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Preparation of Enantioenriched α-Silyl-Benzylcarbamates

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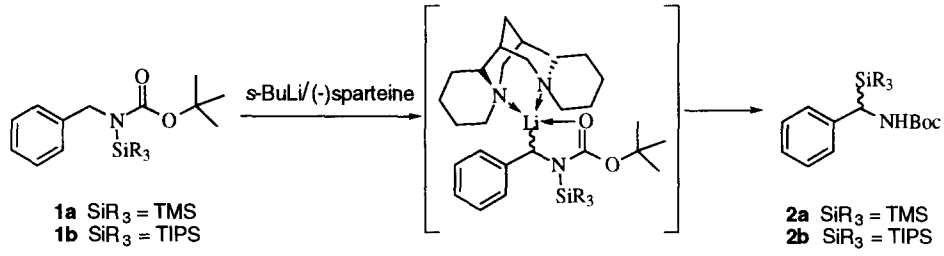
Abstract: The first examples of an enantioselective [1,2] silicon rearrangement are reported. This novel synthetic method lead to the formation of chiral α-substituted benzylamines with an α-silyl group. In the procedure, *N*-Silyl-protected *N*-Boc benzylamines are subjected to enantioselective deprotonation using the chiral complex (-) sparteine•*s*-BuLi to generate chiral benzyllithium intermediates that undergo a [1,2] silicon shift.

In the course of our work on the synthesis of unnatural amino acids,[1] we synthesized[2] *N*-*t*-Boc *N*-silyl benzylamine **1** as substrate for enantioselective deprotonation using the complex *s*-BuLi•(-)sparteine as chiral base.[3] We observed that such substrates underwent a silicon rearrangement, which creates a new C-Si bond (Scheme 1).[4]



Scheme 1

Herein, we report the first examples of a [1,2] silicon rearrangement of achiral *N*-silyl *N*-*t*-Boc benzylamines that generate enantioenriched α-silyl benzylcarbamates such as **2**.[5] The importance of enantioenriched benzylsilanes in medicinal chemistry and chirotechnology makes compounds like **2** useful chiral intermediates since their stereoselective transformations have been reported.[6] The starting *N*-silyl protected carbamates can be easily prepared by treatment of *N*-Boc benzylamine with a silyl triflate.[2] Treatment of the *N*-*t*-Boc *N*-TMS benzylamine **1a** with the chiral complex, either preformed or formed *in situ*, at -78°C for 3h followed by warming at 0°C resulted in clean rearrangement products in good isolated yields[7] ranging from 51-67%. Results are summarized in Table 1.

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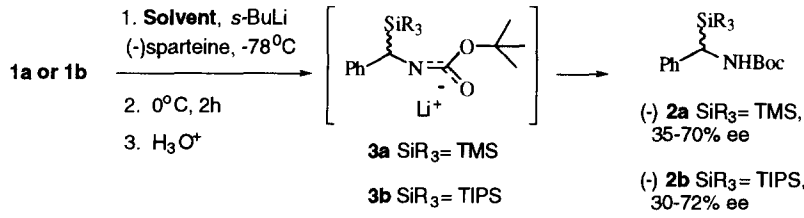
Table 1. Yields and enantiomeric excesses of (-)**2a** obtained using (-)sparteine.*s*-BuLi, preformed or formed *in situ*, as the chiral base.

Entry	Chiral complex	Solvent	Lithiation time (h)	Isolated yield (%)	ee (%)[11]
1	*in situ*	Et_2O	0.5	60	35
2	*in situ*	Et_2O	1	66	35
3	*in situ*	Et_2O	3	63	30
4	preformed	Et_2O	3	56	50
5	*in situ*	Hexane	0.5	67	60
6	*in situ*	Hexane	1	60	65
7	*in situ*	Hexane	3	63	70
8	preformed	Hexane	3	51	55

The results demonstrate that the rearrangement occurs very rapidly and in all cases the (-) enantiomer is obtained preferentially. After 30 min in hexane, a 67% yield is obtained using the complex formed *in situ* (Table 1, entry 5). Longer reaction times did not lead to better yields. The rearrangement is probably driven forward by the stability of the carbamoyl anion (Scheme 2, **3a** and **3b**) relative to the carbanionic starting material. Regarding the enantiomeric excesses, we observed that the duration of reaction and the solvent are important factors.



Scheme 2

To exclude the possibility of an intermolecular silicon transfer, we tried to quench at -78°C the chiral anionic center with trimethylsilyl chloride, an excellent electrophile known to react by retention with organolithiums.[8] The reaction was performed in ether at -78°C during 3h to generate the chiral anionic center using *s*-BuLi.(-)sparteine complex. The external electrophile was then introduced at -78°C and the reaction was allowed to warm and stand at 0°C for 2h before the usual work-up. After purification, compound **2a** was obtained in 65% yield and 30% enantiomeric excess, about the same results were obtained without additional electrophile (Table 1, entry 3). We also tried to quench the reaction with up to 10 electrophile equivalents, but we obtained the same enantiomeric excess. Furthermore, when we used *t*-butyldimethylsilyl chloride as electrophile, the major product (65%) was the intramolecular rearrangement product **2a**. Only traces of the crossing

experiment compound were found. These results strongly suggest that the intermolecular reaction is too slow in comparison with the intramolecular [1,2] rearrangement.

It has been reported by Beak[9] that (-)sparteine.*s*-BuLi complex abstract selectively the Pro-*R* proton in a related system. However, Schlosser[10] reported that the Pro-*S* proton of *N*-Methyl *N*-BOC benzylamine is abstracted selectively by the same chiral complex. In addition, the absolute stereochemistry of the **2a** and **2b** is not known, therefore it is not possible at this point to conclude which proton is abstracted preferentially in our substrate and if the rearrangement occurs with retention or inversion. Work is in progress along these lines. In an attempt to improve enantioselectivities, we tried to rearrange *N*-TIPS benzylcarbamate **1b**. The rearrangement of **1b** was performed under the previous conditions and the results are summarized in Table 2.

Table 2. Yields and enantiomeric excesses of (-)**2b** obtained using (-)sparteine.*s*-BuLi, preformed or formed *in situ*, as the chiral base.

Entry	Chiral complex	Solvent	Isolated yield (%)	ee (%)[11]
1	*in situ*	Et_2O	80	30
2	preformed	Et_2O	80	60
3	*in situ*	Hexane	72	72
4	preformed	Hexane	80	65

In this case, better yields (~80%) were obtained as compared with the *N*-TMS analog. It appears that the more stable *N*-TIPS bond is less influenced by the reaction conditions. On the other hand, the bulkier TIPS group may favorably migrate more rapidly than the TMS group to release steric hindrance. However, the use of *N*-TIPS substrate did not give higher enantiomeric excesses. The best result being 72% ee in hexane with the complex formed *in situ* (Table 2, entry 3).

In conclusion, we have described the first examples of a chiral [1,2] silicon rearrangement of *N*-silyl benzylcarbamates, which are easily prepared.[2] The rearrangement occurs rapidly with good yields and with enantiomeric excesses up to 72%. This novel and simple methodology leads to chiral enantioenriched α-silyl benzyl carbamates that could be subsequently transformed into useful compounds. We are currently exploring the mechanistic details, as well as the scope and the limitation of this transformation.

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References and notes:

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2. Roby, J.; Voyer, N. *Tetrahedron Lett.* **1997**, *38*, 191.
3. (a) For a leading reference on the use of (-)sparteine.*s*-BuLi in enantioselective deprotonation see: Beak,

P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (b) For its use in enantioselective ring opening rearrangements see: Lautens, M.; Gajda, C.; Chui, P. *J. Chem. Soc., Chem.Comm.*, **1993**, 1193-94.

4. The present rearrangement is analogous to the [1,2] Aza-Wittig rearrangement which creates a C-C bond.For a recent review on this transformation see: Vogel, C. *Synthesis*, **1997**, 497.
5. For a recent example of achiral [1,2] silicon rearrangement see: Sieburth, S. McN.; Somers, J. J.; O'Hare, H. K.; Hewitt, G. W. *Appl. Organometal. Chem.* **1997**, *11*, 337.
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7. Typical procedure: At -78°C, 1.1 eq of *s*-BuLi (1.24mmol) was added to freshly distilled (-) sparteine in 3 mL of solvent. The mixture was stirred for 15 min then cannulated to a solution of **1a** or **1b** (1.13mmol) in 1.5 mL of solvent. The resulting mixture was stirred at -78°C for 3h before being warmed to 0°C for 2h. After quenching with 1N HCl, the solution was extracted twice with ether. The organic layers were combined, dried over $MgSO_4$ and evaporated to give the crude product **2a** or **2b**. The latter was purified by flash chromatography with a hexane-AcOEt mixture (9:1) as eluent to give a white solid.
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10. Schlosser, M. and Limat, D. *J. Am. Chem. Soc.*, **1995**, *117*, 11561-70.
11. To determine the enantiomeric excesses, samples were deprotected by treating the *N-t*-Boc compounds with a mixture (1:1) of TFA/CH_2Cl_2 at 0°C for 10 min. Volatile compounds were removed under reduced pressure. The resulting materials were diluted in $CDCl_3$, washed three times with a saturated $NaHCO_3$ solution and dried over K_2CO_3. After filtration, ^1H NMR measurement of the diastereomeric complexes, formed *in situ* by the addition of 1 eq of (*S*) (+)-mandelic acid, were performed. The signals of the α-CH groups of the two diastereomeric complexes are easily measured at 3.03 (major) and 2.81 (minor) ppm.