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Asymmetric Synthesis of 1-Heteroaryl-1-arylalkyl Tertiary Alcohols and 1-Pyridyl-1-arylethanes by Lithiation–Borylation Methodology

Charlotte G. Watson and Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.

V.Aggarwal@bristol.ac.uk

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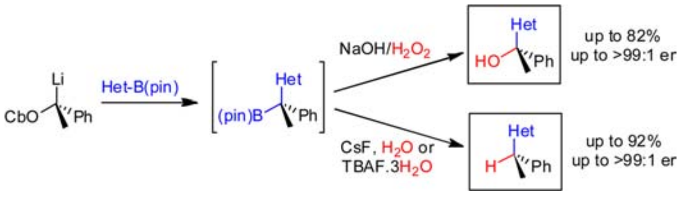
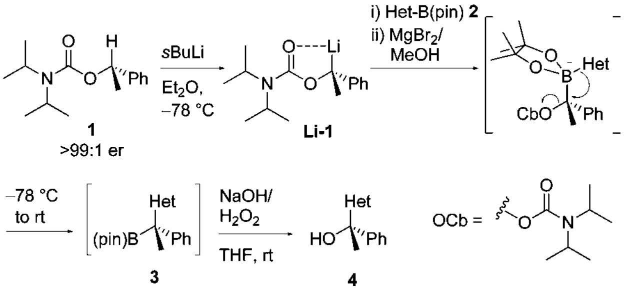
ABSTRACT



The synthesis of highly enantioenriched α-heterocyclic tertiary alcohols has been achieved *via* lithiation–borylation of a configurationally stable lithiated carbamate and heterocyclic pinacol boronic esters followed by oxidation. Protodeboronation of the α-heterocyclic tertiary boronic esters using TBAF·3H$_2$O or CsF gave highly enantioenriched 1-pyridyl-1-arylethanes in high er.

There are a number of methods available for the synthesis of highly enantioenriched tertiary alcohols, most of them involving addition of an organometallic reagent to a ketone catalyzed by a chiral metal/ligand complex.[1–5] However, this method is scarcely reported for pyridyl ketones, which may be due to intrinsic problems of competing coordination of the heteroatom to the metal complex, or to other unwanted side reactions.[6] Due to the prevalence of heterocyclic tertiary alcohols in bioactive molecules,[7] we have sought to address this issue by application of our lithiation–borylation methodology, which provides an alternative route to highly enantioenriched

Scheme 1. Proposed Lithiation–Borylation Route to Heterocyclic Tertiary Alcohols



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10.1021/ol400289v

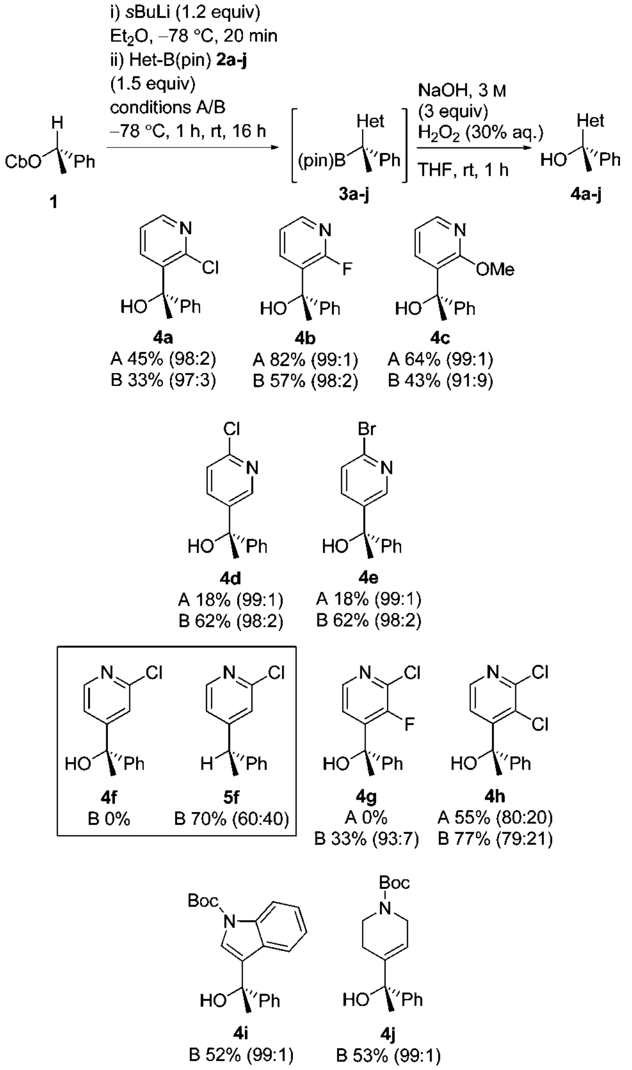
tertiary alcohols.[8] In this process, a benzylic carbamate derived from an enantioenriched secondary alcohol is deprotonated[9] and reacted with a boronic ester to give an intermediate boronate complex; subsequent stereospecific 1,2-metalate rearrangement and oxidation thereafter lead to highly enantioenriched tertiary alcohols (Scheme 1). Herein we report the application of this methodology to the synthesis of α-heterocyclic tertiary alcohols.

We began our studies by preparation of the required starting materials; the enantioenriched carbamate **1** was synthesized by enzymatic resolution of racemic phenylethanol[10] followed by carbamoylation with *N,N*-diisopropylcarbamoyl chloride, giving the carbamate **1** in >99:1 er. The boronic esters were synthesized by condensation of the appropriate boronic acid with pinacol.

Initial attempts to homologate 3-pyridyl pinacol boronic ester proved unsuccessful, which we attributed to its poor solubility in compatible reaction solvents (Et_2O, toluene, hexane, TBME). However, we found that the inclusion of a halogen substituent on the pyridyl ring greatly aided solubility. We subjected boronic ester **2a** to lithiation–borylation using $MgBr_2$/MeOH as an additive to enhance er (method A). Pleasingly, the tertiary boronic ester **3a** was formed in 50% yield (Scheme 2). Subsequent oxidation of **3a** with NaOH/H_2O_2 gave the desired tertiary alcohol **4a** in 76% yield and 98:2 er. When this was carried out without isolation of the intermediate tertiary boronic ester, **4a** was isolated in 45% yield and 98:2 er.

Encouraged by this result, we sought to establish the scope of the lithiation–borylation method using a range of commercially available heterocyclic boronic acids[11] from which we could synthesize the corresponding boronic esters. Continuing the investigation of *ortho*-substituted boronic esters, we utilized the 2-fluoro- and 2-methoxy-substituted pyridyl boronic esters **2b** and **2c** and isolated the tertiary boronic esters **3b** and **3c** in excellent yield. Oxidation of both tertiary boronic esters **3b** and **3c** gave the corresponding tertiary alcohols **4b** and **4c** in high yield and enantiomeric ratio. The additional *ortho*-substituents on the pyridyl ring appear to be well tolerated without detriment to the yield or enantioselectivity of the lithiation–borylation.

Scheme 2. Scope of the Lithiation–Borylation Methodology[a]



[a] Conditions A: **2** added to **Li-1** as a 1 M Et_2O or 0.5 M PhMe solution, subsequent addition of $MgBr_2$/MeOH prior to warming to rt. B: **2** added to **Li-1** as a 1 M Et_2O or 0.5 M PhMe solution (*no* $MgBr_2$/MeOH).

Having established that the lithiation–borylation reaction could be applied to pyridyl boronic esters, we explored reaction conditions with and without $MgBr_2$/MeOH (conditions A and B respectively). In the case of 2-substituted-3-boryl pyridines (**4a**–**c**), a higher er and yield were achieved with the use of $MgBr_2$/MeOH (conditions A), especially in the case of **4c**. This reflects an element of reversibility in the ate complex formation, arising from the increased steric hindrance of the *ortho*-substituted boronic esters. Upon warming the reaction to room temperature, the lithiated carbamate so generated becomes configurationally labile and begins to racemize, and subsequent recombination leads to the tertiary boronic ester with a reduced er (Scheme 3). In the presence of $MgBr_2$/MeOH, the extent of reversibility is reduced relative to 1,2-migration, and any lithiated carbamate that is released is immediately trapped by MeOH, leading to an increased er.

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(6) For a rare example of asymmetric addition to pyridyl ketones using alkyl Grignards, see: (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117. For examples of asymmetric additions to furyl and thiophene ketones with organoaluminium and organzinc nucleophiles respectively, see: (b) Biradar, D. B.; Zhou, S.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 3386. (c) Hatano, M.; Mizuno, T.; Ishihara, K. *Tetrahedron* **2011**, *67*, 4417.

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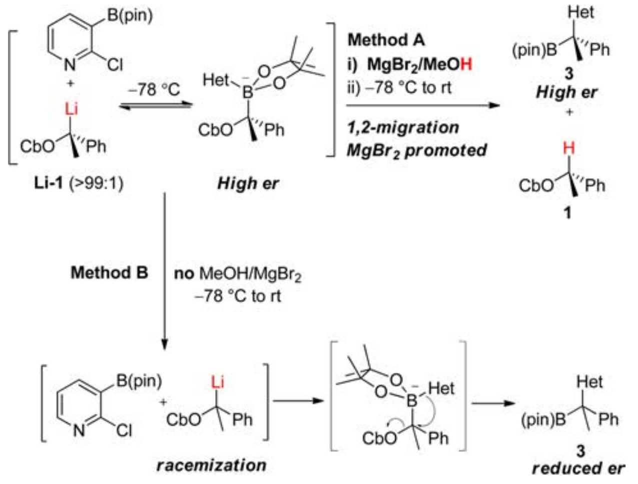
(10) Ou, L.; Xu, Y.; Ludwig, D.; Pan, J.; He, Xu, J. *Org. Process Res. Dev.* **2008**, *12*, 192.

(11) Boronic acids were obtained from Inochem-Frontier.

Indeed, these conditions give the highest possible er in the lithiation–borylation since they are kinetically controlled.

Scheme 3. Beneficial Effect of $MgBr_2$/MeOH upon Lithiation–Borylation with Sterically Demanding Substrates

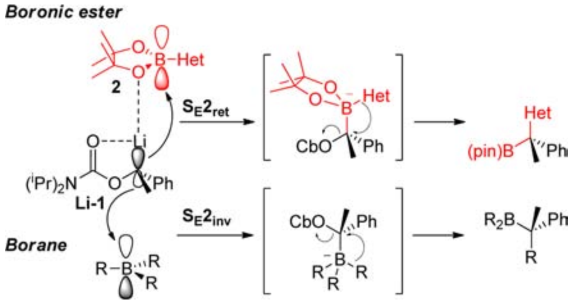


Moving to 2-halo-5-pyridyl boronic esters (**4d**/**4e**) resulted in a dramatic decrease in yield due to competing protodeboronation of the intermediate tertiary boronic esters using $MgBr_2$/MeOH (method A). We therefore explored alternative conditions and found that using a PhMe/Et_2O solvent system *without* the use of $MgBr_2$/MeOH (Method B) led to increased yields of the tertiary alcohols without detriment to the er.

4-Pyridyl boronic esters could also be used but were less successful, giving either low yields or enantioselectivities for **4f**–**4h**. In the case of **4f** using method B, only the *protodeboronated* product **5f** was isolated (with very low enantioenrichment). The low yield of **4g** can also be attributed to the propensity of the tertiary boronic ester to protodeboronate. In fact, when method A was used, protodeboronation was so extensive that none of the desired alcohol could be isolated, and using method B resulted in a low yield of **4g**. However, the tertiary alcohol **4h** was isolated in good yield using method A and excellent yield using method B. The low enantioselectivity observed for **4h** even with the addition of $MgBr_2$/MeOH was a surprise. In fact this is the first and only example where essentially complete retention of stereochemistry in the trapping of the lithiated carbamate by a boronic ester is not obsereved. This may be due to the reduced ability of the boronic ester to coordinate to lithium due to the strong electron-withdrawing groups on the heteroaromatic ring, since, in the absence of coordination (e.g., with boranes), the reaction occurs with complete inversion of stereochemistry (Scheme 4).

The absolute stereochemistry of the tertiary boronic ester **3a** was determined by X-ray crystallography and showed that the lithiation–borylation reaction had occurred with the expected retention of stereochemistry (Figure 1).

Scheme 4. Effect of Precomplexation upon Electrophilic Attack of an Organoborane upon **Li-1**



Other classes of heterocycles were used successfully. The indole boronic ester **2i** and dehydropiperidine boronic ester **2j** led to the successful isolation of the corresponding tertiary alcohols **4i** and **4j** in good yield and very high er.

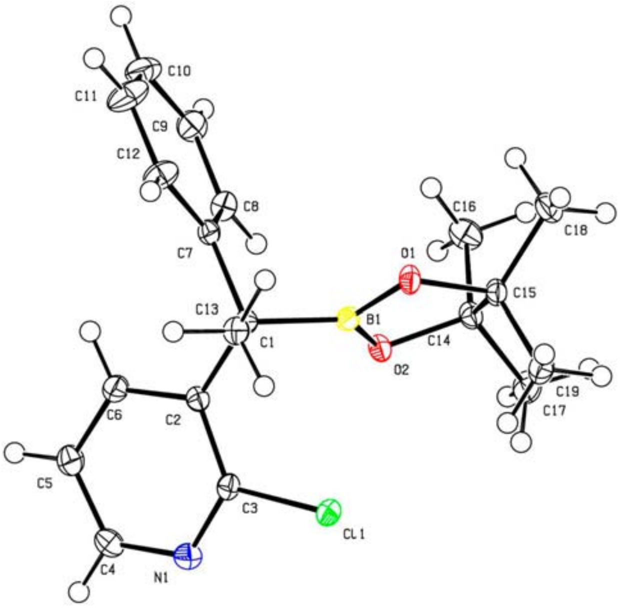
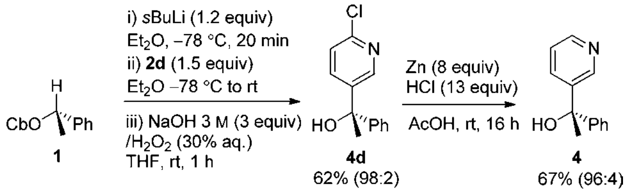


Figure 1. X-ray structure of **3a**. Thermal ellipsoids are drawn at the 50% probability level.

Although unsubstituted pyridyl boronic esters could not be employed in this process, due to their poor solubility, tertiary alcohol **4** could nevertheless be accessed indirectly, following reductive removal of the halogen substituent from the tertiary alcohol **4d** after lithiation–borylation and oxidation, giving tertiary alcohol **4** in 67% yield (Scheme 5).

Following our success at lithiation–borylation with these substrates, we briefly investigated the application of protodeboronation in this context. Since 1,1-diarylalkanes are privileged pharmacophores in medicinal chemistry,[12,13] we were keen to examine whether the heterocyclic analogues could be prepared by protodeboronation of the intermediate tertiary boronic esters. We previously reported two sets

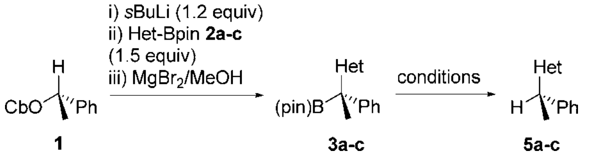
Scheme 5. Preparation of Tertiary Alcohol **4d**

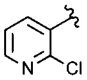
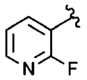
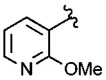


of conditions for the protodeboronation of tertiary boronic esters: CsF/H$_2$O for diarylalkyl boronic esters and TBAF·3H$_2$O for aryldialkyl boronic esters.[14] We initially tested the former conditions and found that the boronic ester **3b** underwent clean and rapid protodeboronation with complete retention of stereochemistry (Table 1, entry 2). However, the protodeboronation of tertiary boronic esters **3a** and **3c** (entries 1 and 3) were found to be very slow with CsF. Application of TBAF·3H$_2$O greatly reduced reaction times and led to the aryl-heteroaryl-alkyl methines **5a** and **5c** in high er.

In conclusion, we have successfully extended our lithiation–borylation methodology to encompass a range of heterocyclic boronic esters. From easily accessible starting materials, we have synthesized several α-heterocyclic tertiary alcohols in good-to-excellent yield with excellent enantioselectivity. However, depending on the nature of the heterocycle, some intermediate tertiary boronic esters are prone to protodeboronation and so can lead to reduced yields. In addition, we have combined the lithiation–borylation methodology with our previously developed protodeboronation conditions to synthesize highly enantioenriched 1-pyridyl-1-arylethanes.

Table 1. Protodeboronation of Tertiary Boronic Esters **3a**−**c**



entry	Het	yield **3**	conditions	yield **5** (er)
1		**3a** 50	TBAF[a]	**5a** 92 (94:6)
2		**3b** 78	CsF[b]	**5b** 92 (>99:1)
3		**3c** 85	TBAF[c]	**5c** 88 (99:1)

[a] TBAF·3H$_2$O (1.5 equiv), toluene, −20 °C to rt, 2 h. [b] CsF (1.5 equiv), H$_2$O (1.1 equiv), dioxane, rt, 2 h. [c] TBAF·3H$_2$O (1.5 equiv), toluene, rt, 30 min.

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Supporting Information Available. Experimental procedures, characterization data, NMR spectra, and CIF of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.