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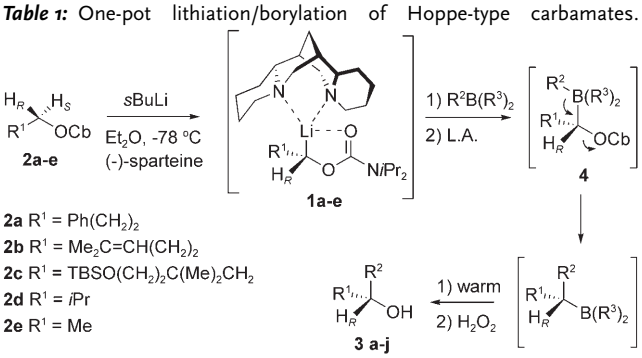
Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters**

*Jake L. Stymiest, Guillaume Dutheuil, Adeem Mahmood, and Varinder K. Aggarwal**

Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

The homologation of chiral boronic esters by Matteson and co-workers represents a landmark contribution in the field of asymmetric synthesis.[1] However, despite achieving exceptionally high enantioselectivities with simple, readily accessible reagents, the methodology has not been widely adopted. One possible factor may be that additional steps are required to control stereochemistry during iterative homologation as a consequence of employing substrate control.[1d,2] Since the stereogenic center created during homologation is dictated by the substrate diol of the boronic ester, if the opposite stereoisomer is required, a three-step sequence is needed to invert (by exchange) the diol stereochemistry.[2] A potentially more powerful and efficient strategy is to employ reagent control in the homologation process. This approach requires a chiral carbenoid that shows high configurational and chemical stability but sufficient reactivity to effect homologation of boronic esters. We have shown that chiral sulfur ylides fulfil some of these criteria and can be used effectively in the homologation of a range of boranes with very high enantioselectivity.[3] However, these ylides do not react with boronic esters and only give low enantioselectivity with borinic esters.[3c] Very recently, Blakemore and co-workers described the application of Hoffmann's α-chloro Grignard reagents[4] (although they found that the lithium derivatives worked better) to effect iterative homologation of boronic esters.[5,6] The chlorosulfoxide precursors were prepared in two steps, but some degree of racemization occurred during the homologation process.[5] Hoppe-type lithiated carbamates, **1a–e**[7] (from lithiation of **2a–e** with *s*BuLi in the presence of (−)-sparteine; see Table 1, where the carbamate moiety is abbreviated OCb) represent another class of chiral carbenoids, which is more readily obtained, and seemed to us to fulfil the requirements for boronic ester homologation. Indeed, Hoppe and co-workers have described the trapping of lithiated carbamates with borates and the subsequent (separate) treatment of the α-carbamoyl alkylboronate with a Grignard reagent to effect 1,2-metalate rearrangement with expulsion of the carbamate moiety. Oxidation of the resultant boronic esters affords the corresponding alcohols with high enantiomeric excesses.[8] However, the direct reaction of lithiated carbamates, such as **1a–e**, with boranes or boronates and further iterative homologations had not been described.[9]

Table 1: One-pot lithiation/borylation of Hoppe-type carbamates.



2a $R^1 = Ph(CH_2)_2$
2b $R^1 = Me_2C{=}CH(CH_2)_2$
2c $R^1 = TBSO(CH_2)_2C(Me)_2CH_2$
2d $R^1 = i$Pr
2e $R^1 = Me$

Entry	Carbenoid precursor	R^2	$(R^3)_2$	Lewis acid	Yield [%] (product)	e.r.[a]
1	**2a**	Et	Et	–	91 (**3a**)	98:2
2		*n*Hex	9-BBN	–	90 (**3b**)	98:2
3		*i*Pr	9-BBN	–	81 (**3c**)	98:2
4		Ph	9-BBN	–	85 (**3d**)	88:12
5		Ph	9-BBN	$MgBr_2$	94 (**3d**)	97:3
6		Et	pinacol	$MgBr_2$	90 (**3a**)	98:2
7	**2b**	Et	Et	–	90 (**3e**)	97:3[b]
8		Ph	9-BBN	$MgBr_2$	71 (**3f**)	95:5
9		Et	pinacol	$MgBr_2$	75 (**3e**)	97:3
10		Ph	pinacol	$MgBr_2$	73 (**3f**)	98:2
11	**2c**	Et	Et	–	67 (**3g**)	95:5[c]
12		Ph	9-BBN	$MgBr_2$	65 (**3h**)	97:3
13		Ph	pinacol	$MgBr_2$	64 (**3h**)	98:2
14	**2d**	Ph	9-BBN	$MgBr_2$	68 (**3i**)	96:4
15		Ph	pinacol	$MgBr_2$	70 (**3i**)	98:2
16	**2e**	Ph	pinacol	$MgBr_2$	70 (**3j**)	97:3

[a] Unless otherwise stated all enantiomeric ratios (e.r.) were calculated using chiral HPLC (Chiracel OD column), [b] The e.r. was determined using ^{1}H NMR of (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid ester,[16] [c] The e.r. was determined using chiral GC on a Supelco Alpha-Dex column.

We found that lithiated carbamates **1a–e** reacted directly with boranes or boronic esters, thus furnishing secondary alcohols **3a–j** in good yield and with high enantioselectivity (Table 1). A number of points are worthy of note:

1) Reactions with 9-BBN (9-BBN = 9-borabicyclo-[3.3.1]nonane) derivatives resulted in clean migration of the boron substituent in **4** rather than the boracycle in all

[*] Dr. J. L. Stymiest, Dr. G. Dutheuil, A. Mahmood, Prof. V. K. Aggarwal
School of Chemistry, University of Bristol
Cantock's Close, Bristol, BS8 1TS (UK)
Fax: (+44) 117-929-8611
E-mail: v.aggarwal@bristol.ac.uk

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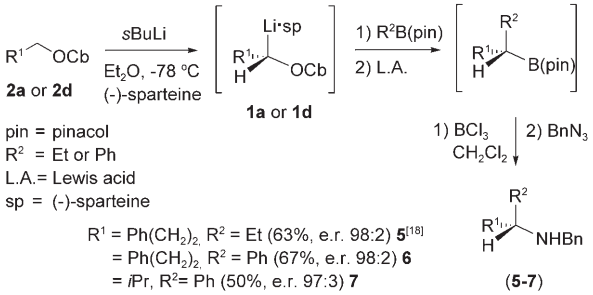
cases. This is highly unusual and has only previously been observed with halide leaving groups.[10]

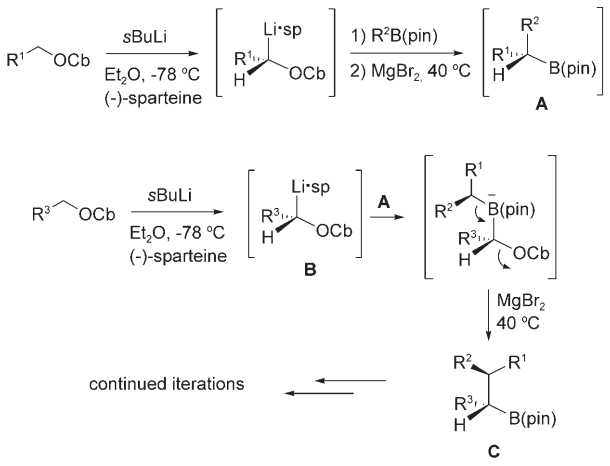
2) In the case of *B*-Ph-9-BBN, higher e.r. was obtained in the presence of $MgBr_2$ (Table 1, entry 4 versus entry 5) whereas in other cases involving aliphatic groups $MgBr_2$ was not found to be necessary.[11,12]
3) 1,2-Metalate rearrangement of ate complexes is much slower in the case of boronic esters than for boranes[13] and required $MgBr_2$ in Et_2O at reflux[14] in the former case, whereas the ate complexes derived from boranes began to rearrange at −40 °C without further additives.[15]
4) A broad range of alkyl carbamates, including those with methyl and with primary and branched secondary alkyl chains can be employed together with a broad range of aryl and alkyl boranes and boronic esters. The methodology, therefore, shows considerable substrate scope.
5) Since the absolute stereochemistries of many of the secondary alcohols are known, and the stereochemistry of Hoppe lithiation is well-established, we are able to conclude that reactions of lithiated carbamates with both the boranes and boronic esters occurred with retention of configuration (**1**→**4**). This result is consistent with previous findings.[8,9]
6) Secondary boronic esters can undergo a host of further transformations, including 1-, 2-, 3-carbon chain extensions, transmetallation to zinc and subsequent trapping with electrophiles, and conversion to amines. Herein, we illustrate the further utility of the borate esters by transformation into amines (Scheme 1).[17] In all cases, the amines **5**–**7** were formed in moderate to good yields and high e.r.



Scheme 1. Amination of intermediate boronate complexes.

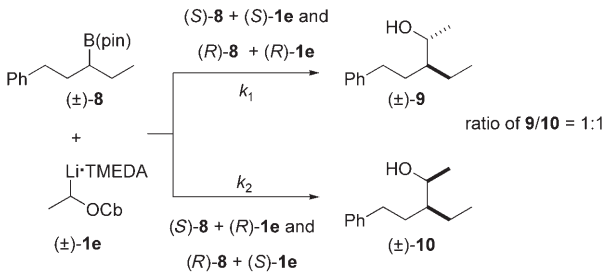
Having shown that lithiated carbamates are effective for reagent-controlled homologation of boranes and boronates, we then considered the iterative process with boronic esters. Indeed, this methodology should allow us to set up scaffolds bearing multiple adjacent stereocenters with high diastereo- and enantioselectivities. Realization of this goal would require the isolation of pinacol boronic ester intermediate **A** and its subsequent use in a second homologation reaction with lithiated carbamate **B** to yield the double homologation product **C** (Scheme 2).

To effectively prepare all four isomers of the alcohol, corresponding to the oxidation of **C**, it was important that the



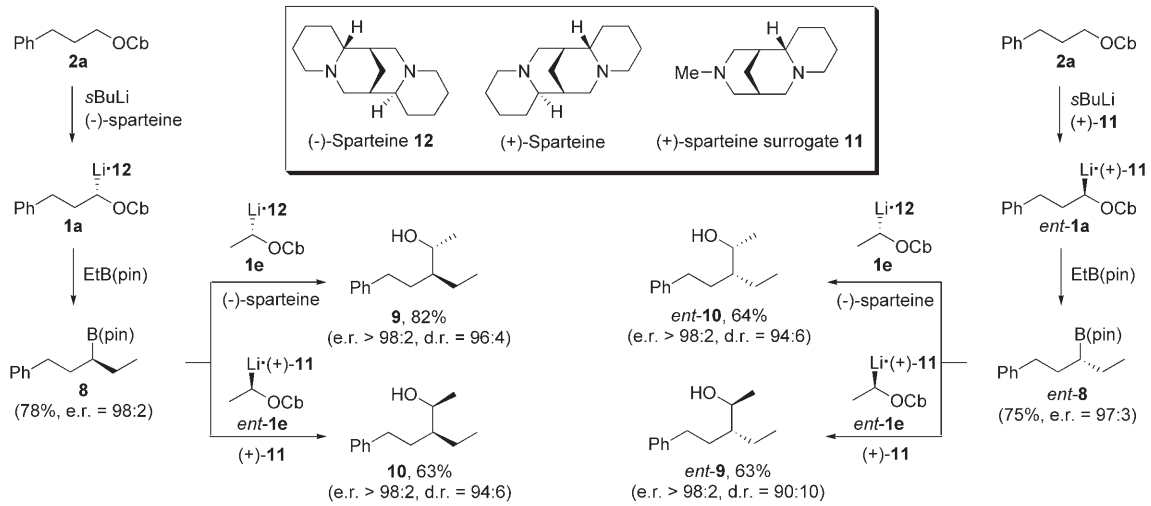
Scheme 2. Proposed iterative homologation of boronic esters.

homologation reaction was not influenced by the stereochemistry in **A** and **B**. This condition was easily tested by reacting (±)-**8** with the racemic lithiated carbamate (±)-**1e**, which is available from lithiation of **2e** with *s*BuLi in the presence of TMEDA (Scheme 3). If (*R*)-**8** reacted with equal rates with both (*R*)- and (*S*)-**1e** then a 1:1 mixture of diastereomers **9** and **10** would result, whereas if the rates were different, one diastereomer would be formed predominantly, thus making it much more difficult to form all four stereoisomers. Experimentally, we found that a 1:1 mixture of **9** and **10** was obtained, thus showing that the rates of reaction k_1 and k_2 are not influenced by the stereochemistry of either partner (Scheme 3).



Scheme 3. Effects of stereochemistry on formation of **9** and **10**.

The iterative homologation process began with lithiation of **2a** (in the presence of (−)-sparteine) with subsequent trapping with EtB(pinacol), which gave the desired boronic ester intermediate **8** in 78% yield and 98:2 e.r. (Scheme 4). Reaction of boronic ester **8** with lithiated carbamate **1e** gave, after oxidative workup, alcohol **9** as a 96:4 mixture of diastereomers with e.r. > 98:2 (major diastereomer **9**; Scheme 4).[19] The other diastereomer (**10**) is potentially accessible by using the opposite enantiomer of the lithiated carbamate, *ent*-**1e**. In practice, this goal was easily achieved using O'Brien's enantiomeric sparteine surrogate (+)-**11**, derived from (−)-cytisine.[20] Indeed, O'Brien and co-workers have shown that diamine (+)-**11** can be effectively used in Hoppe-type lithiation of carbamates to deliver the opposite



Scheme 4. Iterative homologation of boronic esters **8** and *ent*-**8**.

enantiomer to (−)-sparteine with high enantiomeric ratios. Thus, using the opposite enantiomeric carbamate *ent*-**1e** in the same process gave the alternative diastereomer **10** with similarly high diastereo- (94:6 d.r.) and enantioselectivities (e.r. > 98:2; Scheme 4). The enantiomeric pair to **9** and **10** was readily obtained with similarly high d.r. and e.r. by using the same protocol but starting from *ent*-**8**, which was itself derived from the first homologation using O'Brien's enantiomeric sparteine surrogate (+)-**11** (Scheme 4).

These levels of enantio- and diastereoselectivity clearly show that the reaction is dominated by reagent control with no "matching" issues affecting the outcome of the second homologation, even though adjacent stereocenters are created.

In conclusion, we have developed a process for the homologation of boranes and boronic esters using Hoppe-type lithiated carbamates which shows very broad substrate scope. The Hoppe-type lithiated carbamates are effectively chiral carbenoids and are derived from the simplest of reagents: primary alcohols. The power of the methodology lies in its iterative use. Thus, through two cycles of the homologation process, either enantiomer of either diastereomer can be easily accessed through appropriate choice of the chiral diamine employed ((−)-sparteine **12** or (+)-**11**). Application of this versatile methodology in natural product synthesis is currently underway.

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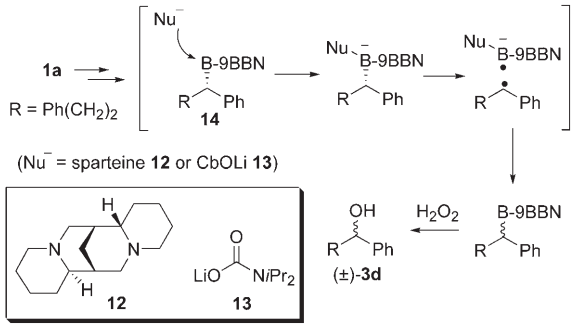
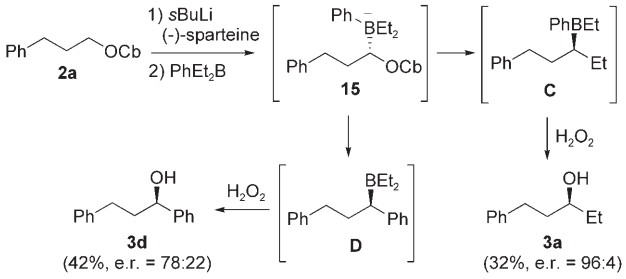
[10] In contrast, reactions of the same boranes with sulfur ylides only show high selectivity in the cases of Ph, alkenyl, and *i*Pr substituents.[3c] In fact, the only other examples where the boron substituent migrates in preference to the boracycle are cases involving a (small) halide leaving group or carbonylation. In all other cases, the boracycle migrates preferentially. Thus the large carbamate moiety is behaving as a small leaving group. For a discussion of the factors influencing the migration of groups on nonsymmetrical ate complexes of organoboranes, see: V. K. Aggarwal, G. Y. Fang, X. Ginesta, D. Howells, M. Zaja, *Pure Appl. Chem.* **2006**, *78*, 215.

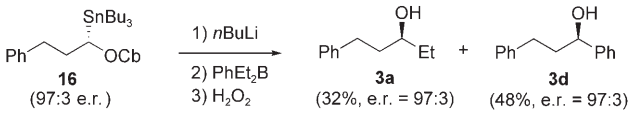
[11] We believe that this additive sequesters either (−)-sparteine **12** or the carbamate leaving group **13**, thus preventing it from binding to the borane **14**, which otherwise results in a degree of homolysis of the benzylic carbon–boron bond, thus lowering the e.r. as seen in the absence of $MgBr_2$ (entry 4, Table 1).



[12] Although it is possible for *B*-Ph-9-BBN to react with the lithiated carbamate with different enantioselectivity to other boranes, we were able to show that the difference in e.r. occurs after ate complex formation. Treatment of lithiated **1a** with the mixed borane $PhEt_2B$ gave, after oxidative workup, a mixture of the two alcohols (**3a** and **3d**) with enantiomeric ratios of 96:4 and 78:22, respectively (see below). Since the two alcohols are derived from the common intermediate **15**, this species must be formed with at least 96:4 e.r. Intermediate **15** undergoes stereospecific migration of Et and Ph groups leading to boranes **C** and **D**, respectively. Oxidation of borane **D** led to substantial loss of e.r. whilst **C** did not. However, boranes related to **D** had been generated in our sulfur ylide reactions with no loss of e.r.[3a] The difference in this case is that **D** is generated in the presence of agents capable of binding strongly to boron ($LiOC(O)NiPr_2$, **13**) or good electron donors ((−)-sparteine, **12**), which, after association, could cause some degree of homolytic cleavage of the C–B bond. This process would, in turn, cause the erosion in e.r. observed.



We have established that it is in fact the diamine ((−)-sparteine, **12**) and not the leaving group ($LiOC(O)NiPr_2$, **13**) that is responsible for the erosion in e.r. Reaction of **16** with *n*BuLi gave the diamine-free lithiated carbamate, which after trapping with $PhEt_2B$ and oxidative workup again furnished the alcohols **3a** and **3d**, but this time with identical e.r. values.



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[14] Rearrangement did not occur at 25 °C (^{11}B NMR). Heating of ate complex **4** at reflux in Et_2O in the presence of $MgBr_2$ for 12 h was required to achieve 1,2-metalate rearrangement.

[15] Observed using varible-temperature ^{11}B NMR spectroscopy; the reaction was monitored beginning at −80 °C and warmed up by 10 °C increments every 5 min over 35 min. Rearrangement of ate complex **4** began at −40 °C.

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[18] The e.r. was determined via conversion of amine **5** to the acetamide by hydrogenolysis and subsequent treatment with Ac_2O in pyridine.

[19] The enhancement of the enantiomeric ratio always occurs when two enantioselective operations are mapped onto the same substrate. In theory, if the first homologation gives an x:y. ratio of enantiomers (97–98:3–2 ratio observed for both (−)-sparteine **12** and (+)-**11**), then, assuming there is no kinetic resolution (both enantiomers of the boronic ester react at the same rate) or double stereo differentiation (the second homologation is not affected by the asymmetric center formed in the first step of the reaction), the ratio of enantiomers for the second homologation will be $x^2:y^2$. (99.8:0.2 expected; e.r. > 98:2 observed). The enantiomeric excess of the doubly homologated product is therefore considerably increased. One can view this as the $x^2:y^2$ rule. This process also generates the diastereomeric compound (amount = $2xy$; 94:6 expected; 90–96:10–4 observed). See the following for previous discussions of enantiomeric amplification: a) E. Negishi, *Dalton Trans.* **2005**, 827; b) V. K. Aggarwal, B. N. Esquivel-Zamora, G. R. Evans, E. Jones, *J. Org. Chem.* **1998**, *63*, 7306; c) S. E. Baba, K. Sartor, J.-C. Poulin, H. B. Kagan, *Bull. Chim. Soc. Fr.* **1994**, *131*, 525.

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