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Is the Elimination of Lithium Alkoxide Easier from a Vinyllithium or from an Alkyllithium? A DFT Study of the Aromatization of 3-Vinylidene-2,3-dihydrobenzofurans to Benzofurans

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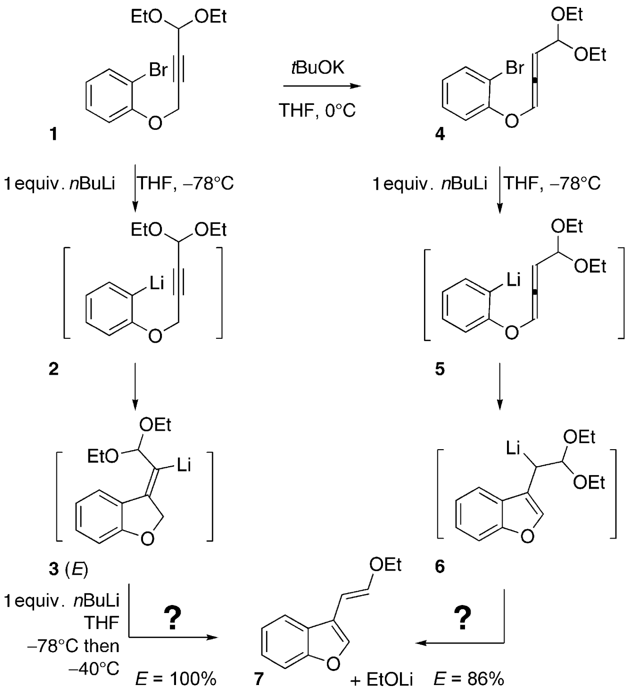
A possible mechanism for the last step of a cascade transformation in which lithiated propargyl ether **2** is converted into 3-vinylbenzofuran **7** is described. Starting from the lithiated *E* olefin **3A**, our DFT computations show that the final departure of lithium alkoxide is not easy unless an excess of *n*BuLi, the importance of which has been noted experimentally, prompts a second deprotonation. This theoretical evidence was further supported by a complementary experiment involving dihydrobenzofuran **10**. The deprotonation of this latter compound by *n*BuLi elicits a spontaneous *syn* elimination, probably through monolithiated intermediates **10Li** and **6**, regioisomers of **3A**. The activation barriers calculated for these various transformations indicate that the elimination of lithium methoxide from β-lithiated acetals requires around 10 times more energy when the precursor is a vinyllithium rather than an alkyllithium. A route passing through a sigmatropic rearrangement was also considered. This triggers the elimination of a molecule of methanol, which acts as a shuttle to transfer a proton from the heterocycle to the vinyl position. However, with the set of reaction coordinates considered, this mechanism passes through high-lying activation barriers unless the conformation of the exocyclic double bond in **3** is *Z* (isomer **3B**).

Introduction

We have recently shown that the propargylic ether **1** or its allenic isomer **4** can be easily transformed into a 3-vinylbenzofuran **7** through a stereocontrolled one-pot cascade process (Scheme 1).[1] Our data suggest that, in THF, a 5-*exo*-dig addition on the triple bond occurs, which leads to an exocyclic vinyllithium **3** with an unexpected *E* configuration. An experimental and theoretical investigation, run in parallel on a model that includes two explicit molecules of THF, sheds some light on the origin of this unprecedented *anti*-selective carbolithiation of an alkyne.[2]

The intramolecular coordination of the lithium cation of aryllithium **2** by a methoxy group in the acetal appendage was shown to play a crucial role in the reaction and in its stereochemical outcome.[1b] Our original theoretical study led us to propose that intermediate **3** was attained through



Scheme 1.

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a relatively low activation barrier (8.3 kcal mol^{-1}). But the final stage of the reaction, the transformation of **3** into 3-vinylbenzofuran **7**, was not considered in these computations. Intriguingly, it has been shown that this step required the presence of a second equivalent of *n*BuLi and the warming of the reaction medium to –40 °C.

The experimental work also encompassed the case of allene **4**, which was transformed under the action of only 1 equiv. of *n*BuLi into benzofuran **7**, even at –78 °C (Scheme 1).[2] In good agreement with this result, a route from **5** to allyllithium **6** through a low-lying TS (+2.5 kcal mol^{-1}) could be identified by DFT. Here again, the final elimination (**6** → **7**), which looks like a simple β-elimination of lithium alkoxide, was not considered.

We wish to discuss herein the details of these final steps. The fact that the intermediate exocyclic vinyllithium **3** results from a carbolithiation reaction (and not from a deprotonation) suggests that the mechanism will most probably follow an E1cB pathway. The stereochemical course of these eliminations is not as predictable as that of the E2 route, and both the *anti* and *syn* processes are documented in the literature.[3] In particular, it has been clearly evidenced that a *syn* process may be favored when a lithiated intermediate is involved: in the *syn* arrangement, coordination between the lithium and the leaving EtO group can develop and accelerate the departure of EtOLi.[4]

Computational Details

In line with the preceding papers, the computations were run at the DFT level of theory by using the B3P86 functional and the 6-31G** basis set, as implemented in the Jaguar 5.0 software.[5] Similarly, the zero-point energy corrections (ZPE), the relaxed potential energy surface (PES) scans, and the characterization of the optima by frequency calculations were systematically employed, but the basis set superposition error (BSSE) was not taken into account. Absolute energies are given at 25 °C. The experimental systems were slightly simplified by replacing the ethoxy groups of the acetal function by methoxy ones. For the sake of clarity, the numbering of the computed molecules in the following has been kept identical to that of the experimental ones (Scheme 1) despite the differences introduced by using a dimethyl acetal instead of a diethyl acetal. Following our previous articles,[1b,2] solvation has been modeled by the use of two explicit THF molecules with the lithium cation in a tetracoordination sphere.

Results and Discussion

In the preceding paper,[2] we started from the three most stable conformers of aryllithium **2** and examined their cyclization to vinyllithium **3**. These three parallel routes are shown in Figure 1. Path A, based on the less stable conformer **2A**, exhibits an intramolecular Li–O coordination and leads, through a TS associated with the lowest energy barrier, to the *E* olefin **3A**. This is in agreement with experiment. In contrast, the lithium cation in conformers **2B** and **2C** interacts with the C≡C triple bond at the expense of the acetal moiety. This leads, through slightly higher-energy TSs, to **3B** and **3C**, two conformers of the unobserved *Z* olefin. Thus, the only pathway taken into account in this paper concerns the relevant *E* intermediate **3A**, the behavior of the virtual **3B** and **3C** *Z* olefins being briefly discussed.

Direct β-Elimination of Lithium Alkoxide from 3A

The original mechanism based on vinyllithium **3A**,[1a] thought to undergo β-elimination of a molecule of lithium ethoxide (Scheme 2), was considered first.

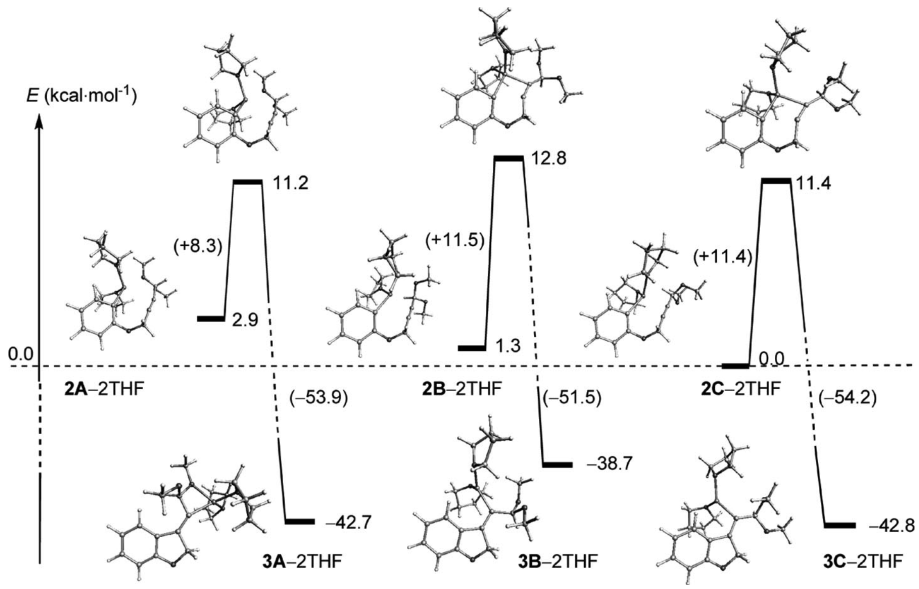
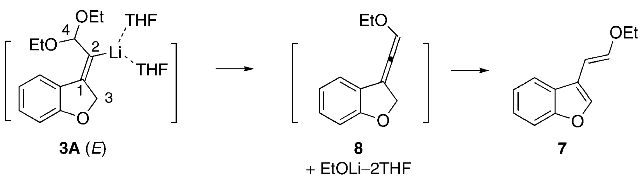


Figure 1. Overall energy characteristics of the three cyclization routes A (left), B (middle), and C (right).



Scheme 2. Original mechanism for the cyclization step, as proposed in ref.[1a].

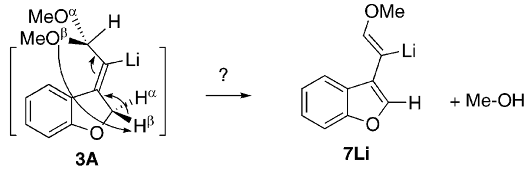
The β-elimination of a lithium alkoxide from a substituted vinyllithium is known to be difficult,[7] but examples of such a phenomenon have been observed before.[8] The resulting exocyclic allene **8** was expected to rearomatize spontaneously into benzofuran **7** by hydrogen migration (Scheme 2).

The calculations started with optimized **3A**–2THF. A progressive shortening of the Li–O_{acetal} distance led first to a more stable conformer **3Aa**, which exhibits different orientations of the acetal and the coordinating THF molecules (Figure 2). After reoptimization, the Li–O distances changed from 2.03/3.19 Å in **3A** to 2.00/3.72 Å in **3Aa**, but no elimination was observed along this reaction coordinate. Restarting from **3Aa**, the potential energy surface was explored by straightening the C1–C2–C4 angle as it proceeds towards the allene. This time, the system passed through a transition state lying more than 15 kcal mol^{-1} above the starting point followed by the elimination of disolvated lithium methoxide and afforded the expected allene **8** (Figure 2). However, these products are less stable than the starting material by about +2.6 kcal mol^{-1} with respect to **3Aa** and +0.7 kcal mol^{-1} with respect to **3A**. Basis-set effects (in particular diffuse functions) were evaluated for the species in Figure 2 by performing single-point calculations using the 6-31+G** basis set.[9] At this higher computational level, the same reaction profile was obtained (the barrier height and reaction energies are modified by about ±0.4 kcal mol^{-1}).

These figures, as well as the relatively high activation barrier, give little credit to a spontaneous transformation in this direction. We thus had to design a different mechanism to account for the results of the experiments.

Elimination of Methanol by Sigmatropic Rearrangement of 3A–C

A sigmatropic rearrangement involving one of the methoxy groups and one of the two protons H^{α} and H^{β} located on the five-membered heterocycle offered an alternative solution. This concerted process would lead to the elimination of a methanol instead of a lithium methoxide and would provide the lithiated **7Li** instead of the diene **7** (Scheme 3). Clearly, the methanol released would ultimately transfer its OH proton and convert **7Li** into **7** plus lithium methoxide.



Scheme 3.

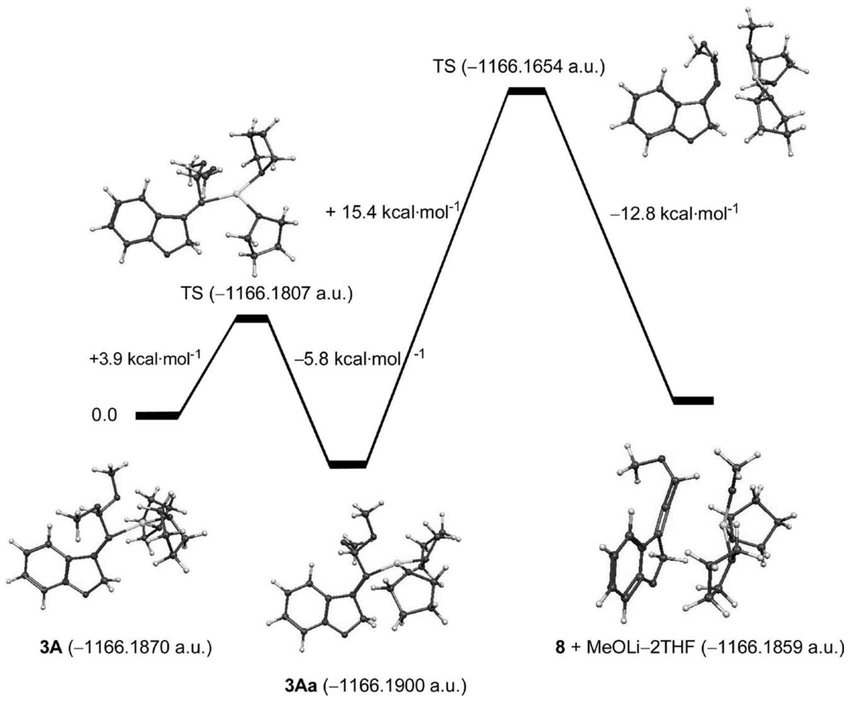


Figure 2. Conversion of **3A** into conformer **3Aa** and then into allene **8** upon straightening of the C1–C2–C4 angle using the 6-31G** basis set.

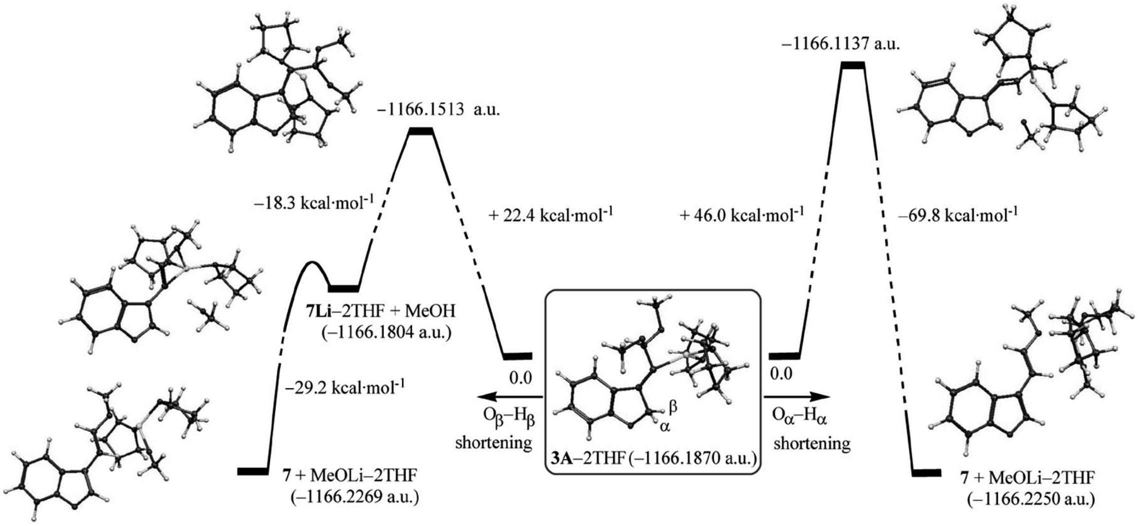


Figure 3. Conversion of **3A** into **7** upon shortening of O^{β}–H^{β} (left) or O^{α}–H^{α} (right).

Interestingly, when the O_{acetal}–H distance is shortened, the final product **7** is always obtained, but through high-lying TSs (Figure 3): +22 and +46 kcal mol^{-1} for H^{β} and H^{α}, respectively. These barriers are not compatible with rapid reactions at low temperatures. Note that depending on which couple, O^{α}–H^{α} or O^{β}–H^{β}, is concerned, the system passes directly to **7** (Figure 3, right) or requires a separate step for the reprotonation of **7Li** by the molecule of methanol released (Figure 3, left). In the latter case, the proton transfer is associated with a small final barrier (value not determined).

Clearly, the *E* configuration of the olefin in **3Aa** is not very favorable to the O_{acetal}–H interaction. To probe a possible influence of the stereochemistry of the olefin on the mechanism of elimination, we considered the two *Z* conformers **3B** and **3C**. It could actually be conceived that **3A** isomerizes into **3B** or **3C** before the elimination, even if the acetal moiety is not supposed to act as a strongly stabilizing group for the vinyllithium.[6]

The conformer of **3B** resulting directly from the carbolithiation step, labeled **3Ba**, was used to start the PES and then QST3 computations (Figure 4). Two different reaction coordinates were considered for the "concerted" elimination/deprotonation process. The first one (O^{β}–H^{β} shortening) yielded a potential energy surface that passes through a low-lying TS **3Bb** (2.0 kcal mol^{-1}, Figure 4) and reached a stable local minimum **3Bc**. This latter is a highly distorted vinyllithium that differs from the starting point by the rotation of two methoxy groups (the lithium changing from a tricoordinate to a tetracoordinate state) and by the C1–C2–Li angle (117.8 to 152.0 ° with $d_{C2–Li}$ = 2.1 Å). At this point, the O^{β}–H^{β} bond length is 2.7 Å. Further shortening of this distance led to a second TS **3Bd** lying 10.7 kcal mol^{-1} higher than **3Bc**, that is, 1.6 kcal mol^{-1} higher than **3Bb**. Therefore, this second stage is the real limiting step of the reaction, about 3.6 kcal mol^{-1} above **3Ba**. The resulting bimolecular system consists of a methanol molecule in interaction with a roughly unchanged vinyllithium (C1–C2–Li = 158.1° and $d_{C2–Li}$ = 2.1 Å). The almost perfect O–H–C alignment (OHC = 174.9°) suggests that **3Bd** resembles the TS for the oxygen-to-carbon proton transfer step[10] despite the relatively atypical O–H and C2–H distances (0.98 and 2.2 Å, respectively).[11] Thus, in the case of the *Z* olefin **3B**, the ultimate part of the cascade can be initiated by the elimination of a methoxide group positioned close to an allylic proton of the dihydrofuran ring. The MeO group then shuttles the proton to the newly formed enol ether double bond in the absence of any intermediate TS. At this stage, the two double bonds are located as in the final 3-vinylbenzofuran ($d_{C1–C2}$ = 1.46 Å, $d_{C1–C3}$ = 1.37 Å, $d_{C2–C4}$ = 1.33 Å, C1–C2–C4 116.3°, C3–C1–C2–C4 175.5°). Overall, this part of the reaction corresponds to the expected *anti* elimination of a lithium methoxide and occurs in a "desynchronized" mode.

Finally, optimization leads to the expected *E* isomer of the 3-vinylbenzofuran **7** coordinated to a lithium methoxide and two THF molecules. A large energy gain (–20.5 kcal mol^{-1} with respect to **3Bc**) is associated with this transformation, priming the aromatization of the heterocycle. Note that the whole sequence taking place after cyclization is more or less concerted. Note also that obtention of (*E*)-**7** at the end of this route opens up the possibility of an overall mechanism in which **3A** would first isomerize to **3B**, through an *E* → *Z* vinyllithium pathway,[6] and then transform into **7** through a low (3.6 kcal mol^{-1}) barrier.

A route based on progressive O^{α}–H^{α} shortening was also explored. It led to the same product **7** through two high-lying intermediates (not represented).

The other *Z* conformer (**3C**) was also considered. In this case, the PES and then QST3 computations were undertaken on **3Ca** (Figure 5). These calculations showed that the lowest-energy pathway implied an O^{α}–H^{α} shortening this time. A simple potential energy surface was obtained showing a single TS along the pathway (**3Cb**, lying

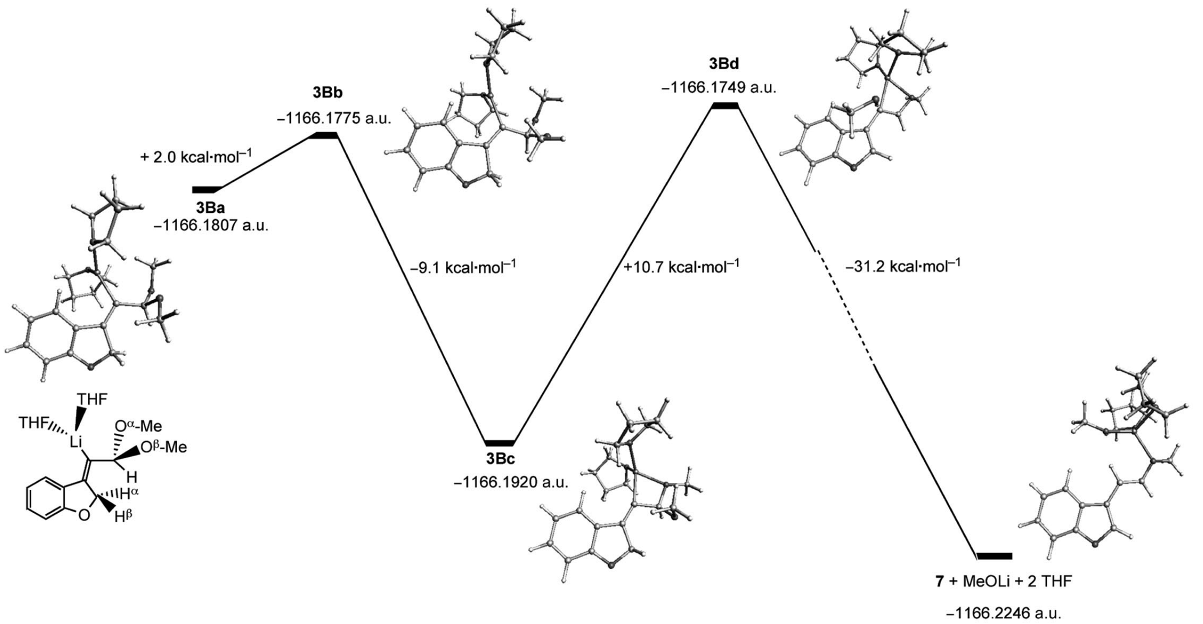


Figure 4. Energy profile for the elimination/proton transfer in the solvated intermediate **3B**.

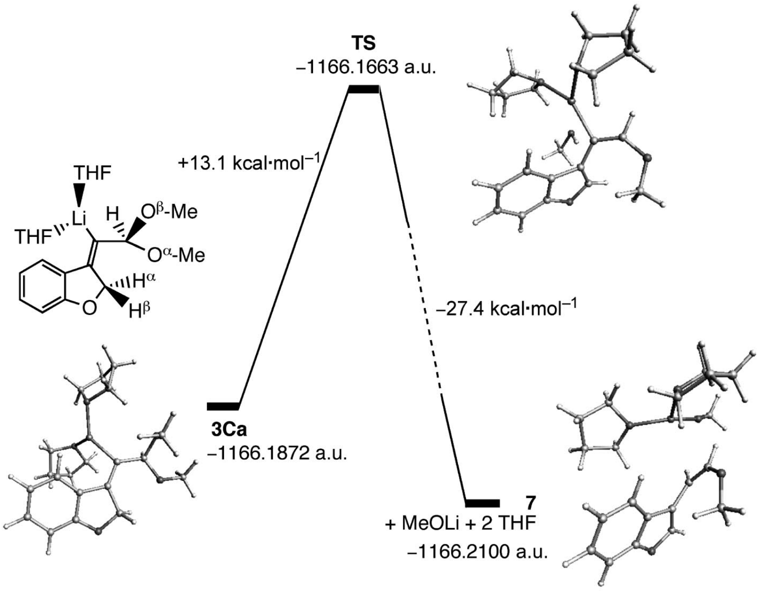


Figure 5. Energy profile for the elimination/proton transfer in the intermediate **3C**.

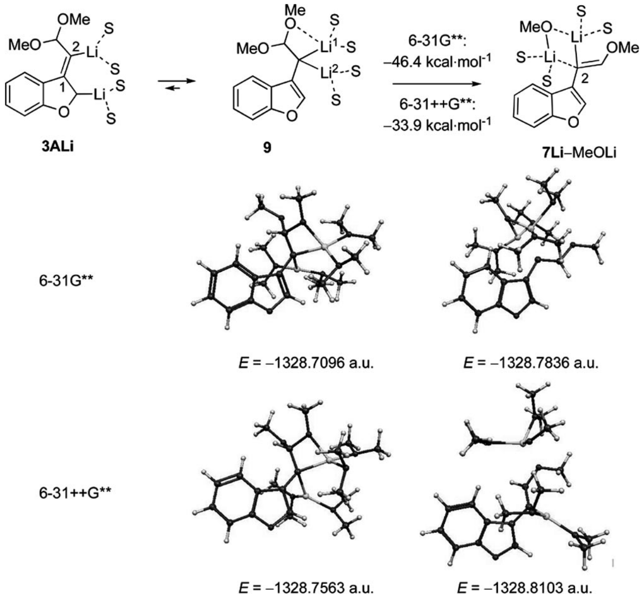
13.1 kcal mol^{-1} above **3Ca**) in which, as above, rearrangement has occurred and the newly formed methanol molecule occupies a position compatible with the final oxygen-to-carbon proton transfer. Again, a large –27.4 kcal mol^{-1} (with respect to the TS) energy gain is associated with the final aromatization of the heterocycle, but the optimization led to the never-observed *Z* isomer of the 3-vinylbenzofuran **7** coordinated to lithium methoxide and two molecules of THF. We were unable to find another pathway connecting **3C** to (*E*)-**7**.

Therefore a mechanism relying on the sigmatropic elimination of methanol seems to be ruled out for the realistic isomer **3A**.

Elimination of Lithium Alkoxide from the Dilithiated Intermediate 3ALi

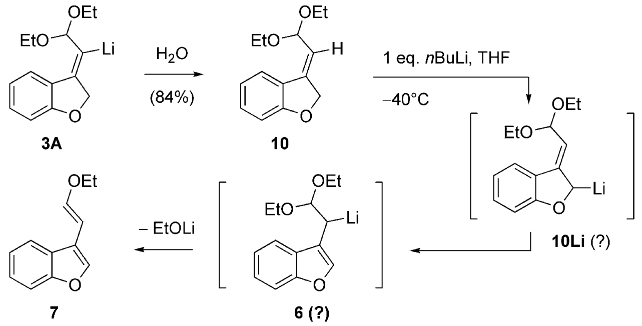
The 2 equiv. of *n*-butyllithium required for the reaction to proceed (Scheme 1)[1] caught our attention. Under these conditions, the somewhat acidic protons[12] of the five-membered ring in **3A**, which are allylic and α to the oxygen atom, could be abstracted, providing a dilithiated entity. We thus pursued our computations using dilithiated **3ALi** as a putative intermediate.[13]

To maintain each lithium cation in a comparable surrounding, the discrete solvation of this bimetallic molecule now required four solvent molecules. This led us to replace the THF molecules used above by dimethyl ether to keep the system a reasonable size. Several starting points have been considered in which the acetal moiety was rotated or the Hα/Hβ atoms were selectively removed. Most situations led spontaneously, by lithiotropy, to the *gem*-dilithiated entity **9** (in which C2–Li1 = C2–Li2 2.06 Å and Li1–Li2 3.39 Å), which does not undergo elimination and is a thermodynamic dead-end (the most stable conformer of **9** is displayed in Scheme 4). However, in one case, the product **7Li**, featuring the expected *E* lateral double bond, was obtained directly without any activation barrier. In fact, **7Li** is obtained as a mixed aggregate with the eliminated lithium methoxide. Its structure features a slightly distorted Li–O–Li–C2 parallelogram ($d_{\text{Li–C2}}$ = 2.298 and 2.184 Å, with dihedral angles ≈ 19°), comparable to those obtained for other mixed aggregates of vinyllithium (Scheme 4).[14] At a higher computational level (6-31++G**), the same trends are conserved, except for the mixed aggregate, which splits into its components. Note that with both basis sets, this route is largely favored in terms of energy.



Scheme 4. Evolution of the dilithiated intermediate **3ALi** by lithiotropy (leading to **9**), followed by elimination (affording **7Li**–MeOLi).

Thus, dilithiated intermediate **3ALi** seems to be able to account for the observed elimination from **3A** and leads to the expected benzofuran without any activation barrier after the deprotonation. This result can explain why an excess of *n*-butyllithium is required to complete the reaction.[1c] To check this mechanism, we examined the separate deprotonation of the *E* intermediate **10**. Experimentally, quenching **3A** with water[1b,2] provided (*E*)-**10**, which was in turn treated with exactly 1 equiv. of *n*BuLi at –40 °C (Scheme 5). The expected diene **7** was recovered in 65% yield, again as the pure *E* isomer. It is worth underlining that i) treating **10** with 1 equiv. *n*BuLi at –78 °C led to no reaction unless 1 equiv. HMPA was added to the medium (**7** was isolated in this case in 67% yield) and ii) treating **3A** directly with 1 equiv. of a stronger base such as *t*BuLi at –78 °C provided **7** in 58% yield. These experimental data, perfectly in line with our own previous results,[12] suggest that the actual p*K* values of the protons noted α and β in Figure 5 are in the range 40–45.



Scheme 5.

From a theoretical point of view, we assumed, for the reasons presented above,[12] that the primary product is **10Li**. This starting allylic carbanion rearranged without an activation barrier into its isomer **6**. Note that **6** is also the product of the carbolithiation of allene **5** (Scheme 1). This local minimum then undergoes a β-elimination of lithium methoxide. To the best of our knowledge the mechanism of this well-known transformation[3] has not been examined by theoretical means. A paper by Tonachini and co-workers deserves to be highlighted in this context because it presents a HF/MP2 study of the stereocontrolled deprotonation of crotonaldehyde dimethyl acetal by a bimetallic superbase.[15] The resulting β-lithioacetal is very similar to the corresponding fragment in **6**. However, the final elimination of lithium or potassium methoxide was not considered in this paper.

This part of the calculations began with a preoptimization of **6**. In particular, the rotation of the acetal group was systematically investigated. Two supplementary local minima were identified corresponding to a rotation of 120 and 240° around the C2–C4 bond. For these three conformers, the elimination was triggered by lengthening the two C–O_{acetal} bonds successively. The results showed that the conformer represented in Figure 6 (left) was more stable than the others by at least 5 kcal mol⁻¹. On lengthening the C–O_{acetal} bond *anti* to the lithium, the system passed through a very low-lying transition state (+0.9 kcal mol⁻¹) to a final complex consisting of the product **7** in interaction with disolvated lithium methoxide. The overall transformation is exothermic by 10.7 kcal mol⁻¹ and the configuration of the exocyclic double bond is *E*, as observed experimentally. Stretching the C–O_{acetal} bond involving the oxygen *syn* to the lithium led to the same product. However, the corresponding TS (not represented) is found about 5.3 kcal mol⁻¹ above the starting point. This significant energy difference suggests that, in the presence of two molecules of THF, the *anti* elimination of lithium methoxide will be favored over the *syn* elimination. Experimentally, the stereoselectivity of the elimination is not total in this case (*E*/*Z* = 86:14, Scheme 1). With the same reaction coordinates, the other conformers of **6** all led to **7** (*E* or *Z*), but through barriers >4 kcal mol^{-1}.

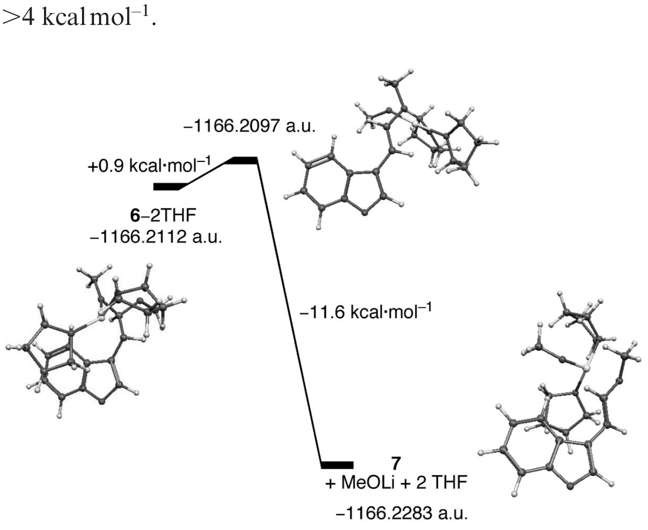


Figure 6. Energy profile of the elimination of MeOLi from the disolvated intermediate **6**.

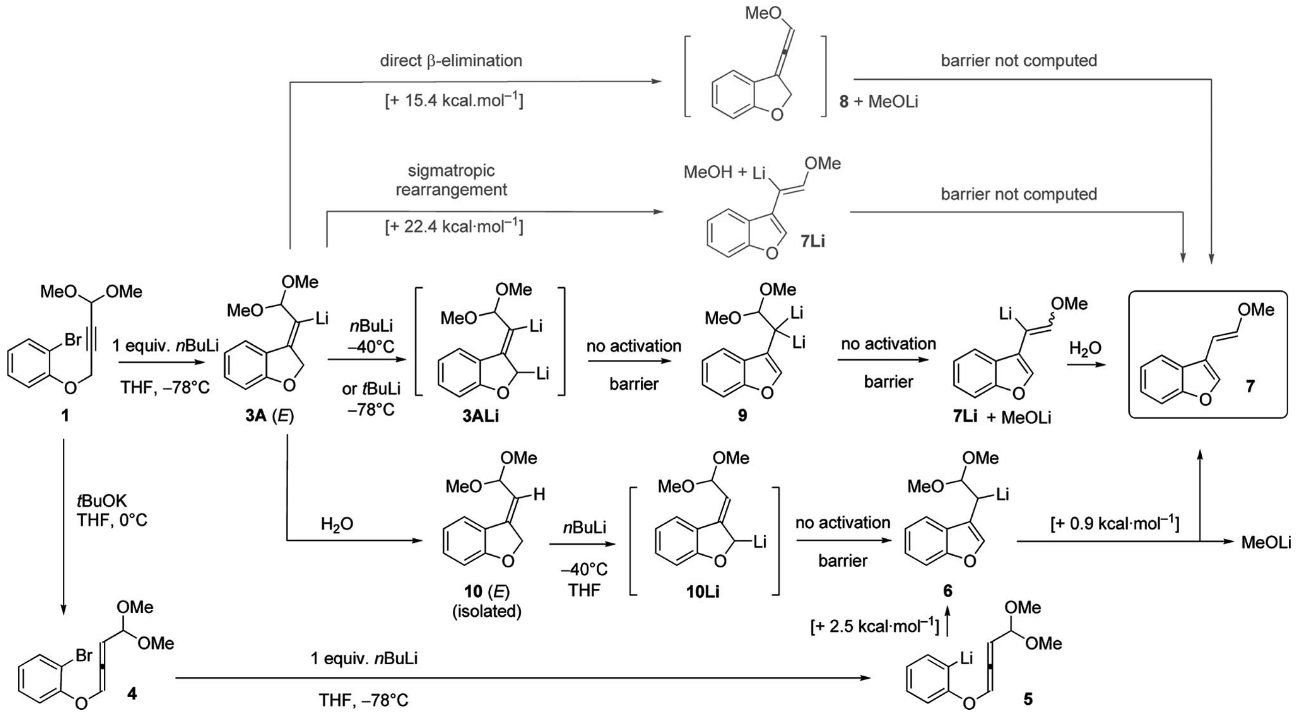
Note that the final part of the transformation of allene **5** into benzofuran **7** passes through the same intermediate **6** (Scheme 1). Thus, the very low activation barriers found for both the cyclization (**5** → **6**, $E^{\ddagger}$ = 2.5 kcal mol^{-1}) and the elimination step (**6** → **7**, $E^{\ddagger}$ = 0.9 kcal mol^{-1}) give an excellent account of the experimental results, which showed that **4** in THF cyclizes directly to **7** in very good yields and stereoselectivity, even at a low temperature (–78 °C).

Conclusions

This study of the transformation of an intermediate 3-vinylidene-2,3-dihydrobenzofuran **3** into 3-vinylbenzofuran **7** by elimination of lithium ethoxide (methoxide) shows that the mechanisms involved are highly dependent on the configuration and conformation of the exocyclic double bond.

The various possible routes for the realistic intermediate (*E*)-**3A** are depicted in Scheme 6. Besides the direct β-elimination route or the sigmatropic rearrangement (in grey), the elimination presenting the lowest activation energy requires an extra deprotonation of the heterocyclic nucleus (and therefore an excess of *n*-butyllithium, as noted experimentally). The resulting *gem*-dilithio intermediate **9** undergoes a spontaneous *syn* elimination and leads to the deprotonated version of the expected product, (*E*)-**7Li**, plus lithium methoxide in the absence of any activation barrier. To further support this hypothesis, we have shown experimentally that the quenching of **3A** with water (Scheme 5) provides an intermediate dihydrobenzofuran **10**. Its deprotonation in a separate step by *n*BuLi affords the diene (*E*)-**7** in yields of 58–67%. DFT calculations suggest that the likely **10Li** primary product is transformed into **6** (which is also the product of the carbolithiation of lithioallene **5**). The more stable conformer of **6** undergoes an extremely easy *anti* β-elimination (through a 0.9 kcal mol^{-1} barrier).

The two "virtual" *Z* vinyllithiums **3B** and **3C** have also been considered. We have shown that a sigmatropic rearrangement could trigger the elimination of an intermediate molecule of methanol, which acts as a shuttle to transfer



Scheme 6. Pathways for the transformation of **1** into 3-vinylbenzofuran **7**. Note that **3ALi** and **10Li** are not local minima.

one proton from the heterocycle to the vinyl position in a separate step. Interestingly, **3B** gives the "real" (*E*)-**7** whereas **3C** leads to the unobserved (*Z*)-**7**.

Regarding the *syn* or *anti* selectivity of the β-elimination of lithium alkoxides by an E1cB mechanism, our results suggest that this problem is relatively meaningless. Indeed, the vinyl or alkyllithium intermediates exhibit a strongly ionic character. Thus, the precise location of the lithium cation is largely dependent on the surrounding coordinations (intramolecular, including the departing alkoxy group, and solvents). The "carbanion" lone-pair, which is a well-localized entity, is likely to provide a more reliable definition of a *syn* or *anti* β-elimination. An Electron Localization Function (ELF) analysis,[16] which is likely to provide a convenient access to this information, is currently being evaluated.

The above data suggest that the elimination of lithium methoxide implies low-energy barriers for sp^3-lithiated carbon atoms (as in **6** or **9**) and much higher ones when an sp^2 carbon atom is concerned (as in **3A**). This is in good accord with experimental results showing that vinyllithium acetals do not easily undergo elimination of lithium alkoxide.[7] In the sp^3 case, the energy barrier seems to be about 10 times smaller than in the sp^2 case (0.9 vs. 10–15 kcal mol^{-1}). The energy range for the sp^2 case remain sufficiently low for there to be a chance that the reaction will occur under specific conditions (of salts, solvents, temperature), also in agreement with other experimental data.[8] Note that these values must be regarded with caution because the validity of our static solvation model may be questionable. However, the origin of the very large difference between the sp^2/sp^3 systems remains unknown and will be detailed in a forthcoming article.

Experimental Section

General Considerations: THF was dried with sodium/benzophenone. All reagents were of reagent grade and were used as such or distilled prior to use. Reactions were monitored by TLC carried out on 0.25 mm E. silica gel coated aluminium plates (60 F254) using UV light for visualization and 7% ethanolic phosphomolybdic acid and heat as developing agents or by GC with a 24-m HP methyl silicon capillary column. E. silica gel (60, particle size 0.04–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded at room temperature at 300 and 75 MHz, respectively, and calibrated by using residual undeuteriated solvent as an internal reference. The solvent used was deuteriochloroform or deuteriobenzene. The mass spectra were obtained under electron impact (EI) conditions at an ionizing potential of 70 eV.

(*E*)-3-(2-Ethoxyvinyl)benzofuran (7):[1a] A solution of *n*-butyllithium (2.05 M in hexane, 0.50 mL, 1.02 equiv., 1.02 mmol) was added to a solution of the dihydrobenzofuran **10** (0.234 g, 1.0 mmol) in anhydrous THF (5 mL) at –78 °C under argon. The temperature was allowed to rise progressively until –40 °C. After 15 min of stirring, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The combined organic phases were dried with anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (5% ethyl acetate in cyclohexane) to provide **7** as a single *E* isomer (0.123 g, 65%) as a yellow oil.

Acknowledgments

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