Acknowledgment. This grant was supported by PHS Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant 7916210. An NIH Postdoctoral Fellowship to J.N.H. (Grant 1F32CA08341-02) is gratefully acknowledged.

Supplementary Material Available: Experimental procedure for the preparation of methyl phthalimido disulfide and spectral data (IR, ^{1}H NMR, and MS) for compounds **3**, **5**, **6**, **8**, **9**, **11**, and **13** (8 pages). Ordering information is given on any current masthead page.

α-Lithioamine Synthetic Equivalents: Syntheses of Diastereoisomers from the Boc Piperidines

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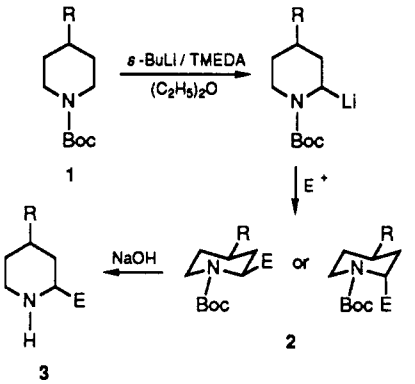
Summary: The α′-lithiations and electrophilic substitutions of selected Boc piperidines provide single or separable diastereoisomeric 2-substituted, 2,4-disubstituted, and 2,4,6-trisubstituted Boc piperidines which are readily hydrolyzed to the substituted piperidines.

Previous studies of the formation of α′-lithioamine synthetic equivalents from secondary amines have shown that piperidines provide an informative and demanding test of the methodology.[1-4] We have recently reported that the *tert*-butoxycarbonyl (Boc) group is an effective activating group for directing α′-lithiation of piperidines.[2] In this paper we provide preliminary results which show that diastereomeric 2-substituted, 2,4-disubstituted, and 2,4,6-trisubstituted piperidines can be prepared readily by this approach.

The reactions we have carried out are shown for the general conversions of **1** to **2** to **3**, with the specific reactants shown as **4**–**23** and the separated products shown as **7**, **9**, **11**, and **12**–**42** in Table I. Structures are shown in the first column for reactants for the lithiation–substitution step while reactants for the hydrolysis step are designated by compound number. The stereochemistries are assigned to the products on the basis of ^{1}H NMR spectra which distinguish the alternatives by molecular symmetry and/or characteristic coupling constants of the C_2 and C_6 protons to the adjacent methylene group. The assignments to the erythro:threo isomer pairs, including **26** and **27**, are based on the larger couplings found between the C_2 and exocyclic protons for the threo isomer in established systems.[5] The assignments were confirmed for **28** by direct comparison of the corresponding benzamides with authentic material, for the amino alcohols **38** (*dl*-conhydrine), **39** (*dl*-β-conhydrine), and **12** by comparison with literature physical properties and for **40** by an X-ray structure determination.[5]

As shown in the table, lithiation of the Boc piperidines followed by reactions with aldehydes provides mixtures of readily separable erythro and threo isomers in which the threo isomer is often in a cyclized form. The substituents for the monosubstituted systems **12**, **14**, **16**, and **19** are shown as equatorial because the proton at C_2 in **12** can be assigned as axial based on its couplings to the adjacent methylene of 5 and 12 Hz. Axial disposition of the methyl group in **6** is consistent with coupling constants of 2 and 3 Hz between the C_2 and the adjacent methylene protons and with $A_{1,3}$ strain.[6] The conformations assigned to **41** and **42** are made to be consistent with those of the monosubstituted systems.



The stereochemistries of the products from **4**–**6** and **8** are consistent with equatorial α′-lithiation followed by retention on electrophilic substitution as previously reported.[1] The formations of both diastereoisomers on reactions with aldehydes and the beneficial effect of a substituent on the piperidine ring on the yields of the alkylation reaction are also consistent with experience with the piperidine amides and formamidines.[1,7] However, the axial substitutions in the formations of the trans 2,6-substituted isomers from the 2,4-disubstituted systems **7** and **9** are different from the previous pattern.[8]

(1) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Seebach, P.; Wykypiel, W.; Lubosch, D.; Kalinowski, H. O. *Helv. Chim. Acta* **1978**, *61*, 3100. (c) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010. (d) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *Ibid.* **1984**, *106*, 3270. (e) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175 and references cited therein.

(2) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, 1197.

(3) For previous uses of carbamates in sterically hindered or additionally activated systems, see: Hassel, T.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 274. Hassel, T.; Seebach, D. *Helv. Chim. Acta* **1987**, *61*, 2237. Armande, J. C.; Pandit, U. K. *Tetrahedron Lett.* **1977**, 897. MacDonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *52*, 4437.

(4) For recent and related chemistry of α-lithioamine synthetic equivalents, see: Pearson, W. H.; Lindbeck, P. C. *J. Org. Chem.* **1989**, *54*, 5651. Comins, D. L.; LaMungon, P. H. *Tetrahedron Lett.* **1989**, 5053.

(5) Stork, G.; Jacobson, R.; Levitz, R. *Tetrahedron Lett.* **1979**, 771. Hill, R. *J. Am. Chem. Soc.* **1958**, *80*, 1609. Pilard, S.; Vaultrer, M. *Tetrahedron Lett.* **1984**, 1555. Hill, R.; Chan, T.; Joule, J. *Tetrahedron* **1965**, *4*, 147.

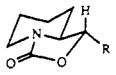
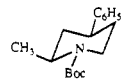
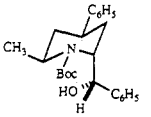
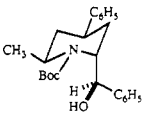
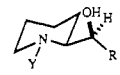
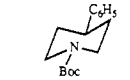
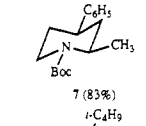
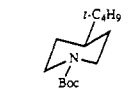
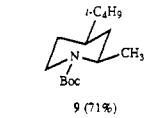
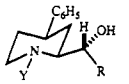
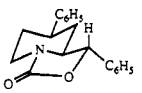
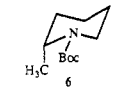
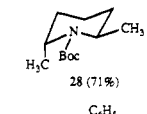
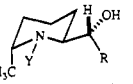
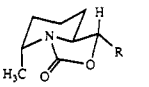
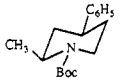
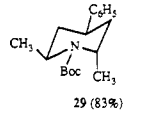
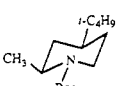
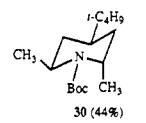
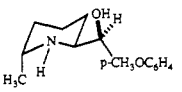
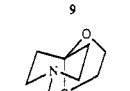
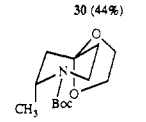
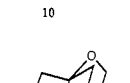
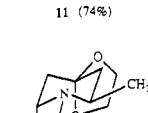
(6) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(7) Sanner, M. A. *Tetrahedron Lett.* **1989**, 1909.

(8) Meyers and co-workers obtained the *cis*-2,6-dimethyl product from the 4-*tert*-butylpiperidine formamidine by analogous chemistry.[1d] The fact that the stereochemistry is influenced by the directing group on nitrogen provides another approach for stereochemical control with this methodology.

0022-3263/90/1955-2578$02.50/0

Table I. Products of the Lithiation-Electrophilic Substitution and of Hydrolysis of Boc Piperidines

reactants		products (yields)[a]		reactants		products (yields)[a]	
							
4	C_6H_5CHO	12, Y = Boc, R = C_6H_5 (39%)	13, R = C_6H_5 (37%)				
4	$p\text{-}CH_3OC_6H_4CHO$	14, Y = Boc, R = $p\text{-}CH_3OC_6H_4$ (25%)	15, R = $p\text{-}CH_3OC_6H_4$ (31%)				
4	$c\text{-}C_6H_{11}CHO$	16, Y = Boc, R = $c\text{-}C_6H_{11}$ (26%)	17, Y = Boc, R = $c\text{-}C_6H_{11}$ (20%)	7	C_6H_5CHO	26 (46%)[b]	27 (46%)[b]
12	NaOH	32, Y = H, R = C_6H_5 (95%)					
14	NaOH	33, Y = H, R = $p\text{-}CH_3OC_6H_4$ (71%)					
							
4	C_2H_5CHO	18, Y = Boc, R = C_2H_5 (16%)[b]	19, Y = Boc, R = C_2H_5 (19%)[b]	5	CH_3I	7 (83%)	
13	NaOH		34, Y = H, R = C_6H_5 (91%)				
15	NaOH		35, Y = H, R = $p\text{-}CH_3OC_6H_4$ (79%)				
16	NaOH	36, Y = H, R = $c\text{-}C_6H_{11}$ (90%)					
17	NaOH		37, Y = H, R = $c\text{-}C_6H_{11}$ (89%)				
18	NaOH	38, Y = H, R = C_2H_5 (91%)		8	$(CH_3)_2SO_4$	9 (71%)	
19	NaOH		39, Y = H, R = C_2H_5 (90%)				
							
5	C_6H_5CHO	20, Y = Boc, R = C_6H_5 (33%)	21 (23%)	6	$(CH_3)_2SO_4$	28 (71%)	
20	NaOH	40, Y = H, R = C_6H_5 (92%)					
							
6	$p\text{-}CH_3OC_6H_4CHO$	22, Y = Boc, R = $p\text{-}CH_3OC_6H_4$ (57%)	23, R = $p\text{-}CH_3OC_6H_4$ (41%)	7	CH_3I	29 (83%)	
6	$c\text{-}C_6H_{11}CHO$	24, Y = Boc, R = $c\text{-}C_6H_{11}$ (16%)[c]	25, R = $c\text{-}C_6H_{11}$ (50%)				
22	NaOH	41, Y = H, R = $p\text{-}CH_3OC_6H_4$ (91%)					
				9	$(CH_3)_2SO_4$	30 (44%)	
23	NaOH						
		42 (92%)		10	CH_3I	11 (74%)	
							
				11	$(CH_3)_2SO_4$	31 (44%)	

[a] Yields are based on the weight of material isolated after chromatography for compounds judged to be 95% pure as judged by pmr spectroscopy. [b] Reaction quenched at −78 °C. [c] This product is obtained in the cyclized form.

The present results illustrate an approach for α substitution of Boc derivatives of unactivated secondary amines in single and sequential steps to provide diastereoisomers. Although the yields are not high in all cases, this method is direct and should be generally useful for amine elaboration.[9] Further investigation will be needed to fully develop the synthetic potential of this approach and to define the structures of the intermediates and pathways of these reactions.

(9) Experimental details are provided for a representative case. **Reaction of 2-Lithio-*N*-(*tert*-butoxycarbonyl)piperidine with Benzaldehyde.** A 0.5 M solution of *N*-(*tert*-butoxycarbonyl)piperidine (**4**) (205 mg, 1.11 mmol) in ether was cooled to −78 °C and treated with TMEDA (167 mg, 1.44 mmol), followed by *s*-BuLi (1.38 M, 1.04 mL, 1.44 mmol) dropwise. The mixture was slowly warmed to −20 °C, stirred for 30 min, and then cooled to −78 °C. The mixture was treated with benzaldehyde (176 mg, 1.66 mmol) in 0.5 mL of ether and slowly warmed to room temperature. The mixture was diluted with 5 mL of water and extracted with ether (5 mL × 5), and then the combined extracts were dried over K_2CO_3. The organic layer was concentrated to give a crude product as yellow oil, which was purified by column chromatography on silica gel with 10% EtOAc/hexane (contains 0.5% Et_3N) as eluent to give *erythro*-*N*-(*tert*-butoxycarbonyl)-α-phenyl-2-piperidinemethanol (**12**) (124 mg, 39%) and *threo*-8-oxa-7-phenyl-1-azabicyclo[4.3.0]nonan-9-one (**13**) (88 mg, 37%). *erythro*-*N*-(*tert*-Butoxycarbonyl)-α-phenyl-2-piperidinemethanol (**12**): ^1H NMR ($CDCl_3$) δ 7.31–7.18 (m, 5 H), 4.84 (d, J = 9.0 Hz, 1 H), 4.22 (m, 1 H), 3.92 (d, J = 12.0 Hz, 1 H), 3.41 (br, 1 H), 2.80 (td, J = 15.0, 3.0 Hz, 1 H), 2.01 (d, J = 12.0 Hz, 1 H), 1.71–1.17 (m, 5 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.5, 142.4, 127.8, 127.2, 126.4, 78.9, 71.6, 56.0, 39.8, 27.8, 24.9, 24.4, 19.1. *threo*-8-Oxa-7-phenyl-1-azabicyclo[4.3.0]nonan-9-one (**13**): ^1H NMR ($CDCl_3$) δ 7.42–7.26 (m, 5 H), 5.00 (d, J = 7.5 Hz, 1 H), 3.92 (dd, J = 12.5, 3.9 Hz, 1 H), 3.41 (m, 1 H), 2.82 (td, J = 12.6, 3.4 Hz, 1 H), 2.00–1.92 (m, 2 H), 1.70 (m, 1 H), 1.52–1.31 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.3, 137.8, 128.6, 125.4, 81.8, 62.2, 41.2, 29.9, 24.0, 22.4.

Hydrolysis of *erythro*-*N*-(*tert*-Butoxycarbonyl)-α-phenyl-2-piperidinemethanol (12). A mixture of *erythro*-*N*-(*Tert*-butoxycarbonyl)-α-phenyl-2-piperidinemethanol (**12**) (189 mg, 0.65 mmol) and sodium hydroxide (104 mg, 2.60 mmol) in 1.2 mL of ethanol was heated to reflux for 30 min. The mixture was stripped, and the residue was dissolved in 4 mL of water and extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give a crude product as solid which was recrystallized from ether to give 118 mg (95%) of *erythro*-α-phenyl-2-piperidinemethanol (**32**) as white solid:[5] mp 140–141 °C; ^1H NMR ($CDCl_3$) δ 7.35–7.27 (m, H), 4.55 (d, J = 5.3 Hz, 1 H), 3.40–3.10 (br, 1 H), 3.02 (d, J = 10.8 Hz, 1 H), 2.76–2.71 (m, 1 H), 2,58 (td, J = 11.7, 2.5 Hz, 1 H), 1.79–1.76 (m, 1 H), 1.62–1.53 (, 2 H), 1.35–1.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.8, 128.2, 127.4, 126.5, 61.9, 46.8, 26.7, 26.2, 24.3. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 732. Found: C, 75.32; H, 8.97; N, 7.32.

Hydrolysis of *threo*-8-Oxa-7-phenyl-1-azabicyclo[4.3.0]nonan-9-one (13). A mixture of *threo*-8-oxa-7-phenyl-azabicyclo[4.3.0]non-9-one (**13**) (150 mg, 0.69 mmol) and sodium hydroxide (111 mg, 2.76 mmol) in 1 mL of ethanol was heated to reflux for 1 h, and then the solvent was removed. The residue was dissolved in 4 mL of water, and the aqueous layer was extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give a crude product, which was recrystallized from ether to give 120 mg of *threo*-α-phenyl-2-piperidinemethanol (**34**) (91%) as white solid: mp 167–169 °C; ^1H NMR ($CDCl_3$) δ 7.38–7.25 (m, 5 H), 4.37 (d, J = 7.4 Hz, 1 H), 4.32 br, 1 H), 2.96 (d, J = 11.8 Hz, 1 H), 2.65–2.49 (m, 2 H), 1.85 (br, 1 H), 1.70 (d, J = 11.7 Hz, 1 H), 1.53 (d, J = 12.4 Hz, 1 H), 1.40–1.10 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 143.0, 128.2, 128.1, 127.4, 126.9, 77.1, 62.3, 46.0, 28.0, 25.5, 24.2. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.22; H, 8.95; N, 7.29.

Acknowledgment. We are grateful to the National Institutes of Health and National Science Foundation for support of this work. We also are grateful to Professor A. I. Meyers for stimulating discussion and spectral comparison, to Professor R. W. Gawley for a discussion of the stereochemistry of these reactions, and to Professor R. Hill for a sample of *trans*-2,6-dimethylpiperidine.

Supplementary Material Available: Experimental data for the preparations of **7**, **9**, **11**, **14-30**, **33**, **35-42**, and **44** and the X-ray structure of **40** (41 pages). Ordering information is given on any current masthead page.

Articles

Kinetics of the Aqueous Periodate Oxidation of Aliphatic Disulfides and Thioethers

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Water-soluble aliphatic disulfides are oxidatively cleaved by borate-buffered periodate at 23 °C. The reaction conditions were selected because they are used for the oxidation of methionine in protein modification, and we wanted to test the reactivity of the disulfide linkage in various bifunctional molecules under these conditions. A colorimetric method was developed which uses 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) to determine the concentrations of periodate. The γ-substituted amine–disulfide **1b** consumes 4 equiv of periodate at a rate which is accelerated 100-fold over that of 4,4′-dithiodibutanol (**1c**) and forms the cyclic sulfinamide **3** and sulfonamide **4**. To account for the stoichiometry and acceleration, we have proposed intermediates in which a nucleophilic sulfur atom attacks an oxygen atom of periodate to give an anhydride or complex rather than invoking direct oxygen atom transfer. The γ- and δ-hydroxy disulfides **1a** and **1c** consume 5 equiv of periodate and are oxidized to the sulfonic acids. The rate of DL-methionine (**2a**) oxidation in water is reported, along with the oxidations of dibutyl sulfide (**2c**) and of 1,5-dithiacyclooctane (**2d**) in 50% aqueous ethanol. The oxidation of **2d** is only 2.1 times faster than the oxidation of **2c**, showing that the transannular sulfur atom in **2d** does not participate in the oxidation. A comparison of the rate of periodate oxidation of disulfides, thioethers, and ethylene glycol under the same conditions shows that it is possible for these processes to be competitive.

Introduction

Periodate is an excellent reagent for the conversion of thioethers to sulfoxides,[1] and, for that reason, it is used in protein modification studies to convert methionine to methonine sulfoxide.[2] Although many of the functional groups present on side chains of amino acids were examined and shown to be resistant to periodate oxidation under the conditions used in protein modification studies, the disulfide group was not studied. Unsubstituted disulfides are rather resistant to oxidation by aqueous periodate[3] because of their insolubility in water, but substituted disulfides such as cystine have been shown to be oxidized slowly to sulfonic acids.[4-6] However, the oxidation of isolated disulfides and cystine itself may not be realistic models of the reactions of disulfides in proteins. For example, we have shown that the concomitant electrophilic–nucleophilic oxidation of aliphatic thioethers and disulfides with aqueous iodine is strongly enhanced by neighboring nucleophiles.[7-13] In order to determine whether the oxidative cleavage of disulfides by periodate can proceed at a rate which is comparable to the rate of oxidation of thioethers, the rate and products of the oxidation of a series of bifunctional, water-soluble, aliphatic disulfides were examined. The three disulfides used are 3,3′-dithiodipropanol (**1a**), bis(3-aminopropyl) disulfide (**1b**), and 4,4′-dithiodibutanol (**1c**).

$$[X(CH_2)_2S]_2$$

1: X = CH_2OH (**a**), CH_2NH_2 (**b**), $(CH_2)_2OH$ (**c**)

Ruff and Kucsman[14,15] studied the periodate oxidation of aliphatic and aromatic thioethers in aqueous alcohol and concluded that oxidation proceeds by a one-step electrophilic oxygen transfer from periodate to the thioether

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