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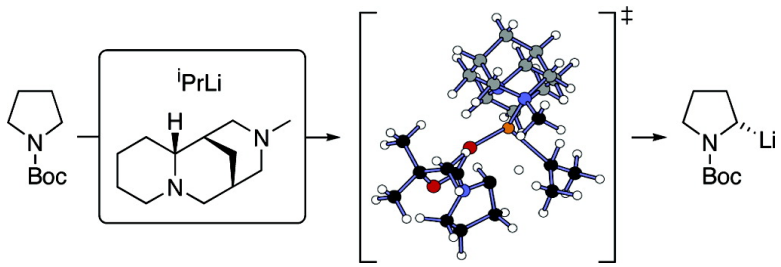

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An Experimental and Computational Study of the Enantioselective Lithiation of *N*-Boc-pyrrolidine Using Sparteine-like Chiral Diamines

Peter O'Brien,*,† Kenneth B. Wiberg,*,‡ William F. Bailey,*,§
Jean-Paul R. Hermet,† and Matthew J. McGrath†

Contribution from the Departments of Chemistry, University of York, Heslington, York YO10 5DD, U.K., Yale University, New Haven, Connecticut 06520-8107, and University of Connecticut, Storrs, Connecticut 06269-3060

Received May 28, 2004; E-mail: paob1@york.ac.uk

Abstract: The enantioselective lithiation of *N*-Boc-pyrrolidine using *sec*-butyllithium and isopropyllithium in the presence of sparteine-like diamines has been studied experimentally and computationally at various theoretical levels through to B3P86/6-31G*. Of the (−)-cytisine-derived diamines (*N*-Me, *N*-Et, *N*-^{n}Bu, *N*-$CH_2{}^{t}$-Bu, *N*-^{i}Pr) studied experimentally, the highest enantioselectivity (er 95:5) was observed with the least sterically hindered *N*-Me-substituted diamine, leading to preferential removal of the *pro-R* proton i.e., opposite enantioselectivity to (−)-sparteine. The experimental result with the *N*-Me-substituted diamine correlated well with the computational results: at the B3P86/6-31G* level, the sense of induction was correctly predicted; the lowest energy complex of isopropyllithium/diamine/*N*-Boc-pyrrolidine also had the lowest activation energy ($\Delta H^{\ddagger} = 11.1$ kcal/mol, $\Delta G^{\ddagger} = 11.5$ kcal/mol) for proton transfer. The computational results with the *N*-^{i}Pr-substituted diamine identified a transition state for proton transfer with activation energies of $\Delta H^{\ddagger} = 11.7$ kcal/mol and $\Delta G^{\ddagger} = 11.8$ kcal/mol (at the B3P86/6-31G* level). Although comparable to (−)-sparteine and the *N*-Me-substituted diamine, these $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ values are at odds with the experimental observation that use of the *N*-^{i}Pr-substituted diamine gave no product. It is suggested that steric crowding inhibits formation of the prelithiation complex rather than increasing the activation enthalpy for proton transfer in the transition state. Three other ligands (*N*-H and *O*-substituted as well as a five-membered ring analogue) were studied solely using computational methods, and the results predict that the observed enantioselectivity would be modest at best.

Introduction

The use of a 1:1 complex of *sec*-butyllithium and (−)-sparteine for the asymmetric deprotonation of a prochiral carbon to give a configurationally stable, nonracemic organolithium is a powerful methodology in asymmetric synthesis.[1,2] Some of the best substrates for such asymmetric lithiations are *O*-alkyl carbamates, as identified by Hoppe et al.,[3,4] and *N*-(*tert*-butoxycarbonyl)pyrrolidine (*N*-Boc-pyrrolidine **1**), as developed by Beak et al.[5] For example, lithiation of *N*-Boc-pyrrolidine **1** using *sec*-butyllithium and (−)-sparteine in diethyl ether at −78 °C and subsequent electrophilic trapping generates substitution products with an enantiomer ratio (er) ≥ 95:5 via preferential removal of the *pro-S* proton. From a mechanistic perspective, kinetic results reported by Beak and Gallagher are consistent with initial formation of a thermodynamically preferred three-component alkyllithium/(−)-sparteine/*N*-Boc-pyrrolidine **1** complex followed by rate-limiting lithiation.[6]

Our interest in the enantioselective lithiation of *N*-Boc-pyrrolidine **1** is two-fold. First, we are interested in evaluating the effect of the diamine structure on the sense and degree of the *N*-Boc-pyrrolidine deprotonation, and we recently described the first example of a chiral diamine that delivers a comparable

† University of York.
‡ Yale University.
§ University of Connecticut.

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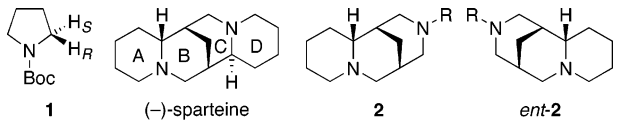
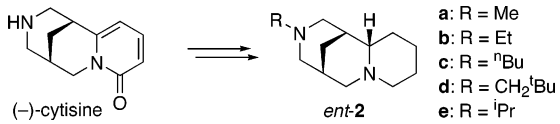


level and opposite sense of enantioselectivity to (−)-sparteine.[7,8] Thus, use of (+)-sparteine-like diamine *ent*-**2a** to lithiate *N*-Boc-pyrrolidine **1** produced a substitution product with er = 95:5 and the opposite sense of asymmetric induction compared to that obtained with (−)-sparteine.[7,9] Second, we are applying ab initio molecular orbital theory to a range of enantioselective lithiation processes, and our computational results on the lithiation of *N*-Boc-pyrrolidine **1** using isopropyllithium and (−)-sparteine were recently reported.[10] The experimental results were accurately reproduced by ab initio calculations at the B3P86/6-31G* level,[11] and the interactions that lead to the enantioselectivity were shown to be mainly steric in origin by application of the ONIUM model of Morokuma et al.[12] in which the *N*-Boc-pyrrolidine **1** and isopropyllithium were treated quantum mechanically and the (−)-sparteine ligand and its interaction with the rest of the complex were treated by molecular mechanics. As well as information from ligand variation and computational studies, reports on solution[13,14] and solid-state[15] structures of alkyllithium/(−)-sparteine complexes also provide useful insight into reactivity.

Despite all of the previous efforts, there remains the intriguing question of exactly what portion of (−)-sparteine's structure is responsible for the observed high enantioselectivity in the lithiation of *N*-Boc-pyrrolidine **1**. Why does (−)-sparteine occupy such a privileged position in terms of asymmetric induction in this reaction? In an attempt to address this issue, we have compared the experimental results for the lithiation of *N*-Boc-pyrrolidine **1** using diamines *ent*-**2a**−**e** (with substituents R of different steric demands) with the results generated from a computational study using diamines **2a**, **2b**, and **2e**. In addition, three modified diamines have been investigated solely from a theoretical perspective. Ligand variation in combined experimental/computational studies using alkyllithium/(−)-sparteine systems has been somewhat limited in previous reports (presumably due to size of the complexes involved in the calculations): *O*-alkyl carbamates [(*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)-cyclohexane only],[4] *N*-Boc-pyrrolidine **1** [(−)-sparteine and (*R*,*R*)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane][10] and *N*-Boc-piperidine [(−)-sparteine only].[16] This is the first detailed study of *ligand variation* using a combined experimental and computational approach in an alkyllithium/(−)-sparteine-mediated process.

Results and Discussion

Enantioselective Lithiation of *N*-Boc-pyrrolidine Using Sparteine-like Diamines. A range of diamines *ent*-**2a**−**e** with *N*-alkyl groups of different steric sizes was prepared from (−)-cytisine extracted from *Laburnum anagyroides* seeds.[17] The preparation of diamines *ent*-**2a**−**d** using a simple three-step route (*N*-acylation, pyridone hydrogenation, and lithium aluminum hydride reduction) has been described previously.[7,18] Diamine *ent*-**2e** was prepared by modifications of this approach (as noted by Kann et al.[19]): (i) reductive alkylation of (−)-cytisine (to give the *N*-^{i}Pr derivative); (ii) pyridone hydrogenation under acidic conditions, and (iii) lithium aluminum hydride reduction.



Diamines *ent*-**2a**−**e** and (−)-sparteine were evaluated in the lithiation−substitution of *N*-Boc-pyrrolidine **1** (Table 1). The typical procedure, analogous to that described by Beak et al.,[5] involved lithiation of *N*-Boc-pyrrolidine **1** using 1.3 equiv of *sec*-butyllithium and diamine in diethyl ether at −78 °C for 5 h followed by trapping with Me_3SiCl. The trimethylsilyl adduct **3** and any recovered starting material were then isolated by chromatography. For direct comparison of the experimental results with those obtained from the computational study (vide infra), we also carried out some reactions using isopropyllithium.

The yield and er of adduct (*S*)-**3** obtained using (−)-sparteine (entries 1 and 2) are comparable to those reported previously

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(8) The most detailed study of ligand variation in the asymmetric lithiation−substitution of *N*-Boc-pyrrolidine **1** has been carried out by Beak et al., but none of the ligands could match the efficacy of (−)-sparteine (no substitution products were obtained with >75% ee and most were <40% ee). Similarly, Kozlowski et al. had limited success (26% ee substitution product) using 1,5-diaza-*cis*-decalins. See: (a) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148. (b) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875. (c) Xu, Z.; Kozlowski, M. C. *J. Org. Chem.* **2002**, *67*, 3072.

(9) The result we obtained using diamine *ent*-**2a** for the lithiation−substitution of *N*-Boc-pyrrolidine **1** has also been verified using diamine **2a** (prepared by a different synthetic approach). See: Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron Lett.* **2002**, *43*, 7155.

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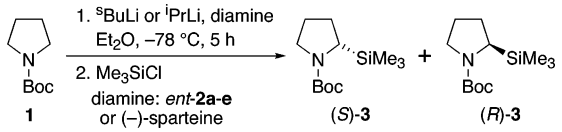
Table 1. Evaluation of Diamines **2a**−**e** in the Lithiation−Substitution of *N*-Boc-pyrrolidine **1**



entry	alkyllithium	diamine[a]	R in *ent*-**2**	major product	proton removed[b]	yield (%)[c]	er[d]	SM (%)[e]
1	sBuLi	(−)-sparteine	−	(*S*)-**3**	*pro-S*	87	95:5	−
2	iPrLi	(−)-sparteine	−	(*S*)-**3**	*pro-S*	78	99:1	−
3	sBuLi	*ent*-**2a**	Me	(*R*)-**3**	*pro-R*	84	5:95	−
4	iPrLi	*ent*-**2a**	Me	(*R*)-**3**	*pro-R*	66	6:94	−
5	sBuLi	*ent*-**2b**	Et	(*R*)-**3**	*pro-R*	73	10:90	−
6	sBuLi	*ent*-**2c**	nBu	(*R*)-**3**	*pro-R*	27	11:89	20
7	sBuLi	*ent*-**2d**	^{t}BuCH$_2$	−	−	35	51:49	36
8	sBuLi	*ent*-**2e**	iPr	−	−	0	−	58

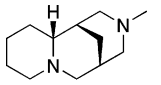
[a] Reaction conditions: (i) 1.3 equiv sBuLi or *i*PrLi, 1.3 equiv diamine, Et_2O, −78 °C, 5 h; (ii) Me_3SiCl; each entry is a specific set of experimental data that has been reproduced with essentially identical results on more than one occasion. [b] Preferential proton removed. [c] Isolated yield (*S*)- or (*R*)-**3** after purification by column chromatography. [d] Enantiomer ratio determined by chiral GC (Chiraldex G-PN: γ-cyclodextrin, propionyl dervative in the 3-position). [e] Isolated yield of recovered *N*-Boc-pyrrolidine **1** after purification by column chromatography.

by Beak et al.,[5] although, in our hands, better enantioselectivity (er 99:1, entry 2) was obtained using isopropyllithium compared to *sec*-butyllithium (er 95:5, entry 1). The (+)-sparteine-like *N*-Me diamine *ent*-**2a** afforded opposite enantioselectivity and isopropyllithium and *sec*-butyllithium behaved in essentially the same way (entries 3 and 4).

When the *N*-alkyl substituent in diamines **2** was changed, some interesting trends were noted. *N*-Et diamine *ent*-**2b** (entry 5) and the *N*-nBu diamine *ent*-**2c** (entry 6) produced slightly lower enantioselectivity (er ∼ 90:10). In contrast, *N*-$CH_2{}^t$Bu diamine *ent*-**2d** generated *racemic* adduct **3** in 35% yield (entry 7). Furthermore, increasing the steric size of the *N*-alkyl substituent in diamines **2** leads to a reduction in the yield of adduct **3** together with recovery of significant amounts of *N*-Boc-pyrrolidine **1** (up to 58%, entries 6−8). The most sterically hindered *N*-iPr-substituted diamine *ent*-**2e** did not generate any isolable adduct **3** under comparable reaction conditions. This is reminiscent of the relatively unsuccessful lithiation of *N*-Boc-pyrrolidine **1** using (−)-isosparteine (∼10% lithiation by GC after Me_3SiCl quench).[8a] When alkyllithium−diamine complexes slowly lithiate *N*-Boc cyclic amine substrates, alkyllithium addition to the carbamate group can become competitive.[16] This could account for the remainder of the mass balance in the reactions that give low conversions to adduct **3**. It is tempting to conclude that more sterically hindered diamine ligands lead to a reduced rate of lithiation in the alkyllithium/diamine/*N*-Boc-pyrrolidine **1** complex, but the results of the computational study with the *N*-iPr-substituted diamine **2e** are not in line with this explanation (vide infra). Instead, formation of the prelithiation complex of alkyllithium/diamine/*N*-Boc-pyrrolidine **1** may be thermodynamically disfavored with the more sterically hindered diamine ligands.

To summarize, the results presented in Table 1 demonstrate the scope and limitations of using (+)-sparteine-like diamines **2** in the lithiation−substitution of *N*-Boc-pyrrolidine **1**. Indeed, use of the *N*-Me diamine *ent*-**2a** and the *N*-Et diamine *ent*-**2b** is recommended for high yield and high enantioselectivity (in the opposite sense to (−)-sparteine) in such reactions (entries 3 and 5).

Table 2. Calculated B3P86/6-31G* Relative Energies of Isopropyllithium/*N*-Me Diamine **2a**/*N*-Boc-pyrrolidine **1** Complexes and Transition States for Proton Transfer[a,b]



2a

complex	ground state H_{rel}	ground state G_{rel}	transition state H_{rel}	transition state G_{rel}	activation energy $\Delta H^{\ddagger}$	activation energy $\Delta G^{\ddagger}$	proton removed[c]
4-Me	2.8	2.3	3.5	2.8	11.8	11.9	*pro-R*
5-Me	0.0	0.0	0.0	0.0	11.1	11.5	*pro-S*
6-Me	3.0	2.4	3.8	3.1	11.9	12.2	*pro-R*
7-Me	3.3	2.9	4.1	4.1	11.9	12.8	*pro-S*

[a] All energies in kcal/mol. [b] B3P86/31-G* energies in kcal/mol corrected for both differences in zero-point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K (corresponding to the lithiation temperature of −78 °C used in the experiments). [c] Preferential proton removed.

Computational Results: Comparison with Experimental Results. For ease of comparison with (−)-sparteine, the calculations described in this section were carried out using the theoretical diamines **2a**, **2b**, and **2e**, corresponding to the same enantiomeric series as (−)-sparteine (i.e. the ABC rings of (−)-sparteine as depicted in this paper). The first set of calculations used the four lowest energy, three-component complexes of isopropyllithium, (−)-sparteine, and *N*-Boc-pyrrolidine **1** that we had previously examined.[10d] The D-ring of (−)-sparteine was deleted from each of these structures to give the truncated *N*-Me sparteine-like diamine **2a**. Geometry optimizations were initially carried out at the HF/3-21G level of theory and vibrational frequencies were calculated for the four optimized structures (**4-Me**, **5-Me**, **6-Me**, and **7-Me**). The calculated frequencies obtained at the HF/3-21G level were scaled by a factor of 0.917, giving an estimate of the zero-point energy (ZPE), and the enthalpy and free energy changes on going from 0 K (corresponding to the computations) to 195 K (−78 °C, the lithiation temperature) were then obtained using these scaled frequencies. The corresponding transition states (**4-Me-TS**, **5-Me-TS**, **6-Me-TS** and **7-Me-TS**) for proton transfer within these complexes were located at the HF/3-21G level using the synchronous transit-guided quasi-Newton method of Schlegel et al.[20] Subsequently, the HF/3-21G-optimized structures for both ground and transition states were reoptimized using B3P86/6-31G*. The results of these calculations are summarized in Table 2 and the structures of the complexes and their corresponding transition states are shown in Figures 1 and 2. Full details of the calculations, including absolute energies, ZPEs, and atomic coordinates for all species are available in the Supporting Information.

Examination of the data in Table 2 reveals that complex **5-Me** has the lowest energy and lowest activation energy ($\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$) for proton transfer from *N*-Boc-pyrrolidine **1** to the complexed isopropyllithium. Moreover, complex **5-Me** leads, via transition state **5-Me-TS**, to removal of the *pro-S* proton of *N*-Boc-pyrrolidine **1**. This result is in agreement with the

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

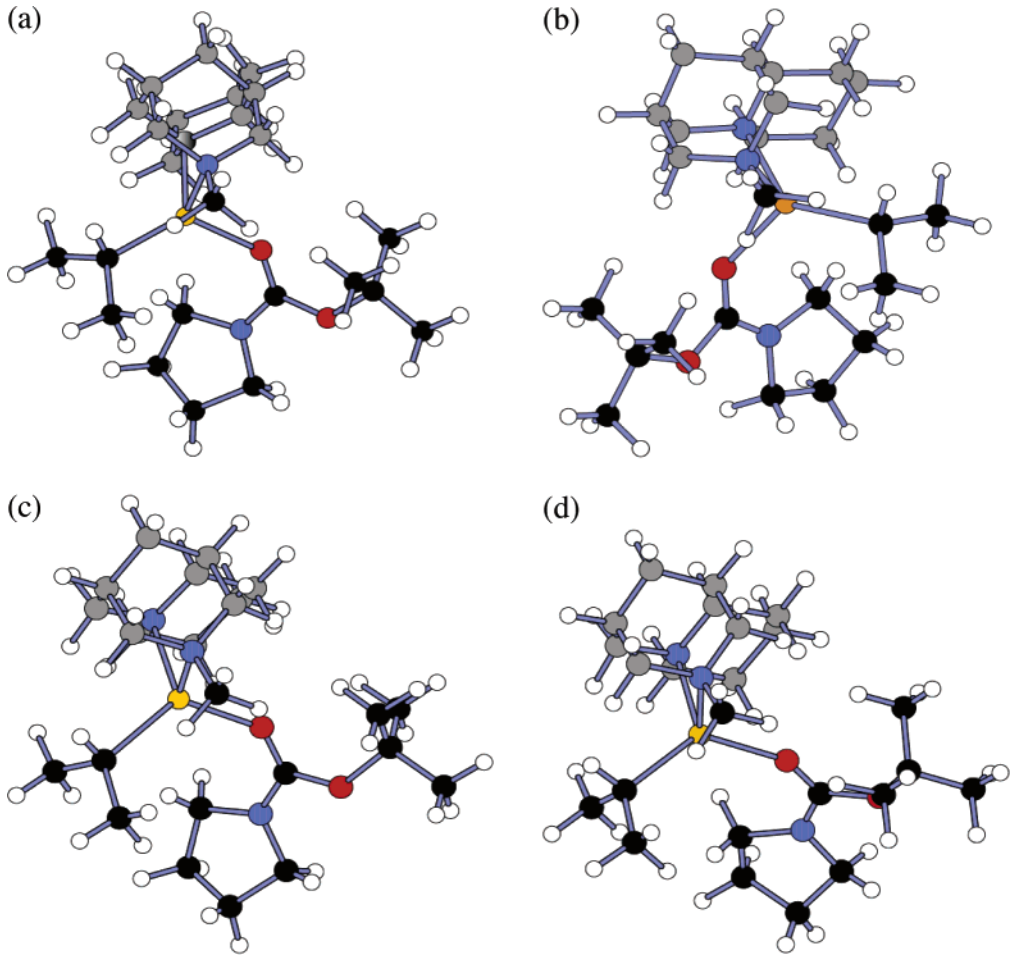


Figure 1. Structures of the isopropyllithium/diamine **2a** (*N*-Me)/*N*-Boc-pyrrolidine **1** intermediate complexes: (a) **4-Me**, (b) **5-Me**, (c) **6-Me**, (d) **7-Me**. The nitrogen atoms are blue, the lithium is orange, the oxygen atoms are red, the core carbons of diamine **2a** are gray, and the *N*-Me carbon of diamine **2a** together with the carbons of *N*-Boc-pyrrolidine **1** and isopropyllithium are black.

experimental observations with the *N*-Me-substituted diamine *ent*-**2a**, which shows a preference for removal of the *pro-R* proton (Table 1, entry 4). Indeed, the calculated activation energies for *pro-S* proton removal of *N*-Boc-pyrrolidine **1** within the isopropyllithium/diamine **2a** complex ($\Delta H^{\ddagger} = 11.1$ kcal/mol, $\Delta G^{\ddagger} = 11.5$ kcal/mol) are reasonable for a reaction that occurs readily at −78 °C and are virtually identical to the activation energies calculated with (−)-sparteine (viz. $\Delta H^{\ddagger} = 10.9$ kcal/mol, $\Delta G^{\ddagger} = 11.5$ kcal/mol).[10d] The lowest energy complex leading to *pro-R* proton removal, complex **4-Me** (Figure 1a), is calculated to be less stable than complex **5-Me** (Figure 1b) ($H_{rel} = 2.8$ kcal/mol, $G_{rel} = 2.3$ kcal/mol), and its transition state (**4-Me-TS**, Figure 2a) has a free energy that is some 3.2 kcal/mol higher (i.e. 0.4 + 2.8 kcal/mol) than the transition state from complex **5-Me**. In addition, the transition state for *pro*-R proton removal (**4-Me-TS**) has an enthalpy that is 4.2 kcal/mol (i.e. 0.7 + 3.5 kcal/mol) higher than the transition state from complex **5-Me**. This is virtually the same result obtained with (−)-sparteine ($\Delta\Delta H^{\ddagger} = 4.5$ kcal/mol, $\Delta\Delta G^{\ddagger} = 3.2$ kcal/mol) and confirms the experimental result that the truncated *N*-Me sparteine ligand **2a** behaves in essentially the same fashion as does (−)-sparteine in this chemistry.

Next, calculations using the more sterically hindered diamines **2b** (*N*-Et) and **2e** (*N*-^{i}Pr) were carried out. Complexes between isopropyllithium, *N*-Boc-pyrrolidine **1**, and diamine **2b** (**4-Et**, **5-Et**, **6-Et**, and **7-Et**) or diamine **2e** (**4-^{i}Pr**, **5-^{i}Pr**, **6-^{i}Pr**, and **7-^{i}Pr**) were initially optimized at the HF/3-21G level. Calculations involving diamines **2b** and **2e** pose additional difficulties, since it is necessary to consider the effect of conformational isomerism arising from rotation about the N−C bond. In the event, as expected, there are three conformational minima for each complex, arbitrarily termed **a**, **b**, and **c**, leading to a total of 12 distinct structural isomers that must be evaluated for each of the *N*-Et (**2b**) and the *N*-^{i}Pr (**2e**) complexes. Geometry optimization of each of the 12 complexes at the HF/3-21G level gave minimum energy structures. In each case, the lowest energy arrangement of the *N*-alkyl group is the one that minimizes the steric interaction between the terminal atoms of the alkyl group and the *tert*-butoxy group of the complexed *N*-Boc-pyrrolidine **1**. Due to the size of these complexes, it was not practical to obtain B3P86/6-31G* energies for all 24 complexes, but a few low-energy complexes were examined at this level, and the results of these calculations are summarized in Tables 3 and 4.

The results for the complexes of the *N*-Et diamine **2b** are shown in Table 3. Vibrational frequencies were calculated at the HF/3-21G level and were scaled by 0.917 to give estimates of the zero-point energies. Complex **5c-Et** is the only low-energy structure at the HF/3-21G level. Nonetheless, B3P86/6-31G* geometry optimizations were carried out for all complexes having relative energies less than 4 kcal/mol, and this exercise

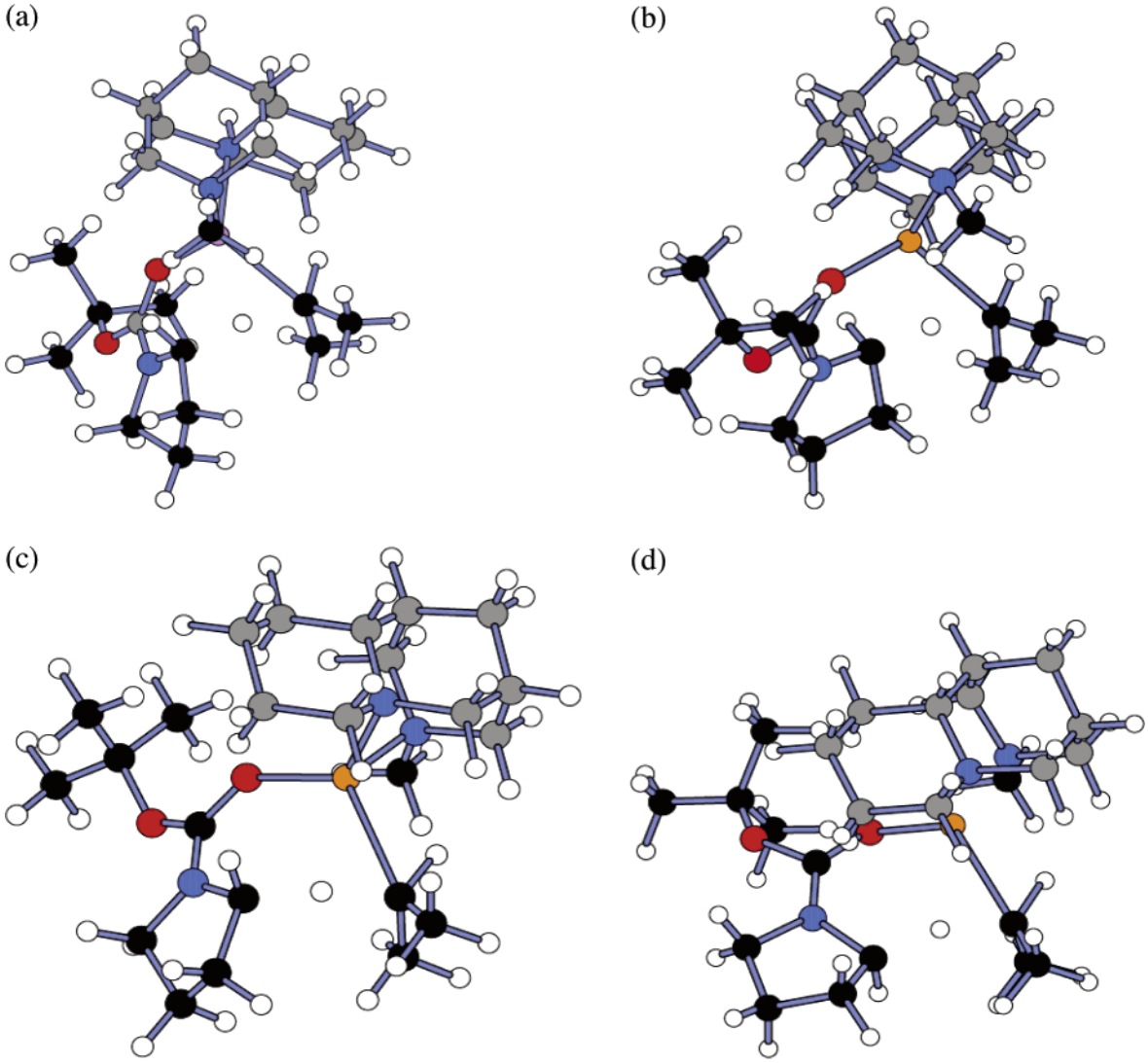


Figure 2. Structures of the transition states leading to deprotonation of *N*-Boc-pyrrolidine **1** using isopropyllithium/diamine **2a** (*N*-Me): (a) **4-Me-TS**, (b) **5-Me-TS**, (c) **6-Me-TS**, (d) **7-Me-TS**. Note that **4-Me-TS** and **6-Me-TS** lead to removal of the *pro-R* proton, whereas **5-Me-TS** and **7-Me-TS** lead to removal of the *pro-S* proton. Colors as in Figure 1.

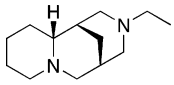
confirmed that complex **5c-Et**, leading to transfer of the *pro-S* proton of *N*-Boc-pyrrolidine **1**, had the lowest energy. Structures of the lowest energy complexes **4c-Et**, **5c-Et**, **6c-Et**, and **7c-Et** are shown in Figure 3; complexes **4c-Et** and **6c-Et** lead to preferential removal of the *pro-R* proton, and complexes **5c-Et** and **7c-Et** lead to preferential removal of the *pro-S* proton.

In each group of complexes (**a**−**c**) there was one (**c**) that was more stable than the other two (Table 3); complexes **5a-Et**, **5b-Et**, and **5c-Et** (Figure 4) are representative. In each case, the lowest energy structure was that in which the terminal methyl of the *N*-Et group is positioned relatively distant from both the *tert*-butoxy group of the complexed *N*-Boc-pyrrolidine **1** and the associated isopropyllithium (Figure 4, complex **5c-Et**). Such an arrangement apparently minimizes nonbonded steric interactions within the complex. Consequently, there is little difference within the prelithiation complex between the interactions of an *N*-Me or an *N*-Et group in the most stable complexes of each diamine ligand (compare complex **4-Me** in Figure 1 with complex **5c-Et** in Figure 3). The lowest energy (H_{rel} and G_{rel}) complex for transfer of the *pro-R* proton of *N*-Boc-pyrrolidine **1** to isopropyllithium using diamine **2b** is complex **6c-Et**, and the next lowest is complex **4c-Et** (Table 3).

It was not practical to locate the transition states for this large number of complexes, but, as we have noted previously, there is generally a good correlation between ground-state energy differences of the complexes and the corresponding transition state energies for the lithiation of *N*-Boc-pyrrolidine **1**.[10d] On the assumption that ground-state energy differences mirror transition state energy differences, complex **5c-Et** should have the lowest transition state energy and the *pro-S* hydrogen of the *N*-Boc-pyrrolidine **1** should preferentially be removed using diamine **2b**, with similar enantioselectivity as the *N*-Me-substituted diamine **2a**. This result is in agreement with the experimental observations (Table 1, entry 5).

The complexes between isopropyllithium, *N*-Boc-pyrrolidine **1**, and the *N*-^{i}Pr diamine **2e** (**4-^{i}Pr**, **5-^{i}Pr**, **6-^{i}Pr**, and **7-^{i}Pr**) were examined in the same fashion as the *N*-Et complexes (Table 4). There are three *N*-^{i}Pr group rotamers to consider for each complex, and the lowest energy structure is the one that has the smallest steric interaction between the *N*-^{i}Pr group and the

Table 3. Calculated Relative Energies of Isopropyllithium/*N*-Et Diamine **2b**/*N*-Boc-pyrrolidine **1** Complexes[a,b]



2b

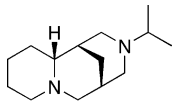
		HF/3-21G			B3P86/6-31G*		proton
complex	τ[c]	H_{rel}	ZPE	G_{rel}	H_{rel}	G_{rel}	removed[d]
4a-Et	64.0	3.0	441.9	2.7	4.0	3.6	*pro-R*
4b-Et	−65.2	4.0	441.9	3.6	–	–	*pro-R*
4c-Et	179.1	2.1	441.6	1.3	3.5	2.7	*pro-R*
5a-Et	73.7	2.9	442.1	3.1	1.4	1.6	*pro-S*
5b-Et	−71.3	1.6	442.3	2.0	0.4	0.8	*pro-S*
5c-Et	178.0	0.0	441.9	0.0	0.0	0.0	*pro-S*
6a-Et	62.4	5.1	442.0	4.7	–	–	*pro-R*
6b-Et	−58.7	5.3	442.1	4.7	–	–	*pro-R*
6c-Et	172.7	2.9	441.9	2.4	2.7	2.2	*pro-R*
7a-Et	62.2	4.6	442.0	4.6	–	–	*pro-S*
7b-Et	−71.8	4.5	442.0	4.2	–	–	*pro-S*
7c-Et	176.0	2.7	441.8	2.3	3.2	2.8	*pro-S*

[a] All energies in kcal/mol. [b] B3P86/31-G* energies in kcal/mol corrected for both differences in zero-point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K (corresponding to the lithiation temperature of −78 °C used in the experiments). [c] Torsional angle (τ) defined by N···N−CH_2−CH_3, where N···N is the line connecting the nonbonded nitrogen atoms of the diamine. [d] Preferential proton removed.

tert-butoxy group of the associated *N*-Boc-pyrrolidine **1**. Due to the long execution times needed for the evaluation of these complexes, only representative zero-point energies were calculated using the HF/3-21G-optimized structures, but the zero-point energies that were computed (Table 4) are quite similar. B3P86/6-31G* geometry optimizations were carried out for the lowest energy complexes (Table 4). Structures of the lowest energy complexes **4a-^{i}Pr**, **5b-^{i}Pr**, and **7b-^{i}Pr** are shown in Figure 5; complex **4a-^{i}Pr** leads to preferential removal of the *pro-R* proton and complexes **5b-^{i}Pr** and **7b-^{i}Pr** lead to preferential removal of the *pro-S* proton.

The transition state for proton transfer within the lowest energy *N*-^{i}Pr complex (**5b-^{i}Pr**), **5b-^{i}Pr-TS**, was located using the synchronous transit-guided quasi-Newton method, and the vibrational frequencies as well as the B3P86/6-31G* geometry (Figure 6) and energy were obtained (HF/3-21G, $\Delta H^{\ddagger} = 18.8$ kcal/mol, $\Delta G^{\ddagger} = 18.9$ kcal/mol; B3P86/6-31G*, $\Delta H^{\ddagger} = 11.7$ kcal/mol, $\Delta G^{\ddagger} = 11.8$ kcal/mol). This indicates that there should be a significant preference for transfer of the *pro-S* proton of the associated *N*-Boc-pyrrolidine **1** with an activation enthalpy of approximately 11.7 kcal/mol. Thus, the *N*-^{i}Pr-substituted diamine **2e** would be expected to behave like the *N*-Me- and *N*-Et-substituted diamines (**2a** and **2e**). This result is perhaps not surprising in the light of the structure of the lowest energy *N*-^{i}Pr complex (Figure 5, complex **4b-^{i}Pr**) which serves to minimize the steric interaction between the methyl groups of the *N*-^{i}Pr group and the *tert*-butoxy group of the complexed *N*-Boc-pyrrolidine **1**. This computational result appears to be at odds with the experimental observation, since no product was isolated upon treatment of *N*-Boc-pyrrolidine **1** with *sec*-butyllithium in the presence of *N*-^{i}Pr-substituted diamine **2e** (Table 1, entry 8). The experimental observation cannot be rationalized by recourse to arguments attributing lack of reaction to a high activation enthalpy for the proton transfer, since the computed activation enthalpy for the *N*-^{i}Pr-diamine **2e** ($\Delta H^{\ddagger} =$ 11.7 kcal/mol) is comparable in magnitude to that for proton transfer within the *N*-Me prelithiation complex ($\Delta H^{\ddagger} = 11.1$ kcal/mol) and within the (−)-sparteine complex ($\Delta H^{\ddagger} = 10.9$ kcal/mol). It is conceivable that low (<10%) yields in alkyllithium/diamine-mediated *N*-Bocpyrrolidine lithiations (e.g. using *N*-^{i}Pr-substituted diamine **2e** or (−)-isosparteine) are due to steric crowding that inhibits formation of the prelithiation complex rather than due to steric crowding increasing the activation enthalpy for proton transfer in the transition state.

Table 4. Calculated Relative Energies of Isopropyllithium/*N*-^{i}Pr Diamine **2e**/*N*-Boc-pyrrolidine **1** Complexes[a,b]

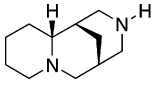


2e

		HF/3-21G				B3P86/6-31G*		proton
complex	τ[c]	E_{rel}	ZPE	H_{rel}	G_{rel}	H_{rel}	G_{rel}	removed[d]
4a-^{i}Pr	59.8, −175.0	1.3	459.2	1.0	−0.1	3.1	1.9	*pro-R*
4b-^{i}Pr	−60.0, 174.8	3.3	459.3	3.2	1.7	3.8	2.3	*pro-R*
4c-^{i}Pr	50.2, −72.0	4.4	–	–	–	–	–	–
5a-^{i}Pr	72.0, −163.8	2.3	459.6	2.3	1.7	1.9	1.3	*pro-S*
5b-^{i}Pr	−66.5, 169.2	0.0	459.6	0.0	0.0	0.0	0.0	*pro-S*
5c-^{i}Pr	−57.3, 65.3	3.6	459.5	3.5	2.8	–	–	–
6a-^{i}Pr	44.0, 168.8	3.7	459.3	3.6	2.4	–	–	–
6b-^{i}Pr	−49.3, −175.2	3.6	459.5	3.6	2.7	–	–	–
6c-^{i}Pr	51.9, −70.1	5.9	–	–	–	–	–	–
7a-^{i}Pr	59.3, −175.8	3.3	459.3	3.2	2.3	3.7	2.8	*pro-S*
7b-^{i}Pr	−54.7, 179.8	3.1	459.3	2.9	2.2	3.1	2.3	*pro-S*
7c-^{i}Pr	52.9, −68.9	4.9	–	–	–	–	–	–

[a] All energies in kcal/mol. [b] B3P86/31-G* energies in kcal/mol corrected for both differences in zero-point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K (corresponding to the lithiation temperature of −78 °C used in the experiments). [c] Torsional angle (τ) defined by N···N−CH(CH_3)−CH_3, where N···N is the line connecting the nonbonded nitrogen atoms of the diamine (the two torsional angles are to each of the methyl groups of the ^{i}Pr goup). [d] Preferential proton removed.

Computational Results: Predictions with Other Sparteine-like Diamines. The computational results for diamines **2a** (*N*-Me), **2b** (*N*-Et), and **2e** (*N*-^{i}Pr) indicate that increasing the size of the *N*-alkyl group in sparteine-like diamines **2** should not adversely affect the enantioselectivity of the lithiation of *N*-Boc-pyrrolidine **1**. However, at the computational level, we were also interested in evaluating the effect of decreasing the steric demands of the *N*-alkyl substituent and of modifying the conformational constraints of the tricyclic fused structure. Hence, complexes derived from diamine **8** (*N*-H substituted), amino



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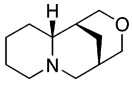

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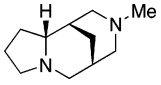


10

ether **9** (*O*-substituted), and diamine **10** (C_5-substituted, with a much more conformationally flexible five-membered ring)[21] were investigated.

In an analogous fashion to the calculations described previously, four complexes of isopropyllithium, *N*-Boc-pyrrolidine **1**, and the *N*-H-substituted diamine **8** (**4-NH**, **5-NH**, **6-NH**, and **7-NH**) as well as the *O*-substituted ligand **9** (**4-O**, **5-O**, **6-O**,

(21) From an experimental point of view, the *N*-H diamine **8** is a "theoretical ligand", as the NH would itself be deprotonated by the alkyllithium base (and presumably diamine **8** would be used in conjunction with 2 equiv of alkyllithium, representing a significant departure from the usual experimental conditions). Amino ether **9** is, to the best of our knowledge, an unknown compound, and we have been unable to prepare diamine **10** in enantioenriched form (ref 7b). See also: Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3623.

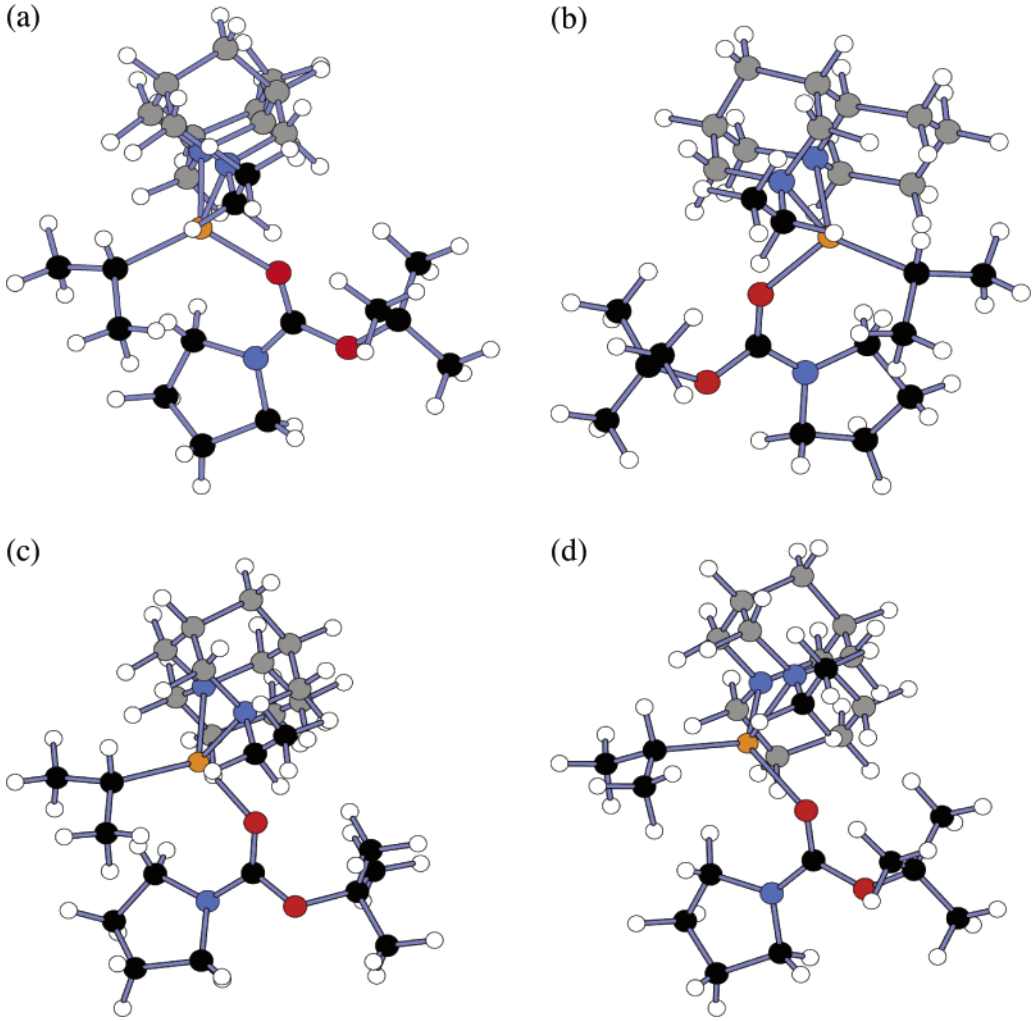


Figure 3. Structures of the lowest energy isopropyllithium/diamine **2b** (*N*-Et)/*N*-Boc-pyrrolidine **1** intermediate complexes: (a) **4c-Et**, (b) **5c-Et**, (c) **6c-Et**, (d) **7c-Et**. Note that complexes **4c-Et** and **6c-Et** lead to removal of the *pro-R* proton, whereas complexes **5c-Et** and **7c-Et** lead to removal of the *pro-S* proton. Colors as in Figure 1; the *N*-Et carbons of diamine **2b** are black.

and **7-O**) were evaluated at the HF/3-21G and B3P86/6-31G* levels (Table 5).

Complex **7-NH**, on geometry optimization, was slowly converted into complex **6-NH**, giving a total of only three low-energy complexes. Of the two lowest energy complexes identified (**4-NH** and **5-NH**), complex **5-NH**, leading to removal of the *pro-S* proton from *N*-Boc-pyrrolidine **1**, was found to be slightly more stable (H_{rel} = 0.9 kcal/mol; G_{rel} = 0.6 kcal/mol at the B3P86/6-31G* level) than complex **4-NH**, leading to removal of the *pro-R* proton. In light of the observation that the difference in ground-state energies of the prelithiation complexes mirrors the difference in transition state energies for proton transfer,[10d] it seems reasonable to suggest that any enantioselectivity engendered by this theoretical ligand would be poor at best. In a similar way, complex **7-O** was slowly converted into complex **6-O** on geometry optimization. The difference in energy (H_{rel} and G_{rel} at the B3P86/6-31G* level) between all three complexes with the *O*-substituted ligand **9** (**4-O**, **5-O** and **6-O**) was quite small, and the results suggest that any enantioselectivity generated using this ligand would be small and in the opposite sense to that obtained with the other sparteine-like diamines **2**. In view of the small energy differences, complexes of the *N*-H substituted diamine **8** and the *O*-substituted amino ether **9** were not examined further. However, these computational results do indicate that the *N*-alkyl substituent in diamines **2** and (−)-sparteine itself plays an important role in the high enantioselectivity observed experimentally (and mirrored in the computational results presented herein and elsewhere[10d]).

To examine the effect of sparteine's A-ring on the enantioselectivity of the lithiation of *N*-Boc-pyrrolidine **1**, the six-membered ring (equivalent to ring A of sparteine) of the *N*-Me diamine **2a** was converted into a more flexible five-membered ring *N*-Me diamine **10**. Geometry optimizations of the complexes of diamine **10** with isopropyllithium and *N*-Boc-pyrrolidine **1** (**4-C$_5$**, **5-C$_5$**, **6-C$_5$**, and **7-C$_5$**) were carried out (Table 6). Interestingly, with complex **7-C$_5$**, there were two protons on the *N*-Boc-pyrrolidine near the central carbon of the isopropyl group with C···H distances of 3.2 and 3.6 Å, and thus both complexes needed to be considered (**7a-C$_5$** and **7b-C$_5$**). Transition states for proton removal from each of complexes **7a-C$_5$** and **7b-C$_5$** were thus located.

Complex **5-C$_5$** has the lowest ground-state energy and complex **4-C$_5$** has the lowest activation energy for proton transfer. The relative transition state energies for removal of a proton is the sum of the ground state relative energy and the

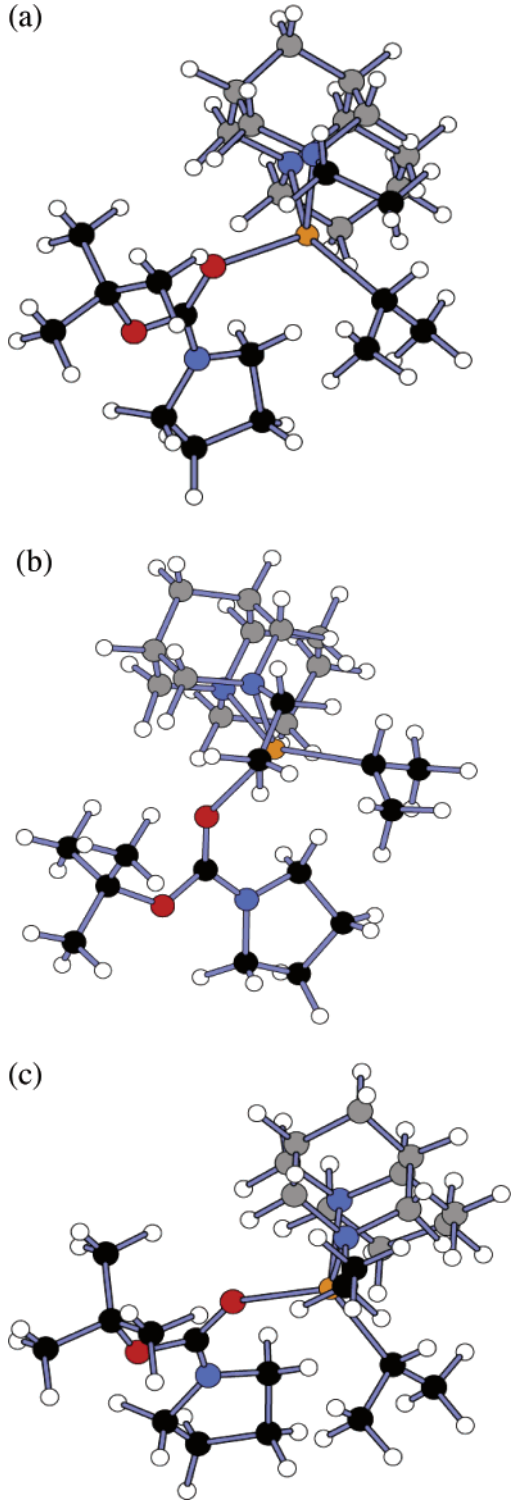


Figure 4. Structures of the isopropyllithium/diamine **2b** (*N*-Et)/*N*-Boc-pyrrolidine **1** intermediate complexes: (a) **5a-Et**, (b) **5b-Et**, (c) **5c-Et**. Note that all three complexes lead to removal of the *pro-S* proton. Colors as in Figure 1; the *N*-Et carbons of diamine **2b** are black.

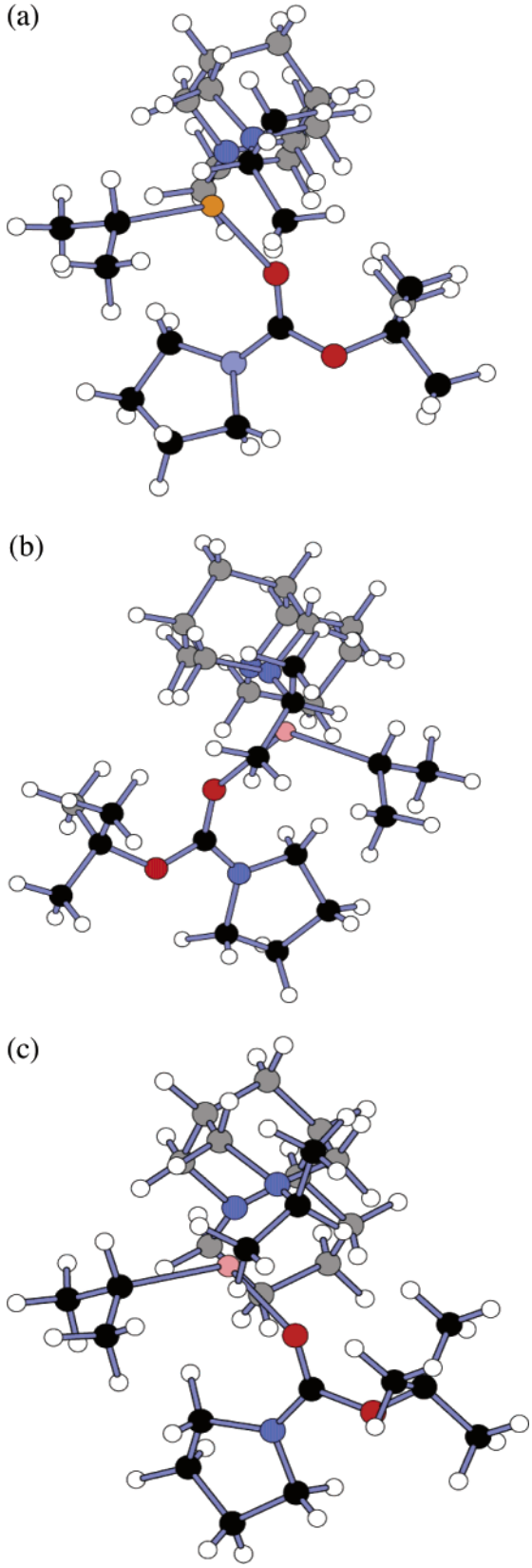


Figure 5. Structures of the lowest energy isopropyllithium/diamine **2e** (*N*-^{i}Pr)/*N*-Boc-pyrrolidine **1** intermediate complexes: (a) **4a-^{i}Pr**, (b) **5b-^{i}Pr**, (c) **7b-^{i}Pr**. Note that complex **4a-^{i}Pr** leads to removal of the *pro-R* proton, whereas complexes **5b-^{i}Pr** and **7b-^{i}Pr** lead to removal of the *pro-S* proton. Colors as in Figure 1; the *N*-^{i}Pr carbons of diamine **2e** are black.

activation energy. As a result, complex **5-C$_5$** has the lowest transition state free energy (11.6 kcal/mol) and complex **4-C$_5$** has the next lowest transition state free energy (1.8 + 11.1 = 12.9 kcal/mol). The other transition states have higher free energies. On the reasonable assumption that **4-C$_5$** and **5-C$_5$** are in equilibrium, the transition state for the reaction of complex **5-C$_5$** has a 1.3 kcal/mol lower energy than that for complex **4-C$_5$**. Thus, the calculations predict that the *pro-S* proton would be removed, but with significantly lower stereoselectivity than

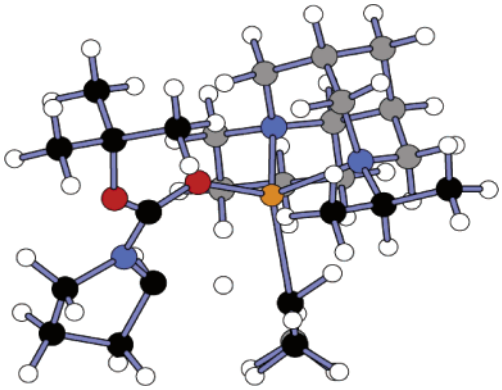
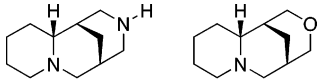


Figure 6. Structure of the transition state for deprotonation from the lowest energy complex between *N*-Boc-pyrrolidine/isopropyllithium/diamine **2e** (*N*-^{i}Pr) (**5b-^{i}Pr-TS** should lead to removal of the *pro-S* proton. Colors as in Figure 1; the *N*-^{i}Pr carbons of diamine **2e** are black.

Table 5. Calculated Relative Energies of Isopropyllithium/Diamine **8** (NH) or Amino Ether **9** (O)/*N*-Boc-pyrrolidine **1** Complexes[a,b]



8 **9**

complex	HF/3-21G H_{rel}	HF/3-21G G_{rel}	B3P86/6-31G* H_{rel}	B3P86/6-31G* G_{rel}	proton removed[c]
4-NH	0.7	0.4	0.9	0.6	*pro-R*
5-NH	0.0	0.0	0.0	0.0	*pro-S*
6-NH	2.3	1.7	1.9	1.3	*pro-R*
4-O	0.3	0.1	0.1	0.0	*pro-R*
5-O	0.7	1.0	0.0	0.5	*pro-S*
6-O	0.0	0.0	0.3	0.4	*pro-R*

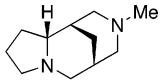
[a] All energies in kcal/mol. [b] B3P86/31-G* energies in kcal/mol corrected for both differences in zero-point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K (corresponding to the lithiation temperature of −78 °C used in the experiments). [c] Preferential proton removed.

found with the six-membered ring *N*-Me diamine **2a**. This lower stereoselectivity arises from the lower activation energy for the reaction of complex **4-C$_5$**, thus reducing the effect found in the ground states of the complexes.

Summary

The experimental results summarized in Table 1 indicate that diamine **2a**, which effectively lacks the D-ring of the parent alkaloid but bears a *N*-Me group, is as effective as (−)-sparteine in mediating the enantioselective lithiation of *N*-Boc-pyrrolidine **1** using *sec*-butyllithium or isopropyllithium. Using (−)-cytisine-derived diamines, it is shown that the presence of an *N*-alkyl substituent more sterically demanding than *N*-Et, such as *N*-^{i}Pr or *N*-CH$_2$^{t}Bu, results in a lower yield of adduct **3** and a loss of enantioselectivity for the process (e.g. er 51:49, 35% yield of **3** using diamine *ent*-**2d** with *N*-CH$_2$^{t}Bu). Significantly, lithiations of *N*-Boc-pyrrolidine **1** using the truncated (+)-sparteine surrogate *ent*-**2a**, readily available from (−)-cytisine, provides essentially equal and opposite enantioselectivity to (−)-sparteine. Our results suggest that diamine *ent*-**2a** is the best (+)-sparteine surrogate for the α-lithiation of *N*-Boc-pyrrolidine **1**. Thus, either enantiomer of 2-substituted pyrrolidines may be prepared via an asymmetric deprotonation strategy, and this could have wide synthetic utility, especially if coupled with Dieter et al.'s recently

Table 6. Calculated B3P86/6-31G* Relative Energies of Isopropyllithium/*N*-Me 5-ring Diamine **10**/*N*-Boc-pyrrolidine **1** Complexes and Transition States for Proton Transfer[a,b]



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complex	ground state H_{rel}	ground state G_{rel}	transition state H_{rel}	transition state G_{rel}	activation energy $\Delta H^{\ddagger}$	activation energy $\Delta G^{\ddagger}$	proton removed[c]
4-C$_5$	2.8	1.8	2.3	1.3	10.6	11.1	*pro-R*
5-C$_5$	0.0	0.0	0.0	0.0	11.2	11.6	*pro-S*
6-C$_5$	2.1	1.5	2.4	1.8	11.4	11.9	*pro-R*
7a-C$_5$[d]	2.0	1.1	2.3	1.5	11.5	12.0	*pro-R*
7b-C$_5$[d]	2.0	1.1	3.5	3.5	12.6	14.0	*pro-S*

[a] All energies in kcal/mol. [b] B3P86/31-G* energies in kcal/mol corrected for both differences in zero-point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 195 K (corresponding to the lithiation temperature of −78 °C used in the experiments). [c] Preferential proton removed. [d] There are two H(2) protons on *N*-Boc-pyrrolidine near the isopropyl central carbon of complex **7-C$_5$** with H···C distances of 3.2 and 3.6 Å; transition states for the removal of each of the protons were located.

reported transmetalation results that expand the reactions available to lithiated *N*-Boc-pyrrolidines.[2d]

The results of the molecular orbital calculations reproduce the experimental observation that diamines **2a** (*N*-Me) and **2b** (*N*-Et), which lack the D-ring of (−)-sparteine, result in essentially the same enantioselectivity in the asymmetric lithiation−substitution of *N*-Boc-pyrrolidine **1** as does (−)-sparteine. These computational results indicate that the etiology of the high enantioselectivity observed in lithiations mediated by (−)-sparteine involves steric interactions within the prelithiation complex (isopropyllithium/diamine/*N*-Boc-pyrrolidine **1**) engendered by the A-, B-, and C-rings of the ligand. The lowest energy prelithiation complexes of isopropyllithium/*N*-Boc-pyrrolidine **1**/(−)-sparteine or diamine **2a** (*N*-Me) also had the lowest activation energies for proton transfer. Replacement of the *N*-Me group in truncated sparteine surrogate **2a** by *N*-H (**8**) or *O* (**9**) is predicted to result in markedly lower enantioselectivity upon lithiation, indicating that the *N*-alkyl substituent in diamines **2** provides a major source of the steric interaction, leading to the observed enantiodifferentiation. In addition, converting ring A of diamine **2a** (*N*-Me) into a five-membered ring leads to a predicted lowering of enantioselectivity during lithiation and suggests that steric interactions in ring A are also of importance. Surprisingly, no product was isolated from the reaction with the *N*-^{i}Pr-substituted diamine **2e**, even though the calculated activation energies were comparable to those established for other ligands (e.g. (−)-sparteine[10d] and the *N*-Me substituted diamine **2a**). One possible explanation is that steric crowding inhibits formation of the prelithiation complex rather than increasing the activation enthalpy for proton transfer in the transition state, a conjecture that is worthy of further investigation. We believe the results presented here validate the use of a combined experimental and computational approach as a way to understanding the subtle factors responsible for high enantioselectivity in asymmetric lithiations mediated by alkyllithiums and (−)-sparteine or sparteine-like diamines.

Computational Methods

Calculations were performed using Gaussian 99.[11] In the case of the B3P86/31-G* geometry optimizations, 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).

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Supporting Information Available: Full experimental procedures and data, $^{1}H/^{13}C$ NMR spectra of new compounds, and a summary of the calculations, including calculated absolute energies, zero-point energies, as well as detailed structural data. This material is available free of charge via the Internet at http://pubs.acs.org.

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