# Influence of the Acetylenic Substituent on the Intramolecular Carbolithiation of Alkynes: A DFT Theoretical Study

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S *Supporting Information*

ABSTRACT: A theoretical study of the intramolecular 5-exo-dig carbolithiation of substituted propargyl *o*-lithioaryl ethers, leading to dihydrobenzofurans, has been performed. The results show that a DFT description of the reaction (B3P86, 6-31G**) matches the experimental data provided that an explicit solvation by two molecules of THF is considered. To take place, the cyclization also implies that the acetylenic chain adopts a conformation in which a significant interaction arises between the lithium and the C≡C triple bond. Reaching the cyclization TS requires the passage of an activation barrier that should not be higher than 12−13 kcal mol^{-1}. From a thermodynamic point of view, the reaction is exothermic whatever the substituent R (from approximately −40 to −62 kcal mol^{-1}). In the starting substrate, a supplementary interaction between the Li and a substituent at the propargylic position can develop, influencing the future double-bond configuration. Thus, derivatives exhibiting an R−Li interaction tend to provide *E* olefins. In contrast, when no coordination between the lithium cation and the terminal R occurs, *syn* carbolithiation takes place, and the configuration of the exocyclic olefin is likely to be *Z*. This hypothesis accounts for most of the experimental results published before.
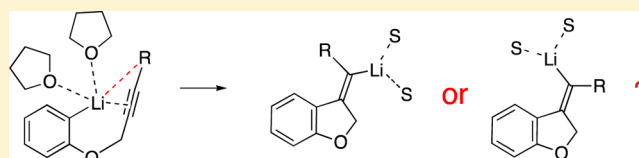
INTRODUCTION

Carbolithiations of alkynes are important reactions to create C−C bonds.[1] Their efficiency and stereochemical characteristics explain the manifold interest they have raised.[2] Theoretical Hartree−Fock plus single-point MP2/6-31G* calculations by Houk, Schleyer, and colleagues[3] established that the addition of LiH to acetylene is a $2\sigma + 2\pi$ addition that occurs in a *syn* fashion and is followed in some cases by cis−trans stereomutation of the resulting vinyl organolithium, thus justifying early experimental results obtained by Mulvaney et al.[4] Advantage can be taken from the intramolecular version of this reaction to promote carbo- and heterocyclizations, affording (hetero)cyclic and polycyclic scaffolds of high synthetic value. Hence, we have previously shown that a propargylic ether such as **1a** cyclizes efficiently into a 3-vinylbenzofuran **6a** through a stereocontrolled one-pot cascade process (Scheme 1).[5]

In THF, 5-exo-dig addition to the triple bond takes place exclusively, affording an exomethylene dihydrobenzofuran **3a** with an unexpected[1c] *E* configuration, observed in the quenched intermediate **4a**. The origin of this phenomenon was rationalized through a series of DFT computations run on a model in which the diethyl acetal used experimentally was replaced by a dimethyl acetal (denoted as **1a′** in the following) and two explicit molecules of THF were included.[6] These results, as well as recent experimental data,[7] show that the terminal acetal moiety plays a dramatic role in this stereocontrol, as a strong and persistent Li−O coordination forces the triple bond into a pro-*E* bending even before the transition state is reached. Beyond this observation, other results in the literature[8] suggest that the terminal propargylic appendage

Scheme 1. Mechanism of the Carbolithiation of Acetal 1a
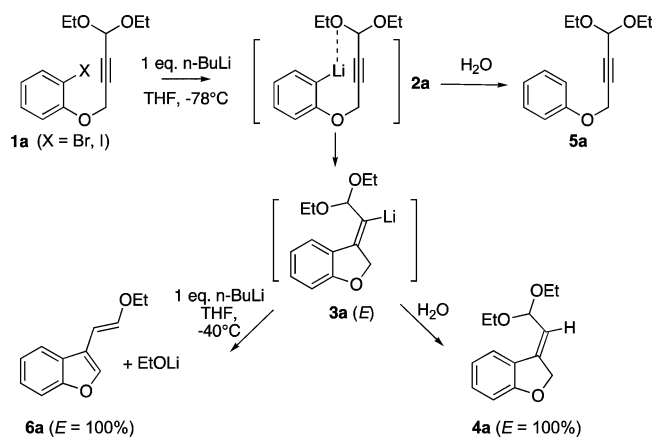
exerts a major influence on the success and stereoselectivity of the carbolithiation step.

This prompted us to undertake a general study of the influence of the terminal propargylic substituent borne by aryl ethers of type **1** on the carbanionic cyclization. Ideally, the results should allow a sorting of the substrates susceptible to undergo carbolithiation and the calculation of the configuration of the resulting olefin.

Experimentally, the role played by the oxygens of the diethyl acetal had been evidenced before: when this function was replaced by a simple methyl group (ether **1c**), no cyclization

was observed.[5a] The acyclic acetal was thus suppressed (**1b**) or replaced by another functional group, such as a phenyl (**1d**), methoxy (**1e–g**), dioxolane (**1h**), dialkylamino (**1k**), trimethylsilyl (**1l**), or thiophenyl group (**1m**) (Figure 1). However,
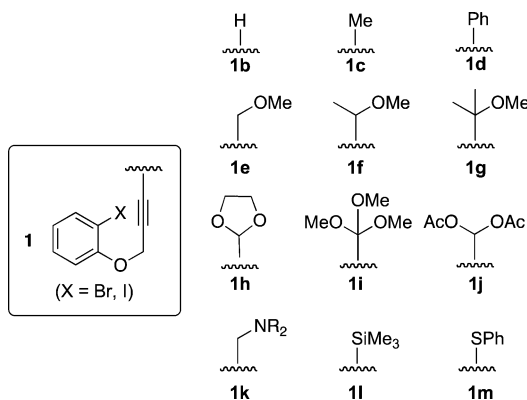

Figure 1. List of substrates **1** evaluated in this work.

when exposed to the previously optimized conditions for the carbolithiation (1 equiv of *n*-BuLi, THF, −78 °C, 15 min), several of these compounds did not cyclize. Thus, propargyl ethers **1b**, **1c**, **1e**, and **1k** led mainly to the corresponding reduction products **5** (indicating an efficient X → Li exchange leading to unreactive aryllithiums) together with unidentified side products. Changing the amount or structure of the base or the standard parameters (solvent, temperature, classical additives) did not improve the situation. In contrast, compounds **1d**, **1f**, **1g**, **1l**, and **1m** cyclized into dihydrobenzofurans **4** when the experimental conditions were slightly tuned.

These puzzling chemical and stereochemical differences prompted us to examine the mechanism of these carbolithiations on a theoretical basis. To compare the influence exerted by the oxygenated substituents, two compounds that were not tested experimentally were added to the list, namely, orthoester **1i** and acylal **1j**. The whole DFT study was restricted to the 5-exo-dig mechanism since it is the only one that has been observed experimentally to date.

■ COMPUTATIONAL DETAILS

In the choice among the plethora of currently available density functionals, the one to apply is always a matter of debate.[9] All functionals have their strengths and weaknesses, and it is recommended to make the selection according to the problem at hand and the type of system under study. In our case, B3P86, a functional on the fourth rung of the Perdew Jacob's ladder, was employed.[10] Being aware that the quality of the results provided by B3P86, as with most hybrid functionals,[11] tends to degrade rapidly with increasing molecular size, we repeated our key computations using the M06-L functional.[12] This latter has been constructed to better account for dispersion and was shown by Ramachandran and colleagues[13] to be well-adapted to problems in organolithium chemistry. The consistency between the data obtained with the two functionals prompted us to prefer B3P86, as our previously published results on similar organometallic systems were obtained with this functional.[6,7] The 6-31G** basis set, which behaved satisfactorily in closely related situations,[6] was chosen. The internal energies given for the minima of the solvated systems include zero-point energy (ZPE) corrections. The transition states (TSs) were located by a relaxed potential energy surface (PES) scan (consisting of geometry optimization at each step while maintaining the scanned variable constant) and then fully optimized and characterized by frequency calculations. We checked that all of the stable structures had no

imaginary frequencies and that the each TS has one and only one. All of the calculations were performed with the B3P86 hybrid functional as implemented in the Jaguar 6.0 software.[14] The TS barrier was defined as the difference between the energy of the TS and that of the starting optimized complex. Similarly, the addition energy was taken as the difference between the energy of the final product and that of the TS. Our previous results on a related exemple[15] suggested that the basis set superposition error (BSSE) could be ignored. The absolute energies are given at 0 K, even if oversolvation by discrete THFs is possible at this temperature.[16] Overall, the level of accuracy imposed by these technical choices can be considered as satisfying in view of the size of the systems and of our previous results.[6c]

■ RESULTS AND DISCUSSION

The crucial role played by the solvent on reactions involving highly polar species such as those implied in this study is well-known and explains the special care that was dedicated to the description of the medium in our model.[17] The solvation scheme we retained for the reagents and intermediates consisted of incorporating two or three explicit THF molecules disposed around the lithium in such a way that this metal was placed in a roughly tetrahedral surrounding (Figure 2).[18] A series of arrangements were systematically tested until the global minimum was located.
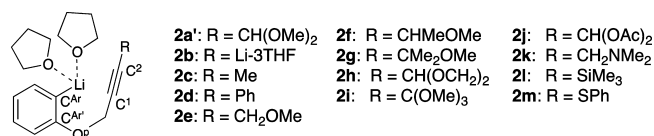

Figure 2. Folded conformer of disolvated intermediates **2**−2THF.

We chose not to include any implicit solvation model since the combination of the two techniques proved unsuccessful in related cases before,[19] at least using DELPHI[20] as a continuum model.[21] The choice of di/trisolvation was justified in a preliminary study detailed in section A below. The solvation number was then kept unchanged all along the reaction pathway.

Two conformers of the aryllithiums **2** that correspond to the threshold orientations of the lateral chain (folded/unfolded; Figure 3) have to be discussed. Actually, the local energy
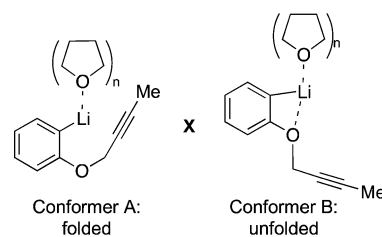

Figure 3. Two threshold conformers of intermediate **2**−*n*THF.

minima of these folded conformations provide a good zeroth-order approximation for the transition state and lead "naturally" to the reaction coordinate (the C^{Ar}−C^1 shortening). This approach also highlights the variations undergone by the substrate upon substitution and changes in the terminal acetylenic appendage. This methodology fits within Lightstone and Bruice's[22] "near attack conformation" (NAC) theory but is based on energy criteria rather than on geometrical ones. Such an approach has proved fruitful in other situations.[23]

It should be noted that when the propargylic position is substituted (Figure 4), successive 120° rotations of the
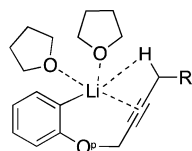

Figure 4. Global coordination of lithium in intermediates 2−2THF.

propargylic center bearing R lead to three threshold conformers. Interestingly, if the propargylic position bears at least one hydrogen, the most stable conformer corresponds to that in which this proton faces the Li cation, reminiscent of an agostic interaction, although the Li−H distances remain long [d(Li−H) = 3.28, 2.98, and 2.98 Å in **2a′**, **2c**, and **2e**, respectively].[24] If two molecules of THF are also taken into consideration (vide infra), the Li⁺ is more or less in a "pentacoordinated" environment.

A. Preliminary Study of the Solvation. We first considered the case of the simple methyl derivative **2c**, which has been shown not to undergo carbolithiation and leads, after hydrolysis, to the sole reduction product **5c**. The structures of **2c** solvated by zero to three THF molecules were fully

optimized, starting from the two orientations of the propargylic chain (A and B in Figure 3), even if obvious geometrical considerations suggested that only conformer A would be compatible with the cyclization process.
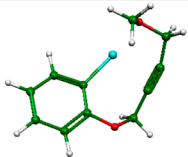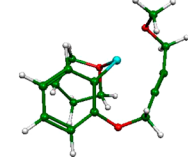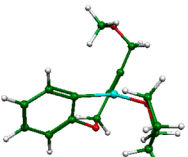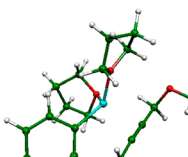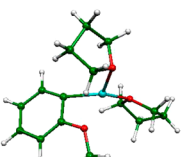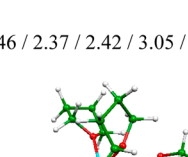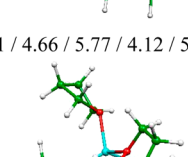
The optimizations indicated that the more stable conformation of **2c** is the one that tends to maximize the coordination of the lithium cation (Table 1). As expected,[25] the Li−THF interaction energy decreases as the level of solvation of **2c** (n in Table 1) increases. In the absence of THF, Li interacts with both the propargylic oxygen (Oᵖ) and the C¹≡C² triple bond. Thus, conformer B is preferred despite the torsion it imposes on the $C^{Ar'}$−C^{Ar}−Li angle (Figure 2) which is ~120° in the folded conformer and ~90° in the unfolded one. When one molecule of THF is taken into account, the two conformers become more or less isoenergetic, the supplementary Oᵖ−Li coordination in B being balanced by the C^{Ar}−Li distortion it enforces. When two THFs are incorporated, form A, in which the cation is surrounded by C^{Ar}, the two THF oxygens, and the triple bond, is preferred over the distorted conformer B and is ready for cyclization (C^{Ar}−C¹ ≈ 3.1 Å). Adding a third THF on the lithium leads to a system in which conformer B is favored by >4 kcal mol⁻¹ (even though the Li−triple bond interaction in conformer A does not vanish completely: Li−C² ≈ 2.6 Å), rendering the reaction unlikely at −78 °C. We can thus consider at this stage that the solvation of

Table 1. Effect of Explicit Solvation by n Molecules of THF on the Conformation of 2c

THF[a] (n)	Conf A (geometry)[b]	E (au)[c]	Conf B (geometry)[b]	E (au)[c]	E_A-E_B[d]
0	3.24 / 2.22 / 2.32 / 3.13	-470.57966	2.03 / 2.37 / 2.63 / 3.50	-470.58182	+ 1.4
1	3.26 / 2.25 / 2.32 / 3.11	-703.79626 (δE_{solv} = -21.0)	2.15 / 2.43 / 2.66 / 3.53	-703.79581 (δE_{solv} = -19.4)	-0.3
2	3.41 / 2.35 / 2.41 / 3.10	-937.00237 (δE_{solv} = -14.5)	2.10 / 4.20 / 5.09 / 4.35	-937.00022 (δE_{solv} = -13.4)	-1.3
3	3.43 / 2.48 / 2.61 / 3.22	-1170.18721 (δE_{solv} = -1.1)	3.07 / 5.24/ 6.08 / 4.40	-1170.19429 (δE_{solv} = -6.9)	+4.4

[a]E(THF) = −233.18307 au. [b]The values correspond to the distances d(Oᵖ−Li), d(Li−C¹), d(Li−C²), and d(C^{Ar}−C¹) in Å. [c]Solvation energy (in kcal mol⁻¹): δE_{solv} = E[**2c**−(n+1)**THF**] − [E(**2c**−n**THF**) + E(**THF**)]. [d]Values in kcal mol⁻¹.

Table 2. Effect of Explicit Solvation by *n* Molecules of THF on the Conformation of 2e

THF (n)[a]	Conf A (geometry)[b]	E (au)	Conf B (geometry)[b]	E (au)	E_A-E_B[c]
0	*(structure)* 3.44 / 2.32 / 2.28 / 3.02 / 2.05	-585.38930	- Ibid -	-585.38930	0.0
1	*(structure)* 3.29 / 2.40 / 2.34 / 3.03 / 2.12	-818.59923	*(structure)* 2.11 / 2.43 / 2.64 / 3.47 / 4.06	-818.59231	-4.3
2	*(structure)* 3.46 / 2.37 / 2.42 / 3.05 / 3.74	-1051.80086	*(structure)* 2.11 / 4.66 / 5.77 / 4.12 / 5.99	-1051.79679	-2.5
3	*(structure)* 3.50 / 3.82 / 2.68 / 3.21 / 3.62	-1284.98637	*(structure)* 2.99 / 4.97 / 5.69 / 4.25 / 6.99	-1284.992340	+3.8

[a] E(THF) = −233.18307 au. [b] The values correspond to the distances $d(O^p-Li)$, $d(Li-C^1)$, $d(Li-C^2)$, $d(C^{Ar}-C^1)$, and $d(O-Li)$ in Å. [c] Values in kcal mol^{-1}.

2c by two, and no more than two, THFs is optimal for the reaction studied. To generalize this analysis, and before drawing conclusions on the solvation scheme, we decided to examine at least one other substrate.

Propargylic derivative **2e** was selected as the second example because of a possible supplementary O−Li coordination with the methoxy group during the course of the reaction (Table 2). In the absence of any THF molecule, only one conformer is found (the unfolded and folded starting points converge toward the same minimum). A strong intramolecular MeO−Li interaction [d(O−Li) = 2.05 Å] that orients the lateral chain in such a way that both the triple bond and the methoxy group surround the lithium cation is computed. When one THF is included, the MeO−Li interaction is lost in conformer B of **2e** [d(O−Li) = 3.47 Å], which is now significantly destabilized with respect to conformer A, in which the MeO−Li coordination is conserved. With two THFs, conformer A remains more stable even though the methoxy appendage does not interact with the lithium anymore. In this case, the Li cation is surrounded by the aromatic ring, the two THF oxygen atoms, and the triple C≡C bond, while in form B the first coordination sphere consists of C^{Ar} plus three oxygen atoms (two THFs and O^p). The trisolvated form of **2e** was also studied (Figure 1 in the Supporting Information).[26] For this system, conformer B is more stable than A by 3.8 kcal mol^{-1}, as for **2c**. In addition, we checked the stability of trisolvated **2a′** (Figure 2 in the Supporting Information) and found a similar result, the unfolded form B being preferred over the folded conformer A by 1.8 kcal mol^{-1}.

In conclusion to this preliminary study, the computed data suggest that explicit disolvation by THF stabilizes the reactive conformer. Going beyond this solvation state stabilizes an unreactive conformer. Thus, the rest of our work on the reactivity of these systems was performed with the **2−2THF** supermolecules. The cyclization process itself, which is not altered by the presence of a third THF molecule, further justifies this choice: this extra solvent is spontaneously expelled along the cyclization route (vide infra).

Limiting the solvation to two molecules of THF significantly simplified the rest of the computations since it limited the study to consistent and comparable supermolecules. It should be noted that several other theoretical studies of organolithium derivatives also successfully employed two THF molecules.[16,27]

B. Intramolecular Cyclization of Lithioaryl Ethers 2. In all of the following, we focus on the geometrical and energy characteristics of the carbolithiation of **2−2THF**.

R = Me (2c). Conformer A of **2c** led to the starting point, TS, and final cyclized product displayed in the top row of Table 3.

Table 3. Characteristic Points along the Cyclization Pathways of 2c and 2d in THF

	Reactive conformer	TS	Product
2c			
E (a.u.)	-937.002374	-936.980747	-937.053449
ZPE (kcal.mol^{-1})	+267.507	+269.482	+267.572
E$_{corr}$ (a.u.)	-936.576075	-936.551300	-936.627046
E‡ (kcal.mol^{-1})		+15.55	
E$_{cycl}$ (kcal.mol^{-1})			-47.53
2d			
E (a.u.)	-1129.317021	-1129.306368	-1129.381405
ZPE (kcal.mol^{-1})	+305.488	+306.304	+306.421
E$_{corr}$ (a.u.)	-1128.830195	-1128.818242	-1128.893092
E‡ (kcal.mol^{-1})		+7.50	
E$_{cycl}$ (kcal.mol^{-1})			-46.97

In the TS, the shortening of the forming $C^{Ar}-C^1$ bond is simultaneous with the creation of a new C^2-Li one [$d(C^{Ar}-C^1)$ = 2.25 Å, $d(Li-C^1)$ = 2.20 Å, $d(Li-C^2)$ = 2.08 Å, $d(C^{Ar}-Li)$ = 2.12 Å]. It should be noted at this stage that (i) this TS is late with respect to that computed for **2a′** [for which $d(C^{Ar}-C^1)$ = 2.74 Å][6] and (ii) the former triple bond adopts a pro-Z configuration (*syn* carbolithiation), in sharp contrast with what was observed during the **2a′** → **3a′** transformation (*anti* carbolithiation; Scheme 1). The associated barrier is ~15.5 kcal mol^{-1}, a value about twice as large as that for **2a′** → **3a′** ($E^{\ddagger}$ = +8.3 kcal mol^{-1}). This probably explains why the carbolithiation of **1c** is not observed at −78 °C despite the final exothermicity of the process (approximately −47 kcal mol^{-1}).

To come back to the solvation issue, we followed the cyclization of **2c−3THF** (conformer A) to evaluate the influence of the third THF molecule on the course of this step. For the sake of space saving, we do not detail the reaction pathway, but the extra THF decoordinates rapidly as the $C^{Ar}-C^1$ distance decreases, and we obtained exactly the same product, **3c−2THF**, plus one THF. This comforted us to limit our work to the disolvated systems.

R = Ph (2d). Phenylacetylene **2d−2THF** was considered next (Table 3 bottom). In this case, the reactive conformer leads to a late TS similar to that of **2c** [$d(C^{Ar}-C^1)$ = 2.16 Å, $d(C^{Ar}-Li)$ = 2.14 Å] with a strong interaction between the electron-rich triple bond and the lithium [$d(Li-C^1)$ = 2.17 Å, $d(Li-C^2)$ = 2.15 Å]. The associated activation barrier is 7.50 kcal mol^{-1}. It should be noted that in compound **2d**, a weak interaction between C_{ipso} of the phenyl ring (NBO charge = $-0.12e$) and the lithium arises, which is known experimentally[28] and is also computed in the TS [$d(C_{ipso}-Li)$ = 2.78 Å]. Because the intensity of this atypical interaction could be misestimated by a standard functional such as B3P86, we repeated the calculations using PBE[29] and the metahybrid GGA functional M06-L.[12,30] The results (Table 1 in the Supporting Information) show that PBE decreases the activation barrier ($E^{\ddagger}$ = +4.93 kcal mol^{-1} but hardly changes $d(C_{ipso}-Li)$, which

decreases to 2.72 Å, while M06-L tends to increase the barrier (+9.96 kcal mol^{-1}) and significantly shortens $d(C_{ipso}-Li)$ to 2.53 Å.

Beyond these differences, the three functionals tested led to similar linear TS intermediates ($C^1-C^2-C_{ipso}$ = 175°), and a *syn* (Z) addition product was obtained. Experimentally, the reaction furnishes a mixture of (Z)- and (E)-**4d**, with the Z/E ratio increasing with the temperature.[7] This discrepancy between theory and experiment can be due to the thermal or solvation effects incorrectly taken into account in our computations, which could become critical in the case of the weaker Li−Ar interaction. Indeed, (i) the computations were run at $T = 0$ K and (ii) the solvation exerts a major influence on the stereochemical outcome of this reaction: when only one THF was included in the calculation, **3d** was obtained as its E isomer, and the activation barrier remained almost the same (+7.26 kcal mol^{-1}). In contrast, when three THFs were considered, one solvent molecule was expelled at an early stage of the cyclization, which then proceeded as before and led to the Z isomer. Overall, the reaction is exothermic with all three functionals ($E_{cycl} \approx -47$, -43, and -40 kcal mol^{-1}, respectively).

Finally, the hypothesis of a $Z \rightarrow E$ postcyclization isomerization[4] facilitated by the benzylidenic character of the resulting vinyllithium can be discarded, as the barrier associated with the double-bond isomerization was found to be about 35 kcal mol^{-1} (Table 4), a value inconsistent with a rapid reaction at −78 °C. In addition, a $Z \rightarrow E$ isomerization is thermodynamically disfavored.

Table 4. $Z \rightarrow E$ Isomerization of the Double Bond in 3d

	Z olefin	TS	E olefin
E (a.u.)	-1129.381405	-1129.324041	-1129.377525
ZPE (kcal.mol^{-1})	+306.421	+305.626	+303.407
E$_{corr}$ (a.u.)	-1128.893092	-1128.836995	-1128.861034
E‡ (kcal.mol^{-1})		+35.20	
E$_{cycl}$ (kcal.mol^{-1})			-15.08

R = CH$_2$OMe (2e). Because the coordinating methoxy appendage is likely to play a role, we considered the A and B arrangements for all three conformers generated by the rotation of this group (see Table 2 in the Supporting Information). The more stable conformer is of type A, and only this one was considered in the rest of the study (Table 5). The $C^{Ar}-C^1$ shortening leads to a late TS [$d(C^{Ar}-C^1)$ = 2.18 Å, $d(C^{Ar}-Li)$ = 2.22 Å] in which the MeO−Li interaction is restored and ensures a global conformation favorable for the cyclization [$d(Li-C^1)$ = 2.29 Å, $d(Li-C^2)$ = 2.29 Å]. The triple bond exhibits a slightly pro-E character in the TS ($C^1-C^2-C_{ether}$ = 162°), while the product features a Z double bond (*syn* carbolithiation). The energy barrier for the cyclization of **2e** is about 12 kcal mol^{-1} even though, experimentally, this cyclization is hardly observed and its yield is ≤5%. Were it possible, the process would remain exothermic (approximately −55 kcal mol^{-1}).

The ~1.5-fold increase in the activation barrier when going from **2a′** [R = CH(OMe)$_2$: +8.3 kcal mol^{-1}] to **2e** (R =

Table 5. Characteristic Points along the Cyclization Pathways of 2e−g in THF

	Reactive conformer	TS	Product
2e			
E (a.u.)	-1051.800860	-1051.787142	-1051.873031
ZPE (kcal.mol^{-1})	+289.093	+292.851	+291.314
E$_{corr}$ (a.u.)	-1051.340157	-1051.320454	-1051.40879
E‡ (kcal.mol^{-1})		+12.36	
E$_{cycl}$ (kcal.mol^{-1})			-55.43
2f			
E (a.u.)	-1091.265481	-1091.249185	-1091.326935
ZPE (kcal.mol^{-1})	+305.799	+308.785	306.947
E$_{corr}$ (a.u.)	-1090.778159	-1090.757105	-1090.837784
E‡ (kcal.mol^{-1})		+13.20	
E$_{cycl}$ (kcal.mol^{-1})			-50.63
2g			
E (a.u.)	-1130.732039	-1130.716155	-1130.792130
ZPE (kcal.mol^{-1})	+323.655	+326.002	+325.034
E$_{corr}$ (a.u.)	-1130.216262	-1130.196638	-1130.274155
E‡ (kcal.mol^{-1})		+12.31	
E$_{cycl}$ (kcal.mol^{-1})			-48.64

CH_2OMe: +12.4 kcal mol^{-1}), despite the MeO−Li interaction computed in both cases, is puzzling. We thought that the difference between the electron densities on the oxygen atoms in the acetal and in the ether could be the origin of this phenomenon. The NBO[31] charge calculated for the oxygen interacting with the lithium in the TS of **2a′** is −0.61e [and d(O−Li) = 2.16 Å], while it amounts −0.59e [and d(O−Li) = 2.12 Å] in the TS of **2e**. By comparison, the NBO charge on the acetalic oxygen that is not interacting with the lithium in **2a′** is −0.58e. These differences are small, but they suggest that one of the oxygens of the dimethoxy acetal coordinates to the lithium cation better than that of a regular methoxy ether group, facilitating the cyclization of **2a′**.

The solvation was considered again in this case, and we double-checked at this stage that the trisolvation was not a determining factor for the cyclization, even for a substrate bearing a chelating oxygen. As above for **2c−3THF**, we found for **2e−3THF** (conformer A) that the same cyclization product **4e−2THF** was obtained upon decreasing the C$_{Ar}$−C^1 distance after early elimination of the extra THF.

R = CHMeOMe (2f). Here the C^{Ar}−C^1 shortening in conformer A of **2f** leads to a TS [d(C^{Ar}−C^1) = 2.29 Å, d(C^{Ar}−Li) = 2.11 Å] in which the triple bond gets close to the lithium [d(Li−C^1) = 2.22 Å, d(Li−C^2) = 2.14 Å] while the methoxy appendage does not participate in the cyclization [d(Li−O) = 3.51 Å] (Table 5). This is probably due to the steric repulsions occurring between the THFs around the lithium and the branched propargylic chain, since the NBO charge calculated

for the oxygen of the methoxy group is −0.59e at the TS, which is identical to that in **2e**. The pro-Z character adopted by the triple bond in the TS, expected in the absence of Li−O interaction, is conserved until the final stage of the reaction, and a Z double bond is obtained (*syn* carbolithiation), in disagreement with the experimental result. The corresponding barrier is relatively high (+13.2 kcal mol^{-1}), a value that probably explains the poor yield measured for this transformation (∼35%). Thermodynamically speaking, the process remains exothermic (approximately −51 kcal mol^{-1}).

It should be noted that another route based on a different reaction coordinate (the dihedral angle Li−C^2−C^1−C^{Ar}) led through a slightly higher barrier (+14.7 kcal mol^{-1}) to the *E*-selective cyclization (see Table 3 in the Supporting Information). These two nearby and thus probably competitive pathways may explain the disparity between the experimental and theoretical data in this case.

R = CMe$_2$OMe (2g). Cyclization of this derivative is observed in THF at −78 °C provided that an excess of *n*-butyllithium (3 equiv) is employed.[7] As above for **2f**, in none of the considered conformers could a MeO−Li intramolecular interaction be evidenced by our calculations (and also as above, the NBO charge on the oxygen amounted to −0.59e). Actually, the more stable conformer (Table 5) is, expectedly, the one in which the C≡C triple bond−lithium interaction is maximized. The transition state is reached at a relatively short C^{Ar}−C^1 distance of 2.27 Å [with d(C^{Ar}−Li) = 2.11 Å, d(Li−C^1) = 2.20 Å, d(Li−C^2) = 2.08 Å], and it lies 12.3 kcal mol^{-1} higher than the starting point. Even at this stage, d(MeO−Li) is long (3.57 Å). Energetically speaking, this barrier is only 0.9 kcal mol^{-1} lower than the previous one, but this seems to be matching the cyclization.

The experimental conditions required for the reaction to take place are somewhat harsher (an excess of BuLi). This extra reagent triggers a conjugate elimination of lithium methoxide and provides directly the 3-vinylbenzofuran **6g** (Scheme 2).

Scheme 2. Experimental Reactivity of Ether 1g
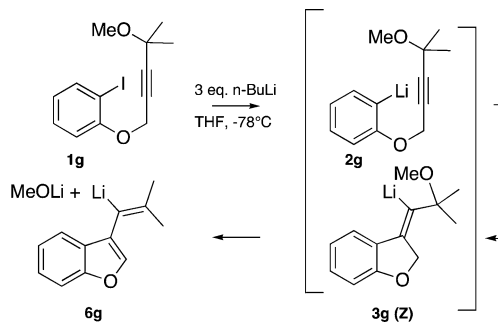
Thus, the configuration of the double bond in **3g** is not known. According to our DFT results, it should be Z. Finally, the exothermicity of the cyclization (−48.6 kcal mol^{-1}) is slightly decreased with respect to those of **3e** and **3f**.

R = CH(OCH$_2$)$_2$ (2h). Experimentally, the replacement of a diethyl acetal by a dioxolane led to a complex mixture of unidentified products and total consumption of the starting material. At the DFT level, only the triple bond interacts with the lithium in the preferred starting conformer, with no interactions between Li and the oxygen atoms of the acetal, as noted above for **2f**. The situation is thus quite different from the acyclic acetal **2a′**, but the computation predicts that the

heterocyclization should take place, the activation barrier being in the 10 kcal mol^{-1} range (Table 6). In the associated TS

**Table 6. Characteristic Points along the Cyclization Pathways of 2h−j in THF**

	Reactive conformer	TS	Product
2h			
E (a.u.)	-1165.370872	-1165.360565	-1165.449412
ZPE (kcal.mol^{-1})	+295.701	+299.169	+298.909
E$_{corr}$ (a.u.)	-1164.899643	-1164.883809	-1164.973071
E‡ (kcal.mol^{-1})		+9.94	
E$_{cycl}$ (kcal.mol^{-1})			-56.01
2i			
E (a.u.)	-1281.428279	-1281.423515	-1281.491365
ZPE (kcal.mol^{-1})	+330.340	+329.433	+331.917
E$_{corr}$ (a.u.)	-1280.901849	-1280.898534	-1280.962422
E‡ (kcal.mol^{-1})		+2.1	
E$_{cycl}$ (kcal.mol^{-1})			-40.09
2j			
E (a.u.)	-1393.806170	-1393.798206	-1393.895997
ZPE (kcal.mol^{-1})	+320.381	+332.157	+325.249
E$_{corr}$ (a.u.)	-1393.295611	-1393.268880	-1393.377680
E‡ (kcal.mol^{-1})		+16.8	
E$_{cycl}$ (kcal.mol^{-1})			-67.95

$[d(C^{Ar}−C^1) = 2.38$ Å, $d(C^{Ar}−Li) = 2.09$ Å, $d(Li−C^1) = 2.22$ Å, $d(Li−C^2) = 2.14$ Å], no O−Li interaction is computed [shortest $d(Li−O) = 3.43$ Å]. After this point, an exothermic (−56 kcal mol^{-1}) *syn* carbolithiation occurs that leads to the Z product. Experimentally, if this reaction effectively occurs, a β-elimination of lithium alkoxide can be anticipated, which would afford the exocyclic alkoxyallene **6h** (Scheme 3). This probably unstable product can explain the experimental failure.

R = C(OMe)$_3$ (2i). This propargylic orthoester has not been tested experimentally. Nevertheless, the high coordination potential of the three methoxy groups borne by a single carbon and the possible electron enrichment of the coordinating oxygen by the two vicinal methoxy groups prompted us to evaluate its reactivity.

The DFT data (Table 6) show that here a strong O−Li interaction takes place in the starting conformer at the expense of the Li−triple bond interaction $[d(O−Li) = 2.17$ Å, $d(Li−C^1) = 2.86$ Å, $d(Li−C^2) = 2.81$ Å]. The associated TS, reached by climbing a strikingly low barrier (2.1 kcal mol^{-1}), keeps these geometrical peculiarities $[d(C^{Ar}−C^1) = 2.36$ Å, $d(O−Li) = 2.00$ Å, $d(Li−C^1) = 2.48$ Å, $d(Li−C^2) = 2.61$ Å]. The charge effect is significant: the oxygen coordinating the Li cation bears a charge

Scheme 3. Putative Reactivity of Dioxolane 1h
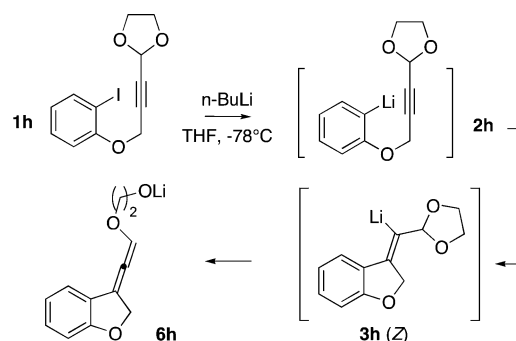
of −0.65e while the two noncoordinating ones carry −0.59e each. This figure suggests again that the O−Li interaction depends directly on the nature of the propargylic oxygenated substituent (compare results for ethers **2e−g** to those for acetal **2a′** and orthoester **2i** in Table 9). This persistently strong O−Li interaction imposes, as before, a pro-E bending of the acetylenic bond. An exothermic (−41 kcal mol^{-1}) *anti* carbolithiation occurs next, providing the E product. Unfortunately, and despite these extremely attractive characteristics, this compound could not be tested experimentally since the precursor of **2i** was hardly accessible.

R = CH(OAc)$_2$ (2j). As in the case of **2i**, this compound proved to be difficult to prepare and was not tested experimentally. In the computed starting complex, no interaction between the lithium and the four oxygen atoms borne by the acyal appendage can be noted, while the triple bond seems to behave as the fourth ligand (Table 6). The computed energy barrier is high (16.8 kcal mol^{-1}) and corresponds to a pro-Z TS, with geometrical characteristics very similar to those of **2h** $[d(C^{Ar}−C^1) = 2.37$ Å, $d(C^{Ar}−Li) = 2.10$ Å, $d(Li−C^1) = 2.24$ Å, $d(Li−C^2) = 2.15$ Å, even for the shortest $d(O−Li) = 3.34$ Å]. After the TS, a strongly exothermic (−68 kcal mol^{-1}) *syn* carbolithiation occurs, affording the theoretical Z product. Thus, were **2j** available, the value of the energy barrier hints that it would not cyclize anyway.

R = CH$_2$NMe$_2$ (2k). This compound was not tested experimentally; however, the corresponding N,N-dibenzyl-aminopropargylic analogue did not cyclize. The data concerning the characteristic points of this reaction are gathered in Table 7. As in the cases of **2e**, **2f**, and **2h**, no Y−Li coordination (Y = O or N) is computed. At the TS, the triple bond bends into a pro-Z configuration $(C^1−C^2−C_{amino} = 151°)$ and interacts strongly with the lithium $[d(C^{Ar}−C^1) = 2.25$ Å, $d(C^{Ar}−Li) = 2.13$ Å, $d(Li−C^1) = 2.21$ Å, $d(Li−C^2) = 2.08$ Å], while the nitrogen is ignored $[d(Li−N) = 4.51$ Å]. These geometrical characteristics are extremely similar to those of **2g** (R = CMe$_2$OMe) and **2h** [R = CH(OCH$_2$)$_2$]. The activation barrier of **2k** is also similar, reaching 12.6 kcal mol^{-1}; this relatively high figure can explain why this family of aminated substrates hardly cyclizes. If the exothermicity of the reaction is in the usual range (−49 kcal mol^{-1}), the configuration of the double bond in the final (theoretical) product is Z but cannot be compared to any experimental data.

R = SiMe$_3$ (2l). Experimentally, the silylacetylene derivative **2l** required fine-tuning of the iodine−lithium exchange conditions.[7,32] With 2.5 equiv of PhLi in THF at −78 °C, the expected dihydrobenzofurane **4l** was obtained as a single Z isomer in 59% yield.

Table 7. Characteristic Points along the Cyclization Pathways of 2k−m in THF

	Reactive conformer	TS	Product
2k (R = NMe₂)			
E (a.u.)	-1071.400617	-1071.383825	-1071.458549
ZPE (kcal.mol⁻¹)	315.208	317.274	315.117
E$_{corr}$ (a.u.)	-1070.898302	-1070.878216	-1070.956379
E‡ (kcal.mol⁻¹)		+12.60	
E$_{cycl}$ (kcal.mol⁻¹)			- 49.05
2l (R = SiMe₃)			
E (a.u.)	-1306.970955	-1306.959564	-1307.018017
ZPE (kcal.mol⁻¹)	+316.658	+320.300	+318.581
E$_{corr}$ (a.u.)	-1306.466328	-1306.268880	-1306.449133
E‡ (kcal.mol⁻¹)		+10.8	
E$_{cycl}$ (kcal.mol⁻¹)			-113.1
2m (R = SPh)			
E (a.u.)	-1527.796400	-1527.791395	-1527.874084
ZPE (kcal.mol⁻¹)	+306.499	+307.370	+306.347
E$_{corr}$ (a.u.)	-1527.307963	-1527.301570	-1527.385888
E‡ (kcal.mol⁻¹)		+4.01	
E$_{cycl}$ (kcal.mol⁻¹)			-52.91

The structure computed for the starting complex suggests that the lithium cation interacts with the triple bond [$d(\text{Li−C}^1)$ = 2.41 Å, $d(\text{Li−C}^2)$ = 2.45 Å] but not at all with the silicon [$d(\text{Li−Si})$ = 3.57 Å; Table 7]. A medium energy barrier (10.8 kcal mol⁻¹) is calculated for the TS, which exhibits geometrical characteristics very similar to those of **2c** [$d(\text{C}^{Ar}−\text{C}^1)$ = 2.22 Å, $d(\text{C}^{Ar}−\text{Li})$ = 2.14 Å, $d(\text{Li−C}^1)$ = 2.19 Å, $d(\text{Li−C}^2)$ = 2.09 Å]. The TS displays a pro-Z orientation and no Si−Li interaction [$d(\text{Si−Li})$ = 3.40 Å]. Beyond this point, an extremely exothermic *syn* carbolithiation occurs (−113 kcal mol⁻¹), affording the Z product in full accord with the experiment.

R = SPh (2m). Experimentally, the thiophenyl derivative **2m** cyclizes efficiently (78%). However, the configuration of the exocyclic olefin could not be determined because the double bond migrates swiftly to the endocyclic position (affording a 3-substituted benzothiophene) and the primary product could not be trapped before aromatization. Satisfyingly, a low activation barrier is computed (4.0 kcal mol⁻¹; Table 7), which is associated with a standard TS [$d(\text{C}^{Ar}−\text{C}^1)$ = 2.34 Å, $d(\text{C}^{Ar}−\text{Li})$ = 2.07 Å, $d(\text{Li−C}^1)$ = 2.20 Å, $d(\text{Li−C}^2)$ = 2.25 Å]. At this stage, the system is slightly pro-E ($\text{C}^1−\text{C}^2−\text{S}$ = 168°) despite the absence of a real Li−S interaction[33] [$d(\text{Li−S})$ = 2.95 Å]. The reaction ends with the exothermic cyclization (approximately −53 kcal mol⁻¹), which delivers a (Z)-enol thioether (not confirmed experimentally because of the isomerization).

R = Li−3THF (2b). We ended up this study with the atypical case of the deprotonated true alkyne **1b**. Its synthetic interest has been discussed in the associated experimental paper.[7] The DFT study was conducted on a pentasolvated molecule, three

THFs being placed on the acetylenic lithium and two on the aromatic one. The results show that in the starting folded conformer A a strong Li^{Ar}−triple bond interaction takes place, as evidenced by $d(\text{Li−C}^1)$ = 2.30 Å and $d(\text{Li−C}^2)$ = 2.29 Å. This can be due to the high electron density borne by the triple bond of the acetylide, as illustrated by the sum of the charges on the two carbons [$q(\text{C}^1)$ = −0.29e and $q(\text{C}^2)$ = −0.60e]. However, the computations point out the endothermic character of the reaction (greater than +9 kcal mol⁻¹; Table 8), which is thus not likely to take place, deterring us from

Table 8. Characteristic Points along the Cyclization Pathway of 2b in THF

	Reactive conformer	TS	Product
2b		-	
E (a.u.)	-1604.130759		-1604.116431
ZPE (kcal.mol⁻¹)	+480.095		+479.667
E$_{corr}$ (a.u.)	-1603.365679	-	-1603.352033
E$_{cycl}$ (kcal.mol⁻¹)^a			+9.26

^{a}E$_{cycl}$ was calculated as the difference between E$_{corr}$(reactive conformer) and E$_{corr}$(product).

trying to locate the corresponding TS. Experimentally, this reaction does not work because the iodine−lithium exchange seems to be more rapid than the deprotonation.[34] However, Coldham and colleagues have shown in a similar case that the intramolecular carbolithiation of a true acetylenic derivative does not proceed.[35]

■ CONCLUSION

This theoretical study of the heterocyclization by intramolecular carbolithiation of substituted propargyl *o*-lithioaryl ethers leads to the following conclusions:

(1) A realistic description of the reaction requires explicit solvation by THF. In the absence of this Lewis basic solvent, the lithium cation interacts strongly with the triple bond and overfavors the reactive conformer. Our results suggest that two molecules of THF is the best compromise, even though the solvation of these species could vary along the reaction course. Unfortunately, the dynamic character of the solvation remains difficult to take into account for large systems such as the one considered here, at least using standard DFT methods.

(2) To take place, the cyclization requires the acetylenic chain to adopt a conformation in which it faces the nucleophilic aromatic carbon. This reactive conformer is stabilized by a lithium−C≡C triple bond interaction computed for all the substrates considered here.

(3) At the TS, a supplementary O−Li interaction can occur when the propargylic substituent is oxygenated, as evaluated by the O−Li distance $d(\text{O−Li})$ (Table 9). Its strength is greatly influenced by the exact nature of the propargylic function. The "oxygen-rich" substituents (such as the acetal **2a′** and the orthoester **2i**) build up an electronic charge $q(\text{O})$ on the oxygen interacting with Li that is higher than that calculated for simple ethers (**2e−g**).

This stabilizing factor in turn has a strong influence on the energy barrier, and the TS is reached much more easily for **2a′**

Table 9. Computed Charge of the Oxygen and the O−Li Interaction at the TS

2	R	$d(\text{O−Li})$ (Å)	$q(\text{O})$ (e)	$E^{\ddagger}$ (kcal mol^{-1})
2f	CHMeOMe	3.51	−0.59	13.2
2e	CH$_2$OMe	2.23	−0.59	12.4
2g	CMe$_2$OMe	3.57	−0.59	12.3
2a′	CH(OMe)$_2$	2.16	−0.61	8.3
2i	C(OMe)$_3$	2.00	−0.65	2.1

and **2i** than for **2e**−**g**. It should be noted that when two different substituents are borne by the propargylic carbon (such as in **2f**), the coordinating group is not necessarily oxygenated.

In all cases, the potential fifth coordination of the lithium influences the configuration of the future double bond. However, this effect is difficult to evidence experimentally since not all of the substrates are accessible, and when they have been synthesized, they do not always undergo cyclization (**2c** and **2e** do not react) or they afford a primary product that rearranges (**2g**, **2h**, and **2m**). Nevertheless, the data in Table 10 suggest that *when no coordination is computed between the lithium and the terminal substituent R (i.e., **2c**, **2g**, **2h**, and **2j**−**m**), the configuration of the exocyclic olefin is expected to be Z. Vice versa, the derivatives exhibiting a R−Li interaction (i.e., **2a′** and **2i**) are expected to deliver E olefins.* The experiments are in accord with these hypotheses in three cases out of the four where they can be evaluated (**2a′**, **2d**, and **2l**). The discrepancy in the case of **2f** may be due to the existence of an alternative cyclization route passing through a TS computed to be slightly higher but providing the experimental E isomer.

(4) Reaching the cyclization TS requires climbing an activation barrier that should be not higher than 12−13 kcal mol^{-1}. Beyond these values, the cyclization is not observed, at least at −78 °C (entries 9, 10, and 12 in Table 10).[30] Thermodynamically speaking, the reaction is highly exothermic regardless of R (from approximately −40 to −113 kcal mol^{-1}).

(5) We have plotted the C^1 and C^2 charges, the TS energies, and the characteristic distances between relevant atoms in an effort to relate one of these parameters to the other(s). However, no direct correlation could be evidenced (Table 4 in the Supporting Information). In particular, we could not find a link between the global charge borne by the triple bond and the activation barriers or the double-bond configuration. However, the data show that the 5-exo-dig attack proceeds on carbon C^1,

which bears the smaller negative charge. As expected, at the TS the charge builds up on C^2.

In conclusion, if it is well-admitted that the Li cation acts as an acid toward carbonyl compounds, our results point the finger at the significant π-acidic character of this metal toward alkynes (like Au, Pt,[36] or Ru[37] and similar to I[38]). The above data indicate that standard DFT calculations offer a proper description of this property and can give a good account of both the reactivity and the stereoselectivity of such carbolithiation reactions. The relatively large series of examples considered in this paper (12 substrates) show that such computations have some predictive character even though no rule of thumb can be proposed to anticipate the efficiency and selectivity. In particular, chelation of the lithium cation by a supplementary Lewis base borne by R is neither necessary (see R = Ph) nor sufficient (see R = CH$_2$NMe$_2$).

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Computational details, large tables, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Table 10. Characteristic Values along the Carbolithiation Pathways of Acetylenic Derivatives in THF

entry	2	R	$E^{\ddagger}$ (kcal mol^{-1})	bending	E_{cycl} (kcal mol^{-1})	conf.[a]	tested?	cyclizes?[b]
1	2i	C(OMe)$_3$	+2.1	pro-E	−40.09	E	no	−
2	2m	SPh	+4.0	pro-E	−52.91	Z	yes	yes (?)[c]
3	2d	Ph	+7.50	−	−46.97	Z	yes	yes (E + Z)
4	2a′	CH(OMe)$_2$[d]	+8.3	pro-E	−53.90	E	yes	yes (E)
5	2h	CH(OCH$_2$)$_2$	+9.9	pro-Z	−56.01	Z	yes	yes (?)[c]
6	2j	CH(OAc)$_2$	+10.6	pro-Z	−62.09	Z	no	−
7	2l	SiMe$_3$	+10.8	pro-Z	−113.1	Z	yes	yes (Z)
8	2g	CMe$_2$OMe	+12.3	pro-Z	−48.64	Z	yes	yes (?)[c]
9	2e	CH$_2$OMe	+12.4	pro-E	−55.43	Z	yes	no (−)
10	2k	CH$_2$NMe$_2$	+12.6	pro-Z	−49.05	Z	no	−
11	2f	CHMeOMe	+13.2	pro-E	−50.63	Z	yes	yes (E)[e]
12	2c	CH$_3$	+15.6	pro-Z	−47.55	Z	yes	no (−)

[a]Computed configuration of the double bond. [b]The experimental configuration of the double bond is given in parentheses. [c]The configuration is unknown because of a secondary reaction (see the text). [d]Values taken from refs 6a and 6b. [e]A different route with a slightly higher barrier (+14.7 kcal mol^{-1}) that provides the E isomer was found (see the text).

■ REFERENCES

(1) For recent reviews, see: (a) Marek, I.; Chinkov, N.; Banon-Tenne, D. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., de Meijere, A., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 7, pp 395−478. (b) Fañanás, F. J.; Sanz, R. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, U.K., 2006; Chapter 4, pp 295−379. (c) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Amsterdam, 2007; Vol. 4, Chapter 4.4, pp 872−873. (d) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* 2010, 110, 2366−2447. (e) Guijarro, D.; Pastor, I. M.; Yus, M. *Curr. Org. Chem.* 2011, 15, 2362−2389.

(2) For instance, see: (a) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* 1998, 39, 1745−1748. (b) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem.* 1999, 64, 8616−8626. (c) McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* 2006, 71, 9552−9555. (d) Babu, G.; Orita, A.; Otera, J. *Chem. Lett.* 2008, 37, 1296−1297. (e) Hogan, A.-M. L.; O'Shea, D. F. *Chem. Commun.* 2008, 3839−3851.

(3) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* 1985, 107, 2821−2823.

(4) Mulvaney, J. E.; Gardlund, Z. G.; Gardlund, S. L. *J. Am. Chem. Soc.* 1963, 85, 3897−3898.

(5) (a) Le Strat, F.; Maddaluno, J. *Org. Lett.* 2002, 4, 2791−2793. (b) Le Strat, F.; Vallette, H.; Toupet, L.; Maddaluno, J. *Eur. J. Org. Chem.* 2005, 5296−5305.

(6) (a) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Angew. Chem., Int. Ed.* 2008, 47, 891−893. (b) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Chem.—Eur. J.* 2008, 14, 5159−5167. (c) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Eur. J. Org. Chem.* 2009, 721−729.

(7) Girard, A.-L.; Lhermet, R.; Fressigné, C.; Durandetti, M.; Maddaluno, J. *Eur. J. Org. Chem.* 2012, 2895−2905.

(8) In particular, see: (a) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* 1989, 30, 3901−3904. (b) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* 1990, 31, 627−630. (c) Wu, G.; Cederbaum, F. E.; Negishi, E.-I. *Tetrahedron Lett.* 1990, 31, 493−496. (d) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* 1993, 115, 3080−3090. (e) Krief, A.; Remacle, B.; Mercier, J. *Synlett* 2000, 1443−1446. (f) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* 2003, 44, 7143−7146.

(9) For instance, see: (a) Sousa, S. F.; Fernandes, P. A.; Ramos, M. J. *J. Phys. Chem. A* 2007, 111, 10439−10452. (b) Bühl, M.; Reimann, C.; Pantazis, D. A.; Bredow, T.; Neese, F. *J. Chem. Theory Comput.* 2008, 4, 1449−1459.

(10) (a) Becke, A. D. *Phys. Rev. A* 1988, 38, 3098−3100. (b) Perdew, J. P. *Phys. Rev. B* 1986, 33, 8822−8824. (c) Perdew, J. P. *Phys. Rev. B* 1986, 34, 7406.

(11) For instance, see: (a) Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. v. R. *Org. Lett.* 2006, 8, 3631−3634. (b) Schreiner, P. R. *Angew. Chem., Int. Ed.* 2007, 46, 4217−4219. (c) Wodrich, M. D.; Corminboeuf, C.; Schreiner, P. R.; Fokin, A. A.; Schleyer, P. v. R. *Org. Lett.* 2007, 9, 1851−1854. (d) Song, J.-W.; Tsuneda, T.; Sato, T.; Hirao, K. *Org. Lett.* 2010, 12, 1440−1443.

(12) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* 2006, 125, No. 194101.

(13) Ramachandran, B.; Kharidehal, P.; Pratt, L. M.; Voit, S.; Okeke, F. N.; Ewan, M. *J. Phys. Chem. A* 2010, 114, 8423−8433.

(14) *Jaguar*, version 6.0, release 22; Schrödinger, LLC: Portland, OR, 2002.

(15) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* 2000, 65, 8899−8907.

(16) For instance, see: Popenova, S.; Mawhinney, R. C.; Schreckenbach, G. *Inorg. Chem.* 2007, 46, 3856−3864.

(17) For instance, see: (a) Tuulmets, A.; Pällin, V.; Tammiku-Taul, J.; Burk, P.; Raie, K. *J. Phys. Org. Chem.* 2002, 15, 701−705. (b) Knorr, R.; Menke, T.; Ferchland, K. *Organometallics* 2013, 32, 468−472. For an excellent recent review, see: (c) Reich, H. J. *J. Org. Chem.* 2012, 77, 5471−5491.

(18) For instance, see: (a) Ando, K.; Morokuma, K. *Theor. Chem. Acc.* 2011, 130, 323−331. (b) Incea, H. H.; Dedeoglua, B.; Gula, S.; Aviyentea, V.; Coldham, I. *Mol. Phys.* 2012, 110, 353−359. (c) Sládek, V.; Lukeš, V.; Breza, M.; Ilcin, M. *Comput. Theor. Chem.* 2011, 963, 503−509.

(19) (a) Parisel, O.; Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Org. Chem.* 2003, 68, 1290−1294. (b) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigné, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* 2005, 61, 3325−3334.

(20) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honig, B. *J. Am. Chem. Soc.* 1994, 116, 11875−11882.

(21) Successful strategies using a continuum alone or in combination with discrete solvation have been reported previously. For instance, see: (a) Pratt, L. M.; Mu, R. *J. Org. Chem.* 2004, 69, 7519−7524. (b) Pratt, L. M.; Truhlar, D. G.; Cramer, C. J.; Kass, S. R.; Thompson, J. D.; Xidos, J. D. *J. Org. Chem.* 2007, 72, 2962−2966.

(22) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* 1994, 116, 10789−10790.

(23) Giessner-Prettre, C.; Hückel, S.; Maddaluno, J.; Jung, M. E. *J. Org. Chem.* 1997, 62, 1439−1448.

(24) Inter- and intramolecular Li−H agostic interactions have been evidenced before on many different complexes. See: (a) Scherer, W.; McGrady, G. S. *Angew. Chem., Int. Ed.* 2004, 43, 1782−1806. (b) Brags, D.; Grepioni, F.; Biradha, K.; Desiraju, G. R. *J. Chem. Soc., Dalton Trans.* 1996, 3925−3930. In general, the Li−H distances are much shorter than the ones we computed, lying between 1.80 and 2.20 Å. However, the literature values were either obtained from X-ray data or computed for unsolvated organolithium models. At least in one case, Li−H distances larger than 2.8 Å were measured. See: (c) Armstrong, D. R.; Mulvey, R. E.; Walker, G. T.; Barr, D.; Snaith, R.; Clegg, J. W.; Reed, D. *J. Chem. Soc., Dalton Trans.* 1988, 617−628. The agostic Li−H interaction is also associated with a lengthening of the corresponding C−H bond and a Li−H−C angle approaching 90°.[24b]

(25) Chabanel, M. *Pure Appl. Chem.* 1990, 62, 35−46.

(26) Forms A and B of the other possible conformers of **2e−2THF** corresponding to successive 120° rotations of the MeO group were also considered (Table 2 in the Supporting Information). They all corresponded to local minima, whose energies are also given in Table 2 in the Supporting Information. Only the more stable ones are included in Table 2.

(27) For instance, see: (a) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-López, M. F. *J. Org. Chem.* 2008, 73, 9393−9402. (b) Deora, N.; Carlier, P. R. *J. Org. Chem.* 2010, 75, 1061−1069. (c) Pratt, L. M.; Jones, D.; Sease, A.; Busch, D.; Faluade, E.; Nguyen, S. C.; Thanh, B. T. *Int. J. Quantum Chem.* 2009, 109, 34−42. (d) Pratt, L. M. *J. Mol. Struct.: THEOCHEM* 2007, 811, 191−196.

(28) For instance, see: (a) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* 1990, 112, 8008−8014. (b) Gemünd, B.; Nöth, H.; Sachdev, H.; Schmidt, M. *Chem. Ber.* 1996, 129, 1335−1344. (c) Cuevas, G.; Juaristi, E. *J. Am. Chem. Soc.* 1997, 119, 7545−7549. (d) Franz, D.; Ilkhechi, A. H.; Bolte, M.; Lerner, H. W.; Wagner, M. *Eur. J. Inorg. Chem.* 2011, 5414−5421.

(29) (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* 1996, 77, 3865−3868. (b) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* 1997, 78, 1396−1396.

(30) To make this point perfectly clear, we reran the whole sequence (full optimization of the starting complexes, TSs, and cyclized products) for compounds **2c−f**, **2k**, and **2l** using the M06-L functional. The values are reported in Table 5 in the Supporting Information and show that the activation barrier is systematically higher with M06-L. Nevertheless, the threshold energy value for the cyclization remains in the same range (12−13 kcal mol^{-1}). In addition, the relative ranking of the series we considered is conserved except for **2e**, which shifts position and gets located above **2k**. This result is consistent with the experimental data (**2e** does not cyclize) and solves the discrepancy observed using B3P86. However, this difference, which remains in the range of uncertainty estimates introduced by the model and the method, is the only significant one. We thus chose to pursue our study using B3P86 to remain in line with all of our previous studies.

(31) (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066−4073. (b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735−746. (c) Glendening, E. D.; Landis, C. R.; Weinhold, F. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2012**, *2*, 1−42.

(32) A comparable carbocyclization of a silylacetylene derivative by carbolithiation has been described previously (see ref 6c).

(33) For a fine study of the Li−S interaction, see: Sott, R.; Granander, J.; Dinér, P.; Hilmersson, G. *Tetrahedron: Asymmetry* **2004**, *15*, 267−274.

(34) Clayden, J. *Organolithium: Selectivity for Synthesis*; Pergamon Press: Amsterdam, 2002; pp 114−116.

(35) Coldham, I.; Lang-Anderson, M. M. S.; RathmelI, R. E.; Snowden, D. J. *Tetrahedron Lett.* **1997**, *38*, 7621−7624.

(36) For instance, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (b) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817−7831. (c) Shapiro, N.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2779−2782. (d) Soriano, E.; Marco-Contelles, J. *Top. Curr. Chem.* **2011**, *302*, 1−29.

(37) For instance, see: (a) Trost, B. M.; McClory, A. *Chem.—Asian J.* **2008**, *3*, 164−194. (b) Wang, K. P.; Yun, S. Y.; Lee, D.; Wink, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 15114−15115.

(38) For instance, see: (a) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141−1147. (b) Pradal, A.; Nasr, A.; Toullec, P. Y.; Michelet, V. *Org. Lett.* **2010**, *12*, 5222−5225.