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

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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 $Rh(nbd)_2BF_4$ 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.*, methylidene substrates) are particularly challenging substrates for asymmetric hydroboration.[14] Directed-CAHB of the methylidene 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 methylidene 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

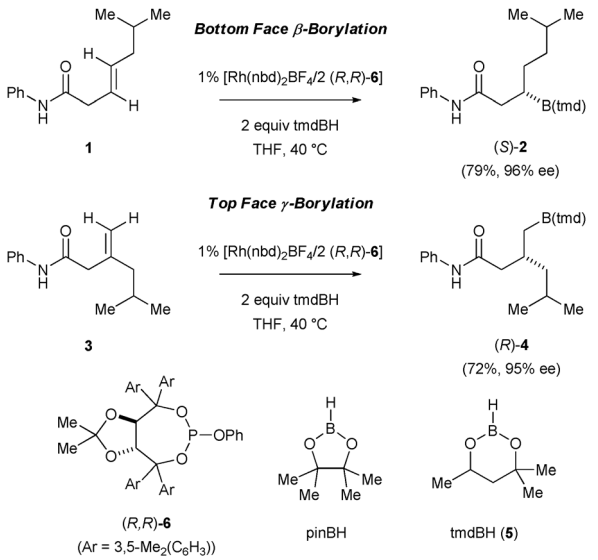
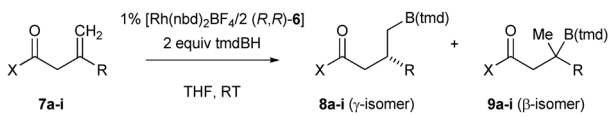


Fig. 1 Regio- and enantioselective carbonyl-directed CAHB of 1,2- and 1,1-disubstituted alkenes (ee determined after oxidation).

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



7	X	R	γ-Isomer	% Yield (% ee)[a]	% Yield **9**[b]
a	NHPh	Me	(*S*)-**8a**	53 (94)	11
b	NHPh	Et	(*R*)-**8b**	60 (92)	10
c[c]	NHPh	$(CH_2)_2Ph$	(*R*)-**8c**	73 (94)	3
d[c]	NHPh	$(CH_2)_3Ph$	(*R*)-**8d**	70 (92)	3
e[c]	NHPh	*c*-C_6H_{11}	(*S*)-**8e**	72 (90)	2
f[c]	NHPh	C_6H_5	(*S*)-**8f**	71 (93)	4
g	O-*t*Bu	Me	(*S*)-**8g**	62 (94)	6
h	O-*t*Bu	Et	(*R*)-**8h**	65 (91)	5
i	O-*t*Bu	*i*-Bu	(*R*)-**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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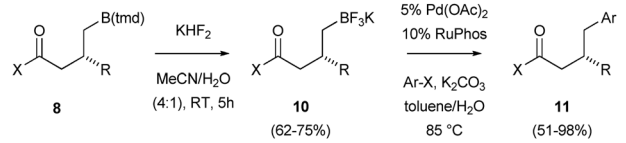
Table 2 Efficient cross-coupling of γ-borylated esters and amides



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

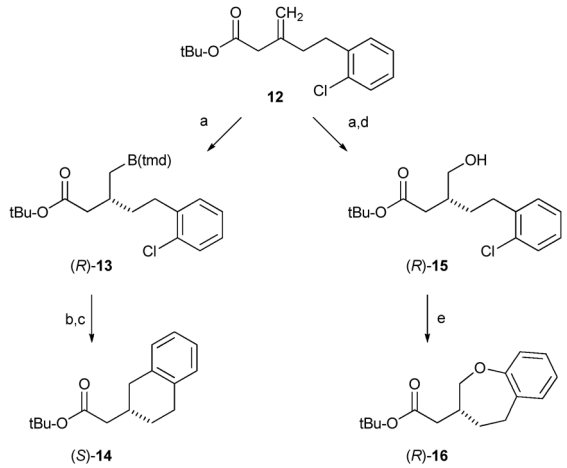
[a] Enantiomeric purity of **8** is given in Table 1. [b] Reaction was run with SPhos in place of RuPhos.

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-trifluoroborato 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 $NaBO_3$ produces γ-hydroxyester (*R*)-**15** (73%, 90% ee). The latter undergoes palladium-catalyzed C–O cross-coupling[18] 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 H_2O_2 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 $NaBO_3$ affords the labile γ-hydroxyester (*R*)-**19** (77%, 91% ee). However, under basic H_2O_2 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% $Rh(nbd)_2BF_4$, 4.1% (*R*,*R*)-**6**, 2 equiv. tmdBH, THF, 40 °C (74%, 90% ee). (b) KHF_2, $MeCN/H_2O$ (76%). (c) 5% $Pd(OAc)_2$, 10% RuPhos, K_2CO_3, $PhMe/H_2O$, 85 °C, 24 h (91%). (d) $NaBO_3$, THF/H_2O (98%). (e) 5% $Pd(OAc)_2$, 10% RuPhos, K_3PO_4, PhMe, 85 °C, 24 h (75%).

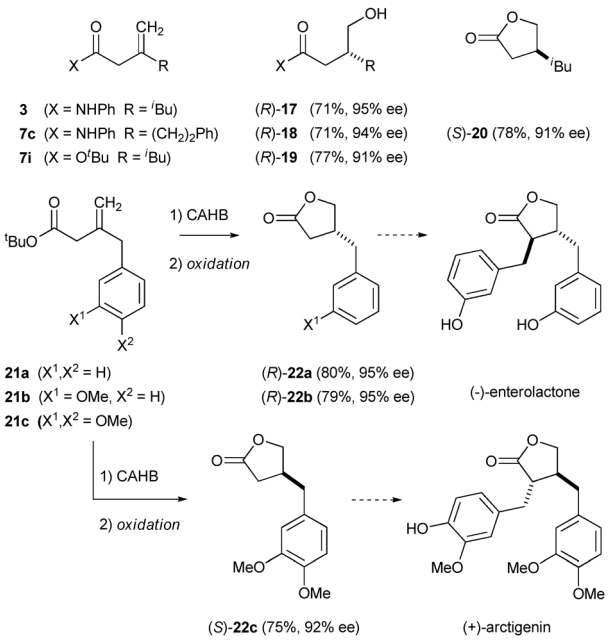


Fig. 2 Preparation of chiral γ-hydroxy amides and esters and β-substituted γ-lactones *via* CAHB-oxidation.

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 $P(OCH_2)_3CH$ to simplify the calculations. In line with experiment, the overall lowest energy structure for the model methylidene substrate is consistent

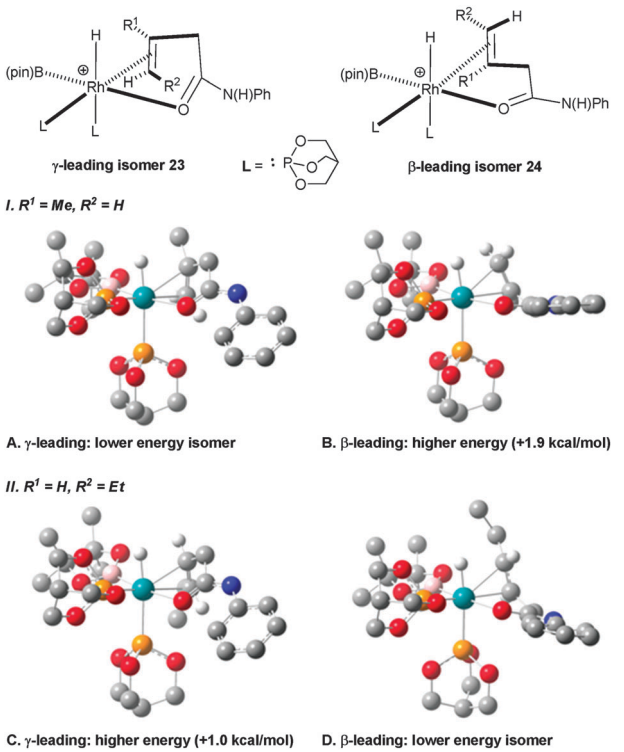


Fig. 3 Relative energies of model octahedral intermediates leading to γ- and β-borylation for 1,1- and (*E*) 1,2-disubstituted substrates (**A**/**B** and **C**/**D**, respectively; only the vinyl C–H and Rh–H included for clarity.

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 methylidene 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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