Synthesis of 3-Aryl-1-aminopropane Derivatives: Lithiation–Borylation–Ring-Opening of Azetidinium Ions

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Dedicated to the memory of Professor Jean Normant

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Abstract In situ generated 2-phenyl-azetidinium ylides react with boronic esters to form acyclic γ-dimethylamino tertiary boronic esters. The transformation is believed to involve the formation of a zwitterionic boronate, which subsequently undergoes ring-opening 1,2-migration, which is promoted by the relief of ring strain. Owing to the configurational instability of the initially formed ylides, which appear to be in equilibrium with the open-chain carbene form, the reaction is not stereospecific. The C–B bond of the γ-dimethylamino tertiary boronic esters can be transformed into a variety of functional groups (C–OH, C–vinyl, C–H, C–BF3), thus giving a diverse selection of 3-aryl-1-aminopropanes, which represent a privileged motif among drug molecules.

Key words 3-aryl-1-aminopropanes, azetidinium ion, lithiation, borylation, ring-opening, boronic esters

Boronic esters are arguably the most versatile of organic functional groups. This group can be transformed to introduce C–O, C–N, C–C, or C–X bonds under mild conditions, a characteristic that makes boronic esters (and boronic acids) extremely valuable late-stage intermediates in medicinal chemistry programs. Although this value has mostly been demonstrated in the context of sp2-hybridised boron-bearing carbon centres (the transformation of aryl and vinyl boronic esters and acids through Suzuki–Miyaura cross-coupling), the diversification of sp3-hybridised boron-bearing carbon centres is much less common, despite the identified need to populate compound libraries with such 3D molecules. However, the relatively recent development of robust and generally applicable methods for the enantioselective preparation of secondary and tertiary alkyl boronic esters, together with stereospecific methods for the subsequent transformation of the C–B bonds, is expected to lead to a step-change in the use of organoboron chemistry in the pharmaceutical industry.

One of the most privileged structural motifs among marketed drugs and drug candidates is the 3-aryl-1-aminopropane unit (Figure 1). Bedaquiline, an antituberculosis agent, is one of the more high-profile and structurally complex members of this class of drug molecule (Figure 1). This motif can be introduced through the addition of aryl metal reagents to β-aminoketones, the hydroformylation/reductive amination of styrenes, the Heck–Matsuda addition of aryl halides/pseudohalides to allyl amines and the electrophilic addition of amine-containing electrophiles to diarylmethyl anions.

Figure 1 Marketed drugs containing the 3-aryl-1-aminopropane motif

We were particularly interested in accessing a diverse selection of 3-aryl-1-aminopropanes 1 through C–B functionalisation of γ-dimethylamino tertiary boronic esters (Scheme 1). We envisioned that these boronic ester intermediates could be accessed through lithiation–borylation of...
azetidinium ions 3. Specifically, we hoped that azetidinium ions 3 could be deprotonated to give ylide/lithium-stabilised carbenoid 4, which could then be trapped with boronic ester 5 to give zwitterionic boronate 6, which in turn could undergo ring-opening 1,2-migration to give γ-amino tertiary boronic ester 2. Ideally, the entire transformation would be stereospecific, a characteristic that would require conditions under which enantiotopically enriched azetidinium ion 3 could be deprotonated to give 4 that rests in the lithium-stabilised carbenoid form (rather than the ylidal form), is configurationally stable, and undergoes stereospecific trapping with a boronic ester 5; the resulting boronate 6 would then undergo 1,2-migration, processes that are usually highly stereospecific and involve inversion at the leaving-group-bearing carbon atom, thus giving enantiomerically enriched tertiary boronic ester 2.

Previous experience within our laboratory gave us cause to be both optimistic and hesitant. For example, we have shown that such ring-opening lithiation-borylation reactions can be carried out with both epoxides 7 and N-Boc aziridines 9 to give the corresponding products 8 and 10 with high levels of enantiospecificity (Scheme 2). However, this type of reaction failed with N-Boc azidines 11, presumably owing to the ring-opening 1,2-migration step being slow (Scheme 2). However, the recent work of Couty and David suggested that ring-opening of the corresponding azetidinium ions might be more facile. Specifically, they showed that cyano-substituted azetidinium ions 3a can be deprotonated with LiHMDS to give ylides 4a that can be trapped with electrophiles; when the electrophile is an aldehyde, ketone, or acrylate, the resulting alkoxide or enolate undergoes an intramolecular S_N2 reaction to open the azetidinium ion (Scheme 2). The ylides were chemically unstable, even at cryogenic temperatures, necessitating that the electrophile be present during their formation. These studies also showed that these stabilised azetidinium ylides are configurationally unstable, even within the short lifetime imposed by in situ trapping. However, the level of configurational stability of less stabilised ylides, such as those derived from phenyl-substituted azetidinium ions, was unclear.

To test our reaction, we first prepared the triflate salt of phenyl-substituted azetidinium ion 3b in four steps from commercially available 3-chloro-1-propiophenone (13) (Scheme 3). Ketone 13 was first reduced to the alcohol and then converted into the corresponding dichloride. A ring-closing double displacement reaction with methylamine gave azetidine 14, which was subsequently N-alkylated in good yield to give azetidinium ion 3b.

With azetidinium ion 3b in hand, we subjected it to the conditions similar to those established by Couty and David—LiHMDS (1.7 equiv), THF, –78 °C, 1 hour, then warming to room temperature—in the presence of EtBpin. Under these conditions, γ-dimethylamino tertiary boronic ester 2b was isolated in 41% yield (Table 1, entry 1). When the putative ylide was generated in the absence of the boronic ester 2, the desired product was not observed, thus highlighting the instability of the ylide. Increasing the amount of base to 3.0 equivalents, adding the base at –20 °C, or subsequently warming the reaction mixture to reflux (to promote 1,2-migration) did not result in improved yields (Table 1, entries 2–4). The use of KHMS and LiTMP in place of LiHMDS led to reduced yields; however, the use of LDA led to a higher yield (57%;
Further investigation informed us that the addition of 2.0 equivalents of this base was optimum (Table 1, entry 10).

Table 1 Optimisation of the Lithiation–Borylation Reaction of Azetidinium Ion 3b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equiv of base</th>
<th>T (°C)</th>
<th>Yield of 2b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>1.7</td>
<td>–78</td>
<td>41b</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>1.7</td>
<td>–20</td>
<td>&lt;5b</td>
</tr>
<tr>
<td>3</td>
<td>LiHMDS</td>
<td>1.7</td>
<td>–78</td>
<td>23d</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>3.0</td>
<td>–78</td>
<td>33d</td>
</tr>
<tr>
<td>5</td>
<td>KHMDS</td>
<td>1.7</td>
<td>–78</td>
<td>26d</td>
</tr>
<tr>
<td>6</td>
<td>LITMP</td>
<td>1.7</td>
<td>–78</td>
<td>26d</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>1.7</td>
<td>–78</td>
<td>57d</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>1.2</td>
<td>–78</td>
<td>16d</td>
</tr>
<tr>
<td>9</td>
<td>LDA</td>
<td>1.5</td>
<td>–78</td>
<td>43d</td>
</tr>
<tr>
<td>10</td>
<td>LDA</td>
<td>2.0</td>
<td>–78</td>
<td>69d</td>
</tr>
<tr>
<td>11</td>
<td>LDA</td>
<td>3.0</td>
<td>–78</td>
<td>58d</td>
</tr>
</tbody>
</table>

a Reactions were carried out using 0.2 mmol of 3b.
b Yield of isolated material.
c After stirring the reaction mixture at –78 °C (1 h), the mixture was warmed to reflux.
d Yield determined by 1H NMR analysis of the crude mixture in the presence of an internal standard.

Having established optimum conditions for this transformation, we explored the scope of the methodology by testing a range of boronic esters (5a–i) (Scheme 4). The use of primary (5a–c) and secondary boronic esters (5d and 5e) gave moderate to good yields of the corresponding γ-dimethylamino tertiary boronic esters 2ba–be. Additionally, the use of allylic boronic ester 5f gave the corresponding product in 45% yield. Aryl boronic esters proved to be more challenging. When electron-rich boronic esters, such as 5g, was employed the expected product 2bg could be isolated in good yield. However, when more electron-poor aryl boronic esters were used, such as phenyl- and 2-thienyl-boronic ester, the corresponding boronic ester products could not be isolated owing to facile protodeboronation. Pleasingly, the unstable boronic ester products could be functionalised in situ, prior to work-up, to give more stable derivatives; the addition of aqueous H2O2/NaOH to the reaction mixture led to the corresponding tertiary alcohols 15bh and 15bi being isolated in good yields. Interestingly, in our experience, similar tertiary boronic esters, not containing a dimethylamino group, do not undergo protodeboronation so readily,4n,17 suggesting that complexation of the boronic ester with the proximal amino group promotes fragmentation. Because protodeboronation can be desirable—γ-amino diarylmethines are prominent members of this family of therapeutics (Figure 1)—we sought conditions to effect this transformation more efficiently. Considering our previously reported conditions for the protodeboronation of diarylalkyl boronic esters,5c upon lithiation–borylation of 3b and 5j, the reaction mixture was warmed to room temperature and CsF (1.5 equiv) and H2O (1.1 equiv) were added sequentially; within 1 hour of stirring the resulting mixture at room temperature, the tertiary boronic ester was completely consumed and, subsequently, diarylmethine 16bj could be isolated in 71% yield (Scheme 5).
To further demonstrate the versatility of these tertiary boronic esters, we subjected 2ba to a variety of conditions to effect functionalisation of the C–B bond (Scheme 6). In situ oxidation of 2ba using H₂O₂/NaOH gave the corresponding tertiary alcohol 15ba in 58% yield. Other oxidizing conditions (NaBO₃·4H₂O, NaBO₃·4H₂O/CH₃COOH,¹⁸ Oxone/acetonate¹⁹ TMANO·2H₂O) were less effective and led to partial oxidation of the tertiary amine group. Olefination of isolated 2ba under modified Zweifel conditions ³¹ with vinyl lithium gave alkene 17ba in 52% yield. Protodeboronation of isolated 2ba using TBADF·3H₂O gave the desired γ-dimethylaminopropyl dialkyl methine 16ba in 73% yield.⁶⁴ We also attempted to transform 2ba into the corresponding trifluoroborate salt using standard conditions (KHF₂, MeOH).²² However, the trifluoroborate moiety underwent partial ligand exchange with the pendant amine to give a mixture of the desired trifluoroborate salt and intramolecularly complexed difluoroborane 18ba (2:1, 82% overall yield), as determined by ¹H and ¹⁹F NMR analysis.²³ Pleasingly, when the crude mixture was heated at reflux in MeCN, complete conversion into 18ba was effected (67% yield).

We then set out to understand the mechanism of the transformation. First, we prepared pyrrolidinium ion 19a and subjected it to the lithiation–borylation conditions to investigate the contribution of relief of ring strain in the putative 1,2-migration step. The substrate, 19a, was prepared through reductive alkylation/alkylation of commercially available 2-phenylpyrrolidine. Upon treatment of a THF solution of 19a and EtBpin at −78 °C with LDA (2 equiv) with subsequent warming to room temperature, 1,2,3,4,7,8-hexahydroazocine 20a (48%) was initially isolated, a species that in solution isomerised over a short period of time into the corresponding benzo-fused 1,2,3,4,5,8-hexahydroazocine 21a; the desired tertiary boronic ester was not observed (Scheme 7). Hexahydroazocine 20a presumably arises from a Sommelet–Hauser rearrangement: proton transfer of the initially formed benzylic ylide to the methylenic ylide followed by a 2,3-sigmatropic rearrangement.²⁴ The transformation suggests that either the Sommelet–Hauser rearrangement is faster than the trapping of the benzylic ylide with EtBpin, or that trapping is indeed efficient but that the subsequent 1,2-migration of the boronate is slow, thus allowing fragmentation back to the ylide. Operation of the latter scenario would suggest that the relief of ring-strain in the 1,2-migration of the azetidinium boronates is an important contributor to the success of the transformation.

The configurational stability of azetidinium ylide 4b was then investigated. Enantiomerically enriched azetidinium ion (R)-3b was prepared from (S)-3-chloro-1-phenylpropan-1-ol, which was obtained through asymmetric reduction of ketone 13.²⁵ When a solution of (R)-3b and EtBpin in THF at −78 °C was treated with LiHMDS followed by an oxidative work-up (aq H₂O₂/NaOH), the resulting tertiary alcohol 15ba was found to be racemic, thus revealing that 4b (like 4a) is configurationally unstable (Table 2, entry 1).

Presumably, lithium-stabilised ylide 4b-Li, should it be an intermediate, would undergo solvent-mediated dissociation into the ylide 4b (deprotonation might lead to 4b directly), which if pyramidalised, undergoes rapid inversion, a process that could occur via the ring-open carbene form of 4b (Scheme 8).¹⁴c,²⁰ We surmised that in a less-coordinating solvent, such as TBME, 4b-Li might be more stable. However, when the lithiation–borylation–oxidation reaction was...
performed in TBME [the nonaflate salt of (R)-3b was used owing to the poor solubility of the corresponding triflate salt in TBME], the tertiary alcohol was again isolated as the racemate. The insolubility of the azetidine substrate frustrated attempts to use even less-coordinating solvents (e.g., hexanes). The use of LDA in place of LiHMDS or the use of even less-coordinating solvents frustrated attempts to use even less-coordinating solvents (e.g., hexanes). The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. The use of LDA in place of LiHMDS or the use of less-sterically hindered neopentylglycol boronic ester, EtBNeo, did not lead to enantiomerically enriched products. 

Table 2 Investigation of the Enantiospecificity of the Lithiation–Borylation–Oxidation Reaction of (R)-3b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic ester</th>
<th>X⁺</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtBpin</td>
<td>F₃CSO₃⁻</td>
<td>LiHMDS</td>
<td>THF</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>EtBpin</td>
<td>F₃CSO₃⁻</td>
<td>LiHMDS</td>
<td>TBME</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>EtBNeo</td>
<td>F₃CSO₃⁻</td>
<td>LiHMDS</td>
<td>TBME</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>EtBpin</td>
<td>F₃CSO₃⁻</td>
<td>LDA</td>
<td>TBME</td>
<td>n.d.</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reactions conducted using 0.3 mmol of (R)-3b. n.d. = not determined.

In conclusion, when 2-phenyl-azetidinium ions are converted into azetidinium ylides, through deprotonation with LDA in the presence of boronic esters, they undergo ring-opening carboxaboration to give γ-dimethylamino tertiary boronic esters. The transformation presumably involves the complexation of the boronic ester with the carbocation of the ylide to form a boronate, which then undergoes ring-opening, 1,2-shift, a process that is promoted by the relief of ring-strain of the azetidinium ion. This strain also contributes to the configurational instability of the in situ formed ylides, which appear to be in equilibrium with the ring-opened carbene form. The C–B bond of the products can be transformed into a range of functional groups to give a selection of highly functionalised 3-arylaminopropanes, which are attractive targets for the pharmaceutical industry.

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard Schlenk manifold techniques. Fine chemicals were purchased from Acros Organics, Alfa Aesar, Inochemistry Frontier Scientific, Sigma-Aldrich, TCI Europe or Santa Cruz Biotechnology and used as received unless otherwise stated. The following pinacol boronic esters were purchased from commercial suppliers: 5e (Frontier Scientific), 5f (Sigma-Aldrich), 5h (Sigma-Aldrich). n-BuLi was received from Acros Organics as a 1.6 M solution in hexane. Lithium diisopropylamide (LDA) was freshly prepared from n-BuLi and distilled diisopropylamine immediately before use. Et₄N and disopropylamine were distilled over CaH₂ before use. Anhydrous MeCN, CH₂Cl₂, Et₂O, THF and toluene were obtained from a purification column composed of activated alumina and stored subsequently over 3 Å molecular sieves. Analytical TLC was carried out on aluminium-backed silica plates (Merck, Silica Gel 60 F254, 0.25). Flash column chromatography was carried out on silica gel (Aldrich, Silica Gel 60, 40–63 μm). Microwave reactions were performed using a Biotage Initiator EXP EU microwave synthesiser. Infrared (IR) spectra were recorded on neat compounds using a PerkinElmer Spectrum One FT-IR spectrophotometer, irradiating between 4000 cm⁻¹ and 600 cm⁻¹. Only strong and selected absorbance values (νmax) are reported. ¹H NMR spectra were acquired using a Joel ECS 300, Joel ECS 400 or Varian 400-MR Fourier transform spectrometer for samples in CDCl₃ or CD₂OD at 301 or 400 MHz as indicated. Chemical shifts (δH) are expressed in parts per million (ppm) and are referred to the residual protio solvent signals of CHCl₃ (7.26 ppm) or MeOH (3.31 ppm). ¹³C NMR coupling constants are expressed in hertz (Hz) and are quoted as apparent multiplicities (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet, dd = doublet of doublets, ps = pseudo). ¹⁹F NMR spectra were recorded at 101 MHz; chemical shifts (δF) and are expressed in ppm. Carbon atoms attached to boron or to bromine are usually not observed due to quadrupolar relaxation. See the Supporting Information for proton and carbon assignments and molecule numbering. ¹H NMR spectra were measured using Norell S-200-QTZ quartz tubes at 128 MHz with complete proton decoupling. Some γ-dimethylamino tertiary boronic esters show two or even three signals, the upfield signals indicative of amine-assisted complexation of CD₃OD (the solvent) and/or H₂O. ¹³C NMR spectra were recorded at 376 MHz. HRMS ESI was performed on either a Bruker Daltonics Apex IV, 7-Tesla FT-ICR or micrOTOF II. MS samples were submitted in EIOAc or CH₂Cl₂. Optical rotations were measured using a PerkinElmer spectrophotometer, irradiating between 4000 cm⁻¹ and 600 cm⁻¹. Only strong and selected absorbance values (νmax) are reported.
observed using a Bellingham + Stanley Ltd. ADP220 polarimeter at 589 nm (Na D-line) in a cell with path length of 1 dm. GC-MS experiments were carried out using an Agilent 6890 apparatus (column: Supelco SLB-5ms capillary column 15 m × 0.25 mm × 0.25 μm).

**Synthesis of Pinacol Boronic Esters from Boronic Acids; General Procedure (GP1)**

A mixture of boronic acid (1.0 equiv), pinacol (1.0 equiv) and anhydrous MgSO4 (4.0 equiv) in Et2O (0.5 M) was stirred at r.t. for 16 h. The reaction mixture was filtered and the solvent was removed in vacuo. The crude material was purified by distillation or flash column chromatography to give the pure boronic ester.

**Lithiation–Borylation of 1,1-Dimethyl-2-phenylazetidin-1-ium Trifluoromethanesulfonate (3b) To Give the Tertiary 3-Dimethylamino-Boronic Ester; General Procedure (GP2)**

To a solution of diisopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added n-BuLi (2.0 equiv) at –78 °C. After stirring for 30 min, the solution was added dropwise to a mixture of azetidinium salt 3b (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm to r.t. The solvent was removed in vacuo and the crude residue was taken up with H2O and extracted with CH2Cl2 (3 times). The combined organic layers were dried over MgSO4 and concentrated under reduced pressure to afford the crude tertiary boronic ester, which was purified by chromatography on silica gel (EtOAc/Et2O = 100:0.5) to afford the pure tertiary alcohol.

**Lithiation–Borylation of 1,1-Dimethyl-2-phenylazetidin-1-ium Trifluoromethanesulfonate (3b) with in situ Oxidation; General Procedure (GP3a)**

To a solution of disopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added n-BuLi (2.0 equiv) at –78 °C. After stirring for 30 min, the solution was added dropwise to a mixture of azetidinium salt 3b (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm to r.t. The reaction mixture was cooled to 0 °C and a 2:1 mixture ofaq NaOH (2.0 M) and 30% H2O2 was added under vigorous stirring. The cooling bath was removed and the reaction mixture was stirred at r.t. for 1 h. The solvent was removed in vacuo and the residue was partitioned between H2O and CH2Cl2. The phases were separated and the aq layer was re-extracted with CH2Cl2 (2 times). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/Et2O = 100:0.5) to afford the pure tertary alcohol.

**Lithiation–Borylation of 1,1-Dimethyl-2-phenylazetidin-1-ium Trifluoromethanesulfonate (3b) with in situ Protodeboronation; General Procedure (GP4)**

To a solution of disopropylamine (2.0 equiv) in anhydrous THF (2.0 M) was added n-BuLi (2.0 equiv) at –78 °C. After stirring for 30 min, the solution was added dropwise to a mixture of azetidinium salt 3b (1.0 equiv) and the boronic ester (1.2 equiv) in dry THF (0.03 M) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm to r.t. CsF (1.5 equiv) was added at r.t., followed by H2O (1.1 equiv) and the reaction mixture was stirred at r.t. for 1 h. The solvent was removed in vacuo and the residue was partitioned between H2O and CH2Cl2. The phases were separated and the aq layer was re-extracted with CH2Cl2 (2 times). The combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/Et2O = 100:0.5) to afford the pure protodeboronated product.

**2-Ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5a)**

Following general procedure GP1, ethylboronic acid (10.0 g, 67.4 mmol) and pinacol (8.0 g, 64.7 mmol) afforded, after distillation (40–50 °C, ambient pressure), boronic ester 5a (10.1 g, 96%) as a colourless liquid. All analytical data matched that previously reported.28

1H NMR (400 MHz, CDCl3): δ = 1.24 (s, 12 H, 4 × C-CH3), 0.95 (t, J = 7.7 Hz, 3 H, CH2–CH2–), 0.76 (q, J = 7.8 Hz, 2 H, CH3).

**4,4,5,5-Tetramethyl-2-phenethyl-1,3,2-dioxaborolane (5b)**

Following general procedure GP1, 2-phenethylboronic acid (10.0 g, 66.7 mmol) and pinacol (7.9 g, 66.7 mmol) afforded pure 5b as a white crystalline solid (15.4 g, >99%), which was used in the next step without further purification. All analytical data matched that previously reported.29

1H NMR (400 MHz, CDCl3): δ = 7.26–7.19 (m, 4 H, Ar-H), 7.14 (m, 1 H, Ar-H), 2.74 (t, J = 8.3 Hz, 2 H, CH2–Ph), 1.21 (s, 12 H, 4 × C-CH3), 1.13 (t, J = 8.2 Hz, 2 H, CH2–B).

**2-Isobutyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5c)**

Following general procedure GP1, isobutylboronic acid (3.5 g, 34.5 mmol) and pinacol (4.1 g, 34.5 mmol) afforded pure 5c as a white crystalline solid (15.4 g, >99%), which was used in the next step without further purification. All analytical data matched that previously reported.29

1H NMR (400 MHz, CDCl3): δ = 1.86 (sept, J = 6.7 Hz, 1 H, CH), 1.25 (s, 12 H, 4 × C-CH3), 0.92 (d, J = 6.7 Hz, 6 H, 2 × CH3), 0.73 (d, J = 7.2 Hz, 2 H, CH3).

**2-Cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5d)**

Following general procedure GP1, cyclohexylboronic acid (1.5 g, 11.7 mmol) and pinacol (1.4 g, 11.7 mmol) afforded, after chromatographic purification (SiO2, PE/Et2O = 20:1), boronic ester 5d as a colourless liquid (2.2 g, 90%). All analytical data matched that previously reported.29

1H NMR (400 MHz, CDCl3): δ = 1.68–1.54 (m, 5 H, cHex–H), 1.38–1.26 (m, 5 H, cHex–H), 1.23 (s, 12 H, 4 × C-CH3), 0.97 (m, 1 H, CH).
2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5g)

Following general procedure GP1, (4-methoxyphenyl)boronic acid (3.0 g, 20 mmol) and pinacol (2.4 g, 20 mmol) afforded boronic ester 5g as a white solid (3.0 g, 85%), which was used in the next step without further purification. All analytical data matched that previously reported.17b

1H NMR (400 MHz, CDCl3): δ = 7.75 (d, J = 8.6 Hz, 2 H, Ar-H), 6.90 (d, J = 8.6 Hz, 2 H, Ar-H), 3.83 (s, 3 H, O-CH3), 1.33 (s, 12 H, 4 × C-CH3).

4,4,5,5-Tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (5i)

Following a modified literature procedure,16 NaBH4 (5.7 g, 150 mmol) was added dropwise to a solution of thiophene (2.0 g, 1.90 mL, 23 mmol) in toluene (66 mL). The reaction mixture was stirred at r.t. for 18 h and was then quenched with H2O (90 mL). The solvent was removed in vacuo and the residue was extracted with Et2O (3 × 50 mL). The combined organic layers were washed with H2O dried over MgSO4 filtered and evaporated under vacuum. Puriﬁcation by column chromatography on silica gel (hexane/EtOAc, 10:1) afforded alcohol (5-S) (2.5 g, 73%) as a white solid.

The ee value was determined by chiral HPLC analysis with a Chiralcel IB column (elucent: hexane/2-propanol = 98:2; flow rate: 1 mL/min; detection: 254 nm), tR (R) = 16.2 min (area% 97), tR (S) = 18.1 min (area% 3). Spectral data matched those previously reported for 23. The optical rotation matched literature data.32

1-Methyl-2-phenylazetidine (14)

Following a procedure by Luisi,16 to a solution of 3-chloro-1-phenylpropan-1-ol (23) (3.1 g, 18.2 mmol) in dry CH2Cl2 (18 mL), a solution of SOCl2 (4.0 mL, 54.6 mmol) in dry CH2Cl2 (5.5 mL) was added dropwise at r.t. After stirring for 1 h, the reaction mixture was poured into H2O (20 mL) and aq NaOH (15% w/v) was added slowly to neutralise the excess of HCl until the pH of the solution was 7. The aq phase was extracted with CH2Cl2 (3 × 30 mL) and the combined organic layers were washed over MgSO4, filtered and evaporated under vacuum to afford 1-phenyl-1,3-dichloropropane that was employed in the next step without further puriﬁcation.

To a solution of 1-phenyl-1,3-dichloropropane in EtOH (23 mL) and Et3N (5.1 mL, 36.4 mmol) in a sealed flask, a solution of MeNH2 (33% w/v in EtOH, 23 mL) was added at r.t. The reaction mixture was heated at 70 °C for 16 h and then allowed to cool to ambient temperature. The solvent was removed in vacuo and HCl (30 mL, 2.0 M) was added. The aq phase was extracted with CH2Cl2 (3 × 40 mL) and subsequently basiﬁed by addition of aq NaOH (15% w/v) until the pH of the solution was >12. The basic aq phase was extracted with CH2Cl2 (3 × 50 mL) and the combined organic layers were dried over MgSO4, ﬁltered and concentrated in vacuo. The crude mixture was puriﬁed by flash silica gel column chromatography (EtOAc/Et2O = 100:0.5) to afford azetidine (14) (1.34 g, 50%, over two steps) as a colourless oil. The analytical data matched that previously reported.16b

1H NMR (400 MHz, CDCl3): δ = 3.78–7.30 (m, 4 H, Ar-H), 7.26–7.22 (m, 1 H, Ar-H), 3.45 (m, 1 H, 3-H), 2.85 (dt, J1 = 9.6 Hz, J2 = 7.1 Hz), 2.33 (s, 3 H, CH3), 2.26 (m, 1 H, 2-H), 2.14 (quin, J = 8.9 Hz, 1 H, 2-H).

1C NMR (101 MHz, CDCl3): δ = 142.99 (Ar-C), 128.46 (2 C, Ar-C), 127.39 (Ar-C), 126.71 (2 C, Ar-C), 71.30 (1-C), 53.06 (3-C), 44.61 (CH3), 27.01 (2-C).

This method was also used for the synthesis of enantiopure azetidine, (R)-14, employing (S)-3-chloro-1-phenylpropan-1-ol of (S)-23 as starting material.16d The absolute conﬁguration of enantioenriched azetidine (R)-14 was assigned assuming retention of conﬁguration in the reaction with SOCl2 and inversion of conﬁguration in the cyclisation step with MeNH2. The ee value for (R)-14 was determined by chiral GC (Cyclolex, i.d.: 90 °C, length: 30 m, i.d.: 0.25). For enantioenriched material, the result was tR (S) = 35.21 (area% 13), tR (R) = 35.57 (area% 87).
1,1-Dimethyl-2-phenylazetidin-1-ium Trifluoromethanesulfonate (3b)

Following a modified procedure by Couty,1b azetidine 14 (515.3 mg, 3.5 mmol) was dissolved in dry Et2O (30 mL). After cooling to 0 °C, methyl trifluoromethanesulfonate (830.7 µL, 7.3 mmol) was added. The mixture was stirred for 1 h, then all the volatiles were removed under vacuum to afford azetidinium triflate 3b (1.07 g, 95%) as an orange oil.

IR (neat): 2936, 1459, 1138, 1111, 1079, 1069, 1052, 988, 839, 757 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.39 (d, J = 7.6 Hz, 2 H, Ar-H), 7.31 (t, J = 7.5 Hz, 2 H, Ar-H), 7.23 (t, J = 7.5 Hz, 2 H, Ar-H), 7.18–7.09 (m, 4 H, Ar-H), 4.24–2.37 (m, 2 H, 5-H), 2.30–2.26 (m, 2 H, 1-H), 2.23 [s, 6 H, N-(CH₃)₂], 2.13–2.02 (m, 4 H, 2-H + 4-H), 1.26 (s, 6 H, 2 × C-CH₃), 1.25 (s, 6 H, 2 × C-CH₃).

¹C NMR (101 MHz, CDCl₃): δ = 146.14 (Ar-C), 144.35 (Ar-C), 129.36 (2 C, Ar-C), 129.23 (2 C, Ar-C), 129.20 (2 C, Ar-C), 128.52 (2 C, Ar-C), 126.67 (Ar-C), 126.48 (Ar-C), 84.72 (2 C, 2 × B-O-C), 57.34 (1-C), 45.77 [2 C, N-(CH₃)₂], 39.42 (2-C), 33.10 (5-C), 32.81 (4-C), 25.34 (4 C, 4 × C-CH₃); C attached to boron not observed.


N,N,5-Trimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-amine (2bc)

According to general procedure GP2, diisopropylamine (140 µL, 1 mmol), n-Buli (625 µL, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (155.7 mg, 0.5 mmol) and 2-isotoul-4,4,5,5-tetramethyl-1,3-dioxaborolane (5c) (110.5 mg, 0.6 mmol) in anhydrous THF (12 mL) afforded, after purification on silica gel (EtOAc/Et₃N = 100:0.5), γ-dimethylamino boronic ester 2bc (79.5 mg, 46%) as a colourless oil.

IR (neat): 2926, 1457, 1371, 1143, 701 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.39 (d, J = 8.0 Hz, 2 H, Ar-H), 7.26 (t, J = 7.6 Hz, 2 H, Ar-H), 7.12 (t, J = 7.3 Hz, 1 H, Ar-H), 2.19 [s, 6 H, N-(CH₃)₂], 2.17–1.99 (m, 4 H, 1-H + 2-H), 1.77 (m, 2 H, 4-H), 1.56 (sept, J = 6.7 Hz, 1 H, CH₃), 1.21 [s, 6 H, 2 × C-CH₃], 1.19 (s, 6 H, 2 × C-CH₃), 0.82 (d, J = 6.7 Hz, 3 H, 3 × CH₃), 0.78 [d, J = 6.7 Hz, 3 H, CH-CH₃]; C attached to boron not observed.


3-Cyclohexyl-N,N-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine (2bd)

According to general procedure GP2, diisopropylamine (140 µL, 1 mmol), n-Buli (625 µL, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (159.5 mg, 0.51 mmol) and 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5d) (126.1 mg, 0.6 mmol) in anhydrous THF (12 mL) afforded, after purification on silica gel (EtOAc/Et₃N = 100:0.5), γ-dimethylamino boronic ester 2bd (84.2 mg, 44%) as a colourless oil.

IR (neat): 2926, 2852, 1450, 1371, 1350, 1300, 1269, 1141, 1036, 852 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.35 (d, J = 7.5 Hz, 2 H, Ar-H), 7.24 (t, J = 7.5 Hz, 2 H, Ar-H), 7.13 (t, J = 7.3 Hz, 1 H, Ar-H), 2.24–2.10 (m, 2 H, 3-H + CH–CH₂–H), 2.17 [s, 6 H, N-(CH₃)₂], 2.02–1.93 (m, 2 H, 1-H + CH–CH–H), 1.89 (m, 1 H, CH–CH₂–H), 1.76–1.48 (m, 5 H, 3 × CH₂–CH–H + 2 × CH₂–H), 1.33 [s, 6 H, 2 × C-CH₃], 1.32 [s, 6 H, 2 × C-CH₃], 1.29–0.91 (m, 5 H, 5 × CH₂–CH–H).

¹C NMR (101 MHz, CDCl₃): δ = 144.80 (Ar-C), 130.16 (2 C, Ar-C), 128.65 (2 C, Ar-C), 126.47 (Ar-C), 84.80 (2 C, 2 × B-O-C), 58.26 (1-C), 48.01 (2-C), 45.45 [2 C, N-(CH₃)₂], 33.92 (CH–CH₂–H), 31.54 (CH₂–CH–H).
30.20 (C=C), 28.42 (C=C), 28.23 (C=C), 27.96 (C=C), 25.68 (2 C, 2 C = C-C), 25.57 (2 C, 2 C = C-C); C attached to boron not observed.

11B NMR (128 MHz, CD2OD): 8 = 33.25.


3-Cyclopentyl-N,N-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-amine (2Be)

According to general procedure GP2, disopropylamine (140 µl, 1 mmol), n-BuLi (625 µl, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (153 mg, 0.5 mmol) and 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5g) (140.5 mg, 0.6 mmol) in anhydrous THF (12 ml) affording, after purification on silica gel [EtOAc/Et3N = 100:0.5], dimethylamino boronic ester 2bg (145 mg, 75%) as a yellow oil.

IR (neat): 2969, 1509, 1431, 1341, 1295, 1181, 1141, 1035, 852 cm⁻¹.

1H NMR (400 MHz, CD2OD): 8 = 7.26–7.10 (m, 7 H, Ar-H), 6.80 (d, J = 8.7 Hz, 2 H, Ar-H), 3.76 (s, 3 H, O-CH3), 2.36–2.28 (m, 2 H, 1, H), 2.20 (s, 6 H, N-(CH3)2), 2.10 (ps, t, J = 7.8 Hz, 2 H, 2, H), 1.15 (s, 6 H, 2 C = C-CH3), 1.14 (s, 6 H, 2 C = C-CH3); C attached to boron not observed.

13C NMR (101 MHz, CD2OD): 8 = 159.08 (Ar-C), 147.75 (Ar-C), 139.18 (Ar-C), 131.32 (2 C, Ar-C), 130.28 (2 C, Ar-C), 128.82 (2 C, Ar-C), 126.54 (2 C, Ar-C), 114.25 (2 C, Ar-C), 84.80 (2 C, 2 × B-O-C), 58.82 (1-C), 55.60 (O-CH3), 45.44 (2 C, N-(CH3)2), 35.85 (2-C), 24.89 (2 C, 2 C = C-CH3), 24.88 (2 C, 2 C = C-CH3); C attached to boron not observed.

1B NMR (128 MHz, CD2OD): 8 = 32.02, 18.66, 15.54.


3-(Dimethylamino)-1,1-diphenylpropan-1-ol (15bh)

According to general procedure GP3a, disopropylamine (140 µl, 1 mmol), n-BuLi (625 µl, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (153 mg, 0.49 mmol) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (5h) (122.5 mg, 0.6 mmol) in anhydrous THF (12 ml) afforing, after purification by flash chromatography on silica gel (EtOAc/Et3N = 100:0.5), tertiary alcohol 15bh (88 mg, 70%) as a white solid.

IR (neat): 2830, 2783, 1446, 1204, 1064, 1019, 963, 891, 841, 777, 751, 716 cm⁻¹.

1H NMR (400 MHz, CDCl3): 8 = 7.50 (ps, d, J = 8.0 Hz, 4 H, Ar-H), 7.32 (ps, t, J = 7.4 Hz, 4 H, Ar-H), 7.20 (ps, t, J = 7.2 Hz, 2 H, Ar-H), 2.42 (s, 4 H, 2 × H + 1-H), 2.23 (s, 6 H, N-(CH3)2).

13C NMR (101 MHz, CDCl3): 8 = 148.07 (2 C, Ar-C), 128.01 (4 C, Ar-C), 126.31 (2 C, Ar-C), 125.84 (4 C, Ar-C), 79.17 (3-C), 56.32 (1-C), 45.10 (2 C, N-(CH3)2), 35.99 (2-C).


3-(Dimethylamino)-1-phenyl-1-(thiophen-2-yl)propan-1-ol (15bi)

According to general procedure GP3b, disopropylamine (140 µl, 1 mmol), n-BuLi (625 µl, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (153.5 mg, 0.5 mmol) and 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (5b) (126.1 mg, 0.6 mmol) in anhydrous THF (12 ml) afforing, after purification by flash chromatography on silica gel (EtOAc/Et3N = 100:0.5), tertiary alcohol 15bi (63.5 mg, 49%) as a white solid.

IR (neat): 2779, 1178, 1068, 847, 699 cm⁻¹.

1H NMR (400 MHz, CDCl3): 8 = 7.56 (d, J = 7.4 Hz, 2 H, Ar-H), 7.33 (t, J = 7.6 Hz, 2 H, Ar-H), 7.22 (t, J = 7.1 Hz, 1 H, Ar-H), 7.18 (d, J = 5.0 Hz, 1 H, 5-H), 6.92 (t, J = 3.6 Hz, 1 H, 1-H), 6.89 (d, J = 3.5 Hz, 1 H, 7-H), 2.52 (m, 1 H, 1-H), 2.47–2.30 (m, 3 H, 1-H + 2-H), 2.24 (s, 6 H, N-(CH3)2).

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3-(4-Chlorophenyl)-N,N-dimethyl-3-phenylpropan-1-amine (16b)

According to general procedure GP4, diisopropylamine (120 μl, 0.88 mmol), n-Buli (550 μl, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (137 mg, 0.44 mmol), 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5j) (138.3 mg, 0.58 mmol), CsF (99.8 mg, 0.66 mmol) and H2O (9 μl, 0.48 mmol) in anhydrous THF (8 mL) afforded, after purification by flash chromatography on silica gel (EtOAc/Et3N = 100:0.5), protodeboronated compound 16bj (85.2 mg, 71%) as a colourless oil.

IR (neat): 2924, 2978, 1489, 1092, 1014, 821, 698 cm⁻¹.


1H NMR (400 MHz, CDCl₃): δ = 7.26–7.24 (m, 8 H, Ar-H), 7.15 (m, 1 H, Ar-H), 3.93 (t, J = 6.0 Hz, 1 H, 1-H), 2.27–2.20 (m, 4 H, 1-H + 2-H), 2.19 [s, 6 H, N-(CH₃)₂].

13C NMR (101 MHz, CDCl₃): δ = 145.52 (Ar-C), 144.96 (Ar-C), 132.94 (Ar-C), 130.36 (2 C, Ar-C), 129.63 (2 C, Ar-C), 129.25 (2 C, Ar-C), 127.83 (2 C, Ar-C), 127.47 (Ar-C), 59.06 (1-C), 49.87 (3-C), 45.43 [2 C, N-(CH₃)₂].

IRMS (ESI): m/z [M + H⁺] calcd for C₁₅H₂₂NO: 208.1696; found: 208.1697.

1-[(Dimethylamino)-3-phenyl-3-ol (15ba)

According to general procedure GP3a, diisopropylamine (140 μl, 1 mmol), n-Buli (625 μl, 1 mmol), 1,1-dimethyl-2-phenylazetidin-1-ium trifluoromethanesulfonate (3b) (155.7 mg, 0.5 mmol) and 2-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5a) (93.6 mg, 0.6 mmol) in anhydrous THF (6 mL) afforded, after purification by flash chromatography on silica gel (CH₂Cl₂/MeOH/Et₂O = 100:0:5), tertiary alchol 15ba (80.4 mg, 58%) as a white solid.

IR (neat): 2936, 2833, 2781, 1464, 1445, 1174, 1042, 1024, 773 cm⁻¹.


1H NMR (400 MHz, CDCl₃): δ = 4.71–4.73 (m, 2 H, Ar-H), 3.74–3.70 (m, 2 H, Ar-H), 2.70 (ps tt, J₁ = 8.4 Hz, J₂ = 0.9 Hz, 1 H, 1-H), 2.28 (td, J₁ = 12.5 Hz, J₂ = 2.6 Hz, 1 H, 1-H), 2.19 (m, 1 H, 1-H), 2.18 [s, 6 H, N-(CH₃)₂].

13C NMR (101 MHz, CDCl₃): δ = 147.04 (Ar-C), 128.01 (2 C, Ar-C), 126.06 (Ar-C), 125.86 (2 C, Ar-C), 78.21 (3-C), 56.23 (1-C), 45.15 [2 C, N-(CH₃)₂].


N,N-Dimethyl-3-phenylpentan-1-amine (16ba)

N,N-Dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-amine (2ba) (63.5 mg, 58%) as a white solid.

IR (neat): 2929, 1453, 1042, 755, 700 cm⁻¹.


3-Ethyl-N,N-dimethyl-3-phenylpent-4-en-1-amine (17ba)

Following a modified literature procedure, n-Buli (1.5 mmol, 940 μl) was added dropwise at r.t. to neat tetravinyltin (0.75 mmol, 140 μl) under an N₂ atm. The reaction mixture was stirred for 30 min; the white solid formed was allowed to settle and the colourless solution was removed by syringe under N₂. The solid (vinyl lithium) was washed with dry pentane (3 × 1 ml), every time adding and removing the solvent by syringe under N₂, and then dissolved in dry THF (1 ml).

N,N-Dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-amine (2ba) (0.3 mmol, 95.2 mg) was dissolved in dry THF (3 ml) and the vinyl lithium solution was added dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, warmed to −42 °C and then stirred at that temperature for an additional 20 min. After that time, NMR analysis of the crude reaction mixture showed complete boronate complex formation. The solution was cooled to −78 °C and a solution of I₂ (1.5 mmol, 380.7 mg) in dry MeOH (2.4 ml) was added dropwise. After stirring for 15 min at −78 °C, a suspension of NaOMe (3 mmol, 126.1 mg) in dry MeOH (1.2 ml) was added. The reaction mixture was allowed to warm to r.t. and stirred for 1 h; then an aq solution of Na₂SO₄ (10 ml) was added. The layers were separated, the organic layer was washed with brine (2 × 5 ml) and the combined aq layers were extracted with CH₂Cl₂ (3 × 5 ml). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/CH₂Cl₂/Et₂O = 100:0:5) to afford alchol 17ba (33.7 mg, 52%) as a colourless oil.

IR (neat): 2937, 2815, 2763, 1462, 1041, 912, 759, 699 cm⁻¹.


3-Ethyl-2,2-difuoruo-1,1-dimethyl-3-phenyl-1α,2α-azaborolidine (18ba)

Following a literature reported procedure, to a rapidly stirred solution of N,N-dimethyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentan-1-amine (2ba) (95.2 mg, 0.33 mmol) in MeOH (3 ml) was added dropwise a solution of KHF₂ (105.4 mg, 1.35 mmol) in H₂O (700 μl) at r.t. The resulting mixture was stirred for 30 min and then concentrated under reduced pressure. The residue was redisolved in a mixture of MeOH/H₂O (1:1 v/v, 6 ml) and evaporated to dryness. This concentration–dissolution cycle was repeated 6 times,
after which $^1$H NMR analysis of an aliquot of the reaction mixture showed no presence of pinacol ($\delta = 1.14$) in acetonitrile-$d_3$. The solid residue was then triturated with dry acetone (5 mL); the liquid phase was carefully decanted and the residual inorganic salts were additionally washed with acetone ($3 \times 1$ mL). The combined washings were collected and concentrated in vacuo to give a 2:1 mixture of the desired tetrafluoroborate salt and azaborolidine $18b$ (82% overall yield). A portion of the mixture (45 mg) was dissolved in dry MeCN (3 mL) and the solution was heated at reflux for 5 h. The reaction mixture was then filtered through a pad of SiO$_2$ and washed with CH$_2$Cl$_2$ to give azaborolidine $18b$ (26.4 mg, 68%) as a white solid.

IR (neat): 2959, 2927, 1467, 1053, 755, 724, 701, 658 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 7.29$ (m, 4 H, Ar-H), 7.12 (m, 1 H, Ar-H), 3.00 (m, 1 H, 1-H), 2.19 (m, 1 H, 2-H), 2.16 (m, 2 H, 3-H, 11-H), 2.14 (m, 1 H, 2-H). 2.04 (m, 1 H, 11-H), 1.87 (m, 1 H, 2-H), 1.47 (m, 1 H, 11-H).

13C NMR (101 MHz, CDCl$_3$): $\delta = 157.32$ (C, CH$_3$), 137.72 (4 C, Ar-C), 129.47 (2 C, Ar-C), 122.07 (2 C, Ar-C), 120.72 (4 C, Ar-C). HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{12}$H$_{18}$N: 176.1430; found: 176.1432.

$\text{(Z)}$-2-Methyl-1,2,3,4,5,10a-hexahydrobenzo$\text{[c]}$azocine ($20a$)

To a solution of diisopropylamine (140 $\mu$L, 1 mmol) in anhydrous THF (500 $\mu$L) was added n-BuLi ($625 \mu$L, 1 mmol) at $-78^\circ$C. After stirring for 20 min at $-78^\circ$C and 10 min at r.t., the solution was added dropwise to a mixture of pyrrolidinium salt ($5a$) (93.6 mg, 0.6 mmol) and 2-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ($5k$) (93.6 mg, 0.6 mmol) in dry THF (12 mL) at $-78^\circ$C. The reaction mixture was stirred at $-78^\circ$C for 1 h and then allowed to warm to r.t. The solvent was removed in vacuo and the crude residue was then dried over MgSO$_4$ and concentrated in vacuo to afford the crude product, which was purified by chromatography on silica gel (EtOAc/Et$_2$N = 100:0.5) to afford the pure azocine $20a$ (42.2 mg, 48%) as a colourless oil.

IR (neat): 2972, 1475, 1256, 1152, 754, 635 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 7.50$ (d, $J = 6.6$ Hz, 2 H, Ar-H), 7.45 ({$\delta$}, $J = 8.6$ Hz, 3 H, Ar-H), 4.87 (dd, $J_1 = 11.5$ Hz, J$_2 = 7.8$ Hz, 1 H, 1-H), 3.82 (t, $J = 7.7$ Hz, 2 H, 4-H), 3.07 (s, 3 H, CH$_3$), 2.69 (s, 3 H, CH$_3$), 2.60 (m, 1 H, 1-H), 2.49 (m, 1 H, 2-H), 2.31 (m, 2 H, 3-H).

13C NMR (101 MHz, CDCl$_3$): $\delta = 131.36$ (Ar-C), 130.85 (2 C, Ar-C), 129.47 (2 C, Ar-C), 128.41 (Ar-C), 120.72 (q, $J = 322.2$ Hz, CF$_3$), 78.69 (1-C), 65.84 (4-C), 50.59 (CH$_3$), 45.18 (CH$_3$), 26.13 (2-C), 19.25 (3-C).

HRMS (ESI): $m/z$ [M + SO$_2$CF$_3$]$^+$ calcd for C$_{12}$H$_{16}$N: 264.1543; found: 264.1551.

1-Methyl-2-phenylpyrroline (24)

Following a procedure reported by Turner,$^{24}$ commercially available 2-phenylpyrrole (3.4 mmol, 500 mg) was suspended in H$_2$O (4 mL) in a microwave test tube and formic acid (3.7 mmol, 141 $\mu$L) and formaldehyde (35% solution in H$_2$O, 3.7 mmol, 320 $\mu$L) were added at r.t. The tube was sealed and was heated using microwave irradiation at $150^\circ$C for 5 min. The reaction mixture was allowed to cool to r.t., then it was basified to pH 14 using an aq solution of NaOH (2.0 M) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude material was purified by Kugelrohr distillation to afford the pure tertiary amine (396 mg, 72%) as a colourless liquid.

IR (neat): 2968, 2775, 1454, 1044, 754, 699 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 7.36$–7.29 (m, 4 H, Ar-H), 7.23 (m, 1 H, Ar-H), 3.24 (td, $J_1 = 9.4$ Hz, $J_2 = 1.8$ Hz, 1 H, 4-H), 3.03 (t, $J = 8.8$ Hz, 1 H, 1-H), 2.22 (m, 1 H, 4-H), 2.17 (m, 1 H, 2-H), 2.17 (s, 3 H, CH$_3$), 1.95 (m, 1 H, 3-H), 1.78 (m, 2 H, 2-H)–3-H).

13C NMR (101 MHz, CDCl$_3$): $\delta = 143.40$ (Ar-C), 128.47 (2 C, Ar-C), 127.62 (2 C, Ar-C), 127.12 (Ar-C), 71.79 (1-C), 57.22 (4-C), 40.62 (CH$_3$), 35.29 (2-C), 22.63 (3-C).

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{11}$H$_{16}$N: 162.1277; found: 162.127719.

1,1-Dimethyl-2-phenylpyridin-1-ium Trifluoromethanesulfonate ($19a$)

Following a modified version of a procedure by Couty,$^{10b}$ pyrroline $24$ (358 mg, 2.22 mmol) was dissolved in dry Et$_2$O (19 mL). After cooling to 0 $^\circ$C, methyl trifluoromethanesulfonate (500 $\mu$L, 4.45 mmol) was added. The mixture was stirred for 1 h at r.t.; then the volatiles were removed under vacuum to afford pyrrolidinium triflate $19a$ (721 g, >99%) as a purple oil.

IR (neat): 2972, 1475, 1256, 1152, 754, 706, 635 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 7.50$ (d, $J = 6.6$ Hz, 2 H, Ar-H), 7.45 ({$\delta$}, $J = 8.6$ Hz, 3 H, Ar-H), 4.87 (dd, $J_1 = 11.5$ Hz, J$_2 = 7.8$ Hz, 1 H, 1-H), 3.82 (t, $J = 7.7$ Hz, 2 H, 4-H), 3.07 (s, 3 H, CH$_3$), 2.69 (s, 3 H, CH$_3$), 2.60 (m, 1 H, 1-H), 2.49 (m, 1 H, 2-H), 2.31 (m, 2 H, 3-H).

13C NMR (101 MHz, CDCl$_3$): $\delta = 131.36$ (Ar-C), 130.85 (2 C, Ar-C), 129.47 (2 C, Ar-C), 128.41 (Ar-C), 120.72 ($J = 322.2$ Hz, CF$_3$), 78.69 (1-C), 65.84 (4-C), 50.59 (CH$_3$), 45.18 (CH$_3$), 26.13 (2-C), 19.25 (3-C).

HRMS (ESI): $m/z$ [M + SO$_2$CF$_3$]$^+$ calcd for C$_{12}$H$_{16}$N: 264.1543; found: 264.1551.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562447.


(22) Bagutski, V.; Ros, A.; Aggarwal, V. K. Tetrahedron 2009, 65, 9956.


(27) We did not observe a cyclopropane side product for the transformation of allyl boronic ester 5f. Boronic ester 5f is much less sterically hindered than 5k, thus leading to fast trapping of the ylide and fast ring-opening 1,2-migration.


