

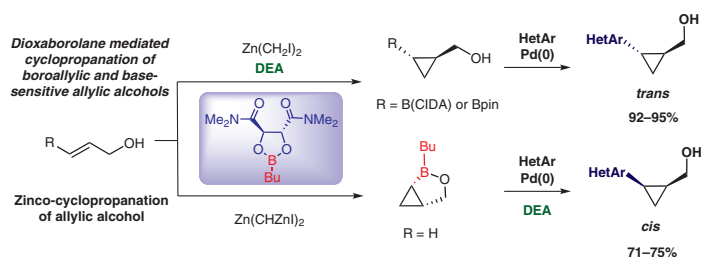
# Enantioselective Synthesis of *cis*- and *trans*-Borocyclopropylmethanol: Simple Building Blocks To Access Heterocycle-Substituted Cyclopropylmethanols

Saheer H. Siddiqui

Chandrasekhar Navuluri

André B. Charette\* 

FRQNT Centre in Green Chemistry and Catalysis, Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montreal, Quebec, H3C 3J7, Canada  
andre.charette@umontreal.ca



Received: 26.06.2019

Accepted: 02.07.2019

Published online: 01.08.2019

DOI: 10.1055/s-0037-1611896; Art ID: ss-2019-z0358-op

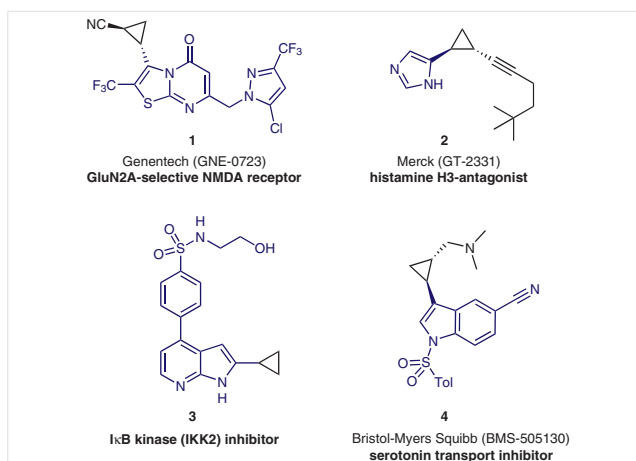
**Abstract** An enantioselective and non-oxidative methodology was developed to obtain enantioenriched cyclopropyl boronates using a diethanolamine-promoted selective decomplexation of dioxaborolane. The non-oxidative decomplexation of the dioxaborolane ligand from the cyclopropylmethoxide species formed in the dioxaborolane-mediated Simmons–Smith cyclopropanation reaction provided the enantioenriched CIDA-based (CIDA = *N*-cyclohexyliminodiacetic acid) borocyclopropane in 92% yield and 95.6:4.4 er. A robustness screen has shown diethanolamine to be compatible with esters, carbamates and *N*-heterocycles, providing a tool to access enantioenriched cyclopropanes carrying not only base-sensitive but oxidizable functional groups as well. Diethanolamine was found to be compatible with the modified zinc-cyclopropanation reaction of allyl alcohol to remove residual dioxaborolane from the corresponding *cis*-*N*-heterocycle cyclopropylmethanol, thereby leading to improved yields.

**Key words** borocyclopropanes, heterocycles, Simmons–Smith reaction, zinc-cyclopropanation, cross-coupling

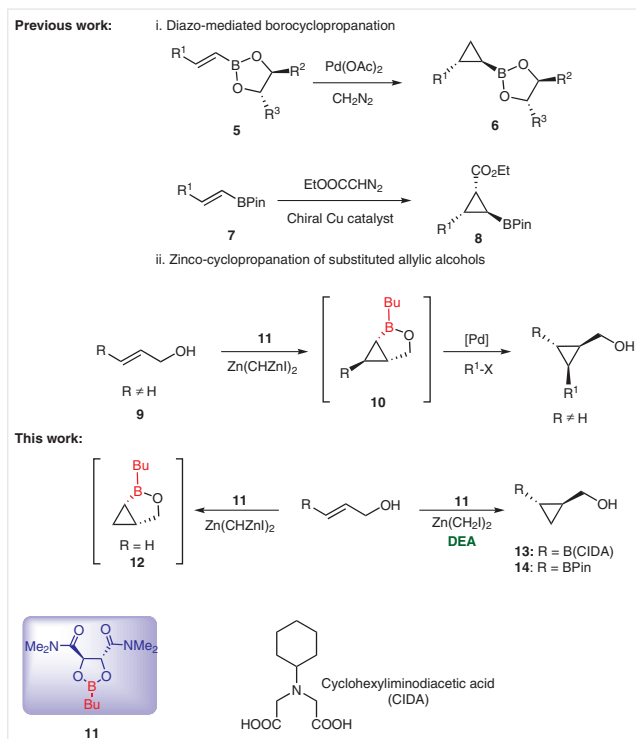
Cyclopropane motifs are ubiquitous in Nature<sup>1</sup> and are widely employed in pharmaceutically and agrochemically relevant compounds.<sup>2</sup> Cyclopropylboronic acids and derivatives are excellent synthons for the rapid introduction of the cyclopropyl motif into complex molecules.<sup>3</sup> Suzuki cross-coupling of these cyclopropylboronic acids with heteroaryls provide heteroaryl-substituted cyclopropanes, which serve as chiral cores in many natural products and biologically active drug candidates.<sup>4</sup> For example, thiazolopyrimidinones comprising the cyclopropane group (Figure 1, 1) serve as *N*-methyl-D-aspartate (NMDA) receptor activity modulators and rely on racemic borocyclopropylmethanols as optimal synthons for the introduction of cyclopropane groups in a racemic fashion.<sup>5</sup> Similarly, borocyclopropane building blocks have been employed in the

synthesis of cyclopropane-containing drug candidates (Figure 1, 2–4), where the products are delivered as racemates requiring chiral HPLC separation.<sup>6</sup> Although an array of methodologies to access substituted borocyclopropane subunits in a diastereoselective manner are available,<sup>7</sup> access to optically active borocyclopropane subunits is often limited. Thus far, asymmetric cyclopropanation methodologies to access enantioenriched borocyclopropanes include palladium-catalyzed cyclopropanation of chiral vinylboronates via diazo decomposition,<sup>8</sup> and copper-catalyzed carbene transfer of ethyldiazoacetate to alkenylboronates for the preparation of chiral 1,2,3-trisubstituted cyclopropanes (Scheme 1, part i).<sup>9</sup> The in situ preparation of enantioenriched borocyclopropanes via the zinc-cyclopropanation of substituted allylic alcohols is an alternative to the use of stoichiometric quantities of diazo compounds (Scheme 1, part ii).<sup>10</sup> The Simmons–Smith reaction has also been employed for the synthesis of chiral vinylpinacolboronates as separable racemic diastereomeric mixtures.<sup>8b</sup>

The Simmons–Smith cyclopropanation mediated by dioxaborolane **11** is a versatile methodology for the conversion of allylic alcohols and allylic ethers into an array of diversely substituted cyclopropane motifs in high enantioselectivities.<sup>11</sup> We report herein the first enantioselective Simmons–Smith cyclopropanation of boronate-bearing allylic alcohols for the preparation of enantioenriched borocyclopropane building blocks.<sup>12</sup> Pinacolate analogues have often been used in borocyclopropanation methodologies.<sup>4–6,13</sup> Many of these derivatives are oils and are prone to decomposition through protodeboronation, and are hence recurrently deemed ‘unstable’ boronic acids.<sup>14</sup> In contrast, cyclopropyltrifluoroborates are solids and display a reduced propensity to undergo protodeboronation, but have limited solubility in moderately polar solvents.<sup>15,16</sup>



**Figure 1** Selected cyclopropane-containing biologically active drug candidates



**Scheme 1** Synthesis of enantioenriched cyclopropylboronates

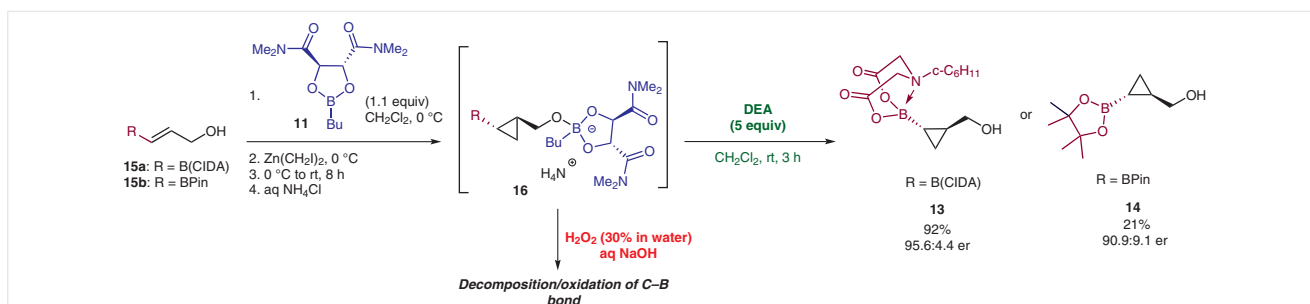
*N*-Methyliminodiacetic acid (MIDA) boronates have emerged as efficient building blocks due to their air stability, crystallinity, monomeric constitution, and compatibility with silica gel chromatography. The most attractive properties of MIDA boronates are their reversibly attenuated reactivity towards anhydrous cross-coupling conditions and compatibility with a wide range of reagents, which make them ideal coupling candidates for late-stage functionalization.<sup>3</sup> For these reasons, we envisioned the use of enanti-

oselective Simmons–Smith cyclopropanation of MIDA boronate bearing allylic alcohol to prepare the corresponding cyclopropylmethanol, which could serve as a robust building block for diversification reactions and the synthesis of cyclopropane-containing chiral cores in complex molecules discussed previously (Figure 1). Our initial Simmons–Smith cyclopropanation attempt was thwarted by two aspects of the reaction: (a) the insolubility of the vinyl MIDA boronate bearing the (*E*)-allylic alcohol in the solvents typically used for dioxaborolane-mediated cyclopropanations, such as dichloromethane, chloroform, and chlorobenzene and (b) decomposition of the boronate under the oxidative conditions used for the removal of dioxaborolane.<sup>11</sup>

To improve solubility, we proposed the replacement of the *N*-methyl substituent in MIDA boronates with a cyclohexyl group to prepare *N*-cyclohexyliminodiacetic acid (CIDA) protected boronates. The CIDA-bearing boronate allylic alcohol **15a** (Scheme 2) can be synthesized on a multigram scale in three steps starting from TBS-protected vinyl-Bpin-bearing (*E*)-allylic alcohol in 80% overall yield. During the synthesis of the free allylic alcohol **15a**, we were pleased to find orthogonal deprotection conditions for boronate substrates bearing silyl protecting groups. The in situ deprotection of the TBS group was a result of a mixture of DMSO, used as a cosolvent, and minimal amounts of water, generated during the CIDA protection, which provided the CIDA boronate allylic alcohol in 20% yield and the TBS-protected allylic alcohol in 60% yield. Heating the crude reaction mixture in DMSO/water (5:1) enhanced the overall yield to 80%.<sup>17</sup> Once obtained, we were pleased to find that the CIDA allylic alcohol **15a** was readily soluble in dichloromethane.

The cyclopropanation reaction with **15a** using  $\text{Zn}(\text{CH}_2\text{I})_2$  (2.2 equiv) and dioxaborolane **11** (1.1 equiv) proceeded smoothly with full conversion of the starting material. However, isolation of the cyclopropylmethanol by decomplexation of the chiral dioxaborolane ligand using hydrogen peroxide and sodium hydroxide led to the complete hydrolysis of the product (Scheme 2). Attempts to use less equivalents of peroxide did not prevent the hydrolysis of the product. The traditional workup conditions for the dioxaborolane-mediated cyclopropanation involves the use of 30% hydrogen peroxide and 2 M sodium hydroxide<sup>29</sup> or the use of highly basic 5 M aqueous potassium hydroxide to decomplex the dioxaborolane from the cyclopropyl methoxide species **16** formed in the reaction. Indeed, the hydrolysis of alkyltriolborates is known to involve harsh oxidative conditions,<sup>18</sup> resulting in narrow functional group compatibility and challenging purifications.<sup>19</sup>

Considering that MIDA boronates are highly labile to aqueous basic conditions and the presence of strong oxidants, we investigated a non-oxidative process for selective decomplexation of the tartaramide–boronate complex in the presence of the CIDA group in intermediate **16**. Diethanolamine (DEA) and ethanolamine have been used for the transesterification of certain pinacolboronate esters



**Scheme 2** Enantioselective borocyclopropanation of borosubstituted allylic alcohols **15a** and **15b**

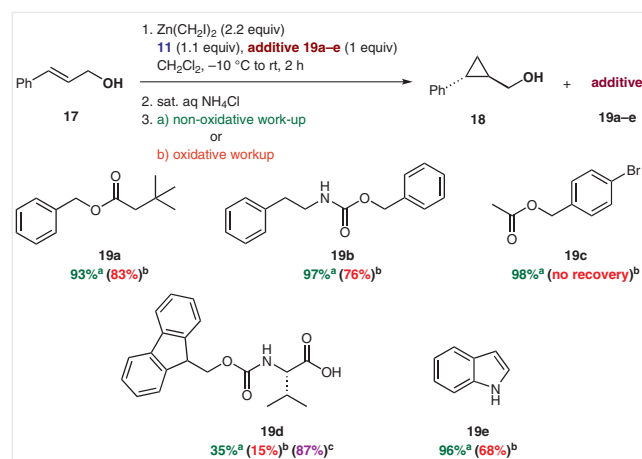
bearing electron-withdrawing groups.<sup>20</sup> However, Szabó recently observed that the diethanolamine cyclic boronate deprotection protocol is unsuccessful for transesterification of some electron-deficient vinylpinacolate analogues.<sup>21</sup> To the best of our knowledge, DEA has not been used for the transesterification of alkyltriolborates. We investigated the use of DEA for the transesterification of the (cyclopropylmethanol)boronate complexes. After extensive screening for isolation conditions, the decomplexation of the boronated intermediate **16** was achieved by direct addition of DEA (5 equiv) to the reaction mixture and stirring for 3 hours at room temperature. Purification of the decomplexed crude product by silica gel chromatography afforded **13** in 92% yield and 95.6:4.4 er (Scheme 2).

For comparative purposes, BPin-substituted allylic alcohol **15b** was subjected to the Simmons-Smith cyclopropanation conditions. After optimization, the pinacol-protected borocyclopropane **14** was obtained in 21% yield with a reproducible 90.9:9.1 er (Scheme 2). The low yield of the pinacol derivative is likely due to the transesterification of the pinacol ligand with excess DEA or due to decomposition by flash chromatography of pinacolboronates. We evaluated the robustness of the DEA decomplexation process using Glorius's intermolecular screening tool<sup>22</sup> for the cyclopropanation of allylic alcohol **17**<sup>11</sup> with five substrates containing base-sensitive functionalities, such as esters and carbamates, as well as indole, to study an example of an oxidizable group (Scheme 3).

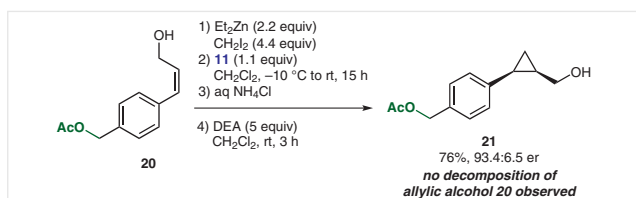
The recovery of the additives is consistently higher with the use of the non-oxidative conditions. The superiority is striking in the case of substrate **19c** (Scheme 3) bearing the acetate functionality, where the non-oxidative decomplexation allows isolation in 98% yield in comparison to no recovery when using the traditional procedure. The base-sensitive Fmoc-group-containing compound **19d** was found to be labile toward both oxidative and non-oxidative protocols, allowing only 35% isolated yield. We investigated the use of a more hindered DEA such as *N*-methyl DEA, and were pleased to find an improved recovery of 87% in comparison to the 15% yield isolated using the oxidative condi-

tions. For highly base-sensitive groups, the *N*-methyl DEA workup is recommended for better yields. Indole was recovered in 96% yield when using the DEA decomplexation, in comparison to 68% recovered when using the traditional decomplexation procedure, demonstrating the use of DEA-promoted cleavage of dioxaborolane to obtain oxidation-sensitive *N*-heterocycle-substituted cyclopropanes, which are typically incompatible with the traditional conditions.<sup>23</sup>

Based on the robustness screen of DEA, cyclopropanation of substrate **20** bearing the sensitive *O*-acetyl group was attempted (Scheme 4). Cyclopropylmethanol **21** bearing the acetate group was obtained in 76% isolated yield. During analysis of the byproducts, it was determined that the moderate yield was not a result of the decomposition of the acetyl allylic alcohol, but due to the lower reactivity of the substrate, evidenced by the recovery of the starting material in 24% isolated yield. Thus, the DEA-promoted decomplexation procedure proved to be quite versatile, and functional groups such as esters, carbamates, and others were shown to be compatible under the new non-oxidative conditions for the decomplexation of **11**.

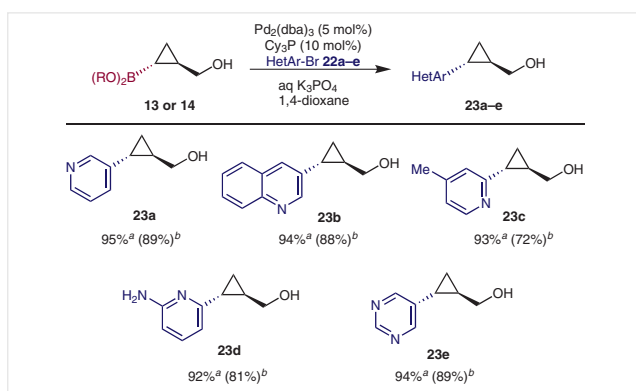


**Scheme 3** Cyclopropanation of allylic alcohol **17**. Workup conditions: <sup>a</sup> Diethanolamine (5 equiv), rt, 3 h; <sup>b</sup>  $\text{H}_2\text{O}_2$  (30% in water), 2 M aq NaOH, rt, 10 min; <sup>c</sup> *N*-Methyldiethanolamine (5 equiv), rt, 3 h.



**Scheme 4** Cyclopropanation of highly base-sensitive substrate

With the two borocyclopropane derivatives in hand, we turned our attention to the cross-coupling conditions for the Suzuki–Miyaura reaction, which is arguably the most effective method to integrate the cyclopropyl moiety into aromatic or heteroaromatic systems.<sup>24</sup> Heterocycles are the most widely used motifs in medicinal chemistry, and to aid introduction of the cyclopropane motif into heterocycles, we evaluated a series of cross-couplings of heteroaryl halides with **13** and **14** to obtain enantioenriched heteroaryl-substituted cyclopropanes. Methods for the cross-coupling of cyclopropylboronic acids and their pinacol analogues have been previously exploited.<sup>3,25</sup> Cross-coupling of cyclopropyl MIDA boronates has been achieved using SPhos and Pd(OAc)<sub>2</sub> to afford excellent yields of the coupled products while the cross-coupling of racemic *trans*-2-(trifluoromethyl)cyclopropyl MIDA boronates in the presence of Pd(OAc)<sub>2</sub> and PCy<sub>3</sub> provides the cyclopropyl adducts in only 17–32% yields.<sup>26</sup> After screening various cross-coupling conditions, we found the use of PCy<sub>3</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> as a suitable combination for the cross-coupling of the CIDA-boronate-bearing cyclopropylmethanol **13** (Scheme 5). It should be noted that cyclopropylboronic acids prepared immediately prior to the reaction can be as effective as the MIDA boronates.



**Scheme 5** Suzuki cross-coupling of borocyclopropanes. <sup>a</sup> Yields obtained when using borocyclopropane **13**. <sup>b</sup> Yields obtained when using borocyclopropane **14**.

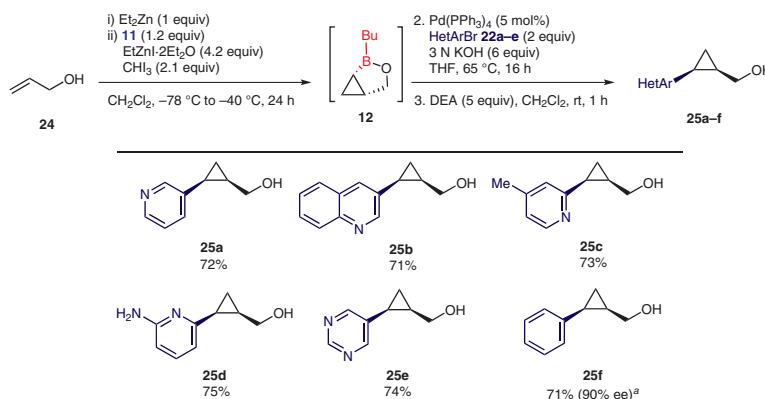
The cross coupling of **13** (95.6:4.4 er) with five heteroaryl bromides in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol%), PCy<sub>3</sub> (10 mol%) and aqueous potassium triphosphate afforded the cross-coupled cyclopropylmethanols **23a–e** in

excellent yields (Scheme 5). When the same coupling reactions were performed with the Bpin-substituted cyclopropane **14** (90.9:9.1 er), lower yields were obtained even though cyclopropane **14** was freshly prepared. The higher cross-coupling efficiency of the CIDA borocyclopropane compared to that of the Bpin-borocyclopropanes can be attributed to stability and controlled the hydrolytic character of tetracoordinate boronates in cross-coupling reactions.<sup>19</sup> Moreover, enantioenriched cyclopropane **13** exhibited benchtop air-stability even after 5 months, while borocyclopropane **14** partially decomposed (by about 20%) over 3 weeks.

Having evaluated an approach to access *trans*-N-heterocycle-substituted cyclopropanes, we turned our attention to the *cis* analogues. Attempts to synthesize the CIDA-bearing *cis*-boronate allylic alcohols failed due to lack of stability. To overcome these challenges, we took to an in situ approach to obtain the disubstituted borocyclopropylmethanol via the enantioselective zinc-cyclopropanation reaction of allyl alcohol followed by cross-coupling with N-heterocycles to prepare *cis*-N-heterocycle-substituted cyclopropanes (Scheme 6). A modified procedure was employed to enhance the yield of the zinc-cyclopropanation of the non-substituted allylic alcohol substrate. Treatment of allyl alcohol **24** with the *gem*-dizinc carbenoid in the presence of chiral ligand **11** led to the cyclic boronate **12**, which was subjected to Suzuki cross-coupling. In the case of allyl alcohol, the product often contained residual dioxaborolane or complexed dioxaborolane, affecting the yield of the reaction. To overcome the lower yield arising from the residual complexed dioxaborolane, the non-oxidative DEA-promoted decomplexation was applied to the crude reaction mixture to obtain the completely decomplexed *cis* isomer. Purification of the crude reaction mixture provided the desired N-heterocycle-substituted cyclopropanes in good yields and excellent enantioselectivity (Scheme 6).

In conclusion, a non-oxidative and enantioselective methodology has been developed that not only allows for the preparation of enantiopure borocyclopropane building blocks, but also provides a tool for the decomplexation of boron-ligated intermediates in the zinc-cyclopropanation reaction. Using this methodology, a novel air-stable enantioenriched CIDA borocyclopropane **13** building block was obtained in 92% yield and 95.6:4.4 er compared to the pinacolborocyclopropane **14** obtained in 21% yield and 90.9:9.1 er. Efficient cross-coupling conditions for the CIDA borocyclopropane allowed access to enantioenriched *trans*-N-heterocycle-substituted cyclopropanes in excellent yields. The non-oxidative DEA decomplexation was also applied in the zinc-cyclopropanation reaction to allow access to the fully decomplexed *cis*-N-heterocycle-substituted cyclopropanes, resulting in higher yields. This work demonstrates a robust and mild alternative for dioxaborolane-mediated cyclopropanations, broadening compatibility with highly base-sensitive and oxidizable substrates.





**Scheme 6** Synthesis of *cis*-heteroaryl-substituted cyclopropanes

Unless otherwise stated, all glassware was oven-dried and/or was flame-dried prior to use and all reactions were set up and carried out under an argon atmosphere<sup>27</sup> with the exclusion of moisture. Anhydrous solvents were obtained either by filtration through drying columns on a GlassContour system (Irvine, CA) (benzene and THF) or by distillation over calcium hydride (Et<sub>3</sub>N, pyridine, CH<sub>2</sub>Cl<sub>2</sub>) or sodium (THF). Absolute EtOH, glacial acetic acid, and Ac<sub>2</sub>O were used as is from commercial bottles. Unless otherwise noted, all solutions are aqueous solutions. Analytical TLC was performed on pre-coated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was aided by UV absorbance (254 nm), UV fluorescence (350 nm), or by using aq potassium permanganate (KMnO<sub>4</sub>), *p*-anisaldehyde, and ninhydrin. Flash column chromatography was performed on silica gel (pore size 60 Å, 230–400 mesh particle size, 40–63 μm particle size) in glass columns for the separation of products. Melting points were obtained on a Buchi melting point B-540 apparatus and are uncorrected. Specific rotations, [α]<sub>D</sub> values, were calculated from optical rotations measured at 25 °C in MeOH at the specified concentrations (*c* in g/100 mL) using a 0.5-dm cell length (*l*) on a Perkin-Elmer Polarimeter 241 at 589 nm, using the general formula: [α]<sub>D</sub><sup>25</sup> = (100 × α)/(*l* × *c*). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AV400, AV500, and AV700 MHz spectrometers. The corresponding chemical shifts for <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra are recorded in CDCl<sub>3</sub> or acetone-*d*<sub>6</sub>, and reported in ppm relative to the chemical shift of tetramethylsilane or the residual CHCl<sub>3</sub> (<sup>1</sup>H: δ = 7.26, <sup>13</sup>C: δ = 77.2), residual (CD<sub>3</sub>)<sub>2</sub>CO (<sup>1</sup>H: δ = 2.09, <sup>13</sup>C: δ = 205.9), or residual (CD<sub>3</sub>)<sub>2</sub>SO (<sup>1</sup>H: δ = 2.54, <sup>13</sup>C: δ = 40.5) as reference. All <sup>13</sup>C NMR spectra were obtained with complete proton decoupling. IR spectra were obtained on a Bruker Vertex Series FTIR (neat). High resolution mass spectra were recorded on an LC-MSD instrument from Agilent technologies 1200 series in positive electrospray ionization (ESI) and atmospheric-pressure chemical ionization (APCI) modes and analytical Supercritical Fluid Chromatography (SFC) were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. SFC data are reported as follows: (column type, eluent, flow rate, pressure; retention time (*t*<sub>R</sub>)). All organic extracts were dried over sodium sulfate and concentrated under vacuum. Et<sub>2</sub>Zn was purchased neat from AkzoNobel and used without further purification. Diethanolamine and *N*-methyldiethanolamine were purchased from Aldrich and were used without further purification. Fmoc-Val-OH was purchased from AAPPTec and used without further purification. Unless specified otherwise, all reagents for Suzuki cross-coupling reactions

were used without further purification and catalysts were handled in the glovebox. All reagents used were purified using standardized protocols.

#### (*E*)-6-Cyclohexyl-2-(3-hydroxyprop-1-en-1-yl)-1,3,6,2-dioxaborocane-4,8-dione (15a)

To a dry microwave vial, (*E*)-2-[[*tert*-butyldimethylsilyloxy]prop-1-en-1-yl]-6-cyclohexyl-1,3,6,2-dioxaborocane-4,8-dione (**15aa**; 440 mg, 1.10 mmol) was added, followed by DMSO (14 mL) and H<sub>2</sub>O (2.8 mL). The vial was sealed and placed under microwave irradiation for 1 h at 130 °C. The reaction mixture was cooled, transferred into a 40 mL flask, diluted with H<sub>2</sub>O (10 mL) and lyophilized until dryness; this gave **15a**.

Yield: 313 mg (99%); white solid; *R*<sub>f</sub> = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>/MeCN, 1:1); mp 117–118 °C.

IR (neat): 2939, 2860, 1740, 1644, 1448, 1326, 1290, 1244 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>): δ = 6.27 (dd, *J* = 13.5, 4.1 Hz, 1 H), 5.82 (d, *J* = 17.8 Hz, 1 H), 4.20–4.13 (m, 2 H), 3.94 (d, *J* = 16.8 Hz, 2 H), 3.74 (s, 1 H), 3.26 (td, *J* = 12.1, 6.1 Hz, 1 H), 2.81 (s, 2 H), 1.89 (d, *J* = 12.5 Hz, 2 H), 1.71–1.49 (m, 4 H), 1.44–1.25 (m, 4 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 169.5 (2 C), 146.3 (2 C), 123.9, 67.0, 64.5, 56.5 (2 C), 27.4 (2 C), 25.51, 25.46.

<sup>11</sup>B NMR (400 MHz, acetone-*d*<sub>6</sub>): δ = 10.7.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>20</sub>BNO<sub>5</sub>: 282.1507; found: 282.1509.

#### (*E*)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ol (15b)

To a stirred solution of (*E*)-*tert*-butyldimethyl[[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]oxy]silane<sup>28</sup> (12.0 g, 40.2 mmol) in EtOH (201 mL) was added dropwise a 3 M solution of trichloroacetic acid in EtOH (46.9 mL). The reaction mixture was stirred for 12 h. The reaction mixture was concentrated, and the residue was diluted with EtOAc (20 mL) and washed with sat. aq NaHCO<sub>3</sub> (2 × 15 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to provide a crude brown oil, which was purified by flash chromatography (silica gel, EtOAc/hexanes, 3:7).

Yield: 4.20 g (57%); yellow oil; *R*<sub>f</sub> = 0.4 (EtOAc/hexane, 3:7).

IR (neat): 3420, 2977, 2929, 1643, 1358, 1317, 1411, 1004, 970 cm<sup>-1</sup>.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.74 (dt,  $J$  = 18.2, 4.2 Hz, 1 H), 5.70 (dt,  $J$  = 18.2, 1.9 Hz, 1 H), 4.24 (dd,  $J$  = 4.2, 1.9 Hz, 2 H), 1.79 (br, 1 H), 1.27 (s, 12 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 151.9, 117.3, 83.5, 64.8 (2 C), 25.0 (4 C).

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_9\text{H}_{17}\text{BO}_3$ : 185.1343; found: 185.1344.

### 6-Cyclohexyl-2-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]-1,3,6,2-dioxaborocane-4,8-dione (**13**)

A 10 mL flame-dried flask was charged with **15a** (48.3 mg, 0.17 mmol), **11** (51.1 mg, 0.19 mmol), and  $\text{CH}_2\text{Cl}_2$  (2 mL). The mixture was sonicated for 1 min to provide a homogeneous solution. In another flame-dried flask, neat  $\text{Et}_2\text{Zn}$  (40.3  $\mu\text{L}$ , 0.4 mmol) was added to  $\text{CH}_2\text{Cl}_2$  (2 mL) at 0 °C; dropwise addition of diiodomethane (63.6  $\mu\text{L}$ , 0.8 mmol) followed. The mixture was stirred at 0 °C for 10 min. The mixture of dioxaborolane **11** and **15a** was cannulated slowly into the reaction flask. After complete addition, the reaction mixture was allowed to stir for 8 h. The mixture remained homogeneous throughout. Upon completion of the reaction, the mixture was quenched with  $\text{NH}_4\text{Cl}$  (2 mL), and diluted with EtOAc (5 mL) and brine (5 mL). The organic layer was separated and the aqueous layer was washed with EtOAc (2  $\times$  5 mL). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. To the resulting residue was added a solution of diethanolamine (93.5 mg, 0.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (750  $\mu\text{L}$ ) and the mixture was allowed to stir for 3 h. After this, the mixture was saturated with silica gel, dried, and directly loaded for flash chromatography (silica gel, EtOAc/hexanes (1:1) then MeCN); this gave product **13**.

Yield: 48.3 mg (92%); 95.6:4.4 er; SFC (Chiralpak OD-H 25cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min):  $t_{\text{R}(\text{major})}$ : 9.76 min;  $t_{\text{R}(\text{minor})}$ : 8.63 min; white solid; mp 132–133 °C;  $R_f$  = 0.3 (MeCN);  $[\alpha]_{\text{D}}^{25}$  +10.8 (c 0.83, MeOH).

IR (neat): 2936, 2861, 1741, 1449, 1292, 1247, 1000, 898  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz, acetone- $d_6$ ):  $\delta$  = 4.13 (dd,  $J$  = 25.9, 16.9 Hz, 2 H), 3.92–3.83 (m, 3 H), 3.67 (dd,  $J$  = 11.1, 5.9 Hz, 1 H), 3.22 (dd,  $J$  = 10.6, 7.6 Hz, 1 H), 2.83 (s, 1 H) 2.12 (ddd,  $J$  = 19.0, 11.3, 8.0 Hz, 2 H), 1.86 (dd,  $J$  = 13.8, 7.5 Hz, 2 H), 1.65 (d,  $J$  = 13.0 Hz, 1 H), 1.58 (dd,  $J$  = 12.2, 3.6 Hz, 1 H), 1.56–1.40 (m, 3 H), 1.28 (tt,  $J$  = 12.8, 3.7 Hz, 1 H), 0.88 (dd,  $J$  = 12.4, 7.5 Hz, 1 H), 0.42–0.36 (m, 2 H), –0.26 to –0.30 (m, 1 H).

$^{13}\text{C}$  NMR (176 MHz, acetone- $d_6$ ):  $\delta$  = 168.8, 168.0, 72.3, 66.4, 65.4, 57.0, 55.1, 27.1, 26.6, 24.7, 24.5, 17.3, 5.9, 1.9.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{22}\text{BNO}_5$ : 296.1664; found: 296.1672.

### Larger-Scale Preparation of **13** (5.6 mmol)

In a 250 mL flame-dried flask, **15a** (1.56 g, 5.6 mmol) and **11** (51.7 g, 6.10 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (25 mL). Sonication for 1 min allowed **15a** to dissolve in the  $\text{CH}_2\text{Cl}_2$ . In another flame-dried flask,  $\text{Et}_2\text{Zn}$  (1.26 mL, 12.2 mmol) was added to  $\text{CH}_2\text{Cl}_2$  (50 mL) and DME (1 mL) at 0 °C; dropwise addition of diiodomethane (1.9 mL, 24.2 mmol) followed. The mixture was stirred at 0 °C for 10 min. The mixture of dioxaborolane **11** and **15a** was cannulated slowly into the cooled reaction flask. After complete addition, the reaction mixture was allowed to stir for 12 h. The reaction remained homogeneous throughout. Upon completion, the mixture was quenched with  $\text{NH}_4\text{Cl}$  (5 mL), and diluted with EtOAc (20 mL) and brine (10 mL). The organic layer was separated, and the aqueous layer was washed with EtOAc (2  $\times$  20 mL). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and con-

centrated under reduced pressure. To the resulting residue was added a solution of diethanolamine (2.92 g, 27.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (21 mL), and the mixture was allowed to stir for 3 h. The crude reaction mixture was loaded directly for flash chromatography (silica gel, EtOAc/hexanes (1:1) then MeCN). This gave product **13** as a white solid spectroscopically identical to **13** obtained at a 0.2 mmol scale.

Yield: 1.52 g (93%); 92.9:7.3 er; SFC (Chiralpak OD-H 25cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min):  $t_{\text{R}(\text{major})}$ : 10.11 min,  $t_{\text{R}(\text{minor})}$ : 8.41 min;  $[\alpha]_{\text{D}}^{25}$  +9.3 (c 1.0, MeOH).

### [(1R,2R)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]methanol (**14**)

Neat  $\text{Et}_2\text{Zn}$  (169  $\mu\text{L}$ , 1.64 mmol) was added to stirred  $\text{CH}_2\text{Cl}_2$  (3 mL) in a flame-dried flask at rt. The solution was cooled to 0 °C and diiodomethane (264  $\mu\text{L}$ , 3.28 mmol) was added dropwise over 5 min while maintaining the temperature at –5 to 0 °C. Once the addition was complete, the mixture was allowed to stir for 10 min, after which a solution of premixed **15b** (137 mg, 0.74 mmol) and **11** (221 mg, 0.82 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added dropwise over 1 min. The resulting mixture was stirred for 6 h at rt. The reaction mixture was diluted with  $\text{NH}_4\text{Cl}$  (1 mL) and EtOAc (3 mL). The organic layer was separated and washed with brine (2 mL). The aqueous layer was extracted with EtOAc (2  $\times$  3 mL) and the organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure. To the residue was added diethanolamine (2.85 g, 27.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (21 mL) and the mixture was allowed to stir for 3 h. The crude reaction mixture was loaded directly onto a column for chromatography (silica gel, EtOAc/hexanes, 1:3). After purification the pure product was obtained as a yellow oil.

Yield: 31 mg (21%); 90.9:9.1 er; TOF (6224) (Chiralpak OJ-RH, 13% MeCN, 0.4 mL/min):  $t_{\text{R}(\text{major})}$ : 20.19 min,  $t_{\text{R}(\text{minor})}$ : 17.74 min;  $R_f$  = 0.3 (EtOAc/hexane, 1:3);  $[\alpha]_{\text{D}}^{25}$  +7.4 (c 0.83, MeOH).

IR (neat): 2977, 2932, 1644, 1425, 1371, 1314, 1141, 1042, 854  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.45 (d,  $J$  = 6.8 Hz, 2 H), 1.65 (s, 1 H), 1.30–1.34 (m, 1 H), 1.21 (s, 12 H), 0.76–0.73 (ddd,  $J$  = 7.7, 6.3, 3.7 Hz, 1 H), 0.56–0.54 (m, 1 H), –0.23 (dt,  $J$  = 9.8, 5.8 Hz, 1 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 83.2, 68.0, 24.8 (2 C), 20.5 (4 C), 9.3, –1.6.

$^{11}\text{B}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 33.1.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$  calcd for  $\text{C}_{10}\text{H}_{19}\text{BO}_3$ : 180.1431; found: 180.1423.

### Larger-Scale Preparation of **14** (5.4 mmol)

Neat  $\text{Et}_2\text{Zn}$  (1.23 mL, 12.0 mmol) was added to a flame-dried flask containing a stir bar,  $\text{CH}_2\text{Cl}_2$  (25.0 mL), and DME (1.13 mL). The solution was cooled to 0 °C, after which diiodomethane (1.93 mL, 23.9 mmol) was added dropwise over 5 min, while maintaining the temperature at –5 to 0 °C. Once the addition was complete, the mixture was allowed to stir for 10 min, after which a solution of premixed **15b** (1.00 g, 5.43 mmol) and **11** (1.61 g, 5.98 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added dropwise over 1 min. The resulting mixture was stirred for 15 h at rt. The reaction mixture was diluted with  $\text{NH}_4\text{Cl}$  (10 mL) and EtOAc (20 mL). The organic layer was separated and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (2  $\times$  10 mL). The organic layers were combined, dried with  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. To the residue was added warm diethanolamine (2.85 g, 27.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (21 mL) and the mixture was allowed to stir for 3 h. Once the reaction was complete, the crude reaction mixture was loaded directly for chromatography (sili-

ca gel, EtOAc/hexanes, 1:3). After purification the pure product was obtained as a yellow oil spectroscopically identical to **14** at the 1.64 mmol scale.

Yield: 452 mg (42%); 89.6:10.3 er; TOF (6224) (Chiralpak OJ-RH, 9% MeCN, 0.4 mL/min):  $t_{R(\text{major})}$ : 25.24 min;  $t_{R(\text{minor})}$ : 21.86;  $[\alpha]_D^{25}$  +7.6 (c 1.0, MeOH).

**Products 19a–e by Rapid Assessment of Functional Groups: Intermolecular Screening Protocol for Non-oxidative Workup; General Procedure D**

To a solution of Et<sub>2</sub>Zn (113  $\mu$ L, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at 0 °C was added diiodomethane (177  $\mu$ L, 2.20 mmol). The mixture was stirred at 0 °C for 10 min to give a white precipitate, to which was added a solution of alcohol **17** (67.1 mg, 0.50 mmol), additive **19** (0.50 mmol), and dioxaborolane **11** (149 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) via a cannula. The resulting mixture was stirred for 2 h at rt and was quenched by the addition of sat. aq NH<sub>4</sub>Cl (5 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et<sub>2</sub>O (5 mL). The two layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic layers were dried and concentrated to afford a colorless residue. Warm diethanolamine (263 mg, 2.50 mmol), weighed into a vial and dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), was transferred to the flask containing the reaction mixture. Additional CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) was used to rinse the diethanolamine and transferred to the flask containing the reaction mixture. The mixture was stirred at rt for 3 h. Silica gel was added to the reaction mixture, which was concentrated, resulting in dry silica gel saturated with the crude reaction mixture. Purification by column chromatography afforded cyclopropane **18** as a colorless oil, which was identical in all aspects to the reported compound,<sup>29</sup> and additives **19a–e**.

**Products 18 and 19a–e by Rapid Assessment of Functional Groups: Intermolecular Screening Protocol for Oxidative Workup; General Procedure E**

To a solution of Et<sub>2</sub>Zn (113  $\mu$ L, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at 0 °C was added diiodomethane (177  $\mu$ L, 2.20 mmol). The mixture was stirred at 0 °C for 10 min to give a white precipitate, to which was added a solution of alcohol **17** (67.1 mg, 0.50 mmol), additive (0.50 mmol), and dioxaborolane **11** (149 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) via a cannula. The resulting mixture was stirred for 2 h at rt and was quenched by the addition of sat. aq NH<sub>4</sub>Cl (5 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et<sub>2</sub>O (5 mL). The two layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic layers were transferred into an Erlenmeyer flask, and a solution containing 2 N aq NaOH (8.7 mL) and 30% aq H<sub>2</sub>O<sub>2</sub> (1.5 mL) was added in one portion. The resulting biphasic solution was vigorously stirred for 10 min, after which the two layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL) and the combined organic layers were washed with 10% aq HCl (10 mL). The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL) and the combined organic layers were successively washed with sat. aq Na<sub>2</sub>SO<sub>3</sub> (10 mL), sat. aq NaHCO<sub>3</sub> (10 mL), and brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification by column chromatography afforded cyclopropane **18** and additive **19a–e**.

**Benzyl 3,3-Dimethylbutanoate (19a)**

*General Procedure D:* Purification by column chromatography (silica gel, EtOAc/hexanes, 1:9) resulted in the recovered additive **19a** (95.9 mg, 93%) and the desired cyclopropane **18** (70.4 mg, 95%).

*General Procedure E:* Recovered additive **19a** (85.6 mg, 83%) and the desired cyclopropane **18** (67.4 mg, 91%).

**Benzyl Phenethylcarbamate (19b)**

*General Procedure D:* Purification by column chromatography (silica gel, EtOAc/hexanes, 1:9) resulted in the recovered additive **19b** (125 mg, 97%) and the desired cyclopropane **18** (69.7 mg, 94%).

*General Procedure E:* Recovered additive **19b** (97.0 mg, 76%) and the desired cyclopropane **18** (70.4 mg, 95%).

**4-Bromobenzyl Acetate (19c)**

*General Procedure D:* Purification by column chromatography (silica gel, EtOAc/hexanes, 1:3) resulted in the recovered additive **19c** (83.7 mg, 98%) and the desired cyclopropane **18** (51.9 mg, 94%).

*General Procedure E:* No recovery of **19c** and the desired cyclopropane **18** (51.9 mg, 94%).

**{[(9H-Fluoren-9-yl)methoxy]carbonyl}-L-valine (19d)**

*General Procedure D:* Purification by column chromatography (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) resulted in the recovered additive **19d** (59.4 mg, 35%) and the desired cyclopropane **18** (68.9 mg, 93%).

*General Procedure E:* Recovered additive **19d** (25.5 mg, 15%) and the desired cyclopropane **18** (69.7 mg, 94%).

**1H-Indole (19e)**

*General Procedure D:* Purification by column chromatography (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) resulted in the recovered additive **19e** (58.0 mg, 99%) and the desired cyclopropane **18** (68.9 mg, 93%).

*General Procedure E:* Recovered additive **19e** (39.8 mg, 68%) and the desired cyclopropane **18** (69.7 mg, 94%).

**N-Methyldiethanolamine Workup for Fmoc-Containing Additive 19d**

To a solution of Et<sub>2</sub>Zn (113  $\mu$ L, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at 0 °C was added diiodomethane (179  $\mu$ L, 2.2 mmol). The mixture was stirred at 0 °C for 10 min to give a white precipitate, to which was added a solution of alcohol **17** (67 mg, 0.5 mmol), **19d** (0.5 mmol), and dioxaborolane **11** (162 mg, 0.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) via a cannula. The resulting mixture was stirred for 2 h at rt and was quenched by the addition of sat. aq NH<sub>4</sub>Cl (5 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et<sub>2</sub>O (5 mL). The two layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  5 mL). The combined organic layers were dried and concentrated to afford a colorless residue. N-Methyldiethanolamine (298 mg, 2.5 mmol) was weighed into a vial, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), and transferred to the flask containing the reaction mixture. Additional CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) was used to rinse the diethanolamine and transferred to the flask containing the reaction mixture. The mixture was stirred at rt for 3 h and was then adsorbed onto silica gel. Purification by column chromatography (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) resulted in the recovered additive **19d** (148 mg, 87%) and the desired cyclopropane **18** (68.9 mg, 93%).

**4-[(1R,2S)-2-(Hydroxymethyl)cyclopropyl]benzyl Acetate (21)**

To a solution of Et<sub>2</sub>Zn (233  $\mu$ L, 2.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.7 mL) at 0 °C was added diiodomethane (365  $\mu$ L, 4.52 mmol). The mixture was stirred at 0 °C for 10 min to give a white precipitate, to which was added a solution of allylic alcohol **20** (212 mg, 1.03 mmol) and dioxaborolane **11** (306 mg, 1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.5 mL) via a cannula.

The resulting mixture was stirred for 15 h at rt and was quenched by the addition of sat. aq NH<sub>4</sub>Cl (15 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et<sub>2</sub>O (15 mL). The two layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 4 mL). The combined organic layers were dried and concentrated to afford a colorless residue. Warm diethanolamine (541 mg, 5.15 mmol), weighed into a vial and dissolved in CH<sub>2</sub>-Cl<sub>2</sub> (4 mL), was transferred to the flask containing the reaction mixture. Additional CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was used to rinse the diethanolamine and transferred to the flask containing the reaction mixture. The mixture was stirred at rt for 3 h. The mixture was stirred at rt for 3 h. Silica gel was added to the reaction mixture, which was concentrated, resulting in dry silica gel saturated with the crude reaction mixture. Purification of the saturated silica by column chromatography (silica gel, EtOAc/hexanes, 1:4) afforded **21**.

Yield: 172 mg (76%); 93.4:6.6 er; SFC (Chiralpak AD-H 25cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min): *t*<sub>R(major)</sub>: 5.65 min; *t*<sub>R(minor)</sub>: 9.73 min; colorless oil; [ $\alpha$ ]<sub>D</sub><sup>25</sup> –20.0 (c 0.20, MeOH).

IR (neat): 3389, 2931, 2871, 1734, 1376, 1226, 1026, 1016 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.28–7.24 (m, 4 H), 5.07 (s, 2 H), 3.47 (dd, *J* = 15.7, 6.3 Hz, 1 H), 3.26 (dd, *J* = 11.6, 8.5 Hz, 1 H), 2.28 (td, *J* = 8.5, 6.2 Hz, 1 H), 2.09 (s, 3 H), 1.54–1.47 (m, 1 H), 1.06 (td, *J* = 8.4, 5.4 Hz, 1 H), 0.89–0.85 (m, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.1, 138.7, 134.0, 129.3 (2 C), 128.6 (2 C), 66.3, 63.9, 21.23, 21.22, 20.7, 8.0.

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>16</sub>O<sub>3</sub>: 243.0991; found: 243.0987.

### (2-Heterylcyclopropyl)methanol Compounds **23a–e** by Suzuki Cross-Coupling of **13**; General Procedure A

To a dried round-bottom flask equipped with a stir bar was added HetArBr **22a–e** (0.28 mmol), **13** (0.14 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (6.4 mg, 5 mol%), and Cy<sub>3</sub>P (3.9 mg, 10 mol%). The vial was sealed with a septum and flushed with argon. To the vial was added dioxane (500  $\mu$ L), and the resulting mixture was stirred at 23 °C for 20 min. To the mixture was then added 3.0 M aq K<sub>3</sub>PO<sub>4</sub> (280  $\mu$ L), and the mixture was degassed by sparging with argon for 20 min. The vial was placed in an oil bath and heated at 110 °C while stirring for 20 h. After completion, the reaction mixture was cooled and diluted with EtOAc (4 mL) and brine (2 mL) and the organic layer was separated. The aqueous layer was washed with EtOAc (2 × 2 mL), dried, and concentrated. Purification by column chromatography provided the coupled products **23a–e**.

### (2-Heterylcyclopropyl)methanol Compounds **23a–e** by Suzuki Cross-Coupling of **14**; General Procedure B

To a dried flask equipped with a stir bar was added HetArBr **22a–e** (0.28 mmol), **14** (0.14 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (6.4 mg, 5 mol%), and Cy<sub>3</sub>P (3.93 mg, 10 mol%). The vial was sealed with a septum and flushed with argon. To the vial was added dioxane (500  $\mu$ L) and the resulting mixture was stirred at 23 °C for 20 min. To the mixture was then added 3.0 M aq K<sub>3</sub>PO<sub>4</sub> (280  $\mu$ L, degassed with argon for 20 min). The vial was placed in an oil bath and heated at 110 °C while stirring for 20 h. After completion, the reaction mixture was cooled and diluted with EtOAc (4 mL) and brine (2 mL) and the organic layer was separated. The aqueous layer was washed with EtOAc (2 × 2 mL), dried, and concentrated. Purification by column chromatography provided the coupled products **23a–e**.

### [(1*S*,2*S*)-2-(Pyridin-3-yl)cyclopropyl]methanol (**23a**)

**General Procedure A:** 3-Bromopyridine (47.1 mg, 0.29 mmol) and **13** (41.3 mg, 0.14 mmol) were used.

Yield: 19.8 mg (95%); pale yellow oil; *R*<sub>f</sub> = 0.3 (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +25.6 (c 0.83, MeOH).

**General Procedure B:** 3-Bromopyridine (47.1 mg, 0.29 mmol) and **14** (27.7 mg, 0.14 mmol) were used.

Yield: 18.6 mg (89%); pale yellow oil.

IR (neat): 3352, 3269, 3002, 2926, 2853, 11642, 1472, 1426, 1109 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.39 (s, *J* = 5.7 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.17 (dd, *J* = 7.8, 4.8 Hz, 1 H), 3.66 (ddd, *J* = 35.5, 11.3, 6.5 Hz, 2 H), 2.03 (br, 1 H), 1.83–1.79 (m, 1 H), 1.48 (dd, *J* = 13.4, 6.1 Hz, 1 H), 1.03–0.97 (m, 2 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 148.5, 147.2, 138.2, 132.9, 123.4, 66.2, 25.4, 19.0, 13.8.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>11</sub>NO: 150.0913; found: 150.0910.

### [(1*S*,2*S*)-2-(Quinolin-3-yl)cyclopropyl]methanol (**23b**)

**General Procedure A:** 5-Bromoquinoline, 98% (58.3 mg, 0.28 mmol) and **13** (41.3 mg, 0.14 mmol) were used.

Yield: 26.2 mg (94%); pale yellow oil.

**General Procedure B:** 5-Bromoquinoline, 98% (58.3 mg, 0.28 mmol) and **14** (27.7 mg, 0.14 mmol) were used.

Yield: 24.5 mg (88%); pale yellow oil; *R*<sub>f</sub> = 0.3 (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +36.3 (c 0.87, MeOH).

IR (neat): 3352, 3303, 3001, 2922, 2854, 1706, 1495, 1332, 1028 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.72 (d, *J* = 2.2 Hz, 1 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 7.70 (s, 2 H), 7.64–7.62 (m, 1 H), 7.52–7.50 (m, 1 H), 3.77 (dd, *J* = 11.3, 6.3 Hz, 1 H), 3.68 (dd, *J* = 11.3, 6.9 Hz, 1 H), 2.02–1.99 (m, 1 H), 1.62–1.58 (m, 1 H), 1.13–1.08 (m, 2 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.6, 146.9, 135.5, 131.3, 129.3, 128.7, 128.2, 127.4, 126.9, 66.3, 25.6, 19.3, 13.9.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>NO: 200.1069; found: 200.1067.

### [(1*S*,2*S*)-2-(4-Methylpyridin-2-yl)cyclopropyl]methanol (**23c**)

**General Procedure A:** 2-Bromo-4-methylpyridine, 98% (48.2 mg, 0.28 mmol) and **13** (41.3 mg, 0.14 mmol) were used.

Yield: 21.3 mg (93%); clear oil.

**General Procedure B:** 2-Bromo-4-methylpyridine, 98% (48.2 mg, 0.28 mmol) and **14** (27.7 mg, 0.14 mmol) were used.

Yield: 16.5 mg (72%); clear oil; *R*<sub>f</sub> = 0.4 (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +44.0 (c 0.56, MeOH).

IR (neat): 3350, 2923, 2850, 1608, 1447, 1376, 1024, 848 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.28 (d, *J* = 5.1 Hz, 1 H), 6.95 (d, *J* = 11.8 Hz, 1 H), 6.86 (d, 1 H), 3.70 (dd, *J* = 11.3, 6.4 Hz, 1 H), 3.58 (dd, *J* = 11.3, 7.1 Hz, 1 H), 2.30 (s, 3 H), 1.95–1.91 (m, 1 H), 1.74 (tdd, *J* = 10.6, 5.3, 3.2 Hz, 1 H), 1.64 (s, 1 H), 1.27–1.24 (m, 1 H), 0.94 (ddd, *J* = 8.6, 5.7, 4.4 Hz, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 161.3, 149.1, 147.2, 122.4, 121.9, 66.4, 25.7, 23.0, 21.1, 14.0.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>NO: 164.1069; found: 164.1069.



**[(1*S*,2*S*)-2-(6-Aminopyridin-2-yl)cyclopropyl]methanol (23d)**

**General Procedure A:** 2-Amino-6-bromopyridine, 98% (48.4 mg, 0.28 mmol) and **13** (41.3 mg, 0.14 mmol) were used.

Yield: 21.1 mg (92%); yellow oil.

**General Procedure B:** 2-Amino-6-bromopyridine, 98% (27.7 mg, 0.14 mmol) and **14** (41.3 mg, 0.14 mmol) were used.

Yield: 18.6 mg (81%); yellow oil;  $R_f = 0.3$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{25} +37.5$  (c 0.85, MeOH).

IR (neat): 3337, 3206, 2927, 2851, 1574, 1464, 1025, 791 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 7.29$  (t,  $J = 7.8$  Hz, 1 H), 6.43 (d,  $J = 7.4$  Hz, 1 H), 6.27 (d,  $J = 8.1$  Hz, 1 H), 3.67 (dd,  $J = 11.3, 6.3$  Hz, 1 H), 3.52 (dd,  $J = 11.2, 7.3$  Hz, 1 H), 1.85–1.82 (m, 1 H), 1.64 (d,  $J = 6.0$  Hz, 1 H), 1.18–1.15 (m, 1 H), 0.88–0.85 (m, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta = 148.5, 147.2, 138.2, 132.9, 123.4, 66.2, 25.4, 19.0, 13.8$ .

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>11</sub>NO: 165.1027; found: 165.1022.

**[(1*S*,2*S*)-2-(Pyrimidin-5-yl)cyclopropyl]methanol (23e)**

**General Procedure A:** 5-Bromopyrimidine, 97% (44.5 mg, 0.28 mmol) and **13** (41.3 mg, 0.14 mmol) were used.

Yield: 19.8 mg (94%); yellow oil.

**General Procedure B:** 5-Bromopyrimidine, 97% (44.5 mg, 0.28 mmol) and **14** (27.7 mg, 0.14 mmol) were used.

Yield: 18.7 mg (89%); pale yellow oil;  $R_f = 0.3$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{25} +38.9$  (c 0.87, MeOH).

IR (neat): 3335, 3003, 2925, 2853, 1721, 1559, 1416, 1076, 1025 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 9.01$  (s, 1 H), 8.46 (s, 2 H), 3.74 (dd,  $J = 11.3, 6.1$  Hz, 1 H), 3.63 (dd,  $J = 11.3, 6.7$  Hz, 1 H), 2.01 (s, 1 H), 1.83–1.79 (m, 1 H), 1.54–1.50 (m, 1 H), 1.05 (ddt,  $J = 24.4, 8.7, 5.4$  Hz, 2 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta = 156.4$  (2 C), 154.8, 136.0, 65.6, 25.2, 16.6, 13.5.

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O: 151.0865; found: 151.0859.

**cis-Cyclopropylmethanol Derivatives 25a–f; General Procedure C**

A solution of **24** (66.5  $\mu$ L, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.6 mL) was added to Et<sub>2</sub>Zn (115  $\mu$ L, 1.1 mmol) in a 50 mL round-bottom flask at 0 °C. Gas evolution was observed. After 5 min, a solution of dioxaborolane **11** (371 mg, 1.37 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was added. The reaction mixture was stirred for 10 min at 0 °C.

In a 50 mL round-bottom flask at –40 °C, neat Et<sub>2</sub>Zn (507  $\mu$ L, 4.92 mmol) was added dropwise to a mixture of I<sub>2</sub> (1.22 g, 4.81 mmol), Et<sub>2</sub>O (0.98 mL, 9.33 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (4.7 mL). Once the I<sub>2</sub> was completely consumed, the reaction mixture was cooled to –78 °C and a solution of CHI<sub>3</sub> (951 mg, 2.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (14 mL) was slowly added to the IZnEt solution. The mixture was stirred at –78 °C for 10 min.

The alkoxide solution was quickly cannulated over the carbenoid solution and the reaction mixture was allowed to reach –40 °C (cryostat bath). The reaction mixture was stirred 24 h at this temperature. The reaction mixture was quenched with sat. aq NH<sub>4</sub>Cl. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  10 mL). The organic layers were gathered and dried over MgSO<sub>4</sub> and the solvents were removed until 500  $\mu$ L under reduced pressure. The intermediate is unstable and highly volatile and care must be taken to avoid loss of the volatile boronate.

The residue was taken up in degassed THF (4.4 mL) and added to a sealed tube containing Pd(PPh<sub>3</sub>)<sub>4</sub> (68.7 mg, 5 mol%) in THF (2.2 mL). Then 3 N aq degassed KOH (2.2 mL) was added followed by the desired coupling partner **22a–e** (2.2 mmol). The reaction mixture was heated at 65 °C overnight (16 h). After the mixture had cooled down, H<sub>2</sub>O was added to it. The aqueous layer was extracted with Et<sub>2</sub>O (3  $\times$  7 mL). The combined organic layers were dried over MgSO<sub>4</sub>. The solvents were removed under reduced pressure. The residue was stirred in diethanolamine (602 mg, 5.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) for 1 h to remove any dioxaborolane bound to the cyclopropane. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and purified by flash chromatography (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 5:95, unless stated otherwise) to provide the desired coupled products **25a–f**.

**[(1*R*,2*S*)-2-(Pyridin-3-yl)cyclopropyl]methanol (25a)**

The product was prepared according to general procedure C using 3-bromopyridine (217  $\mu$ L, 2.28 mmol).

Yield: 92 mg (72%); light yellow oil;  $R_f = 0.23$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{25} -45.2$  (c 1.0, MeOH).

IR (neat): 3264, 3005, 2866, 1573, 1573, 1480, 1418, 1167, 1025 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 8.53$  (s, 1 H), 8.42 (d,  $J = 4.5$  Hz, 1 H), 7.56 (d,  $J = 7.9$  Hz, 1 H), 7.21 (dd,  $J = 7.8, 4.8$  Hz, 1 H), 3.47 (dd,  $J = 11.5, 6.4$  Hz, 1 H), 3.25 (dd,  $J = 11.5, 8.3$  Hz, 1 H), 2.25 (dd,  $J = 14.7, 8.4$  Hz, 1 H), 1.93 (s, 1 H), 1.56 (qt,  $J = 8.5, 6.1$  Hz, 1 H), 1.13 (td,  $J = 8.4, 5.4$  Hz, 1 H), 0.87 (q,  $J = 5.7$  Hz, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta = 151.0, 147.7, 137.0, 134.6, 123.5, 62.9, 21.17, 18.7, 8.0$ .

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>11</sub>NO: 150.0913; found: 150.0912.

**[(1*R*,2*S*)-2-(Quinolin-3-yl)cyclopropyl]methanol (25b)**

The product was prepared according to general procedure C using 3-bromoquinoline (308  $\mu$ L, 2.28 mmol).

Yield: 162 mg (71%); light yellow oil;  $R_f = 0.26$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{25} +38.6$  (c 1.0, MeOH).

IR (neat): 3262, 3064, 3005, 2872, 1571, 1493, 1464, 1417 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 8.86$  (d,  $J = 2.1$  Hz, 1 H), 8.01 (d,  $J = 8.6$  Hz, 1 H), 7.88 (s, 1 H), 7.71 (d,  $J = 8.1$  Hz, 1 H), 7.61 (ddd,  $J = 8.4, 5.1, 1.4$  Hz, 1 H), 7.50–7.46 (m, 1 H), 3.49 (dd,  $J = 11.5, 6.3$  Hz, 1 H), 3.26 (dd,  $J = 11.5, 8.4$  Hz, 1 H), 2.39 (dd,  $J = 14.7, 8.3$  Hz, 1 H), 1.89 (br, 1 H), 1.62 (qt,  $J = 8.5, 6.0$  Hz, 1 H), 1.19 (td,  $J = 8.4, 5.5$  Hz, 1 H), 0.97 (q,  $J = 5.7$  Hz, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta = 152.7, 146.7, 134.7, 131.6, 129.0, 128.9, 127.8, 127.4, 126.8, 62.3, 21.2, 18.6, 7.7$ .

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>NO: 200.1069; found: 200.1066.

**[(1*R*,2*S*)-2-(4-Methylpyridin-2-yl)cyclopropyl]methanol (25c)**

The product was prepared according to general procedure C using 2-bromo-4-methylpyridine (252  $\mu$ L, 2.28 mmol).

Yield: 136 mg (873%); light yellow oil;  $R_f = 0.32$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9);  $[\alpha]_D^{25} +31.1$  (c 1.0, MeOH).

IR (neat): 3350, 3053, 3003, 2849, 1606, 1543, 1480, 1032 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 8.23$  (d,  $J = 5.1$  Hz, 1 H), 7.16 (d,  $J = 0.7$  Hz, 1 H), 6.92 (d,  $J = 5.1$  Hz, 1 H), 3.93 (dd,  $J = 12.1, 3.6$  Hz, 1 H), 3.34 (dd,  $J = 12.1, 8.6$  Hz, 1 H), 2.31 (s, 3 H), 2.15 (td,  $J = 8.6, 6.0$  Hz, 1 H), 1.69–1.50 (m, 1 H), 1.13 (td,  $J = 8.7, 4.7$  Hz, 1 H), 1.00 (dd,  $J = 10.8, 6.0$  Hz, 1 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 160.3, 148.0, 147.9, 126.1, 122.2, 61.3, 22.5, 22.4, 21.0, 10.5.

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for  $\text{C}_{10}\text{H}_{13}\text{NO}$ : 164.1069; found: 164.1071.

#### [(1R,2S)-2-(6-Aminopyridin-2-yl)cyclopropyl]methanol (25d)

The product was prepared according to general procedure C using 2-amino-6-bromopyridine (392 mg, 2.28 mmol).

Yield: 141 mg (75%); bright yellow oil;  $R_f$  = 0.22 (MeOH/ $\text{CH}_2\text{Cl}_2$ , 1:9);  $[\alpha]_D^{25}$  -57.7 (c 1.0, MeOH).

IR (neat): 3332, 3202, 3002, 2860, 1616, 1594, 1324, 1020  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.35 (dd,  $J$  = 8.1, 7.5 Hz, 1 H), 6.67 (d,  $J$  = 7.4 Hz, 1 H), 6.31 (d,  $J$  = 8.2 Hz, 1 H), 4.41 (s, 2 H), 3.93 (dd,  $J$  = 12.0, 3.8 Hz, 1 H), 3.33 (dd,  $J$  = 12.0, 8.8 Hz, 1 H), 2.10 (td,  $J$  = 8.6, 6.0 Hz, 1 H), 1.59–1.51 (m, 1 H), 1.08 (td,  $J$  = 8.7, 4.8 Hz, 1 H), 0.98–0.95 (m, 1 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.4, 157.1, 138.3, 114.8, 105.9, 61.5, 22.3, 21.8, 9.8.

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}$ : 165.1022; found: 165.1022

#### [(1R,2S)-2-(Pyrimidin-5-yl)cyclopropyl]methanol (25e)

The product was prepared according to general procedure C using 5-bromopyrimidine (360 mg, 2.28 mmol).

Yield: 127 mg (74%); light yellow oil;  $R_f$  = 0.27 (MeOH/ $\text{CH}_2\text{Cl}_2$ , 1:9);  $[\alpha]_D^{25}$  -11.2 (c 1.0, MeOH).

IR (neat): 3329, 3009, 2872, 1556, 1415, 1239, 1168, 1026  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.03 (s, 1 H), 8.65 (s, 2 H), 3.57 (dd,  $J$  = 11.4, 6.0 Hz, 1 H), 3.17 (dd,  $J$  = 11.4, 8.6 Hz, 1 H), 2.17 (dd,  $J$  = 14.6, 8.3 Hz, 1 H), 1.78 (s, 1 H), 1.59 (qt,  $J$  = 8.6, 5.9 Hz, 1 H), 1.18 (td,  $J$  = 8.4, 5.5 Hz, 1 H), 0.87 (q,  $J$  = 5.8 Hz, 1 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 157.6 (2 C), 156.6, 132.3, 62.0, 20.5, 16.0, 7.4.

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$ : 151.0866; found: 151.0860.

#### [(1R,2S)-2-Phenylcyclopropyl]methanol (25f)

The product was prepared according to general procedure C using bromobenzene (238  $\mu\text{L}$ , 2.28 mmol).

Yield: 120 mg (71%); 95.2:4.7 er; SFC (Chiralpak AD-H 25cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min):  $t_{R(\text{major})}$ : 6.76 min,  $t_{R(\text{minor})}$ : 4.25 min; light yellow oil;  $R_f$  = 0.45 (EtOAc/hexanes, 1:4);  $[\alpha]_D^{25}$  -22.4 (c 1.0, MeOH).

IR (neat): 3330, 2962, 2865, 1638, 1603, 1496, 1451, 1019  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.32–7.23 (m, 4 H), 7.23–7.17 (m, 1 H), 3.48 (dd,  $J$  = 11.7, 6.3 Hz, 1 H), 3.27 (dd,  $J$  = 11.7, 8.5 Hz, 1 H), 2.30 (td,  $J$  = 8.5, 6.2 Hz, 1 H), 1.54–1.47 (m, 1 H), 1.13 (s, 1 H), 1.05 (td,  $J$  = 8.4, 5.3 Hz, 1 H), 0.89 (dd,  $J$  = 11.4, 5.6 Hz, 1 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 138.4, 129.0 (2 C), 128.5 (2 C), 126.4, 63.1, 21.1, 20.9, 7.8;

HRMS (ESI):  $m/z$  [M +  $\text{NH}_4$ ]<sup>+</sup> calcd for  $\text{C}_{10}\text{H}_{12}\text{O}$ : 166.1226; found: 166.1219.

### Synthesis of Starting Materials

#### 2,2'-(Cyclohexylazanediy)diacetic Acid (CIDA)

To a stirred solution of chloroacetic acid (6.94 mL, 116 mmol) and  $\text{H}_2\text{O}$  (9 mL) was added dropwise aq NaOH (9.28 g, 232 mmol in 30 mL of  $\text{H}_2\text{O}$ ) maintaining the temperature below 30 °C by using an ice bath. The mixture was stirred for 5 min after the addition, and the ice bath was removed. Cyclohexylamine was added dropwise, keeping the temperature below 50 °C. After addition was complete, the reaction mixture was heated at 80 °C for 3 h. A solution of barium chloride dihydrate (12.9 g, 52.9 mmol), dissolved in hot  $\text{H}_2\text{O}$  (24 mL), was added in one portion and the mixture was heated for 30 min. A heavy precipitate of the barium salt of the amino acid separated at once. The stirring was continued, keeping the heating bath at 100 °C, and then the mixture was cooled down and kept in an ice bath. The precipitate was then filtered off. The dry barium salt was placed in a flask into which boiling  $\text{H}_2\text{O}$  (24 mL) was added and heated to boiling; 5 M sulfuric acid (9 mL) was added gradually over 30 min. Once the addition was complete, the mixture was stirred for 10 min and then concentrated under reduced pressure to 5 mL. The solution was filtered on Celite and concentrated.

Yield: 7.38 g (68%); yellow crystalline solid; mp 198–199 °C.

IR (neat): 3012, 2979, 2941, 2856, 1716 1584, 1400, 1240  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz, DMSO):  $\delta$  = 3.44 (s, 4 H), 2.58 (d,  $J$  = 7.6 Hz, 1 H), 1.72 (dd,  $J$  = 17.6, 14.0 Hz, 4 H), 1.52 (d,  $J$  = 12.2 Hz, 1 H), 1.21–1.10 (m, 4 H), 1.10–1.00 (m, 1 H).

$^{13}\text{C}$  NMR (126 MHz, DMSO):  $\delta$  = 173.9, 62.4, 54.1, 29.9, 26.2, 26.0.

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for  $\text{C}_{10}\text{H}_{17}\text{NO}_4$ : 216.1230; found: 216.1227.

#### (E)-2-[3-[(tert-Butyldimethylsilyloxy]prop-1-en-1-yl]-6-cyclohexyl-1,3,6,2-dioxaborocane-4,8-dione (15aa)

To a stirred solution of (E)-tert-butyldimethyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyloxy]silane<sup>28</sup> (4.18 g, 14 mmol) in a mixture of acetone/ $\text{H}_2\text{O}$  (1:1; 94 mL) was added in one portion, sodium periodate (15.0 g, 70.1 mmol) and ammonium acetate (5.57 g, 70.1 mmol). The mixture was stirred at rt for 24 h. The flask was fitted with a short-path distillation setup and at rt the acetone and  $\text{H}_2\text{O}$  were removed to dryness. The resulting white solid was suspended in acetone and stirred for 15 min and then filtered. The filtrate was then concentrated to almost dryness. The crude boronic acid was used immediately for the next step. The crude boronic acid (3.03 g, 14.0 mmol) and 2,2'-(cyclohexylazanediy)diacetic acid (6.00 g, 27.9 mmol) were dissolved in a mixture of DMSO (14 mL) and benzene (85 mL), and the mixture was refluxed using a Dean-Stark condenser for 6 h at 95 °C (internal temperature). The reaction mixture was cooled and concentrated to remove benzene. The residue was diluted with EtOAc (20 mL) and brine (10 mL). The organic layer was washed with  $\text{H}_2\text{O}$  (3  $\times$  10 mL), dried with  $\text{Na}_2\text{SO}_4$ , and concentrated under reduced pressure to afford a light brown solid. Following column chromatography (silica gel,  $\text{CH}_2\text{Cl}_2/\text{MeCN}$ , 1:1), the protected allylic alcohol **15aa** was isolated.

Yield: 3.33 g (60%); white solid;  $R_f$  = 0.5 ( $\text{CH}_2\text{Cl}_2/\text{MeCN}$ , 1:1); mp 132–133 °C.

IR (neat): 2931, 2856, 1747, 1648, 1449, 1252, 1104, 956  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ):  $\delta$  = 6.21 (dt,  $J$  = 17.5 Hz, 1 H), 5.87 (dt,  $J$  = 17.9 1 H), 4.28 (dd,  $J$  = 3.8, 2.0 Hz, 2 H), 4.15 (d,  $J$  = 16.8 Hz, 2 H), 3.93 (d,  $J$  = 16.8 Hz, 2 H), 3.22 (t,  $J$  = 11.9 Hz, 1 H), 1.89 (m, 2 H), 1.71–1.49 (m, 4 H), 1.44–1.24 (m, 4 H), 0.95 (s, 9 H), 0.11 (s, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.1 (2 C), 146.3 (2 C), 67.2, 62.6, 56.6 (2 C), 27.4, 26.3 (2 C), 25.5 (2 C), 25.4 (3 C), 18.7, -5.0 (2 C).

HRMS (ESI):  $m/z$  [M + H] $^+$  calcd for  $\text{C}_{19}\text{H}_{34}\text{BNO}_3\text{Si}$ : 395.2408; found: 395.2416.

#### Base-Sensitive Allylic Alcohol (Z)-4-(3-Hydroxyprop-1-en-1-yl)benzyl Acetate (20)

##### (4-{3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-yn-1-yl}phenyl)-methanol (20a)

To a dry sealed tube was added [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] (304 mg, 0.433 mmol) and copper iodide (82.3 mg, 0.433 mmol). Et<sub>3</sub>N (10.5 mL) was added to the sealed tube and the mixture was flushed with argon while stirring for 5 min. To this was added 4-bromobenzyl alcohol (540 mg, 2.89 mmol), followed by the immediate addition of the TBS-protected propargyl alcohol<sup>30</sup> (1.96 g, 11.5 mmol). The reaction mixture was then stirred for 15 h at 77 °C under an argon atmosphere. The reaction mixture was diluted with EtOAc and washed with 10% HCl solution (2 × 15 mL) and brine (2 × 15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification by column chromatography (silica gel, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9) afforded the coupled product **20a**.

Yield: 670.4 mg (84%); yellow oil.  $R_f$  = 0.5 (MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 1:9).

IR (neat): 3369, 2923, 2857, 1736, 1720, 1231, 1045, 1033, 1017 cm<sup>-1</sup>.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.42 (d,  $J$  = 8.2 Hz, 2 H), 7.28 (d,  $J$  = 8.2 Hz, 2 H), 4.68 (s, 2 H), 4.54 (s, 2 H), 0.94 (s, 9 H), 0.17 (s, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 141.2, 132.0 (2 C), 127.0 (2 C), 122.4, 88.2, 85.0, 65.1, 52.5, 26.1 (3 C), 18.6, -5.0 (2 C).

HRMS (ESI):  $m/z$  [M + H] $^+$  calcd for  $\text{C}_{16}\text{H}_{24}\text{O}_2\text{Si}$ : 277.2; found: 277.7.

##### (Z)-(4-{3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-en-1-yl}phenyl)-methanol (20b)

To a stirred solution of nickel(II) acetate tetrahydrate (883 mg, 3.55 mmol) in EtOH (19.7 mL) under an argon atmosphere was added sodium borohydride (134 mg, 3.55 mmol), resulting in a black amorphous precipitate. After 5 min of stirring, ethylenediamine was added (237 mg, 3.94 mmol). The mixture was then allowed to stir for 30 min under an argon atmosphere. The flask was purged with hydrogen, and alkyne **20a** (1.09 g, 3.94 mmol) was rapidly added to the reaction mixture. The reaction was monitored by NMR. Upon completion, the reaction mixture was filtered over Celite, and the Celite was washed with Et<sub>2</sub>O. The filtrate was washed with brine and extracted with Et<sub>2</sub>O (3 × 10 mL). The filtrate was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to provide the desired pure product **20b**. The solids along with the Celite were quenched in a 10% HCl solution.

Yield: 1.07 g (97%);  $R_f$  = 0.5 (EtOAc/hexane, 1:4).

IR (neat): 2952, 2927, 2855, 1737, 1378, 1227, 1028, 835 cm<sup>-1</sup>.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.34 (d,  $J$  = 8.1 Hz, 2 H), 7.19 (d,  $J$  = 8.1 Hz, 2 H), 6.48 (d,  $J$  = 11.8 Hz, 1 H), 5.83 (dt,  $J$  = 12.0, 6.1 Hz, 1 H), 4.69 (s, 2 H), 4.44 (dd,  $J$  = 6.1, 1.8 Hz, 2 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 139.8, 136.5, 133.0, 129.4, 129.2 (2 C), 127.0 (2 C), 65.3, 60.6, 25.1 (3 C), 18.5, -5.0 (2 C).

HRMS (ESI):  $m/z$  [M + NH<sub>4</sub>] $^+$  calcd for  $\text{C}_{16}\text{H}_{26}\text{O}_2\text{Si}$ : 296.2; found: 296.2.

##### (Z)-4-{3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-en-1-yl}benzyl Acetate (20c)

Anhyd pyridine (12 mL) was added to **20b** (1.19 g, 4.27 mmol) in a dried flask. The mixture was allowed to stir for 10 min and cooled to 0 °C. Upon cooling, acetic anhydride (12 mL) was added dropwise to the mixture. The mixture was allowed to stir for 12 h. Upon completion of the reaction, the mixture was diluted with Et<sub>2</sub>O and washed with 10% HCl (2 × 20 mL), brine (2 × 20 mL), and NaHCO<sub>3</sub> (2 × 20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:4) afforded product **20c**.

Yield: 985 mg (72%); yellow oil;  $R_f$  = 0.6 (EtOAc/hexanes, 1:4).

IR (neat): 3022, 2953, 2928, 2888, 2855, 2070, 2040, 2031 cm<sup>-1</sup>.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.33 (d,  $J$  = 8.1 Hz, 2 H), 7.20 (d,  $J$  = 8.1 Hz, 2 H), 6.48 (d,  $J$  = 11.8 Hz, 1 H), 5.85 (dt,  $J$  = 12.0, 6.1 Hz, 1 H), 5.10 (s, 2 H), 4.44 (dd,  $J$  = 6.1, 1.8 Hz, 2 H), 2.11 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.0, 137.0, 134.8, 133.2, 129.2, 129.1 (2 C), 128.3 (2 C), 66.2, 60.4, 26.1 (3 C), 21.2, 18.4, -5.0 (2 C).

HRMS (ESI):  $m/z$  [M + NH<sub>4</sub>] $^+$  calcd for  $\text{C}_{18}\text{H}_{28}\text{O}_3\text{Si}$ : 338.2; found: 338.2.

##### (Z)-4-(3-Hydroxyprop-1-en-1-yl)benzyl Acetate (20)

Acetate **20c** (330 mg, 1.03 mmol) was loaded into a dried flask containing THF (4.20 mL). The mixture was cooled to 0 °C and TBAF (1.13 mL, 1.13 mmol) was added dropwise. The cooling bath was removed and the mixture was stirred and monitored by TLC until completion. Upon completion, the reaction mixture was quenched with NH<sub>4</sub>Cl (5 mL) and diluted with EtOAc (8 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:1) afforded the desired product **20**.

Yield: 210 mg (99%); yellow oil;  $R_f$  = 0.4 (EtOAc/hexanes, 1:1).

IR (neat): 3389, 3021, 2931, 2871, 1734, 1226, 1026, 1016 cm<sup>-1</sup>.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.33 (d,  $J$  = 8.1 Hz, 2 H), 7.21 (d,  $J$  = 8.1 Hz, 2 H), 6.56 (d,  $J$  = 11.8 Hz, 1 H), 5.92–5.87 (m, 1 H), 5.10 (s, 2 H), 4.43 (dd,  $J$  = 6.5, 1.6 Hz, 2 H), 2.11 (s, 3 H), 1.86 (s, 1 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.1, 136.7, 135.2, 131.8, 130.8, 129.2 (2 C), 128.4 (2 C), 66.2, 59.8, 21.2.

HRMS (ESI):  $m/z$  [M + NH<sub>4</sub>] $^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_3$ : 224.1; found: 224.1.

#### Base-Sensitive Additives

##### Benzyl 3,3-Dimethylbutanoate (19a)

To a suspension of NaH (88.8 mg, 3.70 mmol) in THF (13 mL) at 0 °C was added a solution of benzyl alcohol (385  $\mu\text{L}$ , 3.70 mmol) in THF (5.3 mL). The reaction mixture was stirred at rt for 30 min. The mixture was then cooled to 0 °C and *tert*-butylacetyl chloride (488  $\mu\text{L}$ , 3.51 mmol) was added dropwise. The reaction mixture was allowed to stir at rt for 6 h. The mixture was quenched with sat. aq NH<sub>4</sub>Cl (13 mL) and H<sub>2</sub>O (7 mL) and diluted with EtOAc (13 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 × 13 mL). The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification by flash chromatography (silica gel, hexanes/CH<sub>2</sub>Cl<sub>2</sub>, 8:2 to 6:4) resulted in the desired product **19a**. The NMR spectra matched those in the literature.<sup>31</sup>

Yield: 650 mg (85%).

### Benzyl Phenethylcarbamate (19b)

To a reaction flask containing anhyd THF (16.5 mL) was added 2-phenethylamine (400 mg, 3.30 mmol) and 4-dimethylaminopyridine (20.2 mg, 5 mol%). Benzyl chloroformate was added dropwise to the solution and the reaction mixture was allowed to stir for 6 h. The mixture was quenched with H<sub>2</sub>O (10 mL) and diluted with Et<sub>2</sub>O (13 mL). The aqueous layer was washed with Et<sub>2</sub>O (3 × 20 mL). The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure and the white solid was washed with hexanes to result in the desired product **19b**. The spectra matched those reported in the literature.<sup>32</sup>

Yield: 758 mg (90%)

### 4-Bromobenzyl Acetate (19c)

Additive **19c** was synthesized according to the literature.<sup>8</sup> In a dried flask, 4-bromobenzyl alcohol (600 mg, 3.21 mmol) was dissolved in anhyd pyridine (9 mL). The mixture was allowed to stir for 10 min and cooled down to 0 °C. Upon cooling, acetic anhydride (9.10 mL, 96.2 mmol) was added dropwise to the mixture. The mixture was allowed to stir for 12 h. Upon completion of the reaction, the mixture was diluted with Et<sub>2</sub>O and washed with 10% HCl (2 × 20 mL), brine (2 × 20 mL), and NaHCO<sub>3</sub> (2 × 20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:20) afforded product **19c**. The spectra matched those reported in the literature.<sup>33</sup>

Yield: 640 mg (87%); yellow oil.

### Funding Information

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) (Discovery Grant DG-06438), the Canada Research Chairs program (227346), the Canada Foundation for Innovation (Leaders Opportunity Funds 227346), the Fonds de Recherche du Québec - Nature et Technologies (FRQNT Centre in Green Chemistry and Catalysis; RS-171310), and the Université de Montréal.

### Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611896>.

### References

- (1) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.
- (2) Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712.
- (3) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.
- (4) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651.
- (5) Volgraf, M.; Sellers, B. D.; Jiang, Y.; Wu, G.; Ly, C. Q.; Villemure, E.; Pastor, R. M.; Yuen, P.-w.; Lu, A.; Luo, X.; Liu, M.; Zhang, S.; Sun, L.; Fu, Y.; Lupardus, P. J.; Wallweber, H. J. A.; Liederer, B. M.; Deshmukh, G.; Plise, E.; Tay, S.; Reynen, P.; Herrington, J.; Gustafson, A.; Liu, Y.; Dirksen, A.; Dietz, M. G. A.; Liu, Y.; Wang, T.-M.; Hanson, J. E.; Hackos, D.; Scarsee-Levie, K.; Schwarz, J. B. *J. Med. Chem.* **2016**, *59*, 2760.
- (6) (a) Tedford, C. E.; Phillips, J. G.; Gregory, R.; Panlowski, G. P.; Fadnis, L.; Khan, M. A.; Ali, S. M.; Handley, M. K.; Yates, S. L. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1160. (b) Liddle, J.; Bamborough, P.; Barker, M. D.; Campos, S.; Chung, C. W.; Cousins, R. P. C.; Faulder, P.; Heathcote, M. L.; Hobbs, H.; Holmes, D. S.; Ioannou, C.; Ramirez-Molina, C.; Morse, M. A.; Osborn, R.; Payne, J. J.; Pritchard, J. M.; Rumsey, W. L.; Tape, D. T.; Vicentini, G.; Whitworth, C.; Williamson, R. A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5222. (c) Raheem, I. T.; Schreier, J. D.; Fuerst, J.; Gantert, L.; Hostetler, E. D.; Huszar, S.; Joshi, A.; Kandebo, M.; Kim, S. H.; Li, J.; Ma, B.; McGaughey, G.; Sharma, S.; Shipe, W. D.; Uslander, J.; Vandever, G. H.; Yan, Y.; Renger, J. J.; Smith, S. M.; Coleman, P. J.; Cox, C. D. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 126.
- (7) (a) Sayes, M.; Charette, A. B. *Angew. Chem. Int. Ed.* **2018**, *57*, 13514. (b) Benoit, G.; Charette, A. B. *J. Am. Chem. Soc.* **2017**, *139*, 1364. (c) Spencer, J. A.; Jamieson, C.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 3891. (d) de Meijere, A.; Khlebnikov, A. F.; Sünemann, H. W.; Frank, D.; Rauch, K.; Yufit, D. S. *Eur. J. Org. Chem.* **2010**, 3295. (e) Fontani, P.; Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 4815. (f) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605. (g) Fujioka, Y.; Amii, H. *Org. Lett.* **2008**, *10*, 769. (h) He, J.; Jiang, H.; Takise, R.; Zhu, R. Y.; Chen, G.; Dai, H. X.; Dhar, T.; Shi, J.; Zhang, H.; Cheng, P. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 785. (i) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516. (j) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375. (k) Markó, I. E.; Giard, T.; Sumida, S.; Gies, A.-E. *Tetrahedron Lett.* **2002**, *43*, 2317. (l) Markó, I. E.; Kumamoto, T.; Giard, T. *Adv. Synth. Catal.* **2002**, *344*, 1063. (m) Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 846.
- (8) (a) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986. (b) Luthile, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287.
- (9) Carreras, J.; Caballero, A.; Pérez, P. *J. Angew. Chem. Int. Ed.* **2018**, *57*, 2334.
- (10) Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624.
- (11) (a) Charette, A. B.; Beauchemin, A. *Org. React. (N.Y.)* **2001**, *58*, 1. (b) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.
- (12) For a related preparation of cyclopropane building blocks, see: (a) Chawner, S. J.; Cases-Thomas, M. J.; Bull, J. A. *Eur. J. Org. Chem.* **2017**, 5015. (b) Bajaj, P.; Sreenilayam, G.; Tyagi, V.; Fasan, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 16110.
- (13) Hohn, E.; Paleček, J.; Pietruszka, J.; Frey, W. *Eur. J. Org. Chem.* **2009**, 3765.
- (14) (a) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.
- (15) (a) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (b) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2008**, *74*, 973. (c) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481.
- (16) Lennox, A. J. J. *Organotrifluoroborate Preparation, In Organotrifluoroborate Preparation, Coupling and Hydrolysis*; Springer: Heidelberg, **2013**, 11–36.
- (17) Maiti, G.; Roy, S. C. *Tetrahedron Lett.* **1997**, *38*, 495.
- (18) (a) Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. *Tetrahedron Lett.* **1994**, *35*, 5109. (b) Snow, R. J.; Bachovchin, W. W.; Barton, R. W.; Campbell, S. J.; Coutts, S. J.; Freeman, D. M.; Gutheil, W. G.; Kelly, T. A.; Kennedy, C. A. *J. Am. Chem. Soc.* **1994**, *116*, 10860. (c) Coutts, S. J.; Kelly, T. A.; Snow, R. J.; Kennedy, C. A.; Barton, R. W.; Adams, J.; Krolikowski, D. A.; Freeman, D. M.; Campbell, S. J.; Ksiazek, J. F. *J. Med. Chem.* **1996**, *39*, 2087. (d) Kinder, D. H.; Katzenellenbogen, J. A. *J. Med. Chem.* **1985**, *28*,



1917. (e) Matteson, D. S.; Jesthi, P. K.; Sadhu, K. M. *Organometallics* **1984**, *3*, 1284. (f) Martichonok, V.; Jones, J. B. *J. Am. Chem. Soc.* **1996**, *118*, 950. (g) Martin, R.; Jones, J. B. *Tetrahedron Lett.* **1995**, *36*, 8399.
- (19) Gonzalez, J. A.; Ogba, O. M.; Morehouse, G. F.; Rosson, N.; Houk, K. N.; Leach, A. G.; Cheong, P. H. Y.; Burke, M. D.; Lloyd-Jones, G. C. *Nat. Chem.* **2016**, *8*, 1067.
- (20) (a) Kettner, C. A.; Shenvi, A. B. *J. Biol. Chem.* **1984**, *259*, 15106. (b) Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200. (c) Sun, J.; Perfetti, M. T.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3571. (d) Rettig, S. J.; Trotter, J. *Can. J. Chem.* **1975**, *53*, 1393.
- (21) Zhao, J.; Jonker, S. J. T.; Meyer, D. N.; Schulz, G.; Tran, C. D.; Eriksson, L.; Szabò, K. J. *Chem. Sci.* **2018**, *9*, 3305.
- (22) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.
- (23) (a) Bobbitt, J. M. *Periodate Oxidation of Carbohydrates*, In *Advances in Carbohydrate Chemistry*, Vol. 11; Wolfrom, M. L.; Tipson, R. S., Ed.; Elsevier: Amsterdam, **1956**, 1–41. (b) Copéret, C.; Adolffson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.
- (24) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Molander, G. A.; Jean-Gérard, L. *Org. React.* **2013**, *79*, 1.
- (25) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17.
- (26) Duncton, M. A. J.; Singh, R. *Org. Lett.* **2013**, *15*, 4284.
- (27) Shriver, D. F.; Drezdson, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed; Wiley: New York, **1986**.
- (28) Wang, K.; Bates, R. W. *Synthesis* **2017**, *49*, 2749.
- (29) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.
- (30) Nicolaou, K. C.; Rhoades, D.; Lamani, M.; Pattanayak, M. R.; Kumar, S. M. *J. Am. Chem. Soc.* **2016**, *138*, 7532.
- (31) Joliton, A.; Plancher, J. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 2113.
- (32) Ohtsuka, N.; Okuno, M.; Hoshino, Y.; Honda, K. *Org. Biomol. Chem.* **2016**, *14*, 9046.
- (33) Kumpulainen, E. T. T.; Pohjakallio, A. *Adv. Synth. Catal.* **2014**, *356*, 1555.