Lanthanides in Organic Synthesis

Heathcock / MacMillan Seminar
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I. Properties of the lanthanides
II. Lanthanide metals
III. Divalent lanthanides
IV. Trivalent lanthanides
V. Tetravalent lanthanides
VI. Enantioselective processes

Oxidation States of the Lanthanides

- Most stable oxidation state of the lanthanides is +3
- For dipositive lanthanides Sm$^{2+}$ (f$^6$, nearly half-filled), Eu$^{2+}$ (f$^7$, half-filled), and Yb$^{2+}$ (f$^{14}$, filled) are known with relative stability in H$_2$O being
  
  Eu$^{2+}$ >> Yb$^{2+}$ >> Sm$^{2+}$
- Ce$^{4+}$ (f$^2$) is the only tetrapositive lanthanide stable in water

- Ionization energies reflect relative energies of the 4f, 5d, 6s orbitals
- 6s electrons are removed first, hence first two ionization energies for all lanthanides are essentially the same
- Third ionization usually results from removal of an electron from the 5d orbital
- Fourth ionization energy reflects successive electron occupation of 4f orbitals

Reviews: Molander Chem. Rev. 1992, 92, 29
Properties of the Lanthanide Ions

- Lanthanide contraction: ionic radii decrease regularly with increasing atomic number
- Due to ineffective shielding of the 4f electrons  
  → increased effective nuclear charge
- Ionic radii larger than those of d-block elements, can accommodate up to 9 to 12 ligands

- Upon ionization, f-orbitals are greatly contracted towards the nucleus  
  → effectively eliminates covalent bonding interaction with ligands
- Highly ionic ligand-metal interaction  
  → no need for orbital overlap
- Coordination geometries defined by electrostatic and steric considerations

Organocerium Reagents
Addition to Carbonyls

Barbier Reactions

\[
\begin{align*}
\text{PhI} & \quad \xrightarrow{\text{Ce}^3, \, 0 \, ^\circ \text{C}, \, 4 \text{h}} \quad \text{PhCH(OH)CH}_2\text{Ph} \\
\text{PhCH(OH)CH}_2\text{Ph} & \quad \text{59\%}
\end{align*}
\]

- Ketones and aldehydes react smoothly with organocerium reagents
- Esters and nitriles are unreactive

\[\text{Imamoto J. Org. Chem. 1984, 49, 3904.}\]

\[
\begin{align*}
\text{PhLi} & \quad \xrightarrow{\text{CeCl}_3, \, -78 \, ^\circ \text{C}, \, \text{THF}} \quad \text{PhC}^\oplus\text{Cl}_2
\end{align*}
\]

- Even easily enolizable ketones undergo addition in excellent yields
- Organocerium compounds can be prepared from the corresponding organolithium or organomagnesium compounds

\[\text{Imamoto Tetrahedron Lett. 1984, 25, 4233.}\]

Reformatsky Reactions

\[
\begin{align*}
\text{XCH(OEt)}_2 & \quad \xrightarrow{\text{Ce, cat. I}_2, \, \text{THF}} \quad \text{XCH(OEt)}_2
\end{align*}
\]

\[X = \text{I, Br}\]

\[\text{Fukuzawa J. Org. Chem. 1990, 55, 1628.}\]
**Lanthanide Metals: Sm**

**Cyclopropanation of Allylic Alcohols**

Using samarium, only olefin with allylic hydroxyl group is cyclopropanated.

Samarium offers enhanced diastereoselectivity over conventional reagents.

**Lanthanide Metals: Reductions**

**Dissolving Metal Reductions Using Yb**

Similar to Birch reduction with alkali metal, however avoids strongly basic hydroxide upon workup.

**Hydrogenation Using Lanthanide Alloys**

Reduces alkenes, alkenes, aldehydes, ketones nitriles, imines, and nitro compounds

Not poisoned by amino or halogen containing compounds.
Divalent Lanthanides: Samarium Iodide

Reduction of α-Substituted Ketones and Esters

\[
\begin{align*}
\text{MeO} & \quad \text{Sml}_2 \quad \text{THF-MeOH, -78 °C} \\
\text{H} & \quad \text{OCH}_2\text{OMe} \\
92\% & \\
\text{Me} & \quad \text{Sml}_2 \quad \text{THF-\text{tBuOH}, 25 °C} \\
\text{Me} & \quad \text{Me} \\
87\% & \\
\end{align*}
\]

- α-Halo, sulfoxides, sulfones, and α-oxygenated ketones are reduced
- Primary iodides, esters, and ketones are unaffected

\[
\begin{align*}
\text{C}_9\text{H}_{11}\text{H} & \quad \text{Sml}_2 \quad \text{THF-MeOH, -90 °C} \\
\text{H} & \quad \text{CH}_2\text{COCH}_3 \\
94\% & \\
\end{align*}
\]

Reduction of optically active epoxy ketones gives β-hydroxy ketones without loss of optical purity

Divalent Lanthanides: Samarium Iodide

Intramolecular Barbier Reactions

\[
\begin{align*}
\text{O} & \quad 2 \text{ eq. Sml}_2, \text{ cat. Fe(DMB)}_3 \quad \text{THF / -78 °C to rt} \\
\text{HO} & \quad 80\% \quad 100:0 \text{ d.s.} \\
\end{align*}
\]

- Method overcomes difficulties associated with using Mg, Li, Na
- Synthetically useful for substrates which allow for control of diastereoselectivity

\[
\begin{align*}
\text{O} & \quad 2 \text{ eq. Sml}_2, \text{ cat. Fe(DMB)}_3 \quad \text{THF / -78 °C to rt} \\
\text{HO} & \quad 75\% \quad 1:1 \text{ d.s.} \\
\end{align*}
\]

Divalent Lanthanides: Samarium Iodide

Intramolecular Reformatsky Reactions

\[\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{R}_6 \xrightarrow{2\text{SmI}_2, -78^\circ C/THF}\text{R}_1\text{R}_2\text{R}_3\text{R}_4\text{R}_5\text{R}_6\]

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>R_4</th>
<th>R_5</th>
<th>R_6</th>
<th>yield</th>
<th>d.r.</th>
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</thead>
<tbody>
<tr>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
<td>&gt;200:1</td>
</tr>
<tr>
<td>tBu</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>85</td>
<td>&gt;200:1</td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>85</td>
<td>3:1</td>
</tr>
</tbody>
</table>

- Large substituent in the R_1 position usually results in high diastereoselectivity.

<table>
<thead>
<tr>
<th>n</th>
<th>yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73</td>
<td>&gt;200:1 d.r.</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>29:1</td>
</tr>
</tbody>
</table>

- Reactions to form bicyclic systems proceed with very high diastereoselectivities although yields are sometimes moderate to low.

Divalent Lanthanides: Samarium Iodide

Radical Carbonyl-Alkene Couplings

Mechanism

\[\begin{align*}
\text{R}_1\text{R}_2 & \xrightarrow{\text{SmI}_2} \text{SmI}_2 \cdot \text{EWG} \\
\text{SmI}_2 \cdot \text{EWG} & \xrightarrow{\text{R}_1\text{R}_2} \text{R}_1\text{R}_2\text{SmI}_2 \\
\text{SmI}_2 \cdot \text{EWG} & \xrightarrow{\text{ROH}} \text{DSmI}_2
\end{align*}\]


<table>
<thead>
<tr>
<th>Additive</th>
<th>Time</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 h</td>
<td>71%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>HMPA</td>
<td>1 min</td>
<td>96%</td>
<td>1:1</td>
</tr>
</tbody>
</table>


- HMPA dramatically improves reaction rate and yield.
- Diastereoselectivity is improved when \(\gamma\)-disubstituted lactones are formed.
**Trivalent Lanthanides: Luche Reduction**

Selective 1,2 Reduction of α-Enones

**Mechanism**

NaBH₄ ⇌ CeCl₃ · 7H₂O → BH₄⁻(OR)₇

- Sodium borohydride is rapidly converted to an alkoxide species
- Carbonyl is activated through hydrogen bonding by a lanthanide-bound molecule solvent
- Hard borohydride preferentially attacks the hard carbonyl carbon


\[ \text{NaBH}_4 \xrightarrow{\text{CeCl}_3 \cdot 7\text{H}_2\text{O}} \text{BH}_4^-\text{(OR)}_7 \]

![Diagram of the reaction mechanism](image)


**Trivalent Lanthanides: Reduction of Ketones**

Selective Reduction of Ketones in the Presence of Aldehydes

\[ \text{CHO} \rightarrow 1.5 \text{eq. NaBH}_4, \text{CeCl}_3 \cdot 6\text{H}_2\text{O} \rightarrow \text{OH} \]

1.5:1 EtOH:H₂O 78%

- Eliminates need for three step protection-reduction-deprotection scheme


**Rationale**

- In the presence of lanthanide (III) salts aldehydes yield hydrates
- Ketones remain unaffected

- Hemiketal or Ketal formation is ruled out because similar results (within 5%) were obtained with MeOH and iPrOH

**Imines: Reduction of Ketones**

**ans-Tischenko Reduction**

\[
\begin{align*}
\text{MeCHO} & \quad \text{40% SmI}_2 \\
\text{1.5 h} & \quad \text{anti:syn} > 99:1
\end{align*}
\]

by \(\beta\)-hydroxy stereocenter dominates \(\alpha\)-methyl stereocenter

\[
\begin{align*}
\text{MeCHO} & \quad \text{40% SmI}_2 \\
\text{1.5 h} & \quad \text{89\%} \\
\text{>99:1}
\end{align*}
\]


\[
\begin{align*}
\text{cat. SmI}_2(\text{OtBu}) & \quad \text{THF, rt} \\
\text{89\%}
\end{align*}
\]

**Trivalent Lanthanides: Hetero-Diels-Alder**

\[
\text{CH}_2\text{Cl}_2, \text{rt, 48 h} \quad 94\%
\]

- Exclusive carbonyl addition
- Reactions proceed with high endo selectivity
- Bulky catalyst prefers to occupy exo position

**Inverse Demand**

\[
\text{Yb(fod)}_3 (5\text{ mol }\%) \quad \text{neat, rt, 2h} \quad 60-80\%
\]

R = Me, Ph

**Trivalent Lanthanides: Reduction of Ketones**

**Evans-Tischenko Reduction**

\[
\text{R}_2\text{CHO} \quad 15\% \text{ Sml}_2 \quad \text{anti: syn >99:1}
\]

R\(_1\) = n-hexyl, iPr; R\(_2\) = Me, iPr, Ph

- Asymmetric induction by \(\beta\)-hydroxy stereocenter dominates \(\alpha\)-methyl stereocenter

**Intramolecular Tischenko Reaction**

\[
\text{THF, rt} \quad 89\%
\]

**Tetravalent Lanthanides: Oxidations**

**Selective Secondary Alcohol Oxidation**

\[
\text{OH} \xrightarrow{\text{CAN (10 mol%), NaBrO}_3} \text{MeCN-H}_2\text{O, 80 °C, 0.5 h}} \quad 89\%
\]

**Oxidation of Phenol Ethers**

\[
\begin{align*}
\text{MeO}_x & \quad \text{Ome} \\
\text{MeO}_y & \quad \text{Ome} \\
\text{MeO}_z & \quad \text{Ome} \\
\text{MeO}_w & \quad \text{Ome}
\end{align*}
\]

\[
\xrightarrow{\text{CAN, MeCN-H}_2\text{O}} \quad 71\%
\]

\[\text{R} = \text{TBS}\]

**Oxidation of Nitro Compounds to Ketones**

\[
\begin{align*}
\text{NO}_2 & \quad \text{R}_1 \quad \text{R}_2 \\
\text{TMSCl, Li}_2\text{S} & \quad 25^\circ\text{C, 6-8 h}}
\end{align*}
\]

\[\text{CN, 25 °C} \quad 5 \text{ min.}
\]

**Enantioselective Reactions**

**Europium(III) Hfc Promoted Hetero-Diels-Alder**

\[
\begin{align*}
\text{Me} & \quad \text{OtBu} \\
\text{TMSO} & \quad \text{R} \\
\text{Me} & \quad \text{OtBu} \\
\text{TMSO} & \quad \text{R}
\end{align*}
\]

\[\xrightarrow{\text{Eu(hfc), (1 mol %), neat, -10 °C}} \quad 4 \text{ steps}
\]

\[\text{OMe} \quad \text{OH} \quad \text{Ph} \quad \text{R} \quad \text{Ph}
\]

\[\text{R} = \text{H} \quad 58\% \text{ ee}
\]

\[\text{R} = \text{Me} \quad 55\% \text{ ee}
\]

- Larger C\textsubscript{1} alkoxy substituents gave increased ee

\[
\begin{align*}
\text{OMe} & \quad \text{H} \quad \text{Ac}_2\text{Bu} \quad \text{Eu(hfc), (5 mol %), rt}}
\end{align*}
\]

<table>
<thead>
<tr>
<th>trans</th>
<th>cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>yield</td>
<td>79</td>
</tr>
<tr>
<td>ee</td>
<td>19</td>
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</tbody>
</table>

**References**


Larger C\textsubscript{1} alkoxy substituents gave increased ee
Enantioselective Reactions

Yb(III) BINOL Hetero-Diels-Alder

Yb-BINOL-amine catalyst
20 mol %
CH$_2$Cl$_2$, -78 to 0 °C
94%

Yb(OTf)$_3$
1 mmol
Me
O
N
O
Me
Me
Me
O
Me
CH$_2$Cl$_2$
O
O
Yb
O
TfO
OTf
N
O
R
H
Me
Me
Me

Reaction proceeds only very slowly without BINOL amine not interacting with metal
Larger amines typically give higher ee
Spectroscopic evidence for amine-BINOL H-bonding


Enantioselective Reactions

Yb(III) BINOL Hetero-Diels-Alder: Reversal of Enantioselectivity

20 mol % catalyst
20 mol % additive
MS 4Å
CH$_2$Cl$_2$, 0 °C

<table>
<thead>
<tr>
<th>additive</th>
<th>R</th>
<th>% yield</th>
<th>endo:exo</th>
<th>2S, 3R</th>
<th>2R, 3S</th>
<th>% yield</th>
<th>endo:exo</th>
<th>2S, 3R</th>
<th>2R, 3S</th>
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<tbody>
<tr>
<td></td>
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<td>77</td>
<td>89:11</td>
<td>98</td>
<td>2</td>
<td>83</td>
<td>93:7</td>
<td>9</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>nPr</td>
<td>81</td>
<td>80:20</td>
<td>93</td>
<td>8</td>
<td>81</td>
<td>91:9</td>
<td>10</td>
<td>90</td>
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</tbody>
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**Enantioselective Reactions**

**Heterobimetalllic Catalysis**


**Nitroaldol**

\[ \text{R}_1\text{CHO} + \text{R}_2\text{NO}_2 \quad 3-10 \text{ mol}\% \text{ cat} \quad \text{THF}, -40^\circ \text{C} \rightarrow \text{OH} \text{R}_2 \text{NO}_2 \]

78-97 % yield

74:27 to 93:7 syn:anti

66-97 % ee


Catalyst acts as Lewis acid and Lewis base

**Explanation of syn selectivity**


**Enantioselective Reactions**

**Heterobimetallic Catalysis**

**Michael Reaction**

\[ \text{MeO} \]

\[ \text{MeO} \]

\[ \text{NaO} \]

\[ \text{NaO} \]

\[ \text{NaO} \]

\[ \text{NaO} \]

\[ \text{Li} \]

\[ \text{Li} \]

\[ \text{Li} \]

\[ \text{Li} \]

Li and K catalysts gave poor ee

Metal free La-BINOL complex provides almost no enantioselectivity


<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>89</td>
<td>72</td>
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<td><img src="image2.png" alt="Structure Image" /></td>
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<tr>
<td><img src="image3.png" alt="Structure Image" /></td>
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<td>83</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>93</td>
<td>77</td>
</tr>
</tbody>
</table>
Enantioselective Reactions

Miscellaneous Reactions

Olefim Hydrogenation

\[
\text{Me} = \text{Ph} 
\stackrel{H_2 (1 \text{ atm}), \text{catalyst}}{\longrightarrow} 
\text{Me} = \text{Ph}
\]

100% heptane, -78 °C

96% ee

(Marks, T. J. J. Am. Chem. Soc., 1992, 114, 2761.)

Lanthanide hydrogenation catalysts are highly reactive

\[
\text{R}^+ = (-)-\text{menthyl}
\]

Ketone Reduction

\[
\text{O} 
\text{O}
\stackrel{\text{SnI}_2 \text{THF-HMPA, rt, 30 min}}{\longrightarrow} 
\text{OH}
\]

56% ee

200 mol% quinidine

(Takeuchi Chem. Lett. 1988, 403.)

Summary

- Lanthanide metals are useful for reduction of functional groups and for carbon-carbon bond forming reactions

- Europium, Samarium, and Ytterbium can form relatively stable divalent states. Europium is stable enough to exist in water. SmI\(_2\) is the most widely employed Ln(II) and is used for one electron reductive reactions

- Trivalent lanthanides are hard Lewis acids with high oxophilicity and as such are employed in several highly selective reactions (Luche reduction, hetero-Diels-Alder)

- f-orbital electrons are imperfect shielders and so Ln(III) have their f-orbitals greatly contracted towards the nucleus. This effectively eliminates covalent bonding interactions with ligands and therefore lanthanide-ligand geometries are largely determined by steric considerations. Asymmetric lanthanide promoted processes are therefore less straightforward than those using main group or d-block elements

- Ce(IV) is the only tetrapositive lanthanide which is stable in water and to date is the only synthetically useful Ln(IV) with applications in the oxidation of functional groups such as alcohols and phenol ethers.

- Note: Scandium (3d\(^1\)) and Yttrium (4d\(^1\)) have similar properties to those of the lanthanides and are often treated as lanthanides