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Methods for the Synthesis of Substituted Azetines

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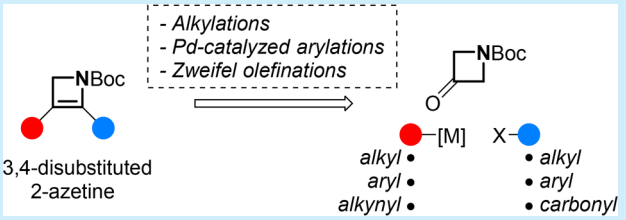
Supporting Information

ABSTRACT: Spurred on by the recent emerging interest from the chemical community for unsaturated four-membered heterocycles, an unprecedented approach to nitrogen-containing four-membered rings has been designed. 3,4-Disubstituted 2-azetines were synthesized from commercially available substrates, allowing for a straightforward access to a new library of chiral functionalized azetidines and amino alcohols. This original approach was applied to efficiently prepare functionalized azobenzenes, an emerging class of molecules with a large potential in photopharmacology.



Small, strained ring systems have recently received increased attention due to their large applicability in drug discovery and development. However, generating these systems is often limited by the availability of efficient and straightforward methods. Among them, azetidines and their unsaturated analogues 2-azetines[1−4] are particularly interesting as they represent a promising pattern for further pharmacological studies.

Apart from the well-known β-lactams penicillin and cephalosporin derivatives, several fused azetidine-containing substances have shown interesting antitumor activities[5] and antinociceptive effects[6] (Figure 1).

Fused β-lactams have also proven to be adequate precursors of azabicyclo[3.2.1]octanes.[7] In the polyoxin family, antibiotic properties were observed on 3-alkylideneazetidine-modified structures.[8]

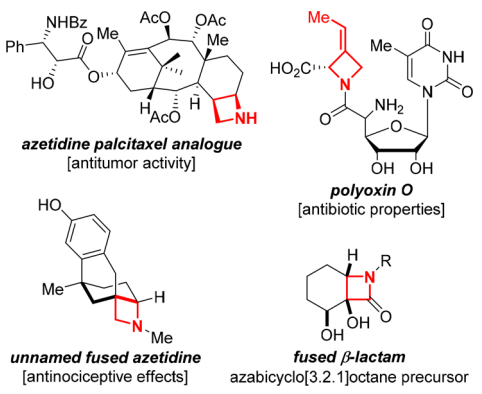


Figure 1. Examples of biologically active azetidine-containing structures or precursors.

Recently, the group of Baran et al. developed a new route for introducing 3-substituted azetidines by using the ring strain of azabicyclo[1.1.0]butane to efficiently modify lead compounds of pharmacological interests.[9] Concurrently, Carreira demonstrated the propensity of spiro-azetidines to modulate biological properties of different targets in drug discovery.[10] While smaller and larger *N*-containing heterocycles have been extensively studied,[1] only a few reports relate the general formation of azetines.[2,11]

With the ambitious objective of generalizing access to polysubstituted azetine architectures—that represent versatile building blocks en route to sophisticated azetidines—we first took on the challenge of identifying a sequence allowing for the regioselective introduction of diverse substituents at positions 3 and 4 (Scheme 1), involving a lithiated species as the key intermediate. While direct functionalization of 4-azetinyllithium could be easily performed in the presence of alkyl, silyl or carbonyl derivatives (conditions A), a more challenging arylation was designed through cross-coupling of the corresponding organoboronate derivatives, obtained through a simple transmetalation. As a matter of fact, transmetalation with $ZnCl_2$ only furnished the cross-coupled compound in low yield (27%, Hodgson et al.). Alternatively, a boron-relayed catalyst-free arylation of azetinyllithium was developed.

Starting from commercial sources of *N*-Boc-3-azetidinone **1**,[12] the introduction of the substituent at position 3 (R^1) was simply performed by employing an adequate organometallic reagent, such as organolithium, organomagnesium, or $PhMe_2SiLi$. Methylation of the resulting crude tertiary alcohol afforded **2a−f** in good to excellent yields over two steps (up to 98%, Scheme 2).[13] α-Lithiation of **2** assisted by coordination of the

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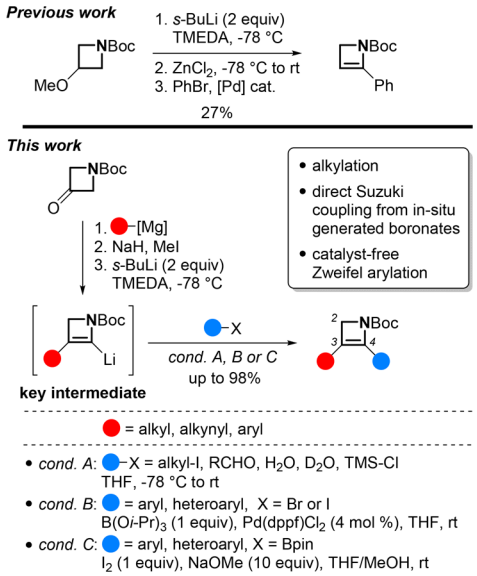
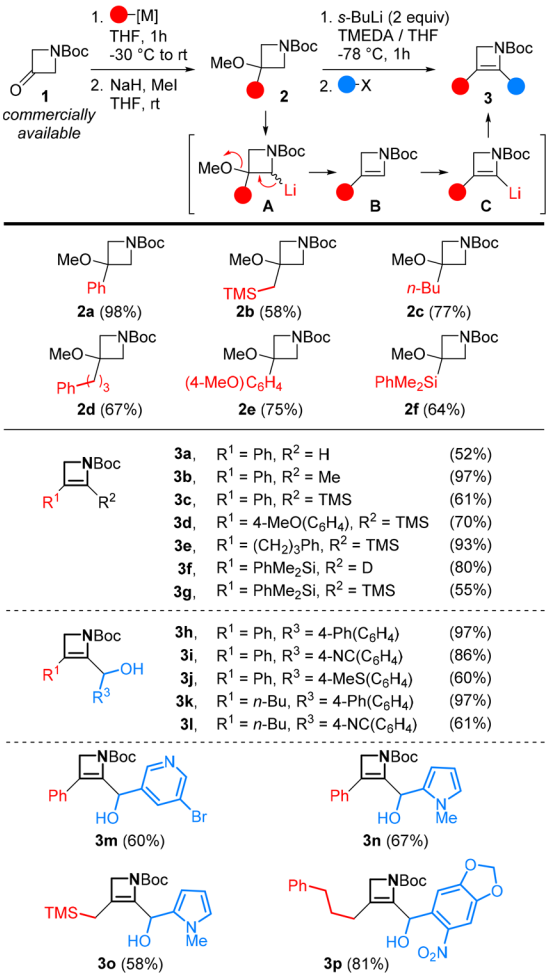
Scheme 1. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



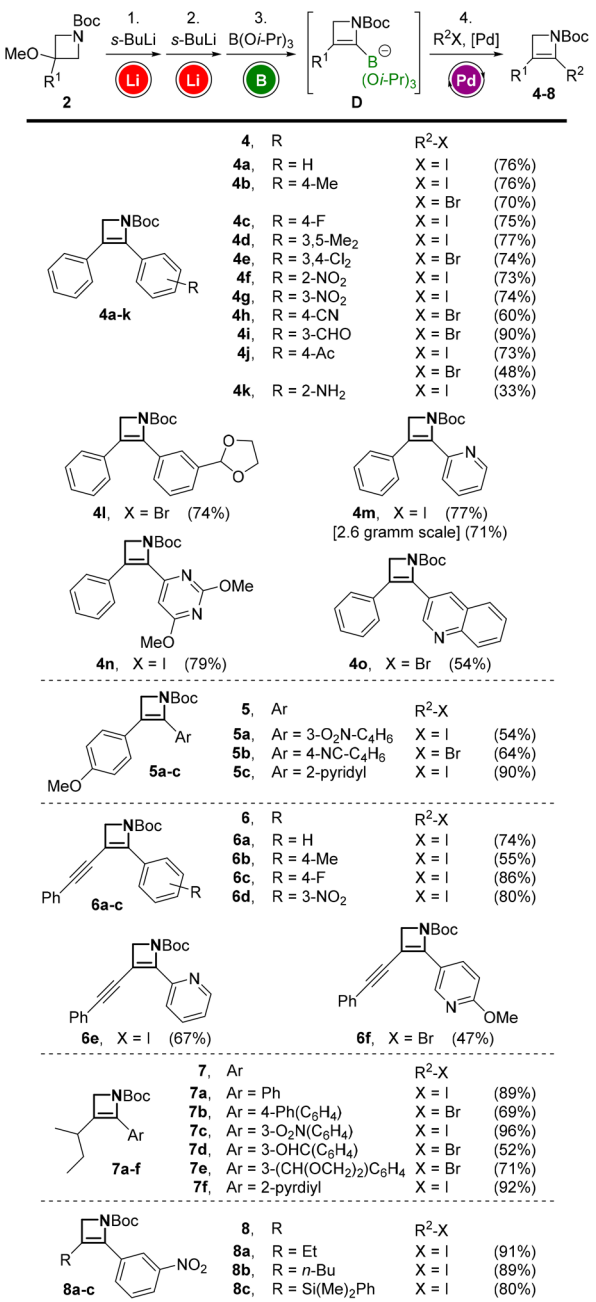
Scheme 2. Our Contribution to the Efficient Synthesis of Disubstituted Azetines



directing group (Boc) on the amine using *s*-BuLi in the presence of TMEDA triggers a β-elimination (**A**, Scheme 2) and intermediary forms a 2-azetine (**B**). With an excess of *s*-BuLi, a second α-metalation of the C(sp^2) can take place to obtain the key 4-azetinyllithium intermediate **C**. Addition of H_2O, D_2O, MeI, or TMSCl allowed the formation of 3-substituted azetines **3a–g** in up to 97% yield (Scheme 2). Aromatic and heteroaromatic aldehydes were also engaged as electrophiles in the reaction, furnishing azetinecarbinols **3h–p** with up to 97% yield.

Second, a similar sequence was designed to in situ generate a boronate derivative **D** (Scheme 3) by trapping the corresponding 4-azetinyllithium **C** with boron isopropoxide. Being a stable species at room temperature, this organoboronate is an excellent candidate to subsequently undergo a Suzuki cross-coupling in a one-pot process. Thus, following the double-lithiation/borylation sequence, a range of aromatic halides were engaged in the

Scheme 3. In Situ Generated 4-Azetinylboronates for Direct Suzuki Coupling



4,	R	R^2-X	
4a,	R = H	X = I	(76%)
4b,	R = 4-Me	X = I	(76%)
		X = Br	(70%)
4c,	R = 4-F	X = I	(75%)
4d,	R = 3,5-Me_2	X = I	(77%)
4e,	R = 3,4-Cl_2	X = Br	(74%)
4f,	R = 2-NO_2	X = I	(73%)
4g,	R = 3-NO_2	X = I	(74%)
4h,	R = 4-CN	X = Br	(60%)
4i,	R = 3-CHO	X = Br	(90%)
4j,	R = 4-Ac	X = I	(73%)
		X = Br	(48%)
4k,	R = 2-NH_2	X = I	(33%)

5,	Ar	R^2-X	
5a,	Ar = 3-O_2N-C_4H_6	X = I	(54%)
5b,	Ar = 4-NC-C_4H_6	X = Br	(64%)
5c,	Ar = 2-pyridyl	X = I	(90%)

6,	R	R^2-X	
6a,	R = H	X = I	(74%)
6b,	R = 4-Me	X = I	(55%)
6c,	R = 4-F	X = I	(86%)
6d,	R = 3-NO_2	X = I	(80%)

7,	Ar	R^2-X	
7a,	Ar = Ph	X = I	(89%)
7b,	Ar = 4-Ph(C_6H_4)	X = Br	(69%)
7c,	Ar = 3-O_2N(C_6H_4)	X = I	(96%)
7d,	Ar = 3-OHC(C_6H_4)	X = Br	(52%)
7e,	Ar = 3-(CH(OCH_2)$_2$)C_6H_4	X = Br	(71%)
7f,	Ar = 2-pyridyl	X = I	(92%)

8,	R	R^2-X	
8a,	R = Et	X = I	(91%)
8b,	R = *n*-Bu	X = I	(89%)
8c,	R = Si(Me)$_2$Ph	X = I	(80%)

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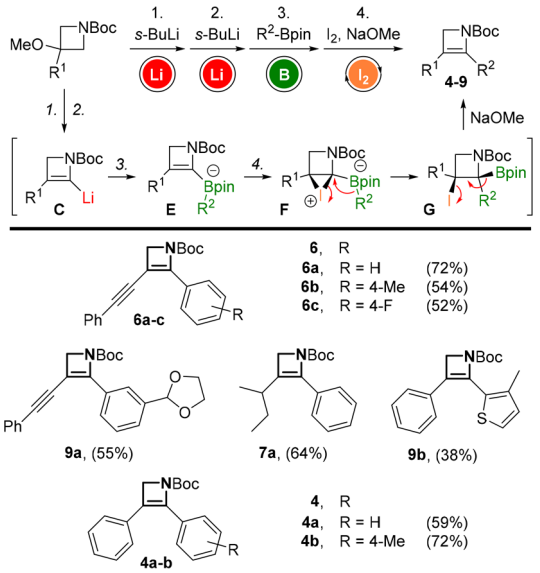
presence of Pd(dppf)Cl_2·CH_2Cl_2 (4 mol %) in THF, and products **4**–**8** were isolated after 48 h at room temperature. Aryl iodides reacted usually faster than the corresponding bromides, leading to the expected compounds in better yields. A wide range of aromatic halides were introduced in this strategy, using 3-arylated (**4a**–**o** and **5a**–**c**), 3-alkynyl (**6a**–**f**), and 3-alkyl substrates (**7a**–**f** and **8a**,**b**), resulting in 4-arylated structures in good to excellent yields (up to 96%). Additionally, the great functional group tolerance of organoboronates allowed us to introduce aromatic aldehydes **4i** and **7d** as well as heteroaromatic moieties (**4m**–**o**, **5c**, **6e**,**f**, and **7f**) in good yields up to 92%, independently from the nature of the substituent at position 3. Structures of these unsaturated *N*-heterocycles were supported by X-ray analysis (**6d** and **8a**).[14] Although full conversion was monitored for the formation of **4k** bearing a free amine, decomposition of the product on silica was noticed and the final azetine could only be isolated in 33% yield. In a more general manner, electron-enriched aromatics led to moderate yields due to fast decomposition (mainly ring opening products) in slightly acidic conditions during purification.

We then pushed the methodology further by developing an unprecedented catalyst-free cross-coupling of the 4-azetinyllithium species, successfully adapting the Zweifel-type olefination strategy. Boronic ester was then added to the in situ generated intermediate **C** (Scheme 4), giving the bis-organoboronate **E**.

Scheme 4. Catalyst-Free Zweifel Arylation of 4-Azetinyllithium Species

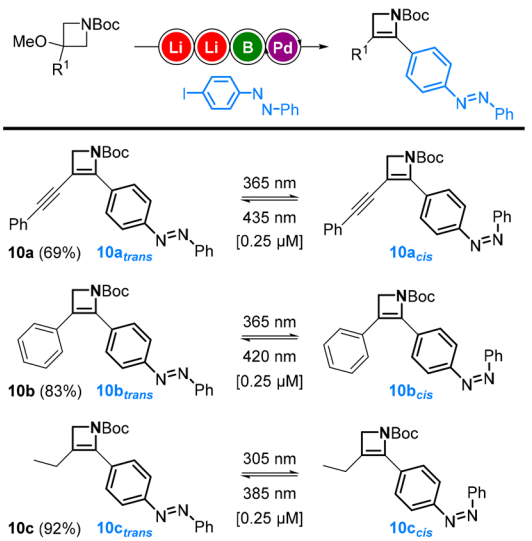


Subsequent addition of iodine furnishes an iodonium **F** that undergoes 1,2-metalate rearrangement, giving the α,β-iodoboronic ester **G**. The addition of a base finally triggers a cis-elimination, resulting in 3,4-disubstituted azetines **4**–**9**. 3-Alkyl-, alkynyl-, and arylazetinyllithium were used with aromatic boronic esters and compounds **4a**,**b**, **6a**–**c**, and **7a**, were obtained with reasonable yields (up to 72%), given the absence of a palladium catalyst. Interestingly, heteroaromatic substrates led to similar results and **9b** was isolated in 38% yield.

Considering the versatility of both arylation sequences and the recent interest brought by the community on diazobenzenes as promising photoswitchable systems for pharmacologic applications,[15] functionalization of azetines at position 4 was explored as a proof of concept.

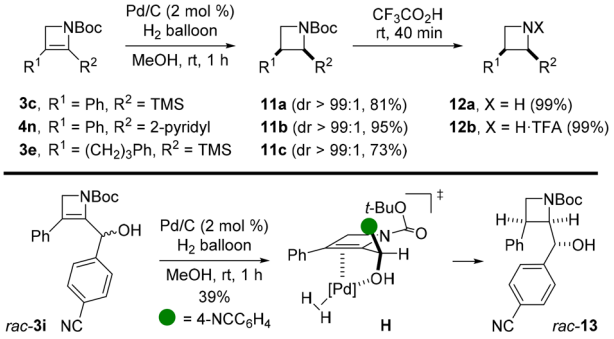
A one-pot sequence terminated by a palladium-catalyzed Suzuki coupling with 4-bromodiazobenzenes led to conjugated systems **10a**–**c** in good yields (Scheme 5). In the dark, **10a**–**c** are

Scheme 5. Application to the Synthesis of 4-Azetinylazobenzenes



present in their thermally stable *trans*-configuration. Irradiation with UV light (λ = 305–365 nm) triggers isomerization to the *cis*-configuration, while irradiation at 385–435 nm allows instant switching to the *trans*-configuration. Performing iteratively on and off photoswitching on these azetinyl-derived azobenzenes did not show any fatigue of the four-membered ring over time, proving the structural stability of the system. Finally, we showed the applicability of 3,4-substituted azetines to the formation of *syn*-2,3-disubstituted azetidines through simple hydrogenation (Scheme 6). Compounds **3e**, **3c**, and **4n** were engaged in the

Scheme 6. Straightforward Access to Stereodefined Azetidines



presence of palladium and hydrogen to give **11a**–**c** under smooth conditions in good yields and with an excellent diastereoisomeric ratio (dr >99:1).[12] Subsequent amine deprotection ultimately led to free azetidines **12a**,**b** in quantitative yields. It is worth noting that this represents a powerful approach to *syn*-azetidines, as most reports relate the formation of *anti*-azetidines.[16]

β-Amino alcohols are important functionalities in organic chemistry as they can serve as ligands in catalysis and are present in a large number of natural and bioactive substances.[17] In an attempt to synthesize stereodefined β-amino alcohols embedded in an azetidine core, we representatively demonstrated (Scheme

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6) that the reduction of chiral 4-azetinylcarbinol *rac*-**3i** could take place with high diastereoselectivities, furnishing *rac*-**13** as a single isomer (dr >99:1:0:0, the relative configuration was determined by X-ray crystallography).[14] The high degree of stereoselectivity observed in this reaction can be attributed to the coordination of the hydroxyl moiety to the palladium in the reduction process. For steric reasons, the aromatic group on the carbinol prefers to be oriented out of the plane, avoiding unfavorable interactions with the large Boc protecting group (**H**) (Scheme 6). This procedure certainly paves the way to new subclasses of chiral strained β-aminoalcohols.

In conclusion, we have demonstrated a very simple and efficient synthetic approach to novel 3,4-disubstituted azetine architectures, paving a new way toward stereodefined 2,3-azetidines. Two parallel approaches have been developed for the facile introduction of aryl and heteroaryl substituents at the position α to the nitrogen, either through a one-pot Suzuki cross-coupling or via catalyst-free arylation. Additionally, we showed the potential applicability of our system to unprecedented photoswitchable molecules, demonstrating their long-term stability. We finally illustrated an unprecedented access to stereodefined β-aminoalcohols that represent important structures in organic, organometallic and bioorganic chemistry. Paths allowing for the formation of these interesting patterns represent important advances in the chemistry of nitrogen-containing four-membered rings and their potential implications in drug-discovery processes.

■ ASSOCIATED CONTENT

Supporting Information

CThe Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02847.

Experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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