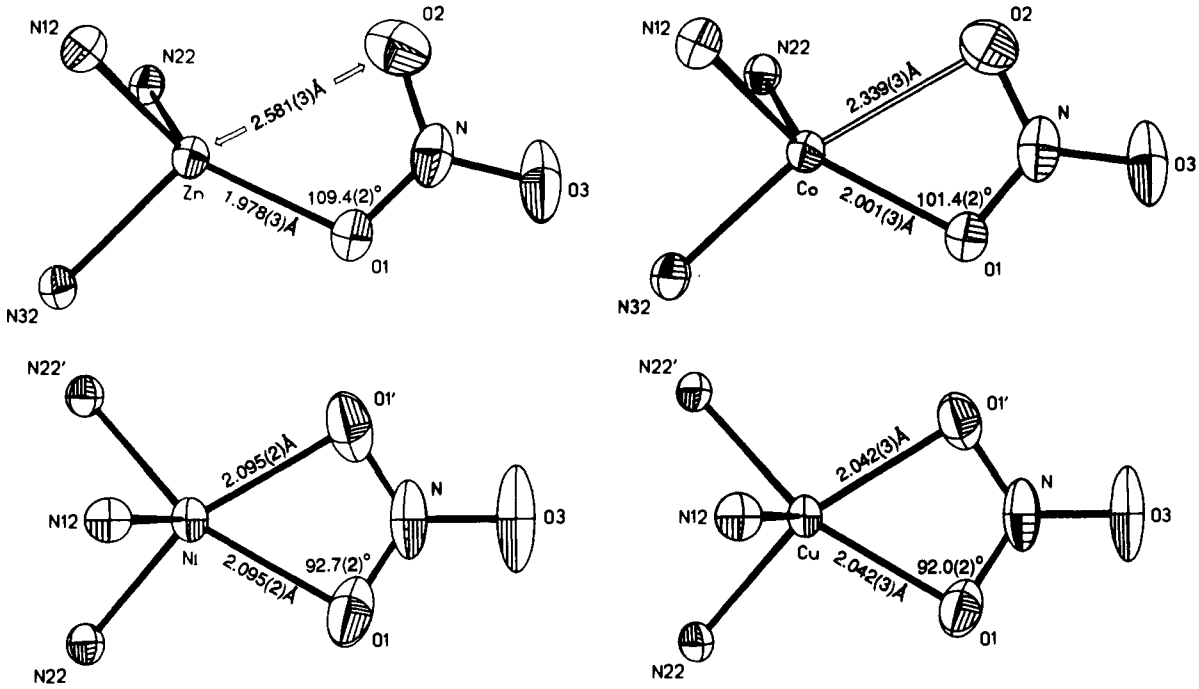

Figure 2. Coordination environment about the metal center in the plane of the nitrate ligand.

carbonate and may also exhibit both unidentate and bidentate coordination modes, observation of the structure of a metal–nitrate complex may provide a good indication as to the coordination mode of the corresponding bicarbonate derivative. The molecular structures of the cobalt, nickel, copper, and zinc complexes $\{\eta^3$-HB(3-Bu^{t}pz)$_3\}$M(NO$_3$) (M = Co, Ni, Cu, Zn), shown in Figure 1, are observed to exhibit a variety of coordination modes of the nitrate ligand. Relevant bond lengths and angles for the complexes $\{\eta^3$-HB(3-Bu^{t}pz)$_3\}$M(NO$_3$) are summarized in Figure 2. Significantly, whereas the nitrate ligand in $\{\eta^3$-HB(3-Bu^{t}pz)$_3\}$Zn(η^1-ONO$_2$) is *unidentate* [Zn–O = 1.978 (3) Å], with only a weak secondary interaction [Zn···O = 2.581 (3) Å],[9] both the nickel and copper complexes exhibit perfectly symmetric *bidentate* coordination of the nitrate ligand with short M–O bond lengths [Cu–O = 2.042 (3) Å; Ni–O = 2.095 (2) Å]. In contrast, the cobalt derivative exhibits a noticeably asymmetric coordination mode [Co–O = 2.001 (3) and 2.339 (3) Å] which is intermediate between unidentate and symmetric bidentate. A simple indication of the increase in bidentate character of the nitrate ligand is provided by observing the decrease in the M–O(*1*)–N bond angle. Thus, the bond angle at oxygen decreases progressively from the tetrahedral value for Zn [109.4 (2)°] with unidentate coordination to ca. 92° for Ni and Cu with symmetric bidentate coordination.

Although there are many factors, for example the pK_a of the coordinated water, that may be responsible for affecting the activity of metal-substituted carbonic anhydrases, the correlation between the order of activity (Zn > Co ≫ Ni and Cu) and the observed coordination mode of the nitrate ligands in the model complexes $\{\eta^3$-HB(3-Bu^{t}pz)$_3\}$M(NO$_3$) (M = Co, Ni, Cu, Zn) is striking. One interpretation of these results, *if* they can be applied to the isoelectronic bicarbonate derivatives, is that a progressive ground-state stabilization of the bicarbonate ligand would be observed for the sequence Zn < Co < Cu and Ni. Stronger binding of the bicarbonate ligand across the series Zn < Co < Cu and Ni may result in slower displacement of the bicarbonate ligand by H_2O and thereby prevent a catalytic cycle operating for Cu and Ni derivatives. This suggestion supports the results of X-ray absorption studies on zinc- and cobalt-substituted carbonic anhydrase in the presence of bicarbonate[1i] and also a recent theoretical analysis which indicates that 5-coordinate intermediates are likely to behave as inhibitors for the carbonic anhydrase catalytic cycle.[3b]

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Supplementary Material Available: Tables of crystal and intensity collection data, atomic coordinates, bond distances and angles, and anisotropic displacement parameters and ORTEP drawings for all structures (33 pages); observed and calculated structure factors for all structures (57 pages). Ordering information is given on any current masthead page.

(9) A similar coordination mode has been observed for the related complex $\{\eta^3$-HB(3-Phpz)$_3\}$Zn(NO$_3$). Alsfasser, R.; Powell, A. K.; Vahrenkamp, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 898–899.

Asymmetric Deprotonations: Enantioselective Syntheses of 2-Substituted (*tert*-Butoxycarbonyl)pyrrolidines

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The elaboration of secondary amines via dipole-stabilized carbanions has developed into a very useful synthetic method.[1] Syntheses of enantiomerically enriched benzylic 2-substituted secondary amines for derivatives which have a chiral activating group on nitrogen have been the most important asymmetric extensions of the methodology.[2-4] Analogous asymmetric sub-

(1) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523. Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59–68. Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437–4442. Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578–2580.

(2) (a) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787 and references cited therein. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974–7978. (c) Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960–2964.

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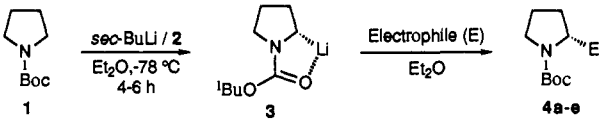
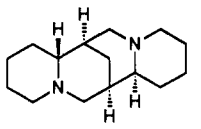
stitutions in systems which are not activated by unsaturation adjacent to nitrogen have been much less successful.[5] Hoppe has recently shown that asymmetric deprotonations can be effected adjacent to the oxygen of a carbamate with *sec*-butyllithium/(−)-sparteine to give a chiral dipole-stabilized carbanion which reacts with electrophiles to give enantiomerically enriched products in yields of 52–86% with ee's of >95%.[6,7]

We now report that this approach is applicable to highly enantioselective syntheses of 2-substituted Boc-pyrrolidines.[8,9] Asymmetric deprotonation of Boc-pyrrolidine (**1**) with *sec*-butyllithium/(−)-sparteine (**2**) gives the chiral organolithium reagent **3**, which undergoes reaction with electrophiles to give the enantiomerically enriched products **4a–e**.[10] The yields range from 55 to 76% with ee's from 88 to 96%. The stereochemistries of **4b** and **4c** were determined to be that of unnatural (*R*)-proline.[11] The stereochemistries of the other products were not determined and are assigned by analogy to **4b** and **4c**. Although the order of mixing did not affect the ee for **4a**, the ee of **4b** eroded to 83% when procedure a was used.



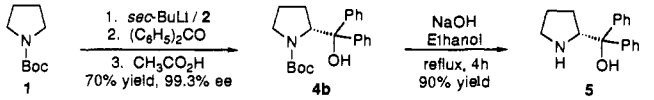


2

Product	E	Yield (%)	ee (%)
4a	$(CH_3)_3Si^a$	71	94
4a	$(CH_3)_3Si^b$	76	96
4b	$(C_6H_5)_2COH^b$	75	90
4c	CO_2H^a	55	88
4d	$CH_3{}^b$	76	95
4e	$(n\text{-}C_4H_9)_3Sn^a$	70	94

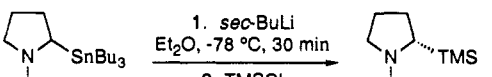
a,b Footnote 10.

The synthetic utility of this methodology is illustrated by the synthesis of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol (**5**).[8c] Boc-pyrrolidine (**1**) was converted to **4b** in 70% yield and 99.3% ee after one recrystallization of the crude material. Deprotection of the Boc group with sodium hydroxide (NaOH) gave **5** in 90% yield. The overall yield of 60% and ee of 99.3% of this synthesis from pyrrolidine compare favorably to results of previous syntheses from proline.[8c]



The two limiting mechanisms which could account for the enantioselectivities observed are as follows: (1) The (−)-sparteine complexes with racemic 2-lithio-Boc-pyrrolidine to favor one of the two possible diastereomeric transition states in electrophilic substitution. (2) The *sec*-BuLi/(−)-sparteine enantioselectively deprotonates **1** to provide **3**, which is configurationally stable and reacts stereospecifically in electrophilic substitution.

In order to differentiate between these possibilities, the lithium–tin exchange reactions of chiral 2-Bu_3Sn-Boc-pyrrolidine (**4e**) and racemic 2-Bu_3Sn-Boc-pyrrolidine (**6**) with *sec*-BuLi were carried out. When chiral 2-lithio-Boc-pyrrolidine was formed with no diamine present and when racemic 2-lithio-Boc-pyrrolidine was formed in the presence of (−)-sparteine, subsequent reaction with trimethylsilyl chloride gave low ee's in both cases and **4a** was obtained in low yield with no diamine present. However, when chiral 2-lithio-Boc-pyrrolidine was formed in the presence of TMEDA, a much higher yield and ee of **4a** were observed. We interpret these results to show that intermediate **3** is not very chemically or configurationally stable in the absence of a diamine and that the enantioselectivities observed in these reactions are primarily the result of an asymmetric deprotonation. These results are consistent with the work of Hoppe.[6]



Starting Material	Added Diamine	Yield (%)	ee (%)
4e	none	8	10
6	(-)-sparteine	60	3
4e	TMEDA	62	67

In summary, we have shown that highly enantiomerically enriched 2-substituted Boc-pyrrolidines can be synthesized in good yields by using *sec*-BuLi/(−)-sparteine to asymmetrically deprotonate Boc-pyrrolidine. This methodology provides the first example of an asymmetric substitution at an unactivated position adjacent to nitrogen using a chiral ligand as the source of asymmetry. Future work will include extensions to other substrates and the development of other chiral ligands for asymmetric deprotonations.

Acknowledgment. We are grateful to Professor Helmchen of the University of Heidelberg for the reaction apparatus. We thank

(3) (a) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076–3078. (b) Gawley, R. E.; Hart, G.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175–181. (c) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002–3004. (d) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211–2217. (e) Rein, K.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 1564–1569.

(4) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1–13. Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944–1954.

(5) The known cases are silylation (96% yield, 100% de) and methylation (30% yield, 100% de) of a chiral piperidinooxazoline (refs 3a,b). Work with other chiral activating groups for unactivated positions has been less successful (ref 2b).

(6) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422–1424.

(7) (−)-Sparteine is an inexpensive and commercially available chiral diamine which has been used in other organometallic reactions with limited success. For a leading reference to past work, see ref 6.

(8) Previous syntheses of chiral 2-substituted pyrrolidines have been limited to a multistep procedure starting from proline. (a) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115. (b) Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron Asymmetry* **1990**, *1*, 877–880. (c) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751–762.

(9) Chiral 2-substituted pyrrolidines and their derivatives have been shown to be very effective as chiral auxiliaries, catalysts, bases, and ligands in asymmetric synthesis. Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 6, pp 165–177. Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, Chapter 4, pp 275–339. Tomioka, K. *Synthesis* **1990**, 541–549. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. Cox, P. J.; Simpkins, N. S. *Tetrahedron Asymmetry* **1991**, *2*, 1–26. Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763–769.

(10) General experimental procedures. Procedure b: To (−)-sparteine in diethyl ether (Et_2O) (1.2 equiv, 0.25 M) at −78 °C was added *sec*-BuLi (1.2 equiv). The mixture was stirred for 15 min and then transferred, the temperature being carefully maintained at −78 °C, to a solution of **1** (1.0 equiv) in Et_2O at −78 °C. The resulting mixture was stirred at −78 °C for 4 h, added to a precooled (−78 °C) solution of the electrophile (1.5 equiv) in Et_2O, and then allowed to slowly warm to room temperature (ca. 3 h). The 2-substituted Boc-pyrrolidines were purified by flash chromatography with ethyl acetate/hexane. Procedure a: The *sec*-BuLi was added to a mixture of **1** and **2** at −78 °C. When methyl iodide was used with procedure a, the yield was 35% with 79% ee. We believe that the use of Et_2O is critical in order to obtain the indicated yields. All Boc-pyrrolidines were characterized by ^1H NMR, ^{13}C NMR, and elemental analysis. All known compounds were judged to be >90% pure by ^1H NMR, ^{13}C NMR, and GC analyses. Details are given in the supplementary material.

(11) Analysis of **4b** was by comparison of the optical rotation of Boc-deprotected **4b** $\{[\alpha]^{26}_D$ +48.2° (*c* 2.61, MeOH)$\}$ to the literature rotation $\{[\alpha]^{21}_D$ +54.3° (*c* 0.261, MeOH)$\}$.[8b] Analysis of **4c** was by comparison of the rotation $\{[\alpha]^{25}_D$ +66.5° (*c* 7.29, $CHCl_3$)$\}$ to the rotation of a sample of **4c** synthesized independently from (*S*)-proline $\{[\alpha]^{24}_D$ −76.4° (*c* 3.94, $CHCl_3$)$\}$. All products were additionally analyzed for ee by chiral chromatography or analytical chromatography of diastereomers.

(12) **Note Added in Proof**: Gawley and co-workers have recently reported a highly stereoselective addition of a chiral piperidinooxazoline to benzaldehyde: Rein, K. S.; Chen, Z. H.; Perumal, P. T.; Echegoyen, L.; Gawley, R. E. *Tetrahedron Lett.* **1991**, *32*, 1941–1944. Pearson and Lindbeck have recently reported stereochemical studies of chiral, acyclic, nonconjugated, nitrogen-substituted, dipole-stabilized carbanions generated by tin–lithium exchange: Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546–8548.

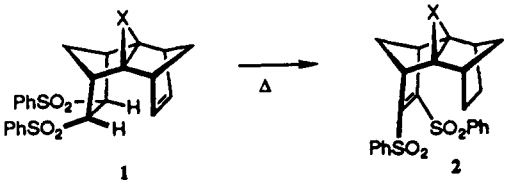
Patrick Murray for the analysis of **4c**. We also thank Dr. T. Rathmann of the FMC Corporation for a gift of *sec*-BuLi. We are grateful for support of this research by the National Science Foundation and the National Institutes of Health.

Supplementary Material Available: Experimental details, enantiomeric purity assays, and spectral data for compounds **1**, **4a–e**, **5**, and **6** (14 pages). Ordering information is given on any current masthead page.

Additions and Corrections

Intramolecular Reaction Rate Is Not Determined Exclusively by the Distance Separating Reaction Centers. The Kinetic Consequences of Modulated Ground State Strain on Dyotropic Hydrogen Migration in Systems of Very Similar Geometric Disposition [*J. Am. Chem. Soc.* **1991**, *113*, 7761–7762]. LEO A. PAQUETTE,* GEORGE A. O'DOHERTY, and ROBIN D. ROGERS

Page 7761: Structure **2** was depicted with a double bond that is not present. The correct reaction is given below:



1 **2**

Book Reviews *

Chemical Information Systems—Beyond the Structure Diagram. Edited by David Bawden (Pfizer Central Research) and Elenor M. Mitchell (Cambridge Crystal Data Centre). Ellis Horwood: Chichester. 1990. 178 pp. $58.00. ISBN 0-13-126582-2.

This is a thin (172 pages plus an index) book that aims to cover a very broad area for chemists in the information field. It developed from a Chemical Structure Association meeting in Durham, England, in 1989. The book contains 10 chapters, an introduction, and a good 6-page subject index, but no author index. The book is divided into five sections, with 1–4 chapters in each section. The sections (with the respective number of chapters in parentheses after the title) are the following: Overview (1), Three-Dimensional Structure Handling (4), Reactions and Synthesis (2), Property Prediction and Analysis (3), and Integrated Systems (1).

The book starts off with an introduction from the editors explaining that the book is designed to cover two areas which are "beyond the structure diagram". These are computation chemistry and access to a wider array of chemical data.

Chapter 1, by S. Ward, describes the management point of view of chemical information for the pharmaceutical industry. It is well-written by an experienced person in the field. The next chapter, by J. Barnard and colleagues, describes activities in the area of representing stereochemistry in two-dimensional structure representations. As the authors point out in the first sentence of this chapter, "this paper is out of place in this book".

Chapter 3 is a presentation of a commercial software system, MACCS-3D, by the company that developed the system. Chapter 4, by P. Willett and his research group at Sheffield, is an excellent introduction to structure (graph) matching techniques of 3-D structures. This probably is the best chapter in the book.

The chapter on the Cambridge Crystal database is primarily a historical presentation of the activities of this center. It also describes the evolution of their software which is used to search the database. As much better software is available from other sources, I found the value of this chapter is for someone who wishes to create their own 3-D database.

The next two chapters are about reactions and synthesis. The first describes a commercial reaction database system, ORAC. As it is one of the few papers published by this company, it merits reading. The second chapter in this section is a good overview of the many synthesis planning programs by F. Loftus, a researcher at ICI Pharmaceutical.

The property prediction and analysis section starts off with a chapter on a new software language, GLOBAL, which the eight authors from Proteus Biotechnology have developed. They then go on to explain how this polymorphic programming environment is a useful tool for many scientific activities of the company. No actual applications are given to chemistry.

The next chapter by D. Rouvray, the longest in the book, describes the use of topological indices for property prediction, with both a historical description and some recent work by the author. This is followed by a chapter by M. Johnson of The Upjohn company, on similarity-based moths for predicting chemical and biological properties. This is a good, but short, discussion of the topic.

The book concludes with a chapter on the progress being made toward integrated chemical information systems by D. Bawden, one of the editors of this book. The chapter contains some very general comments on the subject and describes, very briefly, what is being done at Pfizer in this area.

Overall I found this a useful but somewhat limited book. As the bulk of the chapters are written by people in the UK, it is difficult to expect a wide variety and in-depth coverage of the many opportunities offered by today's computer systems, software, and databases.

Stephen R. Heller, *USDA, ARS*

*Unsigned book reviews are by the Book Review Editor.