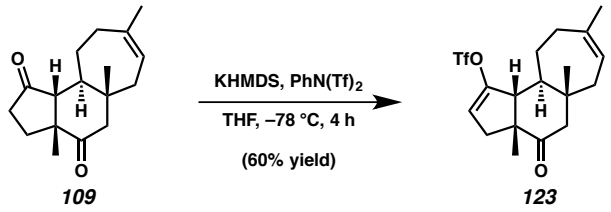
APPENDIX 2

Synthetic Efforts toward Cyanthiwigin F

A2.1 INTRODUCTION AND BACKGROUND

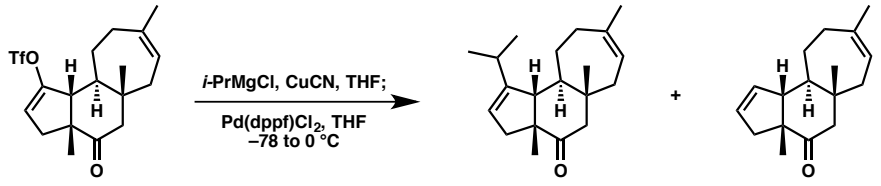
Through our group's synthetic route, cyanthiwigin F (**106**) is accessible from tricycle **109** in two steps.[1] Selective triflation of the A-ring ketone supplied vinyl triflate **123** (Scheme A2.1), which was subjected to cross-coupling conditions to afford the natural product. Unfortunately, the cross-coupling proved quite challenging and was generally plagued by low yields and side product formation. After extensive exploration of transition metal catalysts (e.g., Pd, Cu, Ni) and isopropyl coupling partners (e.g., *i*-PrZnI, *i*-PrMgCl, *i*-PrLi), the combination of [Pd(dppf)Cl_2], *i*-PrMgCl, and CuCN generated **106** as a 1.8:1 mixture (favoring the natural product) with the commonly observed reductive deoxygenation product **122** (Scheme A2.2). The two compounds were inseparable through silica gel column chromatography, with characterization-quality samples attainable only through reverse-phase HPLC.

*Scheme A2.1 Conversion of tricyclic diketone **109** to vinyl triflate **123***



109 *123*

Scheme A2.2 Previously optimized conditions for the final cross-coupling to form cyanthiwigin F



123 *cyanthiwigin F (106)* (41% yield) *124* (23% yield)

A2.2 EFFORTS TOWARD MODIFIED ISOPROPYL INSTALLATION

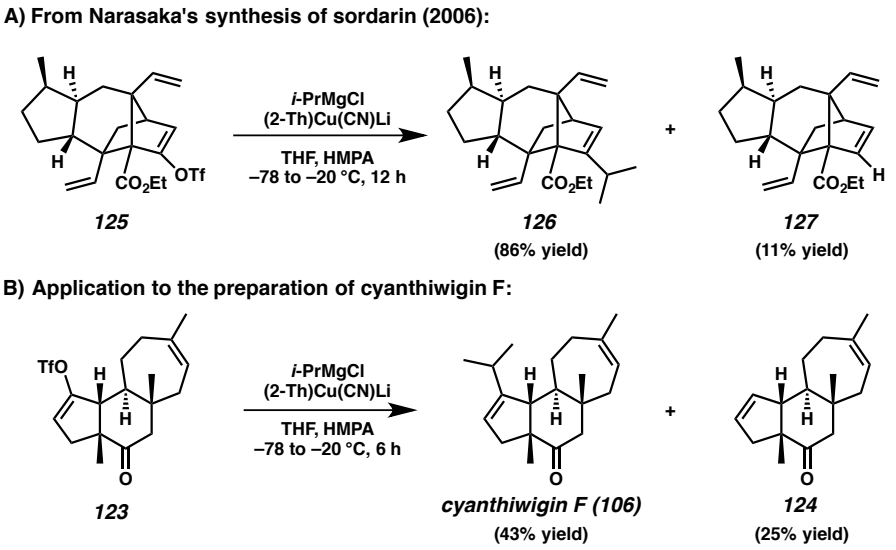
In light of these challenges, we sought to identify a superior alternative to the conditions described above. To this end, we pursued several strategies for the installation of the isopropyl unit.

A2.2.1 DIRECT INSTALLATION VIA CROSS-COUPLING

We began by investigating cross-coupling conditions for the direct installation of the isopropyl unit distinct from those previously examined by our group. Narasaka and co-workers documented an interesting strategy for this transformation (i.e., conversion of vinyl triflate to isopropyl) in their synthesis of sordarin (Scheme A2.3A).[2] Treatment of vinyl triflate **125** with *i*-PrMgCl and a higher-order thienyl-derived cuprate reagent in the presence of HMPA delivered the desired cross-coupling product (**126**) in good yield

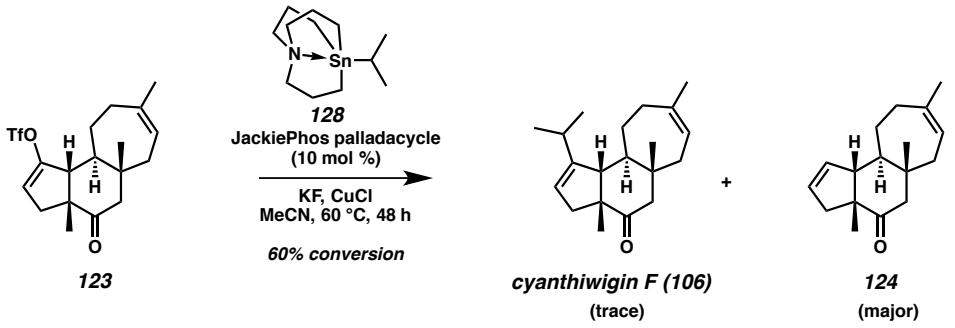
along with only small amounts of the reduction side-product (**127**). Unfortunately, when these conditions were applied to triflate **123**, we observed formation of the desired natural product (**106**) contaminated with reduction product **124** as a 1.7:1 ratio favoring **106**. The yields of each product were nearly identical to those obtained from our group's previously optimized conditions (cf. Scheme A2.3B).

Scheme A2.3 Isopropyl installation using a higher-order cuprate reagent



We next examined isopropyl installation using conditions developed by Biscoe and co-workers for Pd-catalyzed cross-coupling of secondary alkyl azastannatrane nucleophiles with aryl chlorides, bromides, iodides, and triflates.[3] Disappointingly, subjection of vinyl triflate **123** to these conditions using isopropyl-azastannatrane **128** resulted in predominantly the undesired reduction product (**124**) with only trace amounts of the natural product observed (Scheme A2.4).

*Scheme A2.4 Isopropyl installation using Biscoe's azastannatrane reagent (**128**)*



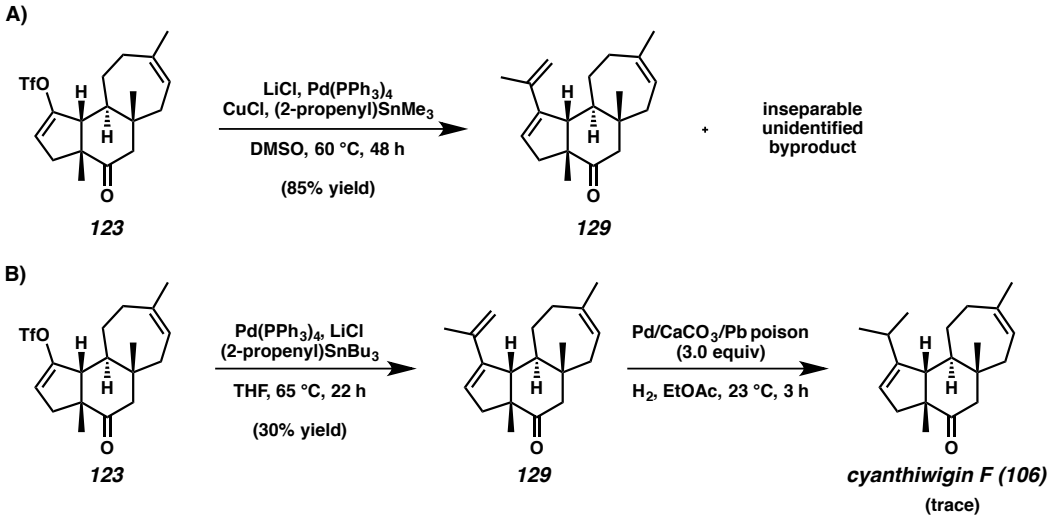
A2.2.2 TWO-STEP INSTALLATION VIA CROSS-COUPLING

Given the apparent difficulties in direct installation of the isopropyl unit, we turned our attention to two-step strategies. One such approach entailed cross-coupling vinyl triflate **123** with an isopropenyl fragment followed by selective hydrogenation to furnish the natural product. To this end, we examined various conditions for cross-coupling, beginning with Corey's Cu-assisted conditions.[4] Despite good conversion of **123**, the desired product (**129**) was contaminated with an unidentified by-product that was unfortunately inseparable from the desired compound likely arising from rearrangement of the isopropenyl fragment (Scheme A2.5A). Fortunately, application of traditional conditions for Stille coupling furnished **129**, albeit in modest yield. Subjection of this compound to superstoichiometric Lindlar's catalyst under hydrogen atmosphere enabled formation of trace amounts of the natural product (**106**).

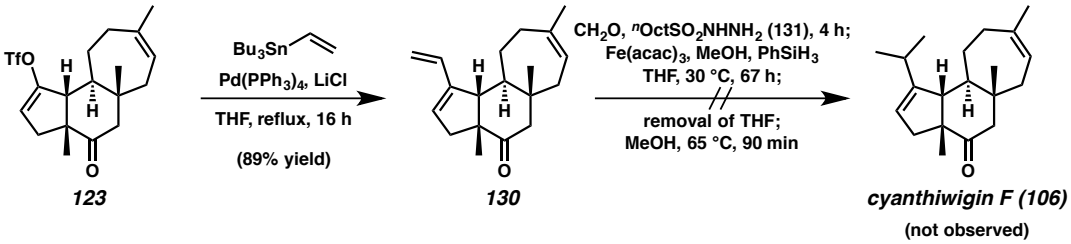
Noting the challenges associated with cross-coupling using isopropenyl partners, we reasoned isopropyl installation might be accomplished using a different two-step approach: vinylation followed by hydromethylation using a procedure developed by the Baran group.[5] We were pleased to find that treatment of **123** with tributylvinylstannane

under Stille conditions afforded the desired vinylated compound **130** in good yield. Disappointingly, however, attempts to effect hydromethylation using the conditions reported by Baran and co-workers were ineffective (Scheme A2.6).

Scheme A2.5 Efforts toward isopropenylation followed by hydrogenation to form ***106***



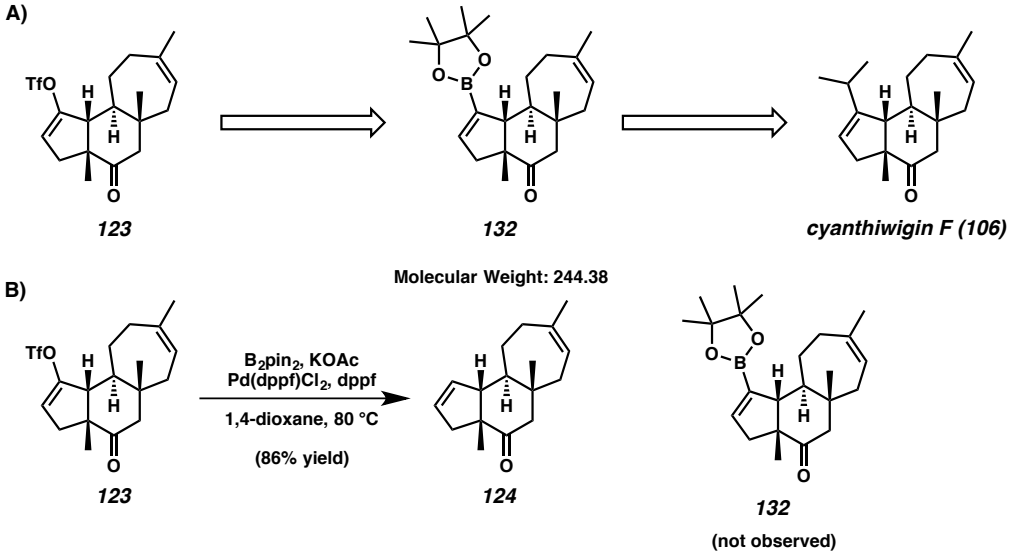
Scheme A2.6 Efforts toward vinylation followed by hydromethylation to form ***106***



Our final approach toward completing the synthesis of cyanthiwigin F through a two-step sequence aimed to reverse the final cross-coupling partners by way of boronate ester **132** (Scheme A2.7A). Regrettably, this strategy remained unexplored due to the

overwhelming dominance of proto-detriflation in efforts to prepare **132** from **123** (Scheme A2.7B).

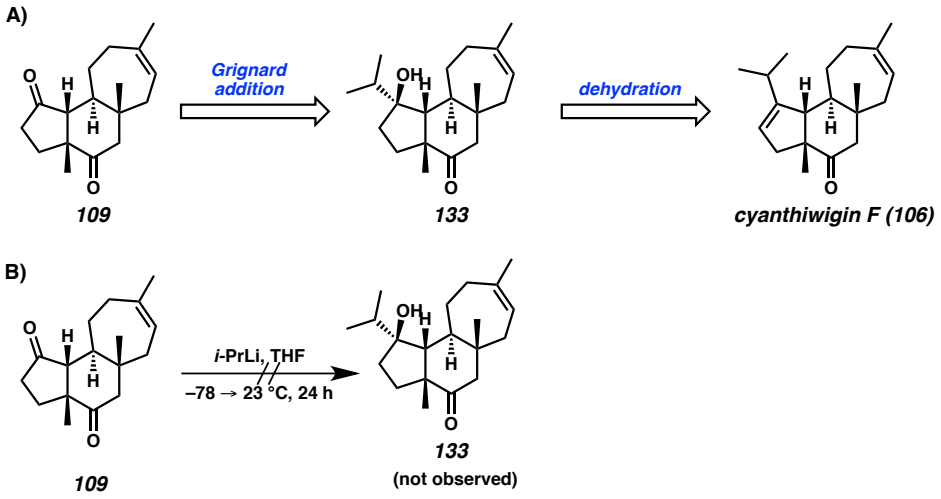
*Scheme A2.7 Efforts toward cross-coupling partner reversal via boronate ester **132***



A2.2.3 ISOPROPYL GRIGNARD ADDITION

Finally, we directed our attention away from cross-coupling strategies and investigated a Grignard addition/dehydration approach. We envisioned that addition of an isopropyl Grignard reagent to the A-ring carbonyl and subsequent dehydration of the resulting alcohol (**133**) using Burgess reagent or Martin's sulfurane would generate the natural product (Scheme A2.8A). While treatment of diketone **109** with *i*-PrMgCl resulted in no reaction, product formation was observed using *i*-PrLi. Unfortunately, this compound did not appear to be the desired product (**133**) (Scheme A2.8B).

Scheme A2.8 Efforts toward Grignard addition followed by dehydration to form ***106***



A2.3 FUTURE DIRECTIONS

As showcased in these investigations in addition to the original optimization studies, the installation of an isopropyl fragment at a sterically hindered site remains a major synthetic challenge. Indeed, a recent example of this issue was reported by Zhou and co-workers in their synthesis of hamigerin B,[6] further underscoring the need for new technologies to assist in the resolution of this difficult transformation. In contrast to the synthetic transformations amenable to modification that were described in the preceding chapter, it is clear through these studies that methodologies for isopropyl cross-couplings have remained underdeveloped over the past decade. As such, the development of new methodologies for this challenging reaction would contribute a great service to the synthetic community.

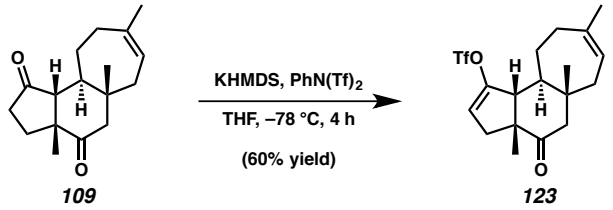
A2.4 EXPERIMENTAL SECTION

A2.4.1 MATERIALS AND METHODS

All reactions were performed at ambient temperature (23 °C) unless otherwise noted. Reactions requiring external heat were modulated to the specified temperatures indicated by using an IKAmag temperature controller. All reactions were performed in glassware flame-dried under vacuum and allowed to cool under nitrogen or argon. Solvents were dried by passage over a column of activated alumina with an overpressure of argon gas.[7] Tetrahydrofuran was distilled directly over benzophenone and sodium, or else was dried by passage over a column of activated alumina with an overpressure of argon gas. Anhydrous *tert*-butanol and nitromethane were purchased from Sigma Aldrich in sure-sealed bottles and used as received unless otherwise noted. Azastannatrane **128**[3] and octane-1-sulfonohydrazide were prepared according to known methods.[5] All other chemicals and reagents were used as received. Compounds purified by flash chromatography utilized ICN silica gel (particle size 0.032–0.063 mm) or SiliCycle® Silia*Flash*® P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å). Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or alkaline permanganate staining. NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR), a Varian Inova 500 spectrometer (at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR), or a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR), and are reported relative to residual $CHCl_3$ (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR) or C_6H_6 (δ 7.16 for ^{1}H NMR, δ 128.06

for ^{13}C NMR). The following format is used for the reporting of ^{1}H NMR data: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum Paragon 1000 spectrometer, and data are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility, or else were acquired using an Agilent 6200 Series TOF mass spectrometer with an Agilent G1978A Multimode source in ESI, APCI, or MM (ESI/APCI) ionization mode. Analytical chiral gas chromatography was performed with an Agilent 6850 GC using a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). Analytical achiral gas chromatography was performed with an Agilent 6850 GC using a DB-WAX (30 x 0.25 mm) column (1.0 mL/min carrier gas flow). Preparatory reverse-phase HPLC was performed on a Waters HPLC with Waters Delta-Pak 2 x 100 mm, 15 μm column equipped with a guard, employing a flow rate of 1 mL/min and a variable gradient of acetonitrile and water as eluent. HPLC visualization was performed by collecting 1 mL fractions after initial injection and analyzing each fraction via TLC. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell.

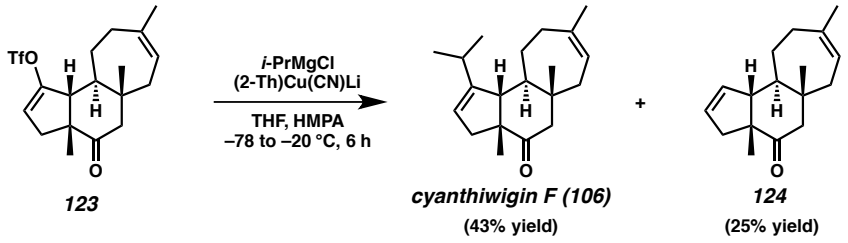
A2.4.2 PREPARATIVE PROCEDURES



109 *123*

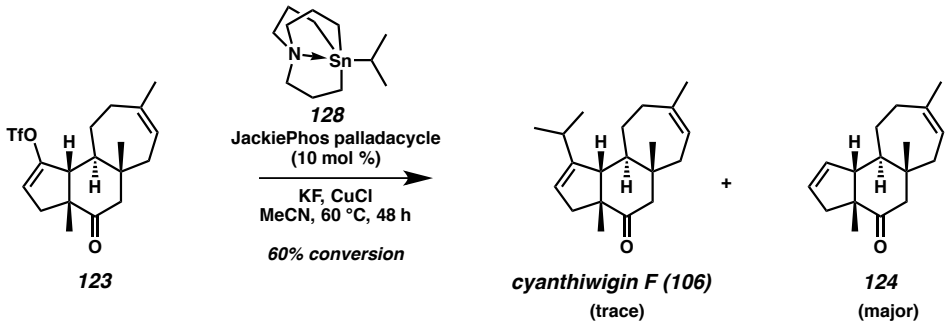
Tricyclic Triflate 123. To a flame-dried flask under argon was added tricyclic diketone **109** (250 mg, 0.960 mmol, 1.0 equiv). Dry PhH (5 mL) was added, then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high vacuum briefly, then dissolved in THF (10 mL). A separate flame dried flask under argon was charged with potassium bis(trimethylsilyl)amide (211 mg, 1.06 mmol, 1.1 equiv) and THF (10 mL). The flask containing diketone **109** was cooled to –78 °C, and the basic solution was cannula transferred into the cooled solution containing the substrate diketone via a positive pressure of argon. Deprotonation was allowed over 30 min. After this time had elapsed, a solution of *N*-phenyl bis(trifluoromethane)sulfonimide (395 mg, 1.10 mmol, 1.15 equiv) in THF (10 mL) was cannula transferred to the anionic solution under a positive pressure of argon. After 3 h, the reaction was quenched via addition of a solution of saturated $NaHCO_{3\,(aq)}$. The phases were separated, and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed, sequentially, with 2 N $NaOH_{(aq)}$ (30 mL), 2 N $HCl_{(aq)}$ (30 mL), and brine (2 x 30 mL). The organic layers were then dried over $MgSO_4$, and the solvent was removed in vacuo after filtration. The crude material was purified over silica gel using 0.5% → 1.0% ethyl acetate in hexanes as eluent to afford triflate **123** as a white solid (226 mg, 60% yield)

that matched previously reported characterization data:[1] R_f = 0.45 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.16 (ddq, *J* = 5.1, 1.7, 1.7 Hz, 1H), 5.08 (dd, *J* = 3.0, 2.0 Hz, 1H), 2.07 (dd, *J* = 10.7, 2.2 Hz, 1H), 2.02 (br. t, *J* = 13.3 Hz, 1 H), 1.94–1.86 (m, 3H), 1.90 (s, 1H), 1.85 – 1.79 (m, 1H), 1.74 (app ddt, *J* = 14.8, 6.8, 1.5 Hz, 1H), 1.59 (s, 3H), 1.57 (d, *J* = 3.4 Hz, 1H), 1.54 (d, *J* = 3.4 Hz, 1H), 1.38–1.31 (m, 1H), 1.35 (dd, *J* = 14.4, 8.5 Hz, 1H), 1.23 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.8, 153.2, 141.9, 121.4, 116.0, 57.6, 54.1, 54.0, 51.2, 41.6, 38.1, 36.5, 32.5, 26.2, 25.0, 23.6, 16.8; IR (Neat film, NaCl) 2932, 1709, 1656, 1423, 1382, 1245, 1211, 1141, 1097, 927 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{23}F_3O_4S$ [M$^+$]: 392.1269, found 392.1273; $[\alpha]^{25}_D$ – 101.9 (*c* 0.63, CH_2Cl_2).



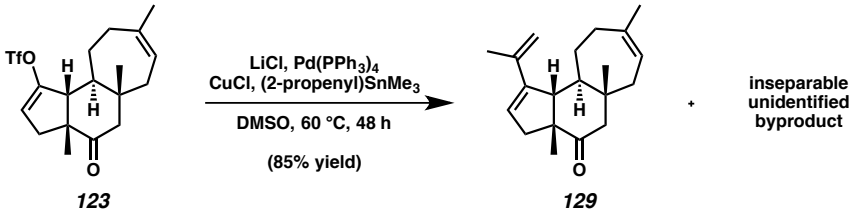
Cyanthiwigin F (106) and Reduction Product (124). A flame-dried flask under argon was charged with lithium 2-thienylcyanocuprate solution (0.25 M in THF, 0.31 mL, 0.0787 mmol, 3.09 equiv) and cooled to –78 °C. Isopropyl magnesium chloride solution (2.0 M in THF, 40 μL, 0.0765 mmol, 3.0 equiv) and HMPA (50 μL) were added, and the resulting mixture was warmed to 0 °C, generating a homogeneous mixture. The reaction was re-cooled to –78 °C, and a solution of tricyclic vinyl triflate **123** (10 mg, 0.0255 mmol, 1.0 equiv) in THF (1.3 mL) was added. The resultingmixture was warmed to –20 °C over 3 hours and then maintained at this temperature for an additional 3 hours.

After this time, the reaction was quenched via addition of a solution of saturated $NH_4Cl_{(aq)}$ and filtered over a pad of Celite. The filtrate was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed, sequentially, with water (20 mL) and brine (20 mL). The organic layers were then dried over $MgSO_4$, and the solvent was removed in vacuo after filtration. The crude material was purified over silica gel using 0.5% → 1.0% Et_2O in hexanes as eluent to afford a 1.7:1 mixture of **106** and **124** as a white solid (5.0 mg, 68% combined yield)

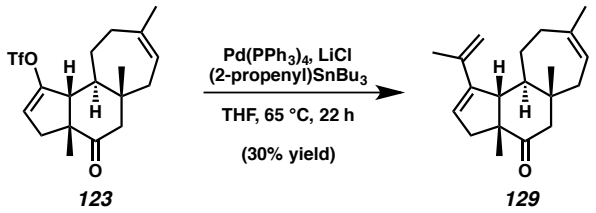


Cyanthiwigin F (106) and Reduction Product (124). A flame-dried Schlenk tube was charged with JackiePhos palladacycle (2.6 mg, 2.29 μmol, 0.10 equiv), potassium fluoride (2.7 mg, 0.0458 mmol, 2.0 equiv), and copper(I) chloride (4.5 mg, 0.0458 mmol, 2.0 equiv). To this mixture was added a solution of azastannatrane **128** (10.4 mg, 0.0344 mmol, 1.5 equiv) and tricyclic vinyl triflate **123** (9.0 mg, 0.0229 mmol, 1.0 equiv) in degassed MeCN (1.0 mL). The reaction vessel was sealed and heated to 60 °C. After 46 hours, heating was discontinued, and the reaction mixture was diluted with Et_2O (5 mL) and washed sequentially with saturated $KF_{(aq.)}$ (10 mL) and brine (10 mL). The organic layers were then dried over Na_2SO_4, and the solvent was removed in vacuo after

filtration. The crude material was purified over silica gel using 0.5% → 1.0% Et_2O in hexanes as eluent to afford a mixture of **106** and **124** (major).



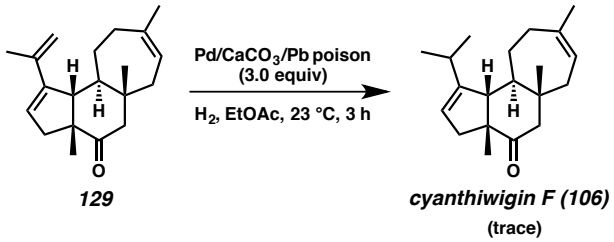
Modified Stille Coupling. In a nitrogen-filled glove box, a flame-dried vial was charged with $Pd(PPh_3)_4$ (2.6 mg, 2.29 μmol, 0.10 equiv), CuCl (11.3 mg, 0.115 mmol, 5.0 equiv), and DMSO (1.0 mL). The resulting mixture was stirred for 5 minutes before a solution of tricyclic vinyl triflate **123** (9.0 mg, 0.0229 mmol, 1.0 equiv) and trimethyl(2-propenyl)stannane (9.1 mg, 0.0275 mmol, 1.2 equiv) in DMSO was added. The vial was sealed with a Teflon-lined cap and electrical tape, and its contents were stirred at 25 °C (ambient temperature in the glove box) for 1 hour, then heated to 60 °C. After 70 hours, heating was discontinued, and the reaction vial was removed from the glove box. The reaction mixture was diluted with Et_2O (5 mL) and washed with a mixture of 5:1 brine/NH_4OH (5% aq.) (10 mL total volume). The phases were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed, sequentially, with water (2 x 20 mL) and brine (2 x 20 mL). The organic layers were then dried over Na_2SO_4, and the solvent was removed in vacuo after filtration. The crude material was purified over silica gel using 2.0% ethyl acetate in hexanes as eluent to afford tricycle **129** along with an unidentified by-product as a colorless oil (5.5 mg, 85% yield).



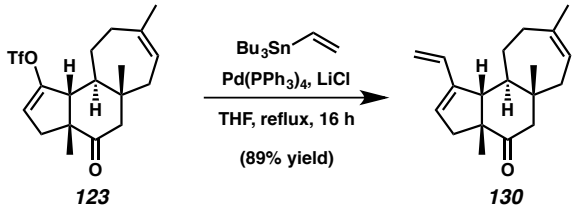
123 ***129***

Dehydrocyanthiwigin F (129). In a nitrogen-filled glove box, a flame-dried vial was charged with $Pd(PPh_3)_4$ (2.6 mg, 1.96 μmol, 0.10 equiv), LiCl (2.6 mg, 0.0608 mmol, 3.1 equiv), and THF (0.5 mL). To the resulting slurry was added a solution of tricyclic vinyl triflate **123** (7.7 mg, 0.0196 mmol, 1.0 equiv) and tributyl(2-propenyl)stannane (4.0 mg, 0.0196 mmol, 1.0 equiv) in THF (1.0 mL). The vial was sealed with a Teflon-lined cap and electrical tape and heated to 70 °C. After 22 hours, during which time the bright yellow solution became colorless, heating was discontinued, and the reaction vial was removed from the glove box. The reaction mixture was diluted with pentane (4 mL) and washed sequentially with water (10 mL), 10% aq. NH_4OH (10 mL), water (10 mL), and brine (10 mL). The organic layers were then dried over $MgSO_4$, and the solvent was removed in vacuo after filtration. The crude material was purified over silica gel using 1.0% Et_2O in hexanes as eluent to afford dehydrocyanthiwigin F (**129**) as a white amorphous solid (1.7 mg, 30% yield): R_f = 0.59 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.33 (m, 1H), 4.90 (s, 2H), 2.77 (d, *J* = 16.9 Hz, 1H), 2.50 (d, *J* = 14.7 Hz, 1H), 2.48 (d, *J* = 10.8 Hz, 1H), 2.21–2.15 (m, 2H), 2.04 (d, *J* = 14.7 Hz, 1H), 2.03 (dd, *J* = 3.6, 17.0 Hz, 1H), 1.95–1.90 (m, 1H), 1.92 (s, 3H), 1.87–1.78 (m, 1H), 1.74–1.69 (m, 1H), 1.72 (s, 3H), 1.58 (m, 1H), 1.10 (s, 3H), 1.07–1.02 (m, 1H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.6, 151.1, 142.4, 142.0, 124.9, 121.3, 113.0, 57.7, 55.3, 55.0, 54.5, 42.9, 42.2, 37.9, 33.2, 27.0, 25.0, 22.3, 21.5, 17.5; IR (Neat film, NaCl) 2922, 2851, 1703, 1456, 1384, 1292, 1074, 886, 814

cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{29}O$ $[M+H]^+$: 285.2218, found 285.2246; $[\alpha]^{25}_D$ –48.9 (*c* 0.17, $CHCl_3$).

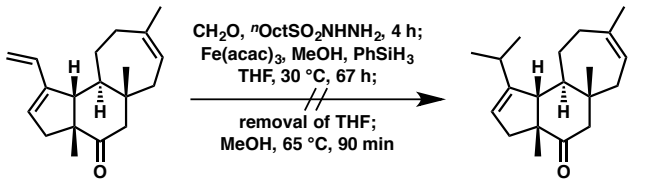


Hydrogenation Procedure. To a flame-dried flask was added a solution of tricycle **129** (1.7 mg, 5.98 μmol, 1.0 equiv) in ethyl acetate (1.0 mL) and Lindlar's catalyst (2.0 mg, 0.0188 mmol, 3.0 equiv). The reaction vessel was evacuated under reduced pressure (~400 Torr) and backfilled with hydrogen gas (3x). After stirring for 4 hours at 23 °C under hydrogen atmosphere, the reaction mixture was filtered over a pad of silica gel, eluting with 20% ethyl acetate in hexanes, and the filtrate was concentrated in vacuo, affording an inseparable mixture of **106** and **129**.



Tricyclic tris-olefin 130. In a nitrogen-filled glove box, a flame-dried vial was charged with $Pd(PPh_3)_4$ (0.3 mg, 0.29 μmol, 0.02 equiv), LiCl (1.9 mg, 0.045 mmol, 3.1 equiv), and THF (0.5 mL). To the resulting slurry was added a solution of tricyclic vinyl triflate **123** (5.7 mg, 0.0145 mmol, 1.0 equiv) and tributyl(vinyl)stannane (4.6 mg, 0.0145 mmol, 1.0 equiv) in THF (1.0 mL). The vial was sealed with a Teflon-lined cap and

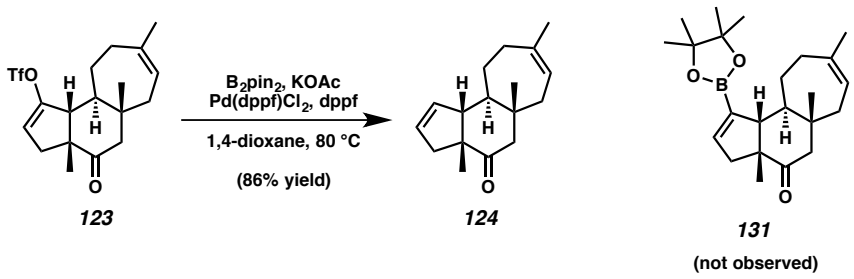
electrical tape and heated to 70 °C. After 18 hours, during which time the bright yellow solution became colorless, heating was discontinued, and the reaction vial was removed from the glove box. The reaction mixture was diluted with pentane (4 mL) and washed sequentially with water (10 mL), 10% aq. NH_4OH (10 mL), water (10 mL), and brine (10 mL). The organic layers were then dried over $MgSO_4$, and the solvent was removed in vacuo after filtration. The crude material was purified over silica gel using 1.0% Et_2O in hexanes as eluent to afford tricyclic tris-olefin **130** as a white amorphous solid (3.5 mg, 89% yield): R_f = 0.32 (10% Et_2O in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.76 (m, 1H), 5.33 (m, 1H), 5.16–5.03 (m, 2H), 2.75 (d, *J* = 17.2 Hz, 1H), 2.50 (d, *J* = 14.8 Hz, 1H), 2.41 (d, *J* = 11.1 Hz, 1H), 2.18 (m, 2H), 2.07–2.03 (m, 1H), 2.04–1.99 (m, 1H), 1.97–1.89 (m, 2H), 1.74–1.68 (m, 1H), 1.73 (s, 3H), 1.62–1.57 (m, 1H), 1.09 (s, 3H), 1.07 (m, 1H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.4, 149.1, 142.4, 135.4, 128.3, 121.3, 114.4, 57.2, 55.4, 54.9, 54.5, 42.6, 42.1, 37.8, 33.0, 27.1, 25.0, 22.4, 17.4.



130 ***cyanthiwigin F (106)*** **(not observed)**

Hydromethylation Procedure. To a solution of formaldehyde (8.0 μL, 0.0777 mmol, 6.0 equiv) in THF (2 mL) under argon was added octane-1-sulfonohydrazide (13.5 mg, 0.0647 mmol, 5.0 equiv) at 23 °C. The resulting solution was stirred for 4 hours, after which time it was added to a solution of tricycle **130** (3.5 mg, 0.0129 mmol, 1.0

equiv) and $Fe(acac)_3$ (9.1 mg, 0.0258 mmol, 2.0 equiv) in THF (0.6 mL) and MeOH (1.0 μL, 0.0258 mmol, 2.0 equiv). The resulting mixture was degassed by freeze-pump-thaw (2x) before the addition of phenylsilane (6.4 μL, 0.0516 mmol, 4.0 equiv). After two more iterations of the freeze-pump-thaw procedure, the reaction was heated to 30 °C and stirred under argon atmosphere for 36 hours. After this time, the volatiles were removed in vacuo, and the reaction vessel was purged with argon before addition of degassed methanol (1.5 mL). The resulting solution was heated to 62 °C. After 90 minutes, the reaction mixture was concentrated in vacuo, and the residue was diluted with ethyl acetate (5 mL) and washed with brine (5 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated to a crude residue. Signals characteristic of the desired product (**106**) were not visible in the crude material by ^1H NMR or TLC analysis.



Unsuccessful Effort to form Boronate Ester 131. In a nitrogen-filled glove box, a flame-dried 1-dram vial was charged with bis(pinacolato)diboron (7.3 mg, 0.0286 mmol, 1.1 equiv), $Pd(dppf)Cl_2$ (1.6 mg, 0.772 μmol, 0.08 equiv), potassium acetate (7.6 mg, 0.0777 mmol, 3.0 equiv), and dppf (1.2 mg, 0.772 μmol, 0.09 equiv). To this mixture was added a solution of vinyl triflate **123** (10.1 mg, 0.0257 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL). The vial was sealed with a Teflon-lined cap and electrical tape, and then heated to 80 °C. After 75 hours, heating was discontinued, and the reaction vessel

was removed from the glove box. The reaction mixture was diluted with hexanes and filtered over a pad of silica gel, eluting with dichloromethane. The filtrate was concentrated and purified over silica gel column chromatography (1% Et_2O in hexanes) to afford reduction product **124** (4.9 mg, 86% yield), which matched previously reported characterization data.

A2.5 NOTES AND REFERENCES

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