Tetrahedron 64 (2008) 7131–7135

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Carbamate-stabilized anions of 2-azabicyclo[2.1.1]hexanes

Grant R. Krow, Philip E. Sonnet *

Chemistry Department, Temple University, Philadelphia, PA 19122, USA

ARTICLE INFO

Article history:
Received 3 March 2008
Received in revised form 21 April 2008
Accepted 23 April 2008
Available online 10 May 2008

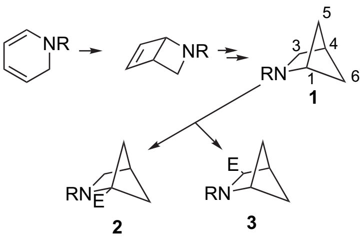
Keywords:
2-Azabicyclo[2.1.1]hexanes
Carbamate anions
Anion complexes
B3P86 computations

ABSTRACT

The regiochemical outcomes for *s*-BuLi/TMEDA deprotonations of *N*-Boc-2-azabicyclo[2.1.1]hexanes had been shown to be temperature dependent. Computational methods have been applied to advance understanding of the complexes that the reagents form, the character of the deprotonations, and hence the experimentally observed regiochemical biases. The tertiary anion is formed more readily than the secondary anion and is also the more stable anion. Computations for the enthalpy of proton abstraction from the analogous *N*-methoxycarbonyl structure also indicate greater stability for the tertiary carbamate anion.

1. Introduction

The 2-azabicyclo[2.1.1]hexane ring system **1** (Scheme 1) has been the focus of synthetic and mechanistic investigations to develop practical routes to variously substituted structures in a regioselective, stereoselective, or enantioselective manner as required.[1] These are bridged 2,4-methanopyrrolidines, and conformationally constrained pyrrolidines have proven to be valuable scaffolds for drug discovery.[2] Development of a rearrangement route to 2-azabicyclo[2.1.1]hexanes,[3] which are themselves accessed photochemically from dihydropyridines,[4] has made this ring system available with various patterns of substitution. A particularly attractive method for obtaining the desired carboxylated azabicyclics would entail deprotonation of carbamates under conditions that have been well investigated and received wide use in synthetic chemistry.[5–7] The resulting anions could then be treated with various electrophiles, for example, CO_2, to obtain methanoprolines.



1
2
3

Scheme 1. Preparations of substituted 2-azabicyclo[2.1.1]hexanes.

Lithiation of the carbamate, 2-*tert*-butoxyoxycarbonyl-2-azabicyclo[2.1.1]hexane **1** ($R{=}CO_2^tBu$), with *sec*-butyllithium/TMEDA in diethyl ether was followed by allowing the anion(s) to react with various electrophiles. This led to products in which substitution had occurred at either the neighboring bridgehead carbon and/or the adjacent methylene carbon.[8] Reactions conducted at 0 °C produced exclusively the tertiary product **2**, while at −78 °C both **2** and **3** were isolated. The present calculations were undertaken, mindful of the seminal work in this field by Wiberg and co-workers,[9] in order to evaluate the complexes that may form, their potential for interconversion, and the energy barriers for anion formation. It was desirable to gain insights for the changes in reaction parameters that would permit selective reaction at the methylene carbon and perhaps thereby open an avenue for stereoselective reactions at that site.

2. Results

Initially we wished to evaluate the exothermicity of complex formation (Table 1). Kinetic studies reported by Beak and Gallagher indicated that such complexes consist of the carbamate, alkyllithium, and diamine.[10] The diamine is added in some cases as a chiral auxiliary; here we added TMEDA to assist in breaking down aggregates normally present in solutions of alkyllithium reagents.[5] The energies of *s*-BuLi, TMEDA, and the two conformers of the carbamate, 2-*N*-*tert*-butoxycarbonyl-2-azabicyclo[2.1.1]hexane, **4** (Fig. 1), were obtained by full optimization at the B3LYP/6-31G(d) level.[11] Complexes were constructed and then optimized for geometry as above. We located two potential energy wells for

---

* Corresponding author.
E-mail address: pes2060@gmail.com (P.E. Sonnet).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.119

Table 1
Energy of formation of complexes[a] (298.15 K)

	Structure	B3LYP/6-31G(d)	$\Delta E_{\text{formation}}$ (kcal/mol)
1.	*s*-BuLi	−165.331661	
2.	TMEDA	−347.745016	
3.	**4**-*s-cis*	−596.485887	
4.	**C1**[b]	−1109.631245	4−(1+2+3)=−0.068681 (−43.1)
5.	**4**-s-*trans*	−596.485856	
6.	**C2**[c]	−1109.630807	6−(1+2+5)=−0.068274 (−42.8)

[a] Energy in hartrees from full optimization, uncorr. (1 Hartree=627.51 kcal/mol).

[b] Lowest energy conformer in which the carbonyl oxygen is oriented toward the tertiary H on C(1).

[c] Lowest energy conformer in which the carbonyl oxygen is oriented toward a secondary H on C(3).

conformations in which the lithiated oxygen was oriented toward the tertiary hydrogen on the neighboring bridgehead carbon, C_1; also two for complementary conformations in which the oxygen was oriented toward C_3. The pairs differed in the orientation of the methyl and ethyl of the *sec*-butyl group, differed little in energy, and we selected the lower energy conformation of each pair labeling them **C1** and **C3**, respectively (Fig. 2). In parallel with the kinetic data reported by Beak[10] and the computations of Wiberg[9] for the structures of complexes of organolithiums, diamines, and carbamates, the formation of these complexes is highly exothermic. The values obtained for **C1** (−43.1 kcal/mol) and **C3** (−42.8) (Table 1) suggest considerable stability. The dihedral angles H–C–(N)–C=O(Li) are +5.1° for **C1**, but +49.0° and −61.3° for the dihedrals involving the two methylene protons. The structural significance of this will be discussed subsequently.

Several methods and basis sets were employed to obtain optimized geometries and energies for complexes **C1** and **C3**, the corresponding anions **A1** and **A3**, and the transition structures separating them (Scheme 2). Transition structures were calculated using the transit-guided quasi-Newton (QST3) method,[13] and were confirmed with a single imaginary frequency. The results in Table 2 uniformly indicate that the lower energy anion is the tertiary anion **A1**. Moreover, as the basis set is improved the difference in energies of $\mathbf{TS_{C1-C3}}$ and $\mathbf{TS_{C3-A3}}$ decreases indicating that formation of the secondary anion is competitive with the interconversion of the complexes.

At this juncture we continue descriptions using data from the geometry of the B3P86/6-31G(d) optimizations that served earlier research on similar complex anions well.[9,12] Data from other computations gave parallel results and did not alter the judgments to follow.

Images of the structures with the TMEDA and butane residues removed for clarity again are shown in Figure 3 in order to illustrate changes in selected bond lengths as the anions are formed. The

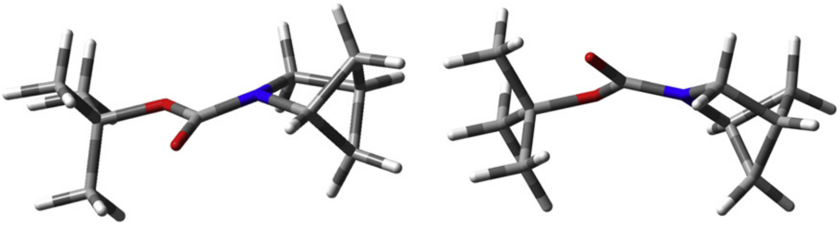


Figure 1. Conformers of **4**, *s-cis* and *s-trans*,resp. Blue is nitrogen; red is oxygen.

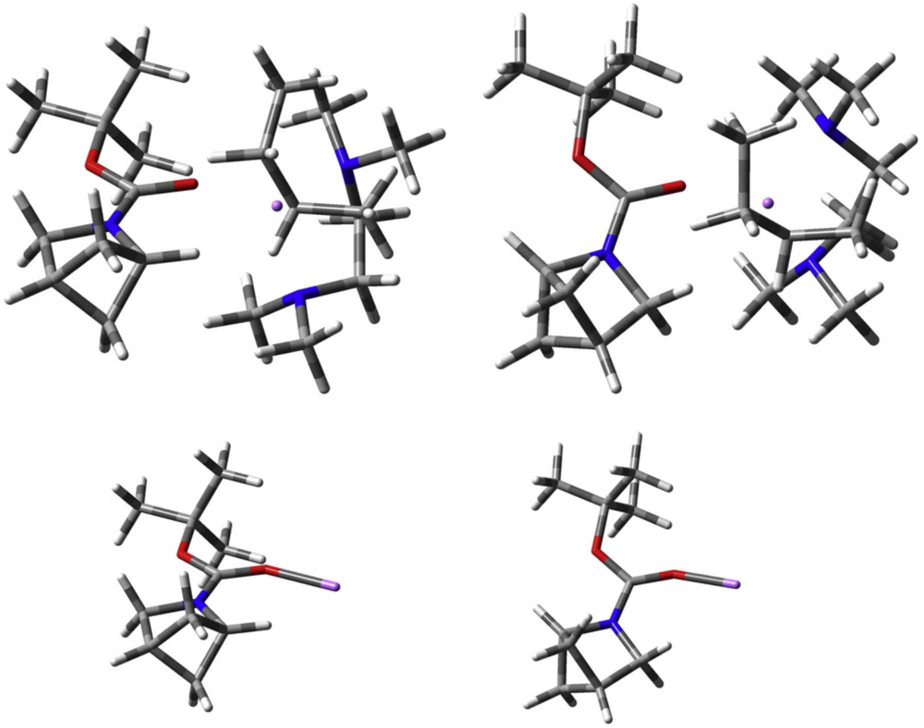
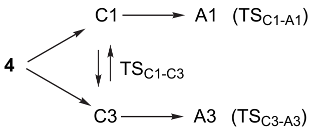


Figure 2. The two conformations of lower energy of the complexed species **C1** and **C3**, respectively. Images with *sec*-butyl and TMEDA removed are shown below. Colors are as before; violet is Lithium.



Scheme 2. Reactions of **1** (R=CO$_2{}^t$Bu) with *s*-BuLi in the presence of TMEDA. Labels reflect the numbering of the azabicyclic system.

Table 2
Relative energies for the structures in Scheme 2 (kcal/mol)[a]

Methods/basis sets	**C1**	**TS$_{C1-C3}$**	**C3**	**TS$_{C1-A1}$**	**A1**	**TS$_{C3-A3}$**	**A3**
HF/3-21G[b]	23.5	42.6	24.1	47.5	0.0	52.3	7.7
B3P86/6-31G(d)[c]	19.8	37.2	20.5	35.7	0.0	40.3	5.8
B3P86/6-31+G(d)[c]	19.4	37.0	20.2	35.9	0.0	40.2	5.6
B3P86/6-31G(d)[d]	20.4	37.6	20.7	35.4	0.0	38.0	5.8
B3P86/6-311+G(d,p)[e]	18.9	36.4	19.5	33.8	0.0	36.5	5.5

[a] Complete details are provided in Supplementary data.

[b] Full optimization with zero point energies scaled by 0.9804.

[c] Single point energies with corrected zero point energies taken from HF geometry.

[d] Full optimization with corrected zero point energies taken from HF geometry.

[e] Single point energies using B3P86 geometry and corrected using the zero point energies taken from HF geometry.

carbonyl oxygen bond of the lithiated structures lengthens while the N–(C=O) distance decreases. Similarly, the N–C_1 and N–C_3 bonds lengthen in response to the developing charges on the deprotonating carbons. Inspection of the potential non-bonded interactions in **C1** and **C3** and their respective transition structures leading to **A1** and **A3** (which includes the TMEDA and *sec*-butyl groups) revealed the following items. In complex **C1** short distances exist between C_1 proton and *sec*-butyl C proton (2.00 Å) and crowding exists between *tert*-butyl and TMEDA with a distance as small as 2.30 Å between protons. However, the dihedral angle H–C–(N)–C=O is 4.47°, and the H–(C=O) distance is 2.68 Å. This is a situation conducive to proton removal induced by dipole stabilization.[5,14] As the proton shifts in **TS$_{C1-A1}$** little change occurs in the short distances noted for **C1** *sec*-butyl and TMEDA protons. The lengths of C_1–N and C=O bonds increase while that of N–(C=O) bond shortens. In **C3** close distances are observed for a C_3 methylene proton with each of two *sec*-butyl protons (2.11, 2.22 Å); the other methylene proton is close to a TMEDA proton (2.26 Å). A methanobridge proton is at a distance of 2.28 Å to a *sec*-butyl C_3 proton. In addition, the TMEDA and *sec*-butyl residues are in closer proximity than in **C1**. The critical dihedral angles (distances) involving the acidic protons are 48.85° (H–[C=O]=2.81 Å) and −61.43° (3.11 Å). The structure of **TS$_{C3-A3}$** shows that the methylene proton that is not transferred is now closer to the TMEDA proton (1.99 Å), and the methanobridge proton to *sec*-butyl C_3 proton distance is reduced to 2.17 Å. No steric relief from crowding of TMEDA and *sec*-butyl is evident. The dihedral angle, C_3–N–C=O, is 13.14°, but the path of proton transfer described by the dihedral H–C_3–(N)–C=O remains diverged at 44.69°. The stabilization to be derived from the carbonyl dipole is presumably offset by π–lone pair repulsion as well as some steric compression beyond that present in the complex **C3**. These calculations are consistent with favorable kinetics for formation of the tertiary anion **A1**.

What are the intrinsic acidities of the relevant protons in the carbamate? Calculations for *N*-(methoxycarbonyl)piperidine showed that the axial protons were more acidic than the equatorial, and that protons distal from the carbonyl were more acidic than those that were proximal.[15] Bonds that were *anti* to the lone pair in each of the possible anions were lengthened. The authors note that the effects were similar to those calculated from cyclohexane anions,[16] and were then ascribed to coupling of the lone pair orbital with those of antiperiplanar antibonding orbitals. An analysis of charge distributions indicated that the acidity of a proton could be related to the ability to disperse the charge of the resulting anion more readily to the carbamate carbonyl oxygen.[15] In the event, the asymmetric lithiations of Boc-piperidine had involved removal of the intrinsically least acidic proton. In light of the value for regioselective deprotonations of bridgehead azabicyclics such as **1**, we evaluated the acidities of the protons of the bicyclic carbamate **5** (Fig. 4) in similar manner at 195 K, which is the temperature at which deprotonations had led to production of both 1- and 3-anions. Specifically, the structures were initially optimized for

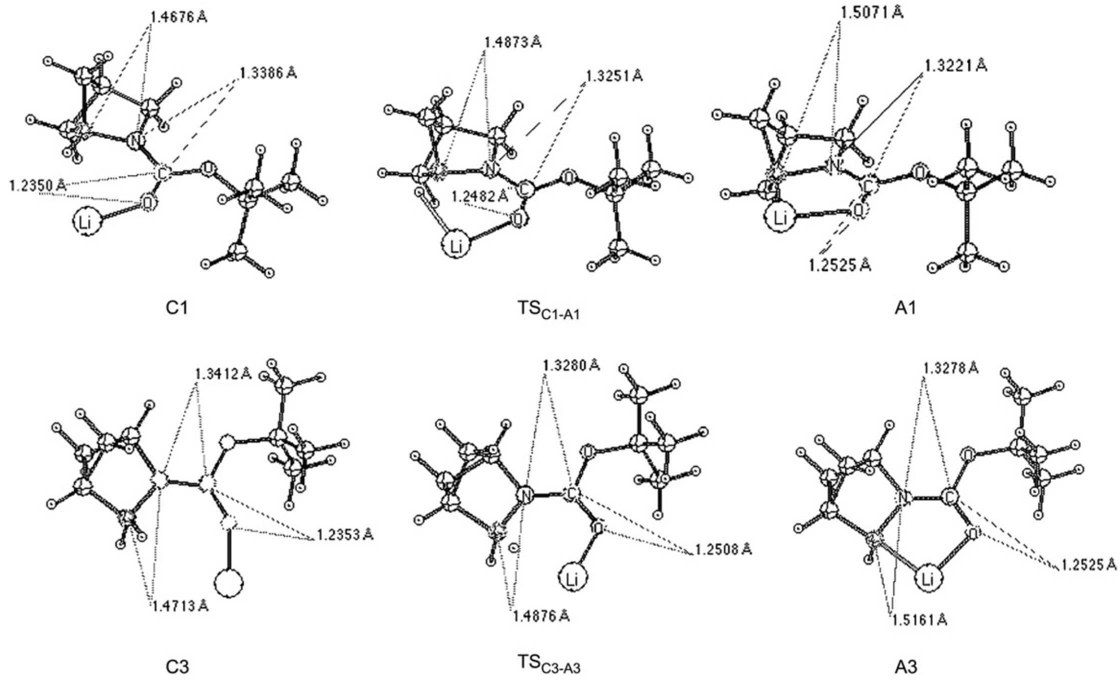
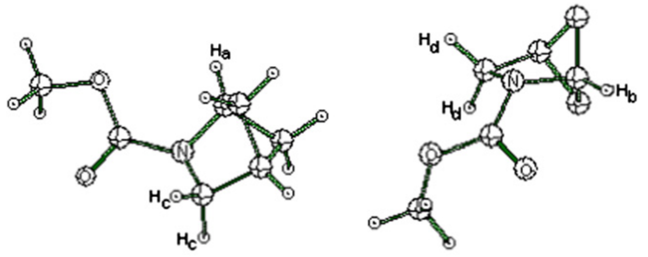


Figure 3. Simplified structures of the complexes, transition structures, and product anions derived from **C1** and **C3** at the B3P86/6-31G(d) level of accuracy.



s-trans-5 s-cis-5

Figure 4. Identities of the acidic protons of the carbamate **5**.

Table 3
Calculated proton abstraction enthalpies for **5**

Structure	B3P86/6-31+G(d)[a]	ZPE[b]	H_{corr}[c]	ΔH[d]	ΔH[e]
s-trans-carbamate	−479.558855	0.179960	−479.557619	0.1	
s-cis-carbamate	−479.558911	0.179861	−479.557745		
H_a	−478.945468	0.162839	−478.944233	385.0	0.0
H_c	−478.937445	0.162718	−478.93621	390.0	5.0
H_b	−478.942035	0.162640	−478.940800	387.1	2.1
H_d	−478.940545	0.162939	−478.939309	388.1	3.1

[a] Full optimization (1 Hartree=627.51 kcal/mol).
[b] Zero point energy uncorrected.
[c] Sum of thermal and electronic enthalpies with zero point correction and calculated for 195 K.
[d] kcal/mol relative to *s-cis*-carbamate.
[e] kcal/mol relative to anion derived by removal of H_a.

Table 4
Bond lengths of the carbamates **5** and their anions (Fig. 4) (Å)[a]

Entry	Structure	1–2(N)	1–5	1–6	2(N)–3	3–4	4–5	4–6	N–(C=O)	C=O	C–O	O–Me
1	*s-trans*-**5**	1.471	1.545	1.549	1.472	1.535	1.554	1.555	1.353	1.221	1.358	1.426
2	*s-cis*-**5**	1.467	1.549	1.545	1.472	1.536	1.555	1.554	1.352	1.221	1.359	1.426
3	*s-trans*-**1**	1.511	1.584	1.584	1.473	1.529	1.545	1.545	1.327	1.243	1.372	1.410
4	*s-cis*-**1**	1.509	1.584	1.584	1.478	1.528	1.544	1.544	1.329	1.227	1.407	1.410
5	*s-trans*-**3**	1.461	1.553	1.549	1.505	1.531	1.577	1.555	1.322	1.235	1.409	1.409
6	*s-cis*-**3**	1.457	1.551	1.550	1.510	1.533	1.576	1.555	1.322	1.247	1.380	1.409

[a] Atom numbering as for **1** (Scheme 1).

geometry at the RHF/3-21G level. The output geometries and force constants were employed to hasten optimizations at the B3P86/6-31+G(d) level of accuracy. Proton abstraction enthalpy was taken as $H_{anion}–H_{conj.acid}$. Enthalpies reported in Table 3 include the uncorrected values, and the values corrected by unscaled zero point energies. Four deprotonations were considered: removal of C_1–H with carbonyl oriented *anti* or *syn* to the proton being removed (**H_a**, **H_b**, respectively) and deprotonation of a C_3–H, again with carbonyl in either of two orientations (**H_c**, **H_d**) (Fig. 4 and Table 3). The more acidic proton is tertiary regardless of carbonyl orientation; the tertiary proton is most acidic when the carbonyl oxygen is distal. The least acidic proton is the C_3–H when the carbonyl is distal, hence the order of acidity is **H_a**>**H_b**>**H_d**>**H_c**.

Examination of bond lengths (Table 4) showed that the N–(C=O) single bond and the O–Me bond is uniformly shortened in the anions, while the C–O single bond was slightly lengthened (entries 3–6 vs 1 and 2). For the tertiary anions **1**, bond lengthening occurred for bonds associated with the anionic carbon, namely C_1–N, and C_1–$C_{5,6}$, while the secondary anions **3** showed lengthened bonds for N–C_3 and the antiperiplanar bond C_4–C_5. The C_4–C_6 bond was essentially unaltered. Moreover, the sums of angles at the base of each potential anion were commensurate with expectations for the greater acidity of the tertiary proton of the bicyclic structure. The angles subtending the lone pair of the tertiary anions totaled 274.3° and 274.6°, while the corresponding values for the secondary anions were 312.5° and 311.1°. As in the complexed anions, the tertiary anion is stabilized by bond angles that permit greater *s* character for the anion pair. In contrast to deprotonations of Boc-piperidine, the anion formed in the bicyclic carbamate **5** involves abstraction of the more acidic proton.

3. Conclusions

The computations reported here are consistent with a rapid interconversion of the *cis*- and *trans*-carbamates **4** when deprotonations were conducted at 0 °C. The more readily deprotonated complex was that which led to the tertiary anion.[17] Deprotonation at the lower temperature (−78 °C) led to a product composition that reflected diminished equilibration of the complexed conformers. The observed reactions involved deprotonation of the more stable *sec*-butyllithium–TMEDA complex and produced the more stable anion. Additionally, by judging the data for deprotonation of **5** in the absence of lithium cation and TMEDA, it is evident that the tertiary carbamate anion is generally the more stable. Alteration of regioselectivity, therefore, will require defining a dynamic kinetic basis for the deprotonation through use of site directing complexing agents or altering the stabilities of the anions themselves by appropriate substitutions.

4. Experimental

Computations were conducted with Gaussian 98 using methods and basis sets as indicated in the text and table footnotes. Complete details are provided in Supplementary data. Geometry optimizations and frequency calculations were used to locate PE minima and obtain thermodynamic data, and transition structures were calculated using the transit-guided quasi-Newton (QST3) method.[17] These were confirmed with a single imaginary frequency.

Acknowledgements

The authors acknowledge financial support from the National Science Foundation (CHE 0515635), and express deep appreciation to Dr. David R. Dalton of Temple University for encouragement and discussions on computational chemistry. We also express appreciation to a reviewer for bringing our attention to additional appropriate literature.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.119.

References and notes

1. For a review of synthetic approaches to 2-azabicyclo[2.1.1]hexanes, see: Krow, G. R.; Cannon, K. C. *Heterocycles* **2004**, *62*, 877.
2. Bunch, L.; Liljefors, T.; Greenwood, J. R.; Frydenvang, K.; Brauner-Osborne, H.; Krogsgaard-Larsen, P.; Madsen, U. *J. Org. Chem.* **2003**, *68*, 1489 and references cited.
3. Krow, G. R.; Lin, G.; Yu, F. *J. Org. Chem.* **2005**, *70*, 590 and references cited.
4. Krow, G. R.; Lee, Y. B.; Walden, S. L.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558.
5. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552; see also: Johnson, T. A.; Curtis, M. D.; Beak, P. *Org. Lett.* **2002**, *4*, 2747.
6. Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282.
7. Werthwein, V. E.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 4443 and references cited.
8. Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 3151.
9. O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. P.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480 and earlier references.
10. Gallagher, D. J.; Beak, P. J. *J. Org. Chem.* **1995**, *60*, 7092.
11. *Gaussian 98*, Revision; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; see, Supplementary data for additional references concerning methods/basis sets employed.
12. Application of the hybrid, ONIOM, method to deprotonation of carbamates has been reported recently, but was judged only modestly successful: Deng, W.; Vreven, T.; Frisch, M. J.; Wiberg, K. B. *J. Mol. Struct., THEOCHEM* **2006**, *775*, 93.
13. Ayala, P. A.; Schlegel, H. B. *J. Chem. Phys.* **1997**, *107*, 375.
14. Bertini, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.
15. Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.
16. Sauers, R. R. *Tetrahedron* **1999**, *55*, 10013 and references cited.
17. For other notable observations of regioselectivity involving Boc-activated α carbon, see: (a) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799; (b) Santiago, M.; Low, E.; Chambournier, G.; Gawley, R. E. *J. Org. Chem.* **2003**, *68*, 8480; (c) Sunose, M.; Peakman, T. M.; Charmant, J. P. H.; Gallagher, T.; MacDonald, S. J. F. *Chem. Commun.* **1998**, 1723.