SELECTIVE C—H OXIDATIONS FOR COMPLEX MOLECULE SYNTHESIS AND DIVERSIFICATION

BY

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DISSERTATION

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Research Advisor: M. Christina White *December 2013*

ABSTRACT

Synthetic chemists are continually challenged to develop more efficient and selective methods for the synthesis of both simple and complex molecules. Traditionally, starting materials for synthesis are derived from petroleum or other natural sources and have been pre-oxidized and pre-activated with reactive functional groups. These functional groups readily participate in a wide range of C—C and other bond forming processes, oxidations, and reductions, referred to as functional group manipulations. In contrast, the C—H bonds that make up the majority of organic frameworks are generally viewed as an inert scaffold upon which the chemistry of other functional groups takes place. Recently a novel strategy for synthesis has emerged that seeks to eliminate the requirement for pre-oxidation and carry out synthetic manipulations directly from a C—H bond, establishing it not simply as a bystander, but as a functional group in its own right. As a result, feedstock materials may be more rapidly transformed into final products. Nature has recognized the power of this approach and routinely oxidizes C—H bonds directly for the purpose of biosynthesis or metabolism. However, central to the application of C—H oxidation in the laboratory is the ability to not only break C—H bonds, but do so in a selective and predictable way. This work describes the development of novel C—H oxidation processes and strategies for their application to the synthesis and diversification of organic molecules.

First, harnessing the abundance and simplicity of α-olefins as starting materials, a Pd(II)/bis-sulfoxide catalyst is utilized to carry out a selective intramolecular allylic C—H oxidation to generate a versatile synthetic intermediate (1,4-dioxanones). In contrast to many C—H oxidations, which transform a simple starting material into a single value added product, dioxanones can diverge to form motifs prevalent in natural products (i.e. differentially protected 1,2-diols, polyoxidized motifs and syn-pyrans). This work represents a novel application of C—H oxidation to achieve synthetic versatility.

A highly selective intermolecular oxidative Heck vinylation is also described that forms di- and polyenes from simple α-olefins. Notably the Heck reaction requires only one pre-activated coupling partner. While traditional intermolecular Heck reactions are generally limited to resonance-activated olefins like styrenes, enol ethers and α,β-unsaturated carbonyls, Pd(II)/bis-sulfoxide catalysis enables a broad range of olefins to be vinylated in high yields and selectivities, expanding the applicability of this reaction in complex molecule synthesis.

Finally, aliphatic C—H oxidation of unactivated bonds is perhaps the most challenging C—H transformation because of the ubiquity and strength of these bonds. Our group reported a non-heme iron catalyst [Fe(PDP)], which demonstrated that aliphatic C—H bonds could be selectively oxidized in both simple and complex molecules in preparative yields. Central to this reactivity was the sensitivity of Fe(PDP) to the electronic, steric and stereoelectronic properties of the substrate that differentiate C—H bonds from one another. This work describes the development of a novel C—H oxidation catalyst [Fe(CF_3-PDP)] that is able to override these inherent substrate biases and access new sites of oxidation based on catalyst control. Furthermore, a predictive model was developed that quantitatively describes the site-selectivity of oxidation as a function of catalyst. The combination of catalyst-controlled reactivity and

quantitative predictability should allow unprecedented application of aliphatic C—H oxidation to the synthesis, diversification, and study of metabolism of organic structures.

ACKNOWLEDGEMENTS

I would like to thank Prof. M. Christina White for pushing me to my fullest potential and never letting me settle for anything except the best. I still vividly recall the decision process and choosing to come to Illinois. I didn't particularly want to move half way across the country to what was the middle of nowhere to me, but I felt Christina's passion for discovering exciting chemistry that pushes the boundaries and her support made it the right place for me to achieve my goals and grow as a scientist and person. I could list off a hundred amazing experiences I had in Christina's lab from getting a crystal of a new catalyst to a western themed poster photo shoot, but it's for her mentorship during challenges that I'm most grateful. At the time, working on an NIH grant, editing a manuscript, battling with reviewers and editors, or discussing my future plans was sometimes difficult and divisive, but I also learned a lot about how to handle challenges and what's important to me.

I would also like to thank Prof. Gary Molander for his mentorship and giving me the opportunity to discover my passion for organic chemistry in the laboratory. It was in the Molander group that I had my first taste of "real" organic chemistry and what working in a top research group is like. I use the skills I learned in the Molander group daily and that foundation allowed me to be prepared for and take on challenges in grad school.

I'm grateful to my thesis committee (Profs. Denmark, van der Donk and Rauchfuss) whose advice and constructive criticism has challenged me consistently over the course of my studies from seminar to prelim to ORP and I've been bettered by each of those experiences.

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come to Illinois was also the opportunity to work with great people and the members of the White group were not only an amazing support system and wealth of knowledge, but also great people. I would I like to thank: Prof. Jared Delcamp, Dr. Dustin Covell aka Darren Corpel, Dr. Erik Stang, Dr. Sean Reed, Dr. Andrew (Roo) Young, Dr. Grant Rice, Dr. Marinus Bigi, Dr. Mark Chen, Tommy (Tom Tom) Osberger, Greg (G-Snake) Snapper, Stephen (Stefan Erkel) Ammann, Shauna Paradine, Iulia (The Qlaw) Strambeneau, Dr. Jennifer Howell, Dr. Don Rogness, Dr. Chao Jiang, Dr. Tobias Thaler and Jinpeng (Jay-Z) Zhao. Their friendship made lab an awesome place to be, even at 1am. I know I'm going to miss glassware sacrifices, "Friday" music, karaoke, occasionally out of hand group parties, heated sports and music discussions, Pizza Hut feasts, song parodies involving lunchmeat theft, the information superhighway, and sweet sweet rootbeer barrels.

I would also like to thank those responsible for running and maintaining the amazing facilities at Illinois. Dr. Vera Mainz, Dr. Dean Olsen and Dr. Linyang Zhu in particular have taught me an immense amount about NMR and enabled all of the research in this thesis. Dr. Danielle Gray obtained X-ray crystal structures for catalyst (*R,R*)-**45**, which was critical for understanding the trajectory restriction strategy for catalyst control, and compounds (+)-**79** and (+)-**84b** in this thesis. Furong Sun and Dr. Haijun Yao obtained the critical high-resolution mass spectrometry data for compound identification and Chuck Wallbaum, Mike Hallock and Dr. Taras Pogorelov provided invaluable assistance with the hardware and software required for the computational studies presented herein. I was also fortunate to have the skills of Don O'Brien, Rich Parrish and Dave Perry nearby to keep glassware in working condition as well as make any contraptions I needed.

The generosity of several outside groups and funding sources also made this research possible. Aldrich Chemical Co., Strem and TCI are thanked for generous gifts of commercial bis-sulfoxide/$Pd(OAc)_2$ (**1**) and Johnson-Matthey for donation of $Pd(OAc)_2$. Dr. Andreas Pfaltz and Dr. Andreas Schumacher are acknowledged for donation of the iridium hydrogenation catalyst used to produce (+)-**84** and Starbucks Corporation for coffe grounds used to obtain the precursor to (-)-**79**. Funding for this research was provided by NIH/NIGMS (GM07615), NIH/NIGMS (2R01 GM076153B), Bristol-Myers Squibb, Boehringer Ingelheim, Amgen, Firmenich and the University of Illinois. I would like to thank the NSF Graduate Research Fellowship program and the University of Illinois/Abbott Laboratories Synthetic Organic Fellowship for supporting me financially.

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My parents have supported me through every step in my life and given me every possible opportunity to succeed. I cannot even begin to express my gratitude. They instilled important lessons in me like evaluating options and making a smart choice, working hard and not accepting a poorly done job, and doing the right thing and taking responsibility. They celebrated with me when things were great and reminded me that family is always there during the challenging times. I think everyday about how fortunate I am to have them as parents.

Finally, my fiancé, Jill, has been there through the best and toughest times in grad school. She's supported me through long working hours and all the uncertainty of a job search so that I could pursue my passion. Although our lives are changing dramatically over the next year, I

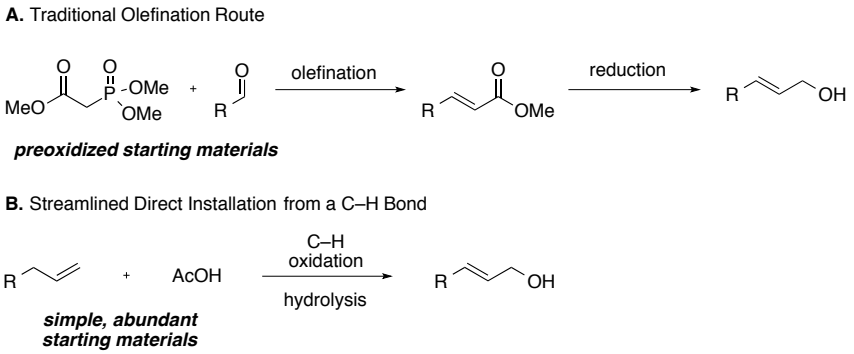
can’t wait to get started in a new place together and there’s not a better person in the world to be beside for it.

TABLE OF CONTENTS

CHAPTER 1: SYNTHETIC VERSATILITY IN C—H OXIDATION

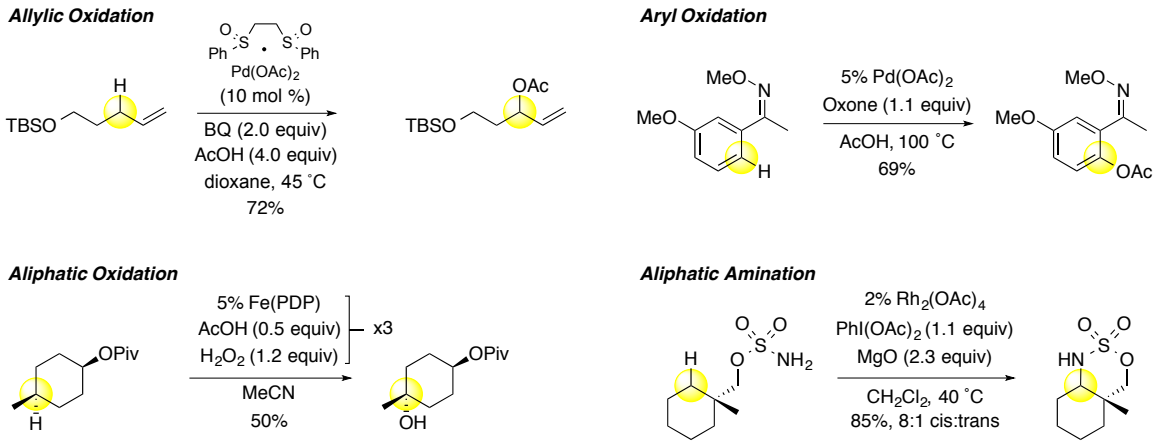
1.1 Introduction

Figure 1. Traditional C–C Bond Formation versus C–H Oxidation



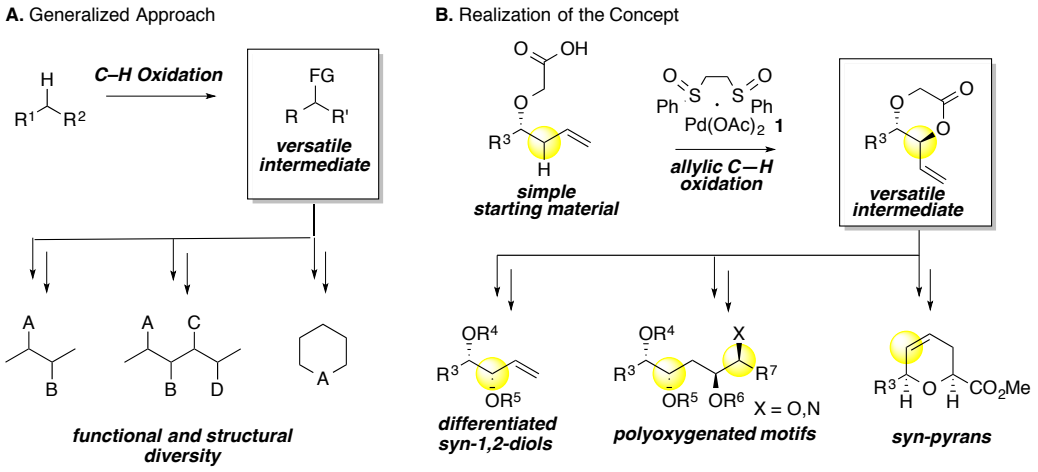
Because of their inertness to most chemical reagents, chemists typically view C—H bonds as inert bystanders, while chemistry is carried out on reactive functional groups. For example, an allylic alcohol could be synthesized from two reactive, pre-oxidized starting materials (an aldehyde and phosphonate) via a Horner-Wadsworth-Emmons olefination. This C—C bond forming reaction can be followed by a functional group manipulation (FGM) to reduce the ester to the desired allylic alcohol (Figure 1A). In contrast, the ability to directly utilize C—H bonds for functionalization provides several advantages. First, simpler starting materials can be used

Figure 2. Some State-of-the-Art C–H Oxidations



without the requirement for pre-activation of both coupling partners. Furthermore, by avoiding FGMs, synthetic sequences can be streamlined, reducing the synthetic effort required to synthesize complex molecules (Figure 1B).[1,2] Our group has successfully applied Pd(II)/bis-sulfoxide catalyst **1** to a wide variety of allylic C—H oxidation reactions including oxidations,[3] aminations,[4] alkylations[5] and dehydrogenations.[6] The ability to use simple and abundant α-olefins as well as mild reaction conditions allowed these reactions to streamline synthesis in a broad range of molecules. Our group and others have also made substantial advances in the C—H functionalization of aryl,[7] and even aliphatic C—H bonds (Figure 2).[8] These studies have firmly established the C—H bond as a viable functional group and opened many new avenues for novel synthetic disconnects.

Figure 3. Synthetic Versatility in C–H Oxidation



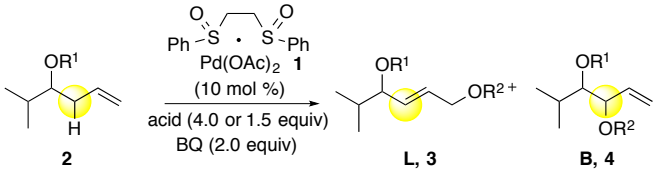
A common feature of these C—H functionalization reactions is the ability to take a simple starting material and in one step access an oxidized, value added product. While this strategy has been broadly successful, I questioned if a novel strategy would allow greater versatility from a common starting material. For example, a C—H oxidation reaction could be applied to a simple starting material to access not just a single product, but rather a versatile intermediate that could diverge to a variety of functionally and structurally diverse products (Figure 3).[9] After exploring

several approaches, 1,4-dioxanones proved to be an ideal target for such a transformation because the oxygens could be differentiated to form orthogonally protected 1,2-diols. Furthermore, the α–olefin could be utilized to iterate C—H oxidation processes to furnish polyoxidized chains. The dioxanone itself was also known to undergo Ireland-Claisen rearrangement to form pyrans.

1.2 Results and Discussion

1.2.1 Initial Studies

Table 1. Intermolecular Allilyc Oxidation for Diol Formation



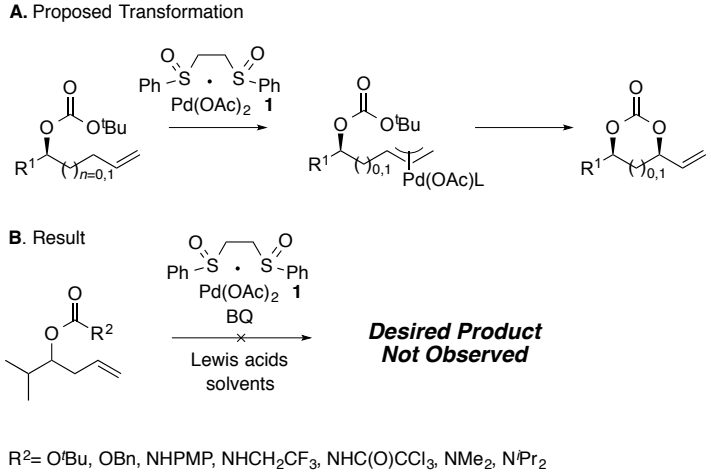
entry	R^1	R^{2a}	additive	isolated yield[b]	**L:B**[c]	*E:Z* (**L**)[d]	dr (**B**)[e]
1	CH_2CO_2Me	Ac	none	11	1:2	>20:1	16:1
2	CH_2CO_2Me	Ac	Cr(salen)Cl	10	>20:1	>20:1	N/A
3	CH_2CO_2Me	*p*-NO_2Bz	none	16	1:2	nd	>20:1
4	CH_2CO_2Me	*p*-NO_2Bz	Cr(salen)Cl	>5	nd	nd	nd
5	Bn (**5**)	*p*-NO_2Bz	none	>5	nd	nd	nd

[a]AcOH (4.0 equiv) or *p*-NO_2BzOH (1.5 equiv) used as the acid nucleophile. [b]Average of 2 runs at 0.5 mmol. [c]Linear(**L**):Branched(**B**) ratio determined by GC of the crude reaction after workup. [d]*E:Z* ratio determined by GC of the crude reaction after workup. [e]Diastereomeric ratio determined by GC of the crude reaction after workup. BQ = 1,4-*p*-benzoquinone, salen = 1,2-cyclohexanediamine-*N,N'*-bis(3,5-di-tert-butylsalicylidine).

One of the key reaction motifs we targeted within the larger goal of achieving synthetic versatility from C—H oxidation was the diol motif. The 1,2- and 1,3-diol oxidation pattern is prevalent in a wide variety of natural products as well as synthetic pharmaceuticals so developing a streamlined C—H oxidation method for their synthesis stood to have a significant impact. Perhaps the most straightforward approach was to simply apply our previously reported intermolecular branched allylic C—H oxidation to substrates containing homo- or bis-

homoallylic oxygenation to yield 1,2- or 1,3-diols. This approach proved insufficient for several reasons. First, homoallylic oxygenation led to very poor yields of products with a variety of acid nucleophiles, additives, and substrates (Table 1).[9] In addition to low yields, a preponderance of the linear regioisomer was formed as opposed to the desired branched diol product. I hypothesized that the proximal oxygen chelates to the palladium and occupies a requisite site for inner-sphere C—O bond formation forcing functionalization to an outer-sphere pathway. The large amount of linear product formed is consistent with an outer-sphere, non-benzoquinone (BQ) dependent process. Furthermore, while substrates with bis-homoallylic oxygenation retained high reactivity, diastereoselectivity was quite poor. In many cases, these diastereomers were very difficult to separate making the intermolecular approach less than ideal.

Figure 4. Carbonate Approach to 1,2- and 1,3-Diols



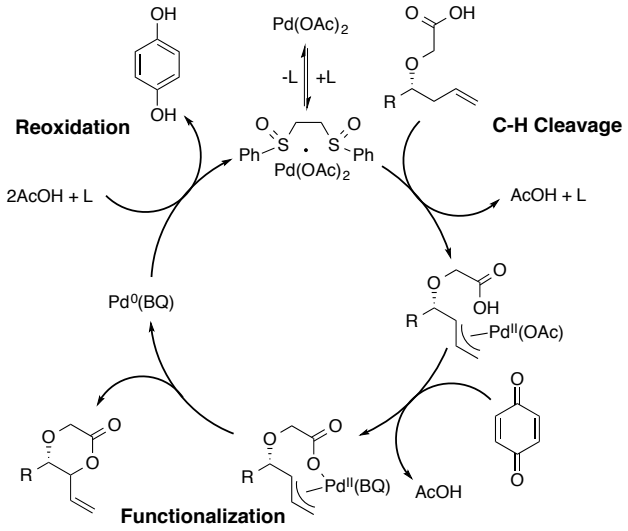
R^2= O^{t}Bu, OBn, NHPMP, $NHCH_2CF_3$, $NHC(O)CCl_3$, NMe_2, N^{i}Pr$_2$

The failure of intermolecular reactivity for diol formation suggested designing an intramolecular tether to both increase reactivity as well as provide improved diastereoselectivity. Inspired by iodolactonizations,[10] I considered that the π-allylPd could act as the electrophile in analogy to an iodonium ion and be susceptible to intramolecular nucleophilic attack by a carbonate (Figure 4). The resulting cyclic carbonate would be readily deprotected to a diol (although the formation of differentially protected diols would be sacrificed) and the α-olefin

could serve as a handle for iteration of this process. I synthesized both homo- and bis-homoallylic *t*-butyl carbonates and subjected these to a wide variety of C—H oxidation conditions with catalyst **1** including Lewis acid additives to increase the electrophilicity of the π-allylPd, solvents, temperatures, cation scavengers to promote loss of *t*-butyl cation, amounts of DMSO and various benzoquinones to promote functionalization. None of the desired product was observed in any case. I also synthesized a variety of carbamates hoping to increase the nucleophilicity of the tether and applied the same set of reaction conditions with no success. I considered that the neutral nature of the nucleophile was proving problematic and explored an alternate approach based on our knowledge of the reaction mechanism.

1.2.2 Design Plan and Reaction Optimization

Figure 5. Serial Ligand Catalysis

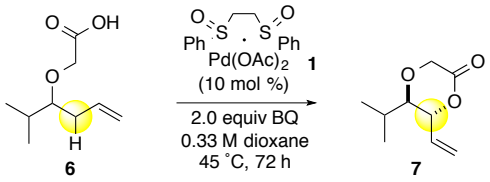


A tethered carboxylic acid, which can be readily accessed from an aldehyde via asymmetric allylation followed by alkylation with bromoacetic acid, provided an excellent starting point based on our knowledge of $Pd(OAc)_2$/bis-sulfoxide catalyzed allylic oxidations. Figure 5 depicts the proposed mechanism for these transformations termed serial ligand catalysis.[3b] The

electrophilic Pd(II)/bis-sulfoxide catalyst binds the unhindered terminal olefin and effects an allylic C—H cleavage. Computations[11] as well as the catalytic incompetence of the chloride counterion catalyst indicate that this likely proceeds via an intramolecular concerted metallation-deprotonation mechanism to form a π-allylPd intermediate and release AcOH. Next, the acidic nature (typical of the types of nucleophiles that have been successfully applied in these reactions) of the carboxylic acid becomes advantageous. The acidity of the acid allows it to be deprotonated under the reaction conditions by a small amount of endogenous acetate base. The resulting carboxylate, although typically poorly nucleophilic) can bind to the Pd(II) intermediate to form a chelated complex. This chelation is a major advantage for this starting material design because it can potentially improve reactivity as well as the diastereoselectivity of product formation. A second ligand exchange may now replace the bis-sulfoxide with BQ, which promotes inner-sphere C—O bond formation to release the dioxanone product. Pd(0) is then be reoxidized by BQ to reenter the catalytic cycle.

Starting from tethered acid **6**, I was pleased to observe 38% yield of the desired dioxanone product **7** with 9:1 diastereoselectivity favoring the *anti*-dioxanone under standard allylic C—H oxidation conditions with catalyst **1** (Table 2, entry 1). Addition of catalytic base had been shown to improve the reactivity of acidic amines in allylic C—H aminations.[4c] 10% DIPEA did modestly improve the yield of the reaction to 46% albeit with a slight diminishment in stereoselectivity (entry 2). However, 10% Cr(salen)Cl Lewis acid, known to increase the rate of functionalization in allylic C—H oxidations,[12] led to a large boost in yield to 83% with 9:1 anti:syn diastereoselectivity (entry 3). Notably, this reaction is operationally simple and run open to air with no precautions taken to exclude moisture. Furthermore, the reaction is amenable to scale up and a 10 mmol scale reaction proceeds with essentially no reduction in yield (80%).

Table 2. Reaction Optimization and Control Experiments



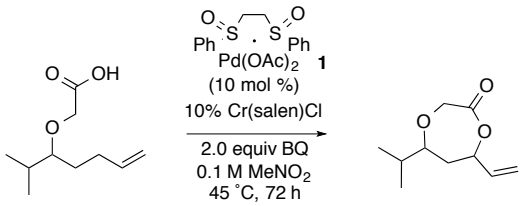
6 **7**

entry	change to standard conditions	isolated yield[a]	dr (anti:syn)[b]
1	none	38	9:1
2	10% DIPEA	46	7:1
3	10% Cr(salen)Cl	83 (80)[c]	9:1
4	10% Pd(OAc)2 instead of Pd(II)/bis-sulfoxide	>5	-
5	2.0 equiv 2,6-Me_2BQ instead of BQ	0	-
6	no Pd catalyst, 10% Cr(salen)Cl	0	-

[a]Average of 2 runs at 0.3 mmol. [b]Ratio determined by ^{1}H NMR. [c]Reaction run on a 10 mmol scale. DIPEA = diisopropylethyl amine.

The diastereomers are readily separated by column chromatography. I also tested for the operation of a serial ligand catalysis mechanism. Absence of bis-sulfoxide ligand resulted in <5% yield, indicating the bis-sulfoxide is required for C—H cleavage (entry 4). Substitution of BQ with 2,6-dimethylbenzoquinone (2,6-Me_2BQ) also led to no product formation because the added steric bulk of this ligand prevents it from effectively binding to the π-allylPd intermediate and promoting functionalization (entry 5). Finally, complete removal of palladium produces no product, indicating the necessity of Pd catalyst in the reaction (entry 6).

Figure 6. 1,3-Diol Precursor



8

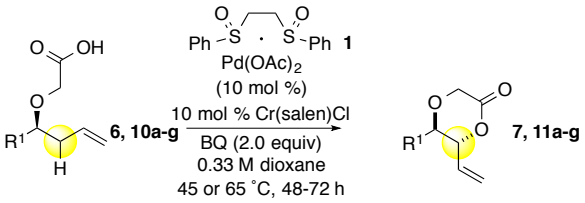
83% **9**
2:1 dr syn:anti

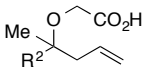
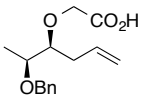
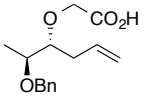
A slightly modified set of reaction conditions was also successful for the formation of a 7-membered 1,3-diol precursor (Figure 6).[13] While the reactivity of this process was quite high, the reaction suffered from moderate diastereoselectivities. Different substituents α–to the oxygen, in

particular bulky *t*-butyl, did not increase the dr, nor did variation of the Lewis acid additive or any combination of solvent and concentration. However, these diastereomers are quite readily separated by standard column chromatography techniques.

1.2.3 Reaction Scope and Chemoselectivity

Table 3. Scope of the Intramoleculer C–H Oxidation



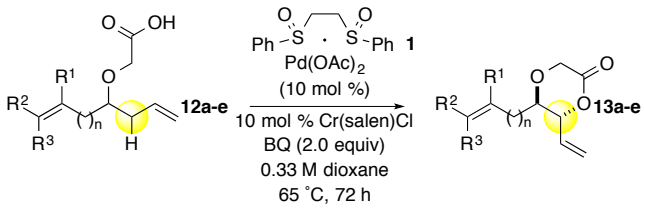
entry	R^1	product	isolated yield[a]	dr (anti:syn)[b]
1	*i*-Pr	(-)-**7**	83 (80)[c]	9:1[d]
2	4-BrPh	**11a**	57	3:1
3	*n*-Pent	**11b**	82	2:1
4	*t*-Bu	**11c**	22	11:1
5		**11d** R^2=Ph	57	3:1
6		**11e** R^2=*n*-Bu	60	3:1
7		(-)-**11f**	62	8:1
8		(+)-**11g**	62	4:1

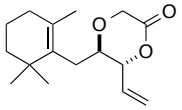
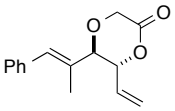
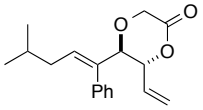
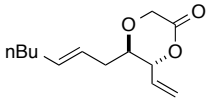
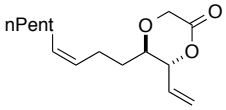
[a]Average of 2 runs at 0.3 mmol. [b]Diastereomeric ratio determined by GC of the crude reaction after workup. [c]Average of 2 runs at 10 mmol. [d]Diastereomeric ratio determined by ^{1}H NMR of the crude reaction after workup.

With optimized conditions in hand for 1,4-dioxanone formation from a simple starting material, I next turned to exploring the scope and functional group tolerance of the reaction (Table 3). Proximal aryl moieties are well tolerated (entry 2). Reactions with unbranched substrates proceeded in good yield, but diminished stereoselectivity (entry 3); whereas a substrate with a bulky quaternary alkyl substituent gave poor yields, but excellent diastereoselectivity (entry 4). Despite the apparent sensitivity to sterics, tertiary centers are well

tolerated (entries 5 and 6). Notably, competing methods for forming these diol products require setting the geometry of a tri-substituted olefin. Additionally, α-stereocenters influence the magnitude of the diastereoselectivity (entries 7 and 8), but the overall diastereomeric outcome of the reaction favoring the *anti*-dioxanone is relayed exclusively from the stereocenter bearing the carboxylic acid tether.

Table 4. Chemoselectivity of the Intramolecular C–H Oxidation



entry	product		isolated yield[a]	dr (anti:syn)[b]
1		**13a**	74	4:1
2		**13b**	77	6:1
3		**13c**	53	7:1
4		**13d**	72	3:1
5		**13e**	52	2:1

[a]Average of 2 runs at 0.3 mmol. [b]Diastereomeric ratio determined by GC of the crude reaction after workup.

I also explored the chemoselectivity of the reaction with a particular focus on orthogonality to other methods. While many methods for 1,2-diol formation exist, the Sharpless asymmetric dihydroxylation (SAD) is one of the most widely used owing to its operational simplicity, high selectivity and functional group tolerance. However, when multiple olefins are present in a

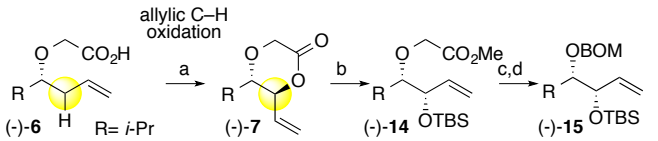
molecule, SAD generally selects for the more electron rich olefin with variable selectivity.[14] For example, SAD of a terminal diene generates a mixture of regioisomeric diols, which are undifferentiated. As a consequence, SAD is generally not used to install diols when multiple olefins are present, necessitating alternate, often lengthy routes and reducing overall synthetic efficiency. In contrast, allylic C—H oxidation to form dioxanones is completely selective for the α-olefin and a variety of other olefins including tetra-, tri-, *cis*-di- and *trans*-di-substituted are all well tolerated highlighting the orthogonal chemoselectivity of this allylic C—H oxidation reaction (Table 4).

1.2.4 Synthetic Versatility: Formation of Differentiated Diols, Polyoxidized Motifs and Pyrans

I next demonstrated the ability of *anti*-1,4-dioxan-2-ones to diverge into motifs of high synthetic value: differentiated *syn*-1,2-diols, polyoxidized chains and *syn*-pyrans. I first developed a streamlined route to chiral *syn*-1,2-diols from dioxanones (Figure 7). Differentiated diols are important in many synthetic sequences where one alcohol must be manipulated independently of the other but are often difficult to access. To achieve this goal, I needed to (1) establish that optically enriched dioxanones can be readily synthesized by allylic C—H oxidation and (2) develop a novel deprotection sequence for converting the chemically inequivalent acyl and ethereal C—O bonds in dioxanones into differentiated diols. The first step was readily accomplished from an aldehyde precursor. A wide variety of asymmetric allylations can be applied to form chiral, non-racemic homoallylic alcohols. In this case, Brown allylation afforded the alcohol in 82% yield and 91% ee which could be alkylated by bromoacetic acid to afford the requisite starting material (-)-**6**. The C—H oxidation reaction to form (-)-**7** proceeded in 83% yield and 9:1 dr anti:syn with no loss of enatioenrichement. Next, base promoted lactone opening

formed a hydroxy acid, which could be protected to afford α-alkoxy ester (-)-**14** in 89% yield. The ethereal C—O bond can now be cleaved under mild reducing conditions by SmI_2[15] to afford an alcohol, which may be protected as desired to afford (-)-**15**. In contrast to other olefin oxidation methods, like SAD, which directly affords unprotected *syn*-1,2-diols, allylic C—H oxidation affords a differentiated diol providing the opportunity for independent manipulation of the oxygens.

Figure 7. Access to Differentiated *syn*-1,2-Diols

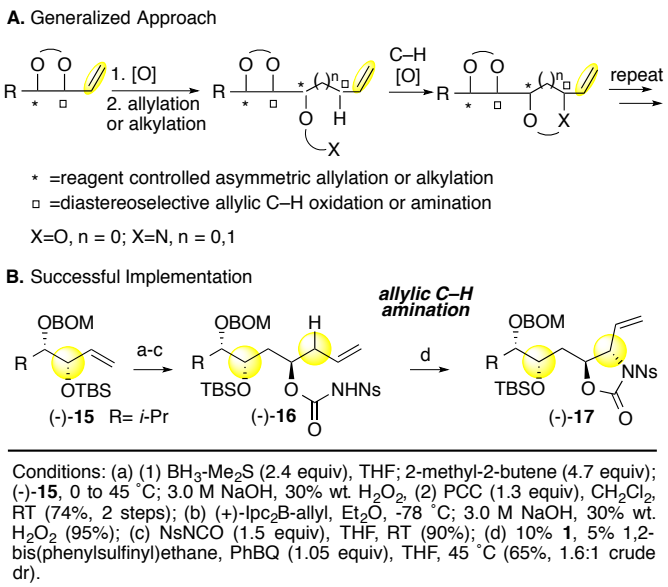


Conditions: (a) 10% 1, 10% Cr(salen)Cl, BQ (2.0 equiv), dioxane, 45 ˚C (72% of >20:1 *anti*-diastereomer; 83%, 9:1 crude dr); (b)(1) LiOH (2.0 equiv), 3:1 THF:H_2O, 0 ˚C, (2) TBSOTf (3.0 equiv), 2,6-lutidine (6.0 equiv), CH_2Cl_2, 0 ˚C, (3) MeI (3.0 equiv), K_2CO_3 (3.0 equiv, DMF, RT (89%, 3 steps); (c) SmI_2 (3.0 equiv), ethylene glycol (1.2 equiv), THF/HMPA, RT (61%, 12% rsm); (d) BOMCl (1.5 equiv), $^iPr_2NEt$ (1.75 equiv), CH_2Cl_2, 0 ˚C to RT (79%).

The α-olefin in (-)-**15** can also be utilized as a functional handle for iterating C—H oxidation processes for the purpose of synthesizing polyoxidized chains (Figure 8).[16] Hydroboration-oxidation of the olefin all the way to the aldehyde oxidation state, allows for reagent-controlled, diastereoselective allylation to form an intermediate homoallylic alcohol, which can be functionalized by nosyl isocyanate to yield carbamate (-)-**16**. From this intermediate, a masked *syn*-1,2-aiminoalcohol can be installed in good yield using Pd(II)/bis-sulfoxide **1** catalyzed allylic amination. Amino-polyols like (-)-**17**, which are generated in optically pure form via this sequence, are found in several classes of natural products, such as bengazole A (a potent antifungal agent) and AAL Toxin T_A.[17] Traditional approaches to these polyoxidized motifs often rely on chiral relay strategies, making the synthesis of multiple stereoisomeric compounds challenging. This sequence highlights the power of diastereoselective C—H oxidation and amination reactions, when used in combination with powerful reagent controlled alkylation

methodology, to facilitate the synthesis of a wide assortment of diastereomers with varied oxygen and nitrogen motifs.

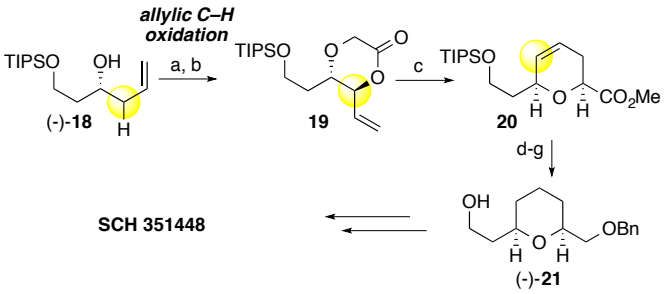
Figure 8. Iterative C–H Oxidation for the Synthesis of Polyoxidized Motifs



Conditions: (a) (1) BH_3-Me_2S (2.4 equiv), THF; 2-methyl-2-butene (4.7 equiv); (-)-**15**, 0 to 45 °C; 3.0 M NaOH, 30% wt. H_2O_2, (2) PCC (1.3 equiv), CH_2Cl_2, RT (74%, 2 steps); (b) (+)-Ipc_2B-allyl, Et_2O, -78 °C; 3.0 M NaOH, 30% wt. H_2O_2 (95%); (c) NsNCO (1.5 equiv), THF, RT (90%); (d) 10% **1**, 5% 1,2-bis(phenylsulfinyl)ethane, PhBQ (1.05 equiv), THF, 45 °C (65%, 1.6:1 crude dr).

Finally, *anti*-dioxanones can also be structurally diversified to form *syn*-pyrans[18] via Ireland-Claisen rearrangement.[19] I examined two case studies to highlight the utility and advantages of C—H oxidation for the synthesis of these motifs. First, this method can be used to form a bifunctional pyran of the type present in many natural products (Figure 9). Starting from a simple alcohol (-)-**18**, Brown allylation, alkylation with bromoacetic acid and intramolecular C—H oxidation affords the dioxanone **19** as a mixture of diastereomers. While these diastereomers could be separated, the difficulty of this separation led me to carry on the mixture. Enolization of the dioxanone with LiHMDS and trapping as the silyl ketene acetal sets up a [3,3] sigmatropic rearrangement. This transformation forms the dihydro pyran **20** with complete relay of the stereochemistry (i.e. 3:1 dr dioxanone to 3:1 dr pyran). Hydrogenation affords a tetrahydropyran, whose diastereomers are easily separated allowing isolation of the pure *syn*-diastereomer. Reduction of the ester and benzyl protection of the resulting alcohol followed by acidic TIPS

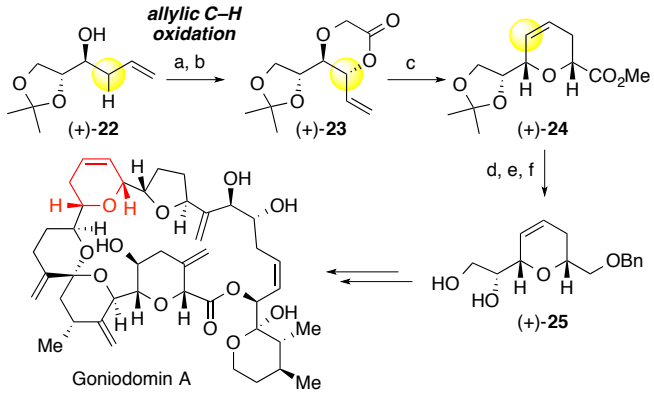
Figure 9. Synthesis of a Bifunctional Pyran



Conditions: (a) NaH (3.0 equiv), BrAcOH (1.1 equiv), THF/DMF 0 ˚C to RT (70%); (b) 10% **1**, 10% Cr(salen)Cl, BQ (2.0 equiv), dioxane, 65 ˚C (83%, 3:1 crude dr, mixture of diastereomers taken forward); (c) (1) LiHMDS (2.0 equiv), 1:1 v:v TMSCl:Et_3N, THF, -78 ˚C then reflux in toluene, (2) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), DMF, RT (83%); (d) 10% wt. of 5% Pd/C, H_2 (1 atm), EtOAc, RT (68% of >20:1 syn-diastereomer, 3:1 crude dr); (e) $LiAlH_4$ (2.0 equiv), THF, 0 ˚C; (f) BnBr (2.0 equiv), NaH (2.0 equiv), DMF, 0 ˚C to RT; (g) 3 M HCl, EtOH, RT (74%, 3 steps).

deprotection yields bifunctional pyran (-)-**21**. This intermediate was previously used in the synthesis of SCH351448.[20]

Figure 10. Synthesis of a Densely Functionalized Pyran



Conditions: (a) NaH (3.0 equiv), BrAcOH (1.1 equiv), THF/DMF 0 ˚C to RT (54%); (b) 10% 1, 10% Cr(salen)Cl, BQ (2.0 equiv), dioxane, 65 ˚C (56% of >20:1 dr anti-diastereomer; 73%, 3:1 crude dr); (c) (1) LiHMDS (2.0 equiv), 1:1 v:v TMSCl:Et_3N, THF, -78 ˚C then reflux in toluene, (2) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), DMF, RT (82%); (d) $LiAlH_4$ (2.0 equiv), THF, 0 ˚C; (e) BnBr (2.0 equiv), NaH (2.0 equiv), DMF, 0 ˚C to RT; (f) 1N HCl, THF, RT (60%, 3 steps).

This synthetic strategy can also be efficiently applied in the synthesis of densely functionalized pyrans (Figure 10). For example, homoallylic alcohol (+)-**22**, after alkylation and intramolecular C—H oxidation, affords 56% of highly oxygenated *anti*-dioxanone (+)-**23** as a single diastereomer. Ireland-Claisen rearrangement relays that stereochemistry to produce *syn*-dihydropyran (+)-**24**. Reduction of the ester and benzyl protection followed by acidic hydrolysis

of the acetonide yields diol (+)-**25**, which was used in the synthesis of goniodomin A. Notably, the C—H oxidation route requires only 7 steps compared to 10 for the previous sequence,[21] highlighting the power of C—H oxidation for streamlining synthetic sequences.

1.3 Conclusions

This work demonstrates the utility of allylic C—H oxidation to access synthetic versatility. Simple starting materials can be rapidly synthesized and transformed into a versatile intermedaiate, *anti*-1,4-dioxan-2-ones. These can then be used as a common starting point to access several motifs prevalent in medicinally interesting natural products. Notably, the C—H oxidation approach provides orthogonal or improved chemoselectivity and efficiency when compared to other state-of-the-art methods.

1.4 Experimental Section

General Information. All intramolecular allylic C—H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were run under an Ar or N_2 atmosphere with dry solvent in flame dried glassware unless otherwise noted. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), dimethylformamide (DMF) and 1,4-dioxane were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, CA). Diisopropylethylamine (DIPEA), triethylamine (TEA), 2,6-lutidine, pyridine and HMPA were distilled from calcium hydride. Commercially available reagents used as received are noted in the individual reaction procedures. 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **1** is available from multiple commercial sources

(Sigma-Aldrich, TCI, Strem) or can be conveniently prepared (see below). No differences in reactivity were observed when the catalyst source was varied.

Solvents were removed by rotary evaporation at ~30 ˚C and ~40 torr unless otherwise noted. Thin-layer chromatography (TLC) was performed with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and/or potassium permanganate and ceric ammonium molybdate staining. Flash chromatography was performed as described by Still et al.[22] using EM reagent silica gel 60 (230-400 mesh). $CDCl_3$ was stored over 4Å molecular sieves.

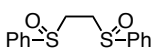
^1H NMR spectra were recorded on a Varian Inova 500NB (500 MHz), Varian Untiy 500 (500 MHz) or Varian VXR 500 (500 MHz) spectrometer and are reported in ppm (δ) using solvent ($CDCl_3$ at 7.26 ppm) as an internal standard unless otherwise noted. Data reported as: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, b=broad, app=apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on Varian Untiy 500 (125 MHz) or Varian VXR 500 (125 MHz) and are reported in ppm using solvent ($CDCl_3$, 77.0 ppm) as an internal standard unless otherwise noted. IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Achiral gas chromatographic (GC) analyses were performed on an Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30 m, 0.32 mm, 0.25 mm). Chiral GC analyses were preformed on an Agilent Technologies 5890A Series instrument equipped with an FID detector using a J&W Scientific β-cyclodextrin column (30m, 0.25 mm, 0.25 μm). Optical rotations were measured in a 1 mL cell with 50 mm path length or a 0.2 mL cell with a 10 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported

as follows: $[\alpha]_{\lambda}^{T^{\circ}C}$ (c=g/100 mL, solvent). Medium pressure liquid chromatography (MPLC) separations were performed on a Teledyne Isco CombiFlashRf system using 24 or 40g Redi Sep Rf Gold silica columns.

Preparation of Pd(II)/bis-sulfoxide Catalyst.

$Pd(OAc)_2$ Recrystallization. $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was dissolved in minimal refluxing benzene. A black precipitate was removed from the refluxing solution by Acrodisc® filtration. The resulting solution was cooled to room temperature without further manipulation. Amber crystals began to form after 15 min. After 2 hr the solution was filtered to give the recrystallized $Pd(OAc)_2$ as gold plates. The recrystallized $Pd(OAc)_2$ was stored for months under an Ar atmosphere with no deleterious effects. A difference in NMR purity was noted between "old" and recrystallized $Pd(OAc)_2$ samples. Reported hydrogen values are normalized ratios of the smallest peak in the acetate region. "Old" $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 1H), 2.10 (s, 3.6H), 2.07 (s, 6.1H), 2.06 (s, 6.1H), 2.03 (m, 15.3H), 2.00 (m, 95.7H), 1.97 (s, 5.7H), 1.95 (s, 6.3), 1.89 (s, 9.4H).

Recrystallized $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.03 (s, 2.8H), 2.00 (s, 40.1H), 1.97 (s, 1.2H), 1.90 (s, 2.3H).



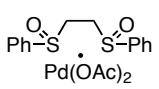
1,2-bis(phenylsulfinyl)ethane. No precautions were taken to exclude moisture or air. A 50 mL round bottom flask was charged with of 1,2-bis(phenylthio)ethane (2g, 8.12 mmol, 1.0 equiv, Oakwood Products Inc.) and glacial acetic acid (12.2 mL). A solution of H_2O_2 (Sigma-Aldrich, 50 wt%, 31.08 mmol, 2.1 mL, 2 equiv) in acetic acid (6.7 mL) was added dropwise at room temperature. After approximately 15 min the solution became homogeneous and turned a pale yellow. An additional 8 mL of acetic acid was then added and the solution allowed to stir

for 24 h at room temperature. The acetic acid was removed with mild heating (45°C) under high vacuum. The pale yellow solid was emulsified in cold ethanol and cold filtered to yield a mixture of the meso and racemic 1,2-bis(phenylsulfinyl)ethane in 92% yield (2.088g).

Recrystallization: To a solution of refluxing acetone (~100 ml) was added the crude ligand mixture (~2g). Acetone was then added slowly to the mixture with reflux until all the powder dissolved. Upon being completely dissolved the mixture was allowed to cool to room temperature. The solution was left at room temperature for an hour then cooled to 4°C over night. (IMPORTANT: The meso recrystallizes out first as small white clumps and extended time is needed to allow the racemic long white needles to crystallize out. The crystals were filtered off with a büchner funnel and rinsed with cold acetone. For all reactions and catalyst preparations performed during this study, only the *meso*-1,2-bis(phenylsulfinyl)ethane ligand was used.)

Meso-1,2-bis(phenylsulfinyl)ethane: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.52 (m, 10H), 3.05 (s, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.29, 131.55, 129.63, 124.10, 47.06. IR (neat) 3048.84, 2970.01, 2922.41, 1442.10, 1036.34, 745.45, 695.70 cm^{-1}

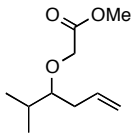
Racemic-1,2-bis(phenylsulfinyl)ethane: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 10H), 3.40 (m, 2H), 2.74 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.55, 131.53, 129.64, 124.08, 47.94. IR (neat, cm^{-1}) 3053.16, 2911.39, 1443.77, 1084.88, 1042.50, 748.52. HRMS (ESI) *m/z* calculated for $C_{14}H_{14}O_2S_2Na$ $[M+Na]^+$: 301.0333, found 301.0320.



1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (1). A flame dried 250 mL flask was charged with *meso*-1,2-bis(phenylsulfinyl)ethane (2.53 g, 9.1 mmol, 1.0 equiv), CH_2Cl_2 (101 mL, 0.09 M), and recrystallized $Pd(OAc)_2$ (2.04 g, 9.1 mmol, 1.0 equiv, see above). The mixture was stirred at 40°C for 24h. The reaction becomes a dark red

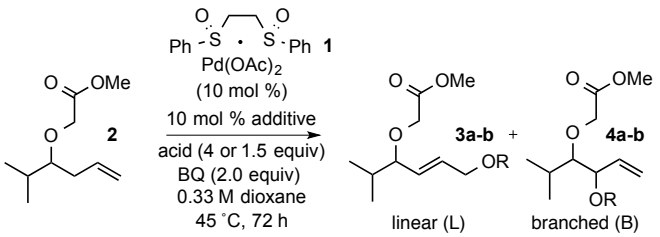
homogenous solution. The solution was concentrated *in vacuo* to incomplete dryness, and then fully dried under a stream of N_2 for 24 hours to give a dark red solid used without further purification. **Note: The catalyst must be stored at below 4 ˚C.** The catalyst very slowly decomposes at ambient temperature; however, it may be stored for prolonged periods (months) at reduced temperatures. ^{1}H NMR and IR data of this catalyst look like *meso*-1,2-bis(phenylsulfinyl)ethane ligand and $Pd(OAc)_2$.

Studies on the Intermolecular C—H Oxidation with Homoallylic Oxygen Substitution

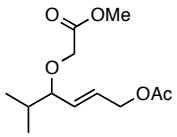


(±)-**Methyl 2-((2-methylhex-5-en-3-yl)oxy)acetate (2a).** No precautions were taken to exclude moisture or air. (±)-2-((2-methylhex-5-en-3-yl)oxy)acetic acid **6** (1.72 g, 10 mmol, 1.0 equiv) was dissolved in 20 mL DMF in a 100 mL round bottom flask. Powdered K_2CO_3 (4.15 g, 30 mmol, 3.0 equiv) and MeI (1.0 mL, 4.26 g, 30 mmol, 3.0 equiv) were added and the reaction stirred at RT for 5 hrs. 20 mL water and 20 mL EtOAc were added and the two layers separated. The aqueous layer was extracted with EtOAc (1x20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (~250 mL) eluting with 5% EtOAc in hexane afforded the title compound (1.42 g, 7.6 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.5, 10.0, 7.0 Hz, 1H), 5.07 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 4.11 (ABq, J = 16.5 Hz, $\Delta\nu_{AB}$ = 20.5 Hz, 2H), 3.72 (s, 3H), 3.15 (q, J = 5.5 Hz, 1H), 2.27 (dd, J = 7.0, 6.0 Hz, 2H), 1.89-1.81 (m, 1H), 0.93 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 135.2, 116.6, 85.6, 67.4, 51.6, 35.0, 30.8, 18.1, 18.0; IR (film): 3078, 2960, 2912, 2875, 1761, 1741, 1641, 1466,

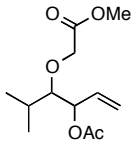
1439, 1387, 1369, 1286, 1207, 1128, 1034, 999, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{18}O_3Na$ $[M+Na]^+$: 209.1154, found 209.1149.



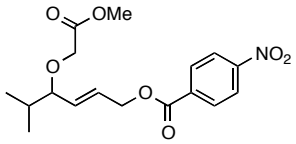
General Procedure for Intermolecular C—H Oxidation. No precautions were taken to exclude moisture or air. A 1 dram vial was charged sequentially with 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **1** (TCI, 25.1 mg, 0.05 mmol, 0.10 equiv), (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N*'-bis(3,5-di-tert-butylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (31.6 mg, 0.05 mmol, 0.10 equiv) if needed, *p*-benzoquinone (Sigma-Aldrich, 108.1 mg, 1.0 mmol, 2.0 equiv), alkene **2a** (93.1 mg, 0.5 mmol, 1.0 equiv), the carboxylic acid, a stir bar and dioxane (1.5 mL). The vial was fitted with a Teflon lined cap and heated to 45 ˚C with magnetic stirring in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature and transferred to a 125 mL separatory funnel with Et_2O (~50 mL). The organic phase was washed with a saturated aqueous solution of sodium meta-bisulfite (1x15 mL) and brine (1x15mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. This crude material was analyzed by gas chromatography to determine the linear to branched (L:B), E to Z and diastereomeric ratio (dr). Purification by flash chromatography on silica (~75 mL) eluting with 15% EtOAc in hexane afforded the allylic ester.



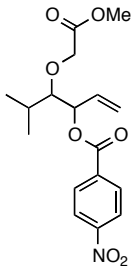
(±)-(*E*)-methyl 2-((6-acetoxy-2-methylhex-4-en-3-yl)oxy)acetate (3a). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dt, *J* = 15.5, 6.0 Hz, 1H), 5.59 (dd, *J* = 15.6, 8.5 Hz, 1H), 4.58 (t, *J* = 4.5 Hz, 2H), 4.03 (ABq, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 48.0 Hz, 2H), 3.73 (s, 3H), 3.49 (app t, *J* = 7.5 Hz, 1H), 2.08 (s, 3H), 1.84 (sextet, *J* = 6.5 Hz, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_{12}H_{20}O_5Na$ $[M+Na]^+$: 267.1208, found 267.1206.



(±)-Methyl 2-((4-acetoxy-2-methylhex-5-en-3-yl)oxy)acetate (4a). Isolated as a mixture with **3a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H), 5.45 (dd, *J* = 7.5, 2.5 Hz, 1H), 5.33 (d, *J* = 18.5 Hz, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 4.26 (ABq, *J* = 16.0 Hz, $\Delta\nu_{AB}$ = 51.5 Hz, 2H), 3.75 (s, 3H), 3.18 (dd, *J* = 8.0, 3.0 Hz, 1H), 2.07(s, 3H), 1.81-1.76 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H).



(±)-(*E*)-4-(2-methoxy-2-oxoethoxy)-5-methylhex-2-en-1-yl 4-nitrobenzoate (4a). Isolated as a mixture with **4b**. Only characteristic peaks reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.0 Hz, 2H), 8.21 (t, *J* = 9.0 Hz, 2H), 5.86 (dt, *J* = 15.5, 6.0 Hz, 1H), 4.88 (d, *J* = 6.0 Hz, 2H), 4.06(ABq, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 45.5 Hz, 2H), 3.73 (s, 3H), 3.54 (app t, *J* = 7.0 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).



(±)-4-(2-methoxy-2-oxoethoxy)-5-methylhex-1-en-3-yl 4-nitrobenzoate (4b). Isolated as a mixture with **3b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.21 (t, *J* = 9.0 Hz, 2H), 6.11 (ddd, *J* = 17.5, 10.0, 7.0 Hz, 1H), 5.44 (d, *J* = 17.5 Hz, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 5.38 (d, *J* = 10.5 Hz, 1H), 4.30 (ABq, *J* = 16.0 Hz, $\Delta\nu_{AB}$ = 38.0 Hz, 2H), 3.73 (s, 3H), 3.37 (dd, *J* = 7.5, 30. Hz, 1H), 1.94-1.82 (m, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_{17}H_{21}NO_7Na$ $[M+Na]^+$: 374.1216, found 374.1223.

Table 1, entry 1. According to the general procedure alkene **2a** was reacted with AcOH (0.11 mL, 120.1 mg, 2.0 mmol, 4.0 equiv). Run 1: 12.4 mg, 0.05 mmol, 10% yield, 2:1 B:L, 15:1 dr of B, >20:1 E:Z of L; Run 2: 13.7 mg, 0.06 mmol, 11% yield, 2:1 B:L, 17:1 dr of B, >20:1 E:Z of L. Average 11% yield, 2:1 B:L, 16:1 dr of B, >20:1 E:Z of L.

Entry 2. According to the general procedure alkene **2a** was reacted with AcOH (0.11 mL, 120.1 mg, 2.0 mmol, 4.0 equiv) with 10% Cr(salen)Cl. Run 1: 10.9 mg, 0.04 mmol, 9% yield, >20:1 L:B, >20:1 E:Z, 15:1; Run 2: 12.1 mg, 0.05 mmol, 10% yield, >20:1 L:B, >20:1 E:Z. Average 10% yield, >20:1 L:B, >20:1 E:Z.

Entry 3. According to the general procedure alkene **2a** was reacted with *p*-nitrobenzoic acid (125.3 mg, 0.75 mmol, 1.5 equiv). Run 1: 28.1 mg, 0.08 mmol, 16% yield, 1.8:1 B:L; Run 2: 25.5 mg, 0.07 mmol, 15% yield, 1.8.1 B:L. Average 16% yield, 1.8:1 B:L.

Entry 4. According to the general procedure alkene **2a** was reacted with *p*-nitrobenzoic acid (125.3 mg, 0.75 mmol, 1.5 equiv) and 10% Cr(salen)Cl. Run 1: 7.2 mg, 0.02 mmol, 4% yield; Run 2: 7.6 mg, 0.02 mmol, 4% yield. Average 4% yield.

Entry 5. Reaction carried out on 0.3 mmol scale. According to the general procedure **5** was reacted with *p*-nitrobenzoic acid (75.2 mg, 0.45 mmol, 1.5 equiv). Run 1: 7.2 mg, 0.02 mmol, 5% yield; Run 2: 6.2 mg, 0.02 mmol, 5% yield. Average 5% yield.

Optimization of the Intramolecular C—H Oxidation Reaction.

General Procedure for Intramolecular C—H Oxidation Optimization. No precautions were taken to exclude moisture or air. A 1 dram vial was charged sequentially with 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **1** (TCI, 15.1 mg, 0.03 mmol, 0.10 equiv), *p*-benzoquinone (BQ, Sigma-Aldrich, 64.8 mg, 0.6 mmol, 2.0 equiv), 2-((2-methylhex-5-en-3-yl)oxy)acetic acid **6** (51.7 mg, 0.3 mmol, 1.0 equiv), a stir bar and dioxane (0.9 mL). The vial was fitted with a Teflon lined cap and heated to 45 ˚C with magnetic stirring in an oil bath for 72 h. The vial was removed, allowed to cool to room temperature and transferred to a 125 mL separatory funnel with Et_2O (~50 mL). The organic phase was washed with a saturated aqueous solution of sodium meta-bisulfite (1x15 mL) and brine (1x15mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. This crude material was analyzed by ^1H NMR to determine the diastereomeric ratio. Purification by flash chromatography on silica (~75 mL) eluting with 20% EtOAc in hexane afforded the dioxanone as a mixture of diastereomers.

Table 2, entry 1. According to the general procedure. Run 1: 20.1 mg, 0.12 mmol, 38% yield, 9:1 dr (anti:syn); Run 2: 19.6 mg, 0.12 mmol, 38% yield, 9:1 dr (anti:syn). Average 38% yield, 9:1 dr (anti:syn).

Entry 2. According to the general procedure with the addition of diisopropylethylamine (DIPEA, 5 μL, 3.9 mg, 0.03 mmol, 0.1 equiv). Run 1: 24.5 mg, 0.14 mmol, 48% yield, 7:1 dr

(anti:syn); Run 2: 22.1 mg, 0.13 mmol, 43 % yield, 7:1 dr (anti:syn). Average 46% yield, 7:1 dr (anti:syn).

Entry 3. According to the general procedure with the addition of (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N*'-bis(3,5-di-tert-butylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (18.9 mg, 0.03 mmol, 0.10 equiv). Run 1: 41.8 mg, 0.24 mmol, 82% yield, 9:1 dr (anti:syn); Run 2: 42.8 mg, 0.25 mmol, 84% yield, 9:1 dr (anti:syn). Average 83% yield, 9:1 dr (anti:syn).

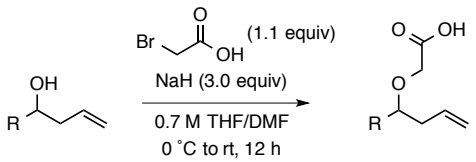
Entry 4. According to the general procedure replacing BQ with 2,6-dimethyl-*p*-benzoquinone (81.7 mg, 0.6 mmol, 2.0 equiv). No product detected by ^{1}H NMR.

Entry 5. According to the general procedure replacing **1** with $Pd(OAc)_2$ (Strem, 6.7 mg, 0.03 mmol, 0.1 equiv). Less than 5% product detected by ^{1}H NMR with nitrobenzene as an internal standard.

Entry 6. According to the general procedure omitting **1** and with (*R*,*R*)-Cr(salen)Cl) (18.9 mg, 0.03 mmol, 0.10 equiv). No product detected by ^{1}H NMR.

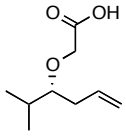
Entry 7. According to the general procedure omitting **1**. No product detected by ^{1}H NMR.

Synthesis of Carboxylic Acid Staring Materials.



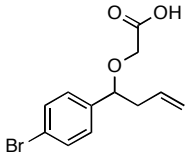
General Procedure for the Synthesis of Carboxylic Acid Starting Materials. A 25 mL round bottom flask was charged in the glove box with NaH (Sigma-Aldrich, 95%) (144 mg, 6 mmol, 3.0 equiv) and a stir bar. The flask was removed from the glove box and placed under N_2. The NaH was suspended in THF (1.3 mL) and the suspension cooled to 0 ˚C and stirred. A separate

25 mL round bottom flask was charged with bromoacetic acid (Sigma-Aldrich, 305.7 mg, 2.2 mmol, 1.1 equiv) and THF (0.5 mL). The resulting solution was added dropwise to the NaH suspension. A substantial evolution of gas was observed. The reaction was stirred for 30 min. at 0 ˚C (or 1h if 60% NaH was used). A separate 25 mL round bottom flask was charged with the alcohol (2.0 mmol, 1.0 equiv) and DMF (1 mL). The resulting solution was added dropwise to the stirring reaction at 0 ˚C. Homoallylic alcohol starting materials were generally synthesized by allylation of the corresponding aldehyde with allyl magnesium bromode, allyl trifluoroborate potassium salt[23] or (+)-*B*-allyldiisopinocamphenylborane[24] (Sigma-Aldrich). The reaction was stirred an additional 30 min. at 0 ˚C before the ice/water bath was removed and the reaction allowed to warm to room temperature and stirred for an additional 12 h. The reaction was cooled to 0 ˚C, diluted with EtOAc (~10 mL) and carefully quenched with 1N HCl (~10 mL), aqueous phase (pH=1). The reaction was transferred to a 125 mL separatory funnel, the phases separated and the aqueous phase extracted with EtOAc (3x10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel eluting with 20% acetone in hexanes afforded the pure acid. Yields are generally between 70-90%. The reaction has been scaled to 30 mmol effectively.

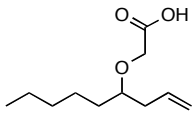


(-)-(*R*)-2-((2-methylhex-5-en-3-yl)oxy)acetic acid (6). The product was obtained according to the general procedure as a light yellow oil starting with (*R*)-2-methylhex-5-en-3-ol (91% ee, Mosher ester analysis). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (br s, 1H), 5.84 (ddt, J = 17.5, 10.0, 7.0 Hz, 1H), 5.11 (d, J = 17.5 Hz, 1H), 5.09 (d, J = 10.0 Hz, 1H), 4.13 (ABq, J = 17.0 Hz, $\Delta\nu_{AB}$ = 20.5 Hz, 2H), 3.22 (app q, J = 6.0 Hz, 1H), 2.33-2.23 (m, 2H), 1.92-1.83 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 134.9,

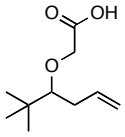
117.5, 86.1, 67.1, 35.0, 30.9, 18.0, 17.9; IR (film): 3465 (br), 3078, 2962, 2912, 2877, 1738, 1641, 1435, 1389, 1369, 1242, 1124, 980, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{16}O_3Na$ $[M+Na]^+$: 195.0997, found 195.0998; $[\alpha]_D^{25} = -7.2^\circ$ (c=1.0, $CHCl_3$).



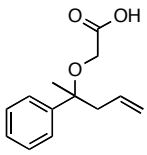
(±)-2-(1-(4-bromophenyl)but-3-enyloxy)acetic acid (10a). The product was obtained according to the general procedure as a light yellow waxy solid. ^1H NMR (500 MHz, $CDCl_3$) δ 11.1 (br s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.74 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.07-5.03 (m, 2H), 4.41 (t, *J* = 7.0 Hz, 1H), 3.97 (ABq, *J* = 17.0 Hz, $\Delta\nu_{AB}$ = 66.5 Hz, 2H), 2.68–2.62 (m, 1H), 2.47-2.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 139.0, 133.5, 131.7, 128.5, 122.0, 117.8, 81.9, 65.3, 41.9; IR (film): 3446 (br), 3066, 3032, 2978, 2943, 2920, 1730, 1641, 1493, 1441, 1362, 1244, 1124, 997, 912 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{13}O_3NaBr$ $[M+Na]^+$: 306.9946, found 306.9945.



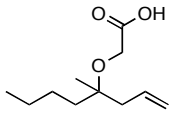
(±)-2-(non-1-en-4-yloxy)acetic acid (10b). The product was obtained according to the general procedure as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 10.4 (br s, 1H), 5.81 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.13-5.08 (m, 2H), 4.13 (s, 2H), 3.46 (app p, *J* = 6.0 Hz, 1H), 2.30 (app t, *J* = 7.0 Hz, 2H), 1.58-1.47 (m, 2H), 1.41-1.22 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 134.2, 117.7, 80.8, 66.1, 38.1, 33.5, 31.8, 24.8, 22.5, 14.0; IR (film): 3369 (br), 3076, 2956, 2933, 2860, 1736, 1641, 1435, 1379, 1242, 1126, 995, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$: 223.1310, found 223.1307.



(±)-2-(2,2-dimethylhex-5-en-3-yloxy)acetic acid (10c). The product was obtained according to the general procedure as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (br s, 1H), 5.91-5.81 (m, 1H), 5.14 (dd, *J* = 17.0, 1.0, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.18 (s, 2H), 3.08 (dd, *J* = 9.0, 2.5 Hz, 1H), 2.40-2.35 (m, 1H), 2.26-2.20 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 136.2, 117.6, 90.5, 70.1, 35.9, 35.6, 26.2; IR (film): 3300 (br), 3078, 2958, 2914, 2873, 1736, 1641, 1481, 1433, 1365, 1244, 1221, 1130, 987, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{18}O_3Na$ $[M+Na]^+$: 209.1154, found 209.1160.

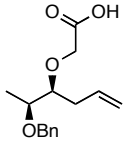


(±)-2-(2-phenylpent-4-en-2-yloxy)acetic acid (10d). The product was obtained according to the general procedure as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.68-5.60 (m, 1H), 5.00 (s, 2H), 3.87 (ABq, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 34.0 Hz, 2H), 2.62 (dq, *J* = 14.0, 7.0 Hz, 2H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 143.0, 133.2, 128.5, 127.6, 126.1, 118.5, 80.5, 60.9, 47.3, 22.9; IR (film): 3440 (br), 3076, 2980, 2935, 2918, 1738, 1641, 1446, 1377, 1223, 1178, 1111, 918 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}O_3Na$ $[M+Na]^+$: 243.0997, found 243.0994.

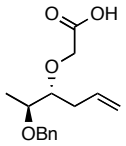


(±)-2-(4-methyloct-1-en-4-yloxy)acetic acid (10e). The product was obtained according to the general procedure as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.4 (br s, 1H), 5.78 (ddt, *J* = 17.0, 10.0, 7.5 Hz, 1H), 5.15-5.09 (m, 2H), 3.99 (s, 2H), 2.34-2.24 (m, 2H), 1.53-1.49 (m, 2H), 1.32-1.27 (m, 4H), 1.20 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 133.1, 118.5, 79.2, 59.5, 42.5, 37.5, 25.6, 23.0, 22.8, 14.0; IR (film): 3437

(br), 3076, 2958, 2935, 2872, 1738, 1641, 1462, 1433, 1379, 1230, 1198, 1120, 997, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$: 223.1310, found 223.1303.

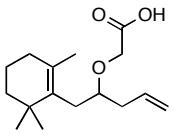


(-)-2-((2*S*,3*S*)-2-(benzyloxy)hex-5-en-3-yloxy)acetic acid (10f). The product was obtained according to the general procedure as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 10.8 (br s, 1H), 7.38–7.30 (m, 5H), 5.72 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H), 5.13 (d, *J* = 16.5 Hz, 1H), 5.11 (d, *J* = 9.5 Hz, 1H), 4.61 (ABq, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 73.5 Hz, 2H), 4.19 (ABq, *J* = 17.0 Hz, $\Delta\nu_{AB}$ = 107.5 Hz, 2H), 3.61 (qd, *J* = 6.5, 2.5 Hz, 1H), 3.53 (td, *J* = 6.5, 2.0 Hz, 1H), 2.37-2.30 (m, 1H), 2.18-2.12 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 137.0, 133.2, 128.6, 128.1, 128.0, 118.7, 84.0, 75.6, 71.0, 68.8, 36.1, 12.4; IR (film): 3450 (br), 3066, 3032, 2980, 2937, 2918, 1728, 1454, 1379, 1273, 1230, 1207, 1120, 1028, 971, 922 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1259, found 287.1247; $[\alpha]_D^{25}$ = -9.7° (c=2.0, $CHCl_3$).

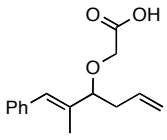


(+)-2-((2*S*,3*R*)-2-(benzyloxy)hex-5-en-3-yloxy)acetic acid (10g). The product was obtained according to the general procedure as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 7.39–7.29 (m, 5H), 5.81 (m, 1H), 5.16-5.13 (m, 2H), 4.63 (ABq, *J* = 11.5 Hz, $\Delta\nu_{AB}$ = 73.5 Hz, 2H), 4.16 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 100.5 Hz, 2H), 3.63-3.58 (m, 1H), 3.34-3.30 (m, 1H), 2.46-2.41 (m, 1H), 2.23-2.17 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.6, 132.7, 128.6, 128.2, 118.8, 84.7, 76.8, 71.3, 68.3, 35.3, 15,2; IR (film): 3465 (br), 3364, 3068, 3033, 2980, 2933, 2912, 1757, 1641, 1454, 1433, 1365, 1271,

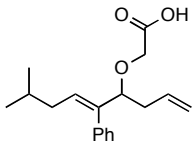
1207, 1120, 918 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1259, found 287.1249; $[\alpha]_D^{25}$ = +37.1° (c=2.0, $CHCl_3$).



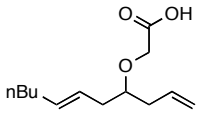
(±)-2-(1-(2,6,6-trimethylcyclohex-1-enyl)pent-4-en-2-yloxy)acetic acid (12a). The product was obtained according to the general procedure as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.4 (br s, 1H), 5.83 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H), 5.18-5.14 (m, 2H), 4.07 (ABq, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 68.0 Hz, 2H), 3.64-3.59 (m, 1H), 2.45 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.33 (dt, *J* = 6.0, 1.0 Hz, 2H), 2.21 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.02-1.92 (m, 2H), 1.66 (s, 3H), 1.64-1.59 (m, 2H), 1.47-1.44 (m, 2H), 0.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 133.9, 133.8, 131.8, 118.4, 82.4, 67.4, 39.7 (2C), 35.0, 33.4, 32.9, 29.4, 28.6, 21.1, 19.2; IR (film): 3438 (br), 3076, 2931, 2870, 1736, 1641, 1433, 1360, 1209, 1126, 995, 914 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{26}O_3$ $[M]^+$: 266.1882, found 266.1873.



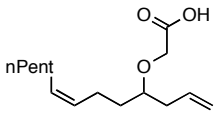
(±)-(*E*)-2-((2-methyl-1-phenylhexa-1,5-dien-3-yl)oxy)acetic acid (12b). The product was obtained according to the general procedure as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 9.4 (br s, 1H), 7.37-7.34 (m, 2H), 7.29-7.24 (m, 3H), 6.48 (s, 1H), 5.83 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.18 (d, *J* = 17.0 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.06 (ABq, *J* = 17.0, 1.0 Hz, $\Delta\nu_{AB}$ = 67.5 Hz, 2H), 3.94 (app t, 1H), 2.60-2.54 (m, 1H), 2.46-2.40 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 136.7, 135.5, 134.2, 129.8, 130.0, 128.2, 126.9, 117.3, 86.6, 64.9, 38.15, 12.5; IR (film): 3454 (br), 3078, 3026, 2980, 2945, 2918, 1738, 1643, 1493, 1443, 1207, 1117, 993, 918 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{18}O_3Na$ $[M+Na]^+$: 269.1154, found 269.1160.



(±)-(*E*)-2-(8-methyl-5-phenylnona-1,5-dien-4-yloxy)acetic acid (12c). The product was obtained according to the general procedure as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.8 (br s, 1H), 7.36-7.27 (m, 3H), 7.10-7.08 (m, 2H), 5.82 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.71 (t, *J* = 7.0 Hz, 1H), 5.10-5.06 (m, 2H), 4.24 (ABq, *J* = 17.0 Hz, $\Delta\nu_{AB}$ = 86.0 Hz, 2H), 4.02 (t, *J* = 6.5 Hz, 1H), 2.28 (t, *J* = 7.0 Hz, 2H), 1.87 (t, *J* = 7.0 Hz, 2H), 1.64 (septet, *J* = 7.0 Hz, 1H), 0.85 (d, *J* = 1.5 Hz, 3H), 0.84 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 138.7, 137.4, 134.5, 132.3, 129.2, 128.1, 127.1, 117.5, 85.8, 65.2, 38.6, 37.5, 28.6, 22.4, 22.3; IR (film): 3465 (br), 3080, 3057, 3020, 2956, 2929, 2870, 1730, 1643, 1495, 1464, 1441, 1385, 1367, 1244, 1119, 1026, 991, 914 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{24}O_3Na$ $[M+Na]^+$: 311.1623, found 311.1628.

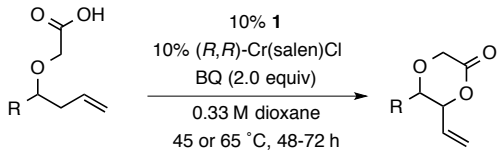


(±)-(*E*)-2-(undeca-1,6-dien-4-yloxy)acetic acid (12d). The product was obtained according to the general procedure as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (br s, 1H), 5.81 (ddt, *J* = 16.0, 10.5, 7.5 Hz, 1H), 5.55-5.50 (m, 1H), 5.41-5.35 (m, 1H), 5.14-5.10 (m, 2H), 4.13 (s, 2H), 3.47 (p, *J* = 6.0 Hz, 1H), 2.33-2.29 (m, 2H), 2.25 (t, *J* = 6.0 Hz, 2H), 2.01 (q, *J* = 7.0 Hz, 2H), 1.36-1.28 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 134.7, 134.1, 124.8, 118.0, 80.8, 66.4, 38.1, 36.9, 32.3, 31.5, 22.2, 13.9; IR (film): 3354 (br), 3078, 2958, 2929, 2873, 1732, 1643, 1435, 1377, 1352, 1240, 1128, 972, 916 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1467, found 249.1458.



(±)-(*Z*)-2-(trideca-1,7-dien-4-yloxy)acetic acid (12e). The product was obtained according to the general procedure as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (br s, 1H), 5.81 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H), 5.41-5.29 (m, 2H), 5.12 (d, *J* = 17.5 Hz, 1H), 5.10 (d, *J* = 9.5 Hz, 1H), 4.13 (s, 2H), 3.48 (app p, *J* = 5.5Hz, 1H), 2.32 (app t, *J* = 6.5 Hz, 2H), 2.12 (app q, *J* = 7.0 Hz, 2H), 2.01 (app q, *J* = 7.0 Hz, 2H), 1.67-1.53 (m, 2H), 1.36-1.25 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 134.0, 131.0, 128.5, 117.9, 80.4, 66.3, 38.1, 33.6, 31.5, 29.3, 27.2, 23.0, 22.5, 13.9; IR (film): 3438 (br), 3078, 3005, 2956, 2927, 2858, 1734, 1643, 1439, 1363, 1244, 1128, 995, 916 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{26}O_3Na$ $[M+Na]^+$: 277.1780, found 277.1786.

Scope of the Intramolecular C—H Oxidation Reaction



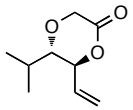
General Procedure for Intramolecular C—H Oxidation. No precautions were taken to exclude moisture or air. A 1 dram vial was charged sequentially with 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **1** (TCI, 15.1 mg, 0.03 mmol, 0.10 equiv), (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N*'-bis(3,5-di-tert-butylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (18.9 mg, 0.03 mmol, 0.10 equiv), *p*-benzoquinone (Sigma-Aldrich, 64.8 mg, 0.6 mmol, 2.0 equiv), the carboxylic acid (0.3 mmol, 1.0 equiv), a stir bar and dioxane (0.9 mL). The vial was fitted with a Teflon lined cap and heated to 45 or 65 ˚C with magnetic stirring in an oil bath for 48-72 h. The vial was removed, allowed to cool to room temperature and transferred to a 125 mL separatory funnel with Et_2O (~50 mL). The organic phase was

washed with a saturated aqueous solution of sodium meta-bisulfite (1x15 mL) and brine (1x15mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. This crude material was analyzed by gas chromatography or ^{1}H NMR to determine the diastereomeric ratio. Purification by flash chromatography on silica (~75 mL) afforded the dioxanone as a mixture of diastereomers. In general a second chromatographic purification allowed for isolation of the pure major diastereomer.

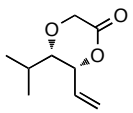
The stereochemistry of four of the dioxanone compounds has been unambiguously determined. 1. (-)-**7** by comparison to spectra reported in the literature[19a] and an NOE experiment. 2. (-)-**11f** from an NOE experiment. 3. **19** by conversion to (-)-**21** and comparison to spectra reported in the literature.[20] 4. (+)-**23** by an NOE experiment and conversion to (+)-**25** and comparison to spectra reported in the literature.[21] All other diastereomers are assigned based on analogy. Qualitatively, the allylic proton of the *anti*-diastereomer appears as an apparent triplet in the ^{1}H NMR, while the coresponding resonance of the *syn*-diastereomer appears as a doublet. However, in general an NOE experiment is required to assign the stereochemistry of the dioxanone unambiguously as *J*-values are generally not diagnostic.

When a mixture of diasetereomers is reported, all peaks are reported for the major diastereomer in the ^{1}H NMR. Only characteristic peaks are reported for the minor diastereomer in the ^{1}H NMR. ^{13}C NMR and IR peaks for mixtures of diastereomers are reported together.

Although a chiral Lewis acid is used to promote the reaction, no appreciable difference in reactivity or selectivity of the reaction is observed when different enantiomers of the Lewis acid are used with a chiral substrate.

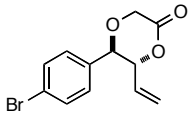


***anti*-(-)-(5*S*,6*S*)-5-isopropyl-6-vinyl-1,4-dioxan-2-one (7).** (-)-(*R*)-2-((2-methylhex-5-en-3-yl)oxy)acetic acid (-)-**6** (51.7 mg, 0.30 mmol, 1.0 equiv) was reacted according to the general procedure at 45 ˚C for 48 h. Purification by flash chromatography eluting with 20% EtOAc in hexanes gave a mixture of diastereomers as a light yellow oil. Run 1: 41.8 mg, 0.24 mmol, 82% yield, 9:1 dr (anti:syn) by NMR; Run 2: 42.8 mg, 0.25 mmol, 84% yield, 9:1 dr (anti:syn) by NMR. Average 83% yield, 9:1 dr (anti:syn). The diastereomers were separated by flash chromatography on silica eluting with gradient 10 to 20% Et_2O in petroleum ether. Major product (*anti*-diastereomer, less polar) obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.5, 10.5, 7 Hz, 1H), 5.48 (d, *J* = 17.5 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 4.85 (app t, *J* = 9.0 Hz, 1H), 4.35 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 133.0 Hz, 2H), 3.25 (dd, *J* = 9.0, 2.5 Hz, 1H), 2.90 (septet of doublets, *J* = 6.5, 2.5 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.92, (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 131.8, 120.8, 82.3, 79.9, 65.9, 27.9, 20.0, 15.0; IR (film): 3087, 2970, 2937, 2879, 1753, 1470, 1429, 1367, 1344, 1265, 1234, 1113, 1007, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{15}O_3$ $[M+H]^+$: 171.1021, found 171.1015; $[\alpha]_D^{25}$ = -39.4˚ (c=1.0, $CHCl_3$); [ee]= 91% (β-cyclodextrin, 85 ˚C isothermal, t_R(*S*,*S*) = 41.31 min., t_R(*R*,*R*) = 42.71 min.). These data are in agreement with those reported in the literature.[19a] No erosion of ee occurred from the starting alcohol (91% ee, *vide supra*) after alkylation and intramolecular C—H oxidation.

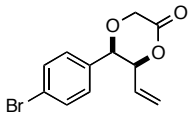


***syn*-(+)-(5*S*,6*R*)-5-isopropyl-6-vinyl-1,4-dioxan-2-one.** Minor product (*syn*-diastereomer, more polar) obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.46-5.43 (m, 2H), 4.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.39 (ABq, *J*

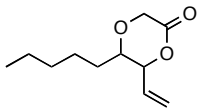
= 18.0 Hz, $\Delta\nu_{AB}$ = 87.5 Hz, 2H), 3.35 (dd, *J* = 10.0, 2.5 Hz, 1H), 1.70-1.60 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.90, (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 130.8, 121.4, 81.9, 80.3, 66.5, 29.0, 19.4, 17.8; IR (film): 3086, 2966, 2877, 1747, 1473, 1431, 1430, 1390, 1348, 1227, 1119, 1007, 937, 872 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{14}O_3Na$ $[M+Na]^+$: 193.0841, found 193.0833; $[\alpha]_D^{25}$ = +48.5˚ (c=1.0, $CHCl_3$). These data are in agreement with those reported in the literature.[19a]



***anti*-(±)-5-(4-bromophenyl)-6-vinyl-1,4-dioxan-2-one (11a).** (±)-2-(1-(4-bromophenyl)but-3-enyloxy)acetic acid **10a** (85.5 mg, 0.30 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 48 h. Purification by flash chromatography eluting with 20% EtOAc in hexanes gave the mixture of diastereomers as a light yellow oil. Run 1: 48.9 mg, 0.17 mmol, 56% yield, 3:1 dr (anti:syn) by GC; Run 2: 48.9 mg, 0.17 mmol, 58% yield, 2.5:1 dr (anti:syn) by GC. Average 57% yield, 3:1 dr (anti:syn). The diasteromers were separated by MPLC eluting with gradient 5 to 30% Et_2O in petroleum ether. Major product (*anti*-diastereomer, less polar) obtained as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.58 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.92 (app t, *J* = 8.0, 1H), 4.54 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 102.5 Hz, 2H), 4.37 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 134.1, 131.8, 130.4, 129.1, 123.2, 120.7, 83.8, 78.6, 65.9; IR (film): 3087, 2987, 2920, 2877, 1753, 1597, 1491, 1427, 1410, 1367, 1319, 1263, 1232, 1119, 1072, 1011, 941 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{11}O_3NaBr$ $[M+Na]^+$: 304.9789, found 304.9803.

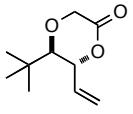


***syn*-(±)-5-(4-bromophenyl)-6-vinyl-1,4-dioxan-2-one.** Minor product (*syn*-diastereomer, more polar) obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.71 (ddd, *J* = 17.0, 11.0, 6.5 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 5.24 (d, *J* = 17.0 Hz, 1H), 5.05-5.02 (m, 2H), 4.59 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 61.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 134.0, 131.7, 129.9, 127.5, 122.4, 121.1, 82.2, 75.4, 66.0; IR (film): 3087, 2924, 2875, 1751, 1595, 1491, 1429, 1406, 1377, 1329, 1221, 1126, 1072, 1009, 941 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{11}O_3NaBr$ $[M+Na]^+$: 304.9789, found 304.9782.

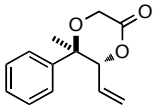


***anti*- and *syn*-(±)-5-pentyl-6-vinyl-1,4-dioxan-2-one (11b).** (±)-2-(non-1-en-4-yloxy)acetic acid **10b** (60.1 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 45 ˚C for 48 h. Purification by flash chromatography eluting with 20% EtOAc in hexanes gave an inseparable mixture diastereomers as a light yellow oil. Run 1: 51.7 mg, 0.25 mmol, 84% yield, 2:1 dr (anti:syn) by GC; Run 2: 47.6 mg, 0.23 mmol, 79% yield, 2:1 dr (anti:syn) by NMR. Average 82% yield, 2:1 dr (anti:syn). ^{1}H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 5.76 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.47 (d, *J* = 17.0 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H), 4.68 (app t, *J* = 8.0 Hz, 1H), 4.36 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 122.0 Hz, 2H), 3.36 (td, *J* = 9.0, 2.5 Hz, 1H), 1.61-1.22 (m, 8H), 0.88 (t, *J* = 6.5 Hz, 3H), minor product (*syn*-diastereomer): δ 5.96 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H), 4.77 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.38 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 61.0 Hz, 2H), 3.81-3.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) reported as a mixture of diastereomers δ 167.1, 167.0, 131.8, 130.9, 121.2, 121.1, 84.2, 82.7, 76.0, 74.5, 65.8, 65.7, 31.5 (2C), 30.3, 29.9, 25.0, 24.6, 22.4, 13.9; IR (film): 3087, 2954, 2931,

2862, 1753, 1457, 1429, 1344, 1259, 1223, 1117, 1011, 937 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1334, found 199.1335.

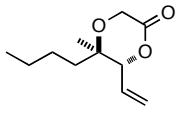


***anti*-(±)-5-(*tert*-butyl)-6-vinyl-1,4-dioxan-2-one (11c).** (±)-2-(2,2-dimethylhex-5-en-3-yloxy)acetic acid **10c** (55.9 mg, 0.3 mmol, 1.0 equiv), was reacted according to the general procedure at 65 ˚C for 24 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexane gave a mixture of diastereomers as a light yellow oil. These data proved to be irreproducible, but yields for the reaction were low, generally between 15 and 30% Run 1: 13.1 mg, 0.07 mmol, 24% yield, 11:1 dr (anti:syn) by GC; Run 2: 10.9 mg, 0.06 mmol, 20% yield, 9:1 dr (anti:syn) by NMR. Average 22% yield, 10:1 dr (anti:syn). ^{1}H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 5.85 (ddd, J = 17.5, 10.5, 8.0 Hz, 1H), 5.45 (d, J = 17.0 Hz, 1H), 5.38 (d, J = 10.5 Hz, 1H), 4.92 (app t, J = 8.0 Hz, 1H), 4.30 (ABq, J = 17.5 Hz, $\Delta\nu_{AB}$ = 163.0 Hz, 2H) 3.15 (d, J = 8.5 Hz, 1H), 0.99 (s, 9H);^{13}C NMR (125 MHz, $CDCl_3$) major product (*anti*-diastereomer) δ 167.8, 134.4, 120.7, 83.1, 82.3, 67.3, 66.1, 34.1, 26.6; IR (film): 3086, 2960, 2912, 2875, 1755, 1645, 1481, 1429, 1398, 1365, 1346, 1323, 1261, 1236, 1122, 1032, 989, 943 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0997, found 207.1001.



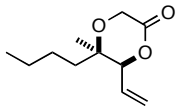
***anti*-(±)-5-methyl-5-phenyl-6-vinyl-1,4-dioxan-2-one (11d).** (±)-2-(2-phenylpent-4-en-2-yloxy)acetic acid **10d** (66.1 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave a mixture of diastereomers as a light yellow oil. Run 1: 38.7 mg, 0.18 mmol, 59% yield, 3:1 dr (anti:syn) by GC; Run 2: 35.3 mg, 0.16 mmol, 54% yield, 3:1 dr (anti:syn) by GC. Average 57% yield, 3:1 dr (anti:syn). The diastereomers were separated nearly

completely by MPLC eluting with gradient 0 to 20% Et_2O in petroleum ether. Major product (*anti*-diastereomer, less polar) isolated as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.5-7.48 (m, 2H), 7.4 (t, *J* = 7.5 Hz, 2H), 7.35-7.32 (m, 1H), 5.91 (ddd, *J* = 17.0, 10,0, 7.0 Hz, 1H), 5.42-5.39 (m, 2H), 5.20 (d, *J* = 6.5 Hz, 1H), 4.40 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 34.5 Hz, 2H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 139.9, 131.2, 128.8, 128.4, 126.2, 120.9, 84.0, 75.7, 61.9, 21.9; IR (film): 3087, 3060, 3028, 2987, 2922, 2850, 1751, 1645, 1495, 1446, 1365, 1244, 1219, 1113, 1022, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1021, found 219.1016. Minor product (*syn*-diastereomer, more polar) characteristic peaks reported from mixture of diastereomers isolated as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 16.5, 11.0, 5.5 Hz, 1H), 5.05, (d, *J* = 5.5 Hz, 1H), 1.71 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 140.3, 132.2, 128.3, 127.7, 125.4, 119.8, 85.0, 75.1, 61.7, 23.7.

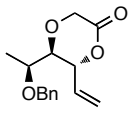


***anti*-(±)-5-butyl-5-methyl-6-vinyl-1,4-dioxan-2-one (11e).** (±)-2-(4-methyloct-1-en-4-yloxy)acetic acid **10e** (60.1 mg, 0.30 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave a mixture of diastereomers as a light yellow oil. Run 1: 37.2 mg, 0.19 mmol, 62% yield, 3:1 dr (anti:syn) by GC; Run 2: 33.7 mg, 0.17 mmol, 57% yield, 3:1 dr (anti:syn) by GC. Average 60% yield, 3:1 dr (anti:syn). Diastereomers separated by flash chromatography on silica gel eluting with gradient 10 to 20% Et_2O in petroleum ether. Major product (*anti*-diastereomer, less polar) obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.44 (d, *J* = 17.0 Hz, 1H), 5.36 (d, *J* = 10.5 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.32 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 38.5 Hz, 2H), 1.54-1.50 (m, 2H), 1.42-1.23 (m, 4H), 1.17 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 131.3,

120.4, 85.4, 73.3, 61.3, 36.9, 24.5, 23.0, 16.7, 13.9; IR (film): 3084, 2956, 2873, 1755, 1468, 1429, 1383, 1362, 1257, 1228, 1111, 1022, 1007, 937 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$: 221.1154, found 221.1154.

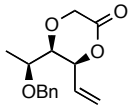


***syn*-(±)-5-butyl-5-methyl-6-vinyl-1,4-dioxan-2-one.** Minor product (*syn*-diastereomer, more polar) characteristic peaks reported from mixture of diastereomers isolated as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.5, 11.0, 7.0 Hz, 1H), 5.45 (d, *J* = 17.5 Hz, 1H), 5.37 (d, *J* = 10.5 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.29 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 62.5 Hz, 2H), 1.70-1.52 (m, 2H), 1.36-1.32 (m, 4H), 1.24 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 131.3, 120.3, 86.8, 73.4, 61.1, 30.4, 24.4, 23.0, 21.2, 14.0; IR (film): 3087, 2956, 2941, 2873, 1753, 1468, 1429, 1381, 1360, 1259, 1113, 935 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$: 221.1154, found 221.1149.

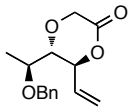


***syn,anti*-(-)-(5*R*,6*R*)-5-((*S*)-1-(benzyloxy)ethyl)-6-vinyl-1,4-dioxan-2-one (11f).** (-)-2-((2*S*,3*S*)-2-(benzyloxy)hex-5-en-3-yloxy)acetic acid **10f** (79.3 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 25% EtOAc in hexane gave a mixture of diastereomers as a light yellow oil. Run 1: 49.4 mg, 0.19 mmol, 63% yield, 8:1 dr (anti:syn) by GC. Run 2: 48.1 mg, 0.18 mmol, 61% yield, 8:1 dr (anti:syn) by GC. Average 62% yield, 8:1 dr (anti:syn). The diastereomers were separated by flash chromatography on silica eluting with gradient 10 to 30% Et_2O in petroleum ether. Major product (*anti*-diastereomer) obtained as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 5.82 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.46 (d, *J* = 17.5 Hz, 1H), 5.37 (d, *J* = 10.5 Hz, 1H), 4.91 (app t, *J* = 8 Hz, 1H), 4.56 (ABq, *J* = 11.5 Hz,

$\Delta\nu_{AB}$ = 61.5 Hz, 2H), 4.36 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 110.5 Hz, 2H), 3.72-3.68 (m, 1H), 3.56 (dd, *J* = 8.5, 4.0 Hz, 1H), 1.27 (d, *J* = 6.5 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 137.7, 132.1, 128.4, 127.8, 127.7, 120.5, 80.8, 77.7, 73.2, 71.2, 65.1, 15.0; IR (film): 3087, 3064, 3032, 2981, 2933, 2873, 1753, 1454, 1429, 1375, 1263, 1230, 1117, 1055, 993, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103, found 285.1105; $[\alpha]_D^{25}$ = -3.2° (c=1.0, $CHCl_3$).

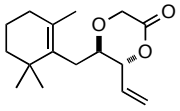


***syn,syn*-(+)-(5*R*,6*S*)-5-((*S*)-1-(benzyloxy)ethyl)-6-vinyl-1,4-dioxan-2-one.** Minor product (*syn*-diastereomer) obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.92 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H), 5.40 (d, *J* = 10.5 Hz, 1H), 5.37 (d, *J* = 17.0 Hz, 1H), 5.15 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.46 (ABq, *J* = 11.0 Hz, $\Delta\nu_{AB}$ = 167.0 Hz, 2H), 4.41 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 68.0 Hz, 2H), 3.69 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.49 (dq, *J* = 9.0, 6.0 Hz, 1H), 1.34 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 137.6, 131.0, 128.5, 127.9, 127.7, 121.3, 81.1, 77.6, 73.5, 70.5, 66.2, 16.3; IR (film): 3087, 3066, 3032, 2978, 2927, 2877, 1745, 1454, 1429, 1346, 1284, 1219, 1176, 1122, 1070, 1001, 937 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103, found 285.1102; $[\alpha]_D^{25}$ = +59.0° (c=1.0, $CHCl_3$).



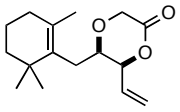
***anti,anti*-(+)-(5*S*,6*S*)-5-((*S*)-1-(benzyloxy)ethyl)-6-vinyl-1,4-dioxan-2-one (11g).** (+)-2-((2*S*,3*R*)-2-(benzyloxy)hex-5-en-3-yloxy)acetic acid **10g** (79.3 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 25% EtOAc in hexane gave a mixture of diastereomers as a light yellow oil. Run 1: 57.0 mg, 0.19 mmol, 64% yield, 4:1 dr (anti:syn) by GC. Run 2: 47.5 mg, 0.18 mmol, 60% yield, 4:1 dr (anti:syn) by GC. Average 62% yield, 4:1 dr (anti:syn). The diastereomers were separated nearly completely by MPLC eluting with gradient 5 to 30% Et_2O

in petroleum ether. Major product (*anti*-diastereomer, less polar) isolated as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 5.61 (ddd, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.31-5.27 (m, 2H), 5.16 (app t, *J*= 8.0 Hz, 1H), 4.50 (ABq, *J* = 11.5 Hz, $\Delta\nu_{AB}$ = 167.0 Hz, 2H), 4.46 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 161.5 Hz, 2H), 3.71 (qd, *J* = 6.5, 2.0 Hz, 1H), 3.29 (dd, *J* = 9.5, 2.0 Hz, 1H), 1.34 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 137.5, 131.2, 128.5, 128.1, 128.0, 120.9, 80.5, 78.6, 71.2, 70.7, 66.0, 15.2; IR (film): 3087, 3064, 3032, 2978, 2933, 2875, 1753, 1498, 1454, 1427, 1342, 1296, 1267, 1228, 1157, 1113, 1072, 1003, 937 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103, found 285.1100; $[\alpha]_D^{24}$ = +41.5° (c=1.0, $CHCl_3$). Minor product (*syn*-diastereomer, more polar) characteristic peaks reported from mixture of diastereomers isolated as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 17.5, 10.5, 8.0 Hz, 1H), 5.45 (d, *J* = 17.0 Hz, 1H), 5.44 (d, *J* = 10.5 Hz, 1H), 4.88 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.61 (s, 2H), 4.46 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 91.5 Hz, 2H), 3.80 (dd, *J* = 7.0, 3.0 Hz, 1H), 3.57 (app p, *J* = 6.5 Hz, 1H), 1.21 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 138.2, 130.7, 128.4, 127.6 (2C), 121.6, 80.8, 78.4, 73.9, 72.3, 65.8, 16.0.

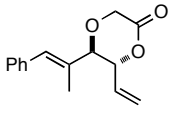


***anti*-(±)-5-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)-6-vinyl-1,4-dioxan-2-one (13a).** (±)-2-(1-(2,6,6-trimethylcyclohex-1-enyl)pent-4-en-2-yloxy)acetic acid **12a** (79.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave a mixture of diastereomers as a light yellow oil. Run 1: 74.5 mg, 0.23 mmol, 76% yield, 3.5:1 dr (anti:syn) by GC; Run 2: 57.3 mg, 0.22 mmol, 72% yield, 3.5:1 dr (anti:syn) by GC. Average 74% yield, 3.5:1 dr (anti:syn). The diastereomers were separated by MPLC eluting with 5 to 30% Et_2O in petroleum ether. Major product (*anti*-diastereomer) obtained as a light yellow oil ^{1}H

NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H), 5.52 (d, *J* = 17.5 Hz, 1H), 5.46 (d, *J* = 10.5 Hz, 1H), 4.68 (app t, *J* = 8.0 Hz, 1H), 4.31 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 147.0 Hz, 2H), 3.54 (td, *J* = 8.5, 3.5 Hz, 1H), 2.30-2.20 (m, 2H), 1.98-1.94 (m, 2H), 1.62-1.57 (m, 5H), 1.45-1.42 (m, 2H), 0.97 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 132.2, 132.1, 130.9, 121.4, 84.9, 76.9, 65.9, 40.0, 34.8, 33.1, 29.4, 29.0, 28.4, 21.0, 19.3; IR (film): 3086, 2931, 2873, 1751, 1460, 1427, 1360, 1259, 1225, 1124, 1011, 943 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$: 287.1623, found 287.1626.

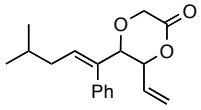


***syn*-(±)-5-((2,6,6-trimethylcyclohex-1-en-1-yl)methyl)-6-vinyl-1,4-dioxan-2-one.** Some of the major product contaminates the spectra of the minor product. Minor product (*syn*-diastereomer) obtained as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (ddd, *J* = 18.0, 10.5, 7.5 Hz, 1H), 5.50-5.45 (m, 2H), 4.79 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.36 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 88.0 Hz, 2H), 3.88 (dt, *J* = 5.5, 2.5 Hz, 1H), 2.21-2.17 (m, 1H), 2.09-2.06 (m, 1H), 1.97-1.94 (m, 2H), 1.62-1.57 (m, 5H), 1.46-1.43 (m, 2H) 0.98 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 133.4, 130.9, 130.5, 121.8, 82.9, 76.4, 66.3, 39.9, 33.0, 29.7, 29.2 (2C), 28.3, 20.7, 19.3; IR (film): 3086, 2927, 2872, 1747, 1460, 1429, 1362, 1261, 1221, 1120, 1012, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}O_3Na$ $[M+Na]^+$: 287.1623, found 287.1627.



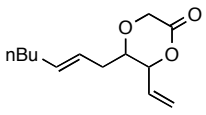
***anti*-(±)-5-((*E*)-1-phenylprop-1-en-2-yl)-6-vinyl-1,4-dioxan-2-one (13b).** (-)-(*R*,*E*)-2-(2-methyl-1-phenylhexa-1,5-dien-3-yloxy)acetic acid **12b** (73.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave a mixture of diastereomers as a light yellow oil. Run 1: 47.6 mg, 0.19 mmol, 65% yield, 7:1 dr (anti:syn) by GC; Run 2: 53.7

mg, 0.21 mmol, 70% yield, 7:1 dr (anti:syn) by GC. Average 67% yield, 7:1 dr (anti:syn). A second chromatography using MPLC eluting with gradient 5 to 20% Et_2O in petroleum ether afforded the pure major diastereomer as the only observable product. Major product (*anti*-diastereomer) obtained as a light yellow oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), 7.28-7.35 (m, 3H), 6.60 (s, 1H), 5.80 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.50 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.37 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.03-5.00 (m, 1H), 4.49 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 100.5 Hz, 2H), 3.96 (d, *J* = 9.0 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 136.2, 131.8, 131.7, 131.3, 128.9, 128.2, 127.3, 120.0, 82.5, 81.8, 65.5, 14.1; IR (film): 3082, 3055, 3026, 2983, 2918, 1751, 1601, 1493, 1444, 1363, 1265, 1232, 1115, 1009, 924 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{16}O_3Na$ $[M+Na]^+$: 267.0997, found 267.1000.

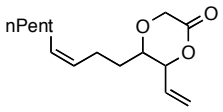


***anti*- and *syn*-(±)-5-((*E*)-4-methyl-1-phenylpent-1-en-1-yl)-6-vinyl-1,4-dioxan-2-one (13c).** (±)-(*E*)-2-(8-methyl-5-phenylnona-1,5-dien-4-yloxy)acetic acid **12c** (86.5 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 10% EtOAc in hexanes gave an inseparable mixture of diastereomers as a light yellow oil. Run 1: 47.5 mg, 0.16 mmol, 55% yield, 6:1 dr (anti:syn) by GC; Run 2: 43.7 mg, 0.15 mmol, 51% yield, 6:1 dr (anti:syn) by GC. Average 53% yield, 6:1 dr (anti:syn). ^{1}H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 7.37-7.29 (m, 3H), 7.17-7.15 (m, 2H), 5.89 (t, *J* = 7.5 Hz, 1H), 5.76 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.34 (d, *J* = 11.0 Hz, 1H), 4.74-4.71 (m, 1H), 4.43 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 87.0 Hz, 2H), 4.08 (d, *J* = 9.5 Hz, 1H), 1.91-1.81 (m, 2H), 1.68-1.60 (m, 1H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), minor product (*syn*-diastereomer): δ 6.01 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9,

137.1, 136.7, 135.8, 135.6, 134.0, 131.3, 130.8, 129.5, 129.1, 128.9, 128.6, 128.1, 127.6, 127.4, 120.8, 120.2, 81.8, 81.4, 80.4, 66.2, 65.5, 37.5, 37.1, 28.7, 28.5, 22.5, 22.4, 22.2; IR (film): 3082, 3055, 3022, 2956, 2927, 2897, 2870, 1755, 1495, 1466, 1427, 1367, 1340, 1265, 1227, 1111, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{22}O_3Na$ $[M+Na]^+$: 309.1467, found 309.1454.

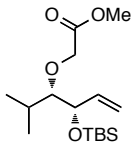


***anti*- and *syn*-(±)-(*E*)-5-(hept-2-en-1-yl)-6-vinyl-1,4-dioxan-2-one (13d).** (±)-(*E*)-2-(undeca-1,6-dien-4-yloxy)acetic acid **12d** (67.9 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave an inseparable mixture of diastereomers as a light yellow oil. Run 1: 48.5 mg, 0.22 mmol, 72% yield, 3:1 dr (anti:syn) by GC; Run 2: 47.7 mg, 0.21 mmol, 71% yield, 3:1 dr (anti:syn) by GC. Average 72% yield, 3:1 dr (anti:syn). ^1H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 5.75 (ddd, J = 17.5, 10.5, 7.0 Hz, 1H), 5.54-5.44 (m, 1H), 5.41-5.36 (m, 1H), 5.45 (d, J = 17.5 Hz, 1H), 5.38 (d, J = 10.0 Hz, 1H), 4.71 (app t, J = 8.5 Hz, 1H), 4.34 (ABq, J = 18.0 Hz, $\Delta\nu_{AB}$ = 115.5 Hz, 2H), 3.42-3.38 (m, 1H), 2.37-2.32 (m, 1H), 2.20-2.13 (m, 1H), 2.02-1.96 (m, 2H), 1.34-1.23 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H), minor product (*syn*-diastereomer): δ 5.95 (ddd, J = 17.5, 10.0, 7.5 Hz, 1H), 4.78 (d, J = 7.5 Hz, 1H), 4.37 (ABq, J = 18.0 Hz, $\Delta\nu_{AB}$ = 57.0 Hz, 2H), 3.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.7, 134.8, 134.6, 131.6, 130.7, 123.3, 123.2, 121.3, 121.0, 83.3, 82.1, 75.7, 74.3, 65.6, 33.6, 33.3, 32.1, 31.3 (2C), 22.1, 13.8; IR (film): 3087, 2956, 2927, 2872, 2838, 1753, 1427, 1344, 1261, 1228, 1122, 1011, 974, 939 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1413, found 224.1417.



(Z)-5-(non-3-en-1-yl)-6-vinyl-1,4-dioxan-2-one (13e). (±)-(*Z*)-2-(trideca-1,7-dien-4-yloxy)acetic acid **12e** (64.8 mg, 0.3 mmol, 1.0 equiv) was reacted according to the general procedure at 65 ˚C for 72 h. Purification by flash chromatography on silica eluting with 20% EtOAc in hexanes gave an inseparable mixture of diastereomers as a light yellow oil. Run 1: 36.9 mg, 0.15 mmol, 49% yield, 2:1 dr (anti:syn) by GC; Run 2: 40.7 mg, 0.16 mmol, 54% yield, 2:1 dr (anti:syn) by GC. Average 52% yield, 2:1 dr (anti:syn). ^{1}H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 5.75 (ddd, *J* = 17.5, 10.5, 8.0 Hz, 1H), 5.49-5.39 (m, 2H), 5.35-5.25 (m, 2H), 4.86 (app t, *J* = 8.0 Hz, 1H), 4.34 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 137.0 Hz, 2H), 3.38 (app t, *J* = 9.0 Hz, 1H), 2.21-2.13 (m, 2H), 2.05-1.95 (m, 2H), 1.65-1.51 (m, 2H), 1.39-1.25 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H), minor product (*syn*-diastereomer): δ 5.97 (ddd, *J* = 17.0, 10.0, 7.5 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.37 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 75.0 Hz, 2H), 3.82-3.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.9, 131.7, 131.6 (2C), 130.9, 127.7, 127.5, 121.3 (2C), 84.3, 82.7, 75.1, 73.6, 65.8, 65.7, 31.5, 30.3, 29.9, 29.3, 27.1 (2C), 22.8, 22.5, 22.4, 14.0; IR (film): 3086, 3006, 2956, 2927, 2856, 1753, 1645, 1458, 1429, 1344, 1259, 1225, 1122, 1003, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1804, found 253.1803.

Differential Diol Protection and Iterative C—H Oxidation

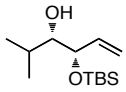


(-)-Methyl 2-(((3*S*,4*S*)-4-((tert-butyldimethylsilyl)oxy)-2-methylhex-5-en-3-yl)oxy)acetate (14). No precautions were taken to exclude air or moisture. Dioxanone (-)-**7** (242.0 mg, 1.4 mmol, 1.0 equiv) was dissolved in 3:1 THF:H_2O (2.1:0.7 mL) in a 10 mL round

bottom flask and the solution was cooled to 0 ˚C. $LiOH{\cdot}H_2O$ (117.5 mg, 2.8 mmol, 2.0 equiv) was added in one portion and the reaction stirred at 0 ˚C for 30 min. Aqueous pH 4 buffer (3 mL) was added and the pH of the reaction was adjusted to ~4 by careful addition of 1M H_3PO_4. The reaction was diluted with EtOAc (~5 mL), the layers separated and the aqueous extracted with EtOAc (3 x 5 mL). The combined orgainc layers were dried (Na_2SO_4), filtered and concentrated. The crude material was dissolved in CH_2Cl_2 (7 mL) in a 25 mL round bottomed flask and the solution cooled to 0 ˚C. 2,6-lutidine (0.98 mL, 8.4 mmol, 6.0 equiv) was added by syringe followed by dropwise addition of TBSOTf (Oakwood Products, Inc., 0.97 mL, 4.2 mmol, 3.0 equiv). The reaction was stirred for 1 h at 0 ˚C then quenched with 1 M HCl (~10 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with sat. aq. NH_4Cl (2 x 15 mL) to ensure hydrolysis of the TBS ester, dried ($MgSO_4$), filtered and concentrated. The crude material was dissolved in DMF (7 mL) and esterified with MeI (Sigma-Aldrich, 0.26 mL, 4.2 mmol, 3.0 equiv) and K_2CO_3 (580.5 mg, 4.2 mmol, 3.0 equiv) overnight. Quench with HCl and workup as above followed by purification by flash chromatography on silica (~75 mL) eluting with 5% EtOAc in hexane afforded the title compound (441.1 mg, 1.2 mmol, 87% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.24 (d, J = 17.0 Hz, 1H), 5.13 (d, J = 10.5 Hz, 1H), 4.29 (ABq, J = 16.0 Hz, $\Delta\nu_{AB}$ = 57.5 Hz, 2H), 4.25 (app t, J = 6.0 Hz 1H), 3.73 (s, 3H), 2.99 (app t, J = 5.0 Hz, 1H), 1.88-1.80 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.3, 115.8, 89.1, 76.0, 69.9, 51.5, 29.0, 25.8, 20.2, 18.1, 17.1, -4.4, -4.9; IR (film): 3080, 2956, 2931, 2885, 2858, 1766, 1743, 1471, 1439, 1389, 1363, 1255, 1207, 1130, 1082, 1030, 1005, 928 cm^{-1};

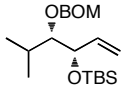
HRMS (ESI) *m/z* calc'd for $C_{16}H_{33}O_4Si$ $[M+H]^+$: 317.2148, found 317.2143; $[\alpha]_D^{25}$ = -23.7° (c=1.0, $CHCl_3$).

Procedure for the Preparation of SmI_2 as a Solution in THF. An oven dried 100 mL schlenk flask was charged in the glove box with samarium powder (Strem, ~40 mesh, 6.0 mmol, 1.2 equiv) and a stir bar. The flask was removed from the glove box and put under a stream of N_2. THF (35 mL) was added by syringe. Separately, with precautions taken to exclude light, diiodoethane (Sigma-Aldrich) was dissolved in Et_2O (30 mL) and washed with 0.2 M sodium thiosulfate (1x10 mL) and water (1x10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to give a brilliant white solid, which was dried for 30 min. on hi-vacuum. This purification should be carried out immediately prior to preparation of SmI_2 as the white solid turns brown even if kept under intert atmosphere in the dark. Purified diiodoethane (1.42 g, 5.0 mmol, 1.0 equiv) was dissolved in THF (5 mL) and added by syringe to the vigorously stirred suspension of Sm in THF. The solution gradually turns green then deep blue indicating formation of the reagent. The solution was stirred for 5h (we have noted a dependence of the reaction time on which batch of Sm powder is used sometimes requiring stirring overnight) at room temperature then titrated with a 0.1 M solution of I_2 in PhH to give a yellow end point. SmI_2 concentrations were generally between 0.05 and 0.06 M.



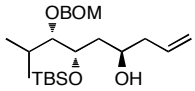
(-)-(3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylhex-5-en-3-ol. Ester (-)-**14** (183.6 mg, 0.58 mmol, 1.0 equiv) was dissolved in HMPA (1.8 mL) in a 100 mL round bottom flask wrapped in aluminum foil. Ethylene glycol (39 μL, 43.4 mg, 0.7 mmol, 1.2 equiv) was added by syringe. A freshly prepared deep blue solution of SmI_2 in THF (3.0 equiv) was cannulated into the reaction flask and the reaction was allowed to stir at room temperature for 12h. The reaction was quenched with 1N HCl and diluted with EtOAc. The layers were

separated and the aqueous layer extracted with EtOAc (3x10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (~125 mL) eluting with 5% Et_2O in petroleum ether afforded the title compound (86.7 mg, 0.35 mmol, 62% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H), 5.22 (d, *J* = 17.0, 1H), 5.15 (d, *J* = 10.5, 1H), 4.07 (app t, *J* = 6.5 Hz, 1H), 3.12 (q, *J* = 5.5 Hz, 1H), 2.39 (d, *J* = 5.0 Hz, 1H), 1.75-1.69 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 116.5, 79.3, 75.6, 29.5, 25.8, 20.1, 18.1, 16.7, -3.9, -4.9; IR (film): 3577, 3080, 2958, 2931, 2899, 2860, 1471, 1390, 1362, 1255, 1076, 1043, 1005, 930 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{28}O_2NaSi$ $[M+Na]^+$: 267.1756, found 267.1753; $[\alpha]_D^{25}$ = -4.0° (c=1.0, $CHCl_3$).



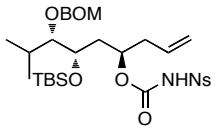
(-)-(5*S*,6*S*)-5-isopropyl-8,8,9,9-tetramethyl-1-phenyl-6-vinyl-2,4,7-trioxa-8-siladecane (15). (-)-(3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2-methylhex-5-en-3-ol (122.2 mg, 0.5 mmol, 1.0 equiv) and a few crystals of TBAI (Sigma-Aldrich) were dissolved in CH_2Cl_2 (1 mL) in a 10 mL round bottom flask. The solution was cooled to 0 °C and DIPEA (0.15 mL, 0.88 mmol, 1.75 equiv) was added by syringe followed by BOMCl (TCI, 0.12 mL, 0.75 mmol, 1.5 equiv) dropwise by syringe. The solution was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with H_2O (5 mL) and diluted with EtOAc (10 mL). The organic layer was washed with 1N HCl (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (~125 mL) eluting with 2% EtOAc in hexane to give the title compound (143.9 mg, 0.39 mmol, 79% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 5.90 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.27 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.15 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.91(ABq, *J* = 7.0 Hz, $\Delta\nu_{AB}$ = 76.0 Hz, 2H), 4.67 (ABq,

J = 12.0 Hz, $\Delta\nu_{AB}$ = 84.5 Hz, 2H), 4.25 (app t, J = 6.0 Hz, 1H), 3.28 (app t, J = 6.0 Hz, 1H), 1.89-1.83 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.1, 128.3, 127.7, 127.5, 115.6, 96.5, 86.7, 76.0, 69.9, 29.0, 25.9, 20.6, 18.1, 17.5, -4.5, -4.8; IR (film): 3089, 3066, 3032, 2956, 2931, 2887, 2858, 1496, 1471, 1403, 1387, 1363, 1254, 1144, 1105, 1082, 1025, 924 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{21}H_{36}O_3NaSi$ $[M+Na]^+$: 387.2331, found 387.2334; $[\alpha]_D^{24}$ = -53.1˚ (c=1.0, $CHCl_3$).



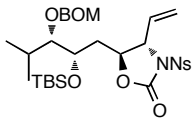
(-)-(4*R*,6*S*,7*S*)-7-((benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)-oxy)-8-methylnon-1-en-4-ol. BH_3-Me_2S (Sigma-Aldrich, 85 μL, 67.6 mg, 0.89 mmol, 2.35 equiv) was dissolved in THF (1 mL) in a 25 mL round bottom flask and the solution cooled to 0 ˚C. 2-methyl-2-butene (Sigma-Aldrich, 0.19 mL, 125.5 mg, 1.79 mmol, 4.7 equiv) was added dropwise and the solution stirred at 0 ˚C for 2 h. A solution of alkene (-)-**15** (138.8 mg, 0.38 mmol, 1.0 equiv) in THF (1 mL) was added dropwise to the borane solution. The reaction was gradually warmed to 45 ˚C and stirred overnight at which point the reaction was cooled to 0 ˚C and H_2O (1 mL), 3M NaOH (0.2 mL) and 30% wt. H_2O_2 (0.4 mL) were added. Stirring was continued at room temperature for 3h. The reaction was worked up and passed through a plug of silica (~100 mL) eluting first with 5% EtOAc to remove the non-polar boron byproducts followed by 20% EtOAc in hexane, which was collected and concentrated. The crude was dissolved in CH_2Cl_2 (1.5 mL) in a 25 mL round bottom flask. PCC (79.8 mg, 0.37 mmol, 1.2 equiv), 4 Å MS (120 mg) and celite (120 mg) were added in one portion and the reaction was stirred at room temperature for 6 h. The reaction mixture was plugged through silica (~100 mL) with 20% EtOAc in hexane and the solvent concentrated. The crude aldehyde was azeotropically dried with PhH (3 x 5 mL). The aldehyde was allylated according to the procedure of Brown.[25]

Purification by flash chromatography on silica (~75 mL) eluting with 10% EtOAc in hexane afforded the title compound (114.1 mg, 0.27 mmol, 75% yield, 3 steps) as a colorless oil and 5:1 mixture of diastereomers. A second chromatographic purification was required to remove excess diisopinocampheol byproduct and obtain diastereomerically pure material. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.83 (ddt, *J* = 16.0, 11.0, 7.0 Hz, 1H), 5.13-5.10 (m, 2H), 4.83 (ABq, *J* = 7.0 Hz, $\Delta\nu_{AB}$ = 48.5 Hz, 2H), 4.66 (ABq, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 25.5 Hz, 2H), 4.10-4.07 (m, 1H), 3.87-3.82 (m, 1H), 3.37 (app t, *J* = 6.0 Hz, 1H), 2.84 (br s, 1H), 2.24-2.21 (m, 2H), 1.91-1.84 (m, 1H), 1.73 (ddd, *J* = 14.5, 10.5, 4.0 Hz, 1H), 1.63 (ddd, *J* = 14.5, 6.5, 2.0 Hz, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 134.8, 128.3, 127.7, 127.5, 117.5, 96.1, 85.7, 72.4, 70.1, 67.8, 42.7, 39.0, 28.9, 25.8, 20.7, 18.5, 17.9, -4.4, -5.0; IR (film): 3070, 3033, 2954, 2929, 2858, 1722, 1641, 1471, 1387, 1363, 1257, 1076, 1041 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{42}O_4NaSi$ $[M+Na]^+$: 445.2750, found 445.2745; $[\alpha]_D^{24}$ = -21.4° (c=1.0, $CHCl_3$).



(-)-(4*R*,6*S*,7*S*)-7-((benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)oxy)-8-methylnon-1-en-4-yl (4-nitrophenyl)sulfonylcarbamate (16). (-)-(4*R*,6*S*,7*S*)-7-((benzyloxy)methoxy)-6-((*tert*-butyldimethylsilyl)oxy)-8-methylnon-1-en-4-ol (42.2 mg, 0.10 mmol, 1.0 equiv) was dissolved in THF (1 mL) in a 10 mL round bottom flask under N_2. *p*-Nitrobenzenesulfonyl isocyanate (34.2 mg, 0.15 mmol, 1.5 equiv) was added and the reaction stirred at room temperature for 1 h at which point TLC showed complete consumption of the starting material. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and diluted with EtOAc (~5 mL). The layers were separated and the organic layer was washed with brine (1 x 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash

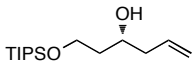
chromatography on silica (~50 mL) eluting with 15% EtOAc in hexane with 1% AcOH afforded the title compound (58.3 mg, 0.090 mmol, 90% yield) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 8.5 Hz, 2H), 7.39-7.28 (m, 5H), 5.57 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.01 (app p, *J* = 6.0 Hz, 1H), 4.97-4.89 (m, 2H), 4.72 (ABq, *J* = 7.0 Hz, $\Delta\nu_{AB}$ = 50.0 Hz, 2H), 4.61 (ABq, *J* = 12.0 Hz, $\Delta\nu_{AB}$ = 37.5 Hz, 2H), 3.82-3.77 (m, 1H), 3.24 (app t, *J* = 6.0 Hz, 1H), 2.33-2.28 (m, 1H), 2.21-2.15 (m, 1H), 1.90-1.84 (m, 1H), 1.82-1.76 (m, 1H), 1.70-1.63 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 149.5, 144.1, 137.6, 132.3, 129.7, 128.4, 127.7, 124.0, 118.5, 95.4, 84.7, 75.1, 70.2, 69.8, 38.3, 36.4, 28.8, 25.7, 20.6, 18.7, 17.8, -4.3, -4.8; IR (film): 3246 (br), 3109, 3072, 3032, 2956, 2931, 2889, 2858, 1751, 1643, 1608, 1535, 1441, 1350, 1313, 1288, 1254, 1227, 1167, 1090, 1039 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{31}H_{46}N_2O_9NaSiS$ $[M+Na]^+$: 673.2591, found 673.2602; $[\alpha]_D^{26}$ = -15.6° (c=1.0, $CHCl_3$). Note: one peak is missing in the ^{13}C NMR, which we believe is overlapped by another peak. The identity of this compound was confirmed by ^{1}H NMR, HRMS and its reactivity to form **9** (*vide infra*).



(-)-(4*S*,5*S*)-5-((2*S*,3*S*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)-3-((4-nitrophenyl)sulfonyl)-4-vinyloxazolidin-2-one (17). According to the procedure of White,[1] a 1/2 dram vial was charged sequentially with carbamate (-)-**16** (58.3 mg, 0.09 mmol, 1.0 equiv), 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate **1** (Strem, 4.6 mg, 0.09 mmol, 0.10 equiv), phenyl-*p*-benzoquinone (Acros, 17.4 mg, 0.095 mmol, 1.05 equiv), 1,2-bis(phenylsulfinyl)ethane (1.3 mg, 0.045 mmol, 0.05 equiv) a stir bar and THF (136 μL). The vial was fitted with a Teflon lined cap and heated to 45 ˚C with

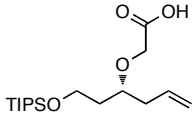
magnetic stirring in an oil bath for 24 h. The vial was removed, allowed to cool to room temperature and transferred to a 25 mL separatory funnel with CH_2Cl_2 (~5 mL). Sat. aq. NH_4Cl (~2 mL) and brine (~2 mL) were added. The layers were separated and the aqueous extracted with CH_2Cl_2 (3 x 5mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude was analyzed by ^1H NMR to determine the dr, 1.6:1 (syn:anti). Purification by flash chromatography on silica (~50 mL) eluting with gradient 10 to 20% Et_2O in hexane afforded the title compound (40.9 mg, 0.058 mmol, 65% yield) as a mixture of diasteromers. The diastereomers were separated by MPLC eluting with gradient 0 to 10% Et_2O in petroleum ether. Major product (*anti*-diastereomer) isolated as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) *anti*-diastereomer δ 8.38 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H), 7.39-7.26 (m, 5H), 5.73-5.66 (m, 1H), 5.40 (d, J = 17.0 Hz, 1H), 5.39 (d, J = 10.0 Hz, 1H), 4.80 (ABq, J = 6.5 Hz, $\Delta\nu_{AB}$ = 58.0 Hz, 2H), 4.66 (ABq, J = 12.0 Hz, $\Delta\nu_{AB}$ = 20.0 Hz, 2H), 4.53 (dd, J = 8.0, 3.5 Hz, 1H), 4.47-4.44 (m, 1H), 3.98-3.93 (m, 1H), 3.27-3.23 (app t, J = 5.5 Hz, 1H), 2.07-2.00 (m, 1H), 1.93-1.89 (m, 1H), 1.85-1.80 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H), 0.85 (s, 9H) 0.05 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9 (2C), 143.4, 137.7, 132.7, 130.1, 128.5, 127.7, 127.6, 124.2, 121.7, 96.2, 85.7, 78.2, 70.2, 69.9, 65.1, 37.0, 28.8, 25.8, 20.6, 18.8, 17.8, -4.2, -4.9; IR (film): 3109, 3033, 2956, 2929, 2893, 2858, 1786, 1606, 1535, 1471, 1404, 1381, 1350, 1317, 1255, 1180, 1144, 1126, 1093, 1039, 945 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{31}H_{44}N_2O_9NaSiS$ $[M+Na]^+$: 671.2435, found 671.2241; $[\alpha]_D^{27}$ = -26.9° (c=1.0, $CHCl_3$).

Synthesis of a Tetrahydropyran Intermediate in the Synthesis of SCH351448.

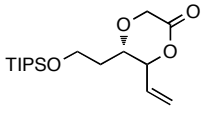


(+)-(*R*)-1-(triisopropylsiloxy)hex-5-en-ol (18). According to the procedure of Brown,[25] a 50 mL 3-neck flask was charged in the glove box with (+)-*B*-methoxydiisopinocampheylborane (Sigma-Aldrich, 3.32 g, 10.5 mmol, 1.05 equiv) and a stir bar. The flask was fitted with an apparatus for air-free filtration into a 100 mL 3-neck flask and all other openings sealed with rubber septa. The apparatus was removed from the glove box and put under N_2. Et_2O (10 mL) was added to the flask and the solution cooled to 0 ˚C. A solution of allylmagnesium bromide (0.83 M in Et_2O, 12.0 mL, 10 mmol, 1.0 equiv) was added dropwise to the borane solution at 0˚C, stirred for 10 min. at that temperature then allowed to warm to room temperature for an additional 1 h, at which point the solution had turned milky white. The flask was put under hi-vacuum for 1h to remove the Et_2O. The resultant solids were extracted with pentane (2 x 15 mL) and filtered into the 100 mL 3-neck flask to give a colorless solution of the borane in pentane. The flask was put under hi-vacuum for 1h to remove the pentane. The resulting colorless oil was dissolved in Et_2O (20 mL) and cooled to -100 ˚C (liquid N_2/EtOH). A solution of 3-(triisopropylsiloxy)propanal[20] (2.42 g, 10.5 mmol, 1.05 equiv) in Et_2O (10 mL) and cooled to -78 ˚C was cannulated slowly into the reaction mixture down the side of the flask. After the addition was complete, the reaction was stirred at -100˚C for an additional 30 min. at which time MeOH (0.2 mL) was added and the reaction was allowed to warm to room temperature. 3 M NaOH (4 mL) and 30% wt. H_2O_2 (8 mL) were added the reaction heated to reflux for 4 h to complete the oxidation of the auxiliary. The reaction was allowed to cool to room temperature and transferred to a separatory funnel with Et_2O (~40 mL). The layers were separated and the aqueous layer extracted with Et_2O (3x20 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (1 x 10 mL) and brine (1 x 10 mL). The organic layer was

dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel (~250 mL) eluting with 3% EtOAc in hexanes afforded the title compound (2.396 g, 8.3 mmol, 83% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.14-5.07 (m, 2H), 4.01-3.98 (m, 1H), 3.93-3.88 (m, 2H), 3.56 (d, *J* = 2.0 Hz, 1H), 2.31-2.22 (m, 2H), 1.71-1.67 (m, 2H), 1.06 (m, 21H); $[\alpha]_D^{25}$= +7.4˚ (c=1.0, $CHCl_3$), lit. $[\alpha]_D^{24}$ = +7.6˚ (c=1.0, $CHCl_3$). These spectral data match those previously reported in the literature.[20]

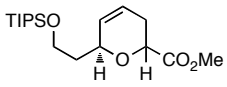


(-)-(*R*)-2-(1-(triisopropylsilyloxy)hex-5-en-3-yloxy)acetic acid. Alcohol (+)-**18** (2.18 g, 8.0 mmol, 1.0 equiv) was reacted according to the general procedure for the synthesis of carboxylic acid starting materials described above to afford the title compound (1.85 g, 5.6 mmol, 70% yield) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (br s, 1H), 5.83-5.75 (m, 1H), 5.16-5.12 (m, 2H), 4.19 (ABq, *J* = 16.5 Hz, $\Delta\nu_{AB}$ = 42.5 Hz, 2H), 3.92 (p, *J* = 5.5 Hz, 1H), 3.82 (p, *J* = 5.5Hz, 1H), 3.70 (p, *J* = 6.5 Hz, 1H), 2.35 (t, *J* = 6.0 Hz, 2H), 1.77 (q, *J* = 6.0 Hz, 2H), 1.10-1.06 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 133.8, 118.1, 78.4, 66.6, 60.2, 38.4, 36.7, 17.9, 11.8; IR (film): 3300, 3080, 2943, 2867, 1738, 1641, 1464, 1385, 1246, 1109, 995, 916, 883 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{35}O_4Si$ $[M+H]^+$: 331.2305, found 331.2297, $[\alpha]_D^{25}$ = -22.5˚ (c=1.0, $CHCl_3$).



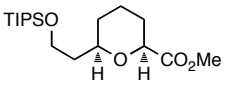
(5*S*)-5-(2-(triisopropylsilyloxy)ethyl)-6-vinyl-1,4-dioxan-2-one (19). (-)-(*R*)-2-(1-(triisopropylsilyloxy)hex-5-en-3-yloxy)acetic acid (331 mg, 1.0 mmol, 1.0 equiv) was reacted according to the general procedure for intramolecular C—H oxidation at 65 ˚C for 72 h. Purification by flash chromatography on silica gel (~125 mL) eluting with 10% EtOAc in hexanes afforded the title compound as a light yellow oil (273 mg, 0.83 mmol, 83% yield) and an

inseparable 2:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) major product (*anti*-diastereomer): δ 5.78 (ddd, *J* = 18.0, 10.5, 7.5 Hz, 1H), 5.49 (d, *J* = 17.5 Hz, 1H), 5.41 (d, *J* = 11.0 Hz, 1H), 4.76 (app t, *J* = 8.0 Hz, 1H), 4.35 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 124.5 Hz, 2H), 3.86-3.77 (m, 2H), 3.67 (td, *J* = 9.5, 2.5 Hz, 1H), 1.88-1.82 (m, 1H), 1.64-1.56 (m, 1H), 1.13-1.03 (m, 21H), minor product (*syn*-diastereomer): δ 5.99 (ddd, *J* = 18.0, 10.5, 7.5, 1H), 4.82 (dd, *J* = 7.0, 2.0 Hz, 1H), 4.38 (ABq, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 66.5 Hz, 2H), 4.14-4.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 167.0, 131.6, 131.1, 121.3, 121.2, 84.3, 82.8, 72.5, 71.1, 65.8, 65.7, 58.6, 58.3, 33.6, 33.4, 17.9 (2C), 11.8; IR (film): 3035, 2945, 2868, 1741, 1464, 1439, 1383, 1288, 1180, 1099, 1014 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{33}O_4Si$ $[M+H]^+$: 329.2148, found 329.2140.



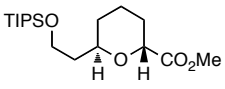
(6*S*)-methyl 6-(2-(triisopropylsilyloxy)ethyl)-3,6-dihydro-2*H*-pyran-2-carboxylate (20). According to the procedure of Burke,[26] to a freshly prepared solution of LiHMDS (6.0 mmol, 3.0 equiv) in THF (15 mL) at -78 ˚C in a 100 mL round bottom flask was added the clear supernatant resulting from centrifugation of a 1:1 v:v mixture of TMSCl (Sigma-Aldrich) and Et_3N (7 mL total added). The resulting mixture was stirred for 15 min. at -78 ˚C at which time a solution of dioxanone **14** (657.0 mg, 2.0 mmol, 1.0 equiv) in THF (10 mL) was cannulated dropwise into the reaction using THF (~2 mL) to complete the transfer. The reaction was stirred for 2 h at -78 ˚C then allowed to warm to room temperature. Toluene (~40 mL) was added and the reaction flask was fitted with a reflux condenser, submerged in an oil bath and heated to reflux (~110 ˚C) for 12-24 h. The reaction was allowed to cool to room temperature and the solvent removed via rotary evaporation. The crude material was dissolved in DMF (5 mL) esterified with MeI (Sigma-Aldrich, 0.15 mL, 2.4 mmol, 3.0 equiv) and K_2CO_3 (330.0 mg,

2.4 mmol, 3.0 equiv) for 24 h at room temperature. The reaction was quenched with 1N HCl and diluted with EtOAc (~10 mL). The layers were separated and the aqueous extracted with EtOAc (3x10 mL). the combined organic layers were dried ($MgSO_4$), filtered and concentrated. GC of the crude material showed the dr to be 3:1 (syn:anti), the same as the starting dioxanone. Purification by flash chromatography on silica (~125 mL) eluting with 5% EtOAc in hexane afforded the title compound (660.1 mg, 1.7 mmol, 83 % yield) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) major product, (*anti*-diastereomer) δ 5.81-5.77 (m, 1H), 5.73 (app t, J = 12.5 Hz, 1H), 4.41 (br s, 1H), 4.22 (dd, J = 10.5, 4.0 Hz, 1H), 3.86-3.78 (m, 2H), 3.75 (s, 3H), 2.39-2.32 (m, 1H), 2.29-2.25 (m, 1H), 1.90-1.72 (m, 2H), 1.12-1.02 (m, 21H), minor product (*syn*-diastereomer) δ 4.61-4.55 (m, 1H), 4.37 (app t, J = 6.0 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.7, 130.9, 128.8, 130.4, 129.8, 123.2, 122.3, 72.9, 72.4, 69.8, 68.4, 59.9, 59.4, 52.0, 38.3, 37.6, 28.1, 27.1, 17.9, 11.9; IR (film): 3087, 2943, 2868, 1755, 1464, 1385, 1344, 1254, 1227, 1101, 1012, 947 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{35}O_4Si$ $[M+H]^+$: 343.2305, found 343.2302.

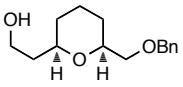


(-)-(2*S*,6*R*)-methyl 6-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-carboxylate. Dihydropyran **20** (325.4 mg, 0.95 mmol, 1.0 equiv) was dissolved in EtOAc (10 mL, 0.1 M) in a 25 mL round bottom flask containing a stir bar. 5% Pd/C (Sigma-Aldrich, 32.5 mg, 10 wt. %) was added and the flask sealed with a rubber septum. H_2 was bubbled through the solution until all starting material was consumed as indicated by TLC (3-6 hrs). The reaction was filtered through a short plug of celite and silica with EtOAc and concentrated. Purification and separation of diastereomers by flash chromatography on silica eluting with 5% EtOAc in hexane afforded the title compound (222.8 mg, 0.63 mmol, 68% yield as a single diastereomer,

quantitative yield based on starting *syn*-**15**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.98 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.85 (ddd, *J* = 10.0, 8.5, 4.5 Hz, 1H), 3.76-3.72 (m, 1H), 3.73 (s, 3H), 3.60-3.55 (m, 1H), 1.93-1.89 (m, 2H), 1.84 (ddt, *J* = 14.0, 8.5, 5.0 Hz, 1H), 1.69 (ddt, *J* = 13.5, 8.5, 5.5 Hz, 1H), 1.63-1.48 (m, 3H), 1.34-1.27 (m, 1H), 1.08-1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 77.2, 75.2, 59.6, 52.2, 39.4, 31.1, 29.1, 23.7, 18.2 (2C), 17.9, 12.5, 12.2; IR (film): 2943, 2893, 2866, 1765, 1741, 1462, 1438, 1365, 1296, 1198, 1100, 1053 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{37}O_4Si$ $[M+H]^+$: 345.2461, found 345.2455; $[\alpha]_D^{25}$ = -30.4° (c=1.0, $CHCl_3$).



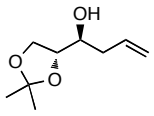
(-)-(2*R*,6*R*)-methyl 6-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-carboxylate. Minor diastereomer isolated as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, *J* = 4.5 Hz, 1H), 3.93-3.87 (m, 1H), 3.81-3.76 (m, 2H), 3.73 (s, 3H), 1.99-1.96 (m, 1H), 1.87-1.60 (m, 5H), 1.53-1.46 (m, 1H), 1.35-1.29 (m, 1H), 1.09-1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 72.8, 71.3, 60.4, 52.0, 39.0, 30.8, 27.2, 20.0, 18.2, 12.2; IR (film): 2943, 2893, 2866, 1753, 1738, 1464, 1443, 1383, 1365, 1238, 1194, 1167, 1119, 1101, 1053, 1012, 996 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{37}O_4Si$ $[M+H]^+$: 345.2461, found 345.2455; $[\alpha]_D^{25}$ = -15.9° (c=1.0, $CHCl_3$).



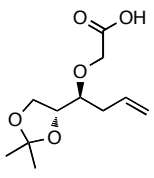
(-)-2-((2*R*,6*S*)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)ethanol (21). (-)-(2*S*,6*R*)-methyl 6-(2-((triisopropylsilyl)oxy)ethyl)tetrahydro-2*H*-pyran-2-carboxylate (82.7 mg, 0.24 mmol, 1.0 equiv) was dissolved in THF (2 mL) in a 25 mL round bottom flask. The solution was cooled to 0 ˚C and solid $LiAlH_4$ (Sigma-Aldrich, 18.2 mg, 0.48 mmol, 2.0 equiv) was added in one portion. The reaction was stirred at 0 ˚C for 1 h at which point the reaction was complete by TLC. H_2O was added carefully to the reaction mixture until the evolution of gas

ceased. $MgSO_4$ and celite were added, the mixture diluted with EtOAc and stirred vigorously for 15 min. The entire mixture was filtered through a pad of silica with 30% EtOAc in hexane. The filtrate was concentrated and transferred to a 25 mL round bottomed flask under Ar. DMF (1.6 mL) and BnBr (Sigma-Aldrich, 57 μL, 0.48 mmol, 2.0 equiv) were added and the solution was cooled to 0 ˚C. NaH (Sigma-Aldrich, 60% wt., 19.2 mg, 0.48 mmol, 2.0 equiv) was added in one portion. The reaction was stirred at 0 ˚C for 30 min then allowed to warm to room temperature for an additional 4 h, at which point the reaction was complete by TLC. The reaction was quenched with 1 N HCl and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 x 10mL) and the combined organic layers dried ($MgSO_4$), filtered and concentrated. The crude was plugged through a pad of silica with 20% EtOAc in hexane, the filtrate concentrated and dissolved in EtOH (1mL). 3 M HCl (1 mL) was added and the reaction was stirred at room temperature for 6 h at which point the reaction was complete by TLC. The reaction was diluted with EtOAc and brine and worked up as above. Purification by flash chromatography on silica gel (~75 mL) eluting with 50% EtOAc in hexane afforded the title compound (129.3 mg, 0.18 mmol, 74% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.32 (m, 3H), 7.29-7.26 (m, 2H), 4.53 (ABq, J = 12.0 Hz, $\Delta\nu_{AB}$ = 19.5 Hz, 2H), 3.83-3.76 (m, 2H), 3.64-3.58 (m, 2H), 3.46-3.38 (m 2H), 3.33 (br s, 1H), 1.86-1.75 (m, 2H), 1.69-1.63 (m, 1H), 1.58-1.49 (m, 3H), 1.38-1.21 (m, 2H); $[\alpha]_D^{24}$ = -13.7˚ (c=1.0, $CHCl_3$), lit $[\alpha]_D^{25}$= -12.8˚ (c=1.0, $CHCl_3$). These spectral data match those previously reported in the literature.[20]

Synthesis of a Dihydropyran Intermediate in the Synthesis of Goniodomin A.

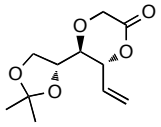


(+)-(*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (22). Zn powder (Sigma-Aldrich, 51.8 mmol, 3.39 g, 2.0 equiv) was suspended in THF (20 mL) in a 50 mL round bottom flask fitted with an addition funnel. The solution was cooled to 0 ˚C and freshly distilled (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde[27] (25.9 mmol, 3.37 g, 1.0 equiv) was added, followed by allyl bromide (Sigma-Aldrich, 51.8 mmol, 6.23 g, 4.5 mL, 2.0 equiv) dropwise through an addition funnel over 10 min. After the addition was complete the reaction was stirred at 0 ˚C for 4 h. Sat. aq. NH_4Cl (20 mL) was added dropwise through the addition funnel over 30 min and the reaction was diluted with EtOAc (20 mL). The insoluble solids were filtered off. The layers were separated and the aqueous extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. NMR of the crude showed a 10:1 dr (anti:syn). Purification and separation of the diastereomers by flash chromatography on silica (~250 mL) eluting with gradient 10 to 40% Et_2O in petroleum ether afforded the pure *anti*-diastereomer (2.89 g, 16.8 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, J = 17.5, 10.0, 7.0 Hz, 1H), 5.18-5.14 (m, 2H), 4.04-4.00 (m, 2H), 3.95-3.91 (m, 1H), 3.80-3.75 (m, 1H), 2.36-2.30 (m, 1H), 2.26-2.17 (m, 1H), 1.99 (d, J = 3.5 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H); $[\alpha]_D^{25}$= +16.6˚ (c=1.1, $CHCl_3$), lit. $[\alpha]_D^{25}$ = +15.1˚ (c=1.0, $CHCl_3$). These spectral data match those previously reported in the literature.[28]



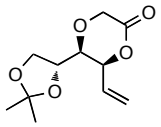
(+)-2-(((*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-yl)oxy)acetic acid. Alcohol (+)-**22** (1.17 g, 6.8 mmol, 1.0 equiv) was reacted according to the general procedure for

the synthesis of carboxylic acid starting materials described above. Due to the acid sensitive nature of the acetonide, the reaction was quenched with sat. aq. NH_4Cl and the pH carefully adjusted to ~3 with 1 M H_3PO_4. Purification by flash chromatography on silica (~250 mL) eluting with 25% acetone in hexanes afforded the title compound (850.2 mg, 3.7 mmol, 57% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 5.80 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 5.17-5.13 (m, 2H), 4.24 (ABq, J = 17.5 Hz, $\Delta\nu_{AB}$ = 63.0 Hz, 2H), 4.17-4.13 (m, 1H), 4.03-3.95 (m, 2H), 3.69-3.66 (m, 1H), 2.35-2.23 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 132.9, 118.8, 109.5, 79.5, 77.0, 68.1, 64.5, 35.8, 26.0, 25.2; IR (film): 3438, 3080, 2983, 2931, 1743, 1643, 1433, 1373, 1221, 1126, 1059, 922 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{18}O_5Na$ $[M+Na]^+$: 253.1052, found 253.1046; $[\alpha]_D^{25}$ = +36.6° (c=1.0, $CHCl_3$).

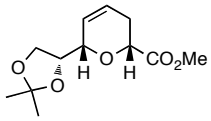


***anti*-(+)-(5*S*,6*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-vinyl-1,4-dioxan-2-one (23).** (+)-2-(((*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-yl)oxy)acetic acid (483.5 mg, 2.1 mmol, 1.0 equiv) was reacted according to the general procedure for intramolecular C—H oxidation described above at 65 ˚C for 72 h. GC of the crude reaction mixture showed the dr to be 3:1 (anti:syn). Purification by flash chromatography on silica (~125 mL) eluting with 20% EtOAc in hexane afforded a mixture of diastereomers (352.2 mg, 1.5 mmol, 73% yield). The diastereomers were separable by flash chromatography on silica (~125 mL) eluting with gradient 10 to 20% EtOAc in hexanes. Major product (*anti*-diastereomer, more polar) obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ; 5.97 (ddd, J = 16.5, 10.5, 6.0 Hz, 1H), 5.50 (d, J = 17.0 Hz, 1H), 5.39 (d, J = 11.0 Hz, 1H), 4.88 (dd, J = 8.0, 6.5 Hz, 1H), 4.36 (ABq, J = 17.5 Hz, $\Delta\nu_{AB}$ = 103.0 Hz, 2H), 4.18 (q, J = 6.0 Hz, 1H), 4.08-4.05 (m, 1H), 4.01-3.98 (m, 1H), 3.52 (dd,

J = 8.0, 6.0 Hz), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 131.9, 119.6, 110.2, 81.2, 75.9, 74.3, 65.8, 65.0, 26.4, 25.2; IR (film): 3093, 2989, 2931, 2893, 1751, 1373, 1354, 1221, 1124, 1090, 1063, 1003, 939 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{16}O_5Na$ $[M+Na]^+$: 251.0895, found 251.0891; $[\alpha]_D^{25}$ = +9.3˚ (c=1.0, $CHCl_3$).

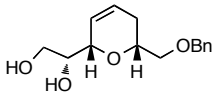


***syn*-(-)-(5*S*,6*S*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-vinyl-1,4-dioxan-2-one.** Minor product (*syn*-diastereomer, less polar) obtained as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.50-5.46 (m, 2H), 5.04 (d, *J* = 6.5 Hz, 1H), 4.40(ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 58.0 Hz, 2H), 4.08-4.05 (m, 1H), 3.98-3.92 (m, 2H), 3.74 (dd, *J* = 8.5, 2.5 Hz, 1H), 1.43 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 130.6, 121.5, 110.1, 80.7, 75.3, 73.6, 67.1, 65.8, 26.9, 25.0; IR (film): 3089, 2989, 2935, 2885, 1751, 1358, 1254, 1219, 1122, 1089, 1063, 1003 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{16}O_5Na$ $[M+Na]^+$: 251.0895, found 251.0887; $[\alpha]_D^{25}$ = -74.6˚ (c=1.0, $CHCl_3$).



(+)-(2*R*,6*S*)-methyl 6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,6-dihydro-2H-pyran-2-carboxylate (24). According to the procedure of Burke,[26] to a freshly prepared solution of LiHMDS (2.4 mmol, 3.0 equiv) in THF (6 mL) at -78 ˚C in a 50 mL round bottom flask was added the clear supernatant resulting from centrifugation of a 1:1 v:v mixture of TMSCl (Sigma-Aldrich) and Et_3N (2.8 mL total added). The resulting mixture was stirred for 15 min. at -78 ˚C at which time a solution of dioxanone (+)-**18** (182.6 mg, 0.8 mmol, 1.0 equiv) in THF (4 mL) was cannulated dropwise into the reaction using THF (~2 mL) to complete the transfer. The reaction was stirred for 2 h at -78 ˚C then allowed to warm to room temperature. Toluene (~30

mL) was added and the reaction flask was fitted with a reflux condenser, submerged in an oil bath and heated to reflux (~110 ˚C) for 12-24 h. The reaction was allowed to cool to room temperature and the solvent removed via rotary evaporation. The crude material was dissolved in DMF (5 mL) esterified with MeI (Sigma-Aldrich, 0.15 mL, 2.4 mmol, 3.0 equiv) and K_2CO_3 (330.0 mg, 2.4 mmol, 3.0 equiv) for 24 h at room temperature. The reaction was quenched with sat. aq. NH_4Cl and diluted with EtOAc (~10 mL). The layers were separated and the aqueous extracted with EtOAc (3x10 mL). the combined organic layers were dried ($MgSO_4$), filtered and concentrated. GC of the crude material showed the dr to be 3:1 (syn:anti), the same as the starting dioxanone. Purification by flash chromatography on silica (~125 mL) eluting with 10% EtOAc in hexane afforded the title compound (162.5.2 mg, 0.67 mmol, 82% yield) as a light yellow oil and single diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95-5.88 (m, 2H), 4.23 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.14-3.99 (m, 3H), 3.76 (s, 3H), 2.39-2.27 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 126.9, 124.6, 109.5, 77.4, 75.8, 72.5, 66.8, 52.1, 28.0, 26.7, 25.3; IR (film): 3043, 2987, 2954, 2935, 2897, 2846, 1763, 1741, 1441, 1371, 1290, 1255, 1221, 1182, 1101, 1072, 952 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{18}O_5Na$ $[M+Na]^+$: 265.1052, found 265.1042; $[\alpha]_D^{25}$ = +41.0˚ (c=1.0, $CHCl_3$).



(+)-(*R*)-1-((2*S*,6*R*)-6-((benzyloxy)methyl)-5,6-dihydro-2H-pyran-2-yl)ethane-1,2-diol (25). Dihydropyran (+)-**24** (145.4 mg, 0.6 mmol, 1.0 equiv) was dissolved in THF (2 mL) in a 25 mL round bottom flask under Ar. The solution was cooled to 0 ˚C and solid $LiAlH_4$ (Sigma-Aldrich, 45.5 mg, 1.2 mmol, 2.0 equiv) was added in one portion. The reaction was stirred at 0 ˚C for 1 h at which point the reaction was complete by TLC. H_2O was added carefully to the reaction mixture until the evolution of gas ceased. $MgSO_4$ and celite were added

and the mixture was diluted with EtOAc, then stirred vigorously for 15 min. The entire mixture was filtered through a pad of silica with 50% EtOAc in hexane. The filtrate was concentrated and transferred to a 25 mL round bottomed flask. DMF (2 mL) and BnBr (Sigma-Aldrich, 0.14 mL, 205.2 mg, 1.2 mmol, 2.0 equiv) were added and the solution was cooled to 0 ˚C. NaH (Sigma-Aldrich, 60% wt., 48 mg, 1.2 mmol, 2.0 equiv) was added in one portion. The reaction was stirred at 0 ˚C for 30 min then allowed to warm to room temperature for an additional 4 h, at which point the reaction was complete by TLC. The reaction was quenched with sat. aq. NH_4Cl and diluted with EtOAc. Workup and silica plug as above with 20% EtOAc in hexane gave the crude fully protected dihydropyran. The crude material was dissolved in THF (3 mL), and 1 N HCl (0.5 mL) was added. The reaction was stirred at rt for 24h. The reaction was quenched with sat aq. $NaHCO_3$ (~10 mL), diluted with Et_2O (~10 mL). The aqueous was extracted with Et_2O (3x10 mL), dried, $MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (~75 mL) eluting with gradient 50 to 100% EtOAc in hexane gave the title compound (94.5 mg, 0.36 mmol, 60% yield, three steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.97-5.93 (m, 1H), 5.69 (dt, *J* = 10.0, 1.5 Hz, 1H), 4.57 (s, 2H), 4.40 (s, 1H), 3.84-3.78 (m, 2H), 3.69-3.65 (m, 2H), 3.52 (d, *J* = 5.0 Hz, 2H), 2.75 (d, *J* = 7.0 Hz, 1H), 2.47 (d, *J* = 5.5 Hz, 1H), 2.20-2.13 (m, 1H), 2.00-1.94 (m, 1H); $[\alpha]_D^{25}$ = +29.6˚ (c=1.0, $CHCl_3$), lit. $[\alpha]_D^{25}$ = -30.9˚ (c=1.0, $CHCl_3$) for the enantiomer. These spectral data are in agreement with those previously reported for the enantiomer in the literature.[21]

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CHAPTER 2: OXIDATIVE HECK VINYLATION FOR THE SYNTHESIS OF COMPLEX DIENES AND POLYENES

2.1 Introduction

The Heck reaction has been widely studied and is a particularly desirable process for synthesis due to its ability to emply only one activated coupling partner.[29] For example, it allows a simple olefin to be combined with an aryl or vinyl bromide or organometallic reagent. This stands in contrast to traditional methods for forming arylated olefins or dienes, which utilize two activated components (i.e. Suzuki cross-coupling or HWE-olefination).[30] While the Heck reaction has been productively applied in synthesis intramolecularly, it has found limited application intermolecularly due to several important limitations. First, the reaction is generally restricted to resonance activated olefins (e.g. styrenes, α,β-unsaturated carbonyls, and enol ethers) to achieve high regio- (i.e. internal:terminal olefin formation) and stereoselectivity (i.e. *E:Z*).[31,32,33] Second, an excess of one coupling partner is usually required (up to 3 equiv). Finally, and particularly detrimental for diene and polyene formation, Pd—H intermediates in the Heck reaction are prone to reinsert and cause olefin migrations and isomerizations leading to reduced selectivities.[34]

Recently, our group and others reported highly efficient Heck arylations, which addressed many of theses issues.[35] Notably, fragment-coupling quantities of olefin can be utilized reducing wasted reagent and making the reaction applicable in complex molecule synthesis where both coupling partners are valuable. Additionally, very high stereoselectivities are observed with non-resonance activated olefins, dramatically expanding the scope of the reaction. The advantageous features of the Heck reaction as well as the prevalence of dienes and polyenes in synthesis led us

to explore the application of Pd(II)/bis-sulfoxide catalysis (previously proven successful for oxidative Heck arylation) to vinylations.

2.2 Results and Discussion

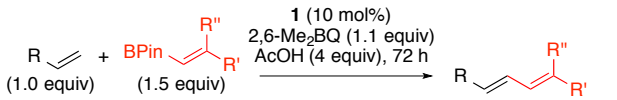
Suitable reaction conditions were developed for the oxidative Heck vinylation reaction. While the conditions for arylation of non-resonance activated olefins with boronic acids served as a starting point, yields for the vinylation under these conditions were poor necessitating several key changes. First, replacing benzoquinone (BQ) with 2,6-dimethylbenzoquinone (2,6-Me_2BQ) prevented vinylation of the oxidant with the vinyl reagent. Second, switching to pinacol boronate vinyl coupling partners led to improved the stability of these reagents under the acidic reaction conditions. Finally, increasing the concentration of the reaction and the polarity of the solvent (2.0 M DMF), also thought to stabilize Pd(II) reaction intermediates, led to an efficient reaction. Most significantly, only 1.5 equiv excess of the boron coupling partner was required and very high stereoselectivity (>20:1 *E:Z*), regioselectivity (>20:1 internal:terminal) and olefin selectivity (>20:1 conjugated:allylic) were observed. These selectivities can be attributed in part to the short-lived nature of Pd—H intermediates under these acidic, oxidative reaction conditions. The equilibrium [LPdH(OAc) + AcOH ⇌ LPd(0) + 2AcOH + BQ → LPd(II)$(OAc)_2$ + DHQ] lies towards Pd(0) and free AcOH and is driven forward by reoxidation of Pd(0) to Pd(II) by BQ.

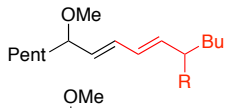
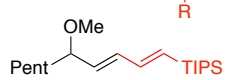
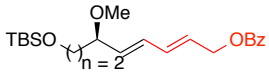
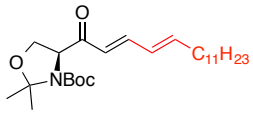
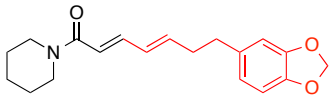
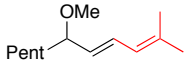
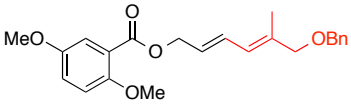
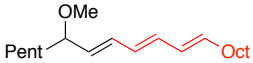
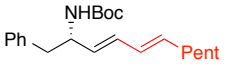
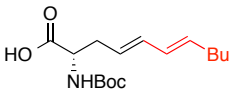
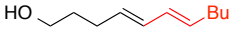
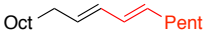
In collaboration with Jared Delcamp, I explored the olefin scope of this reaction as well as its ability to streamline synthetic sequences.[36] Examination of the boron component indicated that a wide range of aliphatic vinyl boron reagents couple under these optimized conditions. Vinyl boronic esters substituted in the allylic position with both alkyl and oxygen moieties are

excellent coupling partners (Table 5, entries 1 and 2). Interestingly, bulkier vinyl boron reagents afford diene products in higher yields than unsubstituted reagents, presumably by slowing homo-coupling pathways. Ethylene triisopropylsilyl (TIPS) boronic ester coupled in synthetically useful yields to give the ethylene homologated TIPS product, which is amenable to further cross-couplings upon activation (entry 3). Optically enriched compounds substituted with stereogenic centers in the allylic position undergo vinylation with no erosion in optical purity (entry 4). Although not a requirement for high selectivities, resonance activated α-olefins also undergo vinylation using only one equivalent of substrate (entries 5 and 6). In addition to *trans*-disubstituted reagents, trisubstituted-vinyl boronic esters couple smoothly (entries 7 and 8). Excitingly, triene products are synthetically accessible in excellent selectivities and good yields by coupling dienyl boronic esters with simple α-olefins (entry 9).

Examination of the olefin coupling partner showed that substrates with allylic oxygen or nitrogen functionality, capable of chelating to the palladium, provide excellent regio- and stereoselectivities (>20:1 internal:terminal and >20:1 *E:Z*) that are not highly sensitive to the vinyl boron reagent (entries 1-10). Significantly, as the functionality is transposed to the homoallylic or bis-homoallylic positions, the regioselectivity of insertion (internal versus terminal olefin products) remains >20:1; however, the stereoselectivity (*E:Z* selectivity) decreases to 6:1 (entries 11 and 12). Previously, we had observed that Pd(II)/bis-sulfoxide catalyzed oxidative Heck *arylations* provided uniformly high (>20:1) stereoselectivity, irrespective of allylic substitution. This variance may be due to the smaller size of the vinyl versus aryl group resulting in higher rotational freedom prior to β-hydride elimination. Consistent with our previous observations, olefinic alcohols do not give carbonyl compounds *via* palladium hydride mediated migration of the double bond, a common feature of many other

Table 5. Scope of the Oxidative Heck Vinylation



entry	product[a]		E:Z[b]	% isolated yield[c,d]
1		R = Pr **26**	>20:1	79[e]
2		OAc **27**	>20:1	62
3		**28**	>20:1	62[f]
4		(+)-**29**	>20:1	50
5		(-)-**30**	>20:1	53
6		**31**	>20:1	66
7		**32**	>20:1	71
8		**33**	10:1	72
9		**34**	14:1	52
10		(-)-**35**	>20:1	54
11		(+)-**36**	6:1	51
12		**37**	6:1	54[g]
13		**38**	6:1	42[h,i]

[a]Internal:terminal and conjugated:allylic olefin isomer ratios >20:1 unless otherwise noted. [b]Selectivities based on crude ^{1}H NMR. [c]Average of 2 runs at 0.5 mmol scale. [d]Generally 20-30% olefin starting material remained with mass balances of 80-90%. The boron coupling partner was generally completely consumed. [e]20:1 internal:terminal. [f]17:1 internal:terminal. [g]1.75 equiv BPin used. [h]2:1 conjugated:allylic and 5:1 internal:terminal. [i]40% recovered starting material (81% mass balance).

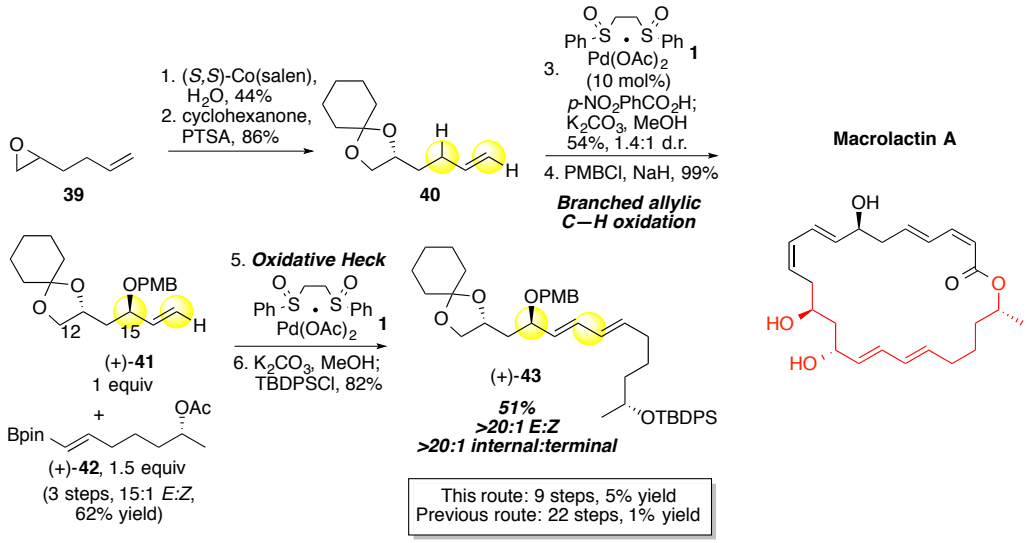
Heck systems (entry 12).[34e,37] Finally, unsubstituted aliphatic substrates undergo oxidative Heck arylation with diminished regio- and stereoselectivities (5:1 internal:terminal; 6:1 *E:Z*), poor directionality in β-hydride elimination (2:1 conjugated versus allylic diene products) and low yields due to a loss in reactivity (entry 13). This result suggests that chelating functionality

capable of directing Pd—vinyl insertion to place the Pd at the internal position of the olefin is important in achieving high internal:terminal olefin selectivities.

The ability of the Pd(II)/sulfoxide-catalyzed Heck vinylation to operate stereoselectively with broad scope using fragment coupling levels of substrates enables the streamlining potential of this powerful cross-coupling reaction to be explored in the synthesis of medicinally relevant complex diene targets. Macrolactin A, a scarce marine macrolide with potent antiviral properties, has three diene moieties embedded in its 24-membered macrocyclic ring.[38] The synthesis of the C16,C18 (*E,E*)-diene segment, has been previously achieved via Stille and Sonogashira cross-couping[39] methods as well as Julia olefination/elimination sequences.[40] We envisioned that an oxidative Heck vinylation approach would be highly efficient, in part because of the relative ease of accessing functionalized, optically enriched α-olefin building blocks. Utilizing the HKR reaction,[41] the C12-C13 diol was readily accessed from epoxy hexene **39** in high enantiomeric purity (99% ee). Exploiting the allylic C—H bond, the C15 alcohol was directly installed via Pd/sulfoxide-catalyzed allylic esterification.[3b] Synthesis of the optically enriched olefin coupling partner (+)-**42** proceeded in just 4 steps from commercial material. In contrast, synthesis of the analogous alkyne coupling partner for the Sonagashira route started with fully oxygenated chiral pool material that required 9 steps for elaboration.[39d] The vinyl boronic ester coupling partner (+)-**42** was also generated efficiently (three steps) via cuprate alkylation of (*R*)-propylene oxide followed by cross-metathesis[42] with commercial 1-propenylboronic ester. Oxidative Heck coupling of (+)-**41** and (+)-**42** proceeded in 51% yield and afforded the complex (*E,E*)-diene (+)-**43** as one regio- and stereoisomer. In total, the oxidative Heck route to reported C12-C24 segment (+)-**43** of macrolactin A proceeded in only 9 steps and 5% overall yield. This compares

favorably to the previously reported Sonagashira route that proceeded in 22 steps and 1% overall yield.

Figure 11. Streamlined Synthesis of the Macrolactin A C12-C24 Segment



2.3 Conclusions

The Pd(II)/sulfoxide-catalyzed oxidative Heck vinylation reaction offers an alternative cross-coupling strategy for the generation of dienes and polyenes that requires pre-activation of only one vinylic partner. This reaction proceeds with unprecedented selectivities for the formation of these sensitive products and is demonstrated to efficiently streamline the synthesis of complex molecules. The ability to use the much broader class of non-resonance activated olefins, fragment coupling quantities of olefin (1 equiv) and vinyl borane (1.5-2 equiv) and the suppression of Pd—H isomerization pathways are novel features of this method that make it amenable to furnishing *E*-dienes and polyenes in complex molecule settings.

2.4 Experimental Section

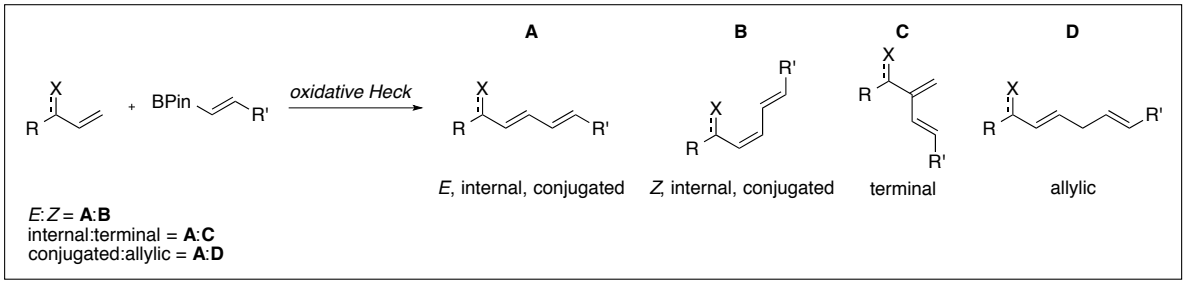
General Information. All commercially obtained reagents for the Heck arylation reaction were used as received: 2,6-dimethyl-1,4-benzoquinone (2,6-Me_2BQ, Sigma-Aldrich). Solvents dioxane, tetrahydrofuran (THF), diethyl ether (Et_2O), and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous *N,N*-dimethylformamide (DMF) (Sure Seal) was obtained from Sigma-Aldrich and used as received. All Heck vinylation reactions were run under N_2 with minimal exposure to moisture. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and potassium permanganate staining. Flash column chromatography was performed as described by Still[22] using EM reagent silica gel 60 (230-240 mesh). ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.23 ppm). ^{19}F NMR spectra were recorded on a Varian Unity-400 (376 MHz) or Varian-500 (470 MHz) spectrometer and are reported in ppm using a 1% C_6F_6/$CDCl_3$ standard referenced to -164.3 ppm. Regioselectivity of the Heck addition was determined by NMR analysis of the crude mixture. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry

Laboratory. Optical rotations were obtained using a JAS.CO P-1020 digital polarimeter and a 3.5 x 100 mm cell.

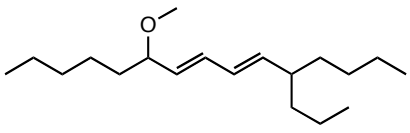
Synthesis of catalyst 1: A flame dried 250 mL flask was charged with 2.53 g (9.1 mmol, 1.0 equiv) of 1,2-bis(phenylsulfinyl)ethane, 101 mL (0.09 M) of CH_2Cl_2, 10 uL (1 ul/10 mL CH_2Cl_2) of H_2O and 2.04 g (9.1 mmol, 1.0 equiv) of $Pd(OAc)_2$. The mixture was stirred at 40 ˚C for 24h as a sealed reaction. The reaction becomes a dark red homogenous mixture during the reaction time. The solution was concentrated *in vacuo* to dryness then placed in the freezer (to firm the slightly sticky solid) overnight to give a dark red solid used without further purification. Notes: (1) The catalyst is stored at 0 ˚C under ambient atmosphere. (2) The addition of water during the complexation was found to give more reproducibly active batches of catalyst. (3) Commercial catalyst also worked for this reaction, albeit typically at lower yields (~20-30% less product; i.e. for a 55% yielding reaction, 39-44% yield was received). (4) Palladium acetate without the nitrate impurity peaks formed the highest performance catalysts [See: Bakhmutov, V. I.; Berry, J. F.; Cotton, A.; Ibragimov, S. and Murillo, C. A. *Dalton Trans.* **2005**, 1989.] (5) If the catalyst is found to be sticky rather than solid after concentration and freezer treatment, the catalyst may be either placed under flowing nitrogen overnight or taken up in CH_2Cl_2 and concentrated several times.

General Procedure. To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.1 mmol, 10 mol%) and 2,6-dimethylbenzoquinone (1.1 mmol, 1.1 equiv) in one portion. The following liquids were added via syringe through the septum sequentially: DMF (0.5 mL, 2.0 M), acetic acid (4.0 mmol, 4 equiv), terminal alkene coupling partner (1.0 mmol, 1.0 equiv) and vinylic boronic ester coupling partner (1.5 mmol, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial

with stirring at 40°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography. The crude selectivities were determined by ^{1}H NMR. *E* and *Z* refer to the geometry of the newly formed internal olefin and the identity of the *E* and *Z* isomers was assigned by coupling constants (*J*) in all cases. See compound **37** for diagnostic peaks and coupling constants of both isomers.

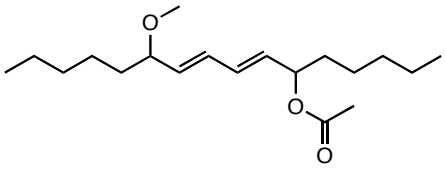


Substrate Scope.



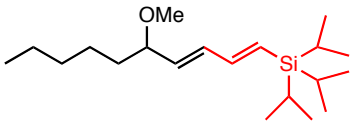
(6*E*,8*E*)-10-methoxy-5-propylpentadeca-6,8-diene (26): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv) and (*E*)-4,4,5,5-tetramethyl-2-(3-propylhept-1-enyl)-1,3,2-dioxaborolane (0.75 mmol, 200.0 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the

mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (6*E*,8*E*)-10-methoxy-5-propylpentadeca-6,8-diene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. 20:1 and *E:Z* >20:1. Run 1 (110.6 mg, 0.40 mmol, 79%); run 2 (110.6 mg, 0.40 mmol, 79%). **Average Yield = 79%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.99 (dd, *J* = 15.0, 10.0 Hz, 1H), 5.44 (dd, *J* = 15.0, 9.0 Hz, 1H), 5.38 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.52 (app q, *J* = 7.5 Hz, 1H), 3.27 (s, 3H), 2.02-1.94 (m, 1H), 1.66-1.56 (m, 1H), 1.52-1.42 (m, 1H), 1.42-1.16 (m, 16H), 0.96-0.82 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 133.2, 131.5, 129.3, 82.6, 56.3, 42.8, 37.8, 35.9, 35.3, 32.1, 29.7, 25.3, 23.1, 22.8, 20.6, 14.4, 14.3 (2C). IR (neat, cm^{-1}) 3016, 2954, 2929, 2872, 2860, 2818, 1458, 1377, 1120, 1095, 989. HRMS (EI) *m/z* calculated for $C_{19}H_{36}O$ $[M]^+$: 280.2766, found 280.2775.



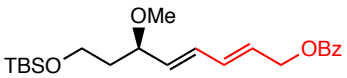
(7*E*,9*E*)-11-methoxyhexadeca-7,9-dien-6-yl acetate (27): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv) and (*E*)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-1-en-3-yl acetate (0.75 mmol, 222.0 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to

removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 7% ethyl acetate/hexanes as eluent to yield (7*E*,9*E*)-11-methoxyhexadeca-7,9-dien-6-yl acetate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (93.0 mg, 0.30 mmol, 60%); run 2 (97.7 mg, 0.32 mmol, 63%). **Average Yield = 62%.** Spectral data are reported for a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26-6.04 (m, 2H), 5.57 (dd, *J* = 15.2, 7.2 Hz, 1H), 5.51 (dd, *J* = 14.8, 7.6 Hz, 1H), 5.23 (app q, *J* = 6.8 Hz, 1H), 3.51 (app q, *J* = 7.6 Hz, 1H), 3.23 (s, 3H), 2.03 (s, 3H), 1.68-1.48 (m, 3H), 1.48-1.36 (m, 1H), 1.36-1.16 (m, 12H), 0.90-0.80 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 135.6 (d), 131.9 (d), 131.6, 131.5, 82.3, 74.6 (d), 56.5, 35.8, 34.6, 32.0, 31.8, 25.2 (d), 25.0, 22.8, 22.7, 21.6, 16.5, 14.3 (d). IR (neat, cm^{-1}) 3023, 2956, 2931, 2860, 2819, 1739, 1466, 1371, 1238, 1120, 1093, 1018, 991. HRMS (EI) *m/z* calculated for $C_{19}H_{34}O_3$ $[M]^+$: 310.2508, found 310.2508.



Triisopropyl((1*E*,3*E*)-5-methoxydeca-1,3-dienyl)silane (28): To a flame dried 2 mL borosilicate vial with a N_2 balloon was added 3-methoxyoct-1-ene (0.28 mmol, 39.8 mg, 1.0 equiv) and (*E*)-triisopropyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)silane (0.42 mmol, 130.2 mg, 1.5 equiv) via pipet. DMF (0.14 mL, 2.0 M) and acetic acid (1.12 mmol, 67.2 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.028 mmol, 14.1 mg, 10 mol%) and

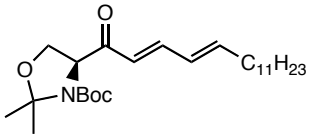
2,6-dimethylbenzoquinone (0.31 mmol, 41.9 mg, 1.1 equiv) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 2% ethyl acetate/hexanes as eluent to yield triisopropyl((1*E*,3*E*)-5-methoxydeca-1,3-dienyl)silane as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. 17:1 and *E*:*Z* >20:1. Run 1 (56.2 mg, 0.17 mmol, 62%); run 2 (56.6 mg, 0.17 mmol, 62%). **Average Yield = 62%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, *J* = 18.8, 10.0 Hz, 1H), 6.16 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.74 (d, *J* = 18.8 Hz, 1H), 5.49 (dd, *J* = 15.2, 8.0 Hz, 1H), 3.53 (app q, *J* = 7.6 Hz, 1H), 3.25 (s, 3H), 1.66-1.52 (m, 1H), 1.52-1.39 (m, 1H), 1.39-1.10 (m, 6H), 1.14-0.94 (m, 21H), 0.86 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 135.9, 134.3, 128.9, 82.3, 56.5, 35.8, 32.1, 25.3, 22.8, 18.9, 14.3, 11.1. IR (neat, cm^{-1}) 2956, 2941, 2891, 2866, 1581, 1464, 1381, 1367, 1130, 1095, 883. HRMS (EI) *m*/*z* calculated for $C_{20}H_{40}OSi$ $[M]^+$: 324.2849, found 324.2840.



(+)-(*R*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-methoxyocta-2,4-dienyl benzoate (29): To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*R*)-*tert*-butyl(3-methoxypent-4-enyloxy)dimethylsilane (0.21 mmol, 48.3 mg, 1.0 equiv) and (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl benzoate (0.42 mmol, 121.0 mg, 2.0 equiv) via pipet. DMF (0.11 mL, 2.0 M) and acetic acid (0.84 mmol, 50.4 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.02 mmol, 10.5 mg, 10 mol%) and 2,6-

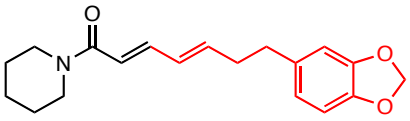
dimethylbenzoquinone (0.23 mmol, 31.4 mg, 1.1 equiv) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 10% ethyl acetate/hexanes as eluent to yield (*R*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-methoxyocta-2,4-dienyl benzoate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (41.0 mg, 0.11 mmol, 50%); run 2 (41.8 mg, 0.11 mmol, 50%). **Average Yield = 50%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.37 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.20 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.86 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.58 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 2H), 3.76 (app q, *J* = 7.6 Hz, 1H), 3.73-3.65 (m, 1H), 3.60 (dt, *J* = 10.0, 6.0 Hz, 1H), 3.24 (s, 3H), 1.82-1.71 (m, 1H), 1.70-1.56 (m, 1H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 135.7, 133.7, 133.2, 131.3, 130.4, 129.8, 128.6, 127.0, 78.7, 65.2, 59.4, 56.6, 38.9, 26.1, 18.5, -5.1, -5.2. IR (neat, cm^{-1}) 3033, 3016, 2953, 2929, 2858, 2819, 1722, 1471, 1452, 1381, 1362, 1287, 1176, 1105, 1070, 1026, 991, 949, 837. HRMS (ESI) *m*/*z* calculated for $C_{22}H_{34}O_4SiNa$ $[M+Na]^+$: 413.2124, found 413.2121. Enantiopurity of the product was determined by synthesis of the racemic product followed by HPLC analysis with a Daicel Chemical Industries, LTD chiral OD-H, 0.46 cm x 25 cm column. A flow rate of 1.0 mL/min and 43 psi with 10% *i*-PrOH/hexanes as eluent gave the *R*-isomer at 4.783 min and the *S*-isomer at 5.179 min. Enatiopurtiy was determined to be >99%. $[\alpha]^{24}_D$ = +2.4˚ (c = 1.0, $CHCl_3$). Cleavage

of the benzoyl group yields a known alcohol whose spectral data have previously been reported and are in agreement.[43]



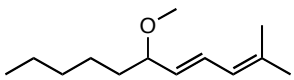
(-)-(*S*)-*tert*-butyl-4-((2*E*,4*E*)-hexadeca-2,4-dienoyl)-2,2-dimethyloxazolidine-3-carboxylate (30): To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*S*)-*tert*-butyl 4-acryloyl-2,2-dimethyloxazolidine-3-carboxylate (0.20 mmol, 50.0 mg, 1.0 equiv) and (*E*)-4,4,5,5-tetramethyl-2-(tridec-1-enyl)-1,3,2-dioxaborolane (0.30 mmol, 90.3 mg, 1.5 equiv) via pipet. DMF (0.1 mL, 2.0 M) and acetic acid (0.78 mmol, 46.8 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.02 mmol, 9.8 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.22 mmol, 29.4 mg, 1.1 equiv) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 7% ethyl acetate/hexanes as eluent to yield (*S*)-*tert*-butyl 4-((2*E*,4*E*)-hexadeca-2,4-dienoyl)-2,2-dimethyloxazolidine-3-carboxylate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (46.5 mg, 0.11 mmol, 54%); run 2 (45.2 mg, 0.10 mmol, 52%). **Average Yield = 53%.** Only diagnostic peaks are reported for the minor rotamer. ^{1}H NMR (400 MHz, C_6D_6) δ major rotamer: 7.32 (dd, *J* = 15.6, 11.2 Hz, 1H), 6.15 (d, *J* = 15.2 Hz, 1H), 5.89 (m, 1H), 5.73 (m, 1H), 4.27 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.66 (m, 2H), 1.88 (s, 3H), 1.80 (m, 2H), 1.55 (s, 3H), 1.33 (s,

9H), 1.3-1.0 (m, 18H), 0.84 (t, J = 7.2, 3H). minor rotamer: 7.30-7.20 (m, 1H), 6.10 (d, J = 15.2 Hz, 1H), 5.90-5.80 (m, 1H), 5.70-5.58 (m, 1H), 4.56 (m, 1H), 3.75 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ major rotamer: 196.6, 152.3, 147.1, 146.5, 144.8, 129.8, 123.8, 96.0, 80.5, 66.6, 65.6, 33.9, 32.9, 30.7, 30.6, 30.4 (2C), 30.1, 29.5, 28.9, 26.2, 25.0, 23.7, 14.9. minor rotamer: 196.1, 152.9, 148.7, 146.0, 144.7, 129.9, 125.0, 95.0, 66.2, 65.4. IR (neat, cm^{-1}) 3011, 2927, 2855, 1710, 1632, 1596, 1459, 1266, 1248, 1206, 1174, 1096, 1063, 1002. HRMS (ESI) *m/z* calculated for $C_{26}H_{46}NO_4$ $[M+H]^+$: 436.3427, found 436.3426. $[\alpha]^{27}_D$ = -41.8° (c = 2.5, $CHCl_3$) . Spectral data has previously been reported and is in agreement.[44]



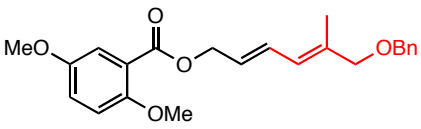
(2*E*,4*E*)-7-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one (31): To a flame dried 2 mL borosilicate vial with a N_2 balloon was added 1-(piperidin-1-yl)prop-2-en-1-one (0.15 mmol, 21.3 mg, 1.0 equiv) and (*E*)-2-(4-(benzo[*d*][1,3]dioxol-5-yl)but-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.23 mmol, 69.5 mg, 1.5 equiv) via pipet. DMF (0.08 mL, 2.0 M) and acetic acid (0.61 mmol, 36.7 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.015 mmol, 7.5 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.17 mmol, 23.0 mg, 1.1 equiv) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 30% ethyl acetate/hexanes as eluent to

yield (2*E*,4*E*)-7-(benzo[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)hepta-2,4-dien-1-one as a crystalline solid. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (31.1 mg, 0.10 mmol, 65%); run 2 (31.6 mg, 0.10 mmol, 66%). **Average Yield = 66%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 14.4, 10.8 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.24 (d, *J* = 14.8 Hz, 1H), 6.16 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.02 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.90 (s, 2H), 3.58 (br s, 2H), 3.45 (br s, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.39 (app q, *J* = 7.6 Hz, 2H), 1.67-1.58 (m, 2H), 1.58-1.48 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 147.8, 145.9, 142.7, 141.1, 135.4, 129.7, 121.4, 119.3, 109.0, 108.4, 101.0, 47.0, 43.4, 35.2 (2C), 36.9, 25.8, 24.9. IR (neat, cm^{-1}) 3016, 2995, 2935, 2854, 1651, 1622, 1599, 1502, 1489, 1439, 1356, 1246, 1120, 1038, 999, 935. HRMS (ESI) *m/z* calculated for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1756, found 314.1750. Spectral data has previously been reported and is in agreement.[45]



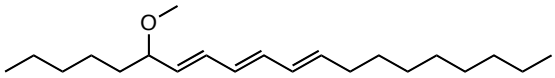
(*E*)-6-methoxy-2-methylundeca-2,4-diene (32): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (0.75 mmol, 136.5 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic

layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (*E*)-6-methoxy-2-methylundeca-2,4-diene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (68.6 mg, 0.35 mmol, 70%); run 2 (69.6 mg, 0.36 mmol, 71%). **Average Yield = 71%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.82 (d, *J* = 11.2 Hz, 1H), 5.34 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.52 (app q, *J* = 8.0 Hz, 1H), 3.23 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.62-1.50 (m, 1H), 1.48-1.37 (m, 1H), 1.37-1.18 (m, 6H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 131.4, 129.3, 124.6, 82.9, 56.2, 36.0, 32.1, 26.2, 25.3, 22.8, 18.5, 14.3. IR (neat, cm^{-1}) 3018, 2958, 2929, 2858, 2817, 1660, 1448, 1377, 1184, 1120, 1095, 985, 960. HRMS (EI) *m/z* calculated for $C_{13}H_{24}O$ $[M]^+$: 196.1827, found 196.1825.



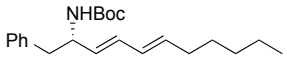
(2*E*,4*E*)-6-(benzyloxy)-5-methylhexa-2,4-dienyl 2,5-dimethoxybenzoate (33): To a flame dried 2 mL borosilicate vial with a N_2 balloon was added allyl 2,5-dimethoxybenzoate (0.23 mmol, 51.1 mg, 1.0 equiv) and (*E*)-2-(3-(benzyloxy)-2-methylprop-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.35 mmol, 99.4 mg, 1.5 equiv) via pipet. DMF (0.12 mL, 2.0 M) and acetic acid (0.92 mmol, 55.2 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.023 mmol, 11.6 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.25 mmol, 34.4 mg, 1.1 equiv) in one portion. A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40°C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50

mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (2*E*,4*E*)-6-(benzyloxy)-5-methylhexa-2,4-dienyl 2,5-dimethoxybenzoate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* 10:1. Run 1 (62.4 mg, 0.16 mmol, 71%); run 2 (63.3 mg, 0.17 mmol, 72%). **Average Yield = 72%.** The E- and Z-isomers of this product are inseparable. The Z-isomer is visible in the ^{1}H NMR but is minor and the spectral data are not reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 6H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.94 (d, *J* = 9.5 Hz, 1H), 6.67 (dd, *J* = 15.0, 11.5 Hz, 1H), 6.15 (d, *J* = 11.0 Hz, 1H), 5.90 (dt, *J* = 15.0, 6.5 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 4.00 (s, 2H), 3.89 (s, 3H), 2.82 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 153.7, 153.1, 138.5, 136.5, 130.1, 128.5, 127.8, 127.7, 126.8, 125.7, 120.7, 119.7, 116.1, 114.0, 75.5, 71.9, 65.6, 56.9, 56.0, 14.6. IR (neat, cm^{-1}) 3062, 3030, 2999, 2935, 2914, 2850, 2837, 1728, 1500, 1454, 1417, 1356, 1317, 1284, 1242, 1215, 1180, 1068, 1047, 972. HRMS (ESI) *m/z* calculated for $C_{23}H_{26}O_5Na$ $[M+Na]^+$: 405.1678, found 405.1670. This molecule has previously been reported; however, no spectral data was available.[46]



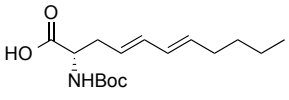
(7*E*,9*E*,11*E*)-6-methoxyicosa-7,9,11-triene (34): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), 3-methoxyoct-1-ene (0.50 mmol, 71.0 mg, 1.0 equiv) and 2-((1*E*,3*E*)-dodeca-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.75 mmol, 219.0 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the

vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 3% ethyl acetate/hexanes as eluent to yield (7*E*,9*E*,11*E*)-6-methoxyicosa-7,9,11-triene as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* 14:1. Run 1 (78.0 mg, 0.26 mmol, 51%); run 2 (81.1 mg, 0.27 mmol, 53%). **Average Yield = 52%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26-5.86 (m, 4H), 5.73 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.47 (dd, *J* = 14.4, 8.0 Hz, 1H), 3.55 (app q, *J* = 8.4 Hz, 1H), 3.26 (s, 3H), 2.10 (app q, *J* = 6.8 Hz, 2H), 1.68-1.54 (m, 1H), 1.52-1.16 (m, 19H), 0.96-0.83 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 133.5 (2C), 133.0, 130.3, 129.8, 82.6, 56.3, 35.9, 33.0, 32.1 (2C), 29.7, 29.5 (2C), 29.4, 25.3, 22.9, 22.8, 14.3 (2C). IR (neat, cm^{-1}) 3016, 2956, 2927, 2854, 1456, 1358, 1215, 1093, 995. HRMS (EI) *m/z* calculated for $C_{21}H_{38}O$ $[M]^+$: 306.2923, found 306.2931.



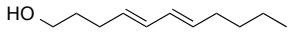
(-)-*tert*-butyl ((*S*,3*E*,5*E*)-1-phenylundeca-3,5-dien-2-yl)carbamate (35): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv) and *tert*-butyl (*S*)-(1-phenylbut-3-en-2-yl)carbamate (0.5 mmol, 123.7 mg, 1.0 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv) and *trans*-1-hepten-1-ylboronic acid pinacol ester (0.75 mmol, 168.1 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and

Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 5% ethyl acetate/hexanes as eluent to yield the title compound as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (89.5 mg, 0.26 mmol, 52%); run 2 (96.7 mg, 0.28 mmol, 56%). **Average Yield = 54%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.24-7.18 (m, 3H), 6.09 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.99 (dd, *J* = 15.5, 10.5 Hz, 1H), 5.65 (td, *J* = 15.0, 7.0 Hz, 1H), 5.50 (dd, *J* = 15.0, 5.5 Hz, 1H), 4.46 (br s, 2H), 2.85 (d, *J* = 5.5 Hz, 2H), 2.06 (app q, *J* = 7.0 Hz, 2H), 1.41 (s, 9H) 1.40-1.24 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 137.6, 135.2, 130.8, 130.4, 129.5, 129.3, 128.3, 126.3, 79.3, 52.8, 41.9, 32.6, 31.4, 28.9, 28.3, 22.5, 14.0. IR (neat, cm^{-1}) 3350, 3026, 2958, 2927, 2858, 1703, 1496, 1454, 1390, 1365, 1248, 1171, 1016, 989. HRMS (ESI) *m/z* calculated for $C_{21}H_{38}O$ $[M+H]^+$: 344.2590, found 344.2600. $[\alpha]^{27}_D$ = -3.9° (c = 1.0, $CHCl_3$).



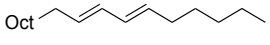
(+)-(*S*,4*E*,6*E*)-2-((*tert*-butoxycarbonyl)amino)undeca-4,6-dienoic acid (36): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%), 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv) and (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enoic acid (0.5 mmol, 107.6 mg, 1.0 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv) and *trans*-1-hexen-1-ylboronic acid pinacol ester (0.75 mmol, 157.6 mg, 1.5 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 °C for 72 hours. After 72

hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 20% acetone/hexanes as eluent to yield the title compound as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* 6:1. Run 1 (76.4 mg, 0.26 mmol, 51%); run 2 (75.8 mg, 0.25 mmol, 50%). **Average Yield = 51%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.00 (dd, *J* = 14.5, 10.5 Hz, 1H), 5.65 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.44 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.02-4.92 (m, 1H), 4.42-4.32 (m, 1H), 2.64-2.50 (m, 2H), 2.04-2.12 (m, 2H), 1.45 (s, 9H), 1.40-1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 155.5, 134.8 (2C) 129.5, 124.1, 80.2, 75.4, 53.0, 32.2, 31.4, 28.3, 22.2, 13.9. Minor peaks in the ^{13}C are attributable to the minor olefin isomer and are not tabulated. IR (neat, cm^{-1}) 3411, 2962, 2926, 1714, 1504, 1394, 1367, 1252, 1164. HRMS (ESI) *m/z* calculated for $C_{16}H_{28}NO_4$ $[M+H]^+$: 298.2018, found 298.2024. $[\alpha]^{26}_D$ = +23.8˚ (c = 1.5, $CHCl_3$).



(4*E*,6*E*)-undeca-4,6-dien-1-ol (37): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), *trans*-1-hexen-1-ylboronic acid pinacol ester (0.88 mmol, 184.9 mg, 1.75 equiv) and 4-penten-1-ol (0.5 mmol, 43.1 mg, 1.0 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K-

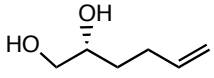
$_2CO_3$ (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with 15% ethyl acetate/hexanes as eluent to yield the title compound as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* 6:1. Because in many cases *E*:*Z* selectivities for these reactions are >20:1, comparing the coupling constants of each isomer to more rigorously assign *E* and *Z* was not possible. For this substrate, a ^{1}H-^{1}H TOCSY1D experiment was used to obtain diagnostic coupling constants for the minor isomer, which indicate *cis*-stereochemistry of the newly formed internal olefin as anticipated. Run 1 (47.0 mg, 0.28 mmol, 56%); run 2 (43.9 mg, 0.26 mmol, 52%). **Average Yield = 54%.** ^{1}H NMR (500 MHz, $CDCl_3$) δ *E*-isomer: 6.06-5.97 (m, 2H), 5.61-5.53 (m, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.15 (app q, *J* = 7.0 Hz, 2H), 2.05 (app q, *J* = 7.5 Hz, 2H), 1.70-1.62 (m, 2H), 1.40 (br s, 1H), 1.37-1.26 (m, 4H), 0.89 (t, *J* = 7.5 Hz, 3H); *Z*-isomer diagnostic peaks: 6.35 (dd, *J* = 15.0, 11.5 Hz, 1H), 5.94 (app t, *J* = 11.0 Hz, 1H), 5.66 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.32 (dt, *J* = 9.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0, 131.0 (2C), 130.0, 62.5, 32.3, 32.2, 31.5, 28.9, 22.2, 13.9. IR (neat, cm^{-1}) 3338, 3014, 2956, 2927, 2872, 1456, 1365, 1059, 987. HRMS (EI) *m*/*z* calculated for $C_{11}H_{20}O$ $[M]^+$: 168.1514, found 168.1514.



(10*E*,12*E*)-octadeca-10,12-dien-8-one (38): To a flame dried 2 mL borosilicate vial with a N_2 balloon was rapidly added catalyst **1** (0.05 mmol, 25.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.55 mmol, 75.0 mg, 1.1 equiv). The following liquids were added via syringe through the septum sequentially: DMF (0.25 mL, 2.0 M), acetic acid (2.0 mmol, 132.0 mg, 4.0 equiv), *trans*-1-hepten-1-ylboronic acid pinacol ester (0.75 mmol, 168.1

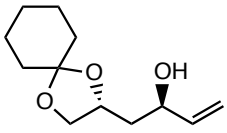
mg, 1.5 equiv) and 1-undecene (0.5 mmol, 77.2 mg, 1.0 equiv). A stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) and Na_2SO_3 (sat. aq.) [50 mL] was added and stirred rapidly to ensure mixing of the biphasic layers for 30 minutes. The organics were separated and rinsed once with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (125 mL SiO_2) with hexanes as eluent to yield the title compound as a clear oil. The crude selectivities determined by ^{1}H NMR are *E*:*Z* 6:1, internal:terminal 5:1 and 2:1 conjugated:allylic. Remaining starting material was inseparable from the product isomers. Identifiable starting material peaks are identified on the reported spectrum. Run 1 (52.6 mg, 0.21 mmol, 41%); run 2 (54.1 mg, 0.22 mmol, 43%). **Average Yield = 42%.** Because of the large number of inseparable isomers present, only diagnostic peaks for each isomer are tabulated. ^{1}H NMR (500 MHz, $CDCl_3$) δ *E*-isomer: 6.06-5.92 (m, 2H), 5.62-5.50 (m, 2H); *Z*-isomer: 6.31 (dd, J = 15.0, 10.5 Hz, 1H), 5.95 (app t, J = 11.0 Hz, 1H), 5.66 (dt, J = 11.0 Hz, 1H), 5.29 (app q, J = 9.0 Hz, 1H); terminal: 4.87 (s, 1H), 4.48 (s, 1H); allylic: 5.62-5.52 (m, 4H). HRMS (EI) *m*/*z* calculated for $C_{18}H_{24}$ $[M]^+$: 250.2661, found 250.2661. A ^{13}C NMR spectrum is provided, but due to the complexity of product identification, peaks have not been tabulated.

Synthesis of the Macrolactin A C12-C24 Segment



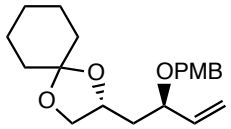
(*R*)-hex-5-ene-1,2-diol: The title compound was synthesized according to a published procedure with matching spectrum.[41] Enantiopurity was determined to be 98.5% by chiral GC comparison of acetonide protected resolved diol and racemic diol. The racemic

acetonide was formed through opening of the racemic epoxide according to literature precedent,[47] followed by acetonide protection according to literature precedent.[48]



(-)-(*R*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-2-ol: *Ketal Protection*: To a flame dried, N_2-filled round bottom flask was added (*R*)-hex-5-ene-1,2-diol (50.0 mmol, 5.80 g, 1.0 equiv), cyclohexanone (50 mL, 1.0 M), benzene (100 mL, 0.5 M) and *p*-toluenesulfonic acid (2.5 mmol, 475.0 mg, 0.05 equiv). The solution was stirring at room temperature overnight. After complete consumption of the starting material by TLC, the solution was filtered directly through a thin pad of silica gel with 50% ethyl acetate:hexanes. The organics were concentrated, placed under high vacuum with a dry ice trap for 2 hours, and then the crude mixture was purified via silica gel chromatography with 7% ethyl acetate:hexanes to give (*R*)-2-(but-3-en-1-yl)-1,4-dioxaspiro[4.5]decane as a clear oil (43.0 mmol, 8.40 g, 86%). *Pd(II) BisSO Catalyzed Allylic C-H Oxidation*: To a round bottom flask was added (*R*)-2-(but-3-en-1-yl)-1,4-dioxaspiro[4.5]decane (1.0 mmol, 196.0 mg, 1.0 equiv) and dioxane (3.0 mL, 0.33 M). The solution was purged with O_2 for 5 minutes and kept under a positive O_2 pressure during the remainder of the set up. *p*-Nitrobenzoic acid (2.0 mmol, 334.0 mg, 2.0 equiv), benzoquinone (2.0 mmol, 216.0 mg, 2.0 equiv) and catalyst **1** (0.1 mmol, 50.0 mg, 0.10 equiv) were added in one portion. The flask was sealed under O_2 with a ground glass stopcock and Teflon tape. The mixture was heated to 45 ˚C for 48 hours before cooling to room temperature. To the mixture was added 50 mL MeOH and 50 mL K_2CO_3 (sat. aq.). The reaction was then rapidly stirred at room temperature for 6 hours. The solution was rinsed with H_2O (2x) after addition of CH_2Cl_2. The organics were dried over $MgSO_4$, concentrated, then purified by silica gel chromatography (1 L SiO_2) with 3% MeOH:CH_2Cl_2 as eluent to give (*R*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-

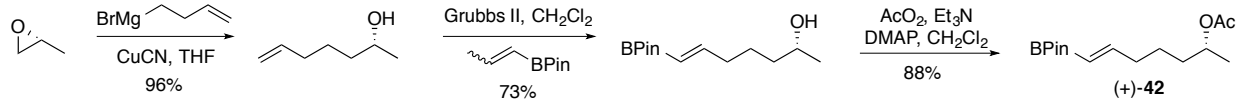
yl)but-3-en-2-ol (1.4:1 dr, 54% combined, lower R_f diastereomer is the *R*, *R* disastereomer on SiO_2 with 2% MeOH:CH_2Cl_2 as eluent) as a single diasteromer in the form of a pale oil (0.32 mmol, 67.8 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 16.0, 10.5, 5.5 Hz, 1H), 5.30 (d, *J* = 17.0 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 1H), 4.41-4.30 (m, 2H), 4.08 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.59 (app t, *J* = 7.5 Hz, 1H), 2.54 (d, *J* = 5.0 Hz, 1H), 1.90-1.84 (m, 1H), 1.78-1.72 (m, 1H), 1.66-1.54 (m, 8H), 1.43-1.36 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 114.4, 109.6, 72.9, 70.1, 69.1, 39.7, 36.5, 35.1, 25.1, 24.0, 23.8. IR (neat, cm^{-1}) 3452, 2937, 2862, 1448, 1365, 1281, 1232, 1163, 1101, 1038, 991, 926. HRMS (ESI) *m/z* calculated for $C_{12}H_{20}O_3Na$ $[M+Na]^+$: 235.1310, found 235.1316. $[\alpha]^{24}_D$ = -2.9° (c = 1.0, $CHCl_3$).

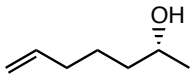


(+)-(*R*)-2-((*R*)-2-((4-methoxybenzyl)oxy)but-3-en-1-yl)-1,4-dioxaspiro[4.5]decane (41): To a flame dried, N_2 filled round bottom flask was added (*R*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-2-ol (2.64 mmol, 0.56 g, 1.0 equiv) and DMF (13.2 mL, 0.2 M). The solution was cooled to 0 ˚C and NaH (3.96, 95.0 mg, 1.5 equiv) was added slowly. After stirring for 30 minutes, flamed dried KI (10.6 mmol, 1.50 g, 4 equiv) and PMBCl (3.17 mmol, 496.0 mg, 0.43 mL, 1.2 equiv) were added. The flask was allowed to warm to room temperature and was stirred overnight. After extraction with hexanes and rinsing with H_2O, the organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel chromatography with 15% ethyl acetate:hexanes as eluent to give (*R*)-2-((*R*)-2-((4-methoxybenzyl)oxy)but-3-en-1-yl)-1,4-dioxaspiro[4.5]decane as a clear oil (2.61 mmol, 0.87 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.75 (ddd, *J* = 17.5, 10.5, 8.0 Hz, 1H), 5.29 (d, *J* = 15.0 Hz, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.40 (ABq, Δν = 119.0 Hz, *J* = 11.0 Hz, 2H), 4.24 (app t, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.96-3.91 (m, 1H), 3.80 (s, 3H),

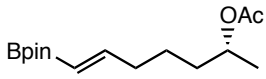
3.51 (t, *J* = 6.0 Hz, 1H), 1.85-1.73 (m, 2H), 1.62-1.53 (m, 8H), 1.44-1.33 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.7, 130.6, 129.3, 116.9, 113.7, 108.8, 77.4, 72.9, 70.1, 69.6, 55.2, 40.2, 36.6, 35.4, 25.2, 24.0, 23.9. IR (neat, cm^{-1}) 2935, 2862, 1614, 1514, 1448, 1365, 1248, 1165, 1101, 1038, 930. HRMS (ESI) *m/z* calculated for $C_{20}H_{29}O_4$ $[M+H]^+$: 333.2066, found 333.2075. $[\alpha]^{24}_D$ = +35.9° (c = 1.0, $CHCl_3$). The absolute and relative stereochemistry of this compound were verified by converting it to the known terminal acetonide and free allylic alcohol.[49] The spectral data are in agreement.

Boron Coupling Partner (+)-**42** Synthesis



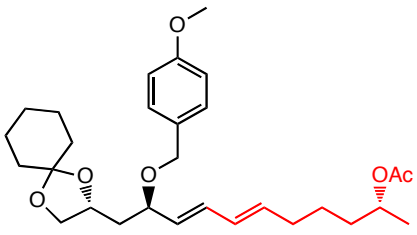


(-)-(*R*)-hept-6-en-2-ol: The title compound was synthesized according to a published procedure with matching spectrum.[50] Measured: $[\alpha]^{25}_D$ = -10.1° (c = 0.46, $CHCl_3$); Literature (*S*-enantiomer): $[\alpha]^{20}_D$ = +10.0° (c = 0.75, $CHCl_3$).



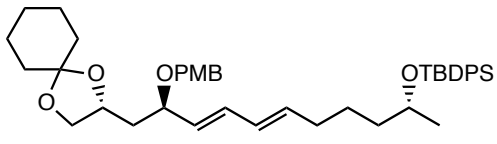
(+)-(*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-yl acetate (42): *Grubbs Cross Metathesis*: To a flame dried, N_2-filled round bottom flask was added Grubbs II (0.09 mmol, 76.4 mg, 0.03 equiv), CH_2Cl_2 (15 mL, 0.2 M), (*R*)-hept-6-en-2-ol (3.0 mmol, 0.336 g, 1.0 equiv) and 4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane (3.0 mmol, 0.504 g, 1.0 equiv). The mixture was then refluxed for 48 hours. After this time, the solution was concentrated and purified by silica gel chromatography with 10% ethyl acetate:hexanes → 30% ethyl acetate:hexanes as eluent to give (*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-ol as a clear oil (2.19 mmol, 0.526 g, 73%). *Acetate Formation:* (*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-ol (0.4 mmol, 95.7

mg, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL, 0.2 M). Acetic anhydride (0.8 mmol, 0.076 mL, 2.0 equiv), triethyl amine (0.8 mmol, 0.111 mL, 2.0 equiv) and 4-dimethylaminopyridine (0.04 mmol, 4.9 mg, 0.1 equiv) were added sequentially. The mixture was stirred at room temperature overnight. After complete consumption of the starting material was observed by TLC, the solution was extracted with H_2O, the organics were separated, dried over $MgSO_4$, and concentrated. The crude mixture was purified by silica gel chromatography with 15% ethyl acetate:hexanes to give (*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-yl acetate as a clear oil (0.35 mmol, 99.3 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dt, *J* = 18.0, 6.4 Hz, 1H), 5.44 (d, *J* = 18.0 Hz, 1H), 4.95-4.83 (m, 1H), 2.16 (q, *J* = 6.8 Hz, 2H), 2.02 (s, 3H), 1.65-1.37 (m, 4H), 1.27 (s, 12H), 1.20 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 154.0, 83.3, 71.0, 35.7 (2C), 29.9, 25.0, 24.2, 21.6, 20.2. IR (neat, cm^{-1}): 2978, 2929, 2856, 1738, 1460, 1363, 1321, 1244, 1146, 1020, 1001, 972, 850. HRMS (ESI) *m/z* calculated for $C_{15}H_{28}BO_4$ $[M+H]^+$: 283.2083, found 283.2079. $[\alpha]^{26}_D$ = +6.3° (c = 1.0, $CHCl_3$).



(+)-(2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl acetate: To a flame dried 2 mL borosilicate vial with a N_2 balloon was added (*R*)-2-((*R*)-2-(4-methoxybenzyloxy)but-3-enyl)-1,4-dioxaspiro[4.5]decane (0.10 mmol, 33.2 mg, 1.0 equiv) and (*R*,*E*)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-2-yl acetate (0.15 mmol, 42.3 mg, 1.5 equiv) via pipet. DMF (0.05 mL, 2.0 M) and acetic acid (0.40 mmol, 24.0 mg, 4.0 equiv) were added via syringe through the septum. The vial was rapidly opened followed by quick addition of catalyst **1** (0.01 mmol, 5.0 mg, 10 mol%) and 2,6-dimethylbenzoquinone (0.11 mmol, 15.0 mg, 1.1 equiv) in one portion. A

stir bar was added and the head spaced flushed with N_2 prior to removing the balloon and sealing the vial with stirring at 40 ˚C for 72 hours. After 72 hours the mixture was diluted with diethyl ether (50 mL) and a solution of 5% K_2CO_3 (aq.) [50 mL] was added. The organics were separated and rinsed once more with 5% K_2CO_3 (50 mL). The organic layer was dried with $MgSO_4$ and filtered. After concentration, the crude product was purified via silica chromatography (75 mL SiO_2) with 20% ethyl acetate/hexanes as eluent to yield (2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl acetate as a clear oil. The crude selectivities determined by ^{1}H NMR are int.:term. >20:1 and *E:Z* >20:1. Run 1 (24.8 mg, 0.051 mmol, 51%); run 2 (24.0 mg, 0.051 mmol, 51%). **Average Yield = 51%.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.15 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.03 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.67 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.45 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.88 (app q, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.24 (d, *J* = 11.6 Hz, 1H), 4.25-4.15 (m, 1H), 4.01 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.93 (dt, *J* = 8.4, 4.4 Hz, 1H), 3.78 (s, 3H), 3.48 (t, *J* = 8.0 Hz, 1H), 2.08 (q, *J* = 6.8 Hz, 2H), 2.01 (s, 3H), 1.80-1.72 (m, 2H), 1.64-1.30 (m, 14H), 1.24-1.14 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 159.3, 135.1, 132.8, 131.7, 130.9, 130.0, 129.5, 114.0, 109.1, 73.2, 71.0, 70.2, 69.9, 55.5, 40.7, 36.8, 35.7, 32.6, 25.4, 25.2, 24.2, 24.1, 21.6, 20.2. IR (neat, cm^{-1}) 3012, 2937, 2860, 1736, 1612, 1514, 1448, 1369, 1248, 1165, 1101, 1070, 1038, 993, 933. HRMS (ESI) *m/z* calculated for $C_{29}H_{42}O_6Na$ $[M+Na]^+$: 509.2879, found 509.2878. $[a]^{24}_D$ = +32.8˚ (c = 1.0, $CHCl_3$).



(+)-*tert*-butyl(((2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2 yl)oxy)diphenylsilane (43): To a round bottom flask was added (2*R*,6*E*,8*E*,10*R*)-10-((4-

methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl acetate (0.042 mmol, 20.4 mg, 1.0 equiv), MeOH (1.0 mL, 0.042 M) and K_2CO_3 (1.0 mg K_2CO_3/1.0 mg acetate, 20.4 mg). The mixture was stirred for 3 hours at room temperature and monitored by TLC before filtering off the K_2CO_3 with CH_2Cl_2. The organics were concentrated, then CH_2Cl_2 (1.0 mL, 0.042 M) was added to the alcohol intermediate followed by *t*-butyldiphenylsilyl chloride (0.25 mmol, 69.3 mg, 6.0 equiv) and imidazole (0.25 mmol, 17.0 mg, 6.0 equiv). The mixture was stirred at room temperature for 3 hours and monitored by TLC. The reaction mixture was passed through a pad of silica gel with 15% ethyl acetate:hexanes as eluent. After concentration the crude mixture was purified by silica gel chromatography with 10% ethyl acetate:hexanes as eluent to give *tert*-butyl(((2*R*,6*E*,8*E*,10*R*)-10-((4-methoxybenzyl)oxy)-11-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)undeca-6,8-dien-2-yl)oxy)diphenylsilane (82%, 0.034 mmol, 23.3 mg) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73-7.70 (m, 4H), 7.42-7.34 (m, 6H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.31 (dd, *J* = 15.0, 10.0 Hz, 1H), 6.01-5.96 (m, 1H), 5.64 (dt, *J* = 15.0, 6.5 Hz, 1H), 5.45 (dd, *J* = 15.0, 8.0 Hz, 1H), 4.38 (ABq, Δν = 122.0 Hz, *J* = 11.0 Hz, 2H), 4.22 (t, *J* = 6.0 Hz, 1H), 4.07-4.02 (m, 2H), 3.97-3.92 (m, 1H), 3.85 (q, 6.0 Hz, 1H), 3.80 (s, 3H), 3.50 (t, *J* = 8.0 Hz, 1H), 2.10 (m, 1H), 2.02-1.96 (m, 2H), 1.81-1.77 (m, 2H), 1.62-1.55 (m, 8H), 1.42-1.32 (m, 5H), 1.07 (s, 9H), 1.06 (d, *J* = 2.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 135.3, 134.9, 134.5, 132.5, 130.8, 129.4, 129.1 (2C), 127.4, 127.2, 127.1, 113.5, 108.6, 72.7, 69.7, 69.4, 69.1, 55.0, 40.3, 38.6, 36.4, 35.1, 32.3, 26.3, 25.0, 24.5, 23.8, 23.6, 22.9, 19.0. IR (neat, cm^{-1}) 3070, 2933, 2858, 1612, 1514, 1462, 1427, 1363, 1248, 1111, 1038, 991, 933, 821, 740, 702. HRMS (ESI) *m/z* calculated for $C_{43}H_{58}O_5SiNa$ $[M+Na]^+$: 705.3951, found 705.3951. $[\alpha]^{24}_D$ = +30.2° (c = 1.0, $CHCl_3$).

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CHAPTER 3: CATALYST-CONTROLLED ALIPHATIC C—H OXIDATIONS WITH A PREDICTIVE MODEL FOR SITE-SELECTIVITY

3.1 Introduction

Aliphatic C—H oxidation plays a role in diverse biological processes including biosynthesis and metabolism using a wide variety heme and non-heme oxidation enzymes.[51] The ability to harness these transformations in the laboratory with operational simplicity and stands to have a substantial impact on synthesis because C—H bonds are present in all classes of molecules (e.g. biological macromolecules, natural products, pharmaceuticals, organic materials). As nature has recognized, the ubiquity of C—H bonds affords many opportunities to diversify the properties of organic molecules by directly installing hydrogen bond donors and acceptors like alcohols and ketones. Because so many C—H sites are available, various combinations of oxidation pattern, stereochemistry and oxidation state can be explored to tune biological activity. Furthermore, because the C—H functional group is the "default," these diverse molecules can all be accessed from a common, readily accessed starting material. A non-chemical analogy is the construction of houses. Builders construct an empty frame of the house (i.e. the carbon hydrogen skeleton of molecules), which is then filled with appliances, decorations and furniture to suit the owner's needs (i.e. oxidation patterns to confer biological activity). The biosynthesis of Taxol provides a dramatic example of this strategy. The unfunctionalized taxadiene carbon-hydrogen framework of the molecule can be synthesized from geranyl geranyl phosphate using cyclase enzymes.[52] Then a series of tailoring enzymes install the individual sites of oxidation on the molecule. This pattern was presumably evolved from countless others for its function in the producing organism.

In contrast, synthetic chemists utilize a prefabrication strategy and synthesize fully functionalized pieces of the molecule and stitch them together. This would be analogous to fully constructing and filling individual rooms of a house and assembling them at a later date. This

approach removes the flexibility inherent in having an empty house to fill as desired. For example in the laboratory, synthesizing Taxol itself requires a massive synthetic effort[53] to produce just one compound. If other analogues were desired, *de novo* synthesis of each would be required at untold cost of time and resources. This issue becomes even more critical considering that nature has not evolved natural products to cure human disease. Therefore, there is no guarantee that the natural compounds are ideal for human uses. The synthesis of other related compounds is necessary to fully explore the chemical and biological space of a particular framework.

The challenge of achieving these reactions in the laboratory is threefold. First, although the ubiquity of C—H bonds allows for diversity, it also presents a major challenge for selectivity. A catalyst must distinguish not just between a few sites, but rather among many within complex molecules. Furthermore, the strength of C—H bonds requires a very reactive catalyst that must be appropriately controlled and stabilized to avoid self degradation or rampant reactivity. Finally, given such reactive catalysts, it is questionable if the other, more reactive functional groups will be tolerated or torn to shreds by the oxidant.

The field of aliphatic C—H oxidation in the laboratory evolved like many[54] from the study of biological enzymes as described above. Chemists quickly recognized the tremendous opportunities in synthesis if such reactivity could be harnessed on a laboratory scale. Early research in the area established that small molecules could functionalize aliphatic C—H bonds using iron or other metals in a porphyrin framework similar to the heme active site of natural monooxygenase enzymes;[55] however, these reactions were low yielding, the selectivities were not fully explored, and the yields and reaction stoichiometries were not suited for synthesis. In a separate approach, modulating ligands were eliminated and the reactivity of free hydroxyl

radicals was explored.[56] While C—H oxidation occurred, the yields, functional group tolerance and selectivity of the process was poor. The discovery that non-heme small molecule catalysts could be synthesized in the laboratory and achieve the same C—H oxidation reactivity opened up new avenues of ligand design because of the inherent flexibility and modularity of the non-heme system compared porphyrins.[57] In 2007, our lab demonstrated that preparative and predictable aliphatic C—H oxidations were accessible using a novel non-heme oxidation catalyst Fe(PDP).[58] This catalyst oxidized C—H bonds under convenient laboratory conditions (open to air, room temperature, acetonitrile solvent, hydrogen peroxide oxidant). Furthermore, it achieved selectivity that could be understood based on the inherent properties of the C—H bonds within the substrate. Just as olefins or other functional groups are differentiated by their electronic, steric and stereoelectronic properties, C—H bonds can be selectively oxidized if a catalyst is sufficiently sensitive to the subtle differences between bonds.

The reactivity of Fe(PDP) represents a classic example of substrate control in which a combination of substrate features direct the catalyst to oxidize at a particular position. Electronics (favoring electron rich C—H bonds), sterics (favoring less sterically hindered sites) and stereoelectronics (favoring sites where hyperconjugation or strain relief is possible) all influence the site or sites of oxidation. This stands in analogy to olefin dihydroxylation for example wherein the osmium catalyst will oxidize at the most electron rich, least sterically hindered olefin.[14] Fe(PDP) relies on the constructive *combination* of these inherent factors to favor a single site of oxidation within a molecule. While it provides good selectivity in many organic molecules because of the pervasiveness of these inherent reactivity differences among C—H bonds, the substrate ultimately dictates site-selectivity. As a result, site-selectivity suffers when individual factors diverge to favor distinct sites and modulating the magnitude of

selectivity or achieving oxidation at alternate sites is not currently possible without chemically changing the substrate (*e.g.* incorporation of specific functionality that binds to the catalyst and directs oxidation).[59]

Catalyst controlled selectivity provides a means of directly enhancing or overturning the substrate's inherent selectivity preference. Such challenges in selectivity are still at the forefront in asymmetric catalysis[60] and site-selective modification of reactive functionality.[61] Aliphatic C—H oxidation presents the additional challenge of requiring a catalyst reactive enough to oxidize very inert bonds, yet that maintains the capacity for its control elements to differentiate the subtle features of bonds ubiquitous within organic molecules. Catalyst control is a common aspect of enzymatic C—H oxidations.[62] However, despite significant efforts to adopt the enzymatic strategies of utilizing shape[63] and functional group recognition[64] elements, efficient and general small molecule catalyst control in aliphatic C—H oxidations had not yet been achieved. The challenges associated with creating a discrete match between catalyst and substrate have led to extreme catalyst designs—e.g. complete encapsulation of the catalyst active site to select on the basis of substrate topology—thereby limiting the scope to one or a few similar substrates. Herein we describe a small molecule catalyst that utilizes a trajectory restriction strategy to achieve predictable, catalyst-controlled site-selectivity while maintaining substrate generality.

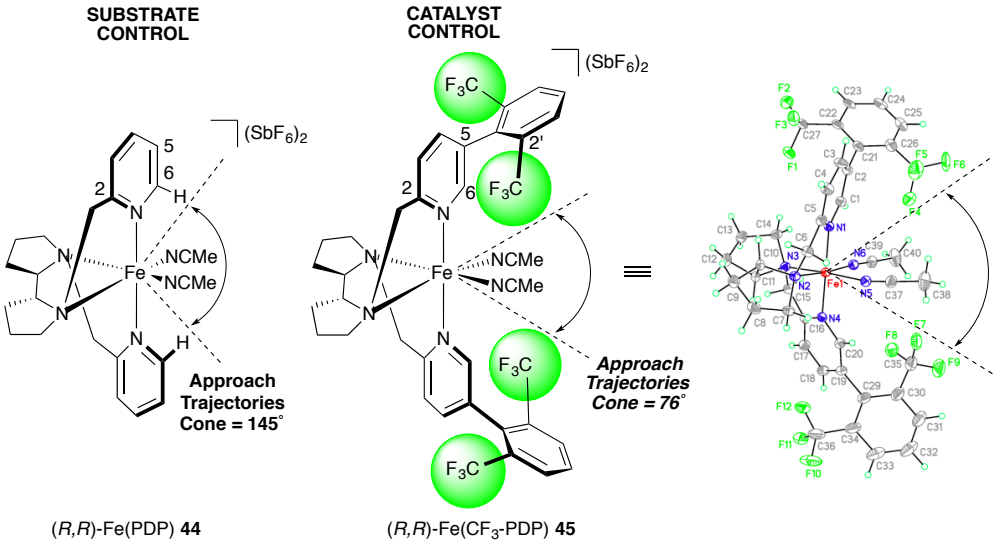
3.2 Results and Discussion

3.2.1 Catalyst Design

I endeavored to generate a small molecule catalyst that incorporates minimal steric blocking elements[65] to restrict the trajectories of approach of certain C—H bonds to the iron

oxo.[66] I hypothesized that such a catalyst could alter intrinsic substrate bias by rendering catalyst-substrate non-bonding interactions paramount, while maintaining structural flexibility such that substrates of diverse topologies are accommodated. Examining the three-dimensional (3D) structure of (*R,R*)-Fe(PDP) (**44**) reveals a wide 145˚ cone of possible approach trajectories of a substrate to the active Fe-oxo (cone defined by the innermost edges of the PDP ligand—the pyridine C6 hydrogens—and the iron center as measured from the catalyst crystal structure) (Figure 12). A wide cone allows many open trajectories for the substrate to approach

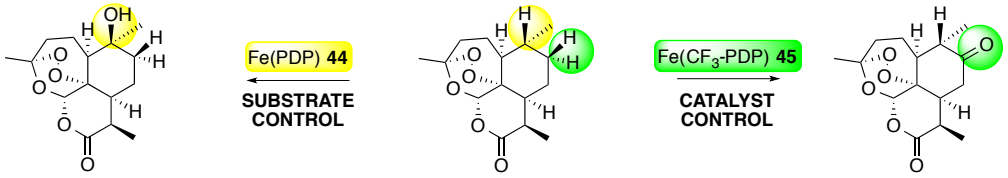
Figure 12. A Trajectory Restriction Strategy for Catalyst-Controlled Aliphatic C–H Oxidations



the catalyst so that a combination of electronic and steric/stereoelectronic factors influence site-selectivity variably depending on the substrate. I therefore sought to achieve trajectory restriction by narrowing this cone. Modifications at the pyridine 6-position of catalyst **44** were found to suppress C—H oxidation reactivity, supporting reports that non-heme iron catalysts with too much steric hindrance near the oxo often exhibit greatly diminished C—H oxidation reactivity.[67] I therefore considered modifications at the more remote pyridine 5-position and synthesized a ligand with CF_3 groups at the ortho positions of pendent aryl rings (Figure 12). Ortho di-substitution enforces a perpendicular biaryl alignment. In this conformation the CF_3 substituents

necessarily extend towards the periphery of the catalyst active site, thereby narrowing the cone of possible approach trajectories via modifications remote from the oxo. The CF_3 group proved to be an ideal fit for my catalyst design because it is sterically large (estimated to be comparable to an isopropyl group, but rotationally symmetric)[68] and also electronically deactivates the ligand towards oxidation. X-ray crystallographic analysis of this catalyst [(*R,R*)-Fe(CF_3-PDP) (**45**)] clearly shows the large CF_3 groups disposed towards the active site. Importantly, the minimum cone of possible substrate approach trajectories has been narrowed to only 76˚, compared to 145˚ in Fe(PDP) (**44**). According to our hypothesis, these ligand modifications will force more significant catalyst-substrate non-bonding interactions on the restricted path to the Fe-oxo. As a result, hindered C—H sites, even if electronically or stereoelectronically activated, will reach the catalyst iron oxo less frequently, thereby altering site-selectivity. For example, the more hindered 3˚ site of (+)-**46** would be excluded by the catalyst leading to the desired catalyst controlled, site-divergent selectivity for 2˚ oxidation (Figure 13).

Figure 13. Catalyst-Controlled Site-Divergent Oxidation of (+)-Artemisinin

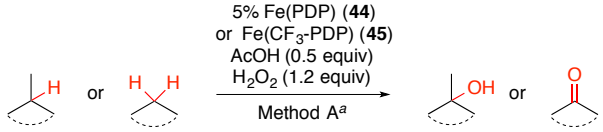


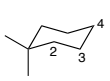
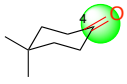
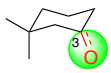
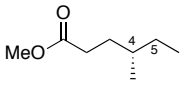
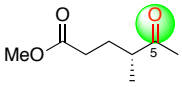
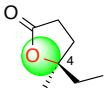
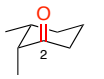
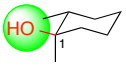
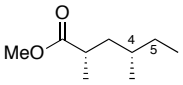
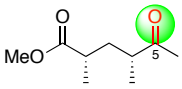
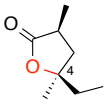
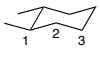
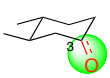
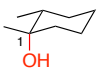
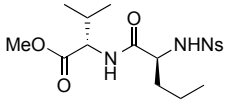
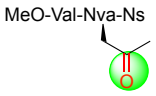
(+)-artemisinin **46**

3.2.2 Hypothesis Testing: Simple Substrates

I first examined the ability of Fe(CF_3-PDP) (**45**) to alter the intrinsic site-selectivities of oxidation previously reported with Fe(PDP) (**44**) over a topologically diverse selection of simple substrates. In 1,1-dimethylcyclohexane (**47**), the three 2˚ sites are electronically equivalent and modestly differentiated by a bulky *gem*-dimethyl group at C1, rendering the proximal C2 positions sterically hindered. Consequently, (*S,S*)-**44** provides a modest site-selectivity for

Table 6. Catalyst-Controlled Oxidation of Simple Substrates



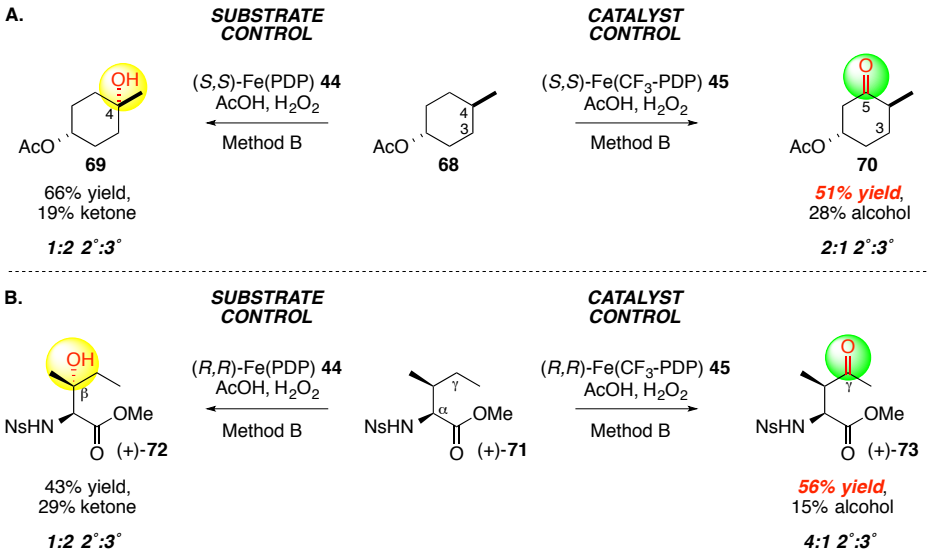
entry (catalyst)	starting material %RSM	oxidation products % yield[b,c]			product ratio[d]
					
	47[e]	**48**	**49**	**50**	**distal: proximal**
1 (**44**)	15	17	32	21	2:1
2 (**45**)	21	14	47[f]	11	6:1
					
	(+)-**51**	(-)-**52**	(+)-**53**		**2°:3°**
3 (**44**)	23	17	48		1:3
4 (**45**)	28	24	31		1:1.4
					
	54[e]	**55**	**56**	**57**	**2°:3°**
5 (**44**)	12	6	9	55	1:4
6 (**45**)	13	20	12	33	1:1.1
					
	(+)-**58**[g]	(+)-**59**	(+)-**60**		**2°:3°**
7 (**44**)	16	41	27		1:1
8 (**45**)	8	51	11		4:1
					
	61[e]	**62**	**63**	**64**	**2°:3°**
9 (**44**)	11	28	22	29	2:1
10 (**45**)	15	44[h]	26[i]	7	10:1
					
	(+)-**65**[g,j]	(+)-**66**	MeO-Val-Nva-Ns		**2°:3°**[k]
11 (**44**)	32	24	27		1:1
12 (**45**)	8	51	6		9:1

[a]Method A: iterative additon protocol; [5% Fe catalyst, 0.5 equiv AcOH, 1.2 equiv H_2O_2, MeCN]x3. [b]Average of 3 runs. [c]Yields are of isolated material unless otherwise noted. [d]Crude ratio determined by GC analysis. [e]Yields determined by GC analysis. [f]Includes 18% 3β-hydroxy product. [g]Starting material was recycled 1 time. [h]Includes 6% 3β-hydroxy product. [i]Includes 5% 2α-hydroxy product. [j]Method B: slow addition protocol; 25% Fe catalyst, 0.5 equiv AcOH, 5.0 equiv H_2O_2, MeCN, 1h. [k] ^{1}H NMR ratio. Ns=4-nitrobenzenesulfonyl.

oxidation distal to the bulky *gem*-dimethyl group at C1 (2:1 distal:proximal, Table 6, entry 1).[58b] In contrast, with (*S,S*)-**45**, the ligand restricts access of C2 to the active oxidant, resulting in an improved 6:1 distal:proximal selectivity (entry 2). The oxidation of linear ester (+)-**51** and *cis*-1,2-dimethylcyclohexane (**54**) with (*S,S*)-**44** affords oxidation at the more electron rich 3˚ sites in preference to the 2˚ sites (3:1 and 4:1 3˚:2˚, entries 3 and 5). Previously, altering this site-selectivity to favor the less electronically activated 2˚ sites necessitated *chemically changing the substrate* (i.e. the substrates inherent reactivity factors) to create more steric hindrance at the 3˚ sites. For example, α-methylated derivative (+)-**58** and *trans*-1,2-dimethylcyclohexane (**61**) introduce increased steric hindrance at the 3˚ C4 and C1 sites respectively and encourage modest levels of 2˚ oxidation with (*S,S*)-**44** (1:1.5 and 1:1.7 3˚:2˚, entries 7 and 9). In contrast, even for the relatively unhindered substrates (+)-**51** and **54**, catalyst (*S,S*)-**45** diverts reactivity towards the electronically disfavored 2˚ sites (entries 4 and 6). Oxidation by (*S,S*)-**45** of substrates with increased steric hindrance at the 3˚ sites now results in significant and synthetically useful levels of selectivity for 2˚ oxidation ((+)-**58**: 4:1 2˚:3˚; (**61**): 10:1 2˚:3˚; entries 8 and 10). Catalyst-controlled improvement of selectivity can further be applied in a more complex dipeptide setting. While (*R,R*)-**44** affords no selectivity for the oxidation of (+)-**65** due to competing electronic and steric effects (1:1 2˚:3˚, entry 11), (*R,R*)-**45** provides 51% yield of norvaline oxidation with excellent 9:1 2˚:3˚ selectivity (entry 12).

In addition to enhancing selectivity in previously poorly selective reactions, I questioned if catalyst **45** can also completely overturn the substrate's inherent selectivity to favor an alternate site. Oxidation of *trans*-4-methylcyclohexyl acetate (**68**) with (*S,S*)-**44** provides selectivity for 3˚ oxidation based primarily on electronics to afford alcohol **69** in 66% yield (1:2

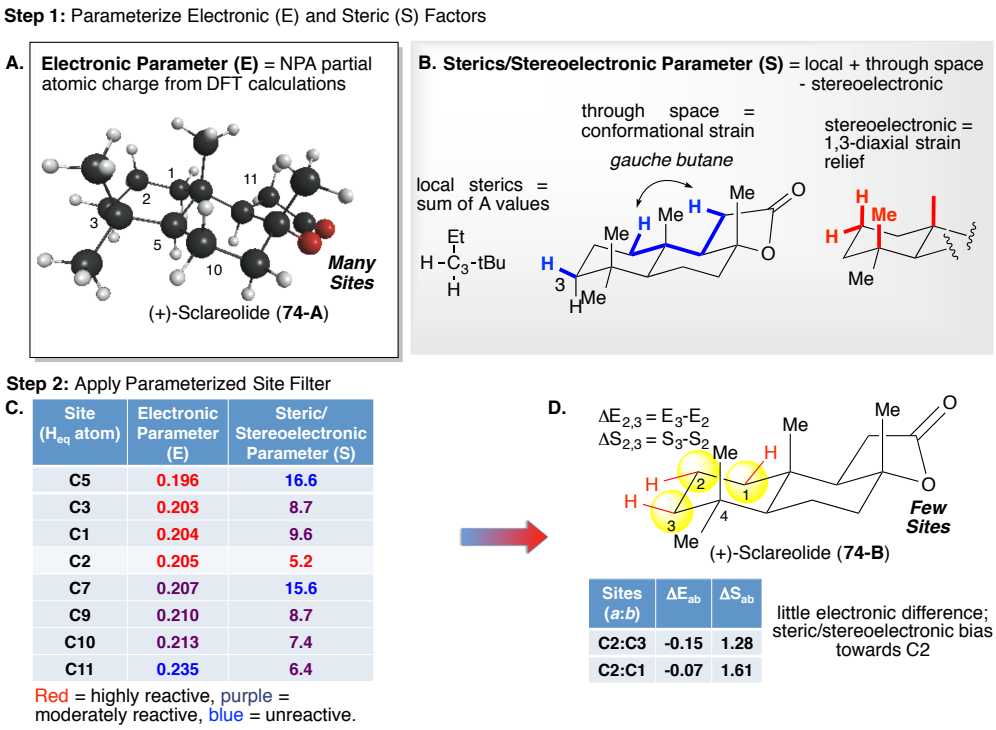
Figure 14. Catalyst-Controlled Site-Divergent Oxidation of Simple Substrates



2°:3°, Figure 14A). Despite the sterically encumbered axial disposition of the C4 3° C—H bond, the electron withdrawing acetate group significantly deactivates the competing 2° sites at C2/6 and C3/5. Catalyst (*S,S*)-**45** overturns this selectivity by exploiting a significant catalyst-substrate repulsive non-bonding interaction with C4 and affords oxidation at the electronically deactivated C3/5 site in 51% isolated yield of ketone **70**. Significantly the same effect is observed with a topologically distinct (acyclic) and functionally dense isoleucine substrate [(+)-**71**]. Oxidation with (*R,R*)-**44** affords 43% of alcohol (+)-**72** as the major product (1:2 2°:3°, Figure 14B); whereas, catalyst (*R,R*)-**45** leads to a turnover of site-selectivity affording the methylene oxidation product, γ-ketone (+)-**73**, in a preparatively useful 56% yield (4:1 2°:3°). Consistent with our working hypothesis, this data shows that catalyst **44**'s site-selectivities are dictated by the subtle interplay of electronic and steric/stereoelectronic factors *within the substrate* whereas selectivities with catalyst **45** rely primarily on *non-bonding interactions between the catalyst and the substrate*. It is significant to note that catalyst **45** affects changes in site-selectivity relative to catalyst **44** under a uniform set of operationally simple reaction conditions while maintaining preparatively useful yields.

3.2.3 Structure-based Catalyst Reactivity Models for Substrate Analysis and Site-Selectivity Prediction

Figure 15. Quantitative Analysis of Substrate Properties

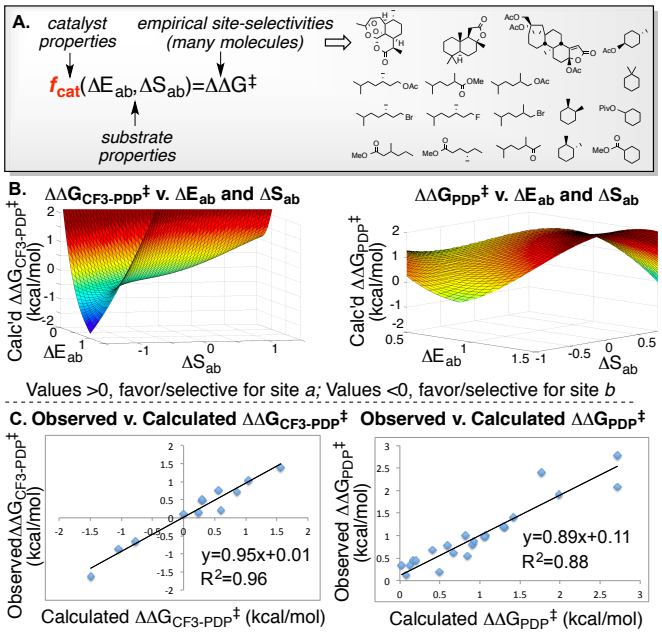


To broadly impact synthetic strategy, catalysts that exert control on site-selectivities of oxidation must do so in a *predictable* way on a diverse range of complex molecules.[8] I therefore sought to develop structure-based catalyst reactivity models that would enable the most likely sites of oxidation on a molecule to be identified and then to quantitatively describe and predict the site-selectivity afforded by each catalyst. To simplify the analysis of complex molecules with many potential sites of oxidation, I first developed a site filter that identifies likely sites of oxidation based on parameterization of electronic, steric, and stereoelectronic factors within the substrate. A conformational search of the molecule (e.g. (+)-sclareolide (**74**)) was performed with Molecular Operating Environment (MOE) 11,[69] followed by DFT geometry optimizations of the lowest energy conformers at the B3LYP/6-31G(d) level using Gaussian 09[70] to locate the global energy minimum (Figure 15A). Using this structure as a foundation, the electronic

parameter (E) was obtained by calculating the natural partial atomic charges (NPA, B3LYP/6-311++G(d,p)) of equatorial methylene and 3˚ hydrogens of each site. These values were systematically categorized across all substrates as highly reactive (red, from lowest E up to a 5% increase), moderately reactive (purple, from upper limit of the red region up to an additional 5% increase) and unreactive (blue, anything over the purple region). In (+)-**74**, C5, C3, C1, and C2 (E = 0.196, 0.203, 0.204, and 0.205, lowest charge corresponds to most electron rich, Figure 15C), for example, are electronically activated relative to C10 and C11 (E = 0.213 and 0.235). We also parameterized the steric/stereoelectronic environment at each site using three constituent values: local sterics, through space sterics and stereoelectronics (Figure 15B). Local sterics—defined as substituents covalently attached to the site in question—are calculated by approximating each substituent as a simple group (e.g. methylenes~ethyl, methines~isopropyl, quaternary centers~*tert*-butyl), assigning a value based on Winstein-Holness values ("A values"),[71] and summing these values. Through-space steric interactions (e.g. gauche butane-like and 1,3-diaxial interactions) were assigned a value based on conformational strain. Additionally, we consider if through space steric interactions leading to ring strain may be alleviated in the transition state for C—H oxidation (e.g. C2 experiences a 1,3-diaxial interaction that is relieved slightly during oxidation) leading to a stereoelectronic activation of that site.[58b,72] Combining these three values makes up the steric/stereoelectronic parameter (S) for a given site and these parameters were also systematically categorized using the same criteria as E but using 40% increases). Based on the E and S values, a parameterized site filter could be implemented: only sites with either two red or one red and one purple parameter are considered susceptible to oxidation. Applying the parameterized site filter to (+)-sclareolide (**74**) reveals three likely sites of oxidation, C1, C2, and C3 (Figure 15C,D). Therefore, even though there are numerous

possible sites of oxidation on a complex molecule, the likely sites of oxidation can be easily narrowed down to a few sites.

Figure 16. Structure-Based Catalyst Reactivity Models



I next sought to develop a model that mathematically relates each catalyst's site-selectivities to the properties of the substrate. I hypothesized that the difference in electronics ($\Delta E_{ab}=E_b-E_a$) and sterics/stereoelectronics ($\Delta S_{ab}=S_b-S_a$), which describe the relative reactivity between the sites identified using the site filter (*a* and *b*), could be proportional to the experimentally determined site-selectivities (*a*:*b*)[58] expressed as a difference in transition state energies ($\Delta\Delta G^{\ddagger}\approx 1.36\log(a:b)$). Note that E and S values are normalized for this calculation as described in chapter 3.4.6. The parameterization described in Figure 15 was carried out for a set of molecules. For sites identified as likely to be oxidized by the parameterized site filter, ΔE_{ab} and ΔS_{ab} were calculated. These data were fit as a function of catalyst $f_{cat}(\Delta E_{ab}, \Delta S_{ab})$ $\Delta\Delta G^{\ddagger}$ to obtain a 3D free energy relationship[73] expressed by an equation for each catalyst (Figure 16A,B). In examining the surface for Fe(CF_3-PDP) (**45**) oxidations, site-selectivity (i.e. $\Delta\Delta G^{\ddagger}$, Z-axis) correlates

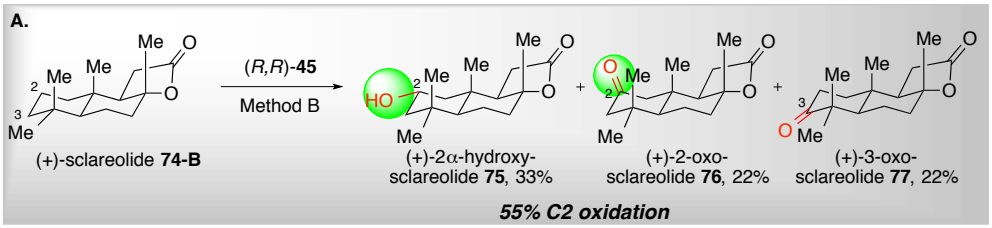
strongly with the ΔS_{ab} parameter and is highest when there is a large difference in sterics/stereoelectronics between two sites (ΔS_{ab}) in either direction: the difference in electronics (ΔE_{ab}) can be negligible or *even large in the opposite direction*. The correlations expressed computationally are fully consistent with the empirical observation that Fe(CF_3-PDP) (**45**) induces catalyst-controlled changes in $\Delta\Delta G^{\ddagger}$ as a result of non-bonding interactions between the catalyst and the substrate. In contrast the surface for Fe(PDP) (**44**) oxidations predicts that site-selectivity is highest when electronic and steric/stereoelectronic differences between two sites are large in the same direction. This mathematically expresses the empirical observation that Fe(PDP) (**44**) oxidations are controlled by the confluence of favorable steric/stereoelectronic and electronic properties within the substrate. Comparing the calculated $\Delta\Delta G^{\ddagger}$ values with those experimentally derived for catalysts **45** and **44** for all substrates used to create the models provides a good linear fit (Figure 16C). In addition to further validating our hypothesis that the basic physical organic chemistry parameters of electronics and sterics/stereoelectronics of a substrate correlate to site-selectivities in C—H oxidation, this finding also demonstrates for the first time that this relationship can be expressed quantitatively and can be *varied* based on catalyst structure.

3.2.4 Catalyst-Controlled Aliphatic C—H Oxidations of Complex Molecules

I next sought to evaluate the scope of Fe(CF_3-PDP) (**45**)'s ability to alter intrinsic site-selectivities in complex molecule settings as well as the capacity for the structure-based catalyst reactivity models to describe the resulting divergent selectivities. I first applied the reactivity models for catalysts **44** and **45** to the oxidation of (+)-sclareolide (**74**) (Figure 17). The parameterized site filter predicts that C1, C2 and C3 are likely to be oxidized. A first order

Figure 17. Application of Models to (+)-Sclareolide Oxidation

A.



B.

catalyst	% (+)-**75**[a]	% (+)-**76**	% (+)-**77**	% RSM	C2:C3 oxidation[b]
(*R,R*)-Fe(PDP) **44**	-	46	32	9	1.4:1
(*S,S*)-Fe(PDP) **44**	-	26	26	9	1:1
(*R,R*)-Fe(Me_2Ar-PDP) **78**	15	26	19	13	2:1
(*R,R*)-Fe(CF_3-PDP) 45[c]	**33**	**22**	**22**	**7**	**3:1**
(*S,S*)-Fe(CF_3-PDP) **45**[c]	16	23	32	14	1.2:1

[a]Average of two runs at 0.3 mmol. Yields are of isolated material. [b]Isolated ratio. [c]Starting material was recycled once. RSM=recovered starting material.

C. $f_{cat}(\Delta E_{ab}, \Delta S_{ab})=\Delta\Delta G^{‡}$

Sites (*a*:*b*)	ΔE_{ab}	ΔS_{ab}
C2:C3	-0.15	1.28
C2:C1	-0.07	1.61

little electronic difference; steric/stereoelectronic bias towards C2

D. Calculated and Observed Values for Catalysts **44** and **45**

Sites (*a*:*b*)	Calc'd ΔΔG‡ (kcal/mol)		Obs ΔΔG‡ (kcal/mol)		Calc'd Ratio		Obs Ratio	
	45	44	45	44	45	44	45	44
C2:C3	0.77	0.44	0.56	0.20	4:1	2:1	3:1	1.4:1
C2:C1	1.03	0.80	1.03	0.90	6:1	4:1	6:1	5:1

understanding of the reactivity of this molecule can be obtained by examining the difference parameters ΔE_{ab} and ΔS_{ab} (Figure 17C). Positive values indicate that the parameter favors site *a*, while negative values favor site *b*. In (+)-**74** for example, the small $\Delta E_{2,3}$=-0.15 value indicates the sites are electronically similar, while the $\Delta S_{2,3}$=1.28 indicates a strong steric preference for C2. Next, the equations for each model are easily utilized by solving the equations to obtain the calculated $\Delta\Delta G^{‡}$. Catalyst **44**'s reactivity model indicates that, despite the steric preference for C2, the minimal electronic differences between these sites will lead to site-selectivities of 2:1 (C2:C3) and 4:1 (C2:C1), consistent with our experimentally observed selectivities with catalyst **44** of 1.4:1 (C2:C3) and 5:1 (C2:C1) (Figure 17D) resulting in 46% isolated yield of (+)-2-oxo-sclareolide (**75**).[58b] In contrast, catalyst **45**'s reactivity model reveals an amplification of the steric/stereoelectronic term and predicts a C2:C3 selectivity of 4:1 and C2:C1 selectivity of 6:1, closely matching the experimentally observed values with catalyst **45** of 3:1 (C2:C3) and 6:1

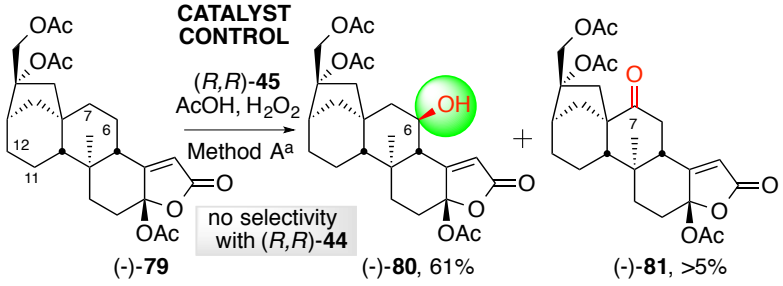
(C2:C1) that afford C2 product with an enhanced yield of 55% (Figure 17A,B,D). I also examined the oxidation of (+)-**74**, with an alternate catalyst (*R,R*)-Fe(Me_2Ar-PDP) (**78**). Instead of 2,6-diCF_3 aryl rings at the pyridine 5-position, this catalyst incorporates 2,6-diMe-4-CF_3 arenes. Importantly, the ortho-methyl group is significantly smaller than CF_3 leading to a catalyst predicted to be of intermediate cone angle between catalysts **44** and **45**. Consistent with the trajectory restriction hypothesis for catalyst control, (*R,R*)-**78** oxidizes (+)-**74** with an intermediate 2:1 C2:C3 site-selectivity, indicating a marginal amount of catalyst control (Figure 17B).

Another interesting aspect of catalyst-controlled oxidation of (+)-**74** is the presence of a new product, (+)-2α-hydroxy-sclareolide (**75**). For the majority of oxidations with Fe(PDP) (**44**), once a C—H bond at a methylene site is oxidized, the initially formed alcohol serves to hyperconjugatively activate the site towards a second C—H oxidation to furnish the ketone. Alcohol products are only observed in cases where extreme steric hindrance prevents oxidation of the second C—H bond; for example in the oxidation of dihydropleuromutilone[58b] and triacetoxy tricalysiolide B (*vide infra*). Because of the less hindered nature of equatorial C—H bonds, >20:1 dr is observed favoring equatorial hydroxylation. However, with trajectory restricted catalyst **45** and to a lesser extent **78**, the catalyst itself is able to restrict approach of the alcoholic 2˚ C—H bond resulting in 33% and 15% alcohol selective methylene oxidation respectively. Again, a clear trend is observed as the approach cone of the catalyst is narrowed. This effect is not limited only to rigid complex molecules like (+)-**75** and a small amount of alcohol selective methylene oxidation is also observed in simple substrates **47** and **61**. These results indicate that further catalyst modifications may furnish a highly alcohol selective catalyst for methylene oxidation. This methodology would serve as an additional point of diversification

in complex molecules based on oxidation state and stereochemistry and therefore the hydrogen bond donating/accepting characteristics of the site.

Not only catalyst identity, but also the chirality of the catalyst has an impact on reaction yields and in some cases site-selectivties. For example, (+)-**74** oxidation exhibits clear matched/mismatched reactivity using the different antipodes of both catalysts **44** and **45** leading to lower reactivity with the (*S,S*)-enantiomer (Figure 17B). While the precise interactions leading to this mismatch are not currently known, it is reasonable to expect that as different antipodes of the chiral catalysts approach a chiral molecule, there will be distinct interactions leading in some cases to undesirable steric clash. This effect is observed across all complex molecules and further examples can be seen in Section 3.4.8.

Figure 18. Incluencing Selectivity in a Non-selective Reaction



Data for (-)-**79**

Sites (*a*:*b*)	ΔE_{ab}	ΔS_{ab}
C6:C7	-0.35	1.09
C6:C11	-0.48	1.27
C6:C12	0.11	1.28

Input into Structure-Based Reactivity Model

Results for Catalysts 44 and 45

C6:C7	calc'd $\Delta\Delta G^{\ddagger}$ (kcal/mol)	Calc'd Ratio	Observed Ratio
cat. 2	1.4	11:1	>10:1
cat. 1	-0.1	1:1	1:1

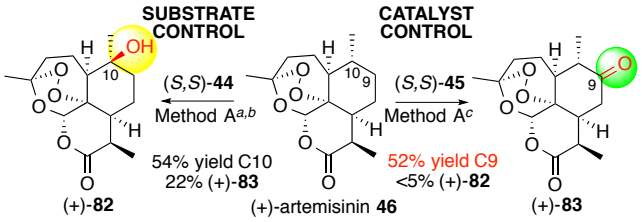
[a]Average of 3 runs, SD=3%. Starting material was recycled once.

Applying the parameterized site filter to (-)-triacetoxy tricalysiolide B (**79**), a putative metabolite of the diterpene cafestol found in coffee[74] having eight potential sites of oxidation, revealed four likely sites of oxidation: C6, C7, C11 and C12. Evaluation of the electronic and steric difference parameters between these sites indicates that the selectivity factors are in

opposition; there is a strong steric preference for C6 and an electronic preference for C7 and C11 (Figure 18). Using C6 as our reference in catalyst **44**'s reactivity model, we calculate moderate site-selectivity ratios of 1:1.1 (C6:C7), 1:1.4 (C6:C11) and 4:1 (C6:C12), due to these divergent electronic and steric/stereoelectronic factors within the substrate. These calculated values are fully consistent the experimental findings that oxidation of (-)-**79** with (*R,R*)-Fe(PDP) (**44**) furnishes (-)-6β-hydroxy-triacetoxy tricalysiolide B (**80**) in 26% yield and (-)-7-oxo-triacetoxy tricalysiolide B (**81)** in 18% yield with no site-selectivity (1:1 C6:C7). The mass balance of this reaction is also poor (only 10% recovered starting material), suggesting unselective oxidation at other activated sites. Although these off pathway oxidation products have not been fully characterized, peaks consistent with other ketones are present in the crude ^{1}H NMR. In contrast, catalyst **45**'s reactivity model calculates an 11:1 C6:C7 ratio with higher mass balance due to its ability to respond to large steric/stereoelectronic difference parameters ($\Delta S_{6,7}$ = 1.09, $\Delta S_{6,11}$ = 1.28, $\Delta S_{6,12}$ = 1.28). Notably, the extreme steric hindrance of the axial hydrogen at C6 retards over oxidation of the alcohol to the ketone by both catalysts **44** and **45**. Experimentally, oxidation of (-)-**79** with (*R,R*)-**45** affords (-)-**80** *in a 61% isolated yield* with a significant catalyst-dependent increase in site-selectivity of C6:C7 oxidation from 1:1 to >10:1. It is significant to note that excellent enhancement of site-selectivity for C6 oxidation with catalyst **45** is observed despite the opposing electronic difference parameter favoring C7.

The greatest challenge for catalyst control is to override the inherent site-selectivity of oxidation to favor an alternate site. Catalyst **45** achieved this in the oxidation of simple substrates *trans*-4-methylcyclohexyl acetate (**68**) and protected isoleucine (+)-**71**, and we sought to further challenge this catalyst in a complex molecule setting. Applying our parameterized site filter to (+)-artemisinin (**46**)—having nine potential sites of oxidation—eliminates all but C10 and C9 on

Figure 19. Overriding Inherent Site-selectivity of C-H Oxidation.



Sites (a:b)	Calc'd Ratio	Observed Ratio
C9:C10	1:1.3	1:2

Sites (a:b)	ΔE_{ab}	ΔS_{ab}
C10:C9	1.48	-1.70

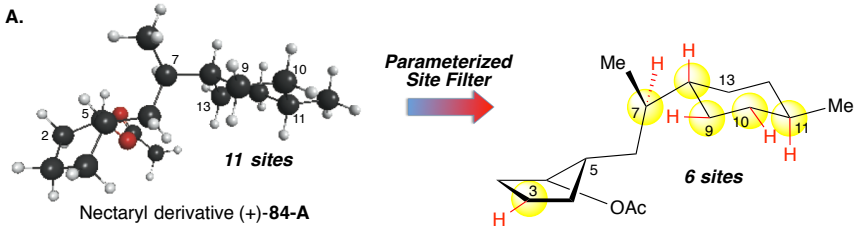
Sites (a:b)	Calc'd Ratio	Observed Ratio
C9:C10	17:1	11:1

[a]Average of 3 runs. [b]Starting material recycled twice. [c]Starting material recycled x4. SD=2%.

the basis of very unfavorable electronics and/or sterics at alternate sites. Catalyst **44** is calculated to give a 1.3:1 C10:C9 ratio because it responds to the divergent biasing factors within the substrate: a strong electronic preference for 3˚ oxidation at C10 ($\Delta E_{10,9}$ = 1.48) and an opposing steric preference for 2˚ oxidation at C9 ($\Delta S_{10,9}$ = -1.70) (Figure 19). Consistent with this, oxidation of (+)-**46** with (*S,S*)-**44** afforded 54% yield of (+)-10β-hydroxy-artemisinin (**82**) with 23% yield of (+)-9-oxo-artemisinin (**83**) in a useful 2.3:1 C10:C9 selectivity.[58a] Despite the substrate's strong electronic bias favoring 3˚ oxidation, the structure-based reactivity model for catalyst **45** calculates a 17:1 ratio favoring 2˚ C9 oxidation based on the large steric difference parameter. This may be understood on the basis of catalyst **45**'s ability to exploit non-bonding interactions between its biaryl ligand and the substrate's rigid lactone ring system to restrict approach trajectories of the electron rich C10 3˚ C—H bond to the iron oxo. Gratifyingly, (*S,S*)-**45** dramatically turns over the substrate controlled selectivity seen with (*S,S*)-**44**, oxidizing at the C9 site in an 11:1 2˚:3˚ ratio and furnishing 52% yield of (+)-**83** and <5% (+)-**82** Catalyst **45** is again able to override a strong electronic substrate bias to achieve high site-selectivity at an alternate site based on non-bonding catalyst-substrate interactions. This is analogous to what was observed with (-)-triacetoxy tricalysiolide B (**79**), but on a topologically distinct structure. Notably, previous to this work, only P-450 enzymes evolved in the laboratory *specifically* for the

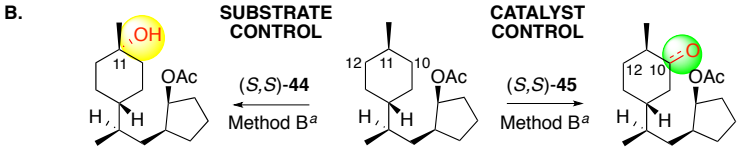
oxidation of (+)-**46** have provided comparable levels of selectivity for C9,[75] highlighting the power of catalyst **45** to access new sites of reactivity without the need for substrate specificity.

Figure 20. Predictably Altering the Inherent Site-selectivity of C-H Oxidation



Sites (*a*:*b*)	ΔE_{ab}	ΔS_{ab}
C11:C10/12	1.22	-1.22
C11:C9/13	1.33	-0.89
C11:C8	0.43	0.17
C11:C7	0.57	0.12
C11:C3	1.27	-1.04

selectivity factors in opposition
electronic bias towards C11;
steric/stereoelectronic bias towards C10/12



Sites (*a*:*b*)	*Predicted Ratio*	Observed Ratio
C10/12:C11	1:1.5	1:1.3

nectaryl derivative (+)-84

Sites (*a*:*b*)	*Predicted Ratio*	Observed Ratio
C10/12:C11	3:1	6:1

[a]Average of 3 runs. Starting material recycled x1. SD=3%. 3:1 ketone:alcohol ratio for **86**.

Mathematical models for catalysts **44** and **45** are strongly supported by the empirical data for substrates incorporated into the original data sets. I next sought to test the predictive power of these models for (+)-nectaryl derivative (**84**), a synthetic terpene-like molecule used in commercial fragrances that had not been included in the data sets for either catalyst. Applying our parameterized site filter, many likely sites of oxidation remained (C11, C10/12, C9/13, C8, C7 and C3): the conformational flexibility of (+)-**84** and electronic similarity of its sites made selective oxidation with either catalyst a challenging prospect (Figure 20A). Aliphatic C—H oxidations of (+)-**84** were predicted using the structure-based reactivity models to modestly favor the more electron rich, tertiary C11 site for catalyst **44** ($\Delta E_{11,10/12}$ = 1.22, 1.5:1 3°: 2°) and the least sterically encumbered C10/12 site for catalyst **45** ($\Delta S_{11,10/12}$ = -1.23, 1:3 3°:2°) (Figure 20B).

Consistent with this calculation, oxidation of (+)-**84** with (*S,S*)-**44** affords 29% yield of C11 3˚ hydroxyl (+)-**85** and 23% yield of the 2˚ C10/12 ketones **86** with modest selectivity between the two sites slightly favoring oxidation at the electronically activated 3˚ site (1.3:1 3˚:2˚). Note that although C10 and C12 are by definition unique sites, the existence of a local molecular plane of symmetry and the distance of the group that breaks this symmetry mean that in practice they behave identically. As a result, I report a single C10/12 site and observe no selectivity between oxidation at one or the other site with either catalyst or catalyst enantiomer. In contrast, catalyst (*S,S*)-**45** is able to overcome the electronic substrate bias towards C11 to furnish 2˚ C10/12 oxidation products **86** in a 52% yield with good selectivity (1:6 3˚:2˚). Even in the absence of bulky axial blocking groups, alcohol selective methylene oxidation at C10/12 is observed with catalyst **45** to furnish a small amount of α-hydroxylated product despite the absence of large axial groups. This example illustrates catalyst **45**'s capacity to affect predictable control on site-selectivity based on non-bonding interactions, even in complex substrates with high degrees of conformational flexibility. Moreover, the site-selectivity algorithms for catalysts **44** and **45** are validated as predictive tools, particularly for substrates whose electronic, steric, and stereoelectronic features are well represented by the substrates incorporated into the original data sets.

3.3 Conclusions

This work shows that catalyst control of site-selectivity in aliphatic C—H oxidations is possible—despite the significant challenges associated with controlling highly reactive intermediates—without necessitating a specific match between one catalyst and one substrate. Using the strategy of trajectory restriction, Fe(CF_3-PDP) (**45**) exploits non-bonding catalyst-

substrate and alters the intrinsic site-selectivities previously reported with Fe(PDP) (**44**) over a broad range of topologically diverse substrates with preparative yields (≥50% mono-oxidized product). It is hoped that a series of catalysts can be developed that respond to different aspects of the substrate and to differing degrees to affect site-divergent oxidations in complex molecules at numerous sites for the purpose of molecular diversification. The development of structure-based catalyst reactivity models confers a greater ability to accurately predict the site of oxidation in complex molecule settings that we expect will enable site-divergent diversification of bioactive molecules with unprecedented precision. Furthermore, the discovery that site-selectivities of oxidation can be mathematically correlated to substrate properties as a function of the catalyst is likely to inform and inspire future catalyst design for selective intermolecular C—H oxidations. The ultimate goal of this research is to develop a computer program that given a substrate structure can predict the site of oxidation, amination, alkylation and halogenation with a wide variety of catalysts as these methodologies and catalysts are developed.

3.4 Experimental Section

3.4.1 General Information.

All C—H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were run under an Ar or N_2 atmosphere with dry solvent in flame dried glassware unless otherwise noted. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), dimethylformamide (DMF), acetonitrile (MeCN), toluene (PhMe) and benzene (PhH) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, CA). Triethylamine and pyridine were distilled from calcium hydride. Commercially available reagents that were used as received are noted in the individual reaction

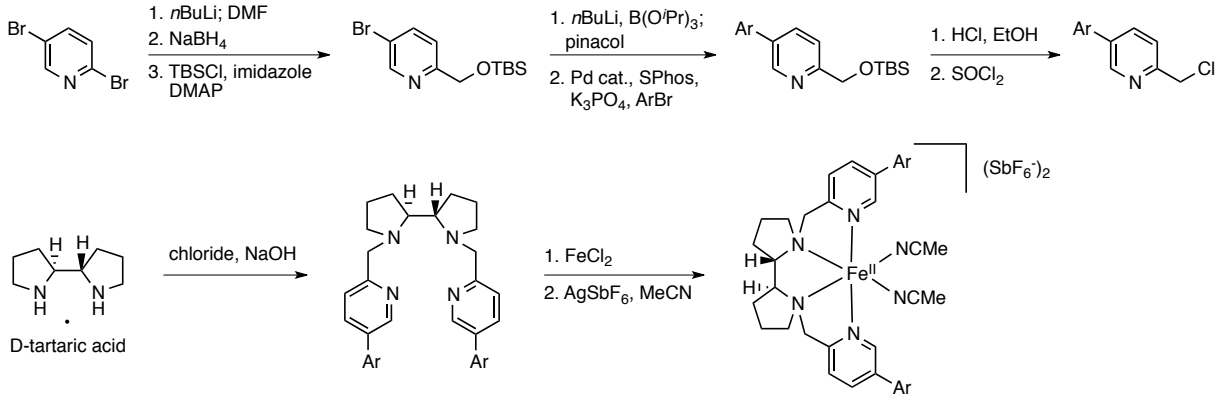
procedures. (*S,S*)- and (*R,R*)-2,2'-bispyrrolidine tartrate were prepared according to the literature procedure.[76] The ee of the diamine was checked by conversion to the dibenzoate and analysis by reverse phase HPLC; obtained either enantiomer in >99% ee (Chiralpak AD-RH, 35:60:5 MeCN:H_2O:*i*-PrOH, 0.3 mL/min., 30 ˚C, t_R(*S,S*)=34.85 min., t_R(*R,R*)=41.68 min.) (*S,S*)- and (*R,R*)-Fe(PDP) (**44**) were prepared according to literature procedures.[58a] (-)-Triacetoxy tricalysiolide B (**79**) was prepared according to the literature procedure from coffee oil.[74]

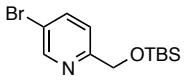
Solvents were removed by rotary evaporation at ~30 ˚C and ~40 torr unless otherwise noted. Thin-layer chromatography (TLC) was performed with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV and/or potassium permanganate or ceric ammonium molybdate staining. Flash chromatography was performed as described by Still et al.[22] using EM reagent silica gel 60 (230-400 mesh). $CDCl_3$ was stored over 4Å molecular sieves.

^{1}H NMR spectra were recorded on a Varian Inova 500NB (500 MHz), Varian Untiy 500 (500 MHz) or Varian VXR 500 (500 MHz) spectrometer and are reported in ppm (δ) using solvent ($CDCl_3$ at 7.26 ppm) as an internal standard unless otherwise noted. Data reported as: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, m=multiplet, b=broad, app=apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on Varian Untiy 500 (125 MHz) or Varian VXR 500 (125 MHz) and are reported in ppm using solvent ($CDCl_3$, 77.0 ppm) as an internal standard unless otherwise noted. ^{19}F spectra were recorded on Varian Untiy 500 (470 MHz) or Varian VXR 500 (470 MHz) and are reported in ppm using $FCCl_3$ (0 ppm) as an external standard. IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Achiral gas chromatographic (GC) analyses were performed on an Agilent

Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30 m, 0.32 mm, 0.25 mm). Optical rotations were measured in a 1 mL cell with 50 mm path length or a 0.2 mL cell with a 10 mm path length on a Jasco P-1020 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[a]_l^{T^\circ C}$ (c=g/100 mL, solvent). Medium pressure liquid chromatography (MPLC) separations were performed on a Teledyne Isco CombiFlashRf system using 12 or 24 g Redi Sep Rf Gold silica columns.

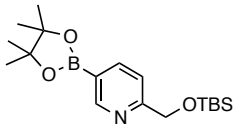
3.4.2 Synthesis and Characterization of Novel C—H Oxidation Catalysts





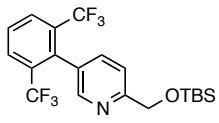
5-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine. 2,5-Dibromopyridine (50.0 g, 211 mmol, 1.0 equiv, Oakwood Products) was suspended in PhMe (0.2 M) in a 2 L round bottomed flask. The suspension was cooled to -78 ˚C and *n*BuLi (160 mL, 253 mmol, 1.2 equiv, 1.6 M in hexanes, Sigma-Aldrich) was added dropwise over 10 min. The reaction was stirred for 2 h at -78 ˚C, at which time DMF (33 mL, 30.8 g, 422 mmol, 2.0 equiv) was added dropwise and stirring continued an additional 1h. The dark solution was warmed to 0 ˚C and MeOH (211 mL) followed by $NaBH_4$ (8.0 g, 211 mmol, 1.0 equiv, Sigma-Aldrich) were added carefully. Stirring was continued for 1 h allowing the reaction to warm to room

temperaure. The reaction was quenched with H_2O (~100 mL). The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude oil. The crude was dissolved in CH_2Cl_2 (340 mL) in a 1 L round bottomed flask. TBSCl (30.8 g, 204 mmol, 1.2 equiv, TCI), imidazole (17.4 g, 255 mmol, 1.5 equiv, Sigma-Aldrich) and DMAP (2.1 g, 17 mmol, 0.1 equiv, Sigma-Aldrich) were added in one portion and the reaction was stirred for 12 h at room temperature. The reaction was quenched with H_2O (100 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~600 mL) eluting with 10% EtOAc/hexanes afforded the title compound (50.8 g, 168 mmol, 80% yield) as a light yellow oil. This comound may also be utilized in crude from after workup for the following pinacol boronate forming step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.40 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.76 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 149.6, 139.1, 121.4, 118.4, 65.5, 25.8, 18.3, -5.4, IR (film): 2954, 2929, 2887, 2858, 1577, 1560, 1470, 1377, 1362, 1257, 1103, 1007, 939, 841, 779 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{21}NOSiBr$ $[M+H]^+$: 302.0576, found 302.0566.



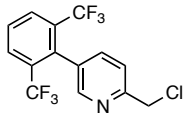
2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine. 5-Bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (20.6 g, 68 mmol, 1.0 equiv) and triisopropyl borate (18.9 mL, 15.4 g, 81.6 mmol, Sigma-Aldrich) were dissolved in THF (136 mL) in a 500 mL round bottomed flask. The solution was cooled to -78 ˚C and *n*BuLi (51 mL, 81.6 mmol, 1.2 equiv, 1.6 M in hexanes) was added over 1 h via syringe

pump. After the addition was complete, the reaction was stirred for an additional 2 h at -78 ˚C, at which time it was allowed to warm to 0 ˚C. The reaction was carefully quenched to pH=6 with 1 M KH_2PO_4. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude oil. The oil was dissolved in PhH (136 mL) in a 250 mL round bottomed flask, to which pinacol (9.6 g, 81.6 mmol, 1.2 equiv, Oakwood Products) was added. The flask was fitted with a dean-stark trap and the reaction was refluxed over night. After cooling to room temperature, water (50 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3x30mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~600 mL) eluting with 20 → 30% EtOAc/hexanes afforded the title compound (15.1 g, 44.4 mmol, 65% yield) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.07 (d, J = 5.0 Hz, 1H), 7.50 (d, J = 10.0 Hz, 1H), 4.85 (s, 2H), 1.35 (s, 12H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 154.5, 142.9, 119.1, 84.0, 66.2, 25.9, 24.8, 18.3, -5.4; IR (film): 2980, 2954, 2931, 2889, 2858, 1600, 1560, 1471, 1363, 1311, 1257, 1215, 1146, 1103, 1024, 1007, 962, 843, 777, 735, 667 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{33}NO_3BSi$ $[M+H]^+$: 350.2323, found 350.2320.



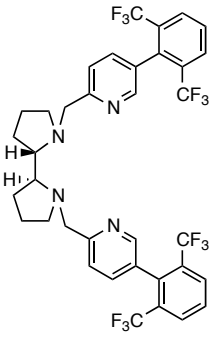
5-(2,6-bis(trifluoromethyl)phenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine. A 50 mL round bottomed flask fitted with a rubber septum was charged with a stir bar, $Pd(OAc)_2$ (74.8 mg, 0.33 mmol, 3 mol %, Johnson Matthey), SPhos (275.1 mg, 0.67 mmol, 6 mol %, Strem), 2-bromo-1,3-bis(trifluoromethyl)benzene (3.25 g, 11.1 mmol, 1.0 equiv, Synquest Laboratories) and K_3PO_4 (4.71 g, 22.2 mmol, 2.0 equiv, Strem). The flask was evacuated and backfilled with N_2 (x3). Toluene (20 mL) and degassed DI

H_2O (2 mL) were added followed by 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.82 g, 16.6 mmol, 1.5 equiv). The rubber septum was quickly replaced with a yellow polyethylene cap and secured with electrical tape. The reaction was heated at 100 ˚C in an oil bath for 16 h, at which time it was allowed to cool to room temperature and quenched with water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~300 mL) eluting with 5% EtOAc/hexanes afforded the title compound in approximately 61% yield with some minor impurities resulting from protiodeborination of the pinacol borane. The product was taken on to subsequent synthetic steps during the course of which, the impurities were removed.



5-(2,6-bis(trifluoromethyl)phenyl)-2-(chloromethyl)pyridine. This reaction was preformed open to air. 5-(2,6-Bis(trifluoromethyl)phenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (2.96 g, 6.8 mmol, 1.0 equiv) was dissolved in EtOH (7 mL) and 3N HCl (7 mL). The reaction was stirred vigorously for 3 h, quenched to neutral pH with saturated $NaHCO_3$, and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude solid. The solid was dissolved in CH_2Cl_2 (34 mL) and $SOCl_2$ (5 mL, 8.09 g, 68 mmol, 10.0 equiv, Sigma-Aldrich) was added dropwise. The reaction was stirred 12 h and quenched to neutral pH with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~250 mL) eluting with 5% EtOAc/hexanes afforded the title compound (1.08 g, 3.0 mmol, 76% yield) as a

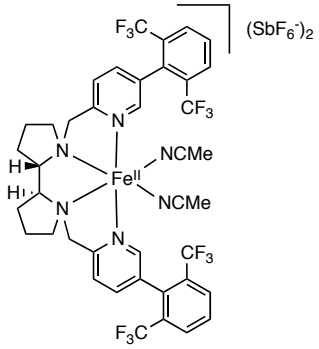
colorless powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 4.76 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 149.4, 138.3, 136.0, 131.7 (q, *J* = 30.3 Hz), 129.4, 129.4 (q, 4.9 Hz), 128.9, 123.0 (q, 274.4 Hz), 120.9, 46.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.9; IR (film): 1599, 1587, 1564, 1375, 1340, 1296, 1209, 1182, 1132, 1103, 1066, 1002, 822, 762, 677 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_9NClF_6$ $[M+H]^+$: 340.0328, found 340.0318.



(2*S*,2'*S*)-1,1'-bis((5-(2,6-bis(trifluoromethyl)phenyl)pyridin-2-yl)methyl)-2,2'-bipyrrolidine [(*S,S*)-Fe(CF_3-PDP)]. This reaction was performed open to air. According to the procedure of White,[58a] a round bottomed flask was charged with a stir bar, 5-(2,6-bis(trifluoromethyl)phenyl)-2-(chloromethyl)pyridine (1.87 g, 5.5 mmol, 2.2 equiv), (*S,S*)-2,2'-bispyrrolidine/D-tatraric acid (725.8 mg, 2.5 mmol, 1.0 equiv), NaOH (640 mg, 16 mmol, 6.4 equiv) and 1:1 CH_2Cl_2:H_2O (10 mL) and the reaction was stirred vigorously at room temperature for 12 h. The reaction was diluted with 1M NaOH and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x5). The combined organic layers were dried (K_2CO_3), filtered and concentrated. Purification by flash chromatography on silica (~125 mL) eluting with 5% MeOH/CH_2Cl_2 with 1% NH_4OH afforded the crude ligand, which was partitioned between CH_2Cl_2 and 1 M NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x5). This extraction removes traces of water and NH_4OH from the column conditions. The combined organic layers were dried (K_2CO_3), filtered and concentrated

to afford the title compound (1.19 g, 1.6 mmol, 64% yield) as a colorless powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 2H), 7.97 (d, *J* = 7.5 Hz, 4H), 7.65 (t, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 3.91 (ABq, *J* = 14.5 Hz, Δν= 274.5 Hz, 4H), 3.08-3.00 (m, 2H), 2.75 (app t, *J* = 6.0 Hz, 2H), 2.29 (q, *J* = 8.5 Hz, 2H), 1.86-1.66 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8 (2C), 148.8 (2C), 137.6 (2C), 136.9 (2C), 131.8 (q, *J* = 29.5 Hz, 2C), 129.3 (q, *J* = 5.5 Hz, 2C), 128.5 (2C), 128.0 (2C), 123.1 (q, *J* = 275.3, 2C), 121.1 (2C), 65.5 (2C), 61.2 (2C), 55.6 (2C), 25.9 (2C), 23.6 (2C); ^{19}F NMR (470 MHz, $CDCl_3$) δ -57.8; IR (film): 3043, 2987, 2954, 2935, 2897, 2846, 1763, 1741, 1441, 1371, 1290, 1255, 1221, 1182, 1101, 1072, 952 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{36}H_{31}N_4F_{12}$ $[M+H]^+$: 747.2357, found 747.2352; $[\alpha]_D^{25}$ = -14.4° (c=1.0, $CHCl_3$).

(*R,R*)-Fe(CF_3-PDP) was also prepared. $[\alpha]_D^{24}$ = +16.2° (c=1.1, $CHCl_3$).

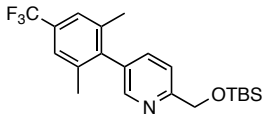


[(*S,S*)-Fe(Fe(CF_3-PDP)$(MeCN)_2$]$(SbF_6)_2$ (45). According to the procedure of White,[58a] a 50 mL round bottomed flask was charged with a stir bar, (*S,S*)-Fe(CF_3-PDP) (1.19 g, 1.6 mmol, 1.0 equiv) and MeCN (9.4 mL). $FeCl_2$-$4H_2O$ (318.1 mg, 1.6 mmol, 1.0 equiv, Strem) was added and the reaction was stirred 24 h at room temperature. Immediately after adding the iron salt, an orange precipitate was observed. The precipitation was completed at the end of the reaction by addition of Et_2O. Solvent was decanted out of the flask via pipette. The resulting solid was washed thoroughly with Et_2O until the washes are colorless and dried under a stream of N_2 for 4 h to yield (*S,S*)-Fe(CF_3-PDP)Cl_2 (1.26 g, 1.4 mmol, 90% yield) as a bright

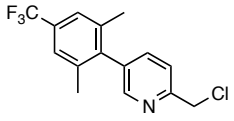
orange powder. HRMS (ESI) *m/z* calc'd for $C_{36}H_{30}ClF_{12}FeN_4$ $[M\text{-}Cl]^+$: 1037.0571, found 1037.0577.

A 50 mL round bottomed flask (the flask should be free of trace metal impurities and not have been cleaned with harsh acidic or basic conditions such as nitric acid or base bath) was charged with a stir bar, (*S,S*)-Fe(CF_3-PDP)Cl_2 (1.27 g, 1.4 mmol, 1.0 equiv) and MeCN (17.5 mL). $AgSbF_6$ (962.3 mg, 2.8 mmol, 2.0 equiv, Strem, stored and weighed out in the glove box with precautions taken to exclude light, air and moisture) was added in 1 portion resulting in immediate precipitation of AgCl and a color change to dark red/purple. The reaction flask was wrapped in foil to exclude light and stirred vigorously for 24 h. The reaction was filtered through Celite® and concentrated nearly to dryness. The catalyst was redissolved in MeCN, filtered through a 0.2 mm Acrodisc® LC PVDF (HPLC certified) and concentrated nearly to dryness. The filtration procedure was repeated (x2) to ensure complete removal of silver salts. The resulting solid was dried under a stream of N_2 for 5 h to yield the title compound (1.81 g, 1.3 mmol, 96% yield) as a light red powder. HRMS (ESI) *m/z* calc'd for $C_{36}H_{30}N_4F_{18}FeSb$ $[M\text{-}(MeCN)_2(SbF_6)]^+$: 265.1804, found 265.1804. Anal. calc'd for $C_{40}H_{36}F_{24}FeN_6Sb_2$ (MW = 1356.08 g/mol): C 35.43, H 2.68, N 6.20, Fe 4.12; found: C 35.16, H 2.39, N 6.52, Fe 4.20. ^1H NMR (500 MHz, CD_3CN) δ 32.34 (br s), 20.81 (br s), 18.67 (br s), 16.66 (br s), 13.36-12.87 (m), 12.14-11.29 (m), 8.36 (s), 7.47 (s), 6.22 (s).

X-ray quality crystals were obtained by dissolving 30 mg of the complex in a ½ dram vial with minimal MeCN and 1 drop PhH. This vial was loosely capped and put into a 20 mL scintillation vial filled with ~7 mL Et_2O. The larger vial was capped tightly. After ~3 days, dark red crystals formed after slow diffusion of the Et_2O into the smaller vial. See page S37 for X-ray crystal structure data.

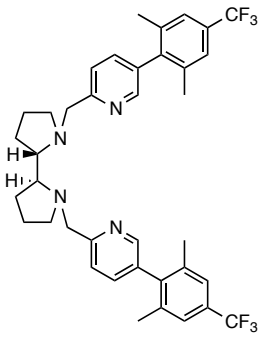


2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2,6-dimethyl-4-(trifluoromethyl)phenyl)pyridine. A 50 mL round bottomed flask fitted with a rubber septum under Ar was charged with a stir bar, $Pd(OAc)_2$ (105.1 mg, 0.47 mmol, 3 mol %), SPhos (384.2 mg, 0.94 mmol, 6 mol %), and K_3PO_4 (6.62 g, 31.2 mmol, 2.0 equiv). Toluene (28 mL) and degassed DI H_2O (3 mL) were added followed by 2-bromo-1,3-dimethyl-5-(trifluoromethyl)benzene (3.95 g, 15.6 mmol, 1.0 equiv, prepared from 2-bromo-1,3-dimethylbenzene)[77] and 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (8.17 g, 23.4 mmol, 1.5 equiv). The rubber septum was replaced with a yellow polyethylene cap and secured with electrical tape. The reaction was heated at 100 ˚C in an oil bath for 16 h at which point it was allowed to cool to room temperature and quenched with water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~300 mL) eluting with 5% EtOAc/hexanes afforded the title compound in approximately 64% yield with some minor impurities resulting from protodeboronation of the pinacol borane. The product was taken on to subsequent synthetic steps during the course of which, the impurities were removed.



2-(chloromethyl)-5-(2,6-dimethyl-4-(trifluoromethyl)phenyl)pyridine. This reaction was preformed open to air. 5-(2,6-bis(trifluoromethyl)phenyl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (3.96 g, 10.0 mmol, 1.0 equiv) was dissolved in EtOH (10 mL) and 1N HCl (10 mL). The reaction was stirred vigorously for 3 h, quenched to neutral pH with saturated $NaHCO_3$, and diluted with CH_2Cl_2. The layers were separated and the aqueous

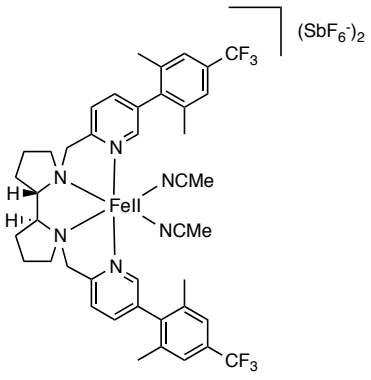
layer was extracted with CH_2Cl_2 (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a crude solid. The solid was dissolved in CH_2Cl_2 (50 mL) and $SOCl_2$ (7.3 mL, 11.89 g, 100 mmol, 10.0 equiv) was added dropwise. The reaction was stirred 12 h and quenched to neutral pH with saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on silica (~250 mL) eluting with 5% EtOAc/hexanes afforded the title compound (2.16 g, 0.72 mmol, 72% yield) as a colorless powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.39 (s, 2H), 4.76 (s, 2H), 2.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 149.1, 140.8, 137.4 (2C) 134.9, 130.2 (q, *J* = 31.3 Hz), 124.3 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.4 Hz), 122.6, 46.4, 21.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -63.1; IR (film): 2968, 2929, 2870, 1475, 1423, 1348, 1225, 1161, 1124, 999, 881, 837 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{14}NF_3Cl$ $[M+H]^+$: 300.0767, found 300.0776.



(2*S*,2'*S*)-1,1'-bis((5-(2,6-dimethyl-4-(trifluoromethyl)phenyl)pyridin-2-yl)methyl)-2,2'-bipyrrolidine [(*S,S*)-Me$_2$Ar-PDP)]. This reaction was performed open to air. According to the procedure of White,[58a] a round bottomed flask was charged with a stir bar, 2-(chloromethyl)-5-(2,6-dimethyl-4-(trifluoromethyl)phenyl)pyridine (580.0 mg, 1.9 mmol, 2.2 equiv), (*S,S*)-2,2'-bispyrrolidine/D-tatraric acid (250.0 mg, 0.88 mmol, 1.0 equiv), NaOH (230.0 mg, 5.6 mmol, 6.4 equiv) and 1:1 CH_2Cl_2:H_2O (4 mL) and the reaction was stirred vigorously at

room temperature for 12 h. The reaction was diluted with 1M NaOH and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x5). The combined organic layers were dried (K_2CO_3), filtered and concentrated. Purification by flash chromatography on silica (~125 mL) eluting with 5% MeOH/CH_2Cl_2 with 1% NH_4OH afforded the crude ligand, which was partitioned between CH_2Cl_2 and 1 M NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x5). This extraction removes traces of water and NH_4OH from the column conditions. The combined organic layers were dried (K_2CO_3), filtered and concentrated to afford the title compound (453.3 mg, 0.68 mmol, 77% yield) as a colorless powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.36 (s, 4H), 3.92 (ABq, *J* = 14.5 Hz, Δν= 337.5 Hz, 4H), 3.12-3.06 (m, 2H), 2.86-2.81 (m, 2H), 2.28 (q, *J* = 9.0 Hz, 2H), 2.07 (s, 6H), 2.06 (s, 6H), 1.91-1.70 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (2C), 148.4 (2C), 141.5 (2C), 137.4 (4C), 136.6 (2C), 133.3 (2C), 129.7 (q, *J* = 31.3 Hz, 2C), 124.1 (q, *J* = 272.4 Hz, 2C), 124.1 (q, *J* = 3.6 Hz, 2C), 122.5 (2C), 65.6 (2C), 61.1 (2C), 55.6 (2C), 25.9 (2C), 23.5 (2C), 21.0 (2C); ^{19}F NMR (470 MHz, $CDCl_3$) δ -63.1; IR (film): 2968, 2918, 2873, 2806, 1599, 1556, 1475, 1441, 1346, 1225, 1161, 1124, 999, 908, 881, 733 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{38}H_{41}N_4F_6$ $[M+H]^+$: 667.3235, found 667.3237; $[\alpha]_D^{25}$ = -20.9° (c=0.7, $CHCl_3$).

(*R,R*)-Me_2Ar-PDP was also prepared. $[\alpha]_D^{24}$ = +19.9° (c=0.7, $CHCl_3$).



[(*S,S*)-Fe(Me$_2$Ar-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (78). According to the procedure of White,[58a] a round bottomed flask was charged with a stir bar, (*S,S*)-Me$_2$Ar-PDP (580.1 mg, 0.95 mmol, 1.0 equiv) and MeCN (4 mL) and CH_2Cl_2 (2 mL). $FeCl_2$-4H_2O (188.9 mg, 0.95 mmol, 1.0 equiv) was added and the reaction stirred 24 h at room temperature. Immediately after adding the Fe salt, an orange precipitate is observed. The precipitation was completed at the end of the reaction by addition of Et_2O. Solvent was decanted out of the flask via pipette. The resulting solid was washed thoroughly with Et_2O until the washes are colorless and dried under a stream of N_2 for 4h to yield (*S,S*)-Fe(Me$_2$Ar-PDP)Cl_2 (528.9 mg, 0.72 mmol, 76% yield) as a bright orange powder. HRMS (ESI) *m/z* calc'd for $C_{38}H_{40}ClF_6FeN_4$ $[M\text{-}Cl]^+$: 757.2195, found 757.2193.

A round bottomed flask (the flask should be free of trace metal impurities and not have been cleaned with harsh acidic or basic conditions such as nitric acid or base bath) was charged with a stir bar, (*S,S*)-Fe(Me$_2$Ar-PDP)Cl_2 (528.9 mg, 0.72 mmol, 1.0 equiv) and MeCN (9 mL). $AgSbF_6$ (494.5 mg, 1.44 mmol, 2.0 equiv, Strem, stored and weighed out in the glove box with precautions taken to exclude light, air and moisture) was added in 1 portion resulting in immediate precipitation of AgCl and a color change to dark red/purple. The reaction flask was wrapped in foil to exclude light and stirred vigorously for 24 h. The reaction was filtered through Celite® and concentrated nearly to dryness. The catalyst was redissolved in MeCN, filtered through a 0.2 mm Acrodisc® LC PVDF (HPLC certified) and concentrated nearly to dryness.

The filtration procedure was repeated (x2) to ensure complete removal of silver salts. The resulting solid was dried under a stream of N_2 for 5 h to yield the title compound (749.1 g, 0.61 mmol, 85% yield) as a light brown powder. Anal. calc'd for for $C_{42}H_{46}F_{18}FeN_6Sb_2$ (MWT = 1276.1911 g/mol): C, 39.53; H, 3.63; N, 6.59 %. Found C, 39.71; H, 3.49; N, 6.24. HRMS (ESI) *m/z* calc'd for $C_{38}H_{40}N_4F_{12}FeSb$ $[M\text{-}(MeCN)_2(SbF_6)]^+$: 957.1449, found 957.1447.

3.4.3 General Methods for Aliphatic C—H Oxidation

Method A: Iterative Addition Protocol. These reactions were performed open to air with no precautions taken to exclude moisture. A 40 mL vial was charged with substrate (0.5 mmol, 1.0 equiv), MeCN (0.75 mL, 0.66 M), AcOH (14.3 mL, 15.0 mg, 0.25 mmol, 0.5 equiv, Fisher Scientific), catalyst (0.025 mmol, 5 mol %) and a stir bar. A separate solution of H_2O_2 (34.6 mL, 0.6 mmol, 1.2 equiv, 50% wt. in H_2O, Sigma-Aldrich) in MeCN (4.5 mL, 0.13 M) was added dropwise to the stirring reaction over ~60s. The first drop of peroxide solution instantly changes the reaction mixture from light red (when using Fe(CF_3-PDP) to a light amber. Subsequent drops of peroxide appear transiently as green in the reaction until a dark amber color is reached and maintained. When no further color changes were observed, the addition rate of the peroxide was increased to complete the addition in ~60 s. **Significant decreases in yield were noted when the peroxide solution was added rapidly.**

After 10 min., a solution of the catalyst (0.025 mmol, 5 mol %) and AcOH (14.3 mL, 15.0 mg, 0.25 mmol, 0.5 equiv) in MeCN (0.5 mL) was added to the stirring reaction, immediately followed by dropwise addition of a second solution of H_2O_2 (34.6 mL, 0.6 mmol, 1.2 equiv, 50% wt. in H_2O) in MeCN (4.5 mL, 0.13 M) as described above. After an additional

10 min., a third addition of catalyst and AcOH followed by dropwise H_2O_2 solution addition was repeated as above and allowed to stir 10 min., for a total reaction time of ~33 min.

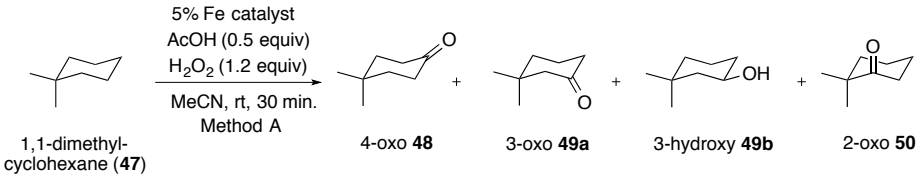
If a crude NMR was desired, the reaction was concentrated via rotary evaporation to a minimal volume, diluted with EtOAc and filtered through a plug of silica (~50 mL) to remove the residual paramagnetic iron catalyst. After rotary evaporation, analysis of the crude by ^1H NMR could be performed. Otherwise, the reaction was concentrated to a minimal volume and loaded directly onto silica gel and purified by flash chromatography. Generally, visualization was accomplished using CAM (ceric ammonium molybdate) staining.

Method B: Slow Addition Protocol. These reactions were performed open to air with no precautions take, to exclude moisture. A 20 mL scintillation vial was charged with substrate (0.3 mmol, 1.0 equiv), MeCN (0.6 mL, 0.5 M), AcOH (8.6 mL, 9.0 mg, 0.15 mmol, 0.5 equiv) and a stair bar. A 1.0 mL syringe was filled with a solution of the catalyst (0.075 mmol, 25 mol %) in MeCN (0.375 mL, 0.2 M). A few drops of this solution were added to the reaction. A 10 mL syringe was filled with a solution of H_2O_2 (86.5 mL, 1.5 mmol, 5.0 equiv, 50% wt. in H_2O) in MeCN (3.75 mL). Both syringes were fitted with 25G needles and loaded into a syringe pump set at an addition rate of 4 mL/h resulting in a slow simultaneous addition of catalyst and oxidant over 1 h to the stirring reaction mixture.[78] Workup as in general procedure A.

"Cycle" refers to the standard iterative or slow addition procedure as described above. "Recycle" refers to collecting starting material from the previous cycle and subjecting it to another oxidation cycle to obtain product. "RSM" is recovered starting material.

3.4.4 Catalyst-Controlled Oxidation of Simple Cyclic and Acyclic Molecules.

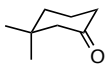
Oxidation of 1,1-dimethylcyclohexane



GC Yield Data. Run 1: 16% RSM, 16% **48**, 35% **49a**, 17% **49b**, 13% **50**, 5.3:1 distal:proximal. Run 2: 24% RSM, 14% **48**, 28% **49a**, 20% **49b**, 11% **50**, 5.8:1 distal:proximal. Run 3: 23% RSM, 13% **48**, 26% **49a**, 18% **49b**, 10% **50**, 5.6:1 distal:proximal. Average RSM: 21±4%. Average **48**: 14±2%. Average **49a**: 29±5%. Average **49b**: 18±2%. Average **50**: 11±2%. Average distal:proximal: 5.6±0.3:1.

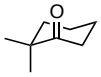
Data for (*S,S*)-Fe(PDP) (**44**) have been previously reported.[58b]

4,4-dimethylcyclohexanone (48). 1,1-dimethylcyclohexane (**47**) (33.7 mg, 0.3 mmol, 1.0 equiv, Sigma-Aldrich) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method A with nitrobenzene (60 mol %) added as an internal standard. Yields were determined by GC analysis of the crude reaction mixture after reaction completion. All product yields are calibrated for response factors relative to starting material, rounded to the nearest whole number and the average of three runs. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (t, J = 6.8 Hz, 4H), 1.67 (app t, J = 7.2 Hz, 4H), 1.09 (s, 6H).



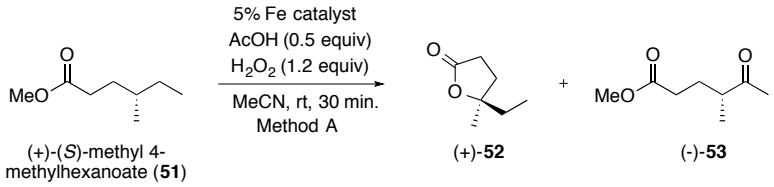
3,3-dimethylcyclohexanone (49a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (app t, J = 6.8 Hz, 2H), 2.15 (s, 2H), 1.91-1.84 (m, 2H), 1.59-1.57 (m, 2H), 0.97 (s, 6H).

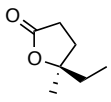
3,3-dimethylcyclohexanol (49b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78-3.68 (m, 1H), 1.98-1.91 (m, 1H), 1.71-1.57 (m, 2H), 1.49-1.37 (m, 1H), 1.32-1.24 (m, 2H), 1.13-1.01 (m, 2H), 0.95 (s, 3H), 0.89 (s, 3H). These spectral data match those reported in the literature.[79]



2,2-dimethylcyclohexanone (50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (app t, J = 6.8 Hz, 2H), 1.86-1.80 (m, 2H), 1.77-1.70 (m, 2H), 1.68-1.64 (m, 2H), 1.11 (s, 6H).

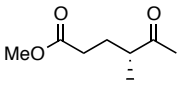
Oxidation of (*S*)-methyl 4-methylhexanoate.





(+)-(*R*)-5-ethyl-5-methyldihydrofuran-2(3*H*)-one (52). (+)-(*S*)-methyl 4-methylhexanoate (**51**) (72.1 mg, 0.5 mmol, 1.0 equiv) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method A. Purification by flash chromatography on silica (~75 mL) eluting with 30% Et_2O/pet ether. Run 1: 30% (+)-**52** (19.7 mg, 0.15 mmol, 30%), (-)-**53** (19.8 mg, 0.13 mmol, 25%), RSM (23.4 mg, 0.16 mmol, 32%), 1.5:1 crude 3˚:2˚ by GC. Run 2: (+)-**52** (21.5 mg, 0.17 mmol, 34%), (-)-**53** (17.7 mg, 0.11 mmol, 22%), RSM (19.2 mg, 0.13 mmol, 27%), 1.4:1 crude 3˚:2˚ by GC. Run 3: (+)-**52** (18.6 mg, 0.15 mmol, 29%), (-)-**53** (19.0 mg, 0.12 mmol, 24%), RSM (18.1 mg, 013 mmol, 25%), 1.2:1 crude 3˚:2˚ by GC. Average (+)-**52**: 31±3%. Average (-)-**53** 24±2%. Average RSM: 28±4%. Average crude 3˚:2˚: 1.4±0.2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.54 (m, 2H), 2.12-2.05 (m, 1H), 1.99-1.93 (m, 1H), 1.77-1.64 (m, 2H), 1.38 (s, 3H), 0.97 (t, J = 8.0 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_7H_{13}O_2$ $[M+H]^+$: 129.0916,

found 129.0913; $[\alpha]_D^{25}$ = +9.0˚ (c=1.0, $CHCl_3$). These spectral data match those reported in the literature.[58a]



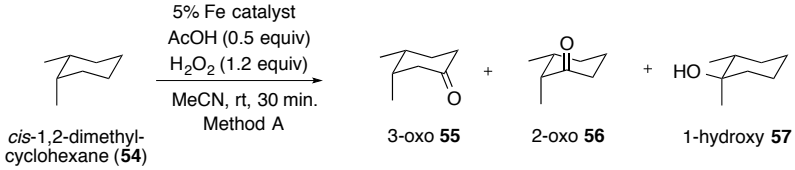
(-)-(*R*)-methyl 4-methyl-5-oxohexanoate (53). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.65-2.53 (m, 1H), 2.35-2.25 (m, 2H), 2.15 (s, 3H), 2.05-1.95 (m, 1H), 1.60-1.72 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_8H_{15}O_3$ $[M+H]^+$: 159.1021, found 159.1026; $[\alpha]_D^{24}$ = -1.2˚ (c=1.2, $CHCl_3$). These spectral data match those reported in the literature.[58a]

Table 7. Catalyst Comparison for the Oxidation of (+)-(*S*)-methyl 4-methylhexanoate (**51**)

Catalyst	% (+)-**52**[a]	% (-)-**53**	% RSM	3˚:2˚[b]
(*S,S*)-Fe(PDP) (**44**)[58a]	48	17	23	3:1
(*S,S*)-Fe(CF_3-PDP) (**45**)	31	24	28	1.4:1

[a]Average of 3 runs at 0.5 mmol. Yields are of isolated material. [b]Crude ratio determined by GC.

Oxidation of *cis*-1,2-dimethylcyclohexane.



GC Yield Data. Run 1: 16% RSM, 20% **55**, 17% **56**, 35% **57**, 1:1.2 2˚:3˚. Run 2: 16% RSM, 20% **55**, 10% **56**, 34% **57**, 1:1.2 2˚:3˚. Run 3: 9% RSM, 19% **55**, 10% **56**, 30% **57**, 1:1 2˚:3˚. Average RSM: 13±4%. Average **55**: 20±1%. Average **56**: 12±1%. Average **57**: 33±3%. Average 2˚:3˚: 1:1.1±0.1.

Data for (*S,S*)-Fe(PDP) (**44**) have been previously reported.[58b]

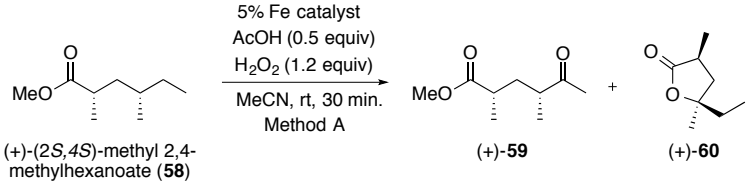
***cis*-3,4-dimethylcyclohexanone (55).** *cis*-1,2-dimethylcyclohexane (**54**) (33.7 mg, 0.3 mmol, 1.0 equiv, Sigma-Aldrich) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method

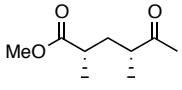
A with nitrobenzene (60 mol %) added as an internal standard. Yields were determined by GC analysis of the crude reaction mixture after reaction completion. All product yields are calibrated for response factors relative to material, rounded to the nearest whole number and the average of three runs. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41-2.37 (m, 1H), 2.36-2.24 (m, 2H), 2.21-2.11 (m, 2H), 2.08-2.20 (m, 1H), 1.85-1.79 (m, 1H), 1.76-1.68 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H).

***cis*-2,3-dimethylcyclohexanone (56).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61-2.55 (m, 1H), 2.38-2.33 (m, 1H), 2.28-2.20 (m, 2H), 1.94-1.81 (m, 3H), 1.68-1.63 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H).

***cis*-1,2-dimethylcyclohexan-1-ol (57).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (m, 3H), 1.52-1.44 (m, 1H), 1.42 (s, 1H), 1.38-1.22 (m, 5H), 1.07 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H).

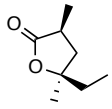
Oxidation of (*2S,4S*)-methyl 2,4-dimethylhexanoate.





(+)-(2*S*,4*R*)-methyl 2,4-dimethyl-5-oxohexanoate (59). (+)-(*2S,4S*)-methyl 2,4-dimethylhexanoate (**58**) (158.2 mg, 1.0 mmol, 1.0 equiv) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method A. Purification by flash chromatography on silica (~125 mL) eluting with 20% Et_2O/pet ether. Run 1: recycled one time for a total of 51% (+)-**59**, 12% (+)-**60**, 10% RSM, 4.0:1 crude 2˚:3˚ by GC; cycle 1 (+)-**59** (74.4 mg, 0.43 mmol, 43%), (+)-**60** (14.4 mg, 0.1

mmol, 10%), RSM (44.5 mg, 0.28 mmol, 28%); cycle 2 (+)-**59** (18.3 mg, 0.11 mmol, 38%), (+)-**60** (4.1 mg, 0.029 mmol, 10%), RSM (11.3 mg, 0.071 mmol, 26%). Run 2: recycled one time for a total of 54% (+)-**59**, 13% (+)-**60**, 7% RSM, 4.0:1 crude 2˚:3˚ by GC; cycle 1 (+)-**59** (67.6 mg, 0.39 mmol, 39%), (+)-**60** (13.0 mg, 0.091 mmol, 9%), RSM (47.5 mg, 0.3 mmol, 30%); cycle 2 (+)-**59** (21.2 mg, 0.12 mmol, 41%), (+)-**60** (4.7 mg, 0.03 mmol, 11%), RSM (16.1 mg, 0.1 mmol, 34%). Run 3: recycled one time for a total of 49% (+)-**59**, 9% (+)-**60**, 7% RSM, 3.9:1 crude 2˚:3˚ by GC; cycle 1 (+)-**59** (64.4 mg, 0.37 mmol, 37%), (+)-**60** (7.4 mg, 0.05 mmol, 5%), RSM (49.4 mg, 0.31 mmol, 31%); cycle 2 (+)-**59** (21.5 mg, 0.12 mmol, 40%), (+)-**60** (5.5 mg, 0.039 mmol, 12%), RSM (11.3 mg, 0.071 mmol, 23%). Average overall yield (+)-**59**: 51±2%, Average overall yield (+)-**60**: 11±2%, Average overall RSM: 8±2%, Average 2˚:3˚: 4.0±0.1:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.60-2.48 (m, 2H), 2.17 (s, 3H), 2.12-2.06 (m, 1H), 1.40-1.34 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_9H_{16}O_3Na$ $[M+Na]^+$: 195.0997, found 195.1006; $[\alpha]_D^{25}$ = +11.0˚ (c=1.0, $CHCl_3$). These spectral data match those reported in the literature.[58a]



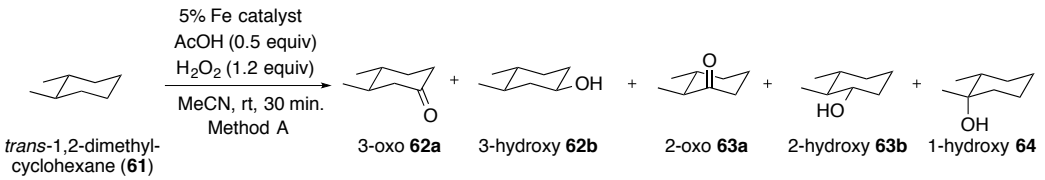
(+)-(3*S*,5*R*)-5-ethyl-3,5-dimethyldihydrofuran-2(3*H*)-one (60). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87-2.78 (m, 1H), 2.20 (dd, *J* = 12.5, 9.0 Hz, 1H), 1.76-1.67 (m, 3H), 1.34 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_8H_{15}O_3$ $[M+H]^+$: 143.1072, found 143.1075; $[\alpha]_D^{25}$ = +3.3˚ (c=0.8, $CHCl_3$). These spectral data match those reported in the literature.[58a]

Table 8. Catalyst Comparison for the Oxidation of (+)-(*2S,4S*)-methyl 2,4-dimethylhexanoate (**58**)

Catalyst	% (+)-**59**[a]	% (+)-**60**	% RSM	2˚:3˚[b]
(*S,S*)-Fe(PDP) (**44**)[58a]	41	27	16	1.5:1
(*S,S*)-Fe(CF_3-PDP) (**45**)[c]	51	11	8	4:1

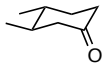
[a]Average of 3 runs at 1.0 mmol. Yields are of isolated material.
[b]Crude ratio determined by GC. [c]Starting material was recycled 1 time.

Oxidation of *trans*-1,2-dimethylcyclohexane.

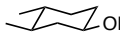


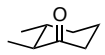
GC Yield Data. Run 1: 16% RSM, 39% **62a**, 6% **62b**, 22% **63a**, 5% **63b**, 7% **64**, 9.1:1 2˚:3˚. Run 2: 17% RSM, 38% **62a**, 8% **62b**, 22% **63a**, 6% **63b**, 9% **64**, 8.7:1 2˚:3˚. Run 3: 12% RSM, 36% **62a**, 5% **62b**, 20% **62a**, 4% **62b**, 6% **64**, 10.9:1 2˚:3˚. Average RSM: 15±3%. Average **62a**: 38±1%. Average **62b**: 6±2%. Average **63a**: 21±1%. Average **63b**: 5±1%. Average **64**: 7±1%. Average 2˚:3˚: 9.9±1:1.

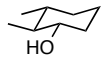
Data for (*S,S*)-Fe(PDP) (**44**) have been previously reported.[58b]

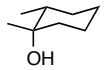


***trans*-3,4-dimethylcyclohexanone (62a).** *trans*-1,2-dimethylcyclohexane (**61**) (33.7 mg, 0.3 mmol, 1.0 equiv, Sigma-Aldrich) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to general procedure A with nitrobenzene (60 mol %) added as an internal standard. Yields were determined by GC analysis of the crude reaction mixture after reaction completion. All product yields are calibrated for response factors relative to starting material, rounded to the nearest whole number and the average of three runs. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36-2.31 (m, 3H), 2.05 (dd, *J* = 11.0, 9.5 Hz, 1H), 2.00-1.96 (m, 1H), 1.54-1.34 (m, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.0 Hz, 3H).

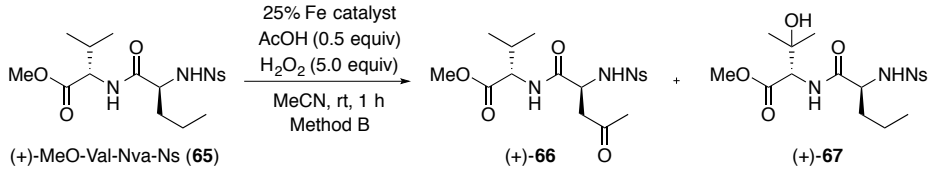
 ***trans*-3,4-dimethylcyclohexan-1-ol (62b).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59 (tt, *J* = 11.0, 4.0 Hz, 1H), 1.98-1.87 (m, 2H), 1.68 (dq, *J* = 13.0, 3.0 Hz, 1H), 1.35 (br s, 1H), 1.26-1.08 (m, 2H), 1.10-0.96 (m, 4H), 0.94-0.84 (m, 6H). These spectral data are in agreement with those previously reported in the literature.[79]

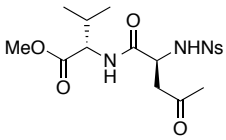
 ***trans*-2,3-dimethylcyclohexanone (63a).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38-2.28 (m, 3H), 2.06-1.98 (m, 1H), 1.88-1.83 (m, 1H), 1.48-1.30 (m, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H).

 ***trans*-2,3-dimethylcyclohexan-1-ol (63b).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.14 (td, *J* = 10.0, 4.0 Hz, 1H), 1.99-1.93 (m, 1H), 1.76-1.67 (m, 2H), 1.61-1.54 (m, 1H), 1.44-1.16 (m, 4H), 1.25 (s, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 3H). These spectral data are in agreement with those previously reported in the literature.[79]

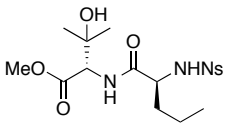
 ***trans*-1,2-dimethylcyclohexan-1-ol (64).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68-1.62 (m, 2H), 1.54-1.48 (m, 2H), 1.46-1.20 (m, 5H), 1.18 (s, 3H), 0.90 (s, *J* = 6.5 Hz, 3H).

Oxidation of MeO-Val-Nva-Ns.



 **(+)-MeO-Val-(γ-oxo-Nva)-Ns (66).** (+)-MeO-Val-Nva-Ns (**65**) (207.7 mg, 0.5 mmol, 1.0 equiv) in MeCN (0.75 mL) was reacted with (*R,R*)-Fe(CF_3-PDP) (**45**) according to Method B. Purification by flash chromatography on silica (~125 mL) eluting with 25%

acetone/hexane. Run 1: recycled 1 time for a total of 48% (+)-**66**, 6% (+)-**67**, 8% RSM, 8.3:1 2°:3° by 1H NMR; cycle 1 (+)-**66** (82.6 mg, 0.19 mmol, 38%), (+)-**67** (9.9 mg, 0.023 mmol, 5%), RSM (54.6 mg, 0.13 mmol, 26%); cycle 2 (+)-**66** (21.5 mg, 0.05 mmol, 31%%), (+)-**67** (2.6 mg, 0.006 mmol, 4%), RSM (16.8 mg, 0.04 mmol, 31%). Run 2: recycled 1 time for a total of 51% (+)-**66**, 6% (+)-**67**, 6% RSM, 9.0:1 2°:3° by 1H NMR; cycle 1 (+)-**66** (87.7 mg, 0.20 mmol, 41%), (+)-**67** (9.7 mg, 0.022 mmol, 4%), RSM (60.0 mg, 0.14 mmol, 29%); cycle 2 (+)-**66** (22.5 mg, 0.052 mmol, 37%), (+)-**67** (2.2 mg, 0.005 mmol, 4%), RSM (11.6 mg, 0.028 mmol, 20%). Average overall (+)-**66**: 51±3%. Average overall (+)-**67**: 6±0.5%. Average overall RSM: 8±3%. Average overall 2°:3°: 8.9±0.6:1.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.25 (br s, 1H), 4.27 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.21 (d, *J* = 4.5 Hz, 1H), 3.67 (s, 3H), 3.23 (dd, *J* = 18.5, 3.0 Hz, 1H), 2.81 (dd, *J* = 18.5, 7.5 Hz, 1H), 2.20 (s, 3H), 2.11-2.06 (m, 1H), 0.80 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 171.5, 169.3, 150.3, 145.3, 128.5, 124.5, 57.6, 52.2, 51.9, 46.5, 30.5, 30.2, 18.8, 17.3; IR (film): 3284, 3109, 2966, 2877, 1739, 1716, 1668, 1531, 1437, 1352, 1313, 1213, 1167, 1093, 1012, 918 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{24}N_3O_8S$ $[M+H]^+$: 430.1284, found 430.1279; $[\alpha]_D^{25}$ = +74.2° (c=1.4, $CHCl_3$).



(+)-MeO-(β-hydroxy-Val)-Nva-Ns (67). Purification by MPLC on silica (24g) eluting with 5→20% acetone/hexane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 1H), 5.99 (d, *J* = 7.5 Hz, 1H), 4.35 (d, *J* = 9.0 Hz, 1H), 3.91-3.84 (m, 1H), 3.75 (s, 3H), 2.71 (br s, 1H), 1.72-1.64 (m, 2H), 1.62-1.52 (m, 1H), 1.28-1.24 (m, 1H), 1.22 (s, 3H), 1.04 (s, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 171.0, 150.1, 145.7, 128.5, 124.3, 71.9, 59.6, 56.7, 52.5, 35.7, 26.8, 26.5, 18.4,

13.5; IR (film): 33.63, 3107, 2962, 2933, 2875, 1739, 1666, 1531, 1437, 1352, 1311, 1209, 1167, 1093 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{26}N_3O_8S$ $[M+H]^+$: 432.1441, found 432.1437; $[\alpha]_D^{25}$ = +18.2˚ (c=1.0, $CHCl_3$).

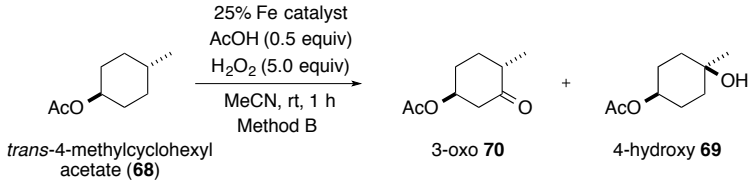
Table 9. Catalyst Comparison for the Oxidation of (+)-MeO-Val-Nva-Ns (**65**)

Catalyst	% (+)-**66**[a]	% (+)-**67**	% RSM	2˚:3˚[b]
(*R,R*)-Fe(PDP) (**44**)	24	27	32	1:1
(*R,R*)-Fe(CF_3-PDP) (**45**)	51	6	8	9:1

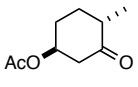
[a]Average of 3 runs at 0.5 mmol. Yields are of isolated material. [b]Ratio determined by ^{1}H NMR.

Oxidation with (*R,R*)-Fe(PDP) (**44**) according to Method B. Run 1: recycled 1 time for a total of 24% (+)-**66**, 24% (+)-**67**, 32% RSM, 1:1 2˚:3˚ by 1H NMR; cycle 1 (+)-**66** (30.8 mg, 0.072 mmol, 14%), (+)-**67** (30.9 mg, 0.072 mmol, 14%), RSM (130.5 mg, 0.31 mmol, 63%); cycle 2 (+)-**66** (21.4 mg, 0.05 mmol, 16%), (+)-**67** (21.5 mg, 0.05 mmol, 16%), RSM (65.6 mg, 0.16 mmol, 51%). Run 2: recycled 1 time for a total of 23% (+)-**66**, 27% (+)-**67**, 35% RSM, 1:1.2 2˚:3˚ by 1H NMR; cycle 1 (+)-**66** (29.8 mg, 0.069 mmol, 14%), (+)-**67** (35.8 mg, 0.083 mmol, 17%), RSM (129.0 mg, 0.31 mmol, 62%); cycle 2 (+)-**66** (19.6 mg, 0.46 mmol, 15%), (+)-**67** (23.5 mg, 0.054 mmol, 18%), RSM (73.7 mg, 0.18 mmol, 57%). Average overall (+)-**66**: 24±2%. Average overall (+)-**67**: 27±3%. Average overall RSM: 32±3%. Average overall 2˚:3˚: 1:1±0.1.

Oxidation of *trans*-4-methylcyclohexyl acetate.

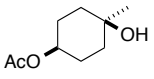


trans-4-methylcyclohexyl acetate (**68**) → 3-oxo **70** + 4-hydroxy **69**



***trans*-4-methyl-3- and 5-oxocyclohexyl acetate (70).** *Trans*-4-methylcyclohexyl acetate (**68**) (46.9 mg, 0.3 mmol, 1.0 equiv) in MeCN (0.5 mL) was reacted with (*S,S*)-Fe(CF_3-

PDP) (**45**) according to Method B. Purification by flash chromatography on silica (~75 mL) eluting with gradient 10→30% acetone/hexane. Run 1: **70** (25.2 mg, 0.15 mmol, 49%), **69** (15.5 mg, 0.09 mmol, 30%), RSM (3.4 mg, 0.022 mmol, 7%), 2.0:1 crude 2˚:3˚ by GC. Run 2: **70** (26.1 mg, 0.15 mmol, 51%), **69** (14.3 mg, 0.083 mmol, 28%), RSM (2.7 mg, 0.027 mmol, 9%), 2.4:1 crude 2˚:3˚ by GC. Run 3: **70** (27.3 mg, 0.16 mmol, 53%), **69** (12.9 mg, 0.076 mmol, 25%), RSM (5.5 mg, 0.035 mmol, 12%), 2.2:1 crude 2˚:3˚ by GC. Average isolated **70**: 51±2%. Average isolated **69**: 28±3%. Average isolated RSM: 9±3%. Average crude 2˚:3˚ by GC: 2.2±0.2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (app septet, J = 5.0 Hz, 1H), 2.77 (ddd, J = 13.5, 5.0, 2.0 Hz, 1H), 2.44-2.38 (m, 1H), 2.36-2.31 (m, 1H), 2.23-2.18 (m, 1H), 2.09-2.02 (m, 1H), 2.04 (s, 3H), 1.79-1.71 (m, 1H), 1.38-1.28 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 170.0, 71.6, 46.8, 44.1, 30.2, 29.1, 21.1, 14.2; IR (film): 2937, 2872, 1738, 1718, 1454, 1431, 1379, 1362, 1240, 1215, 1053, 1032 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{14}O_3Na$ $[M+Na]^+$: 193.0841, found 193.0841.



***trans*-4-hydroxy-4-methylcyclohexyl acetate (69).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (app p, J = 6.5 Hz, 1H), 2.03 (s, 3H), 1.77-1.66 (m, 6H), 1.51-1.44 (m, 2H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 72.0, 68.5, 36.5, 30.0, 27.1, 21.4; IR (film): 3454, 2939, 2872, 1730, 1446, 1365, 1250, 1169, 1138, 1036, 955, 916 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{15}O_3Na$ $[M+Na]^+$: 195.0997, found 195.0997.

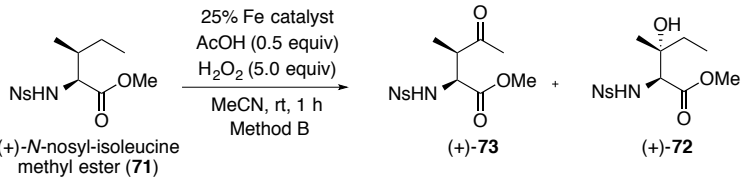
Table 10. Catalyst Comparison for the Oxidation of *trans*-4-methylcyclohexanol acetate (**68**)

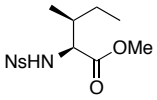
Catalyst	% **70**	% **69**	% RSM	2˚:3˚[b]
(*S,S*)-Fe(PDP) (**44**)	19	66	0	1:2.2
(*S,S*)-Fe(CF_3-PDP) (**45**)	51	28	9	2.2:1

[a]Average of 3 runs at 0.3 mmol. Yields are of isolated material.
[b]Crude ratio determined by GC.

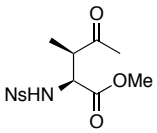
Oxidation with (*S,S*)-Fe(PDP) (**44**) according to Method B. Run 1: **70** (9.4 mg, 0.055 mmol, 18%), **69** (35.4 mg, 0.21 mmol, 69%), 1:2.2 crude 2˚:3˚ by GC. Run 2: **70** (9.3 mg, 0.055 mmol, 18%), **69** (33.2 mg, 0.19 mmol, 64%), 1:2.1 crude 2˚:3˚ by GC. Run 3: **70** (10.5 mg, 0.062 mmol, 21%), **69** (33.8 mg, 0.2 mmol, 65%), 1:2.2 crude 2˚:3˚ by GC. Average isolated **70**: 19±2%. Average isolated **69**: 66±2%. Average crude 2˚:3˚ by GC: 1:2.2±0.1.

Oxidation of L-*N*-nosyl-isoleucine methyl ester.



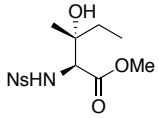


(+)-4-(((2*S*,3*S*)-1-methoxy-3-methyl-1-oxopentan-2-yl)amino)-3-nitrobenzenesulfonic acid (71). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 2H), 5.27 (d, *J* = 9.5 Hz, 1H), 3.88 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.50 (s, 3H), 1.86-1.80 (m, 1H), 1.41-1.35 (m, 1H), 1.18-1.12 (m, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 150.1, 145.6, 128.5, 124.2, 60.4, 52.4, 38.3, 24.5, 15.4, 11.3; IR (film): 1734, 1709, 1523, 1352, 1173, 1092 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}N_2O_6NaS$ $[M+Na]^+$: 353.0783, found 353.0789; $[\alpha]_D^{25}$ = +45.8˚ (c=1.0, $CHCl_3$).



(+)-4-(((2*S*,3*R*)-1-methoxy-3-methyl-1,4-dioxopentan-2-yl)amino)-3-nitrobenzenesulfonic acid (73). (+)-L-*N*-nosyl-isoleucine methyl ester (**71**) (173.2 mg, 0.5 mmol, 1.0 equiv) in MeCN (0.75 mL) was reacted with (*R,R*)-Fe(CF_3-PDP) (**45**) according to Method B. Purification by flash chromatography on silica (~75 mL) eluting with gradient

5→10→20% EtOAc/CH_2Cl_2. Run 1: recycled 1 time for a total of 58% (+)-**73**, 14% (+)-**72**, 7% RSM, 4.1:1 isolated 2˚:3˚; cycle 1 (+)-**73** (79.8 mg, 0.22 mmol, 44%), (+)-**72** (19.9 mg, 0.05 mmol, 11%), RSM (51.9 mg, 0.15 mmol, 30%); cycle 2 (+)-**73** (25.4 mg, 0.07 mmol, 47%), (+)-**72** (8.2 mg, 0.02 mmol, 15%), RSM (11.4 mg, 0.03 mmol, 22%). Run 2: recycled 1 time for a total of 52% (+)-**73**, 17% (+)-**72**, 7% RSM, 3.1:1 isolated 2˚:3˚; cycle 1 (+)-**73** (80.0 mg, 0.22 mmol, 46%), (+)-**72** (24.6 mg, 0.07 mmol, 14%), RSM (37.1 mg, 0.1 mmol, 20%); cycle 2 (+)-**73** (13.5 mg, 0.04 mmol, 33%), (+)-**72** (5.3 mg, 0.01 mmol, 13%), RSM (12.5 mg, 0.04 mmol, 33%). Run 3: recycled 1 time for a total of 58% (+)-**73**, 14% (+)-**72** 10% RSM, 4.1:1 isolated 2˚:3˚; cycle 1 (+)-**73** (77.0 mg, 0.22 mmol, 45%), (+)-**72** (18.0 mg, 0.052 mmol, 10%), RSM (54.7 mg, 0.17 mmol, 33%); cycle 2 (+)-**73** (24.8 mg, 0.049 mmol, 42%), (+)-**72** (6.5 mg, 0.019 mmol, 11%), RSM (16.3 mg, 0.049 mmol, 29%). Average overall yield (+)-**73**: 56±4%. Average overall yield (+)-**72**: 15±2%. Average overall RSM: 7±2%. Average 2˚:3˚: 3.8±0.6:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.44 (s, 3H), 3.34 (qd, *J* = 7.5, 4.0 Hz, 1H), 2.18 (s, 3H), 1.37 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 170.3, 150.0, 146.3, 128.5, 124.0, 60.4, 57.9, 48.7, 28.0, 13.8; IR (film): 3525, 3284, 2974, 2951, 1738, 1531, 1435, 1352, 1313, 1211, 1169, 1092, 930, 856 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{16}N_2O_7NaS$ $[M+Na]^+$: 367.0576, found 367.0581; $[\alpha]_D^{25}$ = +62.6˚ (c=1.0, $CHCl_3$).



(+)-4-(((2*S*,3*R*)-3-hydroxy-1-methoxy-3-methyl-1-oxopentan-2-yl)amino)-3-nitrobenzenesulfonic acid (72) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H), 6.04 (br s, 1H), 3.90 (br s, 1H), 3.45 (s, 3H), 2.37 (br s, 1H), 1.69-1.58 (m, 1H), 1.15 (s, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 150.1, 145.6, 128.5,

124.1, 74.1, 61.4, 52.3, 31.2, 23.3, 7.7; IR (film): 3438, 1741, 1707, 1639, 1531, 1352, 1311, 1167, 1093, 854 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}N_2O_7NaS$ $[M+Na]^+$: 369.0732, found 369.0739; $[\alpha]_D^{25} = +28.0^\circ$ (c=2.0, $CHCl_3$).

Table 11. Catalyst Comparison for the Oxidation of (+)-L-*N*-nosyl-isoleucine methyl ester (**71**)

Catalyst	% (+)-**73**	% (+)-**72**	% RSM	2°:3°[b]
(*R,R*)-Fe(PDP) (**44**)	29	43	10	1:2
(*R,R*)-Fe(CF_3-PDP) (**45**)	56	15	8	4:1

[a]Average of 3 runs at 0.5 mmol. Yields are of isolated material.
[b]Isolated ratio.

Oxidation with (*R,R*)-Fe(PDP) (**44**) according to Method B. Run 1: recycled 1 time for a total of 30% (+)-**73**, 43% (+)-**72**, 10% RSM, 1:1.5 isolated 2°:3°; cycle 1 (+)-**73** (39.6 mg, 0.11 mmol, 22%), (+)-**72** (58.9 mg, 0.16 mmol, 33%), RSM (60.8 mg, 0.18 mmol, 35%); cycle 2 (+)-**73** (12.3 mg, 0.05 mmol, 19%), (+)-**72** (18.3 mg, 0.05 mmol, 29%), RSM (16.8 mg, 0.05 mmol, 27%). Run 2: recycled 1 time for a total of 27% (+)-**73**, 41% (+)-**72**, 7% RSM, 1:1.6 isolated 2°:3°; cycle 1 (+)-**73** (36.5 mg, 0.10 mmol, 20%), (+)-**72** (57.5 mg, 0.16 mmol, 32%), RSM (51.9 mg, 0.15 mmol, 30%); cycle 2 (+)-**73** (12.5 mg, 0.035 mmol, 23%), (+)-**72** (18.5 mg, 0.051 mmol, 34%), RSM (12.2 mg, 0.035 mmol, 23%). Run 3: recycled 1 time for a total of 29% (+)-**73**, 46% (+)-**72**, 12% RSM, 1:1.6 isolated 2°:3°; cycle 1 (+)-**73** (34.8 mg, 0.10 mmol, 20%), (+)-**72** (57.5 mg, 0.166 mmol, 33%), RSM (62.9 mg, 0.19 mmol, 38%); cycle 2 (+)-**73** (15.2 mg, 0.044 mmol, 23%), (+)-**72** (22.0 mg, 0.064 mmol, 33%), RSM (21.6 mg, 0.65 mmol, 34%). Average overall yield (+)-**73**: 29±2%. Average overall yield (+)-**72**: 43±3%. Average overall RSM: 10±3%. Average 2°:3°: 1:1.5±0.1.

3.4.5 Computational Details

The lowest energy conformations of each molecule were located using a stochastic search and MMFF94X force field in Molecular Operating Environment (MOE) version 11.[69] Up to the five lowest energy conformers were submitted to further geometry optimization in Gaussian 09[70] using B3LYP/6-31G(d) to locate the global minimum.

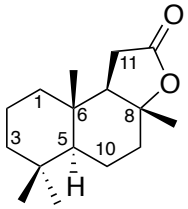
A natural population analysis (NPA) was performed on the energy minimized structure (B3LYP/6-311++G(d,p)) to obtain natural partial atomic charges for all hydrogen atoms. Lower values indicate the site is more electron rich, i.e. smaller positive charge. The expanded basis set was necessary to obtain accurate partial charge data that provides good correlation with the experimental results reported in this and previous papers[58] using Fe(PDP) (**44**) and Fe(CF_3-PDP) (**45**). The only exception are C—H bonds attached to heteroatoms. For example, the C—H bond at C1 in *trans*-4-methylcyclohexyl acetate (**68**) has an NPA value of 0.194 compared to 0.203 and 0.183 at C3/5 and C4 respectively. Yet, we observe no oxidation at C1 with either catalyst **44** or **45**. Similar discrepancies are obtained for other molecules. We believe this discrepancy is the result of the $\sigma \rightarrow \sigma^*$ hyperconjugation term included in NPA calculations. The effect of hyperconjugative activation of a C—H bond by a hereoratom towards oxidation is well known (for example the oxidation of ethereal positions);[58b] however, NPA calculations seem to be overestimating the magnitude of this activation for inductively withdrawing heteroatom containing groups (e.g. OAc, OPiv, etc.). Experimentally, we universally observe no oxidation at these sites indicating that the inductive withdrawing characteristics of these groups dominate. To this end, we automatically exclude any site with an attached EWG from consideration as an oxidizable site. Furthermore, 1˚ sites are uniformly not oxidized under our conditions are and excluded. Interestingly, these sties are often similar in electron richness to 2˚ or 3˚ sites

according to NPA partial charge calculations indicating that the kinetic barrier to 1˚ radical formation is likely a major determining factor. Current electronic calculations do not account for this effect between different C—H bond types and suggests a possible area for refinement. Using the 6-31G(d) basis set provided NPA partial charge data inconsistent with experimental observation.

We also surveyed other measures of electronics at a C—H bond, for example Mulliken partial charges using the 6-31G(d) and 6-311++G(d,p) basis sets. Although Mulliken charges using 6-31G(d) provided qualitatively excellent correlation with the observed reactivity in all compounds, NPA charges provided a better fit to the data in our structure-based catalyst reactivity models (*vide infra*). Mulliken charges using the larger basis set provided poor correlation with experimental data. Finally, we explored ESP and CHelpG electrostatic charges, but these also did not qualitatively agree with experimental results.

Cartesian Coordinates, SCF Energies, Enthalpies and Gibbs Free Energies at 298K for Optimized Structures of Complex Substrates

(+)-Sclareolide (74).



Total SCF energy: -775.413794

Enthalpy at 298K: -775.412850

Gibbs free energy at 298K: -775.471980

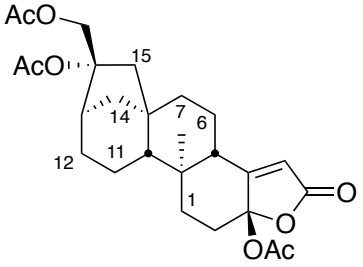
Cartesian coordinates
C -0.82508 2.04107 -0.22515
C -0.30950 0.68122 0.31103
C -0.36859 0.70454 1.85784

C 1.13086 0.45165 -0.20916
C 2.30982 1.39455 0.03961
C 3.47096 0.53405 -0.47971
O 4.56678 0.89247 -0.82380
C 1.76704 -0.92522 0.10302
C 2.08453 -1.27981 1.56452
O 3.07586 -0.77608 -0.54266
C -1.14212 -0.46644 -0.38578
C -0.55195 -1.87120 -0.10703
C 0.92257 -2.01169 -0.55761
C -2.69949 -0.35992 -0.25449
C -3.37147 -1.36133 -1.22205
C -3.11678 1.06262 -0.71746
C -3.24525 -0.65463 1.15924
C -2.34199 2.21118 -0.05933
H -0.43802 -0.28942 2.30382
H 0.52435 1.18880 2.26873
H -1.22582 1.27546 2.22123
H 2.47746 1.63419 1.09695
H 2.27795 2.33671 -0.51225
H 1.02797 0.43574 -1.30494
H 2.80317 -2.10564 1.55668
H 1.20360 -1.60366 2.12148
H 2.54326 -0.44754 2.10658
H 0.99063 -1.89763 -1.64687
H 1.30154 -3.01144 -0.31286
H -1.13824 -2.62753 -0.63787
H -0.63825 -2.12158 0.95774
H -0.96891 -0.29277 -1.46097
H -4.44588 -1.15159 -1.29080
H -3.26667 -2.39919 -0.88828
H -2.95405 -1.28650 -2.23392
H -4.19465 1.19247 -0.54998
H -2.96717 1.12399 -1.80586
H -4.34127 -0.69249 1.13189
H -2.96612 0.10162 1.89567
H -2.89793 -1.62559 1.53099
H -0.57688 2.11856 -1.29429
H -2.65260 3.16405 -0.50641
H -2.60426 2.28354 1.00378
H -0.29571 2.86246 0.27644

Table 12. Calculated Partial Atomic Charges for (+)-Sclareolide (**74**)

H Atom Number (NPA)	NPA Charge (B3LYP/6-311++G(d,p)	H Atom Number (Mulliken)	Mulliken Charge (B3LYP/6-31G(d))
2β	0.189	5α	0.112
10β	0.193	1α	0.126
3α	0.194	3α	0.126
1α	0.195	3β	0.128
5α	0.196	1β	0.134
3β	0.203	2β	0.135
2α	0.204	2α	0.136
1β	0.204	7α	0.137
7α	0.207	10β	0.138
9α	0.210	9β	0.143
9β	0.210	9α	0.147
10α	0.213	10α	0.147
11β	0.225	11β	0.172
11α	0.235	11α	0.179

(-)-Triacetoxy tricalysiolide B (79).



Total SCF energy: -1612.477147

Enthalpy at 298K: -1612.476203

Gibbs free energy at 298K: -1612.572465

Cartesian coordinates
C 2.24500 -1.62400 1.11500
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C 3.63100 0.08700 -0.71500
C 4.45100 -0.61700 0.35100
C 3.72900 -1.89500 0.79200
C 1.46600 1.30700 -1.35700
C 0.03200 -0.49900 0.52400
C -0.76800 0.54600 -0.33100
C 0.12900 1.72900 -0.73700

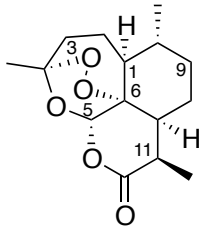
C 1.38500 -1.86800 -1.24100
C -0.89500 -1.68100 0.93800
C -1.50000 -0.11200 -1.52900
C -1.98600 -2.08100 -0.08000
C -2.62000 -0.89200 -0.82900
C -3.22700 0.20000 0.09200
C -1.99200 1.05700 0.50500
O 5.70500 -0.88800 -0.24600
C 4.35800 0.13900 -1.83400
C 5.69500 -0.43400 -1.56500
O 6.64700 -0.56700 -2.28600
O 4.64400 0.13200 1.56500
C 5.21500 1.37700 1.53100
O 5.47600 1.98200 0.52200
O -4.12000 0.93500 -0.81100
C -4.71100 2.08900 -0.40300
O -4.47200 2.64900 0.64500
C -4.06300 -0.31800 1.26500
O -4.98200 -1.34800 0.83300
C -6.27400 -1.00400 0.60700
O -6.72300 0.11100 0.74900
C -7.06700 -2.21200 0.16500
C -5.72000 2.55400 -1.42400
C 5.46600 1.85900 2.94000
H 2.19200 -1.00500 2.02000
H 1.77600 -2.58200 1.36800
H 3.83400 -2.62500 -0.01600
H 4.24300 -2.30500 1.66800
H 2.26200 0.96700 0.58400
H 2.07000 2.19400 -1.58100
H -0.42600 2.37900 -1.42600
H 1.30700 0.79000 -2.31200
H 0.34200 2.33900 0.15400
H 0.27500 0.03500 1.45500
H 2.38000 -2.22100 -1.52500
H 0.78000 -2.75200 -1.01300
H 0.96100 -1.39600 -2.12800
H -0.30500 -2.56900 1.18800
H -1.38400 -1.40000 1.87800
H -1.92200 0.66900 -2.17200
H -0.87900 -0.75400 -2.15600
H -2.75800 -2.66800 0.43100
H -1.55900 -2.74100 -0.84600
H -3.38500 -1.26100 -1.51700
H -1.80800 1.00500 1.58400
H -2.18900 2.10700 0.28600

H 4.09000 0.53300 -2.80600
H -3.42200 -0.80200 2.00300
H -4.61400 0.49600 1.73600
H -8.11200 -1.93200 0.03200
H -6.66400 -2.60000 -0.77700
H -6.98500 -3.01200 0.90900
H -5.37900 2.35600 -2.44300
H -6.64800 1.99600 -1.25600
H -5.91700 3.61800 -1.28200
H 6.24700 1.24500 3.40300
H 5.79000 2.90000 2.91200
H 4.56400 1.75700 3.55100

Table 13. Calculated Partial Atomic Charges for (-)-Triacetoxy Tricalysiolide B (**79**)

H Atom Number (NPA)	NPA Charge (B3LYP/6-311++G(d,p)	H Atom Number (Mulliken)	Mulliken Charge (B3LYP/631G(d))
11β	0.195	9	0.115
6α	0.196	7β	0.134
7β	0.197	7α	0.136
12α	0.200	13	0.137
9	0.201	11β	0.139
11α	0.206	5	0.140
1β	0.207	12α	0.140
7α	0.208	6α	0.142
1α	0.211	15β	0.142
14	0.212	11α	0.143
6β	0.213	14	0.144
15β	0.213	1β	0.146
12β	0.215	1α	0.146
2α	0.216	6β	0.153
5	0.220	12β	0.153
13	0.223	2α	0.162
2β	0.229	2β	0.167
15α	0.240	15α	0.182

(+)-Artemisinin (46).



Total SCF energy: -960.509858

Enthalpy at 298K: -960.508914

Gibbs free energy at 298K: -960.570049

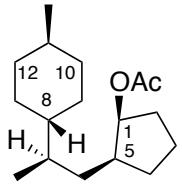
Cartesian Coordinates
C 1.15211 1.32221 0.37261
C 0.78570 2.54744 -0.50638
C 1.80000 3.69169 -0.35454
C -0.63652 3.04982 -0.20050
C 2.54645 0.75191 0.01655
C 2.86401 -0.66516 0.52801
C 1.84456 -1.74009 0.08392
O 0.84025 -1.94821 1.05731
C 2.44656 -3.11325 -0.16411
O 1.21286 -1.32424 -1.14270
C 0.05836 -0.56106 -0.95916
O -1.07154 -1.42936 -1.15718
C -2.29107 -1.26393 -0.56616
C -2.36691 -0.38223 0.67415
C -3.81220 0.04002 0.95714
C 0.05202 0.22288 0.36521
O 0.35029 -0.64456 1.49502
C -1.35363 0.78191 0.65572
C -1.69691 1.94583 -0.28924
O -3.22835 -1.88474 -1.00546
H 2.80174 3.40602 -0.68942
H 1.87302 4.01349 0.69242
H 1.48971 4.55986 -0.94737
H -0.88838 3.86765 -0.88751
H -0.65287 3.48084 0.81203
H 0.80700 2.22628 -1.55986
H 1.17775 1.66226 1.41853
H 2.66061 0.74895 -1.07424
H 3.31493 1.42953 0.40434
H 2.93024 -0.69432 1.62029
H 3.84924 -0.94716 0.13834
H 3.09008 -3.06564 -1.04697
H 1.64998 -3.83850 -0.34824
H 3.03900 -3.43169 0.69837
H -2.03836 -1.04505 1.48681
H -4.23250 0.63133 0.13777
H -3.86157 0.63594 1.87576
H -4.44505 -0.84166 1.07827
H 0.03209 0.14775 -1.79167

H -2.67785 2.35342 -0.02239
H -1.78724 1.59060 -1.32622
H -1.31478 1.19111 1.67575

Table 14. Calculated Partial Atomic Charges for (+)-Artemisinin (**46**)

H Atom Number (NPA)	NPA Charge (B3LYP/6-311++G(d,p)	H Atom Number (Mulliken)	Mulliken Charge (B3LYP/6-31G(d))
10β	0.186	10β	0.126
5	0.187	1α	0.133
9α	0.193	9α	0.133
8β	0.195	9β	0.139
2β	0.204	7α	0.141
9β	0.206	8β	0.144
1α	0.210	2α	0.146
2α	0.212	3β	0.146
3β	0.213	2β	0.151
8α	0.216	8α	0.153
7α	0.216	5	0.153
3α	0.224	3α	0.167
11α	0.253	11α	0.196

(+)-(1*S*,2*S*)-2-((*R*)-2-((1*r*,4*R*)-4-methylcyclohexyl)propyl)cyclopentyl acetate (84).



Total SCF energy: -815.897675

Enthalpy at 298K: -815.896731

Gibbs free energy at 298K: -815.971968

Cartesian coordinates
C 4.12381 -0.92442 -0.35313
C 4.18683 0.57640 -0.68650
C 5.63083 1.08681 -0.74563
C 3.33928 1.37454 0.31999
C 1.89590 0.85478 0.40912
C 1.84308 -0.64785 0.75081
C 0.39154 -1.17146 0.94587
C 0.37978 -2.50864 1.70783
C -0.41016 -1.26093 -0.37339

C 2.67974 -1.44418 -0.27064
C -4.17111 -1.21718 -1.23477
C -2.69531 -1.58662 -1.54362
C -1.93239 -1.38532 -0.21468
C -2.65857 -0.18474 0.41522
O -2.20842 1.00757 -0.29139
C -2.39228 2.19628 0.32777
C -1.85382 3.32711 -0.51971
C -4.14088 -0.45025 0.11856
O -2.91039 2.32396 1.41602
H 4.62855 -1.09662 0.61045
H 4.68643 -1.49736 -1.10283
H 3.73622 0.71394 -1.68329
H 6.12824 0.97167 0.22632
H 5.66803 2.14978 -1.01354
H 6.21975 0.53362 -1.48736
H 3.34027 2.43913 0.04915
H 3.81119 1.30734 1.31255
H 1.39140 1.03737 -0.55101
H 1.34015 1.42540 1.16582
H 0.84613 -3.31067 1.12256
H -0.63937 -2.83106 1.94805
H 0.92673 -2.42620 2.65456
H -0.10610 -0.42968 1.58925
H -0.05654 -2.12630 -0.95122
H -0.21175 -0.37743 -0.99025
H 2.33973 -0.76107 1.72907
H 2.21715 -1.36552 -1.26482
H 2.68684 -2.51111 -0.01448
H -4.79713 -2.11230 -1.15543
H -4.60039 -0.60538 -2.03450
H -2.28346 -0.90756 -2.29995
H -2.58438 -2.60540 -1.93062
H -2.16178 -2.24018 0.43824
H -0.77302 3.20990 -0.65427
H -2.06267 4.27930 -0.03085
H -2.31046 3.30778 -1.51451
H -2.45984 -0.03786 1.47823
H -4.71776 0.47837 0.11342
H -4.54922 -1.07018 0.92558

Table 15. Calculated Partial Atomic Charges for (+)-Nectaryl Derivative (**84**)

H Atom Number (NPA)	NPA Charge (B3LYP/6-311++G(d,p)	H Atom Number (Mulliken)	Mulliken Charge (B3LYP/6-31G(d))
11α	0.180	8β	0.111
8β	0.186	11α	0.115
12β	0.187	7α	0.123
10β	0.187	12β	0.123
9α	0.188	10β	0.124
7α	0.189	10α	0.125
13α	0.191	12α	0.126
10α	0.197	9β	0.128
3α	0.197	9α	0.129
12α	0.198	13β	0.130
6β	0.198	13α	0.130
4β	0.198	6β	0.130
9β	0.199	5α	0.131
13β	0.200	4α	0.135
3β	0.200	3α	0.138
5α	0.201	2β	0.142
4α	0.202	3β	0.143
2β	0.206	4β	0.144
1α	0.207	6α	0.146
6α	0.209	2α	0.158
2α	0.217	1α	0.160

3.4.6 Parameterized Site Filter for Analysis of Substrate Reactivity

In order to simplify the analysis of complex substrates with many possible sites of oxidation as well as provide a basis for further quantification of site-selectivity with Fe(PDP) (**44**) and Fe(CF_3-PDP) (**45**), I developed a systematic procedure for assigning a value to all three reactivity factors (electronics, sterics and stereoelectronics) at a given site.

Electronics: To assign an electronic parameter (E) to a particular site, I calculated the NPA partial charges for all hydrogen atoms in the molecule. Methyl groups and sites directly attached through heteroatoms to electron withdrawing groups were immediately excluded, given that no oxidation is observed at these sites. For methylene sites either: a) the average NPA charge of the

two H-atoms was taken as E for that site if the molecule is conformationally flexible such that the hydrogens are on average nearly equivalent or b) the least hindered H-atom was selected. For example, on a cyclohexane, the less hindered equatorial H-atom was chosen. We consider this simplifying assumption to be valid considering the substantial difference in reactivity between axial and equatorial sites. It is very likely that some initial oxidation at a site does occur at the axial C—H bond; however, it is likely to be such a small percentage that it can be approximated as zero. Furthermore, 1˚ sites are uniformly not oxidized under our conditions and are excluded.

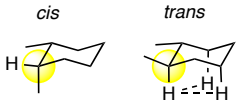
Sterics: To assign a steric value to a particular site we first considered that we needed to account both for the local steric hindrance around a site caused by substituents directly attached to that site as well as through space steric interactions caused by the conformation of the molecule.

Local Sterics: The most challenging issue was to parameterize the sizes of substituents attached to a site in a complex molecule. The sterics of simple groups, like Et, *i*-Pr, etc. have been well studied and parameterized using both empirical and computational methods ranging from Taft parameters,[80] A-values, Charton values,[81] Sterimol parameters,[82] and interference values.[83] Although the substituents at a site in complex molecules are all unique, we hypothesized that a reasonable approximation of the steric hindrance at a site could be obtained by generalizing all substituents: H, Me, OAc, C(O)Me, methylene carbons are approximated as Et, methine carbons as *i*-Pr, quaternary carbons as *t*-Bu. This approximation has the advantage of using a smaller set of parameters to represent the limitless variations in complex molecules as well as using groups that have already been well studied. While any of the previously defined steric parameters mentioned above provides a qualitative view of the relative sterics at a site, A-values provided the best fit for our. Each non-hydrogen substituent at a particular carbon (site)

was approximated as one of the substituents listed above and assigned the corresponding A-value (scale adjusted such that H = 1, Table 16). Although one hydrogen on a methylene site minimally hinders approach to the other, because this hydrogen could be oxidized to give product at that site, we do not count hydrogen substituents on the same site as causing steric hindrance.

Through Space Sterics: The need for a through space steric term is best exemplified by comparing *cis*- and *trans*-1,2-dimethylcyclohexane (Figure 21). The local steric parameter alone treats the tertiary sites in these molecules (C1) as equivalent as they are both attached to approximated substituents Me, Et, and *i*-Pr (2.74+2.79+3.21=8.7 steric parameter for both). However, the reactivity of these molecules is vastly different (cis favors 3˚ oxidation, trans slightly favors 2˚ oxidation. This phenomenon has long been recognized to arise from unfavorable interactions with the other axial hydrogens on the ring as the catalyst approaches in the *trans*-isomer. We therefore examined the geometry-optimized structure of any substrate under consideration and looked for 1,3-diaxial interactions or gauche/eclipsing butane-like interactions that would hinder the target hydrogen. The former were assigned the adjusted A-value for the group causing the 1,3-diaxial hindrance (Table 16) and the latter 0.9 and 2.2 corresponding to the conformational strain of those interactions. Although nearly all sites on a ring experience some 1,3-diaxial interactions with other hydrogens, if the ring site is a methylene, only the equatorial hydrogen is being evaluated and therefore 1,3-diaxial interactions that hinder the axial hydrogen are ignored. However, if the ring site is a methine with an axial C—H bond, that is the only C—H bond available for oxidation, all hindering 1,3-diaxial interactions must be considered.

Figure 21. Need for a Through Space Steric Parameter



-Both sites equivalent local sterics: Me, Et, iPr
-*trans* hindered by other axial groups

Table 16. Adjusted A-Values (H=1)

Substituent	Adjusted A-Value
H	1
OAc	1.78
C(O)Me	2.25
Me	2.74
Et	2.79
i-Pr	3.21
t-Bu	5.8

Stereoelectronics: Stereoelectronic effects can also have a strong impact on site selectivity. Although not examined in this report, hyperconjugative activation of neighboring C—H bonds by ethers and cyclopropane rings is generally so strong as to produce complete selectivity for the activated site.

A weaker form of activation takes the form of transition state strain relief. If a site has an axial group that experiences 1,3-diaxial strain with a large group, activation is possible. At the transition state for oxidation, the carbon becomes slightly planarized, relieving 1,3-diaxial strain slightly. Literature reports estimate that ~20% of the strain is relieved.[72] Therefore, the A-value (unadjusted) for the group causing the strain is multiplied by 0.21 to obtain the stereoelectronic component. Since this is an activating effect, the stereoelectronic term is *subtracted* from the previously obtained steric term to arrive at a combined steric/stereoelectronic parameter (S). While we ignore axial hydrogens on methylene sites when assigning through space sterics because these hydrogens are significantly less prone to oxidation, 1,3-diaxial interactions with the axial hydrogen on a methylene site need to be considered for all sites because abstraction of

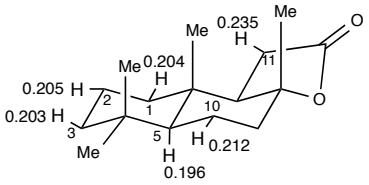
the unhindered equatorial hydrogen causes planarization and relieves strain felt by the axial hydrogen.

The steric/stereoelectronic parameter (S) = Local + Through Space – Stereoelectronics.

Example of Electronic, Steric and Stereoelectronic Analysis: (+)-Sclareolide.

Assigning the Electronic Parameter (E) for Selected Sites in (+)-Sclareolide

Figure 22. NPA Partial Atomic Charges for (+)-**74**



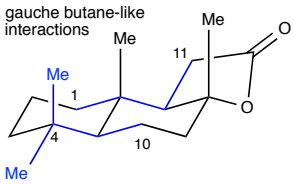
NPA charge = electronic parameter (E)

Table 17. Assigning the Steric/Stereoelectronic Parameter (S) for Sites in (+)-Sclareolide (**74**)

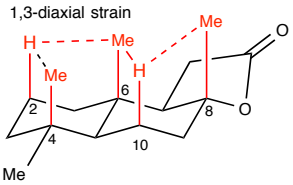
Site (H_{eq} atom)	Substituents Simplified Representation	Adjusted A-values	Through Space (value)	Stereoelectronic (value)	S
C1	Et (C2 is a methylene), *t*-Bu (C6 is quaternary)	2.79, 5.8	gauche to C11 (0.9)	none (0)	9.6
C2	Et, Et	2,79, 2.79	none (0)	2Me C4,C6 (0.365)	5.2
C3	Et, *t*-Bu	2.79, 5.8	none (0)	none (0)	8.7
C5	Et, *t*-Bu, *t*-Bu	2.79, 5.8, 5.8	4 axial H (2)	none (0)	16.6
C7	Et, *t*-Bu, *t*-Bu	2.79, 5.8, 5.8	2 axial H (1)	none (0)	15.6
C9	Et, *t*-Bu	2.79, 5.8	none (0)	none (0)	8.7
C10	Et, *i*-Pr	2.79, 3.21	2 gauche to C4 methyls (1.8)	2Me C6,C8 (0.365)	7.4
C11	C(O)Me, *i*-Pr	2.25, 3.21	Gauche to C1 (0.9)	none (0)	6.4

S=sum A-values+Through Space-Stereoelectronic

Figure 23. Through Space Sterics and Stereoelectronic Activation in (+)-**74**



Through Space Hindrance in (+)-Sclareolide



Stereoelectronic Activation in (+)-Sclareolide

Using the Parameterized Site Filter to Determine Reactive Sites Within a Molecule. In order to simplify analysis of substrate properties, we developed a parameterized site filter to eliminate sites that are too electron poor or sterically hindered to be oxidized by catalyst **44** or **45**. Using percent increases from the lowest value in the electronic and steric/stereoelectronic series, we define three regions: red=highly reactive, purple=moderately reactive, blue=unreactive. Only sites with two red or a red and a purple parameter are likely to be oxidized as all other sites are relatively unreactive. Table 18 depicts this process numerically for (+)-**74** and reveals that only sites C1, C2 and C3 are likely to be oxidized

Table 18. Parameterized Site Filter for Determining Likely Sites of Oxidation for (+)-Sclareolide (**74**)

Site (H_{eq} atom)	Electronic Parameter (E)	Steric/Stereoelectronic Parameter (S)
5	0.196	16.6
3	**0.203**	**8.7**
1	**0.204**	**9.6**
2	**0.205**	**5.2**
7	0.207	15.6
9	0.210	8.6
10	0.212	7.4
11	0.235	6.4
red lower limit	0.196 (lowest E)	5.2 (lowest S)
purple lower limit	0.206 =0.196+5%	7.3 =5.2+40%
blue lower limit	0.216 =0.206+5%	10.2 =7.3+40%

3.4.7 Creating Structure-Based Catalyst Reactivity Models

Having described the process for assigning electronic and steric/stereoelectronic parameters to each site in a molecule and using this information to identify likely sites of oxidation with a parameterized site filter, I sought to provide a quantitative model by which both the magnitude and direction of the site-selectivity could be predicted. This is an especially interesting question

when comparing catalysts **44** and **45**. Because the parameters E and S remain constant, these parameters must have different relative importance for each catalyst to produce the different site-selectivities we observe. To probe these questions I started with a two part hypothesis: 1. the observed site-selectivity is determined kinetically, i.e. related to the $\Delta\Delta G^{\ddagger}$ between the two sites (*a* and *b*) in question and 2. $\Delta G^{\ddagger}$ is related to E and S at a given site. Since we do not have the absolute $\Delta G^{\ddagger}$ for oxidation at a site, we considered that $\Delta\Delta G^{\ddagger}$ would be related to the difference between the E and S parameters (ΔE_{ab} and ΔS_{ab}) of the two sites (*a* and *b*) as a function of catalyst such that $\Delta\Delta G^{\ddagger} = f_{cat}(\Delta E_{ab}, \Delta S_{ab})$. Because we have the E and S parameters for the sites as well as the observed $\Delta\Delta G^{\ddagger}$ from the experimentally measured site-selectivity, a curve can be fit to the data.[73a] The steps for constructing and utilizing our model are described below.

1. Assign the electronic (E) and steric/stereoelectronic (S) parameters at all sites in a molecule.

I selected a range of structurally varied compounds whose oxidation with Fe(PDP) (**44**) has been previously reported as well as the compounds reported herein with both catalyst **44** and **45**. I then preformed the analyses described above to assign E and S at each site (see Table 17 for the results for (+)-**74** for example). These values provided a more concrete representation of the reactivity of each site, rather than more broad generalizations like, "3˚ C—H bonds are more electron rich." In (+)-**74**, electronics are essentially equal, while C2 is preferred sterically; however, these are still mostly qualitative observations. Although they can be used to rationalize the outcome of a reaction, it would be difficult if not impossible to predict the site-selectivity *a priori*.

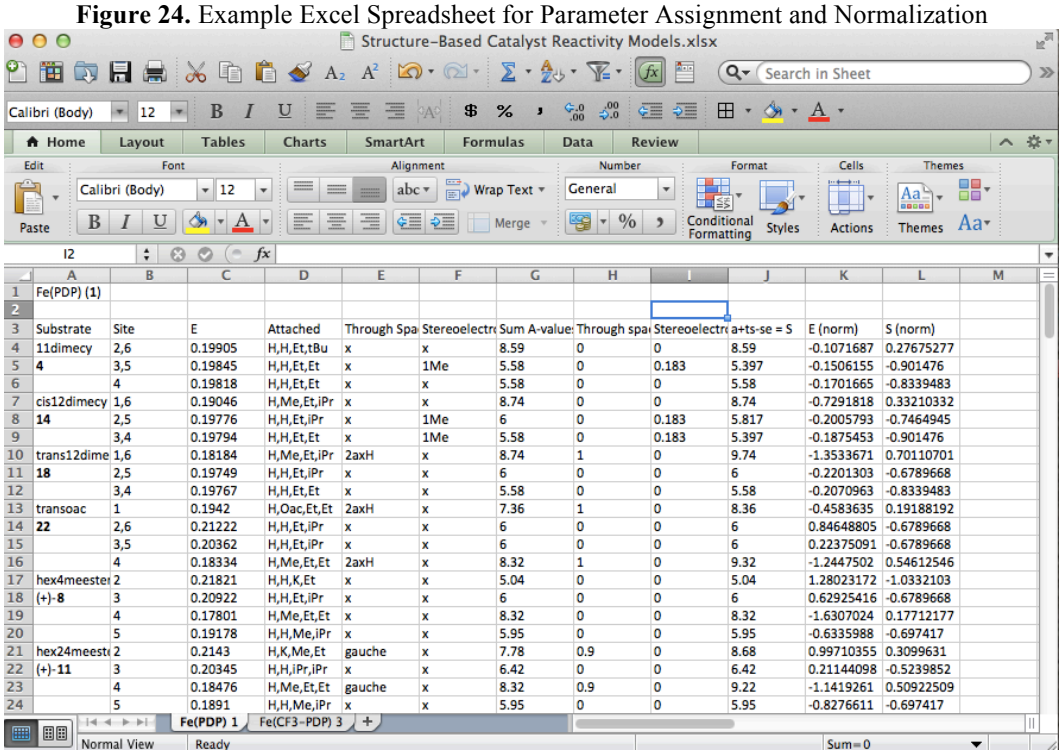
2. Use the E and S data to narrow down the potential sites of oxidation using the parameterized site filter.

See process described above.

3. Normalize E and S

I combined the E and S parameters for all substrates being used into a spreadsheet (25 molecules, ~140 sites). These values were normalized using the equation $P_n=(P-m)/s$, where P_n is the normalized parameter, P is the original parameter, m is the mean of the parameters used and s is the standard deviation of the parameters used. Our data set represents a wide range of values likely to be encountered in many hydrocarbons which would be computationally time consuming for the reader to duplicate. Therefore, the mean and standard deviation values we used are provided so that the reader can obtain normalized values with a small data set of only one molecule: $m_E=0.200533$, $s_E=0.013807$, $m_S=7.839$, $s_S=2.712$. Steps 3 and 4 are most easily carried out using an excel spreadsheet which contains all the E and S values corresponding to each site. Using the cell equation functionality in excel, additional columns for normalized values can be created and calculated simultaneously.

Figure 24. Example Excel Spreadsheet for Parameter Assignment and Normalization



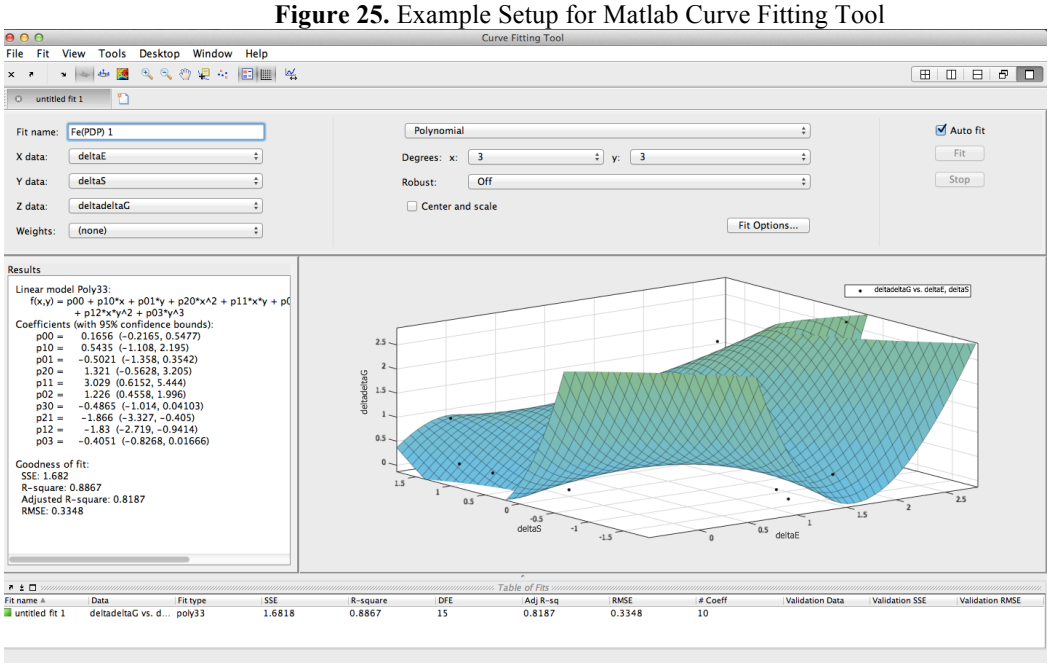
	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Fe(PDP) (1)												
2													
3	Substrate	Site	E	Attached	Through Spa	Stereoelectr	Sum A-value	Through spa	Stereoelectr	a+ts-se = S	E (norm)	S (norm)	
4	11dimecy	2,6	0.19905	H,H,Et,tBu	x	x	8.59	0	0	8.59	-0.1071687	0.27675277	
5	**4**	3,5	0.19845	H,H,Et,Et	x	1Me	5.58	0	0.183	5.397	-0.1506155	-0.901476	
6		4	0.19818	H,H,Et,Et	x	x	5.58	0	0	5.58	-0.1701665	-0.8339483	
7	cis12dimecy	1,6	0.19046	H,Me,Et,iPr	x	x	8.74	0	0	8.74	-0.7291818	0.33210332	
8	**14**	2,5	0.19776	H,H,Et,iPr	x	1Me	6	0	0.183	5.817	-0.2005793	-0.7464945	
9		3,4	0.19794	H,H,Et,Et	x	1Me	5.58	0	0.183	5.397	-0.1875453	-0.901476	
10	trans12dime	1,6	0.18184	H,Me,Et,iPr	2axH	x	8.74	1	0	9.74	-1.3533671	0.70110701	
11	**18**	2,5	0.19749	H,H,Et,iPr	x	x	6	0	0	6	-0.2201303	-0.6789668	
12		3,4	0.19767	H,H,Et,Et	x	x	5.58	0	0	5.58	-0.2070963	-0.8339483	
13	transoac	1	0.1942	H,Oac,Et,Et	2axH	x	7.36	1	0	8.36	-0.4583635	0.19188192	
14	**22**	2,6	0.21222	H,H,Et,iPr	x	x	6	0	0	6	0.84648805	-0.6789668	
15		3,5	0.20362	H,H,Et,iPr	x	x	6	0	0	6	0.22375091	-0.6789668	
16		4	0.18334	H,Me,Et,Et	2axH	x	8.32	1	0	9.32	-1.2447502	0.54612546	
17	hex4meeste	2	0.21821	H,H,K,Et	x	x	5.04	0	0	5.04	1.28023172	-1.0332103	
18	(+)-**8**	3	0.20922	H,H,Et,iPr	x	x	6	0	0	6	0.62925416	-0.6789668	
19		4	0.17801	H,Me,Et,Et	x	x	8.32	0	0	8.32	-1.6307024	0.17712177	
20		5	0.19178	H,H,Me,iPr	x	x	5.95	0	0	5.95	-0.6335988	-0.697417	
21	hex24meeste	2	0.2143	H,K,Me,Et	gauche	x	7.78	0.9	0	8.68	0.99710355	0.3099631	
22	(+)-**11**	3	0.20345	H,H,iPr,iPr	x	x	6.42	0	0	6.42	0.21144098	-0.5239852	
23		4	0.18476	H,Me,Et,Et	gauche	x	8.32	0.9	0	9.22	-1.1419261	0.50922509	
24		5	0.1891	H,H,Me,iPr	x	x	5.95	0	0	5.95	-0.8276611	-0.697417	

4. Calculate ΔE_{ab} and ΔS_{ab} using the equation $\Delta E_{ab} = E_b - E_a$ where E_b and E_b are the *normalized* electronic parameters at site *b* and *a* respectively.

This step requires a reference site to be selected for calculating the *a*:*b* ratio and differences in E and S. Because the site-selectivities of the compounds being used to generate the model equation are known, *a* is selected as the major site for oxidation with Fe(PDP) (**1**). For example, C2 in (+)-sclareolide (**74**) is the major site of oxidation so we calculate C2:C3 using $\Delta E_{2,3} = E_3 - E_2$ and C2:C1 using $\Delta E_{2,1} = E_1 - E_2$.

5. Import the data into Matlab[84] and fit a curve

Figure 25. Example Setup for Matlab Curve Fitting Tool



The data was fit to a third degree polynomial function using the curve-fitting tool. Where $X=\Delta E_{ab}$, $Y=\Delta S_{ab}$ and $Z=\Delta\Delta G^{\ddagger}$. I obtained the following two equations:

$$\Delta\Delta G_{PDP}{}^{\ddagger} = 0.4 + 0.0X - 0.8Y + 1.7X^2 - 3.4XY + 1.2Y^2 - 0.6X^3 - 2.0X^2Y - 1.8XY^2 - 0.3Y^3$$

$$\Delta\Delta G_{CF3-PDP}{}^{\ddagger} = 0.5 - 4.5X - 1.3Y + 9.6X^2 + 6.5XY + 1.8Y^2 - 2.7X^3 - 1.5X^2Y - 1.5XY^2 - 0.4Y^3$$

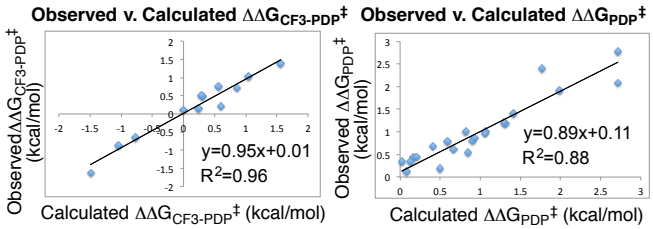
Notably I omitted two molecules (+)-nectaryl derivative (**84**) and (+)-(*2S,4S*)-Methyl 2,4-dimethylhexanoate (**58**) which had not been oxidized previous to this report with one or both of the catalysts. These would provide a test of the predictive power of our model in the future.

6. Use the equation to calculate $\Delta\Delta G^{\ddagger}$

The E and S values for two sites can be normalized, the difference taken and $X=\Delta E_{ab}$ and $Y=\Delta S_{ab}$ input into the equation to obtain $\Delta\Delta G^{\ddagger}$ for either Fe(PDP) (**44**) or Fe(CF_3-PDP) (**45**). We

consider a difference in observed versus calculated $\Delta\Delta G^{\ddagger}$ of 0.3 kcal/mol to be in good agreement while up to 0.5 kcal/mol is acceptable. 0.5 kcal/mol represents the difference between 1:1 and ~2:1 selectivity, meaning an equation predicting within this limit can differentiate between a non-selective (1.5:1 to 1:1), moderately selective (1.6:1 to 3:1) and selective reaction (>3:1). In practice, the differences are often much smaller. The plots of observed versus calculated $\Delta\Delta G^{\ddagger}$ for each catalyst demonstrate the goodness of the fit for the experimental data.

Figure 26. Goodness of Fits for Catalysts **44** and **45**

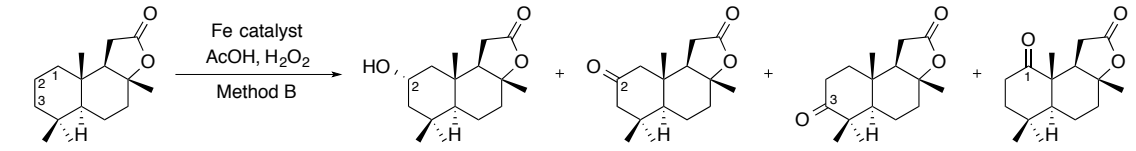


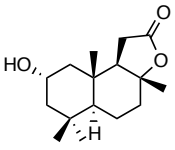
In addition to providing a good fit for the data, these equations also predict the site selectivity for the two substrates omitted from the curve fitting process (+)-**84** and (+)-**58**).

It should be noted that polynomial functions provide predictive power only in and around the region where data points have defined the curve. Because the curve is only defined for reactive sites, other sites on the molecule may not provide accurate predictions with these equations. For this reason, we only examine sites that are considered reactive using our parameterized site filter. We anticipate that as these catalysts continue to be used and site-selectivities reported, the equation can be further refined with the aid of additional data points to provide a wider predictive window.

3.4.8 Catalyst-Controlled Oxidation of Complex Molecules and Application of the Structure Based-Reactivity Models

Oxidation of Sclareolide.

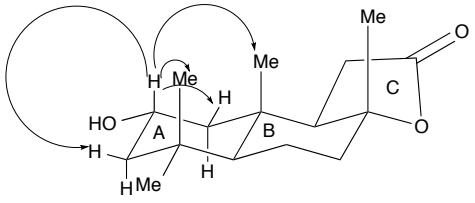




(+)-2α-hydroxy-sclareolide (75). (+)-sclareolide (**74**) (75.1 mg, 0.3 mmol, 1.0 equiv) in MeCN (1.5 mL) was reacted with (*R,R*)-Fe(CF_3-PDP) (**45**) according to Method B. Purification by flash chromatography on silica (~75 mL) eluting with gradient 10→20→30% acetone/hexane. Reported ratios are of isolated material. Overlapping peaks in the crude ^{1}H NMR and GC made accurate C2:C3 ratio determination impossible so isolated ratios are reported. Run 1: recycled one time for a total of 32% (+)-**75**, 20% (+)-**76**, 20% (+)-**77**, 10% (+)-1-oxo, 9% RSM, 2.6:1 C2:C3 oxidation, 52% total C2 oxidation; cycle 1 (+)-**75** (20.8 mg, 0.078 mmol, 26%), (+)-**76** (13.1 mg, 0.05 mmol, 17%), (+)-**77** (13.1 mg, 0.05 mmol, 17%), (+)-**1-OXO** (7.3 mg, 0.028 mmol, 10%), RSM (15.9 mg, 0.064 mmol, 21%); cycle 2 (+)-**75** (4.5 mg, 0.017 mmol, 28%), (+)-**76** (2.7 mg, 0.01 mmol, 16%), (+)-**77** (2.7 mg, 0.01 mmol, 16%), (+)-**1-OXO** trace, RSM (6.5 mg, 0.026 mmol, 41%). Run 2: recycled one time for a total of 32% (+)-**75**, 24% (+)-**76**, 24% (+)-**77**, 9% (+)-**1-OXO**, 6% RSM, 2.3:1 C2:C3 oxidation; cycle 1 (+)-**75** (24.0 mg, 0.09 mmol, 30%), (+)-**76** (13.9 mg, 0.05 mmol, 18%), (+)-**77** (13.9 mg, 0.05 mmol, 17%), (+)-**1-OXO** (7.2 mg, 0.03 mmol, 9%), RSM (23.7 mg, 0.09 mmol, 32%); cycle 2 (+)-**75** (5.3 mg, 0.021 mmol, 27%), (+)-**76** (2.8 mg, 0.012 mmol, 15%), (+)-**77** (2.8 mg, 0.012 mmol, 15%), (+)-**1-OXO** trace, RSM (4.5 mg, 0.018 mmol, 23%). Run 3: recycled one time for a total

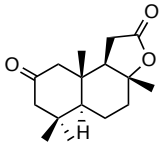
of 36% (+)-**75**, 21% (+)-**76**, 21% (+)-**77**, 8% (+)-**1-OXO**, 7% RSM, 2.7:1 C2:C3 oxidation; cycle 1 (+)-**75** (23.4 mg, 0.088 mmol, 29%), (+)-**76** (13.6 mg, 0.05 mmol, 17%), (+)-**77** (13.6 mg, 0.05 mmol, 17%), (+)-**1-OXO** (6.3 mg, 0.024 mmol, 8%), RSM (18.8 mg, 0.075 mmol, 25%); cycle 2 (+)-**75** (5.2 mg, 0.02 mmol, 25%), (+)-**76** (3.3 mg, 0.013 mmol, 17%), (+)-**77** (3.3 mg, 0.013 mmol, 17%), (+)-**1-OXO**trace, RSM (5.7 mg, 0.023 mmol, 30%). Average overall yield (+)-**75**: 33±2%. Average overall yield (+)-**76**: 22±2% Average overall yield C2 oxidation: 55±4%. Average overall yield (+)-**77**: 22±2%. Average overall yield (+)-**1-OXO**: 9±1%. Average overall RSM: 7±2%. Average ratio C2:C3 oxidation: 2.6:1±0.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 2.42 (app t, *J* = 15.5 Hz, 1H), 2.24 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.07 (d, *J* = 12.0 Hz, 1H), 1.99 (dd, *J* = 15.0, 6.5 Hz, 1H), 1.89 (dd, *J* = 14.0, 3.0 Hz, 1H), 1.84-1.76 (m, 2H), 1.68 (td, *J* = 12.5, 3.5 Hz, 1H), 1.40-1.32 (m, 1H), 1.31 (s, 3H), 1.14 (t, *J* = 12.0 Hz, 1H), 1.07 (dd, *J* = 12.5, 1.5 Hz, 1H), 0.96 (t, *J* = 12.5 Hz, 1H), 0.94 (s, 6H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 86.1, 64.2, 58.8, 56.1, 51.3, 48.3, 38.4, 37.3, 34.7, 33.2, 28.7, 21.7, 21.6, 20.1, 16.1; IR (film): 3396, 2947, 2872, 1770, 1460, 1389, 1367, 1281, 1227, 1196, 1178, 1120, 1036 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{27}O_3$ $[M+H]^+$: 267.1960, found 267.1966; $[\alpha]_D^{23}$ = +27.8° (c=0.5, $CHCl_3$).

Figure 27. NOE Analysis of (+)-**75**

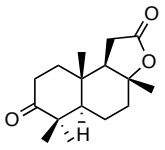


The site of oxidation was confirmed by oxidizing (+)-2α-hydroxy-sclareolide (**75**) to (+)-**76** using DMP and matching the spectral data to those reported in the literature.[58b] The stereochemistry of the 2° alcohol was assigned based on a combination of ^{1}H NMR, ^{1}H-^{1}H

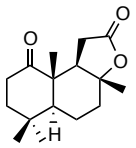
TOCSY and NOESY1D NMR methods. The axial proton at C2 shows NOE correlations with the two axial methyl groups on the A-ring as well as the two adjacent equatorial protons on the A-ring at the C1 and C3 positions.



(+)-2-oxo-sclareolide (76). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (dd, *J* = 14.5, 12.5 Hz, 1H), 2.34-2.14 (m, 7H), 2.03 (app dq, *J* = 14.5, 2.3 Hz, 1H), 1.80 (td, *J* = 12.5, 4.0 Hz, 1H), 1.69 (dd, *J* = 12.5, 3.0 Hz, 1H), 1.49 (qd, *J* = 13.0, 3.5 Hz, 1H), 1.35 (s, 3H), 1.09 (s, 3H), 0.93 (s, 6H); HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, found 265.1804. These spectral data match those reported in the literature.[58b]



(+)-3-oxo-sclareolide (77). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62-2.55 (m, 1H), 2.52-2.46 (m, 1H), 2.48 (dd, *J* = 16.5, 14.5 Hz, 1H), 2.29 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.13 (dt, *J* = 11.5, 3.0 Hz, 1H), 2.00 (dd, *J* = 14.5, 6.5 Hz, 1H), 1.87-1.82 (m, 1H), 1.77-1.70 (m, 2H), 1.63-1.53 (m, 3H), 1.39 (s, 3H), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H); HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, found 265.1805. These spectral data match those reported in the literature.[58b]



(+)-1-oxo-sclareolide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (dd, *J* = 16.5, 6.5 Hz, 1H), 2.67 (ddd, *J* = 14.5, 9.5, 5.0 Hz, 1H), 2.53 (dd, *J* = 17.0, 14.0 Hz, 1H), 2.32-2.24 (m, 1H), 2.15 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.08 (dt, *J* = 11.5, 3.5 Hz, 1H), 1.92-1.80 (m, 2H), 1.70-1.48 (m, 4H),

1.34 (s, 3H), 1.19 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H); HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}O_3$ $[M+H]^+$: 265.1804, found 265.1807. These spectral data match those reported in the literature.[85]

Table 19. Catalyst Comparison for the Oxidation of (+)-Sclareolide (**74**)

Catalyst	% (+)-**75**[a]	% (+)-**76**	% C2 ox.	% (+)-**77**	% (+)-1-oxo	% RSM	C2:C3[b]
(*R,R*)-Fe(PDP) (**44**)[58b]	-	46	46	33	8	9	1.4:1
(*S,S*)-Fe(PDP) (**44**)[58b]	-	26	26	25	9	9	1:1
(*R,R*)-Fe(Me_2Ar-PDP) (**78**)[d]	15	26	41	19	9	13	2:1
(*R,R*)-Fe(CF_3-PDP) (**45**)[c]	33	22	55	22	9	7	3:1
(*S,S*)-Fe(CF_3-PDP) (**45**)[c]	16	23	39	32	6	14	1.2:1

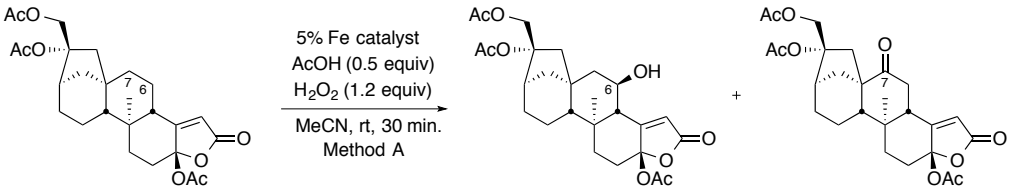
[a]Average of 3 runs at 0.3 mmol unless otherwise noted. Yields are of isolated material. [b]Isolated ratio. [c]Starting material was recycled 1 time. [d]Average of 2 runs at 0.3 mmol.

Oxidation with (*R,R*)-Fe(Me_2Ar-PDP) (**78**) according to general procedure B. Run 1: (+)-**75** (12.0 mg, 0.045 mmol, 15%), (+)-**76** (20.6 mg, 0.078 mmol, 26%), (+)-**77** (15.1 mg, 0.057 mmol, 19%), (+)-**1-OXO** (6.8 mg, 0.026 mmol, 9%), RSM (10.0 mg, 0.04 mmol, 13%). Run 2: (+)-**75** (10.4 mg, 0.039 mmol, 13%), (+)-**76** (22.2 mg, 0.084 mmol, 28%), (+)-**77** (15.9 mg, 0.06 mmol, 20%), (+)-**1-OXO** (6.8 mg, 0.026 mmol, 9%), RSM (12.6 mg, 0.05 mmol, 17%). Average yield (+)-**75**: 15%. Average yield (+)-**76**: 26%. Average yield C2 oxidation: 41%. Average yield (+)-**77**: 20%. Average yield (+)-**1-OXO**: 9%. Average RSM: 15%. Average ratio C2:3 oxidation: 2:1.

Oxidation with (*S,S*)- Fe(CF_3-PDP) (**2**) according to Method B. Run 1: (+)-**75** (11.5 mg, 0.043 mmol, 14%), (+)-**76** (17.5 mg, 0.066 mmol, 22%), (+)-**77** (24.6 mg, 0.09 mmol, 31%), (+)-**1-OXO** (5.5 mg, 0.012 mmol, 4%), RSM (11.9 mg, 0.043 mmol, 14%), 1.2:1 C2:C3 oxidation. Run 2: (+)-**75** (14.3 mg, 0.054 mmol, 18%), (+)-**76** (18.6 mg, 0.07 mmol, 23%), (+)-**77** (26.0 mg, 0.1 mmol, 33%), (+)-**1-OXO** (6.7 mg, 0.025 mmol, 8%), RSM (10.1 mg, 0.04 mmol, 13%), 1.2:1 C2:C3 oxidation. Average yield (+)-**75**: 16%. Average yield **76**: 23%.

Average yield C2 oxidation: 39%. Average yield (+)-**77**: 32%. Average RSM: 14%. Average ratio C2:3 oxidation: 1.2:1.

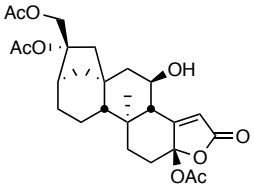
Oxidation of Triacetoxy Tricalysiolide B.



(-)-triacetoxy tricalysiolide B (**79**)

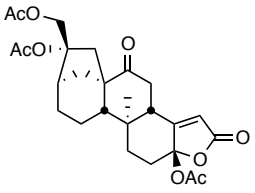
(-)-triacetoxy 6β-hydroxy-tricalysiolide B (**80**)

(-)-triacetoxy 7-oxo-tricalysiolide B (**81**)



(-)-6β-hydroxy-triacetoxy tricalysiolide B (80). Triacetoxy tricalysiolide B (**79**) (71.2 mg, 0.15 mmol, 1.0 equiv) in MeCN (2 mL) was reacted with (*R,R*)-Fe(CF_3-PDP) (**45**) according to Method A. Purification by flash chromatography on silica (~75 mL) eluting with gradient 30→40% acetone/hexane. Residual iron catalyst could not be removed from the crude reaction mixture without either losing oxidized products, broadening the ^{1}H NMR spectrum or running a standard flash column. Therefore, isolated ratios are reported. Run 1: recycled one time for a total of 62% (-)-**80**, >5% (-)-**81**, 15% RSM, >10:1 C6:C7; cycle 1 (-)-**80** (33.2 mg, 0.068 mmol, 45%), (-)-**81** (3.1 mg, 0.006 mmol, 4%), RSM (30.2 mg, 0.064 mmol, 42%); cycle 2 (-)-**80** (12.3 mg, 0.025 mmol, 38%), (-)-**81** (<1 mg, <5%), RSM (12.1 mg, 0.026 mmol, 41%). Run 2: recycled one time for a total of 59% (-)-**80**, <5 (-)-**81**, 17% RSM, >10:1 C6:C7; cycle 1 (-)-**80** (30.5 mg, 0.062 mmol, 42%), (-)-**81** (2.3 mg, 0.005 mmol, 3%), RSM (33.1 mg, 0.07 mmol, 47%); cycle 2 (-)-**80** (13.1 mg, 0.027 mmol, 38%), (-)-**81** (<1 mg, <5%), RSM (11.9 mg, 0.025 mmol, 36%). Run 3: recycled one time for a total of 63% yield (-)-**80**, 5%

(-)-**81**, 18% RSM, >10:1 C6:C7; cycle 1 (-)-**80** (33.4 mg, 0.068 mmol, 45%), (-)-**81** (3.6 mg, 0.008 mmol, 5%), RSM (30.9 mg, 0.065 mmol, 43%); cycle 2 (-)-**80** (13.1 mg, 0.027 mmol, 41%), (-)-**81** (<1 mg, <5%), RSM (12.7 mg, 0.027 mmol, 41%). Average overall yield (-)-**80**: 61±3%. Average overall yield (-)-**81**: <5%. Overall RSM: 16±2%. Average ratio C6:C7 oxidation: >10:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.70 (ABq, J = 12.5 Hz, Δν = 258.5 Hz, 2H), 3.95 (td, J = 10.5, 4.0 Hz, 1H), 2.63-2.61 (m, 1H), 2.56 (br s, 1H), 2.10-2.05 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.96-1.90 (m, 2H), 1.86-1.72 (m, 3H), 1.70-1.46 (m, 7H), 1.32 (d, J = 7.5 Hz, 1H), 1.30-1.21 (m, 2H), 0.90 (s, 3H); HRMS (ESI) *m/z* calc'd for $C_{26}H_{35}O_9$ $[M+H]^+$: 491.2281, found 491.2278. These spectral data match those reported in the literature.[74]



(-)-7oxo-triacetoxy tricalysiolide B (81). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.80 (s, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.5 Hz, 1H), 3.17 (d, J = 15.5 Hz, 1H), 2.77-2.67 (m, 3H), 2.60-2.53 (m, 2H), 2.10-2.05 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.95-1.90 (m, 1H), 1.85-1.65 (m, 7H), 1.65-1.60 (m, 1H), 1.32 (td, J = 14.5, 4.0 Hz, 1H), 1.04 (s, 3H); HRMS (ESI) *m/z* calc'd for $C_{26}H_{33}O_9$ $[M+H]^+$: 489.2125, found 489.2124. These spectral data match those reported in the literature.[74]

Table 20. Catalyst Comparison for the Oxidation of (-)-Triacetoxy Tricalysiolide B (**79**)

Catalyst	% (-)-**80**[a,b]	% (-)-**81**	% RSM	C6:C7[c]
(*S,S*)-Fe(PDP) (**44**)[74]	31	12	10	3:1
(*R,R*)-Fe(PDP) (**44**)	27	19	8	1.4:1
(*R,R*)-Fe(CF_3-PDP) (**45**)	61	<5	17	>10:1
(*S,S*)-Fe(CF_3-PDP) (**45**)[d]	40	<5	37	8:1

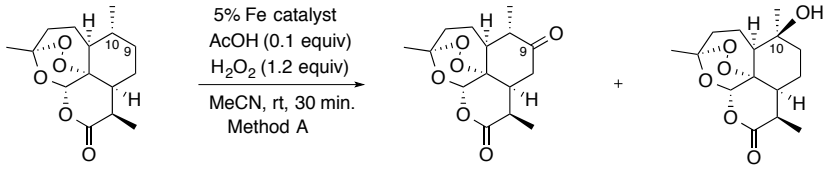
[a]Average of 3 runs at 0.15 mmol unless otherwise noted. Yields are of isolated material. [b]Starting material was recycled 1 time. [c]Isolated ratio. [d]Average of 2 runs at 0.15 mmol.

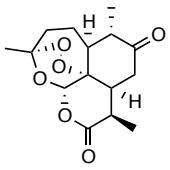
Oxidation with (*R,R*)-Fe(PDP) (**44**) according to Method A. Run 1: recycled 1 time for a total of 21% (-)-**80**, 16% (-)-**81**, 10% RSM, 1.3:1 C6:C7 oxidation; cycle 1 (-)-**80** (14.2 mg, 0.029 mmol, 19%), (-)-**81** (11.9 mg, 0.024 mmol, 16%), RSM (23.8 mg, 0.05 mmol, 33%); cycle 2 (-)-**80** (5.4 mg, 0.011 mmol, 22%), (-)-**81** (3.7 mg, 0.008 mmol, 15%), RSM (7.1 mg, 0.015 mmol, 30%). Run 2: recycled 1 time for a total of 30% (-)-**80**, 19% (-)-**81**, 9% RSM, 1.6:1 C6:C7 oxidation; cycle 1 (-)-**80** (18.1 mg, 0.037 mmol, 24%), (-)-**81** (11.0 mg, 0.023 mmol, 15%), RSM (19.7 mg, 0.042 mmol, 28%); cycle 2 (-)-**80** (3.7 mg, 0.008 mmol, 18%), (-)-**81** (2.7 mg, 0.005 mmol, 13%), RSM (6.4 mg, 0.013 mmol, 32%). Run 3: recycled 1 time for a total of 29% (-)-**80**, 23% (-)-**81**, 8% RSM, 1.3:1 C6:C7 oxidation; cycle 1 (-)-**80** (17.0 mg, 0.035 mmol, 23%), (-)-**81** (13.3 mg, 0.027 mmol, 18%), RSM (19.2 mg, 0.04 mmol, 27%); cycle 2 (-)-**80** (3.8 mg, 0.008 mmol, 19%), (-)-**81** (3.2 mg, 0.007 mmol, 16%), RSM (5.7 mg, 0.012 mmol, 30%). Average overall yield (-)-**80**: 27±5%. Average overall yield (-)-**81**: 19±4%. Average overall RSM: 9±1%. Average ratio C6:C7 oxidation: 1.4±0.2:1. Note: When the reaction is run with (*R,R*)-**44** the C7 ketone is isolated as an inseparable mixture with another ketone. Based on the structure-based catalyst reactivity model, it is very likely that this is the C11 ketone; however, this structure could not be unambiguously assigned by X-ray crystallographic or ^{1}H NMR analysis in contrast to the C7 ketone, which can be selectively crystallized.

Oxidation with (*S,S)*- Fe(CF_3-PDP) (**45**) according to Method A. Run 1: recycled 1 time for a total of 42% (-)-**80**, 6% (-)-**81**, 39% RSM, 7:1 C6:C7 oxidation, cycle 1 (-)-**80** (18.7 mg, 0.038 mmol, 25%), (-)-**81** (2.5 mg, 0.005 mmol, 3%), RSM (43.6 mg, 0.092 mmol, 61%); cycle 2 (-)-**80** (12.2 mg, 0.025 mmol, 27%), (-)-**81** (1.8 mg, 0.004 mmol, 4%), RSM (27.9 mg, 0.059 mmol, 64%). Run 2: recycled 1 time for a total of 38% (-)-**80**, 4% (-)-**81**, 36% RSM, 10:1 C6:C7 oxidation; cycle 1 (-)-**80** (17.2 mg, 0.035 mmol, 23%), (-)-**81** (2.2 mg, 0.004 mmol, 3%), RSM

(42.2 mg, 0.089 mmol, 60%); cycle 2 (-)-**80** (10.9 mg, 0.022 mmol, 25%), (-)-**81** (0.9 mg, 0.002 mmol, 2%), RSM (25.8 mg, 0.054 mmol, 61%). Average overall yield (-)-**80**: 40%. Average overall yield (-)-**81**: <5%. Average overall RSM: 37%. Average ratio C6:C7 oxidation: 8:1.

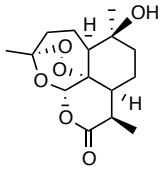
Oxidation of (+)-Artemisinin.





(+)-9-oxo-artemisinin (83). (+)-Artemisinin (**46**) (141.1 mg, 0.5 mmol, 1.0 equiv) in MeCN (2.25 mL) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method A but using reduced loading of AcOH (2.9 mL, 3.0 mg, 0.05 mmol, 0.1 equiv). Purification by flash chromatography on silica (~125 mL) eluting with 10→30% EtOAc/hexane. Run 1: recycled five times for a total of 52% (+)-**83**, <5% (+)-**82**, 7% RSM, 9:1 crude 2°:3° by ^{1}H NMR; cycle 1 (+)-**83** (60.1 mg, 0.2 mmol, 20%), (+)-**24** (3.9 mg, 0.013 mmol, 1%), RSM (194.7 mg, 0.69 mmol, 69%); cycle 2 (+)-**83** (38.8 mg, 0.13 mmol, 19%), RSM (130.4 mg, 0.46 mmol, 67%); cycle 3 (+)-**83** (26.2 mg, 0.088 mmol, 19%), RSM (86.9 mg, 0.31 mmol, 67%); cycle 4 (+)-**83** (15.4 mg, 0.052 mmol, 17%), RSM (56.8 mg, 0.2 mmol, 65%); cycle 5 (+)-**83** (9.1 mg, 0.031 mmol, 15%), RSM (34.5 mg, 0.12 mmol, 61%); cycle 6 (+)-**83** (6.0 mg, 0.02 mmol, 17%), RSM (20.7 mg, 0.073 mmol, 61%). Run 2: recycled five times for a total of 52% yield (+)-**83** <5% (+)-**82**, 8% RSM, 12:1 crude 2°:3° by ^{1}H NMR; cycle 1 (+)-**83** (57.5 mg, 0.19 mmol, 19%), (+)-**82** (3.8 mg, 0.013 mmol, 1%), RSM (192.8 mg, 0.68 mmol, 68%); cycle 2 (+)-**83** (34.3 mg, 0.12 mmol,

17%), RSM (134.3 mg, 0.48 mmol, 70%); cycle 3 (+)-**83** (28.4 mg, 0.096 mmol, 20%), RSM (88.1 mg, 0.31 mmol, 65%); cycle 4 (+)-**83** (15.6 mg, 0.053 mmol, 17%), RSM (59.5 mg, 0.21 mmol, 68%); cycle 5 (+)-**83** (11.3 mg, 0.038 mmol, 18%), RSM (37.3 mg, 0.13 mmol, 63%); cycle 6 (+)-**83** (5.8 mg, 0.02 mmol, 17%), RSM (22.7 mg, 0.073 mmol, 61%). Run 3: recycled five times for a total of 49% (+)-**83**, <5% (+)-**82**, 9% RSM, 12:1 crude 2°:3° by ^{1}H NMR; cycle 1 (+)-**83** (53.3 mg, 0.18 mmol, 18%), (+)-**82** (5.1 mg, 0.017 mmol, 2%), RSM (186.3 mg, 0.66 mmol, 66%); cycle 2 (+)-**83** (39.8 mg, 0.13 mmol, 20%), RSM (128.9 mg, 0.46 mmol, 69%); cycle 3 (+)-**83** (23.6 mg, 0.08 mmol, 17%), RSM (84.5 mg, 0.30 mmol, 65%); cycle 4 (+)-**83** (15.2 mg, 0.051 mmol, 17%), RSM (60.2 mg, 0.21 mmol, 70%); cycle 5 (+)-**83** (9.6 mg, 0.032 mmol, 15%), RSM (36.9 mg, 0.13 mmol, 62%); cycle 6 (+)-**83** (7.4 mg, 0.025 mmol, 19%), RSM (25.3 mg, 0.09 mmol, 69%). Average overall yield (+)-**83**: 51±2%. Average overall yield (+)-**82**: <5%. Average overall RSM: 8±1%. Average ratio 2°:3° oxidation: 11:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 3.47-3.38 (m, 1H), 2.62 (d, *J* = 9.5 Hz, 1H), 2.54-2.46 (m, 1H), 2.32 (app sextet, *J* = 6.5 Hz, 1H), 2.22-2.12 (m, 3H), 2.10-2.03 (m, 1H), 1.83 (td, *J* = 11.0, 7.0 Hz, 1H), 1.72-1.62 (m, 1H), 1.50 (s, 3H), 1.22 (d, *J* = 7.5 Hz, 3H), 1.34 (d, *J* = 6.5 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}O_6$ $[M+H]^+$: 297.1338, found 297.1346; $[\alpha]_D^{23}$ = +58.3° (c=0.6, $CHCl_3$). These spectral data match those reported in the literature.[86]



(+)-10β-hydroxy-arteminin (82). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (s, 1H), 3.35 (dq, *J* = 7.0, 5.5 Hz, 1H), 2.44 (ddd, *J* = 14.5, 13.5, 4.5 Hz, 1H), 2.10 (m, 1H), 2.01 (m, 1H), 1.86-1.72 (m, 4H), 1.66 (dd, *J* = 11.5, 7.0 Hz, 1H), 1.49-1.47 (m, 2H), 1.45 (s, 3H), 1.30 (s, 3H),

1.22 (d, J = 7.0 Hz, 3H); HRMS (ESI) *m/z* calc'd for $C_{15}H_{23}O_6$ $[M+H]^+$: 299.1495, found 299.1496. These spectral data match those reported in the literature.[58a]

Table 21. Catalyst Comparison for the Oxidation of (+)-Artemisinin (**46**)

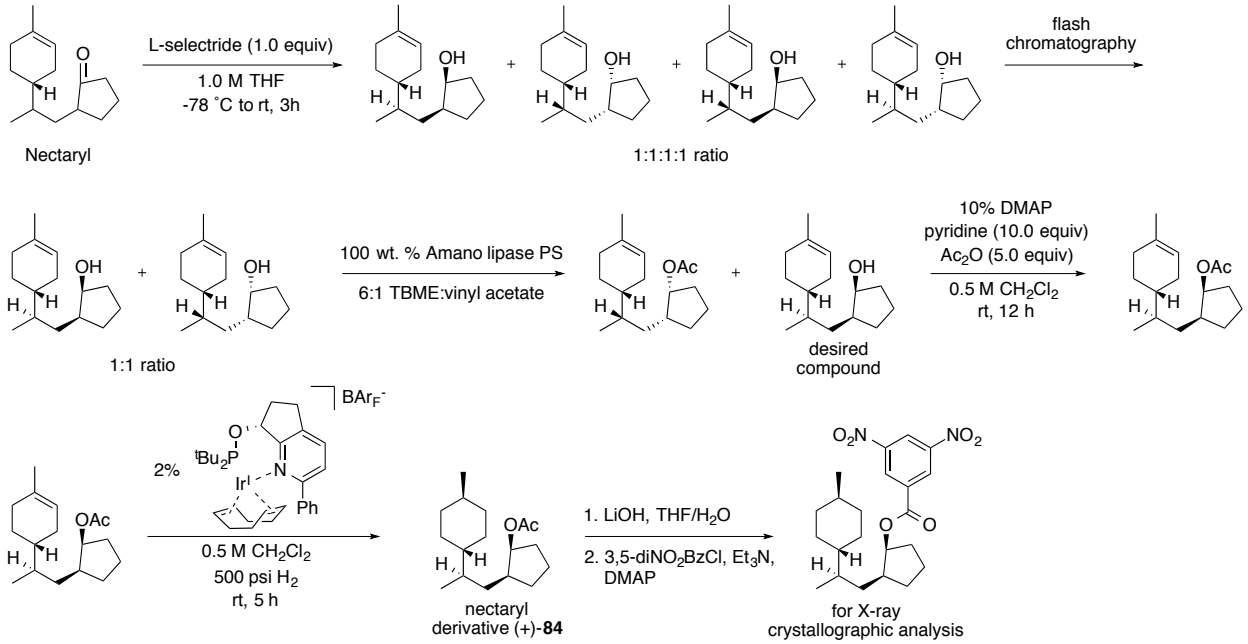
Catalyst	% (+)-**83**	% (+)-**82**	% RSM	2°:3°[b]
(*S,S*)-Fe(PDP) (**44**)[58a]	23[a]	54	8	1:2.3
(*R,R*)-Fe(PDP) (**44**)	10[a]	14	74	1:1.4
(*S,S*)-Fe(CF_3-PDP) (**45**)[c]	**52**[d]	**<5**	**8**	**11:1**
(*R,R*)-Fe(CF_3-PDP) (**45**)	11[a]	trace	65	9:1

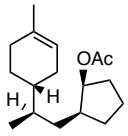
[a]Average of 2 runs at 0.5 mmol. Yields are of isolated material. [b]Crude ratio determined by ^{1}H NMR. [c]Starting material was recycled 5 times. [d]Average of 3 runs at 1.0 mmol.

Oxidation with (*R,R*)-Fe(CF_3-PDP) (**44**) according to Method A but using reduced loading of AcOH (2.9 mL, 3.0 mg, 0.05 mmol, 0.1 equiv). Purification by flash chromatography on silica (~75 mL) eluting with 10→30% EtOAc/hexane. Run 1: (+)-**83** (14.8 mg, 0.05 mmol, 10%), RSM (93.1 mg, 0.33 mmol, 66%). Run 2: (+)-**83** (15.1 mg, 0.051 mmol, 11%), RSM (90.5 mg, 0.32 mmol, 64%). Average yield (+)-**83**: 11%. Average RSM: 65%.

Oxidation of a Nectaryl Derivative.

Figure 28. Preperation of a Derivative of Nectaryl

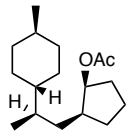




(+)-(1*S*,2*S*)-2-((*R*)-2-((*R*)-4-methylcyclohex-3-en-1-yl)propyl)cyclopentyl acetate.

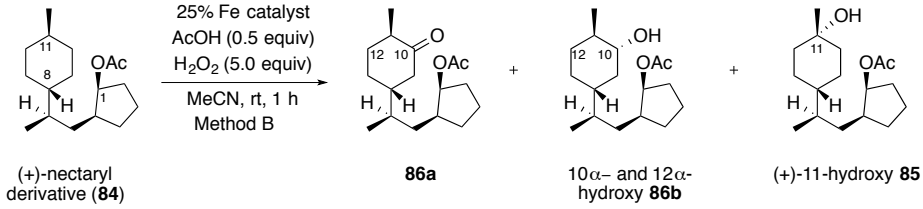
No precautions were taken to avoid air or moisture. (+)-(1*S*,2*S*)-2-((*R*)-2-((*R*)-4-methylcyclohex-3-en-1-yl)propyl)cyclopentanol (2.37 g, 10.6 mmol, 1.0 equiv, prepared according to the procedure of Gatti[87]) was dissolved in CH_2Cl_2 (20 mL, 0.5 M) in a 100 mL round bottomed flask containing a stir bar. Pyridine (8.6 mL, 8.38 g, 106.0 mmol, 10.0 equiv, Sigma-Aldrich), acetic anhydride (5 mL, 5.41 g, 53.0 mmol, 5.0 equiv, Fisher Scientific) and 4-dimethylaminopyridine (DMAP, 130 mg, 1.1 mmol, 10 mol %, Sigma-Aldrich) were added and the reaction was stirred 12 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was washed with 3M HCl (1x10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica (~250 mL) eluting with 5% EtOAc/hexanes afforded the title compound in quantitative

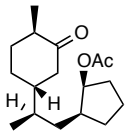
yield (2.79 g, 10.5 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 5.14 (t, *J* = 5.0 Hz, 1H), 2.01 (s, 3H), 1.96-1.84 (m, 5H), 1.79-1.64 (m, 4H), 1.62 (s, 3H), 1.62-1.50 (m, 3H), 1.44-1.30 (m, 3H), 1.22 (qd, *J* = 12.0, 6.0 Hz, 1H), 1.10 (td, *J* = 14.1, 8.9, 5.7 Hz, 1H), 0.84 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 134.0, 121.0, 77.1, 42.1, 38.6, 35.4, 32.9, 32.7, 30.8, 30.4, 29.0, 25.3, 23.4, 21.9, 21.3, 16.7; IR (film): 2960, 2916, 2875, 2837, 1738, 1643, 1435, 1373, 1246, 1018 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{28}O_2Na$ $[M+Na]^+$: 287.1987, found 287.1992; $[\alpha]_D^{25}$ = +103.9° (c=1.2, $CHCl_3$).

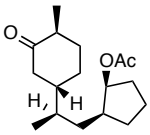


(+)-(1*S*,2*S*)-2-((*R*)-2-((1*r*,4*R*)-4-methylcyclohexyl)propyl)cyclopentyl acetate (84). According to the procedure of Pfaltz,[88] (+)-(1*S*,2*S*)-2-((*R*)-2-((*R*)-4-methylcyclohex-3-en-1-yl)propyl)cyclopentyl acetate was dissolved in CH_2Cl_2 (1.5 mL) in a 1 dram vial containing a stir bar. (+)-(*R*)-[1,5-Cycloocatdien-7-(2-phenyl-6,7-dihydro-5*H*-[1]pyridine)-di-(*tert*-butyl)-phosphinite-iridium(I)]-tetrakis-(3,5-bis(trifluoromethyl)-phenyl)-borate (9.0 mg, 0.006 mmol, 2 mol %) was added and the reaction was pressurized to 500 psi in a hydrogenation bomb while stirring. After 5 h, the pressure was released and the reaction was concentrated. GC of the crude showed 24:1 dr. Flash chromatography on silica (~75 mL) eluting with 2% EtOAc/hexanes afforded the title compound in quantitative yield (79.9 mg, 0.3 mmol) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (t, *J* = 5.0 Hz, 1H), 2.01 (s, 3H), 1.87-1.82 (m, 2H), 1.80-1.63 (m, 5H), 1.60-1.44 (m, 4H), 1.44-1.35 (m, 1H), 1.30-1.20 (m, 2H), 1.10-0.94 (m, 4H), 0.92-0.83 (m, 2H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.81 (s, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 77.2, 42.6, 42.2, 36.1, 35.7, 35.6, 33.2, 33.0, 32.7, 30.4, 30.1, 28.6, 22.7, 22.0, 21.3, 16.8; IR (film): 2949, 2918, 2868, 2854, 1738, 1645, 1448, 1373, 1246, 1018 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{30}O_2Na$ $[M+Na]^+$: 289.2144, found 289.2152; $[\alpha]_D^{23}$ = +59.9° (c=1.2, $CHCl_3$).

The stereochemistry of this compound was assigned based on the stereochemical model proposed by Andersson[89] and confirmed by X-ray crystallographic analysis of the 3,5-dinitrobenzoate ester. To 20 mg of the solid 3,5-dinitrobenzoate ester in a 1 dram vial was added 1 mL hexane, 1 drop of PhH and the minimum amount of acetone needed to completely solubilize the compound. The vial was loosely capped and allowed so slowly evaporate to afford colorless needles suitable for single crystal X-ray crystallographic analysis after 1-2 days.





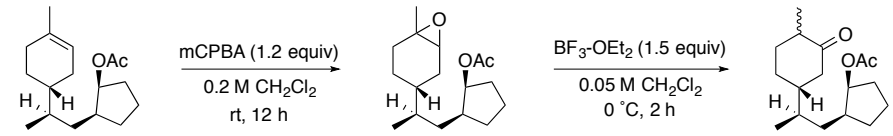


(1*S*,2*S*)-2-((*R*)-2-((1*R*,4*R*)-4-methyl-3-oxocyclohexyl)propyl)cyclopentyl acetate and (1*S*,2*S*)-2-((*R*)-2-((1*S*,4*S*)-4-methyl-3-oxocyclohexyl)propyl)cyclopentyl acetate (86a). (+)-(1*S*,2*S*)-2-((*R*)-2-((1*r*,4*R*)-4-methylcyclohexyl)propyl)cyclopentyl acetate (**84**) (79.9 mg, 0.3 mmol, 1.0 equiv) in MeCN (0.5 mL) was reacted with (*S,S*)-Fe(CF_3-PDP) (**45**) according to Method B. Purification by flash chromatography on silica (~75 mL) eluting with 10→30% EtOAc/hexane. Overlapping peaks in the crude ^{1}H NMR and GC made accurate 2˚:3˚ ratio determination impossible so isolated ratios are reported. Run 1: recycled one time for a total of 40% **86a**, 15% **86b**, 10% (+)-**85**, 10% RSM, 5.4:1 2˚:3˚ oxidation, 55% total 2˚ oxidation; cycle 1 **86a** (27.1 mg, 0.097 mmol, 32%), **86b** (8.5 mg, 0.03 mmol, 10%), (+)-**85** (5.7 mg, 0.02 mmol, 7%), RSM (26.0 mg, 0.1 mmol, 33%); cycle 2 **86a** (6.4 mg, 0.023 mmol, 23%), **86b** (4.1 mg, 0.014 mmol, 14%), (+)-**85** (2.7 mg, 0.01 mmol, 10%), RSM (7.6 mg, 0.029 mmol, 29%). Run 2: recycled one time for a total of 36% **86a**, 12% **86b**, 9% (+)-**85**, 7% RSM, 5.6:1 2˚:3˚ oxidation; cycle 1 **86a** (25.2 mg, 0.09 mmol, 30%), **86b**

(7.6 mg, 0.027 mmol, 9%), (+)-**85** (5.4 mg, 0.02 mmol, 6%), RSM (23.5 mg, 0.088 mmol, 29%); cycle 2 **86a** (4.7 mg, 0.017 mmol, 19%), **86b** (3.3 mg, 0.01 mmol, 14%), (+)-**85** (2.2 mg, 0.008 mmol, 9%), RSM (5.9 mg, 0.02 mmol, 22%). Run 3: recycled one time for a total of 65% **86a**, 19% **86b**, 11% (+)-**85**, 8% RSM, 5.8:1 2˚:3˚ oxidation; cycle 1 **86a** (29.6 mg, 0.11 mmol, 35%), **86b** (11.8 mg, 0.042 mmol, 14%), (+)-**85** (6.8 mg, 0.024 mmol, 8%), RSM (24.3 mg, 0.091 mmol, 30%); cycle 2 **86a** (7.7 mg, 0.027 mmol, 30%), **86b** (4.0 mg, 0.014 mmol, 15%), (+)-**85** (2.5 mg, 0.009 mmol, 10%), RSM (6.1 mg, 0.023 mmol, 25%). Average overall yield **86a**: 51±5%. Average overall yield **86b**: 11±3%. Average overall yield 2˚ oxidation: 56%. Average overall yield (+)-**85**: 9±1%. Average overall RSM: 8±2%. Average ratio 2˚:3˚ oxidation: 5.6±0.2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11, (q, J = 5.0 Hz, 1H), 2.34-2.22 (m, 2H), 2.50-2.01 (m, 2H), 1.99 and 1.98 (s, 3H), 1.90-1.80 (m, 2H), 1.77-1.67 (m, 3H), 1.67-1.34 (m, 7H), 1.31-1.22 (m, 1H), 1,11-1.04 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.87 and 0.85 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 213.3, 170.6, 76.9, 45.6, 45.2, 45.1, 44.1, 41.9, 41.8, 35.8, 35.7, 35.0, 33.1, 32.8, 32.6, 30.2, 29.2, 27.6; IR (film): 2962, 2931, 2872, 1734, 1712, 1452, 1373, 1317, 1248, 1167, 1126, 1020, 972, 941, 887 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{29}O_3$ $[M+H]^+$: 281.2117, found 281.2126.

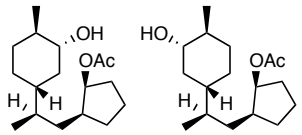
The site of oxidation was confirmed by independent preparation of an authentic standard (see below) and comparison of ^{1}H NMR, ^{13}C NMR, GC and mass spectrometry data.

Figure 29. Assigning the Identity of Products **86a**



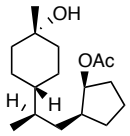
known compound

10-oxo **86a**



(1*S*,2*S*)-2-((*R*)-2-((1*R*,3*R*,4*R*)-3-hydroxy-4-methylcyclohexyl)propyl)cyclopentyl acetate and (1*S*,2*S*)-2-((*R*)-2-((1*S*,3*S*,4*S*)-3-hydroxy-4-methylcyclohexyl)propyl)cyclopentyl acetate (86b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (app t, *J* = 4.5 Hz, 1H), 3.10 (td, *J* = 10.5, 4.5 Hz, 1H), 2.02 (s, 3H), 1.93-1.84 (m, 2H), 1.81-1.67 (m, 5H), 1.61-1.46 (m, 4H), 1.43-1.19 (m, 6H), 1.05-1.13 (m, 1H), 1.02-0.96 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 77.2, 76.7, 42.1, 41.7, 40.3, 37.7, 35.7, 33.3 (2C), 32.7, 30.4, 29.4, 22.0, 21.3, 18.3, 16.6; IR (film): 3421, 2924, 2872, 1736, 1452, 1375, 1250, 1165, 1147, 1124, 1034, 1020, 974, 939, 841 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{31}O_3$ $[M+H]^+$: 283.2273, found 283.2275.

The site of oxidation was determined by oxidizing products **86b** with DMP to afford products **86a** as determined by matching their ^{1}H NMR, ^{13}C NMR, GC and mass spectrometry data. The stereochemistry of the hydroxyl group was assigned based on the coupling constants and splitting pattern of the C10 proton at 3.10 ppm, which is an axial proton coupling to two other axial protons (*J* = 10.5 Hz) and 1 equatorial proton (*J* = 4.5 Hz).



(+)-(1*S*,2*S*)-2-((*R*)-2-((1*s*,4*S*)-4-hydroxy-4-methylcyclohexyl)propyl)cyclopentyl acetate (85). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (app t, *J* = 4.0 Hz, 1H), 2.01 (s, 3H), 1.93-1.83 (m, 2H), 1.79-1.49 (m, 6H), 1.45-1.29 (m, 8H), 1.26-1.20 (m, 1H), 1.19 (s, 3H), 1.12-1.05 (m, 2H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 77.1, 69.3, 42.2, 42.1, 39.0, 38.9, 35.8, 33.0, 32.7, 31.4, 30.4, 25.1, 23.9, 21.9, 21.3, 16.8; IR (film): 3437, 2956, 2926, 2870,

1736, 1720, 1446, 1373, 1248, 1167, 1124, 1020, 973, 941, 910 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{30}O_3Na$ $[M+Na]^+$: 305.2093, found 305.2096; $[\alpha]_D^{23}$ = +46.9° (c=1.0, $CHCl_3$).

The site of oxidation of (+)-**85** was assigned based on ^1H NMR. The two methyl groups in the starting material show up as doublets whereas in the product they appear as a singlet and a doublet. This indicates oxidation at either the C7 or C11 tertiary sites. A 1H-1H TOCSY experiment with 300ms mix time allows the C1 proton a-to the acetate to see coupling to the C7 methyl group. These two protons in the same spin system is only possible if there is a C7 proton (i.e. an unoxidized tertiary site).

Table 22. Catalyst Comparison for the Oxidation of (+)-Nectaryl Derivative (**84**)

Catalyst	% **86a**[a]	% **86b**	% 2° ox.	% (+)-**85**	% RSM	2°:3°[b]
(*S,S*)-Fe(PDP) (**44**)	24	0	24	30	15	1:1.3
(*R,R*)-Fe(PDP) (**44**)	14[c]	0	14	19	15	1:1.4
(*S,S*)-Fe(CF_3-PDP) (**45**)[d]	**41**	**16**	**57**	**9**	**8**	**6:1**
(*R,R*)-Fe(CF_3-PDP) (**45**)	15[c]	9	24	6	33	4:1

[a]Average of 3 runs at 0.3 mmol unless otherwise noted. Yields are of isolated material. [b]Isolated ratio. [c]Average of 2 runs at 0.3 mmol. [d]Starting material was recycled 1 time.

Oxidation with (*S,S*)-Fe(PDP) (**44**) according to Method B. Run 1: **86a** (20.4 mg, 0.072 mmol, 24%), (+)-**85** (23.9 mg, 0.085 mmol, 28%), RSM (10.8 mg, 0.041 mmol, 14%), 1:1.2 2°:3°. Run 2: **86a** (18.6 mg, 0.066 mmol, 22%), (+)-**85** (25.4 mg, 0.09 mmol, 30%), RSM (10.2 mg, 0.038 mmol, 13%) 1:1.4 2°:3°. Run 3: **86a** (21.2 mg, 0.075 mmol, 25%), (+)-**85** (27.5 mg, 0.097 mmol, 32%), RSM (14.5 mg, 0.054 mmol, 18%), 1:1.3 2°:3°. Average yield **86a**: 23%. Average yield 2° oxidation: 23±2%. Average yield (+)-**85**: 29±2%. Average RSM: 14±3%. Average ratio 2°:3° oxidation: 1:1.3±0.1.

Oxidation with (*R,R*)-Fe(PDP) (**44**) according to Method B. Run 1: **86a** (12.0 mg, 0.042 mmol, 14%), (+)-**85** (18.0 mg, 0.063 mmol, 21%), RSM (11.7 mg, 0.045 mmol, 15%). Run 2: **86a** (10.9 mg, 0.039 mmol, 13%), (+)-**85** (14.6 mg, 0.051 mmol, 17%), RSM (12.8 mg, 0.046

mmol, 15%). Average yield **86a**: 14%. Average yield (+)-**85**: 19%. Average RSM: 15%. Average ratio 2˚:3˚ oxidation: 1:1.4.

Oxidation with (*R,R*)- Fe(CF_3-PDP) (**45**) according to Method B. Run 1: **86a** (11.8 mg, 0.042 mmol, 14%), **86b** (7.6 mg, 0.026 mmol, 9%), (+)-**85** (4.4 mg, 0.016 mmol, 5%), RSM (27.9 mg, 0.11 mmol, 35%). Run 2: **86a** (12.4 mg, 0.044 mmol, 15%), **86b** (9.9 mg, 0.035 mmol, 9%), (+)-**85** (5.8 mg, 0.021 mmol, 6%), RSM (23.8 mg, 0.09 mmol, 30%). Average yield **86a**: 15%. Average yield **86b**: 9%. Average yield 2˚ oxidation: 24%. Average yield (+)-**85**: 6%. Average RSM: 33%. Average ratio 2˚:3˚ oxidation: 4:1.

3.4.9 Validating the Predictive Power of the Structure-Based Catalyst Reactivity Models

Parameterized Site Filters for Complex Molecules.

Table 23. Parameterized Site Filter for Determining Likely Sites of Oxidation for (-)-Triacetoxy Tricalysiolide B (**79**)

Site (H_{eq} atom)	Electronic Parameter (E)	Steric/Stereoelectronic Parameter (S)
9	0.201	15.4
11	**0.206**	**9.1**
7	**0.208**	**8.6**
1	0.211	9.5
14	0.212	11.3
6	**0.213**	**5.6**
12	**0.215**	**7.8**
5	0.220	15.7
13	0.223	11.4
15	0.226	12.5
2	0.229	8.4
red lower limit	0.201 (lowest E)	5.6 (lowest S)
purple lower limit	0.211 =0.201+5%	7.8 =5.6+40%
blue lower limit	0.222 =0.211+5%	10.9 =7.8+40%

Table 24. Parameterized Site Filter for Determining Likely Sites of Oxidation for (+)-Artemisinin (**46**)

Site (H_{eq} atom)	Electronic Parameter (E)	Steric/ Stereoelectronic Parameter (S)
10	**0.186**	**10.6**
5	0.187	14.7
9	**0.206**	**6.0**
1	0.210	13.3
2	0.212	6.9
3	0.213	8.6
8	0.216	6.9
7	0.216	12.8
11	0.253	9.1
red lower limit	0.186 (lowest E)	6.0 (lowest S)
purple lower limit	0.195 =0.186+5%	8.4 =6.0+40%
blue lower limit	0.206 =0.195+5%	11.8 =8.4+40%

Table 25. Parameterized Site Filter for Determining Likely Sites of Oxidation for (+)-Nectaryl derivative (**84**)

Site (H_{eq} atom)	Electronic Parameter (E)	Steric/ Stereoelectronic Parameter (S)
11	**0.181**	**9.3**
8	**0.187**	**9.8**
7	**0.189**	**9.6**
10,12	**0.198**	**6.0**
3	**0.198**	**6.5**
9,13	**0.199**	**6.9**
4	0.200	6.9
5	0.201	9.7
6	0.204	9.1
1	0.207	8.7
2	0.211	6.0
red lower limit	0.181 (lowest E)	6.0 (lowest S)
purple lower limit	0.190 =0.181+5%	8.4 =6.0+40%
blue lower limit	0.199 =0.190+5%	11.8 =8.4+40%

Structure-Based Catalyst Reactivity Model Predictions for Likely Sites of Oxidation in Other Substrates in this Report. All calculated and observed $\Delta\Delta G^{\ddagger}$'s are corrected for statistics. For example if there are two equivalent sites in a molecule because of a plane of symmetry, there is twice the likelihood that the site will be oxidized in relation to a site with only one possible outcome. So for example, if we observe a 4:1 ratio for oxidation favoring that site, after correcting for statistics, it is recorded for the purpose of the model as a 2:1 selectivity, $\Delta\Delta G^{\ddagger}$=0.41 kcal/mol. Similarly, if we calculate $\Delta\Delta G^{\ddagger}$=0.50 kcal/mol for that site (2.3:1 selectivity), because the equations report data already corrected for statistics, the calculations would predict that we *observe* a ~5:1 ratio. Substrate **68** exemplifies this correction. There is a plane of symmetry running through C4 and C1 making C3 and C5 equivalent.

Table 26. Calculated $\Delta\Delta G^{\ddagger}$ for All Likely to be Oxidized Sites for Fe(PDP) (**44**)

Substrate	Sites Compared (*a*:*b*)	Calc'd $\Delta\Delta G^{\ddagger}$ (kcal/mol)*	Observed $\Delta\Delta G^{\ddagger}$ (kcal/mol)‡	Obs-calc'd (kcal/mol)
61	C1/6:C2/5	0.45	0.16	-0.29
	C1/6:C3/4	0.34	0.02	-0.32
68	C4:C3/5	1.00	0.82	-0.18
(+)-**74**	C2:C3	0.44	0.20	-0.24
	C2:C1	0.80	0.90	0.10
(-)-**79**	C6:C7	-0.06	0.24	0.30
	C6:C11	-0.20	N/A	N/A
	C6:C12	0.84	N/A	N/A
(+)-**46**	C10:C9	0.18	0.49	0.31

*Output $\Delta\Delta G^{\ddagger}$ has been designed into the equation to be corrected for statistics (i.e. two possible sites C3/5 versus one C4 in **68**). †Observed $\Delta\Delta G^{\ddagger}$ corrected for statistics.

The calculated and observed values match within a reasonable margin of error for all sites where the data can be compared.

Table 27. Calculated $\Delta\Delta G^{\ddagger}$ for All Likely to be Oxidized Sites in the Complex Molecules for Fe(CF_3-PDP) (**45**)

Substrate	Sites Compared (*a*:*b*)	Calc'd $\Delta\Delta G^{\ddagger}$ (kcal/mol)*	Observed $\Delta\Delta G^{\ddagger}$ (kcal/mol) [‡]	Obs-calc'd (kcal/mol)
61	C1/6:C2/5	-0.66	-0.77	-0.12
	C1/6:C3/4	-0.87	-1.05	-0.18
68	C4:C3/5	0.10	0	-0.10
(+)-**74**	C2:C3	0.77	0.56	-0.20
	C2:C1	1.03	1.03	0.0
(-)-**79**	C6:C7	1.40	1.56	0.16
	C6:C11	2.25	N/A	N/A
	C6:C12	1.01	N/A	N/A
(+)-**46**	C10:C9	-1.63	-1.49	0.14

*Output $\Delta\Delta G^{\ddagger}$ has been designed into the equation to be corrected for statistics (i.e. two possible sites C3/5 versus one C4 in **68**). [†]Observed $\Delta\Delta G^{\ddagger}$ corrected for statistics.

The calculated and observed values match within a reasonable margin of error for all sites where the data can be compared. For sites C11 and C12 in (-)-**79**, the model accurately predicts that C11 will not be oxidized; however, C12 seems to be an outlier because of it is predicted to be more reactive than C7 (although still a minor product compared to C6, calc'd C6:C12 5.6:1).

Validating the Structure-Based Catalyst Reactivity Models on Substrates Whose Data was *Not* Used to Create It.

Table 28. E and S Parameters Calculated for Substrates (+)-**58** and (+)-**84**

Substrate	Site	E*	S*	E_n†	S_n†
(+)-**58**	2	0.214	8.7		
	3	0.203	6.4	0.2114	-0.5240
	4	0.185	9.2	-1.1419	0.5092
	5	0.189	6.0	-0.8277	-0.6974
(+)-**84**	1	0.207	8.7		
	2	0.211	6		
	3	0.198	6.5	-0.1636	-0.5018
	4	0.200	6.9		
	5	0.201	9.7		
	6	0.204	9.1		
	7	0.189	9.6	-0.8595	0.6642
	8	0.187	9.8	-0.9986	0.7195
	9/13	0.199	6.9	-0.0999	-0.3469
	10/12	0.198	6	-0.2114	-0.7690
	11	0.181	9.3	-1.4337	0.5461

*Coloring based on the parameterized site filter. Only red-red or red-purple sites considered. †Normalized parameters only reported for likely to be oxidized sites.

Table 29. Calculated Selectivities for Substrates (+)-**58** and (+)-**84** for Oxidation with Fe(PDP) (**44**)

Substrate	Sites Compared (ratio *a*:*b*)	ΔE_{ab}	$\Delta\Delta S_{ab}$	Calc'd $\Delta\Delta G^{‡}$ (kcal/mol)*	Observed $\Delta\Delta G^{‡}$ (kcal/mol)†	obs-calc'd (kcal/mol)
(+)-**58**	5:4	0.3143	1.2066	0.08	0.24	0.16
	5:3	1.0391	0.1734	1.68	N/A	N/A
(+)-**84**	11:10/12	1.2251	-1.2251	0.65	0.49	-0.16
	11:9/13	1.3338	-0.8930	1.26	N/A	N/A
	11:8	0.1734	0.7422	0.74	N/A	N/A
	11:7	0.5742	0.1181	0.91	N/A	N/A
	11:3	1.27	-1.048	0.93	N/A	N/A

*Output $\Delta\Delta G^{‡}$ has been designed into the equation to be corrected for statistics (i.e. two possible sites 10/12 versus one C11 in (+)-**84**). †Observed $\Delta\Delta G^{‡}$ corrected for statistics.

Table 30. Calculated Selectivities for Substrates (+)-**58** and (+)-**84** for Oxidation with Fe(CF_3-PDP) (**45**)

Substrate	Sites Compared (ratio *a*:*b*)	Calc'd $\Delta\Delta G^{\ddagger}$ (kcal/mol)*	Observed $\Delta\Delta G^{\ddagger}$ (kcal/mol)†	obs-calc'd (kcal/mol)
(+)-**58**	5:4	1.21	0.83	-0.38
	5:3	3.84	N/A	N/A
(+)-**84**	11:10/12	-0.28	-0.53	-0.25
	11:9/13	1.14	N/A	N/A
	11:8	0.35	N/A	N/A
	11:7	0.78	N/A	N/A
	11:3	0.36	N/A	N/A

*Output $\Delta\Delta G^{\ddagger}$ has been designed into the equation to be corrected for statistics (i.e. two possible sites 10/12 versus one C11 in (+)-**84**). †Observed$\Delta\Delta G^{\ddagger}$ corrected for statistics.

Using the equation requires setting some site (*a*) as the reference site to which the selectivity of all other sites (*b*) is compared. For new substrates, for which the major site of oxidation is not known, either the most electron rich or least sterically hindered site of sites likely to be oxidized (from the narrowing filter, see page S20) should be selected based on the calculated E and S parameters. For (+)-**58**, the major site was known for catalyst **1**, so C5 was set as the reference site, while for (+)-**84** the most electron rich site was likely to be a major site of oxidation with catalyst **44**, so C11 was selected as the reference site.

The calculations accurately predict the site-selectivity of the reactions, without the need for prior experimental determination. For (+)-**58** the C5:C4 2˚:3˚ ratio is predicted within a small error range (0.16 kcal/mol) for catalyst **44** and (0.38 kcal/mol) for catalyst **45**. Notably, the other likely site of oxidation C3 (as determined by applying our narrowing filter) is predicted to be very unreactive (17 and 600 times less reactive than C5), consistent with the experimental observation that no C3 oxidation is observed. For (+)-**84**, other sites, particularly C7 are predicted to be somewhat reactive compared to C11 for Fe(PDP) **44** and to a lesser extent Fe(CF_3-PDP) **45**. The reduced mass balance of the reaction of (+)-**84** with both catalysts (~70%) are indicative of oxidation at one or more other sites. The GC traces of these reactions confirms

the presence of some minor other products. Although sufficient quantities of these products are not produced to isolate and identify them, we suspect that, as predicted by the equation, small amount of other oxidations are occurring. Importantly, oxidation of (+)-**84**, despite many other likely sites of oxidation, provides preparative yields (52%) of C10/12 oxidation.

3.4.10 X-ray Crystal Structure Data

X-ray Crystal Structure Data for [(*R,R*)-Fe(CF$_3$-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (45).

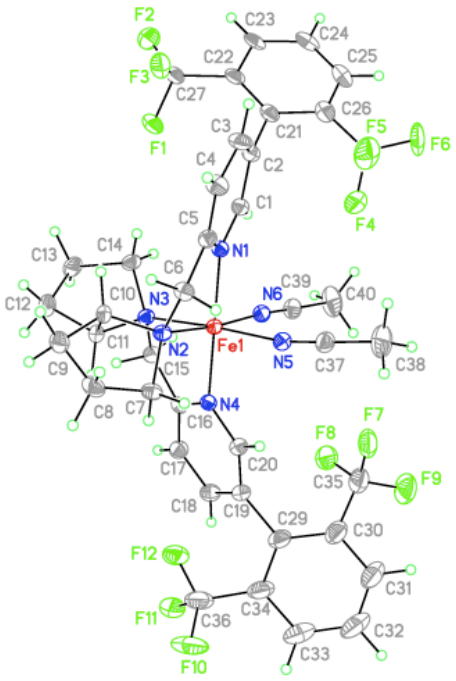


Table 31. Crystal data and structure refinement for bm06uas.

Identification code	bm06uas	
Empirical formula	C42 H39 F24 Fe N7 Sb2	
Formula weight	1397.15	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.7230(18) Å	a= 90°.
	b = 17.163(2) Å	b= 115.0380(10)°.
	c = 12.9667(18) Å	g = 90°.
Volume	2565.3(6) Å^3	

Table 31. Crystal data and structure refinement for bm06uas (continued).

Z	2
Density (calculated)	1.809 Mg/m^3
Absorption coefficient	1.451 mm^{-1}
F(000)	1368
Crystal size	0.505 x 0.388 x 0.114 mm^3
Theta range for data collection	1.73 to 25.36°.
Index ranges	-15<=h<=15, -20<=k<=20, -15<=l<=15
Reflections collected	28092
Independent reflections	9387 [R(int) = 0.0371]
Completeness to theta = 25.36°	99.9 %
Absorption correction	Integration
Max. and min. transmission	0.8829 and 0.6299
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9387 / 3348 / 1099
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0229, wR2 = 0.0551
R indices (all data)	R1 = 0.0241, wR2 = 0.0558
Absolute structure parameter	0.007(10)
Largest diff. peak and hole	0.322 and -0.394 $e.Å^{-3}$

X-ray Crystal Structure Data for the 4-Bromobenzoate ester of (-)-79.

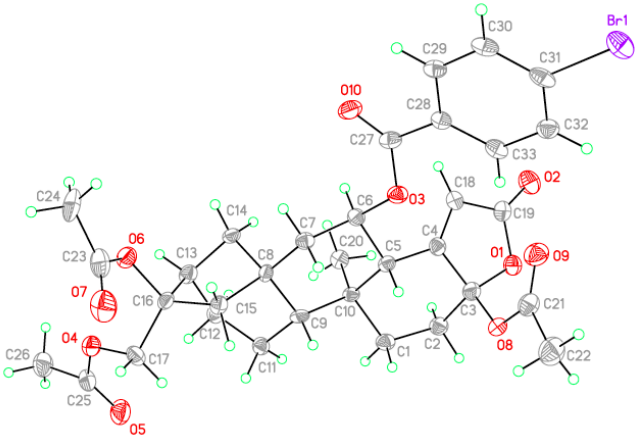


Table 32. Crystal data and structure refinement for bm64uas.

Identification code	bm64uas
Empirical formula	C75 H92 Br2 O23
Formula weight	1521.31
Temperature	183(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1

Table 32. Crystal data and structure refinement for bm64uas (continued).

Unit cell dimensions	a = 9.516(3) Å	a= 92.273(4)°.
	b = 14.050(4) Å	b= 104.028(4)°.
	c = 14.830(4) Å	g = 101.858(4)°.
Volume	1874.1(9) $Å^3$	
Z	1	
Density (calculated)	1.348 Mg/m^3	
Absorption coefficient	1.156 mm^{-1}	
F(000)	796	
Crystal size	0.347 x 0.106 x 0.066 mm^3	
Theta range for data collection	1.42 to 25.32°.	
Index ranges	-10<=h<=11, -16<=k<=16, -17<=l<=16	
Reflections collected	15375	
Independent reflections	11581 [R(int) = 0.0368]	
Completeness to theta = 25.32°	98.9 %	
Absorption correction	Integration	
Max. and min. transmission	0.9441 and 0.7795	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11581 / 252 / 1013	
Goodness-of-fit on F^2	0.975	
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.0895	
R indices (all data)	R1 = 0.0797, wR2 = 0.1027	
Absolute structure parameter	0.009(6)	
Largest diff. peak and hole	0.260 and -0.377 $e.Å^{-3}$	

X-ray Crystal Structure Data for the 3,5-Dinitrobenzoate ester of (+)-84.

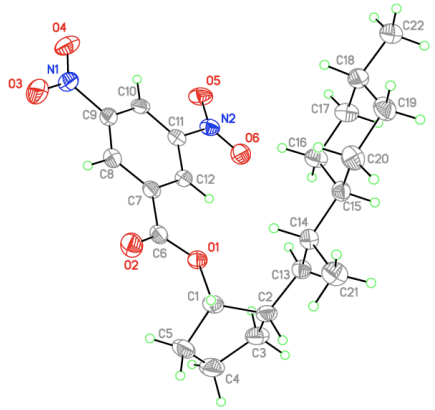


Table 33. Crystal data and structure refinement for bc89uas.

Identification code	bc89uas
Empirical formula	C22 H30 N2 O6
Formula weight	418.48
Temperature	193(2) K
Wavelength	1.54178 Å

Table 33. Crystal data and structure refinement for bc89uas (continued).

Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.8498(3) Å	a= 90°.
	b = 5.9404(2) Å	b= 92.249(2)°.
	c = 18.9767(7) Å	g = 90°.
Volume	1109.50(6) $Å^3$	
Z	2	
Density (calculated)	1.253 Mg/m^3	
Absorption coefficient	0.751 mm^{-1}	
F(000)	448	
Crystal size	0.488 x 0.159 x 0.056 mm^3	
Theta range for data collection	2.33 to 67.56°.	
Index ranges	-11<=h<=10, -6<=k<=7, -22<=l<=22	
Reflections collected	11408	
Independent reflections	3655 [R(int) = 0.0387]	
Completeness to theta = 67.56°	98.2 %	
Absorption correction	Integration	
Max. and min. transmission	0.9614 and 0.7269	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3655 / 9 / 284	
Goodness-of-fit on F^2	1.082	
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 = 0.0999	
R indices (all data)	R1 = 0.0455, wR2 = 0.1041	
Absolute structure parameter	-0.2(2)	
Largest diff. peak and hole	0.127 and -0.150 $e.Å^{-3}$	

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