Asymmetric
Hydride-Transfer
Reduction of Ketones

Ramil Baiazitov

April 23, 2002
CONTENT:

Introduction

Mechanism

Thermodynamics

Choosing and preparation of the catalyst

Chemo- and diastereo-selectivity

Enantioselectivity. Non-Aluminium catalysts

Enantioselectivity. Aluminium achiral catalysts, chiral hydride source

Enantioselectivity. Aluminium chiral catalysts
1. How did it start?

1925- Meerwein and Schmidt reduced acetaldehyde with EtOH/Al(OEt)₃

1925 - Verley reduced butyraldehyde with geraniol, Al(OEt)₃

1926- Ponndorf (sec-alcohols and their aluminum alkoxides)

1937- Oppenauer used acetone and Al(Ot-Bu)₃ to oxidize steroids

Introduction of easier reducible agents (quinones, benzophenones, cycloexanone)

1945- Woodward applied KOt-Bu+Ph₂CO to oxidize Quinine

\[ \text{progesterone} \]
2. DECLINE

**Drawbacks:**

1. Typically stoichiometric use of alkoxide
2. Side-reactions
3. Reversibility?
4. Complex metal hydrides and direct hydrogenation

**Diversity:**

Alkoxides of Mg, B, Zn, Sn(IV), Ti, As(V), Fe(III), alkali metals, lanthanides

Complexes of Zr, Hf, Ir, Ru

Heterogeneous: metal oxides (Al₂O₃), zeolites

**Reviews:**

3. Mechanism

Metal:
1. Activates carbonyl
2. Serves as a template, holding two reactants together
3. Has different affinities for OH/C=O and SM/Prod
(can get deactivated)

Organic part:
1. Intramolecular Hydride-transfer
2. Easily enolizable ketones are inactive

Kinetics (Racemization)
R=Kx[ketone]/[alkoxide]
dS<0

Conclusion
Alkoxide is associated
Ordered TS

3a. SET-mechanism.

Evidence:
1. ESR (first order decay)
2. t-BuO− + Ph2CO → ketyl radical
3. Ketyl radical reacts with LiOiPr

Couldn't find any evidence in case of aliphatic ketones
Aldol reaction observed

4. Thermodynamics

Polarographic determination of Red-Ox potentials.
Cox, F.W. et al JACS 1939, 61, 3364 also 1938, 60, 1151; Robinson C.C. et al JACS 1949, 71, 3622

1. Highest reduction potentials/best reducing agents:
Secondary-dialkyl alcohols (e.g., i-PrOH)

2. Highest oxidation potentials/best oxidizing agents:
Aromatic and aliphatic aldehydes

Note: if catalyst's loading is not negligible, the Red-Ox potential alone becomes less reliable

\[
\begin{array}{cccc}
\text{delta-4-cholestenone} & \text{63mv} & \text{162mv} & \text{270mv} & \text{350mv} \\
1 & 50 & 50^2 & 50^3 & \text{-concentration of the corresponding alcohol in equilibrium}
\end{array}
\]

Trends:
Alkyl groups, conjugated C=C- lower oxidation potential
Alkoxy, carbonyl, carbalkoxy groups in alpha-position- increase oxidation potential (same-for NR2, Cl, NO2)
Table I

**Oxidation Potentials of Aldehydes and Ketones**

<table>
<thead>
<tr>
<th>Aldehyde/Ketone</th>
<th>Oxidation Potential</th>
<th>Reduction Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>0.97</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>0.74</td>
<td>N/A</td>
</tr>
<tr>
<td>Acrolein</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Propionaldehyde</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetone</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-1</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-2</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-3</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-4</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-5</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-6</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-7</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-8</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-9</td>
<td>0.63</td>
<td>N/A</td>
</tr>
<tr>
<td>Acetophenone-10</td>
<td>0.63</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Notes:**
- Oxidation potentials are measured in volts (V).
- Reduction potentials are not available (N/A).
- The values are approximate and may vary slightly.

---

*The carbonyl compound against which Conc (C), Baker (B), Rossow (R), Robinson (Rb), or Ehrlich (E) equals a given compound is indicated in the fifth column of the table, by using the number of the carbonyl compound as the second digit of the column of the table. The values for the methoxycarbonyl, given by Baker, Schiller, are in agreement with the potentials listed in the tables for this compound, if they are based upon a point of zero change, rather than upon the value (150 mV) used in the oxidation reaction. These potentials were observed in a 0.1 N ammonium chloride solution, while the others were reported in a 0.01 N tetraethylammonium hydroxide solution.*

---

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5. Choice of Metal-Alkoxide

From 65% ionic character for the alkoxides of Al, Ti, Zr to 90% for alkali metals and lanthanides

The more ionic - the easier ligand exchange

Al is good for easy preparation and excellent solubility in ROH and CnHm, but requires stoichiometric amount.

Rate of ligand exchange (water), s⁻¹: Al(1)<Mg(10⁻⁵)<Lanthanides (10⁻⁸-⁹)<Li(10⁻¹¹) [1]

Al = stoichiometric amount (however, see 5b)

Protic acids rate-increase [2] CF₃COOH
(50 mol% relative to Al(Oi-Pr)₃ (used 5 mol%)), aldol reaction

Addition of 30 mol% of Al(Oi-Pr)₂Cl increases the rate too
(LA-character increased)

Na, K - low charge density;

Li-small coordination number

Useful for oxidation of N-containing compds.

5a. Choice of Metal-Alkoxide

Lanthanides:

Hard acids, coordination numbers 8-12

Used in 10 mol% amount (Sm(Ot-Bu)I₂ [1], Ln(Oi-Pr)₃ [2,3]) La(III) is the most active [3], Gd(Oi-Pr)₃ is 1000 times as active as Al [2]

Cp₂ZrH₂ can be used in 2 mol% amount [4]

Ir- complexes were used with Ir loading 0.005 mol% [5]

Ru-complexes. See slides 8b,c

5b. Choice of Metal-Alkoxide

5 Mol% cat loading, RT
Double e-philic activation
Also asymmetric

### 5c. Choice of Metal-Alkoxide

Table 2. Catalytic MPV reduction of ketone substrates with new aluminum catalyst 3 and scale-up experiments with 5 g of starting ketones.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield(^{[b]})</th>
<th>Scale-up reaction</th>
<th>Yield(^{[d]})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[°C]</td>
<td>[%]</td>
<td>[°C] [h]</td>
<td>[%]</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>25</td>
<td>0.5</td>
<td>25 2</td>
<td>99(^{[d]})</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CH}_3(\text{CH}_2)_2\text{COCH}_3)</td>
<td>25</td>
<td>5</td>
<td>97</td>
<td>25 5</td>
</tr>
<tr>
<td>3</td>
<td>((\text{CH}_3(\text{CH}_2)_2\text{C})_2\text{O})</td>
<td>25</td>
<td>5</td>
<td>92</td>
<td>25 5</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>25</td>
<td>3.5</td>
<td>25 5</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CH}_3\text{COCl})</td>
<td>25</td>
<td>5</td>
<td>99</td>
<td>25 5</td>
</tr>
<tr>
<td>6</td>
<td>(\text{COC}Cl)</td>
<td>25</td>
<td>1</td>
<td>99</td>
<td>25 3.5</td>
</tr>
<tr>
<td>7</td>
<td>(\text{COC}Cl)</td>
<td>25</td>
<td>5</td>
<td>97</td>
<td>25 9</td>
</tr>
</tbody>
</table>

\(^{[a]}\) The MPV reduction of various ketone substrates was effected with 3 (10 mol%) and \(\text{iPrOH}\) (10 equiv) distilled from \(\text{CaH}_2\) in freshly distilled \(\text{CH}_2\text{Cl}_2\) (0.2 M) under the indicated reaction conditions. \(^{[b]}\) The reaction was carried out in reagent grade \(\text{CH}_2\text{Cl}_2\) (1 M) and distilled \(\text{iPrOH}\) (10 equiv) in the presence of 3 (5 mol%), prepared from \(\text{Al(OiPr)}_3\) and 2, under the given conditions. \(^{[c]}\) Yield of isolated product. \(^{[d]}\) The \(\text{cis/ trans}\) ratio was 17:83. Scale-up: 5 g ketone, 5 mol % cat

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**Diagram:**
- Dimeric Structure
- Pentacoordinate Al-Center
- 7-membered ring
- No mechanism proposed

---

6. Preparation of Catalyst.

1. Reaction of metal with ROH (Al and Ln require some form of activation (HgCl₂, I₂ etc))

2. MXₙ+ROH. Can require NH₃ or alkali metal alkoxide to complete.

3. M(OR)ₙ+R*OH. The affinity of metal: ¹⁰>²⁰>³⁰

4. 2SmI₂+(t-BuO)₂→2Sm(Ot-Bu)I₂ [1]

5. LaCl₃·7H₂O+7 HC(OMe)₃→LaCl₃·4MeOH \[ \text{i-PrOH} \xrightarrow{-\text{MeOH}} \text{LaCl₃·3 i-PrOH} \xrightarrow{\text{BuLi}} \text{La(Oi-Pr)₃} \] [2]

6. AlMe₃+ROH→Al(OR)ₙMe₃-n (can regulate value of n)


7. Selectivity.

1. Chemoselectivity:

$2^0$-ROH are oxidized more easily than $1^0$-ROH (thermodynamics $\rightarrow$ Al?). Protection can be used.

2. Diastereoselectivity:

7a. Selectivity.

<table>
<thead>
<tr>
<th>R1</th>
<th>Cis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>50</td>
</tr>
<tr>
<td>3-Me</td>
<td>55</td>
</tr>
<tr>
<td>4-Me</td>
<td>33</td>
</tr>
<tr>
<td>4-iPr</td>
<td>40</td>
</tr>
<tr>
<td>4-iPr-2-en</td>
<td>39</td>
</tr>
<tr>
<td>(-)-menthone</td>
<td>70</td>
</tr>
<tr>
<td>(+)-camphor</td>
<td>70</td>
</tr>
</tbody>
</table>

Alcohol used Cis, %
- sec-BuOH 75
- 4-Me-pentane-2-ol 72
- 3,3-Me-butane-2-ol 86
Yields >94%


Initial cis-selectivity can be increased by the use of bulky reducing alcohols, Al(Os-Bu)_3. Or by dilution.


<table>
<thead>
<tr>
<th>t, (h)</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>0.3</td>
<td>86</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
| 5      | 5 | 0 | 95 \( \rightarrow \) 1:2 in case Al(Oi-Pr)_3

8. Enantioselectivity.

1. First successive use of chiral alcohol.

Large excess of the alcohol used, no data on the catalyst loading

\[
\text{C}_8\text{H}_{13} + \text{s-Butane-2-ol} \xrightarrow{\text{rac-Al(2-butoxide)}_3} \text{at conv}=60\%, \text{22}\%\text{ee} \xrightarrow{} \text{C}_8\text{H}_{13}
\]

Doering, W. von E.; Young, R. W. *JACS*, 1959, 72, 631

2. First successive use of chiral catalysts.

La, Eu, Yb; 10 mol\%, 1-2 eq of Chiral ligand. RCOMe (R=Pr, Ph, t-Bu)

![Chemical structures](image)

The best ee is for La(OtBu)_3 and cat A: up to 32% ee for R=Ph

8a. Enantioselectivity.

Chiral catalysts, Ln(III)

Conditions: 5mol % cat, 25 eq of acetone, THF, 1hr, RT
No TS proposed. Bulkier R-isomer.

Table 1. Enantioselective MPV Reduction of Aryl Methyl Ketones

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>% ee (conv)</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X = Cl</td>
<td>97 (96)</td>
<td>100 (96)</td>
</tr>
<tr>
<td>2</td>
<td>X = H</td>
<td>98 (74)</td>
<td>83 (74)</td>
</tr>
<tr>
<td>3</td>
<td>X =CHO</td>
<td>96 (77)</td>
<td>100 (77)</td>
</tr>
<tr>
<td>4</td>
<td>X = Cl</td>
<td>94 (71)</td>
<td>51 (88)</td>
</tr>
<tr>
<td>5</td>
<td>X =CHO</td>
<td>92 (70)</td>
<td>42 (36)</td>
</tr>
<tr>
<td>6</td>
<td>X = NO₂</td>
<td>94 (76)</td>
<td>100 (77)</td>
</tr>
<tr>
<td>7</td>
<td>X = Cl</td>
<td>95 (78)</td>
<td>86 (78)</td>
</tr>
<tr>
<td>8</td>
<td>X = H</td>
<td>73 (82)</td>
<td>66 (82)</td>
</tr>
<tr>
<td>9</td>
<td>X =CHO</td>
<td>96 (77)</td>
<td>84 (77)</td>
</tr>
<tr>
<td>10</td>
<td>X = NO₂</td>
<td>97 (95)</td>
<td>99 (95)</td>
</tr>
</tbody>
</table>

* Reactions were carried out on a 5-mmol scale using the conditions given in the text. Products were isolated after complete conversion or 24 h.

Non-linear effects: 80% ee of (R,R) gives the same ee of the product as 100% (R,R).

ee doesn't change upon prolonged exposure to the catalytic system.

Proposed binding of substrate to cat. in case of o-methoxyaryl.

Evans, D.A. et al. JACS 1993, 115, 9800
8b. Enantioselectivity.
Chiral catalysts, Ru(II)

orange crystals

KOH 1eq
Et$_3$NHCl

purple crystals

not t-BuOH
i-PrOH or H$_2$, 80atm
acetone

Figure 1. Molecular structure of 3 in the crystal. All hydrogen atoms except for the hydroxyl at ruthenium, the two protons of the amine ligand, and those at the carbon atoms in the chelate backbone, as well as two water molecules in the lattice have been omitted for the sake of clarity. Selected distances [Å] and bond angles [:]
Ru–H1 1.09(1), Ru–N3–H3 1.99(1), Ru–N2–H2 2.18(1), N1–N3–H3 86(2), N1–N2–H2 175(3), Ru–N3–C1 1.21(2), Ru–N2–C2 1.19(1).

Figure 2. Molecular structure of 2 in the crystal. All hydrogen atoms except for the protons of the amide ligand and those at the carbon atoms in the chelate backbone have been omitted for the sake of clarity. Selected distances [Å] and bond angles [:]
Ru–N1 1.89(6), Ru–N2 2.05(6), N1–H1 0.81(6), N1–Ru–N2 78.9(2), Ru–N1–C1 121.2(5), Ru–N2–C2 114.9(4).

Figure 3. Molecular structure of 3 in the crystal. All hydrogen atoms except for the hydroxyl at ruthenium, the two protons of the amine ligand, and those at the carbon atoms in the chelate backbone, as well as two water molecules in the lattice have been omitted for the sake of clarity. Selected distances [Å] and bond angles [:]
Ru–H1 1.09(1), Ru–N3–H3 1.99(1), Ru–N2–H2 2.18(1), N1–N3–H3 86(2), N1–N2–H2 175(3), Ru–N3–C1 1.21(2), Ru–N2–C2 1.19(1).

8c. Enantioselectivity.

Chiral catalysts, Ru(II)

Reduction of acetophenone:

MeOH, EtOH, i-PrOH, (R,S)-, (R)- and (S)-2-BuOH, all gave (S)-1-Ph-Ethanol 95(+/-.05)%ee. Neutral conditions!

Me2CDOH gave (S)-PhCD(OH)Me, mix with non-deuturated->$k_H/k_D=1.5$

$R=k[\text{cat}]x[i-\text{PrOH}]x[C_2D_6CO]^n$ (0<n<1) Saturation at higher concentrations (H-transfer is RDS). $(CD_3)_2CO+i-\text{PrOH}$. 

~0.2 mol % of cat.

Kinetic resolution:


Aluminum catalysts, chiral hydride source

\[
\begin{align*}
1 & \underset{Al(Oi-Pr)_3}{\xrightarrow{\text{CH}_2Cl_2}} 2 \\
2 & \xrightarrow{\text{H}_2O} 4 \\
3 & \xrightarrow{\text{Me}_2\text{SO}_4} 5 \\
4 & \xrightarrow{\text{NaOH}} 2 \\
5 & \xrightarrow{\text{CH}_2Cl_2} 6 \\
6 & \xrightarrow{\text{Al(Oi-Pr)_3}} 7
\end{align*}
\]

67% of (6), 100% ee, 33% of SM recovered

68% of (2), 100% ee, 32% of (1) recovered, no (3)

2eq of Al(Oi-Pr)_3, 20hrs

Same ratio (4 days, 4eq of Al) => eq. with K=2, complete stereodiff. in the reverse step.

Previously - stereocontrol - only under kinetic cond.

9a. Enantioselectivity.

Aluminum catalysts, chiral hydride source

Table 1. Catalytic MPV Reduction Using Simple Alkylaluminum Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>Al pre-catalyst (10 mol%)</th>
<th>yield (%)</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>AlMe₃</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>AlMe₂Cl</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>AlMe₂Cl₂</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>Al(OPr)₃</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>AlMe₃</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>AlMe₂Cl</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>b'</td>
<td>AlMe₂Cl (neat 1PrOH)</td>
<td>85</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>c</td>
<td>AlMe₂Cl₂</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>Al(OPr)₃</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>AlMe₃</td>
<td>99</td>
<td>12</td>
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<tr>
<td></td>
<td>b</td>
<td>AlMe₂Cl</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>AlMe₃</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>a'</td>
<td>AlMe₃ (65 °C)</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>AlMe₂Cl</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>Al(OPr)₃</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>a</td>
<td>AlMe₃</td>
<td>11</td>
<td>12</td>
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<tr>
<td></td>
<td>b</td>
<td>AlMe₂Cl</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>d</td>
<td>Al(OPr)₃</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

* Reaction conditions: Al pre-catalyst in 21 μM concentration, rt. N₂.

In situ generated catalyst (NMR), aggregation state aged (6 days)- 20% decrease in activity

AlMe₂Cl (LA) better for e-rich (entries 1, 5)

Simple catalyst, catalytic amount

## 9b. Enantioselectivity.

*Aluminum catalysts, chiral hydride source*

### Stereoselective MPV Reduction and Effect of Ligand Additives

<table>
<thead>
<tr>
<th>Product</th>
<th>Entry</th>
<th>Al Reagent (10 mol%)</th>
<th>Ligand</th>
<th>Hydride Source (equiv)</th>
<th>Product Selectivity cis/trans</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Cyclohexanol" /></td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>5,10,15,20-tetraphenyl porphyrin (slide 7a)</td>
<td>'PrOH(4)</td>
<td>20/80</td>
<td>—</td>
</tr>
<tr>
<td><img src="image2" alt="Cyclohexylmethyl chloride" /></td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>—</td>
<td>'PrOH(4)</td>
<td>20/80</td>
<td>—</td>
</tr>
<tr>
<td><img src="image3" alt="Cyclohexanol" /></td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2,7-Dimethyl-1,8-biphenylene-diol (slide 5b)</td>
<td>enantiopure-α-methyl-2-napthyl methanol(1)</td>
<td>—</td>
<td>70</td>
</tr>
<tr>
<td><img src="image4" alt="Cyclohexylmethyl chloride" /></td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>—</td>
<td>enantiopure-α-methyl-2-napthyl methanol(1)</td>
<td>—</td>
<td>68</td>
</tr>
<tr>
<td><img src="image5" alt="Cyclohexanol" /></td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2,7-Dimethyl-1,8-biphenylene-diol (slide 5b)</td>
<td>enantiopure-sec-o-bromophenethyl alcohol(1)</td>
<td>—</td>
<td>82</td>
</tr>
<tr>
<td><img src="image6" alt="Cyclohexylmethyl chloride" /></td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AlMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>—</td>
<td>enantiopure-sec-o-bromophenethyl alcohol(1)</td>
<td>—</td>
<td>86-81&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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*Note:*

- **a** Reaction conditions: toluene (1 mL), 1,2,4,5-tetramethylbenzene (internal standard), N<sub>2</sub>, Al reagent (21 × 10<sup>-6</sup> mol, 10 mol %), substrate (10 equiv), either chiral hydride source (1 equiv, 0 C) or iPrOH (4 equiv, rt). b Reference 10 reports a cis/trans ratio of 8/92. Al(TPP)Cl under our reaction conditions (rt) yields a cis/trans ratio of 20/80.
- **c** Taken from ref 11; reactions carried out at 0 C.
- **d** The absolute configuration of the major enantiomer of the product is opposite that of the chiral hydride source.
- **e** As would be expected for a reversible reaction, the enantioselectivity of the product decreases slowly over time.

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10. Enantioselectivity.

*Chiral aluminum catalysts*

\[
\text{R} + \text{OH} \xrightarrow{\text{cat. (10 mol%)}} \text{R} + \text{OH}
\]

Table 1. Asymmetric MSPV reduction.\[^{[a]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>2-Propanol (equivalents[^{[b]}])</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl</td>
<td>4</td>
<td>99</td>
<td>80 (R)[^{[c]}]</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Br</td>
<td>4</td>
<td>99</td>
<td>80 (S)[^{[d]}]</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₃</td>
<td>4</td>
<td>30</td>
<td>50 (R)[^{[e]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>80</td>
<td>46 (R)[^{[f]}]</td>
</tr>
<tr>
<td>4</td>
<td>CH₂CH(CH₃)₂</td>
<td>4</td>
<td>32</td>
<td>53 (S)[^{[g]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>35</td>
<td>35 (S)[^{[h]}]</td>
</tr>
<tr>
<td>5</td>
<td>CH(CH₃)₂</td>
<td>4</td>
<td>20</td>
<td>61 (S)[^{[i]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>46</td>
<td>50 (S)[^{[j]}]</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>4</td>
<td>54</td>
<td>30 (R)[^{[k]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>58</td>
<td>28 (S)[^{[l]}]</td>
</tr>
<tr>
<td>7</td>
<td>CH₃OCH₃</td>
<td>4</td>
<td>95</td>
<td>8 (R)[^{[m]}]</td>
</tr>
<tr>
<td>8</td>
<td>acetonaphthone[^{[n]}]</td>
<td>4</td>
<td>41</td>
<td>48 (S)[^{[o]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>43</td>
<td>46 (S)[^{[p]}]</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: BINOL (0.02 mmol), AlMe₃ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μL); room temperature, N₂ for 16 h.
[b] Based on substrate. [c] R isomer obtained from reactions with (R)-(+-)-BINOL. [d] S isomer obtained from reaction with (S)-(+-)-BINOL.
[e] acetonaphthone is the whole reactant, not an R group (not shown in Eq. (2)).

1. More e-rich ketone- lower yield, ee.
2. Excess i-ProOH increases the yield
3. Methoxy-group, disrupts chiral TS
4. Bulkier Ar- higher ee.

10a. Enantioselectivity.

Chiral aluminum catalysts

Better yields, same ee.

Favorable equilibrium: 10%(R)-BINOL,

20eq i-PrOH, 20eq Acetone, (R)-phenylethanol
decreased ee from 98 to 93%

Table 2. Electronic effect on the MSPV reduction.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>2-Propanol (equivalents[b])</th>
<th>Yield [%]</th>
<th>Product ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4</td>
<td>54</td>
<td>30 (R)[c]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>80</td>
<td>25 (R)[d]</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>4</td>
<td>44</td>
<td>30 (R)[c]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>62</td>
<td>20 (S)[d]</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>4</td>
<td>55</td>
<td>30 (R)[c]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>55</td>
<td>30 (R)[d]</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>4</td>
<td>70</td>
<td>30 (R)[c]</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>4</td>
<td>70</td>
<td>30 (R)[c]</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: BINOL (0.02 mmol), AlMe₃ (0.02 mmol), ketone (0.20 mmol), and toluene (500 µL); room temperature, N₂ for 16 h.
[b] based on substrate. [c] R isomer obtained from reactions with (R)-(+)-BINOL. [d] S isomer obtained from reactions with (S)-(−)-BINOL.

**10b. Enantioselectivity.**

*Chiral aluminum catalysts, role of the ligand.*

Table 3. Effect of ligand additive on the MSPV reduction.\[^{[a]}\]

\[
\text{R} = \text{Me} \quad \text{R} = \text{CH}_2\text{Cl}
\]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ligand:AlMe(_3)</th>
<th>Yield [%]</th>
<th>ee [%]</th>
<th>Ligand</th>
<th>Ligand:AlMe(_3)</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINOL</td>
<td>1:1</td>
<td>54</td>
<td>30</td>
<td>BINOL</td>
<td>1:1</td>
<td>99</td>
<td>80</td>
</tr>
<tr>
<td>BINOL</td>
<td>2:1</td>
<td>0</td>
<td>–</td>
<td>BINOL</td>
<td>2:1</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>1:1</td>
<td>58</td>
<td>0</td>
<td>1</td>
<td>1:1</td>
<td>99</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>2:1</td>
<td>40</td>
<td>0</td>
<td>1</td>
<td>2:1</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>4:1</td>
<td>20</td>
<td>0</td>
<td>1</td>
<td>4:1</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>25</td>
<td>0</td>
<td>2</td>
<td>1:1</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>1:1</td>
<td>7</td>
<td>0</td>
<td>3</td>
<td>1:1</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Reaction conditions: ligand 1–3 (0.02 mmol), AlMe\(_3\) (0.02 mmol), ketone (0.20 mmol), iPrOH (0.80 mmol), and toluene (500 μL); room temperature, N\(_2\) for 16 h.

---

1. Excess of the ligand-detrimental
2. Primary amines-low yield
   - prevent at all
3. Ligand (1) - same yield, no ee
4. Even (2) works, but worse

10c. Enantioselectivity.

Chiral aluminum catalysts

1. Active catalyst structure proposed see above. [(BINOL)AlMe(THF)] gave the same yield and ee with alpha-Br-acetophenone and i-PrOH

2. 2 sites bound to BINOL, two -to the reagents. If not- lower yield/ee

3. Excess i-PrOH competes with BINOL, => higher yield, but lower ee (not much, however)

11. CONCLUSIONS:

1. An old reaction with a lot to discover.

2. Kinetic or thermodinamic control:
   - stoichiometric amount of Al(Oi-Pr)_3 vs. catalitic amounts of not so tightly bound promoters.

3. Chemo-, diastereo-, enantioselectivity:
   - the best reducing agents (dialky ketones; a,b-unsaturated);
   - the best oxidizing agents (acetone, cyclohexanone, diaryl ketones, aldehydes); 1 or more equivalents;
   - cis-substituted cycloalkanols under kinetic control vs. trans- under thermodinamic;
   - use of chiral alcohols or catalysts (MPV- or hydride-type).

4. Usually basic conditions, but can be neutral:
   - from alkali metal alkoxides, through Al-alkoxides, to Ru(II)-based catalysts;

5. Environmentally friendly, cheap, industrially convenient (heterogenous variant).

6. Very tough to compete with metal hydrides and direct hydrogenation.