1870, 1758, 1494, 1453, 758, 699 cm^{-1}.

Pyrrolidine 15d. Prepared from pyrrolidine **14d** via the same procedure used to prepare pyrrolidine **15a** and was obtained in 79% yield as a 95:5 mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 7.29–7.14 (m, 5 H), 2.97–2.77 (m, 3 H), 2.73–2.67 (m, 1 H), 2.60–2.53 (m, 1 H), 2.06–1.89 (m, 3 H), 1.75–1.65 (m, 1 H), 1.40–1.30 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H); IR (film) 3342, 3060, 2953, 1402, 745, 699 cm^{-1}.

***p*-Nitrobenzamide (+)-16a.** To 76 mg (0.47 mmol) of pyrrolidine **15a** in 10 mL of dichloromethane under Ar was added 0.10 mL (0.71 mmol) of triethylamine followed by 96 mg (0.52 mmol) of *p*-nitrobenzoyl chloride. After 1 h 10% KOH was added and the mixture extracted into ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to 137 mg yellow solid. GC analysis of the crude indicated a 93:7 diastereomeric mixture of products. Column chromatography (20–50% ethyl acetate/hexane) provided 84 mg (58%) of benzamide **16a** and 29 mg (20%) of a mixture of benzamide **16a** and the minor diastereomer: ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 7.6 Hz, 2 H), 7.35–7.23 (m, 5 H), 4.29–4.18 (m, 1 H), 3.74–3.45 (m, 2 H), 3.08–2.96 (m, 1 H), 2.26–2.12 (m, 1 H), 2.05–1.88 (m, 1 H), 1.41 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.6, 148.7, 143.0, 140.6, 128.8, 128.5, 127.4, 127.2, 126.9, 123.7, 60.6, 52.6, 50.0, 34.0, 18.6; IR (film), 3087, 3065, 2917, 1626, 1520, 856, 760, 742, 717, 702 cm^{-1}; $[\alpha]_D$ = +119.2° (*c* 0.48, CH_2Cl_2); mp 94–96 °C.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85. Found: C, 69.53; H, 5.82.

***p*-Nitrobenzamide (+)-16b.** Prepared from pyrrolidine **14b** by the same procedure describing the preparation of benzamide **16a** and was obtained in 60% yield from pyrrolidine **14b** as a 98:2 diastereomeric mixture. Column chromatography (20–30% ethyl acetate/hexane) provided 78 mg (58%) of benzamide **16b**: ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.6 Hz, 2 H), 3.83–3.79 (m, 1 H), 3.43–3.32 (m, 2 H), 2.04–1.92 (m, 1 H), 1.87–1.73 (m, 1 H), 1.69–1.51 (m, 1 H), 1.35 (d, J = 6.2 Hz, 3 H), 1.30–1.21 (m, 6 H), 0.89–0.84 (m, 3 H); ^{13}C NMR ($CDCl_3$), δ 167.3, 148.4, 143.2, 128.3, 123.5, 59.2, 49.4, 46.2, 32.7, 31.3, 30.1, 22.7, 19.1, 13.9; IR (film), 3062, 2959, 2927, 1632, 1522, 1348, 867, 850, 721 cm^{-1}; mp 50–52 °C; $[\alpha]_D$ = +125.4° (*c* 0.28, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64. Found: C, 66.12; H, 7.66.

***p*-Nitrobenzamide (+)-16c.** Prepared from pyrrolidine **15b** via the same procedure used to prepare benzamide **16a** and was obtained in 75% yield as a 97:3 mixture of diastereomers. Column chromatography (20–40% ethyl acetate/hexane) provided 72% benzamide **16c**: ^1H NMR ($CDCl_3$) δ 8.29 (d, J = 8.3 Hz, 2 H), 7.96 (d, J = 8.3 Hz, 2 H), 7.71–7.07 (m, 10 H), 4.62 (m, 1 H), 3.87–3.24 (m, 3 H), 3.11–3.01 (m, 1 H), 2.92 (dd, J = 2.1, 13.6 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.92–1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.4, 148.7, 142.8, 140.9, 137.2, 130.4, 128.8, 128.4, 128.3, 127.5, 127.1, 126.7, 123.7, 64.5, 50.6, 47.1, 35.4, 34.1; IR (film) 3061, 2925, 1631, 1522, 1350, 759, 740, 701, 668 cm^{-1}; mp 159–161 °C; $[\alpha]_D$ = +59.4° (*c* 1.14, CH_2Cl_2).

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74. Found: C, 74.34; H, 5.82.

***p*-Nitrobenzamide (+)-16d.** Prepared from pyrrolidine **15d** via the same procedure used to prepare benzamide **16a** and was obtained in 95% yield as a 98:2 mixture of diastereomers. Column chromatography (10–30% ethyl acetate/hexane) provided benzamide **16d** in 85% yield: ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 2 H), 8.15 (d, J = 8.4 Hz, 2 H), 7.63–7.15 (m, 5 H), 4.05–3.89 (m, 1 H), 3.33–3.13 (m, 2 H), 3.12–2.96 (m, 2 H), 2.24–2.09 (m, 1 H), 1.87–1.73 (m, 1 H), 1.43–1.28 (m, 1 H), 0.96 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 148.0, 143.0, 137.7, 130.1, 128.3, 128.2, 126.5, 123.6, 65.0, 49.9, 36.6, 36.4, 33.1, 18.1; IR (film), 3061, 2960, 1633, 1522, 1349, 777, 743, 722, 704 cm^{-1}; mp 72–74 °C; $[\alpha]_D$ = +127.2° (*c* 1.36, CH_2Cl_2).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21. Found: C, 70.27; H, 6.25.

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Asymmetric Alkylations on Chiral Formamidines. Molecular Mechanics Studies Relating to the Facial Selectivity of the Lithiated Intermediates

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Molecular mechanics studies on the lithiated chiral formamidines **1** and **3** provide an explanation for the observed degree of facial selectivity during alkylation. The energetic origin of the conformers which predominate prior to each alkylation step are found visibly to arise from angle strain and H–H repulsions.

Introduction

In a recent report from this laboratory, we presented a rationalization for the stereochemical dichotomy in first and second alkylation of chiral lithio formamidines **1** and **3**, respectively.[1] That is, alkylation of **1** occurs with very high selectivity (>99:1) on the topside (β-face) whereas the alkylation of **3** occurs with substantial facial selectivity (~9:1) predominantly from the bottomside (α-face). Our explanation of this unexpected result was based on experiments which indicated that the size of the R* group (Me, Ph, *i*-Pr, *t*-Bu) on the chiral auxiliary appeared to be playing a pivotal role in dictating the facial preference. In the first alkylation (**1** → **2**), it was found that the high level of topside selectivity was relatively insensitive to the nature of R*, whereas the bottomside selectivity observed during the second alkylation (**3** → **4**) appeared to be sensitive to the size of R*. As a result, the % de leading to **2** by varying R* could be obtained in 70–98% whereas the % de of **4** by varying R* ranged from 4 to 88%.

The reasons proposed[1] to account for the α-face alkylation of **1** and β-face alkylation of **3** (E_1 = Me) was based on there being two energetically different conformations available to the chelated lithio salts, **1** and **3**.

As semiempirical electronic structure studies[2] on complexes approaching the size of **1** through **4** have largely

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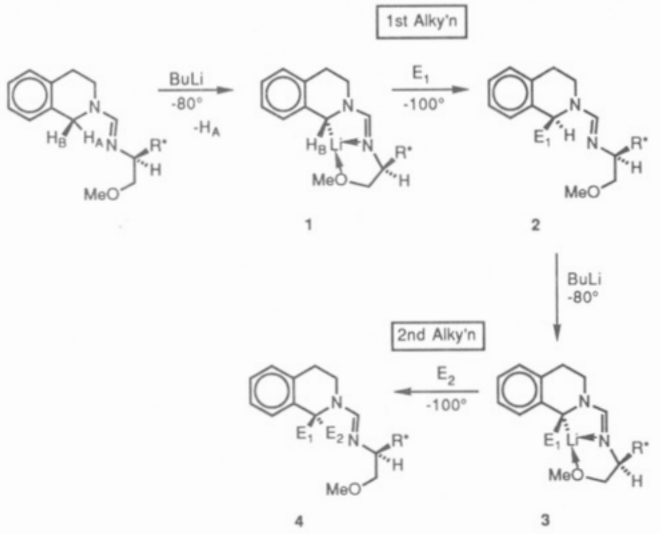

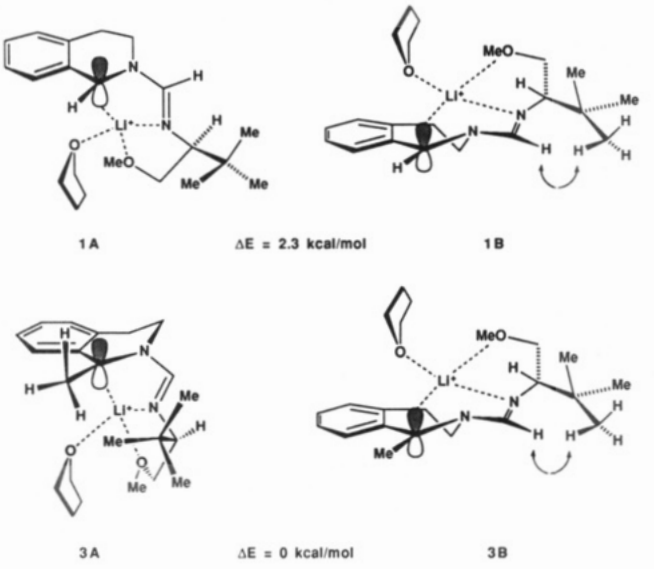

been inconclusive regarding the source of stereoselectivity, perhaps due to extreme difficulty in adequately searching conformational space, a molecular mechanics study has been performed and the results provide a reasonable basis for understanding the different steric environments present during the first and second alkylations. The results of this study are provided below in the Results and Discussion. The details of the theoretical methodology are provided in the Theoretical Details.

Results and Discussion

Prior to the first alkylation the conformation in which the lithio chelate resides on the α-face (**1A**) was found to be more stable by 2.3 kcal/mol than that in which the chelate is on the β-face (**1B**). An analysis of the individual terms (stretch, bond, torsion, etc.) in the energy expression for each diastereomer indicated that this difference in energy is localized in and can be attributed to an increase in angle strain at the asymmetric carbon center in the chiral auxiliary for **1B**. This angle strain is due to a repulsive steric interaction between the vinylic hydrogen of the formamidine moiety and the hydrogens on the *tert*-butyl group which are 2.29 Å apart in the optimized structure. In conformation **1A**, the asymmetric carbon bearing the *tert*-butyl group rotates eliminating this interaction. It is important to note here that even when the *tert*-butyl substituent in **1A**, **1B** is replaced with a methyl group a 2.4 kcal/mol differential is still observed. This energy differential is also found to be localized and is due to nonbonded repulsions between the vinylic formamidine hydrogen and the hydrogens on the methyl group. The nearest hydrogen on the methyl group was found to be 2.50 Å from the vinylic hydrogen. When the methyl or *tert*-butyl group is changed to hydrogen, no energy differential is found since the diastereomers become enantiomers, and the hydrogen is now 2.70 Å from the vinylic hydrogen. This agrees well with the experimental results[1] wherein a relatively small drop (99:1 vs 85:15) in diastereoselectivity was observed when the size of the subtituent R* was varied (R* = *t*-Bu, *i*-Pr, Ph, Me) in the alkylation of **1A**, **1B**.

When the proton on the benzylic carbanion center is replaced by a methyl group **3** (E_1 = Me), the angle strain differential localized at the chiral carbon center of **3B** (as calculated earlier for **1B**) is expectedly still present. However, there appeared an additional energetic differential between the conformations for the lithium complex (**3B**, **3A**) prior to the second alkylation. Conformation **3A** is differentially destabilized by 2 kcal/mol due to a steric repulsion between the chiral auxiliary and the newly inserted methyl at C-1 causing both diastereomers, **3A** and **3B**, to calculate out to the same energy. In conformation **3A**, the ligand moves to minimize the steric interaction between the methyl on the *tert*-butyl group and the methyl at the carbanion carbon at C-1 (Figure 1). Based on experimental results which gave α-face alkylation in 83–88% de,[1] one would expect **3B** to be favored. The methyl–methyl repulsion and resulting distortion of the chiral auxiliary in **3A**, visually observed in Figure 1, is consistent with the experimental observations, but the energetic consequences of this distortion are underestimated in the present force field calculation. To be consistent with experiment, this energy of distortion should be approximately 3 kcal/mol, but we only calculate it to be 2 kcal/mol. Use of a force field[3] with static π-interactions for the carbanion and formamidine π centers rather than a set of self-consistent π-bond orders such as in MMP2[3] is potentially the source of this small differential error. Experimentally,[1] varying the size of R*, the substituent at the chiral center in **3A**, **3B**, had a pronounced effect on the diastereoselectivity.

The same calculational procedure was used for an assumed sp^3-hybridized carbanion in **1** and **3**. For **1**, conformation **1A** was also found to be more stable than **1B** by 2 kcal/mol. As in the sp^2-hybridized model, an analysis of the energy expression leads to this difference in energy being attributed to a 2 kcal/mol increase in angle strain at the chiral carbon center for **1B**. However, for the second alkylation step, a difference between sp^2- and sp^3-hybridized carbanions is observed. The methyl–methyl interaction in **3A** visually observed for the sp^2-hybridized conformation is not present when the carbanion is sp^3 hybridized. Conformation **3A** is again favored due to angle strain which is not consistent with the experimental results. This suggests that the carbanion may, indeed, be mainly planar (sp^2 hybridized) since the pyramidal carbanion (sp^3 hybridized) would not be expected to and did not show any significant methyl–methyl interaction.

The first and second alkylations were also examined in the absence of THF solvent. The first alkylation observations still hold: angle strain at the *tert*-butyl carbon center favors conformation **1A**. In the second alkylation, conformation **3A** surprisingly remains favored by 2 kcal/mol. Due to steric congestion spawned by the presence of a molecule of THF, the C-1 Me ↔ *t*-Bu interaction

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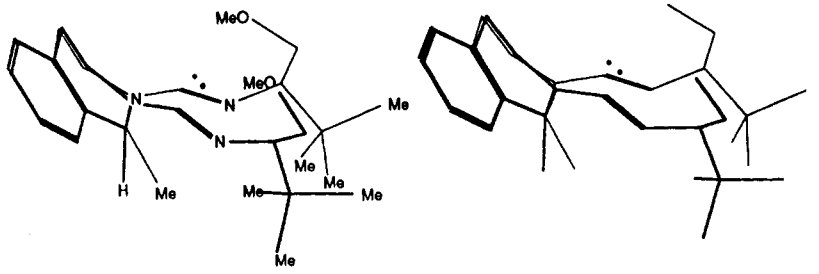

Figure 1. Stereostructures for **3A, B, 1A, B.** The two dots refer to the position of the lithium ions in each structure.

is greater in conformation **3A**. This raises the energy of **3A** by 2 kcal/mol making the diastereomers (**A, B**) of equal energy, suggesting that solvation effects may indeed by very important in the level of diastereoselectivity of the second alkylation. In the case of sp^3 hybridization of the C–Li bond, only very slight changes in conformation and energies were observed when THF was not present.

Summary

Molecular mechanics studies indicate that the most stable conformation for the lithio anion places the chelate on the α-face (**1A**) and alkylation is believed to proceed with inversion of the C–Li linkage to generate the *S*-configuration. The lithio chelate then flips to the β-face for the second alkylation in order to minimize the steric repulsion between the methyl group at C-1 and one of the *tert*-butyl methyl groups. This change in conformation of the lithio species supports the reversal in facial selectivity experimentally observed and also suggests that solvation and hybridization of the carbanion play an important role in these stereoselective alkylations.

Theoretical Details

Energetics for both diasteromeric conformations, one in which the lithio chelate is on the α-face of the isoquinoline plane (**1A, 3A**) and the other which posesses the chelate on the β-face (**1B, 3B**), as well as their optical antipodes were evaluated. All calculations were done in the presence of one THF molecule, the solvent in which these alkylations were performed. Calculations were carried out for both sp^2 and sp^3 hybridization at the carbanion. The substituent, R*, is *tert*-butyl in **1A, 1B, 3A, 3B**, and the hybridization is sp^2 except where noted.

The Dreiding force field[4] is extended in this work to include an atom type for lithium. Since lithium is presumed to be involved in dominantly ionic interactions only van der Waals parameters and a partial charge are needed. The Lennard Jones well depth was assigned a value of 0.005. The Lennard Jones distance of 2.54 was fit to the crystal structure for LiF assuming full +/− ionic species.

The precise determination of electron distributions and hence partial charge distributions for delocalized carbanions is difficult. Ab initio[2] and semiempirical[5] electronic structure techniques have been used to study the electronic and steric factors governing the reactivity of organolithium species. The results can be summarized as saying the bonding between carbon and lithium is predominantly ionic with an admixture of covalent character. We have thus assigned lithium a partial charge of +0.9 and adjusted the charge on the carbanion carbon to achieve reasonable agreement with literature Li–C and Li–O distances of 2.12 and 1.92 Å, respectively. All other partial charges were determined using the recently developed QEq charge equilibration scheme.[6] The partial charges for lithium and the carbanion carbon that best reproduced the average distances were +0.9 and −0.85, respectively.

All of the reported calculations were carried out using the Biograf molecular simulation program,[7] version 2.2. In order to address the large number of conformational degrees of freedom available in the complexes studied, the minimized charge-equilibrated trial structure for each complex was subjected to 10 cycles of annealed dynamics from 0 to 800K with a symmetric temperature ramp of 1 K per 1 fs. Each structure from the resulting collection of structures was reequilibrated. The lowest energy structure from each set was then subjected to the same process until no new lower energy structures were found.

To check the adequacy of the conformational searching methodology used (simulated annealing), we independently determined the energetics for both optical antipodes (enantiomers) as well as the diasteromeric pairs. The enantiomers should have the same energy and as such provide a reasonable test of the searching methodology.

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