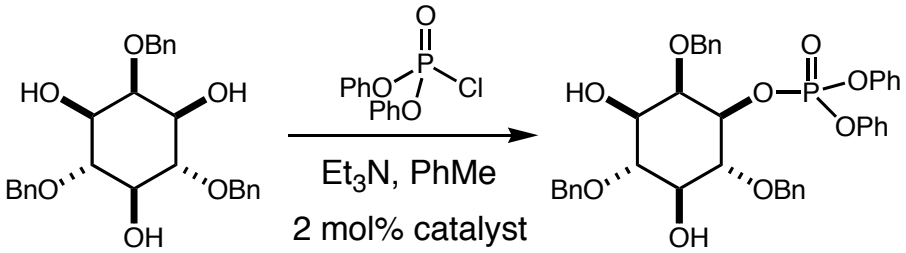
k_{rel} = >50

The conformation / contribution of the peptide backbone is not known

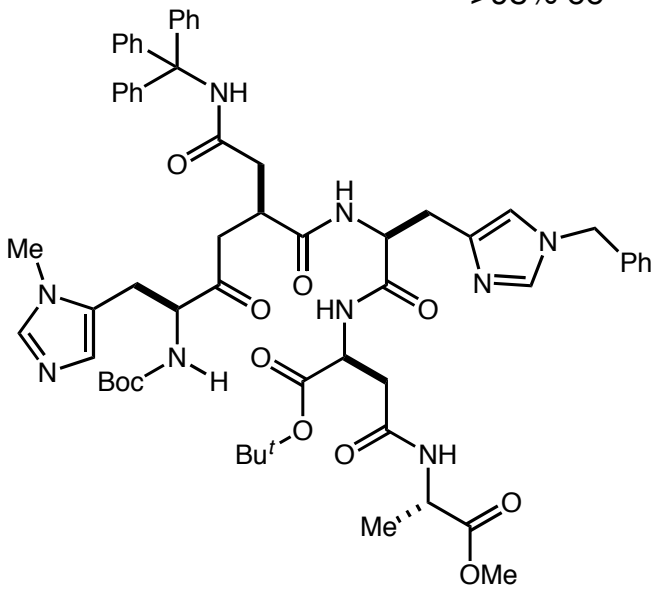
Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522.

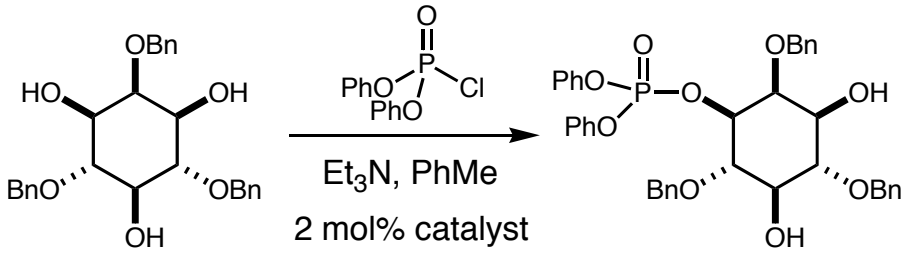
Miller: Development of a Desymmetrising Phosphorylation

Asymmetric phosphorylation of meso triols

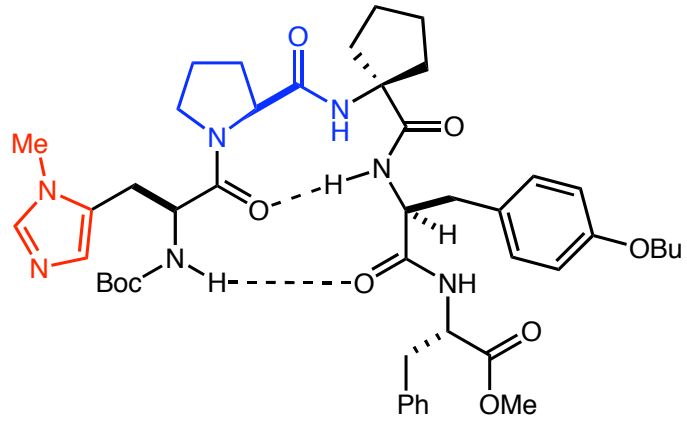


>98% ee





>98% ee



- Two very different peptides give very highly enantioselective phosphorylation in opposite enantioseries

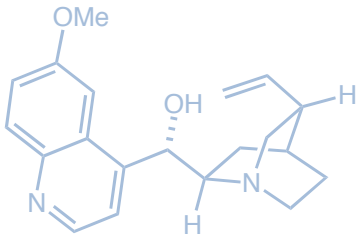
Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.*. **2001**, *123*, 10125.

Designing Asymmetric Variants of Known Nucleophilic Amine Catalysts

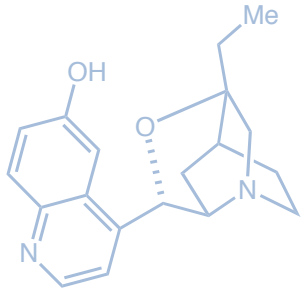
Considerations

- Must be nucleophilc, but maintain good leaving group ability
- Must have a valid chiral pocket to transfer asymmetry to product.

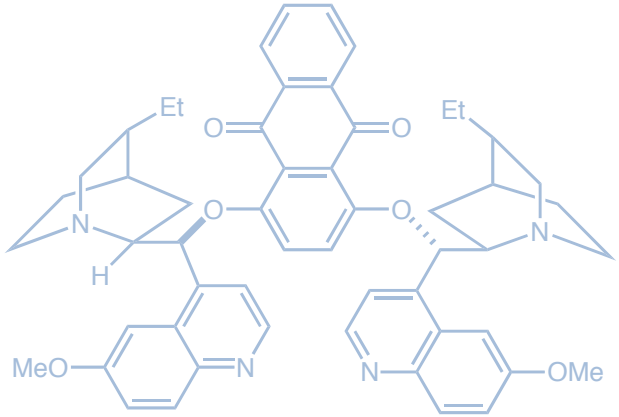
Alkaloids and analogues



Quinine
Wynberg

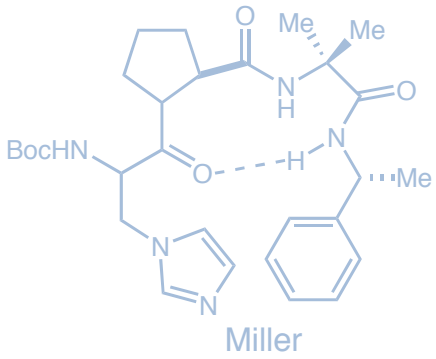


Hatakeyama



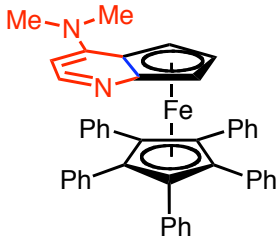
$(DHQD)_2AQN$
Deng

Synthetic chiral analogues of common nucleophilic heterocycles

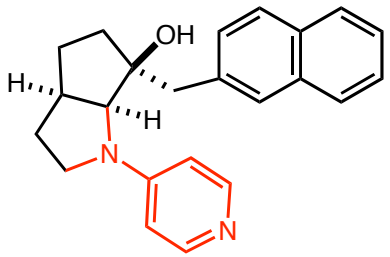


Miller

Synthetic chiral imidazole equivalents



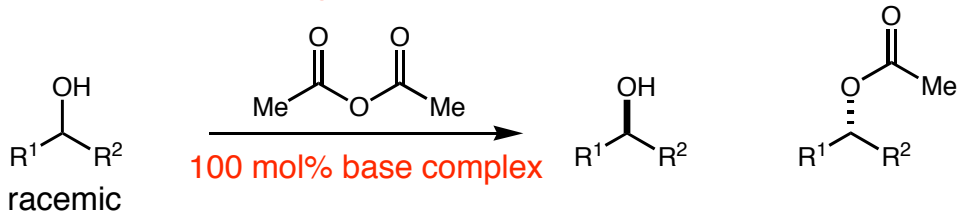
Fu (1998-current)

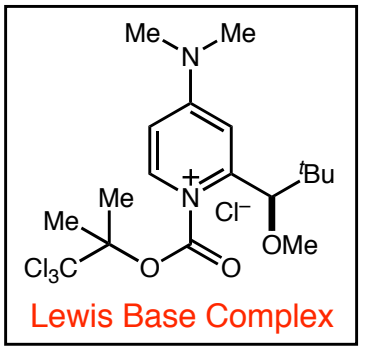


Synthetic chiral DMAP equivalents

Early Attempts to Make Chiral DMAP Equivalents

Vedejs pioneering contribution: kinetic resolution

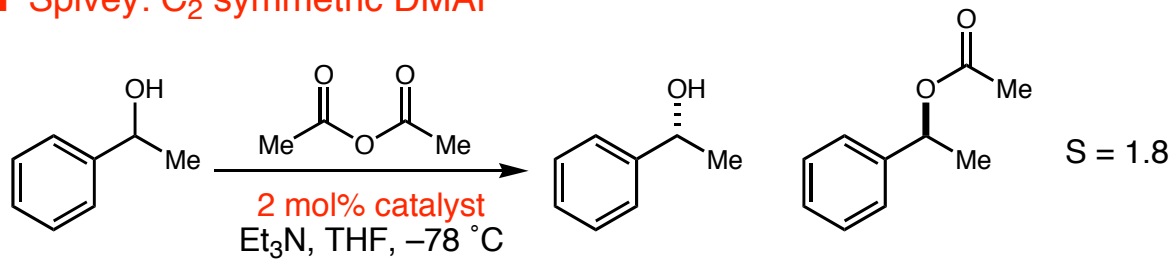


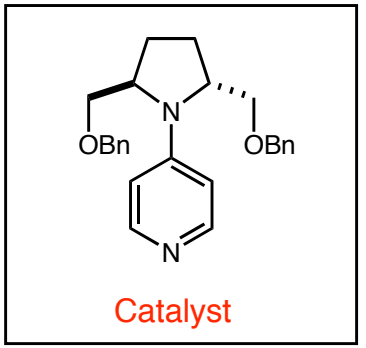


- This DMAP equivalent is not nucleophilic enough to permit catalytic turnover
- A variety of substrates gave good levels of enantioselectivity

Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.
Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

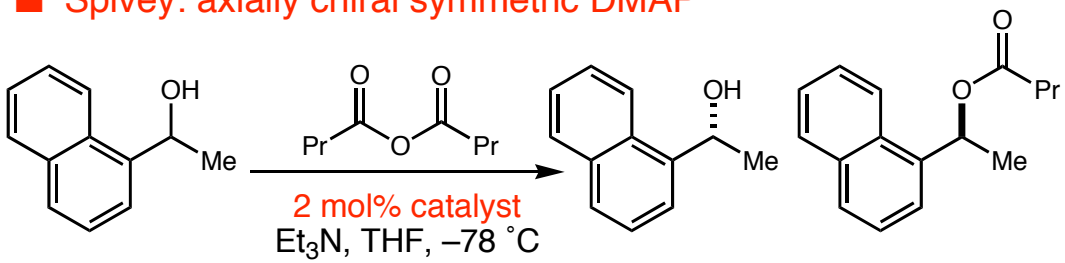
Spivey: C_2 symmetric DMAP

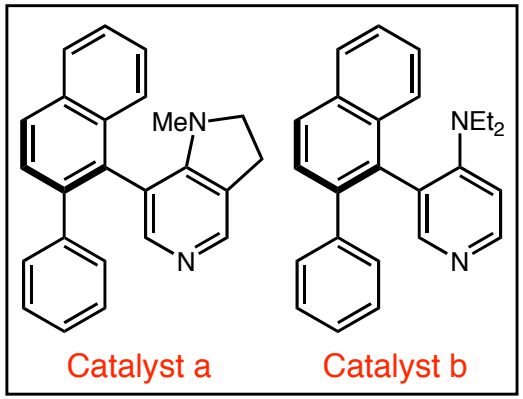




Spivey, A. C et. al.. *J. C. S. Perkin 1* **2000**, *14*, 3460.

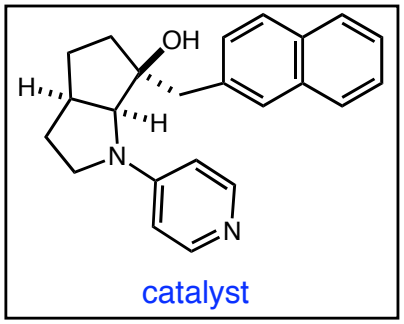
Spivey: axially chiral symmetric DMAP





Spivey, A. C et. al.. *J. Org. Chem.* **2000**, *65*, 3154.
Spivey, A. C et. al.. *J. C. S. Perkin 1* **2001**, *15*, 1785.

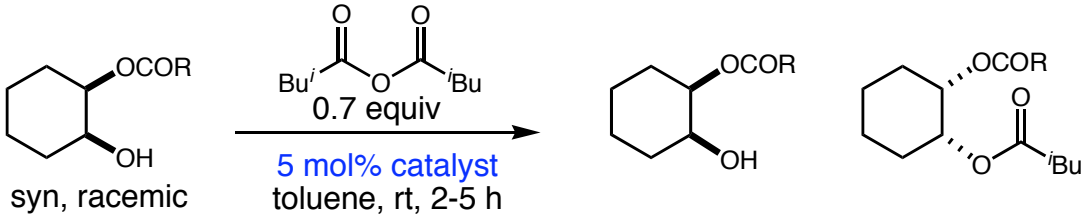
Fuji Chiral DMAP Equivalent: Kinetic Resolution of Alcohols



catalyst

- First non-enzymatic chiral resolution of alcohols

Kinetic Resolution of Alcohols

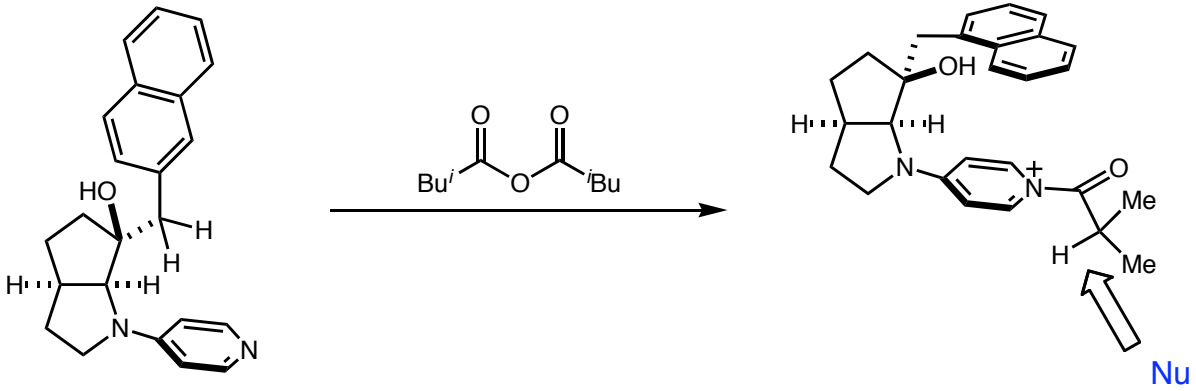


syn, racemic

81->94% ee

68-72% conv.

Induced-fit Mechanism



open conformation

reactive, closed conformation

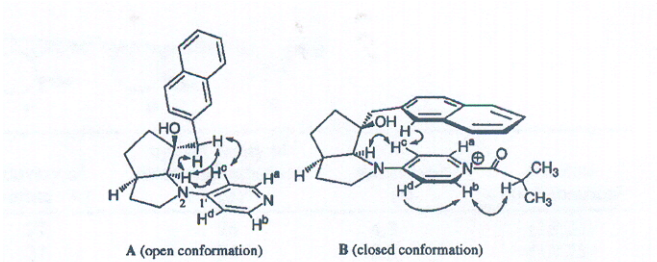


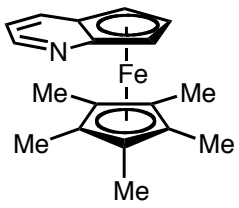
Figure 1. ^{1}H NMR study of **1** (**A**) and its acyliminium ion (**B**) in $CDCl_3$ at 20 °C. Arrows denote the observed NOEs. In **A**, protons H^a, H^b, and H^c, H^d appear at δ 8.01 and 6.37 ppm, respectively. In **B**, protons H^a, H^b, H^c, and H^d appear independently at δ 7.45, 8.73, 5.69, and 6.87 ppm, respectively.

- Take advantage of charged Lewis adduct
- Cation-p interaction holds transition state rigid

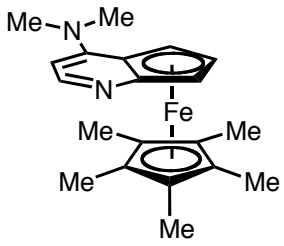
Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170.

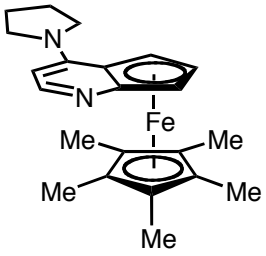
Fu Planar Chirality: Designing an Alternative Chiral DMAP

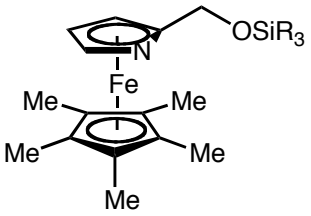
- Fu built a variety of Sandwich complex derived chiral nucleophilic amines



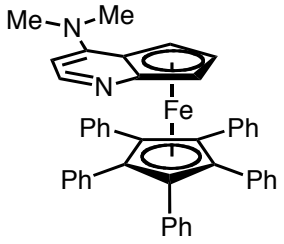
pyridine analogues



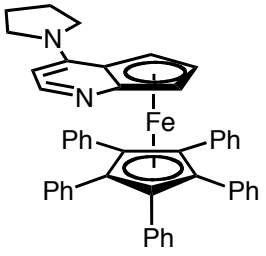




pyrroles analogues



DMAP analogues



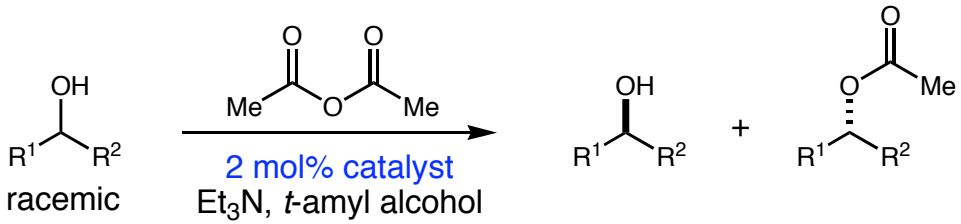
PPY analogues

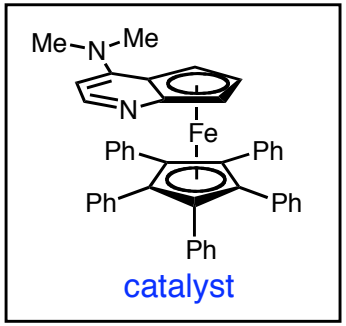
- In general best results were obtained with DMAP and PPY derivatives

France, F.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012.
Fu, Gregory C. *Acc. Chem. Res.* **2004**, *37*, 542-547.

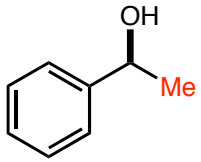
Fu - Planar Chirality: Kinetic Resolution of Alcohols

Kinetic Resolution of Alcohols

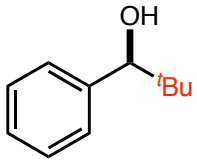




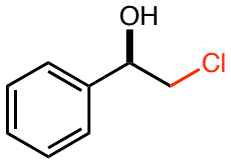
Very high enantioselectivities for Aryl and Cinnamyl alcohols



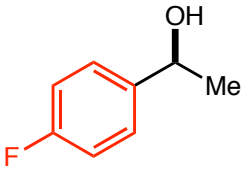
99% ee
55% conv.



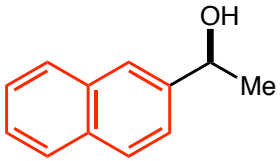
99% ee
55% conv.



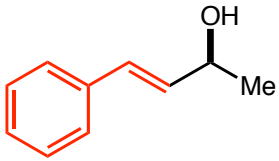
99% ee
55% conv.



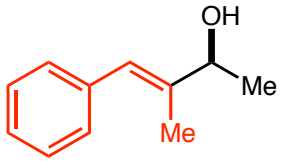
99% ee
55% conv.



99% ee
55% conv.



99% ee
55% conv.

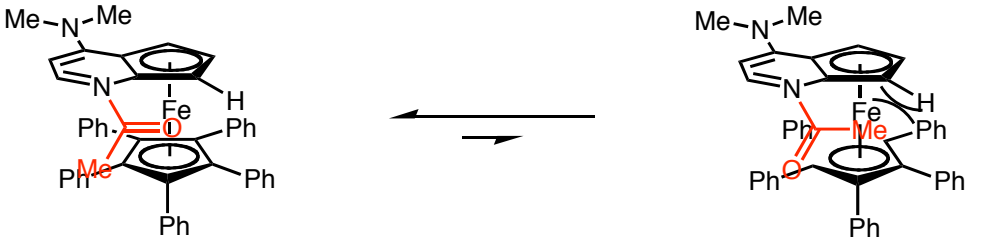


99% ee
55% conv.

Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493.
Ruble, J. C.;Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794-2795.

Fu Chiral DMAP: Origins of Enantioselectivity

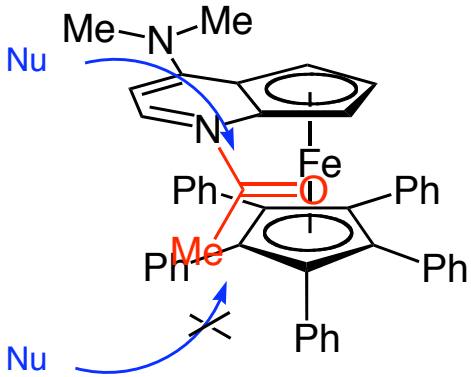
Geometry of acyl rotamers

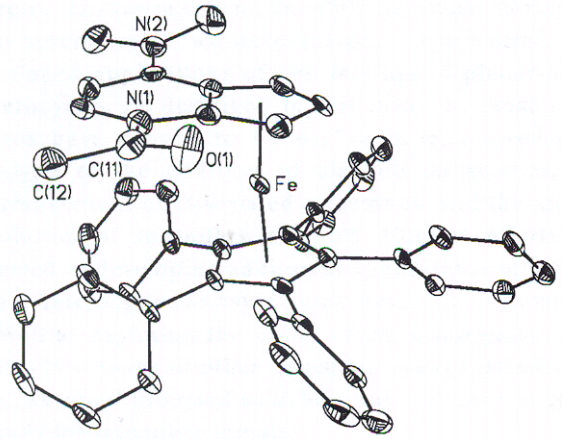


Favoured rotamer

Disfavoured rotamer

Crystal Structure of Acyl salt

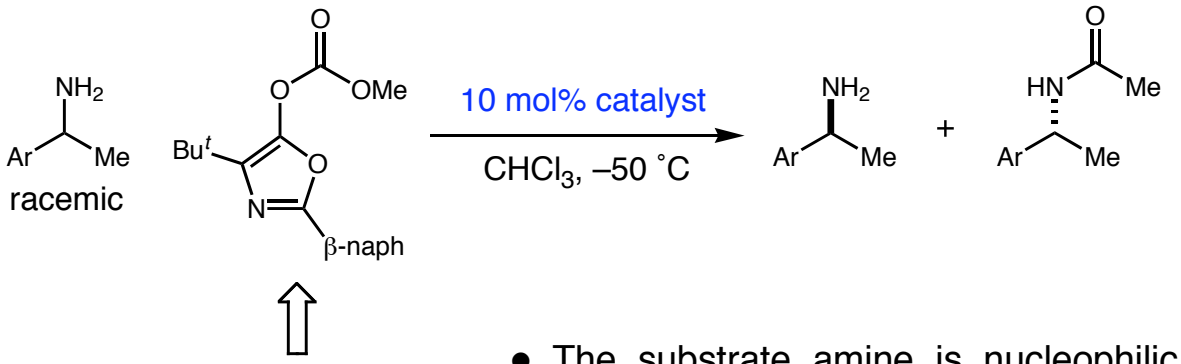




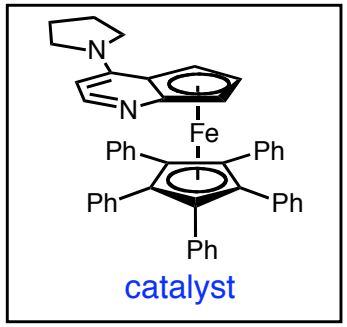
- Acetyl rotamer consistent with minimization of sterics between the methyl R group and ferrocene.
- Selectivity increases as the size of the alkyl group R increases.
- Nucleophile approaches from the top face of the DMAP catalyst.

Kinetic Resolution of Amines

■ First non-enzymatic acylation catalyst for kinetic resolution of amines

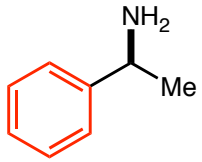


reacts faster with catalyst than substrate amine



- The substrate amine is nucleophilic enough to add directly to most acylating agents – careful selection of acylating reagent proved necessary to render no background reaction

■ Very high enantioselectivities for Aryl and Cinnamyl alcohols



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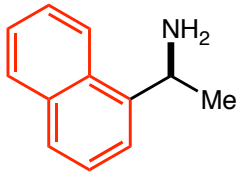

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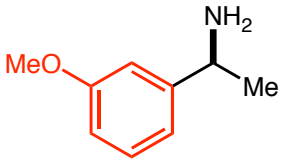

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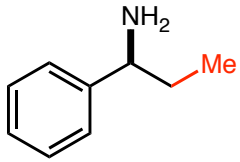
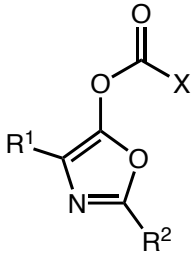


s=16

Arai, S.; Laponnaz-Bellemin, S.; Fu, G. C. *Angew. Chem. Int. Ed.,* **2001**, *40*, 234-236.

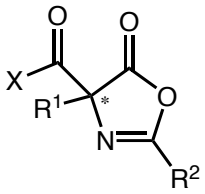
Rearrangement of O-Acylated Azalactones

■ First non-enzymatic acylation catalyst for kinetic resolution of amines



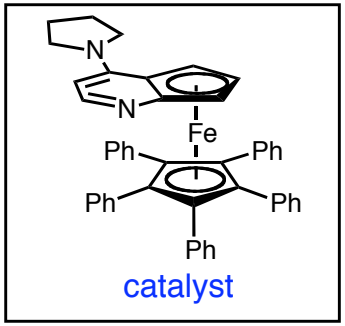
10 mol% catalyst

0 ˚C, t-amyl alcohol
2-6 h

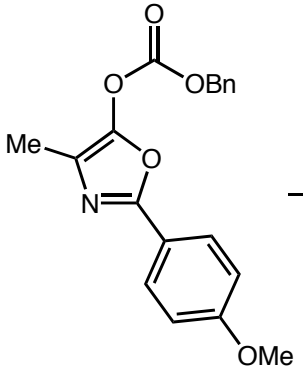


54-90% ee

X = OMe, OBn
R^1 = Me, Et, Bn
R^2 = Me, Ph, PMP

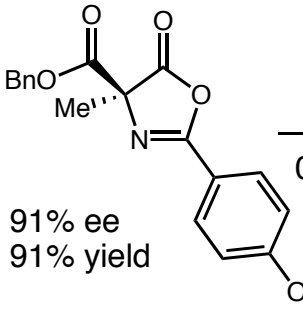


■ Direct synthesis of dipeptides



10 mol% catalyst

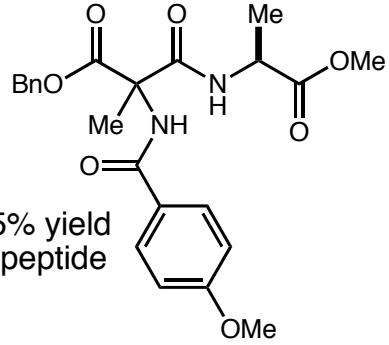
0 ˚C, t-amyl alcohol
2-6 h



91% ee
91% yield

10 mol% catalyst

0 ˚C, t-amyl alcohol
2-6 h

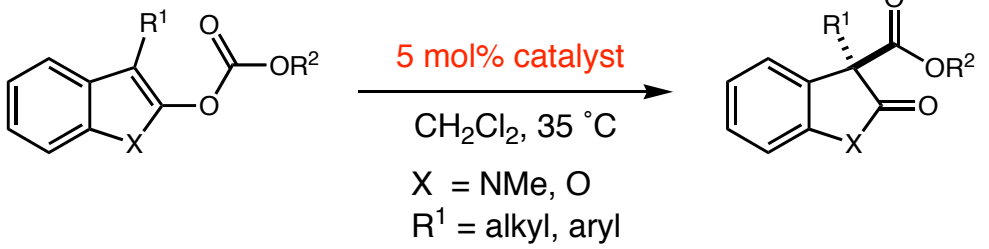


95% yield
dipeptide

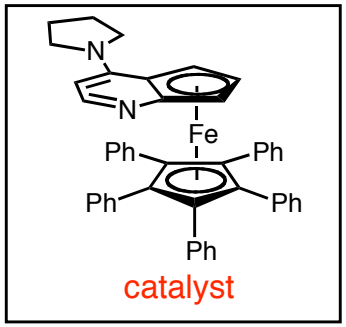
Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.,* **1998**, *120*, 11532-11533.

Chiral Planar DMAP Analogues: Rearrangements

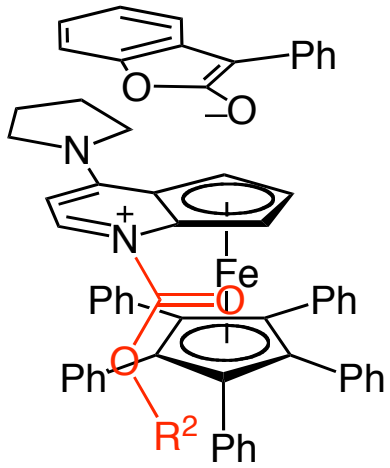
■ Intramolecular rearrangement of *O*-acylated oxindoles and benzofurans



72-95% yield
88-99% ee

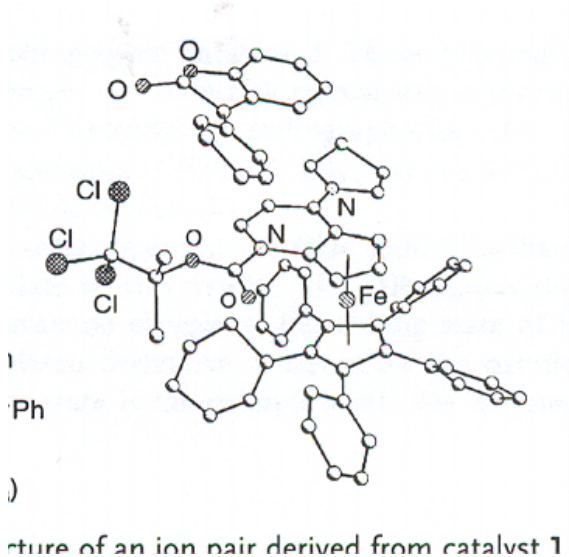


■ A crystal structure was obtained



endo (cation-π)

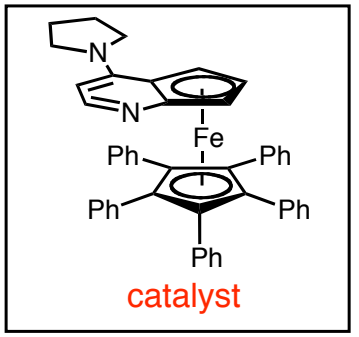
≡



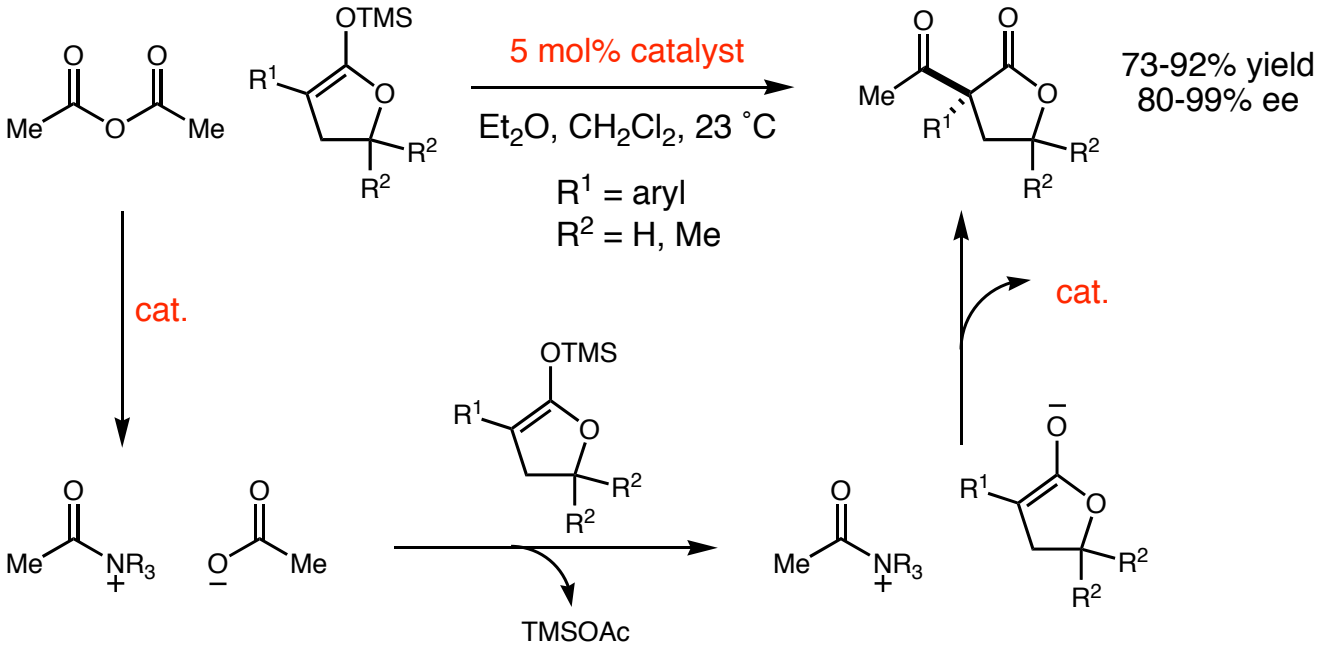
cture of an ion pair derived from catalyst 1

Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.,* **2003**, *42*, 3921-3924.

Chiral Planar DMAP Analogues: Rearrangements



■ Intermolecular C-acylation of silyl ketene acetals

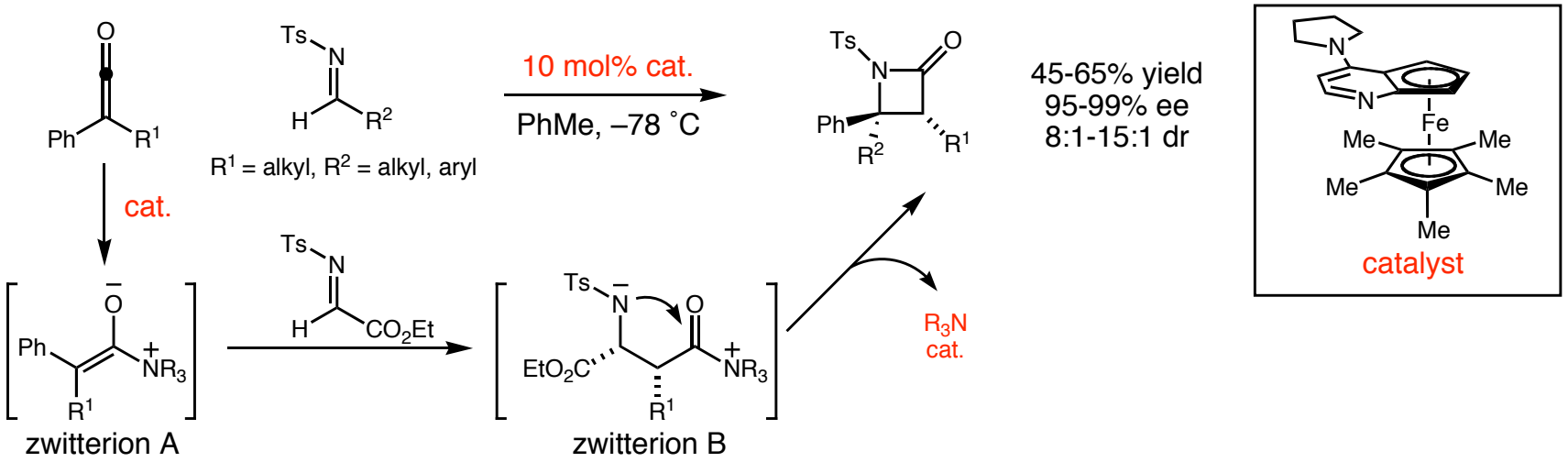


- Currently limited to α-aryl substrates

Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.,* **2003**, *125*, 4050-4051.

Chiral Planar DMAP Analogues: Reactions with Ketenes

■ β-lactam Staudinger synthesis



- Reaction successful for both symmetrical and unsymmetrical ketenes

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579.

Summary and Conclusions

- Chiral amines have become functional nucleophilic catalysts, having been largly overlooked until recently.
- Natural and synthetic alkaloids continue to have success across a variety of reaction types, although definitive stereochemical rationale is not always possible
- Miller's combinatorial approach has successfully obtained catalysts that show high selectivity
- Fu has developed the first truly general synthetic DMAP analogue catalyst system. Led the way in showing that nucleophilic catalysis is a general and useful concept.