Asymmetric Organocatalysis

(emphasis on Enamine catalysis)

Pablo García-Reynaga
VanNieuwenhze Group

Major Players:

Hajos, Parrish, Eder, Sauer, Weichert (Discovery)
Carlos Barbas, Benjamin List, Richard Lerner, David MacMillan (Revival)

Reviews:

1. List *et. al., Chem. Rev.*, **2007**, 107 (12), pp 5471–5569 (enamine catalysis).
2. Pellesier, H, *Tetrahedron*, 63, 9267-9331
3. Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today*, *12*, 8-27.
4. Barbas *et. al.*, Acc Chem Res., 37, 580-591.

Definition (EPA): Green (sustainable) chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle, including the design, manufacture, and use of a chemical product. (Follow 12 principles).

12 Principles of Green Chemistry

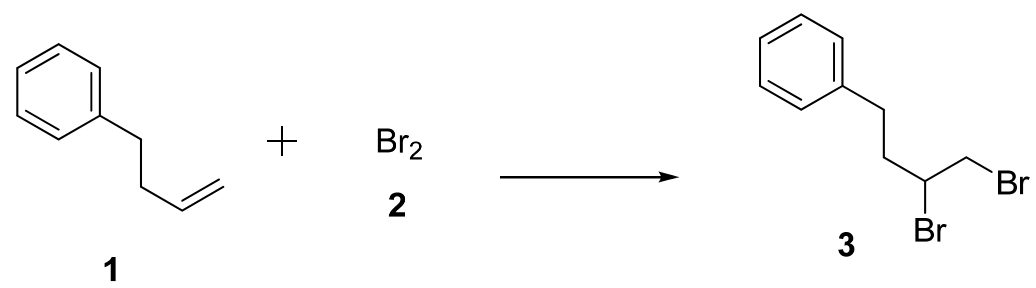
1. Prevention
2. Atom Economy
3. Less Hazardous Chemical Syntheses
4. Designing Safer Chemicals
5. Safer Solvents and Auxiliaries
6. Design for Energy Efficiency
7. Use of Renewable Feedstocks
8. Reduce Derivatives
9. Catalysis
10. Design for Degradation
11. Real-time analysis for Pollution Prevention
12. Inherently Safer Chemistry for Accident Prevention

Journal: *http://www.rsc.org/Publishing/Journals/gc/*

**Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford Univ. Press: New York, 1998, p.30.*

Atom Economy:

$$\text{Atom Economy} = \left(\frac{\text{MW of Product}}{\Sigma\,(\text{MW of Reactants})} \right)$$



$$AE = \frac{MW_3}{MW_1 + MW_2} = \frac{292.01}{132.20 + 159.81} = 100\%$$

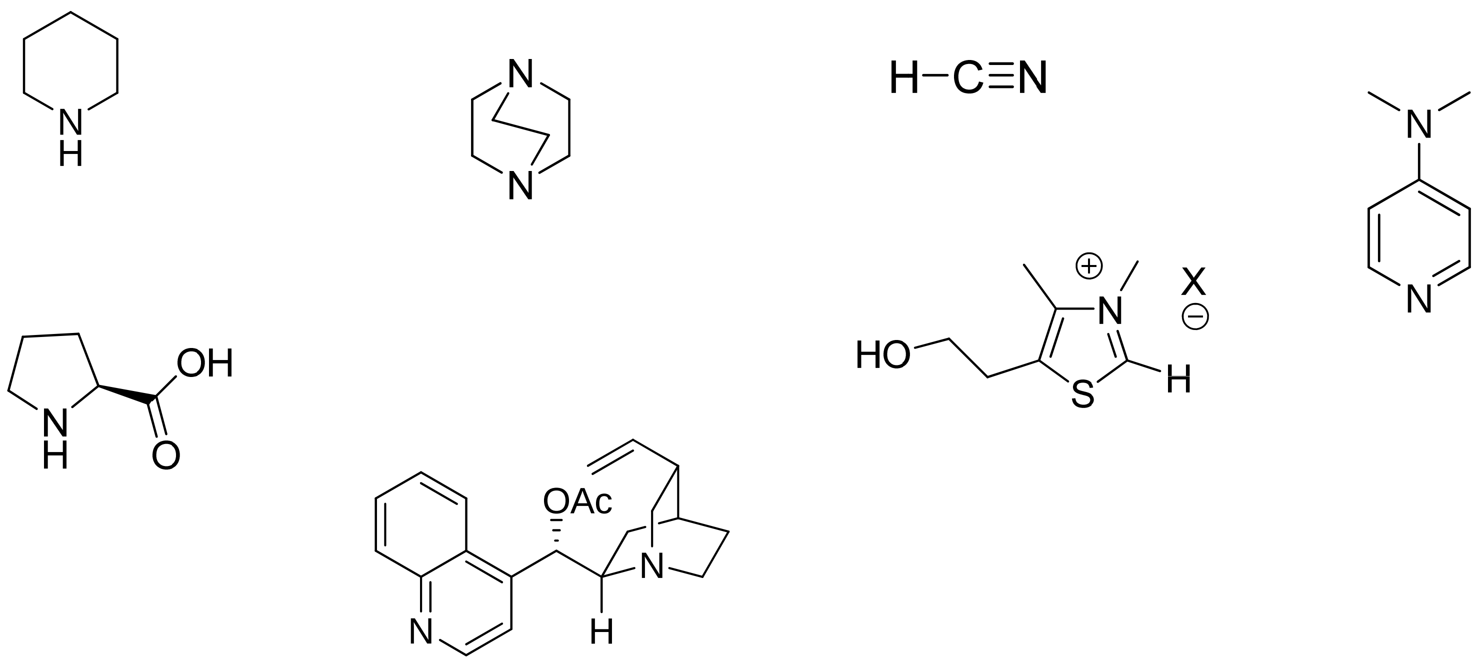
Examples: “click” chemistry, pericyclic reactions, “on water reactions,” catalytic antibodies

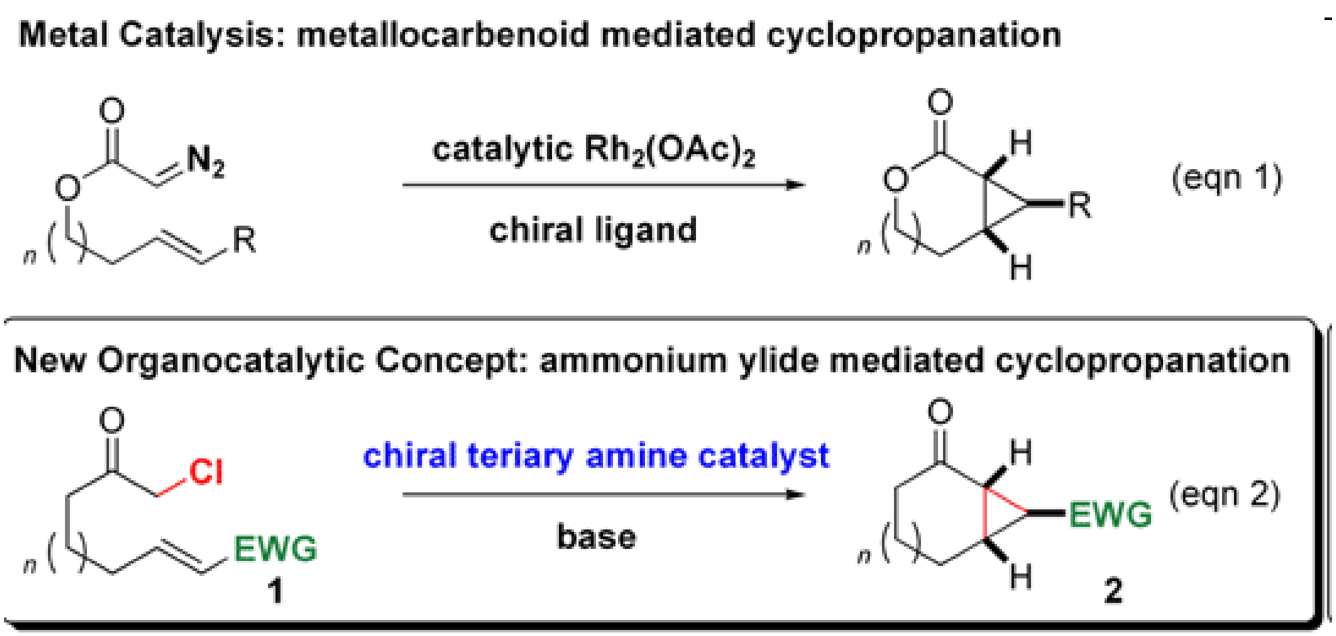
http://*www.rsc.org/education/teachers/learnnet/green/whatis/home.htm*

What is Organocatalysis?

- Organocatalysis is the acceleration of a chemical step by a non metal-containing molecule

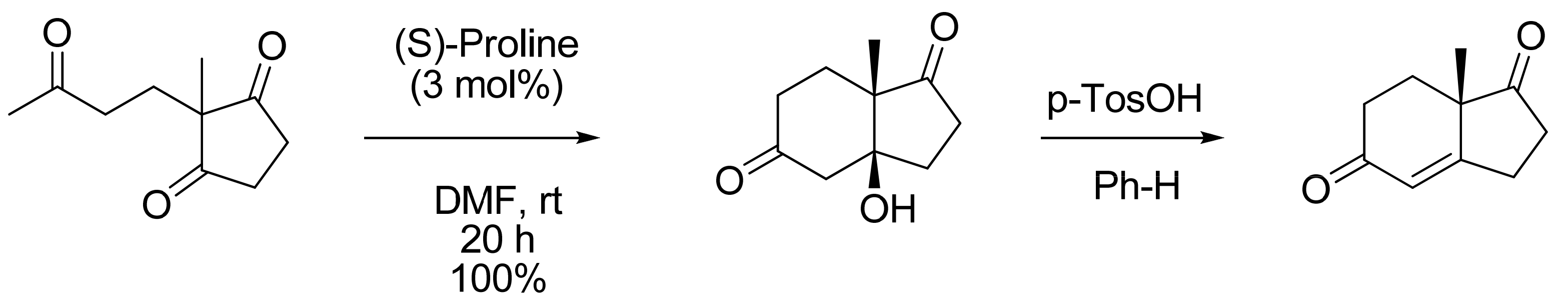
Examples: Proline, Cinchona alkaloids, DMAP, thiazolium salts, etc.

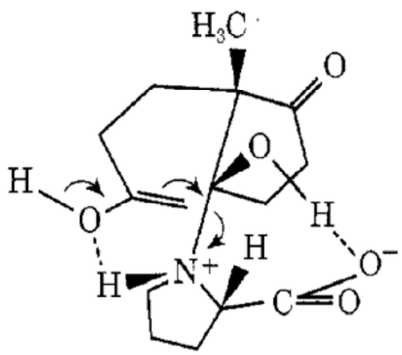


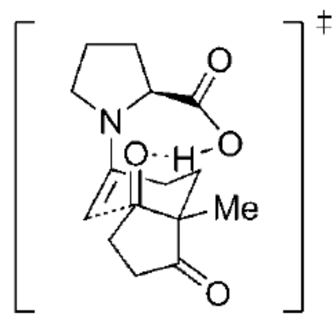


Methods for Catalytic Intramolecular Cyclopropanation

The Hajos-Parrish Ketone: Aminocatalytic Asymmetric Aldol







Hajos-Parrish (1974)

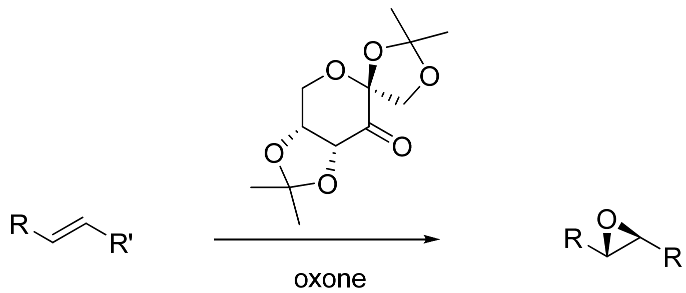
List-Houk (2000)

Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

Hajos, Z. G.;Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

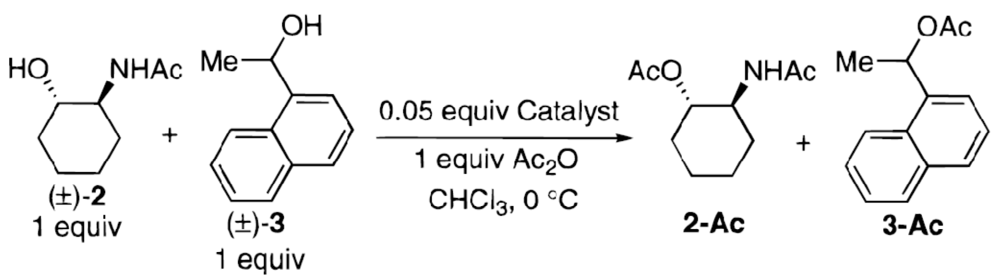
Some major contributions to organocatalysis -1990's

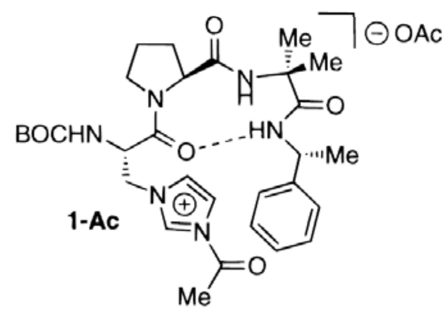
Shi Epoxidation



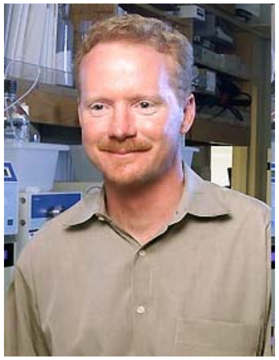
Y. Shi *et. al*. *J. Am Chem. Soc.*, **1997**, *119(46)*, 11224-11235.

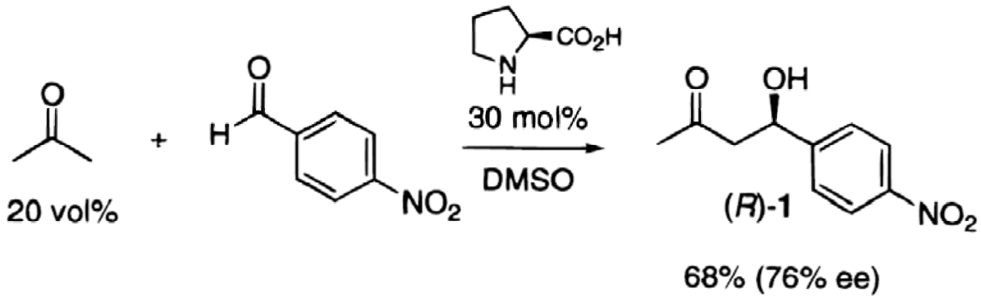
Kinetic Resolution of Alcohols (Miller)



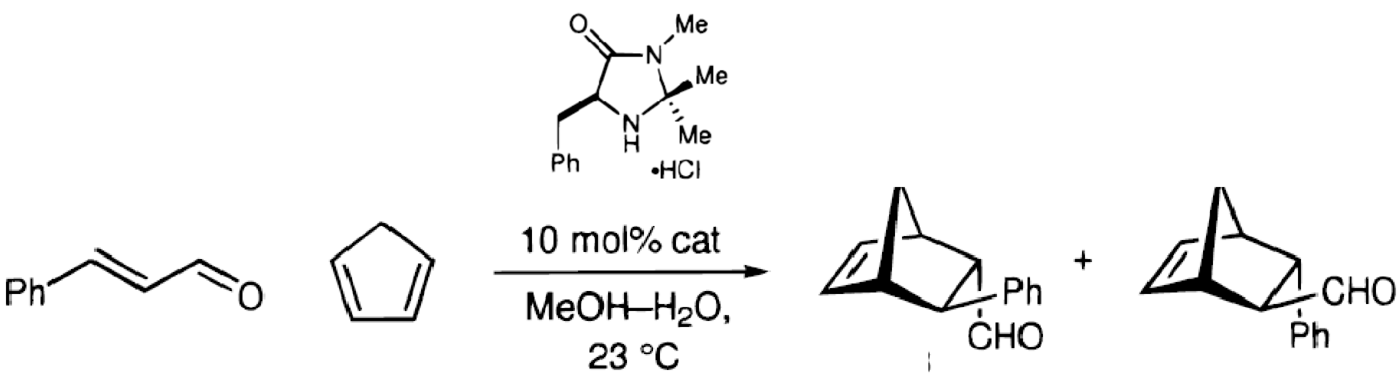


S. Miller *et. al*. *J. Am. Chem. Soc.* **1998**, *120*, 1629-1630.



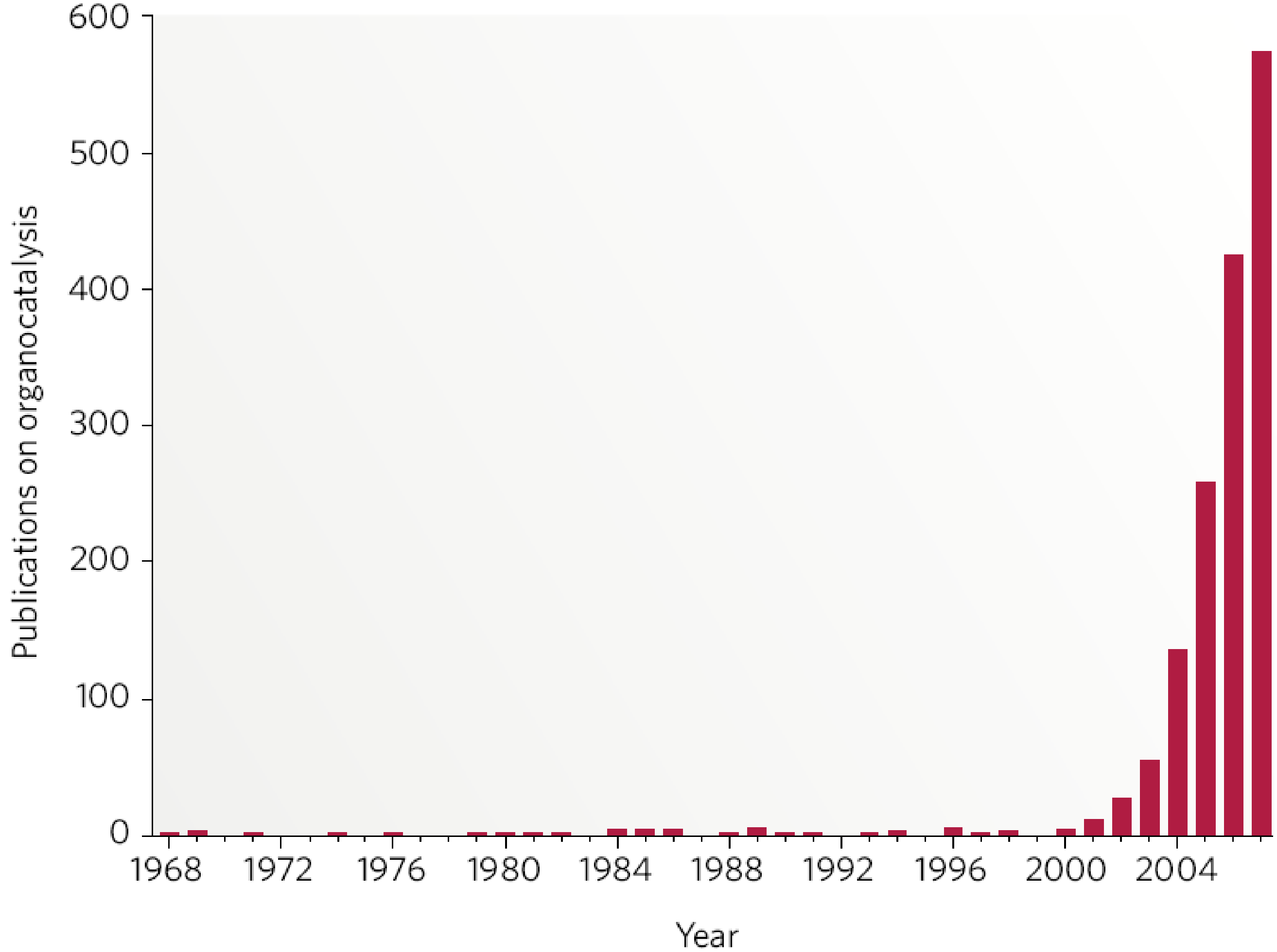


List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395



MacMillan *et. al*. *J. Am. Chem. Soc.*, **2000**, 122 (17), pp 4243–4244

Publications on organocatalysis 1968-2007

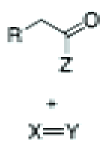
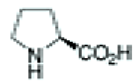
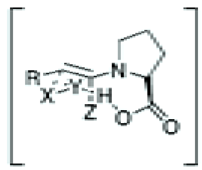
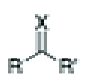
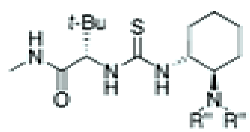
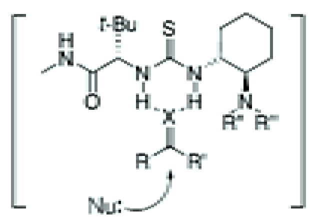
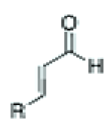
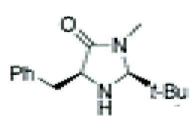
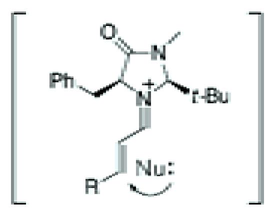


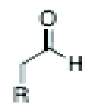
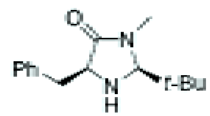
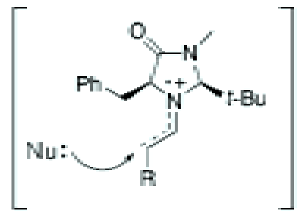
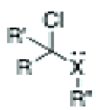
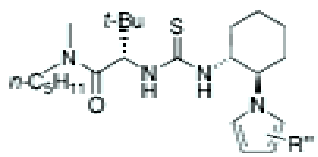
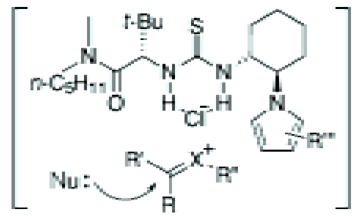
1998-2008: at least 1,500 manuscripts using organocat. in >130 discrete reaction types!

Q.) Why was this field "overlooked"?

- Individual reactions not placed within a larger fied
- Given a name- organocatalysis that people can grasp (ex. Diversity Oriented Synthesis)

General Modes of Activation in Organocatalysis

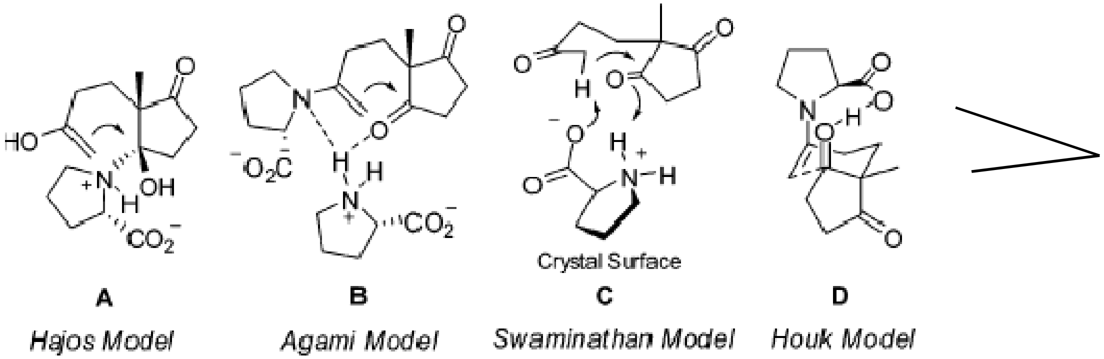
Substrate	Catalyst	Activation mode	Number of new reactions	Examples of new reaction variants	References
Enamine catalysis					
 R = any organic chain or ring system X = C, N, O, S Y = generic organic atom Z = alkyl, H		HOMO activation 	25	• Aldehyde–aldehyde cross aldol coupling • Intramolecular α-alkylation • Mannich reaction • Michael reaction • α-Amination • α-Oxygenation • α-Halogenation • α-Sulphenylation	First application: 1971, ref. 3 First use as a generic mode of activation: 2000, ref. 13
Hydrogen-bonding catalysis					
 X = O, NR R, R', R''' = alkyl, aryl		LUMO activation 	30	• Strecker reaction • Mannich reaction • Ketone cyanosilylation • Biginelli reaction • Pictet–Spengler reaction • Reductive amination	First application: 1996–1999, refs 9–11 First use as a generic mode of activation: 2002, ref. 17
Iminium catalysis					
 R = alkyl, aryl		LUMO activation 	50	• Conjugate Friedel–Crafts reaction • Ketone Diels–Alder reaction • *exo*-Selective Diels–Alder reaction • Mukaiyama–Michael reaction • Conjugate hydride reduction • Conjugate amination • Conjugate oxygenation • Conjugate sulphenylation • Cyclopropanation • Epoxidation, aziridination	First application and first use as a generic mode of activation: 2000, ref. 14

SOMO catalysis						
	 R = alkyl, aryl		SOMO activation 	4	• α-Allylation • α-Enolation • α-Vinylation • α-Heteroarylation	First application and first use as a generic mode of activation: 2007, ref. 25
Counterion catalysis						
	 X = O, NR R, R', R'', R''' = alkyl, aryl		LUMO activation 	2	• Acyl-Pictet–Spengler reaction • Oxocarbenium addition reaction	First application and first use as a generic mode of activation: 2007, ref. 28

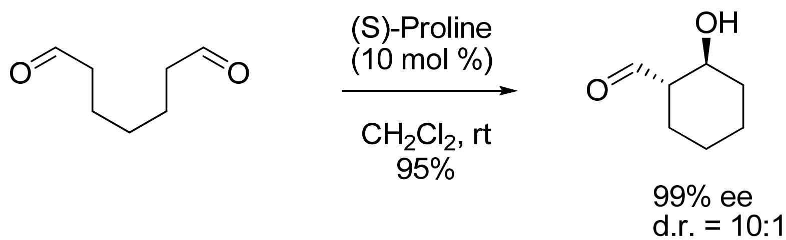
In HOMO activation, the energy of the highest-occupied molecular orbital (HOMO) is increased. In LUMO activation, the energy of the lowest-unoccupied molecular orbital (LUMO) is decreased. In SOMO activation, an electron is located in a singly occupied molecular orbital (SOMO) to generate a highly reactive species that can participate in many reaction types. Nu, nucleophile; Ph, phenyl.

List classification: Lewis Acid, Lewis Base, Bronsted Acid, Bronsted Base

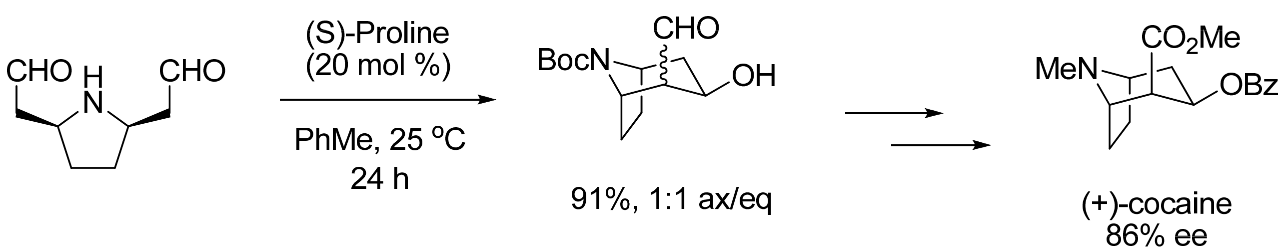
Proposed Mechanistic Models for the H-P-E-S-W Reaction:



Bifunctional

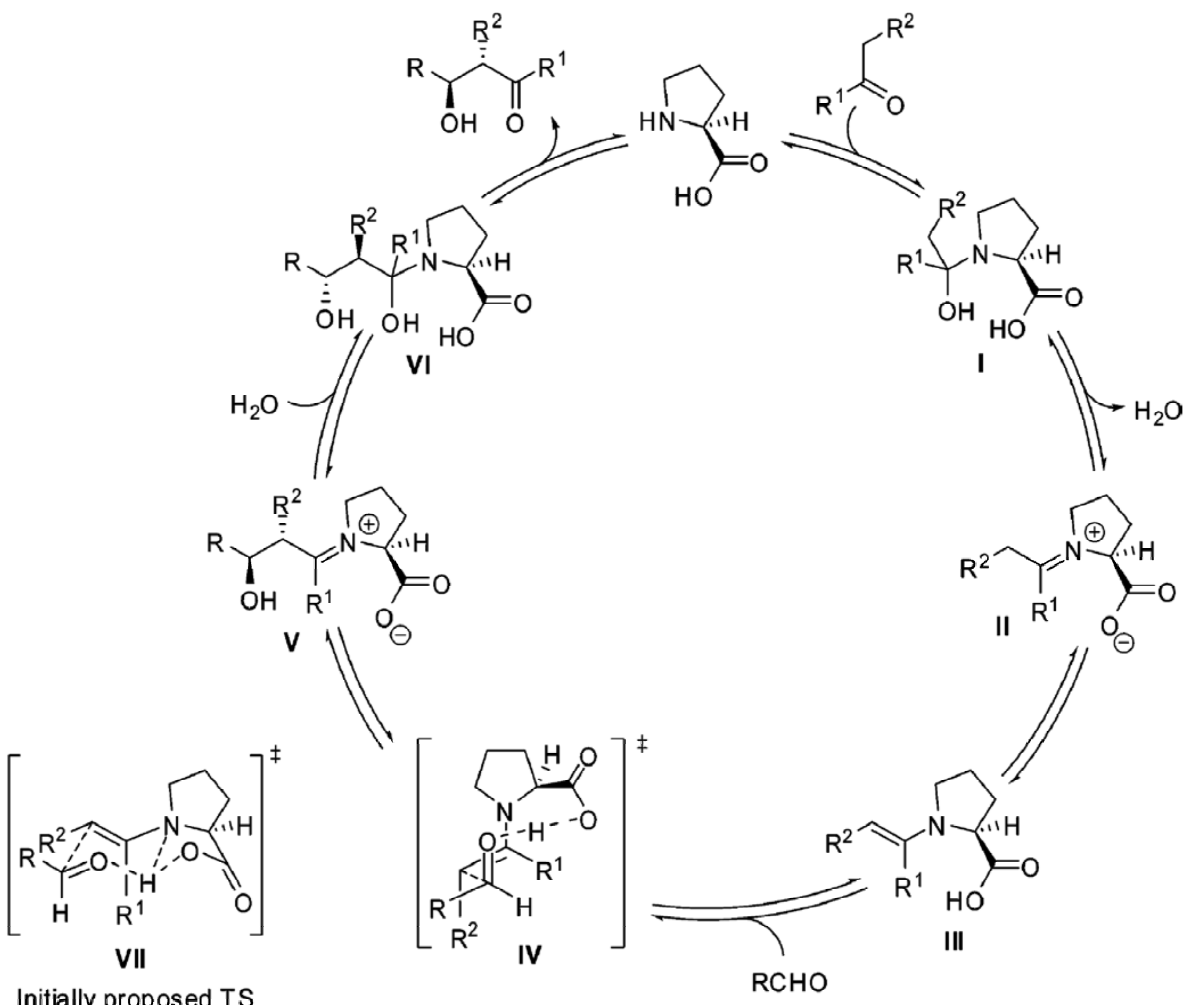


List *et. al. Angew. Chem., Int. Ed.* **2003**, *42*, 2785

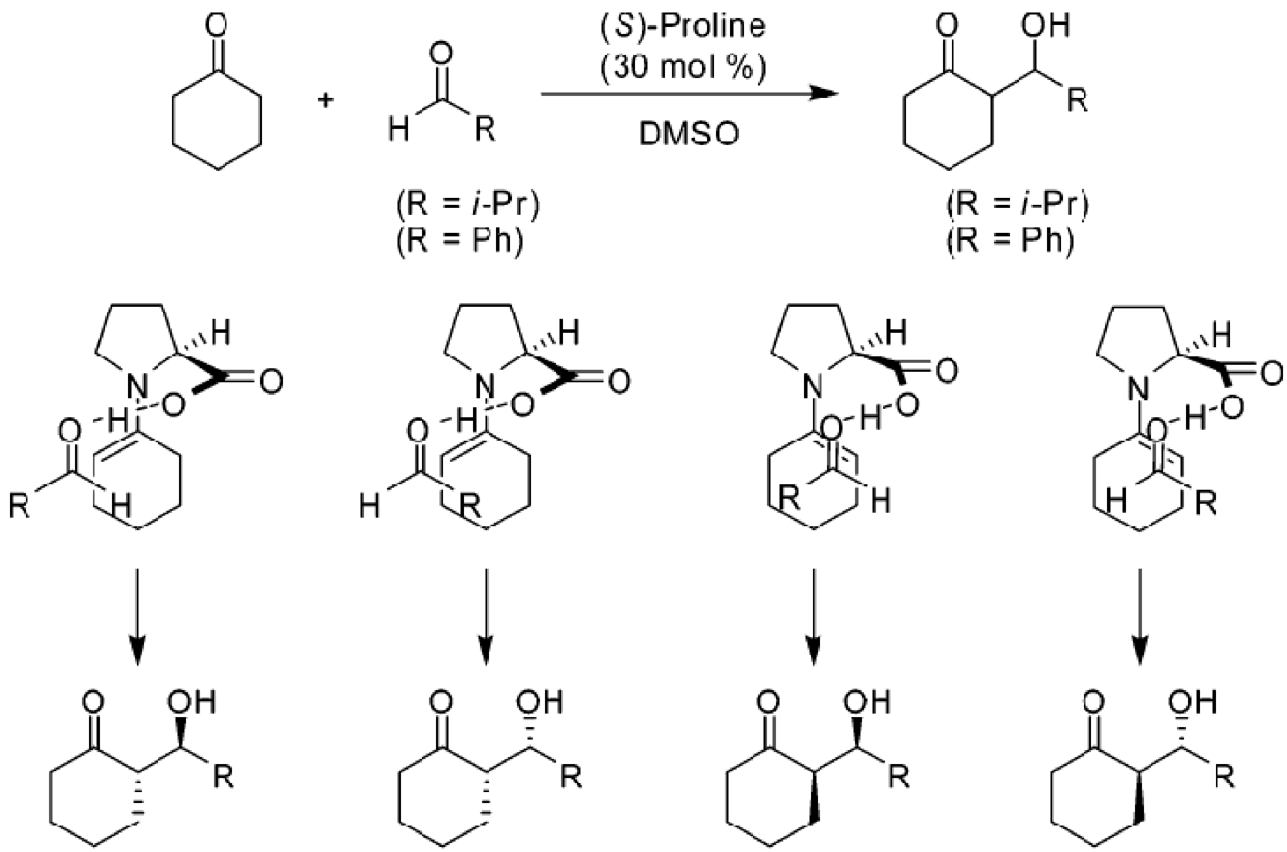


Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305.

Q) Why proline? vs Homo-Proline? (Stork)



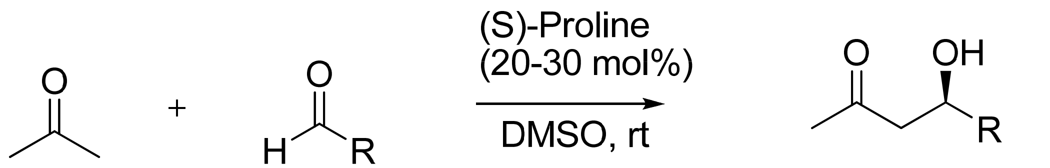
I
II
III
IV
V
VI
VII
H_2O
H_2O
RCHO
Initially proposed TS



R = *i*-Pr	**98.5%** (>99%)	**<1%** (<1%)	**<1%** (<1%)	**1.5%** (<1%)
R = Ph	**46.5%** (54.5%)	**44%** (44.5%)	**6%** (0.1%)	**3.5%** (0.8%)

Experiment (DFT Calculation)

Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem.Soc.* **2003**, *125*, 2475.



54-97% yield
60-96% ee

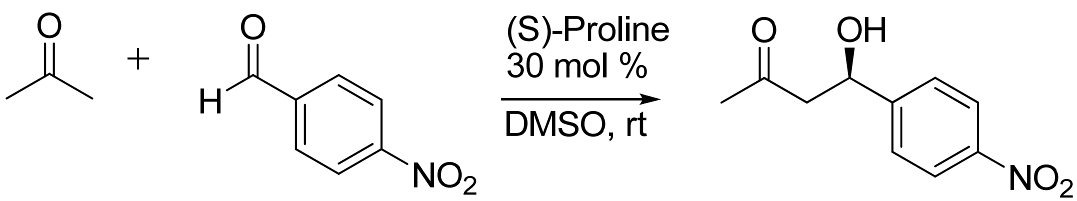
List *et. al. J. Am. Chem. Soc.* **2000**, *122*, 2395.
List, B *et. al.*. *J. Am. Chem. Soc.* **2002**, 5656
List, B. *Synlett* **2001**, 1675

- competes with self-aldolization of aldehyde, unless substituted or non-enolizable aldehydes are used

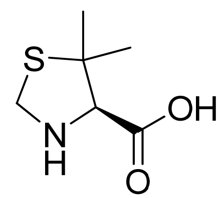
Q) How may this be avoided?

- Use excess of ketone or slow addition of aldehyde acceptor

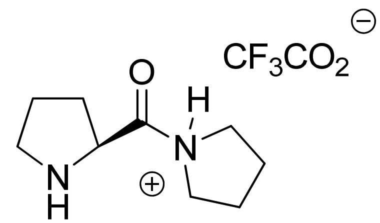
Optimization of "Proline" catalyst



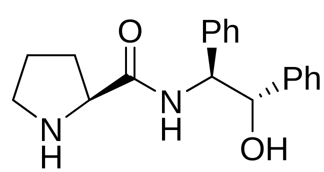
68%, 76% ee



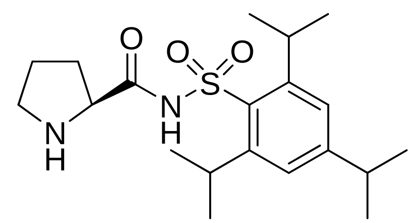
60%, 86% ee



60%, 88% ee



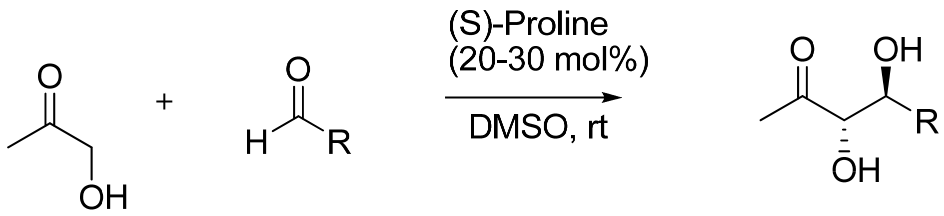
66%, 93% ee



99%, 95% ee

•Water has a beneficial effect

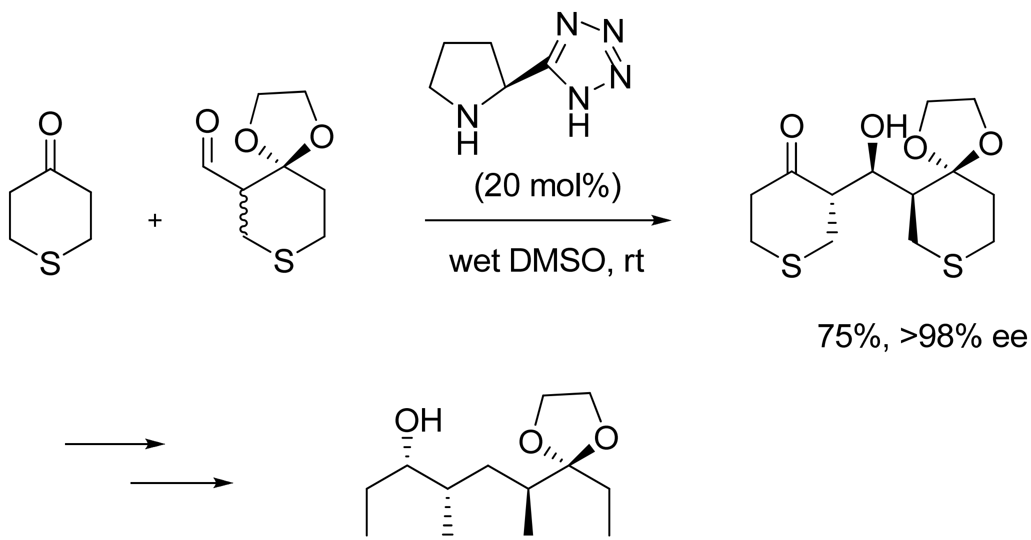
“Asymmetric Dihydroxylation” of (Z) olefins



38-95% yield
67->99% ee

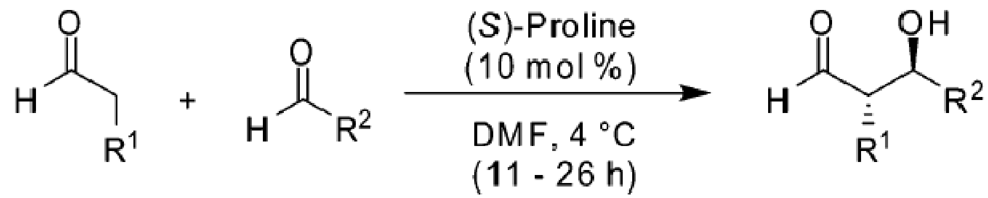
Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

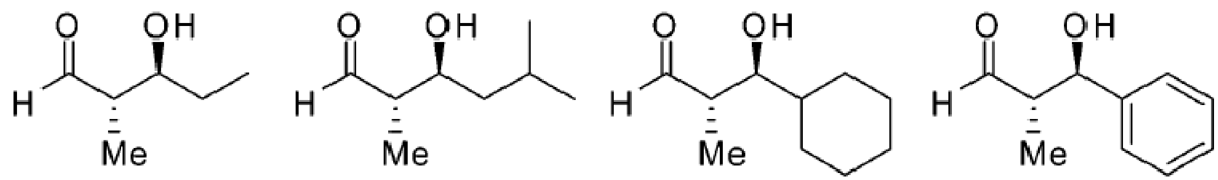
Dynamic Kinetic Resolution



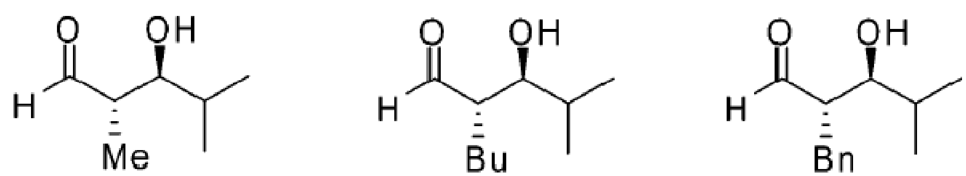
serricornin

D. E. Ward , V. Jheengut , G. E. Beye , *J. Org. Chem.* **2006** , *71* , 8989 -8992





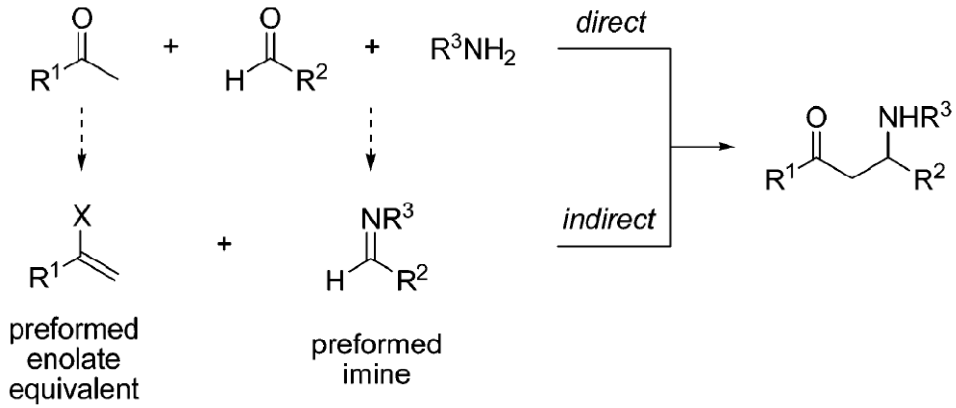
80%	88%	87%	81%
4:1 dr, 99% ee	3:1 dr, 97% ee	14:1 dr, 99% ee	3:1 dr, 99% ee

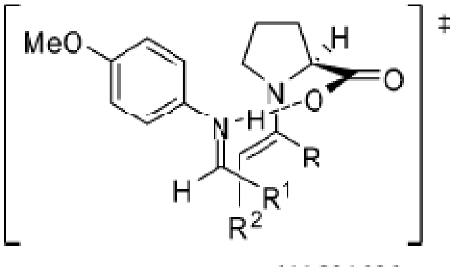


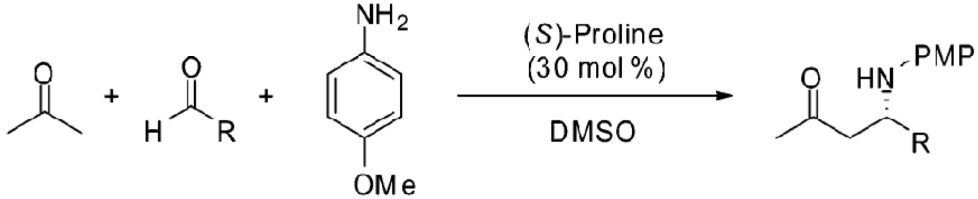
82%	80%	75%
24:1 dr, >99% ee	24:1 dr, 98% ee	19:1 dr, 91% ee

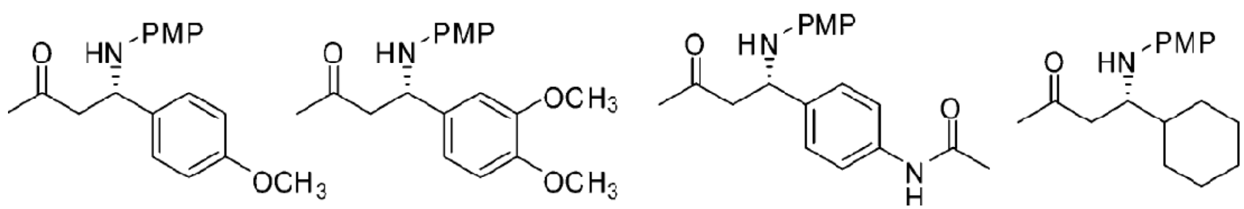
Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*,6798.

Direct and Indirect Mannich Reactions

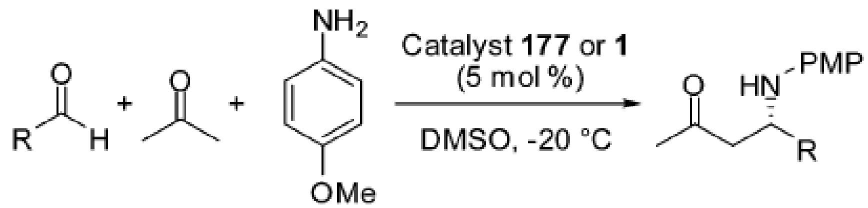


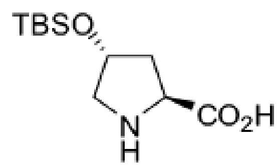




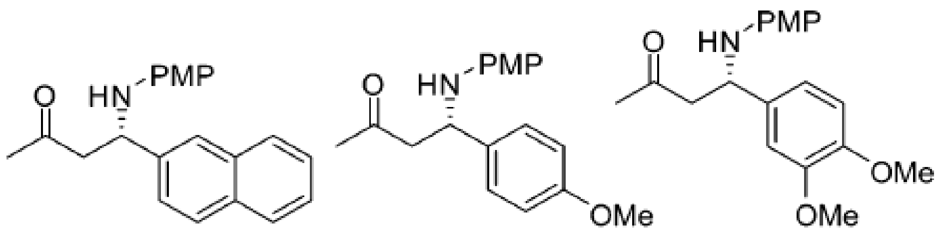


0.1 MPa, 23 °C, 96 h, 0%	0.1 MPa, 23 °C, 96 h, 0%	0.1 MPa, 23 °C, 24 h, 0%	0.1 MPa, 23 °C, 40 h, 23%, 4% ee
200 MPa, -20 °C, 96 h, 99%, 94% ee	200 MPa, -20 °C, 96 h, 65%, 95% ee	200 MPa, -20 °C, 24 h, 82%, 92% ee	200 MPa, -20 °C, 40 h, 90%, 84% ee





177 **1**

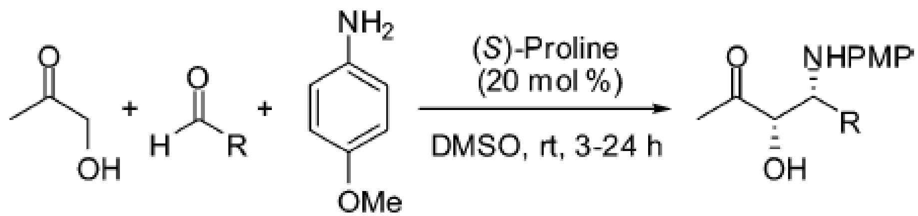


With **177**:	24 h, 62%, 93% ee	20 h, 55%, 90% ee	20 h, 48%, 98% ee
With **1**:	24 h, <5%, n.d ee	20 h, <5%, n.d ee	20 h, <5%, n.d ee

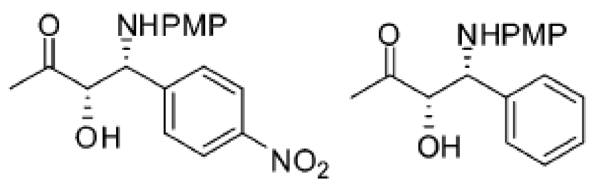
With electron-rich aldehydes, proline is generally inefficient for the direct cat. asymmetric Mannich reaction

- *trans*-4-siloxyproline is superior

"Asymmetric Aminohydroxylation"

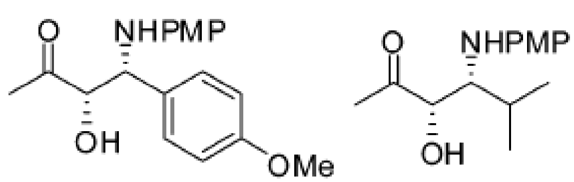


10 vol %   1 equiv   1.1 equiv



92%
20:1 dr, >99% ee

83%
9:1 dr, 93% ee

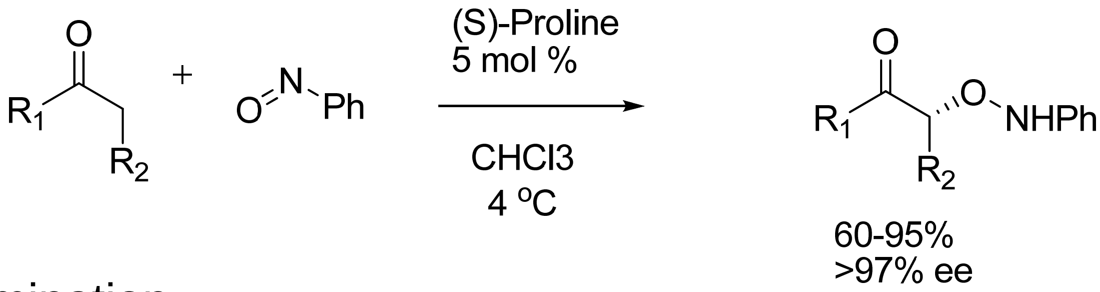


88%
3:1 dr, 61% ee

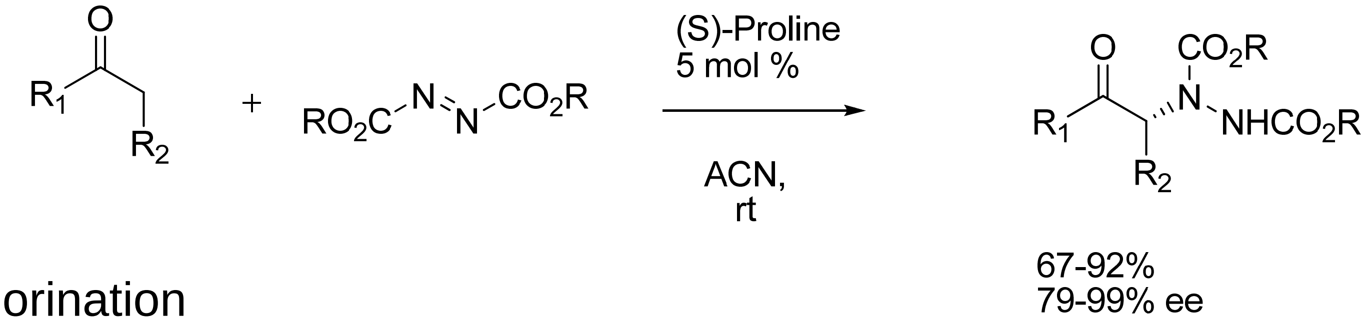
57%
17:1 dr, 65% ee

- Aliphatic branched aldehydes give lower yields and selectivities

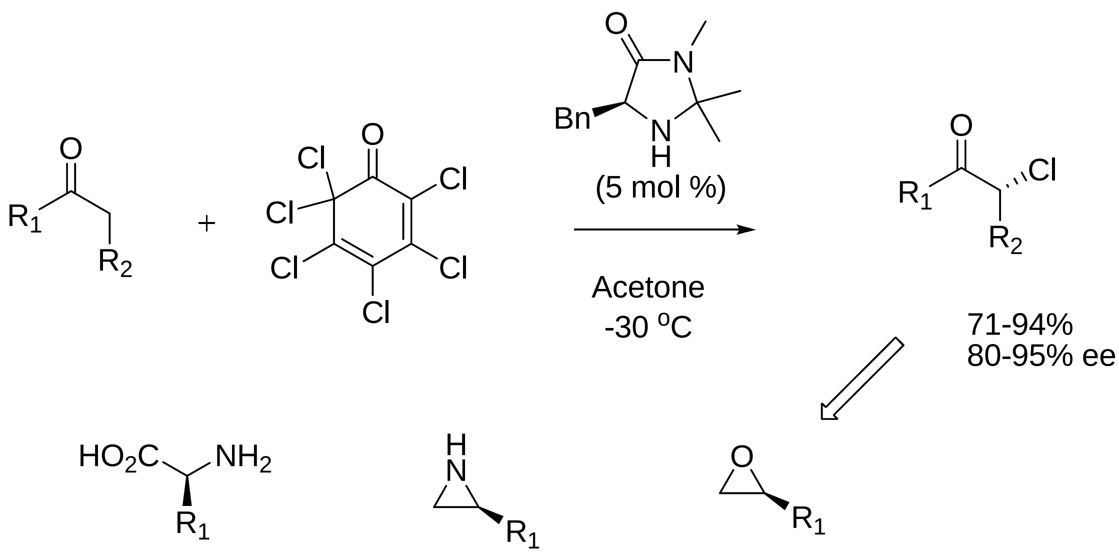
Oxygenation

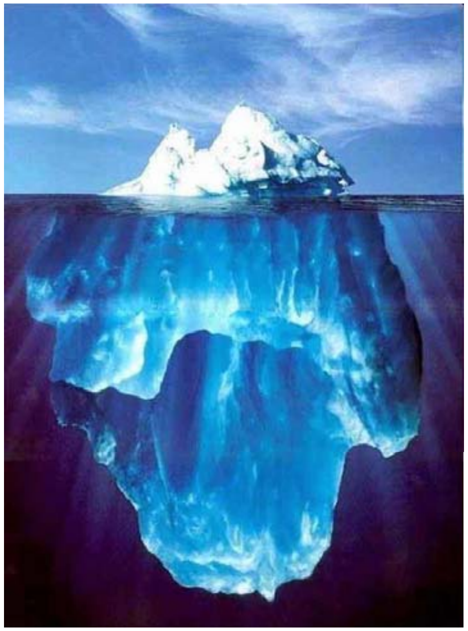


Amination



Chlorination





- Organocatalysis represents a powerful and diverse field
- However, remains an open field (“tip of the iceberg)”
- Complementary to metal-catalysis
- Huge potential from economical/environmental perspective

Drawbacks/ Future Work

- Need effifient, general an asymmetric synthesis of *syn*-aldol adducts
- Yields are variable (cross aldol)
- Catalysts are not entirely general
- Catalysts have become more complex than simple (S)-Pro
- Reactions sometimes need additional tayloring after the organocatalytic process
- Turnover numbers may be improved