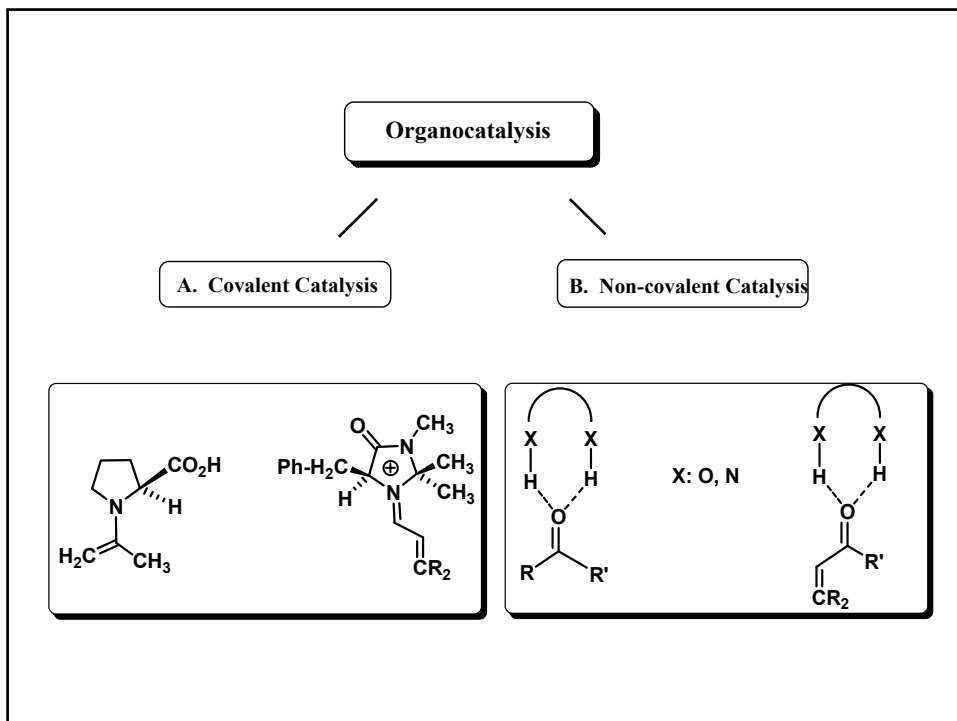


Organocatalysts Involving Enamine and Iminium Ion Intermediates

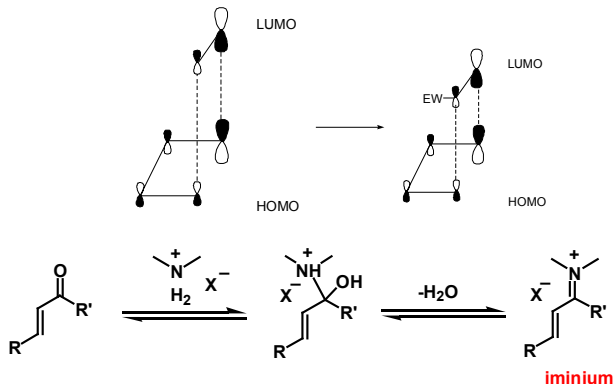
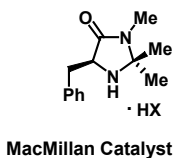
Chen Yuanyuan



History

The conception of **organocatalysis** is firstly proposed by MacMillan in 4+2 D-A reaction.

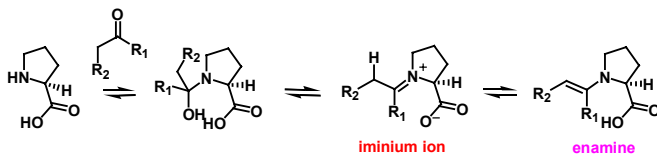
D. W. C. MacMillan



Content

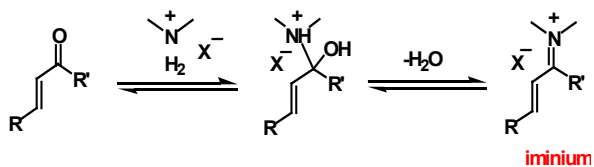
- Enamine catalysis of reactions

- Proline and analogs catalyzed reactions and mechanism research



- Iminium catalysis of reactions

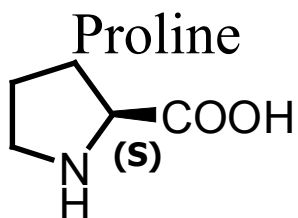
- MacMillan catalyst and derivatives catalyzed reactions and mechanism research



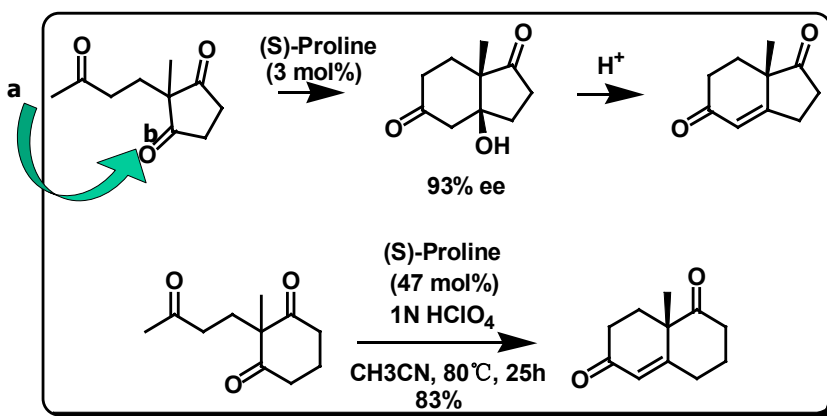
I . Enamine catalysis

Enamine catalyzed reactions and mechanism research

- Proline-catalyzed asymmetric aldol reaction
- Proline-catalyzed nucleophilic addition reactions
- Proline analogues-catalyzed reactions
- Other organic catalysis based on enamine mechanism



1. The proline-catalyzed asymmetric aldol reaction



Hajos-Parrish-Eder-Sauer-Wiechert Reaction

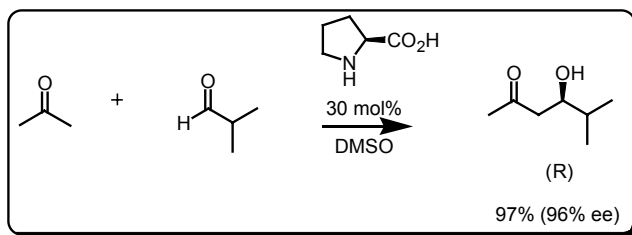
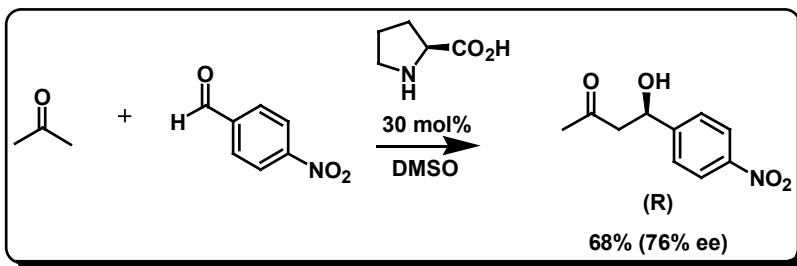
Important features of this reaction are the following:

- (1) Proline is the smallest enzyme.
- (2) Proline is nontoxic, inexpensive.
- (3) The reactions do not require inert conditions and are run at room temperature.
- (4) No prior modification is required.
- (5) The catalyst is water soluble.
- (6) The reactions may be run on an industrial scale.

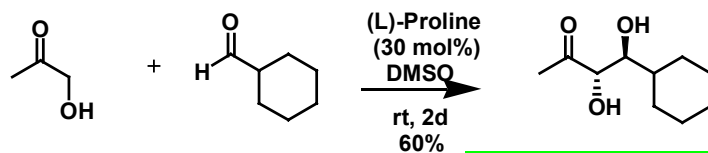
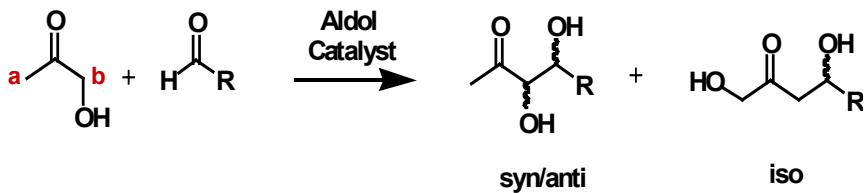
Intermolecular aldolizations

- Aldehyde to ketone
- Aldehyde to aldehyde
- Ketone to ketone
- Enolexo - aldolization

(1) Aldehyde to ketone



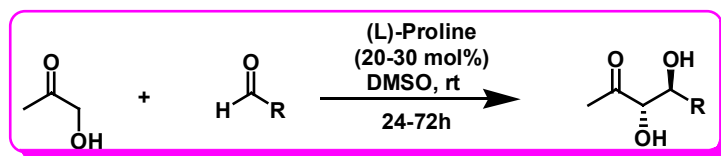
Catalytic Asymmetric Synthesis of *anti*-1,2-Diols



regioselectivity: >20:1
 diastereoselectivity: >20:1
 enantioselectivity: >100:1

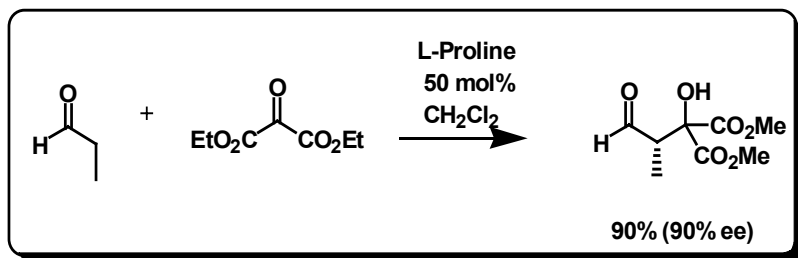
W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386.

Anti-Diols Synthesized Using the Proline-Catalyzed Aldol Reaction



Entry	Product	Yield(%)	dr	ee(%)
(1)		60	>20:1	>99
(2)		62	>20:1	>99
(3)		51	>20:1	>95

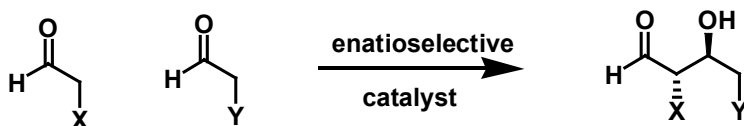
The use of aldehydes for the direct catalytic enantioselective aldol reaction compared with ketones



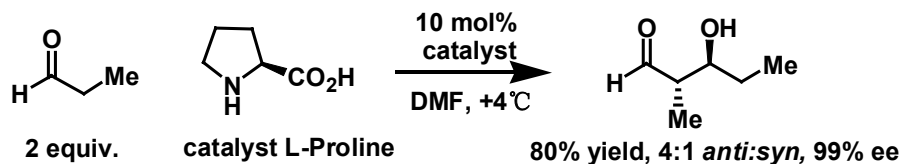
A. Bøgevig, N. Kumaragurubaran and K. A. Jørgensen, *Chem. Commun.*, 2002, 620–621.

(2) Aldehyde to aldehyde

Enantioselective Aldehyde Aldol: Elusive Transformation



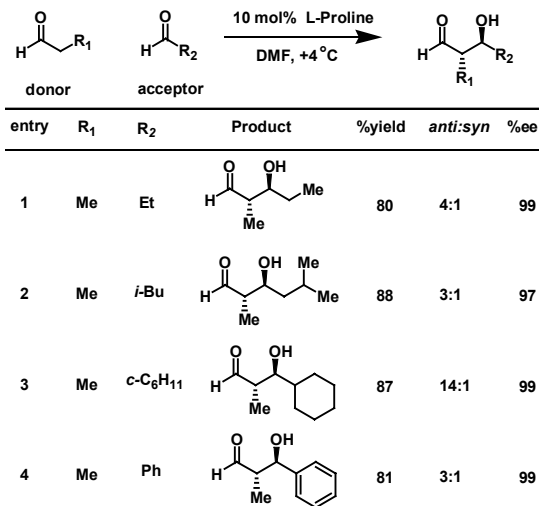
Proline Catalyzed Aldehyde Aldol Dimerization



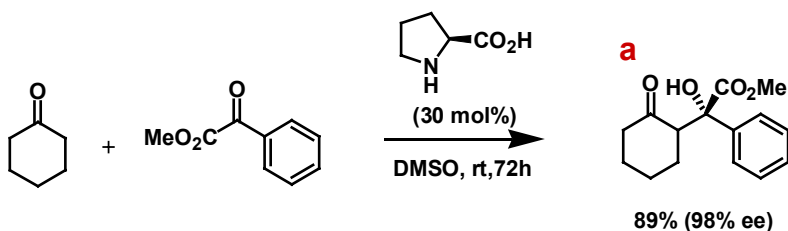
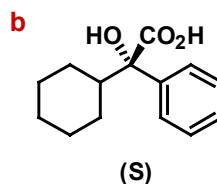
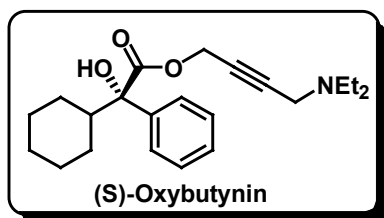
A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, 124, 6798–6799.

“ we have documented the first direct enantioselective catalytic aldol reaction using aldehydes as both the aldol donor and the aldol acceptor.”

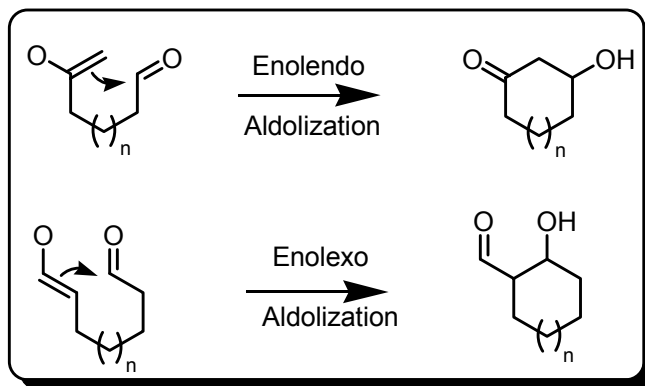
Enantioselective Direct Aldehyde Cross-Aldol Reaction

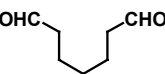
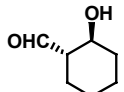
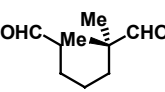
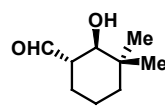
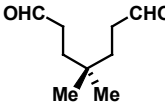
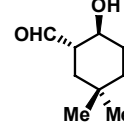


(3) ketone to ketone

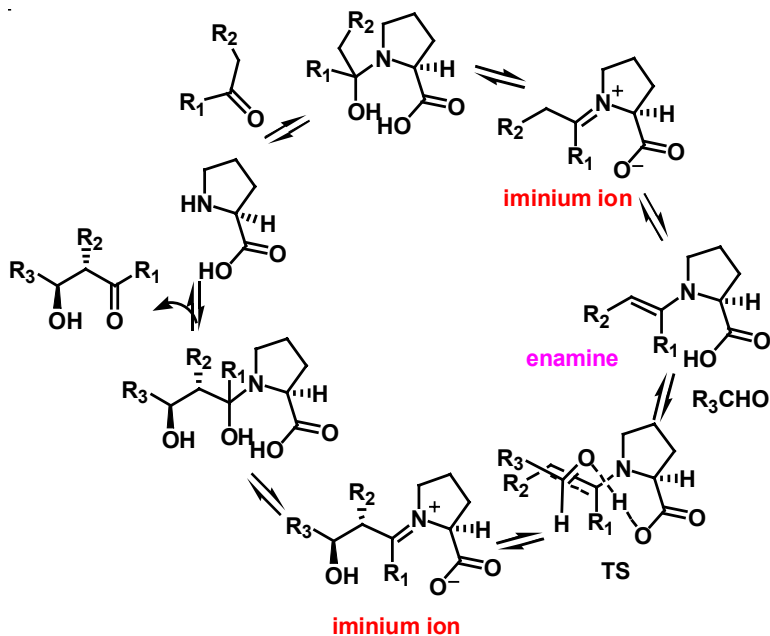
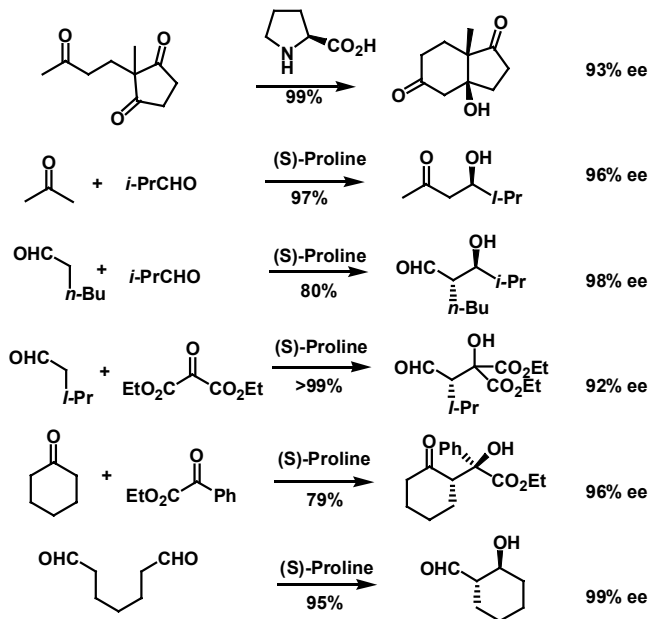


(4) enolexo-aldolization

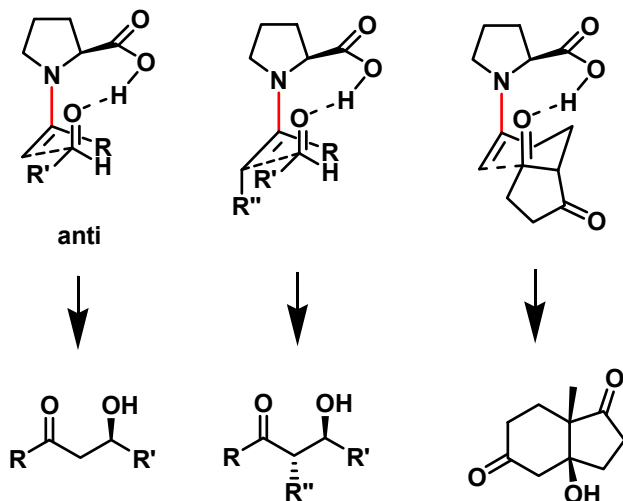
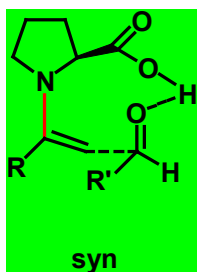


Dicarbonyl	Yield(%)	Products	ee[%]	d.r. [%]
	95		99	10:1
	74		98	>20:1
	75		97	>20:1

Summary of proline-catalyzed aldol reactions



Anti-enamine & Re-face attack

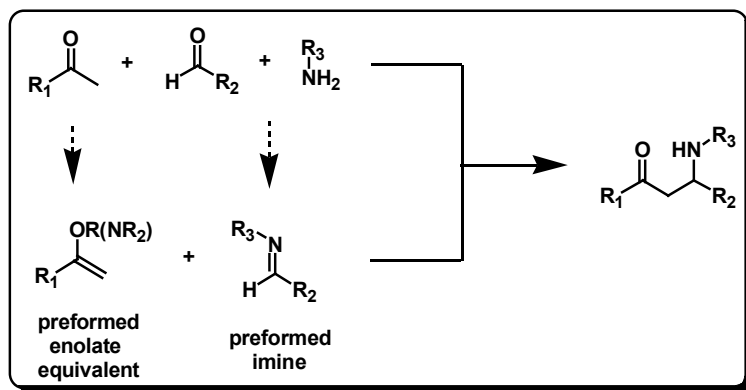


C. Allemann, R. Gordillo, F. R. Clemente, P. H. Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, 37, 558–569.

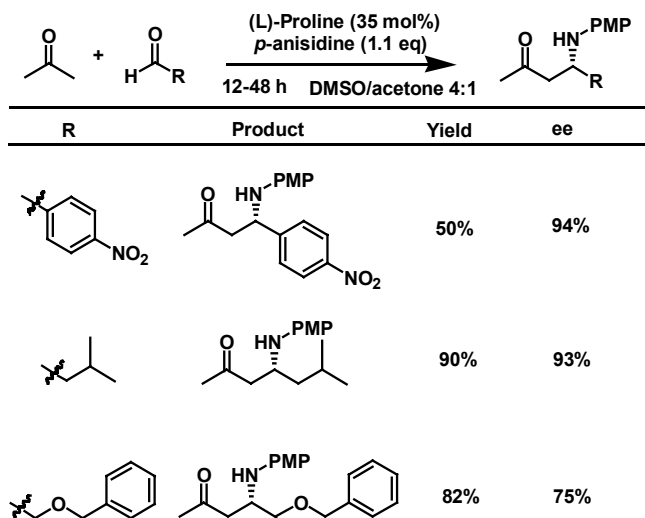
2. Proline catalysis of nucleophilic addition reactions

- Mannich reactions (C=N)
- Azodicarboxylates (N=N) & nitrosobenzene (O=N) reactions
- Michael addition reactions (C=C)

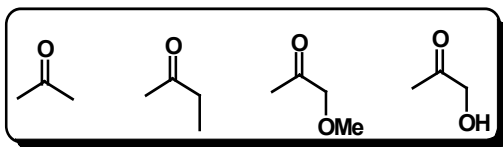
(1) Mannich reactions



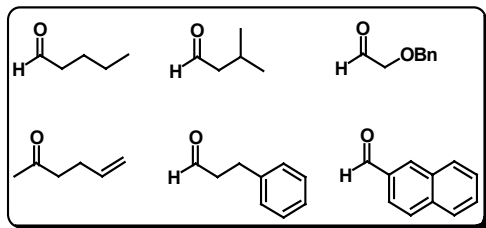
The Direct Catalytic Asymmetric Three-Component Mannich Reaction



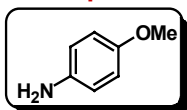
Ketone component



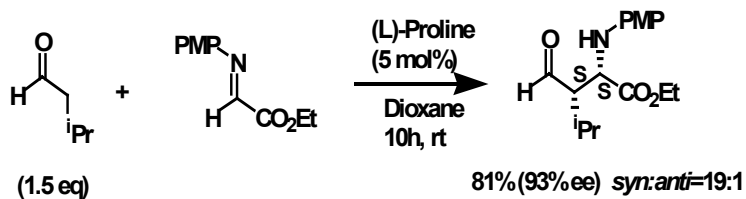
Aldehyde component



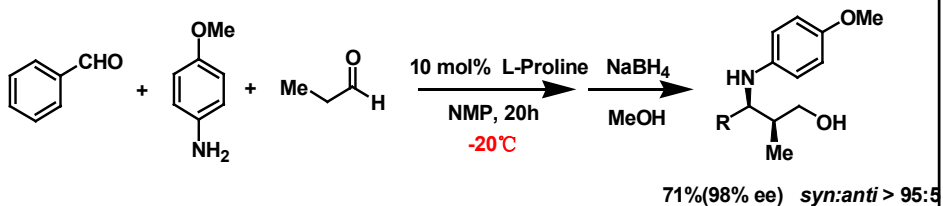
Amine Component



B. List, P. Pojarliev, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827–833.

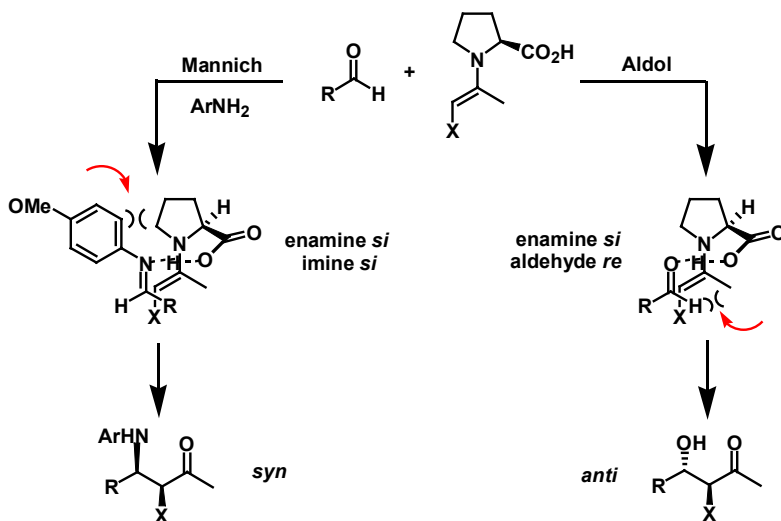


A. Cordova, S. Watanabe, F. Tanaka, W. Notz and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2002, **124**, 1866–1867.



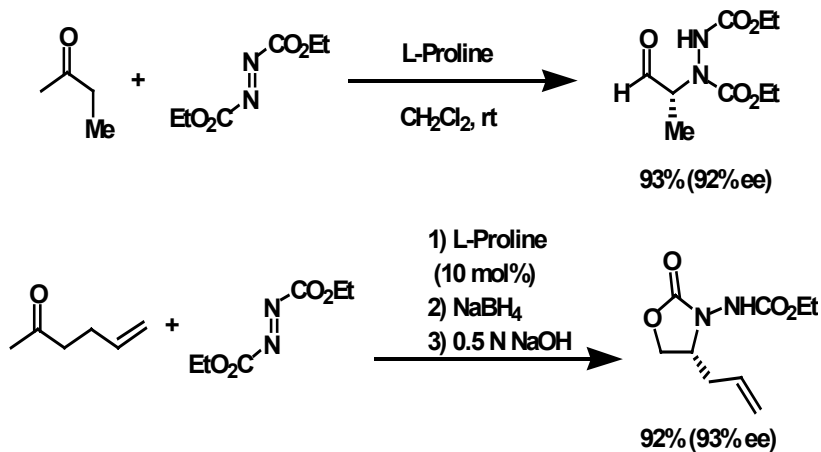
Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji and K. Sakai, *Angew. Chem., Int. Ed.*, 2003, **42**, 3677–3680;

Opposite Enantiofacial Selectivities and Topicities in Aldol and Mannich Transition States

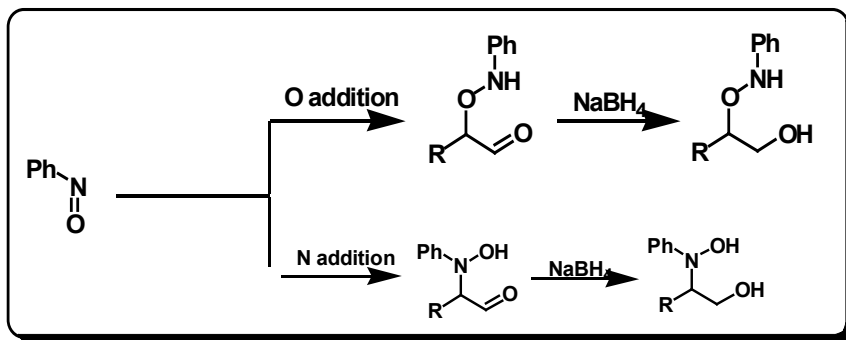


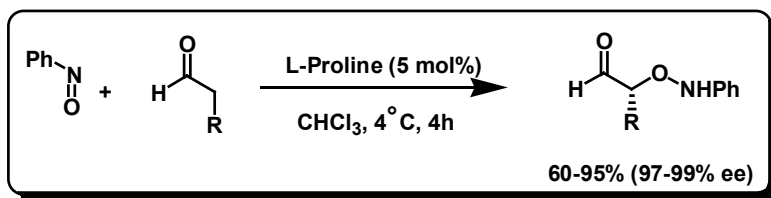
- Mannich reactions (C=N)
- Azodicarboxylates (N=N) & nitrosobenzene (O=N) reactions
- Michael addition reactions (C=C)

(2) azodicarboxylates(N=N) & nitrosobenzene (O=N) reactions

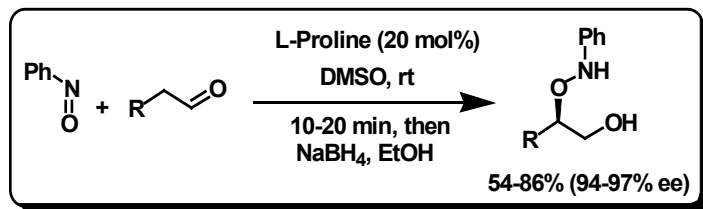


A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2002, 41, 1790–1793.





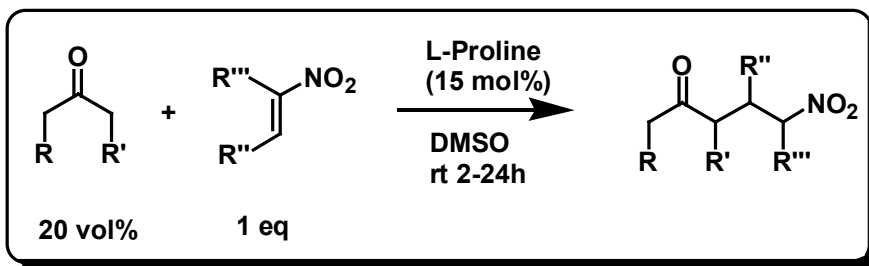
S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808–10809;



G. F. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247–4250;

- Mannich reactions (C=N)
- Azodicarboxylates (N=N) & nitrosobenzene (O=N) reactions
- Michael addition reactions (C=C)

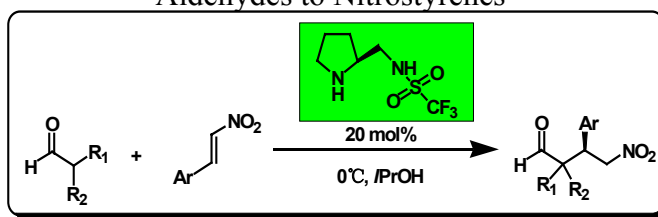
(3) Michael addition reactions



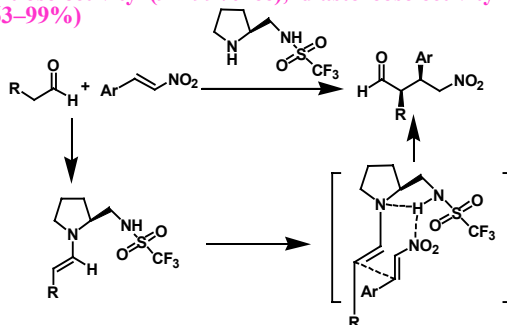
- Yields are typically excellent.
- Enantioselectivities (**ee**) are **poor**, but diastereoselectivities and regioselectivities are good.

B. List, P. Pojarliev and H. Martin, *J. Org. Lett.*, 2001, **3**, 2423–2425 ;

Pyrrrolidine Sulfonamide Catalyzed Michael Addition of Aldehydes to Nitrostyrenes

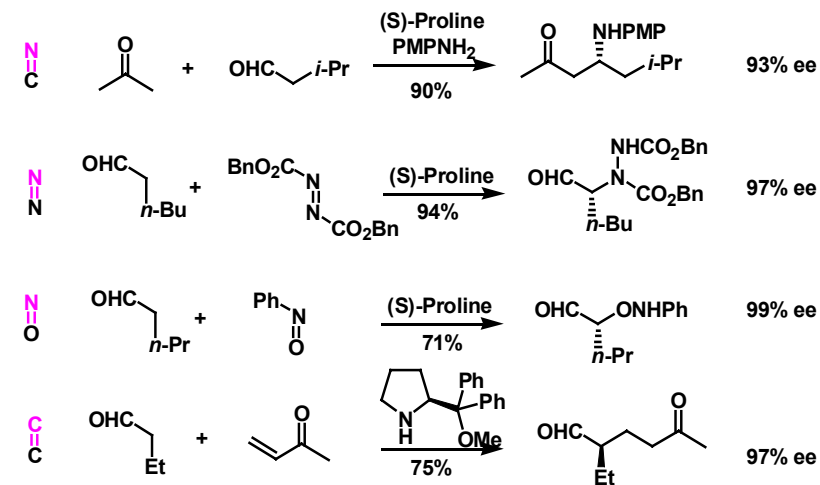


excellent enantioselectivity (94–99% ee), diastereoselectivity (≥20:1 d.r.), and high yields (63–99%)



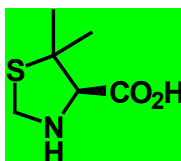
W. Wang, J. Wang and H. Li, *Angew. Chem., Int. Ed.*, 2005, **44**, 1369–1371;

Summary of proline catalysis of nucleophilic additions



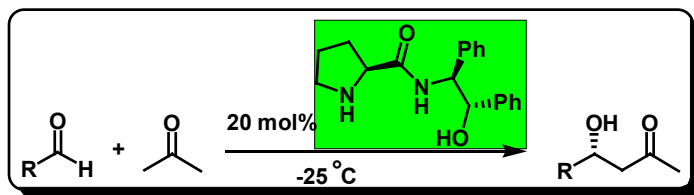
3. Proline analogues catalysis based on enamine mechanism

(1) Proline analogues catalysis of aldol reaction



5,5-dimethyl thiazolidinium
-4-carboxylate (DMTC)

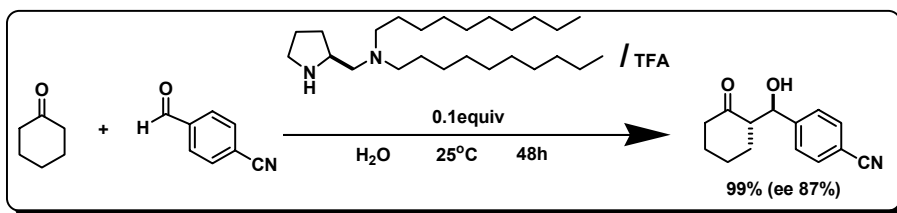
Product	Catalyst	Yield	ee
	DMTC	60%	86%
	(L)-Pro	68%	76%
	DMTC	60%	88%
	(L)-Pro	54%	77%
	DMTC	60%	89%
	(L)-Pro	62%	60%



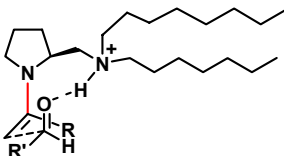
entry	R	yield(%)	ee(%)
1	4-NO ₂ Ph	66	93
2	4-BrPh	77	90
3	4-ClPh	75	93
4	c-C ₆ H ₁₁	85	97
5	<i>i</i> -Pr	43	98
6	<i>t</i> -Bu	51	>99

Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang and Yun-Dong Wu, *J. Am. Chem. Soc.*, 2003, 125, 5262-5263.

Organocatalytic Direct Asymmetric Aldol Reactions in Water



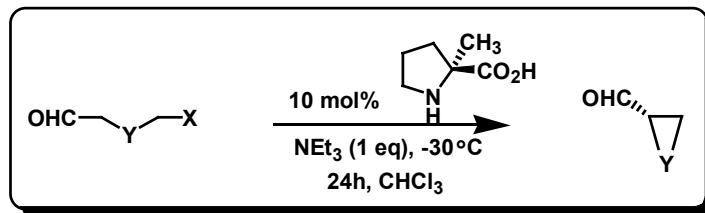
amine-acid bifunctional catalyst



N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, and C. F. Barbás, *J. Am. Chem. Soc.*, 2006, 128, 734-735

(3) Proline analogue catalysis of nucleophilic substitution reactions

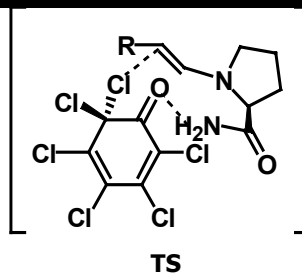
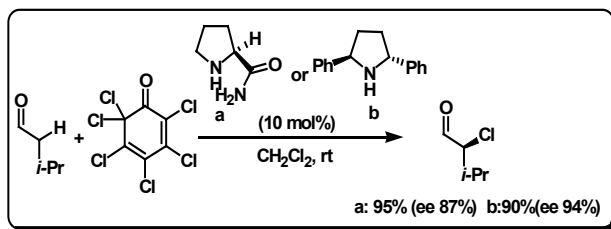
1. Enantioselective Organocatalyzed α -Alkylation of Aldehydes



Substrate	Product	Yield(%)	ee(%)
 (X=I)		92	95
X=Br		90	94

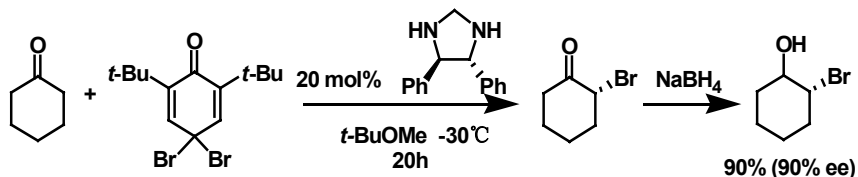
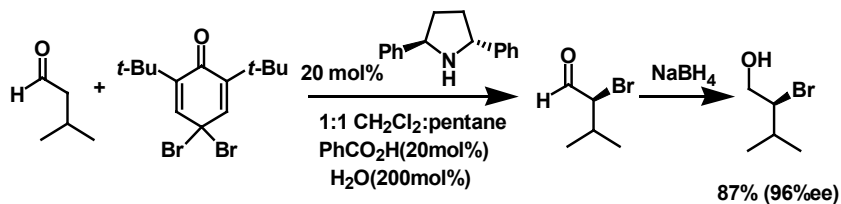
Nicola Vignola and B. List, *J. Am. Chem. Soc.*, 2004, **126**, 450-451;

2. Enantioselective Organocatalyzed α -chlorination of Aldehydes



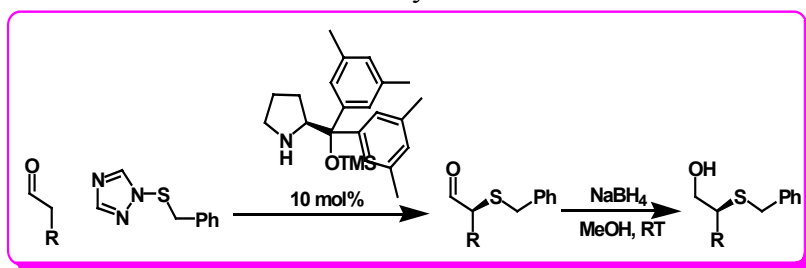
N. Halland, A. Braunton, S. Bachmann, M. Marigo and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 4790-4791.

3. Enantioselective Organocatalyzed α - bromination of Aldehydes



S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton and K. A. Jørgensen, *Chem. Commun.*, 2005, 4821–4823.

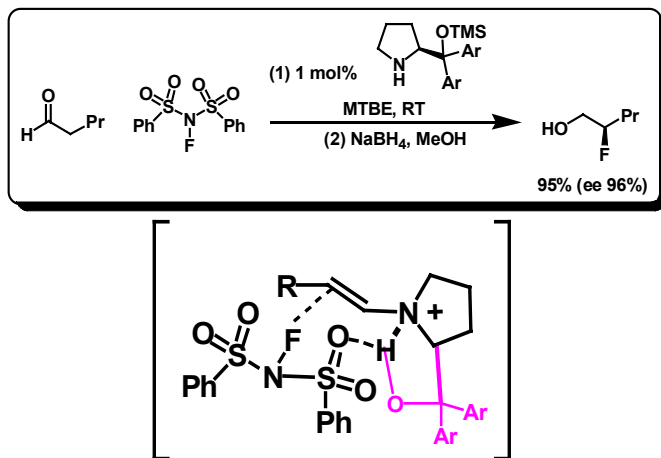
4. Enantioselective Organocatalyzed α - Sulfonylation of Aldehydes



R	Yield (%)	ee (%)
<i>i</i> -Pr	81	98
Me	60	95
Et	85	96
Bn	94	97
allyl	64	96

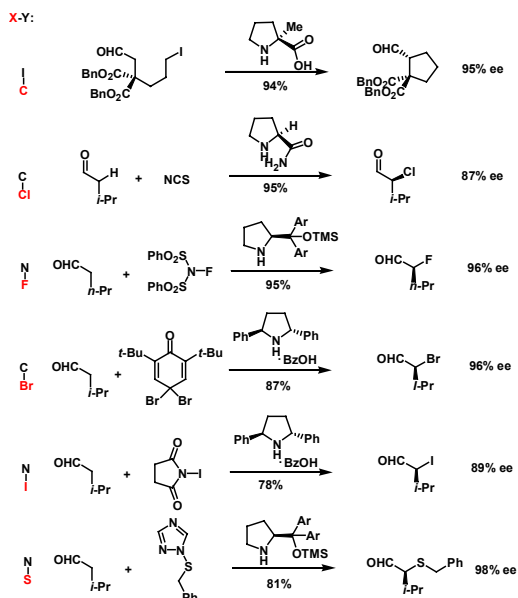
M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, 44, 794.

5. Enantioselective Organocatalytic α - Fluorination of Aldehydes

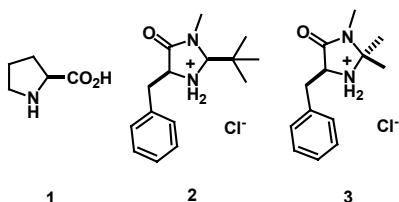
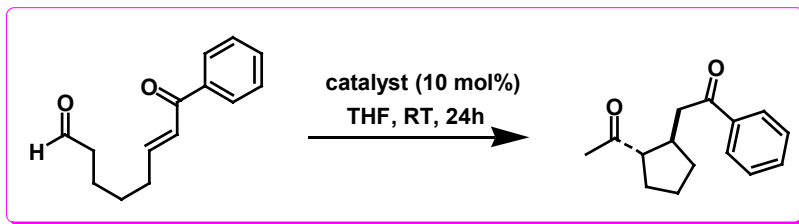


D. D. Steiner, N. Mase and C. F. Barbas, III., *Angew. Chem., Int. Ed.*, 2005, **44**, 3706–3710;

Summary of proline analogue catalysis of nucleophilic substitution reactions



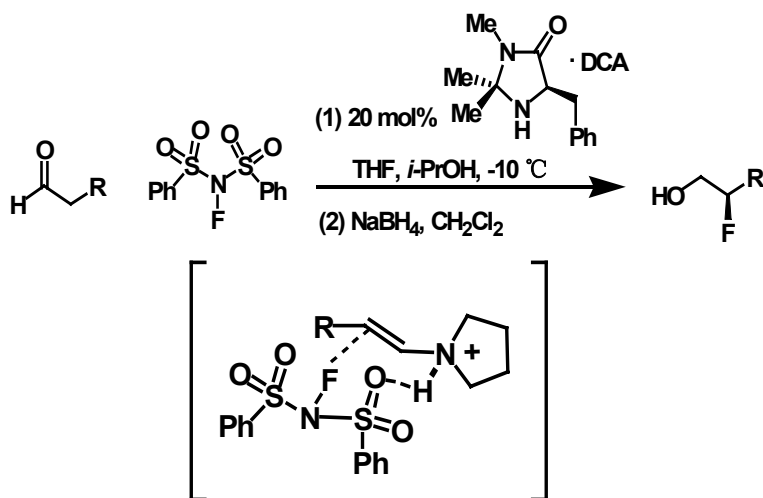
4. Other organic catalysis based on enamine mechanism



Cat.	Yield	d.r.(anti/syn)	ee(anti)
1	85%	2:1	15%
2	99%	19:1	39%
3	99%	24:1	97%

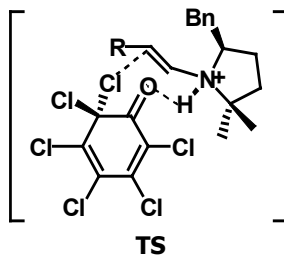
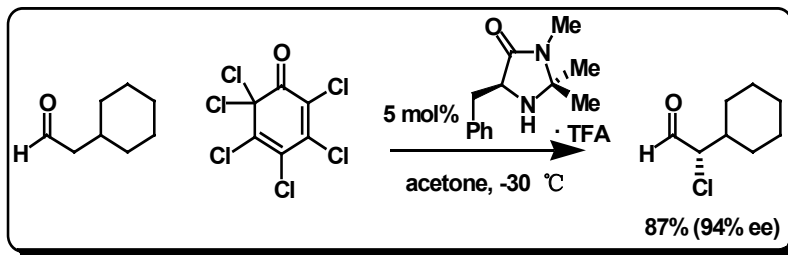
M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 3958–3960;

Enantioselective Organocatalytic α - Fluorination of Aldehydes



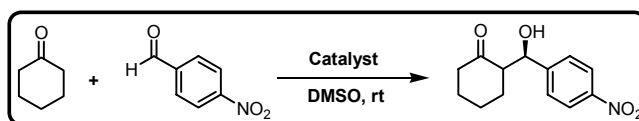
T. D. Beeson and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 8826–8828;

Enantioselective Organocatalyzed α -chlorination of Aldehydes



M. P. Brochu, S. P. Brown and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2004, **126**, 4108–4109;

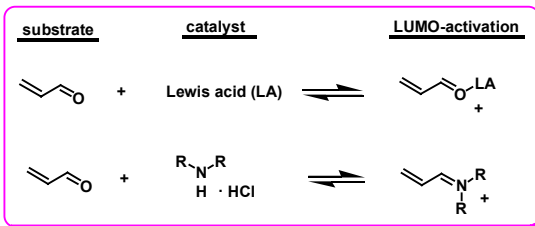
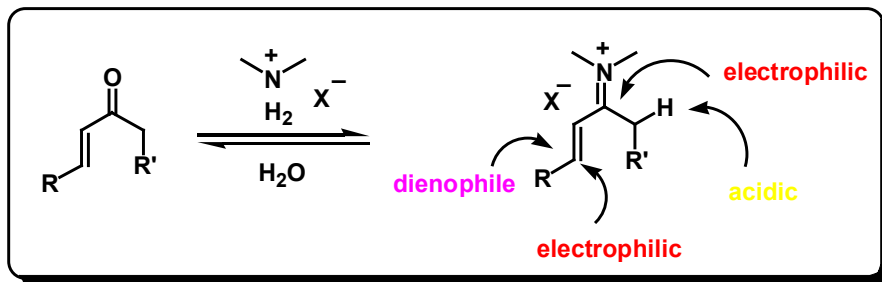
Acyclic amino acid-catalyzed asymmetric aldol reaction



Entry	Catalyst	Yield(%)	dr	ee(%)
1	L-Alanine	95	15:1	99
2	L-Aminobutyric acid	88	6:1	92
3	L-Valine	98	37:1	99
4	L-Norvaline	79	6:1	90
5	L-Alaninol	91	1:2	46
6	L-Arginine	62	1:1	4
7	L-Aspartate	75	5:1	99
8	(R)-Methylbenzylamine	94	1:15	24
9	L-Isoleucine	82	10:1	99
10	L-Serine	80	6:1	99

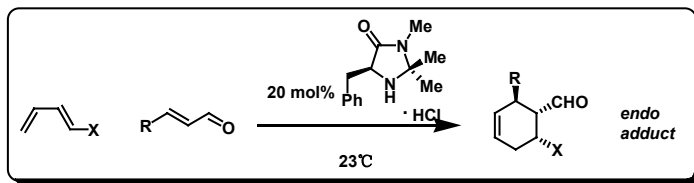
A. Cordova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist and W. Liao, *Chem. Commun.*, 2005, 3586-3588.

II. Iminium catalysis



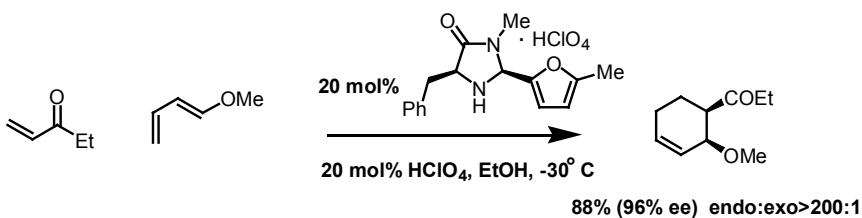
- Diels – Alder Reactions (4+2)
- 1,3-Dipolar Cycloaddition Reactions (3+2)
- Friedel-Crafts Alkylation Reactions
- Epoxidation Reactions
- Cyclopropanation Reactions
- Conjugate Reduction Reactions

1. The First Highly Enantioselective Organocatalytic Diels-Alder Reaction

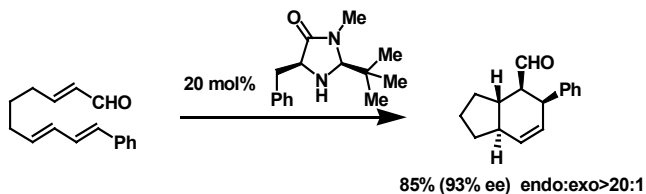


entry	diene	R	product	%yield	exo:endo	%ee
1		Me		75	35:1	96
2		H		82	1:14	94

K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243–4244.

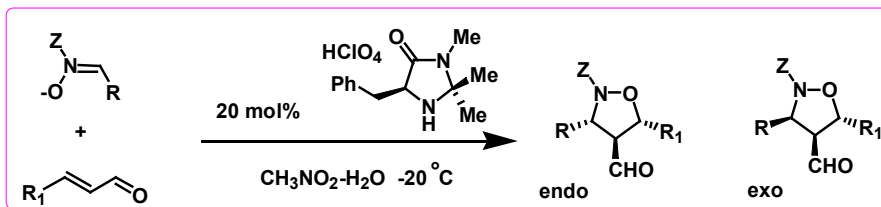


A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 2458–2460.



R. M. Wilson, W. S. Jen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 11616–11617;

2. The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition

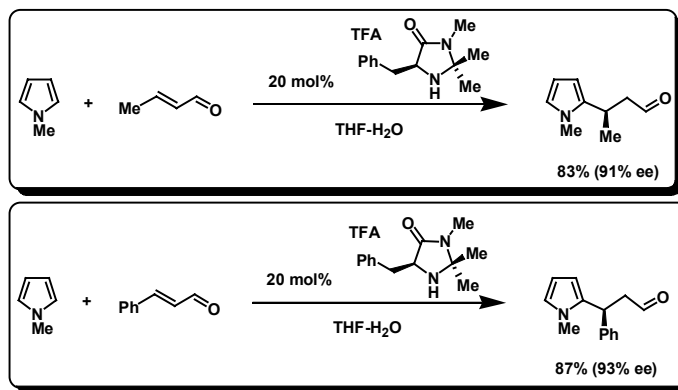


entry	Z	R	R ₁	endo:exo	yield	%ee(endo)
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99

W. S. Jen, J. J. M. Wiener and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 9874–9875.

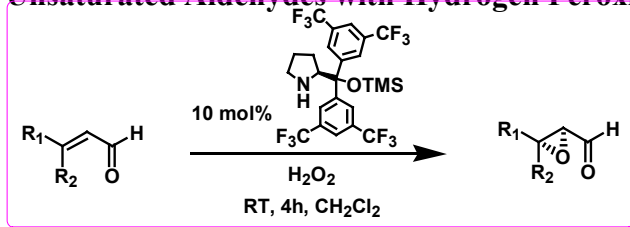
- Diels – Alder Reactions (4+2)
- 1,3-Dipolar Cycloaddition Reactions (3+2)
- Friedel-Crafts Alkylation Reactions
- Epoxidation Reactions
- Cyclopropanation Reactions
- Conjugate Reduction Reactions

3. The First Enantioselective Organocatalytic Friedel-Crafts Alkylation



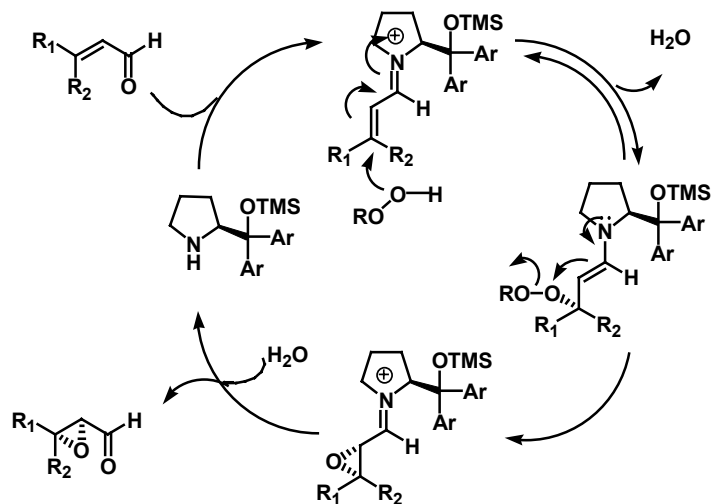
N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370–4371;

4. Asymmetric Organocatalytic Epoxidation of α,β -Unsaturated Aldehydes with Hydrogen Peroxide



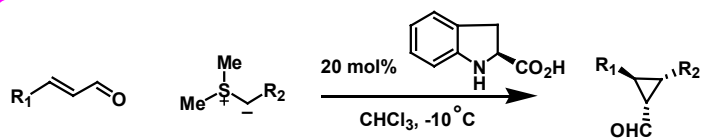
R ₁	R ₂	yield(%)	dr	ee(%)
Ph	H	80	93:7	96
<i>o</i> -NO ₂ -Ph	H	90	91:9	97
<i>o</i> -Me-Ph	H	65	90:10	96

M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964–6965.

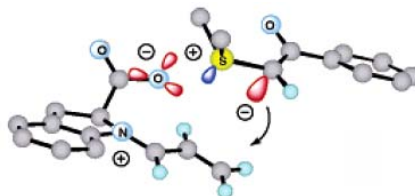
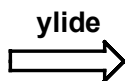
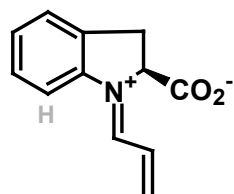


Mechanistic Proposal for the Organocatalytic Epoxidation of α, β -Unsaturated Aldehydes with Peroxides

5. Enantioselective Organocatalytic Cyclopropanations.



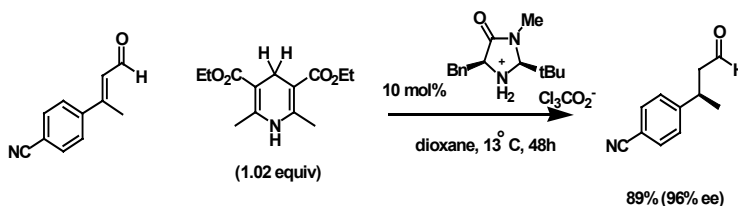
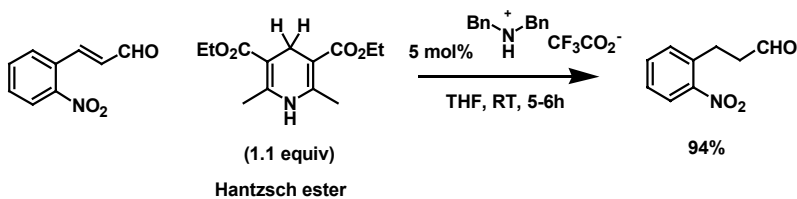
R ₁	R ₂	product	% yield	dr	% ee
Propyl	COPh		85	30:1	95
CH ₂ OAllyl	COPh		77	21:1	91
Propyl	COPhp-Br		67	72:1	92



van der Waals forces lead to selective (Z)-iminium formation

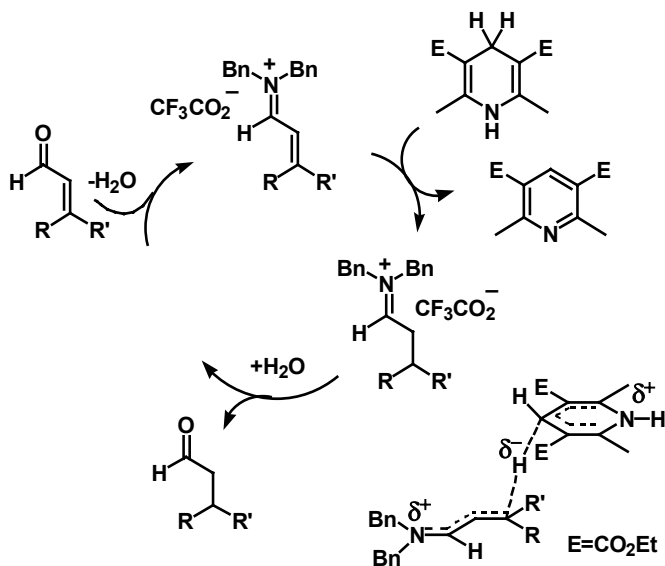
retain electrostatic activation
 good reactivity, high %ee

6. Transfer Hydrogenation: Organocatalytic Conjugate Reduction of α,β -Unsaturated Aldehydes

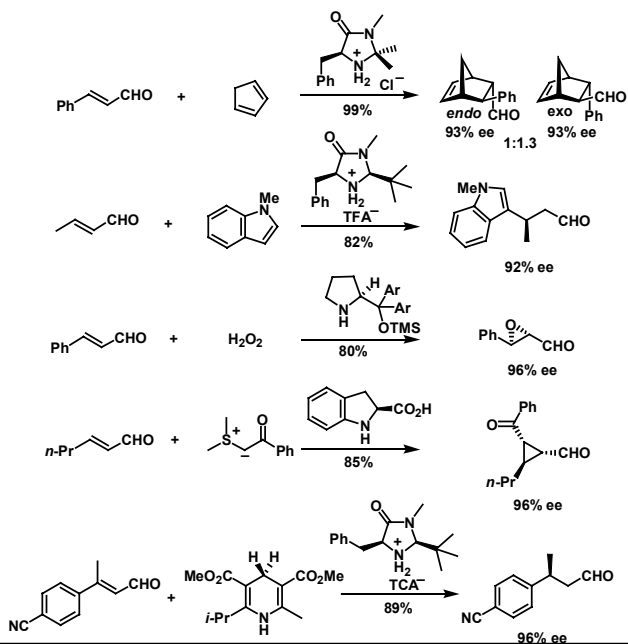


W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660–6662;

W. Yang, M. T. Hechavarria Fonseca, Nicola Vignola, and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108-110.

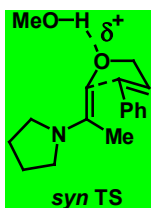
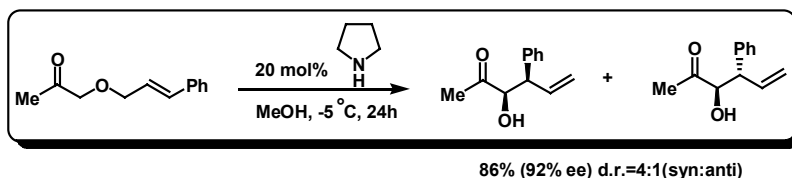


Summary of asymmetric iminium catalysis



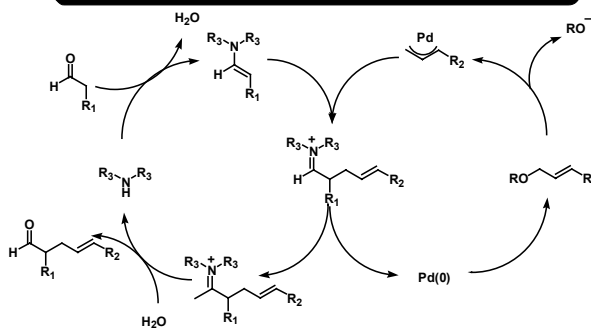
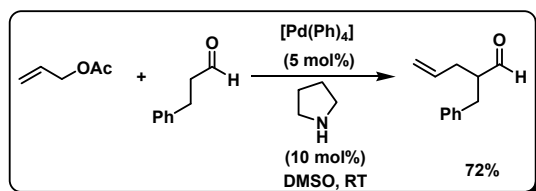
Outlook

1. [2,3] Wittig Rearrangement through Amine Catalysis



A. McNally, B. Evans, and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2006, **45**, ASAP.

2. Intermolecular α -Allylic Alkylation of Aldehydes by Combination of Transition-Metal and Organocatalysis



I. Ibrahem and A. Crdova, *Angew. Chem. Int. Ed.*, 2006, **45**, 1952–1956

Summary

- Enamine catalysis
 - proline
 - proline analogues
 - other organic catalysts
- Iminium catalysis
 - MacMillan catalyst and derivatives

Acknowledgment

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