Organocatalysis: Almost Everything You Wanted to Know, but Never Asked

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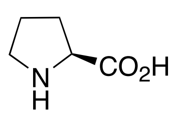
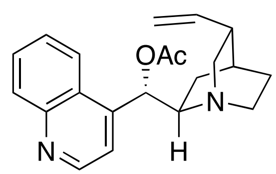
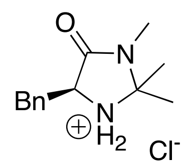
Frontiers in Chemistry
December 17th, 2005

What is an Organocatalyst?

- An organocatalyst is an organic molecule that does not contain a metal which in substoichimetric amounts accelerates a reaction.
- Examples: Proline, Cinchona alkaloids or other secondary amine derivatives







Organocatalysis: Outside "Classic" Chemistry

- Some meteors contain enantiomerically enriched L-alanine and L-isovaline amino acids with ee's up to 15%.
- These amino acids have been shown to catalyze a simple adol reaction to give tetroses.

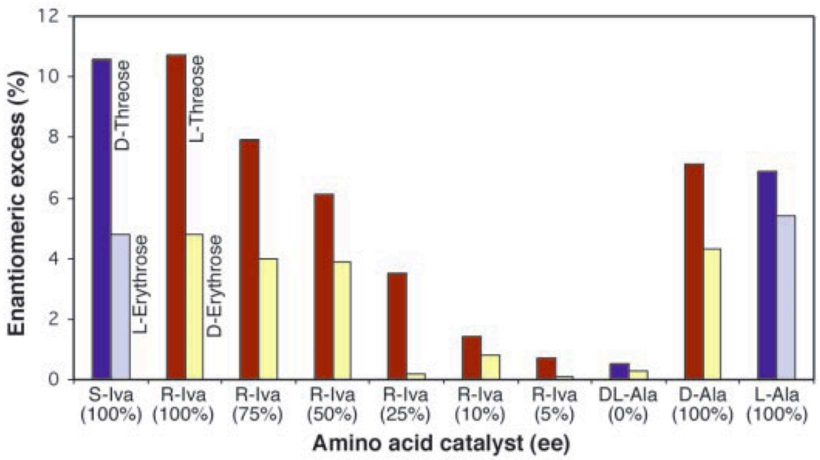
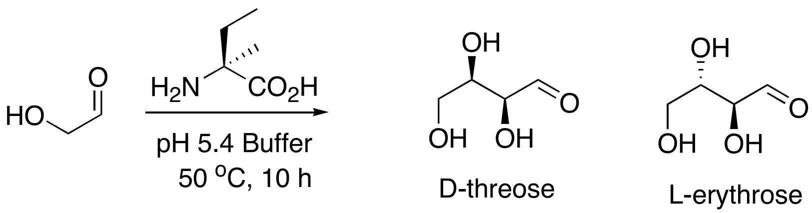


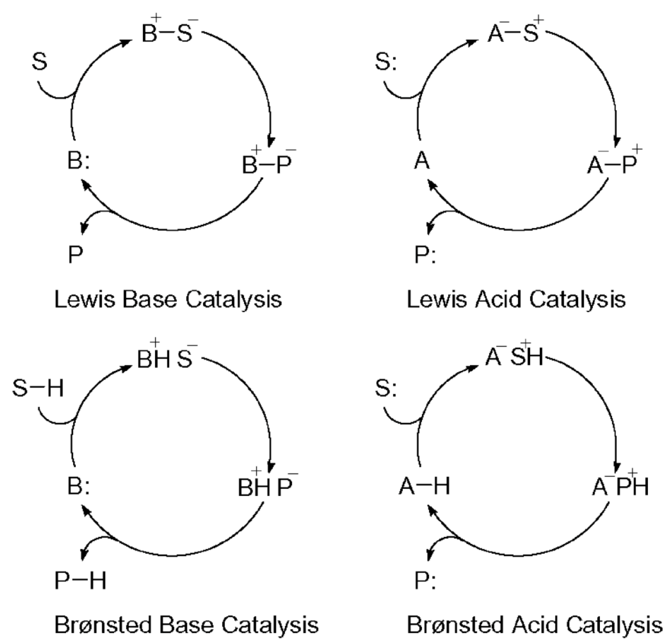
Fig. 1. Effect of amino acid catalyst ee on the asymmetric synthesis of threose and erythrose from glycolaldehyde. S-ivaline is equivalent to L-2-amino 2-methyl butyric acid.



S. Pizzarello, A. Weber, *Science* Vol 303, 1151

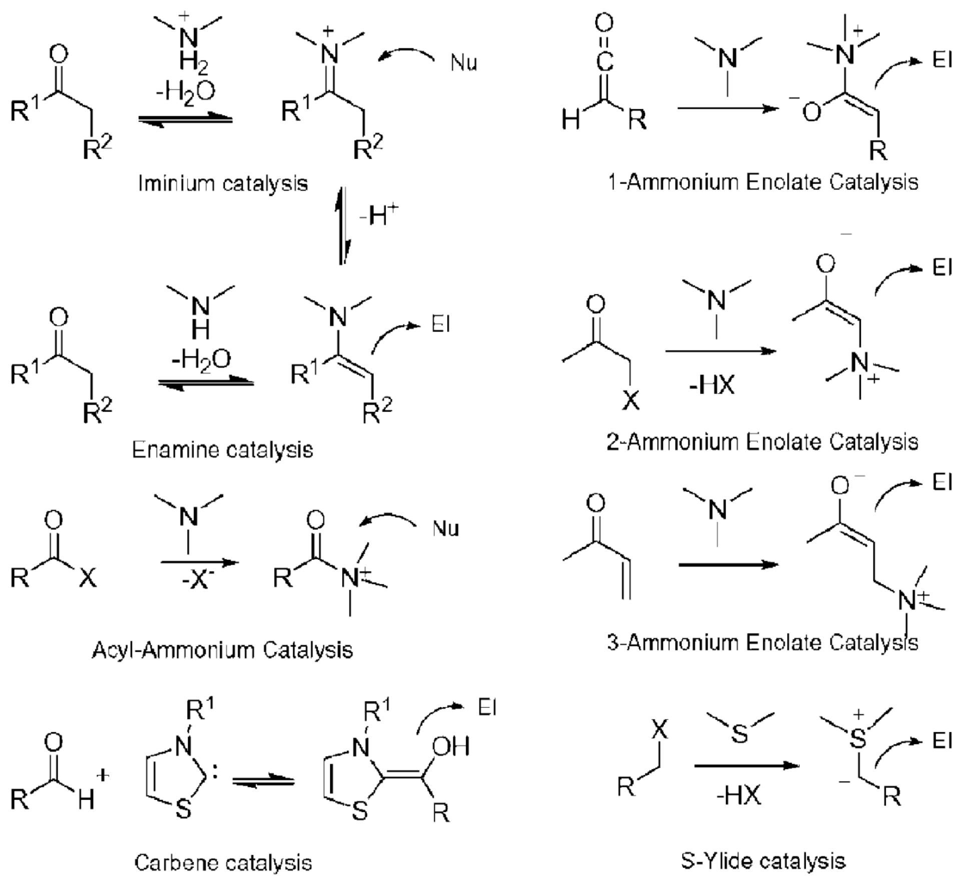
Classification of Organocatalysts

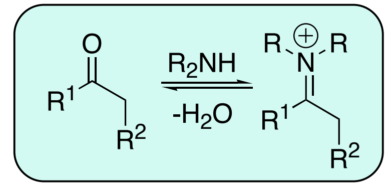
- List recently introduced a system of classification based on the mechanism of catalysis.
- The four categories are Lewis Base, Lewis Acid, Bronsted Base and Bronsted Acid catalysis.



B. List, *Org. Biomol. Chem.*, **2005**, 719

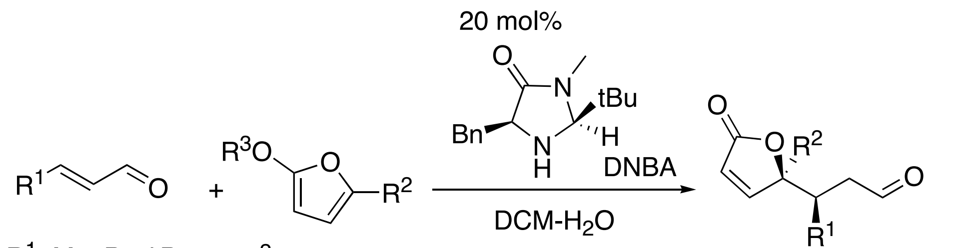
Types of Lewis Basic Organocatalysis





Lewis Basic Organocatalysis: Iminium Ion: 1,4 Additions

Mukaiyama-Micheal



R^1=Me, Pr, *i*-Pr, Ph, CH_2OBz, CO_2Me

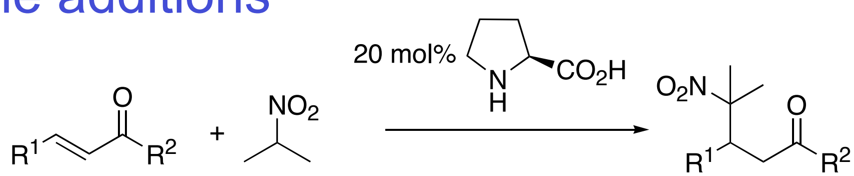
R^2=H, Me, Et, CO_2Me

R^3=TMS, TIPS

6:1 to 31:1 syn:anti
73-87% yield
84-99% ee

D. MacMillan, *J. Am. Chem. Soc.* **2003**,1192

Nitroalkane additions



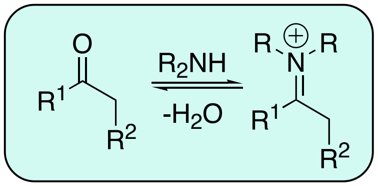
R^1=Ph, *p*-ClPh, *p*-NO_2Ph, *p*-HOPh, 2-thienyl, 2-furyl, 2-pyridyl, *n*-Bu, *i*-Pr, CO_2Me

R^2=Me, Et, *i*-Pr

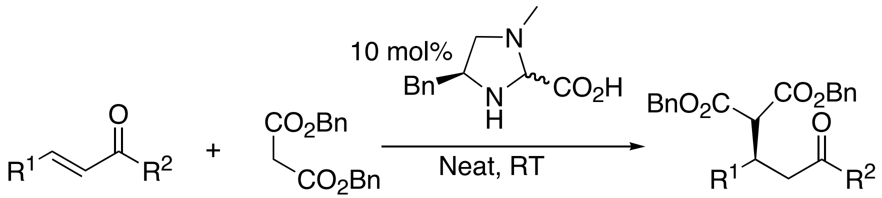
5-100% yield
34-86% ee

K. A. Jorgensen, *J. Am. Chem. Soc.* **2002,** 8831
Also see:
K. A. Jorgensen, *Org. Lett.* **2005**, 3897

Lewis Basic Organocatalysis: Iminium Ion: 1,4 Additions



Malonate Additions



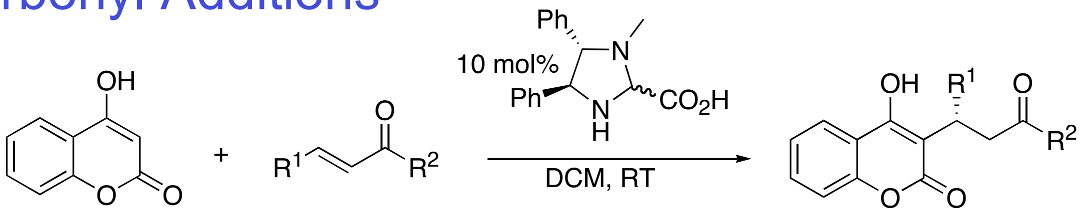
R^1=Ph, *p*-ClPh, *p*-NO_2Ph, *o*-NO_2Ph, *p*-HOPh, Me_2NPh, 2-thienyl, 2-furyl, 2-pyridyl, *n*-Bu, *i*-Pr, CO_2Me, 2-Np

R^2=Me, Et, *i*-Pr

2-99% yield
59-99% ee

K.A. Jorgensen, *Angew. Chem. Int. Ed.* **2003,** 661

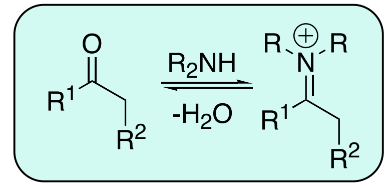
Dicarbonyl Additions



R^1=Ph, *p*-ClPh, *p*-NO_2Ph, *p*-MeOPh, 2-thienyl, 2-furyl, *n*-Bu, *i*-Pr, 2-Np
R^2=Me, Et, *i*-Pr

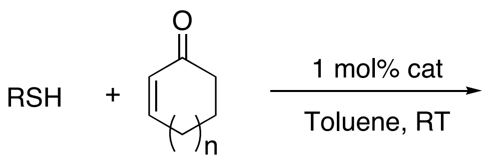
68-99% yield
75-88% ee

K.A. Jorgensen, *Angew. Chem. Int. Ed.* **2003,** 4955



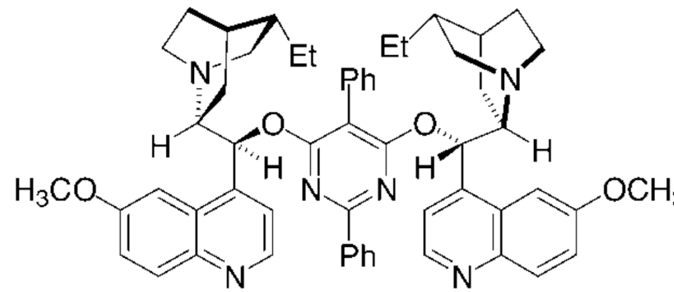
Lewis Basic Organocatalysis: Iminium Ion: 1,4 Additions

Thiol Additions



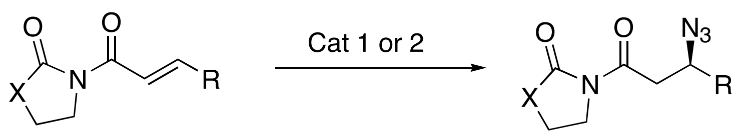
R=Ph, Bn, *p*-tBuPh,
o-MeOPh, *m*-MeOPh
p-MeOPh, *p*-EtOPh,
2-Np
n=0-4

55-91% yield
21-99% ee



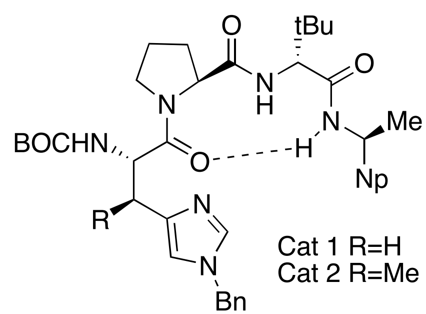
L. Deng, *Angew. Chem. Int. Ed.* **2002,** 338

Azide Additions



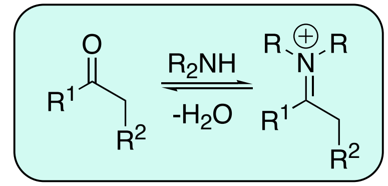
R=Me, Cy, Et,
N-Boc piperidine
X= CH_2 or O

44-97% yield
45-90% ee



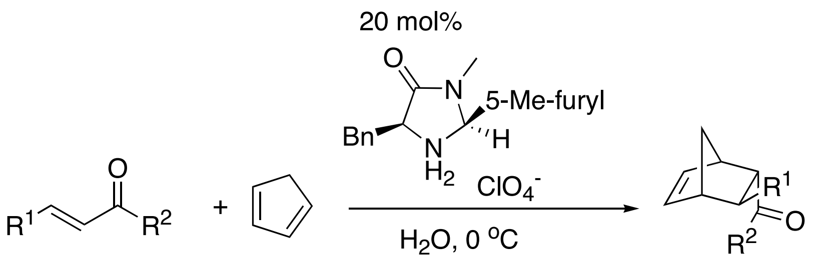
Cat 1 R=H
Cat 2 R=Me

S. Miller, *J. Am. Chem. Soc.* **2002**, 2134



Lewis Basic Organocatalysis: Iminium Ion: Cycloadditions

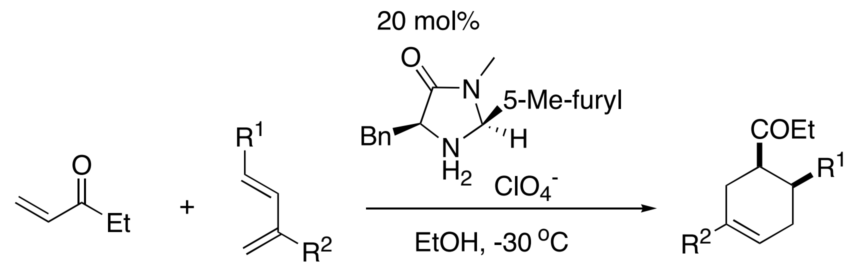
Diels-Alder Reactions



R^1=Me, *n*-Pr, *i*-Pr
R^2=Me, Et, *n*-Bu, *i*-Am

6:1 to 25:1 endo:exo
78-89% yield
61-92% ee

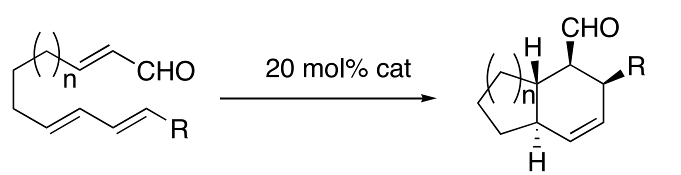
D. MacMillan, *J. Am. Chem. Soc.* **2000,** 4243



R^1=OMe, NHCbz, Me
R^2=H, Ph, Me

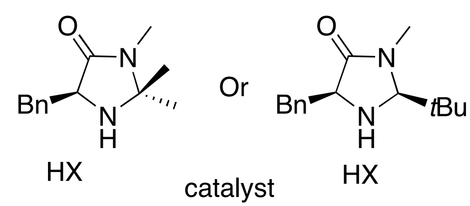
100:1 to 200:1 endo:exo
79-92% yield
85-98% ee

D. MacMillan, *J. Am. Chem. Soc.* **2002**, 2458
Also see:
K. Ishihara, *J. Am. Chem. Soc.* **2005,** 10504



R= Ph, HC=C(Me)H, Vinyl
n=0 or 1

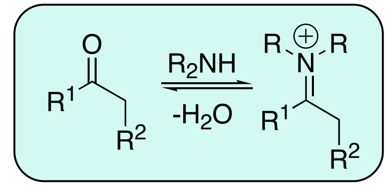
1:20 to 20:1 endo/exo
10-85% yield
77-94% ee



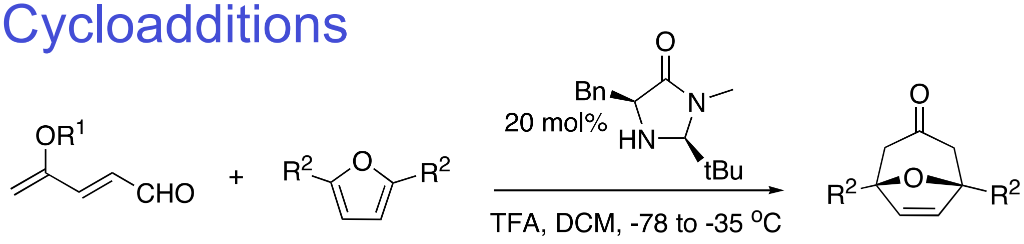
X= -OTf, -Cl, $-ClO_4$

D. MacMillan, *J. Am. Chem. Soc.* **2005**, 11616

Lewis Basic Organocatalysis: Iminium Ion: Cycloadditions



[4+3] Cycloadditions



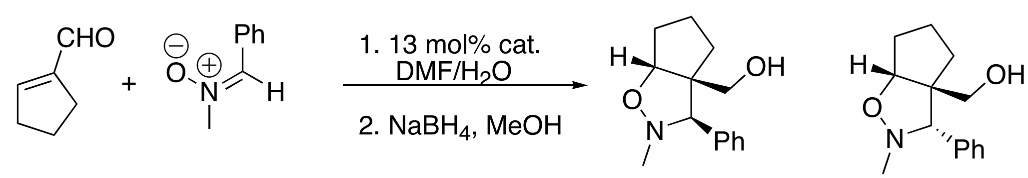
R^1= TMS, TES, TBS, TIPS

R^2=Me, Et,Pr, Ph

100% endo
18-74% yield
80-90% ee

M Harmata, *J. Am. Chem. Soc.* **2003**, 2058

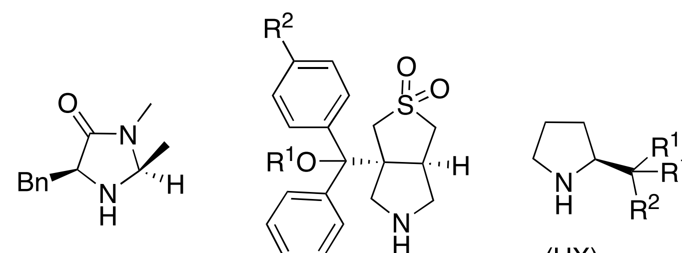
[3+2] Cycloadditons



Major

Minor

3:1 to 97:3 D.r.
7-70% yield
23-93% ee



HX

HX

$(HX)_2$

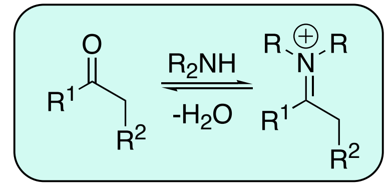
X= -Cl, $-ClO_4$, -OTf

R^1=H or Me
R^2=H or OMe

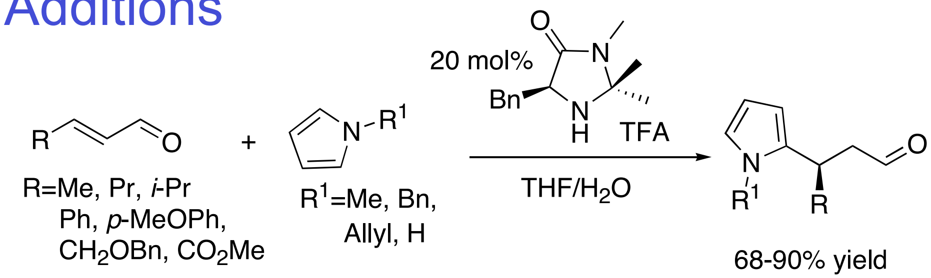
R^1=Me, H or Ph
R^2=OH, OMe, piperidine or pyrrolidine

S. Karlsson, *Tet. Asym.* **2002**, 923

Lewis Basic Organocatalysis: Iminium Ion: Friedel-Crafts Alkylation



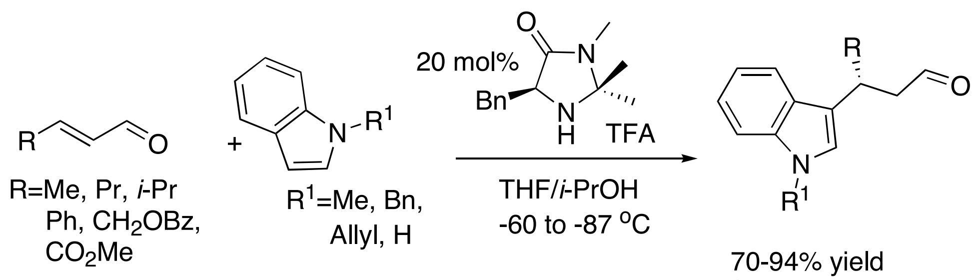
Pyrrole Additions



68-90% yield
87-97% ee

D. MacMillan, *J. Am. Chem. Soc.* **2001**, 4370

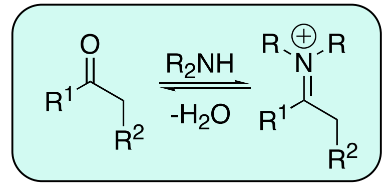
Indol Additions



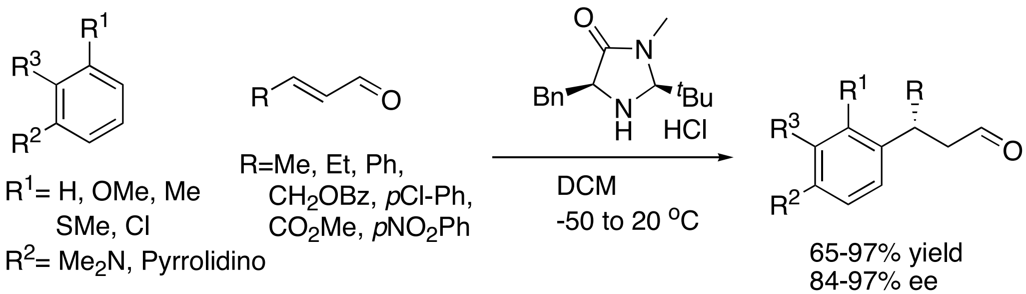
70-94% yield
89-97% ee

D. MacMillan, *J. Am. Chem. Soc.* **2002**,1172

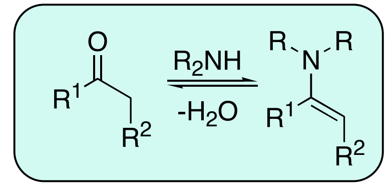
Lewis Basic Organocatalysis: Iminium Ion: Friedel-Crafts Alkylation



Aniline Additions

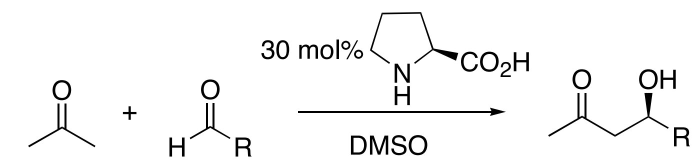


D. MacMillan, *J. Am. Chem. Soc.* **2002**, 7894



Lewis Basic Organocatalysis: Enamine: Aldol Reaction

Ketone-Aldehyde Aldol

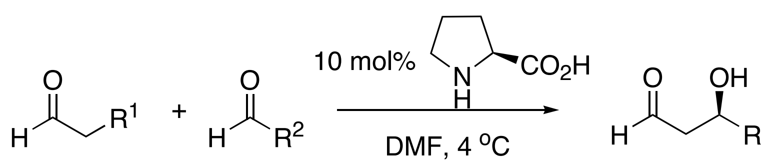


R=Ph, *p*-NO_2Ph, *p*-BrPh, *o*-ClPh, 2-Nap, *i*-Pr

54-97% yield
60-96% ee

B. List, *J. Am. Chem. Soc.* **2002**, 2395
Also see:
L. Gong, *J. Am. Chem. Soc.* **2005,** 9285
C. Barbas III, *Org. Lett.* **2005,** 1383

Aldehyde Cross-Aldol

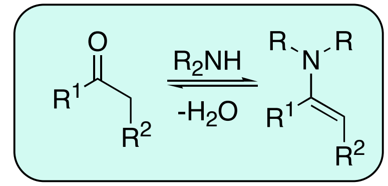


R^1= Me, *n*-Bu, Bn
R^2= Et, *i*-Bu, Cy, Ph, *i*-Pr

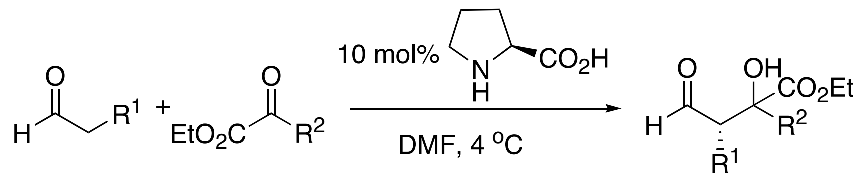
3:1 to 24:1 *anti:syn*
75-88% yield
91 to 99% ee

D. MacMillan, *J. Am. Chem. Soc.* **2002**, 6798

Lewis Basic Organocatalysis: Enamine: Aldol Reaction



Aldehyde-Ketomalonate Aldol



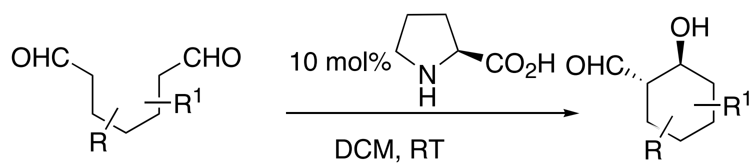
R^1=Me, Et, *i*-Pr, Allyl, hexyl, Ph, H

R^2= CO_2Et, CF_3

81-97% yield
67-90% ee
2 examples
had no induction

K.A. Jorgensen, *Chem. Comm.* **2002,** 6205

Enolexo Aldolization

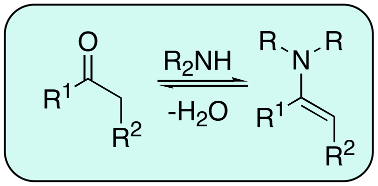


R and R^1= H or Me

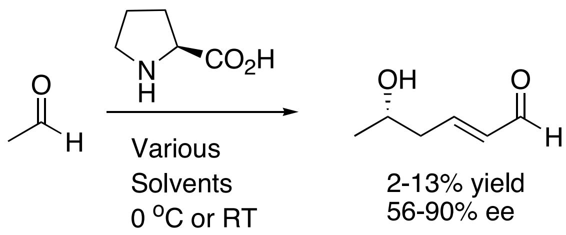
4:1 to 20:1 d.r.
74-95% yield
75-99% ee

B. List, *Angew. Chem. Int. Ed.* **2003,** 2785

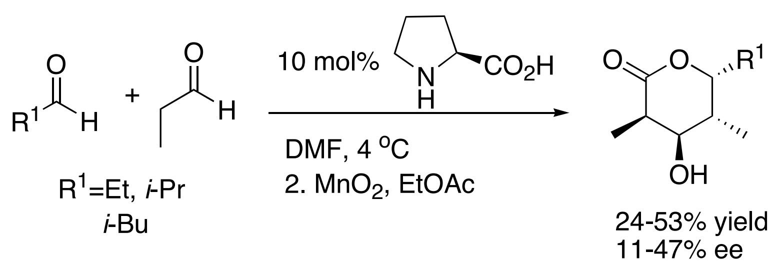
Lewis Basic Organocatalysis: Enamine: Aldol Reaction



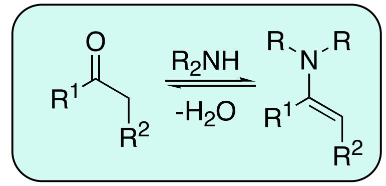
Self-Condensation Reactions



C. Barbas III, *J. Org. Chem.* **2002,** 301

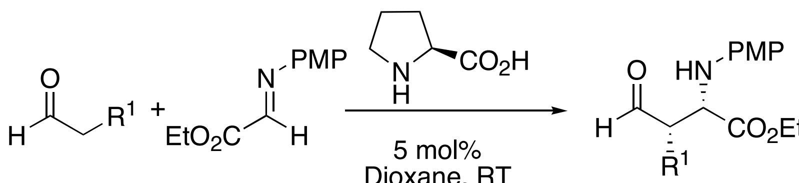


C. Barbas III, *Tet. Lett.* **2002,** 9591



Lewis Basic Organocatalysis: Enamine: Mannich Reaction

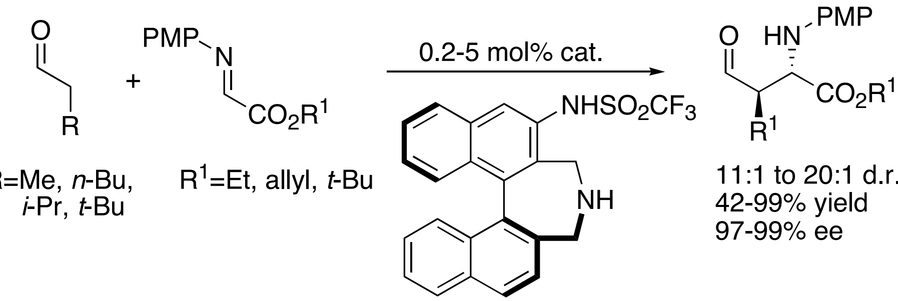
Aldehyde-Imine Mannich Reactions



R^1=Me, Et, *i*-Pr
n-Bu, *n*-Pent,
TBS-propanol,
2-octene, 3 butene

45-89% yield
1.1 to 19:1 d.r.
91-99% ee

C. Barbas III, *J. Org. Chem.* **2003,** 9624

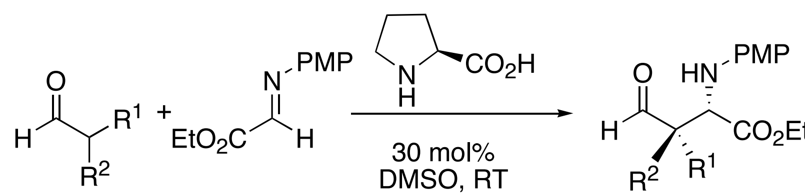


R=Me, *n*-Bu,
i-Pr, *t*-Bu

R^1=Et, allyl, *t*-Bu

11:1 to 20:1 d.r.
42-99% yield
97-99% ee

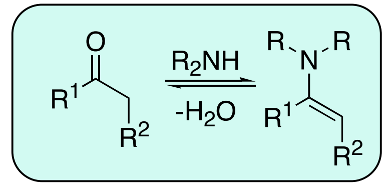
K. Maruoka, *J. Am. Chem. Soc.* **2005,** 16408



R^1=Ph, Thienyl, *p*-tol,
p-*i*-PrPh, *p*-*t*-BuPh,
R^2=Me
R^1=R^2= $(CH_2)_2$

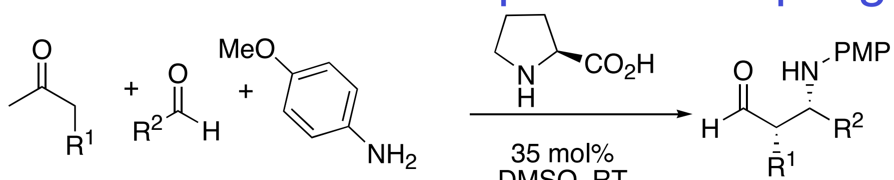
60:40 to 96:4 syn:anti
66-99% yield
55-99% ee

C. Barbas III, *Org. Lett.* **2004,** 2507



Lewis Basic Organocatalysis: Enamine: Mannich Reaction

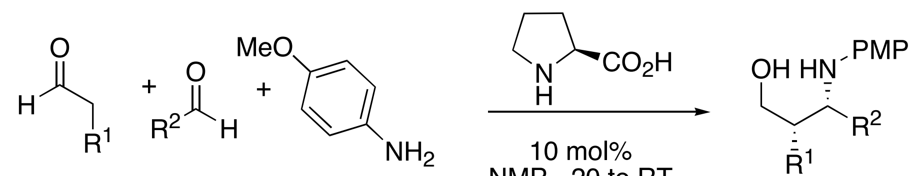
Three Component Coupling Mannich Reactions



R^1=H, Me, OMe, OH
R^2=*p*-NO_2Ph, *n*-Pentyl, *i*-Bu, Bn-ethanol, 3-butene, phenethyl,2-nap, *i*-Pr, *p*-CNPh, *p*-BrPh, *p*-Biphenyl, *p*-tol

3:1 to 20:1 d.r.
35-92% yield
61-99% ee

B. List, *J. Am. Chem. Soc.* **2002,** 827

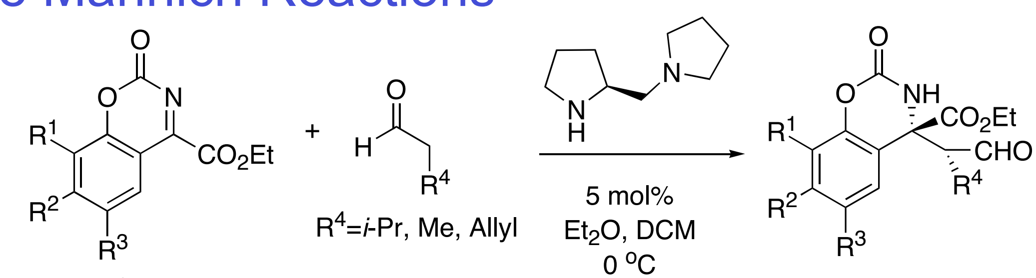


R^1=Me, Et, *n*-Pr
R^2=*p*-NO_2Ph,2-nap, Ph, *p*-ClPh *p*-BrPh, *p*-tol, furyl, pyridine

95:5 syn:anti
10-95% yield
71-99% ee

Y. Hayashi, *Angew. Chem. Int. Ed.* **2003,** 3677

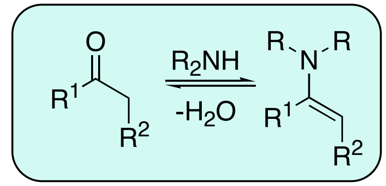
Ketimine Mannich Reactions



R^1=R^2=C_4H_4
R^1=H
R^2=OMe or H
R^3=H, Me, OMe, F

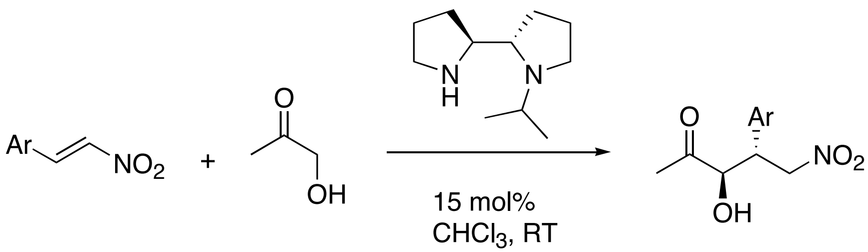
4:1 to 20:1 d.r.
72-99% yield
83-98% ee

K. A. Jorgensen, *Angew. Chem. Int. Ed.* **2004,** 4476



Lewis Basic Organocatalysis: Enamine: Micheal Addition

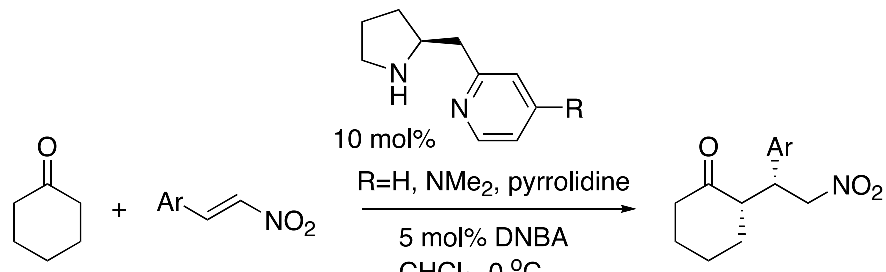
Additions to Nitroalkenes



Ar=Ph, 4-MePh, 4-MeOPh
4-Cl-Ph, 2-CF_3-Ph
2,6-Cl_2Ph, 3,4-Cl_2Ph,
2,4-Cl_2Ph, 1-nap,
thienyl

65-85% yield
96-98% ee

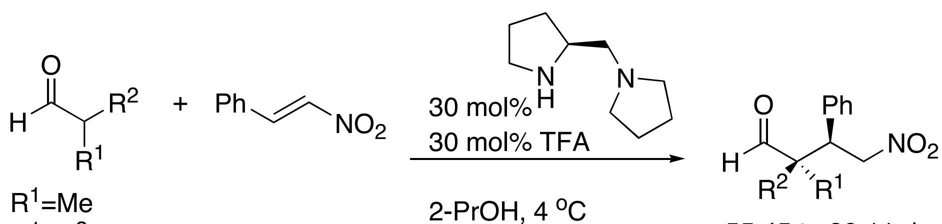
A. Alexakis, *Org. Lett.* **2003,** 2559



Ar= 4-MeOPh, 2-MeOPh
1-nap, 2 nap, thienyl

93:7 to 99:1 d.r.
92-100% yield
88-98% ee

H. Kotsuki, *J. Am. Chem. Soc.* **2004**, 9558

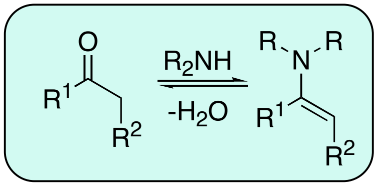


R^1=Me
R^1=R^2= $(CH_2)_4$ or $(CH_2)_5$
R^2=Me, Et, Pr, nonyl, Ph,
4-*i*-PrPh, 4-*t*-BuPh

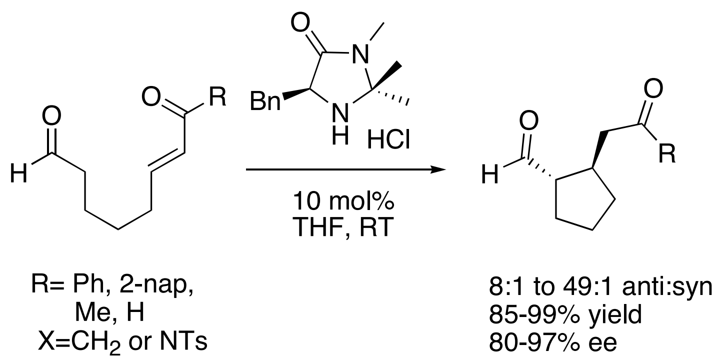
55:45 to 89:11 d.r.
64-95% yield
18-91% ee

C. Barbas III, *Org. Lett.* **2004,** 2527

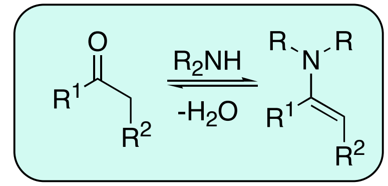
Lewis Basic Organocatalysis: Enamine: Micheal Addition



Additions to Enones

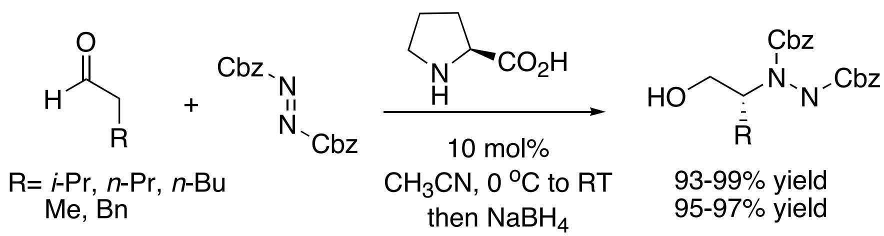


B. List, *Angew. Chem. Int. Ed.* **2004,** 3958



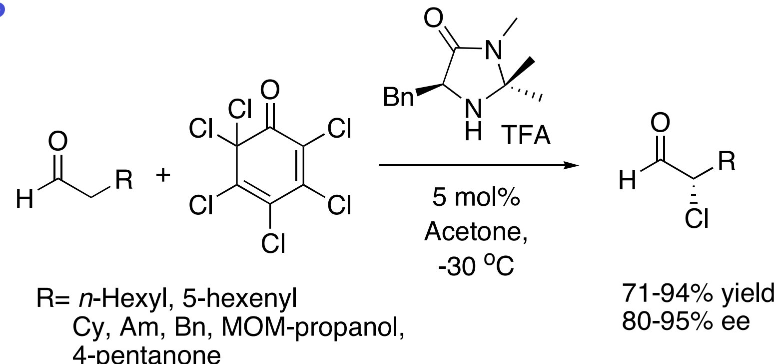
Lewis Basic Organocatalysis: Enamine: Oxidations

α-Aminations



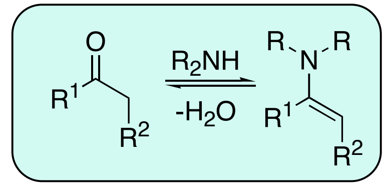
B. List, *J. Am. Chem. Soc.* **2002,** 5656

α-Chlorinations

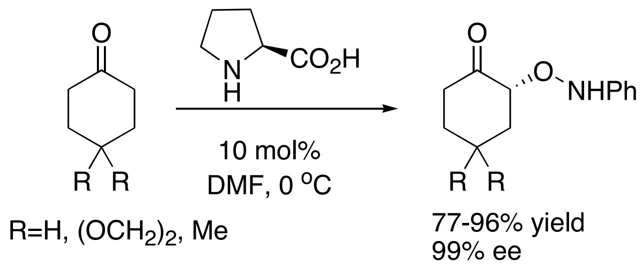


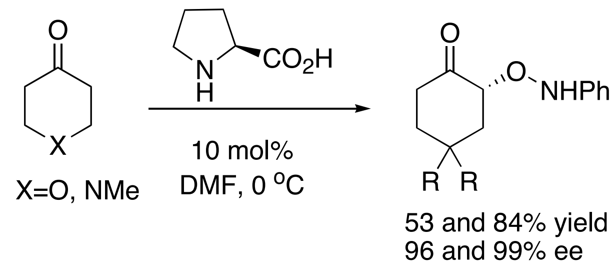
D. MacMillan, *J. Am. Chem. Soc.* **2004,** 4108
Also see: K. A. Jorgensen, *J. Am. Chem. Soc.* **2004,** 4790
For α-Fluorination see: D. MacMillian, *J. Am. Chem. Soc.* **2005,** 8826

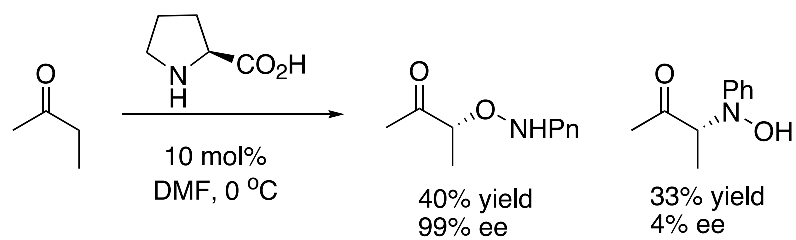
Lewis Basic Organocatalysis: Enamine: Oxidations



α-Aminoxylations

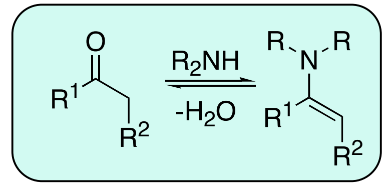




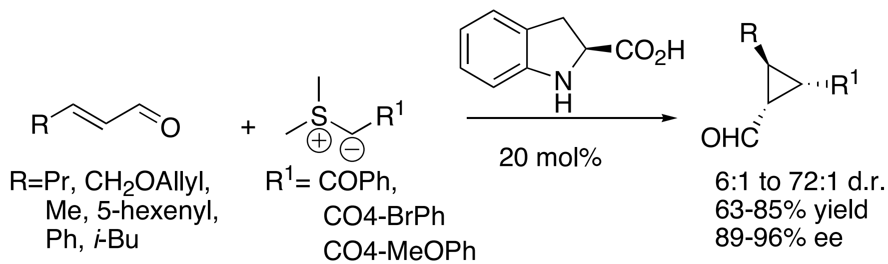


Y. Hayashi, *Angew. Chem. Int. Ed* **2004,** 1112
Also see:
G. Zhong, *Angew. Chem. Int. Ed.* **2003,** 4247
A. Cordova, *Angew. Chem. Int. Ed.* **2004,** 1109
D. MacMillan, *J. Am. Chem. Soc.* **2003,** 10808

Lewis Basic Organocatalysis: Iminium/Enamine Tandem Reactions

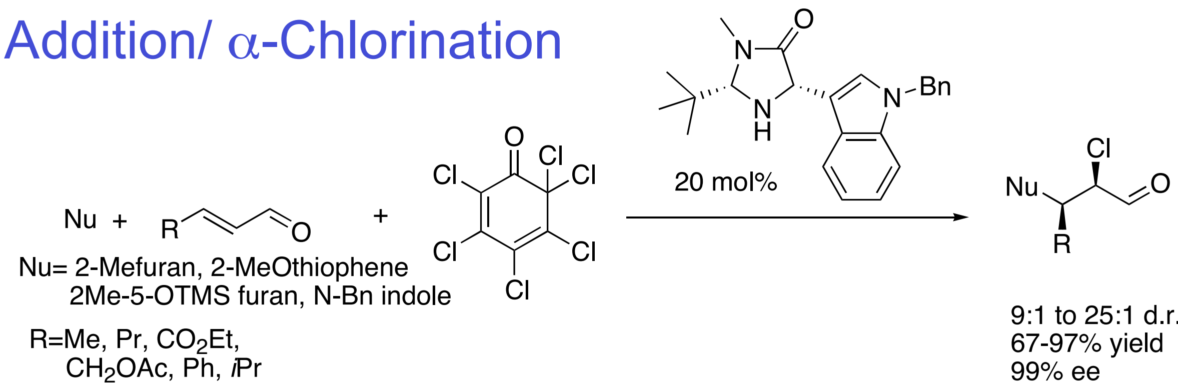


Cyclopropanation



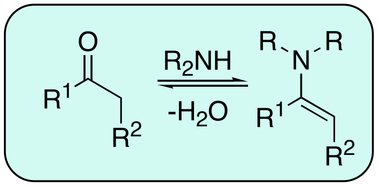
D. MacMillan, *J. Am. Chem. Soc.* **2005,** 3240

1,4 Addition/ α-Chlorination

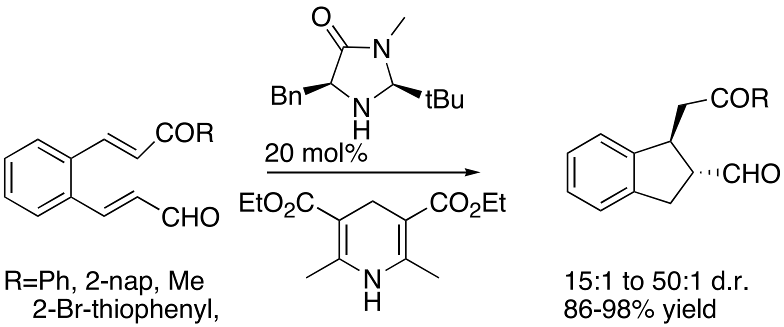


D. MacMillan, *J. Am. Chem. Soc.* **2005,** 15051

Lewis Basic Organocatalysis: Iminium/Enamine Tandem Reactions



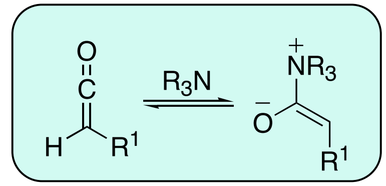
1,4 Reduction/Micheal Addition



R=Ph, 2-nap, Me
2-Br-thiophenyl,

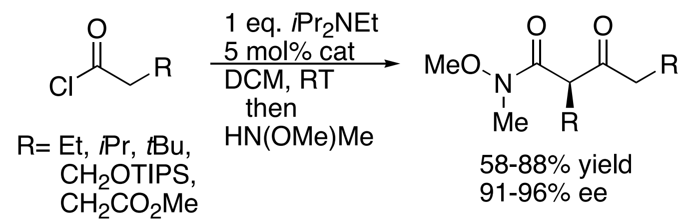
15:1 to 50:1 d.r.
86-98% yield
86-96% ee

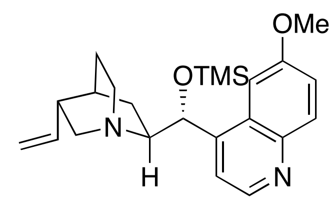
B. List, *J. Am. Chem. Soc.* **2005,** 15036



Lewis Basic Organocatalysis: 1-Ammonium Enolate

Ketene Dimerization

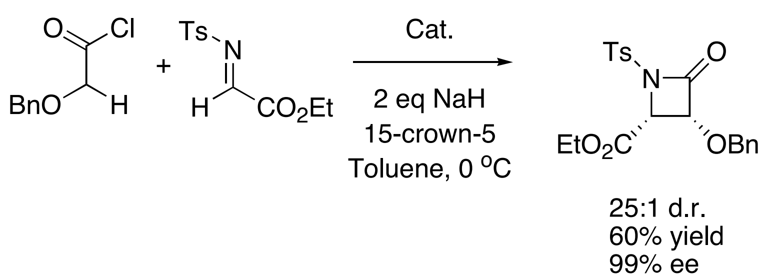


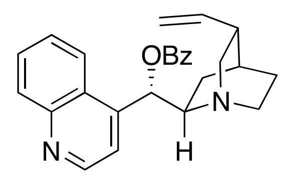


Catalyst

M. Calter, *Org. Lett.* **2003,** 4745

β-Lactam Synthesis

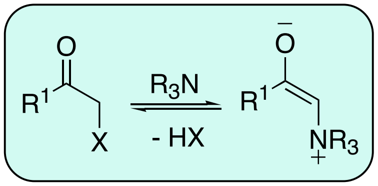




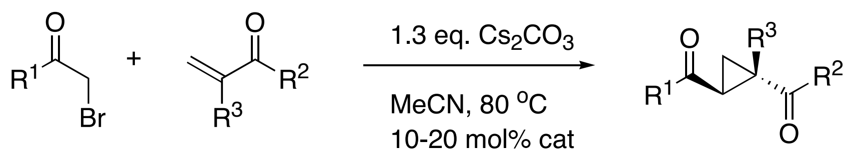
Catalyst

T. Lectka, *Acc. Chem. Res.* **2004,** 592

Lewis Basic Organocatalysis: 2-Ammonium Enolate



Cyclopropanations

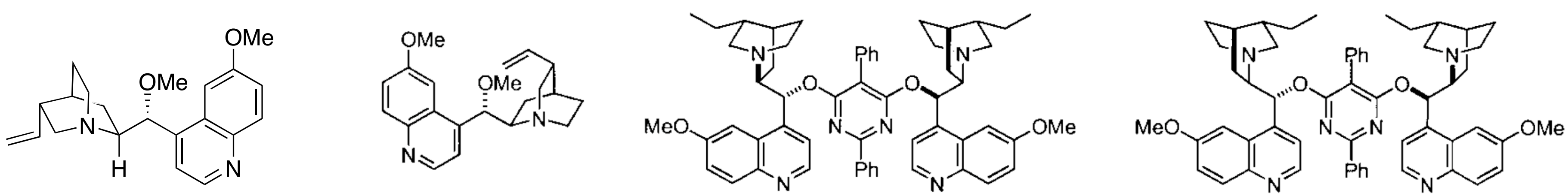


R^1= O*t*Bu, NEt_2, NMe(OMe)

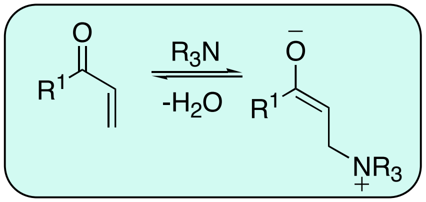
R^2= Ph, 4-Et_2NPh, 4-BrPh, 3-BrPh, OBn, OMe, *n*-pentyl, 3-indole

R^3= H, Me, Boc_2N

53-96% yield
80-97% ee

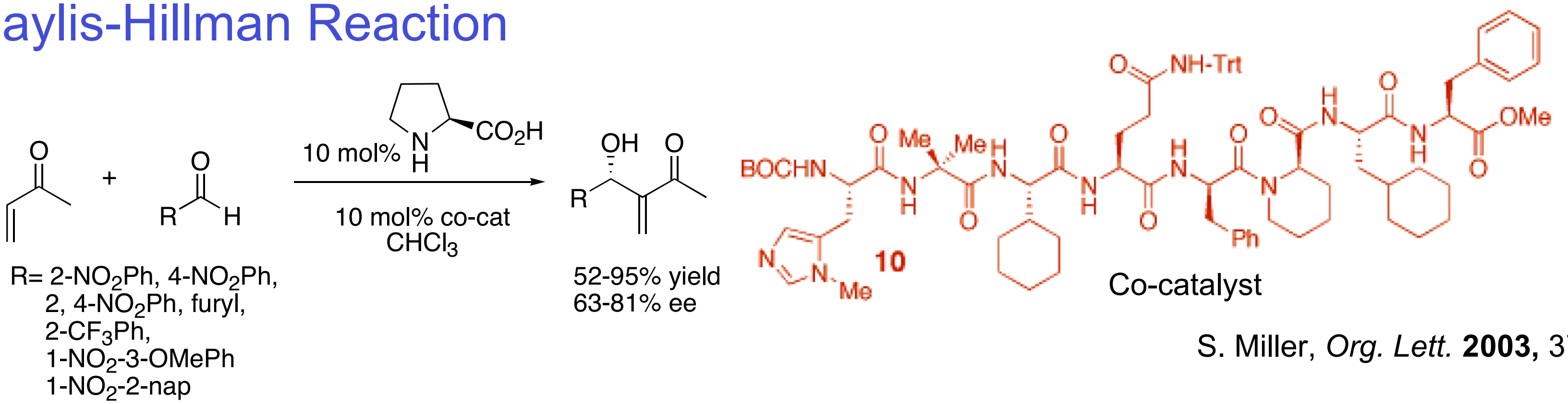


M. Gaunt, *Angew. Chem. Int. Ed.* **2003,** 4641

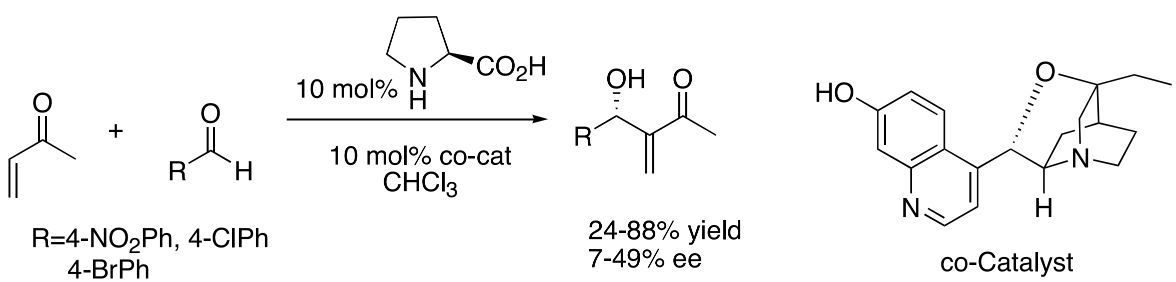


Lewis Basic Organocatalysis: 3-Ammonium Enolate

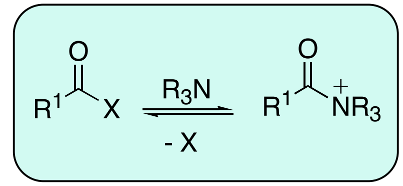
Baylis-Hillman Reaction



S. Miller, *Org. Lett.* **2003,** 3741

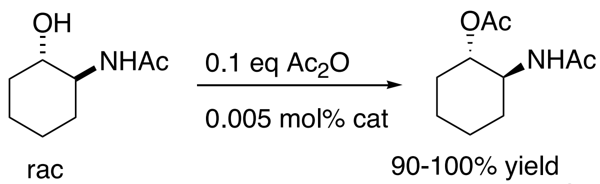


M. Shi, *Tet. Asym.* **2002,** 1941

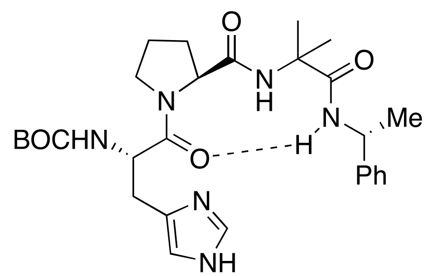


Lewis Basic Organocatalysis: Acyl-Ammonium Ion

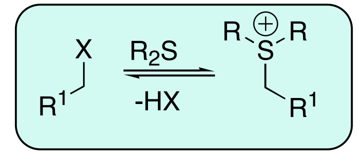
Kinetic Resolution



90-100% yield
(based on Ac_2O)
0-84% ee
depending
on solvent

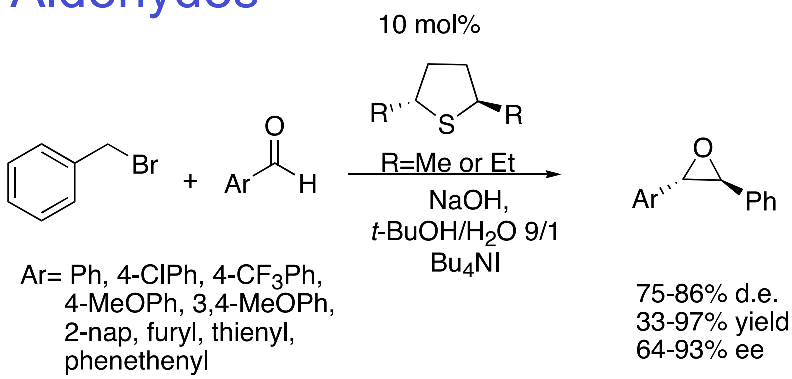


S. Miller, *J. Am. Chem. Soc.* **1998,** 1629
Also see
S. Miller, *Acc. Chem. Res.* **2004,** 601

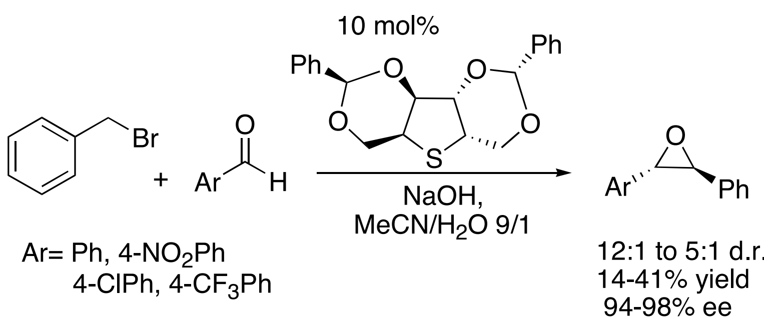


Lewis Basic Organocatalysis: Sulfur Ylide

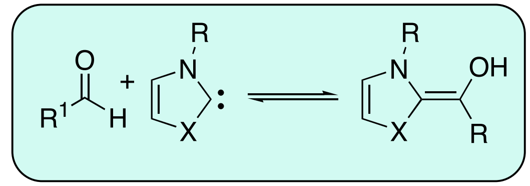
Epoxidation of Aldehydes



P. Metzner, *J. Org. Chem.* **2001,** 5620

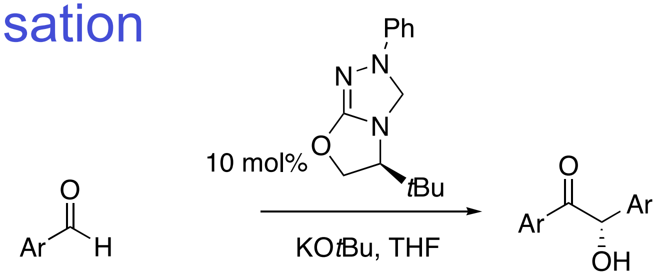


J. Goodman, *Tet. Lett.* **2002,** 5427



Lewis Basic Organocatalysis: Carbene Catalysis

Benzoin Condensation

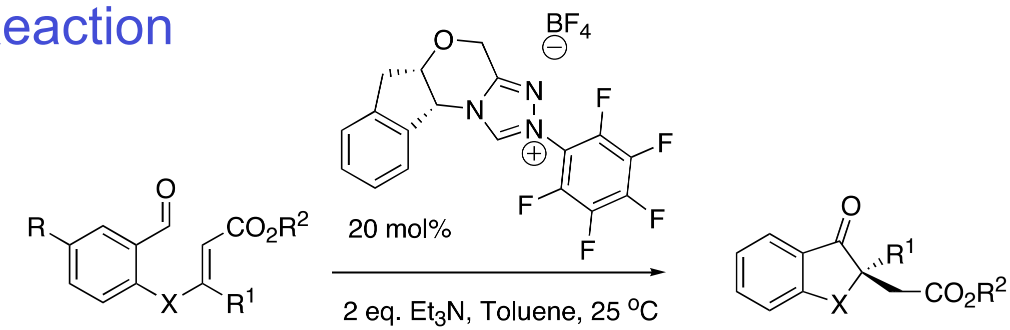


Ar= Ph, 4-FPh, 4-ClPh, 4-BrPh,
3-Cl, 4-Me-Ph, 3-MePh,
4-MeOPh, 2-furyl, 2-nap

8-100% yield
62-91% ee

D. Enders, *Angew. Chem. Int. Ed.* **2002,** 1743

Stetter Reaction

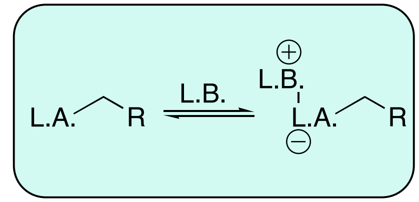


R=H or Br
X=O, S, CH_2
R^1=Et, Me
R^2=Me, Et

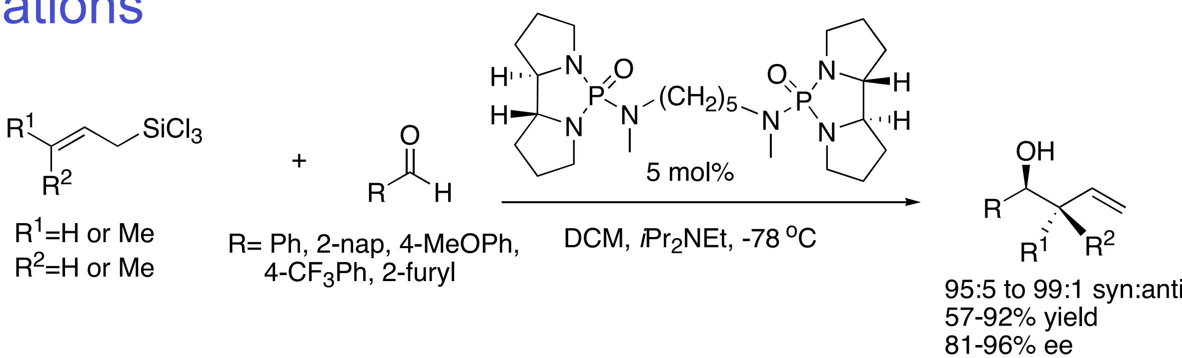
92-96% yield
89-99% ee

T. Rovis, *J. Am. Chem. Soc.* **2004,** 8876

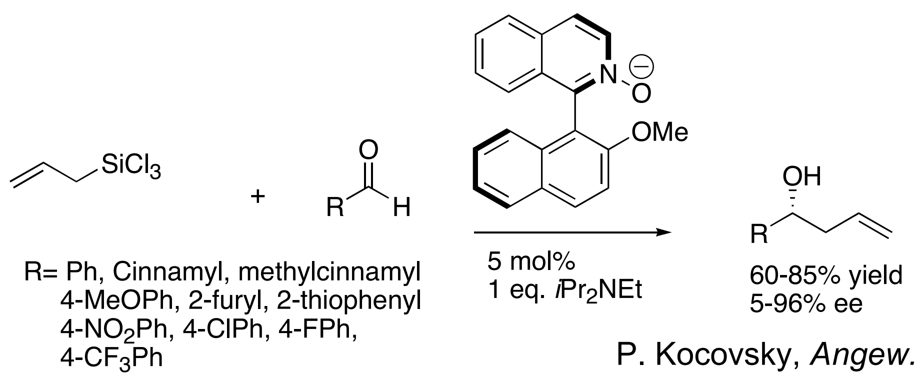
Lewis Basic Organocatalysis: Lewis Acid Activation



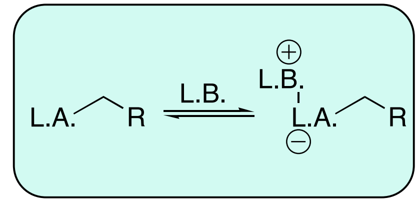
Allylations



S. Denmark, *J. Am. Chem. Soc.* **2001,** 9488

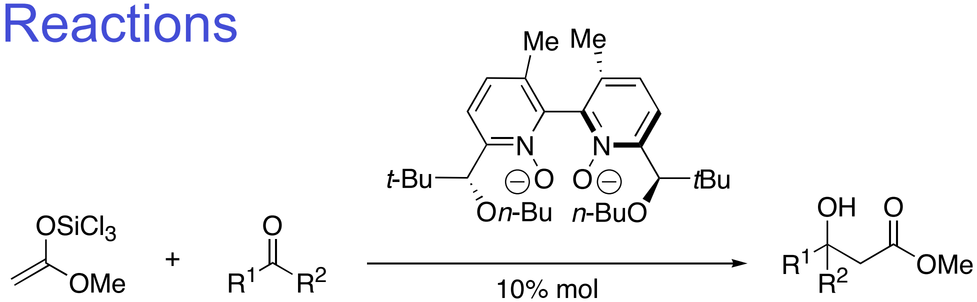


P. Kocovsky, *Angew. Chem. Int. Ed.* **2003,** 3674



Lewis Basic Organocatalysis: Lewis Acid Activation

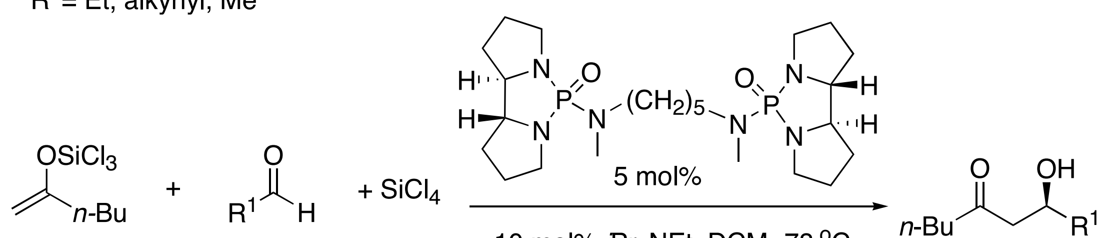
Aldol Reactions



R^1=Ph, 4-CF_3Ph, 4-MeOPh, Cinnamyl, Et, Phenethyl cyclopropyl, Cy, *t*-Bu, 1-nap, 2-furyl
R^2= Et, alkynyl, Me

84-97% yield
60:40 to 93:7 e.r.

S. Denmark, *J. Am. Chem. Soc.* **2002,** 4233



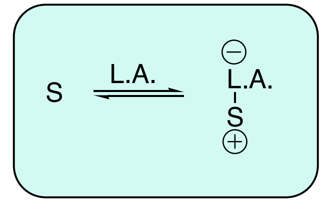
10 mol% *i*Pr_2NEt, DCM -78 °C
then
$NaHCO_3$, KF

R^1=Cinnamyl, methylcinnamyl 1-nap, 2-nap, 4-MeOPh, 4-CF_3Ph, 2-furyl, 2-thiophenyl

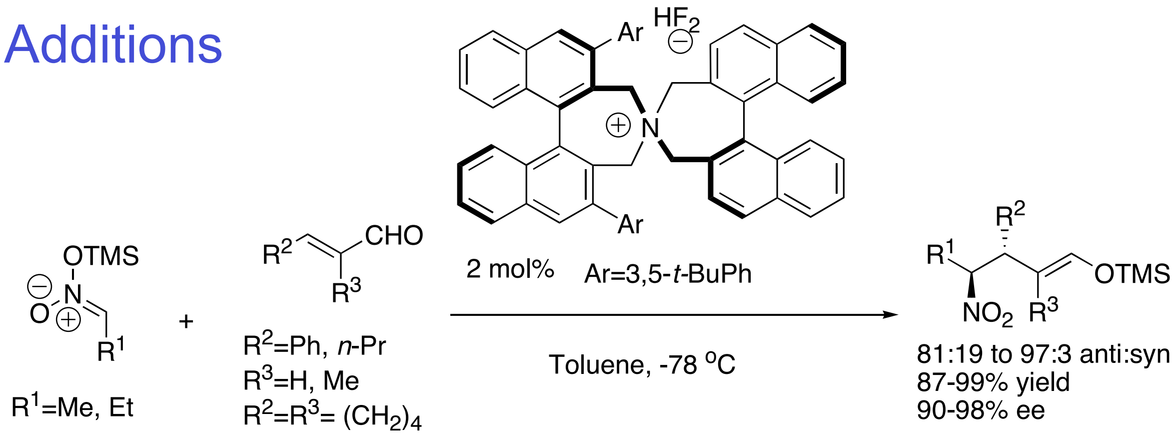
79-98% yield
78:22 to 99:1 e.r.

S. Denmark, *Org. Lett.* **2003,** 2303

Lewis Acidic Organocatalysis:

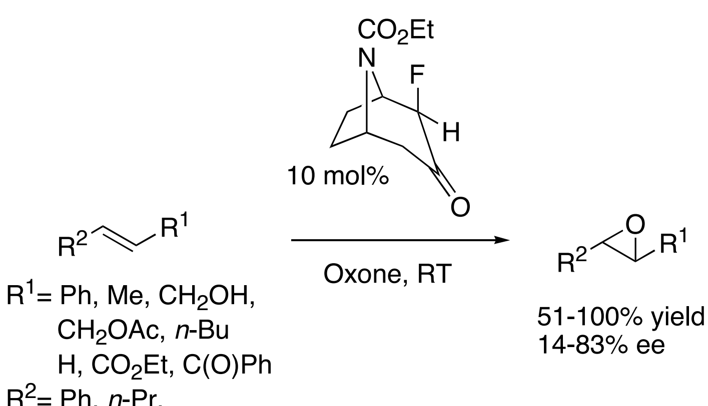


Micheal Additions

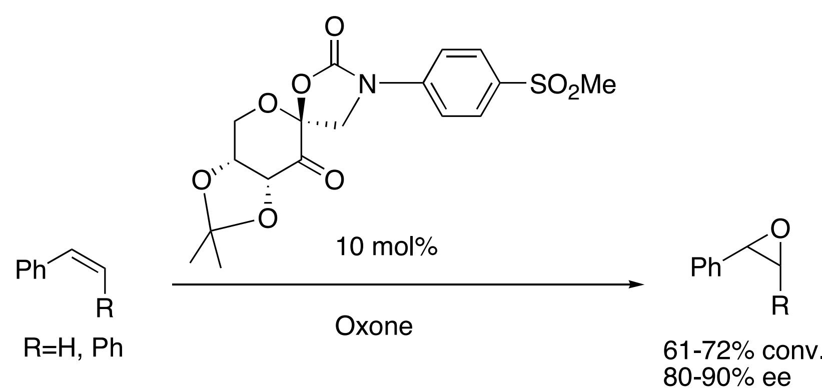


K. Maruoka, *J. Am. Chem. Soc.* **2003,** 9022

Epoxidation

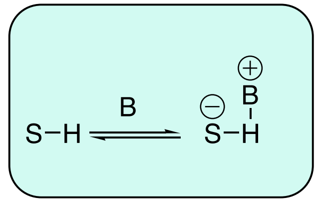


A. Armstrong, *J. Org. Chem.* **2002,** 8610

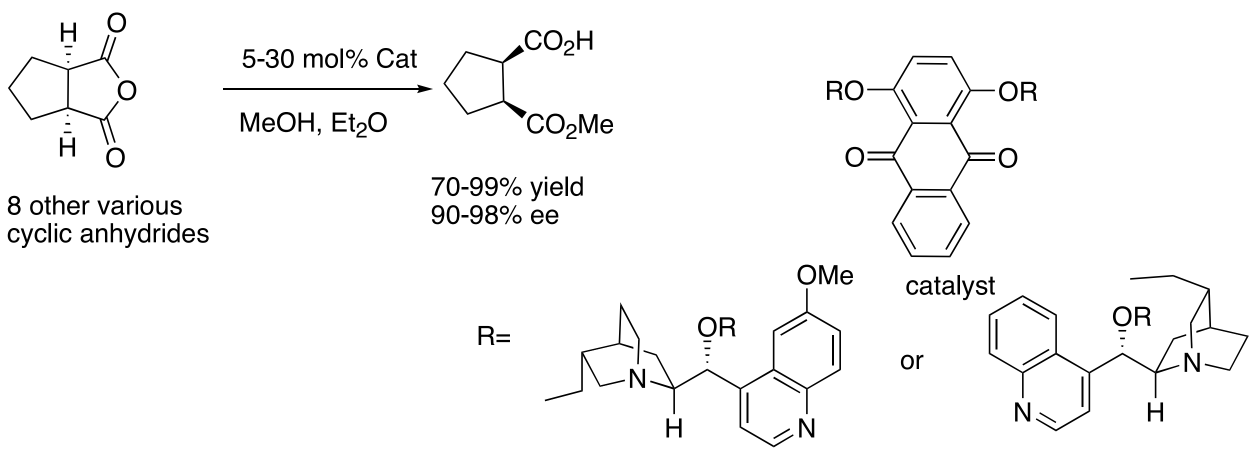


Y. Shi, *Org. Lett.* **2003,** 293

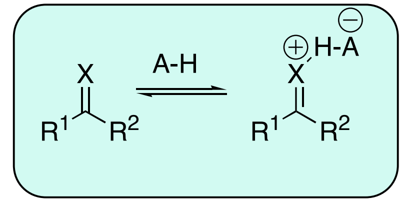
Bronsted Basic Organocatalysis:



Desymmetrization

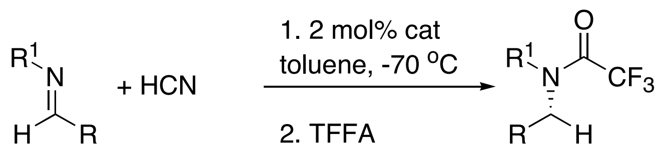


L. Deng, *J. Am. Chem. Soc.* **2000,** 9542



Bronsted Acidic Organocatalysis:

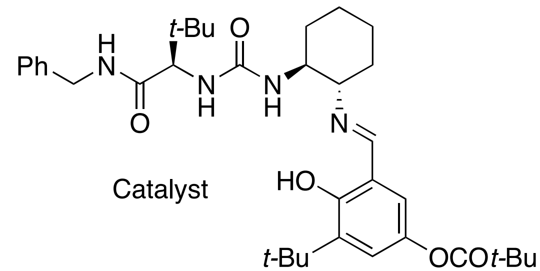
Strecker Reaction



R= Ph, *t*Bu, 4-MeOPh, 3-MeOPh, 2-MeOPh, 4-MePh, 3-MePh, 2-MePh, 4-BrPh, 3-BrPh, 2-BrPh, 4-*t*BuPh, Cy, *t*-Amyl pentyl, *i*Pr, cyclopropyl cyclooctyl

R^1=Allyl, benzyl

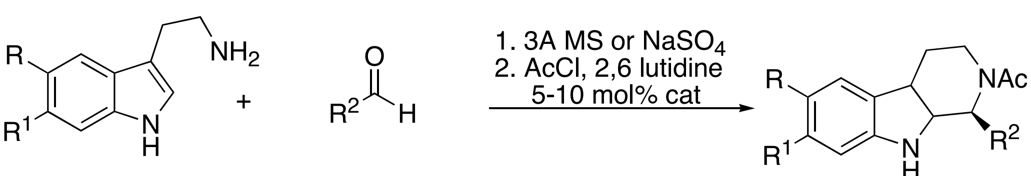
65-99% yield
77-97% ee



Catalyst

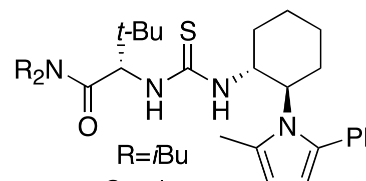
E. Jacobsen, *Angew. Chem.* **2002,** 1336

Acyl-Pictet-Spengler



R=H, OMe
R^1=H, OMe

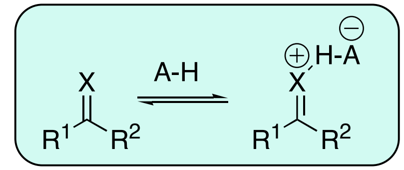
R^2= *i*Pr, *n*-penty, $CH(CH_2CH_3)_2$, $CH_2CH_2OTBDPSI$, *i*Bu



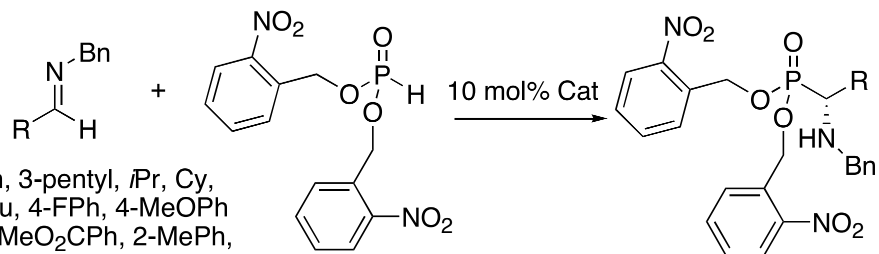
R=*i*Bu
Catalyst

E. Jacobsen, *J. Am. Chem. Soc.* **2004,** 10558

Bronsted Acidic Organocatalysis:

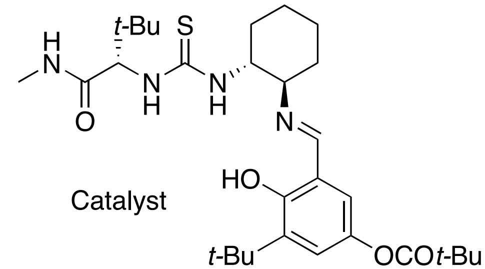


Hydrophosphonylation



R= Ph, 3-pentyl, *i*Pr, Cy, *t*Bu, 4-FPh, 4-MeOPh, 4-MeO_2CPh, 2-MePh, 2-ClPh, 3-ClPh, 4-ClPh, 2-nap, 3-pyridyl, 2-furyl 2-thienyl, 2-pyrrolyl

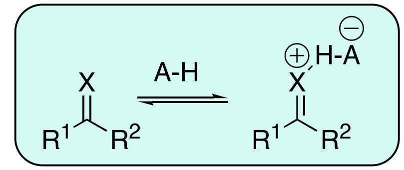
52-98% yield
81-98% ee

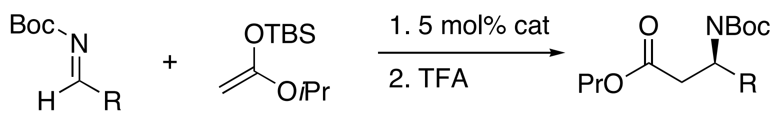


Catalyst

E. Jacobsen, *J. Am. Chem. Soc.* **2004,** 4102

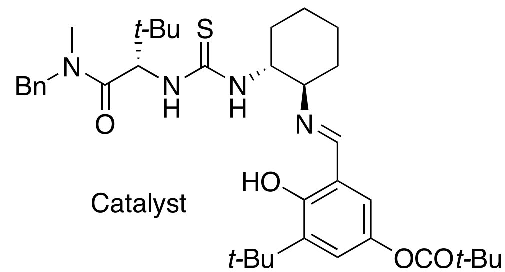
Bronsted Acidic Organocatalysis: Mannich Reactions



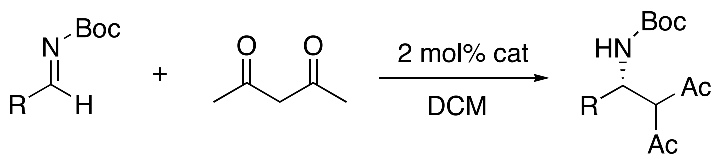


R= Ph, 2-MePh, 3-MePh, 4-MePh, 4-MeOPh, 4-FPh, 3-BrPh, 4-BrPh 1-nap, 2-nap, 2-furyl, 2-thienyl, 3-pyridyl, 3-quinolinyl

84-99% yield
86-98% ee

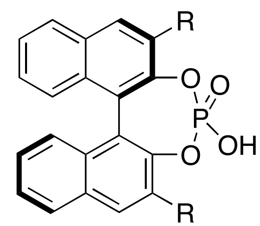


E. Jacobsen, *J. Am. Chem. Soc.* **2002,** 12964



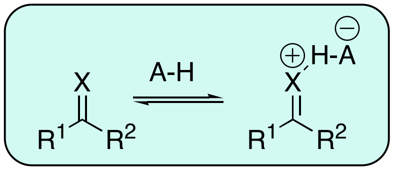
R= 4-MeOPh, 4-MePh, 4-BrPh, 4-FPh, 2-MePh, 1-nap

93-99% yield
90-98% ee

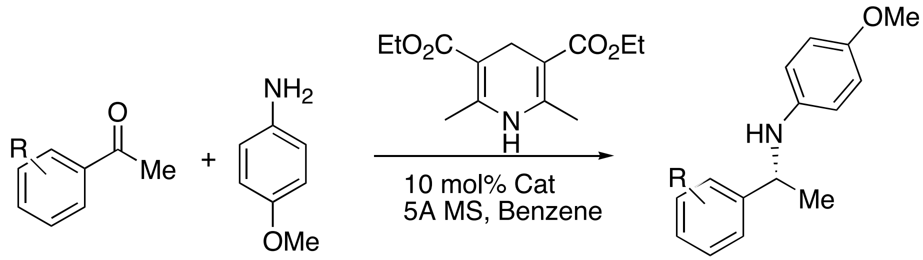


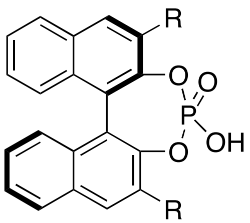
R= 4-(β-Naph)-C_6H_4

M. Terada, *J. Am. Chem. Soc.* **2004,** 5356
For a similar catalyst for Mannich rxn with Silyl ketene acetals see
T. Akiyama, *Angew. Chem.* **2004,** 1592



Bronsted Acidic Organocatalysis: Reductive Amination





R=$SiPh_3$

Catalyst

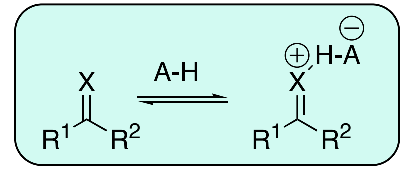
R= H, 4-Me, 4-MeO, 4-NO_2
4-Cl, 4-F, 3-F, 2-F

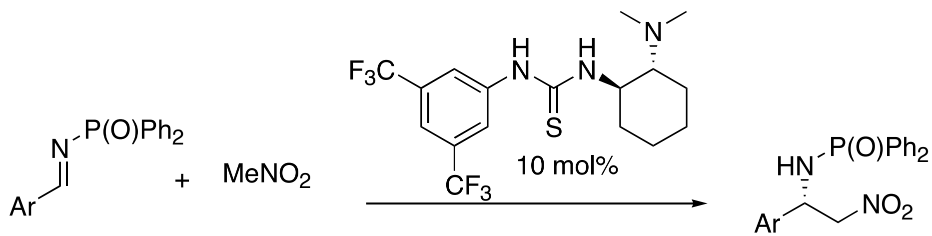
60-87% yield
83-97% ee

Also works well with non-aromatic ketones

D. MacMillan, *J. Am. Chem. Soc. ASAP*
Other examples of reductive amination
M. Reuping, *Org. Lett.* **2005,** 378
B. List, *Angew. Chem. Int. Ed.* **2005,** 7424

Bronsted Acidic Organocatalysis: Aza-Henry Reaction

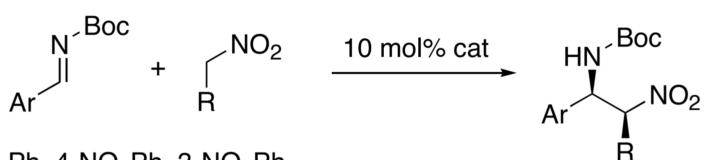




Ar= Ph, 4-MePh, 4ClPh, 2-nap, 2-furyl, 2-pyridyl, 2-thienyl, cinnamyl

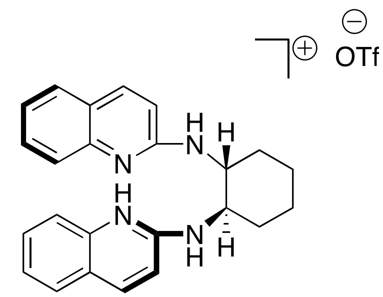
68-91% yield
63-76% ee

Y. Takemoto, *Org. Lett.* **2004,** 625



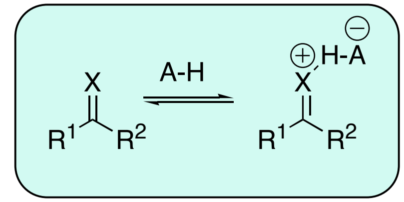
Ar= Ph, 4-NO_2Ph, 3-NO_2Ph
4-CF_3Ph, 4-ClPh, 2-NO_2Ph
R=H or Me

7:1 to 19:1 d.r.
51-69% yield
60-95% ee

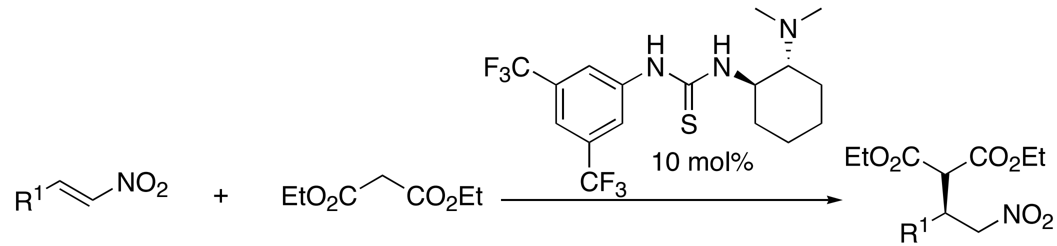


catalyst

J. Johnson, *J. Am. Chem. Soc.* **2004,** 3418



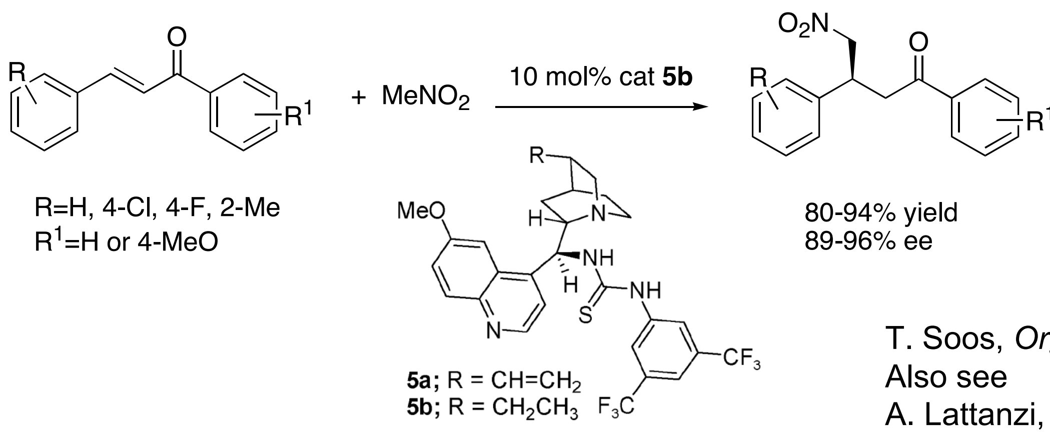
Bronsted Acidic Organocatalysis: Micheal Addition



R^1= Ph, 2,6-MeOPh, 4-FPh, 1-nap, 2-nap, pentyl, *i*Bu

74-95% yield
81-93% ee

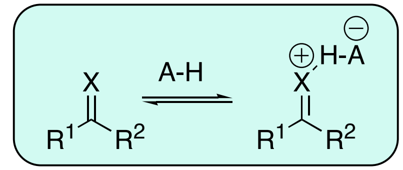
Y. Takemoto, *J. Am. Chem. Soc.* **2003,** 12672



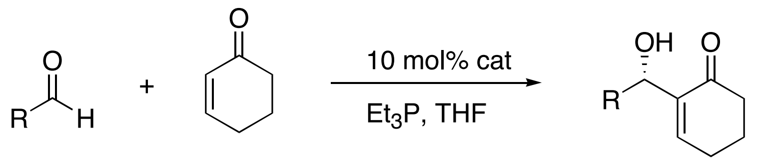
R=H, 4-Cl, 4-F, 2-Me
R^1=H or 4-MeO

80-94% yield
89-96% ee

T. Soos, *Org. Lett.* **2005,** 1967
Also see
A. Lattanzi, *Org. Lett.* **2005,** 2579

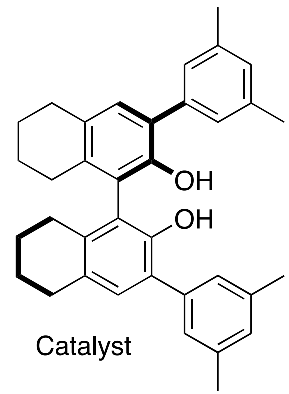


Bronsted Acidic Organocatalysis: Morita-Baylis-Hillman



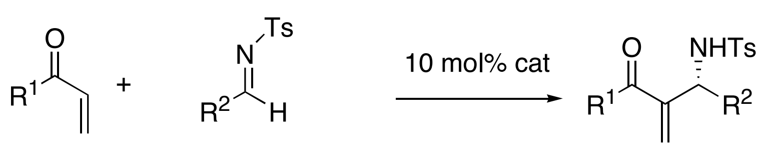
R= Phenethyl, Bn ethanol, 3-hexene, Cy, *i*Pr, Ph, cinnamyl

39-88% yield
67-96% ee



Catalyst

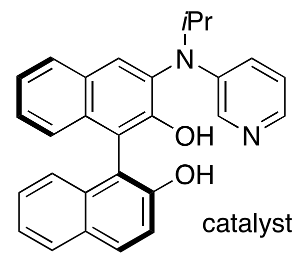
S. Schaus, *J. Am. Chem. Soc.* **2003,** 12094



R[1]=Me, Et, H

R[2]=Ph, 4-ClPh, 3-ClPh,4-BrPh 4-MeOPh, 2-nap 2-furyl, 4-NO_2Ph

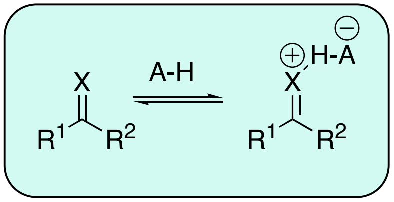
88-100% yield
87-95% ee

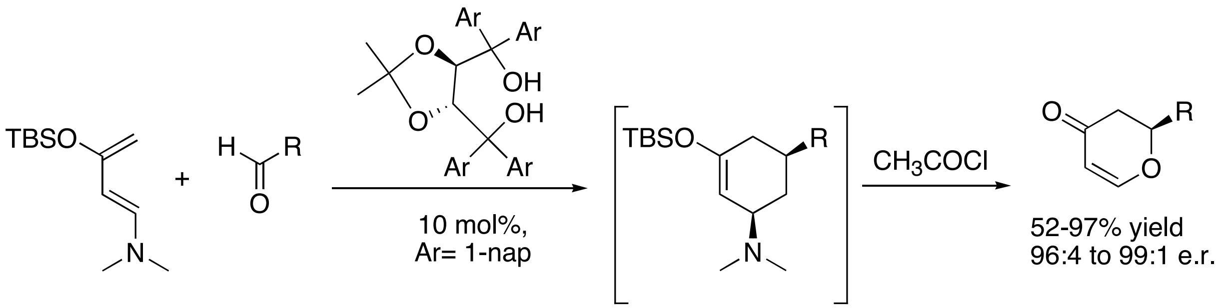


catalyst

H. Sasai, *J. Am. Chem. Soc.* **2005,** 3680
Also See
W. Wang, *Org. Lett.* **2005**, 4293

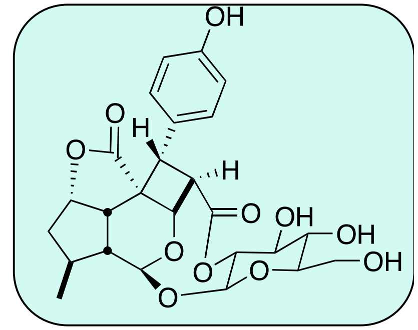
Bronsted Acidic Organocatalysis: Formal [4+2] Cycloaddition

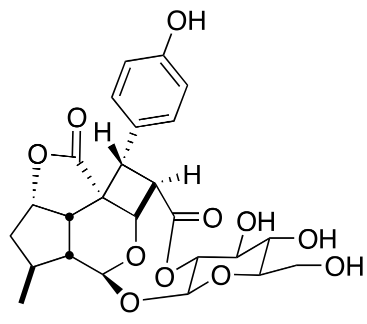




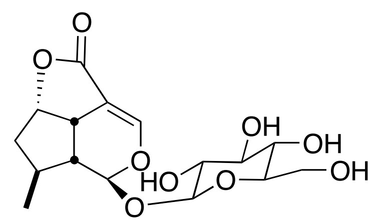
V. Rawal, *Nature* **2003,** 146

Organocatalysis in Total Synthesis: (-)-Littoralisone





(-)-littoralisone

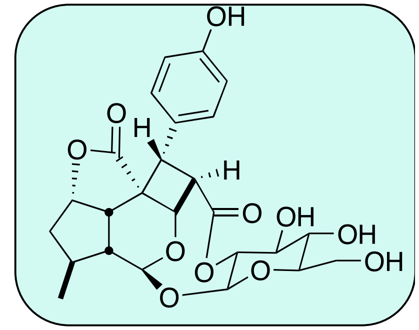


(-)-brasoside

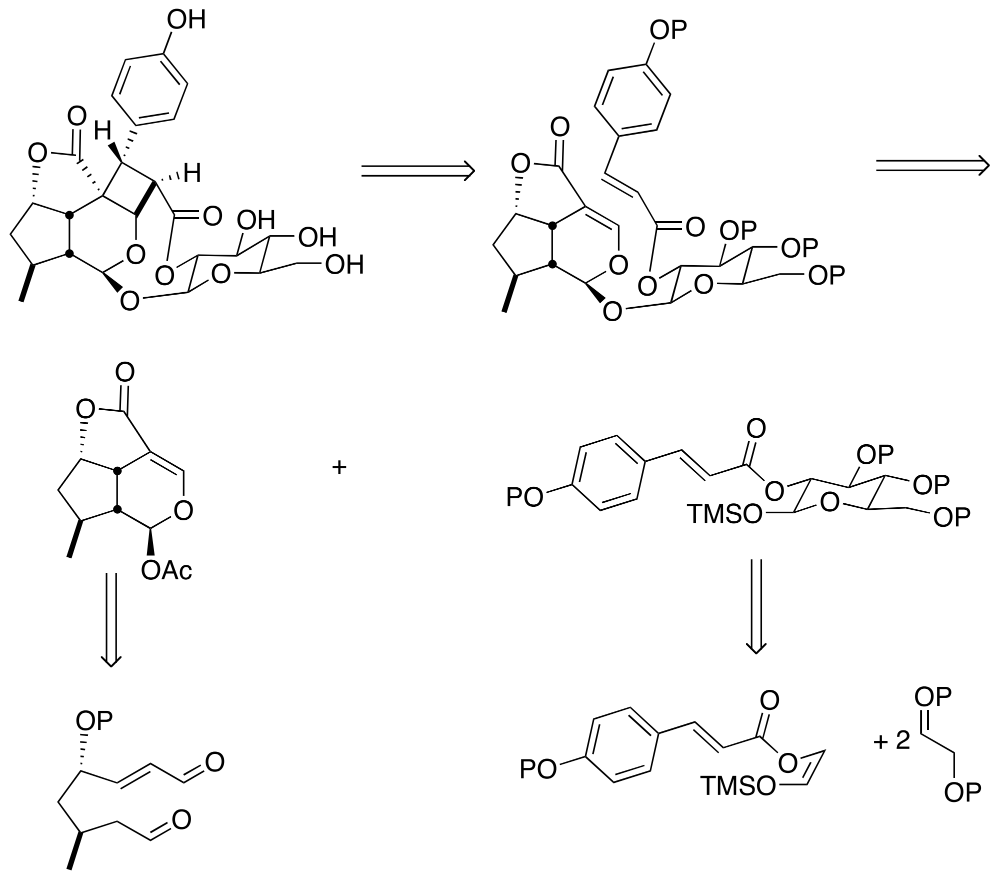
- -Extracted from *Verbena littoralis*, a plant widely used in folk medicine
- -Found to increase nerve growth factor induced neurite outgrowth in PC12D cells

D. MacMillan, *J. Am. Chem. Soc.* **2005,** 3696

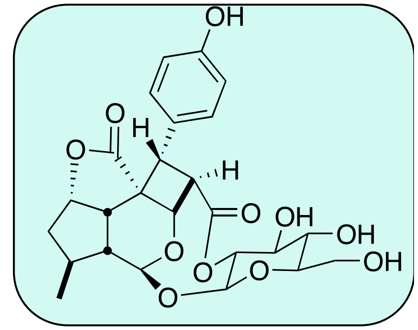
Organocatalysis in Total Synthesis: (-)-Littoralisone



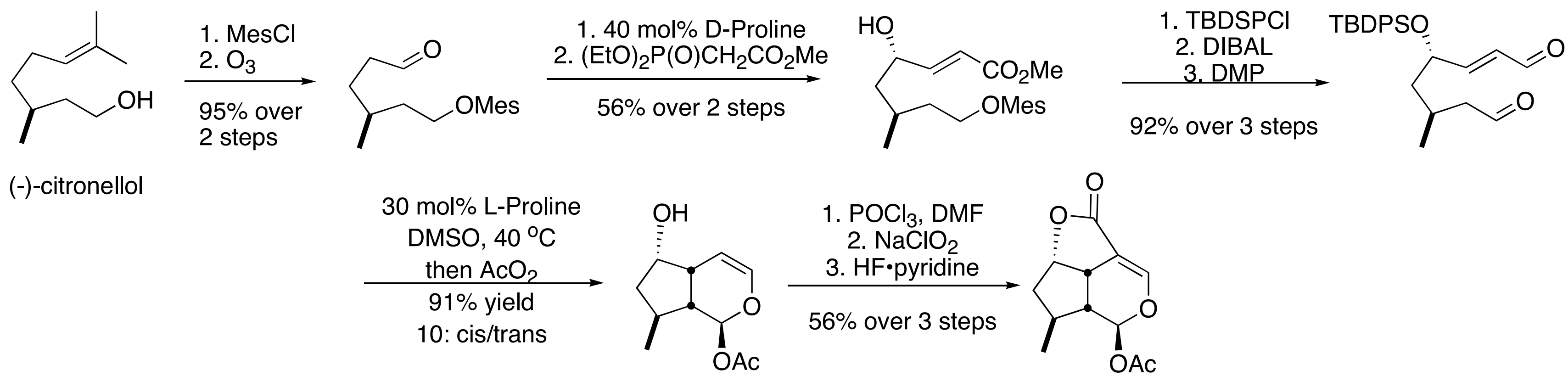
Retrosynthesis



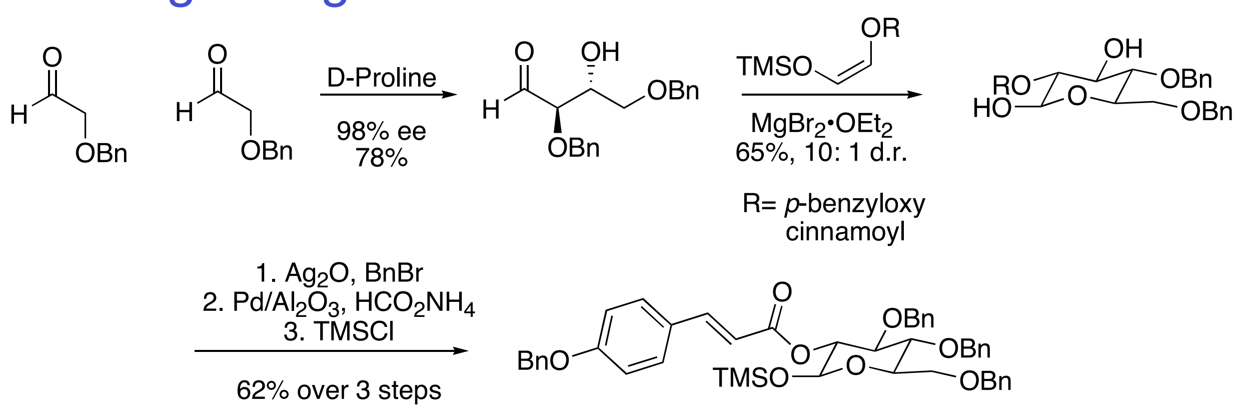
Organocatalysis in Total Synthesis: (-)-Littoralisone



Synthesis of brasoside core

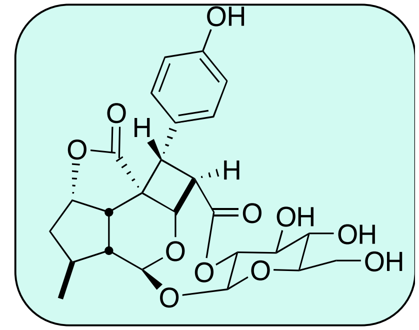


Synthesis of Sugar fragment

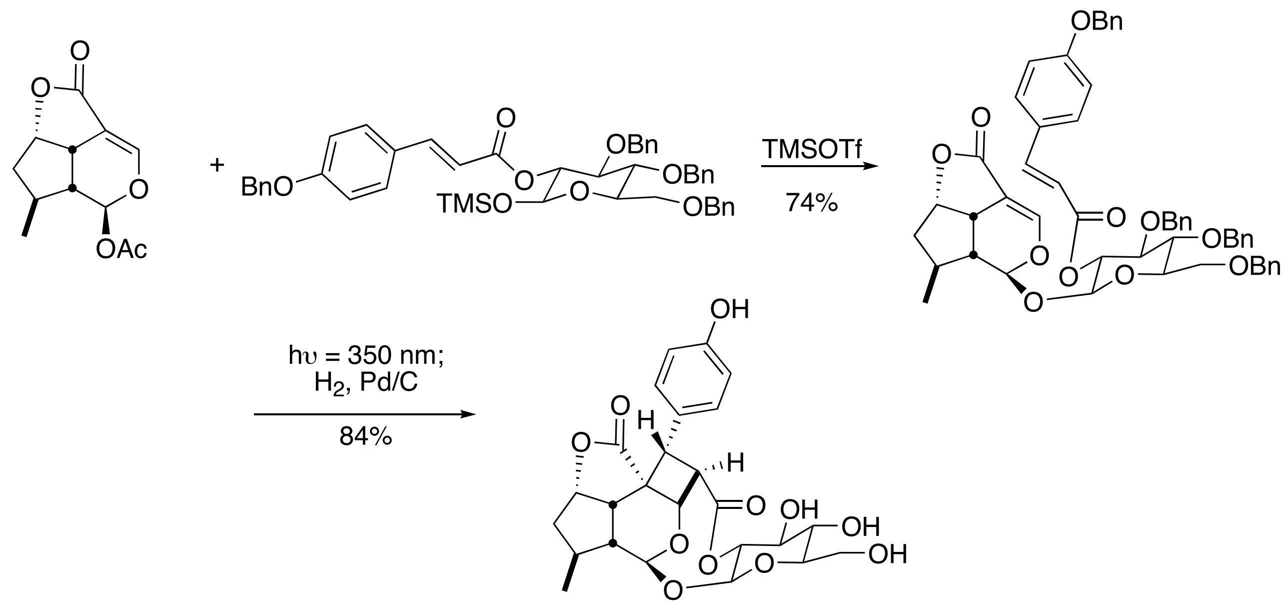


D. MacMillan, *Angew. Chem. Int. Ed.* **2004,** 2152

Organocatalysis in Total Synthesis: (-)-Littoralisone



Fragment Coupling



-First total synthesis of (-)-Littoralisone was completed in 13 steps in 13% overall yield

- Proline was used to in 3 steps to set 4 stereocenters.

Conclusions

- Organocatalysts can be used for a wide arrary of synthetically useful transformations.
- The current state of the art involves the use of chiral secondary amines to form iminium ions or enamines.
- The use of chiral H-bond donors is an immerging area has been shown to be an effective alternative to secondary amines in some reactions.

Future Directions

- Innovation- The world doesn't need a new Diels-Alder catalyst.
- Replacement- Removing the Pd from cross-coupling reactions. There are some examples, but no synthetically viable protocols.
- Discovery- Development of a "privileged" catalyst structure that does multiple reactions extremely well.
- Use- Show practical applications of the catalysts and the reactions they promote.