Determining Stereochemistry by NMR
Enantiomers

(+)A and (-)A are identical by NMR

How do we make them different?

change the situation from enantiomeric to diastereomeric
Diastereomers

- Covalent bonds with other chiral entities
- Ionic bonds with other chiral entities
- Lewis acid/Lewis base complexation
- Chiral solvating agents or additives
Covalent Bonds

The most convenient method is to make an ester or amide linkage with a chiral acid.
Chiral Acids

- Covalent Bonds

- Chiral acids first utilized in the 1960’s

  - mandelic acid
  - O-methylmandelic acid (methyl phenyl acetic acid) (MPA)
  - O-methyltrifluoromethylphenylacetic acid (MTPA)

Rabin and Mislow
*Tetrahedron Lett* **1966**, *4249*
*Top. Stereochem.* **1967**, *2*, 199

Mosher
Covalent Bonds

Be careful of naming conventions

\[\text{(R)-MTPA} \xrightarrow{\text{SOCl}_2} \text{(S)-MTPA-Cl}\]
Mandelate and MTPA based Derivatives

A. MANDELATE

\[
\text{HO} \quad \text{O} \quad \text{H} \\
\text{Ph-C=O-C-C-CMe}_3 \\
\text{H} \quad \text{CH}_3
\]

D. O-METHYL-MANDELATE

\[
\text{MeO} \quad \text{O} \quad \text{H} \\
\text{Ph-C=C=O-C-C-CMe}_3 \\
\text{H} \quad \text{CH}_3
\]

C. MTPA

\[
\text{MeO} \quad \text{O} \quad \text{H} \\
\text{Ph-C=O-C-C-CMe}_3 \\
\text{CF}_3 \quad \text{CH}_3
\]
Preferred conformation can indicate absolute stereochemistry.
Fluorine

- $^{19}$F NMR is an advantage

- Steric repulsion

- Shielded
MPA derivatives can also be used

Trost

Primary alcohols more difficult

Yamaguchi
*Tetrahedron* 1976, 32, 1363
*Tetrahedron Lett.* 1977, 89
*Tetrahedron Lett.* 1977, 4085
New Chiral Acids for Primary Alcohols

Riguera

Amine Derivatives

- Amine Analysis - a variety of derivatives

Hoye


Fukushi, Yajima, Mizutani


Kabayashi


Nájera


Heuman

Hindkley 1969 - observed that the addition of lanthanide Lewis acids induced large changes in chemical shift.

- **Eu(dpm)$_3$**: $\text{tris(dipivaloylmethanato) europium}$
- **Eu(fod)$_3$**: $\text{tris(heptafluoroctanedionato) europium}$
- **Eu(tfn)$_3$**: $\text{tris(tetradecafluorononanedionato) europium}$
Eu(dpm)$_3$-induced shifts of protons in some common environments

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Shift (ppm per mol of shift reagent per mol of substrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCH$_2$NH$_2$</td>
<td>~150</td>
</tr>
<tr>
<td>RCH$_2$OH</td>
<td>~100</td>
</tr>
<tr>
<td>RCH$_2$NH$_2$</td>
<td>30-40</td>
</tr>
<tr>
<td>RCH$_2$OH</td>
<td>20-25</td>
</tr>
<tr>
<td>RCH$_2$COR’</td>
<td>10-17</td>
</tr>
<tr>
<td>RCH$_2$CHO</td>
<td>19</td>
</tr>
<tr>
<td>RCH$_2$CHO</td>
<td>11</td>
</tr>
<tr>
<td>RCH$_2$OCH$_2$R</td>
<td>10</td>
</tr>
<tr>
<td>RCH$_2$CO$_2$CH$_3$</td>
<td>7</td>
</tr>
<tr>
<td>RCH$_2$CO$_2$CH$_3$</td>
<td>6.5</td>
</tr>
<tr>
<td>RCH$_2$CN</td>
<td>3-7</td>
</tr>
</tbody>
</table>
Figure 7.3 60 MHz proton NMR spectra of 0.5 ml of CDCl₃ solution containing 60 mg of n-amyl alcohol and varying amounts of Eu(fod)₃: (a) without shift reagent, (b) 20 mg, (c) 44 mg, (d) 69 mg, (e) 129 mg, (f) 192 mg.
Shift Reagents

Fig. 5.20. $^1$H NMR spectrum of 39 in the presence of the lanthanide shift reagent (LSR) Eu(fod-d$_{27}$)$_3$: (a) Reference spectrum without the addition of LSR. The molar ratio of LSR to 39 is (b) 0.05, (c) 0.10, (d) 0.15. All $^1$H chemical shifts in (a) are larger by about 0.2 ppm as compared with Fig. 3.20.1. Such deviations are due to concentration differences. Designation: "n" denotes endo, "x" is exo.
FIGURE 4-10 The 100 MHz proton spectrum of androstan-2,3-01 with (b) and without (a) added Eu(dpm)$_3$·2pyr (4-50). Spectrum c is a 220 MHz blowup of the region δ 1–5. (Reproduced with permission from P. V. Demarco, T. K. Elzey, and E. Wenkert, J. Am. Chem. Soc., 92, 5737 (1970). Copyright 1970 American Chemical Society.)
Chiral Shift Reagents

Whitesides 1970
Chiral Lewis Base

Lewis Bases - TRISPHAT

Lacour
Chem. Comm. 1997, 2285
Fig. 1 The $^1$H NMR spectra of racemic [Ru(bipy)$_3$(ClO$_4$)$_2$]-xH$_2$O 2 in the absence (a) and presence of (+)-1a [0.5 equiv. (b), 1.0 equiv. (c)]
TRISPHAT Shift

Fig. 2 The $^1$H NMR spectra of [Ru(phen)$_3$(ClO$_4$)$_2$]$\cdot$xH$_2$O 3 in the absence (a) and presence of 1.0 equiv. of (+)-1a: (±)-3b (b) and (+)-3b (c). Spectra (a), (b) and (c) were done in 10, 10 and 7% DMSO in CD$_2$Cl$_2$, respectively.
Chiral Solvating Agent - Triazine

three 1-(1-naphthyl)ethylamino moieties, (Chart 1) as multiselector CSAs for enantiomeric mixtures of derivatized or underivatized compounds (5–27, Charts 2–4).

Review on CSA’S
Chem. Rev. 1991, 91, 1441

Salvadori
J. Org. Chem. 1998, 63, 9197
Figure 1. $^1$H NMR (300 MHz, CDCl$_3$, 25 °C, ppm referred to TMS as internal standard) spectral regions corresponding to the 3,5-dinitrobenzoyl (A), CH (B), and COOMe (C) proton absorptions of racemic 5 (20 mM): (a) free compound; (b) equimolar mixture of 2/(R,S)-5; (c) equimolar mixture of 3/(R,S)-5.
Chiral Solvating Agents - Cyclodextrins

Salvadori


Figure 1. Proposed schematic representation of the structure of 1 in CDCl₃.
**Figure 2.** $^1$H NMR (300 MHz, CD$_3$OD, −20 °C) spectral regions corresponding to the tert-butyl and methyl proton absorptions of 1a (80 mM) for (a) the free compound, (b) the mixture (R,S)-1a/TRIMEB (1:1), (c) the mixture (R)-1a/TRIMEB (1:1) (op 68%).