LINEAR ALLYLIC C-H OXIDATION: METHODS AND UTILITY

BY

NICOLAAS VERMEULEN

DISSERTATION

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Doctoral Committee:

Professor M. Christina White
Professor Paul J. Hergenrother
Professor Jeffery S. Moore
Professor Ralph G. Nuzzo
ABSTRACT

The installation of complex functional groups through the use of C-H oxidation methodologies has the potential to dramatically increase the efficiency of synthetic sequences with respect to resources, time and overall steps to key intermediates. This work describes methods that target complex intermediates to show the scope, wide functional group tolerance, and streamlining utility of our allylic C-H oxidation chemistry. In general, functional groups are installed in complex molecules through the advent of sequential C-C bond forming reactions. This chemistry is not only well known, but has been employed for decades, resulting in the wide array of reaction conditions and electrophile/nucleophile pairs seen in the literature today. In contrast, the deliberate installation of functional groups through unactivated C-H bonds represents a new strategy for the construction of complex intermediates.

Previously, we have reported that the use α-olefins, as an inert and readily available functional group handle, allows for the direct installation of allylic acetates via a Pd(II) catalysis. A clever implementation of this strategy shows its utility and ability to streamline the synthesis of known molecules (e.g. L-galatose). Further exploration of this reaction manifold gives rise to a linear allylic oxidation method requiring only coupling levels of almost any carboxylic acid to render linear (E)-allylic esters.

A significant problem with the Pd(II) allylic C-H oxidation reaction is the need for super-stoichiometric amounts of the oxidant benzoquinone. By employing a Co(II)Salophen catalyst, hydroquinone (the byproduct of benzoquinone oxidation) can be converted to benzoquinone using only molecular oxygen as terminal oxidant. This second catalytic system
was found to be compatible with our allylic C-H oxidation reaction conditions and allows for the use of only catalytic amounts of the palladium-specific oxidant, thereby greatly reducing reaction waste. This process appears to be a general solution and can also be employed with the intera- and inter-molecular allylic C-H amination reactions developed in our lab.
TABLE OF CONTENTS

CHAPTER 1: POLYOL SYNTHESIS THROUGH HYDROCARBON OXIDATION DE NOVO SYNTHESIS OF L-GALACTOSE ................................................................. 1

1.1 INTRODUCTION ................................................................................................. 1
1.2 RESULTS AND DISCUSSION ............................................................................. 3
1.3 CONCLUSION ..................................................................................................... 8
1.4 EXPERIMENTAL SECTION .............................................................................. 9
1.5 REFERENCES .................................................................................................... 29

CHAPTER 2: SYNTHESIS OF COMPLEX ALLYLIC ESTERS VIA C-H OXIDATION VS C-C BOND STRATEGIES ........................................................................ 34

2.1 INTRODUCTION ................................................................................................. 34
2.2 RESULTS AND DISCUSSION ............................................................................. 37
2.3 CONCLUSION ..................................................................................................... 46
2.4 EXPERIMENTAL SECTION .............................................................................. 47
2.5 REFERENCES .................................................................................................... 76

CHAPTER 3: USING OXYGEN AS THE TERMINAL OXIDANT FOR THE LINEAR ALLYLIC C-H OXIDATION AND AMINATION REACTIONS ......................... 81

3.1 INTRODUCTION ................................................................................................. 81
3.2 RESULTS AND DISCUSSION ............................................................................. 82
3.3 CONCLUSION ..................................................................................................... 87
3.4 EXPERIMENTAL SECTION .............................................................................. 88
3.5 REFERENCES .................................................................................................... 101
CHAPTER 4: THE FE(PDP)-CATALYZED ALIPHATIC C—H OXIDATION: A SLOW ADDITION PROTOCOL ........................................................................................................ 105

4.1 INTRODUCTION ........................................................................................................... 105
4.2 RESULTS AND DISCUSSION ...................................................................................... 106
4.3 CONCLUSION ............................................................................................................. 113
4.4 EXPERIMENTAL SECTION ....................................................................................... 114
4.5 REFERENCES ............................................................................................................. 128
CHAPTER 1: POLYOL SYNTHESIS THROUGH HYDROCARBON OXIDATION
DE NOVO SYNTHESIS OF L-GALACTOSE

1.1 INTRODUCTION

Direct oxidation of C-H bonds has the potential to emerge as a powerful approach for introducing oxygen and nitrogen functionality in complex molecule synthesis.\(^1\) Synthetic routes often require subverting the standard reaction pathway of oxygenated functionalities through the use of functional group manipulations (FMGs). These operations are step consuming and can lead to material loss. Our hypothesis is that these steps may be avoided by installing them directly into the hydrocarbon framework.\(^2\) In order for this hydrocarbon oxidation strategy to be competitive with current methods and reach its full potential, C-H oxidation reactions with high levels of chemo-, regio- and stereoselectivity must be developed. We recently described a DMSO-promoted, Pd(OAc)\(_2\)-catalyzed allylic oxidation reaction that furnishes (\(E\))-allylic acetates from \(\alpha\)-olefins with high regio- and stereoselectivities and outstanding functional group tolerance.\(^3\) In this section, we describe methodological C-H oxidation advances that can be applied to a new hydrocarbon oxidation strategy for the rapid assembly of polyol frameworks. We present this strategy in the context of the enantioselective, \textit{de novo} synthesis of differentially protected L-galactose from a commercial, achiral starting material in which all new oxygen functionality has been installed through C-H and C=C bond oxidation reactions.

A short hydrocarbon oxidation strategy for synthesis of chiral polyols is presented in Scheme 1. The key step in this streamlined polyol synthesis is the rapid construction of chiral (\(E\))-2-butene-1,4-diols such as 1. This motif can be rapidly elaborated to polyol structures via asymmetric dihydroxylation (AD). Their dense functionalization, dissonant oxygen
relationship, and the ease with which they can be further elaborated through established olefin oxidation chemistry makes these structures particularly attractive building blocks. Compounds similar to 1 have been routinely employed as intermediates in natural product syntheses to install a diverse range of structures: e.g. 5- and 6-membered mono- and polycyclic ethers, epoxyalcohols, and polyol structures. Notably, compounds analogous to 1 have been used as intermediates in several stereo divergent syntheses of the hexoses. C-C bond forming strategies employed in the syntheses of 1, usually based on Wittig-type olefinations or cross-metathesis reactions, suffer from lengthy sequences due to the difficulty in accessing chiral non-racemic β-hydroxy- aldehyde and -olefin starting materials. Alternatively, using the strategy presented in Scheme 1, may be synthesized directly from protected chiral homoallylic alcohols like 2 via the DMSO/Pd(II)-promoted allylic oxidation. The latter are readily accessible via asymmetric allylation of aldehydes or regioselective vinylation of chiral epoxides (Scheme 1). Nathan L. Labenz showed the initial reactivity of solid carboxylic acid at extreme loadings in the linear allylic oxidation reaction and pioneered the idea of base activation of the acid nuleophile. Dustin J. Covell repeated critical results and contributed the “painful” Payne-rearrangement. In addition he developed the reaction conditions that would lead from intermediate 5 to the final product. Kenneth F. Fraunhoffer should be credited with proposing a hexose synthesis using our linear allylic oxidation reaction as the key intermediate. Portions of this chapter were taken with permission from Covell, D. J.; Vermeulen, N. A.; Labenz, N. A.; and White, M.C. Angew. Chem. Int. Ed. 2006, 45, 8217-8220.
1.2 RESULTS AND DISCUSSION

1.2.1 REACTION OPTIMIZATION

Following literature precedent, the electron donating nature of 4-methoxybenzoate derivatives of chiral \((E)-2\)-butene-1,4-diols 1 make them particularly attractive for their ability to direct asymmetric dihydroxylation (AD) with excellent reagent-controlled diastereoselectivity and minimal acyl transfer.\(^8\) In a previous communications we demonstrated that the DMSO/Pd(II) catalyzed linear allylic oxidation on protected chiral homoallylic alcohols with acetic acid furnishes acetate derivatives of chiral \((E)-2\)-butene-1,4-diols in excellent regio- and stereoselectivities and no erosion in optical purity.\(^2\) Our goal was to develop linear allylic oxidation conditions that would allow \(\alpha\)-olefins to be functionalized using \(p\)-anisic acid 4 and in one step generate a 4-methoxybenzoate derivative of 1 (Scheme 1). Table 1 shows preliminary studies with \(\alpha\)-olefin 3. The aryl acid seemed to be a competent nucleophile in the DMSO/Pd(II) linear allylic oxidation reaction to form hexose precursor 5; however, a number of critical challenges remained. More specifically, extremely high acid loadings were required for product formation and only low yields (15 equiv. 5, 23%, Table 1, entry 1) of product could be obtained. We were encouraged by the observation that significant amounts of \(\alpha\)-olefin starting material remained at the end of the reaction, suggesting that the acid labile acetonide protecting group was stable under these reaction conditions.
conditions. The addition of \(N,N\)-diisopropylethylamine (DIPEA), a non-coordinating base additive, effected a significant increase in yield (45%, Table 1, entry 2). Although the exact role of the base is currently unclear, it is reasonable to hypothesize that it results in increased concentrations of the benzoate anion which consequently allows for faster functionalization of the presumed Pd-\(\pi\)-allyl intermediate. A second yield increase resulted from changing the terminal oxidant from benzoquinone (BQ) to phenyl-benzoquinone (PhBQ, 55%, Table 1, entry 3). Finally, we observed that by increasing the reaction molarity to 2.0 M, fewer equivalents of carboxylic acid were required and higher yields could be obtained (i.e. 2.0 M, 3 equiv. 5, 75% yield, Table 1, entry 6).

Table 1: Reaction Optimization

<table>
<thead>
<tr>
<th>entry</th>
<th>DMSO:CH(_2)Cl(_2) Molarity (M)</th>
<th>Quinone (Q)</th>
<th>Acid (equiv.)</th>
<th>isolated yield(%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.33 M</td>
<td>BQ</td>
<td>15</td>
<td>23%[d]</td>
</tr>
<tr>
<td>2</td>
<td>0.33 M</td>
<td>BQ</td>
<td>15</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>0.33 M</td>
<td>PhBQ</td>
<td>15</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>0.6 M</td>
<td>PhBQ</td>
<td>10</td>
<td>66%</td>
</tr>
<tr>
<td>5</td>
<td>1.0 M</td>
<td>PhBQ</td>
<td>5</td>
<td>67%</td>
</tr>
<tr>
<td>6[e]</td>
<td>2.0 M</td>
<td>PhBQ</td>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td>7[e]</td>
<td>2.0 M</td>
<td>PhBQ</td>
<td>3</td>
<td>71%[e]</td>
</tr>
<tr>
<td>8</td>
<td>2.0 M</td>
<td>PhBQ</td>
<td>3</td>
<td>63%[f]</td>
</tr>
<tr>
<td>9</td>
<td>3.0 M</td>
<td>PhBQ</td>
<td>1.5</td>
<td>50%</td>
</tr>
</tbody>
</table>

[a] DMSO:CH\(_2\)Cl\(_2\) (3:2:1); [b] Linear to branched allylic ester [L:B] and [E:Z] ratios determined by HPLC for material obtained from entries 6 and 7 using authentic branched allylic ester and acetate-deprotected E and Z allylic ester standards: L:B = >300:1; E:Z = 30:1, 36:1 (entries 6 and 7, respectively). [c] Reactions done on a 1mmol scale (3, 262 mg). Yields and selectivities represent an average of at least 2 runs. [d] No DIPEA (\(N,N\)-diisopropylethylamine) was added. [e] Ph[\(\text{Pd}(\text{OAc})_2\)](BF\(_4\)) (10 mol%), 13% of 3 was recovered. [f] Ph[\(\text{Pd}(\text{OAc})_2\)] (6 mol%).

This linear allylic oxidation reaction is exceptionally stereo- and regioselective with selective formation of the linear $E$-isomer (Table 1, entries 6 and 7, L:B = >300:1; $E:Z = 30:1$ to 36:1), and could be run under an air atmosphere with no precautions taken to exclude moisture or O$_2$. Significantly, with these newly developed conditions the catalyst loading may be decreased to 5 mol% with only a minor decrease in yield (Table 1, entry 8, 63%). Preliminary studies also showed that a fragment coupling amount (1.5 equiv.) of carboxylic acid can be employed to obtain useful yields at 3.0 M concentrations of $\alpha$-olefin (Table 1, entry 9, 50%). An additional problem arose as a direct result of the decrease in the functionalization nucleophile: using Pd(OAc)$_2$ as the Pd(II) source added an additional 20% AcOH to the reaction; consequently, the only byproduct observed in the reaction is the allylic acetate. We found this problem can easily be eliminated by using [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ as the Pd(II) source (Table 1, entry 7). These results not only allowed for the rapid synthesis of the desired ($E$)-2-butene-1,4-diols 5, but also provided the initial results for a general linear allylic oxidation reaction that could couple any carboxylic acid to any $\alpha$-olefin with high regio- and stereoselectivity in a single step.

1.2.2 ENANTIOSELECTIVE TOTAL SYNTHESIS OF L-GALACTOSE

To showcase the efficiency of this strategy (installing oxidation through C-H bond oxidation and not C-C forming reaction) in the context of polyol construction, we envisioned the de novo synthesis of differentially protected L-galactose (+)-10 easily obtained, and inexpensive starting materials (Scheme 2).
Scheme 2: Total synthesis of differentially protected L-galactose (−)-10

(Z)-2-Butene-1,4-diol 6 was easily epoxidized with m-chloroperbenzoic acid to give meso-epoxide 8 in 74% yield. This material (7) was then desymmetrized using a known enantioselective Payne rearrangement with oligomeric (R,R)-(salen)Co(III)OTf catalyst. After ketalization, the chiral non-racemic epoxyketal (S,S)-8 could be isolated via distillation.\(^{15,16}\) Selective opening at the terminal position of the epoxide using a vinlylcuprate and subsequent benzyl protection of the alcohol gave the desired protected homoallylic alcohol (−)-3 in 54% overall yield (3-steps, 99% ee).\(^{14,15}\) Linear allylic C-H oxidation of (−)-3 using 10 mol% [Pd(CH\(_3\)CN)\(_4\)](BF\(_4\))\(_2\) in DMSO under the optimized conditions (2 M, PhBQ, 50 mol% DIPEA) with 3 equiv. of p-anisic acid 4 furnished 4-methoxybenzoate derived (E)-2-butene-1,4-diol (+)-5 in 71% yield (w/ 13% recovered (−)-3) as a single isomer (L:B = >300:1; E:Z = 36:1) with no erosion of enantiopurity.\(^{17}\) Alternatively, using 10 mol% Pd(OAc)\(_2\) in DMSO under the same conditions, (+)-5 was obtained in 75% yield with 10% of the allylic acetate product that was difficult to separate via silica gel chromatography. Asymmetric dihydroxylation of (+)-5 proceeded with high selectivity to give the polyol (−)-9 in 96% yield with >20:1 d.r.\(^{18}\) Bis-silyl protection of diol (−)-9 followed by DIBAL cleavage
of the p-methoxybenzoate, Swern oxidation of the resulting primary alcohol, and isopropylidene ketal removal with Zn(NO₃)₆H₂O¹⁹ gave differentially protected L-galactose (-)-10 in 74% yield (4-steps).²⁰ The enantioselective, de novo synthesis of (-)-10 proceeds in a total of 10 linear steps and 20% overall yield from commercial starting material 6.

Several stereodivergent, de novo syntheses of the hexoses from 6 have employed chiral (E)-2-butene-1,4-diois analogous to 5 as intermediates. The C-H oxidation route to 6 (5 steps, 28% overall yield) compares favorably with the Wittig-olefination routes of the previously reported syntheses with respect to number of steps and overall yield (11 steps, 18% overall yield;⁹ 9 steps, 16% overall yield).⁸ Analogous to these previous syntheses, the strategy developed herein provides access to hexose stereoisomers that are complementary to those obtained through aldol-based approaches.²¹

1.2.3 TOWARD THE ENANTIONSELECTIVE TOTAL SYNTHESIS OF D-GLUCOSE

An additional proposed demonstration of the power of our linear allylic oxidation is the synthesis of D-glucose from D-mannitol. This route involves an oxidative cleavage of acetonide protected D-mannitol to yield the acetonide protected aldehyde (Scheme 4). This material can be functionalized through an asymmetric Brown allylation²² followed by protection to yield the desired homo-allylic α-olefin intermediate 11 in 55% overall yield. Early iterations of the linear allylic oxidation reaction provided satisfactory results and furnished the desired chiral (E)-2-butene-1,4-diol product 12 in 71% yield with good selectivities as determined by ¹H NMR (Scheme 3). Unfortunately Sharpless asymmetric dihydroxylation of intermediate 12 was not very successful and afforded only low yields and subpar diastereoselectivity for the desired polyol 13. This can be explained by an unfortunate
miss-matched reagent-reactant interaction and would require extensive optimization. This route was retired due to low yields and selectivities of the necessary intermediates, in addition to the inelegant nature of synthesizing a sugar through degradation of a different sugar.

Scheme 3: Synthesis toward differentially protected D-glucose

\[
\text{Scheme 3: Synthesis toward differentially protected D-glucose}
\]

1.3 CONCLUSION

In conclusion, a mild and efficient hydrocarbon oxidation strategy to intermediate 1 that can be used in the preparation of chiral polyols has been presented. Using this strategy an enantioselective synthesis of differentially protected L-galactose (−)-10 was performed and shown to be competitive with other routes that do not utilize C-H oxidation. Additionally it should be added that the same strategy could be employed to generate other isomers of the hexose family, provided reactivity-related problems during functionalization of the intermediate following the C-H oxidation step can be overcome. This synthesis is enabled by
the development of a highly regio- and stereoselective linear allylic C-H oxidation reaction that generates 4-methoxybenzoate derivatives of chiral \((E)\)-2-butene-1,4-diols directly from readily available protected chiral homoallylic alcohols and carboxylic acids. We anticipate that the structurally simplifying and mild nature of this transformation (i.e. \(2 \Rightarrow 3\), Scheme 1) will render it generally useful in the synthesis of polyoxygenated motifs and in the context of other complex molecules.

1.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents were used as received: 2-phenyl-1,4-benzoquinone (ACROS); \(\text{Pd(OAc)}_2\), \(\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}\), \((1R,2R)-(\cdot)[-1,2\)-Cyclohexanediamino-N,N’-bis(3,5-di-t-butyrsalicylidene)]Cobalt(II) (Strem Chemicals). \(\text{Pd(OAc)}_2\) was stored in a glove box under a nitrogen atmosphere and weighed out in the air prior to use. Solvents tetrahydrofuran (THF), diethyl ether (Et\(_2\)O), and methylene chloride (CH\(_2\)Cl\(_2\)) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N, N-dimethylformamide (DMF) (Sure/Seal) was obtained from Sigma-Aldrich and used as received. \((Z)\)-2-butene-1,4-diol (Fluka) was used as received. All allylic oxidation reactions were run under air with no precautions taken to exclude moisture. All other reactions were run under a balloon of argon gas unless otherwise stated. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25µm). HPLC analysis was performed on an Agilent Technologies 1100 HPLC system with a model 1100 Quaternary Pump, Diode Array Detector, Thermostat, and Autosampler. Thin-layer chromatography
(TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.\textsuperscript{23} using EM reagent silica gel 60 (230-400 mesh). \textsuperscript{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz) or a Varian Unity 500 (500 MHz), or a Varian Unity Inova 500NB spectrometer and are reported in ppm using solvent as an internal standard (CDCl\textsubscript{3} at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration, corresponding carbon atom. Proton-decoupled \textsuperscript{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\textsubscript{3} at 77.0 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\textsuperscript{-1}). All optical rotations were determined on a Perkin Elmer 341 Polarimeter using the sodium D line (589 nm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

Representative Procedure for the Pd(OAc)$_2$ catalyzed Linear Allylic C-H Oxidation of (-)-3 to (+)-5. To a 40 mL borosilicate vial was added sequentially the following: Pd(OAc)$_2$ (22.4 mg, 0.1 mmol, 10 mol%), phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), p-anisic acid (456 mg, 3.0 mmol, 3 equiv.), 4Å molecular sieves (200 mg), (-)-3 (262 mg, 1 mmol, 1 equiv.), DMSO (0.380 mL), CH$_2$Cl$_2$ (0.120 mL), DIPEA (0.087 mL, 0.5 mmol, 0.5 equiv.) and a Teflon\textsuperscript{®} stir bar. The vial was then capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial and in maintaining the temperature centered at 41°C (i.e. 40°C-43°C). Upon completion, the reaction was quenched with sat. aq. NH$_4$Cl solution (1
mL), stirred for 30 minutes, and then transferred to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 mL) was added and the organics were washed with H₂O (50 mL) and 5% aq. Na₂CO₃ solution (2 x 50 mL). (Note: Upon addition of hexanes a significant amount of phenyldihydroquinone will crash out of solution as a black solid. This solid is readily removed in the next step during filtration.) The organic layer was dried (MgSO₄), filtered, and reduced in vacuo. Subsequent transfers were all performed using ether to minimize transfer of phenyldihydroquinone. Purification via flash silica gel chromatography (30% Et₂O/hexanes) gave 309 mg of (+)-(5) as an amber oil. (Run 1 = 74% yield; run 2 = 76% yield) Average = 75% yield. Linear to branched ratios (>300:1) were determined by HPLC using authentic branched allylic product24 [Agilent Zobrax Eclipse XDB-C8, 35% i-PrOH/H₂O, 1 mL/min., tR (linear) = 15.7 min., tR (branched) = 18, 19 min. (mixture of two diastereomers)]. E:Z ratios (30:1) were determined by HPLC using acetonide deprotected E and Z isomers (Symmetry C-18, 40%CH₃CN/H₂O, 1.0 mL/min., tR (E) = 10.1 min., tR (Z) = 11.3 min.) Using this procedure, 32 mg (10%) of the linear acetate product was also formed and was difficult to separate from (+)-(6).

Representative Procedure for the Pd(CH₃CN)₄(BF₄)₂ catalyzed Linear Allylic C-H Oxidation of (-)-3 to (+)-5. To a 40 mL borosilicate vial was added sequentially the following: Pd(CH₃CN)₄(BF₄)₂ (44.4 mg, 0.1 mmol, 10 mol%), phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), p-anisic acid (456 mg, 3.0 mmol, 3 equiv.), 4Å molecular sieves (200 mg), DMSO (0.380 mL), CH₂Cl₂ (0.120 mL), DIPEA (0.122 mL, 0.7 mmol, 0.7 equiv.), and a Teflon® stir bar. The vial was then capped and stirred at 41°C for 1 hour. The vial was cooled to room temperature and (-)-(3) (262 mg, 1 mmol, 1 equiv.) was added. The vial was capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to
keep all reagents off of the walls and contained at the bottom of the vial and in maintaining
the temperature centered at 41°C (i.e. 40°C-43°C). The workup and isolation is identical to
that described for Pd(OAc)$_2$: (Run 1 = 71% yield; run 2 = 69% yield; run 3 = 74% yield)
Average = 71% yield. Approximately 13% of (-)-3 was also recovered. Linear to branched
and E:Z ratios were determined as described above and found to be similar to those
determined for Pd(OAc)$_2$ (L:B = >300:1; E:Z = 36:1).

(3-Hydroxymethyl-oxiranyl)-methanol (7)

To 35 g of ≤77% pure m-chloroperbenzoic acid (Aldrich) in a 1 L separatory
funnel was added dry CH$_2$Cl$_2$ (250 mL). The solution was washed with 1:1 sat. aq.
NaHCO$_3$:H$_2$O solution (2 x 100 mL) and then dried over Na$_2$SO$_4$ until the liquid became
translucent (~ 1 hr). The solution was then filtered into a clean, dry 1 L round bottom flask
pre-marked at approximately 380 mL volume. Dry CH$_2$Cl$_2$ was added to bring the total
volume up to this mark and a 0.65 ml aliquot was removed and titrated using No-D NMR
with a known amount of CHCl$_3$ (~50 µL) as the internal standard.$^{25}$ By this analysis, the
solution was determined to contain 15 g (87.2 mmol, 1.1 equiv.) of mCPBA. A Teflon© stir
bar was added and the atmosphere exchanged for nitrogen. The solution was cooled to 0°C
and (Z)-2-butene-1,4-diol (7) (6.85 mL, 79.3 mmol, 1 equiv.) was added via syringe. The
reaction was allowed to warm to room temperature and became a milky color within one
hour. After 16 hours of stirring, the CH$_2$Cl$_2$ was removed via rotary evaporation, dry ether
(300 mL) was added, and the material was stirred 3 hours at room temperature, after which
the reaction flask was placed in a -20°C freezer for 1 hour. The resulting solids were filtered
off and rinsed with cold, dry ether (5 x 50 mL). The filtrate was left in the freezer overnight
to give a second harvest of crystals which were also filtered and washed with dry, cold ether
to give a total of 6.16 g of a fine white powder (7) (74%).

\[ ^1H \text{NMR (500 MHz, CD}_3\text{OD) } \delta \text{ 3.73 (dd, J = 3.5, 12.3 Hz, 2H), 3.59 (dd, J = 7.0, 12.3 Hz, 2H), 3.14 - 3.11 (m, 2H); } ^{13}\text{C NMR (125 MHz, CD}_3\text{OD) } \delta \text{ 61.2, 57.8).} \]

(2S,3S)-3,4-epoxy-1,2-di-O-isopropylidenebutane-1,2-diol (8)

**Method A: [oligomeric (R,R)-(Salen)-Co(III)OTf]**

To a clean, dry 100 mL round bottom flask with a Teflon® stir bar was added (7) (5.0 g, 48.0 mmol, 1 equiv.), oligomeric (R,R)-(Salen)Co(III)OTf (0.019 g, 0.05 mol%), and CH\(_3\)CN (24 mL). The reaction was vigorously stirred under air until ~70% conversion of starting material was observed (\(^1H\) NMR of an aliquot from the reaction mixture in CD\(_3\)OD; ratio of m @ 3.12 ppm vs. dd @ 2.69 ppm + dd @ 2.76 ppm) (~12 hrs). The reaction mixture was then cooled to 0°C and 2-methoxypropene (5.53 mL, 5.77 mmol, 1.2 equiv.) was added followed by p-TsOH · H\(_2\)O (0.091 g, 0.480 mmol, 0.01 equiv.). The reaction was stirred at 0°C for 1 hour and then the solvents removed slowly (~45 min.) via rotary evaporation at 0°C. The reaction mixture was loaded neat onto a silica column and purified via flash silica gel chromatography (10%-20%-30%-40% Et\(_2\)O/pentane). Removal of the column solvent via distillation at 55°C gave a crude mixture of (8) (~4.67 g, 68% yield by \(^1H\) NMR) and the seven-membered ketal product that was taken forward without further purification.\(^{27}\) (Note: The purity of the starting material for this reaction has a large effect on catalyst loading and overall yield. Inferior batches of (7) should be purified via flash silica gel chromatography in 10%-15% MeOH/CH\(_2\)Cl\(_2\) prior to use.)

**Method B: [commercial (R,R)-(Salen)-Co(III)OAc]^{28}**
To a clean, dry 250 mL round-bottom flask with a Teflon© stir bar was added (7) (2.0 g, 19.2 mmol, 1 equiv.) and (R,R)-(Salen)Co(III)OAc (0.255 g, 2 mol%). THF (9.6 mL) was added and the reaction was vigorously stirred under air until ~70% conversion of starting material was observed (1H NMR of an aliquot from the reaction mixture in CD3OD; ratio of m @ 3.12 ppm vs. dd @ 2.69 ppm + dd @ 2.76 ppm (~12 hrs). The solvent was then removed via rotary evaporation, and dry acetone (9.6 mL) was added. The reaction flask was cooled to 0°C and 2,2-dimethoxypropane (5.7 mL, 48.0 mmol, 2.5 equiv.) was added followed by slow addition of pyridinium p-toluenesulfonic acid (1.21 g, 4.80 mmol, 25 mol%). The reaction was allowed to warm to room temperature and then taken to 50°C for 24 hours. After stirring 24 hours, the reaction mixture was cooled to room temperature, transferred to a 1L separatory funnel, and Et2O (200 mL) and sat. aq. NaHCO3 (25 mL) were added. The aqueous layer was then back extracted [5 x (100 mL Et2O + 4 mL THF)] and the combined organics distilled slowly away at 55°C. Flash silica gel chromatography (10%-20%-30% Et2O/pentane) followed by distillation of the column solvent at 55°C afforded a crude mix of (8) (~1.35 g, 49% yield by 1H NMR) and the seven-membered ketal product that was taken on without further purification.[5] Rf = 0.206 (20% Et2O/Pentane); 1H NMR (500 MHz, CDCl3) δ 4.10 (dd, J = 6.5, 8.5 Hz, 1H), 3.97 (app. q, J= 6.5, 1H), 3.85 (dd, J = 6.5, 8.5 Hz, 1H), 3.03 (dd, J = 2.5, 4.3, 5.6 Hz, 1H), 2.80 (dd, J = 4.0, 5.0 Hz, 1H), 2.67 (dd, J = 2.5, 5.3 Hz, 1H, C4), 1.44 (s, 3H, acetonide CH3), 1.36 (s, 3H, acetonide CH3); 13C NMR (125 MHz, CDCl3) δ 110.0, 76.2, 65.9, 52.0, 43.8, 26.4, 25.5; LRMS (CI) m/z calculated for C7H13O3 [M + H]+: 145.1; found 145.1.[29]

(2S,3S)-3-O-benzyl-1,2-di-O-isopropylidene-5-hexen-1,2,3-triol (-)-(3)
To a clean, dry 100 mL flask with a Teflon® stir bar and under an argon atmosphere was added copper (I) bromide (0.228 g, 1.59 mmol, 0.1 equiv.) and 12 mL dry THF. The reaction flask was covered with aluminum foil to prevent exposure to light and cooled to -40°C. Freshly prepared vinylmagnesium bromide was then added (28.3 mL of a 0.618 M solution in THF, 1.1 equiv.) and the reaction mixture stirred for 10 minutes. A solution of the crude mix of (8) (~2.29 g, 15.9 mmol, 1 equiv.) and the corresponding seven-membered ketal in dry THF (3.75 mL initial volume, 2 x 2.1 mL rinses) at -40°C was then added via cannula, and the reaction stirred at -40°C in the dark for 1 hour. A quench of sat. aq. NH₄Cl solution (15 mL) was added and stirred vigorously as the reaction was allowed to warm to room temperature. Et₂O (100 mL) was added, and the aqueous layer extracted [5 x (50 mL Et₂O + 4 mL THF)]. The combined organics were washed with H₂O (50 mL) and the aqueous layer again back extracted [3 x (50 mL Et₂O + 4 mL THF)]. After drying (Na₂SO₄) and filtering, the solvent was distilled away at 65°C.

To a clean, dry 250 mL round bottom flask was added sodium hydride (0.762 g, 31.8 mmol, 2 equiv.), TBAI (0.507 g, 1.6 mmol, 0.1 equiv.), and anhydrous DMF (50 mL). This flask was cooled to 0°C, and then the reaction mixture containing the crude alcohol from above in DMF (10 mL initial volume, 2 x 5 mL rinses) at 0°C was added dropwise via cannula. The reaction was stirred 1 hour at 0°C and then benzyl bromide (2.02 mL, 16.7 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred until TLC revealed complete conversion of starting material (~1 hr). Upon completion, the reaction flask was cooled to 0°C and H₂O (50 mL) was added. The flask was stirred an additional 5 minutes, and then Et₂O (200 mL) was added. The aqueous layer was extracted with Et₂O (3 x 50 mL), the combined organic layers were dried (MgSO₄),
filtered, and reduced in vacuo. Flash silica gel chromatography (1%-2%-3%-5% EtOAc/hexanes) afforded 3.32 g of (−)-(3) (80% 2 steps) as a clear liquid in 99% ee (HPLC, Chiralcel AD-RH, 50% CH₃CN/H₂O, 0.5 mL/min., tᵣ(minor) = 14.2 min., tᵣ(major) = 15.5 min.). Rᵣ = 0.392 (10% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.31 (m, 4H), 7.30–7.26 (m, 1H), 5.88 (ddt, J = 7.5, 10.0, 17.0 Hz, 1H), 5.11 (dm, J = 17 Hz, 1H), 5.07 (dm, J = 17 Hz, 1H), 4.72 (d, J = 12.0 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.21 (app. q, J = 7.0, 1H), 3.99 (dd, J = 6.5, 8.0 Hz, 1H), 3.71 (app. t, J = 7.8 Hz, 1H), 3.51 (dt, J = 4.5, 6.8 Hz, 1H), 2.31 (m, 1H), 2.23 (m, 1H), 1.43 (s, 3H, acetonide CH₃), 1.37 (s, 3H, acetonide CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 134.5, 128.3, 127.8, 127.5, 117.2, 109.3, 79.2, 77.9, 72.5, 65.8, 35.3, 26.5, 25.4; IR (neat, cm⁻¹) 3066.5, 3023.3, 2986.1, 2935.0, 2878.6, 1641.7, 1455.0, 1071.6; HRMS (ESI) m/z calculated for C₁₆H₂₂O₃Na [M + Na]⁺: 285.1467; found: 285.1480. [α]²²D = -15.6° (c = 1.1, CHCl₃); lit. [α]²₀D = +13.9° (c = 1.1, CHCl₃) (enantiomer).³¹

(2S,3S)-(E)-3-O-benzyl-1,2-di-O-isopropylidene-4-hexen-6-(4-methoxyphenylbenzoate)-1,2,3-triol (+)-(5)

**Method A:** Pd(OAc)₂

To a 40 mL borosilicate vial was added sequentially the following: Pd(OAc)₂ (0.0224 g, 0.1 mmol, 10mol%), phenyl benzoquinone (0.368 g, 2.0 mmol, 2 equiv.), p-anisic acid (0.456 g, 3.0 mmol, 3 equiv.), 4Å molecular sieves (0.200 g), (−)-(3) (0.262 g, 1 mmol, 1 equiv.), DMSO (0.380 mL), CH₂Cl₂ (0.120 mL), diisopropylethylamine (0.087 mL, 0.5 mmol, 0.5 equiv.) and a Teflon© stir bar. The vial was then capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to keep all reagents off of the walls and
contained at the bottom of the vial and in maintaining the temperature centered at 41°C (i.e. 40°C-43°C). Upon completion, the reaction was quenched with sat. aq. NH₄Cl solution (1 mL), stirred for 30 minutes, and then transferred to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the organics were washed with H₂O (50 mL) and 5% aq. Na₂CO₃ solution (2 x 50 mL). (Note: Upon addition of hexanes a significant amount of phenyldihydroquinone will crash out of solution as a black solid. This solid is readily removed in the next step during filtration.) The organic layer was dried (MgSO₄), filtered, and reduced in vacuo. Subsequent transfers were all performed using ether to minimize transfer of phenyldihydroquinone. Purification via flash silica gel chromatography (30% Et₂O/hexanes) gave 0.309 g of (+)-(5) as an amber oil. (Run 1 = 74% yield; run 2 = 76% yield) Average = 75% yield. Linear to branched ratios (>300:1) were determined by HPLC using authentic branched allylic product (Agilent Zobrax Eclipse XDB-C8, 35% i-PrOH/H₂O, 1 mL/min., tᵣ (linear) = 15.7 min., tᵣ (branched) = 18, 19 min. (two diastereomers)). E:Z (30:1) ratios were determined by HPLC using acetonide deprotected E and authentic Z isomers (Symmetry C-18, 40%CH₃CN/H₂O, 1.0 mL/min., tᵣ (E) = 10.1 min., tᵣ (Z) = 11.3 min.) Using this procedure, 0.032 g (10%) of the linear acetate product was also formed and could not be readily separated from (+)-(5).

**Method B :** [Pd(CH₃CN)₄](BF₄)₂

To a 40 mL borosilicate vial was added sequentially the following: [Pd(CH₃CN)₄](BF₄)₂ (0.044 g, 0.1 mmol, 0.1 equiv.), phenyl benzoquinone (0.368 g, 2.0 mmol, 2 equiv.), p-anisic acid (0.456 g, 3.0 mmol, 3 equiv.), 4Å molecular sieves (0.200 g), DMSO (0.380 mL), CH₂Cl₂ (0.120 mL), diisopropylethylamine (0.122 mL, 0.7 mmol, 0.7 equiv.), and a Teflon© stir bar. The vial was then capped and stirred at 41°C for 1 hour. The
vial was cooled to room temperature and (-)-(4) (0.262 g, 1 mmol, 1 equiv.) was added. The vial was capped and stirred at 41°C for 72 hours. Care was taken in maintaining the temperature centered at 41°C (i.e. 40°C-43°C) and in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial. After 72 hours, the reaction was quenched with sat. aq. NH₄Cl solution (1 mL), stirred for 30 minutes, and then transferred via pipette to a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the organics were washed with H₂O (50 mL) and 5% aq. Na₂CO₃ solution (2 x 50 mL). The organic layer was dried (MgSO₄), filtered, and reduced in vacuo. Purification via flash silica gel chromatography (30% Et₂O/hexanes) gave 0.293 g of (+)-(6) as an amber oil with 13% recovered starting material. (Run 1 = 71% yield; run 2 = 69% yield; run 3 = 74% yield) Average = 71% yield. Linear to branched and E: Z ratios were determined as described above and found to be similar to those determined for Pd(OAc)₂ (L:B = >300:1, E:Z = 36:1). R_f = 0.17 (30% Et₂O/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 8.0 (app. dt, J = 2.5, 9.0 Hz, 2H), 7.36–7.25 (m, 5H), 6.93 (app. dt, J = 2.5, 9.0 Hz, 2H), 5.97 (ddt, J = 1.0, 5.5, 15.8 Hz, 1H), 5.74 (ddt, J = 1.5, 8.0, 15.8 Hz, 1H), 4.82 (app. d, J = 5.5 Hz, 2H), 4.68 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.22 (app. q, J = 6.5 Hz, 1H), 3.96 (dd, J = 6.5, 8.5 Hz, 1H), 3.91 (app. t, J = 7.0 Hz, 1H, C1), 3.87 (s, 3H), 3.77 (dd, J = 6.0, 8.8 Hz, 1H), 1.39 (s, 3H, acetonide CH₃), 1.35 (s, 3H, acetonide CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 165.9,163.4, 138.1, 131.7, 129.9, 129.8, 128.3, 127.8, 127.6, 122.4, 113.6, 109.7, 79.7, 77.3, 70.5, 65.7, 64.0, 55.4, 26.4, 25.3; IR (neat, cm⁻¹) 2985.3, 2934.8, 2873.4, 1713.2, 1606.5, 1511.5, 1256.9; HRMS (ESI) m/z calculated for: C₂₄H₂₉O₆ [M + H]⁺: 413.1964, observed: 413.1960; [α]²²_D = +72.5° (c = 1.0, CHCl₃).
To a clean, dry 50 mL recovery flask was added sequentially the following: K₂OsO₄ · 2H₂O (0.007 g, 0.019 mmol, 1 mol%), (DHQD)₂PHAL (0.076 g, 0.095 mmol, 5 mol%), K₃Fe(CN)₆ (1.89 g, 5.72 mmol, 3 equiv.), K₂CO₃ (0.792 g, 5.72 mmol, 3 equiv.), a Teflon© stir bar, deionized water (9.5 mL), and tert-butanol (5 mL). The reaction flask was stirred vigorously until both layers became translucent, at which time MeSO₂NH₂ (0.187 g, 1.91 mmol, 1 equiv.) was added and the reaction was cooled to 0°C. After the solution became opaque, olefin (+)-(5) (0.787 g, 1.91 mmol, 1 equiv.) was added dropwise via pipette in tert-butanol (1.5 mL initial volume, 2 x 1 mL rinses) and the reaction was stirred vigorously at 0°C until completion as indicated by TLC (~3.5 hr). Upon completion, sodium bisulfite (1.81 g) was added slowly and the reaction was allowed to warm to room temperature and stir for 1 hour. EtOAc (10 ml) was added and the aqueous layer extracted with additional EtOAc (3 x 15 mL). The combined organic layers were washed with 2N KOH (1x10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification via flash silica gel chromatography (40% EtOAc/hexanes) afforded 0.818 g (96%) of (-)-(9) as a clear, viscous oil. Rf = 0.190 (40% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.99 (app. dt, J = 2.5, 9.0 Hz, 2H), 7.37-7.28 (m, 5H), 6.92 (app. dt, J = 2.5, 9.0 Hz, 2H), 4.79 (d, J = 11.5 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.40 (dd, J = 5.0, 6.0 Hz, 1H), 4.44-4.35 (m, 2H), 4.19 (app. q, J = 6.5 Hz, 1H), 4.05 (dd, J = 6.5, 8.5 Hz, 1H), 3.86 (s, 3H), 3.85 (app. t, J = 8.0, 1H), 3.74-3.69 (m, 2H), 3.11 (d, J = 5.5 Hz, 1H, OH), 2.81 (d, J = 6.0 Hz, 1H, OH), 1.45 (s, 3H, acetonide CH₃), 1.37 (s, 3H, acetonide CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 166.6, 163.6, 137.8, 131.8, 128.5, 128.1, 128.0, 122.0, 113.7, 109.3, 78.9,
77.0, 74.4, 70.5, 68.7, 66.0, 65.9, 55.4, 26.3, 25.3; IR (neat, cm⁻¹) 3455.5, 2985.2, 2935.9, 1713.2, 1606.5, 1581.4, 1512.3, 1258.5; HRMS (ESI) m/z calculated for C_{24}H_{31}O_8 [M + H]^+: 447.2019; found 447.2012; [α]^{22}_{D} = -16.5° (c = 1.0, CHCl₃).

3-O-benzyl-4,5-di-O-(tert-butyldimethylsilylox)-1,2-di-O-isopropylidene-6-(4-methoxyphenylbenzoate)-l-galacitol

To (-)-(9) (0.818 g, 1.83 mmol, 1 equiv.), in a 50 mL recovery flask under nitrogen with a Teflon© stir bar, was added dry CH₂Cl₂ (12.2 mL). The flask was cooled to 0°C and 2,6-lutidine (1.28 mL, 11.00 mmol, 6 equiv.) was added. Tert-butyldimethylsilyl triflate (1.26 mL, 5.50 mmol, 3 equiv.) was then added dropwise over 15 minutes with vigorous stirring. The reaction was stirred at 0°C for 20 minutes, then allowed to warm to room temperature and monitored via TLC. Upon completion (~40 min.), the reaction was again cooled to 0°C, H₂O (5 mL) was added slowly, and the reaction stirred 15 minutes to quench. EtOAc (10 mL) was added and the aqueous layer was extracted with additional EtOAc (3 x 15 mL). The combined organic layers were washed with H₂O (1 x 5 mL), sat. aq. NaHCO₃ solution (1 x 5 mL), with H₂O (1 x 5 mL), then dried (Na₂SO₄), filtered, and reduced in vacuo. Purification via flash silica gel chromatography (2%-3%-5% EtOAc/hexanes) afforded 1.11 g (90%) of the title compound as a clear, viscous oil. R_f = 0.320 (10% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.99 (app. d, J = 8.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26-7.22 (m, 1H), 6.91 (app. d, J = 8.5 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.62 (dd, J = 3.5, 11.5 Hz, 1H), 4.52 (dd, J = 7.0, 9.0 Hz, 1H), 4.50 (dd, J = 7.5, 14.8 Hz, 1H), 4.09 (dt, J = 3.4, 7.0 Hz, 1H), 4.06 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 3.86 (s,
3H), 3.77 (app. t, J = 3.5 Hz, 1H), 3.69 (app. t, J = 7.0 Hz, 1H), 3.60 (dd, J = 3.5, 7.8 Hz, 1H), 1.43 (s, 3H, acetonide CH\textsubscript{3}), 1.35 (s, 3H, acetonide CH\textsubscript{3}), 0.93 (s, 9H, TBS CCH\textsubscript{3}), 0.87 (s, 9H, TBS CCH\textsubscript{3}), 0.13 (s, 3H, TBS CH\textsubscript{3}), 0.12 (s, 3H, TBS CH\textsubscript{3}), 0.06 (s, 3H, TBS CH\textsubscript{3}), 0.05 (s, 3H, TBS CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 166.1, 163.2, 138.9, 131.6, 128.2, 127.7, 127.3, 122.8, 113.5, 108.9, 83.7, 76.6, 74.9, 74.6, 73.8, 66.7, 66.7, 55.4, 26.8, 25.9, 25.7, 25.3, 18.2, 18.0, -4.0, -4.4, -4.7, -4.8; IR (neat, cm\textsuperscript{-1}) 2954.9, 2930.8, 2887.0, 2858.0, 1716.6, 1606.9, 1581.8, 1512.0; HRMS (ESI) m/z calculated for C\textsubscript{36}H\textsubscript{58}O\textsubscript{8}NaSi\textsubscript{2} [M + Na]\textsuperscript{+}: 697.3568; found 697.3573; \([\alpha]\)\textsubscript{D}\textsuperscript{22} = +31.2° (c =1.0, CHCl\textsubscript{3}).

3-O-benzyl-4,5-di-O-(\textit{tert}-butyldimethylsilanyloxy)-1,2-di-O-isopropylidene-L-galactitol

To the fully protected L-galactitol (1.05 g, 1.56 mmol, 1 equiv.) in a clean, dry 50 mL flask with a Teflon© stir bar under an argon atmosphere was added dry CH\textsubscript{2}Cl\textsubscript{2} (2.85 mL) and the flask was cooled to -78°C. Diisobutylaluminum hydride (1.0 M in CH\textsubscript{2}Cl\textsubscript{2}, 3.89 mL, 2.5 equiv.) was added dropwise and the reaction was stirred vigorously at -78°C. Upon completion (~ 1 hr), -78°C EtOAc (5 mL) was added followed by sat. aq. Rochelle’s salts (15 mL). The reaction was allowed to warm to room temperature and then stirred an additional thirty minutes. H\textsubscript{2}O (25mL) and CH\textsubscript{2}Cl\textsubscript{2} (20 mL) were added and the aqueous layer extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 15 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and reduced \textit{in vacuo}. The residue was purified via flash silica gel chromatography (7% EtOAc/hexanes) to give 0.823 g (98%) of the title compound as a clear oil. \(R_f = 0.267\) (10% EtOAc/hexanes); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.40 (app. d, J = 7.0 Hz, 2H), 7.32 (app. t, J = 7.0 Hz, 2H), 7.29-7.24 (m, 1H), 4.90 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 11.0 Hz),
4.60 (dt, J = 7.0, 8.5 Hz, 1H), 4.08 (dd, J = 7.0, 8.3 Hz, 1H), 3.80 (ddd, J = 3.0, 5.5, 11.6 Hz, 1H), 3.73 (app. q, J = 4.0 Hz, 1H, OH), 3.70 - 3.64 (m, 1H), 3.66, (dd, J = 3.0, 4.5 Hz, 1H), 3.61 (dd, J = 3.0, 9.0 Hz, 1H), 3.58 (app. t, J = 8.0 Hz, 1H), 3.26 (app. dd, J = 5.5, 7.8 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H, TBS CCH$_3$), 0.90 (s, 3H, TBS CCH$_3$), 0.10 (s, 3H, TBS CH$_3$), 0.10 (s, 6H, TBS CH$_3$), 0.08 (s, 3H, TBS CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.3, 128.3, 127.9, 127.6, 108.9, 85.5, 76.5, 75.9, 75.2, 74.8, 66.9, 62.0, 26.9, 25.9, 25.8, 25.4, 18.2, 18.0, -4.2, -4.7, -4.9, -4.9; IR (neat, cm$^{-1}$) 3474.6, 2954.3, 2930.5, 2886.5, 2858.1, 1472.0; HRMS (ESI) m/z calculated for C$_{28}$H$_{53}$O$_6$Si$_2$ [M + H]$^+$: 541.3381; found 541.3376; [$\alpha$]$^D_{22}$ = +7.2° (c =1.0, CHCl$_3$).

4-O-benzyl-2,3-di-O-(tert-butyldimethylsilyloxy)-L-galactopyranose

(10)

To a clean, dry 10 mL round bottom flask with a Teflon© stir bar and an argon atmosphere was added oxalyl chloride (0.161 mL, 1.9 mmol, 1.25 equiv.) and dry CH$_2$Cl$_2$ (4.9 mL). The reaction flask was cooled to -65°C (CHCl$_3$, dry ice) and 0.671 mL of a 5.1M DMSO solution ( 3.42 mmol, 2.25 equiv.) in dry CH$_2$Cl$_2$ was added and stirred for 10 minutes. The differentially protected galactitol (0.823 g, 1.52 mmol, 1 equiv.) in dry CH$_2$Cl$_2$ (1.6 mL initial volume, 2 x 0.33 mL rinse) was then added dropwise via cannula, and the reaction stirred at -65°C for 20 minutes. Triethylamine (0.90 mL, 6.47 mmol, 4.25 equiv.) was added dropwise, the reaction was stirred 15 minutes at -65°C, then allowed to warm to room temperature, and stirred an additional 10 minutes. Water (5 mL) was added and the reaction mixture transferred to a separatory funnel. The aqueous layer was extracted with CHCl$_3$ (3 x 15 mL), the combined organics were dried (Na$_2$SO$_4$), filtered, and reduced in
Conversion of the primary alcohol to the aldehyde was checked by $^1$H NMR in C$_6$D$_6$ and determined to be ~90%.

To the crude aldehyde was added CH$_3$CN (6.6 mL) and Zn(NO$_3$)$_2$ · 6H$_2$O (1.25 g, ~5 equiv.). The reaction was then taken to 50°C and monitored via TLC. Upon completion (~12hrs) the flask was cooled and the CH$_3$CN removed via rotary evaporation. Water (3 mL) and CH$_2$Cl$_2$ (10 mL) were added and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organics were then dried (MgSO$_4$), filtered, and reduced in vacuo. Purification by flash chromatography (1% MeOH/CH$_2$Cl$_2$) gave 0.637 g of a white crystalline solid (-)(10) (84% 2-steps). $R_f$ = 0.104 (1%CH$_2$Cl$_2$); (Note: The product exists as a mixture of anomers, $\alpha$: $\beta$ = 3:2, with the $\beta$ anomer as a mixture of two conformers$^{33}$) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.26 (m, 5H $\alpha$, 10H $\beta$), 5.21 (t, J = 3.5 Hz, 1H, $\alpha$), 4.98 (d, J = 11.0 Hz, 1H $\beta$), 4.93 (d, J = 11.5 Hz, 1H, $\alpha$), 4.75 (d, J = 11.5 Hz, 1H $\beta$), 4.69 (dd, J = 3.5, 9.8 Hz, 1H $\beta$), 4.60-4.56 (m, 2H $\beta$), 4.59 (d, J = 12.0 Hz, 1H, $\alpha$), 4.34 (d, J = 10.0 Hz, 1H $\beta$), 4.08 (ddd, J = 2.5, 8.0 Hz, 1H, $\alpha$), 3.96-3.91 (m, 2H $\beta$), 3.91-3.86 (m, 2H $\beta$), 3.88 (ddd, J = 4.0, 7.0, 11.4 Hz, 1H, $\alpha$), 3.84-3.82 (m, 2H $\beta$), 3.81-3.78 (m, 1H $\beta$), 3.80 (t, J = 2.5 Hz, 1H, $\alpha$), 3.75-3.65 (m, 3H $\beta$), 3.65 (ddd, J = 5.0, 8.5, 11.5 Hz, 1H, $\alpha$), 3.56-3.51 (m, 1H $\beta$), 3.23 (dd, J = 4.5, 9.0 Hz, 1H $\beta$), 2.99 (d, J = 4.0 Hz, OH $\alpha$), 2.62 (dd, J = 3.0, 10.0 Hz, 1H $\beta$), 1.92-1.90 (m, 1H $\beta$), 1.91 (dd, J = 3.5, 9.0 Hz, 1H, OH $\alpha$), 0.95-0.87 (m, 18H $\alpha$, 36H $\beta$), 0.16-0.08 (m, 12H $\alpha$, 24 H $\beta$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.3, 137.9, 137.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 92.4, 81.4, 77.4, 76.7, 75.9, 75.3, 74.5, 74.3, 74.2, 74.1, 73.3, 72.9, 72.2, 71.4, 70.7, 64.0, 62.6, 62.0, 60.8, 29.7, 26.1, 26.0, 25.9, 25.8, 25.7, 18.1, 18.1, 17.9, -4.0, -4.1, -4.3, -4.5, -4.7, -4.8, -4.9, -5.0; IR (neat, cm$^{-1}$) 3417.8, 2956.1, 2929.7, 2894.1, 2857.6, 1472;
HRMS (ESI) m/z calculated for C_{25}H_{46}O_{6}NaSi_{2} [M + Na]^+: 521.2731; found 521.2740; 
[α]^{22}_D = -28.1° (c =1.0, CHCl₃).

1,2,3,6-O-tetraacetyl-4-O-benzyl-L-galactopyranose

To a clean, dry 10 mL recovery flask under a nitrogen atmosphere with a Teflon© stir bar was added (-)-(10) (0.200 g, 0.401 mmol, 1 equiv.) and CH₂Cl₂ (2 mL). The reaction flask was cooled to 0°C and acetic anhydride (0.190 mL, 2.01 mmol, 5 equiv.), triethylamine (0.560 mL, 4.01 mmol, 10 equiv.) and 2,2-dimethylaminopyridine (0.005 g, 0.04 mmol, 0.1 equiv.) were added. The reaction was then stirred at 0°C for 30 minutes, room temperature for 1 hour, and then at reflux for 5 hours. The reaction mixture was then transferred to a separatory funnel and EtOAc (15 mL) was added. The organic layer was washed with 1 M HCl (1 x 15 mL), 10% aq. NaHCO₃ solution (15 mL), and brine (15 mL). The organic layer was then dried (Na₂SO₄), filtered, and reduced in vacuo. THF (0.5 mL) was added to this crude residue along with a Teflon© stir bar and the reaction flask was cooled to 0°C. Tetra-n-butylammonium fluoride (1.0 M in THF, 1.9 mL, 4.75 equiv.) was added slowly, and then the reaction was allowed to warm to room temperature and monitored via TLC. Upon completion, sat. aq. NH₄Cl solution (5 mL) was added and the aqueous layer extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried (Na₂SO₄), filtered, and reduced in vacuo to give a brown residue, which was subsequently dissolved in CH₂Cl₂ (2 mL) and cooled to 0°C. A Teflon© stir bar acetic anhydride (0.190 mL, 2.01 mmol, 5 equiv.), triethylamine (0.560 mL, 4.01 mmol, 10 equiv.) and 2,2-dimethylaminopyridine (0.005 g, 0.04 mmol, 0.1 equiv.) were added. The reaction mixture was again stirred at 0°C for 30 minutes, room temperature for 1 hour, and then at reflux for 5
hours. The reaction mixture was then cooled to room temperature and transferred to a separatory funnel with EtOAc (15 mL). The reaction mixture was then washed with 1 M HCl (1 x 15 mL), 10% aq. NaHCO₃ solution (15 mL), and brine (15 mL). The organic layer was then dried (Na₂SO₄), filtered, and reduced in vacuo to give a thick brown oil. Purification via flash silica gel chromatography (40%EtOAc/hexanes) afforded 0.173 g of a white, foamy oil (98%) as a mixture of anomers (α:β = 55:45). Rᵣ = 0.434 (40%EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.30 (m, 5H α and 5H β), 6.36 (d, J = 3.5 Hz, 1H α), 5.16 (d, J = 8.0 Hz, 1H β), 5.53 (dd, J = 3.5, 11.0 Hz, 1H α), 5.50 (dd, J = 8.0, 10.5 Hz, 1H β), 5.29 (dd, J = 3.0, 11.0 Hz, 1H α), 5.01 (dd, J = 3.0, 10.5 Hz, 1H β), 4.75 (d, J = 11.5 Hz, 1H β), 4.73 (d, J = 11.0 Hz, 1H β), 4.55 (d, J = 11.5 Hz, 1H α), 4.54 (d, J = 11.5 Hz, 1H β), 3.86-3.83 (m, 1H β), 2.13, 2.10, 2.05, 2.04, 2.04, 2.02, 2.01, 2.0 (8s, 12 H α and 12H β); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 170.3, 170.3, 170.2, 169.8, 169.3, 169.1, 169.0, 137.2, 137.1, 128.6, 128.5, 128.5, 128.3, 128.1, 128.1, 128.1, 128.1, 128.1, 92.1, 89.9, 75.2, 75.0, 74.2, 73.6, 73.1, 73.0, 70.4, 70.3, 68.4, 66.9, 62.2, 62.0, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5; HRMS (ESI) m/z calculated for: C₂₁H₂₆O₁₀Na [M + Na]+: 461.1424, observed: 461.1431.³⁴

![Chemical structure](attachment:image)

(2S,3S)-(E)-3-O-benzyl-4-hexen-6-(4-methoxyphenyl benzoate)-1,2,3-triol

To a 1 dram vial was added (+)-(6) (0.041 g, 0.1 mmol, 1 equiv.), CH₃CN (2 mL) and Zn(NO₃)₂ · 6H₂O (0.097 g, 0.19 mmol, 5 equiv.). A Teflon© stir bar was added to the reaction vessel and the reaction was then taken to 50°C and monitored via TLC. Upon completion (~24hrs) the flask was cooled and the CH₃CN removed via rotary evaporation.
Water (1 mL) and CH$_2$Cl$_2$ (5 mL) were added and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organics were then dried (MgSO$_4$), filtered, and reduced in vacuo. Purification by flash silica gel chromatography in 2% MeOH/CH$_2$Cl$_2$ gave 0.025 g of the title compound as a clear oil (70%). $R_f=0.10$ (1%CH$_2$Cl$_2$/MeOH); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.0 (app. dt, $J = 3.0, 8.5$ Hz, 2H), 7.38–7.28 (m, 5H), 6.94 (app. dt, $J = 2.5, 9.0$ Hz, 2H), 6.03 (ddt, $J = 1.0, 5.5, 15.8$ Hz, 1H), 5.80 (ddt, $J = 1.5, 8.0, 15.3$ Hz, 1H), 4.86 (app. dd, $J = 1.5, 5.5$ Hz, 2H), 4.67 (d, $J = 11.0$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 3.94 (app. dd, $J = 1.5, 5.5$ Hz, 1H), 3.87 (s, 3H), 3.74-3.69 (m, 1H), 3.68-3.66 (m, 1H), 3.62-3.57 (m, 1H), 2.84 (d, $J = 3.0$ Hz, 1H, OH), 2.07 (t, $J = 6.0$ Hz, 1H, OH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.9, 163.5, 137.6, 131.7, 130.5, 129.9, 128.5, 128.0, 122.3, 113.7, 80.2, 73.7, 70.6, 63.9, 63.0, 55.4; HRMS (ESI) m/z calculated for: C$_{21}$H$_{25}$O$_6$ [M + H]$^+$: 373.1651, observed: 373.1654.

(2S,3S)-(Z)-3-O-benzyl-4-hexen-6-(4-methoxyphenyl benzoate)-1,2,3-triol

Authentic Z isomer of (+)-(6) for determination of the E:Z selectivity of the linear allylic C-H oxidation reaction was prepared through the following sequence: (−)-(10) was subjected to periodate cleavage to give a terminal aldehyde, followed by Still-Gennari olefination to give the (Z)-$\alpha$,$\beta$-unsaturated methyl ester, which was reduced to the alcohol with diisobutylaluminum hydride, converted to the 4-methoxyphenylbenzoate derivative through dicyclohexylcarbodiimide assisted coupling with $p$-anisic acid, and finally acetonide deprotected with Zn(NO$_3$) $\cdot$ 6H$_2$O. $R_f=0$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 (app. dt, $J = 3.0, 9.0$ Hz, 2H), 7.37-7.28 (m, 5H), 9.92 (app. dt, $J = 3.0, 9.0$ Hz, 2H), 6.02 (dt, $J = 6.5, 11.0$ Hz, 1H), 5.63 (dt, $J = 1.5, 10.5$ Hz, 1H), 4.90 (ddd, $J =$
1.5, 7.0, 13.4 Hz, 1H), 4.84 (ddd, J = 1.5, 6.5, 13.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 11.5 Hz, 1H), 4.38 (dd, J = 7.5, 9.5 Hz, 1H), 3.86 (s, 3H), 3.72-3.78 (m, 1H), 3.70-3.64 (m, 1H), 3.63-3.56 (m, 1H), 2.93 (b s, 1H, OH), 2.25 (b s, 1H, OH); 13C NMR (125 MHz, CDCl3) δ 166.1, 163.5, 137.6, 131.8, 131.7, 130.6, 128.6, 128.0, 127.7, 122.2, 113.7, 75.4, 73.7, 70.7, 62.8, 60.5, 55.4.

(R)-4-(((S)-1-(((4-methoxybenzyl)oxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (11)

1H NMR (400 MHz, CDCl3) δ 7.25 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.93-5.83 (m, 1H), 5.17-5.07 (m, 2H), 4.54 (q, J = 11.2 Hz, 2H), 4.10-3.97 (m, 2H), 3.87 (dd, J = 6.0, 7.8 Hz, 1H), 3.80 (s, 3H), 3.54 (q, J = 4.8 Hz, 1H), 2.46-2.28 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H).

(S,E)-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(((4-methoxybenzyl)oxy)but-2-en-1-yl 4-methoxybenzoate (12)

To a 40 mL borosilicate vial was added sequentially the following: Pd(OAc)2 (0.0224 g, 0.1 mmol, 10mol%), phenyl benzoquinone (0.368 g, 2.0 mmol, 2 equiv.), p-anisic acid (0.456 g, 3.0 mmol, 3 equiv.), 4Å molecular sieves (0.200 g), (-)-(11) (0.292 g, 1 mmol, 1 equiv.), DMSO (0.380 mL), CH2Cl2 (0.120 mL), diisopropylethylamine (0.087 mL, 0.5 mmol, 0.5 equiv.) and a Teflon® stir bar. The vial was then capped and stirred at 41°C for 72 hours. Care was taken in charging and stirring to keep all reagents off of the walls and contained at the bottom of the vial and in maintaining the temperature centered at 41°C (i.e. 40°C-43°C). Upon completion, the reaction was
quenched with sat. aq. NH₄Cl solution (1 mL), stirred for 30 minutes, and then transferred to
a separatory funnel using ethyl acetate (10 mL). Hexanes (40 ml) was added and the
organics were washed with H₂O (50 mL) and 5% aq. Na₂CO₃ solution (2 x 50 mL). (Note:
Upon addition of hexanes a significant amount of phenyldihydroquinone will crash out of
solution as a black solid. This solid is readily removed in the next step during filtration.)
The organic layer was dried (MgSO₄), filtered, and reduced in vacuo. Subsequent transfers
were all performed using ether to minimize transfer of phenyldihydroquinone. Afforded
313mg product (71%) yield. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (app. d, J = 8.8 Hz, 2H),
7.23 (app. d, J = 8.4 Hz, 2H), 6.93 (app. d, J = 9.2 Hz, 2H), 6.86 (app. d, J = 8.8 Hz, 2H),
5.96 (dt, J = 5.6, 15.6 Hz, 1H), 5.83 (ddt, J = 1.2, 7.2, 15.6 Hz, 1H), 4.91-4.81 (m, 2H), 4.57
(d, J = 11.2 Hz, 1H), 4.35 (d, J = 11.6 Hz, 1H), 4.11 (q, J = 6 Hz, 1H), 4.04 (dd, J = 6.4, 8
Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.88-3.76 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H).

(2R,3S,4S)-4-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,3-
dihydroxy-4-((4-methoxybenzyl)oxy)butyl 4-
methoxybenzoate (13) To a clean, dry 50 mL recovery flask
was added sequentially the following: K₂OsO₄ · 2H₂O (0.007 g, 0.019 mmol, 1 mol%),
(DHQD)₂PHAL (0.076 g, 0.095 mmol, 5 mol%), K₃Fe(CN)₆ (1.89 g, 5.72 mmol, 3 equiv.),
K₂CO₃ (0.792 g, 5.72 mmol, 3 equiv.), a Teflon© stir bar, deionized water (9.5 mL), and
tert-butanol (5 mL). The reaction flask was stirred vigorously until both layers became
translucent, at which time MeSO₂NH₂ (0.187 g, 1.91 mmol, 1 equiv.) was added and the
reaction was cooled to 0°C. After the solution became opaque, olefin (12) (0.787 g, 1.91
mmol, 1 equiv.) was added dropwise via pipette in tert-butanol (1.5 mL initial volume, 2 x 1
mL rinses) and the reaction was stirred vigorously at 0°C until completion as indicated by TLC (~3.5 hr). Upon completion, sodium bisulfite (1.81 g) was added slowly and the reaction was allowed to warm to room temperature and stir for 1 hour. EtOAc (10 ml) was added and the aqueous layer extracted with additional EtOAc (3 x 15 mL). The combined organic layers were washed with 2N KOH (1x10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification via flash silica gel chromatography (40% EtOAc/hexanes) afforded (31%) of 13 as a clear, viscous oil. Rf = 0.2 (40% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.0 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 4.76 (d, J = 8.8 Hz, 1H), 4.60 (d, J = 8.8 Hz, 1H), 4.38-4.28 (m, 2H), 4.13-4.09 (m, 2H), 3.97-3.95 (m, 1H), 3.86 (s, 3H), 3.83-3.78 (m, 1H), 3.74 (s, 3H), 1.45 (s, 3H), 1.26 (s, 3H).

1.5 REFERENCES


This reaction has been optimized with commercial (R,R)-(Salen)Co(III)OAc (2 mol%) to give the desired chiral epoxyketal in 50% overall yield (95% ee). Lower yields may be due to epoxide opening by MeOH during ketalization with higher catalyst loadings of the monomeric catalyst. See SI for reaction details.

The diastereomer that corresponds to racemization of the allylic center was independently synthesized and was not detected by HPLC analysis (see SI for details).


(-)-**11** was silyl deprotected and peracetylated to give 1,2,3,6-O-tetraacetyl-4-O-benzyl-L-galactopyranose that was found to be spectroscopically identical to the known compound (see SI for details): L. Ermolenko, N.A. Sasaki, *J. Org. Chem.* **2006**, *71*, 693.


28 Commercially available (1R,2R)-(−)-(1,2-Cyclohexanediamino-N,N′-bis(3,5-di-t-butylsalicylidene))Cobalt(II) can be oxidized to the Co(III)OAc species using AcOH in CH₂Cl₂. see ref. ³


CHAPTER 2: SYNTHESIS OF COMPLEX ALLYLIC ESTERS VIA C-H
OXIDATION VS C-C BOND STRATEGIES

2.1 INTRODUCTION

Many strategies exist for the construction of heteroatom-rich complex compounds through the coupling of simple pre-oxidized molecules. Inherently, oxygenated functional groups often require oxidation state changes and protection/de-protection sequences both to install and be compatible with further manipulations on the molecule. Selective C-H oxidation of pre-assembled hydrocarbon frameworks represents an alternative strategy for the rapid assembly of complex oxygen\textsuperscript{37,38} and nitrogen\textsuperscript{37,39} rich structures at late stages of synthesis. When these reactions are predictably selective, mild, and incorporate the desired functionality without the need for further manipulation, unnecessary functional group manipulations can be bypassed, reducing synthetic steps and increasing overall yield.\textsuperscript{40}

Esterification is one of the most important reactions in organic synthesis and generally involves coupling pre-oxidized carboxylic acid and alcohol fragments.\textsuperscript{41} Often significant synthetic overhead is required to install these oxidized moieties in the correct oxidation state while maintaining functional group compatibility with the remaining functional groups on the desired molecule. Furthermore, coupling generally involves stoichiometric amounts of a condensation reagent, or the generation of an activated, and often unstable, acid derivative. Although catalytic esterification methods exist, they suffer from limited scope and often require one coupling partner to be used in large excess.\textsuperscript{41} A catalytic, general esterification method that oxidatively couples a hydrocarbon with a carboxylic acid would be a significant advance and could possibly exploit the orthogonal reactivity of unreactive C-H in the presence of sensitive functional groups.
Common approaches to linear (E)-allylic esters are shown in Figure 1. A Horner-Wadsworth-Emmons (HWE) or stabilized Wittig olefination approach generally involves taking a pre-oxidized starting material through a four step route: (1) aldehyde formation via oxidation [O] or reduction [H-], (2) olefination to form the α,β-unsaturated ester, (3) reduction to the allylic alcohol, and (4) acylation to obtain the target ester. If other functionality on the molecule is incompatible with this diverse set of conditions (i.e. oxidation, base, reduction), protecting group manipulations are also required. An alternative olefination strategy involves cross-metathesis of a terminal olefin with a pre-formed allylic ester.  

Although highly efficient, challenges associated with this route are predictable control of olefin geometry and the requirement for an excess of one of the olefin coupling partners to achieve high yields. Additionally, as in the HWE route, esterification often requires extensive screening of stoichiometric reagents, many of which generate waste that is difficult to remove from the product. We anticipated that the direct, catalytic coupling of terminal olefins with carboxylic acids via a predictably selective C—H esterification reaction would streamline the synthesis of certain (E)-allylic esters by minimizing the need for oxygenated intermediates.
Allylic C—H Esterification. In 2004, we first described a DMSO-promoted, Pd(OAc)$_2$-catalyzed allylic C—H oxidation of α-olefins with solvent quantities of acetic acid (AcOH) to furnish linear (E)-allylic acetates with high regio- and stereoselectivities and outstanding functional group tolerance (Figure 2A).$^{38}$ As synthetic intermediates, acetates often serve as precursors to more complex esters via the intermediacy of alcohols. Ideally, any carboxylic acid could be directly incorporated into the hydrocarbon framework via C-H oxidation to furnish complex esters. Although this allylic C-H acetoxylation method has since been explored extensively by other researchers with respect to ligands, oxidants, and activators,$^{38f, 38b-j}$ no general linear allylic esterification method has emerged. In a preliminary study directed towards streamlining polyol synthesis, we developed specific conditions to couple $p$-anisic acid and a chiral homoallylic ether to directly furnish a hexose precursor (Figure 2B).$^{40}$ Unfortunately, these conditions did not prove to be general. Here we describe a general reaction manifold for the linear allylic C-H oxidation reaction (LAO) that enables coupling of a wide range of carboxylic acids and α-olefins to furnish complex linear (E)-allylic ester products (Figure 2C). Jared H. Delcamp verified critical results and assisted in the characterization of a number of compounds. Portions of this chapter were taken with permission from Vermeulen, N. A.; Delcamp, J. H.; and White, M.C. J. Am. Chem. Soc. 2010, 132, 11323.
2.2 RESULTS AND DISCUSSION

2.2.1 OPTIMIZATION OF A GENERAL LINEAR ALLYLIC C-H OXIDATION

Our working mechanistic hypothesis for the Pd(OAc)$_2$/DMSO catalyzed LAO reaction suggests that a carboxylate counterion on the palladium is needed to effect C-H cleavage to form a π-allyl-Pd intermediate, and that high concentrations of DMSO and AcOH are optimal for effecting functionalization.$^{43}$ Within this original reaction manifold, challenges encountered in expanding the scope of the LAO to a general esterification method included: (1) formation of allylic acetate by-products from the Pd(OAc)$_2$ catalyst, (2) requirement for high equivalents of carboxylic acid, and (3) poor solubilities of many carboxylic acids in DMSO. Switching to a Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ catalyst that can undergo counterion exchange with the carboxylic acids eliminated acetate by-products. The introduction of $N,N$-diisopropylethylamine (DIPEA), believed to promote functionalization through deprotonation of the acid, enabled lowering the amount of carboxylic acid from solvent quantities to 1.5-3 equiv.$^{39,40b}$ Increasing the amount of
DIPEA from 50 to 70 mol% and lowering the amount of DMSO to 1.4 equiv. made possible using more CH$_2$Cl$_2$ as a solvent to improve solubility of both the $\alpha$-olefin and the carboxylic acid. Collectively, these changes significantly widened the range of complex allylic esters that could be generated via C-H oxidation.

The expansive scope and streamlining potential of this methodology is represented in the construction of known allylic ester intermediates (Table 2). Oxidative coupling of unsaturated aryl acids and $\alpha$-bromo-carboxylic acids with allyl arenes provides a direct and modular route to compounds 14$^{44}$ and 15$^{45}$ (entries 1-5), some of which have been shown to exhibit antibacterial and antifungal activities$^{44}$ (entry 1). It is notable that 1.5 equivalents of acid can be used with only a moderate reduction in isolated yield (entry 2). This feature of the reaction is particularly significant when using complex carboxylic acids that require lengthy synthetic sequences to prepare (vide infra). A decrease in the reaction time (72h$\rightarrow$ 24h) and catalyst loadings (10 mol% $\rightarrow$ 5 mol%) is possible while maintaining synthetically useful yields (entries 3 and 4, respectively). It is interesting to note that under these modified conditions even fatty acids, insoluble at high concentrations of DMSO, are useful functionalization reagents (entry 6).$^{46}$

Bi-functional allylic esters 17$^{47}$ and 18$^{48}$ have been synthesized via N,N-dicyclohexyl carbodiimide/4-dimethylaminopyridine (DCC/DMAP) coupling of the respective carboxylic acids and mono-protected ($E$)-pent-2-en-1,5-diol (synthesized via a HWE route, Table 1, entries 7 and 9). Although DCC is one of the most widely used coupling reagents to form esters in organic synthesis, it is a potent sensitizer and generates by-products (dicyclohexylurea) that are relatively insoluble and difficult to remove.$^{49}$ In contrast, direct, oxidative coupling of the same carboxylic acids with silyl-protected penten-ol afforded 17 and 18 in good yields, half the number of steps, and without the use of any stoichiometric condensing reagents (entries 7 and 9).
We have found that the reduced form of the quinone oxidant is easily removed via aqueous, basic extraction during the workup procedure (see Experimental). Significantly, reactions run under the previously reported conditions for benzylation (Fig. 2B) resulted in significantly lower yields. (Table 2, entries 8 and 10).

Table 2: Linear Allylic Oxidation (LAO) for the Construction of Known Allylic Ester Intermediates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isolated Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E:Z&lt;sup&gt;b&lt;/sup&gt;</th>
<th>L:B&lt;sup&gt;b&lt;/sup&gt; (crude)</th>
<th>steps</th>
<th>C-H</th>
<th>C-C</th>
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<tr>
<td>1</td>
<td>70%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
<td>1</td>
<td>3</td>
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<tr>
<td>2</td>
<td>61%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
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<td>53%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&gt;20:1</td>
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<sup>a</sup> Isolated yields of >20:1 L:B. Unless otherwise noted, E:Z does not change after purification.<sup>b</sup> Crude values by <sup>1</sup>H NMR. <sup>c</sup> 1.5 equiv. acid. <sup>d</sup> 24h reaction time. <sup>e</sup> 5 mol% Pd[CH<sub>2</sub>CN<sub>4</sub>]_2(BF<sub>4</sub>)<sub>2</sub>. <sup>f</sup> Using previously published conditions, ref. 39b. <sup>g</sup> THP protected version of this compound was made, <sup>h</sup> determined after methanalysis and acetylation by <sup>1</sup>H NMR. <sup>i</sup> Determined by <sup>1</sup>H NMR of purified material. Adapted from Vermeulen et al. J. Am. Chem. Soc. 2010, 132, 11323.
Both α- and β-amino acids can be used as coupling partners in the oxidative esterification reaction without any epimerization. It is significant to note that t-butyl ester (+)-19 can be synthesized via a C-C bond-forming route with equal efficiency to the C-H oxidation route by alkylating symmetric dibromo-2-butene with the enolate of acetic acid t-butyl ester (Table 1, entry 11). However, when a more complex ester is required, for example to afford orthogonally protected aspartate (+)-20, the C-H esterification reaction enables a significant streamlining of the route (entry 12). It is notable that in all cases examined, the E:Z selectivity of this C-H esterification reaction does not drop below 10:1.

2.2.2 SYNTHETIC STREAMLINING USING THE LINEAR ALLYLIC ESTERIFICATION REACTION

A series of case studies were undertaken to evaluate the strategic advantages of constructing complex allylic esters via C-H oxidation routes versus C-C bond forming routes. A total synthesis of (-)-lepadiformine features an (E)-allylic ester intermediate (-)-21 that undergoes diastereoselective amino acid enolate Claisen rearrangement followed by a ring closing metathesis to forge the complex tricyclic backbone (Scheme 4). Starting from a fully oxidized starting material 23 (1,4-butanediol), allylic ester (-)-21 was generated through a classic series of reactions: monoprotection, oxidation, HWE olefination, reduction, and DCC-mediated esterification with cyclic amino acid (-)-22. This route is reliable and generally high-yielding; however, it requires 5 steps. Additionally, 2 of steps are needed but ultimately wasteful oxidation state manipulations. Direct installation of the (E)-allylic ester from the catalytic coupling of a terminal olefin and carboxylic acid affords a dramatic streamlining effect on this route. Using 1.5 equivalents of the same cyclic amino acid (-)-22, oxidative C-H esterification of TBDPS-
protected 5-hexen-1-ol 26 provided (-)-21 in only 2 steps and 50% overall yield. The importance of using fragment coupling quantities of reagents is underscored here, as an 8-step sequence is required to synthesize carboxylic acid (-)-22.

Scheme 4: C-H oxidation vs C-C bond forming strategies for the synthesis of key linear allylic ester intermediate (-)-21 in the synthesis of (-)-lepadiformine

Synthetic routes for chiral molecules are often driven by practical considerations of availability of chiral starting material. In addition to providing more expedient routes to (E)-allylic esters, a C-H oxidation approach expands the options for using simpler chiral starting materials by minimizing total oxygenation. Chiral (E)-allylic ester (-)-27, an intermediate en route to (-)-laulimalide, was previously obtained from a highly oxygenated chiral pool material (S)-β-hydroxy-γ-butyrolactone (-)-28. Manipulation of the pre-installed oxygen functionality to arrive at the desired structure required a six-step HWE route comprised of 2 protections, serial reductions, and esterification (Scheme 5). In contrast, C-H esterification is a simplifying transform that enables targeting less oxygenated intermediates. For example, precursors for
LAO, optically enriched bis-homoallylic alcohols, can be directly accessed via allylation of chiral terminal epoxides that are now readily available via hydrolytic kinetic resolution (HKR) methodology.\textsuperscript{54} Thus, an alternative approach to (−)-27 starts with allylation and protection of commercially available tert-butyldimethylsilyl (S)-(+)−glycidyl ether to afford enantiomerically enriched bis-homoallylic ether (−)-31 in just 2 steps. Benzoic acid was used as the coupling partner to afford the desired (E)-allylic ester (−)-27 in half the number of steps (3 steps) and comparable overall yield to the olefination route (Scheme 5).

**Scheme 5: C-H oxidation vs C-C bond formation routes in the synthesis of linear E-allylic ester intermediate (−)-27 en route to (−)- laulimalide**

While terminal olefins may also be used as intermediates in olefination sequences, FGMs are generally required. To illustrate this point, we compare a C-H oxidation strategy to an olefination strategy to allylic ester (±)-32, which serves as a precursor to trans-fused polycyclic ethers in brevetoxins (Scheme 6).\textsuperscript{55} Both routes start with alkylation and protection of cyclohexene oxide to rapidly afford homologous terminal olefin intermediates 34 and 37. The
established HWE sequence to allylic alcohol 35 requires that the terminal olefin be oxidatively cleaved to afford the aldehyde precursor for olefination followed by reduction of the allylic ester to the desired oxidation state. The resulting (E)-allylic alcohol 35 was subsequently coupled to an acyl chloride to form the desired (E)-allylic ester (±)-32 in a total of 6 steps and 19% overall yield (Scheme 6). In the C-H esterification route, olefin 37 can be coupled directly to 2,4-dichlorobenzoic acid to furnish desired product (±)-32 in a total of only 3 steps and 47% overall yield (Scheme 6).

**Scheme 6: C-H oxidation vs C-C bond forming routes proceeding via analogous terminal olefin intermediates**

Adapted from Vermeulen et. al J. Am. Chem. Soc. 2010, 132, 11323
Scheme 7: C-H oxidation vs cross-metathesis route for the formation of complex allylic esters

An olefination strategy that is analogous to a C-H oxidation strategy for the construction of (E)-allylic esters is cross metathesis. These C-C bond forming routes are expedient because they also utilize terminal olefins and install the desired oxygen moiety directly without further manipulation (Figure 1). Challenges associated with this method center around the ability to control and predict E:Z selectivity of the newly formed internal olefin. In contrast, linear C-H oxidation methodology under these mild conditions generates E-allylic oxygenates with selectivities that are 10:1 or higher. Both the olefination and C-H oxidation routes to macrocyclic lactam (+)-38, a peptidomimetic, began with alkylation of macrocyclic amide 39 to furnish homologous compounds 40 and 43 (Scheme 8). Allylation of the amino acid Boc-L-phenylalanine via DIC-mediated esterification was required to furnish metathesis coupling partner (-)-42. Cross-metathesis coupling of allylated compounds 40 and (-)-42 (2 equiv.) provided phenylalanine derived macrocycle (+)-38 in 28% overall yield with an E:Z selectivity...
of 1.2:1. Using a linear C-H esterification strategy, direct C-H esterification of 43 with 1.5 equiv. of commercial Boc-L-phenylalanine (+)-41 furnished (+)-38 in 40% overall yield with an E:Z selectivity of 17:1 (Scheme 7).

2.2.3 IMPROVEMENT OF THE LINEAR ALLYLIC ACETOXYLATION

Although our previously reported allylic C-H acetoxylation reaction showed broad functional group tolerance, acid sensitive substrates were not well tolerated under those conditions which employed solvent quantities of AcOH. We hypothesized that these new conditions employing only 1.5-3.0 equiv. of carboxylic acid and 70 mol% base may further expand the scope of this powerful transformation (Table 3).

Terminal olefin substrates containing moderately acid-sensitive moieties such as primary tert-butyl N-tosyl carbamates and ketals showed improvements in yield (51% → 86%; 50% → 63%, respectively) with no erosion of selectivities under the new conditions (Table 3, entries 1 and 2). However, substrates containing highly acid-sensitive functionality, i.e. primary TBS ethers, triphenylmethyl (Tr) ethers, and p-methoxybenzyl (PMB)-acetals, all showed significant improvements in isolated yields (Table 3, entries 5-8, 10-11). Significantly, when AcOH loadings were reduced to 3 equiv. under the original reaction conditions, only trace reactivity was observed (Table 3, entry 9).
2.3 CONCLUSION

In summary, this study introduces the first general, predictably selective C-H oxidation method for the direct synthesis of complex allylic esters. The ability to forge esters using a catalytic method that couples two highly stable compounds, carboxylic acids and terminal olefins, provides an attractive alternative to methods that use stoichiometric amounts of coupling reagents or require reactive, unstable intermediates. The milder conditions that employ low loadings of carboxylic acid and catalytic base also enable broadening the substrate scope of the allylic C-H acetoxylation reaction to include acid-sensitive moieties. Strategic as well as practical advantages emerge when comparing C-H oxidation versus C-C bond forming routes for the synthesis of complex allylic esters. Introduction of oxygen functionality late in a sequence,
without the need for further manipulation, provides a significant streamlining of the route by eliminating FGMs such as oxidation state changes, protection/deprotection sequences, and functional group transformations. Moreover, the ability to utilize simpler, less oxygenated intermediates expands the options with respect to chiral starting materials, often leading to more efficient routes. Based on the generality and predictable selectivity of this C-H oxidation method along with the strategic advantages it enables, we anticipate that it will find widespread use in complex molecule syntheses.

2.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents were used as received: 2-phenyl-1,4-benzoquinone (ACROS); Pd(CH₃CN)₄(BF₄)₂ (Aldrich) was stored in a glove box under a argon atmosphere and weighed out in under argon prior to use, all other reagents where purchased from least expensive supplier and used directly unless otherwise stated. Solvents diethyl ether (Et₂O) and methylene chloride (CH₂Cl₂) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N,N-dimethylformamide (DMF) (Sure/Seal) was obtained from Sigma-Aldrich and used as received. All allylic oxidation reactions were run under air with no precautions taken to exclude moisture. All other reactions were run under a balloon of argon gas unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.⁵⁷ using EM reagent silica gel 60 (230-400 mesh). ¹H NMR spectra were recorded on a Varian Unity 400 (400 MHz), a Varian Unity 500 (500 MHz), or a Varian Unity Inova 500NB 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, quin. = quintet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration, corresponding carbon atom. 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 77.23 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$^{-1}$). All optical rotations were determined on a Perkin Elmer 341 Polarimeter using the sodium D line (589 nm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Medium pressure liquid chromatography (MPLC) was used in cases with difficult silica chromatography separations and consists of a prep-HPLC pump, hand-packed 12g MPLC silica column and fraction collector.

Method Notes: These notes are intended to help with the preparation of compounds not described in this communication and should be used with discretion. The reaction is dependent on concentration with an optimal range of 1M or greater. Below this threshold of concentration the reaction is dramatically slower. Other solvents can be used. These consist mainly of other chlorinated hydrocarbons (chloroform, dichloroethane) but can be changed to ethereal solvents limited mainly by starting material, coupling acid solubility, and slightly diminished yields or selectivities. Stirring is crucial; appropriate stirring involves slow steady mixing at approximately 300 rpm (achieved after 1hr at 40$^\circ$C when the reaction becomes black and viscous). Due to the high viscosity of the reaction mixtures a bigger stir bar is more appropriate. The temperature is also important with an effective range of 40 to 45 $^\circ$C. Much lower temperatures result in dramatically slower reactivity and the inability to form a solution. Higher
temperatures result in decreased yields due to by-product formation. The Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ catalyst is moisture sensitive and decomposes to a wet dull yellow powder, easily distinguished from the bright yellow crystals of good catalyst.

General Procedure: To a 4 mL borosilicate vial was first added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere. The following reagents were then added in one portion under ambient atmosphere: phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), carboxylic acid (3.0 mmol, 3.0 equiv.), two 4Å molecular beads (50 mg). Finally, DMSO (100 µL, 1.4 mmol, 1.4 equiv.), CH$_2$Cl$_2$ (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added sequentially via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before starting material (1.0 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) [Note 1]. The solution was diluted with diethyl ether (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution twice [Note 2]. The organic layer was dried with MgSO$_4$, filtered, and reduced in vacuo. Purification was achieved via flash silica gel chromatography.

Notes: (1) The excess quinone may be reduced by addition of solid Na$_2$SO$_3$ (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5% K$_2$CO$_3$ (aq.) solution. The resulting biphasic mixture is then stirred rapidly for 30 minutes before continuing with the extraction. (2) If an inseparable emulsion forms, filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. Note: (1) All yield are of column purified material with >20:1 L:B. E:Z ratios did not change after silica column purification unless otherwise noted. (2) All reference numbers in the tables and figures refer to the reference numbers from the text.
(E)-cinnamyl 3-(2,4-dimethoxyphenyl)acrylate (14)

To a 4 mL borosilicate vial was added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), (E)-3-(2,4-dimethoxyphenyl)acrylic acid (624 mg, 3.0 mmol, 3.0 equiv.), two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (100 µL, 1.1 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon® stir bar. This solution was stirred at 41°C for 5 minutes before allyl benzene (118 mg, 1.0 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with diethyl ether (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO$_4$, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (20% Et$_2$O/hexanes) gave (E)-cinnamyl 3-(2,4-dimethoxyphenyl)acrylate as a white solid. Note: Product streaks somewhat on silica gel with diethyl ether; however, to ensure good separation from PhBQ this mixture is necessary. The crude selectivities were determined to be L:B >20:1 and E:Z >20:1 by $^1$H NMR for entries 1-5 in table 1. Run 1 (224.0 mg, 0.69 mmol, 69%); run 2 (220.0 mg, 0.68 mmol, 68%); run 3 = (233.0 mg, 0.72 mmol, 72%) Average = 70% yield. 1.5 equivalents acid: Run 1 (185.0 mg, 0.57 mmol, 57%); run 2 (201.0 mg, 0.62 mmol, 62%); run 3 (204.0 mg, 0.63 mmol, 63%). Average = 61% yield. 24 hour reaction time: Run 1 (84.2 mg, 0.26 mmol, 52%); run 2 (85.9 mg, 0.27 mmol, 53%). Average =53% yield. 5 mol % catalyst loading: Run 1 (103.7 mg, 0.32 mmol, 64%); run 2 (105.3 mg, 0.33 mmol, 65%). Average = 65% yield. 1.2 equiv. PhBQ: Run 1 (116.7 mg, 0.36
mmol, 72%) [not reported in Table 2]. Rf = 0.2 (20% Et2O/hexanes). 1H NMR (500 MHz, CDCl3) δ 7.95 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 7.0 Hz, 2H), 7.33 (app. t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.5, 1H), 6.70 (d, J = 16.0 Hz, 1H), 6.51 (dd, J = 9.0, 2.0 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1H), 6.45 (d, J = 2.5 Hz, 1H), 6.37 (dt, J = 16.0, 6.0 Hz, 1H), 4.86 (dd, J = 6.0, 1.0 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 167.9, 162.9, 160.1, 140.7, 136.5, 134.1, 130.7, 128.8, 128.1, 126.8, 123.9, 116.7, 115.9, 105.4, 98.6, 65.0, 55.6 (2C). IR (neat, cm⁻¹) 3080, 3062, 3026, 3004, 2936, 2839, 1706, 1605, 1160. HRMS (ESI) m/z calculated for C20H20O4Na [M + Na]+: 347.1259; found: 347.1257. Spectral data has previously been reported for this compound.⁵⁸

(E)-3-(benzo[d][1,3]dioxol-5-yl)allyl 2-bromo-3-(3,4,5-tri-methoxyphenyl)propanoate (15)

To a 4 mL borosilicate vial was added Pd(CH3CN)4(BF4)2 (11.1 mg, 0.025 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (92.0 mg, 0.5 mmol, 2.0 equiv.), 2-bromo-3-(3,4,5-trimethoxyphenyl)propionic acid⁵⁹ (239.4 mg, 0.75 mmol, 3.0 equiv.), two 4Å molecular beads (30 mg) in one portion under ambient atmosphere. DMSO (25 µL, 0.29 mmol, 1.1 equiv.), CH2Cl2 (125 µL), and DIPEA (30 µL, 0.18 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before safrole (41 mg, 0.25 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K2CO3 (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-
30 mL diethyl ether. The organic layer was dried with MgSO$_4$, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (30% Et$_2$O/hexanes) gave (E)-3-(benzo[d][1,3]dioxol-5-yl)allyl 2-bromo-3-(3,4,5-trimethoxyphenyl)propanoate as a pale yellow thick oil. The crude selectivities determined by $^1$H NMR in deuterobenzene are L:B >20:1 and E:Z 16:1. Run 1 (85.2 mg, 0.18 mmol, 71%); run 2 (80.1 mg, 0.17 mmol, 67%); run 3 = (80.4 mg, 0.17 mmol, 67%). Average = 68% yield. (16:1 E:Z after silica column purification). $R_f$ = 0.15 (30% Et$_2$O/hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.90 (d, $J$ = 1.6 Hz, 1H), 6.80 (dd, $J$ = 8.0, 1.6 Hz, 1H), 6.75 (d, $J$ = 8.0 Hz, 1H), 6.56 (d, $J$ = 16.0 Hz, 1H), 6.42 (s, 2H), 6.05 (dt, $J$ = 16.0, 6.4 Hz, 1H), 5.96 (s, 2H), 4.80-4.71 (m, 2H), 4.41 (dd, $J$ = 8.8, 6.8 Hz, 1H), 3.81 (s, 9H), 3.43 (dd, $J$ = 14.0, 8.8 Hz, 1H), 3.18 (dd, $J$ = 14.0, 6.8 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.2, 153.3, 148.1, 147.8, 134.8, 132.3, 130.3, 121.6, 120.1, 108.3, 106.2, 105.8, 101.2, 66.6, 60.8, 56.1, 45.1, 41.4. IR (neat, cm$^{-1}$) 2998, 2940, 2839, 1738, 1591. HRMS (EI) m/z calculated for C$_{22}$H$_{23}$BrO$_4$ [M]: 478.06271; found: 478.06254. Spectral data matches that previously reported.$^{59}$

(E)-3-(4-hydroxy-3-methoxyphenyl)allyl palmitate (16)

To a 4 mL borosilicate vial was added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), palmitic acid (768 mg, 3.0 mmol, 3 equiv.), two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (100 µL, 1.1 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon® stir bar. This solution was stirred at 41°C for 5 minutes before 4-allyl-2-methoxyphenol (164 mg, 1.0 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was
transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was
diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with NH₄Cl (sat. aq.) solution 2x.
Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo.
Purification via flash silica gel chromatography (5% Et₂O/hexanes) gave (E)-3-(4-hydroxy-3-methoxyphenyl)allyl palmitate as a clear oil. The crude selectivities determined by ¹H NMR are L:B >20:1 and E:Z >20:1. Run 1 (272.0 mg, 0.65 mmol, 65%); run 2 (263.0 mg, 0.63 mmol, 63%); run 3 = (268.0 mg, 0.64 mmol, 64%) Average = 64% yield. Rᶠ= 0.2 (5% Et₂O/hexanes; elutes with and just after the brightly colored PhBQ). ¹H NMR (400 MHz, CDCl₃) δ 6.94-6.82 (m, 3H), 6.57 (d, J = 16.0 Hz, 1H), 6.14 (dt, J = 15.6, 6.8 Hz, 1H), 4.71 (dd, J = 6.8, 1.2 Hz, 2H), 3.91 (s, 3H), 2.34 (dt, J = 7.6, 2.8 Hz, 2H), 1.7-1.55 (m, 2H), 1.4-1.2 (s, 24H), 0.88 (t, J = 6.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 146.8, 146.1, 134.6, 129.0, 121.1, 120.8, 114.6, 108.5, 65.3, 56.1, 34.6, 32.1, 29.9, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.2, 22.9, 14.4. IR (neat, cm⁻¹) 2921, 2850, 1732, 1708. HRMS (ESI) m/z calculated for C₂₆H₄₃O₄ [M + H]⁺: 419.3161; found: 419.3155. Spectral data matches that previously reported.⁶⁰

(E)-5-(tert-butyldimethylsilyloxy)pent-2-enyl 2-(3,4-difluorophenyl)acetate (17)

General Conditions: To a 4 mL borosilicate vial was added Pd(CH₃CN)₄(BF₄)₂ (22.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (184 mg, 1.0 mmol, 2 equiv.), 3,4-difluorophenylacetic acid (259 mg, 1.5 mmol, 3 equiv.), two 4Å molecular beads (30 mg) in one portion under ambient atmosphere. DMSO (50 µL, 0.57 mmol, 1.1 equiv.), CH₂Cl₂ (250 µL), and DIPEA (60 µL, 0.35 mmol, 0.7 equiv.) were added via glass syringe
followed by a Teflon® stir bar. This solution was stirred at 41°C for 5 minutes before tert-butylidimethyl(pent-4-enyloxy)silane (100 mg, 0.5 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K₂CO₃ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (5% Et₂O/hexanes) gave (E)-5-(tert-butyldimethylsilyloxy)pent-2-eny 2-(3,4-difluorophenyl)acetate as a clear oil. The crude selectivities determined by ¹H NMR are L:B 6:1 and E:Z 11:1. Run 1 (113.0 mg, 0.31 mmol, 62%); run 2 (113.0 mg, 0.30 mmol, 61%); run 3 = (106.0 mg, 0.29 mmol, 57%). Average = 60% yield. (11:1 E:Z and >20:1 L:B after silica column purification). Note: When 4 equiv. acid is used 133mg, 69% yield, L:B=27:1, E:Z=17:1.

**Previous Conditions:** To a 4 mL borosilicate vial was added Pd(OAc)₂ (11.2 mg, 0.05 mmol, 10 mol %), phenyl benzoquinone (184 mg, 1.0 mmol, 2 equiv.), 3,4-difluorophenylacetic acid (259 mg, 1.5 mmol, 3 equiv.), and 4Å molecular sieves (50 mg). DMSO (190 µL), CH₂Cl₂ (60 µL), and DIPEA (43 µL, 0.25 mmol, 0.5 equiv.) were added via glass syringe followed by a Teflon® stir bar. tert-Butylidimethyl(pent-4-enyloxy)silane (100 mg, 0.5 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K₂CO₃ (aq.) solution 2x. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (5%
Et₂O/hexanes) gave (E)-5-(tert-butyldimethylsilyloxy)pent-2-enyl 2-(3,4-difluorophenyl)acetate as a clear oil. The crude selectivities determined by ¹H NMR are L:B 9:1 and E:Z 10:1. Run 1 (55.1 mg, 0.15 mmol, 30%); run 2 (57.0 mg, 0.15 mmol, 31%). Average = 31% yield. (10:1 E:Z and >20:1 L:B after silica column purification). R_f = 0.15 (5% Et₂O/hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.14-7.07 (m, 2H), 7.00-6.96 (m, 1H), 5.77 (dt, J = 15.5, 7.0 Hz, 1H), 5.61 (dtd, J = 16.5, 6.5, 1.0 Hz, 1H), 4.55 (d, J = 6.0 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 3.58 (s, 2H), 2.27 (app. q, J = 7.0, 2H), 0.89 (s, 9H), 0.04 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 151.0 (dd, J = 65.9, 12.8 Hz), 149.1 (dd, J = 65, 12.9 Hz), 133.5, 130.9 (t, J = 5.0 Hz), 125.6 (app. s), 125.5, 118.5 (d, J = 17.4 Hz), 117.4 (d, J = 17.4 Hz), 65.9, 62.5, 40.5, 35.9, 29.8, 26.0, 18.5, -5.19. ¹⁹F NMR (376 MHz, CDCl₃) δ -138.1 (quin., J = 9.4 Hz, 1F), -140.7 (m, 1F). IR (neat, cm⁻¹) 2953.6, 2929.6, 2903.9, 2858.5, 1740.0, 1520.3. HRMS (ESI) m/z calculated for C₁₉H₂₉F₂O₃Si [M + H]⁺: 371.1854; found: 371.1849. The TBS deprotected compound has been synthesized via standard TBAF deprotection and matches the spectral data previously reported.⁶¹

(E)-5-(tert-butyldimethylsilyloxy)pent-2-enyl 3-(tert-butoxy-carbonyl)propanoate (18)

**General Conditions:** To a 4 mL borosilicate vial was added Pd(CH₃CN)₄(BF₄)₂ (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), Boc-β-Ala-OH (567.0 mg, 3.0 mmol, 3 equiv.), two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (100 µL, 1.1 mmol, 1.1 equiv.), CH₂Cl₂ (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before tert-butyldimethyl(pent-4-enyloxysilane (200 mg, 1mmol, 1 equiv.) was added neat using a
microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K₂CO₃ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (15% Et₂O/hexanes) gave \((E)-5-(\text{tert-butyldimethylsilyloxy})\text{pent-2-enyl 3-}(\text{tert-butoxycarbonyl})\text{propanoate}\) as a clear oil. The crude selectivities determined by \(^1\)H NMR are L:B 9:1 and E:Z 11:1. Run 1 (197.0 mg, 0.51 mmol, 51%); run 2 (194.0 mg, 0.50 mmol, 50%); run 3 = (190.0 mg, 0.49 mmol, 49%) Average = 50% yield. (11:1 E:Z and >20:1 L:B after silica column purification).

Previous Conditons: To a 4 mL borosilicate vial was added Pd(OAc)₂ (11.2 mg, 0.05 mmol, 10 mol %), phenyl benzoquinone (184 mg, 1.0 mmol, 2 equiv.), Boc-β-Ala-OH (283.5 mg, 1.5 mmol, 3 equiv.), 4Å molecular sieves (50 mg). DMSO (190 μL), CH₂Cl₂ (60 μL), and DIPEA (43 μL, 0.25 mmol, 0.5 equiv.) were added via glass syringe followed by a Teflon© stir bar. tert-Butyldimethyl(pent-4-enyloxy)silane (100 mg, 0.5 mmol, 0.5 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K₂CO₃ (aq.) solution 2x. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (15% Et₂O/hexanes) gave \((E)-5-(\text{tert-butyldimethylsilyloxy})\text{pent-2-enyl 3-}(\text{tert-butoxycarbonyl})\text{propanoate}\) as a clear oil. The crude selectivities determined by \(^1\)H NMR are
L:B 11:1 and E:Z 7:1.  Run 1 (45.0 mg, 0.12 mmol, 23%); run 2 (41.2 mg, 0.11 mmol, 21%); run 3 (46.4 mg, 0.12 mmol, 24%) Average = 23% yield. (7:1 E:Z and >20:1 L:B after silica column purification). $R_f= 0.2$ (20% Et$_2$O/hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.78 (dt, $J = 15.0, 7.0$ Hz, 1H), 5.62 (dt, $J = 15.0, 6.5$ Hz, 1H), 5.02 (br s, 1H), 4.54 (d, $J = 6.0$ Hz, 2H), 3.65 (t, $J = 6.5$ Hz, 2H), 3.39 (app q, $J = 5.5$ Hz, 2H), 2.52 (t, $J = 6.0$ Hz, 2H), 2.28 (app q, $J = 6.5$ Hz, 2H), 1.43 (s, 9H), 0.88 (s,9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.6, 156.0, 133.3, 125.7, 65.6, 62.7, 36.3, 36.1, 34.8, 28.6, 26.1, 18.6, -5.1. IR (neat, cm$^{-1}$) 3371, 2955, 2930, 2858, 1719, 1506. HRMS (ESI) m/z calculated for C$_{19}$H$_{38}$NO$_5$Si [M + H]$^+$: 388.2519; found: 388.2518. Spectral data is in agreement with that previously reported.$^{62}$

To a 4 mL borosilicate vial was added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (22.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (184.0 mg, 1.0 mmol, 2 equiv.), N-α-Fmoc-L-phenylalanine (291.0 mg, 0.75 mmol, 1.5 equiv.), two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (50 µL, 0.55 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (250 µL), and DIPEA (61.0 µL, 0.35 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before tert-butyl hex-5-enoate$^{63}$ (85.0 mg, 0.5 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-
30 mL diethyl ether. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (20% EtOAc/hexanes) gave (S,E)-tert-butyl 6-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoyloxy)hex-4-enoate as a clear thick oil. The crude selectivities are indistinguishable by ¹H NMR. Column purified L:B selectivity was determined by ¹H NMR to be >20:1. E:Z selectivity was determined to be 17:1 after methanolysis of the product followed by acetylation of the resulting alcohol. Run 1 (147.1 mg, 0.26 mmol, 53%); run 2 (149.9 mg, 0.27 mmol, 54%). Average = 54% yield. (>20:1 L:B after silica column purification). Rᶠ= 0.1 (20% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 6.0 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34-7.24 (m, 5H), 7.10 (broad d, J = 6.4 Hz, 2H), 5.82-5.72 (m, 1H), 5.56 (dt, J = 15.2, 6.4 Hz, 1H), 5.27 (d, J = 8.0 Hz, 1H), 4.67 (app. q, J = 6.0 Hz, 1H), 4.56 (d, J = 6.8 Hz, 2H), 4.44 (dd, J = 10.8, 7.2 Hz, 1H), 4.33 (dd, J = 10.4, 6.8 Hz, 1H), 4.21 (t, J = 7.2 Hz, 1H), 3.20-3.06 (m, 2H), 2.40-2.26 (m, 4H), 1.44 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 171.5, 155.7, 144.1, 144.0, 141.5, 135.9, 135.5, 129.7, 128.8, 128.0, 127.4, 127.3, 125.4, 125.3, 124.3, 120.2 (2C), 80.7, 67.1, 66.2, 55.0, 47.4, 38.4, 34.8, 28.3, 27.8. IR (neat, cm⁻¹) 3341, 2978, 1727. HRMS (ESI) m/z calculated for C₃₄H₃₈NO₆ [M + H]⁺: 556.2699; found: 556.2695. [α]D²⁵ = +9.0º (c=1.1, CHCl₃). Spectral data has been previously reported.⁶⁴

![Chemical structure](image)

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-succinic acid 1-tert-butyl ester 4-[5-(2-oxo-2-phenyl-ethoxycarbonyl)-pent-2-enyll]ester (20)

To a 4 mL borosilicate vial was added Pd(CH₂CN)₄(BF₄)₂ (22.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere, followed by a Teflon© stir bar, phenyl benzoquinone (184 mg, 1.0...
mmol, 2 equiv.), Fmoc-\textit{L}-aspartic acid \textit{4-\textit{tert}-butyl ester} (617 mg, 1.5 mmol, 3 equiv.), two 4Å molecular beads (30 mg) in one portion under ambient atmosphere. DMSO (50 μL, 0.57 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (250 μL), and DIPEA (60 μL, 0.35 mmol, 0.7 equiv.) were added via glass syringe. This solution was stirred at 41°C for 5 minutes before hex-5-enoi acid 2-oxo-2-phenyl-ethyl ester (116 mg, 0.5 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO$_4$, filtered, and reduced \textit{in vacuo}. Purification via flash silica gel chromatography (10-40% Et$_2$O/hexanes) gave 2-(9H-Fluoren-9-ylmethoxycarbonylamino)-succinic acid \textit{1-\textit{tert}-butyl ester} 4-[5-(2-oxo-2-phenyl-ethoxycarbonyl)-pent-2-enyl]ester as a clear oil. The crude L:B selectivity was determined by $^1$H NMR to be \textit{>20:1}. E:Z selectivity was determined to be 18:1 after methanolysis of the product followed by acetylation of the resulting alcohol. Run 1 (225.0 mg, 0.35 mmol, 70%); run 2 (231.0 mg, 0.36 mmol, 72%); run 3 (241.0 mg, 0.38 mmol, 75%); run 4 (221.1 mg, 0.35 mmol, 69%). Average = 72% yield. \textit{(>20:1 L:B after silica column purification). R$_f$ = 0.2 (40% Et$_2$O/hexanes). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90 (app. d, $J$ = 8.0 Hz, 2H), 7.76 (d, $J$ = 7.6 Hz, 2H), 7.64-7.56 (m, 3H), 7.49 (t, $J$ = 8.0 Hz, 2H), 7.40 (t, $J$ = 7.2 Hz, 2H), 7.31 (t, $J$ = 7.6 Hz, 2H), 5.90-5.76 (m, 2H), 5.66 (dt, $J$ = 15.6, 6.4 Hz, 1H), 5.34 (s, 2H), 4.57 (d, $J$ = 6.4 Hz, 2H), 4.65-4.50 (m, 1H), 4.44-4.30 (m, 2H), 4.23 (t, $J$ = 6.8 Hz, 1H), 3.01 (dd, $J$ = 16.8, 4.4 Hz, 1H), 2.85 (dd, $J$ = 16.8, 4.4 Hz, 1H), 2.60 (app t, $J$ = 6.8 Hz, 2H), 2.47 (app q, $J$ = 6.8 Hz, 2H), 1.47 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 192.3, 172.4, 170.9, 169.8, 156.2, 144.1, 144.0, 141.5,
134.4, 134.2, 129.1, 128.0, 127.9, 127.3, 125.4, 125.1, 120.2 (2 peaks), 82.9, 67.4, 66.2, 65.6, 51.1, 47.3, 37.1, 33.3, 28.1, 27.6 (2 peaks), 82.9, 67.4, 66.2, 65.6, 51.1, 47.3, 37.1, 33.3, 28.1, 27.6. IR (neat, cm\(^{-1}\)) 3358, 3067, 2928, 1737 (broad). HRMS (ESI) m/z calculated for \(\text{C}_{37}\text{H}_{40}\text{NO}_9\) [M + H]: 642.2703; found: 642.2695. \([\alpha]_{D}^{26} = +12.3^\circ\) (c=1.0, CHCl\(_3\)). Compound was found to be >99% ee through SCF analysis (mobile phase CO\(_2\), column chiralpak-AS, 12% MeOH, 2.5 mL/min, 125 barr) with retention times of 19.3 min for (-)-7 and 22.1 min for (+)-7. Spectral data matches previously reported data.

(5S,E)-1-tert-butyl 2-(6-(tert-butyldiphenylsilyloxy)hex-2-enyl) 5-(benzyloxymethyl)pyrroldine-1,2-dicarboxylate (21)

To a 4 mL borosilicate vial was added Pd(CH\(_3\)CN)\(_4\)(BF\(_4\))\(_2\) (22.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (184 mg, 1.0 mmol, 2 equiv.), (5S)-5-(benzyloxymethyl)-1-(tert-butoxycarbonyl)pyrroldine-2-carboxylic acid (250 mg, 0.75 mmol, 1.5 equiv.), two 4Å molecular beads (30 mg) in one portion under ambient atmosphere. DMSO (50 \(\mu\)L, 0.57 mmol, 1.1 equiv.), CH\(_2\)Cl\(_2\) (250 \(\mu\)L), and DIPEA (60 \(\mu\)L, 0.35 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon\(^\circledR\) stir bar. This solution was stirred at 41°C for 5 minutes before tert-butyl(hex-5-enoxy)diphenylsilane (170 mg, 0.5 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K\(_2\)CO\(_3\) (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO\(_4\), filtered, and reduced in vacuo. Purification via flash silica gel chromatography (10-40% Et\(_2\)O/hexanes) gave (5S,E)-1-tert-butyl 2-(6-(tert-
butyldiphenylsilyloxy)hex-2-enyl) 5-(benzyloxymethyl)pyrrolidine-1,2-dicarboxylate as a pail oil. The crude selectivities are >20:1 L:B (determined from crude $^1$H NMR) and 15:1 $E$:Z (determined after hydrolysis to ($E$)-6-(tert-butyldiphenylsilyloxy)hex-2-en-1-ol). Run 1 (171.0 mg, 0.26 mmol, 51%); run 2 (184.5 mg, 0.28 mmol, 55%); run 3 = (168.0 mg, 0.25 mmol, 50%). Average = 52% yield. Rf = 0.2 (5% EtOAc/hexanes). Note: NMRs are a mixture of two diastereomers and two rotamers: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J$ = 7.5 Hz, 4H), 7.46-7.26 (m, 11H), 5.82-5.70 (m, 1H), 5.62-5.50 (m, 1H), 4.64-4.46 (m, 4H), 4.36-4.05 (m, 2H), 3.74-3.35 (m, 4H), 2.40-1.85 (m, 6H), 1.70-1.62 (m, 2H), 1.43 (s, 3H), 1.41 (s, 6H), 1.07 (s, 9H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 173.3, 172.8, 154.4, 154.0, 138.7, 138.5, 136.7, 136.2, 135.7, 134.1 (2 peaks), 129.8, 128.6, 128.5, 127.8, 127.7, 127.6, 124.0 (2 peaks), 80.3, 80.2, 73.4, 71.2, 70.9, 65.8, 63.3, 60.3, 59.9, 57.6, 57.4, 31.9 (2 peaks), 29.1, 28.8 (2 peaks), 28.6, 28.5, 28.0, 27.3, 27.0, 26.5, 19.4. IR (neat, cm$^{-1}$) 2962, 2931, 2860, 1744, 1700. HRMS (ESI) m/z calculated for $C_{40}H_{54}NO_6Si$ [M + H]$^+$: 672.3720; found: 672.3737. $[\alpha]^{26}_D$ = -35.6$^\circ$ (c=1.0, CHCl$_3$). Spectral data matches previously reported data.$^{66}$

![Chemical Structure](attachment:image.png)

**(E)-5-(tert-butyldimethylsilyloxy)pent-2-enyl 2-(3,4-difluorophenyl)acetate (27)**

To a 4 mL borosilicate vial was added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere, followed by phenyl benzoquinone (368 mg, 2.0 mmol, 2 equiv.), benzoic acid (366 mg, 3 mmol, 3 equiv.), two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (100 µL, 1.1 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon® stir bar. This solution was stirred at 41°C for 5 minutes before (S)-(2-(4-methoxybenzyl)oxy)hex-5-enyloxy)(tert-
butyl)dimethylsilane (350 mg, 1 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K₂CO₃ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (5% EtOAc/hexanes) gave (E)-5-(tert-butyldimethylsilyloxy)pent-2-enyl 2-(3,4-difluorophenyl)acetate as a clear thick oil. The crude selectivities determined by ¹H NMR are L:B >20:1 and E:Z >20:1. Run 1 (287.0 mg, 0.61 mmol, 61%); run 2 (291.0 mg, 0.62 mmol, 62%); run 3 = (306.0 mg, 0.65 mmol, 65%) Average = 63% yield. R_f= 0.1 (5% Et₂O/hexanes). ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, J = 8.0, Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.25 (d, J = 9.2 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.87 (dt, J = 15.2, 7.2 Hz, 1H), 5.73 (dt, J = 15.2, 6.4 Hz, 1H), 4.76 (d, J = 6.4 Hz, 2H), 4.45 (s, 2H), 3.88 (app quin., J = 5.6, 1H), 3.80 (s, 3H), 3.40-3.30 (m, 2H), 2.45-2.35 (m, 1H), 2.30-2.20 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 159.4, 133.0, 132.5, 130.7, 130.6, 129.8, 129.4, 128.5, 126.6, 114.0, 74.1, 73.2, 71.2, 65.7, 55.5, 38.0, 26.0, 18.4, -4.2, -4.5. IR (neat, cm⁻¹) 2959, 2926, 2857, 1720, 1270, 1249. HRMS (CI⁺) m/z calculated for C₂₇H₃₇O₅Si [M-H]: 469.24103; found: 469.24112. [α]²⁷_D = -10.9° (c=1.0, CHCl₃). (-)-8 was found to be >99% ee after TBS ether deprotection to form the free alcohol followed by SCF analysis (mobile phase CO₂, column chiralpak-OD, 7% MeOH, 3.0 mL/min, 125 barr) with retention times of 15.0 min for (+)-8 (free alcohol) and 16.0 min for (-)-8 (free alcohol). Compound has previously been synthesized, however; no spectral data was provided.
(E)-5-(2-((4-bromobenzyloxy)methoxy)cyclohexyl)pent-2-enyl 2,4-dichlorobenzoate (32)

To a 2 mL borosilicate vial was added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (15 mg, 0.03 mmol, 10 mol%) under argon atmosphere, followed by phenyl benzoquinone (122 mg, 0.66 mmol, 2 equiv.), 2, 4-dichlorobenzoic acid (254 mg, 1.3 mmol, 4 equiv.), one 4Å molecular beads (20 mg) in one portion under ambient atmosphere. DMSO (35 µL, 0.36 mmol, 1.1 equiv.), CH$_2$Cl$_2$ (170 µL), and DIPEA (40 µL, 0.23 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before 1-bromo-4-(((2-(pent-4-enyl)cyclohexyloxy)methoxy)methyl)benzene (122 mg, 0.33 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO$_4$, filtered, and reduced in vacuo. Purification via flash silica gel chromatography (5% Et$_2$O/hexanes) gave (E)-5-(2-((4-bromobenzyloxy)methoxy)cyclohexyl)pent-2-enyl 2,4-dichlorobenzoate as a clear thick oil. MPLC was required to separate the branched ester (1% EtOAc:Hx). The crude selectivities determined by $^1$H NMR are L:B 8:1 and E:Z 15:1. Run 1 (111.0 mg, 0.20 mmol, 60%); run 2 (109.0 mg, 0.19 mmol, 59%); run 3 = (117.0 mg, 0.21 mmol, 63%) Average = 61% yield. (15:1 E:Z and >20:1 L:B after silica column purification). R$_f$ = 0.1 (10% Et$_2$O/pentane). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.80-7.74 (m, 1H), 7.50-7.40 (m, 3H), 7.30-7.24 (m, 1H), 7.20 (d, J = 6.4 Hz, 2H), 5.86 (dt, J = 15.0, 7.0 Hz, 1H), 5.64 (dt, J = 15.5, 6.5 Hz, 1H), 4.90-4.84 (m, 2H), 4.75 (d, J
= 6.5 Hz, 2H), 4.73-4.68 (m, 1H), 4.57 (s, 2H), 3.26-3.16 (m, 1H), 2.24-2.14 (m, 1H), 2.12-1.98 (m, 2H), 1.94-1.82 (m, 2H), 1.73 (br s, 1H), 1.63 (br d, J = 10.0 Hz, 1H), 1.42-1.30 (m, 1H), 1.30-1.10 (m, 4H), 1.00-0.86 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.8, 138.5, 137.7, 137.2, 135.1, 132.7, 131.7, 131.2, 129.6, 128.7, 127.2, 123.4, 121.7, 93.6, 80.7, 69.0, 66.7, 42.9, 32.4, 31.6, 30.4, 29.7, 25.4, 24.8. IR (neat, cm\(^{-1}\)) 3093, 3029, 2929, 2857, 1732, 1586. HRMS (Cl) m/z calculated for C\(_{26}\)H\(_{30}\)O\(_4\)BrCl\(_2\) [M + H\(^+\)]: 555.07045; found: 555.07092. Compound has previously been synthesized, however; no spectral data was provided.

\((S,E)\)-4-(6-oxo-1,3,5-dioxazepan-5-yl)but-2-enyl 2-(tert-butoxycarbonylamino)-3-phenylpropanoate (38)

To a 2 mL borosilicate vial was added Pd(CH\(_3\)CN\(_4\))(BF\(_4\))\(_2\) (11.1 mg, 0.025 mmol, 10 mol%) under argon atmosphere, followed by phenyl benzoquinone (97 mg, 0.5 mmol, 2 equiv.), Boc-L-phen alanine (100 mg, 0.38 mmol, 1.5 equiv.), one 4Å molecular beads (20 mg) in one portion under ambient atmosphere. DMSO (25 \(\mu\)L, 0.29 mmol, 1.1 equiv.), CH\(_2\)Cl\(_2\) (125 \(\mu\)L), and DIPEA (30 \(\mu\)L, 0.18 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon\(^\circledR\) stir bar. This solution was stirred at 41°C for 5 minutes before homo-allylic lactam (77.0 mg, 0.25 mmol, 1 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with 1:1 diethyl ether:hexanes (50 mL) and washed with 5% K\(_2\)CO\(_3\) (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO\(_4\), filtered, and reduced \textit{in vacuo}. Purification via flash silica gel chromatography (10-40% Et\(_2\)O/hexanes) gave
(S,E)-4-(6-oxo-1,3,5-dioxazepan-5-yl)but-2-enyl 2-(tert-butoxycarbonylamino)-3-phenylpropanoate as a clear oil. The crude selectivities were determined to be >20:1 L:B (based on crude ¹H NMR) and 17:1 E:Z (based on hydrolysis of the product and examination of the corresponding alcohol by ¹H NMR). Run 1 (84.7 mg, 0.15 mmol, 59%); run 2 (86.1 mg, 0.15 mmol, 60%); run 3 = (28.5 mg, 0.05 mmol, 62%). Average = 60% yield. R_f = 0.23 (50% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.20 (m, 3H), 7.13 (d, J = 7.0 Hz, 2H), 5.82-5.54 (m, 2H), 5.02-4.92 (m, 1H), 4.64-4.52 (m, 3H), 4.20-3.92 (m, 4H), 3.58-3.50 (m, 2H), 3.48-3.36 (m, 4H), 3.36-3.24 (m, 2H), 3.14-3.00 (m, 2H), 1.80-1.24 (m, 25H). Note: Rotamer peaks are present in the ¹³C NMR. ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 169.9, 169.5, 155.3, 136.2, 130.8, 130.6, 129.6, 129.5, 128.8, 127.3, 126.3, 125.5, 80.0, 71.9, 71.6, 70.9, 70.3, 70.2 (2 peaks), 70.2, 65.3, 64.9, 54.7, 47.8, 47.6, 46.7, 45.1, 38.6, 29.6, 28.8 (2 peaks), 28.6, 28.5, 28.2, 27.6, 27.5, 27.2, 26.8 (2 peaks), 26.0, 25.8, 25.2, 24.4, 24.3. IR (neat, cm⁻¹) 3443, 3324, 2932, 2859, 1742, 1715, 1645. HRMS (ESI) m/z calculated for C₃₂H₅₁N₂O₇ [M + H]⁺: 575.3696; found: 575.3694. [α]²⁰D = +4.1° (c=0.7, CHCl₃). Spectral data matches previously reported data.⁶⁹

Table 3 Procedures:

2004 JACS Procedure: To a 4 mL borosilicate vial was first added Pd(OAc)₂ (11.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere. The following reagents were then added in one portion under ambient atmosphere: benzoquinone (108 mg, 1.0 mmol, 2 equiv.) and 4Å molecular powder (108 mg). Finally, DMSO (1.5 mL, 1.65 g, 21 mmol, 42 equiv.), AcOH (1.5 ml, 1.57g, 26 mmol, 52 equiv.), and starting material (0.5 mmol, 1.0 equiv.) were added sequentially via glass syringe followed by a Teflon© stir bar. The vial was then capped and
stirred at 41°C for 72 hours. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) [Note 1]. The solution was diluted with diethyl ether (50 mL) and washed with 5% K₂CO₃ (aq.) solution twice [Note 2]. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification was achieved via flash silica gel chromatography. Notes: (1) The excess quinone may be reduced by addition of solid Na₂SO₃ (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5% K₂CO₃ (aq.) solution. The resulting biphasic mixture is then stirred rapidly for 30 minutes before continuing with the extraction. (2) If an inseparable emulsion forms, filter the solution through a pressed pad of celite with 20-30 mL diethyl ether.

2004 JACS Procedure with 3 equiv. acetic acid (0.33M): To a 4 mL borosilicate vial was first added Pd(OAc)₂ (11.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere. The following reagents were then added in one portion under ambient atmosphere: benzoquinone (108 mg, 1.0 mmol, 2 equiv.) and 4Å molecular powder (108 mg). Finally, DMSO (1.5 mL, 1.65 g, 21 mmol, 42 equiv.), AcOH (86 µl, 90.2 mg, 1.5 mmol, 3 equiv.), and starting material (0.5 mmol, 1.0 equiv.) were added sequentially via glass syringe followed by a Teflon© stir bar. The vial was then capped and stirred at 41°C for 72 hours. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) [Note 1]. The solution was diluted with diethyl ether (50 mL) and washed with 5% K₂CO₃ (aq.) solution twice [Note 2]. The organic layer was dried with MgSO₄, filtered, and reduced in vacuo. Purification was achieved via flash silica gel chromatography. Notes: (1) The excess quinone may be reduced by addition of solid Na₂SO₃ (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5% K₂CO₃ (aq.) solution. The resulting biphasic mixture is then stirred
rapidly for 30 minutes before continuing with the extraction. (2) If an inseparable emulsion forms, filter the solution through a pressed pad of celite with 20-30 mL diethyl ether.

2004 *JACS* Procedure with 3 equiv. acetic acid (0.17M): To a 4 mL borosilicate vial was first added Pd(OAc)$_2$ (11.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere. The following reagents were then added in one portion under ambient atmosphere: benzoquinone (108 mg, 1.0 mmol, 2 equiv.) and 4Å molecular powder (108 mg). Finally, DMSO (2.91 mL, 3.21 g, 40.8 mmol, 82 equiv.), AcOH (86 µL, 90.2 mg, 1.5 mmol, 3 equiv.), and starting material (0.5 mmol, 1.0 equiv.) were added sequentially via glass syringe followed by a Teflon© stir bar. The vial was then capped and stirred at 41°C for 72 hours. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) [Note 1]. The solution was diluted with diethyl ether (50 mL) and washed with 5% K$_2$CO$_3$ (aq.) solution twice [Note 2]. The organic layer was dried with MgSO$_4$, filtered, and reduced *in vacuo*. Purification was achieved via flash silica gel chromatography. Notes: (1) The excess quinone may be reduced by addition of solid Na$_2$SO$_3$ (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5% K$_2$CO$_3$ (aq.) solution. The resulting biphasic mixture is then stirred rapidly for 30 minutes before continuing with the extraction. (2) If an inseparable emulsion forms, filter the solution through a pressed pad of celite with 20-30 mL diethyl ether.

**New General Procedure:** To a 4 mL borosilicate vial was first added Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ (22.2 mg, 0.05 mmol, 10 mol %) under argon atmosphere. The following reagents were then added in one portion under ambient atmosphere: phenyl benzoquinone (184 mg, 1.0 mmol, 2 equiv.) and two 4Å molecular beads (50 mg). Finally, DMSO (50 µL, 0.7 mmol, 1.4 equiv.),
CH\textsubscript{2}Cl\textsubscript{2} (250 \mu\text{L}), and DIPEA (60.0 \mu\text{L}, 0.35 mmol, 0.7 equiv.), acetic acid (90 mg, 86 \mu\text{L}, 1.5 mmol, 3.0 equiv.) were added sequentially via glass syringe followed by a Teflon\textregistered stir bar. This solution was stirred at 41°C for 5 minutes before starting material (0.5 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped and stirred at 41°C for 72 hours. Upon completion as determined by NMR, the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL) \[\text{Note 1}\]. The solution was diluted with diethyl ether (50 mL) and washed with 5\% K\textsubscript{2}CO\textsubscript{3} (aq.) solution twice \[\text{Note 2}\]. The organic layer was dried with MgSO\textsubscript{4}, filtered, and reduced \textit{in vacuo}. Purification was achieved via flash silica gel chromatography. Notes: (1) The excess quinone may be reduced by addition of solid Na\textsubscript{2}SO\textsubscript{3} (2 g) to a reaction mixture diluted with 50 mL of EtOAc and 50 mL of a 5\% K\textsubscript{2}CO\textsubscript{3} (aq.) solution. The resulting biphasic mixture is then stirred rapidly for 30 minutes before continuing with the extraction. (2) If an inseparable emulsion forms, filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. Note: (1) All yield are of column purified material with >20:1 L:B. E:Z ratios did not change after silica column purification unless otherwise noted. (2) All reference numbers in the tables and figures refer to the reference numbers from the text.

\text{(E)}-5-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)pent-2-en-1-yl acetate (44) from 1,1-dimethyl (4-methylphenyl)sulfonyl(4-pentenyl)carbamate.\textsuperscript{70} \textbf{Old}: The crude selectivities were determined to be L:B = 12:1 and E:Z = 8:1 by \textsuperscript{1}H NMR. Run 1 (102.0 mg, 0.25 mmol, 51\%); run 2 (98.8 mg, 0.25 mmol, 50\%); Average = 51\% yield. (8:1 E:Z and >20:1 L:B after silica column purification). \textbf{New}: The crude selectivities were determined to be L:B = >20:1 and E:Z = 9:1 by \textsuperscript{1}H NMR. Run 1 (150.4 mg, 0.37 mmol, 75\%); run 2 (147.3 mg, 0.37 mmol, 74\%); Average = 75\% yield. (9:1 E:Z and >20:1 L:B after silica column
purification). $R_f = 0.15$ (20% EtOAc/hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 5.76 (dt, $J = 15.5$, 7.0 Hz, 1H), 5.66 (dt, $J = 15.5$, 6.0 Hz, 1H), 4.50 (d, $J = 6.0$ Hz, 2H), 3.86 (appt, $J = 7.5$ Hz, 2H), 2.50 (q, $J = 7.5$ Hz, 2H), 2.42 (s, 3H), 2.04 (s, 3H), 1.32 (s, 9H). 13$^C$ NMR (125 MHz, CDCl$_3$) $\delta$ 170.7, 150.8, 144.1, 137.4, 131.2, 129.2, 127.8, 126.8, 84.2, 64.7, 46.2, 33.0, 27.8, 21.5, 20.9. IR (neat, cm$^{-1}$) 2980, 2935, 1732. HRMS (ESI) m/z calculated for C$_{19}$H$_{27}$NO$_6$NaS [M + Na]$^+$: 420.1457; found: 420.1460.

(E)-3-(1,4-dioxaspiro[4.5]dec-6-yl)-2-propen-1-ol acetate (45) from 6-allyl-1,4-dioxaspiro[4.5]decane.$^{71}$ 

Old: The crude selectivities were determined to be L:B >20:1 and E:Z >20:1 by $^1$H NMR. Run 1 (119 mg, 0.49 mmol, 49%); run 2 (120.5 mg, 0.50 mmol, 50%); Average = 50% yield.$^{71a}$ New: The crude selectivities were determined to be L:B >20:1 and E:Z >20:1 by $^1$H NMR. Run 1 (75 mg, 0.31 mmol, 63%); run 2 (79.1 mg, 0.33 mmol, 65%); Average = 64% yield. $R_f = 0.1$ (20% EtOAc/hexanes). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.79 (dd, $J = 15.5$, 7.5 Hz, 1H), 5.60 (dt, $J = 15.5$, 6.0 Hz, 1H), 4.51 (d, $J = 6.0$ Hz, 2H) 3.96-3.80 (m, 4H), 2.34-2.26 (m, 1H), 2.04 (s, 3H), 1.76-1.60 (m, 4H), 1.58-1.34 (m, 3H), 1.18-1.12 (m, 1H). 13$^C$ NMR (125 MHz, CDCl$_3$) $\delta$ 170.8, 135.1, 125.1, 109.9, 65.3, 65.1, 64.9, 48.2, 35.2, 30.0, 24.3, 23.8, 21.0. IR (neat, cm$^{-1}$) 2937, 2885, 2864, 1739. HRMS (ESI) m/z calculated for C$_{13}$H$_{20}$O$_4$Na [M + Na]$^+$: 263.1259; found: 263.1258. Spectral data matches that previously reported.$^{16a}$

(E)-4-(2-(4-methoxyphenyl)-1,3-dioxolan-4-yl)but-2-en-1-yl acetate (46) from 2-(4-methoxyphenyl)-4-(pent-4-en-1-yl)-1,3-dioxolane.$^{72}$ Old: Run 1 (trace product); run 2 (trace product); Average <5% yield. New: The crude selectivities were
determined to be L:B = 12:1 and E:Z = 12:1 by \(^1\)H NMR. Run 1 (81.0 mg, 0.28 mmol, 55%); run 2 (73.0 mg, 0.25 mmol, 50%); Average = 53% yield. (12:1 E:Z and >20:1 L:B after silica column purification). \(R_f = 0.2\) (5% EtOAc/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(^1\)H NMR (500 MHz, CDCl\(_3\)) Major Diastereomer: δ 7.42-7.36 (m, 2H), 6.94-6.86 (m, 2H), 5.86-5.77 (m, 1H), 5.75 (s, 1H), 5.75-5.67 (m, 1H) 4.53 (d, \(J = 6.0\) Hz, 2H), 4.34-4.20 (m, 1H), 4.07 (dd, \(J = 8.0, 7.0\) Hz, 1H), 3.81 (s, 3H), 3.76 (dd, \(J = 7.5, 6.0\) Hz, 1H), 2.56-2.32 (m, 2H), 2.06 (s, 3H). Minor Diastereomer: δ 5.88 (s, 1H), 4.53 (d, \(J = 6.0\) Hz, 2H), 4.32-4.25 (m, 2H), 3.81 (s, 3H), 3.65 (dd, \(J = 8.0, 7.0\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) Major Diastereomer: δ170.7, 160.5, 130.4, 128.1, 127.8, 127.2, 113.8, 104.1, 75.9, 69.4, 64.8, 55.3, 36.6, 20.9. Minor Diastereomer: δ 160.3, 129.7, 103.3, 75.3, 70.1, 36.2. IR (neat, cm\(^{-1}\)) 3003, 2939, 2883, 2841, 1738. HRMS (ESI) m/z calculated for C\(_{16}\)H\(_{21}\)O\(_5\) [M + H]\(^+\): 293.1389; found: 293.1383.

\(\text{TBSO} \quad \text{OAc}\)

**(E)-5-((tert-butyldimethylsilyl)oxy)pent-2-en-1-yl acetate** (47) from tert-butyldimethyl(pent-4-en-1-yloxy)silane.\(^{73}\) **Old:** The crude selectivities were determined to be L:B = 4:1 and E:Z = 8:1 by \(^1\)H NMR. Run 1 (23.0 mg, 0.09 mmol, 18%); run 2 (24.0 mg, 0.09 mmol, 19%); run 3 (16.8 mg, 0.07 mmol, 13%); Average = 17% yield. (8:1 E:Z and >20:1 L:B after silica column purification).

**Old with 3 equiv. acetic acid (0.33M):** The crude selectivities were determined to be L:B = 4:1 and E:Z = 5:1 by \(^1\)H NMR. Run 1 (11.0 mg, 0.043 mmol, 9%); run 2 (12.5 mg, 0.05 mmol, 10%); Average = 10% yield. **Old with 3 equiv. acetic acid (0.17M):** The crude selectivities were determined to be L:B = 3:1 and E:Z = 5:1 by \(^1\)H NMR. Run 1 (8.9 mg, 0.035 mmol, 7%); run 2 (9.0 mg, 0.035 mmol, 7%); Average = 7% yield. **New:** The selectivities were determined to be L:B = 8:1 (crude) and E:Z = 12:1 (after column) by \(^1\)H NMR. Run 1 (79.0 mg,
0.31 mmol, 61%); run 2 (70 mg, 0.27 mmol, 54%); Average = 58% yield. (12:1 E:Z and >20:1 L:B after silica column purification). R<sub>f</sub> = 0.1 (10% Et<sub>2</sub>O/hexanes). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) \( \delta 5.77 \text{ (dt, } J = 15.5, 7.0 \text{ Hz, 1H}), 5.63 \text{ (dt, } J = 15.5, 6.0 \text{ Hz, 1H}), 4.51 \text{ (d, } J = 6.5 \text{ Hz, 2H}), 3.65 \text{ (t, } J = 7.0 \text{ Hz, 2H}), 2.27 \text{ (dq, } J = 7.0 \text{ Hz, 2H}), 2.05 \text{ (s, 3H)}, 0.88 \text{ (s, 9H)}, 0.04 \text{ (s, 6H) }. \)<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) \( \delta 170.8, 132.8, 125.7, 65.1, 62.4, 35.8, 25.9, 21.0, 18.3, -5.3. \) IR (neat, cm<sup>-1</sup>) 2953, 2931, 2897, 2858, 1743. HRMS (ESI) m/z calculated for C<sub>13</sub>H<sub>27</sub>O<sub>3</sub>Si [M + H]<sup>+</sup>: 259.1729; found: 259.1720.

\[
\begin{align*}
\text{OAc} & \quad \text{(E)-5-(trityloxy)pent-2-en-1-yl acetate } (48) \text{ from ((pent-4-en-1-yloxy)methanetriyl)tribenzene.}\end{align*}
\]

**Old:** The crude selectivities were determined to be L:B = 4:1 and E:Z = 8:1 by <sup>1</sup>H NMR. Run 1 (63.0 mg, 0.16 mmol, 32%); run 2 (67.1 mg, 0.18 mmol, 35%); Average = 34% yield. (8:1 E:Z and >20:1 L:B after silica column purification). **New:** The crude selectivities were determined to be L:B = 10:1 and E:Z = 11:1 by <sup>1</sup>H NMR. Run 1 (133.0 mg, 0.34 mmol, 69%); run 2 (127.0 mg, 0.33 mmol, 66%); Average = 68% yield. (11:1 E:Z and >20:1 L:B after silica column purification). R<sub>f</sub> = 0.1 (10% Et<sub>2</sub>O/hexanes). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) \( \delta 7.48-7.44 \text{ (m, 6H)}, 7.34-7.29 \text{ (m, 6H)}, 7.27-7.22 \text{ (m, 3H)}, 5.82 \text{ (dt, } J = 15.5, 7.0 \text{ Hz, 1H}), 5.65 \text{ (dt, } J = 15.5, 6.0 \text{ Hz, 1H}), 4.53 \text{ (dd, } J = 7.0 \text{ Hz, 2H}), 3.15 \text{ (t, } J = 6.5 \text{ Hz, 2H}), 2.40 \text{ (q, } J = 6.0 \text{ Hz, 2H}), 2.06 \text{ (s, 3H) }. \)<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) \( \delta 170.7, 144.2, 132.9, 128.6, 127.7, 126.9, 125.7, 86.4, 65.0, 62.9, 33.0, 20.9. \) IR (neat, cm<sup>-1</sup>) 3086, 3059, 3024, 2931, 2872, 1739. HRMS (ESI) m/z calculated for C<sub>26</sub>H<sub>26</sub>O<sub>3</sub>Na [M + Na]<sup>+</sup>: 409.1780; found: 409.1784.

Selected Starting Material

\[
\begin{align*}
\text{TBSO} & \quad \text{tert-Butyldimethyl(pent-4-enyloxy)silane } (\text{starting material for 17 and 18}) \end{align*}
\]
A 200mL round bottom flask was added 4-penten-1-ol (2.5 g, 58.0 mmol), THF (100 mL) and a Teflon® stir bar. The solution was cooled to 0°C and NaH (2.8 g, 4.0 equiv.) was added by portions. The reaction was allowed to stir for 30 minutes. After the solution turns a yellow color, t-Butyl(dimethyl)silyl chloride (TBSCl, 5.8 g, 1.5 equiv.) and tetrabutyl ammonium iodide (TBAI, 500 mg) were added. The reaction was monitored by TLC until completion (~2 hrs). The reaction was quenched with sat. aq. NH₄Cl solution (10 mL) and the organics extracted with water. The organic layer was dried (MgSO₄), filtered, and reduced in vacuo. Purification via flash silica gel chromatography (1% Et₂O/hexanes) gave 7.7 g of tert-butyldimethyl(pent-4-enyloxy)silane as a clear oil (~90% yield). Previously prepared J. Chem. Soc. Perk. Trans. 2000, I, 1915; Tetrahedron Lett. 1995, 36, 819. Rf = 0.3 (1% Et₂O/hexanes). ¹H NMR (500 MHz, CDCl₃) δ 5.86-5.78 (m, 1H), 5.02 (d, J = 17.0 Hz, 1H), 4.95 (d, J = 14.5 Hz, 1H), 3.62 (t, J = 7.0 Hz, 2H), 2.10 (app. q, J = 7.0 Hz, 2H), 1.62 (app. q, J = 6.5, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

Hex-5-enoic acid 2-oxo-2-phenyl-ethyl ester (starting material for (+)-20) To a 100mL flame dried round bottom flask was added phenacylbromide (2.4 g, 12 mmol, 1.2 equiv.), potassium fluoride (1.75 g, 30 mmol, 2.5 equiv.), DMF (20 mL) and Teflon® stir bar. To this suspension was added 5-hexenoic acid (1.14 g, 10 mmol) in DMF (10 mL) and the reaction was stirred for 2 hours at room temperature. The reaction was diluted with diethyl ether (200 mL) and washed with a saturated sodium bicarbonate solution (2 x 50 mL). The organic layers were collected, dried (MgSO₄), filtered, and concentrated in vacuo. Purification via flash silica gel chromatography (5% Et₂O/hexanes) gave 2 g of hex-5-enoic acid 2-oxo-2-phenyl-ethyl ester as a clear oil (~95% yield). Rf = 0.1 (2% Et₂O/hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.91 (app. d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.0 Hz,
1H), 7.48 (t, J = 8.0 Hz, 2H), 5.85-5.75 (m, 1H), 5.34 (s, 2H), 5.06 (d, J = 17.5 Hz, 1H), 5.00 (d, J = 10.0 Hz, 1H), 2.51 (t, J = 7.5 Hz, 2H), 2.16 (q, J = 7.5 Hz, 2H), 1.82 (quin., J = 8.0 Hz, 2H).

13C NMR (125 MHz, CDCl3) δ 192.5, 173.3, 137.9, 134.5, 134.1, 129.1, 128.0, 115.7, 66.1, 33.4, 33.2, 24.2. IR (neat, cm⁻¹) 3068, 2977, 2936, 2869, 1745, 1705. HRMS (ESI) m/z calculated for C14H17O3 [M + H]⁺: 233.1178; found: 233.1171.

**Tert-butyl(hex-5-enyloxy)diphenylsilane from 5-hexen-1-ol (26)**

To a 200 mL round bottom flask was added 5-hexen-1-ol (5.0 g, 50.0 mmol), THF (100 mL) and a Teflon® stir bar. The solution was cooled to 0°C and sodium hydride (2.4 g, 100 mmol, 2 equiv.) was added portionwise. The solution was allowed to stir at room temperature for 0.5 hr. tert-Butyldiphenylchlorosilane (15.0 g, 55.0 mmol) and tetrabutylammoniumiodide (1.8 g, 5.0 mmol) were added and the reaction was monitored by TLC until all starting material was consumed. The reaction was quenched with 5.0 ml ammonium chloride solution (sat. aq.) and diluted with 200 ml of diethyl ether. The organics were extracted with from water, dried (MgSO₄), filtered, and reduced in vacuo. Purification via flash silica gel chromatography (1% Et₂O/hexanes) gave 15.0 g of tert-butyl(hex-5-enyloxy)diphenylsilane as a clear oil (97% yield). Rf = 0.3 (1% Et₂O/hexanes). 1H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 7.6 Hz, 4H), 7.46-7.34 (m, 6H), 5.80 (m, 1H), 5.02-4.92 (m, 2H), 3.67 (t, J = 6.4 Hz, 2H), 2.04 (app. q, J = 7.2 Hz, 2H), 1.63-1.42 (m, 4H), 1.05 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 139.2, 135.8, 134.3, 129.7, 127.8, 114.6, 64.0, 33.7, 32.2, 27.1, 25.3, 19.5. IR (neat, cm⁻¹) 3071, 3050, 2998, 2931, 2858. HRMS (ESI) m/z calculated for C22H31OSi [M + H]⁺: 339.21443; found: 339.21422.

(S)-(2-(4-methoxybenzylloxy)hex-5-enyloxy)(tert-butyl)dimethylsilane ((-)-
Previously made in 3 steps and 71% overall yield. Using the same method this material can be prepared in 2 steps from now commercially available tert-Butyldimethylsilyl (R)-(−)-glycidyl ether with 91% overall yield. Rf = 0.5 (5% Et2O/hexanes). 1H NMR (500 MHz, CDCl3) δ 7.28-7.21 (m, 2H), 6.90-6.85 (m, 2H), 5.82 (m, 1H), 5.04-4.97 (m, 1H), 4.96-4.91 (m, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.88-3.30 (m, 3H), 2.34-2.00 (m, 2H), 1.76-1.46 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). HRMS (Cl+) m/z calculated for C₅₀H₃₃O₃Si [M-H]+: 349.21991 observed: 349.21974. [α]D₂₀ = -21.4° (c=1.0, CHCl₃). Spectral data matched previously reported data.

1-bromo-4-(((2-(pent-4-enyl)cyclohexyloxy)methoxy)methyl)benzene from 2-(pent-4-enyl)cyclohexanol (37) To a 100 mL round bottom flask was added 2-(pent-4-enyl)cyclohexanol (165.0 mg, 1.0 mmol, 1 equiv.), THF (20 mL) and a Teflon stir bar. The solution was cooled to 0°C. Potassium bis(trimethylsilyl)amide (5.0 ml, 0.5 M in toluene, 2.5 mmol, 2.5 equiv.) was added dropwise and the solution was allowed to stir at room temperature for 1 hr. TBAI (38.0 mg, 0.1 mmol) and 1-bromo-4-(bromomethyl)benzene (600 mg, 2.5 mmol) was added as a solution in 10 mL THF. The reaction was allowed to stir overnight. The reaction was quenched with 5 ml saturated aqueous NH₄Cl solution and diluted with diethyl ether. The organics were extracted with from water, dried (MgSO₄), filtered, and concentrated in vacuo. Purification via flash silica gel chromatography (1% Et₂O/hexanes) gave 329mg of 1-bromo-4-(((2-(pent-4-enyl)cyclohexyloxy)methoxy)methyl)benzene as a clear oil (>90% yield). Rf = 0.2 (1% Et₂O/hexanes). 1H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.86-5.74 (m, 1H), 5.02-4.94 (m, 1H), 4.95-4.90, (m, 1H), 4.87 (d, J = 6.8 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.58 (d, J = 4.5 Hz, 2H), 3.23-3.18 (m, 1H), 2.10-0.80
(m, 15H). $^{13}$C NMR (100 MHz, CDCl$_3$) ? 139.3, 137.3, 131.7, 129.6, 121.7, 114.5, 93.5, 80.7, 68.9, 43.3, 34.5, 32.4, 32.0, 30.4, 26.2, 25.5, 24.9. HRMS (CI) m/z calculated for C$_{19}$H$_{28}$O$_2$Br [M + H]$^+$: 367.12726; found: 367.12810.

4-(but-3-enyl)-1,9-dioxa-4-azacyclocloheptadecan-3-one (43)$^{78}$

To a flamed 200 mL round bottom flask was added 1,9-dioxa-4-azacycloheptadecan-3-one$^{13}$ (260.0 mg, 1.0 mmol), THF (2.5 mL) and a Teflon© stir bar. The solution was cooled to 0°C. NaH (120.0 mg, 5.0 mmol, 5.0 equiv.) was added in one portion and the solution was allowed to stir for 0.5 hrs. 1,4-Diiodobutane (1.55 g, 5.0 mmol, 5.0 equiv.) was added in THF (2.5 mL) and the reaction was headed to 80°C in a sealed tube and stirred for 48 hours. [Note: TLC in 50% ethyl acetate:hexanes (CAM charred) should show complete consumption of starting materials. If two less polar spots are visible, dilute the reaction with 20 mL of benzene and add 15 equiv. DBU. Reseal the reaction vessel and heat to 80°C for 30 minutes. Extract with 1M H$_3$PO$_4$.] The reaction was quenched with 5.0 ml saturated NH$_4$Cl and diluted with 200 ml of ethyl acetate. The organics were extracted with from water (100 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification via flash silica gel chromatography (50% EtOAc/hexanes) gave homo-allylic lactam as a clear oil. Average Yield = 67%. Run 1 (210.0 mg, 0.7 mmol, 70%), run 2 (204.0 mg, 0.68 mmol, 68%), run 3 (106.0 mg, 0.35 mmol, 64%). $R_f$ 0.5 (50% EtOAc/hexanes). Note: Rotamers are present in both NMR spectrum. $^1$H NMR (500 MHz, CDCl$_3$) ? 5.85-5.68 (m, 1H), 5.12-4.98 (m, 2H), 4.12 (s, 1H), 4.06 (s, 1H), 3.58 (m, 10H), 2.34-2.24 (m, 2H), 1.80-1.20 (m, 16H). $^{13}$C NMR (100 MHz, CDCl$_3$) ? 169.8, 169.4, 135.8, 134.6, 117.9, 116.8, 71.8, 71.7, 71.5, 71.1, 70.3, 70.2, 70.2, 48.3, 46.1, 45.5, 44.7, 33.4, 32.2, 31.2, 30.6, 29.7, 28.9, 28.8, 28.6, 28.2, 27.7, 27.6, 27.2, 27.0, 26.9,
26.0, 25.9, 25.1, 24.5, 24.4. IR (neat, cm\(^{-1}\)) 2930, 2857, 1740, 1646. HRMS (ESI) m/z calculated for C\(_{18}\)H\(_{34}\)NO\(_3\) [M + H]\(^+\): 312.2539; found: 312.2542.

2.5 REFERENCES


Under a C-H cleavage reaction manifold, high linear regioselectivity may be rationalized by outer sphere functionalization at the least sterically hindered position of a cationic p-allylPd(DMSO)₂ intermediate. However, we cannot exclude the possibility of an alternative, albeit unprecedented, mechanism involving anti-Markovnikov oxy-palladation followed by regioselective b-hydride elimination. Significantly, when using catalytic amounts of a bidentate bis-sulfoxide ligand, high branched regioselectivity for ester formation is observed. Mechanistic studies suggest this arises from inner sphere functionalization from an electronically dissymmetric p-allylPd(BQ)carboxylate species.


CHAPTER 3: USING OXYGEN AS THE TERMINAL OXIDANT FOR THE LINEAR
ALLYLIC C-H OXIDATION AND AMINATION REACTIONS

3.1 INTRODUCTION

Our Pd(II)/bis-sulfoxide catalyzed allylic C-H activation reactions are of immediate use
to synthetic chemists whose goals are to find rapid and convenient routes to intermediates of
natural products and drug candidates. On large scale however, the challenges of high catalyst
loadings (5-10 mol%) relative to Pd(0) methods \(^{79,80}\) and the generation of stoichiometric waste
products from the oxidant must be addressed. Pioneering studies showed that under certain
reaction conditions, molecular oxygen could serve as the terminal oxidant. \(^{81}\) The use of
molecular oxygen as a terminal oxidant could address both problems. \(^{82}\) To date, many of the
molecular oxygen systems reported for allylic oxidations suffer from very specific drawbacks
including: elevated temperatures (60-80\(^\circ\)C) that can negatively affect olefin isomer (E:Z)
constitutional isomer (linear:branched) selectivity, high pressures of \(O_2\) (up to 10 atmospheres)
specialized reactors for safe reaction setup, \(^{83}\) and most often the need for solvent quantities of
nucleophile. \(^{84}\) To circumvent these issues we hypothesized that the addition of an effective co-
catalyst capable of shuttling electrons between catalytic DHQ and molecular oxygen under mild
conditions could be used for our C-H activation reactions and allow us to realize a more ideal
linear allylic oxidation reaction (Scheme 8). \(^{85}\) Tomokazu “Tomo” Mizuno verified and
generated results involving the Co(II) Salophen reaction. Jeff Slayer prepared a number of
starting materials and repeated critical results.
3.2 RESULTS AND DISCUSSION

3.2.1 REOXIDATION CATALYST AND OPTIMIZATION

Several complexes that allow the use of one atmosphere of oxygen as the terminal oxidant in several allylic C-H functionalizations (Table 4) were identified, with Co(II)Salophen preforming the best. Importantly, this catalytic reoxidation manifold maintains modest yields with unactivated substrates and very high selectivities at substantially decreased palladium catalyst loadings (10 $\rightarrow$ 2.5 mol%, Table 4).

Table 4: Reoxidation Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>ReOx. Cat.</th>
<th>Yield</th>
<th>L:B</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>3%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>Co(II)Salophen</td>
<td>30%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>Co(II)TPP</td>
<td>19%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>β-Ketonaminato Co(II)</td>
<td>6%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>Co(II)Salen</td>
<td>19%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>FePC</td>
<td>17%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>7</td>
<td>Mn(II)TPP</td>
<td>3%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>8</td>
<td>MnO2</td>
<td>6%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>9</td>
<td>HMVP</td>
<td>&lt;1%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>VO(acac)$_2$</td>
<td>23%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>11</td>
<td>Co(II)BTC</td>
<td>3%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
Simple optimization of the requisite exogenous base and molarity (Table 5, entry 1 to 5) allows for an efficient linear allylic amination (LAA) using as little as 2.5 mol% Pd catalyst and 2 equivalents of nucleophile (Table 5, entry 6). Alternatively 5 mol% Pd catalyst can be used and only 1.5 equivalents of nucleophile (Table 5, entry 7) to give 65% yield and very high selectivity with an unactivated substrate. Notably, the reaction works well using commercial cobalt catalyst (Table 5, entry 7 and 8). Although as little as 1.1 equivalents of nucleophile can be used it requires additional palladium catalyst for sufficient product formation (Table 5, entry 9 and 10).

An interesting initial result (Table 5, entry 11) shows that air can function as an oxygen source but conversion is lower than the equivalent reaction under an oxygen atmosphere. Due to the practical impact of an oxidation reaction that uses air as the terminal oxidant source, further study of this result is warranted. As control experiments, removal of quinone and oxygen from the reaction shows a dramatic reduction of reactivity (Table 5, entry 12 and 13). It should be
noted that decreasing Co(II) Salophen loading to 1% and 0.5% has only a minimal effect of the productivity of this reaction (Table 5, entries 15 and 16).

3.2.2 SUBSTRATE SCOPE

Table 6: Activated Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
<th>L:B</th>
<th>E:Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>72%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>61%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>49%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>59%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>88%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>90%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Image" /></td>
<td>58%</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

* Using only 2.5% White Catalyst

Complex aromatics are good substrates and give high yields with almost no detectable amount of the branched or Z-isomers by $^1$H NMR (Table 6). Although simple protected allyl
benzenes make good substrates (Table 6, entry 1, safrole), free phenols are also tolerated (Table 6, entry 2). It should be noted that a substation reduction in catalyst loading (to only 2.5 mol% White Catalyst) still gave a moderate yield of 50% with the same high selectivities. Even nitrogen containing compounds are good substrates; a triazole, capable of binding the electrophilic Pd(II) catalyst, is tolerated and gives acceptable yields (Table 6, entry 3) and a protected indole gives good yield (Table 6, entry 4). Silane protected phenols are well tolerated under these mild conditions (Table 6, entry 5) and gives a very good yield of 88%. An aryl triflate, often used as a coupling partner in Pd(0) catalyzed cross-couplings, is well tolerated and gives an excellent yield of the aminated product (Table 6, entry 6). Similarly, the 4-bromo-allyl-benzene, another substrate incompatible with Pd(0) processes, gave a reasonable isolated yield of 58% with excellent L:B and E:Z selectivities (Table 6, entry 7).

Less reactive aliphatic substrates give only low to moderate yields and may require slightly higher catalyst loadings for effective allylic amination (Table 7). Although some early studies suggested that terminal tert-butyl dimethyl silane (TBS) protected alcohols are sensitive to the Co enhanced reaction conditions resulting in very low yield, tert-butyl diphenyl silane protected alcohols are tolerated (Table 7, entry 1). Although the benzyl protected alcohol gave good conversion (>60%), a low yield was obtained (Table 7, entry 2). Co(II) catalyzed decomposition of the product or starting material might explain the discrepancy between conversion and yield; however, additional study of this process is required to prove this.
3.2.3 OTHER METHODS AND LARGE SCALE SYNTHESIS

The same quinone reoxidation process can be applied to other systems that do not require high quinone loadings for functionalization. Using almost identical reaction conditions the intramolecular amination process gave favorable results (Scheme 9); this allows for dramatic simplification of the purification process by removing the majority of the requisite quinone and quinone byproducts. Although this method is still un-optimized it shows promise for large scale application of the intra-molecular branched allylic amination.

Scheme 9: Intramolecular Reaction

Application of the same cobalt/quinone reoxidation cycle in the general linear allylic esterification method was also successful and demonstrates the high compatibility of the cobalt/quinone/O₂ system with a variety of Pd(II) oxidation processes (Scheme 10). Although
substantial optimization might be required, this method would allow for substantial simplification for the work-up of the linear allylic oxidation.

Scheme 10: Intramolecular Reaction

Finally, the new re-oxidation methodology would allow for the large scale synthesis of complex intermediates with minimal purification and excellent catalytic efficiency. One such example is the construction of β-C-glycosides containing oxygen or nitrogen. Our linear allylic C-H oxidation chemistry could allow large scale synthesis of the requisite aminated\textsuperscript{87} or oxygenated\textsuperscript{88} intermediates (Scheme 11).

Scheme 11: Rapid synthesis of β-C-glycosides

3.3 CONCLUSION

In conclusion, the preliminary development of a linear allylic amination reaction with oxygen as terminal oxidant is demonstrated. This process proceeds with good substrate scope and more importantly seems to be translatable to other reaction Pd(II) catalytic methods
developed in our lab. This methodology can easily be expanded to our intramolecular amination and linear allylic esterification systems; this would allow for a broadly applicable and useful modification to palladium catalyzed allylic oxidations. Potentially, this reoxidation manifold would allow large scale synthesis of allylicly oxidized intermediates using our C-H oxidation methodologies by reducing and nearly eliminating the difficulties associated with the product purification and excess oxidant removal. Additionally, further exploration and optimization might allow for a reduction in the Pd(II) catalyst loading by improving the quinone based oxidation system and eliminating possible competitive binding of the dihydroquinone byproduct and Pd(II) catalyst.

3.4 EXPERIMENTAL SECTION

General Information: All commercially obtained reagents were used as received: White Catalyst (Strem) was stored in a freezer under a argon atmosphere; all other reagents where purchased from least expensive supplier and used directly unless otherwise stated. Solvents diethyl ether (Et2O) and methylene chloride (CH2Cl2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Anhydrous N,N-dimethylformamide (DMF) (Sure/Seal) was obtained from Sigma-Aldrich and used as received. All allylic oxidation reactions were run under air with no precautions taken to exclude moisture. All other reactions were run under a balloon of argon gas unless otherwise stated. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.89 using EM reagent silica gel 60 (230-400 mesh). 1H NMR spectra were recorded on a Varian Unity 400
(400 MHz), a Varian Unity 500 (500 MHz), or a Varian Unity Inova 500NB 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, quin. = quintet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration, corresponding carbon atom. 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 77.23 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$^{-1}$). All optical rotations were determined on a Perkin Elmer 341 Polarimeter using the sodium D line (589 nm). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Medium pressure liquid chromatography (MPLC) was used in cases with difficult silica chromatography separations and consists of a prep-HPLC pump, hand-packed 12g MPLC silica column and fraction collector.

Method Notes: These notes are intended to help with the preparation of compounds not described in this communication and should be used with discretion. The reaction is dependent on concentration with an optimal range of 1M or greater. Below this threshold of concentration the reaction is dramatically slower. Stirring is crucial; appropriate stirring involves rapid steady mixing at approximately 600 rpm (achieved after 1hr at 45°C when the reaction becomes black and viscous). Due to the high viscosity of the reaction mixtures a bigger stir bar is more appropriate. The temperature is also important with an effective range of 40 to 50 °C. Much lower temperatures result in dramatically slower reactivity and the inability to form a solution. Higher temperatures result in decreased yields due to by-product formation. The TBAA catalyst is moisture sensitive and decomposes to a wet powder, easily distinguished from the white powder of good catalyst.
General Procedure: To a 5 mL round bottom flask was added, starting material (1 mmol, 1 equiv.), White Catalyst (50.2 mg, 0.1 mmol, 10 mol%), hydroquinone (11 mg, 0.1 mmol, 10 mol%), Co(II) Salophen (9.4 mg, 0.025 mmol, 2.5 mol%), nucleophile (1.5 mmol, 1.5 equiv.). Finally, TBME (1 mL, 1 M) and TBAA (18.1 mg, 0.06 mmol, 6 mol%) was added followed by a Teflon® stir bar (bigger is better as it would allow for better stirring of an very viscous mixture). A condenser was attached using a Teflon® sleeve to seal in the solvent (do not use grease as it is difficult to separate from the product). The condenser was sealed with a rubber septa and a balloon of oxygen was added through a 16-18 gauge needle. The was allowed to stir at 45°C in an oil bath for 72 hours. Upon completion as determined by NMR, the reaction was diluted with a 1:1 ethyl acetate:hexanes solution (50 ml) and plugged though a 3 to 5 cm column of silica gel. About 100 to 150 mL of a 1:1 ethyl acetate:hexanes solution was used to flush the product through the silica and separate it from the Pd and Co catalysts. [Note 1]: The solution can be diluted with diethyl ether (50 mL) and washed with 5% K₂CO₃ (aq.) solution twice to remove excess nucleophile but a plug with silica is still recommended as the Pd or Co will still be in the organic fraction. Purification was achieved via flash silica gel chromatography. [Note 2]: All yield are of column purified material with >20:1 L:B. E:Z ratios did not change after silica column purification unless otherwise noted.

Linear Allylic Amination Products:

(E)-methyl (3-cyclohexylallyl)(tosyl)carbamate (49) Spectral data matched previously reported data.

Data For Table 4:
General Procedure: To a 5 mL round bottom flask was added, allyl cyclohexane (124 mg, 1 mmol, 1 equiv.), White Catalyst (12.6 mg, 0.025 mmol, 2.5 mol %), hydroquinone (11 mg, 0.1 mmol, 10 mol%), reoxidation catalyst (0.025 mmol, 2.5 mol%), methyl-N-tosyl-carbamate (458 mg, 2 mmol, 2 equiv.). Finally, TBME (1.5 mL, 0.66 M) and DIPEA (7.76 mg, 10.5 uL, 0.06 mmol, 6 mol%) was added followed by a Teflon© stir bar (bigger is better as it would allow for better stirring of an very viscous mixture). A condenser was attached using a Teflon© sleeve to seal in the solvent. The condenser was sealed with a rubber septa and a balloon of oxygen was added through a 16-18 gauge needle. The was allowed to stir at 45°C in an oil bath for 72 hours. Upon completion the reaction was diluted with a 1:1 ethyl acetate:hexanes solution (50ml) and plugged though a 3 to 5 cm column of silica gel. About 100 to 150 mL of a 1:1 ethyl acetate:hexanes solution was used to flush the product through the silica and separate it from the Pd and Co catalysts. Product was isolated via silica column chromatography (10% EA/Hex).

Entry 1 (no reoxidation catalyst): Run 1 = 10.5 mg (3%), Run 2 = 10.4 mg (3%) yield
Entry 2 (9.4 mg Co(II) Salophen): Run 1 = 108.8 mg (31%), Run 2 = 98 mg (28%) yield
Entry 3(16.8 mg Co(II) TPP): Run 1 = 56 mg (16%), Run 2 = 77 mg (22%) yield
Entry 4 (7.1 mg Co(II) b-ketonaminate): Run 1 = 14 mg (4%), Run 2 = 27 mg (8%) yield
Entry 5 (15.1 mg Co(II) Salen): Run 1 = 73 mg (21%), Run 2 = 60 mg (17%) yield
Entry 6 (14.2 mg FePC): Run 1 = 53 mg (15%), Run 2 = 63 mg (18%) yield
Entry 7 (21.3 mg, Mn(II) TPP): Run 1 = 10 mg (3%), Run 2 = 7 mg (2%) yield
Entry 8 (2.2 mg MnO₂): Run 1 = 11 mg (3%), Run 2 = 31 mg (9%) yield
Entry 9 (39 mg HMVP): Run 1 = trace (<1%), Run 2 = trace (<1%) yield
Entry 10 (6.6 mg VO(acac)₂): Run 1 = 81 mg (23%), Run 2 = 80 mg (23%) yield
Entry 11(14.8 mg Co(II) BTC): Run 1 = 8 mg (2%), Run 2 = 10 mg (3%) yield
Data For Table 5:

General Procedure: To a 5 mL round bottom flask was added, allyl cyclohexane (124 mg, 1 mmol, 1 equiv.), White Catalyst (12.6 mg, 0.025 mmol, 2.5 mol %, or 25.1 mg, 0.05 mmol, 5 mol % or 50.2, 0.1 mmol, 10 mol %), hydroquinone (11 mg, 0.1 mmol, 10 mol%), Co(II) Salophen (9.4 mg, 0.025 mmol, 2.5 mol%), methyl-N-tosyl-carbamate (458 mg, 2 mmol, 2 equiv. or 343 mg, 1.5 mmol, 1.5 equiv. or 251 mg, 1.1 mmol, 1.1 equiv. ), finally, TBME (1.5 mL, 0.66 M or 1 mL, 1 M) and base (DIPEA 7.76 mg, 10.5 uL, 0.06 mmol, 6 mol% or DIPA 6.1 mg, 8.5 uL, 0.06 mmol, 6 mol% or TBAA 18.1 mg, 0.06 mmol, 6 mol%) was added followed by a Teflon© stir bar (bigger is better as it would allow for better stirring of an very viscous mixture). A condenser was attached using a Teflon© sleeve to seal in the solvent. The condenser was sealed with a rubber septa and a balloon of oxygen (or a balloon filled with house air or tank argon) was added through a 16-18 gauge needle. The was allowed to stir at 45°C in an oil bath for 72 hours. Upon completion the reaction was diluted with a 1:1 ethyl acetate:hexanes solution (50ml) and plugged through a 3 to 5 cm column of silica gel. About 100 to 150 mL of a 1:1 ethyl acetate:hexanes solution was used to flush the product through the silica and separate it from the Pd and Co catalysts. Product was isolated via silica column chromatography (10% EA/Hex).

Entry 1 (DIPEA, 2 eq. Nu, 0.66M): Run 1 = 98 mg (28%), Run 2 = 102 mg (29%) yield
Entry 2 (DIPA, 2 eq. Nu, 0.66M): Run 1 = 109 mg (31%), Run 2 = 98 mg (28%) yield
Entry 3 (TBAA, 2 eq. Nu, 0.66M): Run 1 = 147 mg (42%), Run 2 = 140 mg (40%) yield
Entry 4 (DIPEA, 1.5 eq. Nu, 0.66M): Run 1 = 98 mg (28%), Run 2 = 99 mg (28%) yield
Entry 5 (TBAA, 1.5 eq. Nu, 0.66M): Run 1 = 154 mg (44%), Run 2 = 147 mg (42%) yield
Entry 6 (TBAA, 1.5 eq. Nu, 1M): Run 1 = 169 mg (48%), Run 2 = 148 mg (41%) yield

Entry 7 (5% Pd, TBAA, 2 eq. Nu, 1M): Run 1 = 217 mg (62%) yield

Entry 8 (5% Pd, TBAA, 1.5 eq. Nu, 1M): Run 1 = 228 mg (65%) yield

Entry 9 (10% Pd, TBAA, 1.5 eq. Nu, 1M): Run 1 = 252 mg (72%) yield

Entry 10 (TBAA, 1.1 eq. Nu, 1M): Run 1 = 120 mg (34%) yield

Entry 11 (10% Pd, TBAA, 1.1 eq. Nu, 1M): Run 1 = 224 mg (64%) yield

Entry 12 (TBAA, 1.5 eq. Nu, 1M, Air): Run 1 = 120 mg (34%) yield

Entry 13 (TBAA, 1.5 eq. Nu, 1M, 0 mol% DHBQ): Run 1 = 48 mg (14%) yield

Entry 14 (TBAA, 1.5 eq. Nu, 1M, Argon): Run 1 = 24 mg (7%) yield

Entry 15 (TBAA, 1.5 eq. Nu, 1M, 1% Co): Run 1 = 128.5 mg (37%) yield

Entry 14 (TBAA, 1.5 eq. Nu, 1M, 0.5% Co): Run 1 = 130 mg (37%) yield

(E)-methyl (3-(benzo[d][1,3]dioxol-5-yl)allyl)(tosyl)carbamate (50) This reaction was performed using standard conditions on half scale (0.5 mmol). Run 1 = 138 mg (71%), Run 2 = 143 mg (74%), Run 3, (1 mmol scale) 2.5% White Catalyst = 194 mg (50%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. Spectral data matched previously reported data.

(E)-methyl 2-hydroxy-3-methoxy-5-(3-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)prop-1-en-1-yl)benzoate (51) This reaction was performed using standard conditions on half scale (0.5 mmol). Run 1 = 137 mg (61%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. $^1$H NMR (400 MHz, CDCl3) δ 11.03 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H),
7.41 (s, 1H), 7.32 – 7.21 (m, 2H), 7.06 (d, J = 1.7 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 6.12 (dt, J = 15.7, 6.4 Hz, 1H), 4.58 (d, J = 6.4 Hz, 2H), 3.97 – 3.87 (m, 6H), 3.71 (d, J = 0.5 Hz, 3H), 2.38 (d, J = 8.0 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.78, 152.86, 152.16, 148.82, 144.83, 136.56, 133.29, 129.74, 129.49, 128.62, 127.36, 126.50, 122.72, 119.97, 113.98, 112.49, 56.38, 54.08, 52.62, 48.99, 21.75. Spectral data matched previously reported data.

(E)-methyl (3-(3-(2H-benzo[d][1,2,3]triazol-2-yl)-2-((tert-butyldiphenylsilyl)oxy)-5-methylphenyl)allyl)(tosyl)carbamate (52) This reaction was performed using standard conditions on half scale (0.5 mmol). Run 1 = 179 mg (49%) yield with >20:1 E:Z and >20:1 L:B. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.66 – 7.39 (m, 6H), 7.39 – 7.19 (m, 9H), 7.16 (t, J = 7.5 Hz, 4H), 7.06 (d, J = 15.9 Hz, 1H), 6.03 – 5.90 (m, 1H), 4.26 (d, J = 6.3 Hz, 2H), 3.66 (d, J = 6.9 Hz, 3H), 2.41 (s, 3H), 2.31 (s, 3H), 0.80 (s, 7H), 0.73 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 152.85, 144.91, 144.78, 136.70, 135.21, 132.40, 132.01, 131.47, 130.46, 130.22, 129.74, 129.52, 128.78, 128.74, 127.69, 127.38, 126.66, 125.51, 118.36, 54.03, 48.91, 26.47, 21.86, 20.61, 20.21. IR (neat, cm$^{-1}$) 3072.1, 2958.3, 2956.1, 1484.9, 1417.1, 1355.7, 1305.6.

(E)-tert-butyl 3-(3-(N-(methoxycarbonyl)-4-methylphenylsulfonamido)prop-1-en-1-yl)-1H-indole-1-carboxylate (53) This reaction was performed using standard conditions on half scale (0.5 mmol). Run 1 = 144 mg (59%) yield with >20:1 E:Z and >20:1 L:B. $^1$H NMR (400 MHz,
CDCl$_3$) $\delta$ 8.18 (d, $J = 7.9$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 7.7$ Hz, 1H), 7.62 (s, 1H), 7.43 – 7.20 (m, 5H), 6.78 (dd, $J = 16.0$, 0.5 Hz, 1H), 6.39 – 6.26 (m, 1H), 4.65 (dd, $J = 6.5$, 0.9 Hz, 2H), 3.73 (s, 3H), 2.39 (s, 3H), 1.70 (s, 11H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 152.88, 149.59, 144.71, 136.61, 136.07, 129.47, 128.65, 125.84, 124.85, 124.61, 124.00, 123.07, 120.02, 117.87, 115.49, 84.08, 54.03, 49.42, 28.31, 21.72. IR (neat, cm$^{-1}$) 2977.6, 2931.3, 1735.6, 1596.8, 1554.4, 1452.1. HRMS (ESI) m/z calculated for C$_{25}$H$_{28}$N$_2$O$_6$Na [M + H]$^+$: 507.1556; found: 507.1567.

(E)-methyl (3-(2-((tert-butyldimethylsilyl)oxy)phenyl)allyl)(tosyl)carbamate (54) This reaction was performed using standard conditions. Run 1 = 123mg (58%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (d, $J = 8.4$ Hz, 2H), 7.54 – 7.39 (m, 2H), 7.35 – 7.19 (m, 4H), 6.62 (d, $J = 15.9$ Hz, 1H), 6.25 (dt, $J = 15.8$, 6.4 Hz, 1H), 4.61 (dd, $J = 6.4$, 1.1 Hz, 2H), 3.73 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 152.81, 144.86, 136.51, 135.34, 132.92, 131.85, 129.50, 128.65, 128.25, 124.83, 121.95, 54.09, 48.83, 21.78. IR (neat, cm$^{-1}$) 3035.4, 2956.4, 2925.5, 28.54, 1735.6, 1486.9, 1442.5, 1359.6, 1170.6.

(E)-2-methoxy-4-(3-(N-(methoxycarbonyl)-4-methylphenyl)sulfonamido)prop-1-en-1-yl)phenyl trifluoromethanesulfonate (55) This reaction was performed using standard conditions. Run 1 = 246mg (92%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.14 (d,
\[ J = 8.3 \text{ Hz, 1H}, 7.02 - 6.90 \text{ (m, 2H)}, 6.61 \text{ (d, } J = 15.9 \text{ Hz, 1H}), 6.24 \text{ (dt, } J = 15.8, 6.3 \text{ Hz, 1H}), 4.59 \text{ (d, } J = 6.2 \text{ Hz, 2H}), 3.90 \text{ (s, 3H)}, 3.70 \text{ (s, 3H)}, 2.40 \text{ (s, 3H)}. \]

\[^{13}\text{C NMR (101 MHz, CDCl}_3\text{) } \delta 152.8, 151.5, 145.0, 138.3, 137.9, 136.5, 129.5, 128.6, 126.3, 122.6, 119.2, 111.1, 56.3, 54.1, 48.7, 21.7. \text{ IR (neat, cm}^{-1}\text{) 3072.1, 3010.4, 2960.2, 2850.3, 1739.5, 1600.6, 1504.2, 1444.4, 1421.3, 1361.5.}\]

\[(E)\text{-methyl \ (3-(4-bromophenyl)allyl)(tosyl)carbamate (56) } \]

This reaction was performed using standard conditions. Run 1 = 123mg (58%) yield with >20:1 E:Z and >20:1 L:B by \(^1\text{H NMR.}\)

\[^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.83 \text{ (d, } J = 8.4 \text{ Hz, 2H}), 7.54 - 7.39 \text{ (m, 2H)}, 7.35 - 7.19 \text{ (m, 4H)}, 6.62 \text{ (d, } J = 15.9 \text{ Hz, 1H}), 6.25 \text{ (dt, } J = 15.8, 6.4 \text{ Hz, 1H}), 4.61 \text{ (dd, } J = 6.4, 1.1 \text{ Hz, 2H}), 3.73 \text{ (s, 3H)}, 2.43 \text{ (s, 3H)}. \]

\[^{13}\text{C NMR (101 MHz, CDCl}_3\text{) } \delta 152.81, 144.86, 136.51, 135.34, 132.92, 131.85, 129.50, 128.65, 128.25, 124.83, 121.95, 54.09, 48.83, 21.78. \text{ IR (neat, cm}^{-1}\text{) 3035.4, 2956.4, 2925.5, 28.54.14, 1737.5, 1486.9, 1442.5, 1359.6, 1170.6.}\]

\[(E)\text{-methyl \ (5-((tert-butyldiphenylsilyl)oxy)pent-2-en-1-yl)(tosyl)carbamate (59) } \]

This reaction was performed using standard conditions. Run 1 = 281mg (51%) yield with >20:1 E:Z and >20:1 L:B by \(^1\text{H NMR.}\)

\[^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.84 \text{ (d, } J = 8.3 \text{ Hz, 2H}), 7.71 \text{ (d, } J = 6.0 \text{ Hz, 4H}), 7.67 - 7.35 \text{ (m, 6H)}, 7.25 \text{ (d, } J = 8.1 \text{ Hz, 2H}), 5.96 - 5.76 \text{ (m, 1H)}, 5.75 - 5.52 \text{ (m, 1H)}, 4.44 \text{ (d, } J = 6.1 \text{ Hz, 2H}), 3.86 - 3.59 \text{ (m, 5H)}, 2.63 - 2.27 \text{ (m, 5H)}, 1.08 \text{ (s, 9H)}. \]

\[^{13}\text{C NMR (101 MHz, CDCl}_3\text{) } \delta 152.84, 144.61, 136.68, 135.71, 134.00, 132.17, 129.79, 129.40, 128.67, 127.83, 126.62, 63.46, 53.88, 48.72, 35.75, 27.01, 21.77, 19.37. \text{ Spectral data matched previously reported data.}\]
(E)-methyl (5-(benzyloxy)pent-2-en-1-yl)(tosyl)carbamate (58)

This reaction was performed using standard conditions. Run 1 = 141mg (35%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. Spectral data matched previously reported data.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (d, $J$ = 8.3 Hz, 4H), 7.36 – 7.24 (m, 5H), 5.99 – 5.90 (m, 4H), 5.26 (t, $J$ = 9.5 Hz, 2H), 5.02 (ddd, $J$ = 16.9, 13.1, 7.9 Hz, 4H), 4.74 (d, $J$ = 4.9 Hz, 2H), 4.47 (d, $J$ = 3.5 Hz, 4H), 4.17 (dd, $J$ = 12.3, 4.9 Hz, 2H), 4.04 (dd, $J$ = 12.3, 2.1 Hz, 2H), 3.91 (ddd, $J$ = 9.8, 4.8, 2.2 Hz, 2H), 3.68 (s, 6H), 2.43 (s, 6H), 2.01 (td, $J$ = 7.6, 3.6 Hz, 26H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.78, 170.14, 169.79, 169.62, 152.63, 144.96, 134.96, 134.50, 129.57, 128.56, 126.26, 72.42, 70.68, 70.39, 69.68, 69.01, 62.39, 54.07, 48.20, 21.76, 20.81, 20.79, 20.74.

Intramolecular Amination Products:

$^{(5S)-5-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-3-tosyl-4-vinlyoxazolidin-2-one (59)}$ This reaction was performed using standard conditions. Run 1 = 2.53 g (51%) yield with >20:1 E:Z and >20:1 L:B by $^1$H NMR. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91 (d, $J$ = 8.3 Hz, 2H), 7.31 (d, $J$ = 8.1 Hz, 2H), 5.79 (ddd, $J$ = 17.0, 10.0, 8.6 Hz, 1H), 5.46 (d, $J$ = 17.0 Hz, 1H), 5.36 (d, $J$ = 10.1 Hz, 1H), 4.95 (dd, $J$ = 8.6, 3.7 Hz, 1H), 4.08 – 3.86 (m, 2H), 2.43 (s, 3H), 1.14 (d, $J$ = 6.4 Hz, 3H), 0.86 (d, $J$ = 3.6 Hz, 9H), 0.05 (d, $J$ = 13.3 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.55, 145.38, 135.23, 129.74, 129.63, 129.02, 128.75, 128.71, 120.43, 83.07, 68.02, 59.44, 25.96, 25.88, 25.83, 21.83, 19.18, 18.09, -4.55, -4.69.
Linear Allylic Oxidation Products:

\((E)-\text{cinnamyl 3-}(2,4\text{-dimethoxyphenyl})\text{acrylate}\) (14) To a 4 mL borosilicate vial was added Pd(CH\(_3\)CN)\(_4\)(BF\(_4\))\(_2\) (44.4 mg, 0.1 mmol, 10 mol %) under argon atmosphere, followed by 10 mol% phenyldihydroquinone (18.2 mg, 0.1 mmol, 10 mol%), \((E)-3\text{-}(2,4\text{-dimethoxyphenyl})\text{acrylic acid}\) (624 mg, 3.0 mmol, 3.0 equiv.), 10 mol% Co(II)Salophen and, and two 4Å molecular beads (50 mg) in one portion under ambient atmosphere. DMSO (100 µL, 1.1 mmol, 1.1 equiv.), CH\(_2\)Cl\(_2\) (500 µL), and DIPEA (121.0 µL, 0.7 mmol, 0.7 equiv.) were added via glass syringe followed by a Teflon© stir bar. This solution was stirred at 41°C for 5 minutes before allyl benzene (118 mg, 1.0 mmol, 1.0 equiv.) was added neat using a microsyringe. The vial was then capped with septa cap and a balloon of O\(_2\) was added. The stirred at 41°C for 48 hours. Upon completion (via NMR aliquate), the reaction was transferred to a separatory funnel using minimal methylene chloride (~2 mL). The solution was diluted with diethyl ether (50 mL) and washed with 5% K\(_2\)CO\(_3\) (aq.) solution 2x. Note: If an inseparable emulsion forms filter the solution through a pressed pad of celite with 20-30 mL diethyl ether. The organic layer was dried with MgSO\(_4\), filtered, and reduced in vacuo.

Purification via flash silica gel chromatography (20% Et\(_2\)O/hexanes) gave \((E)-\text{cinnamyl 3-}(2,4\text{-dimethoxyphenyl})\text{acrylate}\) as a white solid. Note: Product streaks somewhat on silica gel with diethyl ether; however, to ensure good separation from PhBQ this mixture is necessary. The crude selectivities were determined to be L:B >20:1 and E:Z >20:1 by \(^1\)H NMR. Run 1 (97.0 mg, 0.30 mmol, 60%); run 2 (96.1 mg, 0.30 mmol, 60%). \textbf{Average = 60% yield.} \(R_f= 0.2\) (20% Et\(_2\)O/hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.95 (d, \(J = 16.0\) Hz, 1H), 7.45 (d, \(J = 8.5\) Hz,
1H), 7.41 (d, \( J = 7.0 \) Hz, 2H), 7.33 (app. t, \( J = 7.5 \) Hz, 2H), 7.26 (t, \( J = 7.5 \), 1H), 6.70 (d, \( J = 16.0 \) Hz, 1H), 6.51 (dd, \( J = 9.0, 2.0 \) Hz, 1 H), 6.48 (d, \( J = 16.0 \) Hz, 1H), 6.45 (d, \( J = 2.5 \) Hz, 1H), 6.37 (dt, \( J = 16.0, 6.0 \) Hz, 1H), 4.86 (dd, \( J = 6.0, 1.0 \) Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H). \( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)) \( \delta 167.9, 162.9, 160.1, 140.7, 136.5, 134.1, 130.7, 128.8, 128.1, 126.8, 123.9, 116.7, 115.9, 105.4, 98.6, 65.0, 55.6 (2C). IR (neat, cm\(^{-1}\)) 3080, 3062, 3026, 3004, 2936, 2839, 1706, 1605, 1160. HRMS (ESI) m/z calculated for C\(_{20}\)H\(_{20}\)O\(_4\)Na \([\text{M + Na}\]^+\): 347.1259; found: 347.1257. Spectral data has previously been reported for this compound.\(^{90}\)

Proposed Targets for the Linear Allylic Oxidation Reaction:

(2R,3S,4S,5S,6R)-2-(acetoxymethyl)-6-((E)-3-((4-methoxybenzoyl)oxy)prop-1-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate

Selected Starting Materials:

2-(3-allyl-2-((tert-butyldiphenylsilyl)oxy)-5-methylphenyl)-2H-benzo[d][1,2,3]triazole \( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta 7.71 – 7.42 \) (m, 4H), 7.42 – 7.20 (m, 8H), 7.15 (t, \( J = 7.5 \) Hz, 4H), 7.03 (d, \( J = 2.1 \) Hz, 1H), 5.73 (ddt, \( J = 16.8, 10.1, 6.6 \) Hz, 1H), 5.10 – 4.92 (m, 2H), 3.34 (d, \( J = 6.6 \) Hz, 2H), 2.28 (s, 3H), 0.78 (s, 9H). \( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta 144.84, 144.76, 136.41, 134.97, 132.60, 132.33, 132.01, 131.82, 131.20, 129.54, 127.22, 126.40, 126.20, 118.27, 116.54, 35.20, 26.32, 20.46, 20.06. Spectral data matched previously reported data.
**tert-butyl 3-allyl-1H-indole-1-carboxylate**  $^1$H NMR (500 MHz, CDCl$_3$) $\delta$

8.39 – 7.91 (m, 1H), 7.56 – 7.50 (m, 1H), 7.49 – 7.29 (m, 2H), 7.28 – 7.20 (m, 1H), 6.11 – 5.99 (m, 1H), 5.23 – 5.09 (m, 2H), 3.49 – 3.43 (m, 2H), 1.68 (t, $J = 2.8$ Hz, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 135.95, 130.62, 124.42, 123.01, 122.44, 119.32, 119.12, 116.32, 115.35, 83.48, 29.65, 28.36. IR (neat, cm$^{-1}$) 3122.2, 3077.9, 3004.6, 2979.5, 2979.5, 2931.3, 2931.3, 2904.3, 2934.9, 1727.9, 1641.1, 1610.3, 1596.8. HRMS (ESI) m/z calculated for C$_{16}$H$_{19}$NO$_2$Na $[M + H]^+$: 280.1313; found: 280.1320. Spectral data matched previously reported data.

**R)-4-benzyl-3-((S)-2-methylpent-4-enoyl)oxazolidin-2-one**  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 – 7.16 (m, 5H), 5.92 – 5.73 (m, 1H), 5.08 (t, $J = 14.9$ Hz, 2H), 4.67 (qd, $J = 6.9, 3.2$ Hz, 1H), 4.26 – 4.10 (m, 2H), 4.02 – 3.72 (m, 1H), 3.28 (dd, $J = 13.3, 3.1$ Hz, 1H), 2.69 (dd, $J = 13.2, 9.9$ Hz, 1H), 2.52 (dt, $J = 13.6, 6.7$ Hz, 1H), 2.23 (dt, $J = 14.0, 7.0$ Hz, 1H), 1.18 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.58, 153.19, 135.19, 135.46, 135.35, 129.50, 129.01, 127.40, 117.31, 66.09, 55.48, 38.18, 38.07, 37.23, 16.53. Spectral data matched previously reported data.

**S)-1-((2R,3aS,4R,6aS)-3a-allyl-1,1,4-trimethyloctahydropentalen-2-yl)ethanol**  $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.91 – 5.79 (m, 1H), 5.04 – 4.93 (m, 2H), 3.81 – 3.69 (m, 1H), 2.13 – 1.98 (m, 2H), 1.86 – 1.79 (m, 1H), 1.69 – 1.45 (m, 4H), 1.39 – 0.93 (m, 16H), 0.99 – 0.87 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 137.80, 116.73, 69.57, 61.00, 53.84, 50.89, 46.76, 42.58, 42.19, 39.59, 33.89, 28.89, 26.49, 24.77, 24.51, 14.21. Spectral data matched previously reported data.
tert-butyl(pent-4-en-1-yloxy)diphenylsilane $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (dd, $J = 5.1$, 2.6 Hz, 4H), 7.50 – 7.06 (m, 6H), 5.89 – 5.50 (m, 1H), 5.00 (dd, $J = 33.5$, 13.7 Hz, 2H), 3.71 (t, $J = 6.3$ Hz, 2H), 2.18 (dd, $J = 13.7$, 6.8 Hz, 2H), 1.74 – 1.26 (m, 2H), 1.11 – 0.75 (m, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 138.86, 135.89, 134.37, 129.83, 127.91, 114.84, 63.59, 32.14, 30.38, 27.19, 19.56. Spectral data matched previously reported data.

(2R,3S,4S,5S,6R)-2-(acetoxymethyl)-6-allyltetrahydro-2H-pyran-3,4,5-triyl triacetate Supplementary crystallographic data for this compound is yet unpublished, .cif file might be available upon request.

3.5 REFERENCES

Whereas Pd(0)-catalyzed reactions commonly feature soft donor ligands such as phosphines to stabilize Pd(0) and prevent aggregation of palladium metal, these ligands generally decompose under oxidizing conditions. Oxidatively stable ligands, such as pyridine, enable catalytic turnover, but they are not as effective as phosphines in preventing catalyst decomposition. See: (a) “Mechanistic Characterization of Aerobic Alcohol Oxidation


83 (a) “Palladium-Catalyzed Intermolecular Aerobic Oxidative Amination of Terminal Alkenes: Efficient Synthesis of Linear Allylamine Derivatives” Liu, G.; Yin, G.; Wu, L. Angew. Chem. Int. Ed. 2008, 47, 4733 –4736. (b) “Intermolecular Aerobic Oxidative Allylic Amination of
Simple Alkenes with Diarylamines Catalyzed by the Pd(OCOCF$_3$)$_2$/NPMoV/O$_2$ System” Shimizu, Y.; Obora, Y.; Ishii, Y. Org. Lett. 2010, 12, 1372-1374.


CHAPTER 4: THE FE(PDP)-CATALYZED ALIPHATIC C-H OXIDATION: A SLOW ADDITION PROTOCOL

4.1 INTRODUCTION

Although allylic C-H oxidation methodology has been shown to be very selective and can open the possibility of new synthetic routes to specific targets the methods still relies on terminal olefins as precursors. The systemic oxidation of simple C-H bonds (not activated by nearby functionality) represents the Holy Grail of modern oxidation strategies. Contemporary synthetic planning focuses on the manipulation of oxidized functionality, often viewing C-H bonds in organic scaffolds as necessary (for structure or function) but not useful for chemical manipulation. As a result, methods that directly transform C-H bonds into C-O, C-N, or C-C bonds could enable the construction of oxidized materials from much more simple intermediates. This should lead to simplified synthetic routes and greater efficiency for the construction of complex targets. For this strategy to be useful, reactions that manipulate C-H bonds at late stages of synthetic routes would have to proceed with predictable and high selectivities.

Previously selective C-H functionalization reactions on complex substrates have been primarily accomplished for activated C-H bonds (i.e. adjacent to a heteroatom or π-system) or via the use of substrate directing groups. In contrast to this, we recently disclosed an iron (Fe)-based small molecule catalyst, Fe(PDP) \([\text{[Fe(II)(PDP)(CH}_3\text{CN)}_2\text{](SbF}_6\text{]}_2\text{]}\) that catalyzes the oxidation of isolated, unactivated sp\(^3\) C-H bonds in complex molecular settings with high and predictable levels of selectivity without the requirement for directing groups. Currently, a set of simple rules based on the electronic and steric properties of the C-H bonds in the molecule allows for predictable oxidation of \(3^\circ\) C-H bonds with 66. Although this method represents a
leap in synthetic utility it still suffers from sub-optimal conversion and high catalyst loadings. General improvements in conversion and yield would render this method much more useful to the synthetic community. Mark S. Chen, responsible for the initial development of catalyst 66 and discovery of its ability to selectively oxidize 3° C-H bonds, verified critical results. Portions of this chapter were taken with permission from Vermeulen, N. A.; Chen, M.S.; and White, M.C. *Tetrahedron*, 2009, 65, 3078-3084.

4.2 RESULTS AND DISCUSSION

4.2.1 OPTIMIZATION OF A SLOW ADDITION PROTOCOL

While the Fe(PDP) aliphatic C-H oxidation reaction enables for the first time the selective oxidation of complex substrates at unactivated, isolated C-H bonds with preparatively useful isolated yields (43-57%), important challenges remain including improving catalyst turnovers and substrate conversions. Currently, three iterative additions of Fe(PDP) catalyst 61 (5 mol%), hydrogen peroxide oxidant (H$_2$O$_2$, 1.2 equiv.), and acetic acid additive (AcOH, 0.5 equiv.) in 10-15 minute intervals are utilized to obtain maximum product yields (Table 8, entry 5). Adding more oxidant alone does not alter product yield (Table 8, entry 2), indicating that catalyst decomposition, not inefficient use of H$_2$O$_2$, is responsible for the modest yields observed. Significantly, with a single addition, increasing the catalyst loading to 15 mol% with or without increasing the amount of oxidant affords no significant improvement in yield and diminishes the selectivity for the 3° hydroxylated product 63 (Table 8, entry 1 vs. entries 3 and 4). These results suggest that increased catalyst concentrations are deleterious to catalyst productivity.
Although new catalyst and reagents (61/H₂O₂/AcOH) are introduced during each cycle of the iterative addition protocol, the later additions fail to promote significantly increased product yields due to deteriorating catalyst reactivity and selectivity in the reaction mixture (Table 8, entry 5). Notably, a fourth addition of 61/H₂O₂/AcOH is ineffective at catalyzing desired product formation (Table 8, entry 5; Table 2, entries 2 and 4). In cases where valuable starting material remains, conversion to product can be achieved using a “recycling protocol” that consists of physically separating (via column chromatography) the starting material from the reaction mixture and re-submitting it to oxidation (Scheme 13, eqs. 1, 2). These results imply that catalyst decomposition products forming during the course of the reaction are interfering with productive oxidations with 61.
In order to investigate if catalyst decomposition proceeds via ligand oxidation, we performed the aliphatic C-H oxidation of 4-methylvaleric acid catalyzed by Fe(PDP) \( \text{Fe(PDP)} \) under the standard iterative addition protocol and recovered the ligand. We obtained 48% isolated yield of the volatile lactone product and recovered 95% of the \((S,S)\)-PDP ligand unoxidized (see Experimental). Collectively, these experimental observations suggested to us that catalyst decomposition is occurring via bi- or multimolecular reactions at the metal center to furnish species that inhibit productive oxidations. This is indicated but the possible formation of a bridged iron-oxo species as indicated by UV spectroscopy of the iron catalyst after exposure to \( \text{H}_2\text{O}_2 \) (µ-oxo diiron (III) compounds: (1) three features between 400 and 500 nm, (2) a shoulder near 525 nm and (3) a broad band near 700 nm, Figure 3). We hypothesized that slow addition of both the catalyst and oxidant over an extended period of time could disfavor these decomposition pathways and improve overall catalyst productivity. An alternative explanation is the increase in overall concentration of the reaction over time, which could allow for more catalyst/reactant interaction and more effective turnover of the catalyst. The iterative protocol has a reaction profile that rapidly decreases the overall concentration of the reaction (0.66M to 0.09M to 0.05M to 0.03M) in 1 minute segments with 15 minutes rest periods. The slow addition protocol allows for a much more gradual decrease in concentration (0.5M to 0.07M) over the course of an hour. Although concentration effects have not been studied in detail, and currently no rate equation for this reaction has been elucidated, it would be valuable to study the effect of concentration on this iron catalyzed C-H oxidation method.
4.2.2 SUBSTRATE SHOWCASE FOR SLOW ADDITION PROTOCOL

We developed a slow addition protocol in which separate solutions of catalyst 61 (15 or 20 mol%, 0.2 M CH$_3$CN) and H$_2$O$_2$ (50 wt% in H$_2$O, 3 or 4 equiv., 0.4 M CH$_3$CN) were simultaneously added over 45 or 60 minutes via syringe pump to a stirring solution of substrate (1.0 equiv., 0.5 M CH$_3$CN) and AcOH (0.5 equiv.). The results in Table 9 are presented with comparison to those obtained using the iterative addition protocol. At comparable catalyst and oxidant loadings (15 mol% 61, 3 equiv. H$_2$O$_2$), the slow addition protocol provides only modest improvements in yields with similar amounts of recovered starting material relative to the iterative addition protocol (Table 8, entry 6; Table 9). However in cases where large amounts of starting material (>20%) were previously observed, the slow addition protocol, performed with slightly increased catalyst and oxidant loadings (20 mol% 61, 4 equiv. H$_2$O$_2$), afforded significant increases in isolated yields of hydroxylated products (11-19%; Table 9, entries 1, 3, 6, 8, 9). In contrast, when the iterative addition protocol is performed with comparable increases in catalyst and oxidant loadings, as previously shown in Table 8, no significant improvement in
yield is observed (Table 8, entry 5; Table 9, entries 2 and 4). Importantly, beyond the excellent yields recorded in Table 9 for these highly challenging transformations, the Fe(PDP) aliphatic C-H oxidation reaction is operationally simple to perform. Catalyst 61 exists as a purple solid that

Table 9: Comparison of Slow Addition to Iterative Addition Protocol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylation Product</th>
<th>Isolated % Yield (rsm$^a$)</th>
<th>slow addition 5 mol% x 3</th>
<th>Iterative addition 5 mol% x 3</th>
<th>slow addition 15 mol%$^b$</th>
<th>20 mol%$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br (\text{HO}) 64</td>
<td>46 (26)</td>
<td>51 (27)</td>
<td>61 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(\text{HO}) 64</td>
<td>49 (15)$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F(_3)C N(\text{HO}) 65</td>
<td>43 (33)</td>
<td>44 (35)</td>
<td>54 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeO (\text{HO}) 66</td>
<td>60 (18)</td>
<td>61 (21)</td>
<td>66 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>AcO (\text{HO}) 67</td>
<td>53 (43)</td>
<td>67 (30)</td>
<td>72 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>O(\text{HO}) 68</td>
<td>43 (42)</td>
<td>45 (32)</td>
<td>50 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F(_3)C N(\text{HO}) 69</td>
<td>33 (87)</td>
<td>40 (59)</td>
<td>46 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>O(\text{NO}) 70</td>
<td>48 (22)</td>
<td>59 (18)</td>
<td>61 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>O(\text{NO}) 71</td>
<td>39 (32) 9:1 [C7-C3]</td>
<td>41 (22) 10:1 [C7-C3]</td>
<td>43 (20)$^f$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>O(\text{OAc}) 72</td>
<td>50 (11) 11:1 [C1:C8]</td>
<td>54 (16) 11:1 [C1:C8]</td>
<td>55 (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Yields of isolated hydroxylated products (0.5 mmol substrate) are an average of two runs. $^b$ rsm = recovered starting material. $^c$ Yields for iterative addition are from reference 7. $^d$ Slow addition of 15 mol% 61 (0.15M in CH\(_2\)CN) and 3 equiv. H\(_2\)O\(_2\) (0.4M in CH\(_2\)CN) via syringe pump over 45 min, into a CH\(_2\)CN solution (0.5M) of 62 (1 equiv.) and AcOH (0.5 equiv.). $^e$ 4 iterative additions of 61 (5 mol%), AcOH (0.5 equiv.), H\(_2\)O\(_2\) (1.2 equiv.). $^f$ Based on one run at 0.5 mmol. Adapted from Vermeulen et. al Tetrahedron. 2009, 65, 3078-3084.
is indefinitely stable under air when refrigerated at 0°C (We have not observed decreases in catalyst 61 hydroxylation activity after ca. 1 year storage at 0°C.) Moreover, with both the iterative and slow addition protocols, reactions are run open to air without excluding moisture under a single set of experimental conditions.

Importantly, the predictable site-selectivities and high chemoselectivities in oxidations catalyzed by 61 are not altered under the slightly more forcing conditions of increased catalyst and oxidant loadings used in the slow addition protocol (Table 9, entries 10, 11). In molecules containing two electronically distinct 3° C-H bonds, as in (+)-71, electrophilic catalyst 61 maintains its selectivity for oxidation of the most electron rich C-H bond (C7). In cases where two 3° C-H bonds are electronically equivalent, as in substrate (-)-72, bulky catalyst 61 persists in oxidizing with high selectivity at the C-H bond that is less sterically hindered. It is important to note, however, that in cases like these where conversions are high or the substrate is robust towards oxidation under the iterative addition protocol, the slow addition protocol does not significantly improve yields. The Fe(PDP) aliphatic C-H oxidation reaction performed under the slow addition protocol remains tolerant of a wide range of functionalities such as halides, esters, carbonates, and electron-deficient amides (Table 9, entries 1-8, 10-11). Consistent with the observation that electron-deficient functionality is compatible with these oxidative conditions, we now report that aromatic functionality substituted with an electron-withdrawing nitro group is also well-tolerated (Table 9, entry 9). In general, we have observed that substitution of electron-withdrawing groups on aromatic rings is crucial for deactivating them towards oxidation.
The most significant simplifying feature of the slow addition protocol is the ability to eliminate the recycling of valuable starting materials while still obtaining comparable yields of oxidized products. For example, we previously reported that the antimalarial compound (+)-artemisinin 73 could be oxidized with 61 under iterative addition conditions to afford (+)-7-hydroxyartemisinin 74 in 34% yield with 41% recovered starting material (Scheme 12). By recycling recovered (+)-73 through the reaction twice (three column chromatographic purifications), a total of 54% isolated yield of (+)-74 could be obtained. Using the slow addition protocol with 20 mol% 1 and 4 equiv. H$_2$O$_2$ (0.5 equiv. AcOH), (+)-74 can now be furnished in 51% isolated yield after only one chromatographic purification (eq. 1). It is significant to note that this reaction proceeds with extraordinary site-selectivity and chemoselectivity. Specifically, (+)-artemisinin 73 is predictably oxidized preferentially at one of five 3° C-H bonds based on electronic considerations and the sensitive endoperoxide moiety is maintained with both oxidation protocols.
Consistent with our hypothesis that the AcOH additive is acting as an ancillary ligand for the active Fe catalyst, we have demonstrated that chiral carboxylic acids may direct highly diastereoselective C-H oxidations of 2° C-H bonds with 61. For example, tetrahydrogibberellic acid analog (+)-75 was previously oxidized with 61 under the iterative addition protocol to afford lactone (+)-76 as a single diastereomer in 37% isolated yield with 40% recovered starting material (Scheme 13). By recycling recovered (+)-75 through the reaction once (two silica column purifications), a total of 52% isolated yield of (+)-76 could be obtained. Using the slow addition protocol with 25 mol% 1 and 5 equiv. H₂O₂ (and no AcOH), (+)-76 can be now synthesized in 51% isolated yield and only one chromatographic purification (eq. 2). It is significant to note that with complex substrates the Fe(PDP) aliphatic C-H oxidation represents an especially powerful late stage oxidation. In considering potential alternative synthetic routes towards natural product analogs such as (+)-76, state-of-the-art methods would require a potentially lengthy total synthesis.

4.3 CONCLUSION

The Fe(PDP) 61 aliphatic C-H oxidation has demonstrated for the first time that, using a highly electrophilic and sterically bulky catalyst, isolated and inert C-H bonds can be selectively oxidized in a predictable fashion based on subtle differences in their electronic and steric
properties. Now a slow addition protocol that enables increasing the catalyst and oxidant loadings to productively drive the aliphatic C-H oxidation reaction to higher conversions without sacrificing site-selectivity or chemoselectivity is shown. The operational advantages of this new procedure are demonstrated by the ability to eliminate the recycling of recovered starting materials in the oxidation of two complex natural product derivatives, while obtaining comparable isolated yields. The increased catalyst productivity with the slow addition protocol, together with the complete recovery of PDP ligand, suggests bi- or multimolecular catalyst decomposition pathways occur at the iron center. Future studies are directed towards identifying the precise structures of these decomposition products, elucidating the mechanism by which they inhibit oxidation, and developing chemical strategies for preventing their formation.

4.4 EXPERIMENTAL SECTION

General information. The following commercially obtained reagents for the C-H oxidation reaction were used as received: H₂O₂ (50 wt% in H₂O, Sigma-Aldrich), AcOH (Mallinckrodt), CH₃CN (Sigma-Aldrich). All oxidation reactions were run under air with no precautions taken to exclude moisture. Fe(S,S-PDP)₆₁ catalyst was prepared as described in reference 95. Supplementary crystallographic data for Fe(S,S-PDP)₆₁ can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif on quoting registry no. CCDC-661933. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instruments equipped with FID detectors using a HP-5 (5% Phenyl)-methylpolysiloxane column (30 m, 0.32mm, 0.25μm). Chiral GC analysis was performed on an Agilent 5890 Series instruments equipped with FID detectors using a J&W cyclodex-β column (30 m, 0.25 mm, 0.25 μm). Thin-layer chromatography (TLC) was
conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate, or vanillin staining. Slow addition protocols were performed using a New Era Pump Systems NE-300 syringe pump. Flash silica gel and reverse-phase silica gel column chromatography were performed using EM reagent silica gel 60 (230-400 mesh) and Versaflash spherical C18 bonded flash silica gel (45-75 um, 70A), respectively. \(^1\)H-NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl\(_3\) at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled \(^{13}\)C-NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl\(_3\) at 77.0 ppm). Mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Chemical ionization (CI) spectra were collected on a Waters 70-VSE spectrometer using methane as the carrier gas. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer. 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\(^{-1}\)). Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 341 polarimeter or using a 1 mL cell with a 5 cm path length on a Jasco DIP-360 digital polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: \([\alpha]_\lambda^{\text{ToC}}\) (c = g/100 mL, solvent). UV-Vis spectra were taken on a Shimadzu PharmaSpec UV-1700 UV-Vis spectrophotometer with 1 cm quartz cuvettes.

**General procedure for slow addition protocol (20 mol% 61).** A 40 mL screwtop vial was charged with the following: substrate (0.5 mmol, 1.0 equiv.), CH\(_3\)CN (1.0 mL, 0.5 M), and
AcOH (15.0 mg, 0.25 mmol, 0.5 equiv.) and a magnetic stir bar. The vial was placed on a stir plate and stirred vigorously at room temperature while open to ambient atmosphere. A 1.0 mL glass syringe was charged with a solution of Fe(S,S-PDP) 61 catalyst (93.1 mg, 0.1 mmol, 20 mol%) in CH$_3$CN (0.5 mL, 0.2 M) and loaded into a syringe pump with addition rate 0.5 mL/1hr (0.0083 mL/min). A 10 mL glass syringe was charged with a solution of H$_2$O$_2$ (50 wt% in H$_2$O, 136 µL, 2.0 mmol, 4.0 equiv.) in CH$_3$CN (5.0 mL, 0.4 M) and loaded into a syringe pump with addition rate 5mL/1hr (0.083 mL/min). Both syringes were equipped with 26G needles and directed into the center of the uncapped vial; precautions should be taken not to touch the sides (Figure 4). The two additions were initiated simultaneously and both Fe(S,S-PDP) 61 catalyst and H$_2$O$_2$ were added to the reaction vial over the course of 1hr. The crude mixture was concentrated via rotary evaporation to a minimal amount of CH$_3$CN. Et$_2$O was added until a brown precipitate formed. The mixture was filtered through a short plug of celite, concentrated by rotary evaporation and purified by flash chromatography.

*Slow addition protocol (15 mol% 61):* Slow addition protocol for oxidation of substrate (0.5 mmol, 1.0 equiv.), AcOH (15.0 mg, 0.25 mmol, 0.5 equiv.) in 1.0 mL CH$_3$CN with one addition of H$_2$O$_2$ (50 wt%, 102.0 µL, 1.5 mmol, 3.0 equiv., 0.4 M) in 3.75 mL CH$_3$CN in a 10 mL glass syringe was added at the rate of 5mL/1hr (0.083 mL/min) over the course of 45 minutes. Addition of 61 (69.9 mg, 0.075 mmol, 15 mol%, 0.2 M) in 0.375 mL CH$_3$CN in a 1.0 mL glass syringe was added at a rate of 0.5 mL/hr (0.0083 mL/min) over the course of 45 minutes.
Figure 4: Photograph of Slow Addition Setup

*General procedure for iterative addition protocol.* A 40 mL screwtop vial was charged with the following: Fe(S,S-PDP) 61 catalyst (23.3 mg, 0.025 mmol, 5 mol%), substrate (0.5 mmol, 1.0 equiv.), CH$_3$CN (0.75 mL, 0.67 M), and AcOH (15.0 mg, 0.25 mmol, 0.5 equiv.) and a magnetic stir bar. The vial was placed on a stir plate and stirred vigorously at room temperature. A solution of H$_2$O$_2$ (50 wt%, 36.8 μL, 0.6 mmol, 1.2 equiv.) in CH$_3$CN (4.5 mL, 0.13 M) was added dropwise *via* syringe over ca. 45-75 seconds. The first drop of peroxide solution instantly changes the reaction mixture from a reddish-purple color to a yellow which quickly dissipates to an orange/purple. Subsequent drops of peroxide continue this fluctuating pattern until an amber color is reached and maintained. When no further color changes are observed, the dropwise addition rate of peroxide is increased so that the addition is completed within 45-75 seconds. *Significant decreases in yield were noted when the peroxide solution was added rapidly.* After ca. 10 minutes, a solution of Fe(S,S-PDP) 1 catalyst (23.3 mg, 0.025 mmol, 5 mol%), AcOH (15 mg, 0.25 mmol, 0.5 equiv.), in CH$_3$CN (0.5 mL) was added *via* glass pipette. This was followed by H$_2$O$_2$ (50 wt%, 36.8 μL, 0.6 mmol, 1.2 equiv.) in CH$_3$CN (4.5 m
mL) added dropwise over ca. 45-75 seconds. A third addition was performed in the same manner for a total of 15 mol% 1, 1.5 equiv. AcOH, and 3.6 equiv. \( \text{H}_2\text{O}_2 \). Each addition was allowed to stir for 10 minutes, for a total reaction time of 30 minutes.

**General procedure for reaction optimization** (Table 8). Oxidation of cis-4-methylcyclohexyl pivalate (62) was performed on 0.1 mmol scale (19.8 mg, 1.0 equiv.). The general procedure under “iterative addition protocol” was followed for entries 1-5, with entries 1,3, and 4 undergoing only one (1) addition of catalyst 61/AcOH and \( \text{H}_2\text{O}_2 \) oxidant. Entry 2 underwent a second addition of only \( \text{H}_2\text{O}_2 \) oxidant. \( \text{H}_2\text{O}_2 \) solutions were added over a period of ca. 45 seconds, unless specified otherwise. An aliquot was removed from the reaction mixture 10 minutes after the final addition of \( \text{H}_2\text{O}_2 \) (unless otherwise specified), and diluted with Et\(_3\)O, filtered through a SiO\(_2\) plug and analyzed by GC. All product yields reported are calibrated for response factors, rounded to the nearest whole number and reported as the average (mean) of two runs.

Table 8, entry 1. \( \text{H}_2\text{O}_2 \) (50 wt%, 7.4 \( \mu \)L, 0.12 mmol, 1.2 equiv.) in 0.9 mL CH\(_3\)CN was added to 61 (4.7 mg, 0.005 mmol, 5 mol%), 2 (19.8 mg, 0.1 mmol, 1.0 equiv.), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv.), in 0.15 mL CH\(_3\)CN.

Table 8, entry 2. \( \text{H}_2\text{O}_2 \) (50 wt%, 7.4 \( \mu \)L, 0.12 mmol, 1.2 equiv.) in 0.9 mL CH\(_3\)CN was added to 61 (4.7 mg, 0.005 mmol, 5 mol%), 2 (19.8 mg, 0.1 mmol, 1.0 equiv.), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv.), in 0.15 mL CH\(_3\)CN. After stirring for 10 minutes with the first addition of \( \text{H}_2\text{O}_2 \), a second addition of \( \text{H}_2\text{O}_2 \) (50 wt%, 7.4 \( \mu \)L, 0.12 mmol, 1.2 equiv.) in CH\(_3\)CN (0.9 mL) was added to the reaction mixture.
Table 8, entry 3. \( \text{H}_2\text{O}_2 \) (50 wt%, 7.4 \( \mu \)L, 0.12 mmol, 1.2 equiv.) in 0.9 mL CH\(_3\)CN was added to 61 (14.0 mg, 0.015 mmol, 15 mol%), 2 (19.8 mg, 0.1 mmol, 1.0 equiv.), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv.), in 0.15 mL CH\(_3\)CN.

Table 8, entry 4. \( \text{H}_2\text{O}_2 \) (50 wt%, 22.2 \( \mu \)L, 0.36 mmol, 3.6 equiv.) in 0.9 mL CH\(_3\)CN was added to 61 (14.0 mg, 0.015 mmol, 15 mol%), 2 (19.8 mg, 0.1 mmol, 1.0 equiv.), AcOH (9.0 mg, 0.15 mmol, 1.5 equiv.), in 0.15 mL CH\(_3\)CN.

Table 8, entry 5. Iterative addition protocol for oxidation of 2 (19.8 mg, 0.1 mmol, 1.0 equiv.) in 0.15 mL CH\(_3\)CN. A fourth addition of 61 (4.7 mg, 0.005 mmol, 5 mol%), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv.), in 0.10 mL CH\(_3\)CN and \( \text{H}_2\text{O}_2 \) (50 wt%, 7.4 \( \mu \)L, 0.12 mmol, 1.2 equiv.) in 0.9 mL CH\(_3\)CN was added. Aliquots for GC analysis were taken 10 minutes after each \( \text{H}_2\text{O}_2 \) addition, immediately before the next solution of 61/AcOH was added.

Table 8, entry 6. Slow addition protocol for oxidation of 62 (99.1 mg, 0.5 mmol, 1.0 equiv.), AcOH (15.0 mg, 0.25 mmol, 0.5 equiv.) in 1.0 mL CH\(_3\)CN with one addition of \( \text{H}_2\text{O}_2 \) (50 wt%, 102.0 \( \mu \)L, 1.5 mmol, 3.0 equiv.) in 3.75 mL CH\(_3\)CN was added at the rate of 5mL/1hr (0.083 mL/min) over the course of 45 minutes. Addition of 61 (69.9 mg, 0.075 mmol, 15 mol%) in 0.375 mL CH\(_3\)CN was added at a rate of 0.5 mL/hr (0.0083 mL/min) over the course of 45 minutes.

Comparison of iterative and slow addition protocols for C-H oxidation (Table 9, Equations 2,3). All reactions were performed on 0.5 mmol scale and are reported as the average of two runs. Yields from iterative addition protocol, purification and full characterization of oxidation products 64-67, (+)-68, (-)-69, (+)-71, (-)-72 in Table 9 and (+)-74 and (+)-76 in Schemes 12 and 13 are available in reference (95). The only modification to any of the purification methods was with (+)-64 which was now purified by flash reverse-phase silica gel
chromatography (20% CH$_3$CN/H$_2$O). All isolated products were compared with previously obtained $^1$H-NMR, $^{13}$C-NMR, ESI-MS data and were found to be identical.

Table 9, compound 64. Slow addition protocol using 1-bromo-5-methylhexane (89.6 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (59.1 mg, 0.303 mmol, 61%), run 2 (58.2 mg, 0.298 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0 mmol, 0%). Average recovered starting material: 0%.

15 mol % catalyst loading: run 1 (50.7 mg, 0.259 mmol, 52%), run 2 (47.7 mg, 0.244 mmol, 49%). Average: 51%. Recovered starting material (rSM): run 1 (25.0 mg, 0.140 mmol, 28%), run 2 (22.4 mg, 0.125 mmol, 25%). Average recovered starting material: 27%.

Table 9, compound 65. Slow addition protocol using 2,2,2-trifluoro-$N$-(6-methylheptan-2-yl)acetamide (112.3 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (63.9 mg, 0.265 mmol, 53%), run 2 (65.1 mg, 0.269 mmol, 54%). Average: 54%. Recovered starting material (rSM): run 1 (28.1 mg, 0.125 mmol, 25%), run 2 (22.5 mg, 0.100 mmol, 20%). Average recovered starting material: 23%.

15 mol % catalyst loading: run 1 (54.2 mg, 0.225 mmol, 45%), run 2 (51.7 mg, 0.210 mmol, 43%). Average: 44%. Recovered starting material (rSM): run 1 (38.2 mg, 0.170 mmol, 34%), run 2 (40.3 mg, 0.180 mmol, 36%). Average recovered starting material: 35%.
Table 9, compound **66**. Slow addition protocol using methyl 6-methylheptanoate (79.1 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

**20 mol % catalyst loading**: run 1 (59.2 mg, 0.340 mmol, 68%), run 2 (55.7 mg, 0.320 mmol, 64%). Average: 66%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0%). Average recovered starting material: 0%.

**15 mol % catalyst loading**: run 1 (54.0 mg, 0.310 mmol, 62%), run 2 (52.3 mg, 0.300 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 (15.8 mg, 0.100 mmol, 20%), run 2 (16.6 mg, 0.105 mmol, 21%). Average recovered starting material: 21%.

Table 9, compound **67**. Slow addition protocol using 5-methylhexyl acetate (79.1 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

**20 mol % catalyst loading**: run 1 (63.2 mg, 0.363 mmol, 73%), run 2 (62.1 mg, 0.356 mmol, 71%). Average: 72%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0 mmol, 0%). Average recovered starting material: 0%.

**15 mol % catalyst loading**: run 1 (59.3 mg, 0.340 mmol, 68%), run 2 (57.4 mg, 0.329 mmol, 66%). Average: 67%. Recovered starting material (rSM): run 1 (25.9 mg, 0.164 mmol, 33%), run 2 (20.7 mg, 0.138 mmol, 26%). Average recovered starting material: 30%.

Table 9, compound (**+**)-**68**. Slow addition protocol using (S)-5-((R)-5,5-dimethyl-2-oxo-1,3-dioxolan-4-yl)-3-methylpentyl acetate (129.2 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).
20 mol % catalyst loading: run 1 (69.9 mg, 0.255 mmol, 51%), run 2 (67.2 mg, 0.245 mmol, 49%). Average: 50%. Recovered starting material (rSM): run 1 (25.8 mg, 0.100 mmol, 20%), run 2 (21.8 mg, 0.084 mmol, 17%). Average recovered starting material: 19%.

15 mol % catalyst loading: run 1 (61.8 mg, 0.225 mmol, 45%), run 2 (62.0 mg, 0.226 mmol, 45%). Average: 45%. Recovered starting material (rSM): run 1 (41.3 mg, 0.160 mmol, 32%), run 2 (40.8 mg, 0.158 mmol, 32%). Average recovered starting material: 32%.

Table 9, compound (-)-69. Slow addition protocol using (S)-4-methyl-2-(2,2,2-trifluoroacetamido)pentyl acetate (127.6 mg, 0.5 mmol, 1.0 equiv.) as substrate. Purification by flash silica gel chromatography (40% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (63.7 mg, 0.235 mmol, 47%), run 2 (61.0 mg, 0.225 mmol, 45%). Average: 46%. Recovered starting material (rSM): run 1 (65.1 mg, 0.255 mmol, 51%), run 2 (62.5 mg, 0.245 mmol, 49%). Average recovered starting material: 50%.

15 mol % catalyst loading: run 1 (54.2 mg, 0.200 mmol, 40%) run 2 (52.8 mg, 0.195 mmol, 39%). Average: 40%. Recovered starting material (rSM): run 1 (74.0 mg, 0.290 mmol, 58%), run 2 (75.1 mg, 0.295 mmol, 59%). Average recovered starting material: 59%.

Table 9, compound 70. Slow addition protocol using 2-nitro-p-cymene (99.6 mg, 0.5 mmol, 90% purity) as substrate. Purification by flash silica gel chromatography (20% EtOAc/hexanes).
20 mol% catalyst loading: run 1 (59.6 mg, 0.305 mmol, 61%), run 2 (58.9 mg, 0.302 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 (8.1 mg, 0.045 mmol, 9%), run 2 (7.2 mg, 0.040 mmol, 8%). Average recovered starting material: 9%.

15 mol% catalyst loading: run 1 (54.6 mg 0.280 mmol, 56%), run 2 (53.7 mg , 0.275 mmol, 55%). Average: 56%. Recovered starting material (rSM): run 1 (16.7 mg 0.093 mmol, 19%), run 2 (15.0 mg, 0.084 mmol, 17%). Average recovered starting material: 18%.

Iterative addition protocol: run 1 (47.6 mg, 0.244 mmol, 49%), run 2 (45.5 mg, 0.235 mmol, 47%). Average: 48% Recovered starting material (rSM): run 1 (19.7 mg, 0.110 mmol, 22%), run 2 (18.8 mg, 0.105 mmol, 21%). Average: 22%. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09 (d, \(J = 1.5\) Hz, 1H), 7.62 (dd, \(J = 2, 8\) Hz, 1H), 7.31 (d, \(J = 8\) Hz, 1H), 2.58 (s, 3H), 1.60 (s, 6H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\); 148.6, 132.7, 131.8, 129.2, 120.8, 72.1, 31.7, 20.0. IR (film, cm\(^{-1}\)):
(neat, cm\(^{-1}\)) 2980.4, 2934.1, 2361.1, 2344.2, 1527.4, 1345.4. HRMS (EI) m/z calc’d C\(_{10}\)H\(_{14}\)O\(_3\)N [M+H]\(^+\): 196.09737, found 196.09745.

Table 2, compound (+)-71. Slow addition protocol using (S)-1-bromo-3,7-dimethyloctane (110.6 mg, 0.5 mmol, 1.0 equiv.) as substrate. Regioselectivity was determined by \(^1\)H-NMR analysis of the crude reaction mixture\(^7\). Purification by flash silica gel chromatography (10% EtOAc/hexanes).

20 mol% catalyst loading: run 1 (50.9 mg, 0.215 mmol, 43%, C7 oxidation; 4.9 mg, 0.021 mmol, 4%, C3 oxidation). Recovered starting material (rSM): run 1 (22.1 mg, 0.100 mmol, 20%).

15 mol% catalyst loading: run 1 (47.4 mg, 0.200 mmol, 40%), run 2 (48.6 mg, 0.205 mmol, 41%). Average C7 oxidation: 41%. Recovered starting material (rSM): run 1 (24.2 mg,
0.110 mmol, 22%), run 2 (23.3 mg, 0.105 mmol, 21%). Average recovered starting material: 22%.

Table 9, compound (-)-72. Slow addition protocol using (1R)-menthyl acetate (99.1 mg, 0.5 mmol, 1.0 equiv.) as substrate. Regioselectivity was determined by 1H-NMR analysis of the crude reaction mixture. Purification by flash silica gel chromatography (20% EtOAc/hexanes)

20 mol % catalyst loading: run 1 (57.9 mg, 0.270 mmol, 54%), run 2 (59.8 mg, 0.280 mmol, 56%). Average: 55%. Recovered starting material (rSM): run 1 (2.0 mg, 0.010 mmol, 2%), run 2 (5.2 mg, 0.026 mmol, 5%). Average recovered starting material: 4%.

15 mol % catalyst loading: run 1 (58.7 mg, 0.274 mmol, 55%), run 2 (55.7 mg, 0.260 mmol, 52%). Average: 54%. Recovered starting material (rSM): run 1 (17.7 mg, 0.089 mmol, 18%), run 2 (12.9 mg, 0.065 mmol, 13%). Average recovered starting material: 16%.

Equation 1, compound (+)-74. Iterative addition protocol for the oxidation of (+)-artemisinin ((+)-73) (0.5 mmol, 141.2 mg, 0.5 mmol, 1.0 equiv.) is similar to the general procedure with the exception that only 3.0 mg AcOH (0.05 mmol, 10 mol%) was added to the reaction and the starting material was initially solvated in 2.25 mL CH₃CN (0.22 M). The subsequent two additions of 61 (5 mol%)/AcOH (10 mol%) in 0.50 mL CH₃CN and H₂O₂ (1.2 equiv.) in 4.5 mL CH₃CN were added without modification from the previously described procedure. Immediately upon completion, the reaction was quenched with a solution of saturated NaHCO₃, extracted with Et₂O (3x 30mL), dried on MgSO₄, filtered and purified by flash silica gel column chromatography (25% EtOAc/hexanes). Upon re-isolation of
starting material *via* chromatography, the oxidation was setup again according to the iterative addition protocol described above with identical reagent stoichiometries (based on equivalents of recovered (+)-73). Altogether, this process of *recycling* recovered starting material was done twice.

Slow addition protocol for the oxidation of (+)-73 (0.5 mmol, 141.2 mg, 1.0 equiv.) was performed identically as described in the general procedure with a single addition of \( \text{H}_2\text{O}_2 \) (50 wt\%, 136.0 \( \mu \text{L} \), 2.0 mmol, 4.0 equiv.) in 5.0 mL and a single addition of 61 (93.1 mg, 0.1 mmol, 20 mol\%) in 0.5 mL CH\(_3\)CN was added over the course of 60 minutes to a solution of (+)-73, AcOH (15.0 mg, 0.25 mmol, 0.5 equiv.) in 1.0 mL CH\(_3\)CN. The substrate was not fully soluble initially, but reached full dissolution by the end of the reaction. Upon reaction completion the crude mixture was concentrated *via* rotary evaporation to a brown residue and purified by flash reverse-phase silica gel column chromatography (20\% CH\(_3\)CN/H\(_2\)O). Note: with slow addition protocol there is no *recycling* of starting material.

**20 mol\% catalyst loading:** run 1 (74.4 mg, 0.249 mmol, 50\%), run 2 (77.6 mg, 0.260 mmol, 52\%). Average: 51\%. Recovered starting material (rSM): run 1 (2.7 mg, 0.010 mmol, 2\%), run 2 (5.6 mg, 0.02 mmol, 4\%). Average recovered starting material: 3\%.

**15 mol\% catalyst loading:** run 1 (71.6 mg, 0.240 mmol, 48\%). Recovered starting material (rSM): run 1 (20.3 mg, 0.072 mmol, 14\%).

Equation 2, compound (+)-76. Iterative addition protocol for the oxidation of 16\(\beta\)-tetrahydrogibberellate diacetate [(+)-75] (108.6 mg, 0.25 mmol, 1.0 equiv.) is similar to the general procedure with the exception that 0.25 mmol of starting material was initially solvated in 1.50 mL CH\(_3\)CN (0.17 M)
and no AcOH was added to the reaction. The subsequent two additions of 61 (5 mol%) in 0.50 mL CH₃CN and H₂O₂ (1.2 equiv.) in 2.25 mL CH₃CN were added without modification from the previously described procedure. The crude mixture was concentrated via rotary evaporation to a brown residue and immediately purified by flash silica gel column chromatography (30/70/1 EtOAc/hexanes/AcOH). Upon re-isolation of starting material via chromatography, the oxidation was setup again according to the iterative addition protocol described above with identical reagent stoichiometries (based on equivalents of recovered (+)-75). This process of recycling recovered starting material was done once.

Slow addition protocol for the oxidation of (+)-75 (217.2 mg, 0.5 mmol, 1.0 equiv.) was performed similarly to the general procedure with the exception that AcOH was not added to the reaction mixture. A single addition of H₂O₂ (50 wt%, 170.0 µL, 2.5 mmol, 5.0 equiv.) in 6.25 mL CH₃CN and a single addition of 61 (116.5 mg, 0.125 mmol, 25 mol%) in 0.625 mL CH₃CN were added over the course of 75 minutes to (+)-75 in 1.0 mL CH₃CN. Upon reaction completion the crude mixture was concentrated via rotary evaporation to a brown residue and purified by flash silica gel column chromatography (30/70/1 EtOAc/hexanes/AcOH). Note: with slow addition protocol there is no recycling of starting material.

15 mol% catalyst loading: run 1 (86.4 mg, 0.200 mmol, 40%). Recovered starting material (rSM): run 1 (84.6 mg, 0.195 mmol, 39%).

20 mol% catalyst loading: run 1 (104.0 mg, 0.240 mmol, 48%). Recovered starting material (rSM): run 1 (54.2 mg, 0.125 mmol, 25%).

25 mol% catalyst loading: run 1 (110.3 mg, 0.255 mmol, 51%), run 2 (109.0 mg, 0.250 mmol, 50%). Average: 51%. Recovered starting material (rSM): run 1 (41.0 mg, 0.095 mmol, 19%), run 2 (39.0 mg, 0.090 mmol, 18%). Average recovered starting material: 19%.
Lactonization of 4-methylvaleric acid and recovery of free (S,S)-PDP ligand after oxidation. Iterative addition protocol for the oxidation of 4-methylvaleric acid (58.1 mg, 0.5 mmol, 1.0 equiv.) was performed similarly to the general procedure with the exception that no AcOH was added to the reaction. The subsequent two additions of 61 (23.3 mg, 0.025 mmol, 5 mol%) in 0.50 mL CH$_3$CN (0.05 M) and H$_2$O$_2$ (50 wt%, 36.8 µL, 0.6 mmol, 1.2 equiv.) in 4.5 mL CH$_3$CN (0.13 M) were added without modification from the previously described procedure. The reaction was run with two different workups; one workup was designed to isolate lactone product and a second workup was designed to isolate (S,S)-PDP ligand.$^{97}$

**Isolation of the lactone product:** The reaction was quenched with a solution of saturated NaHCO$_3$. The aqueous layer was extracted with Et$_2$O (3 × 30 mL) and the organic layers were combined, dried over MgSO$_4$, filtered, and concentrated carefully by rotary evaporation at 0°C to prevent loss of volatile product. The crude product was purified by flash silica gel column chromatography (30% EtOAc/hexanes). The product 5,5-dimethyldihydrofuran-2(3H)-one$^{98}$ was obtained in 27.5 mg (run 1, 0.241 mmol, 48%) and 26.9 mg (run 2, 0.236 mmol, 47%). Average: 48%.

**Isolation of (S,S-PDP) ligand:** The crude reaction was quenched with concentrated NH$_4$OH and concentrated via rotary evaporation at 35°C to dryness in order to remove volatile lactone product. The brown residue was filtered through a SiO$_2$ plug with EtOAc as eluent to obtain free (S,S)-PDP ligand: run 1, 23.1 mg, 0.072 mmol, 95%; run 2, 22.8 mg, 0.071 mmol, 94%; based on 15 mol% (0.075 mmol). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.49 (dd, J = 0.8, 4.8 Hz, 2H), 7.60 (dt, J = 2.0, 7.8 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.11 (dd, J = 5.2, 6.0 Hz, 2H), 4.19 (d, J = 14.0 Hz, 2H), 3.49 (d, J = 14.4 Hz, 2H), 2.99 (p, J = 4.4 Hz, 2H), 2.79 (m, 2H), 2.22
(appq, J = 8.4 Hz, 2H), 1.77-1.64 (m, 8H). $^{13}$C NMR (100 MHz, CDC$_3$) δ 160.4, 148.8, 136.3, 122.7, 121.6, 65.3, 61.1, 55.3, 25.9, 23.5. IR (film, cm$^{-1}$): 2960, 2920, 2872, 2806, 1588, 1570, 1474, 1431, 1366, 1212, 1150, 1120, 1046, 993, 931, 897, 759. HRMS (ESI) m/z calc’d C$_{20}$H$_{27}$N$_4$ [M+H]$^+$: 323.2236, found 323.2239.

UV-Vis Study:

UV-vis analysis of reaction before and after H$_2$O$_2$ addition. All UV-Vis spectra were taken in 1 cm quartz cuvettes with an acetonitrile blank at 21°C between 400-800 nm. A reaction vial was setup identically to Table 1, Entry 1. Before the addition of H$_2$O$_2$, a 10 µL aliquot was taken out of the reaction mixture, diluted to 1 mL with CH$_3$CN (3.3 mM in relation to 61) and examined by UV-vis. After completion of the reaction, a 20 µL aliquot was taken from the crude mixture, diluted to 1 mL with CH$_3$CN (0.95 mM in relation to 61) and examined by UV-vis. The UV-vis spectrum obtained after H$_2$O$_2$ addition reveals several spectroscopic features that are characteristic of bent (μ-oxo) diiron (III) compounds: (1) three features between 400 and 500 nm, (2) a shoulder near 525 nm and (3) a broad band near 700 nm.

4.5 REFERENCES


PDP indicates 2-\{((S)-2-\{(S)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl\}pyrrolidin-1-yl\}-methyl\)-pyridine.


