Lewis Acids In Free Radical Reactions

Outline

I. Early efforts to control stereochemistry in acyclic radical reactions

II. Nucleophilic Radical Reactions
   a. Conjugate addition reactions.
   b. Reactions of oximes, imines, and hydrazones.

III. Electrophilic Radical Reactions
   a. Allylation and Reduction
   b. Atom-Transfer Reactions
   c. Mn(III)-Initiated Cyclizations

Reviews

Renaud and Gerster *ACIEE* 1998, 37, 2562


Zachary Sweeney
Evans Group Seminar
February 23, 2001
Formation of CC Bonds By Addition of Radicals to Alkenes

- Simple alkyl radicals are nucleophilic

\[
\begin{align*}
\cdot & + \underset{\text{Z}}{\text{Z}} \quad \kappa \\
\end{align*}
\]

- Alkenes are attacked almost exclusively at the terminal position of the alkene.

\[
\begin{align*}
R & \cdot \quad \text{SOMO} \\
\quad & \quad \text{LUMO} \\
\quad & \quad \text{HOMO}
\end{align*}
\]

- Reactions are strongly exothermic since a σ-bond is formed and a π-bond is broken.

- According to FMO theory, raising the energy of the SOMO (increasing SOMO-LUMO interactions) will increase the rate of reactions.

- Electrophilic radicals react with electron-rich alkenes. In this case the SOMO-HOMO interaction is dominant.

\[
\begin{align*}
\text{Z} & \quad k_{\text{rel}} \\
\text{CHO} & \quad 34 \\
\text{CO}_2\text{CH}_3 & \quad 6.7 \\
\text{C}_6\text{H}_6 & \quad 1.0 \\
\text{^nC}_4\text{H}_9 & \quad 0.0004
\end{align*}
\]

Giese, ACIEE, 1983, 753.
Allylic Strain Effects in Radical Reactions

- Enolate Radical Chemistry

\[
\begin{align*}
\text{R} & \quad \text{Me} \quad \text{CH}_3 \\
\text{CO}_2\text{Me} & \quad \text{Bu}_3\text{SnH} \quad 20 \, ^\circ\text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{CH}_3 \\
\text{CO}_2\text{Me} & \\
\end{align*}
\]

\[+\]

\[
\begin{align*}
\text{Me} & \quad \text{CH}_3 \\
\text{CO}_2\text{Me} & \\
\end{align*}
\]

- Calculations and EPR studies suggest planar enolate conformation arising from conjugation of the radical with the ester functionality.

\[
\begin{align*}
\text{tBu} & \quad \text{anti} : \text{syn} \\
& \quad 25 : 1 \\
\text{TMS}_3\text{Si} & \quad 16 : 1 \\
\text{Ph} & \quad 2 : 1 \\
\end{align*}
\]

**Ground States**

- A-strain conformation
  - \( E = 0.0 \) kcal/mol
- Felkin-Anh conformation
  - \( E = 1.5 \) kcal/mol

**Transition States**

- \( \text{tBu} \) (anti product)
  - \( E = 0.0 \) kcal/mol
- \( \text{SiH}_3 \) (syn product)
  - \( E = 2.7 \) kcal/mol

Giese, Chemtracts-Organic, 1994, 355
Early Efforts Toward Acyclic Stereochemical Control

- Amide groups were used to provide conformational control.

- C$_2$-symmetric auxiliaries or dipole-dipole effects were used to fix the orientation of the auxiliary.

Porter, JACS, 1989, 111, 8309, 8311.
Early Efforts Toward Auxiliary-Based Control

- Curran, Rebek - auxiliary that can control β-stereoselectivity

\[
\text{EtO}\overset{\text{Xaux}}{\text{C}}O \quad \overset{\overset{^1\text{BuHgCl, NaBH}_4}{\text{CH}_2\text{Cl}_2, -40 \, ^\circ\text{C}}}{\longrightarrow} \quad \text{EtO}\overset{\text{Xaux}}{\text{C}}O + \text{EtO}\overset{\text{Xaux}}{\text{C}}O
\]

- No α-addition was observed under these conditions

- The auxiliary was also effective for radical allylation reactions.

\[
\text{Me}\overset{\text{Xaux}}{\text{C}}O \quad \overset{\text{SnBu}_3, \text{AIBN}}{\text{80 \, ^\circ\text{C}}} \quad \overset{\text{dr = 96:4}}{\text{Me}}\overset{\text{Xaux}}{\text{C}}O
\]

- Auxiliary Synthesized in 7 steps from

Curran, Rebek, JACS, 1992, 114, 7007.
Lewis Acid-Enhanced Reactivity of Unsaturated Esters and Amides

- Lewis acids increase yields of conjugate additions

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{O} & \quad \text{Me} \\
\end{align*}
\]

- Chelate control

\[
\begin{align*}
\text{Me} & \quad \text{OH} & \quad \text{CO}_2 \text{Bu} \\
\text{Me} & \quad \text{OH} & \quad \text{CO}_2 \text{Bu} \\
\end{align*}
\]

Asymmetric Radical Addition to α-Sulfinylcyclopentenones

1) 1.1 equiv Lewis Acid
2) Et₃B, tBuI

Lewis Acid
None
Ti(OiPr)₄
TiCl₂(OiPr)₂

A : B
38:62
56:44
91:9

Auxiliaries can be cleaved with aluminum amalgam in THF/H₂O

Toru, JACS, 1993, 10464.
Toru, JOC, 1997, 7794
Lewis Acid Promoted Diastereoselective Radical Cyclization

- Coordination of the Lewis acid controls s-cis/s-trans conformation of ester

Lewis Acid          | R : S  \\  \\  None | 67:33  \\  BF₃ | 94:6  \\  MAD | 96:4

Nishida, JACS, 1994, 6455.
Enantioselective Lewis Acid Promoted Radical Cyclization

- First report of chiral Lewis Acid mediated radical cyclization

\[
\text{Lewis Acid} \quad \text{Bu}_3\text{SnH}, \text{Et}_3\text{B} \\
\text{CH}_2\text{Cl}_2, -78 \degree \text{C}
\]

\[
\text{CO}_2\text{c-Hex} \quad \text{Lewis Acid} \quad \text{Bu}_3\text{SnH}, \text{Et}_3\text{B} \\
\text{CH}_2\text{Cl}_2, -78 \degree \text{C}
\]

\[
\text{CO}_2\text{R} \quad \text{R} \quad \text{CO}_2\text{R}
\]

- Reactions using the same Lewis Acid and the Weinreb amide provide the S-product in 26% ee.

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>equiv</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Binol)AlMe</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SiPh\text{3}</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>O\text{Al-Me}</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>SiPh\text{3}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lewis Acid Catalyzed Intermolecular Radical Additions

\[
\text{Substrate} \quad \text{Lewis Acid} \quad \text{Yield (%)} \quad \text{dr}
\begin{array}{|c|c|c|c|}
\hline
A & \text{None} & 60 & 1.3:1 \\
A & \text{BF}_3\cdot\text{OEt}_2 & 80 & 1.3:1 \\
A & \text{Et}_2\text{AlCl} & 70 & 4:1 \\
A & \text{Sc(OTf)}_3 & 90 & 15:1 \\
A & \text{Yb(OTf)}_3 & 93 & 25:1 \\
B & \text{Yb(OTf)}_3 & 89 & 45:1 \\
\hline
\end{array}
\]

- Very strong Lewis Acids (i.e. TiCl_4) gave products of hydride reduction.
- Reactions using TMS_3SiH failed.

Optimized Reaction Employing Catalytic Lewis Acid

\[
\begin{align*}
\text{Substrate} & \quad \text{Lewis Acid} & \quad \text{Yield (%)} & \quad \text{dr} \\
A & \text{0.1 equiv Yb(OTf)}_3 & 60 & 16:1 \\
& \text{5 equiv }^3\text{PrI, 2 equiv Bu_3SnH} & & \\
& \text{4 equiv Et}_3\text{B, CH}_2\text{Cl}_2/\text{THF, -78 °C} & & \\
\end{align*}
\]

- dr increased to 23:1 with 0.1 equiv ethylene glycol

Sibi, JACS, 1995, 10779.
Sibi, JACS, 1999, 7517.
Diastereoselective Radical Addition: Effect of the Nucleophile

\[
\text{Yb(OTf)}_3 (1 \text{ eq}) \\
\text{RX (5 eq), Bu}_3\text{SnH (2 eq)} \\
\text{Et}_3\text{B (1 eq), CH}_2\text{Cl}_2/\text{THF} -78 \degree\text{C}
\]

<table>
<thead>
<tr>
<th>RX</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{iPrI})</td>
<td>90</td>
<td>25:1</td>
</tr>
<tr>
<td>(\text{iPrBr})</td>
<td>90</td>
<td>25:1</td>
</tr>
<tr>
<td>(\text{EtI})</td>
<td>84</td>
<td>12:1</td>
</tr>
<tr>
<td>(\text{cHexI})</td>
<td>92</td>
<td>16:1</td>
</tr>
<tr>
<td>(\text{tBuI})</td>
<td>82</td>
<td>14:1</td>
</tr>
<tr>
<td>(\text{MeOCH}_2\text{Br})</td>
<td>84</td>
<td>14:1</td>
</tr>
<tr>
<td>(\text{MeC(O)Br})</td>
<td>85</td>
<td>7:1</td>
</tr>
</tbody>
</table>

Low yields were observed with PhI, MeI, PhCH\(_2\)I, AllyI, AcOCH\(_2\)Br, and BrCH\(_2\)CO\(_2\)Bn.

Sibi, JACS, 1999, 7517
Intermolecular Additions to Fumarate Derivatives

\[
\begin{align*}
\text{N O} & \quad \text{CO}_2\text{Et} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
1 \text{ equiv Lewis Acid} \\
5 \text{ equiv } i\text{PrI, 2 equiv } Bu_3\text{SnH} \\
Et_3B/O_2, CH_2Cl_2, -78 \degree C
\end{align*}
\]

\[
\begin{align*}
\text{N O} & \quad \text{CO}_2\text{Et} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
& \quad i\text{Pr} \\
& \quad Ph
\end{align*}
\]

- All yields > 90%, many lanthanides function well.
- Stoichiometric LA required for high dr, although regioselectivity is still high.

**Synthesis of Nephosteranic Acid:**

\[
\begin{align*}
\text{N O} & \quad \text{CO}_2\text{Et} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

1) Sm(OTf)\text{3} \\
ClCH\text{2}I, Bu\text{3}SnH

1) Bu\text{2}BOT\text{f}, NEt\text{3}; H\text{2}C\text{11}CHO

2) LiOH/H\text{2}O\text{2}

\text{Sibi, ACIEE, 1997, 274}
α-D-Glucopyranoside Derivatives as Auxiliaries

When no LA was used, the product was racemic.
Lower selectivity was observed with 1 equiv of Et₂AlCl.

Tadano, Synlett, 2000, 979

Analogous Cuprate Additions:

66% yield, > 99 : 1 dr

Enantioselective Lewis Acid Catalysis in Radical Conjugate Additions

- Experiments with stoichiometric Lewis Acid

\[
\begin{array}{cccc}
\text{R}_1 & \text{R}_2 & \text{Lewis Acid} & \text{Yield} & \text{ee} \\
\text{Ph} & \text{^1Pr} & (\text{iPrBox})\text{MgI}_2 & 88 & 82 \\
\text{Me} & \text{^1Bu} & (\text{PhBox})\text{Zn(OTf)}_2 & 90 & 82 \\
\end{array}
\]

- Experiments with catalytic Lewis Acid

\[
\begin{array}{cccc}
\text{eq Mg} & \text{Yield} & \text{ee} \\
0.2 & 86 & 67 \\
0.05 & 57 & 40 \\
\end{array}
\]

Sibi, Porter, JACS, 1996, 9200
Improved Selectivity using (Indabox)MgI₂ Complexes

\[
\begin{align*}
\text{Eq LA} & \quad \text{Yield} & \quad \text{ee} \\
1 & \quad 88 & \quad 93 \\
0.2 & \quad 95 & \quad 96 \\
0.05 & \quad 92 & \quad 90
\end{align*}
\]

- Other ligand backbone rings gave lower enantioselectivities (Bu = 82% ee, Pent = 82% ee).
- No other reactions were reported.

Model

- Authors suggest an octahedral model with cis-iodine ligands.
- This model provides the same selectivity that is predicted from a four-coordinate tetrahedral metal-substrate complex.
The Pyrazole Template in Radical Conjugate Additions

An oxazolidinone template gave the opposite enantiomer

Reactions with other Mg(II), Zn(II) salts were unselective.

Unsubstituted pyrazoles gave low yields

Model

Other Conjugate Radical Addition Reactions

Almost 30 Lewis Acids were screened.


Additive was shown to compete with substrate for coordination to the zinc center.

Carbon Radical Addition to Glyoxylic Oxime Ethers

configuration of substrate is controlled by dipole and steric interactions
reaction was also run without Bu$_3$SnH

Chiral Lewis Acid promoted additions

For reactions on solid phase see Naito, Org. Lett., 2000, 1443

Naito, JOC, 2000, 176
Radical Addition to Oxime Ethers: β-Amino Acids

\[
\begin{align*}
&\text{SO}_2 &\text{N} &\text{O} \\
&\text{NOBn} &\text{Ph} &\text{R} \quad \text{Bn} \quad \text{O} \\
&\text{Toluene, 20 °C} & & \\
&\text{BF}_3\text{OEt}_2 (9 \text{ equiv}) & & \\
&\text{RI (30 equiv), Et}_3\text{B (9 equiv)} & & \\
\end{align*}
\]

- no reaction occurred in the absence of BF\(_3\)OEt\(_2\)

\[
\begin{align*}
&\alpha\text{-Substituent required for good selectivity} \\
&\text{as above} \\
&\text{Naito, Org. Lett., 1999, 569}
\end{align*}
\]
Radical Additions to Glyoxylate Imines

\[
\text{MeO}_2\text{C} \quad \text{N} \quad \text{MeO}_2\text{C} \\
\text{OMe} \quad \text{OMe} \quad \text{Ph} \quad \text{Me} \quad \text{Me} \\
\text{+I} \quad \text{MEtx} / \text{O}_2 \quad \text{CH}_2\text{Cl}_2 \\
\text{NHAux} \quad \text{MeO}_2\text{C} \quad \text{Ph} \quad \text{Me} \\
\text{Me} \quad \text{Me} 
\]

via

\[
\text{Et}^* \quad \text{O} \quad \text{O} \quad \text{Et} \quad \text{MeO}_2\text{C} \quad \text{N} \quad \text{MeO}_2\text{C} \\
\text{Me} \quad \text{Me} \quad \text{Ph} \quad \text{Et} \quad \text{Et} \quad \text{Zn} \\
\text{H} \quad \text{Me} \quad \text{Me} 
\]

<table>
<thead>
<tr>
<th>\text{MEtx}</th>
<th>\text{T (°C)}</th>
<th>\text{dr}</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{BEt}_3</td>
<td>20</td>
<td>55 : 45</td>
</tr>
<tr>
<td>\text{ZnEt}_2</td>
<td>-40</td>
<td>8 : 92</td>
</tr>
</tbody>
</table>

- MEtx acts as initiator, chain transfer agent, and activating Lewis acid.
- No Sn is required, however a large excess of MEtx and alkyl iodide is used in these reactions

Sn-Free Radical Reactions

\[
\text{EtM} + \text{O}_2 \longrightarrow \cdot \text{O} \cdot \text{O} \cdot \text{M} + \text{Et}^* \\
\text{Et}^* + \text{RI} \longrightarrow \text{Et-I} + \text{R}^* \\
\text{R}^* + \text{MeO}_2\text{C} \equiv \text{N}^* \text{Aux} \quad \text{Me} \quad \text{Et} \longrightarrow \text{Et}^* + \text{MeO}_2\text{C} \equiv \text{N}^* \text{Aux} \quad \text{Me} \quad \text{Et} \\
\]

Bertrand, Tetrahedron, 2000, 3951.
Intermolecular Radical Addition to Hydrazones

In all reactions A was formed as a single diastereomer.

Several alkyl radicals gave 42-60% yields of addition products in >96:4 dr.

Benzaldimine also provided good selectivities.

Auxiliary Removal:

Friestad, JACS, 2000, 8329
Allylation of $\alpha$-Sulfinyl Radicals

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Lewis Acid</th>
<th>trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>propionitrile</td>
<td>—</td>
<td>77:23</td>
</tr>
<tr>
<td>propionitrile</td>
<td>LiClO$_4$</td>
<td>90:10</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>—</td>
<td>82:18</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>MAD (1)</td>
<td>98:2</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>MABR (1)</td>
<td>98:2</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>MABR (0.1)</td>
<td>90:10</td>
</tr>
</tbody>
</table>

- Selectivities were increased with the use of catalytic amounts of Lewis acid.

Renaud, JACS, 1991, 7803
Renaud, Curran, JACS, 1994, 3547
Stereoselective Reactions of 1,2-Dioxy-substituted Radicals

Bu$_3$SnD / AIBN

CH$_2$Cl$_2$, 10 °C

Felkin-Anh

Chelation Control

Lewis Acid

ZnCl$_2$•OEt$_2$

Ti(OiPr)$_3$Cl

MgI$_2$•OEt$_2$

Chelation/Felkin

1 : 2.5

1 : 1.4

1 : 3

17 : 1

Renaud, JACS, 1995, 6607
Stereoselective Chelation Controlled Reductions

- Reduction in the Absence of Lewis Acid

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \\
\text{I} & \quad \text{MeO} \quad + \quad \text{HSnBu}_3 \\
& \quad \text{AIBN/hv} \quad \rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \\
\text{Me} & \quad \text{Me} \quad \text{MeO} \\
\end{align*}
\]

\[> 25 : 1 \text{ anti : syn}\]

- Reduction under Chelation Control

\[
\begin{align*}
\text{Anti:} \\
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \\
\text{I} & \quad \text{MeO} \quad + \quad \text{HSnBu}_3 \\
& \quad 25\% \text{MgI}_2 \quad \rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{Me} \\
\text{H} & \quad \text{Me} \quad \text{MeO} \\
\end{align*}
\]

\[1 : >25 \text{ anti : syn}\]

\[
\begin{align*}
\text{Syn:} \\
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{I} \quad \text{Me} \\
\text{MeO} & \quad \text{O} \quad + \quad \text{HSnBu}_3 \\
& \quad 2 \text{MgI}_2 \quad \rightarrow \\
\text{MeO} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \quad \text{Me} \quad \text{MeO} \\
\end{align*}
\]

\[4 : 1 \text{ anti : syn}\]

Attributed to unfavorable A<sub>1,2</sub> interactions in C-I bond-breaking step under chelation control.

Guindon, JACS, 1991, 9701
Stereoselective Allylations

Reactions with added Lewis acid proceed more readily.
- increased rate of atom transfer?
- increased rate of allyl addition?

Group Transfer Mechanism

Guindon, JACS, 1996, 12528
Stereoselective Addition to $\alpha$-Methylenebutyrolactones

- Reactions in the absence of Lewis Acid are highly diastereoselective.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Bu} \\
\text{BuI, Bu}_3\text{SnH, Et}_3\text{B} & \quad \text{C}_7\text{H}_8, -50 ^\circ \text{C}
\end{align*}
\]

- A radical is generated by addition of alkyl radical to $\alpha,\beta$-unsaturated ester.
- Major product formed by H• delivery from face opposite phenyl group.

- Reversal of diastereoselectivity using bulky Lewis Acids

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Ph} & \quad \text{Bu}_3\text{Sn-H} \\
\text{Bu, Bu}_3\text{SnH, Et}_3\text{B} & \quad \text{C}_7\text{H}_8, -50 ^\circ \text{C}
\end{align*}
\]

Chelation Controlled 1,3-Asymmetric Induction

**Reduction Reactions**

\[
\text{Ph CO}_2\text{Et} \quad \text{OMe} \quad 3 \text{ MgBr}_2 \cdot \text{OEt}_2 
\]

\[
3 \text{ RI, Bu}_3\text{SnH} \quad \text{Et}_3\text{B, CH}_2\text{Cl}_2, 0 ^\circ \text{C} 
\]

\[
\text{Ph CO}_2\text{Et} \quad \text{OMe} \quad \text{syn} \quad + \quad \text{Ph CO}_2\text{Et} \quad \text{OMe} \quad \text{anti} 
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>86</td>
<td>1 : 1.4</td>
</tr>
<tr>
<td>i-Pr</td>
<td>96</td>
<td>4.3 : 1</td>
</tr>
<tr>
<td>c-Hex</td>
<td>70</td>
<td>3.7 : 1</td>
</tr>
<tr>
<td>t-Bu</td>
<td>91</td>
<td>1 : 3.8</td>
</tr>
</tbody>
</table>

- The allylation reaction did not proceed without Lewis Acid.

**Allylation Reactions**

\[
\text{R'} \quad \text{CO}_2\text{Et} \quad \text{OMe} \quad 3 \text{ MgBr}_2 
\]

\[
\text{EtI, SnBu}_3 \quad \text{Et}_3\text{B, CH}_2\text{Cl}_2, 0 ^\circ \text{C} 
\]

\[
\text{R'} \quad \text{CO}_2\text{Et} \quad \text{OMe} \quad \text{syn} \quad + \quad \text{R'} \quad \text{CO}_2\text{Et} \quad \text{OMe} \quad \text{anti} 
\]

<table>
<thead>
<tr>
<th>R'</th>
<th>Yield</th>
<th>&quot;syn&quot; : &quot;anti&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>48</td>
<td>5.5 : 1</td>
</tr>
<tr>
<td>i-Pr</td>
<td>63</td>
<td>&gt;50 : 1</td>
</tr>
<tr>
<td>t-Bu</td>
<td>56</td>
<td>&gt;50 : 1</td>
</tr>
</tbody>
</table>

Zinc Accelerated Allylation of Bromoglycinate Derivatives

\[
\text{O} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{CO}_2\text{Me} \quad \text{Br} \quad \text{ZnCl}_2 \quad \text{•} \quad \text{OEt}_2 \quad \text{SnBu}_3 \\
\text{CH}_2\text{Cl}_2, -78 \degree \text{C}
\]

<table>
<thead>
<tr>
<th>Equiv ZnCl\textsubscript{2}</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>85</td>
<td>87:13</td>
</tr>
<tr>
<td>0.1</td>
<td>65</td>
<td>67:33</td>
</tr>
</tbody>
</table>

- The reaction did not occur in the absence of ZnCl\textsubscript{2}.

Yamamoto, JACS, 1994, 421

Initial report:

- Both reactions could occur by nucleophilic attack on the corresponding imine.

Diastereoselective Radical Allylation

Two equivalents of Lewis Acid were used in most cases.
Several lanthanide triflates also provide high selectivities.
High (>50:1) selectivities were observed using MeI, iPrI, tBuI, cHexI, MeOCH₂Br, MeC(O)Br, and PhC(O)Br.

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>90</td>
<td>1:1</td>
</tr>
<tr>
<td>BF₃•OEt₂</td>
<td>90</td>
<td>1.0 : 1.8</td>
</tr>
<tr>
<td>MgBr₂•OEt₂</td>
<td>93</td>
<td>&gt;100 : 1</td>
</tr>
<tr>
<td>Yb(OTf)₃</td>
<td>90</td>
<td>&gt;100 : 1</td>
</tr>
</tbody>
</table>

Sibi, JOC, 1996, 6090
Study of ρ Selectivity with Chiral Oxazolidinones

![Chemical structure]

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>93</td>
<td>1:1</td>
</tr>
<tr>
<td>MgBr₂•OEt₂</td>
<td>90</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>Sc(OTf)₃</td>
<td>94</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>Yb(OTf)₃</td>
<td>64</td>
<td>5:1</td>
</tr>
</tbody>
</table>

- Low dr observed using Yb(OTf)₃ could not be explained since this Lewis Acid gave good selectivities when similar radicals were generated by addition.

Sibi, ACIEE, 1996, 190
The Mg-mediated reaction with increasing to >50:1 at RT.

Conclusion: reaction selectivity is dependent on the configuration of starting diastereomer, the reactivity of allyl stannane, and the identity of the Lewis Acid.

Sibi, JACS, 2000, 8873
**Explanation for the Reaction Selectivity**

- Rate of rotation must increase with temperature faster than the rate of trapping with allyl stannane.
- The relative rates of rotation vs. allyl trapping explain why slower reacting allyl reagents show higher selectivity.

Sibi, JACS, 2000, 8873
Enantioselective Reduction/Allylation of an α-Iodolactone

Reduction:

\[
\begin{align*}
\text{I} & \quad \text{OMe} \\
\text{O} \quad \text{O} & \quad \text{I} \\
\end{align*}
\]

i) 1 eq MgI₂, ii) 1 equiv Bu₃SnH

85% yield, 62% ee


Allylation:

\[
\begin{align*}
\text{I} & \quad \text{OMe} \\
\text{O} \quad \text{O} & \quad \text{AlMe} \quad 1 \text{OEt₂} \\
\end{align*}
\]

• More than 1 equiv of Et₂O was detrimental to ee.

<table>
<thead>
<tr>
<th>Equiv Al</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>0.2</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>0.1</td>
<td>83</td>
<td>72</td>
</tr>
</tbody>
</table>

Hoshino, JACS, 1997, 11713
Study of $\rho$ Selectivity with Chiral Lewis Acids

Reactions are clearly not proceeding through a common intermediate.
Possible that equilibria of diastereomers of complex of 2 with chiral Lewis Acid are responsible for lower enantioselectivities observed in reactions starting with 2.
Later investigations discovered that XSnBu$_3$ byproduct negatively effected ee.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>R</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>42</td>
</tr>
<tr>
<td>1</td>
<td>$t$Bu</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>$t$Bu</td>
<td>74</td>
</tr>
</tbody>
</table>

Rxns run under identical conditions using 1 equiv (Phbox)Zn(OTf)$_2$.

Porter, JOC, 1997, 6702
Enantioselective Allylation Using Chiral Lewis Acids

\[ \text{Enamine} + R\text{-I} + \text{Bu}_3\text{SnH} \rightarrow \text{Product} \]

\[ 2 \text{ (Phbox)Zn(OTf)}_2 \text{Et}_3\text{B}, -78^\circ \text{C} \]

- Reaction proceeds well with only 1.5 equiv RI, 1.5 equiv \( \text{Bu}_3\text{SnH} \)
- At higher T, significant amounts of \( \text{SnBu}_3 \) formed.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c\text{Hex}</td>
<td>92</td>
<td>72</td>
</tr>
<tr>
<td>\text{tBu}</td>
<td>85</td>
<td>88</td>
</tr>
</tbody>
</table>

Porter, JACS, 1995, 11029
Enantioselective Reactions of Radicals Generated from $\gamma$-Lactams

![Chemical structure](image)

Model:

Attack from top face

<table>
<thead>
<tr>
<th>Lewis Acid (eq)</th>
<th>$T$ (°C)</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Phbox)Zn(OTf)$_2$ (1)</td>
<td>-78</td>
<td>59</td>
<td>70</td>
</tr>
<tr>
<td>(Indabox)Zn(OTf)$_2$ (1)</td>
<td>-78</td>
<td>96</td>
<td>75</td>
</tr>
<tr>
<td>(Indabox)Zn(OTf)$_2$ (1)</td>
<td>-20</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>(Indabox)Zn(OTf)$_2$ (0.2)</td>
<td>-20</td>
<td>81</td>
<td>69</td>
</tr>
</tbody>
</table>

* Yield was increased with additional Lewis Acid, while ee was unaffected.

Lewis Acid Promoted Atom-Transfer Radical Additions

With Lewis Acid activation, alkenes are nucleophilic enough to react with the radical intermediate.

Atom transfer products can be isolated if alkenes, rather than allyl-metal reagents, are used as nucleophiles.

<table>
<thead>
<tr>
<th>Lewis Acid (1 equiv)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Mg(OTf)₂</td>
<td>16</td>
</tr>
<tr>
<td>Sc(OTf)₃</td>
<td>47</td>
</tr>
<tr>
<td>Yb(OTf)₃</td>
<td>100</td>
</tr>
</tbody>
</table>

Secondary Bromides

Porter, JACS, 1999, 5155
Diastereoselective and Enantioselective Atom Transfer

Diastereoselective Reactions

\[
\begin{align*}
\text{Me} & - \text{Br} \quad \text{or} \quad \text{Me} & - \text{Br} \\
\text{N} & - \text{O} & - \text{N} & - \text{O} & - \text{Ph} & - \text{Br} \\
1 \text{ equiv } \text{Sc(OTf)}_3 & & \text{5 equiv } 1\text{-hexene} & & \text{TMS}_3\text{SiH} & & \text{Et}_3\text{B}, 25 \degree \text{C} & & \text{AIBN} \\
\end{align*}
\]

Yield >90%  
\[ \text{dr} = 96 : 4 \]

Enantioselective Reactions

\[
\begin{align*}
\text{O} & - \text{N} & - \text{O} & - \text{X} & - \text{Me} \\
\text{1 equiv Lewis Acid} & & \text{5 equiv } 1\text{-octene} & & \text{reduction} \\
\text{Et}_3\text{B}, 25 \degree \text{C} & & & & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>Lewis Acid</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>(Phbox)Sc(OTf)₃</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>Br</td>
<td>(Phbox)Zn(OTf)₂</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>I</td>
<td>(Phbox)Zn(OTf)₂</td>
<td>&lt;15</td>
<td>40</td>
</tr>
</tbody>
</table>

Porter, JACS, 1999, 5155
Free-Radical Polymerization of Acrylimides

Diastereoselective Copolymerization

\[ \text{Lewis Acid} \quad \text{Et}_3\text{B}, -78 \degree \text{C} \]

- Degree of copolymerization depended on Lewis Acid. Sc(OTf)_3 in Et_2O gave best results (1:1).
- R = Bn provided > 95:5 diastereoselectivity.

Enantioselective Copolymerization

- To get good copolymerization, 3.7 equiv of Zn were required.
- Polymer was formed in approximately 60% ee.

Porter, JOC, 2000, 775.
Lanthanide Triflates Catalyze Mn(III)-Based Radical Cyclization

Chemical reaction:

\[
\begin{align*}
\text{Me}_2\text{O} & \quad \text{Me} \quad \text{Me} \quad \text{OMe} \\
\text{Me} & \quad \text{Me} \quad \text{OMe} \\
\text{O} & \quad \text{Me} \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{Me} \\
2.2\text{ Mn(OAc)}_3\cdot\text{2H}_2\text{O} & \quad \text{Yb(OTf)}_3 \\
\text{CF}_3\text{CH}_2\text{OH}, 0^\circ\text{C}
\end{align*}
\]

Yield (B/C):

- Lewis Acid: —
  - Time (h): 24
  - Yield (B/C): 36/7

- Yb(OTf)_3 (1.0)
  - Time (h): 3
  - Yield (B/C): 69/10

- Yb(OTf)_3 (0.3)
  - Time (h): 3.5
  - Yield (B/C): 59/8

Lewis Acid increases % of A and also increases electrophilicity of radical intermediate.

Effect of Yb(OTf)_3 on Ketone-Enol Equilibrium:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>% in enol form (in MeOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOEt</td>
<td>0 equiv Yb</td>
</tr>
<tr>
<td>MeC=O</td>
<td>18.1</td>
</tr>
</tbody>
</table>

See V. Cee, Evening Seminar, 4/27/99

Yang, JACS, 2000, 1658
Lewis acids can increase the rate of radical reactions either by activating the radical acceptor or by increasing the reactivity of electrophilic radicals.

Lewis acids can control the stereochemistry of radical reactions by changing the conformation of the radical intermediate or the radical acceptor.

Several auxiliary-controlled reactions proceed with high diastereoselectivity in the presence of Lewis acids.

A few enantioselective Lewis acid-catalyzed reactions have been developed.

The stereoselective reactions that have been developed usually require large amounts of alkyl halide and/or tin reagents.