Communications to the Editor

(−)-Sparteine-Mediated α-Lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine: Enantioselective Syntheses of (*S*) and (*R*) Mono- and Disubstituted *N*-Boc-benzylamines

Yong Sun Park, Mark L. Boys,[1] and Peter Beak*

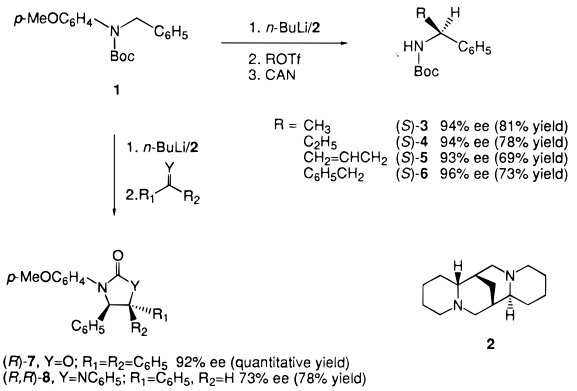
Department of Chemistry
University of Illinois at Urbana-Champaign
Urbana, Illinois 61801

Received November 20, 1995

Asymmetric syntheses which begin with prochiral substrates and involve reactions of organolithium reagents or intermediates under the influence of enantioenriched ligands are being reported at an increasing pace.[2−4] The approach has proven useful for enantioselective syntheses of secondary amines, but extensions to primary amines have not been known.[3−6] In this communication we report controlled asymmetric syntheses of both enantiomers of mono- and disubstituted *N*-Boc-benzylamines with high enantioenrichments from *N*-Boc-*N*-(*p*-methylphenyl)-benzylamine (**1**) in lithiation−substitution sequences mediated by (−)-sparteine (**2**). One application of the approach is illustrated by the preparation of an enantioenriched amino acid.

Addition of a solution of **1** in toluene to a mixture of 1.2 equiv of *n*-butyllithium/**2** at −78 °C in toluene followed by stirring for 10 h, with subsequent addition of methyl and primary alkyl triflates, gives highly enantioenriched alkylation products. These compounds undergo oxidative cleavage of the *p*-methoxyphenyl group with ceric ammonium nitrate (CAN)[7] to provide the *N*-Boc-benzylamines (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, and (*S*)-**6** with 93−96% ee in 69−81% yields. Alkyl triflates give superior results to alkyl halides. Use of methyl iodide as the electrophile for reactions in toluene, ether, *tert*-butyl methyl ether, 1:1 mixture of *tert*-butyl methyl ether and *n*-pentane, and THF gives (*S*)-**3** in yields of 80%, 71%, 81%, 79%, and 81% with ee's of 88%, 66%, 66%, 71%, and 24%, respectively. The reaction in THF does not show the solvent-controlled reversal of enantioselectivity recently reported for reactions of lithiated *N*-Boc-*N*-methylbenzylamine.[4b,d] The absolute configuration of (*S*)-**3** is assigned by comparison of CSP−HPLC retention times with authentic material and of (*S*)-**4** by conversion to a known amino acid (*vide infra*). The assignments to (*S*)-**5** and (*S*)-**6** are based on a correspondence with (*S*)-**3** and (*S*)-**4** as the more retained enantiomer on the CSP−HPLC column.[8]

The use of benzophenone as the electrophile in the sequence gives the oxazolidinone (*R*)-**7** in high yield and 92% ee. The imine *N*-benzylideneaniline (Y = NC_6H_5; R_1, R_2 = C_6H_5, H) affords the imidazolidinones **8** in a diastereomeric ratio of 20:1 with the major isomer (*R*,*R*)-**8** obtained in 78% yield and 73% ee. In each case one recrystallization gave (*R*)-**7** and (*R*,*R*)-**8**, respectively, with >95% ee.



With benzaldehyde as the electrophile, a mixture of the β-amino alcohol (*R*,*S*)-**9** and (*R*,*R*)-**10** is obtained. The amino alcohol is produced in 73% yield and 93% ee and the *trans*-oxazolidinone in 18% yield and 83% ee.[6] When the reaction is quenched with aqueous methanol, a 3:1 mixture of **9** and **10** is obtained, in which (*R*,*S*)-**9** is one isomer and **10** is produced in a 6:1 ratio of (*R*,*R*) isomer and (*R*,*S*) isomer. Cyclization of (*R*,*S*)-**9** to the corresponding oxazolidinone, followed by removal of the *p*-methoxyphenyl group with CAN, produced (*4R*,*5S*)-*cis*-4,5-diphenyl-2-oxazolidinone. Removal of the *p*-methoxyphenyl group of (*R*,*R*)-**10** afforded (*4R*,*5R*)-*trans*-4,5-diphenyl-2-oxazolidinone. Comparisons with authentic materials provided the assignments of the absolute stereochemistry.[9] The configurations shown for **7** and **8** (*vide supra*) are based on analogy to the formations of (*R*,*S*)-**9** and (*R*,*R*)-**10**.[10,11] These assignments are consistent with the same sense of asymmetric substitution for reactions with alkyl triflate, alkyl halide, carbonyl, and imine electrophiles.

(1) Present address: Department of Chemical Sciences, G. D. Searle and Co., Skokie, IL.

(2) (a) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (b) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479. (c) Klein, S.; Marek, I.; Poisson, J. F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853. (d) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (e) Tsukazaki, M.; Tinkl, A.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.

(3) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231 and references cited therein.

(4) For applications to enantioselective syntheses of enantioenriched derivatives of *N*-Boc-*N*-alkylbenzylamines; see: (a) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627. (b) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342. (c) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. (d) We observed a result similar to Schlosser's report[4b] in the enantiomeric excesses for the lithiation−substitution of *N*-Boc-*N*-methylbenzylamine with *s*-BuLi/(−)-sparteine and methyl iodide. In THF, two regioisomers were produced in 85% yield in a ratio of 1.3:1. The major isomer, (*R*)-*N*-Boc-*N*-methyl-α-methylbenzylamine, from the lithiation−substitution at the benzylic position was obtained with −36% ee, and the minor product as *N*-Boc-*N*-ethylbenzylamine from lithiation−substitution at the *N*-methyl group. In toluene, only (*S*)-*N*-Boc-*N*-methyl-α-methylbenzylamine was obtained with 92% ee. Park, Y. S.; Beak, P. Unpublished Results.

(5) For applications and comparisons to alternative methodology, see: Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089. Gawley, R. E.; Zhang, O. *J. Org. Chem.* **1995**, *60*, 5763.

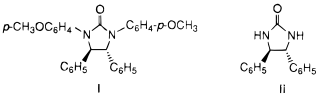
(6) During the reviewing process, the reaction of **1** with *s*-BuLi followed by addition to imines was reported to give a racemic product with high diastereoselectivity, while addition to benzaldehyde showed little diastereoselectivity. Kise, N.; Kashiwagi, K.; Watanabe, M.; Yoshida, J. *J. Org. Chem.* **1996**, *61*, 428.

(7) Tomioka, K.; Inoue, I.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681.

(8) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *56*, 4991.

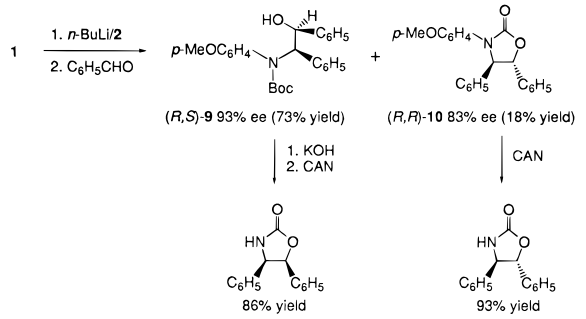
(9) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520. Murthy, K. S. K.; Dhar, D. N. *J. Heterocycl. Chem.* **1984**, *21*, 1721. Stefanovsky, J. N.; Spassov, S. L.; Kurtev, B. J.; Balla, M.; Otvos, L. *Chem. Ber.* **1969**, *102*, 717.

(10) We have also found the same sequence for **1** with the imine *N*-benzylidene-*p*-methoxyaniline gave **i**, which is transformed to **ii** by reaction with CAN, consistent with the *trans* geometry assigned to (*R*,*R*)-**8**.[11]



(11) Sankhavasi, W.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1425.

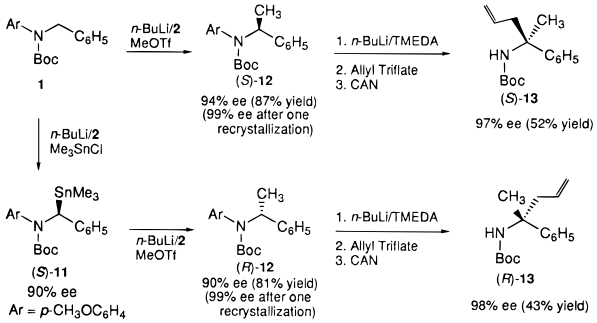
0002-7863/96/1518-3757$12.00/0



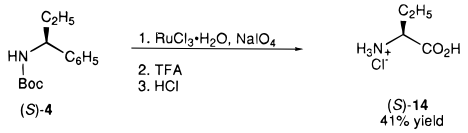
The two limiting pathways for asymmetric replacement of a prochiral hydrogen in a lithiation−substitution sequence are asymmetric deprotonation, in which the enantiochemistry is established in the lithiation to give a configurationally stable carbanion, and asymmetric substitution, in which the configuration is established in the reaction with the electrophile.[2−4,12] Transmetalation of racemic **11** with *n*-BuLi/**2** in toluene at −78 °C followed by reaction with methyl triflate afforded racemic **12**. This result tends to rule out asymmetric substitution and to support asymmetric deprotonation as the enantiodetermining step in the sequence.[13]

Of particular interest is the fact that transmetalation of the tin derivative (*S*)-**11** of 90% ee in the presence of (−)-sparteine followed by addition of methyl triflate affords enantioenriched (*R*)-**12** in 81% yield and 90% ee.[12,13,15,16] The high and opposite enantioselectivities which are obtained by deprotonation−methylation of **1** and by the transmetalation−methylation of (*S*)-**11** thereby provide methodology for syntheses of (*S*)-**12** and (*R*)-**12** in high enantioenrichments from **1**.

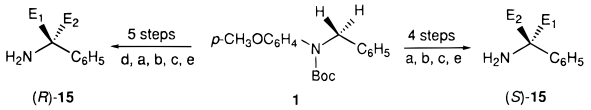
We have found that the configurations of the carbanions obtained by lithiations at the tertiary centers of (*R*)-**12** and (*S*)-**12** can be used for further asymmetric reactions. When (*S*)-**12** of 94% ee is treated with 1.2 equiv of *n*-BuLi/TMEDA in toluene at −78 °C for 8 h followed by addition of MeOD, (*S*)-**12**-d_1 (98%-d_1) is obtained in 89% yield with 94% ee. With (*S*)-**12** of 99% ee as the substrate for *n*-BuLi/TMEDA and allyl triflate as the electrophile, (*S*)-α-allyl-α-methyl-*N*-Boc-benzylamine ((*S*-**13**) is provided in 52% yield and 97% ee. The enantiomer (*R*)-**13** is prepared in 43% yield and 98% ee from (*R*)-**12** of 99% ee by the same reagents. The absolute configurations of **13** are based on comparison to the Mosher amides of previously assigned authentic enantiomers.[17]



An example of the synthetic potential of this methodology is illustrated by the oxidative conversion of (*S*)-**4** to the enantioenriched amino acid (*S*)-**14**.[18] Application of this approach to the syntheses of a variety of highly enantioenriched unnatural amino acids should be useful.



These results provide convenient and efficient synthetic methodology for control of absolute configurations in syntheses of tertiary and quaternary centers of α-substituted and α,α-disubstituted benzylic amines with high enantiomeric excesses. A generalized scheme is shown for syntheses of the disubstituted enantiomers of **15** from **1**. The high diastereoselectivity of the additions to aldehydes and imines should be useful in providing enantioenriched oxazolidones and imidazolidones and their amino alcohols and diamine derivatives. Synthetic applications, determination of the structures of intermediates, and investigation of the mechanism of the reaction are matters of future interest.



a) *n*-BuLi/(-)-sparteine, E_1^+; b) *n*-BuLi/TMEDA, E_2^+; c) CAN; d) *n*-BuLi/(-)-sparteine, Me_3SnCl; e) TFA

Acknowledgment. We are grateful to the National Institute of Health, Institute of General Medicine, and G. D. Searle Inc. for support of this work, and we thank Dr. F. Geiser, Chiral Technologies Inc., for the determination of the enantiomeric excess of **11**.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, (*S*)-**6**, (*R*)-**7**, (*R*,*R*)-**8**, (*R*,*S*)-**9**, (*R*,*R*)-**10**, (*S*)-**11**, (*S*)-**12**, (*R*)-**12**, (*S*)-**13**, (*R*)-**13**, and (*S*)-**14** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9538804

(12) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.

(13) It should be noted that the question of retention or inversion in each step of the sequence is not addressed by these or previous results. The configurations of the organolithium intermediates are not known definitively, and examples of changes in both the sense and extent of enantioselectivity depending on solvent, electrophile, and reaction temperatures are known for similar reactions.[2,4,12] If the configuration of the lithiated intermediate of **1** were to be the same as that reported by Boche[14] for the crystalline complex of *N*-methyl-*N*-pivaloyl-α-lithiobenzylamine/(−)-sparteine, the reaction with electrophiles would proceed with retention.

(14) Boche, G.; Marsch, M.; Harbach, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887.

(15) The tin derivative **11** of 90% ee is prepared in 97% yield by the same sequence used for **3** with trimethyltin chloride as the electrophile. The configuration assigned to (*S*)-**11** is based on analogy to the assignments made by Hoppe of the same configuration for alkylation and stannylation of an oxygen-dipole-stabilized benzylic carbanion at a tertiary center.[16] The organolithium intermediate prepared by tin−lithium exchange is not configurationally stable in the presence of TMEDA.

(16) Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424. Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. Derwing, C.; Hoppe, D. *Synthesis* **1996**, 149.

(17) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.

(18) Carlsen, Per H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1991**, *46*, 3936. Anderson, J. C.; Siddons, D. C.; Smith, S. C.; Swarbrick, M. E. *J. Chem. Soc., Chem. Commun.* **1995**, 1835.