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

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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) borocyclopropanes in 92% yield and 95.6:4.4 er. A robustness screen has shown diethanolamine to be compatible with esters, carboxamides 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 zinco-cyclopropanation reaction of allylic alcohol to remove residual dioxaborolane from the corresponding cis-N-heterocycle cyclopropylmethanol, thereby leading to improved yields.

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

Cyclopropane motifs are ubiquitous in Nature and are widely employed in pharmaceutically and agrochemically relevant compounds. Cyclopropylboronic acids and derivatives are excellent synthons for the rapid introduction of the cyclopropyl motif into complex molecules. 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. 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. 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. Although an array of methodologies to access substituted borocyclopropane subunits in a diastereoselective manner are available, 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, and copper-catalyzed carbene transfer of ethylidiazoacetate to alkylboronates for the preparation of chiral 1,2,3-trisubstituted cyclopropanes (Scheme 1, part i). The in situ preparation of enantioenriched borocyclopropanes via the zinco-cyclopropanation of substituted allylic alcohols is an alternative to the use of stoichiometric quantities of diazo compounds (Scheme 1, part ii). The Simmons–Smith reaction has also been employed for the synthesis of chiral vinylpinacolboronates as separable racemic diastereomeric mixtures.

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. We report herein the first enantioselective Simmons–Smith cyclopropanation of boronate-bearing allylic alcohols for the preparation of enantioenriched borocyclopropane building blocks. Pinacolate analogues have often been used in borocyclopropanation methodologies. Many of these derivatives are oils and are prone to decomposition through protodeboronation, and are hence currently deemed ‘unstable’ boronic acids. In contrast, cyclopropyltrifluoroborates are solids and display a reduced propensity to undergo protodeboronation, but have limited solubility in moderately polar solvents.
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. For these reasons, we envisioned the use of enantioselective 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 insolvency 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.

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%. Once obtained, we were pleased to find that the CIDA allylic alcohol 15a was readily soluble in dichloromethane.

The cyclopropanation reaction with 15a using 
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\text{Zn(CH}_2\text{I)}_2
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(2.2 equiv) and dioxaborolane 11 (1.1 equiv) proceeded smoothly with full conversion of the starting material. However, isolation of the cyclopropylmethanol by decomposition 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 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, resulting in narrow functional group compatibility and challenging purifications.

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.
bearing electron-withdrawing groups. However, Szabó recently observed that the diethanolamine cyclic boronate deprotection protocol is unsuccessful for transesterification of some electron-deficient vinylpinacolate analogues. 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 boronate complexes. After optimization, the pinacolboronate 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 decomplexation 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 for the cyclopropanation of allylic alcohol 17 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-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 conditions. 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.

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.
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.24 Heterocycles are the most widely used motifs in medicinal chemistry, and to aid introduction of the cyclopropyl 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.3,25 Cross-coupling of cyclopropyl MIDA boronates has been achieved using SPhos and Pd(OAc)2 to afford excellent yields of the coupled products 13 and 14 in 92% yield and 95.6:4.4 er compared to the pinacol analogues. Attempts to synthesize the CIDA-bearing cis-boronate allylic alcohols failed due to lack of stability. To overcome these challenges, we took an in situ approach to obtain the disubstituted borocyclopentylmethanol 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 carbenediphosphate 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 building block was obtained in 92% yield and 95.6:4.4 er compared to the pina-coborocyclopropane 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.

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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 to prevent moisture contamination. Anhydrous solvents were obtained either by filtration through alumina columns or by distillation over calcium hydride (Et$_3$N, pyridine, CH$_2$Cl$_2$) or sodium hydride prior to use and all reactions were set up and carried out under an argon atmosphere with the exclusion of moisture. Anhydrous solvents were obtained either by filtration through drying columns (benzene and THF) or by distillation over calcium hydride (Et$_3$N, pyridine, CH$_2$Cl$_2$). All reagents used were purified using standardized protocols.

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

To a dry microwave vial, (E)-2-[(tert-butylimethylsilyl)oxy]prop-1-en-1-yl)-6-cyclohexyl-1,3,6,2-dioxazaborocane-4,8-dione (15aa; 440 mg, 1.10 mmol) was added, followed by DMSO (14 mL) and H$_2$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$_2$O (10 mL) and lyophilized until dryness; this gave 15a.

Yield: 313 mg (99%); white solid; [α]$_D$ = 0.3 (CH$_3$Cl/MeCN, 1:1); mp 117–118 °C.

IR (neat): 2939, 2860, 1740, 1644, 1448, 1326, 1290, 1244 cm$^{-1}$.


(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-butylimethyl[(3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]oxy)silane (120 g; 40.2 mmol) in EtOH (201 mL) was added dropwise a 3 M solution of trichloroacetic acid in EtOH (46.3 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$_3$ (2 × 15 mL). The organic layer was dried with Na$_2$SO$_4$ 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; [α]$_D$ = 0.4 (EtOAc/hexane, 3:7).

IR (neat): 2977, 2929, 1643, 1358, 1317, 1411, 1004, 970 cm$^{-1}$.
6-Cyclohexyl-2-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]-1,3,6,2-dioxaborolane-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 CH2Cl2 (2 mL). The mixture was sonicated for 1 min to provide a homogeneous solution. In another flame-dried flask, neat Et2Zn (40.3 µL, 0.4 mmol) was added to CH2Cl2 (2 mL) at 0 °C; dropwise addition of diiodomethane (63.6 µL, 0.8 mmol) followed. The mixture was stirred at 0 °C for 10 min. The mixture was allowed to stir for 8 h. The mixture remained homogeneous throughout. Upon completion of the reaction, the mixture was quenched with NH4Cl (2 mL) and EtOAc (3 mL). The organic layer was separated and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (2 × 3 mL). The organic layers were combined, dried with Na2SO4 and concentrated under reduced pressure. To the resulting residue was added a solution of diethanolamine (2.92 g, 27.8 mmol) in CH2Cl2 (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, 1:3). After purification the pure product was obtained as a yellow oil.

Yield: 48.3 mg (92%); 95.6:4.4 er; SFC (Chiralpak OD-H, 30 °C, 150 bar, 10% MeOH, 3 mL/min): tR(maj): 10.11 min, tR(min): 8.81 min; [α]25° = -19.3 (c 1.0, MeOH).


1H NMR (400 MHz, CDCl3): δ = 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).

13C NMR (126 MHz, CDCl3): δ = 151.9, 117.3, 83.5, 64.8 (2 C), 25.0 (4 C).

Larger-Scale Preparation of 13 (5.6 mmol)

In a 250 mL flame-dried flask, 15a (1.56 g, 5.6 mmol) and 11 (1.51 g, 6.10 mmol) were dissolved in CH2Cl2 (25 mL). Sonication for 1 min allowed 15a to dissolve in the CH2Cl2. In another flame-dried flask, Et2Zn (1.26 mL, 12.2 mmol) was added to CH2Cl2 (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 NH4Cl (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 × 20 mL). The organic layers were combined, dried with Na2SO4 and concentrated under reduced pressure. To the resulting residue was added a solution of diethanolamine (2.92 g, 27.8 mmol) in CH2Cl2 (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 (1:3) 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 25 cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min): tR(maj): 13.8 min, tR(min): 12.3 min; [α]25° = -49.8 (c 1.0, MeOH).

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; tR major: 25.24 min; tR minor: 21.86; [α]D25 +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 Et2Zn (113 μL, 1.10 mmol) in CH2Cl2 (2.5 mL) at 0 °C was added diiodomethane (177 μL, 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 (67.1 mg, 0.50 mmol), additive 19 (0.50 mmol), and dioxaborolane 11 (149 mg, 1.1 mmol) in CH2Cl2 (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 NH4Cl (5 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et2O (5 mL). The two layers were separated, and the aqueous layer was extracted with Et2O (3 × 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 CH2Cl2 (2.5 mL), was transferred to the flask containing the reaction mixture. Additional CH2Cl2 (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, and additives 18a–e.

**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, 1:3) 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, MeOH/CH2Cl2, 1:9) 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%).

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

**General Procedure D:** Purification by column chromatography (silica gel, MeOH/CH2Cl2, 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-Methyl diethanolamine Workup for Fmoc-Containing Additive 19d**

To a solution of Et2Zn (113 μL, 1.1 mmol) in CH2Cl2 (2.5 mL) at 0 °C was added diiodomethane (179 μL, 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 CH2Cl2 (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 NH4Cl (5 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et2O (5 mL). The two layers were separated, and the aqueous layer was extracted with Et2O (3 × 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 H2O2 (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 Et2O (3 × 5 mL) and the combined organic layers were washed with 10% aq HCl (10 mL). The aqueous layer was extracted with Et2O (3 × 5 mL) and the combined organic layers were successively washed with sat. aq Na2SO4 (10 mL), sat. aq NaHCO3 (10 mL), and brine (10 mL), dried over Na2SO4, 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, 1:3) resulted in the recovered additive 19a (95.9 mg, 93%) and the desired cyclopropane 18 (70.4 mg, 95%).
The resulting mixture was stirred for 15 h at rt and was quenched by the addition of sat. aq NaNH₂ (15 mL). The mixture was transferred into a separatory funnel and the reaction flask was rinsed with Et₂O (15 mL). The two layers were separated, and the aqueous layer was extracted with Et₂O (3 × 4 mL). The combined organic layers were dried and concentrated to afford a colorless residue. Warm diethanol-amine (541 mg, 5.15 mmol), weighed into a vial and dissolved in CH₂Cl₂ (4 mL), was transferred to the flask containing the reaction mixture. Additional CH₂Cl₂ (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 3h. 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 gel by column chromatography (silica gel, EtOAc/hexanes, 1:4) afforded 21.

Yield: 172 mg (76%); 93.4:6.6 er; SFC (Chiralpak AD-H 25 cm, 30 °C, EtOAc/hexanes, 1:4) afforded resulting in dry silica gel saturated with the crude reaction mixture. Purification of the saturated silica gel by column chromatography (silica gel, EtOAc/hexanes, 1:4) afforded 21.

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[(1S,2S)-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$_2$Cl$_2$, 1:9); $\alpha_l^25 +37.5$ ($c$ 0.85, MeOH).

IR (neat): 3264, 3005, 2866, 1573, 1573, 1480, 1167, 1025 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta = 8.53$ (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).

13C NMR (126 MHz, CDCl$_3$): $\delta = 151.0, 147.7, 137.0, 134.6, 123.5, 62.9, 21.17, 18.7, 8.0$.

HRMS (ESI): $m/z$ [M + H$^+$]$^+$ calcd for C$_{13}$H$_{13}$NO: 200.1093; found: 200.1092.

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

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

Yield: 92 mg (72%); light yellow oil; $R_f = 0.3$ (MeOH/CH$_2$Cl$_2$, 1:9); $\alpha_l^25 +45.2$ ($c$ 1.0, MeOH).

IR (neat): 3264, 3005, 2866, 1573, 1573, 1480, 1167, 1025 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta = 8.53$ (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).

13C NMR (126 MHz, CDCl$_3$): $\delta = 151.0, 147.7, 137.0, 134.6, 123.5, 62.9, 21.17, 18.7, 8.0$.

HRMS (ESI): $m/z$ [M + H$^+$]$^+$ calcd for C$_{13}$H$_{13}$NO: 200.1093; found: 200.1092.

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

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

Yield: 162 mg (71%); light yellow oil; $R_f = 0.26$ (MeOH/CH$_2$Cl$_2$, 1:9); $\alpha_l^25 +38.6$ ($c$ 1.0, MeOH).

IR (neat): 3264, 3005, 2872, 1571, 1493, 1464, 1417 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta = 8.86$ (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 (dd, $J = 8.4, 5.1, 1.4$ 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).

13C NMR (126 MHz, CDCl$_3$): $\delta = 152.7, 146.7, 134.7, 131.6, 129.0, 128.9, 127.8, 124.8, 62.3, 21.2, 18.6, 7.7.

HRMS (ESI): $m/z$ [M + H$^+$]$^+$ calcd for C$_{13}$H$_{14}$NO: 200.1069; found: 200.1066.

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

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

Yield: 136 mg (87%); light yellow oil; $R_f = 0.32$ (MeOH/CH$_2$Cl$_2$, 1:9); $\alpha_l^25 +33.1$ ($c$ 1.0, MeOH).

IR (neat): 3350, 3053, 3003, 2849, 1606, 1543, 1480, 1032 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta = 8.23$ (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).
Synthesis

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Synthesis of Starting Materials

2.2’-(Cyclohexylazanediyl)diacetic Acid (CIDA)

To a stirred solution of chloroacetic acid (6.94 mL, 116 mmol) and H₂O (9 mL) was added dropwise aq NaOH (9.28 g, 232 mmol in 30 mL of H₂O) 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 H₂O (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 H₂O (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): 3332, 3202, 3002, 2860, 1616, 1594, 1324, 1020 cm⁻¹.

1H NMR (500 MHz, DMSO): δ = 0.44 (s, 4 H), 3.22 (t, J = 6.2 Hz, 2 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).

13C NMR (126 MHz, DMSO): δ = 157.6 (2 C), 156.6, 132.3, 62.0, 20.5, 16.0, 7.4.


(E)-2-[3-((tert-Butyldimethylsilyl)oxy)prop-1-en-1-yl]-6-cyclohexyl-1,3,6,2-dioxaborocarbone-4,8-dione (15aa)

To a stirred solution of (E)-tert-butylidemethyl(3-[4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]allyl)oxasilane⁶ (4.18 g, 14 mmol) in a mixture of aceton/H₂O (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 aceton and H₂O were removed to dryness. The resulting white solid was suspended in aceton 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 mmol) and 2.2’-(cyclohexylazanediyl)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 H₂O (3 × 10 mL), dried with Na₂SO₄, and concentrated under reduced pressure to afford a light brown solid. Following column chromatography (silica gel, CH₂Cl₂/MeCN, 1:1), the protected allylic alcohol 15aa was isolated.

Yield: 3.33 g (60%); white solid; Rf = 0.5 (CH₂Cl₂/MeCN, 1:1); mp 132–133 °C.

IR (neat): 2931, 2865, 1748, 1648, 1449, 1256, 1104, 956 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 7.32–7.23 (m, 4 H), 7.23–7.17 (m, 1 H), 5.87 (dt, J = 17.9 Hz, 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).
Base-Sensitive Allylic Alcohol (Z)-4-[(tert-Butyldimethylsilyloxy)prop-1-en-1-yl]phenylacetate (20a)

To a dry sealed tube was added [Pd(PPh3)2Cl2] (304 mg, 0.433 mmol) and copper iodide (82.3 mg, 0.433 mmol). The mixture was then stirred for 30 min with argon. The mixture was then cooled to 0 °C and stirred for 6 h. The mixture was quenched with sat. aq NH4Cl (13 mL) and H2O (7 mL) and diluted with EtOAc (13 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 × 8 mL), dried with Na2SO4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:1) afforded the desired product 20b.

1H NMR (500 MHz, CDCl3): δ = 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).
13C NMR (126 MHz, CDCl3): δ = 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 C18H28O3Si: 338.2; found: 338.2.

(Z)-4-[(tert-Butyldimethylsilyloxy)prop-1-en-1-yl]phenylacetate (20c)

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 NH4Cl (5 mL) and diluted with EtOAc (8 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), dried with Na2SO4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:1) afforded the desired product 20.

Yield: 210 mg (99%); yellow oil; Rf = 0.4 (EtOAc/hexanes, 1:1).
IR (neat): 3022, 2953, 2888, 2855, 2070, 2040, 2031 cm–1.
1H NMR (500 MHz, CDCl3): δ = 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), 0.90 (s, 9 H), 0.06 (s, 6 H).
13C NMR (126 MHz, CDCl3): δ = 171.1, 136.7, 135.2, 131.8, 130.8, 129.2 (2 C), 128.3 (2 C), 66.2, 60.4, 26.1 (3 C), 21.2, 18.4, –5.0 (2 C).

Synthesis

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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 (202 mg, 5 mmol). Benzyl chloroformate was added dropwise to the solution and the reaction mixture was allowed to stir for 6 h. The mixture was quenched with H₂O (10 mL) and diluted with Et₂O (13 mL). The aqueous layer was washed with Et₂O (3 × 20 mL). The organic layers were combined, dried with Na₂SO₄, 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.³²

Yield: 758 mg (90%); yellow oil.

4-Bromobenzyl Acetate (19c)

Additive 19c was synthesized according to the literature.³³ In a dried flask, 4-bromobenzyl alcohol (600 mg, 3.21 mmol) was dissolved in anhyd pyridine (9 mL). Acetic anhydride (9.10 mL, anhyd pyridine (9 mL). The mixture was allowed to stir for 10 min at room temp. 4-Bromobenzyl alcohol (600 mg, 3.21 mmol) was dissolved in anhyd THF (16.5 mL) and the reaction mixture was allowed to stir for 6 h. The mixture was filtered and the solution was concentrated under reduced pressure and the white solid was washed with hexanes to result in the desired product 19c. The spectra matched those reported in the literature.³³

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

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Supporting Information

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References


