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Enantioselective Synthesis of Phenylglycines Using (-) Sparteine•*s*-BuLi Complex

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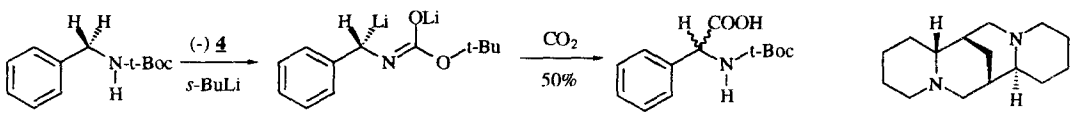
Abstract: The enantioselective synthesis of *N*-*t*-Boc protected phenylglycine derivatives is reported. The synthetic strategy involved the enantioselective deprotonation of *N*-*t*-Boc-*N*-TMS protected benzylamines using the (-) sparteine•*s*-BuLi complex. © 1997 Published by Elsevier Science Ltd.

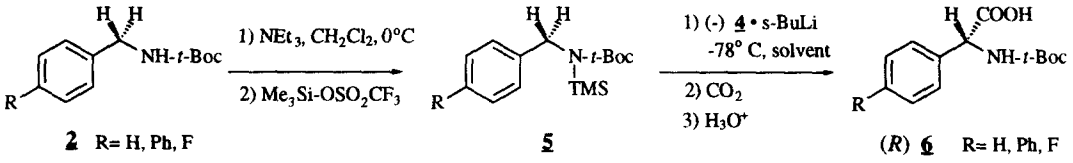
The synthesis of unnatural aminoacids, in particular phenylglycines, is of great interest for their use in medicinal chemistry.[2] As part of our research program on the development of peptide based supramolecular devices[3], we required the preparation of *N*-*t*-Boc protected phenylglycine derivatives **1**. Toward that goal, we sought to synthesize **1** by the strategy illustrated in Scheme 1 using the versatile (-) sparteine **4** •*s*-BuLi complex as chiral base.[4] The key steps were the enantioselective deprotonation of the *N*-*t*-Boc protected benzylamine **2** by the chiral complex and the stereoselective carboxylation of the dianionic specie **3**. Although **1** was prepared by that route in a 50% yield, no chiral induction was observed.[5] This was attributed to the presence of the negative charge on the carbamate which decreases the configurational stability of the benzylic organolithium **3**. Indeed, the replacement of the carbamate proton by a methyl group lead to the enantioselective synthesis of *N*-*t*-Boc protected phenylsarcosine.[6]



2 **3** **1** 0%ee (-) **4**

Scheme 1

Based on that groundwork, we now report a practical enantioselective synthesis of *N-t*-Boc protected phenylglycine derivatives **6**. The strategy (Scheme 2) involves the temporary protection of the carbamate by a trimethylsilyl group using a procedure we described recently.[7] Treatment of the *N*-TMS *N-t*-Boc protected benzylamine **5** with 1 equivalent (-) sparteine•*s*-BuLi complex in ether or hexane followed by addition of CO_2 gave *N-t*-Boc phenylglycine in yields between 10-86% and enantiomeric excesses ranging from 29 to 96%.[8] The reactions were performed either by pre-forming the chiral complex and cannulating it at -78 °C into the reaction mixture or by forming the complex *in situ*. Also, the influence of electron-withdrawing groups at the *para* position of the benzylamine was investigated. The results are reported in Table 1. From these results, several points can be noted.



2 R= H, Ph, F **5** (*R*) **6** R= H, Ph, F

Scheme 2

Table 1. Yields and enantiomeric excesses obtained for the preparation of (*R*) *N-t*-Boc protected phenylglycines **6** in ether and hexane using (-) **4**•*s*-BuLi, pre-formed or formed *in situ*, as the chiral base.

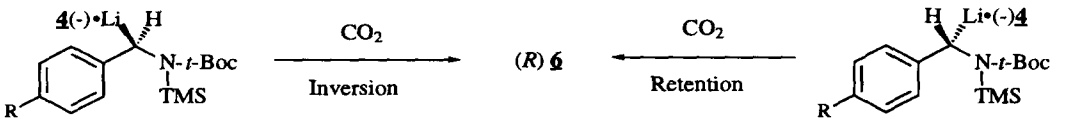
		pre- formed		formed *in situ*	
5 (R)	Solvent	% yield	% ee[9]	% yield	% ee[9]
H	Ether	86	42	45	53
H	Hexane	10	62	37	40
Ph	Ether	28	73	15	44
Ph	Hexane	12	88	41	96
F	Ether	32	64	52	29
F	Hexane	18	84	44	58

In almost all cases, the yields are higher in ether but the enantiomeric excesses are lower than the ones in hexane. In addition, the enantioselectivities are more pronounced generally when using the pre-formed complex (-) sparteine•*s*-BuLi. The notable exception is the case of the *p*-phenyl substrate which leads to the corresponding phenylglycine with 96% ee when forming the chiral complex *in situ*. Finally, the (*R*) enantiomer is always predominant.

To gain insight into the reaction mechanism, the racemic organolithium intermediate leading to **6** was generated in hexane at -78 °C followed by the addition of an hexane solution of (-)sparteine (1.1 eq.). After 3h

of stirring the reaction mixture was quenched with CO_2. The *N*-*t*-Boc phenylglycine was produced with a low 11% ee. The different enantiomeric excesses obtained strongly suggests that the chirality originates most likely from an enantioselective deprotonation process and not by an asymmetric substitution process, as observed recently by Beak[10]. On the other hand, the obtention of the (*R*) enantiomer can be rationalized in two ways. First, the action of the chiral complex on the substrates can generate the (*R*) organolithium 7 that could react with CO_2 with *inversion* (Scheme 3). This mechanism has been reported by Beak in an elegant preparation of *N*-*t*-Boc phenylglycine through enantioselective deprotonation of *N*-*t*-Boc-*N*-(*p*-methoxyphenyl)benzylamine in toluene.[4b] In accord with these results, the deprotonation of **5** (R=H) with complex formed *in situ* in toluene also gave 52% of (*R*) *N*-*t*-Boc phenylglycine with 59% enantiomeric excess.

On the other hand, the deprotonation could occur on the *pro-S* proton yielding the (*S*)-organolithium 7 (Scheme 3). The latter could react with CO_2 with *retention* to give the observed enantiomer of phenylglycines. The propensity of (-)sparteine•sBuLi complex to abstract the *pro-S* proton of prostereogenic methylene groups is known.[11] Furthermore, Schlosser described recently that the (*S*) organolithium of *N*-*t*-Boc-*N*-methyl benzylamine reacted with retention with CO_2 in ether and hexane.[6b]



(*R*) 7 R= H, Ph, F (*S*) 7 R= H, Ph, F

Scheme 3

These two pathways account for the stereochemistry observed in our case. However, it is not possible at this point to determine which one is operating in our processes. We are currently working to elucidate the detailed reaction pathways involved and to explore the synthetic utility of the reported chiral organolithiums. In summary, we reported a short and efficient enantioselective synthesis of N-t-Boc phenylglycines starting from inexpensive and commercially available benzylamines. The strategy involved the generation of configurationally stable benzylic organolithiums with (-) sparteine•*s*-BuLi complex and their stereoselective reaction with CO_2. The (*R*) enantiomer is always favored with enantiomeric excesses varying from 40 to 96% and the (*S*) enantiomer could probably obtained following the stannylation/transmetallation strategy of Beak or by using methylchloroformate as electrophile.[4b]

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8. Typical procure: At -78 °C, 1.1 eq. of *s*-BuLi (1.24 mmol) was added to freshly distilled (-) sparteine in 3 mL of ether. The mixture was stirred for 15 min then cannulated to a solution of **5** (1.13 mmol) in 1.5 mL of ether. The resulting mixture was stirred at -78 °C for 3 h before CO_2 was bubbled through (20 min). After quenching with 2N HCl, the ether layer was separated and extracted with 1N NaOH. The alkaline layer was acidified with 2N HCl and extracted with ether. The organic phase was separated, dried over $MgSO_4$, and evaporated to give the crude product **6**. Trituration with hexane yielded pure **6** as a white powder which was characterized by ^1H and ^{13}C NMR and mass spectrometry.
9. Enantiomeric excesses were determined by polarimetry and by ^1H NMR in $CDCl_3$ by forming diastereoisomeric salts *in situ* with (*S*) (+)-mandelic acid and the methyl ester of phenylglycines obtained after treatment of **6** with CH_2N_2 and 4N HCl in dioxane.
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