Sparteine-Mediated α-Lithiation of *N*-BOC-*N*-Methylbenzylamine: Rapid Racemization and Subsequent Deracemization

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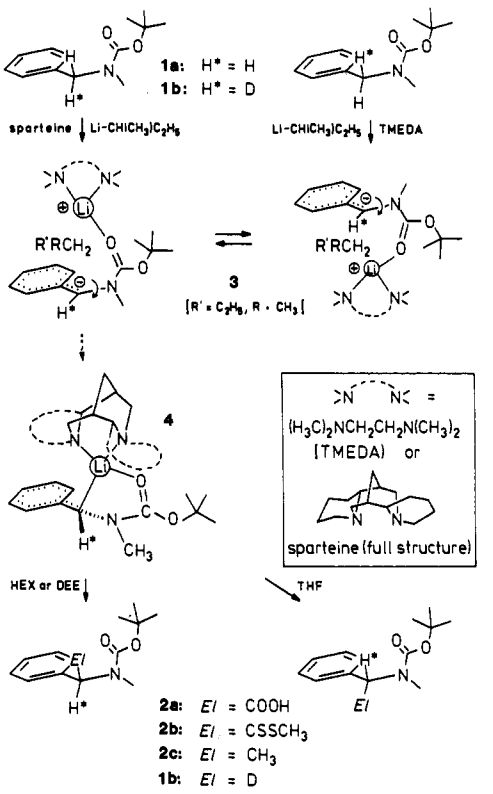
Received May 17, 1995

More than a quarter of a century ago, the Nozaki group[1] studied the asymmetric deprotonation of ethylbenzene using butyllithium in the presence of (−)-sparteine to isolate, after carboxylation, 1-phenylpropanoic acid (≤15%) with a maximum enantiomeric excess (ee) of 30%. Sporadically, other investigations of sparteine as a chiral auxiliary were reported,[2] but none of them proved to have a potential for practical development. The breakthrough was made by Hoppe *et al.*,[3] who found most impressive enantioselectivities when submitting *O*-alkyl, *O*-allyl, and *O*-benzyl carbamates to a *sec*-butyllithium/(−)-sparteine-promoted α-hydrogen/lithium exchange followed by electrophilic trapping. Shortly afterward, Beak *et al.*[4] successfully extended this method to the asymmetric deprotonation of *N*-*tert*-butoxycarbonyl-protected pyrrolidines. Most of the organometallic intermediates involved were configurationally stable[5] and must hence have been endowed with their nonracemic individuality in the very moment of their appearance. There are, however, a few notable exceptions: when converted into their α-lithiated derivatives in the absence of any enantiodiscriminating reagent and *subsequently* treated with sparteine before being trapped by an electrophile, *(E)*-but-2-enyl *N*,*N*-diisopropylcarbamate[3] and *N*-methyl-3-phenylpropanamide[6] gave products with high (≥80%) ee values. Obviously, the chiral auxiliary had preferentially intercepted one component from the equilibrium of rapidly interconverting organometallic antipodes, thus favoring the formation of one of two possible diastereomeric complexes. We wish to elaborate on this point. As our results demonstrate, benzylic carbamates (**1a**,**b**) can be α-lithiated in the presence of (−)-sparteine enantioselectively; they then racemize instantaneously, but, after a while, the original homochirality is restored. Furthermore, our data reveal an unprecendented solvent effect on the stereochemical outcome of the electrophilic substitution.

Scheme 1



Racemic α-D-*N*-BOC-*N*-methylbenzylamine[7] (**1b**) was vigorously stirred with a solution of *sec*-butyllithium and (−)-sparteine (1 equiv of each) in neat tetrahydrofuran (THF) for 4 h at −75 °C before being poured onto dry ice. In addition to 53% of 1-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-1-phenylacetic acid **2a** (*El* = COOH, H* = ^{2}H, isotopic label ≥95%), 39% of the starting material was isolated, in which the (*S*) enantiomer was preponderant to the extent of 25% ee.[8] The efficacity of the kinetic resolution improved to 88 and 85% ee when the sparteine-mediated metalation reaction was conducted in diethyl ether (DEE) or hexane (HEX), respectively. The 88% ee (*S*)-carbamate **1a** thus obtained was metalated with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in neat THF, DEE, and HEX. Carboxylation after 2 h at −75 °C gave a totally racemic product in all three cases (yields of acid **2a**, *El* = COOH, H* = ^{2}H, 47−63%). No metalation of (*S*)-**1b** occurred when *sec*-butyllithium was used in the presence of sparteine. However, when (*S*)-**1b** was *consecutively* treated with *sec*-butyllithium in THF (1 equiv, 4 h at −75 °C), (−)-sparteine (1 equiv, 2 h at −75 °C), and dry ice, optically active acid was formed (82% ee). The deprotonation-promoting transition state

(1) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905−913.

(2) Kretchmer, R. A. *J. Org. Chem.* **1972**, *37*, 2744−2747. Guetté, M. S.; Capillon, J.; Guetté, J. P. *Tetrahedron* **1973**, *29*, 3659−3667. Okamoto, Y.; Suzuki, K.; Kitayama, T.; Yuki, H.; Kageyama, H.; Miki, K.; Tanaka, N.; Kasai, N. *J. Am. Chem. Soc.* **1982**, *104*, 4618−4624.

(3) Hoppe, D.; Zschage, O. *Angew. Chem.* **1989**, *101*, 67−68; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 65−66. Reviews: Hoppe, D.; Krämer, T.; Schwark, J. R.; Zschage, O. *Pure Appl. Chem.* **1990**, *62*, 1999−2006. Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479−1486. See also: Kaiser, B.; Hoppe, D. *Angew. Chem.* **1995**, *107*, 344−346; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323−325.

(4) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, 113, 9708−9710. Beak, P.; Kerrick, S. T.; Wu, S.-d.; Chu, J.-x. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239. In the meantime, this group has also studied the enantioselective metalation and trapping of *N*-BOC-*N*-methylbenzylamine (personal communication by Prof. P. Beak, June 1994). See also: Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627−6630.

(5) Recent accounts of the configurational mobility of α-oxy- and α-amino-substituted alkyllithium compounds: Gawley, R. E.; Zhang, Q.-h. *Tetrahedron* **1994**, *50*, 6077−6088. Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089−6096. Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097−6108.

(6) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516−2518. See also: Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755−9756. Basu, A.; Beak, P. *J. Am. Chem. Soc.*, submitted.

(7) Prepared from [α-^{2}H]benzaldehyde [Chancellor, T.; Quill, M.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1978**, *43*, 1245−1246] by reductive amination [Schlosser, M.; Simig, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1613−1616; **1993**, 163] and subsequent acylation with di-*tert*-butyl carbonate [Ponnusamy, E.; Fotadar, U.; Spisni, A.; Fiat, D. *Synthesis* **1986**, 48−49].

(8) The enantiomeric composition of **1b** was determined by 400 MHz ^{1}H-NMR in the presence of 0.1 equiv of Eu(hfc)$_3$ [(*R*) δ 5.13, (*S*) δ 5.06; 0.1 M in $CDCl_3$; authentic material by formylation and reduction of (*R*)-[α-^{2}H]benzylamine, which was prepared according to the method of Midland *et al.*: Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352−2355]. Also determined were **2a** in the presence of 1.0 equiv of cinchonidine [(*R*) δ 2.72, (*S*) δ 2.70; 0.2 M in $CDCl_3$; authentic material: Kajiyama, S.; Irie, K.; Kido, T.; Koshimizu, K.; Hayashi, H.; Arai, M. *Tetrahedron* **1991**, *47*, 5433−5462], **2b**, after hydrolysis to **2a** (0.6 M KOH in CH_3OH, 30 min at 65 °C; 95%), and **2c**, after hydrolytic removal of the BOC group (1 M HCl in 50% aqueous dioxane, 1 h at 25 °C; 85%) in the presence of 0.05 equiv of Eu(hfc)$_3$ [(*R*) δ 5.22, (*S*) δ 5.15; 0.1 M in $CDCl_3$; authentic material: Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049−1061].

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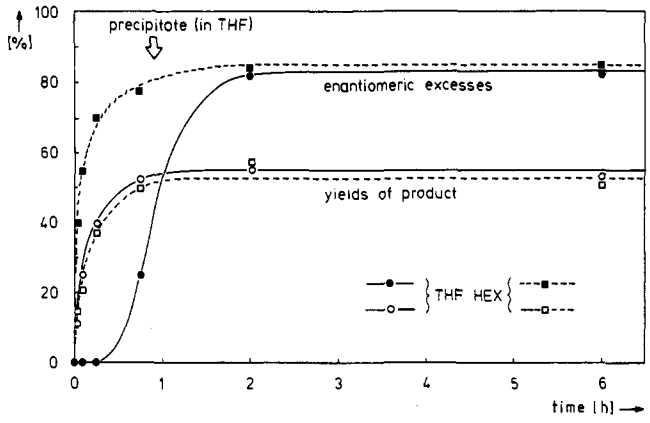


Figure 1. Sparteine-mediated α-lithiation of *N*-BOC-*N*-methyl-benzylamine (**1a**) and subsequent carboxylation in HEX and THF. Yields and enantioselectivities as a function of the metalation time.

obviously collapses to produce an incompletely coordinated, immediately racemizing species (such as **3**) rather than to generate directly the organolithium/diamine adduct (*e.g.*, **4**) (Scheme 1).

All the following experiments were carried out with unlabeled starting material **1a** (H* = ^{1}H). Carboxylation of the lithiated intermediate was found to take place in THF, in a 1:1 mixture of THF/DEE and ethylene glycol dimethyl ether/HEX with *inversion*[9] (85, 26, and 70% ee, respectively), but in *tert*-butyl methyl ether, DEE, and in HEX with *retention*[9] (61, 67, and 81% ee, respectively). In dimethyl ether, completely racemic acid was formed.

The evolution of the reaction has been followed by withdrawing and analyzing samples over a period of 6 h. The increase of yields with time was practically solvent-invariant, reaching the maximum after roughly 1 h (see Figure 1). In HEX and DEE, the ee values started low but climbed rapidly to exceed the 50% level after only a few minutes. In contrast, in THF, little enantioselectivity was observed even after 30 min, although by then metalation was nearly complete. After roughly 40 min, precipitation set in, and simultaneously the ee numbers rose steeply (see Figure 1).

The solvent effect on the stereochemistry holds for various kinds of electrophiles, as exemplified with carbon disulfide, methyl iodide, dimethyl sulfate, and ω-deuteriophenylacetylene. The methyl dithiocarboxylate **2b** (from the lithium dithiocarboxylate and methyl iodide), the methyl homologue **2c**, and the deuterated starting material **1b** had the configuration corresponding to inversion when produced in THF, while the retention mode was obeyed in DEE or HEX. The enantioselectivities observed did not vary significantly with the nature of the electrophile (Table 1).[8]

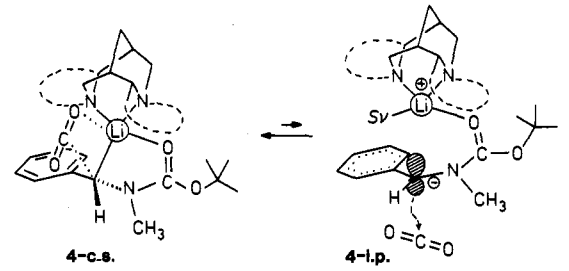
To explain the solvent dependence of our reactions, we postulate a dynamic equilibrium to exist between the organolithium/sparteine contact species **4-cs**, the prevailing ground state structure, and an ion pair **4-ip**, in which the benzyl moiety has been displaced by a solvent molecule (*Sv*) from its coordination to the metal (Scheme 2). The fraction of ion pairs may remain undetectably small under all circumstances, but it will increase when a good donor solvent such as THF is employed. Beyond a certain threshold value, the electrophilic substitution may pass

(9) *Retention* and *inversion* with respect to the proton removed. It is a plausible though unproven conjecture that the benzylic center of the organolithium/(−)-sparteine complex has the (*S*) configuration.

Table 1. Sparteine-Mediated α-Lithiation of *N*-BOC-*N*-methylbenzylamine (**1a**) and Enantioselectivities (ee, %) as a Function of the Solvent and the Electrophile *El*−X (Yields of Products, 43−65%)

El−X	HEX	DEE	THF
CO_2	81 (*R*)	67 (*R*)	85 (*S*)
CS_2	58 (*R*)	51 (*R*)	74 (*S*)
CH_3I	75 (*S*)	62 (*S*)	80 (*R*)
$(CH_3O)_2SO_2$	55 (*S*)	53 (*S*)	68 (*R*)
$DC{\equiv}CC_6H_5$	90 (*S*)	55 (*S*)	85 (*R*)

Scheme 2



partially, if not exclusively, through the ion pair which should prefer the inversion mode in order to avoid steric crowding on the face shielded by the bulky counterion. In contrast, the contact species should be attacked by the electrophile with retention, as is common.

Although compatible with all results collected so far, our mechanistic rationale may be an oversimplification. The crucial organolithium/sparteine intermediate **4** has been modeled according to an X-ray structure[10] of a very similar adduct, but carrying an *N*-pivaloyl instead of the *N*-BOC moiety. We can nevertheless not rule out the formation of *mixed aggregates* in which one molecule of the aminobenzyllithium intermediate (**1**) would coordinate not only with sparteine but also with one molecule of the metalation reagent (*e.g.*, *sec*-butyllithium). The yields conspicuously centering around 50% (much *sec*-butyllithium remaining unconsumed) are suggestive in this respect.

The solvent control over the stereochemical outcome of sparteine-mediated electrophilic substitution reactions is particularly welcome since the auxiliary is available in only one enantiomeric form. Applications to the synthesis of unnatural amino acids and isoquinoline alkaloids are envisaged. For example, we have deprotected (*R*)- and (*S*)-*N*-BOC-*N*-methyl-1-phenylethylamine (75 and 85% ee), prepared as described above, to carry out an *N*-alkylation with 2,2-diethoxyethyl bromide, followed by *ortho*-formylation (by consecutive treatment of the intermediate with butyllithium and *N*,*N*-dimethylformamide), acid-catalyzed cyclization, and reduction (with potassium tri-*sec*-butylborohydride), to provide (*R*)- and (*S*)-(1,2-dihydro-1,2-dimethyl-3-isoquinolyl)methanol in 10% overall yield. Independent of these practical considerations, we are intrigued by the emerging possibilities to gain insight into subtle details of organometallic reactions.

Acknowledgment. This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern, Switzerland (Grants 20-36'385-92 and 21-41'221.94-Chiral-2).

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