Conference paper

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Exploiting structural and conformational effects for a site-selective lithiation of azetidines

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Abstract: Interest in molecular structures bearing four-membered heterocycles (FMHs) is growing due to the possibility to explore new regions of the chemical space and get new lead molecules. Our interest in the development of divergent synthesis of functionalized FMHs, prompted us to disclose factors affecting the reactivity of nitrogen-bearing FMHs towards metalating agents. Our investigations demonstrated that structural factors and conformational preferences need to be considered in planning a site-selective functionalization of azetidines. It will be showed how such factors could have pivotal importance in the reactivity of FMHs.

Keywords: azetidines; heterocycle chemistry; lithiation; peptidomimetics; stereocontrol; TRAMECH VIII.

Nowadays more than before, modern organic synthesis can count on several versatile strategies for the functionalization of a specific site for a given molecule. In most reactions where a carbon–hydrogen bond can be chemo-, regio-, and/or stereoselectivity replaced by a carbon–carbon or carbon–heteroatom bond, such a site-selectivity could be realized by the participation of directing groups (DG) [1]. This approach has been significantly exploited to selectively activate and functionalize the *ortho* position of aromatic rings [2–8]. The directing groups, very often play a role in forming complexes with metals, and are able to direct metalation to "proximal" sites kinetically rather than thermodynamically favored. In lithium chemistry, this phenomenon has been termed as the complex induced proximity effect (CIPE) and, as recently reported by Beak and Snieckus, "it can be used as a heuristic model regardless of the detailed reaction mechanism. The concept can be applied to explain unexpected lithiations at sites formally remote from, but conformationally in proximity to, a functional group that is likely complexed by a lithiating reagent" [9, 10]. In this statement, it is recalled how the conformation (or even the configuration) retained by the molecule could play an important

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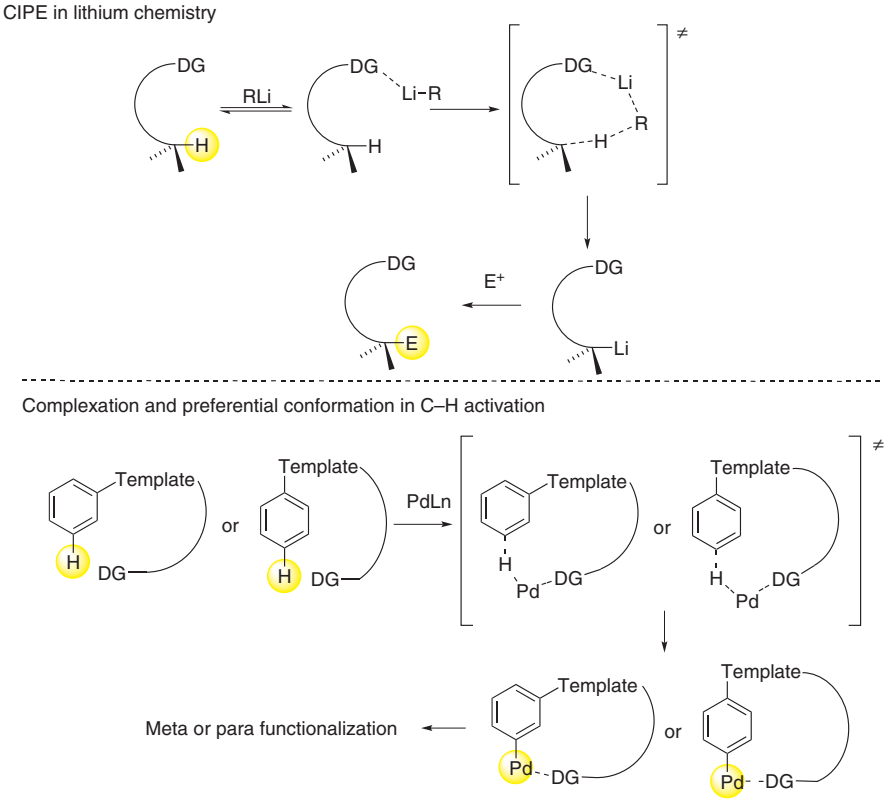
role in metalation reactions. In fact, both complexation phenomena and preferential conformations (configurations) are two key factors to be taken into consideration in site-selective functionalization.

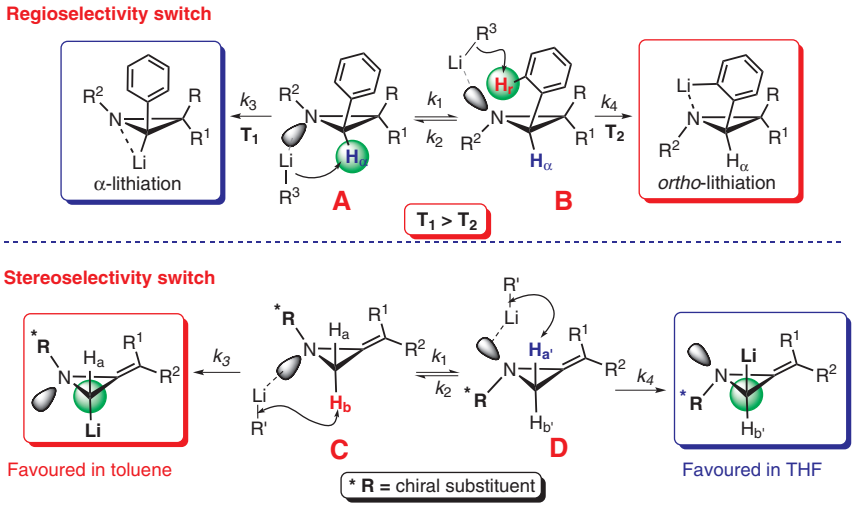
In Scheme 1 is reported how CIPE is exploited in lithium chemistry. Nevertheless, the dualism complexation/preferential-conformation have recently found important applications in transition-metal catalyzed C–H activations. In fact, it has been demonstrated that "remote" meta and even para positions of an aromatic ring, could be regioselectively functionalized by designing a molecular template able to deliver the directing group in close proximity to the desired site of functionalization (Scheme 1) [11, 12]. This approach paves the way to new thinking in modern organic synthesis and offers the possibility to exploit a single molecule for multiple synthetic purposes.

As far as the dualism complexation/conformation (or configuration) is concerned, in our early reports, focused on the lithiation/functionalization of aziridines, we demonstrated that either regioselectivity or stereoselectivity are affected by complexation phenomena and configurational preference related to the nitrogen inversion (NI) [13–17].

As reported in Scheme 2, the regioselectivity switch, observed with aziridines bearing an *N*-alkyl substituent, has been rationalized by taking into account several factors such as solvent, temperature, CIPE, the Curtin–Hammett principle and preferential configuration at the nitrogen atom. Indeed, considering that *N*-alkyl-2-arylaziridines exist as an equilibrating mixture of two *N*-invertomers, at low temperature (i.e. –78 °C) their interconversion rate is slower with respect to the lithiation rate (k_3, $k_4 >> k_1$, k_2) so that complex **B** (Scheme 2) is favored and *ortho*-lithiation occurs. At higher temperature (i.e. 0 °C), the NI occurs faster with respect to the lithiation reaction so it happens that, according to the Curtin–Hammett principle, complex **B** reacts faster (k_1, $k_2 >> k_4 > k_3$) and benzylic α-lithiation is observed. Thus, what we now term "dynamic control of reactivity" has been proved. The most important consequence of this model is the possibility to

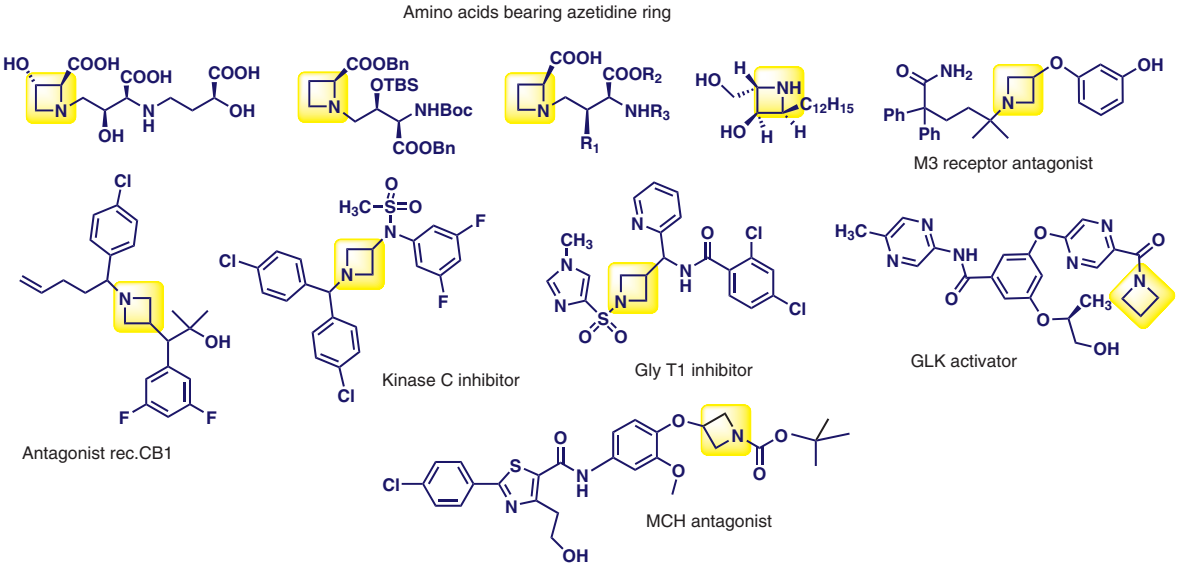


Scheme 1: Relationship between complexation and site-selectivity.



Scheme 2: Examples of "dynamic control of reactivity".

prepare structurally different molecules using the same starting material. Similarly, the stereoselectivity switch observed in the lithiation/functionalization sequence of chiral non racemic *N*-alkyl-2-alkylideneaziridines has been rationalized on the basis of complexation phenomena and configurational preferences at the ring's nitrogen [18]. In this case, a deprotonative dynamic resolution (D-DR) mechanism was proposed, and the stereoselectivity was found to be dependent on the nature of the solvent, the relative amount of the two invertomers (**C**, **D** in Scheme 2), the rates of NI (k_1, k_2) and the rates of deprotonation (k_3, k_4). In continuation of our research in the field of the "dynamic control of reactivity," based on the relationship between complexation and conformational (or configurational) preference [19], we recently evaluated the possibility to extend this concept for a site-selective functionalization of four-membered heterocycles (FMHs) such as azetidines, and we report in this conference paper our recent findings. The chemistry of this kind of heterocycle is emerging as an active research area, because of the importance of azetidines in catalysis, stereoselective synthesis, medicinal chemistry [20–22] and synthetic building block strategies [23–25]. The azetidine core is emerging as highly appealing within medicinal and agrochemical industries because of its occurrence in several biologically active natural compounds and drug candidates (Scheme 3) [26–34].

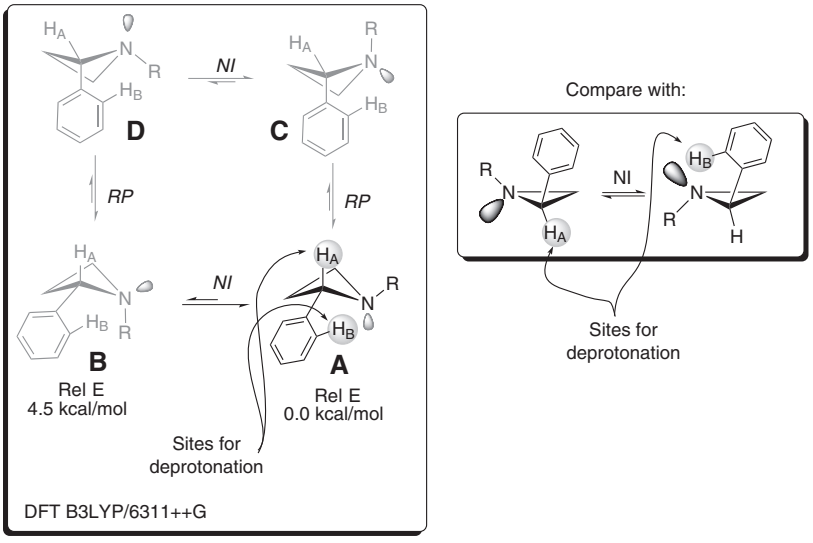


Scheme 3: Biologically relevant azetidine-bearing molecules.

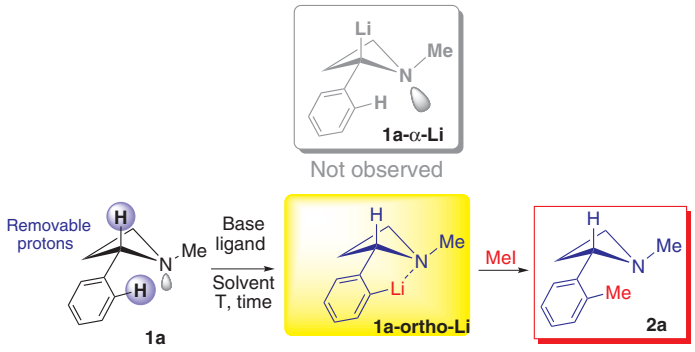
In striking contrast to higher and lower homologue heterocycles such as aziridines, pyrrolidines and piperidines, azetidines have received much less attention [35–40]. Our investigations started studying *N*-alkyl-2-arylazetidines and comparing their reactivity with that shown by the lower homologue aziridines (Schemes 2 and 4). We envisaged that *N*-alkyl-2-arylazetidines could show dynamic phenomena associated with both the NI, and to the additional ring puckering (RP) [41–43]. Such a dynamic process (Scheme 4) involves four different conformational isomers (**A**–**D**). By DFT calculations, conformers **C** and **D**, likely for axial 1,3 ring strain, were found to be unstable, while between the most stable *N*-invertomers **A**, and **B**, the invertomer **A**, having a trans arrangement between the *N*-methyl group and the phenyl ring, was found as lower in energy and its structure confimed by VT-NMR and NOESY experiments.

As reported in Scheme 4, and according to the model of dynamic reactivity (see infra), two sites of lithiation could be recognized in *N*-alkyl-2-arylazetidines: (a) the *ortho* aromatic position (by a selective removal of H_B) and (b) the α-benzylic position (by a selective removal of H_A). From a qualitative point of view, removal of H_B would represent the kinetic process while removal of H_A would represent the thermodynamic process. When *N*-methyl-2-phenylazetidine **1a** was subjected to deprotonation with alkyllithiums, a regioselective *ortho*-lithiation was observed at temperatures as high as 20 °C (Scheme 5) [44]. The use of hexyllithium as a more versatile and sustainable base emerged from this study [45], and two protocols were optimized in the presence or absence of the ligand tetramethylethylendiamine (TMEDA).

The observed reactivity revealed that the nitrogen lone pair was likely playing a role in either facilitating the lithiation, generating a pre-lithiation complex, or stabilizing the lithiated intermediate by intramolecular chelation. This hypothesis was supported by reactivity studies that demonstrated that the *ortho*-lithiation reaction does not occur at low temperature (i.e. –78 °C) and that the presence of TMEDA speeds up the reaction. In the absence of TMEDA the *ortho*-lithiation reaction proved to be slower requiring 16 h to completion, thus suggesting a role for the azetidine nitrogen lone pair in de-aggregating the base before making the reactive complex. Remarkably, α-benzylic lithiation, leading to **1a-α-Li** (Scheme 5), was never observed with azetidine **1a** even running the reaction at 60 °C. These data also disclosed the role as an *ortho*-directing metalation group (*o*-DMG) of the azetidine ring just as seen in the case of 2-arylaziridines [46]. In order to further assess the role as *o*-DMG of the azetidinyl ring and exploit it for synthetic purposes, *N*-methyl-2-arylazetidines **1b–h** were subjected to lithiation/methylation studies (Scheme 6). The regioselectivity as well as the power as o-DMG of the azetidinyl ring was evaluated. The results of this study are collected in Scheme 6, and a comparison is made with strictly related non cyclic directing groups such as dimethylaminomethyl and methoxy groups.

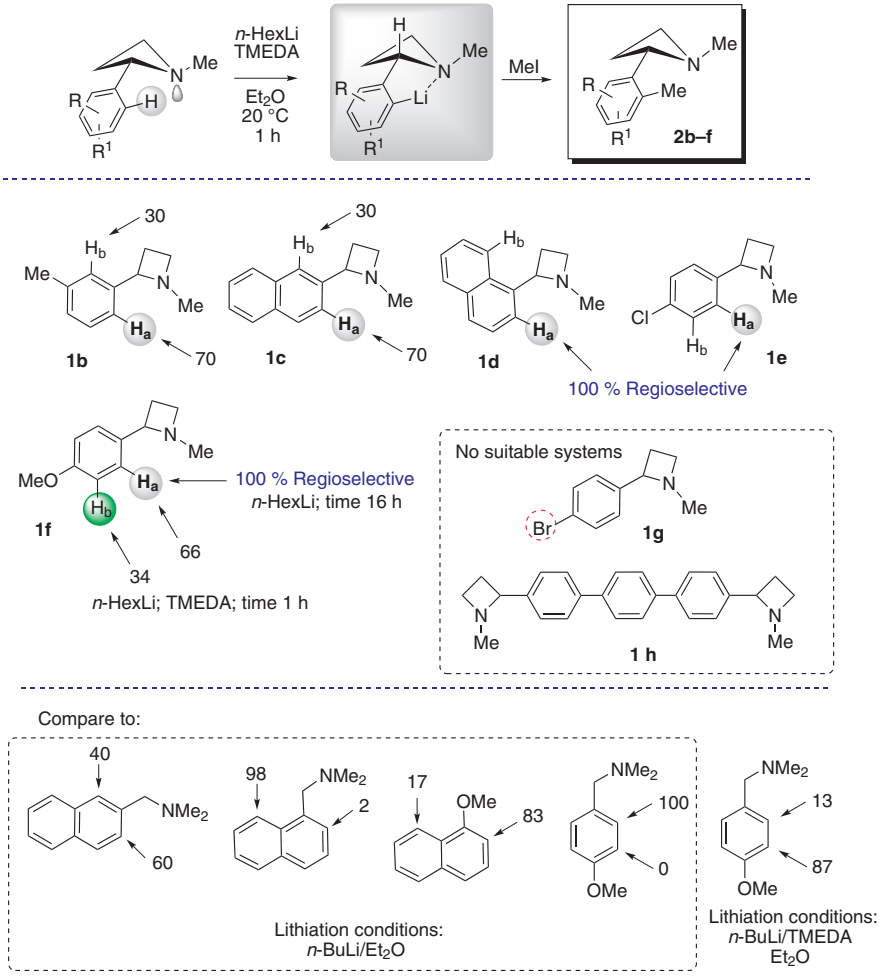


Scheme 4: Dynamics in *N*-alkyl-2-arylazetidines and aziridines.



Base (equiv)/ligand(equiv)	Solvent	T (°C)	Time	Yield (%)
n-HexLi (2)	Et_2O	20	16 h	93
n-HexLi (1.3)/TMEDA(1.3)	Et_2O	20	1 h	95

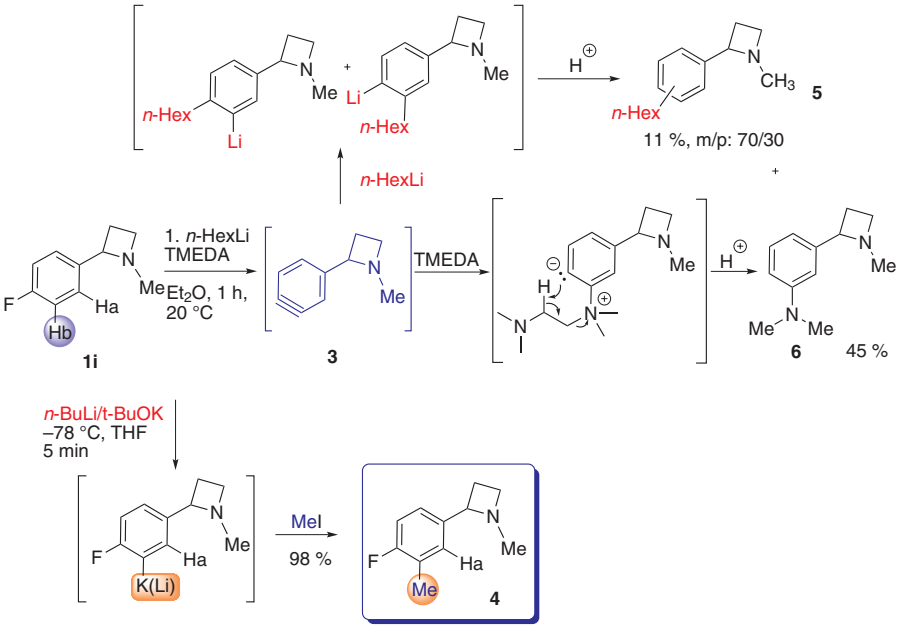
Scheme 5: Lithiation of a *N*-alkyl-2-phenylazetidine.



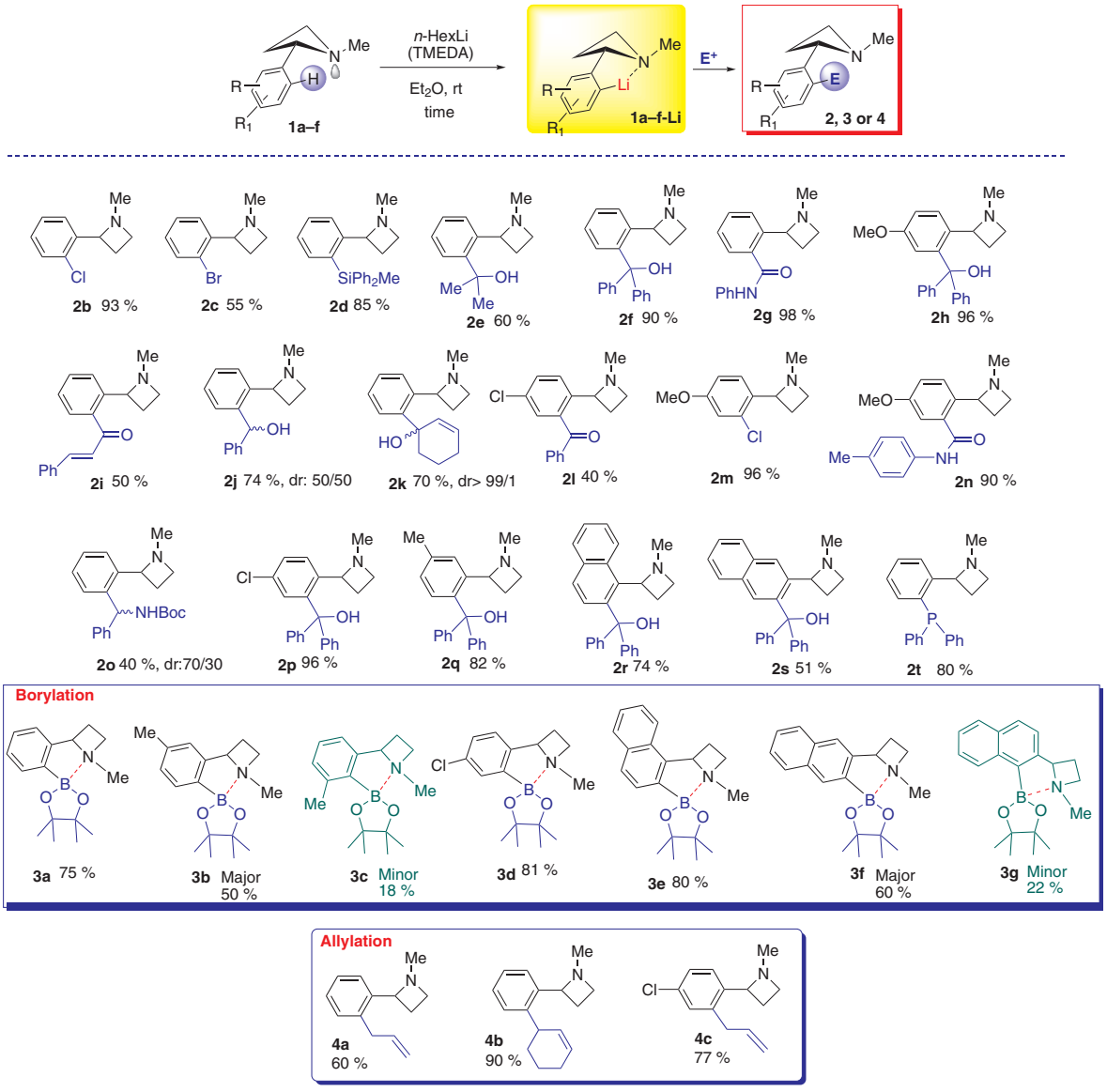
Scheme 6: Ortho-directing ability of the azetidine ring.

Exclusive *ortho*-lithiations were observed with **1b** and **1c**, jointly with a good regioselectivity (70:30) with the proton Ha being preferentially removed. Such a result is in line with what has been reported for the analogous β-dimethylaminomethyl naphthalene (Scheme 6). Remarkably, in the case of 1-naphthylazetidine **1d**, where a *peri*-lithiation may occur, a very selective *ortho*-lithiation takes place. In striking contrast, the *peri*-lithiation reaction largely predominates with the open-chain analogue, the 1-dimethylaminomethyl naphthalene, and a competition between *ortho*- and *peri*-lithiation occurs in the lithiation of α–methoxynaphthalene [47]. Halogenated aromatics were also considered. Lithiation of *p*-chlorophenyl azetidine **1e** occurred regioselectively *ortho* to the azetidinyl ring whereas the *p*-bromophenyl azetidine **1g** which resulted was unsuitable for this protocol because of a competing bromine/lithium exchange reaction (Scheme 6). Attempts to deprotonated bisazetidine **1h** also failed because of the low solubility of this compound in most of the solvents compatible with the lithiation protocol. Interestingly, with methoxy-substituted arylazetidine **1f** (Scheme 6), a competition between the azetidine ring and the methoxy group was observed (66:34 ratio of regioisomers). Lithiation of **1f** with both *n*-HexLi and *n*-BuLi in the presence of TMEDA resulted in a slight preference in favor of the azetidine ring (Scheme 6), in striking contrast to what was reported for the corresponding open-chain analogous *N,N*-dimethyl-*p*-methoxybenzylamine where, under similar reaction conditions, a marked preference for the methoxy group (87:13 ratio of regioisomers) occurred [48]. Nevertheless, when performing the lithiation reaction in the absence of TMEDA, a regioselective lithiation was realized with the selective removal of H_a, according to the open-chain analogous *N,N*-dimethyl-*p*-methoxybenzylamine (Scheme 6). With fluoro-phenyl azetidine **1i**, a selective removal of H_b, *ortho* to the fluorine group was observed using *n*-HexLi in the presence of TMEDA, followed by a very fast LiF elimination leading to benzyne derivative **3** which undergoes nucleophilic addition of *n*-HexLi and TMEDA. Products **5** and **6** were the only isolable derivatives in this case. A regioselective metalation was achieved reacting **1i** with the Schlosser's super base LIC-KOR (*n*-BuLi/*t*-BuOK) at –78 °C in THF. A selective metalation at the position adjacent to the fluorine atom occurred under these reaction conditions, leaving the position *ortho* to the azetidinyl ring untouched, and providing methylated derivative **4** upon reaction with MeI (Scheme 7) [49, 50].

The scope of the *ortho*-lithiation/electrophilic trapping sequence was assessed with 2-arylazetidines **1a–f** (Scheme 8). The protocol could be successfully applied for a regioselective *ortho* functionalization of the aromatic ring of 2-arylazetidines. Several electrophiles such as MeI, $Ph_2MeSiCl$, Br^+ and Cl^+ sources, ketones, unsaturated ketones [51], imines, aldehydes, Weinreb amides [52–54], Ph_2PCl and isocyanates [55, 56], were found effective, and functionalized azetidines **2b–t** were obtained in good to excellent yields (Scheme 8).



Scheme 7: Ortho-directing ability of the azetidine ring: the Fluorine effect.



Scheme 8: Scope for the azetidine-mediated *ortho*-lithiation.

Pinacol boronates **3a–g** were also prepared in good yields by reaction of *ortho*-lithiated azetidines with boropinacolate (*i*-PrOBpin), while the problematic coupling with allyl halides, was realized by previous transmetalation of the lithiated intermediates with CuCN·2LiCl. The putative arylcuprates cleanly coupled with allylic bromides, giving the allyl derivatives **4a–c** in good yields (Scheme 8).

The observed reactivity proves the role of the azetidine ring as DMG, explained assuming the coordinating role of the nitrogen, as already noticed in the case of 2-arylaziridines or other aromatic rings bearing Lewis basic heteroatoms [57–59]. The coordinating role of the azetidine nitrogen during the deprotonation process, was assessed by evaluation of the intra- and intermolecular kinetic isotope effects (KIE) as demonstrated by Beak [60], Collum [61] and Clayden [62]. Appreciable intra- and intermolecular KIE were noticed (k_H/k_D values >5 were found) either in the presence or absence of the competing ligand TMEDA. On the basis of KIE experiments, it was assumed that the *ortho*-lithiation in 2-arylazetidines likely proceeds through a two-step mechanism involving a fast reversible complexation followed by a rate-limiting deprotonation step [63].

The possibility to further functionalize the aromatic ring by an additional azetidine-directed lithiation/trapping sequence was evaluated. By looking to the X-ray structures of mono-functionalized azetidines **2d**,

2g and **2n** reported in Fig. 1, a peculiar arrangement of the aryl group at the C2 of the azetidine ring was noticed. In fact, the aryl groups occupy a pseudo-equatorial position and are trans oriented with respect to the nitrogen substituent. Remarkably, regardless of the nature of the firstly introduced electrophile, the residual *ortho*-protons of the aryl rings were all oriented towards the lone pair of the azetidine nitrogen in the solid state.

We questioned that such a stereochemical preference could be retained in solution, thus affecting a further selective *ortho*-lithiation. **A** conformational analysis at DFT level, run on conformers **A** and **B** (Fig. 1), revealed conformer **A** as the most stable, while conformer **B** was higher in energy by about 2.5 kcal/mol. Such a preferential conformation was demonstrated in solution by ^{1}H NMR analysis of mono-functionalized azetidine **2a**. The VT NMR experiments, in the range of temperature 370–200 K, did not bring any significant line broadening and signal splitting, and 1D-NOESY experiments revealed proximity interactions according to conformer **A** as depicted in Fig. 2. The ^{1}H-NMR spectra of conformers **A** and **B** were also calculated, using the GIAO-DFT method at the SMD/MPW1PW91/6-311G++(2d,p) level of theory, and spectra compared with the experimental one [39, 64, 65]. The calculated ^{1}H-NMR spectra for the two conformers revealed important differences. In particular, the simulated ^{1}H NMR spectrum of conformer **A** was found very similar to the experimental one (Fig. 2). This is likely as a consequence of a preferential conformation, a marked difference in chemical shifts could be seen for the residual *ortho* protons (Ho' in Fig. 2) of conformers **A** and **B**.

From a reactivity point of view, such assumption allows to predict the site of metalation on the basis of the model based on complexation and conformational preference (see infra). As reported in Fig. 2, for proximity reasons, conformer **A** would be lithiated at the *ortho* position and conformer **B** at the lateral benzylic position. However, a second lithiation at the residual *ortho*-position was expected. Remarkably, and according to

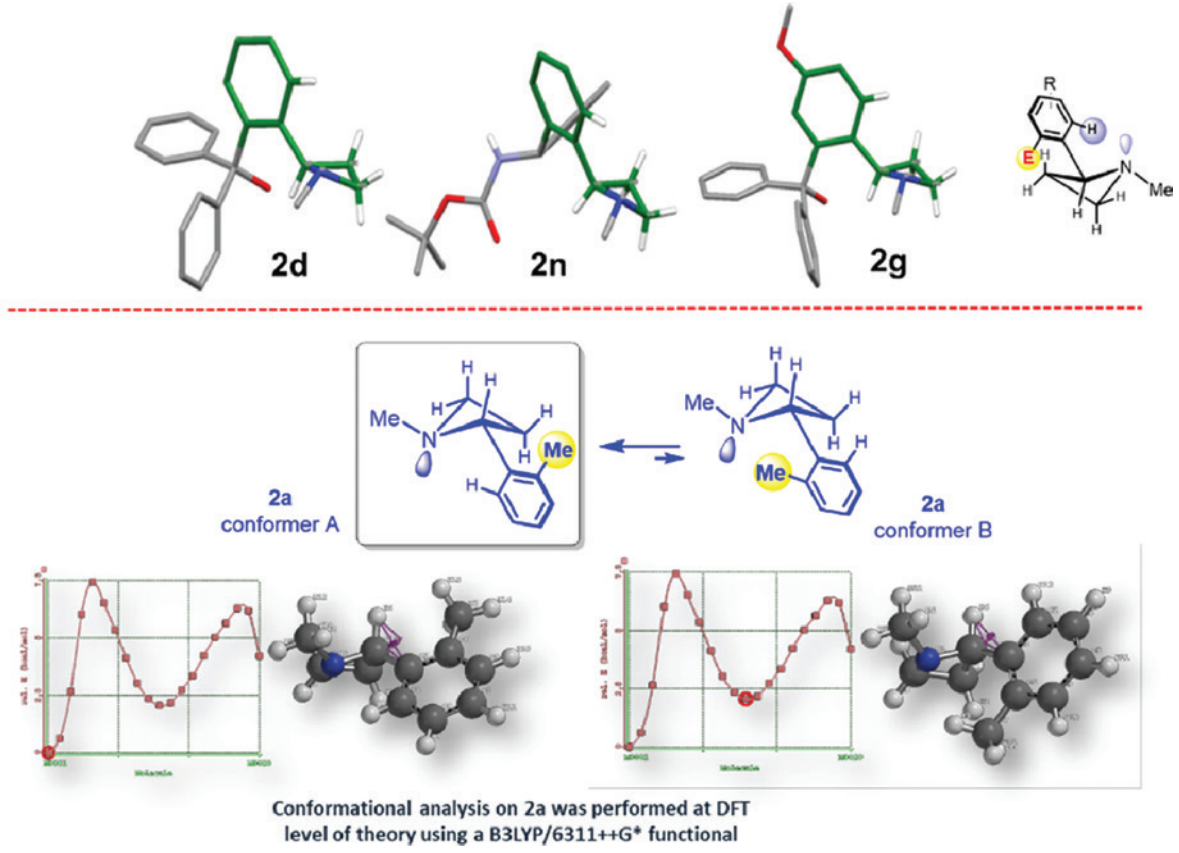


Fig. 1: Structural features in 2-arylazetidines.

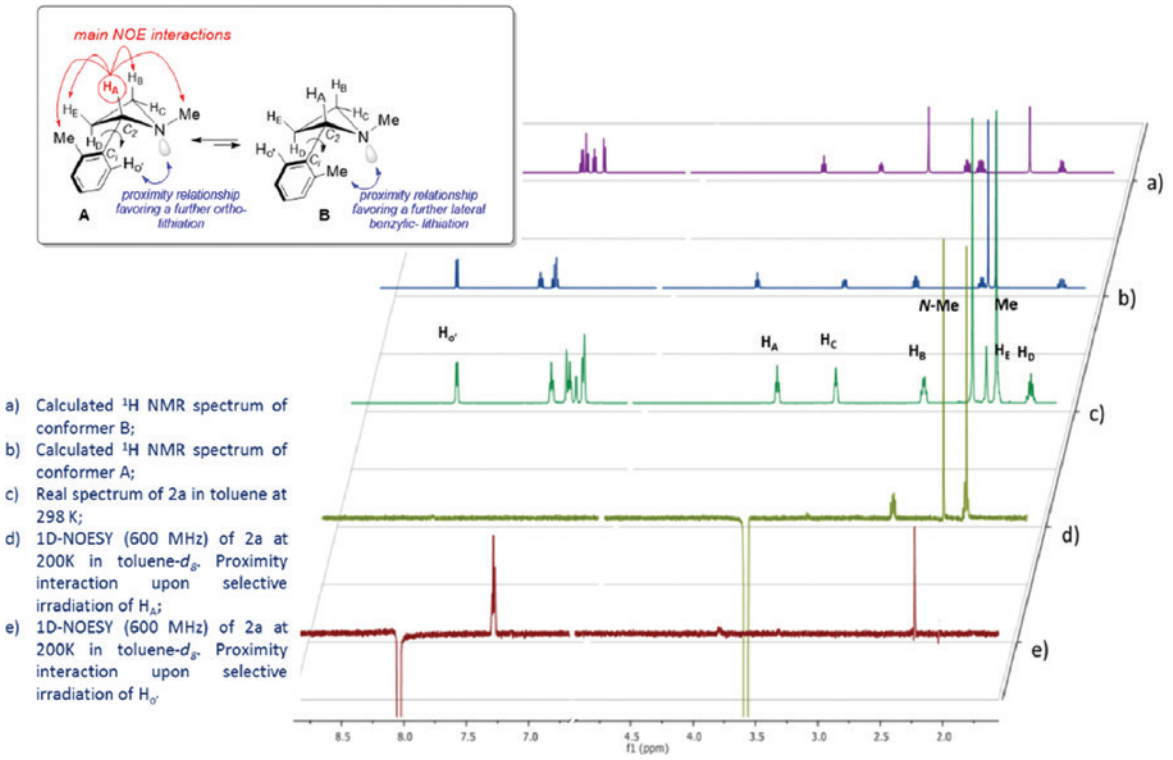
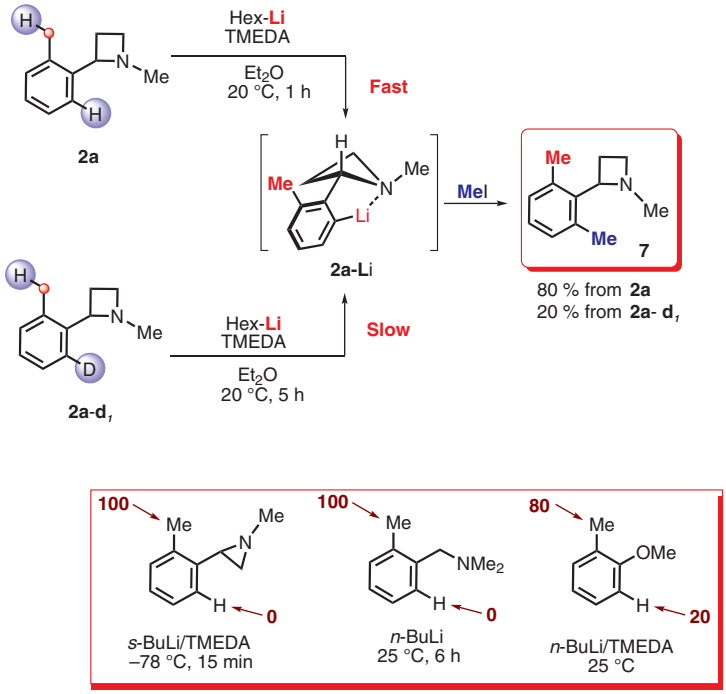


Fig. 2: Proving the preferential conformation in 2-arylazetidines.

our expectations, when *ortho*-methyl substituted azetidines **2a** and **2a–d1** were subjected, in two separate experiments, to lithiation/electrophilic trapping furnished exclusively the product of *ortho* functionalization **7** (Scheme 9). It was noticed that, the lithiation of **2a–d1** occurred slowly with respect to **2a** likely for a kinetic

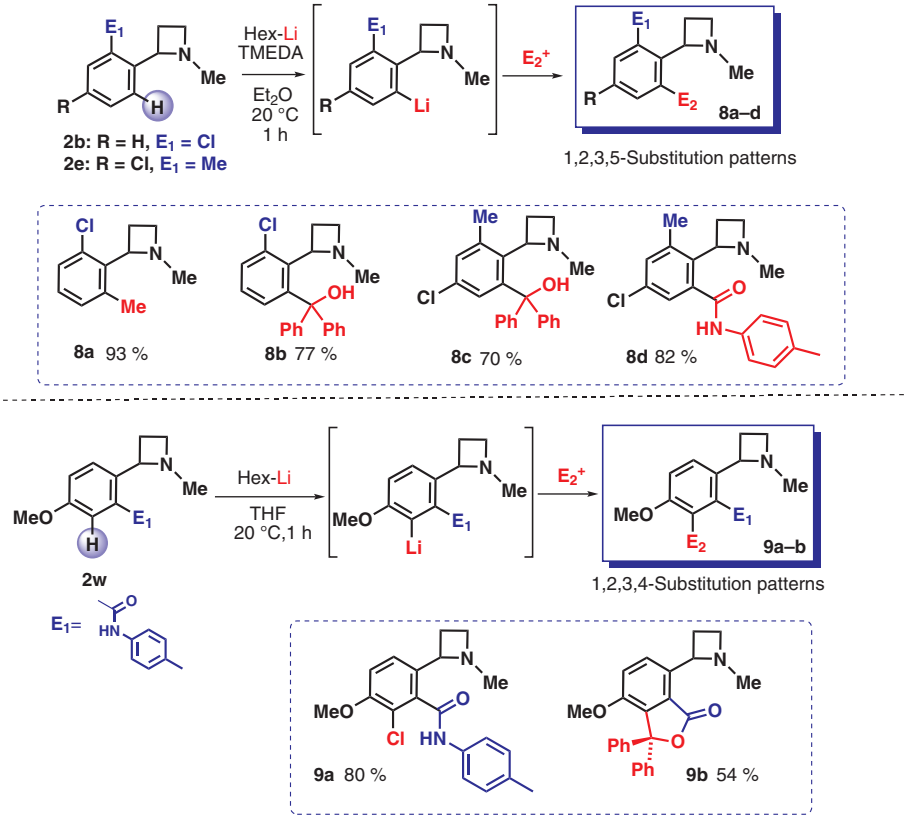


Scheme 9: Preferential conformation and reactivity.

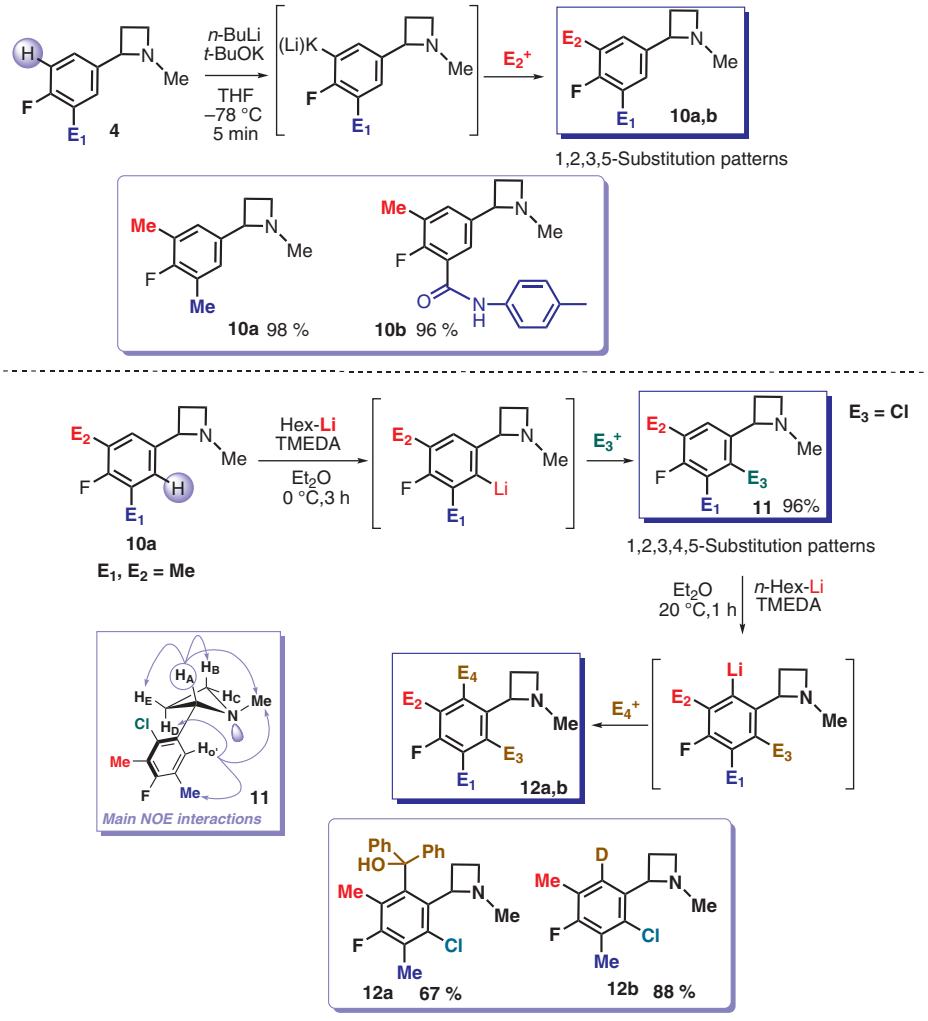
isotope effect. However, no evidence for a lateral trapping product were provided by ^{1}H NMR analysis of the crude reaction mixtures. It is worth pointing out that such result is in striking contrast to what was observed in the case of *ortho*-tolylaziridines where exclusive lateral lithiation occurs. Similarly, lateral benzylic regioselectivity was observed for other *ortho*-methyl substituted arenes bearing the methoxy or the *N,N*-dimethylaminomethyl directing groups (Scheme 9) [66–69]. It is reasonable to ascribe the omitted lateral lithiation to the preferential conformation of the aromating ring that put the *ortho*-methyl substituent far away from the coordination site that is the azetidine nitrogen [70–72]. Such a preferential conformation guarantees a proximity relationship favoring the *ortho*-lithiation.

The preferential conformation kept by *ortho*-substituted 2-arylazetidines, was further exploited in a polysubstitution of the aromatic ring by sequential azetidine-directed *ortho*-lithiation/trappings. The possibility to introduce new substituents in a predictable position by a fine tuning of the reaction conditions has been demonstrated. In the case of azetidines **2b**,**e**, the regioselectivity could be addressed using the coordinating capability of the azetidine ring (Scheme 10), so that tri- and tetrasubstituted azetidines **8a–d** could be prepared in good to excellent yields. Remarkably, in the functionalization of **2e** the lateral benzylic lithiation was not observed.

With azetidine **2w**, bearing three coordinatively competent directing groups on the aromatic ring, (Scheme 10), the use of *n*-HexLi in THF at 20 °C allowed a very selective deprotonation at the most activated position for the simultaneous presence of the methoxy and the amido groups. The *ortho*-position adjacent to the azetidine ring was unreactive under these reaction conditions. Trapping of the *ortho*-lithiated intermediate with electrophiles furnished azetidines **9a,b** having a tetra-substituted aromatic ring with a 1,2,3,4 substitution pattern. An intramolecular displacement of the amido moiety took place in the trapping reaction with benzophenone leading to **9b**. Our approach based on the site-selective metalation was employed for an exhaustive functionalization of the aromatic ring (Scheme 11). Starting from azetidine **4**, by reiterating the



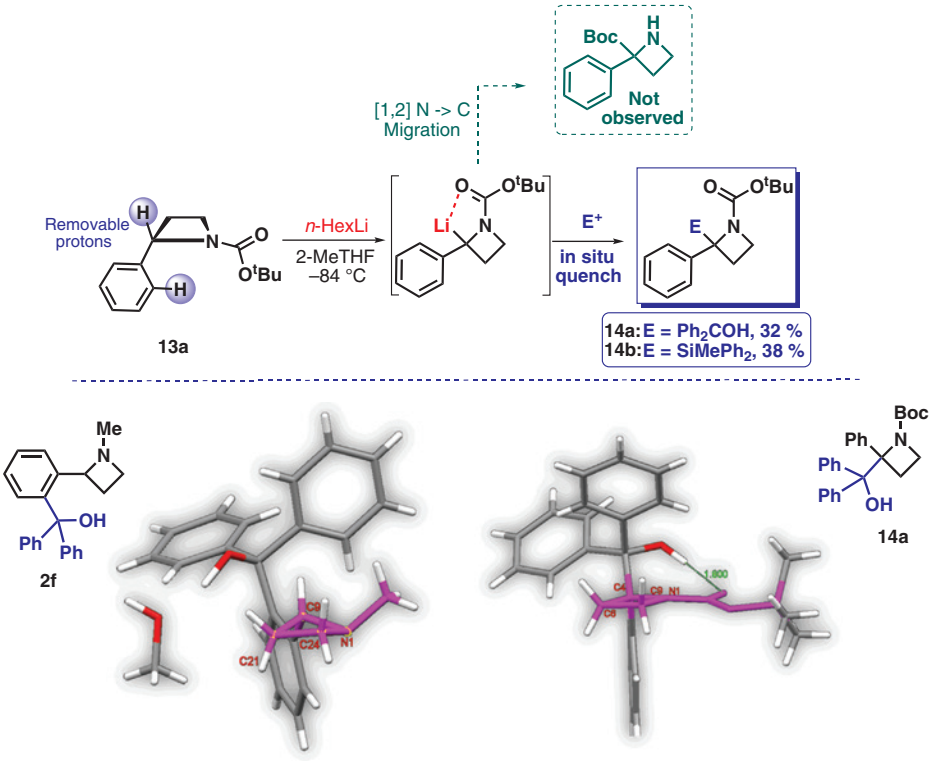
Scheme 10: Site-selective functionalization by *ortho*-lithiation/trapping sequences.



Scheme 11: Site-selective functionalization by *ortho*-lithiation/trapping sequences.

metalation/trapping sequence under different reaction conditions (i.e. super base LIC-KOR), a regioselective functionalization at the *ortho* positions adjacent to the fluorine atom leading to azetidines **10a,b** in very good yields. Exploiting the *ortho*-directing ability of the azetidine ring, a further lithiation on **10a**, proved that penta-substituted aromatics could be obtained. Surprisingly, NOESY experiments on **11** (Scheme 11) revealed proximity interactions according to a preferential conformation which could again favor the *ortho* hydrogen/lithium permutation. Thus, the aromatic ring of **11** was exhaustively functionalized simply applying once more the azetidine-directed *ortho*-lithiation/electrophilic trapping protocol. Azetidines **12a,b** bearing a fully substituted aromatic ring were prepared (Scheme 11). The structure of derivatives **12** proves how useful this approach could be in modern synthesis.

The investigations on the reactivity of 2-arylazetidines went further, evaluating the reactivity of systems lacking the coordinating ability at the nitrogen as in the case of *N*-Boc-2-phenylazetidine **13a**. In fact, in this case, the *N*-electron-withdrawing group would drastically reduce the lone pair availability, and the coordinating capability of the nitrogen. As a consequence, an increased thermodynamic acidity of the benzylic proton was expected. Lithiation experiments on **13a**, revealed that only α-benzylic lithiation occurred rather than *ortho*-lithiation, and that the putative lithiated intermediate could be intercepted, with modest yields, only under "in situ" quench technique (Scheme 12) [73]. However, only trapping with benzophenone and $Ph_2MeSiCl$ could be realized leading to adducts **14a**,**b**. At the beginning of the investigation, the reason for this behavior was not clear and it was ascribed to a chemical instability of the lithiated intermediate. The

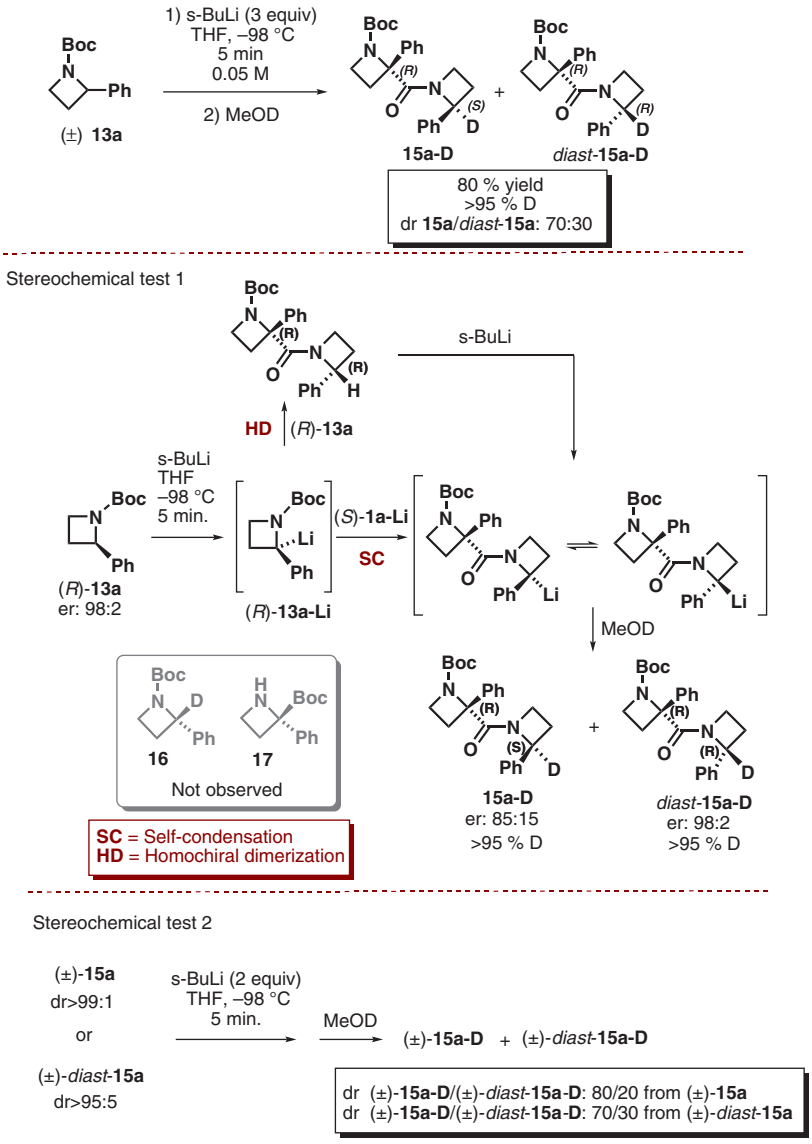


Scheme 12: Azetidine's nitrogen substituent and regioselectivity of the lithiation.

possibility of a [1, 2] migration of the Boc group, as seen in the case of *N*-Boc-2-arylaziridines was also ruled out [74].

Structural differences between *N*-alkyl- and *N*-Boc-2-phenylazetidines were deduced by crystallographic X-ray analysis on derivatives **2f** and **14a**. As reported in Scheme 12, **14a** lack the lone pair availability resulting an almost planar nitrogen atom, likely unable to form complexes with lithiating agents. A deeper investigation of *N*-Boc azetidine **13a**, disclosed a peculiar reactivity scenario [75]. In fact, after extensive experimental trials, we found that, by reacting **13a** with s-BuLi (3 equiv) as the lithiating agents in THF at –98 °C for 5 min at 0.05 M concentration, an unexpected dimerization occurred, leading to diastereomeric dimers **15a** and *diast*-**15a** (Scheme 13). It is worth mentioning that as such dimerization, to the best of our knowledge, has never been reported in the lithiation of higher and lower homologues as *N*-Boc aziridines, pyrrolidines and piperidines.

A stereochemical investigation of this lithiation/dimerization/deuteration sequence, carried out on chiral non racemic azetidine (*R*)-**13a** and diastereomerically pure dimers **15a** and *diast*-**15a**, shed some light on the mechanism of the dimerization. In the first stereochemical test (Scheme 13), optically active azetidine (*R*)-**13a** (er: 98/2) was lithiated under optimized conditions, and quenched with MeOD obtaining highly enantioenriched deuterated dimers (*R*,*S*)-**15a-D** (er 85:15) and (*R*,*R*)-*diast*-**15a-D** (er 98:2) in 70:30 diastereomeric ratio respectively, (Scheme 13). This result could be explained by two different reaction pathways: (a) a two-step sequence (homochiral dimerization, HD), involving the reaction of (*R*)-**13a-Li** with its neutral precursor, leading to *diast*-**15a** which is further deprotonated; (b) a single-step dimerization of (*R*)-**13a-Li** (self-condensation, SC), directly leading to the lithiated dimer. In both pathways, an equilibrium between the lithiated dimers is involved. The slight erosion observed in (*R*,*S*)-**15a-D** (er 85:15) could be the result of a propensity of (*R*)-**13a-Li** to racemize under the reaction conditions. In the second stereochemical test, the equilibrium between lithiated dimers **15a** and *diast*-**15a** (Scheme 13) was demonstrated. A lithiation/deuteration run on **15a** (dr >95:5) or *diast*-**15a** (dr >95:5) furnished mixtures of diastereomeric dimers **15a-D** and *diast*-**15a-D**

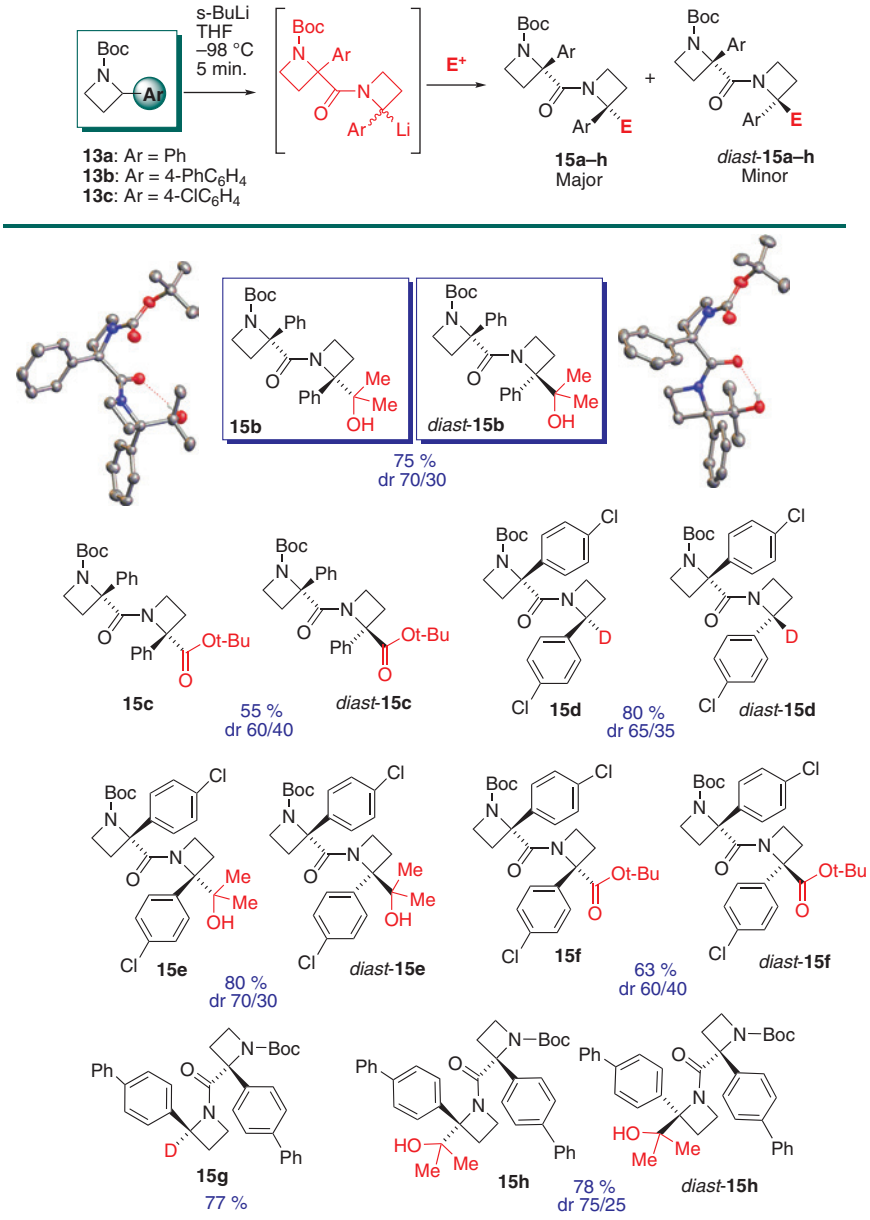


Scheme 13: Reactivity of *N*-Boc-2-phenylazetidine.

having a similar sense of stereoinduction, just as seen in the dimerization of **15a**, although with slightly different ratios (Scheme 13). The stereochemical evidences seem to support the SC pathway of α-lithiated *N*-Boc azetidines, followed by the epimerization of the corresponding lithiated dimers. However, the HD pathway cannot be completely ruled out at the moment. Remarkably, the stereochemical study revealed the possibility to access chiral azetidine-based peptidomimetics.

The scope of the reaction was explored with readily available *N*-Boc-2-arylazetines **13a–c**, that were lithiated and effectively trapped with several electrophiles (Scheme 14). By deuteration, hydroxyalkylation and carboxylation, dimers **15a–h** were prepared in good yields although, in some cases, with modest diastereoselectivity. However, mixtures of diastereomeric dimers of the kind of **15** and *diast*-**15** could be easily separated by flash chromatography (Scheme 14). Remarkably, the introduction of a tert-butoxycarbonyl unit, as in the case of **15c,f** and *diast*-**15c,f** furnished constrained dipeptides, with protected N- and C-terminals, of potential interest in medicinal chemistry programmes [76–78].

It is worth pointing out that the characterization of such dimeric azetidines was not a simple task because of their low solubility and due to poorly resolved NMR spectra for the presence of rotamers. The use of 2D NMR



Scheme 14: Scope of the lithiation/dimerization sequence.

experiments and HRMS analyses were used for supporting the proposed structures, that were confirmed by X-ray analysis for **15b** and *diast*-**15b** (Scheme 14). The X-ray structures revealed different packing and torsion angles in the case of **15b** and *diast*-**15b**, and such information was used to assign the relative configuration to other diastereoisomeric pairs. In fact, X-ray analysis of **15b** displays, in the solid state, a torsional angle of –80.40° between the C=O groups; while in *diast*-**15b** such a torsional angle was 129.52° (Fig. 3). We proved that such preferential conformations in diastereomeric dimers, strictly related to their stereochemistry, were kept in solution, and in all cases where such relative configuration was manifested. As a consequence of such stereochemical preference, a marked difference in chemical shifts of the methylene protons resulted as shown in Fig. 3. Interestingly, in all the cases where stereoisomers **15** and *diast*-**15** were separable by chromatography, it resulted **15** as the first eluted, and *diast*-**15** as the second eluted. On the basis of these considerations, the (*R**,*S**) relative configuration was assigned to the first eluted (major stereoisomers **15**), and the (*R**,*R**) relative configuration to the second eluted (minor stereoisomers *diast*-**15**) in analogy to reference

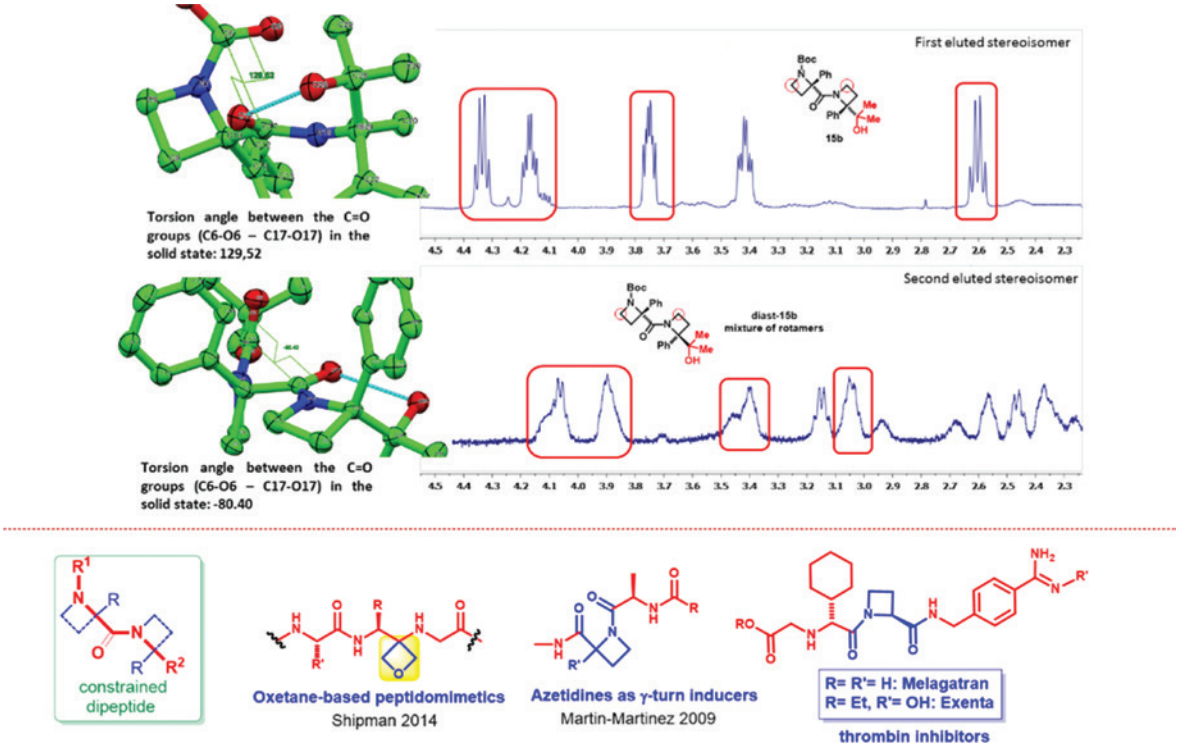


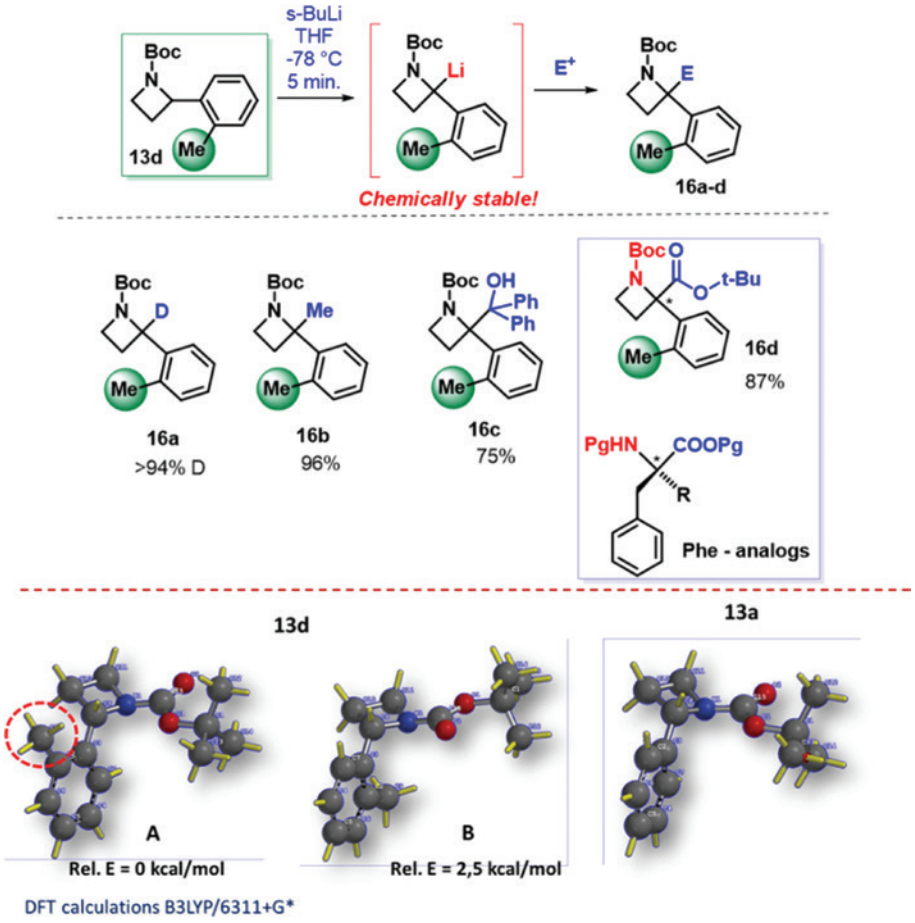
Fig. 3: Structural features of dimeric azetidine-based peptidomimetics.

compounds **15b** and *diast*-**15b**. Such structural information is, in our opinion, relevant due to the importance of constrained peptides and peptidomimetics bearing small heterocycles in medicinal chemistry, as demonstrated by recent studies by Shipman [79], Phillips [80] and Martín-Martínez [81]. The azetidine ring is also a core motif in peptidomimetic drugs such as melagatran or exenta.

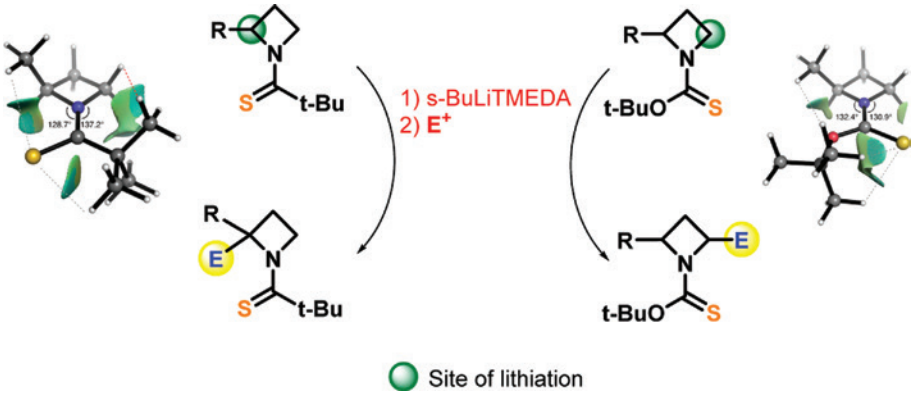
Almost unexpectedly, *N*-Boc-2-(o-tolyl)azetidine **13d** behaved differently, with respect to **13a–c**, when subjected to the lithiation/deuteration sequence with s-BuLi (2.5 equiv) in THF at –78 °C for 10 min (Scheme 15). Surprisingly, and in striking contrast to **13a–c**, lithiated azetidine **13d** was found to be chemically stable, and did not undergo any dimerization furnishing the corresponding deuterated azetidines **16a** in high yield (>94 % D). It is worth mentioning that lithiated azetidines **13a–c** decomposed at –78 °C. Lithiated azetidine **13d-Li** was reacted with some electrophiles furnishing 2,2-disubstituted azetidines **16b–d** (Scheme 15). This remarkable result could be ascribed to a surprising "*ortho*-effect" which is able to influence the reactivity of α-lithiated azetidines preventing dimerization. From a synthetic point of view, the introduction of the *ortho*-aromatic substituent gives the possibility to access 2,2-disubstituted azetidines and constrained aminoacids as in the case of **16d** which can be considered a cyclic analog of phenylalanines (Scheme 15) [82–84].

Such a chemical stability of **13d-Li**, and its low propensity to undergo dimerization, has been ascribed again to a preferential conformation retained by the o-tolyl substituent. DFT calculations and conformational analysis run on **13d**, demonstrated that the most stable conformer sets the *o*-methyl group syn to the α-proton of the azetidine ring (**A** in Scheme 15). This shielding role of the methyl group is expected to be relevant even in other *ortho*-substituted azetidines and it is currently under investigation in our laboratory.

However, in a recent report, Hodgson and co-workers demonstrated that the site-selectivity (2- or 4-position, Scheme 16) observed in the lithiation/trapping sequences of *N*-thiopivaloyl- or *N*-tert-butoxythiocarbonyl-2-alkyl-substituted azetidines, is likely a result of a preferential conformation assumed by the N-substituent [85]. In fact, both ^{1}H NMR and computational studies support the hypotheses that the regiodivergent reactivity might be ascribed to different rotamer preferences in both azetidines. As a direct consequence, a surgical functionalization of the azetidine ring could be accomplished by choosing the suitable N-thiocarbonyl substituent (Scheme 16) [86–88].



Scheme 15: *Ortho*-effect and regioselectivity of the lithiation.



Scheme 16: Preferential conformation and regioselectivity of the lithiation.

In conclusion, reactivity studies on azetidines allowed the assessing of the importance of structure and preferential conformations in site-selective functionalization of C–H bonds. In particular, we focused our attention on lithiation chemistry disclosing the close relationship between complexation and preferential-conformation, introducing the concept of "dynamic control of reactivity". This is the possibility to obtain structurally different molecules from the same starting material or to control the reactivity on preferential conformation basis. We believe that this could constitute a new important paradigm in lithiation chemistry, where complexation play a prominent role and could expand behind the well-known CIPE.

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