CHIRAL [1,3,2]OXAZABOROLES: PREPARATION AND USE IN ORGANIC SYNTHESIS

(S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO[1,2-C][1,3,2]OXAZABOROLE
CATALYSTS WITH CHIRAL [1,3,2]OXAZABOROLE FRAMEWORK

Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317
Stepanenko, Viatcheslav; Tetrahedron: Asymmetry 2006, V17(1), P112-115
Shan, Zixing; Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry 2005, V35(4), P275-279
1- SUBSTITUTED (S)-TETRAHYDRO-3,3-DIPHENYL-1H,3H-PYRROLO[1,2-C][1,3,2]OXAZABOROLES

Number of References in CAS Database for Each Catalyst

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tr>
<td>S</td>
<td>39</td>
<td>204</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>R</td>
<td>8</td>
<td>142</td>
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PART I: SYNTHESIS
RETROSYNTHETIC ANALYSIS FOR SUBSTITUTED 1-METHYL[1,3,2]OXAZABOROLE 1

\[
\text{(S)-Me-CBS CATALYST}
\]

\[
\text{Boronic Reagent} \quad \text{Ph} \quad \text{Me}
\]

\[
\text{AN} \quad \text{H} \quad \text{Ph}
\]

\[
\text{X=OR, Hal} \quad \text{P=Bn, Tr, Boc, CO}_2\text{R}
\]

\[
\text{R, R}^1 = \text{Alk, Bn, Ar} \quad \text{(NCA) N-CarboxyAnhydride} \quad \text{(S)-L-Proline}
\]

4
SYNTHESIS OF (S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO-[1,2-C][1,3,2]OXAZABOROLE: BORONIC REAGENTS

Chirality, 15(8), 674-679; 2003
Organometallics, 23(10), 2362-2369; 2004
86% Journal of the American Chemical Society, 109(25), 7925-6; 1987

99% Organic Letters, 5(23), 4249-4251; 2003
Journal of Organic Chemistry, 58(10), 2880-8; 1993
SYNTHESIS OF (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE

Tetrahedron, 59(10), 1797-1804; 2003

64% Heteroatom Chemistry, 14(1), 42-45; 2003

Tetrahedron: Asymmetry, 14(1), 95-100; 2003

Tetrahedron, 49(23), 5127-32; 1993

60% Journal of Organic Chemistry, 67(22), 7769-7773; 2002

SYNTHESIS OF (S)-(−)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE, CONTINUATION


Organic Syntheses, 74, 50-71; 1997

Ger., 4416963, 13 Jul 1995
SYNTHESIS OF (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE PRECURSOR#1: NCA

Organic & Biomolecular Chemistry, 1(18), 3238-3243; 2003

Organic Syntheses, 74, 50-71; 1997

Tetrahedron, 50(30), 9051-60; 1994
NUCLEOPHILIC ADDITION TO NCA: BY-PRODUCTS EXPLANATION

Table I. Pro-NCA Addition to Grignard

<table>
<thead>
<tr>
<th>entry</th>
<th>grignard</th>
<th>substrate, M</th>
<th>solvent</th>
<th>temp, °C</th>
<th>time, h</th>
<th>yield, %</th>
<th>ee, %</th>
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<td>78</td>
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<td>THF</td>
<td>45</td>
<td>2</td>
<td>43</td>
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<td>6</td>
<td>PhMgCl</td>
<td>0.2</td>
<td>THF</td>
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<tr>
<td>7</td>
<td>PhMgCl</td>
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<td>THF/tol</td>
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<td>3</td>
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<td>8</td>
<td>PhMgCl</td>
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<td>THF/CH₂Cl₂</td>
<td>−15</td>
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<td>99.2</td>
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<tr>
<td>9</td>
<td>PhMgBr</td>
<td>0.2</td>
<td>THF/Et₂O</td>
<td>−15</td>
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<tr>
<td>10</td>
<td>PhMgCl</td>
<td>0.4</td>
<td>THF</td>
<td>−15</td>
<td>3</td>
<td>78</td>
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<td>3</td>
<td>73</td>
<td>99.2</td>
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</table>

*Enantiomeric excess (ee) determined by capillary GC analysis of the (R)-MPTA amide derivative. *Inverse addition.*
SYNTHESIS OF A CARBOXYETHYL-PROTECTED L-PROLINE DERIVATIVE

84% Journal of Organic Chemistry, 70(3), 898-906; 2005
97% Tetrahedron: Asymmetry, 16(5), 1055-1060; 2005
Helvetica Chimica Acta, 86(1), 91-105; 2003
95% Tetrahedron: Asymmetry, 14(1), 95-100; 2003
95% Synthetic Communications, 25(10), 1523-30; 1995
COMPARISON OF TWO ATTRACTIVE WAYS TO (S)-(-)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE: WHICH ONE IS THE BEST?


1. Organic & Biomolecular Chemistry, 1(18), 3238-3243; 2003
2. Organic Syntheses, 74, 50-71; 1997

1. Organic & Biomolecular Chemistry, 1(18), 3238-3243; 2003
2. Organic Syntheses, 74, 50-71; 1997
If synthesized via methyllithium, the price of 40 g of methylboronic acid would be ca $200
OPTIMIZED SYNTHESIS OF (S)-Me-CBS 1


3. Organometallics, 4(5), 816; 1985
PART II: USE OF CHIRAL CATALYSTS

RECENT DATA, EXAMPLE # 1

Enantioselective borane reduction of acetophenone with spiroborate esters 4–12 as catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>mol %</th>
<th>Yield (%)</th>
<th>ee%</th>
<th>Conf.</th>
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<td>92</td>
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<td>4</td>
<td>10</td>
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<td>R</td>
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<td>5</td>
<td>84</td>
<td>88</td>
<td>R</td>
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<tr>
<td>4</td>
<td>4</td>
<td>2.5</td>
<td>85</td>
<td>75</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>85(\Delta)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>10</td>
<td>87</td>
<td>90</td>
<td>R</td>
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<td>10</td>
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<td>S</td>
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<td>S</td>
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<td>R</td>
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<td>16</td>
<td>12</td>
<td>5</td>
<td>95</td>
<td>98</td>
<td>R</td>
</tr>
</tbody>
</table>

*1 equiv of ketone : 1 equiv of borane at rt, 1 h.
*Purified by Kugelrohr distillation.
*Determined by GC on a chiral column (CP-Chiralsil-DexCB).
\(\Delta\)Crude product.
*Traces of ketone was left after 3 h.

Stepanenko, Viatcheslav; Tetrahedron: Asymmetry 2006, V17(1), P112-115
EXAMPLE # 2

Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317
CARBONYL GROUP REDUCTIONS: YIELDS AND ee.

\[
\begin{align*}
\text{R} & = \text{Me, R'} = \text{Pr, i-Bu, i-Pr, t-Bu} \\
\text{R} & = \text{Ph, R'} = \text{Me, Et} \\
\text{R} & = \text{Me, R'} = 4-\text{Py}
\end{align*}
\]

Table 1. Enantiomer Excess (% ee) of \((R)\)-Secondary Alcohols Obtained from Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by \((R.S)-1, (S.S)-1, (R.S)-2,\) and \((S.S)-2^a\)

<table>
<thead>
<tr>
<th>Ketone Structure</th>
<th>(R,S)-2</th>
<th>(S,S)-2</th>
<th>(R,S)-1</th>
<th>(S,S)-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,S)-2</td>
<td>47</td>
<td>50</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>(S,S)-2</td>
<td>6</td>
<td>14</td>
<td>32</td>
<td>....</td>
</tr>
<tr>
<td>(R,S)-1</td>
<td>53</td>
<td>....</td>
<td>64</td>
<td>....</td>
</tr>
<tr>
<td>(S,S)-1</td>
<td>23</td>
<td>42</td>
<td>64</td>
<td>....</td>
</tr>
</tbody>
</table>

\(^a\) All reductions were performed in a ketone/borane/catalyst molar ratio of 1:0.6:0.1 in THF at 0–5° for 2 h; exception: 20 h for 1-(pyridin-4-yl)ethanone and gave \((R)\)-secondary alcohols in high yield. The ee of \((R)\)-secondary alcohols were obtained by comparison with the maximum of specific rotations (see [6–12], resp.) and analysis of the \(^1\)H-NMR spectra of diastereoisomeric phosphite esters formed with the phosphorochloridite of \((4R,5R)\)-trans-2,2-dimethyl-\(\alpha,\alpha,\alpha',\alpha'\)-tetraphenyl-1,3-dioxolane-4,5-dimethanol as a chiral derivatizing agent [3][13].

Liu, Dejun; Helvetica Chimica Acta 2004, V87(9), P2310-2317
MECHANISM OF CHIRAL CATALYST ACTION PROPOSED

A

\[ \begin{align*}
\text{H}_2 & \quad \text{H}_2\text{B THF} \\
\text{R'} & \quad \text{O BH}_3 \\
\text{R} & \quad \text{O BH}_2
\end{align*} \]

B

C

D

E
EXAMPLE#3:
THE USE OF (R)-Me-CBS CATALYST IN PANAXYTRIOL SYNTHESIS

Scheme 1. Antitumor components of Panax ginseng, panaxytriol (1)

Scheme 2. Enantioselective Synthesis of Left-Hand Piece Using CBS Reduction Reaction conditions: (a) (R)-Me-CBS, BMS, -30 C, 10 min, 75%, >99% ee; (b) NBS, cat. AgNO₃, acetone, rt, 1 h, 100%.

Scheme 3. A proposed model for the CBS reduction of 2.

Straightforward Synthesis of Panaxytriol: An Active Component of Red Ginseng
Yun, H.; Danishefsky, S. J. Org. Chem.; (Note); 2003; 68(11); 4519-4522.
**EXAMPLE#4: COMPARISON OF MISC CHIRAL CATALYSTS**


<table>
<thead>
<tr>
<th>entry</th>
<th>reagent and/or catalyst</th>
<th>alcohol</th>
<th>t</th>
<th>yield</th>
<th>ee</th>
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</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BH$_3$:SMe$_2$ / (S)-6</td>
<td>(S)-5</td>
<td>&lt;15 min</td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BH$_3$:SMe$_2$ / (S)-7</td>
<td>(S)-5</td>
<td>&lt;15 min</td>
<td>83%</td>
<td>95%</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BH$_3$:SMe$_2$ / (4S,5R)-8</td>
<td>(S)-5</td>
<td>&lt;15 min</td>
<td>80%</td>
<td>70%</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(−)-9</td>
<td>(R)-5</td>
<td>overnight</td>
<td>93%</td>
<td>92%</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(−)-10</td>
<td>(R)-5</td>
<td>overnight</td>
<td>47%</td>
<td>39%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were carried out by addition of 4 (1 mmol) to a mixture of BH$_3$:SMe$_2$ (1.2 mmol) and catalyst (1 mmol) in THF. <sup>b</sup>Reduction was performed with 2.5 mmol of 4 in neat 9 (10 mmol) according to ref. 10. <sup>c</sup>Reduction was performed with 1.3 mmol of 4 in neat 10 (15 mmol) according to ref. 11. *Isolated yield after chromatography. *Determined by $^{19}$F NMR analysis of the corresponding Mosher esters.
(S)-Me-CBS CATALYST IN THE SYNTHESIS OF PHOMACTINS

Selectivity: 98:2 = Sin:Anti, 75% Yield