VIP Quaternary Centers

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Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications**

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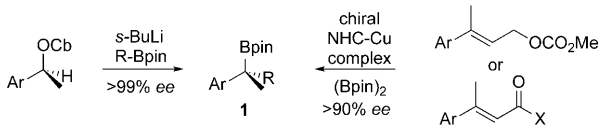
The creation of quaternary stereogenic centers with high enantioselectivity is challenging, in part, because of the high steric repulsion between the substituents on the carbon center that is generated during construction. Nevertheless, significant progress has been made towards this goal in recent years, even in conformationally flexible acyclic systems.[1] However, whilst in many cases high e.r. values have been achieved, the selectivities are invariably substrate-dependent.

We have approached this problem from a different perspective and considered the possibility of employing stereospecific homologations of tertiary boronic esters **1**. Such boronic esters can be easily prepared from the corresponding secondary alcohols with very high e.r. values by using the methodology developed by our group,[2] or alternatively, by borylation of allylic carbonates/Michael acceptors reported by Hoveyda and co-workers (Scheme 1).[3] However, whilst the homologation reaction



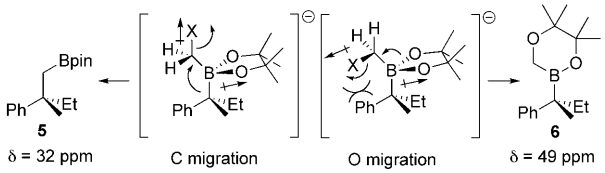
Scheme 1. Synthesis of chiral tertiary boronic esters. Cb = *N*,*N*-diisopropylcarbamoyl, Bpin = pinacolboryl, NHC = N-heterocyclic carbene.

may seemingly appear to be a straight forward extension of the literature it should be noted that hindered tertiary boranes (e.g., thexyl) have often been employed as non-migrating groups in homologations of boranes,[4] and examples of related transformations of tertiary boronic esters are rare.[5,6] Furthermore, extending methodology from secondary to tertiary substrates is rarely straightforward as the extra steric demand often results in lower selectivity or alternative reaction pathways being followed.[7] Herein we describe our success in creating quaternary stereogenic centers with very high e.r. values and with a range of versatile functional groups; the subsequent application of the methodology in synthesis is also presented.

We began our studies using the tertiary boronic ester **2a** which was subjected to standard Matteson homologation conditions[6] using chloromethyl lithium[6b] at low temperature. However, whilst the homologated alcohol product was obtained after oxidation in reasonable yield, almost 20% of the oxidation product **4**, seemingly derived from the starting material **2a**, was also isolated even when a large excess (4.0 equiv) of $LiCH_2Cl$ was employed (Scheme 2).

Analysis of the reaction by ^{11}B NMR spectroscopy prior to oxidation revealed that in addition to the signal of desired boronic ester **5** at $\delta = 32$ ppm, a new peak at $\delta = 49$ ppm was observed, which is indicative of the presence of borinic ester **6**.[8] This ester must have formed from the unexpected migration of the oxygen substituent[9] instead of the normally favored carbon migration, presumably as a consequence of the very hindered nature of the boronic ester. We reasoned that using a bulkier and less polar leaving group (smaller dipole moment) would favor the conformation required for C migration and therefore explored $LiCH_2Br$ as an alternative reagent.[10] Making this simple modification resulted in an improved yield of the desired homologated product (83% yield) with only about 5% of the product derived from O migration (Scheme 2).

This reagent was applied to a series of tertiary boronic esters and the results are summarized in Table 1. The reaction worked well with dialkylaryl boronic esters bearing electron-



Entry	Reagent	Equiv	Yield **3a**	% O migration
1	$LiCH_2Cl$	2.2	71%	20%
2	$LiCH_2Cl$	4.0	63%	20%
3	$LiCH_2Br$	2.2	83%	5%

Scheme 2. ^{11}B NMR investigation and optimization of the C- versus O migration in the homologation of boronic ester **2a**.

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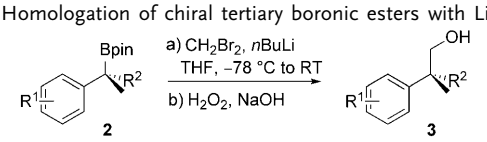
Table 1: Homologation of chiral tertiary boronic esters with $LiCH_2Br$.[a]



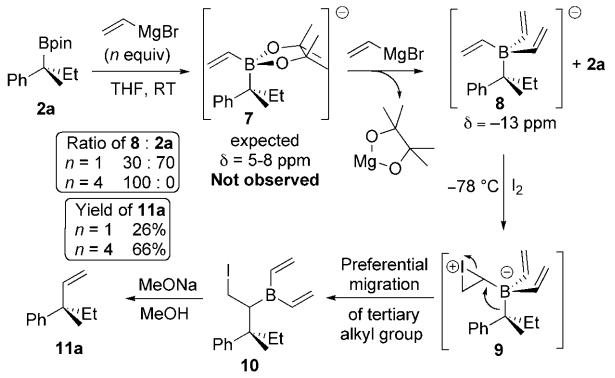
Entry		Boronic ester R¹	R²	e.r.		Product Yield [%][b]	e.r.[c]
1	**2a**	H	Et	>99:1	**3a**	83	>99:1
2	**2b**	*p*Cl	Et	>99:1	**3b**	88	>99:1
3	**2c**	*p*MeO	Et	>99:1	**3c**	62	99:1
4	**2d**	H	allyl	>99:1	**3d**	82	>99:1
5	**2e**[d]	H	*i*Pr	>99:1	**3e**	37	>99:1
6	**2f**	*p*MeO	Ph	98:2	**3f**	41	98:2

[a] 2.5 equiv of CH_2Br_2 and 2.2 equiv of *n*BuLi were used. [b] Yield of isolated product. [c] Determined by either HPLC or GC analysis using a chiral stationary phase (for details refer to the Supporting Information). [d] Neopentyl glycol boronic ester was used (the pinacol boronic ester gave 30% yield).

rich and electron-deficient aromatic rings (entries 1–3), and with substrates bearing an allyl substituent (entry 4). However, the tertiary boronic ester **2e** bearing an especially hindered *i*Pr substituent was more challenging and gave a 37% yield of the homologated product, but only when the less hindered neopentyl glycol boronic ester was used in place of the pinacol ester (entry 5). Evidently, severe steric hindrance of the boronic ester slows down the addition of bromomethyllithium to the boronic ester and competing decomposition pathways of the organolithium occur instead. The diarylalkyl boronic ester **2f** was able to undergo the homologation reaction to afford the alcohol **3f**, bearing a congested bis(aryl)-substituted quaternary sterogenic center, in 41% yield. In all cases complete chirality transfer occurred leading to quaternary centers with very high e.r. values.

Having established an efficient protocol for the preparation of quaternary centers bearing an α-primary alcohol functionality, we focused on the introduction of a vinyl group. Quaternary centers bearing a vinyl group represent an important structural motif due, not only to their preponderance in a number of natural products but also to their considerable versatility in synthesis. Our investigation started by subjecting the tertiary boronic ester **2a** to standard Zweifel olefination conditions[11] (1 equiv of vinylmagnesium bromide and subsequent addition of iodine and sodium methoxide), which afforded product **11a**, but in only 26% yield (Scheme 3). By monitoring the reaction using ^{11}B NMR spectroscopy, we were surprised to observe a 30:70 mixture of the borane ate-complex **8** ($\delta = -13$ ppm) and starting boronic ester **2a**. Interestingly, the expected boronic ester ate-complex **7** was not observed under these reaction conditions.[8,12] Nonetheless, the relatively high yield of **11a** after isolation, considering the low conversion into an ate-complex observed, implies preferential migration of the tertiary substituent over the two vinyl groups in the zwitterionic species **9**.[13] When 4 equivalents of vinylmagnesium bromide were used, we observed complete conversion into **8** and we were able to isolate alkene **11a** in 66% yield.

The modified protocol was then applied to the same representative series of tertiary boronic esters and they were



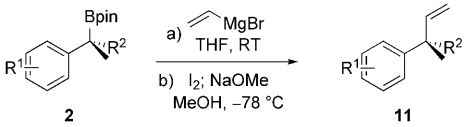
Scheme 3. ^{11}B NMR investigation and optimization of vinylation of boronic ester **2a**.

converted into the vinylated product with very high e.r. values (Table 2). In the case of the highly hindered substrates **2e** and **2f**, the more reactive vinyllithium was found to be considerably superior to vinylmagnesium bromide, thereby furnishing the adducts in good yields. As before complete chirality transfer accompanied these reactions.

To enhance the methodology further we turned our attention to exploring alternative homologations of tertiary boronic esters for the construction of chiral quaternary centers α to a carbonyl group.[1] Thus, treatment of the boronic ester **2a** with $LiCHCl_2$[5] furnished the chiral aldehyde **12** directly after oxidative workup (Scheme 4). In a manner analogous to the Zweifel olefination, we tested the reaction of ethoxy vinyllithium with boronic ester **2a**, and after a brief acid hydrolysis obtained the corresponding ketone **13** in good yield with an excellent e.r. value. This example represents a novel, direct conversion of a boronic ester into a ketone.

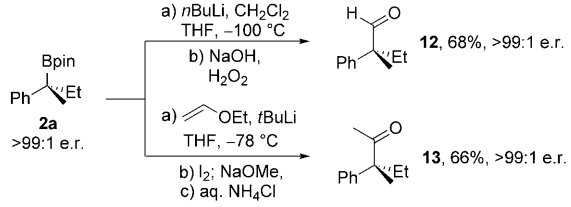
Attempts to introduce an adjacent stereogenic center by reaction with a primary or secondary stereodefined lithiated carbamate were unsuccessful. No ate complex was formed

Table 2: Zweifel-type olefination of chiral tertiary boronic esters.[a]

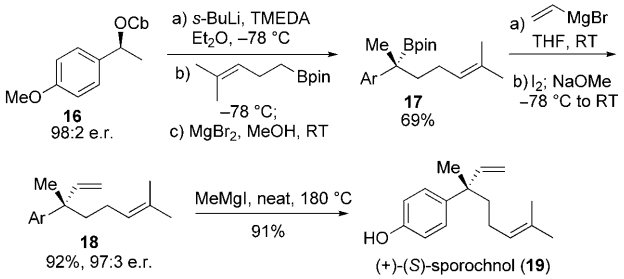


Entry		Boronic ester R¹	R²	e.r.		Product Yield [%][b]	e.r.[c]
1	**2a**	H	Et	>99:1	**11a**	66	>99:1
2	**2b**	*p*Cl	Et	>99:1	**11b**	79	>99:1
3	**2c**	*p*MeO	Et	>99:1	**11c**	62	>99:1
4	**2d**	H	allyl	>99:1	**11d**	79	>99:1
5	**2e**[d]	H	*i*Pr	>99:1	**11e**[e,f]	58	>99:1
6	**2f**	*p*MeO	Ph	98:2	**11f**[e,g]	92	98:2

[a] 4 equiv of vinylmagnesium bromide were added at RT with subsequent addition of 4 equiv of I_2 and 8 equiv of NaOMe at −78 °C. [b] Yield of isolated product. [c] Determined by either HPLC or GC analysis using a chiral stationary column (for details refer to the Supporting Information). [d] Neopentyl glycol boronic ester was used (the pinacol boronic ester gave only decomposition). [e] 4 equiv of vinyllithium was added at −78 °C with subsequent addition of I_2 (4 equiv) and NaOMe (8 equiv) at −78 °C. [f] The yield with vinylmagnesium bromide was 52%. [g] No reaction was observed with vinylmagnesium bromide.



Scheme 4. Functional group transformation of boronic ester **2a**.

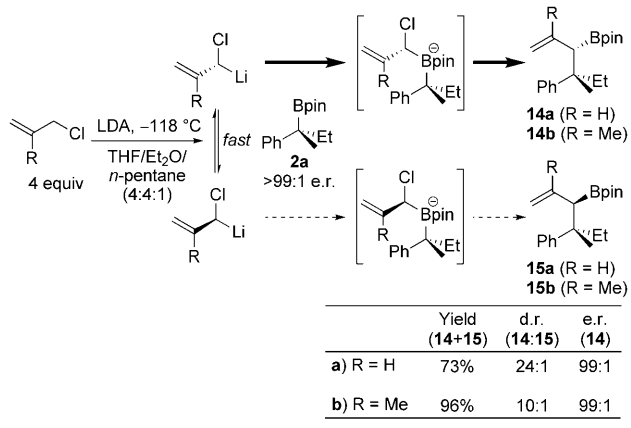


Scheme 6. Synthesis of (+)-(*S*)-sporochnol (**19**). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylene-diamine.

presumably because of the high steric hindrance of both the electrophilic tertiary boronic ester and the nucleophilic lithiated carbamate. However, the less hindered 1-chloro-allyllithium[14] was able to react with the tertiary boronic ester **2a** and gave the homologated allylic boronic esters **14a**/**15a** with surprisingly high diastereoselectivity (24:1) and complete stereospecificity (Scheme 5).[15] 1-Chloro-methallyllithium also reacted efficiently with high diastereoselectivity. The structure of the major diastereoisomer **14b** was determined by X-ray analysis.[16] When one equivalent of 1-chloro-allyllithium was reacted with an excess of the boronic ester **2a** (4 equiv), **14a**/**15a** were obtained in 60% yield and again with a high d.r. value (12:1). This result indicates that 1-chloro-allyllithium undergoes rapid racemization during the reaction (dynamic kinetic resolution) and that the high diastereoselectivity observed is because one enantiomer of 1-chloro-allyllithium reacts with the chiral tertiary boronic ester significantly more rapidly than the other enantiomer (Scheme 5). The homologation of the tertiary boronic ester **2a** with 1-chloro-allyllithium reagents represents a powerful method for the synthesis of chiral allylboronic esters bearing two contiguous stereocenters with high diastereocontrol. We are currently investigating the factors responsible for the unusually high diastereoselectivity observed.

To illustrate its utility, the methodology of homologation and vinylation of chiral tertiary boronic esters has been applied to the synthesis of the natural product (+)-sporochnol[17] and the serotonin antagonist (*S*)-1,2-diphenyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-1-butanone.[18]

(+)-Sporochnol (**19**) is a monoterpene-substituted phenol that is known to be a chemical defense compound and to exhibit feeding deterrence activity towards reef fish.[19] Of the

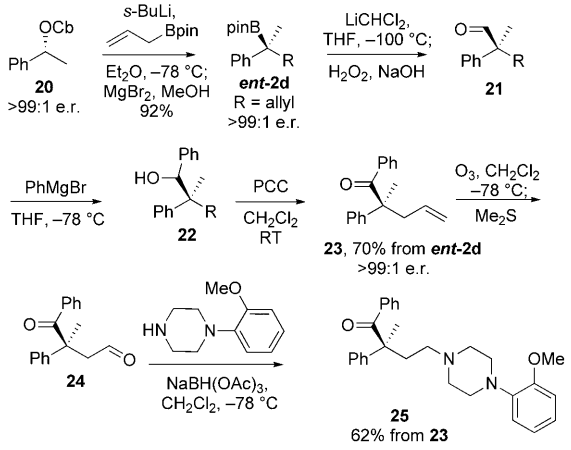


	Yield (**14**+**15**)	d.r. (**14**:**15**)	e.r. (**14**)
a) R = H	73%	24:1	99:1
b) R = Me	96%	10:1	99:1

Scheme 5. Homologation of boronic ester **2a** with chloro allyllithium reagents. LDA = lithium diisopropylamide.

syntheses reported,[17] the shortest is attributed to Hoveyda and co-workers, and involves a copper-catalyzed allylic substitution that furnished the target concisely, albeit with low enantioselectivity.[17a] Our synthesis is presented in Scheme 6. The key steps involve lithiation/borylation of the chiral carbamate **16** which gave the chiral tertiary boronic ester **17**, and subsequent vinylation using our newly established methodology to afford **18** efficiently and with essentially complete chirality transfer. Deprotection of the phenol then completed the synthesis. Our route represents a significant improvement in terms of the number of steps and selectivity to those reported to date.

(*S*)-1,2-Diphenyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-1-butanone (**25**) belongs to a family of arylpiperazines that are potential pharmaceutical agents for the treatment of depression and related disorders.[18] Denmark et al. have previously reported an efficient synthesis of this pharmaceutical that utilized enantioselective allylation of aldehydes as a key step for the construction of the quaternary stereocenter.[20] Our synthesis of the serotonin antagonist is shown in Scheme 7. Lithiation/borylation of the carbamate **20**, and then homologation with dichloromethyllithium gave the aldehyde **21** directly. Addition of PhMgBr and subsequent oxidation afforded the ketone **23** in 70% yield over three steps. Oxidative cleavage of the olefin in **23** with ozone and subsequent reductive amination using the commercially available piperazine gave the target pharmaceutical **25** in a highly efficient manner and with complete enantioselectivity.



Scheme 7. Synthesis of (*S*)-1,2-diphenyl-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-methyl-1-butanone. PCC = pyridinium chlorochromate.

In conclusion, we report the preparation of a broad range of substrates bearing versatile functional groups with quaternary stereogenic centers and very high enantioselectivities using the lithiation/borylation reaction and subsequent one-carbon homologation or vinylation.[21] Especially noteworthy is the generation of contiguous quaternary and tertiary stereogenic centers with high d.r. values and essentially perfect enantioselectivity.

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[12] It is possible that the severe steric hindrance between substituents on the boron atom in **7**, together with the Mg salts present, promote ring-opening of the pinacol ester to give an intermediate borinic ester. This electrophilic species can then be attacked by vinylmagnesium bromide again, ultimately leading to borane ate-complex **8**.

[13] This result is rather surprising since Zweifel found that thexyl and alkenyl groups migrate at similar rates when a bis(alkenyl) thexylborane was treated with I_2 and NaOH; see Ref. [11b].

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[15] Reaction of racemic **2a** with racemic 1-chloro-allyllithium gave the same 24:1 ratio of diastereoisomers. This ratio reflects the relative rates of reaction of the two diastereomeric pairs (e.g., $R+R$ *vs.* $R+S$) without the intervention of kinetic resolution.

[16] CCDC 800577 contains the supplementary crystallographic data for allyl boronic ester **14b**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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