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Sean M Smith  
*University of Nebraska-Lincoln*

Gia L. Hoang  
*University of Nebraska-Lincoln*, ghoang2@huskers.unl.edu

Rhitankar Pal  
*University of Nebraska-Lincoln*

Mohammad O. Bani Khaled  
*University of Nebraska-Lincoln*

Liberty S. W. Pelter  
*Purdue University Calumet*

*See next page for additional authors*

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γ-Selective directed catalytic asymmetric hydroboration of 1,1-disubstituted alkenes†

Sean M. Smith,a Gia L. Hoang,a Rhitankar Pal,a Mohammad O. Bani Khaled,a Liberty S. W. Pelter,b Xiao Cheng Zenga and James M. Takacsaa

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Directed catalytic asymmetric hydroboration of 1,1-disubstituted alkenes afford γ-dioxaborato amides and esters in high enantiomeric purity (90–95% ee).

Chiral organoboronates are useful synthetic intermediates for a growing number of stereospecific transformations.1 As such, there is renewed interest in enantioselective methods for their preparation.2–7 We reported advances in the carbonyl-directed catalytic asymmetric hydroboration (CAHB) of (E)- and (Z)-disubstituted and trisubstituted alkenes contained within a β,γ-unsaturated amide framework.8,9 Their rhodium-catalysed reactions employ simple chiral monophosphite ligands to produce β-borylated products regio- and enantioselectively. For example, directed-CAHB of 1 by pinacolborane (pinBH) or 4,4,6-trimethyl-1,3,2-dioxaborinane (tmdBH, 5)10 using Rh(nbd)2BF4 in conjunction with TADDOL-derived phosphite (R,R)-6 gives β-dioxaborato amide (S)-2 in high enantiomeric purity (tmdBH: 79% (96% ee); pinBH: 77% (95% ee), Fig. 1). Only trace amounts of the regioisomeric γ-substituted product are formed (<3%).

As highlighted in several recent reports,13 1,1-disubstituted alkenes (i.e., methyldiene substrates) are particularly challenging substrates for asymmetric hydroboration.14 Directed-CAHB of the methyldiene substrate, β,γ-unsaturated amide 3, affords predominantly (R)-4 (tmdBH: 72% (95% ee); pinBH: 68% (60% ee); Fig. 1). In contrast to unsaturated amide 1, the isomeric substrate 3 affords the γ-borylated, rather than β-borylated, product predominantly. Equally unexpected, using the same chiral ligand and catalyst, tmdBH adds to opposite faces of the alkene in the isomeric substrates.

The results obtained for a series of methyldiene substrates are summarized in Table 1. Amides 7a–e bearing a primary or secondary alkyl substituent and the phenyl-substituted amide 7f give their respective γ-borylated product predominantly (i.e., 8a–f, 90–94% ee). Our previous reports of carbonyl-directed CAHB used amide directing groups exclusively (i.e., –C(O)N(H)Ph and –C(O)N(Me)OMe). Here, we find that the β,γ-unsaturated tert-butyl esters serve equally well; 7g–i afford γ-borylated esters 8g–i (91–94% ee). Competing alkene reduction and formation of the β-borylated regioisomer 9

![Fig. 1](https://example.com/fig1.png)

**Table 1** Enantioselective CAHB of 1,1-disubstituted alkenes 7a–7i

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>γ-Isomer</th>
<th>% Yield (% ee)</th>
<th>% Yield 9&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>NHPh</td>
<td>Me</td>
<td>(S)-8a</td>
<td>53 (94)</td>
</tr>
<tr>
<td>b</td>
<td>NHPh</td>
<td>Et</td>
<td>(R)-8b</td>
<td>60 (92)</td>
</tr>
<tr>
<td>c'</td>
<td>NHPh</td>
<td>(CH2)2Ph</td>
<td>(R)-8c</td>
<td>73 (94)</td>
</tr>
<tr>
<td>d'</td>
<td>NHPh</td>
<td>(CH2)3Ph</td>
<td>(R)-8d</td>
<td>70 (92)</td>
</tr>
<tr>
<td>e'</td>
<td>NHPh</td>
<td>c-C6H11</td>
<td>(S)-8e</td>
<td>72 (90)</td>
</tr>
<tr>
<td>f'</td>
<td>NHPh</td>
<td>C6H5</td>
<td>(S)-8f</td>
<td>71 (93)</td>
</tr>
<tr>
<td>g</td>
<td>O-Bu</td>
<td>Me</td>
<td>(S)-8g</td>
<td>62 (94)</td>
</tr>
<tr>
<td>h</td>
<td>O-Bu</td>
<td>Et</td>
<td>(R)-8h</td>
<td>65 (91)</td>
</tr>
<tr>
<td>i</td>
<td>O-Bu</td>
<td>i-Bu</td>
<td>(R)-8i</td>
<td>78 (91)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield and (% ee) of 8; enantiomeric purity determined by chiral HPLC analysis after oxidation and for 7g–i subsequent amidation. <sup>b</sup> Isolated yield of β-isomer 9. <sup>c</sup> Reaction run at 40 °C.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc36199j
account for the remainder of products formed; regiocontrol is most problematic for amide substrates bearing relatively small substituents (i.e., 7a–b, R = Me or Et).

Trifluoroborate salts are excellent reagents for Suzuki–Miyaura cross-coupling reactions.** The relative energies of a series of octahedral intermediates formed upon two-point binding of amide substrates followed by oxidative addition of borane were evaluated by DFT (Fig. 3, 23A–C and 24B-D).

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**Fig. 2 Preparation of chiral γ-hydroxy amides and esters and β-substituted γ-lactones via CAHB-oxidation.

**Fig. 3 Relative energy structure for the model methylidene substrate is consistent...
Notes and references


11 See also: M. Rubina, M. Rubin and V. Gevorgyan, J. Am. Chem. Soc., 2003, 125, 7198.

12 The chirality of tmdBH was shown to be inconsequential, see ref. 10.


21 Computational studies were performed using density functional theory (DFT) implemented in the ab initio package Gaussian09. B3LYP functional along with 6-31+G(d,p) (all non-metal atoms) and LANL2DZ (Rh) basis sets was employed. Frequency calculations were performed at the same level of theory for each of the optimized structures to check for the absence of any imaginary frequencies. See ESIF for more details.