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Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates

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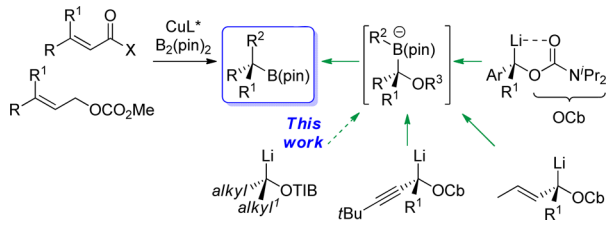
Supporting Information

ABSTRACT: Simple, secondary 2,4,6-triisopropyl benzoates (TIB esters) and secondary dialkyl *N*,*N*-diisopropyl carbamates have been reported to be resistant to deprotonation by strong bases. We have found that the combination of *s*BuLi (1.6 equiv) and TMEDA (6 equiv) in CPME at −60 °C enables deprotonation of unactivated secondary dialkyl TIB esters, but not the carbamates. These carbanions were reacted with a range of neopentyl boronic esters which, after 1,2-metalate rearrangement and oxidation, gave a range of tertiary alcohols in high yield and universally high *er*. Further functional group transformations of the tertiary boronic esters were demonstrated (conversion to quaternary centers, C-tertiary amines) together with application of the methodology to the synthesis of the simplest unbranched hydrocarbon bearing a quaternary center, (*R*)-4-ethyl-4-methyloctane, validating the synthetic utility of the methodology.

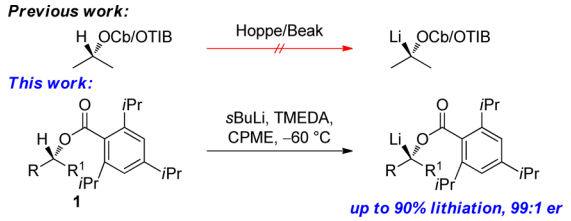
The broad use and versatility of boronic esters in organic synthesis has fueled considerable interest in the development of asymmetric methods for their synthesis.[1] Of the different classes of boronic esters, tertiary (3°) boronic esters are the most difficult to prepare in high enantiomeric ratio (*er*) since they cannot be accessed by commonly used methods such as hydroboration. Nevertheless, a number of synthetic methods have been developed, the most notable being asymmetric nucleophilic *β*-borylation of Michael acceptors[2] and allylic carbonates[3] (Scheme 1).

Scheme 1. Methods To Synthesize Tertiary Boronic Esters



Our own contributions have included the synthesis of 3° benzylic,[4] allylic,[5] silyl-substituted,[6] and propargylic[7] boronic esters using the lithiation/borylation reaction of the corresponding carbamates, a process that is capable of delivering 3° boronic esters with >99:1 *er* (Scheme 1). This broad-ranging methodology, however, has a significant limitation: the secondary (2°) carbamate from which it is derived must have a sufficiently acidic proton that can be removed by strong base. Without enhanced acidity, deprotonation cannot occur, as reported by Hoppe[8] and Beak[9] on simple, unactivated isopropyl substrates (Scheme 2).

Scheme 2. Deprotonation of Secondary Alkyloxy Substrates



Indeed, dialkyl *α*-oxy carbanions that are not mesomerically stabilized are rare in the literature and have not previously been prepared by deprotonation. Cohen reported the reductive lithiation of $Me_2C(OMe)SPh$ to form the corresponding *α*-lithio ether,[10] and the cyclopropyl-OTIB has been deprotonated, but this case benefits from the increased acidity of cyclopropyl protons.[11] Therefore, at the outset, it seemed that a general synthesis of all-alkyl-substituted 3° boronic esters using lithiation/borylation methodology of unactivated 2° carbamates or benzoates was not achievable. In this Communication, we report our success in finding conditions for deprotonating these extremely reluctant substrates and show that simple 2° dialkyl alcohols can now be converted into 3° alkylboronic esters (and therefore 3° alcohols) in very high *er*.

We began our studies by the preparation of the 2° benzoate **1a** and carbamate **2**.[12] As noted above, Hoppe[8] and Beak[9] reported that isopropyl carbamate and benzoate could not be deprotonated (Scheme 2). Beak's conditions (*s*BuLi/TMEDA in THF) were tested using a lithiation/deuteration procedure so that the degree of lithiation could be readily assessed by ^{1}H NMR. However, in keeping with the literature, we found that <10% deprotonation of either benzoate **1a** or carbamate **2** occurred (Table 1, entries 1 and 2). Lithiation at the benzylic position was not observed in these or any subsequent reactions.[13] Solvent and additives can play a significant role in lithiation reactions, so we tested benzoate ester **1a** under a range of conditions.

We were gratified to find that simply switching from THF to diethyl ether immediately gave a positive result (entry 3). The extent of lithiation was increased further upon the use of cyclopentyl methyl ether (CPME) as the solvent and by raising the temperature to −50 °C (entries 4 and 5) without loss of *er*. A

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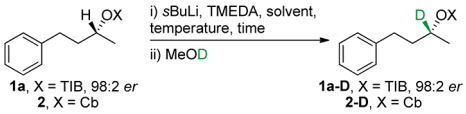
Table 1. Optimization of Deprotonation Conditions



entry	X	temp (°C)	solv	sBuLi/TMEDA (equiv)	time (h)	1a[a]/2-D (%D)
1	TIB	−78	THF	2/2	4	10
2	Cb	−78	Et_2O	2/2	4	<5[b]
3	TIB	−78	Et_2O	2/2	4	60[c]
4	TIB	−78	CPME	2/2	4	70
5	TIB	−50	CPME	2/2	1	74
6	TIB	−50	CPME	2/6	1	92
7	TIB	−50	CPME	1.6/6	1	89
8	TIB	−60	CPME	1.6/6	2	87
9	Cb	−50	CPME	1.6/6	1	10[d]

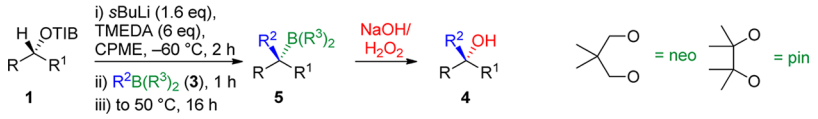
[a]Yield of **1a-D** and recovered **1a** was >90%. [b]Yield of **2-D** and recovered **2** was 33%. [c]Results with Et_2O were found to be variable, and the number given for %D is an average of three reactions (49%, 55%, 76%). [d]Yield of **2-D** and recovered **2** was 49%.

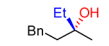
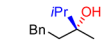
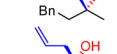
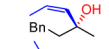
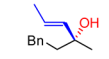
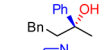
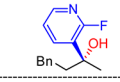
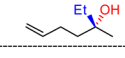
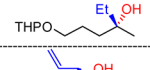
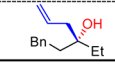
further enhancement was observed with excess TMEDA (6 equiv, entries 6 and 7). The analogous *N*,*N*-diisopropyl carbamate **2** was tested under these optimum conditions, but little deuterium incorporation was observed, indicating the superiority of the TIB ester in promoting lithiation (entry 7 vs 9).[14]

Having identified the optimum conditions for lithiation, we tested the borylation reaction with EtB(pin) **3a** (Table 2, entry 1). After addition of the boronic ester at −60 °C (this gave higher yields than at −50 °C), the reaction mixture was heated at 50 °C for 16 h, and subsequent oxidation gave the 3° alcohol in 72% yield and 97:3 *er*. The slight erosion in *er* was investigated but was not found to be due to reversibility in formation of the boronate complex as determined by the two-electrophile test.[15,16] Alternative boronic esters were therefore tested, and the neopentyl boronic ester was found to give *complete* retention of stereochemistry and high yield (entry 2).

Reaction with triethylborane was also examined, and it gave the same alcohol **4aa** with high *er* but in lower yield than the corresponding boronic esters (entry 3). Interestingly, the reaction occurred with complete retention of configuration. This contrasts with reactions of 2° benzylic carbamates, where reactions with boronic esters occurred with retention while those with boranes occurred with inversion.[4a] Evidently, in the absence of mesomeric stabilization, Li-**1a** retains its tetrahedral shape, making retention the only available pathway in reactions with both classes of electrophiles.

Table 2. Scope and Limitations of Lithiation/Borylation Reactions of Secondary Dialkyl-Substituted TIB Esters[a]



Entry	1	er[b]	R	R1	3	R2	(R3)2	4	Product	Yield (%)[c]	er[b]
1	a	99:1	$BnCH_2$	CH_3	a	Et	pin	aa		71	97:3
2	”	”	”	”	a’	Et	neo	aa		80	99:1
3[d]	”	”	”	”	a’’	Et	Et_2	aa		49	98:2
4[e]	”	”	”	”	b	*i*Pr	neo	ab		74	99:1
5[e]	”	”	”	”	c		neo	ac		69	98:2[f]
6	”	”	”	”	d	allyl	neo	ad		73	99:1
7	”	”	”	”	e		neo	ae		78	99:1
8	”	”	”	”	f		neo	af		77	99:1
9	”	”	”	”	g	Ph	neo	ag		71	99:1
10[e]	”	”	”	”	h		neo	ah		73	99:1[g]
11[h]	b	99:1		CH_3	a’	Et	neo	ba		72	99:1
12[i]	c	99:1	THPO 	CH_3	a’	Et	neo	ca		56 (93)[j]	98:2
13[i]	d	99:1	$BnCH_2$	Et	d	allyl	neo	dd		40 (78)[j]	99:1

[a]Abbreviated procedure: (i) *s*BuLi (1.6 equiv) was added to a solution of **1** (0.5 mmol) and TMEDA (6 equiv) in CPME (3 mL) at −60 °C and stirred for 2 h (lithiation time). (ii) A solution of **3** (2 equiv) in CPME (0.5 mL) was added and reaction stirred for 1 h at −60 °C (ate complex formation). (iii) The reaction was heated at 50 °C (migration temperature) for 16 h. (iv) THF (3 mL) was added, reaction cooled to 0 °C, and premixed $NaOH/H_2O_2$ added. [b]Determined by chiral GC, HPLC, or SFC. [c]Isolated yield. [d]Migration temperature 20 °C for 4 h; 6 equiv of BEt_3 used. [e]Migration temperature 70 °C. [f]MeOH (2 equiv) was added after ate complex formation. Without MeOH, **4ac** formed in 54% yield and 88:12 *er*. [g]TMSCl (6 equiv) was added after ate complex formation. Without TMSCl, **4ah** formed in 68% yield and 84:16 *er*. With MeOD (2 equiv), **4ah** formed in 34% yield and 98:2 *er*, along with 45% of the protodeboronation product. [h]Lithiation time 4 h. [i]Lithiation time 8 h. [j]Yield brsm.

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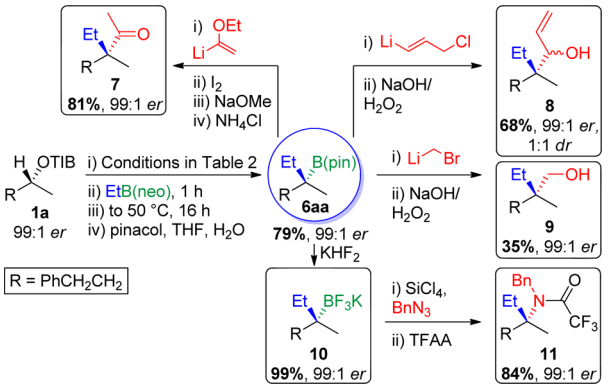
A range of boronic esters were then tested to map out the scope of the reaction. In addition to primary alkyl boronic esters (entry 2), more hindered 2° alkyl boronic esters worked efficiently (entry 4) as well as more functionalized boronic esters including propanoyl (entry 5), allyl (entry 6), *E*- and *Z*-vinyl (entries 7 and 8), phenyl (entry 9), and pyridyl boronic esters[17] (entry 10). They all delivered 3° boronic esters, which after oxidation gave 3° alcohols in high yields and ≥98:2 *er*.

Initially, the use of propanoyl boronic ester **3c** and pyridyl boronic ester **3h** in the lithiation/borylation/oxidation reaction gave reduced *er* in the product 3° alcohols (88:12 *er* for **4ac** and 84:16 *er* for **4ah**) under standard conditions. However, simply adding MeOH or TMSCl[18] after ate complex formation in the reactions with propanoyl boronic ester **3c** and pyridyl boronic ester **3h**, respectively, restored the high levels of selectivity (≥98:2 *er*) achieved with other substrates (entries 5 and 10). The erosion in *er* was again investigated but was not found to be due to reversibility in formation of the boronate complex as determined by the two-electrophile test.[15,19] The exact role of the additive in promoting high selectivity remains intriguing, especially since transformations after ate complex formation (1,2-migration and oxidation) are expected to be stereospecific.

The scope of the TIB ester component was also examined with a range of synthetically useful functional groups. These included a terminal alkene (entry 11), a THP-protected alcohol (entry 12), and, to examine steric effects, an α-ethyl substituent (instead of methyl, entry 13). These more challenging substrates required longer deprotonation times but nevertheless delivered 3° boronic esters and 3° alcohols in good yields and high *er*'s.

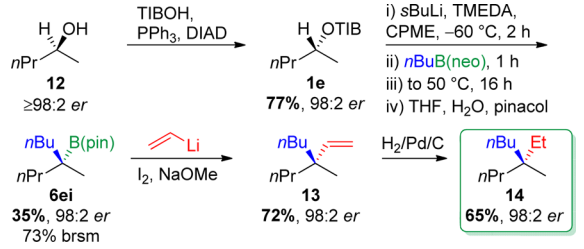
We wished to demonstrate the synthetic utility of the intermediate boronic esters by conversion to other function groups, so we converted the unstable neopentyl boronic ester **5aa** to the isolable pinacol ester **6aa** (Scheme 3).[20] Pinacol ester

Scheme 3. Functional Group Transformations of Tertiary Boronic Esters



6aa was homologated under modified Zweifel olefination[21,22] conditions with lithiated ethyl vinyl ether to give the quaternary α-substituted ketone **7** in 81% and 99:1 *er* (Scheme 3). Pinacol ester **6aa** was also reacted with (3-chloroprop-1-en-1-yl)-lithium[23] (generated via tin−lithium exchange) to form the corresponding 2° allylic boronic ester, which was oxidized to give allylic alcohol **8** in high yield, 99:1 *er*, and with 1:1 *dr* (as expected).[24] One-carbon homologation using bromomethyl-lithium[22,25] (generated in situ from dibromomethane and *n*BuLi) gave the desired primary alcohol **9** after oxidation in 35% yield.[26] Similar yields were obtained with $LiCH_2Cl$. We also transformed **6aa** into its corresponding trifluoroborate salt **10** in high yield

Scheme 4. Synthesis of (*R*)-4-Ethyl-4-methyloctane



(99%),[27] which was converted into the C-tertiary amine **11** in 84% and 99:1 *er* upon treatment with $SiCl_4$ and benzyl azide.[28]

To demonstrate the generality of the methodology, we decided to undertake a synthesis of the archetypal chiral molecule, (*R*)-4-ethyl-4-methyloctane, the simplest unbranched hydrocarbon bearing a quaternary center (Scheme 4).[29] Our synthesis began with a Mitsunobu reaction between TIBOH and commercially available (*R*)-2-pentanol **12**, which gave TIB ester **1e** in high yield (77%) and 98:2 *er*. The key step utilizing **1e** and *n*BuB(neo) **3i**, followed by in situ transesterification with pinacol, afforded the desired trialkyl-substituted 3° boronic ester **6ei** in 35% yield (73% brsm) and excellent *er* (98:2). Although lithiation was slow,[30] a considerable amount of the TIB ester **1e** was recovered, thereby improving the efficiency of the key step. Attempts to increase the extent of lithiation by increasing time, temperature, or stoichiometry of reagents led to lower overall yields. Finally, Zweifel olefination[21,22] (75%, 98:2 *er*[31]) and hydrogenation (65%) gave **14** in just four steps, providing the shortest and most selective synthesis of this archetypal chiral molecule.

In conclusion, we have developed conditions for the first time to deprotonate unactivated secondary alkyl TIB esters lacking groups that acidify the adjacent proton. These carbanions were reacted with a range of neopentyl boronic esters which, after 1,2-metalate rearrangement and oxidation, gave a range of tertiary alcohols[32] in high yield and universally high *er*. Such compounds are difficult to obtain in high *er* using current methods. Further functional group transformations of the hindered tertiary boronic esters were demonstrated together with the application of the methodology to the shortest synthesis of the simplest unbranched hydrocarbon bearing a quaternary center. This addition to the methodology now enables essentially any secondary alcohol to be converted into a tertiary boronic ester with very high *er*.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Secondary TIB esters were prepared from the corresponding enantioenriched 2° alcohol by Mitsunobu reaction with HOTIB. The 2° alcohols were prepared by asymmetric reduction of the corresponding enone [see: (a) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529] followed by hydrogenation. They were also prepared by ring-opening of commercially available enantiopure epoxides [for details, see: (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307]. For reviews on the synthesis of enantioenriched dialkyl 2° alcohols, see: (c) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331. (d) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659. (e) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (f) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (g) Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139.

(13) Efficient benzylic lithiation has been reported on related substrates with one fewer atom linking the directing group and the benzylic hydrogen ($PhCH_2CH_2NHC(O)R$) [(a) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1991**, *32*, 1693] or two fewer atoms ($PhCH_2CH_2C(O)NHR$) [(b) Laumer, J. M.; Kim, D. D.; Beak, P. *J. Org. Chem.* **2002**, *67*, 6797 (c) Pippel, D. J.; Curtis, M. D.; Du, H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2].

(14) See Supporting Information for further optimization.

(15) Reversion of the ate complex to the starting lithiated TIB ester and boronic ester at elevated temperatures followed by racemization of the lithiated species before readdition could cause reduced *er* in the product. Addition of a second, more reactive electrophile (in this case MeOD) after ate complex formation at −60 °C would trap any lithiated species formed in the reverse reaction, preventing racemization and readdition, and therefore lead to higher *er*. It would also give **1a-D**. See ref 4b.

(16) In this case no **1a-D** was observed when MeOD was added in the two-electrophile test, and there was no improvement in *er*.

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(18) The use of MeOH as an additive for pyridyl boronic ester reaction gave increased *er* but also significant amounts of protodeboronation of the intermediate 3° boronic ester. Allyl bromide was also effective at increasing the *er* in pyridyl boronic ester reaction, but TMSCl was optimal. See SI for details.

(19) In the reactions of propanoate boronic ester **3c** and pyridyl boronic ester **3h**, no **1a-D** was observed when MeOD was added in the two-electrophile test, but a substantial improvement in the *er* was observed for both cases. See SI for details.

(20) Direct transesterification of the neopentyl boronic ester by pinacol alone was unsuccessful. However, using *water* and pinacol, transesterification was achieved in high yield. The reaction is assumed to occur via the boronic acid or the partially hydrolyzed neopentyl ester.

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