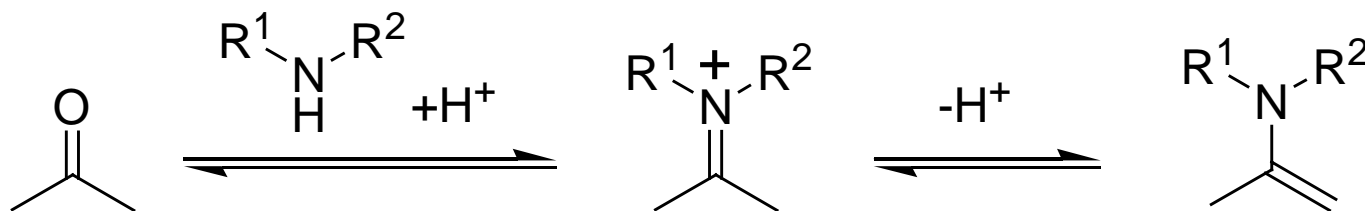


What is Organocatalysis?

➤ Organocatalysis is the acceleration of chemical reactions with an organic compound that does not contain a metal atom

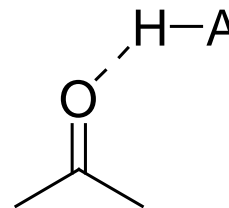
➤ Reaction Pathways?

➤ via covalent activation complexes (enamine and iminium ion)



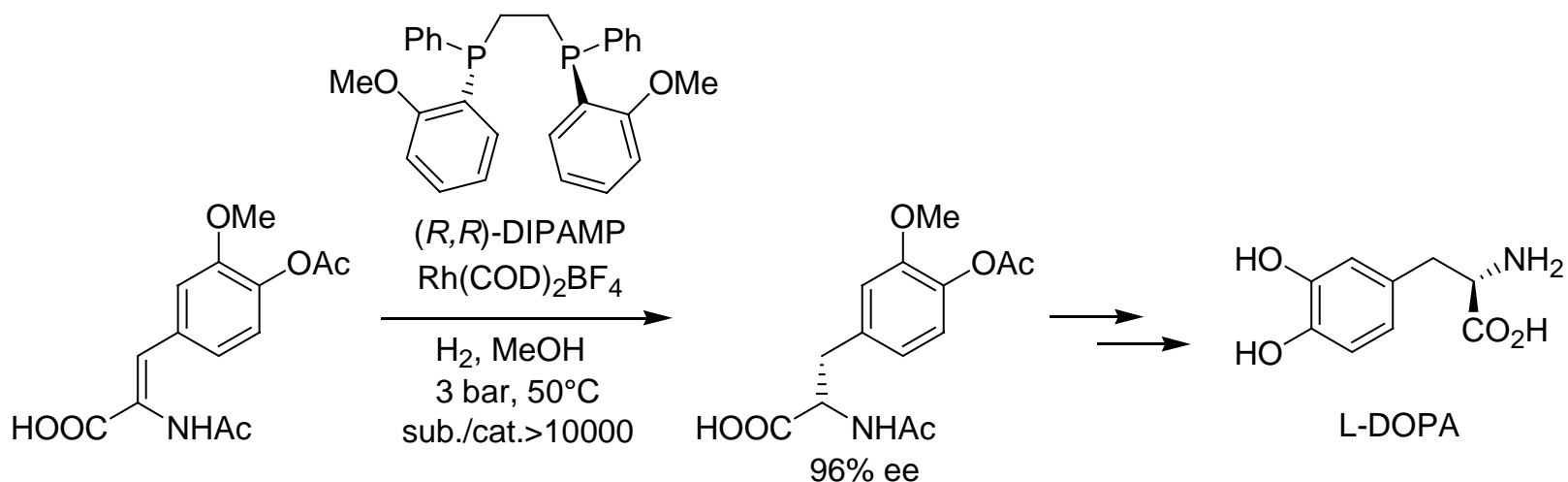
➤ via noncovalent activation complexes (H-bonding or ion pairing)

➤ C-C bond-forming reactions



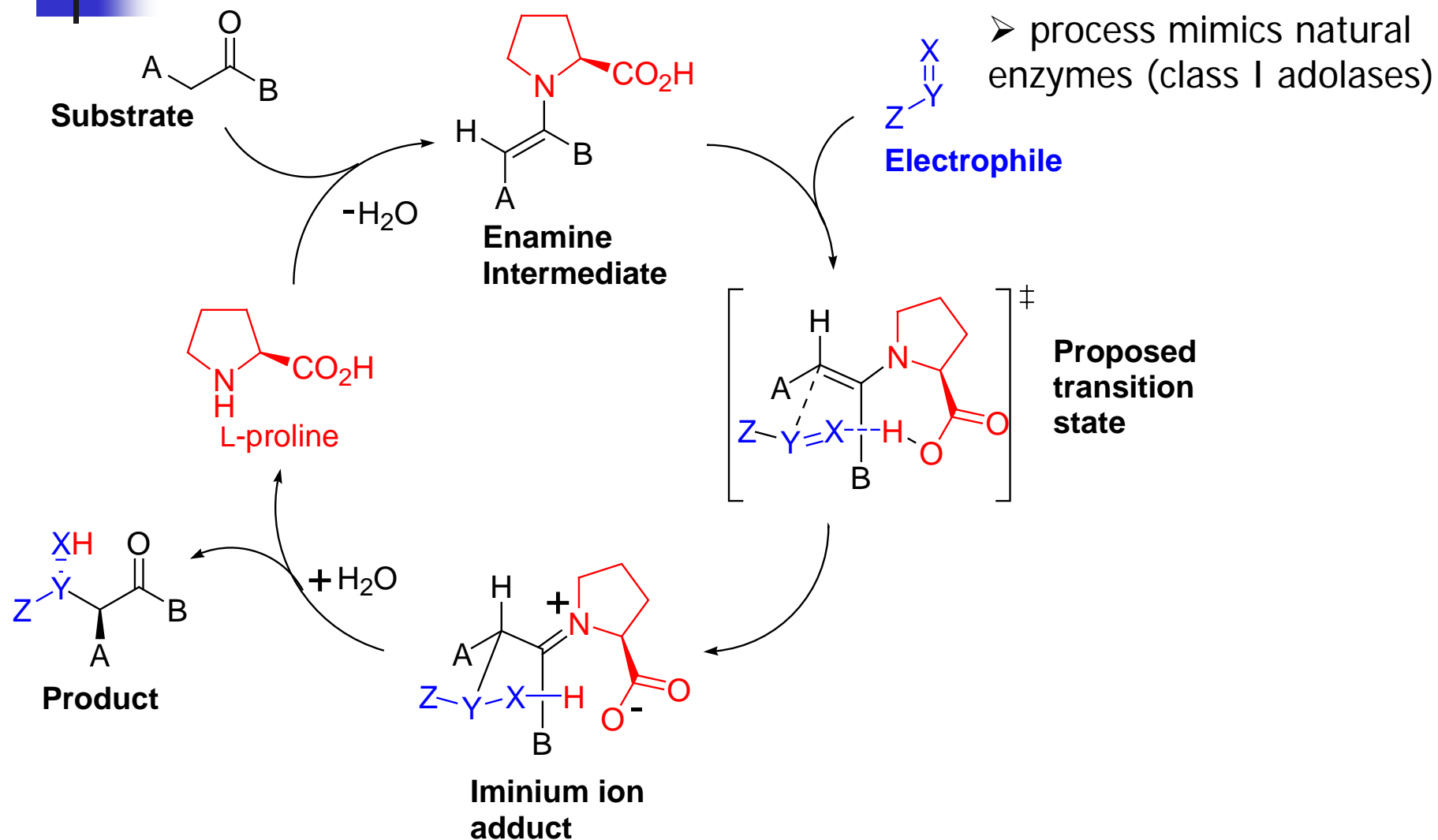
Advantages of Organocatalysis Over Metal Catalysis

- Many metals are poisonous, which often presents a problem with the production process in the chemical and pharmaceutical industry

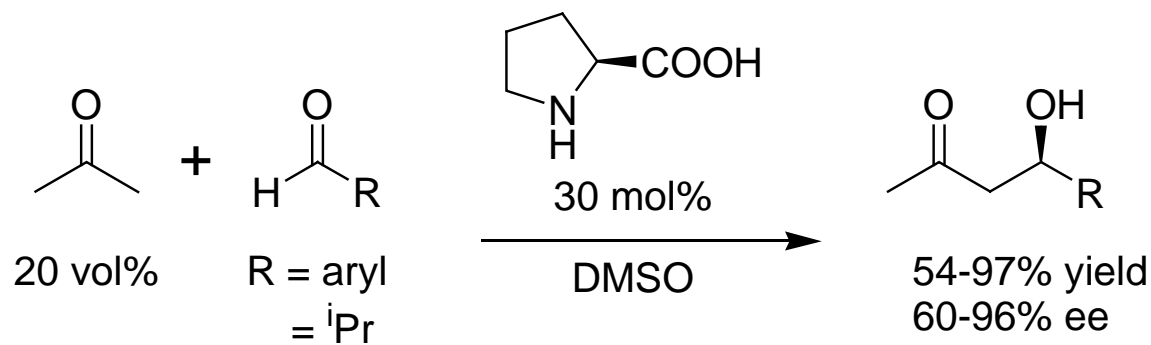


- Often difficult to immobilize traditional Lewis acids on polymers or other stationary phases
- Metal-free reactions can typically be run under aerobic conditions

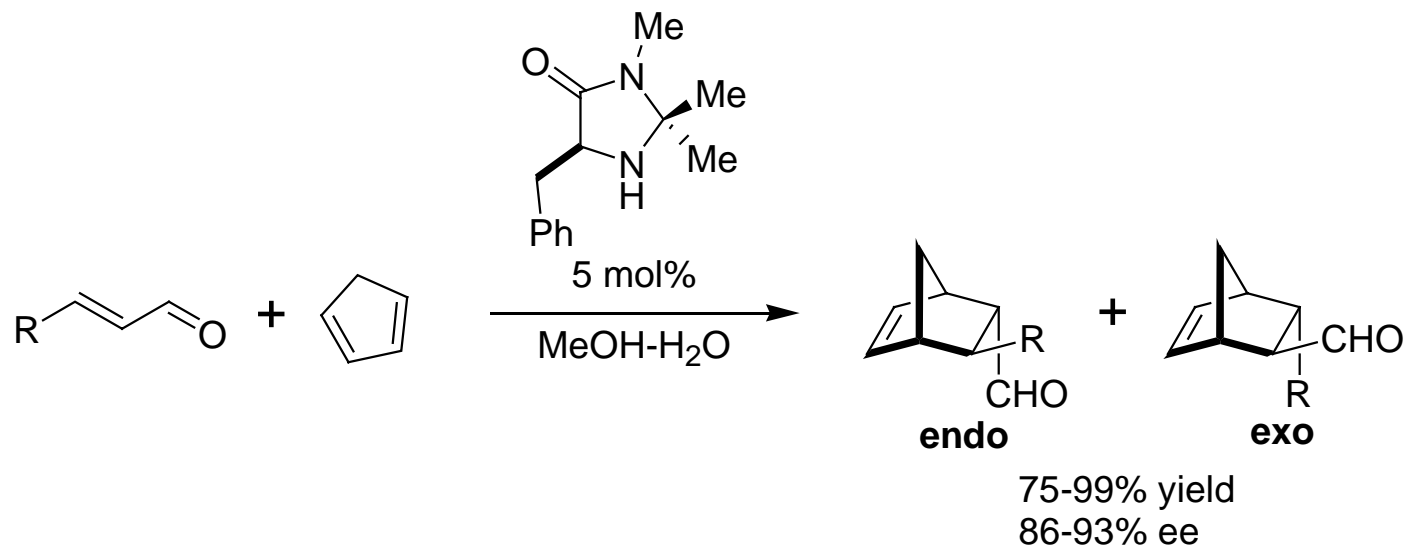
Proposed Mechanism of Proline Catalyzed Aldol Addition



Recent Examples of Asymmetric Organocatalysis

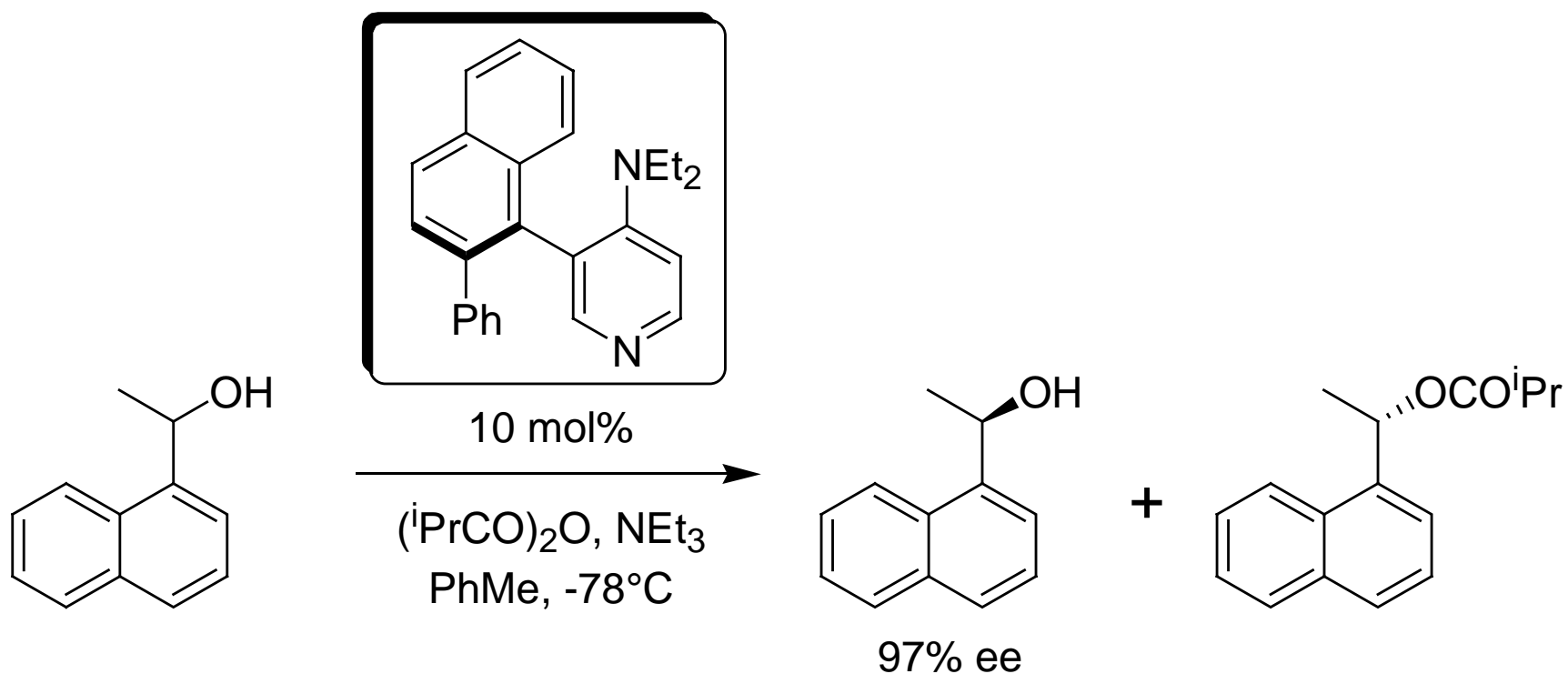


Barbas III, C. F.; Lerner, R. A.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 2395



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

Chiral DMAP as Lewis Base Catalyst

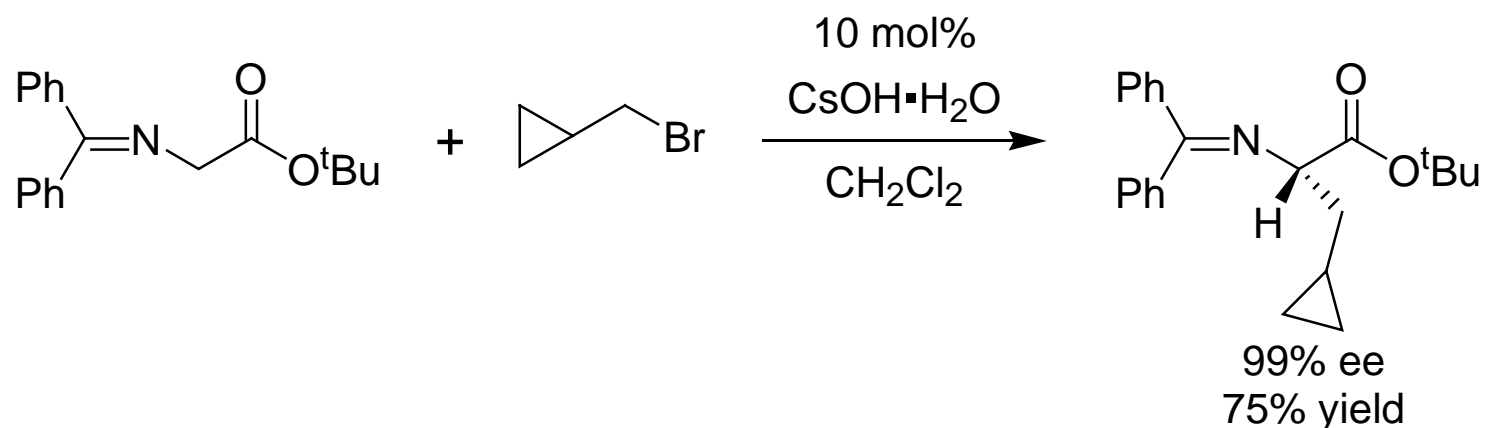
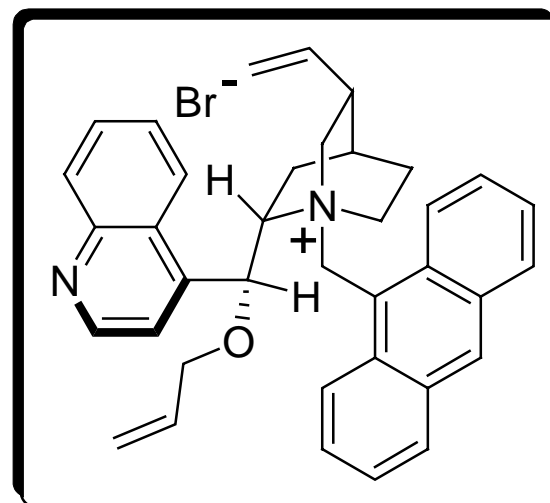


➤ kinetic resolution of secondary alcohols

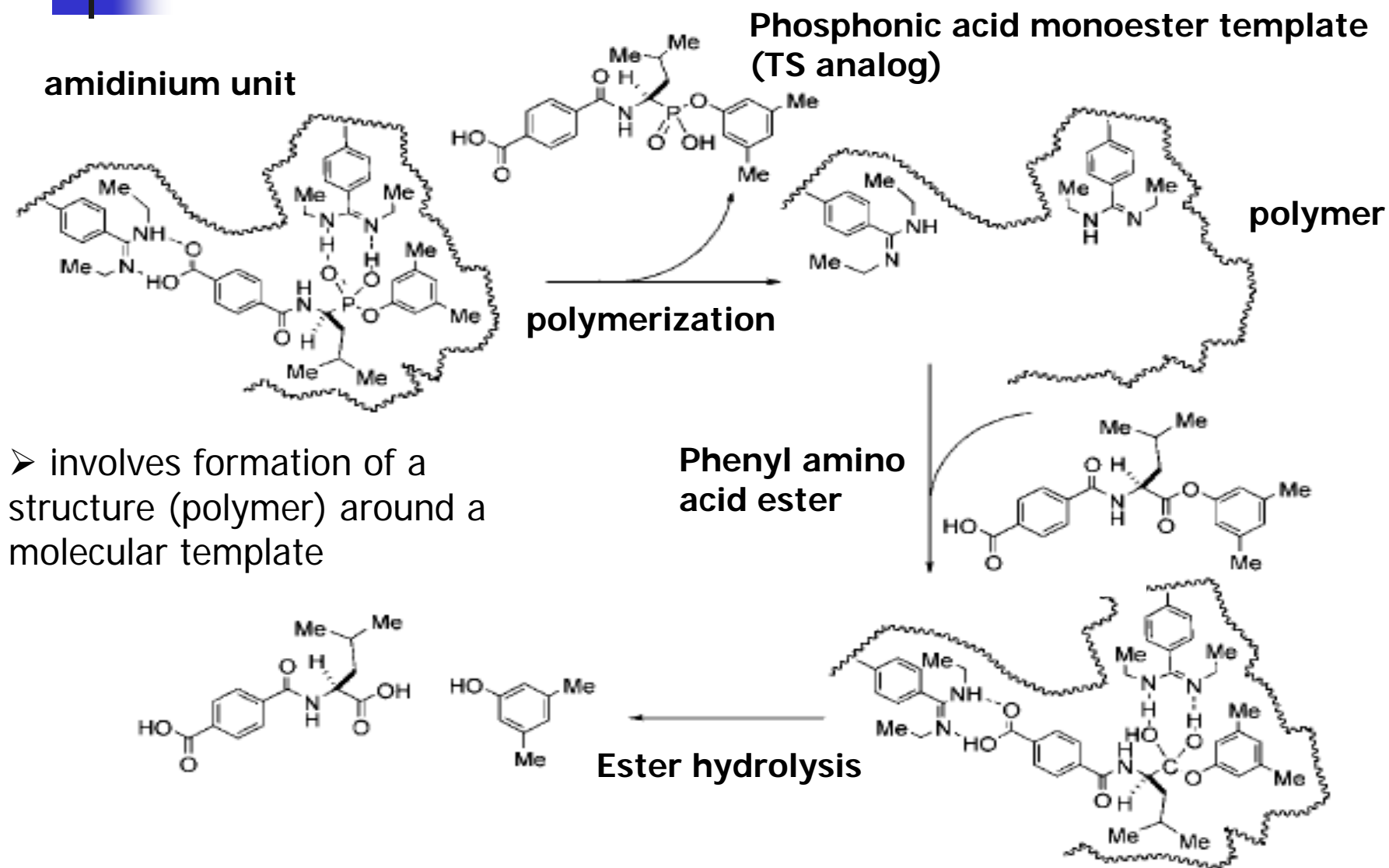
Asymmetric Phase Transfer Catalysis

- two- or three- phase systems (aqueous/apolar solvent mixtures)
- chiral catalyst acts as an ion shuttle
- can also act as template to direct approach of reagent

Cinchona-alkaloid catalyst

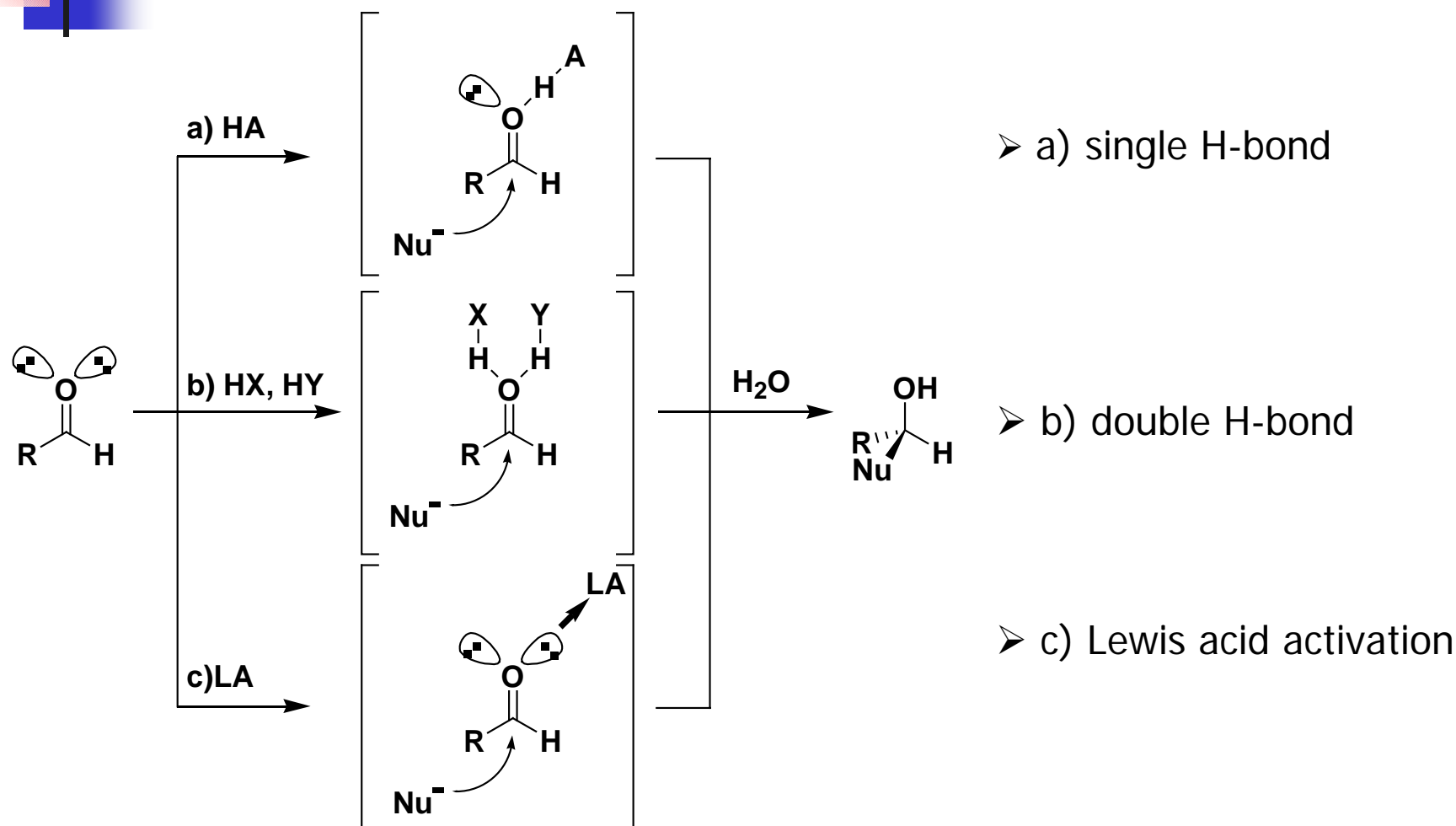


Molecular Imprinting



➤ involves formation of a structure (polymer) around a molecular template

Electrophilic Activation via Noncovalent Interactions



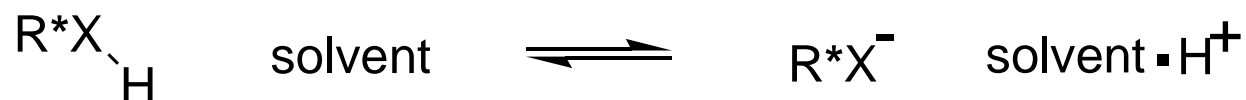
➤ coordination lowers the energy of the LUMO ($C=O \pi^*$), activating the group towards nucleophilic attack



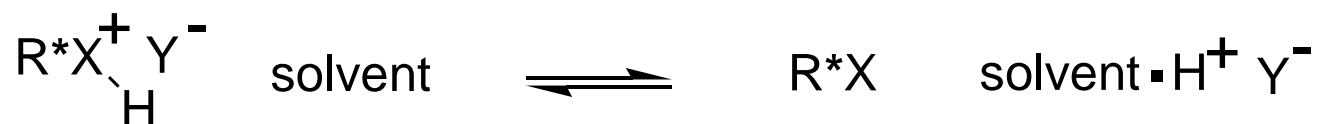
The Proton and Hydrogen Bonding

- the proton can form hydrogen bonds and can be divided into two classes: polar covalent and polar ionic

polar covalent

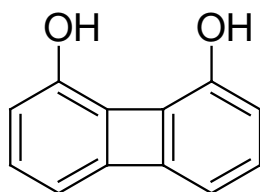


polar ionic



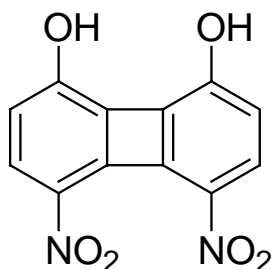
- energy of H-bond in the gas phase is in the range of 2-20 kcal/mol, much weaker than a covalent bond
- until recently, this weak interaction was seldom used as a force for promoting chemical reactions

Early Hydrogen Bonding Catalysts



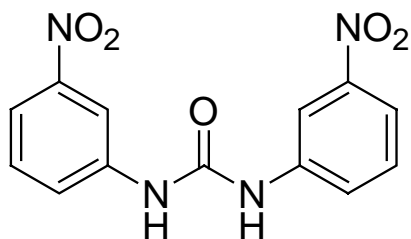
Hine biphenylenediol catalyst
activation of epoxides towards
nucleophilic attack

1980's



Kelly biphenylenediol catalyst
rate acceleration of Diels-Alder reaction

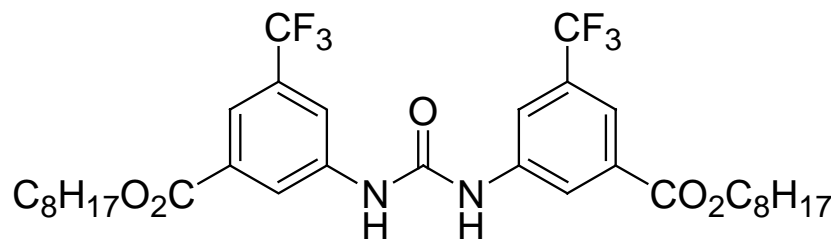
1990



Etter urea catalyst

diaryl ureas bearing EWG's
readily form cocrystals with
a variety of proton acceptors

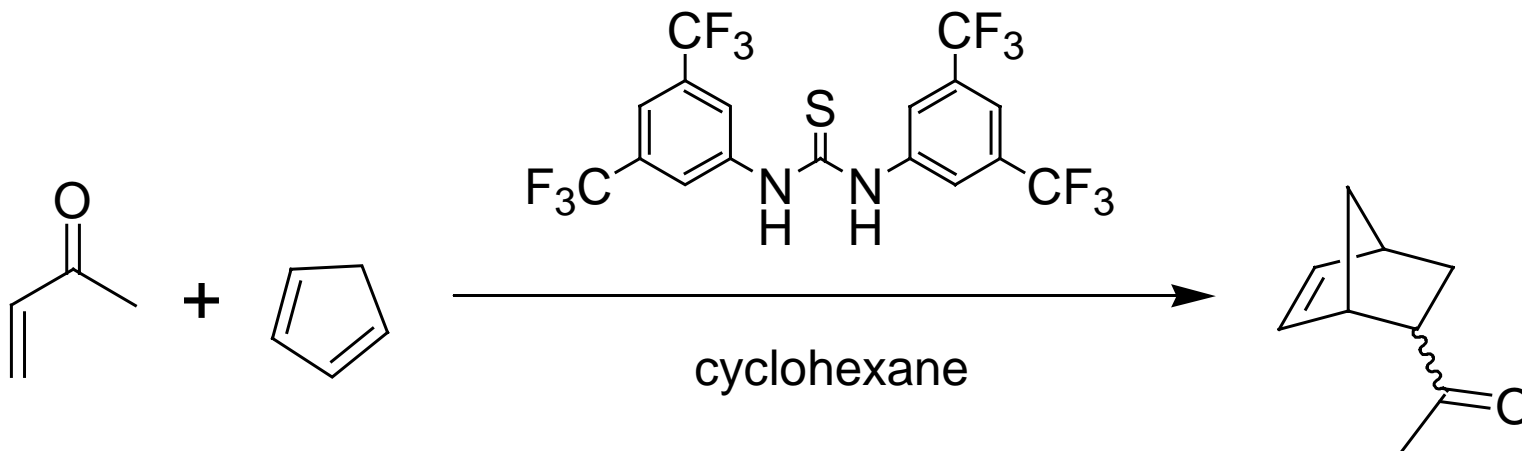
1988



Curran's Diarylurea
catalyzed sulfoxide allylations

1994

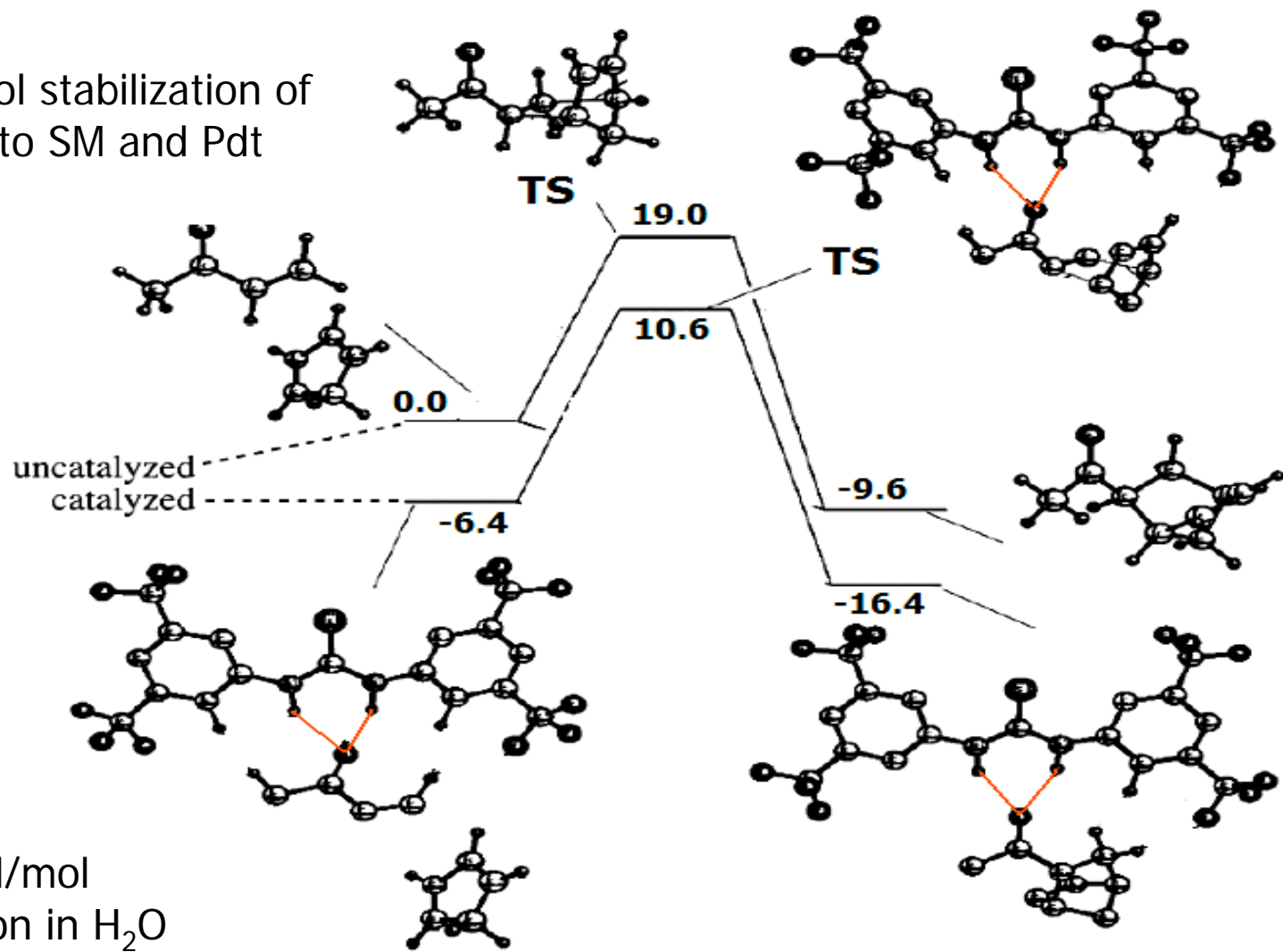
Thiourea Catalyzed Diels-Alder Reaction



- 8.8 fold rate acceleration observed for thiourea catalyzed Diels-Alder reaction
- computational studies were performed for both the catalyzed and uncatalyzed reactions
- the effectiveness of the thiourea catalyst in water was also examined

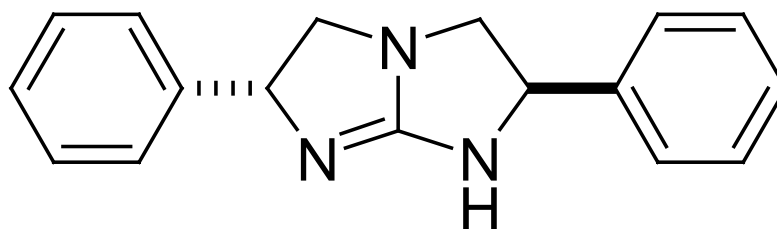
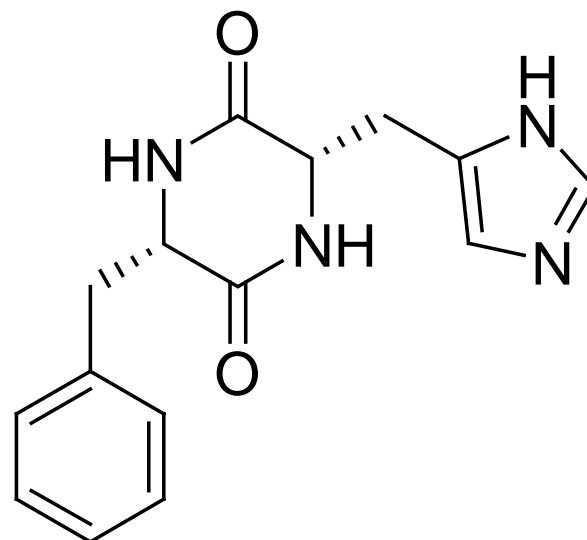
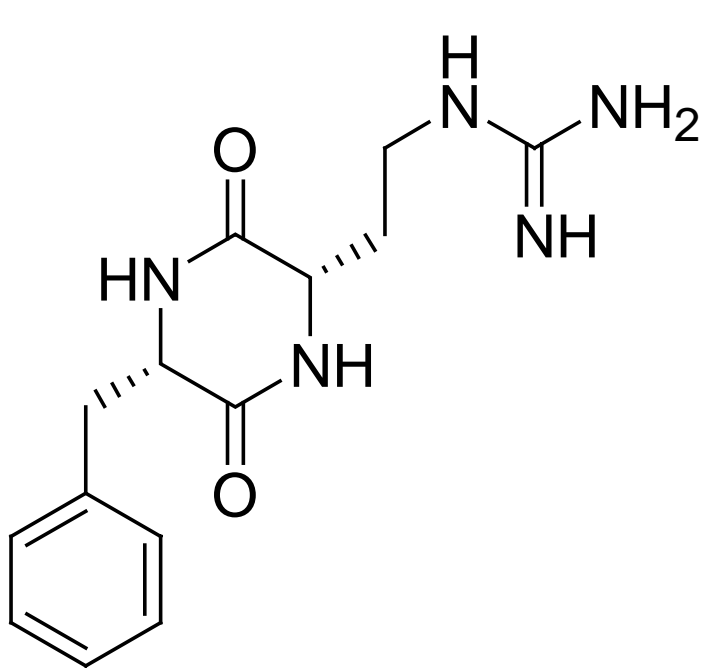
Computational Studies With Thiourea Catalyzed Diels-Alder Reaction

➤ 2 kcal/mol stabilization of TS relative to SM and Pdt



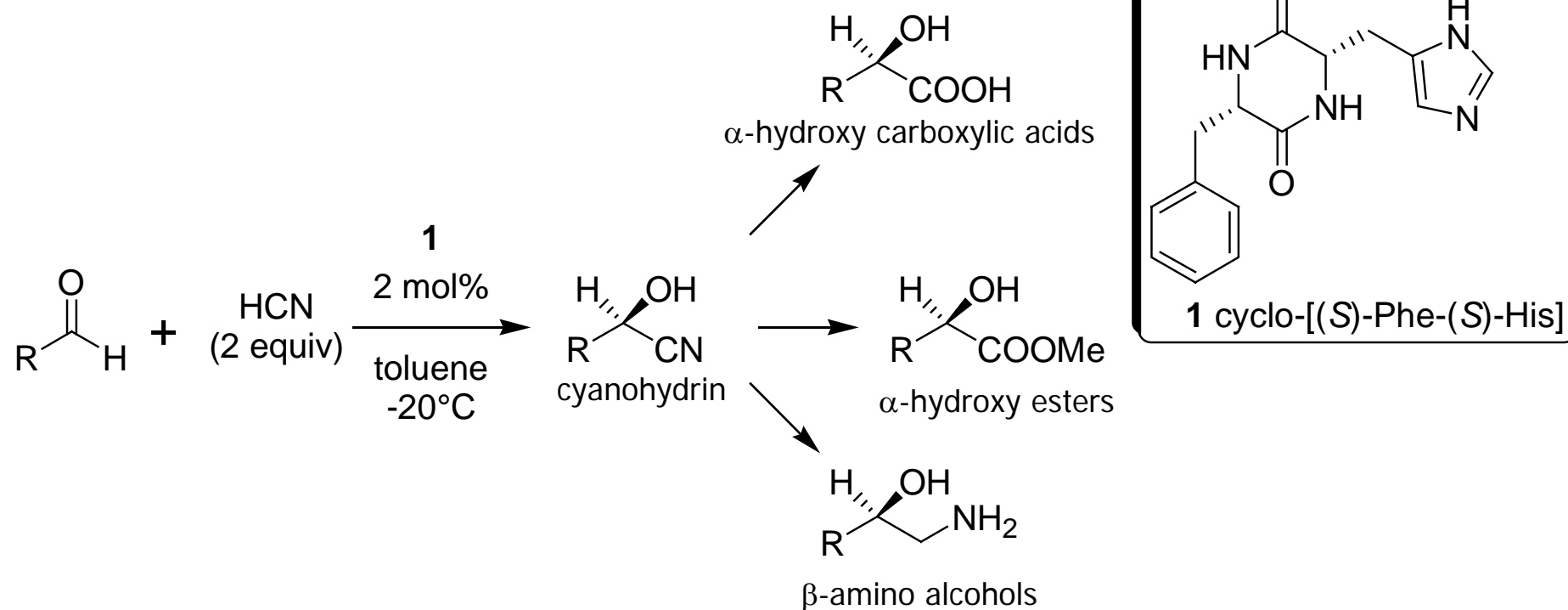
➤ 1.7 kcal/mol stabilization in H₂O

Diketopiperazine and Bicyclic Guanidine Catalysts



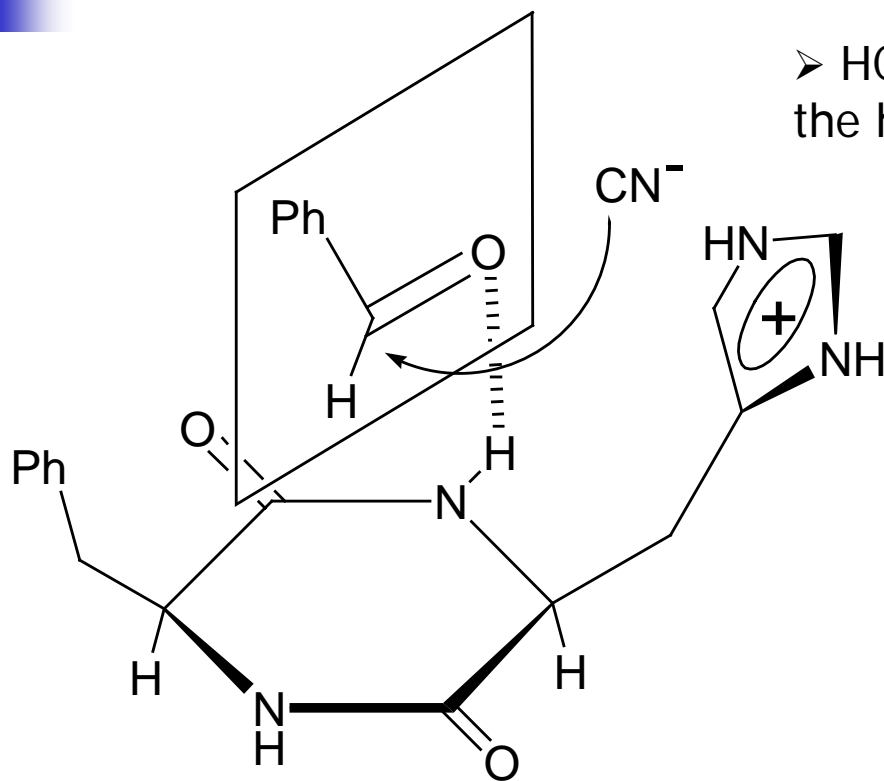
Asymmetric Hydrocyanation Using Cyclic Dipeptide Catalyst

- objective was to design catalyst using synthetic dipeptides as an alternative to oxynitrilase



- high optical yields with aromatic aldehydes, except those with EWG
- aliphatic aldehydes gave moderate to high asymmetric inductions

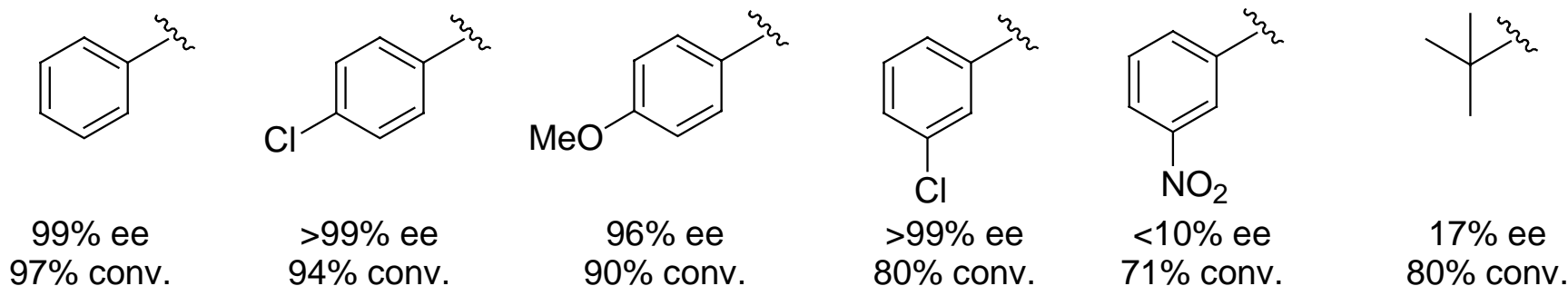
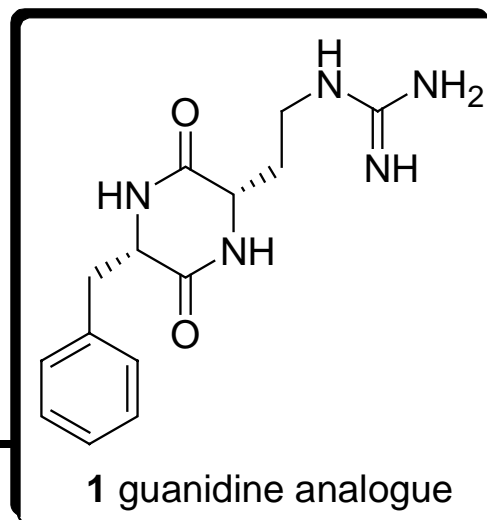
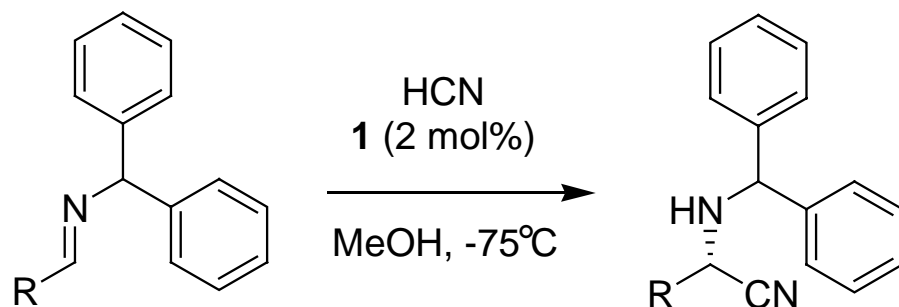
Model for Sense of Stereoselectivity



➤ HCN interacts with basic imidazole of the histidine residue

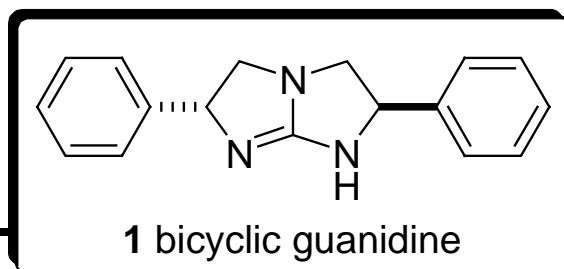
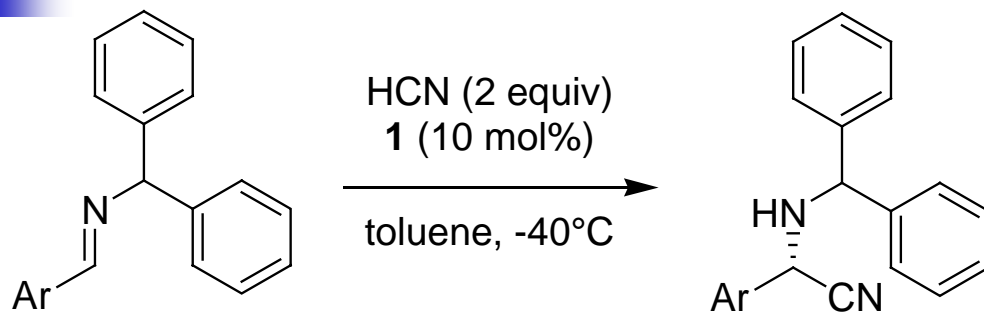
- *si*-face attack of the activated carbonyl group
- replacing *S*-phenylalanine residue with *S*-alanine, *S*-valine, and *S*-proline resulted in low stereoselectivity
- acyclic precursor *Z*-(*S*)-Phe-(*S*)-His-OMe showed no asymmetric induction

Asymmetric Strecker With Guanidine Cyclic Dipeptide Catalyst

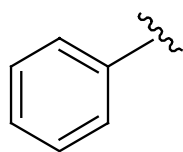


- replaced imidazole with more basic guanidine side chain to accelerate proton transfer
- simultaneous deprotection and hydrolysis in 6N HCl, 60°C, for 6 h provides amino acids with no loss of optical purity

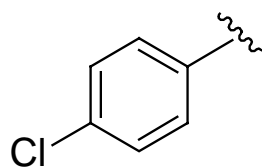
Asymmetric Strecker With Bicyclic Guanidine



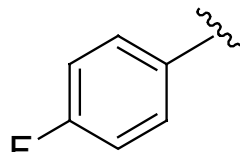
Ar =



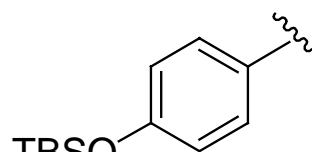
86% ee
96% yield



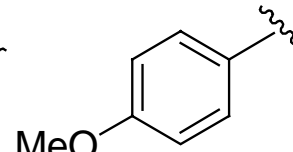
81% ee
88% yield



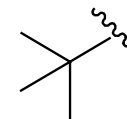
86% ee
97% yield



88% ee
98% yield



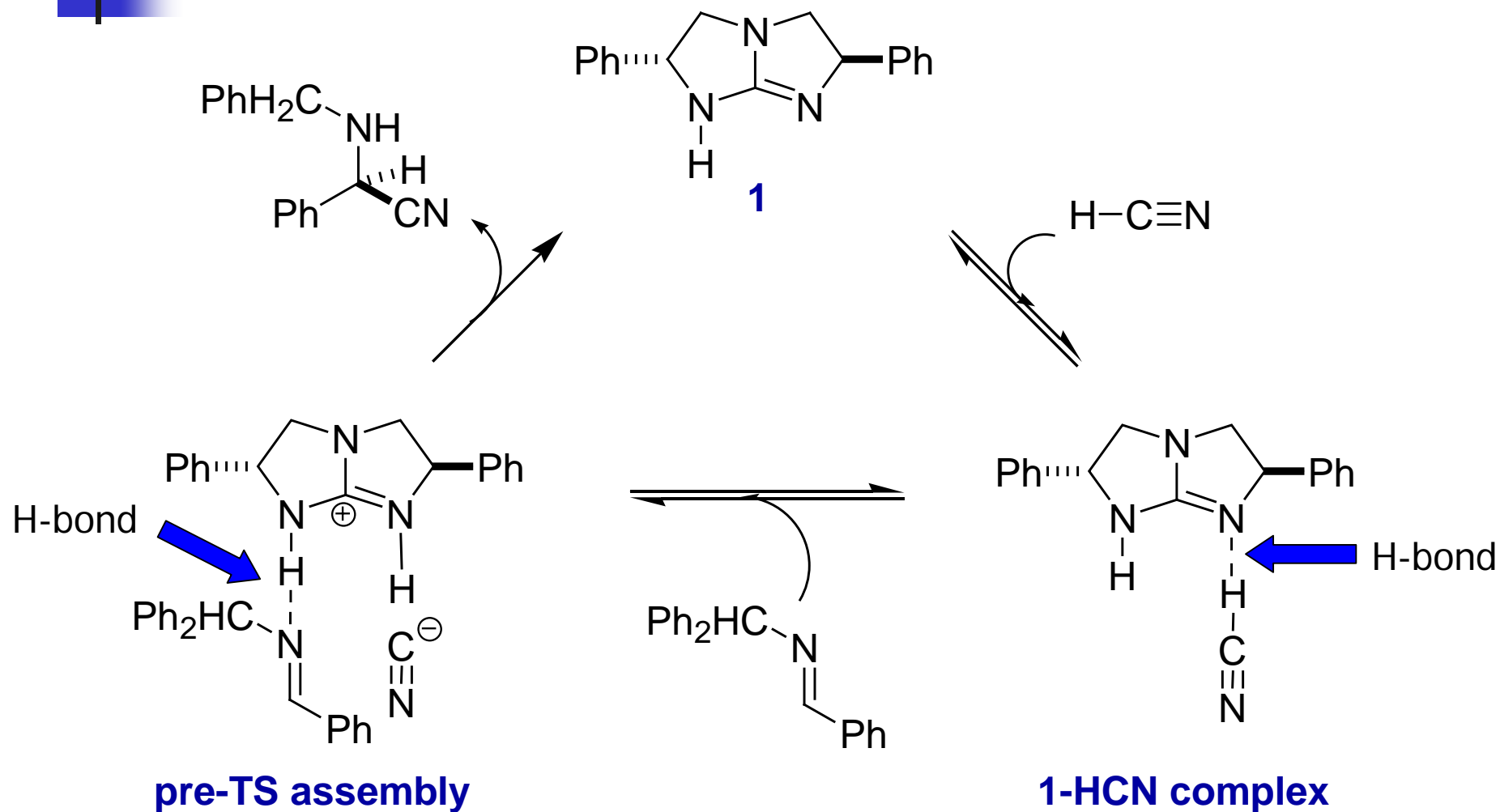
84% ee
99% yield



(S)
84% ee
95% yield

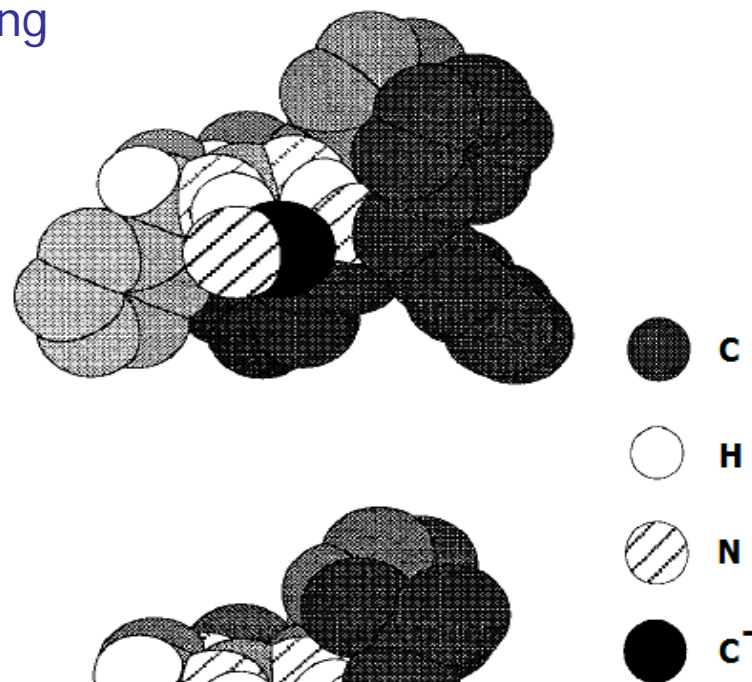
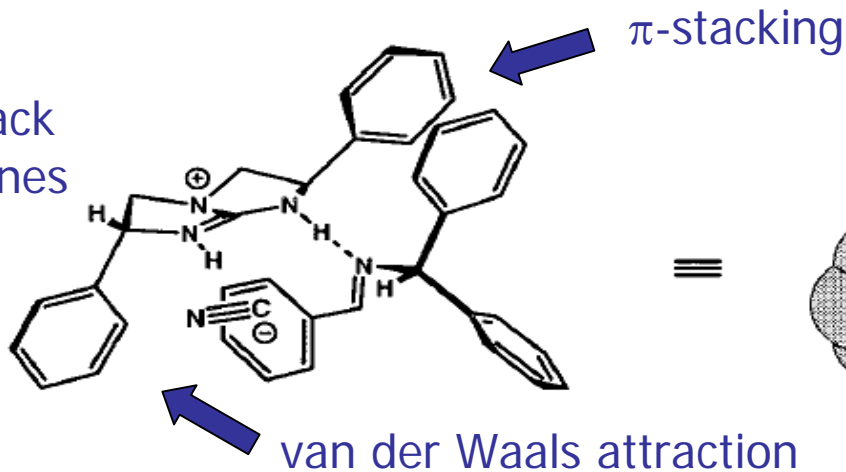
- in the absence of catalyst **1**, no reaction was observed
- the *N*-methyl-**1** was entirely inactive as a catalyst
- benzhydryl cleavage and nitrile hydrolysis successful without loss of optical purity
- guanidine catalyst can be recovered for reuse by extraction with oxalic acid

Catalytic Action of Bicyclic Guanidine

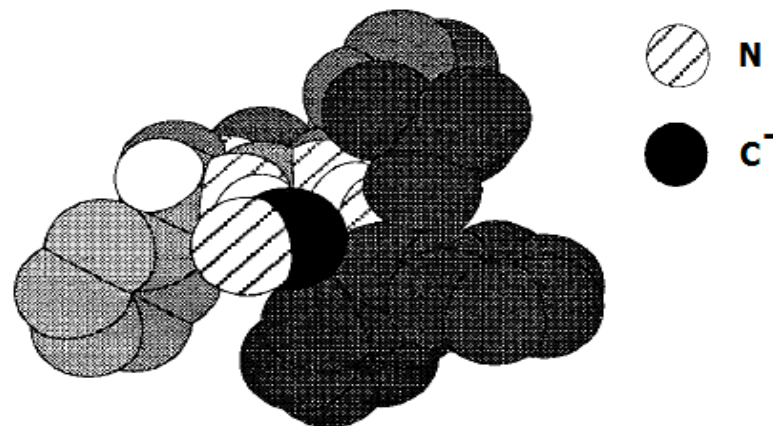
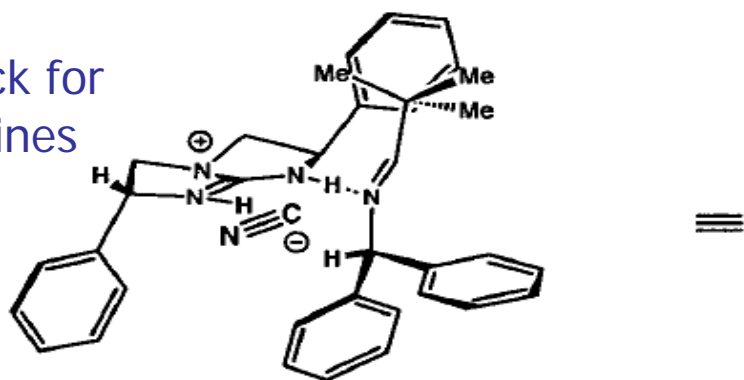


Model of Pre-TS Assemblies

re face attack
for aryl imines

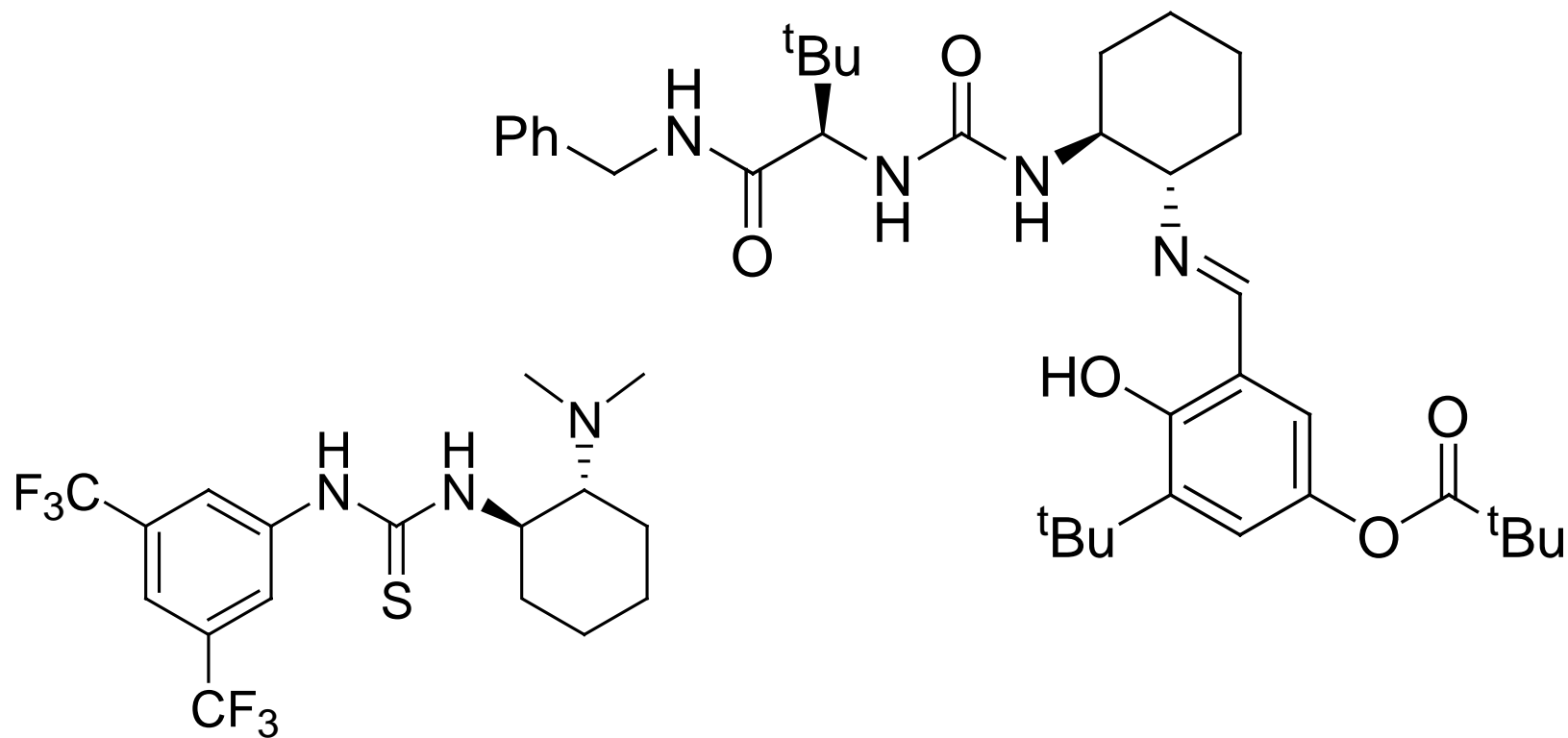


si face attack for
aliphatic imines

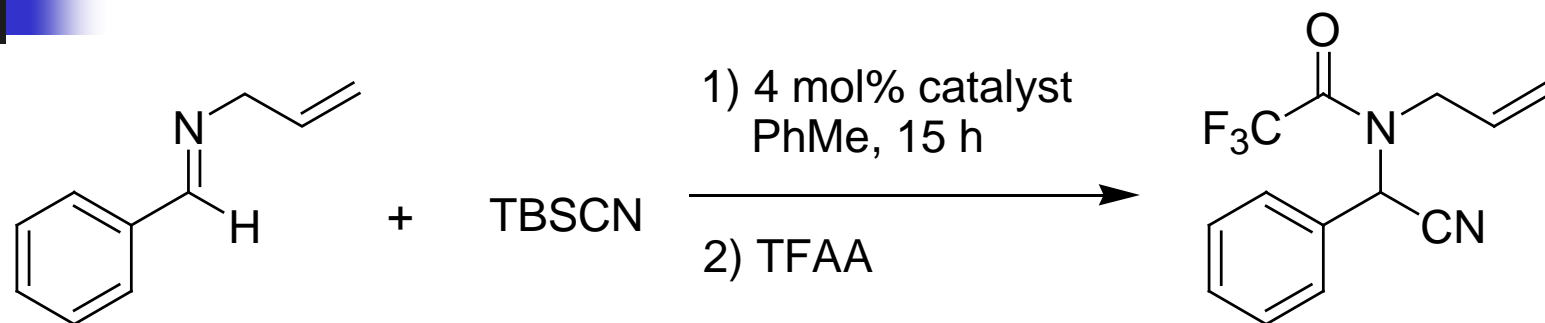


➤ alkyl groups incur steric repulsions in the vacant quadrant of guanidinium where imine aryl gains van der Waals attraction

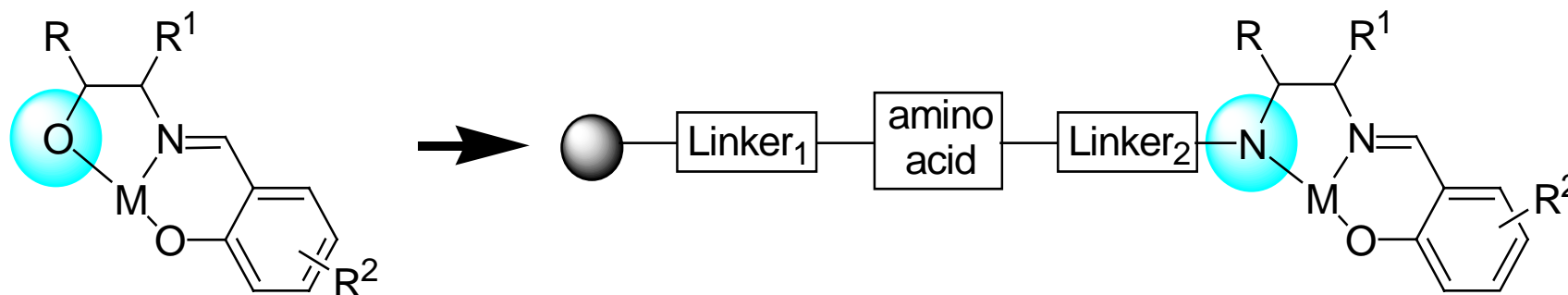
Urea and Thiourea Catalysts



Concept for the Solid-Phase Synthesis of Tridentate Schiff Base Complexes



- parallel library approach for evaluation of Schiff base complexes



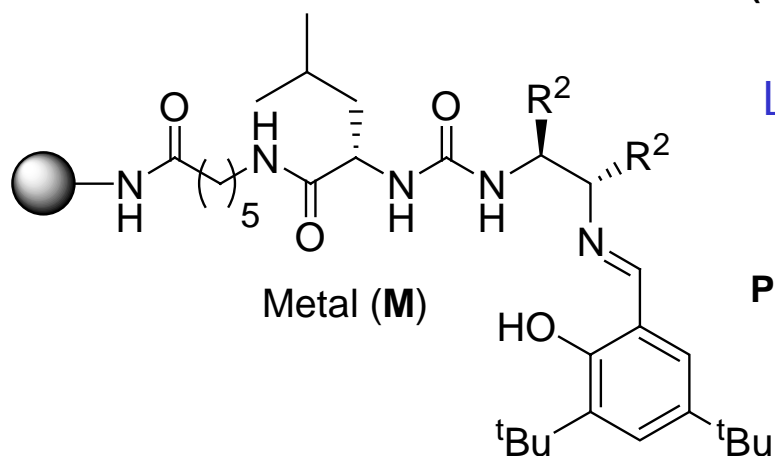
tridentate Schiff base complex

- amino acid was incorporated as an additional diversity element
- the resulting ligand system was evaluated and optimized for the reaction above

Parallel Library Results

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	0	5
conv. (%)	59	30	61	69	63	68	55	91	95	84	94	34

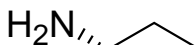


- L-leucine derived catalysts provided best results
- 3-*tert*-butyl derivatives afforded highest ee' s
- thiourea linker enhanced the ee by 10%

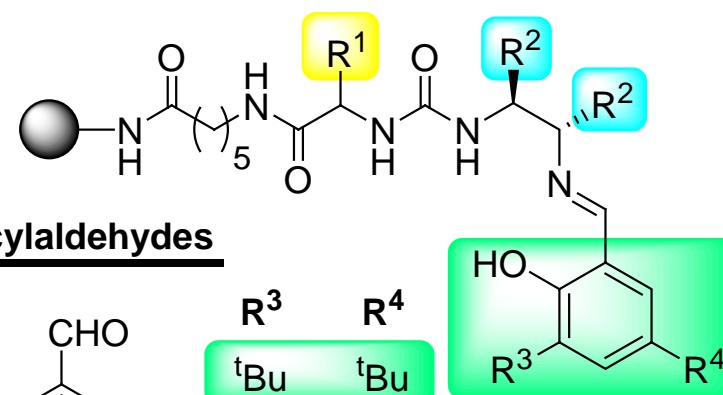
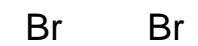
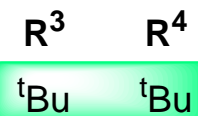
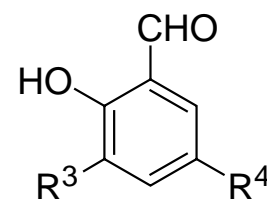
Library 2: 48 Compounds

Amino Acid
Leu, D-Leu, His
Phg (Phenylglycine)

Diamines

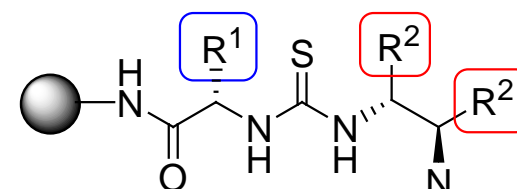
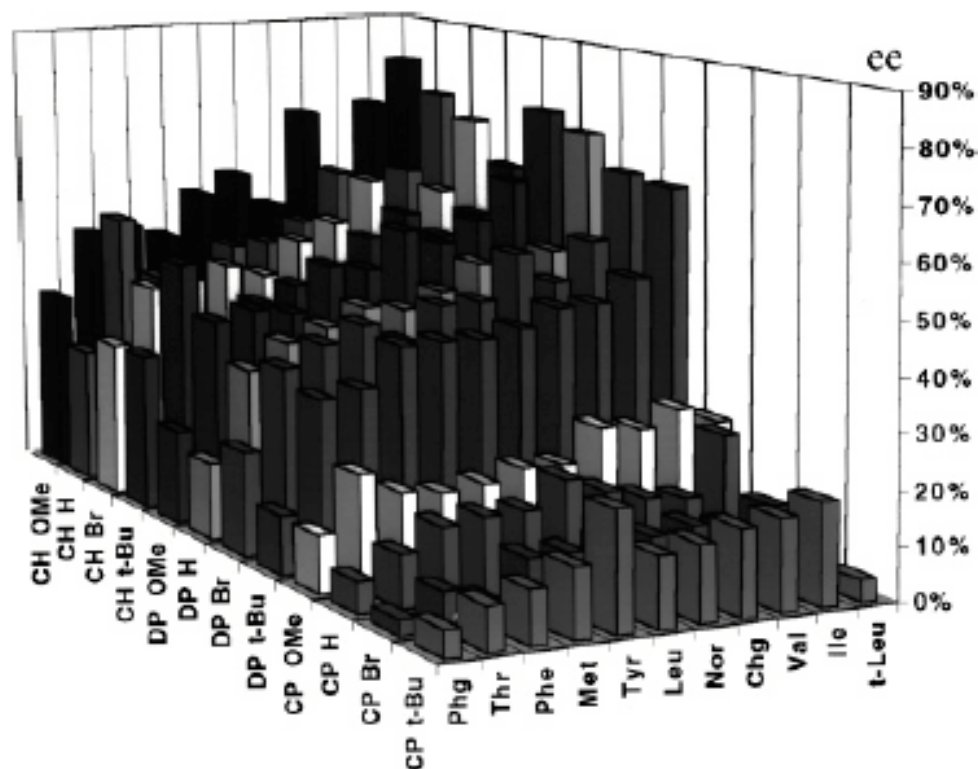


Salicylaldehydes



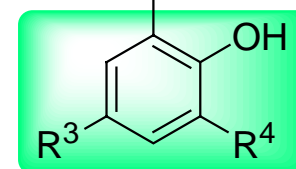
Parallel Library Results

Library 3: 132 Compounds



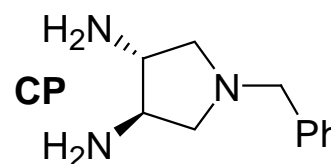
L-Amino Acids

Leu, Ile, Met, Phe,
Tyr (O^tBu), Val, Thr (O^tBu),
Nor (Norleucine), Phg,
Chg (Cyclohexylglycine)
t-Leu (*tert*-Leucine)



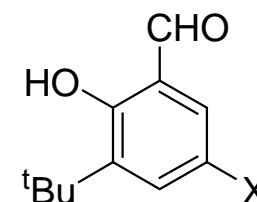
(R,R)-Diamines

CH, DP



Salicylaldehydes

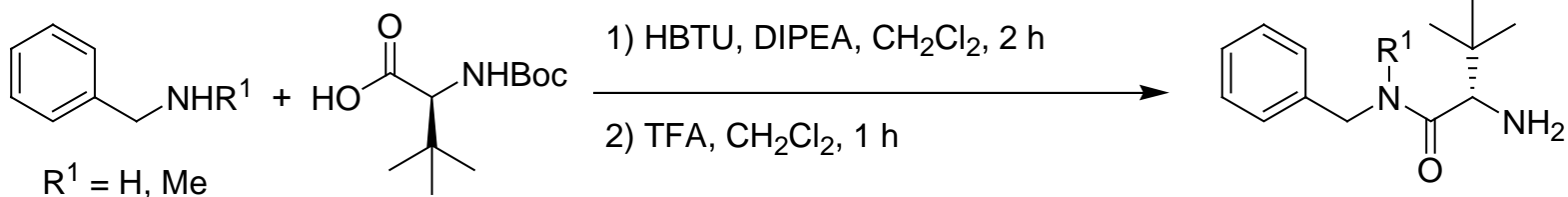
X = OMe



H
^tBu
Br

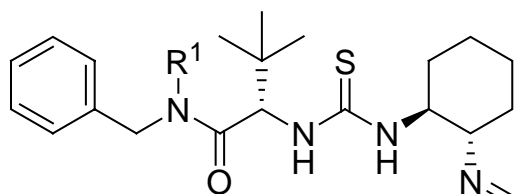
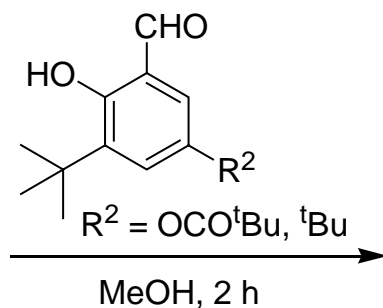
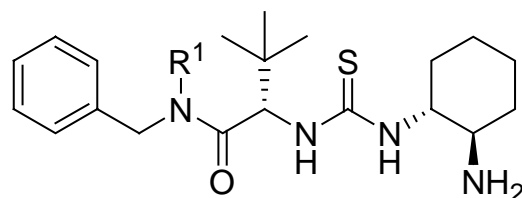
- 132 thiourea derivatives were prepared incorporating nonpolar AA' s and 3-*tert*-butyl salicylaldehyde derivatives
- *t*-Leu-CH-OMe was tested as solution-phase catalyst to give 71% yield & 91% ee

Synthesis of Urea Catalyst



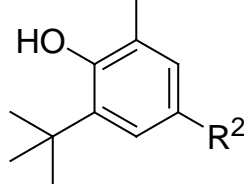
1) CICSCI, $\text{CH}_2\text{Cl}_2/\text{sat NaHCO}_3$ (1:1), 20 min

2) (*R,R*)-1,2-diaminocyclohexane, CH_2Cl_2 , 20 min



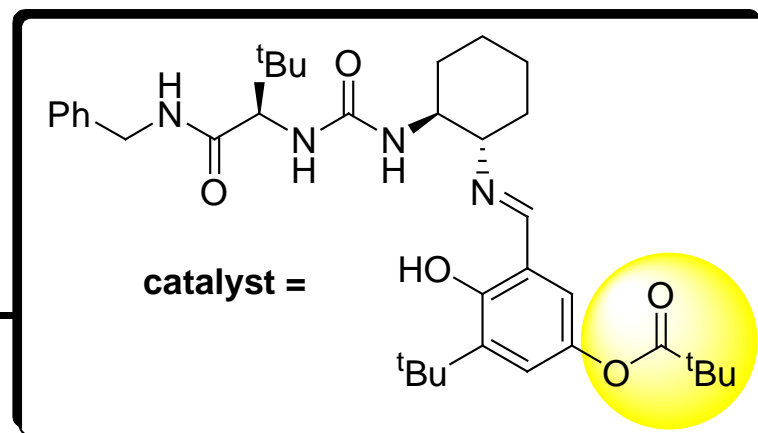
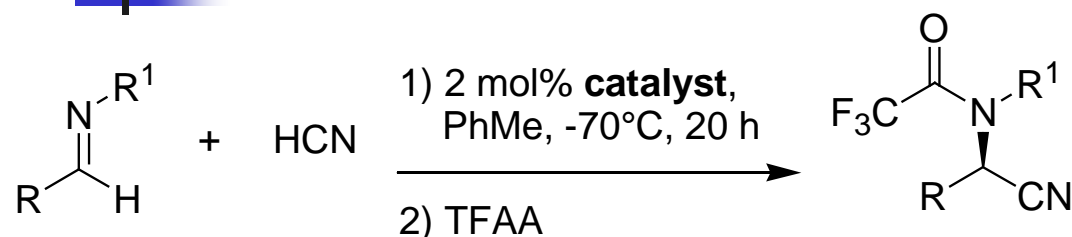
1b ($\text{R}^1 = \text{H, R}^2 = \text{OCO}^t\text{Bu}$)

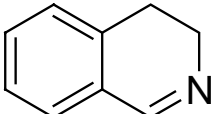
1c ($\text{R}^1 = \text{Me, R}^2 = ^t\text{Bu}$)



- catalyst **1b** & **1c** (86%, 5 steps)
- only a single chromatographic purification step

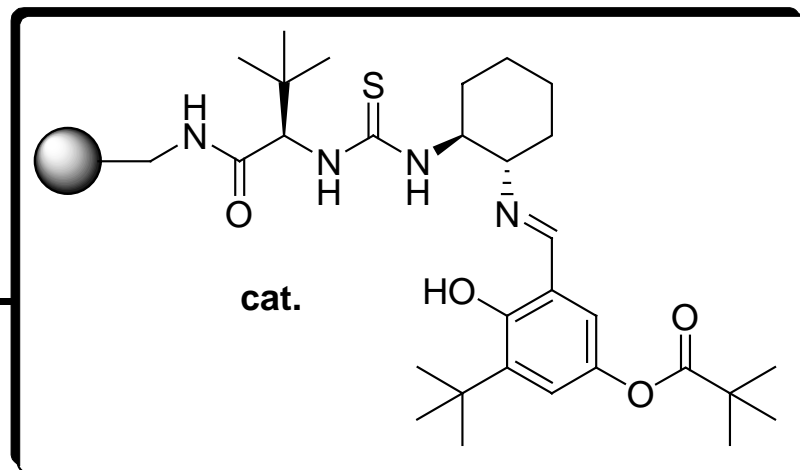
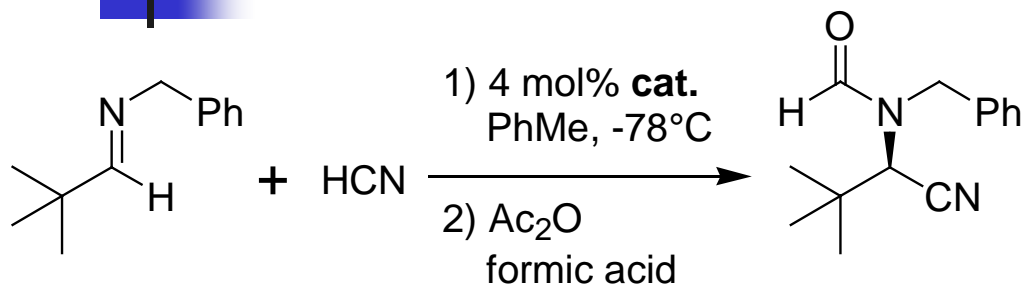
Solution-Phase Asymmetric Strecker of Aldimines



Imine	R ¹	Yield[%]	ee[%]
R			
C ₆ H ₅	allyl	74	95
<i>p</i> -BrC ₆ H ₄	allyl	89	89
<i>tert</i> -butyl	allyl	75	95
<i>tert</i> -butyl	benzyl	88	96
pentyl	benzyl	69	78
		88	91

- 5-pivaloyl-substituted Schiff base proved to be superior catalyst after an optimization library of 70 compounds
- thiourea derivatives slightly more enantioselective than urea in resin-bound catalysts
- both *E* and *Z*-aryl imines provide high enantioselectivity

Preparative Strecker Reactions With Resin-Bound Catalyst



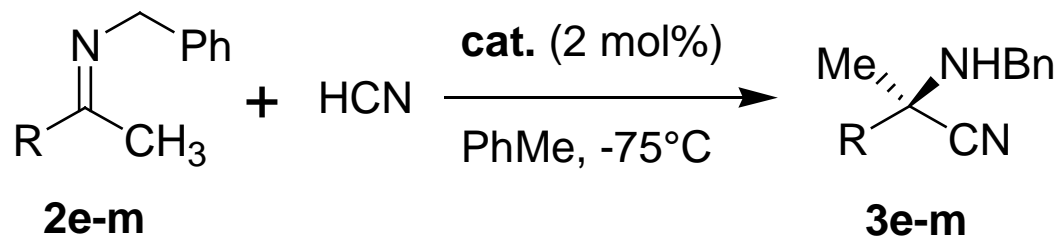
Cycle	Yield (%)	ee (%)
1	97	92
2	98	93
3	98	93
4	97	93
5	97	92
6	96	93
7	98	93
8	97	93
9	98	93
10	98	93

➤ catalyst removed by filtration from previous reaction mixture and rinsed with toluene prior to reuse

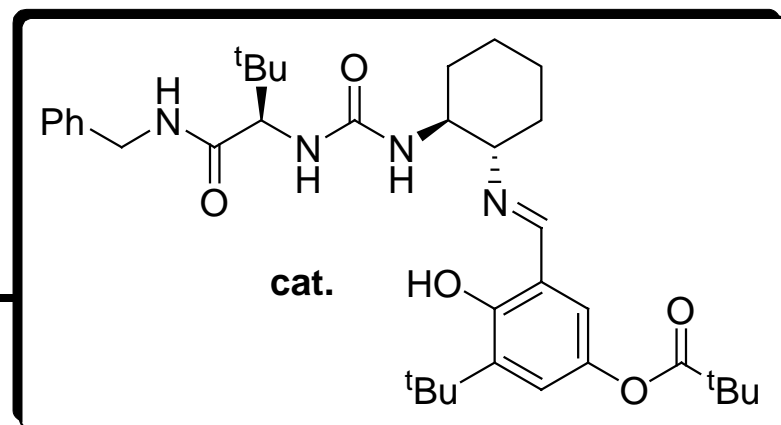
➤ yields typically higher than solution-phase reactions

➤ no loss of catalyst reactivity or product enantioselectivity was observed after ten catalyst recycles

First Examples of Asymmetric Strecker With Ketoimines



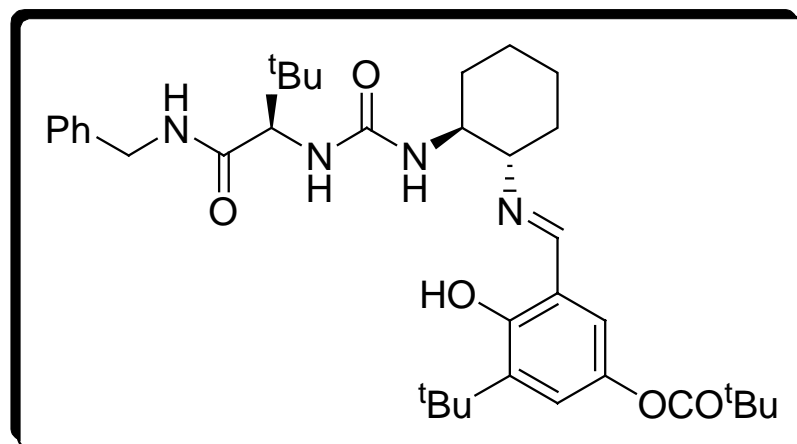
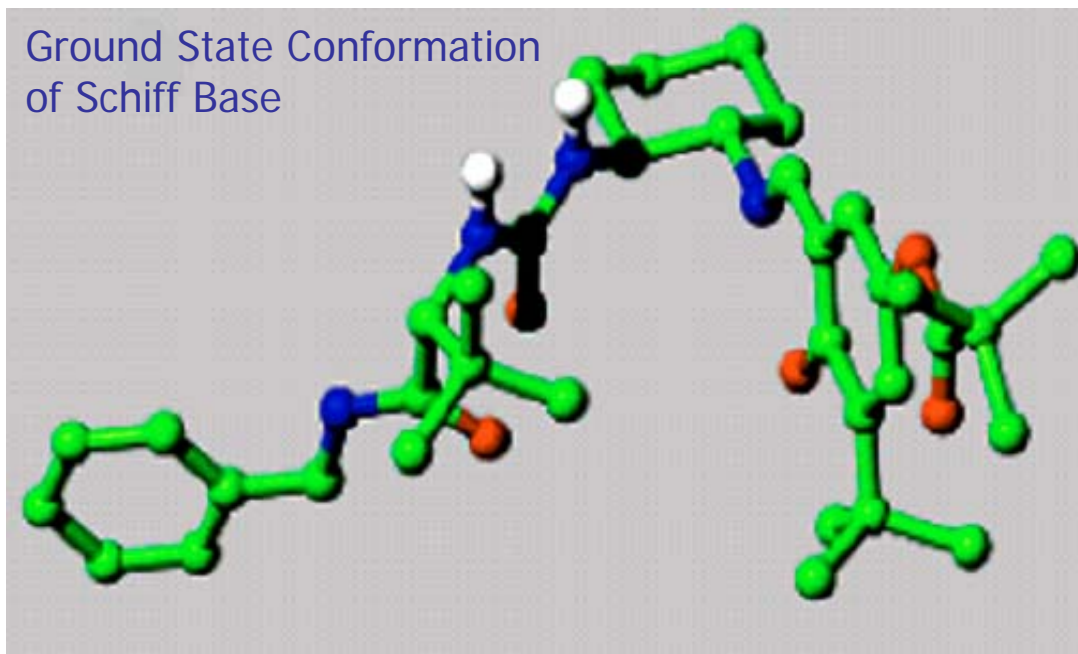
Product	R	t (h)	yield (%)	ee (%)
3e	C ₆ H ₅	24	97	90
3g	<i>p</i> -BrC ₆ H ₄	80	quant	93
3h	<i>p</i> -NO ₂ C ₆ H ₄	80	quant	93
3i	<i>p</i> -MeOC ₆ H ₄	60	98	88
3k	<i>m</i> -BrC ₆ H ₄	60	97	91
3l	<i>o</i> -BrC ₆ H ₄	90	45	42
3m	<i>tert</i> -butyl	15	98	70



- precursors to α -substituted amino acids
- *N*-benzyl more stable than *N*-allyl (85% ee when R=C₆H₅)
- *N*-benzyl could be removed in quantitative yield with no loss in optical purity

Structural and Mechanistic Studies

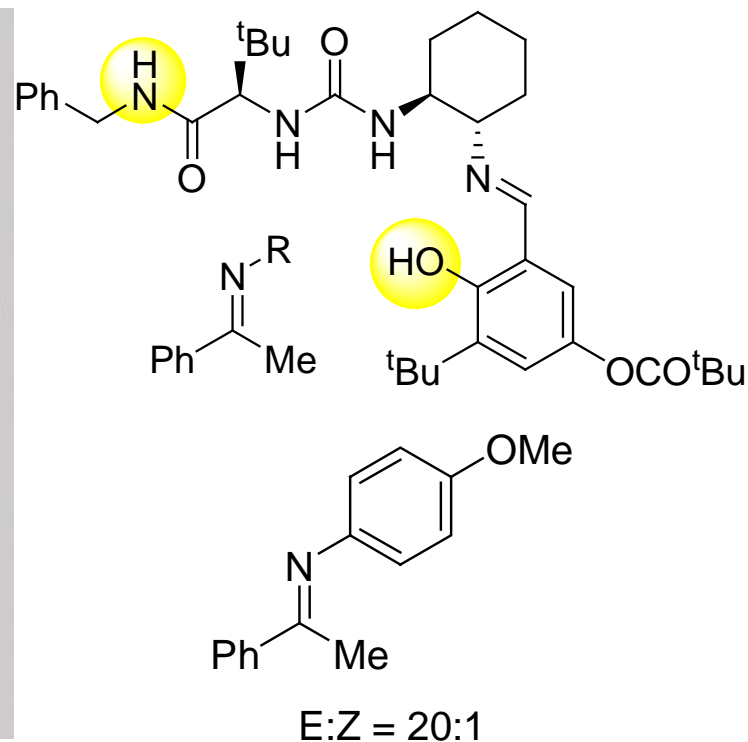
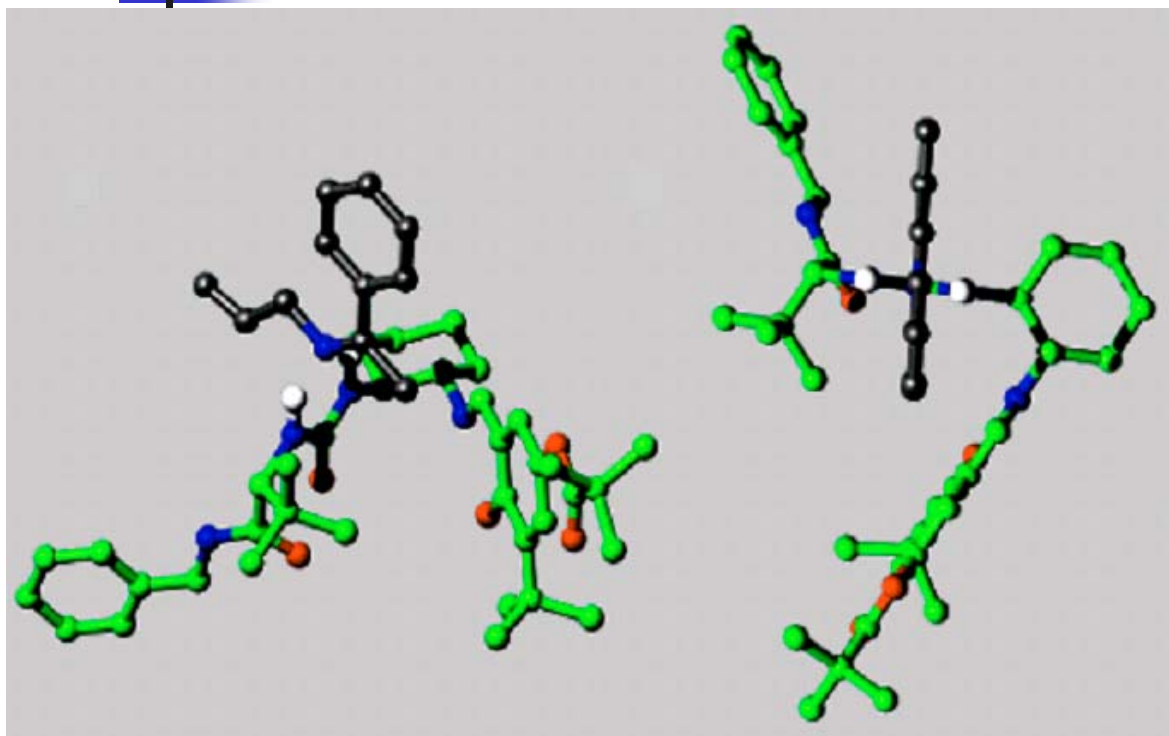
Ground State Conformation of Schiff Base



➤ determined through ROESY and NOE NMR experiments

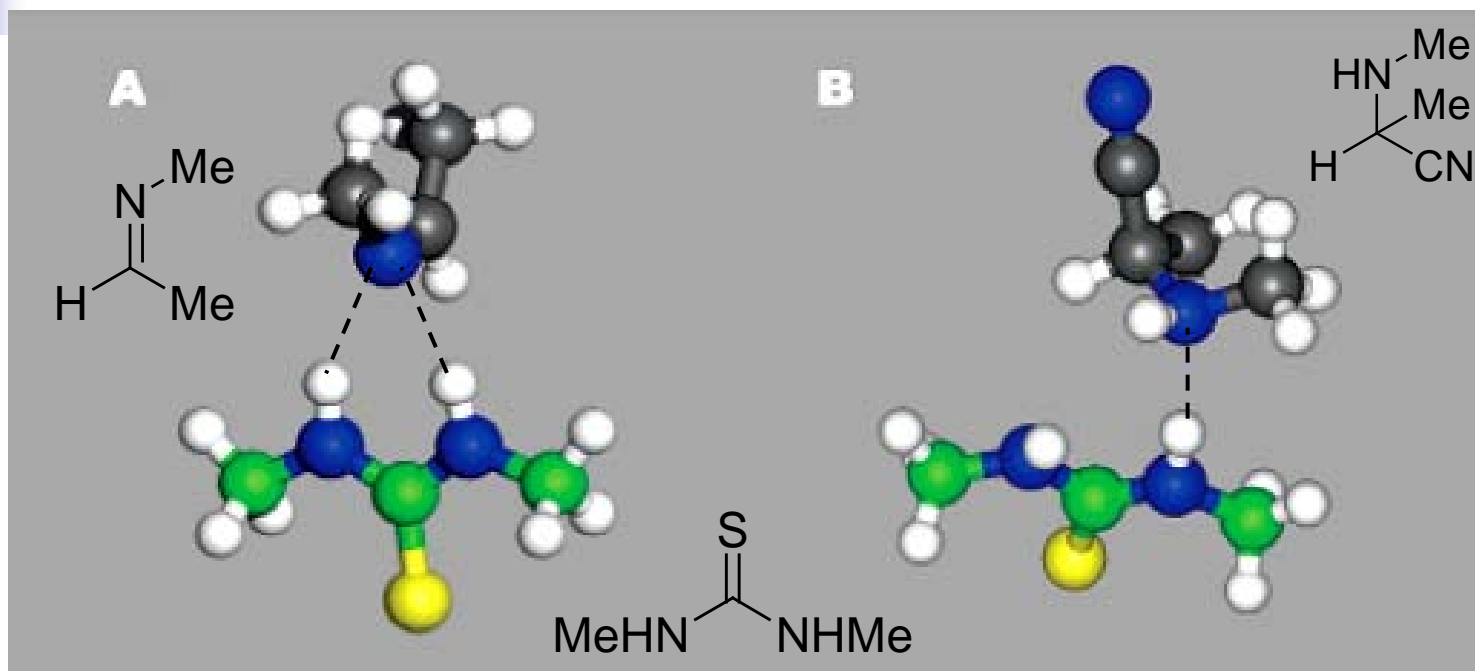
- NMR experiments are in agreement with calculated energy-minimized geometry (Gaussian)
- first order dependence on catalyst and HCN, and saturation kinetics with respect to imine
- Strecker reaction obeys Michaelis-Menten kinetics
- implicates reversible formation of an imine-catalyst complex; presumably through H-bond?

Solution Structure of Imine-Catalyst Complex Determined by NMR



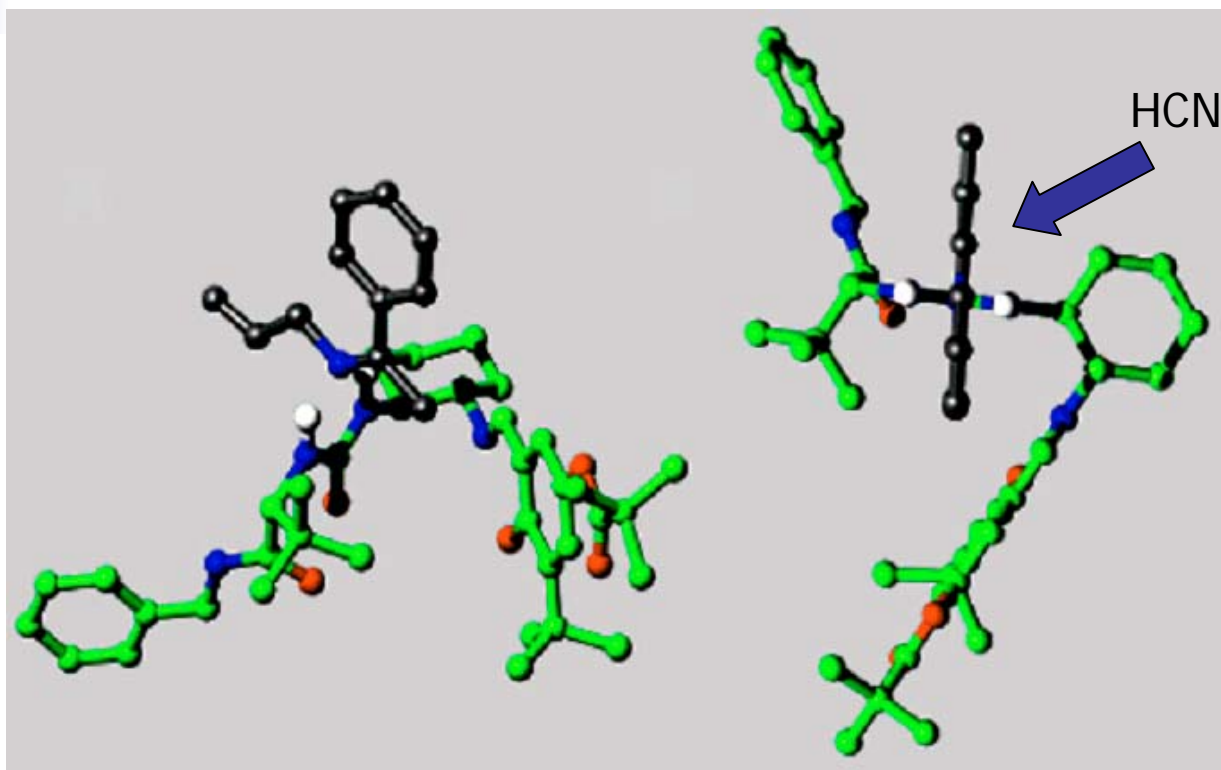
- deletion of amide and phenolic proton did not suppress activity, but alkylation of urea protons resulted in dramatic loss of activity
- imine substrate interacts solely with the urea hydrogens
- NMR NOE experiments provided evidence for favorable binding with the Z-isomer

Evidence for Bridging H-bond



- computational calculations with *N,N'*-dimethylthiourea and (*Z*)-ethylidene methylamine
- energy minimization revealed preference for a double H-bond over a single H-bonded
- bridging interaction in catalyst-imine complex (**A**, 10.0 kcal/mol) is stronger than classic H-bond in catalyst-product complex (**B**, 6.3 kcal/mol) which is a plausible explanation for catalyst turnover

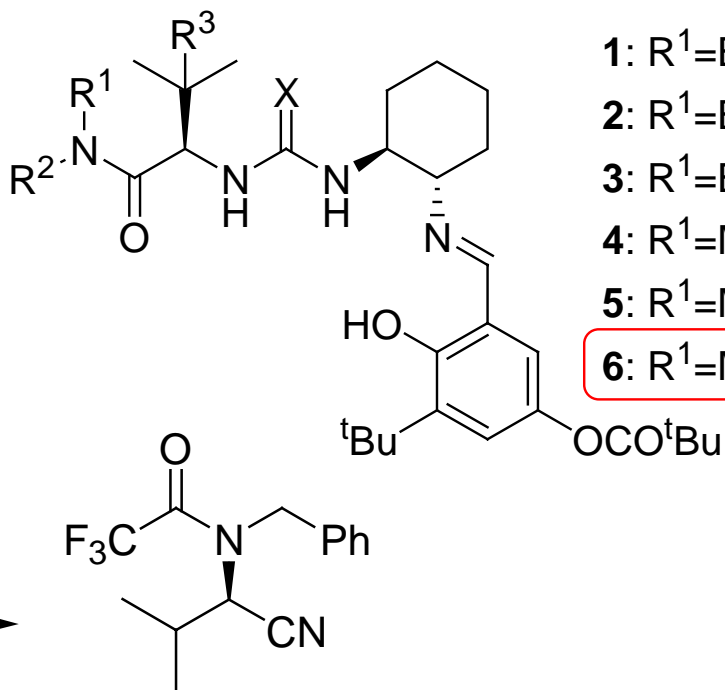
Characteristics of Catalyst-Imine Complex



- large group on imine carbon directed away from catalyst. High ee obtained regardless of steric and electronic properties of the substrate
- small group on imine carbon aimed directly into catalyst. Ketoimines bearing larger substituents are poor substrates

Model-Driven Optimization

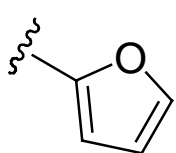
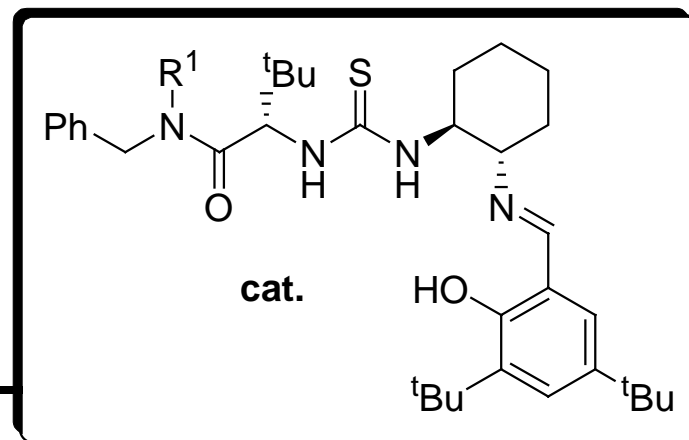
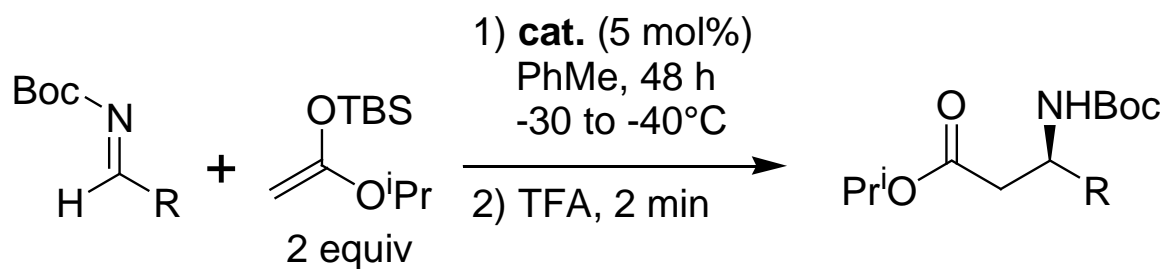
➤ increase steric bulk of amino acid and amide



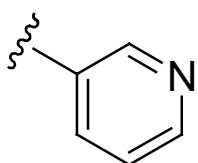
catalyst	ee (%)	catalyst	ee (%)
1	80.0	4	95.8
2	93.5	5	96.6
3	93.1	6	97.0

➤ overall increase of up to 17% ee

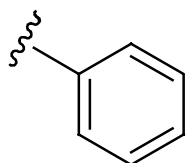
Asymmetric Catalytic Mannich Reactions



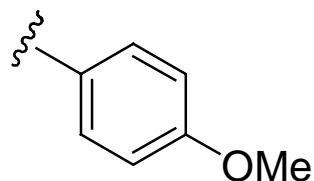
91% ee
84% yield



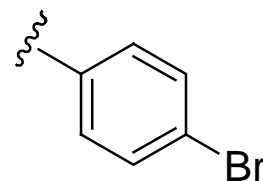
98% ee
99% yield



97% ee
95% yield



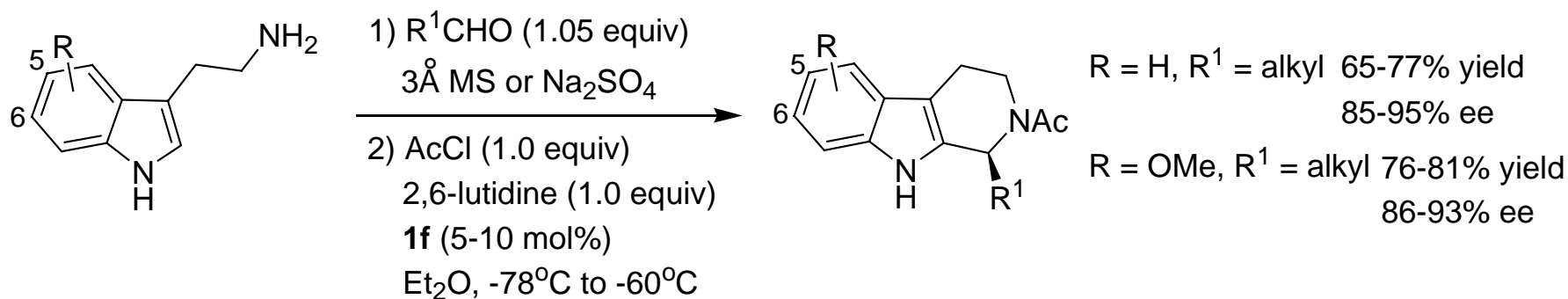
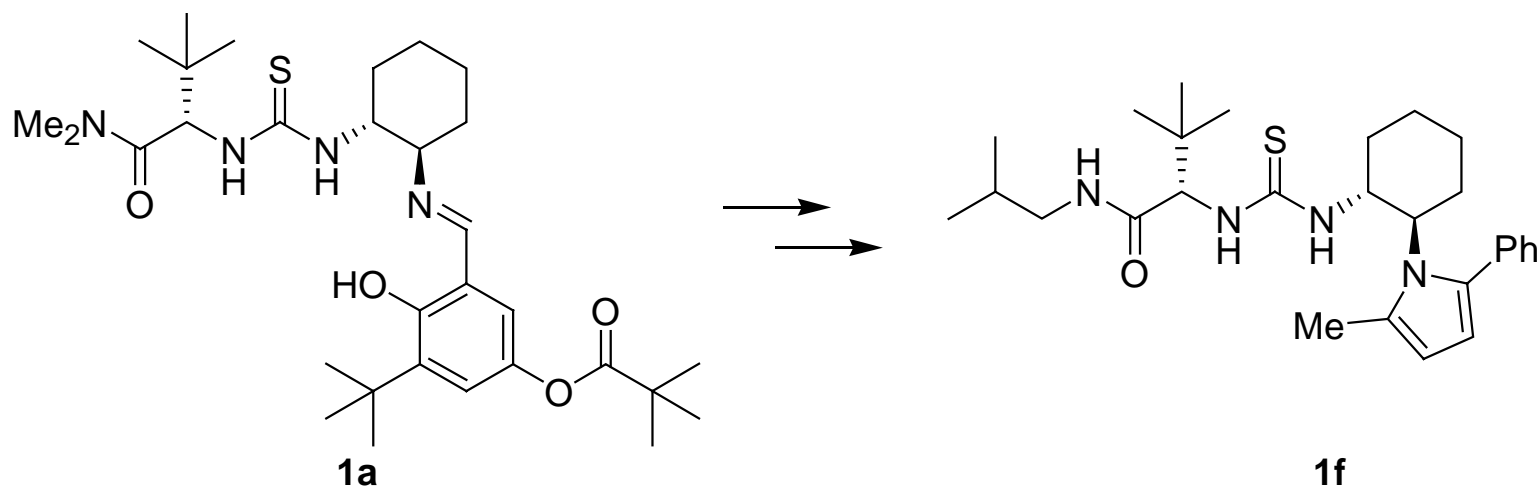
86% ee
91% yield



94% ee
93% yield

- more electrophilic *N*-Boc imine was found to undergo reaction
- ~45% conversion (R=Ph) in absence of catalyst
- variation of catalyst structure, silyl ketene acetal, and reaction temperature increased the rate of catalyzed pathway relative to background reaction

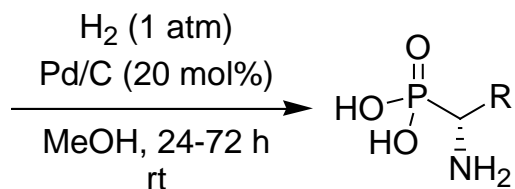
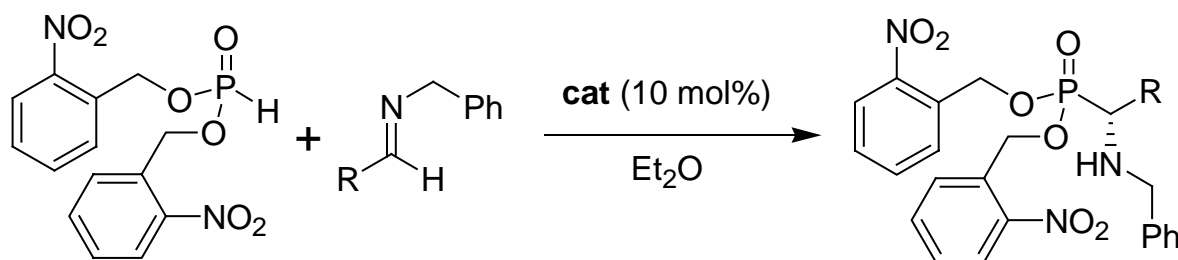
Acyl-Pictet-Spengler Reaction



➤ all chiral ureas and thioureas, and (salen)aluminum complexes resulted in no desired product with Pictet-Spengler reaction

"Privileged" Dipeptide Thiourea Catalyst?

Hydrophosphonylation of imines

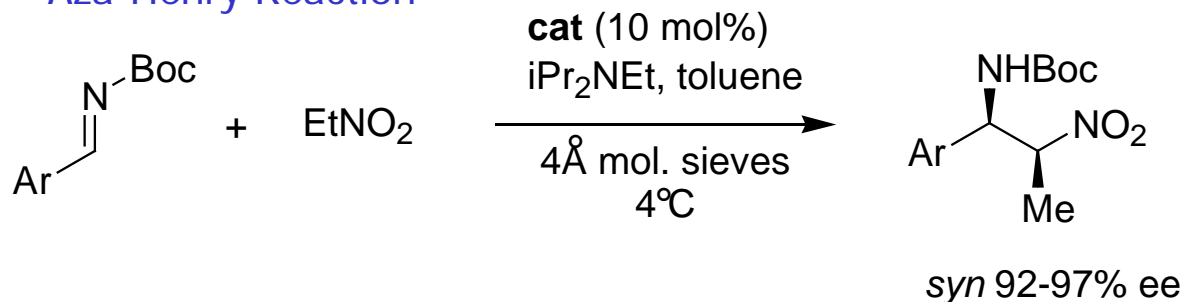


81-99% ee

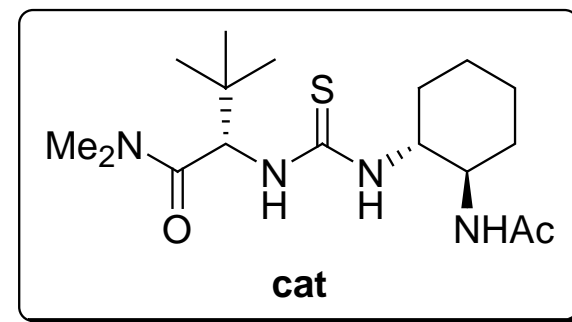
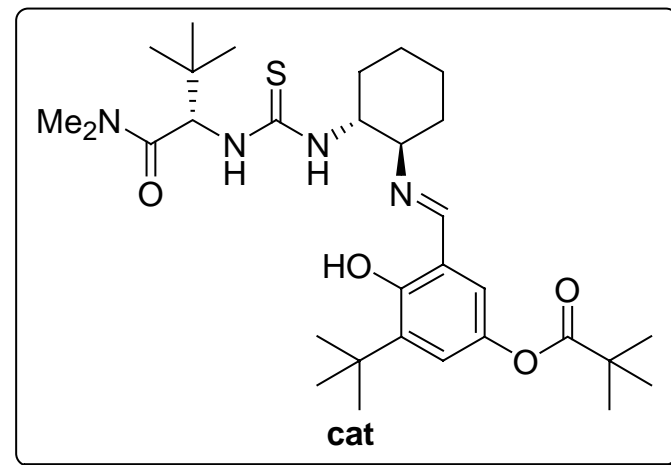
➤ α -amino phosphonate derivatives have antibacterial and antifungal activity

Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102

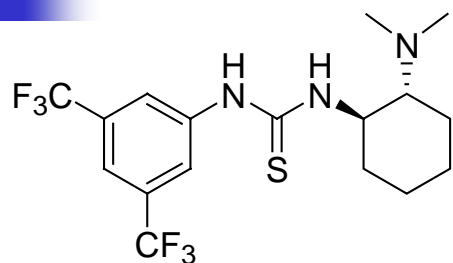
Aza-Henry Reaction



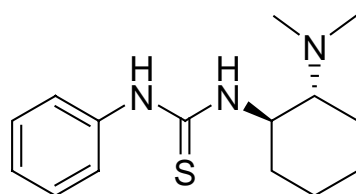
Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466



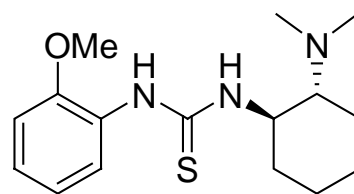
Bifunctional Organocatalysts: Enantioselective Michael Reaction



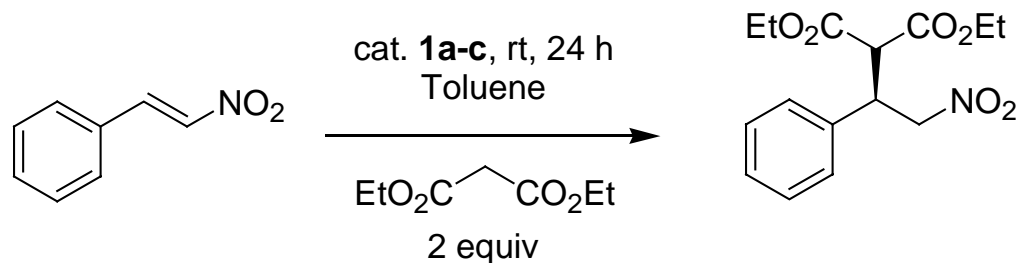
1a



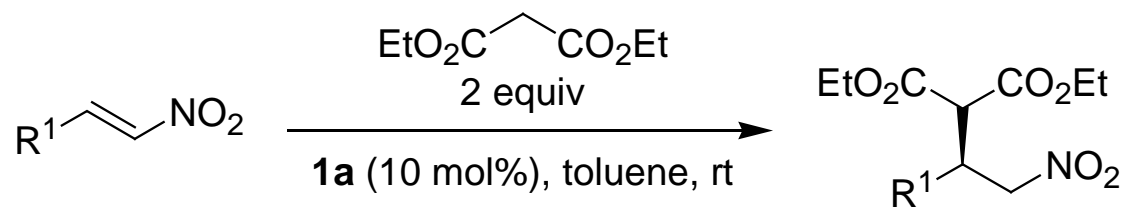
1b



1c

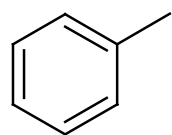
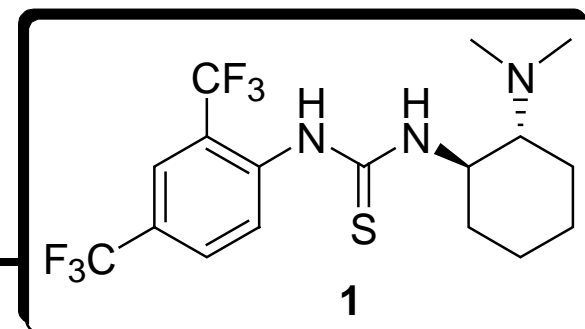
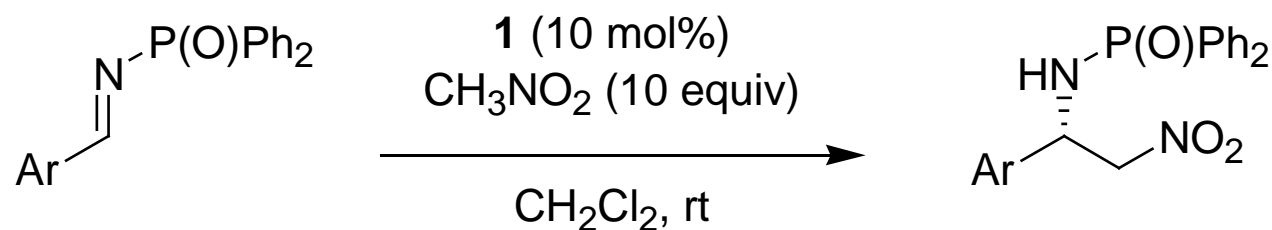


cat.	% yield	%ee
1a	86	93
1b	58	80
1c	40	52

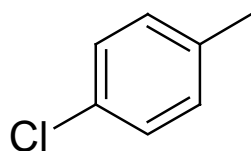


R ¹	% yield	%ee
4-F-Ph	87	92
2-thienyl	74	90
1-naphthyl	95	92
<i>tert</i> -butyl	88	81

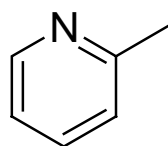
Bifunctional Thiourea Catalyzed Aza-Henry of Phosphinoylimines



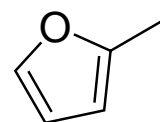
87% yield
67% ee



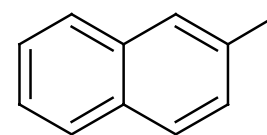
76% yield
67% ee



91% yield
68% ee

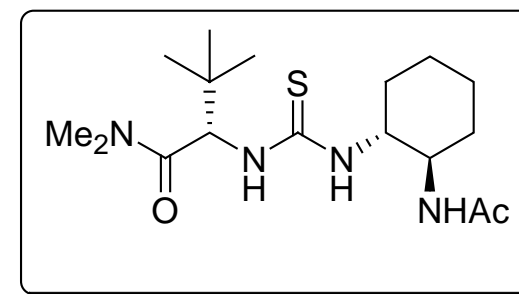


85% yield
76% ee

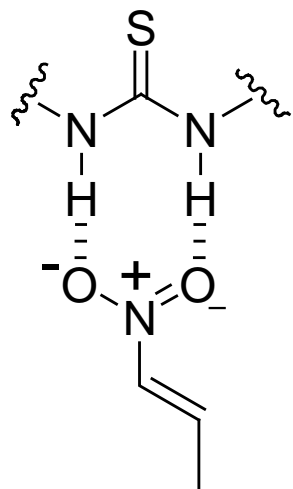


78% yield
70% ee

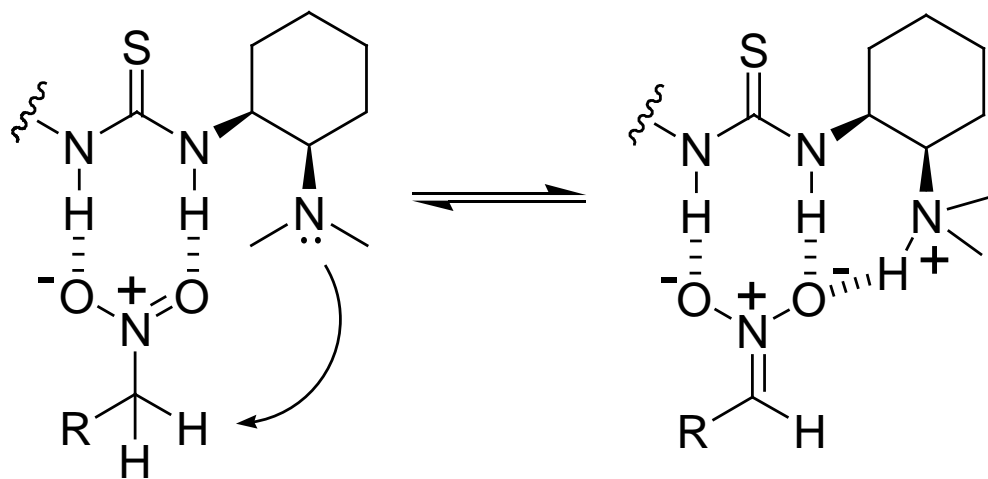
- bifunctional nature of catalyst is necessary for high conversion
- not as selective as Jacobsen's catalyst for aza-Henry of *N*-Boc imines



Proposed Activation of Bifunctional Thiourea

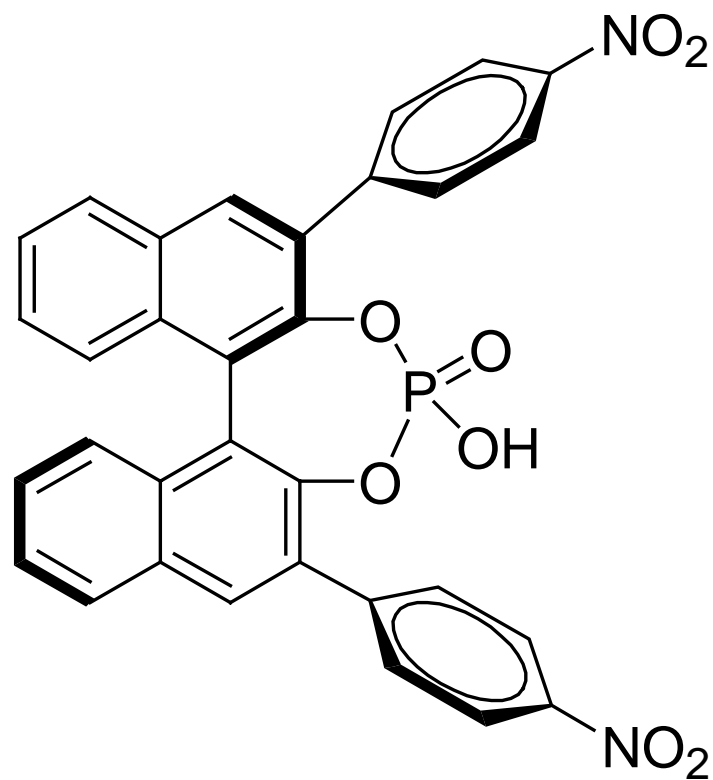


➤ Electrophilic activation in Michael reaction of malonates to nitroolefins

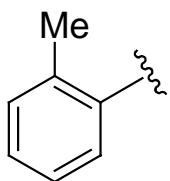
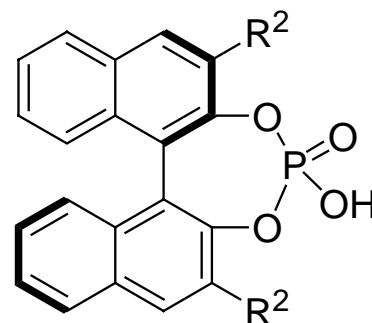
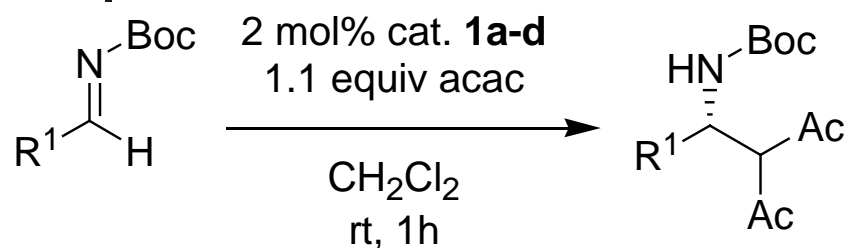


➤ activation of nitroalkane to give reactive nitronate in aza-Henry reaction of phosphinoylimines

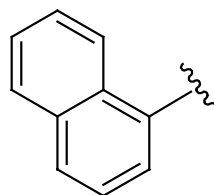
Phosphoric Acid Catalysts



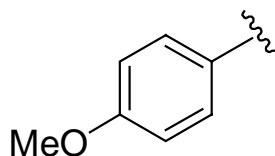
Chiral Phosphoric Acid Catalyzed Mannich Reaction



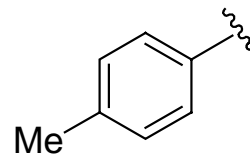
93% ee
94% yield



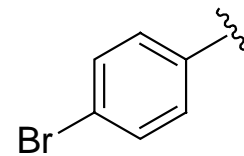
92% ee
99% yield



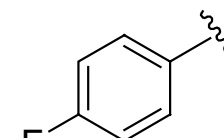
90% ee
93% yield



94% ee
98% yield



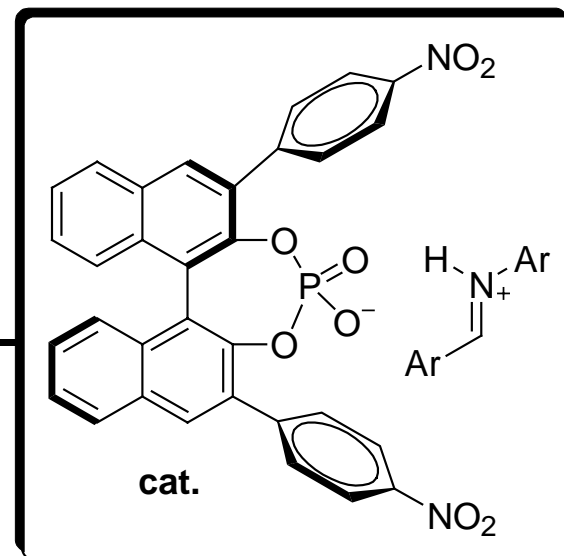
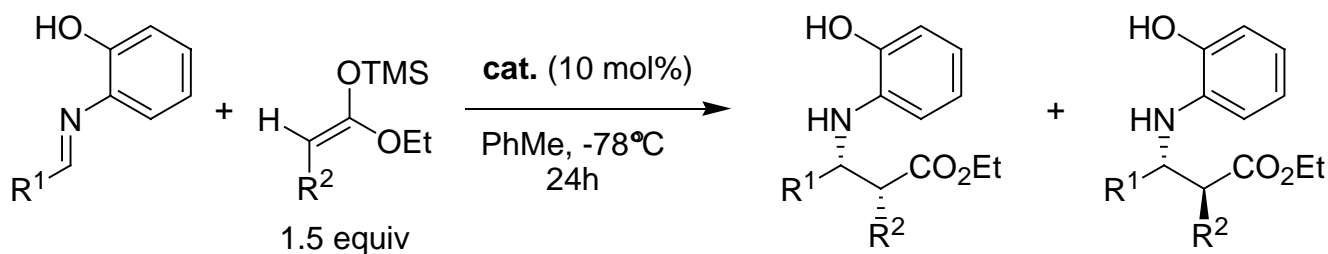
98% ee
96% yield



96% ee
94% yield

- cyclic structure with P(V) atom prevents free rotation
- pKa of 1.39 facilitates H-bonding with imine
- possible bifunctional catalyst with Lewis basic site of the phosphoryl oxygen
- increase in %ee from **1a** (12%) to **1d** (95%)

Chiral Phosphoric Acid Catalyzed Mannich Reaction

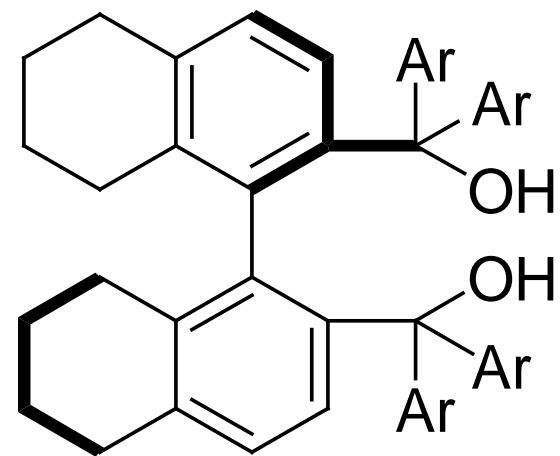
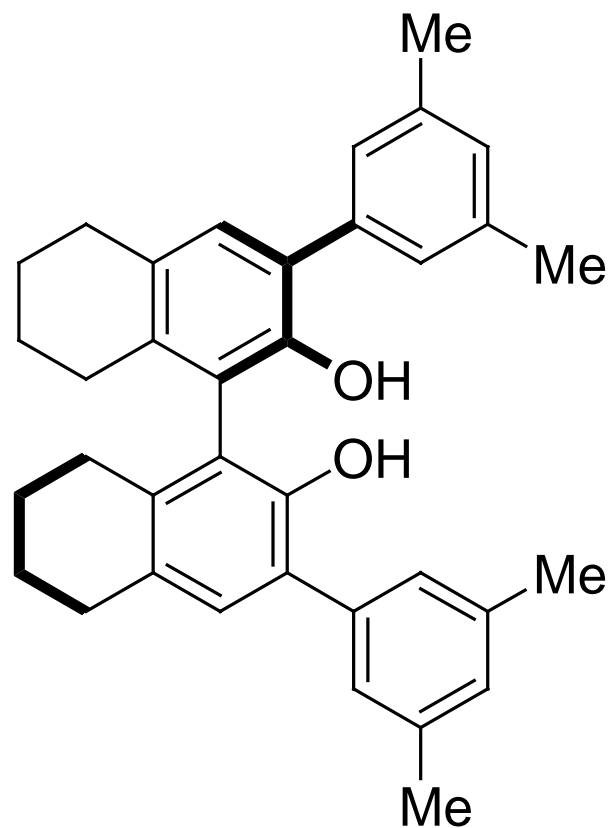
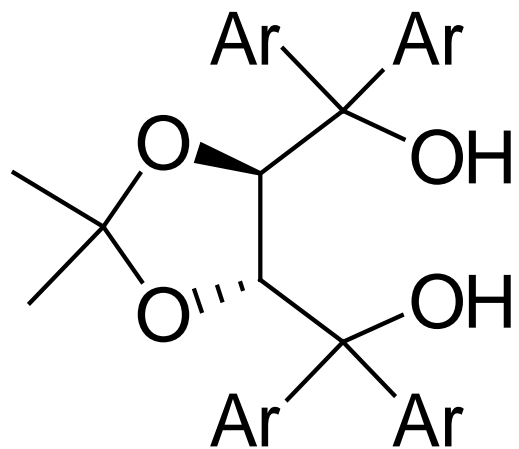


R ¹	R ²	yield(%)	syn/anti	ee (%)
C ₆ H ₅	Me	quant	87:13	96
<i>p</i> -FC ₆ H ₄	Me	quant	91:9	84
2-Thienyl	Me	quant	94:6	88
<i>p</i> -MeOC ₆ H ₄	Me	98	92:8	88
PhCH=CH	Me	97	95:5	90
PhCH=CH	PhCH ₂	45	95:5	90

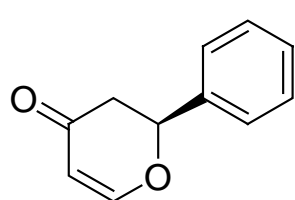
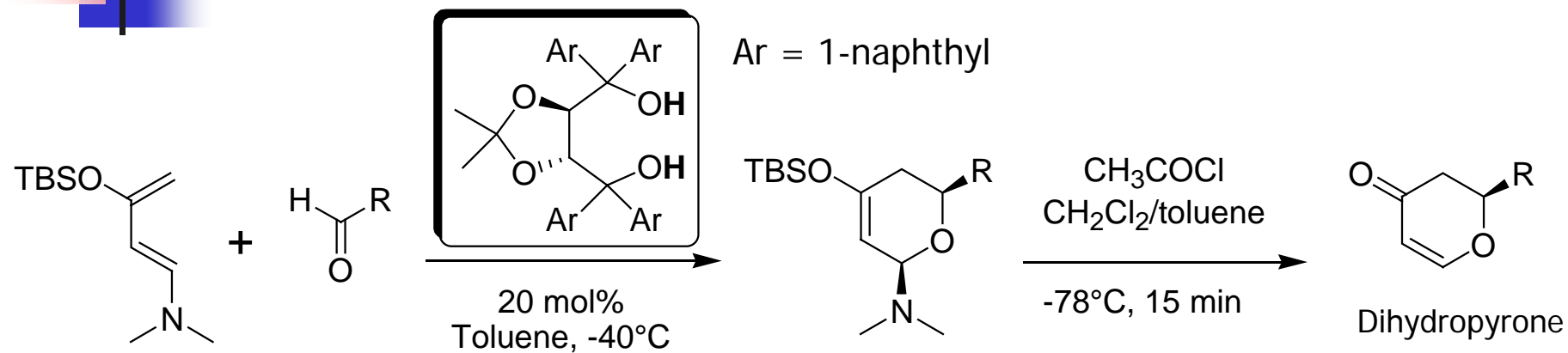
➤ 4-nitrophenyl groups improved enantioselectivity and increased reaction rate

➤ 2-hydroxy substituent necessary for high enantioselectivity

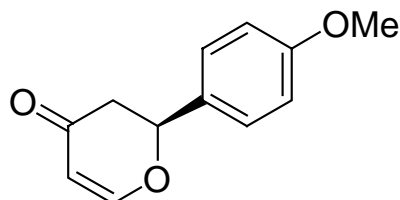
Chiral Alcohol Catalysts



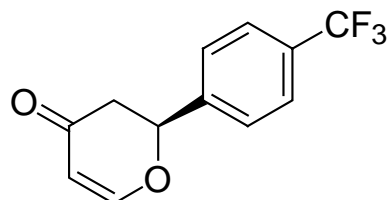
TADDOL Catalyzed Hetero-Diels-Alder



>99:1 er
70% yield



97:3 er
68% yield

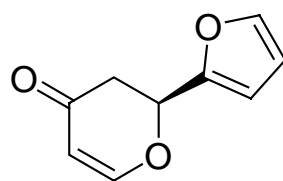


97:3 er
68% yield

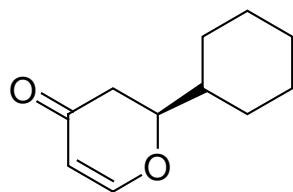
➤ HDA reaction was accelerated in protic solvents

➤ *S*-enantiomer produced preferentially

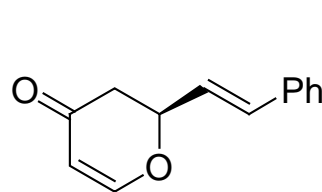
➤ monomethyl and dimethyl ether derivatives were inactive



96:4 er
67% yield

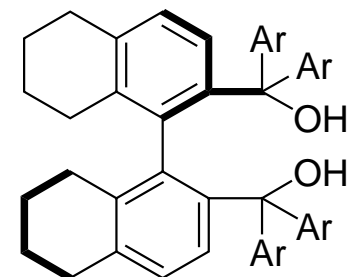
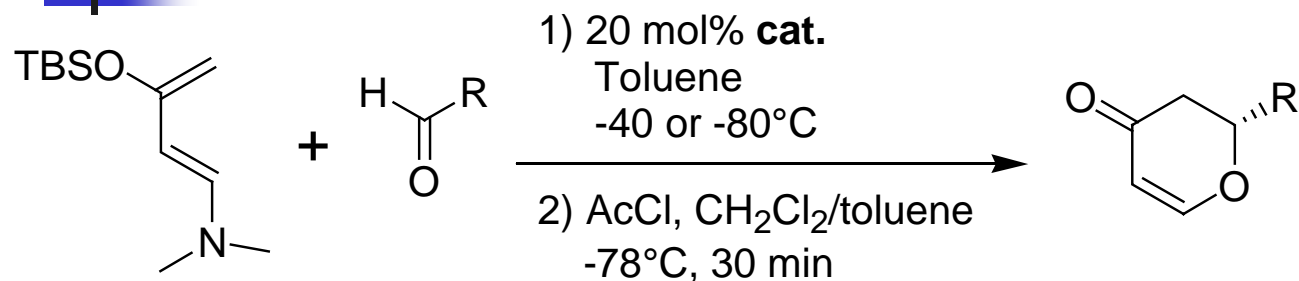


93:7 er
64% yield

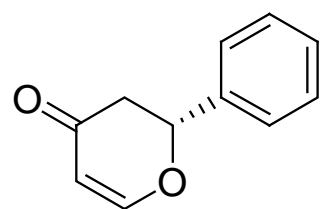


97:3 er
52% yield

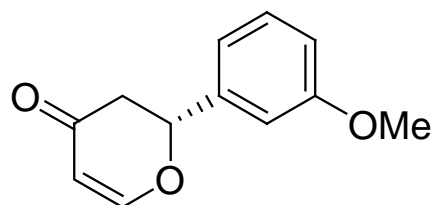
Axially Chiral Biaryl Diol Catalyzed Hetero-Diels-Alder



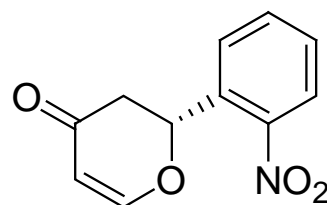
cat. Ar = 4-F-3,5-Et₂C₆H₂



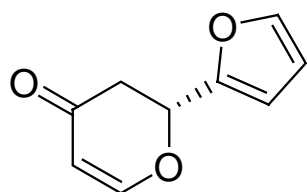
98% ee
84% yield



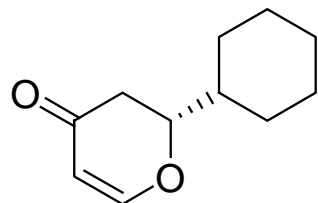
98% ee
86% yield



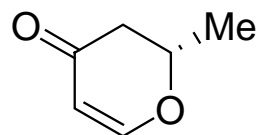
98% ee
93% yield



>99% ee
96% yield



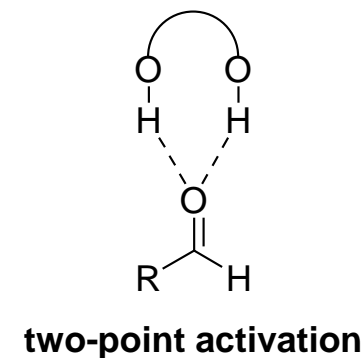
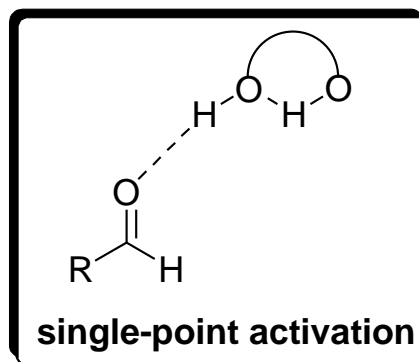
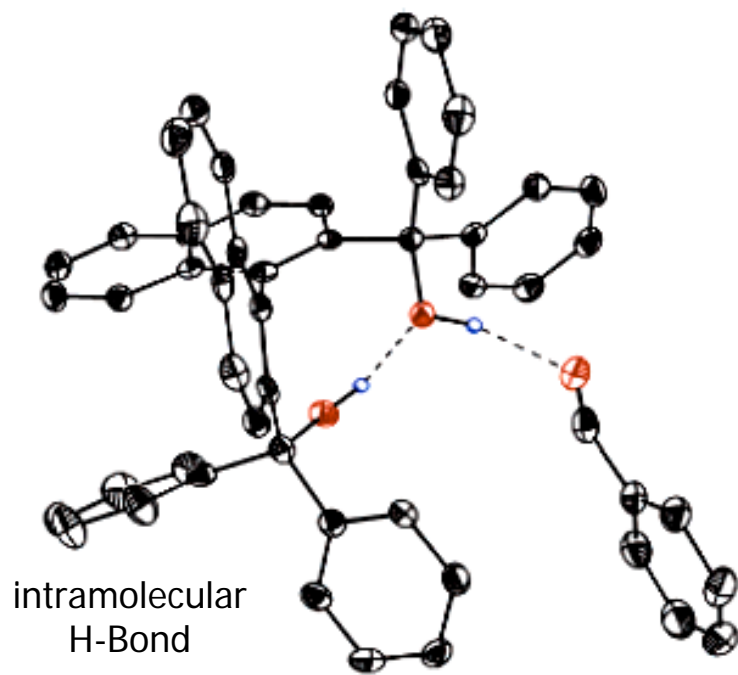
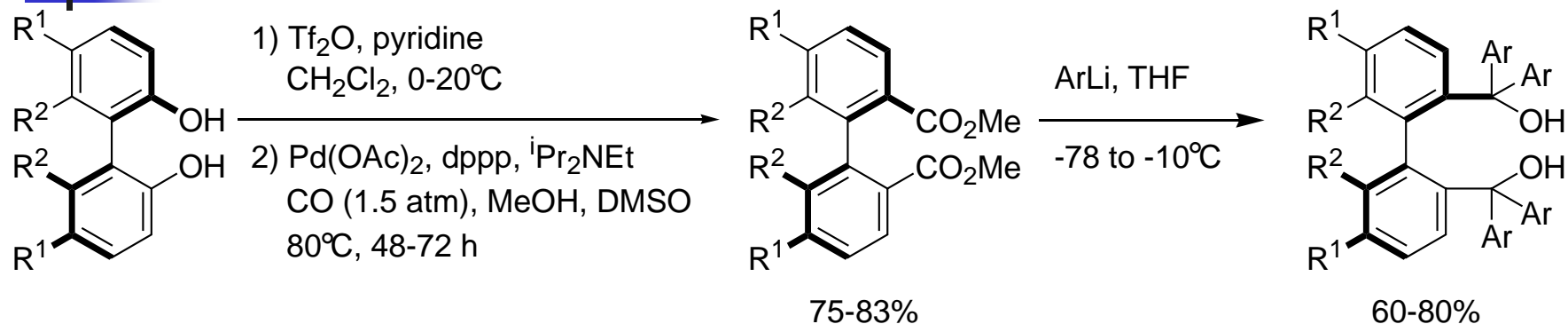
84% ee
99% yield



97% ee
75% yield

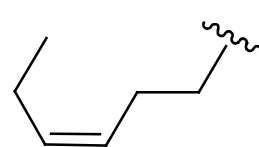
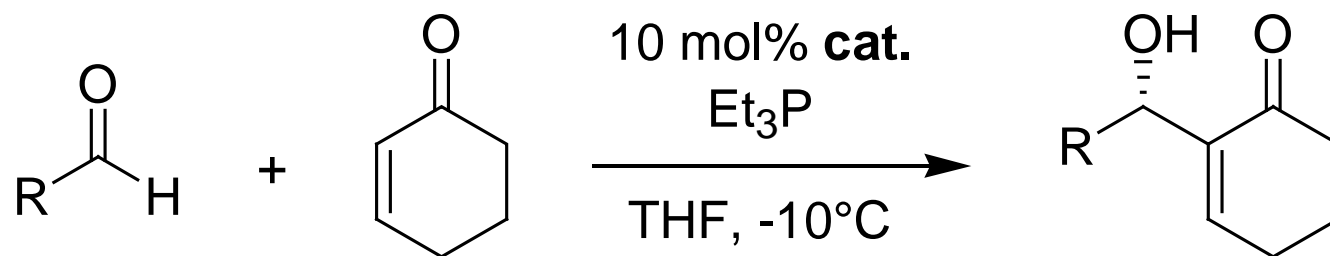
- BAMOL catalyst superior to TADDOL catalyst
- BAMOL is more effective with aliphatic aldehydes

Synthesis of BAMOL Catalyst and H-bond Evidence

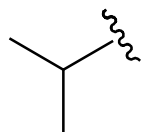


- X-ray structure of an inclusion complex of 2,2'-bis-(diphenylhydroxymethyl)binaphthylene
- single-point activation also seen with TADDOL

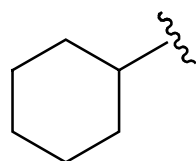
BINOL-Derived Catalysts for Asymmetric Morita-Baylis-Hillman



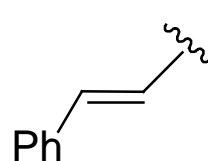
96% ee
72% yield



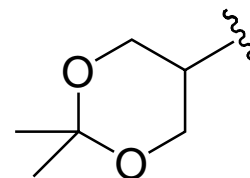
95% ee
82% yield



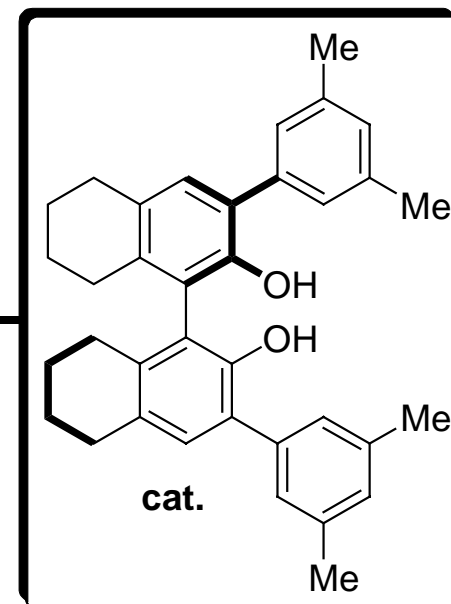
96% ee
71% yield



81% ee
39% yield

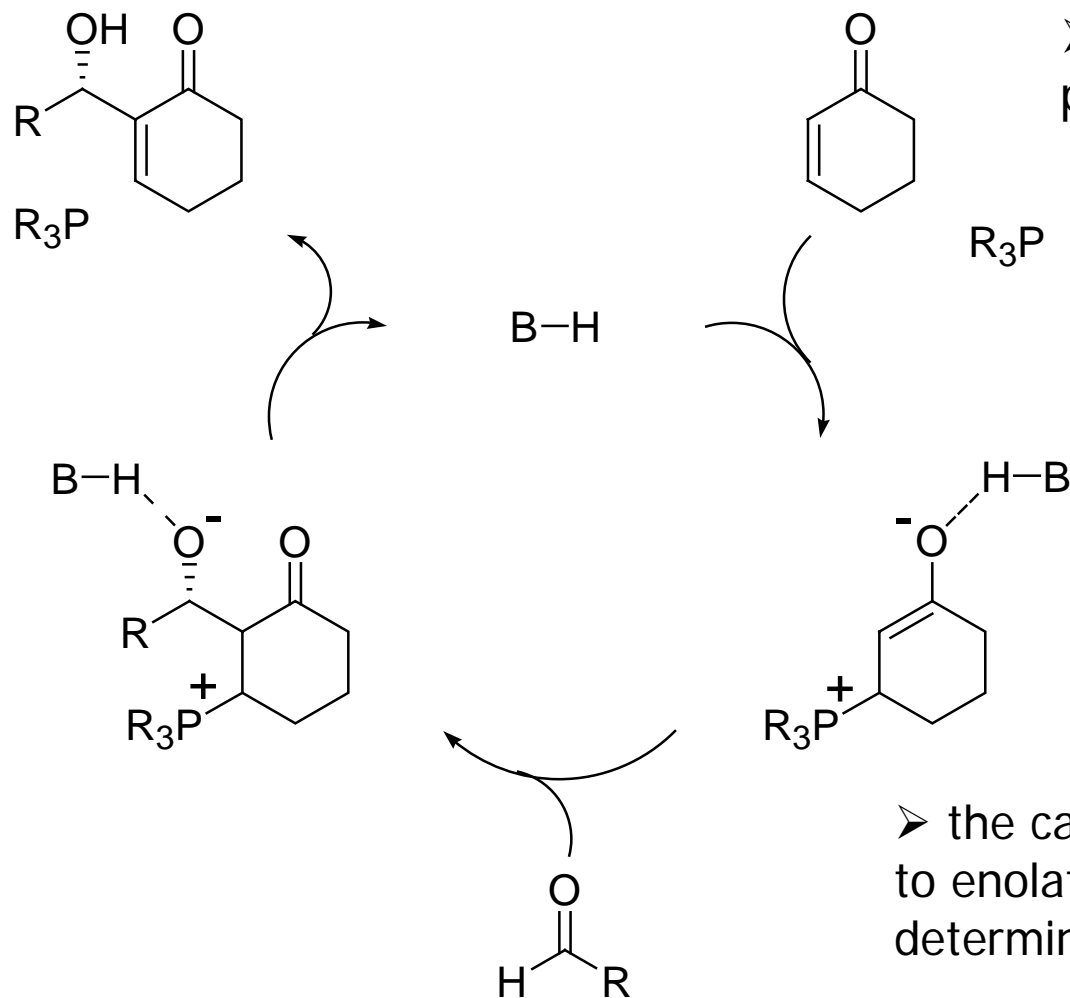


92% ee
70% yield



- saturation of the BINOL derivative and substitution at the 3,3'-positions gave highest enantioselectivities
- conjugated aldehydes resulted in low yields and low enantioselectivities
- removal of one Brønsted equivalent resulted in diminished activity

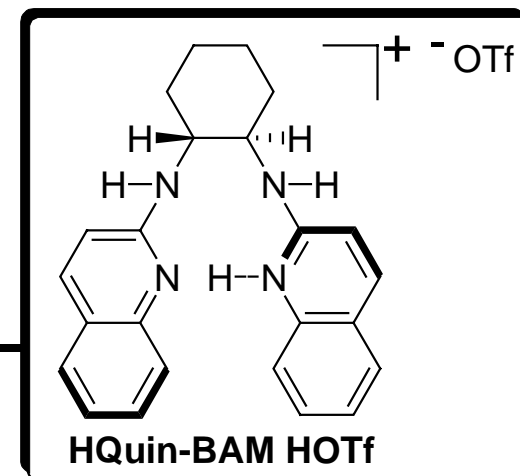
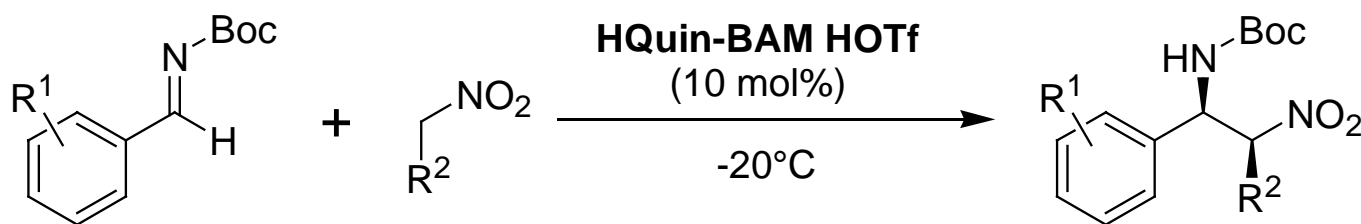
Proposed Catalytic Cycle With Bronsted Acid



➤ catalyst (B-H) may serve to promote conjugate addition step

➤ the catalyst remains hydrogen bonded to enolate in the enantioselectivity-determining aldehyde addition step

Chiral Proton-Catalyzed Aza-Henry



R ¹	R ²	yield(%)	dr	ee (%)
H	H	57		60
<i>p</i> -NO ₂	H	61		82
H	CH ₃	69	14:1	88
<i>p</i> -Cl	CH ₃	59	17:1	82
<i>m</i> -NO ₂	CH ₃	51	11:1	89
<i>o</i> -NO ₂	CH ₃	62	7:1	82
<i>p</i> -NO ₂	CH ₃	60	7:1	90

➤ 5% of β-aminonitroalkane formed after 5 days in absence of catalyst (vs 57% for R¹=R²=H)

➤ addition of HQin-BAM alone failed to accelerate the reaction and no enantioselection was observed

➤ proton plays a key role in both substrate activation and asymmetric induction



Considerations for Developing Hydrogen Bonding Catalysts

- the catalysts should be somewhat rigid; the bi- or multidentate nature of catalyst-substrate binding amplifies the catalytic effectiveness and restricts the degrees of freedom
- the binding interactions must not be excessively large as is the case for traditional Lewis acids because this will inevitably lead to product inhibition
- catalysts should be water-compatible or even catalytically active in water



Conclusions

- Hydrogen bonding, along with other interactions, can accelerate chemical reactions and induce enantioselectivity
- It is very probable that the interactions of the organocatalytic systems described are dominated by bidentate hydrogen bonding
- Immobilization and library optimization of non-covalent organocatalysts is straightforward
- Jacobsen's dipeptide thiourea can be considered a "privileged" chiral catalyst
- Classical organometallic ligands, in the absence of a metal, have also been used successfully in chiral proton catalysis
- Hydrogen bonding catalysis using small organic molecules mimics the action of enzymes and antibodies



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