Synthesis of Both Enantiomers of Phenylglycine Using (-)-Sparteine

Claude Barberis, Normand Voyer*

Département de chimie, Université Laval, Ste Foy, Québec, Canada G1K 7P4
Fax +1 (418) 656-7916; E-Mail: normand.voyer@chm.ulaval.ca
Received 14 April 1999

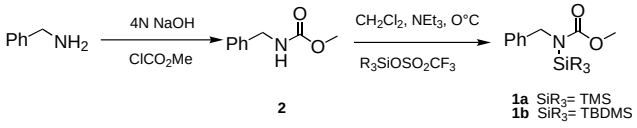
Abstract: The enantioselective synthesis of both enantiomers of the *N*-Moc phenylglycine derivatives is reported. The synthetic strategy shows the influence of *N*-protecting groups in the enantioselective deprotonation and carboxylation of *N,N*-protected benzylamine **1** using *s*-BuLi·(-)-sparteine complex **4** as chirality source.

Key words: enantioselective deprotonation, (-)-sparteine, carboxylation, silicon rearrangement, phenylglycine

In the development of enantioenriched unnatural aminoacids synthesis,[1] we explored the possibility of generating both enantiomers of *N*-protected phenylglycine using (-)-sparteine[2] as sole chiral source. Herein we report that a judicious choice of appropriate *N*-silyl protecting groups allows the selective preparation of both (*R*) and (*S*) *N*-Moc protected phenylglycine.

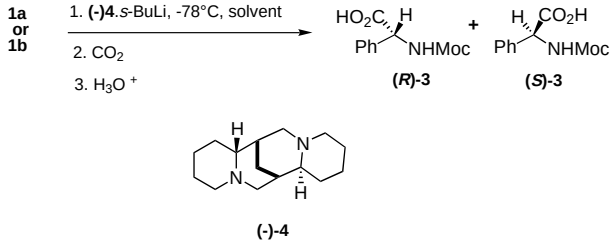
As premise to this work, Schlosser[3] described in 1995 an inversion of configuration of chiral organolithium intermediates in the synthesis of *N*-methyl phenylsarcosine due to a solvent effect. The process was a rapid racemization followed by restoration of the enantiomeric integrity. Also, Hoppe and Beak suggested[4] that the inversion of configuration at benzylic center can occur depending on the electrophile nature, as observed with CO_2 and methylchloroformate. On the other hand, Beak[5] developed a convenient method to obtain the ent-enantiomer not available directly with (-)-sparteine using a Sn/Li exchange process.

Our strategy though uses *N*-silylated *N*-Moc primary amines that are easily prepared using a practical method we have developed.[6] Compounds **1a** and **1b** were prepared in 80-90% yields using methylchloroformate in 4N NaOH followed by a carbamate silylation with silyl triflate reagents in dichloromethane in the presence of triethylamine (Scheme 1).



Scheme 1

They were submitted to deprotonation conditions (Scheme 2) using 1.1 equivalent of (-)-sparteine **4**·*s*-BuLi complex as chiral base.[7] 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*. The influence of the solvent and *N*-protecting groups were investigated. The results are summarized in Table 1.



Scheme 2

Table 1 Yields and enantiomeric excesses obtained in the preparation of the (*R*) and (*S*)-Moc-protected phenylglycines **3** using **(-)4**·*s*-BuLi, pre-formed or formed *in situ*, as chiral base.

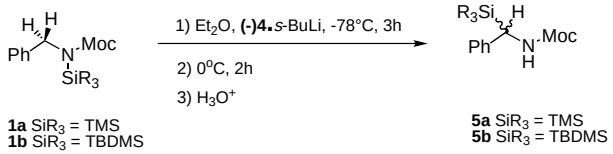
-SiR_3	Solvent	Complex	%Yield	%ee[8]
TMS	Et_2O	preformed	30	50(*R*)
,,	,,	*in situ*	33	49(*R*)
,,	Hexane	preformed	25	62(*R*)
,,	,,	*in situ*	30	37(*R*)
TBDMS	Et_2O	preformed	28	48(*S*)
,,	,,	*in situ*	32	27(*S*)
,,	Hexane	preformed	24	45(*S*)
,,	,,	*in situ*	22	24(*S*)

The results show that the *R* isomer is preferentially obtained from **1a** in roughly 30% yield and enantiomeric excesses varying from 37-62%. These results are very similar to the ones obtained with *N*-TMS *N*-Boc benzylamines.[1] Therefore switching to the less bulkier *N*-Moc has no direct influence on the yield and selectivity of the reaction process. These results indicate that the carbamate protecting group has mainly a stabilizing effect on the benzyllithium intermediates. However, when we used a bulkier silyl group such as TBDMS, we obtained about the same yields and enantiomeric excesses but, surprisingly, with the (*S*) isomer of **3**.

These results illustrate the direct influence of the silyl group on the selectivity of the process. In all cases with **1b**, the (*S)* isomer is formed preferentially over the (*R*)

isomer. This dramatic change in the enantioselectivity can occur at the deprotonation step or at the carboxylation step.

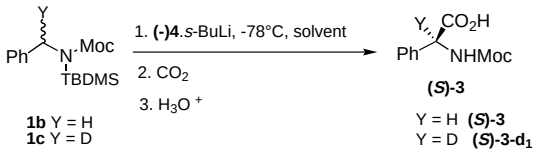
To confirm which proton was abstracted during the deprotonation step, we examined the silyl rearrangement of the compounds **1a** and **1b** (Scheme 3). Indeed, we have reported recently the enantioselective migration of a silicon group from nitrogen to carbon for *N*-silyl *N*-Boc benzylamine.[9] The experimental procedure involved the generation of the benzylic lithium intermediates at -78°C for 3h, and warming to 0°C for 2h, followed by the usual work-up.



Scheme 3

With both **1a** and **1b**, we observed that the molecules rearrange with excellent yields (up to 80%). Most importantly, we also obtained the same $[\alpha]_D$ sign for **5a** and **5b**. These observations strongly suggest that the same absolute configuration is generated in **5a** and **5b** and that the same proton is abstracted by the chiral complex. Therefore, the deprotonation step is not responsible for the inversion of configuration observed in the process described in Scheme 2. The inversion occurs most probably during the carboxylation step. It is possible that the bulkier TBDMS protecting group forces CO_2 to add by inversion instead of retention as shown with related systems by Schlosser.[3]

To confirm that the deprotonation step was not responsible of this inversion of stereochemistry, we generated the racemic deuterated **1c** and proceeded to the deprotonation/carbonylation sequence as shown in Scheme 4. In accord with Beak,[5] a decrease in the yield and ee (Table 2) was observed indicating that the reaction proceeds through an enantioselective deprotonation. Therefore, the carbonylation step is responsible for the inversion of configuration observed with the TBDMS substrate **1b**.



Scheme 4

Moreover, differents mode of reaction of CO_2 with benzylic organolithiums have also been observed.[10] This lack of selectivity of CO_2 probably explains, at least in part, the low enantiomeric excesses observed. We are currently investigating the stability of benzyllithium intermediates, and optimizing the processes leading to both (*R*) and (*S*) *N*-Moc protected phenylglycine. These results will be published in due course.

Table 2 Yields and enantiomeric excesses obtained in the preparation (*S*)-Moc-protected phenylglycines **(*S*)-3 and (*S*)-3-d$_1$** using **(-)-4**•*s*-BuLi as pre-formed chiral base.

Y	Reactant	%Yield	%ee[8]
H	1b	28	48(*S*)
D	2b	23	32(*S*)

In summary, we reported a new approach to generate both enantiomers of the *N*-Moc phenylglycine. We observed that inversion of configuration was not only a solvent effect but combined effects between stereoselective carboxylation and steric hindrance. This methodology will be helpful in the future to prepare chiral synthons for the synthesis of peptidomimetics incorporating unnatural aminoacids.

Acknowledgment

The financial support of Merck Frosst Canada, the NSERC of Canada, the Université Laval, and the Fonds FCAR du Québec is gratefully acknowledged.

References and Notes

(1) a) Voyer, N.; Roby, J.; Chénard, S.; Barberis, C. *Tetrahedron Lett*. **1997**, *38*, 6505; b) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627.
(2) (+)-sparteine is not commercially available. For a leading reference on the use of (-)-sparteine in enantioselective deprotonation see: a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.; b) Hoppe, D.; Hense, T., *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282.
(3) Schlosser, M.; Limat, D. *J. Am. Chem. Soc*., **1995**, *117*, 12342.
(4) Carsten, A.; Hoppe, D. *Tetrahedron*, **1994**, *50*, 6097. See also Ref. 2b.
(5) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc*., **1997**, *119*, 11561. See also ref. 2a.
(6) Roby, J.; Voyer, N. *Tetrahedron Lett*., **1997**, *38*, 191.
(7) Typical procedure: At -78°C, 1.1 eq. of *s*-BuLi (1.24 mmol) was added to freshly distilled (-)-sparteine (Sigma-Aldrich) in 3mL of solvent. The mixture was stirred for 15 min then cannulated to a solution of **1a** or **1b** (1.13 mmol) in 1.5 mL of solvent. The resulting mixture was stirred at -78°C for 3h before CO_2 was bubbled through (20 min). After quenching with 2N HCl, the organic 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 products **3**. Trituration with hexane yielded pure **3** as a white powder which was characterized by ^1H and ^{13}C NMR and mass spectrometry.
(8) Enantiomeric excesses were determined by polarimetry with authentic materials (synthesized from commercially phenylglycine (Aldrich)), and by ^1H NMR in C_6D_6 using a

shift reagent Eu(hfc)$_3$ with the methyl ester of **3** prepared using CH_2N_2. a) Versleijen, J. P.; Sanders-Hovens M. S.; Vanhommerig, S. A.; Vekemans, J. A. Meijer, E. M. *Tetrahedron*, **1993**, *49*, 7793; b) Vekemans, J. A. J. M.; Versleijen, J. P. and Buck H. M. *Tetrahedron Asym.*, **1991**, *2*, 949.

(9) Barberis, C.; Voyer, N. *Tetrahedron Lett.*, **1998**, *39*, 6807.

(10) a) Kaufmann, E.; Sieber, S.; Von Ragué Schleyer, P. J. Am. Chem. Soc., **1989**, *111*, 4005; b) Hoppe, D.; Carsten, A.; Krämer, T.; *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 1424.

Article Identifier:
1437-2096,E;1999,0,07,1106,1108,ftx,en;S06599ST.pdf