DOI: 10.1002/chem.200701834

A Case of *anti* Carbolithiation of Alkynes Resulting from Intramolecular Lithium Coordination

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Abstract: The mechanism of the intramolecular carbolithiation of lithiated propargylic ether **2** has been investigated both experimentally and theoretically. The results show that the action of one equivalent of *n*-butyllithium on **1** is sufficient to trigger halogen–lithium exchange and the subsequent heterocyclization step. Interestingly, the reaction stops at the stage of dihydrobenzofuran **6**; no spontaneous elimination of lithium ethylate was observed. The fact that the *E* configuration of this adduct was exclusively produced suggests that the reaction proceeds by following an unprecedented *anti* addition on the alkyne. According to DFT calculations, this unexpected outcome is related to the intramolecular coordination of the lithium by one oxygen atom of the terminal acetal appendage: the O–Li interaction, which persists all along the ring-closure process, drives the cation to the *E* site of the final olefin. The calculations also show that in the absence of this coordination (as in conformers B and C of acetal **2**), the *Z* olefin that results from a classical *syn* addition of the aryllithium should be obtained. The experiments were repeated with allene **1d**. In this case, one equivalent of *n*-butyllithium suffices to trigger not only the exchange and the cyclization, but also the final elimination of lithium ethoxide. The DFT results indicate that the intramolecular addition of the original aryllithium on the central carbon atom of the allene **2b** yields the expected benzofuran skeleton **3b**, which bears a lithiated lateral chain at the 3-position. Both cyclizations go through low-lying transition states, as is expected for rapid reactions at low temperature.

Keywords: alkynes · carbolithiation · cyclization · density functional calculations · stereoselectivity

Introduction

A previous experimental study showed that the halogen–lithium exchange that takes place at low temperature on propargylic acetal **1**, or its allenyl isomer **1b**, triggers a heterocyclization and yields 3-vinylbenzofurane **5** in good yield and with good-to-total *E* control of the lateral double bond.[1] It was proposed in the case of **1** that this reaction relies on an anionic cascade that begins with a 5-*exo-dig* intramolecular nucleophilic addition of aryllithium **2** on the triple bond. The vinyllithium **3**, which is expected to result from a *syn* addition,[2] would then undergo a β-elimination of lithium ethylate to provide the exocyclic allene **4**. Finally, this latter product can isomerize into the 3-vinylbenzofurane **5** (Scheme 1). This rapid reaction prohibits the characterization of the intermediates and it explains the speculative character of the proposed mechanism. The details of the cyclization process for allene **2b** were not discussed. An intramolecular addition of the aryllithium on the central carbon of the allenic appendage, directly followed by an elimination of lithium ethoxide was expected (Scheme 1).

We thus decided to undertake an experimental and theoretical study to separately detail the cyclization and elimination steps, in view of the determination of the structure of the different intermediates, the activation energies, and the origin of the *E* control over the double bond formation. Beyond the particular case of this heterocyclization, the car-

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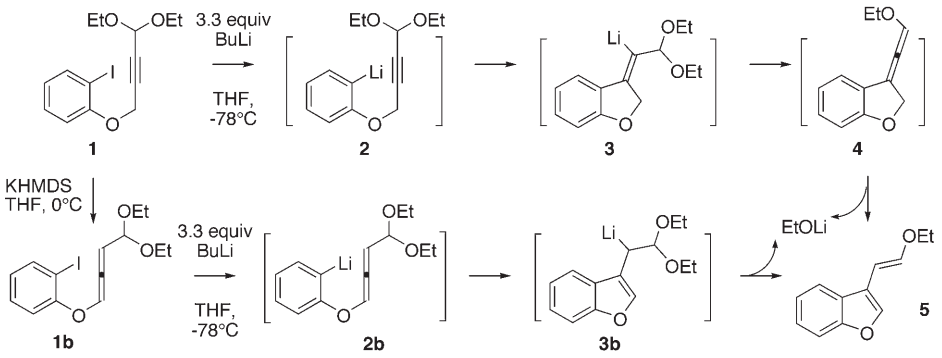
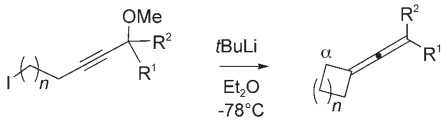


Scheme 1. Putative mechanisms for the anionic heterocyclization of propargylic **1** or allenic **1b** acetal in benzofuran **5**.

bometallation reaction is the object of a sustained interest, and important papers and reviews that describe its applications in synthesis have been published recently.[3]

Let us first discuss the case of alkyne **1**. Intramolecular carbolithiations of triple bonds that are associated with β-eliminations have been observed in other situations. In particular, Bailey and Aspris have reported a comparable phenomenon with propargylic ethers (Scheme 2).[4] In this case,



Scheme 2. Anionic heterocyclization of propargylic ethers in exocyclic allenes.[4] KHMDS = potassium hexamethyl disilazide.

however, no migration of the double bond was observed, and exocyclic allenes were efficiently recovered. This intriguing difference in behavior, which might be related to the mobility of the α proton, to the *syn*/*anti* character of the lithium methoxide elimination, or to the recovery of the aromaticity upon rearrangement was also worth investigating.

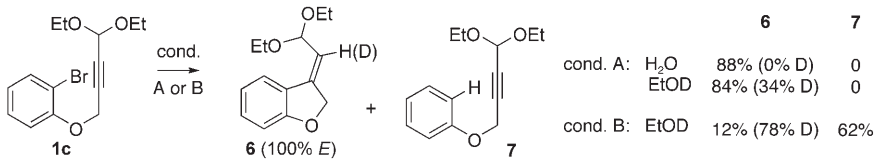
The analysis of the cascade that is reported in Scheme 1 has been restricted to the cyclization, elimination, and proton-transfer steps. The theory underlying the halogen–lithium exchange process has been extensively examined recently,[5] and is not considered in this paper. In contrast, theoretical studies that are devoted to the carbometallation reaction are relatively scarce. Two early ab initio Hartree–Fock (HF) studies that were published by Nakamura and colleagues underlined the importance of the metal–multiple bond interaction in the course of the reaction between methyllithium and cyclopropene[6] or acetylene.[7] In parallel, papers by Bailey and co-workers described the key intermediates along the intramolecular cyclization of 5-hexen-1-yllithium (at the HF level)[8] and of a styrene derivative (at the DFT-B3LYP level).[9] In both cases, a double bond–lithium interaction is shown to play an important role in the organization of the transition state, at least in the absence of explicit solvent molecules.

Our own study was first conducted on the aryllithium **2**, which was unsolvated and then solvated by two discrete solvent molecules (diethyl ether or THF). The case of solvated allenyllithium **2b** was considered separately. In this first paper, we focus on the details of the carbolithiation step, the elimination is fully described in a paper that is currently in preparation.

Computational details: The size of the systems that are considered led us to restrict our computations to the DFT level. The B3P86 functional and 6–31G** basis set, which behave satisfactorily in related situations[10] were retained. All the calculations were performed by using the Jaguar 5.0 software.[11] The energy given for the minima of the solvated systems include the zero-point energy corrections (ZPE). The transition states were obtained by relaxed potential energy surface (PES) scans, then fully optimized and characterized by frequency calculations. Our previous results in the field[10a] suggest that the basis set superposition error (BSSE) can be ignored in these cases. The electron localization function (ELF) relies on a topological approach of the chemical bond that is described in original articles by Savin, Silvi et al.[12] We[13] and others[14] have shown in previous works that this tool can help to determine the bonding scheme in systems that present ill-defined valences, such as noncovalent organolithium aggregates. Therefore, we thought that such an electron distribution, which implicitly takes into account the superposition of the resonance forms could provide useful information on the electron reorganization that is induced by the rearrangement of the intermediates. In the ELF figures presented hereafter, the color code characterizes the cores (magenta), the monosynaptic (red) and disynaptic (green) valence basins, and the hydrogens (blue).

Results and Discussion

Experimental investigation: We first checked experimentally if a single equivalent of *n*-butyllithium could prompt the heterocyclization and give access to the putative vinyllithium intermediate. The original experiments in THF had clearly shown that a significant excess of *n*-butyllithium (3.3 equiv) was required to obtain benzofuran **5** in decent yields. With respect to the previous procedure, the iodoaryl **1** was conveniently replaced by the more stable bromoaryl **1c**. This latter compound was treated with exactly one equivalent of *n*-butyllithium at −78 °C in THF (Scheme 3). To our delight, quenching the medium with water led to the ethylidenic dihydrobenzofuran **6** in 88% yield.[15] The ^{1}H NMR spectrum of this compound, when recorded in



Scheme 3. Cyclization of propargylic ether **1c** under the influence of *n*BuLi. Conditions A: i) 1.0 equiv *n*BuLi/THF, −78 °C; ii) H_2O or EtOD. Conditions B: i) 1.0 equiv *n*BuLi/Et_2O, −78 °C; ii) EtOD.

$CDCl_3$, was relatively puzzling. The fortuitous superposition of the vinylic signals and that of the acetal explains that **6** could easily be mistaken for aromatic **7**, and its unambiguous identification required the recording of the spectrum in [D_6]benzene. NOE experiments that were run in this solvent showed that **6** was obtained as the *E* isomer exclusively, which is a result that was completely unexpected for the carbolithiation of an alkyne.[16] Isolating **6** also demonstrated that the intermediate **3** (*E*, Scheme 1) was not necessarily undergoing a β-elimination step in THF. This contrasts with our previous results that were obtained with lithioallenes[17] and is in complete discrepancy with the mechanism that is proposed in Scheme 1.

Attempts to treat **3** with various electrophiles (PhCHO, MeI, $PhCH_2Br$, TMSCl) have remained unsuccessful, whereas quenching the medium with EtOD led to 34% deuterated **6**. We thought that this mediocre reactivity could be due to an early protonation of **3** by an unexpected source of protons in the medium. We thus tried to replace one equivalent of *n*-butyllithium by two equivalents of *tert*-butyllithium to avoid the in-situ formation of *n*-butylbromide;[18] however, the chemical yield and the deuteration level remained practically unchanged. Repeating the experiment in freshly distilled [D_8]THF instead of regular THF did not trigger a deuteration; this excludes the participation of the solvent. This low reactivity could be related to the formation of bulky and relatively inert aggregates of **3** in THF. Vinyllithium is known to form tetramers and dimers in an 8:1 ratio at −90 °C in this solvent,[19] and this compact organization is most probably reinforced in the case of **3** by the intramolecular coordination that is imposed by the oxygen atoms of the acetal appendage. However, the literature suggests that vinyllithiums that result from the carbolithiation of a triple bond could be efficiently trapped by electrophiles.[20] We thus tried to adapt our conditions to those that are described in the corresponding papers, but disappointing results were obtained when warming the reaction medium and when adding one equivalent (with respect to *n*-butyllithium) of hexamethylphosphoramide (HMPA) or lithium bromide to the reagents (good yields, low deuteration). Repeating the deuteration experiment in diethyl ether at −78 °C led to dihydrobenzofuran **6** in only 12% yield (which was not improved by using two equivalents of *n*-butyllithium), but with 78% label incorporation (Scheme 3). The rest consisted of ether **7**, of which the labeling ratio was not determined. Note that the latter yield could be enhanced by increasing the temperature (up to −50 °C or even room temperature); however, the product was contaminated by several unidentified side products, even when quenching the reaction after a few minutes at −50 °C.

The fact that **6** was recovered as the geometrically pure *E* isomer remained very surprising because the acetal group, in contrast to a silyl or phenyl moiety,[21] can hardly be considered to be a stabilizing entity that is capable of triggering the post-cyclization isomerization of a double bond. Furthermore, the isomerizations that have been reported in literature occurred at room temperature, whereas the experiment that is reported here was maintained at −78 °C until the final quench. The origin of this puzzling phenomenon, which suggests a possible *anti* carbolithiation of the alkyne is difficult to determine on experimental bases. We thus decided to pursue the investigation by theoretical means and we were nicely rewarded.

Theoretical examination of the unsolvated propargylic acetal 2: Because of the relatively large size of the system and the long computational runs that are often associated with the shallow potential surfaces of the organolithium species, the study was first conducted without taking the solvent into account, either implicitly by using a continuum technique[22] or explicitly by taking into account a discrete number of solvent molecules to simulate the solvation first shell.[23] The optimization of the starting aryllithium derivative was performed first. Two local minima were identified, one of which was more stable by 12.8 kcal mol^{-1} (Figure 1). The interconversion pathway between these conformers was not studied because of this large energy difference. In the more-stable situation, the lithium cation is tricoordinated by C_{Ar}, one of the oxygen atoms of the acetal moiety (d(Li–O_{acetal}) = 2.0 Å), and by the C≡C bond (d(C^1–Li) ≈ 2.40 and d(C^2–Li) ≈ 2.30 Å). The less-stable conformer exhibits a lithium atom that is dicoordinated by C_{Ar} and the oxygen atom of the ether. Note that the more stable arrangement (E = −700.2021 u.a.) also brings the nucleophilic carbon atom, C_{Ar} to within a favorably short distance of the acetylenic carbon atom (3.02 Å). When the distance between C_{Ar} and C^1, which is taken as the reaction coordinate, was shortened, the energy increased, and the system reached a transition state in which the five-membered heterocycle is preformed. At this stage, the lithium cation is coordinated by the aromatic carbon, C^1 and the original oxygen atom. The corresponding activation energy was found to be 3.8 kcal mol^{-1}. Pursuing the C–C bond formation leads to the expected benzofuranic structure that exhibits an exocyclic *E* double bond (d(C^1–C^2) = 1.36 Å), in accord with the experimental data. Interestingly, the lithium cation lies out of the aromatic plane and remains coordinated to the acetal oxygen atom. It was confirmed that this corresponded to a true local minimum (no negative frequency) by performing the calculations with Jaguar 5.0 as well as Gaussian 98.[24] Additionally, a

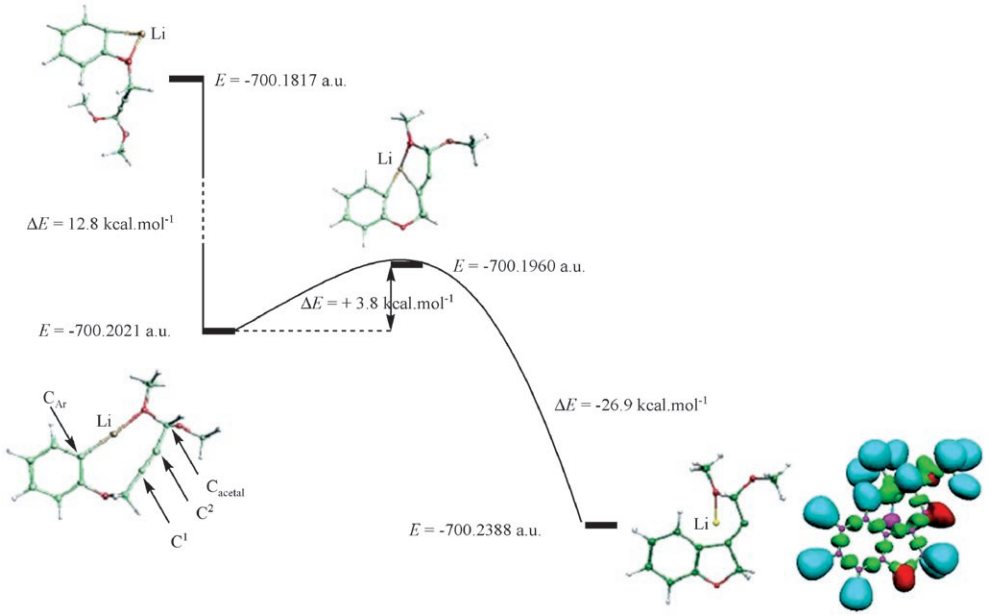


Figure 1. Energy profile for the cyclization of the unsolvated propargylic acetal **2**. The localization domains of the ELF representation corresponds to $\eta(r) = 0.75$.

lone pair that was localized on C^2 and oriented within the aromatic plane *anti* to the newly formed C–C bond could be visualized by resorting to an ELF (see Computational Details) analysis (Figure 1). The highly ionic character of the C–Li bond in vinyllithium[10c] explains this spectacular lack of directionality.[25] Thus, it seems that the O–Li intramolecular coordination keeps the cation out of the vinyl plane, and is responsible for the final *E* configuration of the double bond in **6Li**.

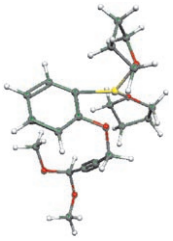
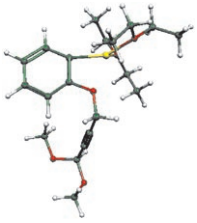
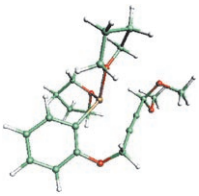
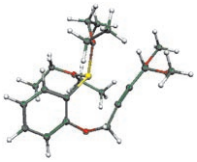
Justifying such surprising results required pursuing our investigation on a model that is as realistic as possible. We thus included the solvent in our calculations because: 1) no transition state that links unsolvated **6Li** to more advanced intermediates along the elimination process could be located and 2) the above results suggest that the lithium coordination can exert a strong influence on the course of the reaction. To avoid possible artifacts, we preferred to incorporate discrete solvent molecules (THF or diethyl ether).[1] In consideration of the experimental results that show that the cyclization is difficult in diethyl ether, we considered the solvation by both THF and diethyl ether to better understand the origin of the detrimental influence of the latter solvent. We did not replace diethyl ether by the smaller dimethyl ether to keep the full steric effect of the ethyl groups.[23a]

Solvated system: effect of the solvent on the orientation of the lateral chain of 2: Our previous experience with the computational treatment of solvated organolithium species prompted us to incorporate explicit solvent molecules rather than to apply the polarizable dielectric field that is imposed by a continuum model.[23b,26] We first considered the influence of the two solvents on the two local minima of **2** that are described above (Figure 1). The solvation of the lithium cation is relatively variable, the tri- and tetracoordinations are most frequently encountered. We privileged a tetracoordination and chose to add two solvent molecules to the system, the other ligands were C_{Ar} or C^2, and either one of the oxygen atoms of the acetal appendage, the oxygen atom of the ether tether, or the triple bond. This led to two families of conformers (folded/unfolded) in each solvent that were independently reoptimized. The results that are presented in Table 1 show that reasoning on the sole conformations cannot account for the observed results: the more stable folded conformer is preferred over the stretched one both in THF and diethyl ether. However, the energy gap between the conformers is five times smaller in diethyl ether, which suggests that the hard-to-cyclize stretched arrangement becomes somewhat competitive in this solvent. This is likely to slow the reaction, as was observed experimentally.

Conformers of propargylic acetal 2 in THF: On the basis of the experimental data, THF was the sole solvent to be considered in the following. The full optimization of the solvated folded conformer of **2** indicated that three local minima that correspond to the three staggered arrangements of the acetal group lie within less than 3 kcal mol^{-1} of each other (Figure 2).

Interestingly, in the overall more stable C conformer that is considered above, the lithium atom does not lie in the phenyl plane but remains connected to the C_{Ar} atom. The coordination sphere is completed by the triple bond and the two THF molecules, and leaves the acetal oxygen atoms in an "*anti*" arrangement. A similar chelation pattern is found for conformer B. In these two situations, the lithium atom is coordinated to the two oxygen atoms of the THF molecules, and undergoes π-binding[27] with the triple bond. Thus, the

Table 1. The DFT-optimized minima of the two conformers of disolvated **2**, their absolute (E), and ZPE-corrected (E_{corr}) energies. The relative energies are given in parenthesis.

THF		Diethyl ether	
conformer	energy	conformer	energy
	$E=-1166.6050$ a.u. ZPE = 310.5 kcal mol^{-1} $E_{corr}=-1166.1102$ a.u (5.5 kcal mol^{-1})		$E=-1169.0979$ a.u. ZPE = 336.4 kcal mol^{-1} $E_{corr}=-1168.5618$ a.u. (1.1 kcal mol^{-1})
unfolded		unfolded	
	$E=-1166.6130$ a.u. ZPE = 310.0 kcal mol^{-1} $E_{corr}=-1166.1190$ a.u. (0.0 kcal mol^{-1})		$E=-1169.0965$ a.u. ZPE = 334.4 kcal mol^{-1} $E_{corr}=-1168.5636$ a.u. (0.0 kcal mol^{-1})
folded		folded	

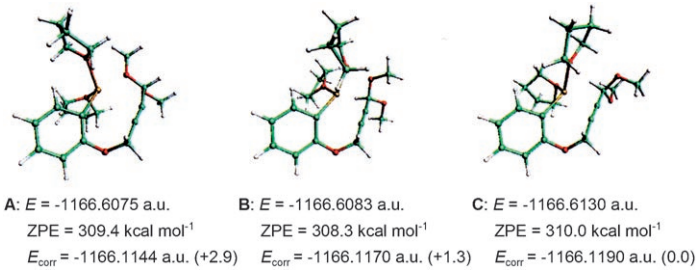


Figure 2. Three conformers of acetal **2** that are solvated by two THF, their absolute (E), ZPE-corrected (E_{corr}) and relative energies (in parenthesis).

energy surfaces (PES). The highest barrier that was located by this technique lies at about 4.4 kcal mol^{-1} above the ground state. This relatively low value suggests that the acetal group rotates almost freely around the propargyl axis, and the interconversion between the conformers cannot be regarded as the limiting step of the reaction. Therefore, the three conformers had to be considered for the rest of the work.

Cyclization of propargylic acetal 2: The study of the cyclization was undertaken according to the approach that is described above for conformers A–C. When the C_{Ar}–C^1 bond length is decreased, the system goes through a transition state in the three cases (checked by frequency calculations) in which the coordination of the lithium atom is only slightly altered: a strong Li–O_{acetal} coordination is observed in situation A, whereas a Li–C^2 "bonding" appears in the transition state of B and C (Figure 3). Comparing the C_{Ar}–C^1 bond

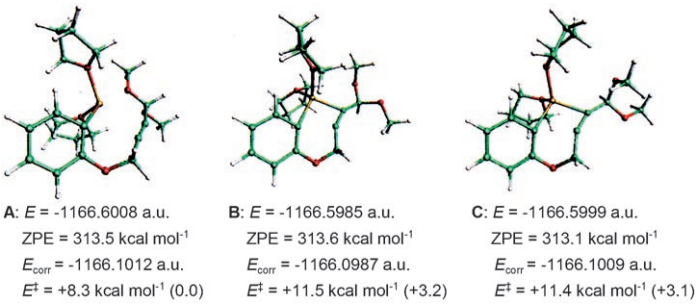


Figure 3. Transition states between conformers of acetal **2** that are solvated by two THF, and cyclized product **3**, the absolute (E) and corrected (E_{corr}) energies, the activation barriers ($E^{\ddagger}$), and the difference between the activation barriers ($\delta E^{\ddagger}$; in parentheses).

Li–O_{acetal} distance is significantly increased with respect to the nonsolvated situation by the introduction of the two THF molecules (d(Li–O_{acetal}) = 3.19 and 3.84 Å in conformer B and C, respectively). In contrast, for conformer A, the Li–O_{acetal} coordination is unchanged (d(Li–O_{acetal}) = 2.16 Å) and the lithium atom is surrounded by three oxygen atoms, and C_{Ar} (d(Li–C^1) = 2.82 Å cannot be considered to be a coordination anymore). The measurement of the dihedral angles shows, however, that the lithium atom is not in a regular tetrahedral surrounding. The zero-point energy (ZPE) calculations that were run for the three conformers A–C led to relatively small values; this reflects the somewhat rigid organization of the molecule. After ZPE correction, the relative order of stability is unaltered, but the energy differences between A, B, and C decrease (Figure 2).

Before considering the reaction profile, we examined the energy barriers that separate the three conformers in an attempt to identify the proper limiting step of the transformation. Thus, a rotation of the C^2–C_{acetal} bond has been imposed on conformer A to scan the corresponding potential

lengths in the three TSs suggests that a relatively early transition state is reached in A, whereas the transition state is later in C and B (d(C_{Ar}–C^1) = 2.74, 2.38, 2.33 Å, respectively). The activation barriers (ca. 8 to 12 kcal mol^{-1}) are significantly higher than in the unsolvated situation (3.8 kcal mol^{-1}). The lowest one is associated with the less-stable conformer A, whereas the barriers for B and C are of comparable heights. This particularity confines the three transitions states in a narrow energy range, and thus the three arrangements are considered in the next step of the study. The ZPE corrections are comparable for the three transition states, and do not change the relative stability order.

Pursuing the potential energy scan to completion led to three structures, which were then fully optimized. As expected, a benzofuran nucleus that featured an exocyclic double bond was obtained in the three cases (Figure 4). Note that A features an *E* double bond (in full agreement with the experimental data, vide supra) whereas conformers B and C exhibit a *Z* double bond. In A, the flexible interactions between the lithium atom and C^2 plus the O_{acetal} atoms keep the cation in a tetracoordinated state and ≈30° outside the plane of the heterocycle and of the double bond (C_{Ar}–C^1–C^2–Li = 211° and C^1–C^2–Li = 148°). Running a ELF analysis shows that the electronic doublet, which is still considered to be a lone pair (red),[10c] is located between the C^2 and the lithium atoms. In both conformers B and C, a similarly atypical vinyllithium moiety is obtained: the metal remains out of the heterocyclic plane (C_{Ar}–C^1–C^2–Li = 346 and 337°, respectively), with C^1–C^2–Li = 118 and 112°, and the lithium atom is tricoordinated. The ELF analysis for B and C confirms these points. Further, the three products lie in a 6.3 kcal mol^{-1} range, which is decreased to 2.7 kcal mol^{-1} when the ZPE is taken into account. Interestingly, this correction changes the relative stability order: it renders the two lowest conformers A and C quasi-isoenergetic. In the three situations A, B, and C, the reaction is similarly exothermic (in the 50 kcal mol^{-1} range).

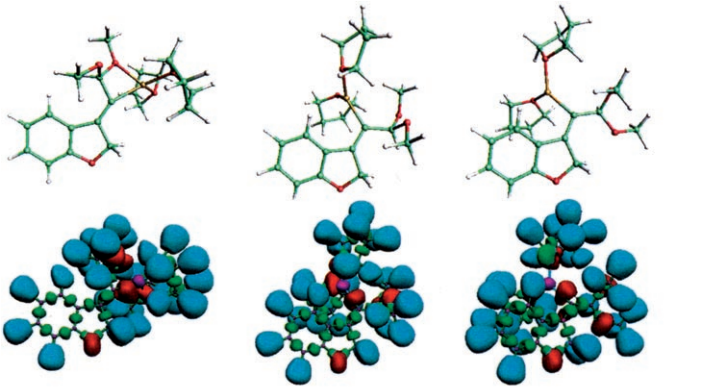


Figure 4. Optimized products **3**, the absolute (*E*), ZPE-corrected (E_{corr}) and condensation energies ($E_{cond} = E^{+} - E_{corr}$), as well as the energy differences between conformers/isomers (δE, in parenthesis). The localization domains of the ELF representation (bottom) correspond to $\eta(r) = 0.75$.

The data that are obtained by the theoretical treatment of the cyclization can be summarized, see Figure 5. This graphical representation demonstrates that the three possibilities remain competitive. However, as mentioned above, only process A affords an *E* vinyllithium, which is in agreement with the experimental observations that are presented below.

The intriguing feature of the cyclization is the *E* selectivity that is associated with the cyclization of A. To get a deeper insight into this process, snapshots of the system during its evolution along the PES, which results from the C_{Ar}–C^1 shortening are provided in Figure 6. Step I shows the situation about 0.1 Å after the TS. It indicates that the d_{CAr-Li} increases and the lithium "slides" more or less parallel to the phenyl plane. The resulting acetal coordination forces

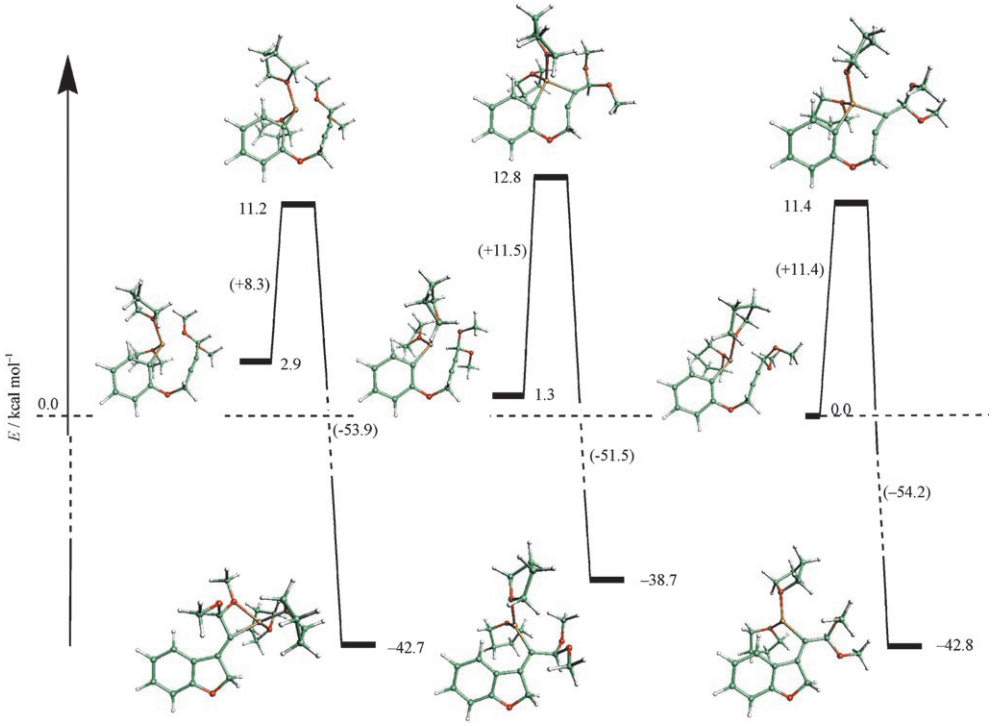


Figure 5. Overall energy characteristics of the three cyclization routes (A left, B middle, C right).

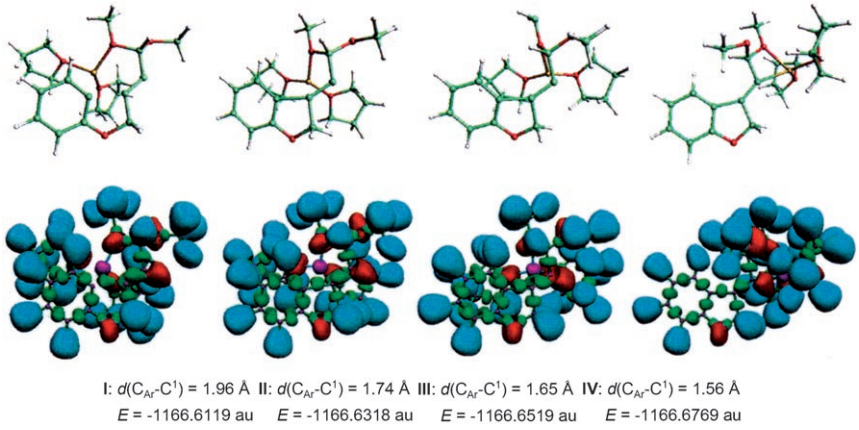


Figure 6. Four snapshots along the PES of the A cyclization process.

the double bond to adopt an *E* configuration, and the lone pair is already localized on the C^2 atom, whereas a valence basin appears between C_{Ar} and C^1. In step II, the C_{Ar}–C^1 bond is reinforced and the lithium atom continues its movement parallel to the newly formed benzofuran nucleus. This goes on during step III, the acetal group pivots to accompany the lithium atom. At step IV, an intermediate that is close to the cyclization product is obtained in which the *E* double bond is formed, and the C^2–Li bond length has reached its final value.

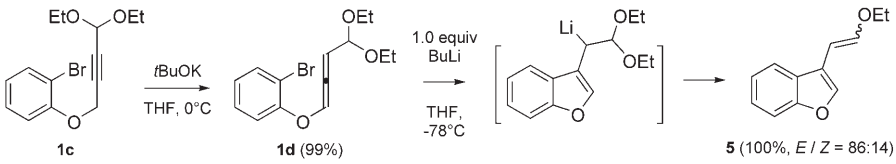
Thus, it seems that the robust Li–O_{acetal} coordination in A controls the configuration of the double bond. Therefore, our calculations suggest that the unprecedented *anti* character of this carbolithiation[2c] can be explained by the strong intramolecular coordination, which derails the reaction from its usual course.

Cyclization of allenyl isomer 1d: The previous study had evidenced the facile cyclization of allene **1b** (Scheme 1) in reaction conditions that were comparable to those that were employed for **1** (Scheme 1). The yield of this step was good (85% instead of 62% for **1**) but the selectivity was slightly diminished (*E*/*Z* = 86:14 instead of 100:0). A complementary experiment was thus performed to check that the cyclization takes place if only one equivalent of *n*-butyllithium is added to the allene. Bromoallene **1d**, which was prepared from **1c** according to a simple and quantitative isomerization procedure was used instead of iodoallene **1b**. When performed at −78 °C in THF, the cyclization reaction led to a quantitative transformation of **1d** into **5** as a 86:14 *E*/*Z* mixture (Scheme 4).

It is noteworthy that **1d** does not require an excess of *n*-butyllithium to trigger the final elimination; this indicates that this step follows a different mechanism.

We first carried out a full optimization of the structure of **2b** (Scheme 1) that was solvated by two explicit molecules of THF. Interestingly, the allenyl lateral chain adopts mainly one conformation (except for meaningless local minima that are due to rotations of the acetal) in which the large distances between the lithium atom and the oxygen atoms of the acetal group forbid all Li–OMe interactions (Li–O = 6.1 and 5.8 Å, Figure 7). When the distance between C_{Ar} and C^1, which was taken as before as the reaction coordinate to scan the PES was shortened, the system reached a transition state for C_{Ar}–C^1 = 3.0 Å. At this stage, the allene undergoes a twisting of the double bonds (the three sp^2 carbon atoms are misaligned, C^2–C^1–C^3 = 167°). The corresponding activation energy was found to be 2.5 kcal mol^{-1}, compared to the 8–12 kcal mol^{-1} that was calculated for the cyclization of **2** (Figure 6). This low barrier can explain the good yields that were obtained experimentally. Pursuing the C–C bond shortening leads to the expected benzofuran **3b**, which bears a lithiated lateral chain at the 3-position (Figure 7). This ring closing is an exothermic process (−48.8 kcal mol^{-1}), which is slightly larger than that calculated for **2**→**3** (−38.7 to −42.8 kcal mol^{-1}).

Note that the lateral chain of benzofuran **3b** is an alkyllithium, whereas it is a vinyllithium in **3**. One can thus



Scheme 4. Cyclization of allene **1d** under the influence of 1.0 equiv of *n*BuLi.

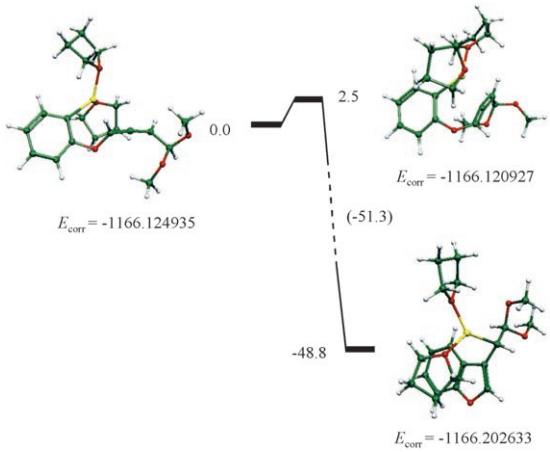


Figure 7. Energy diagram for the cyclization of allene **2b**. E_{corr} refers to the absolute energy of the compounds after ZPE corrections (in a.u.). The relative energies on the diagram are in kcal mol^{-1}.

expect that the mechanism of the final β-elimination will be quite different from that involving **3**. These two routes will be detailed in a forthcoming article.

Conclusion

This paper details the mechanism of the intramolecular carbolithiation of lithiated propargylic ether **2**. The experimental results show that one equivalent of *n*-butyllithium triggers the halogen–lithium exchange and the subsequent heterocyclization step to afford a dihydrobenzofuran nucleus that bears an exocyclic vinyllithium moiety. The NMR spectroscopic study on the adduct has shown that this reaction results from an unprecedented *anti* addition on the alkyne. DFT calculations show that this unexpected characteristic is related to the intramolecular coordination of the lithium atom by one oxygen atom of the terminal acetal appendage. This persisting O–Li interaction is observed all along the cyclization pathway, and drives the cation to the *E* site of the olefin. The calculations show that in absence of this coordination (as in conformers B and C), the *Z* olefin that would result from a classical *syn* addition should be obtained. The experiments were repeated on the allene **1d**. In this case, one equivalent of *n*-butyllithium suffices to trigger the exchange, the cyclization, and the final elimination of lithium ethoxide. The DFT results suggest that the intramolecular addition of the original aryllithium on the central carbon atom of the allene **2b** yields the expected benzofuran skeleton, which bears a lithiated lateral chain at the 3-position that is ready for a β-elimination process. This cyclization goes through a low-lying transition state, as is expected for a rapid reaction at low temperature.

The complete description of the reaction requires a detailed study of the mechanism of the final elimination step. This work is under way on the *E* and *Z* olefins that result from the cyclization of conformers A–C. The results will be reported in due time.

Experimental Section

General consideration: THF and Et_2O were dried from Na/benzophenone. All reagents were of reagent grade and were used as such or distilled prior to use. Reactions were monitored by TLC, which was carried out on 0.25 mm E. silica-gel-coated aluminium plates (60 F254) by using UV light as a visualizing agent, and 7% ethanolic phosphomolybdic acid and heat were used as a developing agent, 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. ^1H and ^{13}C NMR spectra were recorded at room temperature at 300 and 75 MHz respectively, and were calibrated by using residual undeuterated solvent as an internal reference. The solvent was $CDCl_3$ or [D_6]benzene. The mass spectra were obtained under electron impact conditions (EI) at 70 eV ionizing potential.

1-Bromo-2-(4,4-diethoxybut-2-ynyloxy)benzene (1c): Diisopropylazodicarboxylate (10.30 mL, 52 mmol, 1.0 equiv) was added dropwise to a solution of 4,4-diethoxy-but-2-yn-1-ol[1a] (8.21 g, 52 mmol), 2-bromophenol (6.18 mL, 52 mmol, 1.0 equiv), and triphenylphosphine (13.63 g, 52 mmol, 1.0 equiv) in THF (300 mL) at 0°C under argon. The solution was warmed to room temperature, stirred for 3 h and washed by adding 0.4 M NaOH (100 mL). The mixture was diluted by Et_2O (150 mL) and washed again by 0.4 M NaOH solution (2×100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. Pentane (300 mL) was added to the residue to precipitate triphenylphosphine oxide. After filtration, the resulting brown liquid was purified by column chromatography (30% EtOAc in cyclohexane) to give the pure product **1c** (14.97 g, 92%) as a yellow liquid. ^1H NMR ($CDCl_3$): $\delta=1.20$ (t, $J=7.2$ Hz, 6H), 3.55 (qd, $J=7.2$, 9.4 Hz, 2H), 3.68 (qd, $J=7.2$, 9.4 Hz, 2H), 4.83 (d, $J=1.1$ Hz, 2H), 5.28 (t, $J=1.1$ Hz, 1H), 6.88 (td, $J=7.5$, 1.5 Hz, 1H), 7.07 (dd, $J=7.5$, 1.5 Hz, 1H), 7.27 (td, $J=7.5$, 1.5 Hz, 1H), 7.55 ppm (dd, $J=7.5$, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=15.2$, 54.1, 61.0, 79.7, 83.7, 91.4, 112.5, 114.4, 123.1, 128.7, 133.8, 154.2 ppm; EIMS: *m*/*z* (%): 313 (21) $[M]^+$, 311 (21) $[M]^+$, 268 (34), 188 (27) $[M-OEt]^+$, 160 (68) $[M-(OEt)_2]^+$, 131 (62) $[M-CH(OEt)_2]^+$, 85 (85), 68 (100).

1-Bromo-2-(4,4-diethoxybuta-1,2-dienyloxy)benzene (1d): Potassium *tert*-butoxide (0.179 g, 1.6 mmol, 1.6 equiv) was added portionwise to a solution of acetylene **1c** (0.313 g, 1.0 mmol) in THF (10 mL) at 0°C under N_2. The mixture was stirred for 20 min at 0°C and H_2O (10 mL) was added. The organic layers were washed with a saturated solution of NaCl (5 mL), dried over anhydrous $MgSO_4$, and concentrated to give the allene **1d** (0.312 g, 99%) as a brown oil. ^1H NMR ($CDCl_3$): $\delta=1.16$ (t, $J=7.1$ Hz, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 3.50 (m, 4H), 4.91 (dd, $J=5.6$, 1.1 Hz, 1H), 5.79 (t, $J=5.6$ Hz, 1H), 6.96 (m, 2H), 7.19 (dd, $J=1.5$, 7.9 Hz, 1H), 7.26 (td, $J=1.5$, 7.9 Hz, 1H), 7.55 ppm (dd, $J=1.5$, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=15.4$, 15.5, 61.4, 61.9, 100.1, 105.9, 114.3, 119.6, 120.9, 125.1, 128.7, 133.8, 153.7, 197.3 ppm.

3-(2-Ethoxyvinyl)benzofuran (5): A 2.05 M solution of *n*-butyllithium in hexane (0.95 mL, 0.51 mmol, 1.03 equiv) was added to a solution of the allene **1d** (0.156 g, 0.50 mmol) in anhydrous THF (2.5 mL) at −78°C under an argon atmosphere. After 15 min of stirring, the mixture was hydrolyzed with H_2O (4 mL). The aqueous phase was separated and extracted with Et_2O (3×4 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and concentrated to provide a mixture two isomers of benzofuran **5**[1] (0.094 g, 100%, *E*/*Z*=86:14) as a brown oil.

E isomer: ^1H NMR ($CDCl_3$): $\delta=1.27$ (t, $J=7.1$ Hz, 3H), 3.83 (q, $J=7.1$ Hz, 2H), 5.76 (d, $J=13.2$ Hz, 1H), 6.98 (d, $J=13.2$ Hz, 1H), 7.18 (m, 2H), 7.37 (dd, $J=1.7$,.2 Hz, 1H), 7.42 (s, 1H), 7.55 ppm (dd, $J=1.5$, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=15.2$, 65.9, 95.6, 112.0, 117.3, 120.8, 123.0, 124.8, 126.8, 140.7, 148.50, 156.0 ppm.

Z isomer: ^1H NMR ($CDCl_3$): $\delta=1.21$ (t, $J=7.1$ Hz, 3H), 3.86 (q, $J=7.1$ Hz, 2H), 5.24 (d, $J=6.4$ Hz, 1H), 6.20 (d, $J=6.4$ Hz, 1H), 7.05–7–45 (m, 4H), 7.87 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=15.7$, 69.0, 93.8, 111.4, 115.4, 119.5, 122.4, 124.2, 127.2, 143.6, 146.8, 154.6 ppm; MS (CI, CH_4): *m*/*z* (%): 189 (100) $[M+H]^+$, 161 (29); IR: $\tilde{\nu}=2926$, 1380, 1127 cm^{-1}.

(*E*)-3-(2,2-Diethoxyethylidene)-2,3-dihydrobenzofuran (6 and 6D): A 2.37 M solution of *n*-butyllithium in hexane (0.51 mL, 1.2 mmol, 1.2 equiv) was added to a solution of the acetal **1c** (0.313 g, 1.0 mmol) in anhydrous THF (5 mL) at −78°C under argon atmosphere. After 15 min of stirring, the mixture was deuterolyzed with EtOD (0.6 mL). After 15 min of stirring, H_2O (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3×5 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography (10% EtOAc in cyclohexane) to provide a mixture of **6** and **6D** (0.197 g, 84%, *H*/*D*=66:34) as an orange liquid.

Compound ***6***: ^1H NMR ($CDCl_3$): $\delta=1.23$ (t, $J=7.2$ Hz, 6H), 3.58 (qd, $J=7.2$, 9.4 Hz, 2H), 3.71 (qd, $J=7.2$, 9.4 Hz, 2H), 5.10 (d, $J=1.1$ Hz, 2H), 5.55 (m, 2H), 6.87 (d, $J=7.9$ Hz, 1H), 6.94 (t, $J=7.9$ Hz, 1H), 7.22 (td, $J=1.2$, 7.9 Hz, 1H), 7.62 ppm (d, $J=7.9$ Hz, 1H); ^1H NMR ([D_6]benzene): $\delta=1.12$ (t, $J=7.2$ Hz, 6H), 3.45 (qd, $J=7.2$, 9.4 Hz, 2H), 3.59 (qd, $J=7.2$, 9.4 Hz, 2H), 4.63 (dd, $J=1.5$, 2,3 Hz, 2H), 5.43 (dt, $J=2.3$, 5.6 Hz, 1H), 5.56 (dt, $J=1.5$, 5.6 Hz, 1H), 6.77 (td, $J=1.5$, 7.6 Hz, 1H), 6.82 (d, $J=7.6$ Hz, 1H), 6.95 (td, $J=1.5$, 7.6 Hz, 1H), 7.86 ppm (d, $J=7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=15.7$, 60.7, 75.6, 98.1, 111.0, 116.8, 121.2, 124.3, 126.2, 131.3, 139.8, 165.4 ppm; EIMS: *m*/*z* (%): 234 (1) $[M^+]$, 188 (80) $[M-OEt]^+$, 160 (21) $[M-(OEt)_2]^+$, 131 (100) $[M-CH(OEt)_2]^+$.

Compound ***6D***: ^{1}H NMR ([D$_6$]benzene): $\delta = 1.12$ (t, $J = 7.2$ Hz, 6H), 3.45 (qd, $J = 7.2$, 9.4 Hz, 2H), 3.61 (qd, $J = 7.2$, 9.4 Hz, 2H), 4.63 (d, $J = 1.5$ Hz, 2H), 5.56 (s, 1H), 6.77 (td, J = 1.5, 7.6 Hz, 1H), 6.83 (d, $J = 7.6$ Hz, 1H), 6.95 (td, $J = 1.5$, 7.6 Hz, 1H), 7.88 ppm (d, $J = 7.6$ Hz, 1H); EIMS: *m/z* (%): 235 (1) $[M]^+$, 189 (80) $[M-OEt]^+$, 161 (21) $[M-(OEt)_2]^+$, 132 (100) $[M-CH(OEt)_2]^+$.

(4,4-Diethoxybut-2-ynyloxy)benzene (7): A 2.0 M solution of *n*-butyllithium in hexane (1.0 mL, 2.0 mmol, 2.0 equiv) was added to a solution of the acetal **1c** (0.313 g, 1.0 mmol) in anhydrous Et_2O (5 mL) at −78 °C under an argon atmosphere. After 15 min of stirring, the mixture was hydrolyzed with H_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography (10% EtOAc in cyclohexane) to provide **7** (0.624 g, 62%) as a yellow liquid and a mixture of **6** (0.120 g, 12%,) as a yellow liquid. ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (t, $J = 6.8$ Hz, 6H), 3.56 (qd, $J =$ 7.2, 9.4 Hz, 2H), 3.70 (qd, $J = 7.2$, 9.4 Hz, 2H), 4.75 (s, 2H), 5.29 (s, 1H), 6.98, 7.29 ppm (m, 5H); MS (EI): *m/z* (%): 234 (5) $[M]^+$, 189 (60) $[M-OEt]^+$, 161 (47), 131 (22), 85 (100), 68 (95).

Acknowledgements

Computations have been carried out at the Centre de Ressources Informatiques de Haute-Normandie (CRIHAN, St Etienne-du-Rouvray) and the Centre Informatique National de l'Enseignement Supérieur (CINES, Montpellier). ALG acknowledges the PUNCHorga interregional network for a PhD fellowship. We warmly thank Prof. H. Oulyadi (Univ. Rouen) for his continuous help and spectroscopic contribution to this program. We would also like to express our gratitude to Dr. C. Giessner-Prettre (LCT, University Paris VI) for her important input to these results.

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Received: November 21, 2007
Published online: April 25, 2008

