

Cite this: *Chem. Commun.*, 2011, **47**, 9918–9920

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## COMMUNICATION

## 2-Lithiated-2-phenyloxetane: a new attractive synthon for the preparation of oxetane derivatives†‡

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Received 20th June 2011, Accepted 14th July 2011

DOI: 10.1039/c1cc13670d

A valuable and direct method to access 2-substituted-2-phenyloxetanes by electrophilic quenching of the corresponding 2-lithiated derivative has, for the first time, been described. 2-Lithiated-2-phenyloxetane was found to be configurationally unstable. Evidence is presented to show that electron-transfer processes are also operative in the coupling reactions with electrophiles.

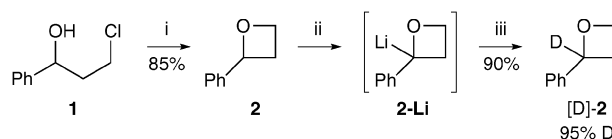
Oxetanes, the closest homologs to epoxides, are an important group of four-membered cyclic ethers that can undergo a wide range of chemical transformations and whose ring motif is also found in many natural products that exhibit a range of biological activities.<sup>1</sup> The importance of oxetanes as versatile building blocks in synthetic and medicinal chemistry as well as in material and agrochemical sciences has dramatically increased over the last ten years with the development of new and efficient methods for their preparation.<sup>2</sup> Despite recent advances, their reactivity towards organometallic reagents has only been scarcely explored compared to that of ethers and epoxides.<sup>3</sup> A closer perusal of the literature reveals that, to date, organolithium and organomagnesium reagents have been shown to be effective in triggering Lewis acid-catalysed oxetane-ring-opening reactions only, exploiting the strain of the four-membered ring.<sup>4</sup>

In the 1980s, the reactivity of 3,3-disubstituted oxetanes towards alkylolithiums was first investigated by Klumpp and coworkers:<sup>5</sup> nucleophilic substitution at C-2 always competed with  $\alpha$ -lithiation. Quenching of the reaction mixture with a deuterium source, however, provided no  $\alpha$ -deuterated products. Metalated oxetanes have also been shown to occur as intermediates in the isomerisation of (*E*)-1-benzyloxy-2,3-epoxyalkanes to unsaturated diols upon treatment with the superbasic mixture, lithium diisopropylamide/potassium *tert*-butoxide.<sup>6</sup> In the 1990s, the carbenoid nature<sup>7</sup> of  $\alpha$ -lithiated ethers was unambiguously proved by Boche and coworkers.<sup>8</sup> In general, aggregation and solvation of lithium carbenoids are crucial factors to be taken into

consideration for a proper tuning of their reactivity toward a nucleophilic/electrophilic behavior.<sup>9</sup> In the case of  $\alpha$ -lithiated styrene oxide, for example, its dichotomous reactivity could successfully be tuned in THF by the concentration.<sup>10</sup> Inspired by the intensive interest in the field of  $\alpha$ -lithiated oxiranes,<sup>11</sup> we became intrigued by the possibility both of generating an  $\alpha$ -lithiated oxetane chemically stable on the timescale of its reactions and of investigating its reactivity. Herein, we report an efficient route to 2-substituted phenyloxetanes obtained exploiting the nucleophilic character of 2-lithio-2-phenyloxetane, **2-Li**, chosen as a model of a stabilised intermediate. Stereochemical integrity of such a reactive species has also been tackled.

2-Phenyloxetane **2** (Scheme 1) was straightforwardly prepared in 85% yield by basic cyclisation of 3-chloro-1-phenyl-1-propanol **1**, as similarly reported for other cases.<sup>4b</sup> Treatment of a precooled ( $-78\text{ }^{\circ}\text{C}$ ) THF solution (0.2 M) of **2** (1 equiv.) with *s*-BuLi (1.4 equiv.) led to regioselective generation of **2-Li** through a clean hydrogen–lithium exchange. Quenching of the reaction mixture after only 5 min with MeOD gave deuterated oxetane [D]-**2** (<sup>1</sup>H NMR analysis) (90% yield, 95% D). As for the bases and the nature of the solvents, we ascertained that (a) both lithium diisopropylamide (LDA) and *n*-BuLi were ineffective (THF,  $-78\text{ }^{\circ}\text{C}$ , 5 min) and also that (b) no deprotonation occurred when *rac*-**2** was treated with *s*-BuLi employing toluene or hexane as the sole solvent.<sup>12</sup> On the other hand, lithiation of **2** with *s*-BuLi in Et<sub>2</sub>O afforded, after MeOD quenching, [D]-**2** with only 10% D even after 15 min deprotonation time.

The chemical stability of **2-Li** in THF was also checked at longer reaction time: after 30 min stirring at  $-78\text{ }^{\circ}\text{C}$ , followed by quenching with MeOD, [D]-**2** was recovered with the same yield and deuterium content. The temperature proved to be critical. Indeed, at a temperature higher than  $-78\text{ }^{\circ}\text{C}$ , **2-Li** mainly underwent decomposition with the formation of a complex reaction mixture of unidentified products. It is also worth pointing out that even running the deprotonation of oxetane **2** (1 equiv.) in THF with *s*-BuLi (1.4 equiv.) at  $-78\text{ }^{\circ}\text{C}$



**Scheme 1** (i) *t*-BuOK/THF, 4 h,  $25\text{ }^{\circ}\text{C}$ . (ii) *s*-BuLi, THF,  $-78\text{ }^{\circ}\text{C}$ , 5 min. (iii) MeOD.

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† This paper is dedicated to the memory of Professor Gernot Boche, an outstanding scientist, whose pioneering contributions to the field of lithium carbenoids continue to inspire.

‡ Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of <sup>1</sup>H/<sup>13</sup>C NMR spectra for compounds **2c**–**4**, **4** and **6**. See DOI: 10.1039/c1cc13670d

**Table 1** Synthesis of 2-substituted 2-phenyloxetanes **2a–l**

Oxetanes <b>2a–l</b> (Yield %) <sup>a</sup>		
1	2	3
4	5	6
7	8	9
10	11	12

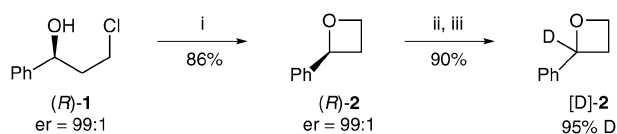
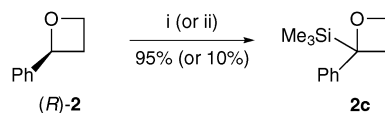
<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> Overall isolated yields in both diastereomers. <sup>c</sup> Diastereomeric ratio = 2 : 1. <sup>d</sup> Inseparable mixture of diastereomers. <sup>e</sup> Relative configuration has not been assigned. <sup>f</sup> Diastereomeric ratio = 1.2 : 1. <sup>g</sup> Separable mixture of diastereomers.

in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), followed by quenching with MeOD, led to both minor yield (50%) and deuterium content (62% D) of [D]-**2**.<sup>13</sup>

With efficient reaction conditions in hand, we surveyed the nucleophilicity of **2-Li** towards representative, structurally diverse electrophiles in order to prepare 2,2-disubstituted derivatives. The reactions of **2-Li** with alkyl halides (MeI, EtI) as well as with Me<sub>3</sub>SiCl and *n*-Bu<sub>3</sub>SnCl proceeded efficiently, thereby giving the desired substitution products **2a–d** in excellent yields (86–95%) (Table 1, entries 1–4). Similarly, **2-Li** underwent efficient benzylation and benzoylation (60–70% yield) upon exposure to benzyl chloride and *N,N*-dimethylbenzamide (Table 1, entries 5 and 6). Aliphatic and aromatic aldehydes and ketones (pivalaldehyde, *p*-chlorobenzaldehyde, acetaldehyde, acetone, isopropyl phenyl ketone, and benzophenone) also reacted smoothly, thereby affording the expected addition products **2g–l** in very good yields (70–82%) (Table 1, entries 7–12), albeit with poor diastereoselectivity (dr = 1.2–2 : 1) at the newly created stereogenic centres (Table 1, entries 7–9 and 11). Of particular note, enolisation did not appreciably complicate the additions, as reaction of **2-Li** with acetaldehyde, acetone and isopropyl phenyl ketone did furnish the corresponding hydroxyalkylated products **2i–k** in 75–82% yield, respectively (Table 1, entries 9–11).

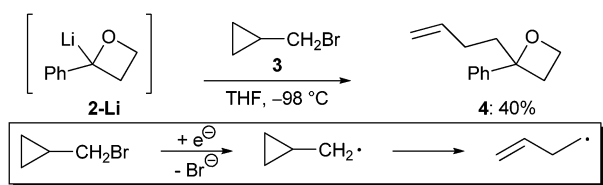
Attention was then turned towards investigating the configurational stability of **2-Li**. To this end, enantiomerically enriched (*R*)-**2** (er 99 : 1) was similarly prepared in 86% yield by stereospecific basic cyclisation of commercially available 3-chloro-1-phenyl-1-propanol (*R*)-**1** (er = 99 : 1) (Scheme 2).<sup>4b</sup>

The deprotonation of (*R*)-**2** with *s*-BuLi (1.4 equiv.) in THF at –78 °C, followed by quenching with MeOD, gave completely

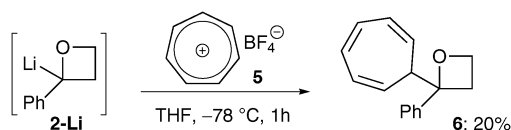
**Scheme 2** (i) *t*-BuOK/THF, 4 h, 25 °C. (ii) *s*-BuLi, THF, –78 °C, 5 min. (iii) MeOD.**Scheme 3** (i) *s*-BuLi, THF/Et<sub>2</sub>O (3 : 2), –116 °C, Me<sub>3</sub>SiCl (*in situ* quenching). (ii) *s*-BuLi/TMEDA, Et<sub>2</sub>O, –116 °C, Me<sub>3</sub>SiCl (*in situ* quenching).

racemic [D]-**2** (90% yield, 95% D) after a 5 min reaction time (Scheme 2). Even an *in situ* trapping experiment with Me<sub>3</sub>SiCl as the electrophile at –116 °C both in THF/Et<sub>2</sub>O (3 : 2) (as the sole solvent mixture) and Et<sub>2</sub>O in the presence of TMEDA (1 equiv.)<sup>14</sup> essentially gave racemic silane **2c** in 95% and 10% yield, respectively (Scheme 3). The configurational lability of lithiated oxetane **2-Li** in ethereal solvents was thereby revealed.

Additionally, in contrast to what was observed in the case of lithiated styrene oxides,<sup>11c</sup> even the employment of hexane/TMEDA was ineffective to hinder the racemisation of **2-Li**. Indeed, once such a reactive intermediate was generated by treating (*R*)-**2** with *s*-BuLi (1.4 equiv.) at –78 °C in the foregoing solvent mixture (hexane/TMEDA), it similarly underwent very quick racemisation to give, after *in situ* quenching with Me<sub>3</sub>SiCl, again, completely racemic **2c** (40% yield). In previous work,<sup>13</sup> we ascertained that  $\alpha$ -lithiated styrene oxide is either configurationally stable at –100 °C in THF or it reacts with all electrophiles under strict stereoretention.<sup>10,13</sup> One possibility to explain the missing configurational stability exhibited by **2-Li** in polar solvents is that an enhanced stability of the carbanion by resonance increases planarisation of the carbanionic center and the formation of a solvent-separated ion pair.<sup>15</sup> In such a case, intra- and intermolecular dynamic processes may promote racemisation, thereby facilitating the migration of the lithium cation from one enantiotopic face to the other. Lithiated oxetane **2-Li**, however, as stated above, undergoes racemisation in non-polar hydrocarbon solvents as well. Thus, epimerisation also through a higher aggregate<sup>16</sup> cannot be ruled out at least at present as we do not know the aggregation state of **2-Li**.<sup>15</sup> Astonished by the *completely racemic* substitution product **2c** obtained upon an *in situ* quenching of **2-Li** with Me<sub>3</sub>SiCl (Scheme 3), we also wondered whether a single-electron transfer (SET) mechanism competes with a polar one. To determine if such a radical pathway was also operational in the reaction with electrophiles, lithiated oxetane **2-Li** was reacted in THF at –98 °C with cyclopropylmethyl bromide **3**, which is a very fast radical probe. The only product isolated by column chromatography (40% yield) (with almost 50% of the starting substrate remaining) was the linear butenyl-substituted oxetane **4** resulting from coupling with the more stable butenyl radical further to the radical opening of the cyclopropyl ring (Scheme 4). The formation of **4** is consistent with an SET mechanism.<sup>17</sup>



Scheme 4



Scheme 5

To the best of our knowledge, such a mechanism is sometimes operative in the case of  $\alpha$ -aminoorganolithiums but it has never been observed, to date, for  $\alpha$ -alkoxyorganolithiums.

The reactivity of **2-Li** with tropylium tetrafluoroborate **5**, which is one of the most stable non-benzenoid aromatic carbenium ions much less prone to undergo an SET process<sup>18</sup> was also investigated (Scheme 5). The occurrence of one-electron transfer towards cation **5** would give rise to a troyl radical which is known to dimerise to ditroyl.<sup>18b,c</sup> However, the only compound detected in the crude reaction mixture and isolated (20% yield)<sup>19</sup> was the covalently bonded  $\alpha$ -troylated adduct **6**. This “negative” result neither excludes nor confirms the intervention of an SET process, since the rates of both the polar and the radical coupling reactions have not been measured.<sup>17</sup>

In summary, we have shown for the first time that the regioselective  $\alpha$ -deprotonation of 2-phenyloxetane is possible (*s*-BuLi, THF, -78 °C) and that the carbanionic character of the corresponding  $\alpha$ -lithiated species obtained can be fruitfully exploited for synthesising phenyl-substituted derivatives with a variety of different electrophiles well-accommodated onto the oxetane core.<sup>20</sup> Evidence for configurational instability (in both polar and non-polar solvents) was also found for  $\alpha$ -lithiated phenyloxetane, **2-Li**, with radical processes competing with polar enantiomerisation mechanisms most likely in those reactions where either electrophiles that are easily reduced (e.g. benzophenone) or “activated” halides (e.g. benzyl chloride) are involved. Support for this came from the isolation of the butenyl-coupled product **4** in the reaction of **2-Li** with the “activated” halide cyclopropylmethyl bromide **3**.<sup>17</sup> Expectations of considerable synthetic utility rest upon the control of stereochemistry, which could be achieved particularly by asymmetric substitution of chiral lithiated oxetanes that can undergo dynamic equilibration. This issue is currently being investigated in our laboratory.

This work was financially supported by MIUR-FIRB (Code: CINECA RBF12083M5N), the University of Bari, and Interuniversities Consortium C.I.N.M.P.I.S. We are especially grateful to Professor Saverio Florio for his sustained interest and support in this study and to Prof. Robert E. Gawley for valuable discussions.

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- Running the deprotonation of (*R*)-**2** with *s*-BuLi at -116 °C in Et<sub>2</sub>O in the absence of TMEDA, **2c** formed in less than 5% yield (<sup>1</sup>H NMR and GC-MS analysis); thus, its er could not be determined.
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