CHAPTER 2[†]

A Second-Generation Synthesis of

the Cyanthiwigin Natural Product Core

2.1 INTRODUCTION

Recognizing the vast potential of late-stage diversification research programs for the study of biologically active complex molecules as outlined in the previous chapter, our group is interested in conducting such studies using a late-stage intermediate in our previously reported syntheses of cyanthiwigins F, B, and G.[1] The cyanthiwigin natural product framework is an ideal scaffold for late-stage diversification studies due to its structural complexity and inclusion of multiple handles for diversification as well as the existence of a concise synthetic route for its preparation. However, many new technologies have been developed that we realized could be exploited to further expedite preparation of the cyanthiwigin core, an important aim given the sizable quantities needed for diversification studies. This chapter presents the challenges in large-scale

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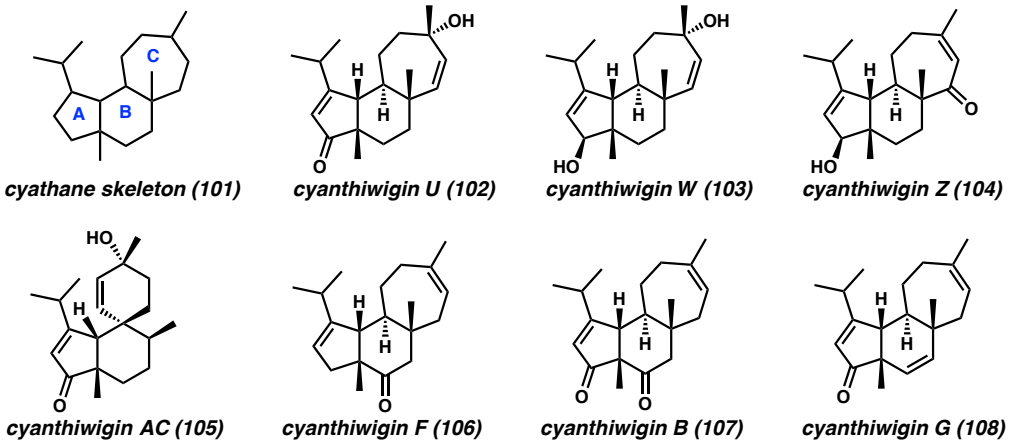
synthesis faced in the original route and presents the solutions we devised to address them.

2.1.1 BACKGROUND AND PREVIOUS SYNTHESIS

Isolated from the marine sponges *Epipolasis reiswigi* and *Myrmedioderma styx*, the 30 known cyanthiwigins constitute part of a larger class of diterpene natural products called the cyathanes, which display a vast array of biological properties including antimicrobial activity, antineoplastic action, stimulation of nerve growth factor synthesis, and κ-opioid receptor agonism.[2] The cyanthiwigins themselves exhibit a range of biological activities against such disease agents as HIV-1 (cyanthiwigin B), lung cancer and leukemia cells (cyanthiwigin C), and primary tumor cells (cyanthiwigin F).

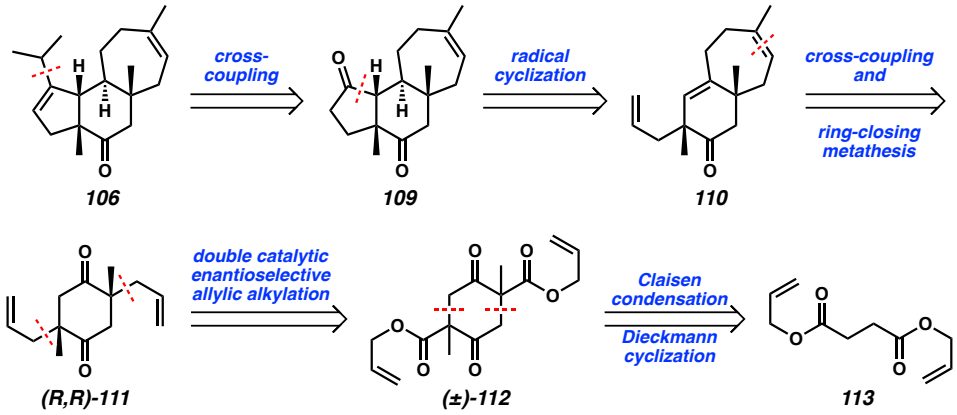
*Figure 2.1 Cyathane carbon skeleton (**101**) and selected cyanthiwigin natural products*



In addition to these interesting biological properties, their structural complexity has made the cyanthiwigins attractive target molecules for total synthesis.[2c] Specifically, the cyanthiwigins contain four contiguous stereocenters, including two quaternary

stereocenters at the A–B and B–C ring junctures of the tricyclic carbon skeleton (**101**, Figure 2.1). The first cyanthiwigin total synthesis was reported in 2005, when the Phillips group completed the synthesis of cyanthiwigin U (**102**),[3] and they later employed their strategy to access cyanthiwigin W (**103**) and cyanthiwigin Z (**104**).[4] Cyanthiwigin AC (**105**), a unique member of the natural product family featuring a spirocyclic framework instead of the 5–6–7 tricyclic fused core, was prepared by the Reddy laboratory in 2006,[5] and in 2008 our group accomplished the synthesis of cyanthwigin F (**106**),[1a] later applying the core strategy to access cyanthiwigin B (**107**)[1b] and cyanthiwigin G (**108**).[1b]

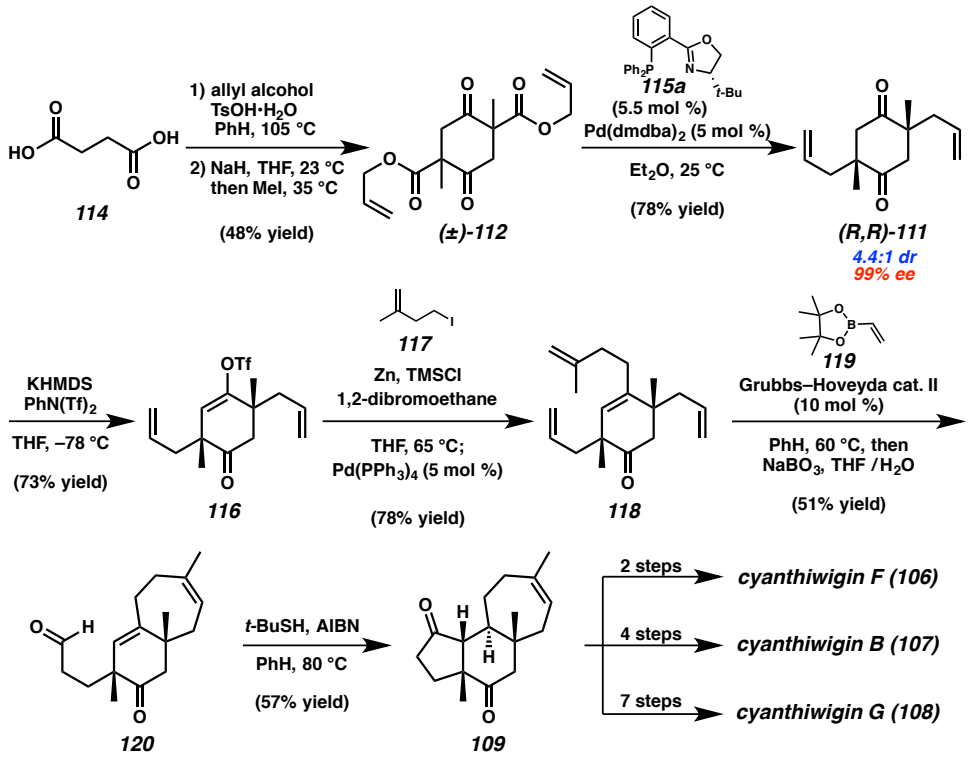
Scheme 2.1 Stoltz's retrosynthetic analysis of cyanthiwigin F



Our group's retrosynthetic strategy toward cyanthiwigin F (**106**) focused on early construction of the central B-ring and rapid installation of the two all-carbon quaternary stereocenters at the A–B and B–C ring junctures of the natural product (Scheme 2.1). Late-stage construction of the five-membered A-ring to form tricyclic diketone **109** could be accomplished from bicyclic ketone **110**, which would be assembled through triflation, cross-coupling, and ring-closing metathesis (RCM) of diketone **111**. Critically, this

symmetrical intermediate could be accessed through our group's enantioselective decarboxylative allylic alkylation methodology,[6] allowing the two quaternary stereocenters to be established from symmetrical bis-(β-ketoester) **112**, which itself would be constructed from diallyl succinate (**113**) by way of tandem Claisen condensation/ Dieckmann cyclization.

Scheme 2.2 Stoltz's synthesis of cyanthiwigins F, B, and G (2008, 2011)



The forward synthesis began with preparation of diallyl succinate (**113**) from succinic acid (**114**) via double Fischer esterification. Subsequent treatment of **113** with sodium hydride induced tandem Claisen condensation/Dieckmann cyclization, and quenching with methyl iodide furnished bis-(β-ketoester) **112** as a 1:1 mixture of meso and racemic diastereomers. This mixture was subjected to conditions for Pd-catalyzed

enantioselective allylic alkylation, which gratifyingly delivered diketone *(R,R)*-**111** in high yield and diastereoselectivity and excellent enantioselectivity.[7] Significantly, this unusual transformation exemplified a powerful application of stereoablative enantioselective alkylation methodology, enabling concurrent selective installation of two stereocenters from a complex mixture of diastereomers. Desymmetrization of **113** via monotriflate formation generated vinyl triflate **116** as a suitable substrate for Negishi coupling with alkyl iodide **117**, allowing access to tetraene **118**. Ring-closing metathesis (RCM)[8] to assemble the seven-membered C ring followed by cross-metathesis with boronic ester **119** and subsequent oxidation furnished bicyclic aldehyde **120**. Finally, A ring formation was achieved through radical cyclization of **120**. The resulting tricyclic diketone **109** was elaborated to cyanthiwigins F, B, and G in 2, 4, and 7 steps, respectively.[9] Notably, no protecting groups were used in this concise 7-step route to tricycle **109**.

2.1.2 CHALLENGES IN LARGE-SCALE SYNTHESIS

With this efficient route to the cyanthiwigin carbon framework available, we recognized an opportunity to employ tricycle **109** as a scaffold from which to conduct late-stage diversification studies. To accomplish this, the synthetic sequence outlined in Scheme 2.2 would need to be repeated on a large scale to generate sizable quantities of **109**. While the conversion of succinic acid (**114**) to bis-(*β*-ketoester) **112** was readily performed on 100-gram scale, the ensuing double catalytic enantioselective alkylation proved cumbersome on large scale due to relatively high catalyst and ligand loadings and low reaction concentrations (0.01 M) necessitated by poor catalyst solubility in diethyl

ether, the optimal solvent for stereoselectivity. Similarly, while vinyl triflate formation and subsequent Negishi coupling to generate tetraene **118** proceeded smoothly on large scale, another bottleneck arose at the formation of bicyclic aldehyde **120**. Although the initial RCM progressed rapdily with full conversion, the ensuing cross-metathesis was sluggish. A significant amount of intermediate **110** was routinely isolated even after prolonged reaction times and use of excess **119**. Re-subjection of **110** to cross-metathesis conditions with **119** generally produced low yields, returning large quantities of **110**.

2.2 MODIFIED SYNTHETIC TRANSFORMATIONS

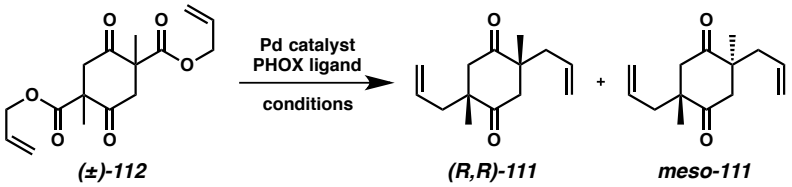
We envisioned that these obstacles to the large-scale preparation of tricycle **109** could be overcome using modern technologies developed after our group devised the initial synthetic route to **109** in 2008. For the reasons described in the previous section, we focused our efforts on the two most problematic transformations: 1) the double asymmetric decarboxylative alkylation and 2) the formation of bicyclic aldehyde **120**.

2.2.1 DOUBLE ASYMMETRIC DECARBOXYLATIVE ALKYLATION

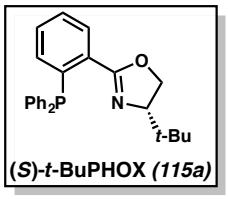
Despite producing desired *(R,R)*-**111** in good yields and selectivities, the key double asymmetric decarboxylative alkylation suffered from two major limitations to scaling: 1) relatively high loadings of catalyst $Pd(dmdba)_2$ and phosphinooxazoline (PHOX) ligand **115a**, both of which are available only through multistep preparations, and 2) low reaction concentrations (0.01 M) required due to low catalyst solubility in diethyl ether, the optimal solvent for maximizing stereoselectivity. Indeed, performance of this

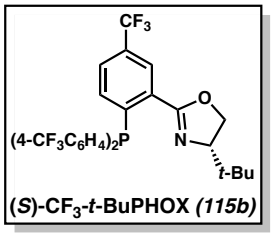
transformation on 15 g of substrate **112** required 2 g of $Pd(dmdba)_2$, 1 g of PHOX ligand **115a**, and over 3 L of solvent, an experimentally risky setup, considering the potential for diethyl ether to ignite in large volumes.

Table 2.1 Effect of the PHOX ligand on the double catalytic enantioselective allylic alkylation of ***112***



Entry	Pd cat. (mol %)	PHOX (mol %)	Solvent	Conc	Temp	Yield	dr	ee
1	$Pd(dmdba)_2$ (5.0)	***115a*** (5.5)	Et_2O	0.01 M	25 °C	78%	4.4 :1	99%
2	$Pd(dmdba)_2$ (5.0)	***115a*** (5.5)	2:1 PhMe:Hex	0.10 M	25 °C	75%	3.4:1	99%
3	$Pd(dmdba)_2$ (5.0)	***115b*** (5.5)	Et_2O	0.01 M	25 °C	92%	4.3:1	99%
4	$Pd(OAc)_2$ (0.25)	***115a*** (2.5)	TBME	0.10 M	40 °C	83%	2.2:1	97%
5	$Pd(OAc)_2$ (0.25)	***115b*** (2.5)	TBME	0.10 M	40 °C	93%	3.5:1	99%



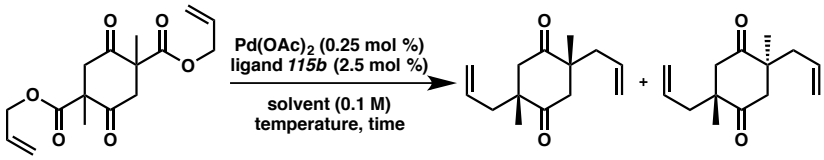


To address these issues, we investigated different solvent systems at a higher concentration of substrate **112** (0.10 M) and found that using a 2:1 mixture of toluene and hexane resulted in yields and ee's comparable to those of the original reaction conditions (Table 2.1, Entry 1) but markedly lower dr (Entry 2). Variation of the PHOX ligand showed that use of the electron-poor ligand (*S*)-CF_3-*t*-BuPHOX (**115b**)[10] in the catalytic system resulted in significantly higher yields, dr's, and ee's (Entry 3). Pleased by this improvement, we also sought to lower the loadings of Pd catalyst and PHOX ligand by application of our group's recently developed protocol for enantioselective alkylation that employs drastically lower loadings of catalyst and ligand.[11] Notably, the Pd precatalyst used in this protocol, $Pd(OAc)_2$, is commercially available, obviating the need to prepare

$Pd(dmdba)_2$. Although initial application of the standard conditions using ligand **115a** provided *(R,R)*-**111** in unsatisfactory dr (Entry 4), the use of ligand **115b** once again resulted in a dramatic improvement (Entry 5).

Encouraged by this observation, we set out to elucidate the optimal reaction conditions using the new catalyst system. To this end, we examined several different solvent systems and temperatures (Table 2.2). The yield was not substantially affected by decreasing the temperature from 40 to 30 °C (Entries 1–2), but the use of diethyl ether as the solvent resulted in lower yields (Entry 3). Interestingly, the use of toluene as the solvent greatly improved both the yield and dr (Entry 4), but the previously optimal solvent system, 2:1 toluene/hexane significantly impeded the reaction (Entry 5). Finally, we discovered that lowering the temperature further to 25 °C in toluene supplied the optimal yield and dr (Entry 6).

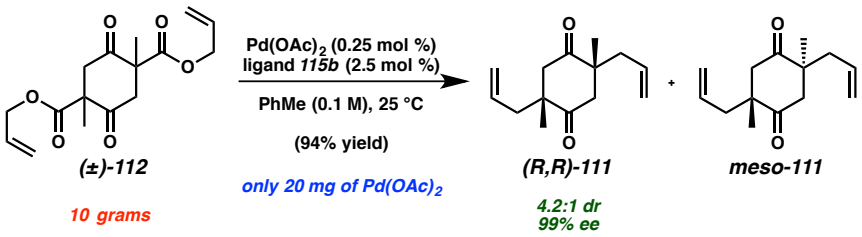
Table 2.2 Optimization of the low-catalyst-loading conditions for enantioselective alkylation



Entry	Solvent	Temperature	Time	Yield	dr	ee
1	TBME	40 °C	5 h	93%	3.5:1	99%
2	TMBE	30 °C	5 h	97%	3.6:1	99%
3	Et_2O	30 °C	5 h	88%	3.7:1	99%
4	PhMe	30 °C	5 h	99%	4.3:1	99%
5	2:1 PhMe:Hex	30 °C	24 h	45%	2.8:1	97%
6	PhMe	25 °C	16 h	97%	4.9:1	99%

We were pleased to find that the reoptimized conditions for the double catalytic enantioselective allylic alkylation were also effective on a large scale. When 10 g (32.4 mmol) of bis(*β*-ketoester) **112** was subjected to the new alkylation conditions, the desired diketone *(R,R)*-**111** was formed in 94% yield with good dr and excellent ee (Scheme 2.3). Remarkably, only 20 mg of Pd catalyst and 480 mg of PHOX ligand were required, greatly facilitating the scaling of this crucial step. Furthermore, only 250 mL of solvent was required for this large-scale reaction, permitting simple set-up and avoiding the saftey issues associated with large volumes of solvent. Overall, the modified conditions produced diketone *(R,R)*-**111** in higher yield with comparable selectivity while requiring 10 times less solvent, less than half the amount of PHOX ligand, and 20 times less Pd than the original conditions. Moreover, the use of a commercial Pd source eliminated the need to prepare $Pd(dmdba)_2$, further expediting the synthesis of the cyanthiwigin core (**109**).

*Scheme 2.3 Large-scale preparation of diketone **111** using the modified alkylation conditions*

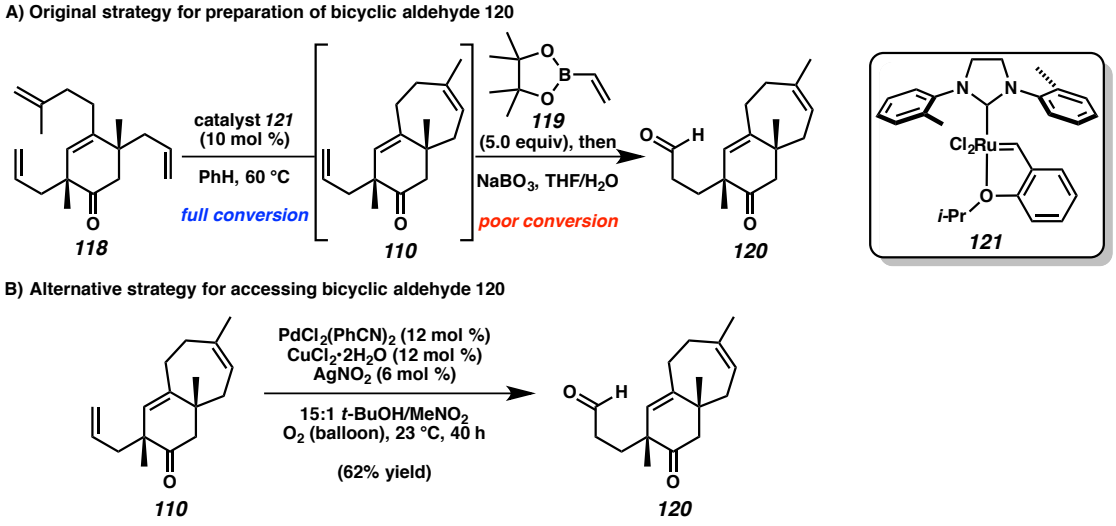


2.2.2 FORMATION OF THE PENULTIMATE BICYCLIC ALDEHYDE

Having succesfully applied the low-catalyst-loading allylic alkylation procedure to the preparation of diketone **111**, we turned our attention to the other transformation in

need of modification: the formation of bicyclic aldehyde **120**. As previously described, the cross-metathesis between RCM product **110** and vinylboronic ester **119** catalyzed by modified Grubbs–Hoveyda catalyst **121** proceeded sluggishly, generally returning sizable amounts of unreacted **110** (Scheme 2.4A). We hypothesized that the suboptimal performance of the reaction was due to unfavorable steric interactions arising from bulky boronic ester **119** with the quaternary stereocenter proximal to the site of reactivity in bicyclic triene **110**. Noting the efficiency of the aldehyde-selective Tsuji–Wacker reaction developed by the Grubbs group,[12] we hypothesized that this robust methodology could be used to convert the accumulated quantities of bicycle **110** to aldehyde **120**. Gratifyingly, this hypothesis was validated by the successful oxidation of **110** to aldehyde **120** in moderate yield under nitrite-modified Tsuji–Wacker conditions (Scheme 2.4B). Notably, this approach toward the preparation of **110** not only enabled productive recycling of the accrued **110** but also circumvented the preparation of boronic ester **119**, which was generally preferred over purchase due to cost and purity considerations.

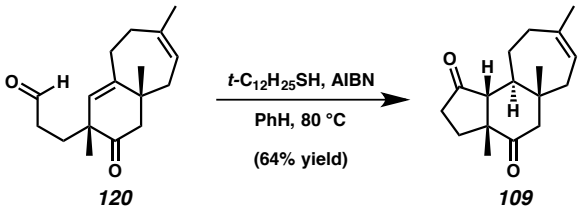
*Scheme 2.4 Preparation of bicyclic aldehyde **120***



2.2.3 COMPLETION OF THE CYANTHIWIGIN CORE

With bicyclic aldehyde **120** in hand, we proceeded to the final step of the synthesis of **109**, azobis-(isobutyronitrile) (AIBN)-initiated radical cyclization to form the A-ring.[13] Initial attempts to effect the transformation using the original conditions tended to provide **109** in low yields, an observation attributed to possible loss of the *tert*-butylthiol propagator through evaporation facilitated by the elevated temperature. To mitigate this issue, we found that the use of *tert*-dodecanethiol as the propagator resulted in more consistent yields and avoided the odor associated with *tert*-butylthiol (Scheme 2.5).

*Scheme 2.5 Completion of the synthesis of **109** through radical cyclization of **120***



120 *109*

2.3 CONCLUDING REMARKS

In summary, we have developed a second-generation synthesis of the cyanthiwigin natural product core (**109**) using catalytic methodologies that have been developed within the past several years.[14] These modifications have proven essential in scaling the synthetic route, effectively setting the stage for late-stage diversification studies of the complex tricyclic framework.

2.4 EXPERIMENTAL SECTION

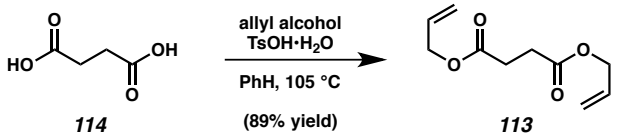
2.4.1 MATERIALS AND METHODS

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.[15] 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. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received with the exception of palladium(II) acetate (Sigma Aldrich) which was stored in a nitrogen-filled govebox. Grubbs's Ru catalyst **121**[8] was donated by Materia Inc. and used without further purification. (*S*)-*t*-BuPHOX (**115a**),[16] (*S*)-CF_3-*t*-BuPHOX (**115b**),[10] 4-iodo-2-methyl-1-butene (**117**),[17] vinyl boronate ester **119**,[18] and bis(3,5-dimethoxydibenzylideneacetone)palladium[19] were prepared according to known methods. 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.

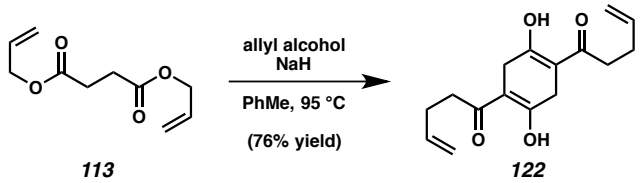
2.4.2 PREPARATIVE PROCEDURES

2.4.2.1 PREPARATION OF BIS-(β-KETOESTER) 112



114 *113*

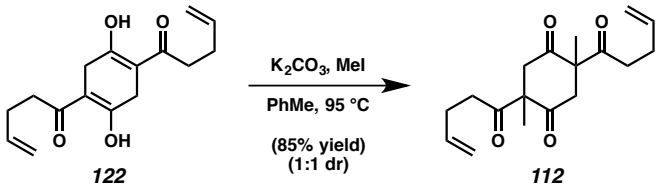
Diallyl Succinate (113). To a solution of succinic acid (**114**, 40.0 g, 338.7 mmol) in benzene (300 mL) was added TsOH • H_2O (0.21 g, 1.2 mmol, 0.003 equiv). After brief mixing, allyl alcohol (70 mL, 1.01 mol, 3.00 equiv) was added to the reaction, and the flask was fitted with a Dean–Stark trap and reflux condenser under nitrogen. The reaction was heated to 105 °C and allowed to reflux over 12 h. After collection of 13 mL H_2O from the Dean–Stark trap, the reaction was allowed to cool to room temperature and was quenched by slow treatment with saturated $NaHCO_{3(aq)}$ until gas evolution halted. The phases were separated, and the organic layer was washed with saturated $NaHCO_{3(aq)}$ (2 x 40 mL) and brine (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, and solvent was removed in vacuo after filtration. The resulting colorless oil was dried under high vacuum to afford diallyl succinate (**113**, 59.8 g, 89% yield). This material was carried into the next step without further purification: R_f = 0.35 (10% Et_2O in pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 2H), 5.31 (ddt, *J* = 17.0, 1.6, 1.3 Hz, 2H), 5.23 (ddt, *J* = 10.4, 1.3, 1.1 Hz, 2H), 4.60 (ddd, *J* = 5.9, 1.3, 1.3 Hz, 4H), 2.67 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 132.1, 118.5, 65.5, 29.2; IR (Neat film, NaCl) 3086, 2942, 1738, 1649, 1413, 1377, 1271, 1157, 990, 932 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{10}H_{14}O_4$ $[M]^+$: 198.0892, found 198.0888.



113 ***122***

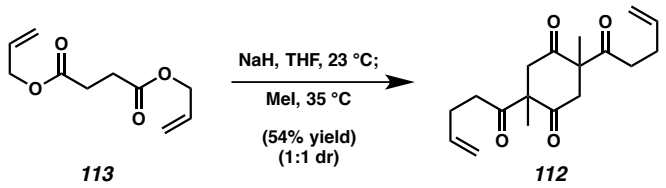
Diallyl Succinylsuccinate (122). To a flame dried flask under argon was added NaH (60% in mineral oil, 25.0 g, 630.6 mmol, 2.50 equiv) and toluene (125 mL). To this was added, dropwise, neat allyl alcohol (4.14 mL, 70.6 mmol, 0.28 equiv) with vigorous stirring. After gas evolution had ceased, neat diallyl succinate (**113**, 50.0 g, 252.2 mmol, 1.00 equiv) was added dropwise, and the reaction was heated to 95 °C. The reaction flask was fitted with a reflux condenser, and reaction was allowed to proceed over 10 h. After ca. 15 min, an additional portion of toluene (125.0 mL) was added to the reaction to ensure fluidity of the mixture. Once the reaction had completed by TLC, the flask was cooled to room temperature, and the solvent was removed in vacuo. The crude solid was immediately suspended in CH_2Cl_2, and then acidified by addition of 2 N $HCl_{(aq)}$ (350 mL). The biphasic mixture was allowed to stir over 2 h, after which time all solids had dissolved. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and solvent was removed in vacuo to yield a crude orange solid. The crude residue was recrystallized twice from a mixture of petroleum ether and acetone to afford diallyl succinylsuccinate (**122**) as a flaky white solid (26.9 g, 76% yield) that matched previously reported characterization data:[1] R_f = 0.6 (15% ethyl acetate in hexanes) ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.11 (s, 2H), 5.95 (dddd, *J* = 17.1, 10.7, 5.7, 5.7 Hz, 2H), 5.35 (ddt, *J* = 17.3, 1.6, 1.3 Hz, 2H), 5.27 (ddt, *J* = 10.4, 1.3, 1.3 Hz, 2H), 4.69 (ddd,

J = 5.3, 1.3, 1.3 Hz, 4H), 3.22 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 168.8, 131.7, 118.4, 93.1, 65.2, 28.5; IR (Neat film, NaCl) 1666, 1647, 1684, 1451, 1389, 1329, 1219, 1204, 1133, 1061, 961, 843, 783 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{14}H_{16}O_6$ $[M]^+$: 280.0947, found 280.0948.



Bis(*β*-ketoester) 112. Prior to use in the reaction, acetone was dried by stirring it over anhydrous calcium sulfate, and then passing the solvent over a short plug of silica. Potassium carbonate (5.80 g, 43.9 mmol, 4.10 equiv) and diallyl succinylsuccinate (**122**, 3.00 g, 10.7 mmol, 1.00 equiv) were suspended in acetone (21.3 mL). After addition of solvent to the solids, the reaction mixture was fitted with a reflux condenser and then was heated to 50 °C. To this mixture was added methyl iodide (3.40 mL, 54.5 mmol, 5.10 equiv). The reaction was stirred vigorously to ensure completion. (Note: If reaction is not stirred, or if stirring is not efficient, potassium carbonate will collect into a solid aggregate and the reaction will halt. Breaking up these solid collections with a spatula is typically enough to reinitiate reaction, though in some cases additional methyl iodide may be required.) After 6 h, the reaction was allowed to cool and then was passed through filter paper. The remaining solids were washed with additional CH_2Cl_2 to ensure complete solvation of any precipitated product trapped within the potassium carbonate. The collected organic layers were combined and concentrated to yield an amorphous semi-solid, which was purified over silica gel using 15% → 20% ethyl acetate in hexanes

as eluent. Compound **112** was afforded as two diastereomers in a 1 : 1 ratio. The less polar diastereomer (by TLC analysis with 20% ethyl acetate in hexanes) was obtained as a white, fluffy solid, and the more polar diastereomer was obtained as a thick, yellow oil (1.4 g for each diastereomer, 2.8 g for combined diastereomers, 85% yield) that matched previously reported characterization data.[1] **Diastereomer A**: R_f = 0.30 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 17.3, 10.4, 5.8, 5.8 Hz, 2H), 5.30 (app dq, *J* = 17.3, 1.3 Hz, 2H), δ 5.26 (app dq, *J* = 10.4, 1.3 Hz, 2H), δ 4.60 (app ddd, *J* = 5.9, 1.3, 1.3 Hz, 4H), δ 3.14 (d, *J* = 15.2 Hz, 2H), δ 2.80 (d, *J* = 15.2 Hz, 2H), δ 1.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 170.6, 131.0, 119.7, 66.8, 57.6, 48.1, 20.8; IR (Neat film, NaCl) 2988, 2940, 1749, 1708, 1420, 1375, 1281, 1227, 1132, 1076, 911, 809, 744 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_6$ [M^+]: 308.1260, found 308.1263. **Diastereomer B**: R_f = 0.20 (20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 17.1, 10.4, 5.7, 5.7 Hz, 2H), δ 5.31 (app dq, *J* = 17.2, 1.5 Hz, 2H), δ 5.27 (app dq, *J* = 10.3, 1.5, 2H), δ 4.62 (app ddd, *J* = 5.4, 1.5, 1.5 Hz, 4H), δ 3.47 (d, *J* = 15.6 Hz, 2H), δ 2.63 (d, *J* = 15.9 Hz, 2H), δ 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 169.9, 131.1, 119.1, 66.7, 56.6, 47.1, 21.5; IR (Neat film, NaCl) 3088, 2984, 2940, 1747, 1722, 1649, 1454, 1422, 1381, 1275, 1233, 1196, 1110, 984, 934 cm^{-1}. HRMS (EI) *m/z* calc'd for $C_{16}H_{20}O_6$ [M^+]: 308.1260, found 308.1263.

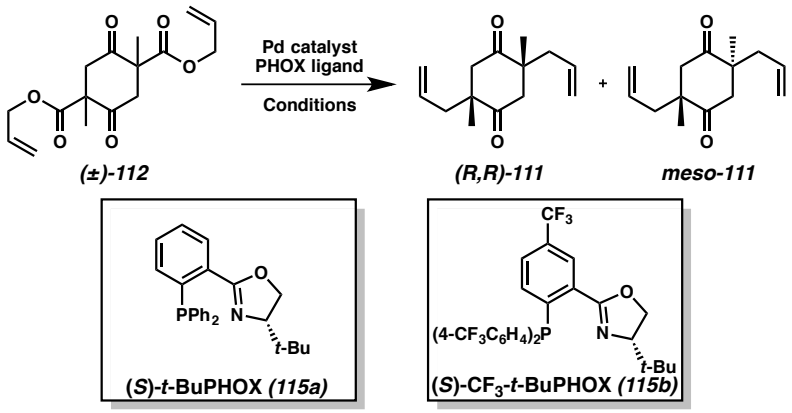


113 ***112***

Alternative Preparation of Bis(*β*-ketoester) 112. A flame dried round bottom flask was charged with NaH (60% in mineral oil, 4.44 g, 111.0 mmol, 2.2 equiv). The flask was briefly vacuum purged, and then was backfilled with argon. The solid NaH was then suspended in freshly distilled (or freshly dispensed) THF (40 mL). The resulting suspension was cooled to 0 °C in an ice water bath. After cooling, the NaH slurry was treated with a THF solution (20 mL) of diallyl succinate (**113**, 10.0 g, 50.4 mmol) added via cannula. The reaction was allowed to gradually warm to room temperature overnight (12 h). The next morning the reaction was heated to 40 °C to encourage completion of the Claisen condensation/Dieckmann cyclization process. After 24 h at this temperature, TLC analysis revealed total consumption of diallyl succinate (**113**). The reaction was cooled to 35 °C, and then a single portion of MeI (8.16 mL, 131.2 mmol, 2.6 equiv) was introduced via syringe. After an additional 12 h at 35 °C, the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (40 mL). The organic layer was separated from the aqueous layer, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and filtered. The crude material obtained upon removal of solvent in vacuo was further purified via column chromatography over silica using 15% → 20% ethyl acetate in hexanes as eluent. Compound **112** was afforded as two diastereomers in a 1 : 1 ratio, again as both a white solid and a clear oil (2.1 g for each diastereomer, 4.2 g for combined diastereomers, 54% yield). All spectroscopic data was identical to that reported above.

2.4.2.2 OPTIMIZATION OF THE DOUBLE CATALYTIC ENANTIOSELECTIVE ALLYLIC ALKYLATION

Table 2.3 Investigation of the influence of Pd catalyst and PHOX ligand

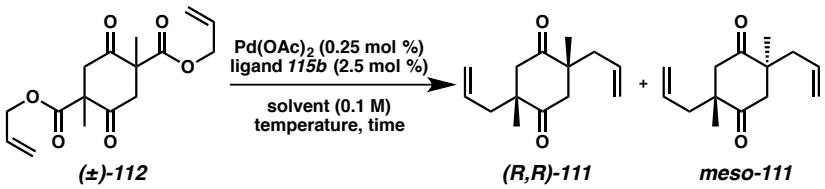


Entry	Pd cat. (mol %)	PHOX (mol %)	Solvent	Conc.	Temp.	Yield	d.r.	ee
1	$Pd(dmdba)_2$ (5.0)	*115a* (5.5)	Et_2O	0.01 M	25 °C	78%	4.4 : 1.0	99%
2	$Pd(dmdba)_2$ (5.0)	*115a* (5.5)	2:1 PhMe:Hex	0.10 M	25 °C	75%	3.4 : 1.0	99%
3	$Pd(dmdba)_2$ (5.0)	*115b* (5.5)	Et_2O	0.01 M	25 °C	92%	4.3 : 1.0	99%
4	$Pd(OAc)_2$ (0.25)	*115a* (2.5)	TBME	0.10 M	40 °C	83%	2.2 : 1.0	97%
5	$Pd(OAc)_2$ (0.25)	*115b* (2.5)	TBME	0.10 M	40 °C	93%	3.5 : 1.0	99%

Diketone 111. In a nitrogen-filled glovebox, a 20-mL scintillation vial equipped with a magnetic stir bar was charged with palladium catalyst and PHOX ligand. The solids were diluted with solvent (amount based on indicated concentration of substrate), the vial was sealed with a Teflon-lined cap, and the mixture was stirred at ambient temperature (25 °C) in the glovebox for 30 minutes. Neat bis-β-ketoester **112** was added to the mixture,[20] and the vial was once again sealed and heated to the indicated temperature for the specified amount of time. Reaction progress was monitored by TLC. Upon full

conversion of the substrate to the desired product, the reaction was allowed to cool to ambient temperature and removed from the glovebox. Concentration in vacuo followed by purification by silica gel column chromatography (3% ethyl acetate in hexanes) afforded diketone **111** as a colorless oil that matched previously reported characterization data:[1] R_f = 0.38, 10% ethyl acetate in hexanes; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.68 (dddd, *J* = 18.3, 10.2, 6.9, 6.9 Hz, 2H), 5.17–5.09 (comp. m, 3H), 5.07–5.04 (m, 1H), 2.82 (d, *J* = 14.7 Hz, 2H), 2.38 (d, *J* = 15 Hz, 2H), 2.34 (app ddt, *J* = 13.2, 6.9, 1.0 Hz, 2H), 2.09 (app ddt, *J* = 13.5, 7.8, 0.9 Hz, 2H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 212.8, 132.4, 120.0, 49.4, 48.4, 43.8, 24.3; IR (Neat Film, NaCl) 3078, 2978, 1712, 1640, 1458, 1378, 1252, 1129, 1101, 998, 921 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1463, found 220.1466; $[\alpha]^{25}_D$ –163.1 (*c* 0.52, CH_2Cl_2). Diastereomeric ratio and enantiomeric excess were determined by GC analysis. Chiral GC assay (GTA column): 100 °C isothermal method over 90 min. Retention times: 67.7 min (Major enantiomer, C_2 diastereomer), 74.1 min (Minor enantiomer, C_2 diastereomer), 77.4 min (*meso* diastereomer). Achiral GC assay (DB-Wax column): 100 °C isotherm over 2.0 min, ramp 5 °C/min to 190 °C, then 190 °C isotherm for 10.0 min. Retention times: 18.5 min (C_2 diastereomer), 18.7 min (*meso* diastereomer).

Table 2.4 Investigation of the influence of solvent and temperature

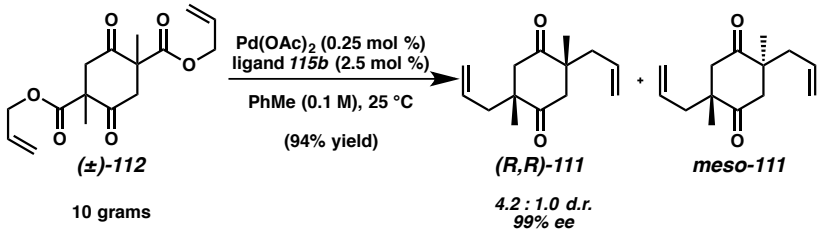


Entry	Solvent	Temperature	Time	Yield	d.r.	ee
1	TBME	40 °C	5 h	93%	3.5 : 1.0	99%
2	TMBE	30 °C	5 h	97%	3.6 : 1.0	99%
3	Et_2O	30 °C	5 h	88%	3.7 : 1.0	99%
4	PhMe	30 °C	5 h	99%	4.3 : 1.0	99%
5	2:1 PhMe:Hex	30 °C	24 h	45%	2.8 : 1.0	97%
6	PhMe	25 °C	16 h	97%	4.9 : 1.0	99%

Allylic Alkylation Procedure. In a nitrogen-filled glovebox, $Pd(OAc)_2$ (1.4 mg, 6.3 μmol) was weighed into a 20-mL scintillation vial and dissolved in solvent (10 mL). In a separate 1-dram vial, (*S*)-CF_3-*t*-Bu-PHOX (**115b**) (3.7 mg, 6.3 μmol) was dissolved in solvent (1 mL). To a 2-dram vial equipped with a magnetic stir bar, 1.0 mL of the $Pd(OAc)_2$ solution was added (14 μg, 0.63 μmol, 0.25 mol %) followed by 1.0 mL of the (*S*)-CF_3-*t*-BuPHOX solution (3.7 mg, 6.3 μmol, 2.5 mol %), washing with an additional 0.5 mL of solvent. The vial was sealed with a Teflon-lined cap, and the mixture was stirred at ambient temperature (25 °C) in the glovebox for 30 minutes. Neat bis-*β*-ketoester **112** (77 mg, 0.25 mmol, 1.0 equiv) was added to the mixture, and the vial was once again sealed and heated to the indicated temperature for the specified amount of time. Reaction progress was monitored by TLC. Upon full conversion of the substrate to the desired product (R_f = 0.38, 10% ethyl acetate in hexanes), the reaction was allowed to

cool to ambient temperature and removed from the glovebox. Concentration in vacuo followed by purification by silica gel column chromatography (3% ethyl acetate in hexanes) afforded diketone **111** as a colorless oil that matched previously reported characterization data (see above).

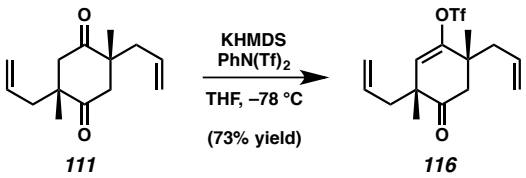
2.4.2.3 SCALE-UP OF THE DOUBLE CATALYTIC ENANTIOSELECTIVE ALLYLIC ALKYLATION



Large-Scale Allylic Alkylation Procedure. An oven-dried 500-mL round-bottom flask equipped with a magnetic stir bar was cooled to room temperature under vacuum in the antechamber of a nitrogen-filled glovebox. In the glovebox, the flask was charged with $Pd(OAc)_2$ (18 mg, 0.081 mmol, 0.25 mol %), (*S*)-CF_3-*t*-BuPHOX (**115b**) (480 mg, 0.81 mmol, 2.5 mol %), and toluene (300 mL). The flask was capped with a rubber septum, secured with electrical tape, and the contents were stirred at ambient temperature (25 °C) in the glovebox. After 1 hour, the septum was removed, and neat bis-(β-ketoester) **112** (10 g, 32 mmol, 1.0 equiv) was added to the bright yellow solution in one portion. The flask was re-sealed, and stirring continued at ambient temperature for 48 hours, at which time the reaction was removed from the glovebox and concentrated in vacuo to a dark orange oil. Purification by silica gel column chromatography (3% ethyl

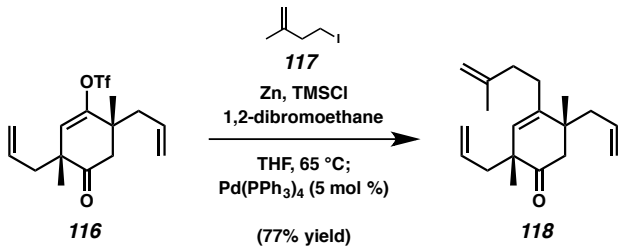
acetate in hexanes) afforded pure diketone **111** as a colorless oil (6.7 g, 94% yield) that matched previously reported characterization data (see above).

2.4.2.4 PREPARATION OF TETRAENE 118



Triflate 116. A flask was charged with potassium bis(trimethylsilyl)amide (1.49 g, 7.49 mmol, 1.10 equiv) in the glovebox, and then was transferred to a manifold line outside of the glovebox under argon. The solids were dissolved in THF (180 mL), and the resulting solution was stirred while being cooled to –78 °C. To this alkaline solution was added, dropwise, neat diketone **111** (1.50 g, 6.80 mmol, 1.00 equiv). The solution immediately turned yellow, and viscosity increased. Deprotonation was allowed over 30 min, after which time the anionic solution was transferred by cannula into a solution of *N*-phenyl bis(trifluoromethane)sulfonimide (2.91 g, 8.17 mmol, 1.20 equiv) in THF (60 mL) at –78 °C. Reaction was allowed to proceed at this temperature over 6 h, after which time the mixture was brought to room temperature. The anionic reaction was quenched with brine (100 mL). The phases were separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL) and ethyl acetate (1 x 100 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over $MgSO_4$, and the solvent was removed in vacuo after filtration. The crude oil obtained was loaded onto a silica gel column and eluted with 2% Et_2O in pentane. This afforded triflate **116** as a colorless oil

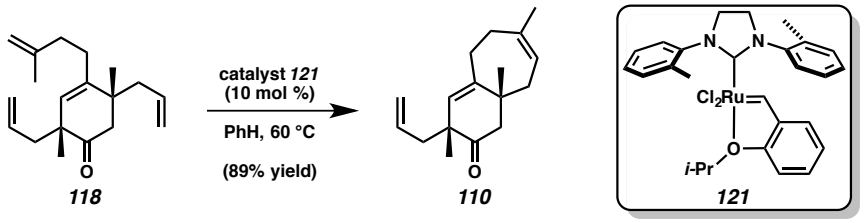
(1.75 g, 73% yield) that matched previously reported characterization data:[1] R_f = 0.40 (5% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.58 (comp. m, 2H), 5.63 (s, 1H), 5.22–5.03 (comp. m, 4H), 2.71 (d, *J* = 14.3 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 2.49–2.30 (comp. m, 2H), 2.24 (app ddt, *J* = 13.5, 6.9, 1.3 Hz, 1H), 2.09 (app ddt, *J* = 13.8, 8.24, 1.2 Hz, 1H), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 152.0, 132.6, 132.1, 122.9, 120.6, 119.7, 49.2, 48.9, 43.8, 43.0, 42.1, 25.2, 24.6; IR (Neat film, NaCl) 3081, 2980, 2934, 1721, 1673, 1641, 1457, 1416, 1214, 1141, 1010, 923.6, 895.2, 836.2 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{19}O_4SF_3$ [M^+]: 352.0956, found 352.0949; $[\alpha]^{25}_D$ –6.5 (*c* 1.15, CH_2Cl_2).



Tetraene 118. A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with zinc dust (0.70 g, 11 mmol, 7.5 equiv) and evacuated and backfilled with argon (3x) before addition of THF (30 mL). Trimethylsilyl chloride (59 μL, 0.47 mmol, 0.33 equiv) and 1,2-dibromoethane (0.15 mL, 1.7 mmol, 1.2 equiv) were added sequentially to the suspension by syringe, and the flask was sealed and heated to 65 °C. After 15 minutes, the mixture was cooled to 23 °C, and neat alkyl iodide **117** (0.27 mL, 2.1 mmol, 1.5 equiv) was added by syringe. The flask was re-sealed and heated to 65 °C for 2 hours. Meanwhile, in a nitrogen-filled glovebox, a separate flame-dried conical flask was charged with a solution of triflate **116** (0.50 g, 1.4 mmol, 1.0 equiv) and

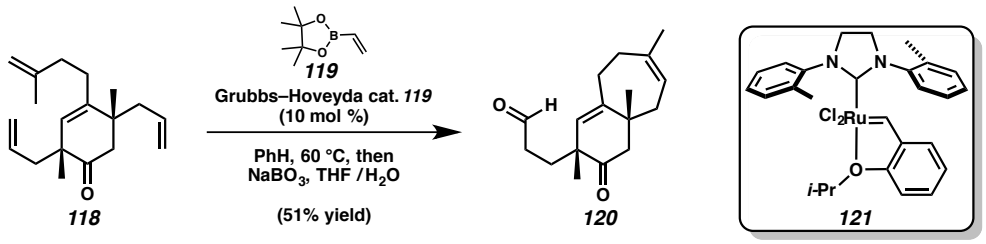
tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.071 mmol, 0.05 equiv) in THF (16 mL). This solution was added to the suspension in the Schlenk flask at 23 °C, the flask was sealed, and the resulting olive green mixture was heated to 65 °C. After 3 hours, the reaction was cooled to 23 °C and filtered over a pad of Celite, washing with excess diethyl ether (150 mL). The filtrate was diluted with brine and extracted with diethyl ether (4 x 50 mL), and the combined organics were washed sequentially with brine (50 mL) and saturated sodium thiosulfate (3 x 50 mL). The organic layer was dried over magnesium sulfate before filtration and concentration in vacuo. The crude residue was purified by silica gel column chromatography (1% → 2% → 3% Et_2O in hexanes) to afford pure tetraene **118** as a colorless oil (0.30 g, 77% yield) that matched previously reported characterization data:[1] R_f = 0.50 (5% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77–5.61 (comp. m, 2H), 5.20 (s, 1H), 5.10–4.97 (comp. m, 4H), 4.74 (d, *J* = 8.8 Hz, 2H), 2.56 (d, *J* = 13.5 Hz, 1H), 2.40–2.13 (comp. m, 8H), 2.05–1.98 (m, 1H), 1.77 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 214.4, 145.5, 142.5, 134.1, 134.0, 128.6, 118.6, 117.9, 110.1, 49.5, 48.7, 44.4, 44.3, 43.2, 36.5, 28.6, 26.5, 24.7, 22.7; IR (Neat Film, NaCl) 3076, 2996, 2928, 2360, 1715, 1639, 1455, 1376, 1320, 1298, 1261, 1229, 1138, 1093, 996, 916, 887 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{19}H_{28}O$ $[M]^+$: 272.2140, found 272.2138; $[\alpha]^{25}_D$ –72.4 (*c* 0.22, CH_2Cl_2).

2.4.2.5 PREPARATION OF BICYCLIC ALDEHYDE 120



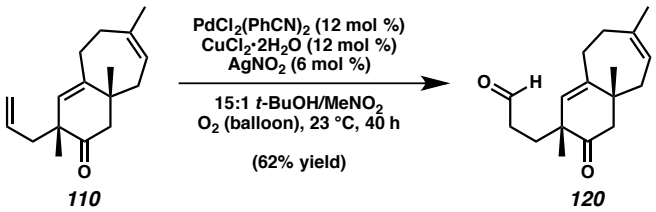
Bicyclic Triolefin 110. To a flame dried flask was added tetraolefin **118** (160 mg, 588 mmol, 1.00 equiv). This oil was dissolved in benzene (5 mL), and then azeotroped from this solvent. This process was repeated three times, and then the resulting residue was dissolved in benzene (28 mL) and sparged with argon for 30 min. After the sparge time had elapsed, a single portion of Grubbs–Hoveyda catalyst **121** (34.0 mg, 59.0 μmol, 0.10 equiv) was added to the solution. The reaction was then heated to 40 °C. (Note: tetraolefin **118** and bicyclic triolefin **110** are difficult to separate by TLC in a wide variety of solvent systems, and frequently are seen to co-spot. In order to afford more efficient separation via TLC, the use of silver nitrate treated silica gel TLC plates is very effective.) After 20 min at 40 °C, the reaction had completed by TLC, and so was quenched via the addition of ethyl vinyl ether (20 mL). The solvents were removed in vacuo, and the resulting crude mixture was purified via chromatography over silica gel using 0.5% → 1.0% → 1.5% → 3.0% Et_2O in petroleum ether as eluent. This afforded bicyclic triene **110** as a colorless oil (128 mg, 89% yield) that matched previously reported characterization data:[1] R_f = 0.50 (5% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (dddd, *J* = 16.8, 10.2, 8.4, 6.5 Hz, 1H), 5.33 (dddd, *J* = 6.9, 5.4, 2.9, 1.5 Hz, 1H), 5.19 (s, 1H), 5.01–4.93 (comp. m, 2H), 2.73 (dd, *J* = 13.4, 0.6 Hz, 1H), 2.53 (dddd, *J* = 13.2, 11.7, 5.3, 0.6 Hz, 1H), 2.45–2.39 (m, 2H), 2.22–2.17 (m, 1H), 2.22 (app

ddt, J = 13.5, 8.4, 0.9 Hz, 1H), 2.11–2.03 (m, 2H), 2.11 (app ddt, J = 13.5, 6.5, 1.4 Hz, 1H), 2.03 (d, J = 13.5 Hz, 1H), 1.65 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 145.3, 138.5, 134.0, 129.2, 120.2, 117.8, 51.7, 49.0, 46.3, 44.9, 37.4, 29.5, 28.1, 25.8, 23.7; IR (Neat film, NaCl) 3076, 2961, 2927, 1711, 1639, 1452, 1372, 1225, 1163, 997, 916 cm^{-1}; HRMS (EI) m/z calc'd for $C_{17}H_{24}O$ [M^+]: 244.1827, found 244.1821; $[\alpha]^{25}_D$ –96.7 (*c* 1.33, CH_2Cl_2).



Bicyclic Aldehyde 120. A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with tetraene **118** (0.25 g, 0.92 mmol, 1.0 equiv). Dry benzene (2 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 and backfilled with argon, before dilution with benzene (10 mL). A solution of Grubbs–Hoveyda catalyst **121** (26 mg, 0.046 mmol, 0.05 equiv) in THF (10 mL) was added slowly, and the resulting mixture was stirred at 25 °C. After 1 hour, boronate ester **119** (0.78 mL, 4.6 mmol, 5.0 equiv) was added dropwise, and another portion of catalyst **121** (26 mg, 0.046 mmol, 0.05 equiv) in THF (10 mL) was added. The olive green mixture was heated to 40 °C. After 20 hours, the reaction was cooled to 0 °C, and ethyl vinyl ether (0.4 mL) was added to quench remaining catalyst. Volatiles were removed in vacuo, and the resulting residue was passed through a plug of silica, eluting with 20%

ethyl acetate in hexanes (300 mL). Upon concentration, the resulting oil was diluted with THF (30 mL) and water (30 mL), treated with sodium perborate monohydrate (0.55 g, 5.5 mmol, 6.0 equiv), and stirred at 23 °C for 1.5 hours. The phases were separated, and the aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organics were washed with brine and dried over magnesium sulfate. Upon filtration and concentration, the crude reside was purified by silica gel column chromatography (5% ethyl acetate in hexanes) to furnish pure aldehyde **120** as a colorless oil (0.11 g, 46% yield) that matched previously reported characterization data:[1] R_f = 0.20 (10% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (app t, *J* = 1.3 Hz, 1H), 5.38–5.31 (m, 1H), 5.15 (s, 1H), 2.70 (d, *J* = 13.6 Hz, 1H), 2.59–2.32 (comp. m, 5H), 2.12 (d, *J* = 13.8 Hz, 1H), 2.24–2.04 (comp. m, 2 H), 1.89–1.64 (comp. m, 3 H), 1.67 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 201.6, 146.4, 138.7, 129.0, 120.1, 51.6, 47.7, 39.9, 37.6, 37.2, 33.1, 29.6, 27.8, 25.9, 23.9; IR (Neat film, NaCl) 2960, 2927, 2360, 2341, 1711–1710 (overlapping peaks), 1452, 1374, 1296, 1163 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{17}H_{24}O_2$ [M^+]: 260.1776, found 260.1784; $[\alpha]^{25}_D$ –83.5 (*c* 1.09, CH_2Cl_2).

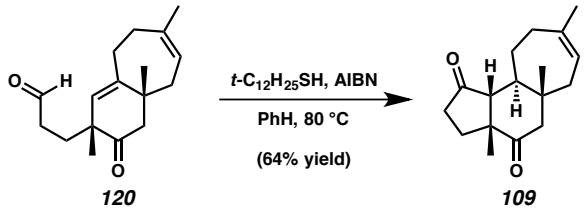


110 *120*

Alternative Preparation of Bicyclic Aldehyde 120. To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (5.7 mg, 0.015 mmol, 0.12 equiv), copper(II) chloride dihydrate (2.6 mg, 0.015 mmol, 0.12 equiv), and silver nitrite (1.2 mg, 0.0075 mmol, 0.06 equiv). The flask was capped

with a rubber septum, and *tert*-butyl alcohol (2.3 mL) and nitromethane (0.20 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **110** (30 mg, 0.12 mmol, 1.0 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 20 hours, at which time another half portion of the catalyst system (2.9 mg Pd, 1.3 mg Cu, 0.6 mg Ag) was added to the reaction mixture. After 20 hours, the reaction mixture was diluted with water (4 mL) and extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over sodium sulfate, then filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (3% ethyl acetate in hexanes), furnishing aldehyde **120** as a colorless oil (20 mg, 62% yield) that matched previously reported characterization data (see above).

2.4.2.6 PREPARATION OF TRICYCLIC DIKETONE 109



120 *109*

Tricyclic Diketone 109. A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with aldehyde **120** (20 mg, 0.076 mmol, 1.0 equiv). Dry benzene (2 mL) was added, and then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high

vacuum and backfilled with argon. *tert*-Dodecanethiol (54 μL, 0.23 mmol, 3.0 equiv) and azobisisobutyronitrile (19 mg, 0.12 mmol, 1.5 equiv) were added, and the resulting mixture was diluted with benzene (5 mL), then freeze-pump-thawed (3x) and backfilled with argon. The flask was sealed, and the contents were heated to 80 °C. After 48 hours, the reaction was cooled to 23 °C and concentrated in vacuo. The crude oil was purified by silica gel column chromatography (5.0% → 7.5% → 10.0% ethyl acetate in hexanes) to afford tricyclic diketone **109** as an amorphous solid (13 mg, 64% yield) that matched previously reported characterization data:[1] R_f = 0.40 (10% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.33 (ddq, *J* = 5.13, 5.13, 1.71 Hz, 1H), 2.65 (d, *J* = 14.5 Hz, 1H), 2.55–2.49 (m, 1H), 2.41–2.28 (m, 2H), 2.27–2.21 (m, 1H), 2.20–2.12 (m, 1H), 2.02 (d, *J* = 14.5 Hz, 1H), 2.01–1.93 (m, 2H), 1.89 (dd, *J* = 12.2, 1.2 Hz, 1H), 1.83–1.72 (m, 3H); 1.74 (s, 3H), 1.09 (s, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 218.0, 212.8, 142.6, 121.0, 63.2, 52.6, 51.0, 47.8, 42.3, 40.1, 34.4, 32.4, 31.4, 25.4, 24.1, 21.7, 17.3; IR (Neat Film, NaCl) 2961, 2926, 2868, 1735, 1705, 1576, 1453, 1380, 1149 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{24}O_2$ $[M]^+$: 260.1777, found 260.1776; $[\alpha]^{25}_D$ –158.6 (*c* 0.925, CH_2Cl_2).

2.5 NOTES AND REFERENCES

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(7) Diketone **111** is isolated as an inseparable mixture of *(R,R)* and meso stereoisomers, with a negligible amount of the *(S,S)* isomer observed. The diastereomers are separated later in the synthetic sequence upon the formation of tricycle **109**.

(8) The RCM and cross-metathesis reactions were carried out using a modified version of Grubbs–Hoveyda catalyst II (**121**, Scheme 2.4A). For details, see: Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org*. *Lett*. **2007**, *9*, 1589–1592.

(9) The double catalytic enantioselective allylic alkylation strategy was also applied by our group to the synthesis of the carbocyclic core of the gagunin natural product family. For details, see: Shibuya, G. M.; Enquist, J. A., Jr.; Stoltz, B. M. *Org*. *Lett*. **2013**, *15*, 3480–3483.

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(20) Substrate **112** is formed as a 1:1 mixture of the racemic and meso diastereomers, which are readily separable by silica gel column chromatography. The double catalytic enantioselective alkylation is effective on the diastereomeric mixture of **112**, but for ease of operation a single diastereomer was used for screening experiments.