Michael Andresini,[†] Sonia De Angelis,[†] Antonella Uricchio,[†] Angelica Visaggio,[†] Giuseppe Romanazzi,[‡] Fulvio Ciriaco,[§] Nicola Corriero,[∥] Leonardo Degennaro,* [†] and Renzo Luisi*[,†]

[†]Department of Pharmacy-Drug Sciences, University of Bari "A. Moro", Via E. Orabona 4, Bari 70125, Italy
[‡]DICATECh, Politecnico di Bari, Via E. Orabona 4, Bari 70125, Italy
[§]Department of Chemistry, University of Bari "A. Moro", Via E. Orabona 4, Bari 70125, Italy
[∥] Institute of Crystallography, CNR, Via Amendola 122/O, Bari 70125, Italy

The present study reports, for the first time, the synthesis and structural features of azetidine–borane complexes, as well as their reactivity in lithiation reactions. A temperature–dependent stereoselectivity has been disclosed in the reaction of borane with *N*–alkyl–**2**–arylazetidines, allowing for a stereoselective preparation of azetidine–borane complexes **2** and **3**. A regioselective hydrogen/lithium permutation, at the benzylic position, was observed in lithiation reactions of complexes possessing a syn relationship, between the ring proton and the BH_3 group. In contrast, scarce or no reactivity was noticed in complexes lacking such a stereochemical requirement. The configurational stability of the lithiated intermediates has also been investigated, in order to shed some light on the stereoselectivity of the lithiation/electrophile trapping sequence. Calculations helped in supporting experimental observations, concerning structure and reactivity of these azetidine–borane complexes. Data suggest that the BH_3 group could promote the lithiation reaction likely by an electrostatic complex induced proximity effect. Interestingly, a new synthetic strategy for the synthesis of *N*–alkyl–**2,2**–disubstituted azetidines has been developed.

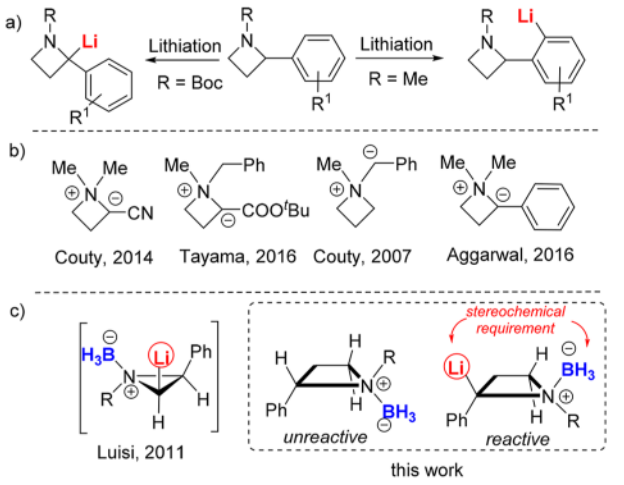
INTRODUCTION

The four-membered heterocycle azetidine represents an interesting scaffold in medicinal chemistry and agrochemistry,[1] due to its peculiar chemical properties (such as robustness and molecular rigidity), allowing for an efficient tuning of pharmacological properties displayed by molecules including such unit.[2,3] In addition, azetidine-bearing molecules have been used as ligands for transition metals, and as chiral auxiliaries.[4] Several methodologies are available for the preparation of azetidines, mostly based on the construction of the cyclic core by intramolecular cyclization reactions.[5] However, such strategies suffer the limitations due to multistep synthesis, and a previous installation of other functionalities before the ring-forming step. A more direct approach makes use of an already formed azetidine ring, which can be functionalized by a metalation/trapping sequence.[6] Recent studies on the lithiation of *N*-protected azetidines shed some light on the structural factors playing a key role in the metalation reaction.[7] For example, we disclosed that in the lithiation of 2-arylazetidines, the nature of the *N*-group is able to affect the regioselectivity of the metalation reaction. In fact, when an electron-withdrawing group is installed on the azetidine's nitrogen, exclusive α-lithiation is observed.[8] In striking contrast, the presence of an electron-donating alkyl group converted the azetidine ring into an *ortho*-directing group promoting exclusive *ortho*-lithiation (Scheme 1a).[9]

According to what was previously observed with the lower homologue aziridines, the availability of the nitrogen lone pair is crucial for deciding the regioselectivity of the metalation (lithiation).[10] In continuation of our research interest in the chemistry of azetidines, we describe herein the preparation of unprecedented azetidine–borane complexes reporting structural features and their reactivity toward lithiating agents. The investigation started from the observation that quaternization of the azetidine nitrogen could promote ring metalation. Recent examples by Couty,[11] Tayama,[12] and Aggarwal[13] demonstrated that ring metalation was feasible and that the corresponding azetidine ylide intermediates showed a peculiar reactivity undergoing to either Stevens or Sommelet–Hauser rearrangements, as well as borylation, and ring-opening reactions (Scheme 1b). Holding onto previous results on the

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 1. General Aspects on the Metalation of Azetidines

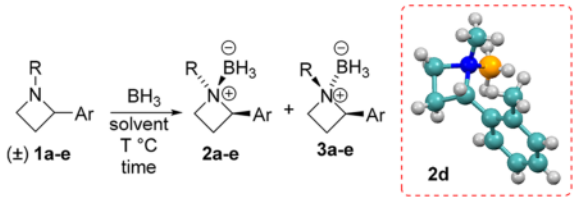


highly stereo- and regioselective lithiation of aziridines−borane complexes[14] (Scheme 1c), we were eager to demonstrate if azetidine−borane complexes could be regioselectively lithiated and trapped without undergoing ring opening or rearrangement.

■ RESULTS AND DISCUSSION

By reacting azetidines **1a−e** with a THF solution of BH_3, diastereomeric azetidine−borane complexes **2a−e** and **3a−e** were obtained as solids after 5 min at 0 °C (Table 1, entries 1−5). The diastereomeric complexes resulted by a syn and anti attack of the boron atom with respect to the aromatic ring, leading to complexes **2** and **3**, respectively. Interestingly, we noticed a temperature-dependent change of the **2**/**3** diastereomeric ratio. In particular, the amount of complex **2** slightly increased at a low temperature (i.e., −78 °C, Table 1, entries 6 and 7). By contrast, when a solution of distereomeric complexes (enriched in **2**) was heated up to 80 °C, a switch in the composition was observed in favor of complexes **3** (Table 1, entries 8−11). As an exception, complex **2c** was found to be stable even at high temperatures. The relative stereochemistry of complexes **2** and **3** was ascertained by NMR and NOE experiments (see Supporting Information) and, in the case of **2d**, demonstrated by single-crystal X-ray analysis.[15]

Table 1. Synthesis of Diastereomeric Azetidine−Borane Complexes



entry	1[a]	R	Ar	solvent	t (min)	T (°C)[b]	dr 2/3[c]
1	**1a**	Me	Ph	THF	5	0	80:20
2	**1b**	Et	Ph	THF	5	0	80:20
3	**1c**	^{t}Bu	Ph	THF	5	0	95:5[d]
4	**1d**	Me	*o*-tolyl	THF	5	0	72:28
5	**1e**	Me	*m*-xylyl	THF	5	0	78:22
6	**1a**	Me	Ph	THF	60	−78	99:1
7	**1b**	Et	Ph	THF	60	−78	90:10
8	**1a**	Me	Ph	2-MeTHF	60	40	69:31
9	**1a**	Me	Ph	2-MeTHF	180	80	20:80
10	**1d**	Me	*o*-tolyl	2-MeTHF	180	80	9:91
11	**1e**	Me	*m*-xylyl	2-MeTHF	180	80	10:90

[a]Racemic azetidines were used for complexation with BH_3. [b]See the Supporting Information for reaction conditions. [c]Diastereomeric ratio established by ^{1}H NMR on the crude reaction mixture. [d]Diastereomeric ratio did not change even upon warming the sample at 70 °C for several hours.

The variability of the diastereomeric ratio in complexes **2** and **3** could be explained taking into consideration two factors, namely: (a) the role of the ethereal solvent and (b) the azetidine's nitrogen inversion. In fact, as reported in Figure 1, it is likely that the solvent could take up BH_3 from the azetidine nitrogen, and the temperature, as well as the nature of the R group and nitrogen's stereochemistry, could affect this equilibrium.[16] Additionally, the nitrogen dynamics in free azetidines **1** must be taken into consideration. As depicted in Figure 1, invertomer **A** is likely the most stable, and this would explain the prevalent formation of complexes **2** at lower temperatures (Table 1, entries 1−7).[17] Nevertheless, higher temperatures could affect all of the equilibriums in Figure 1, favoring the formation of the most stable complex, **3**. It is reasonable to assume that **2** are kinetic complexes and **3** the thermodynamic ones. With the aim to support these hypotheses, other experiments were executed. A diastereomeric ratio **2a**/**3a** of 85:15 was observed when performing the complexation reaction in a nonpolar solvent such as dichloromethane, thus confirming that **2a** is the kinetic product. In addition, to support the role of the ethereal solvent in the isomerization **2a** → **3a**, toluene was used as the solvent. When a solution of **2a** in toluene was refluxed and the progress was monitored by ^{1}H NMR (see the Supporting Information), the **2a** → **3a** transition occurred slower than in 2-MeTHF, and after 41 h, a diastereomeric ratio **2a**/**3a** of 39:61 was obtained jointly with a small amount of free azetidine **1a**. It is likely that, upon heating, a partial loss of BH_3 occurs and that the free azetidine promotes the isomerization according to the mechanism reported in Figure 1. In order to provide more evidence supporting our hypotheses, an NMR and computational investigation was run on complexes **2a** and **3a**. Complexes **2a** and **3a** were first separated by flash chromatography and separately subjected to ^{11}B and ^{1}H NMR analysis in THF-d_8 at 60 °C. In Figure 1, the change observed in the ^{11}B NMR spectra for the transition **2a** → **3a** is reported. A similar experiment was executed on pure complex **3a**, but without any evident change in composition after 3 days in THF-d_8 at 60 °C (see the Supporting Information). DFT calculations at the B3LYP 6-311-G level of theory also confirmed that complex **3a** was 1.4 kcal/mol more stable than **2a** (see the Supporting Information), thus supporting the rationale in Figure 1.

Next, we investigated the reactivity of diastereomeric complex **3a** in lithiation reactions. Initially, we tested the conditions used for the lithiation of aziridine−borane complexes.[14] Optimal conditions employed 3 equiv of *sec*-BuLi, at −50 °C in THF for 5 min (Table 2, entry 3). A longer reaction time was needed to reduce the equiv of base (Table 2, entry 1), while lithiation at higher temperatures (−20 or 0 °C) resulted in a lower yield in deuterated products (Table 2, entries 5 and 6). However, all of the lithiation experiments, run in THF, led to a diastereomeric mixture of deuterated products, **2a-D** and **3a-D**, with **3a-D** being the most abundant.

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

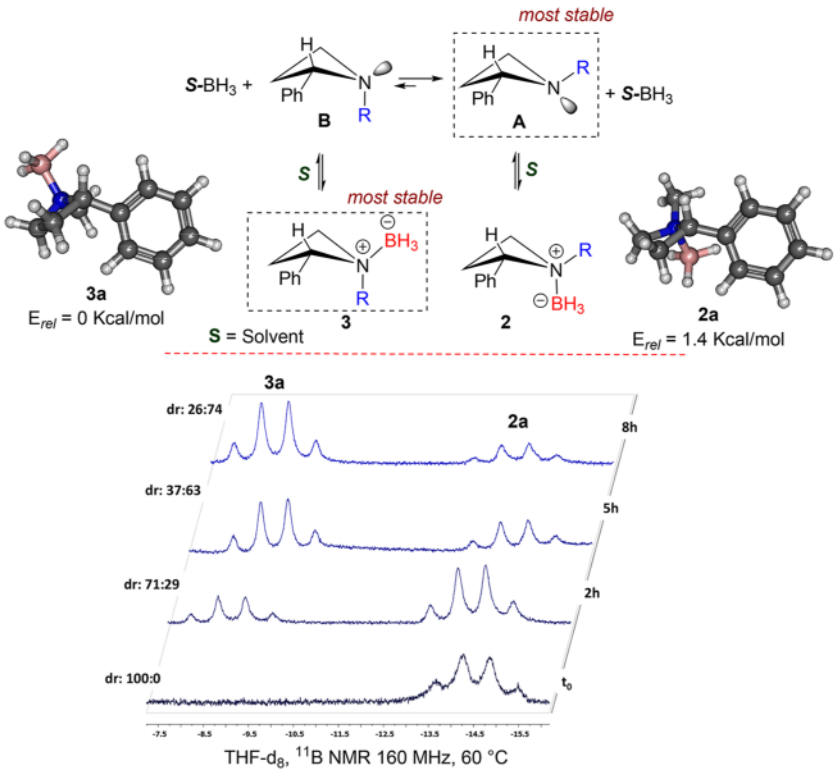
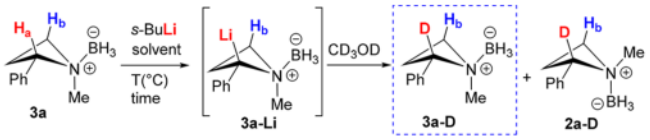


Figure 1. Rationale for temperature-dependent diastereomeric switch for complexes **2** and **3**.

Table 2. Lithiation of Azetidine–Borane Complex 3a



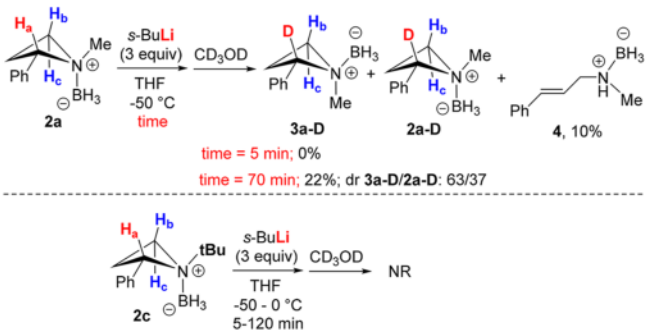
entry	T (°C)	solvent	base (equiv)	t (min)	dr 3a-D/2a-D	yield (%)[a]
1	−50	THF	1.5	120	76:24	>99
2	−50	THF	3	60	76:24	>99
3	−50	THF	3	5	79:21	98
4	−78	THF	3	5	75:25	96
5	−20	THF	3	5	37:63	84[b]
6	0	THF	3	5	38:62	52[c]
7	−50	toluene[d]	3	5	38:62	97
8	−50	toluene[d]	3	60	36:64	>99
9	−50	toluene[e]	3	5		0

[a]Yield determined by ^{1}H NMR analysis. [b]Residual protonated complexes **3a** and **2a** were found, respectively, in a 61:39 diastereomeric ratio. [c]Residual protonated complexes **3a** and **2a** were found, respectively, in a 75:25 diastereomeric ratio. [d]TMEDA (3 equiv) was employed as a ligand. [e]Reaction run without TMEDA.

The use of toluene as the solvent, in the presence of tetramethylethylenediammine (TMEDA) as the ligand, again produced a mixture of **2a-D** and **3a-D** but with a reversed stereoselectivity with respect to THF (Table 2, entries 7 and 8). It is worth mentioning that, based on an electrostatic complex induced proximity effect (e-CIPE),[18,19] lithiation must occur syn to the BH_3, and protons H_a and H_b could be potentially removed (Table 2). In all cases, lithiation was found highly regioselective, with the proton H_a (syn to the BH_3 group) preferentially removed.

For sake of comparison, we investigated the reactivity of complexes **2a** and **2c** (Scheme 2). In this case, according to

Scheme 2. Reactivity of Diastereomeric Complexes 2a and 2c



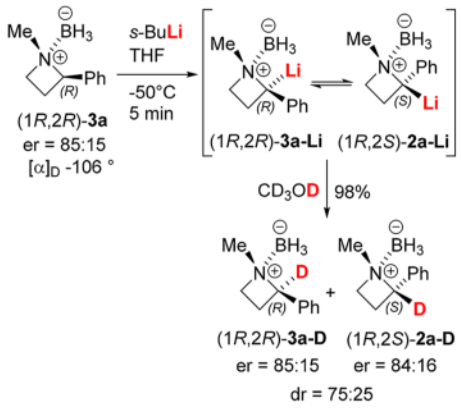
what was observed with the aziridine–borane complex, regioselective removal of H_c was expected.[14] Nevertheless, **2a** was found less reactive than **3a**; in fact, when **2a** was reacted with *sec*-BuLi under the same optimal reaction conditions adopted for **3a** (Table 2, entry 3), no reaction occurred, and unreacted starting material was recovered (Scheme 2). However, prolonging the lithiation time up to 70 min, **2a** underwent, to some extent, benzylic lithiation (removal of H_a), producing **3a-D** and **2a-D** in 22% yield, with a dr of 63:37, respectively.[20] Interestingly, product **4**, derived from a β-elimination reaction, was also found in the reaction mixture. This latter result could be explained considering that the thermodynamic acidity of the benzylic position competes with the propensity of the strained ring to undergo β-elimination, leading to product **4**. The sensible reluctance of **2a** to undergo full deprotonation under the optimal conditions adopted for **3a**

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

could likely be ascribed to the assistance of the BH_3 group in **3a**, possessing the suitable stereochemical requirement. Complex **2c** was, however, found unreactive under varied reaction conditions. It is likely that this diastereomer does not meet the stereochemical requirement (i.e., proximity H_c–BH_3) needed for lithiation, and in addition, there could be a steric effect brought about by the bulky *N*-substituent.[21]

Next, in order to explain the presence of a diastereomeric mixture in the lithiation/trapping experiments, the configurational stability of the lithiated intermediate generated from **3a** was investigated (Scheme 3). Upon lithiation/deuteration

Scheme 3. Evaluating the Configurational Stability of Lithiated (1*R*,2*R*)-3a

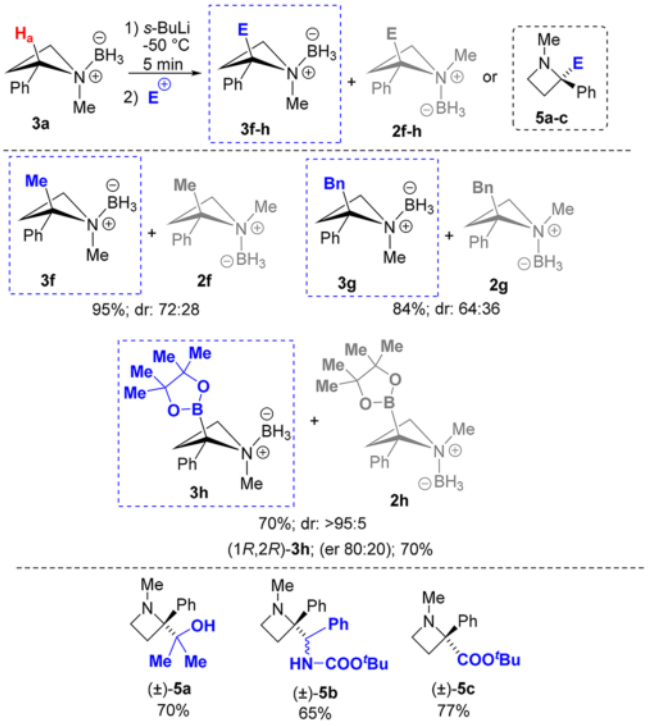


under optimized conditions (Table 1, entry 3), chiral complex (1*R*,2*R*)-**3a** (er 85:15) furnished a mixture of (1*R*,2*R*)-**3a-D** (er 85:15) and (1*R*,2*S*)-**2a-D** (er 84:16) in a 75:25 diastereomeric ratio, respectively, as ascertained by chiral HPLC analysis (see the Supporting Information).

From the experiment run on (1*R*,2*R*)-**3a**, it is possible to conclude that the lithiated intermediates are configurationally unstable and that exclusive inversion at the lithiated carbon occurs.[22] On the basis of these results, we investigated the reaction of lithiated complex **3a** with representative electrophiles (Scheme 4). As reported in Scheme 3, alkylation, benzylation, and borylation furnished complexes **2f–h** and **3f–h** with good yields and a variable degree of stereoselectivity (Scheme 4). Interestingly, the main diastereomer resulted from the introduction of the electrophile syn to the BH_3 group. However, the stereoselectivity seemed to be dependent on the electrophile, as observed in the borylation reaction, furnishing only diastereomer **3h**.[23] The lithiation/borylation sequence run on (1*R*,2*R*)-**3a** led to enantioenriched (1*R*,2*R*)-**3h** (er 80:20) in 70% yield and as a single diastereomer (Scheme 4).

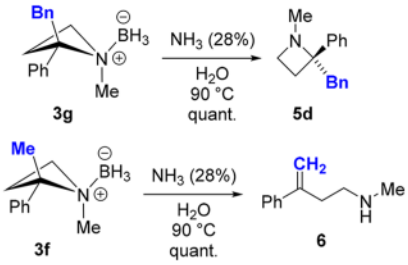
In the reactions with acetone, *N*-Boc benzylidene imine, and *tert*-butyldicarbonate, the corresponding BH_3-free azetidines **5a–c** were isolated after flash chromatography (see the Supporting Information) probably as a consequence of the presence of a basic site in the product (i.e., O and N) able to interact with the BH_3 group. These results are, in our opinion, remarkable because they open the possibility to functionalize selectively the benzylic position of *N*-alkyl-2-arylazetidines. It is worth mentioning that an electron-withdrawing group is required for benzylic lithiation of these systems (Scheme 1, a). Nevertheless, *N*-Boc-2-phenylazetidines undergo dimerization after lithiation at the benzylic position.[7,8] Thus, this strategy would allow for a facile and effective functionalization

Scheme 4. Scope of the Lithiation/Trapping Sequence of Complex 3a



at the benzylic position of *N*-alkyl-2-arylazetidines by a sequence of BH_3 complexation/lithiation/electrophile trapping/BH_3 removal. With the aim to demonstrate this, we explored the possibility to remove the BH_3 group in complexes **3f** and **3g**. As reported in Scheme 5, by refluxing complex **3g** in

Scheme 5. Deprotection of Azetidine–Borane Complexes 3

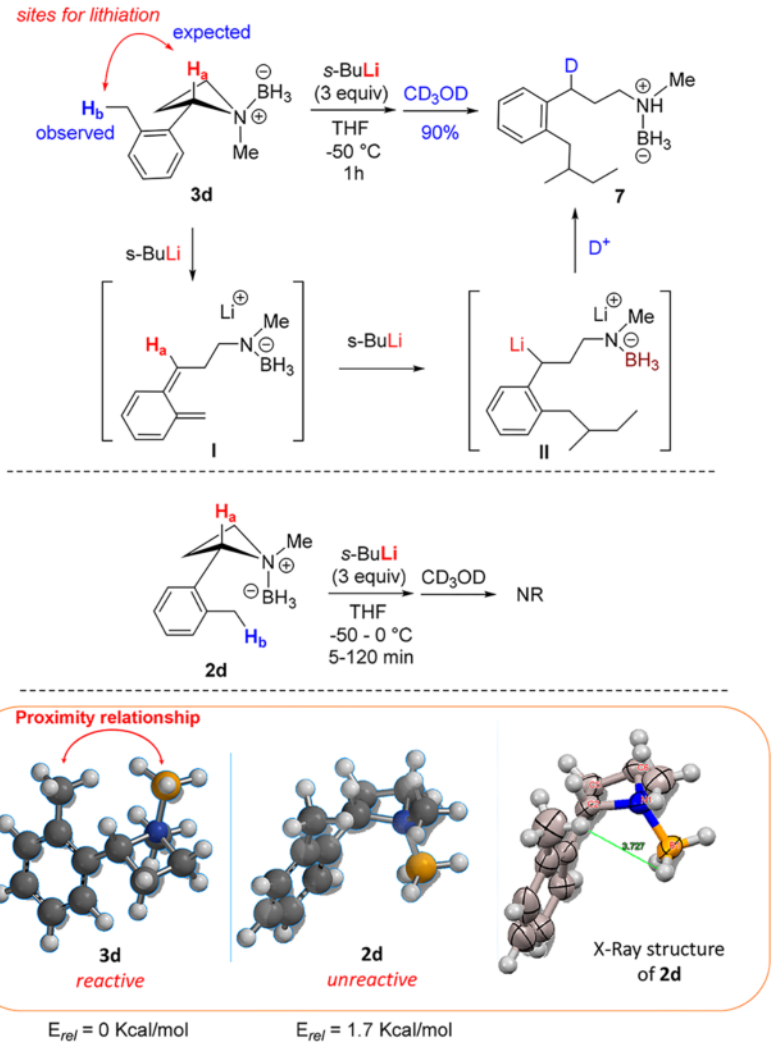


aqueous NH_3 (28% w/w), free azetidine **5d** was obtained quantitatively. However, under the same conditions, complex **3f** undergoes β-elimination, furnishing exclusively alkene **6** (Scheme 5).

A surprising result was obtained in the lithiation of complex **3d**, bearing an *ortho*-methyl group on the aromatic ring, and in principle susceptible of lithiation at two benzylic positions (H_a and H_b in Scheme 5). Upon reaction of **3d** with *s*-BuLi (3 equiv), exclusive formation of ring-opening product **7** was observed after quenching with CD_3OD (Scheme 5). This result could be explained, as reported in Scheme 5, taking into consideration a regioselective lateral deprotonation (removal of H_b), followed by dearomatization, and azetidine ring opening, leading to intermediate **I**. Nucleophilic attack of *s*-BuLi to **I** furnished intermediates **II** that could react with CD_3OD. For sake of comparison, the lithiation of azetidine complexes **2d** was also investigated. According to what was

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 6. *ortho*-Effect in the Lithiation of Complexes 2d and 3d



observed with complexes **2a** and **2c** (Scheme 2), complex **2d** was also found unreactive, under varied reaction conditions, likely for the lack of the syn stereochemical requirement between the BH_3 group and the benzylic protons (see below).

Equilibrium geometries, calculated at the B3LYP 6-311+G level of theory, for complexes **2d** and **3d** revealed a proximity relationship between the *ortho*-methyl and BH_3 groups in **3d** (Scheme 6). In the case of **2d**, the optimized structure is very similar to the X-ray structure (reported in Scheme 6 for comparison), in which the *ortho*-methyl and BH_3 groups sit trans to each other. Thus, it is likely that the proximity relationship in **3d** would promote an e-CIPE favoring lateral lithiation.

■ CONCLUSIONS

In conclusion, this work reported, for the first time, structural features of azetidine−borane complexes. Synthetic studies demonstrated a temperature-dependent stereoselectivity in the reaction of borane with *N*-alkyl-2-arylazetidines in polar solvents such as THF or 2-MeTHF. The lithiation studies disclosed a regioselective hydrogen/lithium permutation at the benzylic position of azetidine **3a**. The syn relationship, between the ring proton and the BH_3 group, seems to be a needed stereochemical requirement for the lithiation to occur. In fact, poor or no reactivity was observed in complexes lacking such a stereochemical requirement (i.e., **2a**, **2c**, and **2d**). The variable degree of stereoselectivity observed in the lithiation/electrophile trapping sequence has been ascribed to the configurational instability of the lithiated intermediates. Calculations helped in supporting experimental observations concerning structure and reactivity toward lithiating agents. This investigation provides useful information on the role of the BH_3 group in promoting the lithiation reaction, likely by an e-CIPE, and introduces a new synthetic strategy for the synthesis of *N*-alkyl-2,2-disubstituted arylazetidines. Further investigations are underway in our laboratory in order to further exploit the synthetic potential of these complexes. Results will be reported in due course.

■ EXPERIMENTAL SECTION

General (Standard Techniques). THF and Et_2O were freshly distilled under a nitrogen atmosphere over Na/benzophenone. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2. Hexyllithium was purchased as a hexane solution. The solution was filtered on Celite before using, and the title of base was established by the titration method. The solvent toluene was freshly distilled under a nitrogen atmosphere over CaH_2. All of the chemicals and solvents used were commercially available (TCI Europe, Fluorochem, VWR, Aldrich Chemical Co.) and used without further purification. Melting points were uncorrected and recorded with a Büchi melting point B-545 instrument. Resonance spectra were

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

recorded using Bruker 300 and 600 MHz and Agilent 500 MHz (^{1}H NMR 400, 500, 600 MHz; ^{13}C NMR 75, 125, 150 MHz; ^{11}B NMR 160 MHz) units, and $CDCl_3$, CD_3OD, THF-d_8, or toluene-d_8 were used as solvents. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), coupling constant in Hz, integration]. Chemical shifts are reported in ppm. Infrared spectra of the compounds were recorded neat, as film, as KBr discs as indicated, by a PerkinElmer 283 spectrometer in cm^{-1} or by using an ATR spectrophotometer. ESI-MS analysis was performed on an Agilent 110 LC/MSD mass spectrometer with the ionic single quadrupole trap system and Exalibur data system. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel thick plates (Merck) with the fluorescence indicator F-254; visualization was performed using a UV lamp (254 nm) or using a $KMnO_4$ 0.02 M solution. Enantiomeric ratios and enantiomeric excesses were determined with HPLC Agilent 1260, chiral column (Lux_1-Cellulose), following the condition reported. For flash chromatography, silica gel 70−230 mesh and 230−400 mesh was used. Optical rotation $[a]_D^{20}$ values were measured by using a polarimeter with 1 dm cell path length; the concentration (c) is expressed in g/100 mL. All reactions and reagents sensible to oxygen and water were carried out using a dry nitrogen atmosphere. The title of base (*sec*-BuLi) was determined by titration with *N*-phenylbenzamide, following the procedure reported in the literature.[24]

General Preparations of 1-Alkyl-2-arylazetidines (1a−c,e). For procedure A, according to the procedure reported in the literature,[9] to a solution of commercially available 3-chloro-2-arylpropan-1-ones (10 mmol, 1 equiv) in MeOH (10 mL) cooled at 0 °C was added 756 mg of $NaBH_4$ (2 equiv) slowly, and the solution was stirred at room temperature for 2 h. Methanol was distilled off under reduced pressure, and 25 mL of Et_2O and H_2O was added. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. 3-Chloro-1-arylpropan-1-ols were obtained without further purification. To a solution of 3-chloro-1-arylpropan-1-ol (10 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at 25 °C was added a solution of $SOCl_2$ (30 mmol, 3 equiv) in CH_2Cl_2 (3 mL) dropwise. After 2 h at 25 °C, the reaction mixture was poured into water and aqueous NaOH (15% p/v) was slowly added to neutralize the excess of HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give 1-aryl-1,3-dichloropropane, which was employed without further purification. To a solution of 1-aryl-1,3-dichloropropane in EtOH (12.5 mL) and Et_3N (20 mmol, 2 equiv) at 25 °C was added a solution of R-NH_2 in EtOH (9.7 equiv). The reaction mixture was refluxed for 24 h and then allowed to cool to room temperature. The solvent was removed in vacuo, and aqueous $NaCO_3$ (15% p/v) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude mixture was purified to give the desired azetidine. This procedure was used for the synthesis of chiral azetidine (*R*)-**1a**, $[\alpha]_D^{20}$ −16 (c 1, $CHCl_3$). Enantiomeric excess = 70%. Chiral (*R*)-3-chloro-1-phenylpropan-1-ol (er = 91:9) was prepared by reduction of the corresponding ketone by using the (*R*)-CBS catalyst as reported.[9]

For procedure B, according to the reported procedure,[9] to a solution of 1-methyl-2-phenylazetidine **1a** (210 mg, 1.43 mmol) in dry Et_2O (7.42 mL) was added TMEDA (3.65 mmol, 2.5 equiv). Subsequently, a solution of hexyllithium (2.3 M in hexane, 2.86 mmol, 2 equiv) was added dropwise, and the solution was stirred at room temperature for 1 h under a dry nitrogen atmosphere. Then, MeI (3.56 mmol, 2.5 equiv) was added and after 20 min, the reaction was quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and evaporated under reduced pressure.

*1-Methyl-2-phenylazetidine (**1a**).* The compound was prepared according to general procedure A and purified by flash column chromatography (SiO_2, dry loaded, 100% Et_2O) to afford the title azetidine as a colorless oil, R_f = 0.45 (100% Et_2O); 65% yield, 957 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.32 (m, 4H), 7.27−7.23 (m, 1H), 3.88 (t, J = 8.2 Hz, 1H), 3.49−3.44 (m, 1H), 2.86 (dt, J = 9.7, 7.0 Hz, 1H), 2.34 (s, 3H), 2.31−2.25 (m, 1H), 2.15 (quint, J = 9.2, 1H); ^{13}C NMR (150 MHz, toluene-d_8): δ 144.0, 128.5, 127.3, 126.9, 71.4 (C_q), 53.0, 44.2, 28.0. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{10}H_{13}NNa$, 170.0940; found, 170.0938. IR (film, cm^{-1}): ν 2959, 1452, 1190, 964, 745.

*(R)-1-Methyl-2-phenylazetidine ((R)-**1a**).* The compound was prepared accordingly to the reported procedure.[9] $[\alpha]_D^{20}$ +113 (c 1, $CHCl_3$), enantiomeric ratio (er) = 85:15.

*1-Ethyl-2-phenylazetidine (**1b**).* The compound was prepared according to general procedure A and purified by flash column chromatography (SiO_2, dry loaded, 100% Et_2O) to afford the title azetidine as a colorless oil. R_f = 0.40 (100% Et_2O); 61% yield, 982 mg. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41−7.42 (m, 2H), 7.34−7.31 (m, 2H), 7.25−7.22 (m, 1H), 3.94 (t, J = 8.2 Hz, 2H), 3.47−3.44 (m, 1H), 2.8 (dt, J = 7.5, 9.5 Hz, 1H), 2.66−2.61 (m, 1H), 2.46−2.41 (m, 1H), 2.31−2.32 (m, 1H), 2.11 (quint, J = 9.1 Hz, 1H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 143.9, 128.4, 127.2, 126.7, 69.7(C_q), 53.1, 50.9, 27.1, 12.8. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{11}H_{15}NNa$, 184.1097; found, 184.1095. IR (film, cm^{-1}): ν 2961, 1450, 1191, 964, 752.

*1-tert-Butyl-2-phenylazetidine (**1c**).* The compound was prepared according to general procedure A and purified by flash column chromatography (SiO_2, dry loaded, 100% Et_2O) to afford the title azetidine as a colorless oil. R_f = 0.45 (100% Et_2O); 78% yield, 1.477 g. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51−7.49 (m, 2H), 7.32−7.29 (m, 2H), 7.23−7.20 (m, 1H), 4.30 (t, J = 8.0, 1H), 3.18−3.13 (m, 2H), 2.19−2.14 (m, 1H), 1.94 (quint like, J = 8.5 Hz, 1H), 0.89 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 146.3, 128.2, 127.1, 127.0, 62.4, 53.0, 43.2, 27.0, 25.3. IR (film, cm^{-1}): ν 2966, 1454, 1236, 1065, 758, 699. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{20}N$, 190.1596; found, 190.1590.

*1-Methyl-2-o-tolylazetidine (**1d**).* The compound was prepared according to general procedure B by using azetidine **1a** and purified by flash column chromatography (SiO_2, dry loaded, CH_2Cl_2/MeOH 90:10) to afford the title azetidine as a colorless oil. R_f = 0.60; 65% yield, 150 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.14 (dt, J = 11.4, 7.1 Hz, 2H), 4.09 (t, J = 7.9 Hz, 1H), 3.50−3.46 (m, 1H), 2.98−2.92 (m, 1H), 2.44−2.37 (m overlapping s at 2.39 ppm, 4H), 2.24 (s, 3H), 1.97 (quint like, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 134.5, 129.9, 126.6, 125.4, 68.5, 53.2, 44.8, 26.7, 18.8. IR (film, cm^{-1}): ν 2958, 1458, 1351, 1192, 967, 748. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{11}H_{15}NNa$, 184.1097; found, 184.1090.

*1-Methyl-2-(2′,4′-dimethylphenyl)azetidine (**1e**).* The compound was prepared according to general procedure A and purified by flash column chromatography (SiO_2, dry loaded, CH_2Cl_2/MeOH 90:10) to afford the title azetidine as a colorless oil. R_f = 0.60; 67% yield, 1.174 g. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 7.7 Hz, 2H), 6.96 (s, 1H), 4.04 (t, J = 8.1 Hz, 1H), 3.47 (t, J = 7.6 Hz, 1H), 2.94−2.90 (m, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H), 1.95 (quint like, J = 9.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 136.1, 134.4, 130.8, 126.8, 125.5, 68.4 (C_q), 53.2, 44.9, 27.0, 21.2, 18.8. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{18}N$, 176.1439; found, 176.1434. FT-IR (film, cm^{-1}): ν 2958, 2770, 1446, 1350, 1193, 967, 809.

General Preparations of 1-Borane-1-alkyl-2-arylazetidines (2a−e/3a−e). For procedure A, to a solution of 1-alkyl-2-arylazetidines **1a−e** (10.6 mmol) in 8 mL of THF was added a solution of BH_3·THF (1 M in THF) dropwise (13.73 mmol, 1.3 equiv) at 0 °C. The solution was stirred at 0 °C for 5 min and then at room temperature for 10 min. The solvent was distilled off under reduced pressure to give a diastereomeric mixture of 1-borane-1-alkyl-2-arylazetidines **2a−e**/**3a−e**.

For procedure B, isomerization of 1-borane-1-methyl-2-arylazetidines **2a**, **2d**, and **2e**. A solution of 1-borane-1-methyl-2-arylazetidine (10.6 mmol) in 8 mL of 2-MeTHF was stirred at 80 °C under reflux

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

for 6 h and then cooled at room temperature. The solvent was distilled off under reduced pressure to give a mixture of 1-borane-1-alkyl-2-arylazetidines **2a,d-e**/**3a,d-e** (dr 3:2; see Table 1).

(1S,2R*)-1-Borane-1-methyl-2-phenylazetidine (**2a**).* Waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 70% yield, 1.195 g (procedure A), 14% yield, 239 mg (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.44−7.39 (m, 5H), 4.75 (dd, J = 10.9, 8.0 Hz, 1H), 3.61 (td, J = 8.8, 2.5 Hz, 1H), 3.55 (quart like, J = 8.7, 1H), 3.17 (quint like, J = 10.1, 1H), 2.82 (s, 3H), 2.29 (dtd, J = 10.6, 7.9, 2.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 133.8 (C_q), 129.6, 129.5, 128.2, 74.2, 59.8, 53.8, 20.5. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −14.6 (q, J_{B-H} = 100.7 Hz). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{10}H_{17}BN$, 162.1454; found, 162.1433. FT-IR (ATR, cm^{-1}): ν 2969, 2265, 1451, 1150, 750.

(1R,2R*)-1-Borane-1-methyl-2-phenylazetidine (**3a**).* Waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 17% yield, 290 mg (procedure A), 70% yield, 1.195 g (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.45−7.39 (m, 5H), 5.25 (t, J = 8.6 Hz, 1H), 3.99 (q, J = 8.6 Hz, 1H), 3.37$_5$ (td, J = 9.8, 5.6 Hz, 1H), 2.84−2.77 (m, 1H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 133.7 (C_q), 129.5, 129.0, 128.8, 73.0, 59.5, 45.6, 19.0. ^{11}B NMR (160 MHz, THF-d_8, ppm): δ −8.7 (q, J_{B-H} = 96.8 Hz). HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{10}H_{17}BN$, 162.1454; found, 162.1439. FT-IR (film, cm^{-1}): ν 2967, 2260, 1453, 1360, 883. For (1*R*, 2*R*)-1-borane-1-methyl-2-phenylazetidine ((1*R*,2*R*)-**3a**), the enantiomeric ratio (er = 85:15) of the optically active diastereoisomer was determined by HPLC analysis (Supporting Information, page S3), $[\alpha]_D^{20}$ −106 (c 1, $CHCl_3$).

(1R,2S*)- and (1R*,2R*)-1-Borane-1-ethyl-2-phenylazetidine (**2b/3b**).* Waxy solid, prepared following procedure A, 98% yield, 1.819 g, inseparable mixture of stereoisomers (**2b** major/**3b** minor = 90:10). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50−7.37 (m, 5H major, 5H minor), 5.34 (t like, J = 8.1 Hz, 1H minor), 4.75 (t like, J = 9.2 Hz, 1H major), 3.82−3.72 (m, 1H minor), 3.67−3.60 (m, 2H minor), 3.54−3.49 (m, 1H major), 3.47−3.43 (m, 1H major), 3.20−3.08 (m, 2H major), 3.00−2.95 (m, 1H major), 2.83−2.76 (m, 1H minor), 2.68−2.62 (m, 1H minor), 2.46−2.36 (m, 1H minor), 2.27 (dt, J = 13.2, 5.1 Hz, 1H major), 1.24 (t, J = 7.3 Hz, 3H major), 0.99 (t, J = 7.2 Hz, 3H minor). ^{13}C NMR major (150 MHz, $CDCl_3$): δ 134.4, 130.0, 129.2, 128.0, 73.8, 60.7, 56.8, 20.7, 9.9. ^{11}B NMR (160 MHz, $CDCl_3$): δ major −16.31 (q, J_{B-H} = 96.3 Hz), minor −11.27 (q, J_{B-H} = 94.9 Hz). FT-IR (ATR, cm^{-1}): ν 2970, 2258, 1449, 1160, 961. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{11}H_{18}BNNa$, 198.1430; found, 198.1425. IR (film, cm^{-1}): ν 2970, 2258, 1449, 1160, 961.

(1R,2S*)- and (1R*,2R*)-1-Borane-1-tert-butyl-2-phenylazetidine (**2c/3c**).* White solid, mp 255 °C (dec), prepared following procedure A, 98% yield, 2.110 g, inseparable mixture of diastereoisomers (**2c** major/**3c** minor = 95:5). Selected signals of major **2c**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.56 (m, 2H), 7.42−7.29 (m, 3H), 5.25 (t like, J = 9.5 Hz, 1H), 3.73 (q like, J = 8.5 Hz, 1H), 3.22 (t like, J = 9.0 Hz, 1H), 3.10 (quint like, J = 10.0 Hz, 1H), 2.15−2.07 (m, 1), 1.34 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 135.5, 131.5, 129.0, 127.7, 66.4, 62.2, 52.0, 25.7, 20.5. ^{11}B NMR (160 MHz, $CDCl_3$): δ −17.49 (q, J_B = 95.1 Hz). FT-IR (ATR, cm^{-1}): ν 2980, 2292, 1392, 1286, 909. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{13}H_{22}BNNa$, 226.1743; found, 226.1735. IR (film, cm^{-1}): ν 2980, 2292, 1392, 1286, 909.

(1R,2S*)-1-Borane-1-methyl-2-(ortho-tolyl)azetidine (**2d**).* Waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 5% yield, 93 mg (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.76−7.74 (m, 1H), 7.32−7.27 (m, 2H), 7.20−7.18 (m, 1H), 5.08$_5$ (dd, J = 10.5, 8.2 Hz, 1H), 3.60 (td, J = 9.0, 3.0 Hz, 1H), 3.55 (dd, J = 17.7, 8.7, 1H), 3.18 (quint like, J = 10.1 Hz, 1H), 2.88 (s, 3H), 2.41 (s, 3H), 2.27 (dtd J = 11.2, 8.1, 3.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 137.4 (C_q), 132.1 (C_q), 130.9, 130.5, 129.3, 125.8, 70.5, 59.3, 54.9, 20.7, 20.5. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −14.4 (q, J_{B-H} = 98.5 Hz). FT-IR (ATR, cm^{-1}): ν 2968, 2249, 1448, 1165, 760. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{11}H_{18}BNNa$, 198.1430; found, 198.1428. IR (film, cm^{-1}): ν 2969, 2270, 1449, 1175, 770.

(1R,2R*)-1-Borane-1-methyl-2-(ortho-tolyl)azetidine (**3d**).* Waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 81% yield, 1.503 g (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.53−7.51 (m, 1H), 7.34−7.26 (m, 3H), 5.44 (dd, J = 9.0, 6.1 Hz, 1H), 3.89 (td, J = 9.2, 5.6 Hz, 1H), 3.49 (q like, J = 9.4 Hz, 1H), 2.97−2.89 (m, 1H), 2.66−2.59 (m, 1H), 2.47 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 140.0 (C_q), 132.3 (C_q), 131.4, 129.6, 127.9, 126.3, 70.1, 60.1, 46.4, 20.5, 19.5. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −8.86. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{11}H_{18}BNNa$, 198.1430; found, 198.1432. FT-IR (ATR, cm^{-1}): ν 2967, 2258, 1448, 1165, 770.

(1R,2S*)-1-Borane-1-methyl-2-(2,4-dimethylphenyl)azetidine (**2e**).* White solid, mp 114.5−117.5 °C. Column chromatography on silica gel (hexane/AcOEt 8:2): 6% yield, 120 mg (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.62$_5$ (d, J = 8.02 Hz, 1H), 7.11$_5$ (d, J = 8.05 Hz, 1H), 7.01 (s, 1H), 5.04$_5$ (dd, J = 7.45, 9.7 Hz, 1H), 3.58 (td, J = 8.9, 3.0 Hz, 1H), 3.52 (dd, J = 17.7, 8.7 Hz, 1H), 3.15 (quint like, J = 10.1, 1H), 2.86 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H), 2.29−2.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 139.2, 137.2, 131.3, 130.8, 129.2, 126.6, 70.4, 59.2, 54.8, 21.3, 20.8, 20.4. ^{11}B NMR {1H} (160 MHz, $CDCl_3$, ppm): δ −14.5 (s). ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −14.5 (q, J = 93.7 Hz). HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{12}H_{20}BNNa$, 212.1583; found, 212.1591. IR (NaCl, cm^{-1}): ν 2970, 2262, 1614, 1448, 1169, 800.

(1R,2R*)-1-Borane-1-methyl-2-(2,4-dimethylphenyl)azetidine (**3e**).* White solid, mp 40.7−41.9 °C. Column chromatography on silica gel (hexane/AcOEt 8:2): 79% yield, 1.583 g (procedure B). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.39 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 7.39 (d, J = 7.9 Hz, 1H), 5.40 (dd, J = 9.0, 6.2 Hz, 1H), 3.87 (td, J = 9.3, 5.6 Hz, 1H), 3.46 (dd, J = 18.0, 9.4 Hz, 1H), 2.95−2.85 (m, 1H), 2.63−2.55 (m, 1H), 2.43 (s, 3H), 2.34 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, ppm): δ 139.7, 139.4, 132.1, 129.2, 127.7, 126.8, 69.8, 59.8, 46.2, 21.1, 20.3, 19.4. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −9.0 (q, J = 100.4 Hz). IR (NaCl, cm^{-1}): ν 2967, 2263, 1615, 1450, 1167, 809. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{12}H_{20}BNNa$, 212.1583; found, 212.1592.

General Procedure of a Metalation/Electrophile Trapping Sequence for the Synthesis of 1-Borane-1-methyl-2,2-Disubstituted Azetidines. To a solution of (1*R**,2*R**)-1-borane-1-methyl-2-phenylazetidine (**3a**) (70 mg, 0.43 mmol) in dry THF (8 mL), under an inert atmosphere, stirred at −50 °C was added a solution of *sec*-BuLi (1.4 M hexane solution, 1.29 mmol, 3 equiv) dropwise. The solution was stirred at −50 °C for 5 min, and then the electrophile was added. The reaction was stirred at the same temperature for a variable time (5−120 min) depending on the electrophile used. The reaction was stopped with an aqueous solution of NH_4Cl, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The same procedure has been applied for metalation/deuteration of (1*R**,2*S**)-1-borane-1-methyl-2-phenylazetidine (**2a**).

(1R,2R*)- and (1R*,2S*)-1-Borane-1-methyl-2-deuterium-2-phenylazetidine (**3a-D/2a-D**).* These compounds, as a mixture of diastereoisomers, were prepared following the general procedure [electrophile = CD_3OD (100 μL, excess), stirring with electrophile = 5 min] as a white solid: 99% yield, 69 mg. Selected data for major **3a-D**, ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.47−7.38 (m, 5H), 4.00 (q like, J = 8.9 Hz, 1H), 3.37 (td, J = 10.0, 5.6 Hz, 1H), 2.81−2.79 (m, 1H), 2.72−2.64 (m, 1H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 133.6, 129.6, 129.0, 128.8, 72.6 (t, J = 23.2 Hz), 59.5, 45.6, 18.9. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −12.0 (q, J = 93.3 Hz). Selected data for minor **2a-D**, ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.43−7.37 (m, 5H), 3.62−3.51 (m, 2H), 3.14 (q like, J = 9.9 Hz, 1H), 2.81 (s, 3H), 2.31−2.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 133.7, 129.5, 129.4, 128.1, 73.6 (t, J = 20.8 Hz), 59.7, 53.6, 20.4. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −17.1 (s). ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −17.1 (q, J = 103.4 Hz). HRMS (ESI-

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

TOF): m/z [M + Na]$^+$ calcd for $C_{10}H_{15}BDNNa$, 185.1333; found, 185.1341. FT-IR (ATR, cm^{-1}): ν 2968, 2270, 1450, 1150, 750.

*(1R,2R)- and (1R,2S)-1-Borane-1-methyl-2-deuterium-2-phenylazetidine, (1R,2R)-**3a-D**/(1R,2S)-**2a-D**)*. The enantiomeric ratio of both optically active diastereoisomers was determined by HPLC analysis (Supporting Information, pages S3 and S4).

(1R,2R*)-1-Borane-1,2-dimethyl-2-phenylazetidine (**3f**)*. The compound was prepared following the general procedure [electrophile = CH_3I (3 equiv, 1.29 mmol, 132 mg), stirring with electrophile = 5 min] as a waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 68% yield, 51 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.45−7.30 (m, 5H), 4.02−3.96 (m, 1H), 3.23−3.16 (m, 2H), 2.32 (s, 3H), 2.30−2.24 (m, 1H), 1.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 141.2 (C_q), 128.7, 128.4, 125.8, 74.8 (C_q), 57.6, 49.9, 28.7, 27.9. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −13.9 (q, J_{B-H} = 95.3 Hz). HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{11}H_{18}BNNa$, 198.1425; found, 198.1424.

(1R,2R*)-1-Borane-1-methyl-2-benzyl-2-phenylazetidine (**3g**)*. The compound was prepared following the general procedure [electrophile = benzyl bromide (3 equiv, 1.29 mmol, 240 mg), stirring with electrophile = 5 min] as a white solid, mp 132−133 °C. Column chromatography on silica gel (hexane/AcOEt 8:2): 54% yield, 58 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.45−7.01 (m, 8H), 6.56$_S$ (d, J = 7.7 Hz, 2H), 4.18−4.11 (m, 1H), 3.96$_S$ (d, J = 13.3 Hz, 1H), 3.66$_S$ (d, J = 13.3 Hz, 1H), 3.26$_S$ (dt, J = 9.4, 9.3 Hz, 1H), 2.91 (q like, J = 11.8 Hz, 1H), 2.58−2.54 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 139.2 (C_q), 136.1 (C_q), 130.7, 128.7, 128.4, 127.8, 127.3, 126.6, 78.3 (C_q), 57.8, 50.4, 45.0, 24.9. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −13.9 (s). ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −13.9 (q, J = 97.76 Hz). HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{17}H_{22}BNNa$, 274.1741; found, 274.1749. IR (NaCl, cm^{-1}): ν 2324, 1449, 1150, 700.

(1R,2S*)-1-Borane-1-methyl-2-benzyl-2-phenylazetidine (**2g**)*. The compound was prepared following the general procedure [electrophile = benzyl bromide (3 equiv, 1.29 mmol, 240 mg), quenching time= 5 min] as a waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 30% yield, 32 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.45−6.94 (m, 8H), 6.52 (d, J = 8.5 Hz, 2H), 3.82−3.68 (m, 2H), 3.50 (d, J = 12.0 Hz, 1H), 3.37 (d, J = 12.0 Hz, 1H), 3.11 (q, J = 10.7 Hz, 1H), 2.97 (s, 3H), 2.36−2.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.0 (C_q), 134.9 (C_q), 130.7 (2C), 128.0, 127.8, 127.4, 127.1, 126.9, 78.0 (C_q), 58.6, 46.3, 42.9, 24.8. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −11.1 (s). HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{17}H_{22}BNNa$, 274.1741; found, 274.1747. IR (NaCl, cm^{-1}): ν 2324, 1448, 1147, 700.

(1R,2R*)-1-Borane-1-methyl-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine (**3h**)*. The compound was prepared following the general procedure [electrophile = 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv, 1.29 mmol, 240 mg), quenching time = 120 min] as a pale yellow waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 67% yield, 82 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.50−7.48 (m, 2H), 7.39−7.36 (m, 2H), 7.33−7.29 (m, 1H), 4.09 (dd, J = 17.7, 8.9 Hz, 1H), 3.26 (td, J = 9.4, 4.6 Hz, 1H), 2.95−2.89 (m, 1H), 2.85−2.79 (m, 1H), 2.24 (s, 3H), 1.26 (s, 6H), 1.22 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 137.6 (C_q), 128.2, 128.2, 128.1, 84.8 (C_q), 60.2, 47.6, 24.9, 23.3. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ 30.5 (s), −10.2 (q, 90.9 Hz). HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{16}H_{27}B_2NNaO_2$, 310.2126; found, 310.2130. (1*R*,2*R*)-1-Borane-1-methyl-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine (1*R*,2*R*)-**3h**. $[\alpha]_D$ −2 (c 0.5, $CHCl_3$). The enantiomeric ratio of the optically active diastereoisomer was determined by HPLC analysis (Supporting Information, page S5).

*2-(1-Methyl-2-phenylazetidin-2-yl)-propan-2-ol (**5a**)*. The compound was prepared following the general procedure [electrophile = dry acetone (5 equiv, 2.05 mmol, 118 mg), stirring with electrophile = 30 min] as a pale yellow solid, mp 65−68 °C. Column chromatography on silica gel (CH_2Cl_2/MeOH 85:15): 70% yield, 62 mg. ^{1}H NMR (500 MHz, CD_3OD, ppm): δ 7.49−7.41 (m, 5H), 4.02 (s, 1H), 3.42−3.38 (m, 1H), 3.33−3.31 (m, 1H), 3.07−3.02 (m, 1H), 2.96−2.90 (m, 1H), 2.85 (s, 3H), 1.26 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD, ppm): δ 129.8 (3C), 129.1, 85.5 (C_q), 74.5, 52.6, 41.4, 26.4, 25.3, 25.1. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO$, 206.1539; found, 206.1542. IR (NaCl, cm^{-1}): ν 3326, 2915, 1446, 1263, 1099.

*tert-Butyl(1-methyl-2-phenylazetidin-2-yl)-phenylmethylcarbammate (**5b**)*. The compound was prepared as an isolated diastereomer, whose dr and stereochemistry are not assigned, following the general procedure [electrophile = *tert*-butylbenzylidenecarbamate (2.5 equiv, 1.25 mmol, 210 mg), stirring with electrophile = 60 min], as a pale yellow oil. Column chromatography on silica gel (hexane/AcOEt 8:2): 65% yield, 98 mg. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.39−7.30 (m, 3H), 7.26−7.22 (m, 2H), 7.07−7.02 (m, 2H), 6.85−6.82 (m, 2H), 3.31−3.26 (m, 1H), 2.75−2.47 (m, 1H), 2.14−1.97 (m, overlapping 2.01 (s, 3H) 1H), 1.45−1.33 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 156.2 (C_q), 139.1 (C_q), 136.5, 128.6, 127.9, 127.4, 127.1, 126.5, 79.2, 74.4, 59.9 (C_q), 49.6, 38.9, 28.3, 23.2. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{22}H_{29}N_2O_2$, 353.2224; found, 353.2224. IR (NaCl, cm^{-1}): ν 2922, 1720, 1454, 1366, 246, 1168, 1099, 700.

*tert-Butyl(1-methyl-2-phenylazetidin-2-yl)carboxylate (**5c**)*. The compound was prepared following the general procedure [electrophile = di-*tert*-butyl dicarbonate (2.5 equiv, 1.25 mmol, 273 mg), stirring with electrophile = 30 min] as a waxy solid. Column chromatography on silica gel (hexane/AcOEt 7:3): 77% yield, 82 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.47−7.23 (m, 5H), 3.36−3.26 (m, 2H), 2.87−2.82 (m, 1H), 2.37 (s, 3H), 2.38−2.34 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8 (C_q), 142.1 (C_q), 128.1, 127.0, 125.3, 81.5 (C_q), 75.0 (C_q), 51.5, 39.81, 29.3, 28.1. IR (NaCl, cm^{-1}): ν 2928, 1719, 1447, 1367, 1255, 1162, 1121, 698. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{15}H_{22}NO_2$, 248.1651; found, 248.1644.

*(Cinnamyl(methyl)ammonio)trihydroborate (**4**)*. The compound was prepared as a waxy solid. Column chromatography on silica gel (hexane/AcOEt 8:2): 10% yield, 7 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.47−7.28 (m, 5H), 6.63 (d, J = 15.9 Hz, 1H), 6.31 (ddd, J = 15.8, 8.1, 6.4 Hz, 1H), 3.75−3.70 (m, 1H), 3.32 (dtd, J = 13.5, 7.9, 0.7 Hz, 1H), 2.57 (d, J = 5.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 137.1, 135.8 (C_q), 128.9, 128.6, 126.8, 121.6, 59.0, 41.3. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −9.4 (q, J_{B-H} = 98.4 Hz). IR (ATR, cm^{-1}): ν 3187, 2945, 2262, 1158, 969. HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{10}H_{16}BNNa$, 184.1273; found, 184.1265. IR (film, cm^{-1}): ν 2959, 1452, 1190, 964, 745.

Metalation/Deuteration Procedure of (1R,2R*)-1-Borane-1-methyl-2-(ortho-tolyl)azetidine (**3d**)*. To a solution of (1*R*,2*R*)-1-borane-1-methyl-2-(*ortho*-tolyl)azetidine (**3d**) (0.29 mmol, 51 mg) in 5 mL of dry THF stirred at −50 °C was added a solution of *sec*-BuLi (1.4 M hexane solution, 0.87 mmol, 3 equiv) dropwise, and the solution was stirred at a low temperature for 5 min. Then, 100 μL of CD_3OD (excess) was added, and after 5 min, the reaction was quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude product of the reaction was purified by flash chromatography (hexane/AcOEt = 7:3).

*1-Borane-3-deuterio-3-(2-(2-methylbutyl)phenyl)propyl)-methylammonium (**7**)*. The compound was prepared as a diastereomeric mixture and as a waxy solid, and stereochemistry and dr were not assigned. Column chromatography on silica gel (hexane/AcOEt 8:2): 75% yield, 51 mg. Selected data for the major isomer, ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.16−7.11 (m, 4H), 2.97−2.89 (m, 1H), 2.71−2.60 (m, 3H), 2.52 (s, 3H), 2.36 (ddd, J = 13.7, 8.4, 2.3 Hz, 1H), 1.96 (q, J = 7.7 Hz, 2H), 1.63−1.55 (m, 1H), 1.46−1.38 (m, 1H), 1.24−1.17 (m, 1H), 0.92 (t, J = 7.4 Hz, 3H), 0.86$_S$ (d, J = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 139.3 (C_q), 138.4, 130.5, 128.9, 126.2, 126.1, 56.9, 42.1, 39.9, 36.4, 29.5, 29.5 (t, J = 19.3 Hz), 27.8, 19.0, 11.6. ^{11}B NMR (160 MHz, $CDCl_3$, ppm): δ −14.7$_S$ (q, J = 91.4 Hz). HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{15}H_{27}BDNNa$, 257.2272; found, 257.2285. IR (ATR, cm^{-1}): ν 3022, 2964, 2289, 1735, 1371.

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX

General Procedure for *N*-Deborylation of 1-Borane-1-methyl-2-phenylazetidines (3f−g). In a reaction flask, 0.167 mmol of α-functionalized 1-borane-1-methyl-2-phenylazetidine was dissolved in AcOEt (3 mL). An aqueous solution of NH_3 28% (1 mL) was added, and the solution was stirred at 90 °C under reflux for 3 h. The crude product of the reaction was dried over Na_2SO_4, filtered, and evaporated under reduced pressure.

*1-Methyl-2-benzyl-2-phenylazetidine (**5d**).* The compound was prepared following the general procedure as a colorless oil. Column chromatography on silica gel (Et_2O): 91% yield, 36 mg. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.25−7.06 (m, 6H), 6.98−6.90 (m, 2H), 6.76−6.68 (m, 2H) 3.49−3.42 (m, 1H), 3.37 (d, *J* = 12.57 Hz, 1H), 3.27 (td, *J* = 8.2, 6.8 Hz, 1H), 3.05 (d, *J* = 12.57 Hz, 1H), 2.57 (s, 3H), 2.44−2.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 146.8 (C_q), 137.5 (C_q), 130.7, 127.8, 127.7, 126.4, 126.1, 125.8, 71.5 (C_q), 51.2, 40.8, 38.7, 28.3. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N$ 238.1590; found, 238.1596.

*N-Methyl-3-phenylbut-3-en-1-amine (**6**).* The compound was prepared following the general procedure as a brown oil. Column chromatography on silica gel (hexane/AcOEt 8:2): 90% isolated yield, 24 mg. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.28 (m, 5H), 5.40 (s, 1H), 5.21 (s, 1H), 3.12−3.08 (m, 2H), 3.02−2.99 (m, 2H), 2.76 (s, 3H), 2.01 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.2, 138.9, 128.8, 128.2, 126.0, 115.6, 56.9, 43.1, 30.6. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}N$ 162.1283; found, 162.1277.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01441.

Crystal data for compound **2d** (CIF)

Characterization of new compounds (^{1}H, ^{13}C, and ^{11}B NMR, COSY, HSQC, and NOESY spectra), HPLC analysis of enantioenriched compounds, computational data for compounds **2a**, **2d**, **3a**, and **3d**, and X-ray analysis of **2d** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: leonardo.degennaro@uniba.it.

*E-mail: renzo.luisi@uniba.it.

ORCID

Giuseppe Romanazzi: 0000-0001-5053-7883

Leonardo Degennaro: 0000-0002-2187-9419

Renzo Luisi: 0000-0002-9882-7908

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the project Laboratorio Sistema code PONa300369 financed by MIUR, the University of Bari. We are grateful to Marina Zenzola for the precious contribution in the preparation of some compounds studied in this work.

■ REFERENCES

(1) (a) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-release amination. *Science* **2016**, *351*, 241−246. (b) Maetani, M.; Zoller, J.; Melillo, B.; Verho, O.; Kato, N.; Pu, J.; Comer, E.; Schreiber, S. L. Synthesis of a bicyclic azetidine with in vivo antimalarial activity enabled by stereospecific, directed C(sp3)-H arylation. *J. Am. Chem. Soc.* **2017**, *139*, 11300−11306.

(2) (a) Brandi, A.; Cicchi, S.; Cordero, F. M. Novel Syntheses of Azetidines and Azetidinones. *Chem. Rev.* **2008**, *108*, 3988−4035. (b) Couty, F.; Evano, G. Azetidines: New Tools for the Synthesis of Nitrogen Heterocycles. *Synlett* **2009**, *2009*, 3053−3064. (c) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257−8322. (d) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. Small Heterocycles in Multicomponent Reactions. *Chem. Rev.* **2014**, *114*, 8323−8359. (e) Han, M.; Song, C.; Jeong, N.; Hahn, H.-G. Exploration of 3-Aminoazetidines as Triple Reuptake Inhibitors by Bioisosteric Modification of 3-α-Oxyazetidine. *ACS Med. Chem. Lett.* **2014**, *5*, 999−1004.

(3) (a) Han, Y.; Han, M.; Shin, D.; Song, C.; Hahn, H.-G. Exploration of Novel 3-Substituted Azetidine Derivatives As Triple Reuptake Inhibitors. *J. Med. Chem.* **2012**, *55*, 8188−8192. (b) Bräuner-Osborne, H.; Bunch, L.; Chopin, N.; Couty, F.; Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. Azetidinic amino acids: stereocontrolled synthesis and pharmacological characterization as ligands for glutamatereceptors and transporters. *Org. Biomol. Chem.* **2005**, *3*, 3926−3936. (c) Honcharenko, D.; Zhou, C.; Chattopadhyaya, J. Modulation of Pyrene Fluorescence in DNA Probes Depends upon the Nature of the Conformationally Restricted Nucleotide. *J. Org. Chem.* **2008**, *73*, 2829−2842. (d) Maetani, M.; Kato, N.; Jabor, V. A. P.; Calil, F. A.; Nonato, M. C.; Scherer, C. A.; Schreiber, S. L. Discovery of Antimalarial Azetidine-2-carbonitriles That Inhibit P. falciparumDihydroorotate Dehydrogenase. *ACS Med. Chem. Lett.* **2017**, *8*, 438−442.

(4) (a) Couty, F. In *Science of Synthesis*; Schaumann, E., Enders, D., Eds.; Thieme: Stuttgart, 2009; Vol. *40a*, pp 773−816. (b) Rousseau, G.; Robin, S. In *Modern Heterocyclic Chemistry*, 1st ed.; Alzerez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. *1*, pp 163−268. (c) Schnitzer, T.; Wennemers, H. Influence of the Trans/Cis Conformer Ratio on the Stereoselectivity of Peptidic Catalysts. *J. Am. Chem. Soc.* **2017**, *139*, 15356−13362.

(5) Kirichok, A. A.; Shton, I. O.; Pishel, I. M.; Zozulya, S. A.; Borysko, P. O.; Kubyshkin, V.; Zaporozhets, O. A.; Tolmachev, A. A.; Mykhailiuk, P. K. Synthesis of Multifunctional Spirocyclic Azetidines and Their Application in Drug Discovery. *Chem. - Eur. J.* **2018**, *24*, 5444−5449.

(6) (a) Degennaro, L.; Antermite, D.; Luisi, R. Recent advances in the chemistry of metallated azetidines. *Org. Biomol. Chem.* **2017**, *15*, 34−50. (b) Hodgson, D. M.; Pearson, C. I.; Thompson, A. L. α-Lithiation−Electrophile Trapping of N-Thiopivaloylazetidin-3-ol: Stereoselective Synthesis of 2-Substituted 3-Hydroxyazetidines. *J. Org. Chem.* **2013**, *78*, 1098−1106.

(7) Parisi, G.; Zenzola, M.; Capitanelli, E.; Carlucci, C.; Romanazzi, G.; Pisano, L.; Degennaro, L.; Luisi, R. Exploiting structural and conformational effects for a site-selective lithiation of azetidines. *Pure Appl. Chem.* **2016**, *88*, 631−648.

(8) Parisi, G.; Capitanelli, E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. Easy access to constrained peptidomimetics and 2,2-disubstituted azetidines by the unexpected reactivity profile of α-lithiated *N*-Boc-azetidines. Chem. *Chem. Commun.* **2015**, *51*, 15588−15591.

(9) Zenzola, M.; Degennaro, L.; Trinchera, P.; Carroccia, L.; Giovine, A.; Romanazzi, G.; Mastrorilli, P.; Rizzi, R.; Pisano, L.; Luisi, R. Harnessing the *ortho*-Directing Ability of the Azetidine Ring for the Regioselective and Exhaustive Functionalization of Arenes. *Chem. - Eur. J.* **2014**, *20*, 12190−12200.

(10) (a) Degennaro, L.; Trinchera, P.; Luisi, R. Recent Advances in the Stereoselective Synthesis of Aziridines. *Chem. Rev.* **2014**, *114*, 7881−7929. (b) de Ceglie, M. C.; Musio, B.; Affortunato, F.; Moliterni, A.; Altomare, A.; Florio, S.; Luisi, R. Solvent- and Temperature-Dependent Functionalisation of Enantioenriched Aziridines. *Chem. - Eur. J.* **2011**, *17*, 286−296. (c) Affortunato, F.; Florio, S.; Luisi, R.; Musio, B. *α- vs* Ortho-Lithiation of N-Alkylarylaziridines: Probing the Role of the Nitrogen Inversion Process. *J. Org. Chem.* **2008**, *73*, 9214−9220. (d) Degennaro, L.; Pisano, L.; Parisi, G.; Mansueto, R.; Clarkson, G. J.; Shipman, M.; Luisi, R. Nitrogen

Stereodynamics and Complexation Phenomena as Key Factors in the Deprotonative Dynamic Resolution of Alkylideneaziridines: A Spectroscopic and Computational Study. *J. Org. Chem.* **2015**, *80*, 6411−6418.
(11) (a) Couty, F.; David, O.; Larmanjat, B.; Marrot, J. Strained Azetidinium Ylides: New Reagents for Cyclopropanation. *J. Org. Chem.* **2007**, *72*, 1058−1061. (b) Lo, C.; David, O.; Couty, F. Alkylation/elimination from azetidinium ylides: an entry to functionalized acrylonitriles. *Tetrahedron Lett.* **2014**, *55*, 535−537. (c) Drouillat, B.; d'Aboville, E.; Bourdreux, F.; Couty, F. Synthesis of 2-Phenyl- and 2,2-Diarylpyrrolidines through Stevens Rearrangement Performed on Azetidinium Ions. *Eur. J. Org. Chem.* **2014**, *2014*, 1103−1109.
(12) (a) Tayama, E.; Watanabe, K.; Matano, Y. Ring-Strain Effects in Base-Induced Sommelet−Hauser Rearrangement: Application to Successive Stereocontrolled Transformations. *Eur. J. Org. Chem.* **2016**, *21*, 3631−3641. (b) Tayama, E.; Watanabe, K.; Sotome, S. Structural and mechanistic studies of the base-induced Sommelet−Hauser rearrangement of N-α-branched benzylic azetidine-2-carboxylic acid-derived ammonium salts. *Org. Biomol. Chem.* **2017**, *15*, 6668−6678.
(13) Casoni, G.; Myers, E. L.; Aggarwal, V. K. Synthesis of 3-Aryl-1-aminopropane Derivatives: Lithiation−Borylation−Ring-Opening of Azetidinium Ions. *Synthesis* **2016**, *48*, 3241−3253.
(14) Azzena, U.; Dettori, G.; Pisano, L.; Musio, B.; Luisi, R. BH_3-Promoted Stereoselective β-Lithiation of N-Alkyl-2-phenylaziridines. *J. Org. Chem.* **2011**, *76*, 2291−2295.
(15) The CCDC depository number for **2d** is 1845835.
(16) Shipman and co-workers reported that structural factors could affect the B−N dative bonds in azetidine boronate complexes: Hoang, C. T.; Prokes, I.; Clarkson, G. J.; Rowland, M. J.; Tucker, J. H. R.; Shipman, M.; Walsh, T. R. Study of boron−nitrogen dative bonds using azetidine inversion dynamics. *Chem. Commun.* **2013**, *49*, 2509−2511.
(17) Musio, B.; Clarkson, G. J.; Shipman, M.; Florio, S.; Luisi, R. Synthesis of Optically Active Arylaziridines by Regio- and Stereospecific Lithiation of N-Bus-Phenylaziridine. *Org. Lett.* **2009**, *11*, 325−328.
(18) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225. (b) Gessner, V. H.; Strohmann, C. Lithiation of TMEDA and its Higher Homologous TEEDA: Understanding Observed α- and β-Deprotonation. *J. Am. Chem. Soc.* **2008**, *130*, 14412−14413. (c) Strohmann, C.; Gessner, V. H. From the alkyllithium aggregate $[\{(nBuLi)_2.PMDTA\}_2]$ to lithiated PMDTA. *Angew. Chem., Int. Ed.* **2007**, *46*, 4566−4569.
(19) Vedejs, E.; Kendall, J. T.; Prasad, A. S. B.; Russel, J. S. The stereochemistry of aziridine borane lithiation: diastereoselectivity and enantioselectivity. *Tetrahedron* **2003**, *59*, 9849−9856.
(20) It is worth noting that for both **2a** and **3a** lithiation occurs at the benzylic position. Nevertheless, lithiation of **3a** resulted straightforward likely because of the syn relationship of H_a with the BH_3 group. In addition, product **4** was never observed in the lithiation of **3a**.
(21) Attempts to optimize lithiation of **2a** were unsuccessful.
(22) The possibility of inversion at the nitrogen was ruled out as a consequence of the observed stability of complex **3a** in THF (see the Supporting Information).
(23) For literature concerning the stereoselectivity of reactions involving organolithium compounds, see: (a) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds*; RSC Publishing, 2008; pp 207−215. (b) Clayden, J. *Organolithium: Selectivity for Synthesis, Tetrahedron Organic Chemistry Series*; Pergamon Press, 2002; Vol. 23.
(24) Degennaro, L.; Musio, B.; Luisi, R. In *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, Germany, 2014; Chapter 7, pp 191−223.

DOI: 10.1021/acs.joc.8b01441
J. Org. Chem. XXXX, XXX, XXX−XXX