Isoprene-mediated lithiation of imidazole derivatives: mechanistic considerations

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Dedicated to Professor William F. Bailey on the occasion of his 65th birthday

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Abstract

The isoprene-mediated lithiation, with lithium metal, of different imidazole derivatives is an interesting methodology for their functionalization. Studies of different possible intermediates involved in the reaction employing density functional theory calculations, at the B3LYP/6-311++G(d,p) level are considered. A plausible mechanism is described, in which isoprene is reduced, to the corresponding radical anion, in the presence of $Li_{(s)}$, acting then as a base deprotonating *N*-methylimidazole (NMI) and producing the 1,1-dimethylallyl radical. This radical is further reduced by the excess of lithium proceeding once more as a base. This final step produces stable final products that compensate the previous equilibriums, making favourable the whole process.

Keywords: Isoprene-mediated lithiation, lithium metal, mechanism, DFT calculations, imidazole

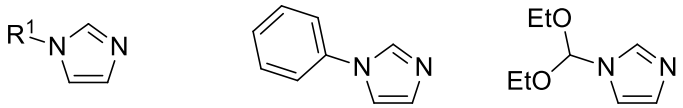
Introduction

Compounds classified as heterocyclic probably constitute the largest and the most varied family of organic compounds, and often display important bioactivities. Actually, more than 67% of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database contain heterocyclic rings.[1] Indeed, the remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs.[2]

Lithium metal in combination with a substoichiometric amount of an arene, as an electron carrier, has become a very versatile methodology in the preparation of organolithium

intermediates.[3] A significant variety of functionalized organolithium reagents have been prepared by means of this protocol.[4] Additionally the arene-promoted lithiation has been employed in the preparation of polylithiated synthons[5] and in the generation of active nanoparticles by activation of other transition metals.[6] In the last years, interesting mechanistic studies on the arene-catalyzed lithiation process have been taken into consideration, providing interesting information regarding this well-established methodology.[7]

Recently, we also found that lithium metal, without any additive, is able to generate 2-lithio-*N*-methylimidazole (2-Li-NMI) from *N*-methylimidazole (NMI, **1**), although the use of isoprene during the lithiation process gave an improvement in the results.[8] Thus, in the last five years, we have been working on the use of isoprene as a promoting lithiation agent for the generation of different lithio-imidazole derivatives. Isoprene-mediated lithiation of 1-alkyl- **1**-**4**,[8,9] 1-phenyl-**5**[10] and 1-(diethoxymethyl)imidazole **6**[11] has been reported (Figure 1). Thus, concerning the role of isoprene in the reaction, we have considered, from the beginning, that it can act as an electron carrier agent[12] and/or as a hydrogen acceptor.[13] Lithium metal, under certain reaction conditions, can produced the ring opening of the THF,[7] employed as solvent, generating the corresponding alcoholate which could act as a base.[14] However, the mixture $Li_{(s)}$/isoprene did not produced any traces of 1-butanol after hydrolysis.[15] In this work we consider some interesting studies towards understanding the isoprene-mediated lithiation of imidazole derivatives.



1, R^1 = Me
2, R^1 = cyclohexyl
3, R^1 = 1-methylheptyl
4, R^1 = 1-cyclohexylethyl

5

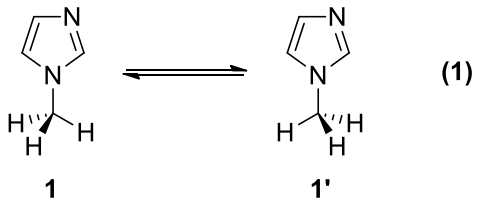
6

Figure 1. Imidazole derivatives employed in the isoprene-mediated lithiation.

Results and Discussion

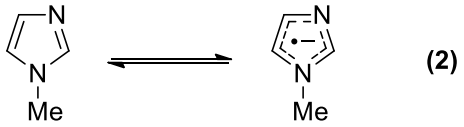
We considered the study of the generation of 2-Li-NMI from NMI **1** employing isoprene as an additive during the process. Firstly, in order to obtain a theoretical qualitative description of the experimental reactivity for the isoprene/NMI/$Li_{(s)}$ system, semiempirical calculations[16] for NMI, *s-cis*- and *s-trans*-isoprene, both as neutral and anionic species, were performed. Soon it was evident that this protocol provided largely defective data when quantitative analyses of the energies involved were sought after. Density functional theory calculations[17] of neutral and anionic structures, energies, and harmonic vibrational analysis of $NMI^{(-1)}$, and *s-cis*- and *s-trans*-$isoprene^{(-1)}$, as well as related species, were carried out thereafter using the Becke-Lee-Yang-Parr (B3LYP) exchange-correlation functional,[18] in an attempt to attain larger accuracies in the

calculations and set the foundations for a theoretical description of the reactivity and the processes involved. The geometries of the isolated neutral and anionic species have been optimized both in the gas phase using the 6-311++G (d,p) basis set.[19,20]



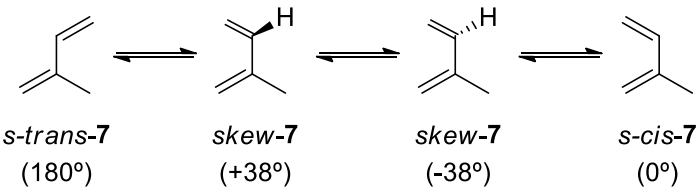
1 **1'** **(1)**

The substrate NMI was found to occur in only one conformation **1**, being a stationary point as confirmed by vibrational analysis. Additionally, the corresponding methyl rotamer **1'** appears as a saddle point some 1.17 kcal mol^{-1} above ($\Delta G^{o\ddagger}$) conformers of type **1** and was not considered in the calculations (Equation 1). Regarding the anionic NMI **1**$^{-}$, the geometry of the minimum is well defined and resembles that of the neutral NMI with the corresponding bond lengthening within the ring (Equation 2). The relevant calculated energies and thermodynamic functions are described later.



1 **1**$^{\bullet -}$ **(2)**

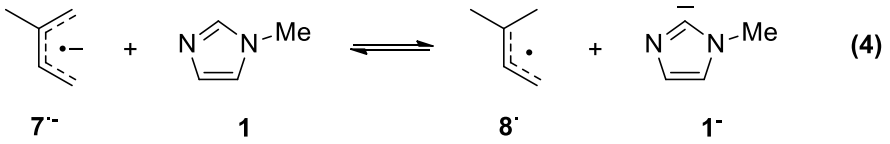
On the other hand, isoprene **7** appears as a mixture of *s-trans*, gauche and *s-cis* conformers in 95.3% (*s-trans*) and the rest (*ca.* 4.7%) corresponding to the gauche (or *skew*), the *s-cis* being too scarcely populated to be detected, according to vibrational spectroscopy and gas electron diffraction studies.[21] According to our calculations for the equilibrium depicted in Equation 3, three conformers were also detected, corresponding to the *s-trans*-**7** (180º dihedral),[22] *skew*-**7** (38º dihedral)[23] and *s-cis*-**7** (0º dihedral),[24] in relative amounts of 97.1:2.7:0.2 respectively, being in excellent agreement with the experimental observations. For the anionic species, the *s-trans*-isoprene radical anion (*s-trans*-**7** $^{-}$)[25] retains the antiperiplanar geometry of the *s-trans*-**7** after the electron capture, and both the *skew*-**7** and the *s-cis*-**7** converge to the same synperiplanar anion (*s-cis*-**7** $^{-}$)[26] after the electron capture. This latter conformer is the energetic minimum, with a meager difference of ΔG^{o}_{isom} = –1.1 kcal mol^{-1} for the equilibrium between *s-trans*-**7** $^{-}$ and *s-cis*-**7** $^{-}$ (K^{o} = 6.4). In both cases, similar bond lengthening respect to the neutral molecule was observed.



(3)

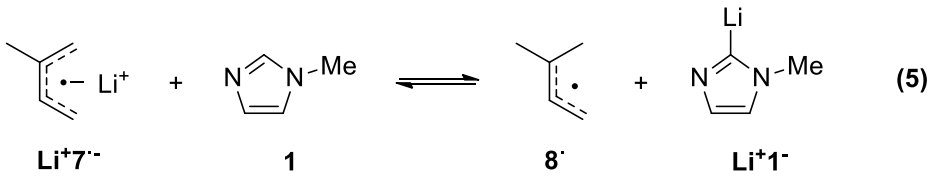
Electron affinity (EA) calculations. In the context of the quantum mechanics, the experimental values of adiabatic electron affinity (*AEA*) of several small molecules have been well correlated by the use of the functional hybrid B3LYP with different basis sets, such as 6-31+G(d),[27] which has been considered to provide satisfactory reliable results. The B3LYP/6-311++G(d,p) method, with vibrational energy corrections at 0 K (*ZPE*) has been recently employed in the calculation of adiabatic electron affinities of small-medium size molecules (up to 6 heavy atoms).[28] For bigger molecules, up to 15-20 heavy atoms, theoretical calculations in the level of B3LYP/6-31G(d) with *ZPE* corrections have been used in the calculation of *AEA*.[29] In this work, *AEA*s have been calculated employing the above mentioned method with the incorporation of the *ZPE* corrections in all the cases.[30] The calculated *EA* for NMI **1**[31] is –0.39 eV, and for isoprene are –0.43 eV (for *s-trans*-isomer) and –0.29 eV (for *skew*-isomer).[32] The small difference between these *EA*s, which is within the ±0.21 eV of average absolute deviation calculated for this method in comparison with experimental values,[33] did not provide any significant evidence regarding the possible mechanism.

Proton affinity calculations: isolated anions. In order to set out a plausible reaction mechanism, different calculations in gas phase were carried out to obtain the estimation of the proton affinities for some species involved in the process. The considered process, which is represented in Equation 4, shows the deprotonation of NMI by the isoprene radical-anion **7** $^{\bullet-}$,[26] generating the corresponding radical **8** [34] and the deprotonated NMI **1**$^{-}$.[35] This preliminary result, employing isolated anions, showed that the deprotonation between the isoprene radical-anion **7** $^{\bullet-}$ and the NMI **1** is a highly unfavorable process, having an activation free energy of $\Delta G^{o}_{(4)}$ = 14.5 kcal mol^{-1} (K^{o} = 2.5×10^{-11}) for the *s-trans* and *s-cis*-**7** $^{\bullet-}$ equilibrium mixture.



7$^{\bullet-}$ **1** **8**$^{\bullet}$ **1**$^{-}$ **(4)**

Proton affinity calculations: stabilized anions with Li^{+}. The previous unfavorable results, for Equation 4, can be rationalized taking into consideration that the calculations were performed for the isolated anions in gas phase without the stabilizing effect of the counterions. Thus, the observed energetic balance is principally due to the contribution of NMI (as the only neutral and stable species in the equilibrium). For that reason we considered the deprotonation reaction having the Li^{+} as counterion of the anionic species, as depicted in Equation 5.



From the data analysis, we observed that the cationic stabilization modified the equilibrium in the expected direction.[36] The free energy balance is far more equilibrated, with a $\Delta G^{o}_{(5)}$ = 1.8 kcal mol^{-1} (K^{o} = 4.6×10^{-2}). The structure of the species **Li^{+}7$^{\cdot -}$** and **Li^{+}1^{-}** are depicted in Figure 2. These results predicted a deprotonation equilibrium between the isoprene radical-anion **Li^{+}7$^{\cdot -}$** and the NMI **1**, providing the reaction intermediates **Li^{+}1^{-}** and 1,1-dimethylallyl radical **8**. The slightly endergonic balance of this first step, can be made up for a subsequent reaction, essentially irreversible, where radical **8$^{\cdot}$** would react.

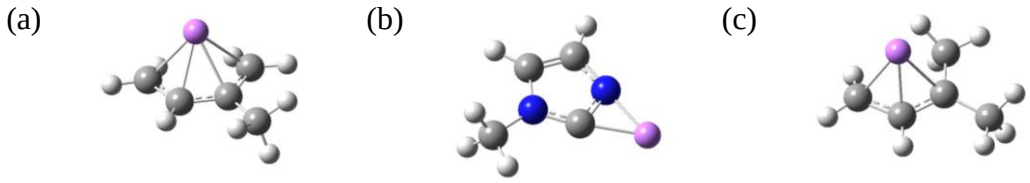
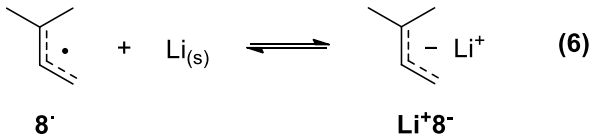


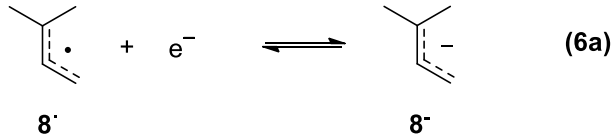
Figure 2. (a) Calculated structure for **Li^{+}7$^{\cdot -}$**; (b) calculated structure for 2-lithio-*N*-methylimidazole **Li^{+}1^{-}**; (c) calculated structure for dimethylallyllithium **Li^{+}8^{-}**.

Reaction of dimethylallyl radical. The 1,1-dimethylallyl radical **8$^{\cdot}$** is an unstable reaction intermediate and it can progress in various manners. Without dismissing the typical behavior of the radicals (such as coupling processes, dismutations, etc.), we considered at this point that radical **8$^{\cdot}$** mainly would be transformed into the corresponding anion stabilized with Li^{+} (1,1-dimethylallyllithium, **Li^{+}8^{-}**) by reaction with the excess of Li$_{(s)}$ in the reaction medium (Equation 6).

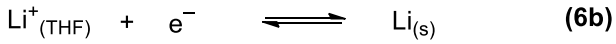


In Equation 6, it is involved a condensed phase, so a strict analysis of the process employing calculations is hampered. However, due to the fundamentally irreversible nature of the process, the thermodynamic parameters of the process were estimated employing some approximations and the experimental values of the reduction potentials, knowing full well that these approximations did not affect significantly the energetic balance of the global process, which is highly exergonic. For such purpose,

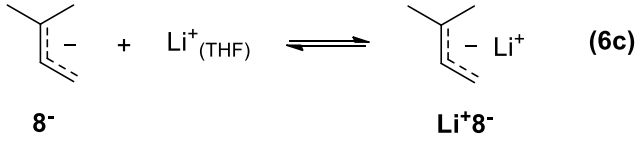
a) the values of the half-reactions of reduction depicted in Equations 6a and 6b were used, considering the calculated *EA* for the radical **8**$^{\cdot}$ in gas phase[34] and the experimental redox potential for $Li^{+}_{(THF)}/Li_{(s)}$, to obtain an approximated value of $\Delta G^{o}_{(6)}$;
b) the energy of solvation of Li^{+} in THF and the energy of formation of the **Li^{+}8^{-}** ion pair were equated (Equation 6c). This implies that $\Delta G^{o}_{(6c)} = 0$, what simplify the thermodynamic estimations for the overall process. These estimations, which are without doubt conservative (*vide infra*), avoid including solvation energies, what would make an exceedingly tedious calculation, as well as unnecessary.



(6a)

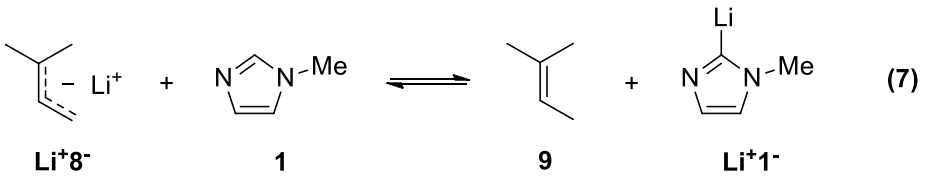


(6b)



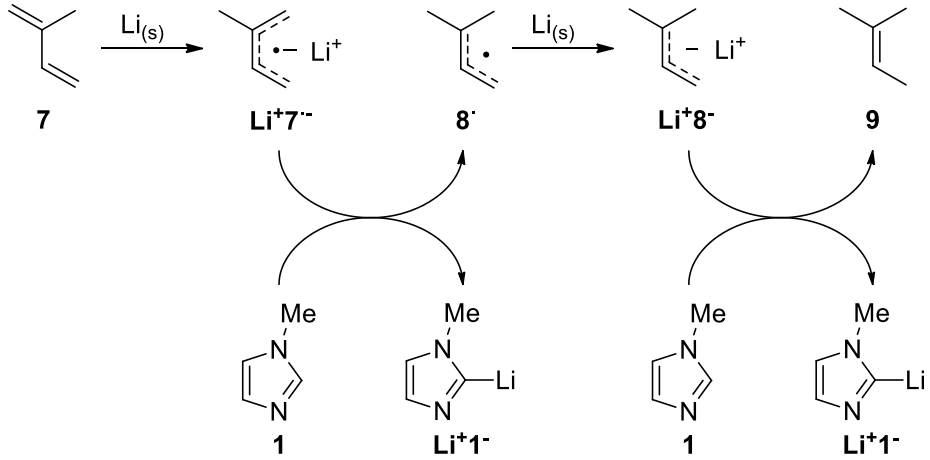
(6c)

Strictly, the solvation energies for intermediates **8**$^{\cdot}$ and **8**$^{-}$ were not estimated in the approximation done in 6c, as well as the energy of the ion pair $\mathbf{Li^{+}8^{-}}_{(THF)}$ formation from the corresponding THF solvated ions, being all of them exergonic contributions.[37] The free energy variations in standard conditions for both half-reaction redox were calculated: $\Delta G^{o}_{(6a)} = -7.7$ kcal mol^{-1},[38] and $\Delta G^{o}_{(6b)} = 75.9$ kcal mol^{-1}.[39] As expected, the standard free energy variation for Equation (6), $\Delta G^{o}_{(6)} = -83.6$ kcal mol^{-1}, showed an irreversible process ruled by the high redox potential of $Li_{(s)}$ in THF. Thus, the reduction of the radical **8**$^{\cdot}$ by metal lithium means adding an essentially irreversible step to the initial proposed step (slightly endergonic), what moves the different equilibriums to the formation of the corresponding products.
Final step. Finally, the corresponding calculations for deprotonation of NMI by 1,1-dimethylallyllithium **Li^{+}8^{-}** (Figure 2) were considered (Equation 7).[40] The variation of free energy for this last step, $\Delta G^{o}_{(7)} = -12.0$ kcal mol^{-1} ($K^{o} = 6.8\times10^{8}$), shows an exergonic favorable process. With this final step, the reagents were transformed to the stable final products, with the mediation of isoprene in the deprotonation step of NMI.



Conclusions

The deprotonation step in Equation 4, which uses the radical anion of isoprene **Li$^+$7** $^-$ as base, is slightly endergonic. Thus, this step can be considered the rate determinant step, among the postulated steps in homogenous phase. The protonation of **7** $^-$ occurs, in principle, at the $C_{(1)}$ of isoprene. This carbon is the one supporting the highest charge density and has the highest contribution to the HOMO, both as a free anion as well as forming an ionic pair with Li^+. The methylenic character of $C_{(1)}$ [as well as $C_{(4)}$] in **7** $^-$ can facilitate the approximation to the most acidic proton of NMI (the one in position 2), and the corresponding radical 1,1-dimethylallyl **8**$^\cdot$ is formed. The following irreversible reduction of **8**$^\cdot$ with $Li_{(s)}$, depicted in Equation 4, moves the previous equilibriums to the products. Finally, the formed dimethylallyllithium **Li$^+$8** $^-$ in that reduction can act also as a base deprotonating another molecule of NMI, so the isoprene can participate in substoichiometric amount compare to NMI (Scheme 1).[41]



Scheme 1. Proposed mechanism for the isoprene-mediated lithiation of *N*-methylimidazole employing lithium metal.

Although, there is no contribution regarding calculations of specific kinetic studies yet, the information provided by those would be, in any case, an incomplete vision of the process. Many of the heterogeneous processes involved, such as the initial isoprene reduction with $Li_{(s)}$ giving

Li^{+}8 $^{-}$ (which was deliberately omitted in the whole treatment) are not readily accessible from a theoretical point of view. Indeed, they are likely to be controlled by a mass-transport phenomenon, which is associated with complex, heterogeneous kinetics. To conclude, we have to say that different mechanisms, as well as alternative mechanisms running in parallel to this one cannot be ruled out, but they have not been further considered.

Acknowledgements

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References and Notes

1. (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (b) Xu, J.; Stevenson, J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177. (c) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.
2. (a) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses and Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (c) Polshettiwar, V.; Varma, R. S. *Pure Appl. Chem.* **2008**, *80*, 777. (d) Pastor, I. M.; Yus, M. *Curr. Chem. Biol.* **2009**, *3*, 385.
3. (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155-161. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225. (c) Yus, M. *Synlett* **2001**, 1197. (d) Yus, M. In *The Chemistry of Organolithium Compounds;* Rappoport, Z.; Mareck, I. Eds.; J. Wiley & Sons: Chichester, 2004; Ch. 11, 647.
4. (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155. (b) Najera, C.; Yus, M. *Org. Prep. Proced. Int.* **1995**, *27*, 383. (c) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67. (d) Yus, M.; Foubelo, F. *Rev. Heteroatom. Chem.* **1997**, *17*, 73; (e) Guijarro, D.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 713. (f) Yus, M.; Foubelo, F. *Targets Heterocycl. Syst.* **2002**, *6*, 136. (g) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867. (h) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453. (i) Chinchilla, R.; Najera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139. (j) Guijarro, D.; Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2010**, *14*, in press. (k) Guijarro, D.; Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2010**, *14*, in press.

5. (a) Foubelo, F.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1. (b) Alonso, F.; Meléndez, J.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2628. (c) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459.
6. (a) Guijarro, A.; Gómez, C.; Yus, M. *Trends Org. Chem.* **2001**, *8*, 65. (b) Alonso, F.; Radivoy, G.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2563. (c) Alonso, F.; Yus, M. *Chem. Soc. Rev.* **2004**, *33*, 284.
7. (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455. (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574.
8. Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2005**, *61*, 11148.
9. Pastor, I. M.; Torregrosa, R.; Yus, M. *Lett. Org. Chem.* **2010**, *7*, 373.
10. Torregrosa, R.; Pastor, I. M.; Yus, M. *Arkivoc* **2008**, (*vii)*, 8.
11. Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2007**, *63*, 947.
12. De Nicola, A.; Einhorn, J.; Lucke, J.-L. *J. Chem. Res (S)* **1991**, 278.
13. German Patent 19849197, 2000; Lischka, U.; Hauk, D.; Rittmeyer, P.; Wietelmann, U. *Chem. Abstr.* **2000**, *132*, 137554.
14. For the cleavage of the THF ring employing Li and 4,4'-di-*tert*-butyl-1,1'-biphenyl, giving lithium 4-lithiobutoxide and its used as base, see: Streiff, S.; Ribeiro, N.; Désaubry, L. *Chem. Commun.* **2004**, 346.
15. A mixture of lithium (15 mmol) and isoprene (3 mmol) was stirred in THF (10 mL) during 24 h, and after quenching the reaction mixture with ethanol an aliquot was injected in GCL and GC-MS giving no traces of 1-butanol.
16. Steward, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
17. (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864-B871. (b) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133.
18. (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; González, C.; Pople, J. A. *GAUSSIAN03*, Revision D.01, Gaussian, Inc. Pittsburgh PA, 2003. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. (c) Stephens, P. J.; Devlin, F. J.; Chablowski, C. F.; Frishe, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

19. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.
20. Analytic second derivative calculations, which yield the harmonic frequencies, were performed on the optimized geometries at the same level of theory to ensure that the optimized geometries are true minima on the potential energy surface and to provide corrections for the zero-point energy (*ZPE*) effects. All the frequencies found were real.
21. Traetteberg, M.; Paulen, G.; Cyvin, S. J.; Panchenko, Y. N.; Mochalov, V. I. *J. Mol. Struct.* **1984**, *116*, 141.
22. Calculated data [B3LYP/6-311++G(d,p)] for isolated *s-trans*-**7**, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.2559; ΔH^o = –195.2491; ΔS^o = 74.347; ΔG^o = –195.2844.
23. Calculated data [B3LYP/6-311++G(d,p)] for isolated *skew*-**7**, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.2515; ΔH^o = –195.2445; ΔS^o = 75.466; ΔG^o = –195.2804.
24. Calculated data [B3LYP/6-311++G(d,p)] for isolated *s-cis*-**7**, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.2505; ΔH^o = –195.2443; ΔS^o = 72.048; ΔG^o = –195.2785.
25. Calculated data [B3LYP/6-311++G(d,p)] for isolated *s-trans*-**7** $^-$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.2403; ΔH^o = –195.2329; ΔS^o = 77.674; ΔG^o = –195.2698.
26. Calculated data [B3LYP/6-311++G(d,p)] for isolated *s-cis*-**7** $^-$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.2409; ΔH^o = –195.2331; ΔS^o = 80.943; ΔG^o = –195.2715.
27. Chang-Guo, J.; Nichols, A.; Dixon, D. *J. Phys. Chem. A* **2003**, *107*, 4184.
28. Lu, J.; Zhu, S.; Zhou, Z.; Wu, Q.; Zhao, G. *Int. J. Quant. Chem.* **2006**, *106*, 2073.
29. Borisov, Y. U.; Garret, B. C.; Mazunov, V. A.; Nekrasov, Y. S. *J. Struct. Chem.* **2005**, *46*, 591.
30. For the best of our knowledge, there are not experimental values for the *EA* of NMI and isoprene yet. For calculations on the *EA* of the *N*-methyl-5-methylimidazolyl radical, see: Villano, S. M.; Gianola, A. J.; Eyet, N.; Ichino, T.; Kato, S.; Bierbaum, V. M.; Lineberger, W. C. *J. Phys. Chem. A* **2007**, *111*, 8579.
31. Calculated data [B3LYP/6-311++G(d,p)] for isolated NMI **1**, in gas phase (thermodynamic parameters calculated at 298.15 and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –265.5035; ΔH^o = –265.4971; ΔS^o = 74.650; ΔG^o = –265.5326. And for the radical anion of NMI (**1**$^{\cdot -}$), in gas phase (thermodynamic parameters calculated at 298.15 and 1 atm and all the values are zero

point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –265.4890; ΔH^{o} = –265.4826; ΔS^{o} = 75.798; ΔG^{o} = –265.5187.

32. Unfortunately, those values are in the range of the absolute deviation (±0.21 eV) expected for this method according to the calculated *EA* data for 12 small molecules and compared with the corresponding experimental *EA*: Takahata, Y.; Chong, D. P. *J. Braz. Chem. Soc.* **1999**, *10*, 354.
33. Takahata, Y.; Chong, D. P. *J. Braz. Chem. Soc.* **1999**, *10*, 354.
34. Calculated data [B3LYP/6-311++G(d,p)] for isolated radical **8**$^{\cdot}$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.8350; ΔH^{o} = –195.8273; ΔS^{o} = 80.926; ΔG^{o} = –195.8658.
35. Calculated data [B3LYP/6-311++G(d,p)] for isolated anion NMI **1**$^{-}$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –246.8852; ΔH^{o} = –264.8789; ΔS^{o} = 73.473; ΔG^{o} = –264.9138.
36. Calculated data [B3LYP/6-311++G(d,p)] for isolated *s-cis*-**Li**$^{+}$**7**$^{\cdot -}$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –202.7814; ΔH^{o} = –202.7733; ΔS^{o} = 80.817; ΔG^{o} = –202.8117. And for the radical anion of 2-lithio-NMI **Li**$^{+}$**1** $^{\cdot -}$, in gas phase (thermodynamic parameters calculated at 298.15 and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –272.4456; ΔH^{o} = –272.4383; ΔS^{o} = 73.473; ΔG^{o} = –272.4756.
37. Calculated data [B3LYP/6-311++G(d,p)] for isolated anion **8**$^{-}$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –195.8486; ΔH^{o} = –195.8407; ΔS^{o} = 78.616; ΔG^{o} = –195.8781. And for the anionic pair **Li**$^{+}$**1** $^{-}$, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –203.3896; ΔH^{o} = –203.3813; ΔS^{o} = 80.498; ΔG^{o} = –203.4195.
38. The electron affinity of **8**$^{\cdot}$ is *EA* = +0.37 eV.
39. It was estimated by means of Nerst equation, after converting to the SHE the corresponding experimental redox potential of Li^{+}/Li: Mortensen, J.; Heinze, J. *Tetrahedron Lett.* **1985**, *26*, 414.
40. Calculated data [B3LYP/6-311++G(d,p)] for isolated 2-methyl-2-butene **9**, in gas phase (thermodynamic parameters calculated at 298.15 K and 1 atm and all the values are zero point energy (*ZPE*) corrected: energies and enthalpies in a.u., entropies in e.u.): ΔE_{0K} = –196.4658; ΔH^{o} = –196.4579; ΔS^{o} = 79.501; ΔG^{o} = –196.4957.
41. After performing the reaction employing the standard conditions (excess of lithium, 20 mol% of isoprene in THF at 25 ºC), the presence of 2-methyl-2-butene was detected in the reaction medium by GC-MS (EI at 70 eV on an Agilent 5973 spectrometer).

