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Regioselective functionalization of 2-arylazetidines: evaluating the *ortho*-directing ability of the azetidinyl ring and the α-directing ability of the *N*-substituent†‡

Leonardo Degennaro,*[a] Marina Zenzola,[a] Piera Trinchera,[a] Laura Carroccia,[a] Arianna Giovine,[a] Giuseppe Romanazzi,[b] Aurelia Falcicchio[c] and Renzo Luisi*[a]

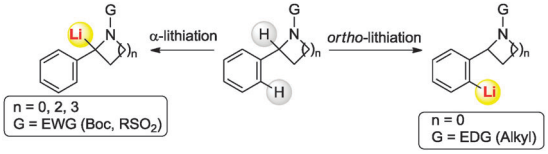
The regioselective lithiation–functionalization of 2-arylazetidines has been explored. The nature of the *N*-substituent is mainly responsible for a regioselectivity switch. *ortho*-Lithiation occurred, using hexyllithium as a greener base, in *N*-alkylazetidines, while α-benzylic lithiation has been observed with *N*-Boc azetidines.

Regioselectivity represents a very important aspect in planning a synthetic strategy. Within synthetic protocols involving lithiated intermediates, usually generated by deprotonation of suitable starting materials, this aspect is particularly relevant. In fact, several factors could affect the regioselectivity of a lithiation reaction such as the nature of the functional groups already installed into the molecule, or the presence of special functional groups able to direct the lithiation itself.[1] For example, it has been demonstrated that the regioselectivity of the lithiation of some *N*-benzyl amine derivatives is dependent on the nature of the *N*- and ring-substituent, as well as the reaction conditions.[2] In a research project aimed at developing new methodologies for the functionalization of nitrogenated small heterocycles, the importance of such factors in the regioselective lithiation of 2-arylaziridines was highlighted.[3] It was demonstrated that *N*-alkyl-2-aryl aziridines could give *ortho*-lithiation, while 2-arylaziridines bearing an electron-withdrawing group, such as Boc (^{t}BuOCO) or Bus (^{t}BuSO$_2$), as the *N*-substituent, almost exclusively undergo α-lithiation.[4] Similarly, other 2-aryl substituted nitrogenated heterocycles such as *N*-Boc-2-aryl pyrrolidines and piperidines, extensively studied by Coldham, O'Brien, Gawley *et al.*,[5] undergo exclusive α-lithiation. In striking contrast, the regioselectivity of the hydrogen–lithium exchange reaction in 2-aryl pyrrolidines and piperidines, bearing an electron-donating group, such as an alkyl group as the *N*-substituent, to the best of our knowledge, has not been reported. However, it has been reported that *N*-alkyl-2-phenyl pyrrolidines could generate a stable *ortho*-lithiated intermediate by bromine–lithium exchange[6] or lithiation could occur by Lewis acid activation.[7] Some examples of regioselective lithiation on 2-aryl substituted nitrogen-bearing heterocycles are presented in Table 1. However, to our surprise, we noticed that some systems were not covered. We focused our attention to the almost unexplored four-membered ring azetidine. This aza-heterocycle is appealing because of its occurrence in several biologically active natural molecules and drug candidates.[8]

It is worth mentioning that, despite the large amount of work on the metalation–electrophile trapping on aza-heterocycles, there are only few examples concerning the metalation (lithiation) of azetidines. Pioneering work by Seebach *et al.*[9] and recent reports by Hodgson *et al.* deal with the α-lithiation of azetidines bearing an electron-withdrawing group as the *N*-substituent.[10] To the best of our knowledge there are no reports on the lithiation of 2-arylazetidines bearing either an EWG or EDG as the *N*-substituent (Table 1).

Herein, we wish to report the first successful use of the azetidinyl ring as an effective *ortho*-directing group for the regioselective functionalization, under very mild conditions, of 2-aryl derivatives, and preliminary results on the effect of

Table 1 Regioselective lithiation of nitrogenated 2-aryl heterocycles



Heterocycle	*n*	α-Lithiation	*ortho*-Lithiation
Aziridine	0	√[3]	√[4]
Azetidine	**1**	**X**	**X**
Pyrrolidine	2	√[5]	√[a,6]
Piperidine	3	√[5]	X

√ = reported; X = not reported. [a] Generated by Br–Li exchange.

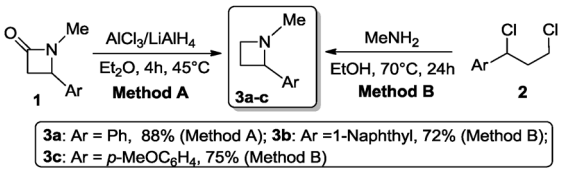
[a] *Department of Pharmacy – Drug Sciences, University of Bari, "A. Moro" Via E. Orabona 4, Bari 70125, Italy. E-mail: renzo.luisi@uniba.it, leonardo.degennaro@uniba.it*

[b] *DICATECh, Polytechnic of Bari, Via E. Orabona 4, Bari 70125, Italy*

[c] *Istituto di Cristallografia (IC-CNR), Via Amendola 122/o, 70125 Bari, Italy*

† This work is dedicated to the memory of Prof. Robert (Bob) Gawley.

‡ Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H–^{13}C NMR spectra of new compounds. CCDC 969537 and 969538. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48555b



Scheme 1 Synthesis of 2-arylazetidines.

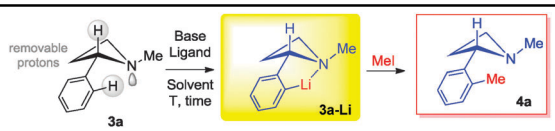
the *N*-substituent on the regioselectivity of the lithiation. As a first step, we embarked in the preparation of *N*-methyl-2-arylazetidines. Two main routes were employed for the preparation of azetidines **3a–c**: the reduction of 2-azetidinones **1** and the cyclization of dichloro derivatives **2** with $MeNH_2$ (Scheme 1).[11]

In order to optimize the lithiation reaction, 1-methyl-2-phenylazetidine **3a** was chosen as a model substrate, and reacted under the conditions provided in Table 2 using MeI as the electrophile and *n*-hexyllithium (*n*-HexLi) as the base.[12] We were pleased to find exclusively *ortho*-methylated azetidine **4a** in 43% yield by using *n*-HexLi in Et_2O at 20 °C for 1 h (entry 1). Better yields (up to 93%) were observed upon prolonging the lithiation time (entries 2 and 3). With the aim to get high conversion with a reduced reaction time, the role of TMEDA was investigated (entries 4–6). As expected, the use of TMEDA accelerates the lithiation reaction and higher conversions could be obtained even with an amount of 20% (entries 4–6).[13] However, conditions of entry 6 were chosen as a good time–yield compromise. The observed *ortho*-directing ability of the azetidine ring could be explained assuming the coordinating role of the nitrogen, just as seen in the case of aziridines.[3] NOESY experiments on **3a** and X-ray analysis on **4h** confirmed a *trans* arrangement between the *N*-methyl group and the phenyl ring (see ESI‡).[14]

With the optimized conditions in hand, we applied this protocol to 2-arylazetidines **3b** and **c**. In these cases, we envisaged two possible sites of deprotonation (H_a and H_b in Scheme 2). Quite surprisingly, in the case of naphthylazetidine **3b**, where the peri lithiation might be considered, product **4b** was isolated in 96% yield as the result of a very selective *ortho*-lithiation (Scheme 2). The result is, in our opinion, remarkable because it reveals an opposite regiochemistry with respect to that reported for the open-chain analogue α-dimethylaminomethyl naphthalene. In this latter case peri lithiation predominates upon treatment with *n*-BuLi in ether–hexane.[15]

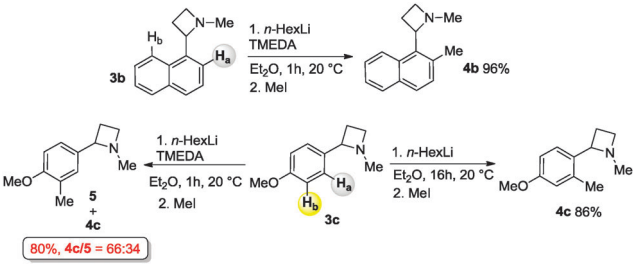
In the case of azetidine **3c** bearing a "competitor" directing group, a mixture of regioisomers **4c** and **5** was observed under the optimized

Table 2 Optimization of the *ortho*-lithiation of **3a**



Entry	Base (equiv.)/ligand (equiv.)	Solvent	*T* (°C)	Time (h)	Yield[a] (%)
1	*n*-HexLi (1.5)	Et_2O	20	1	43
2	*n*-HexLi (1.5)	Et_2O	20	4	71
3	***n*-HexLi (2)**	**Et_2O**	**20**	**16**	**93**
4	*n*-HexLi (1.3) TMEDA (0.2)	Et_2O	20	1	60
5	*n*-HexLi (1.3)/TMEDA (0.2)	Et_2O	20	4	83
6	***n*-HexLi (1.3) TMEDA (1.3)**	**Et_2O**	**20**	**1**	**95**

[a] Yield of isolated product.



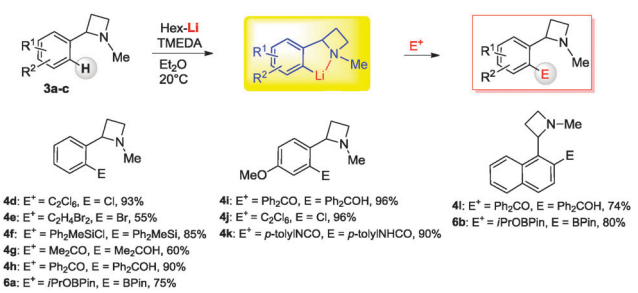
Scheme 2 Examples of regioselective functionalization of azetidines.

conditions (entry 6, Table 2). Nevertheless, gratifyingly a regioselective lithiation *ortho* to the azetidinyl ring was observed without using TMEDA (entry 3, Table 2). In this latter case, the directing ability of the azetidinyl ring over the OMe group is worth noting.

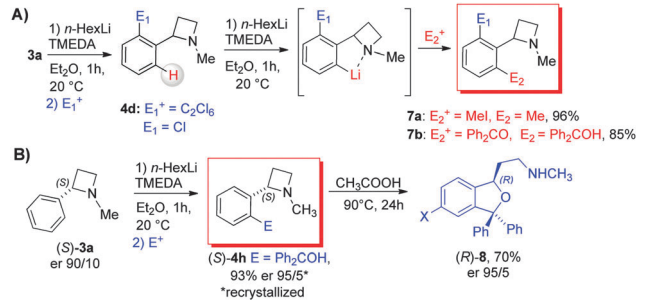
Next, we tested the scope of the methodology in the *ortho* C–H functionalization of azetidines **3a–c** with a variety of representative electrophiles (Scheme 3). Functionalized azetidines **4a–l** were regioselectively prepared in high yields.

Interestingly, combining the azetidine-assisted *ortho*-lithiation with the Li–B exchange with boropinacolate (iPrOBpin), arylboronates **6a,b** were prepared (Scheme 3). Encouraged by these results, we envisioned further synthetic applications for *ortho*-lithiated 2-arylazetidines. The directing ability of the azetidinyl ring was exploited in a double functionalization of **3a**. First **3a** was converted into the *ortho*-chloro derivative **4d** which was subjected, after isolation, to another regioselective lithiation–electrophile trapping sequence affording 2,6-disubstituted azetidines **7a,b** in excellent yields (Scheme 4A). The stereoselectivity was also addressed using enantioenriched azetidine (*S*)-**3a**. The lithiation–trapping sequence furnished azetidine (*S*)-**4h**, without loss of the optical purity (Scheme 4B). The inherent ring strain of the azetidine was exploited for an acid-catalyzed cyclization promoted by the azetidinyl carbinol (*S*)-**4h**. Highly enantioenriched (er 95 : 5) phthalan (*R*)-**8** was obtained in 70% yield.[16]

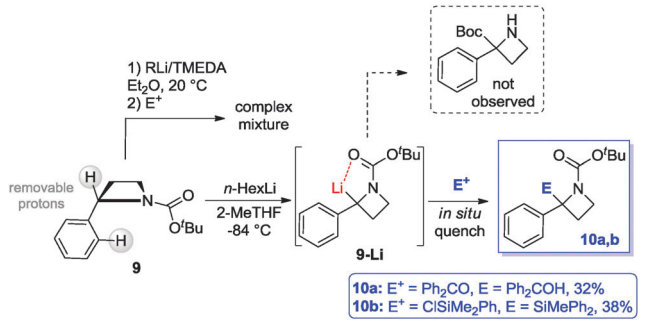
In order to confirm our initial expectations (see Table 1) on the ability of the *N*-substituent in directing the regioselectivity of the lithiation, we prepared azetidine **9** bearing an electron-withdrawing group, such as the Boc group, as the nitrogen substituent. In this case, because of the poor coordinating ability of the azetidine nitrogen, the *ortho*-lithiation would not be expected. In fact, when azetidine **9** was subjected to deprotonation reactions under the optimized conditions (entries 3 and 6, Table 2), only complex reaction mixtures were obtained (Scheme 5). However, performing the reaction at low temperature (−84 °C), using *n*-HexLi in a coordinating solvent (2-MeTHF), under *in situ* quench conditions, we were happy to isolate (although in



Scheme 3 Scope of the azetidine-directed *ortho*-aryl C–H functionalization.



Scheme 4 Applications of the azetidine-directed *ortho*-aryl C–H functionalization.



Scheme 5 Regioselective α-lithiation of *N*-Boc azetidine.

moderate yields) exclusively α-functionalized azetidines **10a,b**. It is worth mentioning that this is the first case of successful trapping of an α-lithiated *N*-Boc-2-phenylazetidine. Previous attempts on *C*-unsubstituted *N*-Boc-azetidine resulted in complex mixtures and decomposition.[10b] The structure of **10a** was confirmed by X-ray analysis which also revealed a *quasi-planar* arrangement of the azetidine ring according to a poor availability of the *N*-lone pair.[17] A different arrangement of the 4-membered ring is recognizable for *ortho*-functionalized azetidine **4h** (see ESI‡). All the attempts to capture the lithiated intermediate **9-Li** by external quenching failed. Decomposition was always observed, while the expected *N* to *C* [1,2]-migration product,[18] obtained in the case of lithiated *N*-Boc-aziridines,[3a] was never found.

In conclusion, our preliminary results demonstrate that 2-aryl-azetidines could be lithiated regioselectively depending on the nature (EWG or EDG) of the *N*-substituent. The *ortho*-lithiation appears to be a simple method for the regioselective *ortho*-C–H functionalization of aryls mediated by the azetidinyl ring. In addition, the directing role of the azetidinyl ring, likely related to a preferential conformation, is responsible for the high regioselectivity observed in the lithiation of the 1-naphthyl derivative **3b**, and for the double functionalization of **3a** never proved in the case of 2-arylaziridines. A regioselectivity switch (*ortho vs.* α) could be realized simply by using an electron-withdrawing group as the *N*-substituent although the *in situ* quench was mandatory using the Boc group. Further studies focused on the synthetic application of the methodology to more challenging systems, as well as on the search for a more suitable *N*-substituent for the α-benzylic lithiation are underway.

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