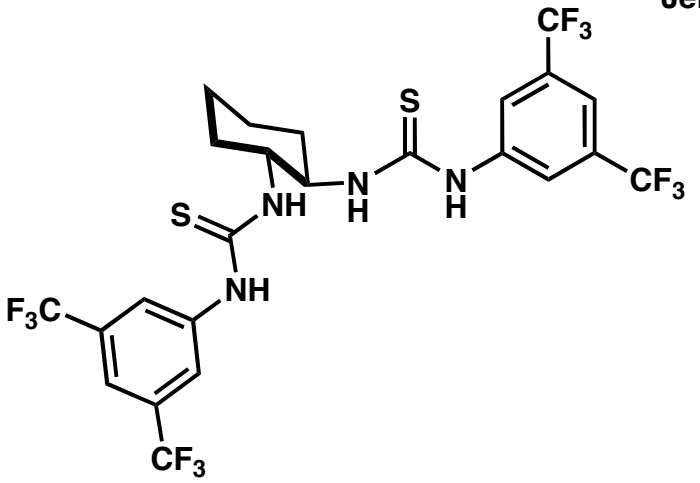
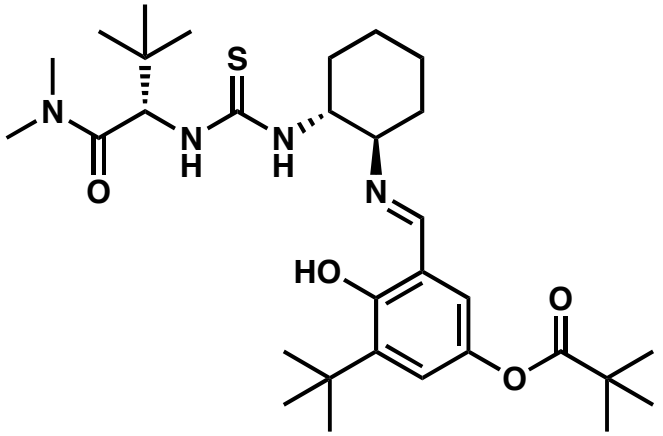
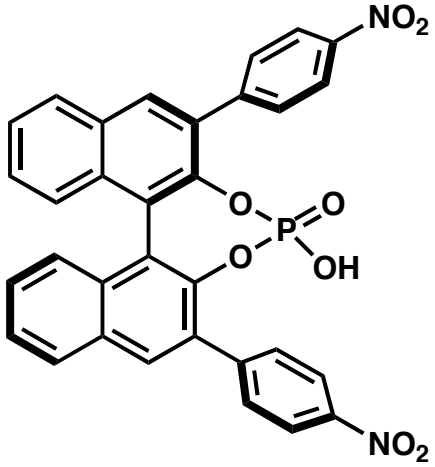
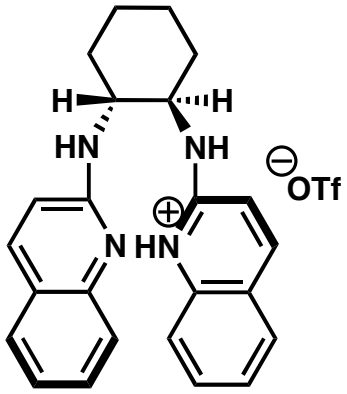
Brønsted Acids in Asymmetric Catalysis

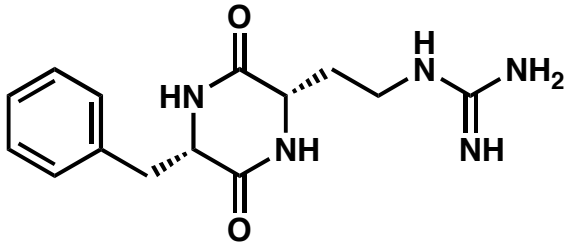
Literature Seminar
Jenn Stockdill, Stoltz Research Group
15 November 2004

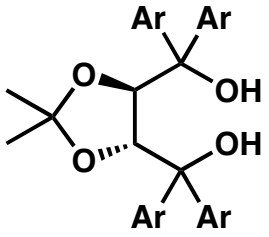












Outline

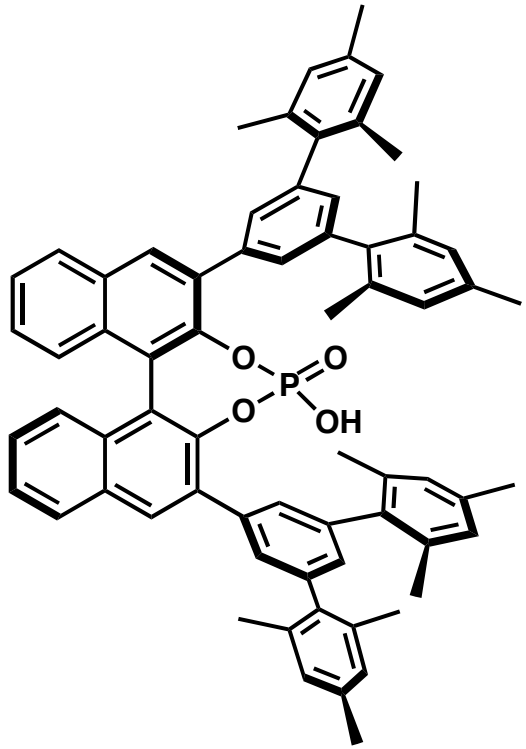
I. Introduction

- **Benefits of Organic Catalysts**
- **Early Developments -- Racemic Catalysts**

II. Catalysts in Asymmetric Reactions

- **HCN Addition to Aldehydes**
- **The Strecker Reaction**
- **The Mannich Reaction**
- **The Aza-Friedel-Crafts Reaction**
- **Hydrophosphination of Imines**
- **The Acyl-Pictet-Spengler Reaction**
- **The Aza-Henry Reaction**
- **Michael Reaction of Malonates to Nitroolefins**
- **The Baylis-Hillman Reaction**
- **The Diels-Alder Reaction**

III. Summary

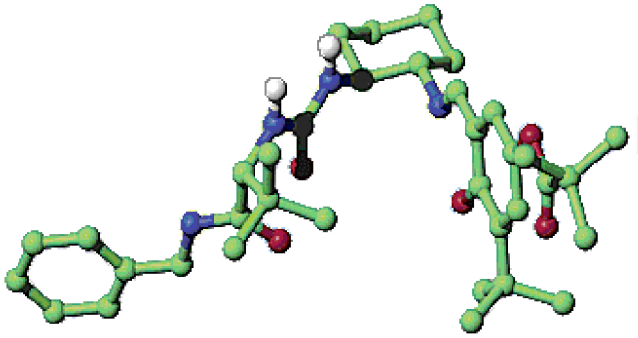


Reviews:

- Pihko, P. M. Activation of Carbonyl Compounds by Double Hydrogen Bonding: An Emerging Tool in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062-2064.
- Schreiner, P. R. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **2003**, *32*, 289-296.

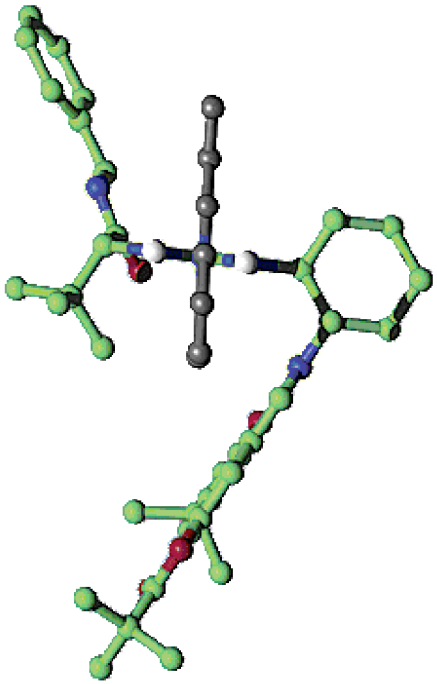
- Dalko, P. I. and Moisan, L. Enantioselective Organocatalysis. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748.

Why Organic Catalysts? Why Hydrogen-Bonding?



- The usual suspects (drawbacks to metal-catalysis)
  - cost
  - toxicity
  - sensitivity & stability issues
  - product inhibition
  - amenable to high-throughput process/medicinal chemistry?
  - ability to attach to solid support

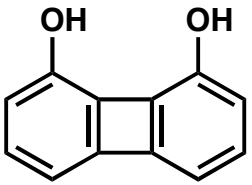
- Why not regular protic acids?
  - Reactions catalyzed by H^+ often contain functionality sensitive to strong acids
  - reaction partner quenching
  - side reactions - elimination, epimerization, polymerization



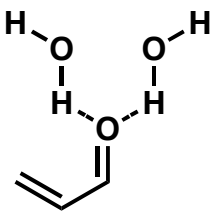
- Hydrogen-bonding -- eliminate need for H^+
  - catalyst-stabilized transition state
  - proton transfer in transition state (TS) (concept precedented in enzymes

- Selectivity
  - utilize lone-pairs of carbonyl to acheive bidentate binding through double H-bonding

Double H-Bonding -- Non-Enantioselective Catalysts

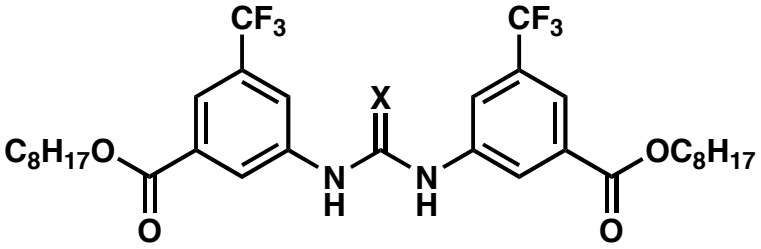


Hine biphenylene diol catalyst (epoxide opening)
J. Org. Chem. **1985**, *50*, 5096-9.
J. Org. Chem. **1987**, *52*, 2083-6.

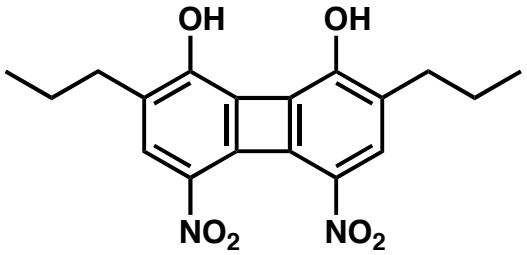


Jorgenson model for H_2O-catalyzed Diels-Alder Reactions and Claisen Rearrangements

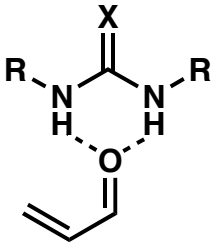
J. Am. Chem. Soc. **1991**, *113*, 7430-2.
J. Am. Chem. Soc. **1992**, *114*, 10966-8.



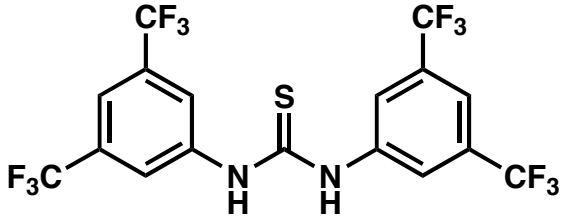
Curran urea and thiourea catalysts (sulfoxide allylation &Claisen rearrangents)
J. Org. Chem. **1994**, *59*, 3259-61.
Tet. Lett. **1995**, *36*, 6647-50.



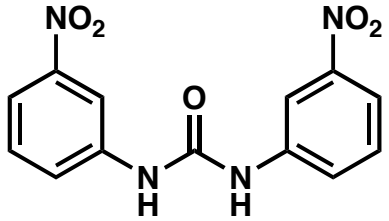
Kelly biphenylene diol catalyst (Diels-Alder)
Tet. Lett. **1990**, *31*, 3381-4.



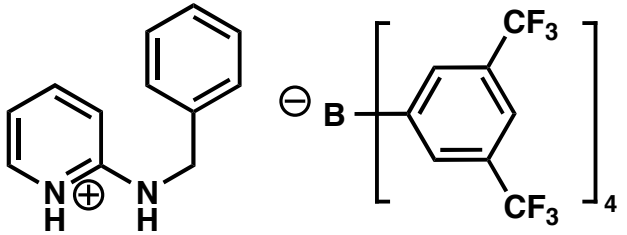
Binding model for catalysis by ureas and thioureas



Schreiner thiourea catalyst (Diels-Alder)
Chem. Soc. Rev. **2003**, *32*, 289-96.

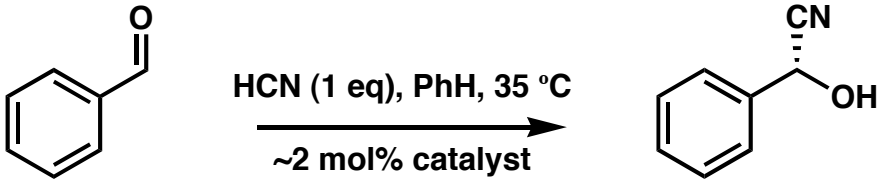


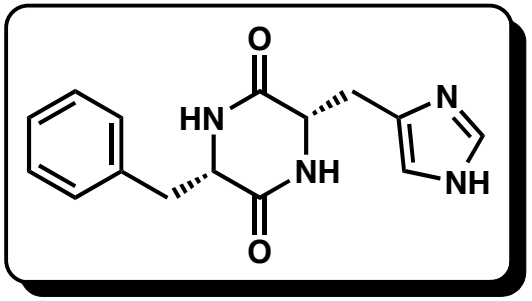
Etter Urea Catalyst (co-crystallizes)
J. Am. Chem. Soc. **1988**, *110*, 5896-7.



Göbel aminopyridinium catalyst (diastereoselective Diels-Alder)
J. Org. Chem. **2000**, *65*, 1697-701.

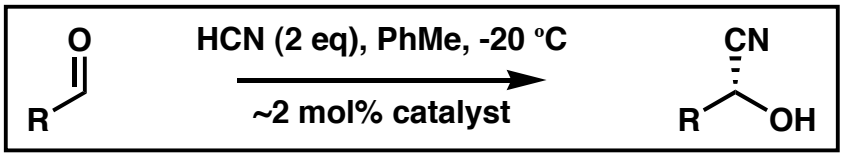
Asymmetric HCN Addition to Aldehydes



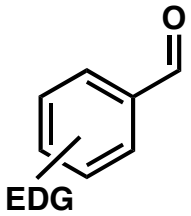


Run	Time (h)	% Conv	% ee
1	0.5	40	90
2	1	80	76
3	4	80	69
4	16	90	21
5	72	90	12

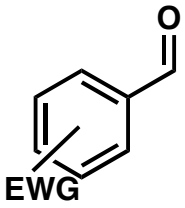
Inoue, et al. *J. Chem. Soc. Chem. Comm.* **1981**, 229-230.



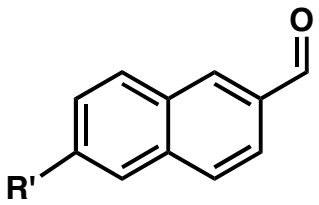
R = alkyl: 2.5-8h, 44-96% yield, 18-71% ee



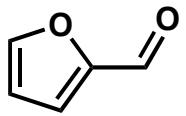
8-10h
45-97% conv.
78-97% ee



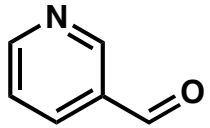
2.5-8h
99-100% conv.
4-53% ee



R' = H: 1.5h, 61% conv., 91% ee
R' = OMe: 6h, 88% conv., 73% ee



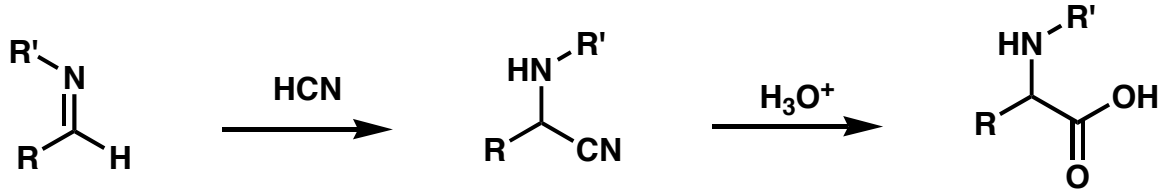
8h
60% conv.
42% ee

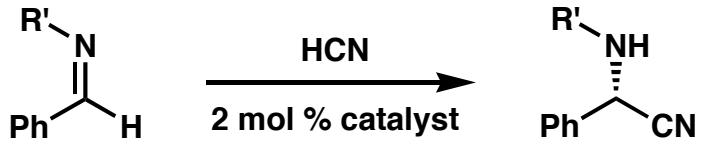


0.5h
73% conv.
54% ee

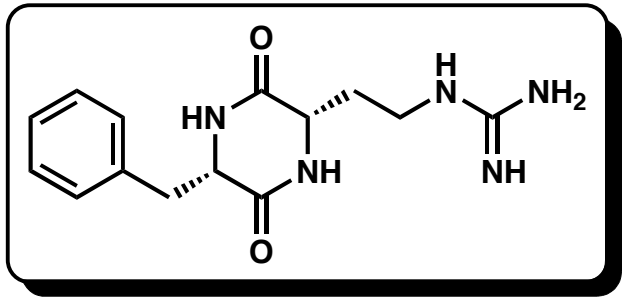
J. Org. Chem. **1990**,*55*, 181-185.

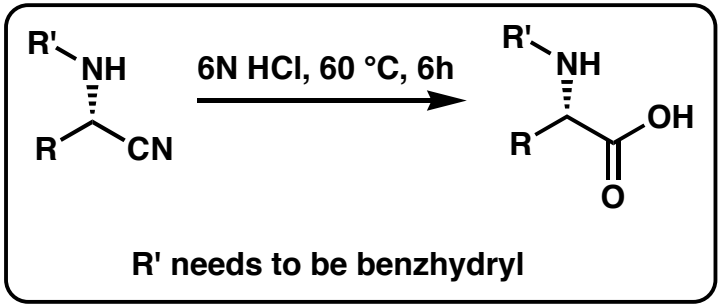
The Strecker Amino Acid Synthesis

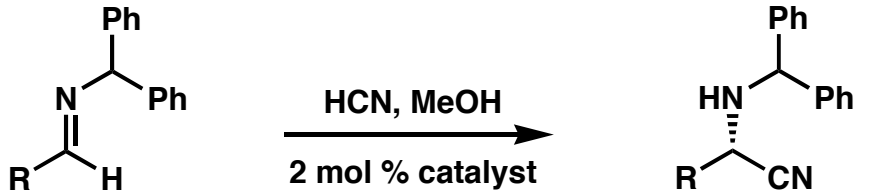




R'	solvent	yield, %	ee,%
p-OMeBn	MeOH	97	>99
3,4,5-$(OMe)_3PhCH_2$	MeOH	98	>98
Ph_2CH	MeOH	95	>99
t-BuOCO	*i*-PrOH	88	75



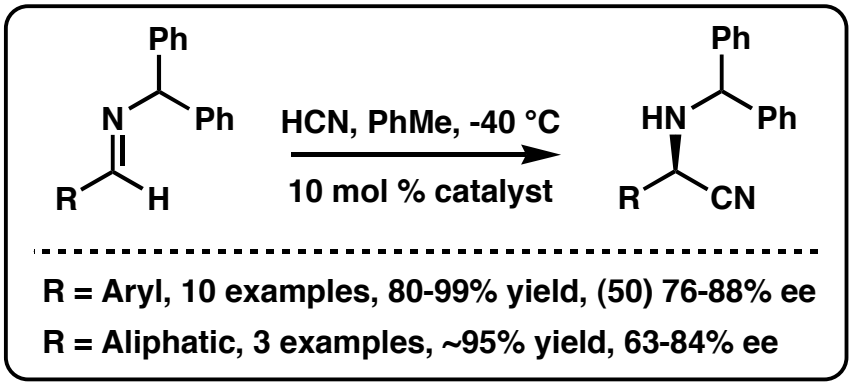


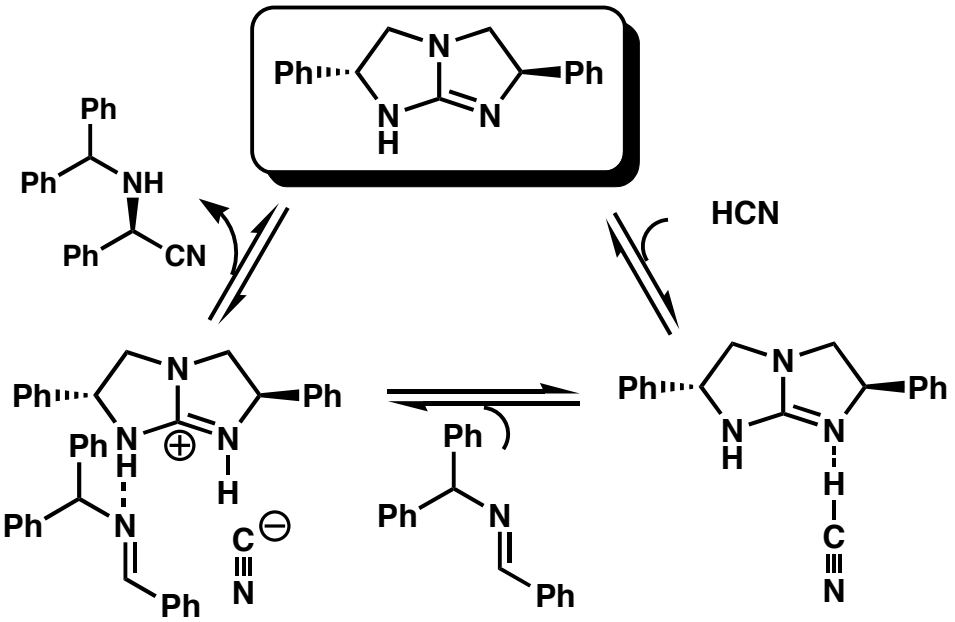


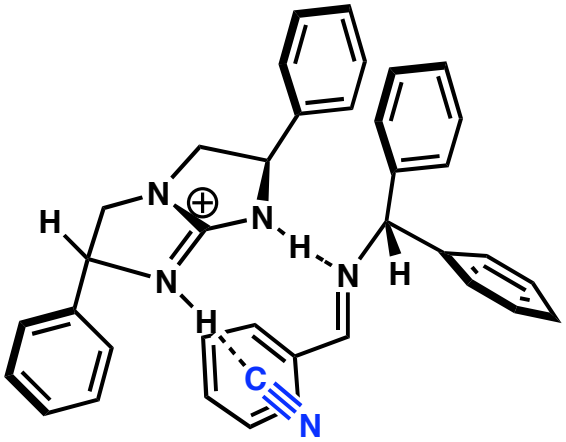
R	T, °C	yield, %	ee,%
Ph	-25	97	>99
p-ClPh	-75	94	>99
p-OMePh	-75	90	96
m-ClPh	-75	80	>99
m-OMePh	-75	82	80
m-NO_2	-75	71	<10
3-pyridyl	-75	86	<10
2-furyl	-75	94	32
i-Pr	-75	81	<10
t-Bu	-75	80	17

Lipton, et al. *J. Am. Chem. Soc.* **1996**, *118*, 4910-1.

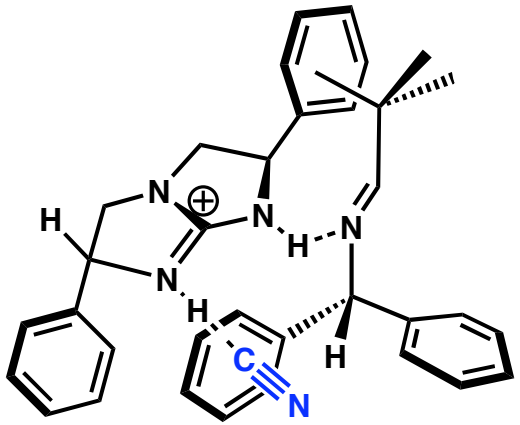
The Strecker Amino Acid Synthesis







Pre-transition-state assembly for aryl benzhydryl aldimines

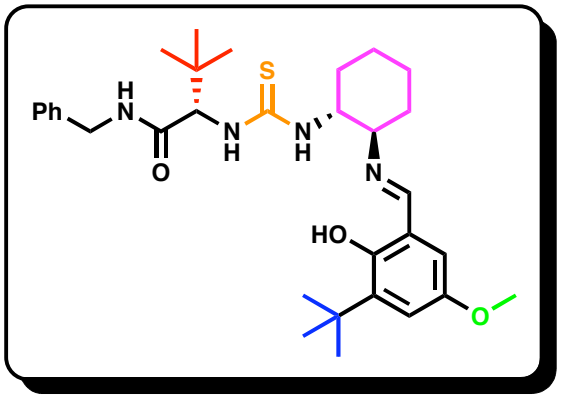


Pre-transition-state assembly for alkyl benzhydryl aldimines

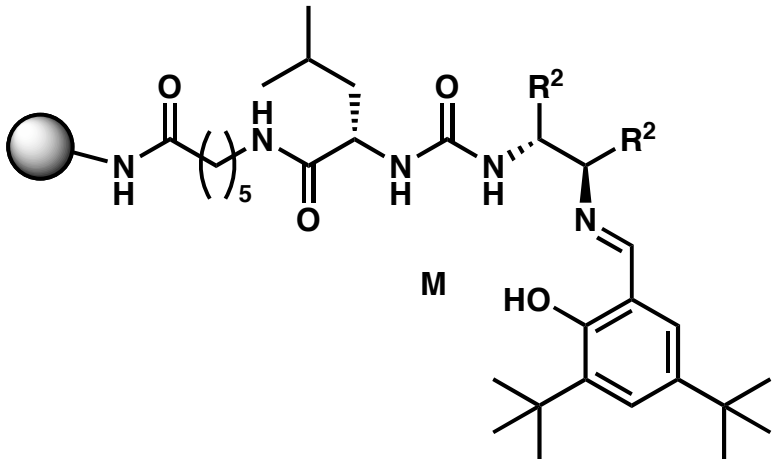
Corey, et al. *Org. Lett.* **1999**, *1*, 157-60.

The Strecker Amino Acid Synthesis

Catalyst Identification via Parallel Library Synthesis

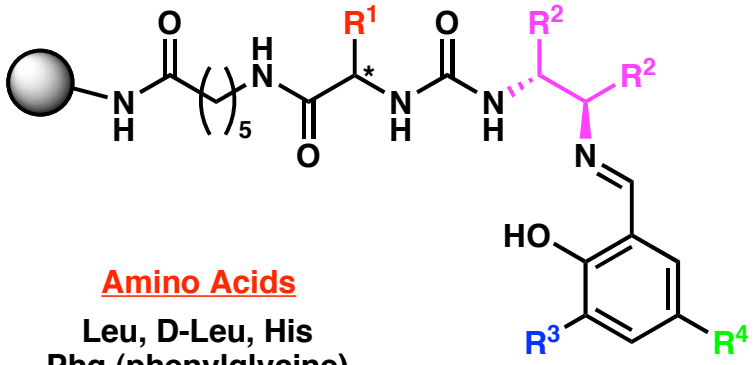


Library 1 - 12 Compounds



M	None	Ti	Mn	Fe	Ru	Co	Cu	Zn	Gd	Nd	Yb	Eu
% ee	19	4	5	10	13	0	9	1	2	3	9	5
% conv.	59	30	61	69	63	68	55	91	95	84	94	34

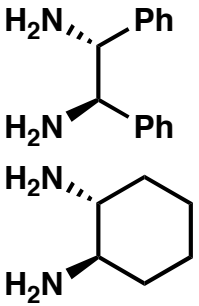
Library 2 - 48 Compounds



Amino Acids

Leu, D-Leu, His
Phg (phenylglycine)

Diamines



Salicylaldehydes

R^3	R^4
t-Bu	*t*-Bu
t-Bu	H
H	*t*-Bu
t-Bu	OMe
Br	Br
t-Bu	NO_2

Key Results

AA derived from Leu

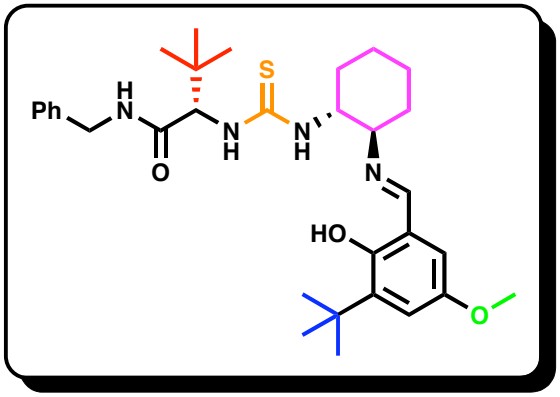
(*R,R*)-diamines matched case: L-Leu (32% ee)
mismatched: D-Leu (5% ee)

R^3 = *t*-Bu

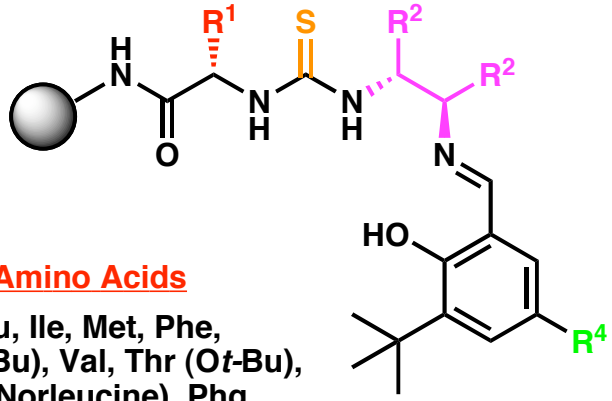
Jacobsen, et al. *J. Am. Chem. Soc.* **1998**, *120*, 4901-2.

The Strecker Amino Acid Synthesis

Catalyst Identification via Parallel Library Synthesis



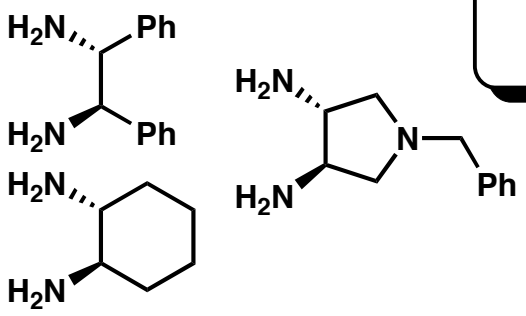
Library 3 - 132 Compounds



Amino Acids

Leu, Ile, Met, Phe,
Tyr (O*t*-Bu), Val, Thr (O*t*-Bu),
Nor (Norleucine), Phg,
Chg (Cyclohexylglycine), *t*-Leu

Diamines



Salicylaldehydes

t-Bu, H, Br, OMe

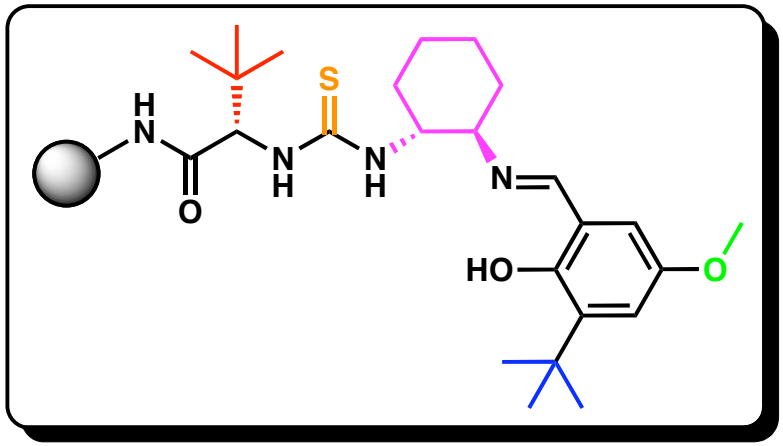
Key Results

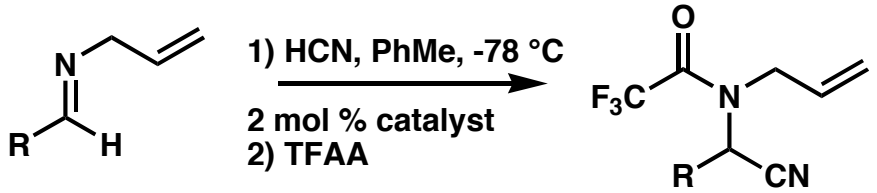
AA = *t*-Leu

Diamine = cyclohexyl

Salicylaldehyde = OMe

Optimized Catalyst



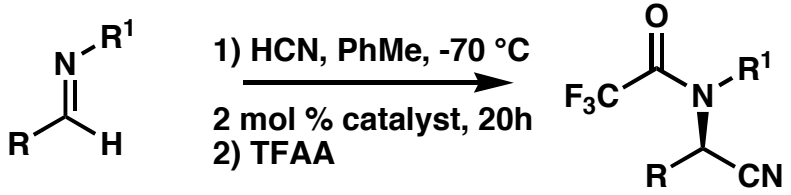


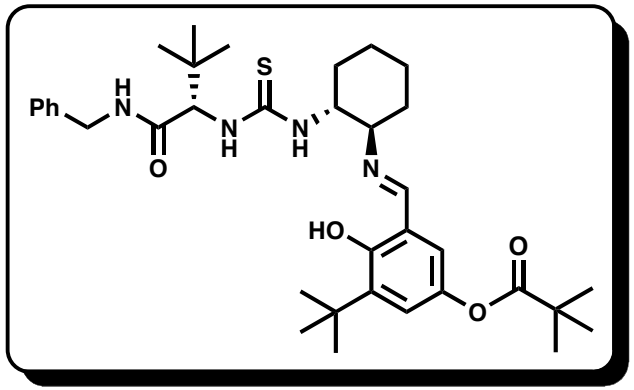
R	yield, %	ee,%
p-OMePh	78	91
p-BrPh	65	86
2-naphthyl	88	88
t-butyl	70	83
cyclohexyl	77	83

Jacobsen, et al. *J. Am. Chem. Soc.* **1998**, *120*, 4901-2.

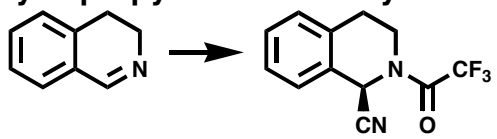
The Strecker Amino Acid Synthesis

A General Catalyst for Aldimines

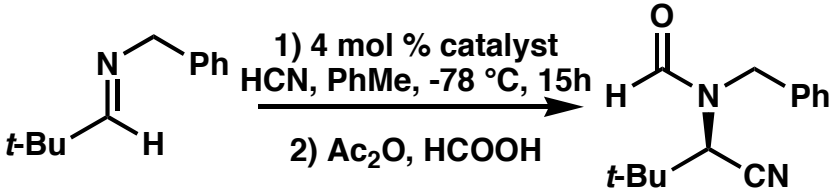




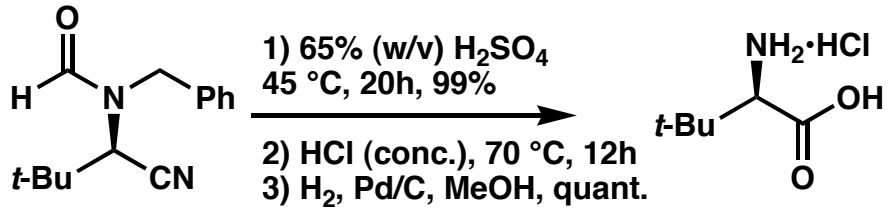
R	R^1	% yield	% ee
C_6H_5	allyl	74	95
t-butyl	allyl	75	95 (91)
p-OMePh	allyl	98	95
m-OMePh	allyl	99	93
o-OMePh	allyl	93	77
p-MePh	allyl	99	95
m-MePh	allyl	97	96
o-MePh	allyl	96	95
p-BrPh	allyl	89	89
m-BrPh	allyl	87	90
o-BrPh, 36h	allyl	88	95
p-*t*-BuPh	allyl	89	97
cyclooctyl	allyl	65	90
cyclohexyl	allyl	88	86
cyclohexyl	benzyl	85	87
t-butyl	benzyl	88	96 (93)
1-cyclohexenyl	benzyl	90	91 (87)
neopentyl	benzyl	85	90 (87)
pentyl	benzyl	69	78
i-propyl	benzyl	74	79
cyclopropyl	benzyl	89	91
		88	91



Preparative reactions using resin-bound catalyst



10 cycles of catalyst, yield 96-98% each time,
92-93% ee each time



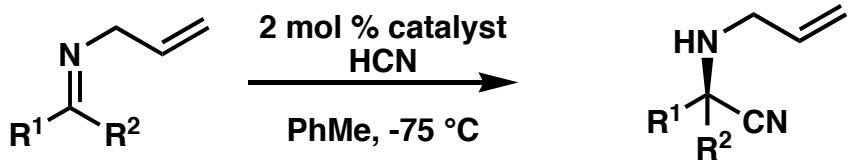
>99%ee
(recrystallized)

>99% ee
84% overall yield

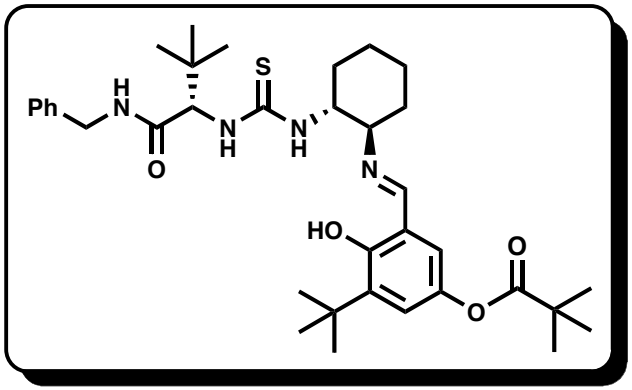
Jacobsen, et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-81.

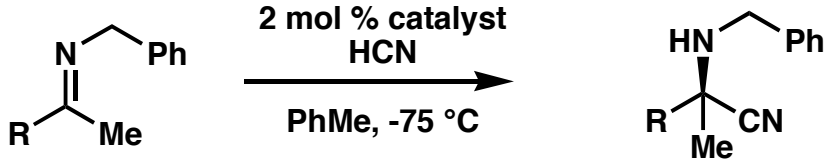
The Strecker Amino Acid Synthesis

Also a General Catalyst for Ketoimines

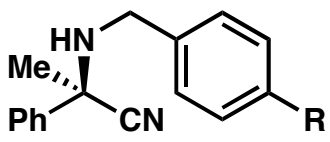


R^1	R^2	time, h	% yield	% ee
Ph	Me	30	97	85
Ph	Et	17	96	69
2-naphthyl	Me	65	97	89
$PhCH_2CH_2$	Me	17	98	41

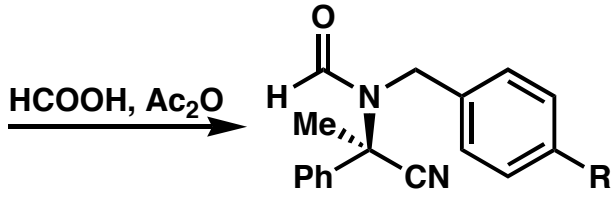




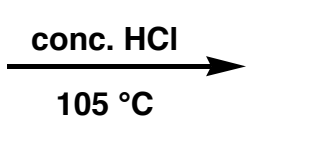
R	time, h	% yield	% ee
Ph	24	97	90
p-MePh	80	98	91
p-BrPh	80	quant	93
		(76)	(>99.9)
p-NO_2Ph	80	quant	93
		(79)	(>99.9)
p-OMePh	60	98	88
p-CF_3Ph	65	quant	95
		(75)	(>99.9)
m-BrPh	60	97	91
o-BrPh	90	45	42
t-butyl	15	98	70

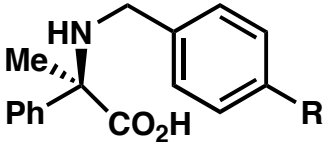


R=H, 90% ee
R=Br, >99.9% ee

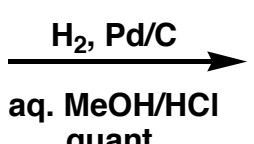


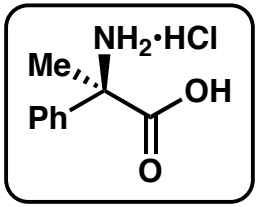
R=H, 97% yield
R=Br, 98% yield





R=H, 97% yield
R=Br, 98% yield



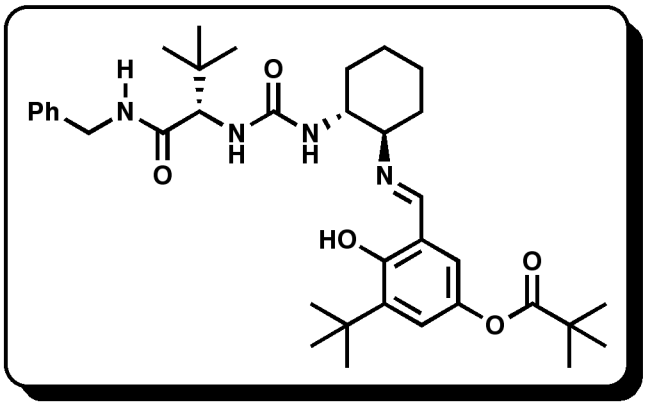


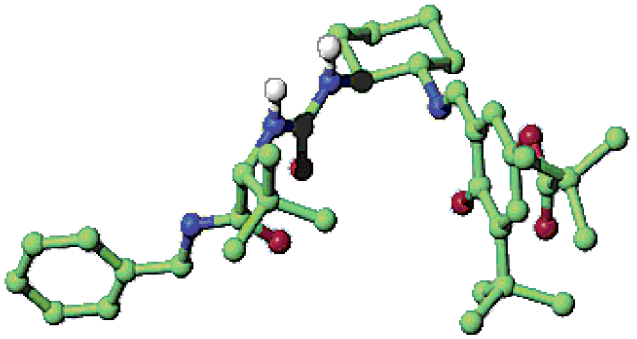
R=H, 92% overall yield, 90-91% ee
R=Br, 93% overall yield, >99.9% ee

Jacobsen, et al. *Org. Lett.* **2000**, *2*, 867-70.

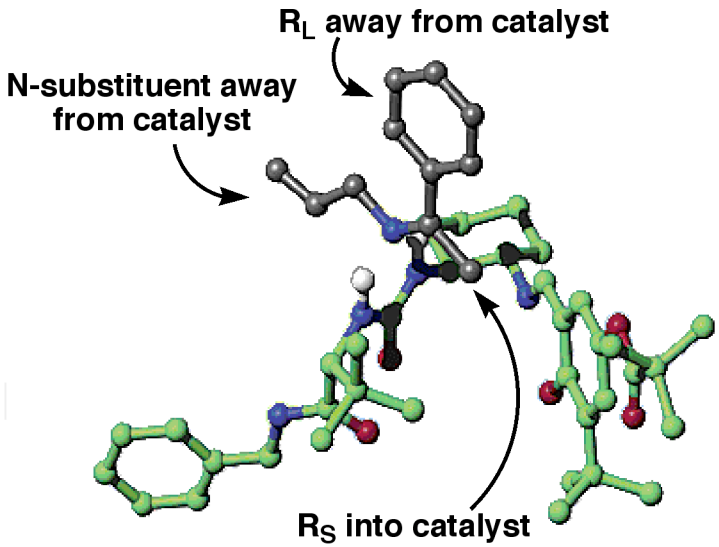
The Strecker Amino Acid Synthesis

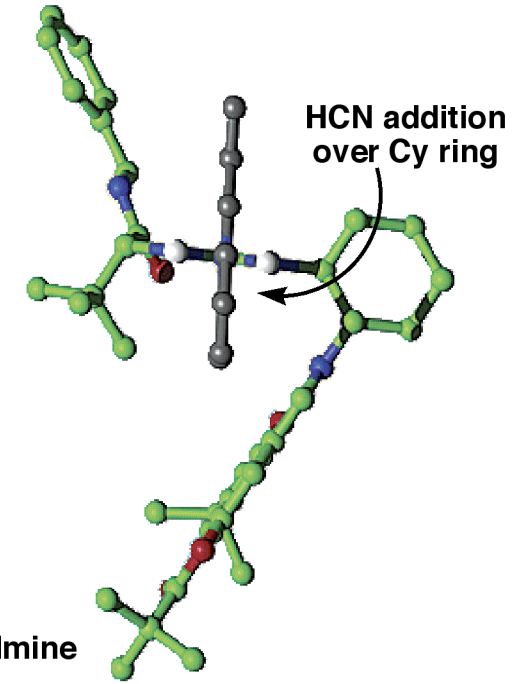
Mode of Action for Jacobsen Catalyst





Jacobsen Catalyst in Solution





Jacobsen Catalyst with Coordinated Imine

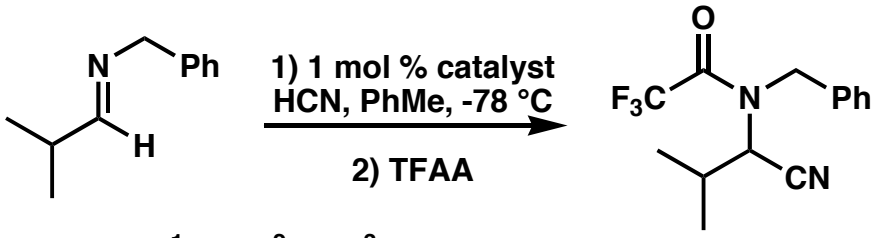
- Ground state conformations confirmed by ROESY and NOE.
- Catalyst obeys Michaelis-Menten kinetics (first order in catalyst and HCN).
- Saturation kinetics of imine substrate indicate reversible formation of imine-catalyst complex.
- Urea/thiourea protons were identified as the only essential protons for catalysis.
- Reactive imine stereoisomer (*Z*-imine) was determined by NMR titration with the catalyst.
- Confirmed by reactivity of cyclic imines.
- Double H-bond: urea/imine: 8.5 kcal/mol, thiourea/imine: 10 kcal/mol; H-bond to pdt: 5.0 and 6.3 kcal/mol, respectively.

Jacobsen, et al. *J. Am. Chem. Soc.*, **2002**, *124*, 10012-4.

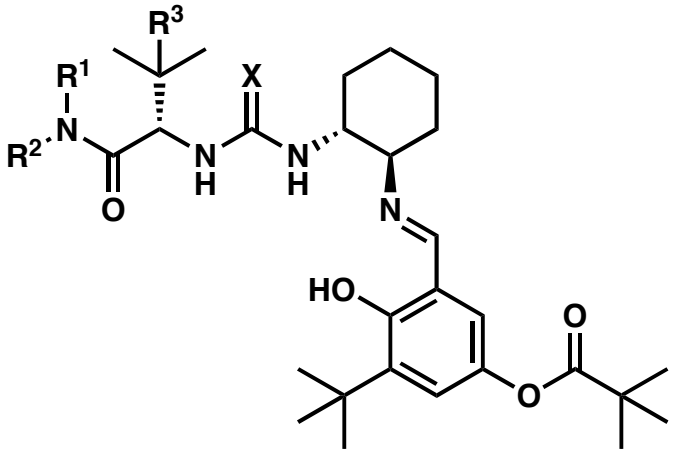
The Strecker Amino Acid Synthesis

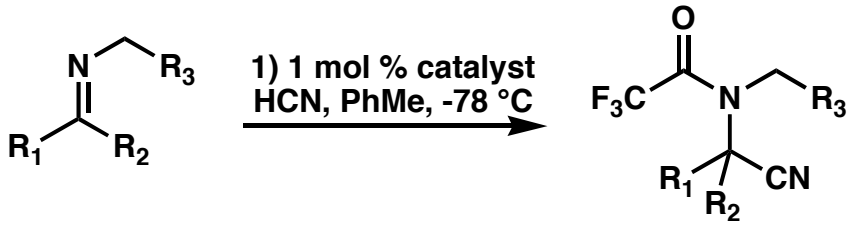
Mode of Action for Jacobsen Catalyst

Can face selectivity be altered by amino acid bulk?

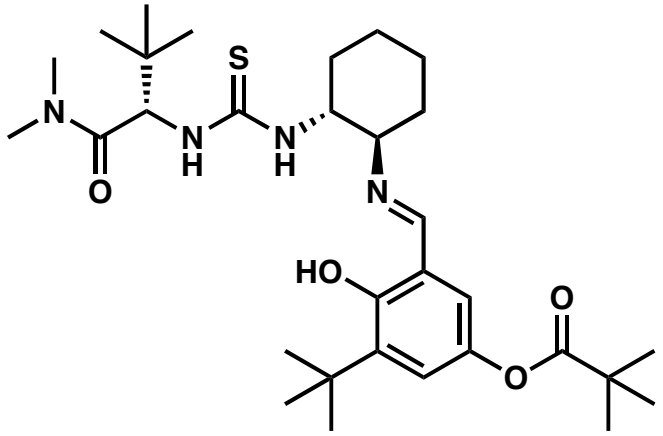


R^1	R^2	R^3	X	% ee
Bn	H	Me	O	80.0
Bn	Me	Me	O	93.5
Bn	Bn	Me	O	93.1
Me	Me	Me	O	95.8
Me	Me	Ph	O	96.6
Me	Me	Ph	S	97.0



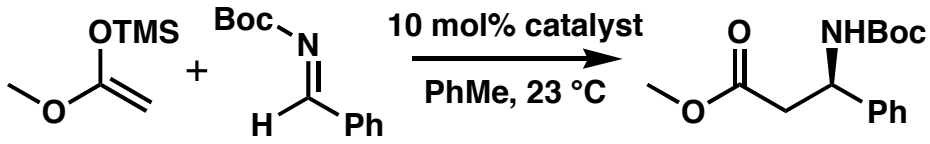


	R_1	R_2	R_3	catalyst = original % ee	= new % ee
Previous problem substrates	*i-Pr*	H	Ph	80	97
	n-pent	H	Ph	79	96
	t-Bu	Me	Ph	70	86
Previous good substrates	Ph	Me	*p*-BrPh	92	96
	t-Bu	H	Ph	96	99.3
	Ph	H	Ph	96	99.3

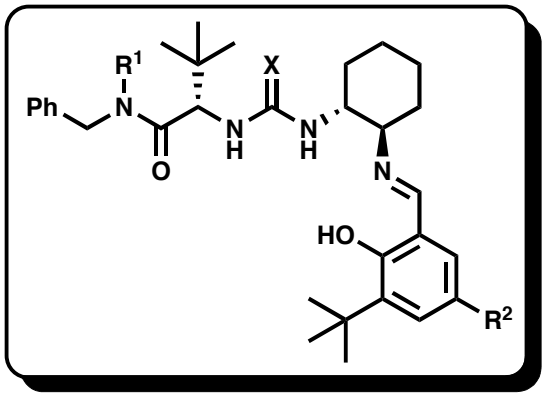


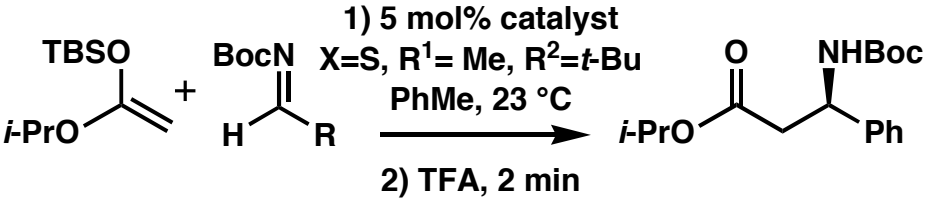
Jacobsen, et al. *J. Am. Chem. Soc.* **2002**, *124*, 10012-4.

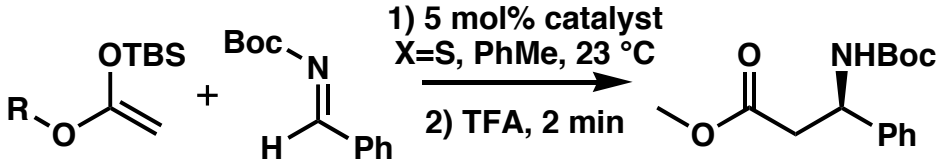
The Mannich Reaction



R^1	R^2	X	time, h	% conv	% ee
H	OCO(*t*-Bu)	O	25	92	47
H	OCO(*t*-Bu)	S	8	90	70







R	R^1	R^2	temp, °C	time, h	% conv	% ee
Me	H	OCO(*t*-Bu)	23	5.5	90	54
Et	H	OCO(*t*-Bu)	23	3.5	90	63
i-Pr	H	OCO(*t*-Bu)	23	2.0	93	68
i-Pr	H	OCO(*t*-Bu)	*-40*	*48.0*	*90*	*91*
t-Bu	H	OCO(*t*-Bu)	23	21.5	91	51

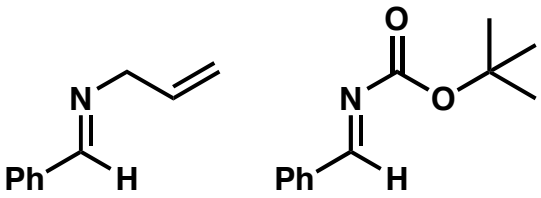
R	temp, °C	time, h	% yield	% ee
Ph	-40	48	95	97
o-MePh	-30	48	88	91
m-MePh	-30	48	98	94
p-MePh	-30	48	87	96
p-OMePh	4	48	91	86
p-FPh	-30	48	88	93
m-BrPh	-30	48	96	92
p-BrPh	-30	48	93	94
1-naphthyl	-30	48	93	87
2-naphthyl	-30	48	88	96
2-furyl	-40	48	84	91
2-thienyl	-30	48	99	96
3-quinolinyl	-30	48	99	96
3-pyridyl	-30	48	99	98

Jacobsen, et al. *J. Am. Chem. Soc.* **2002**, *124*, 12964-5.

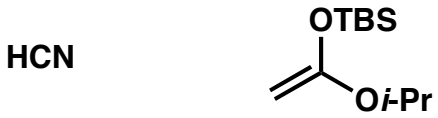
The Mannich Reaction

Mechanism of Stereoinduction for Jacobsen Catalyst -- Same as Strecker Reaction?

Aldimines for Strecker and Mannich reactions differ electronically and sterically.



Nucleophiles are also sterically and electronically different.

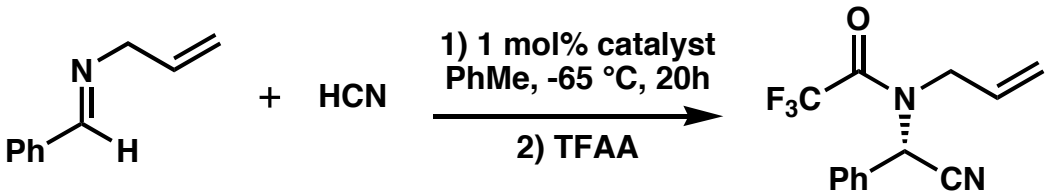


Modifications tested:

- **Amide bond and urea functionalities**
- **Amino acid**
- **Salicylaldimine**
- **Diamine linker**

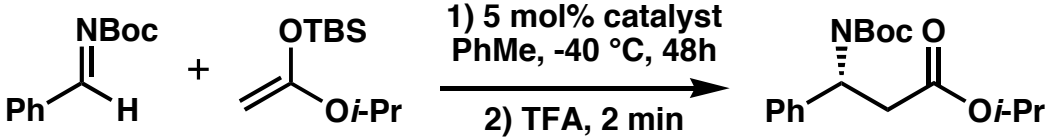
<u>Reference Reactions for Structure-Activity Studies:</u>

Strecker Reaction:

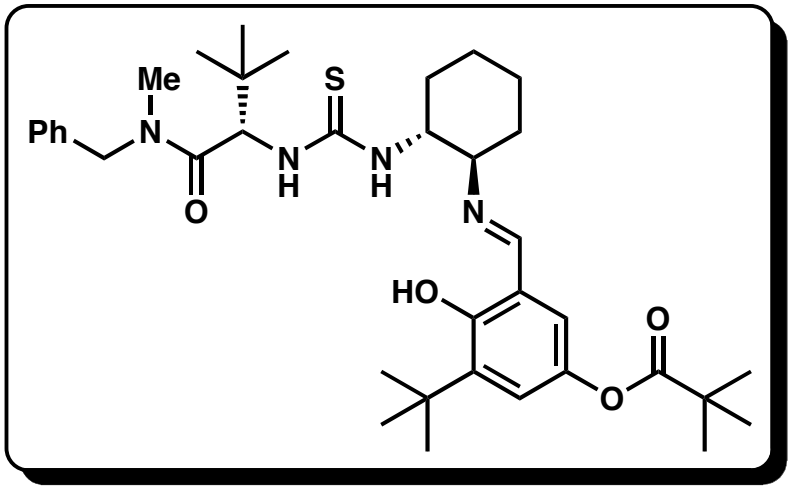


98% ee
100% conv.

Mannich Reaction:



97% ee
96% conv.

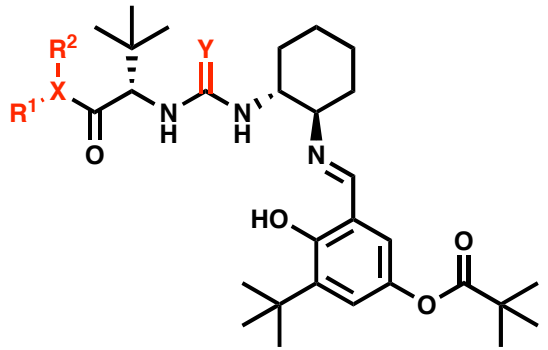


Jacobsen, et al. *Synlett* **2003**, 1919-22.

The Mannich Reaction

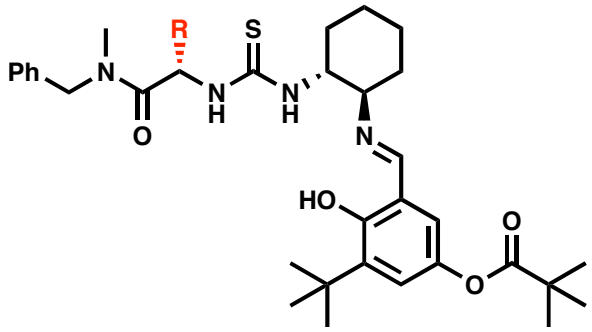
Mechanism of Stereoinduction -- Amide Bond, Urea, and Amino Acid Influence

R^1	R^2	X	Y	Strecker % ee	Mannich % ee
Bn	Me	N	S	98	97
Bn	H	N	S	98	91
Bn	H	N	O	97	81
Bn	Bn	N	S	98	97
Bn	Bn	N	O	97	82
Me	Me	N	S	99	86
Me	Me	N	O	98	80
i-Bu	*i*-Bu	N	S	95	93
Cy	H	N	O	97	84
Bn		O	O	80	44



- Thiourea enhances enantioselectivity for both reactions; effect is more dramatic for Mannich reaction.
- Tertiary amides provided better selectivity than secondary amides, again, more dramatic for Mannich.
- Esters are not acceptable replacements for amides.
- For the Strecker reaction, the sterically smaller N,N-dimethyl amide catalyst was better than the sterically larger N,N-diisobutyl amide. The opposite was true for the Mannich reaction.

R	Strecker % ee	Mannich % ee
i-Pr (L-Val)	96	51
Me (L-Ala)	91	22
Ph (L-Phg)	92	38
CMe_2Ph (D-2-amino-3-methyl -3-phenylbutyric acid)	98	90



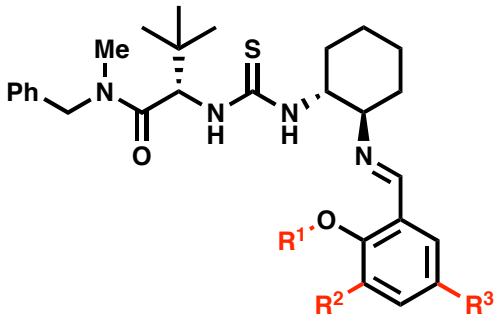
- For the Mannich reaction, the amino acid identity is integral to the efficacy of the catalyst. Bulky amino acids are essential, but increasing the bulk too much also lowers the enantioselectivity somewhat.
- The Strecker reaction is not significantly altered by the amino acid size.

Jacobsen, et al. *Synlett* **2003**, 1919-22.

The Mannich Reaction

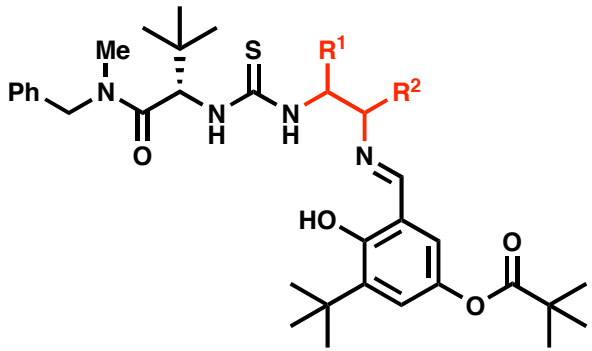
Mechanism of Stereoinduction -- Salicylaldimine and Diamine Influences

R^1	R^2	R^3	Strecker % ee	Mannich % ee
H	*t*-Bu	*t*-Bu	92	97
H	*i*-Pr	*t*-Bu	92	97
H	Me	*t*-Bu	91	96
H	H	H	94	91
Me	*t*-Bu	*t*-Bu	64	92
1-hydroxy-2-naphthyl			67	94 (98)[in THF]



- The Strecker reactionwas largely insensitive to changes in R^2, but altering R^3 resulted in significant drops in ee. (Recall the original catalyst gave an ee of 98% where R^2= *t*-Bu and R^3= OCO*t*-Bu).
- The identity of the R^2 group was inconsequential for the Mannich reaction, as was the R^3 group (original catalyst gave an ee of 97%).

R^1	R^2	configuration	Strecker % ee	Mannich % ee
Ph	Ph	(*R,R*)	98	80
t-Bu	*t*-Bu	(*R,R*)	NR	NR
-$(CH_2)_4$-		(*S,S*)	27(*R*)	90

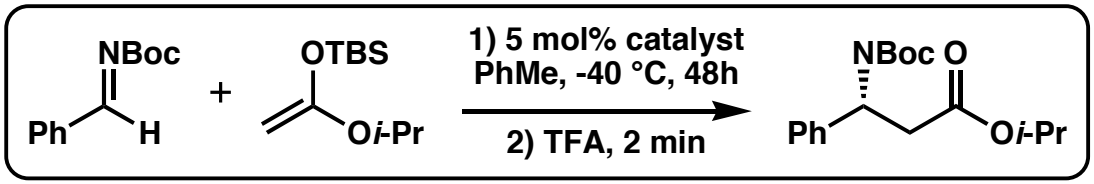


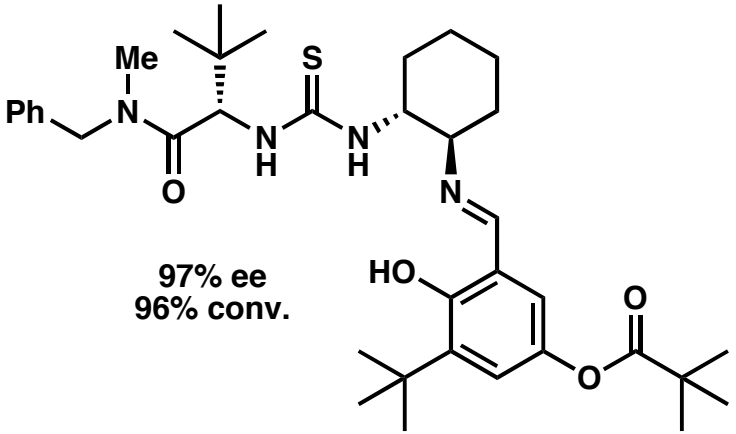
- The Strecker reaction tolerates substitution of the (*R,R*)-cyclohexyl unit with an (*R,R*) diphenylethylene, but it does not tolerate further increase in steric bulk or the mismatched (*S,S*) cyclohexyl unit.
- The Mannich reaction suffers from replacement of the cyclohexyl unit by the diphenylethylene and is also unreactive with the bulky diamine. However, reversing the configuration of the diamine is well-tolerated and, interestingly, provides the same sense of stereoinduction in high ee.

Jacobsen, et al. *Synlett* **2003**, 1919-22.

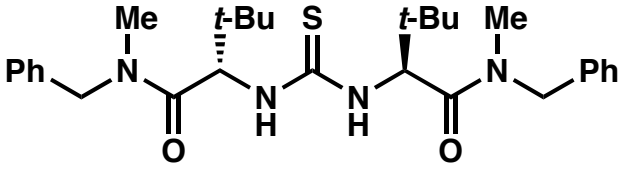
The Mannich Reaction

Simplified Catalysts Based on Structure-Mechanism Studies

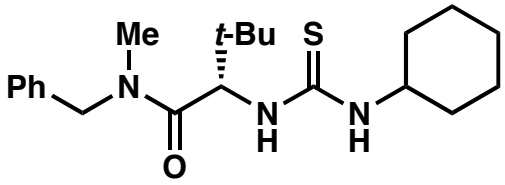




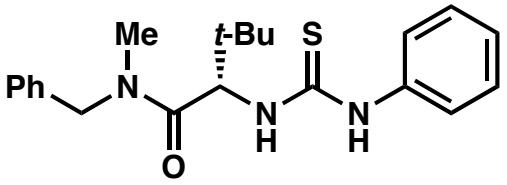
97% ee
96% conv.



37% ee
42% conv.



90% ee
90% conv.

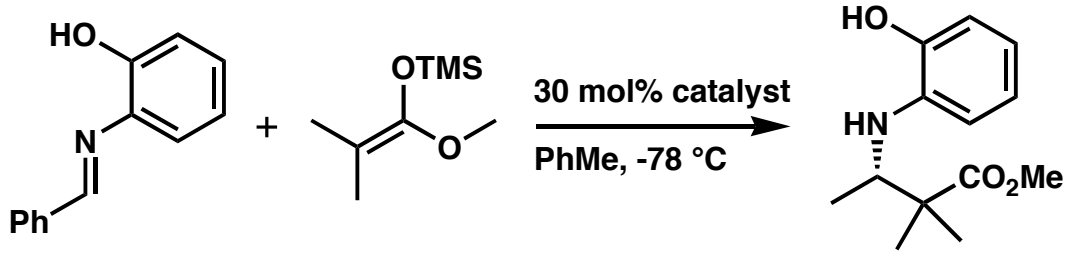


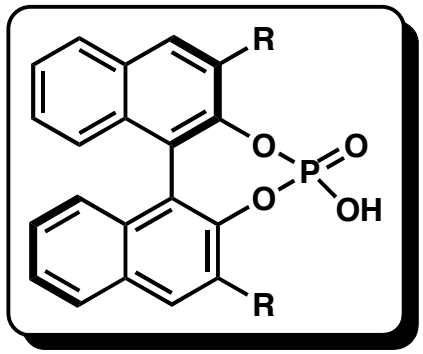
94% ee
100% conv.
(in THF)

- Schiff base and diamine linker are unnecessary for the efficient catalysis of the Mannich reaction.
- The C_2-symmetric catalyst is ineffective, perhaps due to the significant increase in bulk in the right half of the compound.
- Returning to a C_1-symmetric compound revives catalytic activity.
- Further modification of the cyclohexyl ring to a phenyl ring brings the ee nearly to the original catalyst ee, accompanied by an increase in conversion.

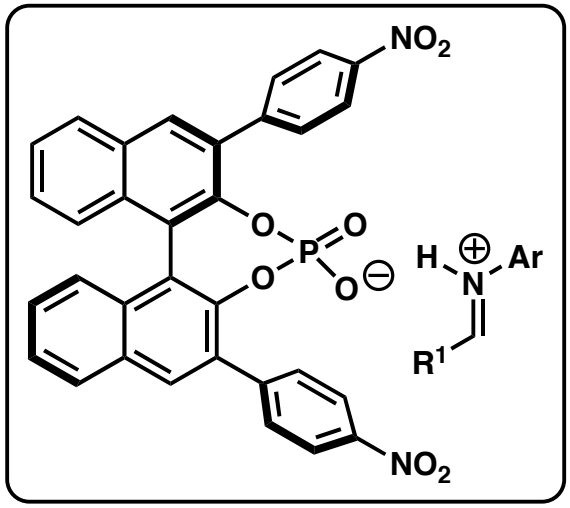
Jacobsen, et al. *Synlett* **2003**, 1919-22.

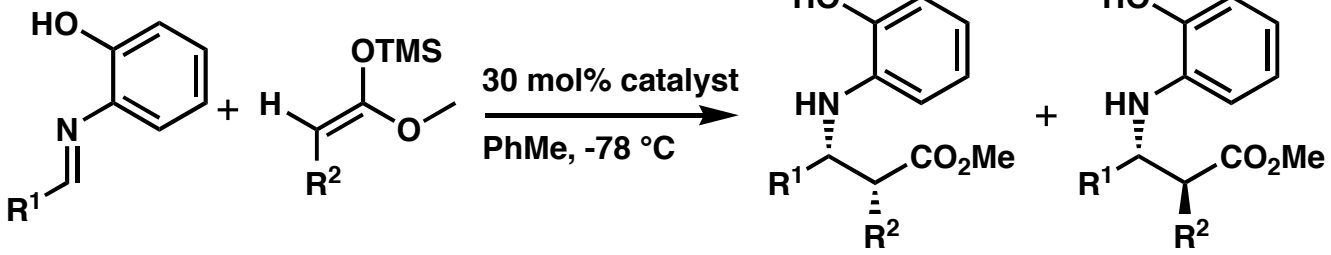
The Mannich Reaction





R	time, h	% yield	% ee
H	22	57	0
Ph	20	100	27
2,4,6-Me_3Ph	27	100	60
4-OMePh	46	99	52
4-NO_2Ph	4	96	87



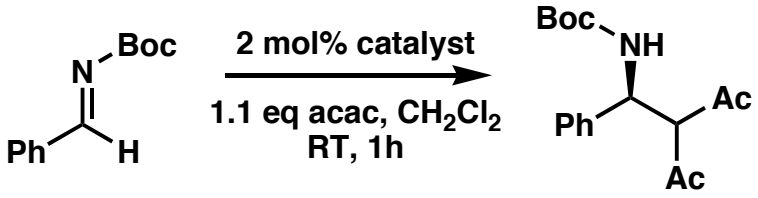


R^1	R^2	R^3	% yield	syn/anti	% ee syn
Ph	Me[a]	Et	100	87:13	96
p-OMePh	Me[a]	Et	100	92:8	88
p-FPh	Me[a]	Et	100	91:9	84
p-ClPh	Me[a]	Et	100	86:14	83
p-MePh	Me[a]	Et	100	94:6	81
2-thienyl	Me[a]	Et	81	94:6	88
styrenyl	Me[a]	Et	91	95:5	90
Ph	Bn[a]	Et	100	93:7	91
p-OMePh	Bn	Et	92	93:7	87
styrenyl	Bn[a]	Et	65	95:5	90
Ph	Ph_3SiO[b]	Me	79	100:0	91

[a] *E*/*Z*=87:13
[b] *E*/*Z*=91:9

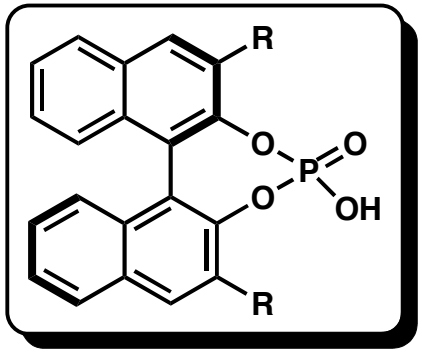
Akiyama, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-8.

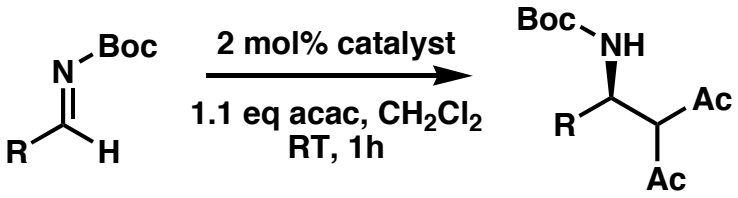
The Mannich Reaction



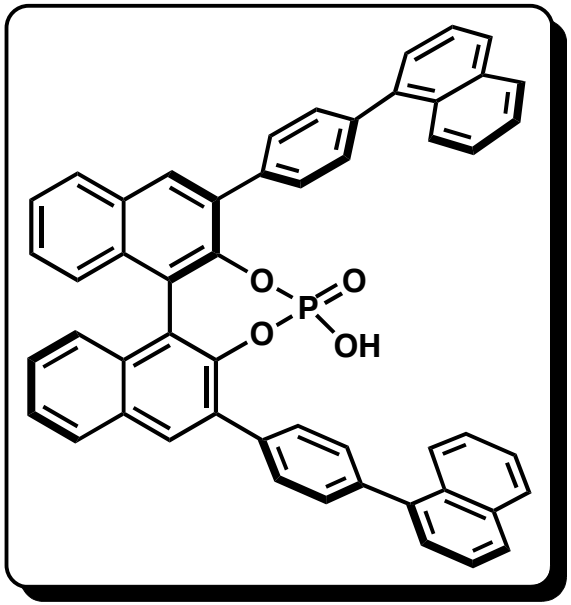
R	% yield	% ee
H	92	12[a]
Ph	95	56
4-biphenyl	88	90
4-(β-naph)-Ph	99	95

[a]opposite enantiomer



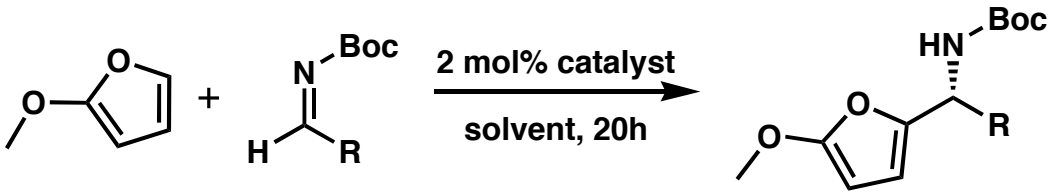


R	% yield	% ee syn
p-OMePh	93	90
p-MePh	98	94
p-BrPh	96	98
p-FPh	94	96
o-MePh	94	93
1-naphthyl	99	92

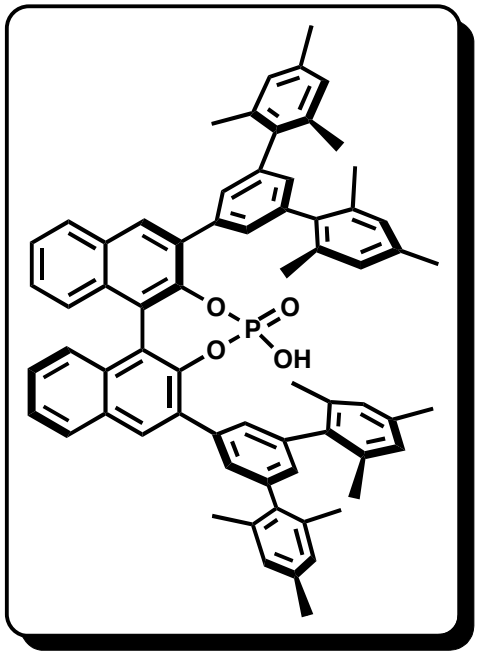


Terada, et al. *J. Am. Chem. Soc.* **2004**, *126*, 5356-7.

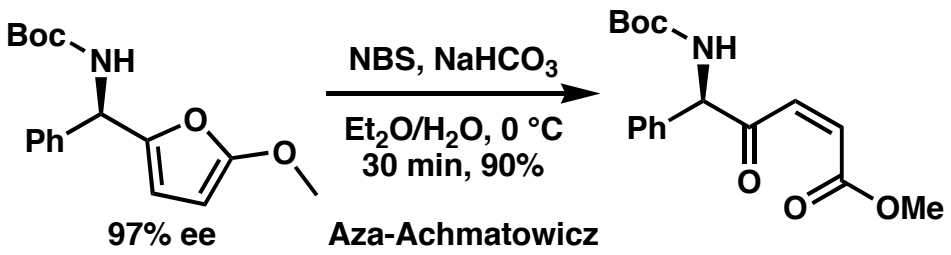
Aza-Friedel-Crafts Alkylation of Furan

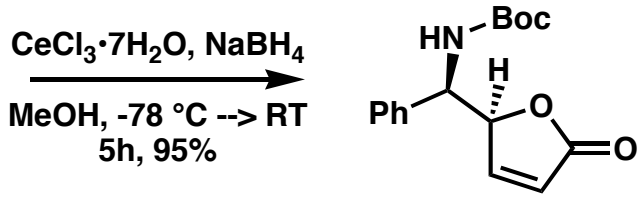


Solvent, R=Ph	temp, °C	% yield	% ee
THF	0	70	83
i-Pr_2O	0	80	79
PhMe	0	88	83
PhCl	0	79	83
$CHCl_3$	0	83	84
CH_2Cl_2	0	82	88
$(CHCl_2)_2$	0	87	90
$(CH_2Cl)_2$	0	86	82
$(CH_2Cl)_2$	-20	89	95
$(CH_2Cl)_2$	-35	87	97



R (DCE, -35 °C, 24h)	% yield	% ee
p-OMePh	95	96
o-MePh	84	94
m-MePh	80	94
p-MePh	96	97
o-BrPh	85	91
m-BrPh	89	96
p-BrPh	86	96
p-ClPh	88	97
p-FPh	82	97
1-naphthyl	84	86
2-naphthyl	93	96
2-furyl	94	86
Ph	95	97

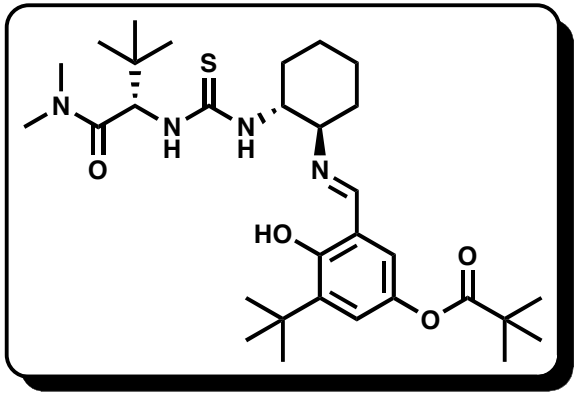


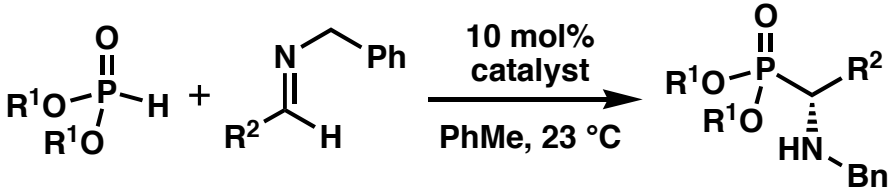


syn/anti = 85:15
96% ee syn

Terada, et al. *J. Am. Chem. Soc.* **2004**, *126*, 11804-5.

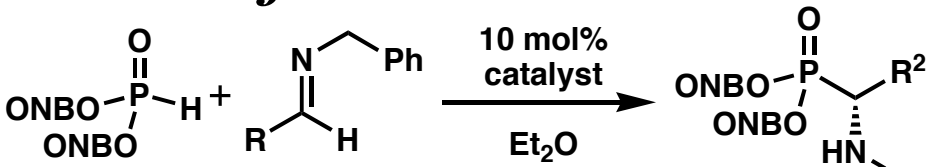
Hydrophosphonylation of Imines



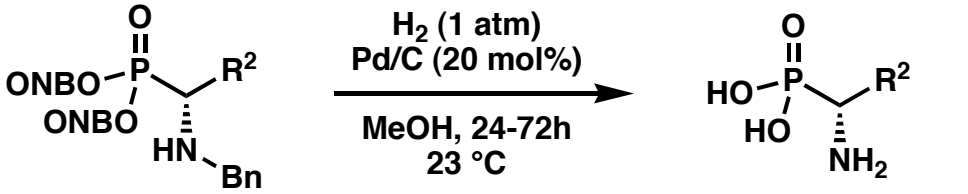


R^1	R^2	time, h	% conv	% ee
Ph	Ph	1	100	77
	3-pentyl	1	100	80*
CH_2CF_3	Ph	1	100	72*
	3-pentyl	1	100	53*
2-cyanoethyl	Ph	2	83	68
	3-pentyl	2	85	77
2-chloroethyl	Ph	8	89	90
	3-pentyl	8	91	84
2-methoxyethyl	Ph	32	50	43
	3-pentyl	8	65	59
p-nitrobenzyl	Ph	24	86	78
	3-pentyl	18	90	73
o-nitrobenzyl	Ph	26	99	93
	3-pentyl	24	100	90

Jacobsen, et al. *J. Am. Chem. Soc.* **2004**, *126*, 4102-3.



R	temp, °C	time, h	% yield	% ee
Ph	4	72	87	98
3-pentyl	4	24	90	96
i-Pr	4	24	93	90
Cy	4	24	91	90
t-Bu	4	72	83	93
$Me_2C=CH$	4	7	91 (64)	82 (99)
p-OMePh	4	48	90	96
p-CO_2MePh	23	48	78	96
o-MePh	4	72	81	92
o-ClPh	4	72	52	96
m-ClPh	23	48	83	98
p-ClPh	4	72	87	99
2-naphthyl	4	72	86	98
3-pyridyl	23	48	77	96
2-furyl	4	72	89	92
2-thienyl	23	48	89	94
2-pyrrolyl	4	18	86	81



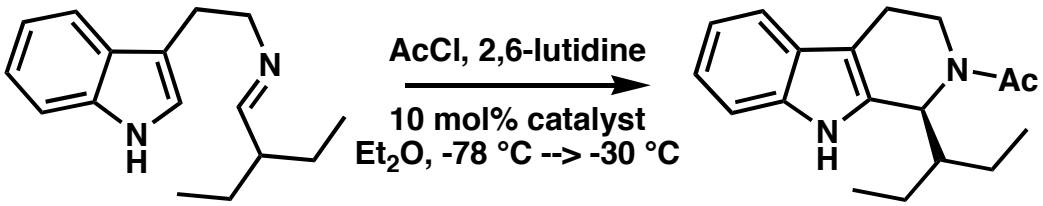
R = Ph (98% ee)
R = 3-pentyl (96% ee)
R = $Me_2C=CH$- (99% ee)

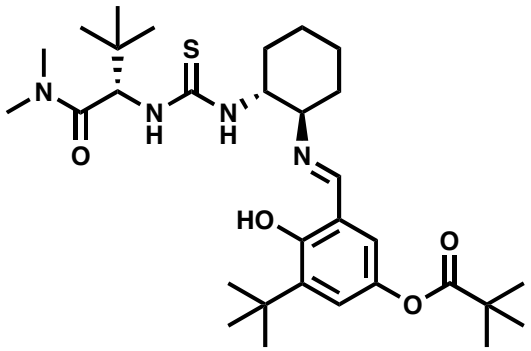
R = Ph (87% yield, 97% ee)
R = 3-pentyl (89% yield, 96% ee)
R = *i*-Bu [(*R*)-Leu^P] (93% yield, 98% ee)

The Acyl-Pictet-Spengler Reaction

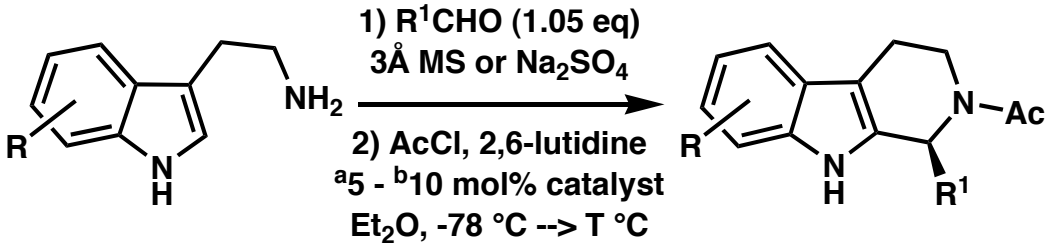
- Pictet-Spengler imine substrates are fairly unreactive; normally strong Brønsted acids, naked Lewis acids or high temperatures are required to promote the reaction.
- All compounds initially tested were unreactive unless at high temps.
- No ee was observed due to the temps required.
- Activate the substrate? --> Acyl-Pictet Spengler

Catalyst Optimization Reaction:

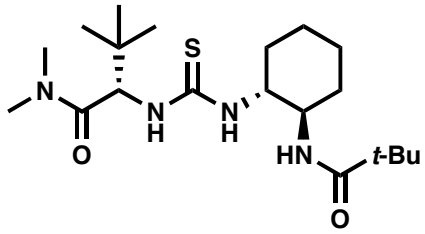




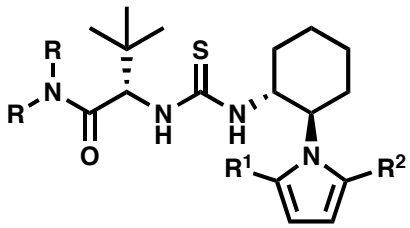
65% yield, 59% ee



R	R^1	T, °C	% yield	% ee
H	$CH(CH_2CH_3)_2$	-30	65[a]	93
H	$CH(CH_3)_2$	-40	67[b]	85
H	*n*-pentyl	-60	65[b]	95
H	$CH_2CH(CH_3)_2$	-60	75[b]	93
H	CH_2CH_2OTBS	-60	77[b]	90
5-OMe	$CH(CH_2CH_3)_2$	-40	81[a]	93
6-OMe	$CH(CH_2CH_3)_2$	-50	76[b]	86



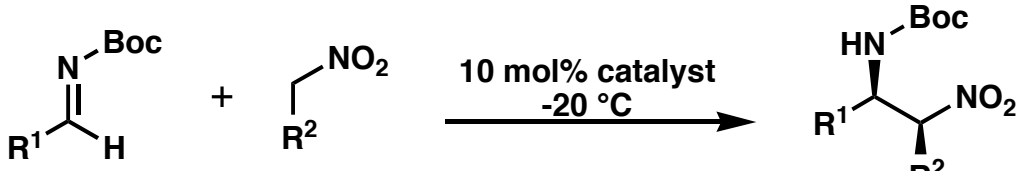
45% yield, 61% ee



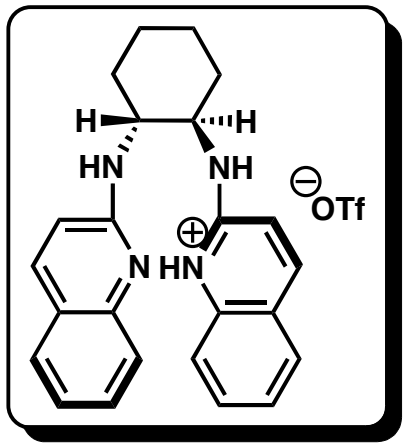
R = R^1 = R^2 = Me: 65% yield, 77% ee
R = Me, R^1 = R^2 = Ph: 55% yield, 71% ee
R = R^1 = Me, R^2 = Ph: 70% yield, 93% ee
R = *i*-Bu, R^1 = Me, R^2 = Ph: 70% yield, 93% ee

Jacobsen, et al. *J. Am. Chem. Soc.* **2004**, *126*, 10558-9.

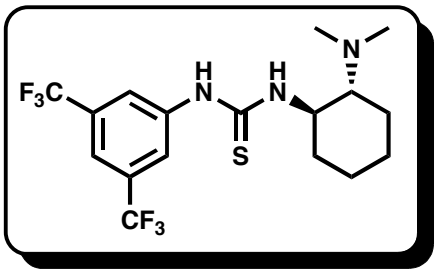
The Aza-Henry Reaction

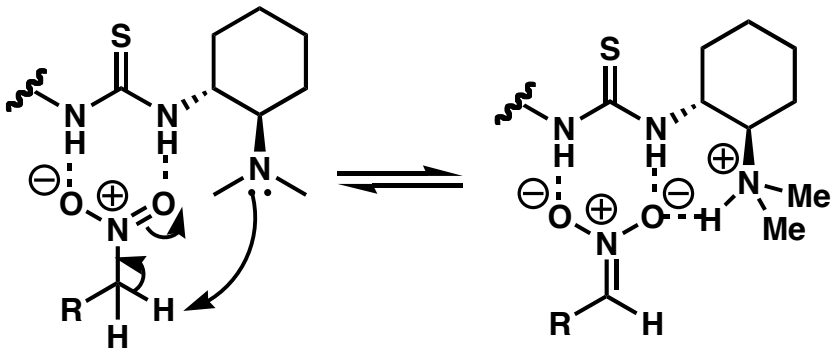


R^1	R^2	% yield	dr	% ee
Ph	H	57	--	60
p-NO_2Ph	H	61	--	82
m-NO_2Ph	H	65	--	95
Ph	Me	69	14:1	59
p-CF_3OPh	Me	53	19:1	81
p-ClPh	Me	59	17:1	82
m-NO_2Ph	Me	51	11:1	89
o-NO_2	Me	62	7:1	82
p-CF_3Ph	Me	50	19:1	84
p-NO_2Ph	Me	60	7:1	90

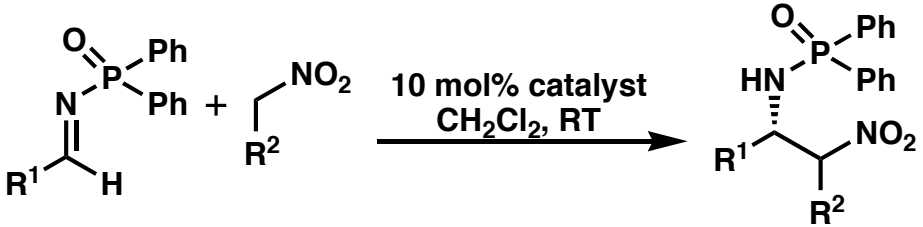


Johnston, et al. *J. Am. Chem. Soc.* **2004**, *126*, 3418-9.



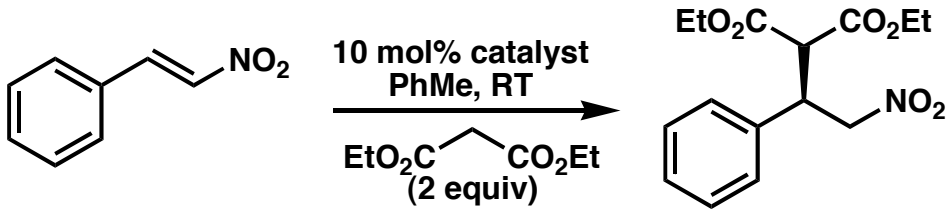


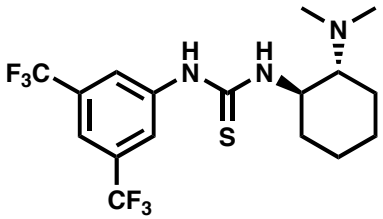
Takemoto, et al. *Org. Lett.* **2004**, *6*, 625-7.



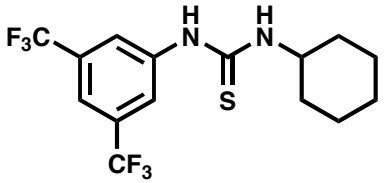
R^1	R^2	% yield	dr	% ee
Ph	H	87	--	67
p-MePh	H	72	--	63
p-ClPh	H	76	--	67
2-naphthyl	H	78	--	70
2-furyl	H	85	--	76
2-pyridyl	H	91	--	68
2-thienyl	H	57	--	64
cinnamyl	H	68	--	65
Ph	Me	83	73:27	67

The Michael Reaction of Malonates to Nitroolefins

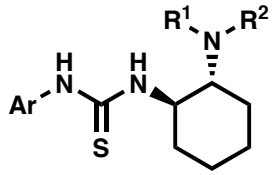




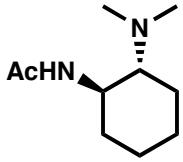
24h, 86% yield, 93% ee



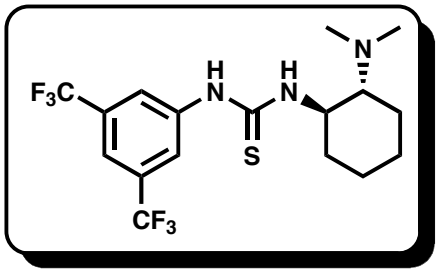
+TEA: 24h, 57% yield, 0% ee

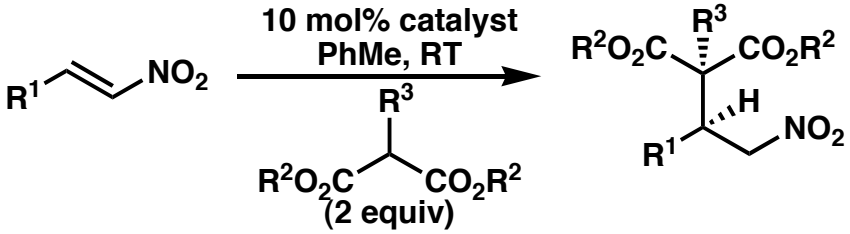


Ar = 3,5-$(CF_3)_2$Ph, $R^1 = R^2 =$ *o*-$(CH_2)_2$Ph
48h, 29% yield, 91% ee
Ar = 3,5-$(CF_3)_2$Ph, R^1 = Me, R^2 = *i*-Pr
48h, 76% yield, 87% ee
Ar = Ph, $R^1 = R^2$ = Me
48h, 58% yield, 80% ee
Ar = 2-OMePh, $R^1 = R^2$ = Me
48h, 40% yield, 52% ee



24h, 14%yield, 35% ee

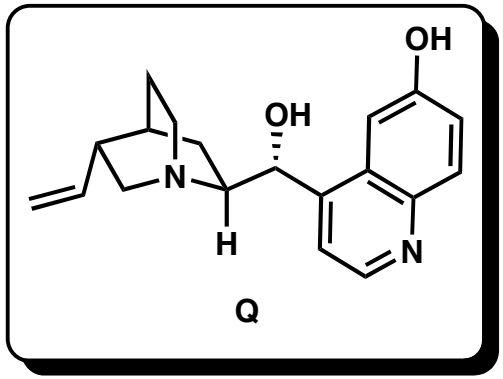




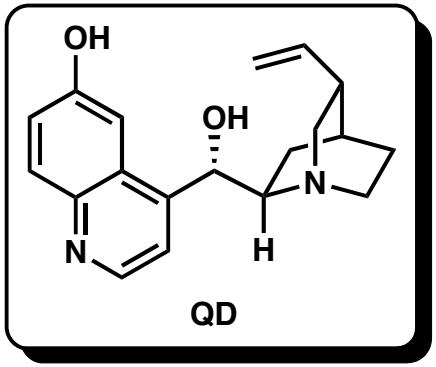
R^1	R^2	R^3	time, h	% yield	% ee
Ph	Et	H	24	86	93 (*S*)
2,6-$(OMe)_2$Ph	Et	H	72	87	93 (*S*)
p-FPh	Et	H	12	87	92 (*S*)
1-naphthyl	Et	H	24	95	92 (-)
2-thienyl	Et	H	48	74	90 (-)
pentyl	Et	H	48	78	81 (*S*)
i-Bu	Et	H	48	88	81 (*S*)
Ph	Me	Me	36	88	81 (*S*)

Takemoto, et al. *J. Am. Chem. Soc.* **2003**, *125*, 12672-3.

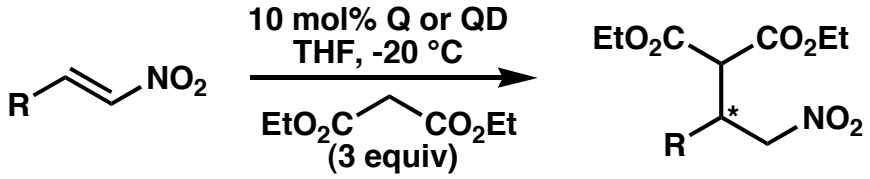
The Michael Reaction of Malonates to Nitroolefins



Q



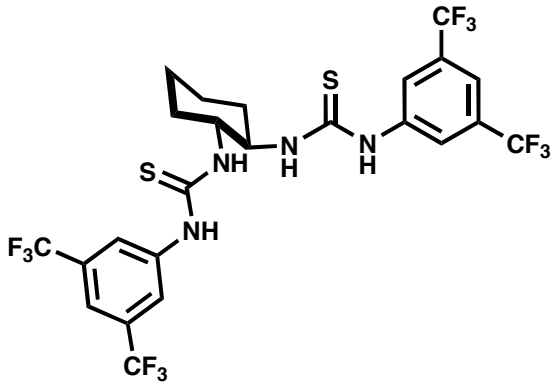
QD



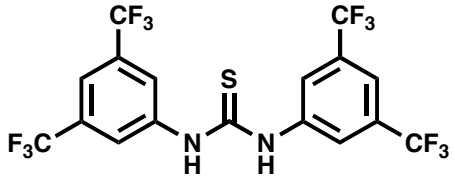
R	time, h (QD)	% yield (QD)	% ee (QD)
Ph	36 (36)	97 (99)	96 (93)
p-FPh	36 (36)	97 (97)	97 (94)
p-ClPh	36 (36)	97 (97)	97 (94)
p-BrPh	36 (36)	99 (98)	96 (94)
p-MePh	36 (44)	97 (97)	98 (94)
p-(*i*-Pr)Ph	36 (39)	95 (96)	97 (93)
p-OMePh	44 (47)	90 (94)	97 (95)
m-MePh	36 (36)	97 (99)	98 (96)
o-MePh	36 (36)	95 (97)	98 (96)
o-FPh	36 (36)	97 (94)	97 (95)
o-NO_2Ph	69 (72)	90 (88)	97 (92)
1-naphthyl	36 (36)	99 (99)	98 (92)
2-thienyl	36 (44)	99 (96)	98 (95)
2-furyl	36 (36)	97 (95)	98 (96)
3-pyridinyl	36 (36)	98 (99)	96 (92)
pentyl	72 (72)	86 (84)	94 (92)
i-Bu	72 (72)	86 (84)	94 (92)
cyclohexyl	108 (108)	71 (80)	94 (91)

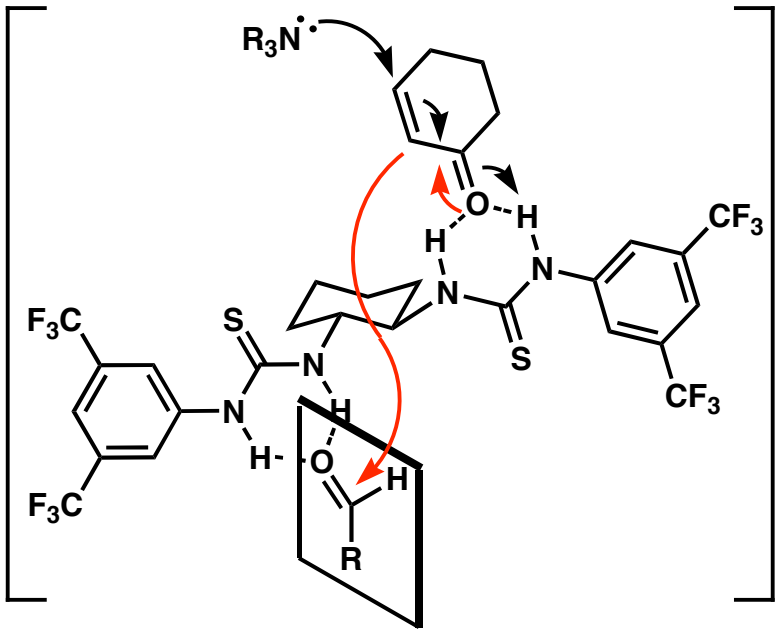
Deng, et al. *J. Am. Chem. Soc.* **2004**, *126*, 9906-7.

The Baylis-Hillman Reaction

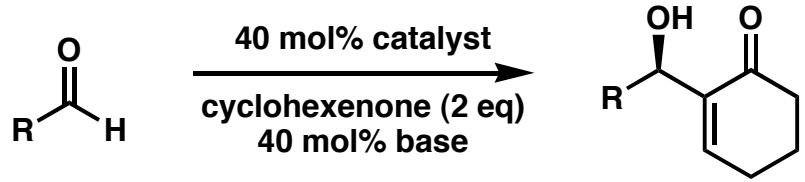


- Achiral reaction experiences a 60-fold increase in rate upon addition of the achiral thiourea catalyst.
- NMR experiments indicate that the catalyst interacts with both the enone and the aldehyde.
- Asymmetric catalyst was designed based on idea for one catalyst to bind to both reaction partners at once, allowing for further rate increase by proximity effects.





Proposed Transition State



R	Base	temp, °C	time, h	% yield	% ee
Ph	DMAP	-5	72	88	33
	Imid	RT	120	40	57
o-CF_3Ph	DMAP	-5	72	38	30
m-CF_3Ph	DMAP	-5	72	88	19
p-CF_3Ph	DMAP	-5	72	99	33
	Imid	4	120	95	44
-$(CH_2)_2$Ph	DMAP	-5	72	33	59
hexyl	DMAP	-5	72	63	60
i-Pr	DMAP	-5	72	67	60
cyclopentyl	DMAP	-5	72	55	86
cyclohexyl	DMAP	-5	72	72	90

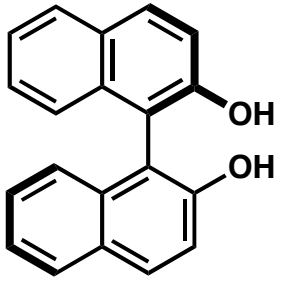
- Base screen indicated that DMAP provides the best yields and imidazole provided the highest ee.
- Aromatic aldehydes -- low ee, generally higher yields
- Aliphatic aldehydes -- higher ee, generally lower yields

Nagasawa et al. *Tet. Lett.* **2004**, *45*, 5589-92.

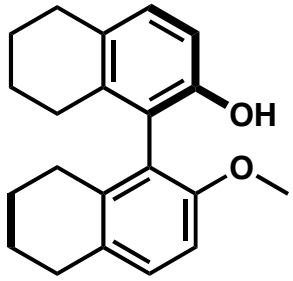
The Morita-Baylis-Hillman Reaction

Catalyst Screen:

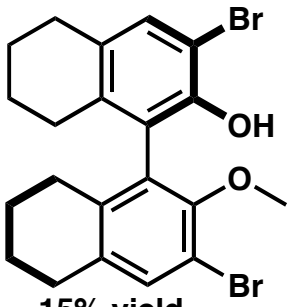
R^1 = CH_2CH_2Ph, 2 mol% catalyst, PEt_3, THF, 0 °C



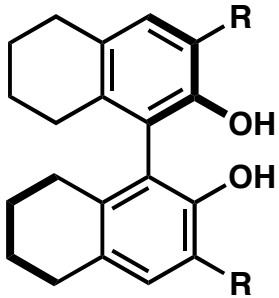
5% yield
0% ee



43% yield
3% ee



15% yield
3% ee

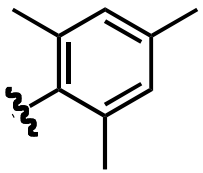


R = H, 73% yield, 48% ee

R = Br, 73% yield, 79% ee

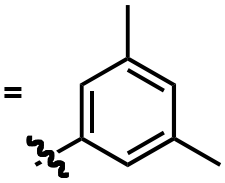
R = Ph, 69% yield, 86% ee

R =



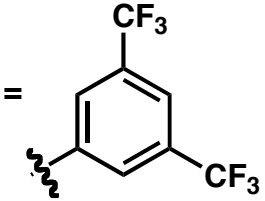
9% yield, 31% ee

R =



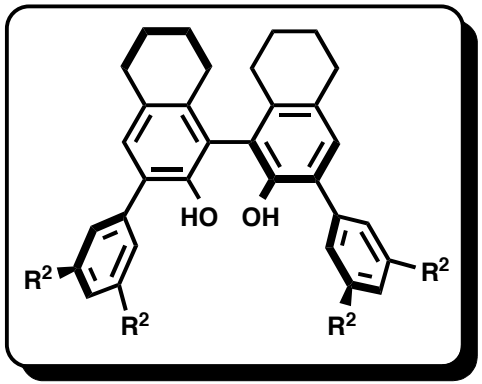
70% yield, 88% ee

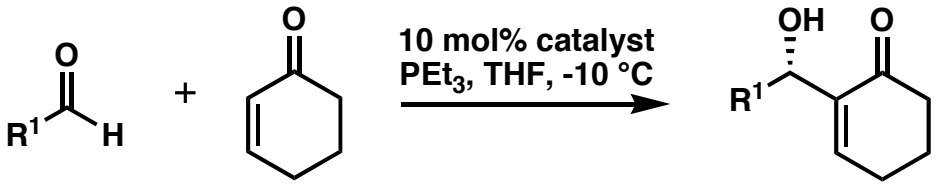
R =

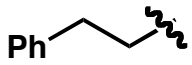
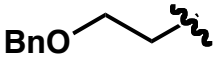
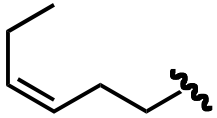
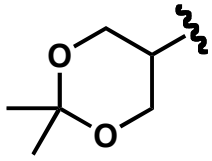
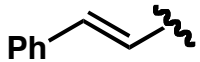


84% yield, 86% ee

Schaus, et al. *J. Am. Chem. Soc.* **2003**, *125*, 12094-5.





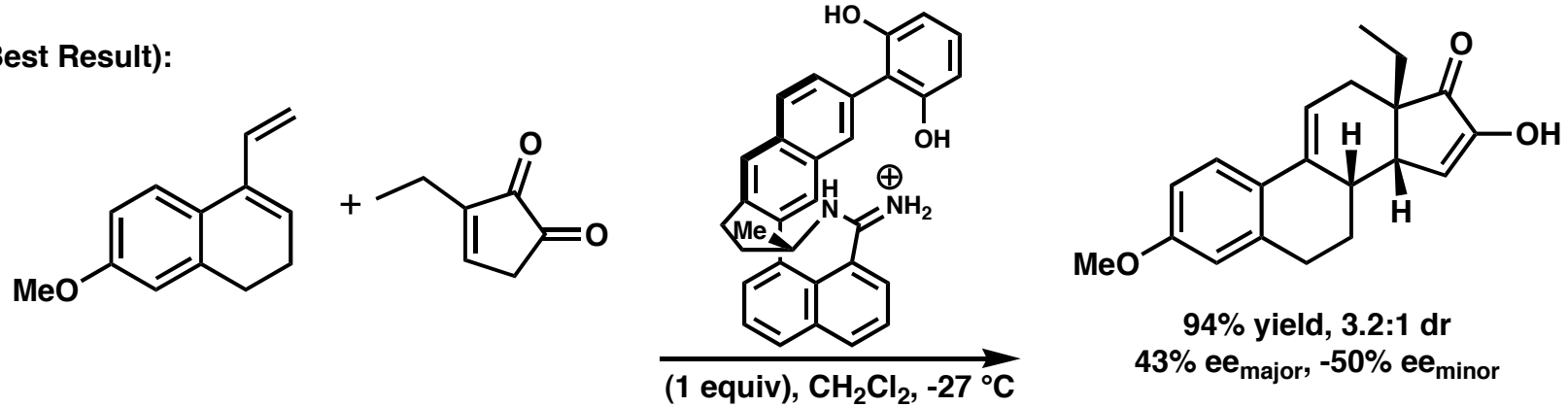
R^1	R^2	% yield	% ee
	CF_3	88	90
	CF_3	74	82
	CH_3	72	96
cyclohexyl	CH_3	71	96
i-propyl	CH_3	82	95
	CH_3	70	92
phenyl	CF_3	40	67
	CH_3	39	81

The Diels-Alder Reaction

Key Sources of Inspiration:

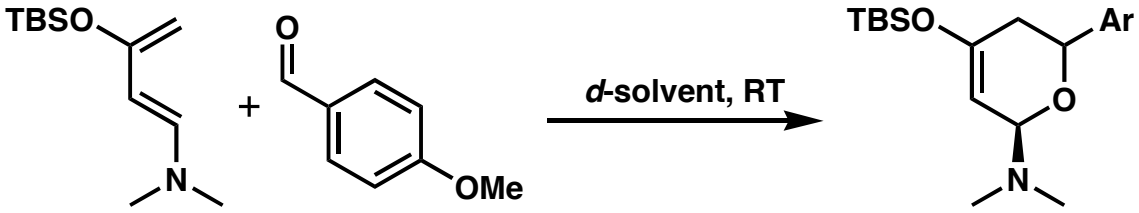
- **Double H-bonding in urea catalysts (as already discussed)**
- **Success of BINOL catalysts (already discussed)**
- **Diels-Alder catalysis acheived by Göbel et. al.** (*Org. Lett.* **2000**, *2*, 179-81.)
- **Solvent-acccelerated hetero-Diels-Alder reactions.** (*J. Am. Chem. Soc.* **2002**, *124*, 9662-3.)

Göbel (Best Result):



94% yield, 3.2:1 dr
43% ee_{major}, -50% ee_{minor}

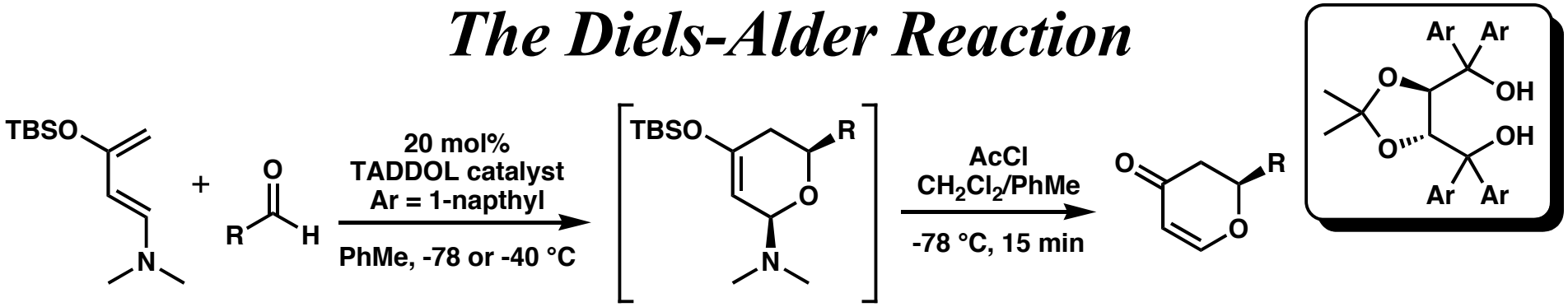
Rawal's solvent-acccelerated hetero-Diels-Alder reactions:



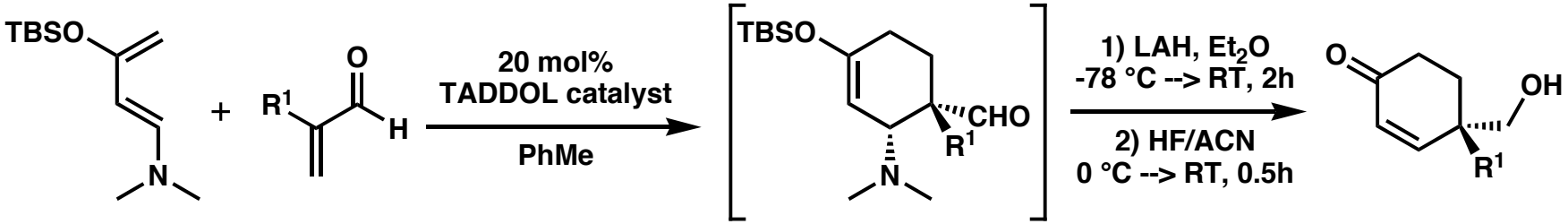
Solvent	dielectric constant	relative rate
THF-d_8	7.6	1.0
benzene-d_6	2.3	1.3
ACN-d_3	37.5	3.0
$CDCl_3$	4.8	30
t-butyl alcohol-d_{10}	10.9	280
i-propyl alcohol-d_8	18.3	630

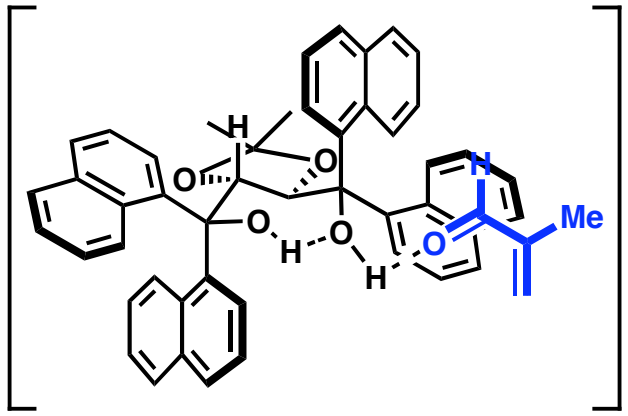
Rawal, et al. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5846-50.
Nature, **2003**, *424*, 146.

The Diels-Alder Reaction



- First highly enantioselective H-bond catalyzed cycloadditon
- Yields 52-97%, aliphatic ≥ 83% ee, aromatic ≥ 95% ee





R^1	Ar	time	temp, °C	% yield	% ee
Me	phenyl	2 d	-80	30	31
Me	2-naphthyl	2 d	-80	45	33
Me	1-naphthyl	2 d	-80	83	91
Me	1-naphthyl	15 min	21	75	40
Me	1-naphthyl	6 h	0	75	52
Me	1-naphthyl	1 d	-20	85	65
Me	1-naphthyl	1 d	-40	74	76
Me	1-naphthyl	2 d	-80	83	91
H	1-naphthyl	2 d	-80	77	73
Me	1-naphthyl	2 d	-80	83	91
Et	1-naphthyl	2 d	-80	83	88
i-Pr	1-naphthyl	2 d	-80	81	92
Bn	1-naphthyl	2 d	-80	82	89
CH_2CH_2OTBS	1-naphthyl	2 d	-80	80	86

Rawal, et al. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5846-50. **and** *Nature*, **2003**, *424*, 146.

Summary

- By utilizing double hydrogen-bonding, chiral organic catalysts can accomplish rotational control and organized transition states.

- Brønsted acids are unique as catalysts because of their ability to readily dissociate from the product, allowing catalyst turnover without any parallel catalyst pathways.

- Because there is no need to coordinate to a metal center, only to the compound itself, the scope of novel catalysts that could be developed is expansive, and catalysts can be more readily optimized for a specific reaction, if the need arises.

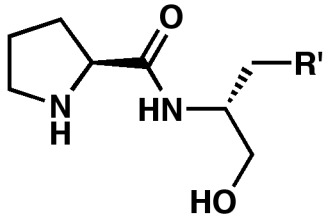
- With no metal center, the chiral framework also has the opportunity to be closer to the reacting center than with Lewis acid catalysts.

- A variety of well-known reactions have been cayalyzed asymmetrically using Brønsted acid catalysts that serve as hydrogen-bond donors. They include HCN addition to aldehydes, the Strecker reaction, the Mannich reaction, the Aza-Friedel-Crafts reaction, hydrophosphination of imines, the acyl-Pictet-Spengler reaction, the Aza-Henry reaction, Michael Reaction of malonates to nitroolefins, the Baylis-Hillman reaction and its Morita modification, and hetero- and all-carbon Diels-Alder reactions.

"Hydrogen bonding by a simple chiral alcohol to a carbonyl group can accomplish what has previously been considered to be in the domain of enzymes, catalytic antibodies and chiral metal-based Lewis acids. These studies indicate the broad potential for hydrogen-bond catalysis in asymmetric synthesis."
~ V. H. Rawal

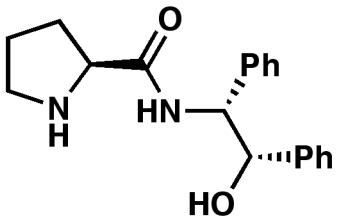
The Direct Aldol Reaction

Catalyst Screen (R = *p*-NO_2Ph)

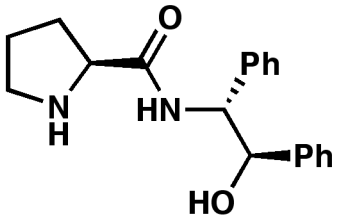


R' = H, 25 °C, 12h
84% yield, 46% ee

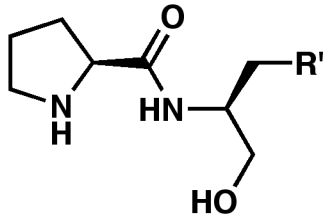
R' = *i*-Pr 25 °C, 12h
78% yield, 33% ee



25 °C, 12h
63% yield, 49% ee

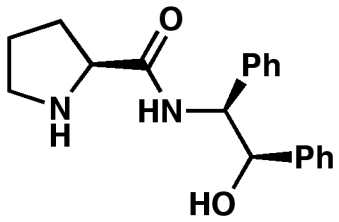


25 °C, 12h
77% yield, 44% ee

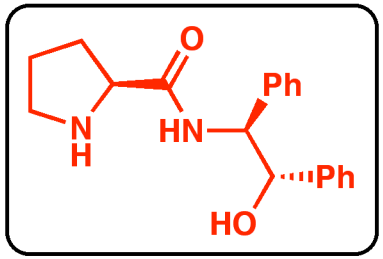


R' = H, 25 °C, 12h
75% yield, 48% ee

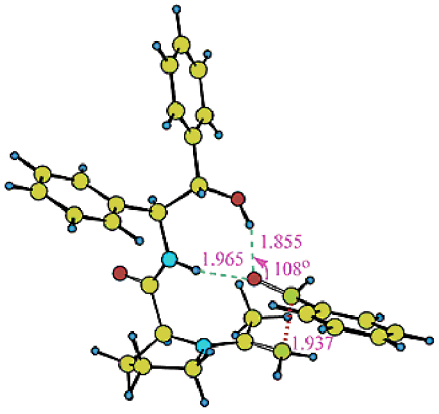
R' = *i*-Pr 25 °C, 12h
89% yield, 52% ee

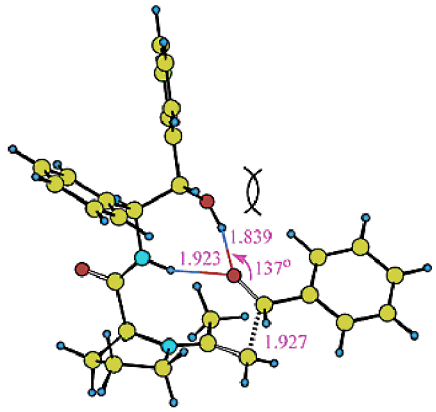


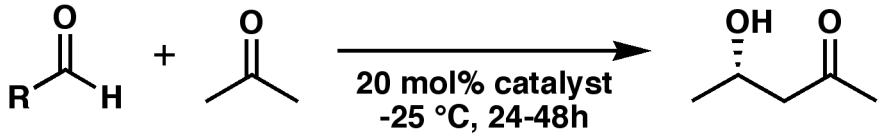
25 °C, 12h
76% yield, 64% ee



25 °C, 12h, 89% yield, 69% ee
0 °C, 12h, 68% yield, 78% ee
-25 °C, 24h, 66% yield, 93% ee







R	% yield	% ee
p-NO_2Ph	66	93
p-BrPh	77	90
p-ClPh	75	93
o-ClPh	83	85
Ph	51	83
1-naphthyl	76	81
2-naphthyl	93	84
p-MePh	48	84
m-NO_2Ph	63	87
cyclohexyl	85	97
i-Pr	43	98
t-Bu	51	>99
n-Pr	17	87
n-Bu	12	86
cyclohexyl	77	98 (10 mol% cat.)
cyclohexyl	48	98 (5 mol& cat.)

Wu, et. al. *J. Am. Chem. Soc.* **2003**, *125*, 5262-3. **and** *Chem. Soc. Rev.* **2004**, *33*, 65-75.