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 cyclopropylmethenoxide 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 zinco-cyclopropanation reaction of allylic alcohol to remove residual di-oxaborolane 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\(^1\) and are widely employed in pharmaceutically and agrochemically relevant compounds.\(^2\) Cyclopropylboronic acids and derivatives are excellent synthons for the rapid introduction of the cyclopropyl motif into complex molecules.\(^3\) Suzuki cross-coupling of these cyclopropylboronic acids with het-eroaryls provide heteroaryl-substituted cyclopropanes, which serve as chiral cores in many natural products and biologically active drug candidates.\(^4\) For example, thiazolopyrimidinones comprising the cyclopropane group (Figure 1, 1) serve as N-methyl-D-aspartate (NMDA) receptor activity modulators and rely on racemic cyclopropylmethanols as optimal synths for the introduction of cyclopropane groups in a racemic fashion.\(^5\) 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.\(^6\) Although an array of methodologies to access substituted borocyclopropane sub-units in a diastereoselective manner are available,\(^7\) 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,\(^8\) and copper-catalyzed carbene transfer of ethylidioate to alkylboronates for the preparation of chiral 1,2,3-trisubstituted cyclopropanes (Scheme 1, part i).\(^9\) 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).\(^10\) The Simmons–Smith reaction has also been employed for the synthesis of chiral vinylpinacolboronates as separable racemic diastereomeric mixtures.\(^8b\)

The Simmons–Smith cyclopropanation mediated by di-oxaborolane 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.\(^11\) We report herein the first enantioselective Simmons–Smith cyclopropanation of boronate-bearing allylic alcohols for the preparation of enantioenriched borocyclopropane building blocks.\(^12\) Pinacolate analogues have often been used in borocyclopropanation methodologies.\(^5\),\(^6\),\(^6b\),\(^7\) Many of these derivatives are oils and are prone to decomposition through protodeboronation, and are hence recurrently deemed ‘unstable’ boronic acids.\(^14\) In contrast, cyclopropyltrifluoroborates are solids and display a reduced propensity to undergo protodeboronation, but have limited solubility in moderately polar solvents.\(^15\),\(^16\)

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany
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.3 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 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.11

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

The cyclopropanation reaction with 15a using Zn(CH₂I)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 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.19

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
bearng 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 allylic alcohols. We investigated the use of DEA for the transesterification of (cyclopropylmethyl)boronate complexes. After extensive screening for isolation conditions, the decomplexation of the boron methanol boronate complexes. After optimization, the pinacol derivative is likely due to the transesterification of 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 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 acetol 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 the acetate group.

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 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-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 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 the acetate group.

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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 explored.3,25 Cross-coupling of cyclopropyl MIDA boronates has been achieved using SPPhos and Pd(OAc)2 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)2 and PCy3 provides the cyclopropyl adducts in only 17–32% yields.26 After screening various cross-coupling conditions, we found the use of PCy3 and Pd(dba)3 as a suitable combination for the cross-coupling of the CIDA-borocyclopropane 13 (Scheme 5). It should be noted that cyclopropylboronic acids prepared immediately prior to the reaction can be as effective as the MIDA boronates.

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 decomposition of boron-ligated intermediates in the zinco-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 zinco-cyclopropanation reaction to allow access to the fully decoupled 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.

The cross coupling of 13 (95.6:4.4 er) with five heteroaryl bromides in the presence of Pd(dba)3 (5 mol%), PCy3 (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.19 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-borate allylic alcohols failed due to lack of stability. To overcome these challenges, we took to an in situ approach to obtain the disubstituted borocyclopentylmethane via the enantioselective zinco-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 zinco-cyclopropanation of the non-substituted allylic alcohol substrate. Treatment of allyl alcohol 24 with the gem-dizinc carbendio 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).
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 with the exclusion of moisture. Anhydrous solvents were obtained either by filtration through drying columns on a Glass Contour system (Irvine, CA) (benzene and THF) or by distillation over calcium hydride (Et3N, pyridine, CH2Cl2) or sodium and potassium permanganate (KMN04). p-Anisaldehyde, and ninhydrin. Flash column chromatography was performed on silica gel (pore size 60 Å, 230–400 mesh particle size, 40–63 mm 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]D values, were calculated from optical rotations measured at 25 °C in MeOH at the general formula: [α]D(c, l) = 205.9), or residual [(CD3)2SO (1H: δ = 2.54, 13C: δ = 32.2)]. 1H NMR (400 MHz, acetone-d6) was 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-dioxazaborocane-4,8-dione (15a)

To a dry microwave vial, (E)-2-[(tert-butyl(dimethyl)silyl)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 H2O (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 H2O (10 mL) and lyophilized until dryness; this gave 15a.

Yield: 313 mg (99%); white solid; [α]D = 0.3 (CH3Cl/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-butyldimethyl[[(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]oxy]silane20 (12.0 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 NaHCO3 (2 × 15 mL). The organic layer was dried with Na2SO4 and concentrated under reduced pressure to provide a crude brown oil, which was purified by flash chromatography (silica gel, EtOAc/hexanes, 3:7). 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.
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).


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 (483 mg, 0.17 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 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 NH4Cl (2 mL), and diluted with EtOAc (20 mL) and brine (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 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 (1:1)) 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%); 92.9:7.1 er; SFC (Chiralpak OD-H 25 cm, 30 °C, 150 bar); [fκ(major): 10.11 min, fκ(minor): 8.41 min; [α]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 Et2Zn (169 µL, 1.64 mmol) was added to stirred CH2Cl2 (3 mL) in a flame-dried flask at rt. The solution was cooled to 0 °C and diiodomethane (264 µL, 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 CH2Cl2 (2 mL) was added dropwise over 1 min. The resulting mixture was stirred for 6 h at rt. The reaction mixture was diluted with NH4Cl (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 × 3 mL) and the organic layers were combined, dried with Na2SO4 and concentrated under reduced pressure. To the residue was added diethanolamine (2.85 g, 27.1 mmol) in CH2Cl2 (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); [fκ(major): 20.19 min, [fκ(minor): 17.74 min; Rf = 0.3 (EtOAc/hexane, 1:3); [α]25 +7.4 (c 0.83, MeOH).

IR (neat): 2977, 2932, 1644, 1425, 1371, 1314, 1141, 1042, 854 cm–1.


Larger-Scale Preparation of 14 (5.4 mmol)

Neat Et2Zn (1.23 mL, 12.0 mmol) was added to a flame-dried flask containing a stir bar, CH2Cl2 (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 (1.00 g, 5.98 mmol) in CH2Cl2 (25 mL) was added dropwise over 1 min. The resulting mixture was stirred for 15 h at rt. The reaction mixture was diluted with NH4Cl (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 × 10 mL). The organic layers were combined, dried with Na2SO4 and concentrated under reduced pressure. To the residue was added warm diethanolamine (2.85 g, 27.1 mmol) in CH2Cl2 (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 (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); [fκ(major): 20.19 min, [fκ(minor): 17.74 min; Rf = 0.3 (EtOAc/hexane, 1:3); [α]25 +7.4 (c 0.83, MeOH).

IR (neat): 2977, 2932, 1644, 1425, 1371, 1314, 1141, 1042, 854 cm–1.


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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): $\delta_{\text{major}}$: 25.24 min; $\delta_{\text{minor}}$: 21.86; $\delta_{\text{LO}}$: +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 dioxidomethane (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 17 (67 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 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 Et₂Zn (113 µL, 1.10 mmol) in CH₂Cl₂ (2.5 mL) at 0 °C was added dioxidomethane (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 18 (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 (298 mg, 2.50 mmol) was weighed into a vial and dissolved 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. N-Methyldiethanolamine (298 mg, 2.50 mmol) was weighed into a vial, dissolved in CH₂Cl₂ (2.5 mL), and 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 and then was adsorbed onto silica gel. Purification by column chromatography (silica gel, MeOH/CH₂Cl₂, 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 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%).

**[(9H-Fluoren-9-yl)methoxy|carbonyl]-l-valine (19d)**

**General Procedure D**: Purification by column chromatography (silica gel, MeOH/CH₂Cl₂, 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/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-Methyldiethanolamine 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 dioxidomethane (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 18 (67 mg, 0.50 mmol), additive 19 (0.50 mmol), and dioxaborolane 11 (162 mg, 0.6 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. N-Methyldiethanolamine (298 mg, 2.50 mmol) was weighed into a vial, dissolved in CH₂Cl₂ (2.5 mL), and 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 and then was adsorbed onto silica gel. Purification by column chromatography (silica gel, MeOH/CH₂Cl₂, 1:9) resulted in the recovered additive 19d (148 mg, 87%) and the desired cyclopropane 18 (68.9 mg, 93%).

**General Procedure E**: Recovered additive 19d (148 mg, 87%) and the desired cyclopropane 18 (68.9 mg, 93%).

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

To a solution of Et₂Zn (233 µL, 2.26 mmol) in CH₂Cl₂ (3.7 mL) at 0 °C was added dioxidomethane (365 µL, 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, 1.63 mmol) and dioxaborolane 11 (306 mg, 1.13 mmol) in CH₂Cl₂ (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 NH₄Cl (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 diethanolamine (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 3 h. Sili-cal gel was added to the reaction mixture, which was concentrated, resulting in a dry silicagel 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%); 93:7 er; SFC (Chiralpak AD-H 25 cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min):

IR (neat): 3389, 2931, 2871, 1734, 1376, 1226, 1026, 1016 cm⁻¹.

Yield: 172 mg (76%); pale yellow oil; [α]D₂⁵ +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⁻¹.

HRMS (ESI): m/z [M + H⁺] calcd for C₉H₁₁NO: 150.0913; found: 150.0910.

[(1S,2S)-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; Rf 0.3 (MeOH/CH₂Cl₂, 1:9); [α]D₂⁵ +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.

[(1R,2R)-2-(Quinolin-3-yl)cyclopropyl]methanol (23b)

General Procedure A: 3-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; [α]D₂⁵ +36.3 (c 0.87, MeOH).


[(1R,2R)-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: 16.5 mg (72%); clear oil; Rf 0.56, MeOH.

Yield: 16.5 mg (72%); 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: 21.3 mg (93%); clear oil.

[(1S,2S)-2-(3-Methylcyclopent-1-en-1-yl)cyclopropyl]methanol (23d)

General Procedure A: 3-Methylcyclopent-1-en-1-ylboronic acid (40.2 mg, 0.28 mmol) and 13 (41.3 mg, 0.14 mmol) were used. Yield: 16.1 mg (72%); clear oil; Rf 0.3 (MeOH/CH₂Cl₂, 1:9); [α]D₂⁵ +44.0 (c 0.56, MeOH).

HRMS (ESI): m/z [M + H⁺] calcd for C₁₉H₂₃NO₂: 257.1571; found: 257.1571.

[(1R,2R)-2-(3-Methylcyclopent-1-en-1-yl)cyclopropyl]methanol (23e)

General Procedure A: 3-Methylcyclopent-1-en-1-ylboronic acid (40.2 mg, 0.28 mmol) and 14 (27.7 mg, 0.14 mmol) were used. Yield: 16.1 mg (72%); clear oil; Rf 0.3 (MeOH/CH₂Cl₂, 1:9); [α]D₂⁵ +44.0 (c 0.56, MeOH).

HRMS (ESI): m/z [M + H⁺] calcd for C₁₉H₂₃NO₂: 257.1571; found: 257.1571.
[(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; \( \delta = 0.3 \) (MeOH/CHCl3, 1:9); \( \alpha \delta_{25} +37.5 \) (c 0.85, MeOH).

IR (neat): 3262, 3064, 3005, 2872, 1571, 1493, 1464, 1417 cm⁻¹.

HRMS (ESI): \( m/z \) [M + H]⁺ calcd for C₁₃H₁₄NO: 200.1069; found: 200.1065.

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

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

Yield: 136 mg (873%); light yellow oil; \( \delta = 0.3 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +45.2 \) (c 1.0, MeOH).

IR (neat): 3262, 3055, 2872, 1571, 1450, 1167, 1025 cm⁻¹.


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

A solution of 24 (66.5 µL, 1.1 mmol) in CH₂Cl₂ (4.6 mL) was added to Et₂Zn (115 µL, 1.11 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 CH₂Cl₂ (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 Et₂Zn (507 µL, 4.92 mmol) was added dropwise to a mixture of \( t \) (1.22 g, 4.81 mmol), Et₂O (0.98 mL, 9.33 mmol), and CH₂Cl₂ (4.7 mL). Once the \( t \) was completely consumed, the reaction mixture was cooled to –78 °C and a solution of CH₂Cl₂ (951 mg, 2.42 mmol) in CH₂Cl₂ (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 NH₄Cl. The aqueous layer was extracted with Et₂O (3 × 10 mL). The organic layers were gathered and dried over MgSO₄ and the solvents were removed until 500 µL 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[PPh₃]₄ (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, H₂O was added to it. The aqueous layer was extracted with Et₂O (3 × 7 mL). The combined organic layers were dried over MgSO₄. The solvents were removed under reduced pressure. The residue was stirred in diethanolamine (602 mg, 5.72 mmol) in CH₂Cl₂ (3 mL) for 1 h to remove any dioxaborole bound to the cyclopropane. The residue was taken up in CH₂Cl₂ and purified by flash chromatography (silica gel, MeOH/CH₂Cl₂ 5:95, unless stated otherwise) to provide the desired coupled products 25a–f.

[(1R,2S)-2-(Pyridin-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; \( \delta = 0.23 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +38.6 \) (c 1.0, MeOH).

IR (neat): 3119, 2966, 2872, 1571, 1524, 1493, 1464, 1417 cm⁻¹.


[(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; \( \delta = 0.26 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +38.6 \) (c 1.0, MeOH).

IR (neat): 3226, 3064, 3005, 2872, 1571, 1493, 1464, 1417 cm⁻¹.

[(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 (873%); light yellow oil; \( \delta = 0.32 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +31.1 \) (c 1.0, MeOH).

IR (neat): 3500, 3035, 3003, 2849, 1606, 1543, 1480, 1032 cm⁻¹.

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

Yield: 163 mg (873%); light yellow oil; \( \delta = 0.32 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +31.1 \) (c 1.0, MeOH).

IR (neat): 3300, 3503, 3003, 2849, 1606, 1543, 1480, 1032 cm⁻¹.

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

Yield: 163 mg (873%); light yellow oil; \( \delta = 0.32 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +31.1 \) (c 1.0, MeOH).

IR (neat): 3300, 3503, 3003, 2849, 1606, 1543, 1480, 1032 cm⁻¹.

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

Yield: 163 mg (873%); light yellow oil; \( \delta = 0.32 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +31.1 \) (c 1.0, MeOH).

IR (neat): 3300, 3503, 3003, 2849, 1606, 1543, 1480, 1032 cm⁻¹.

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

Yield: 163 mg (873%); light yellow oil; \( \delta = 0.32 \) (MeOH/CHCl₃, 1:9); \( \alpha \delta_{25} +31.1 \) (c 1.0, MeOH).

IR (neat): 3300, 3503, 3003, 2849, 1606, 1543, 1480, 1032 cm⁻¹.
13C NMR (126 MHz, CDCl3): δ = 160.3, 148.0, 147.9, 126.1, 122.2, 61.3, 22.5, 22.4, 21.0, 10.5.

[(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; Rf = 0.22 (MeOH/CH2Cl2, 1:9); [α]D25 +57.7 (c 1.0, MeOH).
IR (neat): 3330, 2962, 2865, 1638, 1603, 1496, 1451, 1019 cm–1.
1H NMR (500 MHz, CDCl3): δ = 7.35 (d, 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).
13C NMR (126 MHz, CDCl3): δ = 158.4, 157.1, 138.3, 114.9, 105.9, 61.5, 22.3, 21.8, 9.8.

[(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; Rf = 0.27 (MeOH/CH2Cl2, 1:9); [α]D25 +11.2 (c 1.0, MeOH).
IR (neat): 3329, 3009, 2872, 1556, 1415, 1239, 1168, 1026 cm–1.
1H NMR (500 MHz, CDCl3): δ = 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).
13C NMR (126 MHz, CDCl3): δ = 157.6 (2 C), 156.6, 132.3, 62.0, 20.5, 16.0, 7.4.

[(1R,2S)-2-(Phenylcyclopropyl) methanol (25f)
The product was prepared according to general procedure C using benzobromene (328 µL, 2.28 mmol).
Yield: 120 mg (71%); 95.2:4.7 er; SFC (Chiralpak AD-H 25 cm, 30 °C, 150 bar, 10% MeOH, 3 mL/min): tR (major): 6.76 min, tR (minor): 4.25 min; light yellow oil; Rf = 0.45 (EtOAc/hexanes, 1:9); [α]D25 +22.4 (c 1.0, MeOH).
IR (neat): 3330, 2962, 2865, 1638, 1603, 1496, 1451, 1019 cm–1.
1H NMR (500 MHz, CDCl3): δ = 7.32–7.23 (m, 4 H), 7.23–7.17 (m, 1 H), 7.12 (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).
13C NMR (126 MHz, DMSO): δ = 173.9, 62.4, 54.1, 29.9, 26.2, 26.0.

(E)-2-[(tert-Butyldimethylsilyl)oxy]prop-1-en-1-yl)-6-cyclohexyl-1,3,6,2-dioxazaborocane-4,8-dione (15a)
To a stirred solution of (E)-tert-butyldimethyl(3-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxy]silane28 (4.18 g, 14 mmol) E-hexyl-1,3,6,2-dioxazaborocane-4,8-dione (15aa)
In a mixture of acetone/H2O (1:1; 94 mL) was added in one portion, sodium periodate (15.0 g, 71.0 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 H2O were removed to dryness. The resulting white solid was suspended in acetonitrile 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) 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. The reaction mixture was cooled immediately for the next step. The protected allylic alcohol methyl-1,3,2-dioxaborolan-2-yl)oxy}silane28 (4.18 g, 14 mmol)
To a stirred solution of chloroacetic acid (6.94 mL, 116 mmol) in acetone and stirred for 15 min and then filtered. The filtrate was concentrated to dryness. The resulting white solid was suspended in acetonitrile 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) 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, 2856, 1747, 1648, 1449, 1252, 1104, 956 cm–1.
1H NMR (400 MHz, acetone-d6): δ = 7.41 (dt, J = 17.9, 1.0 Hz), 5.87 (dt, J = 17.9 1 Hz), 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).

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

(4-[(tert-Butyldimethylsilyl)oxy]prop-1-en-1-yl)phenyl)methanol (20a)

To a dry sealed tube was added [Pd(PPh3)2Cl2] (304 mg, 0.433 mmol) and copper iodide (540 mg, 2.89 mmol), followed by the immediate addition of the TBS-protected propargyl alcohol20 (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 layer was dried with Na2SO4, and concentrated. Purification by column chromatography (silica gel, MeOH/CH2Cl2, 1:9) afforded the coupled product 20a.

Yield: 670.4 mg (84%); yellow oil; Rf = 0.5 (MeOH/CH2Cl2, 1:9).


(2Z)-4-[(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 alkene 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 EtOAc. The filtrate was washed with brine and extracted with EtOAc (3 × 10 mL). The filtrate was dried with Na2SO4 and concentrated under reduced pressure to provide the desired pure product 20b.

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

HRMS (ESI): m/z [M + H]+ calcd for C14H20O2Si: 277.2; found: 277.7.

Benzylic 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 μL, 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 μL, 3.51 mmol) was added dropwise. The reaction mixture was filtered over Celite, and the Celite was washed with EtOAc. The filtrate was washed with brine and extracted with EtOAc (3 × 10 mL). The organic layer was concentrated, dried with Na2SO4, and concentrated under reduced pressure to provide the desired product 19a.


Base-Sensitive Additives

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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 (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 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.

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 (RS-171310), and the Université de Montréal.

Supporting Information
Supporting information for this article is available online at 10.1055/s-0037-1611896.

References


