Reagent-Controlled Asymmetric Homologation of Boronic Esters by Enantioenriched Main-Group Chiral Carbenoids

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Presentation Outline

• Introduction
• Recent applications of 1,2-metalate rearrangements
• Key innovations and synthetic utility
• Next directions and future applications
Introduction

Mattson & Mah

$SN_2$ displacement of $\alpha$-haloalkyl boronic esters

Hoffmann group

Chiral carbenoid stability

Satoh group

Metal carbenoid synthesis and stability

Blakemore group

$\text{O}^-$

$\text{S}^+$

$\text{Ph}$

$p$-Tol

$\text{Cl}$

$\text{EtMgCl}$

or $n$-BuLi

% ee > 98 %

M = MgCl or Li

% ee = 59 - 96 %

High % ee via reagent control through 1,2-metalate rearrangement
Recent Applications of 1,2-Metalate Rearrangements

Substrates act as a new source of olefins

Recent Applications of 1,2-Metalate Rearrangements

1,2-Metalate rearrangements of \( \alpha \)-alkoxyalkyl cuprates

(a) BuLi (5.4 equiv)
CuBr·SMe\(_2\) (1.1 equiv)
Et\(_2\)O·SMe\(_2\),
\(-110^\circ\text{C}\), 1 h

(b) allyl bromide (6.0 equiv)
\(-110^\circ\text{C}\) to r.t. over 12 h

5 M = SnBu\(_3\)

6 M = Li

\( \text{Bu}_2\text{CuLi} \)

5

6

\( \text{2Li}^+ \)

\( \text{2Li}^+ \)

\( \text{1,2-metallate rearrangement} \)

7 (54%)

allyl bromide

Nucleophilic Displacement of α-Bromoalkyl Boron Compounds

SN$_2$ displacement of neighboring halogen
Alkyl migration favored over alkoxide due to stronger B-O bond

Preparation of Functionalized Carbenoid Reagents

\[
\begin{align*}
4 & \xrightarrow{R^3 M} 5 + 6 \\
R^1 &= \text{toly} \\
X, R^2 &= \text{aziridine} \\
R^3 &= \text{Ethyl} \\
M &= \text{MgBr} \\
R^1 &= \text{Phenyl, toly} \\
X &= \text{F, Cl, Br} \\
R^2, R^3 &= \text{alkyl} \\
M &= \text{Li}
\end{align*}
\]


Sulfoxide/metal exchange occurs
\(\alpha\)-alkylhalo magnesium species more stable
\(\alpha\)-alkylhalo lithium species more reactive
α-Halogenation occurs with inversion at sulfur center
Diastereomers (9 & 10) isolated via multiple recrystallization in acetone
Isolate enantiomer 9 in >97 % ee (HPLC)

Mechanism of $\alpha$-Halogenation

Diastereomers are separated through multiple recrystallizations

Stability of $\alpha$-Chiral Magnesium Carbenoids

* Results reproduced by Blakemore

Transition State of Carbenoid Addition

\[ \text{ClMg} \quad \text{Ph} \quad \text{Cl} \quad \xrightarrow{\text{Me}_2\text{AlCl}} \quad \text{PhCHO} \]

\[ \text{VS.} \]

\[ \begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Cl}
\end{align*} \]

\((R, R)\)

\[ \begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Cl}
\end{align*} \]

\((S, R)\)

\[ \text{dr} = 93 \ (R, R): 7 \ (S, R) \]
Sulfoxide/Lithium Exchange

Evidence of lithium carbenoid generation from $\alpha$-halosulfoxides

Stereospecific Reagent Controlled Homologation (SRHC)

Matteson and Mah

Hoffmann & Satoh groups

R^1-B(OR)_2 + ClMgCl → R^2-B(OR)_2

aq NaOH/H_2O_2 → R^1OH

Syn diast. in high ee

Anti diast. in high ee

1,2-metalate rearrangement -MgCl_2

Boron ate-complex
Powerful Synthetic Applications

Methodology allows (via reagent control):

1) Choice of desired diastereomer product
2) Formation of desired diastereomer in high ee

Syn diast. in high ee

Anti diast. in high ee

J. Maciejewski
Oxidative Workup

\[
\begin{align*}
&\text{R}^1\text{B(OR)}_2 \quad \text{R}^2\text{B(OR)}_2 \\
&\begin{array}{c}
\text{R}^1\text{B(OR)}_2 \quad \text{R}^2\text{B(OR)}_2 \\
\text{R}^1\text{B(OR)}_2 \\
\text{R}^1\text{B(OR)}_2
\end{array}
\end{align*}
\]
Stereospecific Reagent Controlled Homologation (SRCH)

1) Carbenoid reagents must be configurational and chemically stable

Results from Blakemore
2) Ate-complex formation and breakdown must occur stereospecifically

Indirect SN$_2$ displacement of chlorine (1,2-rearrangement)
Inversion of stereochemistry at chiral center
Stereospecific Reagent Controlled Homologation (SRCH)

3) Metalate rearrangement must occur after ate-complex formation

Product not allowed to reenter the coupling reaction cycle

Prevents unwanted oligomerization
Observations With Magnesium Carbenoids

Low to modest yields with range of % ee
Reaction performs best using preformed conditions
Non-polar solvent increased % yield and % ee

<table>
<thead>
<tr>
<th>Mg carbenoid</th>
<th>Boronic ester</th>
<th>% Yield range</th>
<th>% ee range</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Catechol (20)</td>
<td>11 - 44</td>
<td>36 - 76</td>
</tr>
<tr>
<td>19</td>
<td>Neopentyl glycol (21)</td>
<td>0 - 56</td>
<td>n/a - 82</td>
</tr>
</tbody>
</table>

![Mg carbenoid 19](image1)

![Boronic ester 20](image2)

![Boronic ester 21](image3)
Promising Results With Lithium Carbenoids

Good yields with high % ee
Lithium best if Barbier-type conditions used

<table>
<thead>
<tr>
<th>Li carbenoid</th>
<th>Boronic ester</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>Neopentyl glycol (21)</td>
<td>0 - 86</td>
<td>n/a - 96</td>
</tr>
</tbody>
</table>

![Li carbenoid](image1.png)
![Boronic ester](image2.png)
Summary

- New type of C-C bond formation demonstrated
- Methodology allows for stereochemical control of products
- Homologated products obtained in range of % yield and % ee
- Promising results from lithium carbenoids
Next Directions/Future Applications

Continue to expand on unexpected Li carbenoid results

\[
\begin{align*}
\text{p-Tol} & \quad \text{S}^+ \quad R^2 \quad \text{Cl} \\
& \quad \text{LiR}^1 \quad \rightarrow \quad \begin{bmatrix}
\text{Li} & \text{R}^2 \\
\text{Cl} & \text{R}^3 \quad \text{B(OR)}_2
\end{bmatrix}
\end{align*}
\]

Test methodology using more complex \( R^2 \) and \( R^3 \) groups
Continue to work to optimize reaction conditions
Thank you

Acknowledgements:

Professor Wipf
Synthesis of $\alpha$-Chiral Sulfoxides

Carried out by Blakemore and co-workers