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) 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 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 cyclopropylmethanols 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 ethylidiazooacetate 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 recurrently deemed ‘unstable’ boronic acids. In contrast, cyclopropyl trifluoroborates 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 cyclopropagation 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 cyclopropagation 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.\textsuperscript{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 \(\text{15a}\) (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 \(\text{15a}\), 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%.\textsuperscript{17} Once obtained, we were pleased to find that the CIDA allylic alcohol \(\text{15a}\) was readily soluble in dichloromethane.

The cyclopropanation reaction with \(\text{15a}\) using \(\text{Zn(CH}_2\text{I}_2}\) (2.2 equiv) and dioxaborolane \(\text{11}\) (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\textsuperscript{29} or the use of highly basic 5 M aqueous potassium hydroxide to decomplex the dioxaborolane from the cyclopropyl methoxide species \(\text{16}\) formed in the reaction. Indeed, the hydrolysis of alkyltriolborates is known to involve harsh oxidative conditions,\textsuperscript{18} resulting in narrow functional group compatibility and challenging purifications.\textsuperscript{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 \(\text{16}\). Diethanolamine (DEA) and ethanolamine have been used for the transesterification of certain pinacolboronate esters.
bearing electron-withdrawing groups.\textsuperscript{20} However, Szabò recently observed that the diethanolamine cyclic boronate deprotection protocol is unsuccessful for transesterification of some electron-deficient vinylpinacolate analogues.\textsuperscript{21} To the best of our knowledge, DEA has not been used for the transesterification of alkyltrioleborates. 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 pinacolboronates. We evaluated the robustness of the DEA decomplexation process using Glorius’s intermolecular screening tool\textsuperscript{22} for the cy-clopropanation of allylic alcohol 17\textsuperscript{11} 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.\textsuperscript{23}

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.\textsuperscript{24} 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.\textsuperscript{3,25} Cross-coupling of cyclopropyl MIDA boronates has been achieved using SPhos and Pd(OAc)\textsubscript{2} to afford excellent yields of the coupled products while the cross-coupling of racemic allylic alcohol 20 observed no decomposition 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 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 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.

The cross coupling of 13 (95.6:4.4 er) with five heteroaryl bromides in the presence of Pd\textsubscript{2}(dba)\textsubscript{3} (5 mol%), PCy\textsubscript{3} (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.\textsuperscript{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-boronic allylic alcohols failed due to lack of stability. To overcome these challenges, we took an in situ approach to obtain the disubstituted borocyclopropylmethanol 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 zinc-cyclopropanation of the non-substituted allylic alcohol substrate. Treatment of allyl alcohol 24 with the gem-dizinc carbeneid 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 GlassContour system (Irvine, CA) (benzene and THF) or by distillation over calcium hydride (Et3N, pyridine, CH2Cl2) or sodium hydride (Et2Zn, pyridine, CH2Cl2) or sodium acetate (THF). Absolute EtOH, glacial acetic acid, and Ac2O were used as is without further purification and were used without further purification. Fmoc-Val-OH was purified from AkzoNobel and used without further purification. Diethanolamine and neat from AkzoNobel and used without further purification. Diethyldiethanolamine were purchased from Aldrich.

Yield: 4.20 g (57%); yellow oil; 

1H NMR (400 MHz, acetone-d6): \( \delta = 6.27 \) (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, \( J = 12.1 \) Hz, 1 H), 2.81 (s, 2 H), 1.89 (d, \( J = 12.5 \) Hz, 2 H), 1.71–1.49 (m, 4 H), 1.10–1.01 (m, 2 H).


(Y)-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-butyldimethylsilyl)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; \( R_f = 0.3 \) (CH2Cl2/McCN, 1:1); mp 117–118 °C.

IR (neat): 2939, 2860, 1740, 1644, 1448, 1326, 1290, 1244 cm–1.

1H NMR (400 MHz, acetone-d6): \( \delta = 6.27 \) (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, \( J = 12.1 \) Hz, 1 H), 2.81 (s, 2 H), 1.89 (d, \( J = 12.5 \) Hz, 2 H), 1.71–1.49 (m, 4 H), 1.10–1.01 (m, 2 H).


(Y)-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-butyl(dimethyl)silyl[(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ally]oxy)silane28 (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).

Yield: 4.20 g (57%); yellow oil; \( R_f = 0.4 \) (EtOAc/hexane, 3:7).

IR (neat): 3420, 2977, 2929, 1643, 1358, 1317, 1411, 1104, 970 cm–1.

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A 10 mL flame-dried flask was charged with 15a (483 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 (1.26 mL, 12.2 mmol) was added to CH2Cl2 (50 mL) and DME (1 mL). 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 (2 mL) and EtOAc (2 mL) and washed with brine (10 mL). The organic layer was separated and the aqueous layer was washed with EtOAc (2 × 20 mL). The organic layer was concentrated under reduced pressure. To the residue was added warm MeOH. The mixture was stirred for 3 h at rt. 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%); 90:9:1 er; TOF (6224) (Chiralpak OJ-RH, 13% MeCN, 40 ml/min; t(minor): 17.4 min; t(major): 17.1 min; Rf=0.3 MeCN/hexane, 1:3); [α]25 +7.4 (c 0.83, MeOH).

IR (neat): 2977, 2932, 1644, 1425, 1371, 1134, 1141, 1042, 854 cm⁻¹.

1H NMR (500 MHz, acetone-d6): δ = 4.13 (d, J = 25.9, 16.3 Hz, 2 H), 3.92–3.83 (m, 3 H), 3.67 (dd, J = 11.1, 5.9 Hz, 1 H), 1.22 (d, J = 10.6, 7.6 Hz, 1 H), 2.83 (s, 1 H) 2.12 (dd, 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), 1.56–1.50 (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).

13C NMR (176 MHz, acetone-d6): δ = 168.8, 168.0, 72.3, 66.4, 65.4, 57.0, 55.1, 27.1, 26.6, 24.7, 24.5, 17.3, 59.2, 19.9.

HRMS (ESI): m/z [M + H]+ calc 293.6164; found: 293.6172.

Larger-Scale Preparation of 14 (5.4 mmol)

Neat Et2Zn (169 mL, 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 (2.95 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 for chromatography (silica gel, EtOAc/hexanes, 1:3). After purification the pure product was obtained as a yellow oil.

Yield: 50% (15.3 mg); 90:9:1 er; TOF (6340) (Chiralpak OJ-RH, 13% MeCN, 40 ml/min; t(minor): 17.4 min; t(major): 17.1 min; Rf=0.3 MeCN/hexane, 1:3); [α]25 +7.4 (c 0.83, MeOH).

IR (neat): 2977, 2932, 1644, 1425, 1371, 1134, 1141, 1042, 854 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 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 (dd, 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).

13C NMR (101 MHz, CDCl3): δ = 83.2, 68.0, 24.8 (2 C), 20.5 (4 C), 9.3, –1.6.

18N NMR (400 MHz, CDCl3): δ = 33.1.

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): 68 min: 19a, 98% ee; [ε]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 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 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.

**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%).**

**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%).**

**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%).**

**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, 1.10 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 mg, 0.50 mmol), additive (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-Methyl diethanolamine (298 mg, 2.5 mg) 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 was then 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%).

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

To a solution of Et2Zn (233 µL, 2.26 mmol) in CH2Cl2 (3.7 mL) at 0 °C was added diiodomethane (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. 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 discrimination of the saturated silica by column chromatography (silica gel, EtOAc/hexanes, 1:4) afforded 21.

To a dried round-bottom flask equipped with a stir bar was added HetArBr 22a–e (0.28 mmol), 13 (0.14 mmol), Pd₂dba₂ (6.4 mg, 5 mol%), and Cy₃P (3.9 mg, 10 mol%). The vial was sealed with a septum and flushed with argon. To the vial was added dioxane (500 μL), and the resulting mixture was stirred at 23 °C for 20 min. To the mixture was then added 3.0 M aq K₂PO₄ (280 μL) 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-Heterocyclopropyl)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), Pd₂dba₂ (6.4 mg, 5 mol%), and Cy₃P (3.9 mg, 10 mol%). The vial was sealed with a septum and flushed with argon. To the vial was added dioxane (500 μL) and the resulting mixture was stirred at 23 °C for 20 min. To the mixture was then added 3.0 M aq K₂PO₄ (280 μL) 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-Heterocyclopropyl)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), Pd₂dba₂ (6.4 mg, 5 mol%), and Cy₃P (3.93 mg, 10 mol%). The vial was sealed with a septum and flushed with argon. To the vial was added dioxane (500 μL) and the resulting mixture was stirred at 23 °C for 20 min. To the mixture was then added 3.0 M aq K₂PO₄ (280 μL) 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.
[(1S,5S)-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; \( \beta_0^{19} \text{MeOH} = 0.3 \) (MeOH/CHCl\(_3\), 1:9); \([a]_D^{15} +37.5 (c 0.85, \text{MeOH}). \)

IR (neat): 3027, 2925, 2853, 1721, 1553, 1416, 1076, 976 cm\(^{-1}\).

HRMS (ESI): \( m/z \) [M + H]\(^+\) calcd for C\(_8\)H\(_{10}\)N\(_2\)O: 151.0865; found: 151.0865.

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

General Procedure A: 5-Bromopyrimidine, 97% (445 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% (445 mg, 0.28 mmol) and 14 (27.7 mg, 0.14 mmol) were used. Yield: 18.7 mg (89%); pale yellow oil; \( \beta_0^{19} \text{MeOH} = 0.3 \) (MeOH/CHCl\(_3\), 1:9); \([a]_D^{15} +38.9 (c 0.87, \text{MeOH}). \)

IR (neat): 1662, 1558, 1417, 1343, 1120, 1025 cm\(^{-1}\).

HRMS (ESI): \( m/z \) [M + H]\(^+\) calcd for C\(_8\)H\(_{13}\)NO: 150.0913; found: 150.0912.

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

A solution of 24 (665 mg, 1.1 mmol) in CH\(_2\)Cl\(_2\) (4.6 mL) was added to Et\(_2\)Zn (115 mg, 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\(_2\)Cl\(_2\) (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\(_2\)Zn (507 mg, 4.92 mmol) was added dropwise to a mixture of \( \beta_0^{12} \) (2.2 g, 481 mmol), Et\(_2\)O (0.98 mL, 9.33 mmol), and CH\(_2\)Cl\(_2\) (4.7 mL). Once the \( \beta_0^{12} \) was completely consumed, the reaction mixture was cooled to ~70 °C and a solution of CHI\(_2\) (951 mg, 2.42 mmol) in CH\(_2\)Cl\(_2\) (14 mL) was slowly added to the IZnEt solution. The mixture was stirred at ~70 °C for 10 min.

The alkoxide solution was quickly cannulated over the carbenoid solution and the reaction mixture was allowed to reach ~40 °C (crysostat bath). The reaction mixture was stirred 24 h at this temperature. The reaction mixture was quenched with sat. aq NH\(_4\)Cl. The aqueous layer was extracted with Et\(_2\)O (3 × 10 mL). The organic layers were gathered and dried over MgSO\(_4\) 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[PPh\(_3\)]\(_4\) (68.7 mg, 0.50 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\(_2\)O was added to it. The aqueous layer was extracted with Et\(_2\)O (3 × 7 mL). The combined organic layers were dried over MgSO\(_4\). The solvents were removed under reduced pressure. The residue was stirred in diethanolamine (602 mg, 5.72 mmol) in CH\(_2\)Cl\(_2\) (3 mL) for 1 h to remove any dioxaborolane bound to the cyclopropane. The residue was taken up in CH\(_2\)Cl\(_2\) and purified by flash chromatography (silica gel, MeOH/CH\(_2\)Cl\(_2\), 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; \( \beta_0^{19} \text{MeOH} = 0.23 \) (MeOH/CHCl\(_3\), 1:9); \([a]_D^{15} -45.2 (c 1.0, \text{MeOH}). \)

IR (neat): 3264, 3005, 2866, 1573, 1573, 1480, 1418, 1167, 1025 cm\(^{-1}\).

HRMS (ESI): \( m/z \) [M + H]\(^+\) calcd for C\(_9\)H\(_{14}\)NO: 190.0937; found: 190.0937.

[(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; \( \beta_0^{19} \text{MeOH} = 0.26 \) (MeOH/CHCl\(_3\), 1:9); \([a]_D^{15} +38.6 (c 1.0, \text{MeOH}). \)

IR (neat): 3262, 3064, 3005, 2872, 1571, 1493, 1464, 1417 cm\(^{-1}\).

HRMS (ESI): \( m/z \) [M + H]\(^+\) calcd for C\(_9\)H\(_{13}\)NO: 158.0913; found: 158.0912.

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

The product was prepared according to general procedure C using 4-bromo-4-methylpyridine (252 μL, 2.28 mmol). Yield: 136 mg (87%); light yellow oil; \( \beta_0^{19} \text{MeOH/CHCl\(_3\)}, 1:9; \)

\([a]_D^{15} +31.1 (c 1.0, \text{MeOH}). \)

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

HRMS (ESI): \( m/z \) [M + H]\(^+\) calcd for C\(_9\)H\(_{13}\)NO: 200.1069; found: 200.1066.

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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; \( \text{Rf} \) = 0.22 (MeOH/CHCl₃, 1:9); [\( \alpha \rceil _{D} \rceil ^{25} = -57.7 \text{ (c 1.0, MeOH).} \]

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

HRMS (ESI): \( m/z \) [M + H\(^+\)] \(^{\text{calcld for C}_{16}H_{18}ClNO: 288.1071; \text{found: 164.1071.} \)

\([\text{IR(25)}]-2\text{-}(6\text{-Aminopyridin-2-yl)cyclopropyl}]\text{methanol (25d)}\)

\( \delta = 6.67 \text{ (d, J = 7.4 Hz, 1 H)}, 3.33 \text{ (dd, J = 12.0, 3.8 Hz, 1 H)}, 2.10 \text{ (td, J = 8.6, 6.0 Hz, 1 H)}, 1.59–1.51 \text{ (m, 1 H)}, 1.08 \text{ (td, J = 8.7, 4.8 Hz, 1 H)}, 0.98–0.95 \text{ (m, 1 H).} \]

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

HRMS (ESI): \( m/z \) [M + H\(^+\)] \(^{\text{calcld for C}_{10}H_{13}NO: 165.1022; \text{found: 165.1022.} \)

\([\text{IR(25)}]-2\text{-}(\text{Pyrimidin-5-yl)cyclopropyl}]\text{methanol (25e)}\)

Yield: 120 mg (71%); 95.2:4.7 er; SFC (Chiralpak AD-H 25cm, 30 °C, 1 bar, 238 L/min, 10 mL/min, 10:90 MeOH)...

Yield: 127 mg (74%); light yellow oil; \( \text{Rf} \) = 0.27 (MeOH/CHCl₃, 1:9); [\( \alpha \rceil _{D} \rceil ^{25} = -11.2 \text{ (c 1.0, MeOH).} \]

IR (neat): 3232, 3009, 2872, 1556, 1415, 1239, 1168, 1026 cm\(^{-1}\).

HRMS (ESI): \( m/z \) [M + H\(^+\)] \(^{\text{calcld for C}_{12}H_{15}NO: 181.1227; \text{found: 181.1227.} \)

\([\text{IR(25)}]-2\text{-}(\text{Butyldimethylsilyl)oxy\text{-prop-1-en-1-yl}}-6\text{-cyclohexyl-1,3,2-dioxaborolan-2-yl}]\text{methanol (25f)}\)

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.

HRMS (ESI): \( m/z \) [M + H\(^+\)] \(^{\text{calcld for C}_{10}H_{17}NO: 216.1230; \text{found: 216.1227.} \)

\([\text{IR(25)}]-2\text{-}\text{Butyldimethyl(silyl)}\text{-prop-1-en-1-yl}}-6\text{-cyclohexyl-1,3,2-dioxaborolan-2-yl}]\text{methanol (25g)}\)

To a stirred solution of (E)-tert-butylidemethyl[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]oxysilane \(^{14a} \) (4.18 g, 14 mmol) in a mixture of acetone/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 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 mmol) and 2,2′′-(cyclohexylamidene)diacetic acid (6.00 g, 27 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 \(^{15a} \) was isolated.

Yield: 3.33 g (60%); white solid; \( \text{Rf} \) = 0.5 (CH₃Cl/MeCN, 1:1); mp 132–133 °C.

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

HRMS (ESI): \( m/z \) [M + H\(^+\)] \(^{\text{calcld for C}_{10}H_{13}NO: 165.1022; \text{found: 165.1022.} \)

\([\text{IR(25)}]-2\text{-}\text{Butyldimethyl(silyl)oxy\text{-prop-1-en-1-yl}}-6\text{-cyclohexyl-1,3,2-dioxaborolan-2-yl}]\text{methanol (25h)}\)

To a stirred solution of \([\text{IR(25)}]-2\text{-}\text{Butyldimethyl(silyl)oxy\text{-prop-1-en-1-yl}}-6\text{-cyclohexyl-1,3,2-dioxaborolan-2-yl}]\text{methanol (25h)}\) 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 \(^{15a} \) was isolated.

Yield: 3.33 g (60%); white solid; \( \text{Rf} \) = 0.5 (CH₃Cl/MeCN, 1:1); mp 132–133 °C.
13C NMR (126 MHz, CDCl3): δ = 169.1 (2 C), 146.3 (2 C), 146.2 (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).


Base-Sensitive Allylic Alcohol (Z)-4-[(tert-Butyldimethylsilyloxy)prop-1-en-1-yl]benzyl Acetate (20)

(4-[(tert-Butyldimethylsilyloxy)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 (82.3 mg, 0.433 mmol). Et3N (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 alcohol30 (1.96 g, 11.5 mmol). The reaction mixture was stirred for 15 h at 77 °C under an argon atmosphere. The reaction mixture was cooled to 0 °C and quenched with sat. aq NH4Cl (13 mL). The mixture was then cooled to 0 °C and acetic anhydride (12 mL) was added dropwise to the mixture. The reaction mixture was stirred at rt for 6 h. The mixture was filtered over Celite, and the Celite was washed with THF (4.20 mL). 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 coupled product 20a.

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


(2Z)-4-[(tert-Butyldimethylsilyloxy)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 EtO. The filtrate was washed with brine and extracted with Et2O (3 × 10 mL). The filtrate was dried with Na2SO4 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%); Rf = 0.5 (EtOAc/hexanes, 1:1).

IR (neat): 3022, 2953, 2928, 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), 6.48 (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).

13C NMR (126 MHz, CDCl3): δ = 169.8, 147.8, 146.1, 141.2, 132.0 (2 C), 127.0 (2 C), 88.2, 85.0, 65.1, 52.5, 26.1 (3 C), 18.6, –5.0 (2 C).


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 allowed to stir at rt 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 × 13 mL). The organic layers were combined, dried with Na2SO4, and concentrated. Purification by flash chromatography (silica gel, hexanes/CH2Cl2, 8:2 to 6:4) resulted in the desired product 19a. The NMR spectra matched those in the literature.31

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 (202 mg, 5 mmol). Benzyl chlorofomate 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.

Yield: 758 mg (90%)

4-Bromobenzyl Acetate (19c)

Additive 19c was synthesized according to the literature. 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 with EtOAc (2 × 20 mL), dried with Na₂SO₄, and concentrated under reduced pressure. Purification by column chromatography (silica gel, EtOAc/hexanes, 1:20) afforded product 19c.

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

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Supporting Information

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References


