Enantioselective Synthesis

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Synthesis of Highly Enantioenriched C-Tertiary Amines From Boronic Esters: Application to the Synthesis of Igmesine**

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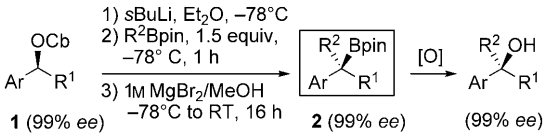
Tertiary alkylamines are common motifs in many natural products and pharmaceuticals but access to them in enantiomerically enriched form can sometimes present a major challenge. A standard route to these compounds involves the addition of nucleophiles, for example, organometallic reagents[1] or cyanide[2] to ketimines, but other indirect methods have also been reported.[3] Whilst many of these methods have been successful in delivering high levels of stereocontrol, the level of selectivity is highly substrate-dependent.

We recently reported a conceptually new method for the synthesis of tertiary alcohols that routinely delivered more than 98% *ee* over a broad range of substrates (Scheme 1).[4] In



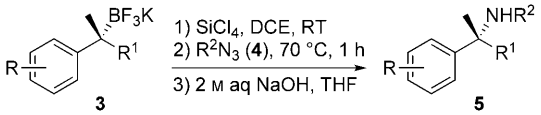
1 (99% *ee*) **2** (99% *ee*) (99% *ee*)

Scheme 1. Synthesis of highly enantioenriched tertiary boronic esters and tertiary alcohols. Cb = C(O)N*i*Pr$_2$.

this process, lithiation of secondary carbamates **1** followed by treatment with boronic esters and subsequent addition of $MgBr_2$/MeOH gave the tertiary boronic esters **2**, which were finally oxidized to tertiary alcohols in high *ee*. We reasoned that isolation of the intermediate tertiary boronic esters and subsequent amination could provide a new route to C-tertiary alkylamines in high *ee*. Whilst amination of primary and even secondary boronic esters had been reported,[5–7] the much more challenging tertiary boronic esters had not. We therefore embarked on this study and now report that C-tertiary alkylamines can indeed be obtained in more than 98% *ee* using this methodology.

Of the reported amination transformations, Matteson's direct conversion of a potassium trifluoroborate salt into an amine[7] turned out to be the most efficient and reliable,[8] and after some modification of the reaction conditions[9] this protocol was ultimately successful. Thus, a broad range of tertiary boronic esters were first converted into the corresponding trifluoroborates **3** and then treated with $SiCl_4$ and an alkyl azide (Table 1). Using this protocol with benzyl azide

Table 1: Amination of tertiary potassium trifluoroborates with alkyl azides.[a]



3 **5**

Entry	**3**[b]	R	R^1	**4**	R^2	**5**	Yield [%] (*ee* [%])[c]
1	**a**	H	Et	**a**	Bn	**aa**	94 (99)
2	**a**	H	Et	**b**	PMB	**ab**	73 (99)
3	**a**	H	Et	**c**	*c*PrCH$_2$	**ac**	89 (99)
4	**b**	H	*c*Hex	**a**	Bn	**ba**	78 (99)
5	**c**	4-Cl	*i*Pr	**a**	Bn	**ca**	76 (99)
6	**d**	2-F	*c*Hex	**a**	Bn	**da**	47 (99)
7	**e**	H	4-ClC$_6$H$_4$	**a**	Bn	**ea**	74 (99)
8	**f**	H	3-MeOC$_6$H$_4$	**a**	Bn	**fa**	69 (99)

[a] Bn = benzyl, DCE = 1,2-dichloroethane, PMB = *para*-methoxybenzyl. [b] The *ee*'s of all trifluoroborates **3a**–**f** were 99%. [c] Yields of isolated product are given; *ee*-values of amines **5** were determined by chiral HPLC following derivatization as their trifluoroacetamides (see Supporting Information for details).

4a, the tertiary trifluoroborate **3a** was converted into the tertiary benzylamine **5aa** in 94% yield and 99% *ee* (entry 1). The methodology could be extended to other substituted benzylic and alkyl azides (entries 2, 3). In terms of the scope of the tertiary trifluoroborate, hindered alkyl groups (*i*Pr, *c*Hex; entries 4–6) and even diarylalkyl trifluoroborates (entries 7, 8) could all be employed, leading to C-tertiary alkyl amines with very high *ee*. The latter two examples are noteworthy as the diarylalkyl boron intermediates are especially prone to homolysis and radical recombination but no erosion in *ee* was observed.

Some limitations of the methodology however, were uncovered. For example, the homoallylic trifluoroborate salt **6** only gave the tertiary amine **7** in 14% yield together with ketone **8** in 75% yield (Scheme 2, see Supporting Information for a mechanistic discussion on the origin of **8**).

The *para*-methoxy analogue of the trifluoroborate **3f** was also ineffective. Since both the *meta*-methoxy substrate **3f** and the *para*-methoxybenzylic secondary trifluoroborate salt[10] worked well, it showed that this limitation was specific to the tertiary, electron-rich diaryl trifluoroborate salt.

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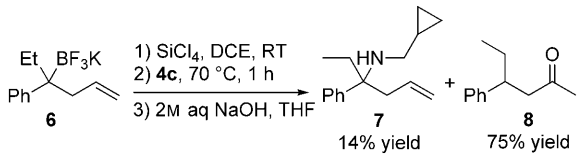
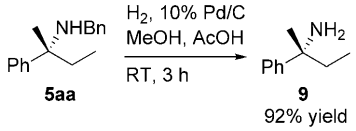


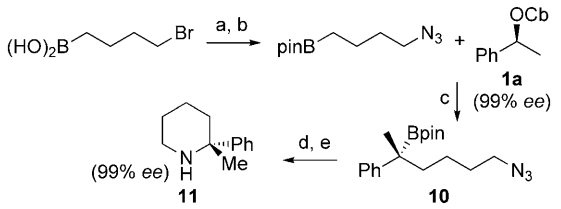
Scheme 2. Unexpected formation of methylketone side-product **8** during attempted amination of homoallylic trifluoroborate **6**.

In a representative example we have shown that the C-tertiary secondary alkylamines can be selectively debenzylated to give the C-tertiary primary alkylamines by catalytic hydrogenolysis (Scheme 3).[11]



Scheme 3. Representative example for the selective deprotection of C-tertiary benzylamines.

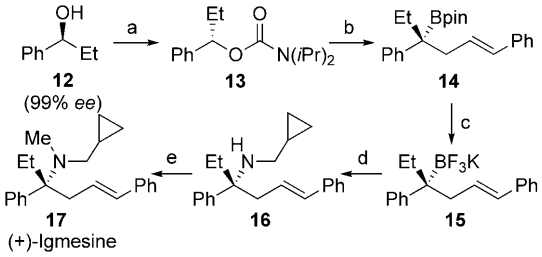
In order to broaden the scope of the methodology we have considered its application towards cyclic substrates particularly since certain 2,2-disubstituted piperidines (e.g. **11**) have emerged as promising neurokinin 1 (NK_1) antagonists that possesses unique antidepressant, anxiolytic, and antiemetic properties.[12] We were therefore keen to explore the potential of our methodology to target this important class of compounds (Scheme 4). The key steps involved lithiation of



Scheme 4. Synthesis of (+)-piperidine **11**. Reagents and conditions: a) pinacol, $MgSO_4$, Et_2O, RT, 97%; b) nBu_4NBr, NaN_3, H_2O/EtOAc, 80°C, 16 h, 96%; c) *sec*-butyllithium (1.1 equiv), −78°C, 20 min; then $N_3(CH_2)_4BPin$ (1.2 equiv), −78°C, 1 h; then 1 M $MgBr_2$ in MeOH (1.2 equiv), −78°C, 10 min, then RT, 16 h; then 1 M aq KH_2PO_4, 74%; d) 4.5 M aq KHF_2 (2.5 equiv), MeOH, RT, 30 min, evaporation; then 60% aq MeOH, 10 min and evaporation (9×), 95%; e) $SiCl_4$, (1.5 equiv), DCE, RT, 1 h; 80°C, 1 h; then 2 M aq NaOH, RT, 1 h, 53%.

carbamate **1a** followed by borylation with the required boronic ester which gave the tertiary boronic ester **10** in 74% yield and 99% *ee*. Subsequent conversion to the trifluoroborate salt followed by treatment with $SiCl_4$ (second key step) gave piperidine **11** in 53% yield and 99% *ee*.

Finally, we considered the application of this methodology to a stereocontrolled synthesis of the pharmaceutical igmesine (**17**),[13] a compound which shows significant activity across a spectrum of challenging disease areas including depression,[14] cancer,[15] and diarrhoea.[16] The activity of this pharmaceutical resides in the (+)-enantiomer but the absolute configuration had not been established, thus providing further impetus for the need for its stereocontrolled synthesis.[13] However, such a target posed some potential difficulties because it would involve a homoallylic trifluoroborate salt—a motif that was found to be somewhat problematic in the amination step. Nevertheless, we reasoned that the additional substitution might retard the unwanted [3+2] cycloaddition and give a higher yield of the desired amination product. We therefore embarked on the synthesis, although with some trepidation. Starting from the commercially available secondary alcohol **12**, following carbamate formation **13** the key lithiation–borylation reaction under the optimized conditions[4a] furnished the tertiary boronic ester **14** in 92% yield and with perfect enantioselectivity (Scheme 5).



Scheme 5. Synthesis of (+)-igmesine. Reagents and conditions: a) iPr_2NCOCl (1.05 equiv), NEt_3 (1.1 equiv), CH_2Cl_2, reflux, 24 h, 92%; b) *sec*-butyllithium (1.1 equiv), −78°C, 20 min; then cinnamyl boronic acid pinacol ester (1.2 equiv), −78°C, 1 h; then 1 M $MgBr_2$ in MeOH (1.2 equiv), −78°C, 10 min, then RT, 16 h; then 1 M aq KH_2PO_4, 92%; c) 4.5 M aq KHF_2 (2.5 equiv), MeOH, RT, 30 min, evaporation; then 50% aq MeOH, 10 min and evaporation (5×), 98%; d) $SiCl_4$, (2 equiv), DCE, RT, 1 h; *c*$PrCH_2N_3$ (2 equiv), 80°C, 30 min; then 2 M aq NaOH, RT, 1 h, 56%; e) 37% aq CH_2O, $NaHB(OAc)_3$, DCE, RT, 16 h, 99%.[18]

Subsequent conversion to the trifluoroborate salt **15** followed by amination with cyclopropyl azide (**4c**) gave the C-tertiary secondary amine **16** in 56% yield, again without erosion of enantioselectivity. This showed that the limitation in scope highlighted above applied to the parent homoallylic substrate **6** but not necessarily to other substituted homoallylic groups. Finally, methylation gave (+)-igmesine (**17**) in an overall yield of 46% and a total of just five synthetic steps starting from commercially available alcohol **12**. The modular nature, high levels of stereocontrol, and brevity are noteworthy features of the synthesis. Finally, as the optical rotation of **17**·HCl ($[\alpha]_D^{23}$ +45.7) matched the optical rotation of the active enantiomer ($[\alpha]_D^{25}$ +49.7),[17] our stereoselective synthesis enables us to establish the absolute configuration of (+)-igmesine as being *R*.

In summary, we have shown that tertiary boronic esters, readily available in high *ee* using the lithiation–borylation reaction, can be converted into tertiary alkylamines including 2,2-disubstituted piperidines with very high *ee*. Such com-

pounds are not easily accessible in high *ee* by alternative methods and the synthetic utility of the methodology has been demonstrated in the synthesis and determination of absolute configuration of the pharmaceutical igmesine.

Experimental Section

General procedure for the aminations of tertiary potassium trifluoroborates with alkylazides. $SiCl_4$ (189 mg, 1.10–2.00 mmol) was added to a stirred suspension of trifluoroborate salt **3a–f** (1.00 mmol) in anhydrous 1,2-dichloroethane (2 mL) under a slightly positive pressure of argon, and the reaction mixture was stirred at ambient temperature for 0.5–2 h. Then, the respective azide **4a–c** (1.20–2.00 mmol) was added, the mixture was heated to 70 °C and stirred at this temperature for 1 h. After cooling, the reaction mixture was diluted with THF (2 mL) and quenched with 2 M aq. NaOH (5 mL). After stirring for an additional 1 h, the reaction vessel was disconnected from argon line and the reaction mixture was extracted with diethyl ether (3 × 10 mL). Combined extracts were washed with brine (10 mL) and dried over anhydrous K_2CO_3. Crude product obtained after solvents removal was purified by flash chromatography and/or subsequent kugelrohr distillation.

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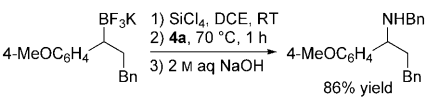

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