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Azetidine-Borane Complexes: Synthesis, Reactivity and Stereoselective Functionalization

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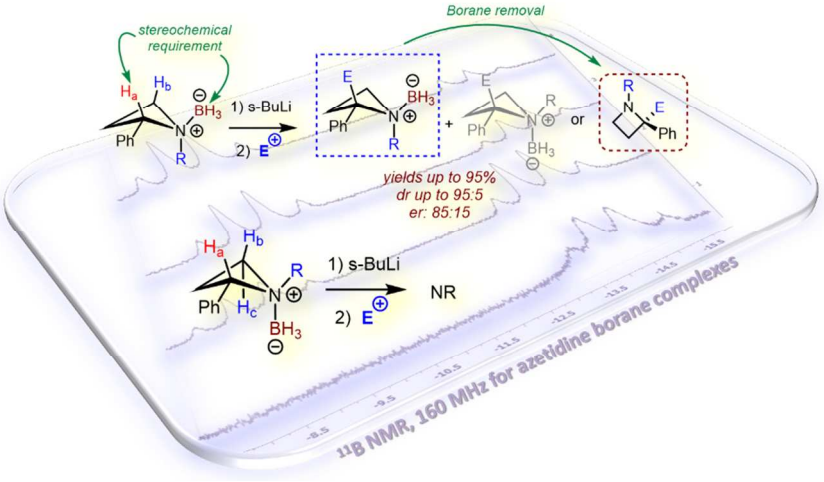


Abstract

The present study reports, for the first time, 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

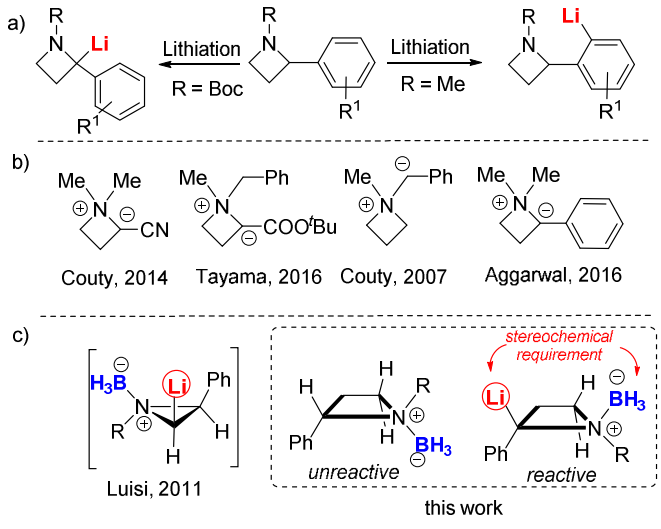
permutation, at the benzylic position, was observed in lithiation reactions of complexes possessing a syn relationship, between the ring proton and the BH_3 group. In contrast, scarce or no reactivity was noticed in complexes lacking such a stereochemical requirement. The configurational stability of 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 1, a).[9]

According to what 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 towards 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 1, b). Holding on previous results on the highly stereo- and regio-selective lithiation of aziridines-borane complexes[14] (Scheme 1, c), we were keen to demonstrate if azetidine-borane complexes could be regioselectively lithiated, and trapped without undergoing ring opening or rearrangement.

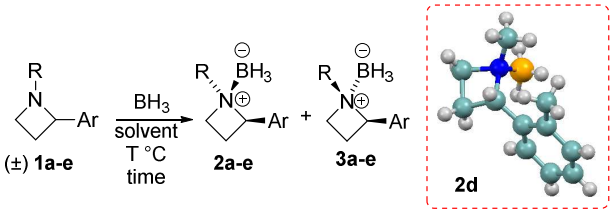


Scheme 1. General aspects on the metalation of azetidines.

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 minutes 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 low temperature (i.e. -78 °C, Table 1, entries 6,7). By contrast, heating a solution of distereomeric complexes (enriched in **2**) up to 80 °C, a switch in the composition was observed in favor of complexes **3** (Table 1, entries 8-11). As exception, complex **2c**, was found stable even at high temperature. 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	Time (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 supporting information for reaction conditions. [c]Diastereomeric ratio established by ^{1}H NMR on the crude reaction mixture. [d] Diasteromeric ratio didn't 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; b) the azetidine's nitrogen inversion. In fact, as reported in Figure 1, it is likely that the solvent could take up the 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 temperature (Table 1, entries 1-7).[17] Nevertheless, higher temperature could affect all 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 performing the complexation reaction in a non polar 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 use as the solvent. Refluxing a solution of **2a** in toluene, and monitoring the progress by ^{1}H NMR (see supporting information), the **2a** → **3a** transition occurred slower than in 2-MeTHF, and after 41 hours 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 promote the isomerization according to the mechanism reported in Figure 1. In order to provide more evidences supporting our hypotheses, we run a NMR and computational investigation on complexes **2a** and **3a**. Complexes **2a** and **3a** were firstly separated by flash chromatography, and separately subjected to ^{11}B and ^{1}H NMR analysis in d_8-THF at 60 °C. In Figure 1 is reported the change observed in the ^{11}B NMR spectra for the transition **2a** → **3a**. A similar experiment was executed on pure complex **3a**, but without any evident change in composition after 3 days in d_8-THF at 60 °C (see Supporting Information). DFT calculations at B3LYP

6-311-G level of theory also confirmed that complex **3a** was 1.4 Kcal/mol more stable than **2a** (see SI), thus supporting the rationale in Figure 1.

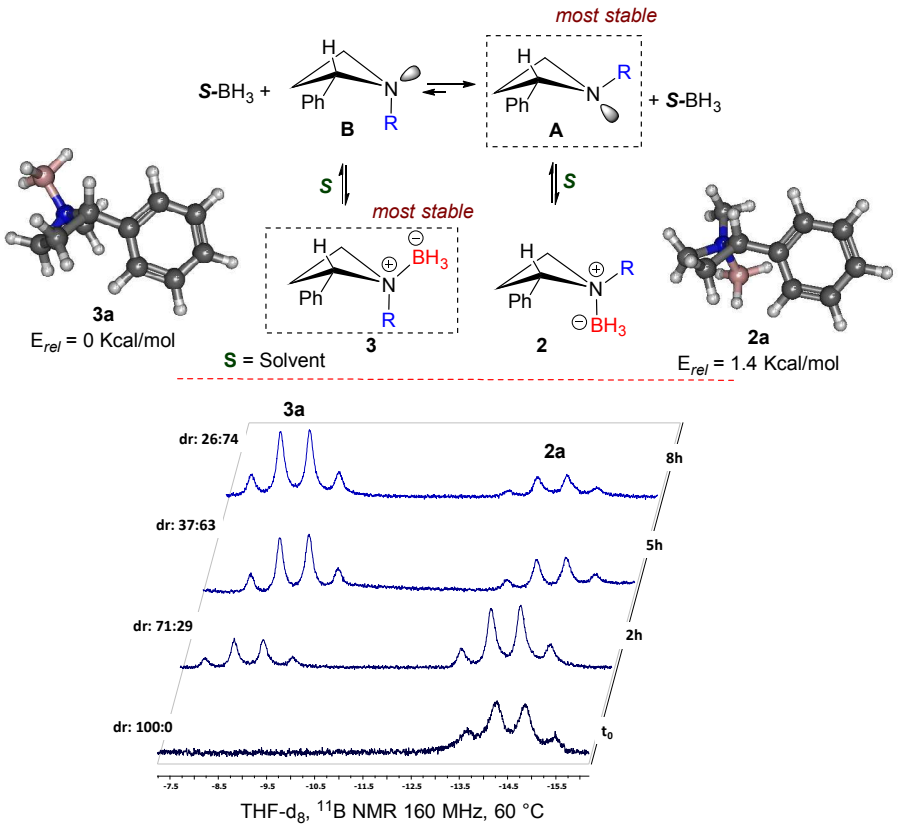
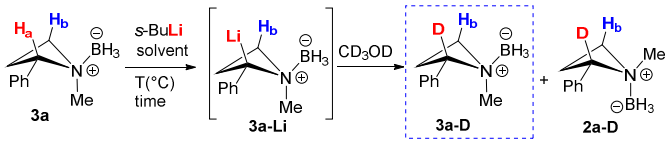


Figure 1. Rationale for temperature – dependent diastereomeric switch for complexes **2** and **3**

Next, we investigated the reactivity of diastereomeric complex **3a** in lithiation reactions. Initially, we tested the conditions used for the lithiation of aziridines-borane complexes.[14] Optimal conditions employed 3 equiv of s-BuLi, at -50 °C in THF for 5 min (Table 2, entry 3). A longer reaction time was needed reducing the equivalent of base (Table 2, entry 1), while lithiation at higher temperature (-20 °C or 0 °C) resulted in lower yield in deuterated products (Table 2, entries 5 and 6). However, all the lithiation experiments, run in THF, led to a diastereomeric mixture of deuterated products **2a-D** and **3a-D** being the latter the most abundant. 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, 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, the lithiation was found highly regioselective being the proton H_a (syn to the BH_3 group) preferentially removed.

Table 2. Lithiation of azetidine borane complex **3a**.

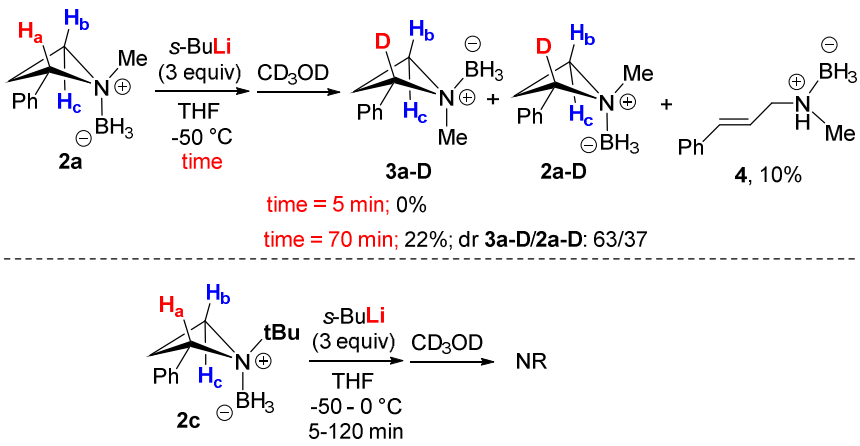


entry	T (°C)	solvent	base (equiv.)	time (min.)	dr 3a-D/2a-D	yield (%)[a]
1	-50	THF	1.5	120	76/24	>99
2	-50	THF	3	60	76/24	>99
3	-50	THF	3	5	79/21	98
4	-78	THF	3	5	75/25	96
5	-20	THF	3	5	37:63	84[b]
6	0	THF	3	5	38:62	52[c]
7	-50	toluene[d]	3	5	38:62	97
8	-50	toluene[d]	3	60	36:64	>99
9	-50	toluene[e]	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 ligand. [e]Reaction run without TMEDA.

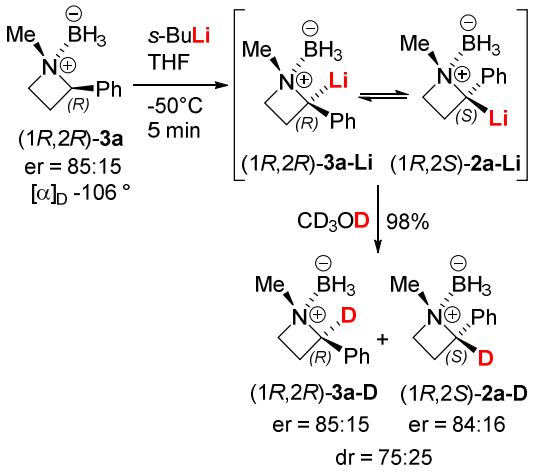
For sake of comparison, we investigated the reactivity of complexes **2a** and **2c** (Scheme 2). In this case, according to what observed with aziridines borane complex, regioselective removal of H_c was expected.[14] Nevertheless, **2a** was found less reactive than **3a**; in fact, when **2a** was reacted with s-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, to 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**, deriving from a β-elimination

reaction, was also found in the reaction mixture. This latter result could be explained considering the thermodynamic acidity of the benzylic position that compete with the propensity of the strained ring to undergoing β-elimination leading to product **4**. The sensible reluctance of **2a** to undergo full deprotonation under the optimal conditions adopted for **3a**, 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]



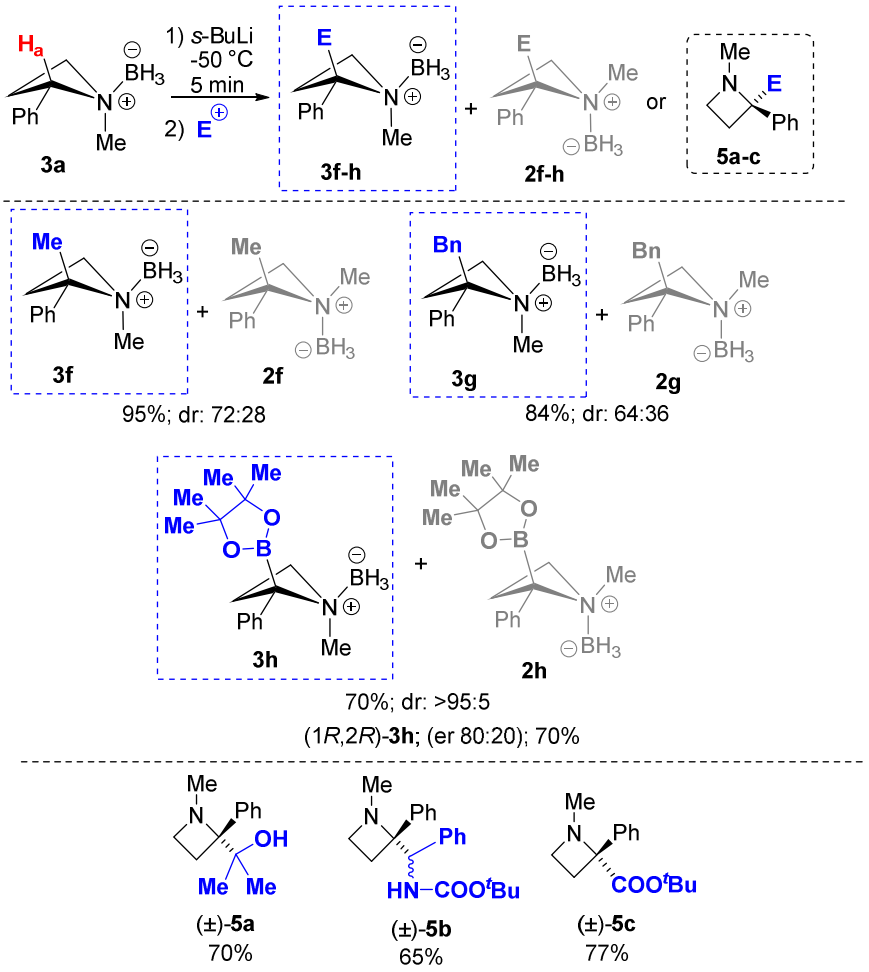
Scheme 2. Reactivity of diastereomeric complexes **2a** and **2c**.

Next, in order to explain the presence of a diastereomeric mixture in the lithiation/trapping experiments, the configurational stability of the lithiated intermediate generate from **3a** was investigated (Scheme 3). Upon lithiation/deuteration 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 75:25 diastereomeric ratio respectively, as ascertained by chiral HPLC analysis (see SI).



Scheme 3. Evaluating the configurational stability of lithiated (1*R*,2*R*)-**3a**.

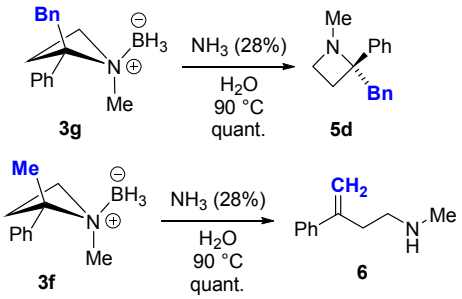
From the experiment run on (1*R*,2*R*)-**3a**, it is possible to conclude that the lithiated intermediates are configurationally unstable, and that exclusive inversion at the lithiated carbon occurs.[22] Based on these results, we investigated the reaction of lithiated complex **3a** with representative electrophiles (Scheme 4). As reported in Scheme 3, alkylation, benzylation, borylation furnished complexes **2f-h** and **3f-h** with good yields and a variable degree of stereoselectivity (Scheme 4). Interestingly, the main diasteromer 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 single diastereomer (Scheme 4).



Scheme 4. Scope of the lithiation/trapping sequence of complex **3a**.

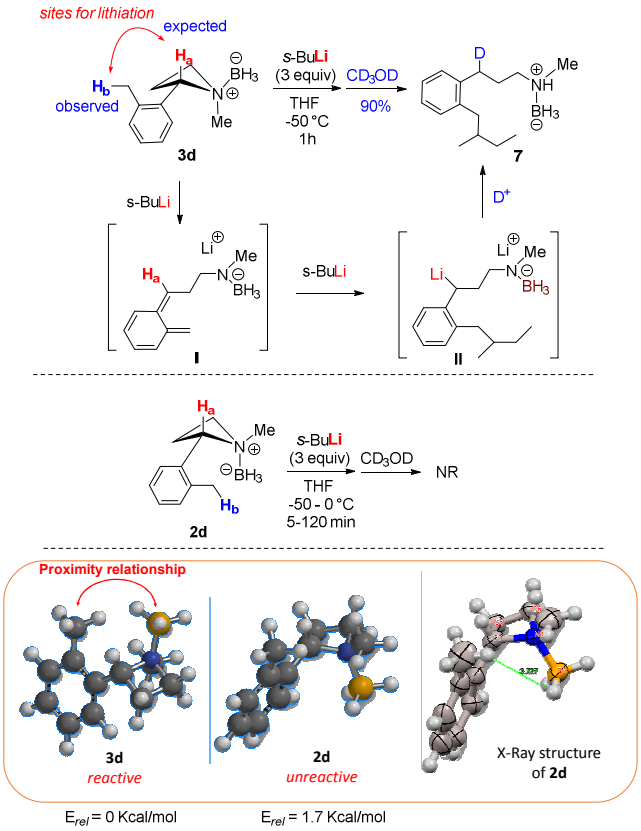
In the reactions with acetone, N-Boc benzylidene imine, and tert-butyldicarbonate the corresponding BH_3-free azetidines **5a-c** were isolated after flash chromatography (see supporting information) probably as a consequence of the presence of a basic site in the product (i.e. O, N) able to interact with the BH_3 group. These results are, in our opinion, remarkable because 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 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**,**g**. As reported in Scheme 5, by refluxing complex **3g** in 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).



Scheme 5. Deprotection of azetidine borane complexes **3**.

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 observed with complex **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 infra).



Scheme 6. Ortho-effect in the lithiation of complexes **2d** and **3d**.

Equilibrium geometries, calculated at 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**, 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 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 towards lithiating agents. This investigation provides useful information on the role of the BH3 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 was 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 hexane solution and was filtered on celite before using and title established by titration method. The solvent toluene was freshly distilled under nitrogen atmosphere over CaH_2. All the chemicals and solvents used were commercially available (TCI Europe, Fluorochem, VWR, Aldrich Chemical Company) and used without further purification. Melting points were incorrected and recorded with Büchi melting point B-545. Resonance spectra were recorded using BRUCKER 300, 600, AGILENT 500 MHz (^{1}H NMR 400, 500, 600 MHz, ^{13}C-NMR 75, 125, 150 MHz e ^{11}B NMR 160 MHz), $CDCl_3$, 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. Infra-red spectra of the compounds were recorded neat, as film, as KBr disc as indicated, by a

Perkin-Elmer 283 spectrometer in reciprocal centimetre (cm^{-1}) or by using ATR spectrophotometer. ESI-MS analysis were performed on Agilent 110 LC/MSD mass spectrometer with ionic single quadrupole trap system and Exalibur data system. Analytical thin layer chromatography (TLC) was performed on precoated silica gel thick plates (Merck) with fluorescence indicator F-254; visualization was performed using a UV lamp (254 nm) or using a $KMnO_4$ 0,02M 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 were 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 reagent sensible to oxygen and water were carried out using nitrogen dry atmosphere. The title of base (*sec*-BuLi) was determined by titration with *N*-phenylbenzamide, following the procedure reported in literature.[24]

General Preparations of 1-alkyl-2-arylazetidines, 1a-c, e.

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, 756 mg of $NaBH_4$ (2 equiv.) were added slowly, and the solution was stirred at room temperature for 2 hours. Methanol was distilled off under reduced pressure and 25 mL of Et_2O and H_2O were added, the aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic phases were dried over Na_2SO_4, filtered and the solvent 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, a solution of $SOCl_2$ (30 mmol, 3 equiv.) in CH_2Cl_2 (3 mL) was added dropwise. After 2 hours 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 x 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 that 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, a solution of R-NH_2 in EtOH (9,7 equiv.) was added. The reaction mixture was refluxed for 24 hours 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 x 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]

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), TMEDA (3.65 mmol, 2.5 equiv.) was added. Subsequently, a solution of hexyllithium (2.3M in hexane, 2.86 mmol, 2 equiv.) was added dropwise and the solution was stirred at room temperature for 1 hour under dry nitrogen atmosphere. After, MeI (3.56 mmol, 2.5 equiv) was added and after 20 minutes the reaction was quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure.

1-Methyl-2-phenylazetidine (1a). 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 colourless oil, Rf = 0.45 (100% Et_2O); 65%, 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}) υ: 2959, 1452, 1190, 964, 745.

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

1-Ethyl-2-phenylazetidine (1b). 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 colourless oil. Rf = 0.40 (100% Et_2O); 61%, 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(Cq), 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}) υ: 2961, 1450, 1191, 964, 752.

1-*terz*-Butyl-2-phenylazetidine (1c). 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 colourless oil. Rf = 0.45 (100% Et_2O); 78%, 1.477g.^{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}) υ: 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). 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 colourless oil. Rf = 0.60; 65%, 150 mg. ^{1}H NMR (400 MHz, CDCl3) 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}) υ: 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). 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 colourless oil. Rf = 0.60; 67%, 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* = 7.6Hz, 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 (Cq), 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}) υ 2958, 2770, 1446, 1350, 1193, 967, 809.

General preparations of 1-borane-1-alkyl-2-arylazetidines 2a-e/3a-e.

Procedure A. To a solution of 1-alkyl-2-arylazetidines **1a-e** (10,6 mmol) in 8 mL of THF a solution of BH_3·THF (1M in THF) was added dropwise (13.73 mmol, 1.3 equiv.) at 0°C. The solution was stirred at 0°C for 5 minutes, then at room temperature for 10 minutes. The solvent was distilled off under reduced pressure to give a diastereomeric mixture of 1-borane-1-alkyl-2-arylazetidines **2a-e**/**3a-e**.

Procedure B: isomerization of 1-borane-1-methyl-2-arylazetidines **2a**, **2d**, **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 for 6 hours, then cooled at room temperature. The solvent was distilled off under reduced pressure to give a mixture of 1-borane-1-alkyl-2-arylazetidine **2a,d-e**/**3a,d-e** (dr 3/2 see table 1).

(1*S, 2*R**)-1-Borane-1-methyl-2-phenylazetidine (2a)**. Waxy solid. Column chromatography on silica gel (Hexane/AcOEt 8:2), 70% yield, 1.195g (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}) υ 2969, 2265, 1451, 1150, 750.

(1*R, 2*R**)-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, $J_{B\text{-}H}$ = 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}) υ 2967, 2260, 1453, 1360, 883. **(1*R*, 2*R*)-1-borane-1-methyl-2-phenylazetidine, (1*R*, 2*R*)-3a.** The enantiomeric ratio (er = 85/15) of optically active diastereoisomer was determined by HPLC analysis (see page S3), $[\alpha]_D^{20}$ = –106 (c = 1, $CHCl_3$).

(1*R, 2*S**)- and (1*R**, 2*R**)-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, $J_{B\text{-}H}$ = 96.3 Hz), minor –11.27 (q, $J_{B\text{-}H}$ = 94.9 Hz). FT-IR (ATR, cm^{-1}) υ 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}) υ: 2970, 2258, 1449, 1160, 961.

(1*R, 2*S**)- and (1*R**, 2*R**)-1-Borane-1-*t*-butyl-2-phenylazetidine (2c/3c)**. White solid, m.p. = 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 the 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 = 95.1Hz). FT-IR (ATR, cm^{-1}) υ 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}) υ: 2980, 2292, 1392, 1286, 909.

(1*R, 2*S**)-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, 8.2Hz, 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, $J_{B\text{-}H}$ = 98.5 Hz). FT-IR (ATR, cm^{-1}) υ 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}) υ: 2969, 2270, 1449, 1175, 770.

(1*R,2*R**)-1-borane-1-methyl-2-(*ortho*-tolyl)azetidine (3d).** Waxy solid. Column chromatography on silica gel (Hexan/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}) υ 2967, 2258, 1448, 1165, 770.

(1*R,2*S**)-1-borane-1-methyl-2-(2,4-dimethylphenyl)azetidine (2e)**. White solid, m.p.= 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}) υ: 2970, 2262, 1614, 1448, 1169, 800.

(1*R, 2*R**) -1-borane-1-methyl-2-(2,4-dimethylphenyl)azetidine (3e)**. White solid, m.p. = 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^{13}C NMR (125 MHz, $CDCl_3$) 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}) υ: 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 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 inert atmosphere, stirred at –50°C a solution of *sec*-BuLi (1,4M hexane solution, 1,29 mmol, 3 equiv.) was added dropwise. The solution was stirred at

–50°C for 5 minutes, then the electrophile was added and the reaction stirred at the same temperature for a variable time (5-120 min) depending of used electrophile. The reaction was stopped with an aqueous solution of NH_4Cl, the aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic phases were dried over Na_2SO_4, filtered and the solvent 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.**

(1*R, 2*R**)-** and **(1*R**, 2*S**)-1-Borane-1-methyl-2-deuterium-2-phenylazetidine (3a-D/2a-D)**. Mixture of diastereoisomers. Prepared following general procedure [Electrophile = CD_3OD (100 μL, excess), stirring with electrophile = 5 minutes], 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-TOF) m/z $[M+Na]^+$ calcd for $C_{10}H_{15}BDNNa$ 185.1333; found 185.1341. FT-IR (ATR, cm^{-1}) υ 2968, 2270, 1450, 1150, 750.

(1*R*, 2*R*)- and **(1*R*, 2*S*)-1-borane-1-methyl-2-deuterium-2-phenylazetidine, (1*R,2R*)-3a-D/(1*R,2S*)-2a-D).** The enantiomeric ratio of both optically active diastereoisomers was determined by HPLC analysis (see page S3-4).

(1*R,2*R**)-1-borane-1,2-dimethyl-2-phenylazetidine (3f)**. Prepared following general procedure [Electrophile = CH_3I (3 equivalents, 1.29 mmol, 132 mg), stirring with electrophile = 5 minutes], 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, $J_{B\text{-}H}$ = 95.3 Hz). HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{18}BNNa$ 198.1425; found 198.1424.

(1*R,2*R**)-1-borane-1-methyl-2-benzyl-2-phenylazetidine (3g)**. Prepared following general procedure [Electrophile = benzyl bromide (3 equivalents, 1.29 mmol, 240 mg), stirring with electrophile = 5 minutes], white solid, m.p. 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_5 (d, J = 7.7 Hz, 2H), 4.18–4.11 (m, 1H), 3.96_5 (d, J = 13.3 Hz, 1H), 3.66_5 (d, J = 13.3 Hz, 1H), 3.26_5 (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 (Cq), 136.1 (Cq), 130.7, 128.7, 128.4, 127.8, 127.3, 126.6, 78.3 (Cq), 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}) υ: 2324, 1449, 1150, 700.

(1*R,2*S**)-1-borane-1-methyl-2-benzyl-2-phenylazetidine (2g)**. Prepared following general procedure [Electrophile = benzyl bromide (3 equivalents, 1.29 mmol, 240 mg), quenching time= 5 minutes], 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 (Cq), 134.9 (Cq), 130.7 (2C), 128.0, 127.8, 127.4, 127.1, 126.9, 78.0 (Cq), 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}) υ: 2324, 1448, 1147, 700.

(1*R,2*R**)-1-borane-1-methyl-2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidine (3h)**. Prepared following general procedure [Electrophile = 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equivalents, 1.29 mmol, 240 mg), quenching time = 120 minutes], 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 optically active diastereoisomer was determined by HPLC analysis (see page S5).

2-(1-Methyl-2-phenylazetidin-2-yl)-propan-2-ol (5a). Prepared following procedure [Electrophile = dry acetone (5 equivalents, 2.05 mmol, 118 mg), stirring with electrophile = 30 minutes]**,** pale yellow solid, m.p. 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 (Cq), 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}) υ: 3326, 2915, 1446, 1263, 1099.

***tert*-Butyl(1-methyl-2-phenylazetidin-2-yl)phenylmethylcarbammate (5b)**. Isolated diastereomer whose dr and stereochemistry are not assigned. Prepared following general procedure [Electrophile = tert-butylbenzylidenecarbamate (2.5 equivalents, 1.25 mmol, 210 mg), stirring with electrophile = 60 minutes], pale yellow oil. Column chromatography on silica gel (Hexane/AcOEt 8:2), 65% yield, 98 mg. ^{1}H NMR (300 MHz, CDCl3, 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, CDCl3, ppm) δ: 156.2 (Cq), 139.1 (Cq), 136.5, 128.6, 127.9, 127.4, 127.1, 126.5, 79.2, 74.4, 59.9 (Cq), 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}) υ: 2922, 1720, 1454, 1366, 246, 1168, 1099, 700.

***tert*-Butyl(1-methyl-2-phenylazetidin-2-yl)carboxylate (5c)**.

Prepared following general procedure [Electrophile = di-tert-butyl dicarbonate (2.5 equivalents, 1.25 mmol, 273 mg), stirring with electrophile = 30 minutes], 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}) υ: 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).

Waxy solid. Column chromatography on silica gel (Hexan/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, $J_{B\text{-}H}$ = 98.4 Hz). IR (ATR, cm^{-1}) υ: 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}) υ: 2959, 1452, 1190, 964, 745.

Metalation/Deuteration Procedure of (1*R, 2*R**)-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, a solution of *sec*-BuLi (1,4M hexane solution, 0,87 mmol, 3 equiv.) was added dropwise and the solution was stirred at low temperature for 5 minutes. Then, 100 µL of CD_3OD (excess) were added and after 5 minutes the reaction was quenched with an aqueous solution of NH_4Cl. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic phases were dried over Na_2SO_4, filtered and solvent removed under reduced pressure. Crude of reaction was purified by flash chromatography (Hexane/ AcOEt = 7:3).

1-borane-3-deuterio-3-(2-(2-methylbutyl)phenyl)propyl)methylammonium (7)

Diastereomeric mixture, stereochemistry and dr not assigned. Waxy solid. 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_5 (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_5 (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}) υ: 3022, 2964, 2289, 1735, 1371.

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 were 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 hours. Crude of reaction was dried over Na_2SO_4, filtered, evaporated under reduced pressure.

1-Methyl-2-benzyl-2-phenylazetidine (5d)

Prepared following general procedure, colourless 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 (Cq), 137.5 (Cq), 130.7, 127.8, 127.7, 126.4, 126.1, 125.8, 71.5 (Cq), 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)**

Prepared following general procedure, brown oil. Column chromatography on silica gel (Hexan/AcOEt 8:2), isolated yield 90%, 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.

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Supporting Information

Supporting Information is available free of charge on the ACS Publications website. Characterization of new compounds (^{1}H and ^{13}C NMR, ^{11}B, COSY, HSQC, NOESY spectra), HPLC analysis of enantioenriched compounds, computational data for compounds **2a, 2d, 3a, 3d**, and X-ray analysis of **2d.**

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[21] Attempts to optimize lithiation of **2a** were unsuccessful.

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