Enantioselective Synthesis

Full Chirality Transfer in the Conversion of Secondary Alcohols into Tertiary Boronic Esters and Alcohols Using Lithiation–Borylation Reactions**

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Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

A general method for the preparation of fully substituted carbon atoms (e.g. quaternary stereogenic centers[1] or tertiary alcohols[2]) that routinely gives high enantioselectivities ($> 96\%$ *ee*) with broad substrate scope is one of the most challenging goals in organic synthesis.[3] Our research group has recently described a conceptually new method that comes close to meeting such a challenge (Scheme 1).[4] In this process, readily available enantioenriched secondary alcohols
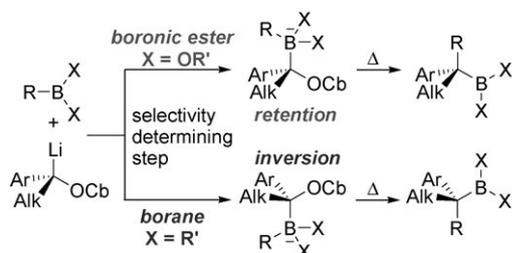

Scheme 1. Lithiation–borylation of enantioenriched secondary carbamates.

were first converted into carbamate compounds. Lithiation and subsequent reaction with boron reagents gave, after oxidative workup, tertiary alcohols with high *ee* values. Perhaps the most intriguing facet of this novel methodology was that in all cases the reactions occurred with essentially complete inversion of configuration when boranes were employed but almost complete retention of configuration when boronic esters were used. Although the reaction worked well for simple substrates ($> 90\%$ *ee*), we have found that the introduction of sterically more demanding groups in the carbamate or boronic ester or the introduction of electron-withdrawing aromatic groups in the carbamate resulted in a

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considerable erosion of enantioselectivity. Herein, we provide a rationale for the observed decrease in enantioselectivity and through understanding the intricacies of the process, we also present a solution to the problem that now results in $> 98\%$ *ee* for all the substrates tested, even the most demanding.

The problem we encountered is illustrated in Scheme 2 (and expanded in the Supporting Information). Thus, reaction of the *para*-chlorophenyl-substituted carbamate **1c** with

n	Yield (ee), %
1.1	63 (40)
1.5	94 (86)
3.0	92 (96)
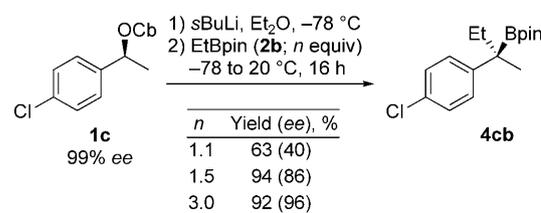
Scheme 2. Example of the dependence of *ee* values on the stoichiometry of the boronic ester.
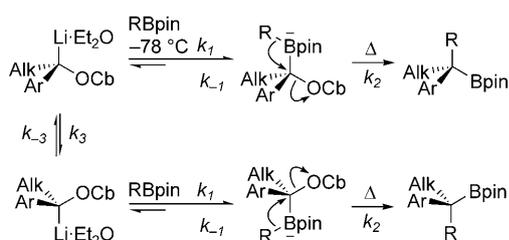
EtBpin **2b** (1.1 equiv) gave the tertiary boronic ester with only 40% *ee*. Furthermore, we observed an unusual dependence of the *ee* value on the stoichiometry: increasing the stoichiometry of **2b** from 1.1 equivalents to 3 equivalents led to an increase in the *ee* value of the product **4cb** from 40% to 96% *ee*.

Although a number of possible explanations can be advanced for this observation, we focused on the possible scenario shown in Scheme 3. We suspected that the critical issue was not the selectivity in the formation of the ate-complex, for which it would be difficult to rationalize the dependence of the *ee* value on stoichiometry, but instead the fate of the ate-complex upon warming. Even though the desired stereospecific 1,2-migration occurred upon warming, it was also possible that competing dissociation of the ate-complex (k_{-1}) back to the starting lithiated carbamate and boronic ester species might also take place.[5] This dissociation could be followed by racemization of the lithiated carbamate and subsequent erosion of the *ee* value. The dependence of the *ee* value on the stoichiometry can therefore be understood. At low stoichiometry, reversion to starting materials results in a low concentration of the boronic ester, and so the subsequent recombination of the lithiated carbamate with RBpin is inevitably slow. This pathway gives the lithiated

Scheme 3. Dissociation of ate-complex as a possible cause of erosion in *ee* values.

Scheme 4. Suitable electrophiles for trapping experiments.

carbamate time to racemize[6] prior to recombination, which results in a low *ee* value. At high stoichiometry, the larger concentration of the boronic ester results in a more rapid recombination of the lithiated carbamate with RBpin and so there is less time available for racemization to occur, thus a higher *ee* value is observed. The fact that lower *ee* values were observed with hindered boronic esters and electron-deficient aromatic carbamates is consistent with this model because in both cases the rate of the reverse reaction would be enhanced and the rate of the forward reaction would be lower.

If this model is correct, the addition of a second, more reactive electrophile than the boronic ester after ate-complex formation should result in the trapping of any lithiated carbamate formed from the reverse reaction. This trapping would prevent recombination of the racemized lithiated carbamate with the boronic ester and would therefore lead to a higher *ee* value of the tertiary alcohol. We decided to test this idea using three different electrophiles (D_2O, TMSCl, and allyl bromide) with the hindered boronic ester **2c** (1.2 equiv; Scheme 4). In all three cases the tertiary boronic ester **4ac** was formed with complete retention of configuration (99% *ee*), which shows that the addition of the boronic ester to the lithiated carbamate **Li-1a** is completely stereoselective.[7] In fact, this simple test allows the determination of the maximum *ee* value achievable in a lithiation–borylation reaction for any substitution pattern.

To obtain a more complete picture of the fate of various intermediates along the lithiation–borylation pathway, we have developed a new reaction sequence (Scheme 5). Thus, after treatment of the lithiated carbamate **Li-1** with the boronic ester over 30 minutes, allyl bromide (electrophile 1; 1 equiv) was added and the mixture was stirred for 15 minutes at −78 °C. This allylation would result in the trapping of any lithiated carbamate that had not reacted with the boronic
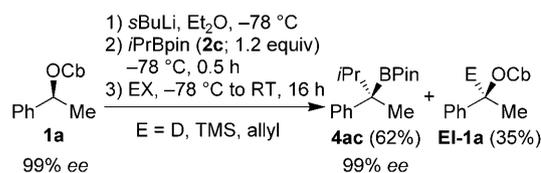
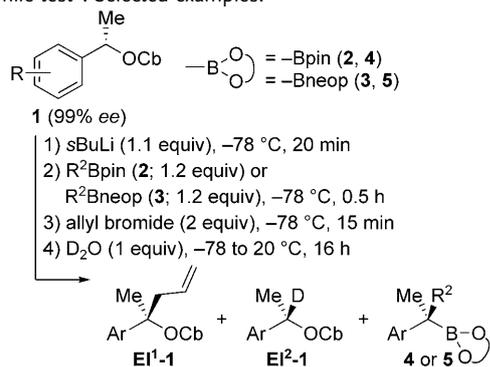ester to form the ate-complex. Next, D_2O (electrophile 2; 1 equiv)—which is a more reactive electrophile than allyl bromide towards the lithiated carbamate **Li-1a**—was then added and subsequent warming would give a series of products in ratios that reflected the efficiency of all three individual reaction steps. Thus, any recovered carbamate **1** would show the efficiency of the deprotonation step (typically, 97%), the amount of allylated carbamate would show the extent of the reaction of the lithiated carbamate with the boronic ester, whereas the amount of deuterated carbamate would reflect the fraction of the ate-complex that reverted back into starting materials upon warming. Application of this two-electrophile test shown in Scheme 5 to a series of substrates is summarized in Table 1 and revealed the following: 1) the reaction of the lithiated carbamate derived from **1a** with *i*PrBpin was incomplete after 30 minutes because 9% of the allylated carbamate **El¹-1a** was isolated, thus showing that the formation of the ate-complex is slow enough to be quantified (Table 1, entry 1). 2) A greater proportion of the deuterated carbamate **El²-1** was obtained with the more electron-deficient aryl carbamate compared to the phenyl carbamate (54% vs. 25%; compare Table 1, entries 2 and 1) and with the more hindered pinacol ester compared to the neopentyl glycol ester (54% vs. <2%; compare Table 1, entries 2 and 3). With boronic ester **3d** bearing the less hindered neopentyl boronic ester but more hindered boron substituent together with the hindered aryl carbamate **1f** considerable reversion of the ate-complex still occurred, and generated 29% of the deuterated carbamate **El²-1f** (Table 1, entry 4). These results show that the stability of the ate-complex depends on both the steric and electronic effects of both the lithiated carbamate and the boronic ester species.

Although this strategy was clearly successful in enhancing the *ee* value of the product, it did so at the expense of yield. To address this issue we needed to enhance the relative rate of the 1,2-migration (k_2) and so we considered the use of Lewis acids. After some preliminary experimentation[8] we found
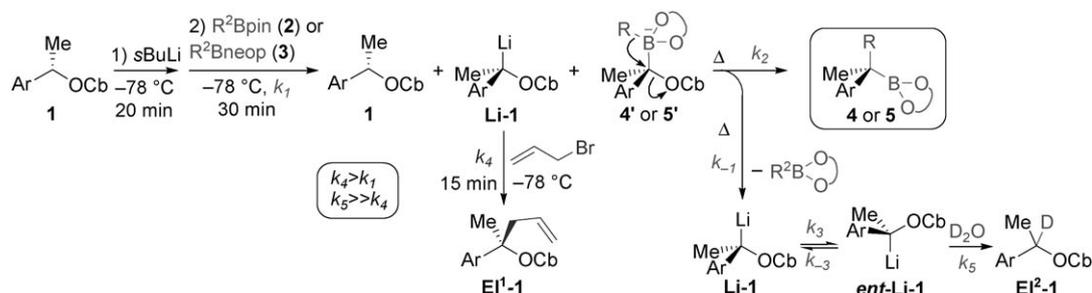
Scheme 5. Mechanistic representation of the "two-electrophile test" aimed to quantify the fate of reactive intermediates in the lithiation–borylation reaction.

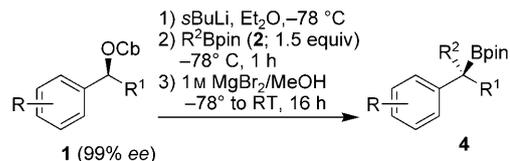**Table 1:** Study of the borylation 1,2-migration reaction by the "two-electrophile test". Selected examples.

Entry	Substrate		$R_2B\begin{smallmatrix}O\\O\end{smallmatrix}$		Yield [%] (ee [%])[b]		
	1	R_{Ar}	**2 or 3**	R^2	EI^1-1	EI^2-1	**4 or 5**
1	**1a**	H	**2c**	iPr	9	25	**4ac** 60 (99)
2	**1c**	4-Cl	**2c**	iPr	17	54	**4cc** 27 (99)
3	**1c**	4-Cl	**3c**	iPr	<2	<2	**5cc** 92 (99)
4	**1f**	2-Me	**3d**	cHex	<2	29	**5fd** 48 (98)

[a] Yield of isolated product. [b] The *ee* values were determined after oxidation of an aliquot of **4/5** (see the Supporting Information).

Table 2: Preparation of highly enantioenriched tertiary pinacolboronic esters.

Entry	Substrate			R^{2}Bpin		Yield of **4** [%][a]
	1	R	R^1	**2**	R^2	(ee [%])[b]
1	**1a**	H	Me	**2c**	iPr	**4ac** 92 (99)
2	**1a**	H	Me	**2d**	cHex	**4ad** 87 (99)
3	**1b**	H	Et	**2a**	Me	**4ba** 71 (99)
4	**1b**	H	Et	**2c**	iPr	**4bc** 74 (99)
5	**1b**	H	Et	**2d**	cHex	**4bd** 61 (99)
6	**1b**	H	Et	**2e**	cinnamyl	**4be** 91 (99)[c]
7	**1b**	H	Et	**2f**	4-BrC$_6$H$_4$	**4bf** 82 (99)[c]
8	**1c**	4-Cl	Me	**2b**	Et	**4cb** 91 (99)
9	**1c**	4-Cl	Me	**2c**	iPr	**4cc** 89 (99)
10	**1c**	4-Cl	Me	**2d**	cHex	**4cd** 75 (99)
11	**1d**	4-F	Me	**2c**	iPr	**4dc** 88 (99)
12	**1d**	4-F	Me	**2d**	cHex	**4dd** 69 (99)
13	**1e**	2-F	Me	**2c**	iPr	**4ec** 64 (96)[d]
14	**1e**	2-F	Me	**2g**	Ph	**4eg** 74 (99)[c]
15	**1f**	2-Me	Me	**2g**	Ph	**4fg** 64 (99)[c,e]
16	**1g**	2-MeO	Me	**2c**	iPr	**4gc** 79 (99)[e]
17	**1g**	2-MeO	Me	**2d**	cHex	**4gd** 65 (99)[c,e]
18	**1g**	2-MeO	Me	**2g**	Ph	**4gg** 93 (99)[c,e]

[a] Yield of isolated product. [b] The *ee* values were determined after oxidation of an aliquot of **4** (see the Supporting Information). [c] Used 1.2 equivalents of boronic ester. [d] After addition of **2c** the reaction mixture was stirred at −78°C for 3 hours. Note that the use of **3c** instead of **2c** resulted in an increased yield and *ee* value for **5ec** (Table 3, entry 8). [e] The carbamate was deprotonated in the presence of TMEDA within 10 minutes. THF = tetrahydrofuran, TMEDA = *N,N,N′,N′*-tetramethyl-ethylenediamine.

that use of MgBr$_2$ in MeOH fulfilled our requirements, and led to both high yields and high *ee* values (Table 2). Presumably, the MgBr$_2$ enhances the k_2/k_{-1} ratio, while the MeOH reprotonates any lithiated carbamate generated from the dissociation of the ate-complex, thus preventing it from eroding the *ee* value. These new reaction conditions were found to be general over a broad range of substrates (Table 2).

Carbamate **1a** gave complete retention of configuration with both *i*PrBpin **2c** and *c*HexBpin **2d** (Table 2, entries 1 and 2). The more hindered carbamate **1b** also reacted with high enantioselectivity with all the boronic esters explored from the least hindered **2a** to the most hindered alkyl **2d**, as well as allyl and aryl substrates (**2e–f**, respectively; Table 2, entries 3–7). The dramatic enhancement of selectivity is illustrated in the reaction outlined in entry 10 of Table 2: only 49% *ee* was observed under the former conditions[4a] but under the new conditions 99% *ee* was obtained. Aryl carbamates bearing electron-withdrawing substituents in the *para* position also gave high enantioselectivities even with the most sterically demanding boronic esters (Table 2, entries 8–12). These examples represent some of the most demanding reaction partners as these substrates are most prone to reversibility in ate-complex formation and thus erosion in *ee* values, but nevertheless they gave essentially high enantioselectivities. Additional steric hindrance in the *ortho* position was also tolerated again, and led to high selectivities in the formation of tertiary boronic esters (Table 2, entries 13–18).

The tertiary pinacolboronic esters **4** provide a very promising pool of chiral building blocks of exceptionally high enantiomeric purity for many applications.[9,10] However, they could not always be oxidized directly to the corresponding alcohols by treatment with H$_2$O$_2$/NaOH (aq), but instead required a solvent exchange from Et$_2$O to THF prior to
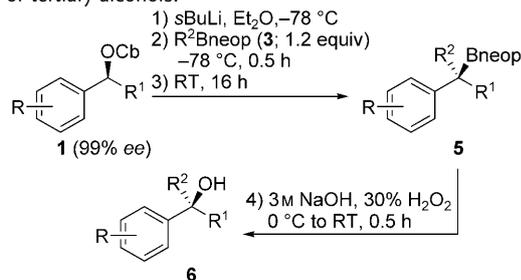
oxidation. This change was especially needed the case of **4gc** and **4gd** (Table 2, entries 16 and 17).

Because of the issues relating to slow oxidation, we investigated the less hindered neopentyl boronic esters instead of pinacol esters. Furthermore, as they are less hindered than pinacol esters they were expected to be less prone to undergo dissociation of the respective ate-complexes (as revealed in the "two-electrophile test"; compare Table 1, entries 2 and 3) and so more likely to give higher *ee* values. As a slight drawback, the neopentyl boronic esters have to be synthesized from the corresponding acids because unlike many of the pinacol esters they are not commercially available and are less stable to chromatography on silica gel.[11]

Thus, a second set of reaction conditions was established employing neopentyl boronic esters instead of pinacol esters and the results are summarized in Table 3. This study revealed that certain advantages accrued with these substrates: 1) high *ee* values were achieved without the need for MgBr$_2$/MeOH[12] over a broad range of substrates, 2) the tertiary boronic esters could be oxidized to the alcohols directly in one pot without solvent exchange.

Once again high yields and enantioselectivities were obtained even with the most demanding substrates, for

Table 3: Preparation of highly enantioenriched tertiary neopentylboronic esters or tertiary alcohols.

Entry	Substrate			R²Bneop			Yield of 5/6 [%][a]	
	1	R	R¹	3	R²			(ee [%][b])
1	1a	H	Me	3d	cHex	6ad	–	94 (99)
2	1b	H	Et	3c	iPr	6bc	–	98 (99)
3	1b	H	Et	3d	cHex	6bd	–	94 (99)
4	1c	4-Cl	Me	3c	iPr	6cc	–	95 (99)
5	1c	4-Cl	Me	3d	cHex	6cd	–	95 (99)
6	1d	4-F	Me	3c	iPr	5/6dc	63	79 (99)
7	1d	4-F	Me	3d	cHex	6dd	–	87 (99)
8	1e	2-F	Me	3c	iPr	5/6ec	67	74 (99)
9	1f	2-Me	Me	3d	cHex	5/6fd	65[c]	48 (98)[d,e]
10	1g	2-MeO	Me	3c	iPr	5/6gc	89	92 (96)[d]
11	1g	2-MeO	Me	3d	cHex	5/6gd	70	68 (96)[d,e,f]

[a] Yield of isolated boronic esters 5 (first column) or alcohols 6 (second column; formed in a one-pot operation). [b] The *ee* values were determined after oxidation of an aliquot of 5 (see the Supporting Information). [c] 97% *ee*. [d] The carbamate was deprotonated in the presence of TMEDA within 10 minutes. [e] Ethereal solution of D₂O was added at −78 °C after addition of R²Bneop. [f] Isolated boronic ester was oxidized according to procedure GP3A in the Supporting Information.

example, reactions between hindered or electron-withdrawing carbamates with hindered boronic esters (Table 3).

In conclusion, we have demonstrated that the lithiation–borylation of secondary carbamates to give tertiary boronic esters (or tertiary alcohols) is accompanied by considerable erosion in *ee* values as a result of the intermediate ate-complex dissociating back to the starting lithiated carbamate—a species that is prone to racemization upon warming. The dissociation–racemization pathway can be essentially eliminated through the use of either MgBr₂/MeOH or neopentyl boronic esters in place of pinacol esters. These two sets of reaction conditions now provide essentially complete chirality transfer in the lithiation–borylation reaction and lead to tertiary boronic esters (or tertiary alcohols) with exceptionally high *ee* values in all cases, even the most demanding.

[1] For recent examples, see: a) G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451–9454; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291–9294; b) T. Tsubogo, S. Saito, K. Seki, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13321–13332; c) J. P. Das, H. Chechik, I. Marek, *Nat. Chem.* **2009**, *1*, 128–132; d) Y. Lee, B. Li, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 11625–11633; for a review, see: e) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; f) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; g) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888.

[2] a) S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425; b) U. Schneider, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13824–13825; c) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2009**, *20*, 65–67; d) I. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665; for a recent review, see: e) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675.

[3] For general reviews, see: a) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; b) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; c) M. M. Hussain, P. J. Walsh, *Acc. Chem. Res.* **2008**, *41*, 883–893; d) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614.

[4] a) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782. These reactions are based on the seminal studies by Hoppe on the lithiation and trapping of secondary benzylic carbamates. See: b) D. Hoppe, A. Carstens, T. Krämer, *Angew. Chem.* **1990**, *102*, 1457–1459; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1424–1425; c) A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097–6108.

[5] H. C. Brown, N. Vasumathi, N. N. Joshi, *Organometallics* **1993**, *12*, 1058–1067.

[6] The lithiated secondary benzylic carbamates are generally configurationally unstable above −60 °C.

[7] These reactions show that the pinacol ester B−O bonds of the ate-complex are essentially stable and do not undergo ring opening under the reaction conditions employed. This ring opening would have given an intermediate alkoxide which would have been trapped by the electrophiles employed, but this was not observed.

[8] We first optimized the ate-complex formation using carbamate 1c and boronic ester 2c as these are a particularly challenging pair of substrates. Using 1.5 equivalents of boronic ester 2c and leaving it to react with the lithiated carbamate for 1 hour at −78 °C led to complete ate-complex formation (no allylated material was formed).

[9] Conversion of tertiary boronic esters into trifluoroborates: a) V. Bagutski, A. Ros, V. K. Aggarwal, *Tetrahedron* **2009**, *65*, 9956–9960; and their reactions with aldehydes: b) A. Ros, V. K. Aggarwal, *Angew. Chem.* **2009**, *121*, 6407–6410; *Angew. Chem. Int. Ed.* **2009**, *48*, 6289–6292.

[10] Tertiary trifluoroborates can also be converted into the corresponding tertiary amines: V. Bagutski, V. K. Aggarwal, unpublished results.

[11] Tertiary neopentylboronic esters 5 could, in general, be isolated by distillation or, in certain instances (Table 3, entries 6, 8–11), by dry column vacuum chromatography (DCVC) techniques. For details see the Supporting Information.

[12] In fact, the use of MgBr₂/MeOH with neopentylglycol esters caused a significant decrease in yield of the desired products 5 as result of B−O bond cleavage (instead of 1,2-migration). This outcome was determined by ¹¹B NMR analysis of the reaction mixture which showed a major signal for borinic esters at 50–53 ppm.