



HAL
open science

Unprecedented directed lateral lithiations of tertiary carbons on NHC platforms

Andreas A. Danopoulos, Pierre Braunstein, Elixabete Rezabal, Gilles Frison

► **To cite this version:**

Andreas A. Danopoulos, Pierre Braunstein, Elixabete Rezabal, Gilles Frison. Unprecedented directed lateral lithiations of tertiary carbons on NHC platforms. *Chemical Communications*, 2015, 51, pp.3049-3052. 10.1039/C4CC08434A . hal-01086025

HAL Id: hal-01086025

<https://hal.science/hal-01086025>

Submitted on 21 Nov 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Unprecedented directed lateral lithiations of tertiary carbons on NHC platforms†

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

Andreas A. Danopoulos,^{*a, b} Pierre Braunstein,^{*b} Elixabete Rezabal^c and Gilles Frison^{*c}www.rsc.org/

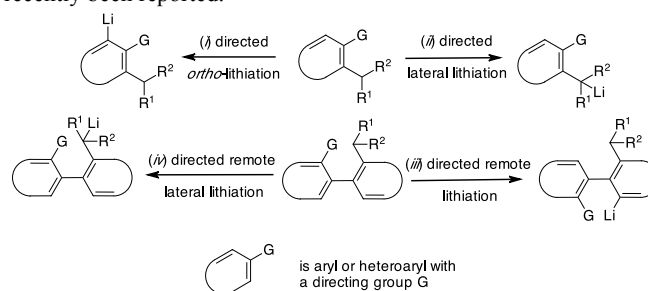
Unexpected and unprecedented directed remote lateral lithiation at one CH(CH₃)₂ of the 3-(2,6-di-isopropylphenyl) wingtip took place upon the reaction of functionalised N-heterocyclic carbene-type molecules with excess of LiCH₂SiMe₃, leading to dilithiated dianionic 4-amido-N-heterocyclic carbenes. DFT calculations show that the nature of the isolated species are under thermodynamic control.

Organolithium species, formed by the reaction of a lithiating reagent (e.g. alkyl Li) with C-H bonds of a (hetero)aromatic ring that is substituted by a directing group G, are at the core of a powerful synthetic methodology for the selective functionalisation of aromatics by metalation/lithiation.¹⁻³ G can direct deprotonation-metalation at various types of C-H bonds (as summarised in Scheme 1), most importantly adjacent aromatic C-H bonds (*ortho*-metalation), benzylic C-H bonds of an alkyl substituent *ortho*- to G (*lateral*, exocyclic metalations) and exocyclic C-H bonds at *remote* positions, including C-H bonds at neighbouring aromatic rings. The regioselectivity of lithiation, dictated by the competition of *ortho*- vs. *lateral*- and *ortho*- vs. *remote*-lithiation is dependent on many factors, e.g. the nature of alkyl Li, temperature, solvents, co-ligands *etc.*⁴ The role of polymeric aggregates on the regioselectivity control in directed metalations has been reviewed,⁵ while superbasic reagents produce mixtures of metalated products after long reaction times.⁶ Directed remote lateral benzylic deprotonation leading to *isolable* carbanionic lithium complexes is unknown.

The derivatisation of imidazole-type NHC molecules *via* direct metalation followed by quenching with electrophiles is attracting current interest since the report on lithiation of IPr (IPr = N,N'-bis-diisopropylphenyl-imidazol-2-ylidene) at the C4 by *n*-BuLi⁷ and the related direct zincation by alkali metal mediated zincation.⁸ Backbone metalation of the imidazole C4 in amido-functionalised NHC complexes of lanthanides by potassium reagents leading to heterometallic potassium lanthanide aggregates was also reported.⁹

Herein, we report unprecedented directed remote lateral lithiation at one *o*-CH(CH₃)₂ of a DiPP wingtip in NHC-type molecules. The reactions are fast and quantitative in THF at room temperature, which is to be contrasted to the widely known

disfavored lateral lithiation at alkyl-substituted benzylic positions, ascribable to steric and electronic reasons. The only examples of lateral benzylic lithiation of *o*-iPr to form *tert.* carbanions have recently been reported.^{10, 11}

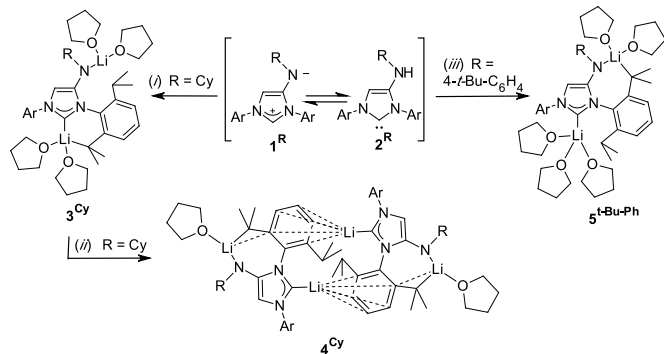


Scheme 1. Directed lithiations (top) and directed remote lithiations (bottom) at aromatic rings.

Reaction of the tautomeric mixture of 4-amido-imidazoliums (**1**^{Cy}) and 4-amino-carbenes (**2**^{Cy}) (for **1**^{Cy} \rightleftharpoons **2**^{Cy}, $K_{RT} \approx 0.33$)¹² in THF with 2 equiv. Me₃SiCH₂Li gave **3**^{Cy} (Scheme 2(i) and Fig. 1A), after crystallisation from THF/pentane, that features the monomeric, overall *dianionic* NHC ligand co-ordinated to two Li ions: one bound to *N*_{exo} (crystallographic Li2) and the second (crystallographic Li1) bound to the CMe₂ of a tertiary carbanion (henceforth Li atoms bound to CMe₂ are denoted as Li*); in **3**^{Cy}, Li* is also bound to the C_{NHC}.[‡] The coordination of both Li atoms is completed by THF co-ligands. Remarkably, and in contrast to the NHC ring metalation examples cited above,^{7,8} the second equivalent of Me₃SiCH₂Li did not metalate the remaining endocyclic C-H but rather the remote lateral CH(CH₃)₂ of the DiPP ring.

The angles at Li1 are affected by the formation of the chelate ring (*i.e.* short Li1-C_{NHC} and unequal angles at C_{NHC}). The planarity at the *N*_{exo} is consistent with an amido functionality bound to Li2, which also interacts with the C_{ipso} of the metalated ring (*ca.* 3.028 Å). With the aim to replace a Li cation with Me₃Si, 1 equiv. Me₃SiCl was added to a solution of **3**^{Cy} in ether. Instead, recrystallisation from pentane at -40 °C gave **4**^{Cy} (Scheme 2(ii) and Fig. 1B).[‡] **4**^{Cy} adopts in the solid state a dimeric structure with bridging Li1 and

Li3 bound to the C_{NHC} and interacting with the π -electrons of the metalated rings; no THF co-ligand is bound to Li1/Li3 atoms (see ESI). In contrast to **3^{Cy}**, the Li* (Li2/Li4) is now bound to the N_{exo}, resulting in a 'zwitterionic-type' electronic arrangement, with the anionic locus around the N_{exo}-Li*-CMe₂ moiety and the cationic locus centered at Li1/Li3.



Scheme 2. Reagents and conditions: (i) 2 equiv. Me₃SiCH₂Li, THF, RT, 83% yield, crystals from THF/pentane; (ii) 1 equiv. Me₃SiCl, ether, RT, 64-74% yield, crystals from pentane; (iii) 2 equiv. Me₃SiCH₂Li, THF, RT, 77% yield, crystals from THF. ‡

Dimer **4^{Cy}** can be viewed as a contact ion pair lithium lithiate.¹³ Although the details have not yet been elucidated, it appears that Me₃SiCl and/or Et₂O trigger partial THF dissociation which in turn leads to reorganisation of the lithiated species.

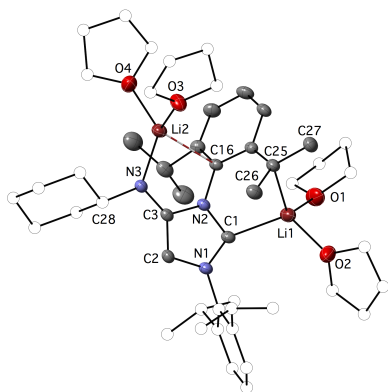


Figure 1A. The structure of **3^{Cy}** that features the monomeric, overall dianionic NHC ligand co-ordinated to two Li ions. ‡

Whereas C_{NHC}-bound Li* was observed in **3^{Cy}**, lithiation of (**1^{t-Bu-Ph}** ⇌ **2^{t-Bu-Ph}**), (*K_{RT}* = 0), resulted in the dilithiated **5^{t-Bu-Ph}** with N_{exo}-bound Li* (Scheme 2(iii) and ESI). ‡

Unexpectedly, in all the dilithiated species isolated, the Li-C_{NHC} distances¹⁴ are significantly shorter than those of the Li*-CMe₂. However, metrical data trends cannot be unequivocally rationalised due to the influence of differing number of coordinated ether-type co-ligands at the various Li centres. In contrast, the Li-N_{exo} bond distances show little variation falling within the range of 3-coordinate anionic N-Li distances (average 1.985 Å) and consistent with Li-N_{amido} description and planarity at N_{exo}. The structural features in the lithiated ring are also worth noting: the CMe₂ substructure is planar (sums of angles at CMe₂ 354.65°-358.40°) and the endocyclic C-C distances are unequal, with C-CMe₂ distances short (1.385(3)-1.417(3) Å), and distances of C-CMe₂ to the other endocyclic C atoms significantly longer than typical aromatic bonds. This motif points to partial de-aromatisation and

contribution of a dimethyl-methylene-cyclohexadienyl form (Fig. S6 in ESI). ‡ The Li* is part of a distorted lithia-cyclopropenyl ring involving the C-CMe₂ unit. Similar distortions were observed in the only other metalated DiPP ring reported recently.^{10, 11}

Diverse types of directing groups have been studied in conjunction to C-H lithiations, including electrophilic (e.g. *sec.* and *tert.* amides -C(=O)NHR, -C(=O)NRR', esters C(=O)OR, acids C(=O)OH, imidazolines, etc.) or non-electrophilic (e.g. -OR, -NH₂, -NHR, etc.).¹⁵ Insight into the nature of the directing group involved (Scheme 3) and the factors responsible for the formation of **3^{Cy}** and **5^{t-Bu-Ph}** was gained by DFT studies.

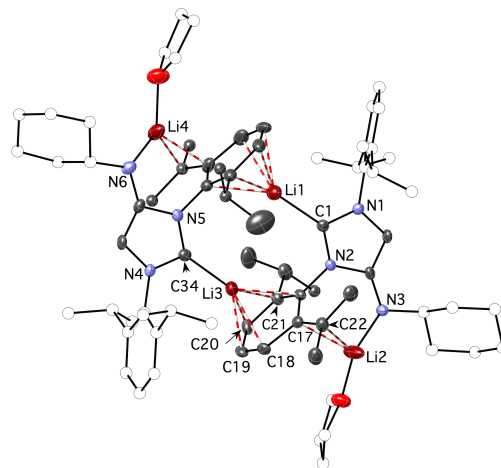


Figure 1B. The dimeric structure of **4^{Cy}**. ‡

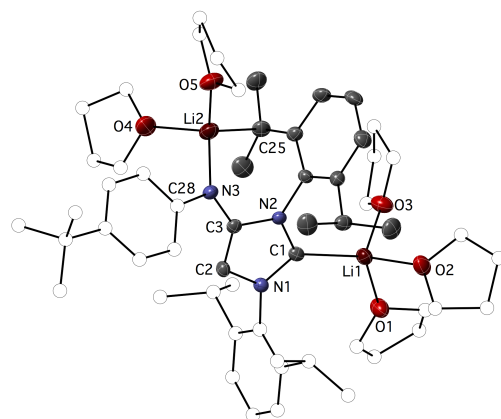
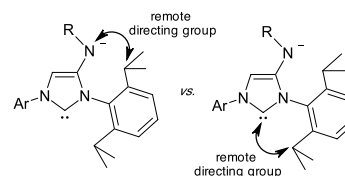


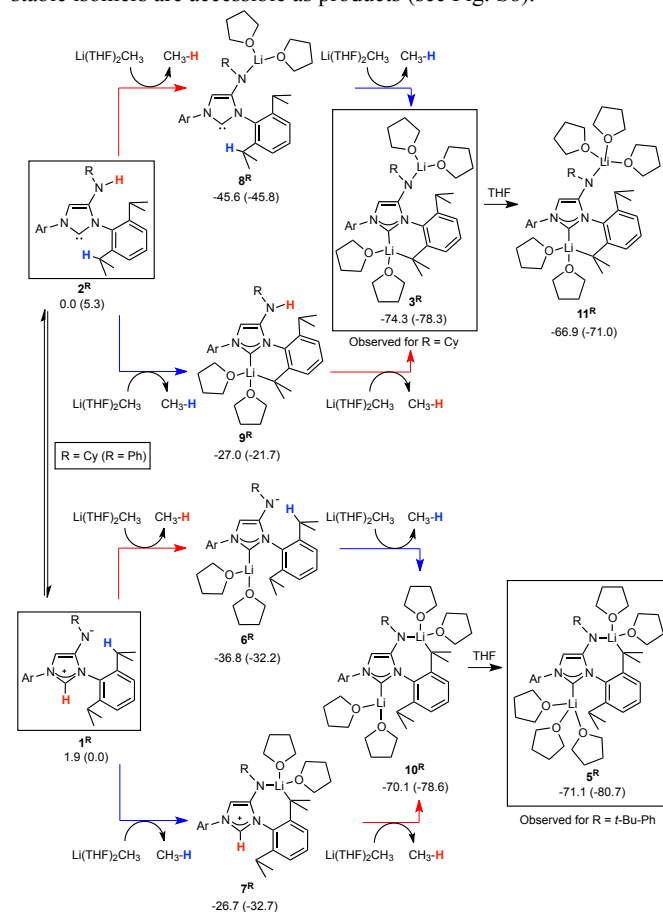
Figure 2. The structure of the dilithiated complex **5^{t-Bu-Ph}**, only one disordered *t*-Bu and THF containing O3 and O5 are shown. ‡



Scheme 3.

Starting from the tautomers **1^R** and **2^R** (R = Cy,¹² Ph¹⁶), the energies of the products obtained by the sequential reaction with one and two LiCH₃(THF)₂ were computed (Scheme 4). For both substituents the most stable products from the first lithiation were the amido-carbenes **8^R**, after N_{exo}-lithiation of the **2^R** tautomers. In the subsequent lithiation, for R = Cy, **3^{Cy}** (Li* bound to C_{NHC}) is the

most stable, while for R = Ph, 10^{Ph} (Li^* bound to N_{exo} and two THF molecules/Li) is slightly more stable than the 3^{Ph} analogue. Addition of one more THF ligand to the three coordinate Li of 3^{R} and 10^{R} confirms that 5^{Ph} is the most stable for R = Ph. These results agree with experimental data and suggest that the nature of products is controlled thermodynamically. Since for R = Ph, the most stable species after the first lithiation cannot be considered direct precursor (e.g. by sequential deprotonation) to the observed product, an equilibrium along the reaction path should be established to account for the final result. This hypothesis was tested by calculating the transition state between simplified models of 3^{R} and 10^{R} . The low energy barrier between these two isomers (5.4 kcal/mol) demonstrates that, independently of the reaction pathway, the most stable isomers are accessible as products (see Fig. S8).



Scheme 4. Reaction paths computed at the IEFPCM(THF)/M06-2X/6-31++G(d,p) level. Relative energies in kcal/mol for R = Cy (Ph in bracket).

In contrast to the common metalation of the *o*-methyls of the mesityl wingtips in NHC complexes, metalation of $-\text{CH}(\text{CH}_3)_2$ of the DiPP wingtips (leading to $-\text{CH}(\text{CH}_3)(\text{CH}_2\text{M})$) is also very rare.^{17,18} The unique reactivity described herein involving $-\text{CH}(\text{CH}_3)_2$ metalation of the DiPP wingtips opens new perspectives, in particular in view of the widespread use of this substituent in NHC chemistry. Metal catalysed functionalisation of the *i*-Pr of the DiPP to allyl or alkene complexes, *via* initial C-H metalation has also been rarely observed.¹⁹

For comparison, when organopotassium bases in excess were reacted with the analogous tautomeric mixture of 4-amido-imidazolium and 4-amino-carbene, remote metalation did not occur and the excess of base (benzyl potassium) was incorporated into an organometallic copolymeric structure.¹²

In conclusion, we have described unprecedented lithiation reactions of the tertiary C in $\text{CH}(\text{CH}_3)_2$ of the DiPP wingtip in a remote substituted amido NHC, and rationalised the observed reactivity and regioselectivity by DFT methods. The scope of the reaction, its underlying mechanism and its potential as a tool for accessing new NHC ligands and complexes is now being studied in our laboratory.

The USIAS, CNRS, Région Alsace and Communauté Urbaine de Strasbourg are thanked for the award of fellowships and a Gutenberg Excellence Chair (2010–11) to AAD. We thank the CNRS, the MESR (Paris), the UdS and the ucFRC, (www.icfrc.fr) for funding and the Service de Radiocristallographie (UdS) for the crystal structures. The computational work was performed using HPC resources from GENCI-CINES/IDRIS (Grant 2014-x2014 086894).

Notes and references

^a Institute for Advanced Study (USIAS), Université de Strasbourg (UdS), 4 rue Blaise Pascal, 67081 Strasbourg Cedex, France.

^b Laboratoire de Chimie de Coordination, Institut de Chimie (UMR 7177 CNRS), UdS, 4 rue Blaise Pascal, 67081 Strasbourg Cedex, France.

^c Laboratoire de Chimie Moléculaire, Ecole Polytechnique and CNRS, 91128 Palaiseau Cedex, France.

† Warmly dedicated to Prof. D. M. P. Mingos on the occasion of his 70th birthday and for his outstanding contributions to chemistry.

‡ Electronic Supplementary Information (ESI) available: Experimental and X-ray crystallographic data. CCDC 1020248 (3^{Cy}), 1020257 (4^{Cy}), 1020254 ($5^{\text{t-Bu-Ph-THF}}$). See DOI: 10.1039/c000000x/

- J. Clayden, *The Chemistry of Organolithium Compounds*, Wiley, Chichester, 2004.
- M. C. Whisler, S. MacNeil, V. Snieckus and P. Beak, *Angew. Chem. Int. Ed.*, 2004, **43**, 2206-2225.
- D. Tilly, J. Magolan and J. Mortier, *Chem. Eur. J.*, 2012, **18**, 3804-3820.
- J. T. B. H. Jastrzebski, A. M. Arink, H. Kleijn, T. W. Braam, M. Lutz, A. L. Spek and G. van Koten, *J. Am. Chem. Soc.*, 2013, **135**, 13371-13378.
- H. J. Reich, *Chem. Rev.*, 2013, **113**, 7130-7178.
- D. Wilhelm, T. Clark, P. v. R. Schleyer, J. L. Courtneidge and A. G. Davies, *J. Am. Chem. Soc.*, 1984, **106**, 361-367.
- Y. Wang, Y. Xie, M. Y. Abraham, P. Wei, H. F. Schaefer, P. von R. Schleyer and G. H. Robinson, *J. Am. Chem. Soc.*, 2010, **132**, 14370-14372.
- D. R. Armstrong, S. E. Baillie, V. L. Blair, N. G. Chablos, J. Diez, J. Garcia-Alvarez, A. R. Kennedy, S. D. Robertson and E. Hevia, *Chem. Sci.*, 2013, **4**, 4259-4266.
- P. L. Arnold and S. T. Liddle, *Organometallics*, 2006, **25**, 1485-1491.
- A. Campbell Smith, M. Donnard, J. Haywood, M. McPartlin, M. A. Vincent, I. H. Hillier, J. Clayden and A. E. H. Wheatley, *Chem. Eur. J.*, 2011, **17**, 8078-8084.
- M. A. Vincent, A. Campbell Smith, M. Donnard, P. J. Harford, J. Haywood, I. H. Hillier, J. Clayden and A. E. H. Wheatley, *Chem. Eur. J.*, 2012, **18**, 11036-11045.
- A. A. Danopoulos and P. Braunstein, *Chem. Commun.*, 2014, **50**, 3055-3057.
- C. Eaborn, P. B. Hitchcock, J. D. Smith and A. C. Sullivan, *J. Chem. Soc., Chem. Commun.*, 1983, 827-828; W. Clegg, M. R. J. Elsegood, L. Horsburgh, R. E. Mulvey and M. J. Ross, *Chem. Ber.* 1997, **130**, 621-631
- S. Bellemin-Lapponnaz and S. Dagorne, *Chem. Rev.*, 2014, **114**, 8747-8774.
- J. C. Clayden in *Tetrahedron Organic Chemistry Series*, ed. J. C. Clayden, Elsevier, 2002, vol. Volume 23, pp. 9-109.
- Unpublished results.
- C. Y. Tang, W. Smith, A. L. Thompson, D. Vidovic and S. Aldridge, *Angew. Chem., Int. Ed.*, 2011, **50**, 1359.
- O. Rivada-Wheelaghan, B. Donnadieu, C. Maya and S. Conejero, *Chem. Eur. J.*, 2010, **16**, 10323-10326.
- C. Y. Tang, W. Smith, D. Vidovic, A. L. Thompson, A. B. Chaplin and S. Aldridge, *Organometallics*, 2009, **28**, 3059-3066.