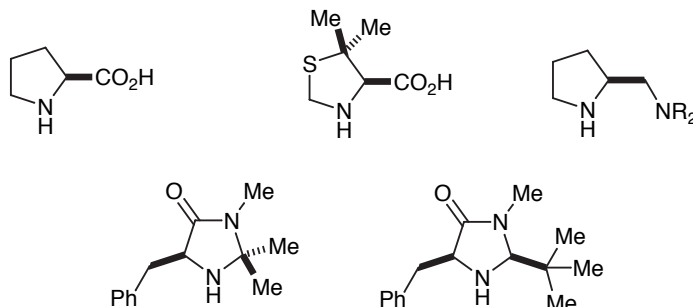


# Asymmetric Organocatalysis Using Chiral Amines

## Contents:

Background  
Aldol reactions  
Mannich reactions  
Amination/Oxidation reactions  
Michael reactions  
Cycloaddition reactions  
Alkylation reactions



An Evans Group Friday Seminar

Jonathan Lawrence

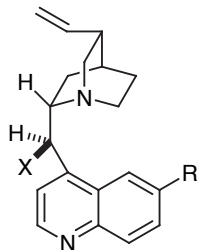
November 14<sup>th</sup> 2003

## Revent Reviews:

List, B. "Proline Catalyzed Asymmetric Reactions", *Tet.* **2002**, *58*, 5573-5590  
Miller, S. "Amino Acids and Peptides as Asymmetric Organocatalysts", *Tet.* **2002**, *58*, 2481-2495  
List, B. "Asymmetric Aminocatalysis", *Synlett* **2001**, *11*, 1675-1686  
Dalko, P. "Enantioselective Organocatalysis", *ACIEE* **2001**, *40*, 3726-3748

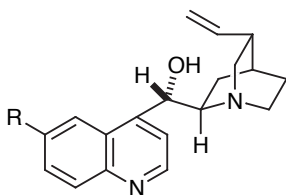
## Other Chiral Amines

### Cinchona alkaloids:

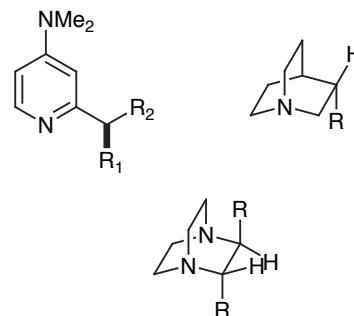


R = OMe, X = OH [(-)-quinine]  
R = H, X = OH [(-)-cinchonidine]

### The "nucleophilic" catalysts



R = OMe [(+)-quinidine]  
R = H [(-)-cinchonine]



## Reviews:

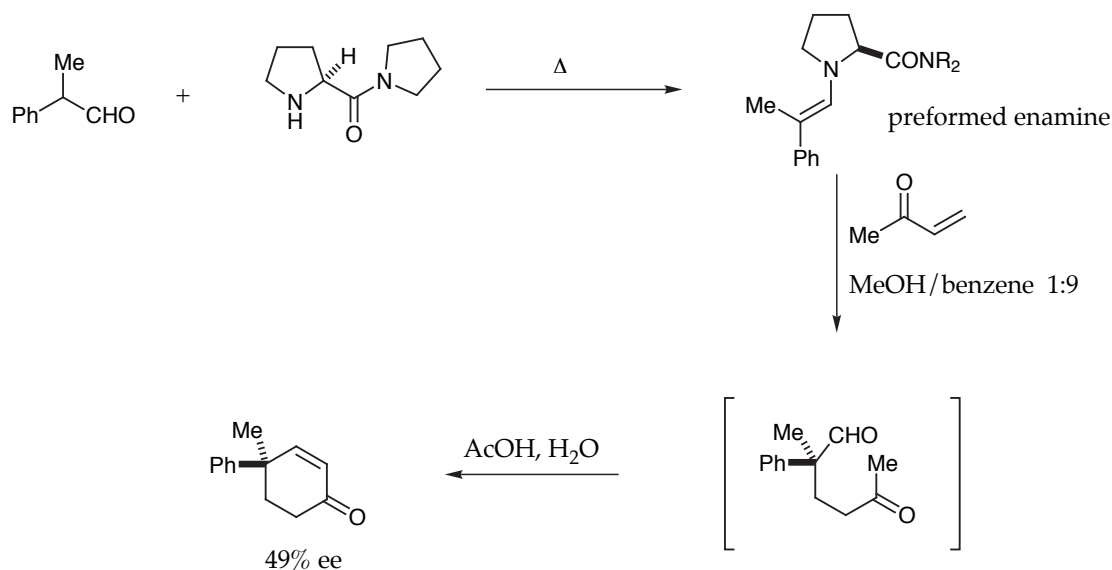
Pracejus, H. *Fortschr. Chem. Forsch.* **1967**, *8*, 493.  
Morrison, J., Mosher, H. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, **1971**.  
Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

## Relevant Group Seminars:

Karl Scheidt, *Asymmetric Catalysis with Chiral Lewis Bases (Part I)*, March 2001  
Hemaka Rajapakse, *Nonmetal-Based Asymmetric Catalysis (Part II)*, March 2001  
Essa Hu, *Asymmetric Catalysis with Chiral Lewis Bases (Part III)*, March 2001  
Jake Janey, *Asymmetric Catalysis with Chiral Lewis Bases (Part IV)*, March 2001

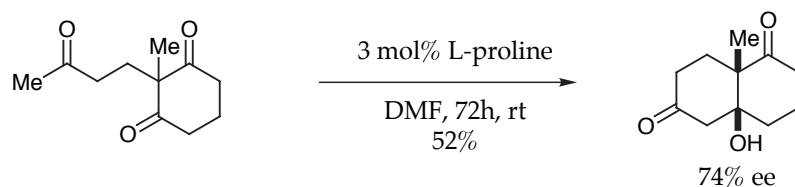
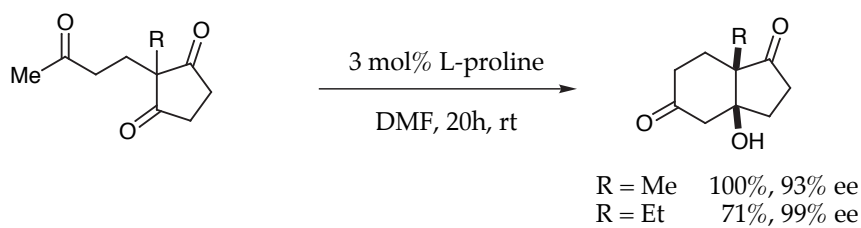
## Preliminary Findings

Yamada, 1969:



Yamada, S. *TL* **1969**, *10*, 4237.

## The Seminal Experiments

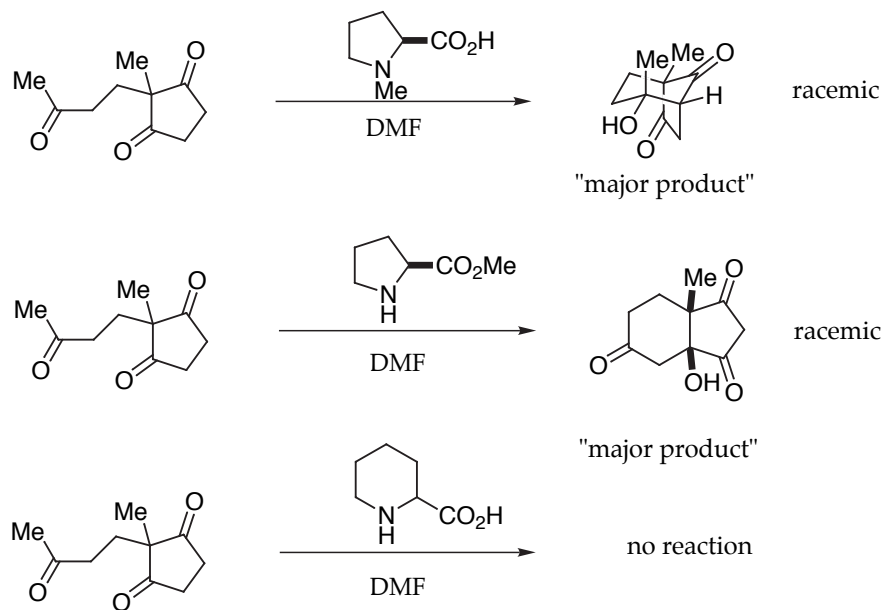


- ♦ the use of protic solvents severely diminishes enantioselectivity
- ♦ other amino acids as catalysts lead to decreased chemical yield and enantioselectivity
- ♦ Eder, Sauer, and Weichert obtained the corresponding aldol condensation products in similar optical purity using 47 mol% L-proline and 1N HClO<sub>4</sub>

Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.

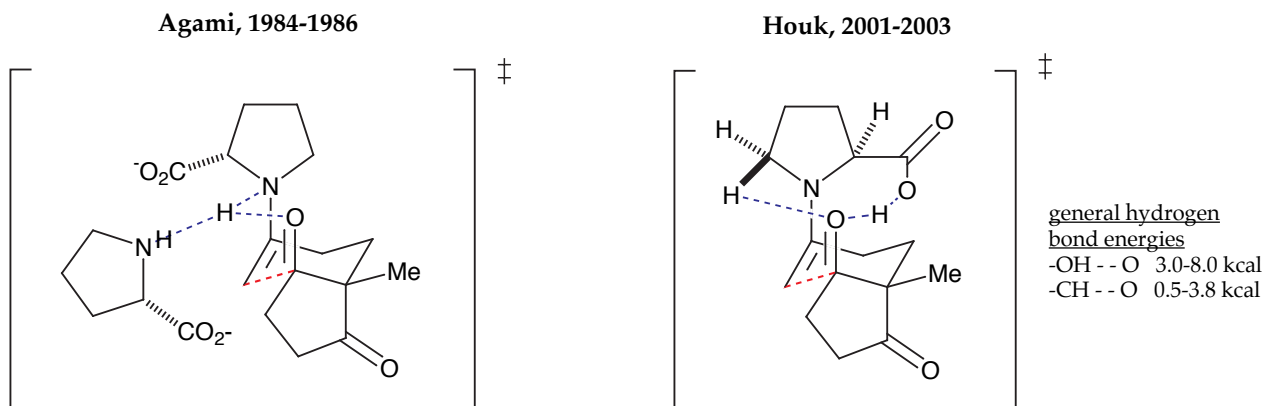
Eder, U., Sauer, G., Weichert, R. *ACIEE* **1971**, *10*, 496.

## Effect of the Catalyst



Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.

## Transition States



- ♦ favorable (enamine) N-H---O hydrogen bond
- ♦ N-H *anti* to carboxylate electrostatically favored
- ♦ reaction is second-order in proline (non-linear effect observed)
- ♦ second proline acts as a proton shuttle, allowing enamine to be nucleophilic

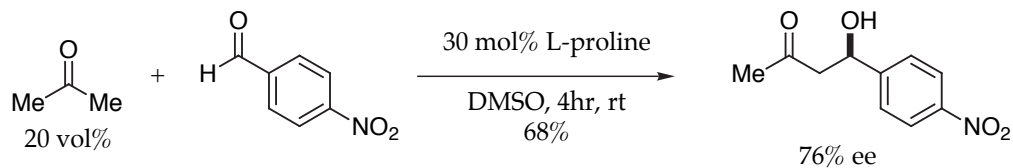
Agami, C. *TL* **1986**, *13*, 1501.  
 Houk, K. *JACS* **2001**, *123*, 12911.  
 Houk, K., List, B. *JACS* **2003**, *125*, 16.

- ♦ N-H---O hydrogen bond does not lower energy of transition state
- ♦ favorable O-H---O hydrogen bond
- ♦ additional NC-H---O hydrogen bond further stabilizes system
- ♦ reaction is first order in proline (supported by kinetic data) and no non-linear effect observed

for a discussion on  $R_3N^+-C-H\cdots O=C$  bonds, see:  
 Houk, K. *JACS*, **2002**, *124*, 7163.

## Direct Aldol Addition 1

The initial reaction:



Catalyst screen:

(selected examples)

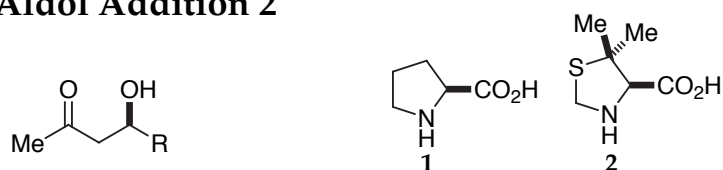
compound	% yield	% ee	compound	% yield	% ee
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	< 10	--		67	73
	55	40		85	78
	< 10	--		> 50	-62
				66	86 *

List, B., Barbas, C. *JACS*, **2000**, *122*, 2395-2396  
\*Barbas, C. *JACS*, **2001**, *123*, 5260-5267

## Direct Aldol Addition 2

Substrate scope:

variation of the aldehyde



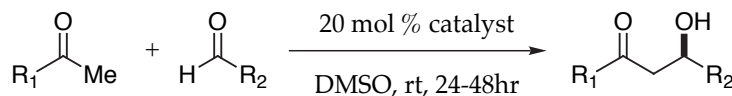
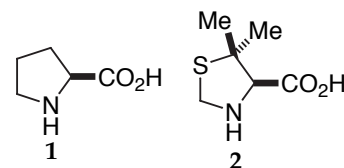
product R =	cat.	% yield	% ee	product R =	cat.	% yield	% ee
	1	68	76		1	94	69
	2	60	86		2	71	74
	1	62	60		1	54	77
	2	60	89		2	60	88
	1	74	65		1	97	96
	2	65	67		2	61	94

- DMTC 2 is catalyst of choice for aromatic aldehydes, although chemical yield decreases due to slower rate of reaction
- $\alpha$ -unbranched aldehydes yield no appreciable amount of product with proline catalyst 1 due to enolization and self-aldolization under reaction conditions (DMSO/acetone = 4:1)

List, B. *JACS*, **2000**, *122*, 2395.  
Barbas, C. *JACS*, **2001**, *123*, 5260.

## Direct Aldol Addition 3

Substrate scope:  
variation of the ketone donor

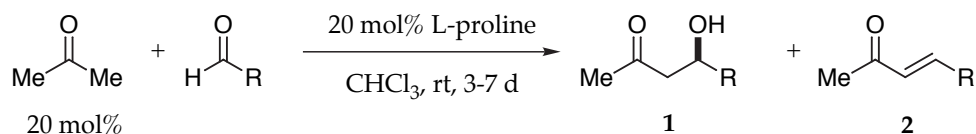


product R =	cat.	% yield	% ee
	1	65	77
	2	57	74
	1	60	80
	2	<5	---
	1	<i>syn</i> 24	67
	1	<i>anti</i> 35	90
	2	<i>syn</i> 21	69
	2	<i>anti</i> 41	89

Barbas, C. *JACS*, 2001, 123, 5260.

## Direct Aldol Addition 4

Substrate scope:  
use of  $\alpha$ -unbranched aldehydes



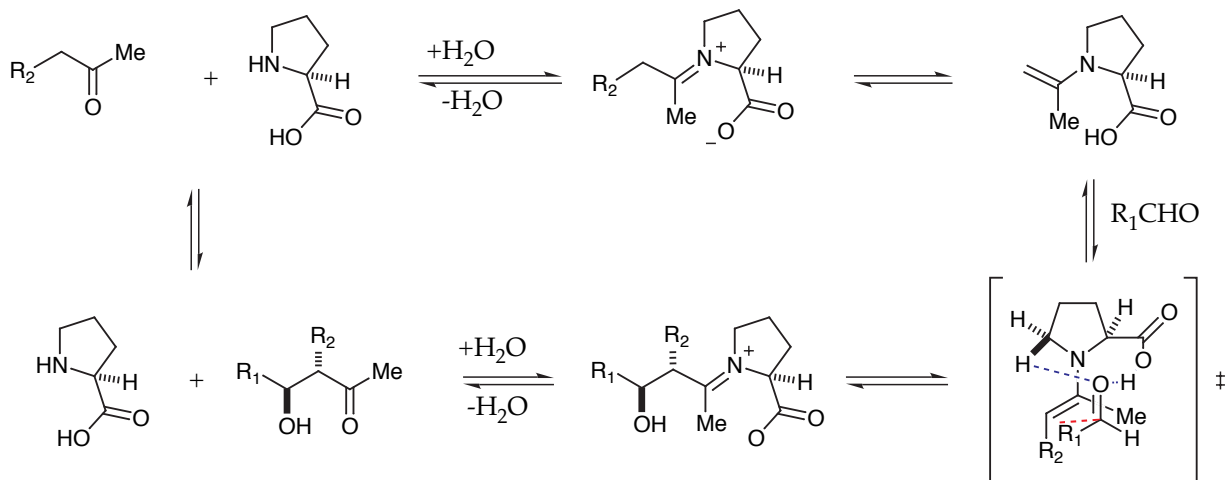
product R =	% yield 1	% yield 2	% ee
	29	0	70
	31	38	67*
	35	40	73*
	34	35	72
	23	46	61
	34	42	73*
	22	50	36

\* reaction performed neat in acetone

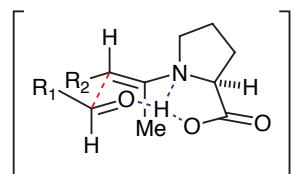
- use of cyclic ketones (cyclopentanone, cyclohexanone) result in moderate yield and diastereoselectivity, and up to 95% ee
- enone products arise from a Mannich addition-elimination sequence

List, B. *OL* 2001, 3, 573.

## Direct Aldol Reaction Mechanism



previously proposed T.S.:  
metal-free Zimmerman-Traxler model



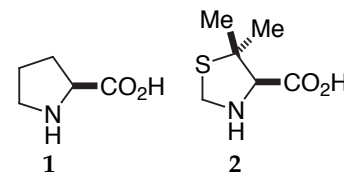
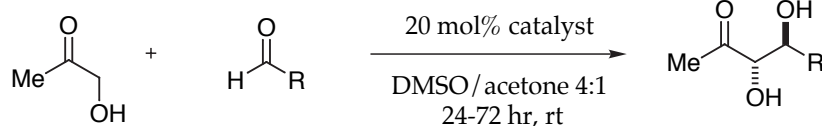
Houk's calculated T.S.

- ◆ synclinal approach of aldehyde
- ◆ R<sub>1</sub> in pseudo-equatorial position
- ◆ C-H -- O distance ~ 2.4 Å
- ◆ DFT calculations in DMSO

List, B. *JACS* **2000**, *122*, 2395.

List, B., Houk, K. *JACS* **2003**, *125*, 2475.

## Synthesis of *Anti*-1,2-Diols



product R =	cat.	dr	% yield	% ee
	1	>20:1	60	>99
	2	>20:1	45	95
	1	>20:1	62	>99
	2	---	<5	---
	1	>20:1	51	>99
	2	---	<5	---
	1	3:2	95	67 (32)
	2	3:2	60	92 (78)

product R =	cat.	dr	% yield	% ee
	1	1:1	83	80 (n.d.)
	2	1:1	52	95 (50)
	1	3:1	62	79 (33)
	2	---	<5	---
	1	1.7:1	38	>97 (84)
	2	---	<5	---
	1	2:1	40	>97 (97)
	2	---	<5	---

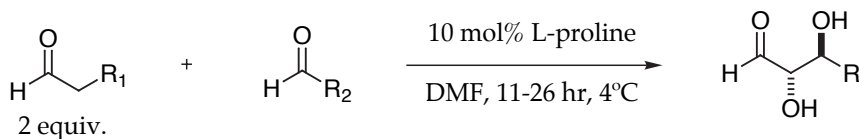
List, B. *JACS*, **2000**, *122*, 2395.

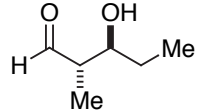
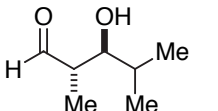
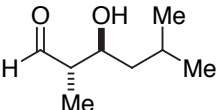
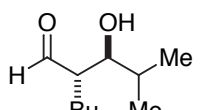
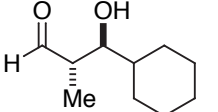
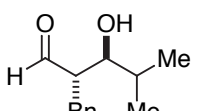
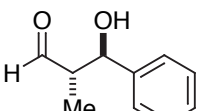
Barbas, C. *JACS*, **2001**, *123*, 5260.

more substituted enamine formed due to:

- ◆ increased acidity of proton removed
- ◆ increased stability of enamine due to O<sub>n.b.</sub> --> π\* C=C

## Use of Aldehydes as Donors in Direct Aldol

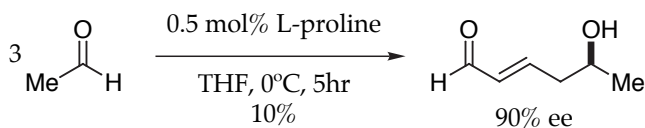


product R =	dr	% yield	% ee	product R =	dr	% yield	% ee
	4:1	80	99		24:1	82	>99
	3:1	88	97		24:1	80	98
	14:1	87	99		19:1	75	91
	3:1	81	99				

♦ reaction requires lower catalyst loading, shorter times, and only 2 equivalents of aldehyde donor

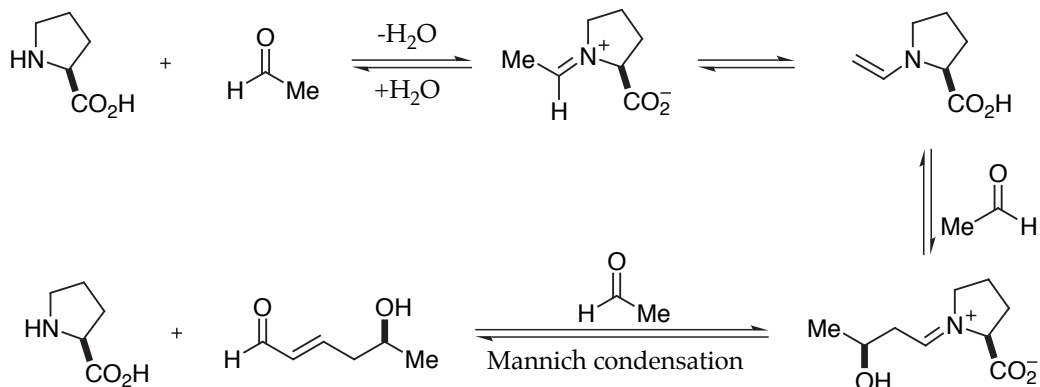
MacMillan, D. *JACS*, 2002, 124, 6798.

## Trimerization of Acetaldehyde



- ♦ THF at 0°C was found to be the optimal conditions for yield and ee (DMSO @ rt = 13% y, 57% ee, CHCl<sub>3</sub> @ rt = 2% y, 68% ee)

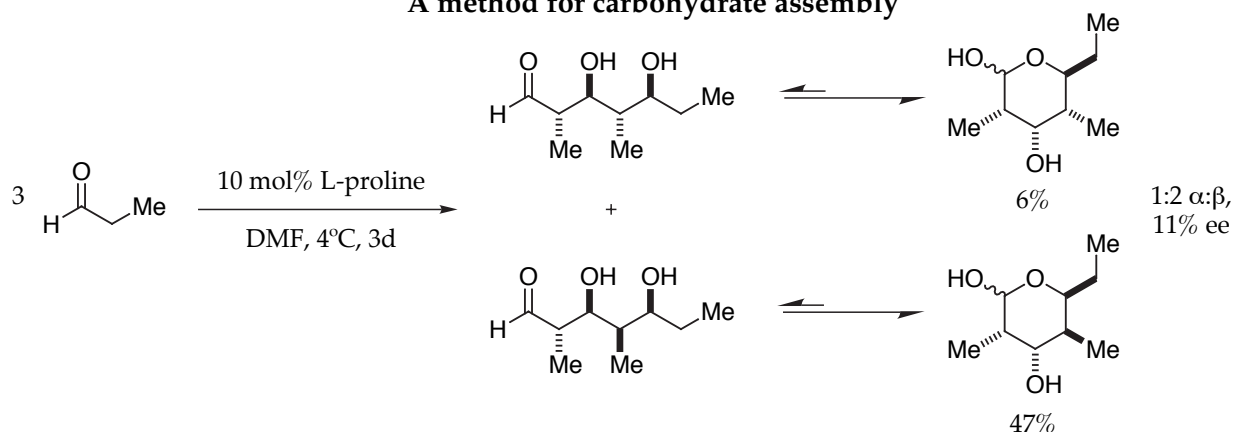
### Mechanism:



Barbas, C. *JOC*, 2002, 67, 301.

## Propionaldehyde Trimerization

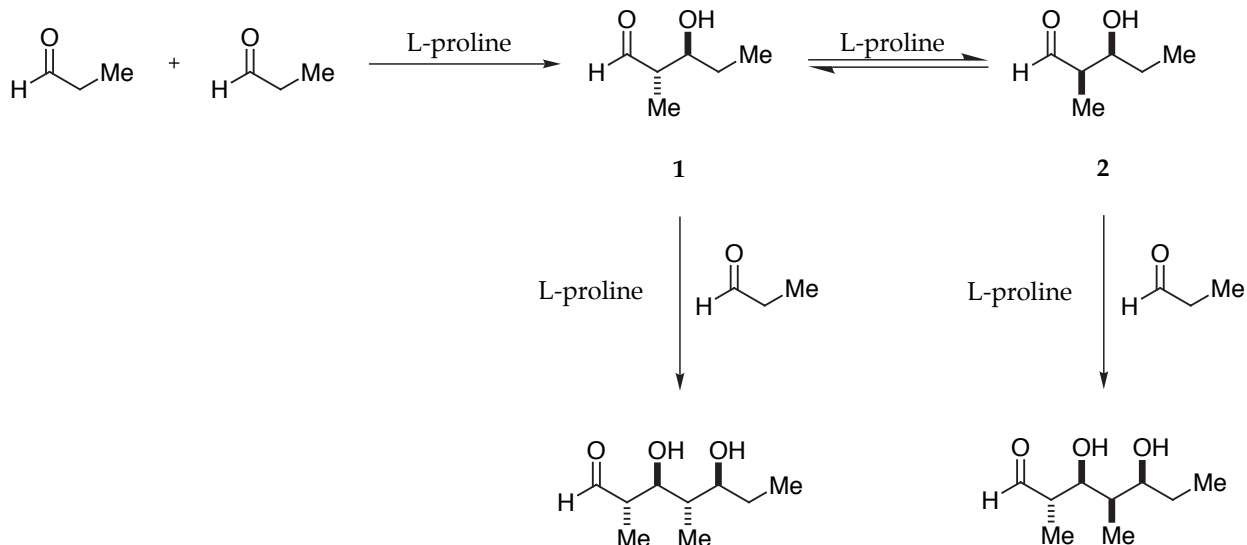
### A method for carbohydrate assembly



- ♦ reaction analogous to an aldolase enzyme that furnishes the minor product shown above
- ♦ propionaldehyde added slowly dropwise in order to obtain trimer over dimer products
- ♦ enantioselectivity erodes with longer reaction times (after 10 hr product ee = 47%)
- ♦ substituent at C-6 variable by using 1 eq. of corresponding aldehyde and 2 eq. of propionaldehyde

Barbas, C. *TL*, 2002, 43, 9591.

## Mechanism of Propionaldehyde Trimerization

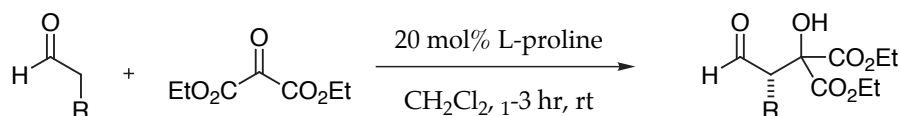


- ♦ incubating isolated 1 with L-proline led to formation of 2 through epimerization (1:1 ratio of 1:2 after 96 hr)

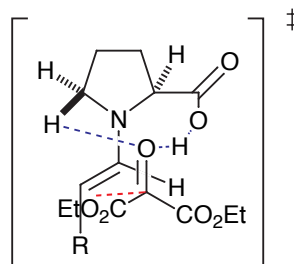
Barbas, C. *TL* 2002, 43, 9591.



## Aldehyde Aldol Addition to Activated Carbonyl Compounds



product R =	% yield	% ee
Me	90	90
Et	91	85
<i>i</i> -Pr	88	85
	94	88
<i>n</i> -Hex	91	84
Ph	97	0

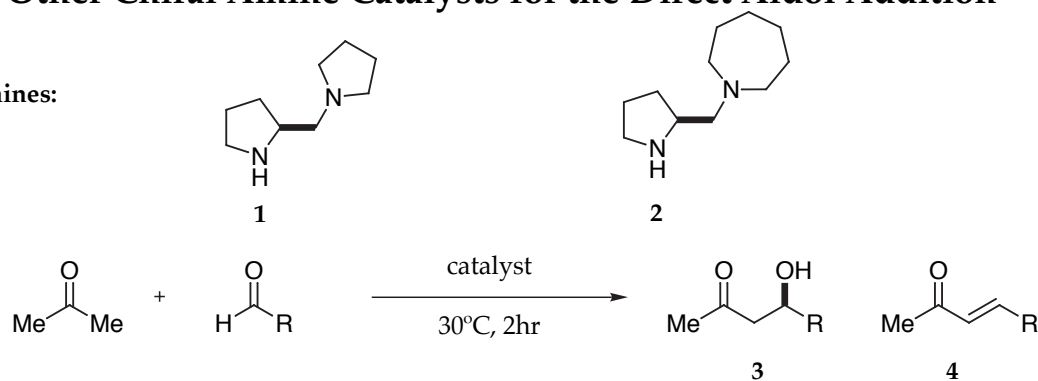


Jorgensen, K. *Chem. Comm.* **2002**, 620.

- ♦ protection of the aldehyde as the dioxolane prevents epimerization of the  $\alpha$  center during column chromatography

## Other Chiral Amine Catalysts for the Direct Aldol Addition

Chiral diamines:



product R =	cat.	% yield 3	% ee	% yield 4
	1.5 mol% <b>1</b> •2TfOH + 1.5 mol% <b>1</b>	60	88	7
	3 mol% <b>2</b>	72	93	7
	1.5 mol% <b>1</b> •2TfOH + 1.5 mol% <b>1</b>	37	83	32
	3 mol% <b>2</b>	13	91	25

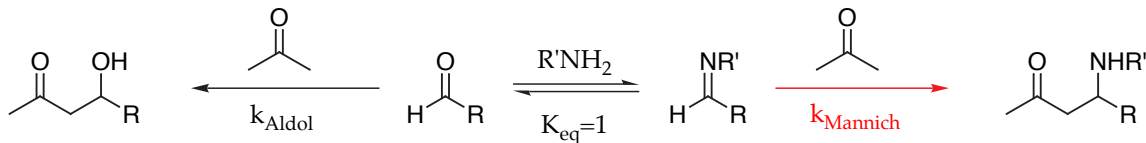
- ♦ proposed mechanism similar to that of proline catalyzed reactions, with proton transfer from protonated tertiary N to O

Yamamoto, *Tet.* **2002**, 58, 8167.

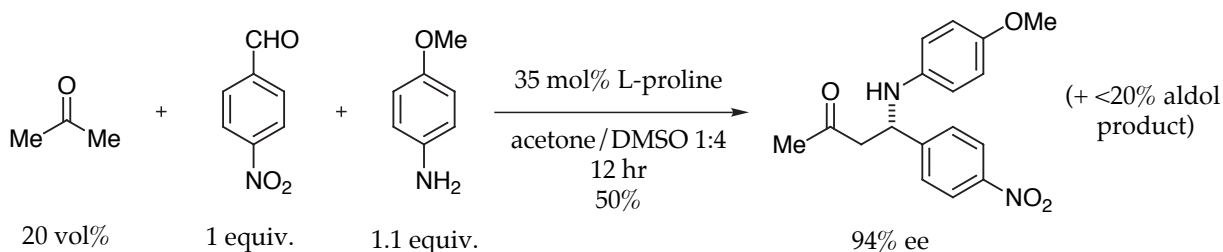
# Mannich Reaction: First Report

## Required Conditions:

- ♦ enamine addition must be faster to the imine than to the corresponding aldehyde
- ♦ formation of the aldimine from a primary amine must be faster than the aldol addition
  - ♦ NMR studies show that  $K_{eq}(\text{aldehyde} \rightleftharpoons \text{imine}) = 1$



## 3-component reaction verifies hypotheses:

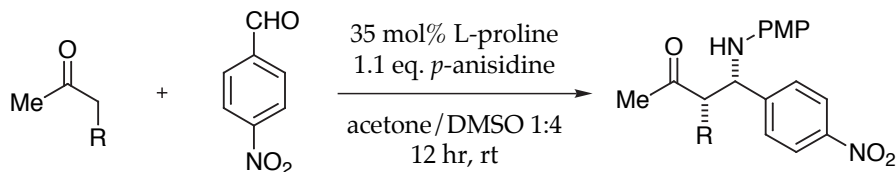


- ♦ 10 mol% proline and 1.3 eq ketone used without loss of efficiency

List, B. *JACS*, 2000, 122, 9336.

## Mannich Reaction: Scope

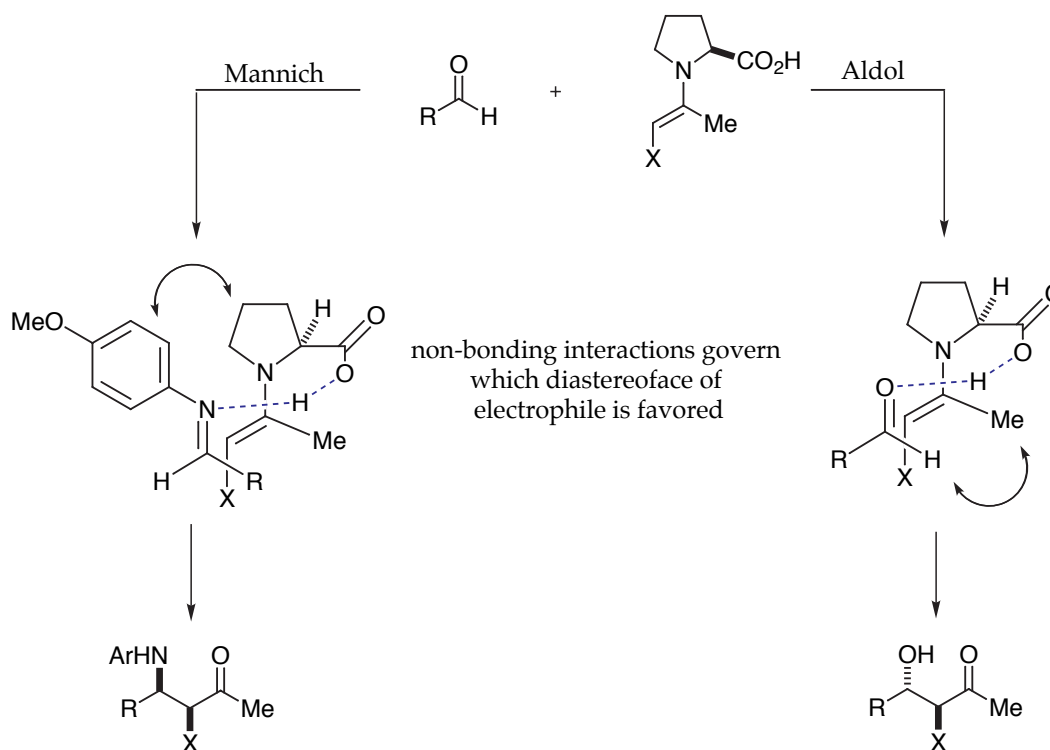
### Variation of the ketone donor:



R =	product	% yield	dr	% ee	
Me		2.5	95	>20:1	99
		1	---	>20:1	94
OMe			93	>20:1	98
OH			92	>20:1	>99

List, B. *JACS*, 2000, 122, 9336.

## Mannich Reaction: Transition States



List, B. *JACS* 2002, 124, 827.

## Mannich Reaction: Scope 2

### Variation of the aldehyde:

- ♦ aliphatic aldehydes, including  $\alpha$ -unbranched are good substrates (60-90% yield, 73-93% ee)
- ♦ aromatic aldehydes are excellent substrates, (79-92% yield, 61-99% ee)

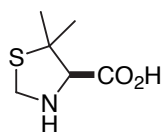
Effect of electron donation from the aldehyde:

R =	% yield	dr	% ee
CN	88	15:1	99
H	83	9:1	93
Me	85	5:1	86
OMe	88	3:1	61

### Variation of the catalyst:

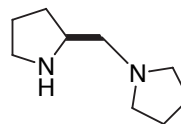
- ♦ proline proves to be the best catalyst, with other catalysts affording reduced yield and optical purity.

Reaction of acetone with isovaleraldehyde:



List, B. *JACS* 2002, 124, 827.

60% y., 16% ee

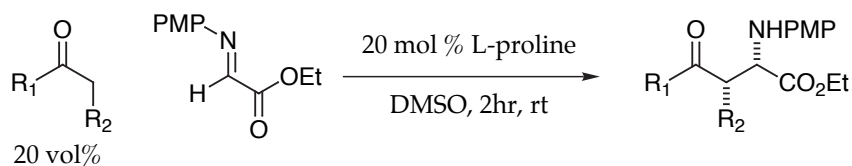


26% y., 0% ee

## $\alpha$ -Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to  $\alpha$ -amino acids

Addition of ketones:



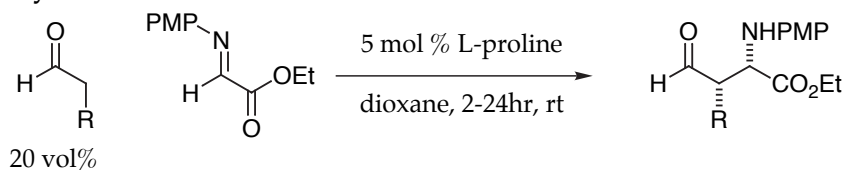
product	% yield	dr	% ee
	86	---	99
	72	>19:1	>99
	79	>19:1	>99
	62	>19:1	99
	47	>19:1	>99
	81	>19:1	>99

Barbas, C. *JACS* 2002, 124, 1842

## $\alpha$ -Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to  $\alpha$ -amino acids

Addition of aldehydes:



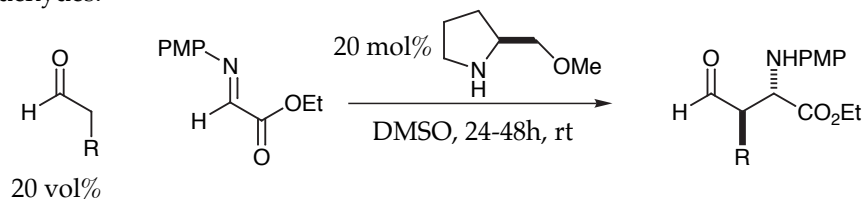
R =	% yield	dr	% ee
Me	72	1.1:1	99
Et	57	1.5:1	99
<i>i</i> -Pr	81	>10:1	93
<i>n</i> -Bu	81	3:1	99
<i>n</i> -Pent	89	>19:1	>99
	71	>19:1	>99

- ♦ aqueous workup or column chromatography may lead to decreased diastereoselectivities
- ♦ reaction has been performed in aqueous media (Barbas, *TL* 2003, 44, 1923)

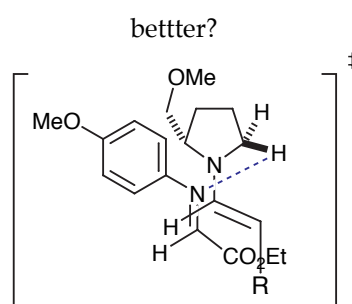
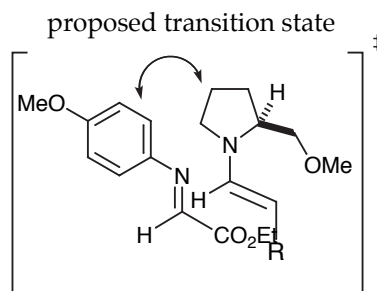
Barbas, C. *JACS* 2002, 124, 1866.

## Anti-Selective Mannich Reaction

Addition of aldehydes:



R =	% yield	dr	% ee
Et	44	1:1	75
<i>i</i> -Pr	52	10:1	82
<i>n</i> -Bu	54	10:1	74
<i>t</i> -Bu	57	>10:1	92
<i>n</i> -Pent	78	>10:1	76
<i>n</i> -Hex	68	>19:1	76

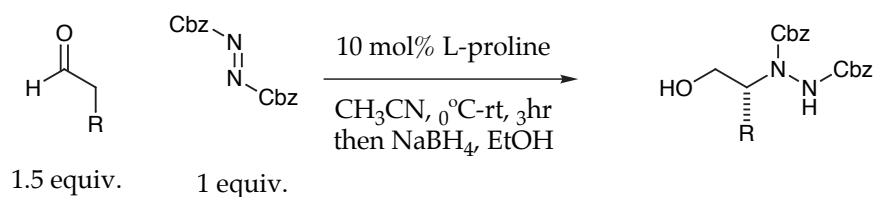


For a review of SMP use in asymmetric synthesis, see:  
Enders, D. *Synthesis* **1996**, 1403.

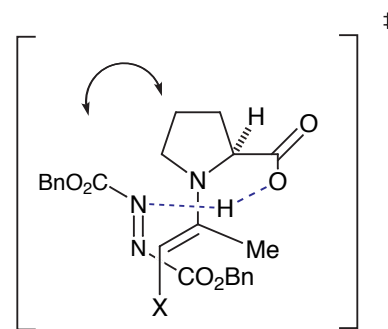
Barbas, C. *TL* **2002**, *43*, 7749.

## Direct $\alpha$ -Amination 1

Addition of aldehydes:



R =	% yield	% ee
Me	97	>95
<i>n</i> -Pr	93	>95
<i>n</i> -Bu	94	97
<i>i</i> -Pr	99	96
Bn	95	>95

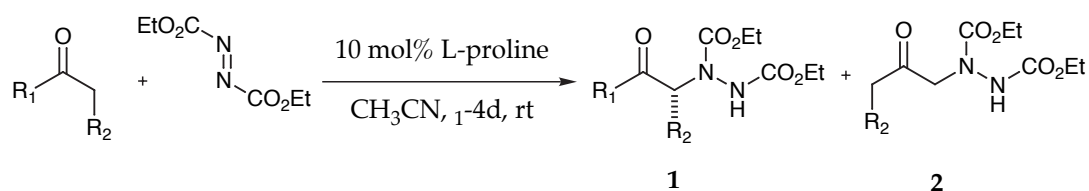


♦ longer reaction time leads to epimerization, so aldehyde is reduced *in situ*

List, B. *JACS* **2002**, *124*, 5656.

## Direct $\alpha$ -Amination 2

Addition of ketones:

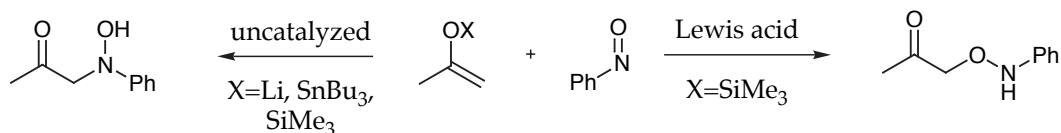


product 1	ratio 1:2	% yield (1+2)	% ee
	10:1	80	95 (93)
	4.5:1	92	98 (94)
	3:1	99	99 (99)
	---	79	94 (93)

Jorgensen, *JACS* **2002**, *124*, 6254.

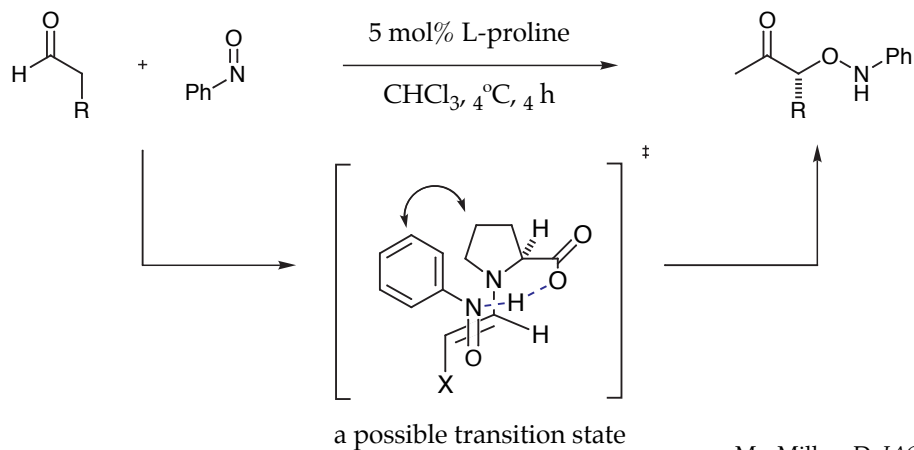
## $\alpha$ -Oxidation of Aldehydes with Nitrosobenzene 1

The choice of reaction conditions determine N or O selective addition:



Yamamoto, H. *OL*, **2002**, *4*, 3579.

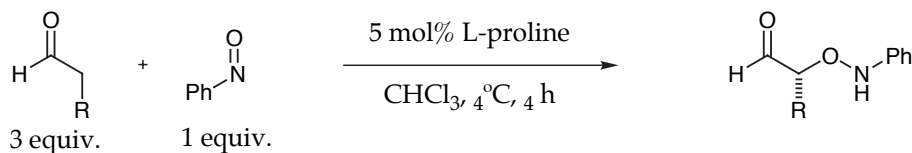
Larger basicity of nitrogen allows proline to catalyze O-nucleophilic addition:



MacMillan, D. *JACS* **2003**, *125*, 10808.

## $\alpha$ -Oxidation of Aldehydes with Nitrosobenzene 2

Aldehyde scope:



R =	% yield	% ee	R =	% yield	% ee
Me	88	97	Bn	95	97
<i>n</i> -Bu	79	98	Ph	60	99
<i>i</i> -Pr	85	99	(CH <sub>2</sub> ) <sub>3</sub> OTIPS	76	98
CH <sub>2</sub> CH=CH <sub>2</sub>	99	96	CH <sub>2</sub> -(3'-N-methyl indole)	83	98

♦ product most easily isolated as the primary alcohol (NaBH<sub>4</sub> reduction)

MacMillan, D. *JACS* **2003**, *125*, 10808.

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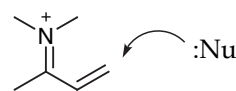
## Asymmetric Organocatalysis of the Michael Reaction

Two mechanistic possibilities exist:



enamine

or



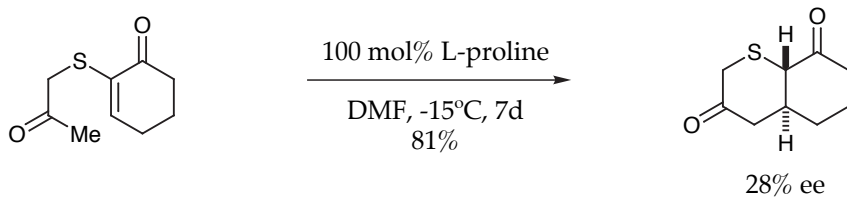
imminium

Examples include:

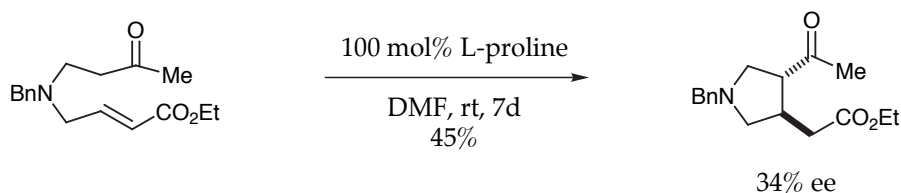
additions to:  
alkylidene malonates  
 $\alpha,\beta$ -unsaturated nitroalkenes

additions of:  
malonate esters  
nitroalkanes  
aromatics (Friedel-Crafts reactions)  
silyloxy furans  
Diels-Alder reaction  
Dipolar cycloaddition

## Michael Additions using Enamine Catalysis: Moderate Success has been Achieved



Kozikowski, A. *JOC*, **1989**, *54*, 2275.

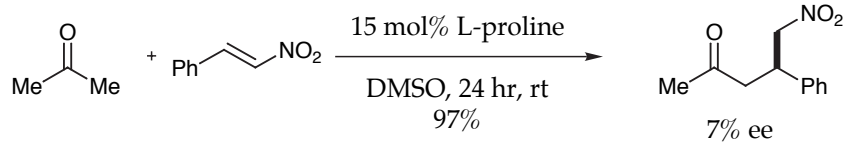


Momose, T. *J.Chem.Soc., Perkin Trans.*, **1992**, 509.

## Enamine Catalysis: Examples 2

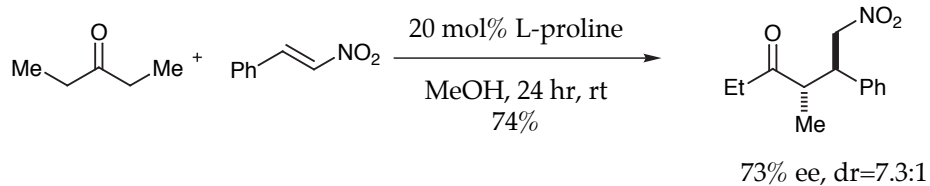
### Recent examples:

List:



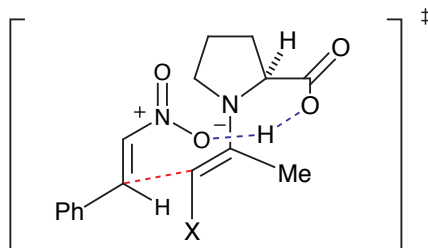
List, B. *OL* **2001**, *3*, 2423.

Enders:



- ♦ use of MeOH as solvent increases ee

Enders, *Synlett* **2002**, 26.

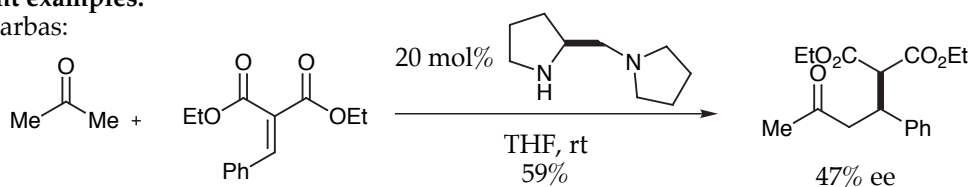




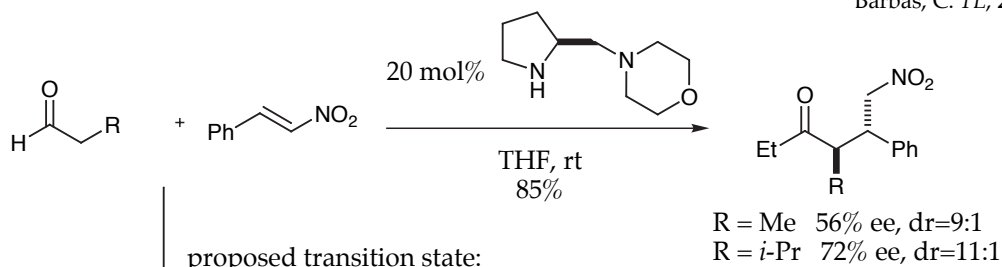
## Enamine Catalysis: Examples 3

Recent examples:

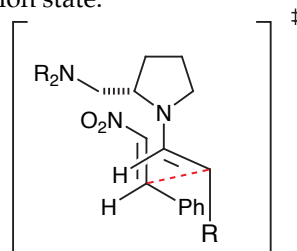
Barbas:



Barbas, C. *TL*, 2001, 42, 4441.

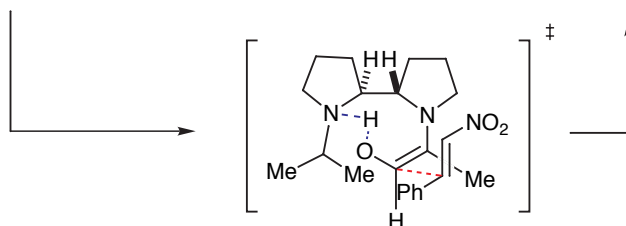
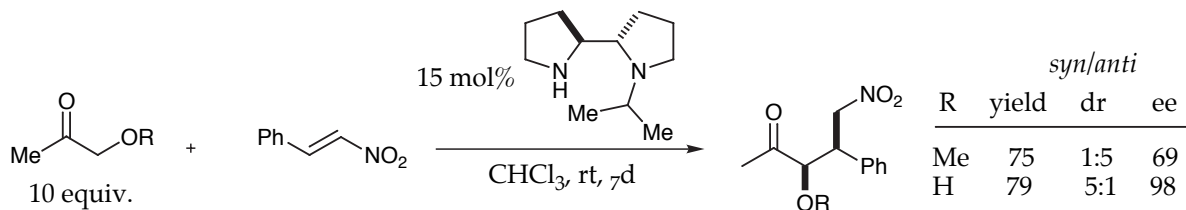


proposed transition state:



Barbas, C. *OL* 2001, 3, 3737.

## A Highly Enantioselective Michael Addition Using Enamines A New Chiral Diamine Catalyst

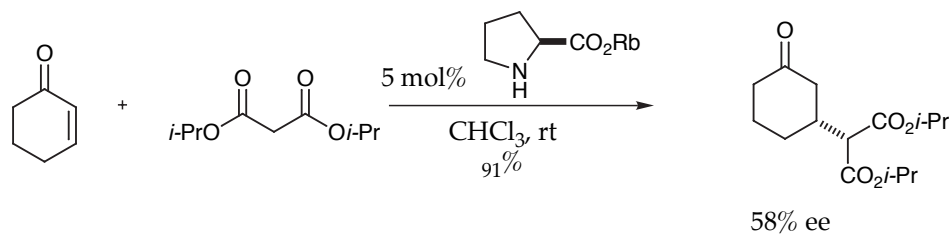


- with variation of aromatic group on nitroolefin:  
ee = 96-98%  
dr = 3.5:1 - 19:1
- selection of aromatic groups used:  
tolyl, *p*-methoxyphenyl, *p*-chlorophenyl, 2-thienyl

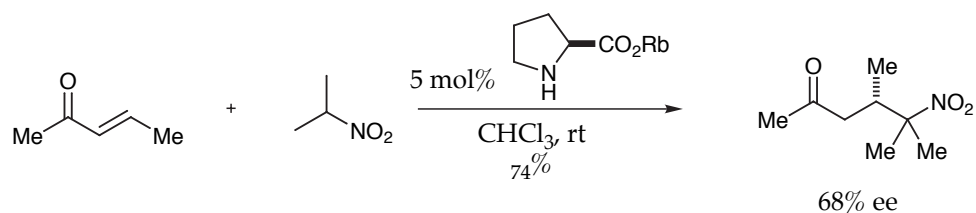
Alexakis, A. *OL*, 2003, 5, 2559.

## Imminium Catalysis of Conjugate Additions 1

Proline has been used with only mild success:



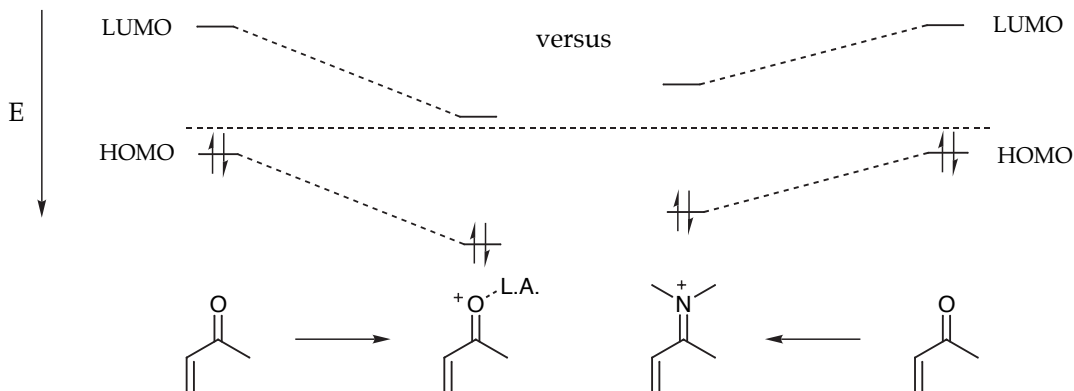
♦ Proline rubidium salt gives lower ee in the Hajos-Parrish-Weichert reaction



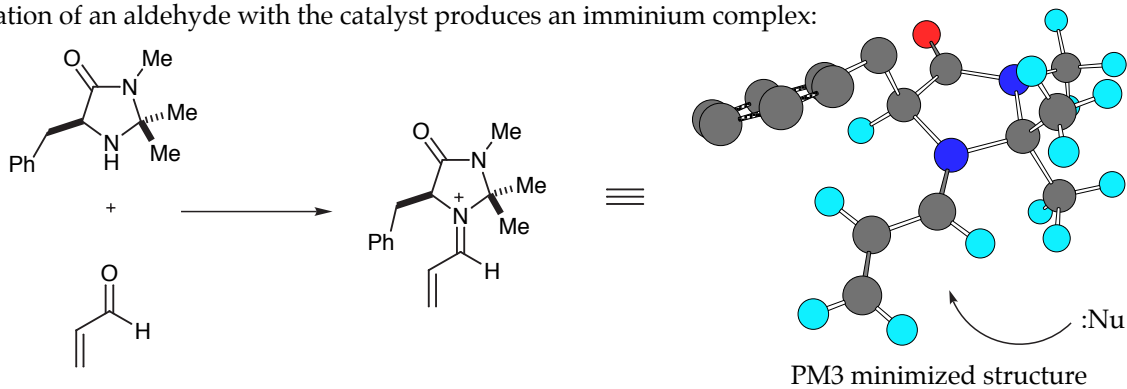
Yamaguchi, *JOC* 1996, 61, 3520.

## MacMillan Introduces A New Catalyst

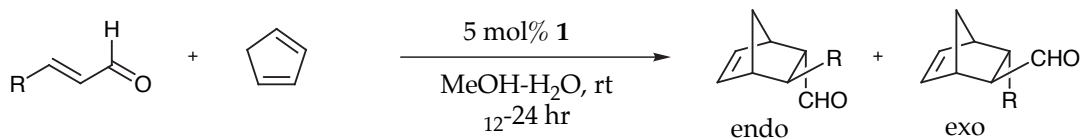
Imminium ion formation lowers the LUMO of the system and allows catalysis to occur:



Condensation of an aldehyde with the catalyst produces an imminium complex:

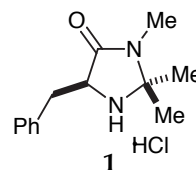


## Diels-Alder Cycloaddition 1



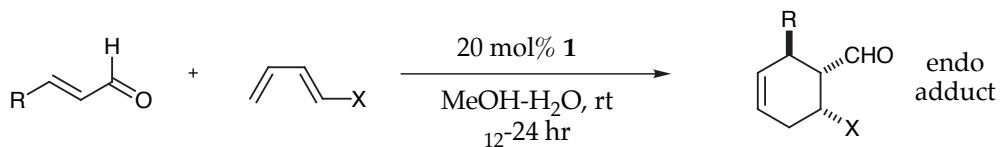
### Dienophile scope:

R =	% yield	endo:exo	% ee(endo)	% ee(exo)
Me	75	1:1	86	90
<i>n</i> -Pr	92	1:1	86	90
<i>i</i> -Pr	81	1:1	84	93
Ph	99	1.3:1	93	93
Furyl	89	1:1	91	93



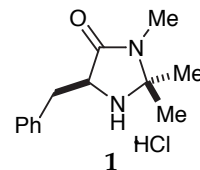
MacMillan, D. *JACS* **2000**, *122*, 4243.

## Diels-Alder Cycloaddition 2



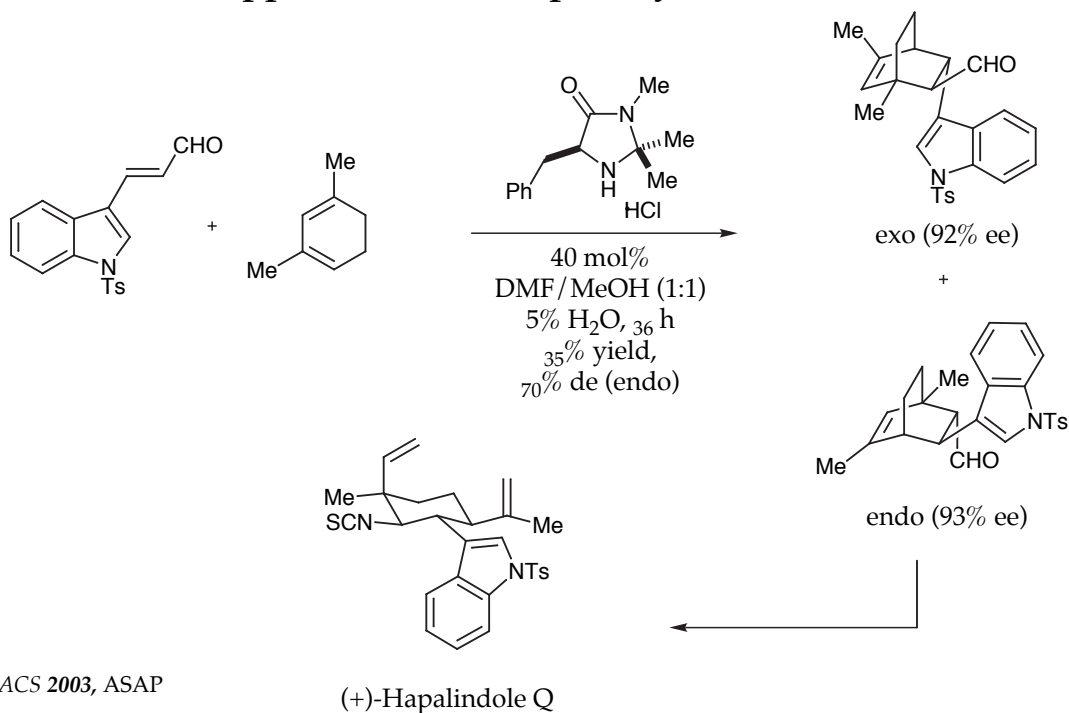
### Diene scope:

diene	R	product	% yield	exo:endo	% ee
	Me		75	35:1	96
	H		82	1:14	94
	H		84	---	89
	H		90	---	83
	Me		75	---	90
	H		75	1:5	90
	H		72	1:11	85

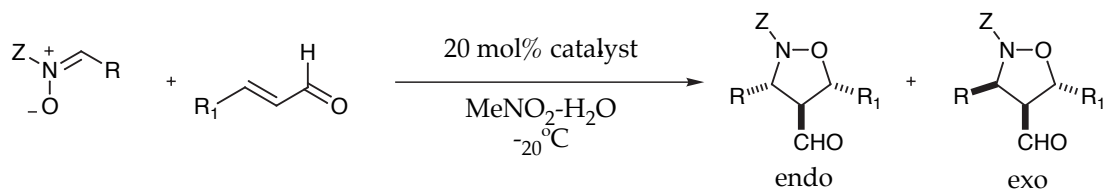


MacMillan, D. *JACS* **2000**, *122*, 4243.

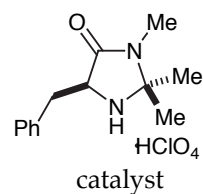
## Application to Complex Synthesis



## Nitron Cycloaddition

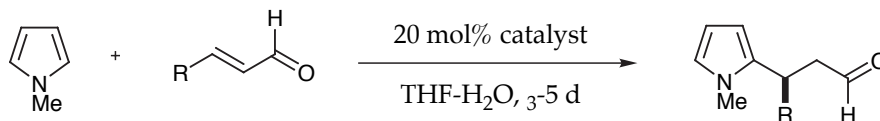


Z	R	R <sub>1</sub>	endo:exo	yield	ee (endo)
Bn	Ph	Me	94:6	98	94
allyl	Ph	Me	93:7	73	98
Me	Ph	Me	95:5	66	99
Bn	C <sub>6</sub> H <sub>4</sub> Cl-4	Me	92:8	78	95
Me	C <sub>6</sub> H <sub>4</sub> Cl-4	Me	93:7	76	94
Bn	C <sub>6</sub> H <sub>4</sub> OMe-4	Me	98:2	93	91
Me	C <sub>6</sub> H <sub>4</sub> Me-4	Me	93:7	82	97
Bn	2-naphth	Me	95:5	98	93
Bn	c-Hex	Me	99:1	70	99
Bn	Ph	H	81:19	72	90
Bn	Ph	H	86:14	80	92
Bn	C <sub>6</sub> H <sub>4</sub> Cl-4	H	85:15	80	90
Bn	C <sub>6</sub> H <sub>4</sub> Cl-4	H	80:20	80	91
Bn	2-naphth	H	81:19	82	90
Bn	C <sub>6</sub> H <sub>4</sub> OMe-4	H	91:9	83	90

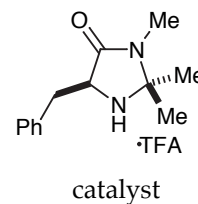


- HClO<sub>4</sub> proved to be the best Bronsted acid cocatalyst to promote only enantioselective catalysis
- high endo selectivity attributed to favorable placement of R group away from geminal dimethyl substituents on catalyst

## Friedel-Crafts Alkylation 1: Pyrroles

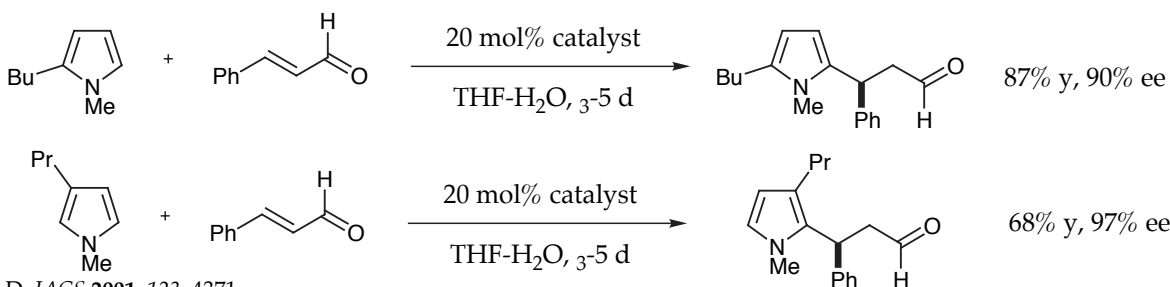


R	temp(°C)	yield	ee
Me	-60	83	91
<i>n</i> -Pr	-50	81	90
<i>i</i> -Pr	-50	80	91
Ph	-30	87	93
PMP	-30	79	91
CH <sub>2</sub> OBn	-60	90	87
CO <sub>2</sub> Me	-50	72	90



♦ use of *N*-benzyl pyrrole and *N*-allyl pyrrole give similar results

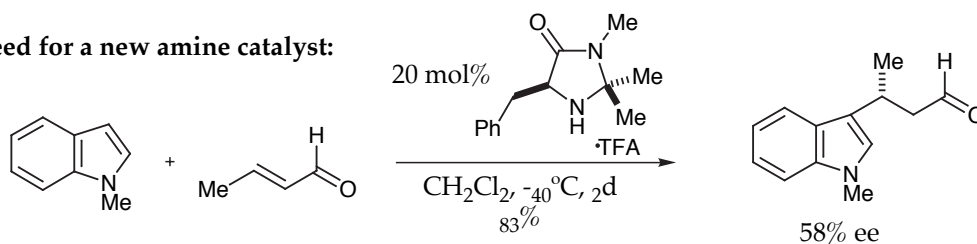
Substitution on the pyrrole is also possible:



MacMillan, D. *JACS* **2001**, *123*, 4371.

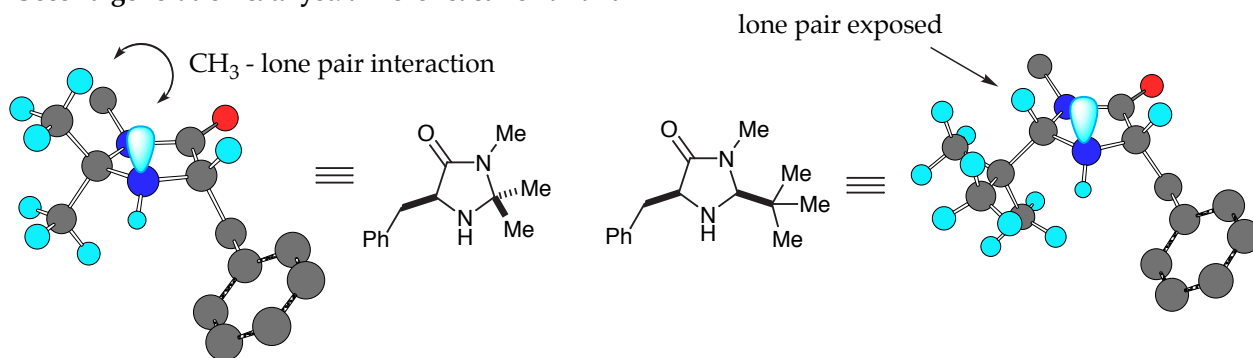
## Alkylation of Indoles 1

The need for a new amine catalyst:



♦ Indole is less electron-rich than pyrrole, so is less nucleophilic toward conjugate addition

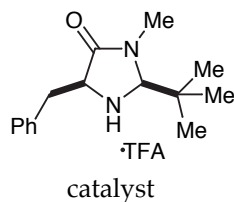
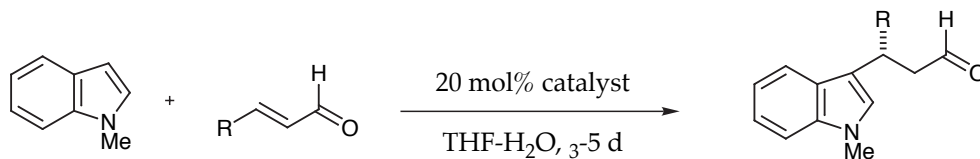
Second generation catalyst: a more reactive variant



♦ Kinetic studies indicate rate of reaction influenced by iminium formation as well as carbon-carbon bond forming event

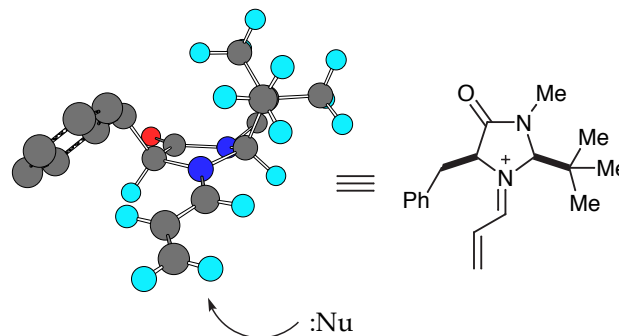
MacMillan, D. *JACS* **2002**, *124*, 1172.

## Alkylation of Indoles 2



R	temp(°C)	yield	ee
Me	-83	82	92
<i>n</i> -Pr	-60	80	93
<i>i</i> -Pr	-50	74	93
Ph	-55	84	90
CH <sub>2</sub> OBz	-83	84	96
CO <sub>2</sub> Me	-83	89	91

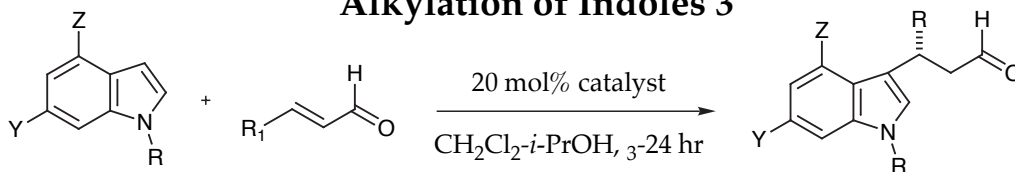
An increase in rate of reaction and enantioselectivity:



- ◆ increased top-face coverage
- ◆ nucleophile-geminal dimethyl interaction removed

MacMillan, D. *JACS* 2002, 124, 1172.

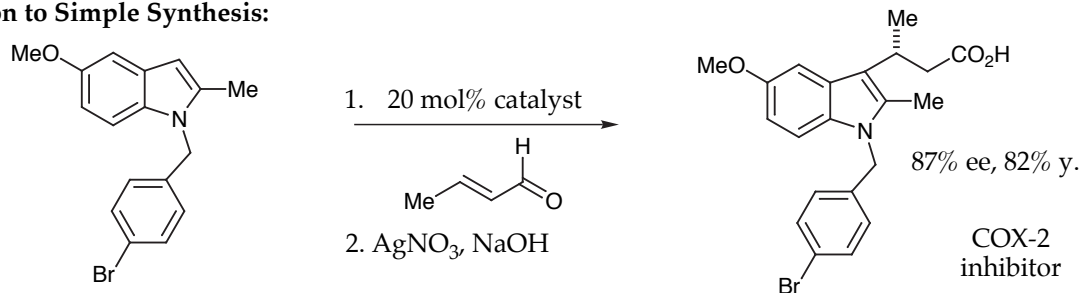
## Alkylation of Indoles 3



Indole Scope:

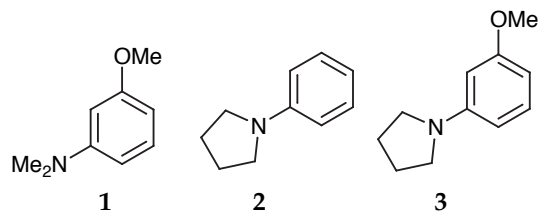
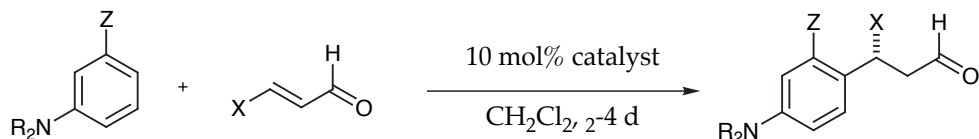
R	Y	Z	R <sub>1</sub>	temp(°C)	% yield	% ee
Me	H	H	Me	-87	82	92
H	H	H	Me	-60	72	91
allyl	H	H	Me	-72	70	92
Bn	H	H	Me	-60	80	89
H	H	Me	-CH <sub>2</sub> OBz	-60	94	94
Me	H	OMe	-CH <sub>2</sub> OBz	-87	90	96
H	Cl	H	-CH <sub>2</sub> OBz	-60	73	97

Application to Simple Synthesis:

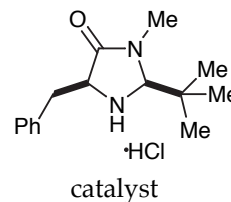


MacMillan, D. *JACS* 2002, 124, 1172.

## Alkylation of Benzenes



aniline	X	temp(°C)	% yield	% ee
1	Me	-40	86	89
2	Me	-20	70	87
1	Et	-50	68	88
1	CH <sub>2</sub> OBz	-20	89	92
2	CH <sub>2</sub> OBz	+20	73	90
1	CO <sub>2</sub> Me	-20	90	92
2	CO <sub>2</sub> Me	-20	97	97
3	Ph	-50	82	84
3	<i>p</i> -ClPh	-10	87	92
1	<i>p</i> -NO <sub>2</sub> -Ph	-10	87	92
2	<i>p</i> -NO <sub>2</sub> -Ph	-20	82	90

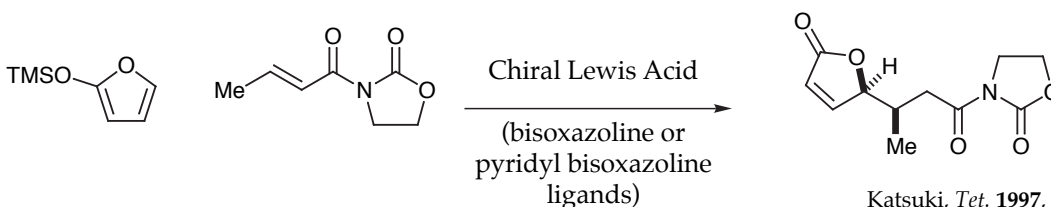


- ♦ other substituted anilines used with similar results
- ♦ catalyst loading can be lowered to 1% without significant loss of yield and enantioselectivity

MacMillan, D. *JACS* 2002, 124, 7894.

## Mukaiyama-Michael Reaction 1

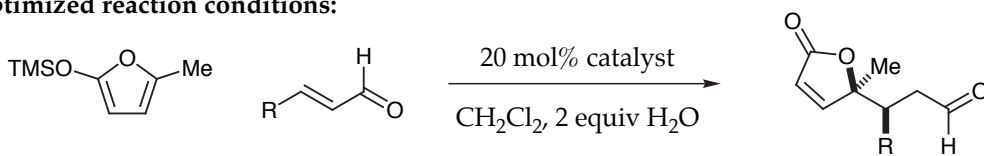
Previous Michael additions with silyloxy furans:



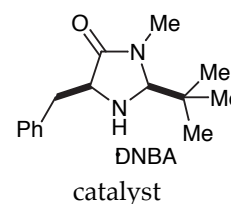
Katsuki, *Tet.* 1997, 53, 17015  
Desimoni, G. *Tet.* 2001, 57, 10203

- ♦ note that Lewis acids promote 1,2-addition products when possible, such as  $\alpha,\beta$ -unsaturated enals

Optimized reaction conditions:

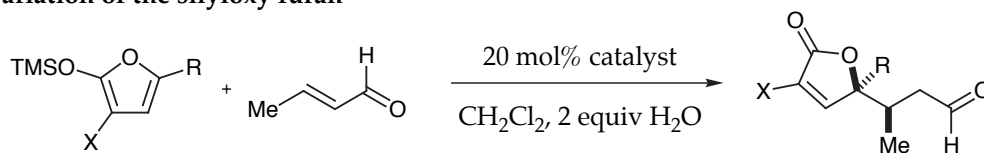


R	temp (°C)	% yield	syn:anti	% ee
Me	-70	81	22:1	92
<i>n</i> -Pr	-50	87	31:1	84
<i>i</i> -Pr	-20	80	7:1	98
Ph	-40	77	1:6	99
CH <sub>2</sub> OBz	-70	86	20:1	90
CO <sub>2</sub> Me	-60	84	11:1	99



## Mukaiyama-Michael Reaction 2

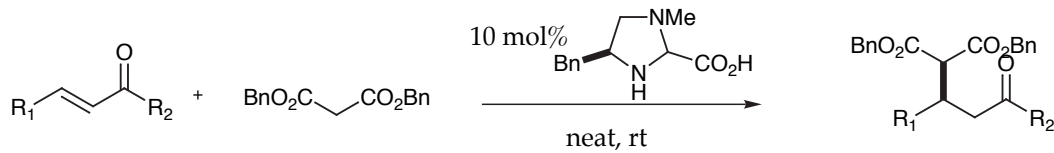
### Variation of the silyloxy furan



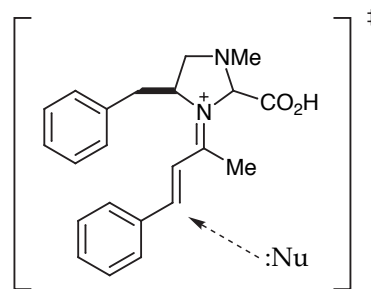
R	X	% yield	<i>syn:anti</i>	% ee	
H	H	87	8:1	90	
Me	H	80	22:1	92	
Et	H	83	16:1	90	
CO <sub>2</sub> Me	H	86	6:1	98	TFA as cocatalyst
CO <sub>2</sub> Me	H	83	1:7	98	TfOH as cocatalyst
Me	Me	73	24:1	90	

MacMillan, D. *JACS* **2003**, *125*, 1192.

## Another Chiral Amine Catalyst Asymmetric Michael Additions



R <sub>1</sub>	R <sub>2</sub>	% yield	% ee
<i>p</i> -NO <sub>2</sub> Ph	Me	84	89
<i>p</i> -NMe <sub>2</sub> Ph	Me	58	77
2-furyl	Me	75	92
2-pyridyl	Me	95	88
<i>n</i> -Bu	Me	61	91
<i>i</i> -Pr	Me	33	84
MeO <sub>2</sub> C	Me	59	59
Ph	Me	86	99
Ph	Et	66	95
Ph	<i>i</i> -Pr	2	94



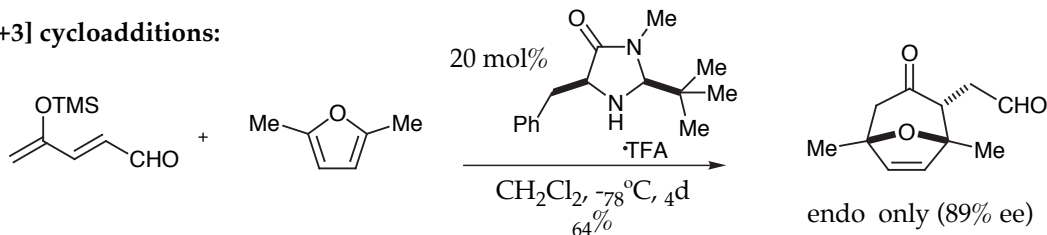
- ♦ Nitroalkane additions to  $\alpha,\beta$ -unsaturated ketones has also been performed in good to excellent selectivity (Jorgensen, K. *JOC* **2002**, *67*, 8331.)

Jorgensen, K. *ACIEE* **2003**, *42*, 661.



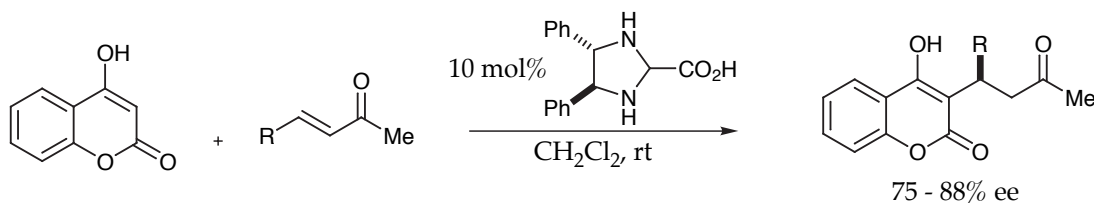
## A Listing of Other Asymmetric Organocatalytic Reactions

### [4+3] cycloadditions:



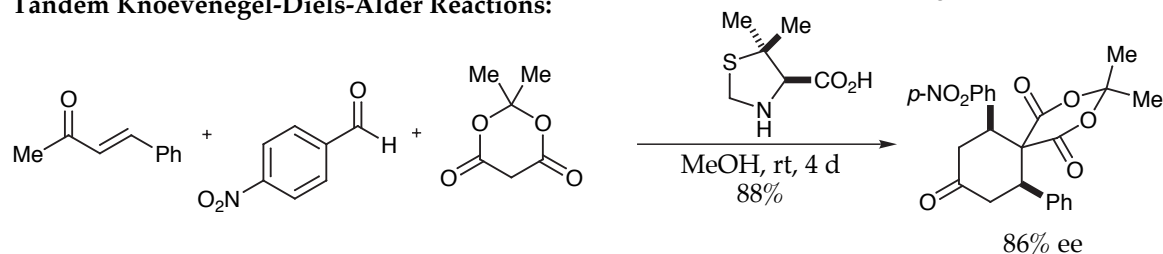
Harmata, M. *JACS*, **2003**, *125*, 2058.

### Michael Reactions:



Jorgensen, K. *ACIEE* **2003**, *42*, 4955

### Tandem Knoevenegel-Diels-Alder Reactions:



Barbas, C. *ACIEE* **2003**, *42*, 4233

## Summary

- ♦ Reactions are direct:
  - Donors can be used without modification -- no need to deprotonate or silylate prior to reaction
  - Electrophiles can be generated *in situ* (Mannich reaction) most of the time
- ♦ Catalysts are:
  - inexpensive
  - commercially available or easily prepared in both enantiomeric forms
  - non-toxic
  - recoverable
- ♦ Many reactions can be run at room temperature, under an aerobic atmosphere, with wet solvents
- ♦ Many types of reactions can be catalyzed; for some reactions, organocatalysis is the only highly efficient way known (Mannich and Mukaiyama-Michael additions)
- ♦ Reaction yield and enantioselectivity is highly dependent on solvent system so require "fine tuning"
- ♦ Only reactions that use ketones or aldehydes as donors (electrophiles for Michael additions) can be catalyzed

*Organocatalysis using small molecules is a field that has emerged only within the past decade. It is bound to receive increasing attention in the future; as a result, new catalysts will emerge which will allow for the catalysis of reactions previously unutilized in the realm of organocatalysis.*