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Organolithium Chemistry

Intramolecular Carbolithiation of Alkynes: *anti* Selectivity**

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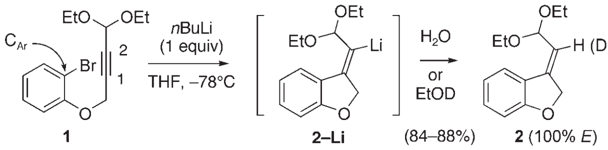
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Carbometalation reactions, which involve the addition of an organometallic reagent across a C–C multiple bond, are among the simplest methods for functionalizing olefins and alkynes.[1] Organolithium derivatives are well known to promote these transformations and have proved particularly useful for cyclization and heterocyclization steps, as demonstrated elegantly by Bailey and co-workers,[2] Negishi and co-workers,[3] and others.[4] We reported previously a simple process for the conversion of propargylic ethers into 3-vinylbenzofuranes, furopyridines, and indoles through a carbolithiation–elimination sequence;[5] however, the mechanism of this efficient reaction remained unexplored. We now report experimental and theoretical details concerning the carbolithiation step and its unexpected stereochemical course.

We chose to focus our study on the model case of the formation of the dihydrobenzofuran **2** in an attempt to characterize some of the intermediates along the reaction pathway. Previous studies had shown that a significant excess of *n*-butyllithium (3 equiv) was necessary for the reaction to reach completion. However, the role played by this reagent was unclear. In fact, upon the addition of exactly one equivalent of *n*BuLi, 3-(2,2-diethoxyethylidene)-2,3-dihydrobenzofuran (**2**) was recovered in good yield (Scheme 1).

Careful bidimensional NMR spectroscopic analysis in deuterotoluene[6] showed that **2** was obtained solely as the *E* isomer, which suggested that addition to the alkyne had occurred in an *anti* fashion. To our knowledge, the *anti* addition of an organolithium reagent to an alkyne has never been reported previously. When the reaction was quenched with EtOD instead of water, the expected deuterated exocyclic alkene was obtained with 34% labeling. When diethyl ether was used as the solvent, **2** was still formed at −78 °C with *E* selectivity, but in poor yield (12%, 78% labeling). Thus, one equivalent of *n*BuLi is sufficient to trigger the cyclization but does not elicit the β elimination of lithium ethoxide.



Scheme 1. Stereoselective *anti* intramolecular carbolithiation of **1**.

This puzzling stereochemical result prompted us to undertake a DFT computational study of the carbometalation step. This reaction has seldom been the object of theoretical studies.[7] We simplified our model slightly by replacing the ethyl acetal with a methyl acetal and selected the B3P86 functional and the 6-31G** basis set on the basis of our previous results in this field.[8] Zero-point energy (ZPE) corrections were included in the computations. The electron-localization function (ELF) used relies on a topological approach of the chemical bond.[9] Such an electron distribution, which implicitly takes into account the superposition of the resonance forms, provides useful information on the electron reorganization induced by the rearrangement of the intermediates.[10]

The model considered in this study was the lithiated aryl compound **1–Li** derived from **1**[11] and solvated by two explicit molecules of THF. We chose this model to ensure tetracoordination to the lithium ion, which is surrounded initially by C_{Ar} and one oxygen atom of the acetal. The full optimization of **1–Li** 2THF led to a "folded" conformer in which the triple bond faces the lithium cation.[12] In the conformer that reacts via the lowest-energy transition state (TS), coordination between one of the oxygen atoms of the acetal and the cation was also observed (Li–O(acetal): 2.16 Å). The TS was then localized through a potential-energy scan (PES) by decreasing the C(Ar)–C(1) distance (Scheme 1). The reoptimization of this primary TS led to the identification of an early transition state in which the coordination of the lithium ion to the three oxygen atoms is conserved (Figure 1). The relatively low energy barrier of 8.3 kcal mol^{-1} to the formation of this transition state is compatible with a rapid reaction at −78 °C. Further shortening of the reaction coordinate provided the

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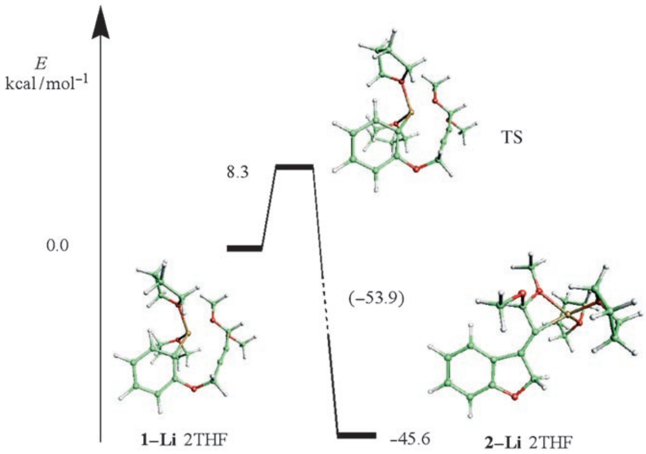

Figure 1. Energy diagram for the cyclization of **1–Li** 2THF into (*E*)-**2–Li** 2THF; green C, white H, red O, orange Li.

expected *E* dihydrobenzofuran **2–Li** after a considerably exothermic reaction ($\Delta_rH < -45$ kcal mol^{-1}).

To gain better insight into the origin of this unusual *E* selectivity, we next focused our attention on the evolution of the system between the TS and **2–Li**. Four snapshots extracted from the PES are displayed in Figure 2. The first illustrates the situation when the distance from C(Ar) to the lithium atom has increased by about 0.1 Å with respect to that in the TS. Thus, the largely ionic C(Ar)−Li bond lengthens, and the Li ion moves so that the plane in which it is coordinated to the three oxygen atoms is nearly parallel with the plane of the aromatic ring. The persisting acetal coordination forces the forming double bond to adopt an *E* configuration. Simultaneously, the lone pair of electrons is localized on C(2), whereas a valence basin appears between C(Ar) and C(1). In the next step, the C(Ar)−C(1) bond is reinforced, and the lithium coordination plane continues its movement parallel to the newly formed benzofuran nucleus. The third snapshot shows the continuation of this movement with the pivoting of the acetal group to accompany the lithium ion. In the fourth snapshot, an intermediate similar to the condensation product is observed in which the *E* double bond has formed and the C(2)–Li distance has reached its final value. Thus, it seems that the robust Li–O(acetal) coordination, which diverts the reaction from its usual course, explains the *anti* character of this carbolithiation and the final configuration of the double bond.

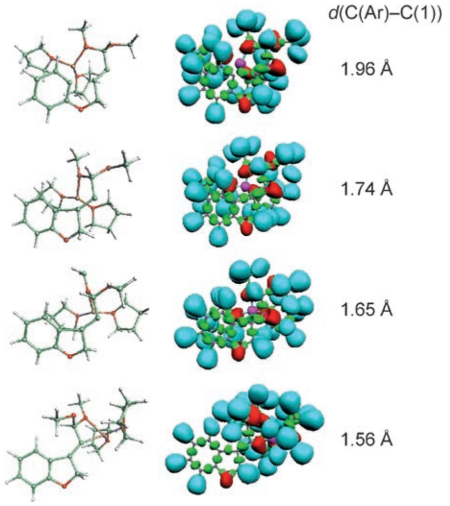

Figure 2. Four snapshots along the cyclization of **1–Li**. In the ELF representations (right), the cores are shown in magenta, the monosynaptic and disynaptic valence basins in red and green, respectively, and the hydrogen atoms in blue.

In **2–Li**, the flexible interactions between the lithium ion and C(2) together with the Li–O(acetal) interaction keep the cation in a tetracoordinated state and approximately 30° outside the plane of the heterocycle and the double bond (C(Ar)-C(1)-C(2)-Li: 211°; C(1)-C(2)-Li: 148°). The effect of the observed coordination is also illustrated by the cyclization of a folded conformer[11] in which the Li–O(acetal) interaction does not take place (Figure 3). In this case, a later and higher-energy TS (+11.4 kcal mol^{-1}) is found in which the triple bond is bent to prefigure the future *Z* olefin.

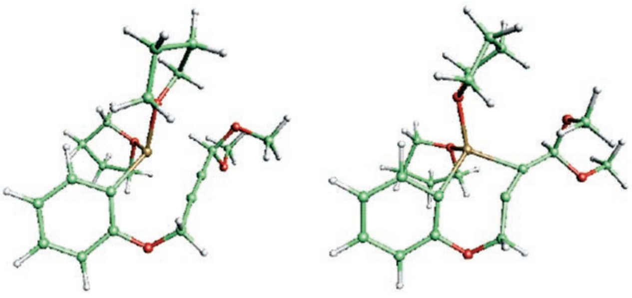

Figure 3. Uncoordinated conformer of **1–Li** (left) and the transition state for its cyclization (right).

In conclusion, the bromoaryl compound **1** is transformed stereoselectively upon treatment with *n*-butyllithium (1 equiv) into the dihydrobenzofuran **2**. The reaction proceeds via a low-lying transition state responsible for the *anti* addition to the alkyne. DFT calculations suggest that intramolecular coordination of the lithium cation by one oxygen atom of the terminal acetal appendage is responsible for this previously unobserved stereochemical outcome. The O–Li interaction is observed throughout the cyclization and drives the cation to the appropriate site on the double bond, finally leading to the formation of the *E* product upon hydrolysis. Complementary calculations show that in the absence of this coordination (as in the conformer depicted in Figure 3), the *Z* olefin that results from a classical *syn* addition should be obtained via a transition state with a higher energy barrier. Overall, these data suggest that the stereochemical outcome of such carbolithiation reactions could be controlled through the appropriate design of the substrate.

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[1] See, for example: a) M. J. Mealy, W. F. Bailey, *J. Organomet. Chem.* **2002**, *646*, 59 – 67; b) J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Amsterdam, **2002**; c) I. Marek, N. Chinkov, D. Banon-Tenne in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, chapt. 7, pp. 395 – 478; d) F. J. Fañanás, R. Sanz in *The Chemistry of Organolithium Compounds*, *Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2006**, chap. 4, pp. 295 – 379.

[2] a) W. F. Bailey, J. J. Patricia, P. J. Delgobbo, *J. Org. Chem.* **1985**, *50*, 1999 – 2000; b) W. F. Bailey, T. V. Ovaska, T. K. Leipert, *Tetrahedron Lett.* **1989**, *30*, 3901 – 3904; c) W. F. Bailey, T. V. Ovaska, *Tetrahedron Lett.* **1990**, *31*, 627 – 630; d) W. F. Bailey, T. V. Ovaska, *J. Am. Chem. Soc.* **1993**, *115*, 3080 – 3090.

[3] G. Wu, F. E. Cederbaum, E. J. Negishi, *Tetrahedron Lett.* **1990**, *31*, 493 – 496.

[4] a) S. A. Kandil, R. E. Dessy, *J. Am. Chem. Soc.* **1966**, *88*, 3027 – 3034; b) H. R. Ward, *J. Am. Chem. Soc.* **1967**, *89*, 5517 – 5518; c) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **2003**, *44*, 7143 – 7146.

[5] a) F. Le Strat, J. Maddaluno, *Org. Lett.* **2002**, *4*, 2791 – 2793; b) F. Le Strat, D. C. Harrowven, J. Maddaluno, *J. Org. Chem.* **2005**, *70*, 489 – 498.

[6] In $CDCl_3$, the NMR signals for the vinylic and acetalic hydrogen atoms of **2** are superimposed.

[7] For leading references, see: a) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, K. B. Wilberg, *J. Am. Chem. Soc.* **1991**, *113*, 5720 – 5727; b) E. Nakamura, Y. Miyachi, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1992**, *114*, 6686 – 6692; c) E. Nakamura, M. Nakamura, Y. Miyachi, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1993**, *115*, 99 – 106; d) W. F. Bailey, M. J. Mealy, K. B. Wilberg, *Org. Lett.* **2002**, *4*, 791 – 794; e) R. Sanz, J. M. Ignacio, M. A. Rodriguez, F. J. Fañanás, J. Barluenga, *Chem. Eur. J.* **2007**, *13*, 4998 – 5008.

[8] See, for example: a) A. Corruble, D. Davoust, S. Desjardins, C. Fressigné, C. Giessner-Prettre, A. Harrison-Marchand, H. Houte, M.-C. Lasne, J. Maddaluno, H. Oulyadi, J.-Y. Valnot, *J. Am. Chem. Soc.* **2002**, *124*, 15267 – 15279; b) C. Fressigné, A. Lautrette, J. Maddaluno, *J. Org. Chem.* **2005**, *70*, 7816 – 7828.

[9] a) B. Silvi, A. Savin, *Nature* **1994**, *371*, 683 – 686; b) A. Savin, B. Silvi, F. Colonna, *Can. J. Chem.* **1996**, *74*, 1088 – 1096; c) A. Savin, R. Nesper, S. Wengert, T. F. Fässler, *Angew. Chem.* **1997**, *109*, 1892 – 1918; *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 1808 – 1832.

[10] For other applications of ELF in organic and organometallic chemistry, see, for example: a) D. B. Chesnut, *J. Phys. Chem. A* **2000**, *104*, 7635 – 7638; b) C. Fressigné, J. Maddaluno, A. Marquez, C. Giessner-Prettre, *J. Org. Chem.* **2000**, *65*, 8899 – 8907; c) E. Matito, J. Poater, F. M. Bickelhaupt, M. Sola, *J. Phys. Chem. B* **2006**, *110*, 7189 – 7198.

[11] The theory underlying the halogen–lithium exchange process has been examined recently in detail: a) G. Boche, M. Schimeczek, J. Cioslowski, P. Piskorz, *Eur. J. Org. Chem.* **1998**, 1851 – 1860; b) K. Ando, *J. Org. Chem.* **2006**, *71*, 1837 – 1850; for a recent experimental study, see: W. F. Bailey, M. R. Luderer, K. P. Jordan, *J. Org. Chem.* **2006**, *71*, 2825 – 2828.

[12] Three “folded” conformers related by rotations of 120° of the terminal acetal appendage were localized. They differ in energy by less than 3 $\mathrm{kcal\,mol^{-1}}$.