Enantioselective Borylations

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Denmark Group Meeting
Sept. 14th 2010
30.000-foot View

Good yield
Good dr
Good er
Good chemoselectivity
Enantioenriched Organoboranes
What to do with them...

Crudden C. M. et. al., Chem. Commun. 2009, 6704–6716
Enantioselective Borylations

- Addition of HB(OR₂) to styrenes
- Addition of HB(OR₂) to olefins with electron withdrawing groups
- Addition of HB(OR₂) to other olefins
- Desymmetrizations and Cyclopropanations
- Addition of B₂(OR₂)₂ to simple alkenes
- Addition of B₂(OR₂)₂ to higher olefins
Alkene Monoborylation

Scheme 4. Rhodium-catalyzed asymmetric hydroboration of styrene with ligands 7a-f. a) [Rh(cod)$_2$]BF$_4$ (1.0 mol%), 7a-f (1.2 mol%), catecholborane (1.2 equiv), solvent; b) 3m KOH, H$_2$O$_2$.

84%, 85% ee

80%, 58% ee

69%, 93% ee

50%, 84% ee

81%, 82% ee

Alkene Monoborylation

\[ \text{Ar} \equiv \text{R} \xrightarrow{\text{CuCl (3 mol \%), NaO\textsubscript{t}Bu (6 mol \%)}} \text{BP} \text{Pin} \]
\[ 5 \text{ (3.3 mol \%), PinBH (1.2 equiv) toluene} \]
\[ \text{Ar} \equiv \text{R} \]

- Very good ee (82–93%) even with o-substituents
- Naphthyl groups gave poor ee
- 61–95% yield


61%, 88% ee
90%, 91% ee
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β-borylation

L1 (R)-(S)-josiphos

L2 (R)-(S)-NMe2-PPh3-mandyphos

EWG = Ester, nitrile, amide, ketone

R = alkyl, aryl, branched alkyl

High yield (89–97%), 82–92 % ee. Insensitive to character of R-group or ketone/ester fragment

MeOH additive found to be critical for this reaction

Yun J. et. al., Angew. Chem. Int. Ed. 2008, 47,
β-borylation

**Investigated solvent effects:**
- MeOH, iPrOH and tBuOH all effective
- Solvent affects product enantiomer ratio

**Results:**
- Steric factors at $R^1$ are minimal for all classes.
- Mainly controlled by $R^2$ for ketones.
- Can add into extended dienones.

With Rh(phebox) 77%, 93% ee

Yun’s Addition into Cyclic Enones

\[
\begin{align*}
R - C = O + B_2\text{pin}_2 & \rightarrow R - C = O \quad \text{2 mol\% CuCl, 3 mol\% NaOt-Bu} \\
& \quad \text{4 mol\% L7} \\
& \quad \text{2 equiv. MeOH, THF, rt, 24 h}
\end{align*}
\]

92% yield, >99% ee

0% yield

β-borylation: Yun’s Mechanism


β–borylation

- PF$_6$ salt hypothesized to accelerate catalyst regeneration by formation of LiPF$_6$
- No protic additive necessary
- Wide scope in R for n=0,1,2: various aryl, unbranched and branched alkyl (80–99% yield, 70–98% ee)

Shibasaki M., et al. J. AM. CHEM. SOC. 2009, 131,
Fernandez’ NHC borylation

- ee better for syn than anti
- Syn ee 35–74%, anti ee 5–42%
- Poor dr (70:30 syn best case)
- $R_2$ is an alkoxy group for all substrates

Fernandez et. al. Organometallics, 2009, 28, 659
β-borylation – Hoveyda

Viable with esters, thioesters, ketones
MeOH is not required (can access boron enolate for further transformations)
Can add to alkyl-substituted esters as well

Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132,
Stereochemical Model

No $\alpha$-substituted $\alpha,\beta$-unsaturated esters tried to check proposal

Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132, 106
DFT Calculations

1,4 addition

1,2-addition

Marder T. B. et. al. Organometallics 2008, 27, 4443
DFT Calculations with Esters

1,4-addition

Marder T. B. et. al. Organometallics 2008, 27, 4443–4454
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trans-Alkene Monoborylation

\[
\text{MeO} - \text{C} - \text{MeO} \quad \xrightarrow{(i)} \quad \text{MeO} - \text{C} - \text{OH} \\
\text{QuinapRh}^+ \quad >98\%; \ 88\% \text{ e.e.}; \ 77\% \text{ yield}
\]

trans-Alkene Monoborylation

\[ \text{13} \quad \text{CuCl, KOt-Bu, MeOH, THF, } -50^\circ\text{C, 48 h} \]

\[ \text{7.5 mol % CuCl, 30 mol % KOt-Bu, MeOH, THF, } -50^\circ\text{C, 48 h} \]

99:1 er, 80% yield

Hoveyda A. H. et al. J. AM. CHEM. SOC. 2009, 131,
Borylation of (Z)-allylcarbonates

- 64–70%, >90% ee for R=alkyl
- No aryl demonstrated
- No branching at the α-position of R tolerated

Ito et al., Pure Appl. Chem., 80,
Stereochemical Model
Hindered Alkene borylation

- Scope only demonstrated for alkyl substrates.
- Norbornene additive increases ee.
- Amide required for 2-point binding.
- Stereospecific.

\[
\text{Ph} - \text{N} - \text{O} - \text{C} - \text{H} - \text{N} - \text{Ph} \\
\text{R}^E - \text{C} - \text{R}^Z
\]

1) 1\% Rh(nbd)\textsubscript{2}BF\textsubscript{4} \\
2.1\% 3, 2.0 PinBH \\
10\% norbornene \\
THF, rt, 24 h \\
2) aq. NaOH, H\textsubscript{2}O\textsubscript{2}

\[
\text{Ph} - \text{N} - \text{O} - \text{C} - \text{H} - \text{N} - \text{Ph} \\
\text{R}^E - \text{C} - \text{R}^Z
\]

3a Ar = C\textsubscript{6}H\textsubscript{5} \\
b Ar = 4-MeC\textsubscript{6}H\textsubscript{4} \\
c Ar = 4-^t\text{BuC}\textsubscript{6}H\textsubscript{4} \\
d Ar = 3,5-Me\textsubscript{2}C\textsubscript{6}H\textsubscript{3}

**Figure 2.** Comparing the yield of *anti*-6 (□) and its enantiomeric excess (●) over time with (red) and without (blue) added norbornene.
Addition into Trisubstituted olefins

• Stereospecific $S_N2'$ addition, no $S_N2$ products detected.
• Also works with disubstituted alkenes (er $>90:10$)

Hoveyda A. H. et. al., J. AM. CHEM. SOC. 2010, 132, 10634–10637
Monoborylation of Dienes

\[
\text{Cu(O-\text{t-Bu}) (5 mol \%) (R,R)-Me-DuPhos (5 mol \%)} \\
\begin{array}{c}
\text{2 (1.5 equiv), } -20 ^\circ \text{C} \\
\text{THF, MeOH (2.0 equiv)}
\end{array}
\]

\[
\text{Cu(I) cat. (5 mol \%)} \\
\text{t-BuOH (2.0 equiv) toluene, rt, 2 h}
\]

\[
\text{Cu(I) cat.: Cu(O-\text{t-Bu})/(R,R)-Me-DuPhos}
\]

\[
\text{Cu(I) cat. (5 mol \%)} \\
\text{MeOH (5.0 equiv) THF, -40 ^\circ \text{C}, 26 h}
\]

\[
\text{83\%, 96\% ee} \\
\text{3k/4k 4:96}
\]

Ito H. et. al., J. AM. CHEM. SOC. 2010, 132,
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Borodesymmetrization

\[
\begin{align*}
1a & \rightarrow \text{Cu(OtBu)-ligand (5.0 mol %) or CuCl-K(OtBu)-ligand (5.0 mol %)} \\
& \text{bis(pinacolato)diboron (2)} \\
& (1.5 \text{ equiv), } -20^\circ \text{C} \\
& \rightarrow [\text{iPrOCO}_2]_2 \text{C} \text{H}_5 \text{B (pin)} \\
& 3a, 3a', 3i
\end{align*}
\]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCHO (1.0 \text{ equiv)} \rightarrow 0^\circ \text{C, 18 h, base H}_2\text{O, RT, 2 h}</td>
<td>81%</td>
<td>97% ee</td>
<td>98:2 dr</td>
</tr>
<tr>
<td></td>
<td>36% yield</td>
<td>84% ee</td>
<td>36% yield, 84% ee</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>95% ee</td>
<td>99:1 dr</td>
</tr>
</tbody>
</table>

Ito et. al., Angew. Chem. Int. Ed. 2010, 49, 5
Stereochemical Course

Ito et. al., Angew. Chem. Int. Ed. 2010, 49, 5
Gevorgyan’s Cyclopropanes

- $R^3$ is H, otherwise rearrangement to furans observed.
- Esters, Alkyl, Aryl groups tolerated. Excellent ee (>87%, >94% yield).
- Further Suzuki coupling possible.

Gevorgyan V. et. al., J. AM. CHEM. SOC. 2003, 125, 71.
Group Problem

Propose a mechanism, and explain the selectivities

Synthesis of bifunctionalized cyclopropanes from allylcarbonate borylation

Synthesis of Cyclopropanes

Ito et. al., J. AM. CHEM. SOC. 2010, 132, 11440–11442

$$\text{Ar} \quad \text{OP(O)(OR)}_2 + (\text{pin})B-B(\text{pin}) \quad 3 \ (1.2 \text{ equiv})$$

$$\begin{align*}
\text{CuCl (5 mol\%)} \\
(R,R)-i\text{-Pr-DuPhos (6 mol\%)}
\end{align*}$$

$$\text{K(O-t-Bu) (1.0 equiv)}$$

$$\text{toluene/THF, rt}$$

$$\begin{align*}
\text{(1R,2R)-4b-p} \\
\text{B(pin)}
\end{align*}$$
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Styrene diborylation

2.5 mol% Pt$_2$(dba)$_3$
6 mol% (R,R)-L8
B$_2$(pin)$_2$ (1.05 equiv)
THF, 60 °C
then H$_2$O$_2$

\[
\begin{array}{ccc}
\text{substrate} & \text{yield (%)} & \text{ee (%)} \\
\hline
n\text{-hexyl} & 83 & 92 \\
\text{Me} & 77 & 94 \\
\text{Ph} & 80 & 94 \\
\text{cyclohexyl} & 87 & 94 \\
\text{Me} & 46 & 90 \\
\text{Me} & 52 & 87 \\
\text{Me} & 86 & 93 \\
\text{TBDPS} & 84 & 86 \\
\text{TBDPS} & 93 & 90^d \\
\text{TBDPS} & 92 & 90 \\
\end{array}
\]

(R,R)-L8: Ar = 3,5-diethylphenyl

Morken J. P. et. al. J. AM. CHEM. SOC. 2009, 131, 13210–13211
Diborylation of Terminal Olefins

- Best ee’s (>93%) when allylic position is a quaternary center
- Highly sensitive to substitution
- 41–82% yields, 48–77% over two steps for terminal olefin no allylic hydrogens
- Can couple with numerous bromides and triflates

Morken J. P. et al., ORGANIC LETTERS 2004, 6, 131-133
Extensions by Morken

- Best results with trans alkenes (>97% ee)
- Poor selectivity observed without steric hindrance at allylic position for terminal alkenes.

Morken J. P. et. al., J. Org. Chem. 2005, 70,
Alkene Diborylation

1,1-disubstituted gives poor ee (25–41%), moderate yield (67–79%)
Good ee (>90%) for trisubstituted, poor yield (8–17%)

Alkene Diborylation

\[ y = 0.9176x + 0.55 \]
\[ R^2 = 0.9993 \]


\[
\begin{align*}
C_6D_5 & + C_6H_5 & \xrightarrow{5\% \text{ (nbd)Rh(acac) \ B_2cat_2}} & D & \xrightarrow{5\% (S)-Quinap \ \text{THF, 23°C}} & C_6D_5 & + C_6H_5
\end{align*}
\]

85% 17-\textit{D}_8
15% 17-\textit{D}_7\textit{H}_1

17-\textit{H}_8
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Diborylation of Dienes

- 70–92% yield, >84% er
- Cyclic, acyclic dienes
- Low yield when α–carbon is a quaternary center
- NR with Z–diene

Morken J. P. et. al. J. AM. CHEM. SOC. 2009, 131,
Allene borylation

\[ \text{R} \equiv \text{B(pin)} \quad \text{B(pin)} \quad \text{B(pin)} \quad \text{B(pin)} \]

1. 6 mol % \((R,R)-2\)
2. 5 mol % Pd\(_2\)(dba)\(_3\)
3. 1.2 equiv B\(_2\)(pin)\(_2\)

22 °C, 10 h

2. \(R^2\text{CHO} (0.6 \text{ equiv})\)

22 °C, 14 h

3. NaOH, H\(_2\)O\(_2\)

Morken J. et. al., J. AM. CHEM. SOC. 2007, 129, 87
Morken J. P. et. al., ORG. LETT. 2005, 7, 5505-550
Allene Borylation

Scheme 6

(MR)-6-Pd(0) + B₂(pin)₂ + (R)-9-d₁

Path B

(R,R)-6-Pd-B

Decyl

(R,R)-Z-10-d₁

Path C

Path D

(R)-11

Morken J. et. al., J. AM. CHEM. SOC. 2007, 129, 87
Allene Borylation One-Pot

- R alkyl, branched, benzyl, aryl 37–62% yield, 91–94% ee
- Can couple with aryl, vinyl halides, pseudohaloalides

Morken J. P. et. al., ORGANIC LETTERS 2006, 8,
Allene borylation – Tandem Reactions

Morken J. P. et. al. J. AM. CHEM. SOC. 2006, 128, 74-75
## Sequential Alkyne Diborylation

Can also control regioselectivity based on NHC catalyst

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 5" /></td>
<td>78</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td>60</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td><img src="image" alt="Structure 7" /></td>
<td>76</td>
<td>97:3</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /></td>
<td>61°</td>
<td>97.5:2.5</td>
</tr>
</tbody>
</table>

Hoveyda A. H. et al. J. AM. CHEM. SOC. 2009, 131,
Silaborations

![Chemical structures and reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal complex&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>Ligand&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>Time [h]</th>
<th>Conversion [%]&lt;sup&gt;[c]&lt;/sup&gt;</th>
<th>ee [%] (product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>(S)-10</td>
<td>48</td>
<td>84</td>
<td>57 (3)</td>
</tr>
<tr>
<td>2</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>(S)-11</td>
<td>48</td>
<td>50</td>
<td>27 (3)</td>
</tr>
<tr>
<td>3</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12</td>
<td>48</td>
<td>52</td>
<td>32 (3)</td>
</tr>
<tr>
<td>4</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>13</td>
<td>48</td>
<td>26</td>
<td>21 (3)</td>
</tr>
<tr>
<td>5</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>14</td>
<td>48</td>
<td>11</td>
<td>13 (3)</td>
</tr>
<tr>
<td>6</td>
<td>Pt(acac)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15</td>
<td>48</td>
<td>92</td>
<td>58 (ent-3)</td>
</tr>
</tbody>
</table>

Conclusions

- Asymmetric Borylation is a highly selective and synthetically useful of installing C–B bonds.
- Products are versatile and can be used in allylations, oxidations, cross-coupling reactions etc.
- Can synthesize tertiary allylic alcohols, and tertiary chiral allylborons.
- Boron is a cheap and non-toxic element.
- Product stability limits the utility of boron chemistry – more stable boron esters will increase use.
- Asymmetric borylation of cis–alkenes continues to be an unsolved problem.