# Asymmetric Catalysis by Chiral Hydrogen-Bond Donors

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Current Literature Presentation
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# General Description of Hydrogen-Bond

**Definition:**

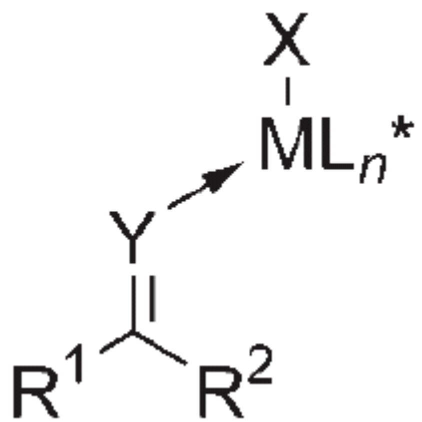
An ***XH···A*** interaction is called a "***hydrogen bond***", if ***1***. it constitutes a local bond, and **2**. XH acts as a proton donor to A.

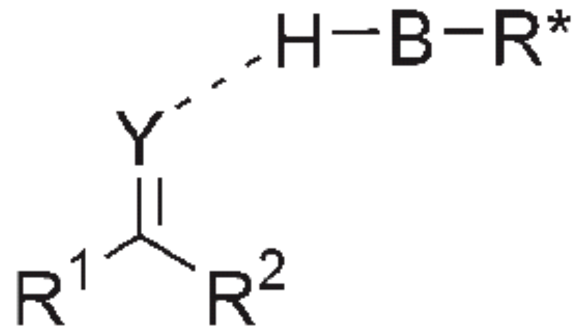
**Hydrogen-bond phenomena:**

- **In structural determination:**
  1. The unusual and complex properties of bulk water;
  2. The ability of proteins to fold into stable three-dimensional structures;
  3. The fidelity of DNA base pairing;
  4. The binding of ligands to receptors.
- **In catalysis:**
  1. Hydrogen bonding to an electrophile serves to decrease the electron density of this species, activating it toward nucleophilic attack. This principle is employed frequently by Nature's catalysts, enzymes, for the acceleration of a wide range of chemical processes.
  2. From late 1990s, organic chemists have begun to appreciate the tremendous
     potential offered by hydrogen bonding as a mechanism for electrophile activation in smallmolecule,synthetic catalyst systems.
  3. In particular, chiral hydrogenbond donors have emerged as a broadly applicable class of catalysts for enantioselective synthesis.

# Generic Electrophile Activation

## —Lewis acid versus Brønsted acid




Highly tunable (**M,X, L***)
Well defined interactions

Somewhat tunable (**Structure of R*B, *p*K$_a$**)
Dominant mechanism in biocatalysis
Loosely defined interactions

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# Properties and catalytic mechanism of H-bond

Properties of H-bond:

| | Strong | Moderate | Weak |
|---|---|---|---|
| type of bonding | mostly covalent | mostly electrostatic | electrostatic |
| length of H-bond [Å] | 1.2–1.5 | 1.5–2.2 | 2.2–3.2 |
| bond angles [°] | 175–180 | 130–180 | 90–150 |
| bond energy [kcal mol$^{-1}$] | 14–40 | 4–15 | $<4$ |
| typical example | intramolecular NH···N bond in conjugate acid of proton sponge | NH···O=C bonds in peptide helices and sheets | bonds involving CH donors to N or O acceptors |

Catalytic mechanism:

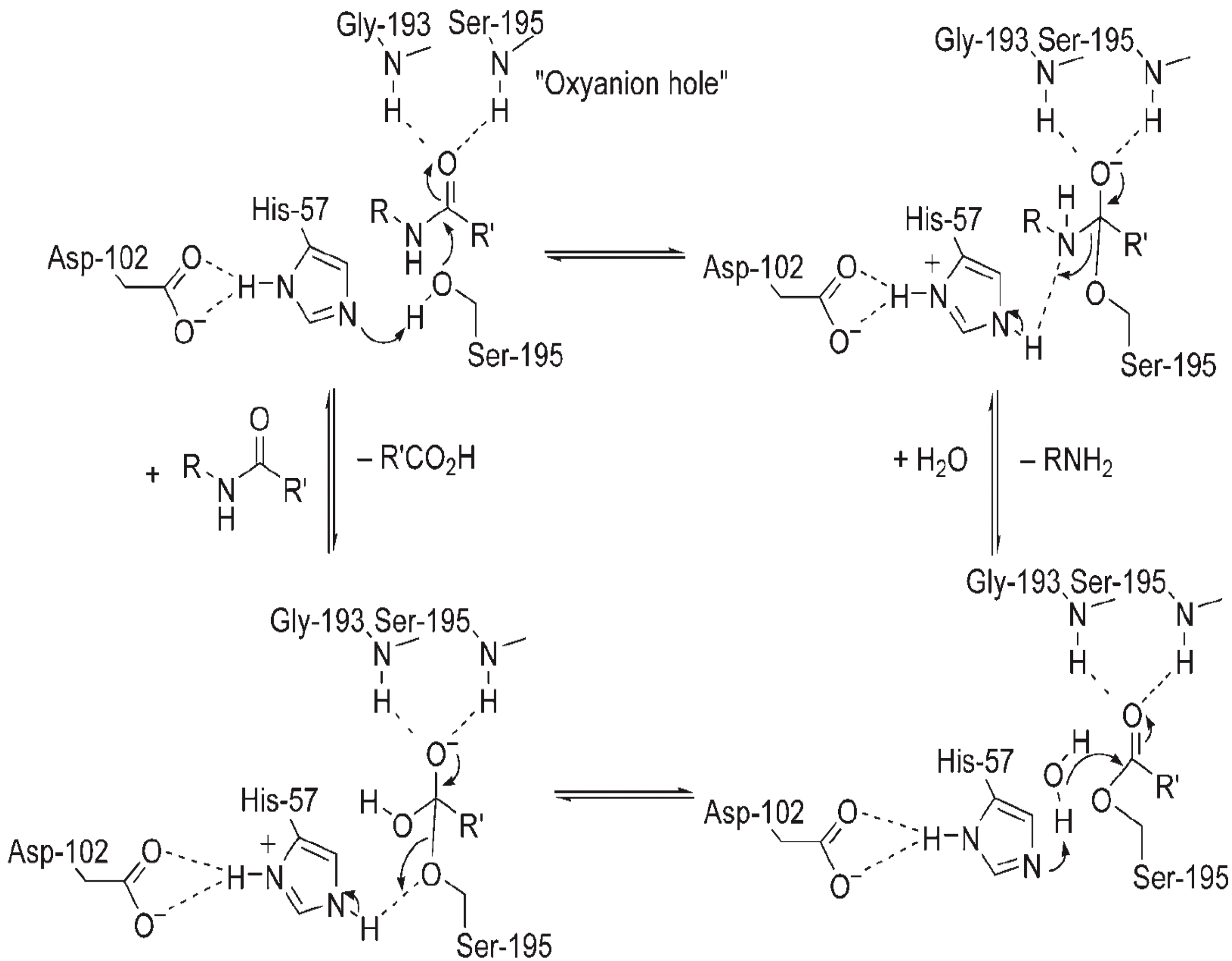
*Specific* acid catalysis: reversible protonation of the electrophile in a pre-equilibrium step prior to nucleophilic attack

*General* acid catalysis: proton transfer to the transition state in the rate-determining step

G.A. Jeffrey, *An Introduction to Hydrogen Bonding. A Theoretical Perspective*, Oxford University Press, Oxford, **1997**.

# Hydrogen Bonding in Biological Catalysis

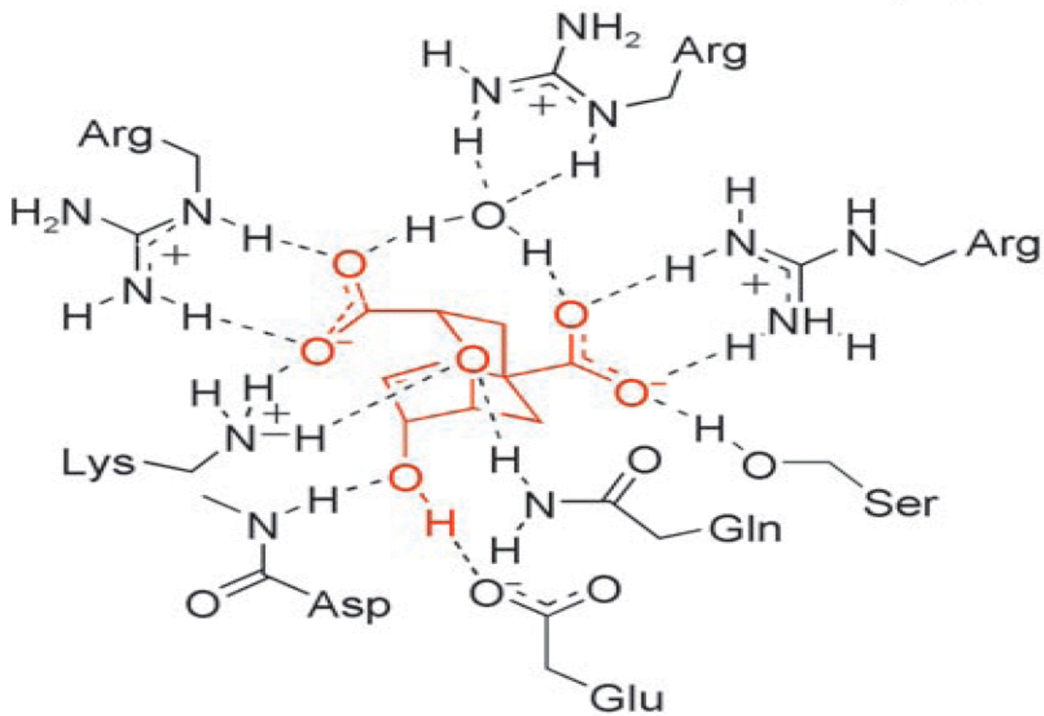
## —An Example of Serine Proteases




C. W. Wharton in *Comprehensive Biological Catalysis, Vol. 1* (Ed.:M. Sinnott), Academic Press, London, **1998**, pp. 345 – 379.

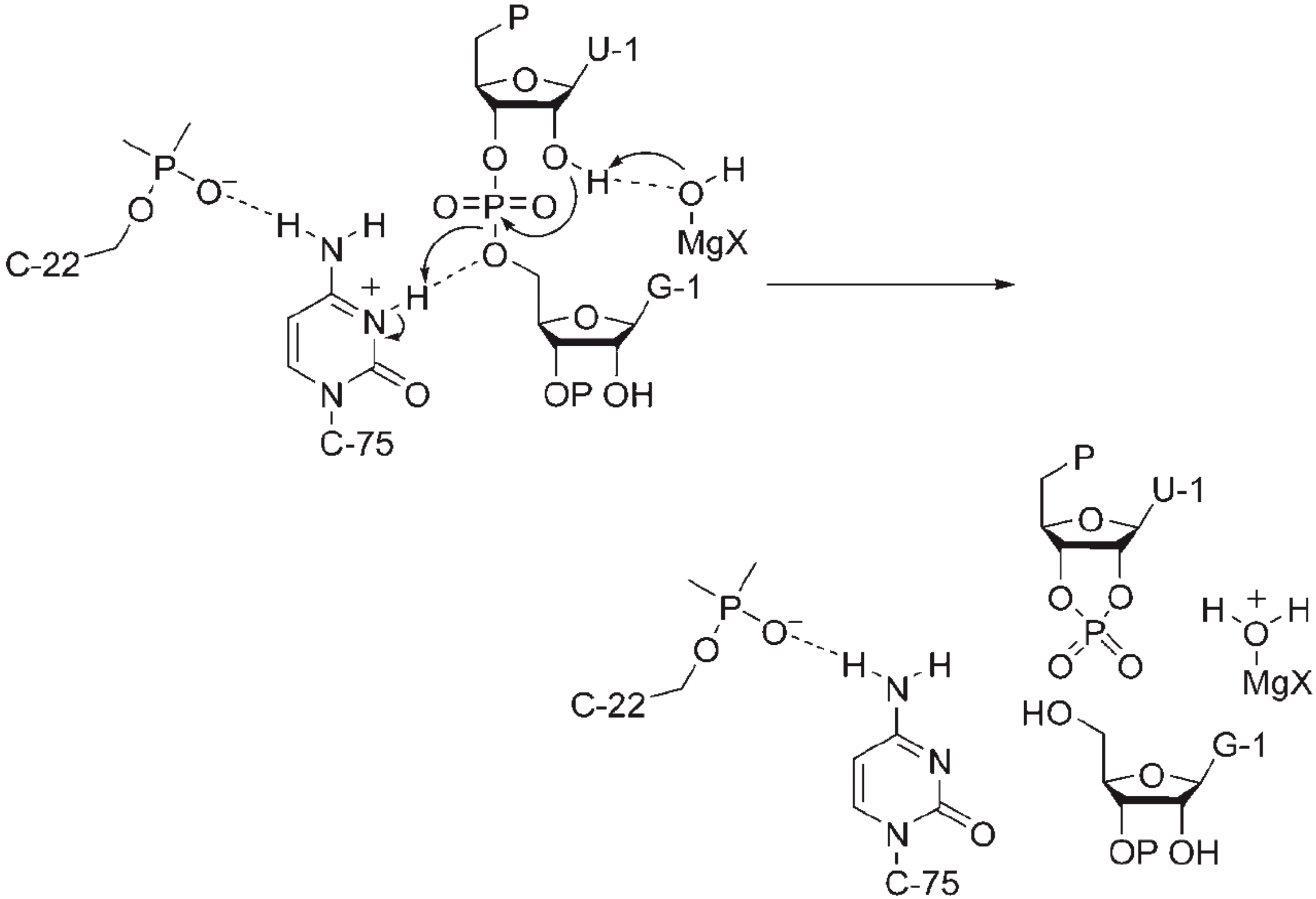
# Hydrogen Bonding in Biological Catalysis
## —An Example of Chorismate Mutase


chorismate prephenate




B. Ganem, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 936 – 945.

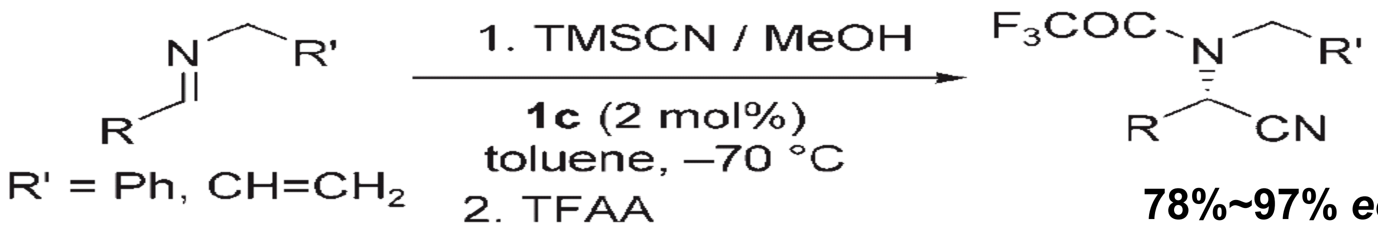
# Hydrogen Bonding in Biological Catalysis
## —An Example of Hepatitis Delta Virus Ribozyme



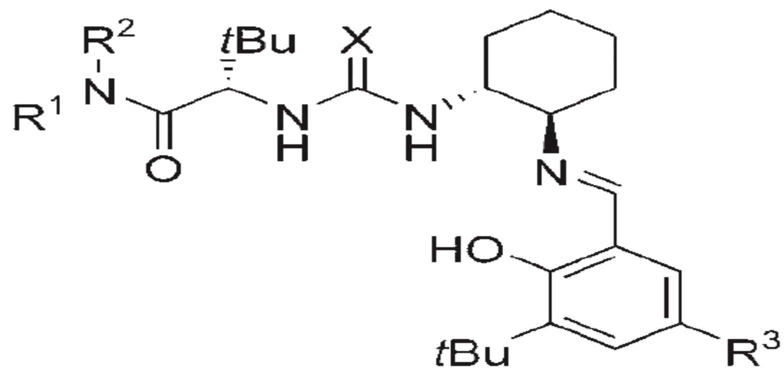

A. R. FerrT-D AmarT, K. Zhou, J. A. Doudna, *Nature* **1998**,395, 567 – 574**.**

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## — Ureas/Thioureas as Double Hydrogen-Bond-Donor Catalysts




**78%~97% *ee***
**65%~99% yield**




**1a**: $R^1$ = Bn, $R^2$ = H, $R^3$ = $OCH_3$, X = S
**1b**: $R^1$ = Bn, $R^2$ = H, $R^3$ = OCO*t*Bu, X = O
**1c**: $R^1$ = $R^2$ = $CH_3$, $R^3$ = OCO*t*Bu, X = S
**1d**: $R^1$ = Bn, $R^2$ = $CH_3$, $R^3$ = *t*Bu, X = S

M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc*. **1998**, 120, 4901 – 4902;
M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed*. **2000**, 39, 1279 – 1281.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

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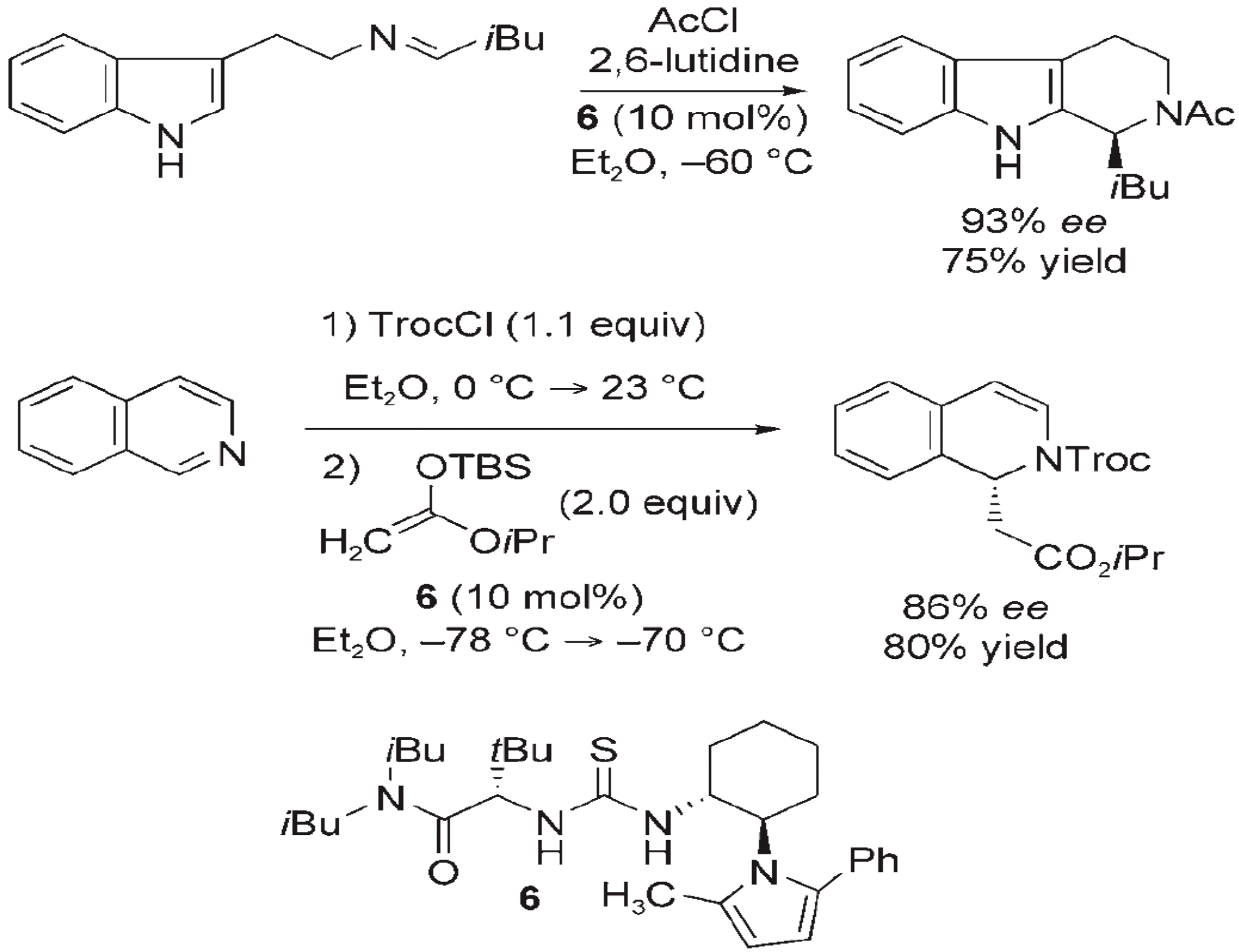
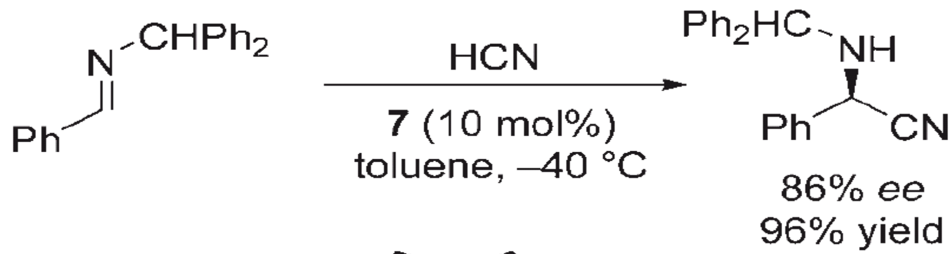
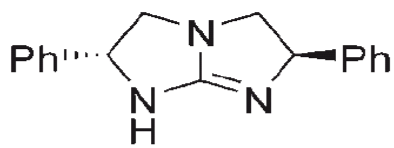



M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, 126, 10558 – 10559.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## —Chiral Guanidinium/Amidinium ion as Double Hydrogen-Bond-Donor Catalysts



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E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, 1, 157 – 160.

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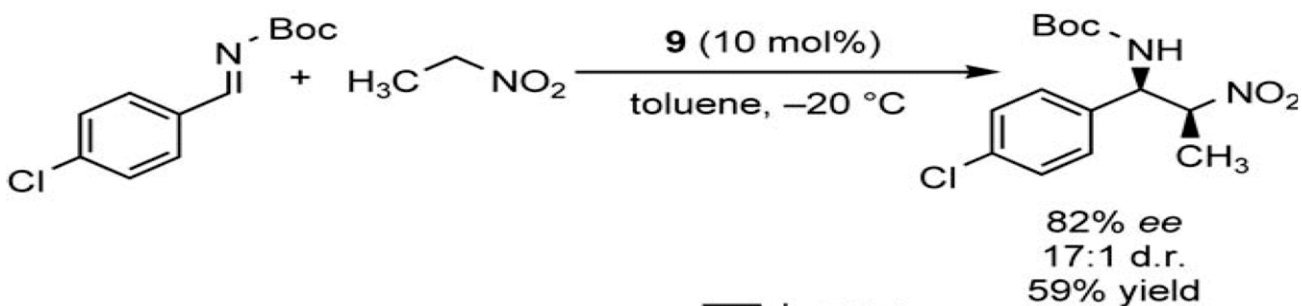


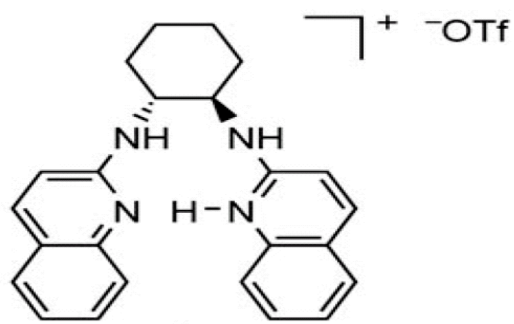

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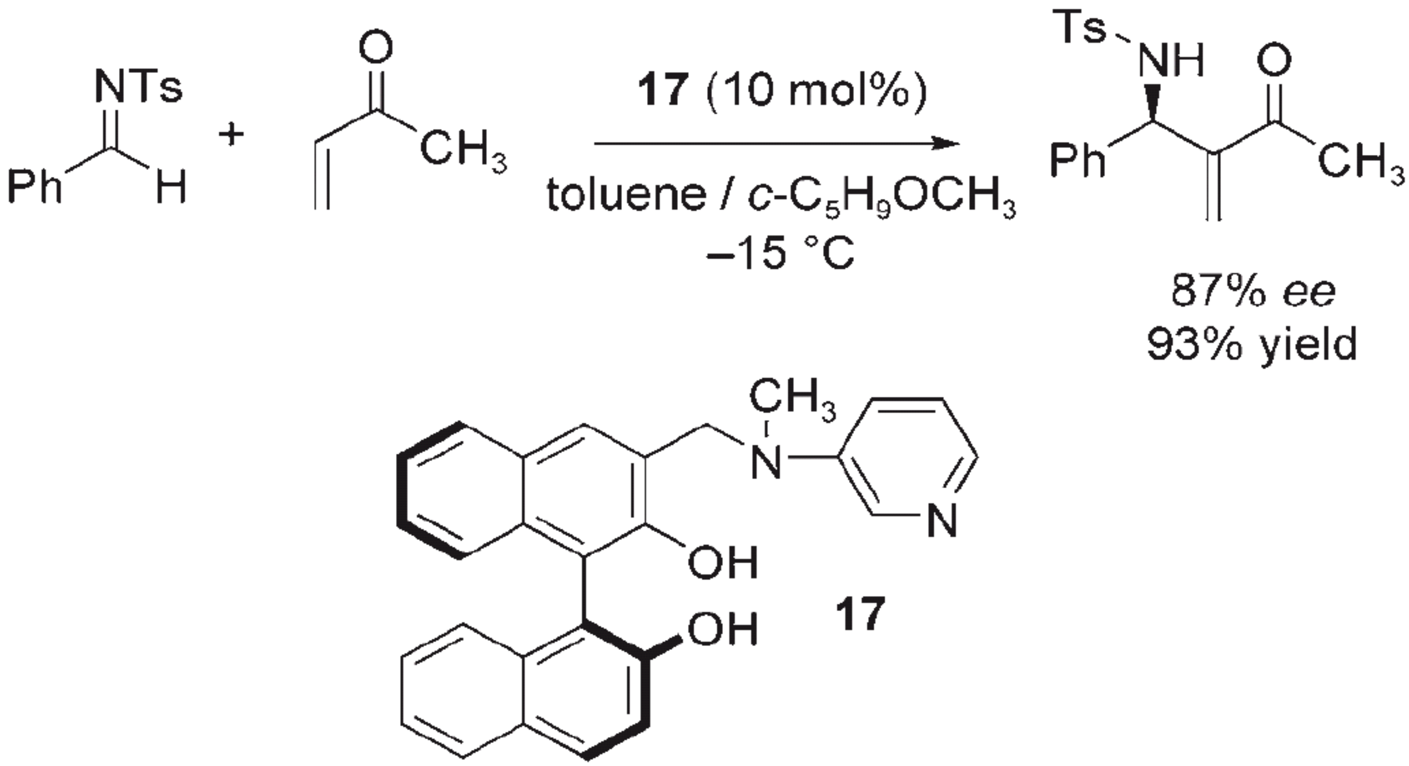
B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, 126, 3418 – 3419.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

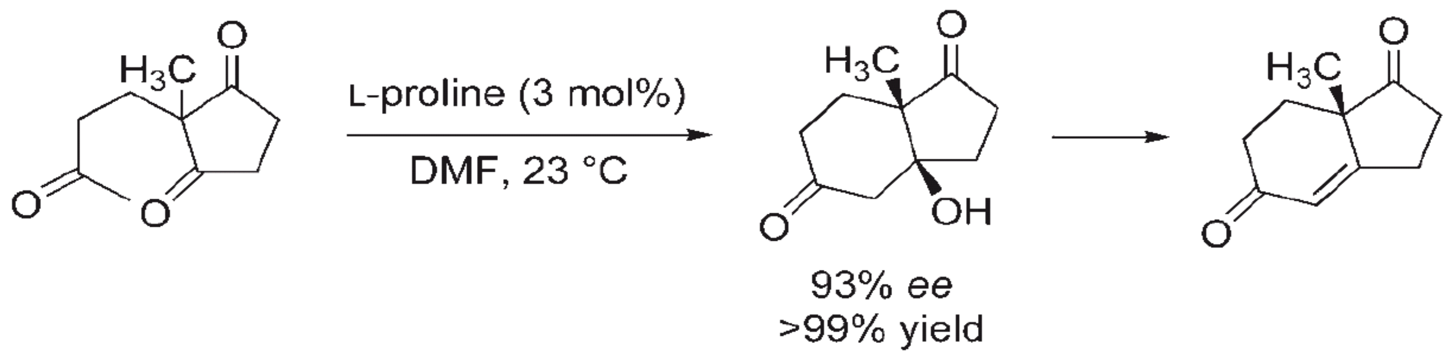
## —BINOL Derivatives as Single Hydrogen-Bond-Donor Catalysts

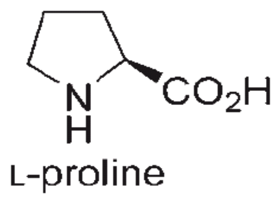


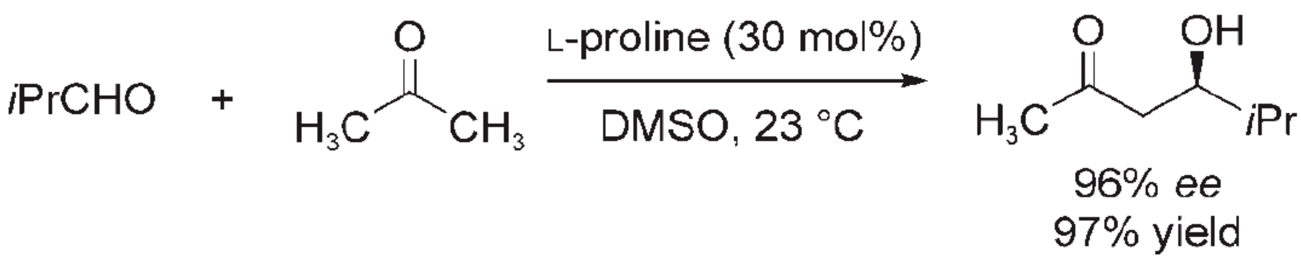

K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc*. **2005**, 127,3680 – 3681.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## —Proline Derivatives as Bifunctional Hydrogen-Bond Donor Catalysts



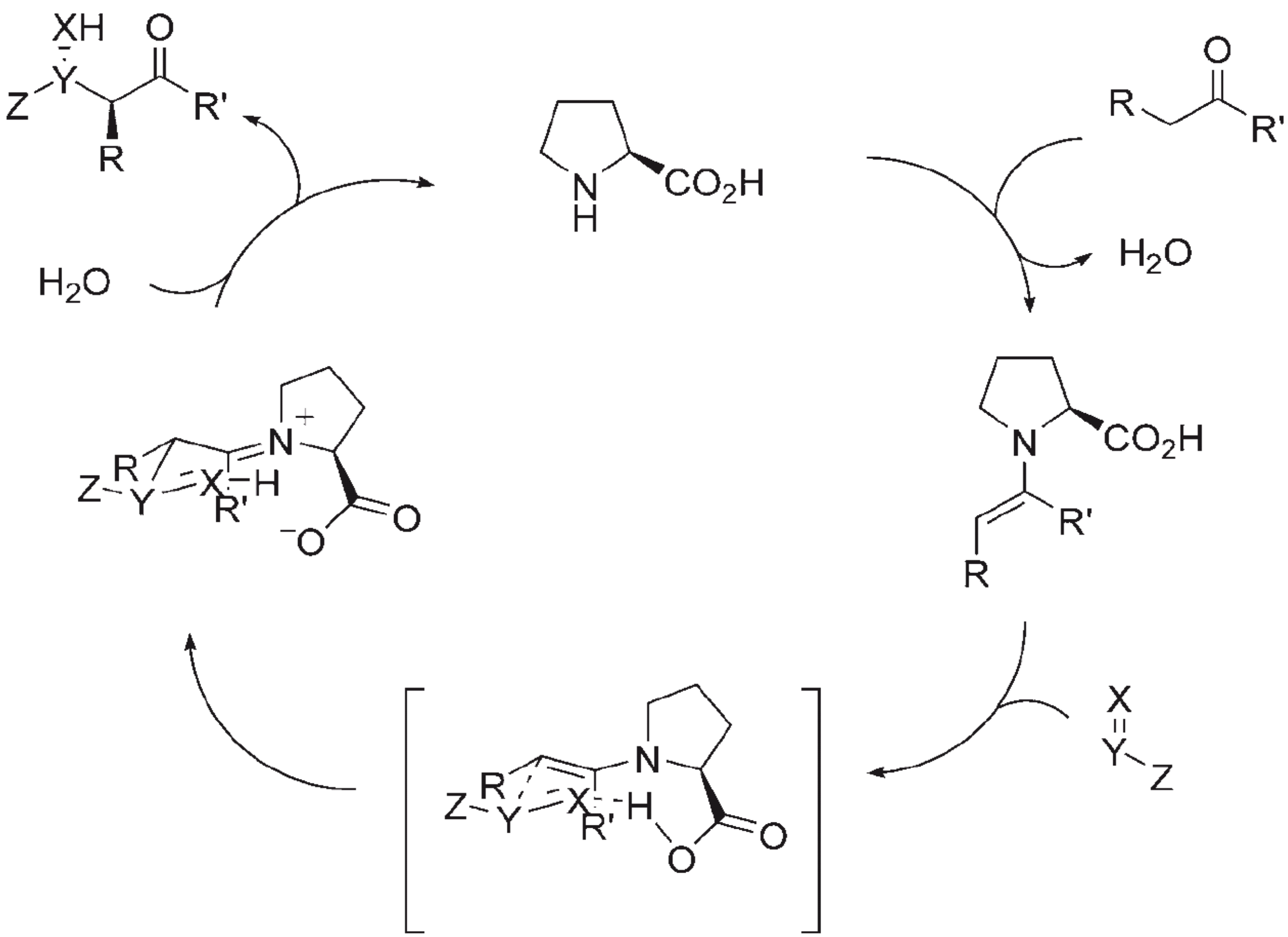





Z. G. Hajos, D. R. Parrish, (Hoffman-La-Roche), *German Patent DE 2102623*, 1971 [Chem. Abstr. **1972**, 76, 59072];
U.Eder, G. Sauer, R. Wiechert, (Schering AG), *German Patent DE 2014757*, 1971 [Chem. Abstr. **1972**, 76, 59072];
B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, 122, 2395 – 2396.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

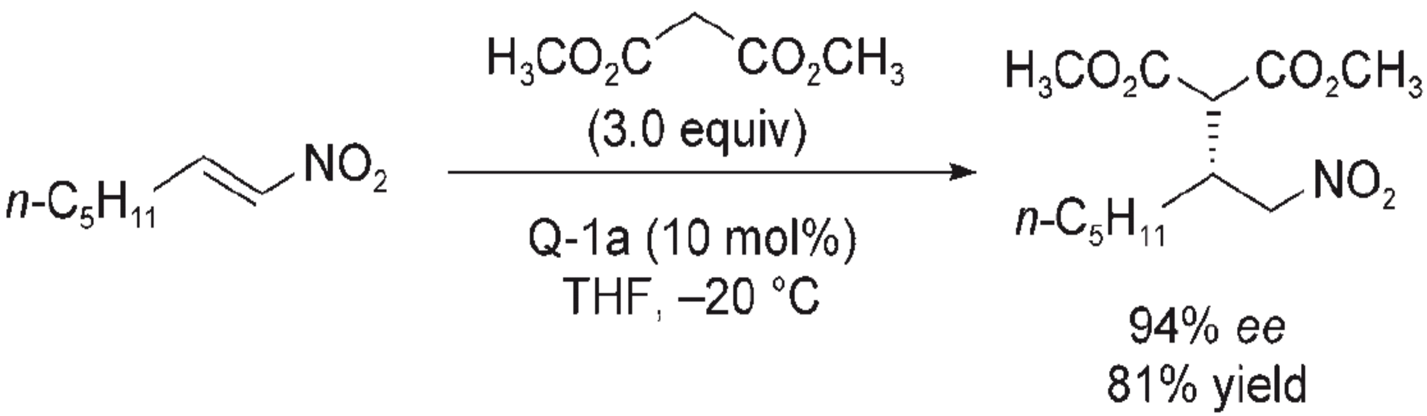
## —Proline Derivatives as Bifunctional Hydrogen-Bond Donor Catalysts

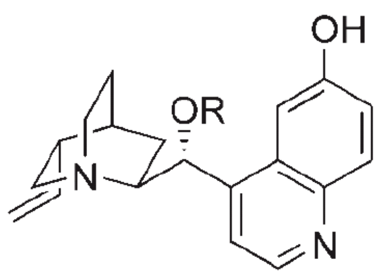



M. E. Jung, *Tetrahedron* **1976**, 32, 3 – 31.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## —Cinchona Alkaloids as Bifunctional Hydrogen-Bond Donor Catalysts



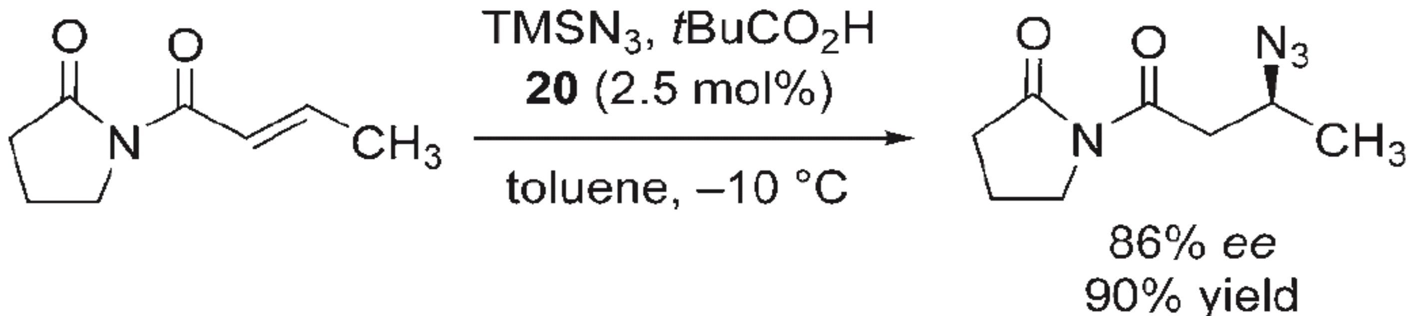



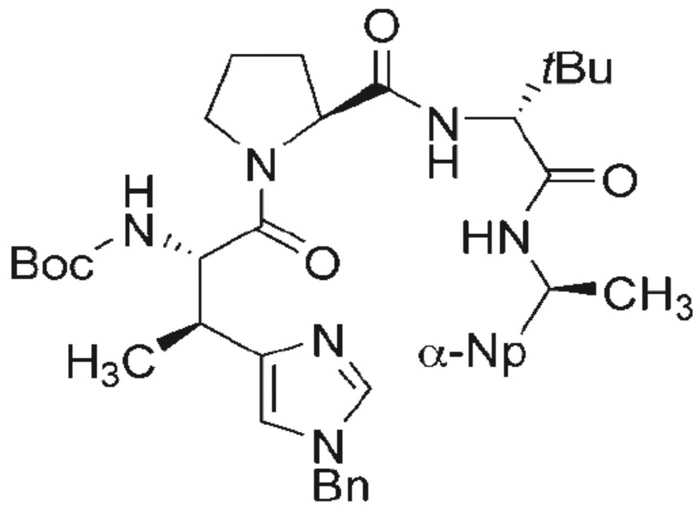

Q-1a: R = H

H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc*. **2004**, 126, 9906 – 9907.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## —Oligopeptide as Bifunctional Hydrogen-Bond Donor Catalyst

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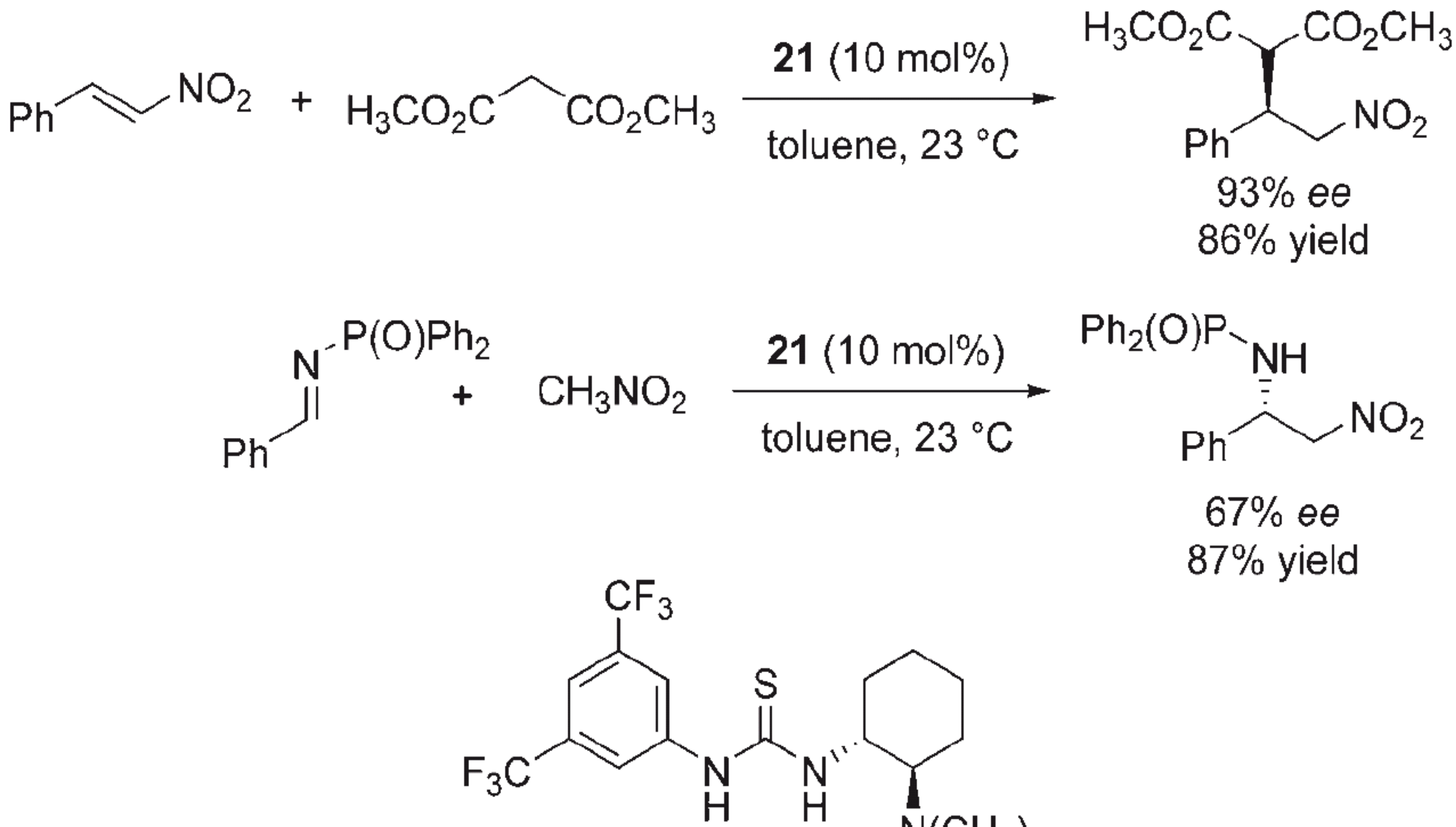
D. J. Guerin, S. J. Miller, *J. Am. Chem. Soc.* **2002**, 124, 2134 –2136.

# Hydrogen Bonding in Small-Molecule Synthetic Catalysis

## —Bifunctional Thiourea as Bifunctional Hydrogen-Bond Donor Catalyst

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T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, 125,12672 – 12673.

# Conclusions

1. With new modes of reactivity being identified and novel catalyst structures being designed, the scope of asymmetric H-bond donor catalysis will undoubtedly continue to expand;

2. With relatively easier synthesis and modular nature of the H-bond donor catalysts, efficient combinatorial approaches can be applied toward the discovery of new catalysts;

3. A more detailed mechanistic explorations of this H-bond donor catalysis is definitely needed in order to realize the full potential of this chemistry.