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COMMUNICATION

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

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Directed catalytic asymmetric hydroborations 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.^{2–9} 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.^{10,11} 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**)¹² 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.*, methylenide substrates) are particularly challenging substrates for asymmetric hydroboration.¹⁴ Directed-CAHB of the methylenide 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 methylenide 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

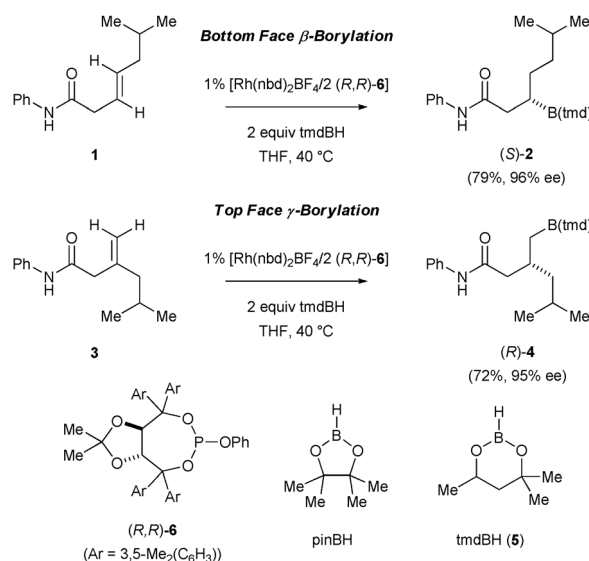


Fig. 1 Regio- and enantioselective carbonyl-directed CAHB of 1,2- and 1,1-disubstituted alkenes (ee determined after oxidation).

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

7	X	R	γ -Isomer	% Yield (% ee) ^a	% Yield ^{9b}
a	NHPh	Me	(<i>S</i>)- 8a	53 (94)	11
b	NHPh	Et	(<i>R</i>)- 8b	60 (92)	10
c	NHPh	(CH ₂) ₂ Ph	(<i>R</i>)- 8c	73 (94)	3
d	NHPh	(CH ₂) ₃ Ph	(<i>R</i>)- 8d	70 (92)	3
e	NHPh	<i>c</i> -C ₆ H ₁₁	(<i>S</i>)- 8e	72 (90)	2
f	NHPh	C ₆ H ₅	(<i>S</i>)- 8f	71 (93)	4
g	O- <i>t</i> Bu	Me	(<i>S</i>)- 8g	62 (94)	6
h	O- <i>t</i> Bu	Et	(<i>R</i>)- 8h	65 (91)	5
i	O- <i>t</i> Bu	<i>i</i> -Bu	(<i>R</i>)- 8i	78 (91)	4

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

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**

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Table 2 Efficient cross-coupling of γ -borylated esters and amides

Entry	Trifluoroborate ^a	Aryl halide	% Yield
1	(<i>S</i>)- 10a	Chlorobenzene	81
2 ^b	(<i>S</i>)- 10a	3-Bromoanisole	71
3	(<i>S</i>)- 10a	Methyl-4-bromobenzoate	70
4	(<i>S</i>)- 10g	Chlorobenzene	82
5	(<i>S</i>)- 10g	3-Bromoanisole	82
6	(<i>S</i>)- 10g	Methyl-4-bromobenzoate	88
7	(<i>R</i>)- 10i	Chlorobenzene	80
8	(<i>R</i>)- 10i	3-Bromoanisole	92
9	(<i>R</i>)- 10i	Methyl-4-bromobenzoate	94
10	(<i>R</i>)- 10i	3-Chlorothiophene	98
11	(<i>R</i>)- 10i	5-Chloro-2-furaldehyde	84
12	(<i>R</i>)- 10i	5-Chloro-2-fluoropyridine	51
13	(<i>R</i>)- 10h	3-Chlorothiophene	80

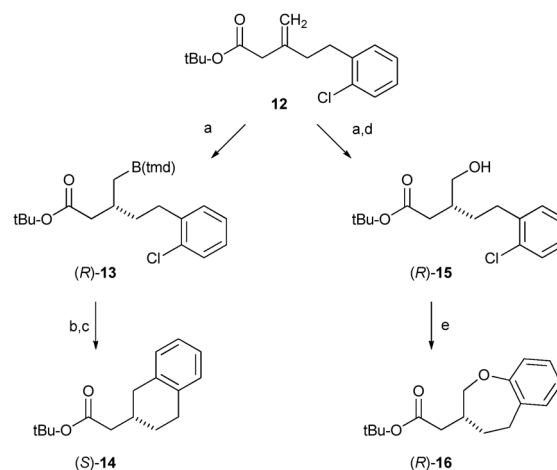
^a Enantiomeric purity of **8** is given in Table 1. ^b Reaction was run with SPhos in place of RuPhos.

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.¹⁵ Using Molander's conditions,⁸ the γ -borylated amide (*S*)-**8a** is cleanly converted to γ -trifluoroborate amide (*S*)-**10a** (65%). The latter readily undergoes palladium-catalyzed cross-coupling with several representative aryl halides (70–81%, Table 2 entries 1–3) complementing the cross-couplings of β -borylated carbonyl derivatives.¹⁶ The *tert*-butyl ester derivatives (*S*)-**10g** and (*R*)-**10i** react similarly (80–94%, entries 4–9). Heteroaromatic cross-couplings are also promising (entries 10–12). For example, trifluoroborate (*R*)-**10h** couples to 3-chlorothiophene (80%, entry 13) giving the precursor to a chiral antispasmodic compound previously reported only as the racemate.¹⁷

Directed CAHB can also be used to set the stage for intramolecular cross-couplings. CAHB of *tert*-butyl ester **12** produces (*R*)-**13** (74%, 90% ee, Scheme 1). Subsequent conversion to the corresponding trifluoroborate (76%) followed by palladium-catalyzed intramolecular cross-coupling affords (*S*)-**14** in excellent yield (91%). Alternatively, hydroboration followed by mild oxidation with NaBO₃ produces γ -hydroxyester (*R*)-**15** (73%, 90% ee). The latter undergoes palladium-catalyzed C–O cross-coupling¹⁸ to afford the novel seven-membered ring ether (*R*)-**16** (75%).

Directed CAHB of amides **3** and **7c** using (*R,R*)-**6** followed by oxidative work-up with basic H₂O₂ gives the respective γ -hydroxyamides (*R*)-**17** and (*R*)-**18** (71% yield for each, 95 and 94% ee, respectively) (Fig. 2). Similarly, CAHB of *tert*-butyl ester **7i** followed by mild oxidation with NaBO₃ affords the labile γ -hydroxyester (*R*)-**19** (77%, 91% ee). However, under basic H₂O₂ work-up conditions, the intermediate γ -hydroxyester spontaneously lactonizes to afford a chiral β -substituted γ -lactone. For example, CAHB of *tert*-butyl ester **7i** using ligand (*S,S*)-**6** affords lactone (*S*)-**20** (78%, 91% ee); the latter has been used as a precursor to the anticonvulsant drug



Scheme 1 (a) 2% Rh(nbd)₂BF₄, 4.1% (*R,R*)-**6**, 2 equiv. tmdBH, THF, 40 °C (74%, 90% ee). (b) KHF₂, MeCN/H₂O (76%). (c) 5% Pd(OAc)₂, 10% RuPhos, K₂CO₃, PhMe/H₂O, 85 °C, 24 h (91%). (d) NaBO₃, THF/H₂O (98%). (e) 5% Pd(OAc)₂, 10% RuPhos, K₃PO₄, PhMe, 85 °C, 24 h (75%).

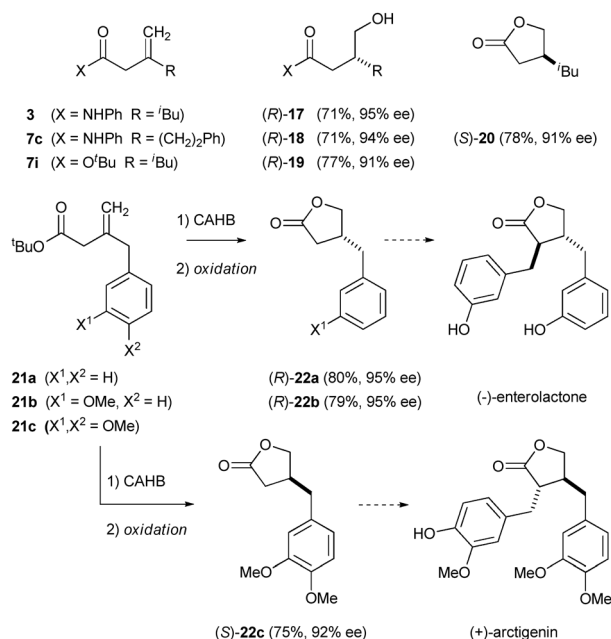


Fig. 2 Preparation of chiral γ -hydroxy amides and esters and β -substituted γ -lactones *via* CAHB-oxidation.

pregabalin.¹⁹ Similarly, *tert*-butyl ester **21a** gives (*R*)-**22a** (80%, 95% ee) and **21b** gives (*R*)-**22b** (79%, 95% ee) using the catalyst with (*R,R*)-**6**. With the enantiomeric ligand (*i.e.*, (*S,S*)-**6**), CAHB-oxidation of **21c** affords (*S*)-**22c** (75%, 92% ee). β -Substituted butyrolactones undergo diastereoselective alkylation and have been used in syntheses of the lignan natural products (–)-enterolactone and (+)-arctigenin.²⁰

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**).²¹ The modelled structures employ the symmetric borane pinBH and the caged phosphite P(OCH₂)₃CH to simplify the calculations. In line with experiment, the overall lowest energy structure for the model methylene substrate is consistent

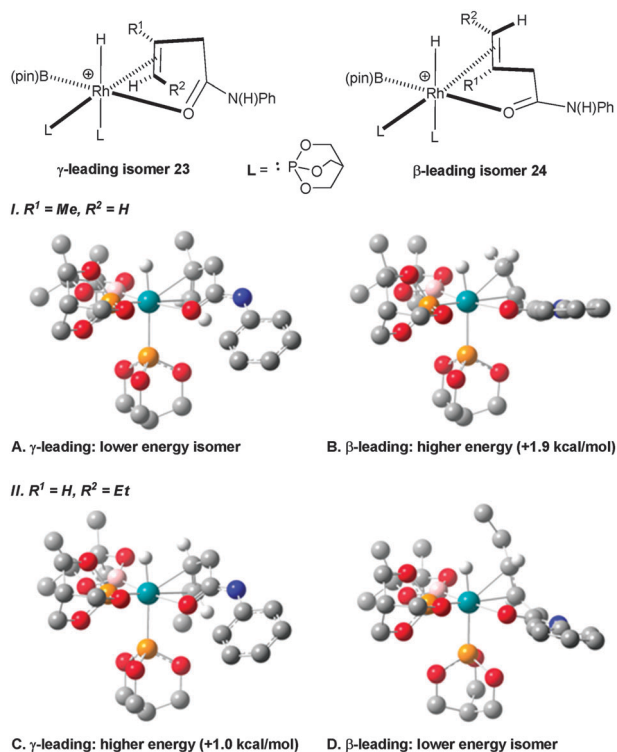


Fig. 3 Relative energies of model octahedral intermediates leading to γ - and β -borylation for 1,1- and (*E*) 1,2-disubstituted substrates (A/B and C/D, respectively); only the vinyl C–H and Rh–H included for clarity.

with favored formation of the γ -borylated product upon alkene insertion into the Rh–H bond (*i.e.*, **A**); the lowest energy structure leading to β -borylation (*i.e.*, **B**) is calculated to be about 1.9 kcal higher in energy and arises from complexation to the opposite face of the π -system. Structures **C** and **D** model a simple 1,2-disubstituted alkene with the (*E*)-geometry (*i.e.*, a model for amide **1**). Consistent with the experimental observations, the β -leading isomer **D** is favored for this substitution pattern.

In contrast to tri- and other disubstitution patterns, CAHBs of β,γ -unsaturated methylenedioxy amides and esters afford the γ -borylated product and proceed in the opposite sense of asymmetric induction. Chiral γ -borylated derivatives are intermediates for inter- and intramolecular cross-couplings, the formation of chiral γ -hydroxy carbonyl derivatives, and β -substituted- γ -lactones. Preliminary computational studies suggest that the preferred conformation of the chelated substrate relative to the Rh–H bond may explain the observed regio- and π -facial selectivity. Further studies are in progress.

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