CHAPTER 4[†]

The Cyanthiwigin Natural Product Core as a Complex Molecular Scaffold

for Comparative Late-Stage C–H Functionalization Studies

4.1 INTRODUCTION

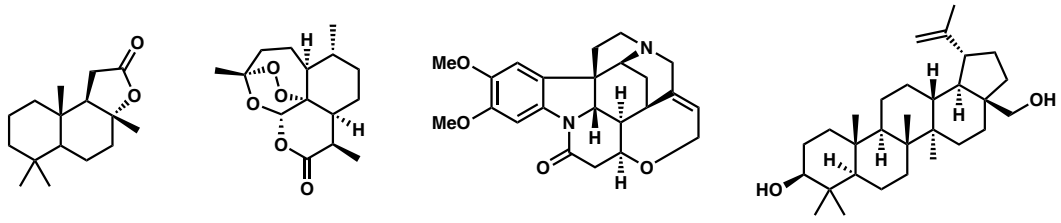
With access to large quantities of the cyanthiwigin natural product core, we were ready to undertake studies in late-stage diversification. As active participants in the NSF Center for Selective C–H Functionalization (CCHF), we envisioned that the tricyclic compound could serve as a scaffold from which to probe the reactivity of complex molecules under various conditions for C–H functionalization. To this end, we carried out a comparative study of late-stage C–H oxidation methodologies. The results of these investigations are described herein.

[†] This work was performed in collaboration with the Du Bois group at Stanford University through the NSF Center for Selective C–H Functionalization. Portions of this chapter have been reproduced from a manuscript and supporting information intended for submission at *J. Am. Chem. Soc.*

4.1.1 BACKGROUND

The selective functionalization of unactivated C–H bonds has long fascinated the chemical community, having even been referred to as a "Holy Grail" of synthetic chemistry.[1] C–H bonds are ubiquitous in organic molecules, and the direct conversion of these traditionally inert moieties to other functional groups has the potential to streamline synthetic strategies while reducing waste generation. Recognizing this potential, developers of C–H functionalization methodologies often include in their reports examples of commercially available complex substrates such as sclareolide (**1**) or artemisinin (**186**) (Figure 4.1). While wisdom gained from this practice has contributed to the successful application of C–H functionalization in total synthesis,[2] a complementary approach involving comparison of many different methodologies on a single complex scaffold would greatly improve understanding of the fate of complex molecules under conditions for C–H functionalization. Furthermore, the direct comparison of various protocols for the same transformation on a single substrate would be a good indicator of how practical a method might be in the synthesis of a complex molecule.

Figure 4.1 Commercially available complex molecules employed in previous C–H functionalization studies

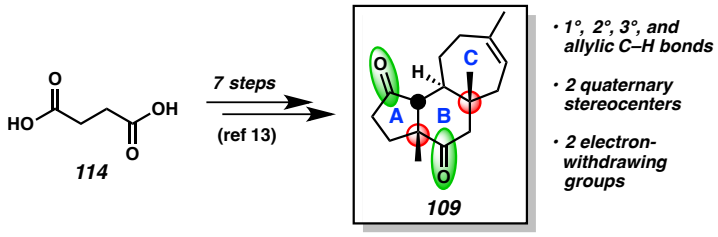


The concept of diversifying complex scaffolds using C–H functionalization has gained much traction within the last decade,[3] with various research groups communicating derivatizations of molecules as diverse as drug candidates,[4] organic light-emitting diodes (OLEDs),[5] metal–organic frameworks (MOFs),[6] and polymers, most commonly by way of $C(_{sp^2})$–H functionalization.[7] However, few reports exist detailing comparative studies of methodologies for $C(_{sp^3})$–H oxidation on a single complex scaffold. An account by Davies and Beckwith explores various conditions and catalysts for C–C bond formation on the complex alkaloid brucine (**187**, Figure 4.1)[8] while a report by Du Bois and Malik compares the efficacies of various C–O bond-forming methods on relatively simple substrates.[9] However, so far the only comparative study involving C–O bond formation on a complex scaffold was disclosed by Baran and co-workers in 2014,[10] outlining the oxidation of betulin (**188**) in conjunction with the optimization of physicochemical properties relevant to drug discovery.[11,12]

With this in mind, we envisioned that the tricyclic carbon framework of the cyanthiwigin natural product family (**109**) could serve as a complex scaffold on which to conduct a comparative study of C–H oxidation methodologies. Tricycle **109** is readily available from succinic acid (**114**) in an efficient 7-step sequence previously developed by our group[13] and features an A–B–C tricyclic fused carbon skeleton containing a variety of C–H bonds. Additionally, the presence of two quaternary stereocenters allows for assessment of steric influences while the two carbonyl moieties enable examination of electronic factors (Figure 4.2). Elucidating the behavior of tricycle **109** under various conditions for C–H oxidation would provide insights into the reactivity of complex molecules complementary to the previously reported findings on commercially available

scaffolds. This report is not intended as an exhaustive survey of all known strategies for C–H oxidation but rather as a sampling of a balanced cross-section of the C–H oxidation literature. We have chosen to focus on intermolecular strategies, which do not require the installation and removal of directing functionalities as most intramolecular methods do.[14]

*Figure 4.2 Availability of the cyanthiwigin core (**109**) from succinic acid (**114**) and features relevant to reactivity under common conditions for C–H oxidation*



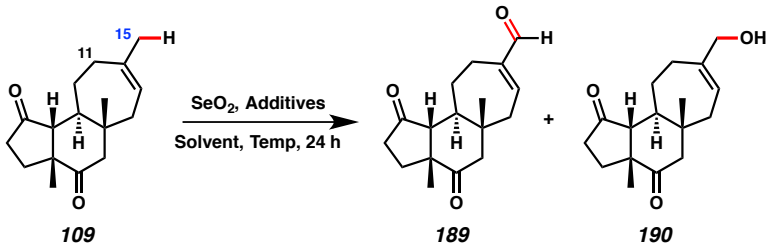
4.2 OXYGENATION VIA C–H FUNCTIONALIZATION

The introduction of oxygen atoms into carbon frameworks has been shown to significantly influence aqueous solubility and other physicochemical properties of complex molecules,[10] resulting in important implications for biological activity.[15] As such, various oxygen transfer reagents exist for the oxygenation of functionalized substrates.[16] In constrast, the oxidation of unactivated C–H bonds, such as those present in many natural products and other complex molecules, is a more recent field of study. Interest in C–H oxygenation has grown rapidly over the past two decades due to the potential for introducing oxygen atoms at sites inaccessible under conventional oxidation conditions. To this end, we began our investigations into the reactivity of the cyanthiwigin core by examining the formation of C–O bonds.

4.2.1 ALLYLIC C–H ACETOXYLATION

We first targeted the most activated C–H bonds in the cyanthiwigin framework, those at allylic positions. Treatment of **109** with stoichiometric quantities of selenium dioxide in refluxing ethanol[17] afforded enal **189** in moderate yield (42%) along with allylic alcohol **190** (22%) (Table 4.1, Entry 1). In contrast, the use of catalytic selenium with stoichiometric *tert*-butyl hydroperoxide (TBHP) at room temperature[18] enabled formation of **190** as the major product, with only trace amounts of enal **189** observed in the crude reaction mixture (Entry 2). Interestingly, in both of these experiments, oxidation was observed only at the C15 methyl despite a priori assumptions that the endocyclic C11 position would be favored.[19]

*Table 4.1 Allylic oxidation of the cyanthiwigin core (**109**) using selenium dioxide*

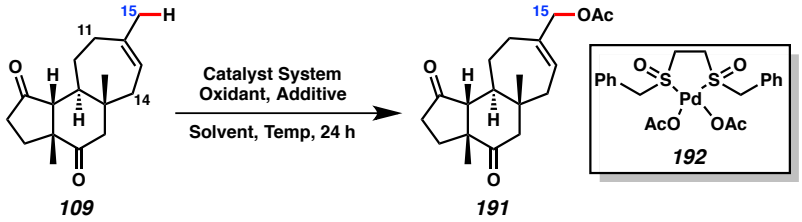


109 **189** **190**

Entry	SeO_2 loading	Additives	Solvent	Temp.	Yield[c]	***189*** : ***190***
1[a]	1.0 equiv	none	25:1 EtOH/H_2O	95 °C	64%	1.8 : 1.0
2[b]	10 mol %	TBHP, AcOH	CH_2Cl_2	23 °C	53%	0 : 1.0[d]

[a] Conditions adapted from ref 17. [b] Conditions adapted from ref 18. [c] Combined isolated yields of **189** and **190**. [d] Trace amount of enal **189** was observed in the crude reaction mixture.

Table 4.2 Comparison of Pd-catalyzed allylic C–H acetoxylation methods on tricycle ***109***



Entry	Cat. System (mol %)	Oxidant	Additive	Solvent	Temp.	Yield[e]
1[b]	$Pd(OAc)_2$ (5) 4,5-diazafluorenone (5)	O_2	NaOAc, AcOH	1,4-dioxane	60 °C	trace[f]
2[c]	$Pd(OAc)_2$ (10)	BQ	4Å MS	1:1 DMSO/AcOH	40 °C	0[f]
3[c]	Pd cat ***192*** (10)	BQ	none	1:1 CH_2Cl_2/AcOH	40 °C	trace[f]
4[d]	$Pd(hfacac)_2$ (7.5)	Oxone	4Å MS	5:1:1 MeCN/AcOH/Ac_2O	60 °C	0[f]
5	$Pd(OAc)_2$ (10)	Oxone	none	1:1 AcOH/$CH_3CH_2NO_2$	95 °C	31%

[a] Conditions adapted from: [b] ref 20, [c] ref 21, [d] ref 22. [e] Isolated yield. [f] Starting material was recovered (>90%).

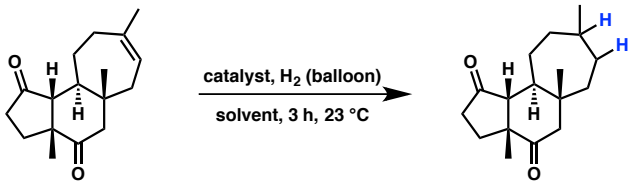
Shifting our attention to more recently developed procedures for allylic oxidation, we investigated the efficacies of various conditions employing Pd catalysis (Table 4.2). Efforts to effect allylic C–H acetoxylation using catalytic $Pd(OAc)_2$ with either O_2 or benzoquinone (BQ) as the oxidant, strategies reported previously by Stahl[20] and White,[21] respectively, resulted in little to no conversion of tricycle **109** (Entries 1–2). Employing Pd^{II} complex **192** as the catalyst and changing the solvent system improved conversion only slightly (Entry 3). Interestingly, although conditions developed previously by our group for allylic acetoxylation using Oxone as the terminal oxidant[22] were ineffective for the oxidation of **109** (Entry 4), modification of the conditions resulted in the formation of C15 acetoxylation product **191** in modest yield (Entry 5). The temperature of these modified conditions was significantly higher than those of the previous experiments, suggesting that oxidation of the C15 allylic C–H bonds is an energy-intensive process.

Notably, no oxidation was observed at the C11 and C14 positions, likely due to steric factors.[23]

4.2.2 HYDROGENATION OF THE CYANTHIWIGIN CORE

While the alkene functionality was instrumental in the allylic oxidation studies, it proved to be a liability in the exploration of methods for C–H hydroxylation,[24] an important strategy in the modulation of physicochemical properties of lead candidates in drug discovery.[10] To render the cyanthiwigin framework compatible with common C–H hydroxylation conditions, we sought to remove the C-ring olefin through hydrogenation (Table 4.3). After unsuccessful attempts using catalytic (Entry 1) or superstoichiometric Pd/C in various solvent systems (Entries 2–5), we were delighted to find that PtO_2 catalyzed the transformation smoothly with 100% conversion of **109** (Entry 6).

*Table 4.3 Catalyst and solvent optimization for hydrogenation of the cyanthiwigin core (**109**)*

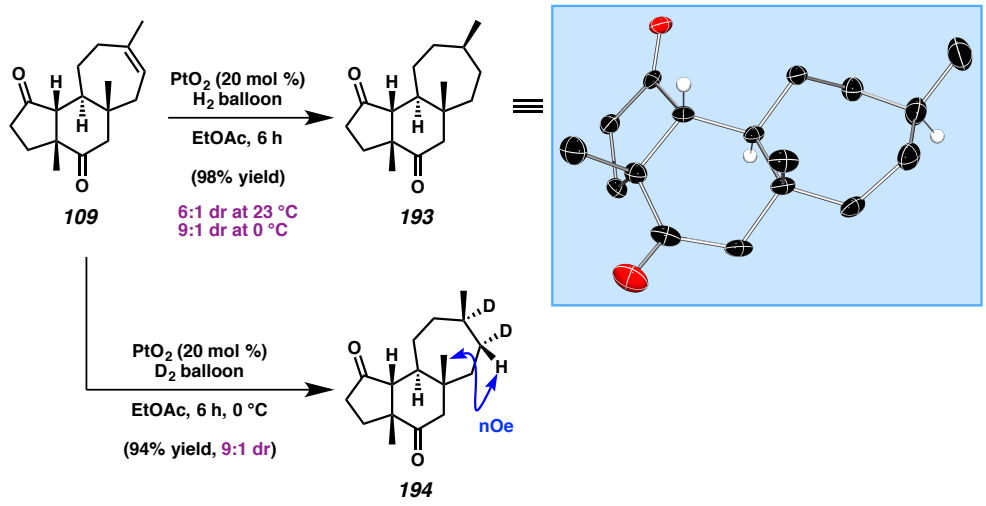


109 ***193***

Entry	Catalyst	Cat. Loading	Solvent	Conversion
1	Pd/C	3 mol %	EtOAc	0
2	Pd/C	2.3 equiv	EtOAc	0
3	Pd/C	3.5 equiv	AcOH/EtOAc (2:1)	0
4	Pd/C	3.0 equiv	AcOH/EtOAc (5:2)	0
5	Pd/C	3.0 equiv	TFA/EtOAc (3:1)	0
6	PtO_2	20 mol %	EtOAc	100%

When hydrogenation was carried out at ambient temperature, saturated tricycle **193** was obtained in 6:1 dr, whereas when the temperature was lowered to 0 °C, the dr increased to 9:1 (Scheme 4.1).[25] To facilitate structural determination of the major diastereomer, deuterium-labeled compound **194** was prepared, enabling stereochemical elucidation by nOe analysis. This assignment was further substantiated by an X-ray crystal structure of compound **193**. The stereoselectivity of the reaction likely arises from steric constraints, with hydrogenation occurring preferentially on the more accessible α-face of **109**.

*Scheme 4.1 Structural determination for saturated tricycle **193** facilitated by NMR analysis of deuterated tricycle **194** and X-ray crystallography*

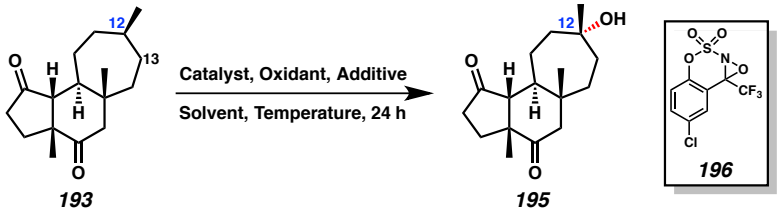


4.2.3 TERTIARY C–H HYDROXYLATION

With saturated tricycle **193** in hand, we proceeded to conduct a comparative study of 3° C–H bond hydroxylation (Table 4.4). Initial investigations using catalytic $RuCl_3 \bullet xH_2O$ supplied tertiary alcohol **195** in moderate yield (Entry 1),[26] and the milder

(Me_3tacn)$RuCl_3$ system proved even more effective (Entry 2).[27] Unfortunately, metal-free conditions catalyzed by oxaziridine **196** resulted in significantly lower yields of **195**, suffering from low conversion and epimerization at the C12 position, presumably through ionization of the tertiary alcohol in situ (Entry 3).[28] Likewise, the use of excess dimethyldioxirane (DMDO) provided only small quantities of **195**, returning primarily unreacted **193** (Entry 4).[29] Fe-catalyzed[30] and Mn-catalyzed[9] protocols were similarly inefficient, although starting material was consumed in both cases (Entries 5–6). Formation of smaller quantities of another product suspected to arise from C13 oxidation was also observed.

*Table 4.4 Comparison of tertiary C–H hydroxylation methods on saturated tricycle **193***



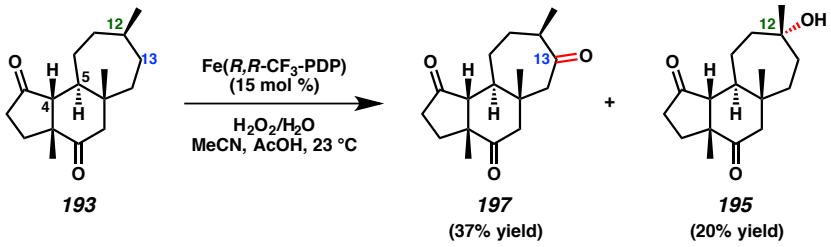
Entry	Catalyst (mol %)	Oxidant	Additive	Solvent	Temp.	Yield[h]
1[b]	$RuCl_3$•xH_2O (5)	$KBrO_3$	pyridine	MeCN	60 °C	42%[i,m]
2[c]	(Me_3tacn)$RuCl_3$ (2)	CAN	$AgClO_4$	*t*-BuOH/H_2O	23 °C	64%[i,m]
3[d]	oxaziridine ***196*** (20)	Oxone	none	HFIP/H_2O	70 °C	21%[i,m]
4[e]	none	DMDO	none	acetone	23 °C	15%[i]
5[f]	Fe(*S,S*-PDP) (15)[j]	H_2O_2	AcOH	MeCN	23 °C	22%[k,n]
6[g]	$Mn(OTf)_2$ (0.1)	AcOOH	bipy	AcOH/H_2O	23 °C	20%[l,n]

[a] Conditions adapted from: [b] ref 26, [c] ref 27, [d] ref 28, [e] ref 29b, [f] ref 30, [g] ref 9. [h] Isolated yield. [i] Starting material was recovered. [j] Iterative protocol was employed (3 x 5 mol %). [k] Reaction time = 30 min. [l] Reaction time = 90 s. [m] Minor product with opposite stereochemistry at C12 was also observed. [n] Ketone product **197** derived from 2° C–H oxidation at C13 was also observed.

4.2.4 SECONDARY C–H OXIDATION

To elucidate the structure of the presumed C13 oxidation product, tricycle **193** was subjected to oxidation by Fe(*R*,*R*-CF_3-PDP), a modified Fe-PDP catalyst known to prefer oxidation of 2° over 3° C–H bonds.[31] Indeed, ketone **197** was formed as the major product, with a smaller amount of C12 oxidation product **195** also isolated (Scheme 4.2). In this experiment as well as the tertiary C–H hydroxylation studies, oxidation was not observed at the C4 or C5 positions, likely due to deactivation by the nearby carbonyls and torsional strain associated with the axial configuration of those C–H bonds.[32] Although the yields of product formation in this system vary, it is interesting that all of the C–H hydroxylation conditions studied oxidized the same region of **193** and, with one exception (cf. Scheme 4.2), stereoselective C–H hydroxylation of C12 is observed as the major oxidation product. In terms of synthetic design, this points to electronically remote 3° C–H bonds as the most likely to be oxidized and could provide enough confidence to the practitioner to incorporate this design feature into a complex plan.

*Scheme 4.2 Secondary C–H oxidation of saturated tricycle **193***



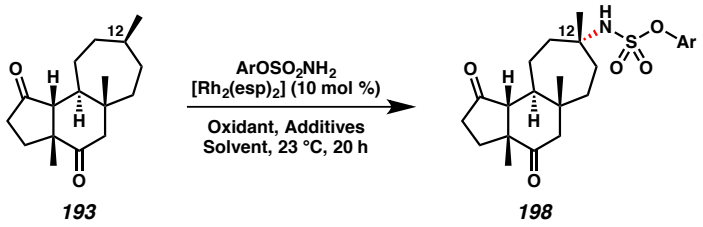
4.3 NITROGENATION VIA C–H FUNCTIONALIZATION

We next turned our attention to the formation of C–N bonds, an important research area due to the ubiquity of nitrogen-containing bioactive molecules.[33] Nitrogen atoms influence biological activity through the basicity of the nitrogen lone pair and the capacity for hydrogen bonding, which can also be modulated through substitution. Despite the vital roles nitrogen atoms play in bioactive molecules, however, nitrogenation in nature is generally not accomplished through direct C–N bond formation. Instead, most nitrogen atoms are introduced downstream of C–O bonds, often through condensation reactions.[34] As such, direct C–N bond formation via synthetic catalysis represents an especially significant accomplishment because such strategies can effectively access nitrogenated molecules for which no biosynthetic pathways exist.[35]

4.3.1 TERTIARY C–H AMINATION

Noting these considerations, we commenced our investigations into nitrogenation with C–H amination. Application of Du Bois's Rh-catalyzed methodology[36] enabled formation of C12 amination product **198a** in modest yield (Table 4.5, Entry 1). Pleasingly, a revised set of conditions featuring fewer additives furnished C–H amination product **198b** in greatly improved yield, with the remaining mass balance composed of unreacted **193** (Entry 2). Access to fluorine-containing product **198c** was also achieved in good yield through the modified protocol (Entry 3). In all cases, C–H functionalization occurred selectively at C12 with retention of stereochemistry.

Table 4.5 Tertiary C–H amination of saturated tricycle ***193***



193 ***198***

Entry	Ar	Oxidant	Additives	Solvent	Product	Yield[b]
1[a]	2,6-FC_6H_3	$PhI(OAc)_2$	$PhMe_2CCO_2H$ MgO, 5Å MS	*i*-PrOAc	***198a***	30%[c]
2	C_6H_5	$PhI(OPiv)_2$	Al_2O_3	*t*-BuCN	***198b***	70%[c]
3	4-FC_6H_4	$PhI(OPiv)_2$	Al_2O_3	*t*-BuCN	***198c***	72%[c]

[a] Conditions were adapted from ref 36. [b] Isolated yield. [c] Starting material was recovered.

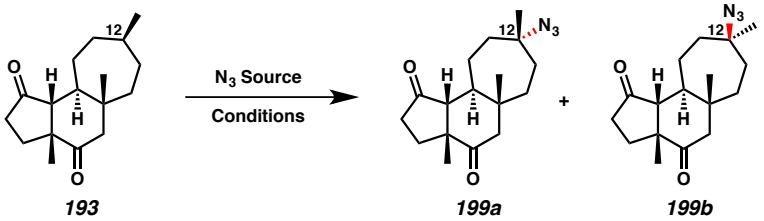
4.3.2 TERTIARY C–H AZIDATION

Encouraged by the success of the C–H amination reactions, we next examined various conditions for C–H azidation. Organic azides are readily reduced to primary amines and can be useful intermediates in the preparation of a variety of nitrogen-containing compounds.[37] A metal-free protocol reported by Tang and co-workers[38] effected C–N bond formation smoothly at the C12 position (Table 4.6, Entry 1). Likewise, Hartwig's Fe-catalyzed strategy afforded comparably high conversion of **193** (Entry 2).[39] In both cases two products were isolated and characterized as diastereomers **199a** and **199b**.

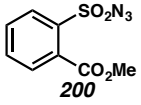
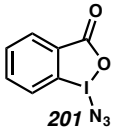
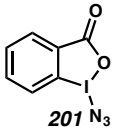
The lack of stereoselectivity matches results from the methodological reports and indicates a loss of stereochemical information at the reactive site during the reaction mechanism, which both Tang and Hartwig propose as proceeding through a radical intermediate. Also in agreement with Hartwig's findings, efforts to initiate azidation using benzoyl peroxide resulted in poor yields and substrate decomposition (Entry 3). As

was observed in the 3° C–H amination and 3° C–H hydroxylation studies, azidation of **193** occurred exclusively at the C12 position. Overall, the high conversions and regioselectivities of the C–H azidation reactions indicate good potential for synthetic applications, although more development in stereochemical control is needed for more universal utility in chemical synthesis.

*Table 4.6 Tertiary C–H azidation of saturated tricycle **193***



193 ***199a*** ***199b***

Entry	N_3 Source	Conditions	Yield[c]	***199a*** : ***199b***
1[a]	 ***200***	$K_2S_2O_8$, $NaHCO_3$ MeCN/H_2O, 85 °C, 24 h	90%[d]	1.0 : 1.9
2[b]	 ***201*** N_3	$Fe(OAc)_2$, *i*-Pr-pybox MeCN, 35 → 50 °C, 24 h	86%[d]	1.2 : 1.0
3[b]	 ***201*** N_3	BzOOBz, ABCN DCE, 84 °C, 24 h	13%	0 : 1.0

[a] Conditions adapted from ref 38. [b] Conditions adapted from ref 39. [c] Combined isolated yields of **199a** and **199b**. [d] Starting material was recovered.

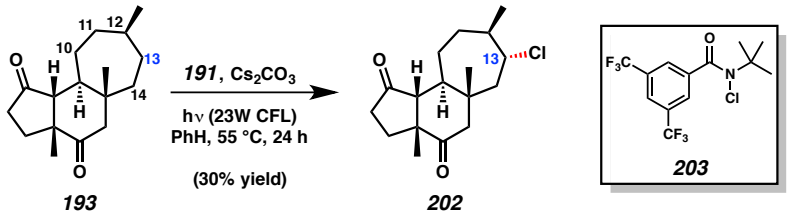
4.4 SECONDARY C–H CHLORINATION

Having successfully effected C–O and C–N bond formation on saturated tricycle **193**, we rounded out our studies with C–X bond formation. Site-selective halogenation is an important aim in chemical synthesis due to the versatility of alkyl halides as synthetic

building blocks.[40] Noting the existence of over 2000 chlorine-containing natural products,[41] Alexanian and co-workers developed a protocol for site-selective C–H chlorination enabled by visible light and an *N*-chloroamide reagent.[42] Significantly, in contrast to previously reported methodologies, the Alexanian procedure avoids the use of strong acid solvents[43] and superstoichiometric substrate,[44] two major synthetic limitations, especially in the context of late-stage functionalization using precious materials.

After efforts to fluorinate the hydrogenated cyanthiwigin core (**193**) proved challenging,[45] we turned to Alexanian's procedure for C–H chlorination and were pleased to find that irradiation of **193** with visible light (23W CFL) in the presence of *N*-chloroamide **203** effected 2° C–H chlorination at C13, generating chloride **202** in modest yield (Scheme 4.3). The remaining mass balance consisted of recovered starting material in addition to small quantities of unassigned dichlorinated products.[46]

Scheme 4.3 Secondary C–H chlorination of saturated tricycle ***193***



With the A- and B-rings deactivated by the electron-withdrawing carbonyls, the C-ring remains the most viable location for oxidation. As discussed in Alexanian's original report, the regioselectivity of this reaction is strongly influenced by steric constraints due to the bulkiness of the chlorinating reagent, *N*-chloroamide **203**. Accordingly, chlorination occurs primarily at the C13 position, the least sterically encumbered site in

the C-ring. Although the C11 position appears relatively unhindered as well, it is possible that anisotropic effects from the A-ring ketone cause electronic deactivation since the cupped conformation of the tricyclic system brings the A-ring carbonyl in proximity to the C10 and C11 positions on the C-ring. Finally, the stereoselectivity of the C13 oxidation can also be explained by sterics, as chlorination occurs preferentially on the less sterically burdened α-face of **193**, resembling the facial selectivity observed in the hydrogenation of **109** (cf. Scheme 4.1).

4.5 CONCLUDING REMARKS

Through these investigations, we have examined the reactivity of a complex natural product core in a comparative study of various known methods for C–H oxidation. Having observed that selenium dioxide is the most effective catalyst for selective allylic oxidation of **109**, we conclude that the direct allylic C–H acetoxylation of trisubstituted olefins in complex scaffolds remains a challenging transformation that could benefit from further methodological development, although the use of catalytic selenium dioxide is a significant advance. Additionally, while many methods for 3° C–H hydroxylation and amination proceed with good conversion and stereoselectivity, protocols for 3° C–H azidation tend to permit epimerization at the site of oxidation, limiting applications in chemical synthesis despite overall high conversion. Finally, there remains much room for growth in the area of C–Cl bond formation by C–H functionalization, although the ability to isolate a single enantiopure product in serviceable, albeit suboptimal, yield is an impressive feat and a convenient resource for the chlorination of organic compounds.

To conclude, the results of these experiments indicate that electronic and steric factors play significant roles in the regio- and stereoselectivity of most C–H oxidation reactions of complex molecules, corroborating previous accounts by other research groups. Furthermore, the tendency for functionalization to occur at just one site (C12) in the 17-carbon saturated cyanthiwigin core (**193**) under vastly differing conditions for C–H oxidation lends credence to the concept of "innate" functionalizations guided by the intrinsic reactivities of C–H bonds within the substrate.[47] This finding also highlights the importance of methodologies exhibiting alternative regioselectivities (e.g. C13-selective oxidations) since they enable chemists to target less inherently reactive C–H bonds as desired. We anticipate the insights derived from these investigations will enhance understanding of complex molecules with respect to predicting sites of reactivity in C–H oxidation reactions, thereby amplifying the applicability of C–H functionalization as a tool in chemical synthesis.

4.6 EXPERIMENTAL SECTION

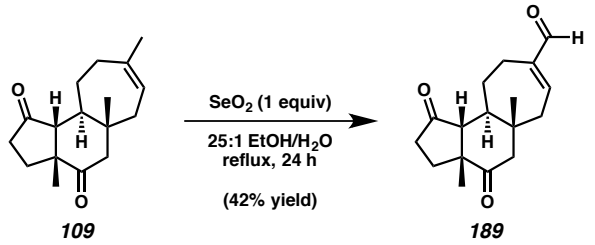
4.6.1 MATERIALS AND METHODS

Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. Dried and deoxygenated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.[48] Methanol (Fisher Scientific) was distilled from magnesium methoxide immediately prior to use. 1,2-dichloroethane (Fisher Scientific) and hexafluoroisopropanol (Matrix Scientific) were distilled from calcium hydride immediately prior to use. Isopropyl acetate was distilled and stored over activated molecular sieves (5Å) immediately prior to use. Anhydrous ethanol, *tert*-butanol, and dimethylsulfoxide (DMSO) 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. Catalysts $(Me_3tacn)RuCl_3$, benzoxathiazine **204**, $Mn(OTf)_2$, and $Rh_2(esp)_2$ were donated by the Du Bois group (Stanford) and used without further purification. The Fe(*S*,*S*-PDP) catalyst was donated by the Sarpong group (UC Berkeley) and used without further purification. The Fe(*R*,*R*-CF_3-PDP) catalyst was donated by the White group (UIUC) and used without further purification. Dimethyldioxirane (DMDO),[49] 2,6-difluorophenyl sulfamate,[36] sulfonyl azide **200**,[50] hypervalent iodine reagent **201**,[51] and *N*-chloroamide **203**[42] were prepared according to known procedures. *p*-Benzoquinone was recrystallized from petroleum ether prior to use. Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E.

Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. 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 in terms of chemical shift relative to residual $CHCl_3$ (δ 7.26 and δ 77.16 ppm, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on KBr plates, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using a 100 mm path-length cell.

4.6.2 PREPARATIVE PROCEDURES

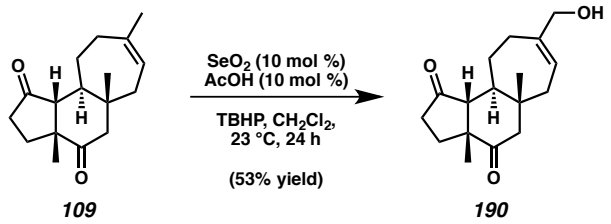
4.6.2.1 ALLYLIC C–H OXIDATION OF 109 BY SELENIUM DIOXIDE



109 *189*

Tricyclic Enal 189. A solution of selenium dioxide (5.5 mg, 50 μmol, 1.00 equiv) in 25:1 ethanol/water (1.0 mL) was added dropwise to a solution of tricyclic diketone **109** (13.0 mg, 49.9 μmol, 1.00 equiv) in absolute ethanol (2.5 mL), and the resulting mixture was heated to reflux (95 °C). After 24 hours, the reaction was allowed to cool to 23 °C and extracted with diethyl ether (2 x 5 mL). The combined organic extracts were washed with water (10 mL) and dried over sodium sulfate. Filtration followed by concentration in vacuo afforded the crude residue, which was purified by silica gel column chromatography (10% → 20% → 40% → 60% ethyl acetate in hexanes), furnishing enal **189** as a colorless oil (5.7 mg, 42% yield). R*f* = 0.25 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.39 (s, 1H), 6.67 (dddd, *J* = 8.8, 5.0, 2.5, 1.4 Hz, 1H), 3.02 (ddt, *J* = 15.4, 6.6, 1.6 Hz, 1H), 2.78 (d, *J* = 14.5 Hz, 1H), 2.62–2.53 (m, 2H), 2.45–2.37 (m, 1H), 2.36–2.30 (m, 1H), 2.27 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.20 (ddt, *J* = 15.4, 6.6, 1.6 Hz, 1H), 2.15 (d, *J* = 14.4 Hz, 1H), 1.96–1.78 (m, 4H), 1.12 (s, 3H), 1.09–1.00 (m, 1H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 217.1, 211.6, 193.0, 150.9, 148.2, 62.7, 52.4, 51.1, 47.5, 43.3, 40.4, 34.4, 31.5, 23.9, 22.5, 21.7, 17.6; IR (Neat Film, KBr) 2927, 1732,

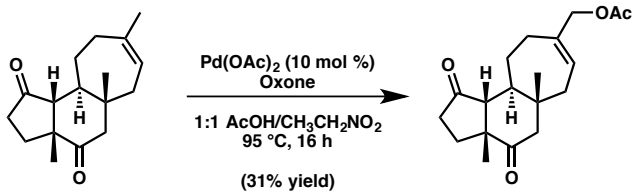
1704, 1682, 1456, 1384, 1262, 1178, 1155, 915, 732 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{22}O_3$ $[M\bullet]^+$: 274.1569, found 274.1558; $[\alpha]^{25}_D$ –71.5 (*c* 0.57, $CHCl_3$).



Allylic Alcohol 190. A round-bottom flask was charged with selenium dioxide (0.3 mg, 2.5 μmol, 0.10 equiv), *tert*-butyl hydroperoxide (5.5 M solution in decane, 12 μmol, 6.3 μmol, 2.50 equiv), and acetic acid (1 drop), and the resulting mixture was diluted with dichloromethane (0.50 mL) and stirred at 23 °C. After 30 minutes, a solution of tricyclic diketone **109** (6.6 mg, 25.3 μmol, 1.00 equiv) in dichloromethane (1.5 mL) was added, and stirring was continued over the next 24 hours. After this time, the reaction mixture was filtered over Celite, and the filtrate was concentrated. The resulting residue was diluted with diethyl ether (5 mL) and washed with 10% aq. potassium hydroxide solution (5 mL), water (5 mL), and brine (5 mL). The organic layer was separated and dried over sodium sulfate before filtration and concentration. The crude residue was purified by silica gel column chromatography (10% → 20% → 35% → 40% → 50% ethyl acetate in hexanes), affording allylic alcohol **190** as a colorless oil (7.0 mg, 53% yield). R*f* = 0.16 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.61 (t, *J* = 6.7, 13.6, 1H), 4.04 (s, 2H), 2.68 (d, *J* = 14.7 Hz, 1H), 2.59–2.51 (m, 1H), 2.42–2.30 (m, 3H), 2.17–2.04 (m, 3H), 2.06 (d, *J* = 14.7 Hz, 1H), 1.92–1.82 (m, 3H), 1.81–1.74 (m, 1H), 1.17–1.11 (m, 1H), 1.11 (s, 3H), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.8,

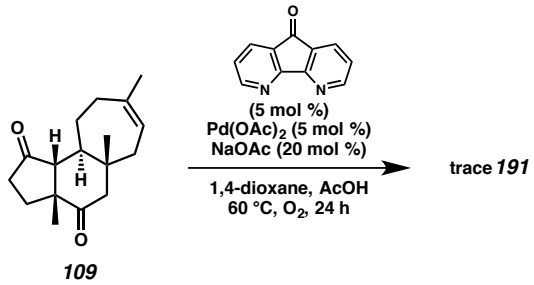
212.5, 145.4, 121.9, 67.5, 63.1, 52.5, 51.0, 47.8, 42.0, 40.0, 34.4, 31.4, 28.7, 24.6, 21.8, 17.3; IR (Neat Film, KBr) 3446 (br), 2925, 2853, 1733, 1704, 1456, 1384, 1178, 1149, 1024, 732 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{24}O_3$ $[M\bullet]^+$: 276.1726, found 276.1716; $[\alpha]^{25}_D$ –68.0 (*c* 0.31, $CHCl_3$).

4.6.2.2 PALLADIUM-CATALYZED ALLYLIC C–H ACETOXYLATION

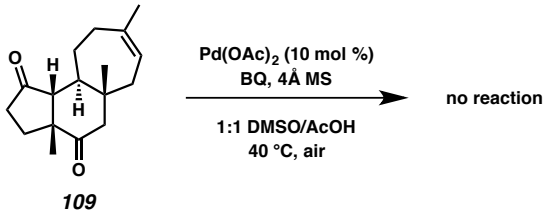


Allylic Acetate 191. A flame-dried 1-dram vial was charged with tricyclic diketone **109** (10.0 mg, 38.1 μmol, 1.00 equiv), palladium(II) acetate (0.9 mg, 3.8 μmol, 0.10 equiv), and Oxone (13 mg, 42 μmol, 1.10 equiv), and the resulting mixture was diluted with 1:1 acetic acid/nitroethane (0.30 mL total). The vial was sealed with a Teflon-lined cap and heated to 95 °C. After 24 hours, heating was discontinued, and the reaction mixture was quenched with aq. sodium bicarbonate (1.0 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The resulting crude residue was purified by silica gel column chromatography (10% → 30% ethyl acetate in hexanes), delivering allylic acetate **191** as a colorless oil (3.9 mg, 31% yield). R*f* = 0.14 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (dd, *J* = 8.8, 5.3 Hz, 1H), 4.47 (s, 2H), 2.68 (d, *J* = 14.6 Hz, 1H), 2.60–2.50 (m, 1H), 2.40–2.29 (m, 3H), 2.16–2.12 (m, 2H), 2.10–2.05 (m, 1H), 2.07

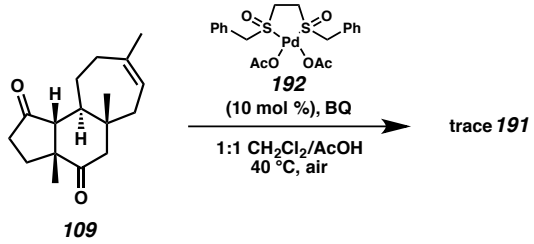
(s, 3H), 2.04–2.01 (m, 1H), 1.92–1.77 (m, 4H), 1.11 (s, 4H), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.8, 212.3, 171.1, 140.6, 125.8, 68.8, 63.0, 52.5, 51.0, 47.8, 42.0, 39.9, 34.4, 31.4, 28.8, 24.4, 21.8, 21.2, 17.3; IR (Neat Film, KBr) 2919, 2850, 1736, 1703, 1458, 1384, 1227, 1025, 959 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{26}O_4$ $[M\bullet]^+$: 318.1831, found 318.1823; $[\alpha]^{25}_D$ –58.2 (*c* 0.25, $CHCl_3$).



Unsuccessful Procedure 1. A flame-dried round-bottom flask was charged with tricycle **109** (10.0 mg, 38.1 μmol, 1.00 equiv), sodium acetate (0.6 mg, 7.7 μmol, 0.20 equiv), palladium(II) acetate (0.4 mg, 1.9 μmol, 0.050 equiv), and 4,5-diazafluorenone (0.4 mg, 1.9 μmol, 0.050 equiv). This mixture was diluted with 1,4-dioxane (0.70 mL) and acetic acid (0.20 mL), and oxygen gas (balloon) was bubbled through the resulting solution for 10 minutes. The reaction mixture was then heated to 60 °C while being stirred vigorously. After 24 hours, heating was discontinued, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes), returning predominantly unreacted **109** (9.1 mg, 91% recovery).

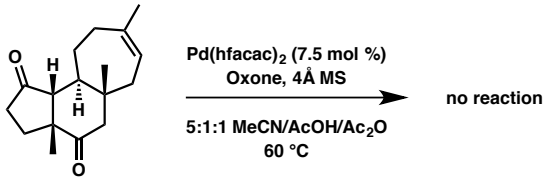


Unsuccessful Procedure 2. A flame-dried 1-dram vial was charged with palladium(II) acetate (0.3 mg, 1.46 μmol, 0.10 equiv), *p*-benzoquinone (3.2 mg, 29.2 μmol, 2.00 equiv), and activated 4Å molecular sieves (10 mg). To this mixture was added a solution of tricyclic diketone **109** (3.8 mg, 14.6 μmol, 1.00 equiv) in DMSO (1.0 mL). Acetic acid (1.0 mL) was added, and the vial was sealed with a Teflon-lined cap and heated to 40 °C. After 24 hours, heating was discontinued, and the reaction mixture was quenched with aq. saturated ammonium chloride (2.0 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 10 mL) and dried over magnesium sulfate. After filtration and concentration, the crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes), returning predominantly unreacted **109** (3.5 mg, 92% recovery).



Unsuccessful Procedure 3. A flame-dried 1-dram vial was charged with palladium catalyst **192** (0.7 mg, 1.46 μmol, 0.10 equiv) and *p*-benzoquinone (3.2 mg, 29.2 μmol, 2.00 equiv), and activated 4Å molecular sieves (10 mg). To this mixture was added a solution of tricyclic diketone **109** (3.8 mg, 14.6 μmol, 1.00 equiv) in dichloromethane

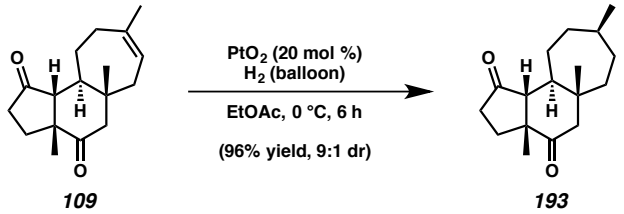
(1.0 mL). Acetic acid (1.0 mL) was added, and the vial was sealed with a Teflon-lined cap and heated to 40 °C. After 24 hours, heating was discontinued, and the reaction mixture was quenched with aq. saturated ammonium chloride (2.0 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with water (2 x 10 mL) and dried over magnesium sulfate. After filtration and concentration, the crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes), returning predominantly unreacted **109** (3.4 mg, 90% recovery).



109

Unsuccessful Procedure 4. A flame-dried 1-dram vial was charged with tricyclic diketone **109** (7.3 mg, 28.0 μmol, 1.00 equiv), palladium(II) hexafluoroacetylacetonate (1.1 mg, 2.10 μmol, 0.075 equiv), and Oxone (21.5 mg, 70.1 μmol, 2.50 equiv). Activated 4Å molecular sieves (20 mg) were added, and the reaction vessel was evacuated and backfilled with argon twice before addition of acetonitrile (0.50 mL) and 1:1 acetic acid/acetic anhydride (0.20 mL) which had been pre-dried over 4Å molecular sieves. The vial was sealed with a Teflon-lined cap, and the reaction mixture was stirred at 23 °C for 5 minutes before heating to 60 °C. After 8 hours, the reaction was removed from heat and filtered over a pad a silica gel, eluting with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes), returning predominantly unreacted **109** (6.9 mg, 95% recovery).

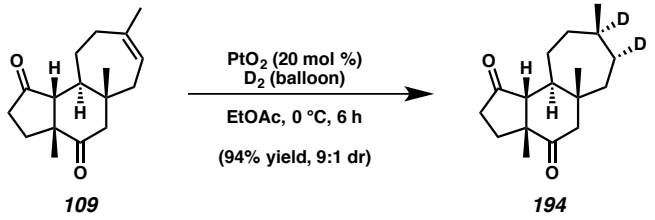
4.6.2.3 HYDROGENATION AND DEUTERATION OF TRICYCLE 109



109 *193*

Saturated Tricycle 193. To a solution of tricyclic diketone **109** (15.0 mg, 57.6 μmol, 1.00 equiv) in ethyl acetate (10 mL) was added platinum dioxide (2.6 mg, 11.4 μmol, 0.20 equiv), and the resulting suspension was cooled in an ice/water bath. A hydrogen balloon connected to a three-way adapter was fitted to the flask, and the headspace was evacuated for 3 minutes (~400 Torr) and backfilled with hydrogen gas. This process was repeated twice more, after which the reaction mixture was allowed to stir at 0 °C under hydrogen atmosphere. Within a few minutes, the color of the reaction mixture changed from brown to black. After 6 hours, the solvent was removed in vacuo, and the resulting residue was passed through a pad of silica gel, eluting with 20% ethyl acetate in hexanes (150 mL). Concentration of the filtrate afforded saturated tricycle **193** as a colorless oil which required no further purification (14.5 mg, 96% yield). Crystals for X-ray diffraction were grown using slow evaporation of trace amounts of dichloromethane and d_3-chloroform at –20 °C over a 5-month period. R*f* = 0.43 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (d, *J* = 15.2 Hz, 1H), 2.55–2.44 (m, 1H), 2.43–2.21 (m, 2H), 2.05 (d, *J* = 14.8 Hz, 1H), 1.90 (d, *J* = 12.6, Hz, 1H), 1.86–1.73 (m, 2H), 1.55–1.48 (m, 2H), 1.47–1.38 (m, 3H), 1.38–1.21 (m, 4H), 1.11 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.2, 213.1,

62.3, 52.8, 51.0, 45.0, 42.0, 41.8, 34.4, 34.3, 31.5, 31.1, 29.3, 23.4, 21.8, 21.4, 19.1; IR (Neat Film, KBr) 2952, 2919, 1737, 1705, 1458, 1384, 1172, 1124, 1052 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{27}O_2$ $[M+H]^+$: 263.2011, found 263.2020; $[\alpha]^{25}_D$ –61.3 (*c* 0.31, $CHCl_3$).

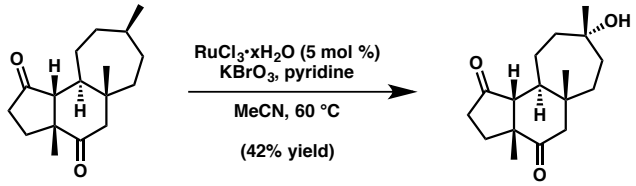


109 ***194***

Deuterated Tricycle 194. To a solution of tricyclic diketone **109** (11.7 mg, 44.9 μmol, 1.00 equiv) in ethyl acetate (8.0 mL) was added platinum dioxide (2.1 mg, 9.2 μmol, 0.20 equiv), and the resulting suspension was cooled in an ice/water bath. A deuterium balloon connected to a three-way adapter was fitted to the flask, and the headspace was evacuated for 3 minutes (~400 Torr) and backfilled with deuterium gas. This process was repeated twice more, after which the reaction mixture was allowed to stir at 0 °C under deuterium atmosphere. Within a few minutes, the color of the reaction mixture changed from brown to black. After 6 hours, the solvent was removed in vacuo, and the resulting residue was passed through a pad of silica gel, eluting with 20% ethyl acetate in hexanes (150 mL). Concentration of the filtrate afforded deuterated tricycle **194** as a colorless oil which required no further purification (11.2 mg, 94% yield). R*f* = 0.43 (25% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (d, *J* = 14.8 Hz, 1H), 2.55–2.47 (m, 1H), 2.40–2.31 (m, 1H), 2.31–2.24 (m, 1H), 2.04 (d, *J* = 14.7 Hz, 1H), 1.89 (d, *J* = 12.5 Hz 1H), 1.87–1.82 (m, 1H), 1.77–1.71 (m, 1H), 1.64 (ddd, *J* = 12.5, 9.8, 1.5 Hz, 1H), 1.56–1.51 (m, 1H), 1.43–1.36 (m, 3H), 1.32–1.28 (m, 1H), 1.25

(m, 1H), 1.10 (s, 3H), 0.90–0.85 (m, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.2, 213.1, 62.3, 52.8, 51.0, 45.0, 41.9, 41.8, 34.3, 34.2, 31.1, 30.8, 28.8 (t, J = 18.2, 36.5 Hz), 23.3, 21.8, 21.4, 19.0; IR (Neat Film, KBr) 2953, 2924, 1736, 1702, 1458, 1384, 1173, 1144, 1052, 804 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{24}O_2{}^2H_2$ $[M\bullet]^+$: 264.2058, found 264.2047; $[\alpha]^{25}_D$ –77.7 (*c* 1.12, $CHCl_3$).

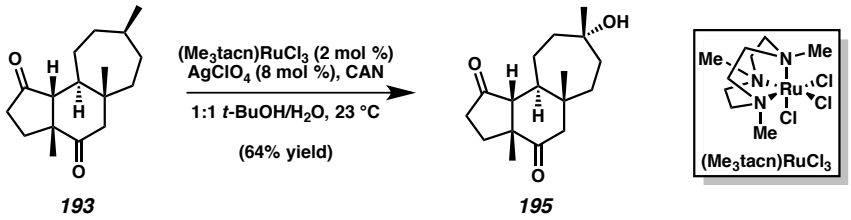
4.6.2.4 TERTIARY C–H HYDROXYLATION OF SATURATED TRICYCLE 193



193 *195*

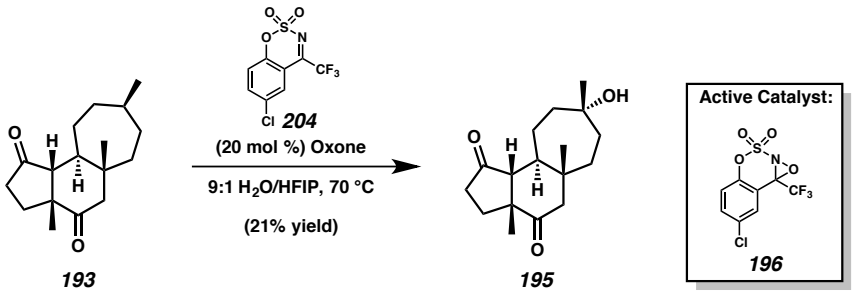
Tertiary C–H Hydroxylation Catalyzed by $RuCl_3$•xH_2O. A 1-dram vial was charged with ruthenium(III) trichloride hydrate (1.0 mg, 0.95 μmol, 0.05 equiv) and potassium bromate (9.6 mg, 57.3 μmol, 3.00 equiv), and water (0.2 mL) and pyridine (0.20 μL, 1.91 μmol, 0.10 equiv) were added sequentially. A solution of tricyclic diketone **193** (5.0 mg, 19.1 μmol, 1.00 equiv) was added, and the vial was sealed with a Teflon-lined cap and heated to 60 °C with vigorous stirring. After 24 hours, heating was discontinued, and the reaction mixture was quenched with saturated aq. sodium sulfite solution (1.0 mL), diluted with water (1.0 mL), and extracted with ethyl acetate (3 x 5 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (10% → 40% → 50% ethyl acetate in hexanes), furnishing tertiary alcohol **195** as a white amorphous solid

(2.2 mg, 42% yield). R*f* = 0.15 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.63 (d, *J* = 15.0 Hz, 1H), 2.59–2.45 (m, 1H), 2.42–2.32 (m, 1H), 2.26 (dt, *J* = 13.3, 10.3 Hz, 1H), 2.08 (d, *J* = 15.1 Hz, 1H), 1.96–1.85 (m, 3H), 1.80–1.71 (m, 3H), 1.71–1.63 (m, 2H), 1.53 (s, 1H), 1.24 (s, 3H), 1.13 (s, 3H), 1.11–1.04 (m, 1H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.2, 212.6, 73.8, 61.5, 52.7, 51.0, 46.9, 42.9, 40.9, 37.1, 36.2, 34.3, 31.2, 31.0, 21.8, 21.2, 19.0; IR (Neat Film, KBr) 3417 (br), 2958, 2925, 2853, 1738, 1704, 1463, 1384, 1261, 1126, 1052, 803 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{24}O_2$ [M–H_2O]: 260.1776, found 260.1769; $[\alpha]^{25}_{D}$ –9.5 (*c* 0.28, $CHCl_3$).

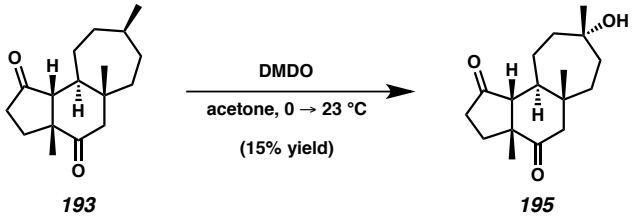


Tertiary C–H Hydroxylation Catalyzed by (Me_3tacn)$RuCl_3$. A 1-dram vial was charged with (1,4,7-trimethyl-1,4,7-triazacyclononane)ruthenium(III) trichloride (0.2 mg, 0.63 μmol, 0.020 equiv), silver perchlorate (0.5 mg, 2.50 μmol, 0.080 equiv), and water (0.5 mL). The vial was sealed with a Teflon-lined cap and heated to 80 °C with vigorous stirring for 5 minutes. The reaction mixture was then allowed to cool to 23 °C, and a solution of saturated tricycle **193** (8.2 mg, 31.2 μmol, 1.00 equiv) in *tert*-butanol (0.50 mL) was added, followed by ceric(IV) ammonium nitrate (51.4 mg, 93.7 μmol, 3.00 equiv). The resulting mixture suspension was stirred at 23 °C for 25 minutes, at which time a second portion of ceric(IV) ammonium nitrate (51.4 mg, 93.7 μmol, 3.00 equiv) was added. After 24 hours, the reaction was quenched with methanol (2 mL), diluted

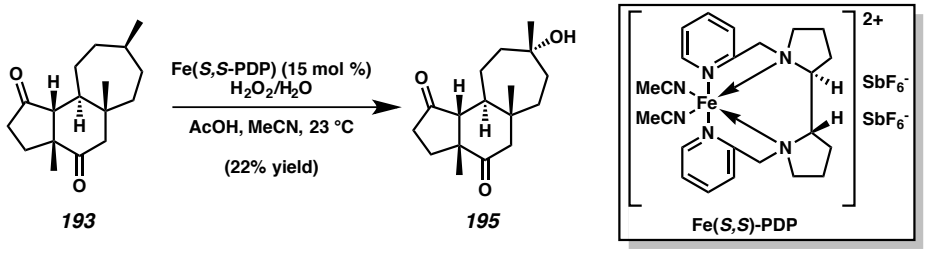
with water (5 mL), and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (10% → 40% → 50% ethyl acetate in hexanes), furnishing tertiary alcohol **195** as a white amorphous solid (5.6 mg, 64% yield).



Tertiary C–H Hydroxylation Catalyzed by Benzoxaziridine 196. A 1-dram vial was charged with saturated tricycle **193** (10.0 mg, 38.1 μmol, 1.00 equiv), benzoxathiazine **204** (2.2 mg, 7.62 μmol, 0.20 equiv), and Oxone (29.3 mg, 95.3 μmol, 2.50 equiv), and this mixture was diluted with 9:1 water/hexafluoroisopropanol (1.0 mL total volume). The vial was sealed with a Teflon-lined cap and heated to 70 °C with vigorous stirring, forming the active catalyst **196** in situ. After 24 hours, the reaction was allowed to cool to 23 °C, diluted with water (5 mL), and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (10% → 20% → 50% → 80% ethyl acetate in hexanes), affording tertiary alcohol **195** as a white amorphous solid (2.2 mg, 21% yield).

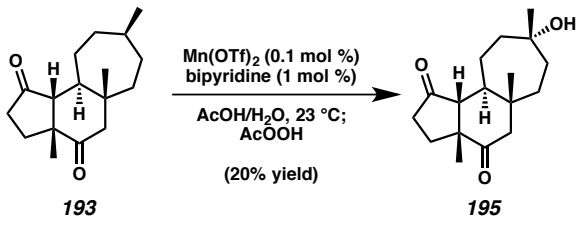


Tertiary C–H Hydroxylation Mediated by DMDO. A solution of dimethyldioxirane in acetone (0.0125 M, 24.4 mL, 0.305 mmol, 8.00 equiv) was added slowly to a solution of saturated tricycle **193** (10.0 mg, 38.1 μmol, 1.00 equiv) in acetone at 0 °C. The resulting mixture was stirred at this temperature for 6 hours before being allowed to gradually warm to 23 °C over 2 hours. After 16 hours at this temperature, the volatiles were removed under reduced pressure, and the crude residue was purified by silica gel column chromatography (10% → 20% → 50% → 80% ethyl acetate in hexanes), affording tertiary alcohol **195** as a white amorphous solid (1.6 mg, 15% yield).



Tertiary C–H Hydroxylation Catalyzed by Fe(*S*,*S*-PDP). To a solution of tricyclic diketone **193** (10.0 mg, 38.1 μmol, 1.00 equiv) and Fe(*S*,*S*-PDP) (1.8 mg, 1.91 μmol, 0.050 equiv) in acetonitrile (1.0 mL) was added acetic acid (1 drop). In a separate vial, a solution of hydrogen peroxide (50 wt % solution in water, 3.0 μL, 45.7 μmol, 1.20 equiv) was diluted with acetonitrile (0.30 mL). This solution was added dropwise very slowly to the solution of **193** and Fe catalyst while stirring. After 10 minutes had elapsed, another solution of Fe(*S*,*S*-PDP) (1.8 mg) in acetonitrile (0.30 mL) was added to the reaction

mixture, followed by acetic acid (1 drop) and dropwise addition of another portion of hydrogen peroxide (3.0 μL) in acetonitrile (0.30 mL). After 10 minutes, this process was repeated once more. Ten minutes after the final addition (total reaction time of 30 minutes), the volatiles were removed in vacuo, and the residue was diluted with diethyl ether (3 mL) and filtered through a pad of silica gel. The filtrate was dried over magnesium sulfate, filtered, and concentrated in vacuo, and the crude residue was purified by silica gel column chromatography (20% → 40% → 60% → 80% ethyl acetate in hexanes) to furnish tertiary alcohol **195** as an amorphous white solid (2.3 mg, 22% yield).



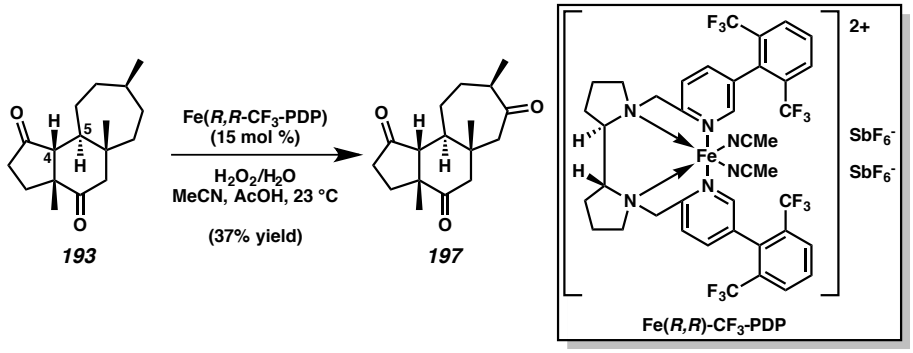
193 ***195***

Tertiary C–H Hydroxylation Catalyzed by $Mn(OTf)_2$. Stock solutions were prepared as follows: manganese(II) triflate (4.4 mg) was dissolved in 9:1 acetic acid/water (1.0 mL) to afford a 0.0125 M solution. 2,2-bipyridine (3.9 mg) was dissolved in acetic acid (1.0 mL) to generate a 0.025 M solution. Commercial peracetic acid was modified by adding 10% aq. potassium hydroxide solution (0.30 mL) to a 35 wt % solution of peracetic acid in acetic acid (1.0 mL).

To a solution of tricyclic diketone **193** (7.0 mg, 26.7 μmol, 1.00 equiv) in acetic acid (0.13 mL) and water (5.3 μL) were added sequentially solutions of manganese(II) triflate (2.1 μL) and 2,2-bipyridine (10.7 μL). The resulting mixture was stirred for 10 minutes,

and then a solution of modified peracetic acid (23.5 μL) was added very slowly in a dropwise fashion. After 90 seconds, the reaction mixture was diluted with acetone (2.7 mL) and stirred for an additional 30 seconds before filtration through a small pad of Celite, rinsing with acetone (5 mL). The filtrate was concentrated under reduced pressure, and the resulting crude residue was purified by silica gel column chromatography (10% → 20% → 50% → 80% ethyl acetate in hexanes) to afford tertiary alcohol **195** as a white amorphous solid (1.5 mg, 20% yield).

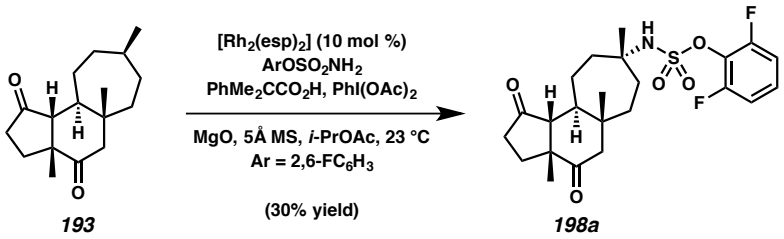
4.6.2.5 SECONDARY C–H OXIDATION OF SATURATED TRICYCLE 193



Triketone 197. To a solution of tricyclic diketone **193** (10.0 mg, 38.1 μmol, 1.00 equiv) and Fe(*R*,*R*-CF_3-PDP) (2.6 mg, 1.91 μmol, 0.050 equiv) in acetonitrile (1.0 mL) was added acetic acid (1 drop). In a separate vial, a solution of hydrogen peroxide (50 wt % solution in water, 3.0 μL, 45.7 μmol, 1.20 equiv) was diluted with acetonitrile (0.30 mL). This solution was added dropwise very slowly to the solution of **193** and Fe catalyst while stirring. After 10 minutes had elapsed, another solution of Fe(*R*,*R*-CF_3-PDP) (2.6 mg) in acetonitrile (0.30 mL) was added to the reaction mixture, followed by

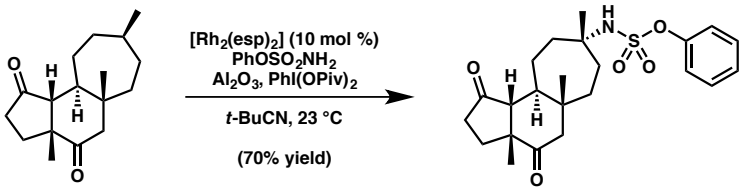
acetic acid (1 drop) and dropwise addition of another portion of hydrogen peroxide (3.0 μL) in acetonitrile (0.30 mL). After 10 minutes, this process was repeated once more. Ten minutes after the final addition (total reaction time of 30 minutes), the volatiles were removed in vacuo, and the residue was diluted with ethyl acetate (3 mL) and filtered through a pad of silica gel. After concentration of the filtrate, the crude residue was purified by silica gel column chromatography (20% → 30% → 50% → 80% ethyl acetate in hexanes) to furnish major product triketone **197** as a colorless oil (3.9 mg, 37% yield). R*f* = 0.40 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (d, *J* = 14.2 Hz, 1H), 2.60–2.46 (m, 4H), 2.44–2.36 (m, 1H), 2.27 (m, 1H), 2.12 (d, *J* = 14.7 Hz, 1H), 2.04–1.97 (m, 1H), 1.94 (m, 1H), 1.83–1.75 (m, 2H), 1.62–1.58 (m, 1H), 1.53–1.48 (m, 1H), 1.47–1.41 (m, 1H), 1.15 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.0, 214.6, 211.8, 61.0, 52.2, 51.2, 47.2, 42.6, 41.4, 40.7, 39.3, 34.4, 31.2, 26.8, 21.9, 18.1, 18.1; IR (Neat Film, KBr) 2960, 2927, 1738 (overlapping peaks), 1704, 1456, 1384, 1261, 1172, 1108, 802 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$: 277.1804, found 277.1819; $[\alpha]^{25}_D$ –6.9 (*c* 0.39, $CHCl_3$). Tertiary alcohol **195** was also isolated (2.1 mg, 20% yield).

4.6.2.6 TERTIARY C–H AMINATION OF SATURATED TRICYCLE 193



Sulfamate Ester 198a. A 1-dram vial was charged with 5Å molecular sieves (30 mg) and magnesium oxide (2.9 mg, 71.6 μmol, 4.00 equiv) and flame dried under vacuum. Upon cooling, the reaction vessel was charged with 2,6-difluorophenyl sulfamate (4.9 mg, 23.3 μmol, 1.30 equiv), 2-phenylisobutyric acid (1.5 mg, 8.95 μmol, 0.50 equiv), and $Rh_2(esp)_2$ (0.2 mg, 0.18μmol, 0.010 equiv), followed by a solution of tricyclic diketone **193** (4.7 mg, 17.9 μmol, 1.00 equiv) in isopropyl acetate (1.0 mL). The resulting green mixture was stirred for 5 minutes before the addition of (diacetoxyiodo)benzene (11.5 mg, 35.8 μmol, 2.00 equiv). The vial was then sealed with a Teflon-lined cap and stirred at 23 °C. After 20 hours, the mixture was filtered through Celite and rinsed with ethyl acetate (15 mL). Concentration of the filtrate and purification of the crude residue by silica gel column chromatography (2% methanol in dichloromethane) afforded pure sulfamate ester **198a** as a colorless oil (2.5 mg, 30% yield). R_f = 0.18 (2% methanol in dichloromethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (td, *J* = 6.1, 3.1 Hz, 1H), 7.02–6.99 (m, 2H), 4.72 (s, 1H), 2.64 (d, *J* = 15.1 Hz, 1H), 2.58–2.48 (m, 1H), 2.45–2.35 (m, 1H), 2.31–2.25 (m, 1H), 2.20–2.13 (m, 2H), 2.10 (d, *J* = 15.2 Hz, 1H), 2.03–1.98 (m, 1H), 1.91 (d, *J* = 12.8 Hz, 1H), 1.81–1.71 (m, 5H), 1.50 (s, 3H), 1.37–1.33 (m, 1H), 1.15 (s, 3H), 1.12 (m, 1H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 101

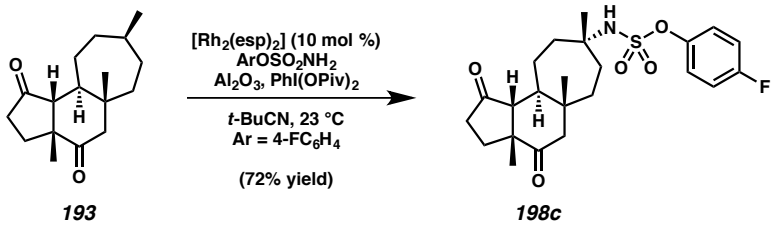
MHz) δ 218.1, 212.3, 156.2 (dd, *J* = 253.2, 4.0 Hz) 130.0 (d, *J* = 29.5 Hz), 127.5 (t, *J* = 18.5, 9.1 Hz), 112.7 (m), 62.1, 61.1, 52.4, 51.0, 46.9, 41.2, 40.7. 36.7, 34.3, 33.5, 31.0, 28.0, 21.8, 20.3, 19.0; ^{19}F NMR ($CDCl_3$, 300 MHz) δ –124.0; IR (Neat Film, KBr) 3261 (br), 2957, 2933, 1737, 1704, 1605, 1497, 1480, 1384, 1300, 1208, 1178, 1012, 861, 745, 734 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{30}NO_5F_2S$ $[M+H]^+$: 470.1813, found 470.1828; $[\alpha]^{25}_D$ –36.4 (*c* 0.23, $CHCl_3$).



193 ***198b***

Sulfamate Ester 198b. A 1-dram vial was charged with aluminum oxide (15.5 mg, 0.152 mmol, 4.00 equiv, Brockmann grade 1, neutral) and flame dried under vacuum. Upon cooling, the reaction vessel was charged with tricyclic diketone **193** (10.0 mg, 38.1 μmol, 1.00 equiv), $Rh_2(esp)_2$ (3.0 mg, 3.81 μmol, 0.10 equiv), and phenyl sulfamate (8.6 mg, 49.5 μmol, 1.30 equiv). The mixture was diluted with pivalonitrile (1.0 mL) and stirred at room temperature. After five minutes, the green reaction mixture had turned navy blue, and di-(pivaloyloxy)iodobenzene (23.2 mg, 57.2 μmol, 1.5 equiv) was added in a single portion. The reaction was stirred at 23 °C for 24 hours, developing a grayish hue during that time. The mixture was filtered through Celite and rinsed with ethyl acetate (15 mL). The filtrate was concentrated, and the crude residue was purified by column chromatography (5% → 15% → 50% ethyl acetate in hexanes) to furnish pure sulfamate ester **198b** as a colorless oil (11.6 mg, 70% yield). R*f* = 0.22 (33% ethyl

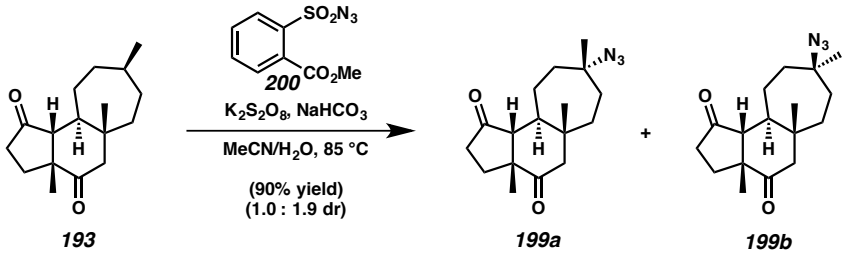
acetate in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.37 (m, 2H), 7.30–7.27 (m, 3H), 4.67 (s, 1H), 2.59 (d, *J* = 15.1 Hz, 1H), 2.54–2.45 (m, 1H), 2.42–2.32 (m, 1H), 2.28–2.20 (m, 1H), 2.11–2.04 (m, 3H), 2.00–1.94 (m, 1H), 1.87 (d, *J* = 8.0 Hz, 1H), 1.79–1.75 (m, 1H), 1.74–1.71 (m, 1H), 1.70–1.64 (m, 4H), 1.45 (s, 3H), 1.31–1.29 (m, 1H), 1.13 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.1, 212.2, 150.4, 129.9, 126.9, 121.8, 61.4, 61.1, 52.5, 51.0, 47.0, 41.4, 40.7, 36.7, 34.3, 33.7, 31.0, 28.3, 21.8, 20.3, 18.9; IR (Neat Film, KBr) 3285 (br), 2958, 2927, 2254, 1736, 1702, 1588, 1488, 1459, 1376, 1194, 1171, 1150, 1054, 913, 859, 782, 731, 691, 647 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{32}NO_5S$ $[M+H]^+$: 434.2001, found 434.1999; $[\alpha]^{25}_D$ –33.5 (*c* 1.16, $CHCl_3$).



Sulfamate Ester 198c. A 1-dram vial was charged with aluminum oxide (15.5 mg, 0.152 mmol, 4.00 equiv, Brockmann grade 1, neutral) and flame dried under vacuum. Upon cooling, the reaction vessel was charged with tricyclic diketone **193** (10.0 mg, 38.1 μmol, 1.00 equiv), $Rh_2(esp)_2$ (3.0 mg, 3.81 μmol, 0.10 equiv), and 4-fluorophenyl sulfamate (9.5 mg, 49.5 μmol, 1.30 equiv). The mixture was diluted with pivalonitrile (1.0 mL) and stirred at room temperature. After five minutes, the green reaction mixture had turned navy blue, and di-(pivaloyloxy)iodobenzene (23.2 mg, 57.2 μmol, 1.50 equiv) was added in a single portion. The reaction was stirred at 23 °C for 24 hours, developing a grayish hue during that time. The mixture was filtered through Celite and rinsed with ethyl acetate (15 mL). The filtrate was concentrated, and the crude residue was purified

by column chromatography (10% → 20% → 25% ethyl acetate in hexanes) to furnish pure sulfamate ester **198c** as a colorless oil (12.4 mg, 72% yield). R*f* = 0.20 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.37 (m, 2H), 7.30–7.27 (m, 3H), 4.67 (s, 1H), 2.59 (d, *J* = 15.1 Hz, 1H), 2.54–2.45 (m, 1H), 2.42–2.32 (m, 1H), 2.28–2.20 (m, 1H), 2.11–2.04 (m, 3H), 2.00–1.94 (m, 1H), 1.87 (d, *J* = 8.0 Hz, 1H), 1.79–1.75 (m, 1H), 1.74–1.71 (m, 1H), 1.70–1.64 (m, 4H), 1.45 (s, 3H), 1.31–1.29 (m, 1H), 1.13 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.1, 212.1, 161.0 (d, *J* = 246.3 Hz), 146.1 (d, *J* = 3.0 Hz), 123.6, (d, *J* = 8.8 Hz), 116.6 (d, *J* = 23.8 Hz), 61.6, 61.1, 52.4, 51.0, 47.0, 41.4, 40.7, 36.7, 34.3, 33.7, 31.0, 28.2, 21.8, 20.3, 18.9; ^{19}F NMR ($CDCl_3$, 300 MHz) δ –115.0; IR (Neat Film, KBr) 3286 (br), 2959, 2927, 1737, 1704, 1500, 1464, 1384, 1360, 1191, 1162, 1010, 987, 870, 849, 803, 736, 639 cm^{-1}; HRMS (ESI+) *m/z* calc'd for $C_{23}H_{31}NO_5FS$ $[M+H]^+$: 452.1907, found 452.1920; $[\alpha]^{25}_D$ –32.0 (*c* 1.24, $CHCl_3$).

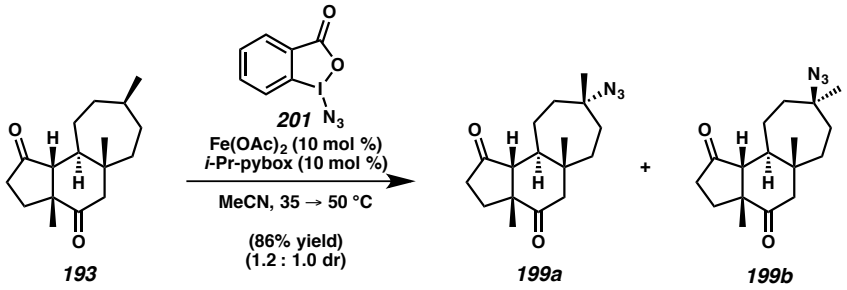
4.6.2.7 TERTIARY C–H AZIDATION OF SATURATED TRICYCLE 193



Tertiary C–H Azidation Mediated by Sulfonyl Azide 200. A flame-dried 1-dram vial was charged with sulfonyl azide **200** (10.6 mg, 44.0 μmol, 1.50 equiv), potassium

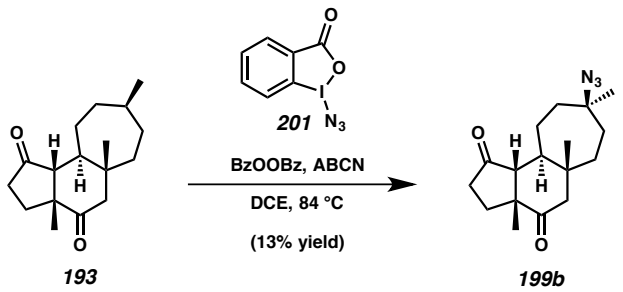
persulfate (23.8 mg, 88.0 μmol, 3.00 equiv), and sodium bicarbonate (2.5 mg, 29.3 μmol, 1.00 equiv). To this mixture was added water (0.4 mL) and a solution of tricyclic diketone **193** (11.2 mg, 42.5 μmol, 1.00 equiv) in acetonitrile (0.6 mL). The reaction vial was sealed with a Teflon-line cap and heated to 85 °C with vigorous stirring. After 24 hours, heating was discontinued, and the reaction mixture was diluted with ethyl acetate (3 mL) and water (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over magnesium sulfate, and the crude residue obtained after filtration and concentration was purified by silica gel column chromatography (10% → 15% → 40% ethyl acetate in hexanes) to afford diastereomers **199a** and **199b** as amorphous solids (4.1 mg **199a** and 7.6 mg **199b**, combined 11.7 mg, 90% yield). **Diastereomer 199a**: R*f* = 0.28 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.61 (d, *J* = 15.1 Hz, 1H), 2.55–2.47 (m, 1H), 2.42–2.33 (m, 1H), 2.30–2.22 (m, 1H), 2.08 (d, *J* = 15.1 Hz, 1H), 2.01–1.94 (m, 1H), 1.94–1.85 (m, 2H), 1.80–1.74 (m, 1H), 1.73–1.70 (m, 1H), 1.70–1.64 (m, 3H), 1.54 (m, 1H), 1.29 (s, 3H), 1.28–1.24 (m, 1H), 1.13 (s, 3H), 1.12–1.07 (m, 1H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.0, 212.2, 64.4, 61.3, 52.6, 51.0, 47.0, 40.8, 39.8, 37.2, 34.3, 33.2, 31.0, 27.2, 21.8, 20.7, 18.8; IR (Neat Film, KBr) 2960, 2923, 2097, 1732, 1704, 1464, 1384, 1260, 1142, 1108, 1052, 802, 641 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{25}O_2$ $[M–N_3]^+$: 261.1855, found 261.1860; $[\alpha]^{25}_D$ –59.5 (*c* 0.31, $CHCl_3$). **Diastereomer 199b**: R*f* = 0.13 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.64 (d, *J* = 15.2 Hz, 1H), 2.53–2.44 (m, 1H), 2.43–2.33 (m, 1H), 2.27–2.18 (m, 1H), 2.05 (d, *J* = 15.1 Hz, 1H), 1.97–1.84 (m, 3H), 1.80–1.73 (m, 1H), 1.73–1.64 (m, 3H), 1.64–1.60 (m, 1H), 1.41–1.34 (m, 2H), 1.32 (s, 3H), 1.28–1.23 (m, 1H), 1.14 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ

218.1, 212.6, 64.4, 60.7, 51.9, 51.1, 45.6, 40.9, 40.6, 36.3, 34.4, 33.0, 30.9, 28.4, 21.8, 20.6, 19.9; IR (Neat Film, KBr) 2959, 2928, 2101, 1736, 1703, 1458, 1384, 1259, 1147, 824 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{26}O_2N_3$ $[M+H]^+$: 304.2025, found 304.2027; $[\alpha]^{25}_D$ –16.6 (*c* 0.75, $CHCl_3$).



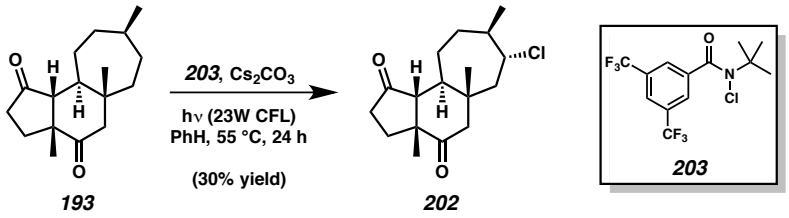
Tertiary C–H Azidation Catalyzed by Iron(II) Acetate. In a nitrogen-filled glovebox, iron(II) acetate (0.4 mg, 2.13 μmol, 0.10 equiv) and *i*-Pr-pybox ligand (0.6 mg, 2.13 μmol, 0.10 equiv) were combined in a flame-dried 1-dram vial and diluted with acetonitrile (0.5 mL) and stirred for 40 minutes at 23 °C, generating a blue solution. After this time, a solution of tricyclic diketone **193** (5.6 mg, 21.3 μmol, 1.00 equiv) was added, followed by hypervalent iodine reagent **201** (12.3 mg, 42.7 μmol, 2.00 equiv). The vial was sealed with a Teflon-lined cap, and the orange mixture was stirred at 35 °C for 4 hours, after which time the temperature was increased to 50 °C. After 20 hours at this temperature, the reaction vial was removed from the glovebox and diluted with diethyl ether (3 mL) and filtered through a pad of basic alumina, rinsing the filter cake with diethyl ether. The filtrate was concentrated, and the crude residue was purified by silica gel column chromatography (10% → 20% → 30% ethyl acetate in hexanes),

furnishing diastereomers **199a** and **199b** as amorphous solids (3.1 mg **199a** and 2.5 mg **199b**, combined 5.6 mg, 86% yield).



Tertiary C–H Azidation Mediated by Benzoyl Peroxide. In a nitrogen-filled glovebox, benzoyl peroxide (0.5 mg, 2.21 μmol, 0.10 equiv) and 1,1'-azobis(cyclohexanecarbonitrile) (0.3 mg, 1.11 μmol, 0.05 equiv) were combined in a flame-dried 1-dram vial and diluted with 1,2-dichloroethane (0.5 mL). A solution of tricyclic diketone **193** (5.8 mg, 22.1 μmol, 1.00 equiv) in 1,2-dichloroethane (0.6 mL) was added, followed by hypervalent iodine reagent **201** (12.8 mg, 44.2 μmol, 2.00 equiv), and the vial was sealed with a Teflon-lined cap and heated to 84 °C. After 24 hours, the reaction vial was removed from the glovebox, and the reaction mixture was filtered through a pad a basic alumina, rinsing with diethyl ether, and the filtrate was concentrated. The resulting crude residue was purified by silica gel column chromatography (10% → 15% → 40% ethyl acetate in hexanes), delivering tricyclic azide **199b** as an amorphous solid (0.9 mg, 13% yield).

4.6.2.8 SECONDARY C–H CHLORINATION OF TRICYCLE 193



Tricyclic Chloride 202. In a flame-dried 1-dram vial, tricyclic diketone **193** (5.0 mg, 19.1 μmol, 1.00 equiv) was diluted with dry benzene (0.50 mL) and concentrated under reduced pressure. This azeotropic drying procedure was repeated twice more before drying under high vacuum (0.65 Torr) for 10 minutes. The vial was wrapped with foil and brought into a nitrogen-filled glovebox, and a solution of *N*-chloroamide **203** (6.6 mg, 19.1 μmol, 1.00 equiv) in benzene (0.30 mL) was added, followed by cesium carbonate (6.2 mg, 19.1 μmol, 1.00 equiv). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and heated to 55 °C in heating block after removing the foil from the reaction vial (note: fume hood lights turned off). Once this temperature had been reached, the reaction vial was irradiated with two 23W CFL bulbs positioned 5 cm from either side of the heating block. After 24 hours, the reaction was removed from heat and immediately diluted with dichloromethane (2 mL) and filtered over a plug of silica gel, rinsing with dichloromethane. Concentration of the filtrate and purification of the crude residue by silica gel column chromatography (7% → 10% → 20% ethyl acetate in hexanes) afforded chlorinated tricycle **202** as a colorless oil (1.7 mg, 30% yield). R*f* = 0.25 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.84 (t, *J* = 9.5, 19.1 Hz, 1H), 2.67 (d, *J* = 15.1 Hz, 1H), 2.55–2.47 (m, 1H), 2.42–2.33 (m, 1H), 2.31–2.23 (m, 1H), 2.22–2.11 (m, 3H), 1.97–1.89 (m, 1H), 1.89–1.83 (m, 2H), 1.81–1.74 (m, 1H), 1.74–

1.62 (m, 3H), 1.15 (m, 1H), 1.14 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 217.9, 211.9, 63.9, 61.3, 52.7, 50.9, 50.8, 46.6, 41.3, 41.0, 34.3, 32.8, 31.1, 21.7, 21.3, 20.2, 18.5; IR (Neat Film, KBr) 3361, 3194, 2922, 2960, 2853, 1732, 1738, 1704, 1469, 1456, 1384, 1261, 1106, 1052, 1023, 800, 764, 705 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{25}ClO_2$ $[M\bullet]^+$: 296.1543, found 296.1550; $[\alpha]^{25}_D$ –24.6 (*c* 0.17, $CHCl_3$).

4.8 NOTES AND REFERENCES

(1) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154–162.

(2) For reviews on C–H functionalization in natural product synthesis, see: (a) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374; (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; (d) Chen, D. Y.-K.; Youn, S. W. *Chem.–Eur. J.* **2012**, *18*, 9452–9474; (e) Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. *Nat. Prod. Rep.* **2014**, *31*, 419–432; (f) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775–8806; (g) Qiu, Y.; Gao, S. *Nat. Prod. Rep.* **2016**, *33,* 562–581.

(3) (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369–375; (b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546–576.

(4) (a) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228; (b) Meyer, C.; Schepmann, D.; Yanagisawa, S.; Yamaguchi, J.; Itami, K.; Wünsch, B. *Eur. J. Org. Chem.* **2012**, *2012*, 5972–5979.

(5) Beydoun, K.; Zaarour, M.; Williams, J. A. G.; Doucet, H.; Guerchais, V. *Chem. Commun*. **2012**, *48*, 1260–1262.

(6) Dröge, T.; Notzon, A.; Fröhlich, R.; Glorius, F. *Chem.–Eur. J*. **2011**, *17*, 11974–11977.

(7) (a) Kondo, Y.; García-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. A. *J. Am. Chem. Soc*. **2002**, *124*, 1164–1165; (b) Jo, T. S.; Kim, S. H.; Shin, J.; Bae, C. *J. Am. Chem. Soc*. **2009**, *131*, 1656–1657.

(8) He, J.; Hamann, L. G.; Davies, H. M. L.; Beckwith, R. E. J. *Nat. Comms*. **2015**, *6*, 5943.

(9) Adams, A. M.; Du Bois, J.; Malik, H. A. *Org. Lett*. **2015**, *17*, 6066–6069.

(10) Michaudel, Q.; Journot, G.; Regueiro-Ren, A.; Goswami, A.; Guo, Z.; Tully, T. P.; Zou, L.; Ramabhadran, R. O.; Houk, K. N.; Baran, P. S. *Angew. Chem., Int. Ed*. **2014**, *53*, 12091–12096.

(11) For a report on the diversity-oriented synthesis of benzanilides via $C(sp^2)$–H oxidation, see: Sun, Y.-H.; Sun, T.-Y.; Wu, Y.-D.; Zhang, X.; Rao, Y. *Chem. Sci*. **2016**, *7*, 2229–2238.

(12) For a study of the biological properties of ingenol derivatives accessed via C(sp^3)–H oxidation see: Jin, Y.; Yeh, C.-H.; Kuttruff, C. A.; Jørgensen, L.; Dünstl, G.; Felding, J.; Natarajan, S. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14044–14048.

(13) (a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231; (b) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem.–Eur. J.* **2011**, *17*, 9957–9969; (c) Kim, K. E.; Stoltz, B. M. *Org. Lett.* **2016**, *18*, 5720–5723.

(14) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169; (b) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843–895.

(15) Fatta-Kassinos, D.; Vasquez, M. I.; Kümmerer, K. *Chemosphere* **2011**, *85*, 693–709.

(16) For leading references, see: (a) *Oxygenases and Model Systems* (Ed.: Funabiki, T.), Kluwer, Boston, **1997**; (b) Groves, J. T.; Quinn, R. *J. Am. Chem. Soc.* **1985**, *107*, 5790–5792; (c) Neumann, R.; Dahan, M. *Nature* **1997**, *388*, 353–355; (d) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289–10297.

(17) Sakuda, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3348–3349.

(18) (a) Ernet, T.; Haufe, G. *Synthesis* **1997**, *1997*, 953–956; (b) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.

(19) Młochowski, J.; Wójtowicz-Młochowska, H. *Molecules* **2015**, *20*, 10205–10243.

(20) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116–15119.

(21) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347.

(22) Xing, X.; O'Connor, N. R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 11186–11190.

(23) Efforts to effect Pd-catalyzed allylic C–H azidation using conditions developed by Jiang and co-workers proved unsuccessful, returning unreacted **109**. For the methodology report, see: Chen, H.; Yang, W.; Wu, W.; Jiang, H. *Org. Biomol. Chem.* **2014**, *12*, 3340–3343.

(24) Application of Ru-catalyzed conditions for C–H hydroxylation to **109** resulted in epoxidation of the olefin.

(25) Lowering the temperature below 0 °C did not yield further increases in dr.

(26) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202–10204.

(27) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810–1813.

(28) Adams, A. M.; Du Bois, J. *Chem. Sci.* **2014**, *5*, 656–659.

(29) For selected examples of dioxiranes as reagents for C–H hydroxylation, see: (a) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1–9; (b) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828. For a study of the molecular dynamics of DMDO C–H oxidation, see: Yang, Z.; Yu, P.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 4237–4242.

(30) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783–787.

(31) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052–14055.

(32) Salamone, M.; Ortega, V. B.; Bietti, M. *J. Org. Chem.* **2015**, *80*, 4710–4715.

(33) (a) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643–647; (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284–287.

(34) For an example, see: Grue-Sorensen, G.; Spenser, I. D. *J. Am. Chem. Soc.* **1983**, *105*, 7401–7404.

(35) (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968–9976; (b) Walsh, C. T. *Science* **2004**, *303*, 1805–1810.

(36) Roizen, J. L.; Zalatan, D. N.; Du Bois, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11343–11346.

(37) (a) Gaoni, Y. *J. Org. Chem.* **1994**, *59*, 6853–6855; (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

(38) Zhang, X.; Yang, H.; Tang, P. *Org. Lett.* **2015**, *17*, 5828–5831.

(39) Sharma, A.; Hartwig, J. F. *Nature* **2015**, *517*, 600–604.

(40) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991.

(41) Gribble, G. W. *Naturally Occurring Organohalogen Compounds: A Comprehensive Update*; Springer-Verlag: Weinheim Germany, **2010**.

(42) Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 696–702.

(43) Minisci, F.; Galli, R.; Galli, A.; Bernardi, R. *Tetrahedron Lett.* **1967**, *8*, 2207–2209.

(44) (a) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070; (b) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. *Science* **2011**, *332*, 448–451; (c) Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563; (d) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547–2550.

(45) Protocols for C–H fluorination yielded either irreproducible results or extremely low conversion of **193**.

(46) Indicated by mass-spectrometry.

(47) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826–839.

(48) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(49) Taber, D. F.; DeMatteo, P. W.; Hassan, R. A. *Org. Synth.* **2013**, *90*, 350–357.

(50) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.

(51) Vita, M. V.; Waser, J. *Org. Lett.* **2013**, *15*, 3246–3249.