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An Experimental and Computational Study of Stereoselectivity and Reactivity in Lewis Acid Promoted Lithiation-Substitution of Tertiary Amines

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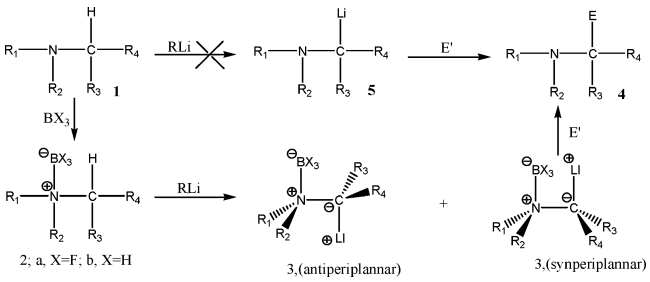
The Lewis acid promoted lithiation−electrophile reaction sequence (1-2-3-4) has emerged as a powerful methodology for forming new bonds at weakly acidic α-C−H centers of tertiary amines and phosphines (Scheme-1).[1−9] Regarding its stereochemical course, Vedjes has inferred that BH_3 complexed aziridines get lithiated syn to the boranato group under conditions of kinetic control, and subsequent reaction with electrophile is retentive.[2] However, in the case of BH_3 complexed cyclic amines having rapidly inverting delocalised α-carbanionic centers, almost exclusive formation of anti substitution products has been observed under certain conditions,[3,4] while BH_3 complexed phospholanes afford nearly equal proportions of syn and anti substitution products.[9] Such substantial formation of anti substitution product is intriguing because the equilibrium position may be expected to lie strongly in favor of the syn lithiated intermediate having a matched alignment of dipoles (*syn*-**3**). However, this crucial issue does not seem to have been examined closely, and no stereochemical investigations on equilibration or relevant computational studies seem to be available.

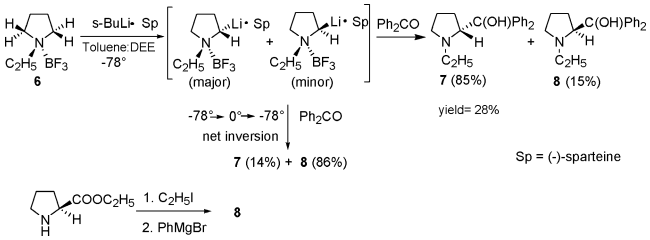
We have found that in the lithiation−benzophenone reaction of BF_3 complexes of *N*-ethyl pyrrolidine and indolizidine, enantiomeric ratios (er) and diasteriomeric ratios (dr) of products change markedly if the lithiated intermediates are subjected to a warm−cool cycle (−78° → 0°, 2 h, → −78°) prior to the addition of the electrophile (Schemes 2 and 3). These results are interpreted in terms of a kinetic syn lithiation followed by net inversion on equilibration at the higher temperature. B3LYP level DFT computations indicate that while in the gas phase the syn arrangement is considerably more stable as expected, the relative stability can shift toward the anti if the solvent dielectric constant or baring of the carbanion are taken into consideration. These computations also reveal strong Li−F bonding in **3a** which may be responsible for superior promotion of lithiation by BF_3.

Deprotonation of **6** in THF at −78 °C with a preformed complex of (−)-sparteine and Schlosser base (*s*-BuLi + *t*-BuO$^-$K$^+$) followed by addition of benzophenone afforded a racemic alcohol in 59% yield. However, when this reaction was carried out in a toluene/DEE (1:1) mixture, using *s*-BuLi as the base, the product **7** was formed (28%) with good enantioselectivity (er 85:15)[10] and its *R* configuration was deduced by correlation of the minor enantiomer (**8**) with L-proline (Scheme 2). For equilibration of the lithiated intermediate, the temperature was raised to a specified level for 2 h and after cooling back to −78 °C, benzophenone was added. Change in enantioselectivity was monitored through specific rotation of the product which decreased in magnitude and then reversed its sign with increasing temperature of the warm−cool cycle (−78 °C, $[\alpha]^{RT}_D$ −26; −50 °C, $[\alpha]^{RT}_D$ −23; −28 °C, $[\alpha]^{RT}_D$ +7; 0 °C, $[\alpha]^{RT}_D$ +23).[11] In DEE as solvent similar inversion in product

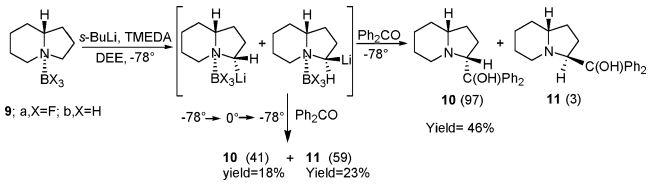
Scheme 1



Scheme 2



Scheme 3



specific rotation was observed and a warm−cool cycle going up to 0 °C gave **8** as the major enantiomer (er 86:14).[10]

Change of product configuration owing to a switch between retentive and invertive substitution with change of electrophile, solvent, countercation, etc. is known.[3,4] Since, in the present study all these parameters remain unchanged, with or without the warm−cool cycle, such reversal is unlikely. Therefore the results may be interpreted in terms of an initial enantioselective syn lithiation, with concurrent dissymmetrisation of the quarternary nitrogen[3] and subsequent net carbanionic inversion on equilibration (Scheme 2).[12] However, it was considered desirable to monitor the stereochemical course of the reaction by incorporating in the substrate another stereocenter, like the bridgehead C−H in indolizidine (Scheme 3).

The BF_3 complex **9a** derived from indolizidine was assigned a trans fused structure assuming complexation with the favored invertomer of the parent amine.[2,13] Further LAH reduction of the BF_3 complex afforded the corresponding BH_3 complex,[7,14] which was purified by silica gel chromatography to get **9b** as an oil. Its ^{1}H NMR exhibited the two equatorial proton low-field signal (δ 3.3−3.4) characteristic of a trans fused structure.[13,20c] Treatment of a solution of **9a** in DEE with a preformed complex of *s*-BuLi

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Table 1. ΔE (in Kcal/mol) for syn-anti Conformations

entry	molecule	solvent dielectric constant (ϵ)	ΔE^a
1	**3a**	0 (gas phase)	21.43
2	**3a**·Me_2O	0 (gas phase)	13.50
3	**3a**	4.335 (DEE)	3.60
4	**3a**	7.58 (THF)	−0.43
5	**3a**	16.39 (methyl phosphate)	−10.07
6	**3a**	0 (gas phase)	19.44
7	**3a**·$2Me_2O$	0 (gas phase)	10.39
8	**3a**	4.335 (DEE)	0.64
9	**3a**	7.58 (THF)	−7.93
10	**3a**	16.39 (methyl phosphate)	[b]
11	$BF_3NHCH_2^-$	0 (gas phase)	−2.94
12	$BH_3NHCH_2^-$	0 (gas phase)	−2.26

[a] ZPE corrected. [b] Syn optimizes to anti.

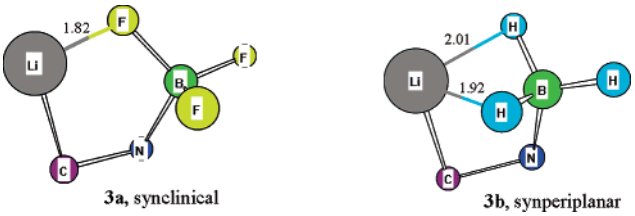

Figure 1.

and TMEDA for 2 h at −78 °C and quenching with Ph_2CO afforded alcohol **10** (46%) almost exclusively (**10**/**11** dr 97:3, no six-membered ring substitution detected). Its structure was confirmed by single-crystal X-ray analysis that showed the bridgehead H and the substituent to be on the opposite faces of the molecule as expected from syn lithiation/substitution of **9a**.[15] Interjection of a warm−cool cycle (−78° → 0°, 2 h, → −78°) before addition of Ph_2CO led to the formation of an isomeric alcohol **11** along with **10** (**11**/**10** dr 59:41). The alcohol **11** is inferred to arise from the anti lithiated intermediate formed on equilibration. Use of PhNCO as electrophile gave essentially similar results. When lithiation of **9a** in DEE/toluene (1:1) was carried out with a preformed complex of (−) sparteine and *sec*-BuLi, the obtained alcohol **10** (28%) exhibited an er of 90:10,[10] and no diastereomeric product could be detected.[16a] In a similar reaction using DEE as the solvent, **10** was obtained (26%) with an er of 97:3. Thus the reaction is highly regio- and diastereoselective and affects a kinetic resolution of racemic **9a**.[16b]

B3LYP/6-31+G* level computations on model lithiated intermediates (**3a**, **3b**, R^1−R^4═H), idealized to minimize substituent effects, reveal the syn arrangement to be more stable by 21.4 kcal/mol. There is a significant decrease in syn−anti energy gap with the binding of two Me_2O molecules to vacant Li coordination sites. However, inclusion of a solvent dielectric constant in simple solvent continuum calculations dramatically increases the relative stability of the anti arrangement, and in a solvent of high dielectric constant like methyl phosphate it becomes considerably more stable (Table 1). Besides this dielectric effect solvation, changes in aggregation[3] or additives[4] can cause ion pair separation.[9] Thus the lithiated intermediate may behave more like a bare carbanion in which the negative charge is directed away from the boranato group[5] (entry 11, 12; Table 1). Although no quantitative correlation of experimental results with idealized computations is warranted at this stage and inversion of relative syn/anti stability with dielectric constant is surprising, this trend and the carbanion baring effect are relevant for understanding the formation of the anti substitution products.[17,18]

An additional feature of interest in these computations is the Li interaction with boranato F and H in *syn*-**3a** and -**3b** (Figure 1). Such interactions in a transition state or a precomplex could be responsible for kinetically controlled syn lithiation (CIPE).[2a,19] Interestingly in **3b** two boron hydrogens approach Li (Li···H, 1.92 and 2.01 Å) while in **3a** only one but closer Li···F contact (1.82 Å) is present.[20] AIM analysis[21] shows low electron sharing only in **3a** ($\rho_{Li\cdots F}$: 0.0342) which is interestingly similar to that in the C−Li bond of **3a** (ρ: 0.0366), and there is a five-membered-ring critical point. Strong fluorine bonding with lithium may have a role in more effective activation of amines by BF_3 as compared to other boron Lewis acids, although, it has been a matter of some controversy.[1] Delineating the effectiveness difference further, we have found that not only BH_3 but also more strongly electron withdrawing BH_2CN fails to promote lithiation of **6**, **9**, and even that of an *N*-alkyl azitidine.[12b,22]

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Supporting Information Available: Representative procedures and characterization of new compounds and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) CSP HPLC was carried out on a Chiralcell OD column. (b) Yields are based on isolated products not taking into account the balance starting material and no basic side products were detected.
(11) Interconversion of enantiomeric α-lithiated *N*-ethyl pyrrolidines, accessed through a multistep sequence, shows similar temperature dependence. (a) Coldham, I.; Dufour, S.; Haxel, T. F. N.; Patel, J. J.; Jimenez, G. S. *J. Am. Chem. Soc.* **2006**, *128*, 10943. (b) Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Haeffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449. (c) BH_3 complexed α-lithiated phospholanes undergo rapid syn−anti conversion even at −100° C (see ref. 9).
(12) (a) Since BF_3 complexed products could not be isolated, initial syn lithiation and subsequent integrity of the quaternary center on nitrogen is based on literature inferences (refs 2 and 3) with BH_3 complexes. (b) Attempted lithiation of corresponding BH_3 and BH_2CN complexes failed (see Supporting Information).
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(14) BF_3 complexes of amines are less amenable to isolation and direct characterization as compared to BH_3 complexes.
(15) (a) CCDC No. 619876. (b) See Supporting Information also.
(16) (a) However, with a warm−cool cycle, formation of diastereomeric products and the lowering of **10** er (56:44) is observed. (b) The yield based on kinetic resolution of racemic **9a** is 56%. No alternate procedure for α-substitution of amino ring juncture, a feature present in a variety of alkaloids, is available.
(17) It also emphasizes the need of more refined solvent treatment, desirably taking into account local and bulk effects, in computations of lithiation-substitution chemistry especially when the observed selectivity is opposite to gas phase predictions or is seemingly counterintuitive. (a) *Topics in Organnometallic Chemistry; Springer-Verlag*: 2003; Vol. 5, pp 1−310. (b) Kessar, S. V.; Singh, P.; Singh, K. N.; Venugopalan, P.; Mahinderu, M.; Kaur, A.; Kapoor, R. *Tetrahedron Lett.* **2005**, *46*, 6753.
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(22) This supports the role of Li−F interaction in BF_3 effectiveness.

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