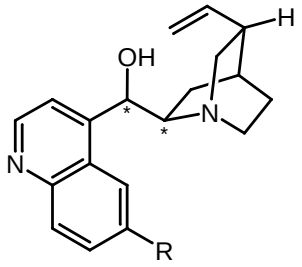
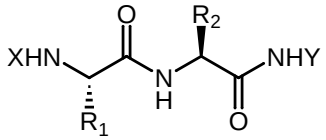
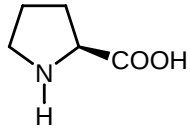
Asymmetric Catalysis with Chiral Lewis Bases (Part III): Cinchona Alkaloids, Peptides, and Prolines

Evans Group Seminar
Essa Hu
March 23, 2001

Reactions:
- Conjugate Addition
- Cyanohydrin Synthesis
- Strecker Reaction
- Desymmetrization
- Kinetic Resolution
- Ketene Chemistry
- Aldol Reaction
- Mannich Reaction
- Michael Addition
- Diels-Alder Reaction
- 1,3-Dipolar Cycloaddition

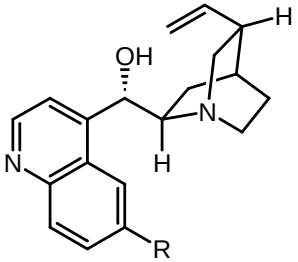


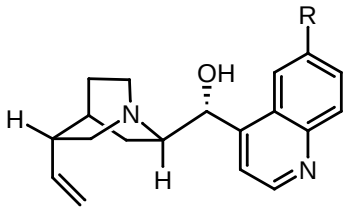




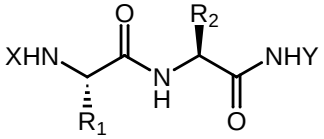
Reviews:
Groger, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 529-532
Noyori, R. "Asymmetric Catalysis with Purely Organic Compounds", *Asymmetric Catalystis in Organic Synthesis*, John Wiley & Sons, Inc., **1994**

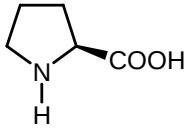
Other relevant seminars:
Favor, D. "Asymmetric Heteroatom Conjugate Additions", Evans Group Seminar, March **2000**
Downey, W. "Recent Advances in Catalytic Asymmetric Conjugate Addition", Evans Group Seminar, March, **2000**
Janey, J. "[2+2] Cycloadditions of Ketenes", Evans Group Seminar, Oct. **1999**
Trotter. W. "Enantioselective Desymmetrization", Evans Group Seminar, April. **1997**





Overview





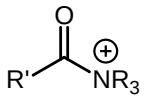
Cinchona alkaloids, peptides, and prolines have been used to catalyze a wide range of reactions.

• These Lewis base catalyzed reactions can be divided into two categories:

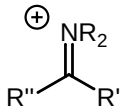
(1) asymmetric catalysis via non-covalent interactions (ionic interaction, hydrogen bonding)

- Conjugate addition
- Cyanohydrin synthesis
- Strecker reaction

(2) asymmetric catalysis via covalent interactions (chiral nucleophile, carbonyl activation)



- Desymmetrization
- Kinetic resolution
- Ketene chemistry

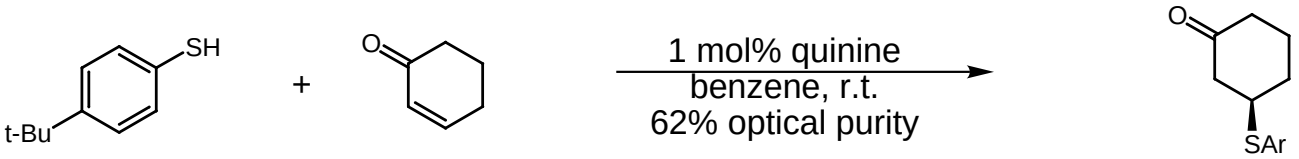


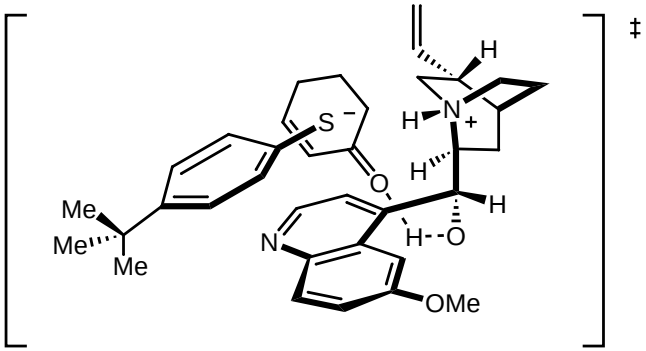
- Aldol reaction
- Mannich reaction
- Michael Addition
- Diels-Alder reaction
- 1,3-dipolar cycloaddition

via non-covalent interactions

Conjugate Addition 1

first examples





[History] Wynberg was the first to use cinchona alkaloids to catalyze various types of conjugate additions (1975). Initially, however, the enantioselectivities were measured *after* crystallizations of the product.

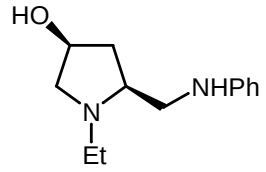
- Cinchona alkaloids served as a bifunctional catalyst: activation of thiol via ion-pair formation and activation of the enone carbonyl via hydrogen bonding.
- Lowering of reaction temperature and concentration increased selectivity but lengthened reaction time.
- Enantioselectivity was strongly solvent dependent. The hydrogen bond accepting solvents and polar solvents lowered the ee.
- Hydroxyl group on the catalyst was essential for high optical purity.

$$\text{optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

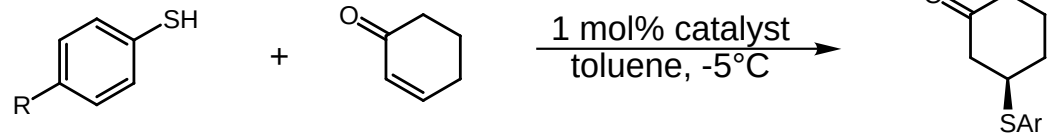
Wynberg, H. *J. Am . Chem. Soc.* **1981**, *103*, 417-430; *Tet. Lett.* **1979**, 2181; *J. Org. Chem.* **1979**, *44*, 2238; *J. Org. Chem.* **1979**, *44*, 1508; *Tet. Lett.* **1977**, *25*, 2181-2182;*Tet. Lett.* **1975**, *46*, 4057-60

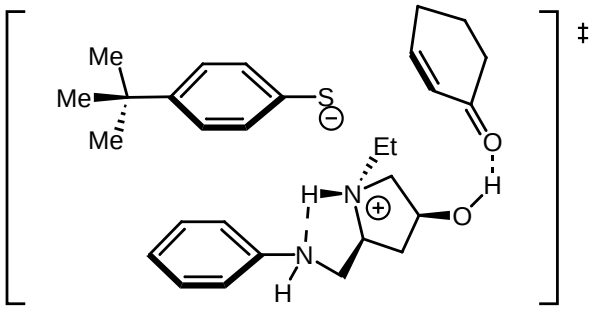
Conjugate Addition 2

proline derivatives



from L-Proline





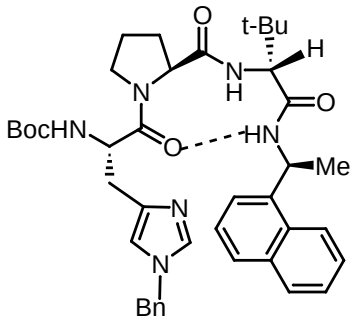
R	yield(%)	ee(%)
H	83	77
Me	75	73
Cl	84	47
MeO	75	83
t-Bu	74	88

- Nonpolar aromatic solvents and carbon tetrachloride were the best solvents for good enantioselectivity.
- Lowering reaction concentration increased the optical yield but decreased the reaction rate.
- Alkanethiols and other sizes of cycloalkenones gave poor yields.

Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277-3282

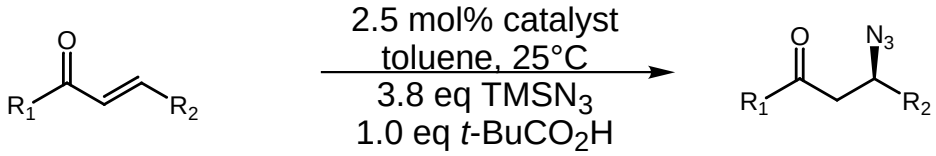
Conjugate Addition 3

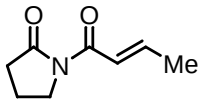
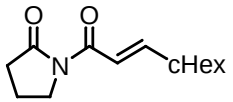
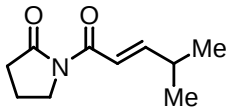
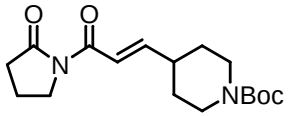
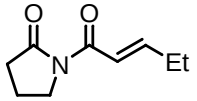
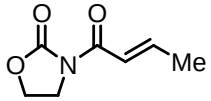
azide delivery



catalyst

- Exchage of L-*t*-Leu with D-*t*-Leu afforded only 14%ee of reaction (a).
- Linear effect was observed.

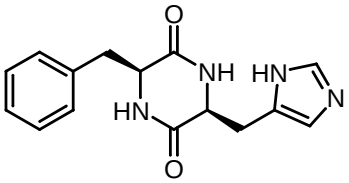


		yield(%)	ee(%)
(a)		97	63
		79	85
		84	82
		85	71
		91	71
		85	45

Miller, S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635-3638; *Org. Lett.* **1999**, *1*, 1107-1109

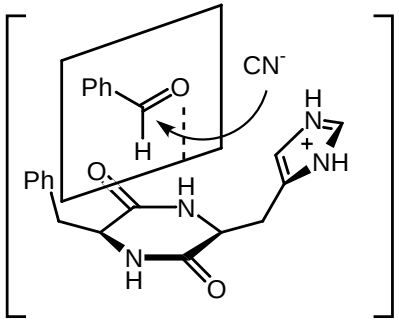
Cyanohydrin Synthesis 1

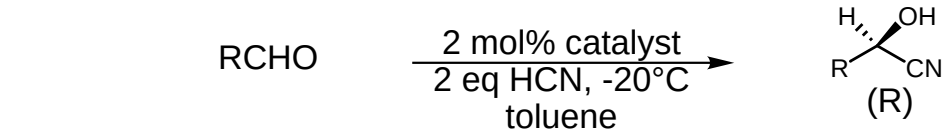
cyclic peptides



cyclo-[(S)-Phe-(S)-His]

Inoue's explanation:





aldehyde	time(h)	conv.(%)	ee(%)
Ph	8.0	97	97
4-MeO-Ph	10.0	57	78
3-MeO-Ph	8.0	83	97
2-MeO-Ph	10.0	45	84
3-PhO-Ph	8.0	97	92
4-Me-Ph	10.0	78	96
4-NO_2-Ph	2.5	99	53
3-NO_2-Ph	8.0	100	4
4-CN-Ph	8.0	100	32
2-naphthaldehyde	1.5	61	91
6-MeO-2-naphthaldehyde	6.0	88	73
furfural	8.0	60	42
nicotin-3-aldehyde	0.5	73	54
cyclohexanecarbaldehyde	2.5	96	58
isobutyraldehyde	5.0	79	71
isovaleraldehyde	5.0	44	18
hexanal	8.0	90	56
pivalaldehyde	5.0	60	58

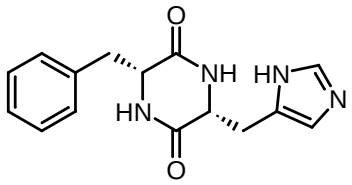
[History] First reported uses of alkaloids in cyanohydrin synthesis were by Bredig (1912) and Prelog (1954). Low selectivities were observed.

- Acyclic dipeptide Z-(S)-Phe-(S)-His-OMe showed no asymmetric induction.

Inoue, S. *J. Org. Chem.* **1990**, *55*, 181-185; Inoue, S. *J. Chem. Soc. Chem. Comm.* **1981**, 229-230; Prelog, V. and Wilhelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634; Bredig, G. and Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7

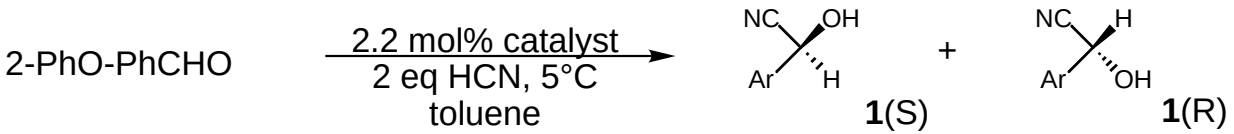
Cyanohydrin Synthesis 2

enantioselective autoinduction



cyclo-[(R)-Phe-(R)-His]

- Cyclic dipeptide and 1(S) complex seemed to be a more active catalyst than the cyclic dipeptide alone.
- First example of enantioselective autoinduction in a catalytic reaction.
- "Enantioselective autoinduction" is defined as an asymmetric reaction promoted by a chiral catalyst into which the chiral product has been incorporated.



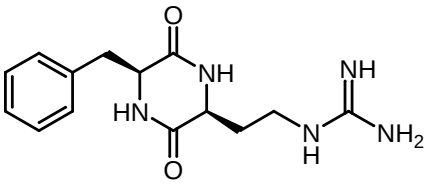
1(S) **1**(R)

conditions	time(h)	conv.(%)	ee(%) of 1
A = just catalyst	0.5	21	34(S)
	1	39	66
	2	92	92
	4	94	92
B = cat + 9 mol% **1(S) of 92%ee**	0.5	**55**	**96**
	1	79	96
	2	92	97
	4	95	97
C = cat + 9 mol% 1(R) of 85%ee	0.5	17	35
	1	38	66
	2	92	92
	4	95	92
A with100% ee catalyst		94	92
A with 85% ee catalyst		89	80
A with 79% ee catalyst		89	76
A with 67% ee catalyst		81	65
A with 40% ee catalyst		62	37
A with12% ee catalyst		27	11
B with 100% ee catalyst		95	96
B with 85% ee catalyst		96	95
B with 79% ee catalyst		96	97
B with 67% ee catalyst		89	96
B with 40% ee catalyst		90	90
B with 12% ee catalyst		79	87
no catalyst, just 9 mol% 1(S) of 92%ee		no reaction	

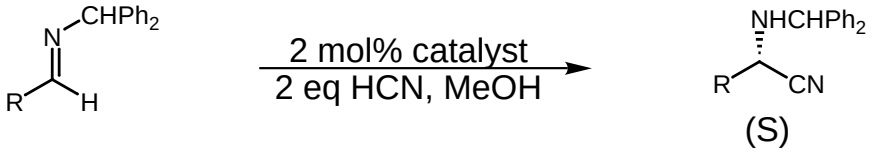
Danda, H. *J. Org. Chem.* **1991**, *56*, 6740-6741; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959

Strecker Reaction 1

cyclic peptides



cyclo-[(S)-Phe-(S)-α-amino-γ-guanidinobutyric acid]

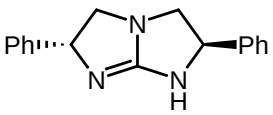


R	temp(°C)	yield(%)	ee(%)
Ph	-25	97	>99
4-Cl-Ph	-25	97	83
4-Cl-Ph	-75	94	>99
4-MeO-Ph	-25	96	64
4-MeO-Ph	-75	90	96
3-Cl-Ph	-75	80	>99
3-MeO-Ph	-75	82	80
3-NO_2-Ph	-75	71	<10
3-pyridyl	-75	86	<10
2-furyl	-75	94	32
i-Pr	-75	81	<10
i-Bu	-75	80	17

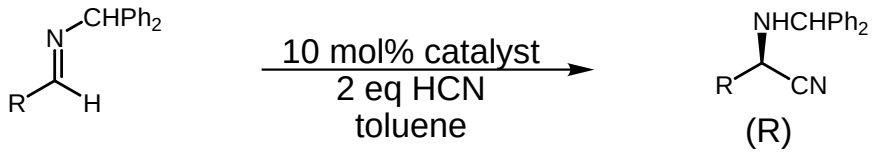
• Inoue's cyclo-[(S)-Phe-(S)-His] catalyst did not afford any asymmetric induction in the Strecker reaction. Lipton attributed this to the inability of the imidazole to accelerate proton transfer of HCN to aldimine.
• Enantioselectivity could be improved by lowering reaction temperature, but increasing catalyst loading did not improve selectivity.

Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911

Strecker Reaction 2



from (R) phenylglycine



R	temp(°C)	time(h)	yield(%)	ee(%)
Ph	-40	20	96	86 (R)
Ph	-20	8	99	82
4-Me-Ph	-40	20	96	80
3,5-xylyl	-40	16	96	79
2-Me-Ph	-20	12	88	50
4-*t*-Bu-Ph	-40	72	80	85
4-TBSO-Ph	-40	38	98	88
4-MeO-Ph	-40	28	99	84
4-F-Ph	-40	23	97	86
4-Cl-Ph	-20	20	88	81
1-naphthyl	-20	12	90	76
pival-	-40	22	95	84 (S)
cyclohexyl	-40	22		76 (S)
n-heptanyl	-40	22		63 (S)

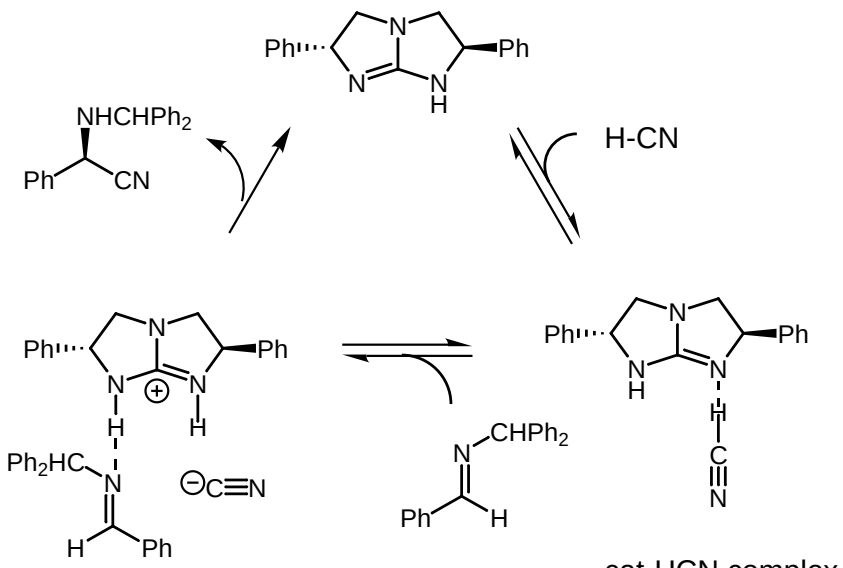
- Catalyst can be recovered via oxalic acid extraction and recycled.
- Without the catalyst, there is no reaction below 10°C.

Corey, E. J. *Org. Lett.* **1999**, *1*, 157-160

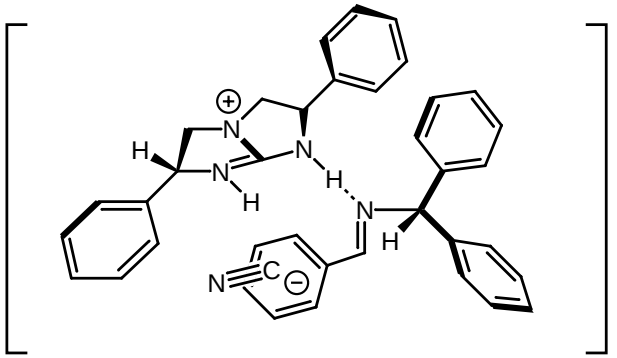
Corey's Mechanism

• No kinetic H/D isotope effect on the reaction rate was detected when HCN was replaced with DCN in the catalytic Strecker reaction.
• Bis-cyclohexyl analog of the catalyst gave much lower enantioselectivity.
• N-Methyl analog of the catalyst is an inactive catalyst.

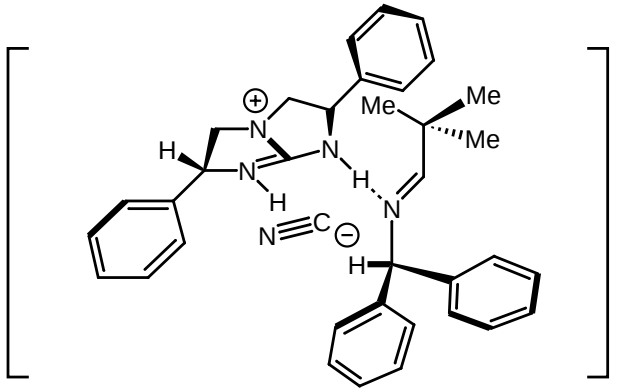
Bifunctional catalyst:



pre-TS assembly with aromatic aldimines



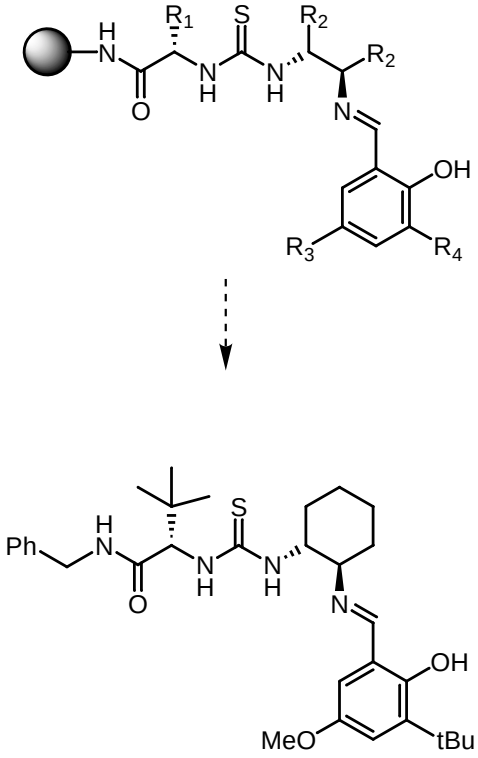
pre-TS assembly with aliphatic aldimines

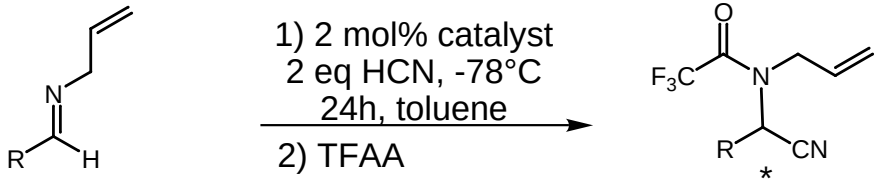


Corey, E. J. *Org. Lett.* **1999**, *1*, 157-160

Strecker Reaction 3

from combinatorial libraries





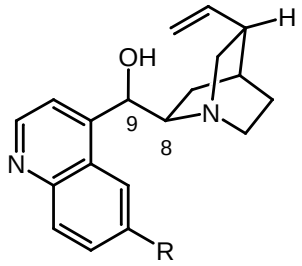
R	yield(%)	ee(%)
Ph	78	91
4-MeO-Ph	92	70
4-Br-Ph	65	86
2-naphthyl	88	88
t-butyl	70	85
cyclohexyl	77	83

Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902

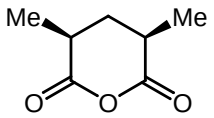
via covalent interactions

Desymmetrization 1

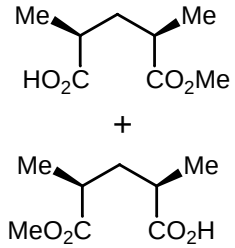
first examples



cinchonine (8R, 9S), R = H
cinchonidine (8S, 9R), R = H
quinine (8S, 9R), R = OMe
quinidine (8R, 9R), R = OMe

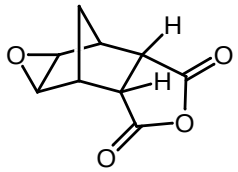


10 mol% catalyst, r.t.
toluene, 4 days, 4 eq MeOH

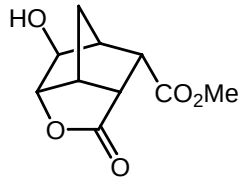


catalyst	er
cinchonine	15:85
cinchonidine	82:18
quinine	80:20
quinidine	16:84

Oda, J. *J. Chem. Soc., Chem. Comm*. **1985**, 1717-1719



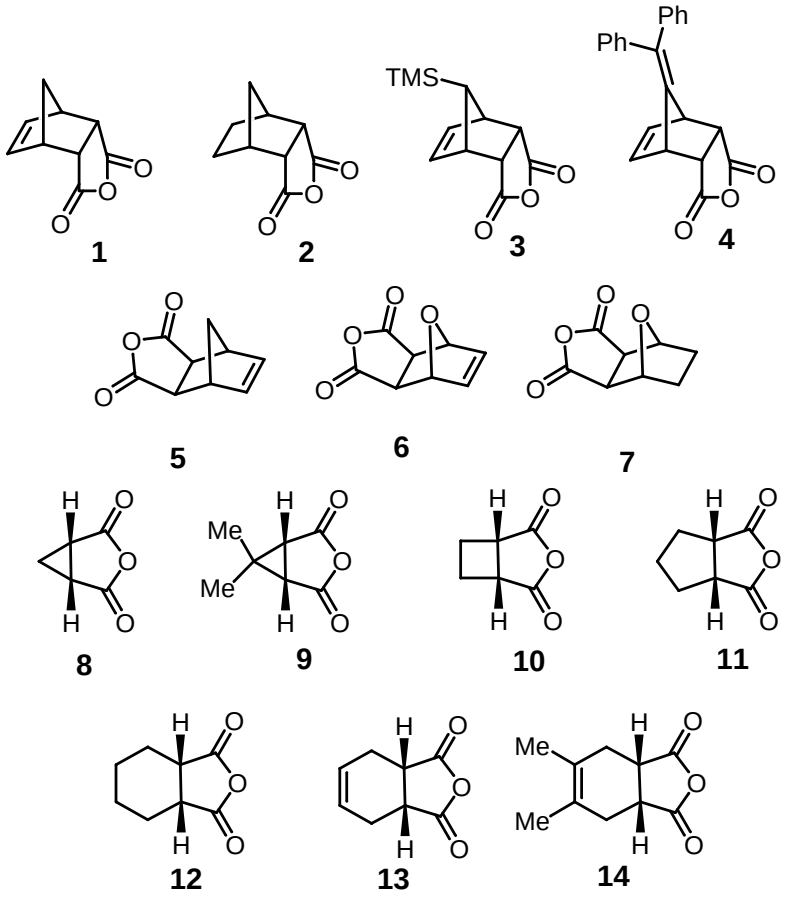
50 mol% quinine, r.t.,
toluene, 3.0 eq MeOH
57% yield, 76% ee



- Neither lowering reaction temperature nor using more polar solvents improved selectivity.
- Bulkier alcohols produced lower ee's.

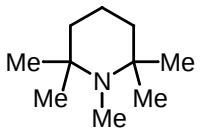
Aitken, R. A. *Tetrahedron: Asymm.* **1990**, *1*, 517-520; *J. Chem. Soc., Chem. Comm.* **1988**, 632-634

Desymmetrization 2



Conditions: 1.1 eq catalyst, 3.0 eq MeOH,
Toluene/CCl_4 (1:1), r.t., 24h

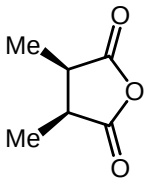
	quinidine		quinine	
Anhydride	ee	yield	ee	yield
1	99	98	99	92
2	94	84	94	86
3	96	99	99	98
4	96	95	92	96
5	96	96	93	94
6	93	61	85	71
7	94	68	93	79
8	85	95	85	95
9	90	97	84	96
10	94	99	87	93
11	95	97	93	99
12	93	98	87	91
13	95	93	93	99
14	97	96	94	97

pempidine 

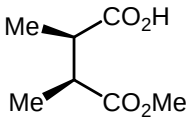
• Quinine loading can be lowered to 10 mol% if 1.0 eq. of pempidine was also added. However, with anhydride **1**, the methanolysis takes 6 days and afforded only 90% ee. Doubling catalyst loading to 0.2 eq gave only a slight increase to 93%ee.
• The use of toxic CCl_4 can be avoided by lowering the solvent concentration from 0.2 M to 0.1 M.
• Catalyst can be recovered and reused without loss of selectivity.
• More polar solvents decreased enantioselectivities.

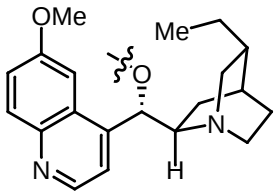
Bolm, C. *J. Org. Chem.* **2000**, *65*, 6984-6991

Desymmetrization 3

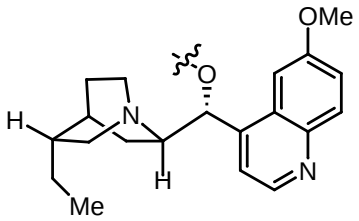


5 mol% catalyst
10 eq MeOH
toluene, r.t.

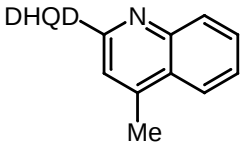




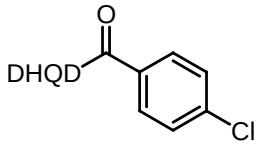
DHQD(dihydroquinidyl)



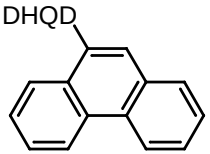
DHQ(dihydroquinyl)



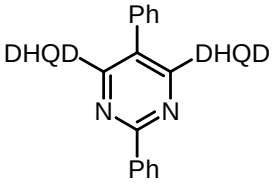
DHQD-MEQ



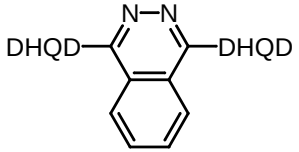
DHQD-CLB



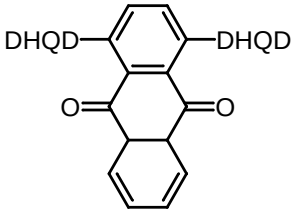
DHQD-PHN



$(DHQD)_2PYR$



$(DHQD)_2PHAL$

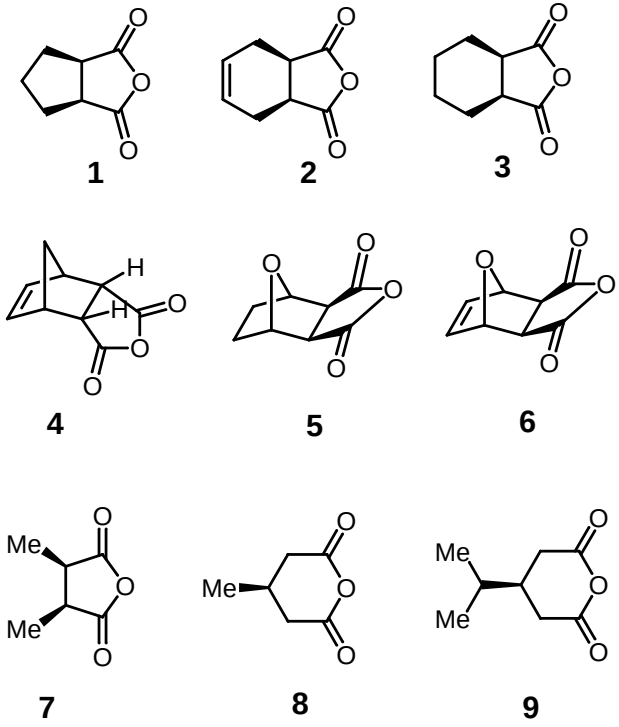


$(DHQD)_2AQN$

catalyst	ee
quinidine	64
DHQD-MEQ	31
DHQD-CLB	32
DHQD-PHN	81
$(DHQD)_2PYR$	13
$(DHQD)_2PHAL$	18
$(DHQD)_2AQN$	**85**

Deng, L. *J. Am. Chem. Soc*. **2000**, *122*, 9542-9543

Desymmetrization 4



Conditions: $(DHQD)_2AQN$ catalyst [or $(DHQ)_2AQN$ catalyst], 10 eq MeOH, ether

anhydride	catalyst (mol%)	temp (°C)	yield (%)	ee(%)
1	8 [8]	-30	99 (90)	95 (93)
2	7 [7]	-20	95 (92)	98 (96)
3	5 [5]	-20	97 (95)	97 (93)
4	10 [20]	-30 (-20)	82 (82)	95 (90)
5	15 [15]	-20	88 (85)	96 (94)
6	20 [20]	-20	74 (71)	92 (86)
7	5 [5]	-20	93 (88)	98 (98)
8	30 [30]	-40 (-35)	70 (56)	91 (82)
9	30 [30]	-40 (-35)	72 (62)	90 (83)

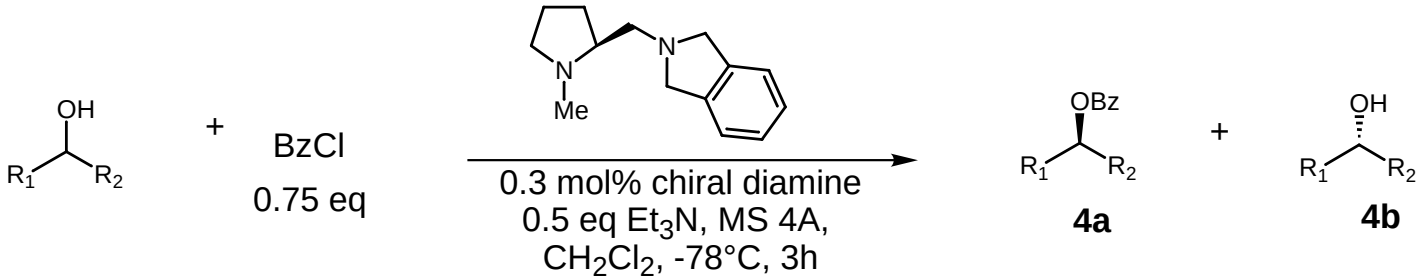
- Replacing toluene with ether as the solvent and lowering the reaction temperature resulted in an increase in enantioselectivity.
- $(DHQD)_2AQN$ and $(DHQ)_2AQN$ formed products of opposite absolute stereoconfiguration.
- Catalyst can be quantitatively recovered and recycled without loss of ee.

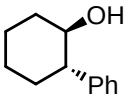
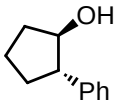
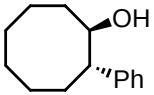
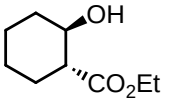
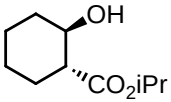
Deng, L. *J. Am. Chem. Soc*. **2000**, *122*, 9542-9543

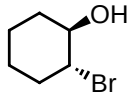
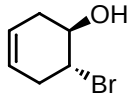
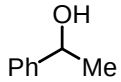
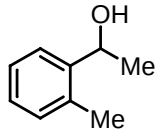
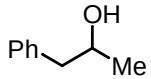
Kinetic Resolution 1

secondary alcohols

$$s = \frac{K_{\text{fast-reacting enantiomer}}}{K_{\text{slow-reacting enantiomer}}}$$



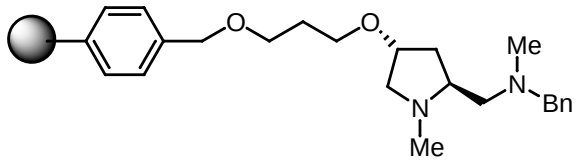
	4a yld	ee	4b yld	ee	s
	49	96 (1S, 2R)	48	95	160
	45	89	42	88	37
	44	95	47	79	88
	46	85	46	81	27
	48	84	46	90	27

	4a yld	ee	4b yld	ee	s
	47	96 (1S,2S)	39	95	130
	46	97	43	91	170
	43	69 (S)	41	67	9
	45	82	49	78	20
	49	46 (S)	39	51	4

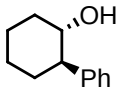
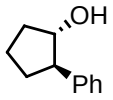
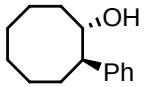
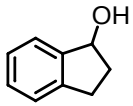
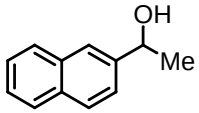
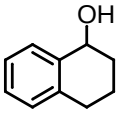
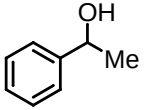
Oriyama, T. *Chem. Lett.* **1999**, 265-266; *Chem. Lett.* **1999**, 265-266; *Tet. Lett.* **1998**, *39*, 3529; Scheidt, K. "Asymmetric Catalysis with Chiral Lewis Bases" Evans Group Seminar, March **2001**

Kinetic Resolution 2

polymer supported proline



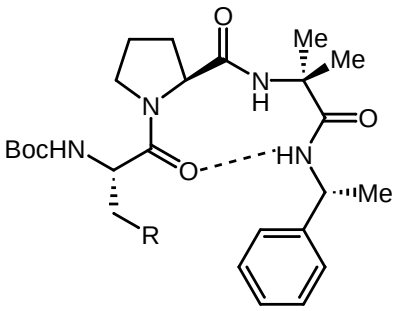
Conditions: 15 mol% catalyst, 0.75 eq BzCl, 0.5 eq Et_3N, MS 4A, CH_2Cl_2, -78°C, 11h

racemic alcohols		ester yield (%)	ee (%)	alcohol yield(%)	ee(%)	S
	solid phase	44	96 (1S, 2R)	45	85	134
	solution phase	48	97 (1S, 2R)	49	97	200
		47	85 (1S, 2R)	49	72	27
		15	78	58	14	9
	solid phase	44	38 (R)	47	30	3
	solution phase	53	37 (R)	47	53	4
	solid phase	46	16 (S)	49	16	2
	solution phase	54	23 (S)	34	33	2
		44	58 (R)	47	50	6
		53	0	24	0	0

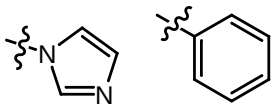
• The polymer supported catalyst was recovered and reused five times without loss of catalyst activitiy or selectivity.

Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868-873

Kinetic Resolution 3

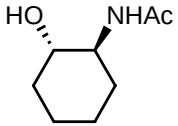


R =



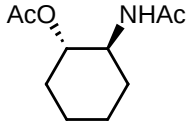
1

2



racemic

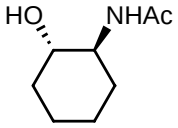
5 mol% catalyst **1**
1.0 eq Ac_2O
toluen, 0°C



84% ee
s = 12.8

---

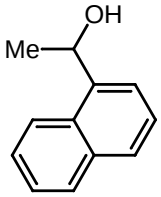
enzyme-like specificity



racemic

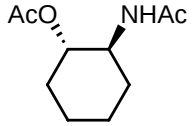
3

+



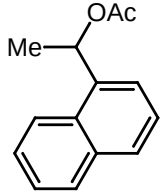
4

5 mol% catalyst
1.0 eq Ac_2O
$CHCl_3$, 0°C



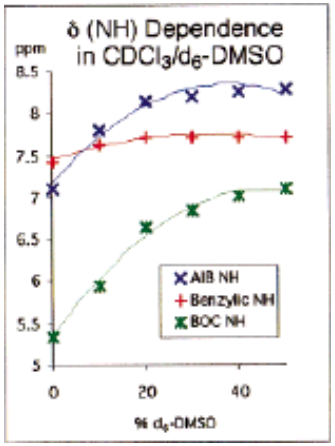
3a

+



4a

• Both imidazoyl functional group and the hydrogen bonding were kinetically significant.

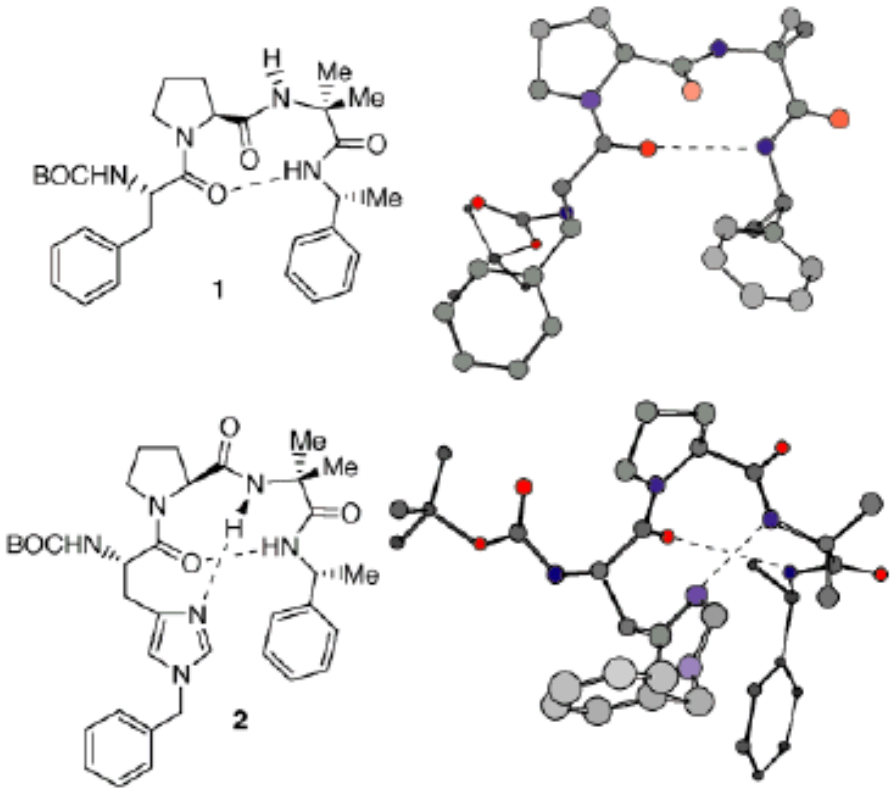


catalyst	3a:4a
N-Me-imidazole	1: 1
1	6: 1
2	no reaction

• NMR experiments indicated that peptide **1** has one unique conformation in nonpolar solvents.

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

X-Ray Crystal Structures and Conformation Studies



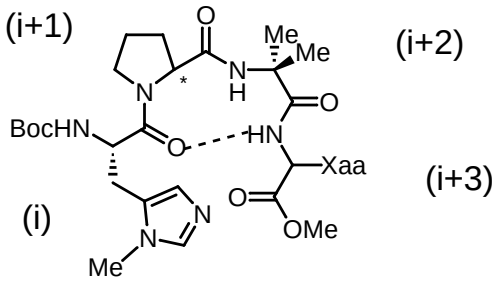
(1) The O-N distance for the Phe C=O oxygen to the C-terminal nitrogen is 3.309 A.

(2) The N-N distance between the π N of the His and the Aib N is short (3.074A). The O-N distance between the His C=O and the benzylic N is 3.129 A.

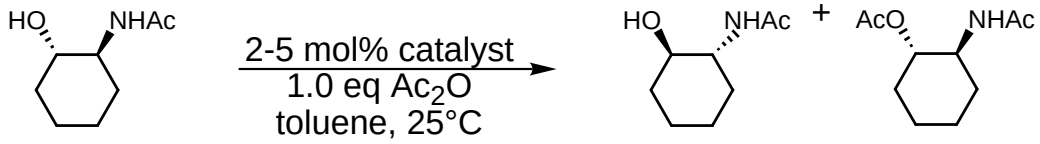
Miller, S. J. *Org. Lett.* **2000**, *2*, 1247-1249

Kinetic Resolution 4

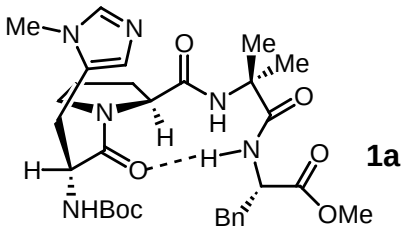
conformational control



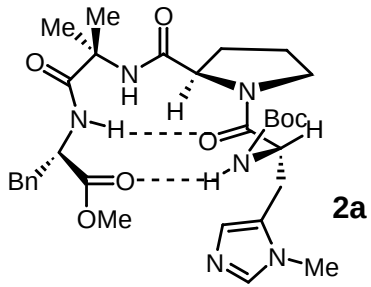
1 (i+1) = L-Pro
2 (i+1) = D-Pro



racemic **3-recovered** **3-Ac**



1a



2a

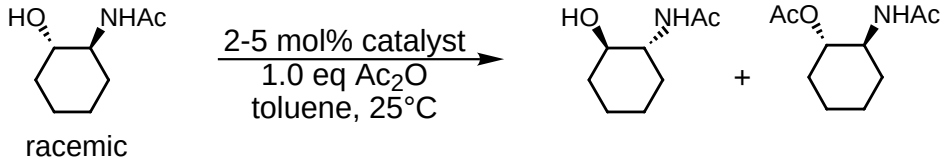
catalyst	conv.(%)	S	ee(%) of **3**	ee(%) of **3-Ac**
1a: Xaa = L-Phe	56	3.0	44 (R,R)	34 (S,S)
1b: Xaa = D-Phe	71	5.7	89 (R,R)	36 (S,S)
1c: Xaa = L-Val	61	3.4	54 (R,R)	35 (S,S)
1d: Xaa = D-Val	63	4.3	65 (R,R)	39 (S,S)
1e: Xaa = Gly	57	3.5	50 (R,R)	38 (S,S)
2a: Xaa = L-Phe	58	28.0	98 (S,S)	73 (R,R)
2b: Xaa = D-Phe	57	14.0	89 (S,S)	66 (R,R)
2c: Xaa = L-Val	61	21.0	99 (S,S)	63 (R,R)
2d: Xaa = D-Val	62	9.2	88 (S,S)	55 (R,R)
2e: Xaa = Gly	63	14	97 (S,S)	57 (R,R)

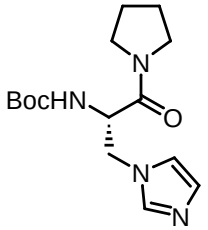
• Replacement of proline amino acids alone, instead of the entire peptide sequence, resulted in diastereomeric peptides with opposite enantiomeric selectivity profiles.

Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784-6785

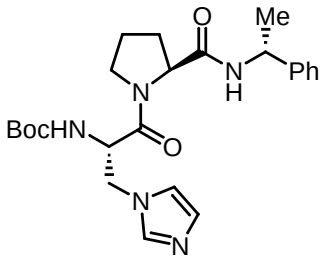
Kinetic Resolution 5

catalyst rigidity and structural complexity

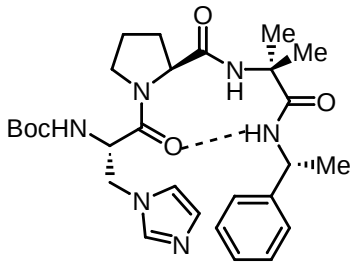




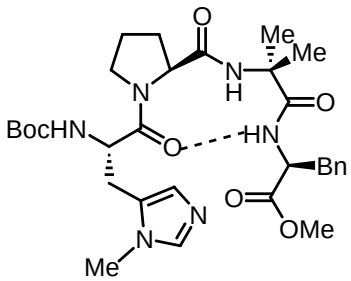
K_{rel} = 1.0



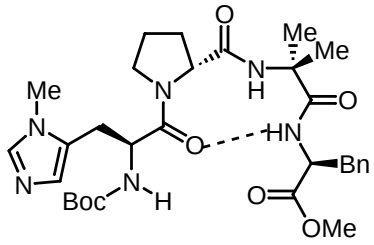
K_{rel} = 3.5 (S,S)



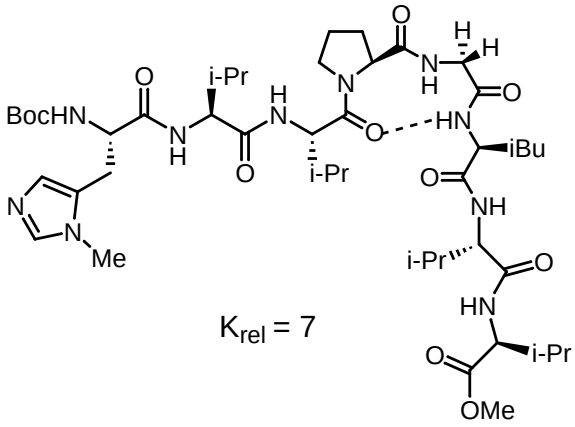
K_{rel} = 17 (S,S)



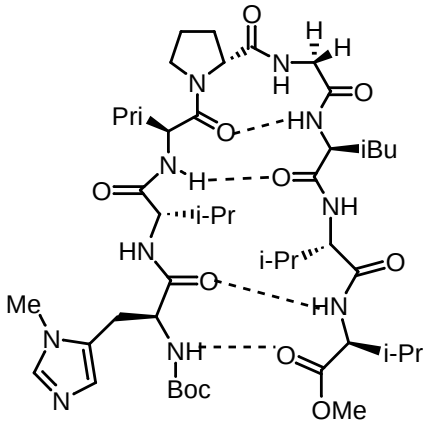
K_{rel} = 3.1 (S,S)



K_{rel} = 28 (R,R)



K_{rel} = 7



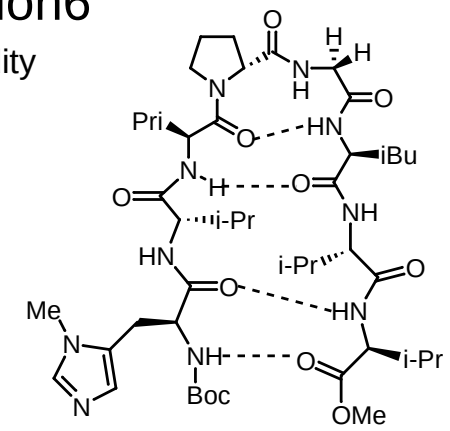
K_{rel} = 51

$$K_{rel} = \frac{K_{fast\text{-}reacting\ enantiomer}}{K_{slow\text{-}reacting\ enantiomer}}$$

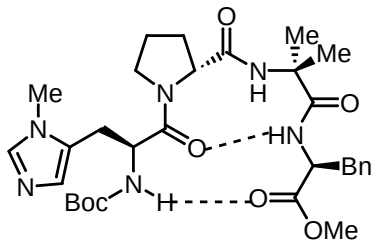
Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643

Kinetic Resolution6

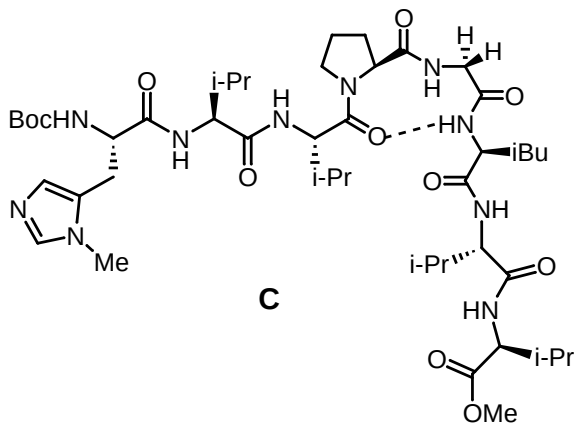
conformational rigidity



A

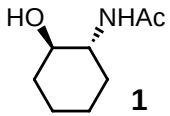


B

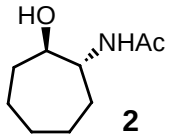


C

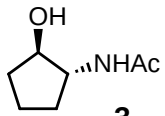
Racemic substrates



1



2



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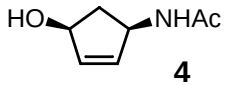


4

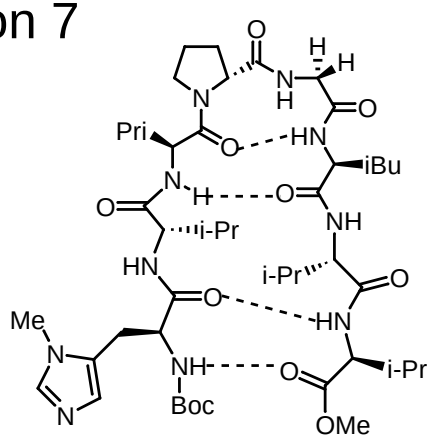
catalyst	substrates	conversion(%)	K_{rel}
A	**1**	**50**	**51**
A	2	45	15
A	3	49	27
A	4	35	1
B	**1**	**49**	**28**
B	2	41	17
B	3	45	6
B	4	49	4
C	**1**	**46**	**7**
C	2	56	2
C	3	45	3
C	4	45	1

Conditions: 1-2 mol% catalyst, 5.9mM in substrate, toluene solvent, at 25°C

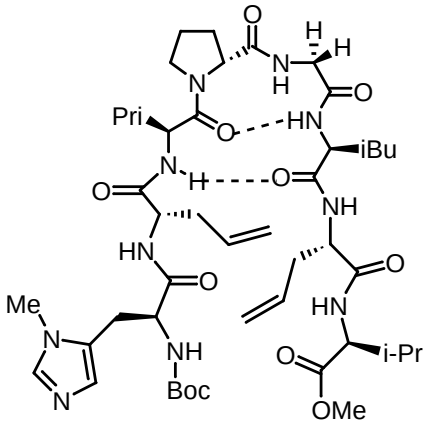
Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643

Kinetic Resolution 7

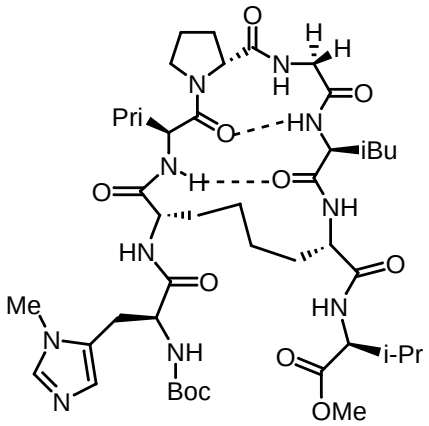
covalent rigidity



A

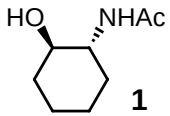


B

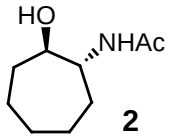


C

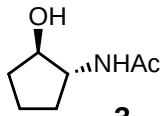
Racemic substrates



1



2



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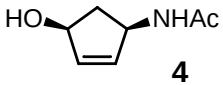


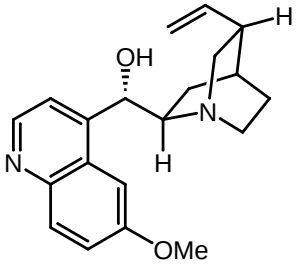
4

catalyst	substrates	conversion(%)	K_{rel}
A	**1**	**50**	**51**
B	**1**	**51**	**20**
B	2	52	8
B	3	51	12
B	4	35	1
C	**1**	**48**	**12**
C	2	56	4
C	3	50	8
C	4	31	1

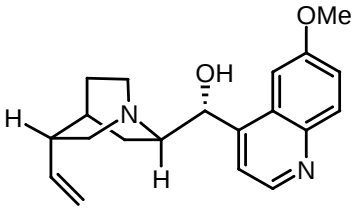
- Some degrees of flexibility is necssary for the selectivity.

Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638-11643

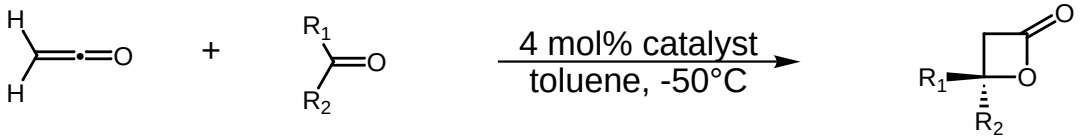
Ketene Chemistry 1



quinidine



quinine



R_1	R_2	quinidine[a] ee(%)	quinine ee(%)	yield(%)[a]
CCl_3	H	98	76	89
CCl_2H	H	45		67
CCl_2CH_3	H	91	76	95
$CCl_2CH_2CH_3$	H	89	70	87
$CCl_2C_6H_5$	H	90	68	89
CCl_3	CH_3	40	85	72
CCl_3	CH_2CH_3			1-2
CCl_3	C_6H_5			NR
CCl_3	4-Cl-C_6H_4	90	65	68
CCl_3	4-NO_2-C_6H_4	89	65	95

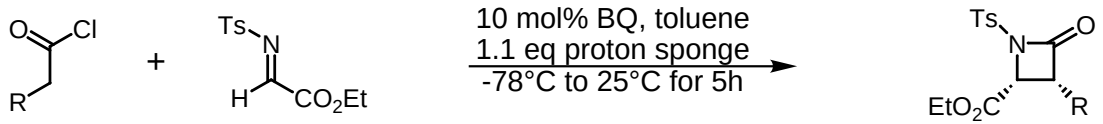
[History] The first reported use of cinchona alkaloids in ketene chemistry was by Pracejus in 1960. The alkaloids were used to induce asymmetric addition of achiral alcohols to ketenes.

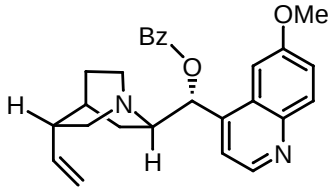
- The two alkaloids gave products with opposite signs of rotation.
- The alkaloid hydroxy group was essential for good stereoselectivity.

Wynberg, H. *J. Org. Chem.* **1985**, *50*, 1977-1979

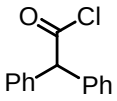
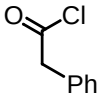
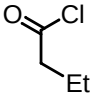
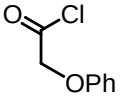
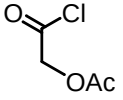
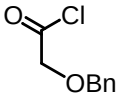
Ketene Chemistry 2

with imines





benzoylquinine (BQ)

	ee(%)	dr(cis/trans)	yield(%) of major diastereomer	
	99	--	36	run in THF
	96	99/1	65	
	99	99/1	57	
	99	99/1	45	
	98	>99/1	61	
	95	99/1	56	

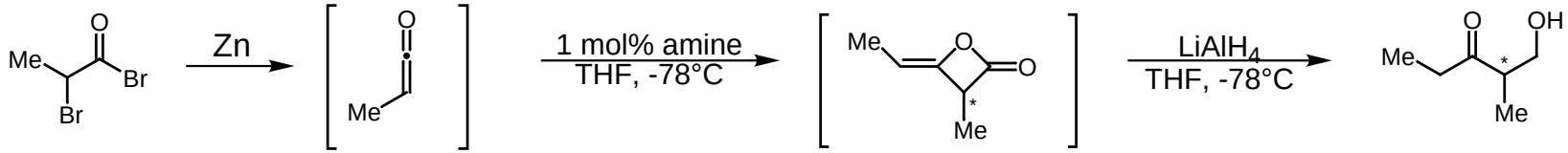
• Without the proton sponge, BQ alone gave low yields. However, simply mixing the acid chloride and proton sponge, without BQ, did not form detectable amounts of ketene.

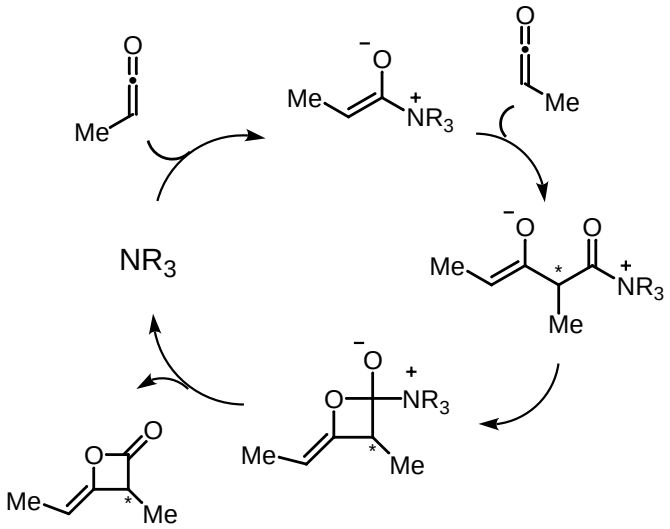
• BQ served as a bifunctional catalyst, both as a shuttle base to liberate HCl from acid chloride and transfer it to the proton sponge and as a nucleophilic catalyst.

Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831-7832

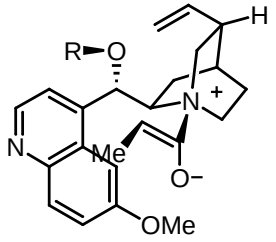
Ketene Chemistry 3

asymmetric dimerization





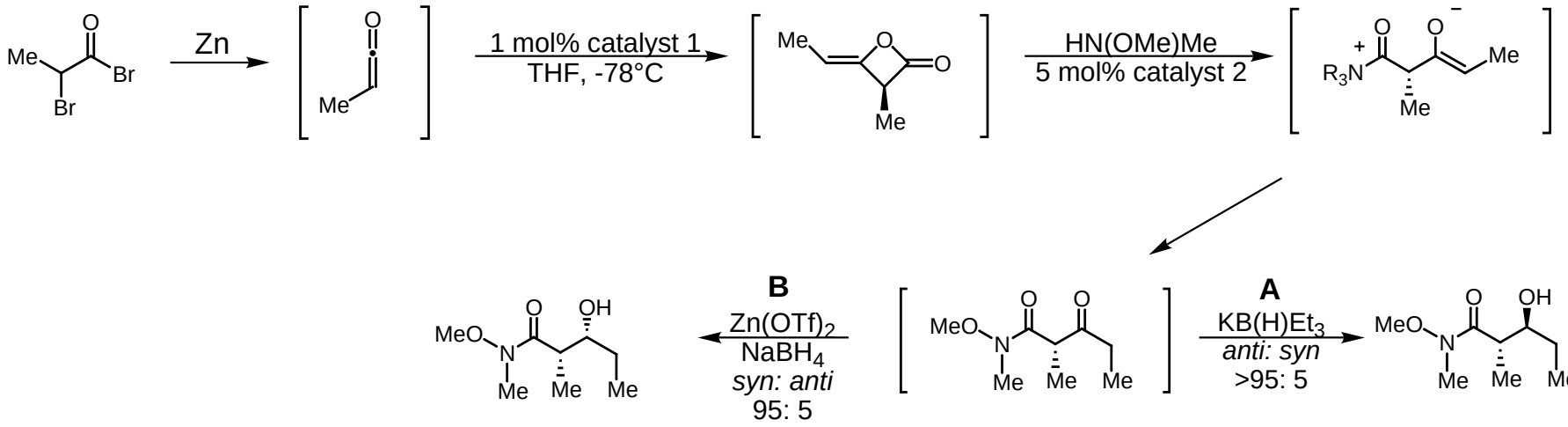
catalyst	ee(%) of product
quinidine	**98 (R)**
propionylquinidine	97 (R)
(trimethylsilyl)quinidine	98 (R)
quinine	70 (S)
propionylquinine	54 (S)
(trimethylsilyl)quinine	93 (S)



• Overall yield for this one-pot reaction is 20% based on 2-bromopropionyl bromide and regardless of the catalyst used.

Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007

Ketene Chemistry 4



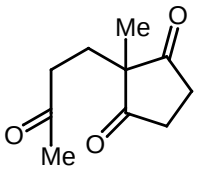
catalyst 1	catalyst 2	reduction conditions	%ee (config.)	% overall yield
quinidine		A	90 (2S,3S)	5
quinidine	DABCO	A	19 (2S,3S)	24.5
quinidine	DMAP	A	77 (2S,3S)	
quinidine	HOBT	A	66 (2S,3S)	
quinidine	pyridone	A	99 (2S,3S)	40
quinidine	pyridone	B	99 (2S,3R)	46
(trimethylsilyl)quinine	pyridone	A	95 (2R,3R)	40
(trimethylsilyl)quinine	pyridone	B	95 (2R,3S)	46

• Without catalyst 2, longer reaction time and higher temperature are required for adequate conversion. This also results in much epimerization.
• Pyridone also contains an acidic proton which could trap the ammonium enolate intermediate and prevent retro-dimerization reaction.

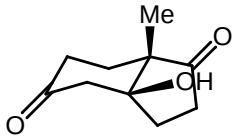
Calter, M. A. *J. Org. Chem.* **1998**, *63*, 5308-5309

Aldol Reaction 1

first examples



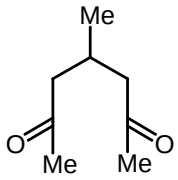
3 mol% L-Proline
DMF, r.t., 20 h, 100% yield
93% optical purity



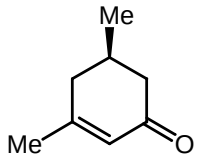
"Hajos-Parrish-Wiechert reaction"

• Use of acetonitrile extended reaction time to 3 days; while use of isopropyl alcohol decreases both the yield (12%) and optical purity (73%) of the reaction.
• In comparison, L-phenylalanine afforded much lower optical purity (19%).

Hajos, A. G. and Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; Eder U. and Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496



L-Proline
43% ee

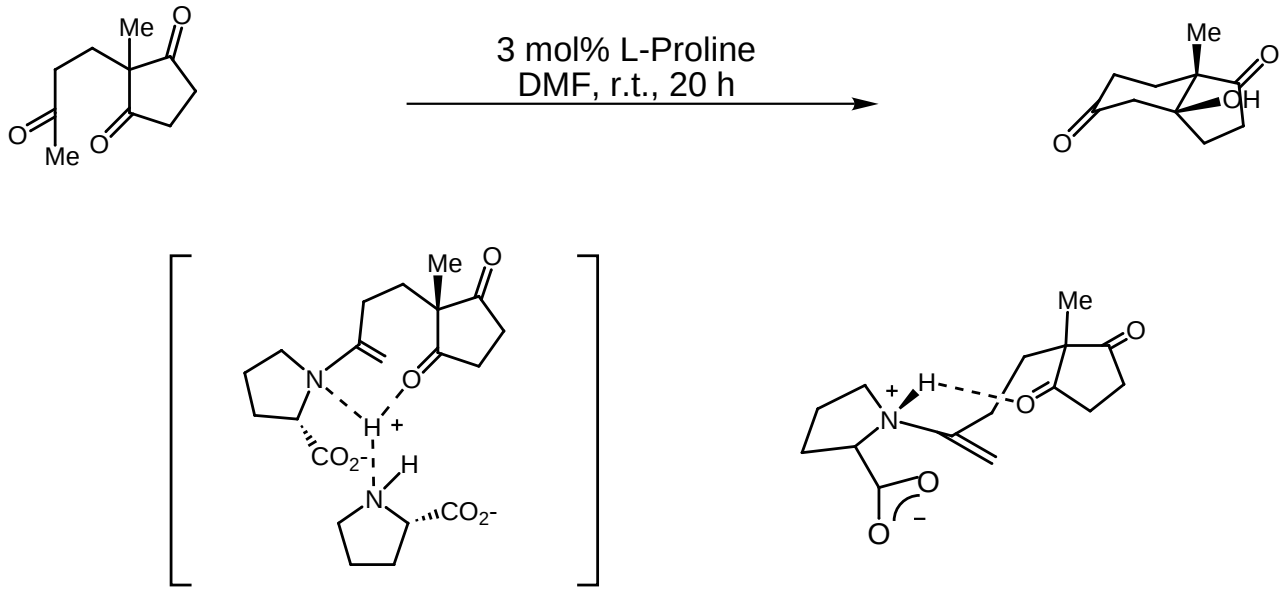


• Acyclic triketones also gave low selectivity.

Agami, C. *Bull. Soc. Chim. Fr.* **1987**, 358-360

Aldol Reaction 2

mechanism of the Hajos-Parrish reaction



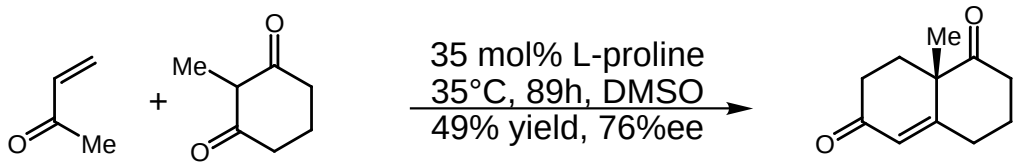
• Agami proposed mechanism: (1) hydrogen bonding effect favored the *si* - face selectivity and (2) bimolecular transition state enabled enamine nitrogen to be nucleophilic enough to form C-C bond.
• Protic solvents resulted in a decrease of selectivity.
• Both Agami and Kagan observed a negative non-linear effect in the Hajos-Parrish reaction.

[History] The Hajos-Parrish reaction was one of the first reactions reported to exhibit non-linear effect. The findings lead to further investigations into the phenomenon of nonlinear effect in asymmetric catalysis.

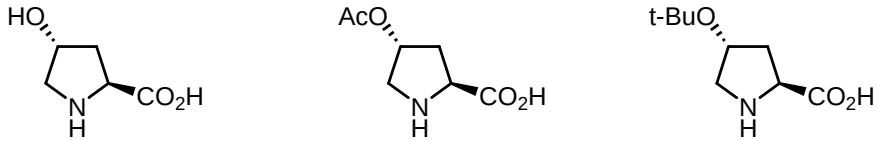
Agami, C. *Bull. Soc. Chim. Fr.* **1987**, 499-507; Agami, C. *Tet. Lett.* **1986**, *27*, 1501-1504; Agami, C. *J. Chem. Soc., Chem. Comm.* **1985**, 441-442; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353-2357

Aldol Reaction 3

asymmetric Robinson annulation



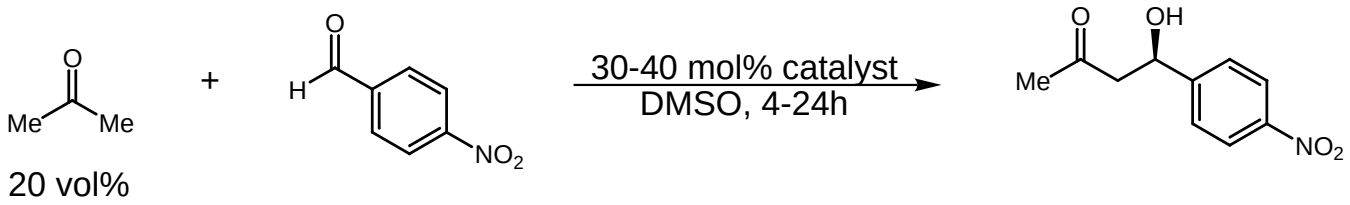
- Proline-like analogs below also catalyzed the reaction sequence from 60% to 75% ee.

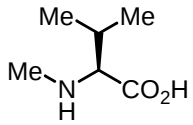
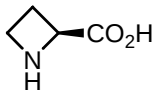
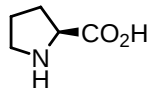
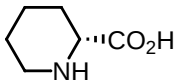


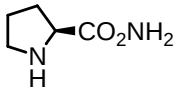
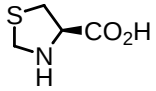
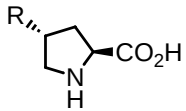
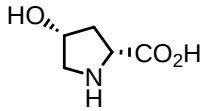
Barbas, C. F. III *Tet. Lett.* **2000**, *41*, 6951-6954

Aldol Reaction 4

asymmetric direct aldol



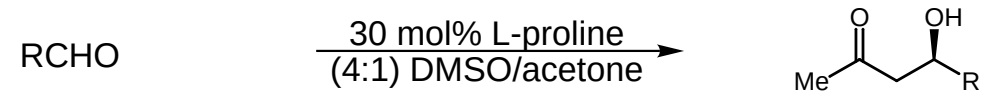
	yield(%)	ee(%)
(L)-His, (L)-Val, (L)-Tyr, (L)-Phe	<10%	n.d.
	<10%	n.d.
	55%	40%
	**68%**	**76%**
	<10%	n.d.

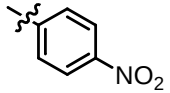
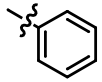
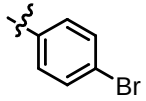
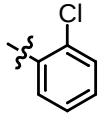
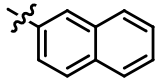
		yield(%)	ee(%)
		<10%	n.d.
		67%	73%
	R = OH R = OtBu R = OAc	85% >50% 70%	78% 62% 74%
		>50%	62%

- High concentration of acetone was necessary to suppress the [1,3]-dipolar cycloaddition side reaction.

List, B. *J. Am. Chem. Soc.* **2000**, *122*, 2395-96

Aldol Reactions 5



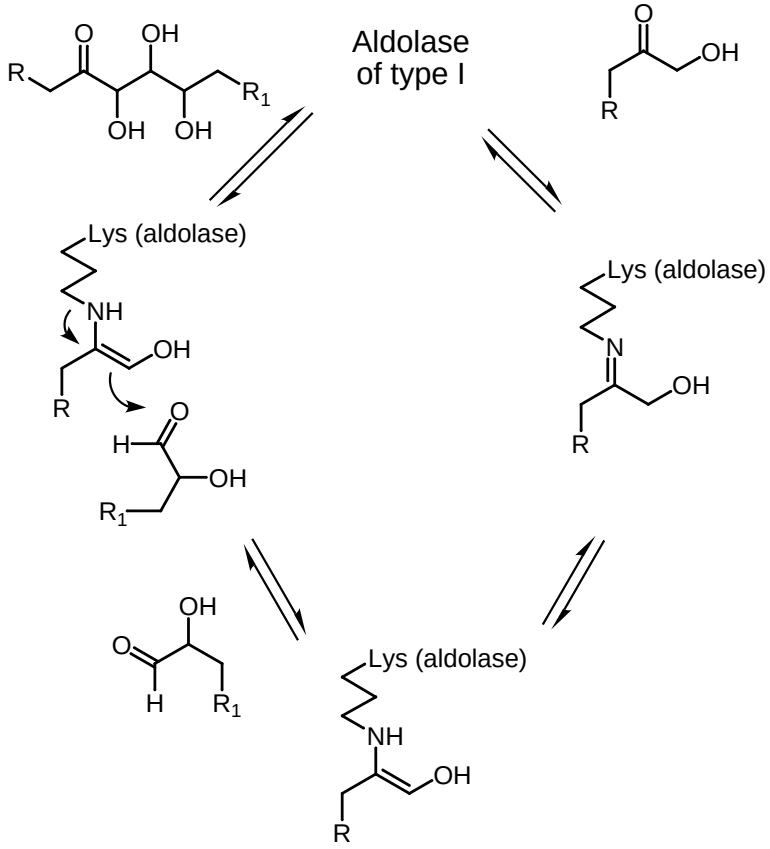
	yield(%)	ee(%)
	68	76
	62	60
	74	65
	94	69
	54	77
	97	96

• Unbranched aldehydes did not afford desired aldol product in (4:1) DMSO/acetone. The yields can be raised to 20%-30% and ee's 30%-70% when using pure acetone or (4:1) chloroform/acetone as solvents. However, self-aldolization side products could not be completely suppressed.

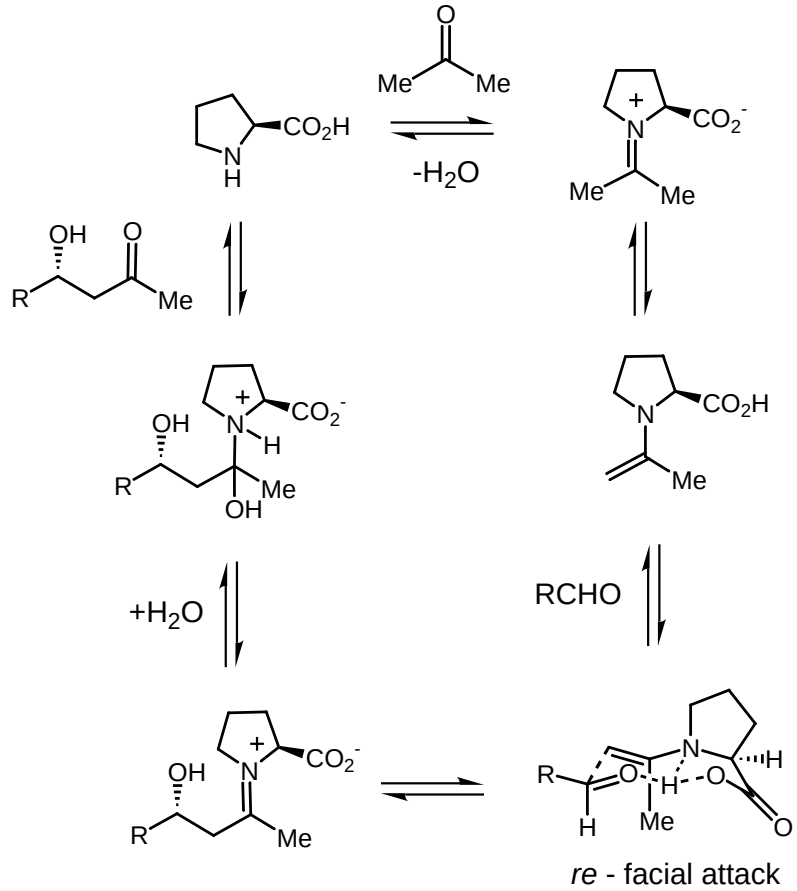
List, B. *J. Am. Chem. Soc.* **2000**, *122*, 2395-96; *Org. Lett.* **2001**, *3*, 573-575

Aldol Reactions 6

Aldolase type I mechanism

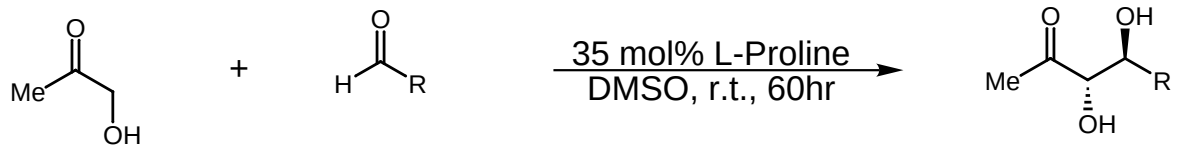


List's enamine mechanism

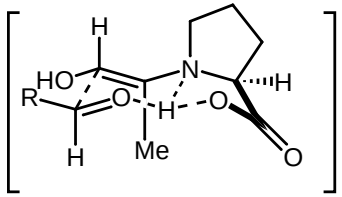


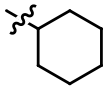
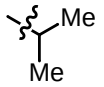
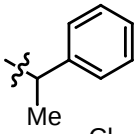
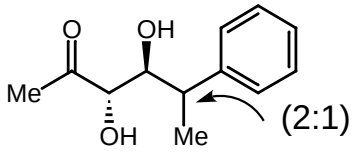
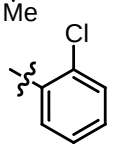
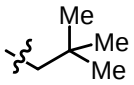
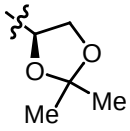
Groger, H. *Angew. Chem. Int. Ed.* **2001**, *40*, 529-532; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 2395-96

Anti Aldol Reaction



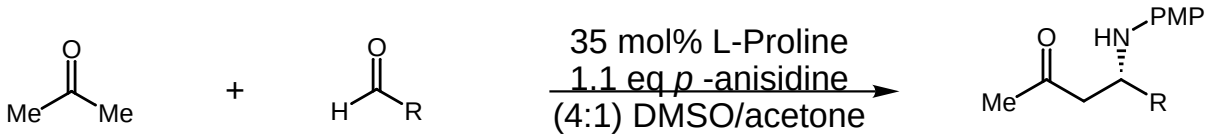
20 vol%

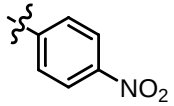
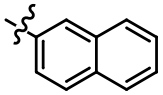
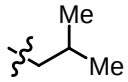


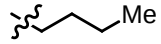
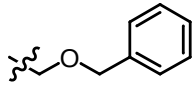
	yield(%)	dr	ee(%)	
	80	>20:1	>99	>20:1 regioselectivity
	62	>20:1	>99	
	51	>20:1	>95	 (2:1)
	95	1.5:1	87	4% regioisomer
	38	1.7:1	>97	15% regioisomer
	40	2:1	>97	

List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387

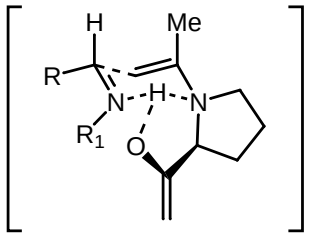
Direct Mannich Reaction

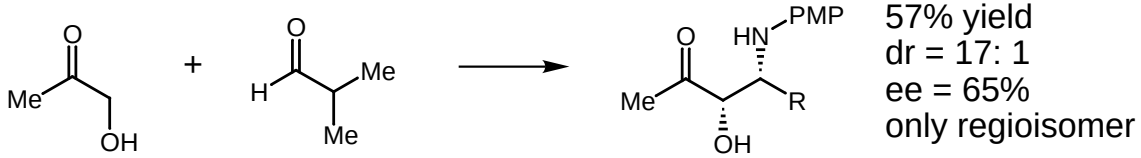


	yield(%)	ee(%)
	50	94
	35	96
	90	93

	yield(%)	ee(%)
	74	73
	82	75
	56	70

- Using the Mannich reactions of isovaleraldehyde in pure acetone, three other anilines were screened: *p*-chloroaniline (56%, 84%ee), *o* -anisidine (43%, <10%ee), and 2-aminophenol (51%, <10%ee).
- Side products observed include aldol addition and condensation products.
- Proline could be quantitatively recovered.
- Screening of other proline derivatives as catalysts resulted in lower yields and ee's.

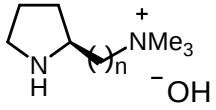




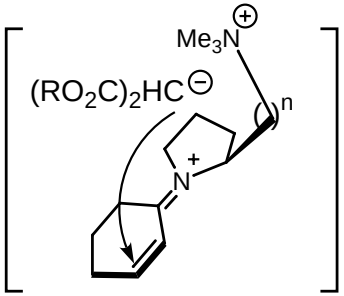
57% yield
dr = 17: 1
ee = 65%
only regioisomer

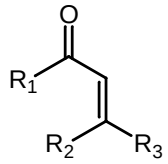
List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337

Michael Addition 1



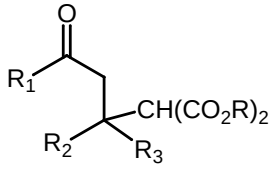
Catalysts
1a n = 1
1b n = 2

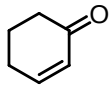
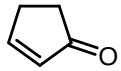
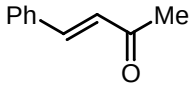




+ $CH_2(CO_2R)_2$

10 mol% catalyst
HFIP, toluene, r.t.
1 week

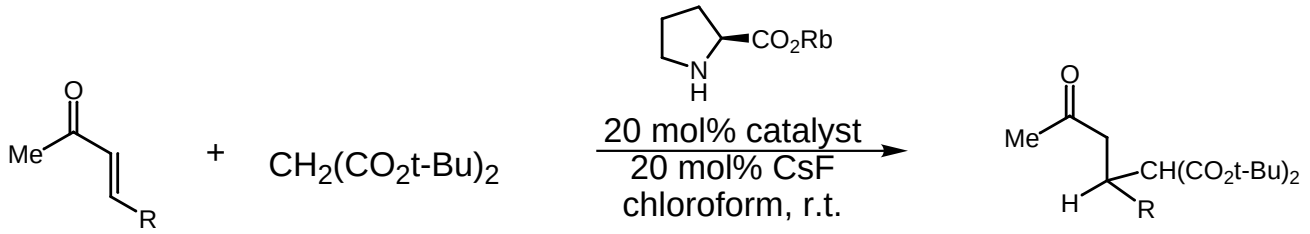


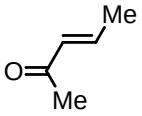
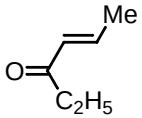
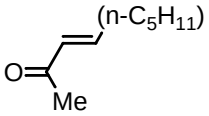
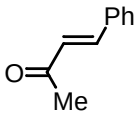
enone	malonate	catalyst	HFIP (eq)	yield(%)	ee(%)
	$CH_2(CO_2Bn)_2$	1a	0	88	3.5
		1a	1	52	21 (S)
		1a	10	61	71
		1b	10	96	49
	$CH_2(CO_2Me)_2$	1a	10	65	69
		1b	10	61	67
	$CH_2(CO_2Bn)_2$	1a	10	62	58
	$CH_2(CO_2Me)_2$	1a	10	56	56
	$CH_2(CO_2Bn)_2$	1a	10	21	68 (R)
	$CH_2(CO_2Me)_2$	1b	10	53	22 (R)

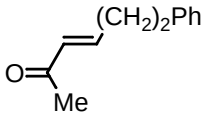
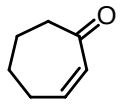
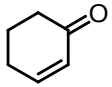
• HFIP was added to "reduce the basicity of the catalyst and to control the formation of the iminium intermediate".

Taguchi, T. *Tett. Lett.* **1994**, *35*, 8805-8808

Michael Addition 2



	time, h	%yield	%ee
	48	65	88 (S)
	96	84	76
	96	92	86
	96	52	76

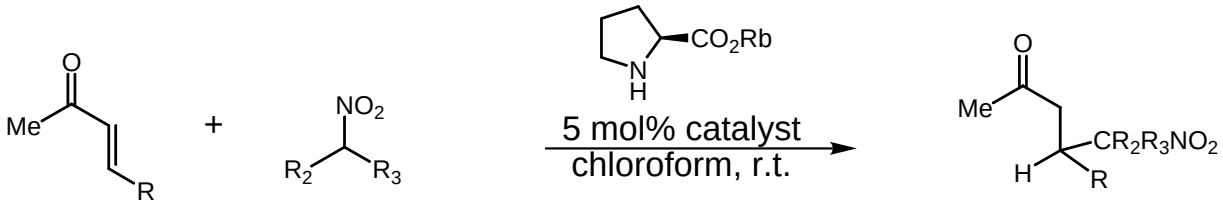
	time, h	%yield	%ee
	96	73	60
	48	75	74 (R)
	48	84	65 (R)
(E)-2-cyclododecenone	96	45	81

- Lithium prolinate and rubidium prolinate produced products of opposite configuration.
- Cyclic (Z)-enones afforded (R) adducts while acyclic (E)-enones afforded (S) adducts.
- Both the secondary amine and counterion are essential for high catalytic activities. Triethylamine, pyrrolidine, L-proline, L-prolinol, and rubidium salts of N-methyl-L-proline and N-benzyl-L-proline all afforded very low yields.
- Addition of CsF allowed for an increase of chemical yield without affecting the stereoselectivity.

Yamaguchi, M. *J. Org. Chem.* **1996**, *61*, 3520-3530; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176-1179

Michael Addition 3

with nitroalkanes



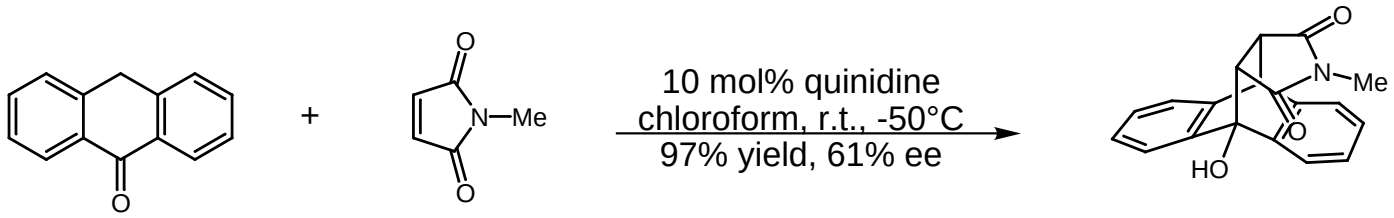
enone/enal	nitroalkane	time(h)	yield(%)	ee(%)
2-cycloheptenone	CH_3NO_2	43	47	41
	i-$C_3H_7NO_2$	43	79	73
	cyclo-$C_5H_9NO_2$	24	74	67
	cyclo-$C_6H_{11}NO_2$	20	84	84
2-cyclohexenone	CH_3NO_2	51	55	45
	n-$C_4H_9NO_2$	19	84 (1:1.4)	53,47
	i-$C_3H_7NO_2$	24	81	59
(E)-3-penten-2-one	CH_3NO_2	17	47	42
	n-$C_4H_9NO_2$	21	64 (1:1)	40,55
	i-$C_3H_7NO_2$	17	74	48
	cyclo-$C_5H_9NO_2$	24	64	59
(E)-3-nonen-2-one	i-$C_3H_7NO_2$	39	91	60
(E)-2-hexenal	i-$C_3H_7NO_2$	24	61	29

- Cyclic (Z)-enones afforded (R) adducts while acyclic (E)-enones afforded (S) adducts.
- Again, ring size, secondary amine, and rubidium are essential for selectivity.

Yamaguchi, M. *Tett. Lett.* **1994**, *44*, 8233-8236

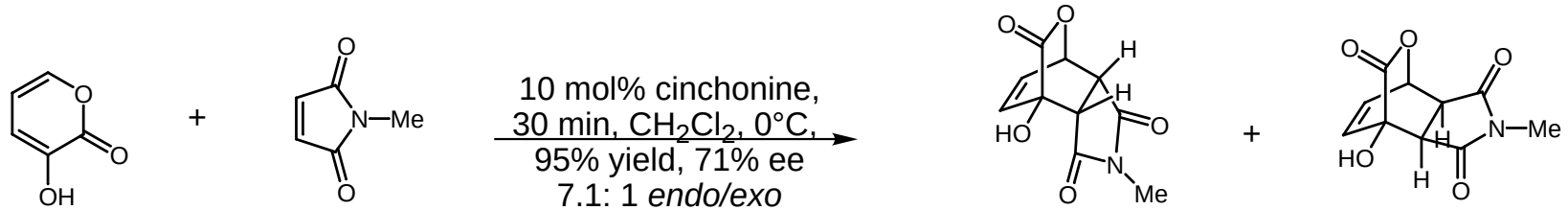
Diels-Alder Reaction 1

first examples



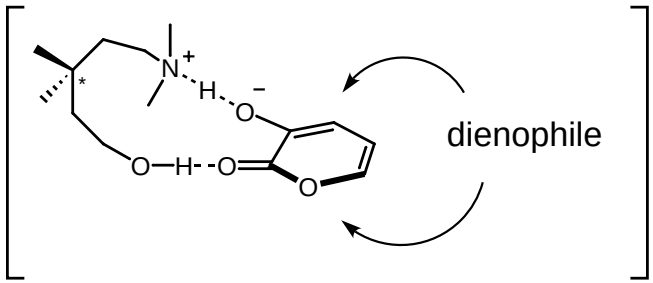
• (S)-prolinol gave only 43% ee at -20°C.
• Along with screening of other bases, a free OH group in the catalyst seemed necessary for achieving a high optical yield.

Kagan, H. B. *Tet. Lett.* **1989**, *30*, 7403-7406



endo-adduct

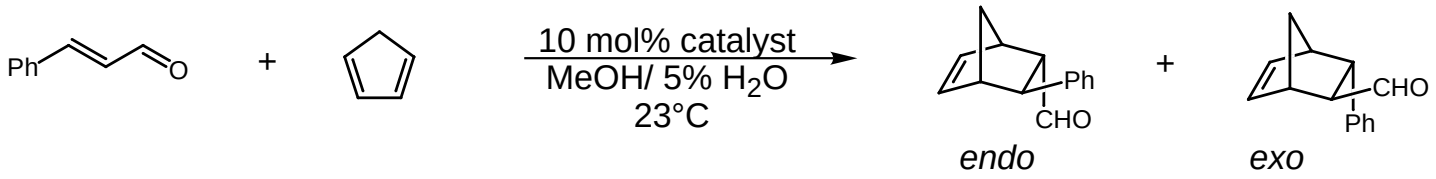
exo-adduct

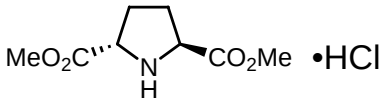
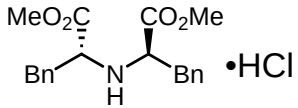
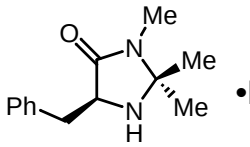


• (S)-prolinol produced 8.5:1 *endo/exo* but only 9% ee.

Okamua, H. and Nakatani, M. *Chem. Lett.* **1996**, 193-194

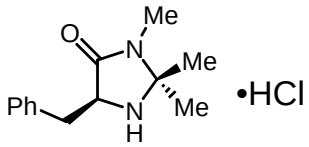
Diels-Alder Reaction 2



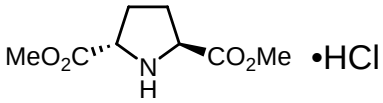
catalyst	time (h)	yield (%)	*exo:endo*	*exo* ee (%)
(S)-Pro-OMe•HCl	27	81	2.7: 1	48 (2R)
(S)-Abr-OMe•HCl	10	80	2.3: 1	59 (2S)
	23	92	2.6: 1	57 (2R)
	84	82	3.6: 1	74 (2R)
	8	99	1.3: 1	93 (2S) with 5 mol% catalyst

MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

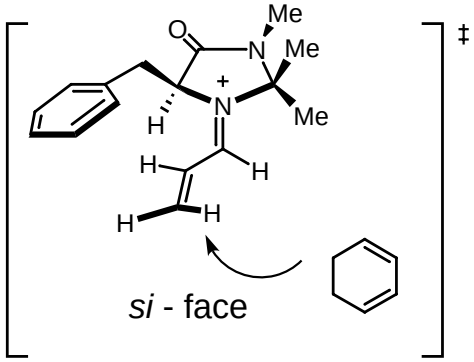
Diels Alder Reaction 3



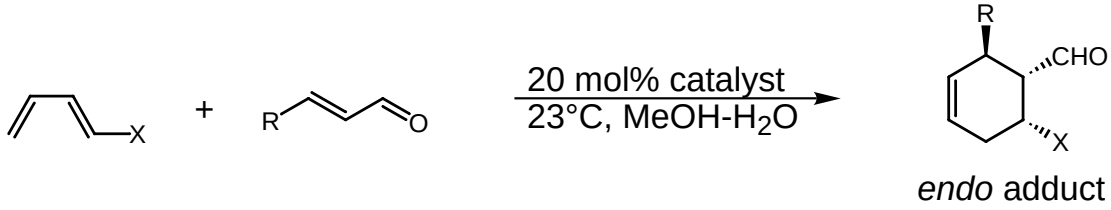
catalyst **A**



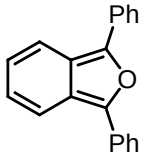
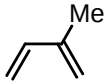
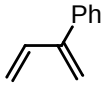
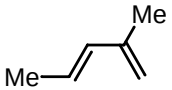
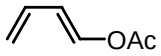
catalyst **B**



• Transition state model was based on Monte Carlo simulation using MM3 force-field; Macromodel V6.5



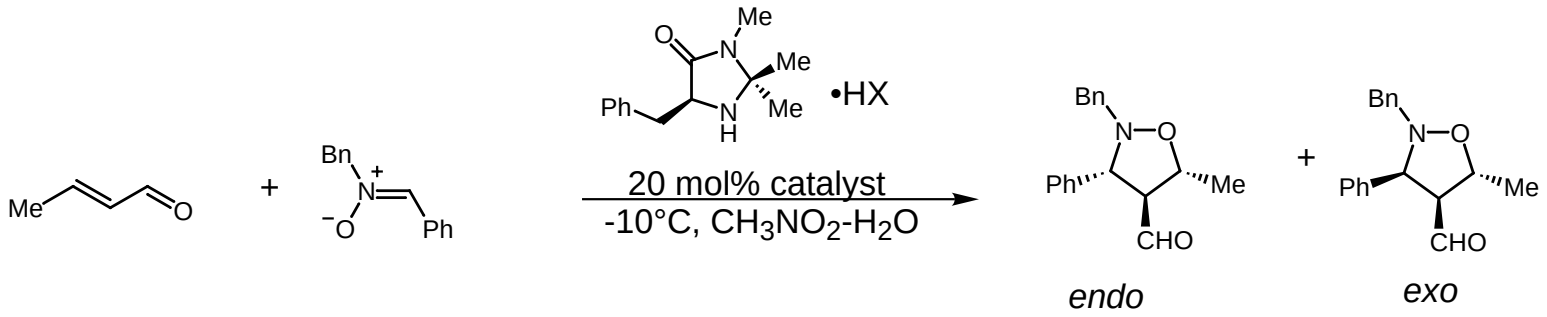
endo adduct

diene	R	yield(%)	*exo:endo*	ee(%)
	Me	75	35: 1	96 with catalyst B
	H	82	1:14	94 with 5 mol% A
	H	84		89
	H	90		83
	Me	75		90
	H	75	1: 5	90
	H	72	1:11	85
	Me	75	1: 1	90

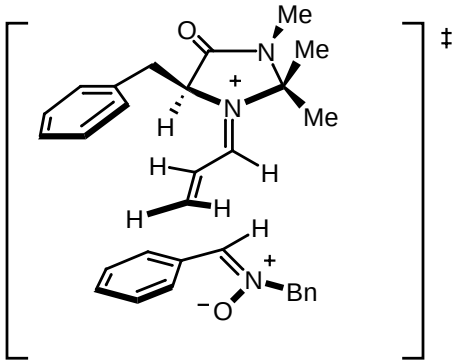
MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244

1,3-Dipolar Cycloaddition

effect of Bronsted Acid co-catalyst



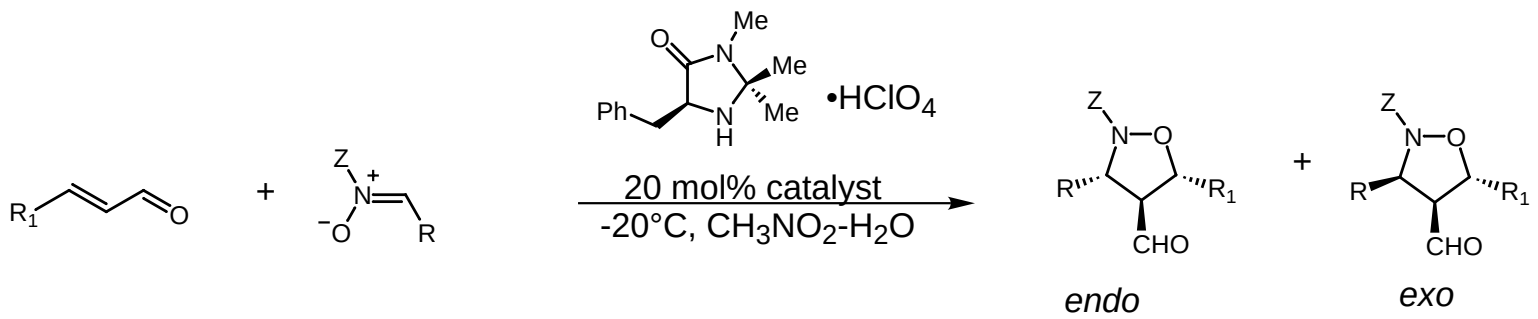
HX co-catalyst	time (h)	yield(%)	*endo:exo*	*endo* ee(%)
HCl	108	70	88:12	95
TfOH	101	88	89:11	90
TFA	80	65	72:28	86
HBr	80	77	94: 6	93
$HClO_4$	80	86	94: 6	90
$HClO_4$ (at -20°C)	100	98	94: 6	94



• Achiral Bronsted acid co-catalyst affected the extent of iminium activation in preference to achiral acid promotion.
• Transition state model was based on analogy to the previous Diels Alder reaction studies.

MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *40*, 9874-9875

1,3-Dipolar Cycloaddition 2



Z	R	R_1	*endo:exo*	yield(%)	*endo* ee(%)
Bn	Ph	Me	94: 6	98	94
Allyl	PH	Me	93: 7	73	98
Me	PH	Me	95: 5	66	99
Bn	4-Cl-Ph	Me	92: 8	78	95
Me	4-Cl-Ph	Me	93: 7	76	94
Bn	4-MeO-Ph	Me	98: 2	93	91
Me	4-Me-Ph	Me	93: 7	82	97
Bn	2-naph	Me	95: 5	98	93
Bn	c-hex	Me	99: 1	70	99
Bn	Ph	H	81:19	72	90

MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *40*, 9874-9875