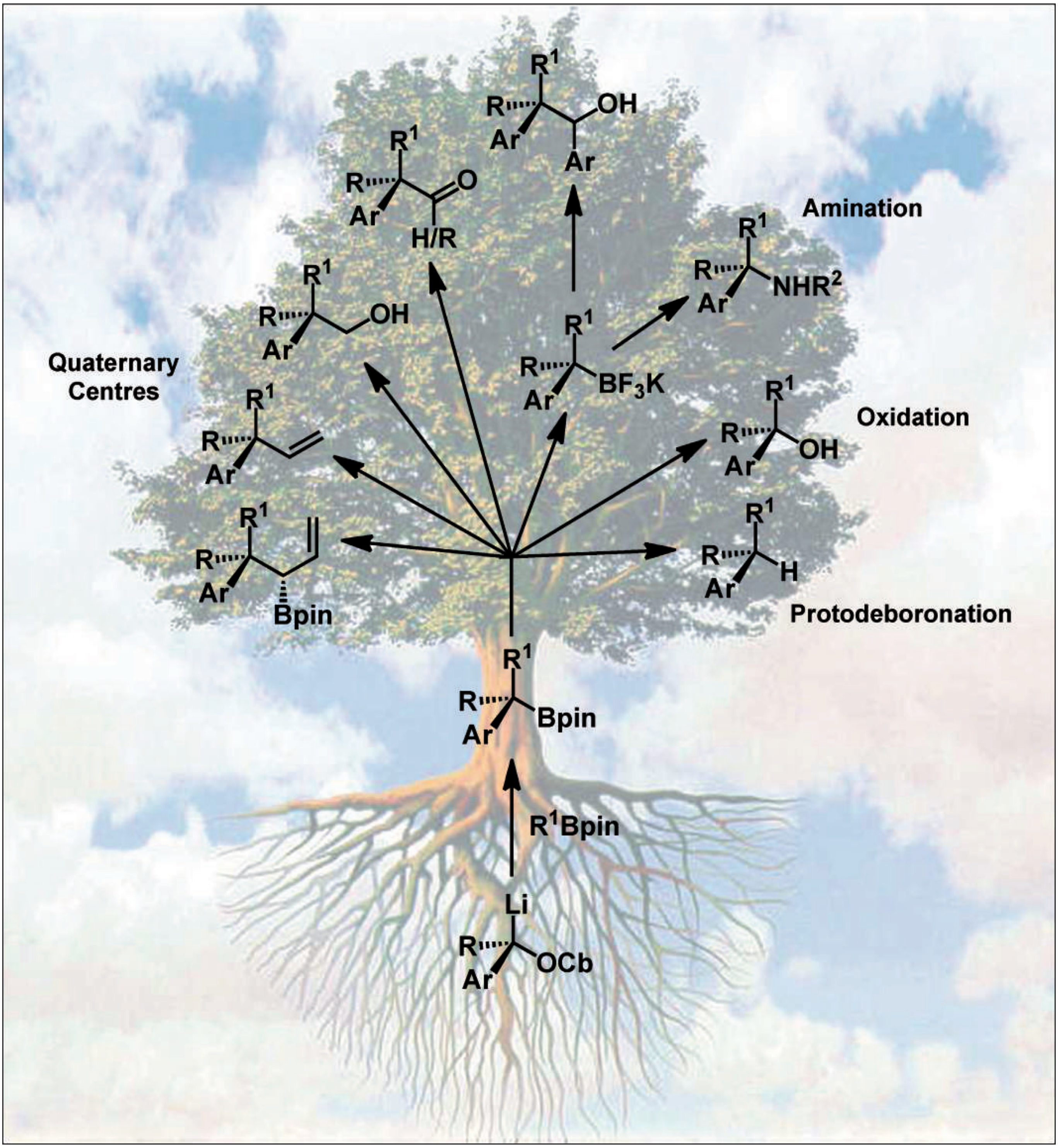
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201102581

Highly Enantioselective Synthesis of Tertiary Boronic Esters and their Stereospecific Conversion to other Functional Groups and Quaternary Stereocentres

Helen K. Scott and Varinder K. Aggarwal*[a]



Abstract: Organoboron compounds are useful in asymmetric synthesis. We have developed an efficient methodology for the highly enantioselective synthesis of tertiary boronic esters from the corresponding secondary benzylic alcohols. Further stereospecific transformations of the boronic ester moiety are described including the preparation of tertiary alcohols, C-tertiary amines and tertiary arylalkanes. Several homologations of tertiary boronic esters have also been developed for the construction of quaternary stereocentres.

Keywords: asymmetric synthesis • boron • homologations • quaternary stereocenters • synthetic methods

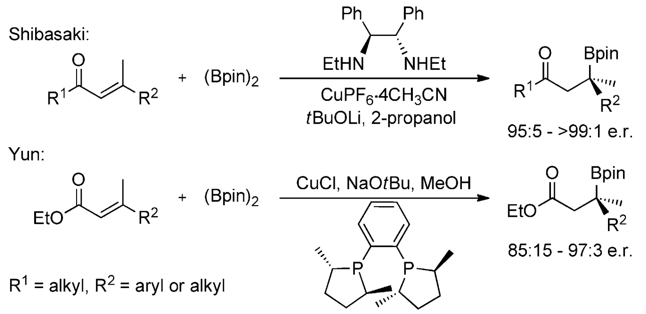
Introduction

The asymmetric synthesis of fully substituted carbon atoms bearing four different substituents, for example, tertiary alcohols, C-tertiary amines[1] and quaternary centres[2] and so forth, is a major synthetic challenge and acts as the ultimate testing ground for new methodology.

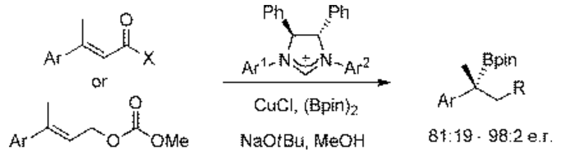
We recognised that if we could create a practical methodology for the generation of tertiary boronic esters with high enantiomeric ratio (e.r.) then, through stereospecific functional group transformations, we could access a range of useful, fully substituted carbon atoms. Hydroboration, pioneered by H. C. Brown in the 1960s, is not a suitable method for the synthesis of tertiary boronic esters, since addition across the double bond occurs in an anti-Markovnikov fashion, delivering the boron to the less hindered carbon.[3] More recently, several catalytic conjugate addition processes have been developed to afford tertiary boronic esters in good levels of e.r. These processes are based on the seminal work of Hosomi[4] and Miyaura[5] who independently described the β-borylation of Michael acceptors. Shibasaki[6] used a chiral diamine–copper complex and Yun[7] used a chiral phosphine–copper complex to catalyze a conjugate borylation of β,β-disubstituted Michael acceptors in the synthesis of tertiary boronic esters (Scheme 1).

Hoveyda independently developed a related 1,4-addition protocol for the borylation of allylic carbonates/Michael acceptors using an N-heterocyclic carbene–copper complex (Scheme 2).[8] All of these reactions are believed to occur via borylcopper complexes.

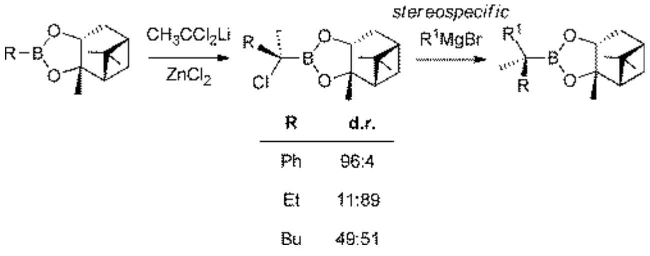
An alternative route to tertiary boronic esters involves the Matteson–Pasto rearrangement.[9] Matteson had shown that addition of dichloromethyllithium to a chiral diol-derived boronic ester and a subsequent $ZnCl_2$ promoted 1,2-metallate rearrangement occurred with very high diastereoselectivity. The α-chloroboronic ester that was formed was subsequently treated with a Grignard reagent, or other nucleophile, to give a secondary alkylboronic ester stereospecifically.[10] However, extension of this strategy to the synthesis of tertiary boronic esters was much less successful, since the diastereoselectivity in the first homologation migration step suffered from unpredictability.[11] High levels of diastereoselectivity were reported for R = Ph, but for alkyl substituents either no diastereoselectivity was observed (R = Bu) or the opposite diastereomer was formed (R = Et, Scheme 3).



Scheme 1. Shibasaki and Yun methodology for the preparation of tertiary boronic esters.



Scheme 2. Hoveyda methodology for the preparation of tertiary boronic esters.



Scheme 3. Matteson methodology for the preparation of tertiary boronic esters.

We had previously shown that chiral secondary boronic esters **1** could be generated in high e.r. from the reactions of boronic esters with Hoppe's lithiated carbamates derived from primary alcohols (Scheme 4).[12] We therefore consid-

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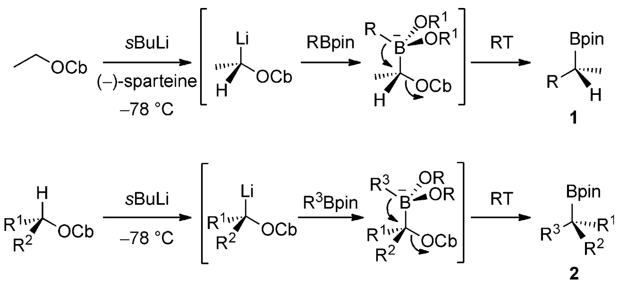
[a] H. K. Scott, Prof. V. K. Aggarwal
School of Chemistry
University of Bristol
Cantocks Close, Bristol, BS8 1TS (UK)
Fax: (+44) 117-925-1295
E-mail: v.aggarwal@bristol.ac.uk



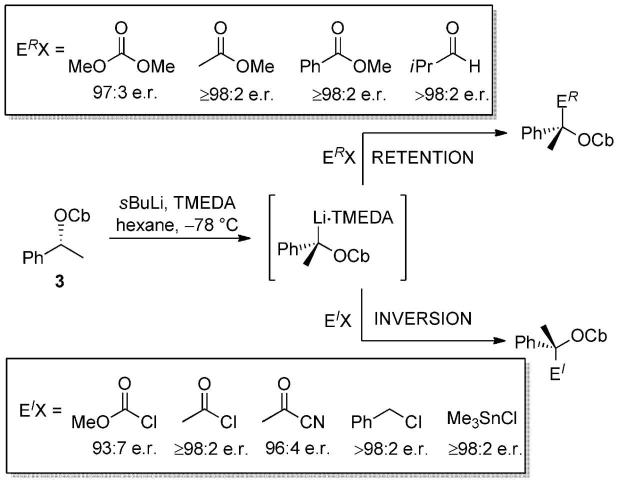
Scheme 4. Lithiation of primary and secondary carbamates for the synthesis of secondary and tertiary boronic esters.

ered the possibility of extending this protocol to the reactions of lithiated carbamates derived from secondary alcohols as a potential route to tertiary boronic esters **2**.

In this Concept article, our inspirations and results for the preparation of tertiary boronic esters are described, followed by the synthetic applications that we have developed to access other functional groups in high e.r. directly from the boronic esters.

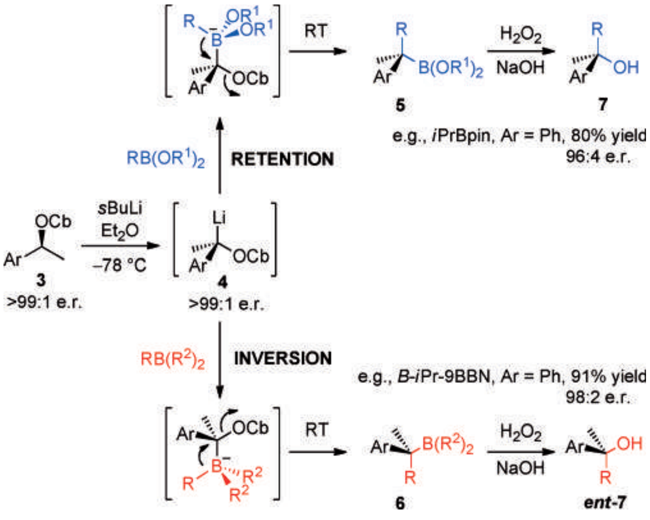
Synthesis of Tertiary Boronic Esters

As indicated above we had previously shown that chiral secondary boronic esters could be generated in high e.r. from the reactions of boronic esters with Hoppe's lithiated carbamates derived from primary alcohols.[13] We wished to investigate the potential for extending this strategy to carbamates derived from secondary alcohols. Hoppe had once again laid the groundwork for this study.[14] He had shown that carbamates derived from secondary alkyl alcohols could not be easily deprotonated.[15] However, those derived from secondary benzylic carbamates **3** could be successfully deprotonated with *s*BuLi at –78 °C and subsequently trapped with various electrophiles with excellent enantioselectivity (Scheme 5).[16] Interestingly, he observed that reactions occurred with either retention or inversion depending on the nature of the electrophile used.



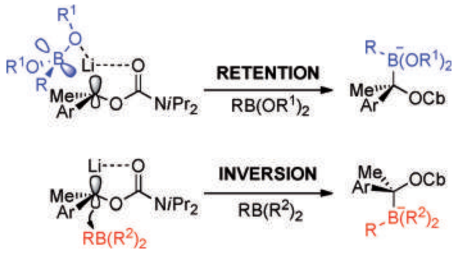
Scheme 5. Electrophilic trapping of secondary lithiated carbamates with retention or inversion.

We therefore initiated an investigation of the reactions of the same carbamates with boron reagents. The chiral secondary alcohols were either commercially available or obtained by Noyori reduction of the corresponding ketone or by an enzymatic resolution of the racemic alcohol. Carbamoylation of the alcohol and subsequent lithiation with *s*BuLi generated the desired lithiated chiral carbenoid **4**, as Hoppe had previously demonstrated. Treatment with either a boronic ester or borane afforded the homologated tertiary organoboron intermediates **5** and **6**, respectively, which were oxidized to the corresponding alcohols[17] **7** and ***ent*-7** in high e.r. (Scheme 6).[18]



Scheme 6. Synthesis of tertiary alcohols from chiral secondary carbamates using the lithiation/borylation methodology.

Interestingly, boronic esters reacted with the lithiated carbamate with retention of stereochemistry, whereas borylation with boranes occurred with inversion of stereochemistry. This unusual observation can be accounted for by considering the interaction between the lithiated carbamate and the boron reagent. In the case of boronic esters, the oxygen of the ester complexes with the lithium of the metallated carbamate and so is delivered on the same face as the metal. In the absence of such complexation, as in the case of the boranes, reaction occurs on the face opposite the metal where there is significant electron density due to the partially flattened nature of the mesomerically stabilized carbanion. The partially flattened nature of the carbanion will also open up the face opposite the metal making it less hindered (Scheme 7). Other electrophiles that cannot complex with lithium, for example, Bu_3SnCl, also react with inversion (Scheme 5).[13] However, it should be noted that reactions of lithiated alkylcarbamates derived from non-benzylic primary alcohols occur with complete retention of stereochemistry with both boranes and boronic esters, presumably because in this case the non-mesomerically stabilized carbanion is es-

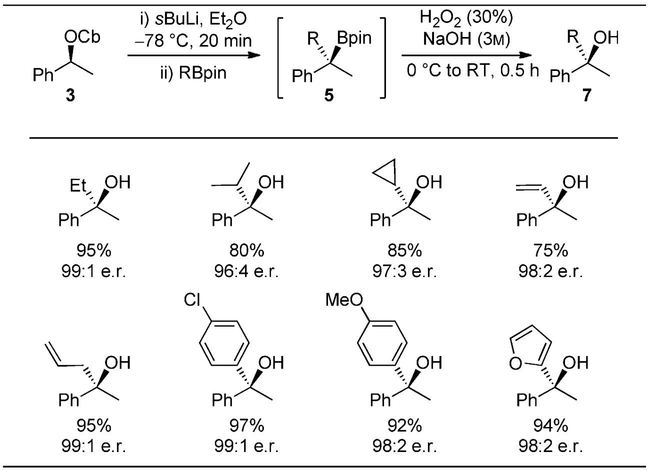


Scheme 7. Rationalisation for the retention versus inversion observed in reactions of lithiated carbamates with boronic esters and boranes respectively.

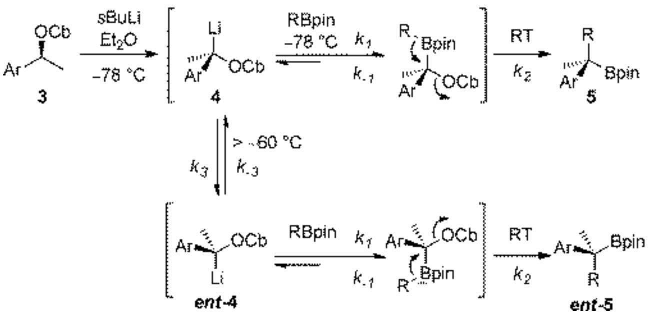
sentially tetrahedral, and has very little electron density and greater steric hindrance opposite the metal.

The consequence of this finding is that from a single enantiomer of a secondary alcohol, either enantiomer of a tertiary alcohol can now be prepared in high yield with a very high degree of enantioselectivity. The protocol shows relatively broad substrate scope and we were able to test a wide range of boronic esters because they were all commercially available. They included alkyl, vinyl, allyl, aryl and heteroarylboronic esters, all of which afforded the corresponding tertiary alcohols **7** in high yields and enantioselectivities (Table 1).

Table 1. One-pot lithiation/borylation/oxidation for the synthesis of tertiary alcohols.



However, when sterically more demanding carbamates or boronic esters were used or electron-withdrawing aromatic groups were present in the benzylic carbamate, considerable erosion of e.r. was observed, for example, p-ClC$_6$H$_4$C(OCb)Me with *i*PrBpin gave an e.r. of 75:25. Through careful mechanistic studies it was found that with these more challenging substrates, the ate complex not only progressed to the product through 1,2-metalate rearrangement upon warming, but competing dissociation back to the lithiated carbamate **4** and boronic ester also occurred. The lithiated carbamate formed by dissociation then began to racemise at elevated temperature (above −60 °C) and subsequent recombination with the boronic ester resulted in erosion of the e.r. (Scheme 8). It was possible to overcome this problem through the addition of MgBr$_2$/MeOH at −78 °C prior to warming of the reaction mixture. It is believed that the MgBr$_2$ enhances the k_2/k_{-1} ratio, while the MeOH reprotonates any lithiated carbamate **4** generated from the dissociation of the ate complex, thus preventing erosion of the e.r. value.[19]



Scheme 8. Dissociation of ate complex as a possible cause of erosion of e.r.

With this enhanced protocol, the lithiation/borylation of secondary carbamates with electron-withdrawing aromatic substituents **8** and sterically bulky boronic esters could now be performed with full chirality transfer even in the most challenging of cases. A variety of migrating groups gave excellent yields including sterically hindered alkyl and aryl substituents. Additional steric hindrance in the *ortho* position of the aromatic substituent was also tolerated, giving excellent yields and e.r. values. Tertiary diarylalkylboronates, including those containing a pyridyl substituent,[20] could also be prepared using this method. The improved protocol now allows access to a wide range of essentially enantiopure tertiary boronic esters **9**, which can be easily oxidised to the corresponding alcohols (Table 2).

Cyclic benzylic carbamates, for example, (*S*)-1-indanyl **10a** and (*S*)-1-tetralyl **10b** carbamates, could also be employed in the lithiation/borylation reaction although they were less straight forward (Table 3). The tetralyl derived substrates (**10b**) gave excellent yields of the tertiary alcohols **11b** but the enantiomeric ratios with both boranes and boronic esters were considerably lower than their acyclic counterparts. The ratios were also very sensitive to the steric nature of the borane/boronic ester leading to almost racemic products with especially hindered substrates, for example, tetralyl carbamate with EtBpin gave an e.r. of 59:41.

Reaction with the indanol-derived carbamates **10a** proceeded with high enantiomeric ratios with boronic esters and with retention of configuration as before. Interestingly, and in contrast to all other reactions studied, reaction with boranes also proceeded predominately with retention of stereochemistry. This tendency for indanyl carbamates to react with most electrophiles with retention is supported by Hoppe's calculations in which he found that the lithiated in-

Table 2. Optimised protocol and substrate scope for the lithiation/borylation of secondary carbamates.

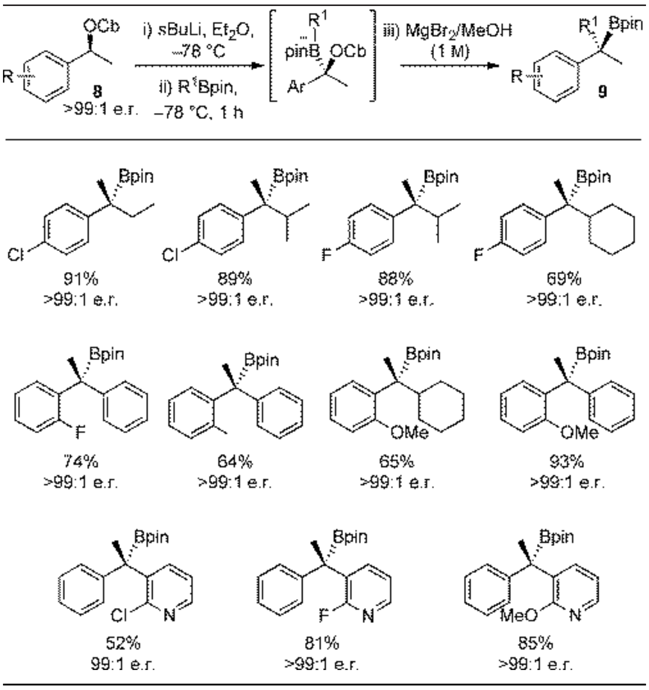
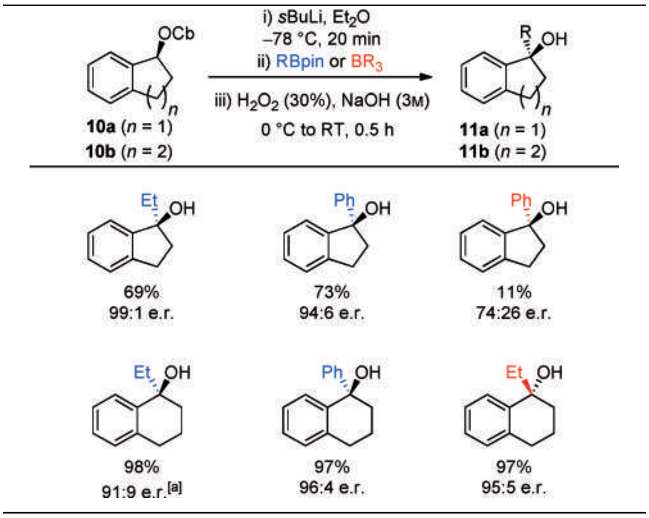


Table 3. One-pot lithiation/borylation/oxidation of indanyl and tetralyl carbamates.



[a] Reaction carried out with ethylene glycol boronic ester.

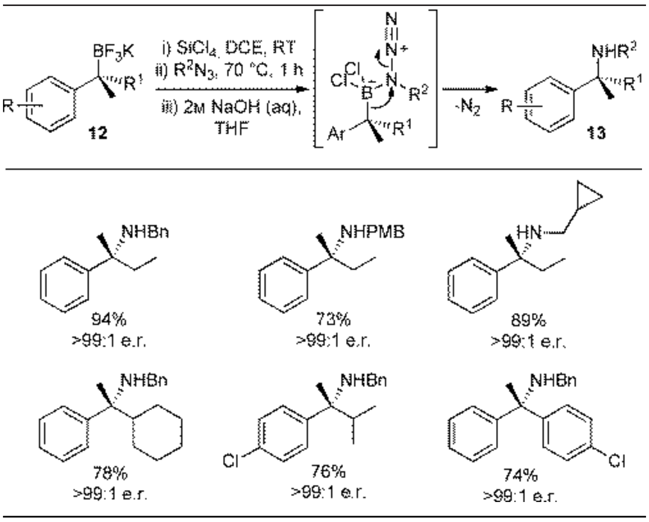
danyl carbamate remained tetrahedral with minimal planarization.[21] Like the primary alkyl lithiated carbamates, which also remain tetrahedral, electrophiles attack the lithiated indanyl carbamate predominantly on the same side as the metal. The enantiomeric ratios of the reactions of the cyclic substrates were insensitive to the use of $MgBr_2$/MeOH and the selectivities observed are believed to reflect the degree of retention/inversion in the addition reaction.

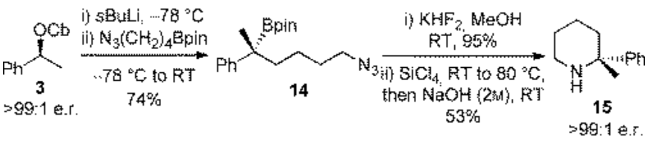
Synthesis of Tertiary Amines

Common approaches to the preparation of tertiary amines usually involve nucleophilic addition to ketimines[22] and even though high levels of stereocontrol have been observed, procedures are often highly substrate dependant. We conceived that amination of tertiary boronic esters could function as an asymmetric route to C-tertiary amines.

Brown used azides in the amination of primary and secondary dichloroboranes that were prepared from the corresponding boronic esters.[23] Matteson reported a more practical method for the conversion of boronic esters into amines: initial conversion to the potassium trifluoroborate salt followed by treatment with $SiCl_4$ (which generated the dichloroborane in situ) and subsequent addition of an azide.[24] Modification of this protocol was ultimately successful in the synthesis of C-tertiary amines. Thus, after converting the tertiary boronic ester into the tertiary potassium trifluoroborate salt **12**,[25] and subsequent treatment with $SiCl_4$ in 1,2-dichloroethane (DCE), followed by an azide furnished the C-tertiary amines **13** in very high e.r. (Table 4).[26] The process was also extended to the preparation of the substituted piperidine **15** in high e.r. (Scheme 9).

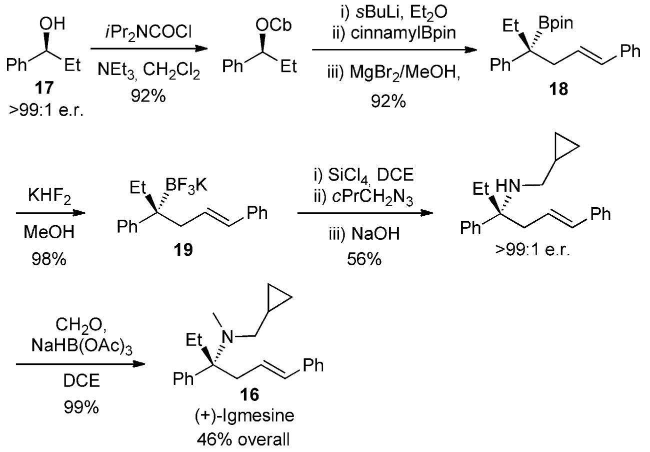
Table 4. Amination of tertiary boronic esters.





Scheme 9. Intramolecular amination of tertiary boronic ester towards piperidine **15**.

The synthetic utility of the amination methodology has been demonstrated in the stereocontrolled synthesis of the pharmaceutical igmesine **16**, a compound that shows significant activity across a spectrum of challenging disease areas, including depression, cancer and diarrhoea, but the absolute configuration of which had not yet been established (Scheme 10). Starting from the commercially available secondary alcohol **17**, carbamoylation followed by our standard lithiation/borylation protocol afforded the tertiary boronic ester **18**, which was easily converted to the potassium trifluoroborate salt **19** in excellent yield. Treatment with $SiCl_4$ followed by cyclopropylmethyl azide achieved amination without any erosion of the e.r. value. A final methylation gave (+)-igmesine **16** in 46 % overall yield, and enabled us to define the absolute stereochemistry as being *R*.



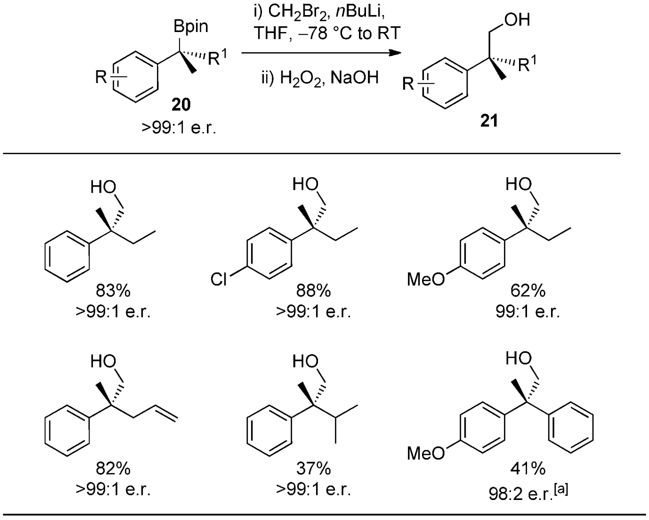
Scheme 10. Synthesis of (+)-igmesine **16**.

Homologations of Tertiary Boronic Esters to Generate Quaternary Stereocentres

Through further stereospecific homologation reactions, tertiary boronic esters can potentially be converted into quaternary centres.

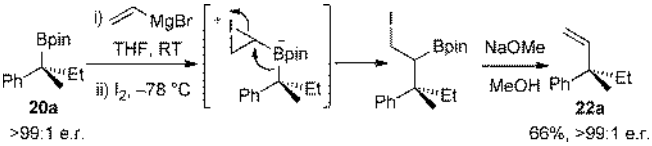
Matteson established an efficient homologation protocol for primary and secondary boronic esters using chloromethyllithium.[7f,27] We found that bromomethyllithium was superior to chloromethyllithium in the 1-carbon homologation of our tertiary boronic esters **20**. Following oxidative work up, alcohol **21** bearing a quaternary centre was obtained in excellent e.r. (Table 5).[28] Both electron rich and electron deficient aromatic substituents worked well, as did boronic esters bearing an allylic substituent. Unsurprisingly, a reduction in the yield was observed for boronic esters with a more sterically congested stereocentre, which slowed down attack by bromomethyllithium, resulting in competing decomposition pathways of the organolithium.

Table 5. Homologation of tertiary boronic esters with $LiCH_2Br$.



[a] Boronic ester substrate made in 98:2 e.r.

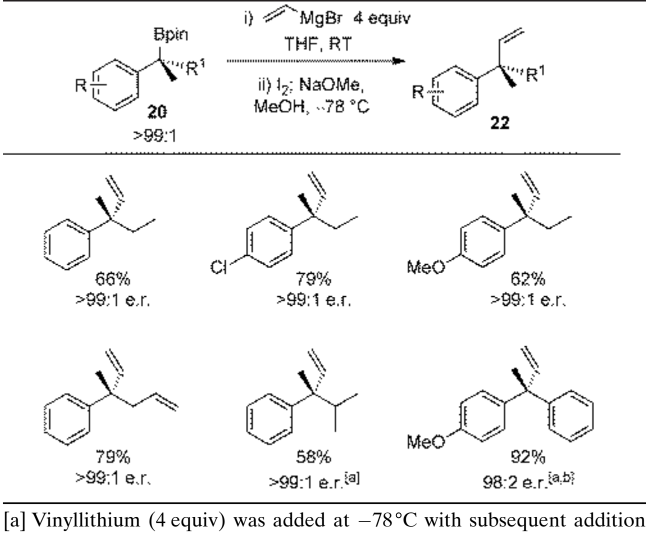
A quaternary centre bearing a vinyl group is a common structural motif in many natural products and is also a useful handle for further synthetic transformations. Application of Zweifel's olefination procedure[29] to our tertiary boronic esters **20** initially proved challenging but upon addition of an excess of vinylmagnesium bromide followed by treatment with iodine and NaOMe/MeOH the desired vinylated products **22** were obtained (Scheme 11).



Scheme 11. Mechanism of Zweifel-type olefination of tertiary boronic esters.

A range of tertiary boronic esters **20** were successfully transformed into vinylated products in high e.r. under these conditions (Table 6).[25] For more hindered substrates, such

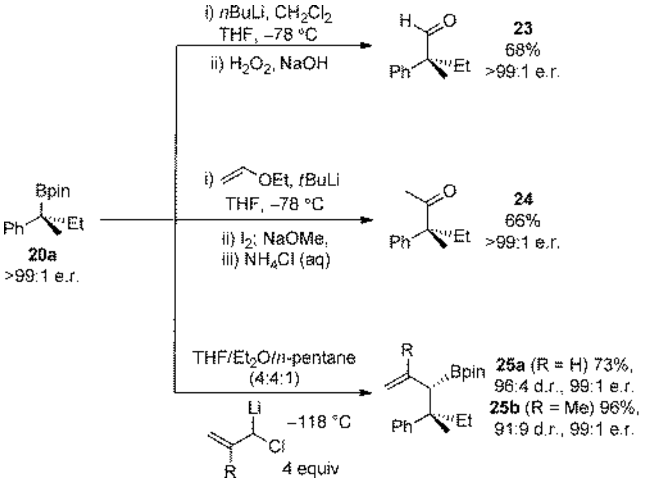
Table 6. Zweifel-type vinylation of tertiary boronic esters.



[a] Vinyllithium (4 equiv) was added at −78 °C with subsequent addition of I_2. [b] Boronic ester substrate was made in 98:2 e.r.

as diarylalkylboronic esters, the more reactive vinyllithium reagent furnished the products in improved yields.

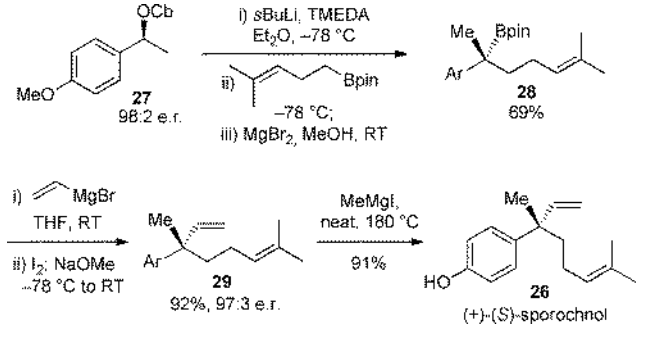
One-carbon homologations of tertiary boronic esters to give quaternary centres bearing aldehyde and ketone functional groups were also reported (Scheme 12).[25] For example, addition of dichloromethyllithium to the tertiary boronic ester **20a** formed the chiral aldehyde **23** after oxidative work up. Using 1-ethoxyvinyllithium, in a manner analogous to Zweifel olefination, afforded ketone **24** after work up with acid.



Scheme 12. Functional group transformations of boronic ester **20a**.

Reaction of 1-chloroallyllithium with tertiary boronic ester **20a** led to the homologated allylic boronic ester **25a** with surprisingly high diastereoselectivity (96:4) and complete stereospecificity (Scheme 12).[30] 1-Chloromethallyllithium also reacted efficiently and again with high diastereoselectivity. This represents a powerful method for the synthesis of chiral allylboronic esters bearing two contiguous stereocentres with high diastereocontrol.

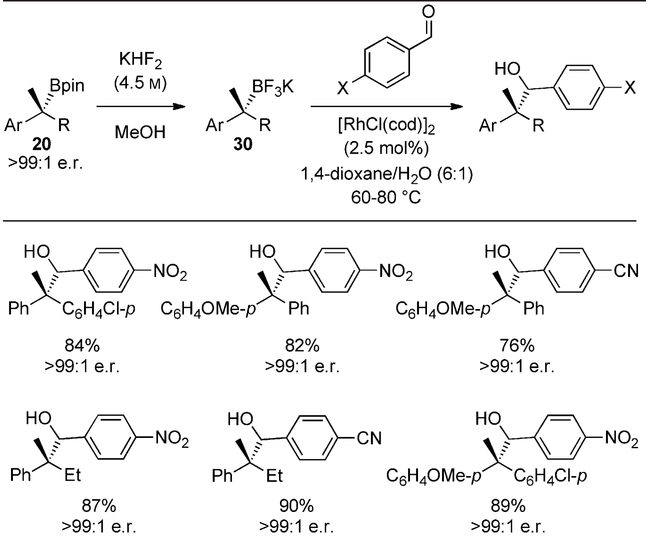
To illustrate the synthetic utility of the methodology, the total synthesis of the natural product, (+)-sporochnol **26**, was carried out (Scheme 13). The key steps involved 1) lithiation/borylation of the chiral secondary carbamate **27** to give the tertiary boronic ester **28**, followed by 2) our newly developed vinylation methodology to afford **29** with essentially complete chirality transfer. Final deprotection of the phenol furnished the target molecule **26**.



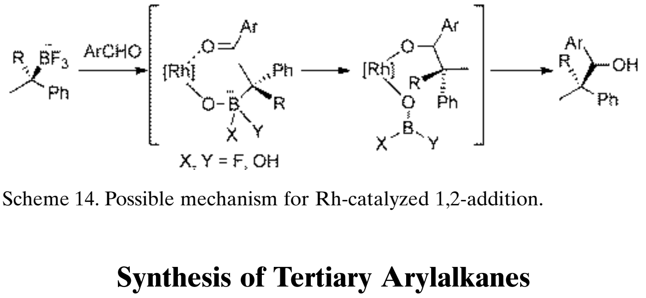
Scheme 13. Synthesis of (+)-sporochnol **26**.

Although boronic esters are electrophilic in nature, we have found that tertiary (and secondary) potassium trifluoroborate salts can act as nucleophiles and add to aldehydes in the presence of $[RhCl(cod)]_2$ catalyst with retention of configuration (Table 7). A range of diarylalkyl and dialkylaryl trifluoroborate salts **30** were successfully employed and high levels of enantiomeric excess (*ee*) were observed throughout.[31]

Table 7. Rhodium-catalyzed 1,2-addition of potassium trifluoroborate salts to aldehydes.



The reaction is believed to occur through a Lewis acid mediated process in which coordination of a hydroxyl-rhodium complex to both the boron derivative and aldehyde occurs prior to C–C bond formation (Scheme 14).

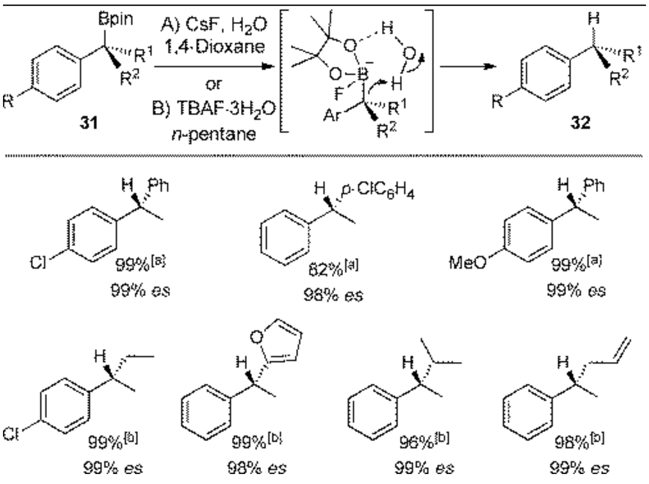


Scheme 14. Possible mechanism for Rh-catalyzed 1,2-addition.

Synthesis of Tertiary Arylalkanes

We recognized that if we could convert the C–B bond of our tertiary boronic esters into a C–H bond this would provide ready access to 1,1-diarylalkanes, which are privileged pharmacophores in medicinal chemistry but remain challenging to prepare.[32] The use of protic acids was not successful and so alternative reagents were explored. Fluoride-based reagents were found to be the most effective, presumably because of the very strong B−F bond providing a greater driving force for the reaction than carboxylic acids (forming a B−O bond). CsF facilitated protodeboronation of diarylalkylboronic esters, whereas the more reactive reagent, TBAF was effective for the protodeboronation of dialkylarylboronic esters.[33] A range of tertiary boronic esters **31** were successfully protodeboronated to afford tertiary arylalkanes **32** with essentially complete retention of stereochemistry, including electron-rich, electron-deficient and sterically hindered substrates (Table 8).

Table 8. Protodeboronation of tertiary boronic esters.

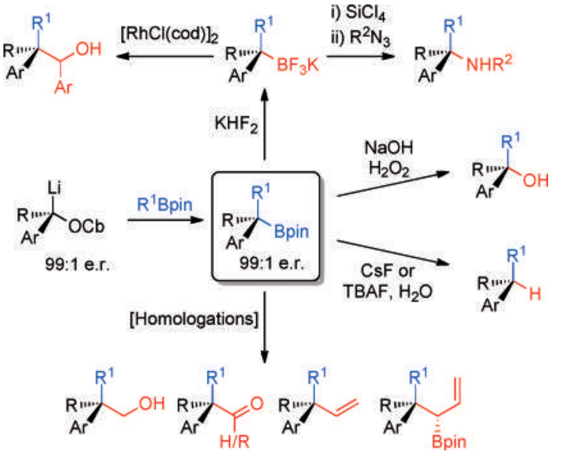


[a] Conditions A (CsF) used. [b] Conditions B (TBAF) used. *es* = enantiospecificity.

Summary and Outlook

We have developed a new method for the preparation of tertiary boronic esters with high enantioselectivity and broad substrate scope. Our protocol involves lithiation of a chiral secondary benzylic carbamate which subsequently reacts with a boronic ester with retention of configuration and, following stereospecific 1,2-metalate rearrangement, affords the tertiary boronic ester. The practicality of the chemistry is enhanced by the fact that methodology for the preparation of chiral secondary benzylic alcohols is very well established and indeed, this class of molecules is perhaps the simplest of chiral molecules to prepare (Scheme 15).

We have further developed a range of stereospecific transformations that can now be performed on these tertiary boronic esters. For example, tertiary alcohols can be prepared using a standard oxidation with basic hydrogen peroxide. In the case of amination, the tertiary boronic ester was first converted into the corresponding potassium trifluoroborate salt, which was subsequently treated with $SiCl_4$ and an azide to give the C-tertiary amine. We have developed a variety of homologation procedures, using both organolithium reagents and rhodium catalysis, to install a quaternary centre with a range of alpha functionality. In other work, we have also developed a highly effective procedure for the protodeboronation of tertiary boronic esters using CsF or TBAF with retention of configuration.[31] The synthetic utility and practicality of these transformations has been demonstrated in natural product synthesis. Further applications to even more complex targets will enable one to map out the scope and limitations of the methodology.



Scheme 15. Summary of functional group transformations with tertiary boronic esters.

Acknowledgements

V.K.A. thanks his co-workers for the hard work in developing this area of research, both practically and intellectually. Thanks to the EPSRC and the European Research Council (FP7/2007-2013, ERC grant no. 246785) for their generous research support.

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