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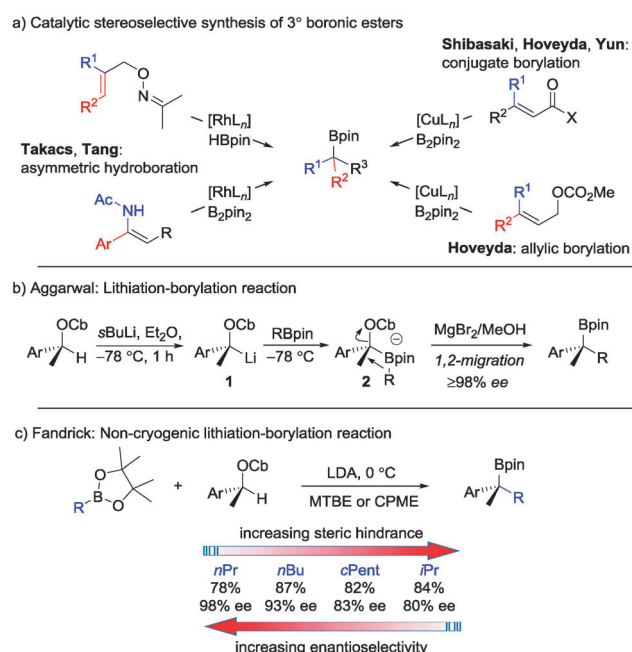
Hindered tertiary neopentyl glycol boronic esters can be prepared by using *in situ* lithiation–borylation of enantiopure secondary benzylic carbamates at $-20\text{ }^{\circ}\text{C}$ with full chirality transfer.

Boronic esters are versatile intermediates in synthesis and there are now numerous methods for their preparation in enantio-enriched form.¹ In the case of tertiary boronic esters, which are more difficult to prepare, a number of stereoselective and stereospecific methods have emerged over recent years (Scheme 1a (ref. 2) and Scheme 1b (ref. 3)). The stereospecific lithiation–borylation of enantiopure secondary carbamates (Scheme 1b), which has been developed in our research group,³ has been employed by others⁴ and indeed has even been scaled up to 24 kg.⁵ For this scale-up, the cryogenic conditions commonly employed (*s*BuLi, $-78\text{ }^{\circ}\text{C}$)⁶ presented challenges. However, Fandrick⁵ discovered that the carbamate could be deprotonated by a weaker base (LDA) and that this deprotonation could be conducted in the presence of pinacol boronic esters (*in situ* conditions) at elevated temperatures ($0\text{ }^{\circ}\text{C}$), to give the corresponding tertiary boronic esters with high levels of enantiospecificity (Scheme 1c). At such an elevated temperature, having the boronic ester present in the reaction mixture during the deprotonation prevents epimerisation and/or decomposition of lithiated carbamate **1**.

With more hindered secondary boronic esters, such as *i*PrBpin, lower levels of enantiospecificity were observed, presumably due to reversible formation of boronate complex **2**. Such a process would return the sensitive lithiated carbamate **1**, which would undergo racemisation and recombination with the boronic ester, thus leading to reduced stereoselectivity $\sim 80\%$ es (Scheme 1b). We have previously found that the addition of MgBr₂/methanol following boronate complex formation enhances the rate of 1,2-migration and quenches any lithiated carbamate generated

Full chirality transfer in the synthesis of hindered tertiary boronic esters under *in situ* lithiation–borylation conditions†

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Scheme 1 State of the art: synthesis of tertiary boronic esters.

by the reverse process thereby leading to high yields and high stereoselectivity.^{3a} Unfortunately, the addition of MgBr₂ in methanol is not compatible with an *in situ* lithiation–borylation reaction. Herein, we address the issue of low selectivity with hindered boronic esters and show that by using neopentyl glycol boronic esters⁷ and LTMP (lithium 2,2,6,6-tetramethylpiperidine) as a base, high levels of enantiospecificity can now be achieved even with some of the most hindered boronic esters under non-cryogenic conditions.

During our investigations of lithiation–borylation methodology we found that the nature of the ligand on boron sometimes affected the enantioselectivity of the process.^{3b,8} This is most dramatically illustrated in the case of the propargylic carbamate **3** where upon moving from the pinacol to the ethylene glycol based isopropyl boronic ester, enantiospecificity increased

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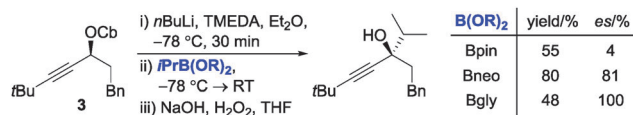
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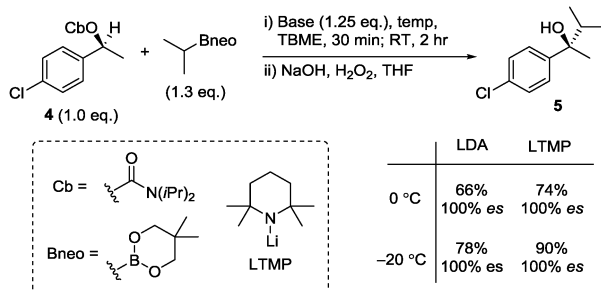


Scheme 2 Influence of the boron ligand on the stereochemical outcome of the lithiation–borylation of **3**; these results are taken from ref. 8a and are shown for comparison to results below (see Scheme 7).

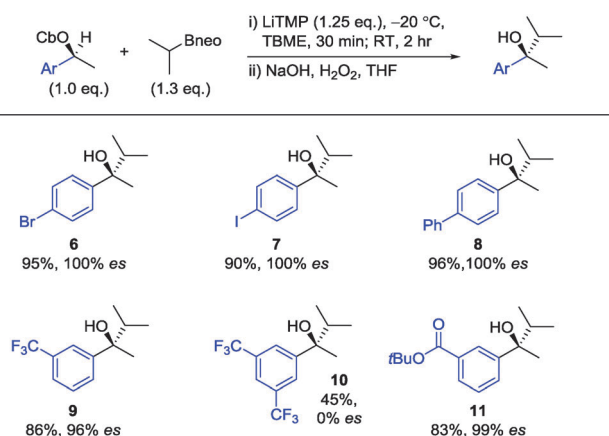
from 4% to 100% (Scheme 2).^{8a} Presumably, as the steric hindrance around boron was reduced, the boronate complex became less prone to reversibility and consequently the intermediate lithiated carbamate suffered less racemisation.

We therefore explored Fandrick's *in situ* conditions⁵ with iPrBneo in place of iPrBpin. These conditions gave tertiary alcohol **5** from **4** with full stereospecificity (100% es, Scheme 3), a substantial improvement on that obtained using the pinacol boronate (80% es).⁵ Other bases were tested and LTMP led to a higher yield (74%). Further improvement in the yield was realised by reducing the temperature from 0 °C to –20 °C, resulting in **5** being isolated in 90% yield and 100% es.

Our optimised conditions were applied to a range of otherwise challenging carbamates (Scheme 4). As noted by Fandrick, the *in situ* conditions involving an amide base in place of an organolithium base enables aryl bromides and iodides to be employed, and so these were initially tested. Using our conditions, these substrates gave the corresponding tertiary alcohols **6** and **7** in high yields and



Scheme 3 Conditions for the homologation of neopentyl glycol boronic esters.



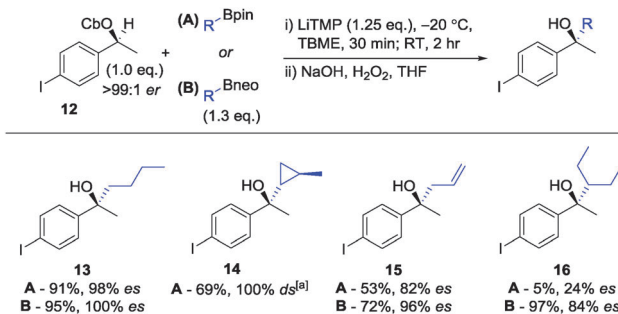
Scheme 4 Carbamate scope for the *in situ* lithiation–borylation of iPrBneo.

complete enantiospecificity. The *para*-phenyl-substituted carbamate is especially prone to racemisation and using iPrBpin gave **8** in low enantiospecificity (83% es). However, using the neopentyl glycol boronic ester, **8** was again obtained in high yield and enantiospecificity. Electron-withdrawing groups on the aromatic ring engenders reversibility in the formation of the boronate complex, thus rendering the lithiated carbamate more prone to racemisation. We found that although a single *meta*-CF₃ group was tolerated, enabling formation of **9** with excellent enantiospecificity, two *meta*-CF₃ groups was a step too far and led to essentially racemic product (**10**).⁹ A hindered ester was compatible with our conditions and gave tertiary alcohol **11** with complete enantiospecificity. This functional group would not have been compatible with the preformed lithiated carbamate. Unfortunately, the use of *ortho*-substituted benzylic carbamates did not lead to the expected products. In contrast, we have previously shown these carbamates do give the expected products in good yield and near-complete enantiospecificity when subjected to our cryogenic lithiation–borylation conditions.^{3a,10}

Because the stereoselectivity of the *in situ* lithiation–borylation reaction is affected by the steric bulk of the boronic ester substituent (R group), we tested a range of boronic esters of varying steric demand and compared both the pinacol (**A**) and neopentyl glycol (**B**) derivatives (Scheme 5). For unhindered *n*Bu (**13**) and cyclopropyl (**14**) boronic esters high enantiospecificity was observed by using pinacol boronic esters (98% es), with neopentyl glycol boronic esters behaving similarly. Surprisingly, with unhindered allyl boronic esters (**15**) the pinacol derivative gave low es (82%) whilst the neopentyl glycol ester provided essentially complete enantiospecificity.

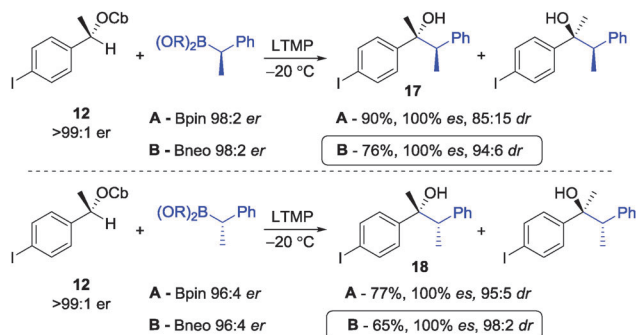
To explore the limits in steric bulk that could be tolerated we turned to 3-pentyl boronic esters.¹¹ Reaction of 3-pentyl-Bpin with **12** under our *in situ* conditions gave only traces of **16** with poor enantioselectivity. Simply switching to the corresponding neopentyl glycol ester significantly increased both the yield and selectivity, thus highlighting the advantages associated with neopentyl glycol derivatives, particularly in their application to hindered systems.

We have previously shown that secondary benzylic pinacol boronic esters form reversible boronate complexes with secondary benzylic carbamates leading to loss of both diastereo- and enantioselectivity.^{8c} The application of *in situ* conditions to the reaction of (*R*)-1-phenylethyl pinacol boronic ester with **12** gave **17** in high yield (90%, Scheme 6), high enantiospecificity (100% es) with respect to



Scheme 5 Influence of boronic ester substituent on the *in situ* lithiation–borylation reaction of **12**.⁹ Because the use of the pinacol boronic ester gave tertiary alcohol **14** with complete diastereospecificity, the corresponding experiment with the neopentyl glycol boronic ester was not carried out.



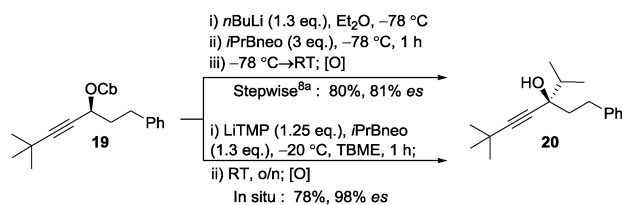


Scheme 6 The influence of boronic ester diol on the stereochemical outcome of homologation of (*R*)- and (*S*)-1-phenylethyl boronic esters with **12** under *in situ* conditions using pinacol (**A**) and neopentyl glycol (**B**) boronic esters.

the boronic ester starting material, but low diastereoselectivity (85:15 dr).¹² Simply switching to the corresponding neopentyl glycol boronic ester gave **17** in 94:6 dr, 100% es and high yield. In contrast, reaction of **12** with both pinacol and neopentyl glycol (*S*)-1-phenylethyl boronic esters gave **18** in high yield and selectivity ($\geq 95:5$ dr, 100% es).¹³ Evidently, there is a significant matched/mis-matched effect operating under the reversible conditions with the pinacol boronic esters that can be minimised by using the neopentyl glycol boronic esters.

As noted above, for substrates that are especially prone to reversibility in boronate formation and therefore racemisation (e.g. **8**), the *in situ* conditions using neopentyl glycol boronic esters can lead to considerably higher levels of enantiospecificity. We therefore tested our *in situ* conditions with the secondary propargylic carbamate **19**, a substrate that only gave 81% es under conditions where the lithiated carbamate was preformed^{8a} (Scheme 7). Under the new *in situ* conditions the tertiary propargylic alcohol **20** was obtained in high yield and excellent enantiospecificity (98% es).¹⁴ This highlights the broad applicability of the new *in situ* lithiation–borylation protocol.¹⁵

In summary, we have found that almost complete enantioselectivity can be achieved in the lithiation–borylation reactions of secondary benzylic carbamates under *in situ* conditions when neopentyl glycol boronic esters are used in place of pinacol boronic esters. These conditions expand the range of tertiary boronic esters that can be prepared with very high selectivity with both increased functional-group and steric tolerance. The improved stereoselectivity results from reduced reversibility in boronate complex formation, a process that otherwise causes racemisation of the sensitive lithiated carbamate.



Scheme 7 Enhanced stereospecificity using *in situ* conditions in the lithiation–borylation reaction of secondary propargylic carbamates.

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- 9 Reducing the steric bulk of the boronic ester reaction partner from *i*Pr to Et had no effect on the stereochemical outcome.
- 10 The *ortho*-bromo isomer of **6** and an *ortho*-methyl substrate (not depicted), did not lead to the expected products. The former substrate did not react whereas the latter gave a mixture of isomeric species derived from its fragmentation into the corresponding *ortho*-quinodimethane followed by (4+2) cycloaddition. See the ESI,† for further details on this side reaction.
- 11 *t*Bu boronic esters were also tested but both pinacol and neopentyl glycol esters failed to react under the *in situ* conditions.
- 12 Enantiospecificity was determined for the major diastereoisomer.
- 13 No epimerisation of the secondary boronic ester stereocentre was observed in either **17** or **18** with pinacol or neopentyl glycol esters. The presence of an electron-withdrawing group in **12** must bias the corresponding boronate complex towards fragmentation to Li-**12** rather than fragmentation of the C–B bond of the secondary boronic ester substrate to form a benzylic anion.
- 14 For the propargylic carbamates, unfortunately the use of a trialkylsilyl substituent in place of a *t*-butyl group led to desilylated products not incorporating the boronic ester organic group.
- 15 We have previously shown that when substituted allylic carbamates are subjected to lithiation–borylation reactions under cryogenic conditions with neopentyl glycol boronic esters as partners, a mixture of products derived from α - and γ -borylation are obtained: (a) A. P. Pulis, PhD thesis, University of Bristol, 2012. However, the use of pinacol boronic esters lead to predominantly the required α -borylation: (b) A. P. Pulis and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2012, **134**, 7570.

