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DFT and experimental study of triallylborane-mediated isomerization of α-allylated azaheterocycles

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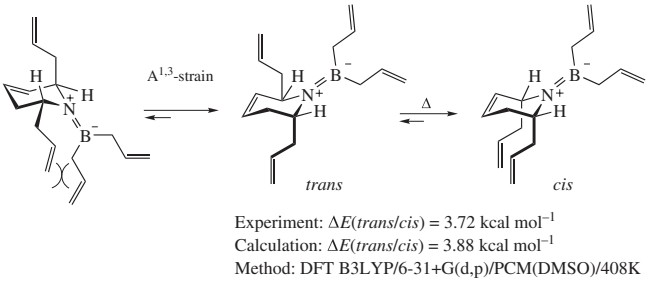
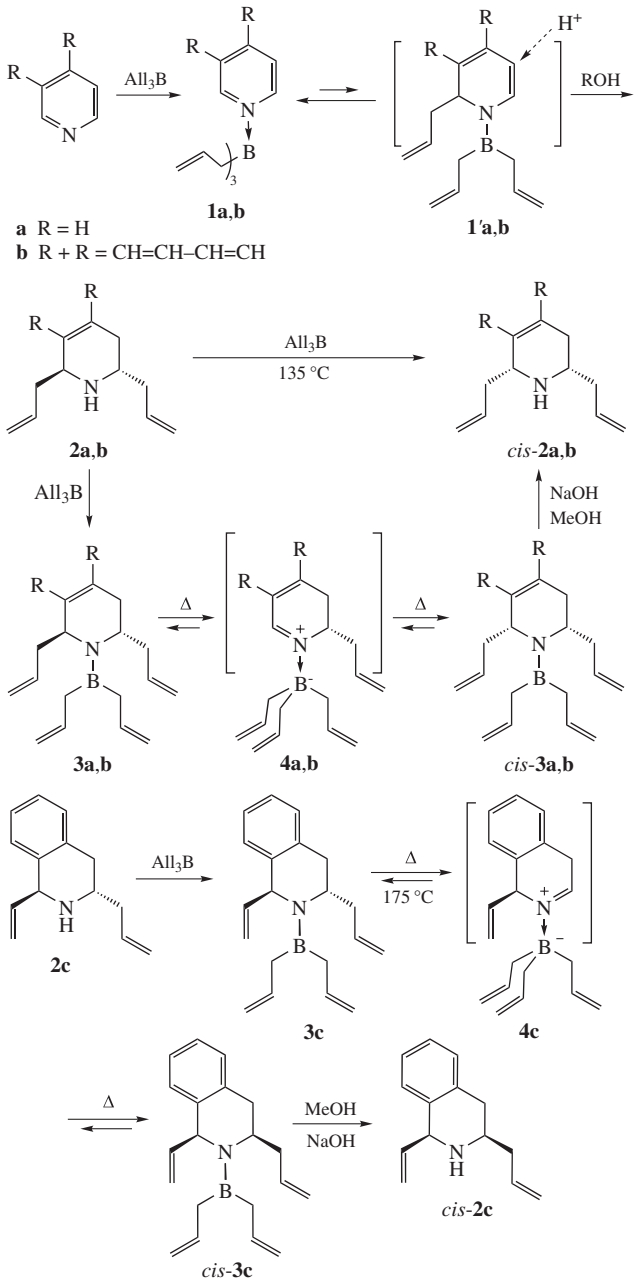
Triallylborane-mediated thermal *trans*/*cis*-isomerization of α-allylated azaheterocycles is a unique stereoselective transformation providing straightforward access to important heterocycles. The main experimental features of this process, namely, thermodynamically controlled isomer ratio, 1,3-allylic strain as a driving force and regioselectivity are quantitatively described by quantum chemical calculations at B3LYP/6-31+G(d,p)/PCM(DMSO) level of theory.



Experiment: ΔE(*trans*/*cis*) = 3.72 kcal mol^{-1}
Calculation: ΔE(*trans*/*cis*) = 3.88 kcal mol^{-1}
Method: DFT B3LYP/6-31+G(d,p)/PCM(DMSO)/408K

Reactions of allylboranes are of extreme importance in synthetic organic chemistry.[1,2] Allylboration of compounds with multiple bonds (C=O, C=N, C≡N, C≡C) is particularly substantial in case of C=N allylation leading to valuable homoallylamines,[3,4] which are versatile and useful intermediates in synthesis of heterocycles, natural products and biologically active molecules.[5] Transformations of piperidine-type homoallylamines are of special interest since such compounds occupy leading positions in the prevalence of alkaloids and pharmaceuticals.[6] They are also utilized in the synthesis of bi- and polycyclic molecules *via* Ru-catalyzed ring closing metathesis.[7] Recently, we found that dichloroacetyl derivatives of diallylated azaheterocycles possess promising grow-stimulating activity on corn seeds.[8] Reductive allylboration of pyridine and isoquinoline with triallylboranes provides straightforward access to *trans*-2,6-diallylated azaheterocycles **2a**,**b** (Scheme 1).[9] Similar reaction using triallylaluminium as carbometallation reagent was developed by Okuda.[10] The first step of the reaction is the formation of triallylborane–pyridine adduct **1a**, existing in equilibrium with aminoborane **1′a**. Generally the equilibrium is shifted entirely to **1a**, but in the case of trimethallylborane–3-bromopyridine adduct aminoborane **1′a**-type becomes the main intermediate (aminoborane **1′b** is also formed with isoquinoline).[11] Aminoborane **1′a** is protonated with alcohol at 50–100 °C followed by *trans*-allylation of the intermediate imine (not drawn) with diallylborinic ester giving rise to **2a**. Another interesting transformation of **2a** into *cis*-**2a** occurring upon heating of **2a** with triallylborane at 130–135 °C (see Scheme 1) was less studied. The suggested intermediate **4a** could not be detected or isolated, because allylboranes are highly reactive toward C=N bonds (even at –100 °C).[12] Nevertheless, the formation of **4a** clearly follows from the change in the configuration. The initial explanation for the emerging *cis*-selectivity was attributed to equatorially located allyl groups in isomer *cis*-**3a**.[13] However, in case of isomerization of *trans*-isoquinoline **2b** the final equilibrium *cis*-**2b**/**2b** ratio was 1 : 1,[14] which was in contradiction to the assumption of equatorial stabilization in *cis*-isomers. To clarify the reason of such significant difference in behaviour of these structurally similar compounds, quantum-chemical calculations were performed.

Preliminary optimization of aminoborane geometries was carried out by the AM1 method, which revealed the presence of 1,3-allylic strain ($A^{1,3}$-strain)[15] in **3a** and *cis*-**3a** (Scheme S1, see Online Supplementary Materials). Similar effect is known for *N*-acyl *cis*-α,α′-diallylated piperidines when allylic groups adopt the axial positions.[14,16] As we herein found, the allyl groups at boron and in the heterocycle fragment in **3a–c** and *cis*-**3a–c** induce an even stronger $A^{1,3}$-strain which would repell the allyl groups towards axial positions. Geometries of **3a** and *cis*-**3a** were used at starting points in mixed Monte-Carlo/Low-Mode Molecular Dynamics conformational search in MacroModel[17] and optimized in Gaussian09[18] at B3LYP[19,20]/6-31+G(d,p)[21]/PCM(DMSO)[22] level of theory (see Online Supplementary Materials), which is known to be reasonably accurate for organic reactions[23] and was shown to be well-grounded in theory.[24,25] A number of lowest-free-energies conformations were used to compute isomer ratios. The most accurate calculated energy difference was ΔE(*cis*-**3b**/**3b**) = –0.44 kcal mol^{-1}, which is quite close to the experimental energy difference ΔE(*cis*-**3b**/**3b**) = = 0.00 kcal mol^{-1} (according to ^{1}H NMR *cis*-**2b**/**2b** = 1 : 1). Calculations performed using extended basis set 6-311+G(d,p), or a different method PBE1PBE, or including D3 correction for dispersion interactions[26] showed overstabilization of the *trans*-isomer (by 0.76 and 1.02 kcal mol^{-1}, respectively) and poorer coincidence with the experimental data, likely due to errors cancellation between B3LYP (no dispersion interactions) and 6-31+G(d,p) (basis set superposition error).[27,28] Therefore, all



Scheme 1

further calculations were carried out using the B3LYP/6-31+G(d,p)/PCM(DMSO) level of theory. The results are summarized in Table 1.

The isomerization of isoquinoline vinyl,allyl derivative **2c** gave rise to a mixture of isomers *cis*-**2c**/**2c** in a ratio 1.54 : 1 according to ^{1}H NMR spectroscopy,[29] which corresponds to ΔE(*cis*-**3c**/**3c**) = 0.35 kcal mol^{-1} (see Scheme 1 and Table 1), and the calculated value ΔE(*cis*-**3c**/**3c**) was –0.23 kcal mol^{-1} (error 0.58 kcal mol^{-1}). In the isomerization experiment with **2a**, the ratio *cis*-**2a**/**2a** was 99 : 1 which corresponded to ΔE(*cis*-**3a**/**3a**) = = 3.72 kcal mol^{-1}. The last computed energy difference is in a very good agreement with the experiment: ΔE(*cis*-**3a**/**3a**) = = 3.88 kcal mol^{-1} (error 0.16 kcal mol^{-1}). Thus, the experimental ratio of isomers in this reaction is accurately described by DFT calculations in the thermodynamic control approximation; the developed approach can be used for quantitative prediction of the title reaction outcome.

Table 1 Comparison of experimental and calculated ΔE for *cis*/*trans*-isomers of compound **3a**–**c**.

Compounds	Ratio	ΔE/kcal mol^{-1}		Error/ kcal mol^{-1}
		Experimental[a]	Calculated	
cis-**3a**/**3a**	99 : 1 (135 °C)	3.72	3.88	0.16
cis-**3b**/**3b**	1 : 1 (135 °C)	0.00	–0.44[b]	0.44
cis-**3c**/**3c**	1.54 : 1 (175 °C)	0.35	–0.23[b]	0.58

[a] The ratios of the corresponding amines (*cis*-**2a**–**c**/**2a**–**c**) were determined by ^{1}H NMR. [b] Sign minus indicates that *trans*-isomer has lower energy.

Another problem of isomerization of aminoboranes **3a**–**c** relates to the presence of two distinct types of allyl groups in their molecules, one of them locates in the so-called 'diallyl position' and theoretically can be more labile, since during the allyl migration, dienes **4a**,**b** stabilized by conjugation are formed (see Scheme 1). Indeed, the isomerization of amines with allyl group connected to 'diallyl position' takes place at 130–135 °C[9] whereas the isomerization of such derivatives, as *trans*-2-allyl-6-methyl-1,2,3,6-tetrahydropyridine or **2c** where immobile methyl or vinyl group locates in the 'diallyl position', effectively proceeds only at higher temperature 175–180 °C.[13,29] To describe the kinetic of the process, activation energies were calculated and the reaction routes were analyzed. Transition state (TS) guesses were generated in Macro Model *via* constrained conformational search[30] (see Online Supplementary Materials) and location of TSs were carried out at B3LYP/6-31+G(d,p)/PCM(DMSO) level of theory. According to our results, cleavage of the bond at the 'diallyl position'-6 *via* $TS_{trans\text{-}6}$ is slightly disfavored by 1.8 kcal mol^{-1} with respect to $TS_{trans\text{-}2}$ though intermediate **4a** is indeed more stable by 4.9 kcal mol^{-1} than **4′a**, and transition state for *cis*-allylation $TS_{cis\text{-}6}$ (Figure 1) is favored by 4.1 kcal mol^{-1} with respect to $TS_{cis\text{-}2}$. The reaction routes interplay was analyzed using the Curtin–Hammett principle.[31–33]

trans-Isomeric aminoborane **3a** undergoes rearrangement to **4′a** through $TS_{trans\text{-}2}$ with 85% probability with the rest ~15% corresponding to rearrangement to **4a** through $TS_{trans\text{-}6}$. Intermediate **4′a** favors rearrangement to **3a** with >99% probability, while **4a** prefers rearrangement to *cis*-**3a** in 85% cases. In the reversed process, transformation of *cis*-**3a** is much more selective towards **4a** relatively to **4′a**, having >99% probability of formation of the first. Thus, the equilibrium is reached faster when allylic group is in 'diallyl position'-6 which is consistent with the experiment. Moreover, the obtained data explain the forced conditions required for the isomerization of **3c** (**2c**) having allyl group only at 2-position. Though allyl groups migrate comparably well from both 2- and 6-positions in **3a** (85% and 15%, because of higher activation barrier for $TS_{cis\text{-}2}$ compared to $TS_{trans\text{-}2}$)

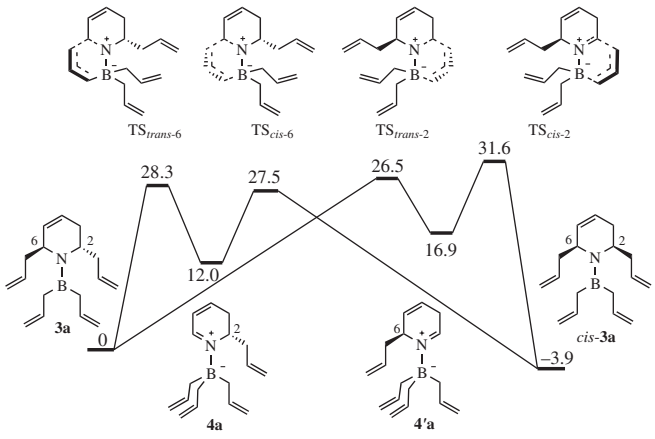
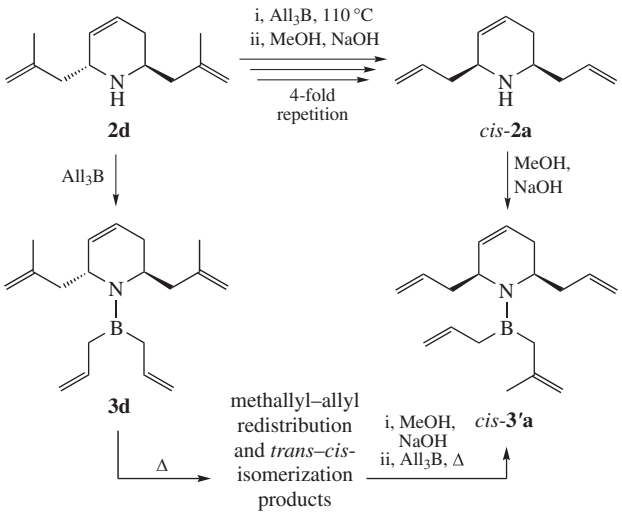


Figure 1 Relative free energies [B3LYP/6-31+G(d,p)/PCM(DMSO)] along the reaction paths (in kcal mol^{-1}) of aminoboranes **3a**, *cis*-**3a** isomerization. Shown structures correspond to one (of the two possible) enantiomer. Energies correspond to the minimal located conformers.



Scheme 2

the further main route of the migration of 2-allyl group (instead of isomerization) becomes circulation between **4′a** and initial position in **3a**. To obtain an additional support for our kinetic calculations, a study of the isomerization-exchange reaction of *trans*-2,6-dimethallyl derivative[34] **2d** was carried out (Scheme 2). Experimentally we found that the minimum temperature of the beginning of this reaction was about 100 °C, however, for a more rapid attainment of the equilibrium, the reaction was carried out at 110 °C (383 K). The reaction was run for 6 h, but after 1 h a small aliquot from the reaction mixture was treated with NaOH solution and the mixture of amines was analyzed by ^{1}H NMR spectroscopy. An overlapping of signals of several products was observed, though signals of the *cis*-**2a** were clearly distinguishable by comparison with authentic sample. The presence of *cis*-**2a** in comparable amount with other products is only possible when migration of methallyl groups is occurred from both positions in the heterocycle, which agrees with the computed close barrier heights.

Calculated potential energies of isomeric aminoboranes which can be formed during methallyl group migration (Figure 2) are quite close (within 1.26 kcal mol^{-1}) and explain the complex NMR spectrum. The difference between the initial **3d**, which is least energetically favorable, and various *cis*-**3d**,**e** ranges from

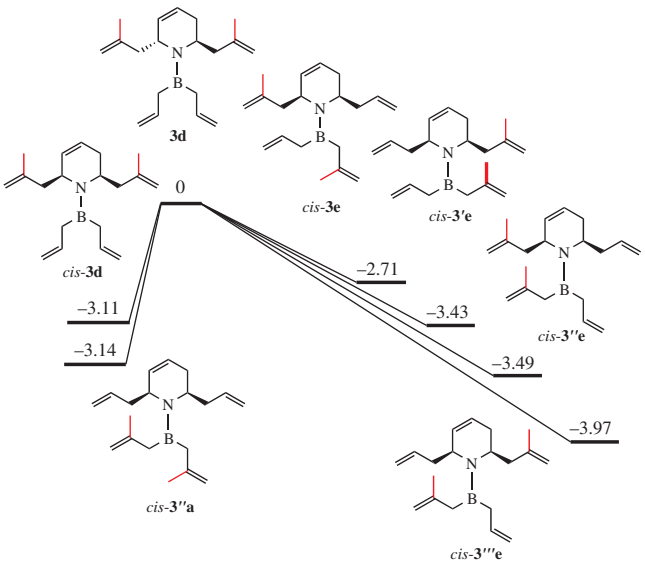


Figure 2 Calculated potential energies (in kcal mol^{-1}) in isomeric and homologous aminoboranes of type **3**.

2.71 to 3.97 kcal mol^{-1}. It is of note that energies of *cis*-**3d** and **3″a** are almost equal (ΔE = 0.03 kcal mol^{-1}). The most stable isomer is *cis*-**3‴e** (–3.97 kcal mol^{-1}) resulted from the migration of one methallyl group from 'diallyl position'. The closest to *cis*-**3‴e** is *cis*-**3″e** (–3.49 kcal mol^{-1}) derived from another methallyl group migration. The energy distribution explains the presence of *cis*-**2a** in the beginning of the reaction. In order to experimentally achieve a complete replacement of the methallyl groups in the heterocycle fragment, it is necessary to conduct four consecutive exchange reactions each with new portion of triallylborane. Thus, both allylic groups migrate simultaneously without significant preference for 'diallyl position'.

Thus, the presented experimental and quantum-chemical data at B3LYP/6-31+G(d,p)/PCM(DMSO) level of theory allows one to elucidate the driving force for *trans*/*cis*-isomerization of mono- and diallylated N-heterocycles, as well as to give a quantitative description of the experimentally observed ratio of isomers. It was proved that isomerization process is thermodynamically controlled and stabilities of aminoboranes play a pivotal role in the stereo- and regioselectivity of the reaction.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.025.

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