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An Expedient Enantioselective Synthesis of *N*-*t*-Boc-Protected Phenylsarcosine.

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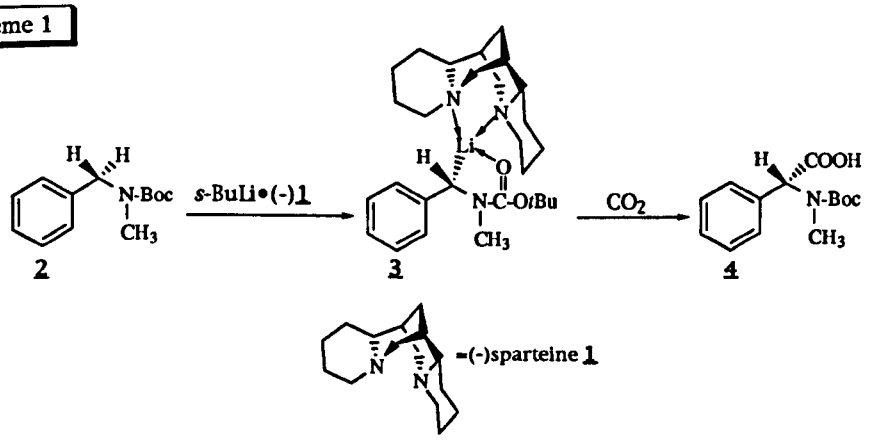
Abstract: Herein we describe a novel approach to the asymmetric synthesis of *N*-*t*-Boc-phenylsarcosine. The synthesis involves the enantioselective deprotonation at the benzylic position of *N*-*t*-Boc-N-methylbenzylamine **2** using the chiral complex *s*-BuLi/(-) sparteine **1** followed by a stereoselective carboxylation.

Derivatives of phenylglycines and phenylsarcosines are useful in the preparation of bioactive peptide analogues with enhanced proteolytic stability and restricted backbone conformations. However, there is no general and direct method for the enantioselective preparation of these types of amino acids. Here, we wish to report our results on the development of an expedient enantioselective synthesis of *N*-*t*-Boc-protected phenylsarcosine ready to use in solid phase peptide synthesis.

Scheme 1



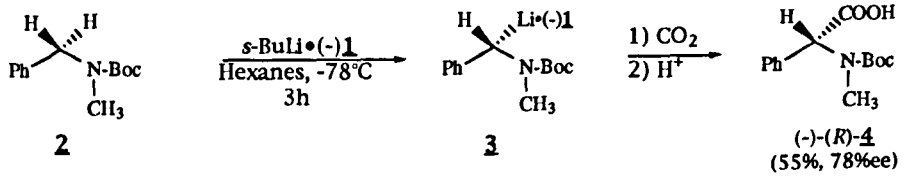
2 **3** **4**

The first step in our synthetic approach involves the enantioselective deprotonation of *N*-*t*-Boc-*N*-methylbenzylamine **2** using the chiral complex *s*-BuLi/(-)sparteine **1** (Scheme 1). This complex has been used recently for the successful enantioselective deprotonation of carbamate protected alcohol[1] and *N*-*t*-Boc-protected pyrrolidine.[2] The chiral benzyllithium generated (**3**) was treated with CO_2 to give directly *N*-*t*-Boc-phenylsarcosine **4**. Recently, chiral α-substituted benzyllithiums like **5** have been shown to be

configurationally stable under certain conditions, especially when they are dipole stabilized[3] and chelated by a diamine ligand.[4]

When compound **2** was deprotonated with the chiral complex *s*-BuLi/(-)**1** in hexanes at -78°C for 3h and quenched with CO_2, (-)-*R*-*N*-*t*-Boc-phenylsarcosine **4** was obtained in a 55% yield with a 78% enantiomeric excess (Scheme 2).[5]

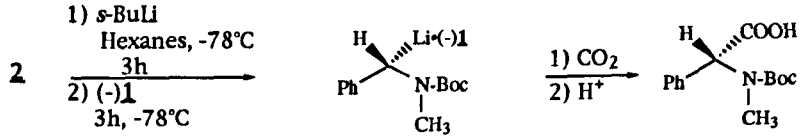
Scheme 2



2 **3** (-)-(*R*)-**4** (55%, 78%ee)

The precomplexation of (-)sparteine **1** and *s*-BuLi is important for the selectivity since the same reaction performed without preforming the complex led to **4** with an 85% yield but with a 39% enantiomeric excess (Scheme 3).

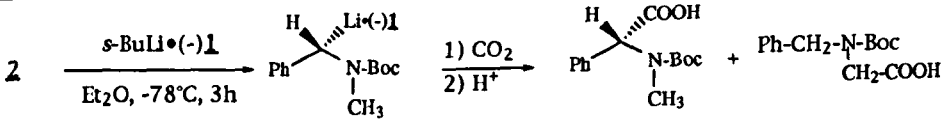
Scheme 3



3 (-)-(*R*)-**4** (82%, 39%ee)

In addition, the enantioselectivity also depends on the solvent. The use of ether instead of hexanes gave roughly the same yield (52%) of the acid **4**, but with a lower enantiomeric excess (60%) (Scheme 4). It is interesting to note that, in ether, 5% of compound **5** was also obtained through deprotonation of the *N*-methyl group. This type of deprotonation has been observed recently[6] in the reaction of *N*-*t*-Boc-protected methylalkylamines.

Scheme 4

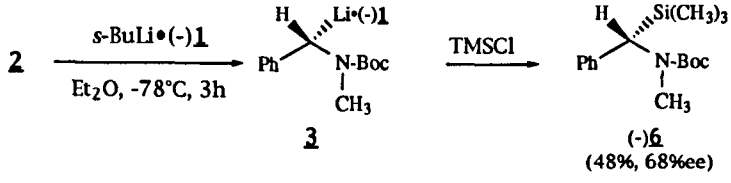


3 (-)-(*R*)-**4** (52%, 60%ee) **5** (5%)

To determine if the reaction mechanism proceeds through an enantioselective deprotonation or an enantioselective substitution as recently observed by Beak[7] for a benzylic organolithium, the racemic intermediate **3** was generated with *s*-BuLi and then (-)sparteine **1** was added. After 1h at -78°C, CO_2 was bubbled through the reaction mixture and the acid **4** was obtained in 39% yield in a racemic form. Therefore, the reaction proceeds via an enantioselective deprotonation.[8]

On the other hand, if the carboxylation of **3** occurs by retention,[9] then the reaction proceeds through the abstraction of the *re* proton of the prostereogenic methylene group of **2**. The preference of the *s*-BuLi/(-) sparteine **1** complex for the *re* proton has been established.[1] However, Hoppe has reported that a benzylic organolithium reacted stereoselectively with CO_2 with inversion.[3] It is therefore difficult at this stage to assess accurately which prostereogenic proton is being abstracted. In addition, it is possible that the reaction of **3** with CO_2 is not completely stereoselective. So to prove this, we trapped the organolithium **3** with TMS chloride an excellent electrophile known to react stereoselectively with organolithiums by retention (Scheme 5).[4] Compound **6** was obtained in a 48% yield with an enantiomeric excess of 68% which is comparable to the results obtained with CO_2. The carboxylation is therefore stereoselective and it appears that the enantioselectivity is limited by the deprotonation step.

Scheme 5



In summary, the results reported demonstrated the viability of this new approach to the enantioselective preparation of *N*-*t*-Boc-phenylsarcosine derivatives ready to use in solid phase peptide synthesis. Furthermore, we have shown that the benzylic organolithium **3** is configurationnally stable under the conditions used and that the mechanism proceeds through an enantioselective deprotonation. We are currently working to optimize this reaction and to apply it to other substrates.

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References and notes:

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3. Beak, P.; William, J.Z. *Chem. Rev.* **1984**, *84*, 471-523.
4. Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1424-25.; Haller, J.; Hense, T.; Hoppe, D. *Synlett* **1993**, 726-8.
5. **Typical experiment:** To a solution of (-)sparteine **1** (Sigma) (1.1 eq, 1.24 mmol) in 3 mL of Et_2O at -78°C, *s*-BuLi (1.1 eq, 1.24 mmol) is added dropwise. The mixture is stirred 15 min then cannulated to a solution of **2**[10] (1 eq, 1.13 mmol) in 1.5 mL of Et_2O at -78°C. The resulting mixture is stirred at -78°C for 3h, then CO_2 is bubbled for 20 min. After 30 min at -78°C, the mixture is warmed to room temperature. The mixture is acidified with 2N HCl and the ether is separated and extracted with 1N NaOH solution. The alkaline layer is separated, acidified with 2N HCl, and extracted with Et_2O. The organic phase is dried, filtered, and evaporated to give a crude colorless oil. The latter is triturated with hexanes to yield **4** as a white powder which was caracterized by ^1H NMR and GCMS. The enantiomeric excesses were determined by optical rotation (litt. value: $[\alpha]_D^{25}$=-134° (c=1 in EtOH) (Kinoshita, H.; Shintani, M.; Saito, T.; Kotake, H. *Bull. Chem. Soc. Jpn* **1971**, *44*, 286-7) and by ^1H NMR using (+)-*R*-naphtylethylamine as chiral shift reagent in $CDCl_3$.
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7. Thayumanavan, S.; Lee, S.; Lui, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, 116, 9755-6; Beak, P.; Du, H. *ibid* **1993**, *115*, 2516-8.
8. As suggested by a referee, another possible explanation for this result is that the purpose of preforming the (-)sparteine•*s*-BuLi complex is to force the chiral ligand to chelate an equilibrating enantiomeric mixture of **3** to form diastereomeric complexes. Therefore, the asymmetric induction could be the result of a kinetic resolution mechanism rather than an enantioselective deprotonation.
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10. *N*-*t*-Boc-*N*-methylbenzylamine **2** was prepared using the procedure of Bold (*Helv. Chim. Acta* **1990**, *73*, 405-10). Briefly, under N_2, *N*-methylbenzylamine (1 eq), di-*t*-butyldicarbonate (2 eq), DMAP (0.1 eq), and triethylamine (9 eq) were dissolved in CH_2Cl_2 and stirred for 60h at 25°C. After washing with 0.1N HCl, the organic phase was dried with anhydrous $MgSO_4$, filtered, and evaporated to give 87% of **2**.

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