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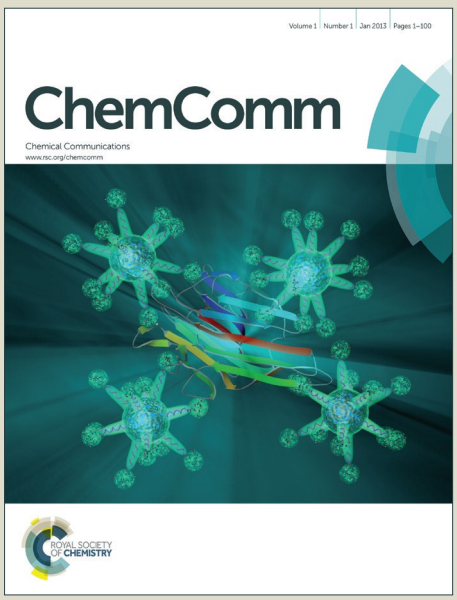

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Easy access to constrained peptidomimetics and 2,2-disubstituted azetidines by unexpected reactivity profile of α-lithiated N-Boc-azetidines

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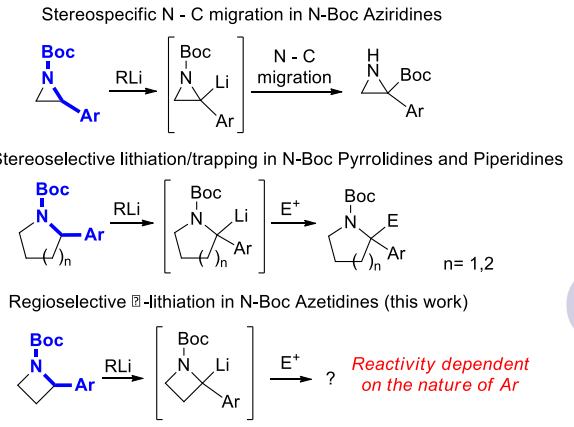
The reactivity profile of lithiated N-Boc-2-arylazetidines has been investigated filling a gap in the chemistry of this kind of four-membered heterocycles. Two unexpected and unprecedented results have been observed: an "ortho-effect" accounting for a regioselective functionalization of the azetidine ring, and a self-condensation leading to new and interesting azetidine-based peptidomimetics.

Saturated nitrogen-bearing heterocycles are an important class of compounds with widespread diffusion in several natural products, marketed drugs and bioactive molecules. With an eye on four-membered heterocycles, azetidines have received much less attention with respect to higher and lower N-bearing homologues.[1] The chemistry of this kind of heterocycle is emerging as an active research area, because of the importance of azetidines in catalysis, stereoselective synthesis and medicinal chemistry.[2] Recent examples are, among others, entries to chiral highly functionalized azetidines, ring opening reactions and synthesis of amino acids incorporating the azetidine nucleus.[3] Owing to structural rigidity brought by this heterocycle, and the capacity to alter pharmacological properties,[4] it is not surprising that some of the recently marketed drugs (Azelnidipine, Melagatran, Exanta) contain the azetidine ring.[5] Our interest in the development of a divergent synthesis of functionalized azetidines, by lithiation/electrophile trapping sequence, prompted us to disclose the ortho-directing ability of the azetidine ring.[6] In *N*-alkyl 2-aryl azetidines, the lone pair availability allowed for a multiple and site-selective functionalization of the aromatic ring. However, when such lone pair availability was missing, as in the case of *N*-Boc 2-aryl azetidines, a switch in regioselectivity is observed and α-lithiation occurs. Nevertheless, in a preliminary investigation we found that *N*-Boc-2-phenylazetidine could be lithiated and trapped at the α-position with low yields and only under internal quenching conditions.[7] Recently, Hodgson reported on the elegant use of other N-activating groups such as N-tert-butoxythiocarbonyl (Botc) and N-thiopivaloyl for successful α-lithiation/trapping of unsubstituted azetidines.[8] In such reports, emerged the fact that the readily installed tert-butoxycarbonyl (Boc) group is unsuitable for effective lithiation/trapping sequences on unsubstituted azetidine, while it is the group of choice in the Csp^2-α-lithiation of azetines.[9]

In Scheme 1 are collected the observed reactivities, towards lithiating agents, of lower and higher homologues *N*-Boc-2-aryl heterocycles (aziridines, pyrrolidines and piperidines). In all cases, the N-Boc group acts as activating group allowing for α-lithiation. Nevertheless, aziridines undergo a fast N-C migration[10] while α-lithiated pyrrolidines and piperidines can be effectively functionalized.[11]



Scheme 1. Reactivity observed in N-Boc 2-aryl heterocycles

Being azetidines a missing link in this reactivity scenario, we decided to investigate further the α-lithiation of *N*-Boc-2-arylazetidines with the aim to understand the reason of such

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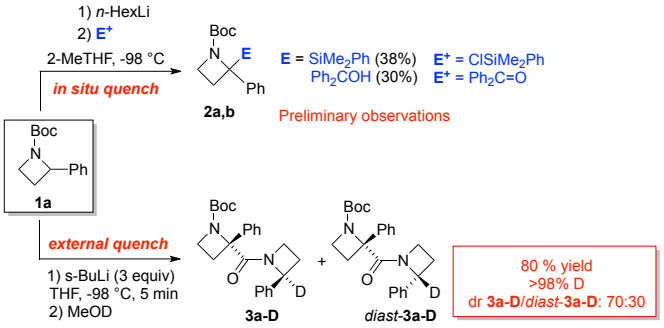
different behavior. We report herein our findings about this study.

We began the study reinvestigating the reactivity of N-Boc-2-phenylazetidine **1a** starting from previous observations, leading to α-functionalized azetidines **2a**,**b** under in situ quench conditions,[7] and running the lithiation reactions under external quench conditions (Scheme 2). Under in situ quench conditions, the base is added to a precooled solution of the azetidine and the electrophile; while under external quench conditions, the electrophile is added, after a definite amount of time, to a cooled solution of the putative lithiated intermediate generated by adding the base to the azetidine. Several reaction parameters as temperature, concentration, solvents, ligands and lithiating agents were carefully varied. The deuteration reaction was evaluated. After an extensive experimental investigation, we found as optimal reaction conditions, for a complete conversion of **1a**, the use of *s*-BuLi (3 equiv) as the lithiating agents in THF at -98 °C for 5 minutes at 0.05 M concentration. An unexpected self-condensation of **1a** was observed, under such reaction conditions, leading to diastereomeric dimers **3a-D** and *diast*-**3a-D** (Scheme 2).

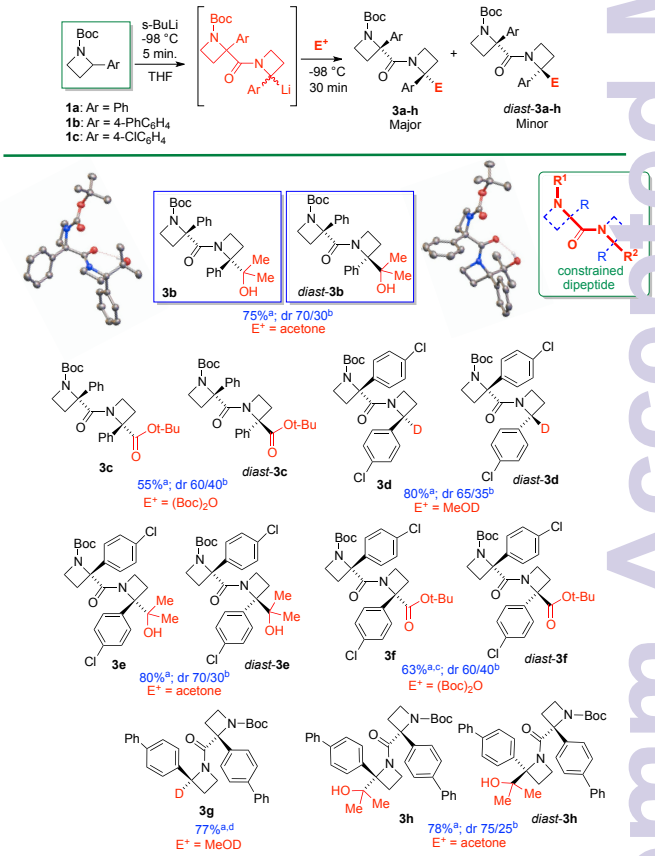


Scheme 2. Lithiation of N-Boc 2-phenylazetidine **1a** under external quench conditions

The use of other lithiating agents (*n*-HexLi, *n*-BuLi, LDA, LTMP) as well as different reaction medium (THF, 2-MeTHF, toluene/tmeda, Et_2O/tmeda) furnished unreacted starting material or complex reaction mixtures depending on concentration, reaction time, and temperature. In fact, higher concentrations (>0.05 M), longer reaction times (>5 min) and temperatures above -98 °C returned only complex reaction mixtures. The expected α-deuterated azetidine (**1a-D**) was observed in trace amount during the optimization study while the N-C migration product never was observed.

Dimeric azetidines **3a-D** and *diast*-**3a-D** represent, to the best of our knowledge, the first example of self-condensation of a Boc stabilized α-lithiated amine. Interestingly, such dimers, easily separable by flash chromatography, show peculiar structures resembling to constrained peptidomimetics which are important scaffolds in medicinal chemistry.[12,13]

In order to verify the applicability of this lithiation/dimerization/electrophile trapping strategy to access azetidine-based peptidomimetics, we explored the scope using readily available *N*-Boc-2-arylazetines **1a-c** and representative electrophiles (Scheme 3). We were glad to observe that this self-condensation takes place also with other α-lithiated 2-arylazetidines. Deuteration, hydroxyalkylation and carbonylation of lithiated dimers occurred with good yields but modest diastereoselectivity using MeOD, acetone and Boc_2O as electrophiles. However, in most cases mixtures of diastereomeric dimers **3** and *diast*-**3** were separable by flash chromatography (Scheme 3). On the other hand, the characterization of such dimeric azetidines was a demanding task because of their low solubility and due to poorly resolved NMR spectra for the presence of rotamers. However, the use of homo and heterocorrelation 2D NMR experiments and HRMS analyses were mandatory to support the proposed structures (see ESI). In the case of **3b** and *diast*-**3b**, prepared by trapping with acetone, X-ray analysis confirmed the structure and relative stereochemistry. The X ray structure revealed different packing and torsion angles for **3b** and *diast*-**3b**, and such information used to assign the relative configuration to diastereoisomeric pairs (see ESI). ‡,§



Scheme 3. Scope of the lithiation/dimerization/electrophile trapping sequence. [a]Overall yield for isolated products. [b]Diastereomeric ratio calculated on the weight of isolated products. [c]Inseparable mixture. [d]Only **3g** was isolated.

Interestingly, the introduction of a *tert*-butoxycarbonyl unit, as in the case of **3c**,**f** and *diast*-**3c**,**f**, provides a constrained dipeptide with potential use in medicinal chemistry programs and having protected N- and C-terminals.[14]

Another surprising and unexpected result was obtained when *N*-Boc-2-(o-tolyl)azetidine **1d** was subjected to lithiation/deuteration sequence under the conditions used for azetidines **1a-c**. In striking contrast to **1a-c**, azetidine **1d** did

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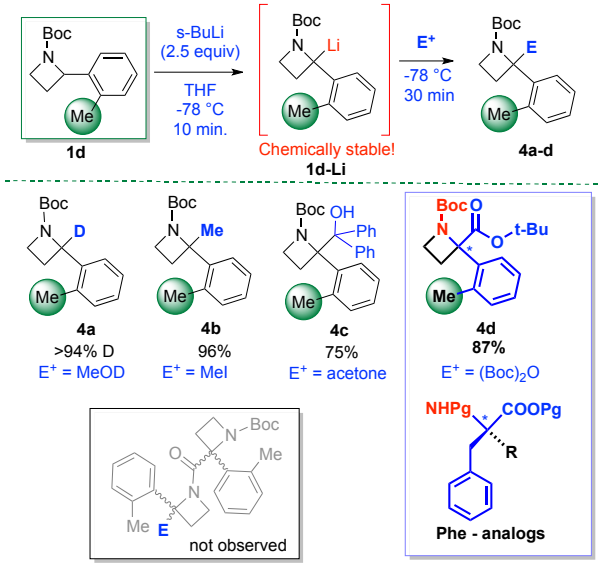
not undergo any self-condensation and the corresponding deuterated azetidines **4a** was obtained with 50% of deuterium content. Full conversion **1d→4a** was obtained running the lithiation/deuteration reaction with *s*-BuLi (2.5 equiv) in THF at -78 °C for 10 min. ^{1}H NMR of the reaction crude did not show any sign of decomposition. It is worth mentioning that azetidines **1a-c** undergo full decomposition at -78 °C. However, lithiated azetidine **1d-Li** was found chemically stable and smoothly reacted with electrophiles leading 2,2-disubstituted azetidines **4b-d** (Scheme 4).



Scheme 4. Effective trapping of α-lithiated N-Boc azetidine

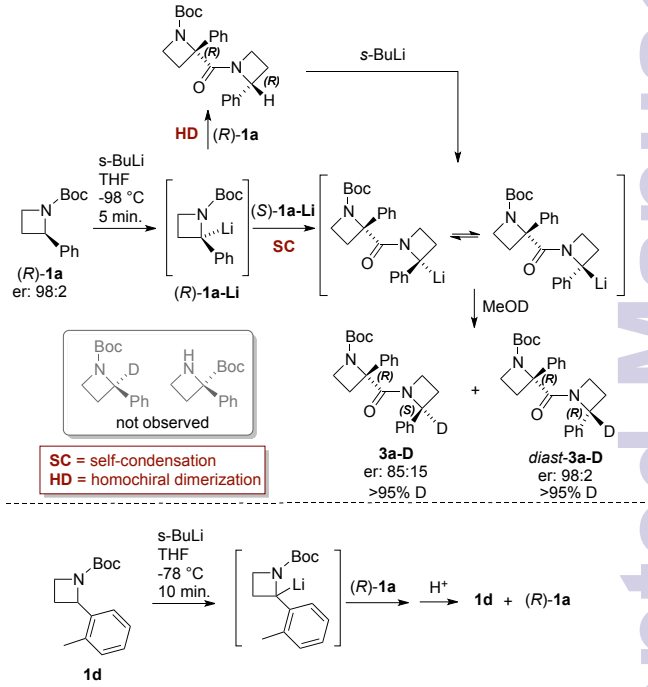
This is, in our opinion, a remarkable result for two main reasons. First, it demonstrates a surprising "ortho-effect" able to switch the reactivity of α-lithiated N-Boc azetidines preventing self-condensation. Second, it gives the possibility for accessing to 2,2-disubstituted azetidines and constrained aminoacids as in the case of **4d** which can be considered a cyclic analog of phenylalanines (see Scheme 4).[15]

We ascribe the chemical stability of **1d-Li**, and its low propensity to undergo self-condensation, to a preferential conformation of the *o*-tolyl substituent. Such reactivity/preferential conformation relationship has been observed in other similar systems.[6] By a conformational analysis and DFT calculations we found that the most stable conformer sets the *o*-methyl group syn to the α-proton of the azetidine ring (see ESI). This suggests that the methyl group acts as a shield hampering self-condensation.

Next, with the aim to get some mechanistic insights for the processes described above, we run a stereochemical investigation performing the lithiation/dimerization/deuteration sequence on chiral non-racemic azetidine (*R*)-**1a**.

As reported in Scheme 5, two possibilities could be envisaged for the dimerization: a) a two steps sequence (reported as homochiral dimerization, HD), involving the reaction of (*R*)-**1a-Li** with its neutral precursor, and leading to *diast*-**3a** which is further deprotonated; b) a single step dimerization of (*R*)-**1a-Li** (reported as self-condensation, SC), giving directly the lithiated dimer. In both pathways, we assumed an equilibrium between the lithiated dimers.

When (*R*)-**1a** was lithiated under optimized condition, quenching with MeOD gave highly enantioenriched deuterated dimers (*R,S*)-**3a-D** (er 85:15) and (*R,R*)-*diast*-**3a-D** (er 98:2) in 70:30 diastereomeric ratio respectively (Scheme 5). This result demonstrates that this strategy could be suitable for the preparation of chiral azetidine-based dipeptides.[§§]



Scheme 5. Stereochemical investigation on the self-condensation of (*R*)-**1a** and attempt to demonstrate the SC pathway.

Attempts to quench (MeOD) the reaction at shorter reaction times (5, 30 sec., 1 min) resulted in large amounts of unreacted starting material. The slight erosion observed in (*R,S*)-**3a-D** (er 85:15) could be the result of a propensity of (*R*)-**1a-Li** to racemize under the reaction conditions as seen in related systems.[16] It is likely that the rate of racemization is similar to the rate of self-condensation. In order to support the hypothesis of SC of lithiated species, azetidine **1d**, which doesn't dimerize, was lithiated and reacted with (*R*)-**1a**. Quenching with MeOH returned **1a** and unreacted (*R*)-**1a**. No evidence for cross self-condensation were found. Next, the equilibrium between lithiated dimers **3a-Li** and *diast*-**3a-Li** was demonstrated with the experiment reported in Scheme . When **3a** (dr >95:5) and *diast*-**3a** (dr >95:5) where subjected separately to lithiation reaction using *s*-BuLi (2 equiv) in THF at -98 °C for 5 min, mixtures of diastereomeric dimers **3a-D** and *diast*-**3a-D** formed upon quenching with MeOD. The sense of stereoinduction was the same in both experiments being **3a-D** the favored stereoisomer just as seen in the self-condensation of **1a**.

Even though the HD pathway cannot be ruled out, our preliminary evidence support the hypothesis of a SC of α-lithiated N-Boc azetidines, followed by the epimerization of the corresponding lithiated dimers.

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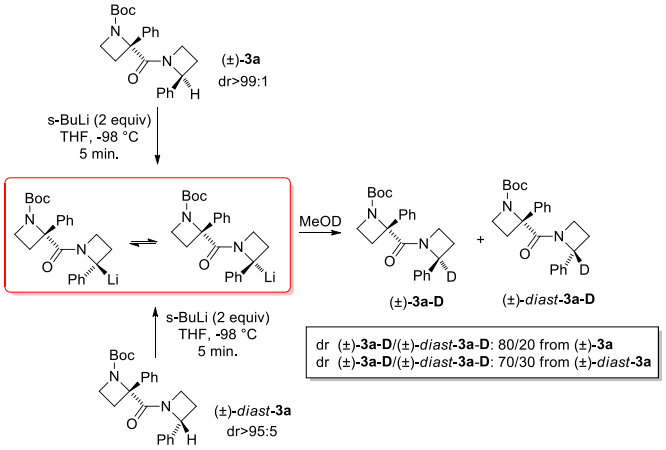

Scheme 6. Evidence for epimerization of lithiated dimers

In conclusion, this investigation demonstrates that *N*-Boc-2-arylazetidines can be regioselectively α-lithiated. The corresponding lithiated intermediates display a reactivity dependent on the substituent of the aromatic ring. Self-condensation to new constrained azetidine-based peptimomimetics occurs when the aromatic ring lack an ortho substituent. In striking contrast, the presence of the ortho-substituent hampers the self-condensation allowing the preparation of 2,2-disubstituted azetidines. Further investigation are underway in order to expand the applicability of this methodology and get further mechanistic insights.

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Notes and references

‡ Crystal data for **3b** and *diast*-**3b**: CCDC 1412576-1412577.

§ The relative stereochemistry was assigned by analogy to **3b** and *diast*-**3b** for which X ray analyses were available. See ESI

§§ We assume that lithiated azetidine (R)-**1a-Li** reacts with retention of configuration just as lithiated N-Boc pyrrolidines and piperidines, see refs. 10, 14.

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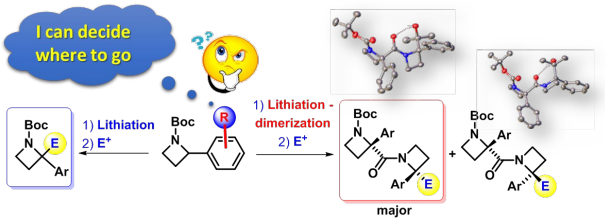

Un unprecedented reactivity profile of lithiated N-Boc-2-arylazetidines gave access either to new azetidine-based peptidomimetics or to a regioselective functionalization of the azetidine ring.

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