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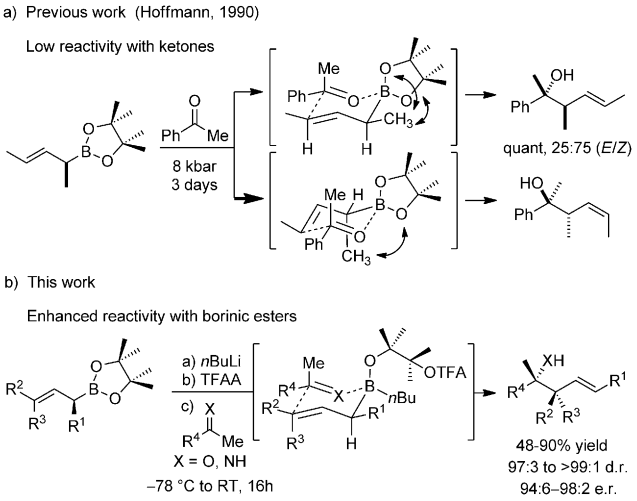
Highly Diastereoselective and Enantiospecific Allylation of Ketones and Imines Using Borinic Esters: Contiguous Quaternary Stereogenic Centers**

*Jack L.-Y. Chen and Varinder K. Aggarwal**

Abstract: *3,3-Disubstituted allylic boronic esters are not sufficiently reactive to react with ketones and imines. However, they can be converted into the corresponding borinic esters by the sequential addition of nBuLi and TFAA. These reactive intermediates possess the perfect balance between reactivity and configurational stability. Their enhanced reactivity allows the highly selective allylation of both ketones and ketimines, and facile access to adjacent quaternary stereocenters with full stereocontrol. The versatility of the methodology is demonstrated in the construction of all possible stereoisomers of a quaternary-quaternary motif and by the allylation of the heterocycles, dihydroisoquinoline and indole.*

The asymmetric allylboration reaction is one of the most reliable and useful methods for the synthesis of homoallylic alcohols.[1] Whilst extraordinarily useful for aldehydes, reactions with less reactive ketones[2] and imines are much more limited, because of the low reactivity of allylic boronic esters. Indeed, Hoffmann[3] reported the crotylation of a pinacol boronic ester with acetophenone and it required high pressure (8 kbar) and extended reaction times (3 days) to achieve full conversion (Scheme 1 a). Nevertheless, several new protocols have been developed and have begun to address such systems, for example, using allylic boronic acids or 1,3-propanediol boronic esters together with binol.[4] However, there are no successful asymmetric examples of the reactions of such poor electrophiles combined with even less reactive 3,3-disubstituted allylic boron reagents. Such a combination would lead to adjacent quaternary-quaternary stereocenters,[5,6] an especially difficult motif to create with control of relative and absolute stereochemistry. There are sporadic reports of diastereoselective allylation of ketones using 3,3-disubstituted allylic boronic acids,[4n,o] but no asymmetric examples have been reported.[7] Likewise, with 3,3-disubstituted allylic boranes,[8] allylations have been achieved with ketones but no examples possessing non-identical groups on the 3-position have been reported. This shows that 3,3-disubstituted allylic boranes are sufficently reactive to engage with ketones but their synthesis with non-identical groups in the 3-position is an issue, perhaps because of their tendency to isomerize through borotropic shifts.



Scheme 1. a) Reaction conditions required for allylboration of ketones with α-substituted boronic esters. b) Proposed allylboration of ketones and imines with α-substituted borinic esters to form contiguous quaternary centers. TFAA = trifluoroacetic anhydride.

As indicated above, 3,3-disubstituted allylic boronic esters are not sufficiently reactive to react with ketones. Between these two extremes of reactivity and stability lie allylic borinic esters. We have discovered a convenient way of generating this unusual class of reagents (by the addition of *n*BuLi to pinacol boronic esters followed by TFAA) and demonstrated that they show much higher *E* selectivity in reactions with aldehydes when compared to the same reactions using pinacol boronic esters.[9] We now show that the enhanced reactivity of these in situ generated borinic esters can be exploited in the allylation of challenging ketones and imines, even when using the least reactive 3,3-disubstituted reagents, with very high diastereoselectivity and complete enantiospecificity for the unprecedented creation of adjacent quaternary-quaternary stereogenic centers.

We began our studies with the synthesis of enantioenriched α-substituted-3,3-disubstituted allylic boronic esters using our lithiation-borylation methodology.[10] This involves deprotonation of a carbamate or hindered benzoate using *s*BuLi with (+)- or (−)-sparteine followed by addition of a vinylboronic ester. The resulting boronate complex undergoes a 1,2-metallate rearrangement upon heating, thus giving the allylic boronic ester. Whilst this worked well for the preparation of allylic boronic esters **1a** and **1b** (see Table 1), other aryl-containing substrates (**1c–f**) initially proved to be

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problematic because of a slow 1,2-metallate rearrangement. We were able to solve this problem by a combination of using a hindered benzoate (which has been shown to be a better leaving group than a carbamate)[11] and solvent exchange from Et_2O to $CHCl_3$.[12] This enhanced methodology enabled the synthesis of the trisubstituted allylic boronic esters **1c–f** with e.r. values in the range from 95:5 to 98:2 .

The enantioenriched α-substituted-3,3-disubstituted allylic boronic esters **1a–f** were subjected to our Lewis-base-promoted allylation reaction with ketones. Thus, the allylic pinacol boronic ester **1a** was treated sequentially with *n*BuLi and TFAA to generate the corresponding borinic ester in situ. The ketone was subsequently added at low temperature and it was found that the reaction went to completion upon warming to room temperature overnight. This demonstrated the considerably higher reactivity of the borinic ester compared to the boronic ester.

We were delighted to find that essentially single diastereoisomers of homoallylic alcohols were formed in good yield and with complete stereospecificity when reacted with acetophenone (Table 1, entries 1, 3, and 5–8). Control experiments revealed that no reaction took place between the allylic boronic esters **1a–f** and acetophenone under ambient conditions after one week, and underscores the much higher reactivity of our allylic borinic esters. Furthermore, the even less reactive dialkyl ketone and the α,β-unsaturated ketone were also suitable coupling partners (entries 2 and 4). Although the use of Lewis acids have been shown to promote the allylboration of aldehydes,[13] we found that their application (e.g. $BF_3{\cdot}OEt_2$[4d]) with ketones was ineffective (see the Supporting Information for details of control experiments and alternative reaction conditions tested).

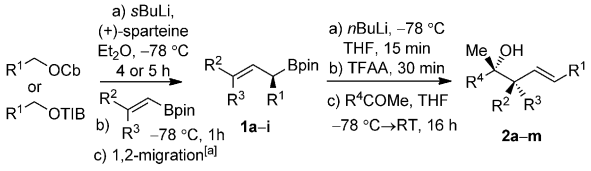
Our α-substituted-3,3-disubstituted allylic borinic esters showed considerably enhanced reactivity over conventional boronic esters as we had desired. The high selectivity that was observed was expected because of $A^{1,3}$ strain associated with the *Z*-substituent R^3 (Scheme 1 b). However, high selectivity was also observed with less substituted allylic borinic esters ($R^3 = H$) provided a secondary alkyl α-substituent was employed (Table 1, entries 9–13).

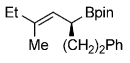
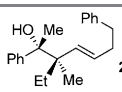
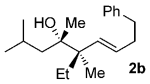
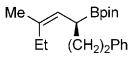
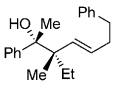
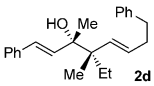
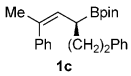
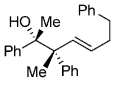
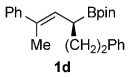
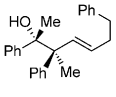
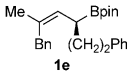
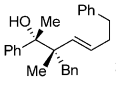
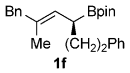
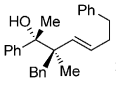
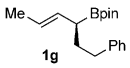
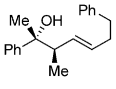
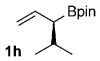
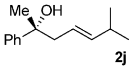
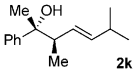
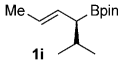
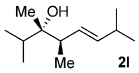
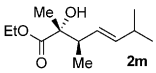
To demonstrate the versatility of this methodology, we wanted to access all four possible stereoisomers in a quaternary-quaternary motif (Figure 1). By using the lithiation-borylation methodology with both *E*- and *Z*-boronic esters (**3a** and **3b**, respectively) and (+)-sparteine and (−)-sparteine (both enantiomers of sparteine are commercially available; see the Supporting Information for details), we were able to access all four possible stereoisomers of the quaternary-quaternary motif in ≥ 99:1 d.r. and ≥ 98:2 e.r., thus validating the versatility of this methodology.

The allylation of imines is one of the most efficient and direct ways of generating homoallylic amines.[1b,14] However, the reaction with imines is more challenging than the allylation of aldehydes because of their lower electrophilicity.[14a] Whilst numerous advances[4r,15] have been made in the allylation of aldimines and ketimines, few cases report the use of 3,3-disubstituted allylic boron reagents.[15m,n]

Reactions of our 3,3-disubstituted allylic boronic esters under the control-reaction conditions (no additives) produced

Table 1: Allylation of ketones with α-substituted allyl, crotyl, and 3,3-disubstituted allylic boronic esters.



Entry	Li-B product	Yield[b]	Product	Yield[b]
1	 **1a**	77% 98:2 e.r.	 **2a**	87% >99:1 d.r.[c] 98:2 e.r.
2			 **2b**	80% >99:1 d.r.[c] 98:2 e.r.
3	 **1b**	74% 98:2 e.r.	 **2c**	83% >99:1 d.r.[c] 98:2 e.r.
4			 **2d**	88% 97:3 d.r.[c] 98:2 e.r.
5	 **1c**	74% 97:3 e.r.	 **2e**	53% >99:1 d.r.[c] 94:6 e.r.
6	 **1d**	68% 96:4 e.r.	 **2f**	69% >99:1 d.r.[c] 96:4 e.r.
7	 **1e**	62% 95:5 e.r.	 **2g**	70% >99:1 d.r.[c] 96:4 e.r.
8	 **1f**	74% 96:4 e.r.	 **2h**	73% >99:1 d.r.[c] 95:5 e.r.
9	 **1g**	78% 98:2 e.r.	 **2i**	85% 76:24 d.r.[c] 98:2 e.r.
10	 **1h**	68% 98:2 e.r.	 **2j**	73% 98:2 d.r.[c] 98:2 e.r.
11			 **2k**	80% 97:3 d.r.[c] 98:2 e.r.
12	 **1i**	72% 98:2 e.r.	 **2l**	71% >99:1 d.r.[c] 97:3 e.r.
13			 **2m**	90% >99:1 d.r.[c] 98:2 e.r.

[a] $MgBr_2{\cdot}OEt_2$, reflux overnight or $Et_2O \rightarrow CHCl_3$, reflux overnight. [b] Yield of isolated product. [c] Determined by GC/HPLC/SFC analysis of the crude reaction mixture using a chiral stationary phase. OCb = *N*,*N*-diisopropyl carbamate, OTIB = 2,4,6-triisopropylbenzoate, THF = tetrahydrofuran.

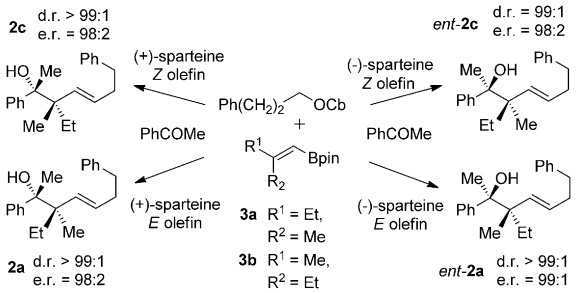
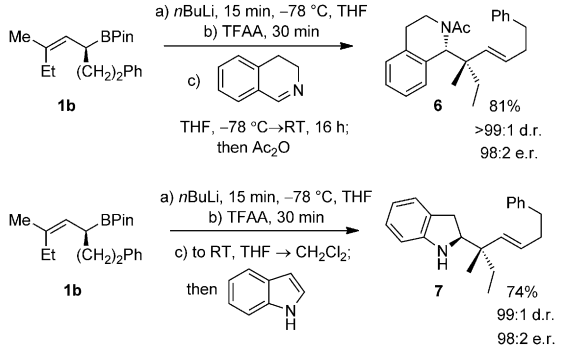


Figure 1. Generation of all possible four stereoisomers of a quaternary-quaternary motif.

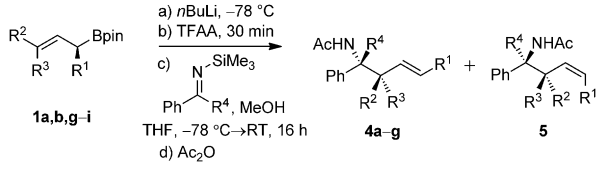
less than 30% conversion with aldimines[16] and less than 10% conversion with ketimines after 2 days. However, using our Lewis-base-activated conditions there was smooth formation of the *E*-homoallylic amines exclusively, in good yield and complete enantiospecificity (Table 2, entries 1–4). Particularly noteworthy is reaction with the acetophenone-derived ketimine, which worked well and again gave very high selectivity in the allylation process. This borinic ester mediated allylboration provides a powerful new method for the construction of homoallylic amines bearing quaternary stereogenic centers and the even more challenging contiguous quaternary-quaternary centers. As before, less substituted allylic borinic esters could also be employed and high selectivity was again obtained when the secondary alkyl α-substituent was employed (entries 5–7). In these cases control experiments showed that the boronic esters were sufficiently reactive to engage with imines, and interestingly the *Z* isomers were favored whereas with borinic esters, *E* isomers were formed with very high selectivity.

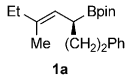
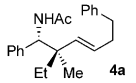
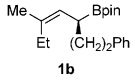
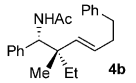
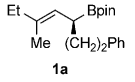
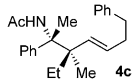
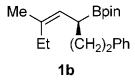
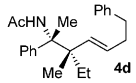
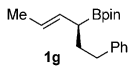
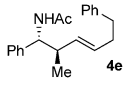
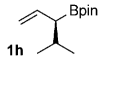
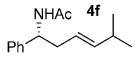
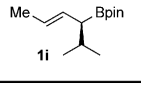
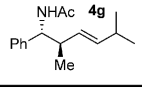
These reaction conditions were also effective for the direct allylation of 3,4-dihydroisoquinoline as well as indole (Scheme 2). Allylation of 3,4-dihydroisoquinoline with **1b**



Scheme 2. Allylation of 3,4-dihydroisoquinoline and indole.

Table 2: Allylation of N-TMS aldimine and ketimines.



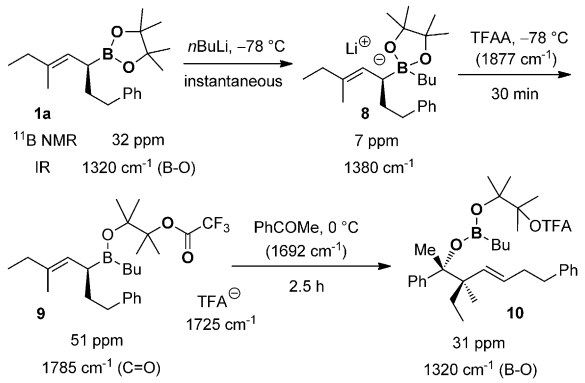
Entry	Boronic ester **1**[a]	R^4	Product	Yield[b,c]	d.r.[d]	e.r.
1	 **1a**	H	 **4a**	81%	>99:1	98:2
2	 **1b**	H	 **4b**	77%	>99:1	98:2
3	 **1a**	Me	 **4c**	48%	99:1	98:2
4	 **1b**	Me	 **4d**	54%	>99:1	98:2
5	 **1g**	H	 **4e**	91% (72%)	73:27 (8:92)	98:2 (98:2)
6	 **1h**	H	 **4f**	76% (87%)	98:2 (13:87)	98:2 (97:3)
7	 **1i**	H	 **4g**	80% (88%)	>99:1 (10:90)	97:3 (98:2)

[a] 98:2 e.r. in each case. [b] Yield of isolated product. [c] Values in brackets: direct reaction of boronic esters without additives (control conditions). [d] Ratio **4**/**5**: Determined by HPLC/SFC analysis of the crude reaction mixture using a chiral stationary phase. TMS = trimethylsilyl.

afforded the resultant homoallylic amide in 81% yield and as a single diastereoisomer. Reaction of **1b** with indole was slow presumably as the substrate had to first isomerize to the imine tautomer.[17] Nevertheless, the substituted benzopyrrolidine **7** was formed in 74% yield as a single diastereoisomer. There are few examples for the direct allylboration of dihydroisoquinolines[15h,n] and indoles,[15n,17] and this methodology allows facile enantio- and diastereocontrolled access to functionalized amines which are useful precursors in the synthesis of alkaloids.

The stereochemical assignment was established by X-ray crystal structures of several compounds derived from the ketone and imine allylation (see the Supporting Information for details) and is in keeping with the model presented in Scheme 1b. It should be noted that the alkoxide substituent on boron is drawn in an axial position because a large anomeric effect through boron is believed to be operative.[18]

To gain insight into the nature of the reactive intermediates, the course of the reaction was monitored by ^{11}B NMR[9] and in situ IR spectroscopy, using ReactIR (Scheme 3). Upon addition of *n*BuLi to the boronic ester **1a** (1320 cm^{-1})[19] at −78 °C, this signal disappeared instantaneously and was replaced by a signal at 1380 cm^{-1}. This new signal is believed to correspond to the boronate complex **8** and is consistent with an upfield shift of the boron signal to $\delta = 7$ ppm. Following addition of TFAA at −78 °C, the characteristic anhydride signal at 1877 cm^{-1} appeared instantly and



Scheme 3. Identification of reactive intermediates and reaction monitoring using ^{11}B NMR and in situ IR spectroscopy (see the Supporting Information).

decreased in magnitude (to baseline) over a period of 30 minutes. At the same time a new signal at 1785 cm^{-1} appeared and corresponded to the trifluoroacetate ester bound to the pinacol in **9**. ^{11}B NMR spectroscopy was indicative of the formation of a borinic ester signal at $\delta =$ 51 ppm. A signal at 1725 cm^{-1} stayed constant throughout the course of the reaction and is attributed to the trifluoroacetate anion. The course of the allylation could be monitored by the immediate appearance of the ketone carbonyl at 1692 cm^{-1} which gradually declined over a period of 2.5 hours at 0 °C. This change was accompanied by an increase in the signal at 1320 cm^{-1}, corresponding to the formation of the boronic ester **10**. This showed that the reaction of the borinic ester with acetophenone at 0 °C was complete after 2.5 hours.

These observations show that the reactions of borinic esters with ketones are extremely facile and rapid, and are complete in just a few hours at ambient temperature and pressure. This contrasts with the very low reactivity of allylic pinacol boronic esters, which have been shown to require high pressure and extended reaction times in related reactions.[3]

In conclusion, we have employed traditionally unreactive 3,3-disubstituted allylic pinacol boronic esters in the allylation of ketones, imines, and aromatic heterocycles. This has been achieved by the in situ generation of reactive borinic esters, which have the perfect balance between stability (no 1,3-borotropic shift) and reactivity. Particularly noteworthy is the ability to create adjacent quaternary-quaternary stereocenters with essentially complete stereocontrol in the reactions with ketones and ketimines. The methodology allows a significant expansion in the scope of the ubiquitous allylboration reaction.

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Communications

Synthetic Methods

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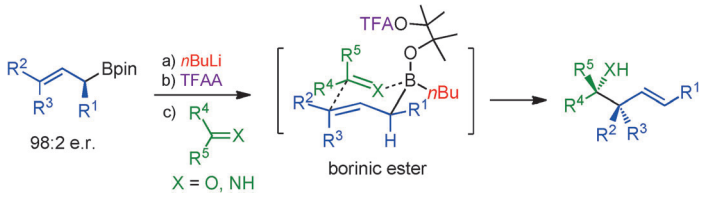
Highly Diastereoselective and Enantiospecific Allylation of Ketones and Imines Using Borinic Esters: Contiguous Quaternary Stereogenic Centers



Goldilocks reactivity: 3,3-Disubstituted allylic borinic esters possess the perfect balance between reactivity and configurational stability to react with both ketones and ketimines, allowing facile access to adjacent quaternary stereocenters with full stereocontrol. Synthesis of all possible stereoisomers of a quaternary-quaternary motif is demonstrated. TFAA = trifluoroacetic anhydride.

