Halogen-Metal Exchange.

Ramil Baiazitov
SED group meeting
03/08/2005
Halogen-Lithium Exchange. Discovery.

The rules:
1. Fluorides and chlorides do not undergo exchange (wait…)
2. Rate decreases in the order: I>Br>Cl
3. The process is reversible, favoring the most stable organolithium
4. The lower the temperature, the better

Marvel, 1927
Gilman, 1938
Wittig, 1939
Halide Choice.

Chloride can be exchanged when metallation or dehydrochlorination are impossible and there is an activating group.
Reversibility.

Typical reaction time is 1-10 min at -78°C.

Atomic electronegativities
H (2.1), C (2.5), F (4.0), Cl (3.0), Br (2.8), I (2.5)

EtI + n-BuLi $\xrightarrow{\text{CO}_2}$ EtCO$_2$H + n-BuCO$_2$H
Et$_2$O, -75°C, 30min
43.4% 34.8%

EtLi + n-BuLi $\xrightarrow{\text{CO}_2}$ EtCO$_2$H + n-BuCO$_2$H
Et$_2$O, -70°C, 15min
48.0% 36.4%

Gilman, H. JACS, 1941, 63, 1441
**Reversibility.**

Equilibrium constants and pKa for PhI + RLi $\rightleftharpoons$ PhLi + RI

<table>
<thead>
<tr>
<th></th>
<th>Li</th>
<th>PhLi</th>
<th>Li</th>
<th>PhLi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.004</td>
<td>1</td>
<td>10</td>
<td>3000</td>
</tr>
<tr>
<td></td>
<td>36.5</td>
<td>37</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\text{PhI} + \text{t-BuLi} \rightarrow \text{PhI} + \text{t-BuLi} + \text{LiI}$

77%

$\text{PhI} \rightleftharpoons \text{PhI} + \text{LiI}$

$\text{PhI} + \text{PhI} \rightarrow \text{PhI}$

Applequist, D. E. *JACS*, 1963, 85, 743

Functional Group Compatibility.

\[
\begin{align*}
\text{BrCO}_2\text{H} & \xrightarrow{\text{BuLi, -100C}} \text{BrCO}_2\text{Li} \xrightarrow{\text{BuLi, -100C to -75C}} \text{PhCO}_2\text{Me} \\
\text{CO}_2\text{H} & \xrightarrow{\text{BuLi, -100C}} \text{BrCO}_2\text{Li} \xrightarrow{\text{BuLi, -100C to -75C}} \text{PhCO}_2\text{Me} \\
\text{NOMe} & \xrightarrow{\text{Et}_2\text{O, -35C}} \text{Li} \xrightarrow{\text{THF, -100C}} \text{NOMe} \\
\text{NC} & \xrightarrow{\text{THF, -100C}} \text{Li} \xrightarrow{\text{THF, -100C}} \text{NC} \\
\text{NO}_2 & \xrightarrow{\text{Me, THF, -100C}} \text{Li} \xrightarrow{\text{THF, -100C}} \text{NO}_2 \\
\text{Cl} & \xrightarrow{\text{Li, THF, -100C}} \text{Li} \xrightarrow{\text{THF, -100C}} \text{Cl} \\
\text{OTBS} & \xrightarrow{\text{I, Et}_2\text{O, -75C}} \text{Li} \xrightarrow{\text{THF, -110C}} \text{OTBS} \\
\text{Cl} & \xrightarrow{\text{Li, THF, -110C}} \text{Li} \xrightarrow{\text{THF, -110C}} \text{Cl} \\
\text{CH}_2\text{I} & \xrightarrow{\text{Li, THF, -75C}} \text{Li} \xrightarrow{\text{THF, -75C}} \text{CH}_2\text{I}
\end{align*}
\]
Examples.

\[
\text{BrO} \quad \text{t-BuLi} \quad \text{LiO TMS} \quad 63\%
\]


\[
\text{Me} \quad \text{Ph} \quad \text{BuLi} \quad \text{Li} \quad \text{warm} \quad \text{Me} \quad \text{Ph} \quad \text{OH} \quad 69\%
\]

Kihara, M. TL, 1990, 31, 5347

\[
\text{Me} \quad \text{Li} \quad \text{BuLi} \quad \text{Ph} \quad \text{EtOH} \quad 70\%
\]

Possible Mechanisms.

1. Four-centered transition state
   \[ \text{RLi} + \text{R}_1\text{X} \rightarrow \left[ \begin{array}{c} \text{R-Li} \\ \text{X-R}_1 \end{array} \right] \rightarrow \text{R}_1\text{Li} + \text{RX} \]

2. Radical mechanism

3. Nucleophilic attack on halogen
   \[ \text{RLi} + \text{R}_1\text{X} \rightarrow \left[ \begin{array}{c} \oplus \\ \text{R}_1\text{X-R Li} \end{array} \right] \rightarrow \text{R}_1\text{Li} + \text{RX} \]
   intermediate
   "ate-complex"

   direct Nu-substitution
First Indications of the Radical Mechanism.

Bryce-Smith, D. J. J. Chem. Soc. 1956, 1603
Ward, H. R. JACS, 1967, 89, 5517
Br-Radical, I-ionic.

Table I. Reaction of *endo*-5-(2-Haloethyl)-2-norbornenes 1–3 with 1-t-BuLi in Pentane/Et₂O (4:1) at −78 °C

<table>
<thead>
<tr>
<th>expt</th>
<th>RX</th>
<th>time (min)</th>
<th>% yield (%)</th>
<th>% d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (X = I)</td>
<td>30</td>
<td>100.0 (100)</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>1440</td>
<td></td>
<td>99.0 (95.0)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>3</td>
<td>2 (X = Br)</td>
<td>180</td>
<td>82.0 (60.8)</td>
<td>15.3 (59.9)</td>
</tr>
<tr>
<td>4</td>
<td>1440</td>
<td></td>
<td>83.0 (60.8)</td>
<td>15.0 (62.6)</td>
</tr>
<tr>
<td>5</td>
<td>3 (X = Cl)</td>
<td>1440</td>
<td>&lt;0.1</td>
<td>&lt;0.1c</td>
</tr>
</tbody>
</table>

*a* All reactions carried out were 0.2 M in t-BuLi and 0.1 M in halide and then quenched with D₂O.  *b* Deuterium content was determined by GC–MS.  *c* Recovered alkyl halide accounts for the material balance.

Radical vs. Ionic.

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

\[ \text{t-BuLi} + \text{X} \rightarrow \text{SET} \]

\[ \text{Li}^+ \rightarrow \text{t-Bu} \cdot \text{Li}^- \rightarrow \text{Li}^+ \text{t-Bu} \cdot \text{C}_1 \text{cage} \]

\[ \text{D}_2\text{O} \rightarrow \text{Li} \]

\[ \text{SH or t-BuLi} \]

\[ \text{D}_2\text{O} \rightarrow \text{Li} \]

\[ \text{Li} \]

\[ \text{D}_2\text{O} \rightarrow \text{Li} \]

\[ \text{Li} \]

\[ \text{5} \]

\[ \text{7} \]
### Higher Temp, More Radical

Table II. Effect of Temperature on the Reaction of endo-5-(2-Iodoethyl)-2-norbornene (1) with t-BuLi in Pentane/Et₂O (4:1)

<table>
<thead>
<tr>
<th>expt</th>
<th>time (min)</th>
<th>temp (°C)</th>
<th>% yield (% d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 + 6</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>-78</td>
<td>100.0 (100)</td>
</tr>
<tr>
<td>2</td>
<td>1440</td>
<td>-78</td>
<td>99.0 (95.0)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>-45</td>
<td>95.0 (95.3)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>-45</td>
<td>93.0 (95.6)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>-23</td>
<td>90.0 (95.8)</td>
</tr>
<tr>
<td>6</td>
<td>2880</td>
<td>-23</td>
<td>92.5 (90.5)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0</td>
<td>96.0 (79.0)</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>0</td>
<td>90.0 (57.8)</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>0</td>
<td>72.0 (35.9)</td>
</tr>
</tbody>
</table>

*(4+6)/(5+7) did not change.

H-abstraction

- All reactions carried out were 0.2 M in t-BuLi and 0.1 M in halide and then quenched with D₂O.
- Deuterium content was determined by GC–MS.

### Less Ether, More Radical

Table IV. Effects of Solvent and Temperature on the Reaction of endo-5-(2-iodoethyl)-2-norbornene (1) with \( t\)-BuLi

<table>
<thead>
<tr>
<th>expt</th>
<th>time (min)</th>
<th>temp (°C)</th>
<th>solvent</th>
<th>1. ( t)-BuLi</th>
<th>2. ( D_2O )</th>
<th>% yield (% d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>-78</td>
<td>pentane/ether(^a)</td>
<td>100.0 (100)(^d)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1440</td>
<td>-78</td>
<td>pentane/ether(^a)</td>
<td>99.0 (95.0)(^e)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>-78</td>
<td>pentane(^b)</td>
<td>8.4 (67.3)(^e)</td>
<td>2.2 (10.6)(^d,e)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>880</td>
<td>-78</td>
<td>pentane(^b)</td>
<td>60.0 (62.5)(^e)</td>
<td>7.0 (10.7)(^e)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1440</td>
<td>-78</td>
<td>pentane(^b)</td>
<td>88.0 (66.0)(^e)</td>
<td>10.0 (12.1)(^e)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2880</td>
<td>-78</td>
<td>pentane(^b)</td>
<td>89.5 (65.4)(^e)</td>
<td>9.8 (11.4)(^e)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>210</td>
<td>-23</td>
<td>pentane(^b)</td>
<td>76.2 (83.0)(^e)</td>
<td>23.0 (34.4)(^e)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>420</td>
<td>-23</td>
<td>pentane(^b)</td>
<td>75.8 (83.4)(^e)</td>
<td>22.5 (37.6)(^e)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>400</td>
<td>-23</td>
<td>pentane(^b,c)</td>
<td>60.0 (17.9)(^e)</td>
<td>39.5 (64.8)(^e)</td>
<td></td>
</tr>
</tbody>
</table>

A. Reactions carried out were 0.2 M in \( t\)-BuLi and 0.1 M in halide and then quenched with \( D_2O \). B. Reactions carried out were 1.0 M in \( t\)-BuLi and 0.1 M in halide. C. \( t\)-BuLi-d9, was used then quenched with \( H_2O \). D. Deuterium content was determined by GC-MS. E. Recovered alkyl halide accounts for the material balance in expt 3 and 4.

---

Cis/trans to deduce the mechanism.

\[
\text{Bu}_3\text{SnH} \quad \xrightarrow{\text{Na}} \quad \text{Ionic} \quad \text{SET}
\]

---

**Cis/trans=4 at rt**

*Brace, 1967*

**Cis/trans=0.32 at rt**

*Garst, 1986*

---

**Table V. Reaction of 6-Bromo-1-heptene (8) with tert-Butyllithium in Pentane/Ether at -78 °C**

<table>
<thead>
<tr>
<th>expt</th>
<th>time (min)</th>
<th>additive</th>
<th>10 % yield (%)</th>
<th>11 other</th>
<th>10 other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>none</td>
<td>39.1 (5.5)</td>
<td>26.0 [5.8]b</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(t = 95.0)c,d</td>
<td>(c = 94.5)c,e</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>none</td>
<td>40.0 (4.3)c</td>
<td>27.6 [5.7]</td>
<td>28.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(t = 98.0)</td>
<td>(c = 93.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1440</td>
<td>none</td>
<td>41.1 (3.6)c</td>
<td>27.2 [5.7]</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(t = 99.2)</td>
<td>(c = 94.5)</td>
<td></td>
</tr>
</tbody>
</table>

---

A. All reactions carried out were 0.2 M in t-BuLi and 0.1 M in halide and then quenched with D20. B. Number in brackets indicates the cis/trans ratio of 1,2-dimethylcyclopentane. C. Deuterium content was determined by GC-MS. D. Deuterium content in the trans-1,2-dimethylcyclopentane. E. Deuterium content in the cis-1,2-dimethylcyclopentane. F. 2 equiv of TMEDA, 4 equiv of HMPA, and 2 equiv of 18-crown-6 were added to the reaction mixture, respectively, after the reaction was complete. E. Dienes, dimer, and coupling products.
The proposed mechanism.

\[
\begin{align*}
\text{X} & \quad \text{t-BuLi} \\
\text{SET} & \quad \text{polar} \\
\text{LiX} & \quad \text{-LiX} \\
\text{cage} & \quad \text{cage} \\
\text{Li} & \quad \text{Li}
\end{align*}
\]

mostly trans

mostly cis

### Cis/trans to deduce the mechanism.

Table V. Reaction of 6-Bromo-1-heptene (8) with tert-Butyllithium in Pentane/Ether at -78 °C

<table>
<thead>
<tr>
<th>expt</th>
<th>time (min)</th>
<th>additive</th>
<th>% yield (d)</th>
<th>% yield (d)</th>
<th>% yield (d)</th>
<th>other</th>
<th>% yield (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>none</td>
<td>39.1(15.5)(^c)</td>
<td>26.0(5.8)(^b)</td>
<td>(t = 95.0)(^c,d)</td>
<td>(c = 94.5)(^c,e)</td>
<td>30.0</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>none</td>
<td>40.0(4.3)(^c)</td>
<td>27.6(6.7)</td>
<td>(t = 98.0)</td>
<td>(c = 93.5)</td>
<td>28.5</td>
</tr>
<tr>
<td>3</td>
<td>1440</td>
<td>none</td>
<td>41.1(3.6)(^c)</td>
<td>27.2(5.7)</td>
<td>(t = 99.2)</td>
<td>(c = 94.5)</td>
<td>29.0</td>
</tr>
</tbody>
</table>

Evidence of the radicals mechanism
1. Large amount of 11
2. High cis/trans ratio
3. High yield of protio-10
4. Lack of cyclization in presence of TMEDA

---

Cis/trans to deduce the mechanism.

Table VI. Reaction of 6-Iodo-1-heptene (9) with tert-Butyllithium in Pentane/Ether at -78 °C

<table>
<thead>
<tr>
<th>expt</th>
<th>time (min)</th>
<th>additive</th>
<th>% yield</th>
<th>% d yield</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>none</td>
<td>44.0</td>
<td>11.3 [1.7]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(16.0)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(t = 96.0)&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 97.1)&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1440</td>
<td>none</td>
<td>43.2</td>
<td>11.4 [1.9]&lt;sup&gt;f&lt;/sup&gt;</td>
<td>45.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(15.8)</td>
<td>(t = 95.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 93.6)</td>
<td></td>
</tr>
</tbody>
</table>

A. All reactions carried out were 0.2 M in t-BuLi and 0.1 M in halide and then quenched with D2O. B. Number in brackets indicates cis/trans ratio of 1,2-dimethylcyclopentane. C. Deuterium content was determined by GC-MS. D. Deuterium content in the trans-dimethylcyclopentane. E. Deuterium content in the cis-I,2-dimethylcyclopentane. F. 2 equiv of TMEDA, 4 equiv of HMPA, and 18-crown-6 were added to the reaction mixture, respectively, after the reaction was complete. G. Dienies, dimer, and coupling

Iodide cyclizes heterolytically

Cis/trans to deduce the mechanism.

Table VIII. Effect of Mode of Addition of tert-Butyllithium in the Reaction of 6-Halo-1-heptenes in Pentane/Ether at -78 °C

<table>
<thead>
<tr>
<th>expt</th>
<th>X</th>
<th>mode of addition</th>
<th>10 % yield (%) d</th>
<th>11 % yield (%) d</th>
<th>other % yield (%) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>normal</td>
<td>39.1</td>
<td>26.0 [5.8]b</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5.5)c</td>
<td>(t = 95.0)c,d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 94.5)c,e</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>inverse</td>
<td>36.5</td>
<td>24.2 [5.5]</td>
<td>28.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(8.0)</td>
<td>(t = 94.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 95.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>normal</td>
<td>44.0</td>
<td>11.3 [1.7]</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(16.0)</td>
<td>(t = 96.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 97.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>inverse</td>
<td>38.0</td>
<td>45.6 [0.03]</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(10.5)</td>
<td>(t = 98.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(c = 95.0)</td>
<td></td>
</tr>
</tbody>
</table>

*All reactions carried out were 0.2 M in t-BuLi and 0.1 M in halide and then quenched with EtOD. *b Number in brackets indicates the cis/trans ratio of 1,2-dimethylcyclopentane. *c Deuterium content was determined by GC-MS. *d Deuterium content in the trans-1,2-dimethylcyclopentane. *e Deuterium content in the cis-1,2-dimethylcyclopentane. *f Dienes, dimer, and coupling products.

Another Proof of Radical Mechanism.

\[
\text{Br} + \text{t-BuLi, -23C} \rightarrow \text{pentane-ether} \rightarrow \text{Li} \rightarrow \text{H} \rightarrow \text{product of radical mechanism (13%)}
\]

**Conclusions**

**Radical mechanism:**
1. With bromides
2. At higher temperature

**Ionic mechanism**
1. With iodides
2. At lower temperature

Newcomb, M. *TL*, 1989, 26, 1183
Ionic Mechanism. $S_N^2$ or Stepwise?

SN2- Gilman, 1951

Ate-complex – Wittig, 1958 (first time the term was used)
Hal-Li Exchange Kinetics and Equilibrium.

PhLi + ArBr = Phl + ArLi

Table II. Equilibrium Constants for Interconversion between Phenyllithium and Aryl Bromides.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\sigma$ value</th>
<th>$K_{obad}^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$-CH$_3$</td>
<td>-0.170</td>
<td>0.60 (0.67)</td>
</tr>
<tr>
<td>$m$-CH$_3$</td>
<td>-0.069</td>
<td>0.88 (0.84)</td>
</tr>
<tr>
<td>$p$-C$_6$H$_5$</td>
<td>+0.009</td>
<td>3.78 (3.79)</td>
</tr>
<tr>
<td>$p$-Cl</td>
<td>+0.226</td>
<td>53</td>
</tr>
<tr>
<td>$m$-CF$_3$</td>
<td>+0.415</td>
<td>289</td>
</tr>
<tr>
<td>$p$-F</td>
<td>+0.062</td>
<td>...</td>
</tr>
<tr>
<td>$p$-OCH$_3$</td>
<td>-0.268</td>
<td>...</td>
</tr>
</tbody>
</table>

$^a$ All reactions were performed in ether at 25.0° using salt-containing phenyllithium. The numbers in parenthesis represent averages of equilibrium constants obtained by approaching the equilibrium from the right. They could not be obtained for $Z = p$-Cl and $Z = m$-CF$_3$. $^b K_{obad} = [C_6H_5Br][ZC_6H_5Li]/[C_6H_5Li]-[ZC_6H_5Br]$. $^c$ Side reaction dominated, metallaion ortho to F. $^d$ Side reaction dominated, metallaion ortho to OCH$_3$.

Figure 2. Dependence between substituent constant $\sigma$ for $Z$ and $K_{obad}$ for halogen-metal interconversions between $C_6H_5Li$ and $ZC_6H_5Br$.

Large positive value of $\rho$ is consistent with the negative charge build up in the TS

Similar ($\rho=2$) for nBuLi + ArBr = nBuBr + ArLi

Roders, H. R. JACS, 1982, 104, 522

Equilibrium: Winkler, H. JACS, 1966, 88, 964
Rates : Winkler, H. JACS, 1966, 88, 969
A Proof of the Ate-Complex Existence.

PhLi + n-Bul → n-BuPh
PhI, THF

Figure 1. Effect of iodobenzene on the rate of reaction of phenyllithium with 1-iodobutane in THF at -78 °C. The points are experimental, the line was calculated by using $k_2 = 7.0 \times 10^{-4}$ L mol$^{-1}$ s$^{-1}$ (test 2) and $K = 5.9$ mol L$^{-1}$ (eq 1).

Figure 2. Results of test 2 as a function of HMPA concentration.

higher concentration of ate-complex decreases rate of substitution

Reich, H. J. JACS, 1985, 107, 4101
Isolation of an Ate-Complex.

Isolation of an Ate-Complex.

![Chemical Structure](image)

**Figure 1.**

**Table I. Selected Bond Distances (Å) and Angles (deg) for 2**

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Distance (Å)</th>
<th>Angle (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(7)–I(1)</td>
<td>2.403 (6)</td>
<td></td>
</tr>
<tr>
<td>C(1)–I(1)</td>
<td>2.331 (5)</td>
<td></td>
</tr>
<tr>
<td>C(1)–C(2)</td>
<td>1.375 (7)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(3)</td>
<td>1.370 (7)</td>
<td></td>
</tr>
<tr>
<td>C(1)–I(1)–C(7)</td>
<td>175.2 (2)</td>
<td></td>
</tr>
<tr>
<td>I(1)–C(1)–C(2)</td>
<td>123.6 (3)</td>
<td></td>
</tr>
<tr>
<td>C(1)–C(2)–F(2)</td>
<td>119.5 (5)</td>
<td></td>
</tr>
<tr>
<td>C(3)–C(4)</td>
<td>1.367 (7)</td>
<td></td>
</tr>
<tr>
<td>C(2)–F(2)</td>
<td>1.366 (5)</td>
<td></td>
</tr>
<tr>
<td>C(3)–F(3)</td>
<td>1.348 (6)</td>
<td></td>
</tr>
<tr>
<td>C(4)–F(4)</td>
<td>1.340 (6)</td>
<td></td>
</tr>
<tr>
<td>C(2)–C(1)–C(6)</td>
<td>114.8 (5)</td>
<td></td>
</tr>
<tr>
<td>C(3)–C(2)–F(2)</td>
<td>116.6 (5)</td>
<td></td>
</tr>
</tbody>
</table>

Farnham, W. B. JACS, 1986, 108, 2449
Balance of evidence now lies in favor of:

1. Aryl bromides or iodides react through ate-complex
2. Primary alkyl iodides react via polar mechanism (w/ Ether)
3. Secondary alkyl iodides polar/radical competition
4. Alkyl bromides react via radical mechanism

Beak, P. JACS, 1992, 114, 3420
1. 2 equiv of $t$-BuLi should be used unless exactly one equiv of RLi is needed. Then use $n$-BuLi

2. If two or more bromines:
   2a. The more stable aryllithium is formed (thermodinamic control)
   2b. Stabilizing groups allow for dianion formation

$$
\begin{align*}
\text{Et}_2\text{N} & \quad \text{Et}_2\text{N} \\
\text{Br} & \quad \text{Li} \\
\text{Br} & \quad \text{Me} \\
\end{align*}
$$

Synthesis of Aryllithiums
Synthesis of Vinyllithiums

Problems to avoid: dehydrohalogenation, metallation

\[
\begin{align*}
\text{Br} & \quad \text{2 t-BuLi} & \quad \text{-120°C} & \quad \text{Li} & \quad \text{PhCHO} & \quad \text{OH} & \quad 76\% \\
\text{C}_4\text{H}_9 & \quad \text{Br} & \quad \text{2 t-BuLi} & \quad \text{-120°C} & \quad \text{C}_8\text{H}_{17}\text{Br} & \quad \text{C}_4\text{H}_9 & \quad \text{C}_8\text{H}_{17} & \quad 77\%
\end{align*}
\]

Seebach, D. TL, 1976, 52, 4839

Problems to avoid: dehydrohalogenation, metallation

\[
\begin{align*}
\text{Br} & \quad \text{2 t-BuLi} & \quad \text{-120°C} & \quad \text{Li} & \quad \text{PhCHO} & \quad \text{OH} & \quad 73\% \\
\text{Ph} & \quad \text{Br} & \quad \text{82%} & \quad \text{Ph}
\end{align*}
\]

Oshima, K. Tetrahedron, 1995, 51, 11681

Problems to avoid: dehydrohalogenation, metallation

\[
\begin{align*}
\text{I} & \quad \text{n-BuLi} & \quad \text{hexane} & \quad \text{25°C} & \quad \text{Li} & \quad \text{E}^+ & \quad \text{Adduct} & \quad \text{Yield}\n\end{align*}
\]

Alkenyl Iodide

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>Electrophile</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>c-C_6H_{11}CHO</td>
<td>61</td>
</tr>
<tr>
<td>n-C_{10}H_{21}</td>
<td>H</td>
<td>H</td>
<td>D_2O</td>
<td>96</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>n-C_{10}H_{21}</td>
<td>n-C_4H_9CHO</td>
<td>100</td>
</tr>
<tr>
<td>n-C_5H_{11}</td>
<td>H</td>
<td>n-C_5H_{11}</td>
<td>Me_3SiCl^b</td>
<td>100</td>
</tr>
<tr>
<td>n-C_5H_{11}</td>
<td>H</td>
<td>n-C_5H_{11}</td>
<td>CH_3I^c</td>
<td>100</td>
</tr>
</tbody>
</table>

Oshima, K. Tetrahedron, 1995, 51, 11681
Synthesis of Functionalized Vinyllithiums

Duhamel, L. Synlett, 1996, 221

Duhamel, L. TL, 1993, 34, 319
Synthesis of Alkyllithiums

RCH_2I \xrightarrow{t{-}BuLi (2.2eq)} RCH_2Li \xrightarrow{pentane/ether} RCH_2Li \rightarrow RCH_2E

-78^\circ C, then rt

\begin{align*}
\text{CH}_3(CH_2)_3I & \rightarrow \text{CH}_3(CH_2)_3CHO & 91 \\
\text{CH}_3(CH_2)_7I & \rightarrow (CH_3)_2C=O & 93 \\
\text{CH}_3(CH_2)_4CH_2I & \rightarrow H_2O & 96 \\
(CH_3)_3CCH_2I & \rightarrow \text{CH}_3(CH_2)_2CHO & 89 \\
c-C_5H_9CH_2I & \rightarrow \text{CO}_2 & 91 \\
\text{Ph(CH}_2)_2I & \rightarrow (CH_2O)_n & 83 \\
\text{BrCH}_2\text{CH}_2\text{Br} & \rightarrow & 92 \\
\end{align*}

A. The alkyllithium was generated at -78 °C by addition of 2.1-2.2 molar equiv of t-BuLi in n-pentane to a 0.1 M solution of the iodide in n-pentane-diethyl ether (3:2 by volume). The cooling bath was removed 5 min after complete addition of t-BuLi, and the reaction mixture was allowed to stand at room temperature for 1 h. B. The reaction mixture was recooled to -78 °C and an excess (typically 2 equiv) of electrophile was added. C. Isolated yield of chromatographically pure product.

Table I. Preparation of Primary Alkyllithiums by Treatment of Alkyl Iodides with tert-Butyllithium

<table>
<thead>
<tr>
<th>RI</th>
<th>yield (%) of RLi^b</th>
<th>GLC yield of RSiMe_3</th>
<th>GLC yield of RI</th>
<th>^1H NMR signal of α-CH_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtI</td>
<td>95</td>
<td>c</td>
<td>c</td>
<td>-0.90 (t, J = 8 Hz)</td>
</tr>
<tr>
<td>n-OctI</td>
<td>95</td>
<td>c</td>
<td>80</td>
<td>-0.90 (t, J = 8 Hz)</td>
</tr>
<tr>
<td>i-BuI</td>
<td>95</td>
<td>c</td>
<td>-1.10 (d, J = 7 Hz)</td>
<td></td>
</tr>
<tr>
<td>neo-PentI</td>
<td>95</td>
<td>95^d</td>
<td>c</td>
<td>-0.68 (s)</td>
</tr>
<tr>
<td>Ph(CH_2)_2I</td>
<td>90</td>
<td>90</td>
<td>85</td>
<td>-0.60 (t, J = 9 Hz)</td>
</tr>
<tr>
<td>H_2C=CH</td>
<td>90</td>
<td>88^e</td>
<td>85</td>
<td>-0.95 (t, J = 9 Hz)</td>
</tr>
<tr>
<td>n-BuC=</td>
<td>80</td>
<td>c</td>
<td>c</td>
<td>-0.80 (t, J = 8.5 Hz)</td>
</tr>
<tr>
<td>C(CH_2)_2I</td>
<td>90</td>
<td>c</td>
<td>c</td>
<td>-2.20 (s)</td>
</tr>
<tr>
<td>Me_3SiCH_2I</td>
<td>90</td>
<td>c</td>
<td>60</td>
<td>-0.8 (t, J = 9 Hz)</td>
</tr>
<tr>
<td>I(CH_2)_4I</td>
<td>95</td>
<td>85</td>
<td>90</td>
<td>0.8 to -1.1 (m)</td>
</tr>
<tr>
<td>I(CH_2)_4I</td>
<td>90</td>
<td>80</td>
<td>c</td>
<td>-0.81 (t, J = 9 Hz)</td>
</tr>
<tr>
<td>I(CH_2)_4I</td>
<td>c</td>
<td>90</td>
<td>60</td>
<td>c</td>
</tr>
<tr>
<td>Cl(CH_2)_4I</td>
<td>c</td>
<td>60</td>
<td>c</td>
<td>c</td>
</tr>
</tbody>
</table>

^a The reaction conditions are as detailed in the text. ^b No significant amounts (<2–3%) of the possible β-elimination or coupling products were present. The amounts of the deiodinated products, i.e., RH, were ≤5%. ^c Not performed. ^d GLC yield of neo-PentSnMe_3. ^e GLC yield of 3-butenyltrimethylstannane.

Negishi, E. J. Org. Chem. 1990, 55, 5406
**Iodine-Mg Exchange. Discovery.**

Iodine-Mg Exchange:

\[
\text{Br} + \text{EtMgBr} \rightarrow \text{MgBr}
\]

**Prevost, C. 1931**

Electron-withdrawing substituents accelerate halogen-Mg exchange.
**Iodine-Mg Exchange. Aryls.**

\[
\begin{array}{c}
\text{FG-}^\text{I} \quad \xrightarrow{i\text{PrMgBr} \ (1.0 \ \text{equiv})} \quad \text{FG-}^\text{MgX} \\
\text{1} \\
\text{FG-}^\text{MgX} \\
\text{2: } X = \text{Br or FG-C}_6\text{H}_4 \\
\text{FG = Br, CN, CO}_2\text{Et} \\
\end{array}
\]

\[\begin{align}
2a: & \quad 25 ^\circ C, 0.5 \ h \\
2b: & \quad -25 ^\circ C, 0.5 \ h \\
2c: & \quad -40 ^\circ C, 1 \ h \\
2d: & \quad -40 ^\circ C, 1 \ h \\
\end{align}\]

Iodine-Mg Exchange. Vinlys, Alkyls.

Knochel, P. Chem Eur. J. 2000, 6, 767
**Functional Group**

**Vancomycin**

1. \( \text{CuCN} \cdot 2\text{LiCl} \) (10 mol%) 
   - \(-20 \rightarrow 25 \, ^\circ \text{C}\)
   - \(63: 83\% \text{, } 60\% \text{ ee}\)

2. \(\text{iPrMgCl}\)
   - \(\text{THF}, -20 \, ^\circ \text{C}, 1 \text{ h}\)
   - \(61\)

3. \(\text{CuCN} \cdot 2\text{LiCl} \) (10 mol%)
   - \(-20 \rightarrow 25 \, ^\circ \text{C}\)
   - \(63: 83\% \text{, } 60\% \text{ ee}\)

4. \(\text{iPrMgBr}\)
   - \(-10 \, ^\circ \text{C}, 3.5 \text{ h}\)
   - \(62\)

5. \(\text{anti substitution}\)
   - \(64: 95\%\)

**Knochel, P. ACIEE 2003, 42, 4302** (review)

**Nicolau, K. C 1999**
Magnesium Ate Complexes.

Oshima, K. JOC 2001, 66, 4333
**i-Pr vs. n-Bu.**

\[
\text{FG} \quad \text{Br} \quad \text{THF}, -78 \degree C, 1 \text{ h} \quad \text{FG} \quad \text{Mg}^n \text{Bu}_2 \text{Li} \quad \text{Electrophile} \quad -78 \degree C \quad \text{FG} \quad \text{E}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(6q)</td>
<td>(\text{CH}_2=\text{CHCH}_2\text{Br})</td>
<td>(3q\text{B})</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>(6q)</td>
<td>(\text{C}_6\text{H}_5\text{CHO})</td>
<td>(4)</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>(6r)</td>
<td>(\text{CH}_2=\text{CHCH}_2\text{Br})</td>
<td>(3r\text{B})</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>(6r)</td>
<td>(\text{C}_6\text{H}_5\text{CHO})</td>
<td>(3r\text{D})</td>
<td>71 (50)</td>
</tr>
</tbody>
</table>

With \(\text{Bu}_3\text{MgLi}\)

**Oshima, K. JOC 2001, 66, 4333**
Another Type of Ate Complexes.

[c] The Grignard reagent was transmetalated with CuCN·2LiCl before reaction with an electrophile. [e] The exchange reaction was conducted in THF/DMPU (1:3).

Knochel, P. ACIEE, 2004, 43, 3333
## Alkenyl Iodides.

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Electrophile} & \text{Product} \\
1 & R=\text{C}_{10}H_{21} & \text{D}_2\text{O} & R=\text{C}_{10}H_{21} \\
23a & R=\text{C}_{10}H_{21} & \text{Me}_3\text{SiCl} & R=\text{C}_{10}H_{21} \\
7 & R=\text{C}_{10}H_{21} & \text{D}_2\text{O} & R=\text{C}_{10}H_{21} \\
11 & R=\text{C}_{10}H_{21} & \text{Me}_3\text{SiCl} & R=\text{C}_{10}H_{21} \\
14 & R=\text{C}_{10}H_{21} & \text{D}_2\text{O} & R=\text{C}_{10}H_{21} \\
23e (E/Z = 11/89) & \text{EtCHO} & \text{Et} & \text{24eF (E/Z = 11/89) 80%} \\
\end{array}
\]

In the text at -78°C
In the table at 0°C

**Oshima, K. JOC 2001, 66, 4333**
Alkenyl Iodides with Knochel ‘s Reagent.

Knochel, P. Org. Lett. 2004, 6, 4215
Knochel, P. Chem. Commun. 2005, 543
**Alkyl Iodides.**

\[
\text{cis-205} \xrightarrow{\text{iPrMgCl, } -40^\circ \text{C, 15 min}} \text{cis-206}
\]

\[
\text{EtO}_2C\text{I} \xrightarrow{\text{CuCN:2LiCl, PhCOCl}} \text{EtO}_2C\text{COPh} \quad \text{cis-207: 73%}
\]

\[
\text{trans-205} \xrightarrow{\text{iPrMgCl, } -40^\circ \text{C, 20 min}} \text{trans-206}
\]

\[
\text{EtO}_2C\text{I} \xrightarrow{\text{CuCN:2LiCl, PhCOCl}} \text{EtO}_2C\text{COPh} \quad \text{trans-207: 65%}
\]

\[
\text{211} \xrightarrow{\text{F}_9\text{C}_4\text{MgBr, Et}_2\text{O, } -45^\circ \text{C}} \text{212: 64%}
\]
Iodine-Mg exchange mechanism.

Yellow color faded over 2 h

Pseudo first order color decay $1 \times 10^{-4}$ s$^{-1}$

Is it an intermediate or a side product?

Hoffmann, R. W. ACIEE, 1998, 37, 824
Iodine-Mg exchange mechanism.

\[
\text{Ph} \text{CH}_2 \text{CH} \cdot \text{CHCH}_2 \text{I} + \text{iPrMgBr} \xrightarrow{2 \text{ min} \atop -78 \, ^\circ \text{C} \atop \text{THF}} ? \xrightarrow{2 \text{ h} \atop -78 \, ^\circ \text{C} \atop \text{THF}} \text{Ph} \text{CH}_2 \text{CH} \cdot \text{CHCH}_2 \text{MgBr} + \text{iPrI}
\]

\[
\text{CH}_3\text{OH(D)} \xrightarrow{k_H / k_D = 2.8} \text{CH}_3\text{OH(D)} \xrightarrow{k_H / k_D = 1.1}
\]

Color and KIE disappearance have the same rate

Figure 2. Proton content (%) in product 6 as a function of the time upon quenching with CH$_3$OH/CH$_3$OD. Conditions: 1.0 equiv of 2, 0.8 equiv of iPrMgBr, THF, −78°C, c = 0.4m.

Hoffmann, R. W. ACIEE, 1998, 37, 824
Iodine-Mg exchange mechanism.

\[
\text{Ph} - I + \text{iPrMgBr} \quad \text{2 min} \quad \begin{array}{c} \rightarrow ? \\ \text{THF} \quad -78^\circ \text{C} \end{array} \quad \text{Ph} - MgBr + \text{iPrI} \quad \text{2 h} \quad \text{THF} \\
\]

Rate of disappearance of 2 is \(5 \times 10^{-2} \text{ Lxmol}^{-1}\text{s}^{-1}\) (by H-NMR)

Rate of appearance of 4 is \(5 \times 10^{-4} \text{ s}^{-1}\)  

Rate of disappearance of 2.94 ppm (dd, intermediate) is \(4 \times 10^{-4} \text{ s}^{-1}\)

\[
\text{Ph} - I + 20 \text{ equiv CH}_3\text{OH}(D) \quad \text{i-PrMgCl} \quad \text{15%} \\
\begin{array}{c} \rightarrow \text{Ph} - \text{I} \\ \text{THF} \quad -78^\circ \text{C} \end{array} \\
\]

KIE suggests protonation of the ate-complex, not carbenoid

Hoffmann, R. W. *ACIEE*, 1998, 37, 824
Iodine-Mg exchange mechanism.

**Figure 2.** Dependence of the rate constant ($\times 10^4$) for the conversion of 5 into 6 at $-78$ °C in THF on the total Mg$^{2+}$ concentration.

**Scheme 4.** Reaction of the Ate-Complex 5 with “Electrophiles”

\[
\begin{align*}
\text{Ph} & \text{CHO}, \text{CCl}_4, \text{TsCl}, \text{TMSOTf}, \\
\text{Bu}_3\text{SnH}, \text{MeNO}_2
\end{align*}
\]

**Scheme 6.** Electron-Transfer Chain Process for the Conversion of 5 to 6

Reference:
Hoffmann, R. W. *Org. Lett.* 2003, 5, 313
Organozinc reagents. Alkyl.

\[
\text{Zn} + \text{EtI} = \text{Et}_2\text{Zn}
\]
Frankland, E. 1849

\[
\begin{align*}
\text{FG-RI} + \text{Et}_2\text{Zn} & \text{ neat} \rightarrow \text{FG-RZnEt} + \text{EtI} \\
& \text{45-55 °C, 1-12 h} \rightarrow (\text{FG-R})_2\text{Zn} \\
\text{reaction condns}^e & \quad \text{products}^f \\
\text{yield}^b,c & \quad (\%) \\
\hline
(\text{FG-R})_2\text{Zn} & \quad \text{O}_2\text{NCH}_2\text{CH(Ph)(CH}_2)_5\text{OAc} \\
(\text{AcO(CH}_2)_5\text{CH}_2)_2\text{Zn} & \quad \text{CH}_2\equiv\text{C(CO}_2\text{Et)(CH}_2)_6\text{OAc} \\
(50, 4) & \quad \text{PhCO(CH}_2)_5\text{OAc} \\
(50, 4) & \quad \text{BuC}=\text{CCH}_2\text{OCO-t-Bu} \\
(50, 4) & \quad \text{74} \\
(\text{t-BuCO}_2\text{CH}_2)_2\text{Zn} & \quad \text{82} \\
(\text{NC(CH}_2)_5\text{Zn})_2 & \quad \text{88} \\
(\text{NC(CH}_2)_3\text{Zn})_2 & \quad \text{87} \\
(\text{NC(CH}_2)_3\text{Zn})_2 & \quad \text{(E)-NC(CH}_2)_3\text{CH}=\text{CHCO}_2\text{Et} \\
(55, 40) & \quad \text{85} \\
(\text{NC(CH}_2)_3\text{Zn})_2 & \quad \text{83} \\
(\text{Cl(CH}_2)_4\text{Zn})_2 & \quad \text{86} \\
(\text{Cl(CH}_2)_4\text{Zn})_2 & \quad \text{90} \\
(0, 1) & \quad \text{Knochel, P. J. Org. Chem. 1992, 57, 1956}
\end{align*}
\]
**Sec-Iodide/Zn-Exchange.**

\[
\begin{align*}
&\text{R}_2\text{I} \quad \text{R}_1 \quad \text{Zn-i-Pr} \\
\text{method A:} & \quad i-\text{Pr}_2\text{Zn} \\
\text{rt, 0.5-10h} & \quad \text{method B:} \\
\text{rt, 2h} & \quad i-\text{Pr}_2\text{Znx}_2\text{MgB}_2 \\
& \quad \text{Me}\text{Me}\text{Me} \\
\text{method B:} & \quad \text{Me}\text{Me}\text{Me} \\
& \quad \text{method B:} \quad 61\% \\
\end{align*}
\]

Knochel, P. *Synlett* 1997, 327

**Aryl/Vinyl Iodide/Zn-Exchange.**

\[
\begin{align*}
&\text{FG-Arl} \quad \text{FG-ArZnR} \quad \text{R} = \text{Et or iPr} \\
&\text{R}_2\text{Zn} \quad \text{FG-ArZnR} \quad \text{FG-Ar-l} \\
&\text{RI} \quad \text{RI} + (\text{FG-Ar})_2\text{Zn} \quad \text{FG-Ar-l} \\
&\text{Nu}^- \quad \text{Zn}^- \quad \text{Nu}^- \quad \text{Met}^+ \quad \text{Met}^+ \\
&\text{2 FG-Arl} \quad i\text{Pr}_2\text{Zn} (1.1 \text{ equiv}) \quad \text{Li(acac) (10 mol\%)} \\
&\text{Et}_2\text{O/NMP (1:10)} \quad \text{25 °C, 12 h} \quad \text{(FG-Ar)}_2\text{Zn} \\
&\text{1a–m:} \quad >90\% \\
\end{align*}
\]

Knochel, P. *ACIEE*, 2004, 43, 1017
Aryl Iodide-Copper Exchange.

3: $X = \text{Br, I}$

FG = ester, ketone, aldehyde; $R =$ Me$_3$CCH$_2$ (1) or PhMe$_2$CCH$_2$ (2)

Knochel, P. ACIEE 2002, 41, 3263
Summary. Applications.

1. Aryl iodides or bromides: n-BuLi, t-BuLi, RMgX, R₂Mg, R₃MgLi
2. Vinyl iodides: t-BuLi, R₃MgLi
3. Alkyl iodides: t-BuLi, Et₂Zn

Summary. Mechanism

1. Aryl bromides or iodides react through ate-complex
2. Primary alkyl iodides react via polar mechanism (w/ Ether)
3. Secondary alkyl iodides polar/radical competition
4. Alkyl bromides react via radical mechanism
5. I-Mg exchange is via “ate-complex”