I. BIOMIMETIC OXIDATIONS USING NON-HEME IRON CATALYSIS. II. PALLADIUM- AND HYPERVALENT IODINE-CATALYZED TANDEM WACKER-DEHYDROGENATION OF TERMINAL OLEFINS

BY

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DISSERTATION

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ABSTRACT

I. BIOMIMETIC OXIDATIONS USING NON-HEME IRON CATALYSIS

Nature’s oxidation catalysts promote a remarkable variety of highly selective oxidation reactions of alkanes, olefins, and arenes. Inspired by this diversity of reactivity, the chemical community has long sought to replicate enzymatic reactivity within the synthetic laboratory, both for the purposes of better understanding enzymatic reaction mechanisms and to advance the frontier of chemical synthesis. In the first part of this thesis, a series of projects exploring novel oxidation reactivity and mechanism, as well as several unique synthetic applications, will be described.

First, a comprehensive study of the use of carboxylic acids as directing groups for non-heme iron catalyzed C—H hydroxylation will be described. Examination of substrates for C—H hydroxylation that featured unfavorable electronic, steric, or stereoelectronic effects demonstrated that carboxylic acids were capable of overcoming these substrate biases during hydroxylation. The developed methodology was utilized to install the C2 oxidation on a taxane derivative, demonstrating the first example of such an oxidation using a small molecule catalyst or reagent.

Second, the unexpected discovery of ‘double oxidation’ products resulting from non-heme iron catalyzed C—H hydroxylation of carboxylic acid-containing substrates will be described. The mechanism accounting for their formation was studied in detail and suggested operation of mixed desaturase/oxygenase reactivity, only previously observed within natural systems. These studies suggested that, in analogy to nature, a short-lived substrate-derived carbon-centered radical either undergoes hydroxyl rebound to provide for C—H hydroxylation or further oxidation to an olefin intermediate en route to ‘double oxidation’.

Third, oxidation of the characteristic furan ring of a cafestol derivative using a non-heme iron catalyst allowed the rapid synthesis of tricalysiolide B, a natural product isolated in 2006 from Japanese tree bark. This result suggested that non-heme iron oxygenases were responsible for metabolizing cafestol to tricalysiolide B within *tricalysia dubia*, and demonstrated how non-heme iron catalysis can be used to rapidly test biosynthetic proposals.

II. PALLADIUM AND HYPERVALENT IODINE-CATALYZED TANDEM WACKER-DEHYDROGENATION OF TERMINAL OLEFINS

Catalytic C—H functionalization reactions promise to increase synthetic efficiency by enabling the direct installation of useful functionality onto traditionally unreactive hydrocarbon frameworks. The White group has pioneered a toolbox of synthetically useful palladium-catalyzed allylic C—H functionalization reactions of terminal olefins, including C—O, C—N, and C—C bond forming reactions. This section will describe the discovery and development of a palladium/hypervalent iodine-catalyzed
tandem Wacker-dehydrogenation reaction, allowing direct access to linear α,β-unsaturated ketones from readily available terminal olefins.
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Chapter 1

**Carboxylic Acids as Directing Groups for Non-heme Iron-Catalyzed C—H Hydroxylations**

1.1 Introduction

The discovery and development of general, selective C—H functionalization reactions has expanded rapidly in the past decade. Perhaps the greatest impediment to the successful implementation of catalytic C—H functionalization reactions is the selectivity challenge. In particular, due to the low reactivity of unactivated C—H bonds under common reaction conditions and the subtle differences between each of the C—H bonds within a substrate, however, few reports describe methods that exhibit useful selectivity for aliphatic sites. A common solution to these challenges is the use of chelating functional groups that direct transition metal catalysts to the desired site of oxidation. For example, C—H oxidation reactions using palladium(II) catalysis often rely upon metallacycle formation following C—H cleavage, and subsequent oxidation with a wide variety of reagents allows catalytic C-O, C-N, and C-X (X = Cl, Br, I, or F) coupling. An alternative to direct transition metal C—H insertion, with concomitant formation of an organometallic intermediate, is reaction of the C—H bond with a ligand on the metal, a strategy exemplified by Rh(II)-catalyzed carbene and nitrene insertions. In this case, there is relatively little direct interaction between the C—H bond and the metal. Instead, the metal catalyzes decomposition of a

![Figure 1.1](image-url)

**Figure 1.1**

**HEME**

**NON-HEME**

**C-H Oxidations using Fe(PDP)**

I. electronic

II. steric

III. stereoelectronic

IV. directed

Fe(S,S-PDP) 1

EWG

H

R

R

H

R

H

H

H

H

H

H

H

H

H

H

H

H

H
primary oxidant to generate a reactive carbene or nitrene ligand in close proximity to the targeted C—H bond. While this approach has enabled the development of an impressive toolbox of synthetically useful directed C—H alkylation and amination reactions, and featured prominently in complex molecule synthesis, an analogous general approach exploiting high valent metal-oxo intermediates for directed C—H hydroxylation has yet to be reported. Notably, while the active oxidant is generated directly on the substrate in the case of Rh-catalyzed carbene and nitrene insertions, a similar approach cannot be applied for reactions proceeding through terminal oxo intermediates. Historically, the study of oxidative heme catalysis enabled the discovery of the first biomimetic alkane and olefin oxidation reactions proceeding through terminal oxo intermediates. Due to the characteristic geometry of the metal-bound heme ligand (two open axial coordination sites, situated trans), it is easy to understand why no general directing heme ligand effect has been discovered using these ligands. Any potential ligand capable of coordinating to the iron oxo intermediate would be forced into an axial position situated 180° from the reactive oxo intermediate, thereby limiting the likelihood of producing a general directing group effect.

Several years ago, the White group reported a non-heme iron(II) catalyst Fe(PDP) that uses H₂O₂ to effect predictably site-selective aliphatic C—H oxidations of 2° and 3° sites. In the course of these studies, the electronic, steric, and stereoelectronic guidelines governing site-selectivity in intermolecular C—H oxidations were delineated. In summary, the electrophilic, sterically hindered oxidant generated from Fe(PDP) and H₂O₂ selects for electron-rich, sterically accessible C—H bonds. Additionally, stereoelectronic effects can engender control of site selectivity in cases where electronic and steric effects do not dominate. Interestingly, we found that acetic acid (AcOH) was an important additive for increasing reactivity and hypothesized that its primary role was as a ligand for the non-heme iron catalyst. In support of this, we found that carboxylic acids demonstrated a pronounced directing effect on the site of C—H oxidation for a small series of simple substrates and enabled a highly selective lactone-forming oxidation of a gibberelic acid derivative. Importantly, in direct contrast to heme-based oxidation catalysts, we realized that tetracoordinate non-heme ligands, with two open cis coordination sites, have the potential for supporting both a terminal oxo and a coordinating directing group in close proximity. If a metal-coordinating directing group could be found, and importantly, shown to be capable of outcompeting the intermolecular background reaction, then we hoped that C—H hydroxylations with orthogonal selectivities to our previous results could be accessed. Herein, we describe a comprehensive evaluation of the selectivity rules governing C—H oxidation of carboxylic acid-containing substrates. Our results demonstrate that carboxylic acid ligation is capable of overcoming unfavorable electronic, steric, and stereoelectronic effects within the substrate by way of enforcing an intramolecular oxidation reaction. As hoped, intramolecular, carboxylic acid-directed oxidations often provide orthogonal selectivities to the intermolecular reaction, thereby broadening the scope of iron-catalyzed C—H hydroxylation. Finally, in a
powerful application, a carboxylic acid directing group enabled the site- and diastereoselective lactonization of a taxane derivative, facilitating installation of the C2 oxidation found within Taxol in a manner reminiscent of the natural hydroxylase enzyme involved in its biosynthesis.\(^\text{10}\)

### 1.2 Results and Discussion

We began our examination of the putative directing group effect with the evaluation of electronically deactivated substrates featuring a single \(3^\circ\) C—H bond. Carboxylic acid methyl esters were chosen as benchmark substrates because, while they lack the critical acid motif, they retain nearly identical electronic character. As expected, doubly deactivated methyl ester 2 was poorly reactive under the optimized conditions (three charges of 5 mol % Fe(PDP) 1 and 1.2 equiv. \(\text{H}_2\text{O}_2\)), affording only 13% yield of the desired butyrolactone product 14 (Table 1.1, entry 1). Moving the electron-withdrawing acetoxy group an additional methylene from the \(3^\circ\) site led to some restoration of reactivity and 15 was isolated in 26% yield (Entry 3); methyl ester 6, with three methylenes separating the acetoxy group from the \(3^\circ\) C—H bond, was the most reactive, affording butyrolactone 16 in 35% yield (Entry 5). As

---

**Table 1.1 Evaluating electronics with carboxylic acid directing groups.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>starting material</th>
<th>lactone product</th>
<th>isolated yield</th>
<th>(\text{ester} = %)</th>
<th>(\text{acid} = %)</th>
<th>(\text{rsmm} = %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me, 2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>H, 3</td>
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<td>H, 13</td>
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</tr>
</tbody>
</table>

*Electron-withdrawing group. *Reactions of methyl esters included 3 x 50 mol% AcOH. *Average of two runs at either 0.3 or 0.5 mmol. *Recovered unreacted starting material. *\(\text{H} \text{NMR} \) yield.
hypothesized, simply removing the methyl ester protecting group and unveiling the carboxylic acid led to a significant increase in reactivity in each case (Entries 2, 4, and 6). For example, acid 7, with three methylenes separating the acetoxy group from the 3° site, led to 63% yield of 16 with complete consumption of starting material. Similarly, while α-chloro ester 8 provided an 11% yield of lactone 17, the corresponding carboxylic acid furnished 17 in 42% yield (Entries 7-8). In accord with these results, protected β-amino ester 10 and cyclohexanone derivative 12 led to low yields of lactone with >40% recovered starting material, while carboxylic acids 11 and 13 provided synthetically useful yields of the desired lactones, again with complete conversion of starting material (Entries 9-12). Next, we examined chiral, non-racemic carboxylic acid 20 using catalyst (S,S)-1 and isolated 51% yield of the desired lactone (Table 1.2); switching to catalyst (R,R)-1 led to lower reactivity, and only 28% yield of 22. This interesting matched/mismatched result suggests that acid 20 coordinates to the chiral catalyst, creating two diastereomeric complexes, resulting in differential reactivity. In accord with this hypothesis, methyl ester 21 gave identical results upon changing catalyst antipode, presumably due to its much lower propensity for catalyst coordination. Furthermore, beginning from racemic acid 20, Fe(PDP)-1 promoted a moderately selective kinetic resolution, providing both recovered starting material and lactone 22 in approximately 30% ee. Our results demonstrate that carboxylic acids can override electronic deactivation, restoring C—H oxidation reactivity to doubly-deactivated substrates by acting as ligands for the metal catalyst.

Next, we evaluated the ability of carboxylate ligation to overcome unfavorable steric effects within substrates. We synthesized conformationally locked methyl esters 23 and 25, featuring either an equatorially or axially disposed 3° C—H bond (Table 1.3). Our lab previously reported that equatorial sites suffer oxidation in preference to axial sites with bulky Fe(PDP) 1, results that agree with reports of C—H hydroxylations mediated by small molecule reagents. In accord with these prior results, equatorial C—H bond-containing substrate 23 provided lactone 29 as the major product, while axial substrate 25 only furnished 9% of lactone 30 arising from axial C—H hydroxylation (Entries 1 and 3). In this latter case, ketone 33, arising from 2° C—H oxidation, was the major product (36% yield). Excitingly, carboxylic acids 24 and 26 each provided 3° hydroxylation products in ≥ 50% yields, demonstrating that

### Table 1.2. Matched/mismatched behavior with a carboxylic acid directing group.

<table>
<thead>
<tr>
<th>substrate</th>
<th>catalyst</th>
<th>rsm</th>
<th>yield</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = H, 20</td>
<td>(S,S)-Fe(PDP)</td>
<td>--</td>
<td>51%</td>
<td>'Matched'</td>
</tr>
<tr>
<td>R = Me, 21</td>
<td>(S,S)-Fe(PDP)</td>
<td>64%</td>
<td>23%</td>
<td>'Mismatched'</td>
</tr>
<tr>
<td></td>
<td>(R,R)-Fe(PDP)</td>
<td>63%</td>
<td>22%</td>
<td>No change</td>
</tr>
</tbody>
</table>

...
the carboxylic acid was capable of directing the Fe(PDP) catalyst to the adjacent 3° site, even when disfavored due to steric inaccessibility (Entries 2 and 4). Notably, despite its small size, stoichiometric oxidant methyl(trifluoromethyl)dioxirane (TFDO)\(^{11}\) failed to provide >30% yields of lactone 30 arising from axial C—H hydroxylation, beginning from either the carboxylic acid or ester (Figure 1.2). In summary, carboxylate ligation enables site-selective C—H hydroxylations using non-heme iron catalyst 1 in cases where steric effects disfavor intermolecular hydroxylation. Moreover, comparison with small molecule reagent TFDO underscored a traditional advantage of transition metal catalysis, the ability to tune reactivity through reversible ligand coordination during catalysis.

Lastly, we examined the impact of carboxylate ligation on stereoelectronic effects, the third set of guidelines used to predict site-selectivity in intermolecular C—H hydroxylations. Methyl ester 27, featuring two sites stereoelectronically activated through hyperconjugative donation from an oxygen atom, underwent nonselective oxidation, furnishing trace quantities of the desired lactone product. The major

![Table 1.3. Evaluating sterics and stereoelectronics with carboxylic acid directing groups.](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>(R)</th>
<th>lactone product</th>
<th>isolated yield(^b)</th>
<th>non-directed product(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(\text{Me, 23} \rightarrow \text{H, 24} \rightarrow \text{tBu} \rightarrow \text{H, 26} \rightarrow \text{Me, 25})</td>
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<td>4</td>
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<tr>
<td>Steroelectronics</td>
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<td>5</td>
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<td>6</td>
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</tr>
<tr>
<td>Non-Directed Oxidation Products</td>
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<tr>
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</table>

\(^a\) Reactions of methyl esters included 3 x 50 mol\% \(\text{AcOH}\). \(^b\) Average of two runs at either 0.3 or 0.5 mmol. \(^c\) GC yield relative to standard curve. \(^d\) Two cycles of Fe(PDP)/\(\text{H}_2\text{O}_2\).
oxidation products derived from 2° oxidation, affording lactone 34 (22% yield), and 3° C—H hydroxylation, pyran ring-opening, and further oxidation to ketoacid 35 (16% yield) (Entry 5). In stark contrast, carboxylic acid 28 provided 3° lactone 31 in 58% yield (Entry 6); the directing group was likely critical for directing a site-selective oxidation and for trapping a presumably unstable hemiketal intermediate as the corresponding lactone. Taken together, our results demonstrate that carboxylic acids can direct Fe(PDP)-catalyzed C—H hydroxylations to sites that are either electronically or sterically disfavored, as well as promote selective hydroxylation of substrates with multiple sites activated toward oxidation. As such, these results comprise a fourth guideline governing site-selectivity in C—H oxidations of carboxylic acid-containing substrates, supplementing the previously defined rules for intermolecular oxidations.

A long-standing goal of the White group is the strategic application of new C—H oxidation methodologies in complex molecule synthesis. One class of molecules of particular appeal is the taxane class of anticancer compounds due to their biosynthetic assembly through a series of enzyme-mediated site- and stereoselective C—H hydroxylations. Having delineated the scope of the carboxylic acid-directed C—H lactonization reaction, we targeted installation of Taxol’s C2 oxidation for two reasons: (1) no literature reports describe C2 oxidation of a taxane using a small molecule catalyst or reagent, (2) examination of a molecular model suggested that the C2 α-hydrogen (oxidation of which would lead to the naturally occurring stereoconfiguration) would be both sterically accessible and situated in close proximity to a carboxylic acid directing group at C4. We began by performing DFT calculations on the energy minimized structure of taxane derivative 39; as expected, the 3° sites were predicted to be the
most-electron rich and therefore the most reactive (Figure 1.3). In particular, the hydrogen at C1 was predicted to be the most favored site of potential oxidation, while the methylene hydrogens at C2 were expected to be less susceptible to oxidation. In accord with this prediction, oxidation of methyl ester 37 led to C1 oxidation product nortaxane 38 (see discussion in Chapter 2 describing this interesting rearrangement) as the major product. In direct contrast, oxidation of carboxylic acid 39 with Fe(S,S)-PDP led to a 49% yield of the desired C2 lactone (20% rsm), demonstrating a complete turnover in site-selectivity enabled by application of the directing group methodology. Notably, this oxidation was both site- and stereoselective and overoxidation to the C2 ketone was not observed. This result represents one of the White group’s most exciting late-stage site-selective C—H oxidations on a complex molecule and further demonstrates the potential utility of carboxylic acids for overriding unfavorable substrate biases during C—H hydroxylation.

Mechanistically, non-heme iron catalyzed C—H hydroxylations are thought to proceed according to the heme paradigm. Initial radical hydrogen abstraction from a high valent iron-oxo generates a short-lived carbon-centered radical and an iron-bound hydroxyl (Figure 1.4). In the presence of a carboxylate ligand, this iron intermediate could be envisioned to provide lactone product via two distinct pathways: (1) carboxylate rebound to generate lactone directly, or (2) hydroxyl rebound followed by lactonization. To differentiate between these two possibilities, 18O-enriched acid 41 (88% doubly labeled) was exposed to the standard reaction conditions. The observation of predominantly singly labeled lactone 42 (87% singly labeled) suggests that hydroxyl rebound provides the lactone product and that carboxylate rebound, if operative, is not a major pathway. Chapter 2 of this manuscript will describe a more in-depth mechanistic study of carboxylic acid-directed C—H oxidation using non-heme iron catalyst 1.

**Figure 1.4**

**A.** Proposed mechanism of Fe(PDP)-catalyzed C-H lactonization.

**B.** Labeling study supports hydroxyl rebound/lactonization.

1.3 Conclusions

Carboxylic acid directing groups facilitate site-selective C—H hydroxylations catalyzed by non-heme iron complex Fe(PDP) (1), demonstrating the first general directing group effect reported for oxidations
proceeding via metal oxo intermediates. Capable of overcoming unfavorable electronic, steric, and stereoelectronic effects within aliphatic substrates, carboxylic acids achieve this by way of coordinating to the metal catalyst and rendering the oxidation reaction intramolecular. As such, these results collectively define a fourth mode of control influencing site-selectivity in Fe(PDP)-catalyzed C—H hydroxylations, often providing for selectivities orthogonal to those observed with the intermolecular reaction. In an exciting application, a carboxylic acid directing group was critical for enabling a site- and stereoselective installation of the C2 oxidation on a taxane derivative. Current limitations include the moderate chemical yields of lactone products, a substrate scope limited to butyrolactones, the facile overoxidation of secondary alcohol products to the corresponding ketones, and the low turnover numbers commonly observed for non-heme iron catalysts. To address these challenges, more robust catalysts with enhanced C—H oxidation reactivity and site- and chemoselectivity will need to be discovered. While current limitations will likely prevent application of the methodology in complex molecule synthesis, and the realization of increased synthetic efficiency inherent in selective C—H functionalization chemistry, the mechanistic insight gleaned will likely aid chemists in their future work.

### 1.4 Experimental Section

**General Information:** The following commercially obtained reagents for the C—H lactonization were used as received: HPLC grade CH$_3$CN (Fisher Scientific), glacial acetic acid (AcOH, Fisher Scientific), 50 wt. % H$_2$O$_2$ solution in water (Aldrich, stored at 4 °C). All C—H lactonization reactions were run under air with no precautions taken to exclude moisture. All products were filtered through a glass wool plug prior to obtaining a final weight. Each antipode of the Fe(PDP) catalyst was prepared as previously described and stored at 4 °C. All other reactions were run under an atmosphere of N$_2$ or Ar gas with dry solvent unless otherwise stated. Dry solvents tetrahydrofuran (THF), methylene chloride (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), methanol (MeOH), and 1,4-dioxane were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methyl polysiloxane column (30m, 0.32mm, 0.25mm). Chiral GC analysis was performed on an Agilent 5890 Series instrument equipped with FID detectors using a J&W cyclodex-β column (30 m, 0.25 mm, 0.25 mm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with potassium permanganate, $p$-anisaldehyde, bromocresol green, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230-400 mesh). $^1$H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Unity-500
(500 MHz), or a Varian Unity Inova 500NB (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C 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 (CDCl₃ at 77.16 ppm). 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. Optical rotations were measured using a 1 mL cell with a 50 mm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: \([\alpha]_D^0 \text{C} (c = g/100 \text{ mL}, \text{solvent}).

**Synthesis of Carboxylic Acids for the C-H Lactonization Reaction**

(±)-7-acetoxy-4-methylheptanoic acid: Into a flame-dried 500 mL round-bottomed flask was added anhydrous CH₂Cl₂ (40 mL) and the flask was cooled to -78 °C while under an atmosphere of N₂. Neat oxalyl chloride (2.50 mL, 28.6 mmol, 1.1 equiv.) was added, followed by a solution of anhydrous DMSO (4.06 mL, 57.2 mmol, 2.2 equiv.) in dry CH₂Cl₂ (20 mL). Stirring followed for 5 min and a solution of 2-methylpent-4-en-1-ol (2.6 g, 26 mmol, 1.0 equiv.) in dry CH₂Cl₂ (15 mL) was added over a period of 5 min. The resulting thick white slurry stirred at -78 °C for 20 min and neat triethylamine (18.0 mL, 130 mmol, 5.0 equiv.) was added over a period of 5 min. Stirring followed at -78°C for 8 min and the cooling bath was removed. The reaction warmed to ambient temperature for 1 h and the organic layer was washed with sat. aq. NaHCO₃, 1 M aq. HCl, and brine (1X each). The organic layer was collected, dried over MgSO₄, and filtered through celite. This solution was treated directly with benzyl (triphenylphosphoranylidene)acetate (10.9 g, 26.6 mmol, ~1 equiv.) and heated to reflux overnight. The crude reaction mixture was concentrated *in vacuo* and purified by filtration through a short silica plug (5% EtOAc/hexanes), affording the desired diene as a clear, colorless oil (4.87 g, 80%, 2 steps).

To a flame-dried 50 mL round-bottomed flask was added 9-BBN (0.5 M in THF, 20 mL, 10 mmol, 1.0 equiv.), followed by a solution of the diene (2.30 g, 10 mmol, 1.0 equiv.) in dry THF (5 mL). The solution stirred under an atmosphere of N₂ at ambient temperature for 0.5 h and to it was added 2 mL H₂O, followed by 12 mL 3 M aq. NaOAc. The resulting biphasic solution was cooled in an ice/water bath while 30% aq. H₂O₂ (6 mL) was added carefully. Stirring followed at ambient temperature overnight and the layers were separated. The organic layer was diluted with Et₂O and collected, dried over MgSO₄, filtered
through celite, concentrated \textit{in vacuo}, and purified by flash chromatography (20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes $\rightarrow$ 60% EtOAc/hexanes), affording a clear, colorless oil (1.67 g, 67%).

The above primary alcohol was treated with Pd/C (10% by weight, 0.5 g) and dissolved in MeOH (25 mL). H$_2$ was passed directly through the reaction mixture for 0.5 h and the reaction stirred at ambient temperature under an atmosphere of H$_2$ for 1 h. The reaction mixture was filtered through celite, concentrated \textit{in vacuo}, and dissolved in CH$_2$Cl$_2$ (30 mL). The crude hydroxyacid was treated with 4-dimethylaminopyridine (164 mg, 1.34 mmol, ~0.2 equiv.), triethylamine (4.7 mL, 34 mmol, ~5 equiv.), and acetic anhydride (3.2 mL, 34 mmol, ~5 equiv.) and stirred under an atmosphere of Ar overnight while at ambient temperature. The reaction was partitioned between 1M aq. HCl and CH$_2$Cl$_2$ and extracted 2X with CH$_2$Cl$_2$. The combined organics were dried over MgSO$_4$, filtered through celite, concentrated \textit{in vacuo}, and purified by flash chromatography (20% EtOAc/hexanes, 1% AcOH). To remove residual Ac$_2$O, the crude product was dissolved in EtOAc and sat. aq. NaHCO$_3$ and stirred for 2h at ambient temperature in the presence of several flakes of DMAP (0.51 g, 37%, 2 steps).

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.04 (t, $J$ = 7.0 Hz, 2H), 2.42-2.28 (m, 2H), 2.05 (s, 3H), 1.73-1.55 (m, 3H), 1.51-1.41 (m, 2H), 1.40-1.32 (m, 1H), 1.23-1.15 (m, 1H), 0.90 (d, $J$ = 6.0 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 179.9, 171.5, 64.9, 32.8, 32.2, 31.8, 31.6, 26.2, 21.2, 19.2. IR (film, cm$^{-1}$): 3100 (br), 2958, 2931, 2873, 1738, 1711, 1456, 1416, 1385, 1367, 1242, 1173, 1038. HRMS (ESI) m/z calc’d C$_{10}$H$_{19}$O$_4$ [M+H]$^+$: 203.1283, found 203.1273.

**3-[(1s,4s)-4-(tert-butyl)cyclohexyl]propanoic acid**

Into a flame-dried 500 mL round-bottomed flask was added solid LiAlH$_4$ (95%, 750 mg, 17.9 mmol, 1.1 equiv.), followed by 50 mL dry THF. The resulting suspension was cooled to 0°C and to it was added solid carboxylic acid (3.0 g, 16.3 mmol, 1.0 equiv.). Stirring followed under a nitrogen atmosphere at ambient temperature for 2h and the reaction was quenched carefully by successive addition of 0.72 mL water, 0.72 mL 15% NaOH, and 2.16 mL water. The resulting heterogeneous mixture was filtered through celite and the filtrate was concentrated \textit{in vacuo}, affording a white, crystalline solid (2.86 g, > 95%).

Into a 200 mL round-bottomed flask containing the primary alcohol product (2.86g, 16.8 mmol, 1.0 equiv.) was added successively para-toluenesulfonyl chloride (3.53. g, 18.5 mmol, 1.1 equiv.), 4-dimethylaminopyridine (415 mg, 3.4 mmol, 0.2 equiv.), 40 mL anhydrous CH$_2$Cl$_2$, and anhydrous triethylamine (2.58 mL, 18.5 mmol, 1.1 equiv.). The resulting yellow, cloudy solution stirred at ambient
temperature overnight under a N\textsubscript{2} atmosphere. The crude reaction mixture was washed with 1M HCl, water, and brine (1X each) and the organics were dried over MgSO\textsubscript{4}, filtered through celite, and concentrated \textit{in vacuo}, affording the desired product as a pale yellow solid (4.0 g, 74%).

While under an inert atmosphere, white powdered CuCl (245 mg, 2.47 mmol, 0.2 equiv.) was weighed into a flame-dried 250 mL round-bottomed flask. Anhydrous Et\textsubscript{2}O (30 mL) was added and the resulting suspension was cooled to 0°C. A solution of allylmagnesium bromide (1.0 M in Et\textsubscript{2}O, 24.6 mL, 24.6 mmol, 2.0 equiv.) was added \textit{via} syringe over approximately 10 minutes and the resulting opaque black solution stirred an additional 10 minutes. This solution was cannulated into a mixture of the tosylate (4.0 g, 12.3 mmol, 1.0 equiv.) in anhydrous Et\textsubscript{2}O (10 mL). After stirring for 10 h at ambient temperature, the reaction mixture had saturated aq. NH\textsubscript{4}Cl carefully added to it. The layers were separated and the aqueous layer was extracted 2X with Et\textsubscript{2}O and 1X with CH\textsubscript{2}Cl. The combined organics were washed 1X each with water and brine, dried over MgSO\textsubscript{4}, filtered through a celite/silica plug, and concentrated \textit{in vacuo}. Flash chromatography (100% hexanes) afforded a clear, colorless liquid containing the desired product as well as the elimination product, 4-\textit{t}-butylvinylcyclohexane (1.74g, 79% of the desired compound).

The above mixture (1.70 g, 8.7 mmol, 1.0 equiv. terminal olefin) was treated with 75 mL CH\textsubscript{3}CN, 75 mL CCl\textsubscript{4}, 110 mL H\textsubscript{2}O, sodium metaperiodate (8.37 g, 39.15 mmol, 4.5 equiv.), and RuCl\textsubscript{3}•3H\textsubscript{2}O (58 mg, 0.22 mmol, 0.025 equiv.) and stirred vigorously for 9h at ambient temperature. The crude reaction mixture was extracted 3X with CH\textsubscript{2}Cl\textsubscript{2} and the combined organics were dried over MgSO\textsubscript{4}, filtered through celite/silica, and concentrated \textit{in vacuo}, affording a purple oil that was purified by flash chromatography (silica, 7% EtOAc/hexanes \rightarrow 10% EtOAc/hexanes, 1% AcOH). The resulting solid was taken up in EtOAc and washed 3X with 3M aq. NaOH. The combined aqueous extracts were washed 1X with CH\textsubscript{2}Cl\textsubscript{2}, the organics were discarded, and the aqueous layer was acidified to pH \sim 2 with 3M aq. HCl and extracted 3x with CH\textsubscript{2}Cl\textsubscript{2}. The combined organics were dried over MgSO\textsubscript{4}, filtered through celite, and concentrated \textit{in vacuo}, affording a white powder (0.50 g, 15%, 4 steps).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): δ 2.34 (dd, \textit{J} = 7.8, 7.0 Hz, 2H), 1.72-1.60 (m, 5H), 1.52-1.42 (m, 4H), 1.14-1.02 (m, 2H) 1.00-0.92 (m, 1H), 0.83 (s, 9H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): δ 180.0, 48.6, 32.7, 32.7, 32.2, 30.4, 27.6, 26.1, 21.7. IR (film, cm\textsuperscript{-1}): 3415 (br), 2945, 2926, 2866, 2832, 1709, 1466, 1363, 1296, 1281, 1207, 945, 910. HRMS (ESI) m/z calc’d C\textsubscript{13}H\textsubscript{24}O\textsubscript{2}Na [M+Na]\textsuperscript{+}: 235.1674, found 235.1673.

3-\textit{[(1r,4r)-4-(\textit{t}-butyl)cyclohexyl]propanoic acid}: The \textit{trans} diastereomer was prepared followed the procedure described above for the synthesis of the \textit{cis} diastereomer, beginning from \textit{trans}-4-\textit{t}-butylcyclohexanecarboxylic acid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 2.37 (t, \textit{J} = 8.0 Hz, 2H), 1.83-1.71 (m, 4H), 1.52 (app q, \textit{J} = 7.6 Hz, 2H),
1.22-1.11 (m, 1H), 1.03-0.80 (m, 5H), 0.83 (s, 9H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 180.6, 48.2, 37.3, 33.5, 32.5, 32.1, 31.9, 27.7, 27.3. IR (film, cm\(^{-1}\)): 2966, 2943, 2920, 2860, 2845, 1705, 1452, 1402, 1360, 1319, 1282, 1200, 941, 908. HRMS (ESI) m/z calc’d C\(_{13}\)H\(_{24}\)O\(_2\)Na [M+Na]\(^+\): 235.1674, found 234.1668.

(±)-3-(tetrahydropyran-2-yl)propanoic acid: To a flame-dried 500 mL round-bottomed flask under an atmosphere of N\(_2\) was added anhydrous CH\(_2\)Cl\(_2\) (35 mL) and the flask was cooled to \(-78^\circ\text{C}\). Oxalyl chloride (2.07 mL, 23.7 mmol, 1.1 equiv.) was added via syringe and a separate solution of anhydrous DMSO (3.36 mL, 47.3 mmol, 2.2 equiv.) in anhydrous CH\(_2\)Cl\(_2\) (12 mL) was added to the resulting solution. Stirring followed at this temperature for 5 min. Next, tetrahydropyran-2-methanol (2.5 g, 21.5 mmol, 1.0 equiv.) in anhydrous CH\(_2\)Cl\(_2\) (10 mL) was added via syringe over a period of 5 min and the resulting thick slurry continued stirring at \(-78^\circ\text{C}\) for 20 min. To this mixture was added dry triethylamine (14.9 mL, 107.5 mmol, 5.0 equiv.) over 5 min; stirring followed for 10 min at \(-78^\circ\text{C}\), at which point the reaction was allowed to warm to ambient temperature for 0.5 h. The reaction was quenched with H\(_2\)O and the organic layer was washed (1X each) with H\(_2\)O, 1M aq. HCl, sat. aq. NaHCO\(_3\), and brine. The organic layer was dried over MgSO\(_4\), filtered through celite, and treated directly with benzyl (triphenylphosphoranylidene)acetate (9.0 g, 21.9 mmol, ~1 equiv.). The resulting mixture was heated to reflux for 3 h under an atmosphere of Ar. The crude reaction mixture was next washed 1X with 1M aq. HCl and filtered through a short silica plug (10% EtOAc/hexanes), affording a yellow oil (3.4 g crude product) that was dissolved in 40 mL iPrOH. 10% Pd(OH)/C (1 g) was added and H\(_2\) was passed continuously through the reaction mixture for several hours. Stirring followed overnight at ambient temperature under at atmosphere of H\(_2\) and the reaction was filtered through celite. The filtrate was concentrated in vacuo and dissolved in 30 mL THF and 10 mL H\(_2\)O, treated with LiOH•H\(_2\)O (2.6 g, 62 mmol), and stirred vigorously at ambient temperature for 60 h. The reaction was partitioned between H\(_2\)O and CH\(_2\)Cl\(_2\) and washed 2X with CH\(_2\)Cl\(_2\). The aqueous layer was acidified with conc. HCl and extracted 3X with CH\(_2\)Cl\(_2\). The combined organics were dried over MgSO\(_4\), filtered through celite, and purified by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes, 1% AcOH), affording the desired compound as a pale yellow oil (1.05 g, 31%, 4 steps).

\(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.00-3.93 (m, 1H), 3.40 (td, \(J = 11.4, 2.8\) Hz, 1H), 3.32-3.24 (m, 1H), 2.55-2.40 (m, 2H), 1.85-1.70 (m, 3H), 1.61-1.40 (m, 4H), 1.33-1.22 (m, 1H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 179.5, 77.0, 68.6, 31.9, 31.2, 30.5, 26.1, 23.5. IR (film, cm\(^{-1}\)): 3109 (br), 2937, 2854, 2740, 1711, 1443, 1417, 1381, 1284, 1265, 1205, 1176, 1088, 1047, 883. HRMS (ESI) m/z calc’d C\(_8\)H\(_{15}\)O\(_3\) [M+H]\(^+\): 159.1021, found 159.1013.
General Procedure for Methyl Ester Synthesis:

The methyl esters used in this study were prepared from the corresponding carboxylic acids by treatment of a 0.3 M solution of the carboxylic acid in DMF sequentially with 5 equiv. K$_2$CO$_3$ and 5 equiv. MeI. The resulting heterogeneous mixture stirred at ambient temperature until full conversion of starting material was noted by TLC or GC analysis. Usually, several hours at ambient temperature were sufficient; otherwise, stirring the mixture overnight resulted in complete conversion. The crude reaction mixture was diluted with Et$_2$O and washed 5X with H$_2$O and 1X with brine. The organic layer was collected, dried over MgSO$_4$, filtered through celite, and the filtrate was concentrated in vacuo to provide the pure methyl ester (typically 60-85% isolated yield).

General Procedures for the Oxidative C-H Lactonization Reaction

General Procedure A
C—H oxidation of Carboxylic Acids (0.5 mmol substrate): Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 1 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH$_3$CN, and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H$_2$O$_2$ (50 wt % in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol % 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt % in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol % 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt % in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN. The reaction stirred a final 10 minutes and was analyzed by TLC. The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et$_2$O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

General Procedure B
C—H oxidation of Non-Carboxylic Acids (0.5 mmol substrate): Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 1 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH$_3$CN, 14.3 µL AcOH (0.25 mmol, 0.5 equiv.), and a magnetic stir
bar. While the resulting deep red solution stirred, a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN. The reaction stirred approx. 16h at ambient temperature to ensure complete lactonization of intermediate hydroxyester products and was thereafter concentrated in vacuo and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et$_2$O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

**Representative procedure for preparation of lactone standard curve:** Stock solutions of nitrobenzene (98.5 mg, 10.00 mL EtOAc) and authentic 5,5-dimethylidihydrofuran-2-one (57.1 mg, 5.00 mL EtOAc) were prepared. To each of nine GC vials was added 500 µL nitrobenzene stock solution (4.9 mg, 0.040 mmol per vial), followed by an aliquot of the lactone stock solution, in increasing amounts (100 µL, 200 µL, …, 900 µL; 0.01 mmol, 0.02 mmol, …, 0.09 mmol). As such, the first GC vial represented a 10% yield of lactone for a 0.10 mmol reaction, while the ninth vial represented a 90% yield of lactone. These solutions were mixed thoroughly and analyzed by GC; a plot of % yield vs. measured lactone/nitrobenzene generated data points that could be readily fit to a linear equation of the form y = mx + b.

**Representative procedure for measurement of GC yield from Carboxylic Acids (0.10 mmol):** The oxidation reaction of 4-methylvaleric acid (11.6 mg, 0.10 mmol) was performed according to general procedure A, immediately subsequent to measurement of the standard curve. After the reaction was complete, nitrobenzene (4.9 mg, 0.040 mmol) was transferred to the reaction mixture from a separate vial using EtOAc. The resulting solution was mixed thoroughly and analyzed by GC, providing the measured lactone/nitrobenzene ratio.
Representative procedure for measurement of GC yield and % conversion from *Non-Carboxylic Acids* (0.10 mmol): The oxidation reaction of ethyl 4-methylvalerate (14.4 mg, 0.10 mmol) was performed according to general procedure B, immediately subsequent to measurement of the standard curve. Nitrobenzene (4.9 mg, 0.040 mmol) was added before the reaction, and an aliquot of the reaction mixture was removed to calculate an initial substrate/nitrobenzene ratio. After the reaction was complete (after 16h stirring period), the solution was again analyzed by GC to measure a final substrate/nitrobenzene ratio and lactone/nitrobenzene ratio. Notably, reactions analyzed 10 min after final addition of H$_2$O$_2$ showed significantly lower yields of lactone product than analysis after 16h, while conversion of starting material remained constant, suggesting incomplete lactonization of hydroxyester intermediates at the 10 min time point.

Scope of the Oxidative C-H Lactonization Reaction

Table 1.1

(±)-5-methyl-5-(1-acetoxymethyl)-dihydrofuran-2-one (14) (Table 1.1, Entry 1): (±)-methyl 5-acetoxymethylpentanoate (56.5 mg, 0.30 mmol) was reacted according to general procedure B using Fe(R,R-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes → 60% EtOAc/hexanes). Run 1 (6.0 mg lactone, 0.035 mmol, 12% lactone; 40.7 mg rsm, 0.216 mmol, 72% rsm); run 2 (6.8 mg lactone, 0.039, 13% lactone; 37.3 mg rsm, 0.198 mmol, 66% rsm). **Average yield:** 13%; **Average rsm:** 69%.

(Table 1.1, Entry 2): (±)-5-acetoxymethyl-4-methylpentanoic acid (52.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(R,R-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 50% EtOAc/hexanes, no AcOH) afforded both unreacted starting material and lactone product as clear, colorless oils. Run 1 (13.6 mg lactone, 0.079 mmol, 26% lactone; 27.6 mg rsm, 0.158 mmol, 53% rsm); run 2 (13.7 mg lactone, 0.080 mmol, 27% lactone; 27.0 mg rsm, 0.155 mmol, 52% rsm). **Average yield:** 27%; **Average rsm:** 53%. $^1$H NMR (CDCl$_3$, 500 MHz): δ 4.16 (AB d, J = 11.5 Hz, 1H), 4.06 (AB d, J = 11.5 Hz, 1H), 2.72-2.58 (m, 2H), 2.25 (ddd, J = 13.0, 10.0, 6.5 Hz, 1H), 2.10 (s, 3H), 2.02 (ddd, J = 13.3, 10.0, 8.0 Hz, 1H), 1.45 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 176.3, 170.5, 83.8, 69.1, 30.6, 29.3, 23.9, 20.9. IR (film, cm$^{-1}$): 2926, 2852, 1776, 1741, 1460, 1381, 1230, 1157, 1047, 945. HRMS (ESI) m/z calc’d C$_8$H$_{12}$O$_4$Na [M+Na]$^+$: 195.0633, found 195.0626.

(±)-5-methyl-5-(2-acetoxymethyl)-dihydrofuran-2-one (Table 1.1, Entry 3): (±)-methyl 6-acetoxymethylhexanoate (60.7 mg, 0.30 mmol) was reacted according to
general procedure B using Fe($R,R$-PDP). Purification by flash chromatography (20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes $\rightarrow$ 60% EtOAc/hexanes). Run 1 (13.9 mg lactone, 0.075 mmol, 25% lactone; 31.8 mg rsm, 0.157 mmol, 52% rsm); run 2 (14.6 mg lactone, 0.078, 26% lactone; 30.8 mg rsm, 0.152 mmol, 51% rsm). **Average yield: 26%. Average rsm: 52%.**

**(Table 1.1, Entry 4):** (±)-6-acetoxy-4-methylhexanoic acid$^{19}$ (56.5 mg, 0.30 mmol) was reacted according to general procedure A using Fe($R,R$-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH $\rightarrow$ 50% EtOAc/hexanes, no AcOH) afforded both unreacted starting material and lactone product as clear, colorless oils. Run 1 (27.1 mg lactone, 0.146 mmol, 49% lactone; 14.2 mg rsm, 0.075 mmol, 25% rsm); run 2 (28.2 mg lactone, 0.151 mmol, 50% lactone; 14.4 mg rsm, 0.077 mmol, 26% rsm). **Average yield: 50%; Average rsm: 26%.**

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.25-4.16 (m, 2H), 2.68-2.54 (m, 2H), 2.20-2.13 (m, 1H), 2.09-1.99 (m, 3H), 2.04 (s, 3H), 1.42 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 176.4, 171.0, 85.1, 60.2, 39.3, 33.5, 29.0, 26.0, 21.1. IR (film, cm$^{-1}$): 2976, 2935, 2915, 2900, 2800, 2720, 2620, 1768, 1738, 1456, 1369, 1240, 1159, 1130, 1097, 1038, 937. HRMS (ESI) m/z calc’d C$_9$H$_{14}$O$_4$Na [M+Na]$^+$: 209.0790, found 209.0784.

(±)-5-methyl-5-(3-acetoxypropyl)-dihydrofuran-2-one (Table 1.1, Entry 5): (±)-methyl 7-acetoxy-4-methylheptanoate (64.9 mg, 0.30 mmol) was reacted according to general procedure B using Fe($R,R$-PDP). Purification by flash chromatography (20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes $\rightarrow$ 60% EtOAc/hexanes). Run 1 (21.1 mg lactone, 0.105 mmol, 35% lactone; 27.0 mg rsm, 0.125 mmol, 42% rsm); run 2 (21.1 mg lactone, 0.105, 35% lactone; 27.5 mg rsm, 0.127 mmol, 42% rsm). **Average yield: 35%. Average rsm: 42%.**

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.12-4.03 (m, 2H), 2.69-2.53 (m, 2H), 2.13-1.98 (m, 2H), 2.05 (s, 3H), 1.79-1.68 (m, 4H), 1.40 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 176.6, 171.1, 86.2, 64.2, 37.4, 33.1, 29.1, 25.6, 23.3, 21.0. IR (film, cm$^{-1}$): 2970, 2939, 1768, 1738, 1456, 1425, 1385, 1365, 1240, 1159, 1097, 1038, 939. HRMS (ESI) m/z calc’d C$_{10}$H$_{16}$O$_4$Na [M+Na]$^+$: 223.0946, found 223.0945.

**(Table 1.1, Entry 6):** (±)-7-acetoxy-4-methylheptanoic acid (60.7 mg, 0.30 mmol) was reacted according to general procedure A using Fe($R,R$-PDP). Purification by flash chromatography (50% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (38.3 mg lactone, 0.191 mmol, 64% lactone); run 2 (37.4 mg lactone, 0.187 mmol, 62% lactone). **Average yield: 63%.** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.12-4.03 (m, 2H), 2.69-2.53 (m, 2H), 2.13-1.98 (m, 2H), 2.05 (s, 3H), 1.79-1.68 (m, 4H), 1.40 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 176.6, 171.1, 86.2, 64.2, 37.4, 33.1, 29.1, 25.6, 23.3, 21.0. IR (film, cm$^{-1}$): 2970, 2939, 1768, 1738, 1456, 1425, 1385, 1365, 1240, 1159, 1097, 1038, 939. HRMS (ESI) m/z calc’d C$_{10}$H$_{16}$O$_4$Na [M+Na]$^+$: 223.0946, found 223.0945.
(S)-3-chloro-5,5-dimethylidihydrofuran-2-one (Table 1.1, Entry 7) (NMR): (S)-methyl 2-chloro-4-methylvalerate (16.5 mg, 0.10 mmol) was reacted according to general procedure B in CD$_3$CN using Fe(R,R-PDP). The crude reaction mixture was filtered through a short silica plug (100% CDCl$_3$) into a round-bottomed flask containing nitrobenzene (4.9 mg, 0.040 mmol). The filtrate was mixed thoroughly and analyzed by $^1$H NMR; yield of lactone product and unreacted starting material calculated relative to nitrobenzene. Run 1 (9% lactone, 66% rsm); run 2 (13% lactone, 68% rsm). **Average NMR yield: 11%**. **Average NMR rsm: 67%**.

(Table 1.1, Entry 8) (Isolated): (S)-2-chloro-4-methylvaleric acid (45.2 mg, 0.30 mmol) was reacted according to general procedure A using Fe(R,R-PDP). Purification by flash chromatography (10% EtOAc/hexanes, 1% AcOH → 20% EtOAc/hexanes, 1% AcOH) afforded both unreacted starting material and the lactone product as clear, colorless liquids. Run 1 (19.3 mg lactone, 0.130 mmol, 43% lactone; 9.9 mg rsm, 0.066 mmol, 22% rsm); run 2: (18.2 mg lactone, 0.122 mmol, 41% lactone; 9.8 mg rsm, 0.065 mmol, 22% rsm). **Average yield: 42%**; **Average rsm: 22%**.

(Table 1.1, Entry 8) (GC): To determine a more accurate yield of the lactone, a standard curve was measured by gas chromatography according to the representative procedure described above. The stock solutions used were: 98.5 mg nitrobenzene in 10.00 mL EtOAc; 74.3 mg lactone in 5.00 mL EtOAc. (S)-2-chloro-4-methylvaleric acid (15.1 mg, 0.10 mmol) was reacted according to general procedure A using Fe(R,R-PDP), and nitrobenzene (4.9 mg, 0.040 mmol) was added following the reaction. Run 1 (48%); run 2 (51%). **Average GC yield: 50%**. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 4.60 (dd, $J$ = 8.5, 7.5 Hz, 1H), 2.67 (dd, $J$ = 14.0, 9.0 Hz, 1H), 2.32 (dd, $J$ = 13.5, 8.0 Hz, 1H), 1.57 (s, 3H), 1.44 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 172.0, 83.6, 51.7, 45.0, 28.7, 28.1. IR (film, cm$^{-1}$): 2981, 2939, 2875, 1776, 1454, 1390, 1377, 1281, 1254, 1192, 1144, 1115, 949. HRMS (ESI) m/z calc’d C$_6$H$_9$O$_2$ClNa [M+Na]$^+$: 171.0189, found 171.0185. [α]$^{26}_{D}$ +10.8° (c 0.52, CHCl$_3$).

(±)-3-[(2,2,2,-trifluoroacetamido)methyl]-5,5-dimethylidihydrofuran-2-one (Table 1.1, Entry 9): (±)-methyl 4-methyl-2-[(2,2,2,-trifluoroacetamido)methyl]pentanoate (63.8 mg, 0.25 mmol) was reacted according to general procedure B using Fe(R,R-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes). Run 1 (20.2 mg lactone, 0.084 mmol, 34% lactone; 30.4 mg rsm, 0.119 mmol, 48% rsm); run 2 (19.4 mg lactone, 0.081 mmol, 32% lactone; 34.4 mg rsm, 0.135 mmol, 54% lactone). **Average yield: 33%**; **Average rsm: 51%**.
**Table 1.1, Entry 10:** (+)-4-methyl-2-[(2,2,2-trifluoroacetamido)methyl]pentanoic acid\(^{20}\) (72.4 mg, 0.30 mmol) was reacted according to general procedure A using Fe(R,R-PDP). Purification by flash chromatography (40% EtOAc/hexanes → 75% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (37.6 mg lactone, 0.157 mmol, 52% lactone); run 2 (37.9 mg lactone, 0.158 mmol, 53% lactone). **Average yield: 53%.** \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.52 (br s, 1H), 3.92-3.83 (m, 1H), 3.43-3.35 (m, 1H), 3.07-2.98 (m, 1H), 2.29 (dd, \(J = 12.5, 9.0\) Hz, 1H), 1.81 (t, \(J = 12.5\) Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 177.5, 157.7 (q, \(J = 37.6\) Hz), 115.9 (q, \(J = 286\) Hz), 84.0, 40.6, 39.3, 38.7, 28.8, 26.9. IR (film, cm\(^{-1}\)): 3319 (br), 3099, 2981, 2935, 2881, 1755, 1722, 1556, 1458, 1379, 1296, 1275, 1211, 1184, 1159, 957. HRMS (ESI) m/z calc'd C\(_9\)H\(_{12}\)NO\(_3\)F\(_3\)Na [M+Na]\(^+\): 262.0667, found 262.0668.

Additionally, oxidation of acid 11 provided ~20% isolated yield of the ‘double oxidation’ product depicted in the inset as a 1:1 mixture of diastereomers, in accord with our earlier report (**Nat. Chem.** 2011, 3, 218). These ‘double oxidation’ products often constitute the majority of the remaining mass balance beginning from carboxylic acid-containing substrates. Notably, these products arise from initial radical abstraction at the expected 3° C—H bond, demonstrating that the carboxylic acid directing group promotes a highly site-selective radical abstraction. We are currently attempting to elucidate the factors determining how much of these products are furnished from a given carboxylic acid-containing substrate.

**1-oxaspiro[4,5]decane-2,8-dione (Table 1.1, Entry 11):** Methyl 3-(4-oxocyclohexyl)propanoate (55.3 mg, 0.3 mmol) was reacted according to a modification of general procedure B using Fe(R,R-PDP), whereby the H\(_2\)O\(_2\) solutions were each added dropwise over a period of 5 min. Purification by flash chromatography (60% EtOAc/hexanes, 0.5% NEt\(_3\)) afforded the lactone product along with minor impurities, and the reaction yield was calculated relative to a known amount of internal standard (nitrobenzene) by \(^1\)H NMR. Run 1 (5.1 mg lactone, 0.030 mmol, 10% lactone; 23.0 mg rsm, 0.125 mmol, 42% rsm); run 2 (5.0 mg lactone, 0.030 mmol, 10% lactone; 23.5 mg rsm, 0.128 mmol, 43% rsm). **Average yield: 10%; Average rsm: 43%.

**Table 1.1, Entry 12:** 3-(4-oxocyclohexyl)propanoic acid\(^{21}\) (51.1 mg, 0.30 mmol) was reacted according to a modification of general procedure A using Fe(R,R-PDP), whereby the H\(_2\)O\(_2\) solutions were each added dropwise over a period of 5 min. Purification by flash chromatography (60% EtOAc/hexanes, 0.5% NEt\(_3\)) furnished the title compound as a clear, colorless oil. \(^1\)H NMR analysis of a crude reaction mixture
(0.1 mmol scale) purified by simple filtration through a short silica plug (100% EtOAc) revealed nearly complete consumption of starting material. Run 1 (22.5 mg lactone, 0.134 mmol, 45% lactone); run 2 (23.6 mg lactone, 0.140 mmol, 47% lactone). **Average yield: 46%.** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 2.72 (td, $J = 14.3$, 6.5 Hz, 2H), 2.69 (app t, $J = 8.5$ Hz, 2H), 2.38-2.34 (m, 2H), 2.26-2.19 (m, 2H), 2.14 (app t, $J = 8.5$ Hz, 2H), 1.98 (td, $J = 13.8$ Hz, 5.5 Hz, 2H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 209.3, 176.0, 83.6, 37.4, 36.7, 32.7, 28.6. IR (film, cm$^{-1}$): 2933, 2873, 1768, 1714, 1458, 1437, 1421, 1248, 1188, 1151, 1103, 947. HRMS (ESI) m/z calc’d C$_9$H$_{12}$O$_3$Na$^{[M+Na]^+}$: 191.0684, found 191.0685.

**Table 1.2**

(S)-3-acetoxy-5,5-dimethylidihydropyran-2-one (Table 1.2): (S)-methyl 2-acetoxy-4-methylpentanoate$^{22}$ (56.5 mg, 0.30 mmol) was reacted according to general procedure B using either Fe(R,R-PDP) or Fe(S,S-PDP). Purification by flash chromatography (20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes). **R,R-PDP**: Run 1 (10.7 mg lactone, 0.062 mmol, 21% lactone; 34.4 mg rsm, 0.183 mmol, 61% rsm); run 2 (11.4 mg lactone, 0.066 mmol, 22% lactone; 36.2 mg rsm, 0.192 mmol, 64% rsm). **R,R-PDP Average yield: 22%; Average rsm: 63%.** S,S-PDP: Run 1 (11.2 mg lactone, 0.065 mmol, 22% lactone; 36.0 mg rsm, 0.191 mmol, 64% rsm); run 2 (11.8 mg lactone, 0.069 mmol, 23% lactone; 35.7 mg rsm, 0.190 mmol, 63% rsm). **S,S-PDP Average yield: 23%; Average rsm: 64%.**

**Table 1.2**: (S)-2-acetoxy-4-methylpentanoic acid$^{23}$ (52.3 mg, 0.30 mmol) was reacted according to general procedure A using either Fe(R,R-PDP) or Fe(S,S-PDP). Purification by flash chromatography (20% EtOAc/hexanes $\rightarrow$ 20% EtOAc/hexanes, 0.5% AcOH $\rightarrow$ 40% EtOAc/hexanes, 0.5% AcOH) afforded both unreacted starting material and the title compound as clear, colorless oils. **R,R-PDP**: Run 1 (14.4 mg lactone, 0.084 mmol, 28% lactone; 15.0 mg rsm, 0.086 mmol, 29% rsm); run 2 (15.3 mg lactone, 0.089 mmol, 30% lactone; 14.6 mg rsm, 0.084 mmol, 28% rsm). **R,R-PDP Average yield: 28%; Average rsm: 29%.** S,S-PDP: Run 1 (26.6 mg lactone, 0.154 mmol, 51% lactone); run 2 (25.8 mg lactone, 0.150 mmol, 50% lactone). **S,S-PDP Average yield: 51%; No rsm.** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.56 (t, $J = 8.5$ Hz, 1H), 2.59 (dd, $J = 13.0$, 9.0 Hz, 1H), 2.15 (s, 3H), 2.05 (dd, $J = 12.8$, 9.5 Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 172.2, 169.9, 82.3, 69.3, 41.2, 29.2, 28.0, 20.8. IR (film, cm$^{-1}$): 2980, 2962, 2939, 2875, 1784, 1747, 1377, 1228, 1095, 924. HRMS (ESI) m/z calc’d C$_8$H$_{12}$O$_3$Na$^{[M+Na]^+}$: 195.0633, found 195.0629. $[\alpha]_{D}^{26}$ -1.7° (c 0.34, CHCl$_3$).
Kinetic resolution with carboxylic acid directing group.

![Chemical structure](image)

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Racemic 2-acetoxy-4-methylpentanoic acid (87.1 mg, 0.50 mmol) was reacted according to general procedure A using either Fe(R,R-PDP) or Fe(S,S-PDP). Purification by flash chromatography (30% EtOAc/hexanes → 30% EtOAc/hexanes, 0.5% AcOH) afforded both unreacted starting material and the lactone product as clear, colorless oils. **R,R-PDP:** 26.3 mg lactone, 0.153 mmol, 31% lactone; 32.2 mg rsm, 0.185 mmol, 37% rsm. **S,S-PDP:** 28.5 mg lactone, 0.166 mmol, 33% lactone; 30.3 mg rsm, 0.174 mmol, 35% rsm.

Lactone 22 was analyzed directly by chiral GC (Astec CHIRALDEX G-TA, 150°C isothermal):

**R,R-PDP:** major enantiomer $t_R = 3.7$ min, minor enantiomer $t_R = 4.4$ min: +34% ee.  
**S,S-PDP:** major enantiomer $t_R = 4.4$ min, minor enantiomer $t_R = 3.7$ min: -35% ee.

Carboxylic acid 20 was converted to the corresponding methyl ester by treating 5 mg of 20 with 0.5 mL DMF, 15 mg K$_2$CO$_3$, and the end of a Pasteur pipette worth of iodomethane and stirring the resulting mixture for 2 h at ambient temperature. The crude reaction mixture was diluted with Et$_2$O and washed 3X with H$_2$O using a separatory funnel. The organic layer was collected, dried over MgSO$_4$, filtered through celite, concentrated in vacuo and analyzed by chiral GC (Astec CHIRALDEX G-TA, 110°C isothermal):

**R,R-PDP:** major enantiomer $t_R = 5.1$ min, minor enantiomer $t_R = 4.5$ min: -28% ee.  
**S,S-PDP:** major enantiomer $t_R = 4.5$ min, minor enantiomer $t_R = 5.1$ min: +31% ee.

Table 1.3
(5r,8r)-8-(tert-butyl)-1-oxaspiro[4,5]decan-2-one (Table 1.3, Entry 1): Methyl 3-[(1s,4s)-4-(tert-butyl)cyclohexyl]propanoate (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(S,S-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes). Run 1 (15.9 mg lactone, 0.076 mmol, 30% lactone); run 2 (18.1 mg lactone, 0.086 mmol, 34% lactone). **Average yield: 32%**.

(Table 1.3, Entry 2): 3-[(1s,4s)-4-(tert-butyl)cyclohexyl]propanoic acid (Run 1: 63.7 mg, 0.30 mmol; run 2: 106.2 mg, 0.50 mmol) was reacted according to general procedure A using Fe(S,S-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded the title compound as a clear, colorless crystalline solid. Run 1 (34.4 mg lactone, 0.164 mmol, 55% lactone); run 2 (55.6 mg lactone, 0.264 mmol, 53% lactone). **Average yield: 54%**.

**1H NMR (CDCl₃, 500 MHz):** δ 2.58 (app t, J = 8.5 Hz, 2H), 2.06 (app t, J = 8.5 Hz, 2H), 1.85-1.79 (m, 4H), 1.78-1.70 (m, 2H), 1.14-1.04 (m, 3H), 0.87 (s, 9H).

**13C NMR (CDCl₃, 125 MHz):** δ 176.8, 87.3, 46.9, 36.9, 32.3, 30.3, 28.7, 27.7, 24.2. IR (film, cm⁻¹): 2945, 2864, 1778, 1454, 1369, 1290, 1207, 1184, 1124, 1055, 980. HRMS (ESI) m/z calc’d C₁₃H₂₂O₂Na [M+Na]⁺: 233.1517, found 233.1507.

Methyl 3-[(1R*,4R*)-4-(tert-butyl)-2-oxocyclohexyl]propanoate (Table 1.3, Entry 1): Methyl 3-[(1s,4s)-4-(tert-butyl)cyclohexyl]propanoate (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(S,S-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (15.1 mg ketoester, 0.063 mmol, 25% ketoester); run 2 (14.0 mg ketoester, 0.058 mmol, 23% ketoester). **Average yield: 24%**.

**1H NMR (CDCl₃, 500 MHz):** δ 3.67 (s, 3H), 2.40-2.17 (m, 5H), 2.06-1.96 (m, 1H), 1.88-1.69 (m, 4H), 1.56-1.42 (m, 2H), 0.88 (s, 9H).

**13C NMR (CDCl₃, 125 MHz):** δ 215.7, 173.6, 51.8, 48.7, 40.5, 32.9, 31.9, 30.1, 27.3, 27.3, 26.4, 21.5. IR (film, cm⁻¹): 2953, 2870, 1739, 1707, 1437, 1367, 1238, 1194, 1174, 1155. HRMS (ESI) m/z calc’d C₁₄H₂₅O₃ [M+H]⁺: 241.1804, found 241.1800.

To confirm this structural assignment, ketoester 32 (5.0 mg, 0.021 mmol, 1.0 equiv.) was dissolved in 0.5 mL anhydrous MeOH and treated with sodium methoxide (95%, 1.8 mg, 0.032 mmol, 1.5 equiv.). After 5h at ambient temperature, the reaction was quenched with water, acidified with 3M aq. HCl, and extracted 3X with CH₂Cl₂. The combined organics were dried over MgSO₄, filtered through
celite, and concentrated *in vacuo*. $^1\text{H}$ NMR analysis established conversion to the thermodynamically favored *trans* isomer identified in Table 1.3, Entry 3 (*vide infra*), thereby confirming the above structural assignment.

**(5s,8s)-8-(tert-butyl)-1-oxaspiro[4,5]decan-2-one (Table 1.3, Entry 3)**: Methyl 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoate (22.6 mg, 0.10 mmol) was reacted according to general procedure B using Fe(S,S-PDP) and analyzed by GC relative to a standard curve. Run 1 (9%); run 2 (9%). **Average GC yield: 9%**.

**(Table 1.3, Entry 4)**: 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoic acid (63.7 mg, 0.30 mmol) was reacted with Fe(S,S-PDP) according to general procedure A. Flash chromatography (10% EtOAc/hexanes $\rightarrow$ 20% EtOAc/hexanes) afforded the title compound as a clear, colorless crystalline solid. Run 1 (32.4 mg lactone, 0.154 mmol, 51% lactone); run 2 (31.1 mg lactone, 0.148 mmol, 49% lactone). **Average yield: 50%**. $^1\text{H}$ NMR (CDCl$_3$, 500 MHz): $\delta$ 2.58 (app t, $J = 8.5$ Hz, 2H), 1.96 (app t, $J = 8.5$ Hz, 2H), 1.96-1.90 (m, 2H), 1.68-1.62 (m, 2H), 1.49-1.36 (m, 4H), 1.05-0.98 (m, 1H), 0.85 (s, 9H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 177.1, 85.7, 47.4, 37.7, 34.3, 32.6, 28.8, 27.7, 23.3. IR (film, cm$^{-1}$): 2943, 2868, 2850, 1763, 1443, 1363, 1226, 1194, 1124, 1005, 953, 933. HRMS (ESI) m/z calc’d C$_{13}$H$_{22}$O$_2$Na $[\text{M+Na}]^+$: 233.1517, found 233.1514.

Methyl 3-[(1R*,4S*)-4-(tert-butyl)-2-oxocyclohexyl]propanoate (Table 1.3, Entry 3): Methyl 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoate (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(S,S-PDP). Purification by flash chromatography (10% EtOAc/hexanes $\rightarrow$ 20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes) afforded unreacted starting material and the ketoester as a clear, colorless oil. Run 1 (21.6 mg ketoester, 0.090 mmol, 36% ketoester; 9.6 mg rsm, 0.042 mmol, 17% rsm); run 2 (21.5 mg ketoester, 0.089 mmol, 36% ketoester; 7.3 mg rsm, 0.032 mmol, 13% rsm). **Average yield: 36%; average rsm: 15%**. $^1\text{H}$ NMR (CDCl$_3$, 500 MHz): $\delta$ 3.66 (s, 3H), 2.46-2.38 (m, 2H), 2.37-2.25 (m, 2H), 2.17-2.10 (m, 1H), 2.10-1.99 (m, 2H), 1.95-1.89 (m, 1H), 1.57-1.38 (m, 3H), 1.31-1.21 (dq, $J = 12.8$, 3.5 Hz, 1H), 0.88 (s, 9H). $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 213.1, 174.2, 51.6, 50.8, 49.3, 44.1, 33.2, 32.9, 31.7, 27.3, 26.7, 24.6. IR (film, cm$^{-1}$): 2954, 2868, 1739, 1711, 1448, 1437, 1367, 1246, 1194, 1173. HRMS (ESI) m/z calc’d C$_{14}$H$_{25}$O$_3$ [M+H]$^+$: 241.1804, found 241.1797.
To confirm this structural assignment, the ketoester 33 (15.0 mg, 0.062 mmol, 1.0 equiv.) was dissolved in 1 mL anhydrous MeOH, cooled in an ice/water bath, and treated with sodium borohydride (8.4 mg, 0.22 mmol, 3.5 equiv.). After 1.5 h at this temperature, the reaction was diluted with H$_2$O and extracted 3X with CH$_2$Cl$_2$. The combined organics were dried over MgSO$_4$, filtered through celite, and concentrated in vacuo, affording a 1:1 mixture of diastereomeric hydroxyesters. The crude product was dissolved in 1 mL benzene, treated with pTsOH•H$_2$O (several crystals), and stirred at ambient temperature for 1.5 h. The reaction was diluted with sat. aq. NaHCO$_3$ and extracted 3X with CH$_2$Cl$_2$. The combined organics were dried over MgSO$_4$, filtered through celite, concentrated in vacuo, and purified by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes), affording a 1:1 mixture of diastereomeric 6-membered lactone products (along with unidentified impurities) (8.5 mg, approx. 50% yield). The $^1$H NMR chemical shifts of the α-ester protons are nearly identical to those of model compounds.$^{26}$ Characteristic $^1$H NMR signals (CDCl$_3$, 500 MHz): 4.57 (m, 1H, cis-fused), 3.89 (td, $J = 10.5, 4.5$ Hz, 1H, trans-fused).

$(\pm)$-1,6-dioxaspiro[4,5]decan-2-one (Table 1.3, Entry 5)$^{27}$: $(\pm)$-methyl 3-(tetrahydroxyran-2-yl)propanoate (17.2 mg, 0.10 mmol) was reacted according to a modification of general procedure B (two cycles of catalyst/oxidant) using Fe($R$,$R$-PDP) and the crude reaction was analyzed by GC relative to a standard curve. Run 1 (2%); run 2 (2%). **Average GC yield: 2%.**

(Table 1.3, Entry 6): $(\pm)$-3-(tetrahydroxyran-2-yl)propanoic acid (47.5 mg, 0.30 mmol) was reacted according to a modification of general procedure A using Fe($R$,$R$-PDP), whereby two cycles of catalyst/H$_2$O$_2$ addition replaced the standard three additions. Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded the lactone as a clear, colorless liquid. Run 1 (27.3 mg lactone, 0.175 mmol, 58% lactone); run 2 (27.0 mg lactone, 0.173 mmol, 58% lactone). **Average yield: 58%.** $^1$H NMR (CDCl$_3$, 500 MHz): δ 3.90 (td, $J = 11.3, 3.5$ Hz, 1H), 3.78-3.73 (m, 1H), 2.76 (ddd, $J = 18.0, 10.5, 9.5$ Hz, 1H), 2.48 (ddd, $J = 17.8, 9.5, 2.5$ Hz, 1H), 2.19 (ddd, $J = 13.0, 9.5, 2.5$ Hz, 1H), 2.02 (ddd, $J = 13.5, 10.5, 9.5$ Hz, 1H), 1.96-1.85 (m, 2H), 1.78-1.54 (m, 4H). $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 176.8, 107.8, 63.5, 34.8, 34.0, 28.3, 24.4, 19.5. IR (film, cm$^{-1}$): 2951, 2879, 2854, 1776, 1450, 1417, 1371, 1286, 1234, 1209, 1130, 1099, 1047, 1009, 972, 943, 908, 885. HRMS (ESI) m/z calc’d C$_8$H$_{12}$O$_3$Na [M+Na]$^+$: 179.0684, found 179.0681.
(±)-Methyl 3-(6-oxotetrahydrofuran-2-yl)propanoate (Table 1.3, Entry 5): (±)-methyl 3-(tetrahydrofuran-2-yl)propanoate (51.7 mg, 0.30 mmol) was reacted according to a modification of general procedure B using Fe(R,R-PDP), whereby two cycles of catalyst/H₂O₂ addition replaced the standard three additions. Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes, 0.5% AcOH) afforded the lactone as an unstable oil, along with minor impurities. Product yield was measured by integration relative to an internal standard, and an analytical sample of the product was obtained by further chromatographic purification. Run 1 (11.8 mg lactone, 0.063 mmol, 21% lactone; 5.8 mg rsm, 0.034 mmol, 11% rsm); run 2 (12.4 mg lactone, 0.067 mmol, 22% lactone; 4.6 mg rsm, 0.027 mmol, 9% rsm). **Average yield**: 22%. **Average rsm**: 10%.

**1H NMR (CDCl₃, 500 MHz):** δ 4.38-4.31 (m, 1H), 3.68 (s, 3H), 2.62-2.51 (m, 3H), 2.50-2.40 (m, 1H), 2.03-1.80 (m, 5H), 1.60-1.50 (m, 1H). **13C NMR (CDCl₃, 125 MHz):** δ 173.6, 171.6, 79.3, 51.9, 30.9, 29.5, 29.4, 28.0, 18.5. IR (film, cm⁻¹): 2954, 2939, 2927, 2854, 1738, 1439, 1371, 1242, 1198, 1174, 1053. HRMS (ESI) m/z calc’d C₉H₁₄O₄Na [M+Na]^+: 209.0790, found 209.0783.

8-methoxy-5,8-dioxooctanoic acid (Table 1.3, Entry 5): (±)-methyl 3-(tetrahydrofuran-2-yl)propanoate 27 (51.7 mg, 0.30 mmol) was reacted according to a modification of general procedure B using Fe(R,R-PDP), whereby two cycles of catalyst/H₂O₂ addition replaced the standard three additions. Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes, 0.5% AcOH). Obtained as a crude oil and quantified relative to an internal standard by 1H NMR analysis. Further chromatographic purification provided an analytical sample. Run 1 (9.7 mg, 0.048 mmol, 16%); run 2 (9.1 mg, 0.045 mmol, 15%). **Average yield**: 16%. **1H NMR (CDCl₃, 400 MHz):** δ 3.67 (s, 3H), 2.72 (app t, J = 6.0 Hz, 2H), 2.60 (app q, J = 6.8 Hz, 2H), 2.57 (app t, J = 7.2 Hz, 2H), 2.40 (app t, J = 7.2 Hz, 2H), 1.92 (app p, J = 7.2 Hz, 2H). **13C NMR (CDCl₃, 100 MHz):** δ 208.2, 178.8, 173.4, 52.0, 41.5, 37.2, 32.9, 27.8, 18.6. IR (film, cm⁻¹): 3215 (br), 2953, 2927, 2852, 1738, 1714, 1439, 1412, 1365, 1209, 1176, 1103. HRMS (ESI) m/z calc’d C₉H₁₄O₅Na [M+Na]^+: 225.0739, found 225.0740.

Figure 1.2

Oxidation of methyl 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoate (25) using methyl(trifluoromethyl)dioxirane (TFDO) (Figure 1.2): To a pre-cooled (~20°C) solution of methyl 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoate 25 (56.6 mg, 0.25 mmol) in 2.5 mL dry CH₂Cl₂ in a 25 mL round-bottomed flask was added 3.4 mL 0.17 M TFDO solution (0.57 mmol, 2.3 equiv.) via Pasteur pipette. The reaction was tightly capped, stirred at -20°C for 0.5 h, and warmed to ambient temperature
for 1h. The crude reaction mixture was concentrated under reduced pressure and purified directly by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Run 1 (16.3 mg lactone 30, 0.078 mmol, 31% lactone 30; 16.2 mg ketoester 33, 0.067 mmol, 27% ketoester 33; 6.3 mg rsm, 0.028 mmol, 11% rsm); run 2 (16.5 mg lactone 30, 0.078 mmol, 31% lactone 30; 16.8 mg ketoester 33, 0.070 mmol, 28% ketoester 33; 8.0 mg rsm, 0.035 mmol, 14% rsm). **Average lactone (30) yield: 31%; Average ketoester (33) yield: 28%; Average rsm: 13%.**

**Oxidation of 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoic acid (26) using methyl(trifluoromethyl)dioxirane (TFDO) (Figure 2):** To a pre-cooled (-20°C) solution of 3-[(1r,4r)-4-(tert-butyl)cyclohexyl]propanoic acid 26 (53.1 mg, 0.25 mmol, 1 equiv.) in 2.5 mL dry CH₂Cl₂ in a 25 mL round-bottomed flask was added 2.4 mL 0.24 M TFDO solution (0.57 mmol, 2.3 equiv.) via Pasteur pipette. The reaction was tightly capped, stirred at -20°C for 0.5 h, and warmed to ambient temperature for 1h. The crude reaction mixture was concentrated under reduced pressure and treated with 1 mL DMF, 104 mg K₂CO₃ (3 equiv.), and 0.05 mL MeI (3 equiv.). Stirring followed overnight at ambient temperature and the resulting mixture was purified directly by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Run 1 (15.1 mg lactone 30, 0.072 mmol, 29% lactone 30; 16.2 mg ketoester 33, 0.067 mmol, 27% ketoester 33); run 2 (14.6 mg lactone 30, 0.069 mmol, 28% lactone 30; 16.9 mg ketoester 33, 0.070 mmol, 28% ketoester 33. **Average lactone (30) yield: 29%; Average ketoester (33) yield: 28%; Average rsm: < 5%.**

**Studies with Taxusin-derived Carboxylic Acid**

**Figure 1.3**

4a-hydro-20-taxusin carboxylic acid [(+)-39]. The alcohol depicted above (171.0 mg, 0.327 mmol, 1 equiv., obtained from BH₃ hydroboration/oxidation of taxusin²⁹) was added to a 40 mL screw-top scintillation vial containing a stir bar, and CH₂Cl₂ (6.5 mL). Dess-Martin periodinane (693.5 mg, 1.64 mmol, 5.0 equiv.) was then added, followed by a drop of water. The reaction was stirred at room temperature until complete conversion of the starting material was observed by TLC (2 h). **Extended reaction times led to low yields and complex product mixtures.** The reaction mixture was then added
dropwise to a stirring solution of saturated Na$_2$S$_2$O$_3$/NaHCO$_3$ (150 mL, 5:1 ratio), and stirred at room temperature for 30 min. The cloudy organic layer was extracted with CH$_2$Cl$_2$ (3x50 mL); the combined organic layers were washed with brine and dried over Na$_2$SO$_4$ (1 hr). After decantation, the solvent was removed to provide the crude aldehyde, which was used immediately for the next step without further purification.

$^1$H NMR (500 MHz, CDCl$_3$, diagnostic peaks): $\delta$ 9.83 (s, 1H), 6.02 (d, $J = 10.5$ Hz, 1H), 5.88 (t, $J = 15.0$ Hz, 1H), 5.86 (d, $J = 10.5$ Hz, 1H), 5.49 (app d, $J = 2.0$ Hz, 1H), 2.82-2.92 (m, 2H), 2.37 (app d, $J = 5.0$ Hz, 1H), 2.26-2.31 (m, 2H).

A 100 mL round bottom flask was charged with the aldehyde from the previous step, 2-methyl-2-butene (11.3 mL, 2M solution in THF), tert-butanol (22.5 mL), and a stir bar. A solution of NaClO$_2$ (930 mg, 10.3 mmol) and NaH$_2$PO$_4$ (655 mg, 5.5 mmol) in water (16 mL) was prepared in a separate scintillation vial. Both the oxidant vial and the reaction flask were cooled to 0°C with an ice bath. The oxidant solution was then slowly added dropwise via pipette to the reaction flask until complete conversion of the starting material was observed by TLC (~8 mL). The reaction flask was then poured into water (70 mL), and extracted with EtOAc (3x50 mL). The combined organic layers were dried over MgSO$_4$, filtered through celite, and evaporated. The crude product was purified by silica flash chromatography (gradient, 20% $\rightarrow$ 30% acetone/hexanes/1% AcOH) to provide the acid as a foamy white solid (148.4 mg, 0.277 mmol, 85% for 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.97 (d, $J = 11.0$ Hz, 1H), 5.86 (t, $J = 8.0$ Hz, 1H), 5.82 (d, $J = 10.5$ Hz, 1H), 5.37 (broad s, 1H), 2.77 (app dt, $J = 15.0$ Hz, 9.8 Hz, 1H), 2.68 (t, $J = 5.8$ Hz, 1H), 2.46 (d, $J = 5.0$ Hz, 1H), 2.14 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.91-1.99 (m, 2H), 1.81-1.82 (m, 1H), 1.70-1.72 (m, 2H), 1.56-1.62 (m, 1H), 1.56 (s, 3H), 1.11 (dd, $J = 14.8$, 7.3 Hz, 1H), 1.07 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 178.9, 170.6, 170.3, 170.0, 169.9, 136.7, 135.0, 76.9, 72.5, 70.7, 69.9, 50.9, 42.0, 40.4, 38.9, 34.0, 32.5 (2 peaks), 31.0, 27.0, 26.7, 22.9, 21.6, 21.4, 20.9, 20.8, 17.0, 14.7; IR (film, cm$^{-1}$): 3264 (broad), 3018, 2948, 2875, 1739, 1699, 1456, 1439, 1373, 1243, 1169, 1117, 1022, 972, 929, 755; HRMS (ESI) m/z calc’d for C$_{28}$H$_{40}$O$_{10}$Na [M+Na]$^+$: 559.2519, found 559.2516; $[\alpha]_D^{26.5} = +97.8^\circ$ (c = 1.9, CHCl$_3$).

**Taxusilactone [(+)-40].** Acid 39 (73.2 mg, 0.136 mmol, 1.0 equiv.) was reacted using the standard procedure with (S,S)-Fe(PDP)(SbF$_6$)$_2$. Following silica flash chromatography (1% $\rightarrow$ 2% $\rightarrow$ 3% $\rightarrow$ 4% $\rightarrow$ 5% MeOH/CH$_2$Cl$_2$), the lactone was isolated as a colorless, waxy solid (run 1: 36.9 mg, 0.0690 mmol, 51% yield; run 2: 34.1 mg, 0.0638 mmol, 47% yield), along with unreacted starting material (run
1: 16.6 mg, 0.0310, 23% recovery; run 2: 11.5 mg, 0.0214 mmol, 16% recovery. **Average (S,S catalyst): 49% yield lactone + 20% recovered starting material.**

Using (R,R)-Fe(PDP)(SbF6)2: Run 1(67.4 mg, 0.126 mmol scale): 17.9 mg, 0.0335 mmol, 27% yield); run 2 (73.1 mg, 0.136 mmol scale): 16.4 mg, 0.0307 mmol, 23% yield). **Average (R,R catalyst): 25% yield lactone.** Although a small amount of starting material was observed by crude 1H NMR, it was unable to be re-isolated from other reaction byproducts.

1H NMR (500 MHz, CDCl3): δ 5.94 (d, J = 10.0 Hz, 1H), 5.74-5.77 (m, 1H), 5.63 (d, J = 10.0 Hz, 1H), 5.31-5.36 (m, 1H), 4.65 (dd, J = 4.8, 2.8 Hz, 1H), 3.33 (dd, J = 13.8, 5.3 Hz, 1H), 2.76 (dd, J = 14.0, 9.5 Hz, 1H), 2.70 (dt, J = 17.3, 9.2 Hz, 1H), 2.19-2.23 (m, 1H), 2.03-2.11 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80-1.86 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.91-1.96 (m, 2H), 1.83-1.84 (m, 1H), 1.71-1.74 (m, 2H), 1.62 (dd, J = 13.8, 4.3 Hz, 1H), 1.58 (s, 3H), 1.13 (dd, J = 14.8, 7.3 Hz, 1H), 1.09 (s, 3H), 0.74 (s, 3H); **13C NMR (125 MHz, CDCl3): δ 175.3, 170.2, 170.1, 169.9, 169.7, 139.0, 136.7, 77.5, 73.1, 69.3, 66.4, 42.7, 42.3, 38.8, 37.9, 37.1, 32.6, 28.3, 27.5, 25.6, 25.4, 23.5, 21.2, 21.1, 20.9, 20.7, 15.8; IR (film, cm⁻¹): 3020, 2962, 2922, 2859, 1777, 1742, 1467, 1441, 1372, 1238, 1184, 1026, 981, 964, 755.5; HRMS (ESI) m/z calc’d for C28H38O10Na [M+Na]⁺: 557.2363, found 557.2363; [α]D^26 = +60.2° (c =1.44, CHCl3).

4a-hydro-20-taxusin carboxylic acid methyl ester [(+)-37]. A flame-dried 10 mL round bottom flask with stir bar was charged with acid 39 (33.2 mg, 0.0619 mmol, 1.0 equiv.) and dry methanol (0.62 mL) under nitrogen. The solution was cooled to 0°C, and trimethylsilyl diazomethane (2M in Et2O, Aldrich) was added dropwise until a yellow color persisted (~ 0.3 mL). The reaction was stirred at 0°C for 30 min, then carefully quenched with 0.15 mL acetic acid (the yellow color immediately disappated, and the solution bubbled). Removal of solvent by rotatory evaporation and purification by silica flash chromatography (20% → 30% → 40% ethyl acetate/hexanes) allowed isolation of the methyl ester as a white foam (24.7 mg, 0.0449 mmol, 72% yield).

1H NMR (500 MHz, CDCl3): δ 5.99 (d, J = 10.5 Hz, 1H), 5.87 (t, J = 9.5 Hz, 1H), 5.83 (d, J = 10.5 Hz, 1H), 5.04 (d, J = 2.0 Hz, 1H), 3.64 (s, 3H), 2.78 (app dt, J = 15.0, 9.5 Hz, 1H), 2.68 (t, J = 5.5 Hz, 1H), 2.45 (d, J = 5.5 Hz, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06-2.11 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.91-1.96 (m, 2H), 1.83-1.84 (m, 1H), 1.71-1.74 (m, 2H), 1.62 (dd, J = 13.8, 4.3 Hz, 1H), 1.58 (s, 3H), 1.13 (dd, J = 14.8, 7.3 Hz, 1H), 1.09 (s, 3H), 0.74 (s, 3H); **13C NMR (125 MHz, CDCl3): δ 173.6, 170.5, 170.3, 169.9, 169.8, 136.7, 135.1, 77.0 (partial CDCl3 overlap), 72.5, 70.7, 70.2, 51.7, 51.1, 41.8, 40.5, 39.0, 34.0, 32.5 (2 peaks), 31.1, 27.1, 26.9, 23.0, 21.7, 21.4, 21.0, 20.8, 16.9, 14.8; IR (film, cm⁻¹): 3016, 2954, 2881, 1739, 1454, 1439, 1371, 1238, 1169, 1117, 1020, 970, 754; HRMS (ESI) m/z calc’d for C29H42O10Na [M+Na]⁺: 573.2676, found 573.2678; [α]D^26 = +75.5° (c = 1.58, CHCl3).
Nortaxane methyl ester [(−)-38]. Methyl ester (+)-37 (24.7 mg, 0.0449 mmol, 1.0 equiv.) was reacted according to the standard procedure (with 0.5 equiv. AcOH). No peaks corresponding to lactone (+)-40 were observed by crude $^1$H NMR. Nortaxane product (−)-38 was isolated by silica flash chromatography (40% ethyl acetate/hexanes) as a colorless oil [run 1: 7.4 mg, 0.0131 mmol, 29% yield; run 2 (32.8 mg starting material, 0.0596 mmol scale): 9.7 mg, 0.0171 mmol, 29% yield].

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.09 (d, J = 10.5 Hz, 1H), 5.77 (d, J = 10.5 Hz, 1H), 5.54 (t, J = 7.3 Hz, 1H), 5.36 (app d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 2.54-2.58 (m, 2H), 2.43 (dd, J = 15.0, 8.5 Hz, 1H), 2.32 (dd, J = 8.5, 5.0 Hz, 1H), 2.07 (s, 3H), 2.02-2.05 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.82 (s, 3H), 1.77-1.78 (m, 1H), 1.55-1.61 (m, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.22-1.29 (m, 1H), 0.77 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 173.3, 170.5, 170.2, 169.7, 168.7, 144.9, 137.8, 79.4, 77.4, 75.5, 69.9, 69.4, 63.4, 51.6, 49.1, 45.0, 40.8, 35.7, 33.6, 27.4, 27.1, 24.8, 22.9, 21.1, 21.0, 20.9, 20.7, 15.8, 11.5; IR (film, cm$^{-1}$): 2949, 1740, 1732, 1462, 1441, 1372, 1238, 1029, 970, 754; HRMS (ESI) m/z calc’d for C$_{29}$H$_{42}$O$_{11}$Na [M+Na]$^+$: 589.2625, found 589.2620; [α]$_D$ 25° = -60.1° (c = 2.26, CHCl$_3$).

**Computational Methods for Analysis of Electronic Structure of (+)-39**

A conformational search was performed using the MMFF force field (‘vacuum’ phase) as implemented in the program Spartan ’10. The lowest energy conformer was selected for ab-initio energy minimization using density functional theory (B3LYP/6-31G$^\ddagger$), providing an energy of 1843.32406 Hartrees. Electrostatic atomic partial charges were calculated for all atoms. Of note are the hydrogen atoms attached to C1 and C2 (see Figure S1); as revealed below, H1 is significantly more electron-rich than either H2α or H2β (as expected when comparing 3° to 2° C—H bonds), rendering it the most likely site of oxidation.

**Electrostatic Charges from B3LYP/6-31G$^\ddagger$**

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Figure S1. Lowest potential energy conformer of (+)-39.

Atomic Electostatic Charges for lowest potential energy conformer of (+)-39.

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Nature of Substrate-derived Intermediate: 18-O Labeling Study

Representative Procedure for Preparation of 18-O Labeled Carboxylic Acids: Into a solution of 4-methylpentanenitrile (100 mg, 0.9 mmol, 1.0 equiv.) and 97% H$_2^{18}$O (120 µL, 6.0 mmol, 6.7 equiv.) in anhydrous 1,4-dioxane (1 mL, 0.9 M) in a 1 dram borosilicate vial was bubbled anhydrous HCl (g) for ~10 seconds. pH paper indicated that the vapor above the reaction mixture had a pH <2 and the reaction vial was tightly capped with a Teflon cap and stirred at ambient temperature for 2h. The pH of the reaction vapor was again checked to ensure a low pH and the resulting reaction mixture stirred overnight at 100°C. $^1$H NMR analysis of a reaction aliquot revealed full conversion of the starting nitrile and the reaction was purified directly by flash chromatography using gradient elution (10% EtOAc/hexanes $\rightarrow$ 20% EtOAc/hexanes $\rightarrow$ 40% EtOAc/hexanes), affording a pale yellow liquid (84 mg, 72%). To measure the isotopic enrichment of the resulting carboxylic acid, the corresponding benzyl ester was prepared (1.0 equiv. carboxylic acid, 4.0 equiv. benzyl bromide, 4.0 equiv. anhydrous triethylamine, and 1 mL anhydrous DMF; stirred mixture overnight at ambient temperature), and submitted for FI isotope ratio mass spectral analysis (88% double incorporation of 18-O).

Oxidation of 18-O labeled 4-methylvaleric acid using Fe(PDP): To a solution of 18-O labeled 4-methylvaleric acid (88% doubly 18-O labeled, 24 mg, 0.20 mmol, 1.0 equiv.) and Fe(S,S-PDP) (9.3 mg, 0.01 mmol, 0.05 equiv.) in 0.3 mL CH$_3$CN was added a solution of 50% H$_2^{16}$O$_2$ (13.8 µL, 0.24 mmol, 1.2 equiv.) in 1.8 mL CH$_3$CN over a period of 1 min. Stirring followed at ambient temperature for 10 min. The crude reaction mixture was filtered through a short silica/celite plug (100% EtOAc) and the resulting
filtrate was concentrated in vacuo. The crude reaction was dissolved in anhydrous DMF (0.75 mL) and to this solution was added anhydrous triethylamine (83 µL, 0.6 mmol, ~3 equiv.) and benzyl bromide (71 µL, 0.6 mmol, ~3 equiv.). Stirring followed overnight at ambient temperature in a capped 1 dram vial and the reaction was thereafter purified directly by flash chromatography (10% EtOAc/hexanes → 40% EtOAc/hexanes → 75% EtOAc/hexanes). Isolated benzylated starting material (9.1 mg), lactone (4.9 mg), and hydroxylactone (~3 mg) were submitted to FI isotope ratio mass spectral analysis. Run 1 (benzylated starting material: 88% doubly incorporated; lactone: 87% singly incorporated, 8% doubly incorporated, 5% no incorporation; hydroxylactone: 78% doubly incorporated, 22% singly incorporated); run 2 (benzylated starting material: 88% doubly incorporated; lactone: 87% singly incorporated, 7% doubly incorporated, 6% no incorporation; hydroxylactone: 71% doubly incorporated, 29% singly incorporated); run 3 (benzylated starting material: 88% doubly incorporated; lactone: 86% singly incorporated, 8% doubly incorporated, 6% no incorporation; hydroxylactone: 85% doubly incorporated, 15% singly incorporated). **Average for benzylated starting material: 88% doubly labeled; average for lactone: 87% singly labeled, 8% doubly labeled; average for hydroxylactone: 78% doubly labeled, 22% singly labeled.**

Notably, re-exposure of labeled lactone (87% singly labeled) to the reaction conditions led to no loss in $^{18}$O label (87% singly labeled after reaction). The isolation of primarily singly 18-O labeled lactone demonstrates that the C—H lactonization reaction proceeds through a hydroxylated intermediate that undergoes rapid lactonization, rather than an alternative mechanism wherein an iron-bound carboxylate undergoes radical recombination with a short-lived carbon-centered radical to provide the lactone directly, without the intermediacy of a hydroxyacid.

![Chemical Diagram](image)

**Oxidation of 18-O labeled 4,4-dimethylvaleric acid using Fe(PDP):** To a solution of 18-O labeled 4,4-dimethylvaleric acid (86% doubly 18-O labeled, 13.8 mg, 0.10 mmol, 1.0 equiv.) and Fe($R,R$-PDP) (4.7 mg, 0.005 mmol, 0.05 equiv.) in 0.15 mL CH$_3$CN was added a solution of 50% aqueous H$_2^{16}$O$_2$ (6.9 µL, 0.12 mmol, 1.2 equiv.) in 0.9 mL CH$_3$CN over a period of 1 min. The reaction stirred 10 min at ambient temperature and was filtered through a short silica/celite plug (100% EtOAc). Unreacted starting material was recovered (13.0 mg, 94% rsm) and submitted for FI isotope ratio mass spectral analysis (86% doubly 18-O labeled).
Generation of a peroxyacid intermediate using \( \text{H}_2\ce{^{16}O}_2 \) would lead to approx. 50% loss in \( \text{18-O} \) label in recovered starting material; because the \( \text{18-O} \) label is fully retained, our results demonstrate that such a pathway is not operative with \( \text{Fe(PDP)} \).

1.5 References

1. A portion of this work was summarized in a previous publication: Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721.


23. The non-racemic α-acetoxy acid was prepared according to the following procedure, \([\alpha]^{39}_D -28° (c 0.17, CHCl₃):\) Kolasa, T.; Miller, M. J. J. Org. Chem. 1987, 52, 4978.


28. Prepared according to the following procedure: Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. J. Am. Chem. Soc. 1989, 111, 6749. Despite extensive experimentation, we were unable to generate solutions of TFDO with concentrations greater than 0.1-0.2 M.

**Substrate-Dependent Mixed Desaturase/Oxygenase Reactivity of Aliphatic C—H Bonds using Non-heme Iron Catalysis**

### 2.1 Introduction

C—H oxidation reactions catalyzed by carboxylate-ligated non-heme iron enzymes are notable not only for their high levels of selectivity, but also for their broad scope. While also serving a structural role, the versatile carboxylate ligand plays the additional critical role of tuning the reactivity of the iron center. Collectively, these enzymes promote a wide range of transformations, including alkane hydroxylations, halogenations, and desaturations as well as arene oxidations, and it is this unparalleled versatility that is most intriguing to the synthetic community (Figure 2.1A). A well-known example, methane monooxygenase, effects hydrocarbon desaturation in addition to its well-known C—H hydroxylation activity. Alternatively, in the biosynthesis of the carbapenem antibiotics, a single enzyme, clavaminate synthase 2, promotes consecutive C—H hydroxylation, oxidative ring closure, and desaturation reactions (Figure 2.1B). Remarkably, this enzyme utilizes a single active intermediate, a high valent iron-oxo, for each of these transformations, relying on subtle active site control to direct a

![Figure 2.1](image-url)

**Figure 2.1**

- **A.** Diversity of reactivity
- **B.** Carbapenam biosynthesis
- **C.** Substrate-dependent mixed oxygenase/desaturase activity
short-lived carbon-centered radical to undergo either hydroxylation, ring closure, or desaturation. Even more strikingly, while the natural guanyl-substituted β-lactam substrate undergoes exclusively C—H hydroxylation, a synthetic substrate, lacking a terminal guanidine group, led to a reversal in selectivity, such that a mixture of desaturation and hydroxylation products were observed (Figure 2.1C).34 Thus far, mixed oxygenase-desaturase activity with unactivated C—H bonds has only been observed in the realm of enzymatic catalysis.

The synthetic community has disclosed a range of biomimetic small molecule transition metal catalysts capable of promoting C—H hydroxylations of aliphatic C—H bonds.35 Only a handful of examples, however, report desaturation activity and the reaction conditions often require stoichiometric pre-formed oxidants or great excesses of starting alkane.36 Several reports describe the observation of both hydroxylated and desaturated products, but in each case, the substrate has featured an activated C—H bond, likely due to a mechanistic requirement for a stabilized radical or cation intermediate. We recently reported a series of predictably site-selective aliphatic C—H oxidations of 2° and 3° sites using the non-heme iron(II) catalyst Fe(PDP)1 and H2O2.7 We found that acetic acid was a critical additive for increasing reactivity and that when the carboxylic acid moiety was incorporated into substrates, γ-butyrolactones were furnished.1,8 As described in Chapter 1 of this manuscript, we next validated the use of carboxylic acids as directing groups for non-heme iron catalyzed C—H hydroxylation, leading to both improvement in site-selectivity and reactivity relative to benchmark non-directing substrates. Unexpectedly, however, while carboxylic acids solved the site-selectivity challenge in the synthesis of γ-butyrolactones, a chemoselectivity problem associated with their use was discovered. We observed the consistent production of over-oxidized products (‘double oxidation’ products) unlikely to result from multiple, consecutive oxidations of a single substrate. Relying on a series of substrate-based mechanistic probes, we determined that carboxylic-acid containing substrates divert Fe(PDP)-catalyzed C—H hydroxylation toward desaturation activity to generate novel ‘double-oxidation’ products. As such, our results comprise the first report of mixed desaturase-hydroxylase activity of aliphatic C—H bonds using a small molecule catalyst. In analogy to nature, we favor a mechanistic explanation relying on the generation of a short-lived carbon-centered radical (lifetime <1 x 10−11 s) that diverges to provide products resulting from either hydroxylation or desaturation. We posit that, as a result of coordination to the metal catalyst, carboxylates promote this unexpected reactivity by changing the trajectory of approach of the short-lived radical to an iron-bound hydroxyl intermediate.37

2.2 Results and Discussion
Evaluation of a series of carboxylic acid-containing substrates under standard Fe(PDP)/H$_2$O$_2$ oxidation conditions, as expected, led to fused bicyclic butyrolactone products in approximately 40% yield (Table 2.1). Unexpectedly, ‘double-oxidation’ products were also consistently isolated in significant amounts. Fe(PDP)-catalyzed non-directed hydroxylations are highly sensitive to the electronic, steric, and stereoelectronic properties of aliphatic C—H bonds. Sites that are proximal to electron-withdrawing groups (EWGs), such as esters, are deactivated toward oxidation. Moreover, 1° C—H bonds are thought to be inert to these conditions. Given this, we were surprised to observe products formally representing two adjacent C—H oxidations, particularly in cases where the second oxidation appeared to occur at a 1° C—H bond. We therefore hypothesized that the observed ‘double oxidation’ products, rather than arising simply from over-oxidation of initially formed lactone, instead resulted from epoxidation of olefins generated in situ via desaturation followed by intramolecular epoxide ring-opening.

To begin our investigations, we evaluated oxidation of prochiral carboxylic acid-containing alkane 52 (Figure 2.2). As expected, a mixture of lactone and hydroxylactone products were isolated. Notably, oxidation of the lactone product under the standard conditions failed to generate detectable quantities of hydroxylactone 53 (data not shown). If hydroxylactone 53 resulted from alkanoic acid 52 via the intermediacy of an olefin intermediate, then oxidation of the corresponding olefin-containing carboxylic acid 54 should provide hydroxylactone 53 as the major product. As hypothesized, hydroxylactone 53 was produced under the standard reaction conditions from alkene 54 as the major

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<th>Table 2.1. ‘Double oxidation’ products</th>
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|-------|-------------------|-----------------|---------------------------|-----------------
| 1     | ![Structure](image1) | ![Structure](image2) | ![Structure](image3) | 43% 46 17% 49b |
| 2     | ![Structure](image4) | ![Structure](image5) | ![Structure](image6) | 42% 47 15% 50b |
| 3     | ![Structure](image7) | ![Structure](image8) | ![Structure](image9) | 43% 48 16% 51b |

*Average of two runs at either 0.3 or 0.5 mmol. **Products 49-51 generated as 1:1 mixtures of diastereomers.
Interested in using enantioinduction as a sensitive probe of mechanism, we further tested this hypothesis by measuring the enantioenrichment in oxidation products generated from these two starting materials using the chiral Fe(PDP) catalyst. Surprisingly, we observed significantly higher enantioenrichment from alkene 54 than from alkane 52 (36% ee vs. 13% ee). The observed discrepancy may be due to other alkanoic acid 52 statistically outcompeting alkenoic acid for binding to the catalyst under conditions where the alkenoic acid is generated in low concentrations \textit{in situ} (based on our reasoning that the larger ee result was a consequence of greater carboxylate ligation to the metal catalyst). Consistent with this explanation, when excess AcOH (10 equiv.) was included in the reaction of alkene 54, hydroxylactone 53 was isolated with enantioenrichment matching that observed when starting with alkane 52 (13% ee). Collectively, these results demonstrate that an olefin intermediate is viable \textit{en route} to ‘double oxidation’.

Under standard non-directed Fe(PDP)-catalyzed C—H oxidation, ‘double-oxidation’ products have never been observed, suggesting that this novel reactivity is substrate-dependent. In accord with these previous results, a substrate lacking a carbonyl-based directing group, protected alcohol 55, failed to form the epoxide product expected if a ‘double oxidation’ pathway were operative (Figure 2.3). Notably, oxidation of alkene 57 under identical conditions provided the corresponding epoxide in 60% yield, demonstrating that this product is stable to the highly oxidizing reaction conditions and therefore should be observed if a desaturation/oxidation pathway were operative from pivalate 55. This substrate-dependence on the differential reactivity of Fe(PDP) is reminiscent of that observed with non-heme iron enzymes. For example, as discussed in the introduction to Chapter 2, while clavaminate synthase 2 catalyzes hydroxylation of a guanidine-protected amine substrate, the analogous free amine primarily undergoes desaturation.
Having demonstrated that oxidation of an in situ-derived olefin intermediate likely accounted for ‘double oxidation’, we next hypothesized that the olefin resulted from acid-catalyzed dehydration of an intermediate hydroxyacid (Figure 2.4). According to this hypothesis, Fe(PDP)-catalyzed C—H hydroxylation would lead to a hydroxyacid intermediate that would either lactonize to form the expected product or undergo dehydration to an olefin. To test this hypothesis, we began with oxidation of alkanoic acid 59 under standard Fe(PDP) conditions, and isolated 28% of the expected lactone 60, with an approximately equimolar amount of ‘double oxidation’ products 61 and 62. When hydroxyacid 63 was exposed to the reaction conditions, however, only minor amounts of ‘double-oxidation’ products 61 and 62 (6% total) were detected by GC analysis. Moreover, oxidation of 59 using methyl(trifluoromethyl)dioxarane (TFDO), an electrophilic oxidant known to proceed via a concerted C—H oxidation pathway, also provided only minor amounts of 61 and 62 (5% total). These results stand in stark contrast to the combined yields of 61 and 62 (37% total) generated when alkanoic acid 59 was oxidized under standard Fe(PDP) conditions. Taken together, our results demonstrate that an alternative mechanism must account for dehydrogenation using Fe(PDP), and moreover, that Fe(PDP)/H_2O_2, unlike TFDO, promotes C—H hydroxylation through a non-concerted mechanism.

Alternatively, we considered that, in direct analogy to nature, carboxylic acid-containing substrates were somehow diverting the usual radical abstraction/hydroxyl rebound to desaturation reactivity. According to this mechanism, a short-lived carbon-centered radical would provide each product, either through hydroxyl rebound or further oxidation. To test this hypothesis, we questioned whether the presence of the carboxylate had rendered the hydroxylation non-stereoretentive through generation of a longer-lived, more stable carbon-centered radical. As described earlier, stereoretentive
hydroxylations were previously noted for non-directed Fe(PDP) C—\textsuperscript{\textit{H}} hydroxylations. Interestingly, carboxylate-directed C—\textsuperscript{\textit{H}} oxidations are also completely stereoretentive with 98\% ee starting material (\textit{S})-\textsuperscript{64} affording 98\% ee lactone (\textit{R})-\textsuperscript{65}. This result dictates that a carbon-centered radical, if a discrete intermediate, would need to have a lifetime <10\textsuperscript{-9} s.\textsuperscript{14,38} Next, we synthesized a carboxylic acid-containing substrate outfitted with a hypersensitive cyclopropane radical clock, previously developed for the study of cytochrome p450-mediated oxidations.\textsuperscript{39} Upon oxidation of ester-substituted cycloproyl carboxylic acid \textsuperscript{66}, we isolated 12\% yield of lactone \textsuperscript{68} and 33\% yield of ketoacid \textsuperscript{67}, but failed to detect any evidence of ring-opened products. Our inability to observe cyclopropane ring opening again suggests that a radical intermediate would need to be extremely short-lived, having a lifetime approximately <10\textsuperscript{-10} s. To provide evidence in support of our mechanistic proposal, we turned to a taxane-based radical probe. Fe(PDP)-catalyzed C—\textsuperscript{\textit{H}} hydroxylation would be expected to occur at C1 of taxane \textsuperscript{69} due to the electron-richness of this site (see Chapter 1 for discussion of DFT calculations). In the event, oxidation led to C1 oxidation, but not to provide the known C1 hydroxylated taxane. Instead, radical abstraction led to electrophilic attack by the proximal olefin, leading to rearranged nortaxane \textsuperscript{70}.\textsuperscript{40} Excitingly, this result provided the first direct evidence for a short-lived carbon-centered radical under non-heme iron catalysis,
reactions long-thought to proceed via radical abstraction chemistry. Additionally, because nortaxanes are well-known within in nature, this result allowed us to propose a novel biosynthetic proposal. Within the literature, nortaxanes have been proposed to arise biosynthetically during the cyclase phase of taxane biosynthesis; alternatively, our results suggest that these ring-contracted compounds could arise during the oxidase phase of biosynthesis, wherein radical abstraction at C1 would lead to either to rearrangement to provide a nortaxane or hydroxyl rebound to provide a C1-hydroxylated taxane (as found within Taxol). An ongoing collaboration with the Sherman group at the University of Michigan seeks to address this proposal using isolated cytochrome p450s.

Although we cannot exclude the possibility of two distinct pathways accounting for hydroxylation and desaturation, we favor the simplest conclusion that Fe(PDP) C-H oxidations, similar to analogous enzymatic systems, uniformly proceed via initial hydrogen abstraction. Carboxylate ligation to the iron-oxo accounts for the strong directing effect we observe on the site of oxidation and likely accounts for diverting the reaction pathway toward dehydrogenation. In enzymatic systems, the mechanistic basis for the substrate-dependent switch between the two reaction pathways remains elusive but is hypothesized to be due to either (1) the orientation of the radical with respect to the reactive iron center that may align the adjacent C—H bond for abstraction or (2) the character of the carbon-centered radical and its tendency to undergo further oxidation to a carbocation.37 The intramolecular nature of the oxidation with carboxylic acid substrates may strongly impact the orientation of the radical during the rebound step and promote a dehydrogenation pathway. Future studies will likely center on better delineating the factors affecting the varying extent of ‘double oxidation’ observed for different substrates.

Finally, as a synthetic lab, we realized that while the predictable generation of mixtures of products is rarely a stated goal of chemists, our discovery had some potential for the late-stage diversification of natural products.41 Toward this end, we synthesized a carboxylic acid-containing derivative of picrotoxinin,42 a well-known GABA inhibitor, and exposed it to the standard reaction conditions (Figure 2.6). As expected, we observed a mixture of lactone and hydroxylactone products resulting from site-selective C—H abstraction at the adjacent 3° site, for a combined yield of 77%. Notably, oxidation of the corresponding methyl ester led to no observed C—H oxidation reactivity due to the strongly electronically-deactivated hydrocarbon core. With lactone 72 and hydroxylactone 73 fitted
with new functional handles, one can readily envision rapid diversification to define structure-activity relationships. Alternatively, access to these compounds without the use of C—H oxidation chemistry would likely necessitate lengthy, de novo syntheses, which could prove prohibitive in a medicinal chemistry setting.

2.3 Conclusions

Carboxylic acid-containing alkane substrates were discovered to provide novel ‘double oxidation’ products under non-heme iron-catalyzed C—H hydroxylation conditions. Application of classical physical organic probes (stereochemistry, cyclopropyl radical clocks, etc…) and insight from natural systems demonstrated that mixed desaturase/hydroxylase activity was operative. Notably, these results constitute the first report of small molecule catalysis of such mixed activity. Additionally, the unexpected production of a nortaxane product from radical abstraction at C1 of taxane derivative 69 led to an intriguing biosynthetic proposal accounting for nortaxane production in natural systems. Future goals include defining the role of the carboxylate ligand in promoting desaturation and designing new desaturation-only catalysts. If one could be discovered, a ‘double oxidation’ catalyst would provide for the formal equivalent of a dihydroxylation of alkanes, and therefore, stand to significantly streamline the synthesis of complex organic molecules.

2.4 Experimental Section

**Synthesis of Carboxylic Acids for the Oxidative C-H Lactonization**

(±)-(1R*,2R*)-2-isopropyl-5-oxocyclohexanecarboxylic acid: Into a flame-dried 250 mL round-bottomed flask was added 4-isopropylcyclohexanone (1.97 g, 14.0 mmol, 1.0 equiv.), anhydrous CH₂Cl₂ (70 mL), and anhydrous triethylamine (9.8 mL, 70.2 mmol, 5.0 equiv.). The resulting clear, colorless solution was cooled to -78°C and to it was added neat TMSOTf (9.34 g, 42.0 mmol, 3.0 equiv.) over 5 min. Stirring of the resulting clear, colorless solution followed at this temperature for 5h while under an atmosphere of N₂. The crude reaction mixture had saturated aq. NaHCO₃ added to it, and after warming to near ambient temperature, the organics were collected, washed 3X with saturated aq. NaHCO₃, dried
over MgSO₄, filtered through celite, and concentrated in vacuo, affording a pale yellow liquid (2.6 g, 87%).

Into a flame-dried 250 mL round bottomed flask was added anhydrous DMSO (125 mL) and the silyl enol ether (2.6 g, 12.2 mmol, 1.0 equiv.) while at ambient temperature. The reaction mixture was purged with oxygen, palladium acetate was added in one portion (275 mg, 1.22 mmol, 0.1 equiv.), and stirring of the black solution followed at ambient temperature under an atmosphere of oxygen for 16 h. The reaction was treated with saturated aq. NH₄Cl at 0°C and the aqueous layer was extracted 3X with Et₂O. The combined organics were washed 3X with water, dried over MgSO₄, filtered through celite/silica, and concentrated in vacuo, affording nearly pure product as a yellow oil (1.62 g, ~90%).

Into a flame-dried 500 mL round-bottomed flask was poured solid CuBr•Me₂S (5.96 g, 29.0 mmol, 2.0 equiv.) and the laboratory lights were turned off. The flask was purged for 5 min with N₂ and to it was added anhydrous THF (80 mL). The resulting suspension was cooled to -78°C and vinylmagnesium bromide (1.0 M in THF, 58 mL, 58 mmol, 4.0 equiv.) and neat TMSCl (3.7 mL, 29.0 mmol. 2.0 equiv) were added simultaneously in a dropwise fashion (15 min.). Stirring followed at -78°C for 0.5 h and neat enone (2.0 g, 14.5 mmol, 1.0 equiv.) was added via syringe. The reaction stirred at this temperature for 3h and was then quenched with water. The reaction was allowed to warm to room temperature and the aqueous layer was extracted 1X with Et₂O. The organic layer was dried over MgSO₄, filtered through celite/silica, concentrated in vacuo, and used without further purification. The crude oil was dissolved in 40 mL CCl₄, 40 mL CH₃CN, and 60 mL H₂O and treated with NaIO₄ (15 g, 70 mmol) and RuCl₃•nH₂O (0.2 g). The reaction stirred overnight at ambient temperature and was partitioned between 1M aq. HCl and CH₂Cl₂. The aqueous layer was extracted 3X with CH₂Cl₂ and the combined organics were dried over MgSO₄, filtered through celite, concentrated in vacuo, and purified by flash chromatography (silica, 20% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes, 1% AcOH). Isolated the product as a viscous yellow oil that solidified after being open to air for several days (1.0 g, 5.4 mmol, 37% yield, 2 steps).

¹H NMR (CDCl₃, 400 MHz): δ 11.45 (br s, 1H), 2.81 (td, J = 9.6, 5.2 Hz, 1H), 2.64-2.47 (m, 2H), 2.45-2.28 (m, 2H), 2.02-1.91 (m, 2H), 1.91-1.80 (m, 1H), 1.60-1.46 (m, 1H), 0.99 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 209.5, 180.3, 46.5, 43.5, 42.4, 40.0, 28.8, 23.8, 21.4, 16.7. IR (film, cm⁻¹): 3207 (br), 2962, 2897, 2877, 1712, 1468, 1421, 1390, 1371, 1336, 1275, 1182. HRMS (ESI) m/z calc’d C₁₀H₁₇O₃ [M+H]⁺: 185.1178, found 185.1175.
(±)-(1R*,2R*)-2-isopropylcyclopentanecarboxylic acid: Into a flame-dried 200 mL round-bottomed flask was added solid CuBr•Me₂S (3.26 g, 15.86 mmol, 2.0 equiv.). The flask was purged 5 min with N₂, anhydrous THF (40 mL) was added, and the resulting suspension was cooled to -78°C. Isopropylmagnesium chloride (2.0 M in THF, 15.9 mL, 31.8 mmol, 4.0 equiv.) was added dropwise, followed by neat TMSCl (2.0 mL, 15.86 mmol, 2.0 equiv.). Stirring of the resulting dark red mixture followed at -78°C for 0.5 h, at which point neat methyl 1-cyclopentene-1-carboxylate (1.0 g, 7.93 mmol, 1.0 equiv) was added dropwise. Stirring followed at -78°C for 1h 20min and the reaction was quenched with 1M aq. HCl. After warming to ambient temperature, the reaction was partitioned between water and Et₂O and extracted 3X with Et₂O. The combined organics were washed 1X with water, dried over MgSO₄, filtered through celite, and concentrated in vacuo (crude dr: ~1.5:1 in favor of cis).

The crude ester was treated directly with LiAlH₄ (900 mg, 23.7 mmol, ~3 equiv.) in anhydrous THF (40 mL) while at 0°C, and thereafter heated to reflux for 4.5 h. After being cooled to near ambient temperature, 0.9 mL water, 0.9 mL 15% aq. NaOH, and 2.7 mL water were added carefully to quench the reaction and the resulting suspension was filtered through celite. The filtrate was concentrated in vacuo and purified by flash chromatography (silica, 5% EtOAc/hexanes → 10% EtOAc/hexanes → 20% EtOAc/hexanes), affording an inseparable mixture of diastereomers.

While at ambient temperature, the mixture of diastereomeric primary alcohols was treated directly with 25 mL acetone and Jones reagent in a dropwise manner until the red color of the reagent persisted, indicating the presence of excess oxidant (~0.5 h). The crude reaction mixture was taken up in Et₂O and water and extracted 3X with Et₂O. The combined organics were dried over MgSO₄, filtered through silica/celite, concentrated in vacuo, and purified extensively by flash chromatography (silica, 100% pentane, 2% AcOH) to afford each pure diastereomer as a clear, colorless oil.

¹H NMR (CDCl₃, 500 MHz) cis diastereomer: δ 2.93 (app t, J = 6.0 Hz, 1H), 1.98-1.75 (m, 4H), 1.70-1.50 (m, 4H), 1.00 (d, J = 7.5 Hz, 3H), 0.91 (d, J = 7.5 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 183.3, 53.5, 46.7, 30.2, 30.0, 29.3, 23.7, 22.7, 22.5. IR (film, cm⁻¹): 3068 (br), 2960, 2872, 1703, 1741, 1471, 1448, 1425, 1296, 1232, 943. HRMS (EI) m/z calc’d C₉H₁₆O₂ [M⁺]: 156.11503, found 156.11595.
General Procedure A

**C-H oxidation of Carboxylic Acids (0.5 mmol substrate):** Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 1 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH$_3$CN, and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating an amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN. The reaction stirred a final 10 minutes and was analyzed by TLC. The crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et$_2$O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

General Procedure B

**C-H oxidation of Non-Carboxylic Acids (0.5 mmol substrate):** Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst 1 (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH$_3$CN, 14.3 µL AcOH (0.25 mmol, 0.5 equiv.), and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating an amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 1 (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 µL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt% in H$_2$O, 34.6 µL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN. The reaction stirred approx. 16h at ambient temperature to ensure complete lactonization of intermediate hydroxyester products and was thereafter concentrated *in vacuo* and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products,
Et₂O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

**Representative procedure for preparation of lactone standard curve:** Stock solutions of nitrobenzene (98.5 mg, 10.00 mL EtOAc) and authentic 5,5-dimethyl-dihydrofuran-2-one (57.1 mg, 5.00 mL EtOAc) were prepared. To each of nine GC vials was added 500 µL nitrobenzene stock solution (4.9 mg, 0.040 mmol per vial), followed by an aliquot of the lactone stock solution, in increasing amounts (100 µL, 200 µL, ..., 900 µL; 0.01 mmol, 0.02 mmol, ..., 0.09 mmol). As such, the first GC vial represented a 10% yield of lactone for a 0.10 mmol reaction, while the ninth vial represented a 90% yield of lactone. These solutions were mixed thoroughly and analyzed by GC; a plot of % yield vs. measured lactone/nitrobenzene generated data points that could be readily fit to a linear equation of the form y = mx + b.

**Representative procedure for measurement of GC yield from Carboxylic Acids (0.10 mmol):** The oxidation reaction of 4-methylvaleric acid (11.6 mg, 0.10 mmol) was performed according to general procedure A, immediately subsequent to measurement of the standard curve. After the reaction was complete, nitrobenzene (4.9 mg, 0.040 mmol) was transferred to the reaction mixture from a separate vial using EtOAc. The resulting solution was mixed thoroughly and analyzed by GC, providing the measured lactone/nitrobenzene ratio.

**Products of the Oxidative C-H Lactonization**

(±)-(3αR*,7αR*)-3,3-dimethylhexahydrosbenzofuran-1,6-dione (47): (±)-(1R*,2R*)-2-isopropyl-5-oxocyclohexanecarboxylic acid (55.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(S,S-PDP). Purification by flash chromatography (50% EtOAc/hexanes → 75% EtOAc/hexanes → 100% EtOAc) afforded the lactone product as a clear, colorless crystalline solid. Run 1 (22.4 mg, 0.123 mmol, 41%); run 2 (23.4 mg, 0.128 mmol, 43%).

**Average yield: 42%**. ¹H NMR (CDCl₃, 500 MHz): δ 2.86 (ddd, J = 15.0, 4.0, 1.5 Hz, 1H), 2.66 (td, J = 13.8, 4.0 Hz, 1H), 2.62-2.55 (m, 1H), 2.41 (dd, J = 14.3, 14.0 Hz, 1H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 1H), 1.66 (qd, J = 12.8, 5.0 Hz, 1H), 1.54 (s, 3H), 1.33 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 207.0, 174.1, 85.5, 50.6, 43.5, 41.3, 40.1, 27.5, 23.8, 21.0. IR (film, cm⁻¹): 2976, 2937, 2879, 1766, 1724, 1712, 1379, 1269, 1242, 1186, 1144, 1072, 1055, 974, 881. HRMS (ESI) m/z calc’d C₁₀H₁₄O₃Na [M+Na]⁺: 205.0841, found 205.0838.
(±)-(3aR*,7aR*)-3-(hydroxymethyl)-3-methylhexahydroisobenzofuran-1,6-dione (50):

(±)-(1R*,2R*)-2-isopropyl-5-oxocyclohexanecarboxylic acid (55.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(S,S-PDP). Purification by flash chromatography (50% EtOAc/hexanes → 75% EtOAc/hexanes → 100% EtOAc) afforded the hydroxylactone products as separable diastereomers (1:1 dr). Product yield was measured by integration relative to an internal standard and an analytical sample of each diastereomer was obtained by further chromatographic purification. Run 1 (8.8 mg, 0.048 mmol, 16% combined); run 2 (7.7 mg, 0.042 mmol, 14% combined). Average yield: 15% (combined yield).

Fast-migrating diastereomer: Rf = 0.49 (100% EtOAc). 1H NMR (CDCl3, 500 MHz): δ 3.81 (AB d, J = 12.5 Hz, 1H), 3.77 (AB d, J = 12.5 Hz, 1H), 3.23 (td, J = 14.3, 4.0 Hz, 1H), 2.86 (dd, J = 4.0 Hz, 1H), 2.65-2.58 (m, 1H), 2.37-2.26 (m, 3H), 2.16-2.09 (m, 1H), 1.97 (qd, J = 12.8, 5.0 Hz, 1H), 1.46 (s, 3H).

13C NMR (CDCl3, 125 MHz): δ 207.1, 175.2, 86.6, 66.1, 50.4, 44.0, 42.1, 40.4, 23.3, 23.1. IR (film, cm⁻¹): 3419 (br), 2924, 2875, 2856, 1763, 1711, 1462, 1419, 1381, 1346, 1302, 1188, 1145, 1122, 1053, 982, 885. HRMS (ESI) m/z calc’d C10H15O4 [M+H]+: 199.0970, found 199.0967.

Slow-migrating diastereomer: Rf = 0.35 (100% EtOAc). 1H NMR (CDCl3, 500 MHz): δ 3.83 (AB d, J = 12.5 Hz, 1H), 3.59 (AB d, J = 12.5 Hz, 1H), 2.90-2.84 (m, 1H), 2.79-2.68 (m, 2H), 2.62-2.55 (m, 1H), 2.46 (dd, J = 14.5, 12.0 Hz, 1H), 2.35 (ddd, J = 16.0, 12.8, 7.0 Hz, 1H), 2.22-2.10 (br s, 1H), 2.08-2.02 (m, 1H), 1.72-1.60 (m, 1H), 1.29 (s, 3H). 13C NMR (CDCl3, 125 MHz): δ 206.9, 174.0, 87.3, 66.1, 43.3, 42.9, 41.3, 40.1, 23.8, 16.7. IR (film, cm⁻¹): 3442 (br), 2924, 2877, 2854, 1759, 1709, 1649, 1458, 1419, 1379, 1344, 1232, 1186, 1053, 976, 881. HRMS (ESI) m/z calc’d C10H15O4 [M+Na]+: 199.0970, found 199.0965.

(±)-(3aR*,6aS*)-3,3-dimethylhexahydrocyclopenta[c]furan-1-one (48): (±)-(1R*,2R*)-2-isopropylcyclopentanecarboxylic acid (Run 1: 78.1 mg, 0.50 mmol; run 2: 46.9 mg, 0.30 mmol) was reacted according to general procedure A using either Fe(R,R-PDP) or Fe(S,S-PDP). Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes) afforded the lactone as a clear, colorless oil. R,R-PDP: Run 1 (33.1 mg, 0.215 mmol, 43%); S,S-PDP: Run 2 (19.6 mg, 0.127 mmol, 42%). Average yield: 43%. 1H NMR (CDCl3, 500 MHz): δ 3.21 (td, J = 8.8, 4.0 Hz, 1H), 2.51 (app q, J = 8.0 Hz, 1H), 2.05-1.93 (m, 2H), 1.73-1.52 (m, 4H), 1.41 (s, 3H), 1.39 (s, 3H). 13C NMR (CDCl3, 125 MHz): δ 180.4, 84.5, 50.4, 46.7, 30.1, 29.3, 28.7, 26.6, 23.9. IR (film, cm⁻¹): 2964, 2872, 1765, 1450, 1389, 1373, 1311, 1275, 1250, 1219, 1161, 1115, 1099, 968, 953. HRMS (ESI) m/z calc’d C9H14O2Na [M+Na]+: 177.0891, found 177.0895.
(±)-(3aR*,6aS*)-3-(hydroxymethyl)-3-methylhexahydrocyclopenta[c]furan-1-one (51):
(±)-(1R*,2R*)-2-isopropylcyclopentanecarboxylic acid (Run 1: 78.1 mg, 0.50 mmol; run 2: 46.9 mg, 0.30 mmol) was reacted according to general procedure A using either Fe(R,R-PDP) (Run 1) or Fe(S,S-PDP) (Run 2). Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes) afforded the hydroxylactones as a 1:1 mixture of diastereomers. Extensive chromatographic purification provided an analytical sample of the slow-migrating diastereomer and an impure sample of the fast-migrating diastereomer. Run 1 (13.5 mg, 0.080 mmol, 16%); run 2 (7.9 mg, 0.046 mmol, 15%). Average yield: 16% (combined yield).

Fast-migrating diastereomer (containing unknown, inseparable impurity): R_f = 0.33 (60% EtOAc/hexanes). 1H NMR (CDCl_3, 500 MHz): δ 3.83 (AB d, J = 12.0 Hz, 1H), 3.65 (AB d, J = 12.0 Hz, 1H), 3.26 (td, J = 9.0, 3.5 Hz, 1H), 2.59 (app q, J = 7.5 Hz, 1H), 2.06-1.91 (m, 2H), 1.74-1.56 (m, 4H), 1.46 (s, 3H). 13C NMR (CDCl_3, 125 MHz): δ 180.0, 85.8, 66.4, 48.7, 46.4, 29.1, 27.4, 26.9, 25.1. IR (film, cm⁻¹): 3425 (br), 2958, 2929, 2873, 1745, 1452, 1379, 1313, 1284, 1219, 1149, 1055, 1039, 958. HRMS (ESI) m/z calc’d C_9H_15O_3 [M+H]^+: 171.1021, found 171.1015.

Slow-migrating diastereomer: R_f = 0.29 (60% EtOAc/hexanes). 1H NMR (CDCl_3, 500 MHz): δ 3.64 (AB d, J = 11.5 Hz, 1H), 3.57 (AB d, J = 11.5 Hz, 1H), 3.30 (td, J = 9.3, 4.0 Hz, 1H), 2.70 (app q, J = 7.5 Hz, 1H), 2.05-1.91 (m, 3H), 1.72 (app q, J = 7.0 Hz, 2H), 1.64-1.56 (m, 2H), 1.34 (s, 3H). 13C NMR (CDCl_3, 125 MHz): δ 180.9, 86.8, 70.5, 47.3, 45.7, 30.4, 29.0, 26.6, 18.8. IR (film, cm⁻¹): 3411 (br), 2956, 2924, 2872, 2854, 1739, 1454, 1381, 1306, 1286, 1227, 1090, 1061, 962. HRMS (ESI) m/z calc’d C_9H_15O_3 [M+H]^+: 171.1021, found 171.1018.

5,5-dimethyldihydrofuran-2-one (Isolated): 4-methylvaleric acid (58.1 mg, 0.50 mmol) was reacted according to general procedure A using Fe(R,R-PDP). The crude reaction mixture was poured over a saturated aqueous sodium bicarbonate solution (50 mL) and extracted 3X with Et_2O (3 x 75 mL). The combined organics were dried over MgSO_4 and filtered through celite. The filtrate was concentrated carefully by rotary evaporation to minimize loss of the volatile product, and before reaching dryness, was loaded onto a column of silica and purified by flash chromatography (50% Et_2O/pentane), affording the title compound as a clear, colorless liquid. Run 1 (27.1 mg, 0.238 mmol, 48%); run 2 (27.6 mg, 0.242 mmol, 48%). Average isolated yield: 48%.

(GC): To determine a more accurate yield of the lactone, a standard curve was measured by gas chromatography according to the general procedure described above. 4-methylvaleric acid (11.6 mg, 0.10 mmol) was reacted according to general procedure A using Fe(R,R-PDP), and nitrobenzene (4.9 mg, 0.040 mmol) was added following the reaction. Run 1 (71%); run 2 (68%). Average GC yield: 70%. 1H NMR (CDCl_3, 500 MHz): δ 2.62 (t, J = 8.0 Hz, 2H), 2.06 (t, J = 8.5 Hz, 2H), 1.43 (s, 6H). 13C NMR
(CDCl₃, 125 MHz): δ 176.7, 84.6, 34.7, 29.4, 27.8. IR (film, cm⁻¹): 2978, 2935, 2881, 1770, 1462, 1389, 1375, 1275, 1254, 1165, 1136, 1111, 958, 933. HRMS (ESI) m/z calc’d C₆H₁₀O₂Na [M+Na]⁺: 137.0578, found 137.0578.

5-(hydroxymethyl)-5-methylidihydrofuran-2-one⁴⁶: 4-methylvaleric acid (58.1 mg, 0.50 mmol) was reacted according to general procedure A using Fe(R,R-PDP). Purification by flash chromatography (40% Et₂O/pentane → 70% Et₂O/pentane), yield quantified relative to nitrobenzene. Run 1 (7.2 mg, 0.055 mmol, 11%); run 2 (7.2 mg, 0.055 mmol, 11%). **Average isolated yield:** 11%. ¹H NMR (CDCl₃, 500 MHz): δ 3.71 (AB d, J = 12.0 Hz, 1H), 3.52 (AB d, J = 12.0 Hz, 1H), 2.76-2.66 (m, 1H), 2.65-2.57 (m, 1H), 2.54-2.39 (br s, 1H), 2.36 (ddd, J = 12.5, 10.5, 6.5 Hz, 1H), 1.92 (ddd, J = 12.8, 10.0, 7.0 Hz, 1H), 1.37 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 177.6, 86.8, 68.5, 29.7, 29.7, 23.2. IR (film, cm⁻¹): 3438 (br), 2978, 2931, 2879, 1763, 1460, 1383, 1302, 1213, 1161, 1099, 1061, 945. HRMS (ESI) m/z calc’d C₆H₁₀O₃Na [M+Na]⁺: 153.0528, found 153.0521.

**Enantioselectivity of Hydroxylactonization**

4-methylvaleric acid (58.1 mg, 0.5 mmol) was reacted according to general procedure A using Fe(R,R-PDP). Purification by flash chromatography (75% EtOAc/hexanes) afforded the desired hydroxylactone product. Approximately 1 mg of the product was dissolved in CH₂Cl₂ (1 mL) in a GC vial and was treated with several crystals of 4-dimethylaminopyridine, three Pasteur pipette tips of triethylamine, and three Pasteur pipette tips of acetic anhydride. The GC vial was capped and placed atop the White group oven for 1-2 h and the resulting acetylated hydroxylactone product was analyzed by chiral GC (J&W cycloex-β, 100°C isothermal); major enantiomer tᵣ = 50.16 min, minor enantiomer tᵣ = 48.19 min. Run 1: 12% ee; run 2: 13% ee. **Average ee:** 13%. Repeating the above procedure with the Fe(S,S-PDP) catalyst led to isolation of hydroxylactone product of 13% ee, with the opposite sense of stereoinduction.
4-methylpent-4-enoic acid (11.4 mg, 0.10 mmol, 1.0 equiv.) was reacted according to a
modification of general procedure A using Fe(R,R-PDP), whereby the standard three cycles of
catalyst/oxidant addition were replaced with a single cycle. Additionally, 10 equiv. AcOH (57.6 µL, 1.0
mmol, 10 equiv.) were included in the reaction mixture prior to oxidant addition as a means of simulating
the reaction conditions under which the putative olefin intermediate would be generated, in low
concentrations, from the corresponding alkane. The crude reaction mixture was filtered through a short
celite/silica plug (100% EtOAc) and the filtrate was concentrated in vacuo. Scale-up reactions (0.2 mmol
starting olefin) provided the hydroxylactone product after flash chromatography (100% EtOAc). Run 1
(19.8 mg, 0.152 mmol, 76%); run 2 (18.2 mg, 0.140 mmol, 70%). **Average isolated yield: 73%**. The
resulting hydroxylactone product was converted to the acetoxy derivative as described above and
analyzed by chiral GC (J&W cyclolex-β, 100°C isothermal); major enantiomer t_R = 50.26 min, minor
enantiomer t_R = 48.10 min. Run 1: 12% ee; run 2 14% ee. **Average ee: 13%**. Repeating the above
procedure with the Fe(S,S-PDP) catalyst led to isolation of hydroxylactone product of 13% ee, with the
opposite sense of stereoinduction.

**Non-directed C-H Oxidation: Absence of ‘Double Oxidation’ Products**

![Diagram of hydroxylactone product]

**4-hydroxy-4-methylpentyl pivalate**: 4-methylpentyl pivalate (55.9 mg, 0.30 mmol)
was reacted according to general procedure B using Fe(R,R-PDP). Purification by
flash chromatography (5% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes) afforded the
tertiary alcohol product as a clear, colorless liquid. Notably, **GC analysis of the crude reaction mixture revealed the absence of the epoxide product prepared as a standard (vide infra)**. Run 1 (29.8 mg
tertiary alcohol, 0.147 mmol, 49%; 7.9 mg rsm, 0.042 mmol, 14%); run 2 (28.5 mg tertiary alcohol, 0.141
mmol, 47%; 7.8 mg rsm, 0.042 mmol, 14%) **Average yield: 48%**. **Average rsm: 14%**. ^1^H NMR (CDCl₃,
500 MHz): δ 4.07 (t, J = 6.5 Hz, 2H), 1.75-1.68 (m, 2H), 1.58 (br s, 1H), 1.54-1.49 (m, 2H), 1.23 (s, 6H),
1.20 (s, 9H). ^13^C NMR (CDCl₃, 125 MHz): δ 178.8, 70.7, 64.8, 40.0, 38.8, 29.4, 27.3, 23.9. IR (film, cm⁻¹
3-(2-methyloxiran-2-yl)propyl pivalate: 4-methylpent-4-en-1-yl pivalate (55.3 mg, 0.30 mmol) was reacted according to general procedure B (3 cycles of Fe(\(R,R\)-PDP)/\(H_2O_2\), although only \(\sim\)1 cycle needed for full conversion of the starting olefin). Purification by flash chromatography (5% EtOAc/hexanes \(\rightarrow\) 15% EtOAc/hexanes) afforded the title compound as a clear, colorless liquid. Run 1 (34.5 mg, 0.172 mmol, 57%); run 2 (38.1 mg, 0.190 mmol, 63%). **Average yield: 60%.** \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 4.07 (t, \(J = 6.5\) Hz, 2H), 2.62 (AB d, \(J = 4.5\) Hz, 1H), 2.60 (AB d, \(J = 4.5\) Hz, 1H), 1.78 - 1.56 (m, 4H), 1.33 (s, 3H), 1.19 (s, 9H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 178.6, 64.1, 56.6, 53.8, 38.8, 33.2, 27.3, 24.5, 21.0. IR (film, cm\(^{-1}\)):\(2962, 2929, 2873, 1730, 1481, 1460, 1396, 1367, 1284, 1157\). HRMS (ESI) m/z calc’d C\(_{11}\)H\(_{22}\)O\(_3\)Na\([M+Na]^+\): 225.1467, found 225.1467.

**Products of the Oxidative C-H Lactonization**

1-oxaspiro[4,4]nonan-2-one\(^{47}\): 3-cyclopentylpropanoic acid (71.1 mg, 0.50 mmol) was reacted according to general procedure A using Fe(\(R,R\)-PDP). Purification by flash chromatography (20% EtOAc/hexanes \(\rightarrow\) 40% EtOAc/hexanes \(\rightarrow\) 60% EtOAc/hexanes) afforded the lactone as a clear, colorless liquid. Run 1 (19.1 mg, 0.136 mmol, 27%); run 2 (20.3 mg, 0.145 mmol, 29%). **Average yield: 28%.** \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 2.58 (t, \(J = 8.0\) Hz, 2H), 2.19 (t, \(J = 8.5\) Hz, 2H), 2.10-1.96 (m, 2H), 1.88-1.78 (m, 2H), 1.75-1.63 (m, 4H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 177.0, 95.2, 38.6, 32.6, 30.0, 23.9. IR (film, cm\(^{-1}\)):\(2962, 2970, 2891, 1770, 1737, 1346, 1242, 1163, 972, 923\). HRMS (ESI) m/z calc’d C\(_8\)H\(_{12}\)O\(_2\)Na \([M+Na]^+\): 163.0735, found 163.0742.

1-oxaspiro[4,4]nonane-2,6-dione\(^{48}\): 3-cyclopentylpropanoic acid (71.1 mg, 0.50 mmol) was reacted according to general procedure A using Fe(\(R,R\)-PDP). Purification by flash chromatography (20% EtOAc/hexanes \(\rightarrow\) 40% EtOAc/hexanes \(\rightarrow\) 60% EtOAc/hexanes) afforded the ketolactone as a white, crystalline solid. Run 1 (12.6 mg, 0.082 mmol, 16%); run 2 (11.5 mg, 0.075 mmol, 15%). **Average yield: 16%.** \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 2.78 (dt, \(J = 17.5, 10.0\) Hz, 1H), 2.56 (ddd, \(J = 17.8, 9.8, 4.5\) Hz, 1H), 2.45-2.29 (m, 4H), 2.16-2.01 (m, 3H), 1.96-1.87 (m, 1H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 213.7, 176.0, 86.8, 35.2, 35.0, 28.8, 28.3, 17.8. IR (film, cm\(^{-1}\)):\(2976, 2954, 2914, 2891, 1772, 1743, 1454, 1412, 1396, 1248, 1223, 1161, 1128, 1039, 980\). HRMS (ESI) m/z calc’d C\(_{8}\)H\(_{10}\)O\(_3\)Na \([M+Na]^+\): 177.0528, found 177.0522.
(5R*,6S*)-6-hydroxy-1-oxaspiro[4.4]nonan-2-one\(49\): 3-cyclopentylpropanoic acid (71.1 mg, 0.50 mmol) was reacted according to general procedure A using Fe\((R,R\)-PDP). Purification by flash chromatography (20% EtOAc/hexanes \(\rightarrow\) 40% EtOAc/hexanes \(\rightarrow\) 60% EtOAc/hexanes) afforded the hydroxylactone along with minor impurities. Product yield was measured by integration relative to an internal standard, and an analytical sample of the product was obtained by further chromatographic purification. Run 1 (17.4 mg, 0.111 mmol, 22%); run 2 (15.8 mg, 0.101 mmol, 20%). **Average yield:** 21%. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 4.14-4.08 (m, 1H), 2.68-2.52 (m, 3H), 2.16-2.08 (m, 1H), 2.05-1.94 (m, 2H), 1.91-1.83 (m, 1H), 1.81-1.74 (m, 3H), 1.66-1.57 (m, 1H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 177.5, 95.2, 76.9, 34.8, 31.7, 29.4, 26.7, 19.3. IR (film, cm\(^{-1}\)): 3435 (br), 2958, 2935, 2881, 1770, 1358, 1236, 1\(\times\)165, 1078, 964. HRMS (ESI) m/z calc’d C\(_8\)H\(_{12}\)O\(_3\)Na [M+Na]\(^+\): 179.0684, found 179.0678.

3-(1-hydroxycyclopentyl)propanoic acid: To a solution of 1-oxaspiro[4.4]nonan-2-one (70 mg, 0.50 mmol, 1.0 equiv.) in 1:1 THF:H\(_2\)O (1 mL each) was added LiOH•H\(_2\)O (42 mg, 1.0 mmol, 2.0 equiv.) and the resulting mixture stirred vigorously at ambient temperature for 1h. 2.0 mL pH 4.0 buffer was added to the reaction mixture, followed by ~25 drops 1M aq. H\(_3\)PO\(_4\) (pH \(\approx\) 4). The reaction mixture was diluted with H\(_2\)O and extracted 4x with Et\(_2\)O. The combined organics were dried over Na\(_2\)SO\(_4\) for 15 min, the desiccant was removed by filtration through celite, and the filtrate was concentrated in vacuo, affording nearly pure product as a white powder (70 mg, 88%). The unstable product was used immediately. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 2.55 (t, \(J = 7.5\) Hz, 2H), 1.95 (t, \(J = 7.5\) Hz, 2H), 1.87-1.76 (m, 2H), 1.71-1.62 (m, 4H), 1.62-1.53 (m, 2H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 179.6, 82.2, 39.8, 35.9, 30.1, 23.8. IR (film, cm\(^{-1}\)): 3350 (br), 2962, 2958, 2935, 2881, 1770, 1358, 1236, 1165, 1078, 964. HRMS (ESI) m/z calc’d C\(_8\)H\(_{14}\)O\(_3\)Na [M+Na]\(^+\): 181.0841, found 181.0838.
Oxidation of 3-(1-hydroxycyclopentyl)propanoic acid using Fe(PDP): 3-(1-hydroxycyclopentyl)propanoic acid (15.8 mg, 0.10 mmol, 1.0 equiv) was reacted according to general procedure A. The crude reaction mixture had 4.9 mg nitrobenzene standard (0.04 mmol, 0.4 equiv.) added to it and the resulting mixture was analyzed by GC. Yields of lactone, ketolactone, and hydroxylactone were then calculated by comparison to standard curves prepared with authentic samples of each product. Run 1 (63% lactone, 1% ketolactone, 4% hydroxylactone); run 2 (61% lactone, 1% ketolactone, 5% hydroxylactone). **Average yields: 62% lactone, 1% ketolactone, 5% hydroxylactone.** In addition, the above procedure was repeated (15.8 mg starting material) and after the oxidation reaction was complete, the crude reaction mixture was filtered through a short silica/celite plug (100% EtOAc). The filtrate was analyzed by $^1$H NMR, revealing trace quantities of hydroxylactone and ketolactone products.

**Oxidation of 3-cyclopentylpropionic acid using methyl(trifluoromethyl)dioxirane (TFDO):** To a pre-cooled (-20°C) solution of 3-cyclopentylpropionic acid (12.4 mg, 0.087 mmol, 1 equiv.) in 1 mL dry CH$_2$Cl$_2$ in a 1 dram vial was added 2.0 mL 0.1 M TFDO$^{28}$ solution cooled to -78°C (0.20 mmol, 2.3 equiv.) via Pasteur pipette. The reaction was capped, stirred at -20°C for 0.5 h, and warmed to ambient temperature for 0.5 h. At this point, GC analysis revealed full conversion of starting material. The crude reaction mixture was concentrated *in vacuo* by rotary evaporation, 4.3 mg nitrobenzene standard (0.035 mmol, 0.4 equiv.) was added, and the reaction was analyzed by GC. Yields of lactone, ketolactone, and hydroxylactone were then calculated by comparison to standard curves prepared with authentic samples of each product. Run 1 (61% lactone, 4% ketolactone, 1% hydroxylactone); run 2 (60% lactone, 3% ketolactone, 1% hydroxylactone). **Average yields: 61% lactone (17), 4% ketolactone (18), 1% hydroxylactone (19).**

**Oxidation of 1-oxaspiro[4.4]nonan-2-one using Fe(PDP):** Lactone product (14.0 mg, 0.10 mmol, 1.0 equiv.) was re-exposed to the reaction conditions of general procedure B. The crude reaction mixture had 4.9 mg nitrobenzene standard (0.04 mmol, 0.4 equiv.) added to it and the resulting mixture was analyzed
by GC. Yields of lactone, ketolactone, and hydroxylactone were then calculated by comparison to standard curves prepared with authentic samples of each product. Run 1 (68% lactone, 2% ketolactone, 1% hydroxylactone); run 2 (64% lactone, 1% ketolactone, 1% hydroxylactone). **Average yields: 66% lactone, 2% ketolactone, 1% hydroxylactone.** In addition, the above procedure was repeated (14.0 mg starting material) and after the oxidation reaction was complete, the crude reaction mixture was filtered through a short silica/ceelite plug (100% EtOAc). The filtrate was analyzed by $^1$H NMR, revealing trace quantities of hydroxylactone and ketolactone products.

**Taxane-derivative Oxidation/Rearrangement**

![Chemical structure of taxane-derivative](image)

1-hydroxy-$\alpha$,20-carbonato-A-nortaxusin [-]-70: (+)-$\alpha$,20-carbonatotaxusin 69 (53.2 mg, 0.094 mmol, 1.0 equiv.) was reacted with ($R,R$)-Fe(PDP) following general procedure B, except that only one oxidation cycle was used. After silica gel column chromatography (gradient, CH$_2$Cl$_2$ → 1% → 2% → 3% MeOH/CH$_2$Cl$_2$), 70 was isolated as a colorless oil (11.6 mg, 0.020 mmol, 21% yield), along with unreacted starting material (15.2 mg, 0.027 mmol, 29% recovery). X-ray quality crystals of 70 were obtained from slow evaporation of CHCl$_3$/acetone.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.11 (d, $J = 10.5$ Hz, 1H), 6.82 (d, $J = 10.5$ Hz, 1H), 5.58 (t, $J = 7.5$ Hz, 1H), 5.26 (t, $J = 2.5$ Hz, 1H), 4.18 (AB, $\Delta\nu = 3.6$ Hz, $J_{ab} = 13.0$ Hz, 2H), 2.59 (d, $J = 8.5$ Hz, 1H), 2.42 (dd, $J = 14.3$, 7.3 Hz, 1H), 2.30 (bs, 1H), 2.17 (dd, $J = 14.0$, 8.3 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.93-1.97 (m, 1H), 1.81 (s, 3H), 1.78-1.83 (m, 1H), 1.71 (dt, $J = 13.1$, 3.7 Hz, 1H), 1.60-1.64 (m, 2H), 1.35 (d, $J = 13.5$ Hz, 1H), 1.29 (s, 3H), 1.16 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR: (125 MHz, CDCl$_3$) $\delta$ 170.6, 170.1, 169.4, 168.6, 146.0, 137.3, 85.3, 79.1, 76.5, 75.7, 69.2, 69.0, 68.8, 62.9, 42.5, 41.6, 39.0, 27.1, 26.5, 26.1, 24.8, 23.7, 21.1, 20.8, 20.6 (2 peaks), 17.4, 11.5; IR (film, cm$^{-1}$): 3556, 2974, 2933, 2873, 2858, 1813, 1745, 1458, 1439, 1373, 1236, 1144, 1070, 1059, 1030, 962, 910, 754; HRMS (ESI) $m/z$ calc’d for C$_{29}$H$_{40}$O$_{12}$Na [M+Na]$^+$: 603.2417, found 603.2416; $[\alpha]_D^{25} = -38.7^\circ$ (c = 1.68, CHCl$_3$).
Reaction of C1-hydroxy taxusin derivative with Fe(PDP). Independently synthesized 1-hydroxy-4α,20-carbonato-taxusin (37.4 mg, 0.0644 mmol, 1.0 equiv.) was reacted following general procedure B with (R,R)-1. No products matching rearranged compound 70 were observed by crude $^1$H NMR or TLC comparison with a known standard, despite 100% conversion.

Single crystal X-ray crystallography data of (-)-70.

Table 1. Crystal data and structure refinement for ba53las.

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Independent reflections 3791 [R(int) = 0.0594]
Completeness to theta = 27.17° 99.4 %
Absorption correction Integration
Max. and min. transmission 0.9877 and 0.9704
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3791 / 231 / 466
Goodness-of-fit on F² 1.027
Final R indices [I>2sigma(I)] R1 = 0.0374, wR2 = 0.0906
R indices (all data) R1 = 0.0507, wR2 = 0.0984
Absolute structure parameter 0(10)
Largest diff. peak and hole 0.377 and -0.177 e.Å⁻³

"CCDC 794910 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

Study of Stereoretention of Oxidative C-H Lactonization

(R)-5-ethyl-5-methyldihydrofuran-2-one: (S)-4-methylhexanoic acid (65.1 mg, 0.50 mmol) was reacted according to general procedure A and purified by flash chromatography (40% Et₂O/pentanes), taking care to concentrate the volatile product below room temperature by rotary evaporation. The title compound was isolated as a clear, colorless liquid. Run 1 (35.3 mg, 0.28 mmol, 56%); run 2 (35.9 mg, 0.28 mmol, 56%). Average yield: 56%. ¹H NMR (CDCl₃, 500 MHz): δ 2.59 (m, 2H), 2.08 (m, 1H), 1.96 (m, 1H), 1.70 (m, 2H), 1.37 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 176.9, 87.3, 33.7, 32.5, 29.3, 25.2, 8.3. IR (film, cm⁻¹): 2974, 2933, 2885, 1768, 1462, 1383, 1240, 1165, 1134, 1103, 937. HRMS (ESI) m/z calc’d C₇H₁₃O₂ [M]⁺: 129.0916, found 129.0914. Enantiomeric excess (ee) was determined by chiral GC analysis (J&W cycloex-β, 85°C isothermal); major enantiomer tᵣ = 15.67 min, minor enantiomer tᵣ = 16.83 min; 98% ee. The starting material was also 98% ee, as determined by chiral GC analysis of the corresponding methyl ester (J&W cycloex-β, 45°C isothermal); minor enantiomer tᵣ = 25.68 min, minor enantiomer tᵣ = 26.18 min; 98% ee. No
erosion in ee was observed.

Cyclopropane Radical Probe Experiment

(±)-4-trans-2-(tert-butoxycarbonyl)cyclopropyl)butanoic acid: To a flame-dried 50 mL round-bottomed flask under an atmosphere of N₂ was added Rh₂(OAc)₄ (20.0 mg, 0.045 mmol, 0.0045 equiv. dimer), methyl 5-hexenoate (1.28 g, 10 mmol, 1 equiv.), and 10 mL dry CH₂Cl₂. While at ambient temperature, a solution of tert-butyl diazoacetate (Aldrich, 2.2 g, 14 mmol, 1.4 equiv.) in 20 mL dry CH₂Cl₂ was added via syringe pump addition over a period of 4h. The crude reaction mixture was filtered through a short plug of neutral alumina and the filtrate was concentrated in vacuo and purified by flash chromatography (hexanes → 3% EtOAc/hexanes → 6% EtOAc/hexanes → 10% EtOAc/hexanes), affording the trans diastereomer as a colorless oil (dr > 10:1, 370 mg, 15% yield). The resulting methyl ester was hydrolysed by stirring with LiOH•H₂O (0.32 g, 7.65 mmol, 5.0 equiv.) in a 3:1 THF:H₂O mixture (12 mL THF, 4 mL H₂O) overnight at ambient temperature. The reaction was acidified with 1M aq. HCl (pH = 2) and extracted 3X with CH₂Cl₂. The combined organics were dried over MgSO₄, filtered through celite, and concentrated in vacuo, affording the title compound as a pale yellow oil (0.33 g, 1.45 mmol, 94%). ¹H NMR (CDCl₃, 500 MHz): δ 2.39 (t, J = 7.5 Hz, 2H), 1.76 (p, J = 7.5 Hz, 2H), 1.44 (s, 9H), 1.32-1.24 (m, 3H), 1.10-1.07 (m, 1H), 0.65-0.61 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 179.8, 173.8, 80.3, 33.6, 32.4, 28.3, 24.3, 21.8, 21.3, 15.1. IR (film, cm⁻¹): 3203 (br), 3005, 2980, 2933, 2870, 1712, 1477, 1456, 1408, 1367, 1342, 1284, 1252, 1155, 1086, 1043, 987, 933. HRMS (ESI) m/z calc’d C₁₂H₂₀O₄Na[M+Na]⁺: 251.1259, found 251.1259.

(±)-4-trans-2-(tert-butoxycarbonyl)cyclopropyl)4-oxobutanoic acid: (±)-4-trans-2-(tert-butoxycarbonyl)cyclopropyl)butanoic acid (Run 1: 57.1 mg, 0.25 mmol, Run 2: 68.5 mg, 0.30 mmol) was reacted according to general procedure A and purified by flash chromatography (10% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes) to separately provide pure unreacted starting material and a mixture of ketoacid 28 and lactones 29 that was further purified by flash chromatography (20% EtOAc/hexanes, no AcOH → 40% EtOAc/hexanes, 1% AcOH) to obtain pure samples of each oxidation product. The title compound was isolated as a white solid. Run 1 (20.5 mg ketoacid, 0.085 mmol, 34% ketoacid; 20.6 mg rsm, 0.090 mmol, 36% rsm); run 2 (22.8 mg ketoacid, 0.094 mmol, 31% ketoacid; 27.0 mg rsm, 0.12 mmol, 40% rsm). Average yield: 33%. Average rsm: 38%. ¹H NMR (CDCl₃, 500 MHz): δ 2.95 (t, J = 7.0 Hz, 2H), 2.69-2.58 (m, 2H), 2.41 (ddd, J = 8.5, 6.0, 4.0 Hz, 1H), 2.12 (ddd, J = 8.5, 6.0, 3.5 Hz, 1H), 1.45 (s, 9H), 1.40-1.35 (m, 2H). ¹³C NMR (CDCl₃, 125
MHz): δ 205.9, 178.4 (br), 172.2, 81.5, 38.1, 28.8, 28.1, 25.4, 17.3 IR (film, cm⁻¹): 3230 (br), 3006, 2980, 2931, 1726, 1695, 1479, 1456, 1404, 1369, 1325, 1252, 1217, 1161, 1103, 1041, 982, 957, 918. HRMS (ESI) m/z calc’d C₁₂H₁₈O₅Na [M+Na]⁺: 265.1052, found 265.1054.

(±)-tert-butyl 2-(5-oxotetrahydrofuran-2-yl)cyclopropanecarboxylate: The title compound was isolated as a colorless oil as a 1.7:1 mixture of diastereomers. Run 1 (6.0 mg, 0.027 mmol, 11%); run 2 (8.0 mg, 0.035 mmol, 12%). Average yield: 12%.

¹H NMR (CDCl₃, 500 MHz): δ 4.23 (q, J = 7.0 Hz, 0.6H), 4.04 (q, J = 7.5 Hz, 0.4H), 2.64-2.48 (m, 2H), 2.43-2.36 (m, 1H), 2.10-2.00 (m, 1H), 1.69-1.57 (m, 2H), 1.45 (s, 9H), 1.21-1.16 (m, 1H), 0.96 (ddd, J = 8.8, 6.5, 4.5 Hz, 0.6H), 0.88-0.84 (m, 0.4H). ¹³C NMR (CDCl₃, 125 MHz): δ 176.8, 172.3, 82.0, 81.0, 28.8, 28.7, 28.2, 28.0 (2C), 25.0, 24.8, 19.5, 18.5, 11.9, 11.5. IR (film, cm⁻¹): 2978, 2929, 2873, 2856, 1780, 1720, 1460, 1419, 1369, 1346, 1311, 1292, 1257, 1217, 1153, 1093, 1041, 1022, 984. HRMS (ESI) m/z calc’d C₁₂H₁₈O₄Na [M+Na]⁺: 249.1103, found 249.1107.

Picrotoxinin Derivative Synthesis and Oxidative C-H Lactonization

Picrotoxinin-8,9-ene [(+)-75]. To a vigorously stirred solution of solid HgCl₂ (1.2 g, 4.42 mmol, 2.6 equiv.) and Zn dust (12 g, 0.184 mol, 108 equiv.) under argon atmosphere (maintained with a rubber septum and balloon) in a 250 mL round bottom flask was added 1M aqueous HCl (30 mL) via syringe. After 15 min, the stirring was stopped, allowing the solution to settle. The liquid was decanted with a syringe, and fresh 1M HCl was added (30 mL), maintaining inert atmosphere. In a separate 250 mL Erlenmeyer flask, chromium(III) chloride hexahydrate (19.5 g, 73.2 mmol, 43 equiv.) was dissolved in 30 mL of 1M HCl. The septum on the flask containing the Zn(Hg) amalgam was quickly removed and the Cr(III)Cl₃
solution was rapidly added by pouring. The septum on the flask was replaced, and the reaction purged with an argon balloon. The reaction was stirred for 1 h, changing from dark forest green to a deep blue color (CrCl$_2$). In a separate 250 mL round bottom flask containing a stir bar, picrotoxinin (74) (500 mg, 1.71 mmol, 1.0 equiv.) was dissolved in acetone (33 mL, degassed for 30 min with argon). The flask was then purged with argon for 5 min. All of the Cr(II)Cl$_2$ solution was added to the solution of substrate, and the reaction allowed to stir for 15 hrs under argon. The reaction was worked up by dilution with CH$_2$Cl$_2$ (150 mL) and water (150 mL). The organic layer was separated, and the aqueous layer extracted twice with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layers were washed with sat. NaHCO$_3$ (2 x 150 mL), dried with MgSO$_4$, and the slurry filtered through celite. Evaporation of solvents yielded white solids, which were further purified by column chromatography on silica gel (40% ethyl acetate/hexane + 5% acetone) to give the diene product as a white solid (275.9 mg, 0.98 mmol, 57% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.39 (dd, $J = 2.0$, 4.0 Hz, 1H), 5.11 (t, $J = 1.5$ Hz, 1H), 4.98 (dd, $J = 4.5$, 3.5 Hz, 1H), 4.87 (d, $J = 1.5$ Hz, 1H), 4.69 (d, $J = 3.0$ Hz, 1H), 3.39 (bs, 1H), 3.35 (dd, $J = 18.0$, 4.0 Hz, 1H), 3.09 (dd, $J = 18.0$, 2.0 Hz, 1H), 2.92 (d, $J = 4.5$ Hz, 1H), 2.15 (s, 1H), 1.95 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR: (125 MHz, acetone- $d_6$) δ 175.8, 164.5, 143.8, 141.6, 135.0, 111.8, 83.5, 80.4, 79.0, 54.3, 50.4, 50.2, 50.0, 23.3, 19.8; IR (film, cm$^{-1}$): 3504 (broad), 2980, 2931, 2864, 1784, 1759, 1649, 1454, 1298, 1215, 1171, 1105, 980, 910; HRMS (ESI) m/z calc’d for C$_{15}$H$_{17}$O$_5$ [M+H]$^+$: 277.1076, found 277.1068; $[\alpha]_D^{25} = +133.6^\circ$ (c = 1.78, EtOH).

**Tetrahydropicrotoxinin [(−)-76].** To 250 mL round bottom flask was added 75 (523.6 mg, 1.9 mmol, 1.0 equiv.), acetic acid (50 mL), and a stir bar. Platinum oxide (10 mg) was added, and the reaction capped with a rubber septum. H$_2$ gas was then bubbled through the solution while vigorously stirring, until white solids began to form in the flask (4-6 hr). The hydrogen balloon was then removed, and additional platinum oxide catalyst was added (6 mg). **CAUTION: The hydrogen in the flask headspace may ignite during catalyst addition. Keep a watch glass nearby to extinguish.** The reaction was stirred an additional 8 hr (with H$_2$ bubbling for 2 h, then stirred with a H$_2$ atmosphere maintained by balloon for 6 h), and then diluted with EtOAc (50 mL). The solution/catalyst mixture was filtered on silica/celite, and the solvent removed to yield white solids. (466.2 mg, 1.58 mmol, 83% yield).

$^1$H NMR (500 MHz, acetone- $d_6$) δ 4.79 (dd, $J = 5.8$, 3.8 Hz, 1H), 4.41 (d, $J = 3.5$ Hz, 1H), 2.90 (t, $J = 10.5$ Hz, 1H), 2.75 (d, $J = 4.0$ Hz, 1H), 2.42 (dd, $J = 12.8$, 6.8 Hz, 1H), 2.36 (app dt, $J = 11.7$, 4.9 Hz, 1H), 2.09-1.94 (m, 4H), 1.57-1.48 (m, 1H), 1.44 (s, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR: (125 MHz, acetone- $d_6$) δ 177.4, 176.1, 83.4, 80.2, 79.2, 55.0, 51.9, 51.8, 51.1, 44.1, 26.6, 26.0, 24.8, 22.3, 20.9; IR (film, cm$^{-1}$): 3504 (broad), 2960, 2926, 2873, 1788, 1745, 1477, 1448, 1389, 1367, 1319, 1228, 1201, 1176, 1126, 1093, 1012, 970, 920; HRMS (ESI) m/z calc’d for C$_{15}$H$_{21}$O$_5$ [M+H]$^+$: 281.1389, found 281.1379; $[\alpha]_D^{25} = -36.2^\circ$ (c = 0.57, EtOH).
Hydroxy methyl ester [(+)-77]. To a 250 mL round bottom flask was added bis-lactone 76 (466.2 mg, 1.66 mmol, 1.0 equiv.), methanol (75 mL), and a stir bar. With stirring, 1N NaOH (75 mL) was slowly added (exothermic!). The reaction was stirred for 3 h at room temperature, then quenched by dropwise addition of 2M HCl until reaching a pH of 2. The reaction then extracted with ether (3 x 300 mL), dried over MgSO₄, filtered through celite, and evaporated to produce a crude white powder. The crude material was further purified by elution through a pad of silica gel (90 x 60 mm) with 50% EtOAc/hexanes (ca. 3L) to provide the methyl ester as a white solid (446.0 mg, 1.43 mmol, 86% yield).

1H NMR (500 MHz, CDCl₃) δ 4.45 (d, J = 4.0 Hz, 1H), 3.77 (dd, J = 11.5, 3.5 Hz, 1H), 3.73 (s, 3H), 2.80 (d, J = 7.0 Hz, 1H), 2.60 (d, J = 12.0 Hz, 1H), 2.18-2.07 (m, 2H), 2.01 (s, 1H), 1.96 (app t, J = 11.8 Hz, 1H), 1.85 (td, J = 13.9, 6.2 Hz, 1H), 1.77-1.71 (m, 2H), 1.56 (dd, J = 14.0, 5.0 Hz, 1H), 1.31 (s, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H); 13C NMR: (125 MHz, CDCl₃) δ 178.8, 172.8, 87.4, 81.4, 69.4, 55.2, 53.9, 51.8, 51.4, 40.6, 37.4, 29.5, 27.5, 22.6, 19.7, 16.1; IR (film, cm⁻¹): 3462 (broad), 2958, 2879, 1764, 1732, 1643, 1437, 1367, 1284, 1228, 1196, 1173, 1068, 1011, 980; HRMS (ESI) m/z calc’d for C₁₆H₂₅O₆ [M+H]⁺: 313.1651, found 313.1646; [α]D²⁵ = +56.5° (c = 1.0, CHCl₃).

Methyl ester acetate [(+)-78]. To a 1-dram screw-top vial was added methyl ester 77 (200.0 mg, 0.64 mmol, 1.0 equiv.), a stir bar, pyridine (1 mL), and acetic anhydride (1 mL). While stirring, N,N-dimethylaminopyridine was added (5.0 mg, 0.041 mmol, 0.06 equiv.), and the reaction was stirred at room temperature for 8 hr. The reaction was then slowly poured onto a stirring solution of sat. NaHCO₃ (ca. 50 mL), and allowed to quench until bubbling stopped (10 min). The mixture was extracted with diethyl ether (3 x 40 mL), and the combined organic layers washed with 1N HCl (5 x 10 mL). After drying the organic layer over MgSO₄, filtration through celite, and evaporation of the solvent, the crude acetate was isolated as a white solid (194.2 mg, 0.55 mmol, 86% yield). This material required no additional purification.

1H NMR (500 MHz, CDCl₃) δ 4.95 (dd, J = 11.8, 3.8 Hz, 1H), 4.49 (d, J = 3.5 Hz, 1H), 3.74 (s, 3H), 2.73 (d, J = 7.5 Hz, 1H), 2.66 (d, J = 12.5 Hz, 1H), 2.31 (td, J = 12.5, 1.0 Hz, 1H), 2.14 (s, 1H), 2.11 (s, 3H), 2.16-2.06 (m, 2H), 1.86 (td, J = 13.5, 6.0 Hz, 1H), 1.68 (septet, J = 7.0 Hz, 1H), 1.53 (dd, J = 14.0, 5.0 Hz, 1H), 1.33 (s, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.5 Hz, 3H); 13C NMR: (125 MHz, CDCl₃) δ 178.9, 172.3, 170.1, 83.4, 81.1, 70.4, 54.9, 54.1, 52.0, 51.6, 37.8, 37.6, 29.3, 27.4, 22.4, 21.2, 19.5, 16.2; IR (film, cm⁻¹): 3489 (broad), 2954, 2933, 2879, 1765, 1738, 1730, 1464, 1439, 1369, 1232, 1194, 1173, 1149, 1036, 1011, 980, 951, 903; HRMS (ESI) m/z calc’d for C₁₈H₂₇O₇ [M+H]⁺: 355.1757, found 355.1745; [α]D²⁵ = +75.0° (c = 0.9, CHCl₃).
Carboxylic Acid [(+)\text{-}71]. This procedure was adapted from Wu and coworkers.\textsuperscript{50} To a dry, 10 mL microwave tube containing methyl ester \textbf{78} (27.8 mg, 0.079 mmol, 1.0 equiv.) was added lithium chloride (200 mg, dried 24 h at 200°C, 0.1 torr) and a stir bar (inside the glove box). Dry DMF (0.5 mL) was added while stirring vigorously under an argon atmosphere for 10 min; the tube was then quickly closed with a teflon cap, and heated to 160°C (~1.5 min ramping time to reach this temperature) in a CEM discover multimode reaction microwave and held at 160°C for 5 min. The resulting brown slurry was cooled to 0°C with an ice bath, followed by dilution with ethyl acetate (2 mL) and 0.1N NaOH (2 mL). An additional stir bar was added, and the biphasic mixture stirred until all the lithium chloride had dissolved (5-10 min). The layers were separated, and the aqueous phase was washed with EtOAc (2 x 2 mL). While still cold, 1N HCl was added until a pH of 1-2 was obtained (usually evident by a color change from pale yellow to near colorless). The product was then extracted with ethyl acetate (3 x 5 mL); the combined organic washings were dried over MgSO\textsubscript{4}, filtered through celite, and evaporated to yield a waxy solid. Purification was carried out by flash chromatography on silica gel (30% acetone/hexanes + 1% AcOH) to isolate the carboxylic acid as a fluffy white solid (12.5 mg, 0.0367 mmol, 46% yield) after repeated azeotropic drying with benzene.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 4.97 (dd, \(J = 12.0, 3.0\) Hz, 1H), 4.50 (d, \(J = 3.5\) Hz, 1H), 2.76 (d, \(J = 7.0\) Hz, 1H), 2.67 (d, \(J = 12.5\) Hz, 1H), 2.30 (app t, \(J = 11.5\) Hz, 1H), 2.12 (s, 3H), 2.17-2.06 (m, 2H), 1.90 (td, \(J = 13.8, 6.3\) Hz, 1H), 1.80 (app t, \(J = 6.5\) Hz, 1H), 1.68-1.65 (m, 1H), 1.60 (bs, 2H), 1.35 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); \textsuperscript{13}C NMR: (125 MHz, CDCl\textsubscript{3}) \(\delta\) 179.4, 177.0, 170.5, 83.7, 81.5, 70.6, 55.1, 54.2, 52.0, 37.9, 37.7, 29.6, 27.7, 22.7, 21.5, 19.7, 16.3; IR (film, cm\textsuperscript{-1}): 3481 (broad), 2964, 2931, 2877, 1739 (2 peaks), 1726, 1468, 1371, 1242, 1173, 1043, 949, 904; HRMS (ESI) \(m/z\) calc’d for C\textsubscript{17}H\textsubscript{25}O\textsubscript{7} \([\text{M+H}]^+\): 341.1600, found 341.1602; \([\alpha]\)\textsubscript{D}\textsuperscript{25} = +120.6° (c = 0.43, CHCl\textsubscript{3}).

Lactone [(+)\text{-}72]. Following general procedure A, acid \textbf{71} (71.4 mg, 0.21 mmol, 1.0 equiv.) was reacted with catalyst (S,S)-\textbf{1}. Analysis of the crude reaction mixture indicated a mixture of diastereomers. [Run 1: (1.6:1 d.r.); run 2: (1.5:1 d.r.); average: 1.6:1 d.r. \(\textbf{73}\alpha/\textbf{73}\beta\). \textsuperscript{1}H NMR, acetone-\textit{d6}.] Flash chromatography with silica gel (gradient, 20%\textgreater30%\textgreater50% acetone/hexanes) was used to isolate the lactone product as white crystals [Run 1: (26.1 mg, 0.077 mmol), 37% yield; run 2 (74.2 mg scale): (29.1 mg, 0.086 mmol, 39% yield); average: 38% yield], along with a mixture of hydroxylactones \textbf{73}\alpha and \textbf{73}\beta [Run 1: (29.6 mg, 0.084 mmol, 40% yield); run 2: (29.7 mg, 0.084 mmol, 38% yield); average: 39% yield]. The hydroxylactone diastereomers could be separated by MPLC (gradient, 0\textgreater50% acetone/hexanes) to obtain pure samples for spectroscopic analysis.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.10 (dd, \(J = 11.8, 3.8\) Hz, 1H), 4.62 (d, \(J = 4.0\) Hz, 1H), 2.80 (d, \(J = 15.0\) Hz, 1H), 2.76 (d, \(J = 7.5\) Hz, 1H), 2.68 (bs, 1H), 2.50 (dd, \(J = 14.5, 6.5\) Hz, 1H), 2.35-2.30 (m, 1H), 2.19 (dd, \(J = 12.3, 8.3\) Hz, 1H).
5.8 Hz, 1H), 2.13 (s, 3H), 1.95 (dd, J = 13.3, 5.3 Hz, 1H), 1.59 (td, J = 13.5, 5.8 Hz, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); \(^{13}\)C NMR: (125 MHz, CDCl\(_3\)) \(\delta\) 178.5, 173.7, 170.0, 84.5, 84.2, 79.8, 70.8, 55.0, 54.1, 48.3, 44.0, 35.3, 28.7, 28.5, 20.7, 20.5, 19.1; IR (film, cm\(^{-1}\))): 3489 (broad), 2954, 2922, 2854, 1780, 1739 (2 peaks), 1464, 1377, 1263, 1240, 1174, 1120, 1072, 1036; HRMS (ESI) m/z calc’d for C\(_{17}\)H\(_{23}\)O\(_7\) [M+H]\(^+\): 339.1444, found 339.1448; \([\alpha]_D^{25}\) = +130.1° (c = 1.22, CHCl\(_3\)).

**Hydroxylactone [(+)-73a].** \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.48 (dd, J = 12.0, 3.5 Hz, 1H), 4.66 (d, J = 4.0 Hz, 1H), 3.86 (d, J = 12.5 Hz, 1H), 3.72 (d, J = 12.5 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 2.75 (d, J = 7.5 Hz, 1H), 2.56 (dd, J = 14.5, 12.0 Hz, 1H), 2.38-2.30 (m, 1H), 2.19 (dd, J = 12.5, 6.0 Hz, 1H), 2.17 (s, 1H), 2.13 (s, 3H), 1.88 (dd, J = 13.3, 5.3 Hz, 1H), 1.58 (td, J = 13.5, 6.0 Hz, 1H), 1.43 (s, 3H), 1.35 (s, 3H); \(^{13}\)C NMR: (125 MHz, CDCl\(_3\)) \(\delta\) 178.7, 175.0, 170.2, 85.5, 84.4, 80.2, 70.9, 66.1, 55.2, 54.0, 48.7, 43.6, 34.6, 28.6, 24.3, 20.9, 19.2; IR (film, cm\(^{-1}\))): 3473 (broad), 2947, 2929, 2873, 1763, 1751, 1462, 1379, 1329, 1286, 1236, 1178, 1119, 1066, 1038; HRMS (ESI) m/z calc’d for C\(_{17}\)H\(_{22}\)O\(_8\)Na [M+Na]\(^+\): 377.1212, found 377.1205; \([\alpha]_D^{25}\) = +132.7° (c = 0.32, EtOH).

**Hydroxylactone [(+)-73b].** \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.11 (dd, J = 11.3, 3.8 Hz, 1H), 4.65 (d, J = 4.0 Hz, 1H), 3.78 (d, J = 12.5 Hz, 1H), 3.58 (d, J = 12.5 Hz, 1H), 2.88 (AB\(_q\), \(\Delta\nu = 34.9\) Hz, \(J_{ab} = 15.0\) Hz, 1H), 2.87 (AB\(_q\), \(\Delta\nu = 22.4\) Hz, \(J_{ab} = 15.0\) Hz, 1H), 2.77 (d, J = 7.5 Hz, 1H), 2.39-2.31 (m, 1H), 2.20 (dd, J = 12.5, 6.0 Hz, 1H), 2.13 (s, 3H), 1.94 (dd, J = 13.5, 6.0 Hz, 1H), 1.66 (bs, 2H); 1.64 (td, J = 13.5, 6.0 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); \(^{13}\)C NMR: (125 MHz, CDCl\(_3\)) \(\delta\) 178.4, 173.5, 170.0, 86.3, 84.1, 79.9, 70.7, 67.4, 55.1, 54.1, 47.9, 37.4, 35.3, 28.5, 20.8, 19.2, 15.9; IR (film, cm\(^{-1}\))): 3464 (broad), 2929, 2872, 2854, 1765, 1749, 1462, 1377, 1329, 1284, 1236, 1186, 1115, 1070, 1036, 982; HRMS (ESI) m/z calc’d for C\(_{17}\)H\(_{25}\)O\(_8\)Na [M+Na]\(^+\): 377.1212, found 377.1220; \([\alpha]_D^{25}\) = +104.7° (c = 0.47, EtOH).

**Reaction of Methyl Ester (+)-78.** Methyl ester 78 (70.9 mg, 0.2 mmol, 1.0 equiv.) was reacted according to general procedure B with catalyst (S,S)-1. Flash chromatography yielded only recovered starting material as a white solid (63.9 mg, 0.18 mmol, 90% recovery). Reaction of methyl ester 33 (63.0 mg, 0.18 mmol, 1.0 equiv.) with catalyst (R,R)-1 under identical conditions also provided only starting material (59.8 mg, 0.169 mmol, 94% recovery).

**Reaction of acid 71 with TFDO.** Acid 71 (95.2 mg, 0.280 mmol, 1.0 equiv.) was added to a brand-new 50 mL round bottom flask equipped with a magnetic stir bar, and dissolved in CH\(_2\)Cl\(_2\) (17 mL). The flask was cooled to
0°C in an ice bath, and a -78°C solution of TFDO (4.2 mL, 0.42 mmol, 1.5 equiv., 0.1M in 1,1,1-trifluoroacetone) was added in one portion via liquid nitrogen-cooled Pasteur pipet. The reaction stirred for 2 h at 0°C, and was then sealed with a plastic cap and allowed to warm to room temperature for 12 h. The solvent was removed by rotatory evaporation at room temperature, and no lactone or hydroxylactone products were detected by crude 1H NMR or TLC comparison with authentic standards.

2.5 References

30. A portion of this work was summarized in a previous publication: Bigi, M. A.; Reed, S. A.; White, M. C. Nat. Chem. 2011, 3, 216.

Chapter 3

Biosynthetic and Derivatization Studies of Tricalysiolide B Using a Non-heme Iron Catalyst

3.1 Introduction

Nature utilizes a toolbox of oxygen-activating metalloenzymes to oxidize olefins and C—H bonds in a highly chemo-, site- and stereoselective manner. Required for both biodegradation and biosynthesis, these enzymes typically feature either heme- or non-heme- iron active sites and are well known for their extensive scope and exquisite selectivity. The active oxidant generated upon oxygen reduction is a high-valent iron-oxo. This intermediate exhibits characteristic reactivity with olefins and C—H bonds. Not surprisingly, chemists have sought to harness the power of these enzymes through the development of biomimetic small molecule catalysts. To date, the most successful approach makes use of iron(II) salts coordinated to amine-based ligands and hydrogen peroxide as terminal oxidant. In analogy to nature’s enzymes, these catalysts are thought to facilitate olefin epoxidation and C—H oxidation through the transient generation of high valent iron oxo intermediates. Recently, the White group described the use of Fe(PDP) (1), featuring a rigid bispyrrolidine ligand backbone, to oxidize 2° and 3° C—H bonds. For the first time, synthetically useful C—H oxidations using a single equivalent of alkane starting material were disclosed, and derivatives of bioactive natural products, including gibberellic acid, artimesinin, and pleuromutilone, were all shown to undergo highly selective C—H oxidation. Inspired by nature’s tailoring enzymes that functionalize complex hydrocarbon cores through selective olefin epoxidations and C—H oxidation, we hypothesized that Fe(PDP) could function as a synthetic, small molecule tailoring enzyme. A program centered around such a hypothesis would consist of isolation of bioactive natural products directly from their natural sources and application of Fe(PDP)-catalyzed oxidations to both probe biosynthetic pathways and provide previously inaccessible derivatives. As proof-of-principle, we desired a readily-available natural product that could be isolated in gram quantities, and through derivatization, provide suitable substrates for our studies.

Figure 3.1. Well-known diterpenes found in coffee, cafestol and kahweol, and the recently isolated ent-kaurene natural product, tricalysiolide B.
Cafestol and kahweol are two bioactive pentacyclic diterpenes found in coffee beans (Figure 3.1). In *Coffea arabica*, the plant responsible for the majority of global coffee production, cafestol comprises 0.6 wt % of the whole bean, while kahweol constitutes 0.3 wt %. These diterpenes belong to the *ent*-kaurene family of natural products, compounds that feature an interesting rearranged steroid core, which prompted total syntheses of both cafestol and kahweol by the Corey group in 1987. Besides their intriguing structure, cafestol and kahweol have received interest because of their widespread ingestion as major constituents of coffee. Cafestol exhibits anticarcinogenic activity in rats and has been suggested to inhibit the progression of Parkinson’s disease. Additionally, regular consumption of boiled coffee raises serum cholesterol levels in humans, and cafestol has been reported to influence cholesterol homeostasis by acting as an agonist for important nuclear receptors. Studies into these terpenes’ biological activity are ongoing, and perhaps surprisingly, few derivatization studies have been described. Recently, a new class of bioactive natural products containing the *ent*-kaurene framework were isolated from the wood of the Japanese tree *Tricalysia dubia*, the tricalysiolides. The relationship of these compounds to cafestol/kahweol is clear: the characteristic furan ring of cafestol/kahweol has been oxidized to provide the tricalysiolides. Hypothesizing that a cytochrome p450-mediated oxidation accounts for the biosynthesis of the tricalysiolides, we sought to apply Fe(PDP)-mediated oxidation as a means of accessing this class of natural products. Efficient oxidation of the furan ring of cafestol using Fe(PDP) could provide evidence that the proposed p450-mediated oxidation was a feasible biosynthetic transformation and, additionally, would allow ready access to the tricalysiolides to aid biological studies. Notably, only milligram quantities of the natural products could be isolated from *T. dubia*, preventing in-depth assay of the compounds’ biological activity. In sum, because of their potential ready availability from coffee beans, promising biological activity, and interesting chemical structures, the tricalysiolides were chosen as model compounds for our C—H oxidation studies into the use of Fe(PDP) as a tailoring enzyme mimic. Herein, we describe a biomimetic Fe(PDP)-catalyzed cafestol furan oxidation reaction that facilitates rapid access to gram scale quantities of tricalysiolide B. With the natural product in hand, we then evaluated its C—H hydroxylation reactivity and report an interesting site-, diastereo-, and chemoselective oxidation, and in collaboration with the Houk group, describe DFT calculations evaluating the role of electronic, steric, and stereoelectronic effects in dictating the reaction’s site selectivity.

### 3.2 Results and Discussion

To access tricalysiolide B, we began by routinely isolating several grams of a mixture of cafestol and kahweol from coffee grounds provided by the Starbucks Corporation using a soxhlet extractor.
Acetylation with acetic anhydride provided the corresponding diacetylated analogues, which could be safely purified by flash column chromatography. Next, hydrogenation of the inseparable mixture of cafestol diacetate and kahweol diacetate with a poisoned Pd(0) catalyst [Pd/CaCO$_3$/Pb(OAc)$_2$] and H$_2$ atmosphere provided cafestol diacetate (79) as a white powder. To test our biosynthetic hypothesis, cafestol diacetate (79) was oxidized with 1 mol% Fe(PDP) I and 1.0 equivalent H$_2$O$_2$, and the crude $\alpha,\beta$-unsaturated aldehyde product was filtered through silica and exposed to standard Pinnick oxidation conditions. Gratifyingly, this procedure provided 80 as a single diastereomer in good yield (59%), demonstrating that the biosynthetic production of the tricalysiolides could proceed via p450-mediated oxidation of cafestol (also isolated from T. dubia). Unfortunately, using forcing Fe(PDP) conditions with multiple equivalents of oxidant failed to provide greater than approximately 10% yields of 80. Lastly, hydrolysis with potassium carbonate in methanol proceeded uneventfully, providing tricalysiolide B (81) in two steps and 54% overall yield from cafestol diacetate. Notably, Fe(PDP)-catalyzed conversion of cafestol diacetate into tricalysiolide B can rapidly provide quantities of the recently isolated natural product sufficient for in-depth derivatization and bioassay studies.

The second goal of our studies was demonstration of rapid diversification of the cafestol core through C—H oxidation. To prepare tricalysiolide B for C—H oxidation using Fe(PDP), 80 was acetylated to provide peracetylated 82. C—H oxidation of ester 82 using Fe($S,S$-PDP) led to recovered unreacted starting material (36%), 2° alcohol 83 (21%) as a single diastereomer, and ketone 84 (9%). Recycling unreacted starting material 1X led to a 31% isolated yield of 83; the low reactivity of triacetoxy tricalysiolide B (82) can, at least in part, be traced to its poor solubility in CH$_3$CN. Notably, major product 83 was isolated as a single diastereomer and the electron-poor olefin found within 82 survived the highly oxidative reaction conditions. The structures of 2° alcohol 83 and ketone 84 were confirmed by X-ray crystallography ($p$-nitrobenzoate derivative for 2° alcohol 83).
The C—H oxidation reactions are notable for several reasons. For example, 82 features three $^3\text{C}–\text{H}$ sites and eight $^2\text{C}–\text{H}$ sites, demonstrating that in forming 83 in synthetically useful yields, the catalyst can promote site-selective oxidations. Additionally, this reaction constitutes a rare case of a chemoselective C—H oxidation in the presence of an olefin: unexpectedly, the electron-deficient olefin found in 82 survived the oxidizing conditions. Lastly, the $^2\text{O}$ alcohol product was isolated as a single diastereomer, demonstrating that, in addition to ensuring site-selectivity, the catalyst was able to select for a single diastereomeric C—H bond. Moreover, although $^2\text{O}$ alcohols are typically unstable toward over-oxidation under the reaction conditions, 83 only suffered minimal over-oxidation to the corresponding ketone. As such, this reaction constitutes a rare example of a chemo-, site-, and diastereoselective C—H oxidation.

To rationalize our results, computational analysis of ester 82 in collaboration with the Houk group at UCLA using density functional theory was undertaken to probe electronic effects, steric effects, and potential 1,3-diaxial strain that could be released upon oxidation at a particular site.\textsuperscript{63, 64} As expected, those methylene C—H bonds nearest the electron-withdrawing furanone and α-acetoxy ester subunits are the most electron-poor C—H bonds (H2 and H15), and therefore the least susceptible to oxidation, while those sites most susceptible to oxidation (H1, H6, H7, H11, H12, and H14) lie furthest from these sites. Interestingly, analysis of these 'activated' sites suggests that their electronic character is too similar in nature to lead to useful selectivities, suggesting that other factors are of increased importance. Analysis of van der Waals radii in the lowest energy conformer of 82 demonstrates that significant repulsion exists between H1 and H11, rendering those sites inaccessible to the bulky Fe(PDP) catalyst. Another factor calculated to be critical is alleviation of 1,3-diaxial strain between the axial C—H bonds at H6 and H14 and the axial CH$_3$ group at C10. Between the equatorial C—H bonds at C6 and C14, C6 is predicted to be more sterically accessible (note that C14 is adjacent to a quaternary center), suggesting that the selectivity observed for production of $^2\text{O}$ alcohol 83 results from a combination of its relative electron-richness, steric accessibility, and potential for reduction of 1,3-diaxial strain. Finally, analysis of the calculated structure reveals that the axial methyl group at C-10 blocks the α-face of 82, preventing the sterically encumbered catalyst from accessing the α-H at C-6. This steric effect likely accounts for the lack of overoxidation of 83 to the ketone oxidation state, as well as explaining the diastereoselectivity of the hydroxylation. With a
new functional handle installed onto the B ring of tricalysiolide derivatives 82, one can envision rapid diversification of 83 to define structure-activity relationships and develop compounds of enhanced bioactivity.

![Figure 3.2](image)

**Figure 3.2.** Values of dotted lines represent distances in Angstroms between indicated hydrogens for the lowest energy conformer. Calculated lowest energy conformer of 82 and calculated NPA charges of equatorial H atoms using B3LYP/6-311++G(d,p).

### 3.3 Conclusions

Herein we report a proof-of-principle experiment describing the use of Fe(PDP) as a tailoring enzyme small molecule mimic. Cafestol, a bioactive diterpene, was easily isolated in gram quantities directly from coffee grounds and, as a means of testing our biosynthetic proposal accounting for the tricalysiolides, subjected to Fe(PDP)-mediated oxidation to access the tricalysiolide class of natural products. In accord with our hypothesis, Fe(PDP)-mediated oxidation succeeded in oxidizing the furan ring of cafestol diacetate. Moreover, we demonstrate how Fe(PDP)-mediated C—H oxidation can readily provide novel derivatives of natural products. In the event, Fe(PDP)-catalyzed C—H oxidation provided for a rare example of a chemo-, site- and diastereoselective methylene oxidation. The utility of the resulting 2° alcohol for further functionalization using classical chemistry (e.g., displacement, oxidation followed by α-carbonyl functionalization, etc…) should be clear. This example demonstrates how installation of a new functional handle onto a hydrocarbon framework directly from the C—H bond can allow rapid entry into new classes of compounds. Moreover, due to the established electronic selectivity rules for non-heme iron-catalyzed C—H oxidation, the sites most likely to suffer oxidation are those distant from pre-oxidized functional groups. Therefore, C—H oxidations are necessarily orthogonal to classical approaches that make use of such pre-oxidized functional groups to install further functionality. Future studies will seek to mimic nature’s ability to use high valent iron oxo intermediates to install a variety of functional groups directly from C—H bonds, including olefins and halogens, as well as develop more selective hydroxylation catalysts.

### 3.4 Experimental Section
Isolation of Cafestol Diacetate and Preparation of Tricalysiolide B and Derivatization Studies

**Cafestol diacetate (79):** ~1 kilogram of coffee beans were continuously extracted using a Soxhlet extractor for 16h with refluxing hexanes. The combined hexanes extracts were concentrated in vacuo, providing ~80g coffee oil that was treated with 50 mL methanol and 2.5g KOH. This mixture stirred 2.5h at ambient temperature under a nitrogen atmosphere and was thereafter partitioned between heptane (200 mL) and methanol (200 mL) containing 10% water. The organic layer was extracted 3X with 10:1 MeOH:H2O (200 mL) and the combined extracts were concentrated in vacuo. The resulting oil was treated with 5g KOH and stirring followed at 40°C for 0.5 h. The crude mixture was partitioned between H2O (200 mL) and 10:1 CH2Cl2:MeOH (200 mL) and the aqueous layer was extracted 5X with 10:1 CH2Cl2:MeOH (200 mL). The combined organics were concentrated in vacuo and acetylated with 25 mL acetic anhydride, 25 mL triethylamine, and 0.5 g 4-dimethylaminopyridine. The acetylation reaction stirred overnight at ambient temperature under an atmosphere of nitrogen and was filtered through a large pad of silica (10% EtOAc/hexanes). The filtrate was concentrated in vacuo and purified by flash chromatography (silica, hexanes → 5% EtOAc/hexanes → 10% EtOAc/hexanes → 20% EtOAc/hexanes). An approximately 1:1 mixture of cafestol and kahweol was isolated as a yellow foam and treated directly with 50 mL EtOH and 0.50 g 10% Pd/CaCO3/Pb(OAc)2. One atmosphere of H2 was passed directly through the reaction mixture for 1h and stirring followed overnight at ambient temperature. Cafestol diacetate was isolated as a fluffy white powder following filtration through a column of celite and concentration under reduced pressure (2.7 g).

**Tricalysiolide B diacetate (80):** To a mixture of 79 (150 mg, 0.375 mmol, 1.0 equiv.), Fe(S,S)PDP 1 (3.4 mg, 0.0036 mmol, 0.01 equiv.), and AcOH (0.0036 mmol, 0.01 equiv., 25 µL of a stock solution prepared by dissolving 8.67 µL AcOH in 1000 µL CH3CN) in 0.58 mL CH3CN was added a solution of H2O2 (50 wt% in H2O, 21.6 µL, 0.375 mmol, 1.0 equiv.) in 3.4 mL CH3CN over a period of 1 minute. The reaction turned
bright red initially and, as the H_2O_2 was added, the expected amber brown color developed. The reaction stirred at ambient temperature for 2h under ambient atmosphere, during which time the solution developed a deep green color. The crude product was filtered through a short silica plug (100% EtOAc), concentrated **in vacuo**, and treated directly with tBuOH (3.7 mL), H_2O (1.5 mL), 2-methyl-2-butene (0.38 mL, 3.6 mmol, ~10 equiv.), NaH_2PO_4•H_2O (0.38 g, 2.8 mmol, 7.5 equiv.), and NaClO_2 (80%, 0.25 g, 2.2 mmol, 5.9 equiv.). Stirred 2h at ambient temperature under ambient atmosphere, concentrated **in vacuo**, and purified directly by flash chromatography (silica, 30% EtOAc/hexanes → 60% EtOAc/hexanes), affording a white powder. Run 1 (0.375 mmol 79): 105.9 mg 80 (65%); run 2 (0.15 mmol 79, reagents scaled accordingly): 37.1 mg 80 (57%); run 3 (0.15 mmol 79, reagents scaled accordingly): 36.1 mg 80 (56%). **Average yield: 59%.**

**1H NMR (CDCl_3, 500 MHz):** δ 5.60 (s, 1H), 4.94 (d, J = 12.5 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 3.59 (br s, 1H), 2.38-3.00 (m, 1H), 1.90-1.80 (m, 2H), 1.70-1.58 (m, 7H), 1.56-1.46 (m, 2H), 1.38-1.29 (m, 2H), 0.84 (s, 3H). **13C NMR (CDCl_3, 125 MHz):** δ 172.2, 171.0, 171.0, 112.9, 104.4, 90.3, 63.4, 53.0, 51.2, 46.9, 44.2, 43.6, 43.3, 39.6, 37.7, 35.5, 34.1, 25.6, 22.5, 21.7, 21.0, 19.3, 14.4. **IR (film, cm⁻¹):** 3379 (br), 2941, 2868, 1738, 1658, 1452, 1369, 1255, 1041, 916. **HRMS (ESI) m/z calc’d C_{24}H_{33}O_7 [M+H]^+: 433.2226, found 433.2228.**

**Fe(PDP)-catalyzed oxidation of 82 (Single run):** Into a 20 mL borosilicate vial was added hydrocarbon substrate (71.2 mg, 0.15 mmol, 1.0 equiv.), followed by 5 mol% Fe(S,S-PDP) catalyst 1 (7.0 mg, 0.0075
mmol, 0.05 equiv.), 2.0 mL CH$_3$CN, 4.29 µL AcOH (0.075 mmol, 0.5 equiv.), and a magnetic stir bar. While the resulting mixture stirred (starting material poorly soluble in CH$_3$CN, so dilute conditions used), a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 1 (7.0 mg, 0.0075 mmol, 0.05 equiv.) and 4.29 µL AcOH (0.075 mmol, 0.5 equiv.) in 0.15 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN was added over 1 min and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 1 (7.0 mg, 0.0075 mmol, 0.05 equiv.) and 4.29 µL AcOH (0.075 mmol, 0.5 equiv.) in 1.3 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN (1 min addition). The reaction stirred for 10 minutes and was concentrated under reduced pressure and purified by flash chromatography (silica, 20% → 40% → 60% acetone/hexanes). Isolated both unreacted starting material and 2$^\circ$ alcohol 83 as white solids, while ketone 84 was isolated as a mixture with several other oxidation products. $^1$H NMR against an internal standard (nitrobenzene) was used to calculate the yield of ketone 84. Purification by MPLC and recrystallization afforded a pure sample of ketone 84 for the purposes of characterization. Run 1: 24.8 mg rsm (35% rsm), 15.5 mg 83 (21%), 9% 84 (NMR yield); run 2: 25.5 mg rsm (36% rsm), 15.7 mg 83 (21%), 9% 84 (NMR yield). Average rsm: 36%. Average 2$^\circ$ alcohol (83): 21%. Average ketone (84): 9%.

83: $^1$H NMR (CDCl$_3$, 500 MHz): δ 6.0 (s, 1H), 4.96 (d, J = 12.5 Hz, 1H), 4.44 (d, J = 12.5 Hz, 1H), 3.95 (app septet, J = 4.5 Hz, 1H), 2.64-2.60 (m, 1H), 2.57-2.54 (m, 1H), 2.10-2.05 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.96-1.91 (m, 2H), 1.86-1.81 (m, 2H), 1.79-1.71 (m, 1H), 1.70-1.55 (m, 6H), 1.54-1.47 (m, 1H), 1.34-1.30 (m, 1H), 1.30-1.21 (m, 2H), 0.90 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 171.0, 170.9, 169.9, 168.7, 166.2, 115.6, 104.6, 89.7, 64.7, 63.3, 54.8, 52.4, 51.3, 49.0, 44.3, 44.2, 43.4, 38.0, 35.8, 33.3, 25.4, 22.5, 21.8, 20.9, 19.0, 15.8. IR (film, cm$^{-1}$): 3437 (br), 2941, 2872, 1765, 1732, 1657, 1454, 1435, 1369, 1254, 1230, 1209, 1171, 1146, 1041, 1014, 999, 916. HRMS (ESI) m/z calc’d C$_{26}$H$_{34}$O$_9$Na [M+Na]$^+$: 513.2101, found 513.2104. [α]$^{25}_D$ -162° (c 0.20, CHCl$_3$).

84: $^1$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-
Fe(PDP)-catalyzed oxidation of 82 (Recycling protocol): Into a 20 mL borosilicate vial was added hydrocarbon substrate (71.2 mg, 0.15 mmol, 1.0 equiv.), followed by 5 mol% Fe(S,S-PDP) catalyst 1 (7.0 mg, 0.0075 mmol, 0.05 equiv.), 2.0 mL CH$_3$CN, 4.29 µL AcOH (0.075 mmol, 0.5 equiv.), and a magnetic stir bar. While the resulting mixture 1 stirred (starting material poorly soluble in CH$_3$CN, so dilute conditions used), a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% 1 (7.0 mg, 0.0075 mmol, 0.05 equiv.) and 4.29 µL AcOH (0.075 mmol, 0.5 equiv.) in 0.15 mL CH$_3$CN was added in one burst. A second solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN was added over 1 min and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% 1 (7.0 mg, 0.0075 mmol, 0.05 equiv.) and 4.29 µL AcOH (0.075 mmol, 0.5 equiv.) in 0.15 mL CH$_3$CN was added in one burst, followed by a third solution of H$_2$O$_2$ (50 wt% in H$_2$O, 10.35 µL, 0.18 mmol, 1.2 equiv.) in 1.3 mL CH$_3$CN (1 min addition). The reaction stirred for 10 minutes and was concentrated under reduced pressure and purified by flash chromatography (silica, 20% → 40% → 60% acetone/hexanes). Isolated both unreacted starting material and 2° alcohol 83 as white solids, while ketone 84 was isolated as a mixture with several other oxidation products. Recovered 20.7 mg (0.044 mmol, 29% rsm) unreacted starting material and re-exposed it to the above reaction conditions by first dissolving it in 0.60 mL CH$_3$CN containing 1.24 µL AcOH and 2.0 mg Fe(S,S-PDP) 1, and scaling the rest of the reagents accordingly [Fe(S,S-PDP): 2.0 mg catalyst, 1.24 µL AcOH, 0.10 mL CH$_3$CN; H$_2$O$_2$ solutions: 3.00 µL H$_2$O$_2$, 0.40 mL CH$_3$CN]. The reaction was purified by flash chromatography as before, affording unreacted starting material and the pure 2° alcohol 83 as white solids, while ketone 84 was isolated as a mixture with several other oxidation products. $^1$H NMR against an internal standard (nitrobenzene) was used to calculate the yield of ketone 84. Run 1: 7.4 mg rsm (10% rsm), 22.1 mg 2° alcohol 83 (30%), 12% ketone 84 (NMR yield); run 2: 7.2 mg rsm (10% rsm), 22.8 mg 2° alcohol 83 (31%), 11% ketone 84 (NMR yield). Average rsm: 10%. Average 2° alcohol (83): 31%. Average ketone (84): 12%.
**Tricalysiolide B (81):** To a solution of 80 (106 mg, 0.25 mmol, 1.0 equiv.) in MeOH (4 mL) was added potassium carbonate (169 mg, 1.23 mmol, 5.0 equiv.) and the resulting suspension stirred at ambient temperature for 1.5 h. The crude reaction mixture was partitioned between H₂O (15 mL) and EtOAc (25 mL) and the aqueous layer was carefully acidified with 3M aq. HCl while being cooled in an ice/water bath (pH = 2), and was then extracted with EtOAc (2X 25 mL). To ensure complete extraction of product, solid sodium chloride was added to the aqueous layer, and a final extraction with EtOAc was performed (25 mL). The combined organics were dried over MgSO₄, filtered through celite, and concentrated in vacuo, affording the desired product as a white powder (80.0 mg, 0.23 mmol, 92%).

**¹H NMR (CD₃OD, 500 MHz):** δ 5.67 (d, J = 2.0 Hz, 1H), 3.73 (d, J = 11.5 Hz, 1H), 3.62 (d, J = 11.5 Hz, 1H), 2.36-2.32 (m, 1H), 2.22-2.19 (m, 1H), 2.08-2.04 (m, 1H), 2.00-1.97 (m, 1H), 1.90-1.79 (m, 2H), 1.78-1.59 (m, 9H), 1.55-1.45 (m, 2H), 1.34-1.27 (m, 2H), 0.90 (s, 3H).

**¹³C NMR (CD₃OD, 125 MHz):** δ 174.0, 172.6, 112.2, 105.6, 81.9, 65.9, 54.1, 52.9, 47.5, 45.4, 44.7, 43.8, 40.1, 37.7, 35.9, 34.2, 26.0, 21.9, 19.3, 14.0. IR (film, cm⁻¹): 3323 (br), 2927, 2866, 1763, 1722, 1657, 1452, 1387, 1338, 1221, 1194, 1151, 1111, 1034, 1018, 991, 966, 930, 914. HRMS (ESI) m/z calc’d C₂₀H₂₉O₅ [M+H]⁺: 349.2015, found 349.2011. [α]²⁴D -174° (c 0.50, MeOH).

**Single crystal X-ray crystallography data of p-bromobenzoate of 82:**

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Z  
Density (calculated)  
Absorption coefficient  
F(000)  
Crystal size  
Theta range for data collection  
Index ranges  
Reflections collected  
Independent reflections  
Completeness to theta = 25.32°  
Absorption correction  
Max. and min. transmission  
Refinement method  
Data / restraints / parameters  
Goodness-of-fit on F^2  
Final R indices [I>2sigma(I)]  
R indices (all data)  
Absolute structure parameter  
Largest diff. peak and hole  

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P1  
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Full-matrix least-squares on F^2  
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R1 = 0.0502, wR2 = 0.0895  
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Single crystal X-ray crystallography data of 84:

Table 1. Crystal data and structure refinement for bc62uas.

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R indices (all data) R1 = 0.0344, wR2 = 0.0891
Absolute structure parameter -0.07(15)
Largest diff. peak and hole 0.211 and -0.183 e.Å^3

"CCDC 794910 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

Computational Details

The most stable conformations were located using MacroModel.\textsuperscript{65} The mixed torsional/low-mode sampling with the OPLS\_2005 force field was employed in the conformational search. Conformers with energies within 5 kcal/mol of the most stable conformer were optimized at higher level using B3LYP/6-31G(d) in Gaussian 09\textsuperscript{66} to locate the global minima. NPA and Mülliken charges were calculated in Gaussian 09.

The Cartesian coordinates (Å), SCF energies, enthalpies at 298K, and Gibbs free energies at 298K for the optimized structures.
All geometries were optimized with B3LYP/6-31G(d).

![Tricalysioliide B triacetate (82)](attachment:image.png)

Tricalysioliide B triacetate (82)

Total SCF energy: \(-1613.08508943\) a.u.
Enthalpy at 298K: -1612.476203 a.u.
Gibbs free energy at 298K: -1612.572469 a.u.

Cartesian coordinates

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Geometries were optimized with B3LYP/6-31G(d). Both NPA and Mülliken charges give the same trend, H2 and H15 are the most electron deficient, and other secondary equatorial hydrogen atoms have similar charges.

### 3.5 References

51. A portion of this work was summarized in a previous publication: Bigi, M. A.; Liu, P.; Zou, L.; Houk, K. N.; White, M. C. *Synlett* **2012**, 23, 2768.
63. NPA charges were calculated using B3LYP/6-311++G(d,p). Mulliken charges using B3LYP/6-31G(d) provided an analogous trend to the NPA charges and are an alternative when minimizing computation power and time are a consideration.
64. These steric and electronic property analyses were all based on calculations of the reactant molecule. Density functional theory (DFT) calculations of transition state structures and selectivities are underway in our labs to verify these selectivity rules.
Chapter 4

Palladium/Hypervalent Iodine Co-catalyzed Tandem Wacker-Dehydrogenation of Terminal Olefins

4.1 Introduction

A premier challenge facing the chemical community in the 21st century is responsible resource utilization. Tandem catalysis, wherein multiple chemical transformations are catalyzed in sequence without the need for the isolation of intermediates, often using a single catalyst, is one modern approach to this challenge. Tandem catalysis holds great promise for enhancing synthetic efficiency, in particular, when used in conjunction with C–H functionalization. C–H functionalization, due to its capacity for generating molecular complexity from readily available commodity chemicals (e.g., olefins, alkanes), is an ideal component of a tandem process and stands to significantly streamline synthetic routes.

For example, the White group recently reported a dehydrogenative Diels Alder reaction of terminal olefins using a palladium(II)/bis-sulfoxide catalyst. In this tandem process, an unstable 1,4-diene is generated directly from a terminal olefin via C–H activation, which then undergoes spontaneous cycloaddition with an electron-deficient olefin. Notably, this reaction affords complex cycloadducts directly from terminal olefins in a single operation, demonstrating the power of tandem catalysis through C–H functionalization.

\[ \text{Figure 4.1. Precedent for proposed tandem Wacker-dehydrogenation of terminal olefins.} \]

A. Wacker oxidation

\[ \text{B. Stahl's results with linear ketones} \]

\[ \text{C. Hypervalent iodine-mediated carbonyl oxidation} \]

\[ \text{D. Proposed Pd-catalyzed dehydrogenation} \]

**α,β-**Unsaturated ketones are a versatile class of synthetic intermediates, readily engaging in Heck reactions, Michael additions, and cycloadditions. Traditionally, these intermediates are prepared via multi-step routes (e.g., selenoxide elimination, Saegusa oxidation) or from preoxidized starting materials (e.g., carbonyl olefination using stabilized ylides, carbonyl oxidation using stoichiometric iodine(V) reagents). Alternatively, we realized that a tandem Wacker-dehydrogenation reaction of terminal olefins would constitute a direct route to these intermediates (Figure 4.1). Pd(II)-catalyzed Wacker oxidation would provide a methyl ketone subject to Pd(II)-catalyzed ketone dehydrogenation, and the overall process would provide α,β-unsaturated ketones in a single operation. Much recent interest
has focused on installing ketone unsaturation in a single step via Pd(II)-catalyzed dehydrogenation of the corresponding ketone.\textsuperscript{77} Despite significant progress, however, no general method has been reported for linear ketone dehydrogenation, due to poor reactivity and competitive overoxidation of the desired $\alpha,\beta$-unsaturated ketone products. To overcome these limitations, we hypothesized that a hypervalent iodine(III) reagent would be capable of generating an iodonium enolate from an intermediate methyl ketone.\textsuperscript{78} The iodine(III) reagent, rather than undergoing well-precedented nucleophilic displacement/reduction with a nucleophile such as acetate, would instead serve to activate the ketone toward nucleophilic attack by palladium (0) generated as a byproduct of Wacker oxidation. As conceived, pre-activation of the linear ketone as the iodonium enolate would hopefully overcome the low inherent reactivity of linear ketones. Moreover, ketone activation via iodonium enolate formation would hopefully obviate the need for external Brönsted acids/high temperatures, and therefore limit undesired overoxidation. Herein, we report the discovery and development of a Pd(II)/hypervalent iodine-catalyzed tandem Wacker-dehydrogenation reaction of terminal olefins. In a single synthetic operation, a range of $\alpha,\beta$-unsaturated ketones were isolated in good yields and selectivities and with broad functional group tolerance from terminal olefins. Unexpectedly, substoichiometric quantities of a hypervalent iodine (III) reagent facilitated the novel tandem process, thereby constituting an unusual example of iodonium catalysis.

### 4.2 Results and Discussion

As shown in Table 4.1, Pd(II)-catalyzed oxidation of terminal olefin 85 under mild conditions [Pd(CH$_3$CN)$_4$BF$_4$]$_2$, 0.67M DMSO, 1,4-benzoquinone, 35 °C] led to a 13% GC yield of $\alpha,\beta$-unsaturated ketone 87, with poor conversion of the intermediate Wacker product (Entry 1). In accord with our hypothesis, addition of stoichiometric Phl(OAc)$_2$ greatly improved the yield of 87 to synthetically useful levels (Entry 2). Moreover, lowering the loading of Phl(OAc)$_2$ to substoichiometric levels led to no diminishment in reactivity, with 25 mol% proving optimal (Entries 3-4). Notably, the successful use of substoichiometric amounts of an I(III) reagent is

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<td>25% Phl(OAc)$_2$</td>
<td>3%</td>
</tr>
<tr>
<td>12</td>
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<td>Pd(TFA)$_2$</td>
<td>25% Phl(OAc)$_2$</td>
<td>36%</td>
</tr>
<tr>
<td>13</td>
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<td>Pd(TFA)$_2$</td>
<td>25% Phl(OAc)$_2$</td>
<td>35%</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>1,2-bis(phenylsulfanyl)</td>
<td>7%</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>No Pd(II)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$ Determined by GC, average of two runs at 0.1 mmol, relative to standard curve, external standard: nitrobenzene. $^b$ Average isolated yield of 87 shown in parantheses (two runs at 0.3 mmol).
consistent with the proposed iodonium catalysis. Interestingly, replacing the PhI(OAc)₂ additive with other common aryl iodonium(III) and iodonium(V) reagents led to comparable results (Entries 5-9). As expected, replacing one equivalent of 1,4-benzoquinone with PhI(OAc)₂, to test if the I(III) reagent was a competent terminal oxidant for the dehydrogenation step, led to significantly reduced conversion to 87 (Entry 10). Finally, other common palladium(II) salts were inferior to Pd(CH₃CN)₄(BF₄)₂ (Entries 11-14), while removing the palladium catalyst entirely led to complete elimination of catalysis (Entry 15).

We next examined the scope of the tandem Wacker-dehydrogenation reaction. As shown in Table 4.2, electron-rich and electron-poor butenylated arenes delivered the desired α,β-unsaturated ketones 88-91 in good yield (Entries 1-4). Ortho-substitution on the arene was tolerated (Entry 5) as was a disubstituted styrenyl olefin within benzopyran 93 (Entry 6). Non-activated substrates also underwent tandem oxidation in good yields and protected oxygen and nitrogen functionality were well-tolerated (Entries 7-9). Amides and esters did not undergo competitive dehydrogenation, demonstrating that the dehydrogenation reaction is chemoselective for ketones over other common carbonyl functionality (Entries 10-11). A γ-stereocenter did not suffer epimerization in 99 despite its potential lability under enolizable reaction conditions; similarly, 100 retained the trans stereochemistry found within the olefin starting material (Entries 12-13). A disubstituted cyclohexene and an acetate enol ether were both well-tolerated, highlighting the predictable selectivity of the Wacker reaction for terminal olefins (Entries 14-15). Finally, estrone derivative 103 was isolated in 57% yield, after recycling starting material once (Entry 16). Taken together, our results demonstrate that the Pd(II)/PhI(OAc)₂-catalyzed tandem Wacker-dehydrogenation readily converts a range of terminal olefins directly into α,β-unsaturated ketones in good yields, with minimal overoxidation and broad functional group tolerance.

To probe the reaction mechanism, we monitored the reaction progress of terminal olefin 85 over time using GC analysis. As expected, Wacker oxidation occurred rapidly, with nearly full conversion to
methyl ketone 86 accomplished within 1 hour. Notably, the Wacker oxidation was not influenced by the addition of PhI(OAc)$_2$. Subsequently, 86 converted directly into $\alpha,\beta$-unsaturated ketone 87 to complete the tandem process, and this dehydrogenation step proceeded sluggishly without PhI(OAc)$_2$. Notably, a significant induction period was observed with respect to the conversion of 86 to 87, with little productive dehydrogenation occurring during the first 12 hours of reaction. Future studies will seek to understand the mechanistic basis for this induction period, particularly with respect to the role of the hypervalent iodine reagent.

Based on our results, we favor the catalytic cycle depicted in Figure 4.2. Pd(II)-catalyzed Wacker oxidation provides a methyl ketone subject to electrophilic attack by an I(III) reagent, providing iodonium enolate A. Next, exchange with Pd(II) generates Pd(II)-enolate C via the potential intermediacy of B, with no change in oxidation state at palladium or iodine. Tautomerization to C-bound Pd-enolate D leads to $\beta$-hydride elimination and $\alpha,\beta$-unsaturated ketone product. Finally, reductive elimination of HX, followed by benzoquinone-mediated reoxidation, allows Pd(II) to re-enter the catalytic cycle. Alternatively, based on our original proposal, we considered path A: iodonium(III) enolate A suffers reductive displacement with Pd(0), affording Pd(II)-enolate D and PhI. We disfavor path A for three reasons: (1) PhI was never observed by $^1$H NMR during dehydrogenation of 2-decanone; (2) replacing 1,4-benzoquinone with 1 equiv. of PhI(OAc)$_2$ led to poor conversion of ketone 2 (Table 4.3, Entries 1-2); (3) if Pd(II) or 1,4-benzoquinone were acting to regenerate an I(III) reagent from PhI, thereby explaining our inability to
observe PhI, then dehydrogenation should proceed similarly beginning from either PhI or PhI(OAc)$_2$. As expected, however, replacing 25 mol% PhI(OAc)$_2$ with 25 mol% PhI again led to poor conversion of ketone 2 (Entry 3). Next, we considered path B: oxidation of iodonium(III) enolate A provides iodonium(V) enolate E, an intermediate previously proposed to undergo dehydrogenation with release of I(III). We disfavor path B for two reasons: (1) dehydrogenation of 2 proceeded sluggishly when IBX, an iodine(V) reagent reported to stoichiometrically dehydrogenate ketones in DMSO, was used as stoichiometric oxidant with or without Pd(II) (Entries 4-5); (2) I(III) reagents are often used as oxidants for Pd(II), while the inverse [Pd(II) acting as an oxidant for I(III)] is unprecedented. Future studies will seek to better understand the reaction mechanism and the role of the critical hypervalent iodine additive.

### 4.3 Conclusions

In summary, we herein report the development of a Pd(II)/hypervalent iodine-catalyzed tandem Wacker-dehydrogenation reaction of terminal olefins. This reaction provides for an expedient synthesis of $\alpha,\beta$-unsaturated ketones directly from terminal olefins and is successful with activated and unactivated substrates, highly selective for terminal olefins and tolerant of a range of useful functional groups. Discovery of a unique example of iodonium catalysis was critical for facilitating the novel tandem process. Preliminary mechanistic studies support the role of an iodonium(III) species as a catalyst promoting palladium enolate formation, while alternative mechanisms involving either oxidation of palladium by hypervalent iodine or vice versa seem less likely. Future challenges include the development of more robust, higher turnover number catalysts (a longstanding challenge for palladium(II) catalysis) and expansion of the substrate scope to include other common carbonyl functionality (e.g., esters, amides).

### 4.4 Experimental Section

Table 4.3. Evaluation of role of hypervalent iodine reagent.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additive</th>
<th>yield 3$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(CH$_3$CN)$_4$(BF$_4$)$_2$</td>
<td>25% PhI(OAc)$_2$</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(CH$_3$CN)$_4$(BF$_4$)$_2$</td>
<td>100% PhI(OAc)$_2$</td>
<td>6%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(CH$_3$CN)$_4$(BF$_4$)$_2$</td>
<td>25% PhI</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(CH$_3$CN)$_4$(BF$_4$)$_2$</td>
<td>100% IBX</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>--</td>
<td>100% IBX</td>
<td>8%</td>
</tr>
</tbody>
</table>

$^a$ Determined by GC, average of two runs at 0.1 mmol, relative to external standard curve; external standard: nitrobenzene.
**General Information:** All commercially obtained reagents for the tandem Wacker/dehydrogenation reaction were used as received [1,4-benzoquinone, dimethyl sulfoxide, Phl(OAc)₂]. Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ was prepared according to the published procedure$^{80}$ as a pale yellow powder and was stored in a glove box under an argon atmosphere. Alternatively, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ purchased from Strem Chemicals could be used successfully and was also stored in a glove box under an argon atmosphere. All Wacker-dehydrogenation reactions were run with no precautions to exclude O$_2$ or 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 stain. Flash chromatography was performed as described by Still using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.). $^1$H NMR spectra were recorded on a Varian Inova-500 (500 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, sext. = sextet, sept. = septet, m = multiplet, b = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled $^{13}$C NMR spectra were recorded on a Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.16 ppm). 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 JASCO DIP-360 digital polarimeter and a 3.5 x 50 mm cell and are reported as follows: [α]$_{D}$ ToC (c = g/100 mL, solvent).

**Preparation of Pd(CH$_3$CN)$_4$(BF$_4$)$_2$**

While in the glove box under an atmosphere of argon, Pd sponge (250 mg, 2.35 mmol, 1.0 equiv.) was weighted into a flame-dried 100 mL 3-necked round-bottom flask. The flask was removed from the glove box, placed under a nitrogen atmosphere, and to it was added 29 mL CH$_3$CN. To the resulting fine gray suspension was quickly added solid NOBF$_4$ (590 mg, 5.50 mmol, 2.15 equiv.). Briefly, evacuated the reaction flask until the solvent began bubbling and then re-filled the flask with N$_2$; this evacuation/N$_2$ re-filling procedure was performed 3X. Stirred at room temperature under N$_2$ for 30 minutes and the previous evacuation/N$_2$ re-filling procedure was again performed 3X. Stirred an additional 30 minutes and performed the evacuation/N$_2$ re-filling procedure a final 3X. The resulting clear, yellow solution stirred overnight at room temperature and was filtered through a glass fritted funnel. The filtrate was concentrated under reduced pressure and the resulting crude product was redissolved in 10 mL CH$_3$CN. 200 mL anhydrous Et$_2$O was layered on top of the CH$_3$CN and the resulting mixture was cooled at -20°C for 4h. The supernatant was decanted and the precipitate was triturated 2X with 10 mL Et$_2$O. The
resulting hygroscopic, light yellow powder was placed under high vacuum for 4 h and stored in the glove box under at atmosphere of argon at room temperature (956 mg, 91%).

**General Procedure for the Pd(II) and Hypervalent Iodine-catalyzed Tandem Wacker/Dehydrogenation Reaction**

While in the glove box, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (0.030 mmol, 0.10 equiv.) was weighed into a ½ dram borosilicate vial. Outside of the glove box, into a ½ dram borosilicate vial containing a Teflon stir bar was sequentially added terminal olefin starting material (0.30 mmol, 1.0 equiv.), 1,4-benzoquinone (0.60 mmol, 2.0 equiv.), and PhI(OAc) (0.075 mmol, 0.25 equiv.). Deionized H$_2$O (0.30 mmol, 1.0 equiv.) was next added via micropipetor. Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ was carefully transferred from the 1st ½ dram vial to the reaction vial using three aliquots of 0.15 mL DMSO (total solvent: 0.45 mL, 0.67 M with respect to terminal olefin). The vial was then sealed with a Teflon cap and placed in an aluminum block to stir at 35°C for 48 hours. The crude reaction mixture was purified directly using flash column chromatography (in general, gradient EtOAc/hexanes was used). For 0.50 mmol reactions, the reagents were scaled accordingly.

**Table 4.1 Procedure**

While in the glove box, Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (0.020 mmol, 0.10 equiv.) was weighed into a ½ dram borosilicate vial. Outside of the glove box, into a 2nd ½ dram borosilicate vial was sequentially added terminal olefin starting material (0.20 mmol, 1.0 equiv.), nitrobenzene (0.08 mmol, 0.40 equiv.) as internal standard, 1,4-benzoquinone (0.40 mmol, 2.0 equiv.), and hypervalent iodine reagent. Deionized H$_2$O (0.20 mmol, 1.0 equiv.) was next added via micropipetor, followed by 0.15 mL DMSO. The reaction vial mixture was stirred vigorously with a Teflon stirring bar and an aliquot was removed to measure the initial SM:nitrobenzene ratio. Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ was transferred from the 1st ½ dram vial to the reaction vial using three aliquots of 0.050 mL DMSO (for a total reaction volume of 0.3 mL, [SM] = 0.67 M) and the reaction vial was then sealed with a Teflon cap and placed in an aluminum block to stir at 35°C for 48 hours. The crude reaction mixture was sampled for GC analysis and the yields of product(s) were quantified relative to a standard curve.

**Preparation of standard curve for Table 4.1**: Stock solutions of nitrobenzene (197.0 mg, 1.60 mmol, 20.00 mL EtOAc) and authentic 8-oxononyl acetate (86) (100.1 mg,, 0.50 mmol, 5.00 mL EtOAc) and (E)-8-oxonon-6-en-1-yl acetate (87) (99.1 mg, 0.50 mmol, 5.00 mL EtOAc) were prepared. To each of
nine GC vials was added 500 µL nitrobenzene stock solution (4.9 mg, 0.040 mmol per vial), followed by an aliquot of the Wacker product 86 or dehydrogenated Wacker product 87 stock solutions, in increasing amounts (100 µL, 200 µL, ..., 900 µL; 0.01 mmol, 0.02 mmol, ..., 0.09 mmol). As such, the first GC vial represented a 10% yield of either Wacker product or dehydrogenated Wacker product for a 0.10 mmol reaction, while the ninth vial represented a 90% yield. These solutions were mixed thoroughly and analyzed by GC; a plot of % yield vs. measured product/nitrobenzene generated data points that could be readily fit to a linear equation of the form \( y = mx + b \).

**Table 4.1 Results**

**Entry 1**: Followed the standard procedure, omitting addition of PhI(OAc)$_2$. Run 1: 12%; run 2: 13%. Average = 13%.

**Entry 2**: Followed the standard procedure, including 1 equiv. (0.20 mmol) PhI(OAc)$_2$. Run 1: 54%; run 2: 57%. Average = 56%.

**Entry 3**: Followed the standard procedure, including 25 mol% (0.050 mmol) PhI(OAc)$_2$. Run 1: 59%; run 2: 58%. Average = 59%.

**Entry 4**: Followed the standard procedure, including 10 mol% (0.020 mmol) PhI(OAc)$_2$. Run 1: 40%; run 2: 35%. Average = 38%.

**Entry 5**: Followed the standard procedure, including 25 mol% (0.050 mmol) PhI(OPiv)$_2$. Run 1: 55%; run 2: 58%. Average = 57%.

**Entry 6**: Followed the standard procedure, including 25 mol% (0.050 mmol) PhI(TFA)$_2$. Run 1: 43%; run 2: 47%. Average = 45%.

**Entry 7**: Followed the standard procedure, including 25 mol% (0.050 mmol) PhIO. Run 1: 49%; run 2: 53%. Average = 51%.

**Entry 8**: Followed the standard procedure, including 25 mol% (0.050 mmol) DMP. Run 1: 57%; run 2: 58%. Average = 58%.

**Entry 9**: Followed the standard procedure, including 25 mol% (0.050 mmol) IBX. Run 1: 57%; run 2: 58%. Average = 58%.

**Entry 10**: Followed the standard procedure, including 1 equiv. (0.20 mmol) PhI(OAc)$_2$ and only 1 equiv. (0.20 mmol) 1,4-BQ. Run 1: 22%; run 2: 27%. Average = 25%.

**Entry 11**: Followed the standard procedure with 25 mol% PhI(OAc)$_2$ using Pd(OAc)$_2$ in place of Pd(CH$_3$CN)$_4$(BF$_4$)$_2$. Run 1: 4%; run 2: 2%. Average = 3%.

**Entry 12**: Followed the standard procedure with 25 mol% PhI(OAc)$_2$ using Pd(TFA)$_2$ in place of Pd(CH$_3$CN)$_4$(BF$_4$)$_2$. Run 1: 36%; run 2: 36%. Average = 36%.
Entry 13: Followed the standard procedure with 25 mol% PhI(OAc)₂ using Pd(TFA)₂ and 4,5-diazafluorenone (10 mol% of each) in place of Pd(CH₃CN)₄(BF₄)₂. Run 1: 35%; run 2: 35%. Average = 58%.

Entry 14: Followed the standard procedure with 25 mol% PhI(OAc)₂ using Pd(OAc)₂/1,2-bis(phenylsulfinylethane) in place of Pd(CH₃CN)₄(BF₄)₂. Run 1: 7%; run 2: 7%. Average = 7%.

Entry 15: Followed the standard procedure with 25 mol% PhI(OAc)₂, omitting addition of Pd(CH₃CN)₄(BF₄)₂. Run 1: 0%; run 2: 0%. Average = 0%.

Table 4.3 Results

Entry 1: Beginning from methyl ketone 86 (0.20 mmol), followed the standard procedure using 1 equiv. BQ. Run 1: 60%; run 2: 59%. Average = 60%.

Entry 2: Beginning from methyl ketone 86 (0.20 mmol), followed the standard procedure, including 1 equiv. (0.20 mmol) PhI(OAc)₂. Run 1: 6%; run 2: 6%. Average = 6%.

Entry 3: Beginning from methyl ketone 86 (0.20 mmol), included 25 mol% PhI and 100 mol% AcOH. Run 1: 14%; run 2: 15%. Average = 15%.

Entry 4: Beginning from methyl ketone 86 (0.20 mmol), included 1 equiv. (0.20 mmol) IBX and no 1,4-BQ. Run 1: 23%; run 2: 22%. Average = 23%.

Entry 5: Beginning from methyl ketone 86 (0.20 mmol), included 1 equiv. (0.20 mmol) IBX and no 1,4-BQ and no Pd(II) catalyst. Run 1: 8%; run 2: 8%. Average = 8%.

Table 2 Substrate Synthesis

4-phenyl-1-butene was purchased from Aldrich; 1-decene was purchased from Aldrich; 5-hexen-1-ol was purchased from Aldrich and protected as the known benzoate under standard conditions; methyl 2-methylhept-6-enoate was prepared according to the known procedure from methyl heptenoate.

Representative Procedure for the Synthesis of Butenylated Arenes

To a flame-dried 100 mL round-bottom flask was added 4-trifluoromethylbenzyl bromide (1.0 g, 4.2 mmol, 1.0 equiv.) and 20 mL anhydrous THF. The reaction flask was cooled in an ice/water bath while under an atmosphere of nitrogen and allylmagnesium bromide was added dropwise (1.0 M in Et₂O, 8.4 mL, 8.4 mmol, 2.0 equiv.). The reaction was stirred for 2h near 0°C and then quenched with saturated aqueous NH₄Cl. The aqueous layer was extracted 3X with CH₂Cl₂ and the combined organics were dried.
over MgSO₄, filtered through celite, and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography (1% → 3% EtOAc/hexanes), affording the desired product as a clear, colorless oil (0.76 g, 90%).

4-(4-methoxyphenyl)-1-butene: Prepared from 4-methoxybenzyl chloride according to the representative procedure as a colorless liquid (66%). $^1$H NMR (500 MHz, CDCl₃) δ 7.12-7.09 (m, 2H), 6.85-6.81 (m, 2H), 5.85 (ddt, $J = 17.0, 10.0, 6.5$ Hz, 1H), 5.06-5.00 (m, 1H), 4.99-4.96 (m, 1H), 3.79 (s, 3H), 2.67-2.64 (m, 2H), 2.37-2.32 (m, 2H); $^{13}$C NMR (125 MHz, CDCl₃) δ 157.9, 138.3, 134.1, 129.4, 115.0, 113.8, 55.4, 35.9, 34.6; IR (film, cm⁻¹): 3076, 3032, 2999, 2978, 2933, 2852, 1639, 1612, 1583, 1512, 1464, 1454, 1441, 1417, 1300, 1246, 1178, 1115, 1038, 997; HRMS (EI) $m/z$ calc'd for C₁₁H₁₄O [M]+: 162.1045, found 162.1038.

4-(4-bromophenyl)-1-butene: Prepared from 4-bromobenzyl bromide according to the representative procedure as a colorless liquid (77%). $^1$H NMR (400 MHz, CDCl₃) δ 7.40 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 8.0$ Hz, 2H), 5.82 (ddt, $J = 17.2, 10.4, 6.4$ Hz, 1H), 5.06-4.96 (m, 2H), 2.68-2.64 (m, 2H), 2.34 (app q, $J = 7.6$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl₃) δ 140.9, 137.7, 131.5, 130.4, 119.7, 115.4, 35.4, 34.9; IR (film, cm⁻¹): 3078, 3024, 2978, 2929, 2858, 1641, 1593, 1489, 1452, 1441, 1201, 1072, 1011; HRMS (EI) $m/z$ calc'd for C₁₀H₁₁Br [M]+: 210.0044, found 210.0053.

4-(4-trifluoromethylphenyl)-1-butene: $^1$H NMR (500 MHz, CDCl₃) δ 7.54 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 5.84 (ddt, $J = 17.0, 10.5, 6.5$ Hz, 1H), 5.05 (dd, $J = 17.0, 1.5$ Hz, 1H), 5.01 (d, $J = 10.5$ Hz, 1H), 2.79-2.76 (m, 2H), 2.40 (app q, $J = 7.0$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl₃) δ 146.1, 137.5, 131.5, 130.4, 115.6, 35.3, 35.2; IR (film, cm⁻¹): 3080, 3047, 3008, 2933, 2860, 1643, 1620, 1443, 1417, 1327, 1165, 1124, 1068, 1020; HRMS (EI) $m/z$ calc'd for C₁₁H₁₁F₃ [M]+: 200.0813, found 200.0814.

4-(o-tolyl)-1-butene: Prepared from 2-methylbenzyl bromide according to the representative procedure as a colorless liquid (77%). $^1$H NMR (500 MHz, CDCl₃) δ 7.16-7.09 (m, 4H), 5.90 (ddt, $J = 17.0, 10.0, 6.5$ Hz, 1H), 5.07 (app dq, $J = 17.0, 1.5$ Hz, 1H), 5.02-4.98 (m, 1H), 2.72-2.68 (m, 2H), 2.36-2.30 (m, 2H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 140.2, 138.4, 136.0, 130.3, 128.9, 126.1, 126.0, 114.9, 34.4, 32.8, 19.4; IR (film, cm⁻¹): 3076,
6-(but-3-en-1-yl)-2,2-dimethyl-2H-chromene: Prepared from 6-(bromomethyl)-2,2-dimethyl-2H-chromene according to the representative procedure as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) d 6.92 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.29 (d, $J = 9.5$ Hz, 1H), 5.85 (ddt, $J = 16.5$, 10.0, 6.5 Hz, 1H), 5.59 (d, $J = 10.0$ Hz, 1H), 5.04 (dd, $J = 17.0$, 1.5 Hz, 1H), 4.97 (dd, $J = 10.0$, 1.0 Hz, 1H), 2.62-2.59 (m, 2H), 2.33 (app q, $J = 7.5$ Hz, 2H), 1.42 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 151.1, 138.4, 134.2, 130.9, 129.0, 126.3, 121.1, 116.2, 114.9, 76.1, 35.9, 34.7, 28.1; IR (film, cm$^{-1}$): 3076, 3039, 3012, 2976, 2927, 2854, 1639, 1614, 1491, 1464, 1439, 1383, 1371, 1371, 1362, 1261, 1211, 1169, 1153, 1128, 1107; HRMS (EI) $m/z$ calc'd for C$_{15}$H$_{18}$O [M+]: 214.1358, found 214.1361.

2-(oct-7-en-1-yl)isoindoline-1,3-dione: 8-bromo-1-octene (0.84 mL, 5.0 mmol, 1.0 equiv.), N,N-dimethylformamide (10 mL), and phthalimide potassium salt (1.02 g, 5.5 mmol, 1.1 equiv.) were added sequentially to a 50 mL round-bottom flask and stirred at 60°C for 20 h. The crude reaction mixture was filtered through celite and the filtrate was partitioned between brine and Et$_2$O. The aqueous layer was extracted 2X with Et$_2$O and the combined organics were washed 2X with 1M aqueous NaOH and 3X with brine. The organics were filtered through a celite/silica plug (Et$_2$O) and concentrated under reduced pressure. Purification by flash chromatography (5% → 10% EtOAc/hexanes) afforded the title compound as a clear, colorless oil (1.21 g, 94%). $^1$H NMR (500 MHz, CDCl$_3$) d 7.83 (dd, $J = 5.5$, 3.5 Hz, 2H), 7.70 (dd, $J = 6.0$, 3.5 Hz, 2H), 5.78 (ddt, $J = 17.5$, 10.5, 6.5 Hz, 1H), 4.97 (dd, $J = 17.0$, 1.5 Hz, 1H), 4.91 (d, $J = 10.0$ Hz, 1H), 3.66 (app t, $J = 7.3$ Hz, 2H), 2.05-2.00 (m, 2H), 1.70-1.63 (m, 2H), 1.40-1.31 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 168.6, 139.1, 134.0, 132.3, 123.3, 114.4, 38.2, 33.8, 28.8 (2 peaks), 28.7, 26.8; IR (film, cm$^{-1}$): 3074, 3032, 2976, 2931, 2856, 1772, 1714, 1639, 1616, 1466, 1437, 1396, 1369, 1338, 1188, 1053; HRMS (EI) $m/z$ calc'd for C$_{16}$H$_{18}$NO$_2$ [M+]: 257.1416, found 257.1413.

1-morpholinohept-6-en-1-one: Added 6-heptenoic acid (0.47 mL, 3.5 mmol, 1.0 equiv.), dichloromethane (15 mL), and carbonyl diimidazole (681 mg, 4.2 mmol, 1.2 equiv.) consecutively to a 40 mL borosilicate vial and stirred under an atmosphere of nitrogen at ambient temperature for 3h. Added morpholine (0.61 mL, 7.0 mmol, 2.0 equiv.) and stirred the resulting mixture overnight at ambient temperature. The crude reaction was concentrated under reduced pressure and purified directly by flash chromatography (50% → 70%
EtOAc/hexanes), affording the title compound as a clear, colorless oil (331 mg, 48%). ¹H NMR (500 MHz, CDCl₃) δ 5.78 (ddt, J = 17.5, 10.5, 6.5 Hz, 1H), 5.01-4.97 (m, 1H), 4.93 (dd, J = 10.0, 1.5 Hz, 1H), 3.66-3.64 (m, 4H), 3.61-3.59 (m, 2H), 3.45-3.43 (m, 2H), 2.32-2.29 (m, 2H), 2.06 (app q, J = 7.0 Hz, 2H), 1.63 (app p, J = 7.5 Hz, 2H), 1.43 (app p, J = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 171.8, 138.6, 114.8, 67.0, 66.8, 46.1, 42.0, 33.6, 33.0, 28.7, 24.8; IR (film, cm⁻¹): 3076, 2926, 2858, 1726, 1643, 1456, 1433, 1362, 1300, 1271, 1234, 1196, 1117, 1070, 1032, 995; HRMS (ESI) m/z calc’d for C₁₁H₁₉NO₂ [M+H]+: 198.1494, found 198.1490.

(R)-6-(benzyloxy)-5-methylhexene: While in the glove box, solid NaH (95%, 130 mg, 5.15 mmol, 2.5 equiv.) was added to a flame-dried 50 mL round-bottom flask. Outside of the glove box, the flask was placed under an atmosphere of nitrogen and to it was added 7 mL anhydrous THF. While being cooled in an ice/water bath, the reaction flask had neat (R)-2-methylhex-5-en-1-ol (235 mg, 2.06 mmol, 1.0 equiv.) added to it. Several crystals of imidazole were added and the cloudy mixture stirred at 0°C for 30 minutes. Benzyl bromide (0.24 mL, 2.06 mmol, 1.0 equiv.) and tetrabutylammonium iodide (78 mg, 0.21 mmol, 0.10 equiv.) were added successively and the reaction stirred 1.5 h at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl and the aqueous layer was extracted 3X with Et₂O. The combined organics were dried over MgSO₄, filtered through celite, concentrated in vacuo, and purified by flash chromatography (2% → 5% EtOAc/hexanes), affording the title compound as a colorless oil (190 mg, 45%). ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.32 (m, 4H), 7.31-7.26 (m, 1H), 5.81 (ddt, J = 17.0, 10.5, 6.5 Hz, 1H), 5.00 (dd, J = 17.5, 2.0 Hz, 1H), 4.94 (dd, J = 10.0, 1.0 Hz, 1H), 4.53-4.48 (m, 2H), 3.33 (AB q, J = 9.0, 6.0 Hz, 1H), 3.26 (AB q, J = 9.0, 7.0 Hz, 1H), 2.16-2.07 (m, 1H), 2.06-1.98 (m, 1H), 1.84-1.75 (m, 1H), 1.59-1.52 (m, 1H), 1.26-1.18 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.2, 138.9, 128.4, 127.6, 127.5, 114.4, 75.9, 73.1, 33.1, 33.0, 31.3, 17.1; IR (film, cm⁻¹): 3066, 3030, 2956, 2927, 2854, 2792, 1641, 1496, 1454, 1414, 1363, 1308, 1255, 1205, 1099, 1028, 995; HRMS (EI) m/z calc’d for C₁₄H₂₀O [M]+: 204.1514, found 204.1520. [α]₂⁰ = -4.3 (c = 0.23, CHCl₃).

trans-2-(but-3-en-1-yl)cyclohexyl acetate: The known racemic trans-alcohol (275 mg, 1.78 mmol, 1.0 equiv.) was dissolved in 10 mL anhydrous CH₂Cl₂ and treated consecutively with 4-dimethylaminopyridine (44 mg, 0.36 mmol, 0.20 equiv.), triethylamine (0.74 mL, 5.34 mmol, 3.0 equiv.), and acetic anhydride (0.50 mL, 5.34 mmol, 3.0 equiv.). The reaction mixture stirred overnight at ambient temperature under an atmosphere of nitrogen; the crude reaction mixture was concentrated under reduced pressure and purified directly by flash chromatography (5% EtOAc/hexanes), affording the title compound as a clear, colorless oil (335 mg,
H NMR (500 MHz, CDCl$_3$) δ 5.78 (ddt, $J$ = 16.5, 10.0, 7.0 Hz, 1H), 5.00 (app dq, $J$ = 17.5, 2.0 Hz, 1H), 4.95-4.92 (m, 1H), 4.49 (td, $J$ = 10.0, 4.5 Hz, 1H), 2.17-2.09 (m, 1H), 2.04 (s, 3H), 2.00-1.92 (m, 2H), 1.92-1.86 (m, 1H), 1.75-1.70 (m, 1H), 1.67-1.62 (m, 1H), 1.62-1.55 (m, 1H), 1.50-1.42 (m, 1H), 1.37-1.24 (m, 2H), 1.23-1.11 (m, 2H), 0.99 (app qd, $J$ = 13.0, 3.5 Hz, 1H); 13C NMR (125 MHz, CDCl$_3$) δ 170.9, 139.0, 114.4, 77.0, 41.4, 31.9, 31.4, 30.8, 30.1, 25.2, 24.6, 21.4; IR (film, cm$^{-1}$): 3078, 2995, 2976, 2935, 2860, 1738, 1641, 1450, 1371, 1242, 1032, 997; HRMS (ESI) m/z calc'd for C$_{12}$H$_{21}$O$_2$ [M+H]$^+$: 197.1542, found 197.1552.

4-(but-3-en-1-yl)cyclohex-1-ene: To a solution of 3-cyclohexene-1-methanol (1.0 mL, 8.6 mmol, 1.0 equiv.) in anhydrous pyridine (10 mL) in an ice/water bath was added solid $p$TsCl (1.89 g, 9.9 mmol, 1.15 equiv.). The resulting clear, yellow solution warmed to ambient temperature and stirred overnight under an atmosphere of nitrogen. The crude mixture was then diluted with CH$_2$Cl$_2$ (50 mL) and the organic layer was washed with 1M aqueous HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over Na$_2$SO$_4$, filtered through celite, concentrated under reduced pressure and the crude tosylate was used without further purification. To a flame-dried 100 mL round-bottom flask was added CuCl (171 mg, 1.7 mmol, 0.20 equiv.) and 21 mL anhydrous Et$_2$O. The reaction was cooled in an ice/water bath and allylmagnesium chloride (1.0 M, 17 mmol, 2.0 equiv.) was added in a dropwise fashion. Stirred at 0°C for 10 minutes and to the resulting gray mixture was added a solution of crude tosylate in 7 mL Et$_2$O over several minutes. The reaction was allowed to warm to ambient temperature and stir overnight. The reaction was then carefully quenched with saturated aqueous NH$_4$Cl and the layers were separated and extracted 3X with Et$_2$O. The combined organics were dried over MgSO$_4$, filtered through celite, concentrated under reduced pressure, and purified by filtration through a silica plug (hexanes). The title compound was isolated as a pale yellow liquid (0.92 g, 79%). 1H NMR (500 MHz, CDCl$_3$) δ 5.83 (ddt, $J$ = 17.0, 10.0, 6.5, 1H), 5.68-5.63 (m, 2H), 5.01 (app dq, $J$ = 17.0, 2.0 Hz, 1H), 4.95-4.92 (m, 1H), 2.14-2.06 (m, 3H), 2.06-2.01 (2H), 1.78-1.71 (m, 1H), 1.69-1.61 (m, 1H), 1.60-1.52 (m, 1H), 1.42-1.30 (m, 2H), 1.26-1.18 (m, 1H); 13C NMR (125 MHz, CDCl$_3$) δ 139.4, 127.2, 126.7, 114.3, 36.0, 33.1, 31.9, 31.3, 29.0, 25.4; IR (film, cm$^{-1}$): 3078, 3022, 2976, 2914, 2848, 1641, 1454, 1435, 993; HRMS (EI) m/z calc'd for C$_{10}$H$_{16}$ [M+H]$^+$: 136.1252, found 136.1256.

4-(hex-5-en-1-yl)cyclohexan-1-one: Solid LiAlH$_4$ (95%, 117 mg, 2.93 mmol, 0.5 equiv.) was added to a solution of 3-ethoxy-6-(hex-5-en-1-yl)cyclohexen-2-enone (1.3 g, 5.8 mmol, 1.0 equiv.) in anhydrous Et$_2$O (12 mL) while being cooled in an ice/water bath. The resulting mixture stirred for 5 min at 0°C and then warmed to room temperature for 30 min. The reaction was judged to be complete by 1H NMR and was thereafter cooled in an ice/water bath and
quenched by careful addition of 8 mL 25% H₂SO₄. After 30 min stirring the crude reaction mixture was partitioned between H₂O and Et₂O. The aqueous layer was extracted 2X with Et₂O and the combined organics were washed successively with saturated aqueous Na₂CO₃ and brine. The organics were collected, dried over MgSO₄, filtered through celite, and concentrated under reduced pressure. The title compound was used without further purification (0.98 g, 95%).

1H NMR (500 MHz, CDCl₃) δ 5.79 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 4.99 (dd, J = 17.5, 2.0 Hz, 1H), 4.92 (d, J = 15.5 Hz, 1H), 2.40-2.26 (m, 4H), 2.10-1.98 (m, 4H), 1.74-1.62 (m, 1H), 1.46-1.24 (m, 8H); 13C NMR (125 MHz, CDCl₃) δ 212.6, 139.0, 114.5, 41.0, 35.5, 33.8, 32.9, 29.1, 26.9; IR (film, cm⁻¹): 3076, 2926, 2856, 1718, 1641, 1462, 1448, 1433, 1333, 1246, 1169, 1128, 993; HRMS (EI) m/z calc'd for C₁₂H₂₀O [M+H]^+: 180.1514, found 180.1521.

4-(hex-5-en-1-yl)cyclohex-1-en-1-yl acetate: 4-(hex-5-en-1-yl)cyclohexan-1-one (0.45 g, 2.5 mmol, 1.0 equiv) was dissolved in 25 mL isopropenyl acetate and treated with pTsOH (30 mg, 0.16 mmol, 0.065 equiv.). The reaction was heated to reflux for 24h, concentrated under reduce pressure, and purified by flash chromatography (hexanes → 2% EtOAc/hexanes → 5% EtOAc/hexanes), affording the title compound as a clear, colorless oil (498 mg, 90%). 1H NMR (500 MHz, CDCl₃) δ 5.80 (ddt, J = 17.0, 10.5, 7.0 Hz, 1H), 5.33-5.32 (m, 1H), 4.99 (dd, J = 17.0, 2.0 Hz, 1H), 4.95-4.92 (m, 1H), 2.29-2.14 (m, 2H), 2.11 (s, 3H), 2.10-2.01 (m, 3H), 1.84-1.70 (m, 1H), 1.60-1.52 (m, 1H), 1.42-1.24 (m, 7H); 13C NMR (125 MHz, CDCl₃) δ 169.7, 148.4, 139.2, 114.4, 113.6, 35.8, 33.9, 32.9, 30.2, 29.2, 28.9, 26.8, 26.7, 21.2; IR (film, cm⁻¹): 3076, 2927, 2854, 1757, 1693, 1641, 1454, 1439, 1367, 1294, 1219, 1039, 995; HRMS (ESI) m/z calc'd for C₁₄H₂₂O₂Na [M+Na]^+: 245.1517, found 245.1524.

Allyl estradiol derivative B: To a solution of the known allyl estrone derivative A ¹⁸⁵ (2.70 g, 8.3 mmol) in anhydrous THF (50 mL) at -78°C
was quickly added solid LiAlH$_4$ (95%, 535 mg, 13.4 mmol, 1.6 equiv.) and the reaction stirred at this
temperature for 30 min. The reaction was carefully quenched by adding 0.54 mL H$_2$O slowly, followed
by 0.54 mL 1M aqueous NaOH, and 3X 0.54 mL H$_2$O. The reaction was allowed to warm to ambient
temperature, filtered through celite, and concentrated under reduced pressure. The resulting white foam
was used without further purification in the next step (2.34 g, 87%). $^1$H NMR (500 MHz, CDCl$_3$) d 7.20
(d, $J$ = 9.0 Hz, 1H), 6.71 (dd, $J$ = 9.0, 3.0 Hz, 1H), 6.63 (d, $J$ = 3.0 Hz, 1H), 5.88 (ddt, $J$ = 17.0, 10.5, 7.0
Hz, 1H), 5.09 (dd, $J$ = 16.5, 2.0 Hz, 1H), 5.04-5.02 (m, 1H), 3.78 (s, 3H), 3.33 (d, $J$ = 7.5 Hz, 1H), 2.90-
2.80 (m, 2H), 2.36-2.26 (m, 2H), 2.23-2.12 (m, 2H), 1.95-1.82 (m, 3H), 1.64-1.52 (m, 2H), 1.52-1.38 (m,
3H), 1.38-1.18 (m, 3H), 0.82 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 157.5, 138.0, 137.9, 132.7, 126.3,
115.8, 113.8, 111.5, 87.4, 55.2, 48.4, 44.1, 44.0, 43.2, 39.6, 38.6, 36.8, 29.8, 29.7, 27.3, 26.3, 12.0; IR
(film, cm$^{-1}$): 3394 (br), 3070, 3037, 2974, 2931, 2868, 1699, 1639, 1610, 1576, 1500, 1454, 1439, 1381,
1338, 1313, 1281, 1255, 1236, 1180, 1146, 1122, 1101, 1038; HRMS (ESI) m/z calcd for C$_{22}$H$_{31}$O$_2$
[M+H]$^+$: 327.2324, found 327.2316. [$\alpha$]$_{25}^\text{D}$ = +36.5 (c = 1.14, CHCl$_3$).

**Benzyloxy estradiol derivative C:** To a solution of the 2° alcohol B (2.30 g, 7.0 mmol, 1.0 equiv.) in anhydrous THF (25 mL) in a
flame-dried 100 mL round-bottom flask at 0°C was added NaH (60% in mineral oil, 840 mg, 21.0 mmol, 3.0 equiv.). The reaction stirred 30 min at 0°C and neat benzyl bromide (2.08 mL, 17.5 mmol, 2.5 equiv.) and solid tetrabutylammonium iodide (259 mg, 0.70 mmol, 0.10 equiv.) were added. The reaction stirred overnight at room temperature, and was then heated to reflux for 18h due to incomplete conversion of starting material. After reflux, the reaction cooled to room
temperature and was partitioned between EtOAc and H$_2$O and the organic layer was washed 3X with H$_2$O. The organic layer was collected, dried over MgSO$_4$, filtered through celite, and concentrated in vacuo.
The crude product was purified by flash chromatography (hexanes $\rightarrow$ 2% EtOAc/hexanes $\rightarrow$ 5%
EtOAc/hexanes), but was only isolated in ~80% purity and used directly in the next step. To a solution of
the benzyloxy allyl derivative (1.87 g, 4.5 mmol, 1.0 equiv.) in anhydrous THF (40 mL) at 0°C was added
1.0M BH$_3$-THF (4.5 mL, 4.5 mmol, 1.0 equiv.) dropwise. The resulting mixture stirred at this temperature
under an atmosphere of argon for 1.5h and was carefully quenched with 1.5 mL 3M aqueous NaOH,
followed by 0.60 mL 30% aqueous H$_2$O$_2$. The quenched reaction stirred at ambient temperature for 1.5h
and was partitioned between H$_2$O and EtOAc. The aqueous layer was extracted 3X with EtOAc and the
combined organics were dried over MgSO$_4$, filtered through celite, concentrated in vacuo, and purified by
flash chromatography (20% $\rightarrow$ 40% EtOAc/hexanes). The primary alcohol was isolated as a white solid
(1.10 g, 56%). $^1$H NMR (500 MHz, CDCl$_3$) d 7.38-7.32 (m, 4H), 7.10-7.26 (m, 1H), 7.20 (d, $J$ = 9.0 Hz,
1H), 6.72 (dd, $J$ = 8.5, 3.0 Hz, 1H), 6.63 (d, $J$ = 3.0 Hz, 1H), 4.74 (d, $J$ = 11.5 Hz, 1H), 4.51 (d, $J$ = 11.5
Hz, 1H), 3.78 (s, 3H), 3.68-3.59 (m, 2H), 3.17 (d, J = 7.5 Hz, 1H), 2.91-2.90 (m, 2H), 2.33-2.25 (m, 1H), 2.23-2.14 (m, 1H), 2.13-2.08 (m, 1H), 2.02-1.94 (m, 1H), 1.88-1.82 (m, 1H), 1.66-1.50 (m, 6H), 1.50-1.38 (m, 2H), 1.38-1.24 (m, 4H), 0.92 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.6, 139.1, 138.1, 132.7, 128.5, 127.9, 127.6, 126.4, 113.9, 111.6, 95.4, 73.1, 63.3, 55.3, 48.9, 43.9, 41.6, 39.0, 38.6, 32.3, 31.5, 30.0 (2 peaks), 27.3, 26.6, 12.7; IR (film, cm$^{-1}$): 3417 (br), 2931, 2864, 1610, 1576, 1498, 1452, 1381, 1352, 1313, 1281, 1255, 1238, 1142, 1093, 1074, 1039; HRMS (ESI) m/z calc’d 7 for C$_{29}$H$_{39}$O$_3$ [M+H]$^+$: 435.2899, found 435.2897. $^{[\alpha]}$D = -21.5 (c = 0.26, CHCl$_3$).

**Benzyloxy estradiol butene derivative D:** The primary alcohol was oxidized according to the procedure of Hoover and Stahl.$^{[86]}$ The primary alcohol (1.1 g, 2.5 mmol, 1.0 equiv.), N-methyl imidazole (19.9 µL, 0.25 mmol, 0.10 equiv.), bipyridine (19.5 mg, 0.125 mmol, 0.05 equiv.), [Cu(CH$_3$CN)$_4$]PF$_6$ (46.6 mg, 0.125 mmol, 0.05 equiv.), and TEMPO (19.5 mg, 0.125 mmol, 0.05 equiv.) were each dissolved in 3 mL CH$_3$CN and added successively to a 100 mL round-bottom flask. The mixture was stirred at ambient temperature under an atmosphere of O$_2$ for 8h, at which point TLC analysis indicated complete consumption of starting material. The crude reaction was filtered through a pad of silica (1:1 Et$_2$O:hexanes) and the filtrate was concentrated under reduce pressure. The resulting aldehyde was used immediately in the next step (1.0 g, 93%). To a flame-dried 3-necked 100 mL round-bottom flask was added MePPh$_3$Br (3.29 g, 9.2 mmol, 4.0 equiv.) and 8 mL anhydrous THF. The flask was cooled in an ice/water bath while under an atmosphere of N$_2$ and solid KO$_2$Bu (95%, 980 mg, 9.3 mmol, 3.6 equiv.) was added quickly; the resulting yellow mixture stirred at 0°C for 1h and the estrone-derived aldehyde was added as a solution in 6 mL anhydrous THF. After stirring 1h at 0°C, the reaction was quenched with saturated aqueous NH$_4$Cl and allowed to warm to ambient temperature. The reaction was partitioned between water and CH$_2$Cl$_2$ and extracted 3X with CH$_2$Cl$_2$. The combined organics were dried over MgSO$_4$, filtered through celite, concentrated in vacuo, and purified by flash chromatography (2% EtOAc/hexanes $\rightarrow$ 5% EtOAc/hexanes). The title compound was isolated as a white solid (0.90 g, 91%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37-7.33 (m, 4H), 7.30-7.25 (m, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 5.83 (ddt, J = 17.0, 10.5, 6.5 Hz, 1H), 5.00 (dd, J = 17.5, 2.0 Hz, 1H), 4.95-4.92 (m, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.16 (d, J = 7.0 Hz, 1H), 2.91-2.80 (m, 2H), 2.32-2.26 (m, 1H), 2.23-2.16 (m, 1H), 2.15-2.06 (m, 2H), 2.06-2.00 (m, 1H), 2.00-1.92 (m, 1H), 1.90-1.83 (m, 1H), 1.73-1.65 (m, 1H), 1.62-1.48 (m, 3H), 1.48-1.38 (m, 1H), 1.38-1.22 (m, 4H), 0.91 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.6, 139.3, 138.1, 132.8, 128.4, 127.8, 127.6, 126.4, 114.3, 113.9 (2 peaks), 111.6, 95.4, 73.1, 55.4, 48.9, 44.7, 44.0, 41.7, 39.0,
8-oxononyl acetate: non-8-en-1-yl acetate was reacted according to a modified version of the general procedure, excluding PhI(OAc)₂ and only stirring at 35°C for 18 h. Purification by flash chromatography (10% → 20% EtOAc/hexanes) afforded the title compound as a colorless oil. \(^1\)H NMR (500 MHz, CDCl₃) \(d\) 4.04 (t, \(J = 7.0\) Hz, 2H), 2.42 (t, \(J = 7.5\) Hz, 2H), 2.13 (s, 3H), 2.04 (s, 3H), 1.64-1.53 (m, 4H), 1.38-1.24 (m, 6H); \(^1^3\)C NMR (125 MHz, CDCl₃) \(d\) 209.3, 171.3, 64.6, 43.7, 30.0, 29.1, 28.6, 25.8, 23.7, 21.1; IR (film, cm\(^{-1}\)): 2935, 2858, 1738, 1716, 1464, 1433, 1412, 1387, 1365, 1242, 1163, 1038; HRMS (ESI) \(m/z\) calc'd for C\(_{11}\)H\(_{21}\)O\(_3\) [M+H]\(^+\): 201.1491, found 201.1492.

\(\text{(E)-8-oxonon-6-en-1-yl acetate:}\) non-8-en-1-yl acetate (55.3 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (10% → 20% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (32.5 mg, 0.164 mmol, 55% yield); run 2 (32.6 mg, 0.164 mmol, 55% yield). **Average yield: 55%.** \(^1\)H NMR (500 MHz, CDCl₃) \(d\) 7.56-7.54 (m, 2H), 7.52 (d, \(J = 16.0\) Hz, 1H), 7.41-7.39 (m, 3H), 6.72 (d, \(J = 16.5\) Hz, 1H), 2.39 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl₃) \(d\) 198.7, 143.5, 134.5, 130.6, 129.0, 128.3, 127.2, 127.1, 125.0, 1045, 982; HRMS (ESI) \(m/z\) calc'd for C\(_{11}\)H\(_{19}\)O\(_3\) [M+H]\(^+\): 199.1334, found 199.1338.

**Table 4.2 Products**

\(\text{(E)-4-phenylbut-3-en-2-one:}\) 4-phenyl-1-butene (66.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 10% EtOAc/hexanes) afforded the title compound as a pale yellow oil. Run 1 (49.0 mg, 0.335 mmol, 67% yield); run 2 (49.6 mg, 0.339 mmol, 68% yield). **Average yield: 68%.** \(^1\)H NMR (500 MHz, CDCl₃) \(d\) 7.56-7.54 (m, 2H), 7.52 (d, \(J = 16.0\) Hz, 1H), 7.41-7.39 (m, 3H), 6.72 (d, \(J = 16.5\) Hz, 1H), 2.39 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl₃) \(d\) 198.5, 143.5, 134.5, 130.6, 129.0, 128.3, 127.2, 27.6;
IR (film, cm$^{-1}$): 3082, 3062, 3043, 3028, 1691, 1668, 1610, 1576, 1495, 1450, 1423, 1358, 1329, 1294, 1257, 1205, 1182, 976; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O [M+H]$^+$: 147.0810, found 147.0813.

(E)-4-(4-methoxyphenyl)but-3-en-2-one: 4-(4-methoxyphenyl)-1-butene (81.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% → 25% EtOAc/hexanes) afforded the title compound as an off-white solid. Run 1 (59.9 mg, 0.340 mmol, 68% yield); run 2 (61.2 mg, 0.347 mmol, 69% yield). **Average yield: 69%**.

$^1$H NMR (500 MHz, CDCl$_3$) $d$ 7.51 - 7.46 (m, 3H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 16.0$ Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 198.6, 161.7, 143.4, 130.1, 127.2, 125.2, 114.6, 55.6, 27.6; IR (film, cm$^{-1}$): 3045, 3005, 2958, 2941, 2914, 2846, 1682, 1601, 1574, 1512, 1464, 1423, 1360, 1302, 1250, 1174, 1109, 1022, 989; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$: 177.0916, found 177.0919.

(E)-4-(4-bromophenyl)but-3-en-2-one: 4-(4-bromophenyl)-1-butene (81.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% → 25% EtOAc/hexanes) afforded the title compound as an off-white solid. Run 1 (59.9 mg, 0.340 mmol, 68% yield); run 2 (61.2 mg, 0.347 mmol, 69% yield). **Average yield: 69%**.

$^1$H NMR (500 MHz, CDCl$_3$) $d$ 7.51 - 7.46 (m, 3H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 16.0$ Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 198.6, 161.7, 143.4, 130.1, 127.2, 125.2, 114.6, 55.6, 27.6; IR (film, cm$^{-1}$): 3045, 3005, 2958, 2941, 2914, 2846, 1682, 1601, 1574, 1512, 1464, 1423, 1360, 1302, 1250, 1174, 1109, 1022, 989; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$: 177.0916, found 177.0919.

(E)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one: 4-(4-(trifluoromethyl)phenyl)-1-butene (81.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% → 25% EtOAc/hexanes) afforded the title compound as an off-white solid. Run 1 (59.9 mg, 0.340 mmol, 68% yield); run 2 (61.2 mg, 0.347 mmol, 69% yield). **Average yield: 69%**.

$^1$H NMR (500 MHz, CDCl$_3$) $d$ 7.51 - 7.46 (m, 3H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 16.0$ Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 198.6, 161.7, 143.4, 130.1, 127.2, 125.2, 114.6, 55.6, 27.6; IR (film, cm$^{-1}$): 3045, 3005, 2958, 2941, 2846, 1682, 1601, 1574, 1512, 1464, 1423, 1360, 1302, 1250, 1174, 1109, 1022, 989; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$: 177.0916, found 177.0919.

(E)-4-(4-bromophenyl)but-3-en-2-one: 4-(4-bromophenyl)-1-butene (63.3 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% → 25% EtOAc/hexanes) afforded the title compound as an off-white solid. Run 1 (43.1 mg, 0.191 mmol, 64% yield); run 2 (41.7 mg, 0.185 mmol, 62% yield). **Average yield: 63%**.

$^1$H NMR (500 MHz, CDCl$_3$) $d$ 7.51 - 7.46 (m, 3H), 6.92 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 16.0$ Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 198.6, 161.7, 143.4, 130.1, 127.2, 125.2, 114.6, 55.6, 27.6; IR (film, cm$^{-1}$): 3045, 3005, 2958, 2941, 2846, 1682, 1601, 1574, 1512, 1464, 1423, 1360, 1302, 1250, 1174, 1109, 1022, 989; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$: 224.9915, found 224.9917.

(E)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one: 4-(4-(trifluoromethyl)phenyl)-1-butene (60.1 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (10% → 20% EtOAc/hexanes) afforded the title compound as a white solid. Run 1 (38.7 mg, 0.181 mmol, 60% yield); run 2 (40.1 mg, 0.187 mmol, 62% yield). **Average yield: 61%**.

$^1$H NMR (500 MHz, CDCl$_3$) $d$ 7.67 - 7.63 (m, 3H), 7.52 (d, $J = 16.5$ Hz, 1H), 6.77 (d, $J = 16.0$ Hz, 1H), 2.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 198.0, 141.4, 138.0, 132.1 (q, $J = 33.3$ Hz), 129.2, 128.5, 126.0 (q, $J = 3.9$ Hz), 123.9 (q, $J = 272.5$ Hz), 27.9; IR (film, cm$^{-1}$): 3051, 3022, 2964, 2926, 1689, 1668, 1616, 1577, 1416, 1362, 1327, 1259, 1207, 1171, 1130, 1113, 1068, 1018, 982; HRMS (ESI) $m/z$ calc'd for C$_{10}$H$_{11}$O$_2$ [M+H]$^+$: 215.0684, found 215.0688.
(E)-4-(o-tolyl)but-3-en-2-one: 4-(o-tolyl)-1-butene (73.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (2% → 5% EtOAc/hexanes) afforded the title compound as a yellow oil. Run 1 (49.1 mg, 0.306 mmol, 61% yield); run 2 (51.0 mg, 0.318 mmol, 64% yield). **Average yield: 63%**. ^1^H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.82 (d, \(J=16.5\) Hz, 1H), 7.57 (d, \(J=7.5\) Hz, 1H), 7.29 (t, \(J=8.0\) Hz, 1H), 7.22 (t, \(J=7.5\) Hz, 2H), 6.65 (d, \(J=16.0\) Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H); ^1^C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 198.4, 140.9, 137.9, 133.4, 130.9, 130.3, 128.2, 126.5 (2 peaks), 27.9, 19.8; IR (film, cm\(^{-1}\))): 3055, 3026, 2972, 2956, 2926, 2870, 1691, 1670, 1645, 1612, 1599, 1485, 1462, 1425, 1360, 1296, 1257, 1257, 1221, 1178, 976; HRMS (ESI) \(m/z\) calc'd for C\(_{11}\)H\(_{13}\)O [M+H]\(^+\): 161.0966, found 161.0964.

(E)-4-(2,2-dimethyl-2H-chromen-6-yl)but-3-en-2-one: 6-(but-3-en-1-yl)-2,2-dimethyl-2H-chromene (64.3 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 10% EtOAc/hexanes) afforded the title compound as a pale yellow oil. Run 1 (44.6 mg, 0.195 mmol, 65% yield); run 2 (44.6 mg, 0.195 mmol, 65% yield). **Average yield: 65%**. ^1^H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43 (d, \(J=16.5\) Hz, 1H), 7.31 (dd, \(J=8.5, 2.0\) Hz, 1H), 7.18 (d, \(J=2.0\) Hz, 1H), 6.78 (d, \(J=8.5\) Hz, 1H), 6.58 (d, \(J=16.0\) Hz, 1H), 6.32 (d, \(J=10.0\) Hz, 1H), 5.66 (d, \(J=10.0\) Hz, 1H), 2.35 (s, 3H), 1.45 (s, 6H); ^1^C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 198.5, 155.5, 143.5, 131.6, 129.9, 127.2, 126.4, 124.9, 121.8, 121.5, 117.0, 77.3, 28.4, 27.6; IR (film, cm\(^{-1}\))): 3039, 3024, 2974, 2929, 1687, 1664, 1616, 1601, 1572, 1491, 1429, 1362, 1325, 1273, 1254, 1213, 1155, 1128, 1107, 978; HRMS (ESI) \(m/z\) calc'd for C\(_{15}\)H\(_{17}\)O\(_2\) [M+H]\(^+\): 229.1229, found 229.1234.

(E)-dec-3-en-2-one: 1-decene (70.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (1% → 3% → 5% EtOAc/petroleum ether) afforded the title compound as a pale yellow oil. Run 1 (46.8 mg, 0.303 mmol, 61% yield); run 2 (45.9 mg, 0.298 mmol, 60% yield). **Average yield: 61%**. ^1^H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.80 (dt, \(J=16.5, 6.5\) Hz, 1H), 6.07 (d, \(J=16.0\) Hz, 1H), 2.24 (s, 3H), 2.24-2.20 (m, 2H), 1.50-1.42 (m, 2H), 1.35-1.25 (m, 6H), 0.89 (t, \(J=7.0\) Hz, 3H); ^1^C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 198.9, 148.8, 131.4, 32.6, 31.7, 29.0, 28.2, 26.9, 22.6, 14.2; IR (film, cm\(^{-1}\))): 2956, 2929, 1699, 1678, 1628, 1466, 1431, 1362, 1254, 1282, 1254, 1176, 978; HRMS (ESI) \(m/z\) calc'd for C\(_{10}\)H\(_{19}\)O [M+H]\(^+\): 155.1436, found 155.1435.

(E)-5-oxohex-3-en-1-yl benzoate: hex-5-en-1-yl benzoate (61.3 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash...
chromatography (5% → 15% → 25% EtOAc/petroleum ether) afforded the title compound as a pale yellow oil. Run 1 (36.0 mg, 0.165 mmol, 55% yield); run 2 (34.4 mg, 0.158 mmol, 53% yield). Average yield: 54%. 1H NMR (500 MHz, CDCl₃) δ 8.02 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 6.84 (dt, J = 16.0, 7.0 Hz, 1H), 6.21 (d, J = 16.0 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 2.71 (qd, J = 6.0, 1.0 Hz, 2H), 2.26 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 198.3, 166.5, 143.1, 133.3, 133.2, 130.0, 129.6, 128.5, 31.9, 27.1; IR (film, cm⁻¹): 3062, 3033, 3006, 2960, 2904, 1720, 1699, 1678, 1630, 1603, 1452, 1427, 1362, 1275, 1176, 1117, 1070, 1026, 976; HRMS (ESI) m/z calc'd for C₁₃H₁₆O₃Na [M+Na]⁺: 241.0841, found 241.0846.

(E)-2-(7-oxooct-5-en-1-yl)isoindoline-1,3-dione: 2-(oct-7-en-1-yl)isoindoline-1,3-dione (77.2, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (15% → 25% → 35% EtOAc/petroleum ether) afforded the title compound as a white solid. Run 1 (46.0 mg, 0.170 mmol, 57% yield); run 2 (46.5 mg, 0.171 mmol, 57% yield). Average yield: 57%. 1H NMR (500 MHz, CDCl₃) δ 7.87-7.83 (m, 2H), 7.74-7.70 (m, 2H), 6.76 (dt, J = 16.0, 7.0 Hz, 1H), 6.07 (d, J = 16.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 2.28 (q, J = 7.0 Hz, 2H), 2.23 (s, 3H), 1.73 (p, J = 7.0 Hz, 2H), 1.56-1.50 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 198.7, 168.5, 147.5, 134.1, 132.2, 131.8, 123.4, 37.7, 32.0, 28.3, 27.0, 25.4; IR (film, cm⁻¹): 3055, 3026, 2972, 2937, 2883, 2864, 1772, 1711, 1670, 1628, 1466, 1437, 1398, 1363, 1335, 1255, 1232, 1219, 1188, 1173, 1039, 984; HRMS (ESI) m/z calc'd for C₁₆H₁₈NO₃ [M+H]⁺: 272.1287, found 272.1290.

(E)-1-morpholinohept-4-ene-1,6-dione: 1-morpholinohept-6-en-1-one (59.2 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (20% → 40% acetone/hexanes) afforded the title compound and the corresponding Wacker product as an inseparable mixture. Further chromatography provided a nearly pure sample of the title compound for characterization as a colorless oil. Run 1 (34.7 mg, 0.164 mmol, 55% yield); run 2 (32.5 mg, 0.154 mmol, 51% yield). Average yield: 53%. 1H NMR (500 MHz, CDCl₃) δ 6.86 (dt, J = 16.0, 6.5 Hz, 1H), 6.10 (d, J = 16.5 Hz, 1H), 3.69-3.67 (m, 4H), 3.64-3.62 (m, 2H), 3.47-3.45 (m, 2H), 2.59 (q, J = 6.5 Hz, 2H), 2.48 (t, J = 7.5 Hz, 2H), 2.25 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 198.7, 170.0, 146.8, 131.9, 67.0, 66.6, 45.9, 42.1, 31.3, 27.6, 27.1; IR (film, cm⁻¹): 2960, 2924, 2912, 2856, 1695, 1672, 1647, 1460, 1439, 1362, 1300, 1271, 1255, 1236, 1194, 1117, 1070, 1028; HRMS (ESI) m/z calc'd for C₁₁H₁₄NO₃ [M+H]⁺: 212.1287, found 212.1289.
(±)-(E)-methyl 2-methyl-6-oxohept-4-enoate: methyl 2-methylhept-6-enoate (78.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (10% → 20% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (47.4 mg, 0.279 mmol, 56% yield); run 2 (47.4 mg, 0.279 mmol, 56% yield). **Average yield:** 56%. $^1$H NMR (500 MHz, CDCl$_3$) d 6.72 (dt, $J = 16.0, 7.0$ Hz, 1H), 6.09 (d, $J = 15.5$ Hz, 1H), 3.69 (s, 3H), 2.67-2.60 (m, 1H), 2.60-2.55 (m, 1H), 2.38-2.32 (m, 1H), 2.24 (s, 3H), 1.20 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 198.4, 175.8, 144.6, 133.0, 51.9, 38.6, 36.2, 27.1, 17.0; IR (film, cm$^{-1}$): 2978, 2954, 2881, 2846, 1738, 1699, 1676, 1630, 1455, 1435, 1362, 1255, 1211, 1196, 1171, 1126, 1092, 1063, 1022, 984; HRMS (ESI) m/z calc’d for C$_9$H$_{15}$O$_3$ [M+H]$^+$: 171.1021, found 171.1027.

(R,E)-6-(benzyloxy)-5-methylhex-3-en-2-one: (R)-6-(benzyloxy)-5-methylhexene (61.3 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 10% → 20% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (40.1 mg, 0.184 mmol, 61%); run 2 (40.1 mg, 0.184 mmol, 61%); **Average yield:** 61%. $^1$H NMR (500 MHz, CDCl$_3$) d 7.37-7.27 (m, 5H), 6.79 (dd, $J = 16.0, 7.0$ Hz, 1H), 6.11 (dd, $J = 16.0$ Hz, 1.0 Hz, 1H), 4.52 (s, 2H), 3.42 (d, $J = 6.0$ Hz, 2H), 2.68 (septet, $J = 7.0$ Hz, 1H), 2.25 (s, 3H), 1.10 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 199.0, 150.5, 138.2, 130.7, 128.5, 127.8, 127.7, 74.0, 73.2, 37.1, 27.0, 16.2; IR (film, cm$^{-1}$): 3064, 3030, 3005, 2966, 2933, 2860, 2796, 1697, 1676, 1628, 1496, 1454, 1425, 1360, 1309, 1255, 1205, 1184, 1155, 1097, 1028, 984; HRMS (ESI) m/z calc’d for C$_{14}$H$_{19}$O$_2$ [M+H]$^+$: 219.1385, found 219.1388. [$\alpha$]$_{D}^{25}$ $+$1.5 (c = 0.13, CHCl$_3$).

The product was analyzed by chiral GC (Astec CHIRALDEX GT-A, 120°C isothermal); major enantiomer $t_R = 109.9$ min, minor enantiomer $t_R = 107.8$ min. $er = 98.4:1.6$. Racemic sample: $t_R = 108.0$, $t_R = 110.1$.

(±)-trans-2-(3-oxobut-1-en-1-yl)cyclohexyl acetate: trans-2-(but-3-en-1-yl)cyclohexyl acetate (58.9 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% → 25% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (40.9 mg, 0.195 mmol, 65%); run 2 (41.4 mg, 0.197 mmol, 66%). **Average yield:** 66%. $^1$H NMR (500 MHz, CDCl$_3$) d 6.59 (dd, $J = 16.0, 8.0$ Hz, 1H), 6.03 (d, $J = 16.0$ Hz, 1H), 4.66 (td, $J = 10.0, 4.5$ Hz, 1H), 2.32-2.25 (m, 1H), 2.22 (s, 3H), 2.04-1.99 (m, 1H), 1.97 (s, 3H), 1.84-1.78 (m, 2H), 1.75-1.69 (m, 1H), 1.40-1.22 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 198.9, 170.6, 149.0, 131.8, 74.8, 46.7, 31.5, 30.8, 26.8, 24.6, 24.4, 21.3; IR (film, cm$^{-1}$): 2935, 2860, 1736, 1699, 1678, 1628, 1450, 1435, 1373, 1238, 1032, 982; HRMS (ESI) m/z calc’d for C$_{12}$H$_{16}$O$_3$Na [M+Na]$^+$: 233.1154, found 233.1162.
(±)-(E)-4-(cyclohex-3-en-1-yl)but-3-en-2-one: 4-(but-3-en-1-yl)cyclohex-1-ene (68.1 mg, 0.50 mmol) was reacted according to the general procedure. Purification by flash chromatography (1% → 3% → 5% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (45.2 mg, 0.301 mmol, 60%); run 2 (43.8 mg, 0.292 mmol, 58%). **Average yield: 59%.** ¹H NMR (500 MHz, CDCl₃) δ 6.79 (dd,  J = 16.0, 7.0 Hz, 1H), 6.08 (dd,  J = 16.5 Hz, 1.0 Hz, 1H), 5.74-5.65 (m, 2H), 2.50-2.42 (m, 1H), 2.25 (s, 3H), 2.20-2.14 (m, 1H), 2.13-2.07 (m, 2H), 1.97-1.89 (m, 1H), 1.87-1.81 (m, 1H), 1.52-1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 199.1, 152.4, 129.5, 127.1, 125.3, 36.7, 30.3, 27.7, 27.0, 24.5; IR (film, cm⁻¹): 3024, 2916, 2856, 2839, 1697, 1676, 1626, 1452, 1437, 1363, 1317, 1254, 1176, 1140, 982; HRMS (ESI) m/z calc'd for C₁₀H₁₅O [M+H]⁺: 151.1123, found 151.1131.

(±)-(E)-4-(5-oxohex-3-en-1-yl)cyclohex-1-en-1-yl acetate: 4-(hex-5-en-1-yl)cyclohex-1-en-1-yl acetate (66.7 mg, 0.30 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 15% EtOAc/hexanes) afforded the title compound as a colorless oil. Run 1 (36.6 mg, 0.155 mmol, 52%); run 2 (35.0 mg, 0.148 mmol, 49%). **Average yield: 51%.** ¹H NMR (500 MHz, CDCl₃) δ 6.80 (dt,  J = 16.0, 6.5 Hz, 1H), 6.08 (d,  J = 16.0 Hz, 1H), 5.33-5.32 (m, 1H), 2.30-2.18 (m, 4H), 2.24 (s, 3H), 2.11 (s, 3H), 2.09-2.05 (m, 1H), 1.86-1.74 (m, 2H), 1.66-1.58 (m, 1H), 1.52-1.37 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.7, 169.6, 148.4, 148.2, 131.5, 113.2, 34.1, 32.5, 30.2, 30.0, 28.7, 27.0, 26.5, 21.2; IR (film, cm⁻¹): 3005, 2918, 2852, 1755, 1695, 1674, 1626, 1454, 1435, 1365, 1254, 1223, 1159, 1149, 1122, 1041, 982; HRMS (ESI) m/z calc'd for C₁₄H₂₀O₃Na [M+Na]⁺: 259.1310, found 259.1320.

α,β-unsaturated ketone 103: estradiol derivative D (86.1 mg, 0.20 mmol) was reacted according to the general procedure. Purification by flash chromatography (5% → 10% acetone/hexanes) afforded Wacker product and the title compound as colorless residues. Wacker product (run 1: 26.0 mg, 0.060 mmol; run 2: 34.5 mg, 0.080 mmol) was re-exposed to the standard reaction conditions (reagents scaled accordingly) and the combined yield of the title compound was reported in Table 2: Run 1 (51.5 mg, 0.116 mmol, 58%); run 2 (48.8 mg, 0.110 mmol, 55%). **Average yield: 57%.** ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.27 (m, 5H), 7.20 (d,  J = 8.5 Hz, 1H), 6.79 (dd,  J = 16.0, 8.5 Hz, 1H), 6.72 (dd,  J = 8.5, 3.0 Hz, 1H), 6.63 (d,  J = 2.5 Hz, 1H), 6.09 (d,  J = 16.0 Hz, 1H), 4.66 (d,  J = 12.0 Hz, 1H), 4.53 (d,  J = 12.0 Hz, 1H), 3.78 (s, 3H), 3.36 (d,  J = 7.5 Hz, 1H), 2.92-2.77 (m, 3H), 2.34-2.29 (m, 1H), 2.24-2.18 (m, 1H), 2.22 (s, 3H), 2.12-2.08 (m, 1H), 1.86-1.75 (m, 2H), 1.62-1.57
(m, 1H), 1.55-1.50 (m, 1H), 1.50-1.40 (m, 2H), 1.38-1.29 (m, 2H), 0.94 (s, 3); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 198.8, 157.7, 152.0, 138.7, 138.0, 132.4, 129.9, 128.5, 127.9, 127.8, 126.4, 114.0, 111.7, 93.3, 72.9, 55.4, 55.3, 49.2, 45.5, 44.8, 44.0, 38.6, 38.3, 30.5, 29.9, 27.2, 26.5, 12.7; IR (film, cm$^{-1}$): 2945, 2904, 2873, 2846, 1695, 1672, 1576, 1498, 1454, 1433, 1358, 1313, 1282, 1254, 1240, 1207, 1178, 1142, 1122, 1099, 1043, 1032, 980; HRMS (ESI) m/z calc'd for C$_{30}$H$_{37}$O$_3$ [M+H]$^+$: 445.2743, found 445.2737. $[^{25}]$$\alpha_\lambda$ = +22.1 (c = 0.19, CHCl$_3$).

4-tert-butylocyclohexanone (46.2 mg, 0.30 mmol) was reacted according to a modification of the general procedure, including a single equivalent of 1,4-benzoquinone, stirring the reaction at 35°C for 24h, instead of 48h, and excluding H$_2$O. Purification by flash chromatography (10% EtOAc/hexanes) afforded a mixture of the product and 4-tert-butylphenol as a colorless oil. Run 1 (7.5:1 product: 4-tert-butylphenol, 38.3 mg product, 84%); run 2 (8.7:1 product: 4-tert-butylphenol, 34.1 mg product, 75%). **Average yield:** 80%.

**Figure SI 4.1: Kinetic Profile**

General procedure was followed, including either 0 mol%, 25 mol%, or 100 mol% PhI(OAc)$_2$. The reaction was monitored by GC analysis, with measurements taken at 2.5 h, 5h, 10h, 24h, 30h, and 36h. Results are reported as the average of three runs, with yields calculated with respect to a standard curve, including error bars for the calculated standard deviation.

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| **25% PhI(OAc)$_2$** |     |   |    |    |    |    |
| Run 1 GC Yield | 2.70 | 7.20 | 18.40 | 46.40 | 52.70 | 55.40 |
| Run 2 GC Yield | 2.40 | 7.80 | 20.80 | 51.20 | 55.70 | 57.50 |
| Run 3 GC Yield | 2.30 | 7.80 | 19.40 | 43.20 | 54.60 | 57.80 |
| Average GC Yield | 2.47 | 7.60 | 19.53 | 46.93 | 54.33 | 56.90 |
| std dev | 0.21 | 0.35 | 1.21 | 4.03 | 1.52 | 1.31 |
### 100% PhI(OAc)$_2$

| Run 1 GC Yield | 3.30 | 7.50 | 22.90 | 52.70 | 56.90 | 60.20 |
| Run 2 GC Yield | 3.00 | 7.20 | 22.30 | 49.10 | 56.30 | 57.20 |
| Run 3 GC Yield | 2.70 | 6.90 | 23.30 | 47.40 | 55.40 | 59.00 |
| Average GC Yield | 3.00 | 7.20 | 22.83 | 49.73 | 56.20 | 58.80 |
| std dev | 0.30 | 0.30 | 0.50 | 2.71 | 0.75 | 1.51 |

**Kinetic Profile w/ 0%, 25%, or 100% PhI(OAc)$_2$**

4.5 References

67. A portion of this work was summarized in a manuscript submitted for publication: Bigi, M. A.; White, M. C. Submitted 2013.


