Allylboration

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Highly Selective Allylborations of Aldehydes Using α,α-Disubstituted Allylic Pinacol Boronic Esters**

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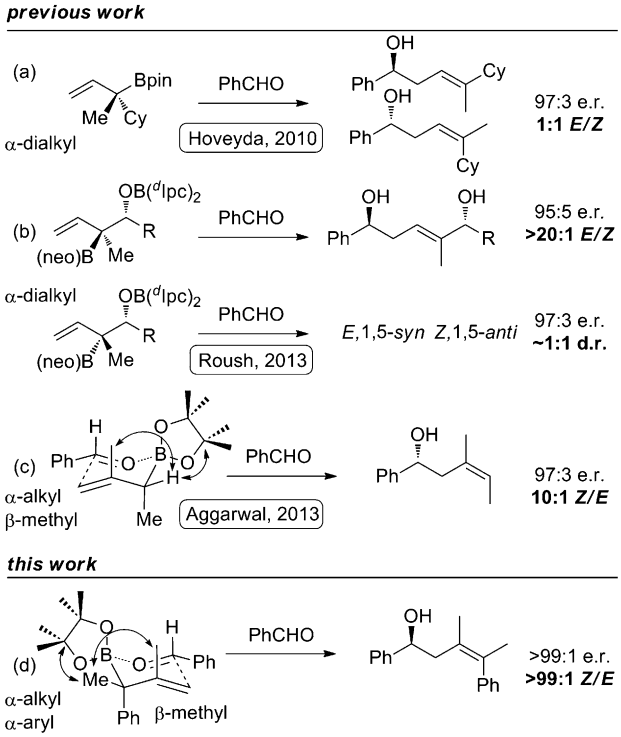
Abstract: *α,α-Disubstituted allylic pinacol boronic esters undergo highly selective allylborations of aldehydes to give tetrasubstituted homoallylic alcohols with exceptional levels of anti-Z-selectivity (>20:1). The scope of the reaction includes both acyclic and cyclic allylic boronic esters which lead to acyclic and exocyclic tetrasubstituted homoallylic alcohols. The use of β-borylated allylic boronic esters gave fully substituted alkenes bearing a boronic ester which underwent further cross-coupling enabling a highly modular and stereoselective approach to the synthesis of diaryl tetrasubstituted alkenes. Computational analysis revealed the origin of the remarkable selectivity observed.*

The asymmetric allylboration of aldehydes is one of the most reliable C–C bond forming reactions in synthesis,[1,2] simultaneously controlling both double bond geometry and *syn*/*anti* stereochemistry[3] of the product, as a consequence of the closed, chair-like transition state (TS) involved.[4] Whilst such reactions have been extensively applied to the synthesis of homoallylic alcohols bearing mono-, di- and trisubstituted[5] alkenes, there are essentially no examples of its application to the synthesis of homoallylic alcohols bearing tetrasubstituted alkenes.[6] Indeed, of all the olefin classes, the stereocontrolled synthesis of tetrasubstituted alkenes is the most challenging.[7,8]

In designing a method to control stereochemistry in allylborations, the critical issue is to control which substituent occupies the axial/equatorial position in the chair TS. Examples from the literature highlighted the challenge we faced: reaction of an α,α-disubstituted allylic boronic ester bearing two very different substituents (Cy/Me) gave a 1:1 *E*/*Z* mixture of homoallylic alcohols albeit in high yield and high enantiomeric ratio (e.r.) (Scheme 1a).[9] Similar results were observed by Roush but subtle effects were clearly in operation since one diastereoisomer gave a 1:1 ratio of *E*/*Z* isomers but the other diastereoisomer gave the *E* isomer exclusively (Scheme 1b).[2a]



Scheme 1. Allylboration of α-substituted allylic pinacol boronic esters. pin = pinacol ester, neo = neopentyl ester, ^{d}Ipc = diisopinocampheyl.

Our own work on allylboration had shown that allylic pinacol boronic esters bearing a β-methyl group led to moderate *Z* selectivity for the trisubstituted alkene, presumably because the large pinacol group and the β-Me group only left a small pocket in which to accommodate the equatorial substituent (Scheme 1c).[10] We were keen to evaluate how the combination of a β-Me group and an α,α-disubstituted allylic boronic ester would fare when tested in the formation of homoallylic alcohols bearing tetrasubstituted alkenes. Here we show that such combinations lead to extraordinarily high levels of *Z*-selectivity for these most challenging of substrates (Scheme 1d).

We started our investigations by the preparation of α-methyl, α-phenyl allylic boronic ester **1a** using our lithiation–borylation methodology[11] between benzylic carbamate **2a** and propenyl pinacol boronic ester. Reaction of **1a** with

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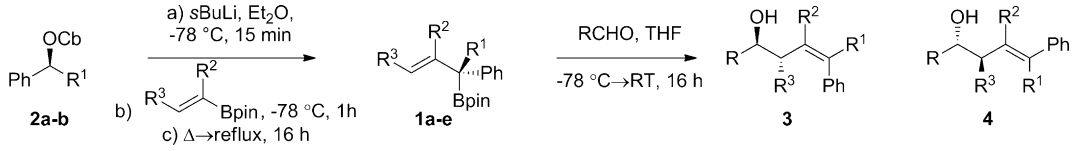
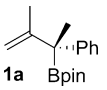
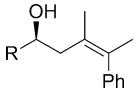
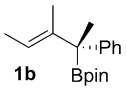
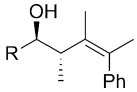
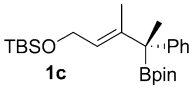
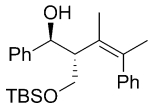
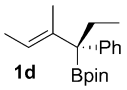
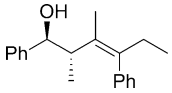
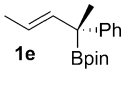
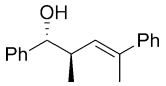
Table 1: Lithiation–borylation–allylboration of secondary benzylic carbamates.



Entry	R^1	R^2	R^3	Yield [%][a]	**1a–e**	R		Yield [%][a]	d.r. (**3:4**)[b]	e.r.[b]
1	Me	Me	H	85		Ph **3aa**		99	>99:1	>99:1
2	–	–	–	–		Cy **3ab**		99	>99:1	>99:1
3	–	–	–	–	**1a**	Me **3ac**		98	>99:1	>99:1
4	Me	Me	Me	87 (85)[c]		Ph **3ba**		99 (99)[c]	>99:1	>99:1
5	–	–	–	–		Cy **3bb**		99	>99:1	99:1
6	–	–	–	–	**1b**	Me **3bc**		98	99:1	>99:1
7	Me	Me	OTBS	84		Ph **3c**		91	>99:1	>99:1
8	Et	Me	Me	90		Ph **3d**		99	98:2	99:1
9	Me	H	Me	90		Ph **3e**		98	14:86	>99:1

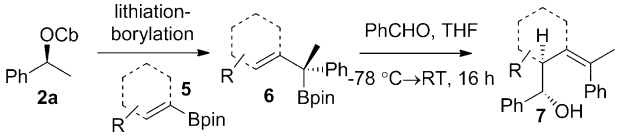
[a] Yield of isolated products. [b] Determined by chiral supercritical fluid chromatography (SFC) of the crude reaction mixture. CbO = *N*,*N*-diisopropyl carbamate. [c] Reaction conducted on 4 mmol scale.

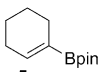
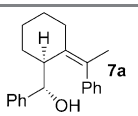
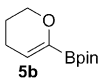
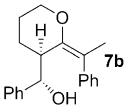
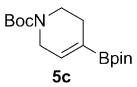
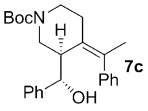
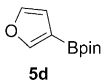
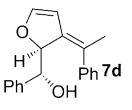
benzaldehyde at low temperature gave the product homoallylic alcohol **3aa** in essentially quantitative yield, with surprisingly high selectivity (>99:1 d.r. and >99:1 e.r.; Table 1, entry 1). By using nuclear Overhauser effect (nOe) correlations, we determined that the product was the *Z*-isomer. We were intrigued by the remarkable selectivity observed and turned to investigating its scope and limitations. Thus, a variety of substituted vinylic pinacol boronic esters were submitted to the lithiation–borylation reaction with different carbamates thereby providing a range of α,α-disubstituted allylic boronic esters **1a–e**, which were tested with a range of aldehydes (Table 1).

In all cases, the same high selectivity was observed provided the allylic boronic esters contained a β-substituent. Thus, if R^3 was H, Me, or CH_2OTBS[12] high selectivity was always observed (Table 1, entries 1–7). The reaction in entry 4 was conducted on gram scale with similar yields and identical selectivities. Replacing the small Me group at R^1 for a larger Et group again led to the same high selectivity (entry 8). Aliphatic aldehydes, including acetaldehyde, worked just as well as aromatic aldehydes (entries 2, 3 and 5, 6). However, boronate **1e**, which lacked a β-alkyl substituent, gave an 86:14 mixture of diastereoisomers (albeit with excellent e.r. for both isomers) but now in favor of the *E*-isomer **4e** (entry 9).

The synthesis of tetrasubstituted exocyclic alkenes[13] can be even more challenging than acyclic ones and we were therefore keen to determine whether this methodology could be applied here too. Thus, using an array of commercially available cycloalkenyl boronic esters,[14] **5a–d**, the requisite allylic boronates **6** were synthesized in high yield and high enantioselectivity using our lithiation–borylation methodology once again (Table 2). Treatment with benzaldehyde furnished the homoallylic alcohols **7** with essentially perfect diastereoselectivity and enantioselectivity as before (entries 1–3). We were pleased to observe that this method-

Table 2: Allylboration of endocyclic allylic boronic esters.

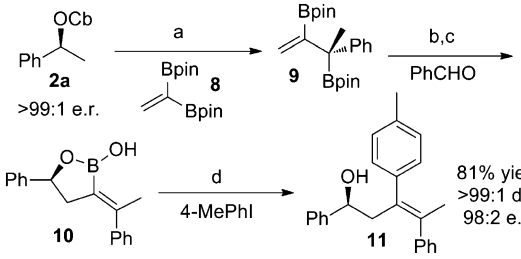


Entry	**5**	Li/B yield [%][a]	Allylboration product **7**	
1	 **5a**	88	 **7a**	99%[a] >99:1 d.r.[b] 99:1 e.r.[b]
2	 **5b**	80	 **7b**	99%[a] >99:1 d.r.[b] 99:1 e.r.[b]
3	 **5c**	88	 **7c**	99%[a] >99:1 d.r.[b] 99:1 e.r.[b]
4	 **5d**	82	 **7d**	81%[a] 95:5 d.r.[b] 99:1 e.r.[b]

[a] Yield of isolated products. [b] Determined by chiral SFC analysis of the crude reaction mixture.

ology was even capable of effecting dearomatization of a furan ring, again with similarly high selectivity (entry 4).[6b]

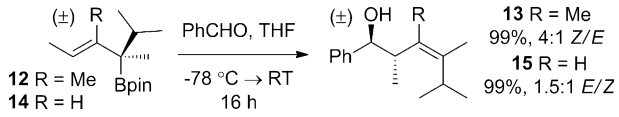
The synthetic utility of the methodology would be further enhanced if variation at the R^2 position was possible. One of the most useful groups is a boronic acid as this would be potentially capable of undergoing Suzuki–Miyaura cross-coupling. We therefore prepared bisboronate **8**[15] and employed it in the lithiation–borylation reaction, furnishing the 1,2-bisborylated product **9** (Scheme 2). Subsequent reaction with PhCHO followed by basic work-up gave the boracyclic hemiester **10** in 95% yield and perfect selectivity. This reaction initially gave a mixture of the pinacol boronic ester and the hemiester[16] but addition of NaOH in the work-up fully converted the mixture into the hemiester. Suzuki–Miyaura cross-coupling[17] with tolyl iodide gave the tetrasubstituted alkene **11** in >99:1 d.r. and 98:2 e.r. Clearly, this chemistry is quite modular as variation in carbamate, aldehyde and aryl halide should allow access to a wide range of tetrasubstituted alkenes.



Scheme 2. Access to diaryl-substituted homoallylic alcohols through Suzuki coupling of boracycle **10**. a) sBuLi, Et_2O, −78 °C, 15 min, then **8**, 1 h, followed by $MgBr_2$/MeOH, Δ, 16 h. 79% yield. b) PhCHO, THF, −78 °C→RT, 16 h. c) NaOH, RT, 1 h, 95% yield. d) [Pd{P(*t*Bu$_3$)}$_2$] (5 mol%), dioxane/H_2O (10:1), 4-MePhI, K_2CO_3, 80 °C, 16 h, 81% yield.

In order to investigate whether the high selectivity observed in the allylboration reaction was a consequence of having an α-phenyl substituent, α,α-dialkyl substituted substrate **12**, bearing two sterically very different substituents, was tested. It was prepared using our lithiation–borylation methodology of secondary allylic carbamates[18] with *i*PrBpin. Treatment of **12** with benzaldehyde in THF at −78 °C led to homoallylic alcohol **13** in excellent yield, but with only 4:1 *Z*-selectivity. Interestingly, reaction of the desmethyl analogue, **14**, led to a 1.4:1 *E*-selectivity in **15**, showing the impact of the β-methyl substituent on stereocontrol (Scheme 3).

DFT calculations for the model systems **Ia** and **Ib**, analogous to **1a** and **1e**, by using the dispersion-corrected B3LYP-D3 functional provided insight into the origin of the unusually high selectivity observed (Figure 1). The calculated free energy of activation at −78 °C lies between 16 and 18 kcal mol^{-1}, consistent with a process taking place in hours between −78 °C and room temperature. In the case of β-methyl substituted allylic boronic ester **Ia**, the transition state in which the phenyl occupies the equatorial position (**TS-Ia*Si***) lies 2.3 kcal mol^{-1} higher in free energy than the corresponding axial TS (**TS-Ia*Re***), in agreement with a very high *Z*-selectivity.



Scheme 3. Allylborations of α-dialkyl allylic boronic esters.

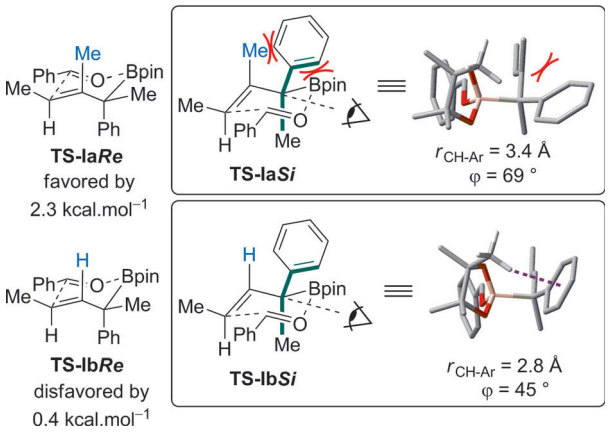
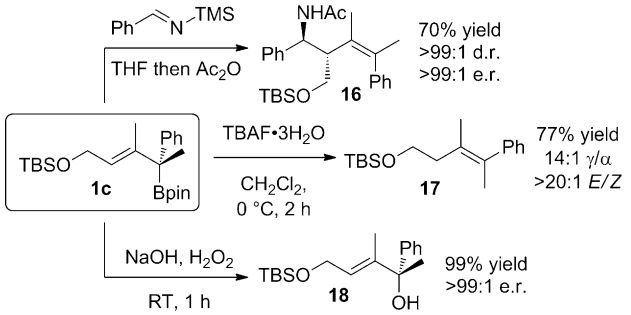


Figure 1. Calculated allylboration transition states.

Inspection of the two TS structures suggests a key role for steric interactions, associated with the short B–O (1.5–1.6 Å) and B–C (1.7–1.8 Å) bonds. The substituent in the more hindered pseudoequatorial position (Ph in **TS-Ia*Si*** vs. Me in **TS-Ia*Re***, see Figure 1) is found to lie close to both a pinacol methyl and the β-substituent. NBO steric analysis confirms this,[19] with the sum of pairwise steric exchange energies between electron pairs lying within the allylic moiety being smaller by 3 kcal mol^{-1} for **TS-Ia*Re*** compared to **TS-Ia*Si***. In the case of β-unsubstituted allylic boronic ester **Ib**, the TS in which the phenyl occupies the equatorial position (**TS-Ib*Si***) is found to be slightly lower in free energy than the corresponding axial TS ($\Delta\Delta G^{\ddagger} = 0.4$ kcal mol^{-1}), in agreement with a moderate *E*-selectivity.

Inspection of **TS-Ib*Si*** revealed that the equatorial phenyl group is able to adopt a face-on orientation with respect to the proximal pinacol methyl group, allowing a stabilizing CH–π interaction. The methyl group lies directly above the phenyl ring, with the nearest proton only 2.8 Å from the center of the ring.[20] In **TS-Ia*Si***, this type of CH–π interaction is precluded as the aryl ring cannot adopt the required orientation due to a steric clash with the β-methyl group. This is illustrated by the difference in dihedral angles, ϕ (in green) between **TS-Ia*Si*** and **TS-Ib*Si***, with the former having a much larger angle (69° vs 45°) due to the rotation of the phenyl ring to avoid clashing with the β-methyl group. For reaction of **12**, calculations predict a lower selectivity (see Supporting Information), apparently because in the less favored TS, the isopropyl group is able to orient itself so as to minimize steric clashes.

The remarkable selectivities observed in the allylborations of aldehydes of these α-phenyl, α-methyl substrates encouraged us to explore other transformations. Using functionalized allylic boronic ester **1c**, it was found that the allylboration of an imine according to the Brown–Ramachan-



Scheme 4. Further transformations of **1c**.

dran protocol[21] proceeded with excellent stereocontrol to yield, following acetylation, the product homoallylic amide **16** as a single isomer (Scheme 4). Protodeboronation with TBAF (tetrabutylammonium fluoride),[12a] whilst furnishing a small amount of the α-product, gave the γ-product **17** with essentially complete diastereocontrol and was chemoselective over desilylation of the *tert*-butyl dimethylsilyl (TBS)-ether. Using nOe analysis, we were surprised to observe that the product alkene was the *E*-isomer. Basic peroxide oxidation gave the tertiary allylic alcohol **18** in quantative yield and as a single isomer.

In summary, we have developed a methodology for the synthesis of tetrasubstituted homoallylic alcohols with exceptional levels of diastereo- and enantioselectivity through the allylboration of aldehydes. Both acyclic and the difficult to access exocyclic alkenes can be synthesized in a highly stereocontrolled manner. Furthermore, through the use of β-boryl-α,α-disubstituted allylic boronic esters, tetrasubstituted homoallylic alcohols bearing a boronic ester were obtained which enabled a highly modular and stereoselective approach to the synthesis of diaryl tetrasubstituted alkenes. Computational analysis revealed that the surprisingly high levels of stereocontrol originated from the combined steric effects of the β-substituent and pinacol group which leave only a small pocket for an equatorial α-substituent in the closed, six-membered transition state.

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