Enantioselective Lithiation

Spencer Jones
MacMillan Group Meeting
March 19, 2008

Key Articles:
Overview

- Introduction to Enantioselective Lithiation
  - Complexation induced proximity effects
  - Use of (−)-sparteine as a ligand for enantioinduction

- Mechanism of Lithiation
  - Kinetics studies
  - Pathways for enantioinduction
  - Substitution phenomena

- Ligands Other Than (−)-Sparteine
  - Initial attempt at finding a sparteine surrogate
  - O'Brien's Ligand

- Catalytic Asymmetric Lithiation

- Synthetically Useful Examples
Complexation Induced Proximity Effects

- Enables Reactivity at sites that are otherwise nonreactive or not thermodynamically favored


Use of (−)-Sparteine as a Ligand for Enantioinduction

(−)-Sparteine is a readily available alkaloid that can serve as a ligand for various metals

(−) sparteine = sp*
$116, 100 \text{ g}$

Metalation in the presence of (−)-sparteine

Use of (-)-Sparteine as a Ligand for Enantioinduction

(-)-Sparteine is a readily available alkaloid that can serve as a ligand for various metals

\[ (-)-\text{sparteine} = \text{sp}^* \]

$116, 100 \text{ g}$

Metalation in the presence of (-)-sparteine

\[ \text{Me} \quad n\text{-BuLi/sp}^* \quad 50 \degree \text{C, Hexane} \quad \text{Me} \quad \text{Li}/\text{sp}^* \quad \text{CO}_2 \quad \text{Me} \quad \text{CO}_2\text{H} \]

30% ee

First Highly Enantioselective Lithiation Using Sparteine

- Chelation directed lithiation provides a configurationally stable, dipole stablized carbanion capable of reacting with several electrophiles.
- The bulky carbamate serves to prevent nucleophilic addition into the carbamate.

\[ R = \text{CH}_3, (\text{CH}_2)_5\text{CH}_3, \text{CH(CH}_3)_2 \]
\[ E = \text{Me}_3\text{SnCl, CO}_2, \text{CH}_3\text{I} \]

52 – 81% yields ≥ 95% ee

Mechanism of Enantioselective Lithiation

Boc-pyrrolidine is asymmetrically lithiated with s-BuLi/sp* and reacts selectively with a variety of electrophiles

\[
\text{Boc} \quad \xrightarrow{s\text{-BuLi/sp}^*} \quad \text{Li/sp}^* \quad \xrightarrow{E} \quad \text{Boc}
\]

\[
\begin{array}{ccc}
\text{Electrophile} & \text{Yield} & \text{ee (‰)} \\
\hline
\text{TMS-Cl} & 87 & 96 \\
\text{PhCOPh} & 75 & 90 \\
\text{CO}_2 & 55 & 88 \\
\text{(CH}_3\text{)}_2\text{SO}_4 & 88 & 94 \\
\text{Sn(Bu)}_3\text{Cl} & 83 & 96 \\
\end{array}
\]

Mechanism of Enantioselective Lithiation

- BuLi/sparteine is present in solution as an organolithium dimer
- If the lithiation were to occur in a single step with the dimer, the reaction order in s-BuLi should be 1, whereas if the reaction occurs via monomer the order should be 0.5

![Chemical structure diagram]

**Reaction Order in Organolithium dimer?**

- Kinetics experiments revealed the lithiation is zeroth order in organolithium dimer

Gallagher, D. J.; Beak, P. J. Org. Chem. 1995, 60, 7092
Mechanism of Enantioselective Lithiation

- The fact that the lithiation is zeroth order in organolithium dimer under pseudo first order conditions suggests the presence of a prelithiation complex, C, with a large equilibrium constant, $K_c$

- The RDS was determined to be the deprotonation step due to the high kinetic isotope effect ($k_H/k_D$)

Gallagher, D. J.; Beak, P. J. Org. Chem. 1995, 60, 7092
Origin of Stereoselectivity in Lithiation

Calculations of the four possible low energy conformers leads to two prelithiation complexes leading to abstraction of pro-S and pro-R hydrogens

Origin of Stereoselectivity in Lithiation

Calculations reveal that abstraction of the pro-S hydrogen is favored due to greater nonbonded interactions in transition state leading to abstraction of the pro-R hydrogen.

Mechanism of Proton Transfer

Tunneling may be operative for deprotonations

\[ \frac{k_H}{k_D} = \frac{98.7}{1.3} = 76 \]

Pathways for Enantioinduction

- Configurational stability of lithiated intermediate cannot be assumed.
- The two limiting pathways for enantioinduction are asymmetric deprotonation, and asymmetric substitution

**Asymmetric Deprotonation**

**Asymmetric Substitution**

Dynamic Thermodynamic Resolution

Dynamic Kinetic Resolution
Establishing the Asymmetric Deprotonation Pathway

- If the enantiodetermining step is postdeprotonative, the ligand should resolve the diastereomeric complexes

\[
\begin{align*}
\text{R} & = \text{H or SnBu}_3 \\
\text{Boc} & \\
\end{align*}
\]

- In addition, the enantioenriched lithiated species should remain enantioenriched in the absence of a chiral ligand

\[
\begin{align*}
\text{96\% ee} & \\
\text{93\% ee, s-BuLi} & \\
\text{74\% ee, s-BuLi/TMEDA} & \\
\end{align*}
\]

Dynamic Thermodynamic Resolution Asymmetric Substitution

- In a dynamic thermodynamic resolution, the enantioselectivity is controlled by $\Delta G$

- Lithiation of o-ethyl aniline gives a slowly equilibrating benzyl lithium. The asymmetric deprotonation pathway is immediately ruled out

![Diagram showing the reaction mechanism]

Dynamic Thermodynamic Resolution Asymmetric Substitution

- Proving a dynamic thermodynamic resolution

\[ \text{PivNH} \xrightarrow{s-\text{BuLi}} \xrightarrow{-25^\circ C} \text{Li} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Exposure of A to sp(^{*}) prior to addition of TMS-Cl</th>
<th>TMS-Cl (equiv.)</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78°C, 15 min</td>
<td>2.3</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>-78°C, 15 min</td>
<td>0.10</td>
<td>82</td>
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<td>3</td>
<td>-25°C, 45 min then -78°C, 30 min</td>
<td>2.1</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
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<td>0.1</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>-25°C, 45 min then -78°C, 30 min</td>
<td>0.50</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>-25°C, 45 min then -78°C, 30 min</td>
<td>0.45</td>
<td>94</td>
</tr>
</tbody>
</table>

Dynamic Thermodynamic Resolution Asymmetric Substitution

Proving a dynamic thermodynamic resolution

\[ \text{PivNH} \xrightarrow{s-\text{BuLi} \ -25^\circC} \text{PivNLi} \]

1. sp*  
2. TMS-Cl

![Reaction diagram]

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Dynamic Thermodynamic Resolution Asymmetric Substitution

Proving a dynamic thermodynamic resolution

\[ \text{PivNH} \xrightarrow{s{-}\text{BuLi}} \text{Me} \]

\[-25^\circ\text{C} \]

\[ \text{PivNLi} \xrightarrow{\text{Li}} \text{Me} \]

\[ 1. \text{sp}^* \]

\[ 2. \text{TMS-Cl} \]

\[ \text{A} \]

\[ \text{TMS} \]

\[ \text{PivNH} \]

\[ \text{TMS} \]

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Dynamic Kinetic Resolution Asymmetric Substitution

In a dynamic kinetic resolution, the enantioselectivity is controlled by $\Delta \Delta G^\ddagger$

Lithiation of o-ethylbenzamide gives rapidly equilibrating benzyl lithium

Dynamic Kinetic Resolution Asymmetric Substitution

Proving that the reaction proceeds under asymmetric substitution

![Chemical structures and reaction scheme](image)

<table>
<thead>
<tr>
<th>reactant (ee)</th>
<th>Ligand</th>
<th>%ee of C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A or B (0%)</td>
<td>sp*</td>
<td>87</td>
</tr>
<tr>
<td>B (87%)</td>
<td>none</td>
<td>5</td>
</tr>
<tr>
<td>B (87%)</td>
<td>TMEDA</td>
<td>1</td>
</tr>
</tbody>
</table>

Dynamic Kinetic Resolution Asymmetric Substitution

- Proving dynamic kinetic resolution over dynamic thermodynamic resolution

\[
\begin{align*}
\text{(i-Pr)}_2N\text{O} & \quad \text{Li/sp*} \\
\text{MeO} & \quad \text{N} \quad \text{N(Bn)}_2
\end{align*}
\]

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

\[
\text{\textup{\textsmaller{-78°C}}}
\]

\[
\begin{align*}
\text{dr} & \quad 1:1.6 \\
& \quad 1:1.6
\end{align*}
\]

- The results suggest a dynamic kinetic resolution, but do not explicitly rule out a dynamic thermodynamic resolution where \(\Delta G^\ddagger\) are the same.

Invertive or Retentive $S_{E2}$

- The stereochemistry in the substituted product may or may not correspond to the stereochemistry of the lithium complex.
- For most non-resonance stabilized carbanions, retentive substitution is usually the observed $S_{E2}$ pathway.

Invertive or Retentive $S_E2$

Resonance stabilized carbanions may undergo invertive or retentive substitution depending on the electrophile.

\[
\begin{align*}
(i-Pr)_2N\text{Me} & \quad \text{Me} \quad \text{O} \quad \text{Li/sp}^* \\
\text{s-BuLi/sp}^* & \quad \text{Me} \quad \text{O} \quad \text{Li/sp}^* \\
\text{Me} & \quad \text{E} \quad \text{Me}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>enantiomeric ratio A : B</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_2C=CHCH_2OTs$</td>
<td>6 : 94</td>
</tr>
<tr>
<td>$H_2C=CHCH_2Cl$</td>
<td>96 : 4</td>
</tr>
<tr>
<td>$n$-BuOTs</td>
<td>2 : 98</td>
</tr>
<tr>
<td>$n$-BuCl</td>
<td>90 : 10</td>
</tr>
<tr>
<td>$n$-BuBr</td>
<td>87 : 13</td>
</tr>
<tr>
<td>$n$-BuI</td>
<td>64 : 36</td>
</tr>
</tbody>
</table>

Invertive or Retentive S\textsubscript{E}2

Retention or inversion can be a function of the reactivity of the electrophile.

<table>
<thead>
<tr>
<th>Inverting Electrophiles</th>
<th>Retaining Electrophiles</th>
<th>Non Selective Electrophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO\textsubscript{2}</td>
<td>MeOD</td>
<td>allyl bromide</td>
</tr>
<tr>
<td>98% ee</td>
<td>94% ee</td>
<td>33% ee\textsuperscript{a}</td>
</tr>
<tr>
<td>allyl triflate</td>
<td>CICO\textsubscript{2}Me</td>
<td>allyl iodide</td>
</tr>
<tr>
<td>96% ee</td>
<td>90% ee</td>
<td>6% ee\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} favoring inversion

Beak et al. suggest that for resonance stabilized carbanions, highly reactive and/or non-lithium coordinating electrophiles proceed with inversion, while less reactive and/or lithium coordinating electrophiles proceed with retention.

Using Invertive or Retentive $S_{E2}$ to Access Either Enantiomer

Because (−)-sparteine is only readily available as one enantiomer the preference for inversion or retention can allow access to either enantiomer.

1. $n$-BuLi/sp*
2. Me$_3$SnCl

Ar = $p$MeOC$_6$H$_4$

1. $n$-BuLi/sp*
2. CO$_2$

77%, 90% ee

1. $n$-BuLi/sp*
2. CO$_2$

95%, 92% ee

1. $n$-BuLi/sp*
2. ClCO$_2$CH$_3$

1. CH$_2$N$_2$
2. CAN

55%, 88% ee

71%, 92% ee

Using Invertive or Retentive $S_E$2 to Access Either Enantiomer

Because (−)-sparteine is only readily available as one enantiomer the preference for inversion or retention can allow access to either enantiomer.

Ligands Other Than (−)-Sparteine

- For carbanions that only undergo retentive substitution, a (+)-sparteine surrogate is required to enter the opposite enantiomeric series
- Deprotonation/trimethylsilylation of Boc-pyrroolidine used as a benchmark

Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. J. Org. Chem. 1995, 60, 8148
Ligands Other Than (−)-Sparteine

- For carbanions that only undergo retentive substitution, a (+)-sparteine surrogate is required to enter the opposite enantiomeric series.
- Deprotonation/trimethylsilylation of Boc-pyrrolidine used as a benchmark.

(-)-sparteine
87%, 96% ee

Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. J. Org. Chem. 1995, 60, 8148
Reason Why Cyclohexanediamine is a Poor Ligand

Transition state models for removal of the pro-R and pro-S hydrogens are approximately isosteric

Reason Why (-) Isosparteine is a Poor Ligand

- Space filling models for complexes of TMEDA, (-)-sparteine and (-)-isosparteine with lithium show that (-)-isosparteine significantly encapsulates lithium.

- The rate of lithiation follows the degree of encapsulation.

<table>
<thead>
<tr>
<th>ligand</th>
<th>lithiation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMEDA</td>
<td>30 min</td>
</tr>
<tr>
<td>sparteine</td>
<td>4 h</td>
</tr>
<tr>
<td>isosparteine</td>
<td>&lt;10%, 4 h</td>
</tr>
</tbody>
</table>

Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. J. Org. Chem. 1995, 60, 8148
Finding a (+)-Sparteine Surrogate

O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction

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O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction.

(-)-sparteine
87%, 90% ee

A (90% ee)
37%, racemic

B (98% ee)
31%, 21% ee

Finding a (+)-Sparteine Surrogate

O'Brien wanted to test structural analogues of sparteine to determine which components of the molecule are responsible for the enantioinduction.

(-)-sparteine
87%, 90% ee

A (90% ee)
37%, racemic

B (98% ee)
31%, 21% ee

C (>90% ee)
84%, 90% ee

Synthesis of O'Brien's (+)-Sparteine Surrogate

(-)-Cytisine has a structure closely related to O'Brien's (+)-sparteine surrogate

(-)-cytisine
250 mg, $850

Et$_3$N, ClCO$_2$Me
CH$_2$Cl$_2$
92%

MeO$_2$C

1. PtO$_2$/H$_2$
EtOH
86%

2. LAH, THF

Me

Laburnum
anagyroides

Comparison of (-)-Sparteine to O'Brien's Ligand

O'Brien's (+)-sparteine surrogate demonstrates approximately equal levels of enantioinduction as that achieved with (-)-sparteine

Catalytic Asymmetric Lithiation

Using a substoichiometric amount of (-)-sparteine affords low yields and selectivities in the deprotonation/substitution sequence

The diamine does not dissociate from the lithiated complex

In order to achieve ligand turnover, O'Brien et al. proposed the use of an achiral stoichiometric diamine to displace the chiral diamine.
Catalytic Asymmetric Lithiation

Several criteria must be met in order to achieve enantioselective lithiation/substitution:

1. Ligand exchange must occur
2. Organolithium must be configurationally stable during and after ligand exchange
3. Deprotonation with s-BuLi/sp* must be faster than with the achiral complex

Using information gained from their studies into designing a (+)-sparteine surrogate, the designed a ligand that should not facilitate deprotonation.

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Using information gained from their studies into designing a (+)-sparteine surrogate, the designed a ligand that should not facilitate deprotonation.

Catalytic Asymmetric Lithiation

Catalytic enantioselective lithiation/substitution works efficiently using the achiral bispidine ligand

1. 1.3 eq s-BuLi
   0.2 eq ligand
   1.2 eq bispidine
2. TMS-Cl

<table>
<thead>
<tr>
<th>ligand</th>
<th>product</th>
<th>yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>sp*</td>
<td>S-TMS</td>
<td>76</td>
<td>90:10</td>
</tr>
<tr>
<td>(+)-sp*</td>
<td>R-TMS</td>
<td>66</td>
<td>6:94</td>
</tr>
</tbody>
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Catalytic Asymmetric Lithiation

Catalytic enantioselective lithiation/substitution works efficiently using the achiral bispidine ligand

\[
\begin{align*}
R = \text{PhCH}_2\text{CH}_2
\end{align*}
\]

1. 1.3 eq s-BuLi
X eq ligand
1.2 eq bispidine
2. Bu_3SnCl

<table>
<thead>
<tr>
<th>ligand</th>
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<th>er</th>
</tr>
</thead>
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<tr>
<td>sp*</td>
<td>0.2</td>
<td>S-SnR_3</td>
<td>77</td>
<td>92:8</td>
</tr>
<tr>
<td>(+)-sp*</td>
<td>0.2</td>
<td>R-SnR_3</td>
<td>72</td>
<td>6:94</td>
</tr>
<tr>
<td>sp*</td>
<td>0.1</td>
<td>S-SnR_3</td>
<td>54</td>
<td>81:19</td>
</tr>
<tr>
<td>(+)-sp*</td>
<td>0.06</td>
<td>R-SnR_3</td>
<td>63</td>
<td>15:85</td>
</tr>
</tbody>
</table>

Synthetic Utility of Asymmetric Lithiation

Anti-homoaldol reaction of allylic N-Boc amines proceeds with high levels of selectivity

\[
\begin{align*}
R = p-\text{MeOC}_6\text{H}_4
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>85</td>
<td>94</td>
<td>90:10</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>66</td>
<td>84</td>
<td>95:5</td>
</tr>
<tr>
<td>Ph</td>
<td>i-Pr</td>
<td>61</td>
<td>90</td>
<td>98:2</td>
</tr>
<tr>
<td>Ph</td>
<td>Cy</td>
<td>66</td>
<td>96</td>
<td>95:5</td>
</tr>
<tr>
<td>Cy</td>
<td>Ph</td>
<td>82</td>
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<td>Me</td>
<td>72</td>
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Whisler, M. C.; Vaillancourt, L.; Beak, P. Org. Lett. 2000, 2, 2655
Synthetic Utility of Asymmetric Lithiation

Changing the lewis acid from Et₂AlCl to Ti(Oi-Pr)₃Cl results in an inversion in the enantiomeric series of the product due to a differing transition state.

<table>
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<th>R'</th>
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<th>ee (%)</th>
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<td>64</td>
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<td>Cy</td>
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Whisler, M. C.; Vaillancourt, L.; Beak, P. Org. Lett. 2000, 2, 2655
Synthetic Utility of Asymmetric Lithiation

- Transmetalation of lithiated Boc-pyrrolidine to zinc enables Negishi coupling with a range of aryl halides

\[
\begin{align*}
\text{N} & \xrightarrow{s\text{-BuLi}/sp^*} \text{N} & \xrightarrow{\text{Li/sp}^*} \xrightarrow{\text{ZnCl}_2} \xrightarrow{\text{Pd(OAc)}_2, \text{Ar-X}} \text{Ar} \\
\text{Boc} & \xrightarrow{\text{MTBE, } -78 \, ^\circ\text{C}} \text{Boc} & \xrightarrow{\text{ZnR}_n} \xrightarrow{\text{tBu}_3\text{P-HBF}_4, \text{RT 12 h}} \text{Boc}
\end{align*}
\]

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<thead>
<tr>
<th>entry</th>
<th>Ar-X</th>
<th>eq ZnCl₂</th>
<th>% yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-Br</td>
<td>1.0</td>
<td>82</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>Ph-Br</td>
<td>0.6</td>
<td>80</td>
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</tr>
<tr>
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<td>Ph-Br</td>
<td>0.3</td>
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</tr>
<tr>
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<td>Ph-Cl</td>
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<td>48</td>
<td>96:4</td>
</tr>
<tr>
<td>5</td>
<td>Ph-OTf</td>
<td>1.0</td>
<td>&lt;5</td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td>p-F-PhBr</td>
<td>1.0</td>
<td>75</td>
<td>96:4</td>
</tr>
<tr>
<td>7</td>
<td>p-NH₂-PhBr</td>
<td>1.0</td>
<td>70</td>
<td>96:4</td>
</tr>
<tr>
<td>8</td>
<td>o-MeO-PhBr</td>
<td>1.0</td>
<td>72</td>
<td>96:4</td>
</tr>
<tr>
<td>9</td>
<td>5-Br-NBoc-indole</td>
<td>1.0</td>
<td>81</td>
<td>96:4</td>
</tr>
<tr>
<td>10</td>
<td>4-Br-indole</td>
<td>1.0</td>
<td>77</td>
<td>96:4</td>
</tr>
<tr>
<td>11</td>
<td>3-Br-pyridine</td>
<td>1.0</td>
<td>60</td>
<td>96:4⁺</td>
</tr>
</tbody>
</table>

4 mol% Pd(OAc)₂, 5 mol% t-Bu₃P-HBF₄.⁺coupling performed at 60 °C.

Synthetic Utility of Asymmetric Lithiation

Transmetalation of lithiated Boc-pyrrolidin-2-yl methyl ester to zinc enables Negishi coupling with a range of aryl halides. The reaction proceeds as follows:

\[
\text{Boc-NH} \overset{\text{s-BuLi/sp}^*}{\underset{\text{MTBE, } -78 \, ^\circ\text{C}}{\longrightarrow}} \text{Boc-NH} \overset{\text{Li/sp}^*}{\underset{\text{ZnCl}_2}{\longrightarrow}} \text{Boc-NH} \overset{\text{t-Bu}_3\text{P-HBF}_4}{\underset{\text{Ar-X, RT, 12 h}}{\longrightarrow}} \text{Boc-NHAr}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-X</th>
<th>eq ZnCl(_2)</th>
<th>% yield</th>
<th>er</th>
</tr>
</thead>
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<tr>
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<td>Ph-Br</td>
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<td>96:4</td>
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</tr>
</tbody>
</table>

4 mol% Pd(OAc)\(_2\), 5 mol% t-Bu\(_3\)P-HBF\(_4\).\(^a\)Coupling performed at 60 °C.

Synthetic Utility of Asymmetric Lithiation

Hoppe demonstrated that O-alkylcarbamates can be deprotonated and trapped with boronic esters to yield precursors to 1,2 metalate rearrangement products.

\[
\begin{align*}
\text{R} & \quad \text{Ni-Pr}_2 \\
\text{R} = \text{PhCH}_2\text{CH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
\text{R}' & \quad \text{NaOH} \\
\text{R}' & \quad \text{THF} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{Bpin} \\
\text{R}' & \quad \text{25} \degree \text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{BPin} \\
\text{R}' & \quad \text{Et}_2\text{O}, -78 \degree \text{C} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Grignard reagent, ( R' )</th>
<th>% yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrMgCl</td>
<td>50</td>
<td>&gt;95</td>
</tr>
<tr>
<td>CyMgBr</td>
<td>70</td>
<td>&gt;95</td>
</tr>
<tr>
<td>( i-\text{PrMgCl} )</td>
<td>56</td>
<td>&gt;95</td>
</tr>
<tr>
<td>( t-\text{BuMgCl} )</td>
<td>64</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

Synthetic Utility of Asymmetric Lithiation

Kocienski et al. recently applied this methodology toward the synthesis of (S)-(−)-N-Acetylcolchinol

![Chemical structure of (S)-(−)-N-Acetylcolchinol]

---

Synthetic Utility of Asymmetric Lithiation

Kocienski et al. recently applied this methodology toward the synthesis of (S)-(−)-N-Acetylcolchinol

\[
\text{R} = \text{ArCH}_2\text{CH}_2
\]
\[
\text{Cb} = \text{CONi-Pr}_2
\]

70%

H\text{O}_2/H_2\text{O} 
K\text{CO}_3 
RT 
73%, 88% ee

1,2-metallate rearrangement

RT, 12 h

Catalytic Asymmetric Variant of Hoppe's Methodology

Using his bispidine exchange ligand, O'Brien was able to achieve a metalation, electrophile trapping, 1,2-metalate rearrangement under catalytic conditions.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Cb} = \text{CONi-Pr}_2 & \quad \text{BPin} \\
\text{1. 1.3 eq s-BuLi} & \quad \text{1. PhMgBr} \\
\quad \text{0.2 eq sp*} & \quad \text{H} \quad \text{−78 °C to RT} \\
\quad \text{1.2 eq bispidine} & \\
\text{Et}_2\text{O, −78 °C, 5 h} & \\
\text{2. B(Oi-Pr)}_3 & \\
\text{3. HCl} & \\
\text{4. Pinacol, pTSA} & \\
\end{align*}
\]

McGrath, M. J.; O'Brien, P. Synthesis, 2006, 13, 2233
Conclusions

- Enantioselective Lithiation/Substitution Generally Proceeds Through Two Limiting Pathways:
  - Asymmetric deprotonation
  - Asymmetric substitution
    - Dynamic thermodynamic resolution
    - Dynamic kinetic resolution

- Work By O'Brien has Produced a (+)-Sparteine Surrogate as Well as the First Catalytic Asymmetric Lithiation/Substitution Reaction

- Lithiated Intermediates Can Be Precursors to Various Transmetallative Processes Such as Homo-Aldol Reactions, Negishi Couplings and 1,2-Metallate Rearrangements