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Lithiation

Harnessing the *ortho*-Directing Ability of the Azetidine Ring for the Regioselective and Exhaustive Functionalization of Arenes

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In memory of Manfred Schlosser

Abstract: This work demonstrates how the directing ability of the azetidine ring could be useful for regioselective *ortho*-C–H functionalization of aryl compounds. Robust polar organometallic (lithiated) intermediates are involved in this synthetic strategy. The reagent *n*-hexyllithium emerged as a safer, yet still effective, basic reagent for the hydrogen/lithium permutation relative to the widely used reagent *n*BuLi. Two different reaction protocols were discovered for regioselective lithiation at the *ortho* positions adjacent to the azetidine ring, which served as a toolbox when other competing directing groups were installed on the aromatic ring. The coordinating ability of the azetidine nitrogen atom, as well as the involvement of dynamic phenomena related to the preferential conformations of 2-arylazetidine derivatives, were recognized to be responsible for the observed reactivity and regioselectivity. A site-selective functionalization of the aromatic ring was achieved for aryl azetidines with either coordinatively competent groups (e.g. methoxy) or inductively electron-withdrawing substituents (e.g. chlorine and fluorine). By fine-tuning the reaction conditions, regioselective introduction of several substituents on the aromatic ring could be realized. Several substitution patterns were accomplished, which included 1,2,3-trisubstitution, 1,2,3,4-tetrasubstitution, and 1,2,3,4,5-pentasubstitution, up to the exhaustive substitution of the aromatic ring.

Introduction

Directed *ortho*-metalation (DoM)[1] is an important methodology for the functionalization of aromatic and heteroaromatic derivatives versus classical aromatic electrophilic substitution. In fact, this methodology allows for regioselective functionalization of aromatic (or heteroaromatic) rings by the intermediacy of carbanionic species, usually generated by deprotonation in the proximity of a directing group. Nevertheless, such hydrogen–lithium permutation depends on several factors, for example, the nature of the directing group, with reference to either its ability to coordinate the metal (lithium), or its inductive electron-withdrawing capability, the nature of the base and the reaction conditions. In other words, the regioselectivity of such metalations cannot always be predicted because the actual combination of thermodynamic and kinetic factors that govern this aspect cannot be accurately assessed. However, scope and limitations of this strategy have been widely investigated[2] and mechanistic studies tried to shed light on this process. The most accepted theories to help rationalize reactivity and regioselectivity rely on the complex-induced proximity effect (CIPE), kinetically enhanced metalation, the triple-ion mechanism, and the override-base mechanism.[3] The boundaries between such mechanisms in some cases are subtle and caution should be taken in the evaluation of the reactivity of aryl compounds in directed metalations, especially if kinetic and mechanistic evidence are missing. Fortunately, synthetic chemists are curious, and research efforts focused on directed metalation still offer the opportunity to discover new directing groups and synthetic pathways to fill the knowledge gap.[4,5] In this context, despite the broad range of heteroatom and carbon-bonded substituents available to perform the hydrogen–metal permutation in aryl compounds, small saturated N-heterocycles have received inadequate attention as potential directing metalation groups (DMGs). The importance of the aziridine ring in the regioselective lithiation of 2-aryl derivatives

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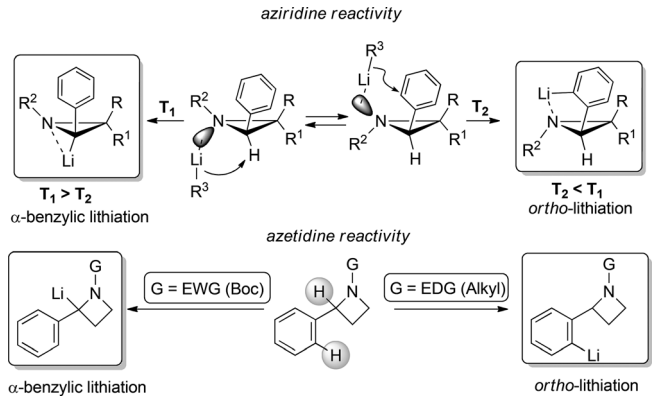
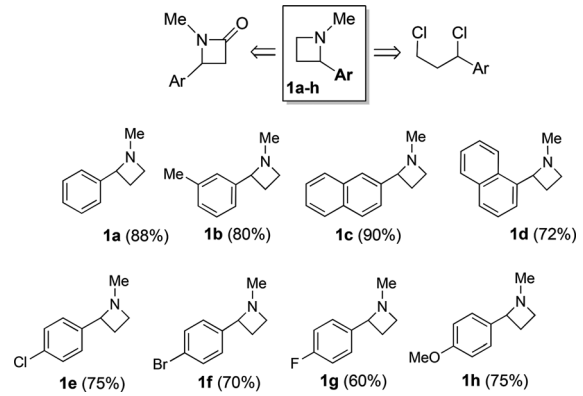


Scheme 1. Nitrogen dynamics and nature of the N-substituent as factors that affect the regioselectivity of the lithiation.



Scheme 2. 2-Arylazetidines used in this study.

has recently been reported by Luisi, Florio, and co-workers.[6] It has been proposed that nitrogen dynamics and coordination effects can play important roles to address the regioselectivity of the lithiation.[7] In fact, *N*-alkyl-2-arylaziridines could be *ortho*-lithiated at low temperatures, whereas α-benzylic lithiation was observed at higher temperatures, which proved that the aziridino group could act as a DMG (Scheme 1).[8] More recently, with the aim to develop new stereo- and regioselective synthetic protocols by using metalated heterocycles, we focused our attention to the almost unexplored four-membered heterocycles thietanes and azetidines.[9] Such heterocycles are appealing, either because of their occurrence in several natural products and biologically active molecules, or due to the lack of methodologies for their direct functionalization.[10] In the case of 2-arylazetidines, in a preliminary communication we reported that the nature of the N-substituent plays an important role in addressing the regioselectivity of the lithiation reaction. In particular, with an electron-withdrawing group [EWG; e.g. *tert*-butoxycarbonyl (Boc)] as the N-substituent, the lithiation occurred at the α-benzylic position, whereas with an electron-donating group (EDG; e.g. alkyl) *ortho*-aromatic lithiation was observed, which disclosed the ability of the azetidine ring to act as a DMG (Scheme 1). However, in striking contrast to aziridines, α-benzylic lithiation was never observed with 2-aryl-*N*-alkylazetidines.

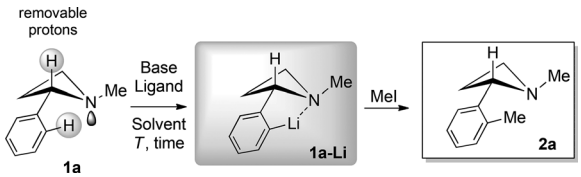
Herein, we report the results of an investigation aimed at understanding the factors that affect the reactivity and regioselectivity of the lithiation of 2-aryl-*N*-alkylazetidines, as well as the use of this azetidine-based DoM tactic for the regioselective and exhaustive functionalization of arenes.

Results and Discussion

With the aim to harness the role of the azetidine ring as a DMG, the reactivity of 2-aryl-substituted azetidines **1a**–**h** was investigated. With the exception of **1a**, regioselectivity and reactivity problems can be envisaged for each system. Azetidines **1a**–**h** were prepared by using two simple strategies from readily available azetidinones or by intermolecular cyclization of 1,3-dichloropropane derivatives (Scheme 2).[11,12]

First, we investigated the reactivity of 1-methyl-2-phenylazetidine (**1a**), chosen as a reference substrate, towards bases other than *n*-hexyllithium (*n*HexLi). We found that *n*HexLi was effective in the regioselective *ortho*-lithiation of **1a** under very mild conditions.[9a] Nevertheless, as reported in Table 1, other organolithium reagents and lithium amides were taken into consideration for two main reasons: 1) to explore the possibility to switch the regioselectivity (i.e. *ortho* versus α-benzylic);

Table 1. Optimization study for the *ortho* lithiation of **1a**.

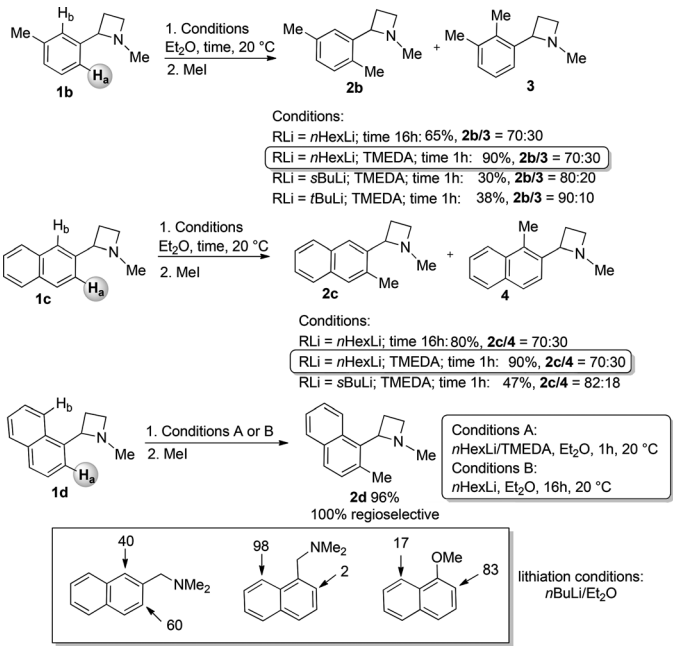


Entry	Base (equiv)	Ligand (equiv)	Solvent	T [°C]	t [h]	Yield [%][a]
1	LDA (1.5)	–	THF	−78	1	–
2	LDA (1.5)	–	THF	0	1	–
3	*s*BuLi (1.5)	–	THF	−78	1	–
4	*s*BuLi (2.5)	–	THF	0	1	–
5	*s*BuLi (2.5)	–	toluene	20	0.5	–
6	*s*BuLi (1.5)	–	Et_2O	20	16	45
7	*n*BuLi (2.5)	–	THF	20	0.5	52
8	*n*BuLi (2.5)	–	THF	20	2	60
9	*n*BuLi (2)	–	Et_2O	20	16	80
10	*n*BuLi (2)	–	toluene	20	18	30
11	*n*HexLi (1.5)	–	Et_2O	20	1	40
12	*n*HexLi (1.5)	–	Et_2O	20	4	71
13	*n*HexLi (2)	–	Et_2O	20	16	93[b]
14	*n*BuLi (2.5)	TMEDA (2.5)	toluene	20	2	60
15	*n*BuLi (2)	TMEDA (2)	Et_2O	20	1	40
16	*s*BuLi (1.5)	TMEDA (1.5)	Et_2O	20	1	65
17	*n*HexLi (1.5)	TMEDA (1.5)	toluene	20	1	65
18	*n*HexLi (1.5)	TMEDA (0.1)	Et_2O	20	2	55
19	*n*HexLi (1.3)	TMEDA (0.2)	Et_2O	20	1	60
20	*n*HexLi (1.3)	TMEDA (0.2)	Et_2O	20	4	83
21	*n*HexLi (1.3)	TMEDA (1.3)	Et_2O	20	1	95[b]
22	*n*HexLi (1.3)	TMEDA (1.3)	Et_2O	50	16	48[c]

[a] Yields calculated by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Yield of isolated product. [c] Deuterium was used as the electrophile. Only *ortho*-deuterated azetidine was observed. The lower yield was ascribed to partial decomposition of *n*HexLi.

2) for benchmarking other bases against *n*HexLi, which is potentially a more sustainable and safer alternative to other alkyllithium reagents.[13] Azetidine **1a** was reacted with common lithiated bases (lithium diisopropylamide (LDA), *s*BuLi, and *n*BuLi) then alkylated with MeI. The resulting crude reaction mixture was analyzed by NMR spectroscopy to ascertain yield, regiochemistry, and conversion. The use of *s*BuLi and LDA either at low or high temperature for short reaction times (0.5–1 h) was ineffective and starting material **1a** was recovered (Table 1, entries 1–5). The use of *s*BuLi for a longer reaction time (16 h) in Et_2O, furnished *ortho*-functionalized azetidine **2a** in 45% yield (Table 1, entry 6). Partial *ortho*-lithiation was observed by using *n*BuLi as the base and performing the reaction in a coordinating solvent, such as THF or Et_2O (Table 1, entries 7–9). Exclusively *ortho*-methylated azetidine **2a** was obtained in 80% yield by using *n*BuLi (2 equiv) in Et_2O at 20 °C (Table 1, entry 9) with a long reaction time (16 h). The use of a non-coordinating solvent, such as toluene, at 20 °C (Table 1, entry 10), resulted in lower conversion and formation of **2a** in 30% yield, even after a long reaction time. The use of *n*HexLi as the base gave a slightly better yield of **2a** than the reaction with *n*BuLi (Table 1, entry 13 versus 9). The effect of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a ligand on the rate of the lithiation reaction was evaluated with *s*BuLi, *n*BuLi, and *n*HexLi (Table 1, entries 14–22). As expected, the use of TMEDA accelerates the lithiation reaction to give higher conversions, even when used in substoichiometric amounts (Table 1, entries 18–20).[14] However, the use of both *s*BuLi/TMEDA (Table 1, entry 16) and *n*BuLi/TMEDA (Table 1, entry 15) resulted in slightly more sluggish reactions with respect to *n*HexLi/TMEDA (Table 1, entry 21). In addition, Et_2O was found to be the solvent of choice because it gave faster and cleaner reactions (Table 1, entry 14 versus 15 and entry 17 versus 21).

This comparative study also demonstrated that *n*HexLi represented a good alternative to *n*BuLi (or *s*BuLi) because it gave similar or better reaction performance. The best conditions for the straightforward *ortho*-lithiation of **1a** are reported in Table 1, entry 21. In this case, the use of TMEDA (1.3 equiv) is mandatory to speed up the deprotonation reaction. Further, with the aim to switch the regioselectivity, lithiation of **1a** was conducted by raising the temperature to 50 °C (Table 1, entry 22). However, even with lower yield, only *ortho*-deuterated azetidine [D]-**1a** was detected. In our opinion, it is interesting that two different sets of reaction conditions (Table 1, entries 13 and 21) could be used for the effective *ortho*-lithiation of azetidine **1a**. The usefulness of two different protocols available to conduct the *ortho*-lithiation will be highlighted in the functionalization of aryl azetidines (see below) with competitive DMGs as aryl substituents. By using the optimized conditions (Table 1, entry 21), we turned out our attention to study the regioselectivity of the lithiation of 2-arylazetidines **1b**–**h**. Even though the regiocontrolled functionalization of an aromatic ring could be challenging, success would give the opportunity to obtain new target molecules by manipulation of the introduced functionalities. Azetidines **1b**–**d**, with two potential sites for deprotonation (H_a and H_b; Scheme 3) were subjected to lithiation under the optimized conditions (Table 1, entry 21) followed by reaction with MeI. As expected, exclusive *ortho*-lithiation was observed for **1b** and **1c**, and both reactions had good regioselectivity (**2b**/**3** and **2c**/**4** ratios = 70:30) with proton H_a preferentially extracted. These results are in line with what has been reported for the open-chain analogue β-dimethylaminomethyl naphthalene (Scheme 3).[15] Attempts to improve the regioselectivity of the lithiation of **1b**–**c** were made by using different reaction conditions and more-hindered lithiating agents (Scheme 3). The use of *n*HexLi without the TMEDA additive (for conditions see Table 1, entry 13) resulted in the same regioselectivity (**2b**/**3** = 70:30) and a lower yield. The use of lithium amides such as LDA and lithiumtetramethylpiperidide (LTMP) were ineffective, whereas the use of *s*BuLi in the presence of TMEDA for 1 h gave slightly better regioselectivity (**2b**/**3** = 80:20 and **2c**/**4** = 82:18) but lower yields (Scheme 3). In the case of **1b**, lithiation with *t*BuLi in the presence of TMEDA at 20 °C for 1 h provided a better regioselectivity (**2b**/**3** = 90:10) but a low yield. Attempts to prolong the lithiation time with both *s*BuLi and *t*BuLi, either in the presence or absence of TMEDA, gave even lower yields, likely because of degradation of the base at 20 °C. Quite surprisingly, in the case of naphthylazetidine **1d**, for which *peri*-lithiation might be considered, product **2d** was isolated in 96% yield as the result of a very selective *ortho*-lithiation (Scheme 3). This result is, in our opinion, remarkable because it reveals an opposite regiochemistry to that observed with the open-chain analogue α-dimethylaminomethylnaphthalene. For the latter, *peri*-lithiation predominates by treatment with *n*BuLi in ether/hexane.[16] However, because our protocol is dissimilar due to the presence of the ligand TMEDA, for the sake of comparison and to assess the role of the azetidine ring, we ran the lithiation of **1d** in the absence of TMEDA (conditions B in Scheme 3). Trapping of the putative lithiated intermediates of **1d** with MeI again oc-



Scheme 3. Regioselective lithiation of 2-arylazetidines.

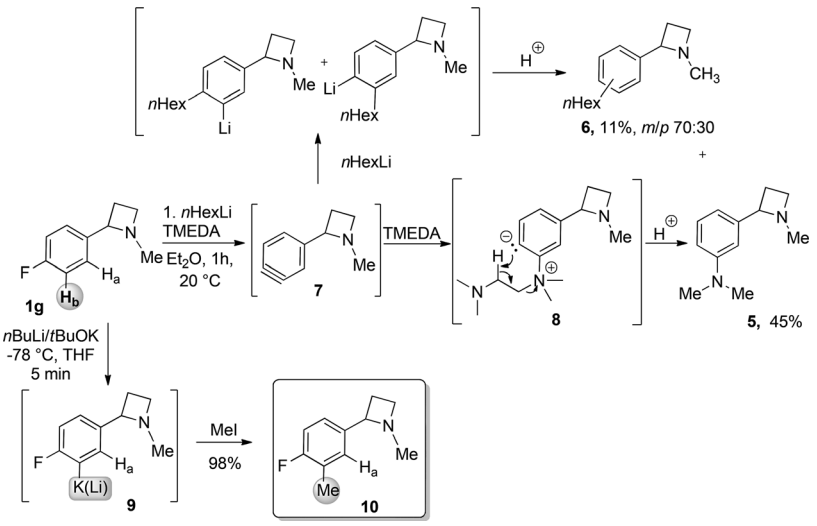
curred regioselectively to lead exclusively to **2 d**. Thus, different behavior can be envisaged for the cyclic versus open-chain tertiary amine.

It is worth mentioning that even with 1-methoxynaphthalene competition between *ortho*- and *peri*-lithiation has been observed (Scheme 3).[17] Aware that halogens could promote *ortho*-lithiation of the aromatic ring mainly by means of their inductive effect,[1a,3f] we also evaluated the regioselectivity in the lithiation of chloro-, bromo-, and fluoro-substituted azetidines **1 e**–**g** (Schemes 4 and 5) by using the optimized conditions (Table 1, entry 21). The inductive effect of the chlorine substituent combined with the *ortho*-directing ability of the azetidine ring, regioselectively provided product **2 e** in high yield (Scheme 4).[18] In the case of **1 f**, a bromine–lithium exchange occurred when *n*HexLi was used as the base; a trial with lithium amide was unsuccessful.[19] The use of the zincate base tBu_2Li-Zn(TMP) (TMP = 2,2,6,6-tetramethylpiperidide), developed by Kondo and co-workers,[20] was also ineffective and resulted in only partial dehalogenation (Scheme 4). Attempts to deprotonate the more challenging bis-azetidine **1 i** (prepared by a Suzuki–Miyaura coupling reaction from **1 f**) under various lithiation conditions also failed, likely due to its very low solubility, and only starting material was recovered (Scheme 4).

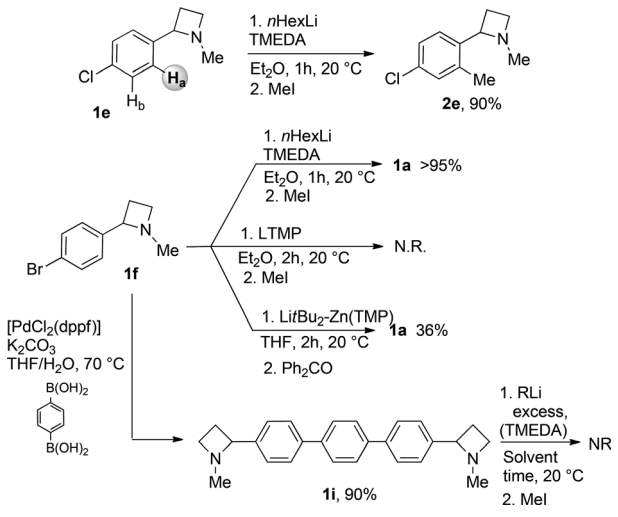
Different results were obtained in the lithiation of **1 g**. In this case, the fluorine substituent behaves as a better directing group with respect to the azetidine ring. However, it is well-documented that fluoroarenes undergo *ortho*-metalation.[21] A regioselective metalation was achieved by reaction of **1 g** with Schlosser's superbase LIC-KOR (*n*BuLi/*t*BuOK) at −78 °C in THF (Scheme 5).[22] Under these reaction conditions, the *ortho* positions with respect to the azetidine ring remained untouched and the metalation reaction occurred smoothly at the position adjacent to the fluorine atom to provide the methylated product **10** in 98% yield.

Nevertheless, lithiation of **1 g** revealed an interesting scenario to give unexpected products **5** (45%) and **6** (11%). The intriguing presence of **5** prompted us to suggest the involvement of aryne **7** (Scheme 5). The ability of **7** to capture nucleophilic species, such as *n*HexLi, produced the *cine*- (*meta*-**6**) and *ipso*-substitution (*para*-**6**) products in a 70:30 ratio, respectively. It is likely that **7** could also intercept TMEDA to give the anilinium salt (intermediate **8**), which affords **5** after β-elimination.[23,24]

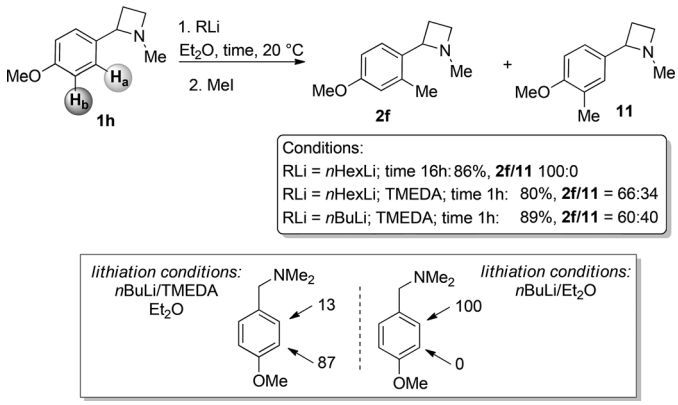
Next, we considered the reactivity of methoxy-substituted arylazetidine **1 h** (Scheme 6). In this case, competition between the azetidine ring and the methoxy group was observed. In particular, the lithiation/trapping sequence of **1 h** by using either *n*HexLi and *n*BuLi in the presence of TMEDA resulted in a mixture of products **2 f** and **11**. The reaction run in the pres-



Scheme 5. Regioselective lithiation of 4-fluorophenylazetidine (**1 g**).



Scheme 4. Regioselective lithiation of 4-chlorophenyl- (**1 e**) and 4-bromophenyl- (**1 f**) azetidines. dppf = 1,1′-bis(diphenylphoshino)ferrocene.



Scheme 6. Regioselective lithiation of methoxyphenylazetidine (**1 h**).

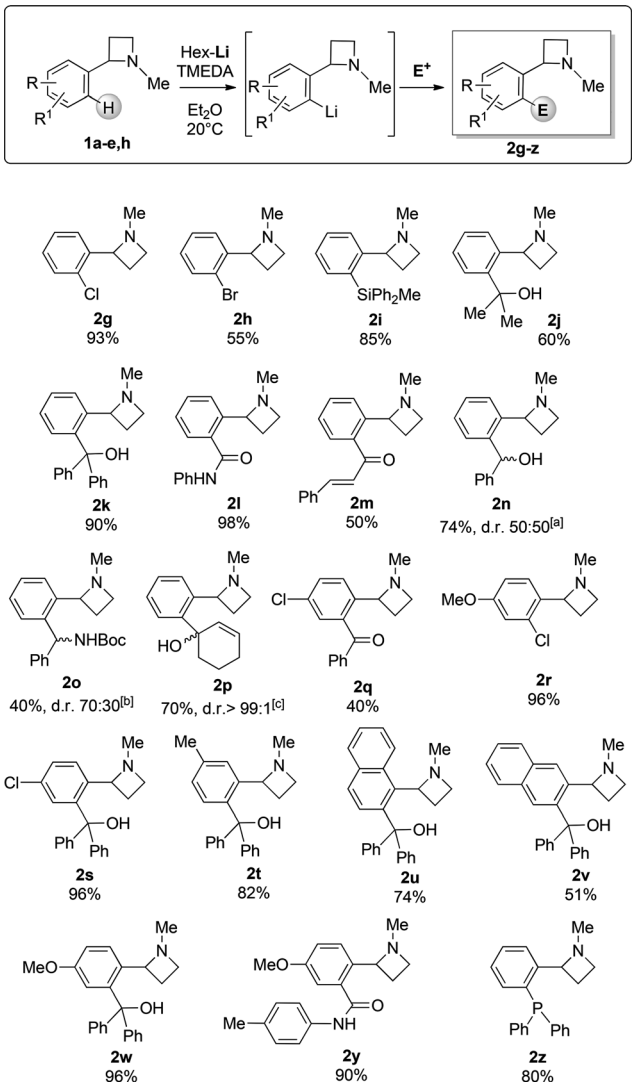
ence of TMEDA disclosed a competition between the azetidine ring and the methoxy group in directing the lithiation reaction. However, a slight preference in favor of the azetidine ring was observed (Scheme 6). This result is in striking contrast to what has been reported for the corresponding open-chain analogue *p*-methoxy-*N*,*N*-dimethylbenzyl amine, for which a marked preference for direction by the methoxy group (87:13 ratio of regioisomers) occurred under similar reaction conditions.[25,3b] Nevertheless, when the lithiation reaction was performed without TMEDA (see Table 1, entry 12 for conditions) we were pleased to find that azetidine **2f** was the sole reaction product after trapping with MeI. In this case, the regioselectivity matched that observed for lithiation of the open-chain analogue *p*-methoxy-*N*,*N*-dimethylbenzyl amine (Scheme 6).

The scope of the methodology was assessed with the azetidines able to undergo the *ortho*-lithiation/electrophilic-trapping sequence. This protocol was successfully applied to the regioselective *ortho* functionalization of lithiated azetidines **1a**–**e** and **1h** with several electrophiles, such as MeI, $Ph_2MeSiCl$, $Br(CH_2)_2Br$, C_2Cl_6, ketones, imines, aldehydes, Weinreb amides, Ph_2PCl, and isocyanates (Scheme 7). Functionalized azetidines **2g**–**z** were obtained in good-to-excellent yields. Nevertheless, poor stereoselectivity was observed for the reaction with prochiral electrophiles, such as benzaldehyde and *N*-Boc-benzylidenimine, which led to **2n**–**o**, whereas the use of cyclohexenone gave **2p** as a single stereoisomer. A single regioisomers, likely for steric reasons, was observed in the reactions of lithiated **1b** and **1c** with benzophenone to afford **2t** and **2v**, respectively.

Trapping *ortho*-lithiated azetidines with boropinacolate (*i*PrOBpin) afforded the corresponding arylboronates **12a**–**e** (Scheme 8).[26] In all cases, the reaction proceeded with good yields and a mixture of regioisomers (**12b** and **12e**) was observed in the lithiation/borylation sequence for azetidines **1b**–**c**. Such derivatives were isolated in good yields by flash chromatography and ^{11}B NMR spectroscopic analysis confirmed an intramolecular B···N dative bond, recently demonstrated by Shipman and co-workers for azetidines tethered to boronate esters (see the Supporting Information).[27]

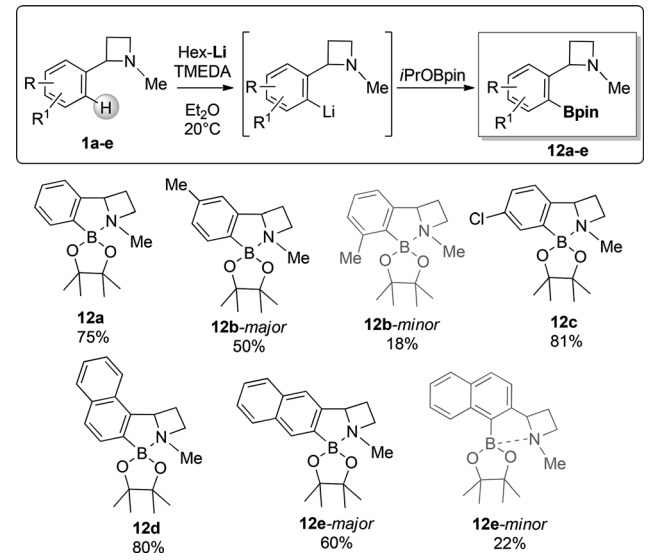
Encouraged by these results, we envisioned further synthetic applications for *ortho*-lithiated 2-arylazetidines. Since the coupling with allyl halides is problematic because of a lithium–halogen exchange reaction, we undertook a transmetalation of lithiated compounds of **1a** and **1e** with CuCN·2LiCl. The putative aryl cuprates cleanly coupled with allylic bromides to give the desired allyl derivatives **13a**–**c** in good yields (Scheme 9).

The reactivity described so far proves the role of the azetidine ring as DMG, and reveals the reaction conditions can address the regioselectivity when additional substituent are installed on the aromatic ring. The observed *ortho*-directing ability of the azetidine ring could be explained by assuming the coordinating role of the nitrogen atom, as seen in the case of 2-arylaziridines or other Lewis basic heteroatoms that bear an aromatic ring.[28,3–5] However, as in the case of *N*-alkyl-2-arylaziridines (Scheme 1), the importance of dynamic phenomena on the reactivity should be taken into consideration. We envisaged that *N*-alkyl-2-arylazetidines could also show dynamic

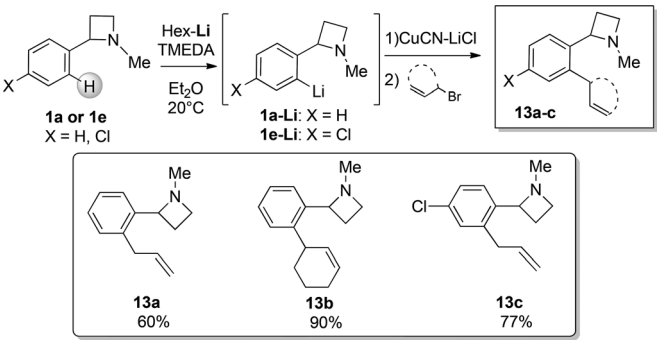


Scheme 7. Scope of the azetidine-directed *ortho*-lithiation. [a] Inseparable mixture of diastereoisomers. [b] The structure of the major isomer and relative configuration was assigned by single-crystal X-ray analysis. [c] A single diastereomer was detected in the ^1H NMR spectrum of the crude reaction mixture.

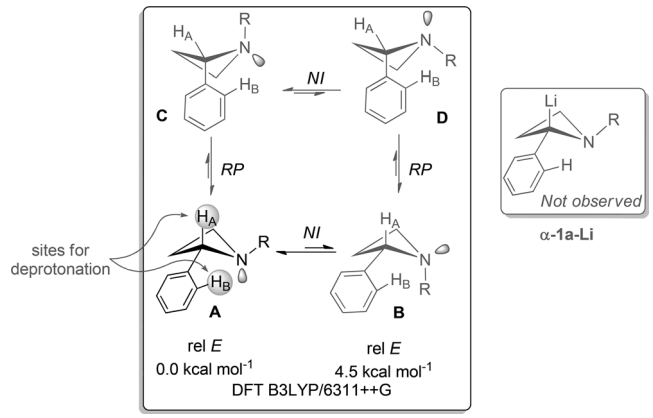
phenomena associated with both nitrogen inversion (NI) and additional ring puckering (RP).[29] In particular, nitrogen inversion is expected to be faster (lower barrier) with respect to the corresponding three-membered ring, but slower (higher barrier) with respect to ring puckering.[30] Such a dynamic process (Scheme 10) involves four different conformational isomers (**A**–**D**) for *N*-alkyl-2-arylazetidines. Nevertheless, conformers **C** and **D**, with the phenyl ring in a pseudo-axial arrangement, are expected to be unstable because of A1,3 ring strain (as demonstrated for other azetidines).[31] Thus, analogously to the three-membered ring aziridines, the most stable N-invertomers **A** and **B** should be considered. We proposed this picture in view of the fact that VT-NMR spectroscopy and NOESY experiments in the range $T = 298$–200 K indicate the presence of one main invertomer with a *trans* arrangement between the *N*-methyl group and the phenyl ring (see the Supporting Information).



Scheme 8. Borylation of *ortho*-lithiated azetidines.



Scheme 9. Allylation of *ortho*-lithiated azetidines.



Scheme 10. Azetidine dynamics.

Single-crystal X-ray analysis of *ortho*-functionalized azetidines **2k**, **2o**, and **2w** also confirmed a *trans* arrangement between the *N*-methyl group and the aromatic group and the puckered conformation for the azetidine ring (Figure 1). DFT calculations at the B3LYP/6-311++G(d,p) level of theory converged into two minima that corresponded to conformers **A** and **B**; the former was more stable by about 4.5 kcal mol^{-1} (see the Supporting Information). For these reasons, we came to the conclusion that conformer **A** (Scheme 10) would be involved in the lithiation reaction. If this assumption is made, then it is likely that the nitrogen lone pair could play a role in facilitating the lithiation, either making pre-lithiation complexes or stabilizing the lithiated intermediate by chelation.[32]

To assess a possible coordinating role of the azetidine nitrogen atom during the deprotonation process, intra- and intermolecular kinetic isotope effects (KIE) were evaluated. As demonstrated by the groups of Beak,[33] Collum,[34] Clayden,[35] KIE experiments are informative as to the number of steps in-

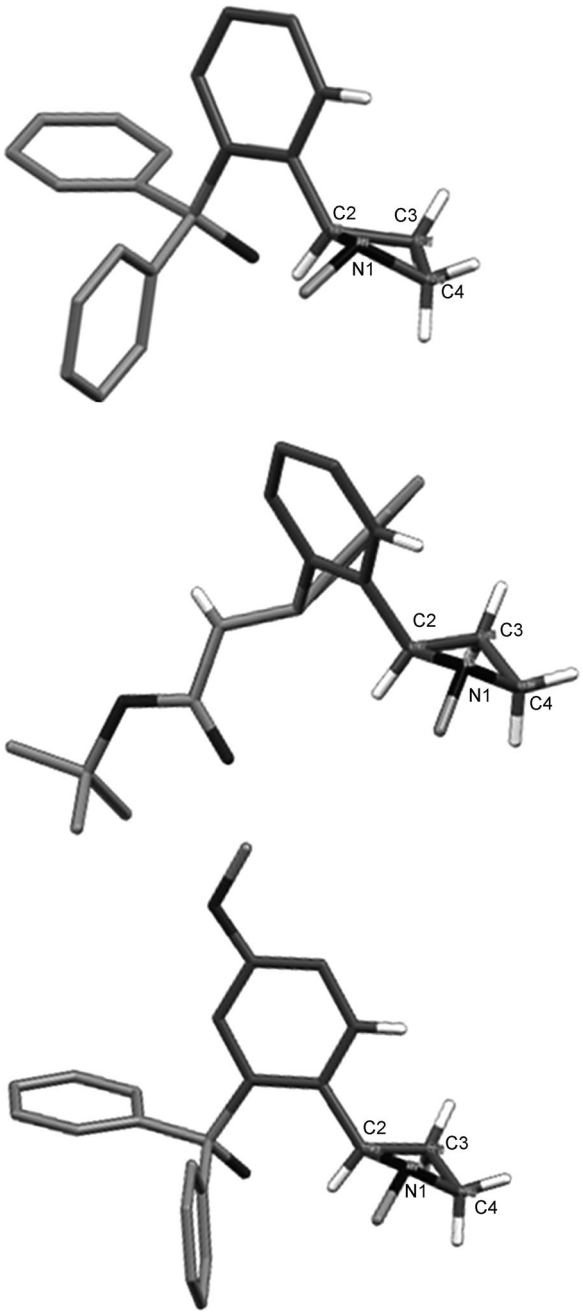
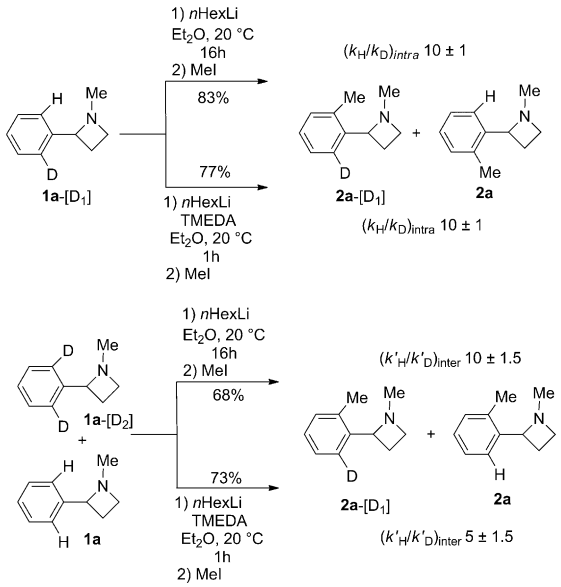


Figure 1. X-ray analysis of **2k** (top), **2o** (middle), and **2w** (bottom); some hydrogen atoms are omitted for clarity.

volved in a directed lithiation process. In particular, a difference between the intra- and intermolecular KIE indicated that the process likely proceeds by a two-step mechanism and that pre-lithiation complexes could be involved. Another option could be the kinetic acceleration imparted by the directing group in the transition state. In both cases, complexation phenomena come into play. The intramolecular KIE for the *ortho*-lithiation of azetidine **1a**-[D_1], was evaluated either in the presence or absence of TMEDA (Scheme 11). In the experiment executed without the ligand TMEDA, $k_H/k_D = 10$. A similar value was observed for the experiment run in the presence of TMEDA ($k_H/k_D = 10$). The intermolecular KIE was evaluated by using almost equimolar mixtures of **1a**-[D_2] and **1a**, again in the presence or absence of TMEDA (Scheme 11). In these cases, the analysis was a little more complicated but from ^{1}H NMR spectroscopy and MS analysis it clearly emerged that product **2a**-[D_1] formed predominantly and that the unreacted starting material was enriched in **1a**-[D_2]. The apparent KIE $k'_H/k'_D = 10$ was found for the reaction performed without TMEDA, whereas $k'_H/k'_D = 5$ was calculated for the reaction performed in the presence of TMEDA (see the Supporting Information). On the basis of the KIE experiments, we assume that the *ortho*-lithiation of 2-arylazetidines likely proceeds by a two-step mechanism with a fast, reversible complexation followed by a rate-limiting deprotonation step.[36] In addition, the fact that benzylic lithiation, which leads to **α-1a-Li** (Scheme 10), was never observed, even when the lithiation reaction was executed at high temperature (Table 1, entry 21), strengthens the hypothesis that conformer **A** (Scheme 10) could be responsible for the observed reactivity.[37]

Assuming the directing ability of the azetidine ring, we explored the possibility of further functionalization of the aromatic group. A careful look at the X-ray structures of monofunctionalized azetidines **2k**, **2o** and **2w** (Figure 1), reveal a peculiar arrangement of the aryl group linked to the C2 carbon atom of the azetidine ring. In all three structures, the aryl groups occupy a pseudo-equatorial position and are *trans* oriented with respect to the nitrogen substituent. In fact, regardless of the nature of the primarily introduced electrophile, in the solid state the residual *ortho* proton of the aryl ring appears oriented towards the lone pair of the azetidine nitrogen.



Scheme 11. KIE studies.

We wondered whether such a stereochemical preference could be retained in solution and, most importantly, if it could be responsible for a further selective *ortho*-lithiation. To verify this hypothesis we searched for this preferential conformation in solution by analysis of the ^{1}H NMR spectra of monofunctionalized azetidine **2a**. In this case, VT-NMR spectroscopy (T = 370–200 K) did not show any significant line broadening or signal splitting. However, 1D-NOESY experiments (mixing time = 750 ms) with **2a** carried out at 200 K revealed proximity interactions in line with conformer **A** (Figure 2).[38]

To strengthen the hypothesis for a preferential conformation, we ran a conformational DFT analysis and the nature of the more stable conformers were elucidated by comparison to experimental and calculated NMR spectroscopic data (see the Supporting Information). The conformations **A** and **B**, found to be the most stable by conformational analysis, were subjected to a full geometry optimization at the DFT-SMD/B3LYP/6-311++G(d,p) level of theory.[39] Vibrational analysis applied to the stationary points proved that all of them were true minima and provided values of free energy. Conformer **A** was the most stable conformer; conformer **B** was higher in energy by about 2.5 kcal mol^{-1}. Subsequently, we wanted to learn whether the conformational picture obtained from DFT geometry computations agreed with the situation observed in NMR experiments. For this purpose, the ^{1}H NMR spectra were calculated for both conformers and compared with the experimental ones. Shielding constants were calculated by using the GIAO-DFT method at the SMD/MPW1PW91//B3LYP/6-311++G(d,p) level of theory; for spin–spin coupling constants J(H,H) the B3LYP functional with the B3LYP/6-311++G(d,p) basis set was used, for consistency with our previous studies.[40]

The ^{1}H NMR spectra calculated for the two conformers revealed important differences. In particular, the simulated ^{1}H NMR spectrum of conformer **A** was very similar to the experimental spectrum (see the Supporting Information). Most likely a consequence of a preferential conformation, a marked difference in chemical shifts can be seen for the residual *ortho* protons ($H_{o'}$ in Figure 2) of conformers **A** and **B**.

Other evidence to support the role of the azetidine nitrogen atom and the hypothesis of a preferential conformation came from the lithiation/trapping experiment with *ortho*-methyl-substituted azetidines **2a** and **2a**-[D_1] (Scheme 12), in which a competitive lateral benzylic lithiation could occur. In fact, in two separate experiments, **2a** and **2a**-[D_1] were subjected to lithiation/electrophilic trapping under the optimized conditions (Table 1, entry 21) and only **14**, the product of double functionalization, was observed (Scheme 12). Nevertheless, the lithiation of **2a**-[D_1] occurred much more slowly with respect to that of **2a**. This was likely a KIE and no traces of lateral trapping product were detected by ^{1}H NMR spectroscopy of the crude reaction mixture. This result is in striking contrast to that

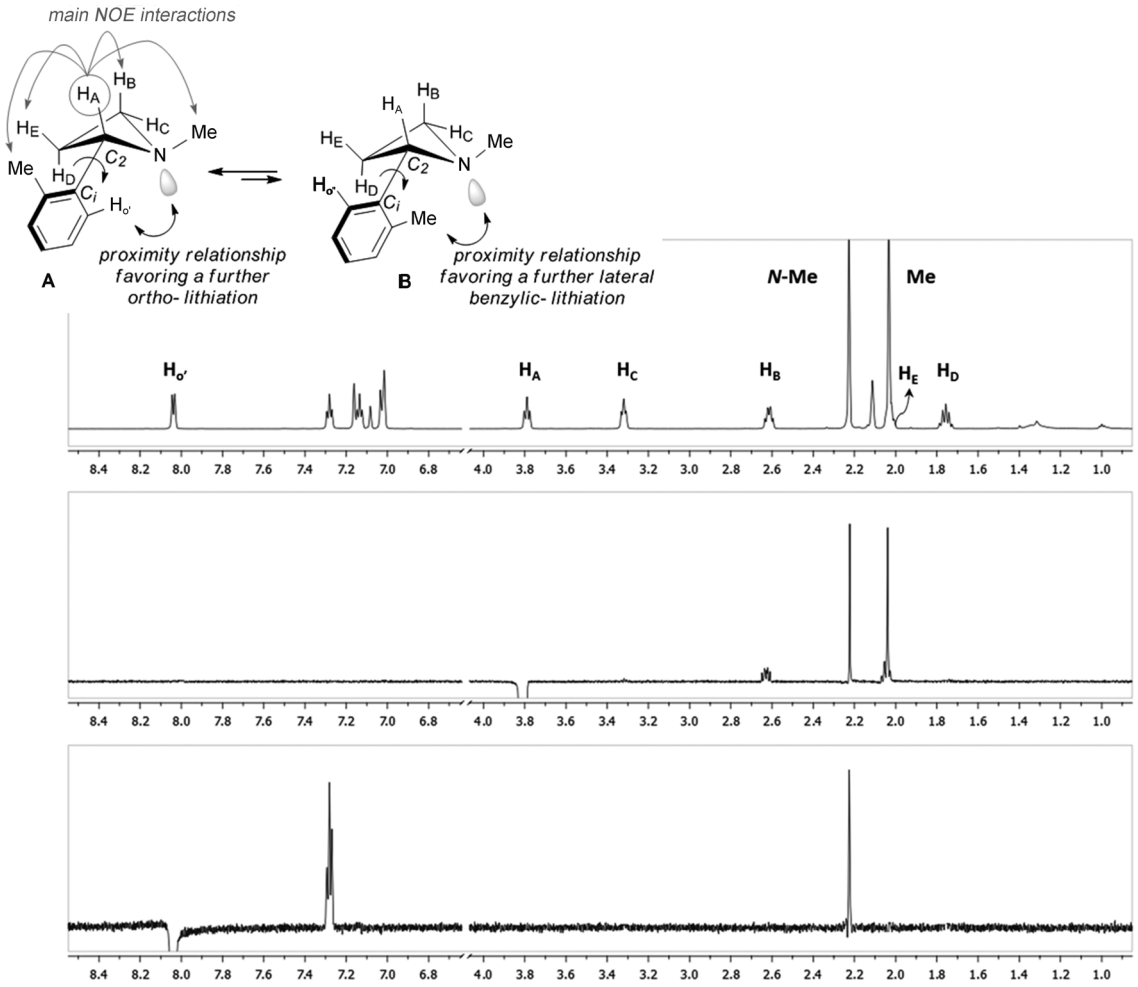
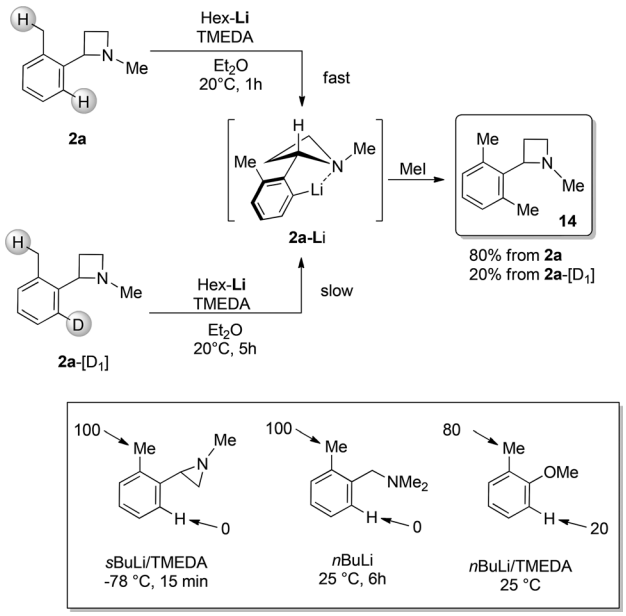


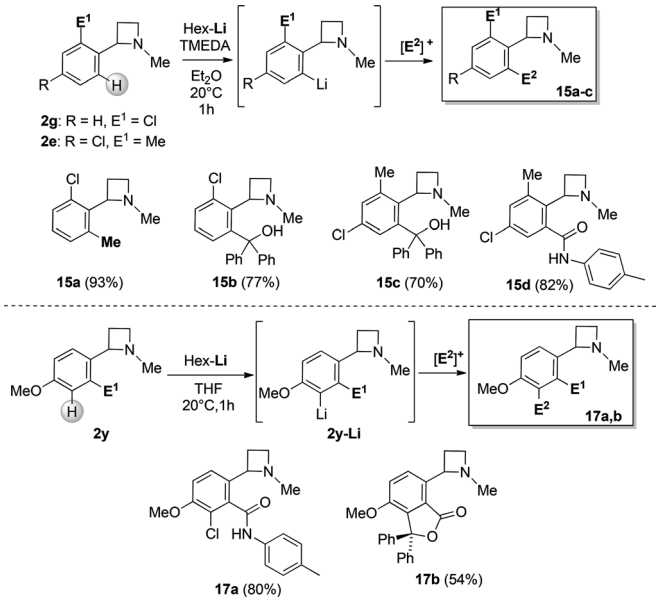
Figure 2. Top) ^{1}H NMR, middle) 1D-NOESY (H_a irradiated), and bottom) 1D-NOESY ($H_{o'}$ irradiated) spectra of **2a** in [D_8]toluene at 200 K.



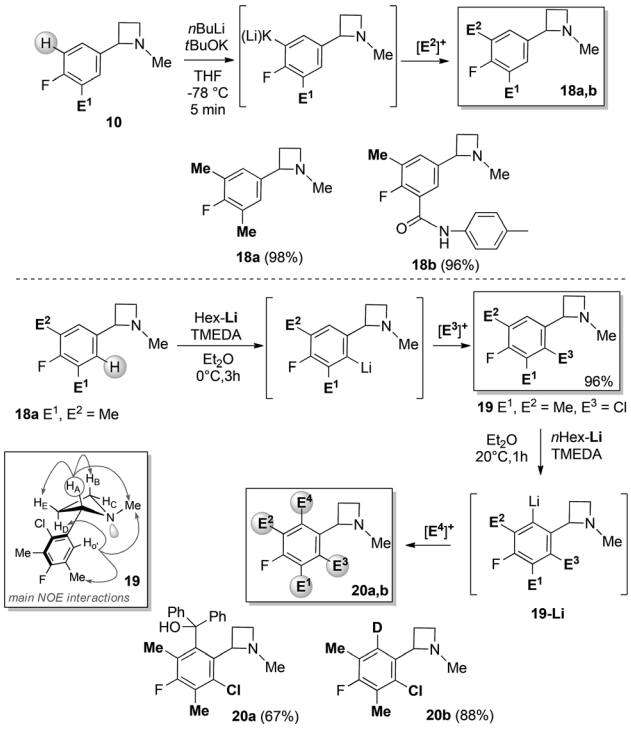
Scheme 12. Attempts to induce lateral lithiation in *ortho*-tolylazetidines.

observed for *ortho*-tolylaziridines, for which lateral lithiation occurred even at low temperature. Such lateral regioselectivity has been observed for other *ortho*-methyl-substituted arenes with a methoxy or *N*,*N*-dimethylaminomethyl directing group (Scheme 12).[41] We again ascribe the lack of lateral lithiation to the preferential conformation of the aromatic ring that places the *ortho*-methyl-substituent distant from the azetidine nitrogen coordination site.[42–44] In our opinion, the presence of a preferential conformation would guarantee a proximity relationship to favor an *ortho*-lithiation.

The preferential *ortho*-lithiation observed for 2-arylazetidines was further exploited for polysubstitution of the aromatic ring. In particular, we envisaged the possibility to introduce new substituents at a predictable position by fine-tuning the reaction conditions. In the case of azetidines **2g** and **2e**, with an inductively electron-withdrawing chlorine substituent on the aryl ring, the regioselectivity could be addressed by exploitation of the coordinating azetidine ring (Scheme 13). By using the optimized conditions (Table 1, entry 21), tri- and tetra-substituted azetidines **15a–c** were easily obtained in good-to-excellent yields (Scheme 13). It is worth noting that in the functionalization of **2e**, again the lateral benzylic lithiation did not occur.[45]



Scheme 13. DoM strategies for the functionalization of azetidine-bearing arenes.



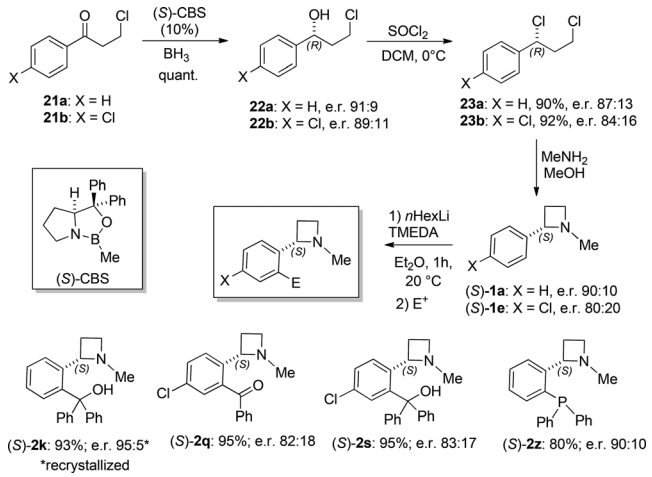
Scheme 14. Example of exhaustive functionalization of fluoroarylazetidines.

More challenging was the case of azetidine **2y**, which bears three coordinatively competent directing groups on the aromatic ring, (Scheme 13). The use of *n*Hex-Li in THF at 20 °C allowed for a very selective deprotonation at the most activated position (simultaneous presence of methoxy and amide groups). The *ortho*-position adjacent to the azetidine ring was unreactive under these conditions. Trapping of the *ortho*-lithiated intermediate **2y-Li** with electrophiles furnished azetidines **17a**,**b** with a tetra-substituted aromatic ring with a 1,2,3,4-substitution pattern. Interestingly, the use of benzophenone as the electrophile gave rise to an intramolecular cyclization leading to functionalized phthalide derivative **17b**. Aware of the importance of fluorinated aryl compounds,[46] we used the site-selective metalation as a tool for an exhaustive functionalization of the aromatic ring (Scheme 14). Starting from azetidine **10** (obtained as reported in Scheme 5), reiteration of the metalation/trapping sequence with the superbase LIC-KOR achieved a straightforward regioselective functionalization at the *ortho* positions adjacent to the fluorine atom. Trapping of the metalated azetidine generated from **10** with electrophiles furnished azetidines **18a**,**b** in very good yields. As proof of concept, the exhaustive functionalization of the aromatic ring was attempted with azetidine **18a,** which has two equivalent residual aromatic protons. Application of the *ortho*-lithiation/electrophilic trapping sequence to **18a** under the reaction conditions that favor deprotonation at the *ortho*-position adjacent to the azetidine ring (Table 1, entry 21), penta-substituted azetidine **19** was obtained in very good yield. Surprisingly, 1D-NOESY experiments for **19** revealed proximity interactions according to a preferential conformation (Scheme 14) as seen in the case of **2a** (see the Supporting Information). Again such a preferential conformation could favor the hydrogen–lithium permutation to allow, in the case of **19**, an exhaustive functionalization. Thus, the aromatic ring of **19** was exhaustively functionalized simply by application of the *ortho*-lithiation/electrophilic-trapping protocol. In this way, azetidines **20a**,**b** with an aromatic ring fully substituted with different groups were prepared (Scheme 14).

The last part of this work aimed to harness the role of the azetidine ring as a DMG. We evaluated the regioselective elaboration of the aromatic ring of enantioenriched azetidines (*S*)-**1a** and (*S*)-**1e**. Chiral nonracemic azetidines (*S*)-**1a** and (*S*)-**1e** were obtained from the corresponding β-chloroketones **21a**,**b** by using the synthetic strategy depicted in Scheme 15. Enantioselective Corey–Bakshi–Shibata (CBS) reduction[47] of **21a**,**b** furnished chloro alcohols **22a**,**b**, which were transformed into the corresponding 1,3-dichloropropane derivatives **23a**,**b** by a retentive nucleophilic substitution with $SOCl_2$.[48] Cyclization with a solution of $MeNH_2$ (30%) in alcohol furnished chiral azetidines (*S*)-**1a** and (*S*)-**1e**, which gave functionalized azetidines (*S*)-**2k**, (*S*)-**2q**, (*S*)-**2s**, and (*S*)-**2z** after the lithiation/electrophilic trapping sequence without loss of optical purity (demonstrated by chiral HPLC analysis).

Conclusion

This study attempted to introduce a synthetic strategy for the regioselective *ortho*-C–H functionalization of aryl compounds mediated by the azetidine ring. Robust lithiated intermediates that reacted with a broad range of electrophiles under very mild conditions are involved in this synthetic strategy. The developed protocol uses the safer reagent *n*HexLi as an effective lithiating agent at room temperature. Two different reaction protocols were optimized for regioselective lithiation at the *ortho*-positions adjacent to the azetidine ring. These conditions



Scheme 15. *ortho* Functionalization of enantioenriched 2-arylazetidines.

served as toolbox when competing directing groups were installed on the aromatic ring. The role of the azetidine nitrogen atom was assessed, as well as the effect of dynamic phenomena related to nitrogen inversion and preferential conformations of the 2-aryl substituent. Both factors account for the lack of benzylic lithiation that occurred with the lower 2-arylaziridines analogues. The possibility to plan a site-selective functionalization of the aromatic ring has been demonstrated with aryl azetidines that bear a coordinatively competent group (e.g. the methoxy group in **2y**), or inductively electron-withdrawing substituents (e.g. chlorine and fluorine in **2g**, **2e**, and **10**). By using appropriate reaction conditions in terms of solvent, temperature and metalating agent, a regioselective introduction of substituents has been realized even in the presence of competing directing groups. Several substitution patterns for the aromatic ring could be accomplished, including 1,2,3-trisubstitution, 1,2,3,4-tetrasubstitution, 1,2,3,4,5-pentasubstitution, and the exhaustive substitution with six groups (derivatives **20a**,**b**).

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Keywords: azetidines · dynamic reactivity · heterocycles · lithiation · regioselectivity

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