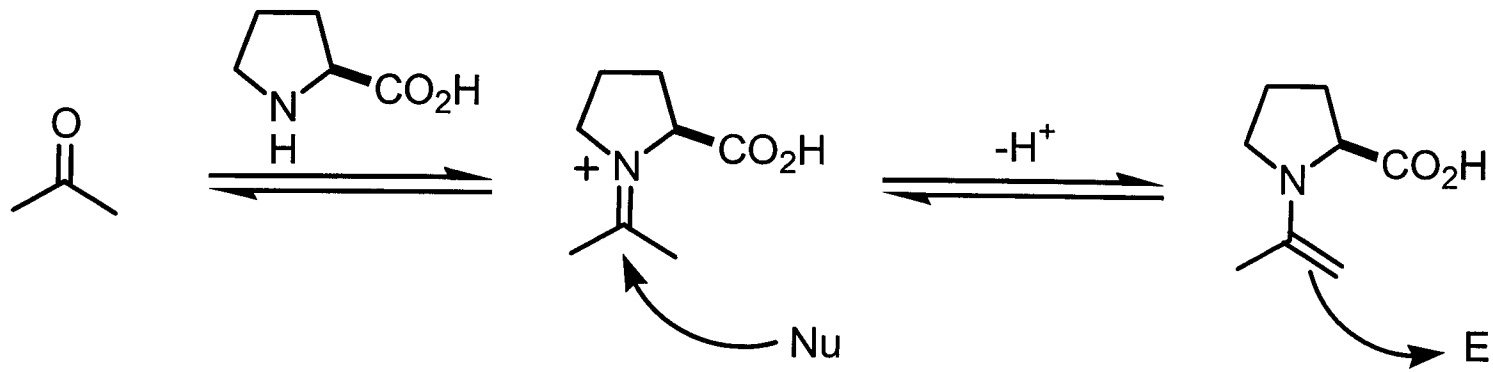
Recent Advances in Enantioselective Aminocatalysis



Justin Montgomery

February 19, 2002

Enantioselective Synthesis

- Has "outgrown" the academic environment
  - Chiral molecules make up close to 1/3 of all drug sales worldwide

- Catalytic Enantioselective Synthesis
  - Elegant
  - Economical

- Metal Catalyzed Enantioselective Synthesis
  - Molecular and structural diversity
  - Various reactivity patterns that are affected by varying ligands
  - But…
    - $$$$$, toxicity, pollution, product contamination

P.I. Dalko; L. Moisan; *Angew. Chem. Int. Ed.* **2001**, *40*, 3727.

Enantioselective Organocatalysis

- Organic molecules can emulate properties usually associated with metals

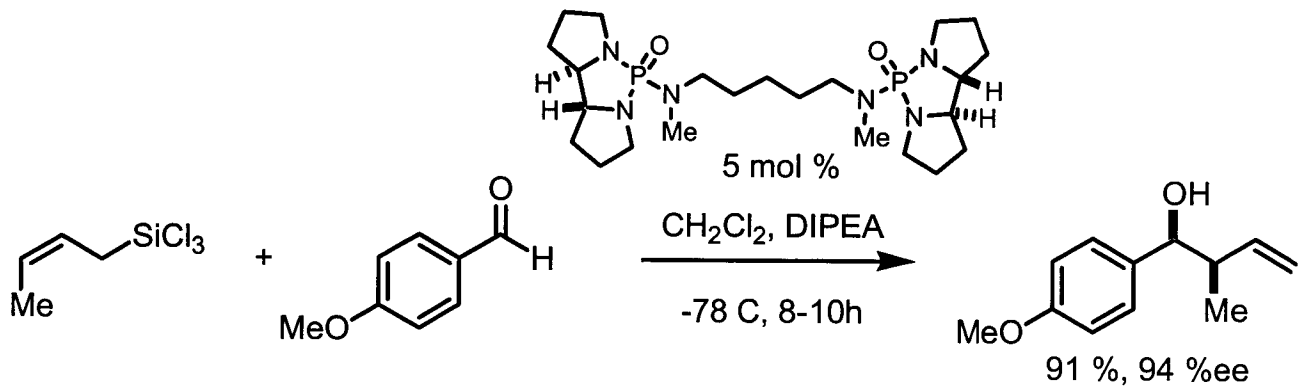
- Preparative advantages
  - Most organocatalyts are air and moisture stable and inexpensive
  - Easily modified for solid-supported synthesis

- More related to enzymatic catalysis than to organometallic processes
  - However, enzymes stabilize a TS‡ through a delicate balance of many factors acting together
  - Organic molecules promote reactions as simple reagents

P.I. Dalko; L. Moisan; *Angew. Chem. Int. Ed.* **2001**, *40*, 3727.

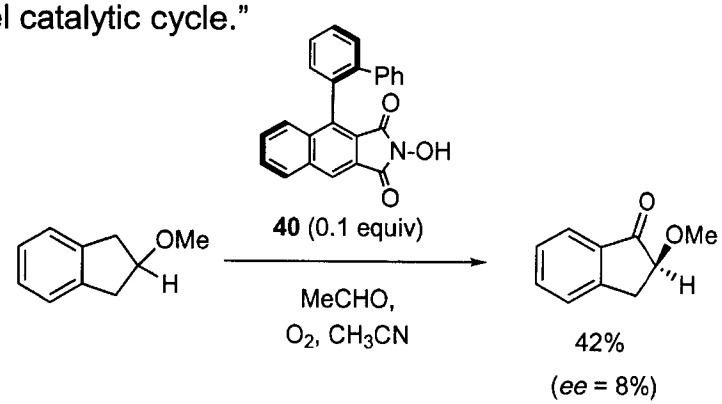
Mechanisms of Organocatalysis

1. "Activation of the reaction based on the nucleophilic/electrophilic properties of the cataylsts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/base activation."



S.E. Denmark; J. Fu; *J. Amer. Chem. Soc.* **2001**, *123*, 9488.

2. "Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle."

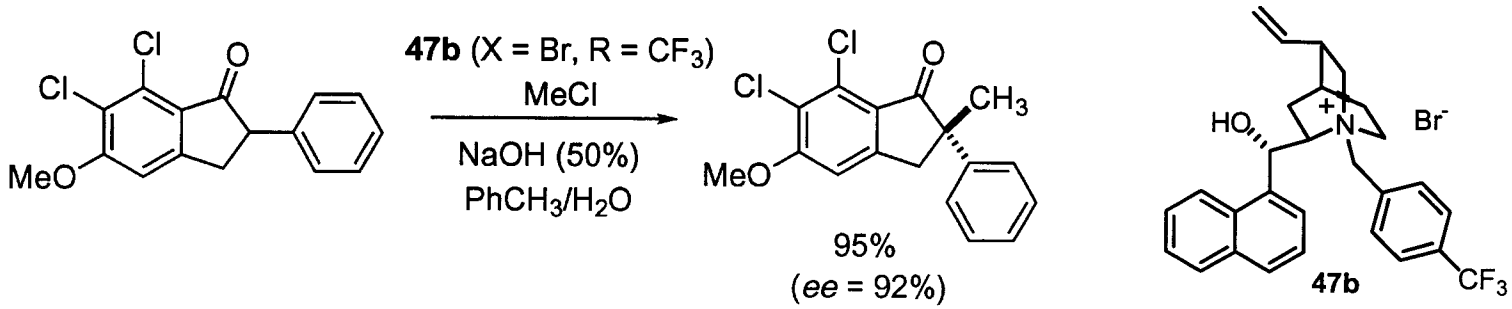


C. Einhorn; J. Einhorn; C. Marcadal-Abbadi; J.L. Pierre; *J. Org. Chem.* **1999**, *64*, 4542.

P.I. Dalko; L. Moisan; *Angew. Chem. Int. Ed.* **2001**, *40*, 3727.

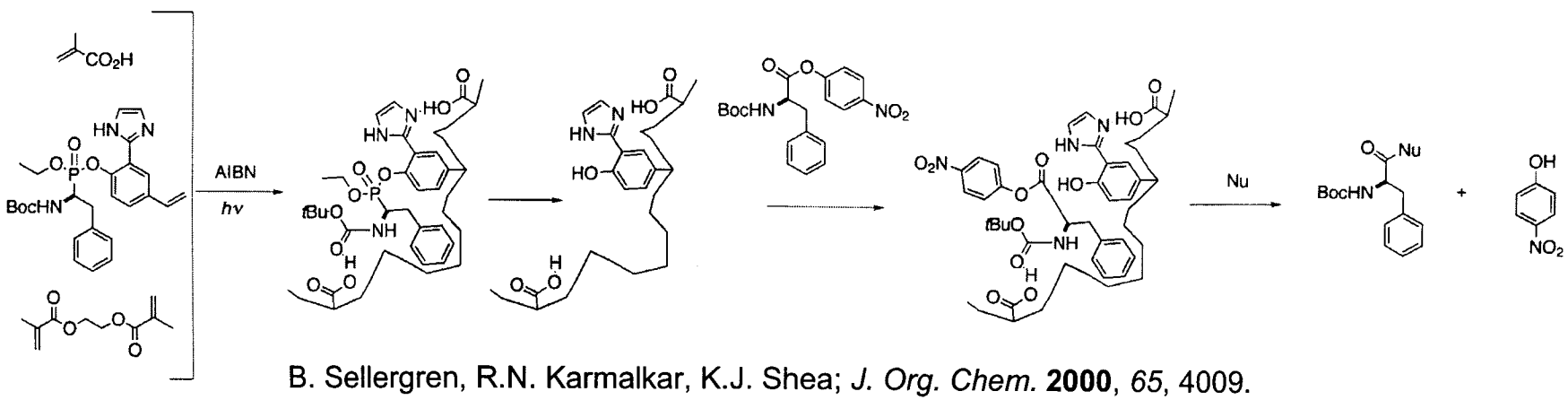
Mechanisms of Organocatalysis - 2

3. "Phase-transfer reactions. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase (i.e. the solid, aqueous, or fluorous phase in which the reaction takes place)."



U.H. Dolling; P. Davis; E.J.J. Grabowski; *J. Amer. Chem. Soc.* **1984**, *106*, 446.

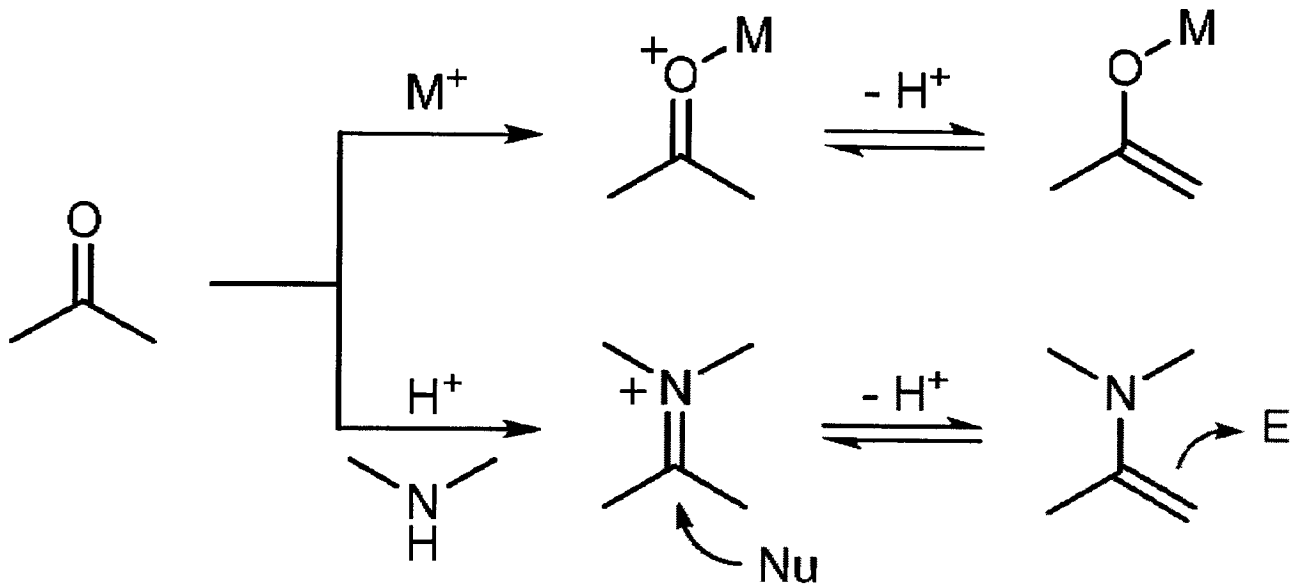
4. "Molecular-cavity-accelerated asymmetric transformations, in which the catalyst may select between the competing substrates, depending on size and structure criteria. The rate acceleration of the given reaction is similar to the Lewis acid/base activation and is a consequence of the simultaneous action of different polar functions."



B. Sellergren, R.N. Karmalkar, K.J. Shea; *J. Org. Chem.* **2000**, *65*, 4009.

P.I. Dalko; L. Moisan; *Angew. Chem. Int. Ed.* **2001**, *40*, 3727.

Aminocatalysis



- Iminium catalysis – utilizes higher reactivity of iminium ion in comparison to a carbonyl species
- Enamine catalysis – catalytically generated eneamine reacts with electrophiles

B. List; *Synlett.* **2001**, 1675.

Organocatalytic Diels-Alder Reaction

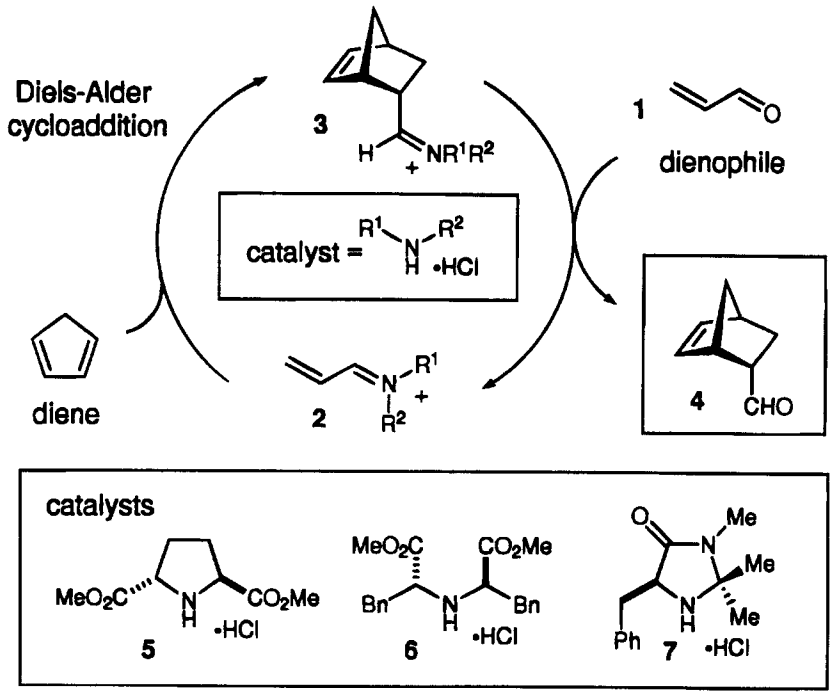
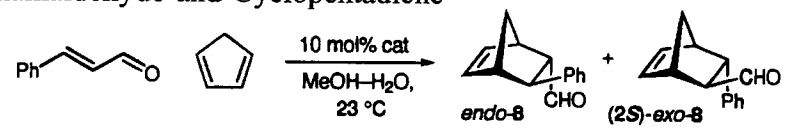


Table 1. Organocatalyzed Diels–Alder Reaction between Cinnamaldehyde and Cyclopentadiene



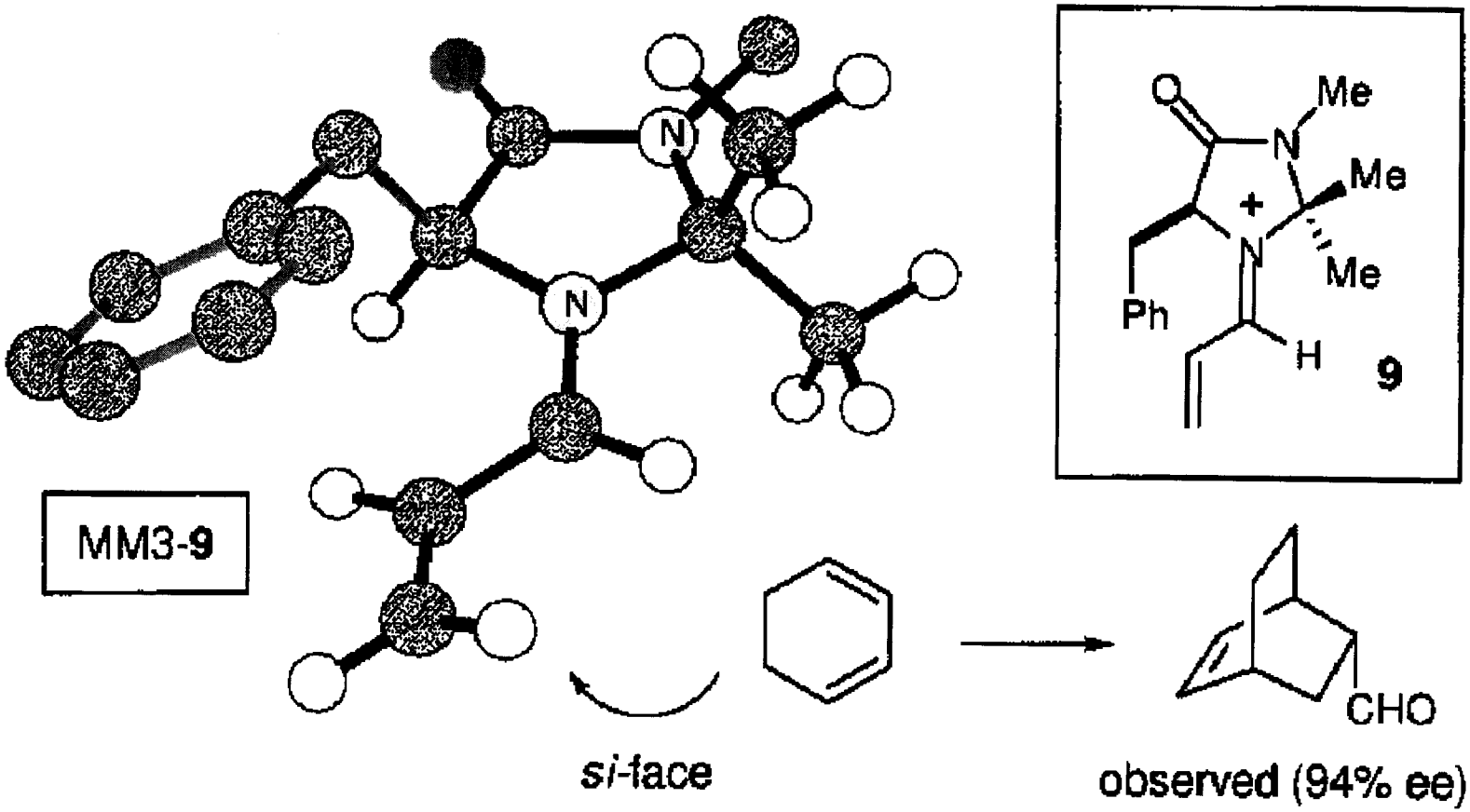
entry	catalyst	time (h)	yield (%)	*exo*:*endo*	*exo* ee (%)[a,b]
1	(*S*)-Pro-OMe•HCl	27	81	2.7:1	48 (2*R*)
2	(*S*)-Abr-OMe•HCl	10	80	2.3:1	59 (2*S*)
3	**5**	23	92	2.6:1	57 (2*R*)
4	**6**	84	82	3.6:1	74 (2*R*)
5	**7**	8	99	1.3:1	93 (2*S*)[c]

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information). [c] Using 5 mol % catalyst.

- Iminium ions lower LUMO much like Lewis acid activation
- Best enantioselectivity through control of iminium geometry

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

Diels-Alder: Origin of Stereocontrol

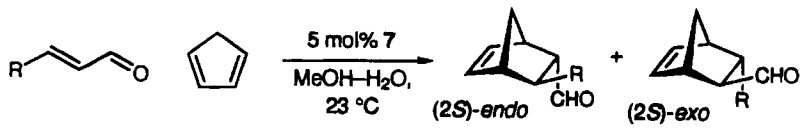


- (*E*)-iminium isomer to avoid steric interactions
- Shielding of the *re* face of the dienophile

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

Diels-Alder: Substrate Variation

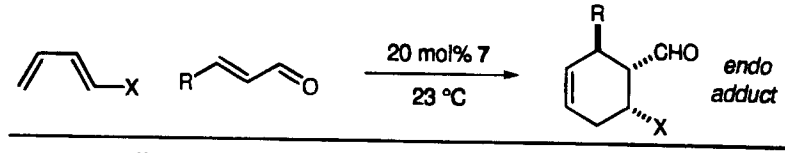
Table 2. Organocatalyzed Diels–Alder Cycloadditions between Cyclopentadiene and Representative Dienophiles

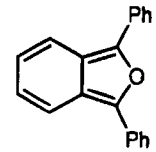
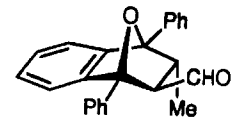
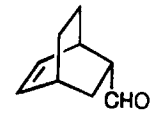
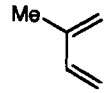
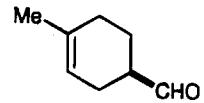
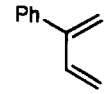
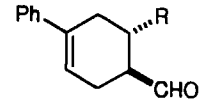
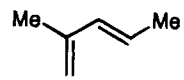
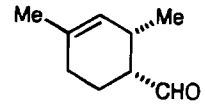
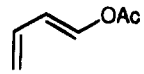
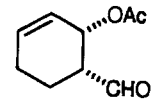


entry	R	time (h)	yield (%)	*exo*:*endo*[a,b]	*exo* ee (%)	*endo* ee (%)
1	Me	16	75	1:1	86 (2*S*)	90 (2*S*)
2	Pr	14	92	1:1	86 (2*S*)	90 (2*S*)
3	*i*-Pr	14	81	1:1	84 (2*S*)	93 (2*S*)
4	Ph	21	99	1.3:1	93 (2*S*)	93 (2*S*)
5	Furyl	24	89	1:1	91 (2*S*)	93 (2*S*)

[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information).

Table 3. Organocatalyzed Diels–Alder Reaction between Acrolein or Crotonaldehyde and Representative Dienes



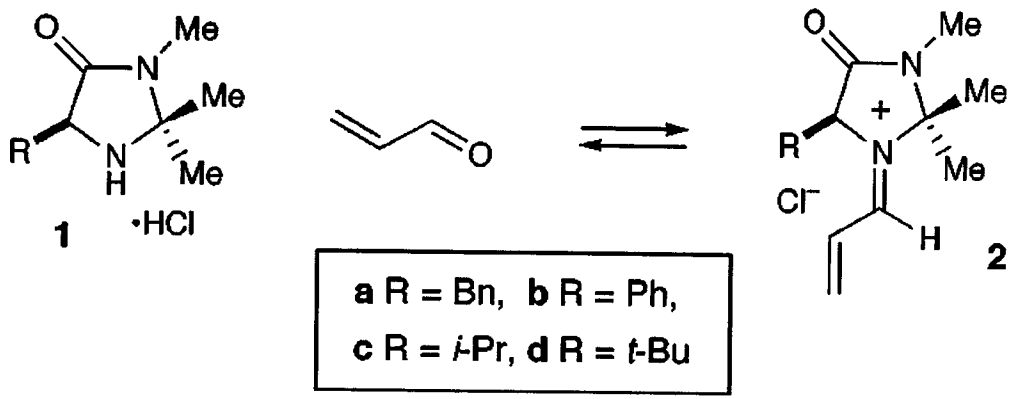
entry	diene	R	product	yield	*exo*:*endo*	% ee[a,b]
1		Me		75	35:1	96[c]
2		H		82	1:14	94[d]
3		H		84	--	89
4		H		90	--	83
5		Me		75	--	90
6		H		75	1:5	90
7		H		72	1:11	85

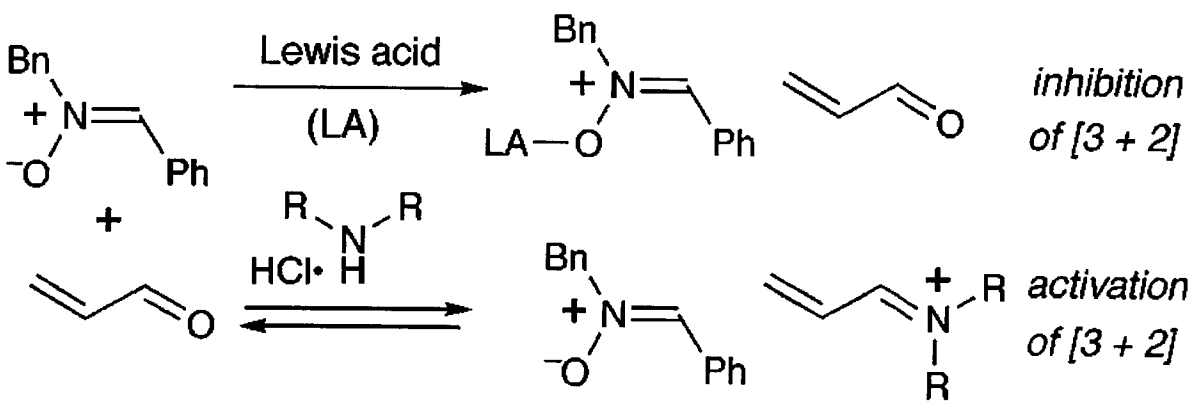
[a] Product ratios determined by GLC using a Bodman Γ-TA or β-PH column. [b] Absolute and relative configurations assigned by chemical correlation to a known compound (Supporting Information). [c] Using catalyst **5**. [d] Using 5 mol % catalyst.

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

Organocatalytic 1,3-Dipolar Cycloaddition

LUMO-Lowering Organocatalysis

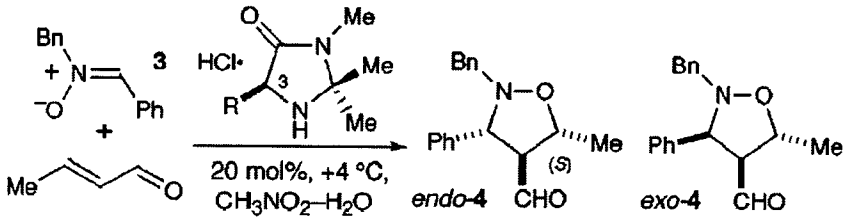




W.S. Jen; J.J.M. Wiener; D.W.C. MacMillan; *J. Am. Chem. Soc.* **2000**, *122*, 9874.

Dipolar Cycloaddition: Optimization

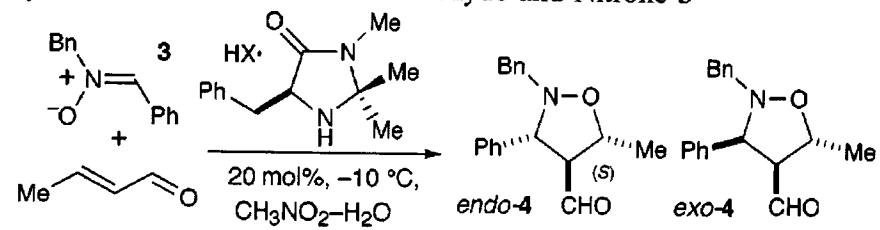
Table 1. Effect of Catalyst Structure on the Dipolar Cycloaddition between Crotonaldehyde and Nitrone **3**



entry	R–(catalyst)	Time (h)	% yield	*exo*:*endo*	% ee (*endo*)[a,b]
1	CH_2Ph (**1a**)	72	70	88:12	93
2	Ph (**1b**)	70	73	78:22	44
3	*i*-Pr (**1c**)	60	68	58:32	42
4	*t*-Bu (**1d**)	70	45	33:66	20
5	CH_2-2-napthyl (**1e**)	48	62	78:22	86
6	$CH_2C_6H_4OMe$-4 (**1f**)	48	77	79:21	89
7	CH_2CH_2Ph (**1g**)	48	72	50:50	69

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Absolute and relative configurations assigned by chemical correlation or by analogy (Supporting Information).

Table 2. Effect of the Brønsted Acid Cocatalyst on the Dipolar Cycloaddition between Crotonaldehyde and Nitrone **3**



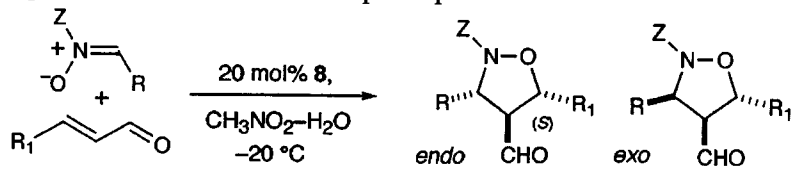
entry	HX co-catalyst	Time (h)	% yield	*endo*:*exo*	% ee (*endo*)[a]
1	HCl (**1a**)	108	70	88:12	95
2	TfOH (**5**)	101	88	89:11	90
3	TFA (**6**)	80	65	72:28	86
4	HBr (**7**)	80	77	94:6	93
5	$HClO_4$ (**8**)	80	86	94:6	90
6	$HClO_4$ (**8**)	100	98	94:6	94[b]

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Reactions performed at −20 °C.

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

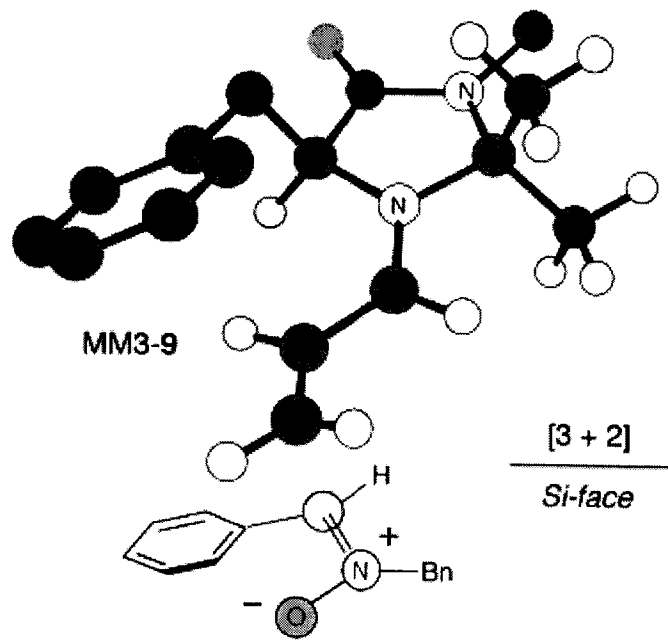
Dipolar Cycloaddition: Variation and Control

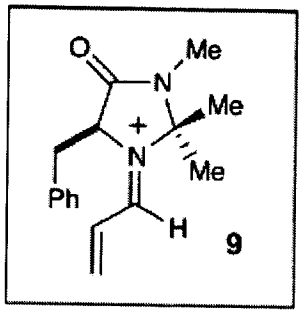
Table 3. Organocatalyzed Dipolar Cycloadditions between Representative Nitrones and Dipolarophiles



entry	Z	R	R_1	*endo*:*exo*	yield	% ee (*endo*)[a,b]
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Me	C_6H_4Cl-4	Me	93:7	76	94
6	Bn	C_6H_4OMe-4	Me	98:2	93	91
7	Me	C_6H_4Me-4	Me	93:7	82	97
8	Bn	2-naph	Me	95:5	98	93
9	Bn	*c*-hex	Me	99:1	70	99
10	Bn	Ph	H	81:19	72	90
11	Bn	Ph	H	86:14	80	92[c]
12	Bn	C_6H_4Me-4	H	85:15	80	90[c]
13	Bn	C_6H_4Cl-4	H	80:20	80	91[c]
14	Bn	2-naph	H	81:19	82	90[c]
15	Bn	C_6H_4OMe-4	H	91:9	83	90[c]

[a] Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with $NaBH_4$. [b] Absolute and relative configurations assigned by chemical correlation or by analogy (Supporting Information). [c] Reactions conducted with catalyst **5**.



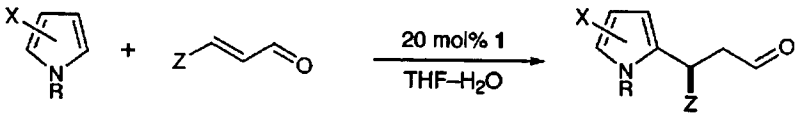


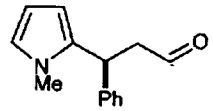
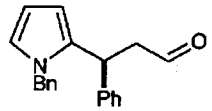
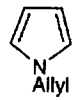
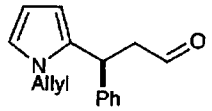
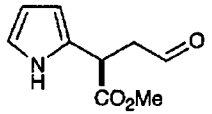
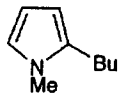
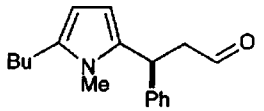
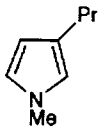
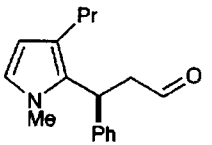
- (*E*)-iminium isomer
- Benzyl blocks *re* face
- *Endo* to minimize sterics

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

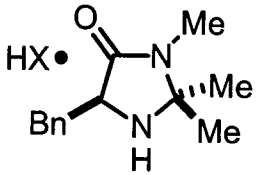
Organocatalytic Friedel-Crafts Alkylation

Table 3. Organocatalyzed Friedel–Crafts Alkylation between α,β-Unsaturated Aldehydes and Representative Pyrroles

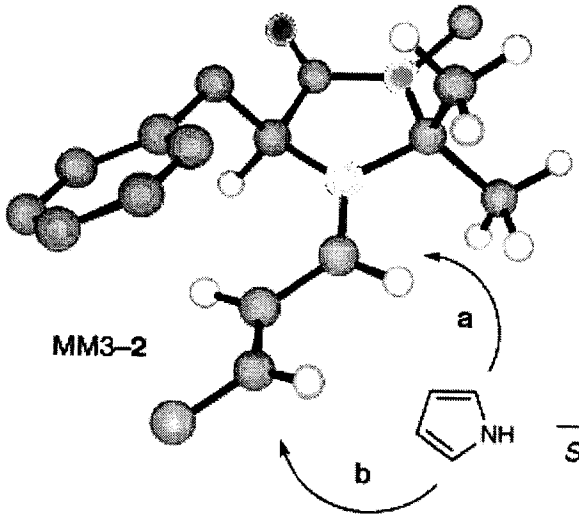


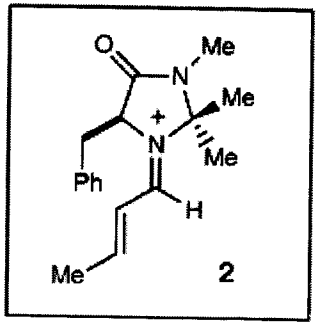
entry	pyrrole	Z	product	yield[a]	% ee[b,c]
1		Ph		87	93[d]
2		Ph		80	89[e]
3		Ph		83	91[e]
4		CO_2Me		74	90[f]
5		Ph		87	90[e]
6		Ph		68	97[c]

[a] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction. [b] Ratios determined by chiral GLC or HPLC. [c] Absolute stereochemistry determined by chemical correlation or by analogy. [d] Using catalyst **1d**. [e] Using catalyst **1c**. [f] Using catalyst **1a**.

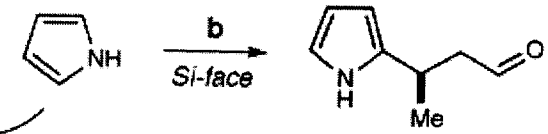


catalyst **1**





2

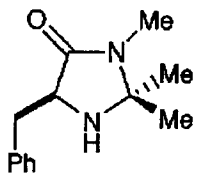


a = conventional acid catalyzed pathway **b** = non-conventional 1,4-addition

Path b favored due to steric demands of catalyst

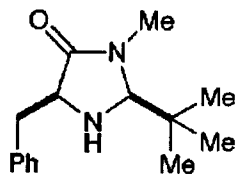
N.A. Paras; D.W.C. MacMillan; *J. Am. Chem. Soc.* **2001**, *123*, 4370.

Organocatalytic Indole Alkylations



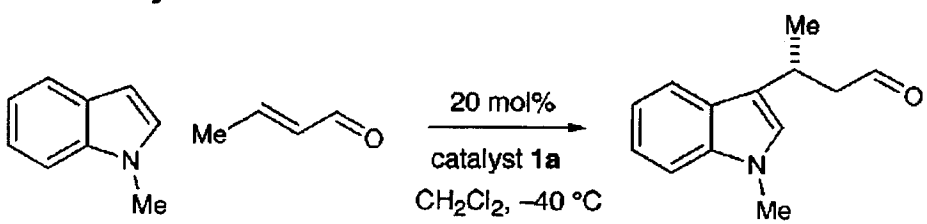
catalyst **1**

cocatalysts =
a = TFA
b = *p*-TSA
c = 2-NO_2PhCO_2H



catalyst **2**

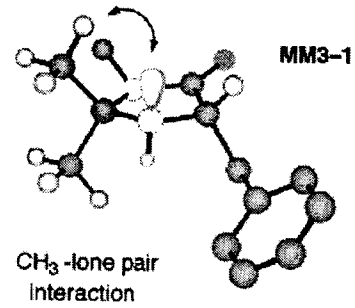
Indole Alkylation



56% ee, 85% yield, 48 h

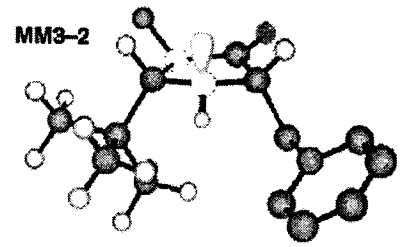
(2)

Computational model of catalyst **1**



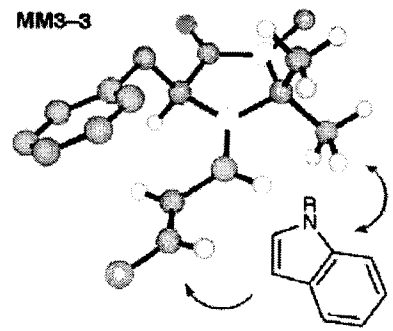
CH_3-lone pair interaction

Computational model of catalyst **2**



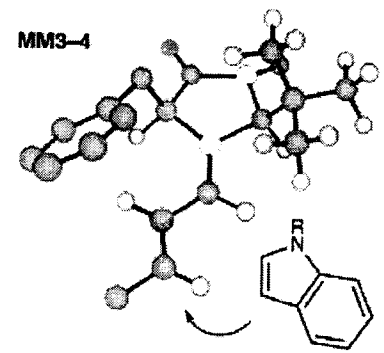
lone pair exposed

Computational model of iminium **3**



Effective *Si*-face coverage
Re-face CH_3-substrate interaction
Diminished substrate addition rate

Computational model of iminium **4**

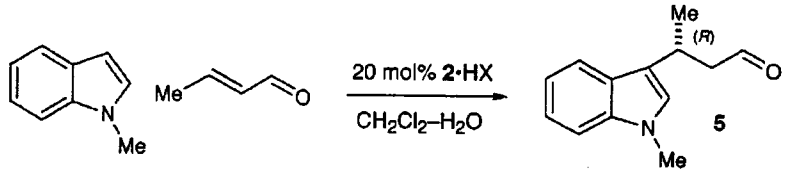


Increased *Si*-face coverage
Re-face addition unhindered
Increased substrate addition rate

J.F. Austin; D.W.C. MacMillan; *J. Am. Chem. Soc.* **2002**, *124*, 1172.

Indole Alkylation: Optimization, Scope, and Utility

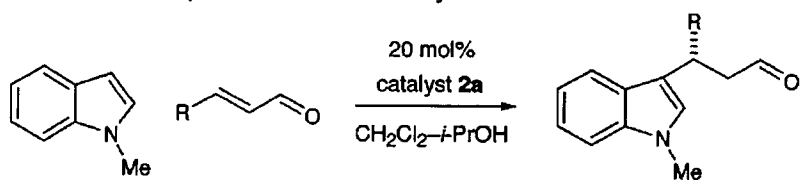
Table 1. Effect of Cocatalyst and Temperature on the Alkylation of *N*-Methylindole with Crotonaldehyde with Catalyst **2**



entry	catalyst	cocatalyst	temp °C	time (h)	% yield	% ee[a,b]
1	**2a**	TFA	−40	1.5	70	85
2	**2b**	*p*-TSA	−40	4	98	88
3	**2c**	2-NO_2PhCO_2H	−40	22	88	88
4	**2b**	*p*-TSA	−83	48	15	80
5	**2a**	TFA	−83	31	84	92
6	**2a**	TFA	−83	19	82	92[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration assigned by chemical correlation to a known compound. [c] Reaction conducted with CH_2Cl_2–*i*-PrOH (85:15 v/v) as solvent.

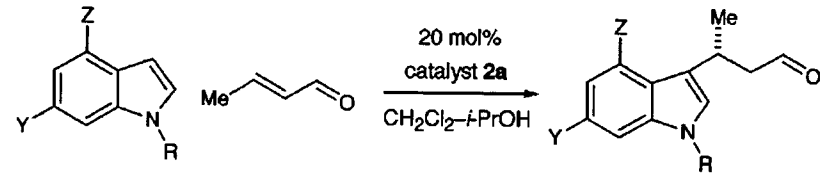
Table 2. Organocatalyzed Alkylation of *N*-Methylindole with Representative α,β-Unsaturated Aldehydes



entry	R	temp °C	time (h)	% yield	% ee[a]
1	Me	−83	19	82	92[b]
2	Pr	−60	6	80	93
3	*i*-Pr	−50	32	74	93
4	CH_2OBz	−83	18	84	96[b]
5	Ph	−55	45	84	90
6	CO_2Me	−83	21	89	91

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation.

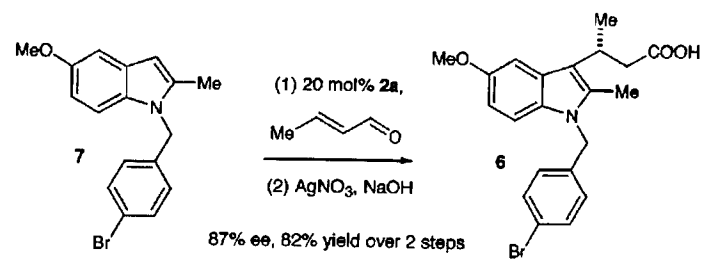
Table 3. Enantioselective Organocatalyzed Alkylation of Representative Indoles with (*E*)-Crotonaldehyde



	indole substituents						
entry	R	Y	Z	temp (°C)	time (h)	% yield	% ee[a]
1	Me	H	H	−87	19	82	92[b]
2	H	H	H	−60	22	72	91[b]
3	allyl	H	H	−72	20	70	92
4	CH_2Ph	H	H	−60	120	80	89[b]
5	H	H	Me	−60	3	94	94[c]
6	Me	H	OMe	−87	19	90	96[c]
7	H	Cl	H	−60	13	73	97[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration determined by chemical correlation. [c] Reaction conducted with (*E*)-$BzOCH_2CH{=}CHCHO$.

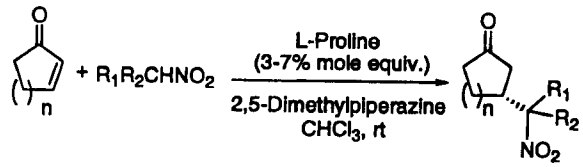
Synthesis of COX-2 Inhibitor



J.F. Austin; D.W.C. MacMillan; *J. Am. Chem. Soc.* **2002**, *124*, 1172.

Michael Addition of Nitroalkanes to Cycloalkenones

Table 1. Conjugate Addition with Nitroalkanes Catalyzed by L-Proline and *trans*-2,5-Dimethylpiperazine[a–c]



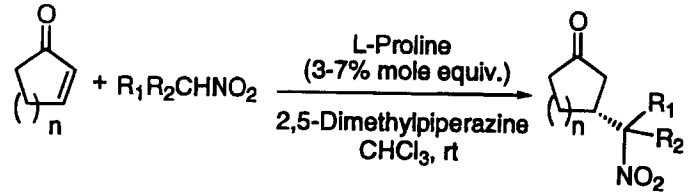
n = 1, 2, 3

n = 1, 2, 3
75-93% *ee*

Entry	NO_2	NO_2	NO_2
1.	66%, 75% *ee* (RbOH, 12% *ee*)	66%, 76% *ee* (RbOH, 37% *ee*)	62%, 76% *ee*
2.	88%, 93% *ee* (RbOH, 59% *ee*)	68%, 93% *ee* (RbOH, 75% *ee*)	73%, 93% *ee* (RbOH, 80% *ee*)
3.	61%, 86% *ee* (RbOH, 73% *ee*)	71%, 87% *ee* (RbOH, 67% *ee*)	49%, 89% *ee* (RbOH, 84% *ee*)

a. Yields (%) of chromatographically homogeneous product; *b.* RbOH % *ee* refers to rubidium prolinate catalyst as in reference 9; *c.* % *ee* measured by ^{13}C-NMR of corresponding ketal with 2*R*,3*R*-2,3-butane diol

Table 2. Conjugate Addition with Nitroalkanes Catalyzed by L-Proline and *trans*-2,5-Dimethylpiperazine[a–c]



n = 1, 2, 3

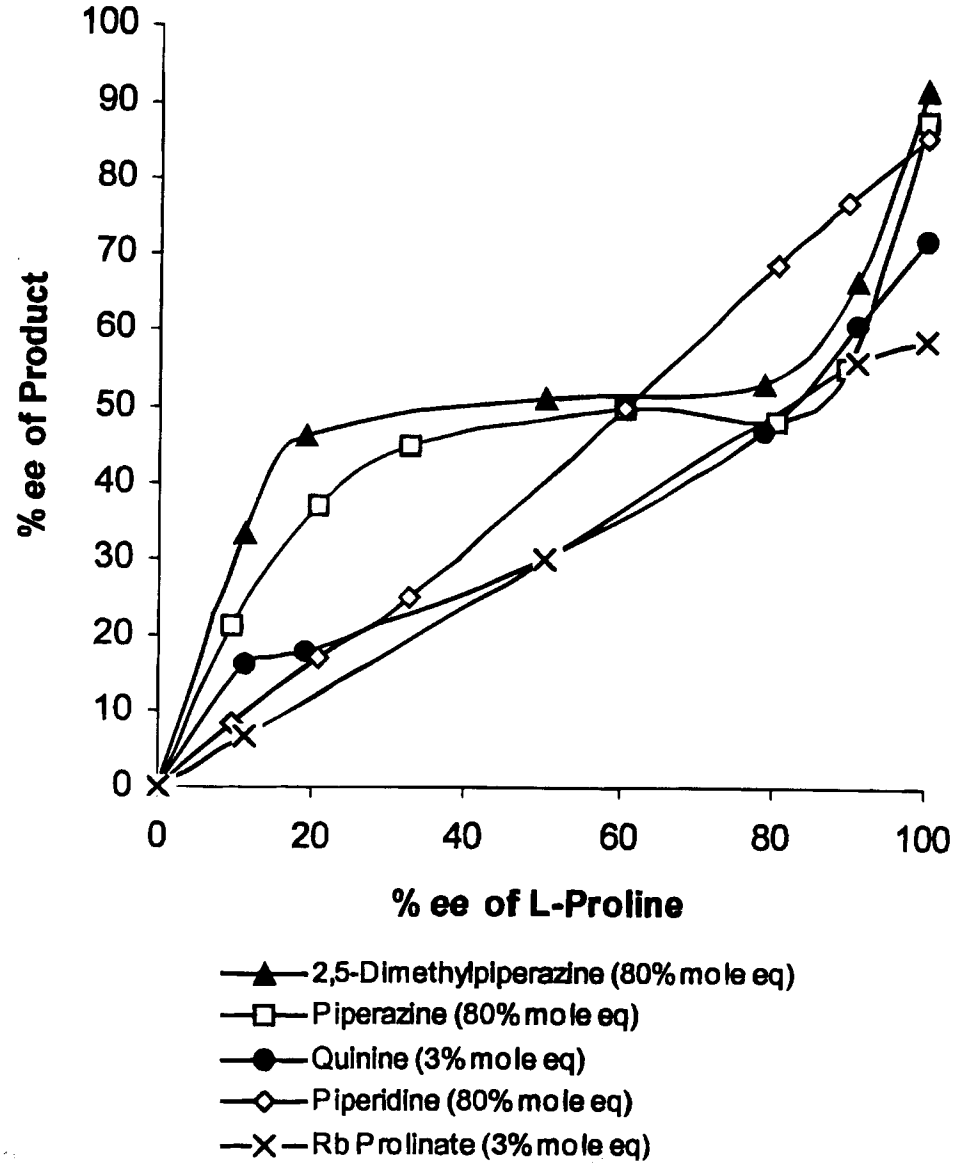
n = 1, 2, 3
62-87% *ee*

Entry	$EtNO_2$	NO_2	$MeNO_2$[d]
1.	71% (1:1)[a] A: 65% *ee*[b] B: 64% *ee*[c] (RbOH, 12% *ee*)	81% (1:1)[a] A: 76% *ee*[b] B: 63% *ee*[c]	30%, 62% *ee*
2.	86% (1:2)[a] A: 72% *ee*[b] B: 74% *ee*[c] (RbOH, 28% *ee*)	71% (1:2)[a] A: 87% *ee*[b] B: 77% *ee*[c] (RbOH, A 65% *ee*, B 58% *ee*)	61%, 71% *ee* (RbOH, 45% *ee*)

a. ratio of isomer A to B; *b.* *ee* of less polar isomer A; *c.* *ee* of more polar isomer B; *d.* 53%, 72% *ee* (RbOH, 41% *ee*) for cycloheptenone substrate (n=3)

S. Hanessian; V. Pham; *Org. Lett.* **2000**, *2*, 2975.

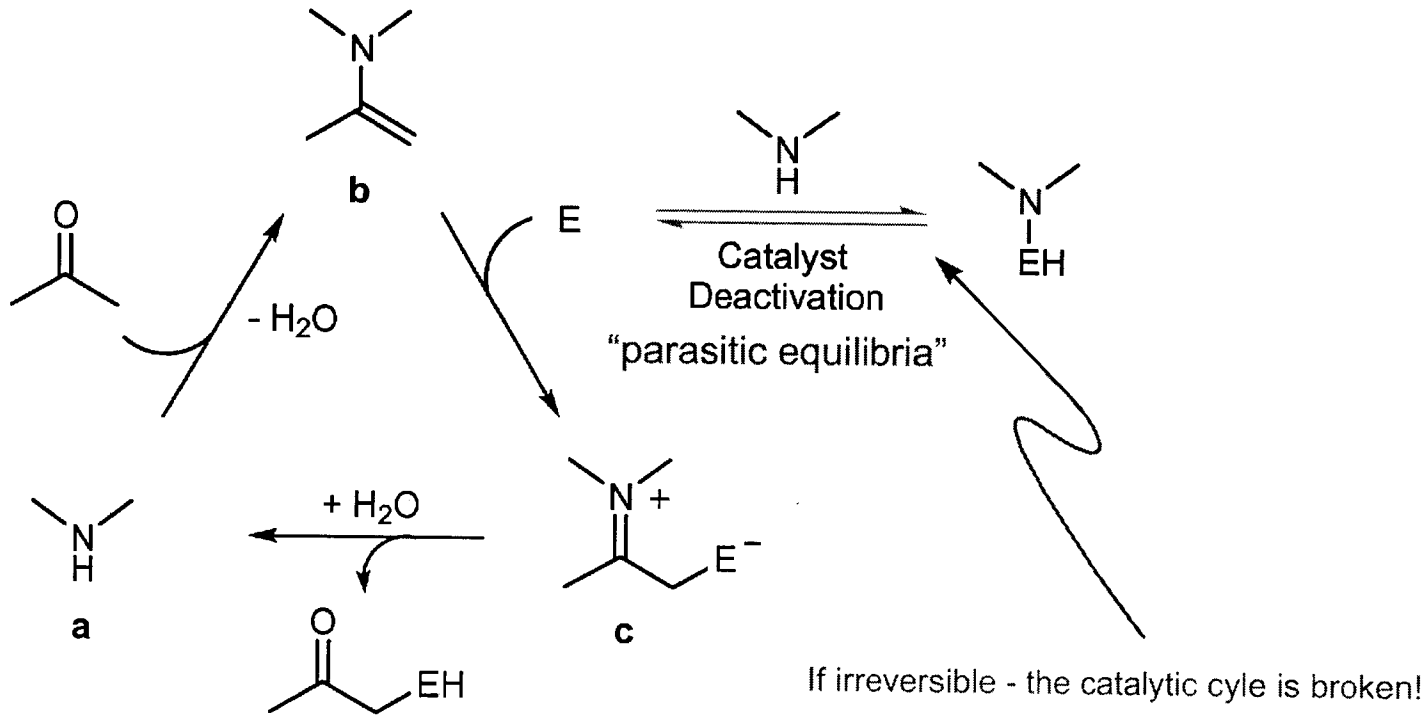
Nonlinear Effects in Michael Addition



"While it is not possible to derive clear mechanistic conclusions in a complex system that comprises a catalyst and an additive, in addition to the nitroalkane and the enone, the results are reminiscent of MLx systems where NLE curves show a similar trend"

S. Hanessian; V. Pham; *Org. Lett.* **2000**, *2*, 2975.

Enamine Catalysis

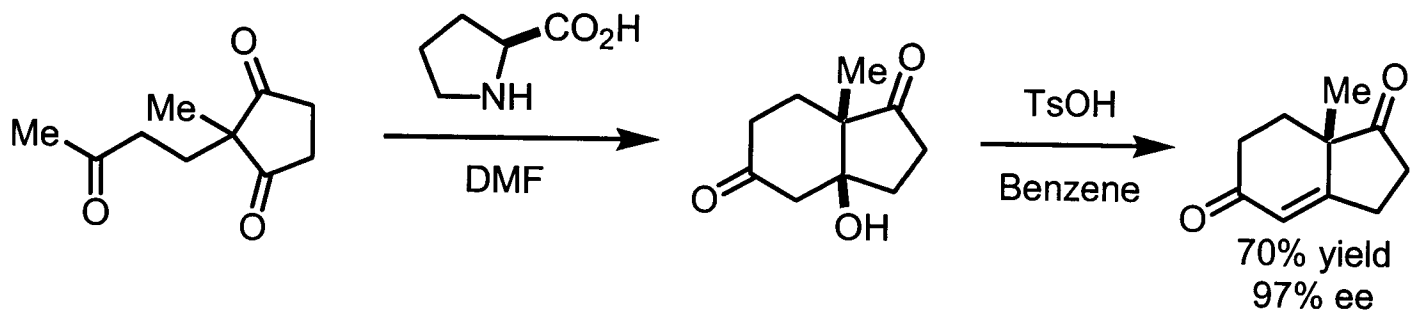


Scheme 6 The enamine catalysis-cycle

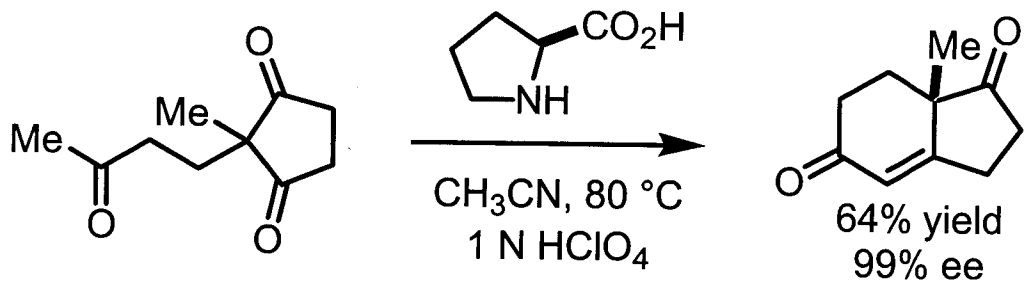
Only electrophiles that react reversibly with catalyst can be used

B. List; *Synlett.* **2001**, 1675.

The Hajos-Parrish-Eder-Sauer-Wiechert RXN

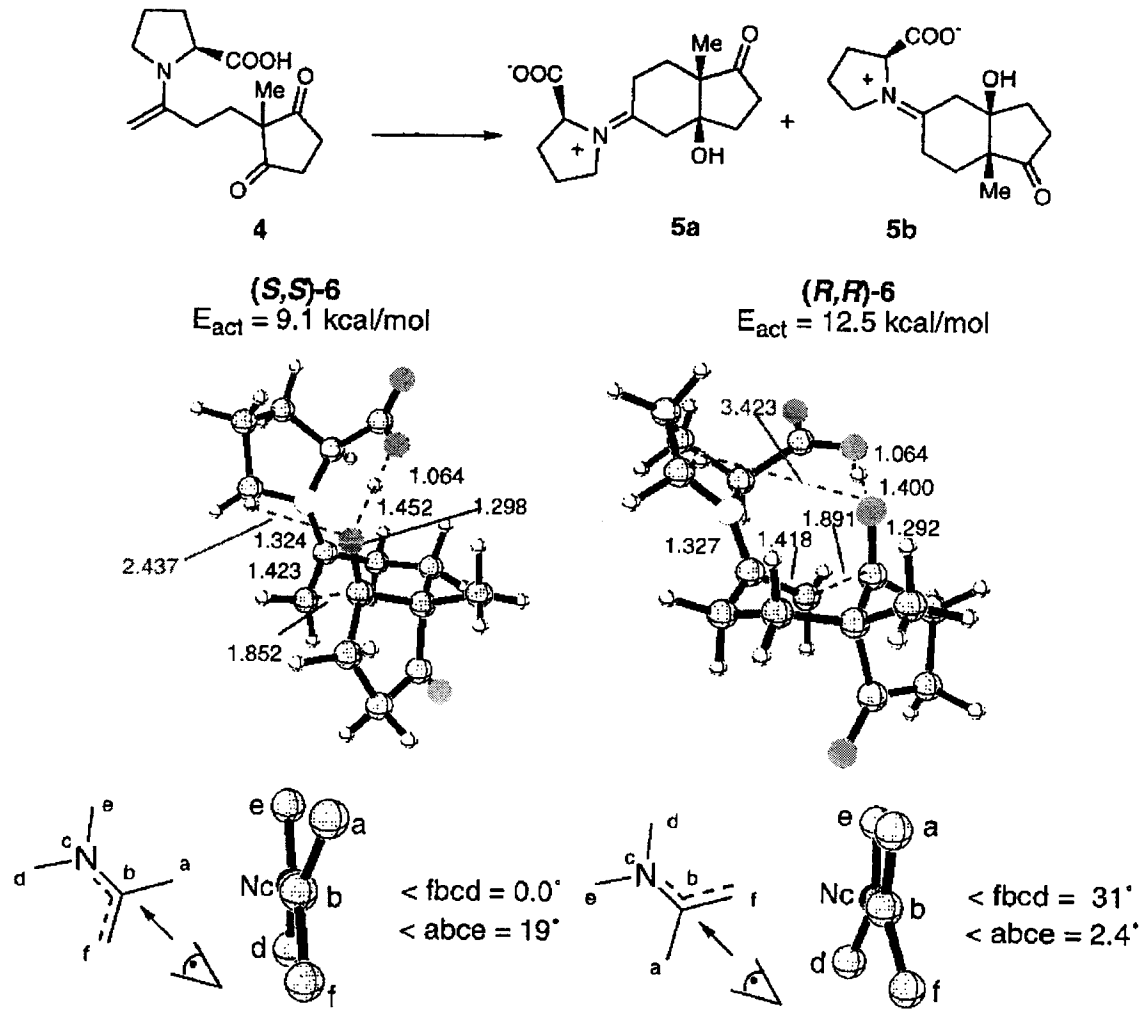


Z.G. Hajos; D.R. Parrish; *J. Org. Chem.* **1974**, *39*, 1615.



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

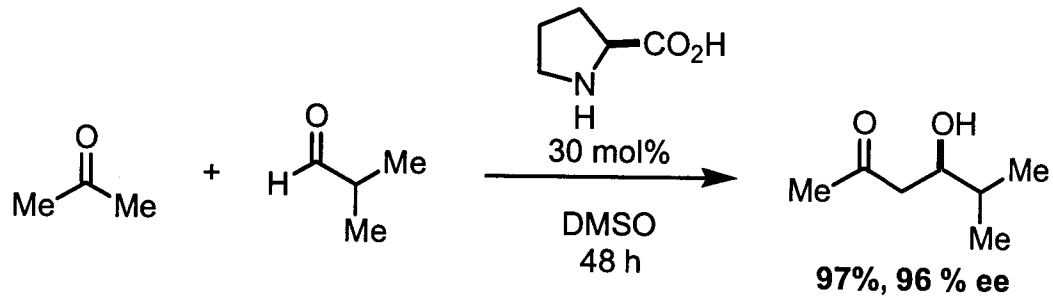
Origin of Stereoselectivity



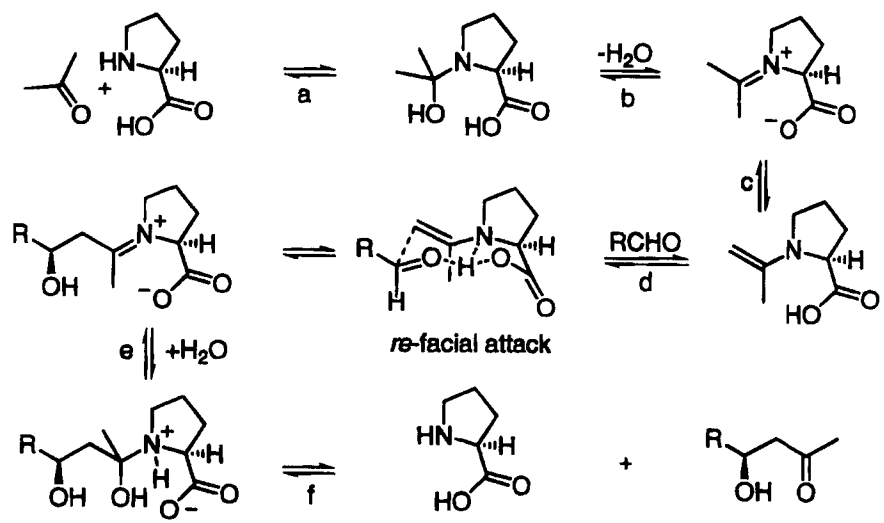
- Chair transition states
- *Cis* ketol is favored over *trans* for primary and secondary amine-catalyzed aldol reactions
- Iminium double bond is less planer in the (*R,R*) transition state
- Most of the partial positive charge resides on the methylene groups adjacent to the nitrogen of proline
- Favorable electrostatic interaction in (*S,S*) transition state is stronger

S. Bahmanyar; K.N. Houk; *J. Am. Chem. Soc.* **2001**, *123*, 12911.

Aminocatalyzed Direct Asymmetric Aldol Reaction



Scheme 1. Proposed Enamine Mechanism of the Proline-Catalyzed Asymmetric Aldol Reaction



Proline functions as a "micro-aldolase"

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

Aldol Reaction: Support for Proposed Mechanism

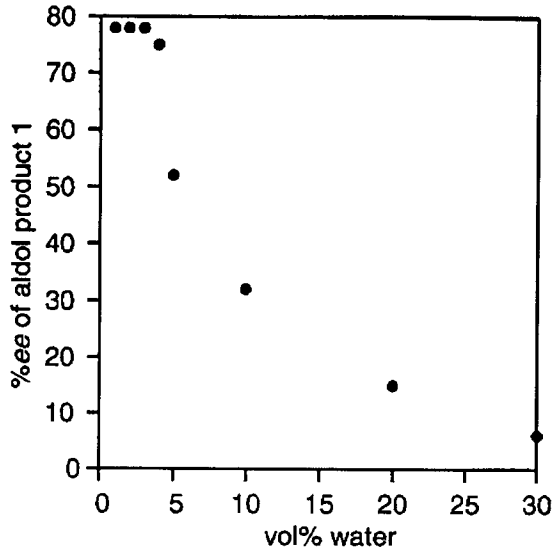


Figure 1. Effect of water on the enantiomeric excess of aldol product **1**.

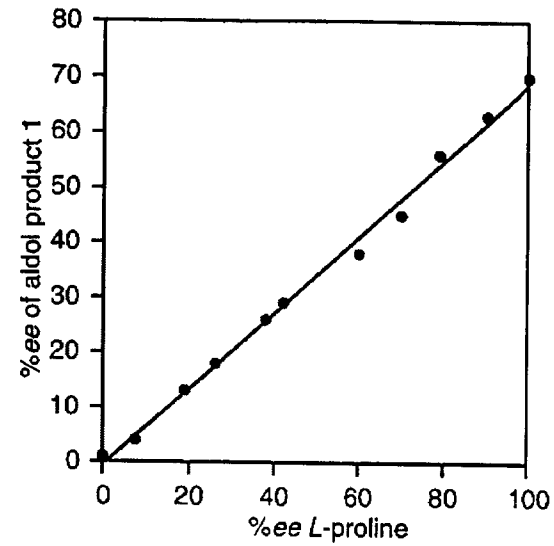


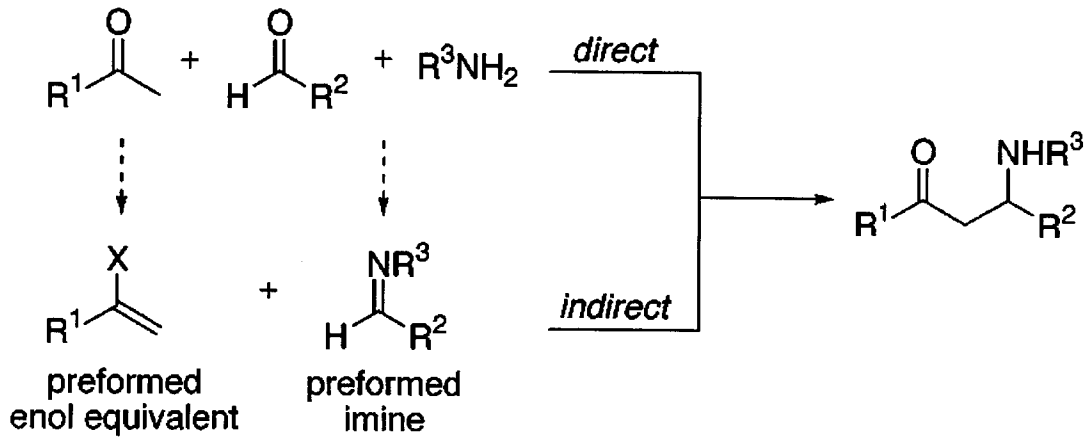
Figure 2. Linear effect in the L-proline catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde in DMSO. The line fits the equation $y = 0.69x - 0.47$, $R^2 = 0.995$.

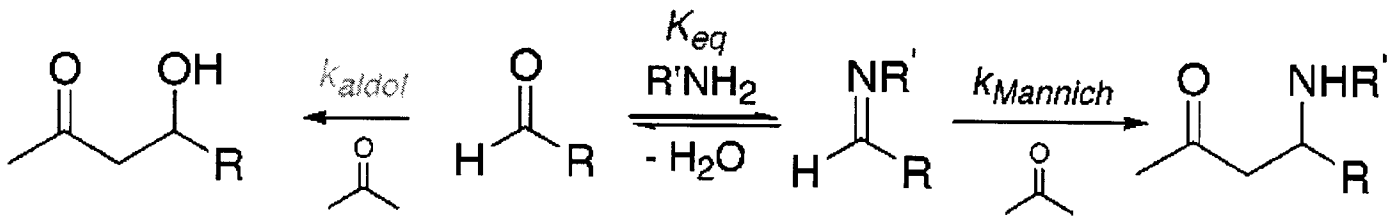
H-bonding is an essential feature of the organized transition state

Consistent with a single molecule of catalyst at the C-C bond forming step

K. Sakthivel; W. Notz; T. Bui; C.F. Barbas III; *J. Am. Chem. Soc.* **2001**, *123*, 5260.

Direct Mannich Reaction





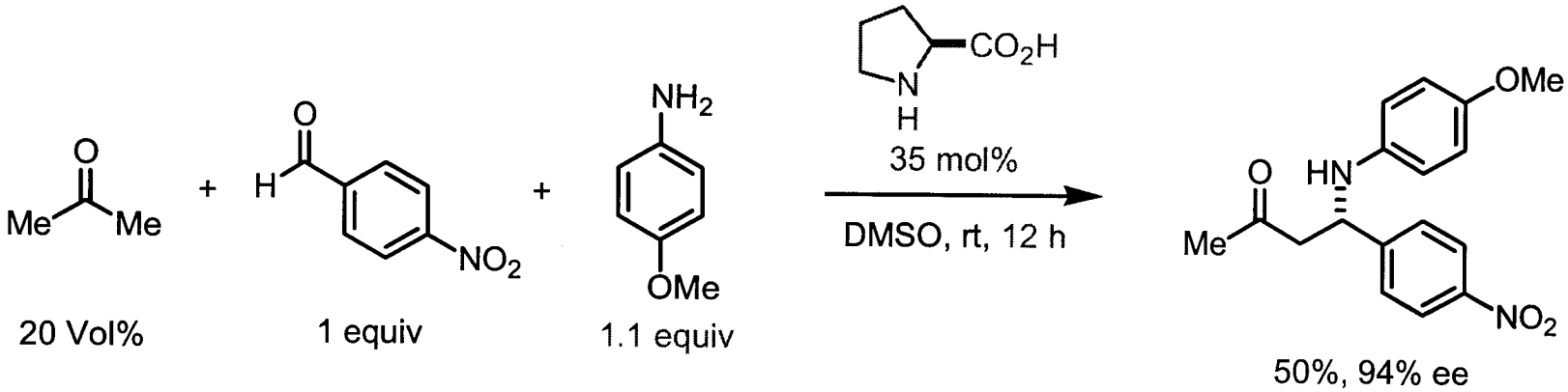
To promote direct Mannich reaction:

- $K_{eq} \geq 1$
- $k_{Mannich} > k_{aldol}$

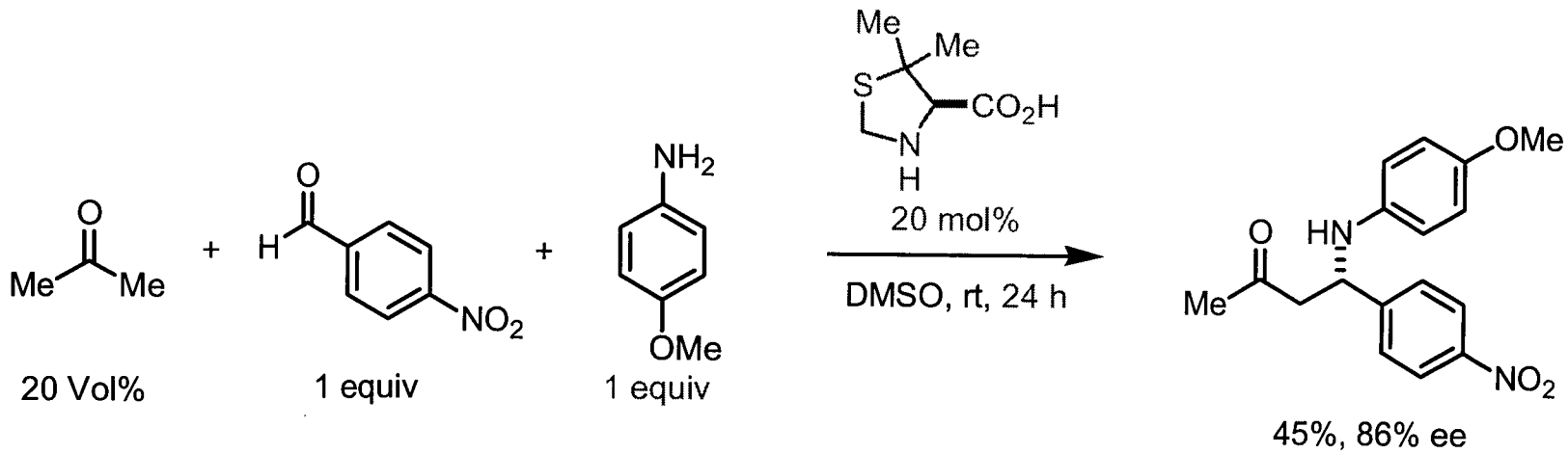
B. List; P. Pojarliev; W.T. Biller; H.J. Martin; *J. Am. Chem. Soc.* **2002**, *124*, 827.

Aminocatalyzed Direct Mannich Reaction

B. List; *J. Am. Chem. Soc.* **2000**, *122*, 9336. - Received June 1, 2000

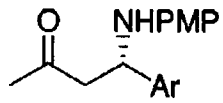
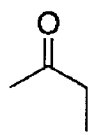
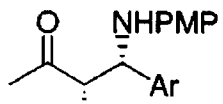
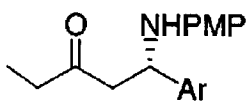
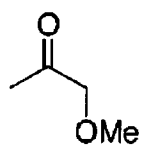
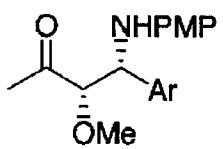
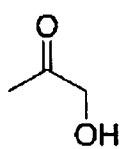
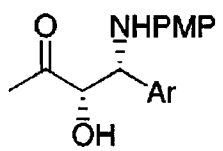


W. Notz; K. Sakthivel; T. Bui; G. Zhong; C.F. Barbas III; *Tetrahedron Lett.* **200**1, *42*, 199. - Received October 23, 2000



Direct Mannich Reaction: Ketone Variation

Table 1. Three-Component Mannich Reactions with Different Ketones (PMP = *p*-Methoxyphenyl, Ar = *p*-$O_2NC_6H_4$)

Ketone	Products	Yield %	de %	ee %
	 **1**	50	-	94
	 **2a**	96 (2a : 2b = 2.5:1)	>95	99
	 **2b**		-	94
	 **3**	93	>95	98
	 **4**	92	>95	>99

Chemoselectivity

- Entry 1 — <20% aldol Product
- Entries 2-4 – essentially no aldol product

Excellent diastereoselectivity

Regioselectivity

- Favors more substituted α-side

Excellent enantioselectivity

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

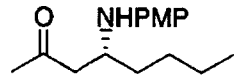
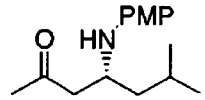
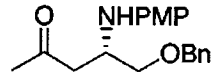
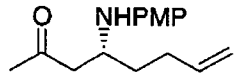
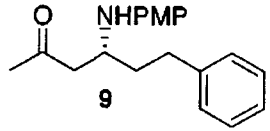
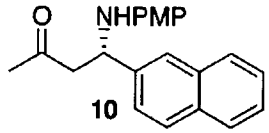
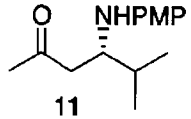
Direct Mannich Reaction: Aldehyde Variation

Unlike proline-catalyzed aldol reactions, α-unbranched aldehydes work well

Low yields for aromatic aldehydes

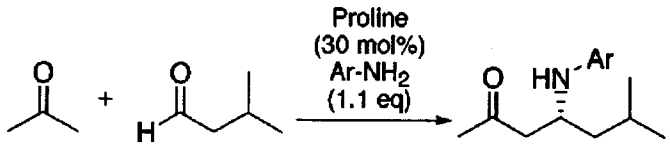
Carried out in 100% acetone so proline can be recovered by filtration and reused

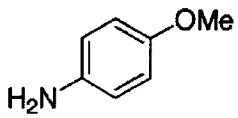
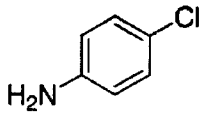
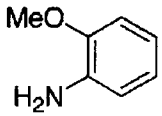
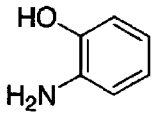
Table 2. Three-Component Mannich Reactions with Different Aldehydes

Entry	Product	Yield %	ee %
1	 **5**	74	73
2	 **6**	90	93
3	 **7**	82	75
4	 **8**	60	80
5	 **9**	80	93
6	 **10**	35	96
7	 **11**	56	70

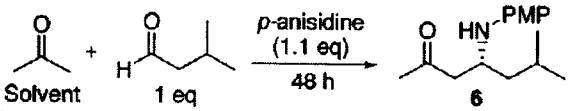
B. List; P. Pojarliev; W.T. Biller; H.J. Martin; *J. Am. Chem. Soc.* **2002**, *124*, 827.

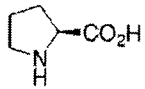
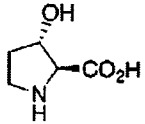
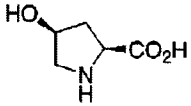
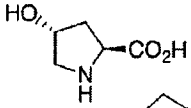
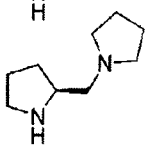
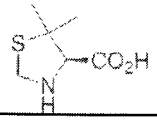
Direct Mannich RXN: Aniline and Catalyst Variation



Entry	Ar-NH_2	Yield %	ee %
1		90	93
2		55	84
3		43	< 10
4		51	< 10

PMP group gives best results and is easily removed through oxidation.



Entry	Catalyst (35 mol%)	Yield %	ee %
1		90	93
2		56	76
3		22	12
4		22	15
5		26	0
6		60	16

Proline is best catalyst.

(Barbas found DMTC best – 45%, 50% ee in 4:1 DMSO:acetone for same reaction.)

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

Optimization Studies

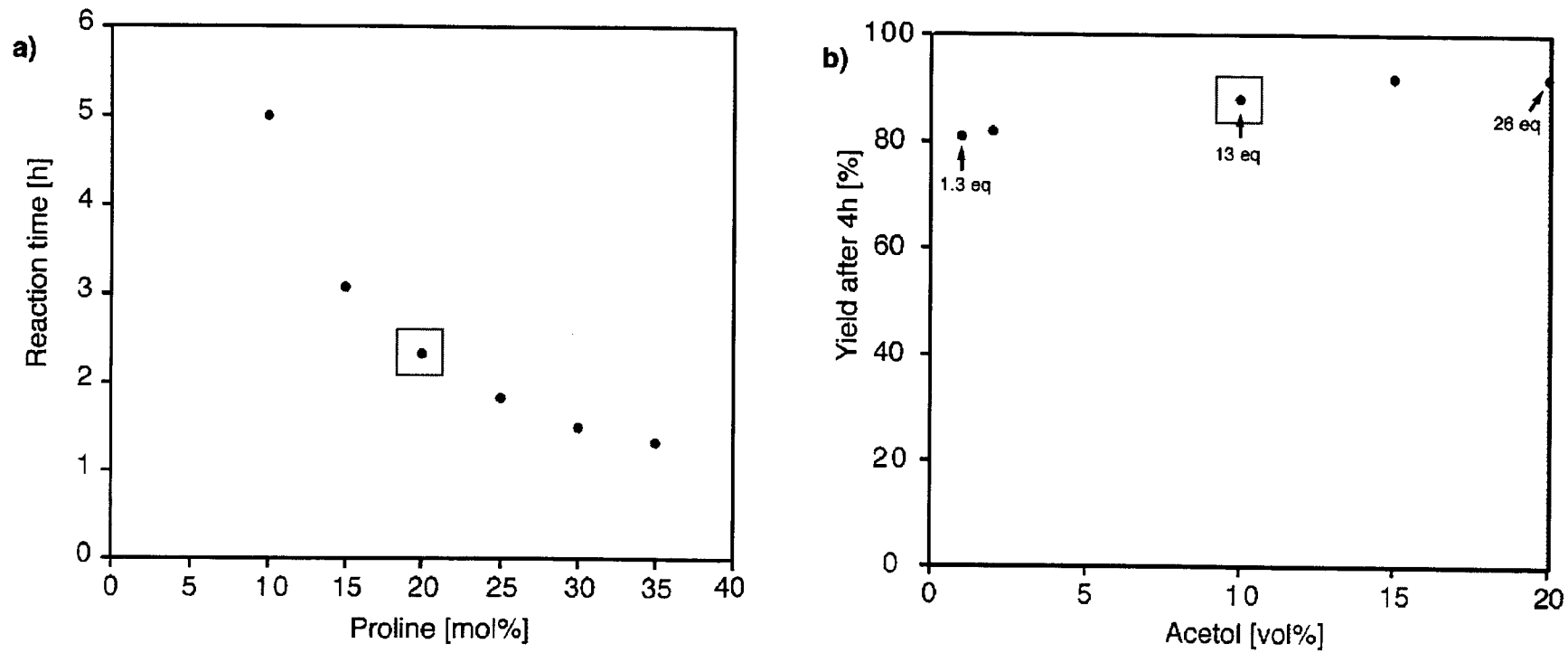


Figure 1. Optimization of catalyst loading and ketone amount in the reaction of *p*-nitrobenzaldehyde with *p*-anisidine and hydroxyacetone (acetol). (a) Variation of catalyst concentration. Conditions: 1 equiv of aldehyde, 1.1 equiv of *p*-anisidine, 10 vol % acetol/DMSO. (b) Variation of acetol concentration. Conditions: 1 equiv of aldehyde, 1.1 equiv of *p*-anisidine, 20 mol % proline.

New standard conditions: 20 mol % proline, 10 vol % hydroxyacetone

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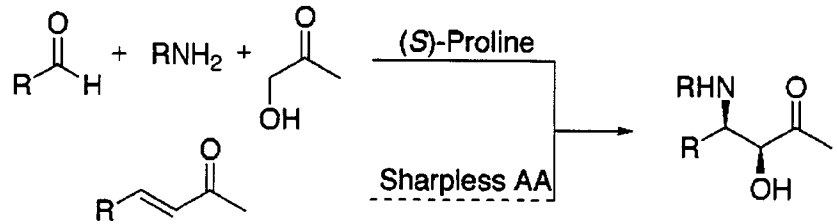
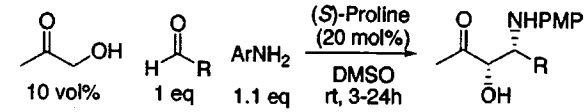
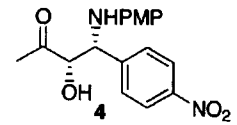
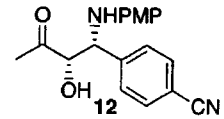
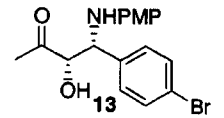
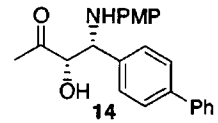
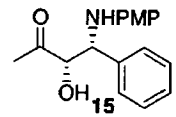
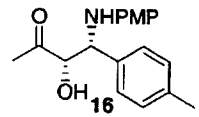
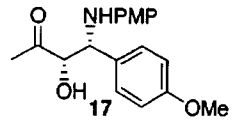
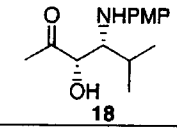
Synthesis of syn-1,2-Amino Alcohols





Entry	Product	Yield %	dr	ee %
1		92	20:1	>99
2		88	15:1	99
3		90	15:1	98
4		79	8:1	94
5		83	9:1	93
6		85	5:1	86
7		88	3:1	61
8		57	17:1	65

High chemo-, regio-, diastereo-, and enantioselectivities

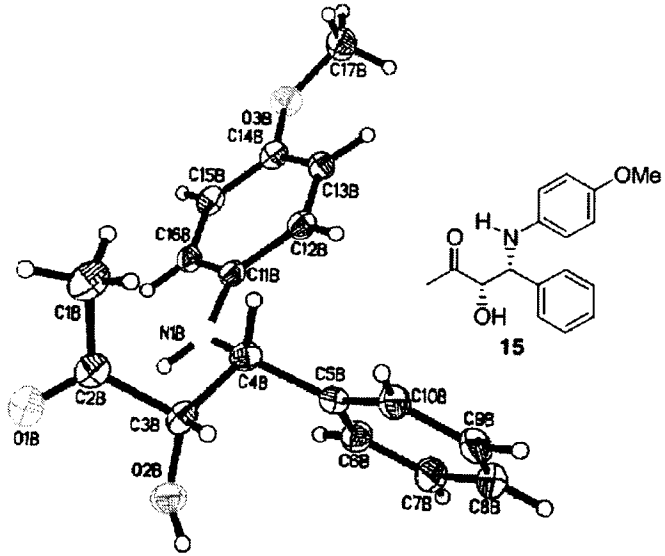
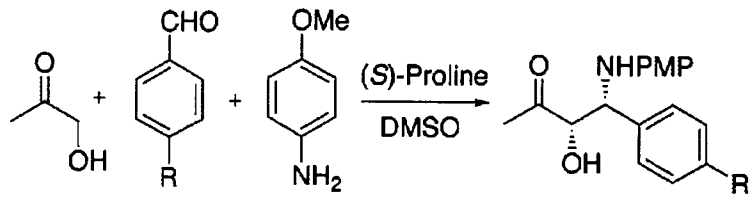


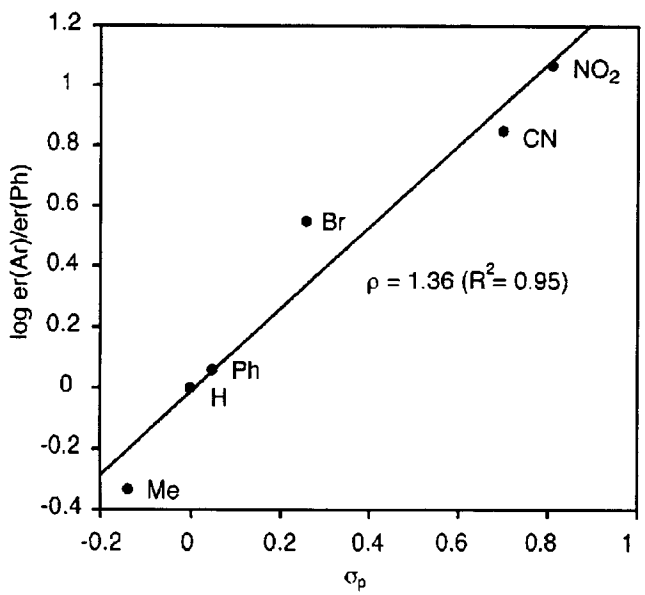
Figure 2. X-ray structure of amino ketone **15** (ORTEP view). The atoms are drawn at 50% probability.

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

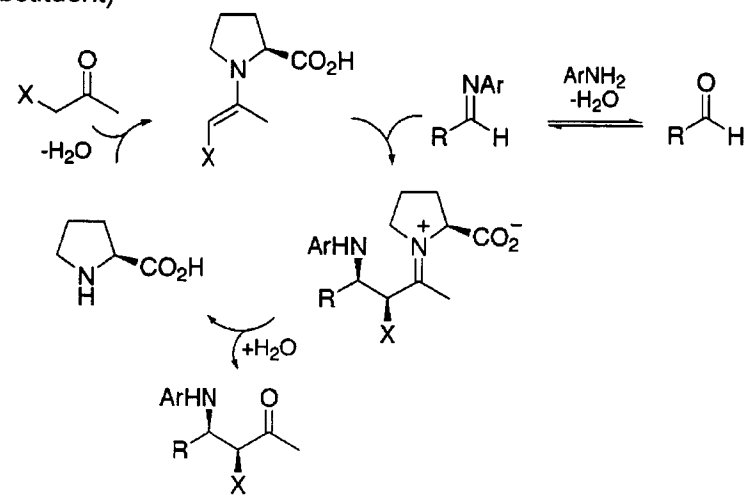
Proposed Mechanism



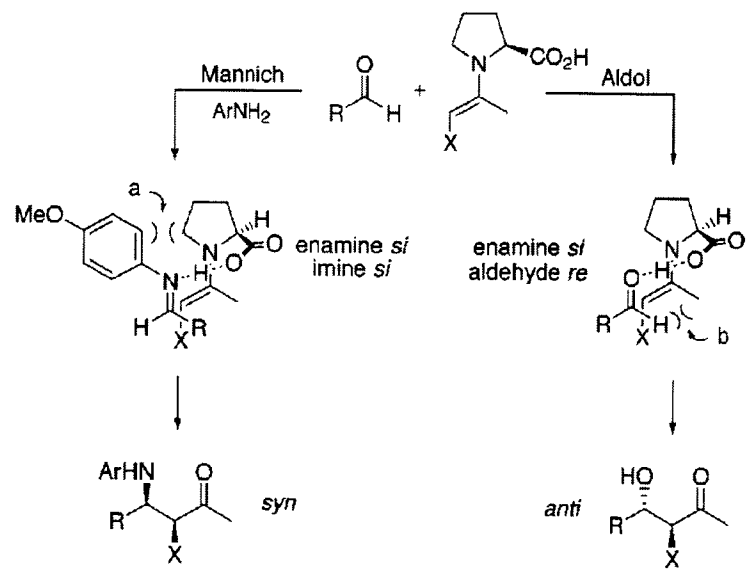
R	σ_p	Yield %	dr	ee %	er
NO_2	0.81	92	20:1	>99	332
CN	0.70	88	15:1	99	199
Br	0.26	90	15:1	98	99
Ph	0.05	79	8:1	94	32
H	0	83	9:1	93	28
Me	-0.14	85	5:1	86	13



Scheme 2. Proposed Mechanism (X = Oxygen or Carbon Substituent)



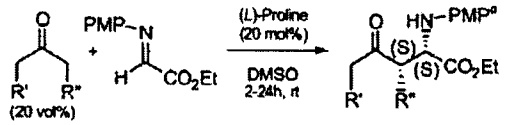
Scheme 3. Opposite Enantiofacial Selectivities and Topicities in Aldol and Mannich Transition States



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

Aminocatalyzed Route to Amino Acids

Table 1. Products from the Proline-Catalyzed Mannich-Reaction of Unmodified Ketones with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



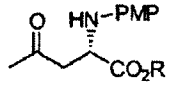
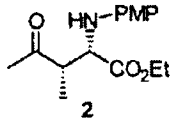
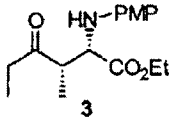
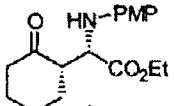
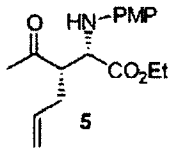
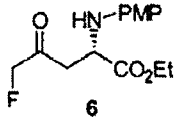
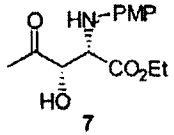
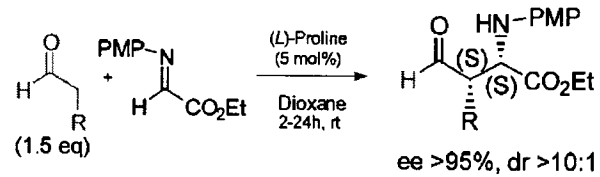
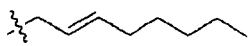
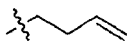
Entry	Product	Yield[b]	dr[c]	ee[d]
(1)	 **1a** (R=Et) **1b** (R=*i*-Pr)	1a: 82% 86%[e] 1b: 85%	- - -	95% 99% 97%
(2)	 **2**	72%	>19:1	>99%
(3)	 **3**	47%	>19:1	>99%
(4)	 **4**	81%	>19:1	>99%
(5)	 **5**	79%	>19:1	>99%
(6)	 **6**	77%	-	61%
(7)	 **7**	62%	>19:1	99%

Table 1. Products from the Proline-Catalyzed Mannich Reaction of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



ee >95%, dr >10:1

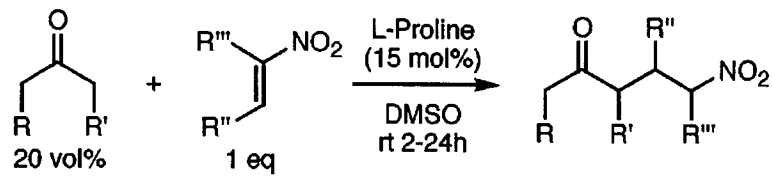
Entry	R	Yield[b]	dr[c]	ee[d]	Product
(1)	*i*-Pr	81%	>10:1 (19:1)[e]	93%	**1**
(2)	Me	72%	1.1:1 (3:1)[e]	99%	**2**
(3)	Et	57%	1.5:1 (7:1)[e]	99%	**3**
(4)	*n*-Bu	81%	3:1 (>19:1)[e]	99%	**4**
(5)	*n*-Pent	81%	>19:1 (>19:1)[e]	>99%	**5**
(6)		89%	>19:1 (>19:1)[e]	99%	**6**
(7)		71%	>19:1 (>19:1)[e]	>99%	**7**

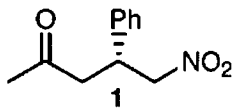
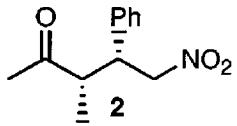
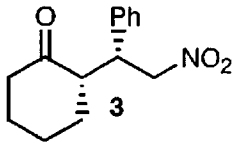
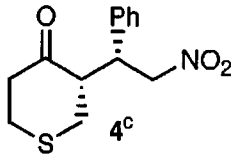
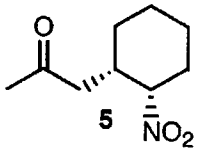
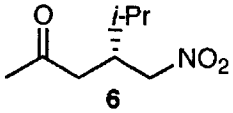
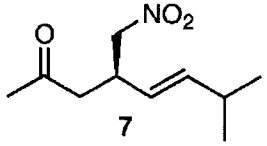
A. Cordova; W. Notz; G. Zhong; J.M. Betancort; C.F. Barbas III; *J. Am. Chem. Soc.* **2002**, *124*, 1842.

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

Proline Catalyzed Michael Additions to Nitroalkenes

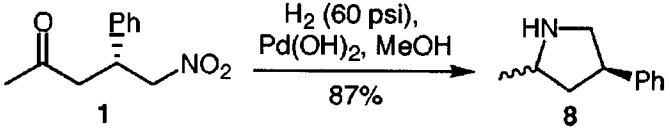
Table 1. Proline-Catalyzed Michael Addition of Unmodified Ketones to Nitroolefins



entry	product	yield	selectivity[a]
1	 **1**	97%	*ee* = 7%
2	 **2**	85%	*rr* > 20 : 1 *dr* = 3 : 1 *ee* = 10%[b]
3	 **3**	94%	*dr* > 20 : 1 *ee* = 23%
4	 **4**[c]	92%	*dr* > 20 : 1 *ee* = 10%
5	 **5**	95%	*dr* = 10 : 1 *ee* = 19%
6	 **6**	87%	not determined
7	 **7**	85%	not determined

[a] For ee, dr, and rr determination, see Supporting Information; rr = regioisomeric ratio. [b] ee of major *syn*-diastereomer. [c] Ten equivalents of the crystalline ketone tetrahydro-thiopyran-4-one was used.

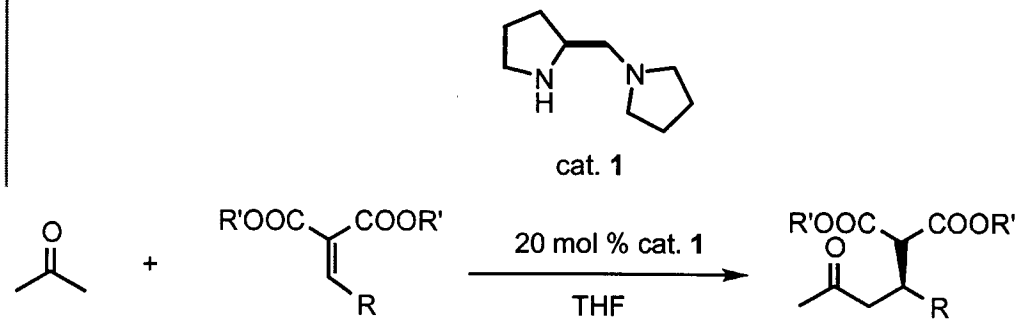
Scheme 2



High yields, diasteroselectivities, and regioselectivities from an operationally simple reaction. New catalysts are being investigated.

Received March 6, 2001 - B. List; P. Pojarliev; H.J. Martin; *Org. Lett.*. **2001**, *3*, 2423.

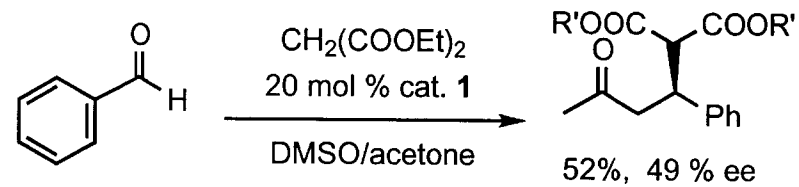
Another Aminocatalyzed Michael Addition



Entry	R	R′	Yield[a]	E.e.[b]
1	Ph	Et	47 (89)	59
2	1-Naphthyl	Et	31 (72)	64
3	2-Naphthyl	Et	60 (84)	55
4	2-Tolyl	Et	17 (86)	70
5	2-CF_3Ph	Et	46 (94)	70
6	2-Furyl	Et	84 (91)	33
7	*n*-Pentyl	Bn	16 (23)	24
8	Cyclohexyl	Bn	27 (42)	14
9	^{i}Pr	Bn	16 (28)	17

[a] Isolated yield after column chromatography; values in brackets refer to yields based on conversion.

[b] Enantioselectivities were determined by chiral-phase HPLC analysis in comparison with authentic racemic material using a Chiralcel AD column (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents.

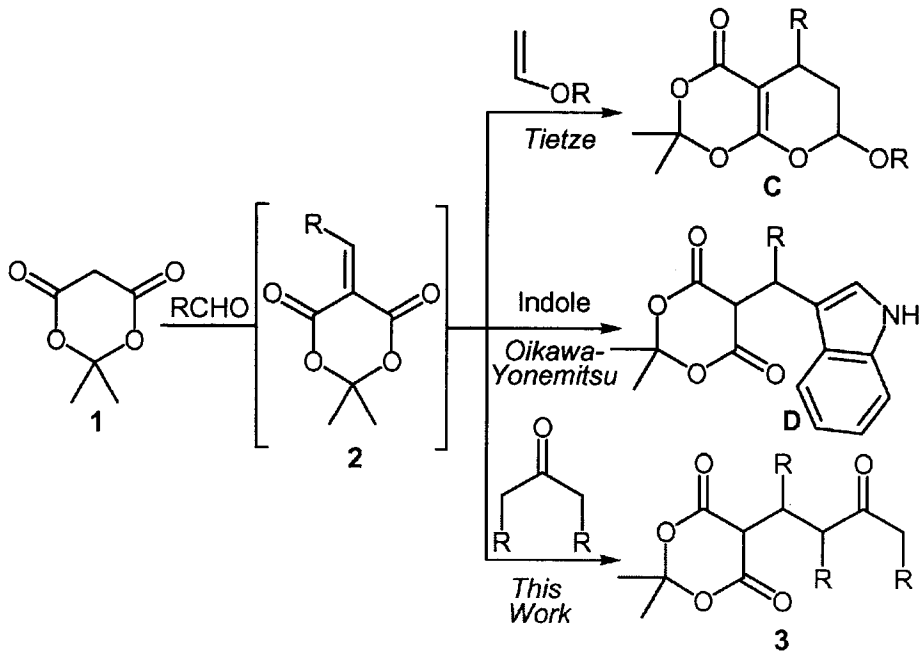


Scheme 3. One-pot Knoevenagel and Michael additions.

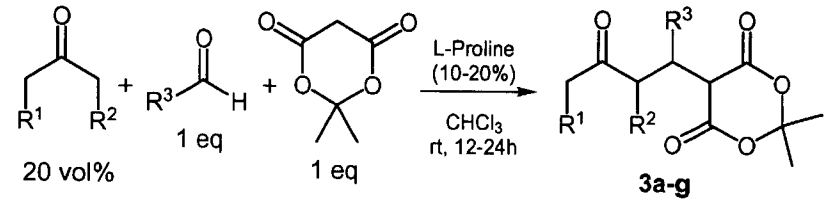
Better enantioselectivities, but further optimization is still needed!

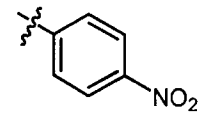
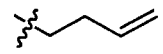
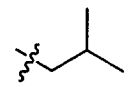
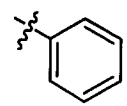
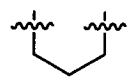
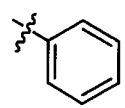
Received March 21, 2001 – J.M. Betancort; K. Sakthivel; R. Thayumanavan; C.F. Barbas III; *Tetrahedron. Lett.*. **2001**, *42*, 4441.

Three-Component RXN of Ketones, Aldehydes, and Meldrum's Acid (Iminium AND Enamine Aminocatalysis)



Scheme 2 Three component reactions involving aldehydes and Meldrum's acid



Entry	Product	R^1	R^2	R^3	Yield	dr[a]
1	**3a**	H	H		78%	
2	**3b**	H	H		83%	
3	**3c**	H	H		79%	
4	**3d**	H	H		51%	
5	**3e**	H	H		65%	
6	**3f**				69%	>95%
7	**3g**				75%	>95%

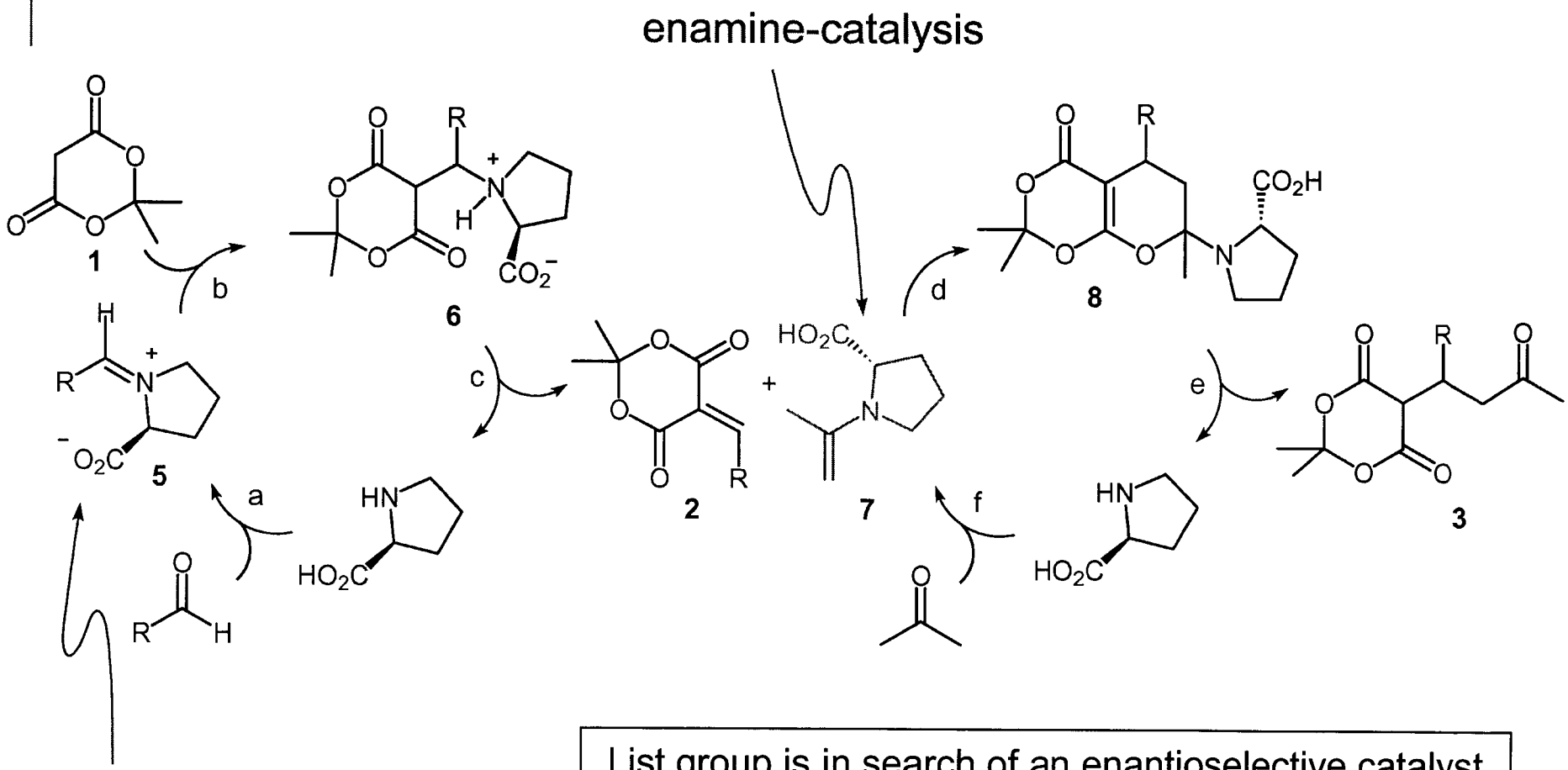
[a] Determined from HPLC and NMR analyses.

No asymmetric induction from proline, but its carboxylate functionality is essential for catalysis.

(pyrrolidine didn't work)

B. List; C. Castello; *Synlett.* **2001**, 1687.

Proposed Mechanism



List group is in search of an enantioselective catalyst for this transformation as well as other substrates that would extend the MCR beyond three components.

B. List; C. Castello; *Synlett.* **2001**, 1687.

Conclusions

- Many asymmetric reactions can be amiocatalyzed
  - Cycloaddition, Friedel Crafts, alkylation, aldol, Mannich, Michael, etc.
- Most aminocatalyzed reactions involve iminium ions or enamines
- The reactions are not sensitive to wet solvents or air
- L-proline is cheap (100 g = $43.10) and D-proline is also available
- Aminocatalysis complements rather than competes with current methods
- Though many proposed mechanisms seem rational, more mechanistic studies are needed
- Most of the information presented was reported in the 21st century