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Tuning carbanion reactivity by complexing with boranes: γ-elimination reaction as a model†

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ABSTRACT: The anion of 3-chloro-3-phenylselenocyclobutanecarbonitrile undergoes in DME, in the presence of alcohols, competitive protonation and γ-elimination reactions [Eqn (1)]. With highly acidic alcohols such as trifluoroethanol the protonation is diffusion controlled and the rate for the cross ring elimination reaction is greater by a factor of three (at an alcohol concentration of 1 M). However, in the presence of BH_3 or Bu_3B, the protonated product becomes dominant. This result is attributed to the binding of the carbanion by the boranes. Experimental data as well as *ab initio* calculations show that the preferred complexation site is the ring carbon and not the cyano nitrogen of the complex. The results also show that direct protonation of the complex is not a viable rationalization of the findings. It is suggested that the enhanced protonation results from the formation of a hydrogen bond between the alcohol and the cyano nitrogen, thus increasing the effective molarity of the proton donor which migrates to the α-carbon upon dissociation of the C—B bond. Copyright © 2004 John Wiley & Sons, Ltd.
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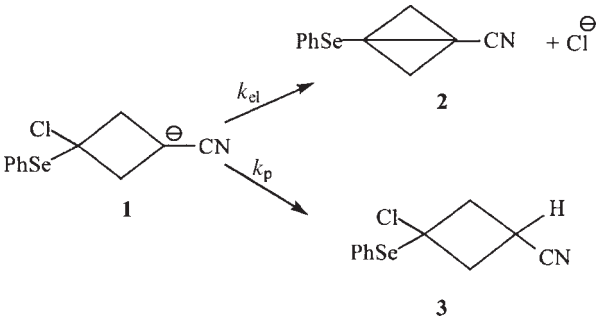
KEYWORDS: γ-elimination; borane; carbanion; bicyclobutane

INTRODUCTION

The nature and reactivity of a carbanion are known to be affected by the ion paired to it.[1] The ability of tri-alkyl boranes to form stable complexes with anions is well established and it is therefore reasonable to expect that the reactivity of a complexed carbanion will differ from that of the free one. Surprisingly, not very much has been published on the modification of carbanion reactivity by boranes. In the absence of prior systematic studies in this field we have conducted some preliminary explorations. Recently we examined the effect of Et_3B on the C/O alkylation ratio in the reaction of 2-nitropropanide anion with *p*-nitrobenzyl bromide and discovered that Et_3B significantly increased the yield of C-alkylation at the expense of O-alkylation.[2] An incidental but interesting observation in that study was that when treated with Et_3B and base, *p*-dinitrobenzene yielded (in 5 min at room temperature, ca 80% isolated yield) *p*-nitroethylbenzene.[3]

In the present work we wish to establish the effect of borane on the product distribution (protonation vs elimination) in the reaction of carbanion **1** as shown in Eqn (1).



(1)

This carbanion is generated by nucleophilic attack of $PhSe^-$ on 3-chlorobicyclobutanecarbonitrile.

We have recently reported a thorough analysis of this reaction in the absence of borane.[4] The major observation was that acidic alcohols such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) react with carbanion **1** to give **3** at a diffusion controlled rate and that the internal elimination to form the bicyclobutane derivative (**2**) has a rate constant of ca $3 \times 10^{10}\ s^{-1}$. Protonation by the less acidic alcohols, *t*-BuOH, *i*-PrOH and MeOH is, as expected, less effective.

RESULTS AND DISCUSSION

The effect of two boranes, BH_3 (added as a THF complex) and tributylborane (Bu_3B), on the product

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distribution in the reaction of **1** [Eqn (1)] was examined. Regardless of the identity of the borane used, the percentage protonation was significantly increased. BH_3 was more effective than Bu_3B in increasing the protonation yield. This was more pronounced mainly with the more sterically hindered alcohols *i*-PrOH and *t*-BuOH. However, the results with BH_3 suffered from a relatively high degree of irreproducibility, probably due to adventitious water and to the destruction of BH_3 by the alcohols. The latter cause was demonstrated by pre-incubation of the BH_3 with the solution containing the alcohol for 10 s, which resulted in a marked decrease in the protonation product. No such effect was found when the BH_3 was first mixed with the nucleophile ($PhSe^-$) and then added to the substrate. The reaction is completed almost on mixing and product distribution remains constant from *ca* 5 s after mixing up to at least 2 h. The results with Bu_3B were much more reproducible.

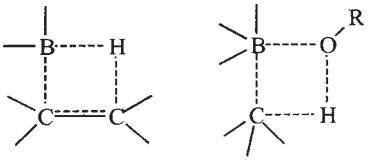
Since borane increases the percentage of protonation, it is clear that the borane must be present at the reaction center at the time of the reaction. Focusing on carbanion **1**, there are two possible coordinating sites: the ring carbon bearing the charge and the nitrile nitrogen. *Ab initio* calculations on a model compound, 2-cyanopropanide anion, using the Gaussian 98 package of programs[5] at the B3LYP/6–31+G* level[6] (all calculations throughout this work were performed at this level), showed that Me_3B binds more strongly to the carbon than to the nitrogen by 6.2 kcal mol^{-1} (1 kcal = 4.184 kJ). Energies and the main structural parameters of all the species calculated in this work are given in Chart 1. However, it is possible that in the case of the cyclobutane ring of **1**, 1–3 diaxial interaction of the Bu_3B with either of the groups Cl or PhSe may cause a preference for N-complexation. Contrary to the above, using the combination of 3,3-dimethylcyclobutanecarbonitrile anion with Me_3B as a model, we found that the preference for C-complexation increased to ca 12 kcal mol^{-1}. This is probably because the N-binding structure imposes more angle strain on the ring since C-1 in the keteiminic structure becomes formally sp^2 hybridized as opposed to sp^3 hydridization in the C-complex.

Effect of BH_3

Presented in Table 1 are the percentage protonations obtained for the five alcohols used at a 1 M molar concentration in dimethoxyethane (DME). The concentrations of phenylselenolate ($PhSe^-Na^+$), 3-chlorobicyclobutanecarbonitrile and the borane reagent are 0.05 M throughout this work unless otherwise noted.

As can be seen from Table 1, BH_3 increases the extent of the protonation in the following order: *t*-BuOH (7.9) > *i*-PrOH (5.4) > MeOH (3.3) ~ TFE (2.8) ~ HFIP (3.4). As TFE and HFIP react with the free carbanion **1** at a diffusion controlled rate, and yet percentage protonation is increased even with these alcohols, it appears that the borane affects the product distribution by slowing the γ-elimination more than the protonation. Within the framework of a non-refined model, an equilibrium may exist between the borane complex and the free carbanion and, in principle, each of the two may lead to the formation of both **2** and **3** or one of them.

As the free carbanion leads preferentially to elimination (**2**), the complexed carbanion appears to favor greatly the protonation path. A mechanism which might be considered, based on analogy with the traditional four centered transition state suggested for hydroboration[7] (**4**), is one in which at the transition state, the proton transfer takes place simultaneously with ligand change on the borane, from carbanion to alkoxide (**5**).



4 **5**

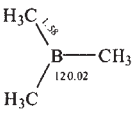
While we cannot exclude this possibility with certainty, we find it somewhat unlikely since in transition state **5** the boron is pentacoordinated (as distinct from a tetracoordinated boron at the hydroboration transition state, **4**). In order to clarify this point further, and since the results with BH_3 were not highly reproducible, we focused our study on the reaction in the presence of Bu_3B.

Effect of tributyborane

Two series of experiments were performed using Bu_3B. In the first, the concentration of the alcohols was changed in the range 0–1 M while that of the other three reactants was kept as 0.05 M. The results are given in Table 2. In the second series, the concentration of the alcohols was 1M, that of the $PhSe^-$ and 3-chlorobicyclobutanecarbonitrile was retained at 0.05 M and the concentration of Bu_3B was varied over the range 0–0.05 M. Results are presented in Table 3 and the dependence of the protonation/elimination ratio vs borane concentration is presented in Fig. 1.

The data in Tables 2 and 3 clearly show that even if the participation of a pentacoordinated boron at the four centered transition state is theoretically a viable option, it cannot be a major route since the highly hindered Bu_3B is also very effective in promoting protonation.

Before we discuss the protonation enhancement mechanism by the borane, we would like to establish more precisely the details of complexation of the carbanion by borane. The aforementioned *ab initio* computations suggested that the preferred complexation site on **1** is not the nitrogen but the carbon atom. Specifically we should address the questions: how does the boron get to the complexation site and what is the ratio of the complexed carbanion to the free one?



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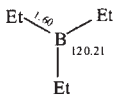

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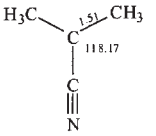

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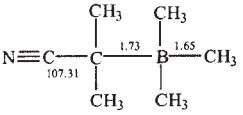

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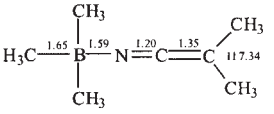

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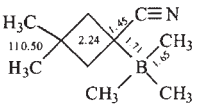

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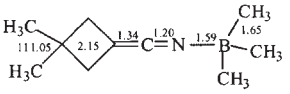

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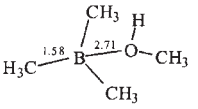

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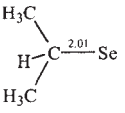

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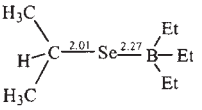

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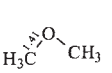

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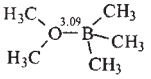

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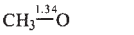

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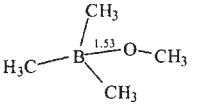

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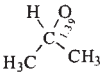

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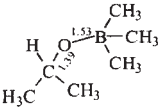

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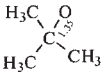

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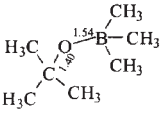

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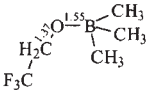

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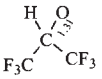

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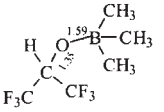

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Chart 1. Bond lengths in angstroms, angles in degree, energies in a.u.

Table 1. Percentage protonation of **1** in DME at room temperature as a function of the alcohol used in the presence and absence of BH_3

ROH[a]	HFIP	TFE	MeOH	*i*-PrOH	*t*-BuOH
	25.2	23.9	18.3	13.9	8.5
BH_3[b]	85.2	67.2	60.8	74.6	67.5

[a] Alcohol concentration is 1.0 M.
[b] BH_3 concentration is 0.05 M.

Table 2. Percentage protonation of **1** in the presence of 0.05 M Bu_3B in DME at room temperature as a function of the concentration of the proton donor

[ROH](M)	HFIP	TFE	MeOH	*i*-PrOH	*t*-BuOH
0	1	0.8	0.7	0.4	0.7
0.05	17.6	19	7.1	2.5	1.3
0.1	25.8	30	11.3	4.2	2.1
0.5	51.6	53	46.2	22	7.3
0.75	58.1	60	57	33	12.5
1	62	64	59	41	14.7

It is highly unlikely that free Bu_3B and the free **1** are fully equilibrated. This is because TFE and HFIP both react with free **1** at a diffusion controlled rate and are present in concentrations as high as 1 M, i.e. more than an order of magnitude excess over the free Bu_3B. Under these conditions, since the protonation will largely supersede equilibration, such an equilibrium cannot be fully established. Moreover, any free borane will be captured by the alkoxides generated in the course of the protonation reaction (probably also at a nearly diffusion controlled rate). Thus, another mechanism which brings the boron to the carbanion must be operating.

Our experiments regarding the stability of BH_3 in the presence of alcohols (pre-incubation with alcohol as opposed to prior mixing of the borane with the nucleophile) indicate that the borane is strongly complexed to the nucleophile-$PhSe^-$. However, as the extent of complexation also depends on competition with other possible electron donors in the solution, we have calculated the complexation energy of various species present in the solution with the borane. For reasons of economy we performed the calculations on model molecules. Thus, the interaction of alcohols with Bu_3B was simulated by the interaction of MeOH with Me_3B; the solvent DME was simulated by Me_2O (with Me_3B), whereas the interaction of borane with the five alkoxides was studied using Me_3B with the actual alkoxides. In these calculations *i*-PrSe[8] mimicked PhSe and Et_3B replaced Bu_3B. For pseudopotentials for Se see Ref. 8, and H. Basch provided the addition of diffuse and polarization functions in a personal communication. Borane binding energies are given in Table 4 and energies and major structural parameters are given in Chart 1.

The data in Table 4 clearly show that binding energies of borane to neutrals are at least an order of magnitude lower than those to anions. We suggest

Table 3. Percentage protonation of **1** in DME at room temperature as a function of Bu_3B concentration in the presence of 1 M ROH

[Bu_3B](M)	HFIP	TFE	MeOH
0	27	25	19
0.005	38	28	25
0.01	37	31	28
0.025	53	46	44
0.05	59	59	56

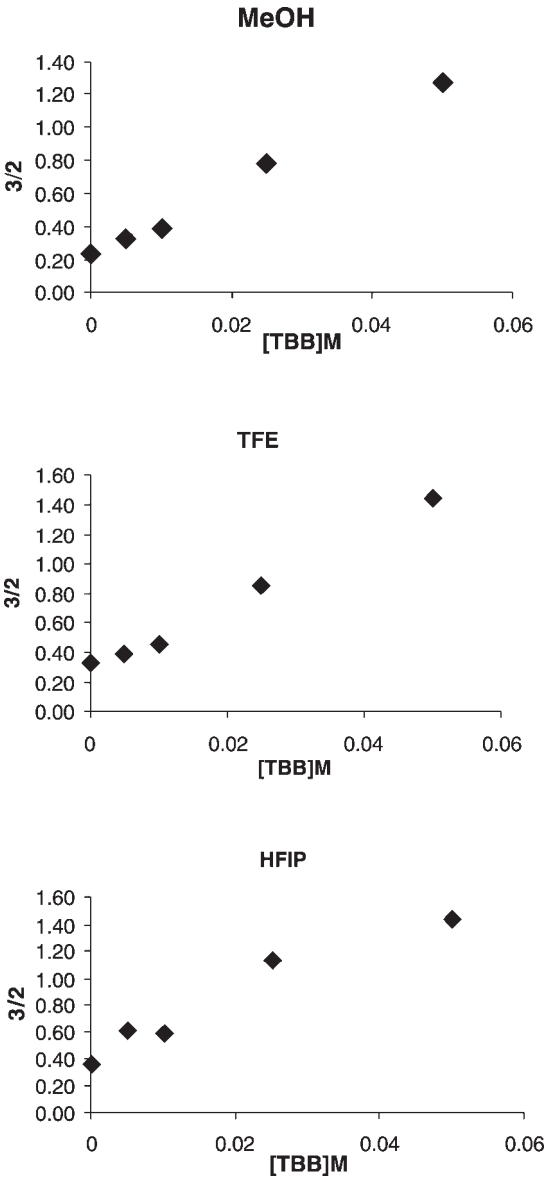


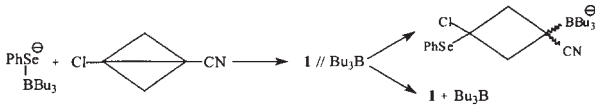
Figure 1. Protonation/elimination ratio as a function of Bu_3B concentration in the presence of 1 M MeOH, TFE and HFIP

Table 4. Complexation energies (B3LYP/6-31+G*) between various donors and boranes

Donor	Borane	Complexation energy (kcal mol^{-1})
$Me_2C—CN^-$ (C)[a]	Me_3B	−36.9
$Me_2C—CN^-$ (N)[b]	Me_3B	−30.7
3-Me_2-cyc-Bu-1-CN anion (C)[a]	Me_3B	−37.4
3-Me_2-cyc-Bu-1-CN anion (N)[b]	Me_3B	−28.7
MeOH	Me_3B	−1.2
i-$PrSe^-$	Et_3B	−15.9
Me_2O	Me_3B	−0.7
MeO^-	Me_3B	−52.3
i-PrO^-	Me_3B	−40.9
t-BuO^-	Me_3B	−40.2
$CF3CH2O^-$	Me_3B	−40.8
$(CF3)2CHO^-$	Me_3B	−29.4

[a] The carbon atom is the complexation site.
[b] The nitrogen atom is the complexation site.

therefore that upon mixing, the boron immediately forms a complex with the nucleophile which, at the beginning of the reaction, is the only negative species present in the solution. Upon its attack on the substrate, the nucleophile sheds the borane, which may either complex with the carbanion or escapes the cage [Eqn (2)].



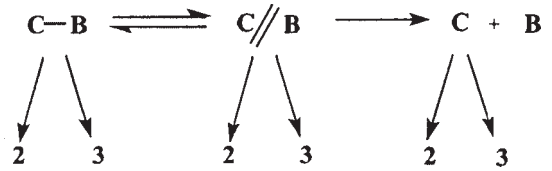
(2)

For the reason stated above, the Bu_3B that diffuses away only has a meager chance of recomplexing with the carbanion before protonation or elimination occurs.

The data in Table 4 also show that boron does not complex effectively to the alcohols (especially in the presence of a large excess of the solvent) and probably does not contribute much to increasing their acidity.

Thus, in the model we propose, the borane rides to the reaction center on the back of the nucleophile ($PhSe^-$) where part of it is captured by the incipient carbanion.

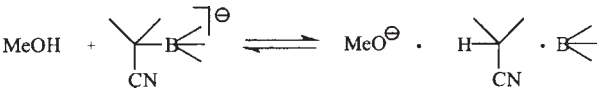
Let us now turn to the mechanism by which borane enhances protonation over elimination relative to the free carbanion. The carbanion formed may exist in three states: borane complexed (**C—B**), an ion–dipole intermediate (**C//B**) and free (**C**) [Eqn (3)].



(3)

These states may in principle undergo both protonation and elimination as does **C**. Clearly, a higher protonation/elimination ratio in the presence of borane implies that protonation is enhanced relative to elimination for at least one of the species, **C—B** or **C//B**.

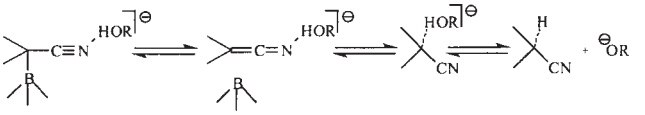
We will first examine direct protonation of the complex **C—B**. As cyclic *syn*-protonation (protonation with retention of configuration as in **5**) is unlikely by the mechanism shown above, we will focus on *anti*-protonation [Eqn (4)]. We were unable to pinpoint the structure of the transition state for this reaction. However, based on point by point search we estimate the activation energy to be around 35 kcal mol^{-1}.



(4)

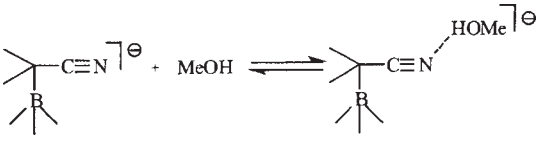
We have found computationally that the equilibrium energy for the protonation by MeOH increases from 3.3 kcal mol^{-1} for the free *i*-PrCN anion to 18.1 kcal mol^{-1} for the borated carbanion. These calculations refer to the gas phase. In DMSO, MeOH is slightly more acidic (2 pK_a units) than MeCN.[9] However, the complexation energy of the carbanion to the borane (ca 35 kcal mol^{-1}) more than compensates for this small difference in acidity. Therefore, the high endothermicity of the *anti*-protonation reaction negates the direct anti-protonation as a possibility.

While we cannot rule out the possibility of protonation on the ion dipole complex **C//B** [Eqn (3)] it is difficult to see why this will be favored more than elimination relative to free carbanion **C**. We would like, therefore, to suggest a mechanism which will account for all the observations made. According to this mechanism, the complexed borane (**C—B**) undergoes neither protonation nor elimination. Rather, it forms a hydrogen bond (probably through the nitrogen) with the alcohol present.[10] This effectively increases the local concentration of the proton donor and when the complex **C—B** is eventually cleaved, C-protonation may take place without having to wait for the alcohol molecule to diffuse toward the carbanion [Eqn (5)].



(5)

Calculations show that the hydrogen bonding to the nitrogen [Eqn (6)] is exothermic by ca 17 kcal mol^{-1}. (It should be noted that in solution this value, which relates to the gas phase, is expected to decrease). This hydrogen bonding also diminishes the capability of the negative charge in **1** to displace the Cl to give **2**.



(6)

From the nitrogen the alcohol may move to the carbon by a series of dissociation–association steps or glide over the π-system in a manner similar to Cram's conducted tour mechanism.[11]

Thus, it is clear that protonation is enhanced not due to increasing the rate constant (which cannot be done for a diffusion controlled reaction) but rather by increasing the effective concentration of the proton donor. It also explains why the increase in the percentage protonation by 0.05 M Bu_3B (in the presence of 1 M ROH) is nearly the same for all the alcohols (2.5-, 2.8-, 3.5- and 2.9-fold for HFIP, TFE, MeOH and *i*-PrOH, respectively) except for the most sterically hindered *t*-BuOH (1.7-fold). This is because hydrogen bonding is not strongly depended on the acidity[12] and therefore all alcohols will enjoy nearly the same increase in the protonation fraction (apparently subjected somewhat to steric effects). This is because Bronsted a which is a measure of the degree of proton transfer is likely to be very small. For related discussions see Ref. 12.

CONCLUSIONS

While we do not want to generalize we would like, on the basis of this study and the limited data available, to suggest that borane differs significantly from metals paired to carbanions in the affect on the carbanion behavior. The high affinity of boranes for carbanions places them closer to hydrogen than to metal cations. In other words, the effect of boranes is not tunable like that of an ion pair. Rather, they evoke more of an ON–OFF response, resembling a proton in this respect. When a carbanion is protonated/borated, its reactivity is in the OFF mode and when it is not bound to proton/borane, it is in the ON mode.

The similarity between boranes and a proton is that their interaction with carbanions is mainly covalent whereas that of metals (apart from Li) is largely ionic. As electrostatic interactions, relative to covalent interactions, are long range, there is plenty of room for tuning. For ion pairs, variation of the solvent and the cation may affect the intimacy of the ion pair from contact to solvent separated and to free ions. For each type of the ion pairs, variation of the metal may affect the reactivity. For boranes, there are hardly intermediate states. The borane is either bound to the carbon and in this case the carbanion's reactivity is quenched, or it is dissociated from the carbon and in the absence of Coulomb interactions the carbanion is free and will react as such. Thus, for example, reducing the binding ability of borane, either by varying the bulkiness of its substituents or their electronic properties, will affect the proportions of the two states (free or bound) but will not introduce an additional state. In fact, in this respect, boron even surpasses the proton since the latter may form hydrogen bonds to the carbanion, whereas boranes will merely have an ion dipole interaction, which is rather weak, especially in solution.

There is, however, a major difference between borated and protonated carbanions. While the latter are neutral, borated carbanions bear negative charge. The consequences of this are two-fold. The first is that being negatively charged it may react as a single electron donor. The second is that in the case of multidentate carbanion, reactivity, albeit largely reduced, may still remain and preferential binding of the boron to one site will shift the reaction center to the other. The present study is an example of the latter statement. The borated complex does not undergo carbon protonation but rather shifts the initial interaction site of the proton donor to the nitrogen.

EXPERIMENTAL

General

NMR spectra were recorded on a 300 MH spectrometer and measured in $CDCl_3$ solution. HPLC analyses were conducted using an Altech Econosil 10 μm, 250 mm long and 4.6 in diameter, column with an eluent of 5% THF in heptane. The same column with a 10 mm diameter was used for preparative separations. All the materials used were analytical-reagent grade. MeOH, *t*-BuOH and *i*-PrOH were dried according to published procedures.[13]

Reactants and products

3-Chlorobicyclobutanecarbonitrile was prepared according to the literature procedure.[14] The products 3-phenylselenobicyclobutanecarbonitrile (**2**) and 3-chloro-3-phenylselenocyclobutanecarbonitrile (**3**) are known compounds.[4]

Reaction procedure

The reactions of 3-chlorobicyclobutanecarbonitrile with PhSeNa in DME were conducted in a glove box under nitrogen at room temperature. To 0.95 ml of a solution containing the substrate, 0.05 ml of a solution containing the PhSeNa was added. In the reactions in the presence of boron (BH_3 and Bu_3B were purchased as 1 M THF solutions sealed under nitrogen), the boron solution was initially added in the appropriate amount to the nucleophile DME solution and aliquots from this solution were added to the DME solution of the substrate. In cases where the reaction was conducted in the presence of alcohol, the alcohol was added to the substrate solution prior to the addition of the salt. Immediately upon mixing, precipitation of NaCl was observed. The mixture was taken out of the glove box and diluted (1 + 9) in the

eluent solvent of the HPLC. Quantitative analyses were routinely carried out by HPLC and occasionally also by NMR. Identical results were obtained within experimental error ($\pm 3\%$).

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