Palladium-Catalyzed Functionalization of C-H Bonds and Alkenes

by

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Abstract

A highly regio- and chemoselective methodology for the ligand-directed palladium-catalyzed C-H activation/acetoxylation of sp$^3$ C-H bonds was developed. The reaction was found to be general with a variety of directing groups such as oxime ethers, isoxazolines and pyridines. In addition, the reaction exhibited high selectivity for the acetoxylation of 1° sp$^3$ C-H bonds.

The ligand directed palladium-catalyzed C-H activation/acetoxylation of sp$^2$ and sp$^3$ C-H bonds was shown to be effective with alternative oxidants such as Oxone and K$_2$S$_2$O$_8$ in place of PhI(OAc)$_2$. The use of these peroxide based oxidants over PhI(OAc)$_2$ is advantageous because they are cheaper and do not release toxic byproducts such as iodobenzene.

A comprehensive investigation to elucidate the factors affecting the C-H activation/acetoxylation by one ligand over another was conducted. It was determined that in the presence of multiple chelating functionalities in a reaction, the substrate bearing the most basic ligand would lead to the predominant product under our reaction conditions. These transformations are believed to proceed via a Pd$^{II/IV}$ catalytic cycle. Mechanistic studies implicate that ligand directed palladium mediated C-H activation is the rate-limiting step in these reactions.

Finally, Pd-alkyl intermediates generated via aminopalladation were intercepted using strong oxidants such as PhI(OAc)$_2$ to afford 1,2-difunctionalized products. Under our optimal conditions, the use of alkenes bearing tethered alcohols, acids, or amines led to the formation of substituted tetrahydrofuran rings, lactones, or pyrrolidines.
Chapter 1

Introduction

The direct catalytic functionalization of C–H bonds is an important challenge in organic chemistry.\textsuperscript{1-7} Traditionally, the introduction of a functional group in a molecule requires a pre-functionalized starting material (Scheme 1.1, pathway a), which might be challenging to access in the context of complex molecule synthesis. In contrast, C–H bonds are ubiquitous in nature; hence their direct transformation to diverse functional groups would be highly desirable (Scheme 1.1, pathway b).

**Scheme 1.1**: Routes for Introducing Functional Groups (FG) into Organic Molecules

\[
\begin{align*}
\text{Pathway a} & : \quad \text{R} - \text{H} \xrightarrow{\text{FG}} \text{R} - \text{FG} \\
\text{Pathway b} & : \quad \text{R} - \text{H} \xleftarrow{\text{FG}} \text{R} - \text{FG}
\end{align*}
\]

The direct functionalization of C–H bonds is challenging because C–H bonds are unreactive and robust. Their low reactivity can be attributed to the fact that they are strong, localized, and unpolarized bonds.\textsuperscript{2,8} Transition metal catalysis can be used to assist in converting C–H bonds to more reactive carbon-metal bonds that can subsequently be functionalized to afford the desired product (Scheme 1.2).

**Scheme 1.2**: Transition Metal-Catalyzed Activation/Functionalization of C–H Bonds

\[
\begin{align*}
\text{R} - \text{H} + \text{cat. [M]} & \xrightarrow{\text{C–H Activation}} \text{R} - \text{[M]} \\
\text{Functionalization} & \quad \Rightarrow \quad \text{R} - \text{FG}
\end{align*}
\]
There were a number of examples of transition metal-catalyzed C–H activation/C–C bond formation prior to our work.\textsuperscript{9} In contrast, C–H activation/carbon–heteroatom bond forming reactions were very limited.\textsuperscript{10} Our initial goal was to develop a transition metal-catalyzed mild, regio-, and chemoselective method to convert C–H bonds to C–O bonds. This transformation would be very useful because C–O bonds are widely prevalent in biologically active molecules. Additionally, the petroleum and chemical industries have interest in finding efficient ways to convert inert alkanes into oxygenated hydrocarbons.

Crabtree and coworkers demonstrated the direct transformation of an arene C–H bond to a C–OAc bond.\textsuperscript{11} In particular, they showed that substrates such as chlorobenzene can be acetoxylated in the presence of catalytic Pd(OAc)\textsubscript{2} and stoichiometric PhI(OAc)\textsubscript{2}. As depicted in Scheme 1.3, a mixture of ortho, meta and para regioisomers of the acetoxylated product were obtained. The authors proposed that PhI(OAc)\textsubscript{2} served as the source of the acetate in the final product, and as an oxidant that effects the oxidative functionalization of the carbon-palladium bond resulting from C–H activation. While this report was an important demonstration that C–H bonds can be oxygenated with readily available catalysts under mild conditions, this reaction was limited by its very low yield, the need for large excess of substrate, and the lack of regioselectivity.

\textbf{Scheme 1.3: Palladium-Catalyzed Acetoxylation of Chlorobenzene with PhI(OAc)\textsubscript{2}}

Our group sought to address the challenge of regioselectivity by employing a ligand directed approach for the palladium-catalyzed oxidative functionalization of C–H bonds. This strategy involves the use of substrates bearing coordinating functional groups, such as L in Scheme 1.4, that can chelate to the metal and direct the activation of a proximal C–H bond. We reasoned that the cyclopalladated complex formed upon C–H
activation could then be functionalized using electrophilic reagents such as PhI(OAc)₂ to afford the desired ortho-oxygenated product.

Scheme 1.4: Regioselectivity via Cyclopalladation

Scheme 1.5: Overall Goal for Direct Transformation of C-H to C-O Bonds

The first step for the proposed reaction, namely ligand-directed C–H activation at Pdᴵᴵ (cyclopalladation), is well documented in literature. One of the earliest reports appeared in 1965 with stoichiometric cyclopalladation of azobenzene (Scheme 1.6). Since this report, there have been examples illustrating cyclopalladation with a variety of directing groups such as pyridines, amines, amides, and oximes. Additionally, Miura, Sames, Fujiwara and others have effectively employed the ligand-directed approach for palladium metal catalyzed C-H activation/C–C bond forming reactions. The feasibility for the oxygenation step is supported by the palladium-catalyzed arene acetoxylation reaction discussed above (Scheme 1.3).

Scheme 1.6: Cyclopalladation of Azobenzene

In 2004, our group reported that the approach shown in Scheme 5 provides an efficient route to the ligand-directed acetoxylation of arene C–H bonds. This methodology was shown to be general with respect to a wide variety of directing groups such as pyridines, pyrazoles, andazo-linkages to afford the acetoxylated products in good
yields (Scheme 1.7). Importantly, these reactions were highly selective for functionalization of the C–H bond adjacent to the chelating group.

**Scheme 1.7:** Palladium-Catalyzed Directed Acetoxylation of Arene C–H Bonds

This reaction was proposed to proceed through a Pd$^{II/IV}$ catalytic cycle. As shown in Scheme 1.8, the key steps of the catalytic cycle are proposed to involve: (i) ligand directed C–H activation to afford the cyclopalladated complex A, (ii) oxidation of A by PhI(OAc)$_2$ to generate the Pd$^{IV}$ intermediate B, and (iii) C–O bond-forming reductive elimination from B to release the desired acetoxylated product and regenerate the Pd$^{II}$ catalyst.

**Scheme 1.8:** Proposed Mechanism for Pd$^{II/IV}$ Catalyzed Arene Acetoxylation

All of our group’s initial work in this area involved functionalization of arene C–H bonds using PhI(OAc)$_2$ as the terminal oxidant. As such, the goals of my research (as outlined in this thesis) were as follows:

Chapter 2: To extend this methodology to the oxidation of sp$^3$ C–H bonds (Scheme 1.9).
**Scheme 1.9:** Palladium-Catalyzed Directed Oxidative Functionalization of sp³ C–H Bonds

Chapter 3: To explore the use of alternative oxidants (particularly peroxides) in place of PhI(OAc)₂ for Pd-catalyzed directed C–H activation/oxidation reactions (Scheme 1.10).

**Scheme 1.10:** Use of Peroxides as the Terminal Oxidant in C–H Activation/Oxidation Reactions

Chapter 4: To determine the factors that control which ligand will direct C–H activation/functionalcization when multiple potential chelating functionalities are present in solution (Scheme 11).

**Scheme 1.11:** Competition Studies Between Multiple Directing Groups

Chapter 5: To oxidatively intercept Pd-alkyl intermediates, generated via aminopalladation of alkenes, to form 1,2-difunctionalized products (Scheme 1.12).

**Scheme 1.12:** Palladium-Catalyzed 1,2-Aminooxygenation of Alkenes
1.1 References


Chapter 2

Palladium-Catalyzed Acetoxylation of sp\textsuperscript{3} C-H Bonds

2.1 Background and Significance

Alkane carbon-hydrogen (C–H) bond activation and functionalization has been a formidable challenge in synthetic organic chemistry. In general, sp\textsuperscript{3} C–H bonds are much more difficult to activate than sp\textsuperscript{2} C–H bonds. The unreactive nature of alkanes is attributed to (i) the lack of available lone pairs, empty orbitals of low energy, or filled orbitals of high energy, (ii) the low polarity of these substrates, and (iii) the high homolytic and heterolytic strength of C–H bonds (typical bond dissociation energies range from 90-110 kcal mol\textsuperscript{-1} and pK\textsubscript{a} values are greater than 40).\textsuperscript{1, 2} In addition, the metal-alkyl intermediates that are generated upon C–H activation (for example, A in Scheme 2.1) are typically susceptible to \(\beta\)-hydride elimination. Alkanes are ubiquitous in nature, and are found in diverse organic compounds, including petroleum, natural gas, organic polymers, natural products, pharmaceuticals, and agrochemicals. Hence, developing a methodology for the direct functionalization C–H bonds in alkanes could have a great practical impact on a variety of different fields.

Scheme 2.1: Transition Palladium-Catalyzed Alkane Functionalization
Many research groups have attempted to address the challenge of alkane oxidation. One of the most promising approaches to alkane C–H activationfunctionalization involves the use of group 10 metal (Pt and Pd) catalysts. Although several promising systems have been developed, most are not suitable for practical use. The most prominent early example comes from the 1970’s by Shi and co-workers. They demonstrated that sp³ C–H bonds of simple alkanes such as methane could be functionalized to C–O bonds using catalytic PtII salts in conjunction with stoichiometric PtIV-based oxidants (Scheme 2.2).

Scheme 2.2: Platinum-Catalyzed Oxidation of Methane

While the mild conditions and simplicity of the catalysts in these reactions are remarkable, the utility of this transformation is limited by (i) the requirement of stoichiometric amounts of PtIV and (ii) low selectivity. For instance, pentane is converted to pentyl chloride with only 56% terminal selectivity (Scheme 2.3). Chlorination at other positions on the alkyl chain was also observed. Despite its limitations, this platinum system shows potentially useful features and would be rendered more practical if the PtIV could be replaced with another strong oxidant.

Scheme 2.3: Pentane Oxidation with PtII

An important recent advancement in Pt-catalyzed alkane oxidation was reported by Periana in 1998. This report demonstrated the oxidation of methane to methylbisulfate using a PtII catalyst (bpym)Pt(Cl)₂ (bpym = bipyrimidine) in fuming...
sulfuric acid with SO$_3$ as the terminal oxidant (Scheme 2.4). The mechanism of this reaction is proposed to involve: (i) electrophilic C–H activation to afford a platinum alkyl complex, (ii) oxidation by SO$_3$ to afford a Pt$^{IV}$ species, and finally (iii) reductive elimination from this Pt$^{IV}$ intermediate to provide methyl bisulfate. This reaction is attractive due to its high yield (90%) and selectivity (81%). Installation of an electron withdrawing sulfonic acid group protects the product from further oxidation. However, the utility of this reaction is limited by the requirement of fuming sulfuric acid and high temperatures (200 ºC). Other hydrocarbon substrates, under these harsh conditions, result in low turnover numbers and low levels of regio- and chemoselectivity.

**Scheme 2.4:** (bpym)Pt(Cl)$_2$-Catalyzed C–H Activation/Oxidation of Methane

Schemes has reported some of the earliest examples of group 10 metal catalyzed alkane C–H functionalization, addressing regioselectivity by using a directing functional group.$^7, 8$ As shown in Scheme 2.5, directed arylation of ortho-tert-butylaniline with phenylvinylsilanol was achieved in the presence of catalytic Pd(OAc)$_2$ using Cu(OAc)$_2$ as a terminal oxidant. A mechanism involving dual coordination of the imine and the thioether to Pd was proposed to lead to the high selectivity for the 1º C–H bond. Though catalytic, the reaction is limited by its modest substrate scope. For example, replacing the tert-butyl in 6 with an iso-propyl moiety resulted in only trace amounts of the desired product 9 (Scheme 2.5).
Sames has also reported one of the first examples of heteroatom-directed oxygenation of sp$^3$ C–H bonds involving the Pt$^{II}$-catalyzed selective functionalization of $\alpha$-amino acids in water.$^9$ As shown in Scheme 2.6, this report demonstrated that subjection of valine to 5 mol % K$_2$PtCl$_4$ and 7 equiv CuCl$_2$ in water at 160 ºC resulted in 56% NMR yield of lactone 11. The reaction was proposed to proceed via chelate-directed electrophilic C–H activation by Pt$^{II}$ followed by oxidative functionalization to form the C–O bond. Although this reaction is an important advancement in directed functionalization of alkyl groups in complex substrates, its utility is limited by the moderate yields and the harsh reaction conditions (particularly the high temperatures and the requirement for large excesses of oxidant). Importantly, there were no examples of palladium-catalyzed directed sp$^3$ C–H activation/C–O bond formation when we started this project.

We aimed to address the challenge of C-H activation/functionalization of sp$^3$ C-H bonds by employing the Pd$^{II/IV}$ catalyzed methodology developed for functionalization of sp$^2$ C–H bonds (Chapter 1, Scheme 1.7). The key step in the sp$^2$ C–H bond
functionalization reaction is the oxidative interception of a palladium-aryl intermediate, generated upon C–H activation, with PhI(OAc)_2 (Scheme 1.8, Chapter 1). Our goal was to generate an analogous palladium-alkyl intermediate via ligand-directed sp^3 C–H bond activation (Scheme 2.7). Oxidative cleavage of the Pd–C bond in with PhI(OAc)_2, would then allow us to install an OAc group at the sp^3 carbon center via the Pd^{IV} intermediate.

While Pd-catalyzed directed sp^3 C–H activation/oxygenation reactions were unprecedented prior to our work, several previous reports had described stoichiometric versions of this transformation. For example, Baldwin and co-workers illustrated that the reaction of pinacolone oxime with stoichiometric K_2PdCl_4 leads to the formation of palladacycle via ligand directed activation of a terminal C–H bond of the tert-butyl group. Subsequent oxidation of with Pb(OAc)_4 was then shown to form the acetoxylated product (Scheme 2.8).

Although this reaction demonstrates the viability of directed sp^3 C–H bond activation, it is impractical for several reasons. First of all, it is stoichiometric in both an expensive Pd^{II} salt and a highly toxic Pb^{IV} salt. Second, it has a very limited substrate scope. As shown in Table 2.1, methylated cyclohexanone oximes 19 and 21 and the steroid derivative 23 were the only substrates that were successfully acetoxylated by
Baldwin using this method. In contrast, isolable palladacycles could not be obtained for substrates that lacked α-branching (for example, 25 in Figure 2.1), for substrates in which the C–H bond and the directing group were not coplanar (for example, 27 and 28 in Figure 2.1), and for substrates that were susceptible to β-hydride elimination upon C–H activation (for example, 25 and 26 in Figure 2.1).

Table 2.1: Substrate Scope for Stoichiometric sp³ C–H Activation/Oxygenation at PdII

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /> (19)</td>
<td><img src="image2" alt="Image" /> (20)</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /> (21)</td>
<td><img src="image4" alt="Image" /> (22)</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /> (23)</td>
<td><img src="image6" alt="Image" /> (24)</td>
<td>76%</td>
</tr>
</tbody>
</table>

Conditions: (i) Na₂PdCl₄, (ii) pyridine (iii) Pb(OAc)₄ and (iv) NaBH₄

Figure 2.1: Substrates That Did Not Form Isolable Palladacycles

Based on this early report, we aimed to develop an efficient palladium-catalyzed method to acetoxylate sp³ C–H bonds that was directed by ketone or aldehyde-derived directing groups. We wanted to use a terminal oxidant that was less toxic and more practical than Pb(OAc)₄. Additionally, in order to make this reaction general for a wide variety of substrates, we hoped to develop reaction conditions under which the relative
rate of oxidative cleavage of the Pd–C bond in 13 was faster than the undesired β-hydride elimination reaction (Scheme 2.9).

**Scheme 2.9: β-Hydride Elimination Versus Oxidation**

Importantly, the proposed methodology could potentially allow access to β-amino alcohols, β-hydroxy ketones, and functionalized β-amino acids (Scheme 2.10). It could also provide a tool for the synthesis and functionalization of alkaloids and polyketides as well as other classes of natural products. The ability to selectively functionalize a variety of C–H bonds to C–O bonds could also allow for the efficient synthesis of drug molecules to be tested in structure-activity relationship (SAR) studies. Finally, the insights gained from this palladium-catalyzed ligand–directed oxygenation of sp³ C–H bonds could then potentially be applied towards functionalization of alkane C–H bonds without the use of directing groups. This would then allow us to address an important challenge of methane oxidation to methanol.

**Scheme 2.10: Potential Applications of the Proposed Reaction**
2.2 Initial Results

Our studies began with using pinacolone oxime 16 as the substrate. This choice was based on Baldwin’s results, which demonstrated the successful oxygenation of the β-C–H bond of 16 using stoichiometric K$_2$PdCl$_4$ and Pb(OAc)$_4$ (Scheme 2.8).$^{12}$ We first subjected 16 to the reaction conditions developed in our lab for sp$^2$ C–H acetoxylation (5 mol % Pd(OAc)$_2$, 1.5 equiv PhI(OAc)$_2$ in AcOH at 100 °C). However, under these conditions we obtained none of the desired oxygenated product 18 and instead recovered the deprotected ketone 29 (Scheme 2.11). This indicates that the relative rate of deprotection of the oxime was faster than the rate of oxime-directed C–H activation at Pd$^{II}$. The ketone product of this deprotection is then expected to be a poor ligand for palladium, and hence unable to direct the functionalization.

**Scheme 2.11:** Attempted Pd-Catalyzed Acetoxylation of Pinacalone Oxime with PhI(OAc)$_2$

\[
\begin{align*}
\text{HO}_2^N & \quad \xrightarrow{5 \text{ mol } \% \text{ Pd(OAc)}_2} \quad \text{O}_2^N \\
\text{(16)} & \quad \text{1.2 equiv PhI(OAc)}_2 \quad \text{AcOH, 100 °C} \\
& \quad \text{(29)} \\
& \quad \text{(18) not observed}
\end{align*}
\]

This result suggested that in order to achieve the desired catalytic oxygenation reaction, we would need to prevent deprotection of the oxime. As depicted in Scheme 2.12, a key step in the proposed mechanism for this deprotection involves nucleophilic attack of the oxime hydroxyl group on the iodine.$^{14}$ Based on this mechanism we hypothesized that replacing the hydroxyl group with an alkyl ether might attenuate the oxidative deprotection while still maintaining the ligand’s coordinating ability to palladium.
Scheme 2.12: Proposed Mechanism for Oxidative Deprotection

Based on this analysis, the oxime ether substrate 30 was synthesized and subjected to the catalytic reaction conditions (5 mol % Pd(OAc)₂, 1.5 equiv PhI(OAc)₂ in AcOH at 100 °C). Gratifyingly, the desired monooxygenated product 31 was obtained in 14% isolated yield along with the corresponding di- (34%) and tri-acetoxylated compounds (15%) (Scheme 2.13). Notably, the use of an excess of PhI(OAc)₂ (4.5 equiv) increased the yield of the tri-oxygenated product 33 to 59%.

Scheme 2.13: Pd-Catalyzed Acetoxylation of Pinacalone Oxime Methyl Ether with PhI(OAc)₂

2.3 Substrate Scope of Pd-Catalyzed Acetoxylation of 1° sp³ C-H Bonds

**Highly Branched Substrates.** We were pleased to find that ligand-directed Pd-catalyzed C–H bond activation/acetoxylation was general with respect to a variety of directing groups (Table 2.2).¹⁵ My colleague Kami Hull demonstrated the use of pyridine directing groups in these reactions, while my work showed that oxime ethers (34-38) and isoxazolines (42-48) are also effective in mediating the desired acetoxylation reaction. Furthermore, acetoxylation was achieved in systems that proceeded via either a five-
membered (entries 1-6) or a six-membered palladacyle intermediate (entry 8). Unlike substrate 48, the six-membered cyclopalladation is not facile with unactivated C-H bonds such as in substrate 46. Selectivity between mono-, di- or tri-acetoxylated products could be tuned by changing the stoichiometry of the oxidant. For example, the di- and tri-acetoxylated products 43 and 45 were formed in 45% and 55% isolated yields using either two or three equivalents of PhI(OAc)$_2$, respectively. Importantly, control reactions (in the absence of Pd catalyst) were run for each substrate, and generally showed no reaction under our standard conditions.

Interestingly, the C–H bond in camphor methyl oxime ether 34 was successfully acetoxylated (entry 1). This is particularly notable because Baldwin was unable to obtain an isolable palladacycle with this substrate. We believe that 34 affords the product under our reaction conditions because, unlike in stoichiometric experiments, a catalytic reaction does not require that the palladacycle have an appreciable lifetime. Instead, it just needs to be generated transiently and then can be intercepted by the oxidant to afford the desired product.
Table 2.2: Scope of Pd-Catalyzed Directed sp$^3$ C–H Activation/Acetoxylation with PhI(OAc)$_2$: Highly Branched Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^a$</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{NMeO}_2) (\text{NMeO}_2)</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>75%$^b$</td>
<td>5</td>
<td>(\text{N-OAc}) (\text{N-OAc}) (\text{OAc}) (\text{OAc})</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>45%$^b$</td>
</tr>
<tr>
<td>2</td>
<td>(\text{MeO}_2) (\text{NMeO}_2)</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>51%$^b$</td>
<td>6</td>
<td>(\text{N-OAc}) (\text{N-OAc}) (\text{OAc}) (\text{OAc})</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>55%$^c$</td>
</tr>
<tr>
<td>3</td>
<td>(\text{MeO}_2) (\text{NMeO}_2)</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>61%$^b$</td>
<td>7</td>
<td>(\text{N-OAc}) (\text{N-OAc}) (\text{OAc}) (\text{OAc})</td>
<td>(\text{OAc}) (\text{OAc})</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{AcO}) (\text{AcO}) (\text{AcO}) (\text{AcO})</td>
<td>(\text{AcO}) (\text{AcO})</td>
<td>63%$^c$</td>
<td>8</td>
<td>(\text{AcO}) (\text{C}_4\text{H}_9)</td>
<td>(\text{AcO}) (\text{C}_4\text{H}_9)</td>
<td>60%</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 5 mol % Pd(OAc)$_2$, 1.5 equiv PhI(OAc)$_2$, AcOH, 100 °C; $^b$ 2.0 equiv PhI(OAc)$_2$ were used; $^c$ 3.0 equiv of PhI(OAc)$_2$ were used

Substrates Containing β-Hydrogens. The substrates presented in Table 2.2 do not bear hydrogens α to the carbon being functionalized. Hence, β-hydride elimination from the palladacyclic intermediate is not a potential competing reaction in these systems. As such, we next turned our attention towards substrates that could undergo β-hydride elimination following C–H activation. We wanted to explore whether the relative rate of oxidative cleavage of intermediate 13 would be faster than the undesired β-hydride elimination under our reaction conditions (Scheme 2.9).

We first synthesized the oxime ether of methyl cyclohexanone. We were pleased to find that subjection of this substrate to our reaction conditions did not afford any of the β-hydride elimination product 53. Furthermore, the desired acetoxylated product 51 was obtained from this reaction, albeit in a modest yield of 4% (Scheme 2.14). This low yield was due to competitive formation of the corresponding ketone 52.
Scheme 2.14: Pd-Catalyzed Reaction of Cyclohexanone Methyl Oxime Ether with PhI(OAc)₂ in AcOH

![Scheme 2.14](image)

The ketone 52 was not formed via oxidative deprotection of the directing group, since substrate 50 also reacted to generate 52 in AcOH in the absence of PhI(OAc)₂. Instead, we theorized that since 50 is less sterically hindered than the previously studied substrates, it was simply undergoing hydrolysis in the reaction medium. This result suggested that the addition of acetic anhydride (Ac₂O) might be used to sequester the water in the reaction mixture and hence prevent this competing hydrolysis. In order to probe this hypothesis, we subjected substrate 50 to the catalytic reaction conditions using 50% AcOH/50% Ac₂O as the solvent in place of pure AcOH. We were delighted to find that these conditions afforded the acetoxylated product 51 in 81% yield.

Scheme 2.15: Pd-Catalyzed Reaction of Cyclohexanone Methyl Oxime Ether with PhI(OAc)₂ in AcOH/Ac₂O

![Scheme 2.15](image)

These optimal reaction conditions were general for a variety of other substrates containing β-hydrogens (Table 2.3).¹⁵ Importantly, products resulting from β-hydride elimination were not observed for any of these substrates, indicating that the oxidative cleavage of the palladacyclic intermediate out-competes β-hydride elimination in these systems. Interestingly, substrates that did not afford isolable palladacycles in the Baldwin system were successfully functionalized under our catalytic conditions (entries 1 and 3).¹¹ Additionally, substrates lacking branching at the α-position (54) were also acetoxylated.
Such systems were challenging to functionalize under the reaction conditions developed by both Baldwin and Sames.

**Table 2.3**: Scope of Pd-Catalyzed Directed sp$^3$ C–H Activation/Acetoxylation with PhI(OAc)$_2$: Substrates with β-Hydrogens

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^a$</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield$^a$</th>
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<tbody>
<tr>
<td>1</td>
<td>MeO-N-C$_6$H$_5$ (54)</td>
<td>MeO-N-C$_6$H$_5$ OAc (55)</td>
<td>39%</td>
<td>5</td>
<td>MeO-N-C$_6$H$_5$ OAc (62)</td>
<td>MeO-N-C$_6$H$_5$ OAc (63)</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>N-O-C$_6$H$_5$ (56)</td>
<td>N-O-C$_6$H$_5$ OAc (57)</td>
<td>37%</td>
<td>6</td>
<td>N-O-C$_6$H$_5$ OAc (64)</td>
<td>N-O-C$_6$H$_5$ OAc (65)</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>MeO-N-C$_6$H$_5$ (58)</td>
<td>MeO-N-C$_6$H$_5$ OAc (59)</td>
<td>74%</td>
<td>7</td>
<td>N-O-C$_6$H$_5$ OAc (66)</td>
<td>N-O-C$_6$H$_5$ OAc (67)</td>
<td>47% (1:1 dr)</td>
</tr>
<tr>
<td>4</td>
<td>tBu-N-C$_6$H$_5$ (60)</td>
<td>tBu-N-C$_6$H$_5$ OAc (61)</td>
<td>86%</td>
<td>8</td>
<td>N-O-C$_6$H$_5$ Ph (68)</td>
<td>N-O-C$_6$H$_5$ Ph (69)</td>
<td>25% (1:1 dr)</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 5 mol % Pd(OAc)$_2$, 1.2 equiv PhI(OAc)$_2$, AcOH/ Ac$_2$O, 100 °C

In the isoxazoline substrates containing a stereocenter, the functionalization of diastereotopic methyl groups proceeded with no selectivity. However, after our initial findings, Yu reported 82% de in the Pd-catalyzed acetoxylation of prochiral methyl groups in oxazoline substrate 70. Notably, substrates in which the tert-butyl group on the tertiary carbon was replaced with other alkyl groups or ethers exhibited lower dr values ranging between 18% and 60%. Based on these results, it appears that both the location of the stereocenter within the substrate as well as the steric nature of the stereocenter and the substrate are key to attaining diastereoselectivity in these C–H activation reactions.
Scheme 2.16: Palladium-Catalyzed Acetoxylation of Prochiral Methyl Groups with Lauroyl Peroxide

Conformational Effects on Reactivity. While conducting these studies we made an interesting observation regarding the reactivity differences between substrates 50 and 60. Both these substrates lead to similar yields of the corresponding products 51 and 61. However, while reaction of substrate 50 took 3 h to reach completion, reaction of 60 was finished in only 5 min. This dramatic difference can be rationalized based on the relative amounts of the reactive conformers of 50-\textit{eq} and 50-\textit{ax} in solution (Scheme 2.17).

Methyl cyclohexanone 50 exists in two conformers of similar energy that are at rapid equilibrium – one in which the methyl group is in the equatorial position (50-\textit{eq}) and one in which the methyl group is in the axial position (50-\textit{ax}). However, only conformer 50-\textit{eq} has the C–H bond of the methyl group co-planar with the oxime, the geometry required for cyclopalladation. In contrast, substrate 60, possessing a \textit{tert}-butyl group on the cyclohexane ring, essentially exists only as the more reactive conformer 60-\textit{eq} with the \textit{β}-C–H bond coplanar with the oxime ether.
**Regioselectivity.** We were next interested in exploring the relative preference for functionalization of 1º relative to 2º sp³ C–H bonds under our reaction conditions. In addition, we wanted to compare the selectivity for the functionalization of sp³ C–H bonds that are four versus five bonds away from the chelating group. Substrate 72 was synthesized in order to investigate both issues. This substrate possesses three potential sites for C–H activation: (i) a 2º β-C-H bond (Hₐ), whose activation would lead to the formation of a five-membered palladacycle intermediate 73, (ii) a primary β-C-H bond (H₈), whose activation would also afford a five-membered palladacycle 74, and (iii) a 1º γ C–H bond (H₉), whose activation would afford the six-membered palladacycle 75 (Scheme 2.18). When 72 was subjected to our reaction conditions, we were pleased to see that C–H activation/acetoxylation proceeded with very high selectivity. This reaction afforded 78% isolated yield of a single product (77), in which a 1º β-C–H bond was acetoxylated. This result indicates that directed C–H activation at Pd(OAc)₂ shows a high preference for 1º over 2º C–H bonds. Notably, the observed selectivity is much higher than that in the Pt-catalyzed Shilov system.⁴ This selectivity is complementary to that obtained using other C–H functionalization methods that proceed by radical or cationic mechanisms.¹,¹⁷,¹⁸ In addition, the results in Scheme 2.18 show that there is a preference
for the formation of five-membered palladacycles over six-membered palladacycles. This preference is further exemplified by the lack of reactivity of substrates such as 64 (Table 2.3) and 46 (Table 2.2). Notably, although formation of both 5- and 6-membered palladacycles is reported in literature,\(^\text{19}\) generally a preference for 5-membered metallacycles has been noted. It has been reasoned that this could be due to the requirement of a square-planar coordination environment at the metal. Six membered palladacycles have been achieved when (i) C-H bonds that can form five-membered metallacycle are absent and (ii) steric features of the substrate influence metallacycle formation.\(^\text{19}\)

**Scheme 2.18:** Regioselectivity in sp\(^3\) C-H Bond Acetoxylation

*Cyclopropane Substrates.* During efforts aimed at expanding the scope of this methodology, an interesting reaction was observed with the cyclopropyl methyl oxime ether substrate 79. Subjection of 79 to the standard reaction conditions (5 mol % Pd(OAc)\(_2\), 1.2 equiv PhI(OAc)\(_2\) in a 1:1 mixture of AcOH/Ac\(_2\)O at 100 °C) resulted in the formation of a ring opened product 81, rather than the expected acetoxylated product 80 (Scheme 2.19). Importantly, control experiments in the absence of Pd(OAc)\(_2\) showed none of product 81, indicating that this reaction is palladium-catalyzed. Interestingly, product 81 was also obtained when the reaction was carried out in the presence of benzoquinone, a weaker oxidant than PhI(OAc)\(_2\) that is traditionally used in Pd\(^{0/II}\)
catalyzed reactions. This result indicates that the acetate in the product is derived from the solvent and further that the reaction does not involve Pd$^{IV}$ intermediates.

**Scheme 2.19**: Pd-Catalyzed Oxime-Directed Oxidative Ring Opening of Cyclopropanes

Substrate 82 also yielded the ring-opened product in 83% yield when subjected to catalytic conditions (5 mol % Pd(OAc)$_2$, 1.5 equiv benzoquinone, 100 °C in AcOH/Ac$_2$O) (Scheme 2.19). However, interestingly, the analogous reaction with ketones 84 and 86 did not afford ring opened products (Scheme 2.19). Instead, unreacted starting material was recovered. This indicates that the oxime ether directs ring opening in the reaction.

Notably, Yu and co-workers observe C-H activation/iodination of the cyclopropane C-H bond, resulting in products similar to 80, instead of ring-opened products such as 81, using oxazoline directing groups.$^{20}$ These transformations occur in
CH\textsubscript{2}Cl\textsubscript{2} at room temperature with 10 mol\% Pd(OAc)\textsubscript{2}, I\textsubscript{2} in conjunction with PhI(OAc)\textsubscript{2}. These results are in sharp contrast to the cyclopropane ring-opening observed in our reactions.

A proposed mechanism for this reaction involves the Pd\textsuperscript{0/II} pathway shown in Scheme 2.20. Simultaneous coordination of the palladium to the oxime ether and cyclopropane could facilitate either intramolecular (path a) or intermolecular (path b) acetate attack on the 3-membered ring to afford intermediate 82a (Scheme 2.20). Subsequent β-hydride elimination from intermediate 82a would then afford product 83.

**Scheme 2.20**: Proposed Mechanism for Pd-Catalyzed Oxidative Ring Opening of Cyclopropanes

Even though we have not conducted detailed mechanistic studies, the above mechanism can be surmised based on preliminary data and on literature precedence. First, the lack of reactivity with ketones 84 and 86, implicates the necessity of a directing group and its possible role in assisting the metal to activate the cyclopropane ring. Second, control reactions of substrates 79 and 82, in the absence of palladium, did not afford even traces of 81 and 83. This result and the fact that benzoquinone is necessary for turnover, together indicate the possibility of a Pd\textsuperscript{II/0} catalytic cycle.

There are a few literature reports of nucleophilic directed ring opening of cyclopropanes at Pd\textsuperscript{II}. For example, Backvall has shown the nucleophilic ring opening of the cyclopropane in substrates such as 2-carene using stoichiometric Pd(Cl)\textsubscript{2}(MeCN)\textsubscript{2} (Scheme 2.21).\textsuperscript{21} He speculates that the palladium binds to the olefin, which assists the metal in activating the cyclopropane for nucleophilic attack by the solvent, acetic acid. The ring-opened palladium complex 89 is then reduced to two isomeric allyl and homoallyl alcohols.
2.4 Competition Studies: sp² versus sp³ C–H bonds

We next desired to investigate the relative rates of functionalization of sp² and sp³ C–H bonds. It has been widely reported that cyclometallation of sp³ C–H bonds is much more difficult at transition metal centers than their sp² counterparts.²², ²³ Several reports have studied the competition between sp² and sp³ C–H bonds in stoichiometric cyclopalladation reactions.²⁴-²⁷ However, the effects of directing group and of chelate ring size on the relative rate of sp² versus sp³ C–H bond functionalization has not been systematically investigated in Pd-catalyzed reactions.

We began our investigations by carrying out a competition experiment between oxime ether substrates 91 and 58, bearing sp² and sp³ C–H bonds, respectively. When 91 and 58 were subjected to the catalytic reaction conditions in the same reaction vessel, a 4.7 : 1 ratio of products 92 : 59 was obtained. After statistical correction for the number of C–H bonds available in each case, we obtain a relative reactivity of 15.6 : 1 for the sp² and sp³ C–H bond, respectively. However, this is not a completely fair comparison, as oxime ether coordination is likely to be favored for the less-sterically hindered substrate 91, thereby further favoring formation of product 92.

Scheme 2.22: Competition Between 91 and 58 in the Same Reaction Vessel
In order to exclude the possibility of varying coordinating abilities of the oxime ether in two different substrates, we designed substrates 93 and 96, which contain both sp$^3$ and sp$^2$ C–H bonds to be functionalized in the same molecule. The Pd-catalyzed acetoxylation of these molecules resulted in preferential functionalization of the sp$^2$ C–H bond (Scheme 2.23). With substrate 96, product 97 was formed exclusively and none of the corresponding sp$^3$ C–H acetoxylation product was observed.

**Scheme 2.23:** Competition Between sp$^2$ and sp$^3$ C–H bonds within the Same Molecule

The formation of 94 as the major product might be due to the greater propensity of arene C–H bonds to undergo C–H activation. Alternatively, this preference of sp$^2$ C–H bond acetoxylation could result from the biases in the oxime isomer conformers. As illustrated in Scheme 2.24, substrate 93 can exist in two different oxime isomer conformations that equilibrate under our reaction conditions. Oxime isomer conformation 93' favors cyclopalladation of the sp$^2$ C-H bond while 93 would lead to C–H activation at an sp$^3$ site.

**Scheme 2.24:** Equilibration between Oxime Isomers
We next carried out a systematic study of the effects of different directing groups on the relative rates of acetoxylation of sp$^2$ and sp$^3$ C–H bonds. We began with studying the competition between sp$^2$ C-H bonds and benzylic C–H bonds. Substrates bearing four different directing groups were synthesized – oxime ether (102), isoxazoline (99), pyridine (105) and pyrazole (108). In these systems, functionalization of the benzylic position would require formation of a six membered palladacyclic intermediate while activation of the arene site would proceed via a 5-membered palladacycle (Table 2.4). As shown in Table 2.4, the pyridine and pyrazole directing groups led to products 106 and 109, resulting from exclusive functionalization of an arene C–H bond (entries 3 and 4). Substrate 102 bearing the oxime ether directing group exhibited somewhat decreased selectivity for acetoxylation of the sp$^2$ C-H bond and produced 103 and 104 in a 12 : 1 ratio (entry 2). Interestingly, the isoxazoline substrate 99 presented only modest preference for sp$^2$ over sp$^3$ C–H bonds, affording a mixture of products 100 and 101 in a 0.8 : 1 ratio. Notably, after correcting for statistics (the number of C–H bonds available), the ratio of sp$^2$ to sp$^3$ for substrate 99 becomes 2 : 1. Hence, the sp$^2$ center is still slightly favored, even here.
Table 2.4: Competition Between Benzylic sp\(^3\) C–H Bonds and sp\(^2\) C–H Bonds as a Function of Directing Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product A</th>
<th>Product B</th>
<th>Ratio A:B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>(99)</td>
<td><img src="image2" alt="Image" /></td>
<td>(100, 27%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td>(102)</td>
<td><img src="image4" alt="Image" /></td>
<td>(103, 58%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td>(105)</td>
<td><img src="image6" alt="Image" /></td>
<td>(106, 65%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td>(108)</td>
<td><img src="image8" alt="Image" /></td>
<td>(109, 90%)</td>
</tr>
</tbody>
</table>

As mentioned above, the ring sizes of the palladacyclic intermediates formed with sp\(^2\) and sp\(^3\) C–H bonds in substrates 99-108 were different. Therefore, we wondered if the selectivity would be reversed if the two ring sizes were switched. However, before answering this question, we sought to determine the largest size palladacycle that could be formed and functionalized under our reaction conditions. Three different directing groups – isoxazoline, pyridine and methyl oxime ether – were selected for this study, and the chain length between the directing group and an appended phenyl ring was systematically varied. As shown in Table 2.5, isoxazoline substrates 113 and 114, which
react via 6- and 7-membered palladacycles, respectively, afforded the acetoxylated products in high yields (entries 2 and 3). However, substrates 117-121, which require formation of 8-, 10-, and 12-membered palladacyclic intermediates, did not form appreciable amounts of the desired acetoxylated products (entries 4, 5, and 6, respectively).

**Table 2.5: Effect of Palladacycle Ring Size on Yields of Pd-Catalyzed C–H Activation/Acetoxylation with Isoxazoline Directing Groups I**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(111)</td>
<td>(112)</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>(113)</td>
<td>(114)</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>(115)</td>
<td>(116)</td>
<td>75%</td>
</tr>
<tr>
<td>4</td>
<td>(117)</td>
<td>(118)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>5</td>
<td>(119)</td>
<td>(120)</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>(121)</td>
<td>(122)</td>
<td>0%</td>
</tr>
</tbody>
</table>
Unlike the isoxazolines, the oxime ether and pyridine directing groups only afforded C–H activation/acetoxylation products via the formation of 5- or 6-membered palladacycles (Table 2.6). The oxime ether substrate 127 provided low (17%) yield of the acetoxylated product 128 generated via a seven-membered palladacycle (entry 3), while the corresponding pyridine substrate 133 showed essentially no reaction (entry 6).

**Table 2.6:** Effect of Palladacycle Ring Size on Yields in Pd-Catalyzed C–H Activation/Acetoxylation with Oxime Ether and Pyridine Directing Groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Major Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>124</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>126</td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>127</td>
<td>128</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>129</td>
<td>130</td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td>131</td>
<td>132</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>133</td>
<td>134</td>
<td>0%</td>
</tr>
</tbody>
</table>
With this data in hand, we predicted that an sp\(^3\) C–H bond that was five bonds away from the chelating group might be functionalized selectively over an sp\(^2\) C–H bond that was further removed. To test this hypothesis, we synthesized isoxazoline substrates 135-141, which all contain an sp\(^3\) C–H bond 5 bonds from the directing group and an sp\(^2\) C–H bond 5, 6, or 7 bonds away from the chelating nitrogen atom (Table 2.7). However, surprisingly, reaction of substrates 135 and 138 afforded predominantly sp\(^2\) C–H functionalization products 136 and 139, along with only traces of 137 and 140. Even when the sp\(^2\) C–H bond was too far to undergo efficient functionalization, such as in substrate 141, the sp\(^3\) C–H bond did not react.

**Table 2.7: Effect of Palladacycle Ring Size on Yields in Pd-Catalyzed C–H Activation/Acetoxylation with Isoxazoline Directing Groups II**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product A 1" /></td>
<td><img src="image3" alt="Product B 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Substrate 2" /></td>
<td><img src="image5" alt="Product A 2" /></td>
<td><img src="image6" alt="Product B 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Substrate 3" /></td>
<td><img src="image8" alt="Product A 3" /></td>
<td><img src="image9" alt="Product B 3" /></td>
</tr>
</tbody>
</table>

We thought that this lack of reactivity might be due to a steric or conformational effect of the alkyl chain in these systems. In order to test this proposal, we replaced the phenyl group with a propyl chain (substrate 62). As shown in Scheme 2.25, even this
substrate afforded only modest 30% yield of the acetoxylated product (compared to 47% for the corresponding i-Pr substituted derivative 66), confirming that this class of substrates exhibits inherently low reactivity.

**Scheme 2.25:** Effect of Sterics on Acetoxylation of 62

We wondered if the effect discussed above was specific to isoxazoline directing groups. Consequently, we repeated the above experiment with oxime ether substrate 144, which could undergo sp$^2$ C–H activation to form a 6-membered palladacycle or sp$^3$ C–H activation to generate a 5-membered palladacycle (Scheme 2.26). Subjection of 144 to the catalytic reaction conditions afforded similar results as the isoxazoline, and only products 145 and 146, resulting from mono- and di-functionalization of the arene, were observed.

**Scheme 2.26:** Competition Between sp$^2$ and sp$^3$ C–H Bonds in Oxime Ether Substrate 144

In all, these results indicate that in general, regardless of the nature of the directing group or the size of the palladacyclic intermediates, the relative rate of functionalization of an arene C–H bond appears to be faster than that of an sp$^3$ C-H bond. However, these studies also emphasize how difficult it is to design systems that really give a fair comparison.
2.5 Functionalization of Secondary sp\(^3\) C-H bonds

As discussed above, the activation of 2\(^o\) sp\(^3\) C–H bonds is even more challenging than that of the corresponding 1\(^o\) substrates. For example, substrate 99, which bears a 1\(^o\) C–H bond and a sp\(^2\) C–H bond proximal to the directing group, reacted to form a 2 : 1 (after statistical correction) mixture of the two possible mono-acetoxylation products (Scheme 2.27). However the analogous substrate 148, where the methyl group is replaced by an ethyl group, afforded only 8% of the 2\(^o\) sp\(^3\) C–H bond functionalized product (Scheme 2.27). Furthermore, this functionalization took place after the sp\(^2\) C–H bond was already acetoxyated (ie, when no other sites were available for directed C–H activation). In addition, substrate 148 contains an “activated” benzylic 2\(^o\) sp\(^3\) C–H bond. These results emphasize that unactivated 2\(^o\) C–H bonds are expected to be even more unreactive.

**Scheme 2.27**: Competition between of 2\(^o\) sp\(^3\) C-H Bond and sp\(^2\) Bond

Several different features were explored in an attempt to promote Pd-catalyzed C–H activation/acetoxylation of unactivated 2\(^o\) sp\(^3\) C–H bonds. These include: (i) increasing branching α to the directing group (substrates 152 and 155 in Figure 2.2), (ii) the use of substrates that would form 5- or 6-membered palladacycles (151, 153-155 and 152, respectively), and (iii) the use of different directing groups. However, none of these substrates afford any of the desired acetoxylated products under our standard conditions (5 mol % Pd(OAc)\(_2\), 1.5 equiv PhI(OAc)\(_2\) in AcOH or AcOH/Ac\(_2\)O at 100 °C).
Figure 2.2: Substrates Containing Unactivated 2° sp\(^3\) C–H Bonds Showing No Reactivity

We believe that the functionalization of 2° sp\(^3\) C-H bonds is challenging for two reasons. First, literature studies show that activation of 2° sp\(^3\) C–H bond at transition metal centers is less thermodynamically favourable. Bergman illustrated this concept through studies of the reaction of Ir complexes with cyclohexane and n-pentane.\(^{28}\) As shown in Scheme 2.28, a \(K_{eq}\) of 10.8 was obtained, indicating that the 1° Ir alkyl complex \(157\) was more stable than the 2° alkyl species \(156\).

Scheme 2.28: Studies of Iridium Complexation with 1° and 2° sp\(^3\) C-H Bonds

Another reason 2° sp\(^3\) C-H bonds are hard to functionalize is due to conformational restriction. It can be challenging to achieve co-planarity between the directing group and the C–H bond, which is known to facilitate C–H activation. As such, we thought we could promote activation of 2° sp\(^3\) C-H bonds, by taking advantage of the double chelation effect and the conformational effects observed earlier (Scheme 2.17).

Double Chelation Effect. The strategy behind ‘double chelation’ is to employ substrates consisting of two different potential directing groups rather than just one. In these systems, the simultaneous coordination of both the ligands to the metal center is expected to lock the Pd proximal to the desired C–H bond (for example, intermediate \(159\) in Scheme 2.29 where \(L_1\) and \(L_2\) are two different chelating ligands for palladium), hence leading to more facile activation of the 2° C–H bond. This concept has been demonstrated in the cyclometalation literature. For example, Canty has shown that the cyclopalladation
of substrate 161 proceeds in 12% yield (Scheme 2.30). In contrast, 2-butylpyridine is unreactive under identical conditions.\textsuperscript{29}

**Scheme 2.29**: Double Chelation Strategy for 2º sp\textsuperscript{3} C–H Bond Activation

\[
\begin{align*}
\text{L}_2 & \quad \text{cat. Pd(OAc)}_2 \quad \text{L}_1 \quad \text{R}_1 \\
(158) & \quad \rightarrow \quad (159) \quad \text{Pd(II)} \quad \text{L}_2 \\
(160) & \quad \text{L}_1 \\
\end{align*}
\]

**Scheme 2.30**: Application of the Double Chelation Strategy

\[
\begin{align*}
\text{Ph(OAc)}_2 & \quad \text{N} \quad \text{N} \\
(161) & \quad \text{Pd(OAc)}_2 \quad \text{AcOH, reflux} \quad 12 \text{ h, 12 \%} \\
(162) & \quad \text{N} \quad \text{OAc} \\
\end{align*}
\]

After the introduction of our chemistry in 2004, several other groups described related Pd-catalyzed reactions involving directed functionalization of sp\textsuperscript{3} C–H bonds. Several of these reports, including work by Daugulis and by Corey, described the use of the double chelation strategy for the functionalization of 2º sp\textsuperscript{3} C–H bonds. In one example, Daugulis demonstrated the arylation of a 2º sp\textsuperscript{3} C–H bond in substrate 163, and proposed a mechanism involving simultaneous coordination of the quinoline and amide directing groups to the Pd\textsuperscript{II} center (Scheme 2.31).\textsuperscript{30} Similarly, Corey successfully transformed a 2º sp\textsuperscript{3} C–H bond in 8-aminoquinoline derivative 166 into a C–OAc bond.\textsuperscript{31} Again, dual chelation of the amide and quinoline functionalities was proposed to be critical for the success of this reaction (Scheme 2.32).
Scheme 2.31: Application of Dual Chelation Strategy: Pd-Catalyzed Arylation of a $2^\circ$ sp$^3$ C–H Bond

![Scheme 2.31](image)

Scheme 2.32: Application of Dual Chelation Strategy: Pd-Catalyzed Acetoxylation of a $2^\circ$ sp$^3$ C–H Bond

![Scheme 2.32](image)

We had similarly reasoned that a dual chelation strategy might be applied in our C–H activation/acetoxylation reactions. In order to investigate this possibility, we synthesized a number of different substrates containing multiple functionalities with the ability to coordinate to the palladium. Substrate 169, containing an oxime ether and an ester functionality, displayed no reactivity under the reaction conditions (5 mol % Pd(OAc)$_2$, 1.5 equiv PhI(OAc)$_2$ at 100 °C in AcOH/MeOH) (Scheme 2.33). Reaction of substrate 171, containing pyridine and oxime ether directing groups, under our standard conditions afforded only product 172, where pyridine-directed functionalization occurred at the $1^\circ$ sp$^3$ C-H bond α to the oxime (Scheme 2.34). Oxime ether derived substrates 174-177 (Figure 2.3), which contain amide and pyridine functionalities as the two directing groups, did not afford an appreciable amount of acetoxylated products under the standard reaction conditions. Optimization studies involving different solvents, temperatures, and catalysts with substrates 174-177, either led to decomposition (substrates 174 and 177) or recovered starting material (substrates 175 and 176). The application of Corey’s conditions with these substrates also produced similar results.\textsuperscript{31}
Scheme 2.33: Dual Chelation Strategy: Ester and Oxime Ether Directing Groups

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{N} & \quad \text{C} \quad \text{O} \\
\text{(169)} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{OAc} & \quad \text{O} \\
\text{N} & \quad \text{C} \quad \text{O} \\
\text{(170)} & \quad \text{Me} \\
\end{align*}
\]

Scheme 2.34: Dual Chelation Strategy: Pyridine and Oxime Ether Directing Groups

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{(171)} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{(172, 6\%)} & \quad \text{Ph} \\
\text{(173, 0\%)} & \quad \text{Ph} \\
\end{align*}
\]

Figure 2.3: Dual Chelation Strategy: Other Substrates Examined

Since substrates 169-177 did not afford any acetoxylation at the 2º positions, we next examined substrates more similar to Corey’s compound 166 under our reaction conditions. Hence, substrate 178, containing an amide and a quinoline as potential directing groups, was synthesized and subjected to 10 mol % Pd(OAc)$_2$, 2 equiv PhI(OAc)$_2$ in AcOH at 100 °C (Scheme 2.35). Gratifyingly, product 180, in which a 2º C–H bond was acetoxylated, was obtained, albeit in low (15%) yield. This low yield appears to be due to competitive N-acetoxylation to form product 179. To address this side reaction, we next examined the analogous N-methylated substrate 181. However, as shown in Scheme 2.35, 181 displayed no reactivity, implicating that the free amide is involved in binding to the palladium and directing C–H activation in substrate 178.
**Scheme 2.35:** Dual Chelation Strategy: 8-Amidoquinoline Derivatives

![Scheme 2.35](image)

**Conformational Lock Effect.** We next sought to explore the application of conformational effects to facilitate $2^\circ$ sp$^3$ C–H bond functionalization. We reasoned that C–H activation would be facilitated in substrates with the $2^\circ$ sp$^3$ C–H bond locked in the same plane as the directing group. To test this hypothesis, we synthesized the methyl oxime ether of trans-decalone (182). In this substrate there are two $\beta$ $2^\circ$ C–H bonds, one in the axial position and the other in the equatorial position. As shown in Scheme 2.36, the C–H bond in the equatorial position is locked in the same plane as the directing group.

**Scheme 2.36:** Conformational Lock Strategy: trans-Decalone Oxime Ether

![Scheme 2.36](image)

We were pleased to find that the trans-decalone oxime ether underwent clean C–H bond acetoxylation under our standard conditions (5 mol % Pd(OAc)$_2$, 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O at 100 °C) to provide 184 in 81% yield as a single diastereomer (Scheme 2.37). Importantly, both NMR coupling constant analysis and x-ray crystallography revealed that this diastereomer contained the acetate in the equatorial position, cis to the proton at the junction of the fused rings. The coupling constant
between H\textsubscript{a} and H\textsubscript{b} was 10.9 Hz, indicating a \textit{trans} relationship. Since oxime ether 182 was an oil, the crystal structure of the deprotected ketone product 185 was obtained (Figure 2.4), and, again, this confirmed the proposed stereochemistry.

\textbf{Scheme 2.37:} Conformational Lock Strategy: Pd-Catalyzed Acetoxylation of \textit{trans}-Decalone Oxime Ether

\begin{equation}
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{N} \\
\text{OMe} \\
\end{array}
\xrightarrow{5 \text{ mol} \% \text{Pd(OAc)}_2, 1.1 \text{ equiv Phl(OAc)}_2, \text{AcOH/ Ac}_2\text{O (1:1)}}
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{AcO} \\
\text{N} \\
\text{H} \\
\text{OMe} \\
\end{array}
\end{equation}

\textbf{Figure 2.4:} Crystal Structure of Deprotected Acetate Product 185

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{image.png}
\end{figure}
\end{center}

\textbf{2.6 Stereochemical Nature of Reductive Elimination}

The high diastereoselectivity of the reaction in Scheme 2.37 indicates that C–H activation and functionalization occur with high stereochemical fidelity in this system. This substrate also serves as a probe for the stereochemical nature of the reductive elimination step. As shown in Scheme 2.38, after oxidation of the cyclopalladated complex 186 to Pd\textsuperscript{IV}, there are two potential pathways through which reductive elimination can take place. These are: (i) external acetate attack via an \textit{S}_\text{N}2-type mechanism leading to inversion of stereochemistry at carbon or (ii) direct reductive elimination of coordinated acetate leading to retention of stereochemistry at carbon. There is precedent for the oxidative functionalization of Pd-alkyl intermediates with both inversion (Scheme 2.39)\textsuperscript{32} and retention (Scheme 2.40)\textsuperscript{33} in the literature.
In order to confirm which mechanism is operating in this system, we studied the stoichiometric conversion of a cyclopalladated trans-decalone oxime complex to the mono-acetoxylated organic product 184. Initial attempts to synthesize a palladacycle of the oxime ether 182 yielded complex mixtures of products that could not be separated. However, literature precedent suggested that palladacycle formation is much more facile for oximes.\(^\text{11}\) Hence, we synthesized the chloride-bridged palladacycle dimer of trans-decalone oxime (189), by stirring 188 in MeOH with stoichiometric Na\(_2\)PdCl\(_4\) and NaOAc at room temperature for 3 days (Scheme 2.41). Reaction of the dimer with pyridine in THF, then afforded the desired chloride-monomer along with Pd(py)\(_2\)(Cl)\(_2\) (py = pyridine) as an impurity (Scheme 2.41). The reaction time was critical in dictating the amount of impurity formed, and 10 min was found to be optimal, leading to a Pd(py)\(_2\)(Cl)\(_2\) : 190 ratio of 1.5 : 1. Multiple purifications by column chromatography and crystallization afforded the desired complex in 93% purity. The chloride monomer was
also transformed to the acetate monomer 191 by reaction with AgOAc in AcOH (Scheme 2.41).

**Scheme 2.41**: Stoichiometric Cyclopalladation of *trans*-Decalone Oxime

The structures of the chloride and acetate monomers 190 and 191 were confirmed by X-ray crystallography. The crystal structures of these complexes are shown in Figures 2.5 and 2.6. As predicted in Scheme 2.41 above, the palladacycles formed via activation of the equatorial β C–H bond.

**Figure 2.5**: X-Ray Crystal Structure of Chloro Monomer 190 (pyridine ligand truncated for clarity)
We next studied the oxidation of 190 and 191 with PhI(OAc)$_2$. Reaction of the acetate monomer 191 with PhI(OAc)$_2$ at 100 ºC in AcOH, provided the acetoxylated ketone product 185 as a single diastereomer. As shown in Scheme 2.12 above, the ketone was presumably formed via deprotection of the oxime in the presence of the hypervalent iodine oxidant. The crystal structure of product 185 is shown in Figure 2.4 and clearly confirms that the OAc group is in the equatorial position. This data definitively demonstrates that the C–O bond-forming reaction proceeds with retention of stereochemistry at the carbon center, which implicates pathway ii in Scheme 2.38.

Interestingly, the reaction of the chloride monomer with PhI(OAc)$_2$ yielded two organic products – the expected acetate compound 185 and the chloride-containing product 192. Importantly, both had the new functional group in the equatorial position, again demonstrating retention of stereochemistry at carbon in this reaction. The stereochemistry of the chloride product 192 was determined via coupling constant analysis (the coupling constant was 10.8 Hz, indicating a trans relationship between the ring junction hydrogen and the hydrogen on the carbon bearing the acetate). The
formation of 185 and 192 in an approximately 1 : 1 ratio implies that C–O and C–Cl bond-forming reductive elimination from Pd$^{IV}$ are competitive under these conditions.

**Scheme 2.43**: Reaction of Complex 190 with Phl(OAc)$_2$ to Form C–O and C–Cl Functionalized Products

![Scheme 2.43](image)

The next question we hoped to address was the relative rates of reductive elimination of different functional groups from Pd. In order to probe this, we carried out the reactions of chloro and acetate complexes 190 and 191 with two additional oxidants – PhICl$_2$ and MeI. Interestingly, the reaction of acetate monomer 191 with PhICl$_2$ afforded the chloride product 192 exclusively (Scheme 2.44), suggesting that despite the acetate ligand initially on the metal, only C–Cl bond-forming reductive elimination took place. Similarly, when MeI was used as the oxidant in the reaction of 191, methylated compound 193 was the sole organic product obtained (Scheme 2.44). Again, the Me group was in the equatorial position (verified by x-ray crystal structure), indicating that reductive elimination occurred with retention.

**Scheme 2.44**: Oxidation of Complex 191 with PhICl$_2$ and MeI

![Scheme 2.44](image)
As shown in Scheme 2.45, reaction of the chloride monomer \( \text{190} \) with MeI formed solely the methylated product \( \text{193} \), indicating preferential C–Me bond forming reductive elimination. As expected subjection of the chloride monomer \( \text{190} \) to PhICl\(_2\) afforded the chloride product \( \text{192} \) (Scheme 2.45).

**Scheme 2.45:** Oxidation of Complex \( \text{190} \) with PhICl\(_2\) and MeI

![Scheme 2.45](image)

The data discussed above suggests that the order of preference for reductive elimination from Pd\(^{IV}\) is Me > Cl > OAc. Notably, we do realize that the *cis* versus *trans* geometry of the ligands in the transient Pd\(^{IV}\) intermediate can also influence the reductive elimination product distribution, since the X ligand must be *cis* to the carbon center for bond formation to take place. Nonetheless, the results thus far suggest a higher preference for reductive elimination of the most nucleophilic ligand. Importantly, the trend observed in the stoichiometric oxidation studies above is consistent with what has been observed in the benzoate Pd\(^{IV}\) complexes studied previously in our lab. Reductive elimination reactions from complexes such as \( \text{194} \) proceeded fastest with more electron donating substituents X on the benzoate ligand (Scheme 2.46). \(^3^4\)
Scheme 2.46: Reductive Elimination from (phpy)$_2$Pd$^{IV}$(O$_2$Car)$_2$ Complexes

![Diagram](attachment:image.png)

Notably, we have not yet been able to observe any appreciable amount of chlorinated or methylated products in catalytic reactions where PhI(OAc)$_2$ was substituted with PhICl$_2$ and MeI. With PhICl$_2$ we observed substrate decomposition and/or unselective chlorination. Reactions with MeI were hampered by the lack of catalytic turnover, and we typically recovered unreacted starting material.

2.7 Deprotection of Directing Groups

As mentioned in the introduction, the advantage of employing oxime ethers and isoxazolines as directing groups for C–H bond acetoxylation is that the products are useful synthons. Through functional group manipulations, we can access β-amino acids, β-hydroxy ketones, β-amino alcohols, and 1,3-diols. Several groups have studied the synthetic applications of isoxazolines. For example, Mapp and co-workers have developed an attractive method to transform isoxazolines into β-amino acids (Scheme 2.47).\textsuperscript{35}

Scheme 2.47: Formation of β-Amino Acids from Isoxazolines

![Diagram](attachment:image.png)

Methyl oxime ethers are robust protecting groups, and hence there are relatively limited literature examples of their deprotection.\textsuperscript{36} In some cases, we have found that
oxime ethers can be deprotected under acidic conditions. However, under those conditions, we also observe competitive elimination and/or hydrolysis of the acetate group. For example, subjection of substrate 198 to 0.5 M HCl in CH₂Cl₂ afforded the hydrolyzed product 200 along with alkene 199 (Scheme 2.48). A similar distribution of undesired products was obtained when the reaction of substrate 198 was conducted in refluxing 1 M AcOH. ³⁶

**Scheme 2.48:** Attempts to Deprotect C–H Activation/Acetoxylation Product 198 with Bronsted Acids

These side reactions could be avoided using a procedure developed by Corey in the synthesis of prostaglandins. ³⁷ Subjection of substrate 184 to Corey’s conditions (2 equiv TiCl₃ and 2 equiv of NH₄OAc, in a refluxing mixture of 1:10 H₂O : dioxane) afforded deprotected β-keto-acetate product like 185 (Scheme 2.49) in 56% yield. This product could then be readily converted to the corresponding β-hydroxy ketone in 75% yield by reaction with 0.1 equiv K₂CO₃ in MeOH (Scheme 2.49).

**Scheme 2.49:** Deprotection of C–H Activation/Acetoxylation Product 184 with TiCl₃
2.8 Conclusion

In summary, Pd-catalyzed selective oxidation of 1º sp$^3$ C–H bonds was achieved using directing groups such as oxime ethers and isoxazolines. Importantly, this reaction was applied to diverse substrates, and competitive β-hydride elimination was not observed. Competition studies between sp$^2$ and sp$^3$ C–H bonds indicated a high preference for sp$^2$ C–H activation-functionalization. The functionalization of an unactivated 2º sp$^3$ C–H bond was achieved by taking advantage of conformational effects in trans-decalone. This reaction proceeded with high diastereoselectivity, and allowed determination that C–O, C–Cl, and C–Me bond-forming reductive elimination from Pd$^{IV}$ all proceed with retention of stereochemistry in this system. These studies also revealed a high preference for the reductive elimination of more nucleophilic ligands, with Me > Cl > OAc. Finally, products from these C–H activation/acetoxylation reactions have been converted to useful synthons via functional group interconversion reactions.

2.9 Experimental Procedure

**General Procedures:** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for $^1$H; 125.70 MHz for $^{13}$C) or a Varian Inova 400 (399.96 MHz for $^1$H; 100.57 MHz for $^{13}$C) spectrometer. $^1$H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m), and broad resonance (br).

**Materials and Methods:** Oxime ether substrates were prepared by reaction of the analogous ketones with MeONH$_2$•HCl/pyridine.$^{38}$ Oximes were obtained as mixtures of E/Z isomers when the α-position was mono or disubstituted. The parent ketones of substrates 8 and 15 were prepared by alkylation of the analogous hydrazones followed by hydrolysis with 1 M HCl. Substrate 56 was prepared following a procedure by Chan.$^{39}$
Isoxazolines were prepared by following a literature protocol.\textsuperscript{35} Substrates that were commercially available were obtained from Acros, Lancaster, Aldrich or TCI America and used as received. PhI(OAc)\textsubscript{2} and Pd(OAc)\textsubscript{2} were obtained from Acros and Pressure Chemical, respectively, and were used as received. Solvents were obtained from Fisher Chemical and used without further purification. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F\textsubscript{254}.

**General Procedure for Palladium-Catalyzed Acetoxylation of sp\textsuperscript{3} C-H bonds:**

3-Methyl-2-butanone O-methyl oxime (200 mg, 1.74 mmol, 1 equiv), PhI(OAc)\textsubscript{2} (621 mg, 1.91 mmol, 1.1 equiv), and Pd(OAc)\textsubscript{2} (19 mg, 0.087 mmol, 0.05 equiv) were combined in AcOH (7 mL) and Ac\textsubscript{2}O (7 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100ºC for 3 h. The resulting mixture was filtered through a plug of glass wool and diluted with pentane (20 mL), and the pentane layer was washed with H\textsubscript{2}O (2 x 20 mL), saturated NaHCO\textsubscript{3} (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered, and concentrated to afford a yellow oil, which was purified by chromatography on silica gel (R\textsubscript{f} = 0.3 in 90% hexanes/10% ethyl acetate). The product 9 was obtained as pale yellow oil (222 mg, 74% yield), which was a 6:1 mixture of the oxime E/Z isomers. Each substrate was optimized for reaction time, equiv of oxidant as indicated below.

The reaction was run with 4.5 equiv of PhI(AcO)\textsubscript{2} for 3.5 h in AcOH. Product 33 was isolated as a off-white solid (R\textsubscript{f} = 0.28 in 70% hexanes/30% ethyl acetate, 62% yield). \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \(\delta\) 4.25 (s, 6H), 3.84 (s, 3H), 2.05 (s, 9H), 1.83 (s, 3H), \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (CDCl\textsubscript{3}): \(\delta\) 170.69, 154.34, 62.41, 62.01, 47.50, 20.95, 11.12. Anal. Calcd for C\textsubscript{13}H\textsubscript{21}NO\textsubscript{3}: C, 51.48, H, 6.98, N, 4.62; Found: C, 51.16, H, 7.07, N, 4.80

![Chemical Structure of Compound](image-url)
The reaction was run with 2.0 equiv of PhI(OAc)$_2$ in AcOH. Product 35 was obtained as a viscous oil (75%, $R_f = 0.3$ in 90% hexanes/10% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 4.32 (d, $J = 12$ Hz, 1H), 4.19 (d, $J = 12$ Hz, 1H), 3.74 (s, 3H), 2.44 (m, 1H), 1.99 (s, 3H), 1.95-1.78 (multiple peaks, 4H), 1.40 (m, 1H), 1.20 (m, 1H), 0.95 (s, 3H), 0.84 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 171.18, 165.94, 61.87, 61.59, 54.17, 48.51, 44.82, 33.49, 28.42, 27.04, 21.12, 20.17, 19.95. Anal. Calcd for C$_{13}$H$_{21}$NO$_3$: C, 65.25, H, 8.84, N, 5.85; Found: C, 65.00, H, 8.83, N, 5.87.

The reaction was run with 2.8 equiv of PhI(OAc)$_2$ in AcOH. Product 37 was obtained as a viscous oil (51% yield). $^1$H NMR (CDCl$_3$): $\delta$ 4.46 (d, $J = 11.7$ Hz, 2H), 4.07 (d, $J = 11.5$ Hz, 2H), 3.79 (s, 3H), 2.50 (m, 2H), 2.05 (s, 3H), 1.68-1.59 (multiple peaks, 6H), 1.53 (m, 1H), 1.13 (s, 3H).

The reaction was run with 1.1 equiv of PhI(OAc)$_2$ in AcOH. Product 39 was obtained as a viscous oil (61% yield). Unreacted starting material (28 mg, 28% recovered) was also isolated. $^1$H NMR (CDCl$_3$): $\delta$ 4.02 (d, $J = 11$ Hz, 1H), 3.97 (d, $J = 11$ Hz, 1H), 3.78 (s, 3H), 2.42 (m, 2H), 2.02 (s, 3H), 1.80-1.64 (multiple peaks, 3H), 1.53 (m, 1H), 1.13 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 171.06, 167.11, 69.32, 61.51, 45.37, 36.16, 27.52, 22.48, 20.99, 20.90. Anal. Calcd for C$_{10}$H$_{17}$NO$_3$: C, 60.28, H, 8.60, N, 7.03; Found: C, 60.57, H, 8.69, N, 6.90.
The reaction was run with 2.0 equiv of PhI(OAc)$_2$ in AcOH. Product 43 was obtained as a viscous oil (45% yield). $^1$H NMR (CDCl$_3$): δ 4.78 (m, 1H), 4.19 (s, 4H), 4.09 (m, 2H), 3.08 (dd, J = 16.5, 10.5 Hz, 1H), 2.77 (dd, J = 16.5, 7.0 Hz, 1H), 2.07 (s, 6H), 2.06 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 170.62, 170.48, 170.46, 159.30, 77.32, 40.52, 36.99, 20.70, 18.50.

The reaction was run with 2.0 equiv of PhI(OAc)$_2$ in AcOH. Product 45 was obtained as a viscous oil (55% yield). $^1$H NMR (CDCl$_3$): δ 7.09 (s, 1H), 7.04 (s, 1H), 5.05 (s, 2H), 4.73 (m, 1H), 3.27 (dd, J = 17.0, 10.5, 1H), 2.87 (dd, J = 17.0, 8.5 Hz, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 2.07 (s, 6H), 1.84 (m, 1H), 1.64 (m, 1H), 1.50 (m, 1H), 1.43-1.37 (multiple peaks, 3H), 0.94 (t, J = 7.0 Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ170.56, 170.22, 156.71, 64.38, 61.95, 44.41, 37.25, 20.66, 20.63. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{16}$H$_{23}$NO$_9$, 304.1913; found, 304.1901.

The reaction was run with 2.0 equiv of PhI(OAc)$_2$ in AcOH. Product 49 was obtained as a viscous oil (60% yield). $^1$H NMR (CDCl$_3$): δ 4.79 (m, 1H), 4.27 (s, 6H), 4.08 (m, 2H), 3.10 (dd, J = 17.0, 10.5 Hz, 1H), 2.79 (dd, J = 17.0, 7.5 Hz, 1H), 2.05 (s, 9H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 170.51, 156.32, 139.08, 136.93, 134.58, 131.15, 127.86, 126.88, 81.04, 64.28, 44.43, 35.00, 27.84, 22.51, 21.09, 21.02, 19.59, 13.96. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{16}$H$_{23}$NO$_9$, 396.1271; found, 396.1263.
The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O. The product 51 was obtained as a clear oil. The two isomers were isolated as pale yellow oils (major isomer: 173 mg, 61% yield; minor isomer: 57 mg, 20% yield). Each of the pure isomers was re-subjected to the reaction conditions and the equilibrium mixture (~3:1) was rapidly reestablished in each case. **Major Isomer:** $^1$H NMR (CDCl$_3$): δ 4.39 (dd, $J = 11.2$, 5.9 Hz, 1H), 3.99 (dd, $J = 11.2$, 8.1 Hz, 1H), 3.74 (s, 3H), 2.76 (m, 1H), 2.46 (m, 1H), 1.96 (m, 2H), 1.99 (s, 3H), 1.67 (m, 2H), 1.40 (multiple peaks, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 171.12, 158.86, 64.92, 61.39, 41.21, 30.40, 25.98, 24.30, 24.08, 21.13. **Minor Isomer:** $^1$H NMR (CDCl$_3$): δ 4.17 (dd, $J = 10.8$, 7.8 Hz, 1H), 4.06 (dd, $J = 10.8$, 6.4 Hz, 1H), 3.76 (s, 3H), 3.65 (m, 1H), 2.28 (m, 1H), 2.12 (m, 1H), 1.99 (s, 3H), 1.86 (m, 1H), 1.75 (m, 1H), 1.57-1.33 (multiple peaks, 4H). Anal. Calcd for C$_{10}$H$_{17}$NO$_3$ (mixture of E/Z isomers): C, 60.28, H, 8.60, N, 7.03; Found: C, 59.90, H, 8.91, N, 6.81.

The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O. The two isomers of 55 were isolated as pale yellow oils (isomer a: 137 mg, 19.5%; isomer b: 137 mg, 19.5%). Each of the pure isomers was re-subjected to the reaction conditions and the equilibrium mixture (~1:1) was reestablished rapidly in each case (as determined by gas chromatography). **Isomer a:** $^1$H NMR (CDCl$_3$): δ 4.20 (t, $J = 7.0$ Hz, 2H), 3.74 (s, 3H), 2.42 (t, $J = 7.0$ Hz, 2H), 2.24, (m, 2H), 1.99 (s, 3H), 1.38 (m, 2H), 1.28 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 171.12, 157.84, 61.62, 61.43, 33.27, 28.23, 27.98, 23.01, 21.10, 13.97. **Isomer b:** $^1$H NMR (CDCl$_3$): δ 4.26 (t, $J = 6.6$ Hz, 2H), 3.76 (s, 3H), 2.56 (t, $J = 6.6$ Hz, 2H), 2.13, (m, 2H), 1.99 (s, 3H), 1.38 (m, 2H), 1.28 (m, 2H) 0.83 (t, $J = 7.3$ Hz, 3H). Anal. Calcd for C$_{10}$H$_{19}$NO$_3$ (mixture of E/Z isomers): C, 59.68, H, 9.52, N, 6.96; Found: C, 59.75, H, 9.25, N, 7.26.
The reaction was run with 2.0 equiv of PhI(OAc)_2 in AcOH. Product 49 was obtained as a viscous oil (60% yield). $^1$H NMR (CDCl$_3$): δ 4.35 (m, 1H), 4.19-4.09 (multiple peaks, 2H), 2.29 (m, 1H), 2.16-2.12 (multiple peaks, 2H), 2.07 (s, 3H), 1.81 (s, 3H), 1.48 (m, 1H), 1.35-1.27 (multiple peaks, 4H), 1.25 (d, J = 7.2 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 171.02, 158.36, 75.73, 75.69, 66.45, 66.40, 35.84, 31.68, 31.37, 29.26, 26.12, 25.21, 22.39, 22.35, 20.93, 19.98, 16.58, 14.04, 13.98, 13.92.

The reaction was run with 1.1 equiv of PhI(AcO)$_2$ for 3 h in AcOH/Ac$_2$O. The product 57 was isolated as a pale yellow oil (R$_f$ = 0.3 in 90% hexanes/10% ethyl acetate, 222 mg, 74% yield), which was a 6:1 mixture of the oxime E/Z isomers. Major Isomer: $^1$H NMR (CDCl$_3$): δ 4.10 (dd, J = 10.9, 7.3 Hz, 1H), 3.99 (dd, J = 10.9, 6.9 Hz, 1H), 3.77 (s, 3H), 2.62 (m, 1H), 1.99 (s, 3H), 1.74 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 171.10, 158.36, 75.73, 75.69, 66.45, 66.40, 39.13, 21.05, 14.95, 11.77. Anal. Calcd for C$_8$H$_{15}$NO$_3$: C, 55.47, H, 8.73, N, 8.09; Found: C, 55.55, H, 8.57, N, 7.81.

The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O. The product 61 was obtained as pale yellow oil (202 mg, 78% yield). $^1$H NMR (CDCl$_3$): δ 4.50 (dd, J = 11.0, 4.4 Hz, 1H), 3.97 (dd, J = 11.0, 8.1 Hz, 1H), 3.75 (s, 3H), 3.27 (m, 1H), 2.39 (m, 1H), 2.08 (m, 1H), 2.02 (s, 3H), 1.86 (m, 1H), 1.55 (m, 1H), 1.24 (m, 1H), 1.09 (m, 1H), 0.94 (m, 1H), 0.83 (s, 9H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 174.09, 158.82, 65.20, 61.45, 47.04,
The reaction was run with 2.0 equiv of PhI(OAc)$_2$ in AcOH. Product 63 was obtained as a viscous oil (30% yield, 1:1). $^1$H NMR (CDCl$_3$): $\delta$ 4.79 (m, 2H), 4.19-4.06 (multiple peaks, 8H), 3.06-2.94 (multiple peaks, 4H), 2.73 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.51 (m, 4H), 1.35 (m, 4H), 0.92 (m, 6H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 170.75, 64.97, 64.87, 64.65, 37.71, 31.02, 30.95, 20.82, 20.75, 20.08, 13.87, 13.83. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{21}$NO$_5$, 294.1317; found, 294.1305.

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 67 was obtained as a viscous oil (47% yield, 1:1). $^1$H NMR (CDCl$_3$): $\delta$ 4.76 (m, 2H), 4.16-4.07 (multiple peaks, 8H), 3.04 (dd, $J$ = 17.0, 10.5 Hz, 2H), 2.75-2.70 (multiple peaks, 4H), 2.08 (s, 12H), 1.18 (d, $J$ = 6.5 Hz, 6H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 186.65, 170.83, 65.17, 49.66, 37.21, 27.77, 20.80, 20.02.

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 69 was obtained as a viscous oil (25% yield, 1:1). Isomer 1: $^1$H NMR (CDCl$_3$): $\delta$ 7.38-7.29 (multiple peaks, 5H), 5.55 (dd, $J$ = 11.0, 8.0 Hz, 1H), 4.21 (dd, $J$ = 11.0, 7.0 Hz, 1H), 4.14 (dd, $J$ = 12.0, 6.0 Hz, 1H), 3.40 (dd, $J$ = 17.0, 11.0, 1H), 3.02 (quin, $J$ = 7.0 Hz, 1H), 2.92 (dd, $J$ = 17.0, 8.0 Hz, 1H), 2.04 (s, 3H), 1.23 (d, $J$ = 7.0 Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 170.81, 159.32, 141.01, 128.68, 128.09, 125.68, 81.46, 65.95, 43.39, 32.83, 20.81, 14.78. Isomer 1: $^1$H NMR (CDCl$_3$): $\delta$ 7.37-7.30 (multiple peaks, 5H), 5.55 (dd, $J$ = 11.0, 7.5 Hz, 1H), 41.63, 32.22, 27.74, 26.98, 24.91, 21.22. Anal. Calcd for C$_{14}$H$_{25}$NO$_3$: C, 65.85, H, 9.87, N, 5.49; Found: C, 65.58, H, 10.10, N, 5.48.
4.20-4.11 (multiple peaks, 2H), 3.40 (dd, J = 17.0, 11.0, 1H), 3.03 (quin, J = 6.5 Hz, 1H), 2.91 (dd, J = 17.0, 7.5 Hz, 1H), 2.01 (s, 3H), 1.23 (d, J = 7.5 Hz, 3H). \(^{13}\)C\(^{1}\)H) NMR (CDCl\(_3\)): \(\delta\) 170.73, 159.27, 141.11, 128.67, 128.08, 125.65, 81.39, 65.91, 43.16, 32.71, 20.76, 14.74. HRMS electrospray (m/z): [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{17}\)NO\(_3\), 270.1106 found, 270.1099.

The reaction was run with 1.1 equiv PhI(OAc)\(_2\) in AcOH/Ac\(_2\)O. The product 72 was obtained as a mixture of the two isomers, as pale yellow oils (major isomer: 189 mg, 65% yield; minor isomer: 38 mg, 13% yield). Each of the pure isomers was re-subjected to the reaction conditions and the equilibrium mixture (~5:1) was re-established rapidly in each case (as determined by gas chromatography). **Major Isomer:** \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 4.07 (pseudo q, \(J = 13.9, 7.8, 6.4\) Hz, 2H), 3.79 (s, 3H), 2.45 (m, 1H), 1.99 (s, 3H), 1.72 (s, 3H), 1.45 (m, 2H), 0.84 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C\(^{1}\)H) NMR (CDCl\(_3\)): \(\delta\) 171.09, 157.09, 65.00, 61.46, 46.03, 22.01, 21.07, 11.48, 11.43. **Minor Isomer:** \(^1\)H NMR (CDCl\(_3\)): 4.16 (dd, \(J = 10.9, 5.6\) Hz, 1H), 4.04 (dd, \(J = 10.9, 8.3\) Hz, 1H), 3.80, (s, 3H), 3.45 (m, 1H), 2.03, (s, 3H), 1.80, (s, 3H), 1.49 (m, 2H), 0.90 (t, \(J = 7.5\) Hz, 3H). Anal. Calcd for C\(_9\)H\(_{17}\)NO\(_3\) (major isomer): C, 57.73, H, 9.15, N, 7.48; Found: C, 57.71, H, 9.40, N, 7.22.

Cyclpropane 79 was reacted with 2.0 equiv Benzoquinone and 5 mol % Pd(OAc)\(_2\) in AcOH/Ac\(_2\)O (1:1, 0.12M) in a 20 mL scintillation vial at 100 °C for 12 h. The resulting mixture was filtered through a plug of glass wool and diluted with pentane (20 mL), and the pentane layer was washed with H\(_2\)O (2 x 20 mL), saturated NaHCO\(_3\) (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over MgSO\(_4\), filtered, and concentrated to afford a yellow oil, which was purified by chromatography on silica gel (R\(_f\) = 0.3 in 90% hexanes/10% ethyl acetate). The product 81 was obtained as a mixture of the two oxime isomers, as pale yellow oils (44%, 3:1). **Major Isomer:** \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 5.89
Cyclpropane 82 was reacted with 2.0 equiv Benzoquinone and 5 mol % Pd(OAc)$_2$ in AcOH/Me$_2$O (1:1, 0.12M) in a 20 mL scintillation vial at 100 °C for 12 h. The resulting mixture was filtered through a plug of glass wool and diluted with pentane (20 mL), and the pentane layer was washed with H$_2$O (2 x 20 mL), saturated NaHCO$_3$ (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated to afford a yellow oil, which was purified by chromatography on silica gel (R$_f$ = 0.3 in 90% hexanes/10% ethyl acetate). The product 83 was obtained as a mixture of the two oxime isomers, as pale yellow oils (47%, 3:1). **Major Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 6.32 (td, $J =$ 16.0, 1.2 Hz, 1H), 6.06 (dt, $J =$ 16.0, 6.0 Hz, 1H), 4.67 (dd, $J =$ 6.0, 1.2 Hz, 2H), 3.90 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 170.41, 154.28, 130.65, 127.72, 64.08, 61.72, 20.72, 9.96. Anal. Calcd for C$_8$H$_7$NO$_3$ (mixture of E/Z isomers): C, 56.13, H, 7.65, N, 8.18; Found: C, 56.02, H, 7.68, N, 8.13.

The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Me$_2$O. The product 94 was obtained as a pale yellow oil (75%). $^1$H NMR (CDCl$_3$): $\delta$ 7.37 (m, 1H), 7.28-7.23 (multiple peaks, 2H), 7.14 (d, $J =$ 8.4 Hz, 1H), 3.91 (s, 3H), 3.94 (septet, $J =$ 6.4 Hz, 1H), 2.26 (s, 3H), 1.09 (d, $J =$ 6.4 Hz, 6H).
The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O. The product 95 was obtained as a pale yellow oil (5%). $^1$H NMR (CDCl$_3$): $\delta$ 7.34-7.29 (multiple peaks, 2H), 7.23-7.15 (multiple peaks, 2H), 7.09 (d, J = 8.4 Hz, 1H), 4.16 (dd, J = 11.2, 7.6 Hz, 1H), 4.04 (dd, J = 11.2, 7.6 Hz, 1H) 3.75 (s, 3H), 2.99 (m, 1H), 1.98 (s, 3H), 1.11 (d, J = 6.4 Hz, 3H).

The reaction was run with 1.1 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O. The product 97 was obtained as a pale yellow oil (57%). $^1$H NMR (CDCl$_3$): $\delta$ 7.18 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.45 (sextet, J = 6.8 Hz, 1H) 2.82 (m, 1H), 2.58 (m, 1H), 2.25 (s, 3H), 1.97 (m, 1H), 1.45 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H).

The reaction was run with 1.02 equiv of PhI(OAc)$_2$ in AcOH. Product 100 was obtained as a viscous oil (27% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.32 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.95 (m, 1H), 4.26-4.18 (multiple peaks, 2H), 3.33 (dd, J = 17.5, 10.5 Hz, 1H), 3.00 (dd, J = 17.5, 7.5, 1H), 2.36 (s, 3H), 2.28 (s, 3H), 2.11 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 170.72, 169.13, 153.61, 148.89, 138.74, 130.07, 128.04, 122.41, 120.14, 77.62, 64.72, 40.37, 20.95, 20.78, 20.09. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{17}$NO$_5$, 314.1004 found, 314.1006.
The reaction was run with 1.02 equiv of PhI(OAc)$_2$ in AcOH. Product 101 was obtained as a viscous oil (34% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.51 (d, $J = 8.0$ Hz, 1H), 7.43 (m, 1H), 7.38-7.37 (multiple peaks, 2H), 5.42 (s, 2H), 4.95 (m, 1H), 4.28 (dd, $J = 12.0$, 4.0 Hz, 1H), 4.21 (dd, $J = 12.0$, 5.5, 1H), 3.53 (dd, $J = 17.0$, 11.0 Hz, 1H), 3.20 (dd, $J = 17.0$, 7.0 Hz, 1H), 2.14 (s, 3H), 2.10 (s, 3H). $^{13}$C{$_1^H$} NMR (CDCl$_3$): $\delta$ 170.82, 170.54, 156.10, 135.79, 129.80, 128.79, 128.35, 127.84, 127.33, 64.88, 64.85, 39.36, 20.79. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{17}$NO$_5$, 314.1004 found, 314.1007.

The reaction was run with 1.02 equiv of PhI(OAc)$_2$ in AcOH. Product 106 was obtained as a viscous oil (65% yield). $^1$H NMR (CDCl$_3$): $\delta$ 8.71 (m, 1H), 7.74 (td, $J = 7.5$, 2.0 Hz, 1H), 7.33-7.25 (multiple peaks, 3H), 7.17 (d, $J = 8.0$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 2.15 (s, 3H), 1.94 (s, 3H). $^{13}$C{$_1^H$} NMR (CDCl$_3$): $\delta$ 169.21, 155.56, 149.26, 148.18, 137.92, 135.86, 133.34, 128.63, 127.76, 124.53, 121.92, 119.76, 20.30, 19.67. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{14}$H$_{13}$NO$_2$, 250.0844 found, 250.0847.

The reaction was run with 1.02 equiv of PhI(OAc)$_2$ in AcOH. Product 109 was obtained as a viscous oil (90% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.73 (d, $J = 2.0$ Hz, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.04 (d, $J = 7.5$ Hz, 1H), 6.42 (t, $J = 2.0$ Hz, 1H), 2.11 (s, 3H), 2.02 (s, 3H). $^{13}$C{$_1^H$} NMR (CDCl$_3$): $\delta$ 169.21, 146.87, 140.54, 137.88, 132.80, 131.42, 129.56, 128.33, 120.72, 105.96, 20.38, 17.34. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{12}$N$_2$O$_2$, 239.0796 found, 239.0787.
The reaction was run with 1.02 equiv of PhI(OAc)$_2$ in AcOH. Product 112 was obtained as a viscous oil (30% yield). $^1$H NMR (CDCl$_3$): δ 7.50 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.46 (td, $J$ = 8.0, 2.0 Hz, 1H), 7.32 (td, $J$ = 8.0, 1.5 Hz, 1H), 7.15 (d, $J$ = 8.0 Hz), 4.91 (m, 1H), 4.27 (dd, $J$ = 12.0, 4.0 Hz, 1H), 4.18 (dd, $J$ = 12.0, 6.0 Hz, 1H), 3.47 (dd, $J$ = 16.5, 10.5, 1H), 3.16 (dd, $J$ = 16.5, 7.0 Hz, 1H), 2.32 (s, 3H), 2.10 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ 170.70, 169.51, 153.55, 148.32, 130.88, 129.36, 126.17, 123.76, 77.46, 64.69, 38.53, 21.14, 20.67. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{14}$H$_{15}$NO$_5$, 300.0848 found, 300.0857.

The reaction was run with 2.1 equiv of PhI(OAc)$_2$ in AcOH. Product 116 was obtained as a viscous oil (75% yield). $^1$H NMR (CDCl$_3$): δ 7.25 (t, $J$ = 8.0 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 2H), 4.74 (m, 1H), 4.10 (t, $J$ = 4.4 Hz, 2H), 2.93 (dd, $J$ = 17.2, 10.8 Hz, 1H), 2.76 (t, $J$ = 7.6 Hz, 2H), 2.63 (dd, $J$ = 17.2, 6.8 Hz, 1H), 2.48 (t, $J$ = 7.2, 2H), 2.31 (s, 6H), 2.06 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ 170.68, 169.11, 153.55, 148.32, 130.88, 129.36, 126.17, 123.76, 77.46, 64.87, 39.74, 26.88, 21.87, 20.83, 20.68. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{18}$H$_{21}$NO$_7$, 386.1216 found, 386.1207.

The reaction was run with 2.1 equiv of PhI(OAc)$_2$ in AcOH. Product 126 was obtained as a viscous oil (89% yield). $^1$H NMR (CDCl$_3$): δ 7.30 (t, $J$ = 8.0 Hz, 1H), 6.98 (d, $J$ = 8.0 Hz, 2H), 3.83 (s, 3H), 3.39 (s, 2H), 2.31 (s, 6H), 1.64 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ
The reaction was run with 2.1 equiv of PhI(OAc)$_2$ in AcOH. Product **128** was obtained as a viscous oil (17% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.27-7.22 (multiple peaks, 2H), 7.18 (t, $J = 7.5$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 3.84 (s, 3H), 2.73 (t, $J = 8.0$ Hz, 2H), 2.42 (t, $J = 8.0$ Hz, 2H), 2.34 (s, 3H), 1.84 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): (mixture of oxime isomers) $\delta$ 169.39, 157.15, 156.47, 148.88, 148.82, 132.94, 132.91, 130.11, 130.06, 127.37, 127.30, 126.15, 122.28, 61.09, 61.05, 36.17, 29.84, 27.30, 26.27, 20.86, 20.80, 20.23, 14.15. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{17}$NO$_3$, 258.1105 found, 258.1105.

The reaction was run with 1.1 equiv of PhI(OAc)$_2$ in AcOH. Product **136** was obtained as a viscous oil (56% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.32-7.23 (multiple peaks, 3H), 7.05 (m, 1H), 4.47 (m, 1H), 3.93 (q, $J = 7.0$ Hz, 1H), 2.67 (dd, $J = 17.0$, 10.0 Hz, 1H), 2.37-2.32 (multiple peaks, 4H), 1.63 (m, 1H), 1.51 (d, $J = 6.5$, 3H), 1.44 (m, 1H), 1.34-1.22 (multiple peaks, 4H), 0.87 (t, $J = 7.0$ Hz, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 169.66, 160.54, 148.60, 133.35, 128.13, 128.00, 126.51, 122.97, 80.63, 40.50, 34.71, 33.54, 27.56, 22.42, 20.86, 17.73, 13.87. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{17}$H$_{23}$NO$_3$, 290.1756 found, 290.1742.

The reaction was run with 1.1 equiv of PhI(OAc)$_2$ in AcOH. Product **139** was obtained as a viscous oil (60% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.28-7.17 (multiple peaks, 3H), 7.04 (d, $J = 8.4$ Hz, 1H), 4.73 (m, 1H), 4.13-4.04 (multiple peaks, 2H), 3.98 (dd, $J = 12.0$, 6.0 Hz,
1H), 3.02-2.84 (multiple peaks, 3H), 2.70-2.59 (multiple peaks, 2H), 2.33 (s, 3H), 2.06 (s, 3H), 1.16 (d, J = 8.0, 3H). $^{13}$C$\{^1$H}$ NMR (CDCl$_3$): δ 170.77, 169.37, 161.72, 149.09, 131.02, 130.86, 127.78, 126.14, 122.58, 122.55, 76.83, 65.02, 64.95, 37.46, 37.53, 35.13, 35.10, 33.31, 21.01, 20.77, 17.97. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{17}$H$_{21}$NO$_5$, 342.1311 found, 342.1311.

The reaction was run with 1.1 equiv of PhI(OAc)$_2$ in AcOH. Product 142 was obtained as a viscous oil (10% yield, 1:1). **Isomer 1:** $^1$H NMR (CDCl$_3$): δ 7.26-7.12 (multiple peaks, 4H), 4.72 (m, 1H), 4.17-4.00 (multiple peaks, 2H), 2.90 (m, 1H), 2.73-2.49 (multiple peaks, 2H), 2.04 (s, 3H), 2.02 (s, 3H), 1.86-1.64 (multiple peaks, 2H), 1.51 (m, 3H).

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 145 was obtained as a viscous oil (43% yield, Oxime Isomers 1:1). **Oxime Isomer 1:** $^1$H NMR (CDCl$_3$): δ 7.31-7.21 (multiple peaks, 3H), 7.01 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H), 3.79 (q, J = 7.0 Hz, 1H), 2.32 (s, 3H), 1.59 (s, 3H), 1.40 (d, J = 7.0 Hz, 3H). $^{13}$C$\{^1$H}$ NMR (CDCl$_3$): δ 169.41, 158.49, 148.94, 133.97, 128.17, 127.74, 126.22, 122.77, 61.33, 61.14, 39.61, 20.87, 17.25, 12.27. HRMS electro spray (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{17}$NO$_3$, 258.1106 found, 258.1096. **Oxime Isomer 2:** $^1$H NMR (CDCl$_3$): δ 7.34 (dd, J = 7.0, 1.5 Hz, 1H), 7.29-7.23 (multiple peaks, 2H), 7.01 (dd, J = 7.5, 2.0 Hz, 1H), 4.71 (q, J = 7.5 Hz, 1H), 3.86 (s, 3H), 2.26 (s, 3H), 1.50 (s, 3H), 1.36 (d, J = 7.5 Hz, 3H). HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{17}$NO$_3$, 258.1106 found, 258.1095.

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 146 was obtained as a viscous oil (22% yield). $^1$H NMR (CDCl$_3$): δ 7.28 (t, J = 8.5 Hz, 1H), 6.95 (d, J = 8.5
Hz, 2H), 3.88 (s, 3H), 3.68 (q, J = 7.0 Hz, 1H), 2.29 (s, 6H), 1.61 (s, 3H), 1.38 (d, J = 7.0 Hz, 3H). $^{13}$C \{^1\text{H}\} NMR (CDCl$_3$): $\delta$ 169.12, 157.44, 149.74, 127.60, 127.48, 120.94, 61.19, 37.66, 20.75, 15.35, 14.03. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{19}$NO$_3$, 316.1161 found, 316.1173.

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 149 was obtained as a viscous oil (83% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.37 (d, $J = 7.6$ Hz, 1H), 7.18 (d, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 4.96 (m, 1H), 4.27-4.18 (multiple peaks, 2H), 3.32 (dd, $J = 17.2$, 6.8, 1H), 2.66 (q, $J = 7.6$ Hz, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.23 (t, $J = 7.6$ Hz, 3H). $^{13}$C \{^1\text{H}\} NMR (CDCl$_3$): $\delta$ 170.74, 169.07, 153.51, 148.83, 144.96, 130.28, 126.37, 121.81, 120.11, 77.65, 64.73, 41.04, 26.51, 20.98, 20.78, 15.68. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{19}$NO$_3$, 328.1161 found, 328.1151.

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 150 was obtained as a viscous oil (8% yield, 1:1). Isomer 1: $^1$H NMR (CDCl$_3$): $\delta$ 7.44 (d, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 7.12 (m, 1H), 5.79 (quin, $J = 6.4$ Hz, 1H), 5.00 (m, 1H), 4.26-4.21 (multiple peaks, 2H), 3.50 (dd, $J = 17.2$, 11.2, 1H), 3.09 (dd, $J = 17.2$, 7.2 Hz, 1H), 2.30 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H), 1.53 (d, $J = 6.4$ Hz, 3H).

The reaction was run with 1.5 equiv of PhI(OAc)$_2$ in AcOH. Product 172 was obtained as a viscous oil (6% yield). $^1$H NMR (CDCl$_3$): $\delta$ 8.59 (d, $J = 5.5$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.67 (td, $J = 9.0$, 1.5 Hz, 1H), 7.25 (m, 1H), 5.35 (s, 2H), 4.26 (t, $J = 6.0$ Hz,
2H), 2.01 (s, 3H), 1.70 (m, 2H), 1.41 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H). $^{13}$C#$^{1}$H NMR (CDCl$_3$): $\delta$ 170.58, 152.66, 152.58, 148.92, 136.29, 123.63, 120.93, 75.12, 54.84, 31.16, 20.72, 19.02, 13.84.

Decalone O-methyl oxime (200 mg, 1.11 mmol, 1 equiv), PhI(OAc)$_2$ (539 mg, 1.66 mmol, 1.5 equiv), and Pd(OAc)$_2$ (12 mg, 0.055 mmol, 0.05 equiv) were combined in AcOH (5 mL) and Ac$_2$O (5 mL) in a 20 mL vial. The vial was sealed with a Teflon lined cap, and the reaction was stirred at 80ºC for 5 h. The reaction mixture was evaporated to dryness and then taken up in 3 mL of pyridine. The pyridine suspension was filtered through a short plug of silica, and the silica was washed with copious ethyl acetate to remove all of the organic products. The resulting solution was concentrated under vacuum to afford a reddish oil, which was purified by chromatography on silica gel ($R_f = 0.3$ in 90% hexanes/10% ethyl acetate). The product 184 was obtained as pale yellow crystals (210 mg, 81% yield). $^1$H NMR (CDCl$_3$): $\delta$ 5.03 (ddd, $J = 10.9, 10.7, 4.8$ Hz, 1H), 3.69 (s, 3H), 3.24 (br d, $J = 13.1$, 1H), 2.0 (m, 1H), 1.93 (s, 3H), 1.91 (d, $J = 10.9$, 1H), 1.81-0.96 (multiple peaks, 12H). $^{13}$C#$^{1}$H NMR (CDCl$_3$): $\delta$ 170.18, 157.54, 70.42, 61.06, 51.70, 43.31, 33.32, 32.97, 31.60, 25.59, 25.38, 23.12, 21.09. Anal. Calcd for C$_{13}$H$_{21}$NO$_3$: C, 65.25, H, 8.84, N, 5.85; Found: C, 65.51, H, 8.79, N, 5.77.

The equatorial stereochemistry of the OAc group of 31 was assigned based on standard analysis of the coupling constants of H$_a$ as shown below:
Product 184 was reacted with 2 equiv TiCl$_3$ and 2 equiv NH$_4$OAc in refluxing degassed AcOH:Dioxane:H$_2$O for 2 h. The reaction was extracted with ether. The ethereal layer was dried over MgSO$_4$, filtered and concentrated. The resulting oil was was purified by chromatography on silica gel (R$_f$ = 0.3 in 90% hexanes/10% ethyl acetate). Product 185 was obtained as white crystalline solid. $^1$H NMR (CDCl$_3$): $\delta$ 5.00 (td, J = 11.2, 5.2 Hz, 1H), 2.38-2.26(multiple peaks, 2H), 2.19-2.04 (multiple peaks, 2H), 1.98 (s, 3H), 1.87-1.66 (multiple peaks, 4H), 1.52-1.48 (multiple peaks, 2H), 1.35-1.11 (multiple peaks, 4H).

**Structure Determination.**

Colorless needles of 185 were grown from an ether solution at -10 deg. C. A crystal of dimensions 0.50 x 0.10 x 0.04 mm was mounted on a standard Bruker SMART CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube ($\lambda$ = 0.71073 A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.980 cm from the crystal. A total of 2338 frames were collected with a scan width of 0.3° in $\omega$ and phi with an exposure time of 60 s/frame. The integration of the data yielded a total of 17004 reflections to a maximum 2$\theta$ value of 46.76° of which 1704 were independent and 1325 were greater than 2$\theta$(I). The final cell constants (Table 1) were based on the xyz centroids of 3514 reflections above 10$\sigma$(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS. No correction for absorption was necessary. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group Pca2(1) with Z = 8 for the formula C$_{12}$H$_{18}$O$_3$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F$^2$ converged at R1 = 0.0538 and wR2 = 0.1379 [based on I > 2sigma(I)], R1 = 0.0769 and wR2 = 0.1585 for all data.

Decalone oxime was reacted with 1.0 equiv Na$_2$PdCl$_4$ and 1.12 equiv NaOAc in MeOH at rt for 3 days. The crude reaction was concentrated in vacuum. The crude red brown solid was dissolved in CH$_2$Cl$_2$ and filtered through celite. The resulting solution is concentrated and dissolved in hot methanol. The crude solid is collected and reacted with 1.0 equiv pyridine in THF for 10 minutes. The crude reaction is concentrated and purified by chromatography on silica gel (50% hexanes/50% ethyl acetate to 35% hexanes/65% ethyl acetate). Product 190 was obtained as yellow solid (93% pure). $^1$H NMR (CDCl$_3$): $\delta$ 9.85 (s, 1H), 8.75 (d, 7.6 Hz, 2H), 7.75 (t, $J$ = 7.6 Hz, 1H), 7.33 (dd, $J$ = 7.6, 6.8 Hz, 2H), 3.07-3.00 (multiple peaks, 2H), 2.07 (m, 1H), 1.97-1.83 (multiple peaks, 2H), 1.68 (m, 1H), 1.57-1.52 (multiple peaks, 2H), 1.43-1.32 (multiple peaks, 4H), 1.14-1.02 (multiple peaks, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 169.15, 152.79, 137.49, 125.10, 60.72, 47.14, 44.06, 33.99, 33.96, 31.18, 28.21, 27.17, 25.34, 23.03, 22.53.

**Structure Determination.**

Pale yellow needles of 190 were grown from a dichloromethane/pentane solution at 22 deg. C. A crystal of dimensions 0.60 x 0.34 x 0.10 mm was mounted on a standard Bruker SMART CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube ($\lambda$ = 0.71073 Å) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.980 cm from the crystal. A total of 3040 frames were collected with a scan width of 0.2° in $\omega$ and phi with an exposure time of 10 s/frame. The integration of the data yielded a total of 17473 reflections to a maximum 20 value of 56.64° of which 3703 were independent and 3525 were greater than 2$\sigma$(I). The final cell constants (Table 1) were based on the xyz centroids of 6708 reflections above 10$\sigma$(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXL (version 6.12) software package, using the space group P2(1)/c with Z = 4 for the formula C$_{15}$H$_{21}$N$_2$OPd. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions with the exception of the oxime hydrogen which was
located on a difference Fourier map. Full matrix least-squares refinement based on $F^2$ converged at $R_1 = 0.0210$ and $wR_2 = 0.0568$ [based on $I > 2\sigma(I)$], $R_1 = 0.0223$ and $wR_2 = 0.0576$ for all data.


\[
\begin{align*}
\text{Product 190} & \text{ was reacted with AgOAc in AcOH at 25°C for 12 h. The reaction was filtered through celite and concentrated. Recrystallization of product 191 with CH}_2\text{Cl}_2 \\
& \text{and hexanes afforded a yellow solid (93% pure).} \\
\text{\textsuperscript{1}H NMR (CDCl}_3\text{): } & \delta 8.66 \text{ (d, 5.2 Hz, 2H)}, 7.75 \text{ (t, } J = 6.8 \text{ Hz, 1H)}, 7.31 \text{ (dd, } J = 6.0 \text{ Hz, 2H)}, 3.13 \text{ (dd, } J = 17.2, 9.2, 1H), 2.80 \text{ (t, } J = 9.2 \text{ Hz, 1H)}, 2.00 \text{ (t, } J = 10.0 \text{ Hz, 1H)}, 1.91-1.76 \text{ (multiple peaks, 4H), } 1.61-1.44 \\
& \text{ (multiple peaks, 3H), } 1.34-1.18 \text{ (multiple peaks, 4H), } 1.05-0.90 \text{ (multiple peaks, 3H).}
\end{align*}
\]

**Structure Determination.**

Colorless blocks of 191 were grown from a dichloromethane solution at 22 deg. C. A crystal of dimensions 0.34 x 0.22 x 0.14 mm was mounted on a standard Bruker SMART CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube ($\lambda = 0.71073$ A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.980 cm from the crystal. A total of 4545 frames were collected with a scan width of 0.2° in $\omega$ and phi with an exposure time of 10 s/frame. The integration of the data yielded a total of 58517 reflections to a maximum 2$\theta$ value of 56.80° of which 4660 were independent and 4297 were greater than 2$\sigma$(I). The final cell constants (Table 1) were based on the xyz centroids of 9446 reflections above 10$\sigma$(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group I4(1)/a with $Z = 16$ for the formula $C_{17}H_{24}N_2O_3Pd$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in both idealized and refined positions. Full matrix least-squares refinement
based on F² converged at R1 = 0.0365 and wR2 = 0.0878 [based on I > 2sigma(I)], R1 = 0.0390 and wR2 = 0.0887 for all data.


General Procedure for Stoichiometric Reactions of Palladacycle Monomers with Oxidants (PhI(OAc)₂, PhICl₂, MeI): Monomers 190 and 191 were reacted with 1.0 equiv of the Oxidant in AcOH at 100 °C for 12 h. The reaction was concentrated and their crude NMR’s taken to determine the ratio and yields of products obtained.

Product 192: ¹H NMR (CDCl₃): δ 4.08 (dt, J = 10.8, 4.0 1H), 2.52-2.41 (multiple peaks, 3H), 2.30-2.26 (multiple peaks, 2H), 2.13-2.09 (multiple peaks, 2H), 1.84-1.49 (multiple peaks, 5H), 1.30-1.19 (multiple peaks, 2H).

Structure Determination.

Colorless plates of 193 were grown from an ether solution at 22 deg. C. A crystal of dimensions 0.28 x 0.20 x 0.05 mm was mounted on a standard Bruker SMART CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (λ = 0.71073 Å) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.980 cm from the crystal. A total of 3698 frames were collected with a scan width of 0.2° in ω and phi with an exposure time of 30 s/frame. The integration of the data yielded a total of 11491 reflections to a maximum 2θ value of 56.68° of which 2558 were independent and 1864 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids of 3409 reflections above 10σ(I). Analysis of the data showed negligible decay during data
collection; the data were processed with SADABS, no correction for absorption was necessary. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P2(1)/n with Z = 4 for the formula C_{11}H_{19}NO. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0459 and wR2 = 0.1178 [based on I > 2sigma(I)], R1 = 0.0709 and wR2 = 0.1307 for all data.

2.10 References


Chapter 3

Oxone and $K_2S_2O_8$ as Alternative Oxidants for C-H Bond Oxygenation

3.1 Background and Significance

Significant current efforts in the literature are focused on the development of “green” catalytic reactions that are safe, scalable, environmentally friendly, and cost effective. In particular, such studies have explored the application of practical green oxidants, such as organic and inorganic peroxides, in transition metal catalyzed transformations. Peroxides are considered practical and green oxidants due to their low toxicity and expense. Two of these oxidants – $H_2O_2$ and Oxone ($2KHSO_5\cdot KHSO_4\cdot K_2SO_4$) – have been especially widely used in the metal catalyzed oxidation of alkenes,$^1, 2$ sulfides$^3$ and alcohols.$^4, 5$ We envisioned that we could apply these peroxide oxidants in our palladium-catalyzed C–H bond oxygenation reactions.

Our group has shown that Pd(OAc)$_2$ in conjunction with PhI(OAc)$_2$ serves as an efficient catalyst to transform sp$^2$ and sp$^3$ C–H bonds to C–OAc bonds, affording acetoxyalted products in excellent yield and extremely high selectivity.$^6-8$ As summarized in Scheme 3.1, the mechanism of these reactions is proposed to involve initial ligand-directed C–H activation to provide cyclometalated Pd$^{II}$ complex A. Complex A is then believed to undergo oxidation by PhI(OAc)$_2$ to afford a Pd$^{IV}$ intermediate B. Both of the acetates from the oxidant are transferred to the metal in this step, and iodobenzene is released as a byproduct. Carbon-oxygen bond forming reductive elimination then affords the final acetoxyalted product.
Even though PhI(OAc)$_2$ serves as an effective oxidant to oxygenate a wide range of substrates, there are some disadvantages associated with its use. The byproduct from these reactions, iodobenzene, is toxic, and, therefore further purification processes are required for its usage. As the equivalents of oxidant increase, the accumulation of this byproduct increases, which reduces the overall atom economy of the system. Additionally, PhI(OAc)$_2$ is relatively expensive, at approximately $1/gram. Based on these disadvantages, we desired to replace PhI(OAc)$_2$ with greener and less costly oxidants such as peroxides.

The key intermediate in Pd-catalyzed C–H bond oxygenation transformations is the Pd$^{IV}$ complex B (Scheme 3.1). We wondered if it would be possible to generate this complex using alternative oxidants. While Pd$^{IV}$ complexes are plausible intermediates, they are typically not easily observed because of their high reactivity. As a result, Pt$^{IV}$ complexes are often used as models for putative Pd$^{IV}$ intermediates, since platinum is in the same group as palladium in the periodic table. It is well known in the literature that Pt$^{II}$ complexes react with oxidants in a very similar fashion to Pd$^{II}$ complexes, but the resulting products are more stable.$^{9-12}$ As shown in Scheme 3.2, Jung and coworkers have shown that it is possible to oxidize Pt$^{II}$ to Pt$^{IV}$, using H$_2$O$_2$ as the oxidant and AcOH as the solvent.$^{13}$ In this reaction, H$_2$O$_2$ serves to oxidize Pt$^{II}$ to Pt$^{IV}$ and AcOH serves as the source of acetate in the final product. If platinum is a true model for palladium, then this result suggests that peroxides in AcOH could potentially be used as stoichiometric oxidants in place of PhI(OAc)$_2$ to generate catalytic intermediate B.
Herrmann and coworkers have reported a rare example where an inorganic peroxide – K$_2$S$_2$O$_8$ – was used as the stoichiometric oxidant in a Pd-catalyzed C–H bond oxygenation reaction.$^{14}$ Subjection of a suspension of K$_2$S$_2$O$_8$ in CF$_3$CO$_2$H/(CF$_3$CO)$_2$O to 20 bar CH$_4$ in the presence of a catalytic amount of Pd$^{II}$ catalyst C led to the formation of CH$_3$O$_2$CCF$_3$ (Scheme 3.3).

Although the authors do not speculate on the mechanism, we believe that the reaction likely proceeds via a high oxidation state Pd$^{IV}$ intermediate analogous to 2 above. Similar to the Jung system, the trifluoroacetic acid is expected to serve as a source of trifluoroacetate groups on the metal, which upon reductive elimination form the product CH$_3$O$_2$CCF$_3$. Although this reaction is a promising initial lead, the requirement of 100 equiv of K$_2$S$_2$O$_8$ as well as the high pressure of methane limits its practical utility.

### 3.2 Initial Screenings of Peroxides

Initial studies focused on applying peroxides as stoichiometric oxidants in the Pd-catalyzed directed acetoxylation of $m$-bromoacetophenone oxime ether. Based on Jung’s report, we chose to employ acetic acid as the reaction media and the source of acetate in the final product. A variety of peroxides were screened under our previously determined
reaction conditions for PhI(OAc)₂-mediated acetoxylation reactions (5 mol % Pd(OAc)₂, 2 equiv of oxidant in AcOH at 100 °C) (Table 3.1). Interestingly, the use of H₂O₂ in this Pd-catalyzed reaction resulted in only 11% of our desired product (entry 1), despite the fact that it was a highly effective stoichiometric oxidant for Pt²⁺ (Scheme 3.2). We rationalize this result based on reports that Pd²⁺ rapidly catalyzes the disproportionation of H₂O₂ to H₂O and O₂ (Scheme 3.4), and O₂ is not capable of oxidizing Pd²⁺ to Pd⁴⁺ in these systems.¹⁵

**Scheme 3.4**: Palladium-Catalyzed Disproportionation of H₂O₂

Other peroxides such as m-chloroperoxybenzoic acid (m-CPBA) and peracetic acid provided slightly higher yields than H₂O₂ (14% and 34%, respectively – entries 3 and 4); however, despite attempts to further optimize these reactions, they never afforded synthetically useful quantities of the product. The most promising results were obtained using the inorganic peroxides Oxone and K₂S₄O₈ as terminal oxidants. These reagents afforded the acetoxylated product in comparable yield as PhI(OAc)₂ (Table 3.1, entries 7 and 8). Notably, use of the tetrabutylammonium salt of Oxone substantially lowered the yield of the acetoxylated product (entry 5), suggesting that increasing the solubility of the oxidant was unfavorable. Importantly, control reactions of substrate 3 with Oxone and K₂S₄O₈, in the absence of Pd(OAc)₂, did not afford any of the desired acetoxylated product 3a. Instead about 25% decomposition of the starting material to a complex mixture of unidentified products was observed.
Table 3.1: Screen of Peroxide Oxidants for the Pd-Catalyzed Acetoxylation of *m*-Bromoacetophenone Oxime Ether

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O₂</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>Urea·H₂O₂</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td><em>m</em>-CPBA</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂CO₃H</td>
<td>18%</td>
</tr>
<tr>
<td>5</td>
<td>(Bu₄N)₂H₂SO₅·HSO₄⁺·SO₄²⁻</td>
<td>21%</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CO₂H</td>
<td>34%</td>
</tr>
<tr>
<td>7</td>
<td>Oxone (2KHSO₅·KHSO₄·K₂SO₄)</td>
<td>68%</td>
</tr>
<tr>
<td>8</td>
<td>K₂S₂O₈</td>
<td>76%</td>
</tr>
<tr>
<td>9</td>
<td>Phl(OAc)₂</td>
<td>81%</td>
</tr>
</tbody>
</table>

Palladium-catalyzed C–H bond acetoxylation with Oxone is an exciting result, because this oxidant is environmentally benign, safe (not explosive like many other peroxides), and inexpensive. These features make Oxone attractive for large-scale applications. We have conducted the reaction of substrate 3 with Oxone effectively at scales ranging from 1 mmol to 66 mmol. When we initially executed the 66 mmol scale reaction in AcOH, we obtained the desired product, via Kugelrohr distillation, in modest 45% yield (in contrast, the yield on 1 mmol scale was 68%). This reduction in yield was due to competitive formation of the hydrolyzed product 3c (Scheme 3.5). The hydrolysis was addressed by addition of 10% acetic anhydride to the reaction mixture, which improved the yield of product 3a to 54% on a 66 mmol scale. Importantly, these large scale reactions were optimized with 3 mol % of Pd(OAc)₂. Further reduction in the amount of catalyst was possible; however, longer reaction times were required.
Scheme 3.5: Large Scale Reaction of $m$-Bromoacetophenone Oxime Ether with Oxone

Scheme 3.6: Product Distribution as a Function of Oxidant Stoichiometry

3.3 Scope of Acetoxylation of $sp^2$ C–H Bonds with Oxone and K$_2$S$_2$O$_8$

We next desired to explore the scope of the acetoxylation of substrates with Oxone and K$_2$S$_2$O$_8$ in AcOH. This reaction was applied to substrates containing a variety of directing groups, including oxime ethers of ketones and aldehydes, amides, and isoxazolines (Table 3.2 and 3.3). We were delighted to see that substrates that required the formation of five (substrates 5-11) and six (substrates 12-13) membered palladacyclic intermediates upon C–H activation were all effectively functionalized by Oxone and K$_2$S$_2$O$_8$. Both electron rich and poor arenes as well as oxidizable functionalities such as benzylic C–H bonds were well tolerated. Notably, substrates 9-13 afforded better yields of the desired acetoxylated products with K$_2$S$_2$O$_8$ than Oxone (Table 3.3). Tuning the stoichiometry of the oxidant allowed for the formation of mono or diacetoxylated products as desired (Scheme 3.6, products 4a and 4b). Acetic anhydride was used in conjunction with AcOH in the reaction for some substrates (particularly electron rich oxime ethers and oxime ethers derived from aldehydes) to attenuate hydrolysis.
Table 3.2: Substrate Scope with Oxone as the Terminal Oxidant

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield with Oxone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield with Phl(OAc)&lt;sub&gt;2&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Substrate" /></td>
<td><img src="#" alt="Product" /></td>
<td>71%</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td><img src="#" alt="Substrate" /></td>
<td><img src="#" alt="Product" /></td>
<td>69%</td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Substrate" /></td>
<td><img src="#" alt="Product" /></td>
<td>63%</td>
<td>57%</td>
</tr>
<tr>
<td>4</td>
<td><img src="#" alt="Substrate" /></td>
<td><img src="#" alt="Product" /></td>
<td>53%</td>
<td>40%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conditions: 5 mol % Pd(OAc)<sub>2</sub>, 1.0-2.0 equiv Oxidant, AcOH or AcOH/NaOAc at 100 °C
Table 3.3: Substrate Scope with K$_2$S$_2$O$_8$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield with K$_2$S$_2$O$_8$</th>
<th>Yield with Pd(OAc)$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 9" /></td>
<td><img src="image2" alt="Product 9a" /></td>
<td>57%</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 10" /></td>
<td><img src="image4" alt="Product 10a" /></td>
<td>75%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 11" /></td>
<td><img src="image6" alt="Product 11a" /></td>
<td>53%</td>
<td>69%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 12" /></td>
<td><img src="image8" alt="Product 12a" /></td>
<td>75%</td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 13" /></td>
<td><img src="image10" alt="Product 13a" /></td>
<td>53%</td>
<td>72%</td>
</tr>
</tbody>
</table>

$^a$Conditions: 5 mol % Pd(OAc)$_2$, 1.0-2.0 equiv Oxidant, AcOH or AcOH/Ac$_2$O at 100 °C

In substrates containing substituents meta to the directing group (for example, 5-10), two different ortho-C–H bonds could potentially be functionalized. In most of these reactions, the sterically less hindered C–H bond was acetoxylated selectively (Table 3.1 and 2, entries 1-4 and 1-2 respectively).$^8$ On the contrary, in the meta-hydroxy substrate 14, the sterically more hindered C–H bond was acetoxylated (Scheme 3.7). We believe that the alcohol and the oxime ether functionalities may chelate to the palladium and thereby afford this reversal of selectivity. Importantly, the selectivity of this reaction was confirmed by synthesizing authentic samples of products 14a and 14b.
Scheme 3.7: Reaction of Substrate 14 with Oxone and PhI(OAc)$_2$

My colleague Hasnain Malik obtained the corresponding yields of products 3a-13a from reactions with PhI(OAc)$_2$. In general, yields with Oxone and K$_2$S$_2$O$_8$ were comparable to those with PhI(OAc)$_2$. However, two notable exceptions were substrates 14 and 15. Subjection of substrate 14 under our catalytic conditions using PhI(OAc)$_2$ resulted in less than 5% of the desired product, presumably due to undesired oxidation of 14 to the corresponding quinone. In contrast, reaction of substrate 14 with Oxone afforded 35% of the desired product (Scheme 3.7). The low yield here is due to decomposition of the starting material to unidentified products. Similarly, reaction of amide 15 with PhI(OAc)$_2$ resulted in decomposition of the starting material, presumably via uncatalyzed reaction between the hypervalent iodine oxidant and the amide functionality. PhI(OAc)$_2$ has been shown to react with amides to form rearranged products via a RCONH(Ph)OAc intermediate. However, reaction of 15 with Oxone afforded 38% of the acetoxylated product 15a (Scheme 3.8). In this case, the balance of material was accounted for as unreacted substrate 15.

Scheme 3.8: Palladium-Catalyzed Oxidation of $m$-Chloroacetanilide

There are some limitations associated with the use of Oxone and K$_2$S$_2$O$_8$ as oxidants in place of PhI(OAc)$_2$. For example, substrates 16-18 resulted in low yields and/or reactivity with these peroxides in comparison with PhI(OAc)$_2$. With substrates 16
and 17, we believe that these limitations are due to competitive N-oxide formation. For example, subjection of quinoxaline 16 to the catalytic reaction conditions with PhI(OAc)$_2$ resulted in a single acetoxylated product 16a in 65% yield. In contrast, subjection of 16 to catalytic conditions with Oxone afforded three products – acetoxylated compound 16a, the N-oxide of the acetoxylated product (16a-O), and the N-oxide of the starting material (16-O). The assignment of the regioselectivity of N-oxidation was made based on comparison of the NMR of 16a to 16a-O following a similar approach taken in literature.$^{20}$

**Scheme 3.9:** Palladium-Catalyzed Reaction of Quinoxaline with Oxone

Similarly, subjection of azobenzene substrate 17 under catalytic conditions with PhI(OAc)$_2$ afforded the desired acetoxylated product 17a in 58% yield. On the other hand, reaction of azobenzene with Oxone yielded significant quantities of the corresponding N-oxide (17-O) along with the acetoxylated product 17a.

**Scheme 3.10:** Reaction of Azobenzene Substrate 17 with Oxone
The yield of the desired acetoxylated product in reactions of substrates bearing pyridine directing groups appears to be hampered by another palladium-catalyzed side reaction. For example, reaction of 2-phenylpyridine with Oxone resulted in the formation of the desired acetoxylated product 18a, diacetoxylated product 18b, and a new compound. As shown in Scheme 3.11, this new compound was identified as the homodimer 18c by Kami Hull. In contrast, reaction of 18 with PhI(OAc)₂ afforded the acetoxylated product 18a (52% yield) and the diacetoxylated product 18b (22% yield), and none of product 18c was observed.

**Scheme 3.11:** Palladium-Catalyzed Reaction of 2-Phenylpyridine with Oxone and PhI(OAc)₂

![Scheme 3.11: Palladium-Catalyzed Reaction of 2-Phenylpyridine with Oxone and PhI(OAc)₂](image)

There were also directing groups that resulted in low yields of the desired acetoxylated product with both Oxone and PhI(OAc)₂ due to uncatalyzed side reactions of the substrate with the oxidant. For example, reaction of oxazoline 19 with both PhI(OAc)₂ and Oxone afforded <5% of acetoxylated product 19a. This low yield is due to uncatalyzed addition of HOAc across the imine.

**Scheme 3.12:** Reaction of Oxazoline with PhI(OAc)₂ and Oxone

![Scheme 3.12: Reaction of Oxazoline with PhI(OAc)₂ and Oxone](image)
3.4 Scope of Acetoxylation of sp$^3$ C–H Bonds with Oxone and K$_2$S$_2$O$_8$

Excitingly, sp$^3$ C-H bonds were also effectively functionalized to afford acetoxylated products with Oxone and K$_2$S$_2$O$_8$. Reaction of substrate 20 with Oxone is particular notable (Scheme 3.13). Even though there are multiple different 1º C–H bonds as well as weaker 2º C–H bonds that could undergo oxidation, high selectivity was observed for the 1º β-C–H bond. This high selectivity for 1º C–H bonds with Oxone suggests strongly against the possibility of radical reaction pathways (common for peroxide reagents with weak O–O bonds) and instead is indicative of a ligand-directed C–H activation at palladium. Notably, the yield of product 20a with Oxone was low in comparison to that with PhI(OAc)$_2$, (45% versus 75%, respectively), and the balance of the material was decomposition of the starting material. Similarly, Pd-catalyzed reaction of Oxone with camphor substrate 21 also afforded the desired acetoxylated product (Scheme 3.13). Finally, the reaction of trans-decalone substrate 22 with Oxone afforded a single diastereomeric product (22a) in 23% yield. The same diastereoselectivity was observed with PhI(OAc)$_2$ (although the product was obtained in significantly higher 81% yield in this case). This result implies that reductive elimination from Pd$^{IV}$ under both the Oxone and the PhI(OAc)$_2$ proceeds via a similar mechanism – with retention of stereochemistry at carbon. The low yields of the desired products with substrates 20-22 were due to decomposition of the starting material under the oxidative conditions. Subjection of the substrate and product individually to the reaction conditions, in the absence of palladium, only led to 60% recovery due to the formation of unidentified decomposition products.
Scheme 3.13: Acetoxylation of sp$^3$ C-H Bonds using K$_2$S$_2$O$_8$

Concurrent to the work described herein, Yu and coworkers reported the use of peroxyster in Ac$_2$O for the Pd-catalyzed oxazoline-directed acetoxylation of sp$^3$ C–H bonds (Scheme 3.14).$^{22}$ They proposed that this reaction proceeds via a Pd$^{II/IV}$ catalytic cycle, where MeCOOOtBu serves to oxidize Pd$^{II}$ to Pd$^{IV}$. The authors also proposed that acetic anhydride is essential for catalytic turnover, and state that it is required both to introduce acetate ligands at Pd$^{IV}$ and to regenerate Pd(OAc)$_2$ by acetylating the Pd-OR complex formed at the end of the catalytic cycle. Notably, this is in sharp contrast to what is observed in our peroxide-mediated C–H bond acetoxylation reaction. First, Ac$_2$O is clearly not required to introduce the OAc group into the products, since high yields of acetoxylated products are observed in the absence of this reagent. Second, Ac$_2$O is not needed for catalytic turnover in our reactions, since we obtain >10 turnovers without any added Ac$_2$O.

Scheme 3.14: Pd-Catalyzed Oxidation of C–H bonds with Peroxyesters
In addition, subsequent to the results described herein, Corey reported the use of Oxone for the Pd-catalyzed oxidation of C–H bonds in amino acid derivatives.\textsuperscript{23} This report described the installation acetates at 2\textdegree{} positions in 8-aminoquinoline derivatives using 20 mol\% Pd(OAc)\textsubscript{2}, 5 equiv Oxone, 1.2 equiv Mn(OAc)\textsubscript{2}, and 10 equiv Ac\textsubscript{2}O in nitromethane at 80 °C (Scheme 3.15). Importantly, the products from this reaction were obtained with high levels of diastereoselectivity and could allow access to β-hydroxy amino acids.

**Scheme 3.15: Acetoxylation Reactions of Amino Acid Derivatives**

![Scheme 3.15](image)

3.5 Formation of Methyl Ethers with Oxone and K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}

We were next interested in using a similar approach for the conversion of C–H bonds to C–OR bonds of ethers, which are also very important and prevalent in biologically active molecules.\textsuperscript{24} A literature search revealed that Pt\textsuperscript{IV} alkoxides could be generated by oxidizing Pt\textsuperscript{II} with H\textsubscript{2}O\textsubscript{2} in methanol.\textsuperscript{25} These products were analogous to those obtained when the same oxidation was carried out in AcOH (Scheme 3.16)

**Scheme 3.16: Platinum Oxidation in Methanol with H\textsubscript{2}O\textsubscript{2}**

![Scheme 3.16](image)

Based on this result, we reasoned that by changing the solvent of our reactions with Oxone or K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} to methanol we might be able to install methyl ethers in the final
products. We were pleased to find that, using Pd(OAc)$_2$ as the catalyst and Oxone or K$_2$S$_2$O$_8$ as oxidants in methanol, we were able to obtain a variety of methoxylated products in good yields (Table 3.4). The methoxylation reactions also exhibited excellent tolerance to benzylic C–H bonds (entries 2, 3 and 6), aryl halides (entries 1 and 5), and aldehyde oxime ethers (entry 2). Similar to the acetoxylation reactions, higher yields of the methoxylated products were obtained when K$_2$S$_2$O$_8$ was used as the oxidant for substrates 12, 29 and 30. On the contrary, substrates 3, 27, 11 and 28 showed better reactivity with Oxone.
Table 3.4: Substrate Scope for Methoxilation Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield with Peroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="Cl-N_OMe" alt="Image" /> (27)</td>
<td><img src="Cl-N_OMe" alt="Image" /> (27b)</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td><img src="H-N_OMe" alt="Image" /> (11)</td>
<td><img src="H-N_OMe" alt="Image" /> (11b)</td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td><img src="H-N_OMe" alt="Image" /> (28)</td>
<td><img src="N_OMe" alt="Image" /> (28b)</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td><img src="H-N" alt="Image" /> (12)</td>
<td><img src="N_OMe" alt="Image" /> (12b)</td>
<td>72%</td>
</tr>
<tr>
<td>5</td>
<td><img src="Br-O" alt="Image" /> (29)</td>
<td><img src="Br-O" alt="Image" /> (29b)</td>
<td>61%</td>
</tr>
<tr>
<td>6</td>
<td><img src="H-O" alt="Image" /> (30)</td>
<td><img src="H-O" alt="Image" /> (30b)</td>
<td>57%</td>
</tr>
</tbody>
</table>

In the methoxilation reactions with electron rich oxime ethers, we observed competing deprotection of the oxime ether. For example, subjection of substrate 6 to Oxone in MeOH afforded 18% of the desired product 6b along with 30% of the ketone 6c (Scheme 3.17). Unlike the AcOH reactions, neither addition of acetic anhydride nor the use anhydrous methanol suppressed the hydrolysis. We believe the hydrolysis reaction
also increases the rate of catalyst decomposition. This was determined when subjecting of the corresponding ketone 6c to the reaction conditions in MeOH resulted in precipitation of Pd black within 5 minutes. This may be due to the poor ligand abilities of the ketone relative to the oxime ether. Without stabilization by coordination of the substrate, the Pd is more likely to undergo decomposition.

**Scheme 3.17**: Hydrolysis of Electron Rich Oxime Ethers under the Reaction Conditions

Unlike the acetoxylation reactions with Oxone and K$_2$S$_2$O$_8$, these methoxylation reactions were very sensitive to temperature and reaction time. Each substrate required a slow ramp of the temperature from room temperature to 45 °C. After stirring the reaction at 45 °C for 5 h, the temperature was then slowly ramped to 60 °C. After another 15 min, the temperature was then ramped slowly to 80 °C. This rigorous care with temperature was necessary to limit competing catalyst decomposition. Palladium(II) species are well known to react with methanol to form palladium hydrides and formaldehyde.$^{26}$ These Pd$^{II}$ hydrides can then undergo reductive elimination of HX to generate Pd$^{0}$ (Scheme 3.18). Catalyst decomposition occurs as Pd$^{0}$ plates out of the reaction rather than getting oxidized to Pd$^{II}$, which is required to initiate the desired Pd$^{II/IV}$ catalytic cycle to form acetoxylated compounds.

**Scheme 3.18**: Potential Catalyst Decomposition Pathway in Alcohol Solvents

Due to the increased rate of catalyst decomposition with alcoholic solvents, we have thus far been unable to achieve high yielding etherification reactions in other
alcohols like isopropanol or ethanol. We believe that as the size of the alcohol increases, the rate of etherification slows down and the rate of catalyst decomposition increases. Notably, the solvent polarity also changes from MeOH (dielectric constant = 32.6) to isopropanol (dielectric constant = 18.3), which could also play a role in the observed reactivity differences. Subjection of amide substrate 12 in ethanol with K$_2$S$_2$O$_8$ afforded the ethoxy product 12c in modest 28% yield. When the alcohol was changed to isopropanol, the yield of the desired isopropoxy product 12d was even lower at 11% (Scheme 3.19).

**Scheme 3.19: Reaction of Peroxides in Other Alcohol Solvents**

3.6 Introduction of Other Nucleophiles at Carbon with Oxone and K$_2$S$_2$O$_8$

As discussed above, we have successfully achieved the Pd-catalyzed conversion of C–H bonds to C–OAc and C–OR bonds using Oxone and K$_2$S$_2$O$_8$ as the oxidants in the corresponding nucleophilic solvent. Based on these results, we speculated that other functionalities could potentially be introduced by using the appropriate nucleophile in an inert solvent. Encouragingly, the Pd-catalyzed reaction of 12 with K$_2$S$_2$O$_8$ in CH$_2$Cl$_2$ in the presence of 10 equiv of benzoic acid afforded benzoate product 12e in modest 11% yield (Scheme 3.20). Similarly, Pd-catalyzed reaction of 12 with K$_2$S$_2$O$_8$ and LiCl in CH$_2$Cl$_2$ afforded the chlorinated product 12f, along with three undesired regioisomeric chlorinated products. These preliminary results are promising, and we anticipate that after further optimization these reactions will prove highly general and effective for converting C–H bonds to C–O, C–N, and C–halogen bonds.
Scheme 3.20: Reaction of Substrate 12 in the Presence of Different Nucleophiles

\[
\begin{align*}
\text{12} & \quad \text{5 mol \% Pd(OAc)}_2 \\
\text{H} & \quad 2.0 \text{ equiv K}_2\text{S}_2\text{O}_8 \\
\text{CH}_2\text{Cl}_2, 100 ^\circ \text{C} & \quad \rightarrow \quad \text{12e} \\
\text{O}_2\text{CPh} & \quad \text{(12e, 11% by GC)} \\
\text{12} & \quad \text{5 mol \% Pd(OAc)}_2 \\
\text{H} & \quad 2.0 \text{ equiv K}_2\text{S}_2\text{O}_8 \\
\text{CH}_2\text{Cl}_2, 100 ^\circ \text{C} & \quad \rightarrow \quad \text{12f} \\
\text{Cl} & \quad \text{(12f, 14% by GC)}
\end{align*}
\]

3.7 Conclusions

In summary, this chapter demonstrates the functionalization of sp\(^2\) and sp\(^3\) C–H bonds to C–O bonds using cost effective and environmentally benign oxidants such as Oxone and K\(_2\)S\(_2\)O\(_8\). With AcOH as the reaction medium, acetate functionality can be installed at carbon. Changing the reaction medium to MeOH allows formation of methyl ether functionalities. These reactions are general across a variety of substrates and tolerate most common functional groups. Furthermore, for the most part, yields obtained with Oxone and K\(_2\)S\(_2\)O\(_8\) are comparable to those obtained with PhI(OAc)\(_2\).

3.8 Experimental Procedure

**General Procedures:** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for \(^1\text{H}; 125.70 \text{ MHz for } \text{ } \text{ } ^13\text{C}\)) unless otherwise noted. \(^1\text{H}\) NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer.
Materials and Methods: Oxime substrates 3-11, 14, 20-22, and 27-28 were prepared following the procedure described previously. The isoxazoline 13 was prepared following a procedure by Mapp and coworkers. The amide substrates 29-30 were prepared by palladium-catalyzed arylation of the corresponding lactone. Substrate 17 was prepared following a procedure by Gokel et al. Pd(OAc)$_2$ was obtained from Pressure Chemical and used as received, and PhI(OAc)$_2$ was obtained from Merck Research Laboratories and used as received. Oxone was obtained from Acros and used as received, and K$_2$S$_2$O$_8$ was obtained from Fisher Chemical and used as received. Solvents were obtained from Fisher Chemical and used without further purification. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F.$^{254}$. Control reactions (in the absence of Pd catalyst) were run for each substrate, and generally showed no reaction. The regioselectivity of acetoxylation and etherification was determined based on coupling constant analysis and assignment of each aromatic proton of the products as detailed below.

![Diagram of molecule](image)

**General Procedure for Table 3.1.** Peroxide (1.75 mmol, 2.0 equiv) and Pd(OAc)$_2$ (9.81 mg, 0.044 mmol, 0.05 equiv) were combined in AcOH (3.7 mL) and Ac$_2$O (3.7 mL) in a 20 mL vial. Substrate 3 (200 mg, 0.88 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 °C for 12 h. The reaction mixture was diluted with ethyl acetate, and the vial was washed with copious diethyl ether. A 10% aqueous solution of Na$_2$SO$_3$ (450 mL) was added to the reaction, and the resulting mixture was stirred at 25 °C for 15 min. The organic and the aqueous layers were separated and the organic layer was extracted with water (2 x 50 mL), NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated. The resulting oil was purified by
chromatography on silica gel to afford two oxime (E/Z) isomers (major oxime isomer: $R_f = 0.25$ in 88% hexanes/12% ethyl acetate; minor oxime isomer: $R_f = 0.23$ in 88% hexanes/12% ethyl acetate). The two oxime isomers were isolated as yellow oils in a ratio of 5:1. The ratio of regioisomers was >20:1.

**Procedure for 66 mmol scale reaction.** Oxone (80.79 g, 131.41 mmol, 2.0 equiv) and Pd(OAc)$_2$ (441 mg, 1.97 mmol, 0.03 equiv) were combined in AcOH (493 mL) and Ac$_2$O (55 mL) in a 1000 mL round bottom flask. Substrate 3 (15 g, 65.7 mmol, 1.0 equiv) was then added to the mixture. The reaction was refluxed for 18 h. The reaction mixture was diluted with ethyl acetate (500 mL) and filtered through a pad of celite and washed with ethyl acetate (1 L). The ethyl acetate, AcOH and Ac$_2$O were removed under reduced pressure. The product was obtained as a yellow oil through Kugelrohr distillation (10.15 g, 54% yield).

**Major Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.56 (d, $J = 2.4$ Hz, 1H$_a$), 7.47 (dd, $J = 8.6$, 2.4 Hz, 1H$_b$), 6.98 (d, $J = 8.6$ Hz, 1H$_c$), 3.97 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): d 168.82, 152.23, 147.02, 132.49, 132.23, 132.09, 124.87, 119.07, 62.07, 20.96, 14.89. **Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.48 (dd, $J = 8.7$, 2.4 Hz, 1H$_b$), 7.32 (d, $J = 2.4$ Hz, 1H$_a$), 7.03 (d, $J = 8.7$ Hz, 1H$_c$), 3.79 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H). IR (thin film): 2937, 1768 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{11}$H$_{12}$BrNO$_3$, 285.0000; found, 285.0005. GC analysis (RESTEK Rtx®-5, FID detector): 99% integration. Anal. Calcd. for C$_{11}$H$_{12}$BrNO$_2$ (mixture of oxime isomers): C, 46.18, H, 4.23, N, 4.90; Found: C, 46.20, H, 4.19, N, 4.90.

**General Method for Directed C-H Bond Acetoxylation with Oxone:** Oxone (783 mg, 1.27 mmol, 0.95 equiv) and Pd(OAc)$_2$ (15 mg, 0.07 mmol, 0.05 equiv) were combined in AcOH (11.2 mL) in a 20 mL vial. Substrate 3 (200 mg, 1.34 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100°C for 12 h. The reaction mixture was diluted with ethyl acetate (25 mL), and the vial was washed with copious diethyl ether. A 10% aqueous solution of Na$_2$SO$_3$ (450 mL) was added to the reaction, and the resulting mixture was stirred at 25 °C for 15 min. The organic and the aqueous layers were separated, and the
organic layer was extracted with water (2 x 50 mL), NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel. Each substrate was optimized for reaction time, solvent (AcOH versus AcOH/Ac$_2$O) and equiv of the oxidant, as indicated below.

Each substrate was optimized for reaction time, solvent (AcOH versus AcOH/Ac$_2$O) and equiv of the oxidant, as indicated below.

The reaction was run for 12 h with 0.95 equiv of Oxone in AcOH. Product 4a was obtained as two oxime E/Z isomers (major oxime isomer: R$_f$ = 0.26 in 89% hexanes/11% ethyl acetate; minor oxime isomer: R$_f$ = 0.25 in 89% hexanes/11% ethyl acetate). The two isomers were isolated as yellow oils (147 mg total, 53% yield, ratio of oxime isomers = 5:1). **Major Oxime Isomer:** $^1$H NMR (CDCl$_3$): δ 7.43 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.37 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.25 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.10 (dd, $J$ = 8.1, 1.2 Hz, 1H), 3.97 (s, 3H), 2.29 (s, 3H), 2.16 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 169.25, 153.44, 147.95, 130.30, 129.72, 129.45, 126.10, 123.21, 61.94, 21.08, 15.09. **Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): δ 7.37 (dd, $J$ = 7.4, 1.8 Hz, 1H), 7.29 (m, 1H), 7.21 (dd, $J$ = 7.6, 1.8 Hz, 1H), 7.14 (dd, $J$ = 8.1, 1.5 Hz, 1H), 3.79 (s, 3H), 2.26 (s, 3H), 2.14 (s, 3H). IR (thin film): 2938, 1764 cm$^{-1}$. Anal. Calcd. for C$_{11}$H$_{13}$NO$_3$ (mixture of oxime isomers): C, 63.76, H, 6.32, N, 6.76; Found: C, 63.88, H, 6.08, N, 6.81.

The reaction was run for 12 h with 1.0 equiv of Oxone in AcOH. Under the reaction conditions the OAc of 5a partially hydrolyzed to the corresponding alcohol. The reaction mixture was concentrated under vacuum and Ac$_2$O (2.4 mL) and pyridine (0.46 mL) was added and the reaction stirred for 18 h. The reaction was stirred in water (5 mL) for 30
minutes and then extracted with ether. The ethereal layer was washed with water (2 x 50 mL), and NaHCO₃ (1 x 50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel to afford the product as a 2:1 mixture of oxime isomers (major oxime isomer: Rₜ = 0.25 in 89% hexanes/11% ethyl acetate; minor oxime isomer: Rₜ = 0.20 in 89% hexanes/11% ethyl acetate). The two oxime isomers were isolated as yellow oils (192 mg total, 71% yield, ratio of oxime isomers = 2:1). The ratio of regioisomers was 11:1.  

**Major Oxime Isomer/Major Regioisomer:** ¹H NMR (CDCl₃): δ 7.23 (d, J = 2.2 Hz, 1Hₐ), 7.16 (dd, J = 8.2, 2.2 Hz, 1Hₜ), 6.98 (d, J = 8.2 Hz, 1Hₜ), 3.97 (s, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H). ¹³C{¹H} NMR (CDCl₃): δ 169.32, 153.53, 145.66, 135.68, 131.33, 130.22, 129.75, 122.79, 61.80, 20.95, 20.65, 15.04.  

**Minor Oxime Isomer/Major Regioisomer:** ¹H NMR (CDCl₃): δ 7.17 (d, J = 8.3, 2.2 Hz, 1Hₜ), 7.02 (dd, J = 8.3 Hz, 1Hₜ), 6.99 (d, J = 2.2 Hz, 1Hₐ), 3.79 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H).  

**Major Oxime Isomer/Minor Regioisomer:** ¹H NMR (CDCl₃): δ 7.23 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 3.96 (s, 3H), 2.30 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H). IR (thin film): 2937, 1765 cm⁻¹. HRMS (ESI, m/z): [M⁺] calcd for C₁₂H₁₅NO₃, 221.1047; found, 221.1052. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration.  

The reaction was run for 12 h with 1.1 equiv of Oxone in AcOH. Under the reaction conditions the OAc of 6a partially hydrolyzed to the corresponding alcohol. The reaction mixture was concentrated under vacuum and Ac₂O (2.2 mL) and pyridine (0.43 mL) was added and the reaction stirred for 18 h. The reaction was stirred in water (5 mL) for 30 minutes and then extracted with ether. The ethereal layer was washed with water (2 x 50 mL), and NaHCO₃ (1 x 50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel to afford the product as a 3:1 mixture of oxime isomers (major oxime isomer: Rₜ = 0.23 in 85% hexanes/15% ethyl acetate; minor oxime isomer: Rₜ = 0.18 in 85% hexanes/15% ethyl acetate).
acetate). The two oxime isomers were isolated as yellow oils (180 mg total, 69% yield, ratio of oxime isomers = 9:1). The ratio of regioisomers was 18:1. **Major Oxime Isomer:**

$^1$H NMR (acetone-$d_6$) (399.97 Hz): δ 7.05 (d, $J = 8.7$ Hz, 1H$_a$), 6.99 (d, $J = 3.0$ Hz, 1H$_b$), 6.95 (dd, $J = 8.7$, 3.0 Hz, 1H$_b$), 3.90 (s, 3H), 3.81 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H).

$^{13}$C{$^1$H} NMR (acetone-$d_6$) (100.57 Hz): δ 169.87, 158.12, 153.83, 142.69, 132.13, 125.17, 115.58, 115.06, 62.14, 56.03, 20.99, 15.12.

**Minor Oxime Isomer:**

$^1$H NMR (CDCl$_3$): δ 7.05 (d, $J = 8.9$ Hz, 1H$_a$), 6.88 (dd, $J = 8.9$, 3.0 Hz, 1H$_b$), 6.70 (d, $J = 3.0$ Hz, 1H$_b$), 3.80 (s, 3H), 3.80 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H). IR (thin film): 2939, 1764 cm$^{-1}$.

Anal. Calcd. for C$_{12}$H$_{15}$NO$_4$ (mixture of oxime isomers): C, 60.75, H, 6.37, N, 5.90; Found: C, 60.97, H, 6.23, N, 6.09

The reaction was run for 12 h with 1.0 equiv of Oxone in AcOH/Ac$_2$O. Product 7a was obtained as an inseparable mixture of four products (R$_f$ = 0.27-0.24) – 2 regioisomers and 2 oxime isomers of each regioisomer – as a clear oil (170 mg total, 63% yield). The identity of the major regioisomer and its oxime isomers was confirmed by independent synthesis, and the NMR spectra reported below are for this independently synthesized product. Gas chromatographic analysis showed that the reaction afforded a 1.6:1 mixture of regioisomers and that each of the regioisomers was a 6:1 mixture of oxime isomers.

**Major Oxime Isomer/Major Regioisomer:** $^1$H NMR (C$_6$D$_6$): δ 7.02 (dd, 9.0, 3.0 Hz, 1H), 6.71 (dd, 8.9, 5.0 Hz, 1H), 6.60 (m, 1H), 3.76 (s, 3H), 1.95 (s, 3H), 1.74 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 169.09, 159.87 (J$_{CF}$ = 245 Hz), 152.29 (J$_{CF}$ = 1.7 Hz), 143.74 (J$_{CF}$ = 2.9 Hz), 131.66 (J$_{CF}$ = 8.0Hz), 124.56 (J$_{CF}$ = 8.7 Hz), 116.16 (J$_{CF}$ = 23 Hz), 115.93 (J$_{CF}$ = 24 Hz), 61.93, 20.80, 14.67. $^{19}$F NMR (CDCl$_3$): δ -116.3 - -116.36 (m).

**Minor Oxime Isomer/Major Regioisomer:** $^1$H NMR (C$_6$D$_6$): δ 6.77 (dd, $J = 8.9$, 5.0 Hz, 1H), 6.62 (dd, $J = 9.0$, 3.0 Hz, 1H), 6.61-6.56 (overlapping peaks), 3.64 (s, 3H), 1.90 (s, 3H), 1.50 (s, 3H). IR (thin film): 2939, 1770 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for
The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as a yellow oil (143 mg, 53% yield). The ratio of oxime isomers 17:1 and regioisomers was $>$20:1 ($R_f = 0.28$ in 90% hexanes/10% ethyl acetate). $^1$H NMR (CDCl$_3$): \(\delta\) 8.07 (s, 1H), 7.28 (d, \(J = 3.0\) Hz, 1H$_a$), 7.01 (d, \(J = 8.9\) Hz, 1H$_c$), 6.93 (dd, \(J = 8.9, 3.0\) Hz, 1H$_b$), 3.99 (s, 3H), 3.82 (s, 3H), 2.31 (s, 3H). $^{13}$C	extsuperscript{1}$^1$H NMR (CDCl$_3$): \(\delta\) 169.69, 157.46, 143.95, 142.54, 125.21, 123.95, 117.37, 110.97, 62.30, 55.79, 20.98. IR (thin film): 2938, 1763 cm$^{-1}$. HRMS (ESI, m/z): [M +] calcd for C$_{11}$H$_{13}$NO$_4$, 223.0845; found, 223.0842. GC analysis (RESTEK Rtx$^\text{®}$-5, FID detector): 100% integration.

**General Method for Directed C-H Bond Acetoxylation with K$_2$S$_2$O$_8$:** K$_2$S$_2$O$_8$ (373 mg, 1.38 mmol, 2.0 equiv) and Pd(OAc)$_2$ (7.7 mg, 0.03 mmol, 0.05 equiv) were combined in AcOH (2.88 mL) and Ac$_2$O (2.88 mL) in a 20 mL vial. Substrate 10 (150 mg, 0.69 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100°C for 12 h. The reaction mixture was diluted with ethyl acetate, and the vial was washed with copious diethyl ether. A 10% aqueous solution of Na$_2$SO$_3$ (50 mL) was added to the filtrate, and the resulting mixture was stirred at 25 °C for 15 min. The organic and the aqueous layers were separated and the organic layer was extracted with water (2 x 50 mL), NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated. The resulting oil was purified by chromatography on silica gel. Each substrate was optimized for reaction time, solvent (AcOH versus AcOH/Ac$_2$O) and equiv of the oxidant, as indicated below.
The reaction was run for 12 h with 1.0 equiv of K$_2$S$_2$O$_8$ in AcOH/Ac$_2$O. The product was obtained as a mixture of two oxime E/Z isomers (major oxime isomer: R$_f$ = 0.27 in 78% hexanes/22% ethyl acetate; minor oxime isomer: R$_f$ = 0.25 in 78% hexanes/22% ethyl acetate). The two oxime isomers were isolated as a pale yellow solid (115 mg total, 57% yield, ratio of oxime isomers = 6:1). The ratio of regioisomers was 6:1. Major Oxime Isomer/Major Regioisomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.78 (d, $J$ = 2.1 Hz, 1H$_a$), 7.68 (dd, $J$ = 8.4, 2.1 Hz, 1H$_b$), 7.27 (d, $J$ = 8.4 Hz, 1H$_c$), 4.01 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 168.26, 151.68, 151.31, 133.65, 133.18, 131.78, 124.51, 117.80, 110.19, 62.24, 20.98, 14.87. Minor Oxime Isomer/Major Regioisomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.66 (dd, $J$ = 8.4, 2.0 Hz, 1H$_b$), 7.52 (d, $J$ = 2.0 Hz, 1H$_a$), 7.29 (d, $J$ = 8.5 Hz, 1H$_c$), 3.79 (s, 3H), 2.89 (s, 3H), 2.14 (s, 3H). Major Oxime Isomer/Minor Regioisomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.67 (t, $J$ = 8.8, 7.8 Hz, 2H), 7.37 (t, $J$ = 7.8 Hz, 1H), 3.98 (s, 3H), 2.38 (s, 3H), 2.16 (s, 3H). IR (thin film): 2230, 1770 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{12}$H$_{12}$N$_2$O$_3$, 232.0848; found, 232.0848. GC analysis (RESTEK Rtx$^\circledR$-5, FID detector): 100% integration.

The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH/Ac$_2$O. The product was obtained as a mixture of two oxime (E/Z) isomers (major oxime isomer: R$_f$ = 0.27 in 87% hexanes/13% ethyl acetate; minor oxime isomer: R$_f$ = 0.25 in 87% hexanes/13% ethyl acetate). The two oxime isomers were isolated as yellow oils (142 mg total, 75% yield, ratio of oxime isomers = 5:1). The ratio of regioisomers was >20:1. Major Oxime Isomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.71 (d, $J$ = 2.3 Hz, 1H$_a$), 7.63 (dd, $J$ = 8.5, 2.3 Hz, 1H$_b$),
The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as a mixture of two oxime (E/Z) isomers (major oxime isomer: $R_f = 0.24$ in 92% hexanes/8% ethyl acetate; minor oxime isomer: $R_f = 0.24$ in 92% hexanes/8% ethyl acetate). The product was isolated as a yellow oil (106 mg total, 53% yield, ratio of oxime isomers = 5:1). **Major Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 8.25 (s, 1H), 7.27 (t, $J$ = 8.0, 7.5 Hz, 1H), 7.12 (d, $J$ = 7.5 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 1H), 3.99 (s, 3H), 2.47 (s, 3H), 2.33 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 169.69, 149.12, 144.60, 139.47, 129.93, 128.84, 123.32, 120.97, 62.19, 21.26, 21.13. **Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.39 (s, 1H), 7.29 (t, $J$ = 7.9, Hz, 1H), 7.10 (d, $J$ = 7.7 Hz, 1H), 6.96 (d, $J$ = 8.1 Hz, 1H), 3.90 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H). IR (thin film): 2969, 1769 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{11}$H$_{13}$NO$_3$, 207.0895; found, 207.0892. GC analysis (RESTEK Rtx$^{®}$-5, FID detector): 99% integration.

The reaction was run for 12 h with 1.5 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as a yellow oil (272 mg, 75% yield). ($R_f = 0.26$ in 15% hexanes/85% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.29-7.21 (multiple peaks, 3H), 7.15 (d, $J$ = 7.6 Hz, 1H), 7.24 (d, $J$ = 8.5 Hz, 1H), 3.99 (s, 3H), 2.31 (s, 3H), 2.17 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 168.62, 152.30, 150.49, 131.07, 128.38 ($^2$J$_{CF}$ = 33 Hz), 126.85 ($^3$J$_{CF}$ = 3.8 Hz), 126.62 ($^3$J$_{CF}$ = 3.6 Hz), 123.60 ($^1$J$_{CF}$ = 272 Hz), 123.91, 62.14, 20.96, 14.93. $^{19}$F NMR (CDCl$_3$): $\delta$ -62.37 (s).

**Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.60 (m, 1H), 7.43 (d, $J$ = 2.7 Hz, 1H), 7.20 (d, $J$ = 8.5 Hz, 1H), 3.76 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H). IR (thin film): 2942, 1770 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{12}$H$_{12}$F$_3$NO$_3$, 275.0769; found, 275.0775. GC analysis (RESTEK Rtx$^{®}$-5, FID detector): 100% integration.
3.70 (t, J = 6.9 Hz, 2H), 2.49 (t, J = 8.0 Hz, 2H), 2.24 (s, 3H), 2.13 (quin, J = 7.2 Hz, 2H). $^{13}$C{$^1$}H NMR (CDCl$_3$): δ 173.88, 168.53, 145.64, 130.80, 127.86, 126.89, 126.25, 123.41, 49.82, 30.94, 20.71, 19.02. IR (thin film): 1766, 1702 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{12}$H$_{13}$NO$_3$, 219.0895; found, 219.0894. GC analysis (RESTEK Rtx$^®$-5, FID detector): 100% integration.

The reaction was run for 12 h with 3.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as a pale yellow viscous oil (79.0 mg, 53% yield) ($R_f$ = 0.26 in 55% hexanes/45% ethyl acetate). $^1$H NMR (CDCl$_3$): δ 7.33 (t, J = 8.1 Hz, 1H), 6.99 (d, J = 8.2 Hz, 2H), 4.70-4.66 (m, 1H), 4.06-4.05 (multiple peaks, 2H), 3.59 (d, J = 3.3 Hz, 2H), 2.78 (dd, J = 17.4, 10.8 Hz, 1H), 2.44 (dd, J = 17.4, 7.8 Hz, 1H), 2.32 (s, 6H), 2.04 (s, 3H). $^{13}$C{$^1$}H NMR (CDCl$_3$): δ 170.72, 169.22, 155.92, 150.10, 128.48, 120.89, 120.64, 77.76, 64.92, 38.22, 23.23, 20.78, 20.69. IR (thin film): 2939, 1769, 1742 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{17}$H$_{19}$NO$_7$, 349.1162; found, 349.1160. GC analysis (RESTEK Rtx$^®$-5, FID detector): 99% integration.

The reaction was run for 12 h with 2.0 equiv of Oxone® in AcOH. The product was obtained as a mixture of two products ($R_f$ = 0.26 in 95% hexanes/5% ethyl acetate). $^1$H NMR of 14a (CDCl$_3$): δ 11.65 (s, 1H), 7.31 (dd, J = 8.1, 1.5 Hz, 1H), 7.06 (dd, J = 7.9, 1.5 Hz, 1H), 6.88 (t, J = 8.0 Hz, 1H), 3.99 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H). $^{13}$C{$^1$}H NMR (CDCl$_3$): δ 169.08, 158.17, 149.79, 139.25, 125.09,
123.98, 119.81, 118.49, 62.54, 20.65, 11.61. IR (KBr): 2943, 1760 cm\(^{-1}\). HRMS (ESI, m/z): [M\(^+\)] calcd for C\(_{11}\)H\(_{13}\)NO\(_4\), 223.0844; found, 223.0843. GC analysis (RESTEK Rtx\(^\text{®}-5\), FID detector): 100% integration. Hydrolyzed (OH) product: \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.96 (t, \(J = 7.5 \text{ Hz}, 2\)H), 6.81 (t, \(J = 7.9 \text{ Hz}, 1\)H), 5.71 (s, 1H), 4.02 (s, 3H), 2.30 (s, 3H).

The reaction was run for 12 h with 1.5 equiv of K\(_2\)S\(_2\)O\(_8\) in AcOH. The product was obtained as a pale yellow viscous oil (38% yield) (\(R_f = 0.26\) in 55% hexanes/45% ethyl acetate). \(^1\)H NMR (C\(_6\)D\(_6\)): \(\delta\) 8.29 (br s, 1H), 7.21 (br s, 1H), 7.07 (br s, 2H), 2.36 (s, 3H), 2.18 (s, 3H).

Oxone (853 mg, 1.39 mmol, 1.0 equiv) and Pd(OAc\(_2\)) (16 mg, 0.07 mmol, 0.05 equiv) were combined in AcOH (11.6 mL) in a 20 mL vial. Substrate 16 (200 mg, 1.39 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was heated at 100 °C for 12 h. The reaction mixture was diluted with chloroform and extracted with water (2 x 50 mL), NaHCO\(_3\) (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO\(_4\), filtered, and concentrated. The resulting oil was purified by chromatography on silica gel (\(R_f = 0.18\) in 80% hexanes/20% ethyl acetate). The product was obtained as a yellow solid (28 mg, 10% yield). mp = 86-88 °C. \(^1\)H NMR (399.96 Hz) (CDCl\(_3\)): \(\delta\) 8.87 (s, 2H), 8.09 (d, \(J = 8.3 \text{ Hz}, 1\)H), 7.84-7.75 (multiple peaks, 2H), 5.80 (s, 2H), 2.10 (s, 3H). \(^{13}\)C\{\(^1\)H\} NMR (100.57 Hz) (CDCl\(_3\)): \(\delta\) 170.85, 145.03, 144.32, 142.83, 141.12, 134.71, 129.71, 129.70, 129.40, 61.85, 21.03. IR (KBr): 2927, 1739 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na] calcd for C\(_{11}\)H\(_{10}\)N\(_2\)O\(_2\), 202.0742; found, 202.0738. GC analysis (RESTEK Rtx\(^\text{®}-5\), FID detector): 99% integration. Along with the product 16a, the N-oxide of the starting material (101 mg, 46% yield), (\(R_f = 0.15\) in 70% hexanes/30% ethyl acetate) and the N-oxide of 16a.
(27.0 mg, 9% yield), (R_f = 0.1 in 70% hexanes/30% ethyl acetate) were obtained, whose spectroscopic data are described below.

![16a-O](image)

{\textsuperscript{1}H NMR (CDCl\textsubscript{3}):} {\delta} 8.70 (d, J = 3.5 Hz, 1H\textsubscript{a}), 8.57 (d, J = 8.7 Hz, 1H\textsubscript{c}), 8.38 (d, J = 3.5 Hz, 1H\textsubscript{b}), 7.88 (d, J = 7.2 Hz, 1H\textsubscript{e}), 7.75 (t, J = 7.3 Hz, 1H\textsubscript{d}), 5.78 (s, 2H), 2.17 (s, 3H).

{\textsuperscript{13}C NMR (CDCl\textsubscript{3}):} {\delta} 170.71, 145.31, 144.05, 137.59, 135.73, 130.83, 129.80, 129.35, 118.94, 61.78, 20.98. IR (KBr): 1735, 1242 cm\textsuperscript{-1}. mp = 112-113 °C. HRMS (ESI, m/z): [M + Na] calcd for C\textsubscript{11}H\textsubscript{10}N\textsubscript{2}O\textsubscript{3}, 218.0691; found, 218.0689. GC analysis (RESTEK Rtx\textsuperscript{®}-5, FID detector): 99% integration. The assignment of the regioselectivity of N-oxidation was made based on comparison of the NMR of 16a-O to 16a as detailed in reference 4.

![16-O](image)

{\textsuperscript{1}H NMR (CDCl\textsubscript{3}):} {\delta} 8.62 (d, J = 3.45 Hz, 1H\textsubscript{a}), 8.37 (d, J = 8.2 Hz, 1H\textsubscript{c}), 8.31 (d, J = 3.46 Hz, 1H\textsubscript{b}), 7.61-7.55 (multiple peaks, 2H\textsubscript{d, e}), 2.73 (s, 3H). {\textsuperscript{13}C \{\textsuperscript{1}H\} NMR (CDCl\textsubscript{3}):} {\delta} 145.04, 144.38, 138.65, 137.59, 131.72, 129.77, 128.77, 116.56, 17.66. mp = 132-133 °C. IR (KBr): 1501, 1309 cm\textsuperscript{-1}. HRMS (ESI, m/z): [M + Na] calcd for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}O, 160.0637; found, 160.0634. GC analysis (RESTEK Rtx\textsuperscript{®}-5, FID detector): 99% integration.
The reaction was run at rt for 12 h with 1.5 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as a pale yellow oil (R$_f$ = 0.26 in 55% hexanes/45% ethyl acetate) (39% yield).

$^1$H NMR (C$_6$D$_6$): δ 7.66-7.56 (multiple peaks, 3H), 7.38 (t, J = 7.6 Hz, 1H), 7.31-7.28 (multiple peaks, 2H), 7.12 (d, J = 8.4 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H).

HRMS (ESI, m/z): [M$^+$] calcd for C$_{10}$H$_{12}$ClNO$_2$, 268.1209; found, 268.1209. Along with the product 17a, the N-oxide of the starting material (36% yield), (R$_f$ = 0.15 in 70% hexanes/30% ethyl acetate) was obtained, whose spectroscopic data is described below.

The reaction was run at rt for 12 h with 1.5 equiv of K$_2$S$_2$O$_8$ or Oxone or PhI(OAc)$_2$ in AcOH. The product was obtained as a yellow oil (78% yield, R$_f$ = 0.15 in 70% hexanes/30% ethyl acetate). $^1$H NMR (C$_6$D$_6$): δ 7.78 (d, J = 7.0 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 (m, 2H) 6.59 (br s, 1H), 4.29 (t, J = 5.0 Hz, 2H), 3.73 (q, J = 5.0 Hz, 2H), 2.09 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ 171.47, 167.55, 134.18, 131.61, 128.60, 126.91, 63.34, 39.55, 20.92. IR (KBr): 1734 cm$^{-1}$. 

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The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was obtained as two oxime (E/Z) isomers (major oxime isomer: $R_f = 0.3$ in 90% hexanes/10% ethyl acetate; minor oxime isomer: $R_f = 0.21$ in 90% hexanes/10% ethyl acetate). The two oxime isomers were isolated as yellow oils (45% yield, ratio of oxime isomers = 5:1). The NMR data was identical to that reported previously for this compound.

The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was isolated as a clear oil ($R_f = 0.28$ in 90% hexanes/10% ethyl acetate), (63% yield). The NMR data was identical to that reported previously for this compound.

The reaction was run for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in AcOH. The product was isolated as a clear oil ($R_f = 0.28$ in 90% hexanes/10% ethyl acetate), (23% yield). The NMR data was identical to that reported previously for this compound.

**General Method for Directed C-H Bond Methoxylation with Oxone:** Oxone® (808 mg, 1.31 mmol, 2.0 equiv) and Pd(OAc)$_2$ (15 mg, 0.07 mmol, 0.1 equiv) were combined in MeOH (5.48 mL) in a 20 mL vial. Substrate 3 (150 mg, 0.66 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was stirred at rt for 12 h and then stirred at 80 °C for another 12 h. The reaction mixture was diluted with ethyl acetate, and extracted with water (2 x 50 mL), NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO$_4$, ...
filtered, and concentrated. The resulting oil was purified by chromatography on silica gel. Each substrate was optimized for reaction time and equiv of the oxidant, as indicated below.

\[
\begin{align*}
\text{N} & \text{O} \\
\text{Me} & \text{Br} \\
\text{M}(3b)
\end{align*}
\]

The reaction was run at rt for 12 h and then stirred at 80 °C for another 12 h, with 2.0 equiv of Oxone®. Product 3b was obtained as two oxime (E/Z) isomers (major oxime isomer: 0.28 Rf = 90% in hexanes/10% ethyl acetate; minor oxime isomer: Rf = 0.26 in 90% hexanes/10% ethyl acetate). The two isomers were isolated as yellow oils. Under the reaction conditions oxime 3b underwent partial hydrolysis to the corresponding ketone. Isolated product (119 mg total, 70% yield, ratio of oxime isomers = 5:1, ratio of oxime to ketone = 4:1). The ratio of regioisomers was >20:1. **Major Oxime Isomer of 3b:** \( ^1H \) NMR (acetone-\( d_6 \)): \( \delta \) 7.51 (dd, \( J = 8.8, 2.6 \) Hz, 1H\( a \)), 7.38 (d, \( J = 2.6 \) Hz, 1H\( b \)), 7.03 (d, \( J = 8.8 \) Hz, 1H\( c \)), 3.90 (s, 3H), 3.87 (s, 3H), 2.10 (s, 3H). \( ^{13}C\{\text{H}\} \) NMR (CDCl\( _3 \)): \( \delta \) 156.64, 155.28, 132.64, 132.16, 128.78, 112.84, 112.69, 61.86, 55.72, 15.77. IR (thin film): 2932, 1606, 1486 cm\(^{-1}\). HRMS (ESI, m/z): [M\(^+\)] calcd for C\(_{10}\)H\(_{12}\)BrNO\(_2\), 257.0051; found, 257.0045. GC analysis (RESTEK Rtx\(^®\)-5, FID detector): 100% integration. **Ketone:** \( ^1H \) NMR (CDCl\( _3 \)): \( \delta \) 7.49 (d, \( J = 2.4 \) Hz, 1H), 7.32 (dd, \( J = 8.7, 2.8 \) Hz, 1H), 6.86 (d, \( J = 8.7 \) Hz, 1H), 4.01 (s, 3H), 2.28 (s, 3H).

\[
\begin{align*}
\text{O} & \text{Me} \\
\text{N} & \text{O} \\
\text{Me} (27b)
\end{align*}
\]

The reaction was run at rt for 12 h and then stirred at 80 °C for another 12 h with 2.0 equiv of Oxone®. The two oxime isomers were isolated as clear oils. (E/Z) isomers (major oxime isomer: Rf = 0.26 in 97% hexanes/3% ethyl acetate; minor oxime isomer: Rf = 0.26 in 97% hexanes/3% ethyl acetate). Under the reaction conditions, oxime 27b
underwent partial hydrolysis to the corresponding ketone (102 mg total, 60% yield, ratio of oxime isomers = 3:1, Ratio of oxime : ketone = 7:1). **Major Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.22 (t, $J = 8.2$ Hz, 1H), 7.02 (dd, $J = 8.1$, 0.9 Hz, 1H), 6.82 (dd, $J = 8.4$, 0.9 Hz, 1H), 4.00 (s, 3H), 3.82 (s, 3H), 2.12 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 158.39, 152.81, 133.83, 129.89, 125.97, 121.64, 109.28, 61.80, 55.98, 15.75. **Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.22 (t, $J = 8.2$ Hz, 1H), 7.01 (dd, $J = 8.1$, 0.9 Hz, 1H), 6.82 (dd, $J = 8.1$ Hz, 0.9 Hz, 1H), 4.02 (s, 3H), 3.82 (s, 3H), 2.32 (s, 3H). IR of 27b (KBr): 2936, 1590, 1573 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{10}$H$_{12}$ClNO$_2$, 213.0557; found, 213.0554. GC analysis (RESTEK Rtx$^\circledR$-5, FID detector): 99% integration. **Ketone:** $^1$H NMR (CDCl$_3$): $\delta$ 7.13 (t, $J = 8.1$ Hz, 1H), 6.95 (dd, $J = 8.0$, 1.1 Hz, 1H), 6.89 (dd, $J = 8.3$, 1.1 Hz, 1H), 3.82 (s, 3H), 2.13 (s, 3H). The reaction was run at rt for 12 h and then the temperature was slowly ramped to 80 °C over 20 minutes for another 12 h with 2.0 equiv of Oxone in MeOH. The product was obtained as two oxime (E/Z) isomers (major oxime isomer: $R_f = 0.25$ in 95% hexanes/5% ethyl acetate; minor oxime isomer: $R_f = 0.24$ in 95% hexanes/5% ethyl acetate). The two oxime isomers were isolated as yellow oils (106 mg total, 59% yield, ratio of oxime isomers = 3:1). **Major Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 8.51 (s, 1H), 7.21 (t, $J = 8$ Hz, 1H), 6.83 (d, $J = 8$ Hz, 1H), 6.74 (d, $J = 8.5$ Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 2.52 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 158.48, 146.23, 139.09, 129.73, 123.55, 119.42, 108.13, 61.89, 55.65, 22.123. **Minor Oxime Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.52 (s, 1H), 7.23 (t, $J = 7.8$ Hz, 1H) 6.84 (d, $J = 7.8$, 1H), 6.74 (d, $J = 8.3$ Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 2.25 (s, 3H). IR (thin film): 2935, 1595 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{10}$H$_{13}$NO$_2$, 179.0946; found, 179.0940. GC analysis (RESTEK Rtx$^\circledR$-5, FID detector): 99% integration.
The reaction was run at rt for 12 h and then stirred at 80 °C for another 12 h with 2.0 equiv of Oxone in MeOH. The product was obtained as a pale yellow oil (R_f = 0.26 in 97% hexanes/3% ethyl acetate). $^1$H NMR (C_6D_6): δ 6.80-6.73 (multiple peaks, 3H), 3.89 (s, 3H), 3.67 (s, 3H), 2.69 (t, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 1.97 (quin, J = 7.5 Hz, 2H). $^{13}$C{$^1$H} NMR (CDCl_3): δ174.42, 146.55, 143.78, 127.36, 122.60, 119.47, 108.74, 56.16, 51.68, 33.71, 29.16, 25.08.

**General Method for Directed C-H Bond Methoxylation with K$_2$S$_2$O$_8$:** K$_2$S$_2$O$_8$ (309 mg, 1.14 mmol, 2.0 equiv) and Pd(OAc)$_2$ (12.8 mg, 0.11 mmol, 0.1 equiv) were combined in MeOH (4.76 mL) in a 20 mL vial. Substrate 30 (100 mg, 0.57 mmol, 1.0 equiv) was then added to the mixture. The vial was sealed with a Teflon lined cap, and the reaction was stirred at rt for 12 h and then stirred at 40 °C for another 12 h. The reaction mixture was diluted with ethyl acetate, and extracted with water (2 x 50 mL), NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated. Each substrate was optimized for reaction time and equiv of the oxidant, as indicated below.

The reaction was run at rt for 12 h and then at 40 °C for 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in MeOH. The product was obtained as a yellow oil (85 mg, 72% yield). (R_f = 0.26 in 25% hexanes/75% ethyl acetate). $^1$H NMR (CDCl$_3$): δ 7.29-7.25 (multiple peaks, 2H), 7.01-6.96 (multiple peaks, 2H), 3.84 (s, 3H), 3.76 (t, J = 7.0 Hz, 2H), 2.56 (t, J = 7.9 Hz, 2H), 2.19 (quin, J = 7.2 Hz, 2H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 175.12, 154.80, 128.60, 128.59, 127.20, 120.85, 111.99, 55.57, 49.90, 31.18, 18.92. IR (thin film): 2945, 1696 cm$^{-1}$. 

105
HRMS (ESI, m/z): [M$^+$] calcd for C$_{11}$H$_{13}$NO$_2$, 191.0946; found, 191.0943. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration.

The reaction was run at rt for 12 h and then stirred at 40 °C for another 12 h with 3.0 equiv of K$_2$S$_2$O$_8$ in MeOH. The product was obtained as a brown solid as a single regioisomer (R$_f$ = 0.25 in 25% hexanes/75% ethyl acetate) (67 mg, 61% yield); mp = 95-110 °C. $^1$H NMR (CDCl$_3$): δ 7.40 (d, $J$ = 2.5 Hz, 1H$_a$), 7.37 (dd, $J$ = 9.0, 2.5 Hz, 1H$_b$), 6.84 (d, $J$ = 8.5 Hz, 1H$_c$), 3.83 (s, 3H), 3.74 (t, $J$ = 7.0 Hz, 2H), 2.55 (t, $J$ = 7.9 Hz, 2H), 2.19 (q, $J$ = 7.7 Hz, 2H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ 175.07, 154.08, 131.46, 131.27, 128.55, 113.47, 112.35, 55.86, 49.79, 31.04, 18.96. IR (KBr): 2924, 1674 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{11}$H$_{12}$BrNO$_2$, 269.0051; found, 269.0046. GC analysis (RESTEK Rtx®-5, FID detector): 100% integration.

The reaction was run at rt for 12 h and then stirred at 40 °C for another 12 h with 2.0 equiv of K$_2$S$_2$O$_8$ in MeOH. The product was obtained as single regioisomer as a viscous pale yellow oil (67.0 mg, 57% yield, R$_f$ = 0.22 in 25% hexanes/75% ethyl acetate). $^1$H NMR (C$_6$D$_6$): δ 7.18 (s, 1H$_a$), 6.85 (d, $J$ = 8.3 Hz, 1H$_b$), 6.50 (d, $J$ = 8.3 Hz, 1H$_c$), 3.39-3.35 (multiple peaks, 2H), 3.28 (s, 3H), 2.17 (t, $J$ = 7.7 Hz, 2H), 2.10 (s, 3H), 1.47 (quin, $J$ = 7.8 Hz, 2H). $^{13}$C($^1$H) NMR (CDCl$_3$): δ 175.19, 152.69, 130.34, 129.14, 129.06, 126.86, 112.02, 55.75, 50.00, 31.25, 20.39, 18.96. IR (KBr): 2932, 1694 cm$^{-1}$. HRMS (ESI, m/z): [M$^+$] calcd for C$_{13}$H$_{15}$NO$_2$, 205.1103; found, 205.1094. GC analysis (RESTEK Rtx®-5, FID detector): 99% integration.
The reaction was run at rt for 12 h and then stirred at 80 °C for another 12 h with 2.0 equiv of Oxone in MeOH. The product was obtained as a pale yellow oil, mixture of two oxime (E/Z) isomers (major oxime isomer: Rf = 0.26 in 97% hexanes/3% ethyl acetate; minor oxime isomer: Rf = 0.26 in 97% hexanes/3% ethyl acetate). Under the reaction conditions, oxime 6b underwent partial hydrolysis to the corresponding ketone (6c mg total, 48% yield, ratio of oxime isomers = 3:1, Ratio of oxime : ketone = 1:1.7). **Major Oxime Isomer:** $^1$H NMR (C$_6$D$_6$): δ 7.55 (d, J = 8.5 Hz, 1H), 7.50 (m, 1H), 7.13 (dd, J = 8.5, 3.0 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.62 (s, 3H). Ketone NMR data is shown below.

$^1$H NMR (C$_6$D$_6$): δ 6.94-6.90 (multiple peaks, 2H), 6.87 (dd, J = 9, 2.5 1H), 4.00 (s, 3H), 3.78 (s, 3H), 2.29 (s, 3H).
3.9 References


Chapter 4

Factors Governing the Dominance of a Directing Group

4.1 Background and Significance

Palladium-catalyzed ligand directed C–H activation/functionalization has emerged as a powerful method for the regioselective conversion of C–H bonds to C–X bonds (X = C, O, Cl, Br, I and F).\textsuperscript{1-10} The ligand directed approach allows for the site selective functionalization of the C–H bond proximal to a directing group in molecules containing an appropriate chelating functionality (Scheme 4.1).

\textbf{Scheme 4.1:} Chelate Directed C–H Activation/Functionalization

![Scheme 4.1](image)

Recently, we and others have shown that this methodology is general with respect to a wide variety of directing groups such as pyridines, oxime ethers, isoxazolines, amides, quinolines, and oxazolines.\textsuperscript{1-9} Importantly, these functionalities are widely prevalent in biologically active molecules.\textsuperscript{11, 12} Hence, this methodology could potentially be used for functionalization of C–H bonds adjacent to chelating groups to generate libraries of synthetic analogues of important pharmaceutical targets.
Figure 4.1: Examples of Biologically Active Molecules Containing a Single Potential Directing Group

The palladium-catalyzed chelate directed functionalization reactions have thus far been demonstrated in molecules bearing a single chelating functionality. Hence, they could be applicable to molecules such as 3, 4 and 5 that contain only one potential ligand (Figure 4.1). However, the vast majority of biologically active molecules contain multiple chelating functionalities (for example, 6, 7, and 8 in Figure 4.2). Subjection of these molecules to C–H activation/functionalization reactions could possibly lead to mixtures of products resulting from functionalization adjacent to the different directing groups present in these compounds. In order to enhance the applicability of these ligand-directed transformations, an understanding of the factors that control functionalization adjacent to one chelating moiety over another is essential. Despite the potential synthetic utility of this chemistry, to date there has been no systematic study to address this important issue. This chapter describes a comprehensive investigation of the factors that govern the dominance of a directing group in palladium-catalyzed activation/functionalization of C–H bonds to C–OAc bonds. The insights gained from this study could ultimately be applied towards transformation of C–H bonds to other C–X bonds (X = Cl, Br, I, F, C, and N) as well.
**Figure 4.2.** Examples of Biologically Active Molecules Containing Multiple Potential Directing Groups

![Molecules](image)

*Figure 4.2: Examples of Biologically Active Molecules Containing Multiple Potential Directing Groups

(6) Atherosclerosis  
(7) Anti-colon cancer  
(8) Alzheimer's

**Strategy:** Our approach towards elucidating the dominance of a directing group involved systematically studying how different directing groups affect the distribution of products in Pd-catalyzed C–H bond functionalization with PhI(OAc)$_2$. As shown in Scheme 4.2, we designed a series of experiments to compete two directing groups against one another in the same reaction flask (mimicking situations where two potential ligands are present within the same molecule). In these systems, 1 equiv of substrate A and 1 equiv of substrate B were subjected to Pd-catalyzed reaction with 1 equiv of PhI(OAc)$_2$. The ratio of acetoxylated products (A-OAc/B-OAc) was then determined, and this value was taken to represent the relative reaction rates of the two directing groups ($k_A/k_B$) under a given set of conditions (Scheme 4.2).

**Scheme 4.2: Competition Studies Between Multiple Directing Groups**

Scheme diagram showing the reaction of A and B with Pd(OAc)$_2$ and PhI(OAc)$_2$ to yield A-OAc and B-OAc.

### 4.2 Substrate Selection and Optimizations

Our studies began with the synthesis of substrates bearing a variety of different directing groups (Figure 4.3). Importantly, the key design elements for these substrates include (i) selection of directing groups shown to be effective ligands for palladium and
present in biologically active molecules, (ii) installation of a methylene unit between the
directing ligand and the aryl ring to limit electronic communication between the directing
group and the arene being functionalized, and (iii) introduction of an electronically
neutral methyl substituent at the meta-position of the aryl ring being functionalized in
order to promote selective mono-acetoxylation of the sterically less hindered C-H bond
(Figure 4.4).

**Figure 4.3. Substrates Synthesized to Conduct Dominance Studies**

Next, we conducted studies to obtain reaction conditions for the palladium-
catalyzed C–H activation/acetoxylation of these substrates. A screen of different solvents,
temperatures and catalyst loadings was performed. A representative set of data for the
solvent and catalyst loading study is illustrated in Table 4.1. Interestingly, there is a
significant solvent effect between different directing groups. While 21 lead to excellent
yields of the acetoxylated product in all solvents, substrate 11 afforded the desired
product only in AcOH/Ac₂O. The catalyst loading could be reduced to 0.1 mol % for substrate 21 and still produce good (47%) yield of acetoxylated product (Table 4.1, entry 6). However, this low catalyst loading led to diminished reactivity for other substrates such as 17 and 11 (entry 6). Hence, we chose to conduct all our further studies with 1 mol % Pd(OAc)₂.

Table 4.1: Optimization Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>% Pd(OAc)₂</th>
<th>Solvent</th>
<th>% GC yield</th>
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<tbody>
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<td>1</td>
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<td>AcOH/Ac₂O</td>
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</tr>
<tr>
<td>2</td>
<td>5</td>
<td>Benzene</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>DCE</td>
<td>39%</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
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</tr>
<tr>
<td>5</td>
<td>1</td>
<td>AcOH/Ac₂O</td>
<td>92%</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>AcOH/Ac₂O</td>
<td>39%</td>
</tr>
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Substrates 11, 13, 15-19, and 21 afforded the desired monoacetoxylated products 23-26 and 30-33 in good to excellent yields under our optimized reaction conditions (1 mol % Pd(OAc)₂, 1.02 – 1.8 equiv PhI(OAc)₂ in AcOH/Ac₂O at 100 ºC) regardless of the nature of the directing group (Table 4.2, entries 1-4 and 8-11). The stronger oxidant PhI(OCCF₃)₂ was required for substrates 9 and 10, and even then only modest (49-55%) yields of products 34 and 35 were obtained (Table 4.2, entries 12 and 13). The low reactivity of 9 and 10 may be due to the larger seven-membered ring required for cyclopalladation with the amide carbonyl in these substrates, since amide substrate 15 affords the acetoxylated product 33 in good yield (entry 11).
Table 4.2: Scope of Substrates Bearing Different Directing Groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
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<td>14</td>
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</table>

Substrates 12 and 14 afforded no appreciable amount of the acetoxylated products 29 and 36 due to their faster relative rate of decomposition under our reaction conditions. Additionally, compounds 20 and 22 afforded the desired acetoxyalted products 27 and 28 in low yields due to competing uncatalyzed acetoxylation at other positions in the molecule. This was surprising to us because substrates bearing the same directing group, but lacking a methylene spacer, afforded good yields of the ortho-acetoxyalted products along with only trace amounts of the undesired products (Scheme 4.3).1,2
4.3 Competition Studies

The competition experiments depicted in Scheme 4.4 above were conducted in two different solvents – an acidic medium (AcOH/ Ac₂O) and a non-acidic medium (benzene). We examined both solvents in order to determine whether the trend of dominance observed was not affected by competitive protonation of the basic directing groups in AcOH. These studies were performed by subjecting a 1:1 molar ratio of two different substrates in either AcOH/ Ac₂O (1:1) or benzene with 1 equivalent of PhI(OAc)₂ and 1 mol % Pd(OAc)₂. Upon completion of the reaction, the yields and ratios of the acetylated products were determined by gas chromatography. The ratio of the products reflected the relative rates of reaction of the two substrates towards C–H activation/acetoxylation. In a representative experiment, the reaction of an equimolar quantity of 18 and 17 in the same vessel afforded the acetylated products 26 and 25 in a ratio of 1:0.4 ($k_{pyrazole}/k_{pyridine} = 2/5$). The same experiment when conducted in benzene also led to 26 as the major product ($26:25 = 1:0.06$), albeit with greater selectivity than in AcOH/ Ac₂O (Scheme 4.4).
Scheme 4.4: Representative Competition Experiment

Interestingly, competition experiments between pyridine 18 and substrates bearing significantly less basic directing groups such as isoxazoline (16), oxime ethers (11 and 13), and amide (15) did not afford an appreciable amount of the acetoxylated products 24, 30-31, and 33 in either AcOH/\text{Ac}_2\text{O} or benzene. Instead, 26 was formed with a selectivity of > 50:1 (Scheme 4.5).

Scheme 4.5: Competition Between Benzylpyridine 18 and Oxime Ether 11

Analogous competition experiments were also conducted between substrates 11, 13, 15 and 16. Interestingly, the two similar oxime ether derivatives 11 and 13 exhibited different reactivity when the solvent was changed from AcOH/\text{Ac}_2\text{O} to benzene (Scheme 4.6). Methyl oxime ether 11 did not afford any of the acetoxylated product 30 in benzene, whilst benzyl oxime ether 13 yielded 28% of product 31.
Scheme 4.6: Competition between Oxime Ethers 13 and 11

The ratios obtained from all of these competition experiments are compiled in Tables 4.3 and 4.4. Based on this data, the reactivity trend depicted in Figure 4.5 was obtained for AcOH/Ac₂O and benzene, respectively. In general, substrate 18, bearing the most basic directing group (pyridine), afforded the predominant acetoxyalted product in the presence of all other chelating ligands in both AcOH/Ac₂O and benzene.
### Table 4.3: Competition Ratios in AcOH/\(\text{Ac}_2\text{O}\)

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<td>(\text{N} = \text{N})</td>
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<td>-</td>
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<tr>
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<td>(0.01 : 1)</td>
<td>(0.01 : 1)</td>
<td>(1 : 0.01)</td>
<td>(1 : 0.01)</td>
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</table>

*Ratio not obtained because starting materials and products have identical retention times by GC.*

In the ratios depicted above the first number refers to the substrate in the column and the second number to the substrate in the row.
Table 4.4: Competition Ratios in Benzene

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</table>

* Ratio not obtained because starting materials and products have identical retention times by GC
* Ratio not obtained because starting materials afford trace amounts of products in benzene

In the ratios depicted above the first number refers to the substrate in the column and the second number to the substrate in the row
Figure 4.5: Relative Reactivity of Directing Groups from Competition Studies in AcOH/Ac₂O and Benzene

Trend in AcOH/Ac₂O

While the trends in the two solvents varied slightly, in general the results were consistent with studies of substituted benzylpyridine derivatives 43a-43f (Scheme 4.7), which were conducted by my colleague Kara Stowers. Kara obtained a Hammett $\rho$ value of -2.01 when she carried out similar competition experiments with these substrates (Scheme 4.7). This $\rho$ value implies that electron rich substrates are dominant in the competition studies.

Scheme 4.7: Electronic Effects with Substituted Benzylpyridine Derivatives
4.4 Individual Rate Studies

We next sought to investigate the reasons for predominant product formation by substrates bearing an electron rich ligand when substrates containing different directing groups were present in the same reaction vessel. In particular, we wondered if benzylpyridine substrate 18, which afforded the major product in the presence of other directing groups, would also exhibit the fastest rate of acetoxylation. In order to probe this, we studied the kinetics of acetoxylation for each substrate individually in separate reaction vessels. The initial rate constant for each substrate was obtained under optimal conditions (1 mol % Pd(OAc)$_2$, 1.02 equiv PhI(OAc)$_2$, at 80 ºC) in both AcOH/Ac$_2$O and in benzene, by monitoring the reaction progress by GC (Table 4.5). The initial rates for acetoxylation of substrates 11, 13, 15-19, and 21 ranged from 0.01 to 0.64 mol/(L)(min) in AcOH/Ac$_2$O and 0.02 to 0.5 mol/(L)(min) in benzene.

Figure 4.6. Representative Initial Rates Data in AcOH/Ac$_2$O

![Representative Initial Rates Data in AcOH/Ac$_2$O](image)
Figure 4.7. Representative Initial Rates Data in Benzene

Notably, in AcOH/Ac₂O, the three substrates bearing very similar heterocyclic nitrogen-containing directing groups – pyridine 18, pyrimidine 21, and pyrazine 19 – exhibited very different initial rates. The pyrimidine reacted 60 times faster than the pyrazine and 4 times faster than the pyridine (Table 4.5, entries 1, 4, and 8). In contrast, substrates bearing two very different directing groups, methyl oxime ether (11) and pyridine (18), showed very similar initial rate constants (entries 4-5).

The solvent had a significant effect on the efficiency of the acetoxylation reactions by certain chelating ligands. For example, the isoxazoline and the pyrazole underwent reaction at similar rate constants in AcOH/Ac₂O, while in benzene the isoxazoline substrate 16 was twice as fast as the pyrazole. Notably, methyl oxime ether 11 and amide 15, which showed good reactivity in AcOH/Ac₂O, led to only trace amounts of the corresponding acetoxylated products in benzene. Additionally, contrary to the competition studies, substrate 18, bearing the most basic directing group – pyridine – did not exhibit the fastest rate of acetoxylation. However, these results were consistent with the data obtained by Kara Stowers with the substituted benzyl pyridines 43a-43f. She obtained a Hammett ρ value of 1.40 when examining the initial rate constants of substituted benzyl pyridine derivatives. This implies that, in contrast to the competition
studies, electron deficient directing groups accelerate the rate of the reaction in individual experiments.

Table 4.5: Initial Rate Constants for Substrates 11, 13, 15-19, and 21 in AcOH/Ac₂O and Benzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$k_{obs}$ (x10⁻¹)</th>
<th>Entry</th>
<th>Substrate</th>
<th>$k_{obs}$ (x10⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AcOH/Ac₂O&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Benzen&lt;b&gt;</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>6.4</td>
<td>5.0</td>
<td>5</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td>2.2</td>
<td>1.0</td>
<td>6</td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td>2.2</td>
<td>0.5</td>
<td>7</td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td>2.0</td>
<td>0.6</td>
<td>8</td>
<td><img src="image8" alt="Image" /></td>
</tr>
</tbody>
</table>

Conditions a: 1 mol % Pd(OAc)₂, 1.02 equiv PhI(OAc)₂, (1:1) 0.12M AcOH/Ac₂O at 80 °C
Conditions b: 5 mol % Pd(OAc)₂, 1.02 equiv PhI(OAc)₂, 0.12M Benzene at 80 °C

4.5 Kinetic Isotope Effect Studies

We next desired to determine the kinetic isotope effect (KIE) in the individual reactions and competition experiments. In order to elucidate the KIE in the individual reactions, the value of $k_{obs}$ with substrate 46 was compared to that of its deuterated analogue 45 in both AcOH/Ac₂O and benzene (Scheme 4.8). From the initial rates, $k_H/k_D$ was calculated to be 3.54 in AcOH/Ac₂O and 1.86 in benzene.
Scheme 4.8: Kinetic Isotope Effect in Individual Rate Studies

\[
\begin{align*}
\text{Scheme 4.8: Kinetic Isotope Effect in Individual Rate Studies} \\
\text{CF}_3 & \quad \text{CF}_3 \\
\text{(45)} & \quad \text{(46)} \\
\frac{k_{H}}{k_{D}} = 1.66 \text{ in C}_6\text{H}_6 & \quad \frac{k_{H}}{k_{D}} = 3.54 \text{ in AcOH/AC}_2\text{O} \\
k_{\text{obs}} = 1.0 \times 10^{-2} \text{ in C}_6\text{H}_6 & \quad k_{\text{obs}} = 0.97 \times 10^{-2} \text{ in AcOH/AC}_2\text{O} \\
k_{\text{obs}} = 3.3 \times 10^{-2} \text{ in AcOH/AC}_2\text{O} & \\
\end{align*}
\]

We next determined the KIE in the competition experiments. The ratio of products at completion was determined when benzylpyridine 47 was subjected to the reaction conditions in the presence of either 46 or its deuterated analogue 45 (Scheme 4.9). The isotope effects obtained from this experiment were 2.32 and 1.65 in AcOH/AC_2O and benzene, respectively.

Scheme 4.9: Kinetic Isotope Effect in Competition Studies

\[
\begin{align*}
\text{Scheme 4.9: Kinetic Isotope Effect in Competition Studies} \\
\text{CF}_3 & \quad \text{CF}_3 \\
\text{(46)} & \quad \text{(47)} \\
1 \text{ mol \% Pd(OAc)}_2 & \quad 1.02 \text{ equiv PhI(OAc)}_2 \\
\text{AcOH/AC}_2\text{O or C}_6\text{H}_6, \quad 80^\circ\text{C} & \quad \text{(48)} & \quad \text{(49)} \\
\frac{k_{H}}{k_{D}} = 1.66 \text{ in C}_6\text{H}_6 & \quad \frac{k_{H}}{k_{D}} = 3.54 \text{ in AcOH/AC}_2\text{O} \\
\text{CF}_3 & \quad \text{CF}_3 \\
\text{(45)} & \quad \text{(47)} \\
1 \text{ mol \% Pd(OAc)}_2 & \quad 1.02 \text{ equiv PhI(OAc)}_2 \\
\text{AcOH/AC}_2\text{O or C}_6\text{H}_6, \quad 80^\circ\text{C} & \quad \text{(50)} & \quad \text{(51)} \\
\frac{k_{H}}{k_{D}} = 1.66 \text{ in C}_6\text{H}_6 & \quad \frac{k_{H}}{k_{D}} = 2.32 \text{ in AcOH/AC}_2\text{O} \\
\end{align*}
\]

4.6 Order of PhI(OAc)_2

In order to gain insight into the relative position of the turnover limiting step in the catalytic cycle, we next investigated the order of the reaction in PhI(OAc)_2 in both the competition studies and the individual reactions. Under our optimal conditions for
acetoxylation with the benzylpyridine substrate 18 (Scheme 4.10), the reaction was found to be zero order in PhI(OAc)$_2$ in both AcOH/Ac$_2$O and benzene (Figure 4.8 and 4.9).

**Scheme 4.10:** Reaction Studied for Determining the Order in PhI(OAc)$_2$

![Scheme 4.10](image)

**Figure 4.8.** Initial Rate Constant as a Function of Oxidant Concentration in AcOH/Ac$_2$O

![Figure 4.8](image)

**Figure 4.9.** Initial Rate Constant as a Function of Oxidant Concentration in Benzene

![Figure 4.9](image)

Next, the order of the reaction in PhI(OAc)$_2$ was obtained under the competition conditions. Similar to the experiment above, the order of PhI(OAc)$_2$ in the competition study between 52 and 18 (Scheme 4.11) was also determined to be zero (Figure 4.10 and 4.11). Both the order studies were done in collaboration with Kara Stowers.
**Scheme 4.11: Reaction Studied for Determining the Order in PhI(OAc)$_2$ (Competition)**

![Scheme 4.11](image)

**Figure 4.10. Initial Rate Constant of 18 in Presence of 52 as a Function of Oxidant Concentration in AcOH/Ac$_2$O**

![Figure 4.10](image)

**Figure 4.11. Initial Rate Constant of 18 in Presence of 52 as a Function of Oxidant Concentration in Benzene**

![Figure 4.11](image)

### 4.7 Discussion

With all these results in hand we sought to address the key mechanistic steps dictating the efficiency of a directing group in palladium-catalyzed ligand directed C–H activation/acetoxylation reactions both in the presence and absence of multiple chelating
functionalities. The proposed mechanism for these acetoxylation reactions, (Figure 4.12) is believed to involve the following steps: (i) ligand coordination to palladium, (ii) C–H activation to form palladacycle B, (iii) oxidation of B by PhI(OAc)$_2$ to afford the Pd$^{IV}$ intermediate C, (iv) C–O bond forming reductive elimination from C to afford complex D, and (v) finally ligand exchange whereby a new substrate molecule displaces the product from the metal. The mechanistic features/requirements for each of the fundamental steps of this catalytic cycle are discussed in detail below.

**Figure 4.12. Proposed Catalytic Cycle for Pd-Catalyzed C–H Bond Acetoxylation**

*Ligand Binding (step i):* The equilibrium constant for ligand binding to Pd$^{II}$ centers is known to be highly dependent on the electronic nature of the coordinating group. For example, Craig has studied $K_{eq}$ for the coordination of substituted pyridines to Pd$^{II}$ pincer complexes (Scheme 4.12).$^{16}$ The log of $K_{eq}$ obtained for binding of differentially substituted pyridines was plotted against the sigma values. These studies demonstrated that the Hammett $\rho$ value for this equilibrium is -1.90 in DMSO. The negative $\rho$ value indicates that, in general, electron rich ligands form stronger bonds to palladium.
Scheme 4.12: Coordination Studies of Substituted Pyridines with Bimetallic Palladium Complexes

\[
\begin{align*}
\text{Et}_2\text{N-Pd-NEt}_2 & \quad \text{Et}_2\text{N-Pd-NEt}_2 \quad \text{Et}_2\text{N-Pd-NEt}_2 \\
\text{DMSO} & \quad \text{DMSO} \\
\text{(54)} & \quad \text{(55)}
\end{align*}
\]

C–H activation (step ii): Ryabov reported the earliest studies on the mechanism of electrophilic arene C–H activation by palladium. His group investigated the kinetics of stoichiometric cyclopalladation of meta- and para-substituted dimethylbenzylamine derivatives with Pd(OAc)$_2$ (Scheme 4.13).\textsuperscript{17} A Hammett $\rho$ value of $-1.6$ and a kinetic isotope effect of 2.02 were obtained for the reaction in CHCl$_3$. Based on this negative $\rho$ value, the authors proposed that cyclopalladation proceeded by a Wheland intermediate that transfers a proton to an acetate ligand on the metal via a highly ordered six-membered transition state (Figure 4.13).

Scheme 4.13: Hammett Studies for Cyclopalladation of Substituted 3° Benzylamines

More recently, computational studies by Macgregor and co-workers provided further insights into the transition state for directed C–H activation at Pd$^{II}$.\textsuperscript{18} They obtained theoretical values of 13 kcal/mol for the activation barrier and 1.2 for the kinetic isotope effect. Based on this data, along with calculations of the transition state, they proposed that the C–H activation reaction proceeds via an agostic C–H complex, rather than a Wheland intermediate (Figure 4.13). This would account for the relatively small
magnitude of $\rho$ observed experimentally. For comparison, $\rho$ for a typical electrophilic aromatic substitution reaction ranges from $-6$ to $-12$.$^{19}$ The agostic complexation is followed by an intramolecular hydrogen transfer via a six-membered transition state to a coordinated acetate. The authors propose that formation of the agostic complex is rate determining in this system; therefore, the small KIE is due to $\text{C-H}$ bond elongation, as opposed to cleavage, in the transition state. Importantly, a similar mechanism has also been proposed by Fagnou$^{20}$ and by Echavarren$^{21}$ for other arene activation reactions at $\text{Pd}^{\text{II}}$.

Figure 4.13: Proposed Transition States for Cyclopalladation

Based on the aforementioned computational and theoretical studies, it is now generally accepted that palladium mediated $\text{C-H}$ activation proceeds via interaction of electrophilic $\text{Pd}$ center with nucleophilic $\text{C-H}$ bond. Hence, more electron deficient directing groups are expected to accelerate the $\text{C-H}$ activation step. For example, Funahashi and co-workers have shown that the cyclopalladation of $N$-benzyltriamines is accelerated when the amine nitrogen bears less electron donating substituents.$^{22}$ As shown in Scheme 4.14, the rate of cyclopalladation to form complex 59 increased significantly when $R$ was changed from $\text{H}$ to $\text{Ph}$ in complex 58.

Scheme 4.14: Directing Group Electronic Effects in the Cyclopalladation of $N$-Benzyl Triamines
Oxidation (step iii): Literature precedent suggests that more electron donating ligands on palladium will increase the rate of oxidation of Pd\textsuperscript{II} complex A to Pd\textsuperscript{IV} complex B by making the palladium more nucleophilic. For example, van Koten and co-workers have reported that the reactivity of cyclometalated N,N-dimethylbenzylamine complexes towards t-butylhydroperoxide (TBHP) increases as the electron density at the metal center increases.\textsuperscript{23} Cationic complex 60 did not react with TBHP, whilst the more electron rich complex 61 reacted to form 62 in 80% yield (Scheme 4.15). These reactions were proposed to proceed via rate-limiting oxidation of Pd\textsuperscript{II} to a Pd\textsuperscript{IV}-oxo species.

Scheme 4.15: TBHP Oxidation of N,N-Dimethylbenzylamine Complexes

Reductive elimination (step iv): Reports in literature suggest that electron withdrawing ligands accelerate C-O bond forming reductive elimination from Pd\textsuperscript{II}.\textsuperscript{24} Based on these reports and the principal of microscopic reversibility with the oxidation step, we propose that reductive elimination from Pd\textsuperscript{IV} will be similarly accelerated by electron deficient ancillary ligands.

Having this information about the expected trends for the different steps in the proposed catalytic cycle, we next sought to speculate on the factors controlling the dominance of a directing group based on our experimental results.

Individual Rate Studies. The kinetic studies of substrates in separate reaction vessels showed that, in general, substrates bearing electron deficient or less basic ligands react faster in the chelate-directed acetoxylation reaction. This is supported by the
positive ρ value (1.4) of the Hammett plot obtained for the acetoxylation of electronically differentiated benzylpyridine derivatives. This is further corroborated by the fact that the pyridine substrate (which bears the most basic chelating group) did not exhibit the fastest initial rate.

As described above, we would expect that both the C–H activation step and the reductive elimination step of the catalytic cycle to be accelerated by electron deficient directing groups. Hence, electronic effects alone cannot distinguish between either one of these steps being turnover limiting. However, the observed kinetic isotope effects of 1.86 and 3.45 in benzene and AcOH/Ac₂O, respectively, suggests a significant contribution of C–H bond breaking to the transition state of this reaction. Importantly, these KIE values are similar to those observed by Ryabov (2.02) and Daugulis (4.4)²⁵ for related stoichiometric and catalytic reactions, respectively. It is also important to note that literature reports have shown that Pd⁴⁺ intermediates analogous to those proposed in our reaction are highly unstable, suggesting that rate-limiting reductive elimination is highly unlikely. In all, this data suggests that C–H activation is the step controlling the rate of these individual reactions.

However, we note that in contrast to the results with the benzylpyridine derivatives, the individual rate studies with substrates 11, 13, 15 and 16 did not show a linear correlation between k_obs and the basicity of the directing group. For example, oxime 11 (pKₐ ~ −2.90)²⁶ reacted at a similar rate to pyrazole 17 (pKₐ ~ 2.18)²⁷ in benzene, despite a difference of 5 pKₐ units between the two functional groups. This lack of direct correlation likely has both steric and electronic origins. First, unlike benzylpyridines 43a-43f, which provide essentially sterically identical coordination environments at the Pd center, compounds 11, 13, 15-19 and 21 differ substantially in terms of both their steric parameters and their conformational flexibility. Literature reports have shown that even relatively subtle steric effects can have a significant influence on the relative and absolute rates of cyclopalladation reactions.²⁸ In addition, the pKₐ of the directing group is not an ideal parameter for predicting the subtle electronic influence of these ancillary ligands on the C–H activation reaction, as it does not take into account the interplay of σ-donor and π-acceptor/donor properties of these directing groups.


*Competition Studies.* The competition studies show that when multiple potential chelating functionalities are present in solution, more electron rich/more basic directing groups react at faster relative rates. This can be concluded based on three key results: *(i)* the large negative \( \rho \) value from Hammett plots with substituted benzylpyridine derivatives, *(ii)* the observation that the most basic directing group (pyridine in substrate 18) out-competes all of the other directing groups among substrates 11, 13, 15-19 and 21 (Figure 4.5) and *(iii)* the fact that heterocyclic ligands with \( pK_a \) values greater than zero (pyridine, pyrimidine, pyrazine, pyrazole) outcompete all substrates with \( pK_a \) values less than zero (oxime ethers, amides and isoxazolines). Based on the considerations above, this suggests that either ligand binding/exchange (steps i and v) or oxidation (step iii) controls the relative reactivity of the two substrates under these conditions. We were able to rule out the latter based the study of the order of the reaction in PhI(OAc)\(_2\). Under our optimal conditions for acetoxylation with substrate 18, the reaction was found to be zero order in PhI(OAc)\(_2\), both in the presence and absence of another substrate (52), (Figures 4.8-4.11).

This result led us to propose that selectivity under these competition conditions is dictated by \( K_{eq} \) for binding of the two substrates to Pd. More specifically, we propose that the relative concentrations of the two coordination complexes (A and A’ in Scheme 4.16) dictate the observed relative rates of reaction, and that this equilibrium favors binding of more electron rich directing group. Literature studies of \( K_{eq} \) for coordination of substituted pyridines to Pd, discussed above, show Hammett \( \rho \) values ranging from \(-1.7\) to \(-2.1\) in DMSO. These are similar to our results in benzene, where \( \rho = -2.01 \).

**Scheme 4.16.** Equilibrium for Substrate Binding Under Competition Conditions

Although ligand binding is the influential step when multiple ligands are present, C-H activation is still rate-limiting. This is supported by the significant KIE observed in
solvent systems, benzene and AcOH/Ac$_2$O. Relative binding abilities of the competing ligands in the reaction mixture will influence the concentration of the palladium bound substrate, complex A (Figure 4.12). The concentration of A will in turn affect the rate of C-H activation. Since substrates bearing electron rich ligands will bind to the metal preferentially over electron deficient ligands, increasing the concentration of coordinated complex A, they will exhibit a faster relative rate of reaction.

The observed effects in the competition studies have important implications for future applications of this chemistry. First, the solvent can clearly have a significant influence on the selectivity of functionalization in the presence of multiple directing groups. Trends for competition studies and rate of reactions were different depending on whether the reaction was carried out in a non-acidic solvent such as benzene or an acidic solvent such as acetic acid. This suggests that solvent selection could be used to obtain, alter, or improve selectivity. Second, these studies can be used to predict relative reactivity, even with substrates like 63 (illustrated later in section 4.8) that do not contain a methylene spacer between the directing group and the arene ring. Future studies will continue to explore how these effects (and the effects of other solvents and additives) translate into predicting and controlling the dominant directing group in other more complex systems.

4.8 Application

Having explored the factors controlling the dominant directing group in the presence of several chelating functionalities, our efforts focused towards applying the insights gained from our study towards selective palladium-catalyzed ligand mediated acetoxylation adjacent to one ligand in a substrate bearing multiple directing groups. In order to do this, substrate 63 containing an amide and a methyl oxime ether was synthesized. Based on the competition studies between substrates 11 and 15, we expected the oxime ether to outcompete the amide, resulting in products of acetoxylation ortho to the oxime ether. We were pleased to find that, consistent with our hypothesis, the reaction of substrate 63 in the presence of 3 mol % Pd(OAc)$_2$ and 2.0 equiv PhI(OAc)$_2$ in AcOH/Ac$_2$O afforded the di-acetoxylated product 64 in 72% isolated yield (Scheme
4.17). Importantly, none of the product derived from acetoxylation of the C–H bond *ortho* to the amide directing group was observed. The acetoxylated product 64 was further elaborated to diverse compounds 65, 66 and 67 employing Pd-catalyzed chelate-directed, chlorination,29 phenylation,3 and acetoxylation methodologies, respectively (Scheme 4.18).

**Scheme 4.17.** Highly Selective Oxime Ether-Directed C–H Acetoxylation of Substrate 63

\[
\text{O} \quad \begin{array}{c}
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{OAc} \\
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\end{array} \\
\]

3 mol % Pd(OAc)\(_2\) 2.0 equiv PhI(OAc)\(_2\) 100 °C, 72%

**Scheme 4.18.** Amide Directed C–H Functionalization of Product 64

\[
\text{O} \quad \begin{array}{c}
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{OAc} \\
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\end{array} \\
\]

5 mol % Pd(OAc)\(_2\) 2.0 equiv PhI(OAc)\(_2\) 100 °C, 59%

\[
\text{O} \quad \begin{array}{c}
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{OAc} \\
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\end{array} \\
\]

5 mol % Pd(OAc)\(_2\) 2.0 equiv NCS 100 °C, 81%

\[
\text{O} \quad \begin{array}{c}
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\text{H} \\
\end{array} \quad \begin{array}{c}
\text{OAc} \\
\text{N-OMe} \\
\text{H} \\
\text{H} \\
\end{array} \\
\]

5 mol % Pd(OAc)\(_2\) 2.0 equiv (mCF\(_3\)Ar)\(_2\)BF\(_4\) 1.5 equiv NaHCO\(_3\), Toluene 100 °C, 78%

The results in Scheme 4.18 show that even though the oxime ether is dominant, if the *ortho* sites are blocked then the amide can direct functionalization. Hence, we next wondered if we could employ a similar strategy towards functionalizing the C–H bond adjacent to the oxime ether in a substrate like 68, which contains both a pyridine and an oxime ether, by blocking the sites *ortho* to the pyridine moiety. Subjection of substrate 68 to standard reaction conditions with 2.0 equivalents of PhI(OAc)\(_2\) afforded the
diactoxylated product 69 in 79% (Scheme 4.19). However, disappointingly, subjection of 69 to catalytic Pd and PhI(OAc)$_2$ did not afford an appreciable amount of acetoxylated product 70. This may be due to the fact that the C–H bonds at the site ortho to the oxime ether are very sterically hindered.

**Scheme 4.19: Intramolecular Competition Between a Pyridine and an Oxime Ether**

Next, substrate 71 was synthesized bearing an oxime ether directing group with the ability to direct C–H activation at two different aryl rings (Scheme 4.20). Based on the competition studies conducted with substrates 11 and 13 in benzene and AcOH/Ac$_2$O, we predicted a greater selectivity in benzene than AcOH. Excitingly, subjection of substrate 71 under the optimized conditions of 5 mol % Pd(OAc)$_2$, 1.02 equiv PhI(OAc)$_2$ in benzene/Ac$_2$O afforded a single acetoxylated product 72. In contrast, subjection of the same molecule in AcOH/Ac$_2$O afforded a 1:1 ratio of products 72 and 73 (Scheme 4.20).

**Scheme 4.20: Controlling Direction of C-H Activation/Functionalization**
4.9 Conclusions

In summary, we have conducted detailed studies on elucidating the electronic requirements of a directing group in Pd-catalyzed directed C–H functionalization reactions. Through mechanistic studies we have determined that the rate-limiting step is C–H activation. However, when multiple ligands are present, the equilibrium of ligand coordination appears to control the relative rate of reaction. Interestingly, there is not a direct correlation between the intrinsic rate and the dominance of a directing group. These important findings allow for the further development of selective and effective transformations.

4.10 Experimental Procedure

**General Procedures:** NMR spectra were obtained on a Varian Inova 400 (399.96 MHz for $^1$H; 100.57 MHz for $^{13}$C; 376.34 MHz for $^{19}$F) unless otherwise noted. $^1$H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer spectrum BX FT-IR spectrometer.

**Materials and Methods:** Pd(OAc)$_2$ was obtained from Pressure Chemical and used as received, and PhI(OAc)$_2$ was obtained from Merck Research Laboratories and used as received. Solvents were obtained from Fisher Chemical and used without further purification unless otherwise noted. THF was purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. HRMS data were obtained on a Micromass AutoSpec Ultima Magnetic
Sector mass spectrometer. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95 % dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 μm df) column.

**Synthesis of Substrates 18, 19, 21, 45-47 and 52**

Substrates 18, 19, 21, 45-47 and 52 were prepared via Pd-catalyzed Negishi coupling of (3-methylbenzyl)zinc(II) bromide with the corresponding halopyridine derivative using a modification of a literature procedure. 30

**Synthesis of Zn reagent:** A three-necked flask was charged with purified zinc dust (1.2 equiv) and anhydrous THF. The mixture was heated to reflux, and 1,2-dibromoethane (0.04 equiv) was added. After heating at reflux for 15 min, the reaction was cooled to room temperature and TMSCl (0.05 equiv) was added. The resulting mixture was stirred at room temperature for 30 min, and then a solution of m-bromoxylenes (1 equiv) in anhydrous THF was added dropwise over a period of 2 h.

**Negishi coupling.** In a Schlenk flask, Pd(OAc)2 (0.05 equiv) and P(o-tolyl)3 (0.1 equiv) were dissolved in anhydrous THF, and this mixture was stirred for 10 min. The halopyridine (1.0 equiv) was then added, and the resulting mixture was cooled to 0 °C. The aryl zinc reagent (2.0 equiv) was added dropwise to this solution over the course of 15 min, and the reaction was allowed to warm to room temperature and stirred overnight. Importantly, 18, 19, 21, 45-47 and 52 were purified by distillation to remove all residual palladium.

![Substrate 18](image)

Substrate 18 was obtained as a clear oil (Rf = 0.28 in 70% hexanes/30% ethyl acetate). 1H NMR (CDCl3): δ 8.56 (dd, J = 4.4, 1.2 Hz, 1H), 7.56 (dt, J = 7.6 Hz, 2.0 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.13-7.03 (multiple peaks, 5H), 4.13 (s, 2H), 2.33 (s, 3H). 13C{1H} NMR (CDCl3): δ 161.02, 149.23, 139.30, 138.06, 136.40, 129.78, 128.34, 127.03, 126.02, 122.99, 121.08, 44.59, 21.30. HRMS electrospray (m/z): [M-H]⁺ calcd for C13H13N, 182.0970; found, 182.0970.
Substrate 21 was obtained as a pale yellow oil (R_f = 0.28 in 70% hexanes/30% ethyl acetate). $^1$H NMR (CDCl$_3$): δ 8.66 (d, $J = 4.8$ Hz, 1H), 7.21-7.15 (multiple peaks, 3H), 7.08 (t, $J = 4.8$ Hz, 1H), 7.02 (d, $J = 6.8$ Hz, 1H), 4.26 (s, 2H), 2.31 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 170.02, 157.17, 138.00, 129.76, 128.32, 127.26, 126.02, 118.48, 45.92, 21.28. HRMS (ESI, m/z): [M-H]$^+$ calcld for C$_{12}$H$_{13}$N$_2$, 183.0922; found, 183.0920.

Substrate 19 was obtained as a clear oil (R_f = 0.28 in 75% hexanes/25% ethyl acetate). $^1$H NMR (CDCl$_3$): δ 8.50- 8.47 (multiple peaks, 2H), 8.40 (d, $J = 2.8$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.08-7.04 (multiple peaks, 3H), 4.13 (s, 2H), 2.32 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 156.53, 144.70, 144.00, 142.24, 138.34, 137.93, 129.67, 128.57, 127.44, 125.94, 41.84, 21.28. HRMS (ESI, m/z): [M-H]$^+$ calcld for C$_{12}$H$_{12}$N$_2$, 183.0922; found, 183.0920.

Substrate 52 was obtained as a colorless oil (R_f = 0.26 in 90% hexanes/10% ethyl acetate). $^1$H NMR (CDCl$_3$): δ 8.74 (d, $J = 4.4$ Hz, 1H), 7.36-7.34 (multiple peaks, 2H), 7.23 (t, $J = 1.9$ Hz, 1H), 7.11-7.07 (multiple peaks, 3H), 4.21 (s, 2H), 2.35 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): δ 162.68, 150.29, 138.71 (q, $^2$J$_{CF} = 33.7$ Hz), 138.40, 138.28, 129.80, 128.63, 127.50, 126.04, 122.80 (q, $^1$J$_{CF} = 271$ Hz), 118.56 (q, $^3$J$_{CF} = 3.6$ Hz), 116.84 (q, $^3$J$_{CF} = 2.9$ Hz), 44.58, 21.32. $^{19}$F{$^1$H} NMR (CDCl$_3$): δ –64.78. HRMS (ESI, m/z): [M-H]$^+$ Calcd for C$_{14}$H$_{12}$F$_3$N, 250.0843; Found, 250.0842.
**Synthesis of Substrates 11, 13, 15-16**

Substrate 16 was prepared from 2-m-tolylacetaldehyde according to a literature procedure. Substrate 16 was obtained as a yellow oil (R_f = 0.28 in 70% hexanes/30% ethyl acetate). ¹H NMR (CDCl₃): δ 7.21 (t, J = 7.4 Hz, 1H), 7.09-7.01 (multiple peaks, 3H), 4.76 (m, 1H), 4.08 (qd, J = 12.0, 4.8 Hz, 2H), 3.64 (q, J = 14.8 Hz, 2H), 2.93 (dd, J = 17.2, 11.2 Hz, 1H), 2.60 (dd, J = 17.2, 6.8 Hz, 1H), 2.33 (s, 3H), 2.02 (s, 3H). ¹³C{¹H} NMR (CDCl₃): δ 170.77, 157.56, 138.57, 135.36, 129.49, 128.72, 127.91, 125.72, 77.36, 65.04, 38.56, 33.85, 21.32, 20.07. IR (thin film): 1742 (br) cm⁻¹. HRMS (ESI, m/z): [M]⁺ calcd for C₁₄H₁₇NO₃, 247.1208; found, 247.1201.

Substrate 17 was prepared from pyrazole and α-bromoxylene according to a literature procedure. Substrate 17 was obtained as a red oil (R_f = 0.24 in 90% hexanes/10% ethyl acetate). ¹H NMR (CDCl₃): δ 7.56 (d, J = 1.6 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.04-7.01 (multiple peaks, 2H), 6.28 (t, J = 2.0 Hz, 1H), 5.28 (s, 2H), 2.33 (s, 3H). ¹³C{¹H} NMR (CDCl₃): δ 139.41, 138.45, 136.47, 129.11, 128.69, 128.62, 128.34, 124.67, 105.82, 55.85, 21.31. HRMS (ESI, m/z): [M-H]⁺ calcd for C₁₁H₁₂N₂, 171.0922; found, 171.0925.

Substrate 11 was prepared from 3-methylphenylacetone and methoxylamine hydrochloride according to a literature procedure. Substrate 11 was obtained as a clear oil as a 1 : 0.4 mixture of oxime isomers. Major oxime isomer: ¹H NMR (CDCl₃): δ 7.20 (m, 1H), 7.07-6.99 (multiple peaks, 3H), 3.91 (s, 3H), 3.44 (s, 2H), 2.35 (s, 3H), 1.75 (s, 3H). ¹³C{¹H} NMR (CDCl₃): δ 156.62, 138.16, 136.78, 129.73, 128.39, 127.44, 126.04,
HRMS (ESI, m/z): [M]^+ calcd for C_{11}H_{15}NO_3, 177.1153; found, 177.1156.

Substrate 12 was prepared from 2-heptanone, hydroxylamine hydrochloride, and α-bromoxylenes according to a literature procedure.\textsuperscript{34} Substrate 12 was obtained as a clear oil as a 1 : 0.9 mixture of oxime isomers (R_f = 0.26 in 97% hexanes/3% ethyl acetate). Major oxime isomer: \textsuperscript{1}H NMR (CDCl_3): δ 7.27 (t, J = 7.6 Hz, 1H), 7.20-7.17 (multiple peaks, 2H), 7.12 (d, J = 7.2 Hz, 1H), 5.07 (s, 2H), 2.40-2.38 (s, 3H), 2.19 (dd, J = 8.0, 7.6 Hz, 2H), 1.89 (s, 3H), 1.56-1.48 (multiple peaks, 2H), 1.37-1.27 (multiple peaks, 4H), 0.91 (m, 3H). \textsuperscript{13}C{\textsuperscript{1}H} NMR (CDCl_3): δ 158.92, 138.18, 137.77, 128.61, 128.25, 128.12, 124.83, 75.15, 35.75, 31.30, 26.15, 22.38, 21.36, 14.07, 13.92. HRMS (ESI, m/z): [M]^+ calcd for C_{15}H_{23}NO, 233.1780; found, 233.1777.

Substrate 13 was prepared from m-tolylacetic acid and dimethylamine according to a literature procedure. The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR data for 13 were identical to those reported in the literature.\textsuperscript{35}

This compound was prepared via the Cu-catalyzed reaction of pyrrolidinone with 1-(4'-bromobiphenyl-4-yl) ethanone according to a literature procedure.\textsuperscript{36} The product was obtained as a yellow solid. \textsuperscript{1}H NMR (CDCl_3): δ 8.02 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.69-7.63 (multiple peaks, 4H), 3.92 (t, J = 6.8 Hz, 2H), 2.67-2.63 (multiple peaks, 5H), 2.20 (quin, J = 7.6 Hz, 2H). \textsuperscript{13}C{\textsuperscript{1}H} NMR (CDCl_3): δ 197.70, 174.37, 144.97, 139.52, 135.64, 135.60, 128.95, 127.58, 126.84, 120.07, 48.65, 32.76, 26.66,
17.97. IR (thin film): 1694, 1682 cm\(^{-1}\). HRMS (ESI, m/z): [M]\(^+\) calcd for C\(_{18}\)H\(_{17}\)NO\(_2\), 279.1259; found, 279.1264.

Substrate 63 was prepared from the corresponding ketone (above) and methoxylamine hydrochloride according to a literature procedure.\(^{33}\) Substrate 63 was obtained as a yellow solid. \(^1\)H NMR (CDCl\(_3\)): \(\delta 7.73-7.69\) (multiple peaks, 4H), 7.63-7.57 (multiple peaks, 4H), 4.02 (s, 3H), 3.90 (t, \(J = 6.8\) Hz, 2H), 2.64 (t, \(J = 8.0\) Hz, 2H), 2.24 (s, 3H), 2.19 (m, 2H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)): \(\delta 174.25, 154.21, 140.94, 138.86, 136.37, 135.33, 127.27, 126.73, 126.41, 120.09, 61.93, 48.68, 32.72, 17.97, 12.51. IR (thin film): 1685 cm\(^{-1}\). HRMS (ESI, m/z): [M]\(^+\) calcd for C\(_{19}\)H\(_{20}\)N\(_2\)O\(_2\), 308.1525; found, 308.1518.

**General Procedure for Directed C-H Bond Acetoxylation:** In a 20 mL vial, PhI(OAc)\(_2\) (0.49-0.86 mmol, 1.02-1.80 equiv) and Pd(OAc)\(_2\) (1.08 mg, 0.0048 mmol, 0.01 equiv) were combined in a mixture of AcOH (2.0 mL) and Ac\(_2\)O (2.0 mL). Substrate (0.48 mmol, 1.0 equiv) was added, the vial was sealed with a Teflon-lined cap, and the resulting solution was heated at 100 °C for 3-24 h. The reaction was cooled to room temperature, and the solvent was removed under vacuum. The resulting brown oil was purified by chromatography on silica gel. Each substrate was optimized for reaction time and equiv of the oxidant, as indicated below.

The reaction was run for 6 h with 1.02 equiv of PhI(OAc)\(_2\). The product 26 was obtained as a yellow oil (86.9 mg, 75% yield, \(R_f = 0.27\) in 70% hexanes/30% ethyl acetate). \(^1\)H NMR (CDCl\(_3\)): \(\delta 8.52\) (dd, \(J = 4.8, 1.6\) Hz, 1H), 7.54 (dt, \(J = 7.6, 1.6\) Hz, 1H), 7.11-7.02 (multiple peaks, 3H), 6.94 (d, \(J = 8.0\) Hz, 1H), 4.06 (s, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.58 (m, 1H), 0.88 (d, \(J = 7.0\) Hz, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)): \(\delta 169.37, 159.88, 149.03, 146.79, 136.44, 135.78, 131.72, 130.83, 128.38, 122.85, 122.24, 121.24, 39.21, 20.78,
20.69. IR (thin film): 1759 cm$^{-1}$. HRMS (ESI, m/z): [M+H]$^+$ calcd for C$_{15}$H$_{15}$NO$_2$, 242.1181; found, 242.1177.

The reaction was run for 3 h with 1.02 equiv of PhI(OAc)$_2$. The product 23 was obtained as a yellow oil (104.7 mg, 90% yield, R$_f$ = 0.28 in 55% hexanes/45% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 8.62 (d, $J = 1.6$ Hz, 2H), 7.20 (s, 1H), 7.08-7.04 (multiple peaks, 2H), 6.92 (d, $J = 8.4$ Hz, 1H), 4.19 (s, 2H), 2.31 (s, 3H), 2.18 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 169.28, 169.14, 157.01, 146.73, 135.60, 131.84, 129.86, 128.47, 122.12, 118.51, 40.88, 20.72. IR (thin film): 1757 cm$^{-1}$. HRMS (ESI, m/z): [M+H]$^+$ calcd for C$_{14}$H$_{14}$N$_2$O$_2$, 243.1134; found, 243.1135.

The reaction was run for 6 h with 1.1 equiv of PhI(OAc)$_2$. The product 24 was obtained as a yellow oil (96.5 mg, 69% yield, R$_f$ = 0.28 in 70% hexanes/30% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.09 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.06 (s, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 4.71 (m, 1H), 4.10-4.01 (multiple peaks, 2H), 3.56 (s, 2H), 2.84 (dd, $J = 17.2$, 10.8 Hz, 1H), 2.51 (dd, $J = 17.2$, 7.6 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.02 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 170.61, 169.14, 156.63, 146.98, 136.14, 131.18, 129.21, 127.10, 122.57, 77.48, 64.86, 38.38, 29.01, 20.69, 20.57. IR (thin film): 1746 (br) cm$^{-1}$. HRMS (ESI, m/z): [M+Na]$^+$ calcd for C$_{16}$H$_{19}$NO$_5$, 328.1161; found, 328.1150.

The reaction was run for 10 h with 1.02 equiv of PhI(OAc)$_2$. The product 25 was obtained as a yellow oil (97.3 mg, 88% yield, R$_f$ = 0.28 in 75% hexanes/25% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.53 (d, $J = 1.6$ Hz, 1H), 7.32 (d, $J = 2.4$ Hz, 1H), 7.14 (dd, $J = 8.4$, 1.6 Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 1.6$ Hz, 1H), 6.26 (t, $J = 2.0$ Hz, 1H), 5.23 (s, 2H), 2.30 (s, 3H), 2.26 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 169.07,
The reaction was run for 4.5 h with 1.1 equiv of PhI(OAc)₂. The product 30 was obtained as a yellow oil as a 1 : 0.42 mixture of oxime isomers (89.2 mg, 79% yield, R_f = 0.28 in 89% hexanes/11% ethyl acetate). Major oxime isomer: ^1^H NMR (CDCl₃): δ 7.06 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.57 (s, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 1.71 (s, 3H). ^1^C{^1^H} NMR (CDCl₃): δ 169.45, 155.09, 146.92, 135.95, 131.52, 128.53, 128.42, 122.12, 61.21, 29.85, 20.86, 20.73, 19.37. IR (thin film): 1763 cm⁻¹. HRMS (ESI, m/z): [M+Na]^+ calcd for C₁₃H₁₄N₂O₂, 253.0953; found, 253.0953.

Minor oxime isomer: ^1^H NMR (CDCl₃): δ 7.08-7.05 (multiple peaks, 2H), 6.92 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.37 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 1.70 (s, 3H). ^1^C{^1^H} NMR (CDCl₃): δ 169.60, 155.70, 147.18, 135.90, 131.52, 128.74, 128.47, 121.97, 70.47, 35.63, 31.23, 26.05, 22.29, 20.90, 20.83, 13.85. IR (thin film): 1763 cm⁻¹. HRMS (ESI, m/z): [M+Na]^+ calcd for C₁₃H₁₇NO₃, 314.1732; found, 314.1729. Minor oxime isomer: ^1^H NMR (CDCl₃): δ 7.23 (d, J = 1.6 Hz, 1H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 4.99 (s, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 2.14 (t, J = 7.6 Hz, 2H), 1.83 (s, 3H), 1.48 (m, 2H), 1.34-1.24 (multiple peaks, 4H), 0.88 (t, J = 7.2 Hz, 3H). ^1^C{^1^H} NMR (CDCl₃): δ 169.33, 158.35, 146.63, 135.40, 130.40, 129.70, 129.24, 121.97, 70.47, 35.63, 31.23, 26.05, 22.29, 20.80, 20.73, 13.85. IR (thin film): 1757 cm⁻¹. HRMS (ESI, m/z): [M+Na]^+ calcd for C₁₇H₂₅NO₃, 314.1732; found, 314.1729.
The reaction was run for 24 h with 1.8 equiv of Phl(OAc)$_2$. The product 32 was obtained as a yellow oil (86.1 mg, 74% yield, $R_f = 0.28$ in 60% hexanes/40% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 8.38 (s, 2H), 8.30 (s, 1H), 7.05 (s, 1H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 9.5$, 8.0 Hz, 1H), 3.99 (s, 2H), 2.23 (s, 3H), 2.13 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 168.79, 155.19, 146.43, 144.30, 143.59, 142.01, 135.54, 131.24, 129.44, 128.42, 122.06, 36.39, 20.41, 20.38. IR (thin film): 1760 cm$^{-1}$. HRMS (ESI, m/z): [M+H]$^+$ calcd for C$_{14}$H$_{14}$N$_2$O$_2$, 243.1134; found, 243.1132.

The reaction was run for 10 h with 1.1 equiv of Phl(OAc)$_2$. The product 33 was obtained as a yellow oil (87 mg, 77% yield, $R_f = 0.28$ in 30% hexanes/60% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.07-7.06 (multiple peaks, 2H), 6.93 (d, $J = 8.8$ Hz, 1H), 3.52 (s, 2H), 2.96 (s, 3H), 2.93 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$): $\delta$ 170.16, 169.45, 146.49, 135.98, 130.63, 128.64, 127.00, 122.09, 37.55, 35.82, 35.57, 20.84. IR (thin film): 1759, 1645 cm$^{-1}$. HRMS (ESI, m/z): [M+Na]$^+$ calcd for C$_{13}$H$_{17}$NO$_3$, 258.1106; found, 258.1101.

The reaction was run for 5 h with 0.10 equiv of Pd(OAc)$_2$ and 2.02 equiv of Phl(OCOCF$_3$)$_2$ in AcOH (4 mL). The product 34 was obtained as a yellow oil (69 mg, 55% yield, $R_f = 0.24$ in 15% hexanes/85% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.09 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.07 (br s, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 4.55 (s, 2H), 3.08 (t, $J = 5.6$ Hz, 2H), 2.42 (t, $J = 6.4$ Hz, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 1.77-1.71 (multiple peaks,
$\mathrm{^{13}C\{}^{1}H\}$ NMR (CDCl$_3$): $\delta$ 169.93, 169.51, 147.14, 135.88, 131.07, 129.42, 128.54, 122.43, 46.88, 44.87, 32.49, 23.03, 21.25, 21.00, 20.90. IR (thin film): 1759, 1639 cm$^{-1}$.

HRMS (ESI, m/z): [M+Na]$^+$ calcd for C$_{13}$H$_{19}$NO$_3$, 284.1263; found, 284.1269.

The reaction was run for 5 h with 0.10 equiv of Pd(OAc)$_2$ and 2.02 equiv of PhI(OCOCF$_3$)$_2$ in AcOH (4 mL). The product 35 was obtained as a yellow oil (58 mg, 49% yield, R$_f$ = 0.24 in 15% hexanes/85% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.06 (br s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 4.34 (s, 2H), 3.13 (t, $J = 7.2$ Hz, 2H), 2.35 (t, $J = 8.0$ Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 1.91 (t, $J = 8.0$ Hz, 2H). $^{13}$C$\{}^{1}H\}$ NMR (CDCl$_3$): $\delta$174.42, 169.91, 146.99, 135.83, 131.19, 129.60, 127.76, 122.45, 46.23, 41.73, 30.74, 20.87, 20.71, 17.57, 17.44. IR (thin film): broad strong peak at 1684 cm$^{-1}$. HRMS (ESI, m/z): [M]$^+$ calcd for C$_{13}$H$_{19}$NO$_3$, 189.1154; found, 189.1154.

The reaction was run for 12 h with 2.0 equiv PhI(OAc)$_2$. The product 40 was obtained as a yellow oil (140 mg, 52% yield, R$_f$ = 0.24 in 75% hexanes/25% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 9.29 (d, $J = 1.2$ Hz, 1H), 8.77 (d, $J = 5.6$ Hz, 1H), 7.80 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.60 (dd, $J = 6.4$, 1.6 Hz, 1H), 7.51 (td, $J = 8.0$, 1.6 Hz, 1H), 7.40 (td, $J = 8.0$, 1.6 Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 2.24 (s, 3H). $^{13}$C$\{}^{1}H\}$ NMR (CDCl$_3$): $\delta$ 169.18, 162.92, 158.91, 157.07, 148.44, 131.42, 130.64, 126.64, 123.65, 120.45, 21.02.

The reaction was run for 4.5 h with 1.02 equiv of PhI(OAc)$_2$. The product 53 was obtained as a colorless oil (135.1 mg, 91% yield, R$_f$ = 0.27 in 79% hexanes/21% ethyl acetate). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.71 (d, $J = 5.5$ Hz, 1H), 7.34 (d, $J = 5.0$ Hz, 1H), 7.11-7.09 (multiple peaks, 2H), 6.96 (d, $J = 8.5$ Hz, 1H), 4.12 (s, 2H), 2.05 (s, 3H). HRMS (ESI, m/z): [M]$^+$ calcd for C$_{18}$H$_{19}$NO$_3$, 284.1263; found, 284.1269.
2.33 (s, 3H), 2.19 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 169.26, 161.59, 150.22, 146.82, 138.66 (q, $^2$J$_{C-F}$ = 33.7 Hz), 136.06, 131.71, 129.95, 128.88, 122.76 (q, $^1$J$_{C-F}$ = 271.7 Hz), 122.43, 118.47 (q, $^3$J$_{C-F}$ = 3.7 Hz), 116.96 (q, $^3$J$_{C-F}$ = 3.7 Hz), 39.47, 20.82, 20.71. $^{19}$F{$^1$H} NMR (CDCl$_3$): $\delta$ –64.85. IR (thin film): 1753 cm$^{-1}$. HRMS (ESI, m/z): [M+Na$^+$] Calcd for C$_{16}$H$_{14}$F$_3$NO$_2$, 332.0874; Found, 332.0868.

Substrate 63 (308 mg, 1.0 mmol, 1.0 equiv), Pd(OAc)$_2$ (6.7 mg, 0.03 mmol, 0.03 equiv), and PhI(OAc)$_2$ (902 mg, 2.8 mmol, 2.8 equiv) were combined in a 20 mL vial and were dissolved in a 1:1 mixture of AcOH and Ac$_2$O (8 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil was purified by column chromatography. The product 64 was obtained as a yellow solid (318 mg, 75% yield, $R_f$ = 0.30 in 20% hexanes/80% ethyl acetate, mp = 234-237 ºC). $^1$H NMR (CDCl$_3$): $\delta$ 7.72 (d, $J$ = 8.8 Hz, 2H), 7.57 (d, $J$ = 8.8 Hz, 2H), 7.28 (s, 2H), 3.95 (s, 3H), 3.92 (t, $J$ = 7.6 Hz, 2H), 2.66 (t, $J$ = 8.0 Hz, 2H), 2.31 (s, 6H), 2.21 (quin, $J$ = 7.6 Hz, 2H), 2.07 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$): $\delta$ 174.30, 168.74, 149.90, 149.23, 142.09, 139.48, 134.50, 127.33, 122.77, 149.90, 129.88, 118.58, 118.88, 62.03, 48.57, 32.72, 20.82, 17.88, 15.50. IR (thin film): 1769, 1686 cm$^{-1}$. HRMS (ESI, m/z): [M+H]$^+$ calcd for C$_{23}$H$_{24}$N$_2$O$_6$, 425.1713; found, 425.1705.

Substrate 64 (51 mg, 0.12 mmol, 1.0 equiv), Pd(OAc)$_2$ (1.3 mg, 0.006 mmol, 0.03 equiv) and PhI(OAc)$_2$ (121 mg, 0.24 mmol, 2.0 equiv) were combined in a 20 mL vial and were dissolved in a 1:1 mixture of AcOH and Ac$_2$O (1 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil
was purified by column chromatography. The product 65 was obtained as a yellow solid as a 1:0.2 mixture of oxime isomers (34 mg, 59% yield, Rf = 0.25 in 10% hexanes/90% ethyl acetate, mp = 64.5-70.1 °C). Major oxime isomer: \( ^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.43 (dd, \( J = 8.0, 2.0 \) Hz, 1H), 7.36-7.34 (multiple peaks, 2H), 7.21 (s, 2H), 3.95 (s, 3H), 3.76 (t, \( J = 6.8 \) Hz, 2H), 2.54 (t, \( J = 8.0 \) Hz, 2H), 2.28-2.22 (multiple peaks, 9H), 2.18 (m, 2H), 2.06 (s, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)): \( \delta \) 174.12, 168.64, 149.76, 149.27, 147.68, 145.93, 141.03, 138.87, 130.92, 128.25, 127.31, 125.04, 123.55, 122.51, 122.40, 118.95, 118.80, 62.05, 49.91, 31.10, 20.91, 20.83, 19.93, 19.24, 15.46. IR (thin film): 1770, 1700 cm\(^{-1}\). HRMS (ESI, m/z): [M+Na]\(^+\) calcd for C\(_{25}\)H\(_{26}\)N\(_2\)O\(_8\), 505.1587; found, 505.1577.

Substrate 64 (51 mg, 0.12 mmol, 1.0 equiv), Pd(OAc)\(_2\) (1.3 mg, 0.006 mmol, 0.05 equiv) and N-chlorosuccinimide (32 mg, 0.24 mmol, 2.0 equiv) were combined in a 20 mL vial and were dissolved in AcOH (1 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 °C for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil was purified by column chromatography. The product 66 was obtained as a yellow solid as a 1:0.5 mixture of oxime isomers (47 mg, 81% yield, Rf = 0.28 in 15% hexanes/85% ethyl acetate, mp = 66.8–73.2 °C). Major oxime isomer: \( ^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.64 (dd, \( J = 5.2, 1.6 \) Hz, 1H), 7.47 (m, 1H), 7.34 (s, 1H), 7.25 (s, 1H), 7.2 (s, 1H), 3.94 (s, 3H), 3.79 (t, \( J = 6.8 \) Hz, 2H), 2.58 (t, \( J = 8.0 \) Hz, 2H), 2.28-2.22 (multiple peaks, 8H), 2.06 (s, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)): \( \delta \) 175.00, 168.57, 149.79, 149.29, 147.59, 141.21, 139.84, 136.19, 132.51, 129.65, 128.98, 128.20, 126.44, 123.80, 118.94, 62.89, 49.84, 32.71, 36.34, 30.91, 20.93, 19.06, 15.41. IR (thin film): 1773, 1694 cm\(^{-1}\). HRMS (ESI, m/z): [M+Na]\(^+\) calcd for C\(_{23}\)H\(_{23}\)ClN\(_2\)O\(_6\), 481.1142; found, 481.1144.
Substrate 64 (51 mg, 0.12 mmol, 1.0 equiv), Pd(OAc)$_2$ (1.3 mg, 0.006 mmol, 0.03 equiv) and [(m-CF$_3$C$_6$H$_4$)$_2$I]BF$_4$ (32 mg, 0.24 mmol, 2.0 equiv), NaHCO$_3$ (15 mg, 0.18 mmol, 1.5 equiv) were combined in a 20 mL vial and were dissolved in a toluene (1 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil was purified by column chromatography. The product 67 was obtained as a yellow solid as a 1:0.3 mixture of oxime isomers (53 mg, 78% yield, R$_f$ = 0.28 in 25% hexanes/75% ethyl acetate, mp = 62.2-65.8 ºC). Major oxime isomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.66-7.57 (multiple peaks, 4H), 7.55-7.49 (multiple peaks, 2H), 7.30 (s, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 3.91 (s, 3H), 3.83 (t, $J$ = 6.8 Hz, 1H), 3.25 (t, $J$ = 6.8 Hz, 1H), 2.57 (t, $J$ = 8.0 Hz, 1H), 2.36 (t, $J$ = 8.0 Hz, 1H), 2.23 (s, 6H), 2.12 (t, $J$ = 7.4 Hz, 1H), 2.03 (s, 3H), 1.88 (t, $J$ = 7.4 Hz, 1H). $^{13}$C {$^1$H} NMR (CDCl$_3$): $\delta$ 175.46, 168.54, 168.48, 149.87, 149.31, 149.21, 141.45, 139.47, 138.62, 136.37, 131.81, 130.75 (q, $^2$J$_{C-F}$ = 32.2 Hz), 129.25, 129.10, 128.82, 128.23, 127.31, 124.93 (q, $^3$J$_{C-F}$ = 3.7 Hz), 124.45 (q, $^3$J$_{C-F}$ = 3.8 Hz), 123.90 (q, $^3$J$_{C-F}$ = 271 Hz), 119.86, 118.98, 118.55, 61.99, 48.54, 32.69, 20.81, 18.85, 17.85, 15.46. $^{19}$F {$^1$H} NMR (CDCl$_3$): $\delta$ -62.57. IR (thin film): 1771, 1694 cm$^{-1}$. HRMS (ESI, m/z): [M+Na]$^+$ calcd for C$_{30}$H$_{27}$F$_3$N$_2$O$_6$, 591.1719; found, 591.1719.

Pyridyl oxime ether substrate (250 mg, 1.11 mmol, 1.0 equiv), Pd(OAc)$_2$ (7.5 mg, 0.03 mmol, 0.03 equiv) and PhI(OAc)$_2$ (715 mg, 2.22 mmol, 2.0 equiv) were combined in a 20 mL vial and were dissolved in a 1 : 1 mixture of AcOH and Ac$_2$O (9.25 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 ºC for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and
the resulting brown oil was purified by column chromatography. The product 68 was obtained as a pale yellow solid (299 mg, 79\% yield, $R_f = 0.26$ in 55\% hexanes/45\% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 8.73 (m, 1H), 7.74 (m, 1H), 7.42 (m, 2H), 7.35 (m, 1H), 7.27 (m, 1H), 4.01 (s, 3H), 2.21 (s, 3H), 2.04 (s, 6H).

Substrate 70 (200 mg, 0.75 mmol, 1.0 equiv), Pd(OAc)$_2$ (8 mg, 0.04 mmol, 0.05 equiv) and PhI(OAc)$_2$ (247 mg, 0.766 mmol, 1.02 equiv) were combined in a 20 mL vial and were dissolved in Benzene (6.3 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 $^\circ$C for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil was purified by column chromatography. The product 71 was obtained as a yellow oil as a 1 : 0.6 mixture of oxime isomers (73 mg, 30\% yield, $R_f = 0.22$ in 91\% hexanes/9\% ethyl acetate). Major oxime isomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.25 (m, 1H) 7.18 (t, $J = 7.0$ Hz, 1H), 7.13 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.04 (d, $J = 7.0$ Hz, 1H), 7.00 (br s, 1H), 6.97 (d, $J = 7.5$ Hz, 1H), 5.07 (s, 2H), 3.42 (s, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 1.75 (s, 3H). Minor oxime isomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.24 (br s, 1H), 7.18-7.12 (multiple peaks, 2H), 7.04-6.96 (multiple peaks, 3H), 5.05 (s, 2H), 3.66 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H), 1.77 (s, 3H).

Substrate 70 (200 mg, 0.75 mmol, 1.0 equiv), Pd(OAc)$_2$ (8 mg, 0.04 mmol, 0.05 equiv) and PhI(OAc)$_2$ (247 mg, 0.766 mmol, 1.02 equiv) were combined in a 20 mL vial and were dissolved in a 1:1 mixture of AcOH and A$_2$O (6.3 mL). The vial was sealed with a Teflon-lined cap, and the mixture was heated at 100 $^\circ$C for 12 h. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the resulting brown oil
was purified by column chromatography. The product was obtained as a yellow oil as a 1:1 mixture of regio isomers 71 and 72. Characterization for the oxime isomers for regioisomer 71 is shown above. Regioismer 72 was obtained in a 1:0.4 mixture of oxime isomers (134 mg, 55% yield, $R_f = 0.22$ in 91% hexanes/9% ethyl acetate). **Major oxime isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.24 (d, $J = 7.0$ Hz, 1H) 7.18-7.17 (multiple peaks, 2H), 7.11 (d, $J = 7.0$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 7.01 (br s, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 5.08 (s, 2H), 3.37 (s, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H), 1.75 (s, 3H). **Minor oxime isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.23 (d, $J = 7.5$ Hz, 1H), 7.18-7.16 (multiple peaks, 2H), 7.11 (d, $J = 7.0$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 7.00 (br s, 1H), 6.92 (d, $J = 8.5$ Hz, 1H), 5.08 (s, 2H), 3.62 (s, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 2.22 (s, 3H), 1.73 (s, 3H).

**General Procedure for Kinetics Experiments.** Kinetics experiments were run in two dram vials sealed with Teflon-lined caps. Each data point represents a reaction in an individual vial, with each vial containing an identical concentration of oxidant, catalyst, and substrate. The vials were charged with PhI(OAc)$_2$ (0.0158 g, 0.049 mmol, 1.02 equiv, added as a solid), substrate (0.048 mmol, 1.0 equiv, added as a 0.96 M stock solution in AcOH), and Pd(OAc)$_2$ (0.11 mg, 0.00048 mmol, 0.01 equiv, added as a 0.0096 M stock solution in AcOH), and the resulting mixtures were diluted to a total volume of 400 mL of a 1 : 1 mixture of AcOH and Ac$_2$O. The vials were then heated at 80 °C for various amounts of time. Reactions were quenched by cooling the vial at 0 °C for 5 min, followed by the addition of a 2% solution of pyridine in CH$_2$Cl$_2$ (2 mL). An internal standard (pyrene) was then added, and the reactions were analyzed by gas chromatography. Each reaction was monitored to ~10% (8.6-11.0%) conversion, and rate constants were calculated for each reaction using the initial rates method. Each kinetics experiment was run in triplicate, and the data shown in the Hammett plots represent an average of these three runs.

**General Procedure for Competition Experiments.** A two dram vial was sequentially charged with PhI(OAc)$_2$ (0.0158 g, 0.049 mmol, 1.02 equiv, added as a solid), substrate A (0.048 mmol, 1.0 equiv, added as a 0.96 M stock solution in AcOH),
substrate B (0.048 mmol, 1.0 equiv, added as a 0.96 M stock solution in AcOH), and Pd(OAc)$_2$ (0.11 mg, 0.00048 mmol, 0.01 equiv, added as a 0.0096 M stock solution in AcOH), and the resulting mixtures were diluted to a total volume of 400 mL of a 1 : 1 mixture of AcOH and Ac$_2$O. The reaction was heated at 80 °C for 12 h, and then cooled to room temperature. A GC standard (pyrene) was added, and the reaction was analyzed by gas chromatography.
4.11 References


Chapter 5

Palladium-Catalyzed 1,2-Difunctionalization of Alkenes

5.1 Background and Significance

Oxidative amination reactions have been an important area of research in organic chemistry.\textsuperscript{1-4} In particular, aminooxygenation reactions of alkenes, leading to vicinally difunctionalized products, with two distinct carbon-heteroatom bonds, provide an attractive route towards the synthesis of small molecules of synthetic and pharmaceutical interest.

The development of a Pd\textsuperscript{II/IV} catalyzed method to form aminooxygentated products could allow access to β-amino alcohols (via intermolecular reactions) and nitrogen containing heterocycles (via intramolecular reactions).\textsuperscript{5, 6} Some of the most common alternative approaches to vicinal amino alcohols involve: (i) functional group manipulations of imine or carbonyl groups via reduction or nucleophilic addition,\textsuperscript{5} (ii) ring opening reactions of epoxides and aziridines,\textsuperscript{5} (iii) aminohydroxylation of olefins,\textsuperscript{5} and (iv) aldol or pinacol-type coupling reactions.\textsuperscript{5} Hydroxyamination of alkenes is the most straightforward route for vicinal amino alcohol synthesis, and the Sharpless Os-catalyzed asymmetric aminohydroxylation reaction (Scheme 5.1) is probably the most widely used of these reactions.\textsuperscript{7}
**Scheme 5.1**: Osmium-Catalyzed Aminohydroxylation of Alkenes

We hope to access vicinal aminooxygenated compounds by developing a Pd^{II/IV} catalyzed route. The two key steps of the proposed reaction involve (i) aminopalladation followed by (ii) oxidative cleavage of the resultant carbon-palladium bond (Scheme 5.2, pathway a).

**Scheme 5.2.** Oxidative Cleavage of Pd-Alkyl Intermediates Formed via Aminopalladation

In order to achieve the desired aminooxygenation transformation, the key challenge that needs to be addressed is competing β-hydride elimination from the Pd-alkyl intermediate A (Scheme 5.2, pathway b). Importantly, several research groups have recently demonstrated that the undesired aminopalladation/β-hydride elimination sequence can be a useful and efficient synthetic transformation. Stahl and co-workers have developed the most effective of these systems. They have demonstrated the oxidative amination of activated and unactivated olefins with nitrogen nucleophiles including carboxamides, carbamates and sulfoamides via a Pd^{II/0} reaction manifold (Scheme 5.3). A representative example is illustrated in Scheme 5.4, and involves the
synthesis of enamide 5 from octene and phthalimide in the presence of 5 mol % Pd(OAc)₂ and O₂ as the oxidant.

Scheme 5.3: Proposed Mechanism for Formation of Enamide 5 Formation

Scheme 5.4. Synthesis of Enamide 5 via Aminopalladation/β-Hydride Elimination

In 1980, Backvall demonstrated that Pd-alkyl intermediates generated upon aminopalladation can be intercepted by strong oxidants at –40 ºC without competing β-hydride elimination. For example, the reaction of trans-butene with stoichiometric Pd(PhCN)₂Cl₂ and dimethylamine afforded the Pd-alkyl intermediate 7, and subsequent addition of Pb(OAc)₄ led to the formation of aminooxygenated product 8. As shown in Scheme 5.5, this reaction was proposed to proceed via trans-aminopalladation followed by oxidative cleavage of the palladium-carbon bond with inversion of stereochemistry at the carbon. The mechanism of aminopalladation was elucidated by trapping the Pd⁺ intermediate 7 with LiAlD₄ at –70 ºC to form deuterated amino butane. Cope elimination of the amine then allowed stereochemical analysis of the deuterated butene. Although this reaction illustrates the feasibility of aminooxygenation, it is limited by the need for a stoichiometric amount of palladium. The electron rich amines used in this reaction (for
example, dimethylamine) coordinate more strongly to palladium than alkenes and therefore inhibit catalytic turnover.

**Scheme 5.5. Stoichiometric Aminoacetoxylation Reaction Reported by Backvall**

\[
\begin{align*}
(6) & \quad \xrightarrow{\text{Pd(PhCN)Cl}_{2}} \quad (7) \quad \xrightarrow{\text{Pb(OAc)$_4$}} \quad (8) \\
\text{Me$_2$N} & \quad \text{Me$_2$N} \quad \text{OAc}
\end{align*}
\]

As described in Chapter 1, we have been able to successfully out-compete β-hydride elimination and intercept cyclopalladated Pd-alkyl intermediates with PhI(OAc)$_2$ via a Pd$^{II/IV}$ catalytic cycle. Based on this and on Backvall’s precedent, we envisioned the development of a Pd-catalyzed aminooxygenation reaction using a Pd$^{II}$ catalyst and PhI(OAc)$_2$ as a strong oxidant. As shown in Scheme 5.6, we speculated that the use of PhI(OAc)$_2$ might allow us to oxidatively intercept the intermediate A (illustrated in Scheme 2). Additionally, the use of moderately nucleophilic phthalimide might attenuate its binding to Pd, hence allowing for catalytic turnover.

**Scheme 5.6. Proposed Pd$^{II/IV}$ Catalyzed Aminooxygenation of Olefins**

Palladium alkyl intermediates generated upon aminopalladation, such as A, have been previously shown to undergo a number of reactions, including olefin insertion, carbonylation, and oxidative cleavage with CuCl$_2$ or CuBr$_2$ to form C–C, C–Cl and C–Br bonds, respectively. For example, Chemler has demonstrated the intramolecular aminochlorination of substrate 9 using 5 mol % Pd(OAc)$_2$ and 4 equiv of CuCl$_2$ (Scheme 5.7). Interestingly, competing β-hydride elimination products such as 12 were not observed in this reaction. Two possible mechanisms have been proposed, and both initiate with an intramolecular aminopalladation to afford intermediate 13 (Scheme 5.8). The first (Scheme 5.8, path a) involves oxidative cleavage of the Pd–C bond in 13 with
CuCl$_2$ via a Pd$^{IV}$ intermediate. The second (Scheme 5.8, path b) proposes a copper assisted ligand transfer to form the C–Cl bond, without a change in oxidation state at Pd$^{II}$.

**Scheme 5.7.** Palladium-Catalyzed Intramolecular Aminochlorination with CuCl$_2$

\[
\begin{align*}
\text{NH}_2\text{Ts} & \quad \xrightarrow{10 \text{ mol} \% \text{ Pd(OOCF$_3$)$_2$} \quad 4 \text{ equiv CuCl$_2$}} \quad \text{K$_2$CO$_3$, THF} \quad 23 \text{ °C, 72\%}} \\
\text{regioselectivity is 2:1} \\
\text{not observed}
\end{align*}
\]

**Scheme 5.8: Proposed Mechanism for Pd-Catalyzed Intramolecular Aminochlorination**

As we began this project, several groups reported Pd-catalyzed intramolecular olefin aminoacetoxylation and diamination reactions similar to the transformation that we proposed. For example, Sorensen demonstrated intramolecular aminopalladation with substrates such as N-tosylamide 16 to form oxazolidinone 17.$^{13}$ The use of Pd(OAc)$_2$ as a catalyst resulted in significant quantities of β-hydride product 18. However, this pathway could be suppressed by employing a chloride-based catalyst. Hence, using 10 mol % Pd(PhCN)$_2$Cl$_2$ and 2 equiv PhI(OAc)$_2$ led to the formation of 17 in 65% yield (Scheme 5.9). Reaction of cinnamyl alcohol-derived N-tosyl carbamate 19 proceeded stereospecifically to afford product 22, which led to speculation that the mechanism involved trans-aminopalladation followed by C–O bond-forming reductive elimination with inversion of stereochemistry at the carbon (Scheme 5.10). However, no other mechanistic experiments were conducted to support this claim. Later reports by Muniz
suggest that cis-aminopalladation followed by reductive elimination with inversion of stereochemistry is more likely.

**Scheme 5.9.** Palladium-Catalyzed Intramolecular Aminoacetoxylation with PhI(OAc)$_2$

\[
\text{TsHN} \quad \text{CH}_2\text{Cl}_2, 60 \, ^\circ\text{C} \quad \xrightarrow{5 \text{ mol } \% \text{ Pd(PhCN)}_2\text{Cl}_2 \text{ and 2 equiv PhI(OAc)$_2$}} \quad \text{TsN} \quad \text{OAc} 
\]

\[\text{(16) to (17), 65%} \quad \text{not isolated}\]

**Scheme 5.10.** Proposed Mechanism for Pd-Catalyzed Intramolecular Aminoacetoxylation

\[
\begin{align*}
\text{trans-Aminopalladation} & : \quad \text{rate-limiting} \\
\text{Reductive Elimination with Inversion} & : \quad \text{S}^\text{N}2\text{-type elimination with inversion of stereochemistry}
\end{align*}
\]

A later report by Muniz and co-workers demonstrated the Pd-catalyzed oxidative intramolecular diamination of olefins.$^{14,15}$ They were able to efficiently generate bicyclic and tricyclic substituted urea derivatives through diamination of substrates such as 23, using 5 mol % Pd(OAc)$_2$ and 2.2 equiv PhI(OAc)$_2$ (Scheme 5.11). The authors did not observe products such as 25, resulting from competing β-hydride elimination. A mechanism involving: (i) rate-limiting cis-aminopalladation to form 27, (ii) oxidation to Pd$^{IV}$ complex 28, (iii) amide dissociation, and (iv) S$^\text{N}2$-type reductive elimination with inversion of stereochemistry at carbon was proposed (Scheme 5.12). Experiments including deuterium labeling, kinetics, solvent effects, electronic substitution effects, and *in situ* NMR investigation were used to elucidate this mechanism.
Scheme 5.11. Palladium-Catalyzed Intramolecular Diamination Reactions

![Scheme 5.11](image)

As discussed above, we desired to develop an intermolecular aminoacetoxylation reaction. Concurrent to our work, Stahl and co-workers published the intermolecular variant of oxidative aminoacetoxylation of olefins. Using phthalimide as the nitrogen nucleophile, they showed high yielding aminoacetoxylation of allyl ether substrates such as 31. They also observed the formation of β-hydride elimination products such as 33, albeit in low yield. They proposed that coordination of the metal with the oxygen in the ether linkage suppressed β-hydride elimination. Through detailed mechanistic experiments, they proposed a mechanism involving cis-aminopalladation followed by SN2-type C–O bond-forming reductive elimination at PdIV with inversion of stereochemistry at carbon.
Scheme 5.13. Palladium-Catalyzed Intermolecular Aminoacetoxylation

\[
\begin{align*}
\text{nPr-}OCH_2-CH\equiv & + \text{NHNCO}_2 \to \text{nPr-}OCH_2-CH(OAc) + \text{nPr-}OCH_2-CH-
\end{align*}
\]

(31) \to (32, 78%) \quad (33, 16%)

5.2 Initial Investigation

Our initial studies focused on the reaction between 1-octene and phthalimide. These substrates were chosen because Stahl had demonstrated their ability to undergo efficient aminopalladation (Scheme 5.4).\(^8\) Gratifyingly, subjecting 1-octene and phthalimide to 5 mol% Pd(OAc)\(_2\) and 1.5 equiv PhI(OAc)\(_2\) in AcOH at 100 °C afforded the 1,2-aminoxygenated product 34 in 21% isolated yield. This low yield was due to competitive formation of two side products: (i) olefin 5 (generated via termination of the reaction by \(\beta\)-hydride elimination) and (ii) diacetoxylated product 35. Notably, Stahl obtained similar results with substrate 3.

Scheme 5.14. Palladium-Catalyzed Reaction of 1-Octene with Phthalimide and PhI(OAc)\(_2\)

\[
\begin{align*}
\text{CH}_3\text{CN, CH}_2\text{Cl}_2, 60 \degree \text{C} & \quad 27\% \quad 41\% \quad 20\% \\
\text{AcOH, 100 \degree \text{C}} & \quad 15\% \quad 21\% \quad 32\%
\end{align*}
\]

Optimization Studies. Several reaction parameters such as solvent, catalyst, and temperature were screened in order to increase the yield of the desired product 34. Solvents such as AcOH led to increased yields of the undesired diacetoxylated product 35, while dichloroethane, CH\(_3\)CN, and CH\(_2\)Cl\(_2\) were most effective in affording 34. Interestingly, reactions in THF only afforded the \(\beta\)-hydride elimination product 5.
A survey of various catalysts revealed that Pd(PhCN)$_2$Cl$_2$ and Pd(CH$_3$CN)$_2$Cl$_2$ (which were found to decrease β-hydride elimination in Sorensen’s system) led to similar yields of products 34 and 5 as Pd(OAc)$_2$. In an attempt to suppress β-hydride elimination, we investigated palladium catalysts containing bidentate and tridentate ligands (Figure 5.1). We thought that having a multicoordinated ligand on the metal would limit vacant cis coordination sites, which are required for β-hydride elimination. Consistent with this hypothesis, Pd(CC)Br$_2$, Pd(CNC)Br$_2$, and Pd(PNP)Cl$_2$ (Figure 5.1) afforded only trace amounts of the β-hydride products; however, the desired product 34 was also obtained in low yield with these catalysts. We next attempted to increase catalyst reactivity by moving to Pd(O$_2$CCF$_3$)$_2$, which contains a more electrophilic Pd center. However, with this catalyst we observed an increase in the relative rate of decomposition of the olefins. Lowering the temperature of the reaction from 100 ºC to 60 ºC did slow down the rate of Pd-catalyzed olefin decomposition.

**Figure 5.1**: Palladium Catalysts Containing Bi- and Tridentate Ligands

Based on all of these studies, the final optimized conditions for this reaction were 5 mol % Pd(OAc)$_2$ and 2 equiv PhI(OAc)$_2$ in CH$_2$Cl$_2$ at 60 ºC, which afforded 41% yield of the desired product 34. Despite these optimization studies, the relative rate of β-hydride elimination versus oxidation was still competitive, and 41% yield of 1,2-difunctionalized product 34 was obtained under these conditions.

*Exploration of Different Olefin and Nucleophile Partners.* We wondered if a different nucleophile partner would provide higher yields in this reaction. As such, a series of carboxamides, carbamates and sulfonamides were investigated; however, only $p$-toluenesulfonamide (TsNH$_2$) and $p$-nitrobenzenesulfonamide (NsNH$_2$) afforded the desired aminoacetoxylated product in greater than 5% yield under the optimized reaction conditions.
conditions from above (5 mol % Pd(OAc)$_2$, 2 equiv PhI(OAc)$_2$ in CH$_2$Cl$_2$ at 60 °C). We next attempted to increase the yield of the desired product with these nucleophiles through the addition of bases. Strong bases such as NaO$_2$Bu and Cs$_2$CO$_3$ either led to decomposition of 1-octene or resulted in greater quantities of the β-hydride elimination product (37). Weak bases such as Na$_2$SO$_4$ and MgO did not hamper the reaction, but also did not improve the yield of 38. However, interestingly, the addition of acetate sources such as NaOAc and LiOAc increased the yield of the desired product 38 to 10%. We believed that solubility was a limitation with using these bases. Hence, tetrabutylammonium acetate was examined as a soluble acetate source, and was found to be optimal for reactions with TsNH$_2$ and NsNH$_2$. With optimal conditions of 5 mol % Pd(OAc)$_2$, 2 equiv PhI(OAc)$_2$, 1 equiv Bu$_4$NOAc, in CH$_2$Cl$_2$ at 60 °C, 1-octene reacted with TsNH$_2$ and NsNH$_2$ to provide 38 and 41 in 18% and 25% yield, respectively, (Scheme 5.15).

**Scheme 5.15.** Palladium-Catalyzed Reaction of 1-Octene with Tosylamine or Nosylamine and PhI(OAc)$_2$

Mechanistic studies by Stahl have shown that aminopalladation of norbornene with TsNH$_2$ occurs in a syn fashion.$^8$ Hence, we decided to screen the reactions with norbornylenes as the olefin partner, since we expected β-hydride elimination to be attenuated in this system due to conformational constraints. Consistent with this hypothesis, reaction of norbornene and TsNH$_2$ (with 5 mol % Pd(OAc)$_2$, 2 equiv
PhI(OAc)₂, 1 equiv Bu₄NOAc, in CH₂Cl₂ at 60 °C) did not afford any of the β-hydride elimination product 44. However, due to low reactivity of the aminoacetoxylation reaction and formation of the undesired diacetoxylation product 45, we obtained the desired product 43 in only 38% yield (Scheme 5.16).

Scheme 5.16. Palladium-Catalyzed Reaction of Norborylene with p-Toluenesulfonamide and PhI(OAc)₂

![Scheme 5.16](image)

We next explored the reactivity of norbornene with phthalimide as the nucleophile. Reaction of norbornene and phthalimide in CH₂Cl₂ with 5 mol % Pd(OAc)₂, 2.0 equiv PhI(OAc)₂ at 60 °C afforded the aminoacetoxylated product 46 and diacetoxylation product 45 in 41% and 23% yield respectively. Optimization reactions screening various solvents, temperatures, bases and catalysts did not improve the yield of 46.

Scheme 5.17: Palladium-Catalyzed Reaction of Norbornene with Phthalimide and PhI(OAc)₂ in CH₂Cl₂

![Scheme 5.17](image)

Interestingly, when the reaction of norborylene and phthalimide with 5 mol % Pd(OAc)₂ and 2 equiv PhI(OAc)₂ was conducted in nitromethane, a new compound (47) was obtained along with the expected 1,2-aminoacetoxylated product 46. Characterization of 47 by NMR spectroscopy and X-ray crystallography revealed that a molecule of nitromethane and a molecule of phthalimide had been incorporated to afford
an unexpected 2,7-disubstituted norbornane derivative. When the solvent was changed from nitromethane to nitroethane, similar reactivity was observed to afford compound 48, albeit in lower yield. In this case, the balance of the material was unreacted starting material (~41%) and the aminoacetoxylated product 46 (22%).

**Scheme 5.18.** Palladium-Catalyzed Reaction of Norbornene with Phthalimide and PhI(OAc)₂ in Nitroalkane Solvents

![Scheme 5.18](image)

Similar connectivity as product 47 and 48 has been observed by Heck in the Pd-catalyzed reaction of phenylmercuric chloride with norbornene.⁷ Reaction of PhHgCl and norbornene with catalytic Li₂PdCl₄ and stoichiometric CuCl₂ afforded exo-2-chloro-7-phenynorbornene (49) (Scheme 5.19). The authors did not speculate on a possible mechanism for the formation of 49.

**Scheme 5.19: Halophenylation of Norbornene**

![Scheme 5.19](image)

*Substrates with Directing Groups.* A substrate design strategy was next employed in an attempt to avoid competitive formation of β-hydride elimination products. In Chapter 2, we proposed that β-hydride elimination in the sp³ C–H functionalization
reactions was attenuated by the formation of a cyclopalladated intermediate. In such an intermediate, coordination of the chelating functionality to the metal provides a cyclic structure, which renders β-hydride elimination conformationally unfavorable. Based on these systems, we reasoned that tethering a chelating group to the nucleophile of the alkene could have a similar effect.

We first explored nucleophile 50, which contains two basic functional groups, an amide and a pyridine. We anticipated that the former could undergo aminopalladation while the latter could subsequently bind to the metal to generate chelated intermediate 51 (Scheme 5.20). However, when reactions of 50 with 1-octene were explored under our optimized conditions (5 mol % Pd(OAc)$_2$, 2 equiv PhI(OAc)$_2$ and 1 equiv Bu$_4$NOAc in CH$_2$Cl$_2$ at 60 °C), 50 and the starting olefin were recovered quantitatively. Despite screening various solvents, temperatures, and bases, we did not observe any reactivity. We believe that the nucleophile may coordinate tightly with the metal and thereby prevent further reaction.

**Scheme 5.20: Use of Directing Group-Containing Nucleophile 50**

\[
\text{C}_6\text{H}_{13} + \text{HN} \xrightarrow{\text{cat. L}_n\text{Pd}^{\text{II}}} \text{N} \xrightarrow{\text{Pd}^{\text{II}}/\text{L}_n} \text{C}_6\text{H}_{13} + \text{OAc}
\]

We next explored alkene substrates that contain either a quinoline or an oxime ether functionality, as these are both known to bind readily to Pd$^{\text{II}}$. We envisioned that interaction between the quinoline or oxime ether and palladium would bring the metal in the proximity of the olefin. Subsequent aminopalladation would then result in a cyclic Pd-alkyl intermediate like 54 or 57 (Scheme 5.21), which would be less susceptible to β-hydride elimination than their acyclic analogues. However, subjection of substrates 53 and 56 to phthalimide with 5 mol % Pd(OAc)$_2$ and 2 equiv PhI(OAc)$_2$ in different solvents at 60 °C, with and without Bu$_4$NOAc, afforded unreacted starting material (with 53) or undesired side reactions of the olefin (with 56).
We hypothesized that 50, 53 and 56 did not exhibit any reactivity towards oxidative amination because the directing group bound tightly to the Pd\textsuperscript{II} catalyst and thereby prevented coordination of the olefin and/or nucleophile. Hence, our next approach was to examine tethering a weaker ligand such as an alcohol to the olefin. In this system, the alcohol could chelate to the palladium and aminopalladation could occur followed by oxidation to produce the desired product (Scheme 5.22).

Initial studies focused on the Pd-catalyzed reaction of 3-butene-1-ol (59) and phthalimide with Phl(OAc)\textsubscript{2} (Scheme 5.22). Consistent with our hypothesis, when 59 was subjected to the optimized reaction conditions with 1-octene (Scheme 5.23), none of the \(\beta\)-hydride elimination product 64 was observed, which was confirmed by synthesizing an authentic sample. However, surprisingly, none of desired product 61 was observed either. Instead, the reaction afforded two tetrahydrofuran products - one incorporating the phthalimide (62) and the second incorporating an acetate (63).
Scheme 5.23: Palladium-Catalyzed Reaction of 3-Butene-1-ol with Phthalimide and PhI(OAc)\(_2\) to form Tetrahydrofurans

\[
\begin{align*}
\text{Scheme 5.24. Palladium-Catalyzed Cyclization of 3-Buten-1-ol} \\
\text{In order to explore the origin of products 62 and 63, we next probed the scope and mechanism of this transformation. These studies are discussed below and divided into four sections. The first two sections describe the scope and mechanism for the formation of product 63. The last two sections focus on efforts towards understanding the generality and mechanistic details of formation of product 62.}
\end{align*}
\]

5.3 Cyclization of Alcohols

We believed that PhI(OAc)\(_2\) was the source of acetate in product 63 (Scheme 5.23). Hence, benzoate derivatives of PhI(OAc)\(_2\) were screened in order to add molecular weight to the products and facilitate isolation. Subjection of 3-butene-1-ol to 5 mol % Pd(OAc)\(_2\) and 2 equiv PhI(OCOPh)\(_2\) in CH\(_3\)CN at 60 \(^\circ\)C afforded the cyclized product 65 in 41% yield (Scheme 5.24).

Other Products Observed in the Reaction:

\[
\begin{align*}
\text{(59)} & \quad \text{(4)} & \quad 5 \text{ mol % Pd(OAc)}_2 & \quad \text{CH}_3\text{CN, 60 °C} \\
\text{(62, 37\%)} & \quad \text{(63, ~30\%)} & \quad \text{(64, not observed)} \\
\text{(65, 41\%)} & \quad \text{(66, 11\%)} & \quad \text{(67, 8\%)} & \quad \text{(68, 10\%)} \\
\end{align*}
\]
The modest yield of this cyclization reaction is believed to be due to side reactions of the 3-butene-1-ol starting material under the reaction conditions. Consistent with this hypothesis, traces of diacetoxyalted aldehyde 67, epoxide containing product 68, and Heck side product 66 were isolated from the reaction. Notably, approximately 5% of product 65 and <5% of products 66 and 68 were observed when the reactions were run in the absence of Pd(OAc)$_2$. The formation of Heck product 66 could be suppressed through the use of (Mesityl)I(CO$_2$Ph)$_2$ in place of PhI(CO$_2$Ph)$_2$. However, this oxidant exhibited lower reactivity for the desired transformation (Scheme 5.25).

**Scheme 5.25: Use of (Mesityl)I(CO$_2$Ph)$_2$ as the Oxidant**

![Scheme 5.25](image)

We speculated that the formation of the diacetoxyalted aldehyde product 67 and epoxide product 68 would be increased by employing more reactive oxidants. Consistent with our hypothesis, when various electronically different iodosobenzoate derivatives were explored, the electron deficient oxidants (para-NO$_2$, CF$_3$, and Br substituted benzoates) led to greater quantities of products 67 and 68. However, the yields obtained with the electron rich benzoate oxidants (para-OMe and CH$_3$ substituted benzoates) were similar to those obtained with PhI(CO$_2$Ph)$_2$. We believe Pd(OAc)$_2$ acts as a Lewis acid to catalyze the formation of the epoxide product 68 and diacetoxyalted product 67 via a mechanism similar to epoxide formation with $m$-CPBA (Scheme 5.26). Subsequent reaction of product 71 with Pd, through $\beta$-hydride elimination, would form aldehyde 67.
The scope of this reaction with respect to the alcohol substrate was next examined. In a representative example, 2-phenyl-l-butanol reacted under the optimal conditions (5 mol % Pd(OAc)$_2$ and 2 equiv of PhI(OAc)$_2$ in CH$_3$CN at 60 °C) to afford 35% of the desired substituted THF ring 73, along with significant amounts of epoxide 74 (Scheme 5.27). Similar yields of THF products were obtained with a variety of other alcohol substrates 75-85 (Table 5.1), and in all cases, analogous epoxide side products were observed. Notably, the THF rings were formed with modest levels of diastereoselectivity, with $dr$ ranging from 1:1 to 2:1.
### Table 5.1: Substrate Scope for Alcohol Cyclization Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (dr)</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>22% (1.4:1)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>37% (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5</td>
<td>30% (1:1)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>8</td>
<td>25% (1.8:1)</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>29% (2:1)</td>
</tr>
</tbody>
</table>

### 5.4 Cyclization of Amines

Analogous cyclization reactions of amino olefins were next examined. Amino olefin substrates containing various protecting groups (Cbz, Ts, Ns, Boc, and urea) were subjected to our optimal reaction conditions (5 mol % Pd(OAc)$_2$ and 2 equiv of PhI(OAc)$_2$ in CH$_3$CN at 60 ºC). Only amines with Ns and Ts protecting groups exhibited trace reactivity towards the cyclization reaction (Scheme 5.28). Upon screening bases with substrates 87 and 90, we determined that NaHCO$_3$ allowed us to access the pyrrolidine products 88 and 91 in about 20% yield. Diacetoxylation of the starting olefin, similar to that observed with 1-octene (Scheme 5.14), was again a competitive pathway in these reactions. The balance of material was accounted for by unreacted starting material.
We next synthesized protected amines 93 and 94, which contain a phenyl substituent in the backbone (Figure 5.2). We anticipated that this group would facilitate cyclization via a Thorpe-like effect. In addition, we synthesized amides 95-97, which we expected to be conformationally biased to undergo cyclization. However, in the reaction of substrates 93-94 and 96-97 under our optimal conditions (5 mol % Pd(OAc)\textsubscript{2} and 2 equiv of PhI(OAc)\textsubscript{2} in CH\textsubscript{3}CN at 60 °C with and without NBu\textsubscript{4}OAc or NaHCO\textsubscript{3}) we either observed unreacted starting material (with 93-97), diacetoxylation of the olefin (with 93 and 94), Heck products (with 96 and 97) or decomposition (with 95).

**Figure 5.2: Additional Amine and Amide Substrates**
5.5 Cyclization of Acids

In order to further explore the scope of these cyclization reactions, we studied substrates containing carboxylic acids as the intramolecular nucleophile. Gratifyingly, subjection of 3-butenolic acid to our reaction conditions (5 mol % Pd(OAc)$_2$, 2 equiv of PhI(OCOPh)$_2$ and 2 equiv NaHCO$_3$ in CH$_3$CN at 60 ºC ) afforded the cyclized lactone product 100 in 56% yield (Scheme 5.29). As shown in Table 5.2, the scope of this cyclization was general for various different substituted acids. Substrates 101-111 cyclized to form lactones in better yields than the alcohols and amines. However, we still obtained low diastereoselectivity with substrates such as 101. The diastereoselectivity did not improve upon addition of Pd catalysts containing various bidentate and tridentate ligands.

Scheme 5.29. Carboxylic Acid Cyclization Reactions

```
5 mol % Pd(OAc)$_2$
2 equiv PhI(OCOPh)$_2$
2 equiv NaHCO$_3$
CH$_2$Cl$_2$, 12 h, 60 ºC

(99) -> (100, 56%)
```
Table 5.2: Substrate Scope of Carboxylic Acid Cyclization Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[101]</td>
<td>[102]</td>
<td>65% (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>[103]</td>
<td>[104]</td>
<td>60%</td>
</tr>
<tr>
<td>3</td>
<td>[105]</td>
<td>[106]</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>[107]</td>
<td>[108]</td>
<td>65% (13:1)</td>
</tr>
<tr>
<td>5</td>
<td>[109]</td>
<td>[110]</td>
<td>56% (1:9)</td>
</tr>
<tr>
<td>6</td>
<td>[111]</td>
<td>[112]</td>
<td>48% (all trans)</td>
</tr>
</tbody>
</table>

Conditions: 5 mol % Pd(OAc)₂, 2 equiv Phl(OCOPh)₂, 2 equiv NaHCO₃, CH₂Cl₂, 60 °C

Reaction of substituted internal olefins did occur with high levels of stereospecificity. For instance, trans-4-ethylbutenoic acid [107] preferentially formed the trans-4,5-substituted lactone [108] with 13:1 selectivity (Table 5.2, entry 4), while cis-4-ethylbutenoic acid [109] preferentially afforded the cis-4,5-substituted lactone [110] with 9:1 selectivity (entry 5).

5.6 Mechanistic Investigations of the Cyclization Reactions

We next explored the role of palladium in these alcohol, amine and acid cyclization reactions. We speculated that there were at least two possible mechanisms: (i)
a Pd$^{\text{II/IV}}$-catalyzed pathway involving 5-endo-trig cyclization followed by oxidation (Scheme 5.30) or (ii) a mechanism involving Pd$^{\text{II}}$ acting as a Lewis acid to promote the formation of iodonium ring 115, that subsequently undergoes cyclization (Scheme 5.31).

**Scheme 5.30.** 5-Endo-trig Cyclization at Pd$^{\text{II}}$

![Scheme 5.30. 5-Endo-trig Cyclization at Pd$^{\text{II}}$]

**Scheme 5.31.** Lewis Acid Catalyzed Cyclization

![Scheme 5.31. Lewis Acid Catalyzed Cyclization]

Importantly, there is limited literature precedent for Pd$^{\text{II}}$-promoted 5-endo trig cyclization reactions. As shown in Scheme 5.32, one example involved an alcohol and one involved an amine nucleophile.$^{18,19}$ In both cases, the final fate of the palladium alkyl intermediate, generated upon cyclization, was β-hydroxy elimination. There is literature precedent for Bronsted acid promoted cyclization of acids with hypervalent iodine oxidants. Butenoic acid was cyclized with PhI(OAc)$_2$ in AcOH in the presence of a strong acid, HBF$_4$ (Scheme 5.33).$^{20}$ Notably, Pd$^{\text{II}}$ complexes have been used as Lewis acid catalysts in Baeyer Villiger oxidations, Diels Alder reactions, and the acetalization of aldehydes and ketones.$^{21}$ Hence, we wondered if the role of palladium in these cyclization reactions was that of a Lewis acid.
Scheme 5.32. Literature Precedent for 5-Endo-trig Cyclization at Pd\textsuperscript{II}

\[
\begin{array}{c}
\text{OH} \quad \text{OH} \\
\text{Bn} \quad \text{NHTs}
\end{array}
\xrightarrow{5 \text{ mol} \% \text{Pd(MeCN)}_2\text{Cl}_2, 0.1 \text{ equiv TBHP}}
\begin{array}{c}
\text{THF, 25 °C} \\
62\% (82\% \text{ ee})
\end{array}
\xrightarrow{20 \text{ mol} \% \text{Pd(MeCN)}_2\text{Cl}_2}
\begin{array}{c}
\text{THF, 25 °C} \\
55\%
\end{array}
\]

Scheme 5.33. Literature Precedent for Bronsted Acid-Catalyzed Cyclization

\[
\begin{array}{c}
\text{O} \quad \text{OH} \\
\text{Ac}
\end{array}
\xrightarrow{\text{PhI(OAc)}_2, \text{HBF}_4}
\begin{array}{c}
\text{H}_2\text{O}, \text{CH}_3\text{COOH} \\
65\%
\end{array}
\]

In order to distinguish between the two mechanisms, a number of control experiments were executed. First, the reactions were conducted with as PhI(O\text{CCF}_3)\text{C}_2, which is a stronger oxidant and more electrophilic reagent than PhI(O\text{CPh})\text{C}_2. As shown in Scheme 5.34, similar reactivity was observed with PhI(O\text{CCF}_3)\text{C}_2 in the presence and absence of the Pd catalyst. In both cases, the THF product 124 was obtained in 41-54\% yield as an approximately 1:1 ratio of diastereomers.
Secondly, Lewis acids such as BF$_3$•Et$_2$O were screened in the reactions in place of the Pd$^{II}$ catalyst. The desired cyclized products were again observed in the presence of BF$_3$•Et$_2$O, albeit in lower yield (Scheme 5.35). Our results and literature precedent led us to hypothesize that the cyclized products are likely forming through a Lewis acid mechanism and not a Pd$^{II/IV}$ cycle.

5.7 Aminooygenation Cyclization Reactions with 3-Alken1-ols

*Initial Results.* We sought to optimize for the THF ring 62 that had incorporated the nucleophile. Subjection of 3-buten-1-ol and phthalimide to 5 mol % Pd(OAc)$_2$ and 2 equiv Phl(OAc)$_2$ in CH$_3$CN at 60 ºC afforded the aminooygenated THF product 62 in 27% isolated yield. This low yield was due to two major side reactions: (i) the
concomitant formation of tetrahydrofuran 63 discussed above (Scheme 5.23) and (ii) competitive undesired side reactions of the alcohol substrate 59 (Scheme 5.24). Notably, no products resulting from β-hydride elimination were observed, presumably due to the formation of a cyclic intermediate. We thought that using additives that can promote formation of free sites at the metal, might facilitate coordination of the nucleophile and the alcohol to the catalyst. Hence we studied the effect of the addition of 10 mol % of various additives to our reaction. Interestingly, additives containing potentially coordinating counterions such as AgI, ZnCl₂, and AuCl₃ led to decreased reactivity, whilst additives with non-coordinating counterions, such as AgBF₄, AgOTf and SbF₅ significantly improved the yield (Table 5.3). Further optimizations showed that two sequential additions of catalyst, silver salt, oxidant and alcohol further increased the yield of this reaction to 45%.

### Table 5.3: Addition of Additives to the Palladium-Catalyzed Reaction of 3-Butene-1-ol with Phthalimide and Phl(OAc)₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>G.C. Yield (Isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>26% (31%)</td>
</tr>
<tr>
<td>2</td>
<td>AgBF₄</td>
<td>42% (50%)</td>
</tr>
<tr>
<td>3</td>
<td>Ag(OTf)</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>Ag₂SO₄</td>
<td>9%</td>
</tr>
<tr>
<td>5</td>
<td>AgF</td>
<td>32%</td>
</tr>
<tr>
<td>6</td>
<td>Ag(OCOCF₃)</td>
<td>25%</td>
</tr>
<tr>
<td>7</td>
<td>Ag₂CO₃</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>AgOAc</td>
<td>5%</td>
</tr>
<tr>
<td>9</td>
<td>AgI</td>
<td>3%</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)₃</td>
<td>21%</td>
</tr>
<tr>
<td>11</td>
<td>ZnCl₂</td>
<td>6%</td>
</tr>
<tr>
<td>12</td>
<td>SbF₅</td>
<td>40%</td>
</tr>
<tr>
<td>13</td>
<td>Sc(OTf)₃</td>
<td>12%</td>
</tr>
<tr>
<td>14</td>
<td>AuCl₃</td>
<td>12%</td>
</tr>
</tbody>
</table>
**Scope of Aminooxygenation Reactions.** With optimal conditions in hand, the scope of this transformation was next studied. We reasoned that a substituent at the allylic position might accelerate the cyclization due to a Thorpe-like effect. We were delighted to find that substrate 72, bearing a phenyl group in the allylic position, afforded the desired product in 77% yield and 10:1 diastereoselectivity. The stereochemistry was confirmed via NMR analysis and an x-ray crystal structure. Electron donating (Table 5.4, entries 2-4 and 8-9) and electron withdrawing (entries 5-7) substituents as well as halogens were tolerated on the phenyl ring. Tertiary alcohols also afforded the desired products in modest yield (entry 13).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Substituents</th>
<th>Major Product</th>
<th>Product #</th>
<th>Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Ph (72)</td>
<td></td>
<td>126</td>
<td>77% (10:1)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(p\text{-MeOC}_6\text{H}_4) (72a)</td>
<td></td>
<td>127</td>
<td>62% (15:1)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(m\text{-MeOC}_6\text{H}_4) (72b)</td>
<td></td>
<td>128</td>
<td>55% (5:4:1)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(o\text{-MeOC}_6\text{H}_4) (72c)</td>
<td></td>
<td>129</td>
<td>63% (7:8:1)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>(p\text{-CF}_3\text{C}_6\text{H}_4) (72d)</td>
<td></td>
<td>130</td>
<td>54% (&gt;20:1)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>(m\text{-CF}_3\text{C}_6\text{H}_4) (72e)</td>
<td></td>
<td>131</td>
<td>60% (16:1)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>(p\text{-BrC}_6\text{H}_4) (72f)</td>
<td></td>
<td>132</td>
<td>56% (&gt;20:1)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2-naphthyl (72g)</td>
<td></td>
<td>133</td>
<td>80% (12:1)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>mesityl (72h)</td>
<td></td>
<td>134</td>
<td>72% (1.4:1)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>(75)</td>
<td></td>
<td>135</td>
<td>30% (1.4:1)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>R = benzyl (125a)</td>
<td></td>
<td>136</td>
<td>27% (1.5:1)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>R = i-propyl (125b)</td>
<td></td>
<td>137</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>(83)</td>
<td></td>
<td>138</td>
<td>47%</td>
</tr>
</tbody>
</table>

Conditions: 10 mol % Pd(OAc)$_2$, 20 mol % AgBF$_4$, 2.0 equiv Phl(OAc)$_2$, CH$_3$CN, 60 °C

While similar yields of products were obtained with different electronically and sterically substituted aryl rings at the allylic position, the diastereoselectivities were affected by the nature of the allylic substituent. In general, the diastereoselectivities were higher for electron withdrawing substituents in the para-position of the aryl ring and for
less sterically hindered aryl substituents. Interestingly, reduced yields and diastereoselectivities were obtained with substrates bearing non-aromatic substituents such as benzyl, methyl or isopropyl groups at the allylic position (Table 5.4, entries 10-12).

In contrast to the reactivity of substrate 83, the reaction of substituted tertiary alcohols such as 143-145, and 147 resulted in either unreacted starting material, decomposition, or the formation of Heck products. Similar reactivity was observed with substrates 139-141 and 143-144 that contained functionalities with the ability to coordinate to the metal, such as another olefin, a carbonyl, or an oxime ether, creating the possibility of dual chelation. Conformationally constrained substrate 148 also afforded only trace amounts of products under our standard conditions.

**Scheme 5.36.** Alkenol Substrates that Exhibited Low Reactivity

Other nitrogen nucleophiles were also examined in this reaction. However, we were surprised to find that p-toluenesulfonamide, p-nitrophenylsulfonamide, oxazolidinone, pyrrolidinone, and succinimide did not react to form even traces of cyclized products under our optimal reaction conditions.

### 5.8 Mechanistic Investigations of Aminooxygenation Cyclization

With the aforementioned results in hand, we were interested in investigating the mechanism of the aminooxygenation transformation. There are at least six distinct mechanistic possibilities for the Pd-catalyzed formation of the phthalimide substituted tetrahydrofuran rings: (i) SN2 reaction of phthalimide with THF 65 (Scheme 5.37), (ii) iodocyclization to form product 149 followed by subsequent intermolecular SN2 reaction
with phthalimide (Scheme 5.38), (iii) Lewis acid catalyzed cyclization (Scheme 5.39),
(iv) Pd-catalyzed 1,2-aminoacetoxylation of the olefin to form product 150 followed by a
subsequent intramolecular S_N2 reaction (Scheme 5.40), (v) 5-endo-trig oxypalladation to
form intermediate 151 followed by oxidatively induced C–N bond forming reductive
elimination (Scheme 5.41), and (vi) aminopalladation of the olefin followed by oxidative
cyclization and C–O bond formation (Scheme 5.42).

**Scheme 5.37**: Mechanistic Pathway (i)

```
\[ \text{O}_2\text{CR} + \text{HN} \text{O} \xrightarrow{\text{S}_\text{N}2} \text{NPhth} \]
```

**Scheme 5.38**: Mechanistic Pathway (ii)

```
\[ \text{OH} \xrightarrow{\text{Pd(OAc)}_2/\text{Phl(OAc)}_2} \text{NPhth} \]
```

**Scheme 5.39**: Mechanistic Pathway (iii)

```
\[ \text{OH} \xrightarrow{\text{Pd(OAc)}_2/\text{Phl(OAc)}_2} \text{NPhth} \]
```

**Scheme 5.40**: Mechanistic Pathway (iv)

```
\[ \text{OH} \xrightarrow{\text{Pd(OAc)}_2/\text{Phl(OAc)}_2} \text{NPhth} \]
```
In order to examine the viability of the first mechanism, compound 65 was synthesized via the previously discussed cyclization reaction (Scheme 5.24). Subjection of product 65 and phthalimide to the standard reaction conditions (10 mol % Pd(OAc)$_2$, 20 mol % AgBF$_4$, 2 equiv PhI(OAc)$_2$ in CH$_3$CN at 60 °C) did not afford any of the aminooxygenated product 62 (Scheme 5.43). This result suggested strongly that product 62 was not formed by mechanism i.

The viability of mechanism ii was examined by preparing an authentic sample of the iodo-substituted THF 149 (Scheme 5.38). Substrate 72 was chosen instead of 59 due to ease of isolation. Compound 153 was treated under the standard reaction conditions with phthalimide (10 mol % Pd(OAc)$_2$, 20 mol % AgBF$_4$, 2 equiv PhI(OAc)$_2$ in CH$_3$CN at 60 °C), and again, we did not observe the formation of product 126. Based on this result, we conclude that mechanism ii is also not a viable route to 126 under our reaction conditions.
Scheme 5.44. Possible S_N2 Reaction between Phthalimide and Iodide Product 153

![Scheme 5.44](image)

The third possible route to 126 would involve Pd acting as a Lewis acid to promote cyclization. In order to probe for this, we examined the reaction in the absence of palladium catalyst and in the presence of BF_3•Et_2O. Substrate 72 was subjected to 10 mol % BF_3•Et_2O with 2 equiv PhI(OAc)_2 in CH_3CN at 60 °C, and as shown in Scheme 5.45, product 126 was again not observed in this control reaction.

Scheme 5.45: Attempt to Obtain Aminooxygenation Product 126 with Catalytic BF_3•Et_2O

![Scheme 5.45](image)

In order to determine if mechanism iv was occurring, we synthesized 154 by subjecting benzyl-protected 3-butenol and phthalimide to our reaction conditions followed by DDQ deprotection (Scheme 5.46). Subjection of 61 to the reaction conditions (10 mol % Pd(OAc)_2, 20 mol % AgBF_4, 2 equiv PhI(OAc)_2 in CH_3CN at 60 °C) did not afford even traces of product 62. This result suggested that mechanism iv was not operational.
**Scheme 5.46. S_N2 Reaction of Aminoacetoxyalted Intermediate 61**

![Diagram](image)

If the reaction were proceeding via 5-endo trig cyclization (mechanism v), then we would expect that conducting the reaction of 4-phenyl-1-butanol and phthalimide in the presence of oxygen instead of PhI(OAc)_2 would form product 157 or its isomers, resulting from β-hydride elimination from intermediate 156 (Scheme 5.47). As seen earlier in examples by Stahl and co-workers (Scheme 5.4) in the absence of a strong oxidant that can intercept the Pd^{II} intermediate, β-hydride elimination is the most favorable pathway. Hence, substrate 155 and phthalimide were subjected to 5 mol % Pd(OAc)_2, 10 mol % AgBF_4 in CH_3CN at 60 °C under 1 atm of O_2. However, this reaction did not provide even traces of 157 or its isomers, suggesting against mechanism v.

**Scheme 5.47. Subjection of 4-Phenyl-3-buten-1-ol to Reaction Conditions with O_2 as the Terminal Oxidant**

![Diagram](image)

With these results in hand, we surmised that the formation of product 62 was catalyzed by palladium through the Pd^{II/IV} amination/oxidation pathway vi. As shown in Scheme 5.48, we envisioned four different pathways for the desired aminooxygenation reactions. The first step of the reaction might involve cis- or trans-aminopalladation. Upon aminopalladation, the reaction could then proceed via two different routes: (i) oxidation to Pd^{IV} followed by reductive elimination via an S_N2 pathway leading to
inversion of configuration at carbon or (ii) chelation of the tethered alcohol to the palladium followed by oxidation to Pd\textsuperscript{IV} and then direct reductive elimination with retention of stereochemistry. Importantly, in the latter case, chelation/oxidation could occur in the opposite order. As mentioned in the background section, both \textit{cis} and \textit{trans} aminopalladation have been observed previously\textsuperscript{9, 13, 15, 16, 23}. Additionally, reductive elimination at Pd\textsuperscript{IV} has been shown to occur with either retention or inversion of stereochemistry at carbon, depending on the substrate and the reaction conditions.

**Scheme 5.48.** Mechanism vi: Aminopalladation Followed by Oxidatively Induced Cyclization

In order to distinguish between these four mechanistic possibilities, the deuterium labelled substrate 157 was synthesized (Scheme 5.49). Subjection of substrate 157 and phthalimide to our reaction conditions afforded the aminoacetoxylated product 158 along with product 159, resulting from β-hydride elimination. The deuterium had scrambled in products 158 and 159. We speculated that the deuterium scrambling in the products might be due to the isomerization of the olefin in the starting material, rather than an inherent lack of stereospecificity of the reaction. Indeed, this hypothesis was confirmed when 157 was subjected to our reaction in the absence of phthalimide and PhI(OAc)\textsubscript{2}. This reaction provided a 1:1 mixture of the \textit{cis} and \textit{trans} isomers of 157.
Because the deuterium-labelled substrate 157 did not provide the desired mechanistic information, we next explored the reactivity of trans- and cis-4-phenylbutenol, 155, with phthalimide, 10 mol % Pd(OAc)$_2$, 20 mol % AgBF$_4$, and 2 equiv PhI(OAc)$_2$ in CH$_3$CN at 60 ºC. In this case, the cis substrate 155 afforded a single diastereomeric product (160) that had a trans relationship between the phenyl ring and the phthalimide (Scheme 5.50). The stereochemistry was confirmed via NMR analysis and an x-ray crystal structure. In contrast, the trans substrate did not afford any of the desired aminooxygenated product under our reaction conditions. This result shows that even if isomerization between cis and trans phenyl butenols occurred under our reaction conditions, only the cis-isomer reacts to form the product. The trans relationship between the phenyl ring and the phthalimide in product 160 led us to believe that either mechanistic pathway a or d (Scheme 5.48) was operational in these reactions.

In order to distinguish between mechanisms a and d, we needed to determine the mechanism of aminopalladation. A prior study by Stahl suggested that the geometry of β-hydride elimination products from Pd$^{II}$ intermediate A or D would provide this information.$^{16}$ As shown in Scheme 5.51, if cis-aminopalladation were operational, then Pd$^{II}$ intermediate 151 would have to undergo σ-bond rotation to achieve the required syn relationship between the Pd and the β-hydrogen to achieve β-hydride elimination. As
such, this reaction would afford the Z-substituted olefin 163 (Scheme 5.51). In contrast, the Pd\textsuperscript{II} product of trans-aminopalladation can undergo direct β-hydride elimination, leading to the E-substituted olefin 165.

**Scheme 5.51: Rationale for Outcome from β-Hydride Elimination**

Subjection of substrate 155 to our optimized reaction conditions in the presence of O\textsubscript{2} instead of PhI(OAc)\textsubscript{2} (to promote termination of the reaction via β-hydride elimination) afforded the β-hydride elimination product 163, albeit in low 3% yield (Scheme 5.52). This result suggests that our reaction goes through a cis-aminopalladation pathway. The low yield in this reaction is due to competitive olefin isomerization of the starting material, which yields the unreactive trans isomer. Interestingly, when the reaction shown in Scheme 5.52, was conducted in the absence of AgBF\textsubscript{4}, we obtained 4% yield of a 1:1 ratio of Z and E substituted β-hydride elimination products (Scheme 5.52), suggesting that cis and trans aminopalladation are competitive under these conditions. Importantly, control experiments showed that neither product 163 nor product 165 isomerized under either set of reaction conditions.
Analyzing all the mechanistic data allowed us to conclude that mechanistic pathway a is governing the reaction (Scheme 5.48). It is notable that during reductive elimination from Pd\textsuperscript{IV}, there exists a choice for either reductive elimination of the acetate, to form aminoacetoxylated product 168, or the alkoxide to form the THF ring 160 (Scheme 5.53). As discussed above, we obtain the THF ring product exclusively. Notably, C–OAc reductive elimination at Pd\textsuperscript{IV} is certainly possible, as it was observed in the C–H activation/acetoxylation reactions. We believe the preference for reductive elimination of the alkoxide over the acetate in the current systems can be attributed to the greater nucleophilicity of the alkoxide as discussed in chapter 2.24

As discussed above, we observe reductive elimination with retention at the carbon. This is in sharp contrast to what was reported by Muniz (Scheme 5.12)\textsuperscript{15} and Stahl (Scheme 5.13)\textsuperscript{16} for related aminopalladation/oxidation reactions. However, other reports have suggested that reductive elimination from high oxidation state Pd complexes can occur with retention at carbon.\textsuperscript{25, 26} We believe that pre-coordination of the alkoxide is a likely reason for reductive elimination occurring with retention in our system.
**Origin of Diastereoselectivity.** We next sought to rationalize the observed diastereoselectivity and the role of silver in the aminoxxygenation reaction. Silver is known to facilitate the dissociation of acetate from group 10 metal centers through coordination.\textsuperscript{27} Based on the results from Scheme 5.52 and Table 5.3, we propose that silver reacts to produce a vacant coordination site on the palladium by promoting dissociation of an acetate ligand. This vacant coordination site allows the palladium to bind to the phthalimide nucleophile, facilitating *cis*-aminopalladation.

Substrates \textbf{169} and \textbf{170}, where the alcohol had been replaced with a carbon, were chosen to elucidate the origin of diastereoselectivity. Subjection of substrate \textbf{170} to our reaction conditions did not lead to any observable reactivity (Scheme 5.54). This was in contrast to substrate \textbf{75}, which yielded 30\% of product \textbf{135}. Substrate \textbf{169} underwent amioacetoxylation to afford product \textbf{172} in 4 : 1 diastereoselectivity along with the β-hydride elimination product \textbf{171} (Scheme 5.54). The diastereoselectivity observed with substrate \textbf{72} is significantly greater than the dr observed with substrate \textbf{169}. This implies that there exists some interaction between the palladium and the alcohol in the transition state for aminopalladation.
These results can be rationalized based on the proposed transition state in Figure 5.3. Here the palladium is interacting with the nitrogen of the nucleophile, the tethered alcohol, and the olefin in a cyclic transition state. In order to avoid unfavorable steric interactions with the coordinated phthalimide, the allylic substituent assumes a pseudo-equatorial position, resulting in a trans delivery of the phthalimide. However, this transition state does not completely explain the observed steric and electronic effects on the diastereoselectivity, particularly with the methyl, benzyl, and mesityl substituted substrates 75, 125a, and 72h. It is possible that alternative and/or competing transition states are accessed in these systems.
5.9 Conclusion

In summary, palladium alkyl intermediates generated via nucleopalladation were intercepted to form carbon-oxygen bonds. Aminopalladation reactions, using nucleophiles such as phthalimide, \( p \)-toluenesulfonamide, and \( p \)-nitrophenylsulfonamide and olefins such as octene and norbornene were explored to form 1,2-aminoacetoxylated products. These products were obtained in low yields due to competitive undesired \( \beta \)-hydride elimination. This undesired pathway was attenuated by tethering chelating functionalities, such as alcohols, amines and acids, to the olefin. Reaction of the tethered olefin in the absence of amine nucleophiles led to formation of acetate substituted cyclic compounds. We propose that these cyclization reactions occur via a Lewis acid catalyzed mechanism to form the tetrahydrofuran, pyrrolidinone, or lactone products, respectively. Reaction of the alkenols in the presence nucleophiles such as phthalimide afforded phthalimide-substituted THF rings. Mechanistic experiments have shown that this aminooxygenated compound is formed by \( cis \)-aminopalladation followed by oxidative cleavage with \( \text{PhI(OAc)}_2 \) to afford the final product with retention of stereochemistry at the carbon.

5.10 Experimental Procedure

**General Procedures:** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for \( ^1\text{H} \); 125.70 MHz for \( ^{13}\text{C} \)) unless otherwise noted. \( ^{19}\text{F} \) NMR spectra were obtained on Varian Inova 300 (282 MHz for \( ^{19}\text{F} \)). \( ^1\text{H} \) NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), broad singlet (br, s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer.

**Materials and Methods:** Alcohol substrates 77, 72, 72a-72h, and 155 were prepared according to literature procedures. Substrate 125a was synthesized by alkylation
of 3-butenoic acid with benzyl bromide followed by LiAlH₄ reduction of the acid to afford the alcohol. PhI(O₂CPh)₂ was prepared according to a literature procedure. Pd(OAc)₂ was obtained from Pressure Chemical and used as received, and PhI(OAc)₂ was obtained from Merck Research Laboratories and used as received. Solvents were obtained from Fisher Chemical. Acetonitrile was freshly distilled from calcium hydride under a nitrogen atmosphere. Dichloromethane, tetrahydrofuran, and diethyl ether were purified using a Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalysts and molecular sieves. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh), and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254. HPLC was performed on a Varian Prostar 210 HPLC using Waters µPorasil® 10 µm silica (19 x 300 mm) columns. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. HRMS data were obtained on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. The geometries of the diastereomeric tetrahydrofuran products were determined based on ¹H NMR nOe studies (substrates 5a-14a) and by X-ray crystallography (3a and 4a).

**Typical Procedure for Olefin reaction with Nucleophile:** Phthalimide (100 mg, 0.68 mmol, 1 equiv), PhI(OAc)₂ (0.440 g, 1.36 mmol, 2 equiv), and Pd(OAc)₂ (8 mg, 0.034 mmol, 0.05 equiv) were combined in CH₂Cl₂ (1.4 mL) in a 20 mL vial. Octene (98 mg, 1.36 mmol, 2.0 equiv) was added to the reaction, the vial was sealed with a Teflon-lined cap, and the reaction was heated at 60 °C for 12 h. The reaction mixture was evaporated to dryness and then taken up in diethyl ether (10 mL). The ether layer was washed with 10% aqueous Et₃N (10 mL), H₂O (2 x 20 mL), saturated aqueous NaHCO₃ (20 mL), and saturated aqueous NaCl (20 mL). The ether extracts were dried over MgSO₄, filtered, and concentrated to afford a red oil, which was purified by chromatography on silica gel.
Product 38 was obtained as a yellow oil (18%). $^1$H NMR (CDCl$_3$): $\delta$ 7.75 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 4.77 (m, 1H), 3.97 (dd, $J = 10.8$, 5.2 Hz, 1H), 3.89 (dd, $J = 10.8$, 3.6 Hz, 1H), 2.42 (s, 3H), 1.94 (s, 3H), 1.47-1.13 (multiple peaks, 8H), 0.84 (t, $J = 6.8$ Hz, 3H).

Product 41 was obtained as a yellow oil (25%). $^1$H NMR (CDCl$_3$): $\delta$ 8.34 (d, $J = 7.2$ Hz, 2H), 8.07 (d, $J = 7.2$ Hz, 2H), 3.99 (dd, $J = 9.2$, 4.0 Hz, 1H), 3.95 (dd, $J = 9.2$, 4.0 Hz, 1H), 3.56 (m, 1H), 1.94 (s, 3H), 1.47-1.13 (multiple peaks, 8H), 0.84 (t, $J = 5.6$ Hz, 3H).

Product 43 was obtained as a yellow oil (38%). $^1$H NMR (CDCl$_3$): $\delta$ 7.74 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 5.11 (d, $J = 9.0$ Hz, 1H), 4.68 (d, $J = 7.5$ Hz, 1H), 3.37 (d, $J = 8.5$ Hz, 1H), 2.42 (s, 3H), 2.10 (m, 1H), 2.04 (s, 3H), 1.98 (d, $J = 4.5$ Hz, 1H), 1.84 (dd, $J = 14.5$, 8.0 Hz, 1H), 1.65 (m, 1H), 1.58-1.46 (multiple peaks, 2H), 1.04 (m, 1H).
Product 45 was obtained as a yellow oil (29%). $^1$H NMR (CDCl$_3$): δ 4.72, (br s, 1H), 4.62 (br s, 1H), 2.48 (m, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 2.04 (s, 3H), 1.94 (s, 3H), 1.94 (m, 1H), 1.70 (m, 1H), 1.59 (m, 1H), 1.21 (m, 1H), 1.13 (m, 1H).

Product 46 was obtained as a yellow oil (42%). $^1$H NMR (CDCl$_3$): δ 7.81 (m, 2H), 7.69 (m, 2H), 4.73 (d, $J = 8.0$ Hz, 1H), 3.59-3.57 (multiple peaks, 2H), 3.47 (d, $J = 4.5$ Hz, 1H), 1.92 (dd, $J = 14.0$, 7.0, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.64 (m, 1H), 1.54 (s, 3H), 1.24 (m, 2H).

Product 47 was obtained as a yellow oil (47%). $^1$H NMR (CDCl$_3$): δ 7.67 (d, $J = 8.0$ Hz, 1H), 7.54-7.51 (multiple peaks, 2H), 7.43 (m, 1H), 4.88 (d, $J = 11.0$ Hz, 1H), 4.75 (d, $J = 11.0$ Hz, 1H), 4.15 (d, $J = 6.4$ Hz, 1H), 4.09 (br s, 1H), 2.95 (br s, 1H), 2.87 (d, $J = 5.2$ Hz, 1H), 1.79 (m, 1H), 1.53 (m, 1H), 1.45 (m, 1H), 1.18-1.10 (multiple peaks, 2H). $^{13}$C {$^1$H} NMR (CDCl$_3$): δ 169.28, 145.79, 132.98, 130.24, 129.77, 128.29, 123.72, 122.38, 85.46, 82.50, 78.97, 59.35, 38.58, 38.08, 37.40, 25.24, 21.36. IR (thin film): 1711, 1552, 1377 cm$^{-1}$. HRMS electrospay (m/z): [M + H]$^+$ calcd for C$_{16}$H$_{16}$N$_2$O$_4$, 301.1188; found, 301.1188.
Product 48 was obtained as a yellow oil (14%). $^1$H NMR (CDCl$_3$): $\delta$ 7.79-7.76 (multiple peaks, 2H), 7.61 (t, $J = 7.0$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 5.23 (q, $J = 6.5$ Hz, 1H), 4.22 (d, $J = 6.5$ Hz, 1H), 4.13 (br s, 1H), 3.11 (d, $J = 4.5$ Hz, 1H), 3.00 (br s, 1H), 1.84 (m, 1H), 1.61 (m, 1H), 1.51 (dd, $J = 14.0$, 6.5 Hz, 1H), 1.32-1.20 (multiple peaks, 2H), 1.04 (d, $J = 6.5$ Hz, 3H). $^{13}$C (1H) NMR (CDCl$_3$): $\delta$ 169.77, 144.15, 133.69, 132.67, 130.33, 129.98, 124.11, 123.45, 122.85, 89.00, 87.91, 78.52, 59.50, 38.69, 37.83, 37.48, 25.19, 21.36, 15.12. IR (thin film): 1711, 1552, 1377 cm$^{-1}$. HRMS (ESI, m/z): [M + H]$^+$ calcd for C$_{16}$H$_{16}$N$_2$O$_4$, 301.1188; found, 301.1188.

**Typical Procedure for Alcohol cyclization:** Phl(O$_2$CPh)$_2$ (90 mg, 2.77 mmol, 2.0 equiv) and Pd(OAc)$_2$ (15 mg, 0.069 mmol, 0.05 equiv) were combined in CH$_3$CN (2.8 mL) in a 20 mL vial. 3-Buten-1-ol (100 g, 1.39 mmol, 1.0 equiv) was added, the vial was sealed with a Teflon-lined cap, and the reaction was stirred at 60 °C for 18 h. The resulting mixture was evaporated to dryness and then taken up in diethyl ether (10 mL). The ether layer was washed with H$_2$O (2 x 20 mL), saturated aqueous NaHCO$_3$ (10 mL), and saturated aqueous NaCl (10 mL). The ether layer was then dried over MgSO$_4$, filtered, and concentrated to afford a red oil, which was purified by chromatography on silica gel ($R_f = 0.28$ in 70% hexanes/30% ethyl acetate).

The product 65 was obtained as a clear oil (113 mg, 42% yield). $^1$H NMR (CDCl$_3$): $\delta$ 8.03 (d, $J = 8.4$ Hz, 2H), 7.56 (m, 1H), 7.43 (t, $J = 7.9$ Hz, 2H), 5.54 (m, 1H), 4.00-3.88 (multiple peaks, 4H), 2.26 (m, 1H), 2.15 (m, 1H). $^{13}$C (1H) NMR (CDCl$_3$): $\delta$ 166.24,
133.07, 129.92, 129.56, 128.32, 75.34, 73.15, 67.09, 32.89. IR (thin film): 1717 cm\(^{-1}\). HRMS (ESI, m/z): [M + H]\(^+\) calced for C\(_{11}\)H\(_{12}\)O\(_3\), 193.0865; found, 193.0865.

The product 68 was obtained as a clear oil (10% yield). \(^1\)H NMR (CDCl\(_3\)): δ 8.06-8.03 (multiple peaks, 2H), 7.58 (m, 1H), 7.46-7.42 (multiple peaks, 2H), 4.36 (t, \(J = 6.8\) Hz, 2H), 4.05-3.86 (multiple peaks, 3H), 1.92 (m, 2H).

The product 73 was obtained as a clear oil (35%, 2:1 dr). \(^1\)H NMR (CDCl\(_3\)): δ 7.35-7.28 (multiple peaks, 5H), 5.19 (quin, \(J = 2.5\) Hz, 1H), 4.28 (dd, \(J = 9.0, 7.0\) Hz, 1H), 4.17 (dd, \(J = 10.5, 5.0\) Hz, 1H), 3.96 (dd, \(J = 9.0, 5.0\) Hz, 1H), 3.89 (dd, 10.5, 2.0 Hz, 1H), 3.47 (m, 1H), 2.10 (s, 3H). \(^13\)C \({}^1\)H NMR (CDCl\(_3\)): δ 170.73, 168.30, 128.82, 127.40, 127.11, 81.37, 73.08, 72.76, 51.18, 29.60. HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{17}\)H\(_{16}\)O\(_3\), 229.0841; found, 229.0839.

The product 74 was obtained as a clear oil (23%). \(^1\)H NMR (CDCl\(_3\)): δ 7.37-7.25 (multiple peaks, 5H), 4.45 (m, 2H), 3.21 (m, 1H), 2.76 (m, 2H), 2.56 (dd, \(J = 4.5, 3.0\) Hz, 1H), 2.04 (s, 3H). \(^13\)C \({}^1\)H NMR (CDCl\(_3\)): δ 170.90, 137.89, 128.72, 127.94, 127.45, 65.46, 53.31, 47.64, 46.03, 20.85. IR (thin film): 1740 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{17}\)H\(_{16}\)O\(_3\), 229.0841; found, 229.0838.
The product 76 was obtained as a clear oil (22%, 1.4:1 dr). $^1$H NMR (CDCl$_3$): $\delta$ 8.05 (m, 2H), 7.57 (m, 1H), 7.44(m, 2H), 5.15 (m, 1H), 4.19-4.15 (multiple peaks, 2H), 3.98 (d, $J = 13.0$ Hz, 1H), 3.55 (dd, $J = 8.5$, 4.5 Hz, 1H), 1.18 (d, $J = 6.5$ Hz, 3H).

The product 78 was obtained as a clear oil (30%, 1:1 dr). $^1$H NMR (CDCl$_3$): $\delta$ 7.99 (d, $J = 8.5$ Hz, 2H), 7.86 (d, $J = 8.5$ Hz, 2H), 7.55-7.42 (multiple peaks, 5H), 5.41 (m, 1H), 4.35 (dd, $J = 9.5$, 6.0 Hz, 1H), 4.29 (dd, $J = 11.0$, 5.0 Hz, 1H), 4.08-4.05 (multiple peaks, 2H), 3.60 (m, 1H).

The product 78* was obtained as a viscous oil (10%). $^1$H NMR (CDCl$_3$): $\delta$ 8.13 (d, $J = 7.0$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H), 7.50-7.41 (multiple peaks, 3H), 7.22 (d, $J = 8.0$ Hz, 2H), 4.66 (d, $J = 6.5$ Hz, 2H), 3.28 (m, 1H), 2.93 (q, $J = 7.0$ Hz, 1H), 2.81 (t, $J = 4.5$ Hz, 1H), 2.61 (dd, $J = 4.5$, 3.0 Hz, 1H).
Mixture of cis and trans Isomers in a 1.0:1.8 ratio. $^1$H NMR (CDCl$_3$): $\delta$ 8.08-8.04 (multiple peaks, 4H), 7.68-7.27 (multiple peaks, 2H), 7.48-7.43 (multiple peaks, 4H), 5.50 (m, 1H), 5.37 (m, 1H), 4.42-4.39 (multiple peaks, 2H), 4.10-4.04 (multiple peaks, 4H), 1.78-1.71 (multiple peaks, 2H), 1.66-1.62 (multiple peaks, 2H), 1.39 (d, $J = 86.5$ Hz, 3H), 1.23 (d, $J = 6.0$ Hz, 3H).

Product 82 was obtained as a yellow oil (37%, 2:1 dr). **Isomer 1**: $^1$H NMR (CDCl$_3$): $\delta$ 7.49-7.43 (multiple peaks, 5H), 7.45-7.38 (multiple peaks, 2H), 7.29-7.25 (multiple peaks, 3H), 5.64 (m, 1H), 4.43 (dd, $J = 10.5$, 5.5 Hz, 1H), 4.08 (dd, $J = 10.5$, 0.5 Hz, 1H), 2.68 (d, $J = 14.0$, 1H), 2.41 (dd, $J = 14.0$, 5.5 Hz, 1H), 1.63 (s, 3H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$ 165.96, 147.25, 132.84, 129.75, 129.45, 128.04, 126.29, 124.69, 84.74, 75.92, 72.77, 45.83, 30.23, 29.68. **Isomer 2**: $^1$H NMR (CDCl$_3$): $\delta$ 8.10 (dd, $J = 8.0$, 1.0 Hz, 2H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 2H), 7.44 (dd, $J = 8.5$, 1.0 Hz, 2H), 7.38 (t, $J = 8.0$ Hz, 2H), 7.27 (t, $J = 7.5$ Hz, 1H), 5.51 (m, 1H), 4.22 (d, $J = 11.0$ Hz, 1H), 4.15 (dd, $J = 11.0$, 5.0 Hz, 1H), 2.75 (dd, $J = 14.0$, 7.0 Hz, 1H), 2.45 (dd, $J = 14.0$, 2.5 Hz, 1H), 1.71 (s, 3H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$ 166.25, 147.25, 133.16, 129.99, 129.63, 128.43, 128.39, 126.76, 124.45, 84.52, 72.29, 45.69, 30.63, 29.70.
Product 83 was obtained as a yellow oil (40%). $^1$H NMR (CDCl$_3$): $\delta$ 7.97 (d, $J = 8.0$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 2H), 5.54 (m, 1H), 4.19 (dd, $J = 11.0$, 5.0 Hz, 1H), 4.03 (d, $J = 11$ Hz, 1H), 2.18 (dd, $J = 14.0$, 7.0, 1H), 2.04 (d, $J = 14.0$ Hz, 1H), 1.72 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H).

Product 86 was obtained as a yellow oil (29%, 2:1 dr). **Cis Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.90 (dd, $J = 7.5$, 1.6 Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.44-7.30 (multiple peaks, 7H), 5.63 (m, 1H), 5.02 (t, $J = 8.0$ Hz, 1H), 4.30 (d, $J = 11.0$ Hz, 1H), 4.11 (dd, $J = 11.0$, 5.0 Hz, 1H), 2.84 (m, 1H), 2.18 (m, 1H). **Trans Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.39-7.29 (multiple peaks, 10H), 5.62 (t, $J = 6.0$ Hz, 1H), 5.11 (dd, $J = 10.5$, 5.0 Hz, 1H), 4.44 (dd, $J = 11.0$, 5.0 Hz, 1H), 4.04 (dd, $J = 11.0$, 2.0 Hz, 1H), 2.54 (dd, $J = 14.5$, 6.0 Hz, 1H), 2.17 (m, 1H).

Product 124 was obtained as a yellow oil (29%, 2:1 dr). **Trans Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.39-7.29 (multiple peaks, 5H), 5.62 (t, $J = 5.0$ Hz, 1H), 5.11 (dd, $J = 10.0$, 5.0 Hz, 1H), 4.44 (dd, $J = 11.5$, 5.0 Hz, 1H), 4.05 (dd, $J = 11.5$, 3.0 Hz, 1H), 2.54 (dd, $J = 14.0$, 5.5 Hz, 1H), 2.17 (dd, $J = 14.0$, 10.0, 5.5 Hz, 1H). **Cis Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 7.38-7.31 (multiple peaks, 5H), 5.56 (m, 1H), 4.93 (t, $J = 9.0$ Hz, 1H), 4.29 (d, $J = 14.0$ Hz, 1H), 4.01 (dd, $J = 14.0$, 6.0 Hz, 1H), 2.86 (quin, $J = 9.0$ Hz, 1H), 2.08 (m, 1H).

**Typical Procedure for Amine cyclization:** PhI(O$_2$CH$_3$)$_2$ (90 mg, 2.77 mmol, 2.0 equiv), NaHCO$_3$ (90 mg, 2.77 mmol, 2.0 equiv) and Pd(OAc)$_2$ (15 mg, 0.069 mmol, 0.05 equiv) were combined in CH$_3$CN (2.8 mL) in a 20 mL vial. Amine (1.0 equiv) was
added, the vial was sealed with a Teflon-lined cap, and the reaction was stirred at 60 °C for 18 h. The resulting mixture was evaporated to dryness and then taken up in diethyl ether (10 mL). The ether layer was washed with H₂O (2 x 20 mL), saturated aqueous NaHCO₃ (10 mL), and saturated aqueous NaCl (10 mL). The ether layer was then dried over MgSO₄, filtered, and concentrated to afford a red oil, which was purified by chromatography on silica gel (Rf = 0.28 in 70% hexanes/30% ethyl acetate).

Product **88** was obtained as a yellow oil (20%). ¹H NMR (CDCl₃): δ 8.40 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 5.17 (m, 1H), 3.57 (q, J = 4.8 Hz, 1H), 3.52 (d, J = 4.8 Hz, 1H), 3.43-3.32 (multiple peaks, 2H), 2.04 (m, 2H), 1.83 (s, 3H).

Product **91** was obtained as a yellow oil (19%). ¹H NMR (CDCl₃): δ 7.72 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.10 (m, 1H), 3.53 (dd, J = 8.8, 5.0 Hz, 1H), 3.46 (dd, J = 12.0, 5.0 Hz, 1H), 3.42 (m, 1H), 4.31 (m, 1H), 2.42 (s, 3H), 1.95-1.93 (multiple peaks, 2H), 1.80 (s, 3H).

**Typical Procedure for Acid cyclization:** PhI(O₂CPh)₂ (90 mg, 2.77 mmol, 2.0 equiv), NaHCO₃ (90 mg, 2.77 mmol, 2.0 equiv) and Pd(OAc)₂ (15 mg, 0.069 mmol, 0.05 equiv) were combined in CH₂Cl₂ (2.8 mL) in a 20 mL vial. 3-Butenoic Acid (100 g, 1.39 mmol, 1.0 equiv) was added, the vial was sealed with a Teflon-lined cap, and the reaction was stirred at 60 °C for 18 h. The resulting mixture was evaporated to dryness and then taken up in diethyl ether (10 mL). The ether layer was washed with H₂O (2 x 20 mL), saturated aqueous NaHCO₃ (10 mL), and saturated aqueous NaCl (10 mL). The ether layer was then dried over MgSO₄, filtered, and concentrated to afford a red oil, which
was purified by chromatography on silica gel ($R_f = 0.28$ in 70% hexanes/30% ethyl acetate).

Product 100 was obtained as a yellow oil (56%). $^1$H NMR (CDCl$_3$): $\delta$ 8.03 (d, $J = 8.0$ Hz, 2H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 4.63 (dd, $J = 11.1$, 4.8 Hz, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 3.00 (dd, $J = 18.5$, 6.7 Hz, 1H), 2.81 (d, $J = 18.5$ Hz, 1H).

Product 102 was obtained as a yellow oil (65%, 1:1 dr). **Cis Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 8.03 (d, $J = 7.5$ Hz, 2H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 5.76 (m, 1H), 4.51 (dd, $J = 11.0$, 4.5 Hz, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 2.91 (quin, $J = 7.5$ Hz, 1H), 1.34 (d, $J = 7.5$ Hz, 3H). **Trans Isomer:** $^1$H NMR (CDCl$_3$): $\delta$ 8.04 (d, $J = 7.0$ Hz, 2H), 7.61 (t, $J = 7.0$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 5.32 (m, 1H), 4.70 (dd, $J = 11.0$, 5.5 Hz, 1H), 4.35 (dd, $J = 11.0$, 3.5 Hz, 1H), 2.91 (m, 1H), 1.44 (d, $J = 7.0$ Hz, 3H).

Product 104 was obtained as a yellow oil (60%). $^1$H NMR (CDCl$_3$): $\delta$ 8.03 (dd, $J = 8.0$, 1.5 Hz, 2H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.46 (t, $J = 8.0$ Hz, 2H), 4.88 (m, 1H), 4.54 (dd, $J = 12.0$, 3.0 Hz, 1H), 4.44 (dd, $J = 12.0$, 5.0 Hz, 1H), 2.69-2.56 (multiple peaks, 2H), 2.43 (m, 1H), 2.14 (m, 1H). IR (thin film): 1776, 1722 cm$^{-1}$.
Product 106 was obtained as a yellow oil (66%). $^1$H NMR (CDCl$_3$): $\delta$ 8.05 (dd, $J = 8.1$, 1.2 Hz, 2H), 7.59 (t, $J = 8.1$ Hz, 1H), 7.46 (t, $J = 8.1$ Hz, 2H), 4.79 (m, 1H), 4.57 (dd, $J = 12.0$, 3.3 Hz, 1H), 4.37 (dd, $J = 12.0$, 6.3 Hz, 1H), 2.22 (dd, $J = 12.9$, 6.3 Hz, 1H), 1.95 (dd, $J = 12.9$, 9.9 Hz, 1H), 1.33 (s, 3H), 1.31 (s, 3H).

Product 108 was obtained as a yellow oil (65%, 13:1 dr). $^1$H NMR (CDCl$_3$): $\delta$ 8.03 (d, $J = 7.5$ Hz, 2H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 2H), 5.37 (dt, $J = 7.5$, 2.0 Hz, 1H), 4.58 (td, $J = 7.0$, 2.0 Hz, 1H), 3.04 (dd, $J = 20.0$, 7.5 Hz, 1H), 2.72 (dd, $J = 20.0$, 2.0 Hz, 1H), 1.88-1.71 (multiple peaks, 2H), 1.10 (t, $J = 7.0$ Hz, 3H).

Product 110 was obtained as a yellow oil (56%, 9:1 dr). $^1$H NMR (CDCl$_3$): $\delta$ 8.02 (dd, $J = 8.0$, 1.5 Hz, 2H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.50-7.46 (multiple peaks, 2H), 5.74 (t, $J = 5.0$ Hz, 1H), 4.57 (m, 1H), 3.02 (dd, $J = 8.5$, 5.5 Hz, 1H), 2.73 (d, $J = 18.5$ Hz, 1H), 1.95 (septet, $J = 7.0$ Hz, 1H), 1.80 (m, 1H), 1.06 (t, $J = 7.0$ Hz, 3H).
Product 112 was obtained as a yellow oil (48%, >50:1 dr). $^1$H NMR (CDCl$_3$): $\delta$ 8.08 (dd, $J = 8.4$, 1.6 Hz, 2H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.52-7.38 (multiple peaks, 8H), 5.75 (br s, 1H), 5.54 (dt, $J = 6.4$, 1.5 Hz, 1H), 3.01 (dd, $J = 18.4$, 6.4 Hz, 1H), 2.78 (dd, $J = 18.4$, 1.5, 1H).

Typical Procedure for Formation of Amino-Tetrahydrofurans: Phthalimide (100 mg, 0.68 mmol, 1 equiv), PhI(OAc)$_2$ (0.440 g, 1.36 mmol, 2 equiv), AgBF$_4$ (13 mg, 0.068 mmol, 0.10 equiv), and Pd(OAc)$_2$ (8 mg, 0.034 mmol, 0.05 equiv) were combined in CH$_3$CN (1.4 mL) in a 20 mL vial. 3-Buten-1-ol (98 mg, 1.36 mmol, 2.0 equiv) was added to the reaction, the vial was sealed with a Teflon-lined cap, and the reaction was heated at 60 ºC for 1 h. The reaction was cooled to room temperature and additional PhI(OAc)$_2$ (0.22 g, 0.68 mmol, 1.0 equiv) along with a solution of Pd(OAc)$_2$ (8 mg, 0.034 mmol, 0.05 equiv) and AgBF$_4$ (13 mg, 0.068 mmol, 0.10 equiv) in CH$_3$CN (0.4 mL) was added to the reaction. Another equivalent of the alcohol (49 mg, 0.68 mmol) was also added, and the reaction was heated at 60 ºC for an additional 8 h. The resulting mixture was evaporated to dryness and then taken up in diethyl ether (10 mL). The ether layer washed with 10% aqueous Et$_3$N (10 mL), H$_2$O (2 x 20 mL), saturated aqueous NaHCO$_3$ (20 mL), and saturated aqueous NaCl (20 mL). The ether extracts were dried over MgSO$_4$, filtered, and concentrated to afford a red oil, which was purified by chromatography on silica gel.

Product 61 was obtained as a yellow viscous oil ($R_f = 0.22$ in 50% hexanes/50% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.85 (dd, $J = 5.6$, 3.1 Hz, 2H), 7.74 (dd, $J = 5.3$, 3.1 Hz,
2H), 4.70 (m, 1H), 4.59 (dd, $J = 11.2, 9.3$ Hz, 1H), 4.46 (dd, $J = 11.2, 4.9$ Hz, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 2.26 (m, 1H), 2.03 (m, 1H), 1.98 (s, 3H), 1.74 (br s, 1H). $^{13}$C $^{1}$H NMR (CDCl$_3$): $\delta$ 170.63, 168.61, 134.16, 131.67, 123.39, 63.51, 59.12, 47.77, 31.42, 20.74.

The second addition of catalyst, oxidant, and alcohol was after 1 h. Product 62 was isolated as a white solid (66 mg, 45% yield, $R_f = 0.10$ in 70% hexanes/30% ethyl acetate). mp = 81.4-84.6 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.83 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.71 (dd, $J = 5.4, 3.1$ Hz, 2H), 4.91 (m, 1H), 4.22 (q, $J = 8.4$ Hz, 1H), 4.04 (t, $J = 8.7$ Hz, 1H), 3.98 (td, $J = 8.4, 5.2$ Hz, 1H), 3.91 (dd, $J = 8.8, 6.9$ Hz, 1H), 2.39 (m, 1H), 2.25 (m, 1H). $^{13}$C $^{1}$H NMR (CDCl$_3$): $\delta$ 167.99, 134.05, 131.77, 123.21, 69.40, 68.34, 49.55, 29.72. IR (thin film): 1700 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{11}$NO$_3$, 240.0637; found, 240.0634.

3-Buten-1-ol was treated with acetic anhydride in pyridine to protect the alcohol functionality. This alkene was then treated with phthalimide and Pd(OAc)$_2$ in PhCN under an oxygen atmosphere at 60 °C for 24 h. The resulting product was deprotected with K$_2$CO$_3$ in MeOH to afford an authentic sample of 64. Product 64 was obtained as a pale yellow viscous oil ($R_f = 0.15$ in 65% hexanes/35% ethyl acetate). $^1$H NMR (CDCl$_3$): $\delta$ 7.89 (dd, $J = 5.2, 3.3$ Hz, 2H), 7.77 (dd, $J = 5.3, 3.1$ Hz, 2H), 5.58 (s, 1H), 5.30 (s, 1H), 3.66 (t, $J = 5.8$ Hz, 2H), 2.68 (t, $J = 5.8$ Hz, 2H), 2.22 (br s, 1H). $^{13}$C $^{1}$H NMR (CDCl$_3$): $\delta$ 167.65, 135.65, 134.41, 131.76, 123.76, 119.83, 59.26, 37.96.
The second addition of catalyst, oxidant, and alcohol was after 10 h. The product was obtained as a 10:1 ratio of diastereomers (154 mg, 77% yield, \( R_f = 0.12 \) in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters \( \mu \)-porasil 19.1 mm). **Major diastereomer** (126): white solid, mp = 105.4-108.2 °C. \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.82 (dd, \( J = 5.4, 3.1 \) Hz, 2H), 7.71 (dd, \( J = 5.4, 3.1 \) Hz, 2H), 7.32-7.27 (multiple peaks, 4H), 7.22 (m, 1H), 5.07 (q, \( J = 8.3 \) Hz, 1H), 4.51 (dd, \( J = 8.6, 7.9 \) Hz, 1H), 4.26-4.17 (multiple peaks, 3H), 3.96 (dd, \( J = 8.7, 7.7 \) Hz, 1H). \(^{13}\)C \{\(^1\)H\} NMR (CDCl\(_3\)): \( \delta \) 167.94, 139.58, 134.15, 131.69, 128.88, 127.37, 127.19, 123.37, 75.04, 68.94, 56.95, 47.29. IR (thin film): 1713 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na\(^+\)] calcd for C\(_{18}\)H\(_{15}\)NO\(_3\), 316.0950; found, 316.0948. **Minor diastereomer:** \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.66 (dd, \( J = 5.4, 3.1 \) Hz, 2H), 7.61 (dd, \( J = 5.5, 3.2 \) Hz, 2H), 7.14-7.08 (multiple peaks, 4H), 7.02 (m, 1H), 5.24 (td, \( J = 8.8, 5.3 \) Hz, 1H), 4.63 (dd, \( J = 10.0, 8.3 \) 1H), 4.57 (dd, \( J = 9.5, 5.3 \) 1H), 4.37-4.32 (multiple peaks, 2H), 3.80 (q, \( J = 9.4, 1H \)). \(^{13}\)C \{\(^1\)H\} NMR (CDCl\(_3\)): \( \delta \) 168.22, 135.43, 133.88, 131.18, 128.33, 128.19, 126.96, 122.99, 71.37, 68.93, 54.00, 48.86.
Structure Determination of 126.

Colorless, needle-like crystals of 126 were grown by diffusion of pentane into a chlorobenzene solution at 22 deg. C. A crystal of dimensions 0.48 x 0.13 x 0.12 mm was mounted on a standard Bruker SMART 1K CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (\(\lambda = 0.71073\) A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 108(2) K; the detector was placed at a distance 4.969 cm from the crystal. A total of 2450 frames were collected with a scan width of 0.5° in \(\omega\) and 0.45° in phi with an exposure time of 30 s/frame. The integration of the data yielded a total of 28419 reflections to a maximum 2\(\theta\) value of 56.60° of which 2053 were independent and 1780 were greater than 2\(\sigma(I)\). The final cell constants (Table 1) were based on the xyz centroids of 7712 reflections above 10\(\sigma(I)\). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P2(1)2(1)2(1) with \(Z = 4\) for the formula C_{18}H_{15}NO_{3}. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on \(F^2\) converged at \(R1 = 0.0297\) and \(wR2 = 0.0689\) [based on \(I > 2\sigma(I)\)], \(R1 = 0.0402\) and \(wR2 = 0.0742\) for all data.

Saint Plus, v. 7.01, Bruker Analytical X-ray, Madison, WI, 2003
The second addition of catalyst, oxidant, and alcohol was after 30 min. The product was obtained as a 15:1 ratio of diastereomers (136 mg, 62% yield, R<sub>f</sub> = 0.08 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). **Major diastereomer** (127): white solid, mp = 129.2-130.8 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.81 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.5, 3.1 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.02 (q, J = 8.4 Hz, 1H), 4.46 (t, J = 8.0 Hz, 1H), 4.23-4.14 (multiple peaks, 3H), 3.90 (dd, J = 8.7, 8.1 Hz, 1H), 3.75 (s, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 167.91, 158.65, 134.08, 131.15, 131.11, 128.36, 123.30, 114.23, 74.98, 68.71, 56.97, 55.18, 46.42. IR (thin film): 1712 cm<sup>–1</sup>. HRMS (ESI, m/z): [M + Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>4</sub>, 346.1055; found, 346.1051. **Minor diastereomer:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.68 (dd, J = 5.0, 3.3 Hz, 2H), 7.62 (dd, J = 5.1, 3.2 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.7 Hz, 2H), 5.18 (td, J = 8.7, 5.2 Hz, 1H), 4.59-4.53 (multiple peaks, 2H), 4.36-4.29 (multiple peaks, 2H), 3.76 (m, 1H), 3.63 (s, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 168.31, 158.31, 133.91, 131.26, 129.37, 127.27, 123.05, 113.62, 71.63, 69.01, 55.09, 54.01, 48.24.

The second addition of catalyst, oxidant, and alcohol was after 3.5 h. The product was obtained as a 5.4:1 ratio of diastereomers (121 mg, 55% yield, R<sub>f</sub> = 0.07 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). **Major diastereomer** (128): white solid, mp = 95.8-100.8 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.81 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.6, 3.1 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H),
6.82 (t, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.2, 2.6 Hz, 1H), 5.07 (q, J = 8.3 Hz, 1H), 4.49 (t, J = 8.2 Hz, 1H), 4.25-4.14 (multiple peaks, 3H), 3.95 (dd, J = 8.2, 2.6 Hz, 1H), 5.07 (q, J = 8.3 Hz, 1H), 4.49 (t, J = 8.2 Hz, 1H), 4.25-4.14 (multiple peaks, 3H), 3.95 (dd, J = 8.6, 7.7 Hz, 1H), 3.77 (s, 3H).

$^{13}$C $^{1}$H NMR (CDCl$_3$): δ 167.88, 159.86, 141.25, 134.11, 131.66, 129.85, 123.32, 119.56, 113.08, 112.43, 74.91, 68.88, 56.76, 55.14, 47.26. IR (thin film): 1712 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{19}$H$_{17}$NO$_4$, 346.1055; found, 346.1056. 

**Minor diastereomer:** $^1$H NMR (CDCl$_3$): δ 7.81 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.6, 3.1 Hz, 2H), 7.22-7.19 (multiple peaks, 2H), 6.84-6.82 (multiple peaks, 2H), 5.02 (q, J = 8.4 Hz, 1H), 4.46 (t, J = 8.3 Hz, 1H), 4.18-4.13 (multiple peaks, 3H), 3.90 (t, J = 8.4 Hz, 1H), 3.75 (s, 3H). $^{13}$C $^{1}$H NMR (CDCl$_3$): δ 167.93, 158.65, 141.25, 134.13, 131.11, 128.37, 123.31, 119.57, 114.23, 74.99, 68.72, 56.97, 55.19, 46.43. The minor diastereomer was isolated in a mixture with the major diastereomer (128); one $^{13}$C resonance of this compound appears to overlap with a resonance associated with 128.

![Chemical Structure](image)

The second addition of catalyst, oxidant, and alcohol was after 3 h. The product was obtained as a 7.8:1 ratio of diastereomers (139 mg, 63% yield, R$_f$ = 0.09 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters $\mu$-porasil 19.1 mm). **Major diastereomer** (129): white solid, mp = 115.8-120.7 °C. $^1$H NMR (CDCl$_3$): δ 7.82 (dd, J = 5.6, 3.0 Hz, 2H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 7.31 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 6.91 (t, J = 8.3 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.14 (q, J = 8.1 Hz, 1H), 4.51 (t, J = 8.2 Hz, 1H), 4.44 (q, J = 7.6 Hz, 1H), 4.21 (d, J = 8.3 Hz, 2H), 4.01 (t, J = 8.4 Hz, 1H), 3.67 (s, 3H). $^{13}$C $^{1}$H NMR (CDCl$_3$): δ 167.99, 157.56, 133.97, 131.80, 128.03, 127.66, 127.18, 123.19, 120.75, 110.42, 72.94, 68.93, 55.18, 55.17, 41.97. IR (thin film): 1712 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{19}$H$_{17}$NO$_4$, 346.1055; found, 346.1054.

**Minor diastereomer:** $^1$H NMR (CDCl$_3$): δ 7.64 (dd, J = 5.3, 3.1 Hz, 2H), 7.59 (dd, J = 5.6, 3.1 Hz, 2H), 7.12 (d, J = 8.5 Hz, 1H), 7.02 (t, J = 8.1 Hz, 1H), 6.73 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 5.41 (q, J = 8.1 Hz, 1H), 4.75 (dd, J = 10.6, 8.0 Hz, 1H), 4.49 (t, J = 8.2 Hz, 1H), 4.25-4.14 (multiple peaks, 3H).
4.36-4.35 (multiple peaks, 2H), 4.29 (t, $J = 7.3$ Hz, 1H), 3.96 (q, $J = 9.3$ Hz, 1H), 3.70 (s, 3H). $^{13}$C $\{^1$H$\}$ NMR (CDCl$_3$): $\delta$ 167.78, 157.06, 133.61, 131.24, 127.91, 127.86, 123.68, 122.67, 119.83, 109.32, 70.53, 69.20, 54.97, 52.34, 42.86.

The second addition of catalyst, oxidant, and alcohol was after 4.5 h. The product 130 was obtained as white solid as a single diastereomer (133 mg, 54% yield, $R_f = 0.18$ in 70% hexanes/30% ethyl acetate). mp = 87.1-89.4 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.83 (dd, $J = 5.6$, 3.3 Hz, 2H), 7.73 (dd, $J = 5.5$, 3.3 Hz, 2H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.5$ Hz, 2H), 5.04 (q, $J = 8.2$ Hz, 1H), 4.53 (dd, $J = 8.6$, 8.0 Hz, 1H), 4.28-4.17 (multiple peaks, 3H), 3.97 (dd, $J = 8.8$, 6.9 Hz, 1H). $^{13}$C $\{^1$H$\}$ NMR (CDCl$_3$): $\delta$ 167.83, 144.29, 134.30, 131.57, 129.47 (q, $^2$J$_{C-F} = 32.3$ Hz), 127.70, 125.86 (q, $^3$J$_{C-F} = 3.9$ Hz), 124.01 (q, $^1$J$_{C-F} = 271$ Hz), 123.46, 74.85, 68.97, 56.98, 47.37. $^{19}$F NMR (CDCl$_3$): $\delta$ –62.59. IR (thin film): 1715 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{19}$H$_{14}$NO$_3$F$_3$, 384.0823; found, 384.0823.

The second addition of catalyst, oxidant, and alcohol was after 12 h. The product was obtained as a 16:1 ratio of diastereomers (147 mg, 60% yield, $R_f = 0.17$ in 70% hexanes/20% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). Major diastereomer (131): white solid, mp = 117.9-120.7 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.83 (dd, $J = 5.3$, 3.0 Hz, 2H), 7.72 (dd, $J = 5.3$, 3.0 Hz, 2H), 7.51-7.41 (multiple peaks, 4H), 5.03 (q, $J = 8.2$ Hz, 1H), 4.54 (q, $J = 8.4$ Hz, 1H), 4.27 (t, $J = 8.4$ Hz, 1H), 4.22-4.16 (multiple peaks, 2H), 3.97 (dd, $J = 8.8$, 6.7 Hz, 1H). $^{13}$C $\{^1$H$\}$ NMR (CDCl$_3$): $\delta$ 167.83, 141.45, 134.27, 131.59, 131.14 (q, $^2$J$_{C-F} = 32.2$ Hz), 130.55 (q, $^4$J$_{C-F} = 1.3$ Hz), 129.46, 123.92 (q, $^1$J$_{C-F} =$
272.6 Hz), 124.30 (q, $^{1}J_{C-F} = 3.7$ Hz), 124.10 (q, $^{1}J_{C-F} = 3.7$ Hz), 123.45, 75.00, 69.05, 57.11, 47.46. $^{19}$F NMR (CDCl$_3$): $\delta$ –62.64. IR (thin film): 1713 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^{+}$ calcd for C$_{19}$H$_{14}$NO$_3$F$_3$, 384.0823; found, 384.0824. **Minor diastereomer:** $^{1}$H NMR (CDCl$_3$): $\delta$ 7.67 (dd, $J = 5.6$, 3.1 Hz, 2H), 7.63 (dd, $J = 5.5$, 3.3 Hz, 2H), 7.37-7.35 (multiple peaks, 2H), 7.30-7.24 (multiple peaks, 2H), 5.26 (m, 1H), 4.64-4.60 (multiple peaks, 2H), 4.38-4.33 (multiple peaks, 2H), 3.84 (q, $J = 9.6$ Hz, 1H). $^{13}$C {$^{1}$H} NMR (CDCl$_3$): $\delta$ 168.14, 147.00, 136.86, 134.08, 131.91, 131.01, 128.72, 125.13 (q, $^{3}J_{C-F} = 3.8$ Hz), 123.79 (q, $^{3}J_{C-F} = 4.0$ Hz), 123.06, 71.27, 68.68, 53.96, 48.64. $^{19}$F NMR (CDCl$_3$): $\delta$ –63.01.

The second addition of catalyst, oxidant, and alcohol was after 12 h. The product 132 was obtained as a white solid as a single diastereomer (142 mg, 56% yield, R$_f$ = 0.19 in 70% hexanes/30% ethyl acetate). mp = 40.7-45.3 °C. $^{1}$H NMR (CDCl$_3$): $\delta$ 7.82 (dd, $J = 5.3$, 3.1 Hz, 2H), 7.71 (dd, $J = 5.5$, 3.1 Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 4.99 (q, $J = 8.2$ Hz, 1H), 4.48 (t, $J = 8.35$ Hz, 1H), 4.24-4.10 (multiple peaks, 3H), 3.92 (dd, $J = 8.7$, 7.4 Hz, 1H). $^{13}$C {$^{1}$H} NMR (CDCl$_3$): $\delta$ 167.84, 138.85, 134.21, 131.86, 131.58, 129.06, 123.40, 121.02, 74.78, 68.81, 56.96, 46.89. IR (thin film): 1713 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^{+}$ calcd for C$_{18}$H$_{14}$BrNO$_3$, 394.0055; found, 394.0055.

The second addition of catalyst, oxidant, and alcohol was after 3 h. The product was obtained as a white solid as a single diastereomer (187 mg, 80% yield, R$_f$ = 0.20 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). **Major diastereomer** (133): white solid, mp = 105.6-108.6 °C. $^{1}$H NMR (CDCl$_3$): $\delta$ 7.83-7.75 (multiple peaks,
5H), 7.71-7.68 (multiple peaks, 3H), 7.46-7.42 (multiple peaks, 3H), 5.18 (q, J = 8.3 Hz, 1H), 4.58 (dd, J = 8.6, 8.0 Hz, 1H), 4.37 (q, J = 7.8 Hz, 1H), 4.32-4.23 (multiple peaks, 2H), 4.07 (dd, J = 8.7, 7.4 Hz, 1H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$ 167.92, 137.02, 134.12, 133.38, 132.55, 131.66, 128.83, 127.62, 127.60, 126.33, 126.21, 125.77, 125.16, 123.35, 75.01, 68.97, 57.01, 47.50. IR (thin film): 1711 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{22}$H$_{17}$NO$_3$, 366.1106; found, 366.1103. Minor diastereomer: $^1$H NMR (CDCl$_3$): $\delta$ 8.05 (d, J = 9.3 Hz, 1H), 7.80 (dd, J = 5.5, 3.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 1H), 7.69 (dd, J = 5.5, 3.1 Hz, 2H), 7.65 (d, J = 6.8 Hz, 1H), 7.49-7.44 (multiple peaks, 4H), 5.38 (q, J = 8.4 Hz, 1H), 5.09 (q, J = 8.0 Hz, 1H), 4.73 (dd, J = 8.7, 8.1, 1H), 4.33 (d, J = 8.3 Hz, 2H), 4.00 (dd, J = 8.8, 7.4 Hz, 1H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$ 168.05, 135.37, 134.15, 133.91, 132.16, 131.64, 128.92, 127.65, 126.34, 125.75, 125.70, 123.37, 123.20, 122.98, 74.81, 68.71, 55.28, 42.46.

The second addition of catalyst, oxidant, and alcohol was after 2.5 h. The product was obtained as a 1.4:1 mixture of diastereomers (164 mg, 72% yield, $R_f$ = 0.24 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters $\mu$-porasil 19.1 mm). Major diastereomer (134): white solid, mp = 111.3-115.3 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.81 (dd, J = 5.3, 3.1 Hz, 2H), 7.70 (dd, J = 5.4, 3.1 Hz, 2H), 6.79 (s, 2H), 5.37 (q, J = 9.5 Hz, 1H), 4.83 (q, J = 9.5 Hz, 1H), 4.42 (t, J = 9.8 Hz, 1H), 4.25 (d, J = 7.6 Hz, 2H), 4.11 (t, J = 8.6 Hz, 1H), 2.36 (s, 6H), 2.19 (s, 3H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$ 168.06, 137.02, 136.02, 134.09, 131.95, 131.61, 130.28, 123.30, 72.12, 68.68, 54.89, 41.08, 20.91, 20.61. IR (thin film): 1714 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{21}$H$_{21}$NO$_3$, 358.1419; found, 358.1414. Minor diastereomer: white solid, mp = 130.6-134.2 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.68 (dd, J = 5.4, 3.0 Hz, 2H), 7.62 (dd, J = 5.5, 3.0 Hz, 2H), 6.64 (s, 2H), 5.33 (td, J = 8.4, 4.6 Hz, 1H), 4.89 (dd, J = 9.7, 8.3 Hz, 1H), 4.61 (dd, J = 9.6, 4.5 Hz, 1H), 4.29-4.20 (multiple peaks, 2H), 3.99 (q, J = 9.2 Hz, 1H), 2.35 (s, 3H), 2.07 (s, 6H). $^{13}$C $^1$H NMR (CDCl$_3$): $\delta$
168.06, 137.85, 135.95, 133.83, 131.30, 129.03, 122.99, 70.86, 67.93, 53.06, 48.13, 21.91, 20.41. IR (thin film): 1710 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{21}\)H\(_{21}\)NO\(_3\), 358.1419; found, 358.1419.

Five reactions, each carried out on a 20 mg scale with respect to phthalimide, were combined for this substrate. The product was obtained as 1:4:1 mixture of diastereomers (47 mg, 30% yield, R\(_f\) = 0.28 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). **Major diastereomer (135):** viscous oil. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.84 (dd, \(J = 5.6, 3.1\) Hz, 2H), 7.73 (dd, \(J = 5.6, 3.1\) Hz, 2H), 4.92 (td, \(J = 8.6, 5.2\) Hz, 1H), 4.32 (dd, \(J = 9.5, 5.1\) Hz, 1H), 4.21 (dd, \(J = 9.5, 8.4\) Hz, 1H), 4.08 (t, \(J = 7.8\) Hz, 1H), 3.80 (dd, \(J = 10.1, 8.1\) Hz, 1H), 2.58 (m, 1H), 0.88 (d, \(J = 7.0\) Hz, 3H). \(^{13}\)C{\(^1\)H} NMR (CDCl\(_3\)): \(\delta\) 168.64, 134.12, 131.55, 123.29, 74.56, 69.15, 53.19, 37.56, 10.53. IR (thin film): 1713 cm\(^{-1}\).

**Minor diastereomer:** white solid, mp = 85.9-87.9 °C. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.84 (dd, \(J = 5.4, 3.1\) Hz, 2H), 7.72 (dd, \(J = 5.6, 3.0\) Hz, 2H), 4.47 (q, \(J = 7.6\) Hz, 1H), 4.28 (t, \(J = 8.1\) Hz, 1H), 4.10-4.02 (multiple peaks, 2H), 3.51 (t, \(J = 7.4\) Hz, 1H), 2.92 (m, 1H), 1.09 (d, \(J = 6.8\) Hz, 3H). \(^{13}\)C{\(^1\)H} NMR (CDCl\(_3\)): \(\delta\) 168.08, 134.08, 131.75, 123.26, 74.85, 68.57, 57.22, 36.83, 16.32. IR (thin film): 1713 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{13}\)H\(_{13}\)NO\(_3\), 254.0793; found, 254.0798.

The second addition of catalyst, oxidant, and alcohol was after 5 h. The product was obtained as 1.5:1 mixture of diastereomers (56 mg, 27% yield, R\(_f\) = 0.25 in 70% hexanes/30% ethyl acetate). The diastereomers were separated by HPLC (90% hexanes/10% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). **Major diastereomer**
(136): off-white viscous oil. \(^1\)H NMR (CDCl\(_3\)): \(\delta 7.74 (dd, J = 5.5, 3.1 \text{ Hz}, 2H), 7.68 (dd, J = 5.4, 3.1 \text{ Hz}, 2H), 7.12-7.08 \text{ (multiple peaks, 4H)}, 6.95 (m, 1H), 4.62 (q, J = 8.3 \text{ Hz}, 1H), 4.25 (dd, J = 8.6, 7.6 \text{ Hz}, 1H), 4.08-4.00 \text{ (multiple peaks, 2H)}, 3.68 (dd, J = 8.76, 7.35 \text{ Hz}, 1H), 3.34 (m, 1H), 2.84 (dd, J = 13.8, 7.6 \text{ Hz}, 1H), 2.72 (dd, J = 13.79, 7.9, 1H). \(^{13}\)C \({}^1\)H NMR (CDCl\(_3\)): \(\delta 167.84, 138.89, 133.91, 131.61, 128.53, 128.32, 126.05, 123.06, 72.98, 68.74, 55.26, 42.28, 37.98.\) IR (thin film): 1712 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{19}\)H\(_{17}\)NO\(_3\), 330.1106; found, 330.1100. 

**Minor diastereomer:** white solid, mp = 81.1-84.8 °C. \(^1\)H NMR (CDCl\(_3\)): \(\delta 7.84 (dd, J = 5.4, 3.1 \text{ Hz}, 2H), 7.74 (dd, J = 5.5, 3.1 \text{ Hz}, 2H), 7.19-7.10 \text{ (multiple peaks, 3H)}, 7.05-7.03 \text{ (multiple peaks, 2H)}, 5.01 (td, J = 8.8, 5.5 Hz, 1H), 4.33 (dd, J = 9.4, 5.5 Hz, 1H), 4.23 (dd, J = 9.4, 8.5 Hz, 1H), 4.05-3.98 \text{ (multiple peaks, 2H)}, 2.86 (m, 1H), 2.67 (dd, J = 13.9, 6.2 Hz, 1H), 2.56 (dd, J = 13.8, 9.7 Hz, 1H). \(^{13}\)C \({}^1\)H NMR (CDCl\(_3\)): \(\delta 168.53, 139.40, 134.18, 131.58, 128.47, 128.22, 126.21, 123.34, 73.36, 69.50, 52.00, 44.16, 32.99.\) IR (thin film): 1712 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{15}\)NO\(_3\), 268.0950; found, 268.0934.

The second addition of catalyst, oxidant, and alcohol was after 1 h. The product 138 was obtained as a white solid (78 mg, 47% yield, R\(_f\) = 0.20 in 70% hexanes/30% ethyl acetate). mp = 93.8-94.6 °C. \(^1\)H NMR (CDCl\(_3\)): \(\delta 7.82 (dd, J = 5.4, 3.1 \text{ Hz}, 2H), 7.71 (dd, J = 5.4, 3.1 \text{ Hz}, 2H), 4.99 (m, 1H), 4.20 (t, J = 9.2 Hz, 1H), 4.04 (t, J = 8.3 Hz, 1H), 2.45 (dd, J = 12.1, 9.6 Hz, 1H), 2.06 (dd, J = 12.1, 9.4 Hz, 1H), 1.48 (s, 3H), 1.31 (s, 3H). \(^{13}\)C \({}^1\)H NMR (CDCl\(_3\)): \(\delta 168.06, 134.06, 131.79, 123.21, 81.14, 66.86, 50.15, 40.40, 28.26, 28.15.\) IR (thin film): 1710 cm\(^{-1}\). HRMS (ESI, m/z): [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{15}\)NO\(_3\), 268.0950; found, 268.0934.
The product 158 was obtained as a yellow oil. $^1$H NMR (CDCl$_3$): $\delta$ 7.88-7.83 (multiple peaks, 4H), 7.73-7.72 (multiple peaks, 4H), 7.23 (t, $J = 7.5$ Hz, 2H), 7.18 (t, $J = 7.5$ Hz, 2H), 6.93-6.84 (multiple peaks, 4H), 6.70 (d, $J = 8.5$ Hz, 2H), 4.81-4.78 (multiple peaks, 2H), 4.50 (dd, $J = 9.5$, 4.5 Hz, 1H), 4.22 (d, $J = 6.0$ Hz, 1H), 4.17-4.09 (multiple peaks, 2H), 3.99 (m, 1H), 3.95 (m, 1H), 2.61 (m, 1H), 2.52 (m, 1H), 2.25 (m, 2H), 1.98 (s, 3H), 1.92 (s, 3H).

The product 159 was obtained as a white solid (78 mg, 47% yield, $R_f$ = 0.20 in 70% hexanes/30% ethyl acetate). mp = 93.8-94.6 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.88 (dd, $J = 5.0$, 2.5 Hz, 4H), 7.75 (dd, $J = 5.0$, 3.0 Hz, 4H), 7.19 (t, $J = 7.5$ Hz, 4H), 6.88 (t, $J = 7.5$ Hz, 2H), 6.72 (d, $J = 8.0$ Hz, 4H), 5.51 (s, 1H), 5.28 (s, 1H), 4.11 (t, $J = 6.0$ Hz, 4H), 2.98 (t, $J = 6.5$ Hz, 4H).

The second addition of catalyst, oxidant, and alcohol was after 7.5 h. The product 160 was obtained as a white solid as a single diastereomer (120 mg, 60% yield, $R_f$ = 0.12 in 70% hexanes/30% ethyl acetate). mp = 125.6-128.4 °C. $^1$H NMR (CDCl$_3$): $\delta$ 7.83 (dd, $J = 5.5$, 3.0 Hz, 2H), 7.72 (dd, $J = 5.5$, 3.5 Hz, 2H), 7.34-7.25 (multiple peaks, 5H), 5.23 (d, $J = 8.0$ Hz, 1H), 4.76 (m, 1H), 4.40 (q, $J = 8.5$ Hz, 1H), 4.29 (td, $J = 8.0$, 5.0 Hz, 1H), 2.59 (m, 1H), 2.41 (m, 1H). $^{13}$C {$^1$H} NMR (CDCl$_3$): $\delta$ 167.94, 139.31, 134.14, 131.71, 128.56, 128.09, 126.01, 123.36, 80.68, 67.82, 56.82, 29.58. IR (thin film): 1712 cm$^{-1}$. HRMS (ESI, m/z): [M + Na]$^+$ calcd for C$_{18}$H$_{15}$NO$_3$, 316.095; found, 316.0941.
Structure Determination of 160.

Colorless, needle-like crystals of 160 were grown by diffusion of pentane into a dichloromethane solution at 22 deg. C. A crystal of dimensions 0.40 x 0.08 x 0.04 mm was mounted on a standard Bruker SMART 1K CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (\(\lambda = 0.71073\) A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 108(2) K; the detector was placed at a distance 4.969 cm from the crystal. A total of 2640 frames were collected with a scan width of 0.6° in \(\omega\) and 0.45° in phi with an exposure time of 75 s/frame. The integration of the data yielded a total of 10058 reflections to a maximum 2\(\theta\) value of 45.32° of which 1947 were independent and 1198 were greater than 2\(\sigma(I)\). The final cell constants (Table 1) were based on the xyz centroids of 2032 reflections above 10\(\sigma(I)\). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P1bar with Z = 2 for the formula C\(_{15}\)H\(_{18}\)NO\(_3\). All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. Full matrix least-squares refinement based on F\(^2\) converged at R1 = 0.0546 and wR2 = 0.1212 [based on I > 2\(\sigma(I)\)], R1 = 0.1094 and wR2 = 0.1415 for all data.

Phthalimide (100 mg, 0.68 mmol, 1 equiv), AgBF₄ (13 mg, 0.07 mmol, 0.10 equiv), and Pd(OAc)₂ (8 mg, 0.034 mmol, 0.05 equiv) were combined in CH₃CN (1.4 mL) in a 20 mL vial. cis-1-Phenyl-buten-4-ol (0.202 g, 1.36 mmol, 2.0 equiv) was added to the reaction. The vial was purged with O₂ and sealed with a Teflon-lined cap, and the reaction was heated at 60 °C for 12 h. The resulting mixture was cooled to room temperature and evaporated to dryness, then taken up in ether (10 mL). The ether layer was washed with 10% aqueous Et₃N (10 mL), H₂O (2 x 20 mL), saturated aqueous NaHCO₃ (20 mL), and saturated aqueous NaCl (20 mL). The ether layer was then dried over MgSO₄, filtered, and concentrated to afford a red oil, which was purified by chromatography on silica gel. The product Z-163 was obtained as a major isomer (>10:1 as determined by HPLC analysis of the crude reaction mixture), (6 mg, 3% yield, Rf = 0.21 in 55% hexanes/45% ethyl acetate). An authentic sample of the E-isomer (165) was obtained by repeating the reaction above in DCE without AgBF₄. These conditions led to a 2:1 mixture of the Z and E-isomers, which could be separated by HPLC (65% hexanes/35% ethyl acetate, 20 mL/min, Waters µ-porasil 19.1 mm). Z-isomer (163):

viscous oil. ¹H NMR (CDCl₃): δ 7.85 (dd, J = 5.3, 3.6 Hz, 2H), 7.75 (dd, J = 5.3, 3.6 Hz, 2H), 7.20-7.15 (multiple peaks, 5H), 6.94 (s, 1H), 3.69 (t, J = 5.1 Hz, 2H), 2.73 (t, J = 5.5 Hz, 2H), 2.56 (br s, 1H). ¹³C {¹H} NMR (CDCl₃): δ 167.79, 134.45, 134.43, 134.32, 131.69, 128.55, 127.95, 127.50, 127.42, 123.86, 58.85, 39.62. IR (thin film): 3461, 1712 cm⁻¹. HRMS (ESI, m/z): [M + Na]⁺ calcd for C₁₈H₁₅NO₃, 316.0950; found, 317.0977. E-isomer (165): ¹H NMR (CDCl₃): δ 7.92 (dd, J = 5.6, 3.1 Hz, 2H), 7.79 (dd, J = 5.6, 3.1 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 6.78 (s, 1H), 3.71 (t, J = 5.4 Hz, 2H), 2.86 (t, J = 5.7 Hz, 2H), 2.55 (br s, 1H).

Discussion of low yield of 163. ¹H NMR studies (with 1,3,5-trimethoxybenzene as an internal standard) were carried out in order to determine the reasons for the low yield of 163 in these transformations. The low yield of 163 appears to be due to several factors.
First, in all of these reactions, the precipitation of Pd black was observed almost immediately (approximately 2 min) after heating was commenced, suggesting that catalyst decomposition is extremely fast (and/or reoxidation of Pd(0) to Pd(II) is very slow) under these conditions). Second, the cis-starting material 155 exhibited low reactivity under these conditions, and significant quantities of unreacted 155 are recovered. In addition, significant isomerization of 155 to the corresponding trans isomer (which is unreactive towards aminopalladation) was observed, particularly at higher catalyst loadings. Finally, $^1$H NMR spectroscopy of the crude mixture showed the presence of a significant quantity of a resonance at 10.03 ppm, consistent with an aldehyde functionality. This suggests that one mode of catalyst decomposition under these conditions likely involves oxidation of the alcohol substrate with concomitant reduction of the Pd catalyst.

The product 171 was obtained as a yellow oil (10% yield). $^1$H NMR (CDCl$_3$): $\delta$ 7.76 (m, 2H), 7.67 (m, 2H), 7.42-7.26 (multiple peaks, 5H), 5.53 (br s, 1H), 5.27 (br s, 1H), 3.83 (m, 1H), 1.33 (m, 2H), 0.85 (t, $J = 7.2$ Hz, 3H).

The product 172 was obtained as a viscous oil (25% yield, 4.5:1). Major Isomer: $^1$H NMR (CDCl$_3$): $\delta$ 7.65 (dd, $J = 5.5$, 3.0 Hz, 2H), 7.59 (dd, $J = 5.5$, 3.0 Hz, 2H), 7.12-7.08 (m, 4H), 7.01 (m, 1H), 4.75 (dd, $J = 10.5$, 2.5 Hz, 1H), 4.66-4.59 (multiple peaks, 2H), 3.40 (td, $J = 10.5$, 3.0 Hz, 1H), 1.68 (m, 2H), 0.75 (t, $J = 7.0$ Hz, 3H).
5.11 References


