Hydrogen Bond Catalysis in Synthesis

IBS 2May2009
Baran GM
Hydrogen Bond Catalysis in Synthesis

Background
For Reviews, see: Jacobsen/Taylor, ACIE 2007, 45, 1520
Connan, ChemComm, 2008, 2499
Takemoto, BCSJ 2008, 81, 785

- Yates/Eaton reported AlCl₃ catalyzed DA in 1960, phenol accelerated was reported years earlier by Wassermann (1942).
- Lewis acid catalysis received ample attention throughout the 20th century, while H-Bonding catalysis was relatively forgotten until the 1980's
- H-bond catalysis vaulted onto the stage in 1981 when Wynberg reported asymmetric conjugate addition reactions with cinchona alkaloids bearing free OH's.
- Concaminant repot by Inoue that diketopiperazines could catalyze the hydrocyanation of benzaldehydes asymmetrically.
- 1998 Jacobsen reported his first catalyst for asymmetric hydrocyanation of aliphatic and aromatic aldehydes, and everybody jumped on the train after this. The irony is, he was trying to design a ligand for a Lewis acid, but found no LA was necessary.
- H-bond can vary between 0.4 (CH•••N) and 40 kcal/mol (NH•••N in proton sponge), but is typically 4-15 kcal/mol
- H-bonds play crucial rolls in biology:
  - H₂O bulk properties
  - Protein folding
  - DNA base pairing
  - Ligand-Receptor binding

1. Selected Hydrogen Bond Donating Catalysts:
- Cinchona-alkaloid based:
  1. (R¹ = lone pair): Wynberg, 1981 (conjugate addition)
  2. (R¹ = p-CF₃-Bn, Br⁻ salt): Grabowskii, 1984 (enolate alk.)
  3. (R = OH): Deng, 2004 (conjugate addition)
  4. Hatakeyama, 1999 (B-H)

- Cinchona-alkaloid based (cont'd):
  5. (Ar = 3,5-CF₃-Ph): Connan, Dixon, Soós, 2005 (conjugate addition, Mannich)
  6. (Ar = 3,5-CF₃-Ph): Hiemstra, 2006 (Henry)

- Thiourea-based catalysts:
  7. (R's = alk or Ar): Jacobsen, 1998 (Strecker, Mannich)
  8. (R's = alk or Ar): Jacobsen, 2004, (P-S and Mannich)
  9. (Ar = 3,5-CF₃-Ph): Takemoto, 2003 (Nu- to nitroolefins)
  10. (R = H or Me): Jacobsen, 2005 (cyanohydrin formation) Berkessel, 2005 (res. of azalactones)
  11. (R = H or Me): Jacobsen, 2006 (Nu- to nitroolefins)
  12. (Ar = 3,5-CF₃-Ph): Ricci, 2005, (F- add'n to nitroolefins)
  13. Wang, 2005 (B-H)
  15. Tsogoeva, 2006 (Nu- to nitroolefins)
Hydrogen Bond Catalysis in Synthesis

Hydrogen Bond Donating Catalysts (cont'd):

- Dual activation thiourea catalysts:
  
  \[
  \begin{align*}
  &\text{16 (Ar = 3,5-CF}_3\text{-Ph): Nagasawa, 2004 (B-H)} \\
  &\text{17 (Ar = 3,5-CF}_3\text{-Ph): Nagasawa, 2005 (Henry)} \\
  \end{align*}
  \]

- Guanidine- and amidine-based catalysts:
  
  \[
  \begin{align*}
  &\text{18: Corey, 1999 (Strecker)} \\
  &\text{19: Göbel, 2000 (4+2)} \\
  &\text{20: Johnston, 2004 (Mannich)} \\
  \end{align*}
  \]

- Chiral (diol) catalysts:
  
  \[
  \begin{align*}
  &\text{21 (Ar = 3,4-bis(3,5-di-tBu-Ph)-Ph): Tareda, 2006 (Nu- to nitroolefins)} \\
  &\text{22 (Ar = 3,4-bis(3,5-di-tBu-Ph)-Ph): Tareda, 2006 (amination of malonates)} \\
  \end{align*}
  \]

- Peptide-based catalysts:
  
  \[
  \begin{align*}
  &\text{23 (Ar = napth, R = alk): Rawal, 2003 (4+2, aldol)} \\
  &\text{24 (Ar = 3,5-CF}_3\text{-Ph): Schaus, 2003 (B-H)} \\
  &\text{25 (Ar = 4-F-3,5-Et-Ph): Rawal/Yamamoto, 2005 (4+2)} \\
  \end{align*}
  \]

- Phosphoric (acid) catalysts:
  
  \[
  \begin{align*}
  &\text{26 (Ar = 3,5-Ph}_2\text{-Ph): Maruoka, 2004 (epoxidation)} \\
  &\text{27: Sasai, 2005 (aza-B-H)} \\
  &\text{28: Yamamoto, 2006 (Mannich)} \\
  \end{align*}
  \]

- Miscellaneous catalysts
  
  \[
  \begin{align*}
  &\text{29: Inoue, 1981 (cyanohydrins)} \\
  &\text{30: Miller, 1998 (acyl xfer)} \\
  &\text{31: Julia, 1980 (epox'n)} \\
  &\text{32: Akiyama/Tareda, 2004 (Mannich)} \\
  &\text{33: Yamamoto, 2006 (4+2)} \\
  &\text{34: Antilla, 2005 (Imine Amidation)} \\
  &\text{35: Bach, 2005 (photocyclization)} \\
  &\text{36: Sigman, 2005 (4+2)} \\
  &\text{37: Mikami, 2005 (4+2)} \\
  \end{align*}
  \]
Hydrogen Bond Catalysis in Synthesis

2. Addition to Imines

A. Mannich Reaction

\[
\begin{align*}
&\text{Ac} \quad \text{Ac} \\
\text{R} &\xrightarrow{\text{32 (2%), rt}} \text{R} \quad \text{R} \\
\text{BnO}_2 &\xrightarrow{\text{CO}_2 \text{Bn}} \text{R} \quad \text{R} \\
\text{O} &\xrightarrow{\text{Oi-Pr}} \text{R} \\
\text{MeO}_2 &\xrightarrow{\text{COMe}} \text{R} \\
\text{NCO}_2 &\xrightarrow{\text{Me}} \text{R} \\
\text{EtO}_2 &\xrightarrow{\text{C}} \text{R} \\
\text{N} &\xrightarrow{\text{Boc}} \text{R}
\end{align*}
\]

R = subst. Ph yield: >90% ee: >90%
R = subst-Ph, 2-furyl yield: >90%
R = Ph, quin, 2-furyl yield: 84-99% ee: >91%
R = Ph yield: 99% dr: 20:1 ee: 94%
R = Ph, 2-furyl, styrene yield: 96-98% dr: >10:1 ee: 93-99%
R = Ph tol, 2-furyl R¹ = Me, CH₂OH, Bn yield: >85% dr: 5:1 to 10:1 ee: >90%
R = Ph, EtPh, Me, i-Pr R¹ = Me, H yield: >80% dr: >10:1 ee: >92%
R = Ph, tol, 2-furyl R¹ = Me, CH₂OH, Bn yield: >85% dr: 5:1 to 10:1 ee: >90%
R = Ph, EtPh, Me, i-Pr R¹ = Me, H yield: >80% dr: >10:1 ee: >92%
R = Ph, naph, 2-furyl yield: 93-95% ee: 85-98%
R = Ph, alk, chx yield: 85 - 95 % ee: 95%

C. Aza-Baylis-Hillman:

\[
\begin{align*}
&\text{R} \quad \text{Ph, 2-furyl, p-OMe-Ph yield: 58-80% (4)} \\
&\text{R} \quad \text{Ph, 2-thioph, m-OMe-Ph yield: 70-90% (4)}
\end{align*}
\]

R = Ph yield: 78% ee: 68%

D. Pictet-Spengler:

\[
\begin{align*}
&\text{NH}_2 \\
&\text{AcCl} \quad \text{2, 6-Lut, 8} \\
&\text{RCHO} \\
&\text{MeO}_2 \quad \text{CO}_2 \text{Et}
\end{align*}
\]

R = alkyl yield: 75-85% ee: >90%
R = alkyl, p-NO₂-Ph yield: 60-85% ee: >85%

E. Friedel-Crafts

\[
\begin{align*}
&\text{MeO} \quad \text{F} \\
\text{R} &\xrightarrow{\text{Boc}} \text{R}
\end{align*}
\]

R = Ph, naph, 2-furyl yield: 93-95% ee: 85-98%
R = Ph, alk, chx yield: 85 - 95 % ee: 95%
Hydrogen Bond Catalysis in Synthesis

**E. Friedel–Crafts (cont’d):**

32 (2%), -30 °C

32 (10%), rt

yield = 99%

ee = 94%

yield = 99%

ee = 92%

yield = 95%

ee = 98%

yield = 84%

ee = 91%

yield = 90-95%

ee > 85%

**F. Strecker:**

RC\(\bar{\text{H}}\)Ph \(\rightarrow\) HCN, 18 (10%), -40 °C

\(\text{NCH}_2\text{Ph}_2\)

\(\text{PhCN}\)

yield > 95%

ee > 80%

**G. Reduction:**

32 (20%), HEH, 60 °C

32 (10%), HEH, 40 °C

yield = 75-85%

ee = 75-85%

yield = 60-90%

ee > 80%

yield = 95%

ee = 94%

yield = 90-95%

ee > 90%

**H. Amidation:**

34 (10%), TsNH₂, rt

R = Ph, p-OMe-Ph, 2-thiophen

yield = 90-95%

ee > 85%

**I. Addition to N-Acyl Iminiums:**

1. Troc-Cl

2. 32 (10%), -78 °C

O\(\text{Me}^\text{TBS}\)

yield = 65%

ee = 94%

**3. 1,2-Addition to Carbonyls**

**A. Aldol Reactions:** These reactions all involve proline catalysis. This constitutes a group meeting of its own, and will not be covered in this group meeting.

**B. Nitro-Aldol (Henry):**

3 or 6 (10%), MeNO₂, -20 °C

3 or 6 (10%), MeNO₂, -20 °C

R = Ph, 3-pyr, N-Boc-2-pyrrole, chiral

yield = 90-95%

ee = 86-91%

17 (10%), KI, KOH, H₂O, -20 °C

O\(\text{N}^\text{Me}\)

R = CH₃OTBS

yield = 90-95%

ee = 86-91%
Hydrogen Bond Catalysis in Synthesis

4. Conjugate (1,4) Addition

A. Heteroatom Addition to enones:

- Ph
  - 9 (10%), PhSH, -40 °C
  - yield = 98%
  - ee > 75%

B. Michael Addition:

- Ph
  - 1 (10%), MVK, -24 °C
  - yield = 82%
  - ee = 90%

D. Friedel–Crafts:

- R = t-Bu, Ph, CF₃
  - yield = 80-90%
  - ee > 80%

E. Cyanation:

- R = H, OMe, NO₂
  - yield = 80-99%
  - ee = 85%, 53% for NO₂

- Ar = Cl, Ph, F, Ph, tol
  - yield = 95%
  - ee = 89-98%

- Ar = Ph
  - yield = 77%
  - ee = 88%

E. Metallo-addition:

- R = Ph, 2-thioph, t-Bu, alk, Br-Ph
  - yield = 86-99%
  - ee = 81-98%
  - dr = 94:6
5. Cycloadditions

A. 4+2 (Diels–Alder) Cycloadditions

1. 23 (20%), -80 °C
2. LAH 3. HF

R = Me, Bn, EIOTBS
yield = 80-85%
ee = 86-91%

R = 2-furyl, styrene, Chx, Ph
yield = 42-96%
ee = 71-94%

B. 2+2 cycloadditions

cat, hv, -15 °C

yield = 67%
ee = 83%
Hydrogen Bond Catalysis in Synthesis

6. Potpourri

PhO
\[ \xrightarrow{\text{Et}_2\text{NH, 30 }^\circ\text{C}} \] PhO-\text{NEt}_2

12.5 fold rate enhancement over phenol

\[ \xrightarrow{\text{80 }^\circ\text{C, cat (10%)}} \] OMe

R = CH$_2$OBn, CH$_2$COCH$_2$, CH$_2$NTsCH$_2$

yield = 90-95%

ee = 73-96%

7. Application to Synthesis


B. Manzacidin A - Deng, JACS 2006, 128, 3928

(not really worth drawing in)


D. (+)-Yohimbine - Jacobsen, OL 2008, 10, 745

(-)-yohimbine

11 steps, 14% overall