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Asymmetric Lithiation–Substitution of Amines Involving Rearrangement of Borates

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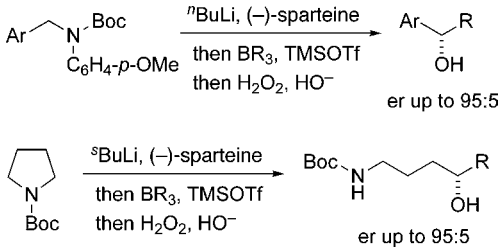
ABSTRACT



Asymmetric lithiation of substituted benzylamines, *N*-Boc-pyrrolidine, or *N*-Boc-indoline using Beak's methodology was followed by electrophilic quench with trialkylboranes. The resulting borate intermediates rearrange with concomitant C–N bond breakage to give, after oxidation, chiral secondary alcohols with high enantioselectivity.

(−)-Sparteine is highly effective as a chiral ligand for the asymmetric deprotonation of several carbamates.[1] The resulting chiral organolithium species can be trapped with a variety of electrophiles.[2] For example, Hoppe and co-workers have described the formation of chiral organolithiums such as **2** by preferential removal of the *pro*-(*S*) proton of carbamate **1** (Scheme 1).[3] A recent extension of this chemistry involves the addition of a borane which, after ate complex formation and stereospecific 1,2-metalate rearrangement with expulsion of the carbamoyloxy moiety, furnishes the homologated borane **3**.[4] Oxidation then gives the secondary alcohol **4** with high enantiomer ratio (er) (e.g., R = CH_2Ph, 91% yield, er 98:2). This sequence was also effective with boronate esters, but higher temperatures were required to trigger the 1,2-metalate rearrangement. Furthermore, the iterative use of this process allows the construction of scaffolds bearing multiple stereocenters with high diastereo- and enantioselectivities.[4a]

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(1) (a) Hoppe, D; Hense, T *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(2) (a) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002. (c) *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer−Verlag: Heidelberg, 2003. (d) Gawley, R. E.; Coldham, I. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; p 997. (e) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2004; p 1055.

(3) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. See also (b) Genet, C.; McGrath, M. J.; O'Brien, P. *Org. Biomol. Chem.* **2006**, *4*, 1376.

(4) (a) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7491. Hoppe has also described reactions of **2** with triisopropyl borate followed by borate ester exchange and addition of a Grignard reagent to give similar products; se:e (b) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett.* **2004**, 2275. For other related examples of reactions of lithiated *O*-alkyl carbamates with triisopropyl borate or an aryl boronate ester, see: (c) McGrath, M. J.; O'Brien, P. *Synthesis* **2006**, 2233. (d) Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193.

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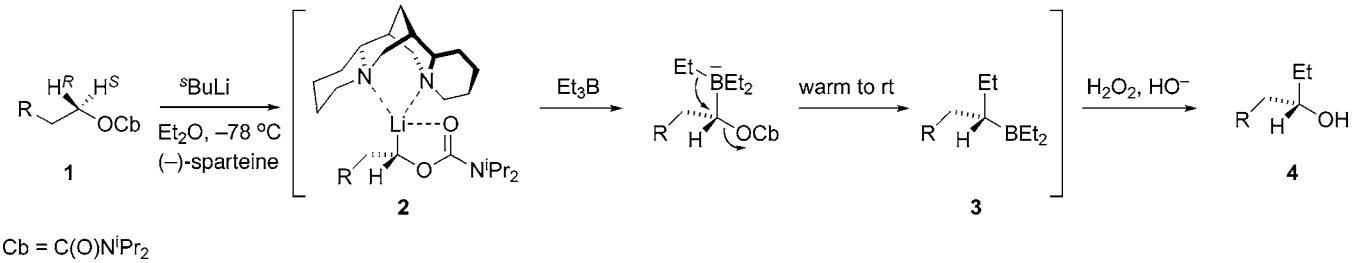
Scheme 1. α-Carbamoyloxyalkyl Boronates



The rearrangement requires the presence of a suitable leaving group, which in the above case is the carbamoyloxy moiety. Rearrangements with loss of a halogen were developed originally by Matteson and co-workers.[5] Recently, methodology involving addition of sulfur ylides to organoboranes has proved highly effective, and in this case, a thioether acts as the leaving group.[6] We wondered whether *N*-linked carbamates (which would be expected to be less good leaving groups than *O*-linked carbamates) would be suitable for this type of chemistry. We were particularly attracted to this study because of the ready availability of a range of chiral α-amino-organolithium species.

The substituted benzylamines **5** are known to undergo asymmetric deprotonation with *n*-BuLi and (−)-sparteine to give the (*R*)-organolithiums **6**, which are configurationally stable at low temperature (Scheme 2).[7] To test the ability of these compounds to undergo electrophilic quench and borate rearrangement, we treated the organolithiums **6** with triethylborane or tributylborane at −78 °C. Subsequent addition of TMSOTf (vide infra) and then warming followed by oxidative workup gave the alcohols **9**. Good yields of the products **9** and high enantioselectivities were obtained (measured using chiral HPLC with a Chiralcel OD column or chiral GC with a *β*-cyclodextrin column) (Table 1).

The secondary alcohols **9** were formed as predominantly the (*S*)-stereoisomer (er up to 95:5). As the oxidative workup (**8** to **9**) proceeds with retention of configuration, and the rearrangement of the borate **7** proceeds with inversion of configuration and then the intermediate **7** must have (*S*)-stereochemistry as drawn in Scheme 2. Since the absolute configuration of the chiral organolithium **6** has been established,[7b] electrophilic quench of the organolithium **6** with boranes must proceed with inversion of configuration. This contrasts with the reaction of the chiral organolithium **2**, which occurs with retention of configuration.[4] However, electrophilic quench with inversion of configuration is known for the organolithium **6**, particularly using reactive and/or non-lithium coordinating electrophiles.[7]

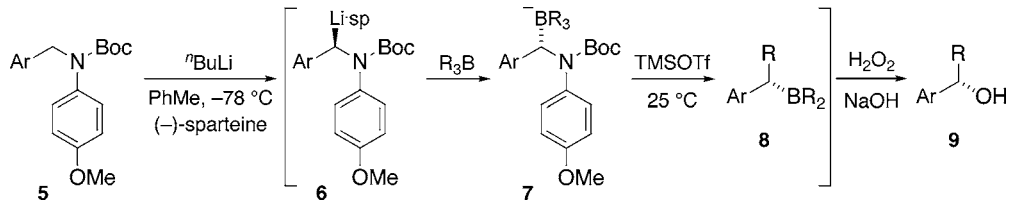
Table 1. Conversion of **5** to **9**

Ar	R	product	yield (%)	er (*S*/*R*)
Ph	Et	**9a**	83	95:5
Ph	Bu	**9b**	82	95:5
p-MeOC$_6$H$_4$	Et	**9c**	82	95:5
p-MeOC$_6$H$_4$	Bu	**9d**	72	95:5
p-FC$_6$H$_4$	Et	**9e**	79	95:5
p-FC$_6$H$_4$	Bu	**9f**	68	92:8
p-MeC$_6$H$_4$	Et	**9g**	62	92:8
p-MeC$_6$H$_4$	Bu	**9h**	64	92:8

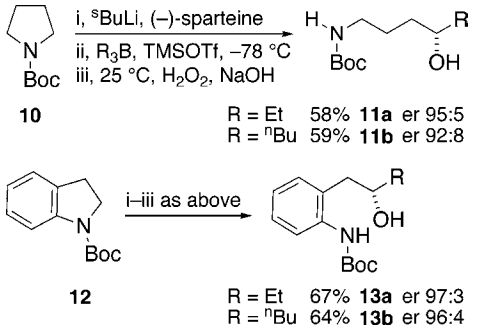
The electrophilic quench and rearrangement was successful for a variety of aryl substituents to give a selection of chiral secondary alcohols **9**. However, workup of the reaction (Ar = Ph, R = Et or *n*-Bu) with the aminating agent NH_2OSO_3H gave the same alcohol (**9a** or **9b)** (rather than the corresponding primary amine), which was isolated in up to 82% yield with low enantioselectivity. This implies that the borane **8a** (and **8b**) does not react with NH_2OSO_3H, which is in contrast to that reported by Aggarwal and co-workers.[6a] This may be due to coordination of the boron to the aniline (or sparteine) to give a species that is unreactive to NH_2OSO_3H and eventually breaks down to the benzyl radical that is oxidized to the alcohol **9**. Addition of $MgBr_2$ or HCl to break up any such complex prior to addition of NH_2OSO_3H was unsuccessful.

To broaden the scope of this chemistry, we explored the asymmetric lithiation of *N*-Boc-pyrrolidine[8] and *N*-Boc-indoline,[9] followed by electrophilic substitution and rearrangement (Scheme 3). Initial investigations revealed that

Scheme 2. Rearrangement of Lithiated Benzylamines (See Table 1)



Scheme 3. Rearrangement of Lithiated Pyrrolidines



the yields of the products **11** were significantly improved by the addition of the Lewis acid TMSOTf, which presumably coordinates to the Boc group to aid rearrangement.[10]

The enantiomer ratios of the products **11** were determined by chiral HPLC (Chiralcel OD column) after conversion to the *p*-bromobenzoate derivatives. The enantiomer ratios of the products **13** were determined directly by chiral HPLC (Chiralcel OD column). The structure of the secondary alcohol **13b** (R = Bu) was confirmed by X-ray structure analysis (see the Supporting Information). To determine the absolute configuration (which was not possible from the X-ray of **13b**), the alcohol **13a** was converted to the derivative **14** and X-ray crystal structure analysis was performed (Figure 1) (see the Supporting Information). On the basis of the refined absolute structure parameter,[11] the product has (*S*)-stereochemistry. As asymmetric deprotonation of *N*-Boc-pyrrolidine and *N*-Boc-indoline occur to give the (*S*)-enantiomer of the organolithiums,[8,9,12] the fact that the (*S*)-enantiomer of the product **13a** (and by assumption **11a**,**b** and **13b**) is formed implies that the electrophilic quench of these organolithiums occurs with retention of configuration at the carbanion carbon to give the borates **15** and **16** (Figure 2). Reaction of *N*-Boc-2-lithiopyrrolidine and *N*-Boc-2-lithioindoline with retention of configuration at the carbanion center is in line with all other known electrophilic quenches of these anions.[1,2,13]

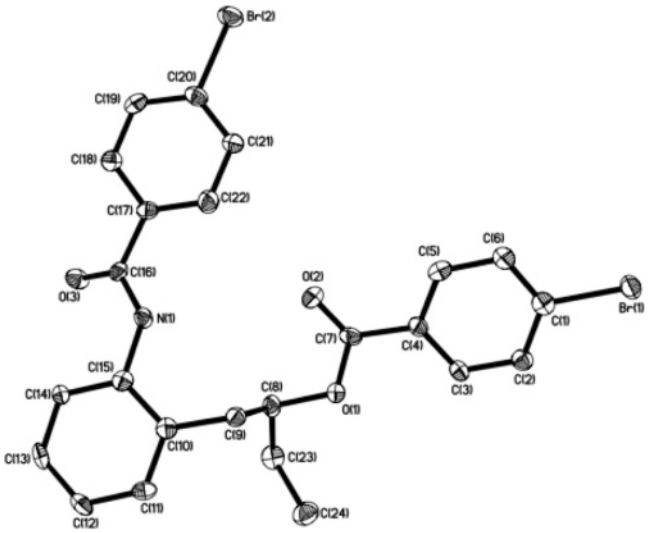


Figure 1. X-ray crystal structure of compound **14**.

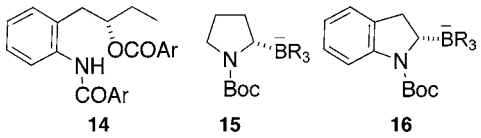


Figure 2. Derivative **14** (Ar = *p*-BrC_6H_4) and borate intermediates **15** (from **10**) and **16** (from **12**), R = Et or ^{n}Bu.

In summary, we have developed the electrophilic quench of several chiral α-amino-organolithiums, followed by rearrangement of the intermediate borates. This gives a selection of chiral secondary alcohols with high levels of enantioselectivity. The *N*-linked carbamates are evidently poorer leaving groups than *O*-linked carbamates, but 1,2-rearrangement of the intermediate ate complexes (formed by electrophilic quench with trialkylboranes) can be promoted by Lewis acid activation.

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Supporting Information Available: Experimental procedures; chiral chromatography traces for the alcohols **9**, **11** (as *p*-bromobenzoate esters), and **13**; crystallographic data for compounds **13b** and **14**; spectroscopic data and NMR spectra for the products **11** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702734U

(5) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.

(6) This chemistry is only applicable to boranes and not boronate esters: (a) Aggarwal, V. K.; Fang, G. Y.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642. (b) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 359. (c) Fang, G. Y.; Wallner, O. A.; Blasio, N. D.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632. For a discussion of leaving group ability of onium ions in this type of reaction, see: (d) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468.

(7) (a) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757. (b) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.

(8) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(9) Bertini Gross, K. M.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.

(10) In related reactions employing boronate esters [e.g., EtB(pin)] instead of boranes, the use of TMSOTf was not sufficient to promote rearrangement. It has been reported that the activation barrier for rearrangement of borate complexes is significantly higher with oxygen substituents on boron compared to carbon substituents. For example, the rearrangement shown in Scheme 1 begins to occur at −40 °C, whereas the related reaction of borate esters requires +40 °C and Lewis acid action ($MgBr_2$). See ref 4a and: (a) Stoddard, J. M.; Shea, K. J. *Chem. Commun.* **2004**, 830. (b) Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 3397.

(11) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.

(12) Gawley, R. E.; Narayan, S.; Vicic, D. A. *J. Org. Chem.* **2005**, *70*, 328.

(13) For electrophilic quench with borates, which occurs with retention of configuration, see: Batsanov, A. S.; Grosjean, C.; Schutz, T.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 6276.