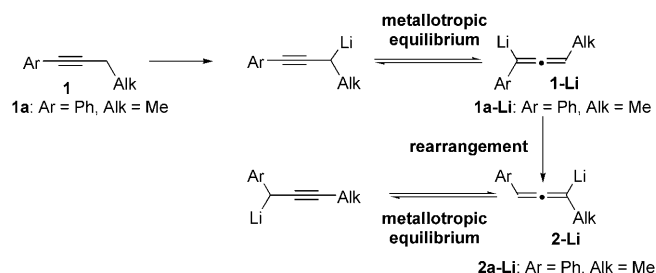


1,3-Li/H Shift of 1-Aryl-1,2-alkadienyl Reagents: An Experimental and Theoretical Study

Nacira Alouane,^[a] Kamel Bentayeb,^[a] Emmanuel Vrancken,^{*[b]} H          ,^{*[c]} and Pierre Mangeney^{*[a]}

The possibility of a metallotropic equilibrium in organolithium compounds derived from propargylic compounds complicates the structural determination^[1] and potential reaction products of these reagents. Their versatility is of great interest, especially for the lithiated 1-aryl-1-alkynes **1** for which an additional rearrangement (Scheme 1) has been ob-



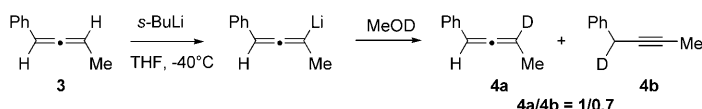
Scheme 1.

served.^[2] Despite its discovery by Klein 40 years ago^[2,3] and its clever applications to allene synthesis,^[4] the mechanism of this reaction is still unclear. Pathways involving either 1,3-H or 1,3-Li/H shifts have been implicated by Klein and Maercker,^[2,3,5] without systematic confirmation. Ma et al.

have reported this transposition to be highly non-reproducible, the only experimentally reproducible conditions are the use of lithium diisopropylamine (LDA) as a base at room temperature.^[4a,b] We faced this troublesome non-reproducibility during the course of our experimental studies on allenyl metals^[6] with 1-phenyl-1-butyne **1a** (Scheme 1) in non-LDA conditions. In line with our theoretical examinations of organolithium compound structures,^[7] we decided to elucidate the origin and mechanism of this shift to master its versatility.

The thermodynamic potential of the rearrangement was first examined computationally, since reversion of the stability of the two isomers (**1-Li** vs. **2-Li**, Scheme 1) as a function of chelation or solvation is the more straightforward explanation for the non-reproducibility. The energetics of the 1,3-shift was thus studied by comparing the relative stabilities of **1a-Li** and **2a-Li** allenic species (Scheme 1), which are suggested to be preferred to the propargylic one from experimental data.^[1] Allenic species **2a-Li** was found to be the most stable isomer, when considering either an uncoordinated anion (3.1 kcal mol⁻¹), or for lithiated species with a naked Li (3.5 kcal mol⁻¹), for solvated systems (continuum: 2.0 kcal mol⁻¹; three discrete OMe₂: 2.9 kcal mol⁻¹), or even for Li coordinated to ethylenediamine (6.4 kcal mol⁻¹).

These computational results were supported by the following experimental findings: treatment of **3** (afforded from hydrolysis of **1a-Li**) by *s*BuLi followed by deuteration counter-intuitively yields only deuteration at the methylated position to give a mixture of **4a** and **4b** in a 1/0.7 ratio (Scheme 2). Similar regioselectivities were previously reported for the deprotonation of phenylallene or **3** by *n*BuLi.^[4d,5]



Scheme 2.

[a] Dr. N. Alouane, K. Bentayeb, Dr. P. Mangeney
Laboratoire de Chimie Organique, UMR CNRS 7611
Institut de Chimie Mol  culaire, FR 2769
case 43, 4 Place Jussieu 75262 Paris Cedex 05 (France)

[b] Dr. E. Vrancken
Institut Charles Gerhardt Montpellier
ENSCM, 8, rue de l  cole Normale, 34296 Montpellier (France)
Fax: (+33) 4-67-14-43-22
E-mail: emmanuel.vrancken@enscm.fr

[c] Dr. H. G          
Laboratoire de Chimie Th          , UMR 7616
UPMC - Univ. Paris 06, CNRS
case 137, 4 Place Jussieu 75262 Paris Cedex 05 (France)

The greater stability of **2⁻** or **2-Li** with respect to the **1⁻** analogues strongly suggests that the 1,3-shift should be observed under all conditions and that its non-reproducibility has to be linked to kinetic factors. To determine the exact role of lithium within this shift, the reaction was experimentally undertaken in the presence and absence of Li chelators (hexamethylphosphoramide (HMPA) and tetramethyl-1,2-ethanediamine (TMEDA)). Lithiation of **1a** by *s*BuLi was initially carried out at -80°C . The reaction mixture was then slowly allowed to reach room temperature and transposition was monitored by deuteration of aliquots sampled at increasing temperature. Rearrangement occurs under three conditions: at 0°C in the absence of chelator, at -20°C in the presence of TMEDA, and at -40°C with HMPA. Reproducibility remained poor in all cases. These results could indicate a mechanism that involves separated ion pairs, the rearrangement taking place in an anionic species free of counter-ion coordination.

An intramolecular 1,3-shift within such an anion was thus theoretically examined. Despite our attempts, no direct shift could be found, and a two-step pathway was determined, which involved transposition of the H from C₁ to C₂ in a first step through transition state (TS) **TS(1a⁻-6⁻)** to yield **6⁻**, and then a second migration through **TS(6⁻-2a⁻)** from C₂ to C₃ (Figure 1). This mechanism is found to be utterly

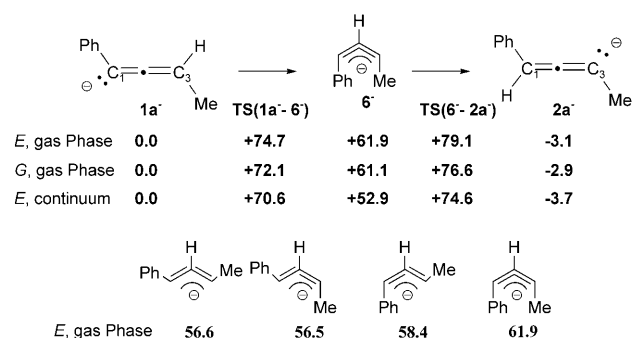
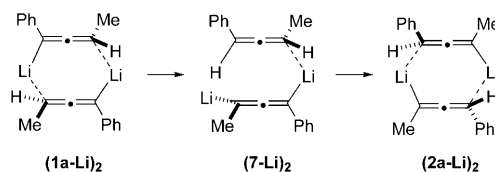


Figure 1. Electronic energies (*E*) and sum of electronic and thermal free energies (*G*) in kcal mol⁻¹ for intramolecular 1,3-shift.

unrealistic since the intermediate **6⁻** is about 60 kcal mol⁻¹ above that of the reactant and the activation energy is larger than 70 kcal mol⁻¹! Attempts at stabilizing intermediate **6⁻** by using another conformational arrangement of the Me and Ph groups have failed, as the conformational isomers of **6⁻** found are all more than 55 kcal mol⁻¹ above **1⁻**. Coordination of the anion to Li⁺ does not lead to much lower barriers, as **6-Li** was found to be 52.6 kcal mol⁻¹ above **1a-Li**, and the two TS were 65.8 and 70.2 kcal mol⁻¹ above **1a-Li**, respectively. Similar results were obtained when the mechanism for a fully unsubstituted model was studied (reaction intermediate 59.1 kcal mol⁻¹ above the reactant, and activation energy equal to 80.3 kcal mol⁻¹), which will be used for further mechanistic studies.

Thus, no intramolecular transposition could be found theoretically and we turned our attention to a mechanism in-

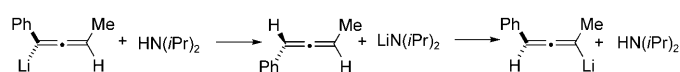
volving a dimeric aggregate (**1a-Li**)₂ (Scheme 3). Hydrogen transfer from one entity to the other, via a dilithiated intermediate (**7-Li**)₂ was envisioned. When the mechanism of the



Scheme 3.

non-substituted lithiated (with two OMe₂ on each Li) system is considered, the corresponding dilithiated intermediate is located 18.6 kcal mol⁻¹ above the reactant, and the activation energy for this reaction is 26.1 kcal mol⁻¹. These values remain much too high to be consistent with a reaction taking place within a few minutes at 0°C .

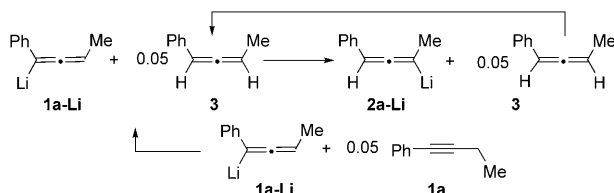
As reproducible conditions involve the use of LDA as a base, a possible mixed aggregate between LDA and **1a-Li** has been envisioned, because such species sometimes exhibit modified basicity with respect to the separated partners.^[8] This hypothesis was experimentally revoked since no transposition occurred when a stoichiometric amount of LDA was added to the pre-formed **1a-Li** and the reaction was allowed to reach room temperature. This last experiment indicates that the role of LDA as a deprotonating agent that allows transposition has to be sought within its conjugate acid, formed after deprotonation of **1a**, and not in the LDA reactant itself. This was verified by adding a catalytic amount of diisopropylamine to the pre-formed **1a-Li**. Under these conditions, transposition occurs cleanly at -20°C . The role of the secondary amine as the key reagent to allow transposition was checked by the following reaction sequence, which thereafter was used as a standard protocol: i) *s*BuLi was added to the propargyl **1a** to pre-form **1a-Li** at -80°C ; ii) the reaction mixture was warmed up to room temperature (RT); iii) the absence of **2a-Li** was checked by deuteration of an aliquot; iv) the reaction mixture was cooled down to -80°C and a catalytic amount (5 mol %) of diisopropylamine was added; v) the reaction mixture was warmed to -20°C where the rearrangement began and then allowed to reach room temperature. A total rearrangement was observed after one hour at 20°C . The following reaction sequence is proposed as a mechanism for the transposition: **1a-Li** (obtained from **1a** by deprotonation either by using an organolithium reagent or by using LDA) reacts with the diisopropylamine (respectively introduced as a catalyst or formed as the conjugate base) to form the allene and LDA (Scheme 4). Deprotonation can then take place on the most



Scheme 4.

favorable site, on the methylated carbon, resulting in the formation of **2a-Li**.

Ma and co-workers recently reported deuterium-labeling experiments of 1-deuterated-1-phenylocta-1,2-diene. A loss of D was observed when LDA was used, whereas a total retention was seen with *n*BuLi, which was attributed by the authors to isotopic effects.^[4d] Nevertheless, according to the difference of pK_a of the two metallation sites of the allene, such a result can be fully explained by a mechanism based on equilibrated proton exchange between bases and conjugate acids, which is impossible with the use of *n*BuLi under anhydrous conditions. Such a reaction sequence can only be performed if LDA and **1-Li** have pK_a values of the same order. Thus to replace diisopropylamine as the catalytic proton transfer agent requires the participation of an acid whose conjugate base is of similar strength to that of **1a-Li**. The obvious choice was to add the allene **3** in catalytic amounts (Scheme 5) under the standard experimental proto-



Scheme 5.

col. The rearrangement, which started at -20°C , afforded a mixture of **2a-Li** and **1a-Li** in a 3/1 ratio after one hour at 20°C . Theoretically, proton exchange between **3** and the monomeric disolvated **1a-Li** exhibits an activation energy of $17.3\text{ kcal mol}^{-1}$, which is fully consistent with the experimental conditions. Similar experimental results were obtained by using a catalytic amount of **1a**. In this case, the transposition was found to be slower (1/1 ratio after 1 h at 20°C).

In conclusion, based on our experimental and theoretical studies, we propose a mechanism involving the exchange of equilibrated protons initiated by a catalytic amount of a proton donor, the most effective of which appears to be diisopropylamine. When confronted with the initial reproducibility problems, we employed drastic experimental conditions to protect the reaction medium from water and air. Most ironically, this deprived us of the transposition to the desired product when the accidental introduction of water (proton source) in the course of the reaction procedure would have certainly led us to the goal.^[9] More interestingly, as long as the mechanism remained uncertain, the 1,3-shift was limited to the alkyl/phenyl substituents. The elucidation of the transposition mechanism would enlarge its scope, allowing a generalization to variously substituted propargyl reagents. Through computational evaluation of the relative thermodynamic stability of the two allenyl lithium isomers, it should be possible to predict the feasibility of this rearrangement, as promotion by a proton donor should be general behavior.

Experimental Section

Diisopropylamine-mediated 1,3-Li shift: A freshly titrated solution of *s*BuLi (2.2 mmol, 1.1 equiv) was slowly added to a solution of 1-phenyl-1-butyne (0.284 mL, 2 mmol) in THF (15 mL) at -80°C under argon. The temperature of the mixture was allowed to reach -40°C in one hour and the reaction mixture was cooled to -80°C . Diisopropylamine [0.042 mL, 0.3 mmol (excess of *s*BuLi + 5% of 1-phenyl-1-butyne)] was then added, and the temperature of the mixture was slowly allowed to reach room temperature. The 1,3-Li shift was monitored by ^1H NMR analyses of aliquots obtained after the deuteration reaction, under anhydrous conditions, with MeOD and found to be complete after one hour at room temperature.

Computational Methods

Full geometry optimizations were systematically conducted with no symmetry restraints using the Gaussian 03 program^[10] within the framework of density functional theory (DFT) using the hybrid B3LYP exchange-correlation functional^[11] and the 6-31+G** basis set for all atoms. Implicit solvation was added when mentioned using the PCM model, and the dielectric constant was implemented for THF ($\epsilon_R = 7.58$).^[12] Frequencies were evaluated within the harmonic approximation. The nature of the transition states was ensured by confirming the presence of a single imaginary frequency. The connection between transition states and minima was ensured by carrying out small displacements of all atoms in the two directions along the imaginary frequency mode and carrying out geometry optimization using these geometries as starting points.

Acknowledgements

The authors thank CCR (Univ. Paris VI, Paris, France), CINES (Montpellier, France), IDRIS (Orsay, France), and CRIHAN (Rouen, France) for computing facilities, and Clariant and the programme franco-algérien de formation supérieure for financial support.

Keywords: allenes • allenyl lithium • density functional calculations • reaction mechanisms

- [1] a) H. J. Reich, J. L. Thompson, *Org. Lett.* **2000**, 2, 783–786 and references herein.
- [2] a) J. Klein, S. Brenner, *Tetrahedron* **1970**, 26, 2345–2352.
- [3] a) J. Klein, S. Brenner, *J. Org. Chem.* **1971**, 36, 1319–1320; b) J. Klein, S. Brenner, *Tetrahedron* **1972**, 28, 5385–5392.
- [4] a) S. Ma, Q. He, *Angew. Chem.* **2004**, 116, 1006–1008; *Angew. Chem. Int. Ed.* **2004**, 43, 988–990; b) S. Ma, Q. He, X. Zhang, *J. Org. Chem.* **2005**, 70, 3336–3338; c) S. Ma, Q. He, X. Jin, *Synlett* **2005**, 514–516; d) J. Zhao, Y. Liu, S. Ma, *Org. Lett.* **2008**, 10, 1521–1523.
- [5] A. Maercker, J. Fischenich, *Tetrahedron* **1995**, 37, 10209–10218.
- [6] a) F. Bernaud, E. Vrancken, P. Mangeney, *Org. Lett.* **2003**, 5, 2567–2569; b) F. Bernaud, E. Vrancken, P. Mangeney, *Synlett* **2004**, 1080–1082; c) N. Alouane, F. Bernaud, J. Marrot, E. Vrancken, P. Mangeney, *Org. Lett.* **2005**, 7, 5797–5800; d) E. Vrancken, N. Alouane, H. Gérard, P. Mangeney, *J. Org. Chem.* **2007**, 72, 1770–1779; e) N. Alouane, E. Vrancken, P. Mangeney, *Synthesis* **2007**, 1261–1264.
- [7] a) H. Gérard, A. de La Lande, J. Maddaluno, O. Parisel, M. E. Tuckerman, *J. Phys. Chem. A* **2006**, 110, 4787–4794; b) A. de La Lande, C. Fressigné, H. Gérard, J. Maddaluno, O. Parisel, *Chem. Eur. J.* **2007**, 13, 3459–3469.

- [8] a) Sun, D. B. Collum, *J. Am. Chem. Soc.* **2000**, *122*, 2459–2463 and references herein; b) K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760.
- [9] As allene **3** was obtained from **1a-Li** by hydrolysis, H₂O can be used as an initiator of the catalytic cycle for rearrangement by in situ formation of the allene. This was ensured experimentally by replacing the 5 mol% of diisopropylamine by 5 mol% of water in our standard reaction protocol to give again a slow rearrangement (**2a-Li**/**1a-Li** = 1/1).
- [10] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
- [11] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; b) B. Miehlich, A. Savin, H. Stoll, H. Preuss, *Chem. Phys. Lett.* **1989**, *157*, 200; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.
- [12] M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43 and references herein.

Received: September 8, 2008

Published online: November 26, 2008