

The Nature of the Hydrogen Bond and its Application Towards Enantioselective Catalytic Reactions

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2/02/05

Lead Material:

Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48.

Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062.

Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*, Springer-Verlag, New York, **1991**.

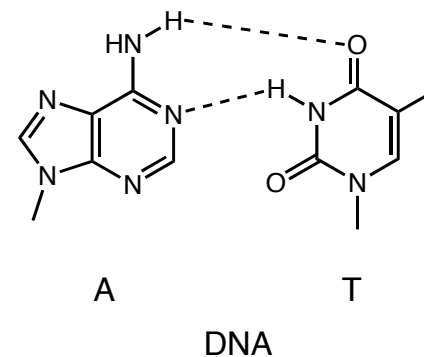
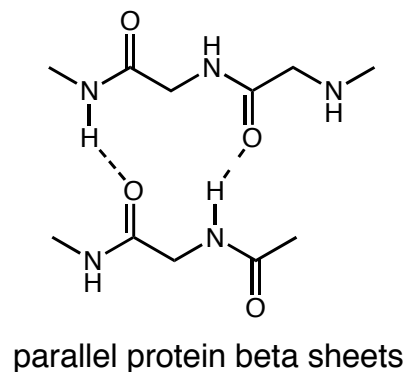
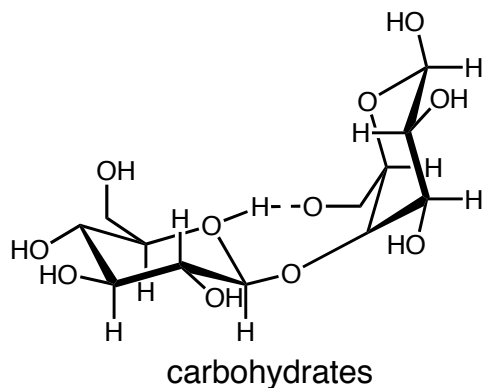
A brief introduction to various hydrogen bond applications

■ Examples of hydrogen bonding are incredibly common

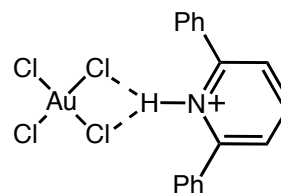
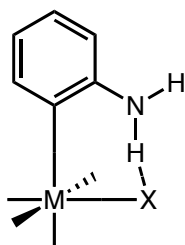
- Mineralogy, material science, organometallics, biochemistry, organic chemistry, supramolecular chemistry, molecular medicine and pharmacy

■ Many important structural functions

- Stabilizes protein folding, organizes DNA, organizes water and carbohydrates



■ Being discovered and elaborated on in bioorganic, organic and inorganic chemistries



Crabtree, R. H. *et al. Inorg. Chem.* **1995**, *34*, 3474.
Saenger, J. W. *Hydrogen Bonding in Biological Structures*, Springer-Verlag, New York, **1991**.
Garrett, R. H. and Grisham, C. M. *Biochemistry*, Harcourt Brace College, Orlando, **1995**.

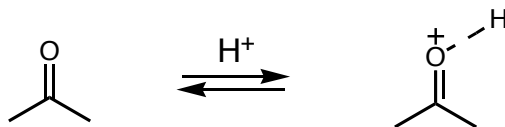
Hydrogen bonds and reactivity

■ The proposed interaction

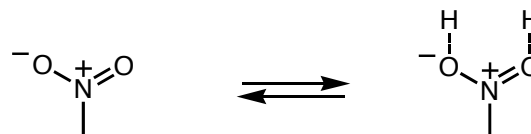
- Charge transfer occurs from an electron lone pair from an acceptor (A) to the antibonding orbital of a donor (D) hydrogen bond



■ Lewis acid activator



- LUMO lowering catalysis



■ Transition state organizer

- Initially seen in enzymes and is now be utilized in current synthesis
- Provide a route for asymmetric catalysis
- Dual reactivity

■ Reaction lubricant

- Can provide a source of energy to facilitate a reaction
- Completes a "circuit" to allow for reaction to occur

The three major types of H bonds and important parameters

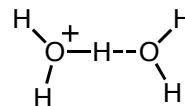
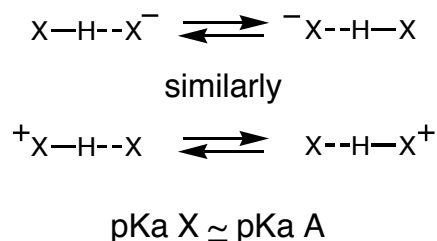
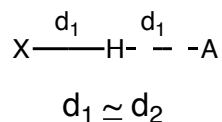
■ General Characteristics

	Strong	Moderate	Weak
interaction type	strongly covalent	mostly electrostatic	electrostatic/ dispersed
bond lengths (Å) H- - -A	1.2–1.5	1.5–2.2	2.2–3.3
lengthening of X–H (Å)	0.08 – 0.25	0.02 – 2.2	>2.2
X–H vs. H- - -A	X–H \simeq H- - -A	X–H < H- - -A	X–H \ll H- - -A
X- - -A (Å)	2.2–2.5	2.5–3.2	>3.2
directionality	strong	moderate	weak
bond angles (°)	170–180	>130	>90
¹ H downfield shift	14–22	<14	
bond energy (kcal/mol)	15–40	4–15	<4

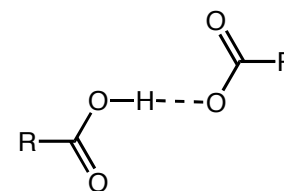
- The "normal" hydrogen could also be termed as the "weak strong" or "strong weak" H bond

Qualitative properties H bond lengths

Strong hydrogen bonds

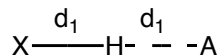


pKa ~ -1.7



pKa ~ 4.76

Moderate hydrogen bonds

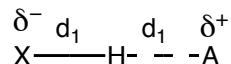


$d_1 < d_2$, X-H is long compared to weak bonds

- moderate bonds have both weak and strong characteristics and tends to be blurred depending upon the experimental treatment
- generally regarded as electrostatic

Weak hydrogen bonds

- C-H donor groups are most widely studied, includes the H-bond pi interaction
- generally regarded as electrostatic/dispersed
- ability to form bifurcated and trifurcated structures



$d_1 < d_2$, X-H is shorter than in moderate H bonds

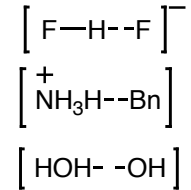
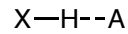
O/N-H bonded species are 2-4 kcal/mol higher with neutral species and 15 kcal/mol higher in charged species

- A reasonable way of thinking about the H-Bond is as a frozen proton transfer event
- Currently no widely accepted theoretical method for predicting H bonds exists

The types of hydrogen bond geometries

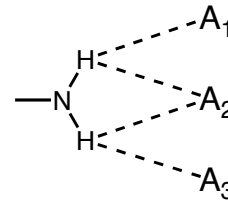
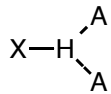
Two centered hydrogen bonds

- most understood and researched



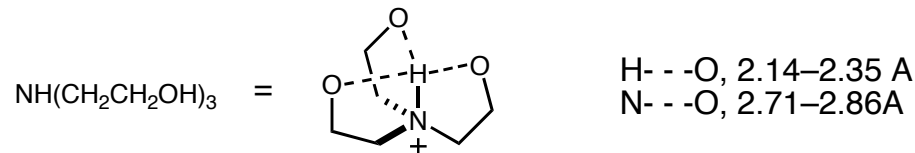
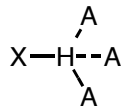
Three centered hydrogen bonds or bifurcated H bond

- most examples are found in biology, especially carbohydrates (~25%) and amino acids (over 25%)



Four centered hydrogen bonds or trifurcated H bond

- Rare, found in molecules that have a high density of donors and acceptors
- Also found in biology



Hydrogen bond energies

■ Energies for some gas phase dimers

Dimer	Energy (kcal/mol)
$[\text{F}-\text{H}-\text{F}]^-$	39
$[\text{H}_2\text{O}-\text{H}-\text{OH}_2]^+$	33
$[\text{H}_3\text{N}-\text{H}-\text{NH}_3]^+$	24
$[\text{OH}-\text{H}-\text{OH}]^-$	23
$\text{H}_4\text{N}^- \cdots -\text{OH}_2$	19
$\text{H}_4\text{N}^- \cdots -\text{Bn}$	17
$\text{HOH}^+ \cdots -\text{Cl}$	13.5

- strong H bonds, HOH- - -Cl is
borderline

Dimer	Energy (kcal/mol)
$\text{COOH}^- \cdots -\text{OCOH}$	7.4
$\text{HOH}^- \cdots -\text{OH}_2$	4.7–5.0
$\text{NCH}^- \cdots -\text{OH}_2$	3.8
$\text{HOH}^- \cdots -\text{Bn}$	3.2
$\text{F}_3\text{C}^- \cdots -\text{OH}_2$	3.1
$\text{MeOH}^- \cdots -\text{Bn}$	2.8
$\text{NH}_3^- \cdots -\text{Bn}$	2.2
$\text{HCCH}^- \cdots -\text{OH}_2$	2.2
$\text{HSH}^- \cdots -\text{H}_2\text{S}$	1.0
$\text{H}_2\text{CCH}_2^- \cdots -\text{OH}$	1.1
$\text{CH}_4^- \cdots -\text{FCH}_3$	0.2

-moderate to weak hydrogen bonds

■ Comparing to other covalent BDE

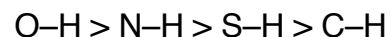
$\text{H}_2\text{C}=\text{CH}_2$	<u>BDE</u>	171	$\text{HO}-\text{OH}$	<u>BDE</u>	51
$\text{Me}-\text{H}$	105	$\text{t-BuO}-\text{Ot-Bu}$	38		
$\text{Ph}-\text{I}$	65	$\text{I}-\text{I}$	36		
$\text{Et}-\text{I}$	53				

- the strongest H bonds start to take on a covalent nature!

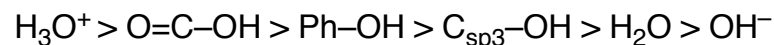
Donor/Acceptor Strengths

■ Relative donor strengths

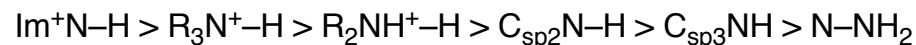
- General rule: donor strength is increased by neighboring electron-withdrawing groups and decreased by electron donating groups



oxygen subclass



nitrogen subclass



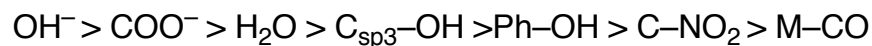
carbon subclass



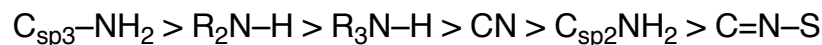
■ Relative acceptor strengths

- General rule: acceptor strength is increased by neighboring electron-donating groups and decreased by electron withdrawing groups

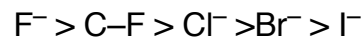
oxygen subclass



nitrogen subclass



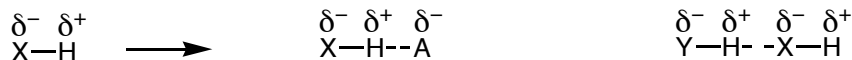
halogen subclass



- These trends are highly dependent on acceptor/donor pairings

Other interesting characteristics

■ Cooperativity



- Charges flow through the X–H sigma bonds. The net result is an overall strengthening of both sigma bonds by ~ 20%
- This effect drives the clustering of polar groups (e.g. carbohydrates)
- Anticooperativity

■ Donor directionality

- the main feature distinguishing a H bond from van der Waals interaction is its preference for linearity
- degree of directionality depends on polarity of donor, $\text{O}-\text{H} > \text{C}\equiv\text{H} > \text{C}=\text{CCH}_2 > \text{CH}_3$

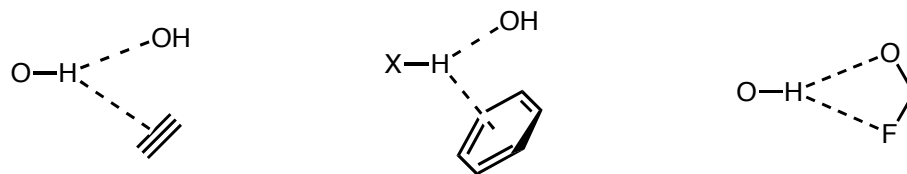
■ Acceptor directionality

- for strong hydrogen bonds, the direction is the same as if a hypothetical proton transfer reaction occurred



- rule of thumb: the electron density on oxygen and nitrogen are diffuse enough that linear geometries are favored

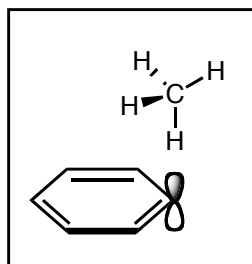
■ Mixed strong/weak interactions



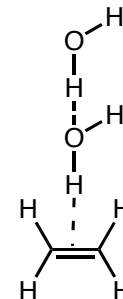
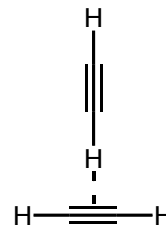
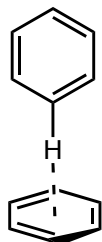
- difficult to assess structural importance

The CH – π interaction – a weak hydrogen bond

■ Intermolecular properties

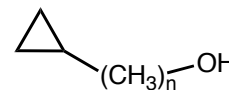
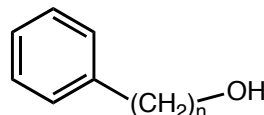
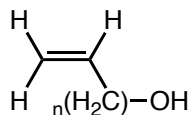


stabilized 2–4 kcal/mol



acceptor substituent effects: $\text{Cl} < \text{D} < \text{CD}_3 < p^-(\text{CD}_3)_2 < \sigma^-(\text{CD}_3)_2 < (\text{CD}_3)_6$ for $\text{C}_6\text{H}_6\text{-nX}_n/\text{CHCl}_3$
 donor substituent effects: $\text{NO}_2 < \text{Br} < \text{Cl} < \text{H} < \text{Me} < \text{NH}_2$ for $\text{C}_6\text{H}_6/\text{CH}_3\text{C}_6\text{H}_4\text{Y}$

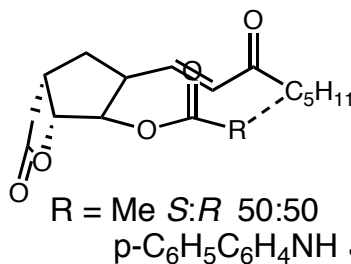
■ Intramolecular properties



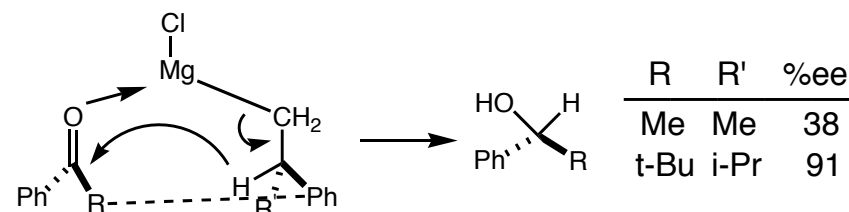
$n = 1, 2$ in most cases

acceptor substituent effects: $\text{NO}_2 < \text{Br} < \text{Cl} < \text{H} \sim \text{Et} < \text{Me} < \text{NH}_2$
 donor substituent effects: $\text{CO}, \text{NMe}, \text{O}$, for $\text{C}_6\text{H}_5\text{CH}_2\text{XCHMe}_2$

■ Reactivity effects



Corey, E. J. *et al.* *J. Am. Chem. Soc.* **1972**, *94*, 8616.



Mosher, H. S. *et al.* *J. Org. Chem.* **1964**, *29*, 37.

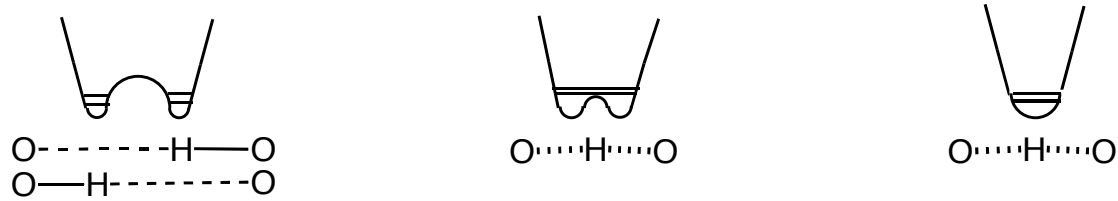
- remote functionalization reactions, diastereofacial and enantiofacial selectivity are all possible

Nishio, M. *et al.* *The CH/ π Interaction Evidence, Nature and Consequences*, Wiley-VCH, Inc., New York, **1998**.

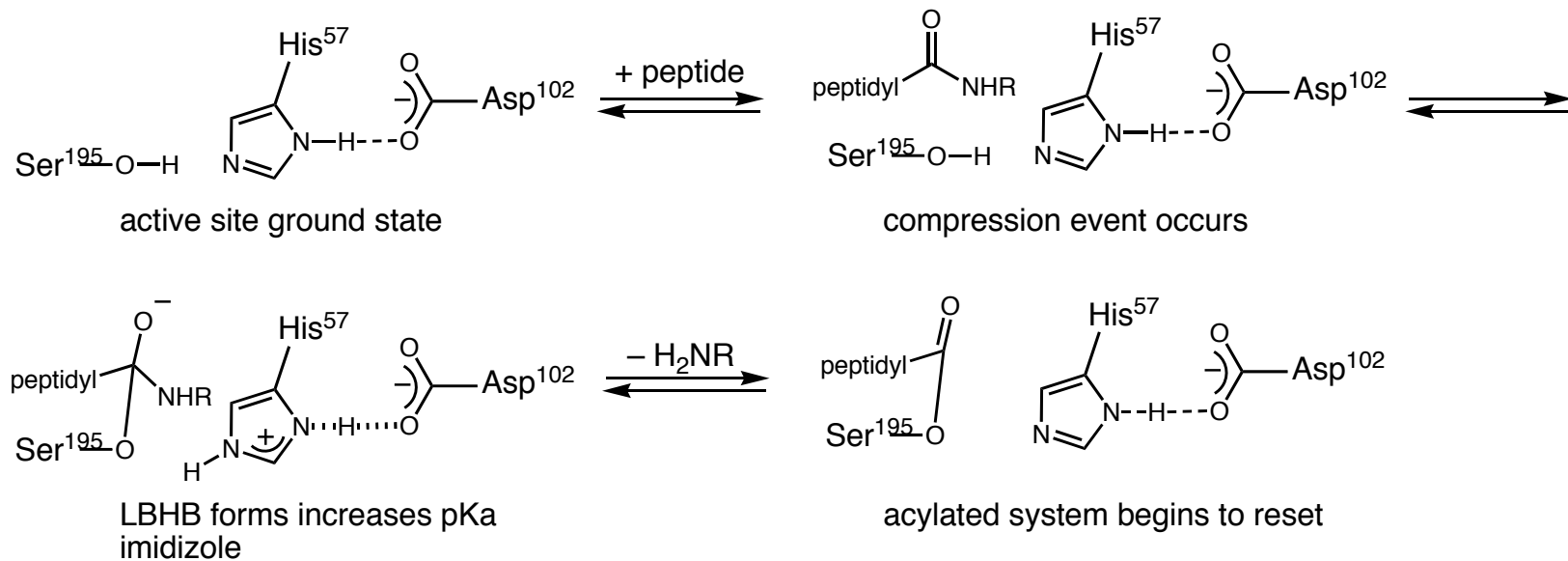
The low barrier hydrogen bond in enzymes

General characteristics

- basically the same as a strong hydrogen bond
- enzymes modulate the pKa of a substrate to match that of the amino acid residue to which it is bonded



Chymotrypsin, a serine protease, and its weak hydrogen/LBHB catalytic cycle

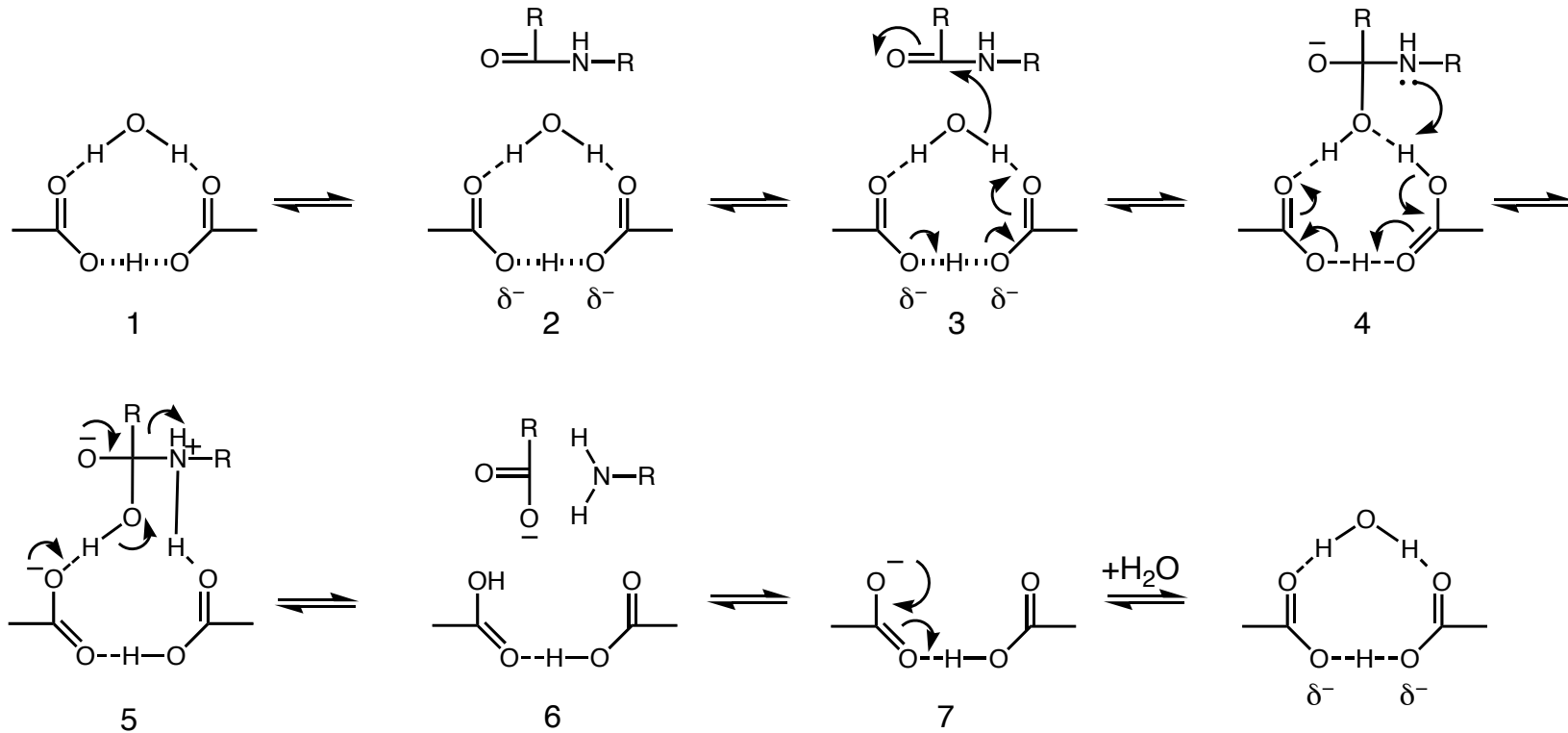


Cleland, W. W. *et al. J. Bio. Chem.* **1998**, 273, 25529.

Cleland, W. W. *Arch. Biochem. Biophys.* **2000**, 382, 1.

Long before round bottom flasks, enzymes roamed the earth

■ Hydrogen bonded scaffold acts as catalytic site for protease activity



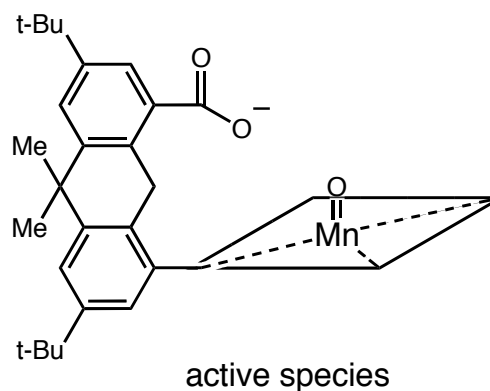
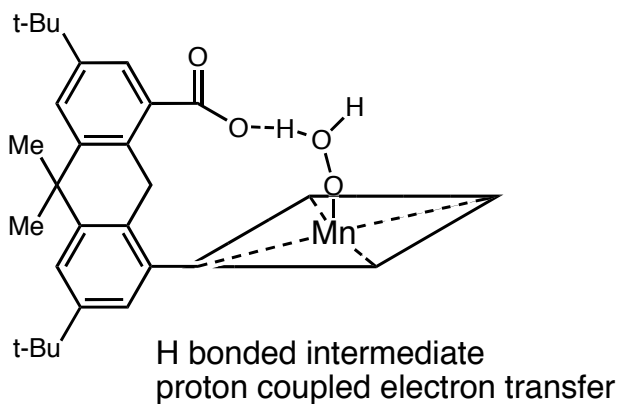
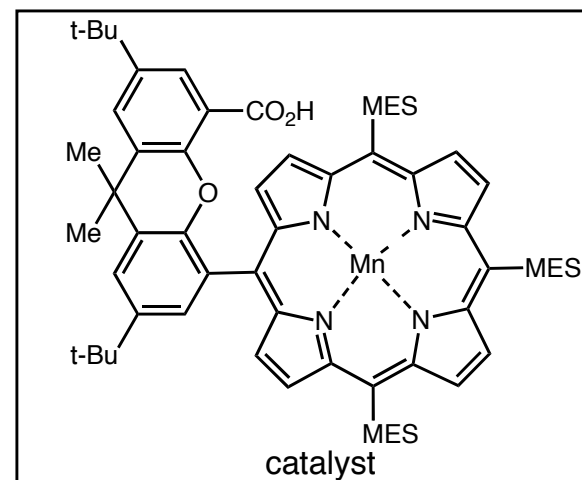
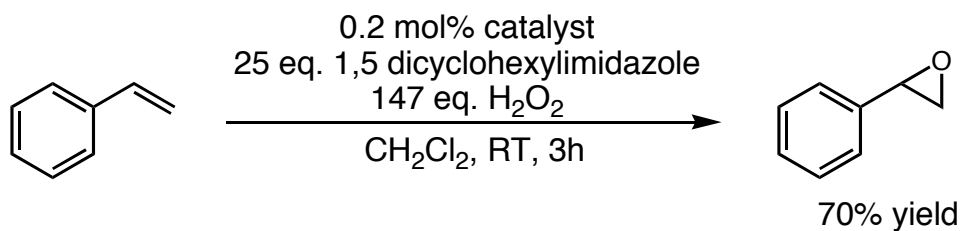
- compounds 1–3 each contain low barrier hydrogen bond.
- electron flow model theory
- LBHB theory
- Alzheimer β -secretase/HIV

Bachovchin, W. W. *et al. Science* **1997**, 278, 1128.

Northrop, D. B. *Acc. Chem. Res.* **2001**, 34, 790.

An example of enzyme mimicry—chemists are learning how to use H bonds

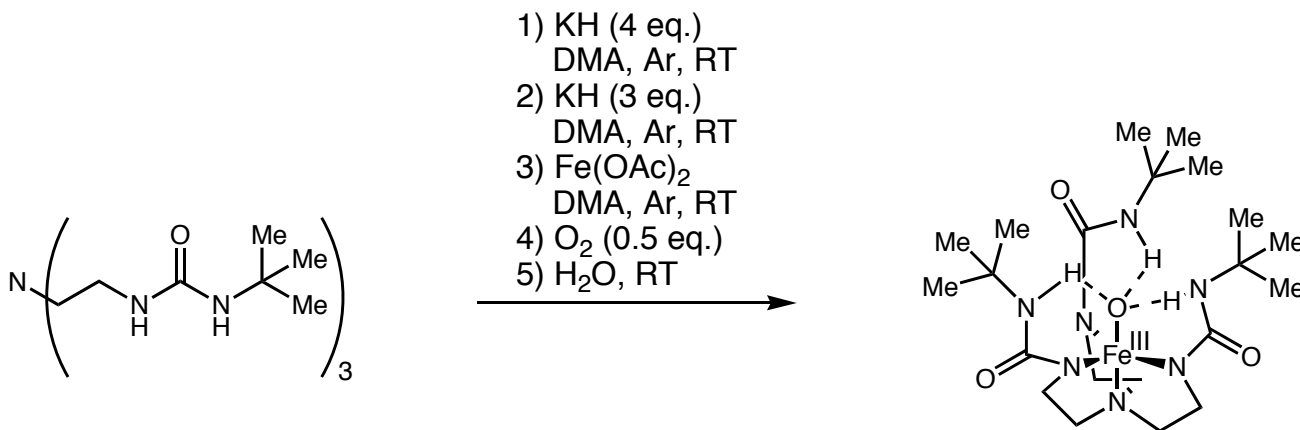
■ A porphyrin-esque approach towards H_2O_2 activation



- Control experiments indicate complex greatly increases rate of epoxidation
- Did not completely rule out any free radical degradation pathways

A non-heme example of O_2 activation

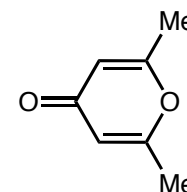
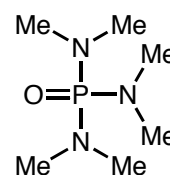
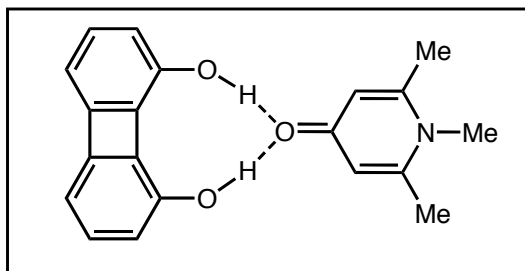
- The first reported example of an iron complex activation of molecular oxygen



- Homolysis of the O_2 bond creates the high spin Fe-oxo species
- Produces a crystallizable-stable oxygen radical species, stabilized by hydrogen bonding
- Compare this to similar cytochrome p450 species that oxidize C-H bonds via similar intermediates

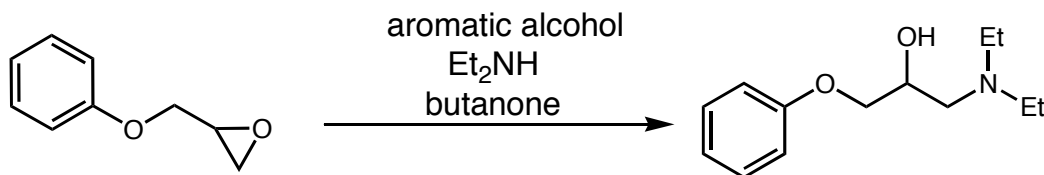
Hine and co-workers develop the first hydrogen bond activated reaction

- The initial idea was based on stable hydrogen bonded crystal structures



- The aryl groups of both donor and acceptor are planar.
- A comparison of 1,8-biphenylenediol (pKa = 8.01) to *m*-nitrophenol (pKa = 8.36) indicated the diol bound 50 x's stronger.

- Rate studies provide convincing proof of a stable hydrogen bond catalyst



catalyst	$10^5 k_c, M^{-2}s^{-1}$	pKa
phenol	6.0	9.99
p-Cl-phenol	7.7	9.41
m-Cl-phenol	8.2	9.12
m-nitrophenol	14.3	8.36
p-cyanophenol	15.3	7.97
p-nitrophenol	17.0	7.15
catechol	11.9	9.36
1-biphenylenol	11.5	8.64
8-methoxy-1-biphenylenol	7.3	9.15
1,8-biphenylenediol	75	8.01

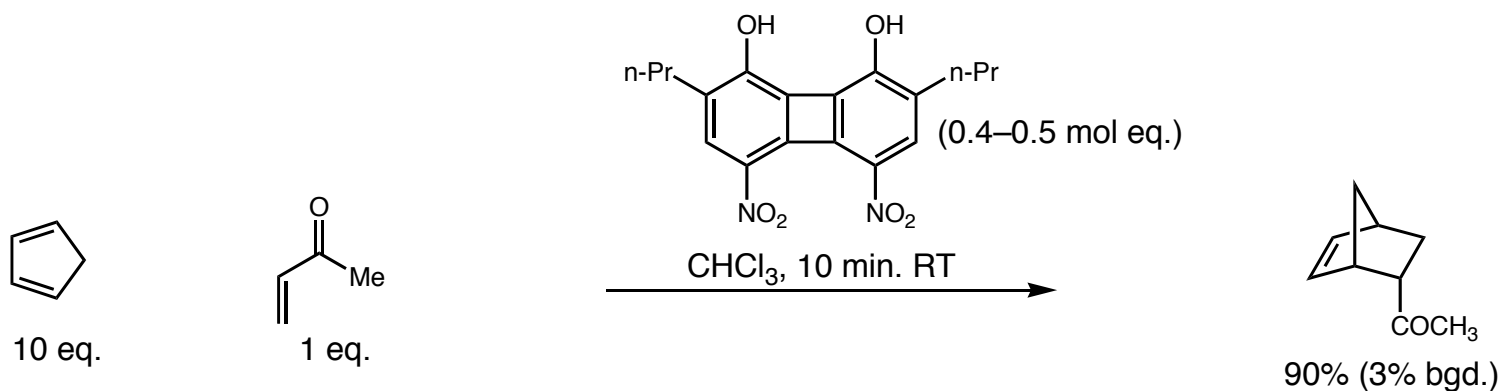
- The only yield reaction was set-up using 57 mol% catalyst and provided the product, after 15 days at 35 °C, in 86% yield.

- used 3.75 eq. catalyst

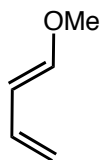
Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2083.
Hine, J. *et al. ibid.* **1985**, *50*, 5096.

Application of Hine's discovery

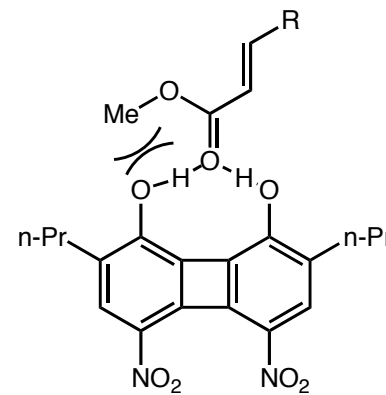
■ Kelly catalyzes the Diels Alder reaction



- Other dienes: 2,3-dimethylbutadiene, 1-methoxybutadiene
- Other dienophiles: acrolein, 2-methylacrolein, 3-methylacrolein, 3-phenyl acrolein, methylacrylate
- Esters and methoxydienes work poorly.



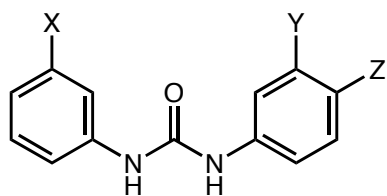
- The methoxy substituent competes with aldehydes for H bonding



Kelly, T. R. *et al. Tet. Lett.* **1990**, *31*, 3381.

Another conceptual step leads to a hydrogen bonding framework

■ A purely crystallographic analysis of urea scaffold/carbonyl structures



<u>X</u>	<u>Y</u>	<u>Z</u>
NO ₂	NO ₂	H
CF ₃	CF ₃	H
NO ₂	H	H
NO ₂	H	NO ₂

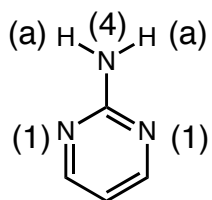
- Finds that ortho EWG's have most prominent effect and may induce aryl-H/CO bonding.

Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896.

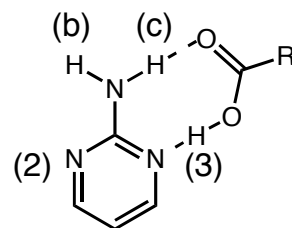
■ A set of rules for predicting H-bond in various molecules is proposed

Some more interesting facets:

- Six membered intramolecular H bond structures are preferred over intermolecular bonding.
- After six membered ring bonding, the remaining H donating/accepting groups interact.
- 2-aminopyrimidine as an illustrative example.



proton accepting ability
N1 > N2 > acid carbonyl > N3 = N4

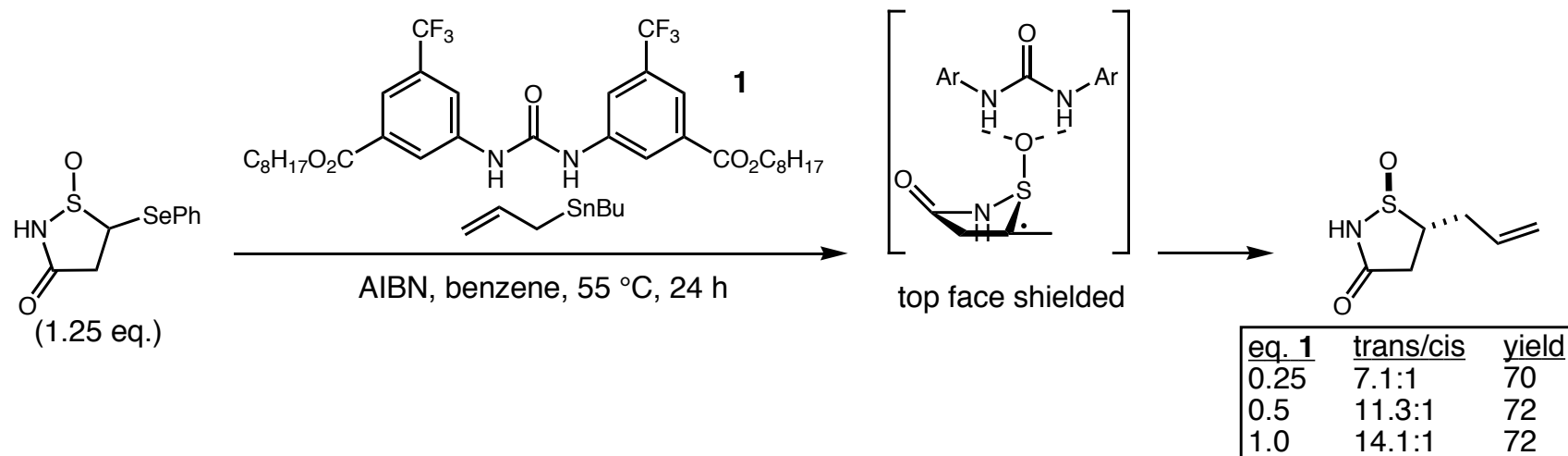


proton donating ability
OH (acid) > H_a > H_b > H_c

Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.

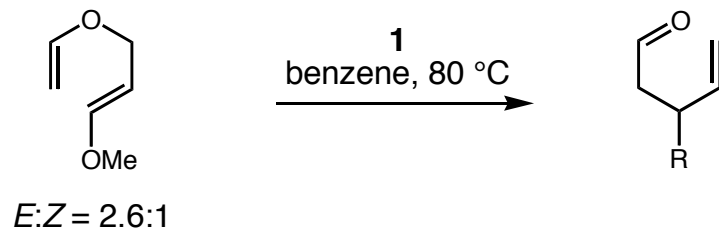
Two mechanistically different reactions, same H bond manifold

Free radical allylation



Curran, D. P.; Kuo L. H. *J. Org. Chem.*, **1994**, *59*, 3259.

Kinetic studies indicate H bonding accelerates the Claisen rearrangement

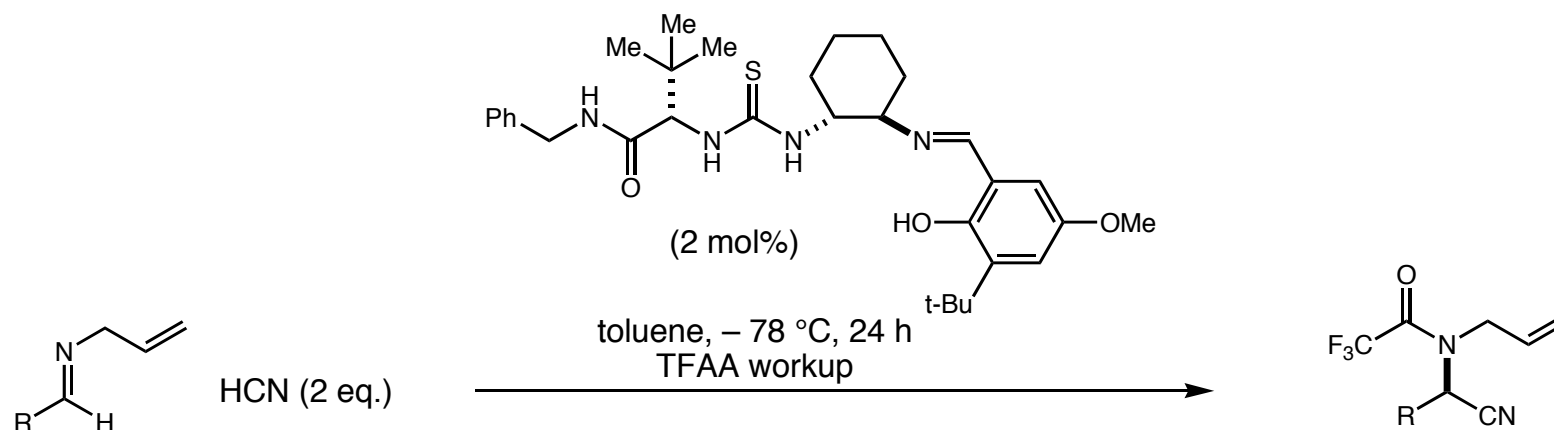


catalyst	eq.	k_{rel}
1	0	1
1	0.1	2.7
1	0.4	5.0
1	1.0	22.4
thiourea	1.0	3-4
DMSO	5 eq.	1.9
DMSO + 1	5eq, 1eq	1.3

Curran, D. P.; Kuo, L. H. *Tet. Lett.* **1995**, *36*, 6647

Jacobsen develops the most efficient and broadly used scaffold to date

- Parallel library generated catalysts to effect the Strecker reaction were screened to provide the thiourea scaffold



- The original goal of the catalyst screen was to incorporate metal binding sites on the scaffold.
- Jacobsen, "a sequence of nonobvious modifications in the catalyst structure."

R	yield (%)	ee (%)
Ph	78	91
<i>p</i> -OCH ₃ C ₆ H ₄	92	70
<i>p</i> -BrC ₆ H ₄	65	86
2-naphthyl	88	88
<i>t</i> -butyl	70	85
<i>c</i> -hexyl	77	83

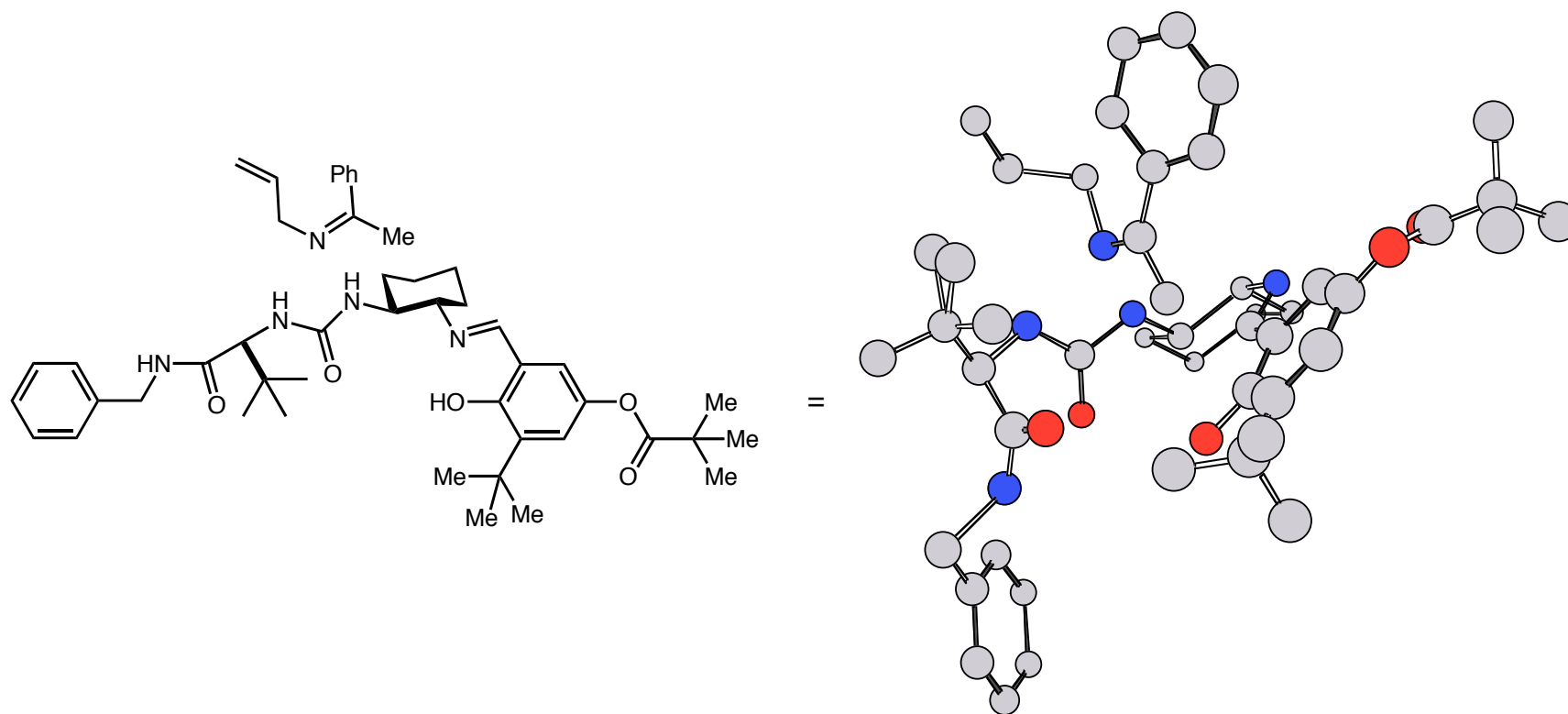
Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* 2000, *39*, 1279. (for substrate scope)

Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407. (for some examples of thiourea catalyzed Diels Alder reactions)

Origins of selectivity in the catalyzed Strecker reaction

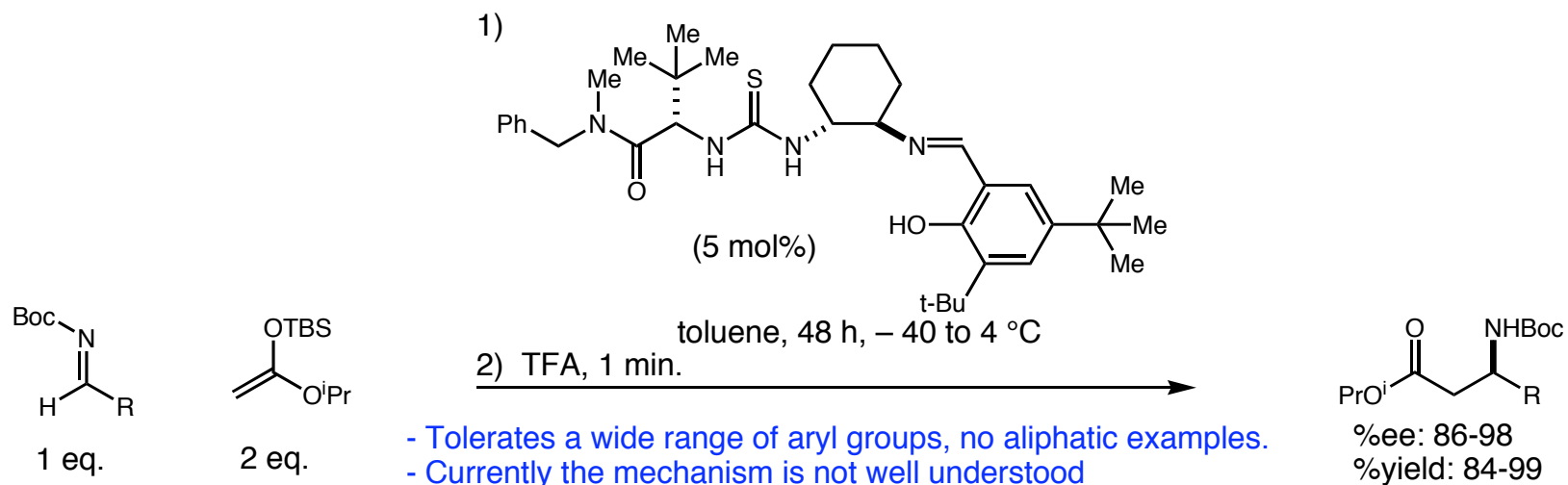
- NMR solution structure and MOLMOL modelling lead to a set of selection rules



- Determined that only the Z-isomer binds the catalyst and is bridged by the urea nitrogens.
- Large groups are directed into solvent.
- The small group is placed directly into the catalyst.
- The N-substituent is directed away from the catalyst.

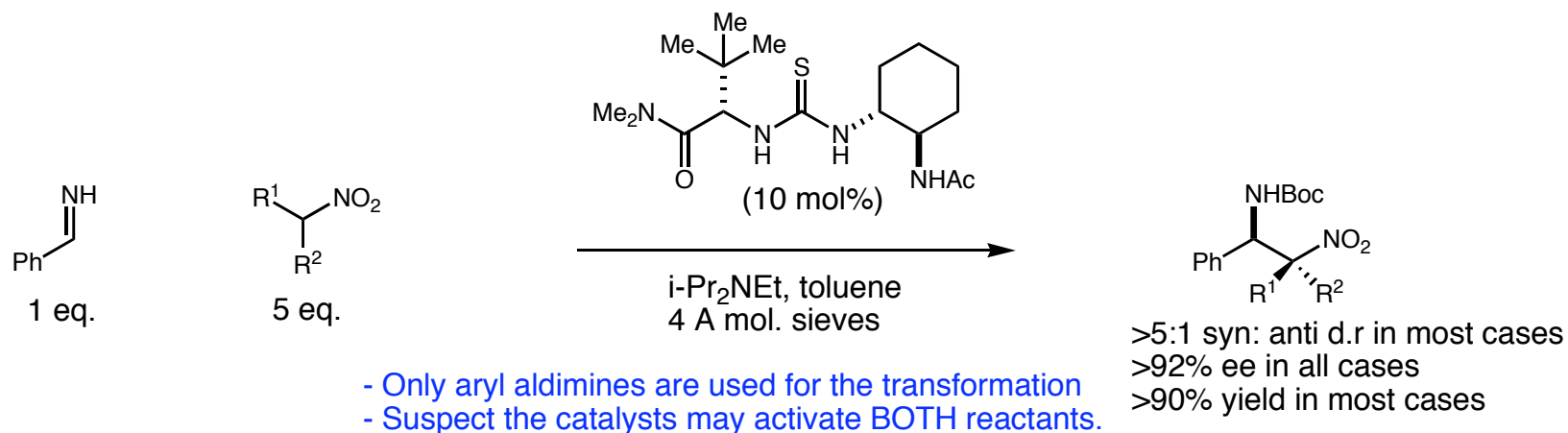
Jacobsen extends this technology towards other transformations

■ Synthesis of B-aryl, B-amino acids via asymmetric Mannich reactions



Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

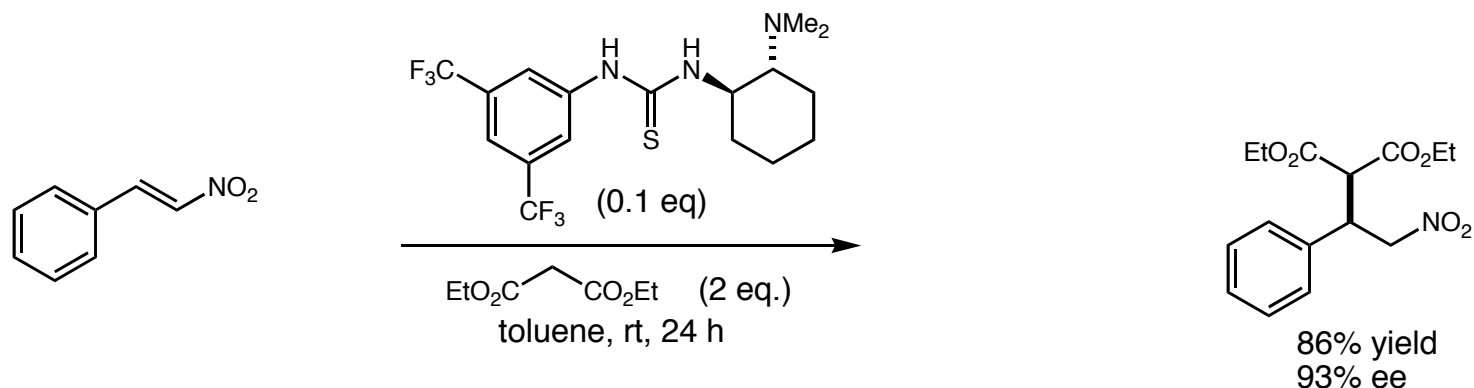
■ Nitro-Mannich reaction



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

Other carbon-carbon bond forming reactions catalyzed by the thiourea scaffold

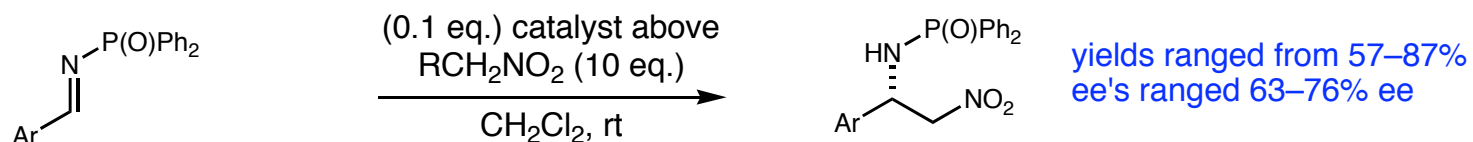
■ Takemoto develops the Michael reaction of malonates and nitroolefins



- aromatic olefins give the best yields and ee in most cases.
- aliphatic olefins give decent yields but lower ee. (81% ee in both examples)

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

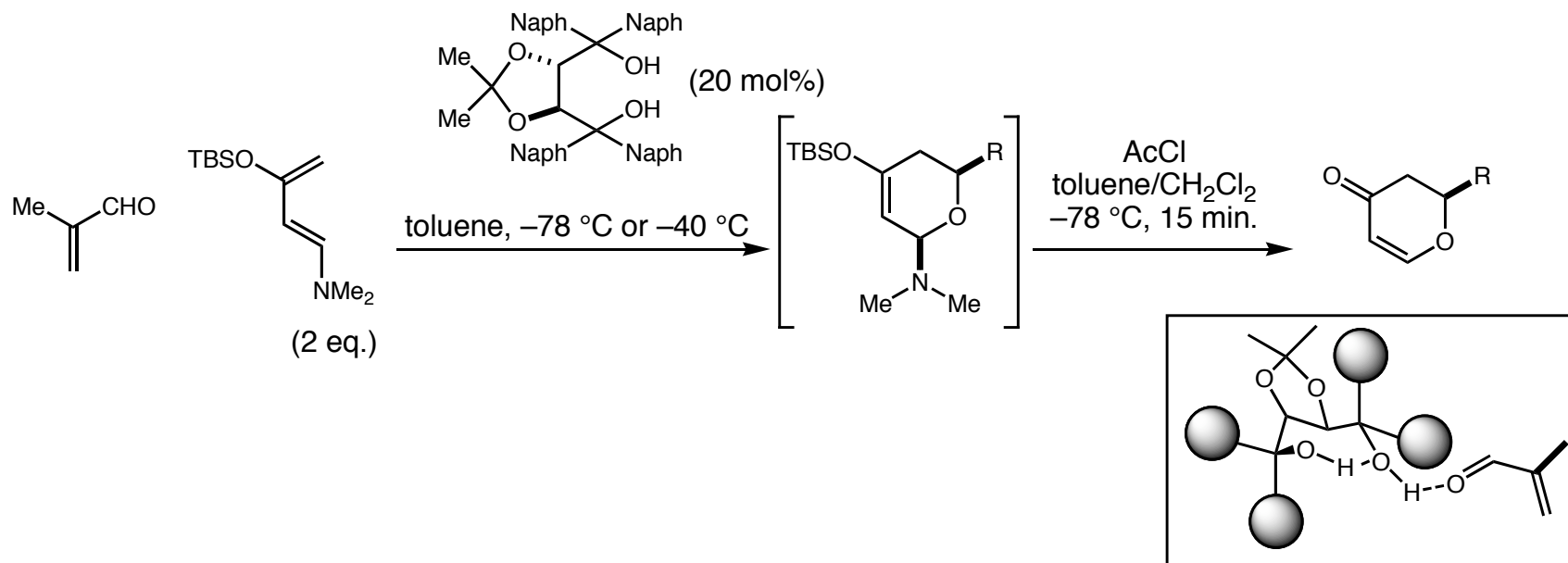
■ Another variant of the Mannich reaction



Takemoto, Y. *et al.* *Org. Lett.* **2004**, *6*, 625.

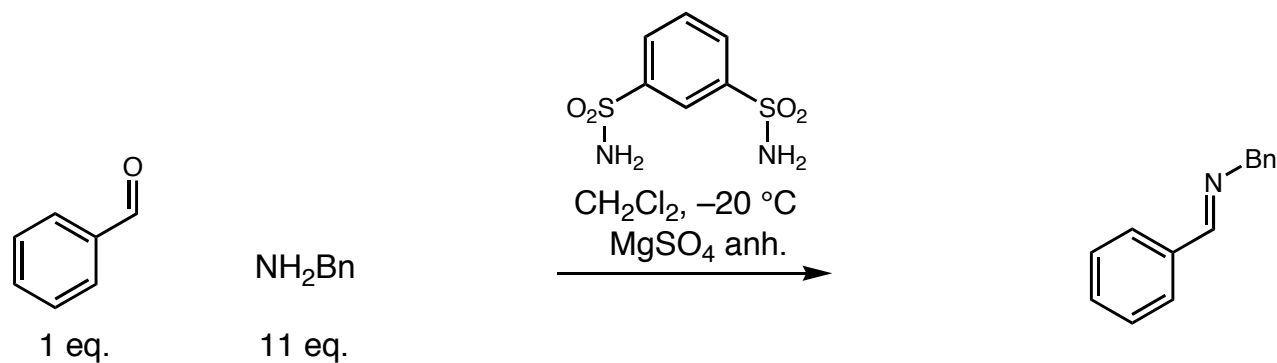
One well known and one not-so-well-known H bond reaction

Rawal's TADDOL catalyzed Diels Alder cycloaddition



Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *1124*, 9662.
Rawal, V. H. et al. *PNAS*, **2004**, *101*, 5846.

Preparation of imines

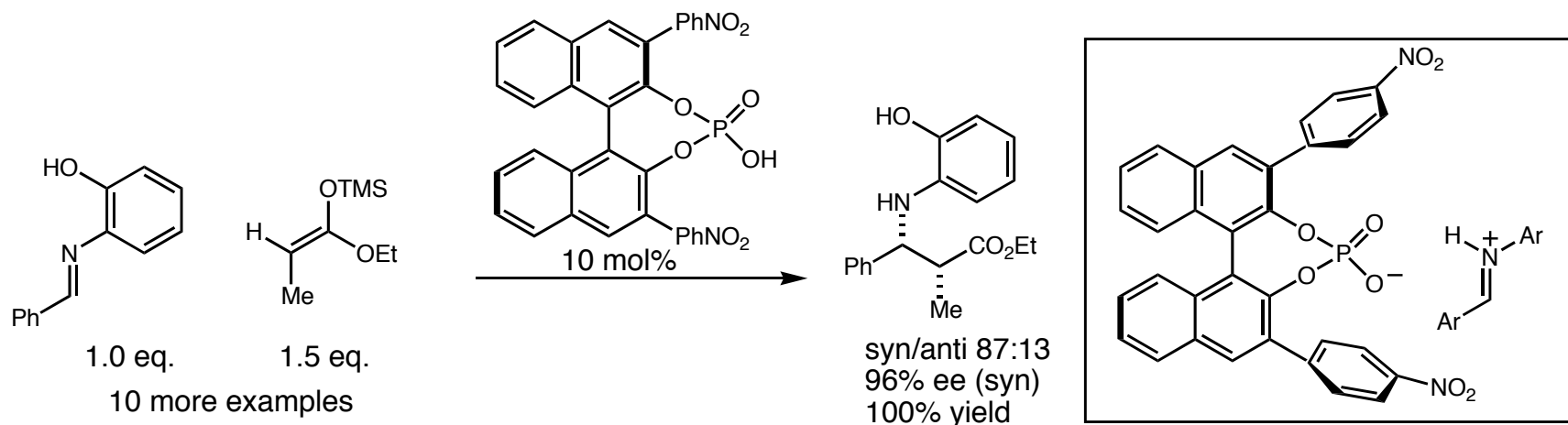


- Only rate of catalyst acceleration was probed.

Crabtree, R. H. et al. *Chem. Commun.*, 1999, 2109.

Chiral Bronsted Acid Catalysis

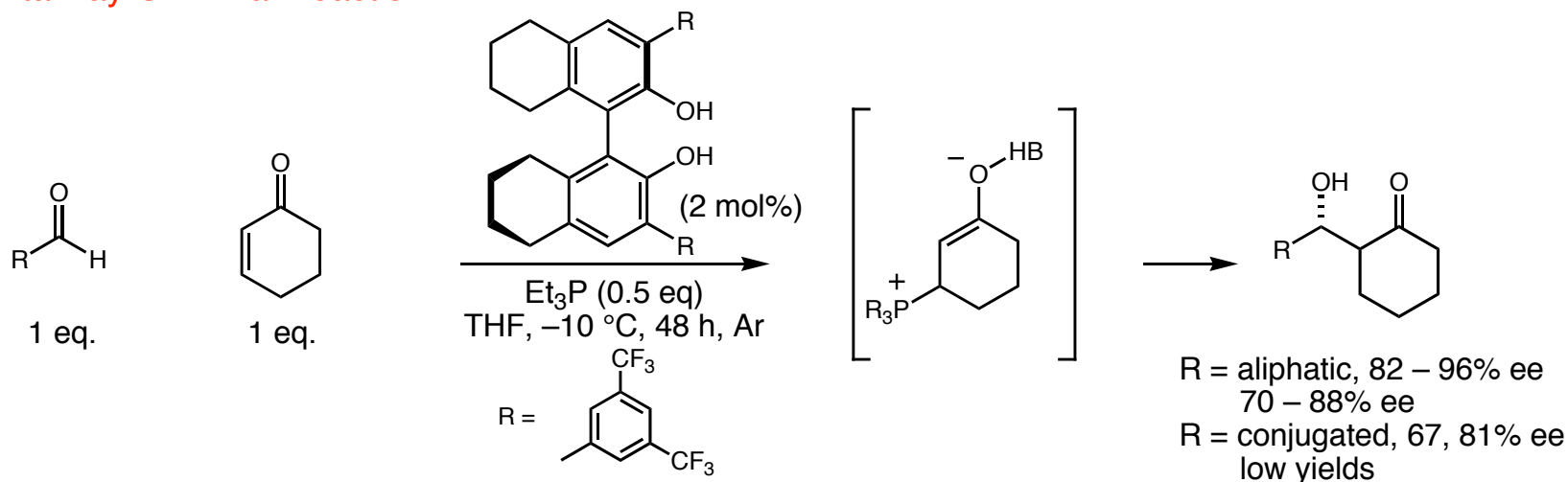
Mannich type reaction



- Only aromatic aldimines are used
- All the yields were high, as was syn/anti selectivity.
- ee's ranged from 81% – 96%

Akiyama, T. *et al. Angew. Chem. Int.* **2004**, *43*, 1566.

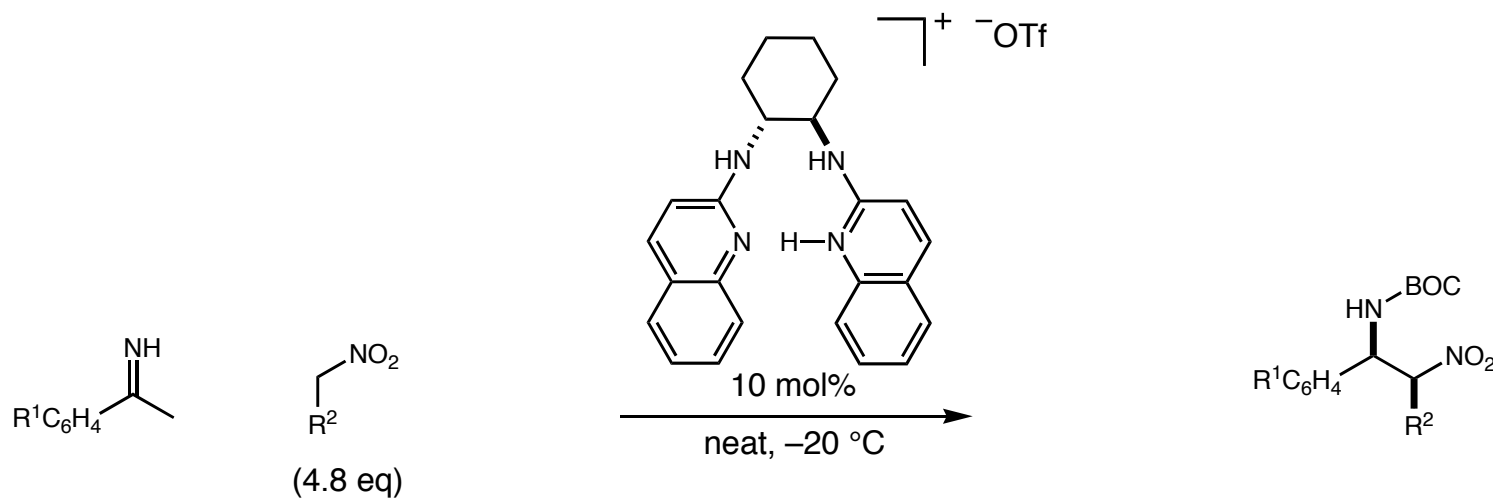
Morita-Baylis-Hillman reaction



Schaus, S. E.; McDougal, N. T. *J. Am. Chem. Soc.* **2003**, *125*, 12094.

Chiral Bronsted Acid Catalysis

■ Aza Henry reaction



- Syn preferred of anti
- Yields range from 51 – 69 %
- mechanism unclear

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

Conclusions

- The hydrogen bond is a fascinating molecule whose theory of interaction needs further development
- A well of chemical reactivity is filled with possibilities
- Theory is not as important as practice
- May be able to exploit a wide range of interactions to develop an asymmetric, catalytic system