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Unexpected lateral-lithiation-induced alkylative ring opening of tetrahydrofurans in deep eutectic solvents: synthesis of functionalised primary alcohols

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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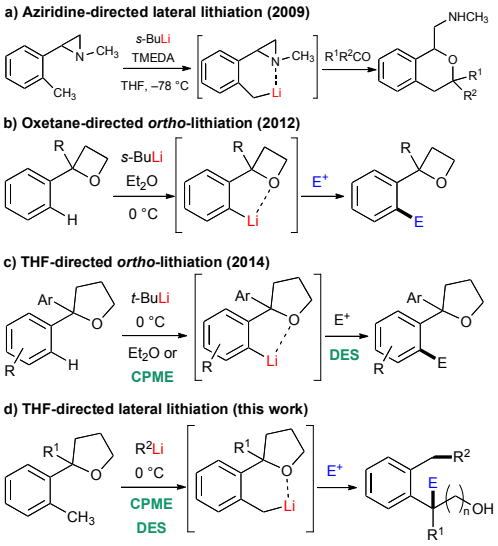
Francesca C. Sassone, Filippo M. Perna, Antonio Salomone, Saverio Florio, and Vito Capriati*

***o*-Tolyl-substituted tetrahydrofurans undergo a highly regioselective ring opening with the concomitant formation of new C–C bonds further to a lateral lithiation reaction. This reaction provides a new method for the synthesis of functionalised primary alcohols and can be run directly in protic eutectic mixtures as benign reaction media at 0 °C and under air, competitively with protonolysis.**

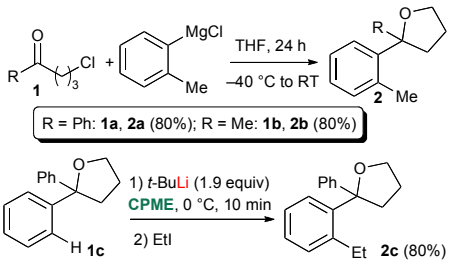
The regioselective lithiation of benzylic alkyl groups *ortho* to a directing group is generally referred to as a directed lateral lithiation (DLL). This methodology, which usefully complements other directed lithiation strategies, in elaborating aromatic systems (e.g., directed *ortho* and remote metalations),[1] has proven to be a valuable tool in both the chain extension at the benzylic position and in the synthesis of fused carbocyclic and heterocyclic systems via the annulation of chain-extended products. A large variety of functional groups (e.g., amides, nitriles, carboxylates, aldehydes, ketones, alcohols, various thio derivatives, etc.) have been found to successfully promote DLL by means of an interplay of coordination and conjugation effects.[2] Advances in the lateral lithiation of substituted aromatics directed by saturated heterocycles, however, have largely remained elusive. A notable exception includes the benzylic lithiation of *o*-tolyl aziridines that have been successfully exploited for the stereoselective preparation of isochromans by the intramolecular cyclisation of the corresponding hydroxyalkylated derivatives (Scheme 1a).[3] To the best of our knowledge, however, lateral lithiation, promoted by saturated oxygen heterocycles, has never been investigated. Our group recently reported the first directed *ortho*-lithiation/functionalisation of both aryloxetanes[4] and aryl-tetrahydrofurans (Schemes 1b,c).[5] In further expanding the above chemistry, we became intrigued by the possibility that a THF moiety might also induce a DLL. In this work, we disclose a new, unexpected, tetrahydrofuran (THF) ring-opening reaction triggered by a laterally lithiated THF derivative, that can be *directly* generated in a glycerol-containing deep eutectic mixture (*DES*), and thus, under more environmentally benign conditions (Scheme 1d).[6]



Scheme 1 Heterocyclic-directed ortho/lateral lithiation

2-Phenyl-2-*o*-tolyltetrahydrofuran **2a** was selected as a model substrate. This compound could be straightforwardly prepared in an 80% yield via an intramolecular Williamson ether synthesis, by reacting a THF solution of the commercially available *o*-tolylMgCl (3 equiv), with 4-chloro-1-phenylbutan-1-one (1 equiv) **1a** for 24 h (Scheme 2). In a preliminary experiment, when an Et_2O solution of **2a** (1 equiv) was treated at 0 °C, and under nitrogen, with *t*-BuLi (1.1 equiv), followed by trapping with MeOD, a new product (**3a-D**) could be isolated in a 30% yield, along with the starting material only

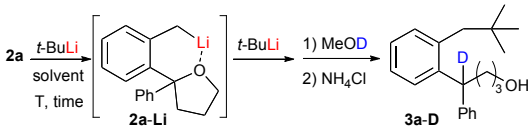
(Table 1, Entry 1). A full spectroscopic characterisation by homonuclear and heteronuclear NMR experiments, and by FT-IR and ESI-MS analysis, revealed that an unexpected THF ring-opening reaction occurred with the formation of a functionalised primary alcohol. This was tethered to the aromatic ring by a four-carbon chain showing the incorporation of both the *t*-BuLi moiety at the benzylic position (apparently, the same position that would have been affected by lithiation) and deuterium (>98% D) at a tertiary carbon centre, as judged by trapping the above reaction mixture with MeOH (compound **3a-H**).



Scheme 2 Synthesis of aryltetrahydrofurans **2a**–**c**

Interestingly, using a two-fold excess of *t*-BuLi, led to an increase of the yield in **3a-D**, up to 80% (Table 1, Entry 2), whereas the employment of temperatures as low as –78 °C, led only to the recovery of the starting material (Table 1, Entry 3). Running the reaction at room temperature resulted in an isolation of **3a-D** in a 55 % yield (Table 1, Entry 4). Building on our recent findings[5] that the THF-directed *ortho*-lithiation could also be also successfully carried out in *DESs*,[6] we next examined the effectiveness of these "green solvents" as benign reaction media for the above deprotonation.[7] Remarkably, when a commercial pentane solution of *t*-BuLi (2 equiv) was added by rapidly spreading it out over a mixture of **2a** (0.5 mmol previously solubilised in 0.5 mL of cyclopentyl methyl ether (CPME))[8] in the choline chloride (ChCl)-glycerol (Gly) *DES* (1:2), at *0 °C, under air*, and under vigorous stirring,[§] adduct **3a-D** could be recovered in a 90% yield and >98% D, and competitively with protonolysis, upon quenching after a 3 min reaction time with MeOD (Table 1, Entry 5). Under these latter conditions, methylation with MeI gave a clean reaction providing alcohol **3b** in an 85% yield with the creation of an all-carbon quaternary stereogenic centre (Scheme 3). Ethylation with EtI was also clean but afforded alcohol **3c** in a 50% yield. The use of carbonyl compounds (e.g., benzophenone, *p*-chlorobenzaldeyde, and acetone) as electrophiles did not lead to the isolation of any hydroxyalkylated adduct; rather, the only products identified in the crude reaction mixture (^{1}H NMR and GC-MS analysis) included alcohol **3a-H** (80% yield) and a mixture of isomeric alkenes **4** (20% yield) (Scheme 3). The latter presumably derives further to a direct β-hydride transfer from the putative sterically hindered intermediate **7** (*vide infra*) to the above electrophiles. On the other hand, complex mixtures were obtained with chlorodiphenylphosphine, allyl bromide, benzyl chloride, and *p*-tolylisocyanate with variable amounts of **3a-H** (15–30%). In the case of *N*-fluorobenzensulfonimide (NFSI) and Me_3SiCl, the main adducts were **5a** (40% yield) and **5b** (41% yield by ^{1}H NMR) (Scheme 3). The latter, however, could only be detected in the crude reaction mixture (^{1}H NMR and GC-MS analysis) and could not be isolated because of its instability on silica gel.

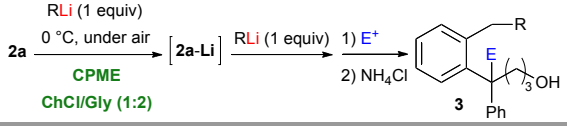
Table 1 Optimization of the regioselective preparation of functionalised alcohol **3a-D** under different conditions.

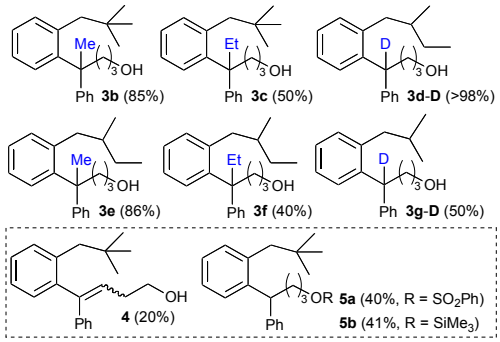


Entry	Time (min)	T (°C)	Solvent	Alcohol **3** yield[a] (%)
1	10	0	Et_2O[b]	**3a-D** (30)[c]
2	"	"	"[d]	" (80)[c]
3	"	–78	"[d]	" (0)
4	"	RT	"[d]	" (55)[c]
5	3	0	CPME/*DES*[d,e]	" (90)[c]

[a] Isolated yield after column chromatography. [b] 1 equiv of *t*-BuLi. [c] >98% D. [d] 2 equiv of *t*-BuLi. [e] *DES*: ChCl/Gly (1/2 molar ratio); 1 g per 0.5 mmol of **2a**.

We next turned our attention to the nature of the bases that would be able to promote such an alkylative THF ring opening in the ChCl/Gly (1:2) eutectic mixture. Assorted bases, such as lithium diisopropylamide (LDA), MeLi, EtLi, *n*-BuLi, and PhLi, have all proved to be ineffective, whereas the use of *s*-BuLi (2 equiv), followed by trapping after a 3 min reaction time with MeOD, MeI, and EtI, provided the corresponding functionalised primary alcohols of **3d-D** (>98% yield, >98% D, dr 1:1), **3e** (86% yield, dr 1:1), and **3f** (40% yield, dr 1:1), respectively (Scheme 2). Similarly, when *i*-PrLi (2 equiv) was used as a base, adduct **3g-D** could be isolated in a 50% yield (>98% D) upon quenching with MeOD (Scheme 3).

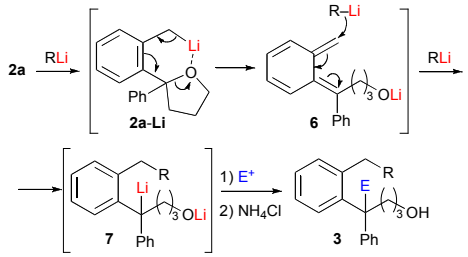




Scheme 3. Site-selected lateral lithiation/ring-opening of **2a** and the preparation of functionalised alcohols **3b**–**3g-D**

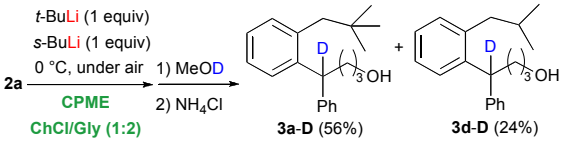
Selective cleavage of etheric C–O bonds is in general of great interest; e.g., for the conversion of cellulosic biomass into liquid fuels and platform chemicals.[9] Selective nucleophilic ring opening of saturated cyclic ethers, larger than oxiranes, with

organo-alkali-metal compounds, have precedent.[10] Only mesomerically stabilised, soft, organolithium compounds, however, are known to be capable of cleaving THF nucleophilically, whereas hard organolithium reagents are generally used in the presence of Lewis acids, such as boron trifluoride ether.[10a] As for Grignard reagents, ring opening with a concomitant C–C bond formation was found only to take place with the highly reactive allyl and benzyl derivatives at a high temperature (150–180 °C) and when the ether is THF or 3,3-dimethyloxetane.[11] Recent complementary approaches to break a THF molecule also include the employment of: "classic"[12] and transition-metal based[13] "frustrated" (sterically hindered) Lewis pairs, *N*-heterocyclic carbene-boryl esters,[14] and nickel-catalyzed cross-coupling reactions of aryl-substituted *O*-heterocycles with Grignard reagents.[15] In consideration of the fact that in DLL *conjugation* with the aromatic ring is mainly responsible for the stabilisation of the benzylic organolithium intermediate, a possible explanation to account for the observed regiochemical outcome of the reactions of *o*-tolyltetrahydrofuran **2a** with strong bases may involve a preliminary transformation of the putative laterally lithiated aryltetrahydrofuran **2a-Li** (originated by the deprotonation of **2a** with a first equiv of base), into the reactive *o*-quinone dimethide alkoxide derivative **6**, as a key intermediate;[16] that is, a net overall 1,4-elimination. The latter would then undergo a nucleophilic conjugate addition by a second equiv of base to give the tertiary benzylic carbanion **7**, which is eventually intercepted by the electrophile to furnish adduct **3** after acid quenching at room temperature (Scheme 4). Electrophiles such as NFSI and Me_3SiCl were instead attacked by the alkoxide moiety of **7** to give ethers (**5a**,**b**) as the final products.



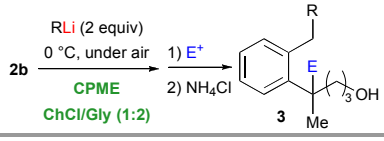
Scheme 4 Proposed mechanism of the formation of alcohol **3**

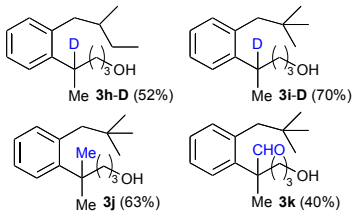
In a competition experiment, when a 1:1 mixture of *t*-BuLi (1 equiv) and *s*-BuLi (1 equiv) was added at 0 °C, and under air, to a mixture of aryltetrahydrofuran **2a** (1 equiv) in CPME and ChCl/Gly (1:2), functionalised alcohols **3a-D** (>98% D) and **3d-D** (>98% D) could be isolated in an 56% and 24% yield, respectively, upon trapping with MeOD. This result is consistent with a faster deprotonation promoted by *s*-BuLi compared to *t*-BuLi. The latter, which has been depleted to a lesser extent, is thus in greater abundance for the second step (Scheme 5). On the other hand, when a similar reaction was performed with 1 equiv each of *t*-BuLi and *n*-BuLi, **3a-D** (>98% D) could now be isolated only in 30% yield upon quenching with MeOD, the remaining 70% being starting material. This result is consistent with a higher reactivity of *t*-BuLi in both deprotonation and addition reactions, with *n*-BuLi acting as a bystander.



Scheme 5 Competition experiment between **2a** and a 1:1 mixture of *s*-BuLi and *t*-BuLi.

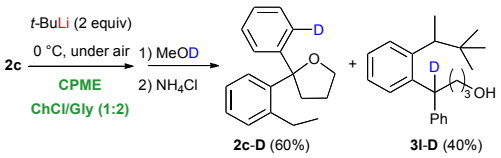
To better define the scope and the amenability of this type of ring-opening process, other substrates were then subjected to investigation. To this end, aryltetrahydrofurans **2b**,**c** were also prepared: the former from the corresponding commercially available chloroketone **1b** (80% yield), the latter by the regioselective deprotonation/ethylation, run in CPME, of diphenyltetrahydrofuran **1c** (80% yield),[5] as outlined in Scheme 2. Gratifyingly, under the above optimised conditions, it was found that bases such as *s*-BuLi (2 equiv) and *t*-BuLi (2 equiv) again worked well providing the corresponding ring-opened products **3h-D** (52% yield, >98% D, dr 1:1), **3i-D** (70% yield, >98% D), and **3j** (63% yield), starting from **2b** and upon trapping with MeOD and MeI (Scheme 6). Notably, deprotonation of **2b** with *t*-BuLi (2 equiv), followed by an interception with DMF, gave the formylated adduct **3k** (40% yield), together with alcohol **3i-H** (40% yield) (Scheme 6).





Scheme 6. Site-selected lateral lithiation/ring-opening of **2b** and the preparation of functionalised alcohols **3h-D**–**3k**

Finally, it was interesting to observe that in contrast to **2a**, for which DLL was the only deprotonation reaction observed further to the treatment with bases, subjecting to lithiation with *t*-BuLi (2 equiv) **2c**, which possesses an ethyl group in an ortho position at one of the two aromatic rings, *ortho*-lithiation seriously competes with lateral lithiation. In the latter case, a mixture of **2c-D** (60% yield, >98% D), as the only regioisomer, and **3l-D** (40% yield, >98% D) was isolated upon trapping with MeOD (Scheme 7). This result may be due to the slower lithiation (lower acidity) of primary benzylic sites compared to the lithiation of methyl groups,[17] and also suggests that *ortho*-lithiation apparently favours functionalisation of the less electron-rich ring.



Scheme 7 Competition between ortho/lateral lithiation in the case of **2c**

Conclusions

In summary, an unexpected highly regioselective ring-opening reaction of *o*-tolyltetrahydrofuran derivatives was discovered. This reaction, which can also be successfully carried out in protic eutectic mixtures, as more environmentally friendly reaction media, and competitively with protonolysis, was found to be triggered by bases such as *s*-BuLi, *i*-PrLi, and *t*-BuLi, presumably as the result of a lateral lithiation. The final adduct contains a primary alcohol moiety that could be further elaborated in synthetic sequences and shows an incorporation in its skeleton of both a second equiv of base at the benzylic position and of an electrophile (if any) at a tertiary carbon atom. Trapping reactions with electrophiles, however, were clean and effective only with a deuterium source and with simple alkyl halides (with the only exception of DMF in the deprotonation of **2b** with *t*-BuLi).[18] There is no doubt, however, that this novel transformation, involving both an intermolecular C-C bond formation and an intramolecular C–O bond breaking reaction in *DES* mixtures, opens a new dimension in the field of "greener" alkylative THF ring-opening processes. Mechanistic aspects, including an investigation of the solution structure of the lithiated intermediate(s) involved, as well as targeted synthetic applications of this reaction, are now actively investigated in our laboratory.

This work was financially supported by the Interuniversities Consortium C.I.N.M.P.I.S..

Notes and references

Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125, Bari, Italy. E-mail: vito.capriati@uniba.it.

Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data, and copies of $^{1}H/^{13}C$ NMR spectra of compounds **2c-D, 3a-H–3l-D**, **4**, and **5a**. See DOI: 10.1039/c000000x/

§ SAFETY NOTE: No particular problems were experienced during this addition. *t*-BuLi, however, is known to be prone to ignition in air and caution should be exercised in adopting the recommended procedure, especially on a larger scale.

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