

Recent advances in the Chemistry of Metallated Azetidines

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The almost unexplored four-membered azetidines represent a particularly interesting class of molecules, among the family of saturated nitrogen heterocycles. Although often challenging to synthesize, substituted azetidines strongly attract chemists because of their importance in catalysis, stereoselective synthesis and medicinal chemistry. This Microreview aims to give a brief summary of modern developments in direct metal-based functionalization of the azetidine ring, focusing on the regio- and stereoselectivity of these reactions, as well as on some useful synthetic applications. It will be highlighted, in particular, how an interplay of factors such as structure, substitutions at both nitrogen and carbon atoms and coordinative phenomena deeply influence the reactivity of the corresponding metallated species, paving the way for easy planning a site-selective functionalization of azetidines.

Introduction

Saturated nitrogen-containing heterocycles represent one of the most privileged structural motifs among natural products, marketed drugs and bioactive molecules and their synthesis and elaboration continue to constitute a major area of synthetic chemical research.¹ In recent years, interest in the effective access to substituted heterocycle derivatives has become even more relevant due to the increasing demand for enhanced degree of saturation and three-dimensionality in drug candidates.^{2,3} Enhanced 3D shapes (directly connected with the increased fraction of sp³ carbon atoms) have been proposed to lead to more beneficial physicochemical, pharmacokinetic and safety properties, such as reduced lipophilicity and improved solubility, permeability and off-target promiscuity.^{2c,d} Among the family of saturated N-bearing heterocycles, the almost unexplored four-membered azetidines represent a particularly interesting class of compounds, since they own a good compromise between a satisfactory stability and a strong molecular rigidity, allowing an efficient tuning of pharmacological properties displayed by molecules bearing this moiety.⁴ Historically, the chemistry of their higher and lower homologues have received much more attention from synthetic chemists with respect to this four-membered aza-heterocycle, as evidenced by several commercial applications.⁵ Despite this, the azetidine core is emerging as highly appealing within medicinal and agrochemical industries because of its occurrence in various biologically active natural compounds⁶ and drug candidates (Fig. 1).^{4b,7} Moreover, azetidines have also found some applications as ligands in metal-catalyzed transformation and as chiral auxiliaries.⁸ The most representative examples, between the numerous practical applications of the azetidine ring, are likely related to recently

marketed drugs such as Azelnipidine (Calblock®)⁹ and Ximelagatran (Exanta®)¹⁰ or to a large variety of 3- and 2-substituted azetidines showing different pharmacological activities (Fig. 1).¹¹ The main reason for the lagging of azetidine chemistry behind its larger and smaller family counterparts, should be recognized in the large lack of effective methodologies associated with the synthesis and functionalisation of this particular ring.^{5e,f} Given these premises, the development of robust synthetic methods to access these building blocks is certainly of high value. Nevertheless, over the past few decades, a varieties of protocols for the preparation of azetidines have been reported.¹² The most common strategies for the synthesis of 2-substituted azetidines involve intramolecular cyclizations of

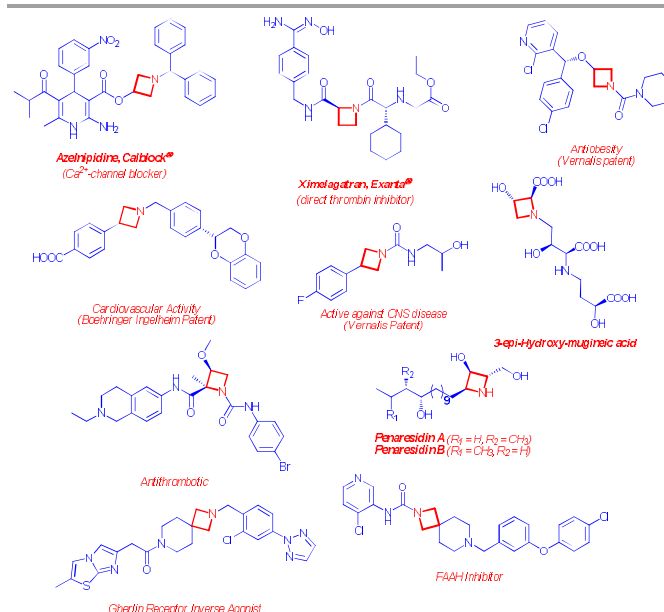


Fig. 1. Noteworthy examples of biologically active drug leads and natural products incorporating the azetidines nucleus. open-chain structures (Scheme 1, path a) or the reduction of readily available 2-azetidinones (Scheme 1, path b).^{4b,13} It is

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worth mentioning the possibility to perform also an asymmetric dehydrative cyclization of 1,3-amino alcohols using 1,1'-carbonyldiimidazole to synthesize 2,3-disubstituted azetidines.¹⁴ However, the well-known kinetically unfavorable cyclization, generally limits these kind of synthetic strategies, resulting often in only moderate yields. Moreover, many of these procedures require several steps and functional group transformations.¹⁵ An interesting three-step nucleophilic addition/ring contraction of α -bromopyrrolidinones has been recently reported by Blanc and coworkers to obtain the corresponding racemic α -carbonylated azetidines (Scheme 1, *path c*).¹⁶ On the other hand, protocols for the aziridine ring expansion using dimethylsulfoxonium methylide have also been documented (Scheme 1, *path d*).^{4a,b} An unresolved limitation of most of these strategies is that the substituents are required to be present on the precursors, prior to the ring formation, thus not enabling straightforward structure-activity relationship (SAR) studies and compounds libraries synthesis of pharmaceutical interest. In this sense, Jamison and co-workers in 2015 described an advantageous two-step synthesis of optically active 2-alkyl azetidines (Scheme 1, *path e*).¹⁷ This latter strategy employs a highly regioselective nickel-catalyzed cross-coupling of enantiomerically pure *N*-tosyl-aziridines with aliphatic organozinc reagents, followed by an intramolecular cyclization. A key factor for the successful outcome of the reaction was the presence of a thiophenyl function tethered to the aziridine ring, which can be easily activated by methylation to trigger the subsequent cyclization.

In this context, a highly appealing alternative strategy that traditionally has been largely employed for the assembly of α -branched amines is undoubtedly represented by the α -deprotonation of a *N*-protected (activated) amine by lithium bases, followed by the trapping with a suitable electrophile (Scheme 1, *path f*). However, the chemistry of lithiated azetidines has been considerably less explored, compared to metallated aziridines, pyrrolidines or piperidines. To date, very

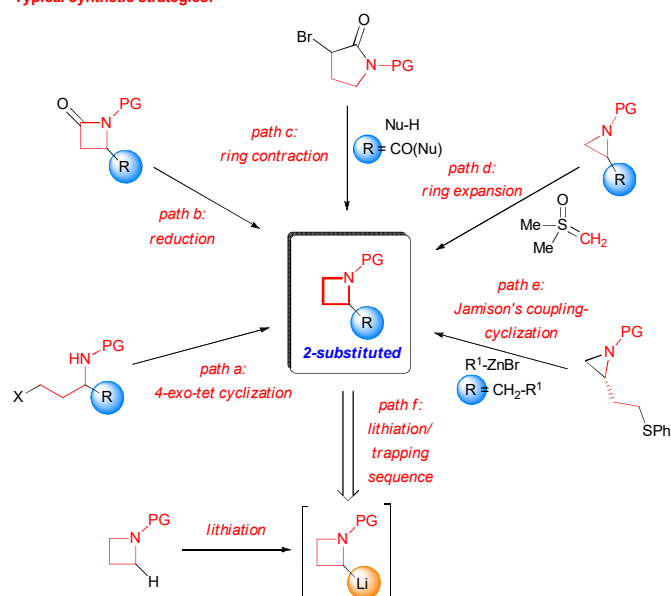
by Seebach *et al.* between 1970s and 1980s, dealing with azetidines bearing electron-withdrawing groups (EWG), both on the nitrogen atom and on the C₂, to activate the α -C-H bond by increasing its acidity (Scheme 2).¹⁸ However, several drawbacks are related to these protocols, including carcinogenicity associated to the lithiation of *N*-nitrosoazetidine **1** with LDA (THF, -78°C)^{18a} and poor prospects for later development of an asymmetric application due to the use of *t*BuLi to achieve the metallation of *N*-(triphenylacetyl)azetidine **2** (THF, -40°C).^{18b,19} In addition, competitive *ortho*-lithiation at the triphenylacetyl protecting group, followed by a carbamoyl 1-3 shift was reported.^{18b} Furthermore, no useful synthetic applications were reported at that time.

Only recently, more systematic studies on the α -lithiation of *N*-protected azetidines have been performed, allowing a better understanding of their reactivity and furnishing mechanistic insights, that could help to fill the knowledge gap. In this review we will discuss recent advances on the reactivity of metallated azetidines, with a focus to their regio- and stereoselective metallation in general and lithiation in particular, also highlighting some useful synthetic applications. Special attention will be dedicated to the interplay of factors such as structure, substitutions at both nitrogen and carbon atoms and complexation phenomena that plays a pivotal role in controlling the reactivity of the corresponding metallated systems.

Lithiation of N-EWG azetidines

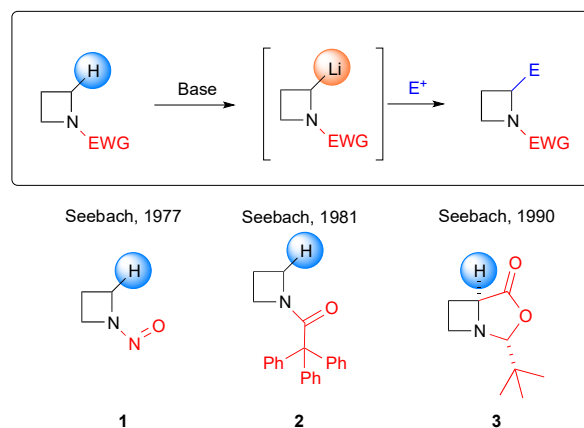
In 2010 Hodgson reported the first example of effective α -lithiation-trapping sequence at the 2-position of azetidines bearing the unusual Seebach's²⁰ *N*-thiopivaloyl activating group (Scheme 3).²¹ The starting thioamide **5** could be obtained by the simple *N*-protection of azetidine **4** with

Typical synthetic strategies:

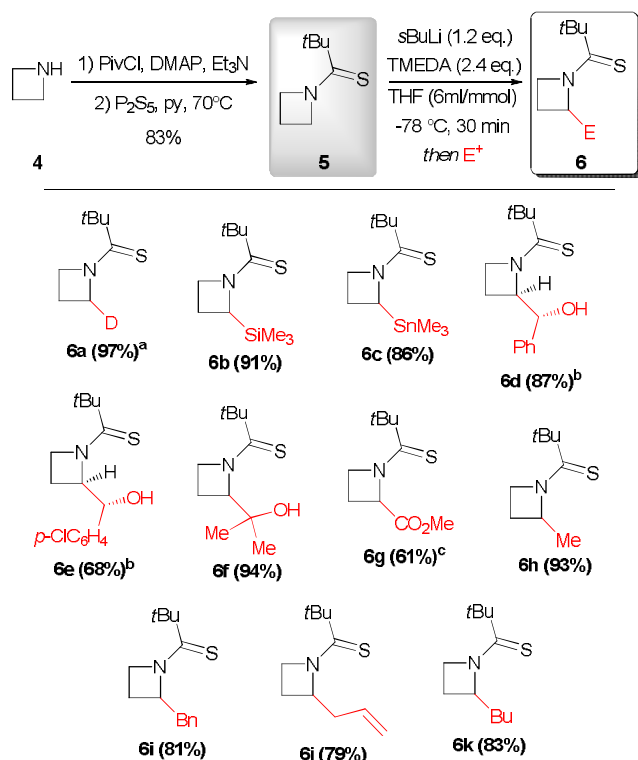


Scheme 1. Representative methods for the synthesis of 2-substituted azetidines. PG = protecting group.

few examples of lithiation of four-membered azetidines have been reported. Pioneering works in this field were carried out



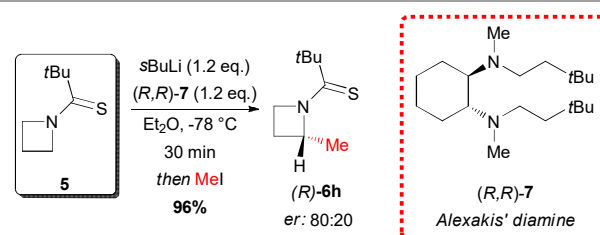
Scheme 2. First reported examples of α -lithiated azetidines.



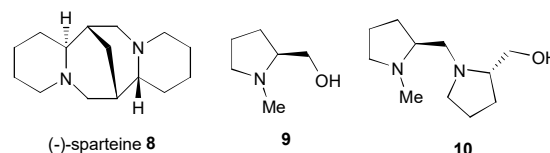
Scheme 3. Preparation, lithiation and electrophilic trapping of *N*-thiopivalamide **5**. All presented yields are referred to the isolated product. ^a100% D, determined by GC-MS and ¹H NMR. ^bMain diastereomer. ^cIsolated as the methyl ester following reaction with TMSCHN₂. py = pyridine, DMAP = 4-dimethylaminopyridine, Piv = pivaloyl.

pivaloyl chloride, followed by treatment with P₂S₅. Subsequent lithiation with *s*BuLi/TMEDA in THF at -78 °C and trapping with several electrophiles after 30 min gave 2-substituted azetidines **6a-k** in excellent yields (Scheme 3). This protocol tolerated a large variety of different electrophiles including silyl- and stannyl chlorides, carbonyl derivatives (including enolizable ones, such as acetone) and alkyl halides. The latter case is notable, since alkylation of dipole-stabilized organolithiums can be sometimes inefficient because of possible SET (single electron transfer) process.²² The reactions using prochiral aldehydes occurred with acceptable diastereoselectivity leading to the isolation of products **6d** and **6e** as main diastereomers.²³ Different EWG on the nitrogen atom, such Boc, *t*BuSO, *t*BuSO₂, PO(OEt)₂, were found to be unsuitable for effective α -lithiation/trapping sequence on unsubstituted azetidines, in contrast to what observed in the case of the corresponding aziridines.²⁴ Undoubtedly, the *N*-thiopivaloyl group played a main role for the successful outcome of this transformation, since when α -metallation of the corresponding pivalamide derivate was performed, only the attack of *s*BuLi at the carbonyl group was observed, while the use of LTMP returned only unreacted starting material. The rationale at the basis of this unique effectiveness (with respect to the classical activating groups) is unknown, but the authors suggested it could be found in the combination of α -position activation and a reduced or even absent tendency for the attack of the lithium base at the thiocarbonyl moiety. It should be stressed that this method allowed also an effective asymmetric variant, by replacing TMEDA with different chiral ligands.²¹ Lithiation of *N*-thiopivaloyl azetidine **5** using Alexakis' *trans*-cyclohexane diamine (*R,R*)-**7**²⁵ in Et₂O gave, after trapping with

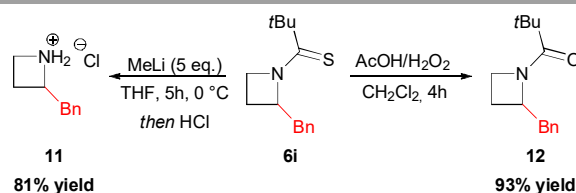
MeI, α -methyl azetidine (*R*)-**6h** in excellent yield (96%) and 80:20 *er* (Scheme 4). However, the use of different chiral ligands, including (-)-sparteine **8** or proline-based ligands **9** and **10**, as well as different solvents (ethereal and not), resulted in lower enantiomeric ratios. Remarkably, the sense of the stereoselectivity of the reaction was opposite to that previously obtained with *N*-Boc pyrrolidine and *N*-Boc piperidine, using *s*BuLi and (-)-sparteine **8** or (*R,R*)-**7**.²⁶ Moreover, clean removal of the *N*-thiopivaloyl protecting group was achieved for azetidine **6i**, by using MeLi; conversion in the corresponding pivalamide **12** could also be obtained by using CH₃CO₃H (Scheme 5).²¹ Some years later, the same author extended such a lithiation approach to *N*-thiopivaloylazetidin-3-ol **13**, allowing access to a range of 2-substituted 3-hydroxyazetidines **14a-i** with generally excellent *trans*-diastereoselectivity. Remarkably, only in the case of deuteration the *cis*-isomer was found to be the major product (Scheme 6).²⁷ To the optimal outcome of the reaction were required 3 equivalents of *s*BuLi, because of the presence of the free hydroxyl substituent, and a higher concentration than in the case of unsubstituted *N*-thiopivaloyl azetidine **5**. The best thermal condition was demonstrated to be -78 °C, since higher temperature led to reduced diastereomeric ratios and no significant improvement is observed at lower temperatures as well. Moreover, the use of TMEDA in THF was also found to be crucial for obtaining optimal yields. The reaction with Mander's reagent (methyl cyanofomate)



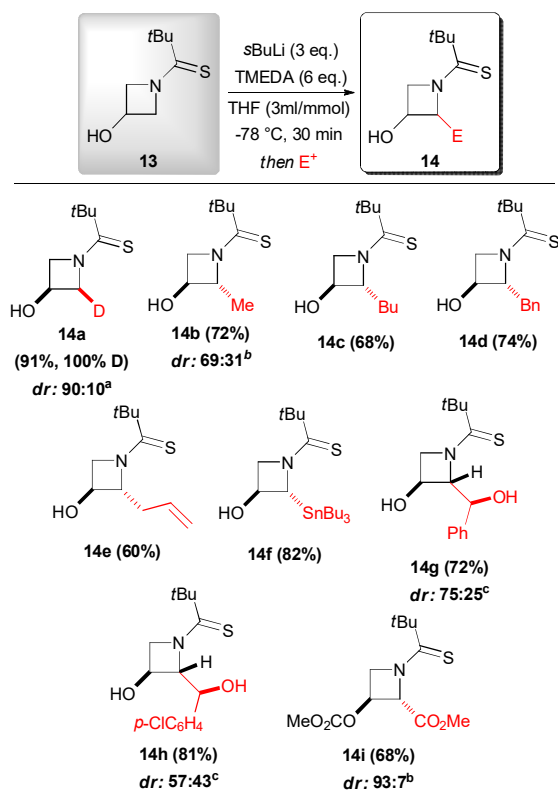
Not effective ligands:



Scheme 4. Asymmetric lithiation-methylation sequence of *N*-thiopivaloyl azetidine **5**.



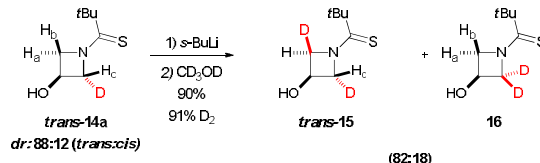
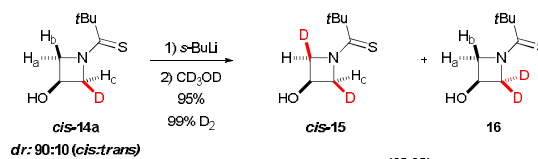
Scheme 5. Removal and transformation of the *N*-thiopivaloyl functionality.



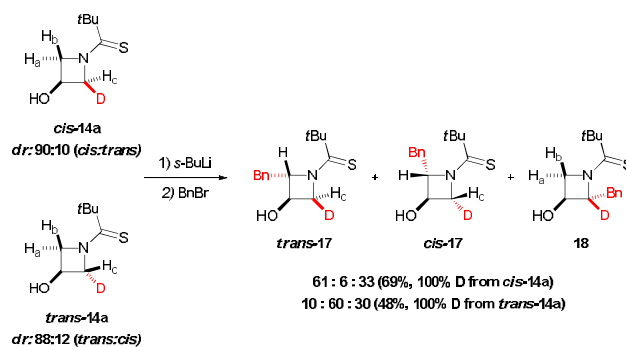
Scheme 6. Electrophilic incorporation into *N*-thiopivaloylazetidino-3-ol **13**. All presented yields are referred to the isolated product. ^aRatio of *cis/trans*: major diastereoisomer shown. ^bRatio of *trans/cis*: major diastereoisomer shown. ^cMixture of epimers at side-chain carbinol: major diastereoisomer shown.

provided C- and O-methoxycarbonilated azetidine **14i**, which is highly attractive, due to the possibility of accessing azetidine-based amino acids (Scheme 6). Noteworthy, subsequent mechanistic investigation on *cis*-**14a** and *trans*-**14a** allowed to get more insights into the stereoselectivity of the lithiation-electrophilic trapping sequence (Scheme 7). Based on deuterium labeling studies, Hodgson suggested that the initial α -deprotonation is preferentially, but not exclusively, *trans*-stereoselective (Scheme 7, *path a*): indeed, removal of the proton *trans* to hydroxyl was hindered in the case of *trans*-**14a** due to the presence of the *trans*-deuterium, accounting for the unequal proportions of 2,2-dideuterated adducts **16** (primary kinetic isotope effect). Moreover, lithiation–benzylation experiments performed on *cis*-**14a** and *trans*-**14a** led to mixtures of three possible diastereomers (Scheme 7, *path b*). Intriguingly, only *trans*-2,2-derivate **18** was observed starting either from *cis*-**14a** and *trans*-**14a**. Thus, these results suggest that there is a strong preference for electrophilic trapping to occur *trans*- to the C-3 lithium alkoxide (aside from deuteration that occurred with a strong *cis*- bias, where probably the alkoxide may have an important role in directing the deuteration *cis* to itself),²⁸ regardless of whether a *cis* or *trans* proton is initially removed at C-2. In other words, the stereochemical outcome of the lithiated azetidino-3-ol trapping depends on the electrophile used but is independent of which α -proton is initially abstracted. However, it should be highlighted that such a kind of speculation must be treated with caution at this early stage, because it is not possible to completely exclude an initial *cis*-deprotonation and because we cannot deduce any information on the stereochemical (in)stability of the lithiated intermediate.

Path a: Lithiation-Deuteration of *cis*- and *trans*-14a



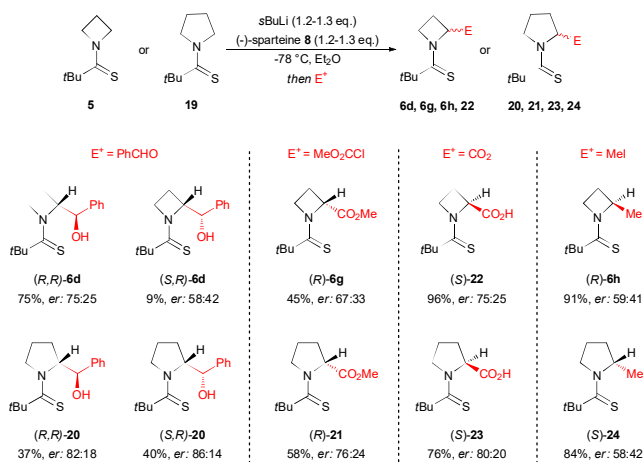
Path b: Lithiation-Benylation of *cis*- and *trans*-14a



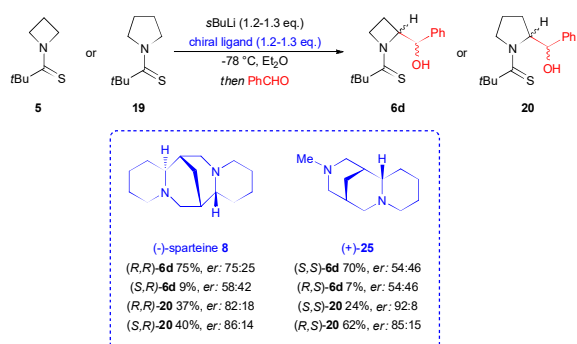
Scheme 7. Stereochemical investigations on the lithiation and electrophilic trapping of Azetidino-3-ol **14a**.

In this context, recently, O'Brien *et al.* clearly demonstrated the intrinsic configurational instability of lithiated *N*-thiopivaloyl azetidine intermediates at -78°C in THF or Et_2O , through seminal mechanistic studies.²⁹ As a direct evidence of this, a wide variation of enantioselectivity and sense of induction was reported, in almost the same reaction conditions, for the lithiation-trapping of *both* *N*-thiopivaloyl azetidine **5** and *N*-thiopivaloyl pyrrolidine **19**, when different electrophiles or different chiral diamines were employed (Scheme 8). As highlighted, the variability of the sense of asymmetric induction strictly depends on the electrophile used. Indeed, with reference to the configuration of the α -carbon, adducts formed using benzaldehyde ((*R,R*)-**6d**, (*S,R*)-**6d**, (*R,R*)-**20** and (*S,R*)-**20**) or methyl chloroformate ((*R*)-**6g** and (*R*)-**21**) presented an opposite configuration to those obtained by trapping with CO_2 ((*S*)-**22** and (*S*)-**23**); whilst, with MeI, products were found to have opposite stereochemistry starting from azetidine or pyrrolidine systems ((*R*)-**6h** and (*S*)-**24**, respectively). In the same way, by using different chiral diamines, it resulted in a significant variation in the level of enantioselectivity starting from azetidine **5** or pyrrolidine **19**. Moreover, when the same lithiated intermediates were generated *via* tin-lithium exchange starting from stannanes **6c** (68:32 *er*) and **26** (72:28 *er*), by using *n*-BuLi in THF at -78°C and benzaldehyde as electrophile, only essentially racemic diastereomers (*R,R*)-**6d**, (*S,R*)-**6d** and (*R,R*)-**20**, (*S,R*)-**20**, respectively, were generated in the absence of any chiral ligand (Scheme 9, *path a*). On the other hand when the same reaction was performed on racemic stannanes **6c** and **26**, in the presence of (-)-sparteine-**8**, diastereomeric adducts (*R,R*)-**6d**, (*S,R*)-**6d** and (*R,R*)-**20**, (*S,R*)-**20** were obtained with a degree of enantioselectivity comparable to that

Path a: different electrophiles



Path b: different chiral amines

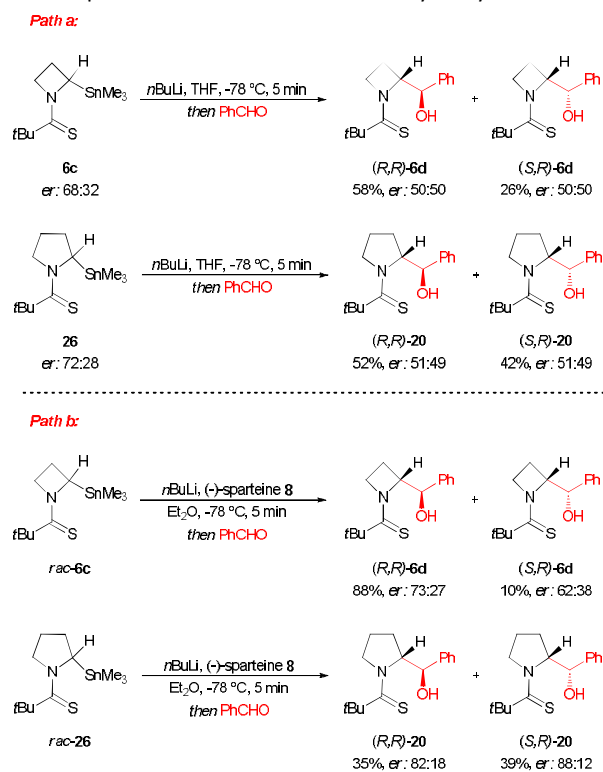


Scheme 8. Asymmetric lithiation-trapping of *N*-thiopivaloyl azetidine **5** and pyrrolidine **19** with different electrophiles and chiral diamines. Major enantiomers shown.

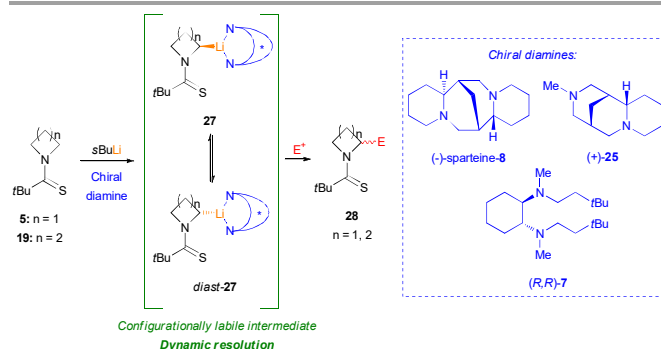
achieved with $s\text{BuLi}/(-)\text{-sparteine 8}$ from azetidine **5** and pyrrolidine **19** (Scheme 9, *path b*). Based on the observation that the organolithium species generated also from *N*-thiopivaloyl pyrrolidine **19** is not configurationally stable at $-78\text{ }^\circ\text{C}$, these authors first concluded that the reason of the difference, in terms of stability, compared to corresponding *N*-Boc pyrrolidines and piperidines (which, on the other hand, are well known to generate configurationally stable organolithium species),^{26,30} should be the *N*-thiopivaloyl group itself, which probably leads to a weaker C-Li bond. In addition, by excluding the possibility of an asymmetric deprotonation to give a configurationally stable lithiated intermediate, it appears clear that the lithiation-trapping, in the presence of a chiral ligand, of *N*-thiopivaloyl azetidine **5** and pyrrolidine **19** must proceed through dynamic resolution of configurationally labile diastereomeric organolithium intermediates **27** and *diast-27* (Scheme 10). It is also reasonable to address the variable enantioselectivity, observed with different electrophiles (under the same conditions), to different rates of trapping, driving to a different configuration of the major product.

In 2015 Hodgson and coworkers described also the effectiveness of the *tert*-butoxythiocarbonyl group (Botc) in promoting azetidine α -lithiation, allowing at the same time mild conditions for deprotection.³¹ *N*-Botc-azetidine **30** could be generated in very good yield (88%) by reaction of the readily available dithiocarbamic acid *O*-*tert*-butyl ester **29** with azetidine **4** (Scheme 11). Intriguing, no evidence of formation of the competitive dithiocarbamate, which

was reported for reaction of tertiary alkyl xanthate esters

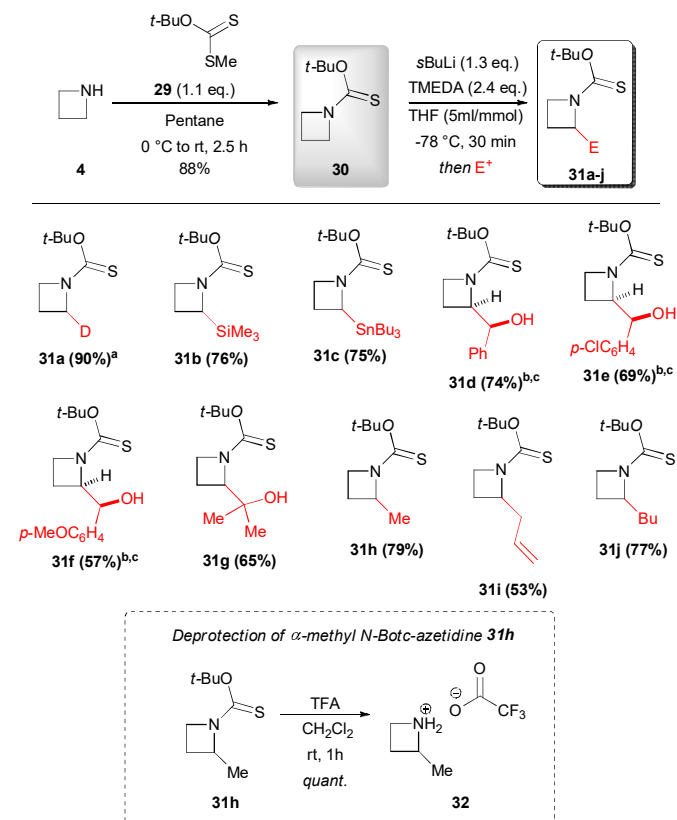


Scheme 9. Investigation on the configurational stability of lithiated *N*-thiopivaloyl azetidine and pyrrolidine generated through tin-lithium exchange.



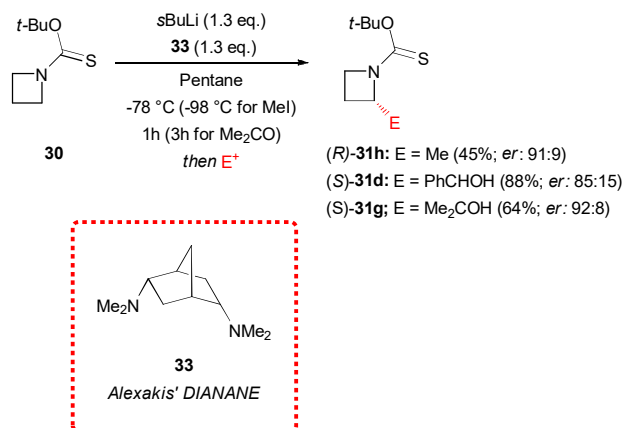
Scheme 10. Dynamic resolution in stereoselective lithiation-trapping of *N*-thiopivaloyl aza-heterocycles **5** and **19**.

with amines,³² was observed. Significantly, *N*-Botc-azetidine **30** could be efficiently lithiated under similar conditions to those previously described for *N*-thiopivaloyl-azetidine **5**, and subsequently trapped with a wide range of electrophiles to give 2-substituted *N*-Boc-azetidines **31a-j** (Scheme 11). Remarkably, silylation, stannylation, alkylation and reaction with carbonyl compounds occurred smoothly (with only a slight lowering of the yields observed for more electron-rich electrophiles such as *p*-anisaldehyde). As mentioned, *N*-Botc-azetidines underwent effective deprotection under mild acidic conditions (no ring opening was observed) as demonstrated for α -methyl *N*-Botc-azetidine **31h**, which was quantitatively converted into the corresponding α -methyl-azetidine **32** by using TFA. Alexakis' DIANANE **33** (*N,N,N',N'*-endo,endo-tetramethyl-2,5-diaminonorbornane)³³ proved to be the optimal chiral ligand for



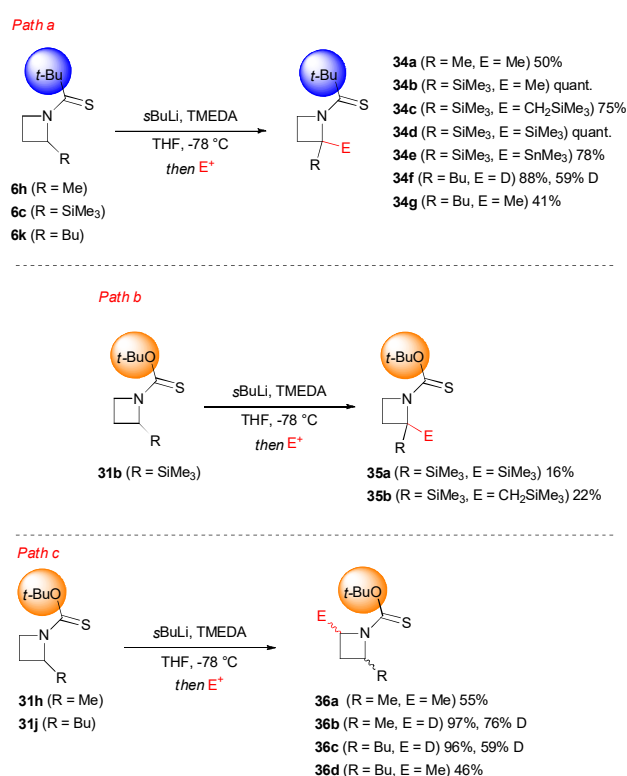
Scheme 11. Preparation, lithiation and electrophilic trapping of *N*-Botc-azetidine **30**. Deprotection of **31h** with TFA. All presented yields are referred to the isolated product. ^a95% D, determined by mass spectrometry. ^b*dr* = 70:30, major diastereomer shown. ^c1.0 equivalent of *s*BuLi was used.

enantioselective α -electrophilic substitution of *N*-Botc-azetidine **30**, if compared to (-)-sparteine **8** and *trans*-cyclohexane diamine (*R,R*)-**7**, providing excellent levels of asymmetric induction (*er* up to 92:8), as described in Scheme 12. The enantioselectivity of the reaction appeared to be strictly dependent also on experimental parameters such as the lithiation time and the reaction temperature. Asymmetric methylation occurred smoothly at -98 °C with 1h lithiation time, using DIANANE **33** in pentane, while lithiation and reaction with benzaldehyde furnished high enantiomeric ratios at -78 °C (lithiation time = 1h). Eventually, in the case of acetone, asymmetric trapping required low temperature (-78 °C) and longer lithiation time (3h).



Scheme 12. Enantioselective α -electrophilic substitution of lithiated *N*-Botc-azetidine **30**.

In addition, ethereal solvents proved to be unsuitable for asymmetric induction, since, as an example, the use of the same DIANANE **33** in Et₂O at -78 °C (lithiation time of 1h) gave α -methylated azetidine (*R*)-**31h** in 64% yield with poor stereoselectivity (*er*: 56:44). However, the authors did not provide any evidence about the configurational stability (or instability) of the lithiated intermediates and the origin of the stereoselectivity; if it was due to an asymmetric deprotonation or a dynamic resolution. According to what observed in the case of lithiated *N*-thiopivaloyl azetidine (Scheme 10), we can speculate that even lithiated *N*-Botc-azetidine could be configurationally labile and a dynamic resolution could be operative. Further study on this topic would be welcome in order to develop asymmetric synthesis of azetidines using the lithiation/trapping strategy.

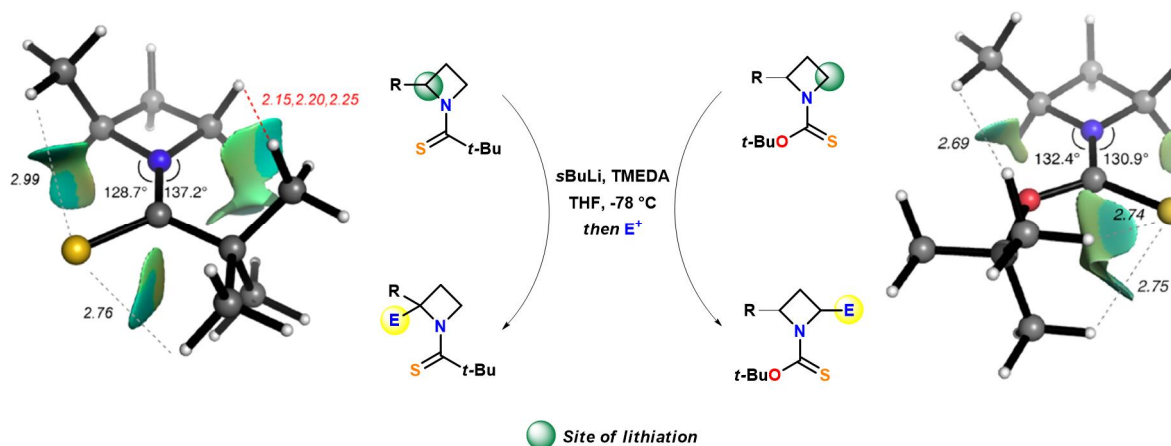


Scheme 13. Lithiation-Electrophile trapping of *N*-thiopivaloyl- and *N*-(tert-butoxycarbonyl)-azetidines.

A crucial point, which requires further detailed description, is represented by the different regioselectivity in the case of a second lithiation shown respectively by *N*-thiopivaloyl- and *N*-Botc-2-substituted azetidines. Almost surprisingly, the former was found to direct lithiation to the already substituted 2-position, thus furnishing preferentially 2,2-disubstituted adduct **34a-g**, even in the presence of unactivating alkyl substituent. (Scheme 13, path a).^{31,34} On the other hand, the use of *N*-Botc allowed similar access to 2,2-disubstitution in considerably lower yields and only in the case of α -(trimethylsilyl)azetidine **31b**, being silyl groups well known to stabilize α -anions (Scheme 13, path b). Differently, 2-unactivated *N*-Botc-azetidines **31h** and **31j** gave access, in a preferential manner, to a 2,4-disubstituted pattern, albeit with no diastereoselectivity (Scheme 13, path c).^{31,34} Hodgson and co-workers demonstrated that the site-

selectivity (2- or 4-position, Scheme 14), observed in the lithiation/trapping sequences of *N*-thiopivaloyl- or *N*-tert-butoxythiocarbonyl-2-alkyl-substituted azetidines, likely was a result of a preferential conformation assumed by the *N*-substituent.³⁴ Indeed, ¹H NMR and computational studies supported the hypotheses that the regiodivergent reactivity might be ascribed to different rotamer preferences in both azetidines, since rotamer interconversion was demonstrated to be not significant under the lithiation conditions.³⁵ In

particular, DFT results suggested, in agreement with NOE studies, a preferential *cis*-rotamer (where the CHMe group is oriented *cis* to the thiocarbonyl group) for *N*-thiopivaloyl-2-methylazetidine ($\Delta G_{cis-trans} = -6.3$ kJ/mol in toluene and -6.1 kJ/mol in THF), ascribed to a relief of unfavorable steric interactions between the α -methyl and the *t*-Bu group, as seen for the *trans* conformer.



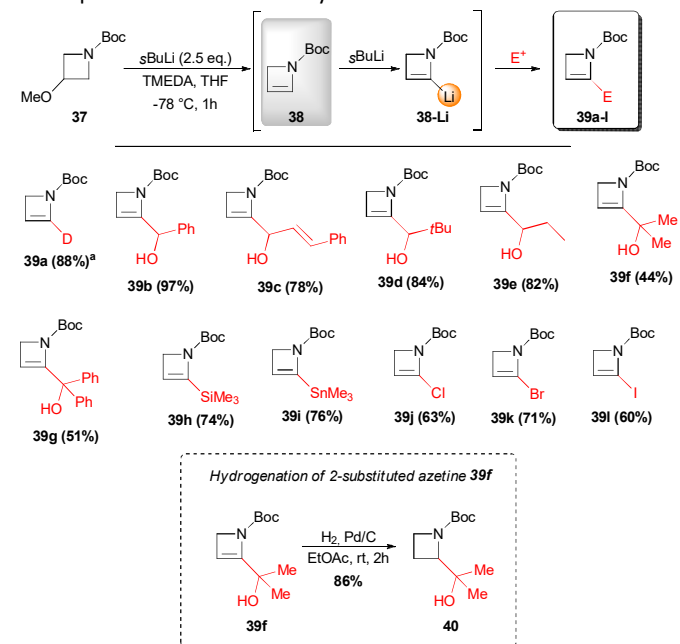
Scheme 14. Regiodivergent (C_2 or C_4) lithiation-electrophilic trapping sequence of *N*-thiopivaloyl- and *N*-(tert-butoxythiocarbonyl)-2-alkylazetidines.

In striking contrast, calculations identify a *trans* rotamer (where the CHMe group is oriented *trans* to the thiocarbonyl group) as the more stable in *N*-Boc-2-methylazetidine ($\Delta G_{cis-trans} = +1.6$ kJ/mol in toluene and $+1.3$ kJ/mol in THF). In this latter case, the presence of the oxygen atom, acting as a “spacer”, might generate this different rotamer bearing the *t*-Bu group effectively far from the azetidine (Scheme 14). As direct consequence, a surgical functionalization of the azetidine ring could be accomplished by choosing the suitable *N*-thiocarbonyl substituent (Scheme 14).

Despite the above-mentioned lack of efficiency of Boc group in promoting the lithiation-trapping of *N*-protected azetidines, the unsaturated and more strained analog *N*-Boc-2-azetidine **38** was found to undergo *s*BuLi-mediated regioselective α -lithiation at the sp^2 carbon, and effectively trapped with different electrophiles, allowing for a straightforward access to 2-substituted-2-azetidines **39a-l**.³⁶ To avoid polymerization of unsubstituted *N*-Boc-azetidine **38**, which smoothly occurs at rt, the latter unsaturated system was generated *in situ* via *s*BuLi-induced α -lithiation/elimination of LiOMe from readily available *N*-Boc-3-methoxyazetidine **37** (Scheme 15). Interestingly, hydrogenation of the derivate **39f** provided the corresponding saturated *N*-Boc-2-substituted azetidine **40**. Allylation and propargylation proceeded efficiently, after transmetalation of the lithiated azetidine **38-Li** to the corresponding organocopper, although with crotyl and prenyl bromides the desired S_N2 -products **41d,e** were always accompanied by the competing S_N2' -derived azetidines **41d',e'** (Scheme 16). However, Negishi coupling of lithiated azetidine **38-Li**, gave 2-phenylated azetidine **42** in 27% yield (Scheme 16).

However, it is worth mentioning that it is possible to functionalize regioselectively the C_2 -position of *N*-Boc-2-phenyl azetidine **43a** (although only in moderate yields), because of the increased thermodynamic acidity of its benzylic proton, as recently reported by Luisi, Degennaro and co-workers.¹³ By performing lithiation at low temperature (-84 °C), using *n*-HexLi in a polar solvent (2-MeTHF) and

under *in situ* quench conditions, exclusively α,α -difunctionalised azetidines **44a,b** were obtained (Scheme 17). Although decomposition was always observed under *external*

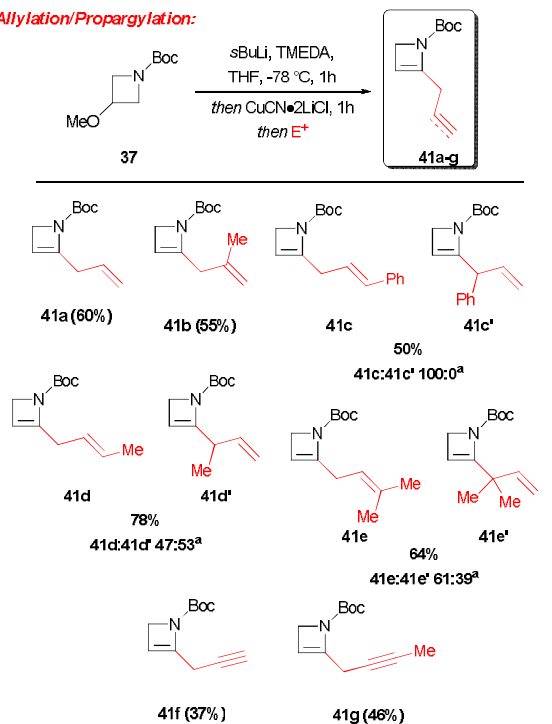


Scheme 15. Preparation, *in situ*-lithiation and direct electrophilic trapping of *N*-Boc-azetidine **38**. Hydrogenation of derived azetidine **39f**. All presented yields are referred to the isolated product. ^a100% D, calculated by ¹H NMR.

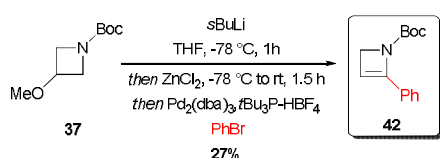
quench conditions, the expected *N* to *C* [1,2]-migration product, observed in the case of lithiated *N*-Boc-aziridines,³⁷ was never detected. In addition, because of the poor coordinating ability of the azetidine's nitrogen, *ortho*-lithiation could not occur. Intriguing,

deeper investigations on *N*-Boc 2-arylazetidines **43a-c**, displayed a peculiar reactivity scenario. Indeed, by lithiating **43a** with *s*BuLi (3 equiv) in THF at $-98\text{ }^{\circ}\text{C}$ for 5 minutes (0.05 M concentration), an unexpected dimerization occurred, leading to diastereomeric dimers **45a-D** and *diast*-**45a-D**, after external quench with MeOD (Scheme 18).³⁸ It should be stressed that such a dimerization, to the best of our knowledge, represents the first example of self-condensation of a stabilized α -lithiated amine, never reported before in the lithiation of higher and lower homologues such as *N*-Boc aziridines, pyrrolidines and piperidines. Moreover, such dimers, easily separable by flash chromatography, show peculiar structures

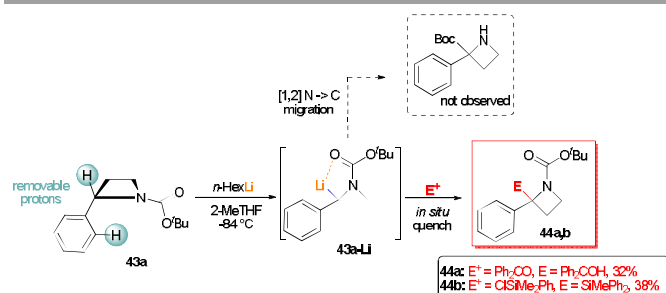
Allylation/Propargylation:



Cross-coupling:



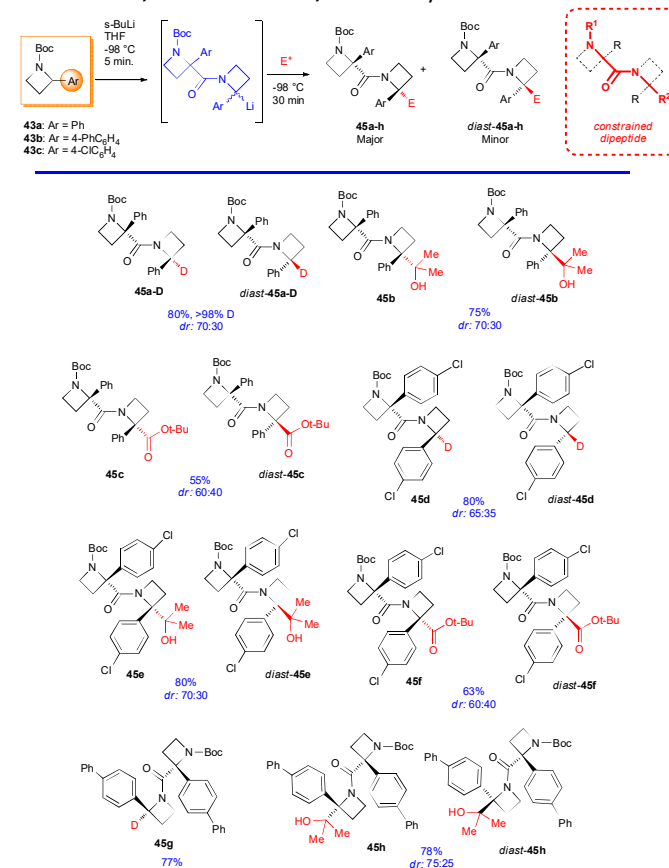
Scheme 16. Copper-mediated allylation and propargylation and Negishi cross-coupling of lithiated azetidine **38-Li**. ^aIsolated ratio.



Scheme 17. Regioselective α -lithiation of *N*-Boc 2-phenylazetidine **43a**.

strictly related to constrained peptidomimetics of great interest in medicinal chemistry.³⁹ The scope of the reaction was explored with

representative electrophiles (Scheme 18). By deuteration, hydroxyalkylation and carboxylation the dimers **45a-h** were obtained in good yields, although with modest diastereoselectivity. Remarkably, the introduction of a *tert*-butoxycarbonyl unit, as in the case of **45c,f** and *diast*-**45c,f** smoothly furnished constrained



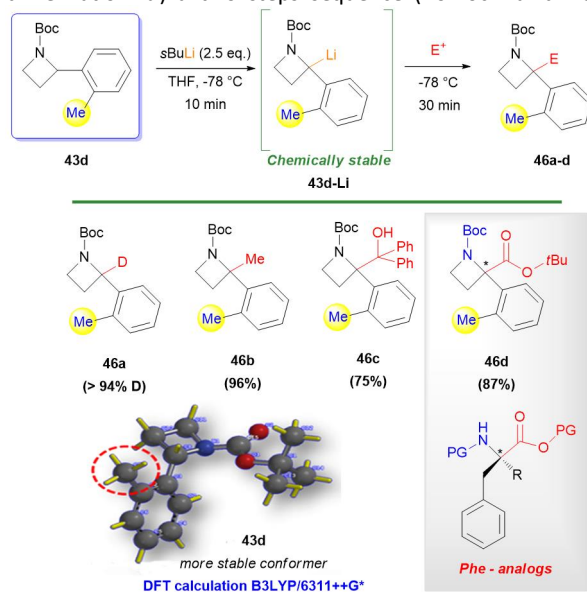
Scheme 18. Scope of the lithiation/dimerization/electrophile trapping sequence.

dipeptides, with protected *N*- and *C*-terminals (Scheme 18).

In striking contrast to **43a-c**, *N*-Boc-2-(*o*-tolyl)azetidine **43d** was found to behave differently when subjected to lithiation/trapping sequence with *s*-BuLi (2.5 equiv) in THF at $-78\text{ }^{\circ}\text{C}$ for 10 min. Surprisingly, lithiated azetidine **43d-Li** was found to be chemically stable (while lithiated azetidines **43a-c** underwent full decomposition at $-78\text{ }^{\circ}\text{C}$) and did not undergo dimerization, furnishing the corresponding 2,2-disubstituted azetidines **46a-d** in high yield (up to 96%, Scheme 19). This remarkable result could be ascribed to a sort of "ortho-effect" able to hamper dimerization and, thus, to provide access to α,α -disubstituted azetidines and constrained aminoacids as in the case of **46d**, a cyclic analog of phenylalanine. Such a chemical stability of **43d-Li**, and its low propensity to undergo dimerization, has been ascribed to a preferential conformation retained by the *o*-tolyl substituent, setting *syn* to the α -proton of the azetidine ring, as suggested by DFT calculations and conformational analysis on **43d** (Scheme 19).

To get more insights into the mechanism of the dimerization process described above, stereochemical investigations on the lithiation/dimerization/deuteration sequence, were performed on chiral non racemic azetidine (*R*)-**43a** and diastereomerically pure dimers **45a** and *diast*-**45a**. Lithiation/deuteration of **45a** (*dr* >95:5) or *diast*-**45a** (*dr* >95:5), provided mixtures of diastereomeric dimers **45a-D** and *diast*-**45a-D** having similar sense of stereoinduction, just

as seen in the dimerization of **43a**, although with slightly different ratios (Scheme 20, *path a*). These results clearly demonstrated an equilibrium between the lithiated dimers **45a-Li** and *diast-45a-Li*. Two different reaction pathways could be envisaged for the dimerization: *a*) a two steps sequence (homochiral dimerization,



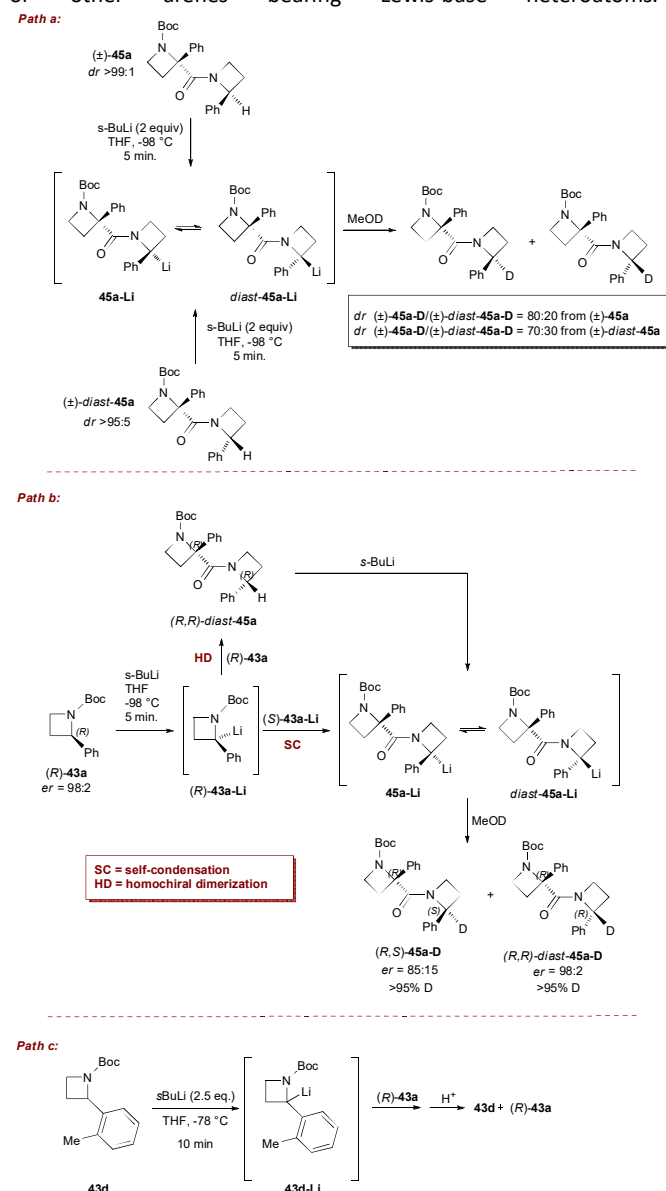
Scheme 19. Effective trapping of lithiated intermediate **43d-Li**.

HD), involving the reaction of (*R*)-**43a-Li** with its neutral precursor, leading to (*R,R*)-*diast-45a* which is further deprotonated; *b*) a single step dimerization of (*R*)-**43a-Li** (self-condensation, SC), directly leading to the lithiated dimer. When optically active azetidine (*R*)-**43a** (98:2 *er*) was lithiated under optimized conditions, quenching with MeOD furnished highly enantioenriched deuterated dimers (*R,S*)-**45a-D** (85:15 *er*) and (*R,R*)-*diast-45a-D* (98:2 *er*), in 70:30 diastereomeric ratio (Scheme 20, *path b*). The slight erosion observed in (*R,S*)-**45a-D** (85:15 *er*) might be due to the propensity of (*R*)-**43a-Li** to racemize under the reaction conditions, likely at rate similar to that of self-condensation. On the other hand, azetidine **43d**, which does not dimerize, was lithiated and reacted with (*R*)-**43a** (Scheme 20, *path c*). No evidence for cross-condensation was found, supporting the hypothesis of a prevalent SC pathway, followed by the epimerization of the corresponding lithiated dimer, although the HD pathway cannot be completely ruled out at the moment. Remarkably, the high enantioselectivity obtained demonstrates the suitability of the process for preparing chiral azetidine-based constrained peptidomimetics.

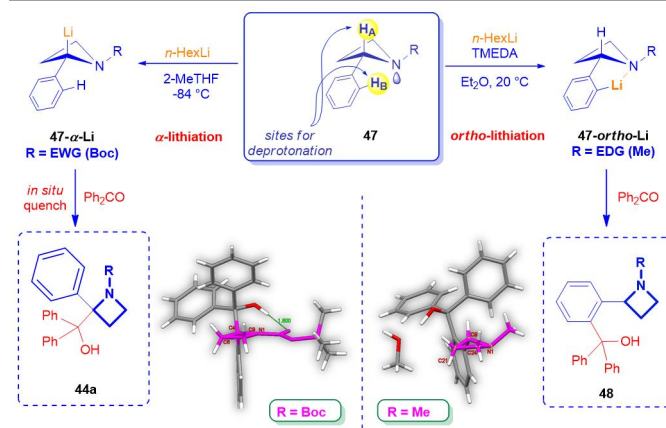
Lithiation of *N*-alkyl azetidines

Differently from azetidines bearing an EWG group as the *N*-substituent, to the best of our knowledge, there are no reports dealing with the α -lithiation of unsubstituted azetidines bearing on the nitrogen atom an electron-donating group (EDG). Recently, Luisi, Degennaro and coworkers described the peculiar reactivity of *N*-alkyl 2-aryl azetidines, which, in striking contrast to *N*-Boc 2-aryl azetidines, cannot be α -lithiated, but smoothly undergo *ortho*-lithiation upon treatment at 20 °C with *n*-HexLi in the presence of TMEDA (Scheme 21).^{13,40} In fact, in this case, the *N*-EDG group would increase the lone pair availability and the coordinating capability of the nitrogen. As a consequence, a drastically reduced thermodynamic acidity of the benzylic proton is expected, together

with a higher capability of the nitrogen to act as an *ortho*-directing metallation group (DMG), just as seen in the case of 2-arylaziridines or other arenes bearing Lewis-base heteroatoms.^{1b}



Scheme 20. Stereochemical investigations on lithiation/dimerization of *N*-Boc 2-phenylazetidine **43a**.

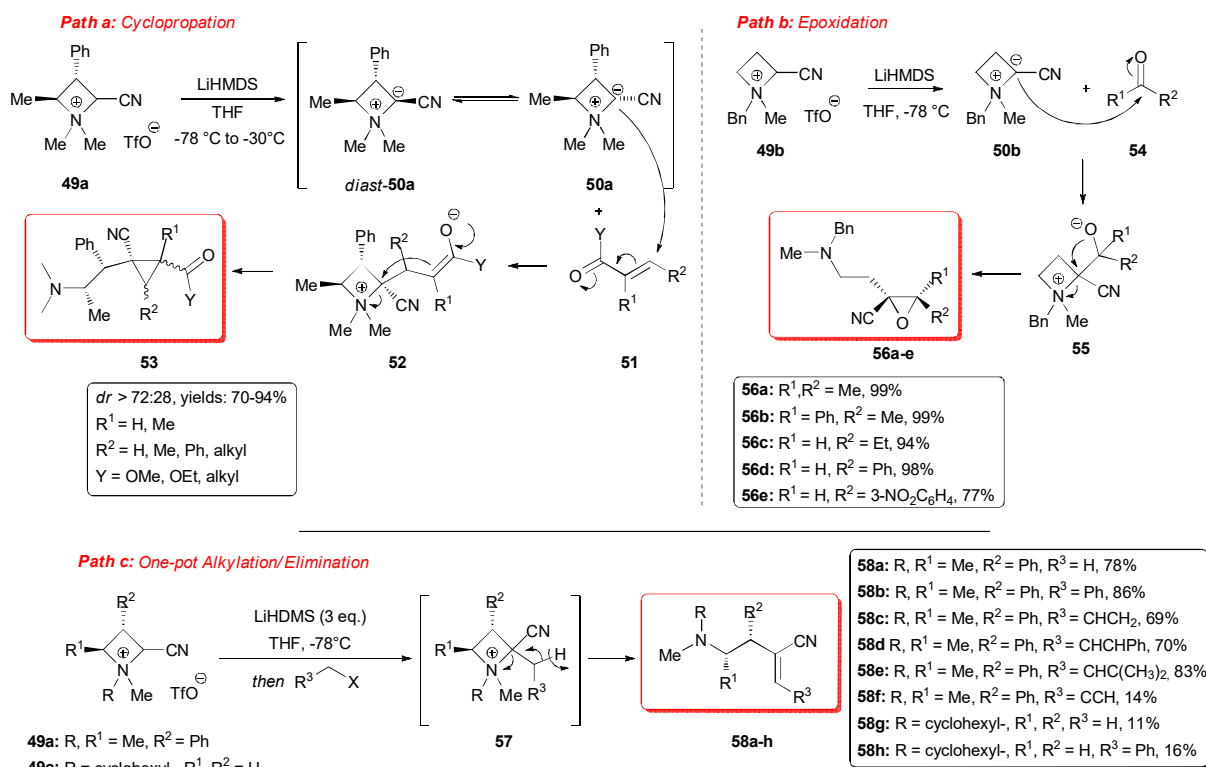


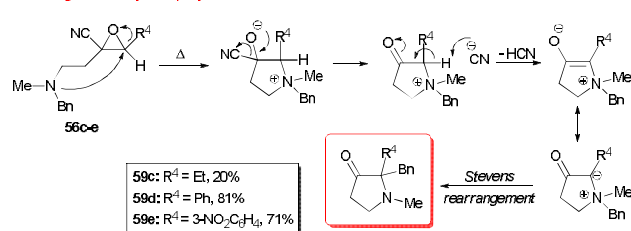
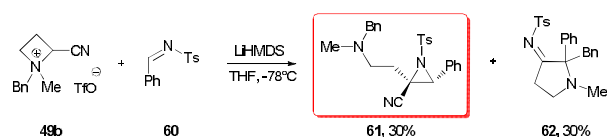
Scheme 21. Comparison of reactivity for in *N*-Boc- and *N*-alkyl-2-phenyl azetidines.

Structural differences between *N*-Boc- and *N*-alkyl-2-phenyl azetidines were deduced by crystallographic X-ray analysis on derivatives **44a** and **48** (Scheme 21). Structure of **48** clearly revealed the nitrogen lone pair availability resulting in an almost tetrahedral nitrogen atom, likely more able to form complexes with lithiating agents, compared to the *quasi*-planar arrangement of the azetidine ring in **44a**.

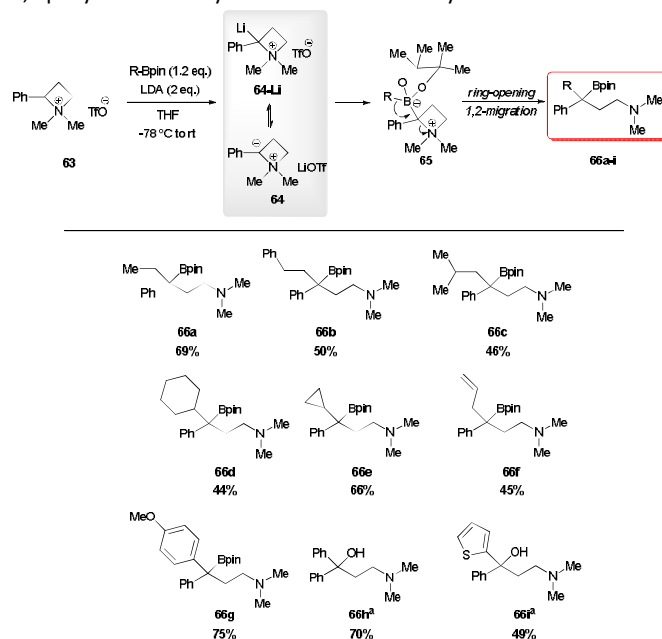
However, a convenient alternative to perform α -deprotonation of *N*-alkyl azetidines lies in their conversion into quaternary azetidinium ions, by alkylation (Scheme 22). Couty and David displayed how 2-cyano-azetidinium ions **49a-c** could be efficiently α -deprotonated at -78°C using a strong non-nucleophilic base (to prevent any competitive ring opening) such as lithium hexamethyldisilazide (LiHMDS).⁴¹ The corresponding azetidinium ylide **50a** was found to have a remarkable ability to promote cyclopropanation when trapped *in situ* with Michael acceptors, giving rise to substituted cyclopropanes in good yields and with a high level of stereocontrol (Scheme 22, *path a*).^{41a} Configurational instability of the anionic centre of the ammonium ylide **50a** was addressed as the reason for the invariable absolute *R*- configuration of the carbon bearing the cyano group. Indeed, it was suggested that diastomeric ylides **50a** and *diast*-**50a** undergo rapid epimerization in which only less hindered **50a** likely attacks alkenes to provide the zwitterionic ammonium enolates **52**, which finally evolves to cyclopropanes **53**, *via* intramolecular $\text{S}_{\text{N}}2$ reaction. In a similar fashion, ylide **50b** was effectively employed to perform facile epoxidation of various aldehydes and ketones with excellent diastereoselectivity (Scheme 22, *path b*).^{41b} In both pathways the chemical instability of ammonium ylides, even at low temperatures, requires the electrophile to be present during their formation. It is important to

underline also that such reactions proved to be ineffective on the larger homologue 2-cyano pyrrolidinium ion, highlighting the crucial role played by the ring strain present in the azetidinium ylides to achieve reaction efficiency, likely ascribable to an enhanced leaving group capability of the ammonium group associated to the final ring strain relief. Additionally, azetidinium ylides, derived from deprotonation of 2-cyano-azetidinium salts **49a,c** as precursors, could efficiently be converted into differently substituted α,β -unsaturated nitriles **58a-h**, through a one-pot two-steps sequence involving trapping, with different alkyl halides, of *in situ* generated azetidinium ylides, followed by a final regioselective elimination (Scheme 22, *path c*).^{41c} Remarkably, the latter reaction was reported to be strictly sensitive to both steric hindrance around the nitrogen atom (as displayed by low yields of *N*-cyclohexyl derivatives **58g,h**) and nature of the starting halide (propargyl bromide gave product **58f** in only 14% yields, while aliphatic halides were ineffective at all). Remarkably, epoxides **56c-e**, obtained from aldehydes, cleanly evolved into the corresponding 2-disubstituted pyrrolidin-3-one adducts **59c-e** upon warming at 50°C . The proposed mechanism involves elimination of hydrogen cyanide with the formation of a different ammonium ylide, which undergoes a classical Stevens rearrangement. This interesting rearrangement was observed also in the case of aziridination of tosylimine **60** (Scheme 23).^{41b} Further insights in the chemistry of azetidinium ylides came recently from Aggarwal and coworkers.⁴² They described the reaction of *in situ* generated 2-phenyl azetidinium ylide **64** with primary and secondary boronic esters (including alkyl-, allyl- and aryl-ones) to give acyclic γ -dimethylamino tertiary boronic esters **66a-i**. Specifically, it was suggested that the transformation proceeded through the trapping of the lithiated carbon of the ylide with the boronic esters to form zwitterionic boronates **65**, which in turn could undergo ring-opening 1,2-migration, likely favored by ring strain release (Scheme 24). Deprotonation of azetidinium ion **63** was performed with LDA

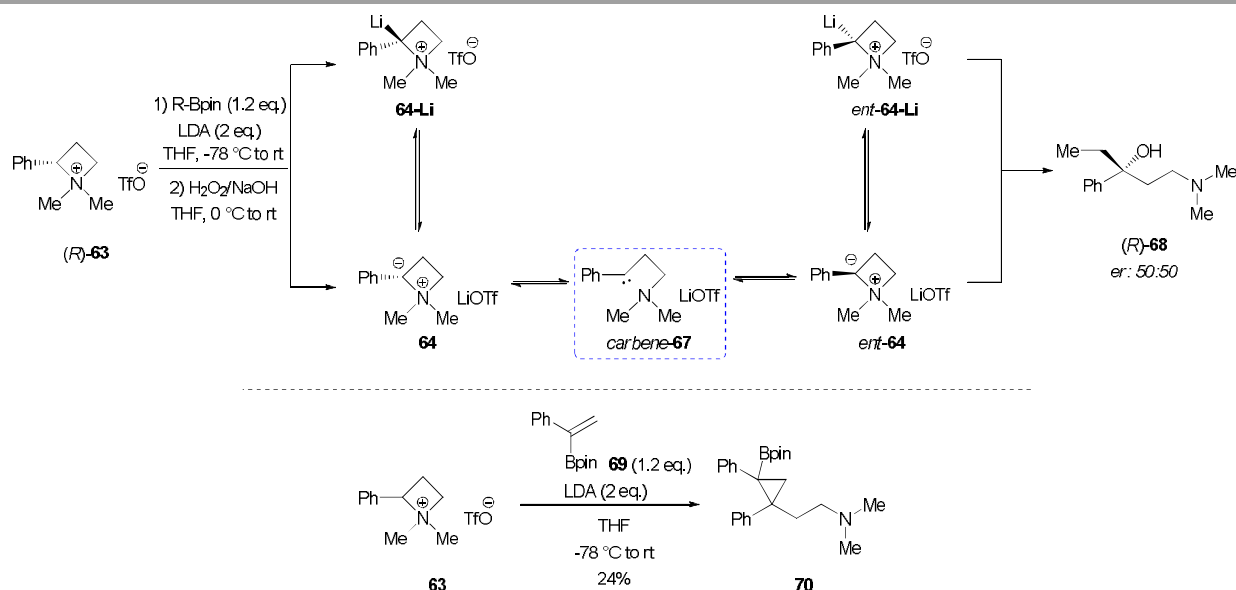


Scheme 22. Strained azetidinium ylides as reagents for cyclopropanation, epoxydation and synthesis of different acrylonitriles.*Rearrangement of cyano epoxydes**Aziridination***Scheme 23.** Intrinsic reactivity of cyano epoxydes and aziridines.

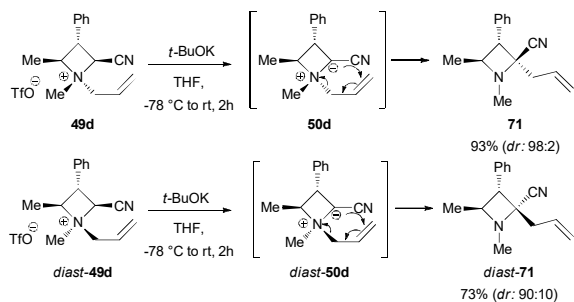
at $-78\text{ }^{\circ}\text{C}$ in THF, and trapping with alkyl boronates furnished the desired products in moderate to good yields. The targeted boronic esters are particularly attractive owing to their great synthetic versatility. Indeed, the C-B bond can be easily functionalized and transformed under mild conditions into a variety of different moieties such as C-OH, C-vinyl, C-H and C-BF₃.⁴³ These authors found the reaction to be not stereospecific (Scheme 25), due to the configurational instability of the initially formed lithium-stabilized ylide **64-Li** (or of ylide **64**, generated directly by deprotonation). They postulated that the rapid inversion might be ascribed to the transient formation of the open-chain carbene **67**, being this hypothesis supported by the formation of cyclopropane **70** when vinyl boronic ester **69** was employed (Scheme 25). Indeed, in the latter case, the targeted boronate did not form or undergo 1,2 migration, probably because of higher steric hindrance, and alternatively carbene **67** could perform cyclopropanation on the starting alkene. However, the rich reactivity displayed by azetidinium ylides is not limited to the above described

**Scheme 24.** Lithiation-borylation of ammonium ion **63**.⁴³ Isolation of the boronic ester was not possible owing to protodeborylation; *in situ* oxidation with H₂O₂/NaOH allowed the isolation of the corresponding tertiary alcohols.

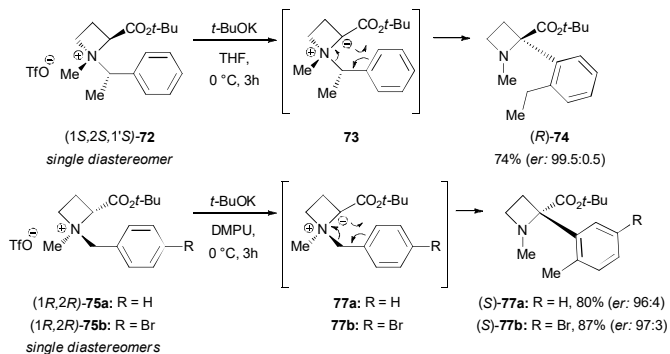
intermolecular reaction with different kind of electrophiles. Alternatively they can react intramolecularly through a [2,3] sigmatropic rearrangement.⁴⁴ The latter pathway easily led to optically active azetidines with an α -quaternary centre, through high level of *N*-to-C chirality transfer, starting both from 2-cyano azetidinium ylides **49d** and *diast*-**49d** (Scheme 26, *path a*)^{44a} and azetidinium-2-carboxylic acid ester derived ammonium salts **72** and **75a,b** (Scheme 26, *path b*).^{44b} Remarkably, only the targeted products derived from Sommelet-Hauser (S-H) rearrangement were observed, with no traces of the competitive [1,2] Stevens

**Scheme 25.** Proposed mechanism of racemization of ylide **64**.

Path a:



Path b:

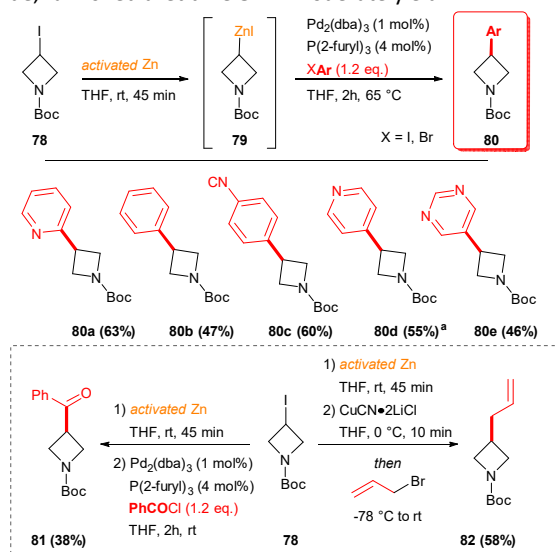


Scheme 26. Asymmetric base-induced [2,3] sigmatropic rearrangement of α -stabilized azetidinium ylides. DMPU = *N,N*-dimethylpropyleneurea.

rearrangement products.⁴⁵

C3-Metallation of azetidines

The most typical strategy to synthesize 3-substituted azetidines, by the corresponding organometallic intermediates, is the cross-coupling through the use of palladium catalysts and phosphine ligands, starting from the corresponding 3-iodo-azetidine.⁴⁶ In such a protocol, an azetidine-zinc complex has to be generated before the subsequent reaction with a suitable aryl halide or with benzyl chloride (Scheme 27). The organozinc species **79** could readily transmetallate with $\text{CuCN}\cdot 2\text{LiCl}$ in THF and by reacting with allyl bromide, furnished azetidine **82** in moderate yield.

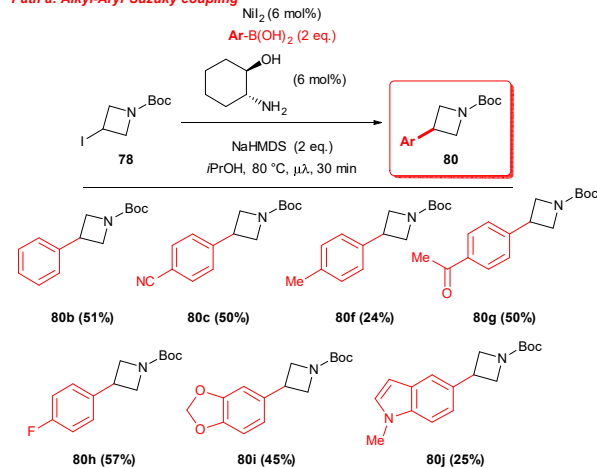


Scheme 27. Pd⁽⁰⁾ mediated cross coupling and transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$ of azetidinium-derived organozinc species **79**. ^aReaction carried out at room temperature.

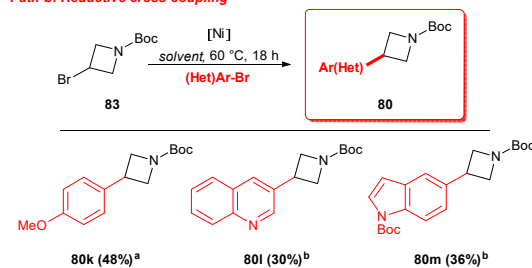
Alternatively, nickel catalyzed procedures in the presence of a ligand have been also reported, allowing the synthesis of 3-functionalised azetidines although with limited success (Scheme 28).⁴⁷ In 2008, Duncion reported an interesting microwaved Suzuki coupling to functionalize 3-iodo-azetidine **78** at the C-3 position.^{47a} The reaction with different aryl-boronic acids proceeded in the presence of catalytic amounts of nickel(II) iodide and *trans*-2-aminocyclohexanol as ligand (Scheme 28, path a).

More recently, Molander showed the possibility to perform a reductive cross coupling, using air-stable Ni(II) sources in the presence of a diamine ligand, an inorganic salt as additive, and a reducing metal, to obtain the incorporation of (hetero)aryl halides at C-3 of the azetidine ring (Scheme 28, path b).^{47b}

Path a: Alkyl-Aryl Suzuki coupling



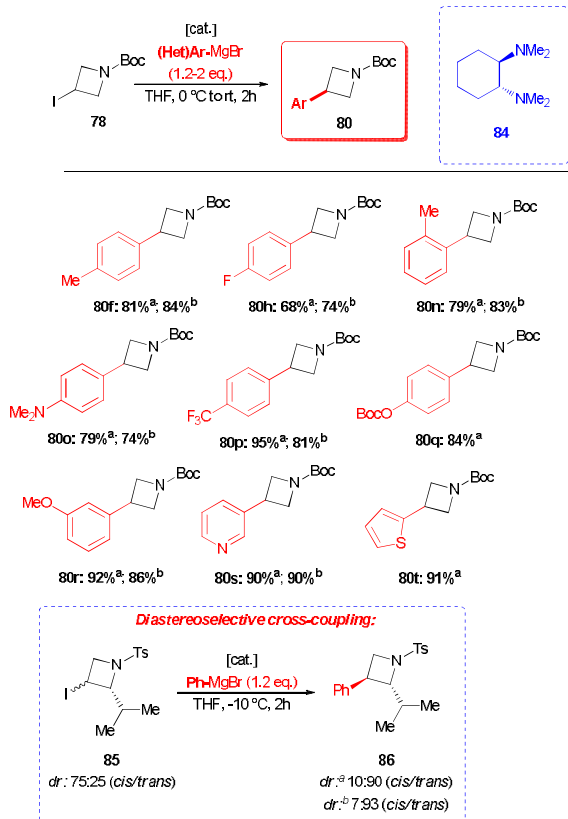
Path b: Reductive cross-coupling



Scheme 28. Ni based strategies for the synthesis of 3-aryl azetidines. ^aNiCl₂·glyme (10 mol%), phenanthroline (20 mol%), 4-ethylpyridine (50 mol%), NaBF₄ (50 mol%), Mn (2 eq.), MeOH (0.2 M). ^bNiI₂ (10 mol%), di-*t*-Bu-bipyridine (10 mol%), 4-ethylpyridine (1 eq.), MgCl₂ (1 eq.), Mn (2 eq.), DMA (0.2 M).

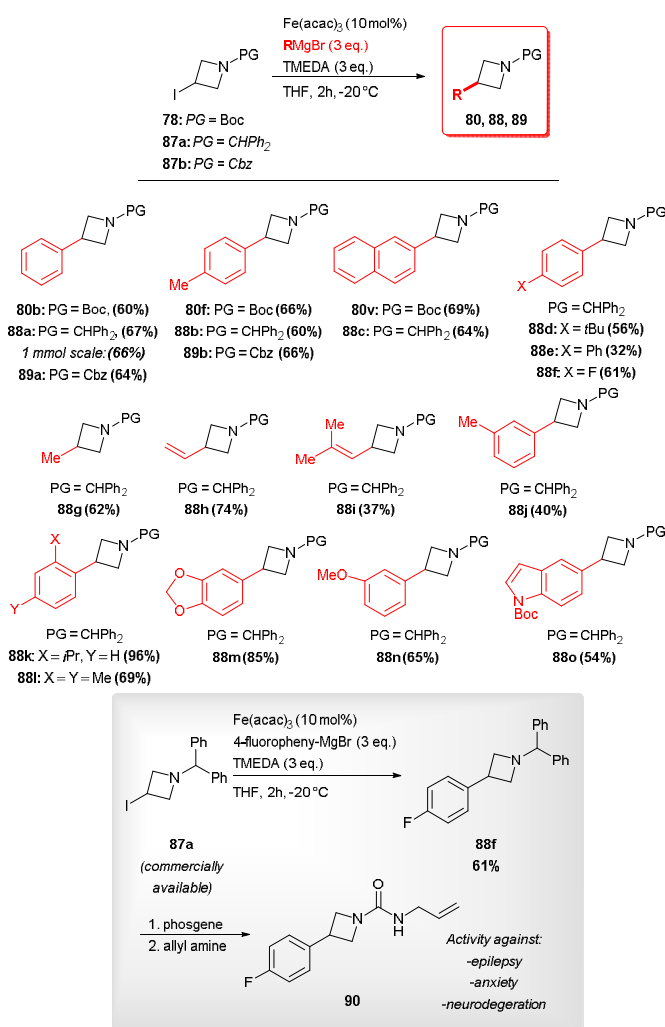
Recently, highly appealing methods for the coupling of azetidine **78** have featured in reports dealing with the employment of cheap iron or cobalt catalysts and readily available organomagnesium reagents in the absence of any additional phosphine ligands.^{48, 49} Cossy and coworkers disclosed that both CoCl_2 and FeCl_2 catalysts allow the smooth reaction between azetidine **78** and a large variety of (hetero)aryl Grignard reagents, generally exhibiting similar performances (Scheme 29).⁴⁸ Products were obtained in high yields and the protocol seemed to tolerate a large variety of functional

groups, but required the use of ligand **84** ((*R,R*)-tetramethylcyclohexan-1,2-diamine). Interestingly, when 2,3-disubstituted iodoazetidines **85** (*dr*: 75:25 *cis/trans*) was treated with PhMgBr in the presence of both catalytic systems the desired product **86** was obtained with a good *trans* diastereoselectivity (Scheme 29). The authors postulated that the inversion of stereochemistry might be ascribed to the formation of a radical intermediate at C-3.



Scheme 29. Iron- and Cobalt-mediated Arylation of Azetidines. ^a[cat.] = CoCl₂ (5 mol%)/**84** (6 mol%). ^b[cat.] = FeCl₂ (10 mol%)/**84** (10 mol%). Ts = Tosyl.

Moreover, Rueping reported a very mild procedure involving Fe(acac)₃ as the catalyst. In addition, this strategy proved to be efficient and chemoselective and to tolerate a variety of (hetero)aryl, vinyl and alkyl Grignard reagents, as well as different protecting groups on the nitrogen atom (Scheme 30).⁴⁹ Remarkably, these authors reported the possibility to scale up the reaction with no decrease of the yield. The synthetic potential of this route could be pointed out in the light of its successful application to the short formal synthesis of the challenging molecule **90** possessing pharmacological activity against central nervous system disorders (Scheme 30).^{11a} The patented reported route for the preparation of this molecule (and structurally related compounds) requires three steps, two days of work and two chromatographic separations to obtain intermediate **88f** in an overall combined yield of 42%.^{11a} Remarkably, by using the developed iron-catalyzed cross-coupling directly on the commercial iodide **87a**, Rueping and coworkers yield compound **88f** in 61%. The latter can be easily converted into the desired molecule **90** through a reported protecting group exchange step.^{11a}



Scheme 30. Rueping's azetidine cross-coupling with Grignard reagents and synthetic application of pharmaceutical interest.

Conclusions and Outlooks

Despite some limitations, the most significant conceptual advances over the past decade in the area of synthesis of differently functionalized azetidine rings, are represented by metallation reactions that led to the direct substitution at C2 and/or C3 of this heterocycle. These strategies are emerging to have an even growing impact in modern medicinal chemistry. The reactivity of the corresponding metallated systems were demonstrated to be extremely dependent on ring strain and on substitutions at both nitrogen and carbon atoms, that, by deeply influencing conformational preferences and coordinative phenomena, allow surgical site-selective functionalization.⁵⁰ Undoubtedly, the most difficult challenge that chemists have to overcome in this scenario, remains the addressing of optimal enantioselective lithiation/trapping sequence, mainly because of the configurational instability of the lithiated azetidine intermediates, which does not allow facile predictability of the stereochemical outcome. The ideal metallation reaction would be easily predictable, in terms of regio- and stereoselectivity, general and functional-group tolerant. Future research in the field of metallated four-

membered azetidines should focus on the use of chiral diamines working in dynamic resolutions and on getting insights of their structure-dependent reactivity by spectroscopic methods, computational studies and X-ray analysis. This will lead to a better and extensive application in synthetic organic chemistry, pharmaceuticals, agrochemicals and advanced materials of such heterocyclic intermediates.

Acknowledgements

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Notes and references

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Azetidines

- Found in natural products and marketed drugs
- Interesting bio- and pharmaceutical properties

