**Di-Boron Reagents and Reactions**

**J. Melendez Matos**

**Preparation of diboronates**

*From unsaturated carbons*

- Transition metal-promoted
- Two possible routes:
  - Catalytic cycle
  - Sequential monoboration

**Unsaturated carbons**

- Multiborylated compounds are currently emerging as useful conjunctive reagents for asymmetric synthesis.
- They can be crafted or manipulated in an enantioselective catalytic fashion and they provide opportunities for multiple sequential bond-forming transformations.

**Cross-coupling reactions**

First discovered by Suzuki, Miyaura, and co-workers in 1993 (*JACS. 1993, 115, 11018*)

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- Two possible routes:
  - Catalytic cycle
  - Sequential monoboration

This work is exclusively centered in diboration of unsaturated substrates because diboration of saturated systems are nowhere to be found.

Also, although transition metal-catalysis is the most common form of catalysis for these systems, a metal-free example (not discussed here) was developed by Hoveyda and his lab (*JACS 2012, 134, 9277*).

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### Differentially-protected diborons from alkynes

**JACS. 2010, 132, 2548.**

- **Catalyst screening**
  - 5 Pd(hu)₂ (O)  |  (4-ClC₆H₄)Pd(2.2)  |  83 | 84:16
  - 6 Pd(hu)₂ (O)  |  1,5-(C₆F₅)C₂H₄Pd(2.2)  |  78  |  96:4
  - 13 [IrCl(cod)] (I)  |  83 | 99:1

### Susuki-Miyaura Scope

- 91% yield
- 96% yield
- 79% yield
- 75% yield
- 88% yield

### Reaction is regiocomplementary to the ‘common’ symmetrical diborons stepwise reactions!

- **(pin)B-B(pin)-based sequence**
  - 1. Pd/C  
  - 2. 5N HCl aq.  
  - 3. 30% H₂O₂

- **B₂(pin)₂-based sequence**
  - 1. Pd/C  
  - 2. 30% H₂O₂  
  - 3. 5N NaOH aq.
Shenvi Group Meeting
Nov. 20, 2014

Di-Boron Reagents and Reactions

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Terminal Alkynes to saturated diboronates
JACS, 2009, 131, 18234.

1.0-100 mol % NHC complex A-C or phosphine
1.0-100 mol % NaOt-Bu
1.1 equiv B2(pin)2, 2.0 equiv MeOH
toluene, 22 °C

R = NHC-Cu complex
B2(pin)2, MeOH

Initial Investigations

5.0 mol % CuCl, 20 mol % NaOt-Bu
0.9 equiv B2(pin)2, 1 equiv MeOH
>98:2 >98% conv

Me

First Trans Diborylation

- Key transition state: Anionic mechanism (trans) vs. interactions between orbitals of the transition metal and the alkyne (cis)

Me

Solution?
Pseudo-Intramolecular Approach

1. Li-base (1equiv), r.t, 30 min

2. B2(pin)2 (1.1 equiv), THF, 75 °C, 24 h

propargylic alcohol to "tether" the molecule
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**Scope and limitations**

![Chemical structures and yields](image)

**Applications?**

1. n-BuLi (1 equiv)  
dioxane, r.t., 30 min

2. $\text{B}_2\text{(pin)}_2$ (1.1 equiv)  
75 °C, 24 h

3. $\text{PdCl}_2\text{(dppf)}$ (5 %)  
dioxane/aq, KOH  
120 °C, 24 h

**Pseudo-intramolecular trans-Diborylation:**

![Chemical reaction and equilibrium](image)

**Equilibrium between cis- and trans-Products:**

![Chemical reaction and equilibrium](image)
Di-Boron Reagents and Reactions

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Application to fragments of Tylonolide and Mycinolide IV

1. normal conditions
2. (n-Bu)4NF; NaOH, 110 °C, tol.
3. (t-Bu)Ph2SiCl, imidazole, DCM

Double Alkylation - Alkylation/Arylation

Same conditions as above:
10 mol% A, 10 mol% CuI,
1.5 equiv allyl-OPO(OEt)2,
1.5 equiv KOt-Bu

76% yield
>98:2 dr, 92.5:7.5 er

One vessel!

Two-vessel, one purific.!
Di-Boron Reagents and Reactions

Alkenes
Hydroxyl-directed

\[
R^3 R^2 B\text{(pin)} \quad \text{NaOH} \quad H_2O_2 \quad (\text{optional})
\]

- Cyclic and acyclic homoallylic and bishomoallylic alcohols
- Alternative to OsO₄-promoted dihydroxilations

Scope
Terminal alkenes

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

50-85% yield
>5:1 dr (≈13:1)

1,1-disubstituted alcohols

\[
R \quad \text{OH} \quad R^2
\]

~65% yield
~17:1

Cyclic alkenes (syn diols)

- Allylic alcohols suffer from diminished dr
- DR is lowered when methoxy-derivative is used instead

Application to the synthesis of C6-C13 spongistatin

\[
\text{OTBDPS} \quad \text{TBPSO} \quad \text{THF, 70 °C, 6-12 h}
\]

- Cyclic and acyclic homoallylic and bishomoallylic alcohols
- Alternative to OsO₄-promoted dihydroxilations

In comparison, look at this old-fashioned synthesis....
Geminal diborons


- The valence deficiency of three-coordinate boron can be used to stabilize anions at adjacent carbon centers.
- They report an alkoxide-promoted deborylative alkylation of geminal boronates that applies to aliphatic primary, secondary, and tertiary derivatives.
- Can enable highly hindered C-C couplings between geminal boronates and alkyl halide electrophiles.
- They also provide the first experimental evidence that these reactions proceed through the intermediacy of alpha-boryl carbanions.
- Given that geminal bis(boronates) are easily accessed on a large scale, this reactivity pattern constitutes a practical strategy for the construction of common alkyl pinacol boronic esters.

Scope

- mono- and di-substituted geminal boronates
- primary and secondary halides
- Cl or Br (I gives lower yields)
- Allylic electrophiles
- Diborylmethane: efficient strategy for single-carbon homologation
Enantioselective boronation of vinyl boronates

**JACS, 2014, 136, 1614.**

There is inherently distinctive reactivity in bis(boronate) esters

\[
\text{R} \cdot \text{B(pin)} \cdot \text{B(pin)} \quad \text{Lewis Base}
\]

vicinal boronates: internal chelation

\[
\text{R} \cdot \text{B(pin)} \cdot \text{B(pin)} \quad \text{geminal boronates: anion stabilization}
\]

The possibilities of mixing them together.....

**JACS, 2014. ASAP DOI: 10.1021/ja510081r**

Chiral tris(boronates)

\[
\text{R} \cdot \text{B(pin)} \quad \text{asymmetric diboration}
\]

Enantioselective vinylboronate diboration

**Conditions:**

- Since Pt/phosphonite complexes are effective in the enantioselective diboration of terminal alkenes, dienes, and imines, they considered them as prospective catalysts for vinyl boronate diboration

\[
\begin{array}{c}
\text{B(pin)} \\
\text{B(pin)} \\
\text{B(pin)}
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Note the use of a "more reactive" regent.

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Deborylative Alkylation

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\begin{array}{c}
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\text{B(pin)} \\
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Stereoselective Intramolecular Deborylative Alkylation

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\text{B(pin)} \\
\text{B(pin)}
\end{array}
\]

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\begin{array}{c}
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\text{B(pin)} \\
\text{B(pin)}
\end{array}
\]
Shibata and coworkers were the first to demonstrate that achiral 1,1-diboronyl esters undergo cross coupling in a chemoselective fashion affording only the mono-coupled product. (JACS. 2010, 132, 11033)

Proposed TS

Further Applications

Or even further applications...
Access to linear and carbocyclic α-chiral (δ-alkoxyallyl) boronates

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Di-Boron Reagents and Reactions

What do they do? Screening....

Pretty normal scope

Having another chiral center in the molecule....

Reaction conditions:
- CuCl (5 mol %)
- ligand (5 mol %)
- (pin)B(pin) (1.5 equiv)
- K(OtBu) (1.0 equiv)
- THF, 0 °C, 12 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl/(R,R)-BezP*</td>
<td>3</td>
<td>95 (81)</td>
<td>97</td>
</tr>
</tbody>
</table>

Convergent coupling for polyol derivatives

Enantioselective boryl substitution in cyclic substrates

Stereoselective modular construction of complex 3,3-disubstituted cyclopentenes

JACS. ASAP. DOI:10.1021/ja506284w

56% yield E2 = 80:20 97:3 dr

60%, 91% ee

60% (2 steps) 97% ee
Strategy for rapid terpene construction: Application to the synthesis of Pumiliside Aglicon

**General Strategy**

- Catalyst: $\text{B}_2(\text{pin})_2$
- Reagents: $\text{R}_1\text{R}_2\text{CHO}$
- Reaction Conditions: Toluene, 60°C, 12 h; then CHO

**Scope**

- **76% yield**
  - >15:1 dr
  - 98:2 er

- **83% yield**
  - 5:1 dr
  - >15:1 er

- **71% yield**
  - 15:1 dr
  - 99:1 er

- **39% yield**
  - >20:1 dr
  - 96:4 er

- **77% yield**
  - 11:1 dr
  - 97:3 er

**Di-Boron Reagents and Reactions**

1. **1% Pt(dba)$_3$**
   - $\text{B}_2(\text{pin})_2$, tol.
   - 60°C, 12 h; then CHO
   - 68% yield
   - >15:1 dr
   - 96:4 er

2. **Mes$_2$N-$\text{N}$-Mes**
   - THF, H$_2$O
   - >96% yield
   - HOAc
   - (75%)