Synthesis of α-Oxygenated Carbonyl Compounds via Dioxygenation, 
Development of Fluorescent Probes

BY

Aditi S. Patil

B.Sc., University of Pune, India 2004 
M.Sc., University of Pune, India 2006

THESIS

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Defense Committee:

Laura L. Anderson, Advisor and Chair, Chemistry 
Tom G. Driver, Chemistry 
Duncan J. Wardrop, Chemistry 
Justin T. Mohr, Chemistry 
Regan J. Thomson, Northwestern University
This thesis is dedicated to my mother ~ Dr. Jyoti Patil
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<tr>
<td>-------------</td>
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<tr>
<td>Ac</td>
<td>Acetyl (CH$_3$C=O)</td>
</tr>
<tr>
<td>bda</td>
<td>Benzyldeneacetone</td>
</tr>
<tr>
<td>bipy (bpy)</td>
<td>2,2'-bipyridyl</td>
</tr>
<tr>
<td>Boc</td>
<td>$t$-Butyloxy carbonyl [COC(CH$_3$)$_3$]</td>
</tr>
<tr>
<td>BOM</td>
<td>Benzyloxymethyl (PhCH$_2$OCH$_2$-alcohol protection)</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl (caution: sometimes used for benzyl)</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal Butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary Butyl</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric Ammonium Nitrate</td>
</tr>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzylxy (BnOC=O)</td>
</tr>
<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cp*</td>
<td>Pentamethylcyclopentadienyl</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic Acid</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper</td>
</tr>
<tr>
<td>CuTC</td>
<td>Copper(I) thiophene-2-carboxylate</td>
</tr>
<tr>
<td>Cys</td>
<td>Cysteine</td>
</tr>
<tr>
<td>DA</td>
<td>Diels-Alder Reaction</td>
</tr>
<tr>
<td>DAST</td>
<td>(Diethylamino)sulfur trifluoride Et$_2$NSF$_3$</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
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LIST OF ABBREVIATIONS (continued)

DCC \(N, N'-\text{dicyclohexyl carbodiimide}\)
DCE 1,2-Dichloroethane
DDQ 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de Diastereomeric Excess
DHP 3,4-Dihydro-2\(H\)-pyran
dr Diastereomeric Ratio
DIBAL Diisobutylaluminum Hydride
Dppe 1,2-Bis(diphenylphosphino)ethane
DMAP 4-Dimethylaminopyridine
DMF Dimethylformamide
DMSO Dimethyl Sulfoxide
\(E\) Entgegen (opposite, trans)
ee Enantiomeric Excess
er Enantiomeric Ratio
LAH Lithium Aluminum Hydride (LiAlH\(_4\))
LDA Lithium Diisopropylamide
LHMDS Lithium Hexamethyldisilazide (LiN(SiMe\(_3\))\(_2\))
\(m\)CPBA \(meta\)-Chloroperoxybenzoic Acid
Ms Methanesulfonyl (Mesyl, CH\(_3\)SO\(_2\))
NBS, NCS \(N\)-Bromo, \(N\)-Chlorosuccinimide
NIS \(N\)-Iodosuccinimide
PCC Pyridinium chlorochromate
LIST OF ABBREVIATIONS (continued)

PC   Phosphatidylcholine
PPTS Pyridinium \( p \)-Toluenesulfonate
Piv   Pivaloyl
iPr  Isopropyl
PS   Phosphatidylserine
PTSA  \( p \)-Toluene sulfonic acid monohydrate
Pyr   Pyridine
RT   Room Temperature
SES  Trimethylsilylethylsulfonyl
TASF  Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF  Tetra-n-butylammonium fluoride
TBDMS  \( t \)-Butyldimethylsilyl
TBDPS  \( t \)-Butyldiphenylsilyl
TBHP  \( t \)-Butylhydroperoxide
TBS  \( t \)-Butyldimethylsilyl (also TBDMS)
TBSCl  \( t \)-Butyldimethylsilyl chloride
TEA  Triethylamine
TES  Triethysilyl
TIPS  Triisopropyl
Tf   Triflate (\( CF_3 SO_2 \))
TFA  Trifluoroacetic acid
THP  Tetrahydropyran
# LIST OF ABBREVIATIONS (continued)

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<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilylchloride</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N’,N”-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane, also Trimethylsilyl</td>
</tr>
<tr>
<td>TsDPEN</td>
<td>N-Tosyldiphenylethlyenediamine</td>
</tr>
<tr>
<td>Tol</td>
<td>Toluene</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl ((p-\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2))</td>
</tr>
<tr>
<td>Z</td>
<td>Zusammen (together, cis)</td>
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SUMMARY

This thesis is divided into two parts. Part I consists of two chapters which describe a new dioxygenation reaction of alkenyl boronic acids to access $\alpha$-hydroxy ketones. The methodology for a diastereoselective dioxygenation has also been reported. Part II also has two chapters which illustrate the importance of protein-lipid interactions and the development of environmentally sensitive fluorescent probes for monitoring these interactions.

In chapter 1, the Chan-Lam coupling of boronic acids and methods to synthesize $\alpha$-hydroxy ketones are briefly reviewed. This is followed by a study on the optimization and the scope of the coupling reaction of alkenyl boronic acids with $N$-hydroxyphthalimide, rearrangement of the ensuing $N$-enoxypthalimides and hydrolysis to release the $\alpha$-oxygenated ketones. Chapter 2 reviews methods to control diastereoselectivity in a [3,3] rearrangement and the use of $N$-hydroxyisoindolinones to control the diastereoselectivity during the dioxygenation process.

Chapter 3 describes the fundamentals of lipids, their interactions with proteins and demonstrates that the use of environmentally sensitive probes is the most desirable method for monitoring these interactions. Chapter 4 exemplifies the development of new environmentally sensitive, thiol reactive probes which can be used for the in-situ determination of phosphatidylserine in the E. coli cell.
Chapter 1

Chapter 1 - Preparation of α-Oxygenated Ketones via the Dioxygenation of Alkenyl Boronic Acids

1.1 Abstract

Aldehydes and ketones that have oxygen substituents at the α-position are important building blocks for the synthesis of a large number of biologically active compounds. Conventional transformations which afford the α-oxygenation products of carbonyl compounds either utilize oxidants that are unstable or involve the removal of halogenated byproducts after displacement with oxygen nucleophiles. A new alternative route to α-oxygenated carbonyl compounds through the dioxygenation of vinyl boronic acids has been developed. This route avoids the use of unstable reagents and provides direct access to α-oxygenated carbonyl compounds directly from internal alkynes.

The dioxygenation of alkenyl boronic acids with N-hydroxyphthalimide has been achieved by a two-step process involving a copper-mediated etherification to form an N-enoxypthalimide and a subsequent [3,3] rearrangement to provide α-hydroxy ketones or α-benzoyloxy ketones, after hydrolysis of the phthalimide imidate intermediate.

\[ \text{Olefination} \rightarrow \text{Enoximation} \rightarrow \text{Rearrangement} \rightarrow \text{Hydrolysis} \]
1.2 Introduction

1.2.1 Boronic Acids in Organic Synthesis

Boronic acids are amongst the most useful classes of organoboron reagents that have become popular in recent years for C–C and C–heteroatom coupling reactions.\(^1\) Unlike many organometallic reagents and most organoboranes, boronic acids are appealing reagents to work with since they have low toxicity, are usually stable to air and moisture and react under mild conditions.\(^2\) The discovery by Suzuki and Miyaura in 1979 that aryl boronic acids could be coupled with an aryl halide using a palladium catalyst sparked the chemistry of boronic acids.\(^3\) Since then, the ubiquitous use of aryl, alkenyl, and alkyl boronic acids for the formation of new C–C, C–N, and C–O bonds in cross coupling reactions is indicative of the importance of these compounds in organic synthesis.\(^4\)

One of the earliest known reactions of aryl boronic acids is their oxidative cleavage, usually with hydrogen peroxide to give phenols, thus leading to the formation of a new C–O bond.\(^5\) Other oxidative reactions with NBS or NIS to give aryl halides have also been reported.\(^6\) Boronic acids have been used in coupling reactions with a variety of heterocyclic halides including thiophenes,\(^7\) thiazoles,\(^7\) furans,\(^8\) isoxazoles,\(^9\) pyridines,\(^10\) pyrimidines\(^11\) and pyrazines\(^12\) to form new C–C bonds, with perfect control of regiochemistry, and which cannot be formed using conventional methods of electrophilic aromatic substitution. Instead of using the more reactive halide functionality, aryl or vinyl triflates, derived from their corresponding ketones, have also been shown to undergo palladium-catalyzed couplings with boronic acids.\(^13\) Coupling of boronate derivatives with aryl tosylates\(^14\) and mesylates\(^15\), catalyzed by nickel and palladium complexes, have also been reported. Sulfonium salts can also be used as coupling partners with boronic acids to form new C–C bonds wherein the sulfonium salt serves as the leaving group.\(^16\) Aryl boronic acids can undergo Ullmann-type C–O and C–N bond forming reactions.
with phenols, amines, amides, ureas, sulfonamides, carbamates, and N-heteroaromatics in the presence of copper salts to give the corresponding diaryl ethers, aryl amines (Scheme 1.1) or N-aryl heterocycles.

Scheme 1.1: Aryl Boronic Acids in the Synthesis of Aryl Amines

Since these N-aryl heterocycles are commonly found in a number of drugs, the Ullmann-type coupling of boronic acids with cheap, commercially available reagents has been used to access large libraries of drug analogs. Although the use of aryl boronic acids for the preparation of a variety of new bonds is well established, the reactivity of alkenyl boronic acids has not been extensively studied. Alkenyl boronic acids have been commonly used in the Suzuki reaction with aryl or vinyl halides or triflates using a Palladium catalyst (Scheme 1.2). This reaction is a powerful method that provides access to conjugated olefins and styrenes.

Scheme 1.2: Suzuki Reaction with Alkenyl Boronic Acids

Alkenyl boronic acids have also been utilized in the synthesis of 2,3-disubstituted piperidines as shown below in Scheme 1.3.
1.3 Chan-Lam Coupling Reactions

This is a Petasis-type reaction, mediated by a Lewis acid, which involves the diastereoselective introduction of aryl and vinyl moieties onto the 2-position of \(N\)-protected piperidinium ions.\(^{26}\) Vinyl boronate esters are more commonly used than their corresponding boronic acid analogs in both the Suzuki reaction and the Chan Lam coupling. These boronate esters have been used in cross coupling reactions with vinyl bromides or triflates to form unsymmetrical 1,3-dienes.\(^{27}\)

1.3 Chan-Lam Coupling Reactions

The copper-mediated C–N, C–O and C–S bond formations between OH, NH, or SH containing nucleophilic substrates and aryl- or alkenyl boronic acids to form the corresponding arylated or alkenylated products are referred to as Chan–Lam coupling reactions.\(^{28}\) The discovery of the copper-promoted Chan–Lam reaction\(^{29-31}\) has greatly advanced carbon–heteroatom cross-coupling chemistry and is a powerful synthetic tool, because of the mild conditions required. Chan-Lam couplings provide simple and modular access to aryl ethers, anilines, and thioethers which are ubiquitous moieties in a wide range of molecules with many important applications.

The Chan-Lam C–X coupling reactions provide a synthetic alternative to the Buchwald-Hartwig cross couplings.\(^{32,33a}\) Buchwald-Hartwig reactions involve a Pd(II)
catalyzed couplings between alkyl halides (or pseudo halides) and amines to form substituted anilines or aryl halides and phenols to form diaryl ethers (Scheme 1.4).\textsuperscript{33b}

\begin{center}
\[
\text{Scheme 1.4: Buchwald-Hartwig Cross Coupling Reaction}
\]
\end{center}

Although this palladium-catalyzed process is a very useful and well-established reaction, it has a few drawbacks. The reaction takes place only at high temperatures and requires the presence of a strong base which makes it incompatible with some functional groups. Also, the palladium catalyst which is essential for the reaction is expensive. The Chan-Lam coupling on the other hand, utilizes Cu(OAc)\textsubscript{2} which is cheap and readily available. The reaction requires a mild base like pyridine and can be carried out at room temperature and under ambient conditions.
1.3.1 Mechanism of the Reaction

A mechanism for Chan–Lam \(N/O\)-arylations has been proposed by Stahl and co-workers based on their study of the methoxylation of tolylboronic ester (Scheme 1.5 and 1.6).\textsuperscript{34} Kinetic and EPR spectroscopic studies revealed that the catalyst resting state consists of a Cu(II) species with weak anionic ligands, such as acetate or methoxide, and the turnover-limiting step is transmetalation of the aryl group from boron to the copper center. Based on the work by Ribas and co-workers,\textsuperscript{35} who observed formation of a well-defined aryl–Cu(III) complex via Cu(II)-mediated C–H bond activation, Stahl and co-workers proposed that reductive elimination does not occur from Cu(II), but rather from an aryl–Cu(III) intermediate, which is formed via oxidation of a transient aryl–Cu(II) intermediate by a second equivalent of Cu(II). Therefore, in the proposed mechanism, the reaction is initiated by transmetalation of the aryl group from boron to Cu(II). The resulting aryl–Cu(II) species is oxidized by another equivalent of Cu(II) to yield an aryl–Cu(III) intermediate that can undergo facile C–O bond formation. Aerobic oxidation of Cu(I) regenerates Cu(II), the resting state of the catalyst.

\[ \text{MeO}_2\text{B(OMe)} + \text{MeOH} \xrightarrow{\text{Cu(OAc)}_2 (5 \text{ mol\%})} \text{O}_2 \xrightarrow{\text{MeOH}} \text{OMe} + \text{MeO}_2\text{B(OMe)}_3 \]

Scheme 1.5: Methoxylation of Tolylboronic Ester
### Scheme 1.6: Proposed Mechanism for the Chan-Lam Coupling Reaction

#### 1.3.2 C–N Bond Forming Reactions

The Chan-Lam reaction has been widely used for C–N bond formation because of its high tolerance of a wide range of functional groups and because the reaction conditions are mild. In 1998, the Chan group demonstrated that a wide range of the N–H containing substrates including amines, amides, imides, ureas, carbamates and sulfonamides, underwent C–N bond formation with $p$-tolylboronic acid to afford the compounds shown below in Scheme 1.7.\(^{29}\)
Lam and co-workers demonstrated that a variety of aromatic heterocycles, such as imidazole, pyrazole, triazoles, tetrazole, benzimidazole, and indazole undergo the Cu-mediated coupling with boronic acids to form nitrogen containing heterocycles. Pyrazoles and imidazoles were particularly amenable to the reaction conditions while electron-poor azoles such as triazoles and tetrazoles gave attenuated yields. This represents another contrasting factor with the Buchwald–Hartwig palladium-catalyzed N-arylation with aryl halides which works for pyrrole, indole and carbazole but not for azoles such as quinazolinediones. Cu-mediated Chan–Lam reactions of propylene glycol boronic esters have also been extended to the coupling of two heteroarenes which provide drug-like small molecules (Scheme 1.8).
Scheme 1.8: Coupling of Two Heteroarenes

In addition, the \( N \)-arylation of electron deficient indoles has been achieved using diisopropylethylamine as the base. Neither triethylamine nor pyridine gave the desired product under these conditions.\(^{38}\)

This Cu-mediated C–N bond formation strategy was further extended by the Liebeskind group who used oxime \( O \)-carboxylates as \( N \)-iminating agents with either copper(I) thiophene-2-carboxylate (CuTC) or Cu(OAc)\(_2\) as the catalyst (Scheme 1.9) under nonbasic and nonoxidizing conditions to afford the \( N \)-arylated or \( N \)-alkenylated imines.\(^{39}\) Other Cu(I) and Cu(II) salts such as CuCl, CuBr, CuI, CuBr\(_2\) were also effective in catalyzing the reaction. The reaction, however, was not stereospecific and gave a mixture of \( E/Z \)-imine isomers.

Scheme 1.9: Coupling with Oxime \( O \)-Carboxylates

Both electronic-rich and neutral boronic acids gave good yields, while electron-withdrawing boronic acids did not work as well under the reaction conditions. Using the more electron deficient \( O \)-pentafluorobenzoyl derived oximes completely suppressed the boronic acid homocoupling side reaction. The reaction with the aryl boronic acids could be carried out in
were employed. In addition, Liebeskind and co-workers also developed an $N$-amidation reaction which involved the coupling of organostannanes and boronic acids with $O$-acetyl hydroxamic acids in the presence of a Cu catalyst to afford $N$-arylated amides (Scheme 1.10).  

![Scheme 1.10: $N$-Amidation Reaction with $O$-Acetyl Hydroxamic Acids](image)

### 1.3.3 C–O Bond Formation

The first report for C(aryl sp$^2$)–O bond formation was from Chan and co-workers in 1998 (Scheme 1.11). When a phenol was treated with an arylboronic acid in the presence of stoichiometric Cu(OAc)$_2$ and a base in dichloromethane at room temperature for one to two days, the corresponding diaryl ethers were obtained in good yields.  

![Scheme 1.11: C(aryl sp$^2$)–O Bond Formation through a Cross-Coupling Reaction](image)

Lam and co-workers extended the methodology to the $O$-arylation of substrates containing an $N$-hydroxy functionality (Scheme 1.12). They reported the $O$-arylation of $N$-hydroxybenzotriazole with $p$-tolylboronic acid to provide the corresponding $O$-phenylated product.
Scheme 1.12: O-Arylation of N-Hydroxybenzotriazoles with p-Tolylboronic Acid

This C–O bond forming arylation methodology was also used in a progression by Hartwig and co-workers for the synthesis of 3,5-disubstituted aryl ethers by a sequential iridium-catalyzed C–H borylation followed by the hydrolysis of the boronic esters with aqueous sodium periodate to the corresponding boronic acids, and a copper-mediated coupling of the crude boronic acids with phenols (Scheme 1.13).\(^{42}\)

Scheme 1.13: Hartwig’s Synthesis of 3,5-Disubstituted Aryl Ethers

### 1.3.4 Chan-Lam Coupling With Alkenyl Boronic Acids

Lam and co-workers also discovered that alkenyl boronic acids undergo analogous copper-promoted alkenylation with N–H or O–H nucleophiles as that reported with aryl boronic acids (Scheme 1.14).\(^{41}\)
Scheme 1.14: With Alkenyl Boronic Acids

Since vinyl boronic acids are more challenging to handle than aryl boronic acids, similar Cu-mediated conditions for C–O and C–N bond forming reactions have been developed for trivinyl boroxines,\(^\text{43}\) vinyl pinacolates\(^2\) or the alkenyltrifluoroborate salts\(^4\) have been used. One of the most significant advances in this area is the Merlic group’s development of an allyl vinyl ether synthesis using vinyl boronates with aliphatic or allylic alcohols in the presence of anhydrous copper(II) acetate (Scheme 1.15). This reaction provides simple access to allyl vinyl ethers which are usually difficult to prepare.\(^4\)

Scheme 1.15: Copper-Promoted Coupling of Vinyl Boronates with Aliphatic Alcohols

We have been successful in diversifying the reactions of alkenyl boronic acids to include dioxygenation and the synthesis of \(\alpha\)-oxygenated ketones, by applying the Chan-Lam coupling with \(N\)-hydroxyphthalimide, to form a new C–O bond. The overall reaction for this process is shown below (Scheme 1.16).
1.4 Dioxygenation Scheme

Towards the goal of alkenyl boronic acid dioxygenation, we have developed a novel etherification of an alkenyl boronic acid 1 with N-hydroxyphthalimide 2 to form an N-enoxophthalimide 3. This N-enoxphthalimide, 3, can undergo a formal [3,3] rearrangement, to give an α-oxygenated aldehyde or ketone in the form of an imidate 4 (Scheme 1.17).

Scheme 1.17: Dioxygenation of Alkenyl Boronic Acids

Hydrolysis of the imidate 4 cleaves the C–O bond and furnishes the desired α-oxygenated carbonyl compound 5. Thus, this new process effectively involves the
introduction of two atoms of oxygen onto the alkenyl boronic acid, converting it to an α-oxygenated aldehyde or ketone and hence has been termed as ‘dioxygenation’. Overall, this process provides α-hydroxy or α-benzoyloxy ketones in three steps from simple starting materials.

1.5 α-Oxygenated Ketones

Although α-oxygenated ketones are found in a number of natural products and drugs, the synthesis of this functional group has proved to be quite a challenge. The conventional methods for α-oxygenation of carbonyl compounds have been shown below in Scheme 1.18.

\[
\begin{align*}
\text{condensation} & : \\
\text{reduction} & : \\
\text{alpha-oxygenation} & : \\
\end{align*}
\]

*Scheme 1.18: Retrosynthetic Pathways for α-Oxygenation of Carbonyl Compounds*

The first retrosynthetic pathway involves C–C bond formation through a condensation reaction such as an acyloin or benzoin condensation. An acyloin condensation is a reductive coupling of two esters using metallic sodium and the benzoin condensation, first reported in 1832, utilizes a cyanide nucleophile or an N-heterocyclic carbene to mediate the reaction between two aromatic aldehydes. Aliphatic aldehydes can
be used in the benzoin condensation when the catalyst employed is a thiazolium salt.\textsuperscript{49}

Although both the acyloin and benzoin condensation have been extensively studied and several modifications have been proposed, they are severely limited by the narrow spectrum of reagents that can be utilized. The acyloin condensation is mostly restricted to esters, while the benzoin condensation works best when one of the coupling partners is benzaldehyde.

The second retrosynthetic pathway involving the reduction of diketones to form a new C–O bond was reported by Shimizu in 2000.\textsuperscript{50} This reaction allows access to α-hydroxy ketones and is excellent for symmetrical diketones. When asymmetric diketones are used, the reduction reaction is difficult to control and since either ketone can be reduced, a mixture of regioisomeric alcohols is obtained. This mixture of alcohols is not easily separable and hence it is hard to obtain pure α-hydroxy ketones in a good yield.

The third retrosynthetic pathway involving the formation of the C–O bond via an oxidation reaction was pioneered by Rubottom in 1974.\textsuperscript{51} The Rubottom oxidation employs \textit{m}CPBA as an oxidant for a silyl enol ether to convert the enol ether to an α-oxygenated ketone. Other reagents which are capable of oxidizing a carbonyl compound to an α-oxygenated carbonyl compound are electrophilic oxidation reagents such as peroxides, oxone, hyperoxygenated metals, oxaziridines or hypervalent iodinated reagents.\textsuperscript{52} The aforementioned electrophilic oxygenation reagents provide the oxidized product in good yields, but they are unstable and potentially explosive. Hypervalent iodination reagents are more stable, but the oxidation reaction of a ketone to an α-oxygenated ketone requires the removal of iodobenzene which forms as a byproduct.\textsuperscript{52d} Hence, these methods for α-oxygenation are not very synthetically viable and are difficult to apply to the large scale synthesis of α-oxygenated ketones. Enamine and palladium catalysis has also allowed access
to α-oxygenated ketones, however, enamine catalysis requires the addition of an external electrophilic oxidation reagent while palladium catalysis works on substituted systems providing only tertiary alcohols.\textsuperscript{53}

The use of the dioxygenation methodology involving the coupling of N-hydroxyphthalimide to alkenyl boronic acids followed by a [3,3] rearrangement and hydrolysis to form α-oxygenated aldehydes and ketones, could be used as an alternative for the synthesis of this exigent functionality. This method avoids the necessity of utilizing carbonyl compounds as precursors for oxidation to the α-oxygenated product. Internal alkynes and commercially available boronate esters have been directly converted to the desired α-oxygenated aldehydes and ketones (Scheme 1.19). Moreover, this methodology circumvents the use of electrophilic oxygenation reagents and the only byproduct from the reaction is phthalimide which is easily removed by base extraction. Also, the nature of the transition state for the [3,3]-sigmatropic reaction allows for the diastereoselective construction of the α-oxygenated stereocenter. Thus, this conversion of alkenyl boronic acids to α-oxygenated ketones provides a unique retrosynthetic disconnection for the preparation of complicated targets containing these challenging motifs.\textsuperscript{54}

\begin{center}
\begin{align*}
\text{HO} & \text{C} & \text{R}^1 & \rightleftharpoons & \text{(HO)₂B} & \text{R}^1 & \rightleftharpoons & \text{R}^1 & \equiv & \text{R}^2 \\
\text{HO} & \text{C} & \equiv & \text{pin} & \rightleftharpoons & \text{pin} & \equiv & \text{HO}
\end{align*}
\end{center}

\textbf{Scheme 1.19: New Retrosynthetic Pathway for α-Oxygenation}
1.6 Arylation of N-Hydroxyphthalimide

The first step towards achieving the dioxygenation of alkenyl boronic acids began with the optimization of conditions for the cross-coupling of alkenyl boronic acids and N-hydroxyphthalimide to form N-enoxypthalimides. Since the copper-mediated arylation of N-hydroxyphthalimide with aryl boronic acids had been reported by Kelly and co-workers in 2001 (Scheme 1.20).  

![Scheme 1.20: Arylation of N-Hydroxyphthalimide](image)

The cross coupling between the N-hydroxyphthalimide 2 and phenylboronic acid 7 was carried out by using stoichiometric Cu(OAc)$_2$ or CuCl. Other Cu (I) or Cu (II) salts were ineffective in promoting the reaction. Three equivalents of the boronic acid were required and pyridine was the best base among the others tested such as Et$_3$N and DMAP. The yield of the O-arylated product 8 did not depend upon the quantity of base used; with 1 equivalent, 5 equivalents and 10 equivalents of base giving similar results. The reaction gave attenuated yields when run under an Argon atmosphere. The reaction could tolerate a wide variety of functional groups including halides, nitriles, aldehydes and esters. Both electron donating and electron deficient boronic acids could be used. After O-arylation of the N-hydroxyphthalimide, hydrazine was used to remove the phthalimide moiety, akin to Gabriel’s synthesis, and release the corresponding aryloxyamine.
1.7 Optimization of Conditions for Coupling of Alkenyl Boronic Acids with N-hydroxyphthalimide

Although the copper-mediated arylation of N-hydroxyphthalimide had been reported, the corresponding process for vinylation had not been reported. Mixtures of copper salts, bases, dessicants as well as equivalents of reagents were tested for their efficacy in promoting the coupling reaction between N-hydroxyphthalimide 2 and the alkenyl boronic acid derived from 2-butyne 1a (Scheme 1.21). The results are shown in Table 1.1.

![Scheme 1.21: Etherification of N-Hydroxyphthalimide with Alkenyl Boronic Acids](image)

As shown in entries 1-4 of Table 1.1, the use of 2 equivalents of boronic acid 1a provided a higher yield of the N-enoxypythalimide 3a for both the copper-mediated and the copper-catalyzed transformations, although the difference in reaction efficiency was more striking for the catalytic process. Cu(OAc)$_2$ was shown to be the optimal catalyst when compared to other Cu(I) and Cu(II) salts (entries 5-9, Table 1.1) and pyridine was shown to be the optimal base when compared to other amines and inorganic bases (entries 10-13, Table 1.1). Neither the copper-mediated nor the copper-catalyzed coupling reaction showed any conversion to the desired product when run in the absence of air, and both transformations required the use of a halogenated solvent. The cross coupling process was fairly insensitive to the choice of desiccant; 4Å molecular sieves and MgSO$_4$ gave the desired product in only slightly attenuated yields. The optimization study concluded that treatment of a 1:2 mixture of N-
hydroxyphthalimide 2: alkenyl boronic acid 1 in 1,2-dichloroethane (DCE) with \( \text{Cu(OAc)}_2 \) (1 equiv or 20 mol%), pyridine (3 equiv), and \( \text{Na}_2\text{SO}_4 \) (4 equiv) in air provided optimal conversion to the desired product 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>([\text{Cu}])</th>
<th>(1a)</th>
<th>Base</th>
<th>% Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Cu(OAc)}_2 ) (1 equiv)</td>
<td>1 equiv</td>
<td>pyr</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Cu(OAc)}_2 ) (1 equiv)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>1 equiv</td>
<td>pyr</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>( \text{CuCl} ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>( \text{CuI} ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Cu(OTr)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Cu(TFA)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>( \text{CuTC} ) (20 mol %)</td>
<td>2 equiv</td>
<td>pyr</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>( \text{Et}_3\text{N} )</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>( \text{DABCO} )</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>imidazole</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>( \text{Cu(OAc)}_2 ) (20 mol %)</td>
<td>2 equiv</td>
<td>( \text{KOTBu} )</td>
<td>NR</td>
</tr>
</tbody>
</table>

$^a$Yields determined by \( \text{H}^1 \) NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

**Table 1.1: Optimization of Reaction Conditions for the Coupling Reaction**

A rationale for the role of \( \text{O}_2 \) in the enhancement of the reaction as well as in the decomposition of the boronic acids has been offered by Lam and co-workers$^1$ for the \( N \)-arylation of saturated heterocycles which could be applied to the above coupling reaction. The copper salt could co-ordinate to the hydroxyl group of the \( N \)-hydroxyphthalimide 2.
After deprotonation by pyridine, the copper complex could undergo transmetalation with the boronic acid 1. Molecular oxygen could then oxidize the copper complex to Cu(III), facilitating the reductive elimination of the N-enoxyphtalimide 3. These strong oxidizing reaction conditions could also lead to peroxide formation which would result in some decomposition of the boronic acid. This happens through formation of a superoxide anion which reacts with the boronic acid (Scheme 1.22). The resulting radical species is reduced by another superoxide anion to form a peroxy anion. This peroxy anion undergoes protonation to form a boron-peroxide in which the alkyl group undergoes an irreversible migration to the peroxide. After hydrolysis of the resulting species, boronic acid and an alcohol are formed. It is because of this decomposition of the boronic acid that two equivalents are required for the reaction.

Scheme 1.22: Decomposition of the Boronic Acid in the Presence of O₂
1.8 Evaluation of the Scope of the Transformation

With the optimal conditions for the cross-coupling reaction in hand, the scope of the transformation was evaluated with a variety of alkenyl boronic acids to determine the tolerance for boronic acid substitution patterns.

The coupling reaction between \( \text{N-hydroxyphthalimide} \ \text{2} \) and a range of alkenyl boronic acids \( \text{1} \) was carried out using stoichiometric amounts of Cu(OAc)\(_2\) as shown in Scheme 1.23. The reaction was also attempted with catalytic Cu(OAc)\(_2\). Although the yields of the \( \text{N-enoxyphthalimide} \ \text{3} \) for the copper-mediated and the copper-catalyzed processes are similar, the reaction times for the copper-catalyzed method are much longer. The results are shown in Tables 1.2, and 1.3.

As shown below, the copper-mediated conditions converted 1- and 2–\textit{trans}-substituted vinyl boronic acids containing both alkyl and aryl systems to the desired product with retention of alkene geometry. Z-Disubstituted alkenyl boronic acids which had substituents on the aryl ring also gave moderate to excellent yields. In addition, disubstituted cyclic alkenyl boronic acids were transformed to the desired \( \text{N-enoxyphthalimides} \ \text{3} \) under the reaction conditions. We therefore concluded that both alkyl- and aryl substituents were tolerated for the boronic acid coupling partner, as were common aryl electron-withdrawing functional groups such as nitro, fluoro, and trifluoromethyl, and common protecting groups such as ketals. Heterocyclic compounds such as the pyranyl substituted boronic acid also worked well under the reaction conditions.
Scheme 1.23: Evaluating Different Alkenyl Boronic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>98%</td>
<td>76%**</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>87%</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>88%*</td>
<td>78%*</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>81%</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>47%**</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>81%*</td>
<td>77%*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>86%</td>
<td>77%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>76%*</td>
<td>67%*</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Chemical Structure" /></td>
<td>70%*</td>
<td>71%*</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>67%*</td>
<td>55%*</td>
</tr>
<tr>
<td>11</td>
<td><img src="image11" alt="Chemical Structure" /></td>
<td>82%*</td>
<td>73%*</td>
</tr>
<tr>
<td>12</td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>63%*</td>
<td>66%*</td>
</tr>
</tbody>
</table>

*Yield<sup>a</sup> refers to the yield for the Cu-mediated reactions and Yield<sup>b</sup> refers to the yields for the Cu-catalyzed reaction. (* Indicates compounds made by Dr. Dong-Liang Mo and ** Indicates compounds made by Heng-Yen Wang).*

| Table 1.2: Scope of the Coupling Reaction with Mono and Disubstituted Boronic Acids |
Table 1.3: Scope of the Coupling Reaction with Cyclic Boronic Acids

The broad scope of the copper-mediated cross-coupling of $N$-hydroxypythalimide and alkenyl boronic acids ultimately provided an array of $N$-enoxypthalimides to screen for the [3,3] rearrangement.
1.9 Limitations of the Methodology

Although both the copper-mediated and the copper-catalyzed transformations have a broad scope and tolerate a number of functional groups, the coupling reaction has a few limitations. Trisubstituted alkenyl boronic acids do not participate in this reaction and neither do alkenyl boronic acids containing ortho-substituted aryl groups as shown in Scheme 1.24. This might be because of unfavorable steric interactions between the boronic acid and the copper complex.

\[
\text{Scheme 1.24: Limitations of the Copper Mediated Coupling Reaction}
\]

1.10 [3,3] Rearrangement to Form the Imidates

Solutions of the \(N\)-enoxypthalimides 3 in \(\text{C}_6\text{D}_6\) or toluene were heated at 80-90 °C for 10-16 h to promote a [3,3] rearrangement and afford dioxygenated alkenyl boronic acids as imidates (Scheme 1.25). These rearrangements occurred in almost quantitative yields, as determined by comparison to an internal standard by H\(^1\) NMR spectroscopy; however, the imidates were unstable when subjected to silica gel chromatography and hence could not be isolated. The \(\alpha\)-oxygenated ketones (in the form of imidates) were immediately subjected to the hydrolysis without further purification. The \(\alpha\)-oxygenated aldehydes (in the form of
imidates) (Scheme 1.26) were not subjected to the hydrolysis conditions to avoid polymerization of the corresponding α-hydroxy aldehydes which would be the product of hydrolysis of the imidates (Scheme 1.27).

Scheme 1.25: [3,3] Rearrangement of the N-Enoxypthalimides to Afford Imidates

Scheme 1.26: Formation of α-Oxygenated Aldehydes

Scheme 1.27: Polymerization of the α-Oxygenated Aldehydes
1.11 Trends in the [3,3] Rearrangement

Several aryl-substituted N-enoxynaphthalimides exhibited thermal reactivity patterns that suggested trends in the [3,3] rearrangement activity of these compounds. N-Enoxynaphthalimide 3c (entry 1, Table 1.4) readily formed the α-oxygenated aldehyde when heated to only 50 °C. This transformation is in contrast to the N-enoxynaphthalimides 3b and 3d (entries 2 and 3, Table 1.4), which rearranged at 90 °C, and 3g, (entry 4), which exhibited no rearrangement reactivity even when heated to 130 °C. N-Enoxynaphthalimides with substitution patterns such as 3h (entry 5 in Table 1.4) with an aryl group and an alkyl group at the 2-position, underwent rearrangements to afford the corresponding imidate product at 80 °C, however, the addition of an electron-donating group to the aryl ring once again reduced the rearrangement temperature to 25-50 °C (3w, entry 6, Table 1.4).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Rearrangement Product</th>
<th>Temperature for Rearrangement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="3c.png" alt="Chemical Structure" /></td>
<td><img src="4c.png" alt="Chemical Structure" /></td>
<td>50 °C</td>
</tr>
<tr>
<td>2</td>
<td><img src="3b.png" alt="Chemical Structure" /></td>
<td><img src="4b.png" alt="Chemical Structure" /></td>
<td>90 °C</td>
</tr>
<tr>
<td>3</td>
<td><img src="3d.png" alt="Chemical Structure" /></td>
<td><img src="4d.png" alt="Chemical Structure" /></td>
<td>90 °C</td>
</tr>
<tr>
<td>4</td>
<td><img src="3g.png" alt="Chemical Structure" /></td>
<td>No Rearrangement</td>
<td>25-130 °C</td>
</tr>
<tr>
<td>5</td>
<td><img src="3h.png" alt="Chemical Structure" /></td>
<td><img src="4h.png" alt="Chemical Structure" /></td>
<td>80 °C</td>
</tr>
<tr>
<td>6</td>
<td><img src="3w.png" alt="Chemical Structure" /></td>
<td><img src="4w.png" alt="Chemical Structure" /></td>
<td>25-50 °C</td>
</tr>
</tbody>
</table>

Table 1.4: Trends in the [3,3] Rearrangement

1.12 Isolation of α-Hydroxy Ketones

Since the imidate products 4 of the [3,3] rearrangement of the \( N \)-enoxyphthalimides 3 were unstable to chromatography conditions, solutions of the imidates were directly
subjected to the next step which was hydrolysis to cleave the C–O bond and liberate the α-hydroxy ketones. An ion-exchange resin, Amberlite IR 140 provided optimal yields for the cleavage of the phthalimide, but silica gel was similarly effective with longer reaction times. The phthalimide byproduct, 9, that formed upon the hydrolysis was removed by base extraction using 1M NaOH (Scheme 1.28).

![Scheme 1.28: Isolation of α-Hydroxy Ketones](image)

The α-hydroxy ketones 5 that could be isolated immediately after hydrolysis were those that contained a bulky aryl substituent (5h-5l, 5v, and 5s) or a long chain alkyl group (5f) which made them non-volatile and water insoluble. The α-hydroxy ketones 5 isolated in this manner are shown below in Table 1.5. Substrates with the fluoro, trifluorometyl, nitro and methyl substituents on the aryl ring were tolerated through both the rearrangement and hydrolysis. These compounds exhibit good yields for the α-hydroxylation sequence. For the compound 5s, (entry 8, Table 1.5) a mixture of diastereomers was obtained. Upon conducting extensive nOe experiments on 5s, it was confirmed that a 60:40 mixture of cis:trans diastereomers was obtained. The cis diasteromer which is the thermodynamically favored product was the major isomer.
Table 1.5: α-Hydroxy Ketones Isolated following the Dioxygenation Scheme

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td><img src="attachment.png" alt="5f" /></td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td><img src="attachment.png" alt="5h" /></td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td><img src="attachment.png" alt="5i" /></td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td><img src="attachment.png" alt="5j" /></td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td><img src="attachment.png" alt="5k" /></td>
<td>86%</td>
</tr>
<tr>
<td>6</td>
<td><img src="attachment.png" alt="5l" /></td>
<td>82%</td>
</tr>
<tr>
<td>7</td>
<td><img src="attachment.png" alt="5v" /></td>
<td>67%</td>
</tr>
<tr>
<td>8</td>
<td><img src="attachment.png" alt="5s" /></td>
<td>82%</td>
</tr>
</tbody>
</table>

These compounds were made by Dr. Dong-Liang Mo, except compound 8 which was made by Heng-Yen Wang.

1.13 Isolation of α-Benzyloxy Ketones

The α-hydroxy ketones 5 which were either water soluble or volatile were protected in solution immediately after the hydrolysis using benzoyl chloride and a base (Scheme 1.29). These ketones could then be isolated as their corresponding benzoates (Table 1.6).

Scheme 1.29: Isolation of α-Benzyloxy Ketones
<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
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<td><img src="image" alt="6a" /></td>
<td>86%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="6m" /></td>
<td>66%*</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="6n" /></td>
<td>67%</td>
</tr>
</tbody>
</table>
| 4     | ![6o](image) | 66%**  
|       |          | dr = 20:80 cis:trans |
| 5     | ![6p](image) | 69%    
|       |          | dr = 55:45 cis:trans |

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
</table>
| 6     | ![6q](image) | 65%   
|       |          | dr = 55:45 cis:trans |
| 7     | ![6r](image) | 66%**  
|       |          | dr = 75:25 cis:trans |
| 8     | ![6t](image) | 69%    |
| 9     | ![6u](image) | 63%*   |

(* Indicates compounds made by Dr. Dong-Liang Mo and ** indicates compounds made by Heng-Yen Wang)

**Table 1.6:** α-Benzyloxy Ketones Isolated following the Dioxygenation Scheme
1.14 Diastereoselectivity Trends in the Rearrangement

The benzoyloxy ketones 6 derived from 3- and 4- substituted cyclohexenyl boronic acids (6p-6r, entries 5-7 in Table 1.6) were obtained in 55:45 and 75:25, cis/trans diastereomeric ratios, respectively. For all these compounds, the cis product, which is the thermodynamically favored product, is the major although the difference is more evident for 6r which has the bulky t-butyl substituent at the 4- position on the cyclohexanone ring. This is in contrast to 6o (entry 4, Table 1.6) which has a methyl group at the 6- position on the cyclohexanone ring. For this substrate, the diastereomeric ratio obtained was 20:80 favoring the more unstable trans diastereomer, thus indicating that the [3,3] rearrangement to form this product was under kinetic control.

Compounds 3o, 3p and 3q (entries 3-5, Table 1.4) underwent [3,3] rearrangements to give 15:85 (for 4o), 50:50 (for 4p, 4q) cis/trans diastereomeric mixtures of the imidate products and subsequent hydrolysis formed compounds 6o, 6p and 6q (entries 4-6, Table 1.6) with no significant change in the diastereomeric ratio. However, hydrolysis and protection of 3r, containing a bulky t-Bu substituent (entry 6, Table 1.3) epimerized the α-benzoyl group, resulting in a change in the cis/trans diastereomeric ratio of 60:40 to 75:25 as shown in Scheme 1.30.
Scheme 1.30: Effect of Hydrolysis on the Diastereoselectivity

Surprisingly, the rearrangement to form 6o (entry 4, Table 1.6) strongly favors formation of the trans diastereomer. It was assumed that this result is due to minimization of steric interactions as the rearrangement to form 4o occurs via a chair transition state (TS1) in Scheme 1.31. In contrast to 4-substituted cyclohexenyl substrates such as 3q, rotation for the approach of the carbonyl oxygen from the higher energy twist conformation to provide the cis diastereomer (Scheme 1.32) is inaccessible for 3o, because of the 6-methyl substituent, which inhibits rotation of the N-enoxypythalimide 3o around the C–O bond. A moderate increase in the cis/trans ratio from 15:85 to 20:80 was observed upon hydrolysis and protection.

To the best of our knowledge, the diastereomeric ratio observed for 6o represents the highest observed in favor of the trans isomer for 2-methylcyclohexanone α-oxygenation. This implies that the dioxygenation of alkenyl boronic acids may not only provide a new retrosynthetic disconnection for the preparation of α-oxygenated carbonyl compounds, but also provides access to relative stereochemical patterns not readily available through enolate oxidation procedures.
**Scheme 1.31**: Hindered Rotation Leads to the Kinetic Product

**Scheme 1.32**: Rotation of C–O Bond Results in Formation of Thermodynamic Product

### 1.15 Single Purification Sequence

During the reaction with an alkenyl boronic acid with a methoxy substituent on the aryl group, it was noticed that the product of the coupling reaction was a 2:1 mixture of the coupling and the α-hydroxy ketone 3w:5w (Scheme 1.33). This inspired us to determine if
the α-hydroxy ketones could be accessed with only a single purification step from the boronic acids.

Scheme 1.33: Using an Alkenyl Boronic Acid with an Electron Donating Aryl Substituent
(This work was done by Dr. Dong-Liang Mo).

To carry out this single purification sequence, the reaction mixture of the N-hydroxyphthalimide 2 and boronic acid 1w was passed through silica gel to remove the Cu(OAc)$_2$. This was followed by heating the crude product to 50 °C for 10 h and hydrolysis, to give the α-hydroxy ketone 5w in 57% yield over three steps (Scheme 1.34).

Scheme 1.34: Single Step Purification Sequence
(This work was done by Dr. Dong-Liang Mo.)

A similarly efficient process was also observed for the transformation of a Z-disubstituted dialkyl boronic acid 1a to a α-benzoyloxy ketone 6a in 67% overall yield with no formal purification of intermediates, only the removal of Cu(OAc)$_2$ prior to rearrangement.
The final product, the α-benzoyloxy ketone 6a was purified on silica gel, the only purification in the sequence (Scheme 1.35).

Scheme 1.35: Single Step Purification with a Dialkyl Boronic Acid

1.16 Exploring the Mechanism for the Reaction

For the future endeavors, to make the dioxygenation stereoselective, it was necessary to probe the mechanism of the reaction. It was imperative to comprehend whether the reaction was intermolecular or intramolecular and whether it followed a radical pathway. The understanding of the nature of the transition state in the pericyclic reaction would provide valuable information that could be used in controlling the stereochemistry for the rearrangement.

1.16.1 Cross-Over Experiment

The diastereoselectivity observed for the rearrangement of the substituted cyclohexenyl boronic acids suggested that the [3,3] rearrangements of N-enoxypthalimides 3 proceeded by a unimolecular pericyclic reaction. The intramolecular nature of the transition state was further supported by a crossover experiment using N-enoxypthalimides 3d and 3x shown below in Scheme 1.36.
Cross-Over Experiment

When a 1:1 mixture of these compounds, the $N$-enoyphthalimide derived from hexenyl boronic acid 3d and the $N$-enoyphthalimide containing a methyl substituent on the benzene ring and derived from the cyclohexenyl boronic acid 3x, was heated in C$_6$D$_6$ at 90 °C for 18 h, the only products obtained were from the intermolecular reaction 4d and 4x and there was no evidence of crossover by $^1$H or $^{13}$C NMR spectroscopy.

1.16.2 Radical Clock Experiment

To investigate the possibility of a radical reaction pathway, a radical clock experiment was tested with $N$-enoyphthalimide bearing a vinyl cyclopropyl group 3y. Upon heating this substrate in either the presence or the absence of Bu$_3$SnH (Scheme 1.37), no indication of the formation of an $\alpha,\beta$-unsaturated aldehyde was observed, suggesting that the [3,3] rearrangement occurs through a two electron pathway and does not follow a radical pathway. This work was done by Heng-Yen Wang.

Scheme 1.37: Radical Clock Experiment
1.17 Conclusion
In summary, the dioxygenation of alkenyl boronic acids 1 with N-hydroxyphthalimide 2 has been achieved through a two-step process involving copper-mediated etherification to form an N-enoxyphthalimide 3 and a subsequent [3,3] rearrangement to provide α-hydroxy ketones 5 or α-benzoyloxy ketones 6 after hydrolysis of the phthalimide imidate 4. This transformation provides a new retrosynthetic disconnection for the preparation of α-oxygenated carbonyl compounds directly from internal alkynes and does not require the use of a highly reactive electrophilic oxygen source or a carbonyl compound as a starting material.

1.18 Supporting Information
1.18.1 General Experimental Information

$^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 µm) mesh silica gel (SiO$_2$). Medium pressure liquid chromatography was performed to force flow the indicated solvent system down columns packed with 60Å (40 – 60 µm) mesh silica gel (SiO$_2$). Unless otherwise noted, all reagents
were obtained from commercial sources and, where appropriate, purified prior to use. THF, CH₂Cl₂, and toluene were dried by filtration through alumina according to the procedure of Grubbs.¹ TMEDA was distilled over CaH₂ and stored under N₂ prior to use. Amberlite-IR120 was washed with CH₂Cl₂ prior to use. Boronic acids 1b and 1c were commercially available from Aldrich and used as received. Boronic acids 1d and 1e were prepared according to a literature procedures. Boronic acids used for the preparation of N-enoxypythalimides that were not commercially available were prepared by: 1) hydroboration of the corresponding alkyne with HBBr₂·SMe₂ followed by hydrolysis, 2) hydrolysis of the corresponding boronic acid pinacol ester, or 3) formation of the corresponding vinyl anion from a hydrazone precursor followed by electrophilic trapping by B(OR)₃ and hydrolysis. The boronic acids were used as isolated from these procedures without further purification.

1.18.2 Experimental Procedures and Characterization Data

I. General procedure A: Preparation of boronic acids from alkynes

A round bottom flask was flame-dried under N₂, charged with an alkyne (1 equiv) and cooled to 0 °C with an ice-water bath. The alkyne was then diluted with a 1M solution of HBBr₂·SMe₂ in CH₂Cl₂ (1.2 equiv) and allowed to stir for 2 h. The reaction mixture was then transferred to 60 mL of a 10:1 mixture of diethyl ether and water and allowed to stir for 15 minutes. The reaction mixture was then diluted with additional diethyl ether (40 mL) and extracted with water (3 x 5 mL). The organic layer was then dried with brine (10 mL) and MgSO₄ and concentrated under reduced pressure to give a crude sample of the alkenyl
boronic acid. This crude sample was then used for the copper-coupling reaction without further purification. Any impurities carried on to the copper-coupling reaction were not observed to affect the efficiency of the process when compared to the use of a pure sample of boronic acid. The alkyne precursors for 1f and 1h are commercially available from Aldrich and were used without further purification. The alkyne precursors for 1i-1l and 1w were prepared according to literature procedures.

\[
\text{HO}_2\text{B} \quad \begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]

1a

2-Butenyl boronic acid 1a: General procedure A was followed using 2-butyne (5.00 g, 92.4 mmol) and a 1M solution of HBB\(_2\)-SMe\(_2\) in CH\(_2\)Cl\(_2\) (81.0 mL, 81.0 mmol). Hydrolysis and workup gave 1a as an off-white solid (6.61 g, 82%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.83 (q, \(J = 6.5\), 1H), 1.80 (d, \(J = 6.5\) Hz, 3H), 1.75 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 143.6, 14.8, 12.7.

\[
\text{HO}_2\text{B} \quad \begin{array}{c}
\text{C}_9\text{H}_{11} \\
\text{C}_9\text{H}_{11}
\end{array}
\]

1f

6-Dodecen-6-yl boronic acid 1f: General procedure A was followed using 6-dodecyn (3.6 mL, 20 mmol) and a 1M solution of HBB\(_2\)-SMe\(_2\) in CH\(_2\)Cl\(_2\) (22 mL, 22 mmol). Hydrolysis and workup gave 1f as an oil (2.74 g, 65%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.67 (t, \(J = 7.0\) Hz, 1H), 2.20-2.19 (m, 4H), 1.43-1.25 (m, 12H), 0.90-0.89 (m, 6H), the OH of the boronic
acid was too broad to be observed above the baseline; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$149.2, 32.3, 32.2, 30.1, 28.9, 28.8, 28.0, 22.7, 22.6, 14.1, 14.0, the C-B resonance was too broad to be observed; IR (thin film) 3229, 2956, 2926, 2858, 1462, 1373, 1335, 728 cm$^{-1}$; HRMS (Cl$^+$) m/z calcd. for C$_{12}$H$_{26}$BO$_2$ (M+H)$^+$ 213.2026, found 213.2028.

![Structure 1h](image)

**1-Phenyl-1-butynyl boronic acid 1h:** A modified version of general procedure A was followed using 1-phenyl-1-butyne (2.8 mL, 20 mmol) and a 1M solution of HBB$_2\cdot$SMe$_2$ in CH$_2$Cl$_2$ (22 mL, 22 mmol). The mixture of HBB$_2\cdot$SMe$_2$ and alkyne was allowed to stir for 12 h at 25 °C and then refluxed for 4h at 70 °C. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et$_2$O:H$_2$O and allowed to stir for 1 h. Workup then gave 1h as an oil (2.5 g, 71%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.62 (d, $J = 7.5$ Hz, 2H), 7.41-7.36 (m, 3H), 6.95 (t, $J = 7.5$ Hz, 1H), 2.26-2.17 (m, 2H), 0.88 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 149.1, 129.2, 128.3, 127.6, 125.8, 22.7, 14.2, the C-B resonance was too broad to be observed; IR (thin film) 3303, 2959, 2933, 2850, 1599, 1500, 1337, 1223, 830 cm$^{-1}$; HRMS (EI) m/z calcd. for C$_{11}$H$_{15}$BO$_2$ (M-OH+MeOH)$^+$ 190.1165, found 190.1168 (in MeOH, one of the OH groups was replaced by OMe).

![Structure 1i](image)
1-(p-F-phenyl)-1-hexynyl boronic acid 1i: A modified version of general procedure A was followed using 1-(p-F-phenyl)-1-hexyne (1.20 g, 7.00 mmol) and a 1M solution of HBr:MeOH in CH₂Cl₂ (8.40 mL, 8.40 mmol). The mixture of HBr:MeOH and alkyne was allowed to stir for 12 h at 25 °C and then refluxed for 4 h at 70 °C. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et₂O:H₂O and allowed to stir for 1 h. Workup gave 1i as an oil (1.10 g, 74%). ¹H NMR (500 MHz; CDCl₃): δ 7.62-7.59 (m, 2H), 7.04-7.00 (m, 2H), 6.88 (t, J = 7.0 Hz, 1H), 2.02-1.99 (m, 1H), 1.42-1.35 (m, 2H), 1.25-1.17 (m, 3H), 0.87 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 160.3 (d, J = 251 Hz), 152.4, 130.6, 130.5, 114.3 (d, J = 9.1 Hz), 31.2, 29.9, 22.3, 13.9, the C-B resonance was too broad to be observed; IR (thin film) 3209, 2959, 2933, 2865, 1597, 1500, 1335, 1223, 830, 732 cm⁻¹; HRMS (EI) m/z calcd. for C₁₃H₁₈BO₂F (M-OH+OMe)⁺ 236.1384, found 236.1386 (in MeOH, one of the OH groups was replaced by OMe).

![Structure of 1i](image.png)

1-(p-NO₂-phenyl)-1-hexynyl boronic acid 1j: A modified version of general procedure A was followed using 1-(p-NO₂-phenyl)-1-hexyne (1.40 g, 6.90 mmol) and a 1M solution of HBr:MeOH in CH₂Cl₂ (8.00 mL, 8.00 mmol). The mixture of HBr:MeOH and alkyne was allowed to stir for 12 h at 25 °C and then refluxed for 4 h at 70 °C. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et₂O:H₂O and allowed to stir for 1 h. Workup gave 1j as an oil (1.44 g, 80 %). ¹H NMR (500 MHz; CDCl₃): δ 8.20 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 6.90 (t, J = 7.0 Hz, 1H), 2.03-2.00 (m, 1H), 1.40-1.31 (m, 2H), 1.24-
1.18 (m, 3H), 0.82 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 152.1, 146.6, 132.3, 131.2, 123.5, 32.4, 26.7, 22.1, 13.8, the C-B resonance was too broad to be observed; IR (thin film) 3509, 3008, 2959, 2922, 2855, 1590, 1511, 1323, 1279, 856, 748 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{16}$NO$_3$BNa (M+Na)$^+$ 272.1070, found 272.1076.

![Diagram of 1k](image)

**1-(p-CF$_3$-phenyl)-1-hexynyl boronic acid 1k:** A modified version of general procedure A was followed using 1-(p-CF$_3$-phenyl)-1-butyne (2.00 g, 8.80 mmol) and a 1M solution of HBBr$_2$·SMe$_2$ in CH$_2$Cl$_2$ (9.00 mL, 9.00 mmol). The mixture of HBBr$_2$·SMe$_2$ and alkyne was allowed to stir for 12 h at 25 ºC and then refluxed for 4h at 70 ºC. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et$_2$O:H$_2$O and allowed to stir for 1 h. Workup gave 1k as an oil (2.20 g, 91%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.49 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.91 (t, $J = 7.5$ Hz, 1H), 2.18-2.12 (m, 1H), 1.43-1.36 (m, 2H), 1.29-1.24 (m, 3H), 0.88 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 153.6, 143.4, 129.3, 129.1, 125.3 (q, $J = 3.8$ Hz), 124.5, 31.2, 29.9, 22.3, 13.8, the C-B resonance was too broad to be observed and the sample was too insoluble to observed further $^{13}$C-$^{19}$F coupling constants; IR (thin film) 3213, 2959, 2929, 2869, 1612, 1317, 1166, 1126, 1066, 837, 722 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{14}$H$_{18}$O$_2$BF$_3$ (M-OH+OMe)$^+$ 286.1352, found 286.1346 (in MeOH, one of the OH groups was replaced by OMe).
1-(p-Me-phenyl)-1-hexynyl boronic acid 1l: A modified version of general procedure A was followed using 1-(p-Me-phenyl)-1-butyne (1.40 g, 8.10 mmol) and a 1M solution of HBr2·SMe2 in CH2Cl2 (9.70 mL, 9.70 mmol). The mixture of HBr2·SMe2 and alkyne was allowed to stir for 12 h at 25 ºC and then refluxed for 4h at 70 ºC. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et2O:H2O and allowed to stir for 1 h. Workup gave 1l as an oil (1.10 g, 62%). 1H NMR (500 MHz; CDCl3): δ 7.82 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 2.38 (s, 3H), 2.29-2.19 (m, 1H), 1.44-1.34 (m, 2H), 1.31-1.21 (m, 3H), 0.92 (t, J = 7.5 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 146.1, 135.0, 129.3, 129.0, 128.2, 31.5, 29.8, 21.3, 21.1, 13.9, the C-B resonance was too broad to be observed; IR (thin film) 3203, 2959, 2926, 2873, 1605, 1410, 1380, 1331, 808, 722 cm⁻¹; HRMS (ESI) m/z calcd. for C14H21O2B (M-OH+MeOH)+ 232.1634, found 232.1639 (in MeOH, one of the OH groups was replaced by OMe).

1-(p-OMe-phenyl)-1-hexynyl boronic acid 1w: A modified version of general procedure A was followed using 1-(p-OMe-phenyl)-1-butyne (1.30 g, 7.00 mmol) and a 1M solution of HBr2·SMe2 in CH2Cl2 (8.40 mL, 8.40 mmol). The mixture of HBr2·SMe2 and alkyne was
allowed to stir for 12 h at 25 °C and then refluxed for 4 h at 70 °C. The reaction mixture was then treated with 105 mL of a 2.5:1 mixture of Et₂O:H₂O and allowed to stir for 1 h. Workup gave 1w as an oil (1.45 g, 85 %). ¹H NMR (500 MHz; CDCl₃): δ 7.94 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 7.0 Hz, 1H), 3.86 (s, 3H), 2.25-2.20 (m, 1H), 1.43-1.35 (m, 2H), 1.29-1.21 (m, 3H), 0.89 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 163.9, 151.5, 130.8, 130.4, 113.7, 55.3, 34.8, 29.9, 22.4, 14.0, the C-B resonance was too broad to be observed; IR (thin film) 3213, 2952, 2929, 2862, 1605, 1406, 1245, 1170, 1032, 798, 725 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₂₁O₃B (M-OH+OMe)⁺ 248.1584, found 248.1593 (in MeOH, one of the OH groups was replaced by OMe).

II. General procedure B: Preparation of boronic acids from boronic acid pinacol esters

A scintillation vial was charged with alkenyl boronic acid pinacol ester (1 equiv), NaIO₄ (3 equiv), and NH₄OAc (3 equiv). These reagents were then diluted with a mixture of acetone and water in a 1:1 ratio to form a 0.04 M solution of the alkenyl boronic acid pinacol ester. The resulting slurry was allowed to stir vigorously for 2 d. The slurry was then filtered and diluted with ethyl acetate or diethyl ether and extracted with water. The organic layer was then dried with brine and MgSO₄ and concentrated under reduced pressure to give a crude sample of the alkenyl boronic acid. This crude sample was then used for the copper-coupling reaction without further purification. Any impurities carried on to the copper-coupling
reaction were not observed to affect the efficiency of the process when compared to the use of a pure sample of boronic acid. The alkenyl boronic acid pinacol ester precursors for 1n, 1m, 1t, and 1u are commercially available from Frontier Scientific and were used as received. The alkenyl boronic acid pinacol ester precursors for 1o, 1p, 1r, 1r, 1s were prepared by literature procedures.

1-Cyclopentenyl boronic acid 1m: General procedure B was used with 1-cyclopentenyl boronic acid pinacol ester (0.097 g, 0.50 mmol), NaIO₄ (0.312 g, 1.50 mmol), and NH₄OAc (0.116 g, 1.50 mmol) to give a crude sample of 1m (0.050 g, 66%). ¹H NMR (500 MHz; CDCl₃): δ 6.83-6.81 (m, 1H), 2.43-2.20 (m, 4H), 1.85-1.79 (m, 2H), the O-H resonances were too broad to be observed; ¹³C NMR (125 MHz, CDCl₃): δ 148.3, 29.3, 28.1, 21.6, the C-B resonance was too broad to be observed; IR (thin film) 2930, 2859, 1626, 1376, 1353, 1320, 1255, 1138, 1070, 1024 cm⁻¹; HRMS (EI) m/z calcd. for C₆H₁₁BO₂ (M-OH+OMe)⁺ 126.0852, found 126.0862 (in MeOH one of the OH groups was replaced by OMe).

1-Cyclohexenyl boronic acid 1n: General procedure B was used with 1-cyclohexenyl boronic acid pinacol ester (0.100 g, 0.480 mmol), NaIO₄ (0.308 g, 1.40 mmol), and NH₄OAc (0.111 g, 1.40 mmol) to give a crude sample of 1n (0.037 g, 61%). ¹H NMR (500 MHz;
CDCl$_3$): $\delta$ 7.00-6.93 (m, 1H), 2.18-2.09 (m, 4H), 1.63-1.62 (m, 4H), the O-H resonances were too broad to be observed; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 145.8, 27.0, 25.4, 22.6, 22.3, the C-B resonance was too broad to be observed; IR (thin film) 2930, 2859, 1626, 1376, 1353, 1320, 1255, 1138, 1070, 1024 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{27}$B$_3$O$_3$ (3(M-OH))$^+$ 324.22395, found 324.22467 (mass found for the trimeric anhydride); mp 122 ºC.

![Pinacol ester s1](image)

**Pinacol ester s1**: A 100 mL round bottom flask was flame-dried under N$_2$ and charged with the N-tosylhydrazone of 2-methylcyclohexanone (1.48 g, 5.28 mmol), hexanes (7.4 mL), and TMEDA (15.8 mL). The resulting slurry was cooled to -78 ºC with a dry ice-acetone bath and a 2.5 M n-BuLi solution in hexane (8.45 mL, 21.1 mmol) was added via syringe. The reaction mixture was allowed to stir at -78 ºC for 1 h and then allowed to warm to 25 ºC. After stirring for an additional 1 h, the reaction mixture was cooled to -78 ºC with a dry ice-acetone bath and pinacol isopropyl borate (2.15 mL, 10.6 mmol) was added via syringe. The reaction mixture was allowed to warm to 25 ºC and stir for 3 h. The reaction was quenched with saturated NH$_4$Cl(aq) solution (5 mL) and extracted with diethyl ether. The organic extracts were combined, dried with MgSO$_4$, and concentrated under reduced pressure. The crude product was purified by medium pressure chromatography (1:50, ethyl acetate: hexanes) to give a light yellow oil (0.422 g, 36%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.52-6.51 (m, 1H), 2.36 (d, $J = 5.0$ Hz, 1H), 2.02 (d, $J = 2.5$ Hz, 2H), 1.67-1.62 (m, 2H), 1.52-1.50 (m, 1H), 1.36-1.33 (m, 1H), 1.25 (s, 12H), 1.03 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz,
CDCl$_3$): $\delta$ 142.3, 83.1, 30.6, 30.2, 26.9, 24.6, 21.7, 19.1, the C-B resonance was too broad to be observed above the baseline; IR (thin film) 2978, 2926, 2869, 1628, 1369, 1311, 1213, 1144, 860, 696 cm$^{-1}$.

![Image of 6-Methyl-1-cyclohexenyl boronic acid](image)

**6-Methyl-1-cyclohexenyl boronic acid 1o:** General procedure B was used with 6-methyl-1-cyclohexenyl boronic acid pinacol ester s1 (0.419 g, 1.89 mmol), NaIO$_4$ (1.30 g, 6.08 mmol), and NH$_4$OAc (0.589 g, 7.64 mmol) to give a crude sample of 1o (0.080 g, 30%) as an amorphous solid. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.93-6.92 (m, 1H), 1.68-1.66 (m, 1H), 1.58-1.56 (m, 1H), 1.47-1.45 (m, 1H), 1.35-1.33 (m, 1H), 1.22-1.18 (m, 1H), 1.10 (d, $J$ = 3.5 Hz, 3H), 0.92-0.89 (m, 1H), 0.79 (t, $J$ = 7.0 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 145.7, 30.3, 29.2, 27.2, 21.4, 18.3, the C-B resonance was too broad to be observed above the baseline; IR (thin film) 3388, 2921, 2869, 1621, 1362, 1320, 1158, 1040, 810, 732 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_7$H$_{13}$O$_2$B (M)$^+$ 140.1005, found 140.1009.

![Image of 3-Methyl-1-cyclohexenyl boronic acid](image)

**3-Methyl-1-cyclohexenyl boronic acid 1p:** General procedure B was used with 3-methyl-1-cyclohexenyl boronic acid pinacol ester (0.100 g, 0.450 mmol), NaIO$_4$ (0.299 g, 1.40 mmol), and NH$_4$OAc (0.109 g, 1.40 mmol) to give a crude sample of 1p (0.050 g, 79%) as an
amorphous solid. $^1$H NMR (500 MHz; CDCl$_3$): δ 6.75-6.73 (m, 1H), 2.27-2.15 (m, 2H), 2.14-2.04 (m, 2H), 1.79-1.72 (m, 2H), 1.51-1.50 (m, 1H), 1.03 (d, $J = 5$ Hz, 3H), the O-H resonances were too broad to be observed; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 151.31, 31.66, 30.97, 25.52, 21.55, 21.18, the C-B resonance was too broad to be observed; IR (thin film) 2959, 2923, 2860, 1623, 1449, 1376, 1313, 1253, 740, 718 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{33}$O$_3$B$_3$ (3(M-OH))$^+$ 366.27090, found 366.27014 (mass found for the trimeric anhydride).

![](image)

4-Methyl-1-cyclohexenyl boronic acid 1q: General procedure B was used with 6-methyl-1-cyclohexenyl boronic acid pinacol ester (0.106 g, 0.472 mmol), NaIO$_4$ (0.303 g, 1.41 mmol), and NH$_4$OAc (0.109 g, 1.41 mmol) to give a crude sample of 1q as an amorphous solid (0.380 g, 56%). $^1$H NMR (500 MHz; CDCl$_3$): δ 6.91-6.90 (m, 1H), 2.36-2.30 (m, 2H), 2.17-2.10 (m, 1H), 1.77-1.72 (m, 3H), 1.19-1.13 (m, 1H), 0.96 (d, $J = 6.5$ Hz, 3H), the O-H resonances were too broad to be observed; $^{13}$C NMR (125 MHz, CDCl$_3$): δ 145.4, 35.6, 31.0, 28.2, 25.6, 22.0, the C-B resonance was too broad to be observed; IR (thin film) 2952, 2914, 1626, 1379, 1324, 1258, 1229, 1093, 1009, 904.45 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{33}$B$_3$O$_3$ (3(M-OH))$^+$ 366.27090, found 366.27178 (mass found for the trimeric anhydride).
4-t-Butyl-1-cyclohexenyl boronic acid 1r: General procedure B was used with 4-t-Butyl-1-cyclohexenyl boronic acid pinacol ester (0.128 g, 0.485 mmol), NaIO₄ (0.340 g, 1.60 mmol), and NH₄OAc (0.149 g, 1.93 mmol) to give a crude sample of 1r (0.042 g, 48%). ¹H NMR (500 MHz; CDCl₃): δ 6.94-6.90 (m, 1H), 2.44-2.40 (m, 1H), 2.22-2.18 (m, 1H), 2.09-2.05 (m, 1H), 1.95-1.90 (m, 1H), 1.87-1.84 (m, 1H), 1.31-1.21 (m, 1H), 1.12-1.06 (m, 1H), 0.88 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 146.4, 44.1, 32.4, 29.0, 27.3, 24.2, 17.4, the C-B resonance was too broad to be observed above the baseline; IR (thin film) 2992, 2974, 2959, 2873, 1451, 1428, 1317, 1283, 1234, 882 cm⁻¹; HRMS (ESI) m/z calcd. for C₃₀H₄₅O₃B₃ (3(M-OH))⁺ 492.41175, found 492.41161 (mass found for the trimeric anhydride).

4-Phenyl-1-cyclohexenyl boronic acid 1s: General procedure B was used with 4-phenyl-1-cyclohexenyl boronic acid pinacol ester (0.246 g, 0.897 mmol), NaIO₄ (0.603 g, 2.69 mmol), and NH₄OAc (0.353 g, 2.69 mmol) to give a crude sample of 1s (0.155 g, 86%). ¹H NMR (500 MHz; CDCl₃): δ 7.34-7.30 (m, 2H), 7.25-7.20 (m, 3H), 7.07 (d, J = 2.5 Hz, 1H), 2.83-2.81 (m, 1H), 2.52-2.51 (m, 1H), 2.33-2.26 (m, 3H), 2.02-2.00 (m, 1H), 1.75-1.72 (m, 1H), the O-H resonances were too broad to be observed; ¹³C NMR (125 MHz, CDCl₃): δ 145.4, 128.4, 126.9, 126.8, 126.1, 39.9, 35.2, 29.9, 26.2, the C-B resonance was too broad to be
observed; IR (thin film) 3086, 3056, 3027, 2956, 2923, 2855, 1629, 1375, 1340, 1265 cm\(^{-1}\);
HRMS (EI) m/z calcd. for C\(_{36}\)H\(_{39}\)O\(_3\)B\(_3\) (3(M-OH))\(^+\) 552.31785, found 552.31834 (mass found for the trimeric anhydride).

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\text{1o}
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3,6-Dihydro-2H-pyran-4-boronic acid 2o: General procedure B was used with 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (0.060 g, 0.29 mmol), NaIO\(_4\) (0.183 g, 0.856 mmol), and NH\(_4\)OAc (0.066 g, 0.86 mmol) to give a crude sample of 1o (0.018 g, 48%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.90-6.89 (m, 1H), 4.26-4.25 (m, 2H), 3.78-3.75 (m, 2H), 2.30-2.29 (m, 2H), the O-H resonances were too broad to be observed; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 144.4, 66.3, 64.3, 25.5, the C-B resonance was too broad to be observed; IR (thin film) 2966, 2926, 2859, 2822, 1635, 1392, 1372, 1317, 1223, 1122 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{15}\)H\(_{21}\)B\(_3\)O\(_6\) (3(M-OH))\(^+\) 330.16174, found 330.16138 (mass found for the trimeric anhydride); decomp. 130 °C.

\[
\text{1u}
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4-Ketal-1-cyclohexenyl boronic acid 1u: General procedure B was used with 4-phenyl-1-cyclohexenyl boronic acid pinacol ester (0.066 g, 0.25 mmol), NaIO\(_4\) (0.160 g, 0.750 mmol), and NH\(_4\)OAc (0.083 g, 0.75 mmol) to give a crude sample of 1u (0.033 g, 70%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.83-6.81 (m, 1H), 3.99 (s, 4H), 2.44-2.40 (m, 4H), 1.74 (m, 2H), the
O-H resonances were too broad to be observed; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 149.4, 96.8, 64.5, 34.1, 30.6, 23.5, the C-B resonance was too broad to be observed; IR (thin film) 3416, 2926, 2895, 1631, 1365, 1343, 1114, 1058, 1028 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_8$H$_{13}$BO$_4$Na (M+Na)$^+$ 207.0805, found 207.0809; mp 128-130 °C.

III. General procedure C: Preparation of boronic acids from N-tosyl hydrazones

![Chemical Reaction]

A 100 mL round bottom flask was flame-dried under N$_2$ and charged with N-tosylhydrazone (1 equiv), hexanes (3 mL/mmol hydrazone), and TMEDA (3 mL/mmol hydrazone). The resulting slurry was cooled to -78 °C with a dry ice-acetone bath and a 2.5 M n-BuLi solution in hexane (4 equiv) was added via syringe. The reaction mixture was allowed to stir at -78 °C for 1 h and then allowed to warm to 25 °C. After stirring for an additional 2 h, the reaction mixture was cooled to -78 °C with a dry ice-acetone bath and B(Oi-Pr)$_3$ or B(OMe)$_3$ was added via syringe. After 2 h the reaction mixture was quenched with 8 M HCl, and acidified to pH 4. The aqueous layer was reserved and the organic layer was extracted with 4 M NaOH (2 x 20 mL). The aqueous phases were then combined and acidified to pH 4 with concentrated HCl, followed by extraction with diethyl ether (3 x 40 mL). The organic layers were then dried with brine and MgSO$_4$ and concentrated under reduced pressure to give a crude sample of the alkenyl boronic acid. This crude sample was then used for the copper-coupling reaction without further purification. Any impurities carried on to the copper-coupling reaction were not observed to affect the efficiency of the process when compared to
the use of a pure sample of boronic acid. The hydrazone precursors were prepared by literature procedures.

\[ \text{1o} \]

6-Methyl-1-cyclohexenyl boronic acid 1o: General procedure C was used on the N-tosyl hydrazone of 2-methylcyclohexanone (2.13 g, 7.61 mmol), n-BuLi (12.2 mL, 30.4 mmol), and B(Oi-Pr)\(_3\) (5.26 mL, 22.8 mmol) to give crude sample 1o (0.138 g, 13%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.93-6.92 (m, 1H), 1.68-1.66 (m, 1H), 1.58-1.56 (m, 1H), 1.47-1.45 (m, 1H), 1.35-1.33 (m, 1H), 1.22-1.18 (m, 1H), 1.10 (d, \(J = 3.5\) Hz, 3H), 0.92-0.89 (m, 1H), 0.79 (t, \(J = 7\) Hz, 1H), the O–H resonances were too broad to be observed; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 145.7, 30.3, 29.2, 27.2, 21.4, 18.3, the C-B resonance was too broad to be observed above the baseline; IR (thin film) 3388, 2921, 2869, 1621, 1362, 1320, 1158, 1040, 810, 732 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_7\)H\(_{13}\)O\(_2\)B (M)\(^+\) 140.1005, found 140.1009.

\[ \text{1v} \]

\(\alpha\)-Tetralone boronic acid 1v: General procedure C was used with \(\alpha\)-tetralone N-tosyl hydrazone\(^{19\)} (2.61 g, 8.30 mmol), n-BuLi (13.3 mL, 33.2 mmol), and B(OMe)\(_3\) (3.70 mL, 33.2 mmol) to give crude sample 1v (0.607 g, 42%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 8.03 (d, \(J = 8.0\) Hz, 1H), 7.54-7.53 (m, 1H), 7.29-7.27 (m, 1H), 7.22-7.18 (m, 2H), 2.82-2.80 (m, 2H),
2.46-2.42 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 149.8, 136.0, 135.0, 127.6, 127.3, 126.8, 126.5, 27.9, 24.6, the C-B resonance was too broad to be observed above the baseline; IR (thin film) 3405, 3021, 2930, 1600, 1486, 1382, 1336, 1275, 1044, 765 cm\(^{-1}\).

IV. Copper-Catalyzed and Copper-Promoted Etherification of \(N\)-Hydroxyphthalimides with Vinyl Boronic Acids (Tables 1.2, 1.3)

![Diagram](image)

**General procedure D:** Copper-promoted etherification of \(N\)-hydroxyphthalimide with vinyl boronic acids. A scintillation vial was charged with \(N\)-hydroxyphthalimide 2 (1 equiv), vinyl boronic acid 1 (2 equiv), Cu(OAc)\(_2\) (1 equiv), and anhydrous Na\(_2\)SO\(_4\) (4-6 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of \(N\)-hydroxyphthalimide. Pyridine (3 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 °C for 12 h. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (1:19 - 1:2; ethyl acetate:hexanes) to give \(N\)-enoxypthalimide 3 as a white solid.
**General procedure E:** Copper-catalyzed etherification of N-hydroxyphthalimide with vinyl boronic acids. A scintillation vial was charged with N-hydroxyphthalimide 2 (1 equiv), vinyl boronic acid 1 (2 equiv), Cu(OAc)$_2$ (20 mol %), and anhydrous Na$_2$SO$_4$ (4-6 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of N-hydroxyphthalimide. Pyridine (3 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 ºC for 12-48 h. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (1:19 - 1:2; ethyl acetate:hexanes) to give N-enoxophthalimide 3 as a white solid.

**N-Enoxophthalimide 3a:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-2-buten-2-yl boronic acid 1a (0.060 g, 0.60 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.256 g, 1.80 mmol), and pyridine (72.6 µl, 0.900 mmol) afforded 3a as a white solid (0.065 g, 98%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.89-7.86 (m, 2H), 7.80-7.76 (m, 2H),
4.85 (q, \( J = 7.0 \text{ Hz, 1H} \)), 1.99 (s, 3H), 1.56 (d, \( J = 7.0 \text{ Hz, 3H} \)); \(^{13}\text{C NMR (125 MHz, CDCl}_{3}\)): \( \delta \) 163.0, 152.4, 134.6, 128.9, 123.7, 96.4, 13.1, 11.2; IR (thin film) 3066, 3004, 2965, 2930, 1791, 1729, 1700, 1609, 1469, 1186 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{12}\)H\(_{11}\)NO\(_3\)Na (M+Na\(^+\)) 240.0637, found 240.0636; mp 112-115 °C.

General procedure E with \( N \)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-2-buten-2-yl boronic acid 1a (0.060 g, 0.60 mmol), Cu(OAc)\(_2\) (0.0108 g, 0.0593 mmol), Na\(_2\)SO\(_4\) (0.256 g, 1.80 mmol), and pyridine (72.6 \( \mu \text{l, 0.9 mmol} \)) afforded 3a after 48 h. \( N \)-Enoxy phthalimide 3a was isolated as a white solid (0.0505 g, 76%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

General procedure D with \( N \)-hydroxyphthalimide 2 (0.164 g; 1.01 mmol), Z-2-buten-2-yl boronic acid 1a (0.201 g, 2.01 mmol), Cu(OAc)\(_2\) (0.183 g, 1.01 mmol), Na\(_2\)SO\(_4\) (0.613 g, 1.80 mmol), and pyridine (240 \( \mu \text{l, 3.015 mmol} \)) afforded 3a as a white solid (0.163 g, 74%).

\( N \)-Enoxyphthalimide 3b: General procedure D with \( N \)-hydroxyphthalimide 2 (0.070 g; 0.43 mmol), \( trans \)-2-cyclohexylvinyl boronic acid 1b (0.132 g, 0.858 mmol), Cu(OAc)\(_2\) (0.078 g, 0.43 mmol), Na\(_2\)SO\(_4\) (0.260 g, 1.32 mmol), and pyridine (100 \( \mu \text{l, 1.29 mmol} \)) afforded 3b as a white solid (0.101 g, 87%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). \(^{1}\text{H NMR (500 MHz; CDCl}_{3}\): \( \delta \) 7.83-7.80 (m, 2H), 7.76-7.74 (m, 2H), 6.39 (d, \( J = 12.5 \text{ Hz, 1H} \)), 5.23 (dd, \( J = 12.5 \text{ Hz, 7.5 Hz, 1H} \)), 1.94-1.88 (m, 1H), 1.66-1.64
(m, 4H), 1.59-1.56 (m, 1H), 1.23-1.16 (m, 2H), 1.12-0.99 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.6, 144.8, 134.7, 128.7, 123.7, 115.8, 35.9, 33.1, 25.9, 25.9; IR (thin film) 2929, 2851, 1799, 1729, 1661, 1467, 1362, 1186, 1122, 1059 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{17}$NO$_3$Na (M+Na)$^+$ 294.1106, found 294.1109; mp 87 ºC.

General procedure E with N-hydroxyphthalimide 2 (0.070 g; 0.43 mmol), trans-2-cyclohexylvinyl boronic acid 1b (0.132 g, 0.860 mmol), Cu(OAc)$_2$ (0.016 g, 0.086 mmol), Na$_2$SO$_4$ (0.260 g, 1.83 mmol), and pyridine (100 µL, 1.29 mmol) afforded 3c after 48 h. N-Enoxy phthalimide 3b was isolated as a white solid (0.086 g, 74%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

![Image of 3c](image_url)

$\textbf{N-Enoxyphthalimide 3c:}$ General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.30 mmol), trans-2-phenylvinyl boronic acid 1c (0.089 g, 0.60 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.30 mmol), and pyridine (0.0724 g, 0.900 mmol) afforded 3c as a white solid (0.069 g, 88%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.92-7.91 (m, 2H), 7.82-7.80 (m, 2H), 7.29-7.20 (m, 5H), 7.16 (d, $J = 12.5$ Hz, 1H), 6.33 (d, $J = 12.5$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.5, 147.3, 134.9, 133.3, 128.8, 128.7, 127.3, 126.2, 124.0, 111.0; IR (thin film) 2922, 2835, 1730, 1600, 1497, 1366, 1179, 1108, 798 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{12}$NO$_3$ (M+H)$^+$ 266.0817, found 266.0811; mp 110-112 ºC.
General procedure E with \(N\text{-hydroxyphthalimide } 2\) (0.050 g; 0.30 mmol), \textit{trans}-2-phenylvinyl boronic acid \(1c\) (0.089 g, 0.60 mmol), \(\text{Cu(OAc)}_2\) (0.011 g, 0.060 mmol), \(\text{Na}_2\text{SO}_4\) (0.187 g, 1.30 mmol), and pyridine (0.0724 g, 0.900 mmol) afforded \(3c\) after 24 h. \(N\text{-Enoxyphthalimide } 3c\) was isolated as a white solid (0.062 g, 78%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).

\[
3c
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\(N\text{-Enoxyphthalimide } 3d:\) General procedure D with \(N\text{-hydroxyphthalimide } 2\) (0.032 g; 0.20 mmol), \textit{trans}-1-hexenyl boronic acid \(1d\) (0.050 g, 0.39 mmol), \(\text{Cu(OAc)}_2\) (0.035 g, 0.20 mmol), \(\text{Na}_2\text{SO}_4\) (0.119 g, 0.838 mmol) and pyridine (46.8 \(\mu\)l, 0.581 mmol) afforded \(3d\) as a white solid (0.039 g, 81%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.88-7.85 (m, 2H), 7.79-7.76 (m, 2H), 6.48 (d, \(J = 12.1\) Hz, 1H), 5.32 (dt, \(J = 12.1, 7.4\) Hz, 1H), 1.98-1.94 (m, 2H), 1.35-1.31 (m, 4H), 0.86 (t, \(J = 7.07\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 162.7, 145.6, 134.7, 128.8, 123.8, 110.0, 31.6, 26.3, 22.1, 13.9; IR (thin film) 2960, 2926, 2855, 1794, 1737, 1736, 1670, 1465, 1366, 1186, 1126 cm\(^{-1}\); HRMS (ESI) m/z calcd. for \(\text{C}_{14}\text{H}_{16}\text{NO}_3\) (M+H\(^+\)) 246.1130, found 246.1126.; mp 41 °C.

General procedure E with \(N\text{-hydroxyphthalimide } 2\) (0.020 g; 0.12 mmol), \textit{trans}-1-hexenyl boronic acid \(1d\) (0.031 g, 0.24 mmol), \(\text{Cu(OAc)}_2\) (0.004 g, 0.02 mmol), \(\text{Na}_2\text{SO}_4\) (0.075 g, 0.053 mmol) and pyridine (0.0295 \(\mu\)l, 0.367 mmol) afforded \(3d\) after 16 h. \(N\text{-Enoxy}
N-Enoxyphthalimide 3e: General procedure D with \(N\)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), \textit{trans}-2-cyclopropylvinyl boronic acid 1e (0.0672 g, 0.601 mmol), Cu(OAc)\(_2\) (0.054 g, 0.30 mmol), Na\(_2\)SO\(_4\) (0.256 g, 1.80 mmol), and pyridine (72.6 µl, 0.900 mmol) afforded 3e as a white solid (0.0333 g, 47%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). \(^{1}\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.88-7.85 (m, 2H), 7.79-7.77 (m, 2H), 6.57 (d, \(J = 12.0\) Hz, 1H), 5.10 (dd, \(J = 12.0\) Hz, \(J = 8.5\) Hz, 1H), 1.30-1.23 (m, 1H), 0.69-0.66 (m, 1H), 0.34-0.33 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 162.7, 145.2, 134.7, 128.8, 123.8, 114.8, 8.3, 6.1; IR (thin film) 3056, 3008, 2959, 2926, 2855, 1795, 1733, 1463, 1265, 874 cm\(^{-1}\); HRMS (ESI) m/z calcd. for \(C_{13}H_{12}NO_3\) (M+H)+ 230.0817, found 230.0823; mp 69-72 °C.

General procedure E with \(N\)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), \textit{trans}-2-cyclopropylvinyl boronic acid 1e (0.0672 g, 0.601 mmol), Cu(OAc)\(_2\) (0.0108 g, 0.0593 mmol), Na\(_2\)SO\(_4\) (0.256 g, 1.80 mmol), and pyridine (72.6 µl, 0.900 mmol) afforded 3e after 24 h. \textit{N}-Enoxyphthalimide 3e was isolated as a white solid (0.0146 g, 21%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).
N-Enoxyphthalimide 3f: General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-6-dodecen-6-yl boronic acid 1f (0.159 g, 0.750 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 μL, 0.901 mmol) afforded 3f as a colorless oil (0.082 g, 81%) after purification using medium pressure chromatography (1:19; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): 𝛿 7.88-7.85 (m, 2H), 7.77-7.76 (m, 2H), 4.67 (t, $J$ = 7.5 Hz, 1H), 2.31 (m, 2H), 1.92-1.73 (m, 2H), 1.70-1.66 (m, 2H), 1.38-1.33 (m, 4H), 1.30-1.23 (m, 6H), 0.91 (t, $J$ = 7.0 Hz, 3H), 0.84 (t, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): 𝛿 162.9, 155.7, 134.6, 129.0, 123.7, 101.3, 31.4, 31.3, 29.9, 27.9, 27.2, 26.0, 22.5, 22.4, 14.1, 14.0; IR (thin film) 2959, 2923, 2860, 1736, 1467, 1366, 1187, 1126, 878, 700cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{27}$NO$_3$Na (M+Na)$^+$ 352.1889, found 352.1875; General procedure E with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-6-dodecen-6-yl boronic acid 1f (0.159 g, 0.750 mmol), Cu(OAc)$_2$ (0.011 g, 0.060 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 μL, 0.901 mmol) afforded 3f after 24 h. N-Enoxyphthalimide 3f was isolated as a white solid (0.078 g, 77%) after purification using medium pressure chromatography (1:19; ethyl acetate: hexanes).
**N-Enoxyphthalimide 3g:** General procedure D with *N*-hydroxyphthalimide 2 (0.057 g; 0.35 mmol), 1-phenylvinyl boronic acid 1g (0.104 g, 0.703 mmol), Cu(OAc)$_2$ (0.064 g, 0.35 mmol), Na$_2$SO$_4$ (0.200 g, 1.41 mmol), and pyridine (84.7 µL, 1.05 mmol) afforded 3g as a white solid (0.080 g, 86%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.92-7.89 (m, 2H), 7.80-7.77 (m, 2H), 7.75-7.74 (m, 2H), 7.41-7.39 (m, 3H), 4.88 (d, $J = 4.0$ Hz, 1H), 4.57 (d, $J = 4.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.5, 162.4, 160.2, 134.8, 134.7, 132.2, 129.7, 128.9, 128.8 128.4, 128.3, 126.3, 126.2, 123.9, 123.8, 86.7; IR (thin film) 3064, 3030, 1794, 1730, 1648, 1493, 1468, 1373, 1262, 1189 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{12}$NO$_3$ (M+H)$^+$ 266.0817, found 266.0817; mp 163ºC.

General procedure E with *N*-hydroxyphthalimide 2 (0.020 g; 0.12 mmol), 1-phenylvinyl boronic acid 1g (0.036 g, 0.24 mmol), Cu(OAc)$_2$ (0.004 g, 0.02 mmol), Na$_2$SO$_4$ (0.070 g, 0.49 mmol), and pyridine (29.6 µL, 0.366 mmol) afforded 3g after 24 h. *N*-Enoxyphthalimide 3g was isolated as a white solid (0.025 g, 77%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

![3h](image)

**N-Enoxyphthalimide 3h:** General procedure D with *N*-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-1-phenyl-1-buten-1-yl boronic acid 1h (0.090 g, 0.51 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3h
as a white solid (0.068 g, 76%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.86-7.85 (m, 2H), 7.76-7.75 (m, 2H), 7.63 (m, 2H), 7.41-7.36 (m, 3H), 5.23 (t, $J = 7.5$ Hz, 1H), 2.09-2.05 (m, 2H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.0, 154.0, 134.6, 131.7, 129.6, 129.3, 129.0, 128.1, 123.7, 108.2, 20.3, 14.9; IR (thin film) 2963, 2934, 2857, 1733, 1366, 1187, 995, 878, 696 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{15}$NO$_3$Na (M+Na)$^+$ 316.0950, found 316.0941; mp 106-108 ºC.

General procedure E with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), Z-1-phenyl-1-butene-1-yl boronic acid 1h (0.132 g, 0.750 mmol), Cu(OAc)$_2$ (0.011 g, 0.061 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3h after 24 h. N-Enoxophthalimide 3h was isolated as a white solid (0.060 g, 67%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).

$^N$-Enoxophthalimide 3i: General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1i (0.166 g, 0.748 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3i as a white solid (0.073 g, 70%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.86-7.85 (m, 2H), 7.77-7.76 (m, 2H), 7.62-7.59 (m, 2H), 7.09-7.06 (m, 2H), 5.24 (t, $J = 7.5$ Hz, 1H), 2.05-2.01 (m, 2H), 1.34-1.28 (m, 2H), 1.26-1.21 (m, 2H), 0.78 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.0,
162.1 (d, J = 248 Hz), 153.4, 134.7, 131.7, 131.66, 128.9, 123.8, 115.2 (d, J = 22 Hz), 107.2, 32.2, 26.4, 22.1 13.8; IR (thin film) 2956, 2933, 2862, 1735, 1593, 1537, 1369, 1227, 845, 695 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₀H₁₉NFO₃ (M+H)⁺ 340.1349, found 340.1350.; mp 76-78 ºC.

General procedure E with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 2i (0.166 g, 0.748 mmol), Cu(OAc)₂ (0.011 g, 0.060 mmol), Na₂SO₄ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3i after 24 h. N-Enoxyphthalimide 3i was isolated as a white solid (0.074 g, 71%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).

![N-Enoxyphthalimide 3i](image)

**N-Enoxyphthalimide 3j:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1j (0.186 g, 0.747 mmol), Cu(OAc)₂ (0.054 g, 0.30 mmol), Na₂SO₄ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3j as a white solid (0.075 g, 67%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). ¹H NMR (500 MHz; CDCl₃): δ 8.26 (d, J = 8.0 Hz, 2H), 7.89-7.86 (m, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.81-7.78 (m, 2H), 5.44 (t, J = 7.5 Hz, 1H), 2.11-2.07 (m, 2H), 1.38-1.32 (m, 2H), 1.28-1.21 (m, 2H), 0.80 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 162.9, 152.1, 148.1, 138.3, 134.9, 130.5, 128.8, 123.9, 123.4, 110.5, 32.1, 26.5, 22.1, 13.8; IR (thin film) 2956, 2926, 2855, 1731, 1601, 1514, 1186, 856, 699 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₀H₁₉N₂O₅ (M+H)⁺ 367.1294, found 367.1286.; mp 119-121 ºC.
General procedure E with $N$-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1j (0.186 g, 0.747 mmol), Cu(OAc)$_2$ (0.011 g, 0.060 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3j after 24 h. $N$-Enoxyphthalimide 3j was isolated as a white solid (0.062 g, 55%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).

$N$-Enoxyphthalimide 3k: General procedure D with $N$-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1k (0.204 g, 0.750 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3k as a white solid (0.098 g, 82%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.86-7.88 (m, 2H), 7.75-7.78 (m, 4H), 7.65 (d, $J = 8.0$ Hz, 2H), 5.34 (t, $J = 7.5$ Hz, 1H), 2.05-2.09 (m, 2H), 1.30-1.36 (m, 2H), 1.21-1.27 (m, 2H), 0.79 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.0, 152.8, 135.4, 134.8, 131.2, 130.0, 128.9, 125.1 (q, $J = 3.7$ Hz), 123.8, 122.9 (q, $J = 270$ Hz), 108.8, 32.2, 26.4, 22.1, 13.8; IR (thin film) 2963, 2929, 2855, 1739, 1327, 1170, 1118, 1070, 849, 699 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{19}$NF$_3$O$_3$ (M+H)$^+$ 390.1317, found 390.1318.; mp 66-68 ºC.

General procedure E with $N$-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1k (0.204 g, 0.750 mmol), Cu(OAc)$_2$ (0.011 g, 0.060 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.901 mmol) afforded 3l after 24 h. $N$-Enoxyphthalimide 3k
was isolated as a white solid (0.087 g, 73%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).

\[ \text{3l} \]

**N-Enoxyphthalimide 3l:** General procedure D with \(N\)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1l (0.163 g, 0.747 mmol), Cu(OAc)\(_2\) (0.054 g, 0.30 mmol), Na\(_2\)SO\(_4\) (0.187 g, 1.32 mmol), and pyridine (72.4 \(\mu\)L, 0.901 mmol) afforded 3l as a white solid (0.065 g, 63%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)) \(\delta\) 7.86-7.84 (m, 2H), 7.76-7.74 (m, 2H), 7.49 (d, \(J = 8.0\) Hz, 2H), 7.18 (d, \(J = 8.0\) Hz, 2H), 5.21 (t, \(J = 7.5\) Hz, 1H), 2.36 (s, 3H), 2.07-2.03 (m, 2H), 1.33-1.28 (m, 2H), 1.25-1.21 (m, 2H), 0.78 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.1, 154.3, 139.2, 139.1, 134.5, 129.6, 129.0, 128.8, 123.7, 106.6, 32.4, 26.5, 22.1, 21.4, 13.9; IR (thin film) 2963, 2926, 2862, 1731, 1675, 1376, 1182, 882, 692 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{21}\)H\(_{22}\)NO\(_3\) (M+H)\(^+\) 336.1600, found 336.1592.; mp 103-105 \(^\circ\)C. General procedure E with \(N\)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1l (0.163 g, 0.747 mmol), Cu(OAc)\(_2\) (0.011 g, 0.060 mmol), Na\(_2\)SO\(_4\) (0.187 g, 1.32 mmol), and pyridine (72.4 \(\mu\)L, 0.901 mmol) afforded 3i after 24 h. \(N\)-Enoxy phthalimide 3l was isolated as a white solid (0.068 g, 66%) after purification using medium pressure chromatography (1:9; ethyl acetate: hexanes).
**N-Enoxyphthalimide 3m:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), 1-cyclopentenyl boronic acid 1m (0.070 g, 0.63 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 μL, 0.901 mmol) afforded 3m as a white solid (0.051 g, 73%) after purification using medium pressure chromatography (1:19; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.89-7.87 (m, 2H), 7.79-7.77 (m, 2H), 4.75-4.74 (m, 1H), 2.60-2.58 (m, 2H), 2.33-2.29 (m, 2H), 2.05-1.99 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.4, 159.0, 134.7, 128.8, 123.9, 99.8, 29.3, 28.1, 21.7; IR (thin film) 2938, 2858, 1736, 1464, 1186, 701 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{13}$H$_{11}$NO$_3$Na (M+Na)$^+$ 252.0637, found 252.0631; mp 100-102 ºC.

General procedure E with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1m (0.070 g, 0.63 mmol), Cu(OAc)$_2$ (0.011 g, 0.060 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 μL, 0.901 mmol) afforded 3m after 24 h. **N-Enoxyphthalimide 3m** was isolated as a white solid (0.048 g, 68%) after purification using medium pressure chromatography (1:19; ethyl acetate: hexanes).
**N-Enoxyphthalimide 3n:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), 1-cyclohexenyl boronic acid 1n (0.077 g, 0.61 mmol), Cu(OAc)$_2$ (0.056 g, 0.31 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (75.5 µL, 0.935 mmol) afforded 3n as a white solid (0.062 g, 83%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.84-7.81 (m, 2H), 7.77-7.74 (m, 2H), 4.97 (t, J = 3.8 Hz, 1H), 2.27-2.25 (m, 2H), 2.02 (td, J = 6.0, 3.8 Hz, 2H), 1.74-1.64 (m, 2H), 1.54-1.50 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.8, 154.7, 134.6, 128.7, 123.6, 98.5, 24.5, 22.8, 22.4, 21.9; IR (thin film) 2928, 2852, 1790, 1730, 1688, 1465, 1445, 1366, 1186, 1120 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{14}$H$_{14}$NO$_3$ (M+H)$^+$ 244.0974, found 244.0976; mp 107 ºC.

General procedure E with N-hydroxyphthalimide 2 (0.036 g; 0.220 mmol), 1-cyclohexenyl boronic acid 1n (0.056 g, 0.44 mmol), Cu(OAc)$_2$ (0.008 g, 0.044 mmol), Na$_2$SO$_4$ (0.135 g, 0.951 mmol), and pyridine (57.1 µL, 0.660 mmol) afforded 3n after 48 h. N-Enoxyphthalimide 3n was isolated as a white solid (0.041 g, 76%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

**N-Enoxyphthalimide 3o:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1o (0.126 g, 0.900 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.32 mmol), and pyridine (72.4 µL, 0.90 mmol) afforded 3o as a white solid (0.032 g, 41%) after purification using medium pressure chromatography (1:4; ethyl
acetate: hexanes:triethylamine). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.87-7.85 (m, 2H), 7.78-7.76 (m, 2H), 4.86 (t, $J$ = 3.0 Hz, 1H), 2.60-2.58 (m, 1H), 2.00-1.98 (m, 2H), 1.88-1.83 (m, 1H), 1.64-1.49 (m, 3H), 1.28 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.9, 158.4, 134.6, 128.9, 123.7, 97.4, 31.0, 29.9, 23.3, 19.3, 18.6; IR (thin film) 3052, 3038, 2982, 2940, 1735, 1653, 1563, 1504, 1425, 899 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{15}$NO$_3$Na (M+Na)$^+$ 280.0950, found 280.0944.; mp 78-80 ºC.

$^3$p

$N$-Enoxyphthalimide $^3$p: General procedure D with $N$-hydroxyphthalimide $^2$ (0.070 g; 0.43 mmol), alkenyl boronic acid $^1$p (0.120 g, 0.850 mmol), Cu(OAc)$_2$ (0.080 g, 0.43 mmol), Na$_2$SO$_4$ (0.260 g, 1.32 mmol), and pyridine (100 µL, 1.29 mmol) afforded $^3$p as a white solid (0.090 g, 86%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.87-7.85 (m, 2H), 7.78-7.76 (m, 2H), 4.81 (d, $J$ = 2.8 Hz, 1H), 2.40-2.26 (m, 3H), 1.86-1.84 (m, 1H), 1.73-1.64 (m, 2H), 1.17-1.12 (ddt, $J$ = 2.8, 10.3, 10.6 Hz, 1H), 0.92 (d, $J$ = 10.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.8, 154.5, 134.6, 128.8, 123.7, 104.5, 30.7, 28.8, 24.5, 22.02 21.1; IR (thin film) 2953, 2929, 2851, 1789, 1740, 1691, 1467, 1358, 1178, 1103 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{15}$NO$_3$Na (M+Na)$^+$ 280.0950, found 280.0944.; mp 78-80 ºC.

General procedure E with $N$-hydroxyphthalimide $^2$ (0.035 g; 0.214 mmol), alkenyl boronic acid $^1$p (0.060 g, 0.428 mmol), Cu(OAc)$_2$ (0.008 g, 0.043 mmol), Na$_2$SO$_4$ (0.131 g, 0.922
(50 μL, 0.642 mmol) afforded 3s after 48 h. **N-Enoxyphthalimide 3p** was isolated as a white solid (0.044 g, 80%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

**N-Enoxyphthalimide 3q:** General procedure D with **N-hydroxyphthalimide 2** (0.050 g; 0.30 mmol), alkenyl boronic acid 1q (0.086 g, 0.61 mmol), Cu(OAc)₂ (0.055 g, 0.30 mmol), Na₂SO₄ (0.187 g, 1.32 mmol), and pyridine (72.4 μL, 0.899 mmol) afforded 3q as a white solid (0.066 g, 84%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

\[ \text{NMR (500 MHz; CDCl}_3\text{): } \delta \ 7.82-7.80 \text{ (m, 2H), 7.75-7.73 \text{ (m, 2H), 4.89 (t, } J = 3.0 \text{ Hz, 1H), 2.34-2.23 \text{ (m, 2H), 2.02 (dd, } J = 3.5 \text{ Hz, 4.0 Hz, 1H), 1.77-1.74 \text{ (m, 1H), 1.65-1.58 \text{ (m, 2H), 1.38-1.35 \text{ (m, 1H), 0.9 (d, } J = 6.1 \text{ Hz, 3H);} } \]  
\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta \ 162.8, 154.5, 134.6, 128.8, 123.6, 98.0, 31.1, 30.4, 28.2, 24.4, 21.0; \text{ IR (thin film) 2921, 2878, 1792, 1740, 1691, 1604, 1470, 1366, 1190, 1076 cm}^{-1}; \text{ HRMS (ESI) } m/z \text{ calcd. for } C_{15}H_{16}NO_3 (M+H)^+ 258.1130, \text{ found 258.1131; mp 109 °C.} \]

General procedure E with **N-hydroxyphthalimide 2** (0.030 g; 0.183 mmol), alkenyl boronic acid 1q (0.052 g, 0.37 mmol), Cu(OAc)₂ (0.007 g, 0.037 mmol), Na₂SO₄ (0.112 g), and pyridine (0.043g, 0.549 mmol) afforded 3q after 30 h. **N-Enoxyphthalimide 3q** was isolated as a white solid (0.037 g, 78%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).
**N-Enoxypthalimide 3r:** General procedure D with *N*-hydroxyphthalimide 2 (0.040 g; 0.24 mmol), alkenyl boronic acid 1r (0.088 g, 0.48 mmol), Cu(OAc)$_2$ (0.044 g, 0.24 mmol), Na$_2$SO$_4$ (0.075 g, 1.1 mmol), and pyridine (60 µL, 0.72 mmol) afforded 3r as an amorphous solid (0.060 g, 83%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.86-7.84 (m, 2H), 7.77-7.75 (m, 2H), 4.94 (d, $J = 5.5$ Hz, 1H), 2.34-2.33 (m, 2H), 2.02-1.99 (m, 1H), 1.92-1.89 (m, 1H), 1.81-1.76 (m, 1H), 1.35-1.23 (m, 2H), 0.84 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.8, 154.6, 134.6, 128.8, 123.7, 98.5, 43.7, 32.1, 27.3, 25.6, 24.1, 23.6; IR (thin film) 3056, 2990, 2978, 2933, 1735, 1421, 1186, 1369, 1168, 1092 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{21}$NO$_3$Na (M+Na)$^+$ 322.1419, found 322.1423.

**N-Enoxypthalimide 3s:** General procedure D with *N*-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1s (0.120 g, 0.594 mmol), Cu(OAc)$_2$ (0.054, 0.30 mmol), Na$_2$SO$_4$ (0.256 g, 1.80 mmol), and pyridine (72.7 µL, 0.901 mmol) afforded 3s as a white solid (0.0627 g, 64%) after purification using medium pressure chromatography (4:1; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.91-7.88 (m, 2H), 7.81-7.77 (m, 2H), 4.94 (d, $J = 5.5$ Hz, 1H), 2.34-2.33 (m, 2H), 2.02-1.99 (m, 1H), 1.92-1.89 (m, 1H), 1.81-1.76 (m, 1H), 1.35-1.23 (m, 2H), 0.84 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.8, 154.6, 134.6, 128.8, 123.7, 98.5, 43.7, 32.1, 27.3, 25.6, 24.1, 23.6; IR (thin film) 3056, 2990, 2978, 2933, 1735, 1421, 1186, 1369, 1168, 1092 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{21}$NO$_3$Na (M+Na)$^+$ 322.1419, found 322.1423.
7.32-7.29 (m, 2H), 7.23-7.19 (m, 3H), 5.08 (t, \( J = 2.5 \) Hz, 1H), 2.84 (dddd, \( J = 15.0 \) Hz, \( J = 8.0 \) Hz, \( J = 5.0 \) Hz, \( J = 3.0 \) Hz, 1H), 2.60-2.53 (m, 1H), 2.47-2.43 (m, 1H), 2.33-2.28 (m, 1H), 2.23-2.17 (m, 1H), 2.09-2.06 (m, 1H), 2.02-1.95 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 162.9, 154.6, 145.8, 134.7, 128.9, 128.5, 126.9, 126.3, 123.8, 98.2, 39.9, 31.0, 29.3, 25.1; IR (thin film) 3027, 2933, 2923, 2848, 1791, 1736, 1698, 1606, 1469, 1186 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{20}\)H\(_{18}\)NO\(_3\) (M+H)\(^+\) 320.1287, found 320.1296; mp 127-131 \( ^\circ \)C.

\( \text{N-Enoxyphthalimide} \ 3t: \) General procedure D with \( \text{N-hydroxynaphthalimide} \ 2 \) (0.022 g; 0.14 mmol), alkenyl boronic acid \( 1t \) (0.035 g, 0.27 mmol), Cu(OAc)\(_2\) (0.025 g, 0.14 mmol), Na\(_2\)SO\(_4\) (0.082 g, 0.58 mmol), and pyridine (32.7 \( \mu \)L, 0.408 mmol) afforded \( 3t \) as a white solid (0.030 g, 91%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.89-7.86 (m, 2H), 7.80-7.77 (m, 2H), 4.99 (t, \( J = 2.5 \) Hz, 1H), 4.14 (dd, \( J = 2.5 \) Hz, 2.5 Hz, 2H), 3.89 (t, \( J = 5.5 \) Hz, 2H), 2.45 (t, \( J = 5.5 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 162.6, 152.1, 134.8, 128.8, 123.9, 97.4, 64.0, 63.9, 25.5; IR (thin film) 2931, 2849, 1790, 1733, 1698, 1609, 1465, 1360, 1230, 1186 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{13}\)H\(_{12}\)NO\(_4\) (M+H)\(^+\) 246.0766, found 246.0766; mp 118 \( ^\circ \)C.

General procedure E with \( \text{N-hydroxynaphthalimide} \ 2 \) (0.044 g; 0.27 mmol), alkenyl boronic acid \( 1t \) (0.070 g, 0.55 mmol), Cu(OAc)\(_2\) (0.008 g, 0.05 mmol), Na\(_2\)SO\(_4\) (0.164 g, 1.16 mmol), and pyridine (65.3 \( \mu \)L, 0.810 mmol) afforded \( 3t \) after 48 h. \( \text{N-Enoxyphthalimide} \ 3t \) was
isolated as a white solid (0.059 g, 89%) after purification using medium pressure chromatography (1:4; ethyl acetate: hexanes).

\[ \text{3u} \]

**N-Enoxyphthalimide 3u:** General procedure D with \( N \)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1u (0.110 g, 0.598 mmol), \( \text{Cu(OAc)}_2 \) (0.054 g, 0.30 mmol), \( \text{Na}_2\text{SO}_4 \) (0.187 g, 1.32 mmol), and pyridine (72.4 \( \mu \text{L}, 0.899 \text{ mmol}) afforded 3u as a white solid (0.079 g, 86%) after purification using medium pressure chromatography (1:3; ethyl acetate: hexanes). \(^1\text{H NMR (500 MHz; CDCl}_3\text{):} \delta 7.83-7.81 \text{ (m, 2H), 7.74-7.76} \text{ (m, 2H), 4.88} \text{ (s, 1H), 3.93} \text{ (s, 4H), 2.49-2.50} \text{ (m, 2H), 2.23} \text{ (s, 2H), 1.88-1.85} \text{ (m, 2H);} \text{ C NMR (125 MHz, CDCl}_3\text{):} \delta 162.7, 153.9, 134.7, 128.8, 107.4, 96.5, 64.5, 64.4, 33.1, 30.6, 23.5; \text{ IR (thin film) 2965, 2934, 2884, 1732, 1375, 1116, 876, 733, 696 cm}^{-1}; \text{ HRMS (ESI) m/z calcd. for } \text{C}_{16}\text{H}_{15}\text{NO}_5\text{Na (M+Na)}^+ 324.0848, \text{ found 324.0850; mp 135-137 °C.} \]

General procedure E with \( N \)-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1u (0.110 g, 0.598 mmol), \( \text{Cu(OAc)}_2 \) (0.011 g, 0.060 mmol), \( \text{Na}_2\text{SO}_4 \) (0.187 g, 1.32 mmol), and pyridine (72.4 \( \mu \text{L}, 0.899 \text{ mmol}) afforded 3u after 24 h. \( N \)-Enoxyphthalimide 3u was isolated as a white solid (0.076 g, 82%) after purification using medium pressure chromatography (1:3; ethyl acetate: hexanes).
**N-Enoxyphthalimide 3v:** General procedure D with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1v (0.106 g, 0.609 mmol), Cu(OAc)₂ (0.054 g, 0.30 mmol), Na₂SO₄ (0.256 g, 1.80 mmol), and pyridine (72.4 μL, 0.899 mmol) afforded 3v as a light orange solid (0.068 g, 76%) after purification using medium pressure chromatography (1:2; ethyl acetate: hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.92-7.90 (m, 2H), 7.81-7.79 (m, 2H), 7.70 (d, J = 7.0 Hz, 1H), 7.28-7.22 (m, 2H), 7.16 (d, J = 7.0 Hz, 1H), 5.26 (t, J = 4.5 Hz, 1H), 2.81 (t, J = 8.0 Hz, 2H), 2.34 (td, J = 8.0 Hz, J = 4.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 162.7, 152.2, 136.7, 134., 128.9, 128.4, 128.3, 127.3, 126.5, 123.9, 121.7, 99.4, 27.8, 21.4; IR (thin film) 3060, 2939, 2890, 2838, 1795, 1733, 1369, 1189, 1125, 874 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₈H₁₃NO₃Na (M+Na)⁺ 314.0793, found 314.0794.; mp 110-114 °C.

General procedure E with N-hydroxyphthalimide 2 (0.050 g; 0.31 mmol), alkenyl boronic acid 1v (0.106 g, 0.609 mmol), Cu(OAc)₂ (0.0108 g, 0.0593 mmol), Na₂SO₄ (0.256 g, 1.80 mmol), and pyridine (72.4 μL, 0.899 mmol) afforded 3v after 48 h. N-Enoxyphthalimide 3v was isolated as a white solid (0.0454 g, 52%) after purification using medium pressure chromatography (1:2; ethyl acetate: hexanes).
IV. Thermal Rearrangement of N-Enoxyphthalimides

General Procedure F: Thermal rearrangement of N-Enoxyphthalimides. A J-Young tube was charged with a 0.1 M solution of N-enoxyphthalimide 3 (1 equiv) in C$_6$D$_6$. The reaction mixture was heated to 80-90 °C for 10-16 h. Benzene-d$_6$ was removed from the reaction mixture under vacuum and imidate 4 was isolated as an amorphous solid or oil.

Imidate 4a: General procedure F was followed with 3a (0.0272 g, 0.125 mmol). Heating the reaction mixture to 80 °C for 16 h afforded imidate 4a (0.0272 g, >95% recovery) as a white solid. $^1$H NMR (500 MHz; C$_6$D$_6$): δ 7.49 (d, J = 6.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 1H), 6.92-6.86 (m, 2H), 5.35 (q, J = 7.0 Hz, 1H), 1.79 (s, 3H), 1.20 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 202.1, 184.9, 180.1, 135.9, 135.2, 132.5, 132.2, 123.6, 120.1, 80.5, 25.3, 15.6; IR (thin film) 3056, 2988, 2926, 2852, 1733, 1616, 1537, 1411, 1066, 734 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{12}$NO$_3$ (M+H)$^+$ 218.0817, found 218.0815; mp 139-142 °C.
Imidate 4b: General procedure F was followed with 3b (0.044 g, 0.16 mmol). Heating the reaction mixture to 90 °C for 10 h afforded imidate 4b (0.044 g, >95%) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 9.31 (d, $J = 6.0$ Hz, 1H), 7.52-7.50 (m, 2H), 7.14-7.12 (m, 2H), 6.96-6.91 (m, 2H), 5.30 (d, $J = 4.5$ Hz, 1H), 1.75-1.57 (m, 7H), 1.14-1.05 (m, 4H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 195.8, 185.3, 179.9, 135.9, 135.0, 132.6, 132.2, 123.6, 120.4, 87.5, 38.6, 28.6, 27.3, 25.8; IR (thin film) 2923, 2855, 1732, 1624, 1538, 1444, 1407, 1358, 1313, 1070 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{14}$H$_{16}$NO$_3$ (M+H)$^+$ 246.1130, found 246.1138.

To obtain a $^1$H NMR yield of this rearrangement a C$_6$D$_6$ solution of 3b (0.042 g, 0.17 mmol) was heated to 90 °C in a J-Young tube in the presence of 1,3,5-trimethoxybenzene (0.010 g, 0.057 mmol) for 12 h. After 12 h of heating at, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 73%.

Imidate 4c: General procedure F was followed with 3c (0.053 g, 0.20 mmol). Heating the reaction mixture to 50 °C for 10 h afforded imidate 4c (0.053 g, >95%) as an amorphous oil.

$^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 9.18 (s, 1H), 7.46 (d, $J = 7.0$ Hz, 1H), 7.28 (d, $J = 7.0$ Hz, 2H),
7.15-7.12 (m, 4H), 7.08 (d, J = 7.0 Hz, 1H) 6.89-6.85 (m, 1H), 6.41 (s, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 191.6, 184.8, 180.1, 135.8, 132.6, 132.3, 129.6, 129.1, 128.9, 128.5, 123.7, 123.2, 120.6, 85.4; HRMS (ESI) m/z calcd. for C$_{16}$H$_{12}$NO$_3$ (M+H)$^+$ submitted.

To obtain a $^1$H NMR yield of this rearrangement a C$_6$D$_6$ solution of 3c (0.051 g, 0.19 mmol) was heated to 90 ºC in a J-Young tube for 12 h. After 12 h of heating, CH$_2$Br$_2$ (X 13.2 µL, 0.17 mmol) was added to the reaction mixture as a reference. $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 76%.

![4d](image)

**Imidate 4d:** General procedure F was followed with 3d (0.025 g, 0.10 mmol). Heating the reaction mixture to 90 ºC for 10 h afforded imidate 4d (0.025 g, >95% recovery) as an amorphous solid. $^1$H NMR (500 MHz; C$_6$D$_6$): $^1$H NMR (500 MHz; C$_6$D$_6$): δ 9.21 (s, 1H), 7.50-7.48 (m, 1H), 7.12-7.10 (m, 1H), 6.92-6.89 (m, 2H), 5.33 (dd, J = 7.6, 5.4 Hz, 1H), 1.62-1.57 (m, 2H), 1.28-1.23 (m, 2H), 1.23-1.14 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 195.43, 179.23, 185.11, 132.63, 132.24, 123.72, 120.38, 84.08, 28.42, 26.86, 22.32, 13.62; IR (thin film) 2959, 2930, 2868, 1733, 1617, 1536, 1467, 1405, 1358, 1315 cm$^{-1}$

$^1$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{18}$NO$_3$ (M+H)$^+$ 272.1278, found 272.1284.

To obtain a $^1$H NMR yield of this rearrangement a C$_6$D$_6$ solution of 3d (0.034 g, 0.14 mmol) was heated to 90 ºC in a J-Young tube in the presence of hexamethylbenzene (0.0038 g, 0.023 mmol) for 12 h. After 12 h of heating at, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 67%.
Imidate 4f: General procedure F was followed with 3f (0.140 g, 0.425 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4f (0.139 g, >95% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): δ 7.50 (d, $J = 7.0$ Hz, 1H), 7.22 (d, $J = 6.5$ Hz, 1H), 7.00-6.94 (m, 2H), 5.57 (dd, $J = 4.5$ Hz, 8.0 Hz, 1H), 2.53-2.46 (m, 1H), 2.33-2.27 (m, 1H), 1.87-1.80 (m, 2H), 1.69-1.67 (m, 2H), 1.47-1.42 (m, 2H), 1.28-1.26 (m, 8H), 0.93-0.89 (m, 6H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 204.2, 185.3, 180.1, 136.0, 135.2, 132.6, 132.3, 123.7, 120.5, 84.3, 38.9, 31.5, 31.3, 30.6, 25.0, 23.0, 22.6, 22.5, 13.9, 13.8; IR (thin film) 2986, 2936, 2850, 1748, 1700, 1548, 1413, 1088, 857 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{28}$NO$_3$ (M+H)$^+$ 330.2069, found 330.2068.

Imidate 4h: General procedure F was followed with 3h (0.070 g, 0.24 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4h (0.070 g, >95% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): δ 7.95 (d, $J = 7.5$ Hz, 2H), 7.46-7.45 (m, 1H), 7.24-7.23 (m, 1H), 7.18-7.17 (m, 1H), 7.09 (t, $J = 7.5$ Hz, 2H), 6.92-6.91 (m, 2H), 6.46-6.43 (m, 1H), 1.93-1.90 (m, 2H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 194.4, 185.4, 180.2,
135.9, 135.3, 135.1, 133.4, 132.5, 132.3, 128.8, 128.5, 123.6, 120.7, 82.1, 25.1, 9.4; IR (thin film) 2985, 2930, 1744, 1700, 1533, 1413, 1071, 853, 718, 696 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{13}\)H\(_{16}\)NO\(_3\) (M+H\(^+\)) \(294.1130\), found 294.1139.

**Imidate 4i:** General procedure F was followed with 3i (0.070 g, 0.21 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4i (0.069 g, >95% recovery) as a yellow oil. \(^1\)H NMR (500 MHz; C\(_6\)D\(_6\)): \(\delta\) 7.90-7.88 (m, 2H), 7.46-7.43 (m, 1H), 7.24-7.22 (m, 1H), 6.92-6.91 (m, 2H), 6.75-6.67 (m, 2H), 6.48-6.46 (m, 1H), 1.99-1.91 (m, 2H), 1.51-1.43 (m, 2H), 1.29-1.19 (m, 2H), 0.84 (t, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 193.1, 185.3, 180.2, 164.9 (d, \(J = 254\) Hz), 135.2, 132.6, 132.4, 131.3, 131.26, 128.1, 123.7, 120.7, 115.8 (d, \(J = 22\) Hz), 81.0, 31.5, 27.4, 22.4, 13.7; IR (thin film) 2956, 2926, 2871, 1743, 1698, 1593, 1541, 1411, 1236, 852, 718 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{20}\)H\(_{19}\)FNO\(_3\) (M+H\(^+\)) \(340.1349\), found 340.1346.

**Imidate 4j:** General procedure F was followed with 3j (0.078 g, 0.21 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4j (0.078 g, >95% recovery) as an
amorphous solid. $^1$H NMR (500 MHz; C$_6$D$_6$): δ 7.77-7.75 (m, 3H), 7.46 (d, $J = 6.0$ Hz, 1H), 7.24-7.22 (m, 2H), 6.95-6.91 (m, 2H), 6.32 (dd, $J = 8.0$ Hz, 4.0 Hz, 1H), 1.95-1.87 (m, 2H), 1.51-1.45 (m, 2H), 1.32-1.22 (m, 2H), 0.87 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 193.9, 185.2, 180.0, 150.4, 138.9, 135.7, 134.9, 132.9, 132.5, 129.3, 123.81, 123.75, 120.7, 81.3, 31.1, 27.4, 22.4, 13.7; IR (thin film) 2959, 2933, 2868, 1746, 1703, 1532, 1411, 1346, 852, 718 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{19}$N$_2$O$_5$ (M+H)$^+$ 367.1294, found 367.1292.

![Image of 4k](image)

**Imidate 4k:** General procedure F was followed with 3k (0.080 g, 0.21 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4k (0.080 g, >95% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): δ 7.90 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 7.0$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.24-7.22 (m, 1H), 6.95-6.90 (m, 2H), 6.45 (dd, $J = 8.0$ Hz, 4.0 Hz, 1H), 1.89-1.98 (m, 2H), 1.46-1.51 (m, 2H), 1.20-1.31 (m, 2H), 0.85 (t, $J = 6.0$ Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 194.0, 185.3, 180.1, 137.5, 135.8, 135.0, 132.7, 132.6 (q, $J = 35$ Hz), 132.4, 128.9, 125.8, 124.2 (q, $J = 342.5$ Hz), 123.7, 120.7, 81.4, 31.2, 27.2, 22.4, 13.7; IR (thin film) 2959, 2930, 2868, 1743, 1703, 1532, 1417, 1320, 1128, 1063, 715 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{19}$F$_3$NO$_3$ (M+H)$^+$ 390.1317, found 390.1321.
**Imidate 4I:** General procedure F was followed with 3I (0.070 g, 0.21 mmol). Heating the reaction mixture to 80 ºC for 12 h afforded imidate 4I (0.070 g, >95% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 8.01 (d, $J = 8.0$ Hz, 2H), 7.48-7.46 (m, 1H), 7.28-7.26 (m, 1H), 6.97-6.92 (m, 4H), 6.63-6.60 (m, 1H), 2.07-2.00 (m, 2H), 2.05 (s, 3H), 1.54-1.48 (m, 2H), 1.28-1.20 (m, 2H), 0.84 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 194.1, 185.4, 180.3, 144.3, 135.9, 135.3, 132.6, 132.5, 132.3, 129.6, 128.7, 123.6, 120.7, 81.2, 31.6, 27.5, 22.4, 21.2, 13.7; IR (thin film) 2959, 2933, 2861, 1739, 1691, 1606, 1537, 1414, 1070, 725 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{22}$NO$_3$ (M+H)$^+$ 336.1600, found 336.1605.

**Imidate 4m:** General procedure F was followed with 3m (0.028 g, 0.12 mmol). Heating the reaction mixture to 80 ºC for 12 h afforded imidate 4m (0.028 g, >95% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 7.49 (d, $J = 7.0$ Hz, 1H), 7.14 (d, $J = 6.5$ Hz, 1H), 6.94-6.85 (m, 2H), 5.46-5.43 (m, 1H), 2.22-2.17 (m, 1H), 1.86-1.73 (m, 2H), 1.64-1.56 (m, 1H), 1.44-1.36 (m, 1H), 1.18-1.15 (m, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 208.5, 185.4, 180.2, 132.5, 132.3, 128.1, 123.6, 122.9, 120.6, 81.5, 34.1, 28.0, 16.5; IR (thin film) 2958, 2923,
2850, 1748, 1700, 1413, 1388, 1088, 852 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{13}H_{12}NO_3\) (M+H)\(^+\) 230.0817, found 230.0806.

Imidate 4n: General procedure F was followed with 3n (0.022 g, 0.090 mmol). Heating the reaction mixture to 90 °C for 10 h afforded imidate 4n (0.022 g, >95% recovery) as a white solid. \(^1\)H NMR (500 MHz; C\(_6\)D\(_6\)): δ 7.52-7.51 (m, 1H), 7.28-7.27 (m, 1H), 6.91-6.90 (m, 2H), 5.61 (dd, \(J = 5.0, 5.0\) Hz, 1H), 2.27-2.24 (m, 1H), 2.16-2.13 (m, 1H), 1.86-1.84 (m, 1H), 1.65-1.61 (m, 1H), 1.42-1.33 (m, 2H), 1.32-1.07 (m, 2H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): δ 201.1, 185.2, 180.5, 136.0, 135.5, 132.5, 132.2, 123.6, 120.6, 82.4, 40.3, 33.0, 26.7, 23.2; IR (thin film) 2947, 2865, 1734, 1620, 1535, 1408, 1360, 1320, 1294, 1073 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{14}H_{13}NO_3\) (M)\(^+\) 243.0895, found 243.0886; mp 128-130 °C.

Imidate 4o: General procedure F was followed with 3o (0.030 g, 0.12 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4o (0.029 g, >95%) as an amorphous solid. \(^1\)H NMR cis diastereomer (500 MHz; C\(_6\)D\(_6\)): δ 7.50 (d, \(J = 6.0\) Hz, 1H), 7.19 (d, \(J = 6.0\) Hz, 1H), 6.90-6.84 (m, 1H), 6.61-6.55 (m, 1H), 6.44 (d, \(J = 6.0\) Hz, 1H), 6.27-6.23 (m, 1H), 2.20-2.15 (m, 1H), 1.88-1.84 (m, 1H), 1.65-1.61 (m, 1H), 1.42-1.33 (m, 2H), 1.32-1.07 (m, 2H); IR (thin film) 2947, 2865, 1734, 1620, 1535, 1408, 1360, 1320, 1294, 1073 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{14}H_{13}NO_3\) (M)\(^+\) 243.0895, found 243.0886; mp 128-130 °C.
6.5 Hz, 1H), 6.94-6.81 (m, 2H), 5.63 (dd, J = 13.0, 7.0 Hz, 1H), 2.24-2.20 (m, 1H), 1.94-1.90 (m, 2H), 1.73-1.65 (m, 1H), 1.52-1.45 (m, 1H), 1.40-1.34 (m, 1H), 1.22-1.17 (m, 1H), 0.82 (d, J = 7.0 Hz, 3H); $^{13}$C NMR cis diastereomer (125 MHz, C$_6$D$_6$): $\delta$ 204.8, 184.9, 180.4, 136.0, 135.4, 132.5, 123.5, 120.6, 82.5, 43.8, 35.6, 33.4, 22.6, 13.9; $^1$H NMR trans diastereomer (500 MHz; C$_6$D$_6$): $\delta$ 7.50 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 6.5 Hz, 1H), 6.94-6.81 (m, 2H), 5.81 (dd, J = 10.0, 5.5 Hz, 1H), 2.69-2.63 (m, 1H), 1.94-1.90 (m, 1H), 1.88-1.83 (m, 1H), 1.52-1.45 (m, 1H), 1.40-1.34 (m, 2H), 1.22-1.17 (m, 1H), 0.96 (d, J = 6.0 Hz, 3H); $^{13}$C NMR trans diastereomer (125 MHz, C$_6$D$_6$): $\delta$ 204.8, 184.9, 180.4, 136.0, 135.4, 132.5, 132.2, 123.6, 120.4, 80.7, 43.9, 33.5, 32.8, 18.9, 15.1; IR (thin film) 3057, 2977, 2938, 2868, 1733, 1613, 1536, 1409, 1267, 1151 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{16}$NO$_3$ (M+H)$^+$ 258.1130, found 258.1130.

Imidate 4p: General procedure F was followed with 3p (0.044 g, 0.16 mmol). Heating the reaction mixture to 90 °C for 14 h afforded imidate 4p (0.044 g, >95% recovery) as an amorphous solid. $^1$H NMR cis diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.72-7.71 (m, 1H), 7.69-7.68 (m, 1H), 7.57-7.56 (m, 2H), 5.84 (d, J = 5.5 Hz, 1H), 2.91-2.86 (m, 1H), 2.55-2.53 (m, 2H), 2.11-2.02 (m, 2H), 1.86-1.85 (m, 1H), 1.71-1.66 (m, 1H), 1.10 (d, J = 5.0 Hz, 3H); $^1$H NMR trans diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.74-7.73 (m, 2H), 7.59-7.57 (m, 2H), 5.44 (d, J = 11.5 Hz, 1H), 2.53-2.44 (m, 2H), 2.30-2.27 (m, 1H), 2.01-1.92 (m, 2H), 1.86-1.85 (m,
1H, 1.64-1.57 (m, 1H), 1.20 (d, J = 5.0 Hz, 3H; \(^1\)H NMR cis diastereomer (500 MHz; C\(_6\)D\(_6\)): \(\delta\) 7.52-7.51 (m, 1H), 7.29-7.27 (m, 1H), 6.96-6.93 (m, 2H), 5.73 (d, J = 5.5 Hz, 1H), 2.50-2.47 (m, 1H), 2.29-2.22 (m, 2H), 1.50-1.39 (m, 4H), 0.93 (d, J = 5.0 Hz, 3H); \(^{13}\)C NMR cis diastereomer (125 MHz, C\(_6\)D\(_6\)): 201.3, 185.8, 180.5, 136.1, 135.4, 132.4, 132.2, 123.6, 120.6, 87.7, 40.0, 39.4, 31.8, 25.2, 18.5; \(^1\)H NMR trans diastereomer (500 MHz; C\(_6\)D\(_6\)): \(\delta\) 7.52-7.51 (m, 1H), 7.21-7.20 (m, 1H), 6.93-6.91 (m, 2H), 5.40 (d, J = 11.5 Hz, 1H), 1.98-1.89 (m, 3H), 1.35-1.26 (m, 3H), 1.18-1.11 (m, 1H), 0.96 (d, J = 5.0 Hz, 3H); \(^{13}\)C NMR trans diastereomer (125 MHz, C\(_6\)D\(_6\)): 200.9, 185.1, 180.5, 135.9, 135.4, 132.4, 132.2, 123.5, 120.5, 85.0, 39.9, 36.0, 29.5, 21.3, 12.3; IR (thin film) 2949, 2866, 1732, 1620, 1534, 1407, 1310, 1137, 1070, 1010 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{15}\)H\(_{16}\)NO\(_3\) (M+H\(^+\)) 258.1130, found 258.1135.

\[
\begin{align*}
\text{4q} \\
\text{dr} &= 50:50; \text{cis:trans}
\end{align*}
\]

**Imidate 4q:** General procedure F was followed with 3q (0.019 g, 0.073 mmol). Heating the reaction mixture to 90 °C for 10 h afforded imidate 4q (0.019 g, >95% recovery) as a yellow oil. \(^1\)H NMR cis diastereomer (500 MHz; C\(_6\)D\(_6\)): \(\delta\) 7.52-7.51 (m, 1H), 7.32-7.30 (m, 1H), 6.92-6.89 (m, 2H), 5.67 (dd, J = 6.5, 6.5 Hz, 1H), 2.17-2.06 (m, 2H), 1.90-1.89 (m, 1H), 1.76-1.73 (m, 1H), 1.40-1.33 (m, 2H), 0.92-0.80 (m, 1H), 0.66 (d, J = 5.0 Hz, 3H); \(^{13}\)C NMR cis diastereomer (125 MHz, C\(_6\)D\(_6\)): 201.2, 185.1, 180.4, 136.0, 135.4, 132.2, 132.1, 120.6, 120.5, 80.0, 39.1, 36.3, 32.4, 27.2, 17.5; \(^1\)H NMR trans diastereomer (500 MHz; C\(_6\)D\(_6\)): \(\delta\)
7.53-7.52 (m, 1H), 7.32-7.31 (m, 1H), 6.94-6.92 (m, 2H), 5.80 (dd, \( J = 6.5, 6.5 \) Hz, 1H), 2.24-2.20 (m, 2H), 1.96-1.92 (m, 2H), 1.43-1.41 (m, 2H), 1.23-1.20 (m, 1H), 0.80 (d, \( J = 5.0 \) Hz, 3H); \(^{13}\)C NMR trans diastereomer (125 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 201.8, 185.2, 180.5, 136.0, 135.4, 132.4, 132.3, 123.5, 123.4, 81.3, 40.5, 38.5, 34.4, 30.1, 20.4; IR (thin film) 2963, 2926, 2868, 1733, 1616, 1528, 1457, 1412, 1317, 1076 cm\(^{-1}\); HRMS (ESI) m/z calcd. for \( \text{C}_{15}\text{H}_{16}\text{NO}_3 \) (M+H)\(^+\) 258.1130, found 258.1135.

\[
\text{4r}
\]

\[
\text{dr} = \text{60:40}; \text{cis:trans}
\]

Imidate 4r: General procedure F was followed with 3r (0.0385 g, 0.1287 mmol). Heating the reaction mixture to 80 °C for 16 h afforded imidate 4r (0.0383 g, >95% recovery) as an amorphous solid. \(^1\)H NMR cis diastereomer (500 MHz; \( \text{C}_6\text{D}_6 \)): \( \delta \) 7.53-7.47 (m, 1H), 7.35-7.34 (m, 1H), 6.97-6.91 (m, 2H), 5.76 (dd, \( J = 12.0, 6.5 \) Hz, 1H), 2.38-2.24 (m, 2H), 2.02-1.95 (m, 1H), 1.64-1.59 (m, 1H), 1.56-1.51 (m, 1H), 1.42-1.35 (m, 1H), 1.05-0.96 (m, 1H), 0.73 (s, 9H); \(^{13}\)C NMR cis diastereomer (125 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 201.5, 185.2, 180.5, 136.0, 135.5, 132.2, 123.6, 120.6, 82.2, 44.9, 41.0, 39.1, 34.1, 27.5, 27.2, 26.7; \(^1\)H NMR trans diastereomer (500 MHz; \( \text{C}_6\text{D}_6 \)): \( \delta \) 7.53-7.47 (m, 1H), 7.21-7.20 (m, 1H), 6.97-6.91 (m, 2H), 5.74 (t, \( J = 7.0 \) Hz, 1H), 2.38-2.24 (m, 1H), 2.11-2.05 (m, 1H), 1.86-1.80 (m, 1H), 1.48-1.45 (m, 1H), 1.31-1.20 (m, 3H), 1.05-0.96 (m, 1H), 0.72 (s, 9H); \(^{13}\)C NMR trans diastereomer (125 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta \) 203.8, 184.9, 180.3, 135.8, 135.3, 133.3, 128.1, 122.8, 120.4, 81.2, 42.1,
41.0, 37.6, 30.5, 26.7, 24.1; IR (thin film) 3056, 2963, 2873, 1762, 1731, 1619, 1541, 1410, 1267, 1073 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₈H₂₂NO₃ (M+H)⁺ 300.1600, found 300.1602.

dr = 55:45; cis:trans

**Imidate 4s**: General procedure F was followed with 3s (0.0284 g, 0.0890 mmol). Heating the reaction mixture to 90 °C for 16 h afforded imidate 4s (0.0275 g, >95% recovery) as an oil. ¹H NMR *cis* diastereomer (500 MHz; C₆D₆): δ 7.54-7.47 (m, 1H), 7.34-7.14 (m, 5H), 6.98-6.93 (m, 3H), 5.83 (dd, J = 13.0, 6.5 Hz, 1H), 2.73 (tdd, J = 13.0 Hz, J = 6.5 Hz, J = 3.0 Hz, 1H), 2.49-1.97 (m, 3H), 1.70-1.64 (m, 1H), 1.49-1.46 (m, 1H); ¹³C NMR *cis* diastereomer (125 MHz, C₆D₆): δ 200.9, 185.2, 180.5, 143.2, 136.0, 135.4, 132.5, 132.3, 128.6, 126.8, 126.7, 123.6, 120.6, 81.5, 41.4, 39.6, 37.3, 33.8; ¹H NMR *trans* diastereomer (500 MHz; C₆D₆) of the minor diasteromer: δ 7.54-7.47 (m, 1H), 7.34-7.14 (m, 5H), 6.98-6.93 (m, 3H), 5.83 (dd, J = 9.5 Hz, J = 5.5 Hz, 1H), 2.99-2.96 (m, 1H), 2.49-1.97 (m, 5H), 1.70-1.64 (m, 1H); ¹³C NMR *trans* diastereomer (125 MHz, C₆D₆): δ 202.2, 184.8, 180.2, 142.0, 135.9, 135.5, 132.3, 132.2, 128.8, 126.9, 126.7, 123.6, 120.5, 80.6, 39.4, 37.0, 36.8, 31.8; IR (thin film) 3060, 3030, 2952, 2930, 2868, 1619, 1729, 1537, 1407, 715 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₀H₁₈NO₃ (M+H)⁺ 320.1287, found 320.1292.
Imidate 4t: General procedure F was followed with 3t (0.062 g, 0.25 mmol). Heating the reaction mixture to 90 °C for 10 h afforded imidate 4t (0.062 g, >95% recovery) as an amorphous solid. ¹H NMR (500 MHz; C₆D₆): δ 7.50-7.48 (m, 1H), 7.18-7.17 (m, 1H), 6.93-6.90 (m, 2H), 5.69 (dd, J = 5.0, 5.0 Hz, 1H), 4.23 (dd, J = 10.0, 5.0 Hz, 1H), 3.61 (dd, J = 10.0, 5.0 Hz, 1H), 3.37 (t, J = 5.0 Hz, 1H), 3.02 (dt, J = 10.0, 5.0 Hz, 1H), 2.21-2.14 (m, 1H), 2.04-2.01 (m, 1H); ¹⁳C NMR (125 MHz, C₆D₆): δ 197.7, 184.9, 180.0, 135.9, 135.0, 132.6, 132.3, 123.7, 120.5, 78.9, 69.7, 68.0, 41.8; IR (thin film) 2966, 2926, 1727, 1613, 1538, 1467, 1408, 1382, 1206, 1073 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₃H₁₂NO₄ (M+H)⁺ 246.0766, found 246.0758.

Imidate 4u: General procedure F was followed with 3u (0.300 g, 0.996 mmol). Heating the reaction mixture to 80 °C for 12 h afforded imidate 4u (0.290 g, >95% recovery) as an amorphous solid. ¹H NMR (500 MHz; C₆D₆): δ 7.51-7.48 (m, 1H), 7.24-7.23 (m, 1H), 6.98-6.91 (m, 2H), 6.11-6.09 (m, 1H), 3.55-3.46 (m, 4H), 2.50-2.44 (m, 2H), 2.21-2.18 (m, 2H), 1.68-1.65 (m, 2H); ¹³C NMR (125 MHz, C₆D₆): δ 200.3, 185.1, 180.3, 136.0, 135.4, 132.5,
132.3, 123.6, 120.6, 107.0, 79.3, 64.6, 64.5, 40.3, 35.6, 34.3; IR (thin film) 2963, 2938, 2890, 1736, 1617, 1533, 1409, 1126, 1027, 718 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{16}$NO$_{5}$ (M+H)$^+$ 302.1004, found 302.1001.

![Image of compound 4v](image)

**Imidate 4v:** General procedure F was followed with 3v (0.0287 g, 0.0986 mmol). Heating the reaction mixture to 80 ºC for 16 h afforded imidate 4v (0.0273 g, 95%) as an orange solid.

$^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 8.16 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 6.0$ Hz, 1H), 7.27-7.25 (m, 2H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.01-6.91 (m, 3H), 6.80 (d, $J = 7.5$ Hz, 1H), 6.03 (dd, $J = 13.5$ Hz, $J = 5.0$ Hz, 1H), 2.61-2.57 (m, 1H), 2.44-2.41 (m, 1H), 2.22 (ddd, $J = 9.0$ Hz, $J = 7.0$, $J = 4.5$ Hz, 1H), 2.06 (ddd, $J = 13.5$, 9.0, 4.5 Hz, 1H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 190.5, 185.6, 180.6, 142.9, 136.1, 135.5, 133.6, 132.5, 132.3, 131.6, 128.5, 127.9, 126.9, 123.5, 120.8, 80.9, 28.9, 27.3; IR (thin film) 3056, 2990, 2926, 2877, 2851, 1739, 1701, 1605, 1541, 1261 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{14}$NO$_3$ (M+H)$^+$ 292.0974, found 292.0976.; mp 134-138°C.
V. Synthesis of α-Hydroxy Ketones and $^1$H NMR Spectroscopy Yields of Imidate Intermediates (Table 1.5)

General Procedure G: Synthesis of α-Hydroxy Ketones. A J-Young tube or Teflon-sealed reaction flask was charged with N-enoxyphthalimide 3 (1 equiv), hexamethylbenzene as an internal standard, and either C$_6$D$_6$ or toluene. C$_6$D$_6$ was used as the solvent if the reaction was run in a J-Young tube and toluene was used if the solvent if the reaction was run on larger scale in a Teflon-sealed reaction flask. The reaction mixture was heated to 70-90 °C for 10-16 h. Reaction mixtures heated in C$_6$D$_6$ were analyzed directly by $^1$H NMR spectroscopy to determine the yield of imidate 4. Reaction mixtures heated in toluene were first concentrated under reduced pressure, dissolved in C$_6$D$_6$, and analyzed by $^1$H NMR spectroscopy to determine the yield of imidate 4. The crude solutions of imidate 4 were then transferred to a scintillation vial, C$_6$D$_6$ was removed under reduced pressure, and the resulting amorphous solid was dissolved in CH$_2$Cl$_2$ to form an 0.1 M solution of 4. Silica gel (0.200 g/ 0.1 mmol of 4) or Amberlite-IR120 resin (0.200 g/ 0.1 mmol of 4) was then added to the CH$_2$Cl$_2$ solution and the reaction mixture was stirred at 25 °C until formation of a white precipitate was observed (20 - 40 min) if Amberlite-IR120 was used or 16 h if SiO$_2$ was used. The silica gel or Amberlite-IR120 resin was then separated from the CH$_2$Cl$_2$ solution and washed with CH$_2$Cl$_2$ (3 x 4 mL). The filtrate was then concentrated under reduced pressure, dissolved in ethyl acetate (20 mL), and extracted with 1M NaOH$_{(aq)}$ (3 x 2
mL) to remove the phthalimide byproduct. The organic layer was then concentrated under reduced pressure and purified by medium pressure chromatography (ethyl acetate:hexane) to give 5 as a white solid.

\[
\begin{align*}
\text{HO} & \\
& \text{C}_6\text{H}_{11} \\
& \text{C}_6\text{H}_{11}
\end{align*}
\]

\textbf{5f}

\textbf{α-Hydroxy Ketone 5f:} General procedure G was followed by heating a C\textsubscript{6}D\textsubscript{6} solution of 3f (0.140 g, 0.425 mmol) in the presence of CH\textsubscript{2}Br\textsubscript{2} (21 μL, 0.30 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 °C, \textsuperscript{1}H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4f was 90%. The imidate was then mixed with silica gel in CH\textsubscript{2}Cl\textsubscript{2} and allowed to stir for 16 h. Treatment with NaOH\textsubscript{(aq)} and purification by chromatography gave 5f as a clear, colorless oil (0.066 g, 78%). \textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): δ 4.18-4.15 (m, 1H), 3.48 (brs, 1H), 2.47-2.41 (m, 2H), 1.80-1.79 (m, 1H), 1.63-1.59 (m, 2H), 1.52-1.46 (m, 2H), 1.37-1.24 (m, 9H), 0.89-0.87 (m, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 212.6, 76.4, 37.8, 33.8, 31.7, 31.4, 24.5, 23.4, 22.5, 22.4, 14.0, 13.9; IR (thin film) 3472, 2959, 2922, 2855, 1709, 1466, 1376, 1130, 1058 cm\textsuperscript{-1}; HRMS (ESI) m/z calcd. for C\textsubscript{12}H\textsubscript{24}O\textsubscript{2}Na (M+Na)\textsuperscript{+} 223.1674, found 223.1670.
**α-Hydroxy Ketone 5h:** General procedure G was followed by heating a C₆D₆ solution of 3h (0.070 g, 0.24 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 ºC, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4h was >95%. The imidate was then mixed with Amberlite-IR120 in CH₂Cl₂ and allowed to stir for 3 h. Treatment with NaOH(aq) and purification by chromatography gave 5h as a yellow oil (0.0351 g, 90%). ¹H NMR (500 MHz; CDCl₃): δ 7.90 (d, J = 8.0 Hz, 2H), 7.63-7.60 (m, 1H), 7.48 (t, J = 8.0 Hz, 2H), 5.07-5.04 (m, 1H), 3.69 (d, J = 6.0 Hz, 1H), 1.98-1.91 (m, 1H), 1.64-1.58 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 202.1, 133.9, 133.8, 128.9, 128.5, 74.0, 28.9, 8.9; IR (thin film) 3472, 2966, 2940, 2873, 1675, 1597, 1451, 1245, 1130, 965, 692 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₀H₁₂O₂Na (M+Na)⁺ 187.0735, found 187.0736.

**α-Hydroxy Ketone 5i:** General procedure G was followed by heating a C₆D₆ solution of 3i (0.070 g, 0.21 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 ºC, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4i was 95%. The imidate was then mixed with Amberlite-IR120 in CH₂Cl₂ and allowed to stir for 3 h. Treatment with
NaOH(aq) and purification by chromatography gave 5i as a white solid (0.038 g, 88%). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.93-7.96 (m, 2H), 7.15 (t, $J = 8.5$ Hz, 2H), 5.12-5.06 (m, 1H), 3.63 (d, $J = 6.5$ Hz, 1H), 1.84-1.82 (m, 1H), 1.53-1.47 (m, 2H), 1.34-1.24 (m, 3H), 0.85 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 200.6, 166.1 (d, $J = 255$ Hz), 131.2, 130.1, 116.1 (d, $J = 18.8$ Hz), 73.0, 35.7, 27.1, 22.5, 13.9; IR (thin film) 3466, 2956, 2933, 2868, 1677, 1593, 1502, 1236, 1132, 1079, 845, 604 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{15}$FO$_2$Na (M+Na)$^+$ 233.0954, found 233.0956; mp 45-47 ºC.

![5j](image)

**α-Hydroxy Ketone 5j:** General procedure G was followed by heating a C$_6$D$_6$ solution of 3j (0.078 g, 0.21 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 ºC, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4j was >95%. The imidate was then mixed with Amberlite-IR120 in CH$_2$Cl$_2$ and allowed to stir for 3 h. Treatment with NaOH(aq) and purification by chromatography gave 5j as a yellow oil (0.038 g, 75%). $^1$H NMR (500 MHz; CDCl$_3$): δ 8.34 (d, $J = 9.0$ Hz, 2H), 8.06 (d, $J = 8.5$ Hz, 2H), 5.12-5.06 (m, 1H), 3.49 (d, $J = 6.5$ Hz, 1H), 1.87-1.82 (m, 1H), 1.58-1.46 (m, 2H), 1.34-1.31 (m, 3H), 0.88 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 201.8, 150.7, 138.5, 129.6, 124.1, 73.7, 35.1, 27.0, 22.4, 13.8; IR (thin film) 3483, 2956, 2929, 2861, 1695, 1601, 1526, 1374, 1275, 1084, 852, 710 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{15}$NO$_3$Na (M+Na)$^+$ 260.0899, found 260.0902.
**α-Hydroxy Ketone 5k:** General procedure G was followed by heating a C₆D₆ solution of 3k (0.080 g, 0.21 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 °C, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4k was >95%. The imidate was then mixed with Amberlite-IR120 in CH₂Cl₂ and allowed to stir for 3 h. Treatment with NaOH(aq) and purification by chromatography gave 5k as a white solid (0.046 g, 86%). ¹H NMR (500 MHz; CDCl₃): δ 8.01 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 5.12-5.08 (m, 1H), 3.57 (d, J = 5.0 Hz, 1H), 1.87-1.83 (m, 1H), 1.56-1.48 (m, 2H), 1.35-1.22 (m, 3H), 0.85 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 201.5, 136.6, 135.0 (q, J = 32 Hz), 128.9, 126.0 (d, J = 2.5 Hz), 122.3, (d, J = 271 Hz), 73.5, 35.3, 27.0, 22.4, 13.9; IR (thin film) 3473, 2959, 2930, 2868, 1684, 1323, 1132, 1066, 858 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₃H₁₅F₃O₂Na (M+Na)⁺ 283.0922, found 283.0927; mp 40-42 °C.

**α-Hydroxy Ketone 5l:** General procedure G was followed by heating a C₆D₆ solution of 3l (0.070 g, 0.21 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 °C, ¹H NMR analysis of the reaction
mixture indicated that the yield of the in situ generated imidate 4l was >95%. The imidate was then mixed with silica gel in CH₂Cl₂ and allowed to stir for 12 h. Treatment with NaOH(aq) and purification by chromatography gave 5l as a yellow oil (0.0352 g, 82%). \(^1\)H NMR (500 MHz; CDCl₃): δ 7.80 (d, \(J = 8.0 \) Hz, 2H), 7.28 (d, \(J = 8.0 \) Hz, 2H), 5.05-5.02 (m, 1H), 3.70 (d, \(J = 6.5 \) Hz, 1H), 2.43 (s, 3H), 1.88-1.83 (m, 1H), 1.54-1.45 (m, 2H), 1.37-1.33 (m, 3H), 0.92 (t, \(J = 7.5 \) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl₃): δ 201.7, 144.9, 131.2, 129.6, 128.7, 73.0, 35.8, 27.1, 22.5, 21.8, 13.9; IR (thin film) 3479, 2959, 2929, 2862, 1671, 1608, 1271, 1133, 979, 826 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{13}\)H\(_{18}\)O\(_2\)Na (M+Na\(^+\) 229.1204, found 229.1203.

\[
\begin{align*}
\text{HO} & \\
\text{C} & \\
\text{Ph} & \\
\text{O} & \\
\end{align*}
\]

\(5s\)

\(\text{dr} = 60:40; \text{cis:trans}\)

**α-Hydroxy Ketone 5s:** A C₆D₆ solution of 3s (0.0231 g, 0.0724 mmol) and trimethoxybenzene (0.0069 g, 0.041 mmol) was heated in a J-Young tube for 12 h at 90 °C. At this time, \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4s was 95%.

A C₆D₆ solution of 3s (0.124 g, 0.388 mmol) was heated in a J-Young tube at 90 °C for 16h. At this time, \(^1\)H NMR analysis indicated that conversion to imidate 4s was complete. The C₆D₆ solution of 4t was then concentrated under reduced pressure and dissolved in CH₂Cl₂. The CH₂Cl₂ solution of 4s was mixed with Amberlite-IR120 (0.2 g/ 0.1 mmol of 4s), and allowed to stir for 30 min. Treatment with NaOH(aq) and purification by chromatography, as
described in general procedure G, gave 5s as an amorphous solid (0.0603 g, 82%). $^1$H NMR cis diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.44-7.23 (m, 5H), 4.34 (dd, $J = 12.0, 6.5$ Hz, 1H), 3.70 (brs, 1H), 3.18 (ddt, $J = 12.0, 6.0, 3.0$ Hz, 1H), 2.74-2.50 (m, 3H), 2.27-2.26 (m, 1H), 1.97-1.70 (m, 2H); $^{13}$C NMR cis diastereomer (125 MHz, CDCl$_3$): $\delta$ 210.8, 143.5, 128.7, 126.7, 126.5, 74.6, 43.2, 41.3, 38.7, 34.9; $^1$H NMR (500 MHz; CDCl$_3$) trans diastereomer: 7.44-7.23 (m, 5H), 4.25 (dd, $J = 10.5, 6.0$ Hz, 1H), 3.52 (bs, 1H), 3.43-3.41(m, 1H), 2.85-2.82 (m, 1H), 2.74-2.50 (m, 3H), 2.17-2.03 (m, 1H), 1.97-1.70 (m, 1H); $^{13}$C NMR trans diastereomer (125 MHz, CDCl$_3$): $\delta$ 211.6, 143.5, 128.8, 126.9, 126.6, 72.3, 39.8, 36.3, 36.2, 31.1; IR (thin film) 3450, 3060, 3027, 2933, 2868, 1717, 1495, 1267, 1102, 738 cm$^{-1}$; HRMS (EI) m/z calcd. for C$_{12}$H$_{15}$O$_2$ (M+H)$^+$ 190.09938, found 190.09968.

\[
\begin{align*}
\text{HO} & \text{C} \\
\text{5v} & \\
\end{align*}
\]

**α-Hydroxy Ketone 5v:** A C$_6$D$_6$ solution of 3v (0.0352 g, 0.121 mmol) and trimethoxybenzene (0.0050 g, 0.030 mmol) was heated to 80 ºC in a J-Young tube for 16 h. At this time, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4v was 94%.

A C$_6$D$_6$ solution of 3v (0.0287 g, 0.0986 mmol) was heated in a J-Young tube at 80 ºC for 16 h. At this time, $^1$H NMR analysis indicated that conversion to imidate 4v was complete. The C$_6$D$_6$ solution of 4v was then concentrated under reduced pressure and dissolved in CH$_2$Cl$_2$. The CH$_2$Cl$_2$ solution of 4v was mixed with Amberlite-IR120 (0.2 g/ 0.1mmol of 4v), and allowed to stir for 1 h. Treatment with NaOH$_{(aq)}$ and purification by chromatography, as
described in general procedure G, gave 5v as a yellow oil (0.0139 g, 87%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.04 (d, $J$ = 7.5 Hz, 1H), 7.53 (t, $J$ = 7.5 Hz, 1H), 7.35 (d, $J$ = 7.5 Hz, 1H), 7.27 (d, $J$ = 7.5 Hz, 1H), 4.39 (dd, $J$ = 13.5, 5.5 Hz, 1H), 3.91 (brs, 1H), 3.19-3.12 (m, 1H), 3.06-3.02 (m, 1H), 2.54 (dt, $J$ = 5.5, 4.5 Hz, 1H), 2.04 (ddd, $J$ = 13.5, 8.5, 4.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.6, 144.4, 134.2, 130.5, 128.9, 127.6, 126.9, 73.9, 31.9, 27.8; IR (thin film) 3479, 2955, 2934, 2875, 1682, 1602, 1460, 1282, 1089, 987 cm$^{-1}$; HRMS (EI) m/z calcd. for C$_{10}$H$_{10}$O$_2$Na(M+Na)$^+$ 185.0578, found 185.0580.

Conversion of 1 and 2w to $\alpha$-Hydroxy Ketone 5w:

![Chemical structure of 5w]

General procedure C (or D) with N-hydroxyphthalimide 2 (0.050 g; 0.30 mmol), alkenyl boronic acid 1w (0.210 g, 0.900 mmol), Cu(OAc)$_2$ (0.054 g, 0.30 mmol), Na$_2$SO$_4$ (0.187 g, 1.30 mmol), and pyridine (72.4 µL, 0.900 mmol) afforded a mixture of 3w and 5w which was separated from the copper reagent using medium pressure chromatography (1:9; ethyl acetate:hexanes). The mixture of 3w and 5w was then subjected to general procedure G and dissolved in C$_6$D$_6$ and heated to 80 ºC for 12 h. The crude product mixture was then mixed with Amberlite-IR120 in CH$_2$Cl$_2$ and allowed to stir for 3 h. Treatment with NaOH$_{(aq)}$ and purification by chromatography gave 5w as an amorphous solid (0.039 g, 57%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.89 (d, $J$ = 8.0 Hz, 2H), 6.96 (d, $J$ = 8.0 Hz, 2H), 5.03-5.01 (m, 1H), 3.87 (s, 3H), 3.74 (d, $J$ = 5.0 Hz, 1H), 1.87-1.85 (m, 1H), 1.54-1.49 (m, 2H), 1.37-1.25 (m,
3H), 0.85 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 200.5, 164.1, 130.9, 126.5, 114.1, 72.7, 55.6, 36.0, 27.1, 22.5, 13.9; IR (thin film) 3473, 2956, 2926, 2858, 1671, 1596, 1509, 1251, 1170, 838 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{13}$H$_{18}$O$_3$Na (M+Na)$^+$ 245.1154, found 245.1151.

VI. Synthesis of α-Benzoyloxy Ketones and $^1$H NMR Spectroscopy Yields of Imidate Intermediates (Table 1.6)

![Diagram of reaction](attachment:image.png)

**General Procedure H: Synthesis of α-Benzoyloxy ketones.** A J-Young tube or Teflon-sealed reaction flask was charged with N-enoxypythalimide 3 (1 equiv), hexamethylbenzene as an internal standard, and either C$_6$D$_6$ or toluene. C$_6$D$_6$ was used as the solvent if the reaction was run in a J-Young tube and toluene was used as the solvent if the reaction was run on larger scale in a Teflon-sealed reaction flask. The reaction mixture was heated to 70-90 °C for 10-16 h. Reaction mixtures heated in C$_6$D$_6$ were analyzed directly by $^1$H NMR spectroscopy to determine the yield of imidate 4. Reaction mixtures heated in toluene were first concentrated under reduced pressure, dissolved in C$_6$D$_6$, and analyzed by $^1$H NMR spectroscopy to determine the yield of imidate 4. The crude solutions of imidate 4 were then transferred to a scintillation vial, C$_6$D$_6$ was removed under reduced pressure, and the resulting amorphous solid was dissolved in CH$_2$Cl$_2$ to form a 0.1 M solution of 4. Amberlite-IR120 resin (0.200 g per 0.1 mmol 4) was then added to the CH$_2$Cl$_2$ solution and the reaction
mixture was stirred at 25 °C until a white precipitate was observed (20-40 min). The Amberlite-IR120 resin was then separated from the CH$_2$Cl$_2$ solution and washed with CH$_2$Cl$_2$ (3 x 4 mL). The filtrate was then concentrated under reduced pressure to form a 0.05 M solution of 4 which was treated with NEt$_3$ (5-8 equiv) and benzoyl chloride (2-4 equiv), and allowed to stir for 3 h. At this time, the reaction mixture was concentrated under reduced pressure and purified by medium pressure chromatography (1:9-1:3 ethyl acetate: hexanes) to afforded 6 as a white solid.

![Image of 6a](image)

**α-Benzoyloxy Ketone 6a:** A mixture of 3a (0.0192 g, 0.0884 mmol) and hexamethylbenzene (0.028 M solution in C$_6$D$_6$) was heated in C$_6$D$_6$ (0.6 mL) in a J-Young tube for 16 h at 80 °C. At this time, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 92%.

A C$_6$D$_6$ solution of 3a (0.110 g, 0.507 mmol) was heated in a J-Young tube at 80 °C for 16 h. At this time, $^1$H NMR analysis indicated that conversion to imidate 4a was complete. The C$_6$D$_6$ solution of 4a was then concentrated under reduced pressure and dissolved in CH$_2$Cl$_2$. Hydrolysis of imidate 4a with Amberlite-IR120 was followed by the addition of NEt$_3$ (0.410 g, 4.05 mmol) and benzoyl chloride (0.285 g, 2.03 mmol) as described in general procedure H. Purification of the crude product by medium pressure chromatography (1:9 ethyl acetate: hexanes) afforded 6a as an amorphous solid (0.0838 g, 86%). $^1$H NMR (500 MHz; CDCl$_3$): δ 8.08 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46-7.43 (m, 2H), 5.31 (q, J = 7.0 Hz, 1H),
2.23 (s, 3H), 1.52 (d, J = 7.0 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 205.8, 165.9, 133.4, 129.8, 129.5, 128.5, 75.5, 25.7, 16.2; IR (thin film) 3063, 2992, 2942, 2878, 1717, 1454, 1359, 1265, 1108, 738 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{11}\)H\(_{12}\)O\(_3\)Na (M+Na)\(^{+}\) 215.0684, found 215.0681.

\[ \text{BzO} \]

6m

**α-Benzoyloxy Ketone 6m:** General procedure H was followed by heating a C\(_6\)D\(_6\) solution of 3m (0.090 g, 0.39 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 °C, \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 92%. Hydrolysis of imidate 4m with Amberlite-IR120 was followed by the addition of NEt\(_3\) (0.446 mL, 3.34 mmol) and benzoyl chloride (0.185 mL, 1.59 mmol). Purification of the benzoyl protected α-oxygenation product by medium pressure chromatography (1:9 ethyl acetate: hexanes) afforded 6m as a yellow oil (0.053 g, 66%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 8.05 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 5.32-5.28 (m, 1H), 2.58-2.53 (m, 1H), 2.47-2.45 (m, 1H), 2.36-2.30 (m, 1H), 2.20-2.15 (m, 1H), 2.03-1.93 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 212.3, 165.8, 133.3, 129.9, 129.5, 128.4, 76.1, 35.0, 28.6, 17.3; IR (thin film) 2956, 2928, 2858, 1717, 1457, 1267, 1106, 708 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{12}\)H\(_{12}\)O\(_3\)Na (M+Na)\(^{+}\) 227.0684, found 227.0691.
**α-Benzoyloxy Ketone 6n:** General procedure H was followed by heating a 0.24 M solution of 3n (0.070 g, 0.29 mmol) in the presence of hexamethylbenzene (0.004 g, 0.02 mmol) in C₆D₆ in a J-Young tube for 10 h. After 10 h of heating at 90 ºC, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate 4n was >95%. Hydrolysis of imidate 4n with Amberlite-IR120 was followed by the addition of NEt₃ (150 µL, 1.43 mmol) and benzoyl chloride (70 µL, 0.57 mmol). Purification of the crude product by medium pressure chromatography (1:6 ethyl acetate: hexanes) afforded 6n as a white solid (0.042 g, 67%). ¹H NMR (500 MHz; CDCl₃): δ 8.10-8.08 (m, 2H), 7.57-7.54 (m, 1H), 7.47-7.42 (m, 2H), 5.42 (dd, J = 5.0, 5.0 Hz, 1H), 2.58-2.57 (m, 1H), 2.49-2.40 (m, 2H), 2.10 (dtd, J = 8.8, 5.1, 2.8 Hz, 1H), 2.01 (ddd, J = 8.8, 5.1, 2.8 Hz, 1H), 1.97-1.89 (m, 1H), 1.86-1.78 (m, 1H), 1.73-1.63 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 204.3, 165.6, 133.2, 129.9, 128.4, 77.0, 40.8, 33.3, 27.3, 23.8; IR (thin film) 2947, 2865, 1711, 1604, 1450, 1317, 1265, 1177, 1109, 1064 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₃H₁₄O₃Na (M+Na)⁺ 241.0841, found 241.0838; mp 86 ºC.

**6o**

dr = 20:80; cis:trans
**α-Benzoyloxy Ketone 60:** A mixture of 30 (0.0212 g, 0.0825 mmol) and trimethoxybenzene (0.0015 g, 0.009 mmol) was heated in C₆D₆ in a J-Young tube for 16 h at 80 °C. At this time, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 86%.

A C₆D₆ solution of 30 (0.0468 g, 0.182 mmol) was heated in a J-Young tube at 80 °C for 16 h. At this time, ¹H NMR analysis indicated that conversion to imidate 40 was complete. The C₆D₆ solution of 40 was then concentrated under reduced pressure and dissolved in CH₂Cl₂. Hydrolysis of imidate 40 with Amberlite-IR120 was followed by the addition of NEt₃ (0.1473 g, 1.456 mmol) and benzoyl chloride (0.1023 g, 0.7281 mmol) as described in general procedure H. Purification of the crude product by medium pressure chromatography (1:9 ethyl acetate: hexanes) afforded 60 as a yellow oil (0.0279 g, 66%). ¹H NMR cis diastereomer (500 MHz; CDCl₃): δ 8.12-8.07 (m, 2H), 7.61-7.55 (m, 1H), 7.49-7.42 (m, 2H), 5.39-5.37 (m, 1H), 2.58 (dq, J = 13.0, 6.0 Hz, 1H), 2.48-2.44 (m, 1H), 2.23-2.09 (m, 2H), 2.07-1.93 (m, 2H), 1.92-1.83 (m, 1H), 1.09 (d, J = 6.0 Hz, 3H); ¹³C NMR cis diastereomer (125 MHz, CDCl₃): δ 208.7, 165.5, 133.1, 130.2, 129.8, 128.3, 77.2, 44.4, 36.1, 33.6, 23.2, 13.9; ¹H NMR trans diastereomer (500 MHz; CDCl₃): δ 8.12-8.07 (m, 2H), 7.61-7.55 (m, 1H), 7.49-7.42 (m, 2H), 5.38 (dd, J = 8.0, 4.5 Hz, 1H), 2.87 (dq, J = 14.0, 7.0 Hz, 1H), 2.23-2.09 (m, 2H), 2.07-1.93 (m, 2H), 1.92-1.83 (m, 1H), 1.66-1.59 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H); ¹³C NMR trans diastereomer (125 MHz, CDCl₃): δ 208.7, 165.5, 133.3, 129.9, 129.8, 128.5, 76.1, 43.2, 35.2, 33.3, 19.7, 15.2; IR (thin film) 3061, 2973, 2938, 2868, 1787, 1719, 1453, 1315, 1209, 1114, 1013 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₁₆O₃Na (M+Na)⁺ 255.0997, found 255.1006.
α-Benzyloxy Ketone 6p: General procedure H was followed by heating a C₆D₆ solution of 3p (0.040 g, 0.16 mmol) in the presence of 1,3,5-trimethoxybenzene (0.002 g, 0.011 mmol) in a C₆D₆ for 12 h. After 12 h of heating at 90 ºC, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was >95%. Hydrolysis of imidate 4p with Amberlite-IR120 was followed by the addition of NEt₃ (100 µL, 0.775 mmol) and benzoyl chloride (40 µL, 0.310 mmol). Purification of the benzoyl protected α-oxygenation product by medium pressure chromatography (1:6; ethyl acetate:hexanes) afforded 6p as a white solid (0.025 g, 69%). ¹H NMR cis diastereomer (500 MHz; CDCl₃): δ 8.10-8.09 (m, 2H), 7.58-7.57 (m, 1H), 7.46-7.45 (m, 2H), 5.44 (d, J = 5.5 Hz, 1H), 2.67-2.65 (m, 1H), 2.55-2.48 (m, 1H), 2.22-1.99 (m, 4H), 1.73-1.67 (m, 1H), 1.15 (d, J = 5.5 Hz, 3H); ¹³C NMR cis diastereomer (125 MHz, CDCl₃): δ 204.8, 165.9, 133.2, 133.1, 129.8, 128.4, 82.2, 40.4, 39.5, 32.7, 25.7, 19.0; ¹H NMR trans diastereomer (500 MHz; CDCl₃): δ 8.09-8.08 (m, 2H), 7.57-7.55 (m, 1H), 7.45-7.43 (m, 2H), 5.06 (d, J = 11.5 Hz, 1H), 2.50-2.41 (m, 2H), 1.97-1.92 (m, 3H), 1.86-1.78 (m, 1H), 1.66-1.57 (m, 1H), 1.08 (d, J = 5.0 Hz, 3H); ¹³C NMR trans diastereomer (125 MHz, CDCl₃): δ 203.8, 165.5, 133.2, 133.1, 129.8, 128.3, 79.8, 40.1, 36.7, 30.0, 22.4, 13.5; IR (thin film) 2959, 2933, 2873, 1717, 1602, 1451, 1309, 1283, 1260, 1174, 1111 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₁₆O₃Na (M+Na)⁺ 255.0997, found 255.0998; mp 98-100 ºC.
**α-Benzyloxy Ketone 6q:** General procedure H was followed by heating a 0.24 M solution of 3q (0.068 g, 0.26 mmol) in the presence of hexamethylbenzene (0.012 g, 0.072 mmol) in a C₆D₆ for 14 h. After 14 h of heating at 90 ºC, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 96%. Hydrolysis of imidate 4q with Amberlite-IR120 was followed by the addition of NEt₃ (0.133 g, 1.32 mmol) and benzoyl chloride (0.074 g, 0.53 mmol). Purification of the benzoyl protected α-oxygenation product by medium pressure chromatography (1:4; ethyl acetate: hexanes) afforded 6q as a white solid (0.040 g, 65%). ¹H NMR cis diastereomer (500 MHz; CDCl₃): δ 8.09-8.08 (m, 2H), 7.59-7.57 (m, 1H), 7.48-7.45 (m, 2H), 5.44 (dd, J = 5.0, 5.0 Hz, 1H), 2.58-2.55 (m, 2H), 2.40-2.33 (m, 2H), 2.08-1.97 (m, 2H), 1.73-1.65 (m, 1H), 1.21 (d, J = 5.0 Hz, 3H); ¹³C NMR cis diastereomer (125 MHz, CDCl₃): δ 205.7, 165.5, 134.6, 133.2, 129.9, 128.4, 75.9, 40.8, 39.3, 35.1, 33.7, 21.0; ¹H NMR trans diastereomer (500 MHz; CDCl₃): δ 8.08-8.07 (m, 2H), 7.56-7.55 (m, 1H), 7.45-7.42 (m, 2H), 5.41 (dd, J = 5.0, 5.0 Hz, 1H), 2.53-2.49 (m, 2H), 2.24-2.12 (m, 2H), 2.02-1.97 (m, 1H), 1.82-1.74 (m, 1H), 1.39-1.38 (m, 1H), 1.08 (d, J = 5.0 Hz, 3H); ¹³C NMR trans diastereomer (125 MHz, CDCl₃): δ 204.4, 165.5, 134.6, 133.1, 129.8, 128.3, 74.9, 39.6, 36.9, 30.9, 27.2, 18.8; IR (thin film) 2959, 2930, 2872, 1717, 1687, 1604, 1583, 1454, 1317, 1275 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₁₇O₃ (M+H)⁺ 233.1178, found 233.1171; mp 95 ºC.
**6r**

\[ \text{dr} = 75:25; \text{cis:trans} \]

**α-Benzoyloxy Ketone 6r**: A mixture of 3r (0.0482 g, 0.161 mmol) and trimethoxybenzene (0.0048 g, 0.029 mmol) was heated in C₆D₆ in a J-Young tube for 16 h at 80 °C. At this time, \(^1\text{H NMR}\) analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 75%.

A C₆D₆ solution of 3u (0.0385 g, 0.129 mmol) was heated in a J-Young tube at 80 °C for 16 h. At this time, \(^1\text{H NMR}\) analysis indicated that conversion to imidate 4r was complete. The C₆D₆ solution of 4r was then concentrated under reduced pressure and dissolved in CH₂Cl₂. Hydrolysis of imidate 4r with Amberlite-IR120 was followed by the addition of NEt₃ (0.1042 g, 1.030 mmol) and benzoyl chloride (0.0724 g, 0.5148 mmol) as described in general procedure H. Purification of the crude product by medium pressure chromatography (1:9 ethyl acetate: hexanes) afforded 6r as an amorphous solid (0.0232 g, 66%). \(^1\text{H NMR}\) cis diastereomer (500 MHz; CDCl₃): \(\delta\) 8.11-8.07 (m, 2H), 7.59-7.53 (m, 1H), 7.47-7.42 (m, 2H), 5.38 (dd, \(J = 12.0, 6.0\) Hz, 1H), 2.57-2.43 (m, 3H), 2.18-2.12 (m, 1H), 1.79-1.73 (m, 2H), 1.54-1.46 (m, 1H), 0.97 (s, 9H); \(^{13}\text{C NMR}\) cis diastereomer (125 MHz, CDCl₃): \(\delta\) 206.1, 165.6, 133.2, 129.9, 129.7, 128.4, 76.6, 45.9, 39.6, 34.3, 32.3, 28.1, 27.7; \(^1\text{H NMR}\) trans diastereomer (500 MHz; CDCl₃): \(\delta\) 8.11-8.07 (m, 2H), 7.59-7.53 (m, 1H), 7.47-7.42 (m, 2H), 5.28 (dd, \(J = 10.5, 5.0\) Hz, 1H), 2.69-2.63 (m, 1H), 2.57-2.43 (m, 1H), 2.34-2.29 (m, 1H), 1.94-1.83 (m, 1H), 1.68-1.60 (m, 1H), 1.43-1.38 (m, 1H), 0.94 (s, 9H); \(^{13}\text{C NMR}\) trans
diastereomer (125 MHz, CDCl$_3$): $\delta$ 206.1, 165.6, 133.4, 129.8, 129.7, 128.5, 76.2, 41.9, 38.0, 32.3, 32.3, 27.4, 26.6; IR (thin film) 3057, 2963, 2908, 2872, 1733, 1719, 1453, 1319, 1267, 1126 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{17}$H$_{23}$O$_3$ (M+H)$^+$ 275.1647, found 275.1641. Ref: OL, 2005, 7 (25), 5729 they report cis pdt, the major isomer.

**a-Benzyloxy Ketone 6t:** General procedure H was followed by heating a 0.24 M solution of 3t (0.060 g, 0.24 mmol) in the presence of hexamethylbenzene (0.003 g, 0.02 mmol) in a C$_6$D$_6$ for 14 h. After 14 h of heating at 90 ºC, $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 96%. Hydrolysis of imidate 4t with Amberlite-IR120 was followed by the addition of NEt$_3$ (170 $\mu$L, 1.22 mmol) and benzoyl chloride (60 $\mu$L, 0.49 mmol). Purification of the crude product by medium pressure chromatography (1:3 ethyl acetate: hexanes) afforded 6t as a white solid (0.037 g, 69%). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.09-8.07 (m, 2H), 7.58-7.55 (m, 1H), 7.45-7.42 (m, 2H), 5.52 (dd, $J = 6.5, 3.0$ Hz, 1H), 4.45 (ddd, $J = 12.5, 6.5, 3.0$ Hz, 1H), 4.29 (ddd, $J = 12.5, 6.5, 3.0$ Hz, 1H), 3.73-3.68 (m, 2H), 2.86-2.79 (m, 1H), 2.79-2.56 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 200.5, 165.1, 133.5, 130.0, 129.9, 128.5, 74.1, 70.6, 68.5, 42.3; IR (thin film) 2975, 2923, 1720, 1606, 1454, 1320, 1274, 1206, 1122, 1099 cm$^{-1}$; HRMS (EI) m/z calcd. for C$_{12}$H$_{12}$O$_4$ (M)$^+$ 220.07356, found 220.07434; mp 78 ºC.
α-Benzoyloxy Ketone 6u: General procedure H was followed by heating a C₆D₆ solution of 3u (0.100 g, 0.332 mmol) in the presence of hexamethylbenzene (0.0162 g, 0.100 mmol) in a J-Young tube for 12 h. After 12 h of heating at 80 °C, ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated imidate was 96%. Hydrolysis of imidate 4u with Amberlite-IR120 was followed by the addition of NEt₃ (0.446 mL, 3.34 mmol) and benzoyl chloride (0.185 mL, 1.59 mmol). Purification of the crude product by medium pressure chromatography (1:2 ethyl acetate:hexanes) afforded 6u as a white solid (0.058 g, 63%). ¹H NMR (500 MHz; CDCl₃): δ 8.07 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.46-7.43 (m, 2H), 5.66 (dd, J = 6.5, 13.0 Hz, 1H), 4.13-4.04 (m, 4H), 2.83-2.76 (m, 1H), 2.51-2.45 (m, 2H), 2.24 (t, J = 7.5 Hz, 1H), 2.09-2.01 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 203.3, 165.4, 135.3, 133.4, 129.9, 128.4, 107.4, 73.7, 65.0, 64.9, 40.3, 35.9, 34.6; IR (thin film) 2959, 2926, 2860, 1720, 1460, 1266, 1107, 1027, 706 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₅H₁₆O₅Na (M+Na)⁺ 299.0895, found 299.0892.; mp 75-78 °C.

Direct conversion 1a and 2 to α-benzoyloxy ketone 6a:
General procedure C with \(N\)-hydroxyphthalimide 2 (0.164 g; 1.005 mmol), Z-2-buten-2-yl boronic acid 1a (0.201 g, 2.010 mmol), Cu(OAc)\(_2\) (0.183 g, 1.005 mmol), Na\(_2\)SO\(_4\) (0.613 g, 1.80 mmol), and pyridine (240 \(\mu\)L, 3.015 mmol) afforded 3a. The crude product mixture was separated from Cu(OAc)\(_2\) by filtering through silica using CH\(_2\)Cl\(_2\). The CH\(_2\)Cl\(_2\) was then removed from crude 3a under reduced pressure and the crude \(N\)-endoxyphthalimide 3a was then subjected to general procedure H. Purification of crude 6a by medium pressure chromatography (1:3 ethyl acetate: hexanes) afforded 6a as an amorphous solid (0.130 g, 67%).

VII. Extended Optimization Table 1.7

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<td>19</td>
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</table>

*a Changing the concentration of base did not have a significant effect on the yield of the transformation. b All reaction were run at 0.1 M. c $^1$H NMR yields based on the use of 1,3,5-trimethoxybenzene as an internal standard.
VIII. Crossover Experiment for [3,3] Rearrangement and Preparation of N-Enoxy Phthalimide 3x.

Crossover Experiment: N-Enoxyphthalimide 3x (0.017 g, 0.066 mmol) and N-Enoxy phthalimide 3d (0.016 g, 0.066 mmol) were dissolved in C₆D₆ (0.5 mL) and transferred to a J-Young tube. An initial ¹H NMR experiment indicated a 1:1 ratio of 3x:3d. The J-Young tube was then heated to 90 ºC for 16 h. A second ¹H NMR experiment indicated a 1:1 ratio of 4x:4d. Since the [3,3] rearrangement can occur using either carbonyl of the phthalimide moiety two regioisomers of 8 were observed in a 1:1 ratio.

Rearrangement of 3x to give imidate 4x as a 1:1 regioisomeric mixture. N-Enoxy phthalimide 3x (0.016 g, 0.060 mmol) and 1,3,5-trimethoxybenzene (0.002 g, 0.009 mmol) were dissolved in C₆D₆ (0.5 mL). The reaction mixture was heated to 90 ºC for 16 h. A ¹H NMR experiment indicated a 95% yield of the desired imidate 4x as a 1:1 mixture of regioisomers. A second batch of N-Enoxyphthalimide 3x (0.028 g, 0.109 mmol) was dissolved in benzene (0.5 mL). The reaction mixture was heated to 90 ºC for 16 h. The solvent was removed under reduced pressure to give a yellow oil (0.028 g, >95% conversion). ¹H NMR (500 MHz; CDCl₃) for 4x: δ 7.48-7.47 (m, 1H), 7.35 (s, 1H), 6.76-6.74 (m, 1H), 5.67 (dd, J = 6.5, 6.0 Hz, 1H), 2.28-2.24 (m, 2H), 1.92 (s, 3H), 1.69-1.64 (m, 2H), 1.45-1.41
(m, 2H), 1.23-1.15 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) for 8a: $\delta$ 201.3, 185.4, 180.8, 143.6, 136.6, 134.1, 132.9, 123.5, 120.5, 82.3, 40.3, 33.1, 26.7, 23.2, 21.1; $^1$H NMR (500 MHz; CDCl$_3$) for 4x': $\delta$ 7.24-7.23 (m, 1H), 7.11 (s, 1H), 6.74-6.72 (m, 1H), 5.64 (dd, $J = 6.5$, 6.5 Hz, 1H) 2.23-2.21 (m, 2H), 1.92 (s, 3H), 1.40-1.35 (m, 4H), 1.18-1.09 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) for 8b: 201.2, 185.1, 180.5, 143.2, 135.9, 134.2, 132.6, 124.5, 121.8, 82.2, 40.2, 33.0, 26.7, 23.2, 21.0; IR (thin film) 2950, 2865, 1727, 1613, 1532, 1431, 1389, 1356, 1294, 1086 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{16}$NO$_3$ (M+H)$^+$ 258.1130, found 258.1129.

**Preparation of N-Enoxyphthalimide 3x:** A scintillation vial was charged with 3-methyl-N-hydroxyphthalimide (0.050g, 0.28 mmol), vinyl boronic acid I$_n$ (0.071 g, 0.56 mmol), Cu(OAc)$_2$ (0.051 g, 0.28 mmol) and anhydrous Na$_2$SO$_4$ (0.187 g, 1.32 mmol). These solids were then diluted with DCE to form a 0.1 M solution of 3-methyl-N-hydroxyphthalimide. Pyridine (0.066 g, 0.84 mmol) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 ºC for 12 h. DCE and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (1:4; ethyl acetate:hexanes) to give N-Enoxyphthalimide 3x (0.068 g, 94%) as a white solid. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.73 (d, $J = 7.7$ Hz, 1H), 7.66 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 4.95 (t, $J = 3.5$ Hz, 1H), 2.51 (s, 3H), 2.30 (t, $J = 6.2$ Hz, 2H), 2.01 (dd, $J = 3.91$, 1.85 Hz, 2H), 1.75 (td, $J = 12.22$, 6.12 Hz, 2H), 1.56 (td, $J = 12.20$, 6.16 Hz, 2H); $^{13}$C NMR (125
MHz, CDCl₃): δ 163.2, 163.1, 154.7, 146.1, 135.1, 129.1, 126.1, 124.3, 123.7, 98.4, 24.6, 22.9, 22.4, 22.2, 22.0; IR (thin film) 2931.27, 2846.42, 1786.72, 1732.73, 1688.37, 1613.16, 1442.49, 1363.43, 1223.60, 1097.30 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₅H₁₆NO₃ (M+H)⁺ 258.1130, found 258.1126; mp 83 °C.

IX. nOe Correlation Characterization of 4q, 4o, 4p, 4s, 6q, 6o, and 6p

Relevant DPFGSE-nOe data (mixing time 2.0 s): the peaks in the ¹H NMR spectra were assigned using ¹H NMR chemical shifts, ¹H-¹H NMR coupling constants, and ¹H-¹H NMR COSY data.

![Diagram of 4q and 6q with arrows indicating no interaction with Hα or Hβ]

4q: cis:trans = 50:50

Imidate 4q: The methyl resonances at 0.80 and 0.66 ppm and the Hₐ methine resonances at 5.80 and 5.67 ppm are distinct for these compounds in C₆D₆. When the methyl resonance at 0.66 ppm is irradiated, no Hₐ methine resonance between 5-6 ppm is observed. When the Hₐ methine resonance at 5.67 ppm is irradiated no methyl resonance is observed. This suggests that the Hₐ methine at 5.67 ppm does not have a through space interaction with a methyl group. When the Hₐ methine at 5.67 ppm is irradiated, the Hₖ methine resonance at 1.39 ppm is inverted as well as the Hₖ α-methylene proton at 2.15 ppm. This suggests that the isomer with the methine resonance at 5.67 ppm and the methyl resonance at 0.66 ppm is the cis isomer. When the methyl resonance at 0.80 ppm is irradiated, the Hₐ methine resonance at
5.80 ppm is inverted. When the Hₐ methine resonance at 5.80 ppm is irradiated, the methyl resonance at 0.80 ppm is inverted. These experiments suggest that the isomer with the methine resonance at 5.80 ppm and the methyl resonance at 0.80 ppm is the *trans* isomer.

\[\text{6q: cis:trans} = 55:45\]

*α*-Benzoyloxy ketone 6q: The Hₐ methine resonances at 5.44 and 5.41 are overlapping for this product in CDCl₃. The two methyl resonances at 1.21 and 1.08 ppm are distinct in CDCl₃. When the methyl resonance at 1.21 ppm is irradiated, the Hₐ methine resonance at 5.44 ppm is not observed. When the Hₐ methine resonance at 5.44 ppm is irradiated the methyl resonance at 1.21 ppm is not observed. These data suggest that one of the methine resonances at 5.44 ppm does not have a through space interaction with the methyl group at 1.21 ppm. When the Hₑ methine at 2.00 ppm is irradiated, the Hₐ methine resonance at 5.44 ppm is inverted as well as the Hₐ α-methylene resonance at 2.35 ppm. These data suggest that the isomer with the Hₐ α-methylene resonance at 2.35 ppm and the methyl resonance at 1.21 ppm is the *cis* isomer. When the methyl resonance at 1.08 ppm is irradiated, the methine resonance Hₐ at 5.41 ppm is inverted. When the Hₐ methine resonance at 5.41 ppm is irradiated, only the methyl resonance at 1.08 ppm is inverted. These experiments suggest that the isomer with the methine resonance at 5.41 ppm and the methyl resonance at 1.08 ppm is the *trans* isomer.
Imidate 4o: The methine resonances H$_a$ at 5.81 and 5.63 ppm are distinct and the methyl resonances at 0.96 and 0.82 overlap for these compounds in C$_6$D$_6$. When the H$_a$ methine resonance at 5.81 ppm was irradiated, the methyl resonance at 0.96 was inverted but the H$_b$ methine resonance at 2.65 ppm was not observed. When the H$_b$ methine resonance at 2.65 ppm was irradiated, the methyl resonance at 0.96 ppm was inverted but the H$_a$ methine resonance at 5.81 ppm was not observed. When the methyl resonance at 0.96 ppm was irradiated, the H$_a$ methine resonance at 5.81 ppm and the H$_b$ methine resonance at 2.65 ppm were inverted. These data suggest that the isomer with the methine resonance at 5.81 ppm and the methyl resonance at 0.96 ppm is the trans isomer. The ratio of the major:minor isomer was too large to collect NOe data for the minor cis isomer.

6o: cis:trans = 20:80

α-Benzoyloxy Ketone 6o: The H$_a$ methine resonances at 5.38 ppm are coincident and the methyl resonances at 1.18 and 1.09 ppm are distinct for these compounds in CDCl$_3$. When the H$_a$ methine resonance at 5.38 ppm was irradiated, the methyl resonance at 1.18 was
inverted but the Hₐ methine resonance at 2.87 ppm was not observed. When the Hₐ methine resonance at 2.87 ppm was irradiated the methyl resonance at 1.18 ppm was inverted but the Hₐ methine resonance at 5.38 ppm was not observed. When the methyl resonance at 1.18 ppm was irradiated, the Hₐ methine resonance at 5.38 ppm and the Hₐ methine resonance at 2.87 ppm were inverted. These data suggest that the isomer with the methine resonance at 5.38 ppm and the methyl resonance at 1.18 ppm is the trans isomer. The ratio of the major:minor isomer was too large to collect nOe data for the minor cis isomer.

4p: cis:trans = 55:45

Imidate 4p: The methyl resonances at 1.20 and 1.10 ppm and the Hₐ methine resonances at 5.84 and 5.44 ppm are distinct for these compounds in CDCl₃. When the methyl resonance at 1.10 ppm is irradiated, the Hₐ methine resonance at 2.90 ppm is inverted but the Hₐ methine resonance at 5.84 ppm is not observed. When the Hₐ methine resonance at 2.90 ppm is irradiated the methyl resonance at 1.10 ppm and the Hₐ methine resonance at 5.84 ppm are inverted. When the Hₐ methine resonance at 5.84 ppm is irradiated the Hₐ methine resonance at 2.90 ppm is inverted but the methyl resonance at 1.10 ppm is not observed. These data suggest that the isomer with the methine resonances at 5.84 and 2.90 ppm and the methyl resonance at 1.10 ppm is the cis isomer. When the methyl resonance at 1.20 ppm is irradiated, the Hₐ methine resonance at 5.44 ppm is inverted. When the Hₐ methine resonance at 5.44 ppm is irradiated, the methyl resonance at 1.20 ppm is inverted. When the Hₐ methine
resonance at 2.29 ppm is irradiated, only the methyl resonance at 1.20 ppm is inverted and the \( H_a \) methine resonance at 5.44 ppm is not observed. These data suggest that the isomer with the methine resonance at 5.44 ppm and the methyl resonance at 1.20 ppm is the \textit{trans} isomer.

\[ 6p: \text{cis:trans} = 55:45 \]

\textbf{\( \alpha \)-Benzoyloxy Ketone 6p:} The methyl resonances at 1.15 and 1.08 ppm and the \( H_a \) methine resonances at 5.44 and 5.06 ppm are distinct for these compounds in CDCl\(_3\). When the methine resonance \( H_a \) at 5.44 ppm was irradiated, the \( H_b \) methine resonance at 2.66 ppm and the methyl resonance at 1.08 ppm were inverted. When the \( H_b \) methine resonance at 2.66 ppm was irradiated, the \( H_a \) methine at 5.44 ppm was inverted and the methyl resonance at 1.08 ppm was inverted. When both methyl groups were irradiated together, both the 5.44 ppm and 5.06 ppm methines were inverted. These data suggest that the isomer with the methine resonance at 5.44 ppm and the methyl resonance at 1.08 ppm is the \textit{cis} isomer. When the \( H_a \) methine resonance at 5.06 ppm was irradiated, the methyl group at 1.15 ppm was inverted but the methine resonance at 1.86 ppm was not observed. When both methyl groups were irradiated together, both the 5.44 ppm and the 5.06 ppm methines were inverted. These data suggest that the isomer with the methine resonance at 5.06 ppm and the methyl resonance at 1.15 ppm is the \textit{trans} isomer.
Imidate 4s: The methine resonances $\text{H}_a$ at 5.98 and 5.83 ppm and the methine resonances $\text{H}_b$ at 3.3 and 2.8 ppm are distinct for these compounds in CDCl$_3$. When the $\text{H}_a$ methine resonance at 5.98 was irradiated, the $\text{H}_b$ methine resonance at 3.31 ppm was inverted but the phenyl resonances were not observed. When the $\text{H}_b$ methine resonance at 3.31 ppm was irradiated, the $\text{H}_a$ methine resonance at 5.98 ppm and the phenyl resonance at 7.38 ppm were inverted. These data suggest that the isomer with the methine resonance at 5.98 ppm is the cis isomer. When the $\text{H}_a$ methine resonance at 5.83 ppm was irradiated the phenyl resonance at 7.56 ppm was inverted but the $\text{H}_b$ methine resonance at 2.83 ppm was not observed. These data suggest that the isomer with the methine resonance at 5.83 ppm is the trans isomer.
Chapter 2 - Diastereoselective Dioxygenation of Alkenyl Boronic Acids via Etherification and Rearrangement of N-Hydroxyisoindolinones

2.1 Abstract

We have developed a new alternative route to α-oxygenated ketones through the dioxygenation of vinyl boronic acids. The overall process consists of a copper-catalyzed etherification of N-hydroxyphthalimide with an alkenyl boronic acid, followed by a subsequent [3,3] rearrangement of the resulting N-enoyphthalimide, and hydrolysis of the ensuing imidate. Our initial discovery has been further modified to afford the diastereoselective dioxygenation of vinyl boronic acids with 3-hydroxyisoindolinones. The scope of the method and the dependence of the diastereoselectivity on the identity of the protecting group and the boronic acid have been evaluated. Relative stereochemistry of the α-oxygenated ketones, mechanistic implications and the assessment of a chiral nonracemic 3-hydroxyisoindolinone as an oxygenation reagent have also been investigated.

![Reaction Scheme](attachment:image.png)

11 examples, dr = 80:20 - >99:1
2.2 \([3,3]\) Rearrangements in Organic Synthesis

The \([3,3]\) sigmatropic reaction, since its discovery in 1912,\(^{58}\) occupies a unique position as a powerful, reliable, and well-defined method for the stereoselective construction of carbon–carbon and carbon–heteroatom bonds.\(^{59}\) While many other reactions can unite two subunits and create a new bond, a sigmatropic rearrangement is unique in its ability to enable structural reorganization and hence is widely utilized in the construction of molecules of high complexity. A recent application that illustrates the \([3,3]\)-sigmatropic rearrangement as a key step in the synthesis of the natural product, Frondosin B,\(^{60}\) is shown below in Scheme 2.1. Frondosins are bioactive sesquiterpene hydroquinones which are being evaluated as new anticancer and antiviral agents.

\[\text{Scheme 2.1: [3,3] Rearrangement in the Synthesis of Frondosin B}\]

An extensive use of sigmatropic rearrangements, including the trichloroacetimidate rearrangement (the Overman rearrangement) was utilized in the synthesis of the anti-influenza agent A-315675 developed at Abbott Laboratories.
(Scheme 2.2). In this synthesis, the bis-trichloroacetimidate undergoes a double [3,3]-
sigmatropic rearrangement through chair-like transition states.\textsuperscript{61}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme.png}};
\end{tikzpicture}
\end{center}

**Scheme 2.2:** Sequential [3,3] Rearrangements in the Synthesis of A-315675

Since [3,3] rearrangement reactions involve bond breaking and bond formation
events that occur through a cyclic array of interacting orbitals, diastereoselectivity is
generally high for these processes.\textsuperscript{62} The potential of [3,3]-sigmatropic rearrangements to
simultaneously create two adjacent stereocentres with high levels of diastereoselectivity
has been exploited extensively in organic synthesis, notably by the application of the
Cope and Claisen rearrangements in total synthesis.\textsuperscript{63} For addressing vicinal quaternary
carbons, these transformations have only been applied in a diastereoselective manner
using substrates containing pre-existing stereogenic centers, either as part of cleavable
auxiliaries or structural features of the target molecule.\textsuperscript{64}
2.2.1 Modes of Diastereoselective and Enantioselective Induction Through Substrate Control

The common method to induce diastereoselectivity and enantioselectivity in a [3,3] sigmatropic reaction is by substrate control. Asymmetric Claisen rearrangements have been studied where intramolecular chirality transfer from a chiral center at any position near the rearrangement system is used to control the stereoselectivity and create enantiomerically enriched products.\textsuperscript{65} This approach was developed by Welch, who employed the amidacetal modification of the Claisen rearrangement reaction, incorporating an optically active amine component into one of the reagents. Addition of an allylic alkoxide to the iminium salt yields a product, which immediately rearranges giving the amide as the major product (Scheme 2.3).\textsuperscript{66}

\begin{center}
\begin{align*}
\text{Scheme 2.3: Distant Chiral Centre Controlling the Stereocchemical Outcome}
\end{align*}
\end{center}

\begin{center}
\begin{align*}
\text{Scheme 2.4: Enders' RAMP Hydrazine as a Chiral Auxiliary in the [3,3] Rearrangement}
\end{align*}
\end{center}
A similar strategy utilizing Enders’ RAMP\(^{67}\) [(\(R\))-1-amino-2-methoxymethylpyrrolidine] hydrazone as a chiral auxiliary to set up the quaternary centre via a [3,3] rearrangement was devised by Enders et al. in the total synthesis of (-) Malyngolide.\(^{68}\) In this reaction (Scheme 2.4), co-ordination of the Li ion with the methoxy group blocks the lower face of the ring system, and hence the rearrangement can occur only from the upper face leading to the observed stereochemistry in the product.

![Scheme 2.5](image)

**Scheme 2.5:** Diastereoselective [3,3] Sigmatropic Aza-Claisen Rearrangement with Minimization of syn-Pentane Interactions

Davies and co-workers reported their results regarding investigations on the double diastereoselective [3,3] sigmatropic aza-Claisen rearrangement of diastereomeric benzyl ethers shown in Schemes 2.5 and 2.6 containing both an \(N\)-\(\alpha\)-methylbenzyl group and an adjacent stereogenic centre.\(^{69}\) The high levels of diastereoselectivity observed upon rearrangement of the chiral amide may be elucidated by the reaction proceeding via the Z-\(N\),\(O\)-silyl ketene aminal through a chair like transition state in which all the bulky alkyl substituents occupy pseudo-equatorial positions (Scheme 2.5). The double diastereoselectivity observed in the rearrangement may be rationalised by the
minimization of both \( \text{syn}-\text{pentane} \) and 1,3-diaxial interactions in the chair transition state. The nitrogen lone pair is assumed to occupy a position between the C(\(\alpha\))Ph and C(\(\alpha\))Me substituents, anti to C(\(\alpha\))H, minimising the dominant \( \text{syn}-\text{pentane} \) interaction with the trimethylsilyloxy group of the ketene aminal. This conformation enables the largest C(\(\alpha\))Ph substituent to occupy a position anti to the \(N\)-allyl fragment, with the C(\(\alpha\))Me group eclipsing the C(3)R substituent.\(^7^1\)

Scheme 2.6: Mismatched Rearrangement Destabilised by 1,3 Diaxial Interactions and \(\text{syn}-\text{Pentane}\) Interactions

To determine whether this highly diastereoselective rearrangement represented the matched or mismatched reaction manifold, the diastereomeric benzyl ether was subjected to rearrangement under identical conditions (Scheme 2.6). In this case, an inseparable mixture of three diastereomeric products was obtained in a 50:30:20 ratio. Application of this transition state model to the mismatched rearrangement indicates that the expected chair transition states would be destabilised by 1,3 diaxial interactions between the C(3)R group and the trimethylsilyloxy group in or by \( \text{syn}-\text{pentane} \) interactions with the C(\(\alpha\))Ph substituent. The difference in energy between these
transition states for the rearrangement is therefore diminished, resulting in the observed low levels of diastereoselectivity.

\[
\begin{array}{c}
\text{NPh} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{array} \xrightarrow{\text{LDA}} \begin{bmatrix}
\text{TBS} \\
\text{N} \\
\text{Ph} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{bmatrix} \xrightarrow{\text{TBSCI}} \begin{array}{c}
\text{TBS} \\
\text{N} \\
\text{Ph} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\end{array} \\
\]

**Scheme 2.7:** Diastereoselectivity Arising from Formation of Energetically Favorable Chair-like Transition State

*N*-silyl ketene acetals generated from prochiral allyl *N*-phenylimidates underwent a diastereoselective Claisen rearrangement as shown in Scheme 2.7. The *N*-phenylimidates when treated with LDA and TBSCI formed the *N*-silyl ketene *N,O*-acetals\(^{72,73}\) which were more than 99% Z-configured to minimize \(A_{1,3}\)-strain.\(^{74}\) The competition between the chair transition state **TS 1** and the boat transition state **TS 2** is responsible for the relative configuration of the products. Since the boat transition state **TS 2** involves eclipsing interactions between the bulky amine and \(R^3\), it is energetically disfavored. The reaction therefore proceeds through the chair transition state **TS 1**, leading to the observed cis-diastereoselectivity in the product.
Scheme 2.8: Diastereoselectivity Controlled by Sterics

Burke et al. have reported the formation of butyrolactones through a [3,3] rearrangement where the rearrangement diastereoselectivity is controlled by the sterics of the substrate\(^{75}\) (Scheme 2.8). These butyrolactones could then be transformed into Isoavenacirolide\(^{76}\) and other related targets. In this case, the selective enolization of a glycolate in the presence of a butenolide afforded the Z-silyl ketene acetal. The [3,3] rearrangement then occurred from the face opposite to the bulky octenyl chain via a chair transition state to afford the exo methylene butyrolactone.

Scheme 2.9: \(A_{1,3}\)-strain and Sterics Controlling Diastereoselectivity

Selective enolization of an allyl ester followed by a diastereoselective [3,3] rearrangement was reported by Pratt et. al.\(^{77}\) The facial selectivity for the rearrangement was directed by allylic strain (Scheme 2.9). The preferred lower energy conformation for the silyl ketene acetal was the one in which the ether oxygen was eclipsed with the allylic proton thus leading to a minization of \(A_{1,3}\)-strain.\(^{78}\) The alkene would then approach the
silyl ketene acetal from the face syn to the smaller carboxybenzyl substituent. The product was obtained in a 80:20 diastereoselective ratio.

Scheme 2.10: A$_{1,3}$-strain and Cieplak Effect Responsible for Diastereoselectivity

The Evans oxazolidinone$^{79}$ was employed by Yamazaki and coworkers (Scheme 2.10) for the diastereoselective Michael addition of the lithiated enolate to the $\beta$-CF$_3$ acrylates to afford the allyl silyl ketene acetals as intermediates.$^{80}$ The rearrangement occurred via the Z-silyl ketene acetal where the lowest energy conformation adopted by the molecule would be the one that would minimize the A$_{1,3}$-strain. Preferential attack by the allyl group syn to the CF$_3$ group would give the product with the observed stereochemistry. This facial selectivity was rationalized by the authors by suggesting that due to the Cieplak effect, the new bond was formed anti to the more electron rich C–C $\sigma^*$ bond.$^{81}$
Scheme 2.11: Diastereoselectivity Controlled by A_{1,2}-Strain

An iterative Claisen rearrangement as shown in Scheme 2.11 was developed by MacMillan and Dong using allylic bis-amines and Yb(OTf)$_3$ as the catalyst.$^{82}$ This process involved a double rearrangement which yielded the product in a high yield and excellent diastereoselectivity. The first rearrangement occurred via the less hindered chair transition state TS 3 to form the syn pentenamide followed by the second rearrangement which was dictated by minimization of A_{1,2}-strain.$^{78}$ This propensity for reducing the allylic strain, led to a preference for TS 5. This hypothesis matches the stereochemistry of the observed product.
Scheme 2.12: Claisen Rearrangement to Access Spirocyclic Oxindoles with Vicinal Quaternary Carbon Centers

An efficient approach to spirocyclic oxindoles with vicinal quaternary carbon centers was reported in 2011 (Scheme 2.12). The reaction involves the Horner-Wadsworth-Emmons olefination of 2-allyloxyindolin-3-ones with cyanomethylphosphonate followed by successive isomerization, deacylation, and an anion-accelerated Claisen rearrangement to give the 3,3-disubstituted oxindoles in high yield and diastereoselectivity. The stereochemistry of the products indicates that the Claisen rearrangement progresses predominantly via a boat-like transition state TS 8 over the chair-like TS 7. The chair-like transition state TS 8 is unfavored because of steric repulsion of the two substituents ($R^1$, $R^2$) with the indole ring (Scheme 2.13).
**Scheme 2.13**: Claisen Rearrangement through a Boat-like Transition State

### 2.2.2 Diastereoselective and Enantioselective Induction Using Chiral Reagents

Asymmetric induction in a [3,3] rearrangement could be brought about by using a chiral reagent or catalyst. Yamamoto et al.\(^8\) reported a modified binaphthol–aluminum catalyst which served as a chiral promoter for the Claisen rearrangement of an aliphatic allyl vinyl ether (Scheme 2.14). In this case a stoichiometric amount of the promoter was required.
Scheme 2.14: Chiral Promoter in an Enantioselective Claisen Rearrangement

Chiral guanidinium catalyzed Claisen rearrangements of cyclic O-allyl β-ketoesters have been reported by Jacobsen and co-workers. The guanidinium functions as a hydrogen bond donor catalyst which controls the stereochemistry during the rearrangement (Scheme 2.15). Chiral azolium salts have been used for the enantioselective annulation reaction between enols and ynals to form enantiomerically enriched dihydropyranones via an N-heterocyclic carbene catalyzed variant of the Claisen rearrangement.

Scheme 2.15: Chiral Guanidinium Catalyzed Claisen Rearrangement
A catalytic diastereoselective reductive Claisen rearrangement was developed by the Morken group in 2002 which is shown in Scheme 2.16. The catalyst prepared from [(cod)RhCl]₂ and Me-DuPhos, was utilized for the chemoselective and stereoselective reduction of allyl acrylates to E-silyl ketene acetals. These intermediates then participated in a Claisen rearrangement via a chair-like transition state, providing γ, δ-unsaturated carboxylic acids with a high level of diastereoselectivity. This method provides an alternative for the ester enolate Claisen rearrangement which requires the use of a strong base for enolate generation. ⁸⁹

Since our methodology for the dioxygenation of alkenyl boronic acids to access α-oxygenated ketones involved a [3,3] rearrangement, we hypothesized that including a stereocenter on the substrate would have some effect in controlling the facial selectivity for the rearrangement and this would enable us to achieve a diastereoselective or an enantioselective rearrangement. To accomplish this chiral induction through substrate control via a distant stereocenter on the molecule, we conjectured the use of 3-substituted-N-hydroxyisoindolinones instead of N-hydroxyphthalimide as precursors for the etherification and rearrangement. This would allow us to examine the
diastereoselectivity for the rearrangement and observe the relative stereochemistry of the product.

2.3 Effect of Neighboring Stereocenter on the [3,3] Rearrangement

While examining the [3,3] rearrangement for the dioxygenation of boronic acids as reported in Chapter 1, we were intrigued by the discovery that having a substituent at the 6-position could alter the stereo-chemical outcome of the reaction as shown in Scheme 2.17.

Scheme 2.17: Effect of a substituent at C6 on the Rearrangement Reaction

This result, where the trans-isomer was the major product, was in contrast to all other substituted cyclohexyl systems which gave the cis-isomer as the major product. An example is shown in Scheme 2.18.

Scheme 2.18: Cis-isomer Predominates in all other Substituted Cyclohexanones
We attributed this result to hindered rotation for the C–O bond because of steric interactions with the 6-methyl substituent. This leads to the higher energy twist boat conformation which results in the trans-isomer (Scheme 2.19).  

Scheme 2.19: Hindered Rotation of the C–O bond because of Steric Interactions

This stereochemical outcome of the reaction, led us to believe that there was an effect that the existing stereocenter had on the [3,3] rearrangement, especially if the existing stereocenter was close to the reaction site. We therefore wanted to investigate the outcome of introducing a stereocenter on the phthalimide portion of the molecule and examining the distereoselectivity of the rearrangement. We have determined that the intramolecular chirality transfer from a stereocenter on the N-hydroxyisolindolinone does occur to make the reaction diasteroselective, and that the nature of the substituent at on the isoindolinone has an impact on controlling the stereochemistry at the newly formed stereocenter (Scheme 2.20).
Scheme 2.20: Diastereoselective [3,3] Rearrangement

2.4 Initial Results

2.4.1 Effect of a Neighboring Hydroxy Group

Scheme 2.21: Effect of a Hydroxy Substituent near the Reaction Site

\[ \text{N-enoxypthalimide 3d} \rightarrow \text{NaBH}_4 \rightarrow \text{EtOH} \rightarrow \text{88\%} \rightarrow \text{3-hydroxy-N-enoxysouindoline 10} \rightarrow \text{70 °C} \rightarrow \text{C}_6\text{D}_6 \rightarrow \text{95\%} \rightarrow \text{11} \rightarrow \text{dr = 75:25} \]

\text{N-enoxypthalimide 3d, was treated with NaBH}_4 \text{ in EtOH, which reduced one of the carbonyls to the alcohol to form the 3-hydroxy-N-enoxysouindoline 10 (Scheme 2.21). When a 0.1 M solution of 10 was heated at 70 °C in C}_6\text{D}_6, a 75:25 ratio of diastereomers for imidate 11 were observed. This proved that the hydroxyl group did have an effect on the [3,3] rearrangement and that the stereochemistry of the substituent at the adjacent stereocenter plays an important role in determining the facial selectivity of the rearrangement.} \]
2.4.2 Effect of a 3-t-butyldimethylsilyloxy Group

Since the compound 11 with a hydroxyl group gave a 75:25 mixture of diastereomers in the [3,3] rearrangement, we envisioned that increasing the bulk of the substituent at the sp<sup>3</sup> center would result in a more diastereoselective reaction. To achieve higher diastereoselectivity, we replaced the hydroxyl group with a t-butyldimethylsilyloxy functionality. Protection of the hydroxyl group in 10 with TBSCl was unsuccessful; hence we devised a synthesis for the 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone as shown below (Scheme 2.22). This route was based on the synthesis of 1,2-oxazaheterocycles containing an isodolone moiety developed by Bartovic in 2000.<sup>91</sup> Protection of the hydroxyl group of N-hydroxyphthalimide gave the O-silylated product. Reduction of one of the carbonyls with sodium borohydride was followed by the in situ migration of the silyl group, to yield the 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13.

![Scheme 2.22: Synthesis of 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone](image)

When the N-hydroxyisoindolinone 13 was treated with cyclohexenyl boronic acid 1n, under the Cu-mediated etherification conditions, we were surprised to discover that instead of isolating the N-enoyisoindolinone, a spontaneous rearrangement occurred under the etherification conditions, to give the imidate product directly (Scheme 2.23). Thus, the etherification and rearrangement could be achieved in a single flask.
Scheme 2.23: Etherification and Rearrangement in a Single-Flask

The diastereomeric ratio obtained was 89:11, which suggested that increasing the steric volume of the substituent had an impact on controlling which face the rearrangement occurred, thus making the reaction more diastereoselective.

2.4.3 Effect of Alkyl Groups at the Stereocenter

After having established that a substituent on the sp³ hybridized carbon of the N-enoxysindolinone has an effect on determining the stereochemistry at the newly formed α-oxygenated stereocenter, we then synthesized compound 20 which had an all carbon quarternary center at C₃. This compound was synthesized according to the procedure developed by Stoltz and co-workers⁹² (Scheme 2.24). 2’-bromoacetophenone 15 was subjected to a Wittig reaction with ethyltriphenylphosphonium iodide in the presence of sodium t-butoxide to yield 1-bromo-2-(but-2-en-2-yl)benzene 16 as a 2:1 mixture of Z:E isomers. Conversion of the bromide to the carboxylic acid was followed by treatment with O-benzylhydroxylamine to give amide 18. A Pd-catalyzed oxidative Wacker cyclization resulted in the desired 3-methyl-3-vinyl-N-benzyloxyisodolinone 19. Hydrogenolysis with hydrogen gas and Pd/C deprotected the benzyl group and also reduced the vinyl functionality to give the 3-ethyl-3-methyl-N-hydroxyisodolinone 20.
Scheme 2.24: Synthesis of N-hydoxyisoindolinone containing a Quarternary Center

There was a two-fold objective behind the synthesis and evaluation of compound 20. First, we wanted to assess whether the Cu-mediated etherification with an alkenyl boronic acid and the ensuing [3,3] rearrangement would occur in the presence of a sterically congested center near the reaction site and secondly to determine whether the presence of an oxygen atom at the stereocenter was critical in making the [3,3] rearrangement diastereoselective.

When compound 20 was subjected to the etherification reaction with cyclohexenyl boronic acid 1n in the presence of Cu(OAc)$_2$, it gave the N-enoxisoindolinone 21n in a 71% yield. This proved that the etherification reaction with the N-hydoxyisoindolinone was not sensitive to steric effects and could occur even when a quarternary center was adjacent to the reactive site. Upon heating compound 21n in benzene, the imidate product 22n was formed in a diastereomeric ratio of 72:28 (Scheme 2.25). This suggests that the [3,3] rearrangement is affected by the steric interactions of
the cyclic TS and that the reaction probably proceeds from the less sterically hindered approach of the carbonyl and the enol ether.

**Scheme 2.25:** Etherification and Rearrangement of 3-ethyl-3-methyl-N-hydroxyisoindolinone

We chose to pursue the OTBS isoindolinone for further studies of the diastereoselective method.

### 2.5 Optimization of the Preparation and Rearrangement of 14z

After discovering the single flask etherification and [3,3] rearrangement, we wanted to optimize the reaction conditions (Table 2.1). With Cu(OAc)$_2$, we realized that the optimum time for the reaction was 12h, which gave us an NMR yield of 100% (entry 4, Table 2.1). The isolated yield in this case was 71%. This suggests that even though the imidate products are stable enough to be isolated, they decompose to some extent on florisil$^\circledR$ during purification. At times less than 12h, the yields for the reaction were significantly lower (entries 1-3, Table 2.1). When 20 mol % of Cu(OAc)$_2$ was used, the reaction required 3d to go to completion during which the imidate product started to decompose. Hence the reaction with 20 mol % of Cu(OAc)$_2$ gave a lower yield of 73%.
(entry 5, Table 2.1). Other Cu salts like CuTC, CuCl and CuBr (entries 6-8, Table 2.1) gave lower yields of the imidate product. Our optimization study concluded that using one equivalent of Cu(OAc)$_2$, two equivalents of boronic acid and three equivalents of pyridine with Na$_2$SO$_4$ as the dessicant in DCE (0.1 M) in the presence of air for 12h led to complete conversion of the isoindolinone to the imidate.

\[
\text{13} \quad \text{N-OH} \quad \text{OTBS} \quad \text{+} \quad \text{1z} \quad \text{B(OH)$_2$} \quad \text{[Cu] (1 equiv or 20 mol\%)} \quad \text{pyr (3 equiv), Na$_2$SO$_4$, DCE, air, 25°C} \quad \text{\text{14z} \quad \text{N} \quad \text{O \quad OTBS}}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>Time</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$ (1 equiv)</td>
<td>2 h</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$ (1 equiv)</td>
<td>3 h</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$ (1 equiv)</td>
<td>8 h</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$ (1 equiv)</td>
<td>12 h</td>
<td>100% (71%)$^b$</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)$_2$ (20 mol%)</td>
<td>3 d</td>
<td>73%</td>
</tr>
<tr>
<td>6</td>
<td>CuTC (1 equiv)</td>
<td>12 h</td>
<td>74%</td>
</tr>
<tr>
<td>7</td>
<td>CuCl (1 equiv)</td>
<td>12 h</td>
<td>57%</td>
</tr>
<tr>
<td>8</td>
<td>CuBr (1 equiv)</td>
<td>12 h</td>
<td>76%</td>
</tr>
</tbody>
</table>

Yield$^a$ refers to NMR yields with 1,3,5-trimethoxybenzene as the internal standard. $^b$ refers to the isolated yield which was 71%.

**Table 2.1:** Optimization of the Single-Flask Dioxygenation
2.6 Evaluating Different Substituents at the Stereocenter

Since the 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone substrate reacted with cyclohexenyl boronic acid to yield the imidate product directly, and with good diastereoselectivity, we wanted to evaluate different functional groups (instead of OTBS), and examine whether we could still achieve the etherification and rearrangement in a single flask reaction while also studying the impact of varying the substituents on the diastereoselectivity of the [3,3] rearrangement. We synthesized N-hydroxyisoindolinones with varying substituents at the stereocenter and used them in the Cu-mediated etherification reaction with indenyl boronic acid 1z (Table 2.2).

![Chemical reactions and structures]

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield</th>
<th>Diastereomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>23z</td>
<td>50%</td>
<td>dr = 92:8</td>
</tr>
<tr>
<td>24z</td>
<td>53%</td>
<td>dr = 92:8</td>
</tr>
<tr>
<td>25z</td>
<td>48%</td>
<td>dr = 97:3</td>
</tr>
<tr>
<td>14z</td>
<td>61%</td>
<td>One diastereomer</td>
</tr>
<tr>
<td>26z</td>
<td>64%</td>
<td>One diastereomer</td>
</tr>
<tr>
<td>27z</td>
<td>44%</td>
<td>One diastereomer</td>
</tr>
</tbody>
</table>

**Table 2.2:** Evaluating the Effect of Different Substituents on the Diastereoselectivity
As seen from Table 2.2 above, for all the substituted \( N \)-hydroxyisoindolinones, both the etherification and rearrangement reactions occurred sequentially and the crude \(^1\)H NMR spectrum of the reaction mixture showed only the imidate product with no traces of the etherification product. The imidates were unstable when subjected to silica gel, but could be isolated using flash chromatography on florisil\textsuperscript{®}. Regarding the effect on the diastereoselectivity; the compounds 23\( z \) and 24\( z \) having a methoxy or an ethoxy functional group gave a 92:8 mixture of diastereomers, while increasing the bulk to an isopropoxy group in 25\( z \), resulted in a slightly higher diastereomeric ratio of 97:3. With a bulky silyloxy group such as OTBS or OTIPS, (14\( z \) and 26\( z \)) only one diastereomer was observed by both \(^1\)H NMR and \(^{13}\)C NMR spectroscopy. Replacing the oxygen-based substituent with an allyl group in compound 27\( z \) also gave the product as a single diastereomer.

Although the [3,3] rearrangement with the \( N \)-hydroxyisoindolinones proceeded with high diastereoselectivity with most of the substituents at the stereocenter, we decided to test the tolerance for the substitution on the boronic acids on the etherification and rearrangement with 13 since it could be easily synthesized in a high yield. The syntheses for all the 3-substituted-\( N \)-hydroxyisoindolinones are shown below.

### 2.6.1 Synthesis of 3-Alkoxyl-\( N \)-Hydroxyisoindolinones

The 3-Alkoxyl-\( N \)-Hydroxyisoindolinones were synthesized as shown below in Scheme 2.26.
Scheme 2.26: Synthesis of 3-Alkoxyn-Hydroxyisoindolinones

THP protection of N-hydroxyphthalimide was followed by reduction of one of the carbonyls with sodium borohydride to yield compound 29. When this compound was treated with 4-toluene sulfonic acid in MeOH, the deprotection of the OTHP group was accompanied by the displacement of the hydroxyl group by MeOH in the presence of the acid to yield the 3-methoxy-N-hydroxyisoindolinone as the product. Upon changing the alcohol solvent from MeOH to EtOH and iPrOH, the corresponding 3-alkoxy-N-hydroxyisoindolinones were obtained.

2.6.2 Synthesis of 3-Silyloxy-N-Hydroxyisoindolinones

The 3-silyloxy-N-hydroxyisoindolinones were synthesized according to Scheme 2.27.

Scheme 2.27: Synthesis of 3-Silyloxy-N-Hydroxyisoindolinones
Protection of the hydroxyl group of $N$-hydroxyphthalimide with either TBSCI or TIPSCI gave the $O$-silylated product. Reduction of one of the carbonyls with sodium borohydride was followed by the in situ migration of the silyl group, to yield the 3-silyloxy-$N$-hydroxyisoindolinones, which were isolated as white solids.

### 2.6.3 Synthesis of 3-Allyl-$N$-Hydroxyisoindolinone

The 3-allyl-$N$-hydroxyisoindolinone was synthesized as per the procedure shown below in Scheme 2.28. Compound 29 was synthesized as before, after protection of $N$-hydroxyphthalimide with THP and reduction with sodium borohydride. The resulting alcohol was protected using pivaloyl chloride to form compound 30. This compound was then subjected to allyltrimethylsilane in the presence of TIPSOTf to give the desired product 27. This reaction was based on the methodology developed by Othman and co-workers$^{93}$ where nucleophilic substitution by allyltrimethylsilane occurs onto the $N$-acyliminium ion formed from 30 in the presence of TIPSOTf.

![Scheme 2.28: Synthesis of 3-Allyl-$N$-hydroxyisoindolinone](image)
After having prepared a variety of hydroxyisoindolinones, we wanted to evaluate the reactivity of 13 with substituted boronic acids and determine the relative stereochemistry of the product.

2.7 Determination of Relative Stereochemistry for the Imidate

The relative stereochemistry for compound 14z was determined by X-ray analysis. The results indicate that the substituent on the hydroxyisoindolinone (Figure 1) and the newly formed stereocenter at the α-oxygenated ketone are on opposite faces. This supports the hypothesis that the [3,3] rearrangement occurs from the sterically less hindered face i.e. opposite to the group at the stereocenter on the hydroxyisoindolinone. The X-ray analysis was done by Prof. Donald Wink at UIC.

![Figure 2.1: Determination of Relative Stereochemistry](image)

Figure 2.1: Determination of Relative Stereochemistry
2.8 Varying the Boronic Acids

2.8.1 Scope and Stereoselectivity with Disubstituted Boronic Acids

After having established the conditions for the single flask reaction and determining the relative stereochemistry of the product, we wanted to examine the tolerance for the substitution on the boronic acids. The substrate that we chose was the 3-\( t \)-butyldimethylsilyloxy-\( N \)-hydroxyisoindolinone 13 and the boronic acids evaluated were disubstituted (Scheme 2.29).

![Scheme 2.29: Evaluation of Disubstituted Boronic Acids](image-url)
The single-flask reaction tolerates acyclic boronic acids with alkyl and aryl substituents at either position of the boronic acid. The reaction with 3-methyl-2-buten-2-yl boronic acid forms compound 14ad (entry 6, Table 2.3) which contains an α-oxygenated quaternary center. This proves that our dioxygenation methodology could be used for the construction of the otherwise difficult to synthesize quaternary stereocenters. The 3-methyl-2-buten-2-yl boronic acid has previously been used in the Suzuki-Miyaura reaction for coupling with aromatic iodides in the presence of Pd(PPh₃)₂Cl₂. It has also been utilized in the Liebeskind-Srogl cross-coupling with borondipyrromethene (BODIPY) dyes in the presence of a Pd catalyst and tris(2-furyl)phosphine as a
ligand. Our reaction which involves the coupling of the 3-methyl-2-buten-2-yl boronic acid with 13 represents the first example for the use of a trisubstituted alkenyl boronic acid in a Chan-Lam coupling reaction.

Regarding the stereoselectivity for the reaction, as seen from Table 2.3, the imidate 14a (entry 1, Table 2.3) was isolated as a single diastereomer. One diastereomer was also observed for the compounds 14h and 14aa, (entries 2 and 3, Table 2.3) which had a phenyl substituent on the boronic acid. The imidates 14ab and 14ac (entries 4 and 5, Table 2.3) were obtained as an 80:20 mixture of diastereomers.

The results for the reaction of 13 with cyclic disubstituted boronic acids are illustrated below in Table 2.4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield$^a$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="14m" /></td>
<td>64%</td>
<td>dr = 80:20</td>
</tr>
<tr>
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<td>dr = 89:11</td>
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<td>3</td>
<td><img src="image" alt="14p" /></td>
<td>64%</td>
<td>dr = 69:31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield$^a$</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="14v" /></td>
<td>66%</td>
<td>One diastereomer</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="14z" /></td>
<td>61%</td>
<td>One diastereomer</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="14ae" /></td>
<td>57%</td>
<td>One diastereomer</td>
</tr>
</tbody>
</table>

Yield$^a$ refers to isolated yields
Table 2.4: Single-Flask Reaction with Cyclic, Disubstituted Boronic Acids.

The Cu-mediated one pot etherification and rearrangement reaction works well with cyclic disubstituted boronic acids (Table 2.4). Large rings as well as fused ring systems give the desired product in moderate yields. With the cyclopentenyl boronic acid 1m, the imidate 14m (entry 1, Table 2.4) was obtained as an 80:20 mixture of diastereomers. Increasing the steric volume of the boronic acid, from the five membered cyclopentenyl boronic acid to the six membered cyclohexenyl boronic acid 1n, led to an increase in the dr of the imidate 14n (entry 2, Table 2.4) to 89:11. Although the imidate 14p (entry 3, Table 2.4) has three stereocenters, only two diastereomers were observed by $^1$H NMR and $^{13}$C NMR spectroscopy in the reaction of 13 with 1p. The imidates derived from the larger ring containing cyclooctenyl boronic acid 14ae (entry 6, Table 2.4) and from the fused ring systems 14v and 14z, (entries 4 and 5, Table 2.4) were isolated as single diastereomers.

The results with the disubstituted boronic acids indicate that the reaction is controlled by steric effects, and a higher diastereomeric ratio is obtained when a bulky boronic acid is used due to increased interactions in the transition state.

2.8.2 Scope and Stereoselectivity with Monosubstituted Boronic Acids

When monosubstituted boronic acids were treated with 13, the only product isolated was the etherification product (Scheme 2.30), though there were traces of the rearrangement product for the compound 31d at when it was kept at room temperature. In this case, the in situ [3,3] rearrangement to form the imidate did not occur, especially for
substrates 31af and 31g. This might be attributed to the fact that the formation of the \( \alpha \)-oxygenated aldehydes has a higher energy barrier since they are less stable than the corresponding \( \alpha \)-oxygenated ketones.

![Scheme 2.30: Etherification Reaction with Monosubstituted Boronic Acids](image)

**Scheme 2.30**: Etherification Reaction with Monosubstituted Boronic Acids

The 1-hexenyl boronic acid 1d gives the imidates as shown below in Table 2.5.

![Table 2.5: N-enoyisoindolinones Isolated using the Etherification Reaction](image)

**Table 2.5**: \( \text{N-enoyisoindolinones Isolated using the Etherification Reaction} \)

As seen above in Table 2.5, the 1-hexenyl boronic acid 1d gives the etherification product 31d in an 82% yield. The reaction also worked with the Z-1-propen-1-yl boronic acid 1af, to form the imidate 31af in a moderate yield of 69%. This could be because of increased steric interactions between the methyl group on the boronic acid and the \( \text{N-hydroxyisoindolinone} \). The 1-phenylvinyl boronic acid 1g also underwent the reaction to form the \( \text{N-enoyisoindolinone} \) 31g.

Heating a solution of the \( \text{N-enoyisoindolinones in toluene-}d_8 \) (Scheme 2.31), gave the imidates as shown below in Table 2.6.
Scheme 2.31: [3,3] Rearrangement using Monosubstituted Boronic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Temperature for Rearrangement</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="14d" /></td>
<td>50 °C</td>
<td>100%</td>
<td>One diastereomer</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="14af" /></td>
<td>65 °C</td>
<td>100%</td>
<td>dr = 75:25</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="14g" /></td>
<td>80 °C</td>
<td>96%</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2.6: Rearrangement to form α-Oxygenated Aldehydes. Yields refer to isolated yields.

It is evident from Table 2.6 that the N-enoxysindolinone 31d has the lowest energy barrier, and can form the imidate 14d at 50 °C. The compound 31af requires a higher temperature of 65 °C and forms the α-oxygenated aldehyde 14af as a 75:25 mixture of diastereomers. The N-enoxysindolinone 31g obtained using 1-phenylvinyl...
boronic acid 1g, also formed the imidate 14g at 80 °C. During our previous studies on N-enoxypthalimide 3g, there was no rearrangement even when it was heated to 130 °C (Scheme 2.32), hence the isoindoline system seems to be more activated than the phthalimide and more susceptible to forming the imidate through the [3,3] rearrangement.

![Scheme 2.32: Rearrangement with the N-Enoxypthalimide](image)

**Scheme 2.32: Rearrangement with the N-Enoxypthalimide**

### 2.9 Role of Cu(OAc)$_2$ in the [3,3] Rearrangement

In order to determine whether the *in situ* rearrangement that followed the etherification was catalyzed by the Cu(OAc)$_2$ present in the reaction mixture, we used the N-enoxysindoline 31d and tested it for the [3,3] rearrangement both in the presence and absence of Cu(OAc)$_2$. The results are shown below in Scheme 2.33.
Scheme 2.33: Determining the role of Cu(OAc)$_2$ in the [3,3] Rearrangement

In the absence of Cu(OAc)$_2$, the $N$-enoxyisoindolinone 31d was stirred in DCE at room temperature overnight. Spectroscopic analysis revealed that after 10h, a 1:1 mixture of the starting material and product was obtained. When the same compound was treated with one equivalent of Cu(OAc)$_2$ in DCE and stirred at room temperature for 10h, there was starting material and some decomposition. These results indicate that the [3,3] rearrangement appears to be thermally driven and does not depend on any catalysis by the Cu(OAc)$_2$. The Cu(OAc)$_2$ may actually be responsible for the decomposition of the $\alpha$-oxygenated aldehyde that forms in the reaction.

2.10 Functionalization of the Imidates

Our one pot etherification and rearrangement had a broad substrate scope and good to excellent diastereoselectivity for the substrates; hence, we wanted to expand the methodology further by demonstrating the synthetic utility of the imidates. We began by screening a variety of conditions for the functionalization of the imidates such as using nucleophiles like NaN$_3$, NaSPh, Lewis acids like ZnCl$_2$, bases like Ag$_2$O and oxidation with DDQ. Conversion of the ketone to an olefin with Tebbe reagent, and treatment with electrophiles such as $m$CPBA and methyl iodide were also attempted but only led to decomposition. We finally discovered that treating the imidate 14z with oxalyl chloride effectively converted it to the $\alpha$-chloro ketone 32 as shown in Scheme 2.34. Since the starting material is racemic, the $\alpha$-chloro ketone isolated is also racemic. An imidate with a fixed configuration at the stereocenter on the hydroxyisoindolinone will have to be utilized to determine the absolute stereochemistry at the $\alpha$-chloro center. Since the
rearrangement is diastereoselective, the configuration at the \(\alpha\)-oxygenated center of the imidate will be determined by the stereochemistry of the center on the isoindolinone, and this in turn would be reflected in the stereochemistry at the \(\alpha\)-chloro center. This transfer of stereochemistry would be observed provided that there was no epimerization during the reaction with oxalyl chloride.

\[\text{Scheme 2.34: Conversion of the Imidate to the } \alpha\text{-Chloro Ketone}\]

We also discovered that treating the imidate 14z with ammonium chloride in aqueous MeOH, hydrolyzed the imidate to form the \(\alpha\)-hydroxy ketone 33 as demonstrated in Scheme 2.35. In this case, the 3-\(t\)-butyldimethylsilyloxyisoindolinone 34 was also isolated along with the desired \(\alpha\)-hydroxy ketone, which supports our methodology where the \(N\)-hydroxyisoindolinone could be used as an auxiliary to control the diastereoselectivity of the rearrangement and then be easily cleaved.

\[\text{Scheme 2.35: Conversion of the Imidate to the } \alpha\text{-Hydroxy Ketone}\]
2.11 Transfer of Chirality

Since our [3,3] rearrangement proceeded with high diastereoselectivity, we wanted to evaluate if the stereochemistry and enantiomeric excess (% ee) of a chiral N-hydroxyisoindolinone could be carried through the etherification and rearrangement reactions and whether the imidate or the final α-hydroxy ketone would have the same enantiomeric excess value as the starting chiral N-hydroxyisoindolinone. We therefore wanted to determine if the stereochemistry of a chiral N-hydroxyisoindolinone would transfer to the imidate and the α-hydroxy ketone through a diastereoselective rearrangement.

2.11.1 Optimization of the Conditions for the Chiral Reduction

We hypothesized that a chiral N-hydroxyisoindolinone could be obtained via a stereospecific reduction of one of the carbonyls of the N-hydroxyphthalimide 2. The chiral reduction was first attempted with the CBS catalyst. The reaction was tried with 12 and the (S)-(−)-o-tolyl-CBS-oxazaborolidine or (R)-(+)−2-methyl-CBS-oxazaborolidine with various boranes such as BH₃·THF, BH₃·pyr, and catechol borane in a variety of solvents. No reaction occurred when (S)-(−)-o-tolyl-CBS-oxazaborolidine was employed as the catalyst, irrespective of the borane or the solvent used. With the (R)-(+)−2-methyl-CBS-oxazaborolidine and BH₃·THF in THF, the reaction did give the reduced product 35 but the yield was low (< 5 %) and there was no migration of the TBS group as illustrated in Scheme 2.36.
Scheme 2.36: Chiral Reduction with CBS Catalyst

With such a low yield, and difficulty in separation from byproducts, we could not effectively determine the enantiomeric ratio (er) of the resulting alcohol. Also, all attempts to force the TBS group to migrate were unsuccessful.

The chiral reduction of the N-allyloxyisoindoline-1,3-dione 36 was therefore endeavored with different reagents and conditions. We chose the N-allyloxyisoindoline-1,3-dione 36 since the OTBS group in the N-t-butyldimethylsilyloxyisoindoline-1,3-dione 12 was sensitive to both acidic and basic conditions. Some of the optimization study is shown in Table 2.7. As seen from Table 2.7, none of the CBS based reagents were successful in reducing the carbonyl group.
Table 2.7: Conditions for the Chiral Reduction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-(+)-2-methyl-CBS-oxazaborolidine, BH$_3$.THF, Toluene</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>(R)-(+)-2-methyl-CBS-oxazaborolidine, BH$_3$.THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>(R)-(+)-2-methyl-CBS-oxazaborolidine, BH$_3$.diethylaniline, Toluene</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>(R)-(+)-2-methyl-CBS-oxazaborolidine, BH$_3$.diethylaniline, THF</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>(1R,2S)-(+)-cis-1-Amino-2-indanol, BH$_3$.THF, Toluene</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>CuF$_2$, (R)-BINAP, Et$_3$SiH</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

The conditions for catalytic asymmetric reductions are shown in Table 2.8. Metals like Ir and Rh had no impact on the reaction and the starting material was isolated with little or no conversion to the product. Using Ru as the metal catalyst, and formic acid as the reducing agent in dichloromethane, namely the Noyori reduction conditions, finally gave some conversion to the product. The reaction optimization is illustrated below.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Source of &quot;H&quot;</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RuCl(R-BINAP)</td>
<td>THF</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>RuCl(R-BINAP)</td>
<td>Toluene</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>THF</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>Toluene</td>
<td>RT</td>
<td>H₂</td>
<td>SM + decomposition</td>
</tr>
<tr>
<td>5</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>THF + 1 equiv EtOH</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>Toluene + 1 equiv EtOH</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>Neopentyl alcohol</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>t-butyl alcohol</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>EtOH</td>
<td>RT</td>
<td>H₂</td>
<td>SM + Some product</td>
</tr>
<tr>
<td>10</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>Allyl alcohol</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>iPrOH</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>1,4-Dioxane</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>RuCl(p-cymene)TsDPEN</td>
<td>DME</td>
<td>RT</td>
<td>H₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>14</td>
<td>RuCl(p-cymene)TsDPEN (0.01 equiv)</td>
<td>CH₂Cl₂, 6 h</td>
<td>RT</td>
<td>HCO₂H + Et₃N</td>
<td>SM:Prod = 2.5:1</td>
</tr>
<tr>
<td>15</td>
<td>RuCl(p-cymene)TsDPEN (0.01 equiv)</td>
<td>CH₂Cl₂, 19 h</td>
<td>RT</td>
<td>HCO₂H + Et₃N</td>
<td>50% isolated yield</td>
</tr>
<tr>
<td>16</td>
<td>RuCl(p-cymene)TsDPEN (0.01 equiv)</td>
<td>CH₂Cl₂, 12 h</td>
<td>40°C</td>
<td>HCO₂H + Et₃N</td>
<td>50% isolated yield</td>
</tr>
<tr>
<td>17</td>
<td>RuCl(p-cymene)TsDPEN (0.1 equiv)</td>
<td>CH₂Cl₂, 6 h</td>
<td>RT</td>
<td>HCO₂H + Et₃N</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>
Table 2.8: Optimization of Conditions for the Chiral Reduction. The Ru catalyst refers to 
Ru(p-cymene)[(R,R)TsDPEN]. RT refers to 25 ºC

The optimization study concluded that using 0.01 equivalents of Ru(p-
cymene)[(R,R)TsDPEN] with formic acid and triethylamine in dichloromethane either at 
room temperature or 40 ºC gave the alcohol product 37 in a 50% yield. However, a 
higher er of 2.1:1 was obtained when the reaction was carried out at room temperature as 
compared to an er of 1.7:1 when the reaction was carried out at 40 ºC. With a higher 
catalyst loading, a significant decrease in the yield was observed. Using hydrogen as the 
reducing agent was ineffective even when a highly polar solvent was used. With these 
optimized conditions in hand, we wanted to explore the effect of other protecting groups 
on the er.

2.11.2 Effect of Protecting Groups on the Chiral Reduction

To investigate the effect that the protecting groups on the N-hydroxyphthalimide, 
had on the chiral reduction, we synthesized substrates with a variety of protecting groups. 
The sterics and electronics of the protecting groups were varied in an effort to determine 
some trend in the chiral reduction which we could use to better the er of the alcohol 
product. As determined above, the allyl protected N-hydroxyphthalimide 36 gave a 50% 
yield of the alcohol product which had an er of 2.1:1 (entry 1, Table 2.9). Increasing the 
size of the protecting group to a t-butyl moiety led to decomposition under the reduction 
conditions (entry 2, Table 2.9). Substituting the allyl group for a benzyl functionality in 
compound 39, gave the desired product with an er of 2.3:1. Placing a naphthyl group (40), 
which is bulkier and more electron withdrawing than the benzyl group led to an increase
in the yield but with a slight decrease in the er. Using the extremely bulk mesityl group, 41, gave the same er as that observed with the benzyl (entries 3, 4 and 5, Table 2.9).

Probing the effect of electronics on the reduction with electron donating and electron withdrawing substituents on the benzyl group, showed that electron-donating groups were tolerated but only decomposition was observed with the $p$-CF$_3$ benzyl group (entries 6 and 7, Table 2.9). All silyl containing protecting groups also led to decomposition.

Thus the enantiomeric ratio of the alcohol product was approximately 2:1, irrespective of the size or the electronics of the protecting group used.
\[
\text{RuO}([\text{cyclohexane}])[[\text{R,R}-\text{TsDPEN}]] \rightarrow \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure 37" /></td>
<td>50%</td>
<td>2.1:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 38" /></td>
<td>Decomposition</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 39" /></td>
<td>50%</td>
<td>2.3:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 40" /></td>
<td>65%</td>
<td>2.1:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 41" /></td>
<td>48%</td>
<td>2.3:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 42" /></td>
<td>Decomposition</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 43" /></td>
<td>44%</td>
<td>2.1:1</td>
</tr>
</tbody>
</table>
Table 2.9: Effect of Protecting Groups on the Chiral Reduction. Determination of er was done by Mosher ester analysis with (R)-(+)–α-Methoxy-α-trifluoromethylphenylacetic acid.\(^\text{102}\)

2.11.3 Testing the Effect of a Chiral \textit{N}-hydroxyisoindolinone

Having optimized the conditions for the chiral reduction and determined that the best er we could obtain was 2:1, we wanted to test our hypothesis for the chirality transfer through the diastereoselective rearrangement.

Protection of the chiral alcohol 37 with TBSCI, followed by deprotection of the allyl group gave the chiral 3-t-butyldimethyl-\textit{N}-hydroxyisoindolinone which was immediately reacted with the indenyl boronic acid 1z. The etherification was directly followed by the rearrangement to give the imidate 45z which had a dr of <95:5. Hydrolysis of the imidate with ammonium chloride gave the α-hydroxy ketone 46 which had an enantiomeric ratio of 1:0.75. Thus starting with an er of 2.1:1 for the chiral 3-hydroxy-\textit{N}-allyloxyisoindolinone, we observed some erosion of chirality since the final product had an er of 1:0.75. This suggests that the rearrangement is highly diastereoselective and probably decides the stereochemistry at the α-oxygenated center on the imidate, but there might be some epimerization either in the presence of Cu(OAc)\(_2\) or during the hydrolysis with ammonium chloride. This route therefore needs further analysis of the imidates with either a chiral GC or chiral SFC to determine the er at the imidate stage.
Scheme 2.37: Reaction Scheme for Evaluating Transfer of Chirality. Determination of er was done by Mosher Analysis with \((R)-(+)\)-\(\alpha\)-Methoxy-\(\alpha\)-trifluoromethylphenylacetic acid. The absolute stereochemistry at the indolinone and the \(\alpha\)-oxygenated stereocenter (above and henceforth) has not been determined. The use of dashes and wedges is just to indicate a chiral center and does not specify the actual configuration at that stereocenter.

2.12 Conclusion

We have developed a new diastereoselective dioxygenation reaction that proceeds with good to excellent diastereoselectivity to form \(\alpha\)-oxygenated ketones as imidates. The reaction of 3-substituted-\(N\)-hydroxyisoindolinones with alkenyl boronic acids forms the \(N\)-enoxyisoindolinones which undergo an \textit{in situ} [3,3] rearrangement to form the imidates. The rearrangement reaction is found to proceed with high diastereoselectivity and the size
of the substituent on the isoindolinone plays an important role in controlling the facial selectivity. The imidate products can be derivatized to α-hydroxy ketones and α-chloro ketones. We have also tried to investigate the transfer of chirality from an enantiomerically enriched \( N \)-hydroxyisoindolinone to the imidates and the α-hydroxy ketones.

2.13 Supporting Information

2.13.1 General Experimental Information:

\(^1\)H NMR and \(^{13}\)C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethysilane on the \( \delta \) scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 µm) mesh silica gel (\( \text{SiO}_2 \)). Medium pressure liquid chromatography was performed to force flow the indicated solvent system down columns packed with 60Å (40 – 60 µm) mesh silica gel (\( \text{SiO}_2 \)). Unless otherwise noted, all reagents were obtained from commercial sources and, where appropriate, purified prior to use. THF, \( \text{CH}_2\text{Cl}_2 \), and toluene were dried by filtration through alumina according to the procedure of Grubbs.\(^1\) TMEDA was distilled
2.13.2 Experimental Procedures and Characterization Data

II. Preparation of 3-substituted-N-hydroxyisoindolinones

2-((tetrahydro-2H-pyran-2-yl)oxy)isoindoline-1,3-dione 28: To a solution of the N-hydroxyphthalimide 2 (5.0 g, 30.65 mmol) in CH$_2$Cl$_2$ (30 ml) at 0 °C, was added the 3,4-dihydro-2H-pyran (1.2 equiv, 3.4 ml, 36.78 mmol) followed by PTSA (0.1 equiv, 0.583 g, 3.07 mmol). The reaction was stirred at 0 °C for 30 mins and then at room temperature for 2 h. The reaction was quenched by the addition of water, and extracted with CH$_2$Cl$_2$ (3 x 15 ml). The organic layer was washed with brine and dried with MgSO$_4$. The solvent was removed under reduced pressure and the crude reaction mixture purified by medium pressure chromatography on silica gel with 1:4 ethyl acetate:hexanes to give 28 as a white solid (5.1 g, 67 %). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.83-7.80 (m, 2H), 7.73-7.72 (m, 2H), 5.42-5.40 (m, 1H), 4.53-4.48 (m, 1H), 3.67-3.63 (m, 1H), 2.12-2.08 (m, 1H), 1.96-1.65 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.8, 134.2, 129.1, 123.4, 103.1, 62.3, 27.7, 24.8, 17.6; IR (thin film) 2963, 2940, 2899, 2858, 1783, 1726, 1613, 1460, 1375, 1280, 1186 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{13}$H$_{13}$NO$_4$Na (M+Na)$^+$ 270.0742, found 270.0740; mp 115 °C.
3-hydroxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)isoindolin-1-one 29: A solution of 2-(((tetrahydro-2H-pyran-2-yl)oxy)isoindoline-1,3-dione 28 (7.5 g, 30.65 mmol) in MeOH (40 ml) was cooled to 0 °C and NaBH₄ (1.5 equiv, 1.7 g, 45.97 mmol) was added slowly to the reaction mixture. After the evolution of H₂ was complete, the reaction was warmed to room temperature and stirred for 2 h when TLC indicated complete consumption of 28. The MeOH was removed in vacuo and the residue dissolved in EtOAc. Saturated NH₄Cl was added followed by extraction with EtOAc (3 x 20 ml). The organic layer was washed with water and brine, dried with MgSO₄ and concentrated under reduced pressure to give 29 as a white solid (7.1 g, 93 %) which was used without further purification. ^1H NMR first diastereomer (500 MHz; CDCl₃): δ 7.82-7.78 (m, 1H), 7.65-7.57 (m, 3H), 5.94 (s, 1H), 5.33-5.28 (m, 1H), 4.38-4.35 (m, 1H), 3.71-3.65 (m, 2H), 1.92-1.85 (m, 6H); ^13C NMR first diastereomer (125 MHz, CDCl₃): δ 165.9, 141.3, 133.4, 129.9, 129.1, 123.8, 123.6, 104.5, 83.5, 64.6, 28.3, 24.9, 19.8; ^1H NMR second diastereomer (500 MHz; CDCl₃): δ 7.78-7.75 (m, 1H), 7.66-7.49 (m, 3H), 5.93 (s, 1H), 5.03-5.02 (m, 1H), 4.17-4.16 (m, 1H), 3.91-3.86 (m, 1H), 3.51-3.50 (m, 1H), 1.86-1.53 (m, 6H); ^13C NMR second diastereomer (125 MHz, CDCl₃): δ 165.3, 141.1, 133.1, 129.8, 128.7, 123.8, 123.3, 103.4, 82.6, 63.9, 30.6, 25.4, 19.7; IR (thin film) 3291, 2946, 2889, 1724, 1675, 1616, 1467, 1388, 1284, 1141 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₃H₁₆NO₄ (M+H)⁺ 250.1079, found 250.1072; mp 129 °C.
3-methoxy-N-hydroxyisoindolinone 23: The above compound 3-hydroxy-2-((tetrahydro-2H-pyran-2-yl)oxy)isoindolin-1-one 29 (1 g, 4.01 mmol) was dissolved in MeOH (15 ml) and PTSA (0.1 equiv, 0.076 g, 0.40 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 h. The MeOH was removed under reduced pressure and the crude reaction mixture purified by medium pressure chromatography on silica gel with 2:1 ethyl acetate:hexanes to give 23 as a white solid (0.503 g, 70 %). 1H NMR (500 MHz; CDCl3): δ 9.98 (bs, 1H), 7.75-7.74 (m, 1H), 7.61-7.59 (m, 1H), 7.52-7.49 (m, 2H), 5.89 (s, 1H), 3.36 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 166.2, 138.4, 132.8, 130.1, 129.9, 123.5, 123.4, 88.3, 53.0; IR (thin film) 3082, 2928, 2830, 1695, 1663, 1613, 1502, 1460, 1353, 1223, 1141 cm⁻¹; HRMS (ESI) m/z calcd. for C9H10NO3 (M+H)⁺ 180.0661, found 180.0668; mp 115 °C.

3-ethoxy-N-hydroxyisoindolinone 24: The 3-hydroxy-2-((tetrahydro-2H-pyran-2-yl)oxy)isoindolin-1-one 29 (1 g, 4.01 mmol) was dissolved in EtOH (15 ml) and PTSA (0.1 equiv, 0.076 g, 0.40 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 h. The EtOH was removed under reduced pressure and
the crude reaction mixture purified by medium pressure chromatography on silica gel with 2:1 ethyl acetate:hexanes to give 24 as a white solid (0.519 g, 67 %). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.74-7.71 (m, 1H), 7.60-7.57 (m, 1H), 7.53-7.48 (m, 2H), 5.89 (s, 1H), 3.72-3.62 (m, 2H), 1.29 (dd, $J$ = 11.5, 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.2, 139.0, 132.8, 129.9, 123.5, 123.4, 87.9, 62.2, 15.3; IR (thin film) 3070, 2975, 2824, 1710, 1666, 1616, 1517, 1467, 1369, 1237, 1160 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{10}$H$_{12}$NO$_3$ (M+H)$^+$ 194.0817, found 194.0820; mp 121 °C.

![Image of chemical reaction](image-url)

**3-isopropoxy-N-hydroxyisoindolinone 25:** The 3-hydroxy-2-((tetrahydro-2H-pyran-2-yl)oxy) isoindolin-1-one 29 (1 g, 4.01 mmol) was dissolved in iPrOH (15 ml) and PTSA (0.1 equiv, 0.076 g, 0.40 mmol) was added to the reaction mixture. The reaction was stirred at room temperature for 12 h. The iPrOH was removed under reduced pressure and the crude reaction mixture purified by medium pressure chromatography on silica gel with 2:1 ethyl acetate:hexanes to give 25 as an amorphous white solid (0.515 g, 62 %). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 9.92 (bs, 1H), 7.70-7.69 (m, 1H), 7.59-7.56 (m, 1H), 7.49-7.45 (m, 2H), 5.85 (s, 1H), 4.28-4.23 (m, 1H), 1.37 (d, $J$ = 6.0 Hz, 3H), 1.31 (d, $J$ = 6.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.0, 139.6, 132.6, 129.8, 129.5, 123.5, 123.2, 87.1, 71.8, 23.4, 22.7; IR (thin film) 3146, 2950, 1780, 1704, 1609, 1464, 1373, 1350, 1180, 1065 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{11}$H$_{14}$NO$_3$ (M+H)$^+$ 208.0974, found 208.0982.
2-((t-butyldimethylsilyl)oxy)isoindoline-1,3-dione 12: To the N-hydroxyphthalimide 2 (5.0 g, 31 mmol) in DMF (15 ml) at 0 ºC was added imidazole (1.5 equiv, 3.2 g, 46.5 mmol) followed by TBSCl (1 equiv, 4.6 g, 31 mmol). The reaction was allowed to warm up to room temperature and stirred at that temperature for 10 h. The reaction was quenched with NH₄Cl and extracted with EtOAc (3 x 20 ml). The organic layer was washed with water and dried with MgSO₄. The crude reaction mixture was purified by medium pressure chromatography on silica gel with 1:3 ethyl acetate:hexanes to give 12 as a white solid (6.87 g, 80 %). ¹H NMR (500 MHz; CDCl₃): δ 7.81-7.78 (m, 2H), 7.72-7.70 (m, 2H), 1.07 (s, 9H), 0.28 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 163.9, 134.1, 129.1, 123.2, 25.6, 18.3, -4.9; IR (thin film) 2934, 2899, 2861, 1793, 1729, 1470, 1378, 1259, 1188, 1132, 1078 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₂₀NO₃Si (M+H)⁺ 278.1212, found 278.1207; mp 58 ºC.

2-((triisopropylsilyl)oxy)isoindoline-1,3-dione 12’: To the N-hydroxyphthalimide 2 (5.0 g, 31 mmol) in DMF (15 ml) at 0 ºC was added imidazole (1.5 equiv, 3.2 g, 46.5 mmol) followed by TIPSCI (1 equiv, 6.63 ml, 31 mmol). The reaction was allowed to warm up to room temperature and stirred at that temperature for 10 h. The reaction was quenched
with NH₄Cl and extracted with EtOAc (3 x 20 ml). The organic layer was washed with water and dried with MgSO₄. The crude reaction mixture was purified by medium pressure chromatography on silica gel (1:3 ethyl acetate:hexanes) to give 12' as a white solid (8.41 g, 85 %). ¹H NMR (500 MHz; CDCl₃): δ 7.80-7.79 (m, 2H), 7.72-7.70 (m, 2H), 1.38-1.33 (m, 3H), 1.18-1.16 (m, 18H); ¹³C NMR (125 MHz, CDCl₃): δ 164.1, 134.1, 129.1, 123.2, 17.6, 12.5; IR (thin film) 2943, 2868, 1789, 1732, 1460, 1378, 1245, 1188, 1132, 1078 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₇H₂₆NO₃Si (M+H)⁺ 320.1682, found 320.1680; mp 78 °C.

![Reaction Scheme](image)

**3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13:** To the 2-((t-butyldimethylsilyl) oxy)isoindoline-1,3-dione 12 (4.0 g, 14.42 mmol) in MeOH (30 ml) at 0 °C was added NaBH₄ (1.5 equiv, 0.818 g, 21.63 mmol). After the evolution of H₂ was complete, the reaction was warmed to room temperature and stirred for 4 h. The MeOH was removed in vacuo and the residue dissolved in EtOAc. Saturated NH₄Cl was added followed by extraction with EtOAc (3 x 20 ml). The organic layer was washed with water and brine, dried with MgSO₄ and concentrated under reduced pressure. The crude reaction mixture was purified by medium pressure chromatography on silica gel (1:1 ethyl acetate:hexanes) to give 13 as a white solid (3.30 g, 82 %). ¹H NMR (500 MHz; CDCl₃): δ 10.08 (bs, 1H), 7.68-7.67 (m, 1H), 7.58-7.54 (m, 1H), 7.46-7.43 (m, 2H), 5.97 (s, 1H), 1.00 (s, 9H), 0.34 (s, 3H), 0.30 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 165.5, 141.9, 132.5, 129.5, 129.3, 123.2, 122.9, 83.2, 25.7, 18.2, -4.1, -4.8; IR (thin film) 3114, 2928,
2886, 2858, 1701, 1616, 1505, 1467, 1398, 1356, 1255, 1158 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{14}H_{22}NO_{3}Si\) (M+H\(^+\)) 280.1369, found 280.1371; mp 147 °C.

3-triisopropylsilyloxy-N-hydroxyisoindolinone 13': To the 2-((triisopropylsilyl)oxy)isoindoline-1,3-dione 12' (4.0 g, 12.52 mmol) in MeOH (30 ml) at 0 °C was added NaBH\(_4\) (1.5 equiv, 0.710 g, 18.78 mmol). After the evolution of H\(_2\) was complete, the reaction was warmed to room temperature and stirred for 4 h. The MeOH was removed in vacuo and the residue dissolved in EtOAc. Saturated NH\(_3\)Cl was added followed by extraction with EtOAc (3 x 20 ml). The organic layer was washed with water and brine, dried with MgSO\(_4\) and concentrated under reduced pressure. The crude reaction mixture was purified by medium pressure chromatography on silica gel (1:1 ethyl acetate:hexanes) to give 13' as a white solid (3.05 g, 76%). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 9.82 (bs, 1H), 7.69-7.67 (m, 1H), 7.57-7.55 (m, 1H), 7.51-7.50 (m, 1H), 7.47-7.44 (m, 1H), 6.26 (s, 1H), 1.37-1.33 (m, 3H), 1.20-1.18 (m, 18H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 165.7, 142.2, 132.5, 129.4, 129.3, 123.2, 123.1, 83.4, 18.1, 18.0, 12.6; IR (thin film) 3089, 2934, 2864, 1685, 1660, 1499, 1460, 1341, 1233, 1163, 1126 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{17}H_{28}NO_{3}Si\) (M+H\(^+\)) 322.1838, found 322.1841; mp 151 °C.
3-oxo-2-(((tetrahydro-2H-pyran-2-yl)oxy)isoindolin-1-yl pivalate 30: The 3-hydroxy-2-(((tetrahydro-2H-pyran-2-yl)oxy)isoindolin-1-one 29 (2.0 g, 8.02 mmol) was suspended in CH$_2$Cl$_2$ (20 ml) at 0 ºC and Et$_3$N (2 equiv, 2.2 ml, 16.04 mmol) was added to the reaction mixture. This was followed by the dropwise addition of PivCl (1.3 equiv, 1.3 ml, 10.43 mmol). The reaction was then stirred at room temperature for 8 h. Saturated NH$_4$Cl was added to the reaction followed by extraction with CH$_2$Cl$_2$ (3 x 10 ml). The organic layer was washed with brine and dried with MgSO$_4$. The solvent was removed under reduced pressure and the residue purified by medium pressure chromatography on silica gel (1:4 ethyl acetate:hexanes) to give 30 as a white solid (1.89 g, 71 %) which is a 1:1 mixture of diastereomers. $^1$H NMR first diastereomer (500 MHz; CDCl$_3$): δ 7.84-7.82 (m, 1H), 7.61-7.59 (m, 2H), 7.46-7.44 (m, 1H), 7.15 (s, 1H), 5.32-5.30 (m, 1H), 4.32-4.25 (m, 1H), 3.72-3.69 (m, 1H), 1.91-1.78 (m, 6H), 1.25 (s, 9H); $^{13}$C NMR first diastereomer (125 MHz, CDCl$_3$): δ 178.5, 166.2, 139.2, 133.2, 130.4, 129.7, 123.9, 123.7, 103.3, 82.2, 62.5, 39.1, 28.3, 26.9, 25.0, 18.3; $^1$H NMR second diastereomer (500 MHz; CDCl$_3$): δ 7.84-7.82 (m, 1H), 7.57-7.53 (m, 2H), 7.41-7.40 (m, 1H), 7.15 (s, 1H), 5.25-5.23 (m, 1H), 4.32-4.25 (m, 1H), 3.63-3.60 (m, 1H), 1.64-1.54 (m, 6H), 1.24 (s, 9H); $^{13}$C NMR second diastereomer (125 MHz, CDCl$_3$): δ 178.5, 165.3, 139.2, 133.1, 130.3, 129.6, 123.8, 123.5, 102.4, 79.3, 62.1, 39.1, 28.1, 26.9, 25.0, 18.1; IR (thin film) 2965, 2868, 1720, 1482, 1391, 1366, 1277, 1201, 1123, 1081 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{24}$NO$_5$ (M+H)$^+$ 334.1654, found 334.1646; mp 83 ºC.
3-allyl-N-hydroxyisoindolinone 27: To the compound 30 (0.400 g, 1.19 mmol) in CH₂Cl₂ (7 ml) was added trimethylallylsilane (2 equiv, 0.38 ml, 2.39 mmol) followed by TIPSOTf (10 mol %, 0.03 ml, 0.119 mmol) and the reaction stirred at room temperature for 10 h. The solvent was removed under reduced pressure and the residue purified by medium pressure chromatography on silica gel (2:1 ethyl acetate:hexanes) to yield 27 as a pale pink oil (0.115 g, 51 %). The compound is unstable and used immediately for the next step. ¹H NMR (500 MHz; CDCl₃): δ 7.72-7.70 (m, 1H), 7.52-7.49 (m, 1H), 7.42-7.39 (m, 2H), 5.64-5.57 (m, 1H), 5.13 (d, J = 17.0 Hz, 1H), 5.00-4.97 (m, 1H), 4.77 (dd, J = 6.2, 3.7 Hz, 1H), 2.94-2.89 (m, 1H), 2.79-2.75 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 165.0, 145.7, 141.7, 131.5, 130.1, 128.4, 123.0, 122.5, 119.5, 61.9, 34.5; IR (thin film) 3076, 2911, 1717, 1616, 1568, 1464, 1373, 1312, 1227, 1180, 1148 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₁H₁₂NO₂ (M+H)⁺ 190.0868, found 190.0861.

V. Copper-Promoted Etherification and Rearrangement of 3-substituted-N-hydroxyisoindolinones with Vinyl Boronic Acids (Table 2.2).
**General procedure J**: Copper-promoted etherification and rearrangement of 3-substituted-N-hydroxyisoindolinones with vinyl boronic acids. A scintillation vial was charged with the 3-substituted-N-hydroxyisoindolinones (1 equiv), vinyl boronic acid 1z (2 equiv), Cu(OAc)$_2$ (1 equiv), and anhydrous Na$_2$SO$_4$ (4-6 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of N-hydroxyisoindolinone. Pyridine (3 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 ºC for 12 h. The reaction mixture was filtered through a plug of florisil® with EtOAc to remove the Cu(OAc)$_2$. The solvents were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography on florisil® (1:4 - 1:2; ethyl acetate:hexanes) to give the α-oxygenated ketones.

![Diagram](image)

**23z**

**dr = 92:8**

**α-oxygenated ketone 23z**: General procedure J with 3-methoxy-N-hydroxyisoindolinone 23 (0.060 g; 0.334 mmol), alkenyl boronic acid 1z (0.107 g, 0.668 mmol), Cu(OAc)$_2$ (0.061 g, 0.334 mmol), Na$_2$SO$_4$ (0.224 g, 1.57 mmol), and pyridine (81 µL, 1.00 mmol) afforded 23z as a white solid (0.049 g, 50%) and a dr of 92:8 after purification using flash chromatography on florisil® (1:4; ethyl acetate: hexanes). $^1$H NMR major diastereomer
(500 MHz; CDCl$_3$): $\delta$ 7.85-7.83 (m, 1H), 7.65-7.64 (m, 1H), 7.57-7.55 (m, 2H), 7.48-7.40 (m, 4H), 5.86 (s, 1H), 5.81 (dd, $J = 7.2$, 5.24 Hz, 1H), 3.87 (dd, $J = 16.98$, 7.23 Hz, 1H), 3.32-3.25 (m, 4H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): $\delta$ 200.4, 169.4, 150.6, 149.0, 135.8, 134.8, 132.4, 130.2, 129.1, 128.1, 126.7, 124.5, 123.2, 121.0, 95.8, 77.6, 53.7, 33.6; $^1$H NMR minor diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.89-7.88 (m, 1H), 7.76-7.73 (m, 1H), 7.57-7.55 (m, 2H), 7.48-7.40 (m, 4H), 5.97 (s, 1H), 5.80 (m, 1H), 3.56 (dd, $J = 16.2$, 7.9 Hz, 1H), 3.14 (s, 3H), 3.00 (dd, $J = 16.2$, 4.6 Hz, 1H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): $\delta$ 200.4, 164.8, 163.1, 149.0, 135.8, 134.8, 132.4, 130.2, 129.1, 128.1, 126.7, 124.5, 123.2, 121.0, 95.8, 77.6, 53.7, 26.7; IR (thin film) 2965, 2930, 1736, 1625, 1603, 1570, 1459, 1395, 1333, 1274, 1189 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{16}$NO$_3$ (M+H)$^+$ 294.1130, found 294.1127; decomposed at 101 ºC.

![24z](image)

**dr = 92:8**

**a-oxygenated ketone 24z:** General procedure J with 3-ethoxy-N-hydroxyisoindolinone 24 (0.080 g; 0.410 mmol), alkenyl boronic acid 1z (0.132 g, 0.820 mmol), Cu(OAc)$_2$ (0.074 g, 0.410 mmol), Na$_2$SO$_4$ (0.298 g, 2.09 mmol), and pyridine (100 µL, 1.23 mmol) afforded 24z as a white solid (0.067 g, 53%) and a dr of 92:8 after purification using flash chromatography on florisil® (1:4; ethyl acetate: hexanes). $^1$H NMR major diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.85-7.84 (m, 1H), 7.87-7.84 (m, 1H), 7.58-7.55 (m, 2H), 7.48-7.41
(m, 4H), 5.90 (s, 1H), 5.79 (dd, \(J = 6.9, 5.3\) Hz, 1H), 3.87 (dd, \(J = 17.0, 6.9\) Hz, 1H), 3.61 (m, 1H), 3.52 (m, 1H), 3.26 (dd, \(J = 17.0, 5.3\) Hz, 1H), 1.21 (t, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR major diastereomer (125 MHz, CDCl\(_3\)): \(\delta\) 200.5, 169.2, 150.6, 149.6, 135.8, 134.8, 132.3, 130.1, 129.0, 128.1, 126.7, 124.5, 123.2, 120.9, 95.1, 77.5, 62.0, 33.7, 15.4; \(^1\)H NMR minor diastereomer (500 MHz; CDCl\(_3\)): \(\delta\) 7.93-7.92 (m, 1H), 7.75-7.74 (m, 1H), 7.58-7.55 (m, 2H), 7.48-7.41 (m, 4H), 5.87 (s, 1H), 5.51-5.50 (m, 1H), 3.79-3.71 (m, 1H), 3.61-3.60 (m, 1H), 3.52-3.50 (m, 1H), 3.31-3.29 (m, 1H), 1.29 (t, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR minor diastereomer (125 MHz, CDCl\(_3\)): \(\delta\) 200.5, 169.2, 150.6, 149.6, 134.3, 134.8, 132.3, 130.1, 129.0, 128.1, 126.7, 124.0, 123.5, 120.9, 95.1, 77.5, 62.0, 33.7, 15.4; IR (thin film) 2972, 2906, 2871, 1726, 1622, 1571, 1470, 1388, 1328, 1261, 1183 cm\(^{-1}\); HRMS (ESI) m/z calcd. for \(\text{C}_{19}\text{H}_{18}\text{NO}_3\text{Si}(\text{M+H})^+\) 308.1287, found 308.1279; decomposed at 110 °C.

\[\text{25z}\]

**\(\alpha\)-oxygenated ketone 25z:** General procedure J with 3-isoproxy-\(N\)-hydroxyisoindolinone 25 (0.080 g; 0.386 mmol), alkenyl boronic acid 1z (0.123 g, 0.772 mmol), Cu(OAc)\(_2\) (0.070 g, 0.386 mmol), Na\(_2\)SO\(_4\) (0.298 g, 2.09 mmol), and pyridine (93 \(\mu\)L, 1.158 mmol) afforded 25z as a white solid (0.060 g, 48%) and a dr of 97:3 after purification using flash chromatography on florisil\(^{\circledR}\) (1:4; ethyl acetate: hexanes) as a
97:3 mixture of diastereomers. $^1$H NMR major diastereomer (500 MHz; CDCl$_3$): δ 7.86-7.84 (m, 1H), 7.66-7.63 (m, 1H), 7.55-7.54 (m, 2H), 7.47-7.40 (m, 4H), 5.83 (s, 1H), 5.69 (dd, $J = 7.6, 4.7$ Hz, 1H), 3.91-3.90 (m, 1H), 3.83 (dd, $J = 16.4, 7.6$ Hz, 1H), 3.32 (dd, $J = 16.4, 4.7$ Hz, 1H), 1.26 (d, $J = 5.9$ Hz, 3H), 1.09 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): δ 200.5, 168.7, 150.5, 135.6, 134.8, 132.2, 130.0, 128.8, 127.9, 126.6, 124.4, 124.0, 123.1, 120.8, 94.2, 77.6, 70.3, 33.5, 23.4, 22.7; $^1$H NMR minor diastereomer (500 MHz; CDCl$_3$): δ 7.94-7.92 (m, 2H), 7.60-7.59 (m, 2H), 7.35-7.29 (m, 4H), 5.87 (s, 1H), 5.44-5.41 (m, 1H), 3.83 (dd, $J = 16.4, 7.6$ Hz, 1H), 3.70-3.63 (m, 1H), 3.05 (dd, $J = 16.4, 3.9$ Hz, 1H), 1.35 (d, $J = 5.0$ Hz, 3H), 1.09 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): δ 200.5, 168.7, 150.3, 134.8, 132.2, 130.1, 128.8, 127.9, 126.6, 124.2, 124.0, 123.1, 120.8, 94.2, 77.6, 70.3, 33.9, 23.4, 22.7; IR (thin film) 2968, 2930, 2855, 1726, 1629, 1577, 1463, 1404, 1372, 1274, 1151 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{20}$NO$_3$ (M+H)$^+$ 322.1443, found 322.1436; decomposed at 120 ºC.

\[
\text{dr = } >95:5
\]

**α-oxygenated ketone 14z:** General procedure J with 3-tert-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.100 g; 0.357 mmol), alkenyl boronic acid 1z (0.114 g, 0.714 mmol), Cu(OAc)$_2$ (0.065 g, 0.357 mmol), Na$_2$SO$_4$ (0.373 g, 2.62 mmol), and pyridine
(86.6 μL, 1.071 mmol) afforded 14z as a white solid (0.086 g, 61%) and a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. \( ^1H \) NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.84-7.83 (m, 1H), 7.65-7.62 (m, 1H), 7.53-7.37 (m, 6H), 5.95 (s, 1H), 5.54-5.52 (m, 1H), 3.76 (dd, \( J = 16.7, 7.8 \) Hz, 1H), 3.43 (dd, \( J = 16.7, 4.5 \) Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), -0.07 (s, 3H); \( ^13C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 200.5, 167.7, 152.6, 150.3, 135.6, 135.1, 131.6, 130.0, 128.5, 127.9, 126.7, 124.3, 122.7, 120.8, 90.7, 77.9, 33.1, 25.8, 18.1, -4.1, -4.6; IR (thin film) 2927, 2854, 1727, 1629, 1609, 1579, 1469, 1396, 1329, 1272, 1186 cm\(^{-1}\); HRMS (ESI) m/z calcd. for \( C_{23}H_{28}NO_3Si \) (M+H)\(^+\) 394.1838, found 394.1846; decomposed at 84-85 °C.

\[ \text{dr} = >95:5 \]

\( \alpha \)-oxygenated ketone 26z: General procedure J with 3-isopropoxy-N-hydroxyisoindolinone 13' (0.080 g; 0.248 mmol), alkenyl boronic acid 1z (0.080 g, 0.497 mmol), Cu(OAc)\(_2\) (0.045 g, 0.248 mmol), Na\(_2\)SO\(_4\) (0.299 g, 2.11 mmol), and pyridine (60 μL, 0.744 mmol) afforded 26z as a white solid (0.069 g, 64%) as a single diastereomer after purification using flash chromatography on florisil (1:3; ethyl acetate: hexanes). \( ^1H \) NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.84-7.83 (m, 1H), 7.65-7.64 (m, 1H), 7.55-7.52 (m, 2H), 7.48-7.38 (m, 4H), 5.98 (s, 1H), 5.37 (dd, \( J = 5.0, 5.0 \) Hz, 1H), 3.70 (dd, \( J = 10.0, 5.0 \) Hz, 1H), 3.53 (dd, \( J = 10.0, 5.0 \) Hz, 1H) 1.05-0.97 (m, 21H); \( ^13C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \)
200.4, 167.0, 152.7, 150.2, 135.4, 135.2, 131.6, 129.8, 128.4, 127.7, 126.6, 124.3, 122.6, 120.6, 90.3, 78.1, 32.6, 17.8, 17.7, 12.1; IR (thin film) 2942, 2864, 1727, 1628, 1606, 1576, 1465, 1396, 1272, 1191 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{26}\)H\(_{34}\)NO\(_3\) (M+H\(^+\)) 436.2308, found 436.2306; decomposed at 114-115 °C.

\[
\text{27z}
\]
\[
dr = >95:5
\]

\textit{a-oxygenated ketone 27z:} General procedure J with 3-allyl-N-hydroxyisoindolinone 27 (0.055 g; 0.290 mmol), alkenyl boronic acid 1z (0.093 g, 0.580 mmol), Cu(OAc)\(_2\) (0.053 g, 0.290 mmol), Na\(_2\)SO\(_4\) (0.205 g, 1.44 mmol), and pyridine (70 μL, 0.870 mmol) afforded 27z as an amorphous white solid (0.058 g, 66%) after purification using flash chromatography on florisil\textsuperscript{©} (1:3; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): δ 7.86-7.84 (m, 1H), 7.67-7.64 (m, 1H), 7.60-7.59 (m, 1H), 7.50-7.35 (m, 5H), 5.81-5.72 (m, 2H), 5.07-5.01 (m, 2H), 4.75 (t, \(J = 6.4\) Hz, 1H), 3.86 (dd, \(J = 17.0, 7.7\) Hz, 1H), 3.23 (dd, \(J = 17.0, 4.6\) Hz, 1H), 2.60-2.57 (m, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): δ 201.0, 168.0, 153.7, 150.8, 135.7, 134.9, 134.4, 132.3, 129.1, 128.0, 127.3, 126.7, 124.5, 122.3, 120.9, 117.4, 68.3, 77.2, 37.6, 33.9; IR (thin film) 2953, 2934, 2855, 1774, 1714, 1600, 1571, 1467, 1381, 1290, 1188 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{20}\)H\(_{18}\)NO\(_2\) (M+H\(^+\)) 304.1338, found 304.1343.
IV. Copper-Promoted Etherification and Rearrangement of $3t$-butyldimethylsilyloxy-$N$-hydroxyisoindolinones with Vinyl Boronic Acids (Tables 2.3 and 2.4).

![Chemical Structure](image)

**General procedure K:** Copper-promoted etherification and rearrangement of $3t$-butyldimethylsilyloxy-$N$-hydroxyisoindolinones with vinyl boronic acids. A scintillation vial was charged with $3t$-butyldimethylsilyloxy-$N$-hydroxyisoindolinone 13 (1 equiv), vinyl boronic acid 1 (2 equiv), Cu(OAc)$_2$ (1 equiv), and anhydrous Na$_2$SO$_4$ (4-6 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of $N$-hydroxyisoindolinone. Pyridine (3 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 °C for 8 h. The reaction mixture was filtered through a plug of florisil® with EtOAc to remove the Cu(OAc)$_2$. The solvents were removed under reduced pressure and the crude reaction mixture was purified by flash chromatography on florisil® (1:4 - 1:2; ethyl acetate:hexanes) to give $\alpha$-oxygenated ketones 14.
**dr = >95:5**

**α-oxygenated ketone 14a:** General procedure K with 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.140 g; 0.50 mmol), Z-2-buten-2-yl boronic acid 1a (0.100 g, 1.00 mmol), Cu(OAc)$_2$ (0.091 g, 0.50 mmol), Na$_2$SO$_4$ (0.470 g, 3.30 mmol), and pyridine (120 µL, 1.50 mmol) afforded 14a as a colorless liquid (0.108 g, 65%) as a single diastereomer after purification using flash chromatography on florisil$^\text{®}$ (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.54-7.44 (m, 2H), 7.43-7.39 (m, 2H), 5.96 (s, 1H), 5.35 (q, $J = 5.0$ Hz, 1H), 2.24 (s, 3H), 1.54 (d, $J = 5.0$ Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 207.2, 168.3, 152.6, 131.6, 130.1, 128.6, 122.8, 120.5, 90.9, 78.5, 25.7, 25.4, 18.1, 16.6, -4.0, -4.6; IR (thin film) 2956, 2928, 2858, 1729, 1625, 1581, 1470, 1401, 1255, 1192, 1116 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{28}$NO$_3$Si (M+H)$^+$ 334.1838, found 334.1844.

**14h**

**dr = >95:5**

**α-oxygenated ketone 14h:** General procedure K with 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.087 g; 0.312 mmol), Z-1-phenyl-1-buten-1-yl boronic acid 1h (0.110 g, 0.624 mmol), Cu(OAc)$_2$ (0.057 g, 0.312 mmol), Na$_2$SO$_4$ (0.320 g, 2.25 mmol), and pyridine (90 µL, 0.936 mmol) afforded 14h as a white solid (0.075 g, 59%)
as a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on florisil®. 

$^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.07-8.05 (m, 2H), 7.60-7.57 (m, 2H), 7.49-7.40 (m, 5H), 6.17 (t, $J = 5.0$ Hz, 1H), 5.94 (s, 1H), 2.09-2.04 (m, 2H), 1.14 (t, $J = 5.0$ Hz, 3H), 0.80 (s, 9H), -0.06 (s, 3H), -0.26 (s, 3H); 

$^{13}$C NMR (125 MHz, CDCl$_3$): 196.9, 168.5, 152.6, 135.4, 133.2, 131.7, 129.9, 128.6, 128.5, 128.4, 122.7, 120.7, 91.1, 79.5, 25.7, 25.4, 18.0, 10.1, -4.3, -4.7; IR (thin film) 2928, 2855, 1699, 1627, 1598, 1576, 1471, 1403, 1218, 1117, 1027 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{24}$H$_{32}$NO$_3$Si (M+H)$^+$ 410.2151, found 410.2157; decomposed at 68 ºC.

**dr** = 80:20

**α-oxygenated Ketone 14m:** General procedure K with 3-tert-butyldimethylsilyloxy-$N$-hydroxyisoindolinone 13 (0.175 g; 0.625 mmol), 1-cyclopentenyl boronic acid 1m (0.140 g, 1.25 mmol), Cu(OAc)$_2$ (0.114 g, 0.625 mmol), Na$_2$SO$_4$ (0.650 g, 4.57 mmol), and pyridine (150 µL, 1.87 mmol) afforded 14m as a colorless liquid (0.138 g, 64%) in an 80:20 ratio of diastereomers after purification using flash chromatography on florisil® (1:3; ethyl acetate: hexanes). 

$^1$H NMR major diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.51-7.48 (m, 2H), 7.41-7.35 (m, 2H), 6.00 (s, 1H), 5.32 (t, $J = 5.0$ Hz, 1H), 2.65-2.60 (m, 1H), 2.41-2.38 (m, 2H), 2.18-2.13 (m, 2H), 1.93-1.88 (m, 1H), 0.94 (s, 9H), 0.19 (s, 3H), 0.01 (s, 3H); 

$^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): $\delta$ 212.3, 168.0, 152.4, 131.7,
129.9, 128.5, 122.7, 120.7, 90.8, 79.2, 35.2, 28.2, 25.8, 18.1, 17.1, -3.8, -4.2; $^1$H NMR minor diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.43-7.35 (m, 4H), 6.00 (s, 1H), 5.32 (t, $J = 5.0$ Hz, 1H), 2.65-2.60 (m, 1H), 2.41-2.38 (m, 2H), 2.18-2.13 (m, 2H), 1.93-1.88 (m, 1H), 0.91 (s, 9H), 0.19 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): $\delta$ 212.3, 168.0, 152.4, 131.7, 129.9, 128.5, 122.7, 120.7, 90.8, 79.2, 35.2, 28.2, 25.7, 18.1, 17.1, -3.8, -4.2; IR (thin film) 2929, 2856, 1706, 1576, 1470, 1401, 1361, 1255, 1099, 1072 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{19}$H$_{28}$NO$_3$Si (M+H)$^+$ 346.1828, found 346.1842.

14n

dr = 89:11

$\alpha$-oxygenated ketone 14n: General procedure K with 3-t-butylidemethylsilyloxy-$N$-hydroxyisoindolinone 13 (0.133 g; 0.476 mmol), 1-cyclohexenyl boronic acid 1n (0.120 g, 0.950 mmol), Cu(OAc)$_2$ (0.086 g, 0.476 mmol), Na$_2$SO$_4$ (0.500 g, 3.52 mmol), and pyridine (110 µL, 1.428 mmol) afforded 14n as a white solid (0.121 g, 71%) in an 89:11 ratio of diastereomers after purification using flash chromatography on florisil® (1:3; ethyl acetate: hexanes). $^1$H NMR major diastereomer (500 MHz; CDCl$_3$): $\delta$ 7.56-7.50 (m, 2H), 7.41-7.37 (m, 2H), 5.97 (s, 1H), 5.58 (dd, $J = 11.7, 5.9$ Hz, 1H), 2.56-2.44 (m, 2H), 2.12-1.94 (m, 4H), 1.87-1.65 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), -0.01 (s, 3H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): $\delta$ 204.7, 168.2, 152.6, 131.8, 129.9, 128.4, 122.7, 120.8, 91.1, 79.9, 40.7, 33.7, 27.5, 25.8, 23.8, 18.1, -3.9, -4.1; $^1$H NMR minor
diastereomer (500 MHz; CDCl$_3$): δ 7.66-7.48 (m, 4H), 6.10 (s, 1H), 5.58 (dd, $J$ = 11.7, 5.9 Hz, 1H), 2.45-2.41 (m, 2H), 2.03-1.82 (m, 4H), 1.68-1.51 (m, 2H), 0.91 (s, 9H), 0.15 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): δ 204.7, 169.5, 152.6, 132.5, 129.9, 128.4, 123.5, 120.8, 91.1, 79.2, 40.7, 33.7, 27.5, 25.8, 23.8, 18.1, -3.9, -4.1; IR (thin film) 2929, 2857, 1731, 1626, 1 575, 1471, 1361, 1328, 1288, 1120, 1025 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{30}$NO$_3$Si (M+H)$^+$ 360.1995, found 360.1988; decomposed at 91 ºC.

\[ \text{14p} \]

\[ \text{dr = 69:31} \]

**$\alpha$-oxygenated ketone 14p:** General procedure K with 3-tert-butyldimethylsilyloxy-$N$-hydroxyisoindolinone 13 (0.100 g; 0.357 mmol), alkenyl boronic acid 1p (0.100 g, 0.714 mmol), Cu(OAc)$_2$ (0.065 g, 0.714 mmol), Na$_2$SO$_4$ (0.373 g, 2.62 mmol), and pyridine (90 μL, 1.07 mmol) afforded 14p as a semi-solid (0.085 g, 64%) as a 69:31 mixture of diastereomers after purification using flash chromatography (1:4; ethyl acetate: hexanes) on florisil$^\circledR$. $^1$H NMR major diastereomer (500 MHz; CDCl$_3$): δ 7.54-7.51 (m, 2H), 7.43-7.41 (m, 2H), 5.98 (s, 1H), 5.27 (d, $J = 10.0$ Hz, 1H), 2.54-2.47 (m, 3H), 2.09-1.95 (m, 4H), 1.18 (d, $J = 5.0$ Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), -0.16 (s, 3H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): δ 204.2, 168.6, 152.7, 133.0, 129.9, 128.4, 122.8, 120.7, 91.2, 85.0, 40.4, 40.0, 32.8, 26.0, 25.8, 25.6, 18.8, -3.9, -4.0; $^1$H NMR minor
diastereomer (500 MHz; CDCl₃): δ 7.58-7.57 (m, 2H), 7.41-7.38 (m, 2H), 6.01 (s, 1H), 5.54 (d, J = 10.0 Hz, 1H), 2.20-2.07 (m, 4H), 1.72-1.62 (m, 3H), 1.10 (d, J = 5.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), -0.11 (s, 3H); ¹³C NMR minor diastereomer (125 MHz, CDCl₃): δ 205.6, 168.2, 152.7, 133.0, 129.9, 129.7, 123.8, 123.1, 82.9, 82.2, 37.4, 31.1, 29.8, 25.8, 23.2, 18.0, 13.6, -3.9, -4.0; IR (thin film) 2928, 2855, 1733, 1626, 1471, 1319, 1249, 1194, 1121, 1046 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₁H₃₂NO₃Si (M+H)+ 374.2151, found 374.2153.

\[ \text{dr} = >95:5 \]

\textit{α}-oxygenated ketone 14v: General procedure K with 3-tert-butyldimethylsilyloxy-\(N\)-hydroxyisoindolinone 13 (0.080 g; 0.287 mmol), alkenyl boronic acid 1v (0.100 g, 0.574 mmol), Cu(OAc)₂ (0.052 g, 0.287 mmol), Na₂SO₄ (0.300 g, 2.11 mmol), and pyridine (70.0 µL, 0.861 mmol) afforded 14v as a white solid (0.077 g, 66%) and a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. ¹H NMR (500 MHz; CDCl₃): δ 8.08-8.06 (m, 1H), 7.61-7.60 (m, 1H), 7.55-7.51 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.34 (m, 1H), 7.30-7.29 (m, 1H), 6.07 (s, 1H), 5.94 (dd, J = 13.1, 4.7 Hz, 1H), 3.32-3.26 (m, 1H), 3.16-3.13 (m, 1H), 2.68-2.64 (m, 1H), 2.50-2.42 (m, 1H), 0.92 (s, 9H), 0.14(s, 3H), -0.05 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 192.9, 168.4, 152.7, 143.1, 133.7, 132.1, 131.9, 129.9, 128.6, 128.5, 127.8, 126.9, 122.7, 120.9, 91.1, 78.1, 29.4, 28.0, 25.9, 18.1, -3.8, -4.1; IR (thin film) 2952, 2928, 2854, 1704,
1626, 1603, 1575, 1471, 1460, 1327, 1249 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{24}\)H\(_{30}\)NO\(_3\)Si (M+H)\(^+\) 408.1995, found 408.1985; decomposed at 128 °C.

\[ \text{14z} \]

\[ \text{dr} = >95:5 \]

**\(\alpha\)-oxygenated ketone 14z:** General procedure K with 3-\(t\)-butyldimethylsilyloxy-\(N\)-hydroxyisoindolinone 13 (0.150 g; 0.536 mmol), alkenyl boronic acid 1z (0.172 g, 1.07 mmol), Cu(OAc)\(_2\) (0.097 g, 0.536 mmol), Na\(_2\)SO\(_4\) (0.500 g, 3.52 mmol), and pyridine (130 µL, 1.61 mmol) afforded 14z as a white solid (0.128 g, 61%) and a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.84-7.83 (m, 1H), 7.65-7.62 (m, 1H), 7.53-7.37 (m, 6H), 5.95 (s, 1H), 5.54-5.52 (m, 1H), 3.76 (dd, \(J = 16.7, 7.8\) Hz, 1H), 3.43 (dd, \(J = 16.7, 4.5\) Hz, 1H), 0.87 (s, 9H), 0.08 (s, 3H), -0.07 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 200.5, 167.7, 152.6, 150.3, 135.6, 135.1, 131.6, 130.0, 128.5, 127.9, 126.7, 124.3, 122.7, 120.8, 90.7, 77.9, 33.1, 25.8, 18.1, -4.1, -4.6; IR (thin film) 2927, 2854, 1727, 1629, 1609, 1579, 1469, 1396, 1329, 1272, 1186 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{23}\)H\(_{28}\)NO\(_3\)Si (M+H)\(^+\) 394.1838, found 394.1846; decomposed at 84-85 °C.
**α-oxygenated ketone 14aa:** General procedure K with 3-tert-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.060 g; 0.214 mmol), alkenyl boronic acid 1aa (0.076 g, 0.429 mmol), Cu(OAc)$_2$ (0.039 g, 0.214 mmol), Na$_2$SO$_4$ (0.224 g, 1.57 mmol), and pyridine (50 µL, 0.642 mmol) afforded 14aa as a white solid (0.053 g, 61%) and a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. $^1$H NMR (500 MHz; CDCl$_3$): δ 7.60-7.51 (m, 4H), 7.44-7.39 (m, 5H), 6.30 (s, 1H), 5.98 (s, 1H), 2.70-2.62 (m, 1H), 2.63-2.53 (m, 1H), 1.00 (t, $J$ = 7.2 Hz, 3H), 0.95 (s, 9H), 0.19 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 205.6, 168.3, 152.6, 134.4, 131.5, 130.1, 128.9, 128.8, 128.5, 128.7, 122.8, 120.7, 91.1, 83.5, 31.5, 25.9, 18.1, 7.1, 4.0, 4.5; IR (thin film) 2930, 2858, 1729, 1625, 1570, 1469, 1388, 1326, 1258, 1193, 1125 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{24}$H$_{32}$NO$_3$Si (M+H)$^+$ 410.2151, found 410.2144; decomposed at 80 °C.

**dr = >95:5**

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**dr = 80:20**
**α-oxygenated ketone 14ab:** General procedure K with 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.105 g; 0.375 mmol), alkenyl boronic acid 1ab (0.096 g, 0.750 mmol), Cu(OAc)$_2$ (0.068 g, 0.375 mmol), Na$_2$SO$_4$ (0.333 g, 2.34 mmol), and pyridine (90 μL, 1.125 mmol) afforded 14ab as a colorless liquid (0.083 g, 61%) and an 80:20 ratio of diastereomers after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. $^1$H NMR major diastereomer (500 MHz; CDCl$_3$): δ 7.52-7.47 (m, 2H), 7.39-7.34 (m, 2H), 5.93 (s, 1H), 5.23 (dd, $J = 13.9, 8.1$ Hz, 1H), 2.68-2.59 (m, 1H), 2.57-2.45 (m, 1H), 1.92-1.88 (m, 2H), 1.06-1.01 (m, 6H), 0.91 (s, 9H), 0.16 (s, 3H), -0.01 (s, 3H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): δ 209.0, 168.7, 152.5, 131.7, 130.0, 128.5, 122.7, 120.4, 90.9, 83.1, 31.5, 25.8, 24.8, 18.1, 9.7, 6.9, -4.0, -4.6; $^1$H NMR minor diastereomer (500 MHz; CDCl$_3$): δ 7.52-7.47 (m, 2H), 7.39-7.34 (m, 2H), 5.92 (s, 1H), 5.38 (q, $J = 6.9$ Hz, 1H), 2.68-2.59 (m, 1H), 2.57-2.45 (m, 1H), 1.64-1.57 (m, 1H), 1.53-1.50 (m, 1H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.06-1.03 (m, 3H), 0.93 (s, 9H), 0.19 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): δ 209.0, 168.7, 152.5, 131.7, 130.0, 128.5, 122.7, 120.4, 90.8, 82.9, 32.1, 25.9, 24.6, 18.2, 9.7, 7.2, -3.9, -4.5; IR (thin film) 2934, 2858, 1726, 1625, 1571, 1464, 1391, 1319, 1249, 1192, 1072 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{32}$NO$_3$Si (M+H)$^+$ 362.2151, found 362.2138.

![14ac](image)

**dr = 80:20**
**α-oxygenated ketone 14ac:** General procedure K with 3-t-butyldimethylsilyloxy-\(N\)-hydroxyisoindolinone 13 (0.100 g; 0.357 mmol), alkenyl boronic acid 1ac (0.111 g, 0.714 mmol), Cu(OAc)\(_2\) (0.065 g, 0.357 mmol), Na\(_2\)SO\(_4\) (0.373 g, 2.62 mmol), and pyridine (86.6 \(\mu\)L, 1.071 mmol) afforded 14ac as a clear oil (0.100 g, 72%) in a 80:20 ratio of diastereomers after purification using flash chromatography (1:4; ethyl acetate: hexanes) on fluorisil. \(^1\)H NMR major diastereomer (500 MHz; CDCl\(_3\)): \(\delta\) 7.56-7.51 (m, 2H), 7.44-7.40 (m, 2H), 5.96 (s, 1H), 5.28 (dd, \(J = 8.5, 4.3\) Hz, 1H), 2.65-2.58 (m, 1H), 2.53-2.46 (m, 1H), 1.95-1.80 (m, 2H), 1.67-1.50 (m, 4H), 1.00 (t, \(J = 7.5\) Hz, 3H), 0.93 (s, 9H), 0.89 (t, \(J = 7.5\) Hz, 3H), 0.18 (s, 3H), 0.01 (s, 3H); \(^{13}\)C NMR major diastereomer (125 MHz, CDCl\(_3\)): 208.8, 168.6, 152.5, 131.8, 130.0, 128.5, 122.8, 120.5, 90.9, 82.0, 40.2, 33.3, 25.8, 18.8, 18.7, 16.3, 13.8, 13.7, -4.0, -4.6; \(^1\)H NMR minor diastereomer (500 MHz; CDCl\(_3\)): \(\delta\) 7.56-7.51 (m, 2H), 7.44-7.40 (m, 2H), 5.94 (s, 1H), 5.23 (dd, \(J = 7.2, 5.2\) Hz, 1H), 2.65-2.58 (m, 1H), 2.53-2.46 (m, 1H), 1.97-1.89 (m, 2H), 1.54-1.48 (m, 2H), 1.33-1.36 (m, 2H), 1.07 (t, \(J = 7.6\) Hz, 3H), 0.96 (t, \(J = 7.6\) Hz, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR minor diastereomer (125 MHz, CDCl\(_3\)): \(\delta\) 208.8, 168.6, 152.5, 131.8, 129.9, 128.5, 122.7, 120.5, 90.6, 81.7, 40.6, 38.1, 25.9, 18.3, 18.1, 16.6, 13.9, 13.7, -3.8, -4.5; IR (thin film) 2960, 2934, 2855, 1736, 1628, 1574, 1398, 1375, 1242, 1198, 1123 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{22}\)H\(_{36}\)NO\(_3\)Si (M+H\(^+\)) 390.2464, found 390.2465.

![Structure](image-url)
**α-oxygenated ketone 14ad:** General procedure K with 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.049 g; 0.175 mmol), alkenyl boronic acid 1ad (0.0.40 g, 0.350 mmol), Cu(OAc)₂ (0.032 g, 0.175 mmol), Na₂SO₄ (0.183 g, 1.29 mmol), and pyridine (40 μL, 0.525 mmol) afforded 14ad as a colorless liquid (0.038 g, 68%) after purification using flash chromatography on florisil® (1:3; ethyl acetate: hexanes). <sup>1</sup>H NMR (500 MHz; CDCl₃): δ 7.51-7.39 (m, 4H), 5.94 (s, 1H), 2.18 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 0.94 (s, 9H), 0.22 (s, 3H), 0.10 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl₃): δ 207.7, 166.7, 152.2, 132.4, 129.9, 128.5, 122.6, 120.5, 90.8, 85.9, 25.9, 24.1, 23.6, 23.4, 18.2, -4.1, -5.0; IR (thin film) 2953, 2926, 2884, 2854, 1719, 1626, 1605, 1578, 1470, 1390, 1255, 1194 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₉H₃₀NO₃Si (M+H)<sup>+</sup> 348.1995, found 348.1994.

![Image of 14ae structure](image_url)

**dr = >95:5**

**α-oxygenated ketone 14ae:** General procedure K with 3-t-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.127 g; 0.454 mmol), alkenyl boronic acid 1ae (0.140 g, 0.909 mmol), Cu(OAc)₂ (0.082 g, 0.454 mmol), Na₂SO₄ (0.470 g, 3.30 mmol), and pyridine (110 μL, 1.362 mmol) afforded 14ae as a colorless liquid (0.101 g, 57%) and a single diastereomer after purification using flash chromatography (1:4; ethyl acetate: hexanes) on florisil®. <sup>1</sup>H NMR (500 MHz; CDCl₃): δ 7.56-7.54 (m, 1H), 7.50-7.48 (m, 1H), 7.43-
7.37 (m, 2H), 5.95 (s, 1H), 5.48 (dd, J = 8.5, 3.8 Hz, 1H), 2.74-2.69 (m, 1H), 2.52-2.39 (m, 1H), 2.25-2.19 (m, 1H), 2.15-2.08 (m, 1H), 2.02-2.01 (m, 2H), 1.87-1.83 (m, 1H), 1.61-1.53 (m, 4H), 1.45-1.37 (m, 1H), 0.92 (s, 9H), 0.14 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 212.7, 168.3, 152.5, 131.7, 129.9, 128.5, 122.7, 120.7, 91.0, 80.3, 41.2, 33.3, 28.1, 25.9, 25.8, 24.9, 23.2, 21.4, -4.0, -4.4; IR (thin film) 2933, 2852, 1724, 1414, 33.3, 28.1, 25.9, 25.8, 24.9, 23.2, 21.4, -4.0, -4.4; IR (thin film) 2933, 2852, 1724, 1622, 1573, 1466, 1395, 1326, 1241, 1186, 1125 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{22}$H$_{34}$NO$_3$Si (M+H)$^+$ 388.2308, found 388.2300.

II. Copper-Promoted Etherification of 3-$t$-butyldimethylsilyloxy-$N$-hydroxy isoindolinones with Monosubstituted Vinyl Boronic Acids (Table 2.5).

![Reaction Scheme](image)

**General procedure I**: A scintillation vial was charged with 3-$t$-butyldimethylsilyloxy-$N$-hydroxyisoindolinone 13 (1 equiv), vinyl boronic acid 1 (2 equiv), Cu(OAc)$_2$ (1 equiv), and anhydrous Na$_2$SO$_4$ (4-6 equiv). These solids were then diluted with 1,2-dichloroethane to form a 0.1 M solution of 3-$t$-butyldimethylsilyloxy-$N$-hydroxyisoindolinone. Pyridine (3 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 ºC for 12 h. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (1:19 - 1:2; ethyl acetate:hexanes) to give $N$-enoxy isoindolinones 31.
**N-enoxisoindolinone 31d:** General procedure L with 3-tert-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.164 g; 0.586 mmol), E-1-hexen-1-yl boronic acid 1d (0.150 g, 1.17 mmol), Cu(OAc)$_2$ (0.106 g, 0.586 mmol), Na$_2$SO$_4$ (0.507 g, 3.56 mmol), and pyridine (143 µl, 1.76 mmol) afforded 31d as a colorless liquid (0.174 g, 82%) after purification using flash chromatography on silica gel (1:4; ethyl acetate: hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.79 (d, $J = 7.4$ Hz, 1H), 7.61 (dd, $J = 7.6, 7.4$ Hz, 1H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 6.45 (d, $J = 12.3$ Hz, 1H), 5.98 (s, 1H), 5.26 (td, $J = 12.3, 7.4$ Hz, 1H), 1.96-1.92 (m, 2H), 1.33-1.29 (m, 4H), 0.95 (s, 9H), 0.86 (t, $J = 6.9$ Hz, 3H), 0.27 (s, 3H), 0.20 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 165.1, 147.1, 142.1, 133.2, 129.8, 128.7, 123.8, 123.1, 107.4, 82.5, 32.0, 26.5, 25.6, 22.1, 18.0, 13.8, -4.3, -4.5; IR (thin film) 2955, 2928, 2857, 1740, 1667, 1466, 1361, 1252, 1203, 1117 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{32}$NO$_3$Si (M+H)$^+$ 362.2151, found 362.2142.

**N-enoxisoindolinone 31af:** General procedure L with 3-tert-butyldimethylsilyloxy-N-hydroxyisoindolinone 13 (0.078 g; 0.277 mmol), Z-1-propen-1-yl boronic acid 1af
(0.048 g, 0.555 mmol), Cu(OAc)\(_2\) (0.050 g, 0.277 mmol), Na\(_2\)SO\(_4\) (0.290 g, 2.04 mmol), and pyridine (70 µl, 0.831 mmol) afforded 31af as a white solid (0.061 g, 69%) after purification using flash chromatography on silica gel (1:4; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.81 (d, \(J = 7.5\) Hz, 1H), 7.63 (t, \(J = 7.5\) Hz, 1H), 7.52 (t, \(J = 7.5\) Hz, 1H), 7.46 (d, \(J = 7.5\) Hz, 1H), 6.39 (dd, \(J = 6.9, 1.4\) Hz, 1H), 6.01 (s, 1H), 4.60 (p, \(J = 6.9\) Hz, 1H), 1.71 (dd, \(J = 6.9, 1.4\) Hz, 3H), 0.97 (s, 9H), 0.29 (s, 3H), 0.22 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 165.3, 148.7, 142.0, 133.3, 129.8, 128.7, 123.8, 123.1, 101.9, 82.8, 25.6, 18.1, 9.3, -4.5, -4.5; IR (thin film) 2928, 2857, 1738, 1669, 1617, 1470, 1353, 1252, 1116, 1071 cm\(^{-1}\); HRMS (ESI) m/z calcd. for C\(_{17}\)H\(_{26}\)NO\(_3\)Si (M+H\(^+\)) 320.1682, found 320.1683; mp 50 ºC.

N-enoxyisoindolinone 31g: General procedure L with 3-\(t\)-butyldimethylsilyloxy-\(N\)-hydroxyisoindolinone 13 (0.060 g; 0.214 mmol), 1-phenylvinyl boronic acid 1g (0.064 g, 0.429 mmol), Cu(OAc)\(_2\) (0.039 g, 0.214 mmol), Na\(_2\)SO\(_4\) (0.224 g, 1.58 mmol), and pyridine (50 µl, 0.642 mmol) afforded 31g as a colorless liquid (0.078 g, 96%) after purification using flash chromatography on silica gel (1:4; ethyl acetate: hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.97-7.95 (m, 1H), 7.87-7.86 (m, 1H), 7.72-7.65 (m, 3H), 7.57-7.37 (m, 4H), 6.17 (s, 1H), 4.88-4.86 (m, 2H), 0.95 (s, 9H), 0.25 (s, 3H), 0.12 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 165.0, 159.8, 142.5, 133.3, 133.2, 129.9, 129.0, 128.8, 128.6, 128.2, 125.9, 123.9, 123.3, 82.8, 25.6, 18.0, -4.4, -4.5; IR (thin film) 2955,
III. Thermal Rearrangement of N-Enoxysindolinones (Table 2.6).

**General Procedure M:** A J-Young tube was charged with a 0.1 M solution of N-enoxysindolinone 31 (1 equiv) in Toluene-$d_8$. The reaction mixture was heated to 50-90 °C for 3-8 h. Toluene-$d_8$ was removed from the reaction mixture under vacuum and imidate 14 was isolated as an oil.

\[
\begin{array}{c}
\text{OTBS} \\
\text{R}_1 \text{O} \equiv \text{N} \\
\text{R}_2 \\
\text{31}
\end{array} 
\xrightarrow{\text{Toluene-}d_8, 50-90 \degree \text{C, 3-8 h}}
\begin{array}{c}
\text{OTBS} \\
\text{R}_1 \text{O} \equiv \text{N} \\
\text{R}_2 \\
\text{14}
\end{array}
\]

**α-oxygenated aldehyde 14d:** General procedure M was followed with 31d (0.040 g, 0.130 mmol). Heating the reaction mixture to 50 °C for 3 h afforded imidate 14d (0.040 g, >95% recovery) as a yellow oil and a single disatereomer. \(^1\)H NMR (500 MHz; C\(_6\)D\(_6\)):

δ 9.51 (s, 1H), 7.28-7.37 (m, 1H), 7.38-6.99 (m, 3H), 5.92 (s, 1H), 5.11-5.08 (m, 1H), 1.68-1.66 (m, 2H), 1.24-1.21 (m, 4H), 1.03 (s, 9H), 0.83 (t, \(J = 5.0 \text{ Hz}, 3\)H), 0.29 (s, 3H),
0.16 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 198.6, 168.6, 152.3, 131.5, 129.8, 128.7, 122.7, 120.2, 91.1, 81.7, 29.2, 27.1, 25.7, 22.4, 18.1, 13.6, -4.0, -4.9; IR (thin film) 2955, 2929, 2858, 1738, 1576, 1400, 1379, 1254, 1122, 1075 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{32}$NO$_3$Si (M+H)$^+$ 362.2151, found 362.2139.

[Diagram of 14af]

**dr = 75:25**

**α-oxygenated aldehyde 14af:** General procedure M was followed with 31af (0.030 g, 0.093 mmol). Heating the reaction mixture to 65 ºC for 3 h afforded imidate 14af (0.030 g, >95% recovery) as a yellow oil and a 75:25 mixture of diastereomers. $^1$H NMR major diastereomer (500 MHz; C$_6$D$_6$): δ 9.40 (s, 1H), 7.36-7.33 (m, 2H), 7.07-6.99 (m, 2H), 5.87 (s, 1H), 5.12 (q, $J = 7.0$ Hz, 1H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.03 (s, 9H), 0.28 (s, 3H), 0.17 (s, 3H); $^{13}$C NMR major diastereomer (125 MHz, CDCl$_3$): δ 197.9, 168.3, 152.9, 131.5,129.7, 128.2, 122.7, 120.3, 90.8, 77.9, 25.7, 19.5, 14.2, -3.9, -4.8; $^1$H NMR minor diastereomer (500 MHz; C$_6$D$_6$): δ 9.45 (s, 1H), 7.36-7.33 (m, 2H), 7.11-7.08 (m, 2H), 5.90 (s, 1H), 5.07 (q, $J = 8.1$ Hz, 1H), 0.81 (d, $J = 8.1$ Hz, 3H), 1.02 (s, 9H), 0.15(s, 3H), 0.02 (s, 3H); $^{13}$C NMR minor diastereomer (125 MHz, CDCl$_3$): δ 198.4, 168.3, 149.2, 132.4, 129.3, 127.8, 123.4, 120.3, 91.0, 82.6, 25.5, 18.1, 14.2, -3.9, -4.7; IR (thin film) 2929, 2885, 2856, 1708, 1626, 1574, 1470, 1399, 1253, 1195, 1118 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{17}$H$_{26}$NO$_3$Si (M+H)$^+$ 320.1682, found 320.1689.
**a-oxygenated aldehyde 14g:** General procedure M was followed with 31g (0.070 g, 0.183 mmol). Heating the reaction mixture to 80 °C for 6 h afforded imidate 14g (0.066 g, 94% recovery) as a yellow oil. $^1$H NMR (500 MHz; C$_6$D$_6$): $\delta$ 7.72-7.72 (m, 3H), 7.50-7.49 (m, 1H), 7.37-7.36 (m, 1H), 7.13-7.07 (m, 4H), 5.92 (s, 1H), 5.32 (d, $J = 7.1$ Hz, 2H), 0.99 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 191.2, 168.6, 153.1, 135.0, 132.7, 129.5, 128.2, 128.1, 127.6, 124.5, 122.5, 120.5, 90.9, 69.1, 25.7, 18.0, -3.9, -4.6; IR (thin film) 2927, 2855, 1707, 1685, 1628, 1598, 1471, 1390, 1249, 1189 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{22}$H$_{28}$NO$_3$Si (M+H)$^+$ 382.1838, found 382.1841.

V. **Functionalization of Imidates**

**2-chloro-2,3-dihydro-1H-inden-1-one 32:** To the imidate 14z (0.040 g, 0.101 mmol) in CCl$_4$ (2 ml) was added the oxalyl chloride (8 µl, 0.101 mmol) and the reaction stirred at room temperature for 12 h. The volatiles were removed in vaccuo and the crude reaction mixture was purified by medium pressure chromatography on silica gel with 1:4 ethyl acetate:hexanes to give 32 as an amorphous white solid (0.012 g, 74 %). $^1$H NMR (500
NMR (125 MHz; CDCl$_3$): $\delta$ 7.84-7.83 (m, 1H), 7.68-7.66 (m, 1H), 7.47-7.43 (m, 2H), 4.56 (dd, $J = 7.3$, 3.8 Hz, 1H), 3.78 (dd, $J = 17.4$, 7.3 Hz, 1H), 3.30 (dd, $J = 17.4$, 3.8 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.2, 150.7, 136.1, 133.8, 128.3, 126.4, 125.1, 55.7, 37.5; IR (thin film) 2956, 2954, 1767, 1726, 1609, 1578, 1470, 1429, 1324, 1277, 1158 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_3$H$_8$OCl (M+H)$^+$ 167.0264, found 167.0273.

2-hydroxy-2,3-dihydro-1H-inden-1-one 33: To a solution of the imidate 14z (0.030 g, 0.076 mmol) in MeOH:H$_2$O (2 ml, 1:1) was added NH$_4$Cl (0.007 g, 0.125 mmol) and the reaction heated to 90 °C for 2 h. MeOH was removed under reduced pressure and the residue was extracted with EtOAc (3 x 7 ml). The organic layer was dried with MgSO$_4$ and concentrated in vacuo. The crude reaction mixture was purified by medium pressure chromatography on silica gel with 1:2 ethyl acetate:hexanes to give 33 as an amorphous white solid (0.006 g, 53 %). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.78-7.76 (m, 1H), 7.66-7.64 (m, 1H), 7.47-7.46 (m, 1H), 7.42-7.39 (m, 1H), 4.54 (dd, $J = 7.8$, 5.1 Hz, 1H), 3.58 (dd, $J = 16.5$, 7.8 Hz, 1H), 3.02 (dd, $J = 16.5$, 5.1 Hz, 1H), 2.92 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 206.3, 150.8, 135.8, 134.0, 128.1, 126.8, 124.4, 74.3, 35.1; IR (thin film) 3469, 2982, 1732, 1609, 1470, 1366, 1299, 1252, 1154, 1047 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_3$H$_8$O (M)$^+$ 148.0524, found 148.0531.
3-((t-butyldimethylsilyl)oxy)isoindolinone 34: To a solution of the imidate 14z (0.030 g, 0.076 mmol) in MeOH:H₂O (2 ml, 1:1) was added NH₄Cl (0.007 g, 0.125 mmol) and the reaction heated to 90 °C for 2 h. MeOH was removed under reduced pressure and the residue was extracted with EtOAc (3 x 7 ml). The organic layer was dried with MgSO₄ and concentrated in vacuo. The crude reaction mixture was purified by medium pressure chromatography on silica gel with 1:1 ethyl acetate:hexanes to give 34 as an amorphous white solid (0.006 g, 53 %) ¹H NMR (500 MHz; CDCl₃): δ 7.81-7.79 (m, 1H), 7.60-7.58 (m, 1H), 7.52-7.49 (m, 2H), 6.49 (bs, 1H), 6.12 (s, 1H), 0.93 (s, 9H), 0.16 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 169.5, 146.2, 134.2, 132.5, 129.5, 123.6, 123.4, 79.2, 25.6, 17.9, -4.0, -4.1; IR (thin film) 3209, 3099, 2931, 2855, 1685, 1609, 1473, 1435, 1350, 1255, 1104 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₂₂NO₂Si (M)+ 264.1420, found 264.1419.

VI. Transfer of Chirality
**N-(allyloxy)isoindoline-1,3-dione 36:** To the N-hydroxyphthalimide 2 (1 g, 6.13 mmol) in DMF (6 ml) at 0 °C was added DBU (1.5 equiv, 1.4 ml, 9.19 mmol) followed by allyl bromide (1.5 equiv, 0.80 ml, 9.19 mmol). The reaction was then stirred at room temperature for 2 h. Water was added to the reaction mixture and it was extracted with CH₂Cl₂ (3 x 20 ml). The organic layer was dried with MgSO₄ and the solvent removed under reduced pressure to give 36 as a white solid (1.2 g, 94 %) which did not require further purification. ¹H NMR (500 MHz; CDCl₃): δ 7.83-7.81 (m, 2H), 7.75-7.73 (m, 2H), 6.14-6.08 (m, 1H), 5.36 (dd, J = 23.0, 5.8 Hz, 2H), 4.69 (d, J = 6.7 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 163.7, 134.4, 131.2, 128.8, 123.5, 122.5, 78.8; IR (thin film) 2943, 1789, 1720, 1606, 1464, 1420, 1375, 1350, 1186, 1113 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₁H₁₀NO₃ (M+H)⁺ 204.0661, found 204.0664; mp 57 °C.

**3-hydroxy-N-allyloxyisoindolinone 37:** To an oven dried 25 ml round bottom flask was added the RuCl(μ-cymene)[(R,R)-TsDPEN] (0.01 equiv, 15 mg) under a N₂ atmosphere followed by CH₂Cl₂ (7 ml). The N-(allyloxy)isoindoline-1,3-dione 36 (0.500 g, 2.46 mmol) was then added followed by Et₃N (4.8 equiv, 1.5 ml, 11.8 mmol) and a dropwise addition of HCO₂H (5 equiv, 0.5 ml, 12.3 mmol) all under a N₂ atmosphere. The reaction was then stirred at room temperature for 19 h. The volatiles were removed under reduced pressure and the residue purified by medium pressure chromatography on silica gel (1:1 ethyl acetate:hexanes) to give 37 as a white solid (0.400 g, 40 %). ¹H NMR (500 MHz;
CDCl$_3$: $\delta$ 7.60-7.59 (m, 1H), 7.58-7.44 (m, 2H), 7.46-7.40 (m, 1H), 6.06-6.01 (m, 1H), 5.88 (s, 1H), 5.61 (bs, 1H), 5.31-5.19 (m, 2H), 4.61 (d, $J = 3.8$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 165.2, 141.2, 132.9, 132.4, 129.7, 128.9, 123.4, 123.2, 120.4, 82.5, 78.2; IR (thin film) 3275, 2938, 1679, 1638, 1609, 1460, 1381, 1312, 1214, 1148, 1065 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{11}$H$_{12}$NO$_3$ (M+H)$^+$ 206.0817, found 206.0822; mp 110 ºC.

**Determination of er:** The 3-hydroxy-N-allyloxyisoindolinone 37 (0.010 g, 0.052 mmol) was dissolved in CH$_2$Cl$_2$ (0.5 ml). DCC (1.3 equiv, 0.014 g, 0.068 mmol) was added followed by (R)-(+) -methoxy-α-trifluoromethylphenylacetic acid (1.3 equiv, 0.016 g, 0.068 mmol) and a few crystals of DMAP. The reaction was stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the residue purified by medium pressure chromatography on silica gel (1:2 ethyl acetate:hexanes) to give the product as a white solid. $^1$HNMR analysis revealed that the product was a 2.1:1 mixture of enantiomers.

3-t-butyldimethylsilyloxy-N-allyloxyisoindolinone: To a solution of the 3-hydroxy-N-allyloxyisoindolinone 37 (0.200 g, 1.05 mmol) in CH$_2$Cl$_2$ (4 ml) at 0 ºC was added imidazole (1.1 equiv, 0.077 g, 1.15 mmol) followed by TBSCI (1.1 equiv, 0.173 g, 1.15 mmol). The reaction was allowed to warm up to room temperature and stirred at that temperature for 10 h. The reaction was quenched with NH$_4$Cl and extracted with EtOAc (3 x 20 ml). The organic layer was washed with water and dried with MgSO$_4$. The crude
reaction mixture was purified by medium pressure chromatography on silica gel with 1:3 ethyl acetate:hexanes to give the 3-\textit{t}-butyldimethylsilyloxy-\textit{N}-allyloxyisoindolinone as an amorphous white solid (0.302 g, 90 %). \textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}): \(\delta\) 7.79-7.78 (m, 1H), 7.59-7.57 (m, 1H), 7.51-7.48 (m, 1H), 7.43-7.42 (m, 1H), 6.13-6.09 (m, 1H), 5.97 (s, 1H), 5.39 (dd, \(J = 17.2, 1.2\) Hz, 1H), 5.31 (dd, \(J = 11.1, 1.2\) Hz, 1H), 4.75 (dd, \(J = 11.1, 7.1\) Hz, 1H), 4.64 (dd, \(J = 11.1, 6.0\) Hz, 1H), 0.97 (s, 9H), 0.30 (s, 3H), 0.24 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 165.1, 141.8, 132.8, 132.1, 129.7, 129.5, 123.5, 123.5, 122.9, 120.2, 82.4, 77.8, 25.6, 18.0, -4.2, -4.3; IR (thin film) 2953, 2931, 2858, 1726, 1467, 1359, 1255, 1198, 1119, 1069 cm\textsuperscript{-1}; HRMS (ESI) m/z calcd. for C\textsubscript{17}H\textsubscript{26}NO\textsubscript{3}Si (M+H)\textsuperscript{+} 320.1682, found 320.1681.

3-\textit{t}-butyldimethylsilyloxy-\textit{N}-hydroxyisoindolinone 44: The barbituric acid (2 equiv, 0.024 g, 0.187 mmol) was mixed with 3-\textit{t}-butyldimethylsilyloxy-\textit{N}-allyloxyisoindolinone (0.030 g, 0.093 mmol) in a 25 ml round bottom flask, Pd(PPh\textsubscript{3})\textsubscript{4} (5 mol \%, 0.005 g, 4.6 \(\mu\)mol) was added to the flask under an atmosphere of N\textsubscript{2}. MeOH (0.8 ml) was added last and the reaction stirred under N\textsubscript{2} atmosphere for 1.5 h after which the MeOH was removed under reduced pressure. EtOAc was added to the reaction and it was extracted with saturated Na\textsubscript{2}CO\textsubscript{3} (8 x 10 ml) to remove all the excess barbituric acid. The organic layer was dried with MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The crude reaction mixture was
purified by medium pressure chromatography on silica gel with 2:1 ethyl acetate:hexanes to give 44 as an white solid (0.020 g, 77 %). The spectral data matches 13.

**Imidate 45z:** Same procedure as that for 14z. The spectral data matches 14z.

**2-hydroxy-2,3-dihydro-1H-inden-1-one 46:** The spectral data matches 33 above.

**Determination of er:** The 2-hydroxy-2,3-dihydro-1H-inden-1-one 46 (0.008 g, 0.053 mmol) was dissolved in CH₂Cl₂ (0.4 ml). DCC (1.3 equiv, 0.014 g, 0.069 mmol) was added followed by (R)-(+)-%methoxy-%trifluoromethylphenylacetic acid (1.3 equiv, 0.017 g, 0.069 mmol) and a few crystals of DMAP. The reaction was stirred at room temperature for 14 h. The solvent was removed under reduced pressure and the residue purified by medium pressure chromatography on silica gel (1:3 ethyl acetate:hexanes) to give the product as a white solid. ¹HNMR analysis revealed that the product was a 1:0.75 mixture of enantiomers.
Chapter 3- Introduction to Lipids and Environment-Sensitive Fluorescent Probes

3.1 Lipids

A lipid bilayer forms the outer stratum in a eukaryotic cell and divides the cell into different structural and functional identities. Lipids, which are an integral part of the cell membrane; control a myriad of cellular processes. Lipid constituents regulate processes such as signal transduction, endomembrane transport, cell proliferation, apoptosis and metabolism. Many lipids serve as site specific membrane signals that regulate the activity of membrane and soluble proteins. Lipids also confer unique dielectric and permeability properties to the cell membrane.

![Lipid Bilayer](https://www.uoguelph.ca/~fsharom/research/research.html)

**Figure 3.1: Lipid Bilayer**

Taken from [www.uoguelph.ca/~fsharom/research/research.html](http://www.uoguelph.ca/~fsharom/research/research.html)

Lipids are generally made up of non-polar fatty acid chains with a phosphate polar head group. They are therefore referred to as phospholipids. Phospholipids make up about 70% of the total lipid content of a mammalian cell. The remaining 30% consists of cholesterol, sphingomyelin and glycopospholipids.
Figure 3.2 depicts the structure of the phospholipid; Phosphatidylcholine. As shown in the figure, the long chain fatty acid has a glycerol backbone which is bound to a phosphate moiety through the free primary alcohol of the glycerol unit. This structure comprising the long chain fatty acid, the glycerol backbone and the phosphate is present in all phospholipids. The phospholipids vary at the group connected to one of the oxygen atoms of the phosphate moiety. When a choline group is bound to the phosphate, the phospholipid is known as Phosphatidylcholine. Instead of a choline, if a serine group is bound to the phosphate, the lipid is known as Phosphatidylserine.\(^{113}\)

![Figure 3.2: Structure of the phospholipid – Phosphatidylcholine](http://hrsbstaff.ednet.ns.ca/)

Among the phospholipids found in the cell membrane, choline containing lipids such as phosphatidylcholine (PC) and sphingomyelin are found in the exoplasmic region of the cell membrane and the aminophospholipids including phosphatidylserine (PS) and phosphatidylethanolamine occur in the cytosolic part of the cell membrane (Figure 3.3).\(^{115}\)
In the phospholipids, PC is the most prevalent and accounts for 40-50% of the total lipid content. Phosphatidylethanolamine (PE) is about 20-45% depending on the type of tissue. Phosphatidylinositol, Phosphatidylserine (PS) and Phosphatidic acid are present in lesser amounts. Although PS is a relatively minor constituent of the cell membrane, its low abundance is outweighed by its physiological properties.

### 3.2 Phosphatidylserine (PS)

Phosphatidylserine was first isolated by Folch and co-workers in 1942. Phosphatidylserine is a phospholipid that is comprised of a long chain fatty acid, a glycerol backbone and the polar head group which consists of phosphate functionality bound to a serine moiety as shown in Figure 3.4. The fatty acid chains in PS vary among different cell types and organelles.
PS is an anionic phospholipid with three ionizable groups; the phosphate functional group, the amino moiety and the carboxylate. PS usually chelates to a Ca ion through the oxygen atoms of the phosphate and the carboxylate. This results in a change in the conformation of the polar head group from linear to cyclic. The chelation is important for some of the biological functions of PS, especially bone formation.

3.2.1 Functions of PS

Since PS is the predominant anionic species on the surface of the lipid, it confers a negative charge on the inner leaflet of the plasma membrane which helps in the binding of polycations and proteins with cationic clusters. This is a mode of protein recruitment for several regulatory and structural proteins such as protein kinase C, annexin, and spectrin. One of the most important functions of PS is in the regulation of apoptosis. When cells undergo programmed cell death, PS moves to the exoplasmic region where it acts as a trigger for macrophage recognition which facilitates the removal of the apoptotic cells (Figure 3.5).
Thus, PS facilitates removal of apoptotic cells and their potentially toxic components in a non-inflammatory manner. This function of PS is especially important for the development of the lungs and the brain and in processes where apoptosis plays an important role.\textsuperscript{132}

PS is responsible for the key signal that starts the coagulation cascade eventually leading to the clotting of blood.\textsuperscript{133} When activated, platelets present in blood expose PS on their outer surface. This exposure of PS triggers the attachment of clotting factors and prothrombin to the platelets. These prothrombinase complexes promote coagulation.\textsuperscript{134} A dysfunction in these PS associated processes can lead to cancer, chronic autoimmunity and infections.\textsuperscript{135} It is therefore imperative to develop a method that allows for the detection, monitoring and quantification of PS and other lipids to understand these complex membrane-mediated biological processes.

### 3.3 Conventional Methods for Lipid Analysis

Conventional methods for the characterization and analysis of lipids involve a physical separation of lipids from cells using a liquid-liquid extraction\textsuperscript{136} or
saponification of the lipid. Thin-layer chromatography is used to separate the lipids into phospholipid classes which can then be derivatized, acetylated using radioactive acetic anhydride, oxidized or measured by colorimetric analysis. These approaches lack the sensitivity required for the analysis of subcellular membranes and are time consuming. More recently, chromatography followed by mass spectroscopy such as GC-MS, LC-MS and nano ESI-FTMS has been used for lipid fingerprinting and classification. These methods, however, involve the isolation of the lipid from the cell and hence do not provide a spatiotemporal in situ quantification of lipid molecules. Also, lipid lability may lead to low reproducibility in sample preparation.

3.4 Fluorescent Probes

The in situ detection of PS in intact cells could potentially be the most effective method for the understanding of lipid mediated processes. Fluorescent probes have been utilized for this purpose. The unique features of fluorescence techniques in comparison with other methods that are capable of monitoring lipid-protein interactions (NMR, FTIR, etc.) are their ultimate sensitivity up to a single-molecule level and their ability to operate in biological systems of varying complexity. Fluorescent probes provide information on the properties of their molecular environment directly by changing their fluorescence characteristics (wavelength maximum, fluorescence intensity, and/or fluorescence lifetime).

The change in the fluorescence signal from light to dark (or the reverse), at a single wavelength, is usually recorded as the change in fluorescence intensity. Because the change in fluorescence intensity can be easily observed, high spectral resolution in
these measurements is not needed. Fluorescence quenching/enhancement is commonly used in different sensing and imaging technologies. Small fluorescent probes or nanoparticles are either covalently conjugated to molecules of interest (such as lipids, proteins and RNA) or used as stains to detect the target compounds (lipids, DNA). In cellular research, these probes can penetrate spontaneously into the cell and label genetically prepared protein binding sites. The labeled proteins can thus be detected as they move through the cytoplasm of the cell (Figure 3.6). This is useful in monitoring the interactions of the proteins with various other sub-cellular components and studying the downstream events of such interactions.

Figure 3.6: Fluorescent Probe Attached to a Protein can be used to monitor the Interactions of the Protein with Lipids. Taken from: http://books.google.com/books “Introduction to Fluorescence Sensing” by Alexander P. Demchenko
Figure 3.7: Real Lifetime Images of Cells in which a Labeled Protein has bound to the Cell Membrane. Taken from: http://books.google.com/books “Introduction to Fluorescence Sensing” by Alexander P. Demchenko

Cell Imaging can be carried out by using a fluorescent probe which is used to bind to a protein. When this labeled protein binds to the cell membrane, the membrane begins to fluoresce, and thus this method can be used for imaging to cells under a microscope (Figure 3.7).

3.5 Environmentally Sensitive Fluorescent Probes

Environment sensitive fluorophores are being used for cell imaging and detection of cellular components. These probes provide information on the properties of their molecular environment directly by changing their fluorescence characteristics (wavelength maximum, fluorescence intensity, and/or fluorescence lifetime). Since we were using the environmentally sensitive fluorescent probes to detect lipid-protein interactions, it was important to understand the membrane properties and how they are reflected in the spectroscopic response of the fluorescent probes.
Microviscosity of lipid membranes (the reciprocal to fluidity) is the measure of frictional resistance to the rotational and translational motion of molecules.\textsuperscript{151} Membrane microviscosity can be estimated by fluorescence anisotropy of rod shaped probes (typically diphenylhexatriene (DPH)), which is a consequence of their rotational motion in the membrane.\textsuperscript{152} Microviscosity could also be measured by the fluorescence intensity of molecular rotors. Molecular rotors are fluorophores that exhibit strong variations in their fluorescence quantum yield depending on their intramolecular rotation, which is in turn dependent on the viscosity of the environment of the rotor. In more viscous media the rotations of the molecular rotor are slowed down, which increases the fluorescence intensity of the fluorophore. After they are incorporated into lipid membranes, these fluorophores monitor the microviscosity of their surroundings at their sites of location.\textsuperscript{153}

The polarity of lipid membranes is a property addressed with the use of fluorescent probes.\textsuperscript{154,155} Initially, the absorption and emission spectra of a probe are measured as a function of polarity by using a solution of the probe in organic solvents of varying polarities. Since the probes are environmentally sensitive, there should be a shift in the emission spectrum of the fluorophore as the polarity of the organic solvents changes from polar to non-polar and this shift can be expressed in empirically established units.\textsuperscript{156} The shift in fluorescence emission is because of the difference in the energies of the fluorophore ground and excited states, which can vary based on the dipole-dipole interactions of the probe with its environment. The effect of the solvent polarity on fluorescence emission is shown below.
After the fluorophore has been excited to higher vibrational levels of the first excited singlet state ($S(1)$), excess vibrational energy is rapidly lost to surrounding solvent molecules. This results in the relaxation of the fluorophore to the lowest vibrational energy level (occurring in the picosecond time scale). Solvent molecules then reorient their dipole around the excited fluorophore, thus assisting in stabilizing and further lowering the energy level of the excited state of the fluorophore. This process is known as Solvent Relaxation (Figure 3.8). The solvent relaxation is a slower process that requires between 10 and 100 picoseconds and has the effect of reducing the energy separation between the ground and excited states of the fluorophore, which in turn results in a red shift (to longer wavelengths) of the fluorescence emission. Increasing the solvent polarity produces a correspondingly larger reduction in the energy level of the excited state, while decreasing the solvent polarity reduces the solvent effect on the excited state.
energy level. The polarity of the fluorophore also determines the sensitivity of the excited state to solvent effects.\textsuperscript{156,157}

Polarity sensing in membranes is an attempt to transfer this concept from the emission in organic solvents to the highly anisotropic structure of lipid bilayers. Thus, a fluorescent probe will exhibit a shift in its emission spectrum or intensity of emission when it moves from the aqueous polar environment of the cytoplasm of the cell to the non-polar environment of a lipid membrane. This is because the low polarity of the lipid molecules will not effectively stabilize the excited state of the fluorophore. This will lead to a larger energy gap between the ground and excited states of the fluorophore, resulting in emission at shorter wavelengths (blue shift).\textsuperscript{103} It is because of this process that a more widely used class of environment-sensitive fluorophores consists of solvatochromic dyes that exhibit shifts in their emission spectra as a function of properties such as the polarity and hydration of their environment. These fluorescent probes exhibit strong changes in dipole moments upon electronic excitation. Dipole-dipole and specific H-bonding interactions of the dyes with their surroundings change the energy of the probe electronic transitions and thus shift the maxima of their excitation and emission spectra.\textsuperscript{103} Typical examples of such dyes are NBD, Prodan, 7-(dialkylamino)-coumarin, and Nile Red as shown in Scheme 3.1.
Scheme 3.1: Structures of Solvatochromic Probes

In these fluorophores, the dipole moment increases dramatically upon electronic excitation due to an intramolecular charge transfer (ICT) from the electron donating dialkylamino group to the electron accepting carbonyl group as represented in Scheme 3.2.

Scheme 3.2: ICT in Prodan

As a result, these dyes exhibit a red shift of their emission spectrum in response to an increase in solvent polarity and the relaxation rates of their surroundings.\(^{158}\) Moreover, an additional strong red shift of the Prodan emission is connected with H-bonding to H-bond donor molecules in the environment.\(^{159}\) Such effects are typical for environment-sensitive
dyes that contain H-bond acceptor groups (such as carbonyl), which are of particular interest for studying membrane hydration. Electrochromic dyes operate by the same photophysical principle as solvatochromic dyes, namely, a strong ICT upon electronic excitation. They are commonly rod-shaped molecules that bear electron donor and acceptor groups on two opposite sides such as the styryl pyridinium dyes (Scheme 3.1).\textsuperscript{160} In these probes, the excitation spectra are also affected by the solvation of the highly polar ground states, which results in a blue-shift of the excitation spectra depending on the composition of the lipid that they are inserted in to.\textsuperscript{161,162}

### 3.6 Conclusion

Environment-sensitive fluorescent probes are important tools for gleaning information about the structure and dynamics in biomembranes. The main advantage of such a probe is the response to change in polarity via a blue shift or increase in intensity. We hypothesized that by taking assistance of this property, we could design a library of environmentally sensitive, thiol reactive fluorescent probes that could be used for the \textit{in situ} determination and quantification of PS in the cell. This would allow us to monitor and understand the complex PS mediated processes and develop a solution for the ailments caused by a dysfunction in these processes.
Chapter 4 – Development of New Environment Sensitive Fluorescent Probes for Lipid-Protein Interactions

4.1 Abstract

Lipids, which are found in cell membranes, control a number of cellular processes through their interactions with proteins. Fluorescent probes have been used to monitor these lipid protein interactions, to gain a better understanding of the complex membrane mediated processes. Commercially available fluorophores utilized for this purpose have several limitations such as photobleaching, damage to cells and difficulty in derivatization. In order to overcome these limitations, a new family of environmentally sensitive fluorescent probes has been synthesized which could be used for the detection and quantification of phosphatidylerine in the cell. These new compounds have low emission in water and very intense emission in hydrophobic solvents making them perfect “turn-on” thiol reactive probes for protein-lipid interactions. Assay results have shown that the new fluorophore can bind irreversibly with a cysteine on the C1B domain of the protein PKCy. This labeled protein then binds to the phosphatidylerine lipid, wherein the fluorescent probe senses a change in its environment from aqueous polar to lipid non-polar, and hence exhibits an increase in the intensity of emission. These new fluorophores have also been used for the imaging of the cell.
4.2 Introduction

The cell membrane is a biological membrane that separates the interior of a cell from the outside environment. In addition to regulating the movement of substances in and out of a cell, the biological function of a cell membrane affects the fundamental physicochemical properties of the cell. The membrane electrostatics, phase state, hydration, and dynamics determine the structure of the cell and control the binding and transport of molecular and ionic species. Cellular membranes are responsible for the correct insertion, proper folding, and functioning of membrane proteins.

Cellular membranes are made up of phospholipids. Among the phospholipids found in the cell membrane, choline containing lipids such as phosphatidylcholine (PC) and sphingomyelin are found in the exoplasmic region of the cell membrane and the aminophospholipids including phosphatidylserine (PS) and phosphatidylethanolamine occur in the cytosolic part of the cell membrane. Although PS is a relatively minor component of most biological membranes, it plays several important roles. A dysfunction in these PS associated processes can lead to cancer, chronic autoimmunity and infections. It is therefore imperative to develop a method that allows for the quantification of PS and other lipids to understand the complex membrane mediated biological processes.

Fluorescent techniques have become popular in the recent years for monitoring lipid processes. The unique features of fluorescence techniques in comparison with other tools that are capable of monitoring these properties (NMR, FTIR, EPR) are their ultimate sensitivity and their ability to operate in biological systems without involving isolation of the lipid membranes. Fluorescent probe approaches, especially
environmentally sensitive fluorophores, provide information on the properties of their environment directly by changing their fluorescence characteristics such as wavelength maximum, fluorescence intensity, and fluorescence lifetime.\textsuperscript{177}

The \textit{in situ} quantitative imaging of cellular lipids with a fluorescent probe has been reported by the Cho group in 2011.\textsuperscript{178} They engineered the epsin \textit{N}-terminal homology (ENTH) domain of membrane protein epsin 1,\textsuperscript{179-181} and labeled it with the commercially available, environmentally sensitive fluorescent probe, 2-dimethylamino-6-acyl-naphthalene (DAN).\textsuperscript{182} When the protein labeled with the polarity sensitive fluorophore was bound to the lipid, [phosphatidylinositol-4,5-biphosphate (PtdIns(4,5)P$_2$)] the change in the environment of the fluorophore, from the polar environment of the protein to the non-polar lipid, resulted in a large blueshift in the emission of DAN which was accompanied by an increase in intensity of emission. This blue shift and increase in the intensity of emission could be used for the quantification of phosphahtidtyinositol in the cell.\textsuperscript{178}

A similar approach has been used for the \textit{in situ} determination of PS by designing and constructing a new red fluorescent, environmentally sensitive probe with tunable emission properties and desirable water solubility which after being used to label the membrane protein PKC$\gamma$,\textsuperscript{183} changes its fluorescence intensity upon binding of PKC$\gamma$ to the lipid PS.

### 4.3 Thiol Reactive Environment Sensitive Probes

Thiol reactive environment sensitive probes are among the most useful probes in biochemistry.\textsuperscript{184} This is because most proteins contain a cysteine which has a free thiol
group. The thiol group of the cysteine could form a disulfide bridge with a thiol on the fluorescent probe.\textsuperscript{185} Another more popular approach involves using the thiol of the cysteine as a nucleophile in a Michael addition reaction with a Michael acceptor on the probe.\textsuperscript{186} The resulting adduct has a strong C–S bond which does not cleave easily. This ensures that the protein remains labeled with the fluorescent probe during the duration of the study. Proteins can also be engineered to introduce a cysteine near the lipid binding site. This helps place the probe in close proximity to the lipid and hence the change in environment around the fluorophore is reflected in its emission.\textsuperscript{187}

4.3.1 Limitations of Currently Used Fluorophores

Currently used thiol reactive fluorescent probes for the \textit{in situ} determination of lipids in cells are 4-chloro-7-Nitro-2-1,3-benzoxadiazole, (NBD chloride),\textsuperscript{188} 2-dimethylamino-6-acyl-naphthalene (DAN), and Nile Red,\textsuperscript{189} (Scheme 4.1). The 7-Nitro-2-1,3-benzoxadiazole (NBD), probe has been developed specifically for the \textit{in situ} determination of PS.\textsuperscript{190} NBD-tagged PS has been used extensively but is not efficient because of the distortion in the structure of the lipid upon insertion of NBD.\textsuperscript{191} The second fluorescent probe, DAN, has favorable spectral properties and can effectively partition into the membrane.\textsuperscript{178,192} It however, has a number of limitations. UV excitation of DAN causes fast photobleaching and could damage the cell. The emission spectrum of DAN overlaps with that of the Enhanced Green Fluorescence Protein\textsuperscript{193} and with the intrinsic fluorescence of other proteins and peptides\textsuperscript{194} but since DAN derivatives with fluorescence emission at longer wavelengths are difficult to synthesize, this represents a major challenge in dual imaging using DAN. The third commonly used fluorophore, Nile
Red,\textsuperscript{189} is a red fluorescent probe that has been used for the determination and quantification of lipids in cells. Since it has an emission at $>600\text{nm}$,\textsuperscript{195} its emission spectrum does not overlap with the intrinsic fluorescence of the cell. But the synthesis of Nile Red is an arduous process and hence its derivatives are rare. This difficulty in synthesis combined with the poor water-solubility of Nile Red\textsuperscript{196} is responsible for the investigation into new red fluorescent probes.

![Scheme 4.1: Currently Used Environmentally Sensitive Fluorescent Probes](image)

**Scheme 4.1:** Currently Used Environmentally Sensitive Fluorescent Probes

### 4.3.2 Desired Properties for New Probe

In order to overcome the limitations of the currently used fluorescent probes, a new probe was designed with the following desirable properties. It was important that the new fluorophore be environmentally sensitive. There should be a change in the emission, preferably a blue shift and an increase in the intensity of emission, when the environment of the fluorophore changed from polar to non-polar. Thus, when the protein labeled with the fluorophore moved from the polar aqueous environment of the cytoplasm of the cell, to the non-polar environment of the lipid, there should be a change in the emission properties of the fluorophore (Figure 4.1). This would signify the binding of the labeled
protein to the lipid and could be used to monitor the lipid-protein interactions.

**Figure 4.1:** Change in the Environment of the Probe results in an Increase in the Intensity of Emission

The fluorophore also had to be soluble in water so that it could be injected into the cell without using organic solvents which would damage the cell. It had to be resistant to photobleaching and hence would not decompose upon exposure to UV light. It should also be easy to synthesize derivatives of the fluorescent probe which would have emissions at longer wavelengths. This would serve a dual purpose; first, the derivatives with emissions at longer wavelengths would not interfere with the intrinsic fluorescence of the cell. Secondly, two fluorophores, one with an emission at a shorter wavelength, and one with an emission at a longer wavelength could be used simultaneously for the *in-situ* determination of two different lipids in the cell. This would help in the better understanding of the complex cellular processes.

### 4.4 Modification of the Protein

The C1B domain of the PKCγ<sup>197</sup> protein was modified such that it could bind irreversibly to the fluorophore without affecting the binding affinity of the protein
towards the lipid membrane. In order to achieve binding to the thiol reactive fluorescent probe, a Cysteine (Cys) residue was required to be present near the lipid binding portion of the protein. The PKCγ protein has several Cys, but none near the lipid binding domain. Most of the Cys on the protein were involved in Zn co-ordination and hence unavailable for binding to the probe. One free Cys residue, not involved in Zn co-ordination and which was present far away from the lipid binding site, was mutated to a Serine (Ser) to prevent it from reacting with the thiol reactive fluorescent probe. An Arginine (Arg) residue present near the lipid binding domain was then mutated to a Cys which, through its free thiol, would serve as a Michael donor and bind to the Michael acceptor on the fluorophore. These modifications reduced the binding affinity of the protein toward the lipid (PS) and necessitated the mutating of two Ser on the membrane binding surface to Trp. After all these modifications, (Figure 4.2) the resulting protein could effectively bind to both the fluorophore and the lipid. This work was done by the Cho lab at UIC.

**Figure 4.2: Modifications to the PKCγ Protein to Ensure Binding to both the Probe and the Lipid**
4.5 Design of New Environmentally Sensitive Probes

Several core structures were examined to find the fluorophore which would meet all the requirements discussed above in terms of water solubility, efficient binding to the protein, environment sensitivity and ease of synthesis. The structure of the fluorophore was modified several times depending on the assays conducted by the Cho lab.

4.5.1 Fluorophore Containing Indolizine Core

Fluorophores with an Indolizine core as shown in Scheme 4.2 were reported by Kim et al. in 2008.198

Scheme 4.2: Fluorophores Containing an Indolizine Core

The authors then investigated the emission properties for these compounds by varying the R¹ and R² groups. They discovered that by changing the electronics of R¹ and R², the emission could be easily tuned as shown in Figure 4.3.198
When $R^1$ was an electron donating group and $R^2 = H$, the compound exhibited blue fluorescence. As $R^2$ was made more electron withdrawing, there was a shift in the emission towards longer wavelengths as exhibited by the compound B4 which has $R^1 = \text{phenyl}$ and $R^2 = \text{nitrile}$. After using DFT calculations, the authors discovered that $R^1$ was the HOMO for the system and $R^2$ was the LUMO. Hence, by placing an electron donating group at $R^1$ and an electron withdrawing group at $R^2$, more electron delocalization would be possible resulting in either orange or red fluorescence. When the HOMO, LUMO gap was decreased by making $R^1$ strongly electron donating (when $R^1 = p$-dimethylaminophenyl) and $R^2$ electron withdrawing ($R^2 = \text{phenyl}$), the compound E3 had yellow fluorescence. By making $R^2$ a strongly electron withdrawing acetyl group and keeping $R^1$ as $p$-dimethylaminophenyl, maximum electron delocalization was achieved and the resulting compound exhibited red fluorescence.

We sought to model our fluorophores on similar lines by using an indolizine core, changing the substituents at $R^1$ and $R^2$, and increasing water solubility.
4.5.2 Target Fluorophores

Our target fluorophores are shown in Scheme 4.3. These fluorescent probes had the indolizine core and the strongly electron donating \( p \)-dimethylaminophenyl group at \( R^1 \) similar to the fluorophore reported by Kim and coworkers.\(^{198} \) Compound \( 1 \) had \( R^2 = H \) and compound \( 2 \), had \( R^2 = \text{acetyl} \). To increase the water solubility of these otherwise hydrophobic substrates, a phosphonate moiety was introduced into the indolizine core. The phosphonate could be further hydrolyzed to the phosphonic acid which would further improve the water solubility. The effect of the phosphonate on the emission properties, however, was not known. The purpose of introducing the maleimide side chain shall be discussed in the next section.

4.5.3 Introducing the Maleimide Side Chain

As mentioned above in Section 4.3, the protein PKC\( \gamma \) was modified to have a free Cys near its lipid binding domain. The thiol of the Cys could serve as a Michael donor and react with a Michael acceptor on the fluorophore (Figure 4.4). It was therefore necessary to introduce a Michael acceptor onto the target fluorophore. The most widely
available and easy to install Michael acceptor, maleimide was therefore chosen to be
installed onto the indolizine core.

![Structure of PKCγ C1B domain](image1)

**Structure of Target Fluorophore**

![Structure of Target Fluorophore](image2)

**Figure 4.4:** Installing a Michael Acceptor on the Target Fluorophore

After the Michael addition reaction, the resulting adduct containing the fluorophore
bound to the protein would constitute the labeled protein and this could be used to
monitor the lipid-protein interactions. The Michael reaction, forming the new C–S bond,
would be an irreversible process, thus ensuring that the fluorophore would not fall off
during the course of the experiment.
4.6 Green Fluorescent Compound

Our synthesis for target fluorophore 47 which had \( R^1 = p \)-dimethylaminophenyl and \( R^2 = H \), was based on the synthesis reported by Kim et. al.\(^{198} \) This resulting compound exhibited green fluorescence. The synthesis for \( 47 \) begins in Scheme 4.4. \( p \)-dimethylaminocinnamaldehyde was synthesized from commercially available \( p \)-dimethylaminobenzaldehyde 49. A Horner-Wadsworth-Emmons reaction between triethylphosphonoacetate 50 and \( p \)-dimethylaminobenzaldehyde 49 resulted in the formation of the \( \alpha,\beta \)-unsaturated ester 51. Reduction with LAH gave the allylic alcohol 52 which was oxidized to the \( p \)-dimethylaminocinnamaldehyde 53 with MnO\(_2\).

![Scheme 4.4: Synthesis of \( p \)-Dimethylaminocinnamaldehyde](image)

The \( p \)-dimethylaminocinnamaldehyde 53 was condensed with mono-Boc protected ethylenediamine 54 to form the imine 55 which was then treated with dimethylphosphite to form the phosphonate 56 in a quantitative yield over two steps. The phosphonate was then converted to the \( \alpha \)-bromo amide 57 using bromoacetyl bromide and triethylamine (Scheme 4.5). The \( \alpha \)-bromo amide 57 is the precursor for the cyclization reaction that forms the indolizine core.
Scheme 4.5: Formation of the α-Bromo Amide

As shown in Scheme 4.6, the α-bromo amide 57 was treated with pyridine. This resulted in an SN2 reaction to form the pyridinium salt. Deprotonation with DBU was followed by cyclization to form the polycyclic system. Aromatization by DDQ resulted in the formation of the green fluorescent compound 58 (Scheme 4.6).

Scheme 4.6: Formation of the Green Fluorescent Compound

The mechanism for the above reaction is shown in Scheme 4.7.
Scheme 4.7: Mechanism of the Reaction to form the Indolizine Core

To convert the green fluorescent compound 58 into the target fluorophore 47, the sulfide acceptor had to be installed. To this end, the Boc group was deprotected with TFA and the resulting free amine 59 was treated with maleic anhydride to form the malemide in 47, which would function as the Michael acceptor for the thiol of the Cysteine (Scheme 4.8).
Scheme 4.8: Final steps in the synthesis of the Green Fluorescent Probe

For the indolizine cores reported by Kim et al.,\textsuperscript{198} placing the \( p \)-dimethylaminophenyl at \( R^2 \) and hydrogen at \( R^1 \), the compound had yellow fluorescence. Our compound having the same groups at \( R^1 \) and \( R^2 \) exhibited green fluorescence. This decrease in the emission could be attributed to the phosphonate group.

4.7 Orange Fluorescent Compound

As per the calculations done by the Kim et al.,\textsuperscript{198} by making \( R^2 \) more electron withdrawing, the HOMO, LUMO gap could be decreased thereby increasing the wavelength of emission. We therefore decided to place an acetyl group at \( R^2 \) which would result in the compound having orange fluorescence. The synthesis for the orange fluorescent compound was similar to compound 47. The \( p \)-dimethylamino cinnamaldehyde 53 was synthesized as shown in Scheme 4.4. It was then converted to the
α-bromo amide 57 following the same sequence as in Scheme 4.5. Cyclization with 4-acetyl pyridine and then rearomatization with DDQ resulted in the desired product 60 (Scheme 4.9).

Scheme 4.9: Synthesis of the Orange Fluorescent Compound

This was followed by deprotection of the Boc group and installation of the malemide to form the desired thiol reactive probe 48 (Scheme 4.10).
4.7.1 Testing the Compound with Phosphatidylserine

The compound 48 which had an emission in the orange region of the spectrum was first bound to the protein via a Michael reaction between the thiol of the Cys in the protein and the malemide of the fluorophore. Once this reaction was complete, the labeled protein 48a was purified by passing it through a column. To a solution of this labeled protein 48a, was added the PS lipid and the emission of the fluorophore in the presence of the lipid was measured. It was expected that there would be a blue shift (to yellow fluorescent) in the emission of the fluorophore in the presence of the lipid. This would be because there would be a change in the environment of the fluorophore from aqueous to non-polar of the lipid when the labeled protein was bound to the PS lipid 48b (Figure 4.5).

![Scheme 4.10: Installing the Malemide Group](image)

**Figure 4.5:** Expected Change in the Emission of the Fluorophore

However, once the PS lipid was added to a solution of the labeled protein 48a, there was no change in the emission of the fluorophore (Figure 4.6).
Figure 4.6: No Change in the Observed Emission of the Fluorophore

This lack of blue shift in the emission could be attributed to a rotation of the fluorophore away from the lipid membrane in 48b as shown in Figure 4.7.

Figure 4.7: Hypothesis to Explain Observed Results

Since the tether length between the maleimide unit and the fluorophore in 48 was three carbon atoms long, we hypothesized that it could allow the rotation of the fluorophore away from the lipid in 48b. Thus, the fluorophore was far away from the non-polar lipid and hence there was no change in the environment of the fluorescent probe. This could
explain the fact that there was no change in the color or the intensity of the emission when the labeled protein was bound to the lipid.

4.7.2 Modification in the Structure of the Fluorophore

Since the fluorophore that we had previously designed did not work well in the presence of the lipid, we decided to introduce some modifications in the structure. From the previous experiment, we had concluded that the tether length between the maleimide and the fluorophore was the problem. Our first approach was to reduce the tether length so that the fluorophore would not be able to rotate away from the lipid membrane. However all attempts to reduce the tether from a three carbon chain to a two or one carbon long tether were unsuccessful. We therefore decided to change the Michael acceptor from a maleimide to an α,β-unsaturated ketone. The easiest method to install this new sulfide acceptor would be to convert the acetyl group at R² in 48 to the α,β-unsaturated ketone 62 (Scheme 4.11). This would serve two purposes, first the α,β-unsaturated ketone would serve as a Michael acceptor to bind to the protein and second, the unsaturated ketone would be more electron withdrawing than the acetyl group, thus further lowering the LUMO. This could result in an increase in the wavelength of the emission, potentially making the compound red fluorescent.
Scheme 4.11: Modifications in the Structure of the Fluorophore

A number of methods were tried to convert the acetyl group at R² in compound 63 to the α,β-unsaturated ketone 62. The compound 63 (Scheme 4.12) was made in a manner similar to Schemes 4.6 and 4.7, but using allyl amine to condense with p-dimethylcinnamaldehyde 53 instead of the Boc protected ethylene diamine. However, the vinyl ketone was extremely reactive and would decompose before it could be isolated (Scheme 4.12).

Scheme 4.12: Converting the Acetyl Group at R² to the α,β- Unsaturated Ketone

Since the conversion of the acetyl group at R² in 63 to the vinyl ketone 62 was not successful, we decided to convert the acetyl group to an α-bromo ketone instead. The α-
bromo ketone in 64 would also function as a Michael acceptor to react with the thiol on the protein, and would be more stable than the vinyl ketone. This conversion was achieved using tertabutylammonium tribromide as shown in Scheme 4.13.

Scheme 4.13: Conversion of the Acetyl Group to the α-Bromo Ketone

The resulting compound 64 exhibited orange fluorescence. When this compound was bound to the protein and then tested in the presence of the PS lipid, it did not show any blue shift but showed an increase in intensity of emission.

Figure 4.8: Plot of Intensity vs Wavelength that Shows an Increase in Intensity of Emission
As shown above, Figure 4.8 is a plot of intensity of emission vs the wavelength of emission for the orange fluorescent compound 64. M4 is the intensity for the protein labeled with the fluorophore. When the lipid phosphatidylcholine (PC) is added to the labeled protein, there is no change in the intensity of emission (shown as 1-PC and 2-PC). However, when the lipid PS is added to a solution of the labeled protein, (shown as 3-PS in the graph) there is a 1000 fold increase in intensity. Upon doubling and then tripling the concentration of PS (shown as 4-PS and 5-PS respectively) there is a 1400 fold increase in intensity. This establishes the fact that fluorophore 64 can be used to monitor protein-PS interactions and is specific for PS.

4.8 Designing new Fluorophores

To complete our library of fluorescent probes, we wanted to synthesize a red fluorescent compound. The indolizine fluorescent probe 64 could be successfully used in a physiological system to monitor lipid-protein interactions, but exhibited orange fluorescence. We therefore decided to explore other fluorophore core structures containing either an α-bromo ketone or a vinyl ketone as the sulfide acceptor, in an attempt to ultimately design and synthesize the desired red fluorescent, thiol reactive, environmentally sensitive probe which could be successfully used to monitor protein-PS interactions.

4.8.1 Naphthopyranone Cores

Naphthopyranones belong to the coumarin family, and are considered as coumarins with an additional fused benzene ring. While coumarins have been known to
have interesting photophysical properties and have been extensively investigated for their
electronic and photonic applications,\textsuperscript{199} there has been limited study on the
naphthopyranones. The fluorescence of naphthopyranones varies drastically depending
upon the position of substituents on the core (Scheme 4.14). Placing an electron donating
group (EDG) at C9 dramatically improves the emission properties. This is because of an
intramolecular charge transfer (ICT) from the EDG group to the carbonyl group of the
lactone. A synergistic effect to enhance the intensity of emission was observed when an
electron withdrawing group (EWG) was placed at C2.\textsuperscript{200}

\begin{center}
\textbf{Scheme 4.14:} ICT in Naphthopyranones
\end{center}

The Naphthopyranones usually have an emission around 510 nm. We wanted to
modify the structures to attempt to make these compounds orange or red fluorescent
while also installing a sulfide acceptor. To synthesize this new fluorophore, we started
with $\alpha$-tetralone 65 which was converted to 1-hydroxy-2-napthaldehyde 66 by using LDA
and ethyl formate followed by aromatization with DDQ. The naphthaldehyde was
converted to the naphthopyranone 67 via a Knovenagel Condensation. This compound 67
exhibited green-yellow fluorescence. With the desired core in hand, the ketone was then
converted to the $\alpha$-bromo ketone 68 (Scheme 4.15). The final compound had green
fluorescence. However, the main problem with these compounds was their limited water
solubility. They were extremely hydrophobic and hence could not be used to even bind to the protein, which is available as an aqueous solution.

We then attempted to synthesize derivatives of the naphthopyranones which would have electron donating groups like methoxy, hydroxyl or substituted amines at C9. We hypothesized that this would not only increase water solubility, but also result in emission at longer wavelengths. However, all endeavors to further derivatize the naphthopyranone core were unsuccessful.

Scheme 4.15: Synthesis of a Probe Containing the Naphthopyranone Core

4.8.2 Nile Red Derivatives

Nile Red 69 is a solvatochromic oxazine dye whose general structure is shown in Scheme 4.16.
**Scheme 4.16:** General Structure of Nile Red

This compound is red fluorescent in organic solvents but is insoluble and non-fluorescent in aqueous media. The Burgess group reported in 2006 that by introducing a hydroxyl group on the core, and modifying the diethyl group on the amine, Nile Red could be made water soluble and fluorescent in an aqueous medium\(^{196}\) (Scheme 4.17).

![Nile Red Derivatives Soluble in Water](image)

**Scheme 4.17:** Nile Red Derivatives that are Water Soluble and Red Fluorescent

We decided to model our next fluorescent probe on this Nile Red Derivative. Since it was already water soluble, we needed to introduce a thiol reactive group on the core so that it could bind with the protein. Our synthesis is shown in Scheme 4.18. 3-aminophenol \(\text{72}\), upon reaction with acrylic acid gave the dicarboxylic acid \(\text{73}\) which was then converted to the dimethylester \(\text{74}\) with methanol. Sodium nitrite and hydrochloric acid were then used to convert the phenol to the nitroso compound \(\text{75}\) which was extremely unstable and was immediately converted to Nile Red \(\text{70}\) upon treatment with naphthol. Nile Red was thus obtained as shiny red crystals, albeit in a low yield.
Scheme 4.18: Synthesis of Nile Red Derivative

The other Nile Red derivative reported by the Burgess group\textsuperscript{196} was synthesized in a manner similar to the one above. Reduction of diester 74 with lithium aluminium hydride gave diol 76 which was converted to the nitoso compound 77. Treatment of 77 with 1,6-dihydroxynaphthol gave the Nile Red derivative 71 (Scheme 4.19).
Scheme 4.19: Synthesis of Water Soluble Nile Red Derivative

Our next strategy was to introduce a nitro group onto the core of either 70 or 71 (either the diester or after protection of the diol in 71) to give 79 which could then be reduced to an amine 80. The amine 80 could condense with maleic anhydride to form maleimide 81 which could serve as a thiol acceptor (Scheme 4.20).

Scheme 4.20: Proposed Modification of Nile Red
However, all attempts to nitrate, brominate or acylate the core of Nile Red failed. Conversion of the phenol to triflate and then cross coupling to introduce an alkene moiety onto the ring, which could be further derivatized, was also unsuccessful. We therefore, decided to try another core structure for the fluorophore.

### 4.9 2-Imino-2,5-Dihydrofuran-3-Carbonitrile Containing Probe

Fluorescent compounds based on a 2-dicyanomethylene-3-cyano-2,5-dihydrofuran core 82 were reported by Tsou et. al. in 2009. These fluorescent dyes enabled visualization of nucleic acids, proteins and metabolites in biological systems (Scheme 4.21). The authors also reported that these probes had red fluorescence (if there was an electron donating group such as aniline in conjugation with the core) and high photo stability.202

![Scheme 4.21: 2-Dicyanomethylene-3-cyano-2,5-dihydrofuran Core](image)

Based on our work with the indolizine cores, we wanted to use $p$-dimethylamiophenyl as the strongly electron donating group, and then reduce the cyano group to install the sulfide acceptor.
Scheme 4.22: Synthesis of Red Fluorescent Compound

Our synthesis started with a Barbier reaction between 2,3-butanedione 83 and allyl bromide in the presence of Zn (Scheme 4.22). The tertiary alcohol 84 obtained underwent a cyclization with malononitrile followed by Knoevenagel condensation of the intermediate 85 with 4-dimethylaminobenzaldehyde. We expected the imine functionality to hydrolyze to the ketone after work up and isolation, and hence the product to contain a 2-oxo-2,5-dihydrofuran-3-carbonitrile core 86 which could be further manipulated to introduce the dicyanomethylene unit. However, upon further analysis with MS, IR and NMR, we concluded that the product of the Knoevenagel condensation was not the expected ketone, but instead was the imino-intermediate of the cyclization reaction 87 (Scheme 4.23). Such imino intermediates have been observed before in the reaction between salicylic aldehyde and malononitrile.\(^{203}\) Since the compound 87 exhibited bright red fluorescence, and could easily react with electrophiles, we decided to further explore this new fluorophore with the 2-imino-2,5-dihydrofuran-3-carbonitrile core.


**Scheme 4.23:** Formation of Fluorophore with 2-Imino-2,5-dihydrofuran-3-carbonitrile Core

The addition of the sulfide acceptor was achieved onto the imine functionality with acryloyl chloride or bromoacetyl bromide to furnish compounds 88 and 89 respectively (Scheme 4.24) which were first tested for their spectroscopic properties and then in the protein assays.

**Scheme 4.24:** Installing the Sulfide Acceptors
4.9.1 Spectroscopic Properties of the Red Fluorescent Compound in Different Solvents

It is known that the emission spectra of fluorescent compounds containing polar substituents on the aromatic rings are sensitive to the chemical and physical properties of solvents.\textsuperscript{204} As shown in Figure 4.9, compound 89 also exhibits solvatochromism wherein the emission bands vary in spectral position, shape and intensity depending upon the nature of the solvent.\textsuperscript{205}

Excitation at 500nm using a concentration of 1mg/ml showed an increase in fluorescence intensity when the solvent used was non-polar. Thus, there was a 1000 fold increase in intensity upon changing the solvent from water to methanol and 4000 fold intensity when the solvent was dichloromethane. When chloroform was used as the solvent, the intensity was increased 12000 times, which after dilution was reduced to 6000. The blue shift of the maxima also corresponds to a decrease in the dielectric constant of the solvent. This confirms that the fluorescence of compound 89 is affected by its environment and that there is an increase in the intensity of emission when the environment of the fluorophore is hydrophobic.
Figure 4.9: Fluorescence Emission Affected by Polarity of Solvents

4.9.2 Protein Labeling and In-Vitro Lipid Binding Assay

The fluorophore 89 was efficiently bound to the protein PKCγ, which then constituted the labeled protein. Varying concentrations of the lipid were then added to a solution of the labeled protein. The results are shown in Figure 4.10.
A 0.67 μM concentration of the labeled protein had an emission of 590 nm and an intensity of emission of about 1000 a.u. When a 10% PS solution was added to the labeled protein, there was a three fold increase in intensity to 3000 a.u. When a 20% PS solution was added, there was a four fold increase in intensity. There was only a slight increase in the intensity of emission when a 30% PS solution was used.

A plot of fluorescence intensity vs percentage of PS (Figure 4.11) showed that there was an initial sharp increase in the intensity, which then reached a maximum at 30% PS.

**Figure 4.10:** Addition of PS to the Labeled Protein
Figure 4.11: Plot of Fluorescence Intensity vs PS percentage

These protein labeling studies and assays were performed by Hamid Afsari in Prof. Wonwha Cho’s lab at UIC.

4.10 Conclusion

In conclusion, we have been successful in designing and synthesizing a library of environmentally sensitive, thiol reactive fluorescent probes for the in situ determination of the lipid-protein interactions. Our fluorescent probes are tunable, easy to synthesize and cover a broad range of the spectrum from blue, green, yellow, orange and red. The most noteworthy of these probes are compounds 64 and 89, which are orange and red fluorescent respectively. These compounds are water soluble, thiol reactive and have been used in the physiological system for the determination of PS in the cell. These new fluorescent probes exhibit an increase in intensity when the labeled protein is bound to the lipid because of a change in environment from aqueous polar of the cell to lipid non-polar. Therefore, they can be used for monitoring the PS-protein interactions in the cells.
and can help in the understanding of these complex lipid mediated processes, which could in turn assist in finding a cure for diseases resulting from a dysfunction in the PS associated processes.

4.11 Supporting Information

4.11.1 Materials and Methods

Reactions were carried out in oven or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Compounds were purchased from Aldrich unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were freshly distilled from sodium/benzophenone, and dichloromethane (DCM) was distilled from calcium hydride (CaH$_2$) under nitrogen atmosphere. Flash chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck precoated silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DRX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26) for $^1$H NMR and chloroform (δ 77.0) for $^{13}$C NMR; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), b (broad), and app (apparent). $^1$H NMR signals that fall within a ca. 0.3 ppm range are generally reported as a multiplet, with a single chemical shift value corresponding to the center of the peak. Coupling constants, $J$, are reported in Hz (Hertz). Electrospray ionization (ESI) mass spectra were recorded on a Waters Micromass Q-Tof Ultima in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass
spectra were obtained using a Micromass AutoSpecTM. IR spectra were recorded using ATI Mattson, Genesis series FTIR.

4.11.2 Experimental Procedures and Characterization Data

![Chemical Structure](attachment:51.png)

\textbf{\textit{\alpha,\beta}}-unsaturated ester 51: To the triethyl phosphonoacetate (2 g, 8.92 mmol) in THF (15 ml) at 0 °C was added NaH (356 mg, 8.92 mmol) and the reaction stirred at 0 °C for 10 mins and then at room temperature for 30 mins. The reaction was again cooled to 0 °C and 4-dimethylaminobenzaldehyde (950 mg, 6.37 mmol), dissolved in THF (4 ml), was added dropwise to the reaction mixture. It was then stirred at room temperature for 2 h and was quenched with saturated NH₄Cl and extracted with EtOAc (3 x 20 ml). The organic layer was washed with brine, dried with MgSO₄ and concentrated \textit{in vacuo}. Flash chromatography with hexane:EtOAc 4:1 gave the desired product 51 (1.11 g, 80 %). $^1$H NMR (500 MHz; CDCl₃): δ 7.62 (d, $J = 16.1$ Hz, 1H), 7.43 (d, $J = 8.5$ Hz, 2H), 6.60 (d, $J = 8.5$ Hz, 2H), 6.18 (d, $J = 16.1$ Hz, 1H), 4.09 (q, $J = 7.4$ Hz, 2H), 3.01 (s, 6H), 1.24 ( t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃): δ 167.9, 151.7, 145.1, 129.7, 122.2, 112.6, 111.8, 60.0, 40.1, 14.4; see Ref 206 for MS data.
Allylic alcohol 52: A solution of lithium aluminium hydride (242 mg, 6.38 mmol) in Et₂O was cooled to 0 °C and the α,β-unsaturated ester 51 (1 g, 4.56 mmol) was added dropwise to it. The reaction was gradually allowed to warm up to room temperature and stirred at that temperature for 2 h. The reaction was cooled to 0 °C and sodium sulfate decahydrate was added until the white precipitate that formed, persisted. MgSO₄ (2 g) was added and the reaction mixture was filtered. The filtrate was concentrated to give the allylic alcohol 52 (770 mg, 77 %). ¹H NMR (500 MHz; CDCl₃): δ 7.30 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 15.8 Hz, 1H), 6.23-6.17 (m, 1H), 4.28 (d, J = 5.9 Hz, 2H), 3.49 (bs, 1H), 2.96 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 150.1, 131.3, 127.6, 125.5, 124.5, 112.7, 63.8, 40.6; see Ref 207 for HRMS.

p-dimethylaminocinnamaldehyde 53: To a solution of the allylic alcohol 52 (1 g, 5.64 mmol) in CH₂Cl₂ (40 ml) was added slowly MnO₂ (2.94 g, 33.85 mmol) and the reaction stirred for 1 h. The MnO₂ was filtered and the filtrate concentrated under reduced pressure. Flash chromatography with hexane:EtOAc 3:1 gave the desired aldehyde 53. ¹H NMR (500 MHz; CDCl₃): δ 9.53 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 15.6 Hz, 1H), 6.62 (d, J = 8.6 Hz, 2H), 6.48 (dd, J = 15.6, 7.90 Hz, 1H), 2.98 (s, 6H);
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.6, 154.1, 152.4, 130.5, 123.5, 121.6, 111.7, 40.0; see Ref 208 for HRMS.

**Imine 55:** To the 4-dimethylaminocinnamaldehyde 53 (2 g, 11.41 mmol), in CH$_2$Cl$_2$ (10 ml) was added the Boc-protected propane-1,3-diamine 54 (2 g, 11.41 mmol) and MgSO$_4$ (1 g) and the reaction stirred at room temperature under an N$_2$ atmosphere for 12 h. The reaction was filtered to remove the MgSO$_4$ and the filtrate concentrated to obtain the imine 55 (3.8 g, 100%) which was used without further purification. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.96 (d, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 15.8$ Hz, 1H), 6.72-6.57 (m, 3H), 3.51 (t, $J = 6.5$ Hz, 2H), 3.20 (t, $J = 6.5$ Hz, 2H), 2.89 (s, 6H), 1.84-1.82 (m, 2H), 1.44 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.8, 155.9, 150.3, 133.3, 129.6, 124.7, 120.1, 111.8, 79.5, 59.4, 49.6, 41.3, 31.5, 28.4.

**Phosphonate 56:** To a solution of the imine 55 (1 g, 3.01 mmol) in MeOH was added dimethylphosphite (0.36 ml, 3.92 mmol) and the reaction refluxed for 10 h. The MeOH was removed under reduced pressure and saturated NH$_4$Cl added to it. This was followed by extraction with EtOAc (3 x 20 ml). The organic layer was washed with brine, dried with MgSO$_4$ and concentrated in vacuo to give the desired product 56 (1.32 g, 100%) as a
yellow liquid which was used without further purification. \( ^1 \)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.41-7.27 (m, 3H), 6.60 (d, \( J = 8.6 \) Hz, 2H) 6.48 (d, \( J = 15.6 \) Hz, 1H), 5.65 (dd, \( J = 9.1, 20.4 \) Hz, 1H), 3.52 (dd, \( J = 10.7, 8.5 \) Hz, 6H), 3.51 (t, \( J = 6.5 \) Hz, 2H), 3.20 (t, \( J = 6.5, 2H \), 2.89 (s, 6H), 1.84-1.82 (m, 2H), 1.44 (s, 9H); \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 155.3, 151.0, 133.3, 129.6, 129.5, 124.7, 111.8, 79.5, 54.3 (d, \( J_{C-P} = 156.2 \) Hz), 53.8 (d, \( J_{C-P} = 7.5 \) Hz), 53.2 (d, \( J_{C-P} = 6.2 \) Hz), 49.6, 41.3, 31.5, 29.6, 28.4.

![Chemical structure of compound 57](image)

**\( \alpha \)-Bromo amide 57:** To the bromoacetyl bromide (0.44 ml, 5.09 mmoles) in anhydrous CH\(_2\)Cl\(_2\) (15 ml) at 0 °C was added dropwise a mixture of 56 (1.5 g, 3.39 mmoles) and Et\(_3\)N (0.70 ml, 5.09 mmoles) in anhydrous CH\(_2\)Cl\(_2\) (4 ml). The reaction was stirred for 10 mins when TLC indicated complete consumption of 56. The reaction mixture was diluted with water (10 ml) and extracted with CH\(_2\)Cl\(_2\) (3 x 10 ml). The organic layer was washed with brine, dried with MgSO\(_4\) and concentrated *in vacuo*. Flash chromatography with hexane:EtOAc 3:1 gave the desired product 57 (1.52 g, 80 %). \( ^1 \)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.24 (d, \( J = 8.7 \) Hz, 2H), 6.69-6.61 (m, 3H), 6.03-5.96 (m, 1H), 5.63 (dd, \( J = 9.1, 20.3 \) Hz, 1H), 3.89 (d, \( J = 10.7 \) Hz, 1H), 3.81 (d, \( J = 10.7 \) Hz, 1H), 3.74 (dd, \( J = 10.7, 8.5 \) Hz, 6H), 3.51 (t, \( J = 6.5 \) Hz, 2H), 3.20 (t, \( J = 6.5, 2H \), 2.93 (s, 6H), 1.84-1.82 (m, 2H), 1.44 (s, 9H); \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 167.2, 150.6, 137.7, 134.4, 127.8, 124.0, 117.0, 113.7, 79.5, 54.6 (d, \( J_{C-P} = 156.4 \) Hz), 53.8 (\( J_{C-P} = 7.1 \) Hz), 53.2 (\( J_{C-P} = 6.3 \) Hz), 49.6, 41.3, 40.3, 31.5, 29.6, 28.4.
**Compound 58:** The compound 57 (1 g, 1.77 mmol) and pyridine (6 ml) were stirred at room temperature under N₂ for 6 h. After the complete consumption of 57 the reaction mixture was diluted with toluene (6 ml) and DBU (0.4 ml, 2.65 mmol) was added to it. The reaction was then stirred at 50 °C for 8 h. To the resulting mixture of non-aromatized and fully aromatized products at 0 °C, was added 2,3-dichloro-5,6-dicyanohydroquinone (DDQ) for oxidative aromatization. The reaction mixture was stirred at 0 °C for an additional 30 min. It was the filtered through a short bed of silica gel and the filtrate concentrated in vacuo. The residue was purified by silica gel flash column chromatography, eluted with hexane:EtOAc 2:1 to afford the desired product 58. ¹H NMR (500 MHz; CDCl₃): δ 8.61 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 8.1, 1H), 7.49(d, J = 8.1 Hz, 2H), 7.14-7.01 (m, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.94-6.76 (m, 1H), 5.23 (d, J = 12.4 Hz, 1H), 3.65-3.60 (m, 2H), 3.56-3.51 (m, 2H), 3.41 (d, J = 10.6 Hz, 3H), 3.32 (d, J = 10.6 Hz, 3H), 3.01 (s, 6H), 2.05-2.01 (m, 2H), 1.57 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 166.4, 155.9, 151.3, 146.8, 135.9, 128.4, 126.9, 125.9, 124.5, 124.4, 123.5, 122.7, 117.2, 112.1, 79.5, 54.9 (d, J_C-P = 155.8 Hz), 53.4 (d, J_C-P = 7.5 Hz), 53.2 (d, J_C-P = 6.2 Hz), 45.6, 41.3, 39.9, 28.4, 26.5.
Green Fluorescent compound 47: To a solution of 58 (100 mg, 0.18 mmol) in CH₂Cl₂ (2 ml) was added three drops of TFA and the reaction stirred at room temperature for 10 h. It was quenched with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 10 ml). The organic layer was dried with MgSO₄ and concentrated under reduced pressure to give 59, which was immediately used in the next step. Toluene (4 ml) was added to the crude reaction mixture of 59, followed by maleic anhydride (88.2 mg, 0.9 mmol) and the reaction heated at reflux for 10 h. Toluene was removed in vacuo and the residue purified on column to yield 47 (73 mg, 76 % over two steps) as an orange liquid. ¹H NMR (500 MHz; CDCl₃): δ 8.61 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 8.1, 1H), 7.49(d, J = 8.1 Hz, 2H), 7.14-7.01 (m, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.94-6.76 (m, 1H), 6.38 (d, J = 5.2 Hz, 2H) 5.23 (d, J = 12.4 Hz, 1H), 3.65-3.60 (m, 2H), 3.56-3.51 (m, 2H), 3.41 (d, J = 10.6 Hz, 3H), 3.32 (d, J = 10.6 Hz, 3H), 3.01 (s, 6H), 2.05-2.01 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 172.3, 167.7, 150.8, 148.6, 139.4, 134.7, 129.1, 127.5, 125.9, 123.8, 123.1, 122.7, 122.3, 118.6, 111.1, 55.1 (d, J_{C-P} = 156.2 Hz), 53.6 (d, J_{C-P} = 7.5 Hz), 53.4 (d, J_{C-P} = 6.3 Hz), 44.8, 42.7, 39.9, 25.9.
Toluene (6 ml) and DBU (0.4 ml, 2.65 mmol) was added to it. The reaction was then stirred at 50 °C for 8 h. To the resulting mixture of non-aromatized and fully aromatized products at 0 °C, was added 2,3-dichloro-5,6-dicyanohydroquinone (DDQ) for oxidative aromatization. The reaction mixture was stirred at 0 °C for an additional 30 min. It was the filtered through a short bed of silica gel and the filtrate concentrated in vacuo. The residue was purified by silica gel flash column chromatography, eluted with hexane:EtOAc 2:1 to afford the desired product 60 (370 mg, 35 %). 1H NMR (500 MHz; CDCl3): δ 8.52 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 7.37-7.33 (m, 3H), 6.86 (d, J = 8.7 Hz, 2H), 5.07 (d, J = 12.9 Hz, 1H), 3.94-3.80 (m, 2H), 3.64-3.57 (m, 2H), 3.39 (dd, J = 12.9 Hz, 1H), 3.94-3.80 (m, 2H), 3.64-3.57 (m, 2H), 3.39 (dd, J = 10.8, 6.9 Hz, 6H), 3.08 (s, 6H), 2.56 (s, 3H), 2.04-2.01 (m, 2H), 1.57 (s, 9H); 13C NMR (125 MHz, CDCl3): δ 201.1, 168.1, 157.3, 155.4, 148.8, 137.1, 129.6, 128.2, 128.1, 127.4, 125.3, 125.1, 122.7, 119.4, 116.3, 67.6, 55.1 (d, J_{CP} = 155.7 Hz), 54.1 (d, J_{CP} = 7.5 Hz), 53.8 (d, J_{CP} = 6.2 Hz), 44.8, 42.4, 41.3, 30.2, 28.1, 25.8.
Orange Fluorescent Compound 48: To a solution of 60 (100 mg, 0.17 mmol) in CH₂Cl₂ (2 ml) was added three drops of TFA and the reaction stirred at room temperature for 10 h. It was quenched with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 10 ml). The organic layer was dried with MgSO₄ and concentrated under reduced pressure to give 13, which was immediately used in the next step. Toluene (4 ml) was added to the crude reaction mixture of 61, followed by maleic anhydride (87.6 mg, 0.85 mmol) and the reaction heated at reflux for 10 h. Toluene was removed in vacuo and the residue purified on column to yield 48 (75 mg, 76% over two steps) as an orange liquid. ¹H NMR (500 MHz; CDCl₃): δ 8.52 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 7.37-7.33 (m, 3H), 6.86 (d, J = 8.7 Hz, 2H), 6.36 (d, J = 5.0 Hz, 2H), 5.07 (d, J = 12.9 Hz, 1H), 3.94-3.80 (m, 2H), 3.64-3.57 (m, 2H), 3.39 (dd, J = 10.8, 6.9 Hz, 6H), 3.04 (s, 6H), 2.56 (s, 3H), 2.04-2.01 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 202.4, 168.6, 166.4, 156.1, 147.4, 137.5, 135.8, 130.1, 129.8, 128.6, 125.7, 124.3, 122.7, 121.6, 120.2, 114.9, 54.8 (d, J_{C-P} = 156.3 Hz), 53.8 (d, J_{C-P} = 7.5 Hz), 53.5 (d, J_{C-P} = 6.2 Hz), 43.9, 42.7, 41.3, 30.1, 26.9.
**N-allylated Orange Fluorescent compound 63:** This compound was prepared in a manner similar to 48, following the sequence in Schemes 4.4, 4.5 and 4.9; but using allyl amine instead of the Boc-protected propane-1,3-diamine. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.43 (d, $J = 7.2$ Hz, 1H), 8.31 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.16 (dd, $J = 7.2$, 0.9 Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 2H), 5.91-5.33 (m, 1H), 5.23 (t, $J = 13.6$ Hz, 2H), 5.11 (d, $J = 12.9$ Hz, 1H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.34 (dd, $J = 10.8$, 6.9 Hz, 6H), 3.00 (s, 6H), 2.56 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.4, 161.2, 150.9, 149.4, 134.2, 134.0, 133.5, 128.3, 124.3, 122.6, 121.7, 121.3, 121.2, 117.7, 114.7, 113.0, 54.6 (d, $J_{C-P} = 156.0$ Hz), 53.3 (d, $J_{C-P} = 7.5$ Hz), 53.1 (d, $J_{C-P} = 6.2$ Hz), 46.1, 40.5, 26.0.

**α-Bromo Keone 64:** To a solution of 63 (50 mg, 0.103 mmol) in CH$_2$Cl$_2$ (2 ml) was added tetrabutylammonium tribromide (74 mg, 0.154 mmol) and the reaction stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the
compound purified by flash chromatography on silica gel, eluted with hexane:EtOAc 3:1 to give 64 (37 mg, 64 %) as an orange solid. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.43 (d, $J = 7.2$ Hz, 1H), 8.31 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.16 (dd, $J = 7.2$, 0.9 Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 2H), 5.91-5.33 (m, 1H), 5.23 (t, $J = 13.6$ Hz, 2H), 5.11 (d, $J = 12.9$ Hz, 1H), 4.34 (s, 2H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.34 (dd, $J = 10.8$, 6.9 Hz, 6H), 3.00 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 194.4, 161.2, 150.9, 149.4, 134.2, 134.0, 133.5, 128.3, 124.3, 122.6, 121.7, 121.3, 120.2, 117.7, 114.7, 113.0, 54.5 (d, $J_{C-P} = 156.0$ Hz), 53.3 (d, $J_{C-P} = 7.5$ Hz), 53.0 (d, $J_{C-P} = 6.2$ Hz), 46.1, 43.1, 40.5.

1-hydroxy-2-naphthaldehyde 66: To a solution of $\alpha$-tetralone 65 (1 g, 6.84 mmol) in THF (15 ml) at -78 °C was added dropwise a solution of LDA (6.84 mmol) and the reaction was stirred at -78 °C for 40 mins. Ethyl formate, (1.1 ml, 13.68 mmol) was then added slowly and the reaction allowed to warm up gradually to room temperature. It was then stirred at room temperature overnight. To the reaction mixture was added EtOH (8 ml) and then a solution of DDQ (1.5 g, 6.84 mmol) in 1, 4-dioxane (1.5 M). The reaction was the stirred for one hour, after which the solvent was removed in vacuo. EtOAc was added to the resulting solid, followed by filtration through a plug of silica. The solvent was removed under vacuum and the crude reaction mixture purified on column by eluting with EtOAc:hexanes 1:40. The product was obtained as a yellow solid (760 mg, 60 %). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 9.95 (d, $J = 4.6$ Hz, 1H), 8.44-8.42 (m, 1H), 7.78-7.76 (m, 1H), 7.66-7.65 (m, 1H), 7.55-7.54 (m, 1H), 7.47-7.45 (m, 1H), 7.37-7.34 (m, 1H); $^{13}$C
NMR (125 MHz, CDCl$_3$): $\delta$ 196.3, 161.9, 137.55, 133.41, 130.62, 127.65, 126.49, 126.17, 124.34, 119.48, 114.29.

**Naphthopyranone 67:** To the 1-hydroxy-2-naphthaldehyde 66 (64 mg, 0.4 mmol) and methyl acetoacetate (43 µl, 0.4 mmol) in dry toluene (2 ml) was added one drop of piperidine and one drop of acetic acid. The reaction flask was then connected to a Dean-Stark apparatus and heated at 110 $^\circ$C for 14 h. Solvent was removed under vacuum and the reaction mixture was purified on column. The product was eluted with EtOAc:hexanes 1:5 and is a yellow solid (77 mg, 81 %). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.53 (s, 1H), 8.52 (d, $J = 8.1$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 1H), 7.69-7.65 (m, 3H), 7.51-7.50 (m, 1H), 2.69 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.4, 159.3, 153.7, 148.2, 136.0, 130.1, 129.6, 128.0, 127.6, 125.0, 124.5, 123.2, 122.5, 113.8, 30.6; HRMS (CI$^+$) m/z calcd. for C$_{15}$H$_{11}$O$_3$ (M+H)$^+$ 239.0708, found 239.0705.

**α-Bromo Ketone 68:** To the naphthopyranone (25 mg, 0.104 mmol) 67 in 1,4-dioxane:Et$_2$O (1:1, 6ml) was added dropwise liquid Br$_2$ (5.3 µl, 0.104mmol) at room temperature. The reaction was stirred for 90 mins and then poured onto ice. A yellow
solid formed which was filtered and washed with MeOH. The product was then recrystallized from EtOH to give yellow crystals (26 mg, 78 %). \( ^1 \)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 8.77 (s, 1H), 8.59-8.57 (d, \( J \) = 8.2 Hz, 1H), 7.92-7.90 (d, \( J \) = 8.2 Hz, 1H), 7.76-7.70 (m, 3H), 7.58-7.50 (m, 1H), 4.80 (s, 2H); \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 188.8, 159.0, 154.1, 150.2, 136.4, 130.5, 128.1, 127.8, 125.4, 124.5, 123.3, 122.5, 120.8, 113.9, 35.8.

**Dicarboxylic Acid 73:** To the 3-aminophenol 72 (500 mg, 4.58 mmol) in water (1 ml) was added acrylic acid (0.94 ml, 13.74 mmol) and the reaction heated at 70 °C for 3 h. After cooling to room temperature, EtOH (2 ml) was added and the reaction kept at 5 °C overnight. The white crystals that formed were filtered and washed with cold EtOH and dried to obtain the desired product (811 mg, 70 %). \( ^1 \)H NMR (500 MHz; acetone-\( d_6 \)): \( \delta \) 7.02-6.98 (m, 1H), 6.28-6.24 (m, 2H), 6.19-6.17 (m, 1H), 3.64 (t, \( J \) = 4.5 Hz, 4H), 2.59 (t, \( J \) = 4.5 Hz, 4H); \( ^{13} \)C NMR (125 MHz, acetone-\( d_6 \)): \( \delta \) 172.6, 158.6, 148.6, 130.0, 104.0, 104.2, 99.6, 46.8, 31.7; See Ref 196 for HRMS.
Dimethylester 74: A solution of the dicarboxylic acid 73 (926 mg, 3.66 mmol) in MeOH (10 ml) along with HCl (10 M, 0.1 ml) was refluxed for 12 h. The reaction mixture was cooled and the MeOH removed under vacuum. The residue was dissolved in EtOAc and the organic layer washed with water (3 x 15 ml). The organic layer was dried with Na₂SO₄ and the EtOAc removed under reduced pressure to give the diester as a yellow viscous liquid (1.03 g, 100 %). ¹H NMR (500 MHz; CD₃OD): δ 7.05-6.95 (m, 1H), 6.21-6.15 (m, 3H), 3.65 (s, 6H), 3.58 (t, J = 7.2 Hz, 4H), 2.55 (t, J = 7.2 Hz, 4H); ¹³C NMR (125 MHz, CD₃OD): δ 173.3, 158.1, 148.2, 130.0, 104.4, 104.0, 99.7, 50.8, 46.7, 32.1; See Ref 196 for HRMS.

Nitroso phenol 75: To a solution of phenol 74 (500 mg, 1.77 mmol) in water (1 ml) at 0 °C was added HCl (10 N, 0.6 ml) followed by slow addition of a solution of sodium nitrite (134 mg, 1.95 mmol) in water (0.8 ml) at 0.05 ml per minute. After the addition of the sodium nitrite, the reaction was stirred at 0 °C for 2.5 h. Water was then removed under vacuum and the residue dissolved in MeOH. It was then dried with MgSO₄, and
MeOH removed under reduced pressure. The nitroso compound obtained (220 mg, 40%) was unstable and used in the next step without further purification. $^1$H NMR (500 MHz; CD$_3$OD): $\delta$ 7.90 (d, $J = 10.0$ Hz, 1H), 6.42 (d, $J = 10.0$ Hz, 1H), 6.20 (s, 1H), 3.78 (t, $J = 7.0$ Hz, 4H), 3.68 (s, 6H), 2.67 (t, $J = 7.4$ Hz, 4H); $^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ 172.1, 157.5, 154.5, 129.9, 123.4, 120.0, 98.0, 50.9, 46.4, 31.5; see Ref 196 for HRMS.

**Nile Red Derivative 70:** The nitroso compound 75 (403 mg, 1.30 mmol) and 1,6-dihydronaphthol (208 mg, 1.30 mmol) were dissolved in MeOH and HCl (10 N, 0.2 ml) was added. The reaction was heated at reflux for 5 h. MeOH was removed under reduced pressure and the residue purified immediately on silica gel, eluted with MeOH:EtOAc 1:10 to give the Nile Red derivative (234 mg, 40%) as a dark brown solid. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 8.03 (d, $J = 8.6$ Hz, 1H), 7.86 (s, 1H), 7.52 (d, $J = 8.6$ Hz, 1H), 7.04 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.78 (s, 1H), 6.61 (d, $J = 8.6$ Hz, 1H), 3.69 (t, $J = 7.1$ Hz, 4H), 3.64 (s, 6H), 2.60 (t, $J = 7.1$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 183.1, 173.1, 161.8, 153.4, 150.9, 147.3, 141.1, 132.8, 131.9, 129.6, 125.7, 124.9, 124.5, 119.9, 111.0, 109.2, 105.9, 51.9, 45.4, 31.1; see Ref 196 for HRMS.
**Diol 76:** A solution of diester 74 (1 g, 3.6 mmol) in THF (15 ml) was added dropwise to at 0 °C to a solution of LiAlH₄ (820 mg, 21.6 mmol) in THF (15 ml). A thick white precipitate formed and the reaction was stirred at room temperature for 2 h. It was quenched with water and filtered to remove the white precipitate. The filtrate was concentrated to yield the diol as a white solid (705 mg, 87%). 

\(^1\)H NMR (500 MHz; CD₃OD): δ 6.31 (t, \(J = 8.1\) Hz, 1H), 5.62 (s, 1H), 5.56 (d, \(J = 7.2\) Hz, 1H), 5.52 (d, \(J = 8.1\) Hz, 1H), 3.12 (t, \(J = 6.0\) Hz, 4H), 2.81-2.73 (m, 4 H), 1.33 (t, \(J = 6.3\) Hz, 4H); \(^13\)C NMR (125 MHz, CD₃OD) δ 167.5, 149.9, 128.9, 108.9, 105.1, 101.5, 60.0, 48.7, 30.3; see Ref 196 for HRMS.

**Nitroso compound 77:** To the phenol 76 (115 mg, 0.50 mmol) in water (0.5 ml) at 0 °C was added HCl (10 N, 0.5 ml) via a syringe pump at 0.03 ml/min. The reaction was stirred at 0 °C for 2.5 h and the filtered to remove the solids that formed. Water was then removed under reduced pressure and the residue dissolved in MeOH. It was the dried with MgSO₄ and concentrated. The nitroso compound obtained (74 mg, 51%) was
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unstable and used in the next step without further purification. \(^1\)H NMR (500 MHz; CD\(_3\)OD): \(\delta\) 7.70 (d, \(J = 10.2\) Hz, 1H), 7.26 (d, \(J = 10.2\) Hz, 1H), 6.49 (s, 1H), 4.02 (t, \(J = 7.4\) Hz, 4H), 3.98 (t, \(J = 7.4\) Hz, 4H), 3.81-3.66 (bs, 2H), 2.02-1.86 (m, 4H); \(^{13}\)C NMR (125 MHz, CD\(_3\)OD) \(\delta\) 166.1, 163.6, 144.8, 123.4, 120.0, 98.0, 58.3, 51.1, 31.8; see Ref 196 for HRMS.

Nile Red Derivative 71: To the nitroso compound 77 (94 mg, 0.37 mmol) in DMF (3 ml) was added 1,6-dihydroxynaphthol (59 mg, 0.37 mmol) and the reaction heated to 130 °C for 5 h. The DMF was removed using vacuum distillation and the residue purified on column, eluted with MeOH:EtOAc 1:10 to give the Nile Red derivative 71 (50 mg, 34 %). \(^1\)H NMR (500 MHz; DMSO-\(d_6\)): \(\delta\) 10.41 (s, 1H), 7.94 (d, \(J = 8.4\) Hz, 1H), 7.86 (d, \(J = 2.7\) Hz, 1H), 7.56 (d, \(J = 9.0\) Hz, 1H), 7.06 (dd, \(J = 6.0, 2.4\) Hz, 1H), 6.82 (d, \(J = 8.4\) Hz, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 4.63 (d, \(J = 4.8\) Hz, 4H), 3.47 (d, \(J = 1.5\) Hz, 4H), 1.66-1.78 (m, 4H); \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta\) 182.3, 161.3, 152.3, 151.9, 147, 139.4, 134.4, 131.4, 128.2, 124.5, 119.1, 110.7, 108.7, 104.8, 97.2, 96.9, 58.9, 48.3, 30.6; see Ref 196 for HRMS.
Tertiary alcohol 84: To the 3,4-butanedione 83 (3 g, 34.8 mmoles) and allyl bromide (5.1 ml, 59.2 mmoles) in DMF (12 ml) was added Zn dust (200 mg) immediately followed by 6 ml of a saturated solution of NH₄Cl in water. After 15 mins, another 100 mg of Zn dust was added followed by 3 ml of saturated NH₄Cl. The reaction was stirred at room temperature for 20 mins when TLC indicated that the 3,4-butanedione was completely consumed. The reaction was quenched by the addition of 10 ml water and 1 ml of 1M HCl. The reaction mixture was extracted with diethyl ether (3 × 15 ml), the organic layer was separated, dried using MgSO₄ and concentrated. Purification by flash chromatography hexane:EtOAc 3:1 offered the desired keto-alcohol 84 (271 mg, 94% yield) as a colorless liquid. \(^1\)H NMR (500 MHz; CDCl₃): δ 5.86 (m, 1H), 5.07-5.05 (m, 2H), 2.51 (m, 1H), 2.33 (m, 1H), 2.31 (s, 3H), 1.24 (s, 3H); \(^13\)C NMR (125 MHz, CDCl₃): δ 211.2, 130.4, 118.2, 93.0, 48.5, 26.2, 22.3; HRMS (ESI) m/z calcd. for C₇H₁₃O₂ (M+H)⁺ 129.09156, found 129.08963.

2-imino-2,5-dihydrofuran-3-carbonitrile 87: To a 50 ml round bottom flask containing malononitrile (284 mg, 4.3 mmoles) and flushed with N₂, was added anhydrous EtOH (10 ml). The reaction was cooled to 0 °C and NaH (60% dispersion in mineral oil, 103 mg,
4.3 mmols) was added. After the evolution of H₂ was complete, the keto-alcohol 84 (500 mg, 3.9 mmols) was added and the ice bath removed. The reaction turned a brown color and was stirred at room temperature for 25 min. 4-dimethylaminobenzaldehyde (581 mg, 3.9 mmols) was added to the reaction mixture followed by three drops of piperidine. The reaction immediately turned red. It was stirred at ambient temperature for two minutes. The solvent was removed under reduced pressure and the product immediately purified by flash chromatography on silica gel using hexane:EtOAc 1:9 to afford the product 87 (740 mg, 60%) as a brown-red solid. 

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\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.48-7.44 \text{ (m, 3H), 6.66-6.58 \text{ (m, 3H), 5.65-5.56 \text{ (m, 1H), 5.10-5.08 \text{ (m, 2H), 3.08 \text{ (s, 6H), 2.69-2.55 \text{ (m, 2H), 1.62 \text{ (s, 3H);}}} \text{C NMR (125 MHz, CDCl}_3\text{): } \delta 169.4, 166.3, 152.4, 143.8, 130.3, 129.7, 122.1, 120.3, 113.5, 111.9, 109.9, 97.6, 91.0, 43.4, 40.1, 25.1; HRMS (ESI) m/z calcd. for C₁₉H₂₂N₃O (M+H)⁺ 308.1763, found 308.1761.}
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**Acrylamide 88:** To the acryloyl chloride (19 µl, 0.234 mmoles) in anhydrous CH₂Cl₂ (6 ml) at 0 °C was added dropwise a mixture of 87 (50 mg, 0.156 mmoles) and Et₃N (40 µl, 0.312 mmoles) in anhydrous CH₂Cl₂ (2 ml). The reaction was stirred for 10 mins when TLC indicated complete consumption of 87. The reaction mixture was diluted with water (10 ml) and extracted with CH₂Cl₂ (3 x 10 ml). The organic layer was washed with brine, dried with MgSO₄ and concentrated *in vacuo*. Flash chromatography with hexane:EtOAc 1:7 gave the desired product 88 (47.3 mg, 81%) as a red solid. 

\[
\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.48-7.44 \text{ (m, 3H), 6.66-6.58 \text{ (m, 3H), 5.65-5.56 \text{ (m, 1H), 5.10-5.08 \text{ (m, 2H), 3.08 \text{ (s, 6H), 2.69-2.55 \text{ (m, 2H), 1.62 \text{ (s, 3H);}}} \text{C NMR (125 MHz, CDCl}_3\text{): } \delta 169.4, 166.3, 152.4, 143.8, 130.3, 129.7, 122.1, 120.3, 113.5, 111.9, 109.9, 97.6, 91.0, 43.4, 40.1, 25.1; HRMS (ESI) m/z calcd. for C₁₉H₂₂N₃O (M+H)⁺ 308.1763, found 308.1761.}
\]
CDCl$_3$): $\delta$ 7.56 (d, $J = 16.1$ Hz, 1H), 7.50 (d, $J = 8.9$ Hz, 2H), 6.67-6.64 (m, 3H), 6.36-6.27 (m, 2H), 5.86 (dd, $J = 9.42$, 2.35 Hz, 1H), 5.61-5.53 (m, 1H), 5.16-5.10 (m, 2H), 3.09 (s, 6H), 2.73-2.63 (m, 2H) 1.65 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.9, 172.5, 171.1, 166.8, 165.2, 152.7, 145.1, 133.3, 130.8, 130.2, 129.6, 121.9, 121.0, 111.9, 109.5, 93.0, 43.4, 40.1, 25.1; HRMS (ESI) $m/z$ calcd. for C$_{22}$H$_{24}$N$_3$O$_2$ (M+H)$^+$ 362.1869, found 362.1871.

**α-Bromoamide 89:** To the bromoacetyl bromide (20 μl, 0.234 mmol) in anhydrous CH$_2$Cl$_2$ (6 ml) at 0°C was added dropwise a mixture of 87 (50 mg, 0.156 mmol) and Et$_3$N (40 μl, 0.312 mmol) in anhydrous CH$_2$Cl$_2$ (2 ml). The reaction was stirred for 10 mins when TLC indicated complete consumption of 87. The reaction mixture was diluted with water (10 ml) and extracted with CH$_2$Cl$_2$ (3 x 10 ml). The organic layer was washed with brine, dried with MgSO$_4$ and concentrated in vacuo. Flash chromatography with hexane:EtOAc 1:7 gave the desired product 89 (63 mg, 94%) as a red solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.60 (d, $J = 16.1$ Hz, 1H), 7.50 (d, $J = 8.9$ Hz, 2H), 6.67-6.64 (m, 3H), 5.63-5.56 (m, 1H), 5.18-5.14 (m, 2H), 4.07 (s, 2H), 3.11 (s, 6H), 2.80-2.74 (m, 1H), 2.66-2.62 (m, 1H), 1.68 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.0, 160.1, 159.0, 152.9, 145.9, 131.1, 129.5, 121.8, 121.2, 111.9, 111.8, 111.5, 109.2, 93.8, 43.4, 40.1, 32.0, 24.9; HRMS (ESI) $m/z$ calcd. for C$_{21}$H$_{23}$N$_3$O$_2$Br (M+H)$^+$ 428.0974, found 428.0977.
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APPENDIX A: $^1$H NMR and $^{13}$C NMR spectra of 3n
APPENDIX B: $^1$H NMR and $^{13}$C NMR spectra of 4n
APPENDIX C: $^1$H NMR and $^{13}$C NMR spectra of 6n
APPENDIX D: $^1$H NMR and $^{13}$C NMR spectra of 3p
APPENDIX E: $^1$H NMR and $^{13}$C NMR spectra of 4p

![Chemical Structure of 4p](image)

![H NMR Spectrum of 4p](image)

![C NMR Spectrum of 4p](image)
APPENDIX F: $^1$H NMR and $^{13}$C NMR spectra of 6p
APPENDIX G: $^1$H NMR and $^{13}$C NMR spectra of 3t
APPENDIX H: $^1$H NMR and $^{13}$C NMR spectra of 4t
APPENDIX I: $^1$H NMR and $^{13}$C NMR spectra of 6t
APPENDIX J: $^1$H NMR and $^{13}$C NMR spectra of 23z

![Diagram of 23z with NMR spectra]
APPENDIX K: $^1$H NMR and $^{13}$C NMR spectra of 14z
APPENDIX L: $^1$H NMR and $^{13}$C NMR spectra of 26z
APPENDIX M: $^1$H NMR and $^{13}$C NMR spectra of 27z
APPENDIX N: $^1$H NMR and $^{13}$C NMR spectra of 14ac
APPENDIX O: $^1$H NMR and $^{13}$C NMR spectra of 14p
APPENDIX P: Full X-ray Determination Data for 14z

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ZERR 4.00 0.0026 0.0010 0.0020 0.000 0.002 0.000
LATT 1
SYMM -x, y+1/2, -z+1/2
SFAC C H N O Si
UNIT 92 108 8 8 4
L.S. 10
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BOND $H
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HTAB
CONF
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    0.065110  0.077370 -0.09510  0.009670 -0.034650
O2  4  1.047181  1.051443  0.293515  11.000000   0.074000 =
    0.139730  0.060610  0.021890 -0.000790  0.009680
N1  3  0.800545  1.009481  0.181250  11.000000   0.062850 =
    0.056050  0.058990 -0.004390  0.010010 -0.010380
O3  4  0.903749  1.135206  0.250109  11.000000   0.055900 =
    0.074100  0.058390 -0.012990  0.013180 -0.009480
C1  1  0.534177  0.749774  0.133531  11.000000   0.069390 =
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H1  2  0.551059  0.862101  0.153890  11.000000  -1.500000
H21  2  0.492911  0.721178  0.159947  11.000000  -1.500000

AFIX 0
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C3  1  0.727132  1.008723  0.199388  11.000000   0.058860 =
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AFIX 13
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APPENDIX P (continued)

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     0.098880  0.080010 -0.009020  0.024470  0.005420

AFIX 43
H17  2  0.659900  1.257428  0.451021  11.000000  -1.200000

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C21  1  0.675998  1.137873  0.339633  11.000000  0.059300 =
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AFIX 43
H16  2  0.630440  1.096695  0.324539  11.000000  -1.200000

AFIX 0
C22  1  0.727852  1.104425  0.286692  11.000000  0.058560 =
     0.052420  0.066540  0.000270  0.011750  0.000300
C23  1  0.572144  0.441585  0.111161  11.000000  0.127220 =
     0.132695  0.192760 -0.046430  0.027200 -0.074790

AFIX 137
H23  2  0.606411  0.353925  0.130247  11.000000  -1.500000
H25  2  0.570677  0.460047  0.048548  11.000000  -1.500000
H24  2  0.526765  0.404309  0.123721  11.000000  -1.500000

AFIX
HKLF 4 1 1 0 0 0 1 0 0 0 1
END
HKLF 4 1 1 0 0 0 1 0 0 0 1
REM  cdwla9_0ma in P2(1)/c
REM  R1= 0.0478 for 1790 Fo > 4sig(Fo) and 0.0500 for all 2159 data
REM  258 parameters refined using 0 restraints
VITA

ADITI PATIL

EDUCATION:
Doctor of Philosophy, Ph.D. in Organic Chemistry
August 2007 - present

Master of Science, M.Sc. in Organic Chemistry
June 2004 - May 2006
University of Pune, Pune, India

Bachelor of Science, B.Sc. in Chemistry
June 2001 - May 2004
University of Pune, Pune, India

WORK EXPERIENCE:
Research Assistant
Department of Chemistry, University of Illinois at Chicago, Chicago, IL
August 2007 - present

Teaching Assistant
Department of Chemistry, University of Illinois at Chicago, Chicago, IL
August 2007 - May 2012

Research Mentor
Illinois Mathematics and Science Academy, Chicago, IL
August 2010 - April 2011

Project Assistant
National Chemical Laboratory, Pune, India
October 2006 - April 2007

Intern
National Chemical Laboratory, Pune, India
December 2005 - April 2006

Research Scholar
Indian Academy of Sciences
Hyderabad central University, Hyderabad, India
May 2005 - August 2005
HONORS & AWARDS:
1) Moriarty Graduate Fellowship, Department of Chemistry, UIC, Chicago, IL
   August 2012 - August 2013
2) ACS Travel Award for the Fall 2012 National Meeting, Philadelphia, PA
   August 2012
3) Abbott Scholar at Abbott Scholar’s Symposium, Abbott Park, IL
   August 2012
4) Silver medal, Master of Science, University of Pune, Pune, India
   May 2006
5) Research Scholar at Indian Academy of Sciences, Hyderabad, India
   May 2005

PROFESSIONAL AFFILIATIONS:
Member, American Chemical Society, Organic Chemistry Division
April 2012 - present

PUBLICATIONS:
1) “Preparation of Enantioenriched α-Oxygenated Ketones by the
2) "Preparation of α-Oxygenated Ketones by the Dioxygenation of Alkenyl Boronic
3) “Improved Method for the Synthesis of β-Carbonyl Silyl-1,3-Dithianes by the
   Double Conjugate Addition of 1,3-Dithiol to Propargylic Carbonyl Compounds,”
   74, 9206
4) “pH-Regulated “Off-On” fluorescence signaling of d-block metal ions in aqueous
   media and realization of molecular IMP logic function,” Sarkar, M.; Bhantia, S.;