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An Experimental and Computational Investigation of the Enantioselective Deprotonation of Boc-piperidine

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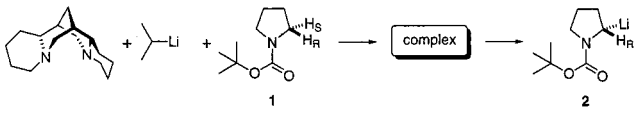
Abstract: The asymmetric deprotonation of *N*-Boc-piperidine (**3**) by the 1:1 complex of a *sec*-alkyllithium and (−)-sparteine has been investigated both experimentally and computationally. The lithiation of **3** with sec-BuLi−(−)-sparteine at −78 °C, which is a much slower process than is the analogous deprotonation of *N*-Boc-pyrrolidine (**1**) and a minor reaction relative to the competing addition of *sec*-BuLi to the carbamate, proceeds with a moderate degree of selectivity (er = 87:13) for removal of the *pro-S* hydrogen of **3**. The related deprotonation of *N*-Boc-4-tosyloxypiperidine (**6**) with two molar equiv of *sec*-BuLi−(−)-sparteine also involves preferential transfer of the *pro-S* hydrogen. The computational study of the deprotonation of (**3**) by *i*-PrLi−(−)-sparteine found that the proton that is preferentially transferred within three-component intermediate complex is the thermodynamically least acidic α-hydrogen of **3**. The asymmetric deprotonation of **3** is calculated to proceed with poor enantioselectivity and to have an activation energy considerably higher than that calculated for deprotonation of *N*-Boc-pyrrolidine (**1**). The experimental and computational results are in good agreement.

Asymmetric deprotonation by an organolithium complexed to (−)-sparteine of a prochiral carbon bonded to the nitrogen or oxygen of a carbamate provides the key step in a new and developing methodology for asymmetric synthesis.[1] A prototypical case is provided by the enantioselective deprotonation of *N*-(*tert*-butoxycarbonyl)pyrrolidine (Boc-pyrrolidine, **1**) by isopropyllithium−(−)-sparteine which proceeds with a high degree of selectivity (er = 97:3) for removal of the *pro*-S hydrogen of **1**[1] to give **2**.[2] The kinetics of the deprotonation are consistent with formation of a thermodynamically favorable three-component complex of alkyllithium, sparteine, and **1** prior to a rate-determining transfer of H_S to the complexed *i*-PrLi.[3] Computational results indicate that the origin of the enantioselectivity observed for the deprotonation is largely a steric phenomenon.[4] The most stable complex, that leading to transfer of the *pro*-S hydrogen of **1**, also has the lowest activation energy for lithiation; an analogous but less stable complex, leading to transfer of the *pro-R* hydrogen of **1**, is more congested and a number of the steric interactions responsible for the higher ground-state energy of this complex persist in the transition state for proton transfer.[4] The relatively large difference in the transition state energies calculated for removal of the *pro-R* and *pro-S* hydrogens of **1** ($\Delta\Delta H^{\ddagger} = 4.5$ kcal/mol, $\Delta\Delta G^{\ddagger} = 3.2$ kcal/mol)[4] are fully consonant with the highly enantioselective character of the process.



1 2

Extension of this asymmetric deprotonation methodology to the piperidine system would be of obvious synthetic utility. Herein we report the first determination of the enantioselectivity and sense of enantoselection in the lithiation of *N*-(*tert*-butoxycarbonyl)piperidine (Boc-piperidine, **3**) by *sec*-BuLi−(−)-sparteine. As detailed below, asymmetric deprotonation of **3** is considerably slower and less enantioselective than is the analogous reaction of **1**. Detailed insight into the factors responsible for the lower enantioselectivity and reduced yields that characterize the asymmetric deprotonation of **3** relative to **1** are provided by ab initio molecular orbital theory.

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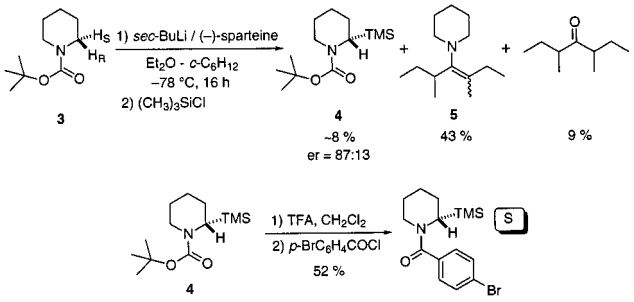
Scheme 1



Results and Discussion

Asymmetric Lithiation of Boc-piperidine. Previous work has established that lithiation of substituted Boc-piperidines by *sec*-BuLi-TMEDA involves removal of an equatorial proton.[5] It is also known that lithiation of Boc-piperidine (**3**) is a much less facile process than is the deprotonation of Boc-pyrrolidine (**1**).[6] Given these preliminaries, the course of the reaction of **3** with *sec*-BuLi−(−)-sparteine was investigated.

As illustrated in Scheme 1, lithiation of Boc-piperidine (**3**) with *sec*-BuLi−(−)sparteine in Et_2O/cyclohexane solution at −78 °C required 16 h for completion of the reaction and, following addition of an excess of trimethylsilyl chloride, only ~8% of 2-trimethylsilyl-Boc-piperidine (**4**) was detected. The major reaction product (43%) was found to be a mixture of the isomeric enamines (**5**) accompanied by ~9% of an isomeric mixture of 3,5-dimethyl-4-heptanones. Apparently, the very slow rate of the lithiation reaction allows the competitive addition of *sec*-BuLi to the carbamate group of **3** to predominate; loss of peperidide from the addition adduct provides the heptanone while loss of *t*-butoxide, followed by a second addition of the alkyllithium and formal dehydration, affords the enamine products (**5**).

A separate, large-scale reaction permitted isolation of a quantity of **4** suitable for determination of the enantioselectivity and sense of enantioselection of the lithiation. Chiral stationary phase (CSP) HPLC analysis of the reaction product revealed that **4** had been generated with an er = 87:13. The (2S) configuration depicted for the major enantiomer (**4**) was established, as shown in Scheme 1, by removal of the Boc group and conversion of the free piperidine to the *p*-bromobenzamide derivative that was suitable for anomalous X-ray diffraction analysis. On the reasonable assumption that trapping of lithiated **3** by trimethylsilyl chloride proceeds with retention of configuration,[1,2] the deprotonation of **3** with *sec*-BuLi−(−)sparteine involves preferential removal of the *pro-S* hydrogen. As noted above, asymmetric lithiation of Boc-pyrrolidine (**1**) also involves preferential removal of the *pro-S* hydrogen, albeit with greater enantioselectivity and in much higher yield than the deprotonation of **3**.

Having established the sense of enantioselection in the asymmetric lithiation of **3**, we revisited the reaction of *N*-Boc-4-tosyloxypiperidine (**6**) with two molar equiv of *sec*-BuLi−(−)-sparteine to afford 1-trimethylsilyl-2-azabicyclo[3.1.0]-hexane (**7**) in 26% yield with 75:25 er (Scheme 2) as first reported five years ago.[7] The azabicyclo[3.1.0]hexane (**7**) was converted to the crystalline *p*-bromobenzamide derivative and the absolute configuration of the product was established as (2R,3R) by anomalous X-ray diffraction analysis. As illustrated in Scheme 2, the reaction of **6** with *sec*-BuLi−(−)-sparteine proceeds via deprotonation at C(2) followed by intramolecular S_N2 displacement of the tosylate and subsequent lithiation at the bridgehead position proximal to the Boc-group.[7] This result is entirely consistent with preferential removal of the equatorial *pro-S* hydrogen of **6** in the asymmetric deprotonation to initiate the cascade, depicted in Scheme 2, that affords **7**.

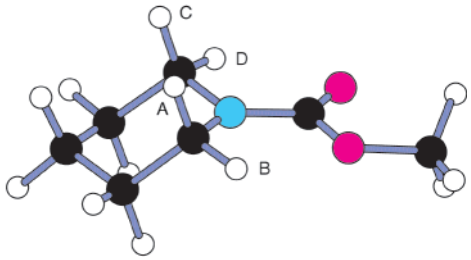
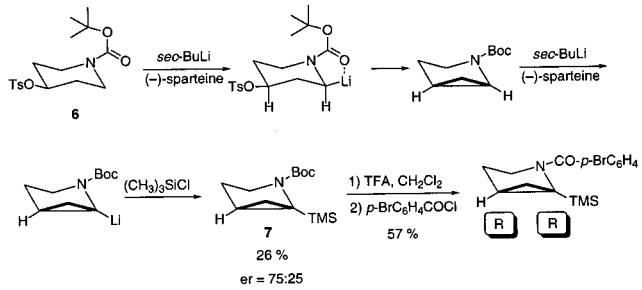


Figure 1. Structure of *N*-(methoxycarbonyl)piperidine; the nitrogen atom is blue, the oxygen atoms are red, lithium is orange.

Scheme 2



The results of these experiments, summarized pictorially in Schemes 1 and 2, demonstrate that the asymmetric deprotonation of a Boc-piperidine by *sec*-BuLi−(−)-sparteine is a relatively slow process that involves preferential abstraction of the equatorial C(2) *pro-S* hydrogen. In light of the success of modern ab initio molecular orbital theory to provide detailed insight into the factors responsible for the asymmetric lithiation of Boc-pyrrolidine (**1**),[4] it seemed worthwhile to investigate the analogous lithiation of Boc-piperidine (**3**) using this approach.

Computational Results. At the inception of the computational study, it was of interest to examine the relative acidities of the α-hydrogens in a piperidine carbamate and we investigated this question at the B3P86/6-31+G* level of theory.[8] To simplify the calculations, *N*-(methoxycarbonyl)piperidine was used as a model for the significantly more complicated Boc-piperidine (**3**). As depicted in Figure 1, the carbamate unit in the lowest energy structure of *N*-(methoxycarbonyl)piperidine is planar and, as a result, there are four diastereotopic protons (labeled A−D) to consider in formation of an anion. The calculated enthalpies for abstraction of each of the four

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Table 1. Calculated B3P86/6-31+G* Proton Abstraction Enthalpies for the α-Hydrogens of *N*-(Methoxycarbonyl)piperidine (Figure 1)[a]

compound	B3P86/6-31+G*	ZPE[b]	H_{corr}[c]	ΔH_{acid}	ΔH_{rel}
N-(methoxycarbonyl-piperidine	−481.22542	127.72	−481.01096		
axial anion, H_A	−480.57471	117.30	−480.37697	397.8	0.0
equatorial anion, H_B	−480.56857	116.68	−480.37172	401.1	3.3
axial anion, H_C	−480.57221	117.16	−480.37460	399.3	1.5
equatorial anion, H_D	−480.56232	116.42	−480.36577	404.9	7.0

[a] Total energies are given in hartrees (1 hartree = 627.51 kcal/mol), other energies are in kcal/mol. [b] Zero point energy. [c] Corrected for both the differences in ZPE and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K.

α-hydrogens, corrected for differences in zero point energies (ZPE) as well as the change in enthalpy on going from 0 to 195 K (−78 °C), are given in Table 1.

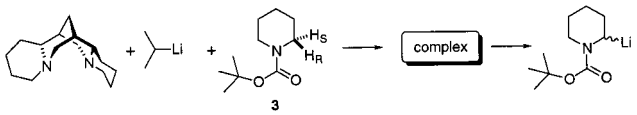
Cursory inspection of the data in Table 1 reveals that the axial α-protons in the carbamate (viz. A and C in Figure 1) are more acidic than are the equatorial α-protons (viz. B and D). Moreover, for a given type of hydrogen (i.e., axial or equatorial), the one distal from the carbonyl oxygen of the carbamate is significantly more acidic than is the same type of proton proximal to that oxygen. Thus, the order of relative acidities in *N*-(methoxycarbonyl)piperidine is: $H_A > H_C > H_B > H_D$. In each of the anions, the bonds located anti to the anionic lone-pair (i.e., an axial C−H bond in the axial ions and the C(3)−C(4) bond in the equatorial ions) were lengthened; detailed structures may be found in Table S1 of the Supporting Information. These structural effects, which are similar to those found for the anions derived from the axial and equatorial C−H bonds of cyclohexane,[9] are presumably due to coupling of the anion lone-pair with the anti-periplanar bond orbitals.

The origin of the sizable difference in the acidities of hydrogens in *N*-(methoxycarbonyl)piperidine was investigated by analysis of the charge distributions in the anions. It should be noted that calculation of charge distribution is fraught with difficulty since such quantities are not well defined and different methods can lead to quite different values for a given atom.[10] Fortunately, the change in charge at a particular atom on going from the carbamate to its anions should give a better indication of the resulting charge distributions than the absolute charges themselves. To this end, we have chosen to use the Natural Population Analysis (NPA) charges of Weinhold and Reed[11] as well as the Hirshfeld charges.[12] It might be noted that the NPA charges are derived from the calculated molecular orbitals and, although they are related to the Mulliken charges, they avoid the difficulties that have been noted for the later.[10] The Hirshfeld charges are derived from the electron density distributions; a set of spherically symmetrical neutral atoms ("pro-atoms") are placed at each nuclear position, a 3-dimensional grid is placed about the molecule, and the electron density is calculated at each point on the grid along with the contribution at each point from each of the pro-atoms. The calculated electron density is then apportioned among the atoms of the molecule in proportion to the contribution from each of the pro-atoms.[12]

The results of the Hirshfeld analysis, giving the calculated charges as well as changes in atomic charge on going from the carbamate to each of the four anions, are found in Table 2; the results of the NPA charge analysis may be found in Table S2 of the Supporting Information.

Although the calculated Hirshfeld (Table 2) and NPA charges (Table S2) differ in magnitude, the overall trends are in general agreement. The Hirshfeld charges are the more convenient in the present context because they avoid the C−H bond charge separation found in the NPA analysis.[11b] The most significant effect appears to involve charge transfer to the carbonyl oxygen (O(18) in Table 2) on formation of the anions and this correlates nicely with the relative acidities (Table 1): removal of H_A, the most acidic proton, results in the largest charge at the carbonyl oxygen while removal of the least acidic hydrogen, H_D, results in the smallest charge at the oxygen site. This result appears reasonable since generation of an axial anion adjacent to the nitrogen of the carbamate by removal of H_A distal to the carbonyl oxygen would lead to charge transfer through a conjugated system of orbitals while resulting in an anion that is well removed from the negative oxygen. Removal of the axial proton proximal to the carbonyl oxygen (H_C) also leads to charge transfer but the resulting anion is less stable than that generated by removal of H_A since the anionic center created by removal of H_C is spatially closer to the negative oxygen. The significance of these results to the matter at hand is this: the intrinsically *least* acidic equatorial α-hydrogen of the carbamate proximal to the carbonyl oxygen (Figure 1, D) is precisely the proton that perforce is transferred in an asymmetric lithiation of Boc-piperidine (**3**).

By analogy with the known course of the asymmetric deprotonation of **1**, the deprotonation of Boc-piperidine (**3**) by *i*-PrLi in the presence of an equivalent of (−)-sparteine most likely also involves formation of a complex prior to proton transfer as shown below. On the reasonable assumption that the structure of the pre-lithiation complex plays a pivotal role in determining the selectivity of the deprotonation, the computational investigation focused on identification of the structures and energies of such species following the procedures used in our study of the asymmetric lithiation of **1**.[4]



3

The four lowest energy Boc-pyrrolidine pre-lithiation complexes identified in our previous study[4] served as the starting point for the present investigation. Each pyrrolidine ring was first converted into a chair piperidine and each of the resulting structures was optimized at the HF/3-21G level. Although this theoretical level sometimes gives unsatisfactory relative energies, it is well established that it usually provides quite good geometries.[13] Two of the structures optimized to give twist-boat conformations for the piperidine ring and, in each case, the piperidine was reconverted to a chair conformation and reoptimized. One of these structures (**8**) retained the chair conformation on reoptimization while the other reverted to a

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Table 2. Hirshfeld Charges and Changes in Charge Distribution on Removal of an α-proton from *N*-(methoxycarbonyl)piperidine (Figure 1)

	charges (e)					change in charge			
atom[a]	parent	anion A	anion B	anion C	anion D	anion A	anion B	anion C	anion D
C1	−0.011	−0.051	−0.052	−0.020	−0.022	−0.040	−0.041	−0.009	−0.011
C2	0.049	−0.274	−0.274	0.33	0.030	−0.323	−0.323	−0.016	−0.019
N3	−0.111	−0.113	−0.120	−0.112	−0.121	−0.002	−0.010	−0.002	−0.011
C4	0.050	0.035	0.032	−0.267	−0.268	−0.016	−0.018	−0.317	−0.319
C5	−0.010	−0.020	−0.021	−0.050	−0.052	−0.009	−0.011	−0.040	−0.041
C6	−0.011	−0.031	−0.035	−0.032	−0.036	−0.020	−0.024	−0.020	−0.025
H7, 2a	0.010	0.000	−0.085	−0.020	−0.017	−0.010	−0.095	−0.030	−0.027
H8,2e	0.022	−0.058	0.000	−0.006	−0.012	−0.080	−0.022	−0.027	−0.034
H9,1a	0.011	−0.062	−0.033	−0.015	−0.010	−0.073	−0.044	−0.025	−0.021
H10,1e	0.015	−0.021	−0.023	−0.013	−0.015	−0.036	−0.038	−0.028	−0.030
H11,4a	0.010	−0.019	−0.016	0.000	−0.083	−0.029	−0.026	−0.010	−0.093
H12, 4e	0.026	0.000	−0.006	−0.052	0.000	−0.027	−0.032	−0.079	−0.026
H13, 5e	0.016	−0.012	−0.014	−0.020	−0.022	−0.028	−0.030	−0.036	−0.038
H14, 5a	0.012	−0.013	−0.009	−0.060	−0.033	−0.025	−0.020	−0.072	−0.044
H15,6a	0.006	−0.026	−0.025	−0.027	−0.026	−0.031	−0.031	−0.032	−0.032
H16,6e	0.014	−0.026	−0.033	−0.027	−0.035	−0.040	−0.046	−0.040	−0.048
C17	0.277	0.238	0.258	0.237	0.254	−0.039	−0.019	−0.040	−0.023
O18,=O	−0.351	−0.428	−0.417	−0.410	−0.396	−0.077	−0.065	−0.059	−0.045
O19,−O−	−0.173	−0.189	−0.195	−0.206	−0.203	−0.017	−0.022	−0.033	−0.031
C20, Me	0.065	0.048	0.047	0.046	0.046	−0.017	−0.018	−0.019	−0.019
H21	0.027	0.008	0.005	0.009	0.008	−0.020	−0.022	−0.019	−0.019
H22	0.030	0.009	0.010	0.005	0.005	−0.021	−0.020	−0.025	−0.025
H23	0.027	0.006	0.005	0.007	0.008	−0.022	−0.022	−0.021	−0.019

[a] The ring atoms are numbered consecutively with C1 on the side of the methoxy group. After each hydrogen, the carbon to which it is attached is given along with its arrangement (axial or equatorial).

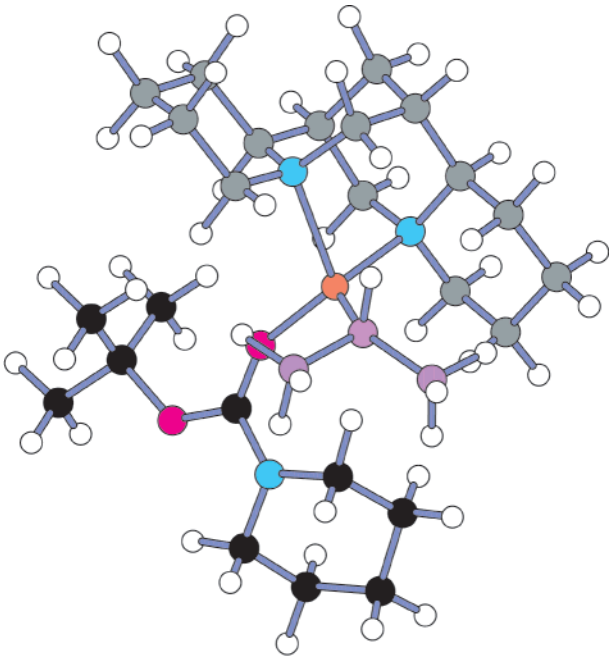

Figure 2. Structure of the lowest-energy complex of Boc-piperidine with *i*-PrLi and (−)-sparteine (**9a**); the isopropyl carbon atoms are purple, other colors as in Figure 1.

twist-boat, some 4 kcal/mol less stable than the lowest energy structure. The two remaining original complexes (**9** and **10**) optimized to give chair conformations of the piperidine ring. An additional set of structures (**9a** and **10a**) were obtained by a 180° rotation of the piperidine ring, which is the only rotation possible that maintains the planar amide unit, and reoptimization.

The structure of the lowest energy (HF/3-21G) three-component complex of **3** with *i*-PrLi and (−)-sparteine identified in this fashion (**9a**) is depicted in Figure 2. The structures of all five pre-lithiation complexes containing piperidine in a chair conformation (**8**, **9**, **9a**, **10**, and **10a**) as well as the higher-energy

Table 3. Calculated Energies of *i*-PrLi/(−)-Sparteine/Boc-Piperidine Complexes and Transition States for Proton Transfer[a]

			H_{rel}				
complex	hydrogen transferred	S^b	(3-21G)	(6-31G*)	$G_{rel}{}^c$	$\Delta H^{\ddagger c}$	$\Delta G^{\ddagger c}$
8	*pro-S*	171.5	2.84	1.84	1.33	13.4	14.3
9	*pro-S*	169.3	0.50	0.08	0.00	13.6	14.2
9a	*pro-R*	168.1	0.00	0.00	0.14	13.3	13.9
10	*pro-S*	171.0	1.74	1.51	1.09	13.2	14.0
10a	*pro-R*	168.4	0.34	0.66	0.74	13.2	13.9
11	*pro-R*		4.0[d]				
transition state							
8-TS		166.8	2.56	1.99	1.56		
9-TS		166.3	1.04	0.41	0.08		
9a-TS		164.6	0.68	0.00	0.00		
10-TS		167.1	2.10	1.37	0.88		
10a-TS		165.2	0.00	0.63	0.51		

[a] All energies in kcal/mol. [b] Calculated entropy in cal/mol-deg. [c] B3P86/6-31+G* energies corrected for both differences in zero point energy and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 195 K, see text. [d] Relative energy without enthalpy correction.

complex having a twist-boat piperidine (**11**) are illustrated in Figure 3, sans sparteine for clarity of presentation, and their HF/3-21G energies are summarized in Table 3. It should be noted that complexes **8**, **9**, and **10**, each of which presents an equatorial *pro-S* hydrogen on the piperidine unit to the anionic methine carbon of the isopropyl group, would be expected to transfer H_S while complexes **9a**, **10a** and **11** would be expected to result in preferential removal of a *pro-R* hydrogen from **3**. In view of the high relative energy of complex **11**, it was not further studied.

Transition states for proton transfer within complexes **8**, **9**, **9a**, **10**, and **10a** were located at the HF/3-21G level using the synchronous transit-guided quasi-Newton method of Schlegel, et al.[14] More satisfactory relative energies for **8**, **9**, **9a**, **10**, and **10a** were calculated via geometry optimizations at the B3P86/6-31G* level of theory starting with the HF/3-21G structures

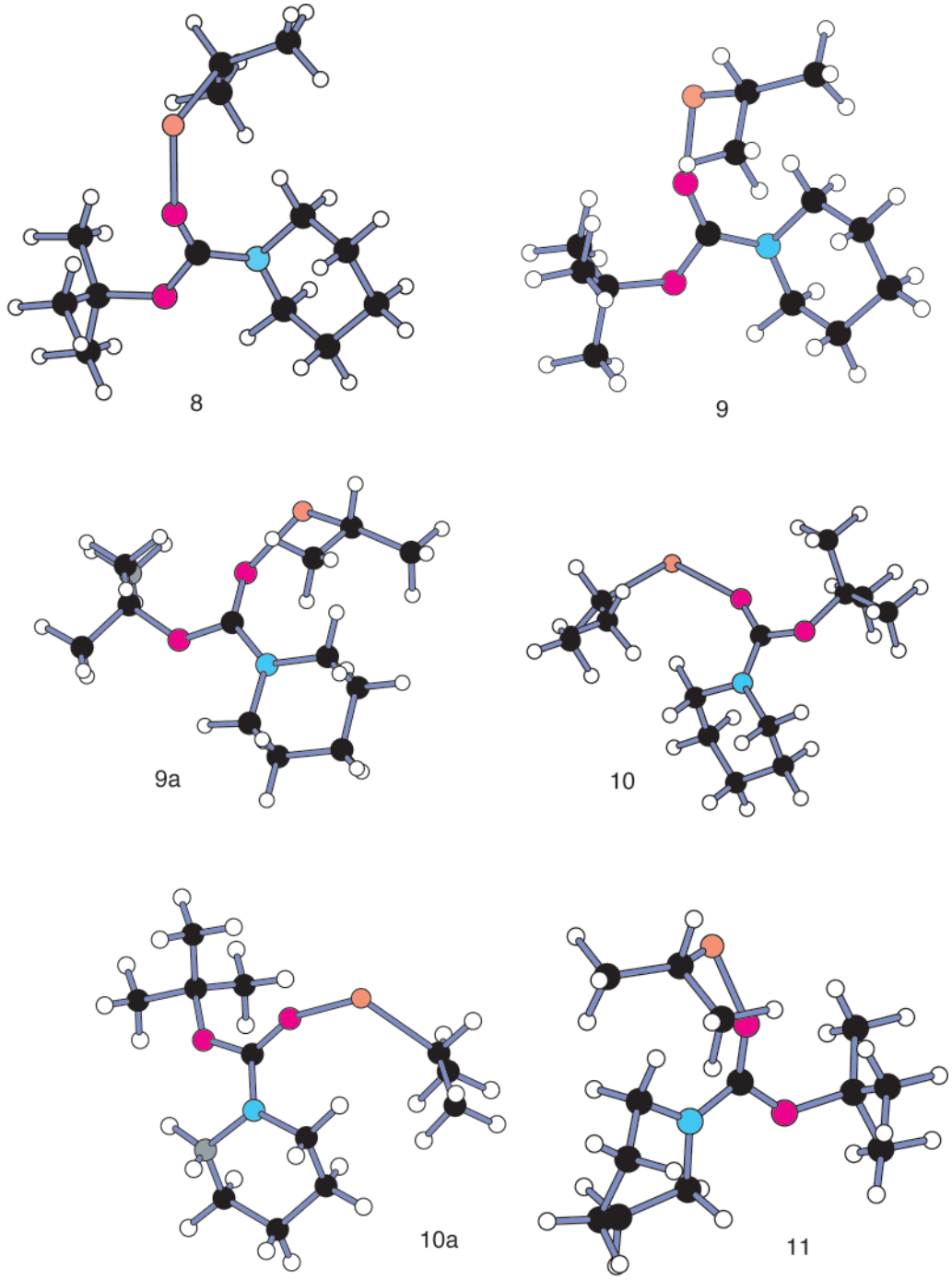

Figure 3. Structures of pre-lithiation complexes (**8**, **9**, **9a**, **10**, **10a**, and **11**). The sparteine ligand has been removed for clarity; colors as in Figure 2.

and these are also summarized in Table 3. The structures and energies of the corresponding transition states, **8-TS**, **9-TS**, **9a-TS 10-TS**, and **10a-TS**, were calculated in the same fashion using the HF/3-21G structures and vibrational frequencies in the inital step. In each case there was just one imaginary frequency corresponding to transfer of an α-hydrogen from **3** to *i*-PrLi The calculated force constants obtained at the HF/3-21G level were scaled by 0.917; zero-point energies (ZPE) and the corrections to the enthalpy (ΔH) and free energy (ΔG) on going from 0 K (corresponding to the calculations) to 195 K (−78 °C, the temperature at which deprotonations were conducted) were then derived using these frequencies. The results of these calculations for both the ground states and transition states of the six complexes are summarized in Table 3; a summary of the intermediate calculations and the corrections may be found in Table S3 of the Supporting Information.

Examination of the results of the calculations, presented in Table 3, indicates that three of the pre-lithiation complexes, **9**, **9a**, and **10a** are significantly more stable than are the other structures and the two most stable complexes, **9** and **9a**, have essentially the same energy. Indeed, whether one focuses on the relative enthalpy difference ($\Delta\Delta H = 0.08$ kcal/mol favoring **9a**) or the free energy difference ($\Delta\Delta G = 0.14$ kcal/mol favoring complex **9**), it is clear that within the limits of the calculation

(14) (a) Peng, C.; Ayale, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49. (b) Peng, C.; Schlegel, H. B. *Isr. J. Chem.* **1994**, *33*, 449.

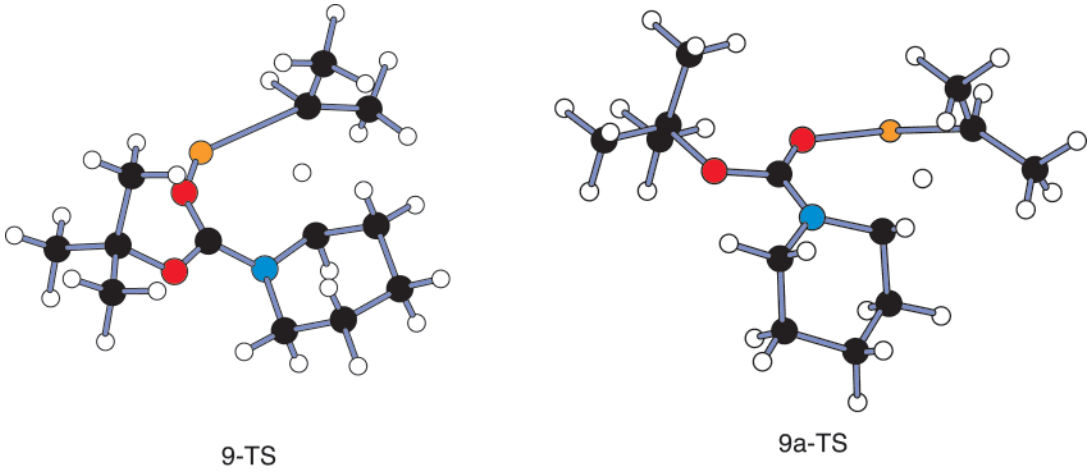

Figure 4. Structures of the two lowest-energy transition states leading to deprotonation of Boc-piperidine (**3**); **9-TS** leads to transfer of the *pro-S* hydrogen and **9a-TS** leads to transfer of the *pro-R* hydrogen. The sparteine ligand has been removed for clarity; colors as in Figure 2.

there is little to distinguish between these two low energy structures. Significantly, the energies of the transition states for proton-transfer mirror the ground-state stabilities of the pre-lithiation complexes. The structures of **9-TS** and **9a-TS** are depicted in Figure 4: the difference in transition state energies for transfer of the *pro-S* hydrogen via **9-TS** and for transfer of the *pro-R* hydrogen via **9a-TS** are quite similar ($\Delta\Delta H^{\ddagger} = 0.41$ kcal/mol and $\Delta\Delta G^{\ddagger} = 0.08$ favoring **9a-TS**). Consequently, the activation energies for proton transfer via **9-TS** and **9a-TS** are comparable in magnitude: $\Delta H^{\ddagger}$ (**9** → **9-TS**) = 13.6 kcal/mol, $\Delta H^{\ddagger}$ (**9a** → **9a-TS**) = 13.3 kcal/mol, $\Delta G^{\ddagger}$ (**9** → **9-TS**) = 14.2 kcal/mol, $\Delta G^{\ddagger}$ (**9a** → **9a-TS**) = 13.9 kcal/mol.[15] It should be noted that these activation energies are much larger than those calculated for transfer of the *pro-S* hydrogen in *N*-Boc-pyrrolidine, **1** (viz., $\Delta H^{\ddagger} = 10.9$ kcal/mol, $\Delta G^{\ddagger} = 11.5$ kcal/mol).[4] The fact that the *least* acidic α-hydrogen of **3** (viz., that corresponding to D in Figure 1) is transferred within the pre-lithiation complex almost certainly contributes in a significant way to the high activation energies calculated for the process and serves to emphasize the crucial role of complex formation in controlling the course of the deprotonation.[16]

Summary

The computational results summarized in Table 3 indicate that deprotonation of Boc-piperidine (**3**) by *i*-PrLi in the presence of an equivalent of (−)-sparteine should be a much slower process than is the analogous lithiation of Boc-pyrrolidine (**1**) due to the relatively high activation energies calculated for removal of the thermodynamically least acidic α-hydrogen of **3** within the pre-lithiation complex. This result accords well with the sluggish lithiation observed in the reaction of **3** with *sec*-BuLi−(−)-sparteine.

Experimentally, as illustrated in Schemes 1 and 2, asymmetric deprotonation of Boc-piperidines by *sec*-BuLi−(−)-sparteine involves preferential transfer of an equatorial *pro-S* hydrogen to the alkyllithium, albeit with a lower enantioselectivity (er = 87:13 and 75:25 for **3** and **7**, respectively) than the corresponding lithiation of **1** to give **2** (er = 97:3). The computational studies are consistent with the modest enantiodifferentiation that characterizes the asymmetric lithiation of Boc-piperidine (**3**) since there appears to be little energetic difference between channels leading to removal of a *pro-R* or *pro-S* proton from **3**.[17]

Experimental Section

General Procedures. All reactions were carried out under a nitrogen atmosphere in glassware which was flame dried before use. All reagents and solvents were obtained from commercial sources and used without further purification, unless otherwise noted. (−)-Sparteine and TMEDA were obtained from Aldrich and distilled under reduced pressure over CaH_2.; diethyl ether was distilled from sodium and benzophenone under a nitrogen atmosphere. *N*-Boc-piperidine (**3**)[6] and *N*-Boc-4-tosyloxypiperidine (**6**)[7] were prepared as previously described. Solutions of *sec*-BuLi in cyclohexane were titrated before use according to the method of Suffert.[18]

^{1}H and ^{13}C NMR spectra were acquired in the University of Illinois VOICE NMR Laboratory on either a Varian U400 or U500 spectrometer. Melting points (mp) were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Analytical HPLC was performed using Rainin HPX pump systems. Enantiomeric ratio analyses were carried out with both racemic and enantioenriched compounds. Analytical chiral stationary phase (CSP) HPLC was performed on Pirkle concept chiral column (Regis Chemical Co., Morton Grove, IL 60053-9975; 25 cm × 4.6 mm i.d.) using mixtures of 2-propanol and hexane.

3,5-Dimethyl-4-(4-phenylpiperidinyl)hept-3-ene (5). To a solution of 531 mg (2.26 mmol) of (−)-sparteine and 322.7 mg (1.74 mmol) of *N*-Boc-piperidine (**3**) in 5 mL of Et_2O at −78 °C was added 2.20 mL of a 1.06 M solution of *sec*-BuLi in cyclohexane (2.26 mmol). The reaction mixture was allowed to warm to ca. −40 °C and stirred for 3 h. The reaction mixture was then cooled to −78 °C for 3 h, and then 378 mg (3.48 mmol) of chlorotrimethylsilane was added. This mixture was allowed to slowly warm to room temperature over 3 h. Workup consisted of addition of 5 mL of water, extraction of the aqueous layer with 5-mL portions of Et_2O, extraction of combined ethereal extracts with two 5-mL portions of 5% aqueous H_3PO_4, drying over anhydrous

(15) As noted previously in connection with the study of the asymmetric deprotonation of *N*-Boc-pyrrolidine (**1**),[4] it was not obvious at the inception of this study that the most stable pre-lithiation complexes (**9** and **9a**) would correspond to the kinetically most favorable lithiation reaction since it was entirely conceivable a priori that ground-state destabilization might result in a lower activation energy for deprotonation via a transition state derived from a less stable pre-lithiation complex.

(16) (a) Beak, P.; Meyers, A. *Acc. Am. Res.* **1986**, *19*, 356. (b) Klumpp, G. *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(17) Although the computational results might be interpreted to imply a slight preference for removal of the *pro-R* hydrogen of **3** (Table 3), the small energy differences are well within the limits expected for calculations involving these large and complex structures.

(18) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

$MgSO_4$, filtration, and concentration under reduced pressure. The residue, 250 mg of a light yellow oil, was purified by flash chromatography on silica gel using 5% EtOAc in hexane to give the isomeric enamines **5** as a light-yellow oil (145 mg, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.8−1.1 (m, 7 H), 1.58 (s, 1.5 H, CH_3), 1.65 (s, 1.5 H, CH_3), 1.15−1.75 (m, 8 H), 1.8−2.2 (m, 4 H), 2.35 (m, 1 H), 2.72 (m, 4 H, CH_2N); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.78, 12.99, 13.02, 13.09, 17.49, 17.80, 18.97, 19.42, 24.81, 24.87, 27.06, 27.08, 27.09, 27.25, 28.10, 28.19, 37.0, 37.49, 52.30, 52.90, 131.1, 131.6, 146.8, 146.9. In this reaction, **4** (∼8%) and 3 5-dimethyl-4-heptanone (∼9%) were detected and identified by GC/MS.

(*S*)-2-(Trimethyl-silyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (4). To a solution of 4.85 g (26.2 mmol) of *N*-Boc-piperidine and 7.98 g (34.1 mmol) of (−)-sparteine in 262 mL of anhydrous Et_2O at −78 °C was added dropwise 26 mL of a 1.31 M solution of *sec*-BuLi in cyclohexane (34.1 mmol). After stirring the resulting mixture for 16 h at −78 °C, 3.70 g (34.1 mmol) of freshly distilled chlorotrimethylsilane was added. The reaction mixture was stirred for an additional 3 h at −78 °C and was then allowed to reach ambient temperature slowly. The mixture was diluted with 100 mL of ether and partitioned with a saturated, aqueous NH_4Cl solution, and the aqueous layer was extracted with three 20-mL portions of ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and then concentrated at reduced pressure. The yellow residue was purified by flash chromatography on silica gel to give 572 mg (8.5%) of the title compound, **(S)-4**, as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers δ 0.03 (s, 9 H, $(CH_3)_3Si$), 1.38 (s, 9 H, $OC(CH_3)_3$), 1.40−1.67 (m, 4 H, CH_2CH_2), 2.61 (bs, 1 H, CH_2), 2.90 (bs, 1 H, CH_2), 3.41 (bs, 1 H, NCH_2), 3.75 (bs, 1 H, NCHSi), 4.22 (bs, 1 H, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) mixture of rotamers δ −1.01, 25.5, 25.7, 25.8, 28.3, 40.3, 46.2, 78.5.

Enantiomeric Assay of (*S*)-4. To a solution of 290 mg (1.37 mmol) of **(S)-4** in 20 mL of methylene chloride at 0 °C was added 1.56 g (13.7 mmol) of trifluoroacetic acid. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. This mixture was concentrated in vacuo to give **(*S*)-2-(trimethylsiyl)piperidine** that was used for the next reaction without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.06 (s, 9 H, $(CH_3)_3Si$), 1.24−1.29 (m, 2 H, CH_2), 1.38−1.41 (m, 1 H, CH_2), 1.51−1.57 (m, 2 H, CH_2), 1.74−1.77 (m, 1 H, CH_2), 1.97−1.99 (m, 1 H, NCH_2), 2.49−2.55 (m, 1 H, NCH_2-Si), 3.02−3.05 (m, 1 H, NCH_2). The (*S*)-2-(trimethylsilyl)piperidine was dissolved in 15 mL of methylene chloride, and 554 mg (5.48 mmol) of triethylamine was added at 0 °C followed by 902 mg (4.11 mmol) of 4-bromobenzoyl chloride. The reaction mixture was stirred at room temperature for 3 h and quenched with water. The aqueous layer was extracted with three 10-mL portions of ether, the combined ethereal layers were dried over $MgSO_4$, filtered, and then concentrated at reduced pressure. The yellow residue was purified by flash chromatography on silica gel to give 241 mg (52% for two steps) of **4-bromophenyl-[2-(trimethylsilyl)piperidin-1-yl]-methanone** as a pale-yellow crystalline material: mp 92−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 9 H, $((CH_3)_3Si)$, 1.19−1.83 (m, 6 H, $CH_2CH_2CH_2$), 7.22−7.27 (m, 2 H), 7.50−7.54 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.91, 23.2, 25.7, 26.7, 44.6, 47.9, 123.1, 128.3, 131.5, 135.7, 168.6. HRMS (FAB) *m*/*z* calcd for $C_{15}H_{22}BrNOSi$ 340.0654, obsd 340.0733.

The enantiomeric ratio of **(S)-4** was determined to be 87:13 by CSP HPLC on a Pirkle concept Whelk-O column with 5%(v/v) isopropyl alcohol/hexane mobile phase and a flow rate 1.5 mL/min. The major enantiomer, which has the (2*S*) absolute configuration as determined by X-ray diffraction, had a retention time of 18.7 min, and the minor enantiomer had a retention time of 14.8 min. Crystals of (2*S*)-4-bromophenyl-[2-(trimethylsilyl)piperidin-1-yl]-methanone suitable for X-ray diffraction of the major enantiomer were grown from methylene chloride/ethyl acetate/pentanes.[19]

(2*R*,3*R*)-1-(Trimethylsilyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic Acid *tert*-Butyl Ester (7). A solution of 2.58 g (11.03 mmol) of (−)-sparteine and 1.78 g (5.01 mmol) of *N*-Boc-4-tosyloxypiperidine in 30 mL of Et_2O was stirred at −78 °C, and 8.50 mL of a 1.30 M solution of *sec*-BuLi in cyclohexane (11.03 mmol) was added dropwise. The reaction mixture was stirred for 5 h at −78 °C, and then 1.19 g (11.03 mmol) of freshly distilled, precooled chlorotrimethylsilane was added. The mixture was allowed to warm slowly to room temperature, diluted with 10 mL of ether, and washed with a saturated, aqueous NH_4Cl; the aqueous layer was extracted with three 10-mL portions of ether. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The yellow residue was purified by flash chromatography on silica gel to yield 332 mg (26%) of the previously reported[7] title compound as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 0.62−0.64 (t, 1 H, J = 5.13 Hz), 0.75 (bs, 1 H), 1.46 (s, 9H), 1.44−1.49 (m, 1 H), 1.67 (bs, 1 H), 1.90−2.08 (m, 1 H), 3.18 (bs, 1 H), 3.52−3.59 (m, 1 H).

Enantiomeric Assay of (2*R*,3*R*)-7. To a solution of 221 mg (0.87 mmol) of **(2*R*,3*R*)-7** in 20 mL of methylene chloride at 0 °C was added 991 mg (8.70 mmol) of trifluoroacetic acid. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. This mixture was concentrated in vacuo, the residue was taken up in 15 mL of methylene chloride and cooled to 0 °C, and 1.70 g (17.2 mmol) of triethylamine was added followed by 380 mg (1.73 mmol) of 4-bromobenzoyl chloride. The reaction mixture was stirred at room temperature for 3 h and quenched with water. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The yellow residue was purified by flash chromatography on silica gel to give 167 mg (57% for two steps) of **(4-bromophenyl)-[1-(trimethylsilyl)-2-azabicyclo[3.1.0]hex-2-yl]-methanone:** mp 62−63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 9 H, $((CH_3)_3Si)$, 0.77 (bs, 1 H, $CHCH_2$, *cyclopropylene*), 0.99 (bs, 1 H, $CHCH_2$, *cyclopropylene*), 1.64−1.74 (bs, 1 H, $CHCH_2CH_2$), 1.92−1.97 (m, 1 H, CH_2CHCH_2), 2.05−2.15 (m, 1 H, $CHCH_2CH_2$), 3.28 (m, 1 H, NCH_2), 3.72 (m, 1 H, NCH_2), 7.32−7.33 (m, 2 H,), 7.50−7.53(m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.55, 18.9, 22.9, 27.5, 51.8, 123.9, 128.6, 131.5, 136.3, 169.5. HRMS (FAB) *m*/*z* calcd for $C_{15}H_{20}BrNOSi$ 337.0498, obsd 338.0575.

The enantiomeric ratio of **(2*R*,3*R*)-7** was determined to be 73:27 by CSP HPLC on a Pirkle concept Whelk-O column with 5% (v/v) isopropyl alcohol/hexane mobile phase with a flow rate 1.5 mL/min. The major enantiomer, which has the (*2R*,*3R*) absolute configuration as determined by X-ray diffraction, had a retention time of 10.9 min; the minor enantiomer had a retention time of 19.7 min. Crystals of (2*R*,3*R*)-(4-bromophenyl)-[1-(trimethylsilyl)-2-azabicyclo[3.1.0]hex-2-yl]-methanone suitable for X-ray diffraction of the major enantiomer were grown from ethyl acetate/diethyl ether/pentanes.[19]

Computational Methods. Calculations were performed as previously described[4] using Gaussian 99.[20] In the case of the B3P86/6-31G* calculations, the long execution times led us to use a relaxed criterion for convergence: namely, a predicted change in energy of less than 1×10^{-5} hartrees (0.005 kcal/mol).

(19) The crystallographic data for (2*S*)-4-bromophenyl-[2-(trimethylsilyl)piperidin-1-yl]-methanone and (2*R*,3*R*)-(4-bromophenyl)-[1-(trimethylsilyl)-2-azabicyclo[3.1.0]hex-2-yl]-methanone have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 169851 and 169850, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: (+44)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

(20) 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.; Ortiz, J. V.; Baboul, A. G.; Cioslowski, J.; 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. *Gaussian 99*, Development Version (revision B.04); Gaussian, Inc.: Pittsburgh, PA, 1998.

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Supporting Information Available: Structural data and NPA charges for anions derived from *N*-(methoxycarbonyl)piperidine, a summary of the calculations, and computed atomic coordinates for complexes and transition states (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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