Design and Synthesis of Scaffolding Ligands for Regio- and Stereoselective Hydroformylation

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DESIGN AND SYNTHESIS OF SCAFFOLDING LIGANDS FOR REGIO- AND
STEREOSELECTIVE HYDROFORMYLATION

a dissertation

by

CANDICE L. JOE

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The Design and Synthesis of Scaffolding Ligands for Regio- and Stereoselective Hydroformylation

Candice L. Joe
Thesis Advisor: Dr. Kian L. Tan

Abstract

Chapter 1. The use of directing groups is a powerful way to control selectivity in organic chemistry. Due to their ability to install new functionality in a reliable fashion, directing groups have had a profound impact on stereoselective, site-selective, and regioselective transformations. More recently, catalytic directing groups have been developed and utilized in a variety of metal-catalyzed transformations, including C-H activation and hydroacylation, and have the potential to be more broadly applied to other transformations.

Chapter 2. Catalytic directing groups have recently been designed for hydroformylation. Based on the design of racemic scaffolding ligand 2.5, enantioenriched ligand 2.42 was synthesized for the asymmetric hydroformylation of *para*-methoxyphenyl (PMP) protected allylic amines. Under mild conditions, a variety of 1,2-disubstituted olefins underwent directed hydroformylation to afford the proximal β-amino alcohol products in good yields and excellent enantioselectivities. The substrate scope has been extended to electronically modified allylic anilines. A modest resonance effect was seen upon the aniline substrate binding to the ligand, which, in turn, manifested in the hydroformylation
reaction results. Thus the first enantioselective reaction performed with a catalytic directing group was demonstrated.

**Chapter 3.** Ligand 3.67 was developed, which promotes aldehyde formation on the distal olefinic carbon relative to the directing functionality on the substrate. This is in contrast to other phosphorus-based directing groups that have been successful at placing the aldehyde on the proximal olefinic carbon. Ligand 3.67 has been applied to the diastereoselective hydroformylation of homoallylic alcohols to afford δ-lactones selectively. Altering the distance between the alcohol and olefin revealed that homoallylic alcohols afford the distal lactone with the highest levels of regioselectivity. Taken together with previous examples of proximal-selective hydroformylation, these results being to more fully address the challenge of controlling regioselectivity in hydroformylation.

**Chapter 4.** The harvesting of energy from light to power chemical transformations is an underdeveloped area. Utilizing p-type silicon nanowires (SiNWs) as a photocathode, the photoelectrochemical carboxylation of aromatic ketones has been developed to afford α-hydroxy carboxylic acids. Utilizing low operating potentials, the direct reduction of carbon dioxide (CO₂) is avoided. Highlighting the synthetic utility of this transformation, two precursors to the NSAID compounds ibuprofen and naproxen were synthesized using CO₂, and abundant C₁ feedstock, and light, a crucial source of energy in nature.
Acknowledgements

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3PG</td>
<td>3-Phosphoglycerate</td>
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<tr>
<td>Ac</td>
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<tr>
<td>acac</td>
<td>Acetylacetonato</td>
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<td>AIBN</td>
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</tr>
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<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine-5’-triphosphate</td>
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<td>ATR</td>
<td>Attenuated Total Reflectance</td>
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<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
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<tr>
<td>DART-TOF</td>
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<td>DIPEA</td>
<td>(N,N)-Diisopropylethylamine</td>
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</tr>
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<td>FG</td>
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<td>Flame ionizing detector</td>
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<td>HPLC</td>
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</tr>
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</tr>
<tr>
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<td>Lithium aluminum hydride</td>
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<td>m</td>
<td>Multiplet</td>
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<td>m-</td>
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</tr>
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<td>MHz</td>
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<td>mL</td>
<td>Milliliters</td>
</tr>
<tr>
<td>n-</td>
<td>Normal</td>
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NaBH₄  
Sodium borohydride

NADPH  
Nicotinamide adenine dinucleotide phosphate

NMR  
Nuclear Magnetic Resonance

nOe  
Nuclear Overhauser Effect

o-  
Ortho

p-  
Para

p-TsOH  
para-toluenesulfonic acid

PCC  
Pyridinium chlorochromate

PEC  
Photoelectrochemical

Ph  
Phenyl

phth  
Phthalimide

Piv  
Pivaloyl

PMP  
para-methoxyphenyl

ppm  
Parts per million

ppt.  
Precipitate

Pr  
Propyl

psi  
Pounds per square inch

q  
Quartet

quant  
Quantitative

rac  
Racemic

rr  
Regioisomeric ratio

rt  
Room temperature
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<td>Ribulose-1,5-bis-phosphate</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SCE</td>
<td>Saturated calomel electrode</td>
</tr>
<tr>
<td>SFC</td>
<td>Supercritical fluid chromatography</td>
</tr>
<tr>
<td>SiNWs</td>
<td>Silicon Nanowires</td>
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<td>SiO₂</td>
<td>Silica</td>
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<tr>
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</tr>
<tr>
<td>VB</td>
<td>Valence band</td>
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<tr>
<td>UV</td>
<td>Ultraviolet</td>
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Chapter 1: The Importance of Directed Reactions in Organic Chemistry

1.1 Introduction

The control of regio- and stereochemistry in organic transformations remains one of the paramount challenges in reaction development. Non-bonding interactions, such as the electronic preferences of the substrate and steric interactions between the substrate and reagent, typically govern the outcome of organic reactions. These “repulsive” interactions result in the reagent approaching from a more sterically accessible trajectory. The electronic nature of the substrate can also bias the chemo- or regioselective outcome of the transformation. These trends can often be reversed through the use of directing groups: functional groups that associate the substrate and reagent prior to the selectivity-determining step.

Demonstrating their importance in synthetic organic chemistry, directing groups have been utilized in a variety of transformations, including oxidation, C-H activation, hydrogenation, hydroformylation and Heck reactions.\(^1\) In some cases, common organic functional groups present in the substrate can serve as a directing group.\(^{1a}\) A directing functionality can also be installed, in additional synthetic steps, to carry out a specific chemical transformation and later removed.\(^{1b}\) More recently, catalytic directing groups

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have been developed, operating via a dynamic association between the substrate and reagent.\textsuperscript{1b,2}

Although the field of directed reactions is quite broad, they are unified by the mechanism in which they achieve selectivity: intramolecularity. Since the association of reaction partners is maintained in the selectivity-determining step, the transition state is highly ordered, which allows for an energetic discrimination between competing reaction pathways.\textsuperscript{3} The reaction is thus intramolecular in nature, resulting in a reduction in activation entropy, which often leads to observed rate-acceleration.\textsuperscript{2} As a result, unexpected stereo- and regio-chemical outcomes are often observed that cannot be explained by steric or electronic parameters alone. Atypical site-selectivities can also result from directed reactions.

1.2 Landmarks in the Development of Directed Reactions

Directed reactions have found wide ranging utility in organic chemistry. Highlighting their importance, two such reactions were recognized as part of the 2001 Nobel Prize in Chemistry. Many directed reactions have been developed for the construction of bonds that were not possible through previous methods; herein, a small collection of those reactions will be described.

1.2.1 Impact on Stereoselective Reactions

Directed reactions have seen prominence in the development of stereoselective reactions. This is due to the fact that the presence of a directing functionality can selectively deliver a reagent to one face of a substrate.

One of the earliest examples of a directed reaction dates back to 1959. Expanding the substrate scope of their seminal communication in 1958, Simmons and Smith reported a substrate-directed cyclopropanation of methoxyarenes. They propose that the Lewis-basic oxygen of the methoxyarene assists in the zinc-mediated cyclopropanation of the pendant disubstituted olefin (1.2, Scheme 1.1, Equation 1). They also observe a proximity effect relative to reactivity, with the meta-substituted arene substrate being less active than 1.1. Building upon this work, Winstein utilized 2-cyclohexen-1-ol (1.4) for alkoxide-directed cyclopropanation to afford syn isomer 1.6 exclusively (Scheme 1.1, Equation 2). While cyclopropanation would typically occur from the least hindered face of the olefin, the pre-coordination of the zinc reagent and the hydroxyl group directs the methylene addition to the neighboring alkene via intermediate 1.5. Converting the alcohol to an acetate functionality results in the attenuation of reactivity. This highlights the importance of the zinc-alkoxide for the observed selectivity and demonstrates an overall enhancement in the rate of the reaction.

Another classic example of a stereoselective bond construction where steric factors are overridden was disclosed by Henbest in 1959 (Scheme 1.2).\(^6\) They reported the substrate-directed epoxidation of 2-cyclohexen-1-ol (1.4) in the presence of a perbenzoic acid to afford the epoxide syn to the alcohol functionality. The formation of a highly ordered polycyclic transition state (1.7) is proposed, which is stabilized by hydrogen-bonding between the alcohol and the perbenzoic acid reagent. The directing ability of the alcohol allows the perbenzoic acid to be delivered to the more sterically congested face of the olefin.

An early example of a metal-catalyzed-substrate-directed reaction, an alkoxide-directed alkene hydrogenation, was described by Thompson and McPherson in 1974 (Scheme 1.3).\(^7\) In the presence of potassium alkoxide 1.9, molecular hydrogen was delivered to the top face of the olefin, presumably from alkoxide-ligated rhodium dihydride complex 1.10, to give syn isomer 1.11 as the only observable product. Notably, the protonated variant of substrate 1.9 was resistant to olefin reduction. Additionally, hydrogenation reactions of the corresponding free alcohol substrate with heterogeneous palladium and platinum catalysts afforded primarily the anti isomer. Through the directing ability of the alkoxide, enhanced reactivity is observed, as well as a reversal in the stereoselectivity that is observed under traditional heterogeneous conditions.

**Scheme 1.3 Directed Hydrogenation via Anionic Coordination**

One of the pioneers of metal-catalyzed asymmetric synthesis was Knowles, who replaced the achiral triphenylphosphine ligands in Wilkinson’s catalyst with chiral phosphine ligands.\(^8\) Using a rhodium complex containing the bidentate ligand DiPAMP, the asymmetric hydrogenation of enamide 1.12 afforded 1.13 in 95% ee (Scheme 1.4). This is a key step in the synthesis of the amino acid L-DOPA, which has proven useful in the treatment of Parkinson’s disease. It is believed that the amide functional group directs

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the hydrogenation to occur from one face of the olefin selectively. Importantly, this was the first example of an asymmetric metal-catalyzed reaction to be used on an industrial scale.

**Scheme 1.4** Knowles’ Directed Asymmetric Hydrogenation in the Synthesis of L-DOPA

![Scheme 1.4](image)

The Sharpless asymmetric epoxidation is one of the first examples of a practical asymmetric reaction enabled by the use of a directing group. Epoxidation of allylic alcohol 1.14 afforded epoxy alcohol 1.15 in 77% yield and 95% ee (Scheme 1.5). Although two tri-substituted olefins are present in the substrate, only the one in close proximity to the free alcohol undergoes epoxidation. The regio- and enantioselectivity in the reaction arises from the binding of the allylic alcohol to the (+)-diethyl tartrate-ligated titanium catalyst, which directs the epoxidation reaction to occur from the bottom face of the olefin. Importantly, though the introduction of a hydroxyl group typically has a net deactivating effect on olefin reactivity towards typical m-CPBA epoxidations, under the Sharpless conditions an overall rate enhancement is observed. Moreover, both the chemo- and stereoselectivity of the transformation can be controlled in a predictable fashion.

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1.2.2 Impact on Site-Selective Reactions

The use of directing groups has also had a profound impact on site-selective reactions. Often, the site-selectivity observed in these reactions could not be predicted based on the inherent substrate bias alone. These reactions are typically sensitive to the distance between the directing group and reactive site, which allows for a high degree of specificity.

The concept of “designer” directing groups was pioneered by Breslow through the numerous examples of selective C-H activation of steroids.\(^{10,11}\) An early example employs a silyl ether tether (1.16) that allows for chlorination selectively at the tertiary C-H bond at the B/C ring junction (1.17, Scheme 1.6, Equation 1). The site-selectivity observed in this reaction is a result of the appropriate distance between the directing group and the B/C ring junction, rather than the inherent reactivity of the C-H bond itself.\(^{10a,10b}\) To further corroborate this point, the incorporation of a larger tether containing a benzophenone moiety (1.18) directs oxidation to occur selectively at the

---


tertiary C-H bond at the C/D ring junction (1.19, Scheme 1.6, Equation 2). In both of these cases, no other steroid isomer was observed, except for unreacted starting material. The design of a directing group that spans the correct distance allows for the effective discrimination between reactive sites in a complex molecule where many similar motifs are present.

Scheme 1.6 Breslow’s Site-Selective Functionalization of Steroids

![Scheme 1.6 Breslow’s Site-Selective Functionalization of Steroids](image)

The use of directing groups has also been important in the development of site-selective C-H activation of arenes. Murai and co-workers demonstrated that the ortho C-H bond of acetophenone 1.20 could be selectively cleaved by a ruthenium catalyst to generate five-membered metallacycle 1.21 (Scheme 1.7). Coordination of ethylene and

---

subsequent insertion into the \textit{ortho} position generated alkylated compound 1.22 in a quantitative yield. Due to a proximity effect between the carbonyl and the \textit{ortho} C-H bond, this transformation proceeds in a highly selective fashion. Since this pioneering work, many reports of \textit{ortho} C-H functionalization have been reported using oxygen and nitrogen-containing directing groups.\(^{13}\)

\textbf{Scheme 1.7 Ortho-Selective C-H Activation}

\begin{align*}
\begin{array}{c}
\text{Me} & \text{O} \\
& \text{Me} \\
\text{Me} & \text{Me}
\end{array}
\text{2 mol \% RuH}_2\text{(CO)(PPh}_3\text{)_3} \\
\text{toluene, reflux} \\
\text{ethylene (6 equiv.)} \\
\begin{array}{c}
\text{Me} & \text{O} \\
& \text{Me} \\
\text{Me} & \text{Me}
\end{array}
\end{align*}

With the groundwork laid for \textit{ortho} selective C-H activation of arenes, the challenge of \textit{meta} selective C-H functionalization has recently been undertaken by the Yu group.\(^{14,15}\) A aromatic linker containing a nitrile functional group was appended to a


benzyl alcohol (1.23). The nitrile functionality coordinates to a palladium catalyst and
delivers it to the meta aromatic C-H bond to afford functionalized arene 1.25 in greater
than 95% selectivity relative to the other possible constitutional isomers (Scheme 1.8).
The excellent meta selectivity is attributed to a macrocyclic 12-membered cyclophane-
like transition state (1.24). Whereas typical site-selectivity in the functionalization of
aromatic rings is governed by the inherent steric or electronic nature of the arene, the use
of the nitrile template allows the intrinsic electronic and steric preferences to be
 overridden.

Scheme 1.8 Yu’s meta-Selective Arene C-H Functionalization

1.2.3 Impact on Regioselective Reactions

The control of regioselectivity remains one of the foremost challenges in many
organic reactions. This obstacle is among the most apparent in the context of olefin
functionalization reactions. The use of directing groups has enabled the predictable and
selective formation of one structural isomer in a variety of transformations.
An early example of a regioselective reaction enabled by a directing group is the selective cleavage of epoxyalcohols, which was demonstrated by Henbest and co-workers in 1959 (Scheme 1.9). Early investigations into this reaction utilized LiAlH₄ as a reducing agent. A typical hydride opening of an epoxide occurs such that the hydride approaches from the least sterically hindered side of the oxirane. The presence of a hydroxyl group in close proximity (1.26) is able to associate with the aluminum reagent (1.27) and deliver the hydride intramolecularly to open the epoxide. Notably, LiAlH₄ reduction of the THP or methyl ether analogues of the alcohol afford the opposite isomer of diol product.

Scheme 1.9 Regioselective Ring-Opening of Epoxy Alcohols

![Scheme 1.9](image)

In 1988, Evans and co-workers reported the use of phosphinites to control the stereo- and regiochemical outcome of rhodium-catalyzed hydroboration with catecholborane (Scheme 1.10). The hydroboration of the phosphonite derived from 2-cyclohexen-1-ol (1.29) affords syn-1,2-diol 1.30 selectively; when the alcohol is protected as the TBS ether (1.31), anti-1,3-diol 1.32 is observed as the major product. In this case, the appropriate choice of directing group allows for the selective formation of each constitutional isomer of product in a stereoselective fashion. Interestingly, hydroboration of a homoallylic phosphinite substrate gives the syn-1,3-diol, which is in

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contrast to the homoallylic TBS ether, which affords a statistical mixture of products. Taken together, these results demonstrate the challenge of designing directing groups that allow one to obtain each isomer of product in a predictable and selective fashion.

**Scheme 1.10 Directed Rhodium-Catalyzed Hydroboration**

Highlighting the power of directed reactions in overturning the inherent substrate selectivity, Feringa and co-workers reported an aldehyde selective Wacker oxidation (Scheme 1.11).\(^\text{17}\) Whereas typical terminal olefins preferentially form the ketone product, in the presence of phthalimide protected allylic amine 1.33, the aldehyde product (1.34) is formed selectively. Not only does the appropriate choice of directing group allow for the control of regiochemistry, but it also allows for the inherent substrate selectivity to be overridden.

1.3 Importance of Directing Groups in Hydroformylation

Hydroformylation is a metal-catalyzed olefin functionalization reaction where the control of regiochemistry is the preeminent challenge. Due to its high affinity for a variety of metal catalysts, phosphorus-based directing groups have gained popularity. In particular, the ability of phosphines to compete with carbon monoxide, which is present in large excess, for coordination sites on the catalytic metal center has made phosphorus-based directing groups effective at controlling both the regio- and stereochemical outcome of the reaction.

The diphenylphosphinobenzoate ester (DPPB) has become one of the most useful directing groups in hydroformylation. Among the first to showcase the synthetic utility of this group was Burke in the total synthesis of (+)-phyllanthocin (Scheme 1.12, Equation 1). Attempts to functionalize the 1,2-disubstituted olefin in 1.36 in the absence of a directing group led to mixtures of regio- and stereoisomers. Introduction of a meta-DPPB group afforded the desired aldehyde in good regio- and stereoselectivities. The

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observation that the *para*-DPPB group displayed minimal reactivity is consistent with the rate-accelerating effect that is often observed through the appropriate choice of directing group. The *m*-DPPB group can be subsequently removed by saponification with aqueous NaOH in MeOH.

**Scheme 1.12** Early Examples of Directing Groups in Hydroformylation

In the presence of homoallylic olefin 1.38, a phosphine directs hydroformylation such that the branched isomer is observed as the sole product (Scheme 1.12, Equation 2). Through an intramolecular chelate between the phosphine, olefin, and rhodium catalyst the observed regiochemical outcome is a result of a preference for a 6-*exo*-trig over a 7-*endo*-trig hydrometallation transition state. In doing so, the inherent substrate preference to afford the linear aldehyde product is overridden by the incorporation of a directing phosphine moiety.

In 2001, Leighton demonstrated that a dibenznophosphol-1-ylmethyl group appended to an allylic alcohol, 1.40, undergoes hydroformylation to afford *anti* branched

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aldehyde 1.41 as the major product (Scheme 1.13, Equation 1).\textsuperscript{21} Showcasing the synthetic utility of this reaction, the phosphine-based directing group is able to control the regio- and stereochemical outcome of the reaction allowing access to propionate aldol products efficiently. This is in contrast to the typical regiochemical outcome for terminal olefins in hydroformylation, where the linear aldehyde is preferred. Removal of the directing group requires LiAlH₄ in dioxane at 150 °C.

**Scheme 1.13 Removable Directing Groups in Hydroformylation**

![Scheme 1.13 Removable Directing Groups in Hydroformylation]

The use of phosphine-based directing groups has also allowed for more challenging substrates to undergo efficient hydroformylation, such as 1,2-disubstituted olefins (Scheme 1.13, Equation 2). In the absence of a directing group, a near 1:1 mixture of aldehyde products would be expected, since the olefinic carbons are sterically similar. In 2007, Breit and co-workers demonstrated that 1.42, containing an o-DPPB ester, affords the aldehyde on the proximal olefinic carbon (1.43) in a highly selective fashion.

The o-DPPB ester group has also been appended to tri-substituted alkene substrates, such as geraniol; hydroformylation occurs with site-, regio-, and stereoselectivity, thus demonstrating the many advantages of directing group chemistry.

1.4 Catalytic Directing Groups

In order to reduce generated waste and avoid additional synthetic steps, the development of catalytic directing groups has emerged as a desirable alternative to control selectivity in organic reactions. Catalytic directing groups maintain all of the advantages of directing group chemistry, but they operate through a dynamic reversible association with the substrate.

Catalytic directing groups have proven to be especially useful in the field of C-H activation. In 1985, Lewis demonstrated that phenol undergoes a rapid and reversible transesterification reaction with triphenylphosphite. Upon coordination of the metal catalyst to the phosphite, cyclometallation and addition of D₂ occurs to afford o-o'-deuterated product 1.44 (Scheme 1.14).

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23 This strategy has also been applied to hydroformylation, but will be discussed more thoroughly in Chapter 2.

Phosphinites exhibit the same ability to undergo transesterification with phenolic substrates. Building upon the work by Lewis and Smith,\textsuperscript{24a} Cole-Hamilton and co-workers reported an efficient rhodium-catalyzed bis-ortho-alkylation of phenol with ethylene to afford 1.45 as product (Scheme 1.15, Equation 1). Bedford and co-workers extended the utility of phosphinite transesterification to perform the intermolecular coupling of aryl halides to the ortho C-H bond of a variety of phenolic substrates (Scheme 1.15, Equation 2).\textsuperscript{25}

\textbf{Scheme 1.14} ortho-Deuteration of Phenols

\begin{center}
\includegraphics[width=0.5\textwidth]{ortho-deuteration.png}
\end{center}

\textbf{Scheme 1.15} Phosphinite-Directed C-H Functionalization Reactions

\begin{center}
\includegraphics[width=0.5\textwidth]{phosphinite-directed.png}
\end{center}

Catalytic directing groups have also been useful in the field of hydroacylation, where the suppression of decarbonylation remains a challenge. Based on a finding by

Suggs that pre-formed pyridyl imines can suppress the decarbonylation pathway. Jun and co-workers reported the catalytic use of 2-amino-3-picoline in the hydroacylation of aryl aldehydes via a rapid transimination pathway (Scheme 1.16). The benzoic acid and aniline additives facilitate rapid turnover in the transimination reaction. Chelation-assisted C-H activation of the aldimine C-H bond and hydrometallation in the presence of an alkene furnishes intermediate 1.46, which, after reductive elimination, affords the ketone product in 98% yield.

**Scheme 1.16** 2-Amino-3-Picoline as a Catalytic Directing Group for Hydroacylation

![Scheme 1.16](image)

**1.5 Conclusions**

Directed reactions occupy a prominent position in organic chemistry because they are able to control the addition of new functionality in a predictable, reliable, and selective fashion. The use of directing groups has allowed for stereochemical outcomes to be observed that could not be predicted based on steric parameters alone. The appropriate

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choice of directing group has enabled great advances in site- and regioselectivity in a variety of transformations that were not possible previously. Recently, systems employing reversible covalent linkages between a scaffold and a substrate have been developed in the form of catalytic directing groups. Employing all of the advantages of directed reactions, catalytic directing groups have been utilized in a variety of metal-catalyzed reactions, such as C-H activation and hydroacylation, and more recently in hydroformylation (Chapter 2).
Chapter 2: Application of an Enantiopure Scaffolding Ligand to the Asymmetric Hydroformylation of Allylic Amines

2.1 Introduction

Hydroformylation is the addition of hydrogen and carbon monoxide gases across an olefin to generate two isomeric $\text{C}_1$-extended aldehyde products.\(^1\)\(^,\)\(^2\) Originally discovered by Otto Roelen in 1938, it has since become one of the most important homogeneously catalyzed industrial processes to date, as it is used to generate over 9 million tons of oxo products each year.\(^3\) The majority of these products are linear aldehydes, which are highly desired for commodity chemical synthesis. Additionally, hydroformylation is an atom-economical reaction and the aldehydes produced are useful for the subsequent construction of carbon-carbon and carbon-heteroatom bonds.

Despite these attractive features, the application of hydroformylation on the laboratory scale remains scarce.\(^4\) This is likely due to the difficulty in controlling the regiochemical outcome of the reaction. Most terminal alkenes preferentially form the linear aldehyde isomer over the branched based on a steric preference in the hydrometallation step (Scheme 2.1, Equation 1). The branched product for terminal olefins can be reliably accessed when the hydrometallated intermediate is electronically stabilized (e.g. styrene, vinyl acetate), but obtaining branched selectivity for the majority

of terminal olefin substrates remains a challenge. 1,2-Disubstituted olefins, on the other hand, are not only less reactive than their terminal alkene counterparts, but also tend to afford even mixtures (1:1) of constitutional isomers. As an aside, the traditional linear and branched nomenclature (Scheme 2.1, Equation 1) does not accurately describe the product distribution for internal olefins; therefore, we categorize the isomers according to the olefinic carbon relative to an established functional group (FG, Scheme 2.1, Equation 2), either proximal or distal, on which the aldehyde forms.

Scheme 2.1 Hydroformylation of Terminal and 1,2-Disubstituted Olefins.

\[
\begin{align*}
\text{R} & \quad \text{Rh catalyst, L} \\
& \quad \text{H}_2/\text{CO} \\
\text{O} & \quad \text{R} \\
& \quad \text{Me} \\
\text{linear} & \quad \text{branched} \\
\end{align*}
\]

\[
\begin{align*}
\text{FG} & \quad \text{Rh catalyst, L} \\
& \quad \text{H}_2/\text{CO} \\
\text{O} & \quad \text{FG} \\
& \quad \text{R} \\
\text{proximal} & \quad \text{distal} \\
\end{align*}
\]

2.1.1 Design of a Catalytic Directing Group for Hydroformylation

Although the use of stoichiometric phosphorus-based directing groups have been a reliable means of controlling selectivity in hydroformylation (Chapter 1), the Tan group believed that the development of a catalytic directing group would confer additional advantages. We envisioned the design of an organic scaffold that could simultaneously form a reversible, covalent bond with a molecule of substrate (SM) and bind to a metal catalyst through a Lewis basic atom (Cat) (Figure 2.1). A directed reaction would form product (P), which would be released to regenerate the scaffold and thereby complete the

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5 Breit, B. *Synthesis* 2001, 1, 1 – 36.
catalytic cycle. Since the scaffold can re-enter the catalytic cycle, this process is rendered catalytic.

**Figure 2.1** Proposed Catalytic Cycle for a Catalytic Directing Group.

In 2008, the Breit\(^6\) and Tan\(^7\) groups simultaneously realized this goal. Breit demonstrated that homoallylic aliphatic alcohols participate in transesterification with phosphinites in the presence of molecular sieves. Once bound to the substrate, the phosphinite coordinates to the rhodium catalyst through the preferential formation of six-membered metallacycle 2.2 (Scheme 2.2). The preference for a 6-\textit{exo}-trig over a 7-\textit{endo}-trig hydrometallation transition state leads to the selective formation of proximal lactol 2.3 in a 99:1 ratio relative to distal product 2.4. The reaction is carried out in the presence of 10 mol % Ph\(_3\)POMe for a variety of 1,2-disubstituted homoallylic and bishomoallylic alcohol substrates.\(^6\)


In contrast, the Tan group developed a catalytic directing group based on an azaphosphole structure (Figure 2.2). Due to their functional similarity to scaffolding proteins, which localize multiple proteins in a functional cluster, these compounds have been termed scaffolding ligands. Critical features of 2.5 include an orthoamide, which serves as the substrate-binding site, and a phosphine moiety, which is able to coordinate and serve as a ligand on a metal catalyst. Importantly, the oxygen substituent (–Oi-Pr) and the phenyl group on phosphorus are in an anti relationship (97:3 anti: syn). This ensures that the metal, which coordinates to the ligand through the phosphorus lone pair syn to the oxygen substituent, is situated on the same side of the ligand as a bound alkene substrate. Through the proximity effect, the appropriate chelated intermediate leads to a directed reaction.

Scheme 2.2 Breit’s Phosphinite Transesterification Strategy.

In contrast, the Tan group developed a catalytic directing group based on an azaphosphole structure (Figure 2.2). Due to their functional similarity to scaffolding proteins, which localize multiple proteins in a functional cluster, these compounds have been termed scaffolding ligands. Critical features of 2.5 include an orthoamide, which serves as the substrate-binding site, and a phosphine moiety, which is able to coordinate and serve as a ligand on a metal catalyst. Importantly, the oxygen substituent (–Oi-Pr) and the phenyl group on phosphorus are in an anti relationship (97:3 anti: syn). This ensures that the metal, which coordinates to the ligand through the phosphorus lone pair syn to the oxygen substituent, is situated on the same side of the ligand as a bound alkene substrate. Through the proximity effect, the appropriate chelated intermediate leads to a directed reaction.


Figure 2.2 Design of Racemic Scaffolding Ligand 2.5.

Scaffolding ligand 2.5 forms a reversible covalent bond to an alcohol via a transacetalization reaction (Scheme 2.3). In the presence of a catalytic proton source, the nitrogen lone pair assists in the expulsion of isopropanol to generate iminium intermediate 2.6. Another alcohol can bind to the scaffolding ligand, which reestablishes the anti relationship relative to the phenyl ring.

Scheme 2.3 Exchange of Alcohols with Scaffolding Ligand 2.5.

Ligand 2.5 has been successful in the regioselective hydroformylation of allylic and homoallylic alcohols, as well as allylic amines, to generate proximal aldehyde products selectively. Homoallylic alcohols bearing an allylic stereocenter undergo directed hydroformylation with 2.5 to afford γ-lactones in a regioselective fashion after oxidation of the generated lactols (Scheme 2.4, Equation 1).7 The major γ-lactone product is also formed in a diastereoselective fashion, with the anti-isomer being favored in a 92:8 ratio over the syn diastereomer. The hydroformylation of 1,2-disubstituted allylic alcohols results in aldehyde formation on the proximal olefinic carbon, which, after
Pinnick oxidation, yields β-hydroxy carboxylic acids (Scheme 2.4, Equation 2). Although higher ligand loadings are necessary (20 mol % 2.5), the substrate scope can be extended to typically unreactive tri-substituted olefins, where β-hydroxy acid 2.12 is isolated as the only detectable product (Scheme 2.4, Equation 3). Highlighting the power of ligand 2.5 as a catalytic directing group, the regioselective hydroformylation of 1,1-disubstituted allylic alcohol 2.13 affords a carboxylic acid product 2.14 bearing a quaternary center (Scheme 2.4, Equation 4). This result contradicts the widely accepted Keulemans’ rule, stating that formyl groups cannot be produced at quaternary carbon centers in hydroformylation. The exchangeable functional group on the substrate was further extended to include allylic amines protected with a 3,5-bis(trifluoromethyl)benzenesulfonyl group (Scheme 2.4, Equation 5). Via an efficient exchange with ligand 2.5, 1,2-disubstituted olefin 2.15 participates in directed hydroformylation to generate β-amino aldehyde 2.16 a 97:3 rr.

Scheme 2.4 Ligand 2.5 in the Regioselective Hydroformylation of Alcohols and Amines.

1. 6 mol % Rh(acac)(CO)$_2$
25 mol % 2.5, 0.2 mol % p-TsOH,
65 °C, 200 psi H$_2$/CO, benzene
2. PCC, NaOAc, 3 Å MS, DCM

\[
\text{HO} \quad \begin{array}{c}
\text{Me} \\
\text{Bu}
\end{array} 
\xleftarrow{\text{2.7}} \text{O} 
\xrightarrow{\text{2.8}} \text{Pentyl}
\]

\[
\text{Me} \quad \begin{array}{c}
\text{Cy}
\end{array} 
\xleftarrow{\text{2.9}} \text{HO} 
\xrightarrow{\text{2.10}} \text{Cy}
\]

\[
\text{Me} \quad \begin{array}{c}
\text{Me}
\end{array} 
\xleftarrow{\text{2.11}} \text{HO} 
\xrightarrow{\text{2.12}} \text{i-Pr}
\]

\[
\text{Ph} \quad \begin{array}{c}
\text{HO}
\end{array} 
\xleftarrow{\text{2.13}} \text{O} 
\xrightarrow{\text{2.14}} \text{OMe}
\]

\[
\text{Me} \quad \begin{array}{c}
\text{Ph}
\end{array} 
\xleftarrow{\text{2.15}} \text{HO} 
\xrightarrow{\text{2.16}} \text{Ph}
\]

The origin for the excellent levels of regioselectivity in favor of the proximal hydroformylation product, for both alcohol and amine substrates, is due to the chelate effect in the catalytic cycle (Figure 2.3). Upon exchange of a generic protected allylic amine substrate onto 2.5, a rhodium catalyst coordinates to the phosphine in the ligand. In the hydrometallation step, both six- and seven-membered metallacycles are possible (2.17 and 2.18, respectively). Similar to the trends observed in ring strain for cycloalkanes, six-membered metallacycle 2.17 is more favored than the corresponding seven-membered
metallacycle 2.18. Carbon monoxide insertion and reductive elimination leads to the preferential formation of the proximal aldehyde. Release of the product and exchange of another molecule of substrate closes the catalytic cycle.

**Figure 2.3** Catalytic Cycle for Directed Hydroformylation with Ligand 2.5.
The intramolecular nature of the hydroformylation with ligand 2.5 allows the regiochemical outcome to be controlled. Due to the down payment in entropy during the pre-association of the substrate and ligand 2.5, the subsequent hydroformylation step is accelerated. This allows less reactive 1,2- and 1,1-disubstituted olefins to undergo hydroformylation efficiently under mild reaction conditions.

2.2 Asymmetric Hydroformylation

Asymmetric hydroformylation is an atom-economical means of generating enantioenriched aldehyde products from relatively inexpensive feedstocks in a single step.14,15 Highlighting their utility to the synthetic community, these optically enriched aldehyde products serve as precursors to other useful functional groups, including as alcohols, amines, imines, and carboxylic acids. Although asymmetric hydroformylation shows great promise in the fine chemical industry, a number of challenges remain. Among the most significant are (1) the concomitant control of regio- and stereochemistry, (2) the development of a chiral ligand that can be applied to a broad range of olefin substrates, and (3) the expansion of the substrate scope to include unactivated, multi-substituted olefins.


Recent developments in enantioselective hydroformylation have focused on symmetric substrates, in which only one constitutional isomer is formed (Scheme 2.5)\textsuperscript{15c, 15f}\textsuperscript{15f} In 2010, Reek reported the use of hybrid phosphine-phosphonite 2.20 for the asymmetric hydroformylation of 2,3-dihydrofuran (2.19), affording 2.21 in 91% ee.\textsuperscript{15d}\textsuperscript{15d} Since only one constitutional isomer is possible during hydroformylation (in the absence of an isomerization/hydroformylation sequence), the issue of controlling the regiochemical outcome of the reaction is avoided.

\textbf{Scheme 2.5} Asymmetric Hydroformylation of Dihydrofurans.

Terminal olefin substrates that have an inherent preference to form the branched product have been extensively studied in asymmetric hydroformylation.\textsuperscript{15} These substrates preferentially form the branched product because the intermediate resulting from hydrometallation is electronically stabilized. Examples of activated olefins include styrene (2.22), vinyl acetate (2.23), and allyl cyanide (2.24) (Scheme 2.6). To this end, a plethora of chiral ligands have been developed for the asymmetric hydroformylation of this class of terminal alkene substrates. In 1993, Takaya and co-workers\textsuperscript{15a} [Scheme 2.6, [(R,S)-Binaphos], as well as Whiteker and Babin\textsuperscript{15b} [Scheme 2.6, [(2R,4R)-Chiraphite], demonstrated the first examples of practical enantioselective hydroformylation of activated substrates, where the branched aldehyde was obtained in high levels of regio-
and enantioselectivity. Ligands containing achiral diol backbones [Scheme 2.6, [(S,S)-Kelliphite]$^{15i}$ and phospholane-type structures [Scheme 2.6, [(S,S)-Esphos]$^{15j}$ have also shown useful levels of regio- and stereocontrol for these electronically biased substrates.

Although these chiral ligands afford enantioenriched aldehyde products in high levels of both regio- and enantioselectivity, the substrate scope is inherently quite limited. Highlighting the challenge of the concomitant control of regio- and stereoselectivity for unactivated alkene substrates, employing $(R,S)$-Binaphos in the asymmetric hydroformylation of simple terminal olefin 1-hexene affords branched aldehyde in 82% ee; however, the regiochemical outcome strongly favors the achiral linear aldehyde product (24:76 branched:linear).$^{16}$
Scheme 2.6 Ligands Developed for the Asymmetric Hydroformylation of Activated Substrates.

More recently, Landis\textsuperscript{17} and Zhang\textsuperscript{18} reported the asymmetric hydroformylation of terminal allylic amines bearing weakly Lewis basic groups (Scheme 2.7). Employing (S,R)-Yanphos and (S,S)-Bisdiazaphos, it was demonstrated that commonly used nitrogen protecting groups directed the hydroformylation to afford useful levels of regioselectivity.


in favor of the branched β-amino aldehyde products. Additionally, the branched products were isolated in high levels enantioselectivity.

**Scheme 2.7** Asymmetric Hydroformylation of Allylic Amines.

In a pioneering report, Clarke and co-workers developed the mixed phosphine/phosphite bidentate ligand, \((S_{ax},S,S)\)-bobphos, for the asymmetric hydroformylation of unactivated terminal olefins in 2012.¹⁹ The branched aldehyde products were formed selectively over the linear isomer in high levels of enantioselectivity. For example, subjecting 1-hexene (2.29) to hydroformylation with \((S_{ax},S,S)\)-bobphos afforded branched aldehyde 2.30 selectively (75:25 branched:linear) in 93% ee (Scheme 2.8). This is an important example of the simultaneous control of regio-

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and stereochemistry in hydroformylation of unactivated terminal olefin substrates. Unfortunately, a rationale for the observed regiochemical outcome has not been disclosed.

Scheme 2.8 Clarke’s Enantioselective Hydroformylation of Unactivated Olefins.

In an alternative strategy, Reek and co-workers reported that self-assembling supramolecular catalyst 2.32 participates in the asymmetric hydroformylation of unactivated internal olefins (Scheme 2.9). Although the conversions are quite low (20%), moderate regio- and enantioselectivities are obtained for major aldehyde product 2.33. For activated substrates, such as styrene, the selectivities and conversions are much higher using this catalyst system.

Scheme 2.9 Reek’s Supramolecular Catalyst for Asymmetric Hydroformylation.

The results by Clarke and Reek employing unactivated olefins are quite impressive; however, they also highlight the challenges remaining in asymmetric hydroformylation. These include improving the regioselectivities for unactivated terminal olefins and moving towards more challenging substrates, such as unsymmetrical disubstituted alkenes. The development of a ligand, or class of ligands, that can be applied to the asymmetric hydroformylation of a broader range of substrates would be a great advancement in the field.

2.3 Design and Synthesis of an Enantiopure Scaffolding Ligand for Asymmetric Hydroformylation

Having developed a catalytic directing group for the regioselective hydroformylation of challenging disubstituted olefin substrates,\textsuperscript{7,10,11,13} the Tan group was interested in developing an enantioenriched catalytic directing group for asymmetric hydroformylation. Initial efforts focused on the resolution of racemic scaffolding ligand 2.5 (Scheme 2.10). Taking advantage of its ability to exchange with alcohols, the racemic ligand mixture was subjected to equilibration conditions in the presence of enantiopure alcohol 2.35 to generate a diastereomeric mixture of compounds (2.36 and 2.37). If this mixture of diastereomers were separated, a single enantiomer of ligand 2.5 could be recovered and utilized in asymmetric hydroformylation. Carrying out this equilibration experimentally, a surprising 31:69 (2.36:2.37) mixture of isomers was observed by \textsuperscript{31}P NMR after full consumption of 2.5 was achieved. We expected a 1:1 mixture of diastereomers; however, this result suggested that epimerization of the phosphorous stereocenter was occurring yielding a thermodynamic mixture of diastereomers. This experimental result is consistent with calculations, which indicate that diastereomer 2.37
is 0.64 kcal/mol more stable than structure 2.36. This calculated energy difference corresponds to a 25:75 (2.36:2.37) mixture of isomers.9

Scheme 2.10 Exchange of Racemic Ligand 2.5 with Enantiopure Alcohol 2.35.

Although calculations support the experimental findings, the observed ratio of diastereomers was quite surprising given that the barrier to phosphorus inversion for a similar phosphine compound, (MeP(o-tolyl)Ph), is ~ 30 kcal/mol.21 Two mechanisms have been posited to explain the configurational instability at phosphorus (Figure 2.4). In the presence of a proton source, iminium 2.38 is a likely intermediate (Figure 2.4, Pathway 1). Since this intermediate is aromatic, the barrier to phosphorus inversion would be lowered through the stabilization of a planar sp2 hybridized phosphorus center.22 Once the alcohol re-approaches, a net epimerization is possible to generate ent-2.5. Alternatively, the basic phosphine can be protonated by a catalytic amount of acid, generating cationic intermediate 2.39 (Figure 2.4, Pathway 2). A ring-opening event affords secondary phosphine 2.40, which has a lower inversion barrier than a tertiary phosphine. Ring closure can afford the other enantiomer of ligand, ent-2.5.

---

With the ultimate goal of extending the scaffolding ligand methodology to catalytic enantioselective hydroformylation, it was necessary to design a scaffold that was a single stereoisomer under the reaction conditions. Taking advantage of this unique epimerization feature, we hypothesized that an additional fixed stereocenter could be installed on ligand 2.5 in the form of a tetrahydroquinoline ring (Figure 2.5). By installing this stereocenter, we thought that the stereochemical information would be relayed to the other two stereocenters present in the ligand.

To test this idea, DFT calculations were carried out on two proposed ligand structures (Figure 2.6). Making the R group on the tetrahydroquinoline ring a methyl substituent resulted in a calculated energy difference of 1.2 kcal/mol between the two
lowest energy diastereomers, which is equivalent to a 90:10 ratio of the two compounds at room temperature. To have predominantly one stereoisomer present, we hypothesized that an energy difference of greater than 3 kcal/mol was necessary. Fortuitously, changing the R group to an isopropyl substituent resulted in a calculated energy difference of 4.8 kcal/mol between the two lowest energy isomers. The fixed nature of the isopropyl substituent should gear the methoxy substituent down to avoid a syn-pentane-like interaction. The orientation of the methoxy group will gear the phenyl group on phosphorus up, which is consistent with previous studies with ligand 2.5. These calculations suggested that we could take advantage of the epimerization observed in ligand 2.5 to ultimately equilibrate all possible stereoisomers of the ligand to one thermodynamically favored diastereomer of ligand to use in asymmetric hydroformylation (2.42, Figure 2.6).
To confirm these predictions experimentally, we designed a synthetic route to ligand 2.42 (Scheme 2.11). The synthesis begins from 2-chloroquinoline (2.43), which was subjected to a manganese-mediated cross coupling reaction with isopropylmagnesium bromide to afford 2-isopropylquinoline 2.44. An asymmetric hydrogenation of 2.44, followed by crystallization with (+)-3-bromocamphor-8-sulfonic acid, enriched 2.45 to 98% ee. Directed ortho-lithiation and trapping with Ph$_2$PCl yields triaryl compound 2.46, which was treated with lithium metal to cleave a phosphorus-phenyl bond and generate secondary phosphine 2.47 upon aqueous work-up.

---

Closure of the tri-cyclic core of the ligand was carried out under kinetic conditions (Scheme 2.11). Using two equivalents of phenyllithium and trapping with Cl₂CH(OMe) gave ligand 2.42 as a mixture of four diastereomers relative to the fixed isopropyl substituent on the tetrahydroquinoline ring. The diastereomeric mixture in 2.42 was equilibrated, in the presence of 4 Å molecular sieves and isopropanol, to one thermodynamically favored stereoisomer of ligand, 2.48.

The equilibration between 2.42 and 2.48 can be observed by ³¹P NMR (Figure 2.7). After kinetic closure, the four diastereomers of 2.42 are present in the ³¹P NMR spectrum. Equilibration of this mixture with isopropanol generates one peak in the ³¹P NMR, which is consistent with one thermodynamically favored diastereomer of ligand.
Figure 2.7 Equilibration of Four Diastereomers of 2.42 to 2.48 by $^{31}$P NMR.

The absolute configuration of 2.48 was further confirmed by X-ray crystallography (Figure 2.8). Complexation of 2.48 with trans-[Rh(CO)$_2$Cl]$_2$ resulted in a crystalline rhodium complex. Notably, the isopropyl substituent on the tetrahydroquinoline ring gears the C-O bond down, which in turn gears the P-Ph group up. This data is consistent with data obtained through calculations.
2.4 Enantioselective Hydroformylation of PMP-Protected Allylic Amines

With enantiopure ligands 2.42 and 2.48 in hand, we sought to apply them to enantioselective hydroformylation. Although it had been previously shown that electron-deficient sulfonamides\textsuperscript{13} undergo efficient exchange and regioselective hydroformylation with racemic ligand 2.5, the 3,5-(bis-trifluoromethyl)sulfonyl protecting group was exotic and difficult to remove. Needing to identify an alternative amine protecting group, our attention turned to aniline-based substrates, in particular the para-methoxyphenyl (PMP) group, due to its ability to be easily removed under oxidative conditions.\textsuperscript{24}

2.4.1 Initial Reaction Optimization with Racemic Scaffolding Ligand 2.5

To ensure that PMP-protected amines exchange onto our scaffolding ligand, an exchange reaction was carried out between ligand 2.5 and allylic amine 2.49 (Scheme 2.12). Equilibrium was reached within 2 hours and the $K_{eq}$ was determined to be $3.8 \pm 0.5$.

Confirming that PMP-protected amines exchange efficiently with scaffolding ligand 2.5, tested this substrate class in hydroformylation. In the case of allylic sulfonamides, no derivatization of the hydroformylation products was necessary. Subjecting PMP-protected allylic amine substrate 2.51 to pre-exchange and hydroformylation conditions should afford the β-amino aldehyde 2.52 and aminol 2.53 products (Scheme 2.13). Attempts to isolate either of these products by silica gel chromatography from the crude hydroformylation mixture were not successful.

The instability of β-amino aldehydes such as 2.52, bearing an electron-rich PMP group, has been reported in the literature. These aldehyde products were found to be unstable to silica gel chromatography. Additionally, the steady degradation of the aldehyde can be monitored by $^1$H NMR over time. The isolation of linear aminol 2.53 was attempted via an alternative synthetic route (Scheme 2.14). Under Ullman coupling conditions, 2.54 was converted to arylated pyrrolidinone 2.55. Attempts to reduce the

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Scheme 2.12 Equilibration Experiment between 2.49 and Ligand 2.5.

Scheme 2.13 Attempted Hydroformylation of Substrate 2.51 to Isolate Authentic Products.

---

amide carbonyl with a variety of reducing agents, including DIBAL-H, resulted in an intractable mixture of products. Thus, we believe that 2.53 is unstable under ambient conditions, as well as the hydroformylation reaction conditions. Due to its decomposition, the accurate quantification of this product is not possible. The electron-rich nature of the amine can lead to an elimination reaction, which would afford various unwanted byproducts.

**Scheme 2.14** Attempt to Independently Synthesize Aminol 2.53.

It was necessary to directly reduce the β-amino aldehyde product after hydroformylation with NaBH₄ to afford the isolable β-amino alcohol product 2.56. After an initial pre-equilibration between the 2.51 and 2.5, a pressure screen was performed (Table 2.1). Incrementally increasing the pressure from 50 psi to 200 psi resulted in diminished conversions and yields of 2.56 (Table 2.1, Entries 1 – 4), with linear product 2.53 not detected in the crude NMR for any reaction. Due to the increasing difference between the conversion and yield of 2.56, it is possible that higher pressures of syngas favor the formation of linear product 2.53. Based on previous findings that a small amount of acid can catalyze the exchange of substrate onto the ligand, the reaction was run at 50 psi with 0.05 mol % p-TsOH. In doing so, 95% conversion and 77% NMR yield of 2.56 was obtained (Table 2.1, Entry 5). This result is consistent with an acid-catalyzed exchange process that favors the directed hydroformylation to generate the branched
product in preference to the unselective background reaction, which would likely form the linear product preferentially. Employing ligand 2.5, the inherent regio-preference of terminal olefin substrate 2.51 is overturned to prefer the branched product.

Table 2.1 Pressure Screen with 2.51 and Ligand 2.5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>Conversion (%)(^{a})</th>
<th>2.56 (%)(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>81</td>
<td>44</td>
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<tr>
<td>3</td>
<td>100</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>5(^{b})</td>
<td>50</td>
<td>95</td>
<td>77</td>
</tr>
</tbody>
</table>

\(^{a}\) Based on \(^{1}\)H NMR using 1,3,5-trimethoxybenzene as an internal standard. \(^{b}\) Run with 0.05 mol % p-TsOH.

Having established that ligand 2.5 can control the regio-chemical outcome of hydroformylation for PMP-protected allylic amines, the reactivity of 1,2-disubstituted olefin substrate 2.57 was probed under the optimized conditions for 2.51 (Scheme 2.15). Although the conversion was modest (50%), 2.58 was formed in a 40% \(^{1}\)H NMR yield. Notably, the difference between conversion and amount of 2.58 observed is low, which indicates that a minimal amount of distal product is formed during the reaction.
Scheme 2.15 Reaction of 1,2-Disubstituted Olefin Substrate 2.57 with Ligand 2.5.

In these small studies of PMP-protected allylic amines with racemic scaffolding ligand 2.5, we were encouraged by the fact that these substrates were able to exchange with the ligand, as well as undergo hydroformylation in a regioselective fashion.

2.4.2 Reaction Optimization with Enantioenriched Scaffolding Ligand 2.42

With a general set of reaction conditions in hand, we were eager to test ligand 2.42, which exists as a mixture of four stereoisomers, in the asymmetric hydroformylation of PMP-protected allylic amines. Similar to the equilibration of 2.42 to one thermodynamically favored diastereomer of –Oi-Pr-bound ligand (2.48, Figure 2.7), 2.42 can be equilibrated to one thermodynamically favored antipode of substrate-ligand complex 2.59 in the presence of allylic amine substrate (Figure 2.9). This phenomenon is observable by $^{31}$P NMR. Therefore, the pre-equilibration step of the hydroformylation mixture ensures that only one stereoisomer of ligand is present during the reaction.

Figure 2.9 Equilibration of Ligand 2.42 and 2.49 by $^{31}$P NMR.
To find a balance between conversion and enantioselectivity, a temperature screen was carried out using 2.42 and disubstituted aniline substrate 2.49 (Table 2.2). Carrying out the reaction at 55 °C resulted in almost complete conversion and modest enantioselectivity of 2.58 (Table 2.2, Entry 1). Lowering the temperature incrementally caused the conversion to decrease slightly, but the enantioselectivity increased, eventually plateauing at 89% when the hydroformylation was carried out at 30 °C (Table 2.2, Entry 4). Examining the enantiopurity of the product, as well as the difference between conversion and yield of 2.58, running the reaction at 35 °C (Table 2.2, Entry 3) gave better results than 45 °C (Table 2.2, Entry 2). When comparing the conversion of the reaction, ligand 2.42 (Table 2.2, Entry 2) seems to be more active than racemic ligand 2.5 (Scheme 2.15) under identical reaction conditions. A rationale for this observation is
that larger ligands are known to be more active in hydroformylation, because the formation of an active monophosphine-ligated-metal is more likely present in solution. The optimal reaction temperature was identified as 35 °C (Table 2.2, Entry 3), since the reaction at 30 °C (Table 2.2, Entry 4) resulted in attenuated conversion.

**Table 2.2** Temperature Screen with 2.49 and Ligand 2.42.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2.58 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>89</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35</td>
<td>79</td>
<td>72</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on 1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

<sup>b</sup> Separated using supercritical fluid chromatography (SFC).

<sup>c</sup> Reaction run using 2.42 which was enriched to 98% ee.

During the course of our optimization studies with 2.42, a procedure was developed to further enrich 2-isopropyltetrahydroquinoline to 98% ee during the ligand synthesis. Taking this material through the synthetic route to afford 2.42 resulted in ligand of higher optical purity. Using enriched ligand 2.42 (98% ee) in the hydroformylation reaction afforded 2.58 in 93% ee (Table 2.2, Entry 5), with similar conversion and yield as Entry 3.
With high levels of enantioselectivity observed, we turned to improving upon the low conversion observed in the reaction. Since the hydroformylation with ligand 2.42 is run under quite mild conditions, we hypothesized that the reaction was being stopped prematurely at 16 hours. When the reaction was carried out for 24 hours, no appreciable increase in conversion was observed (Scheme 2.16, Equation 1). Increasing the loading of ligand 2.42 from 10 mol % to 15 mol % resulted in a modest increase in conversion to 85% (Scheme 2.16, Equation 2) with no dramatic effect on enantioselectivity. Together, these results are consistent with ligand decomposition prior to complete consumption of starting material.

Scheme 2.16 Experiments to Increase Conversion.
2.4.3 Substrate Scope for the Asymmetric Hydroformylation of PMP-protected Allylic Amines

With the optimal conditions in hand using ligand 2.42, the substrate scope was explored (Table 2.3). As previously demonstrated, 2.49 yields the desired proximal amino alcohol in excellent levels of enantioselectivity (92% ee, Table 2.3, Entry 1). Highlighting the scalability of reaction, it was run using 0.50 g (2.8 mmol) 2.49, which afforded the β-amino alcohol in comparable yields and enantioselectivities (61% yield, 92% ee). The hydroformylation was also carried out without pre-exchanging substrate 2.49 onto the ligand. Comparable results were achieved with a marginally lower isolated yield (67% yield, 91% ee). This result suggests that there is no significant background reaction for 1,2-disubstituted olefins using this ligand system. Hydroformylation only occurs once the substrate is bound, which also emphasizes the rate-accelerating affect of the scaffolding ligand.

(E)-olefin 2.57 undergoes hydroformylation efficiently, but is isolated in slightly lower enantiomeric excess (80% ee, Table 2.3, Entry 2) than the corresponding (Z)-olefin 2.49. The same trend is observed when the olefin is substituted with a larger cyclohexyl group. High levels of enantioselectivity are observed in the case of cis-olefin 2.60 (86% ee, Table 2.3, Entry 3), but the product resulting from the hydroformylation of corresponding trans-olefin 2.61 is only isolated in 76% ee (Table 2.3, Entry 4). Highlighting the functional group tolerance of the reaction, benzyl (2.63) and silyl ether (2.64) substrates (Table 2.3, Entries 6 and 7, respectively) afforded the β-amino alcohol products in high enantiomeric excess and good yields. No hydrogenolysis of the benzyl group was observed during the course of the reaction.

A substrate bearing a phthalimide group, 2.65, was among the most active (90% conversion, Table 2.3, Entry 8). The β-amino alcohol was obtained in high levels of enantioselectivity (93% ee), but there is a large discrepancy between the conversion and isolated yield. This is likely due to the known directing ability of amides in hydroformylation. As a result, it is possible that the phthalimide substituent is directing hydroformylation to occur at the distal olefinic carbon (relative to the PMP-protected amine), which subsequently undergoes decomposition and is not observable in the crude \(^1\)H NMR.

---

Table 2.3 Substrate Scope for the Enantioselective Hydroformylation using Ligand 2.42.

![Chemical Structure](image)

1. 15 mol %
2. 2 mol % Rh(acac)(CO)₂ 35 °C, 50 psi H₂/CO, benzene, 16 h
3. NaBH₄, MeOH

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conversion (%)a</th>
<th>Isolated Yield (%)</th>
<th>ee (%)b</th>
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<tbody>
<tr>
<td>1</td>
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<td>85</td>
<td>69</td>
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<td>10</td>
<td>PMPN₂H₂.51</td>
<td>92</td>
<td>64</td>
<td>73</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. b Determined by supercritical fluid chromatography.
A substrate containing an ester functionality 2.66 was also quite active (90% conversion, Table 2.3, Entry 9), and afforded the β-amino alcohol product in good yields and enantiomeric excess (90% ee). Finally, terminal olefin 2.51 underwent hydroformylation efficiently to give the desired product in 73% ee (Table 2.3, Entry 10). The lower isolated yield and optical purity of this product is attributed to an unselective background reaction due to the highly reactive nature of this substrate. This result also emphasizes the importance of a cis substituent on the olefin to obtain higher levels of enantioselectivity.

Since 1,2-disubstituted olefins undergo hydroformylation efficiently with ligand 2.42 under mild reaction conditions, we wondered if a tri-substituted olefin, which are among the least reactive alkene substrates in hydroformylation, could be employed in the reaction. Hydroformylation using prenyl substrate 2.67 at elevated temperatures (95 °C) resulted in 72% conversion of starting material (Scheme 2.17); however, the only product observed was hydrogenation of 2.67.

Scheme 2.17 Attempted Hydroformylation of a Tri-substituted Olefin Substrate.

![Scheme 2.17](image)

2.4.4 A Proposed Stereochemical Model

We propose a simple stereochemical model to explain the lower enantioselectivities obtained for trans olefins compared to cis alkene substrates. To

52
minimize steric interactions with the ligand, we believe that the PMP group will prefer to
orient itself into space, leaving the olefin to reside over the ligand in all cases (Figure
2.10). The major enantiomer of product results from hydrometallation intermediates 2.69
and 2.70. On the other hand, the more energetically favored intermediates are those in
which the vinylic methyl substituent points back over the tetrahydroquinoline ring (2.69
and 2.72) rather than interacting with the phenyl substituent on phosphorus (2.70 and
2.71). In the case of the trans alkene isomer, the intermediate leading to the minor
enantiomer of product (2.72) appears more favorable than the corresponding intermediate
for the cis olefin (2.71). More specifically, intermediate 2.71 has both a methylene group
and the methyl substituent on the olefin interacting with the phosphorus substituent; on
the other hand, only the methylene group present in intermediate 2.72 points towards the
aryl substituent on phosphorus. It is possible that in the case of an E-configured alkene
substrate, the difference in energy between the two prochiral faces of the olefin (2.70 and
2.72) prior to the hydrometallation step are closer in energy than the two intermediates
for the cis olefin (2.69 and 2.71). This hypothesis is consistent with slightly attenuated
enantioselectivities with trans olefin substrates (Table 2.3, Entries 1 and 2).
Figure 2.10 Proposed Stereochemical Model for cis vs. trans Olefin Substrates.

The hypothesis that the facial discrimination of the olefin is dictated by the steric interactions between the substrate and the phenyl substituent on phosphorus is further supported when terminal olefin substrate 2.51 (Table 2.3, Entry 10) is considered. For substrate 2.51, the amino alcohol product is obtained in 73% ee, which is similar to the selectivities observed with trans olefin substrates (Table 2.3, Entries 2 and 4). It is possible that the stereochemical outcome for terminal olefin 2.51 originates from the preference for the methylene group to point towards the tetrahydroquinoline ring rather than the aryl substituent on phosphorus. Therefore, a substituent on the olefin is not required to obtain good levels of enantioselectivity; however, the presence of a Z-configured olefin can further enhance the energetic difference between the two olefin faces when bound to the ligand such that high levels of enantioselectivity are obtained.
2.5 Enantioselective Hydroformylation of Electronically Modified Allylic Anilines

Although the PMP group is a useful protecting group, aniline derivatives are an important class of molecules that are found in biologically active compounds and dyes.\(^\text{28}\) We sought to expand the asymmetric hydroformylation methodology to electronically modified allylic aniline substrates in the presence of our enantiopure scaffolding ligands.\(^\text{29}\)

2.5.1 Exchange Data for Electronically Modified Aniline Substrates

We began our investigation studying the exchange of various electronically modified aniline substrates onto our scaffolding ligands. Ligand 2.5 was chosen for these experiments because it is more readily accessible in large quantities than the enantiopure scaffolding ligands. Additionally, due to the presence of the azaphosphole core in both ligands, we felt that ligand 2.5 would be a useful mimic of ligand 2.48.

For these experiments, aniline-derived allylic amine substrates with a variety of substituents in the \textit{para} position on the aniline ring were synthesized. Although the electronics on the aniline ring do not prevent the binding of any of the tested substrates to the ligand, electron-poor anilines (2.76 and 2.77) have a lower binding affinity than electron-rich counterparts, with the equilibrium for the PMP-protected amine substrate 2.49 lying the farthest to the right (Table 2.4). Notably, all of the \(K_{eq}\) values are within one order of magnitude of one another.

Table 2.4 The Effect of Substrate Electronics on Exchange with Ligand 2.5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>$K_{eq}^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe (2.49)</td>
<td>2.9 ± 0.7</td>
</tr>
<tr>
<td>2</td>
<td>Me (2.73)</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>H (2.74)</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>4</td>
<td>Cl (2.75)</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>5</td>
<td>CN (2.76)</td>
<td>0.64 ± 0.03</td>
</tr>
<tr>
<td>6</td>
<td>NO$_2$ (2.77)</td>
<td>0.43 ± 0.07</td>
</tr>
</tbody>
</table>

$a$ $K_{eq}$ values were determined by $^1$H NMR in triplicate.

To gain further insight into factors that affect substrate/ligand exchange, the experimental $K_{eq}$ values were plotted versus Hammett parameters, $\sigma_p$ and $\sigma_+$(Figure 2.11). The data correlates better to $\sigma_+$ parameters than $\sigma_p$, which is consistent with a minor resonance component upon the secondary aniline substrate binding to ligand 2.5. In terms of the $\sigma_+$ plot, the $\rho$ value is small and negative (-0.47), which suggests only a modest favorability for electron-rich aniline substrates to bind 2.5.
Figure 2.11 Hammett Plots for K\textsubscript{eq} data plotted versus (left) $\sigma^*$ values and (right) $\sigma_{\text{para}}$ values.

One interpretation of this data is that when the aniline substrate is bound to the ligand, the nitrogen lone pair can participate in donation into the $\sigma^*$ of either the C-P or C-N bonds of the ligand.\(^\text{30}\) Electron-donating groups in direct resonance with the nitrogen lone pair would enhance this stabilizing effect, favoring the substrate-ligand complex and pushing the equilibrium to the right (Table 2.4). Alternatively, the nitrogen lone pair in the substrate is conjugated to the aromatic ring, which is a stabilizing effect. When bound to the ligand, the lone pair on the amine is rotated out of conjugation due to the steric repulsion between the aromatic ring of the substrate and the ligand itself. Since electron-withdrawing groups are in direct conjugation with the lone pair on nitrogen, the equilibrium would shift to the left in the case of electron deficient aniline substrates and favor the substrate-ligand complex in the case of electron-rich aniline compounds.

2.5.2 Substrate Scope for the Enantioselective Hydroformylation of Aniline Derivatives

For the hydroformylation studies, allylic benzyl ether substrates were employed, because they are available in large quantities from the geometrically pure, commercially available cis-1,4-butanediol. Since it exists as a single stereoisomer, ligand 2.48 was chosen for these studies.

As reported previously,26 the para-methoxyphenyl (PMP) amine substrate 2.63 gives good yield of the β-amino alcohol product, with high enantioselectivity (92% ee, Table 2.5, Entry 1). Un-substituted (Table 2.5, Entry 3) and electron neutral substrates (Table 2.5, Entries 2 and 4) provide comparable levels of enantioselectivity and good isolated yields are obtained. When an electron withdrawing substituent, such as a nitrile (2.81, Table 2.5, Entry 5) or a nitro group (2.82, Table 2.5, Entry 6), is placed in the para position of the aromatic ring the yields and enantioselectivities significantly decrease. Examination of the gas uptake curves for substrates 2.81 and 2.82 reveal that the reaction stalls prior to reaching complete conversion. This observation is consistent with ligand decomposition during the course of the reaction. A minor amount of ligand decomposition is observed by $^{31}$P NMR in the pre-equilibration step between electron-deficient substrates and ligand 2.48, providing support for the steady loss of ligand during the reaction. A potential rationale for ligand decomposition is that the electron deficient substrates generate a higher concentration of the reactive iminium intermediate, which is prone to decomposition in the absence of a substrate that can favorably intercept it and go on to participate in the reaction.
Table 2.5 Effect of Electronically Modified Aniline Substrates on the Hydroformylation Results.

The Hammett data (Figure 2.11) suggest that there is a modest resonance component in the substrate-ligand exchange step of the reaction. If this is true, we hypothesized that synthesizing a substrate where an electron-withdrawing group is not in direct resonance with the nitrogen lone pair would afford better results. Consistent with this prediction, employing a substrate with a nitro substituent in the meta position (3.84) gave useful levels of enantioselectivity (84% ee) and improved the yield (Table 2.5, Entry 8). Additionally, using an electron-deficient 3-pyridyl substrate (3.85) afforded the
β-amino alcohol product in good enantiomeric excess (87%) and moderate isolated yields (Table 2.5, Entry 9).

To examine how sterics on the aniline ring affect the hydroformylation reaction, ortho-substituted aniline substrates 2.86 and 2.87 were synthesized (Scheme 2.18). Based on electronics alone, the exchange between the substrate and ligand should be favorable. Carrying out the equilibration experiment with 2.48, the substrate-ligand complex was not thermodynamically favored and required multiple cycles for full exchange to occur. Subjecting the generated substrate-ligand complex to hydroformylation resulted in minimal conversion to product. We believe that this is a result of difficulties in binding sterically large substituents to scaffolding ligand 2.48.

Scheme 2.18 Attempted ortho-Substituted Allylic Amine Substrates

2.6 Conclusions

Based on the development of racemic scaffolding ligand 2.5 in the Tan lab, enantioenriched scaffolding ligand 2.42 was designed. By installing a fixed stereocenter on the tetrahydroquinoline ring, ligand 2.42 is able to simultaneously control the regio- and stereochemical outcome of the hydroformylation of PMP-protected allylic amines (Section 2.4). Hoping to expand the substrate scope, the enantioselective
hydroformylation of electronically modified aniline substrates was demonstrated (Section 2.5). Electron-deficient allylic anilines generally gave inferior results in the hydroformylation reaction (in terms of yield and enantioselectivity) when compared to their electron-rich counterparts. Performing equilibration experiments with these substrates revealed that electron-deficient aniline substrates are less favored to bind to scaffolding ligand 2.5 and that there is a minor resonance effect in the exchange step. Taken together, these two studies have allowed us to begin to understand the necessary parameters for a successful enantioselective hydroformylation reaction using this ligand class.

The design and synthesis of ligands 2.42 and 2.48 has allowed for the first asymmetric reaction utilizing a catalytic directing group to be developed. This distinct strategy for inducing asymmetry demonstrates the possibility of using catalytic directing groups to promote other enantioselective reactions.

2.7 Experimental

2.7.1 General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC).
$^{13}$C, and $^{31}$P NMR were performed on either a Varian Gemini 400 MHz or a Varian Unity Inova 500 MHz spectrometers. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C$_6$D$_6$ was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to TMS and referenced to residual solvent for $^1$H and $^{13}$C and external standard (neat H$_3$PO$_4$) for $^{31}$P NMR. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm$^{-1}$. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector with methanol as the modifier. HRMS and X-ray crystal structure data were generated in Boston College facilities. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu-LC-2010A HT. Hydroformylation was performed in an Argonaut Technologies Endeavor Catalyst Screening System using 1:1 H$_2$/CO supplied by Airgas, Inc.

2.7.2 Ligand Synthesis and Characterization

2-isopropyl quinoline$^{31}$ was prepared according to a literature procedure and matches reported spectra.

(S)-2-isopropyl-1,2,3,4-tetrahydroquinoline. In a glovebox, [Ir(COD)Cl]$_2$ (68.0 mg, 0.102 mmol) and (R)-(+)5,5'-Dichloro-6,6'-dimethoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl (132 mg, 0.204 mmol) were

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dissolved in 5 mL THF and stirred for 20 min. The solution was brought out of the
drybox and was added to a solution of 2-isopropyl quinoline (8.71 g, 50.9 mmol) and
iodine (258 mg, 1.02 mmol) in THF (50 mL). The solution was added to a parr bomb
and cooled to 4 °C (cold room). The system was charged to 400 psi and depressurized 3
times with hydrogen gas. The vessel was pressurized to 400 psi hydrogen and the
reaction was stirred vigorously at this temperature for 20 h. The reaction was
concentrated and purified on silica gel (3 – 5% EtOAc/Hex) to yield a yellow oil (8.5 g,
95%). The compound was 94% ee by SFC analysis (OD-H, 1% methanol as modifier,
1.5 mL/min, 150 psi. \( t_R = 12.8 \) min \( t_S = 13.6 \) min).

**Crystalization to higher ee:** Concentrated HCl (5 mL) and water (72 mL) were heated to
50 °C and (S)-2-isopropyl-1,2,3,4-tetrahydroquinoline (7.18 g, 41.0 mmol) was added,
followed by (+)-3-bromocamphor-8-sulfonic acid ammonium salt (13.44 g, 40.96 mmol).
The temperature was raised to 90 °C. Water (500 mL), ethanol (35 mL), concentrated
HCl (25 mL) were added successively to the flask. The suspension was hot filtered and
the filtrate was allowed to cool overnight. The crystals were collected and the parent
compound was recovered by suspending the crystals in ethyl acetate (150 mL) and
washing with 1M Na₂CO₃ (3× 50 mL). The organic layer was dried over magnesium
sulfate, filtered, and concentrated to yield the title compound (3.51 g, 49%) in 98% ee as
determined by SFC. \(^1H\) NMR (CDCl₃, 500 MHz) \( \delta \) 7.02 – 7.06 (m, 2H), 6.68 (ddd, 1H,
\( J = 8.0, 7.0, 1.0 \) Hz), 6.54 (ddd, 1H, \( J = 7.5, 1.0 \) Hz), 3.82 (br s, 1H), 3.10 – 3.14 (m, 1H),
2.80 – 2.89 (m, 2H), 1.97 – 2.02 (m, 1H), 1.70 – 1.81 (m, 2H), 1.09 (d, 3H, \( J = 7.0 \) Hz),
1.06 (d, 3H, \( J = 7.0 \) Hz); \(^13C\) NMR (CDCl₃, 125 MHz) \( \delta \) 145.1, 129.2, 126.8, 121.5,
116.8, 114.0, 57.3, 32.6, 26.7, 24.6, 18.7, 18.3; IR: 3415, 2957, 2871, 2842, 1606, 1483,
HRMS (DART-TOF) calcd. for C_{12}H_{18}N [M+H]^+: 176.1439, found: 176.1448; [α]_D^20 = + 65.3 (c = 0.915, CH₂Cl₂, l = 50 mm).

(S)-8-(diphenylphosphino)-2-isopropyl-1,2,3,4-tetrahydroquinoline. To a 250-mL, three-neck, round-bottom flask was added THF (60 mL) and (S)-2-isopropyl-1,2,3,4-tetrahydroquinoline (5.80 g, 33.1 mmol). The solution was cooled to −78 °C and n-BuLi (18.8 mL, 1.76 M solution in hexane, 33.1 mmol) was added slowly maintaining the internal temperature at or below −70 °C. Upon completion of the n-BuLi addition, the reaction was warmed in an ice water bath to 0 °C, and CO₂ was bubbled through the solution. The red solution color faded quickly. CO₂ bubbling was continued for 45 min and the solvent was removed under high vacuum to yield a foamy yellow semi-solid. The residue was redissolved in THF (60 mL) and cooled to −78 °C. t-BuLi (27.2 mL, 1.40 M solution in pentane, 38.1 mmol) was added, maintaining the internal temperature at or below −70 °C. The solution was warmed to −20 °C for 30 min before being recooled to −78°C. Chlorodiphenylphosphine (6.73 mL, 36.4 mmol) was added as a solution in THF (10 mL) maintaining the internal temperature at or below −70 °C. The solution was stirred overnight, allowing the reaction to warm with the cold bath. 6 M HCl was added (52 mL) and stirred for 45 min. The solution was basified to pH >10 with 10 M NaOH and extracted with ethyl acetate (3 x 70 mL). The organics were dried over MgSO₄, filtered and concentrated. The unreacted starting material was removed by Kugelrohr distillation (120 °C, 0.05 mmHg). The undistilled material was suspended in minimal amount of ethanol and the product precipitated as a white solid (5.9 g, 49%). ¹H NMR (CDCl₃, 500 MHz) δ 7.27 – 7.28 (m, 10H), 6.97 (d,
1H, $J = 7.0$ Hz), 6.61 (app t, 1H, $J = 7.0$ Hz), 6.50 (app t, 1H, $J = 7.0$ Hz), 4.66 (d, 1H, $J = 7.0$ Hz), 3.02 – 3.04 (m, 1H), 2.74 – 2.83 (m, 2H), 1.86 – 1.90 (m, 1H), 1.58 – 1.63 (m, 2H), 0.81 (d, 3H, $J = 6.5$ Hz), 0.78 (d, 3H, $J = 6.5$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 147.7, 147.5, 135.8 (d, $J = 7.4$ Hz), 135.6 (d, $J = 7.4$ Hz), 133.8 (d, $J = 7.4$ Hz), 133.7 (d, $J = 7.4$ Hz), 132.1, 132.11, 128.7, 128.6, 128.5, 128.4, 121.0, 120.9, 117.36, 117.3, 116.1, 116.0, 57.6, 57.5, 32.5, 27.0, 24.2, 18.2; $^{31}$P NMR (CDCl$_3$, 202 MHz) δ –20.7; IR: 3051, 2956, 2870, 2841, 1586, 1489, 1455, 1433, 1278, 1091, 738, 694, 503 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{24}$H$_{26}$NP [M+H]$^+$: 360.1881, found: 360.1870; $[\alpha]_D^{20} = + 80.9$ (c =0.415, CH$_2$Cl$_2$, l = 50 mm).

(S)-2-isopropyl-8-(phenylphosphino)-1,2,3,4-tetrahydroquinoline.

A dry 100-mL round-bottom flask was charged with (S)-8-(diphenylphosphino)-2-isopropyl-1,2,3,4-tetrahydroquinoline (2.50 g, 6.96 mmol) and THF (25 mL). The solution was sparged with argon for 30 min and lithium wire (145 mg, 20.9 mmol) was added. The solution was sparged with argon for an additional 30 min during which time the solution turned orange (Note: you must use argon for this reaction as lithium metal will react with nitrogen). The solution was stirred overnight under argon. Degassed water (2.5 mL) was added and stirred for 15 min, resulting in a colorless solution. The solvent was removed under high vacuum and the residue was quickly extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, filtered and concentrated. Distillation (125 °C, 0.05 mmHg) resulted in an air sensitive colorless oil (1.3 g, 66%) as a 1:1 mixture of diastereomers. The compound was stored under argon. $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.41 – 7.45 (m, 2H), 7.27 – 7.37 (m, 4H), 7.05 – 7.06 (m, 1H), 6.58 – 6.64 (m, 1H), 5.10 (d, 1H, $J = 219$ Hz), 4.31 (br s, 1H), 3.05 – 3.09 (m, 0.5H), 2.92 –
2.96 (m, 0.5H), 2.74 – 2.84 (m, 2H), 1.84 – 1.91 (m, 1H), 1.54 – 1.65 (m, 2H), 0.84 (d, 1.5H, J = 7.0 Hz), 0.82 (d, 1.5H, J = 7.0 Hz), 0.78 (d, 1.5H, J = 7.0 Hz), 0.74 (d, 1.5H, J = 7.0 Hz); 13C NMR (CDCl3, 125 MHz) δ 147.74, 147.71, 147.2, 147.1, 136.2, 136.1, 136.0, 135.9, 132.3, 132.2, 132.1, 132.0, 131.4, 131.3, 128.70, 128.67, 128.66, 128.64, 128.01, 127.98, 116.2, 116.1, 115.7, 115.6, 57.7, 32.6, 32.5, 32.4, 27.2, 27.1, 24.6, 24.0, 18.4, 18.14, 18.12, 18.0; 31P NMR (CDCl3, 202 MHz) δ –61.4, –62.1; IR: 3421, 2958, 2930, 2872, 2843, 1588, 1491, 1457, 1435, 1286, 759, 738, 695 cm⁻¹; HRMS (DART-TOF) calcd. for C18H23NP [M+H]⁺: 284.1568, found: 284.1561; [α]D20 = +53.4 (c = 0.730, CH2Cl2, l = 50mm)

Synthesis of 2.48

(4S)-2-isopropoxy-4-isopropyl-1-phenyl-2,4,5,6-tetrahydro-1H-[1,3]azaphospholo[4,5,1-ij]quinoline. (S)-2-isopropyl-8-(phenylphosphino)-1,2,3,4-tetrahydroquinoline (1.30 g, 4.59 mmol) was dissolved in THF (25 mL). The solution was cooled to –78 °C and PhLi (4.89 mL, 1.97 M solution in pentane, 9.64 mmol) was added dropwise. After stirring for 30 min the flask was transferred to an ice water bath and stirred for an additional 30 min. The dianion solution was added via syringe pump
over 1 h to a solution of dichloromethyl methylether (0.448 mL, 5.05 mmol) in THF (150 mL) at 0 °C. The reaction was stirred for 90 min and the solvent was removed under high vacuum. The resulting residue was brought into a glovebox and extracted with pentane (3 × 10 mL). The pentane extract was filtered through glass fiber filter paper. The crude mixture was distilled (150 °C at 0.05 mmHg) to a yellow oil (490 mg, 33%) that was a mixture of four diastereomers \[^{31}\text{P NMR} (\text{C}_6\text{D}_6, 202 \text{ MHz}) \delta -6.0, -23.2, -25.2, -30.3\]. To the distillate was added \(i\)-PrOH (3 mL) in benzene (3 mL) over 4Å mol. sieves in a glove box. The solution was allowed to sit for 20 h before being filtered. The sieves were washed with benzene. The filtrate was concentrated and resubjected to \(i\)-PrOH (3 mL) in benzene (3 mL) over 4Å mol. sieves. The filtration/resubjection cycle was repeated. The resulting residue was dissolved in pentane (0.3 mL) and crystallized at –37 °C. More material was recrystallized from the mother liquor and the white solids were combined (180 mg, 34%). \(^1\text{H NMR} (\text{CDCl}_3, 500 \text{ MHz}) \delta 7.42 – 7.40 (m, 1H), 7.35 – 7.38 (m, 2H), 7.00 – 7.03 (m, 3H), 6.96 – 6.98 (m, 2H), 6.70 – 6.73 (m, 1H), 5.14 (d, 1H, \(J = 13.0 \text{ Hz})\), 3.98 – 4.01 (m, 1H), 3.37 – 3.40 (m, 1H), 2.42 – 2.44 (m, 2H), 1.82 – 1.86 (m, 2H), 1.55 – 1.61 (m, 2H), 1.17 (d, 3H, \(J = 6.0 \text{ Hz})\), 1.08 (d, 3H, \(J = 6.0 \text{ Hz})\), 0.64 (d, 3H, \(J = 7.0 \text{ Hz})\), 0.50 (d, 3H, \(J = 6.5 \text{ Hz})\); \(^{13}\text{C NMR} (\text{CDCl}_3, 125 \text{ MHz}) \delta 151.3, 136.9, 136.8, 132.1, 132.0, 130.7, 130.6, 130.0, 128.5, 120.0, 119.4, 117.9, 98.3, 67.3, 57.5, 28.8, 24.2, 23.3, 21.6, 21.4, 19.3, 16.0; \(^{31}\text{P NMR} (\text{C}_6\text{D}_6, 202 \text{ MHz}) \delta -22.0 ; \text{IR}\) 3053, 2962, 2929, 2870, 1582, 1455, 1383, 1310, 1288, 1183, 1083, 999, 740, 696 cm\(^{-1}\); \text{HRMS} (DART-TOF) calcd. for C\(_{22}\)H\(_{29}\)NOP [M+H]\(^+\): 354.1987, found: 354.2000. \([\alpha]_D^{20} = +139 (c = 0.340, \text{C}_6\text{H}_6, l = 50 \text{ mm})\).
Note: Table 2.3 substrates were exchanged with the mixture of four 2.42 diastereomers prior to hydroformylation, which effected conversion to one thermodynamically favored diastereomer of substrate-bound ligand, as demonstrated in Figure 2.9.

2.7.3 Complex of Ligand 2.48 Bound to Rhodium

trans-[Rh(2.48)2(CO)(Cl)]. Chlorodicarbonylrhodium (I) dimer (2.7 mg, 0.0070 mmol) and 2.48 (10.0 mg, 0.0280 mmol) were weighed out in a glove box and dissolved in benzene-d₆ and allowed to stand for 12 h in a sealed, screw-top NMR tube. The orange solution was concentrated and dissolved in a minimal amount of benzene/pentane (1:1). The solution was placed in a vial with small holes in the cap and was allowed to slowly evaporate in a glovebox, yielding yellow needles suitable for x-ray diffraction analysis. A single crystal was taken and stored under nitrogen until ready for x-ray diffraction analysis.

X-ray Crystallographic Procedures. Single crystals obtained as described above were used for structural determination. The X-ray intensity data were measured at 100(2) K (Oxford Cryostream 700) on a Bruker SMART APEX CCD-based X-ray diffractometer system equipped with a Mo-target X-ray tube (λ = 0.71073Å) operated at 2000 W power. The crystals were mounted on a goniometer head with silicone oil. The detector was placed at a distance of 6.00 cm from the crystal. For each experiment a total of 2400 frames were collected with a scan width of 0.3° in ω and an exposure time of 20 s/frame. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm to a maximum 2θ angle of 56.54° (0.75 Å resolution). The final cell constants are based upon the refinement of the XYZ-centroids of several thousand reflections above 20 σ(I). Analysis of the data showed negligible decay during
data collection. Data were corrected for absorption effects using the empirical method (SADABS).

The structures were solved and refined by full-matrix least squares procedures on $F^2$ using the Bruker SHELXTL (version 6.12) software package. The coordinates of heavy atoms were found in direct method $E$ maps. The remaining atoms were located after an alternative series of least-squares cycles and difference Fourier maps. Hydrogen atoms were included in idealized positions for structure factor calculations. Anisotropic displacement parameters were assigned to all non-hydrogen atoms. Relevant crystallographic data are summarized in Table 1. Selected bond lengths are given in Table 2.

**Table 2.6 Crystal Data and Structure Refinement.**

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<th>Property</th>
<th>Value</th>
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<tr>
<td>Empirical formula</td>
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</tr>
<tr>
<td>Formula weight</td>
<td>873.22</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 2 1 2 1</td>
</tr>
<tr>
<td>Unit cell dimensions (Å)</td>
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</tr>
<tr>
<td></td>
<td>b = 14.760(3) β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 31.273(7) γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>4246.3(16) Å$^3$</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.366 g/cm$^3$</td>
</tr>
</tbody>
</table>
Absorption coefficient $0.582 \text{ mm}^{-1}$

$F(000)$ 1824

Crystal size $0.12 \times 0.02 \times 0.02 \text{ mm}^3$

Theta range for data collection 2.39 to 28.40.

Index ranges $-12 \leq h \leq 12, -19 \leq k \leq 19, -41 \leq l \leq 41$

Reflections collected 51112

Independent reflections 10497 [R(int) = 0.0955]

Completeness to theta = 28.40° 99.3 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.9885 and 0.9335

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 10497 / 462 / 481

Goodness-of-fit on $F^2$ 1.054

Final R indices [I>2sigma(I)] $R1 = 0.0511, wR2 = 0.0858$

R indices (all data) $R1 = 0.0706, wR2 = 0.0916$

Absolute structure parameter -0.06(2)

Extinction coefficient na

Largest diff. peak and hole 0.602 and -0.870 e $\text{Å}^3$

**Table 2.** Selected bond lengths [Å] and angles [°].

<table>
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<th>Bond</th>
<th>Length [Å]</th>
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<td>Rh(1)-C(45)</td>
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<tr>
<td>Rh(1)-P(1)</td>
<td>2.3004(11)</td>
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<tr>
<td>Rh(1)-P(2)</td>
<td>2.3191(11)</td>
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Rh(1)-Cl(1)       2.3445(10)
O(3)-C(45)         1.158(4)

C(45)-Rh(1)-P(1)   87.38(12)
C(45)-Rh(1)-P(2)   93.07(12)
P(1)-Rh(1)-P(2)    178.17(4)
C(45)-Rh(1)-Cl(1)  177.31(12)
P(1)-Rh(1)-Cl(1)   90.92(4)
P(2)-Rh(1)-Cl(1)   88.69(3)

Figure 2.12 Perspective Drawing of trans[Rh(2.48)_2(CO)(Cl)]. Atoms are represented by thermal ellipsoids at the 50% probability level.
2.7.4 Substrate Synthesis and Characterization

The following compounds were made according to literature procedures and matched reported spectra: (Z)-3-phenylprop-2-en-1-ol, (Z)-(3-chloroprop-1-enyl)benzene, 1,4-but-2-enediol cyclic sulfite, and (Z)-3-cyclohexylprop-2-en-1-ol, (Z)-ethyl 7-hydroxyhept-5-enoate.

\[
\text{N-(but-2-ynyl)-4-methoxyaniline.}^{38} \text{ To } p\text{-anisidine (2.80 g, 22.7 mmol) in CH}_3\text{CN (13 mL) was added 1-bromo-2-butyne (658 } \mu\text{L, 7.58 mmol). The mixture was stirred overnight at room temperature. Saturated aqueous NH}_4\text{Cl (15 mL) was added, and mixture was separated. The aqueous layer was extracted with Et}_2\text{O (3 } \times\text{ 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO}_4, \text{ filtered and concentrated. Column chromatography (10}\% \text{ EtOAc/Hex) afforded a light yellow oil (855 mg, 64%). }^{1}\text{H NMR (CDCl}_3, 400 MHz) } \delta \text{ 6.80 – 6.83 (m, 2H), 6.66 (dd, 2H, } J = 9.0, 2.4 \text{ Hz), 3.83 (q, 2H, } J = 2.2 \text{ Hz), 3.76 (s, 3H), 3.54 – 3.65 (bs, 1H), 1.80 – 1.81 (m, 3H); }^{13}\text{C NMR (CDCl}_3, 101 MHz) } \delta \text{ 152.6, 141.4, 114.8, 114.6, 78.8, 76.4, 55.6, 34.8, 3.4; IR: 3384, 2917, 2932, 1513, 1463, 1235, 1036, 821 cm}^{-1}; \text{ HRMS (DART-TOF) calcd. for } \text{C}_{11}\text{H}_{14}\text{NO}[\text{M+H}]^{+}: 176.1075, \text{ found: 176.1069.}
\]

\[\text{MeO}\]

\[
\text{H} \quad \text{MeO} \quad \text{Me}
\]

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\[34\text{ Chaudhari, S. S.; Akamanichi, K. G. Synlett 1999, 11, 1763 – 1765.}\]
(Z)-N-(but-2-enyl)-4-methoxyaniline (10% E isomer), 2.49. A round-bottom flask was charged with Lindlar’s catalyst (121 mg) and purged with argon. N-(but-2-ynyl)-4-methoxyaniline (855 mg, 4.88 mmol) in EtOH (9 mL) was added followed by quinoline (46.0 µL, 0.390 mmol). The flask was evacuated and refilled with H2 four times, fitted with a H2 balloon, and stirred at room temperature under H2 for 3.5 h. The reaction was filtered through a plug of silica and concentrated. Column chromatography (20% EtOAc/Hex) yielded a light yellow oil (754 mg, 87%).

1H NMR (CDCl3, 400 MHz) δ 6.79 (dd, 2H, J = 9.0, 2.4 Hz), 6.45 (dd, 2H, J = 8.8, 2.4 Hz), 5.53 – 5.69 (m, 2H), 3.76 (s, 3H), 3.73 – 3.75 (m, 2H), 3.37 (bs, 1H), 1.71 (d, 3H, J = 6.3 Hz); 13C NMR (CDCl3, 100 MHz) δ 152.2, 142.6, 127.9, 126.9, 114.8, 114.3, 55.8, 41.8, 13.1; IR: 3290, 2934, 2015, 1608, 1512, 1413, 1249, 1032, 837 cm⁻¹; HRMS (DART-TOF) calcd. for C11H16NO [M+H]+:178.1232, found: 178.1234.

(E)-N-(but-2-enyl)-4-methoxyaniline, 2.57. To p-anisidine (6.13 g, 49.8 mmol) in CH3CN (29 mL) was added crotyl chloride (1.61 mL, 16.6 mmol). The mixture was stirred overnight at 23 °C. Saturated aqueous NH4Cl (15 mL) was added, and mixture was separated. The aqueous layer was extracted with Et2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO4, filtered and concentrated. Column chromatography (20% EtOAc/Hex) afforded a light yellow oil (1.02 g, 35%). 1H NMR (CDCl3, 500 MHz) δ 6.79 – 6.83 (m, 2H), 6.60 – 6.63 (m, 2H), 5.70 – 5.75 (m, 1H), 5.59 – 5.65 (m, 1H), 3.76 (s, 3H), 3.66 (d, 2H, J = 5.9 Hz), 3.44 (bs, 1H), 1.73 (dd, 3H, J = 6.4, 2.4 Hz).

3-cyclohexylprop-2-yne-1-ol.\(^{36}\) To a solution of cyclohexylacetylene (2.40 mL, 18.5 mmol) in THF (23 mL) at \(-78\) °C was added \(n\)-BuLi as a solution in hexanes (12.5 mL, 1.48 M solution in hexane, 18.5 mmol) dropwise over 10 min. The mixture was stirred at \(-78\) °C for 40 min, and paraformaldehyde (778 mg, 25.9 mmol) was added. The mixture was allowed to warm to 23 °C and stirred for 16 h. Saturated aqueous NH\(_4\)Cl (2 mL) was added, followed by Et\(_2\)O (70 mL). The mixture was dried over Na\(_2\)SO\(_4\), filtered through a plug of Celite, and concentrated. The resulting oil was distilled under vacuum (70 °C, 1.25 mmHg) to yield a colorless oil (2.00 g, 78%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 4.25 – 4.27 (m, 2H), 2.36 – 2.40 (m, 1H), 1.78 – 1.81 (m, 2H), 1.65 – 1.72 (m, 2H), 1.52 – 1.58 (m, 2H), 1.37 – 1.45 (m, 2H), 1.17 – 1.34 (m, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 90.6, 78.1, 51.4, 32.6, 29.1, 25.8, 24.9; IR: 3327 (br), 2929, 2854, 1448, 1148, 1017, 986 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_9\)H\(_{15}\)O [M+H]\(^+\): 139.1123, found: 139.1125.

(Z)-(3-chloroprop-1-enyl)cyclohexane (10% (E)-isomer).\(^{33}\) (Z)-3-cyclohexylprop-2-en-1-ol (642 mg, 4.58 mmol) was dissolved in DMF (3 mL). Collidine (1.11 g, 9.16 mmol), lithium chloride (388 mg, 9.16 mmol), and methanesulfonyl chloride (461 µL, 5.95 mmol) were added. After stirring for 12 h, the reaction was diluted with Et\(_2\)O (100 mL), washed with H\(_2\)O, saturated aqueous NH\(_4\)Cl
(50 mL), and brine (50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. Column chromatography (5% EtOAc/Hex) gave a colorless oil (590 mg, 81%). ¹H NMR (CDCl₃, 400 MHz) δ 5.44 – 5.56 (m, 2H), 4.11 (dd, 2H, J = 7.0, 2.2 Hz), 2.28 – 2.38 (m, 1H), 1.62 – 1.76 (m, 5H), 1.05 – 1.36 (m, 5H); ¹³C NMR (CDCl₃, 101 MHz) δ 141.3, 123.2, 39.9, 36.3, 33.0, 25.8, 25.7; IR: 2953, 2925, 2853, 2034, 1970, 1511, 1459, 1260, 1032, 798, 410 cm⁻¹.

(Z)-N-(3-cyclohexylallyl)-4-methoxyaniline (5% (E)-isomer), 2.60. K₂CO₃ (289 mg, 7.56 mmol) and p-anisidine (1.16 g, 9.45 mmol) were diluted with DMF (8 mL), and (Z)-(3-chloroprop-1-enyl)cyclohexane (502 mg, 3.15 mmol) was added. The reaction was heated to 80 °C and stirred overnight. The reaction was cooled and filtered. Water (20 mL) was added, and the mixture was separated. The aqueous layer was extracted with EtOAc (3 × 30mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. Column chromatography (10% EtOAc/Hex) yielded a yellow oil (508 mg, 66%). ¹H NMR (CDCl₃, 400 MHz) δ 6.79 (dd, 2H, J = 9.0, 2.4 Hz), 6.61 (dd, 2H, J = 9.0, 2.4 Hz), 5.38 – 5.47 (m, 2H), 3.75 (s, 3H), 3.73 (d, 2H, J = 5.1 Hz), 3.64 (d, 2H, J = 5.9 Hz), 3.36 (bs, 1H), 2.31 (m, 1H), 1.61 – 1.74 (m, 5H), 1.05 – 1.35 (m, 5H); ¹³C NMR (CDCl₃, 126 MHz) δ 152.2, 142.6, 138.9, 125.0, 114.9, 114.3, 55.8, 42.3, 36.7, 33.3, 26.0, 25.8; IR: 2925, 2850, 1512, 1448, 1245, 1179, 1037, 821 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₆H₂₄NO [M+H]+: 246.1858 found: 246.1860.
(E)-N-(3-cyclohexylallyl)-4-methoxyaniline, 2.61. \(^{40}\)

AuBr₃ (91.7 mg, 0.210 mmol) was suspended in THF (2 mL), and p-anisidine (505 mg, 4.10 mmol) was added. The mixture was stirred under argon at room temperature for 5 min. Cyclohexyllallene (298 µL, 2.05 mmol) was added. After 4 h, the mixture was filtered through a silica plug and concentrated. Column chromatography (10% EtOAc/Hex) yielded a slightly yellow oil (189 mg, 38%). \(^{1}H\) NMR (CDCl₃, 400 MHz) δ 6.78 (dd, 2H, \(J = 9.0, 2.4\) Hz), 6.60 (dd, 2H, \(J = 9.0, 2.4\) Hz), 5.66 (dd, 1H, \(J = 15.5, 6.5\) Hz), 5.50 – 5.57 (app dtd, 1H \(J = 15.5, 5.9, 1.0\) Hz), 3.75 (s, 3H), 3.65 (dd, 2H, \(J = 5.9, 1.0\) Hz), 3.42 (bs, 1H), 1.92 – 2.20 (m, 1H), 1.63 – 1.75 (m, 5H), 1.03 – 1.32 (m, 5H); \(^{13}C\) NMR (CDCl₃, 100 MHz) δ 152.1, 142.5, 139.1, 124.5, 114.8, 114.3, 55.8, 47.2, 40.4, 32.9, 26.1, 26.0; \textbf{IR}: 2923, 2845, 1512, 1447, 1234, 1039, 971, 818 cm\(^{-1}\); \textbf{HRMS} (DART-TOF) calcd. for C₁₆H₂₄NO [M+H]\(^{+}\): 246.1858, found: 246.1860.

\(3\)-phenylprop-2-yn-1-ol. The same procedure as 3-cyclohexylprop-2-yn-1-ol was followed. The resulting oil was distilled under vacuum (93 °C, 1.25 mmHg) to yield a colorless oil (3.64 g, 99%). \(^{1}H\) NMR (CDCl₃, 400 MHz) δ 7.42 – 7.47 (m, 2H), 7.29 – 7.35 (m, 3H), 4.50 (d, 2H, \(J = 4.3\) Hz), 1.69 (bs, 1H); \(^{13}C\) NMR (CDCl₃, 100 MHz) δ 131.7, 128.5, 128.3, 122.5, 87.1, 85.7, 51.7; \textbf{IR}: 3341, 3061, 2866, 1490, 1442, 1032, 953, 756, 691, 524 cm\(^{-1}\); \textbf{HRMS} (DART-TOF) calcd. For C₉H₉O [M+H]\(^{+}\): 133.0653, found: 133.0652.

(Z)-4-methoxy-N-(3-phenylallyl)aniline, 2.62. To \( p \)-anisidine (1.58 g, 12.8 mmol) in CH\(_3\)CN (2 mL) was added \( (Z) \)-(3-chloroprop-1-enyl)benzene (501 mg, 3.28 mmol). The mixture was stirred overnight at room temperature. Saturated aqueous NH\(_4\)Cl (15 mL) was added and mixture was separated. The aqueous layer was extracted with Et\(_2\)O (3 \( \times \) 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO\(_4\), filtered and concentrated. Column chromatography (10% EtOAc/Hex) yielded a yellow oil (369 mg, 47%). ^1H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.25 – 7.29 (m, 2H), 7.14 – 7.21 (m, 3H), 6.68 (d, 2H, \( J = 9.0 \) Hz), 6.49 – 6.56 (m, 1H), 6.47 (dd, 2H, \( J = 9.0, 2.4 \) Hz), 5.68 – 5.74 (dt, 1H, \( J = 11.7, 6.5 \) Hz), 3.90 (dd, 2H, \( J = 6.5, 1.8 \) Hz), 3.64 (s, 3H), 3.46 (bs, 1H); ^13C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 152.3, 142.1, 136.7, 131.3, 130.0, 128.8, 128.3, 127.1, 114.9, 114.4, 55.8, 43.2; IR: 3388, 3022, 2931, 2832, 1512, 1446, 1237, 1074, 820, 700, 517 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{16}\)H\(_{18}\)NO [M+H]^+: 240.1388, found: 240.1390.

(Z)-4-(benzyloxy)but-2-en-1-ol.\(^{41}\) In a dry box, a flame-dried 250-mL round-bottom flask was charged with sodium hydride (467 mg, 19.5 mmol). The flask was capped with a rubber septum and brought out of the dry box. Dry THF (65 mL), was added via syringe and the vessel was brought to 0 °C. 1,4-butene diol (8.0 mL, 20 mmol) was added dropwise to the stirring suspension, resulting in vigorous bubbling. Once addition was complete, the reaction was allowed to warm to room temperature over the course of 30 min. Benzyl bromide (16.2 mmol, 1.92 mL) was added to the flask via syringe and the reaction was allowed to stir overnight. The reaction was concentrated

\(^{41}\) Schmidt, B; Pohler, M.; Costisella, B. Tetrahedron 2002, 58, 7951 – 7958.
and the crude residue was diluted with Et₂O (150 mL). The organic layer was washed with H₂O (3 × 75 mL), dried over MgSO₄, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography (30% EtOAc/Hex) to yield a pale yellow oil (1.82 g, 48%). **¹H NMR** (CDCl₃, 400 MHz) δ 7.29 – 7.37 (m 5H), 5.82 (m, 1H), 5.74 (m, 1H), 4.53 (s, 2H), 4.17 (m, 2H), 4.09 (m, 2H), 1.92 (br s, 1H); **¹³C NMR** (CDCl₃, 100 MHz) δ 138.1, 132.5, 128.7, 128.5, 128.1, 128.0, 72.7, 65.9, 59.0; **IR**: 3409, 1736, 1241, 1070, 1042, 736, 697 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₁₁H₁₅O₂ [M+H]^+: 179.1072, found: 179.1079.

(Z)-(((4-chlorobut-2-en-1-yl)oxy)methyl)benzene.³³ To a 25 mL, flame-dried, round-bottom flask was added LiCl (374 mg, 8.82 mmol), 2,4,6-collidine (2.2 mL, 8.8 mmol), and methanesulfonyl chloride (412 µL, 5.35 mmol). (Z)-4-(benzyloxy)but-2-en-1-ol (786 mg, 4.11 mmol) was added to the flask dropwise as a solution in DMF (3.0 mL). The reaction was allowed to stir overnight. The mixture was diluted with Et₂O (100 mL) and the organics were washed with H₂O (3 × 40 mL), saturated NH₄Cl (3 × 40 mL), and brine (40 mL). The combined organics were dried over MgSO₄ and concentrated. The crude mixture was purified by silica gel chromatography (10% EtOAc/Hex) to yield a pale orange oil (716 mg, 88%). **¹H NMR** (CDCl₃, 500 MHz) δ 7.30 – 7.37 (m, 5H), 5.82 (m, 2H), 4.55 (s, 2H), 4.15 (m, 2H), 4.11 (m, 2H); **¹³C NMR** (CDCl₃, 125 MHz) δ 138.1, 131.0, 128.7, 128.6, 128.0, 127.9, 72.6, 65.3, 39.4; **IR**: 2857, 1736, 1453, 1240, 1072, 736, 697 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₁₁H₁₇ClNO [M+NH₄]^+: 214.0994, found: 214.0999.
(Z)-N-(4-(benzyl oxy)but-2-en-1-yl)-4-methoxyaniline, 2.63.

To a 25 mL, flame-dried, round-bottom flask was added p-anisidine (2.54 g, 20.7 mmol). The vessel was charged with (Z)-(((4-chlorobut-2-ent-1-yl)oxy)methyl)benzene (1.04 g, 5.30 mmol) as a solution in DMF (6 mL). The reaction was allowed to stir overnight. The reaction was diluted with Et₂O (150 mL), washed with H₂O (3×50 mL), saturated NH₄Cl (3×50 mL), dried over MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel chromatography (15% EtOAc/Hex) to yield a dark orange oil (553 mg, 37%).

\[ ^1H \text{NMR} \ (\text{CDCl}_3, \ 500 \text{ MHz}) \delta \text{ 7.29 – 7.38 (m, 5H), 6.80 (d, 2H, } J = 9.0 \text{ Hz}, 6.59 (d, 2H, } J = 8.8 \text{ Hz), 5.79 (m, 2H), 4.56 (s, 2H), 4.16 (d, 2H, } J = 5.1 \text{ Hz), 3.77 (s, 3H), 3.75 (d, 2H, } J = 4.9 \text{ Hz);} \]

\[ ^{13}C \text{NMR} \ (\text{CDCl}_3, \ 125 \text{ MHz}) \delta \text{ 152.6, 142.4, 138.3, 131.1, 128.9, 128.6, 128.0, 127.9, 115.1, 114.6, 72.7, 65.9, 56.0, 42.5; } \text{IR: 2944, 2812, 1509, 1232, 1070, 1030, 817, 735, 697 cm}^{-1}; \]

\[ \text{HRMS (DART-TOF) calcd. for } C_{18}H_{22}N_1O_2 \ [M+H]^+: 284.1651, \text{ found: 284.1649.} \]

(Z)-4-(4-methoxyphenylamino)but-2-en-1-ol. 42 1,4-but-2-enediol cyclic sulfite (1.50 g, 11.2 mmol) was dissolved in DMF (6 mL). K₂CO₃ (3.72 g, 26.9 mmol) and p-anisidine (2.76 g, 22.4 mmol) were added. The reaction was heated to 100 °C for 48 h. The reaction was cooled to room temperature and H₂O (30 mL) was added. The mixture was separated, and the aqueous layer was extracted with Et₂O (3×25 mL). The combined organic layers were washed with H₂O (25 mL), dried over MgSO₄, filtered, and concentrated. Column chromatography (15% EtOAc/Hex) yielded a light yellow oil (1.02

g, 47%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.79 (dd, 2H, $J$ = 9.0, 2.4 Hz), 6.62 (dd, 2H, $J$ = 9.0, 2.4 Hz), 5.68 – 5.82 (m, 2H), 4.25 (dd, 2H, $J$ = 6.3, 1.2 Hz), 3.74 – 3.75 (m, 5H), 2.73 (bs, 2H); $^{13}$C NMR (CDCl$_3$, 101 MHz) $\delta$ 152.6, 141.9, 131.5, 129.5, 114.8, 58.7, 55.7, 42.3; IR: 3361, 2939, 2833, 1512, 1235, 1034, 821 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{16}$NO$_2$ [M+H]$^+$: 194.1181, found: 194.1181.

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

(Z)-N-(4-(tert-butyldiphenylsilyloxy)but-2-enyl)-4-methoxyaniline, 2.64.$^{43}$ To imidazole (222 mg, 3.30 mmol) and DMF (0.6 mL) in a round bottom flask was added (Z)-4-(4-methoxyphenylamino)but-2-en-1-ol (420 mg, 2.17 mmol) dissolved in DMF (0.6 mL). After stirring for 10 minutes, tert-butyldiphenylchlorosilane (610 µL, 2.39 mmol) was added in one portion. After stirring at room temperature for 45 min, H$_2$O (20 mL) was added. The mixture was separated, and the aqueous phase was extracted with Et$_2$O (3×15 mL). The combined organic layers were washed with H$_2$O (25 mL) and brine (25 mL). The resulting organic layer was dried over MgSO$_4$, filtered, and concentrated. Column chromatography (7.5% EtOAc/Hex) yielded a yellow oil (587 mg, 63%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.59 – 7.62 (m, 4H), 7.27 – 7.37 (m, 6H), 6.66 (dd, 2H, $J$ = 9.0, 2.4 Hz), 6.41 (dd, 2H, $J$ = 9.0, 2.4 Hz), 5.65 – 5.70 (m, 1H), 5.45 – 5.51 (m, 1H), 4.23 (dt, 2H, $J$ = 6.3, 0.8 Hz), 3.65 (s, 3H), 3.45 (dt, 2H, $J$ = 6.7, 0.8 Hz), 3.19 (br s, 1H), 0.97 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 152.3, 142.2, 135.6, 133.6, 131.4, 129.7, 128.4, 127.7, 114.8, 114.3, 60.2, 55.8, 42.1, 26.8, 19.2; IR: 2931, 2857, 1513, 1428, 1236, 1074, 1040, 820, 703, 505 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{27}$H$_{34}$NO$_2$Si [M+H]$^+$: 432.2359 found: 432.2345.

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(Z)-2-(4-chlorobut-2-en-1-yl)isoindoline-1,3-dione. \(^{44}\) To a flame-dried round-bottom flask was added potassium phthalimide (2.65 g, 14.3 mmol) followed by DMF (50 mL) under nitrogen. The stirring suspension was charged with (Z)-1,4-dichlorobut-2-ene (3.0 mL, 29 mmol). The mixture was allowed to stir at room temperature overnight. The reaction was diluted with EtOAc (200 mL) and extracted with H\(_2\)O (6 × 75 mL). The combined organics were dried over anhydrous MgSO\(_4\), filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (20\% EtOAc/Hex) to afford the product as a colorless solid (929 mg, 28\%). \(^{1}\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.86 (dd, 2H, \(J = 5.4, 2.9\) Hz), 7.73 (dd, 2H, \(J = 5.4, 3.2\) Hz), 5.80 – 5.86 (m, 1H), 5.68 – 5.72 (m, 1H), 4.38 (dd, 2H, \(J = 7.3, 1.2\) Hz), 4.32 (d, 2H, \(J = 7.8\) Hz) \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 168.0, 134.3, 132.3, 130.1, 127.4, 123.6, 38.8, 34.3; \(\text{IR}\): 1699, 1429, 1242, 1120, 1065, 764, 711, 530 cm\(^{-1}\); \(\text{HRMS (DART-TOF)}\) calcd. for C\(_{12}\)H\(_{11}\)ClNO\(_2\) [M+H]\(^+\): 236.0478, found: 236.0485.

\(\text{(Z)-2-((4-methoxyphenyl)amino)but-2-en-1-yl)isoindoline-1,3-dione, 2.65.}\) \(p\)-Anisidine (3.12 g, 25.4 mmol) was added to a flame-dried, 25 mL, round-bottom flask. The flask was charged with (Z)-2-(4-chlorobut-2-en-1-yl)isoindoline-1,3-dione (854 mg, 3.62 mmol) as a solution in CH\(_3\)CN (9 mL). The reaction mixture was allowed to stir at room temperature overnight. The reaction was diluted with Et\(_2\)O (100 mL), and washed successively with H\(_2\)O (3 × 50 mL).

and saturated NH₄Cl (3 × 50 mL). The combined organics were dried over anhydrous MgSO₄, filtered, and concentrated by rotary evaporation. The crude mixture was purified by silica gel chromatography (30% EtOAc/Hex) to yield the title compound as a yellow solid (761 mg, 65%). \(^1\)H NMR (CDCl₃, 500 MHz) δ 7.85 (dd, 2H, J = 6.9, 3.9 Hz), 7.72 (dd, 2H, J = 6.9, 3.7 Hz), 6.80 (d, 2H, J = 11.2 Hz), 6.68 (d, 2H, J = 11.5 Hz), 5.79 – 5.84 (m, 1H), 5.57 – 5.61 (m, 1H), 4.39 (d, 2H, J = 9.1, 1.5 Hz), 3.95 (d, 2H, J = 8.3 Hz), 3.75 (s, 3H); \(^{13}\)C NMR (CDCl₃, 125 MHz) δ 168.2, 152.6, 142.5, 134.2, 132.4, 131.9, 125.8, 123.5, 115.1, 114.8, 56.0, 42.0, 35.1; IR: 2973, 2826, 1705, 1511, 1390, 1322, 1234, 821, 715 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₉H₁₉N₂O₃ [M+H]⁺: 323.1396, found: 323.1394.

\((Z)\)-ethyl 7-chlorohept-5-enoate. To a 25-mL, flame-dried, round-bottom flask was added LiCl (499 mg, 11.0), 2,4,6-collidine (1.45 mL, 11.0 mmol), and methanesulfonyl chloride (550 µL, 7.18 mmol). (Z)-4-(benzyloxy)but-2-en-1-ol (951 mg, 5.52 mmol) was added to the flask dropwise as a solution in DMF (3 mL). The reaction was allowed to stir overnight. The mixture was diluted with Et₂O (100 mL) and the organics were washed with water (3 × 40 mL), saturated NH₄Cl (3 × 40 mL), and brine (40 mL). The combined organics were dried over MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel chromatography (25% EtOAc/Hex) to afford a pale orange oil (816 mg, 78%). \(^1\)H NMR (CDCl₃, 400 MHz) δ 5.52 – 5.63 (m, 2H), 4.12 (q, 2H, J = 7.4 Hz), 4.07 (d, 2H, J = 7.2 Hz), 2.25 (t, 2H, J = 7.4 Hz), 2.08 – 2.14 (m, 2H), 1.65 – 1.70 (m, 2H), 1.17 – 1.21 (m, 3H); \(^{13}\)C NMR (CDCl₃, 125 MHz) δ 173.6, 135.3, 126.5, 60.5, 39.4, 33.7, 26.6, 24.6,
14.4; IR: 2980, 1732, 1375, 1249, 1180, 758, 730 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{10}\)H\(_{13}\)ClO\(_2\) [M+H]\(^+\): 191.0839, found: 191.0835.

(Z)-ethyl 7-((4-methoxyphenyl)amino)hept-5-enoate, 2.66. A flame-dried, 25 mL, round-bottom flask was charged with p-anisidine (3.68 g, 29.9 mmol). (Z)-ethyl 7-chlorohept-5-enoate (816 mg, 4.28 mmol) was added to the reaction flask as a solution in CH\(_3\)CN (9 mL). The reaction was allowed to stir at room temperature overnight. The reaction was diluted with Et\(_2\)O (150 mL) and washed with H\(_2\)O (3 \times 50 mL) and saturated aqueous NH\(_4\)Cl (3 \times 50 mL). The combined organics were dried over anhydrous MgSO\(_4\), filtered, and concentrated. The crude material was purified by silica gel chromatography (20% EtOAc/Hex) to afford an orange oil (684 mg, 57%). \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 6.77 – 6.79 (m, 2H), 6.58 – 6.60 (m, 2H), 5.49 – 5.61 (m, 2H), 4.12 (q, 2H, \(J = 7.1\) Hz), 3.74 (s, 3H), 3.70 (dd, 2H, \(J = 6.4\) Hz), 2.32 (t, 2H, \(J = 7.3\) Hz), 2.16 (d, 2H, \(J = 7.3\) Hz), 1.72 – 1.75 (m, 2H), 1.25 (t, 3H, \(J = 7.1\) Hz); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 173.7, 152.4, 142.7, 131.8, 128.4, 115.1, 114.6, 60.5, 56.0, 42.4, 33.9, 27.1, 24.9, 14.5; IR: 2936, 2832, 1727, 1511, 1234, 1035, 820 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{16}\)H\(_{24}\)N\(_1\)O\(_3\) [M+H]\(^+\): 278.1756, found: 278.1749.

\(N\)-allyl-4-methoxyaniline, 2.51.\(^{45}\) Allyl chloride (5.29 mL, 65.0 mmol) was added dropwise to a flame dried 500 mL round bottom flask containing a solution of 4-methoxyaniline (8.00 g, 65.0 mmol) and potassium carbonate (21.5 g, 156 mmol) in DMF (148 mL). The solution was heated to 80 °C and was stirred at this temperature overnight. The reaction was cooled to room

temperature, filtered, and diluted with EtOAc (300 mL). The organic layer was washed with water ($4 \times 100$ mL), dried over anhydrous MgSO$_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/Hexanes) to afford an orange oil (7.76 g, 73%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.82 (d, 2H, $J = 8.8$ Hz), 6.62 (d, 2H, $J = 8.8$ Hz), 5.94 – 6.04 (m, 1H), 5.31 (dd, 1H, $J = 17.2, 1.6$ Hz), 5.18 (dd, 1H, $J = 10.4, 1.6$ Hz), 3.77 (s, 3H), 3.75 (dd, 2H, $J = 5.6, 1.6$ Hz), 3.57 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 152.3, 142.5, 136.0, 116.2, 115.0, 114.4, 55.9, 47.6; IR: 3396, 1509, 1230, 1178, 1035, 916, 816 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{12}$H$_{14}$NO [M+H]$^+$: 164.1075, found: 164.1077.

**Equilibration Experiment to Determine $K_{eq}$ (Scheme 2.12)**

In a glove box, a solution of isopropanol (90.0 µL, 1.18 mmol) in C$_6$D$_6$ (1.67 M) was made. The solution was dispensed into three NMR tubes (see table below for amounts). A second solution of (Z)-N-(but-2-enyl)-4-methoxyaniline (70 mg, 0.40 mmol), (±)-2.5 (20 mg, 0.069 mmol), and p-TsOH (350 µL, 5.0 x $10^{-4}$ M in benzene; note benzene was removed prior to mixing with substrate and (±)-2.5) in C$_6$D$_6$ (1.4 mL) was made. The solution was dispensed into three NMR tubes (see table below for amounts). An additional amount of C$_6$D$_6$ was added to each tube to make the total volume 0.7 mL. $^{31}$P NMR were taken immediately then heated to 45 °C. Spectra were acquired at 45 min intervals until equilibrium was reached. All three samples reached equilibrium within 2 h (average $K_{eq} = 3.8$ with standard deviation = 0.5).
Table 2.7 Equilibration Experiment.

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<th>Experiment</th>
<th>Isopropanol Solution</th>
<th>mmol isopropanol</th>
<th>Substrate Solution</th>
<th>mmol substrate</th>
<th>Ratio</th>
<th>$K_{eq}$</th>
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<td>400 µL</td>
<td>0.11</td>
<td>53:47</td>
<td>4.5</td>
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</table>

2.7.5 Reaction Optimization Procedures

**General Hydroformylation Procedure.** The Endeavor was charged with 500 µL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed into the wells. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1 × 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 35 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 50 psi H$_2$/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant reaction temperature of 35 °C and pressure of 50 psi H$_2$/CO for 15 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, a solution of trimethoxybenzene in EtOAc (100 µL, 0.200 M) was added, and the sample was concentrated. The resulting residue was dissolved in MeOH (2 mL) and added to NaBH$_4$ (22.7 mg, 0.600 mmol) in a flame dried flask. The reaction was stirred for 1.5 h. H$_2$O (3 mL) was added, and the layers were separated. The organic layer was extracted with EtOAc (3 × 10 mL), dried over NaSO$_4$, filtered, and concentrated. $^1$H NMRs were taken to determine conversion. The reaction was chromatographed (1% MeOH/CH$_2$Cl$_2$) to
determine isolated yield. SFC or HPLC analysis of the products was used to determine enantioselectivities.

**Pressure Screen with 2.51 and 2.5 (Table 2.1)**

In a dry box, N-allyl-4-methoxyaniline, 2.51, (33 mg, 0.20 mmol) and 2.5 (5.7 mg, 2.0 \times 10^{-2} \text{ mmol}) were mixed in C_6D_6 (0.6 mL) in a sealed NMR tube. The mixture was brought out of the glovebox and was heated to 45 °C for 12 hours. The NMR tube was cooled to room temperature, brought into the drybox and concentrated under reduced pressure to remove generated MeOH from the solution. The resulting residue was dissolved in benzene (1.5 mL), mixed with 2 mol % Rh(acac)(CO)_2 (1.1 mg, 4.0 \times 10^{-3} \text{ mmol}) and injected into the Endeavor, followed by 0.5 mL of benzene to wash the injection port. The reactions were run at 45 °C at the following pressures: 50, 70, 100, and 200 psi H_2/CO.

Note: For Table 2.1, Entry 5 the reaction was set up identically as described in the procedure above, but 0.05 mol % p-TsOH (130 \mu L, 0.0001 mmol, 7.7 \times 10^{-4} \text{ M solution in benzene}) was added to the pre-exchange mixture.

**Reaction of 1,2-Disubstituted Olefin Substrate 2.57 with 2.5 (Scheme 2.15)**

(E)-N-(but-2-enyl)-4-methoxyaniline, 2.57, (35 mg, 0.20 mmol), 2.5 (5.7 mg, 2.0 \times 10^{-2} \text{ mmol}), and 0.05 mol % p-TsOH (130 \mu L, 1.00 \times 10^{-4} \text{ mmol, 7.7 \times 10^{-4} M solution in benzene}) were mixed in C_6D_6 (0.6 mL) in a sealed NMR tube. The mixture was brought out of the glovebox and was heated to 45 °C for 12 hours. The NMR tube was cooled to room temperature, brought into the drybox and concentrated under reduced pressure to remove generated MeOH from the solution. The resulting residue was dissolved in benzene (1.5 mL), mixed with 2 mol % Rh(acac)(CO)_2 (1.1 mg, 4.0 \times 10^{-3} \text{ mmol}) and
injected into the Endeavor, followed by 0.5 mL of benzene to wash the injection port. The hydroformylation was run at 45 °C and 50 psi H₂/CO.

**Temperature Screen with 2.42 and 2.49 (Table 2.2)**

(Z)-N-(but-2-enyl)-4-methoxyaniline, 2.57, (35 mg, 0.20 mmol), 2.42 (6.5 mg, 2.0 × 10⁻² mmol), and 0.05 mol % p-TsOH (130 µL, 1.00 × 10⁻⁴ mmol, 7.7 × 10⁻⁴ M solution in benzene) were mixed in C₆D₆ (0.6 mL) in a sealed NMR tube. The mixture was brought out of the glovebox and was heated to 45 °C for 12 hours. The NMR tube was cooled to room temperature, brought into the drybox and concentrated under reduced pressure to remove generated MeOH and was redissolved in C₆D₆ (0.6 mL). The mixture was heated to 45 °C for 4 hours before being concentrated again in the glovebox. During the pre-exchange, the four diastereomers of 2.42 converge to one substrate-bound-ligand peak in the ³¹P NMR. The resulting residue was dissolved in benzene (1.5 mL), mixed with 2 mol % Rh(acac)(CO)₂ (1.1 mg, 4.0 × 10⁻³ mmol) and injected into the Endeavor, followed by 0.5 mL of benzene to wash the injection port. The reactions were run at 50 psi H₂/CO at the following temperatures: 30, 35, 45, and 55 °C.

**Attempts to Increase Conversion (Scheme 2.16)**

Equation 1 (Increasing the reaction time): The procedure for Table 2.2 was followed using substrate 2.57 (0.4 mmol) at 35 °C for 24 hours.

Equation 2 (Increasing the loading of 2.42): The procedure for Table 2.2 was followed using substrate 2.57 (0.4 mmol) at 35 °C with 15 mol % 2.42 (20 mg, 2.0 × 10⁻² mmol).

**2.7.6 Hydroformylation Results and Product Characterization (Table 2.3)**

**General Hydroformylation Procedure.** The Endeavor was charged with 500 µL of benzene per reaction well to fill the void volume between reactor wall and reaction tube,
and oven dried glass reaction vials were placed into the wells. The Endeavor was sealed and purged with nitrogen (4 × 100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1×100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 35 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 50 psi H₂/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant reaction temperature of 35 °C and pressure of 50 psi H₂/CO for 15 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, a solution of trimethoxybenzene in EtOAc (100 µL, 0.200 M) was added, and the sample was concentrated. The resulting residue was dissolved in MeOH (2 mL) and added to NaBH₄ (22.7 mg, 0.600 mmol) in a flame dried flask. The reaction was stirred for 1.5 h. H₂O (3 mL) was added, and the layers were separated. The organic layer was extracted with EtOAc (3×10 mL), dried over NaSO₄, filtered, and concentrated. 1H NMRs were taken to determine conversion. The reaction was chromatographed (1% MeOH/CH₂Cl₂) to determine isolated yield. SFC or HPLC analysis of the products was used to determine enantioselectivities.

**General Procedure A:** (Z)-N-(but-2-enyl)-4-methoxyaniline (35.4 mg, 0.20 mmol), 2.42 (9.8 mg, 0.030 mmol), and p-toluenesulfonic acid in benzene (130 µL, 1.00 x 10⁻⁴ mmol, 7.70 x 10⁻⁴ M solution) were mixed in C₆D₆ (0.6 mL) and heated to 45 °C for 12 h in a sealed NMR tube. The solution was concentrated in a dry glove box to remove MeOH in the solution and redissolved in C₆D₆. The solution was heated to 45 °C for 4 h before being concentrated again in a glove box. During this pre-exchange, the four diastereomers of 2.42 converge to one substrate-bound ligand peak. The resulting residue
was dissolved in benzene (1.5 mL), mixed with 2 % Rh(acac)(CO)₂ (1.0 mg, 0.0040 mmol), and injected into the Endeavor followed by 0.5 mL benzene to wash the injection port.

**General Procedure B:** The same procedure as Procedure A using 1.75 % Rh(acac)(CO)₂ (0.9 mg, 0.0035 mmol) and 0.03% p-TsOH (83 µL, 6.0 × 10⁻⁵ mmol).

**General Procedure C:** The procedure is the same as Procedure A using 1.5 % Rh(acac)(CO)₂ (0.77 mg, 0.0030 mmol).

**General Procedure D.** Same as procedure A except 1.75 mol% Rh(acac)(CO)₂ (0.9 mg, 0.0035 mmol) was used.

**A Note on Hydroformylation Regioselectivities**

Under the reaction conditions, the undesired linear products likely cyclize to a PMP protected aminal which we were unable to detect in crude NMRs or isolate. Trying to make and isolate this product through other methods also failed. The amount of undesired structural isomer was estimated by two calculations: the difference between conversion and yield of branched product by ¹H NMR (Table 2.8, Column 3) and the difference between conversion and isolated yield (Table 2.8, Column 4). The selectivities are generally greater than 4:1. We feel these numbers underestimate the actual regioselectities, because it does not account for side reactions or decomposition of the aldehyde during hydroformylation. Notably, previous work in our group in the hydroformylation of allylic alcohols and sulfonamides afford regioselectivities of >95:5. The lower regioselectivity for the phthalimide protected substrate may result from directed hydroformylation from the phthalimide functional group. Similarly the terminal
substrate may have a lower regioselectivity due to background reaction that prefers the linear isomer.

**Table 2.8 Hydroformylation Regioselectivities.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Starting Material (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Isolated Yield (%)</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>PMPN&lt;sub&gt;2.49&lt;/sub&gt;</td>
<td>26</td>
<td>70</td>
<td>69</td>
<td>92</td>
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<tr>
<td>PMPN&lt;sub&gt;2.57&lt;/sub&gt;</td>
<td>8</td>
<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>74</td>
<td>80</td>
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<td>12</td>
<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>86</td>
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<tr>
<td>PMPN&lt;sub&gt;2.61&lt;/sub&gt;</td>
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<td>63</td>
<td>45</td>
<td>79</td>
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<tr>
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<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>70</td>
<td>92</td>
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<tr>
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<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>8</td>
<td>77</td>
<td>64</td>
<td>73</td>
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</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard.  
<sup>b</sup> Determined by supercritical fluid chromatography.  
<sup>c</sup> Amount could not be determined accurately due to peak overlap in the <sup>1</sup>H NMR.

**Table 2.3, Entry 1:**
(S)-2-(((4-methoxyphenylamino)methyl)butan-1-ol. General Procedure A was followed. Chromatography (1% MeOH/CH₂Cl₂) yielded a pale yellow oil (26.5 mg, 69%). SFC (OD-H, 4.0 mL/min, 3.0% MeOH, 220 nm, 150 bar, 35 °C) t<sub>rmajor</sub> = 17.80 min and t<sub>rminor</sub> = 19.16 min, 92% ee; <sup>1</sup>H NMR (CDCl₃, 400 MHz) δ 6.78 – 6.82 (m, 2H), 6.66 – 6.70 (m, 2H), 3.80 (dd, 1H, J = 10.8, 3.9 Hz), 3.75 (s, 3H), 3.63 – 3.68 (m, 1H), 3.30 (br s, 1H), 3.20 – 3.24 (m, 1H), 3.11 (dd, 1H, J = 12.1, 8.4 Hz), 1.77 – 1.82 (m, 1H), 1.39 (q, 2H, J = 7.2 Hz), 0.96 – 1.00 (m, 3H); <sup>13</sup>C NMR (CDCl₃, 100 MHz) δ 152.6, 142.4, 115.1, 114.8, 66.1, 55.8, 48.9, 41.8, 22.3, 11.6; IR: 3379, 2961, 2925, 1513, 1464, 1236, 1038, 822 cm⁻¹; HRMS (DART-TOF) calcd. for C<sub>12</sub>H<sub>20</sub>NO₂ [M+H]<sup>+</sup>: 210.1494, found: 210.1498. [α]<sub>D</sub>²⁰ = +8.7 (c = 0.240, CHCl₃, l = 50 mm).

Table 2.3, Entry 2:

![Table 2.3, Entry 2](image-url)
**(S)-2-((4-methoxyphenylamino)methyl)butan-1-ol.** General Procedure A was followed. Chromatography (1% MeOH/CH$_2$Cl$_2$) yielded a pale yellow oil (28.4 mg, 74%). **SFC** (OD-H, 4.0 mL/min, 3.0% MeOH, 220 nm, 150 bar, 35 °C) 80% ee.

**Table 2.3, Entry 3:**

![Chemical Structure](image)

**(S)-3-cyclohexyl-2-((4-methoxyphenylamino)methyl)propan-1-ol.** General Procedure A was followed. Chromatography (1% MeOH/CH$_2$Cl$_2$) yielded a pale yellow oil (41.6 mg, 75%). **SFC** (OD-H, 1.0 mL/min, 6.0% MeOH, 220 nm, 150 bar, 50 °C) $t_{\text{r}}$minor $=11.27$ min and $t_{\text{r}}$major $=12.10$ min, 86% ee; $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.80 (dd, 2H, $J = 6.6, 2.5$ Hz), 6.64–6.67 (m, 2H), 3.77–3.79 (m, 1H), 3.75 (s, 3H), 3.61 (dd, 1H, $J = 10.8, 7.3$ Hz), 3.19 (dd, 1H, $J = 12.0, 3.9$ Hz), 3.06 (dd, 1H, $J = 12.0, 8.6$ Hz), 1.93–2.20 (m, 1H), 1.64–1.75 (m, 5H), 1.28–1.35 (m, 1H), 1.11–1.28 (m, 5H), 0.84–0.93 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 152.7, 142.5, 115.2, 114.9, 67.1, 55.8, 49.9, 37.3, 37.1, 35.1, 33.7, 33.6, 26.6, 26.3, 26.3; IR: 3376, 2921, 2849, 1512, 1448, 1235, 1037, 819 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{17}$H$_{28}$NO$_2$ [M+H]$^+$: 278.2120, found: 278.2117. $[\alpha]_D^{20} = +4.3$ (c = 0.140, CHCl$_3$, l = 50 mm).
Table 2.3, Entry 4:

(S)-3-cyclohexyl-2-((4-methoxyphenylamino)methyl)propan-1-ol. General Procedure A was followed. Chromatography (1% MeOH/CH₂Cl₂) yielded a pale yellow oil (34.2 mg, 62%). SFC (OD-H, 1.0 mL/min, 6.0% MeOH, 220 nm, 150 bar, 50 °C) 76 % ee.

Table 2.3, Entry 5:
(S)-2-benzyl-3-(4-methoxyphenylamino)propan-1-ol. General Procedure A was followed. Column chromatography (1% MeOH/CH2Cl2) yielded a pale yellow solid (24.4 mg, 45%). SFC (OD-H, 1.0 mL/min, 5.0% MeOH, 220 nm, 150 bar, 50 °C) $t_{\text{major}} = 20.83$ min, $t_{\text{minor}} = 24.87$ min, 79% ee; $^1$H NMR (CDCl3, 400 MHz) $\delta$ 7.10 – 7.28 (m, 5H), 6.69 (d, 2H, $J = 8.8$ Hz), 6.49 (d, 2H, $J = 8.8$ Hz), 3.70 (dd, 1H, $J = 10.8$, 3.9 Hz), 3.67 (s, 3H), 3.58 (dd, 1H, $J = 10.8$, 6.5 Hz), 3.05 – 3.15 (m, 2H), 2.87 (br s, 2H), 2.50 – 2.70 (m, 2H), 2.05 – 2.25 (m, 1H); $^{13}$C NMR (CDCl3, 100 MHz) $\delta$ 152.8, 141.8, 139.7, 129.0, 128.5, 126.2, 115.3, 114.8, 65.6, 55.8, 48.6, 41.9, 36.1; IR: 3373, 2926, 1510, 1454, 1235, 1033, 820, 743, 701, 521 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{17}$H$_{22}$NO$_2$ [M+H]$^+$: 272.1651, found: 272.1641. [$\alpha$]$_D^{20} = +50.0$ (c = 0.108, CHCl3, $l$ = 50 mm).

Table 2.3, Entry 6:

(S)-4-(benzyloxy)-2-(((4-methoxyphenyl)amino)methyl)butan-1-ol. General Procedure B was followed yielding a light yellow oil (43.9 mg, 70%). SFC (AS-H, 2.0 mL/min, 3.0% MeOH, 240 nm, 150 bar, 50 °C) $t_{\text{minor}} = 6.53$ min and $t_{\text{major}} = 6.96$ min; 92% ee $^1$H NMR (CDCl3, 500 MHz) $\delta$ 7.30 – 7.37 (m, 5H), 6.76 (d, 2H, $J = 9.0$ Hz), 6.59 (d, 2H, $J$
= 9.0 Hz), 4.59 (s, 2H), 3.74 (s, 3H), 3.69 (m, 2H), 3.59 (m, 2H), 3.13 (d, 2H, J = 6.5 Hz), 2.00 (m, 1H), 1.73 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 152.6, 142.5, 138.1, 128.7, 128.0, 128.0, 115.1, 114.9, 73.5, 68.7, 65.7, 56.0, 48.5, 38.8, 30.3; IR: 3362, 2942, 1511, 1032, 820, 699 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{19}$H$_{26}$NO$_3$ [M+H]$^+$: 316.1919, found: 316.1913. [$\alpha$]$_{D}^{20}$ = +18.0 (c = 0.205, CHCl$_3$, l = 50 mm).

Table 2.3, Entry 7:

(S)-4-(tert-butyldiphenylsilyloxy)-2-((4-methoxyphenylamino)methyl)butan-1-ol.

General Procedure C was followed. Chromatography (1% MeOH/CH$_2$Cl$_2$) yielded a pale yellow oil (61.7 mg, 67%). HPLC (OD-H, 1.0 mL/min, 5.0% i-PrOH: 95% Hexanes, 240 nm) $t_{\text{minor}} = 15.3$ min and $t_{\text{major}} = 21.5$, 90% ee; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.67 (dd, 4H, J = 8.1, 1.5 Hz), 7.37 – 7.46 (m, 6H), 6.77 – 6.78 (m, 2H), 6.61 (dd, 2H, J = 6.9, 2.2 Hz), 3.76 – 3.81 (m, 2H), 3.75 (s, 3H), 3.67 – 3.72 (m, 2H), 3.12 (d, 2H, J = 6.4 Hz), 2.03 – 2.10 (m, 1H), 1.64 (q, 2H, J = 6.1 Hz), 1.07 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 152.4, 142.4, 135.5, 133.4, 129.8, 127.7, 114.9, 114.7, 65.8, 62.2, 55.8, 48.4, 38.0, 32.7,
26.8, 19.1; IR: 3352, 2932, 1513, 1236, 1110, 822, 703, 613, 509 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₈H₃₈NO₃Si [M+H]⁺: 464.2621, found: 464.2622. [α]D²⁴ = +12.3 (c = 0.140, CHCl₃, l = 50 mm).

Table 2.3, Entry 8:

(S)-2-(4-hydroxy-3-((4-methoxyphenylamino)methyl)butyl)isoindoline-1,3-dione.

General Procedure C was followed except only 1 equivalent of NaBH₄ was used in reduction to prevent reduction of the phthalimide protecting group. Column chromatography resulted in a pale yellow solid (38.9 mg, 55%). HPLC (AS-H, 1.0 mL/min, 10.0% i-PrOH: 90% Hexanes, 240 nm) t_major = 89.6 and t_minor = 142.3 min, 93% ee ¹H NMR (CDCl₃, 500 MHz) δ 7.82 (dd, 2H, J = 5.4, 3.1 Hz), 7.70 (dd, 2H, J = 5.5, 3.1 Hz), 6.73 (d, 2H, J = 8.8 Hz), 6.61 (d, 2H, J = 8.8 Hz), 3.80 (m, 2H), 3.78 (d, 2H, J = 6.1 Hz), 3.77 (s, 3H), 3.19 (d, 2H, J = 6.1 Hz), 1.87 (m, 1H), 1.76 (m, 2H Hz); ¹³C NMR (CDCl₃, 125 MHz) 168.7, 152.7, 142.4, 134.2, 132.2, 123.4, 115.1, 115.0, 65.5, 55.9, 48.4, 37.9, 36.2, 28.7; IR: 3378, 2927, 1703, 1512, 1398, 1234, 1037, 720; HRMS
(DART-TOF) calcd. for C$_{20}$H$_{23}$N$_2$O$_4$ [M+H]$^+$: 355.1658, found: 355.1646. [$\alpha]$$_D^{20}$ = +24.0 ($c = 0.105$, CHCl$_3$, $l = 50$ mm).

Table 2.3, Entry 9:

(S)-ethyl 7-hydroxy-6-((4-methoxyphenylamino)methyl)heptanoate. General Procedure A was followed. Column chromatography gave a pale yellow oil (41.9 mg, 68%). SFC (AS-H, 1.0 mL/min, 3.0% MeOH, 240 nm, 150 bar, 50 °C) $t_{\text{minor}}$ = 8.25 min and $t_{\text{major}}$ = 8.95 min 90% ee $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.76 – 6.81 (m, 2H), 6.66 (m, 2H), 4.12 (q, 2H, $J = 7.2$ Hz), 3.75 (s, 3H), 3.62 – 3.78 (m, 2H), 3.10 – 3.18 (m, 2H), 2.31 (t, 2H, $J = 7.4$ Hz), 1.86 (m, 1H), 1.65 (m, 2H), 1.33 – 1.42 (m, 4H), 1.25 (t, 3H, $J = 7.0$ Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 173.8, 153.0, 142.2, 115.5, 115.0, 66.4, 60.5, 56.0, 49.5, 40.1, 34.3, 29.3, 26.8, 25.3, 14.4; IR: 3362, 2933, 1731, 1513, 1251, 1034 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{17}$H$_{28}$NO$_4$ [M+H]$^+$: 310.2018, found: 310.2021. [$\alpha]$$_D^{23}$ = +18.0 ($c = 0.110$, CHCl$_3$, $l = 50$ mm).
Table 2.3, Entry 10:

(S)-3-(4-methoxyphenylamino)-2-methylpropan-1-ol. General Procedure C was followed. Column chromatography gave a pale yellow oil (25.0 mg, 64%). SFC (OD-H, 4.0 mL/min, 3.0% MeOH, 220 nm, 150 bar, 50 °C) $t_{major} =$17.55 min and $t_{minor} =$19.94 min, 73% ee. $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.78 (d, 2H, $J = 9.0$), 6.63 (d, 2H, $J = 8.8$), 3.75 (s, 3H), 3.67 (dd, 1H, $J = 10.8, 4.7$), 3.59 (dd, 1H, $J = 10.6, 7.2$), 3.09 (m, 2H), 2.01 (m, 1H), 0.96 (d, 3H, $J = 6.8$); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 152.7, 142.6, 115.1, 115.1, 68.2, 56.0, 50.7, 35.5, 15.2; IR: 3365, 2929, 1512, 1234, 1034, 819 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{16}$NO$_2$ [M+H]$^+$: 196.1338, found: 196.1340. [$\alpha$]$_D^{20} =$ +2.2 (c = 0.110, CHCl$_3$, l = 50 mm).
Experimental Procedure for Scale-Up Reaction

\((S)-2-((4\text{-methoxyphenylamino})\text{methyl})\text{butan-1-ol}\). General Procedure A was followed. \((Z)-N-\text{(but-2-enyl)}-4\text{-methoxyaniline (502 mg, 2.83 mmol), 2.42 (138 mg, 0.425 mmol), and } p\text{-toluenesulfonic acid in benzene (1.84 mL, 1.42 } \times 10^{-3} \text{ mmol, 7.70 } \times 10^{-4} \text{ M solution in benzene) were mixed in } C_6D_6 (9 \text{ mL}) \text{ and heated to } 45^\circ C \text{ for 3 h in a sealed tube. The solution was concentrated in a dry glove box to remove MeOH in the solution. The resulting residue was dissolved in benzene (21 mL), mixed with 2\% } \text{Rh(acac)(CO)}_2 (14.6 mg, 0.056 mmol), \text{ and 3 mL of the solution was injected into seven Endeavor wells followed by 1.0 mL benzene to wash each injection port. Reaction was run for 22.5 h to yield a pale yellow oil (330 mg, 61\%) in 92\% ee. See above for characterization.}

2.7.7 Stereochemical Proofs

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{MeO} & \quad \text{N} \\
\text{HO} & \quad \text{OH}
\end{align*}
\]

1)Ph\((I)(\text{OAc})_2 
2)Boc\text{O}
(S)-β-Cyclohexylmethyl-γ-Boc-amino alcohol. 46, 47 To (S)-3-cyclohexyl-2-((4-methoxyphenylamino)methyl)propan-1-ol (136 mg, 0.490 mmol, 86% ee) in 1:1 MeOH/CH₂Cl₂ (7 mL) at 0 °C was added iodobenzene diacetate (632 mg, 1.96 mmol) in MeOH (7 mL). After stirring at 0 °C for 30 min, 1M HCl (7 mL) was added and the mixture was stirred for 1 h. The reaction was dilated with CH₂Cl₂ (20 mL), and the layers were separated. The aqueous layer was washed with CH₂Cl₂ (3 × 20 mL), and the combined organics were washed with 1M HCl (20 mL). The combined aqueous layers were neutralized by adding solid Na₂CO₃ until pH 10 was reached. CH₂Cl₂ (20 mL) and di-tert-butyl dicarbonate (0.450 mL, 1.96 mmol) were added, and the mixture was stirred vigorously overnight. The layers were separated, and the aqueous layer was washed with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. Column chromatography (20-40% EtOAc/Hex) yielded a yellow oil (8.8 mg). [α]D²⁰ = +10.5 (c = 0.440, CHCl₃, l = 50 mm).

Known compound: (S) [α]Dref = +23.0 (c = 0.500, CHCl₃). 47

(S)-3-(N-Acetylamino)-2-benzyl-1-propanol. 46, 48 To (S)-2-benzyl-3-(4-methoxyphenylamino)propan-1-ol (58.6 mg, 0.220 mmol, 79% ee) in 1:1 MeOH/CH₂Cl₂ (3 mL) at 0 °C was added iodobenzene diacetate (268 mg, 0.860 mmol) in MeOH (3 mL). After stirring at 0 °C for 30 min, 1M HCl (3 mL) was added and the mixture was stirred

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for 1 h. The reaction was diluted with CH₂Cl₂ (10 mL), and the layers were separated. The aqueous layer was washed with CH₂Cl₂ (3 × 10 mL), and the combined organics were washed with 1M HCl (10 mL). The combined aqueous layers were neutralized by adding solid Na₂CO₃ until pH 10 was reached. CH₂Cl₂ (5 mL) and acetic anhydride (21 µL, 0.22 mmol) were added, and the mixture was stirred vigorously overnight. The layers were separated, and the aqueous layer was washed with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. Column chromatography (5% MeOH/CH₂Cl₂) yielded a yellow oil (2.7 mg, 6%). [α]D²⁰ = +17.2 (c = 0.135, CHCl₃, l = 50 mm). Known compound: (R) [α]D²⁰ = -24.2 (c = +1.59, CHCl₃).⁴⁸

2.7.8 Characterization of Electronically Modified Aniline Substrates for Equilibration Experiments (Table 2.4)

The following compounds were made according to literature procedures and matched reported spectra: N-(but-2-yn-1-yl)-4-methoxyaniline, (Z)-N-(but-2-en-1-yl)-4-methoxyaniline, 2-(but-2-yn-1-yl)isoindoline-1,3-dione,⁴⁹ but-2-yn-1-amine.⁵⁰

\[
\text{N-(but-2-yn-1-yl)-4-methylaniline. To a flame-dried round-bottom flask was added p-toluidine (3.36 g, 31.4 mmol), CH₃CN (30 mL), and 1-bromo-2-butyne (0.55 mL, 6.3 mmol). The reaction was allowed to stir overnight, diluted with Et₂O (100 mL), washed with water (2 × 40 mL), and washed with saturated NH₄Cl (3 × 25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. Purification of the crude mixture}
\]

by column chromatography (5% EtOAc/Hex) afforded the title compound as an orange oil (781 mg, 78%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.01 – 7.04 (m, 2H), 6.60 – 6.62 (m, 2H), 3.85 (s, 2H), 3.71 (br s, 1H), 2.26 (d, 3H, $J = 4.2$ Hz), 1.80 – 1.81 (m, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 145.2, 129.9, 127.7, 113.8, 79.1, 76.5, 34.5, 20.6, 3.5; IR: 3302, 2946, 2822, 1616, 1517, 1249, 806, 502 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{14}$N$_1$ [M+H]$^+$: 160.1126, found: 160.1119.

(Z)-$N$-(but-2-en-1-yl)-4-methylaniline. A flame-dried, round-bottom flask was charged with Lindlar’s catalyst (172 mg) and purged with nitrogen. $N$-(but-2-yn-1-yl)-4-methylaniline (1.23 g, 7.74 mmol) in EtOH (15 mL) was added, followed by quinoline (82 µL, 0.70 mmol). The flask was evacuated and refilled with H$_2$ four times, fitted with a H$_2$ balloon, and stirred at room temperature under H$_2$ for 40 minutes. The reaction was filtered through a plug of silica and concentrated. Column chromatography (10% EtOAc/Hex) yielded an orange oil (1.02 g, 82%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.99 (d, 2H, $J = 7.8$ Hz), 6.55 – 6.58 (m, 2H), 5.63 – 5.67 (m, 1H), 5.55 – 5.59 (m, 1H), 3.74 (d, 2H, $J = 6.6$ Hz), 3.50 (br s, 1H), 2.23 (s, 3H), 1.71 – 1.73 (m, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 146.3, 129.9, 128.1, 127.2, 127.0, 113.3, 41.4, 20.6, 13.3; IR: 3976, 2954, 1616, 1517, 1313, 1256, 805 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{16}$N$_1$ [M+H]$^+$: 162.1283, found: 162.1277.

$N$-(but-2-yn-1-yl)aniline. To a flame-dried, 250-mL, round-bottom flask was added aniline (7.73 mL, 84.8 mmol), CH$_3$CN (85 mL), and 1-bromo-2-butynyl (2.57 g, 17.0 mmol). The reaction was allowed to stir at room temperature overnight. The reaction was diluted with Et$_2$O (100 mL) and was
washed with water (3 x 70 mL) and saturated NH₄Cl (3 x 70 mL). The organic layer was
dried over MgSO₄, filtered, and concentrated in vacuo. Purification using column
chromatography (5% EtOAc/Hex) yielded a yellow oil (1.9 g, 78%). ¹H NMR (CDCl₃,
500 MHz) δ 7.20 – 7.24 (m, 2H), 6.77 – 6.80 (m, 1H), 6.67 – 6.70 (m, 2H), 3.88 (s, 2H),
3.85 (br s, 1H), 1.81 – 1.82 (m, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 147.5, 129.4, 118.4,
113.6, 79.2, 76.3, 34.2, 3.7; IR: 1601, 1502, 1313, 747, 690 cm⁻¹; HRMS (DART-TOF)
calcd. for C₁₀H₁₂N₁ [M+H]⁺: 146.0970, found: 146.0967.

(Z)-N-(but-2-en-1-yl)aniline (7% (E)-isomer). To a flame-dried
50-mL round-bottom flask was added Lindlar’s catalyst (142 mg),
which was purged with nitrogen. To the reaction flask was added, successively, N-(but-
2-yn-1-yl)aniline (1.01 g, 7.02 mmol), EtOH (14 mL), and quinoline (66 µL, 0.56 mmol).
The flask was evacuated and refilled with H₂ four times, fitted with a H₂ balloon, and
stirred at room temperature under H₂ for 40 minutes. The reaction was filtered through a
plug of silica and concentrated. Column chromatography (5% EtOAc/Hex) afforded the
title compound as an orange oil (720 mg, 73%). ¹H NMR (CDCl₃, 500 MHz) δ 7.17 –
7.21 (m, 2H), 6.71 – 6.74 (t, 1H, J = 7.3 Hz), 6.62 – 6.64 (m, 2H), 5.65 – 5.68 (m, 1H),
5.54 – 5.59 (m, 1H), 3.78 (d, 2H, J = 6.6 Hz), 3.69 (d, 2H (E)-isomer, J = 6.1 Hz), 3.63 (br s,
1H), 1.71 – 1.72 (m, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 148.5, 129.4, 127.8, 127.4,
117.6, 113.1, 41.0, 13.3; IR: 2926, 1601, 1503, 1312, 1260, 747, 690, 507 cm⁻¹; HRMS

N-(but-2-yn-1-yl)-4-chloroaniline. To a flame-dried round-
bottom flask was added 4-chloroaniline (1.88 g, 14.7 mmol),
CH\textsubscript{3}CN (15 mL), and 1-bromo-2-butyne (388 \(\mu\)L, 2.94 mmol). The reaction was stirred at room temperature overnight and was diluted with Et\(_2\)O (100 mL). The solution was washed with water (3 x 40 mL) and saturated NH\(_4\)Cl (3 x 40 mL). The organic layer was dried over MgSO\(_4\), filter, and concentrated in vacuo. The crude reaction mixture was purified by column chromatography (20\% EtOAc/Hex) to yield the title compound as a light red solid (331 mg, 66\%). \(^1\text{H}\) NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.15 – 7.17 (m, 2H), 6.59 – 6.61 (m, 2H), 3.86 (s, 2H), 1.81 (s, 3H); \(^{13}\text{C}\) NMR (CDCl\(_3\), 125 MHz) \(\delta\) 146.0, 129.2, 123.1, 114.7, 79.5, 75.9, 34.3, 3.7; IR: 3326, 1599, 1496, 1312, 814, 500 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{10}\)H\(_{11}\)Cl\(_1\)N\(_1\) [M+H]\(^+\) : 180.0580, found: 180.1581.

(Z)-N-(but-2-en-1-yl)-4-chloroaniline. To a flame-dried, 50-mL round-bottom flask was added Lindlar’s catalyst (143 mg), which was immediately purged with nitrogen. The reaction flask was charged, successively, with N-(but-2-yn-1-yl)-4-chloroaniline (1.02 g, 5.68 mmol), EtOH (11 mL), and quinoline (60 \(\mu\)L, 0.51 mmol). The flask was evacuated and refilled with H\(_2\) four times, fitted with a H\(_2\) balloon, and stirred at room temperature under H\(_2\) for 40 minutes. The reaction was filtered through a plug of silica and concentrated. Column chromatography (10\% EtOAc/Hex) afforded the title compound as an orange oil (814 mg, 81\%). \(^1\text{H}\) NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.11 – 7.13 (m, 2H), 6.53 (dd, 2H, \(J = 6.6, 2.2\) Hz), 5.65 – 5.68 (m, 1H), 5.51 – 5.54 (m, 1H), 3.73 (d, 2H, \(J = 6.6\) Hz), 3.64 (br s, 1H), 1.70 – 1.72 (m, 3H); \(^{13}\text{C}\) NMR (CDCl\(_3\), 125 MHz) \(\delta\) 147.0, 129.2, 127.7, 127.4, 122.1, 114.1, 41.1, 13.3; IR: 3326, 1599, 1496, 1311, 1176, 812, 503 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{10}\)H\(_{13}\)Cl\(_1\)N\(_1\) [M+H]\(^+\) : 182.0737, found: 182.0739.
**4-(but-2-yn-1-ylamino)benzonitrile.** A flame-dried, 250-mL round-bottom flask was charged, successively, with K$_2$CO$_3$ (6.00 g, 45.4 mmol), 4-aminobenzonitrile (7.00 g, 56.7 mmol), DMF (140 mL), and 1-bromo-2-butyne (2.51 g, 18.9 mmol). The reaction was allowed to stir overnight at 80°C. Upon cooling to room temperature, the reaction was diluted with EtOAc (200 mL) and was washed with water (2 x 100 mL). The aqueous layer was washed with an additional portion of EtOAc (200 mL) and the combined organics were dried over MgSO$_4$, filtered, and concentrated. Purification by column chromatography (20% EtOAc/Hex) afforded an orange oil (1.32 g, 16%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.42 – 7.44 (m, 2H), 6.60 – 6.62 (m, 2H), 4.47 (br s, 1H), 3.87 – 3.90 (m, 2H), 1.78 (t, 3H, $J$ = 2.4); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 150.6, 133.7, 120.4, 112.9, 99.7, 80.0, 74.8, 33.4, 3.6; IR: 3371, 2212, 1604, 1522, 1324, 1174, 824, 543 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{11}$N$_2$ [M+H]$^+$: 171.0922, found: 171.0923.

**(Z)-4-(but-2-yn-1-ylamino)benzonitrile (5% (E)-isomer).** To a flame-dried, 25-mL round-bottom flask was added Lindlar’s catalyst (112 mg), which was immediately purged with nitrogen. The reaction flask was charged, successively, with 4-(but-2-yn-1-ylamino)benzonitrile (800 mg, 4.70 mmol), EtOH (10 mL), and quinoline (45 µL, 0.38 mmol). The flask was evacuated and refilled with H$_2$ four times, fitted with a H$_2$ balloon, and stirred at room temperature under H$_2$ for 1 hour and 35 minutes. The reaction was filtered through a plug of silica and concentrated. Column chromatography (10% EtOAc/Hex) afforded the title compound as an orange oil (622 mg, 77%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.38 – 7.42 (m, 2H), 6.54 – 6.56 (m, 2H), 5.67 – 5.74 (m, 1H), 5.47 – 5.53 (m, 1H), 4.27 (br s, 1H) 3.79 (t, 2H,
\( J = 5.6 \text{ Hz}, 3.70 – 3.72 \text{ (m, 2H}_{(E)}\text{-isomer}), 1.71 – 1.73 \text{ (m, 3H)}, 1.69 – 1.70 \text{ (m, 2H}_{(E)}\text{-isomer}); \)

\(^{13}\text{C NMR} \) (CDCl\(_3\), 125 MHz) \( \delta \) 151.4, 133.8, 128.5, 126.3, 120.7, 112.4, 98.8, 40.2, 13.3;

\( \text{IR: 3367, 2209, 1602, 1521, 1171, 820, 542 cm}^{-1}; \) \( \text{HRMS (DART-TOF) calcd. for C}_{11}\text{H}_{13}\text{N}_2\text{[M+H]}^+: 173.1079, \text{found: 173.1080}. \)

\( N\)-(but-2-yn-1-yl)-4-nitroaniline. \) To a flame-dried, 50-mL round-bottom flask was added KF (426 mg, 6.17 mmol), K\(_2\text{CO}_3\) (853 mg, 6.17 mmol), and 1-fluoro-4-nitrobenzene (871 mg, 6.17 mmol). The flask was purged with nitrogen and but-2-yn-1-amine (426 mg, 6.17 mmol) was added to the flask as a solution in DMSO (20 mL). The reaction was allowed to stir at room temperature overnight and was quenched by the addition of water (50 mL). The mixture was extracted with Et\(_2\text{O}\) (150 mL) and the organic layer was dried over MgSO\(_4\), filtered, and concentrated \( \text{in vacuo}. \) The crude reaction mixture was subjected to column chromatography (15\% EtOAc/Hex) to afford a yellow solid (660 mg, 56\%). \(^1\text{H NMR} \) (CDCl\(_3\), 500 MHz) \( \delta \) 8.11 (d, 2H, \( J = 9.3 \text{ Hz} \), 6.59 – 6.62 (m, 2H), 4.69 (br s, 1H), 3.93 – 3.95 (m, 2H), 1.79 – 1.80 (m, 3H); \(^{13}\text{C NMR} \) (CDCl\(_3\), 125 MHz) \( \delta \) 152.5, 138.9, 126.4, 111.9, 80.5, 74.4, 33.7, 3.7; \( \text{IR: 3324, 2952, 1616, 1515, 1231, 805, 512 cm}^{-1}; \) \( \text{HRMS (DART-TOF) calcd. for C}_{10}\text{H}_{11}\text{N}_2\text{O}_2\text{[M+H]}^+: 191.0821, \text{found: 191.0819}. \)

\( (Z)-N\)-(but-2-en-1-yl)-4-nitroaniline (14\% (\text{E})\text{-isomer}). \) To a flame-dried, 5-mL round-bottom flask was added Lindlar’s catalyst (9 mg), which was immediately purged with nitrogen. The reaction flask was charged, successively, with \( N\)-(but-2-yn-1-yl)-4-nitroaniline (66 mg, 0.35 mmol), EtOH
(1 mL), and quinoline (3 µL, 0.03 mmol). The flask was evacuated and refilled with H₂ four times, fitted with a H₂ balloon, and stirred at room temperature under H₂ for 40 minutes. The reaction was filtered through a plug of silica and concentrated. Column chromatography (10% EtOAc/Hex) afforded the title compound as a bright yellow oil (60 mg, 90%). ¹H NMR (CDCl₃, 500 MHz) δ 8.07 – 8.11 (m, 2H), 6.52 – 6.55 (m, 2H), 5.71 – 5.77 (m, 1H), 5.46 – 5.49 (m, 1H), 3.85 – 3.87 (m, 2H), 3.77 – 3.79 (m, 2H (E)-isomer), 1.73 – 1.75 (m, 3H), 1.71 – 1.72 (m, 3H(E)-isomer); ¹³C NMR (CDCl₃, 125 MHz) δ 153.4, 138.3, 129.0, 126.6, 125.9, 111.4, 40.5, 13.4; IR: 3378, 1600, 1503, 1471, 1318, 1302, 1283, 1111 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₀H₁₃N₂O₂ [M+H]⁺: 193.0977, found: 193.0985.

2.7.9 Equilibration Experiments with Ligand 2.5 and Electronically Modified Aniline Substrates

General Equilibration Experiment Procedure: In a dry box, a solution of isopropanol (100 µL, 1.31 mmol) in C₆D₆ (1.63 M) was prepared. The solution was dispensed into three NMR tubes (see tables below for amounts). A second solution of (Z)-N-(but-2-enyl)-4-methoxyaniline, 2.49, (70 mg, 0.43 mmol), 2.5 (25 mg, 0.086 mmol), and p-TsOH (298 µL, 7.2 x 10⁻⁴ M solution in benzene; note benzene was removed prior to mixing with substrate and ligand) in C₆D₆ (1.5 mL) was made. The solution was
dispensed into three NMR tubes (see tables below for amounts). An additional portion of 
\( \text{C}_6\text{D}_6 \) was added to bring the total volume of each NMR tube to 0.7 mL. Each reaction 
was allowed to equilibrate overnight at 45 °C. Additional spectra were taken after this 
time period to ensure that equilibrium was reached overnight.

**Table 2.9 Equilibration Experiments with Ligand 2.5 and Electronically Modified Aniline 
Substrates.**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>( i\text{PrOH} ) Solution</th>
<th>( \text{mmol} ) ( i\text{PrOH} )</th>
<th>( \text{Substrate} ) Solution</th>
<th>( \text{mmol} ) ( \text{Substrate} )</th>
<th>Ratio ( S\text{-L:}L )</th>
<th>( K_{eq} )</th>
<th>( (K_{eq})_{avg} ) ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = OMe (2.49)</td>
<td>A 61 µL 0.10</td>
<td>400 µL 0.11</td>
<td>66:34</td>
<td>2.3</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 153 µL 0.25</td>
<td>400 µL 0.11</td>
<td>52:48</td>
<td>2.8</td>
<td>± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 300 µL 0.49</td>
<td>400 µL 0.11</td>
<td>43:57</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = Me (2.73)</td>
<td>A 61 µL 0.10</td>
<td>400 µL 0.12</td>
<td>45:55</td>
<td>1.4</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 153 µL 0.25</td>
<td>400 µL 0.12</td>
<td>36:64</td>
<td>1.9</td>
<td>± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 61 µL 0.10</td>
<td>400 µL 0.11</td>
<td>41:59</td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D 153 µL 0.25</td>
<td>400 µL 0.11</td>
<td>35:65</td>
<td>1.38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = H (2.74)</td>
<td>A 61 µL 0.10</td>
<td>400 µL 0.13</td>
<td>52:48</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 123 µL 0.20</td>
<td>300 µL 0.10</td>
<td>32:68</td>
<td>1.0</td>
<td>± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 300 µL 0.49</td>
<td>400 µL 0.13</td>
<td>28:72</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = Cl (2.75)</td>
<td>A 67 µL 0.10</td>
<td>400 µL 0.12</td>
<td>52:48</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 167 µL 0.23</td>
<td>400 µL 0.12</td>
<td>34:66</td>
<td>1.2</td>
<td>± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 300 µL 0.45</td>
<td>400 µL 0.12</td>
<td>26:74</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = CN (2.76)</td>
<td>A 67 µL 0.10</td>
<td>400 µL 0.13</td>
<td>52:48</td>
<td>0.66</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 153 µL 0.25</td>
<td>400 µL 0.13</td>
<td>26:74</td>
<td>0.66</td>
<td>± 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 245 µL 0.40</td>
<td>400 µL 0.13</td>
<td>17:84</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R = NO(_2) (2.77)</td>
<td>A 61 µL 0.10</td>
<td>400 µL 0.12</td>
<td>35:65</td>
<td>0.50</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B 123 µL 0.20</td>
<td>400 µL 0.12</td>
<td>22:78</td>
<td>0.36</td>
<td>± 0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 184 µL 0.30</td>
<td>400 µL 0.12</td>
<td>14:86</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 2.7.10 Electronically Modified Aniline Substrate Characterization

The following compounds were made according to literature procedures and matched 
reported spectra: \((Z)-(4-(benzyloxy)but-2-en-1-ol)\), \((Z)-(N-(4-(benzyloxy)but-2-en-1-yl)- 
4-methoxyaniline)\), \((Z)-(4-chlorobut-2-en-1-yl)oxy)methyl)benzene, \( \text{2}- 
isobutryl)cyclohexanone\), \( \text{1-iodo-3-nitrobenzene}\), \( \text{3-iodopyridine}\).\(^51\) \(^52\) \(^53\)

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(Z)-N-(4-(benzyloxy)but-2-en-1-yl)-4-methylaniline, 2.78. To a flame-dried 50-mL round-bottom flask was added p-toluidine (3.26 g, 30.5 mmol), (Z)-(((4-chlorobut-2-en-1-yl)oxy)methyl)benzene (1.20 g, 6.10 mmol), and acetonitrile (30 mL). The reaction was allowed to stir overnight at room temperature. The reaction was diluted with Et₂O (100 mL) and was washed with H₂O (3 x 50 mL) and saturated aqueous NH₄Cl (3 x 50 mL). The combined organics were dried over anhydrous MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel chromatography (15% EtOAc/Hex) to afford an orange oil (748 mg, 46%). ¹H NMR (CDCl₃, 500 MHz) δ 7.28 – 7.36 (m, 5H), 7.00 (d, 2H, J = 8.1 Hz), 6.54 (d, 2H, J = 8.6 Hz), 5.74 – 5.82 (m, 2H), 4.54 (s, 2H), 4.15 (d, 2H, J = 4.9 Hz), 3.75 (d, 2H, J = 4.5 Hz), 3.55 (br s, 1H), 2.25 (s, 3H) ¹³C NMR (CDCl₃, 125 MHz) δ 145.9, 138.3, 131.0, 129.9, 129.0, 128.6, 128.0, 127.9, 127.2, 113.4, 72.7, 65.9, 41.9, 20.6; IR: 2946, 2872, 1616, 1518, 1252, 1070, 806, 734, 696 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₈H₂₁N₂O₂ [M+H]⁺: 268.1701, found: 268.1698.

(Z)-2-(4-(benzyloxy)but-2-en-1-yl)isoindoline-1,3-dione. A flame-dried 250-mL round-bottom flask was charged, successively, with (Z)-4-(benzyloxy)but-2-en-1-ol (3.74 g, 21.0 mmol), triphenylphosphine (3.74 g, 21.0 mmol), phthalimide (3.09 g, 21.0 mmol), tetrahydrofuran (105 mL), and diisopropyl azodicarboxylate (4.13 mL, 21.0 mmol). The reaction was allowed to stir at room temperature overnight. The mixture was concentrated to a thick, yellow oil and was subsequently purified by silica gel column chromatography (20% EtOAc/Hex) to give a thick, colorless oil (4.23 g, 65%). ¹H NMR
(CDCl$_3$, 400 MHz) $\delta$ 7.81 – 7.85 (m, 2H), 7.69 – 7.72 (m, 2H), 7.28 – 7.39 (m, 5H), 5.78 – 5.84 (m, 1H), 5.62 – 5.68 (m, 1H), 4.58 (s, 2H), 4.32 – 4.34 (m, 2H), 4.30 – 4.32 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 168.1, 138.4, 134.2, 132.4, 131.0, 128.6, 128.1, 127.9, 126.4, 123.5, 72.7, 65.9, 35.2; IR: 1709, 1390, 1088, 1072, 735, 715, 698 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{19}$H$_{18}$N$_{1}$O$_{3}$ [M+H]$^+$: 308.1287, found: 308.1284.

(Z)-4-(benzyloxy)but-2-en-1-amine. A 100-mL round-bottom flask fitted with a reflux condenser was charged with (Z)-2-(4-(benzyloxy)but-2-en-1-yl)isoindoline-1,3-dione (4.23 g, 13.7 mmol), hydrazine hydrate (1.6 mL, 25.7 mmol), and ethanol (10 mL). The mixture was heated to 70 °C overnight, after which time the reaction turns into a thick solid. The solid was filtered and washed with water (100 mL). The aqueous solution was acidified to pH $\approx$ 2 with concentrated HCl and was washed with Et$_2$O (120 mL). The aqueous layer was then basified to pH $\approx$ 13 by the addition of solid KOH pellets. The resulting solution was transferred to a separatory funnel and washed with Et$_2$O (200 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered, and concentrated to obtain the title compound as a pale yellow oil (1.92 g, 79%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.27 – 7.36 (m, 5H), 5.61 – 5.71 (m, 2H), 4.51 (s, 2H), 4.07 (d, 2H, $J$ = 6.0 Hz), 3.31 (d, 2H, $J$ = 6.1 Hz), 1.13 (br s, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 138.3, 134.9, 128.6, 128.0, 127.8, 126.7, 72.5, 65.7, 39.3; IR: 3067, 2854, 1453, 1088, 734, 696 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{18}$N$_{1}$O$_{1}$ [M+H]$^+$: 178.1232, found: 178.1240.
(Z)-N-(4-(benzyloxy)but-2-en-1-yl)aniline, 2.79.\(^{54}\) To a flame-dried round-bottom flask was added L-proline (325 mg, 2.82 mmol), CuI (537 mg, 2.82 mmol), and K\(_2\)CO\(_3\) (1.17 g, 8.46 mmol). The reaction vessel was evacuated and refilled with nitrogen. (Z)-4-(benzyloxy)but-2-en-1-amine (500 mg, 2.82 mmol) was added to the flask as a solution in DMSO (5 mL), followed by iodobenzene (314 \(\mu\)L, 2.82 mmol). The reaction was heated to 60 °C for 8 hours and then cooled to room temperature. The mixture was diluted with EtOAc (100 mL) and washed with water (70 mL). The organic layer was dried over anhydrous MgSO\(_4\), filtered, and concentrated. The crude material was purified on a column of silica gel (20% EtOAc/Hex) to yield a pale orange oil (301 mg, 42\%). \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta 7.28 – 7.37\) (m, 5H), 7.16 – 7.21 (m, 2H), 6.75 (t, 1H, \(J = 7.3\) Hz), 6.61 (d, 2H, \(J = 7.6\) Hz), 5.74 – 5.83 (m, 2H), 4.55 (s, 2H), 4.15 (d, 2H, \(J = 5.4\) Hz), 3.78 (d, 2H, \(J = 5.6\) Hz), 3.68 (br s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 148.2, 138.3, 130.8, 129.5, 129.1, 128.6, 128.0, 127.9, 117.9, 113.2, 72.7, 65.9, 41.6\); IR: 3027, 2856, 1603, 1504, 1094, 1071, 749, 695 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{17}\)H\(_{20}\)N\(_2\)O\(_1\) [M+H]\(^+\): 254.1545, found: 254.1555.

(Z)-N-(4-(benzyloxy)but-2-en-1-yl)-4-chloroaniline, 2.80. A flame-dried, round-bottom flask was charged, successively, with CuI (537 mg, 2.82 mmol), L-proline (325 mg, 2.82 mmol), and K\(_2\)CO\(_3\) (1.17 g, 8.46 mmol). The reaction vessel was evacuated and refilled with nitrogen. (Z)-4-(benzyloxy)but-2-en-1-amine (500 mg, 2.82 mmol) and 1-bromo-4-chlorobenzene (540 mg, 2.82 mmol) were added to the flask as a solution in DMSO (6 mL). The reaction

was heated to 70 °C overnight and then cooled to room temperature. The mixture was
diluted with Et₂O (100 mL) and washed with water (50 mL). The organic layer was dried
over anhydrous MgSO₄, filtered, and concentrated. The crude mixture was purified by
silica gel column chromatography (20% EtOAc/Hex) to yield the title compound as an
orange oil (358 mg, 44%). ¹H NMR (CDCl₃, 500 MHz) δ 7.28 – 7.37 (m, 5H), 7.10 –
7.13 (m, 2H), 6.49 – 6.51 (m, 2H), 5.79 – 5.84 (m, 1H), 5.70 – 5.75 (m, 1H), 4.54 (s, 2H),
4.14 (d, 2H, J = 6.4 Hz), 3.74 (d, 2H, J = 6.6 Hz), 3.71 (br s, 1H); ¹³C NMR (CDCl₃, 125
MHz) δ 146.7, 138.2, 130.4, 129.4, 129.3, 128.7, 128.0, 127.9, 122.5, 114.2, 72.8, 65.8,
41.7; IR: 2854, 1598, 1496, 1357, 1070, 814, 735, 696, 504 cm⁻¹; HRMS (DART-TOF)

(Z)-4-((4-(benzyloxy)but-2-en-1-yl)amino)benzonitrile, 2.81. To a flame-dried, round-bottom flask was added
K₂CO₃ (420 mg, 3.04 mmol), 4-fluorobenzonitrile (368 mg, 3.04 mmol), (Z)-4-
(benzyloxy)but-2-en-1-amine (700 mg, 3.94 mmol), and DMSO (10 mL), which was
heated to 90 °C overnight. Upon cooling to room temperature, the reaction was
quenched by the addition of water (25 mL) and was diluted with Et₂O (70 mL). The
organic layer was dried over anhydrous MgSO₄, filtered and concentrated by rotary
evaporation. The title compound was obtained by purification on silica gel (20%
EtOAc/Hex) to afford an orange oil (201 mg, 37%). ¹H NMR (CDCl₃, 500 MHz) δ 7.39
– 7.42 (m, 2H), 7.29 – 7.37 (m, 5H), 6.51 – 6.53 (m, 2H), 5.82 – 5.87 (m, 1H), 5.67 –
5.71 (m, 1H), 4.55 (s, 2H), 4.26 (br s, 1H), 4.12 – 4.13 (m, 2H), 3.81 (br m, 2H); ¹³C
NMR (CDCl₃, 125 MHz) δ 151.2, 138.0, 133.9, 130.0, 129.4, 128.7, 128.1, 128.0, 120.6,
112.5, 99.2, 72.9, 65.8, 40.8; **IR:** 3367, 1606, 1525, 1207 cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{18}\)H\(_{19}\)N\(_2\)O\(_1\) [M+H]\(^+\): 279.1497, found: 279.1498.

(Z)-N-(4-(benzyloxy)but-2-en-1-yl)-4-nitroaniline, **2.82.** A flame-dried, round-bottom flask was charged with KF (177 mg, 3.04 mmol), K\(_2\)CO\(_3\) (420 mg, 3.04 mmol), and 1-fluoro-4-nitrobenzene (429 mg, 3.04 mmol). (Z)-4-(benzyloxy)but-2-en-1-amine (700 mg, 3.94 mmol) was added to the reaction vessel as a solution in DMSO (10 mL) and the reaction was allowed to stir at room temperature overnight. The reaction was quenched by the addition of water (20 mL) and was extracted with Et\(_2\)O (70 mL). The organic layer was dried over anhydrous MgSO\(_4\), filtered, and concentrated in vacuo. The crude mixture was subjected to silica gel column chromatography (20% EtOAc/Hex) to afford a bright yellow oil (457 mg, 50%). **\(^1\)H NMR** (CDCl\(_3\), 500 MHz) \(\delta\) 8.07 (d, 2H, \(J = 9.3\) Hz), 7.31 – 7.37 (m, 5H), 6.49 (d, 2H, \(J = 9.3\) Hz), 5.86 – 5.90 (m, 1H), 5.69 – 5.74 (m, 1H), 4.63 (br s, 1H), 4.56 (s, 2H), 4.15 (d, 2H, \(J = 6.4\) Hz), 3.86 – 3.89 (m, 2H); **\(^{13}\)C NMR** (CDCl\(_3\), 125 MHz) \(\delta\) 153.2, 138.4, 138.0, 130.3, 128.9, 128.7, 128.1, 128.0, 126.5, 111.4, 72.9, 65.8, 40.9; **IR:** 3372, 1595, 1299, 1278, 1107, 830, 694 cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{17}\)H\(_{19}\)N\(_2\)O\(_3\) [M+H]\(^+\): 299.1396, found: 299.1407.

(Z)-N-(4-(benzyloxy)but-2-en-1-yl)-3-methylaniline, **2.83.**

To an oven-dried, 10-mL round-bottom flask was added Cul (232 mg, 1.22 mmol) and Cs\(_2\)CO\(_3\) (2.00 g, 6.10 mmol), which was then purged with nitrogen. The flask was then charged, successively, with (Z)-4-(benzyloxy)but-2-en-1-amine (600 mg, 3.05 mmol), 1-iodo-3-methylbenzene (392 µL,
3.05 mmol), DMF (1.5 mL), and 2-isobutyrylcyclohexanone (410 mg, 2.44 mmol). The reaction was allowed to stir vigorously at room temperature overnight. The reaction was filtered through a pad of Celite, washed with EtOAc (100 mL), and subsequently extracted with water (2 x 25 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated. Column chromatography (10% EtOAc/Hex) afforded the title compound as an orange oil (653 mg, 80%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.30 – 7.37 (m, 5H), 7.08 (t, 1H, $J = 7.3$ Hz), 6.56 (d, 1H, $J = 7.1$ Hz), 6.43 – 6.42 (m, 2H), 5.76 – 5.81 (m, 2H), 5.76 (d, 2H, $J = 5.4$ Hz), 3.76 (d, 2H, $J = 5.6$ Hz), 3.63 (br s, 1H), 2.29 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 148.2, 139.2, 138.3, 130.9, 129.3, 129.0, 128.6, 128.0, 127.9, 118.8, 114.0, 110.4, 72.7, 65.9, 41.6, 21.8; IR: 3365, 1604, 1491, 1089, 1070, 769, 735, 692 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{18}$H$_{22}$N$_1$O$_1$ [M+H]$^+$: 268.1701, found: 268.1702.

$^{(Z)}$-N-[(4-(benzyloxy)but-2-en-1-yl)-3-nitroaniline, 2.84.54 A flame-dried, 25-mL round-bottom flask was charged with CuI (271 mg, 1.42 mmol), K$_2$CO$_3$ (984 mg, 7.12 mmol), L-proline (328 mg, 2.85 mmol), and 1-iodo-3-nitrobenzene (886 mg, 3.56 mmol) and was purged with nitrogen. ($^{(Z)}$)-4-(benzyloxy)but-2-en-1-amine (700 mg, 3.56 mmol) was added to the reaction flask as a solution in DMSO (4 mL), which was then heated to 65 °C overnight. The reaction was cooled to room temperature and diluted with EtOAc (125 mL). The organic layer was washed with water (50 mL), separated, dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by column chromatography (15% EtOAc/Hex) afforded the title compound as a bright orange oil (561 mg, 53%). $^1$H NMR (DMSO, 500 MHz) $\delta$ 7.31 – 7.36 (m, 5H), 7.27 – 7.29 (m, 2H), 6.95 – 6.97 (m, 1H), 6.52
- 6.55 (m, 1H), 5.69 – 5.74 (m, 1H), 5.58 – 5.62 (m, 1H), 4.50 (s, 2H), 4.16 – 4.17 (m, 2H), 3.76 – 3.78 (m, 2H); \textbf{^1^H NMR} (CDCl₃, 125 MHz) δ 149.6, 148.9, 138.1, 130.1, 129.9, 129.5, 128.7, 128.1, 128.0, 119.1, 112.4, 106.6, 72.9, 65.9, 41.3; \textbf{IR}: 2857, 1621, 1581, 1344, 1089, 1070, 734, 689, 672 cm\(^{-1}\); \textbf{HRMS} (DART-TOF) calcd. for C\(_{17}\)H\(_{19}\)N\(_2\)O\(_3\) \([M+H]^+\): 299.1396, found: 299.1400.

\[
\text{(Z)-N-(4-(benzyloxy)but-2-en-1-yl)pyridin-3-amine, 2.85.}^\text{51}
\]

To a flame-dried, 10-mL round-bottom flask was added CuI (155 mg, 0.812 mmol) and Cs\(_2\)CO\(_3\) (2.65 g, 8.12 mmol), which was then purged with nitrogen. The flask was charged, successively, with 3-iodopyridine (833 mg, 4.06 mmol), (Z)-4-(benzyloxy)but-2-en-1-amine (959 mg, 4.88 mmol), DMF (2.0 mL), and 2-isobutyrylcyclohexanone (547 mg, 3.25 mmol). The reaction was allowed to stir at room temperature overnight. The crude reaction mixture was filtered through a pad of Celite, washed with EtOAc and concentrated \textit{in vacuo}. Column chromatography (50\% EtOAc/Hex) afforded the title compound as an orange oil (366 mg, 37\%). \textbf{^1^H NMR} (CDCl₃, 500 MHz) δ 8.00 – 8.01 (d, 1H, \(J = 3.0\) Hz), 7.98 (dd, 1H, \(J = 4.6, 1.0\) Hz), 7.29 – 7.35 (m, 5H), 7.06 – 7.08 (m, 1H), 6.83 – 6.86 (m, 1H), 5.81 – 5.86 (m, 1H), 5.72 – 5.76 (m, 1H), 4.54 (s, 2H), 4.13 (d, 2H, \(J = 6.1\) Hz), 3.78 (d, 2H, \(J = 5.1\) Hz), 3.78 (br s, 1H); \textbf{^1^C NMR} (CDCl₃, 125 MHz) δ 144.1, 139.3, 128.1, 136.5, 130.0, 129.7, 128.7, 128.1, 128.0, 123.8, 118.8, 72.8, 65.8, 41.1; \textbf{IR}: 2861, 1519, 1092, 808, 736, 697 cm\(^{-1}\); \textbf{HRMS} (DART-TOF) calcd. for C\(_{16}\)H\(_{19}\)N\(_2\)O\(_1\) \([M+H]^+\): 255.1497, found: 255.1484.
2.7.11 Hydroformylation Procedures and Product Characterization (Table 2.5)

**General Hydroformylation Procedure.** The Endeavor was charged with 500 µL of benzene per reaction well to fill the void volume between the reactor wall and reaction tube. Oven dried glass reaction vials were then placed into the wells. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (4 x 100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 35 °C for 10 minutes. Stirring was stopped, and the Endeavor was charged with 50 psi H₂/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at a constant reaction temperature of 35 °C and pressure of 50 psi H₂/CO for 14 hours. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, a solution of 1,3,5-trimethoxybenzene in CHCl₃ (100 µL, 0.1863 M) was added, and the sample was concentrated. The resulting residue was added, as a solution in MeOH (3 mL), to a flame-dried flask containing NaBH₄ (23.0 mg, 0.600 mmol). The reaction was stirred at room temperature for 1.5 hours. The reaction was quenched by the addition of water (5 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. ¹H NMR spectra were taken to determine conversion. The reaction was chromatographed (1% MeOH/CH₂Cl₂) to determine the isolated yield. HPLC or SFC analysis of the products was used to determine enantioselectivities.

**General Procedure B:** (Z)-N-(4-(benzyloxy)but-2-en-1-yl)-4-methoxyaniline (56.2 mg, 0.200 mmol), 2.42 (9.7 mg, 0.030 mmol), and 0.03% p-toluenesulfonic acid in benzene (83 µL, 6.0 x 10⁻⁴ mmol, 5.71 x 10⁻⁴ M solution in benzene) were mixed in C₆D₆ (0.6 mL)
and heated to 45 °C for 12 h in a sealed NMR tube. The solution was concentrated in a dry glove box to remove MeOH in the solution, and then was redissolved in C₆D₆. The solution was heated to 45 °C for 4 h before being concentrated again in a glove box. During this pre-exchange, the four diastereomers of 2.42 converge to one substrate-bound ligand peak in the ³¹P NMR. The resulting residue was dissolved in benzene (1.5 mL), mixed with 1.75% Rh(acac)(CO)₂ (0.9 mg, 0.0035 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

**General Procedure E:** (Z)-N-(4-(benzylxy)but-2-en-1-yl)-4-methylaniline (53.4 mg, 0.200 mmol), 2.48 (205 µL, 0.146 M solution in C₆D₆, 0.0300 mmol), 0.05% p-toluenesulfonic acid in benzene (175 µL, 1.00 x 10⁻⁴ mmol, 5.71 x 10⁻⁴ M solution in benzene), and C₆D₆ (0.6 mL) were mixed and heated to 45 °C in a sealed NMR tube. The solution was concentrated in a dry glove box to remove i-PrOH, and then was redissolved in C₆D₆. The solution was heated to 45 °C for 4 h before being concentrated again in a glove box. During this pre-exchange, the one diastereomer of 2.48 becomes one substrate-bound ligand peak in the ³¹P NMR. The resulting residue was dissolved in benzene (1.5 mL), mixed with 1.75% Rh(acac)(CO)₂ (0.9 mg, 0.0035 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

**Table 2.5, Entry 1**

![Chemical Structure](image)

(S)-4-(benzylxy)-2-(((4-methoxyphenyl)amino)methyl)butan-1-ol. General Procedure A was followed yielding a light yellow oil (43.9 mg, 70%). **SFC** (AS-H, 2.0 mL/min, 3.0% MeOH, 240 nm, 150 bar, 50 °C) \( t_{\text{minor}} = 6.53 \text{ min} \) and \( t_{\text{major}} = 6.96 \text{ min} \);
92% ee. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.30 – 7.37 (m, 5H), 6.76 (d, 2H, $J = 9.0$ Hz), 6.59 (d, 2H, $J = 9.0$ Hz), 4.59 (s, 2H), 3.74 (s, 3H), 3.68 – 6.70 (m, 2H), 3.55 – 3.62 (m, 2H), 3.12 (d, 2H, $J = 6.5$ Hz), 1.99 – 2.03 (m, 1H), 1.71 – 1.75 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 152.6, 142.5, 138.1, 128.7, 128.0, 128.0, 115.1, 114.9, 73.5, 68.7, 65.7, 56.0, 48.5, 38.8, 30.3; IR: 3362, 2942, 1511, 1032, 820, 699 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{19}$H$_{26}$NO$_3$ [M+H]$^+$: 316.1919, found: 316.1913. $[\alpha]_D^{20} = +18.0$ (c = 0.205, CHCl$_3$, $l$ = 50 mm).

Table 2.5, Entry 2

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(S)-4-(benzyloxy)-2-((p-tolylamino)methyl)butan-1-ol. General Procedure B was followed yielding a light yellow oil (47.4 mg, 79%). HPLC (OD-H, 1.0 mL/min, 23% i-PrOH: 77% Hexanes, 240 nm) $t_{\text{major}}$ = 11.9 min and $t_{\text{minor}}$ = 20.6 min, 92% ee; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.29 – 7.37 (m, 5H), 6.98 (d, 2H, $J = 8.6$ Hz), 6.54 (d, 2H, $J = 8.3$ Hz), 4.54 (s, 2H), 3.69 (d, 2H, $J = 5.1$ Hz), 3.55 – 3.64 (m, 2H), 3.11 – 3.18 (m, 2H), 2.24 (s, 3H), 2.00 – 2.02 (m, 1H), 1.72 – 1.76 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 146.1,
138.1, 129.9, 128.7, 128.0, 127.9, 127.1, 113.6, 73.5, 68.7, 65.4, 47.5, 38.8, 30.3, 20.6; IR: 3380, 2923, 2854, 1521, 1260, 1095, 807 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{19}$H$_{26}$N$_{3}$O$_{2}$ [M+H]$^+$: 300.1964, found: 300.1977. [$\alpha$]$_D^{20}$ = +21.8 (c = 0.330, CHCl$_3$, $l$ = 50 mm).

Table 2.5, Entry 3

(S)-4-(benzyloxy)-2-((phenylamino)methyl)butan-1-ol. General Procedure B was followed, yielding a yellow oil (43.9 mg, 77%). HPLC (OD-H, 1.0 mL/min, 15% $i$-PrOH, 85% Hexanes, 240 nm) $t_{\text{major}}$ = 15.5 min and $t_{\text{minor}}$ = 20.4 min, 91% ee; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.29 – 7.38 (m, 5H), 7.15 – 7.18 (m, 2H), 6.71 (t, 1H, $J$ = 7.3 Hz), 6.60 (d, 2H, $J$ = 7.8 Hz), 4.54 (s, 2H), 3.70 (d, 2H, $J$ = 5.1 Hz), 3.55 – 3.65 (m, 2H), 3.13 – 3.21 (m, 2H), 1.99 – 2.02 (m, 1H), 1.74 – 1.78 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 148.6, 138.0, 129.4, 128.7, 128.0, 117.6, 113.2, 73.5, 68.8, 65.2, 46.8 38.9, 30.3; IR: 2924, 2862, 1602, 1092, 1025, 748, 610 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{18}$H$_{24}$N$_{2}$O$_{2}$ [M+H]$^+$: 286.2807, found: 286.1806. [$\alpha$]$_D^{20}$ = +19.6 (c = 0.310, CHCl$_3$, $l$ = 50 mm).

119
Table 2.5, Entry 4

(S)-4-(benzyloxy)-2-(((4-chlorophenyl)amino)methyl)butan-1-ol. General Procedure B was followed. Column chromatography (1% MeOH/CH₂Cl₂) yielded an orange oil (45.9 mg, 72%). HPLC (OD-H, 1.0 mL/min, 15% i-PrOH: 85% Hexanes, 240 nm) t_major = 13.5 min and t_minor = 18.5 min, 88% ee; ¹H NMR (CDCl₃, 500 MHz) δ 7.29 – 7.38 (m, 5H), 7.07 – 7.10 (m, 2H), 6.47 – 6.50 (m, 2H), 4.53 (s, 2H), 3.68 (d, 2H, J = 4.9 Hz), 3.55 – 3.62 (m, 2H), 3.07 – 3.17 (m, 2H), 1.96 – 2.01 (m, 1H), 1.72 – 1.76 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 147.2, 138.0, 129.2, 128.7, 128.1, 128.0, 122.0, 114.1, 73.5, 68.7, 65.0, 46.8, 38.8, 30.2; IR: 3378, 2924, 2860, 1600, 1500, 1093, 816 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₈H₂₃Cl₁N₁O₂ [M+H]: 320.1417, found: 320.1425. [α]D²⁰ = +20.3 (c = 0.325, CHCl₃, l = 50 mm).
Table 2, Entry 5

(S)-4-((4-(benzyloxy)-2-(hydroxymethyl)butyl)amino)benzonitrile.  

General Procedure B was followed, yielding a pale orange oil (30.3 mg, 49%). **HPLC** (OD-H, 1.0 mL/min, 15% i-PrOH: 85% Hexanes, 220 nm) $t_{\text{major}} = 17.3$ min and $t_{\text{minor}} = 20.3$ min, 65% ee; **$^1$H NMR** (CDCl$_3$, 500 MHz) $\delta$ 7.30 – 7.38 (m, 7H), 6.44 – 6.47 (m, 2H), 4.90 (br s, 1H), 4.53 (s, 2H), 3.70 (d, 2H, $J = 4.7$ Hz), 3.56 – 3.63 (m, 2H), 3.12 – 3.25 (m, 2H), 2.25 (br s, 1H), 1.98 – 2.02 (m, 1H), 1.70 – 1.81 (m, 2H); **$^{13}$C NMR** (CDCl$_3$, 125 MHz) $\delta$ 151.8, 137.9, 133.7, 128.8, 128.2, 128.1, 120.8, 112.3, 98.5, 73.7, 68.7, 64.8, 45.9, 38.8, 30.1; **IR**: 3373, 2922, 2867, 2211, 1606, 1528, 1173 cm$^{-1}$; **HRMS** (DART-TOF) calcd. for C$_{19}$H$_{23}$N$_2$O$_2$ [M+H]: 311.1760, found: 311.1756; [$\alpha$]$_D^{20} = +34.2$ (c $= 0.0900$, CHCl$_3$, $l = 50$ mm).
(S)-4-(benzyloxy)-2-(((4-nitrophenyl)amino)methyl)butan-1-ol. General Procedure B was followed, affording a bright yellow oil (27.2 mg, 41%). **HPLC** (AS-H, 1.0 mL/min, 15% i-PrOH: 85% Hexanes, 220 nm) $t_{\text{major}} = 53.9$ min and $t_{\text{minor}} = 46.6$ min, 52% ee; **$^1$H** NMR (CDCl$_3$, 500 MHz) $\delta$ 8.01 – 8.04 (m, 2H), 7.32 – 7.38 (m, 5H), 6.37 – 6.39 (m, 2H), 5.36 (br s, 1H), 4.54 (s, 2H), 3.71 (br s, 2H), 3.61 (t, 2H, $J = 5.5$ Hz), 3.17 – 3.31 (m, 2H), 2.28 (br s, 1H), 2.00 – 2.05 (m, 1H), 1.71 – 1.81 (m, 2H); **$^{13}$C** NMR (CDCl$_3$, 125 MHz) $\delta$ 153.9, 137.8, 137.7, 128.8, 128.3, 128.2, 126.6, 111.0, 73.7, 68.8, 64.9, 46.2, 38.8, 30.0; **IR**: 3370, 2922, 2855, 1598, 1308, 1279, 1108, 697 cm$^{-1}$; **HRMS** (DART-TOF) calcd. for C$_{18}$H$_{23}$N$_2$O$_4$ [M+H]: 331.1658, found: 331.1657; $[\alpha]_D^{20} = +28.7$ (c = 0.0600, CHCl$_3$, l = 50 mm).
Table 2.5, Entry 7

![Diagram](image)

(S)-4-(benzylxy)-2-((m-tolylamino)methyl)butan-1-ol. General Procedure B was followed. Column chromatography (1% MeOH/CH₂Cl₂) yielded a pale yellow oil (35.8 mg, 60%). **HPLC** (OD-H, 1.0 mL/min, 23% i-ProOH: 77% Hexanes, 240 nm) $t_{\text{major}} = 10.3$ min and $t_{\text{minor}} = 12.3$ min, 89% ee; **¹H NMR** (CDCl₃, 500 MHz) $\delta$ 7.29 – 7.38 (m, 5H), 7.04 – 7.07 (m, 1H), 6.53 (d, 1H, $J = 7.3$ Hz), 6.41 – 6.42 (m, 2H), 4.54 (s, 2H), 3.69 (d, 2H, $J = 5.3$ Hz), 3.55 – 3.63 (m, 2H), 3.11 – 3.19 (m, 2H), 2.27 (s, 3H), 2.00 – 2.02 (m, 1H), 1.73 – 1.77 (m, 2H); **¹³C NMR** (CDCl₃, 125 MHz) $\delta$ 148.6, 139.2, 138.1, 129.3, 128.7, 128.0, 127.8, 118.6, 114.0, 110.3, 73.5, 68.8, 65.3, 46.9, 39.0, 30.3, 21.8; **IR**: 3378, 2919, 2858, 1604, 1092, 1028, 769, 737, 695; **HRMS** (DART-TOF) calcd. for C₁₉H₂₆NO₂ [M+H]: 300.1964, found: 300.1958; $\left[\alpha\right]_D^{20} = +28.2$ (c = 0.160, CHCl₃, l = 50 mm).
(S)-4-(benzyloxy)-2-(((3-nitrophenyl)amino)methyl)butan-1-ol. General Procedure B was followed, affording a bright orange oil (40.4 mg, 61%). HPLC (OD-H, 1.0 mL/min, 7% i-PrOH: 93% Hexanes, 240 nm) $t_{\text{major}} = 55.9$ min and $t_{\text{minor}} = 37.8$ min, 84% ee; $^1$H NMR (CDCl₃, 500 MHz) $\delta$ 7.46 (dd, 1H, $J = 8.1$, 1.5 Hz), 7.28 – 7.37 (m, 6H), 7.21 (t, 1H, $J = 8.1$ Hz), 6.75 – 6.77 (m, 1H), 4.65 (br s, 1H), 4.53 (s, 2H), 3.70 (d, 2H, $J = 4.4$ Hz), 3.56 – 3.64 (m, 2H), 3.14 – 3.24 (m, 2H), 2.48 (br s, 1H), 1.99 – 2.04 (m, 1H), 1.71 – 1.82 (m, 2H); $^{13}$C NMR (CDCl₃, 125 MHz) $\delta$ 149.7, 149.5, 137.9, 129.8, 128.8, 128.2, 128.1, 119.0, 111.8, 105.2, 73.6, 68.7, 65.0, 46.5, 38.8, 30.1; IR: 3386, 2923, 2859, 1527, 1454, 1092, 733, 698 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₈H₂₃N₂O₄ [M+H]: 331.1658, found: 331.1662; $[\alpha]_D^{20} = +19.8$ (c = 0.200, CHCl₃, l = 50 mm).
Table 2.5, Entry 9

(S)-4-((benzyloxy)-2-((pyridin-3-ylamino)methyl)butan-1-ol. General Procedure B was followed, affording a light orange oil (36.5 mg, 64%). HPLC (OD-H, 1.0 mL/min, 21% i-PrOH: 79% Hexanes, 240 nm) \( t_{\text{major}} = 17.2 \text{ min} \) and \( t_{\text{minor}} = 27.6 \text{ min} \), 87% ee; \(^1\)H NMR (CDCl\(_3\), 500 MHz) \( \delta \) 7.93 (br s, 2H), 7.28 – 7.36 (m, 5H), 7.05 (br s, 1H), 6.82 (d, 1H, \( J = 5.0 \text{ Hz} \)), 4.52 (s, 2H), 4.26 (br s, 1H), 3.70 (d, 2H, \( J = 4.7 \text{ Hz} \)), 3.55 – 3.63 (m, 2H), 3.11 – 3.21 (m, 2H), 1.98 – 2.02 (m, 1H), 1.73 – 1.77 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 144.8, 138.4, 138.0, 136.0, 128.7, 128.1, 128.0, 128.1, 123.9, 118.7, 73.5, 68.7, 64.8, 46.3, 38.7, 30.1; IR: 2858, 1589, 1091, 794, 734, 632 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{17}\)H\(_{23}\)N\(_2\)O\(_2\) [M+H]: 287.1760, found: 287.1759; \([\alpha]_D^{20} = +3.52\) (c = 0.465, CHCl\(_3\), \( l = 50 \text{ mm} \)).
Isolation, and subsequent characterization, of the branched amino aldehyde products has proven difficult due to the decomposition of the aldehyde functionality on silica gel, as well as alumina. Over the course of 24 hours, the branched amino aldehyde also decomposes in an NMR tube in the presence of CDCl₃. As a result, crude ¹H NMR spectra are typically not taken prior to reduction to the amino alcohol in order to prevent decomposition. According to Procedure B, using (Z)-N-(4-(benzyloxy)but-2-en-1-yl)-4-chloroaniline as substrate, the stirring paddles were washed with EtOAc into the reaction vials. The crude reaction mixtures were concentrated. Analysis of the crude reaction mixture directly after hydroformylation shows complete conversion and the predominant formation of the branched amino aldehyde.
2.7.12 Spectral Data

For published NMR Spectral Data for Section 2.4: Enantioselective Hydroformylation of PMP-Protected Allylic Amines, see the following link:
http://pubs.acs.org/doi/suppl/10.1021/ja107433h

For published NMR Spectral Data for Section 2.5: Enantioselective Hydroformylation of Electronically Modified Allylic Anilines, see the following link:
http://pubs.acs.org/doi/suppl/10.1021/jo201328d

Representative Spectral Data for Ligands 2.42 and 2.48, as well as substrates are included here.
$^1$H NMR Spectrum for 2.45

Sample Name: TER-4-242
Archive Directory:
Sample Directory:
File: TER-4-242.H

Pulse Sequence: Proton (400 MHz)  
Solvent: d613
Data collected on: Jul 21 2010

Temp: 25.0 C / 298.1 K
Operator: KIt

Relax. delay 1.000 sec
Pulse 90.0 degrees
Avg. time 2.049 sec
Width 993.8 Hz
2 repetitions

$^{13}$C NMR Spectrum for 2.45

Sample Name: TER-4-242
Archive Directory:
Sample Directory:
File: TER-4-242.C

Pulse Sequence: Carbon (400 MHz)  
Solvent: d613
Data collected on: Jul 21 2010

Temp: 25.0 C / 298.1 K
Operator: KIt

Relax. delay 1.000 sec
Pulse 45.0 degrees
Avg. time 2.049 sec
Width 2048.0 Hz
22 repetitions

Line broadening: 0.5 Hz
FT size 48000
Total time 12 min
$^{1}$H NMR Spectrum for 2.46

Sample Name: 2-methyl-3-bromo-3-phenylpropanoic acid
Archive directory: name
Sample directory:

Pulse Sequence: Proton (H) 1D
Solvent: d6-DMSO
Data collected on: Jul 20 2013

Temp: 298 K / 298.1 K
Operator: HJC

Relax delay 1.0 sec
Pulse 90° degrees
Acq. time 2.14 sec
Width 8012.8 Hz
10 repetitions

$
^{13}$C NMR Spectrum for 2.46

Sample Name: 2-methyl-3-bromo-3-phenylpropanoic acid
Archive directory: name
Sample directory:

Pulse Sequence: Carbon (C) 1D
Solvent: d6-DMSO
Data collected on: Jul 20 2013

Temp: 298 K / 298.1 K
Operator: HJC

Relax delay 1.0 sec
Pulse 90° degrees
Acq. time 1.32 sec
Width 16346.6 Hz

100 repetitions

$

129$
$^{31}$P NMR Spectrum for 2.46

$^1$H NMR Spectrum for 2.47
$^{13}\text{C}$ NMR Spectrum for 2.47

$^{31}\text{P}$ NMR Spectrum for 2.47
$^1$H NMR Spectrum for 2.42

$^{31}$P NMR Spectrum for 2.42
$^1$H NMR Spectrum for \textbf{2.48}

$^{13}$C NMR Spectrum for \textbf{2.48}
$^{31}$P NMR Spectrum for 2.48

$^1$H NMR Spectrum for 2.49
**$^{13}$C NMR Spectrum for 2.49**

**$^1$H NMR Spectrum for 2.58**
$^{13}$C NMR Spectrum for 2.58

$^1$H NMR Spectrum for 2.53
$^{13}$C NMR Spectrum for 2.53

$^1$H NMR Spectrum for Amino Alcohol Product of 2.53 after Hydroformylation
$^{13}$C NMR Spectrum for Amino Alcohol Product of \textbf{2.53} after Hydroformylation
Chapter 3: Distal-Selective Hydroformylation of Homoallylic Alcohols

3.1 Introduction

Achieving remote selectivity in organic transformations remains an unsolved challenge. Enzymes are the exception, as they can impart impressive levels of specificity through the rigid geometry obtained from the enzyme-substrate complex. This complex, which is organized by a network of non-covalent interactions, allows for the selective functionalization of a particular site in the substrate while essentially ignoring the other functional groups present. Inspired by enzymes and their ability to obtain remote selectivity, organic chemists have pursued “molecular recognition” strategies\(^1\) to achieve selective catalysis. In molecular recognition, a linker tethers the substrate and reactive site together though either covalent or non-covalent interactions (Figure 3.1). The appropriate choice of linker allows for the selective functionalization of the substrate at a remote site.

Figure 3.1 Molecular Recognition Strategy Leading to Remote Functionalization.

---

3.1.1 Examples of Remote Selectivity in C-H Functionalization

To date, only a handful of such tethers have been reported to obtain remote-selectivity; the majority of these examples are reported in the field of C-H functionalization. As previously mentioned in Chapter 1, Breslow reported a silyl ether linker for the site-selective C-H functionalization of steroids in 1977 (Scheme 3.1).\(^2\),\(^3\)

Although many sterically and electronically similar tertiary C-H bonds exist in 3.1, chlorination occurs exclusively at the B/C ring junction. Utilizing the molecular recognition strategy, Breslow demonstrated that the appropriate choice of linker between the directing group and tertiary C-H bond allows for the selective functionalization at a single site in a complex molecule, such as a steroid.

Scheme 3.1 Breslow’s Silyl Ether Tether for Remote C-H Functionalization of Steroids.

\[\text{(1)}\]

---


More recently, Yu and co-workers reported the meta-selective C-H olefination of arenes (Scheme 3.2). This work stands in stark contrast to the myriad examples of directed ortho-selective C-H activation. The observed site-selectivity originates from the installation of a nitrile-containing linker, which can coordinate to a palladium catalyst and selectively deliver it to the remote meta C-H bond for activation and further functionalization.

Scheme 3.2 Yu’s meta-Selective C-H Olefination.

In 2009, Crabtree and co-workers reported a manganese catalyst for the selective C-H oxidation of non-steroidal anti-inflammatory drug (NSAID) Ibuprofen, 3.6 (Scheme 3.3). The catalyst, [(terpy’)Mn(OH2)(µ-O)2Mn(OH2)(terpy’)](NO3)3, contains a Mn(µ-O)2Mn reactive center and a terpyridine ligand bearing a carboxylic acid residue. The carboxylic acid functionality in 3.6 is anchored into the ligand through a double hydrogen


bond interaction. This interaction between the substrate and ligand ultimately prevents the formation of side-product 3.8. As a result, the benzylic methylene group on the iso-butyl group is in the correct orientation for oxidation to occur, leading to the formation of 3.7 as the major product. In this case, remote C-H functionalization is enabled through a hydrogen-bonding network (3.9), which mimics the actions of enzymes.

**Scheme 3.3** Crabtree’s Molecular Recognition Catalyst for the Oxygenation of C-H Bonds.

```
HOOC---Me
        |      | Oxone, MeCN
        |      |
4.6  |  MeCN
Catalyst

3.6

Catalyst = [(terpy')Mn(OH2)(µ'O)2Mn(OH2)(terpy')]3+
```

3.7 98.5%

3.8 1.5%

3.9
3.1.2 Obtaining Distal-Selectivity in Hydroformylation

A critical challenge in hydroformylation is the control of regioselectivity. Substrates sometimes possess an inherent regio-preference that can be amplified or exploited. The origin of this bias is often due to electronic effects, which is demonstrated by the many examples of asymmetric hydroformylation of activated substrates, such as styrene, vinyl acetate, and allyl cyanide (Chapter 2). Steric parameters also govern the inherent regiochemical outcome of many hydroformylation reactions. Straight-chain terminal olefin substrates have an inherent preference to form the linear aldehyde product to avoid penalizing steric interactions with the rhodium catalyst in the hydrometallation step.

The development of 2,2’-bis[(diphenylphosphino)methyl]-1,1’-biphenyl (BISBI), a large bite-angle bidentate phosphine ligand, amplifies the selectivity for the linear isomer to 1:66 (3.10:3.11) when 1-hexene undergoes hydroformylation (Scheme 3.4).

With a bite angle of approximately 113°, the BISBI ligand prefers to bind in the equatorial-equatorial plane of the trigonal bipyramidal rhodium complex. Upon

---


coordination of the olefin, a conformation exists where steric hindrance is minimized, which leads to the selective formation of the linear isomer. In the case of unactivated terminal olefins, however, devising a strategy to override the inherent substrate bias and access the less favored product, in this case the branched aldehyde, remains a critical challenge.

**Scheme 3.4 Amplification of Linear Selectivity with BISBI.**

Olefins, such as 1,2-disubstituted substrates, pose an alternative challenge. Not only are they less reactive than their terminal olefin counterparts, but there is often no steric or electronic differentiation between the two olefinic carbons (Figure 3.2). In the case of substrates where no innate substrate bias exists, the paramount challenge is to identify a strategy to synthesize either isomer of product in a predictable and selective fashion. Theoretically, this can be achieved by the development of two ligands, where one ligand (L₁) could bias a substrate to form the proximal aldehyde product and the other (L₂) leads to the selective formation of the distal isomer for the same olefin (Figure 3.2).
**Figure 3.2** The Challenge of Controlling Regioselectivity in Hydroformylation.

The development of [bis(2,4-di-tert-butyl)pentaerythritol]diphosphite (Alkanox) has begun to address this challenge.\(^{10}\) In the hydroformylation of 2-pentene, an unactivated disubstituted olefin, the two isomeric aldehyde products were isolated in a 73:27 ratio (3.13:3.14, Scheme 3.5). In this reaction, the Alkanox ligand is able to discriminate between an ethyl versus a methyl substituent on the alkene, allowing 3.13 to be formed selectively. An obvious drawback of this ligand system is that only 12% conversion is observed. Furthermore, they do not provide a rationale for the observed selectivity using this ligand. This further highlights the dual challenge of designing a ligand system that affords high levels of reactivity and selectivity for disubstituted olefins in hydroformylation.

---

Scheme 3.5 Ligand Control for the Hydroformylation of 1,2-Disubstituted Olefins.

The use of directing groups has been a crucial development in obtaining predictable levels of regioselectivity in hydroformylation and expanding the substrate scope to more highly substituted alkenes. In particular, directing groups have been effective at accessing the branched isomer for terminal olefins,11 and forming the aldehyde on the proximal olefinic carbon for multi-substituted alkenes12 (Chapter 1).

Employing catalytic directing groups in hydroformylation has improved upon the overall efficiency of this process, and has ultimately allowed for the concomitant control of regio-13 and stereochemistry14 (Chapter 2).

In general, directed hydroformylation has been limited to placing the aldehyde on the proximal olefinic carbon relative to the directing functionality. While the generation of the proximal isomer in a selective fashion is an important advancement in the field of hydroformylation, it is also serves as a limitation. In the context of unactivated, 1,2-

\[ \text{Me} \equiv \text{Me} \]

1 mol % Rh(acac)(CO)₂
6 mol % Alkanox
300 psi H₂/CO, 120 °C, DCM

\[ \begin{align*}
3.12 & \quad \text{Me} \equiv \text{Me} \\
3.13 & \quad \text{H} \equiv \text{O} \\
3.14 & \quad \text{Me} \equiv \text{Me}
\end{align*} \]

12% conversion
73:27 \text{rr} (3.13:3.14)


disubstituted olefin substrates, the challenge of distal-selective hydroformylation has gone relatively unaddressed.

A notable example of distal-selective hydroformylation utilizing a stoichiometric phosphorus-based directing group was reported by Burke and co-workers in the total synthesis of (+)-phyllanthocin (Scheme 3.6). They hypothesized that the methyl ester in the natural product could be derived from a directed hydroformylation through the appropriate choice of phosphorus-based directing group appended to the axial alcohol. They focused their efforts on the diphenylphosphino benzoate (DPPB) ester group, first with the phosphorus unit in the para position of the aromatic ring (3.15). They isolated incorrect constitutional isomer 3.16 in 8% yield, as well as unreacted starting material. The low conversion employing 3.15 highlights the low reactivity of disubstituted olefins in hydroformylation. By placing the phosphine in the meta position (3.17), distal aldehyde 3.18 was isolated, relative to the position of the directing group, in 68% yield. The enhanced reactivity when going from a para- to a meta- substituted DPPB ester enforces the need for the correct distance between the directing group and the olefin to obtain the desired structural isomer. Moreover, it demonstrates the rate-accelerating affect that can occur through the appropriate choice of directing functionality.

Scheme 3.6 Distal-Selective Hydroformylation in the Total Synthesis of (+)-phyllanthocin.

Supramolecular ligands, which form by the self-assembly of smaller components, have been developed for distal-selective hydroformylation. Inspired by enzymes, both the Breit \(^17\) and Reek \(^18\) groups designed systems that take advantage of non-covalent interactions, placing the substrate in a rigid orientation relative to the rhodium catalyst, which enhances both the reactivity and selectivity in the hydroformylation reaction.

In 2011, Reek and co-workers developed supramolecular bisphosphine ligand \(3.20\) containing an anion receptor backbone (Scheme 3.7).\(^{18a}\) A “pocket” is generated


when the ligand is bound to the rhodium catalyst, which selectively bind substrates containing anionic functional groups. Subjecting 4-pentenolate ion 3.19 to hydroformylation with ligand 3.20 afforded excellent conversions (95%) and a 40-fold preference for the formation of linear aldehyde 3.22. In the presence of protonated or methyl ester analogues that cannot bind in the pocket, the linear aldehyde is only formed in a 3-fold excess, presumably via a steric preference. Additionally, lower conversions (~40%) are observed for the carboxylic acid and methyl ester analogues, affirming the rate-accelerating effect that results from the pre-association of 3.19 and ligand 3.20.

**Scheme 3.7** Reek’s Supramolecular Catalyst for Hydroformylation of Anionic Substrates.

Using the same anion recognition backbone, the Reek group appended phosphite groups to their self-assembling supramolecular ligand for the distal-selective hydroformylation of vinyl arene substrates. Through π-benzyl stabilization with the adjacent aromatic ring, these substrates prefer to form an α-arylalkyl intermediate, which would lead to the aldehyde being placed on the proximal olefinic carbon (relative to the aromatic ring). Employing vinyl-2-carboxyarene 3.23 and ligand 3.24 in the hydroformylation reaction afforded distal aldehyde product 3.26 in a 98% isolated yield.
(Scheme 3.8). Similar to their previous studies with ligand 3.20, they believe that the carboxylate anion is strongly bound within the pocket of ligand 3.24 when coordinated to rhodium. This interaction severely restricts the movement of the alkene at the metal center so that it can only rotate in such a way that hydrometallation occurs on the distal olefinic carbon. Prior to this report, no general systems to overturn the inherent substrate selectivity for vinylarenes were known.

Scheme 3.8 Reek’s Supramolecular Catalyst for the Hydroformylation of Vinyl Arenes.

In 2008, Breit and co-workers developed a supramolecular catalyst system for the hydroformylation of unsaturated carboxylic acid substrates. The catalyst (3.28) contains an acylguanidinium unit for the recognition of carboxylic acids and a phosphine, which serves as a metal-binding site. Hydroformylation of internal alkene 3.27 affords distal aldehyde product 3.30 in an 11-fold preference over proximal aldehyde 3.29.
(Scheme 3.9). A control experiment where the hydroformylation was carried out in the presence of PPh$_3$ as ligand rather than 3.28 resulted in attenuated conversions (20%) and a moderate preference for proximal aldehyde 3.29 (1.7:1, 3.29:3.30). Using self-assembling ligand 3.28, the rate- and selectivity-determining hydrometallation step becomes intramolecular in nature, which results in rate-acceleration and a regiochemical outcome that overturns the inherent substrate preference.

**Scheme 3.9** Breit’s Acylguanidine Supramolecular Catalyst System.

Breit demonstrated that the distance between the carboxylic acid functionality and the olefin has a large effect on both reactivity and selectivity (Table 3.1). A terminal olefin substrate with one methylene group between the carboxylic acid and the olefin (3.31) affords the linear aldehyde in a 23-fold preference over the branched product (Table 3.1, Entry 1). Simply inserting an additional methylene group between the olefin and carboxylic acid (3.32) dramatically decreases the preference for the linear product (Table 3.1, Entry 2). Consistent with a directed reaction proceeding through a highly ordered transition state, the regioselectivity is highly dependent on the distance between the directing functionality and the olefin.
Table 3.1 Effect of Olefin Tether on Hydroformylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Conv (%)</th>
<th>rr (branched:linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n = 1 (3.31)</td>
<td>100</td>
<td>1:23</td>
</tr>
<tr>
<td>2</td>
<td>n = 2 (3.32)</td>
<td>73</td>
<td>1:3.6</td>
</tr>
</tbody>
</table>

The specificity for $\beta,\gamma$-unsaturated carboxylic acid substrates allows ligand 3.28 to display impressive activity and regio-control. The origin of this distal selectivity is attributed to a 13-membered chelate between the substrate, 3.28, and a rhodium catalyst in the hydrometallation step (3.33, Figure 3.3). A similar large 14-membered metallacycle is observed using Burke’s stoichiometric directing group in the total synthesis of (+)-phyllanthocin (3.34, Figure 3.3). It is possible that the regiochemical outcome in both examples originates from the formation of a less strained, larger metallacycle during the hydrometallation step in the hydroformylation catalytic cycle. This is in contrast to directed proximal-selective hydroformylation, where the formation of smaller metallacycle intermediates is typically observed.
Compared to proximal-selective hydroformylation, there is a dearth of distal-selective hydroformylation catalysts. Additionally, the current systems focus on using non-covalent interactions to drive selectivity, thus limiting the substrate scope. To fully realize the potential of directing group chemistry, we set out to design a phosphine based ligand that used covalent interactions to control distal selectivity. Beyond developing a selective catalyst, these studies have also helped expand our understanding of the factors that control regioselectivity in olefin functionalization reactions.

### 3.2 Design of a Distal-Selective Scaffolding Ligand

One major limitation of the Breit and Reek systems is the need for a functional group in the substrate that can hydrogen bond to the supramolecular catalyst to obtain high levels of reactivity and selectivity. We envisioned the design of a scaffold that would utilize reversible covalent bonds to pre-organize the substrate and the ligand prior to hydroformylation. Combining the design elements in Breit’s supramolecular catalyst (3.28), the Tan lab organocatalyst for diol functionalization (3.36), as well as our previous scaffolding ligands (3.35), we targeted a small collection of ligands with the substructure 3.37 (Figure 3.4). A critical feature for this class of ligands is an oxazolidine...
core, which the Tan lab has previously shown to bind alcohols. These ligands also possess a triaryl phosphine moiety, which serves as the metal binding site.

**Figure 3.4** Developing a Distal Selective Scaffolding Ligand.

![Scaffolding Ligand for Asymmetric Hydroformylation](image)

**3.35** Scaffolding Ligand for Asymmetric Hydroformylation

**3.36** Organocatalyst for Site-Selective Functionalization of 1,2-Diols

**3.37** Proposed Distal-Selective Ligand Design

The observed selectivity utilizing Breit’s supramolecular catalyst arises form a 13-membered metallacycle in the hydrometallation step. Appending a homoallylic alcohol to our proposed distal-selective ligand design reveals that a similar 13-membered chelate (3.38) would occur in the hydrometallation step of the catalytic cycle (Figure 3.5). Additionally, when examining the linkers developed for remote C-H functionalization (Section 3.1.1) the metallacycles leading to functionalization are also macrocyclic in nature. Similar to the Breit example, they contain an aromatic ring within the macrocycle. We hypothesize that the incorporation of an arene imparts structural rigidity on the cyclic structure, which limits the degrees of rotational freedom. With these observations in hand, we were curious to see whether distal-selectivity could be observed employing the general ligand design 3.37 in the hydroformylation reaction.

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This ligand design (3.37) is quite attractive because there is great potential for diversification. For example, the oxazolidine backbone is derived from amino acids, which provides a breadth of opportunity to explore various substitution patterns around the exchange ring. The triarylphosphine moiety can also be altered both sterically and electronically. We were eager to learn how each modification effects the hydroformylation reaction and ultimately use this knowledge to rationally design a distal selective hydroformylation ligand that displays high activity and selectivity.

Given the potential for modularity, a synthetic route to these ligands was developed that would be conducive to facile diversification (Scheme 3.10). Depending on the electronic nature of the phosphine, two syntheses allowed rapid access to (3-bromophenyl)diarylphosphine (3.40) starting from commercially available 3-iodo-bromobenzene. In the first route, using the appropriate secondary phosphine oxide, a palladium-catalyzed cross-coupling of the aryl iodide generates a triaryl phosphine oxide. Trichlorosilane mediated reduction of the phosphine oxide affords 3.40 in variable yields. Alternatively, the aryl iodide can selectively undergo a Grignard exchange with isopropylmagnesium bromide, followed by trapping with the appropriate chlorodiaryl phosphine to obtain 3.40 in good yields. After isolation of 3.40, lithium-halogen exchange and trapping with N,N-dimethylformamide yields the corresponding aldehyde
product with the general structure 3.41, which can be subjected to reductive amination conditions with a variety of amino alcohols. Formation of the aza-orthoester moiety occurs using \(N,N\)-dimethylformamide dimethyl acetal in the presence of methanol to generate ligands with the general structure 3.37.

**Scheme 3.10** Synthetic Route for Distal-Selective Hydroformylation.

![Scheme 3.10](image)

The synthetic route is amenable to scalability in good yields and only a few steps. Ligand 3.46, which is derived from \(L\)-valine, was synthesized in four steps from 3-iodobromobenzene to afford 3.7 g of product (Scheme 3.11). Importantly, aldehyde 3.44 is a key intermediate that can be isolated on gram scale when altering the substitution pattern on the oxazolidine ring. Subjection of 3.44 to reductive amination with a variety of amino alcohols provides rapid access to a collection of ligands from a common intermediate that is accessible on gram scale.
Scheme 3.11 Gram-Scale Synthesis of Ligand 3.46.

3.3 Distal-Selective Hydroformylation of Homoallylic Alcohols

With access to a large quantity of ligand 3.46, we explored its performance in hydroformylation. Although the exchange between alcohols and the oxazolidine core was previously demonstrated by our group, we wanted to confirm that the presence of the external phosphine unit did not have an unexpected deleterious effect. An equilibrium experiment was carried out between cis-3-hexen-1-ol and ligand 3.46 (Scheme 3.12). Monitoring the exchange by $^1$H NMR revealed that equilibrium was reached after two hours, with a calculated $K_{eq}$ value of 0.51. A favorable exchange reaction is necessary for obtaining high levels of regioselectivity in the hydroformylation reaction because it helps to ensure that a directed pathway predominates. The exchange reaction was a particular concern in the case of ligands of substructure 3.37, because they contain a triaryl phosphine group, which can participate in an unselective background reaction to afford poor regioselectivity.
After confirming that alcohol substrates exchange with ligand 3.46, the activity of 3.46 in hydroformylation was investigated. Based on a 13-membered chelate in the hydrometallation step (3.38) that is similar to the Breit example, we examined the distal-selectivity in the hydroformylation reaction with homoallylic alcohol substrates. Upon hydroformylation of homoallylic alcohols, both isomeric aldehydes cyclize intramolecularly to form lactol products. For the ease of analysis and separation, these lactols were subjected to PCC oxidation to generate the corresponding lactones. Triphenylphosphine was used as the ligand to examine the inherent substrate selectivity. Modest conversion was obtained (52%) with a slight preference for the formation of the proximal lactone when PPh₃ was used as the ligand (Table 3.2, Entry 1). By simply switching to ligand 3.46, an increase in conversion was observed (Table 3.2, Entry 2); more importantly, however, the regiochemical outcome was reversed and the distal lactone was formed selectively (22:78 proximal:distal). Compared to the unselective reaction using PPh₃ as the ligand, it is clear that ligand 3.46 was able to differentiate the two electronically and sterically similar olefinic carbons and ultimately form the aldehyde on the one distal to the alcohol functional group selectively.
Table 3.2 Preliminary Regioselective Data for cis-3-Hexenol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>rr (3.49:3.50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>52</td>
<td>54:46</td>
</tr>
<tr>
<td>2</td>
<td>3.46</td>
<td>73</td>
<td>22:78</td>
</tr>
</tbody>
</table>

*Based on ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

To ensure that ligand 3.46 contained the optimal ligand backbone for obtaining distal-selectivity, we surveyed a number different ligand bacbones (Scheme 3.13). Altering the metal binding site to contain an ortho-substituted phosphine (3.51) rather than meta-substituted arene (3.46) afforded only modest regioselection for distal lactone 3.50. Changing the phenyl ring in 3.46 to an N-methylimidazole moiety (3.52) gives similar conversion, but a slight erosion in regioselectivity for the distal isomer is observed. Increasing the size of the oxazolidine from a five-membered ring (2.46) to a six-membered ring (3.53) gives 60% conversion and a 35:65 rr, which is not a considerable improvement upon the results obtained with ligand 3.46 (Table 3.2, Entry 2). With this data in hand, found that the oxazolidine ring size, as well as the distance between the exchange ring and the metal binding site, in ligand 3.46 were optimal for obtaining high levels of regioselectivity in favor of the distal isomer for homoallylic alcohol substrates.
Having established that 3.46 generates the distal lactone product selectively, a ligand loading screen was undertaken to investigate how the ligand:metal ratio effects the outcome of the reaction. As the ligand loading increases relative to the rhodium catalyst, an increased preference for distal lactone 3.50 is observed. At relatively low ligand:metal ratios (Table 3.3, Entries 1 – 2), high conversions are observed with minimal levels of regiocontrol. Since ligand 3.46 contains a triphenylphosphine moiety, these results are consistent with an unselective background reaction. Further increasing the ligand loading affords slightly lower conversions, with the regioselectivity plateauing at approximately 22:78 (Table 3.3, Entry 4). In terms of identifying an appropriate balance between conversion and regioselectivity, the optimal ligand:metal ratio lies between 2.5:1 and 5:1 (Table 3.3, Entries 2 and 3).
In the hydroformylation of homoallylic alcohols, ligand 3.46 forms the distal lactone selectively. Relative to control reactions with PPh₃, which show poor levels of regiocontrol, ligand 3.46 can effectively discriminate between the two olefinic carbons.

### 3.4 Distal- and Diastereoselective Hydroformylation of Homoallylic Alcohols

Having shown that ligand 3.46 directs the hydroformylation to favor the distal aldehyde product for homoallylic alcohols, we turned our attention to homoallylic alcohol substrates bearing an allylic stereocenter. In 2008, the Tan lab reported that directed hydroformylation using racemic scaffolding ligand 3.55 affords the anti diastereomer of the proximal γ-lactone product in high levels of diastereo- and regioselectivity (Scheme 3.14, Equation 1). With this precedent in hand, we wondered if the same substrate could be used with the new scaffolding ligand design (3.37) to selectively afford the distal δ-lactone product (Scheme 3.14, Equation 2). Using this new ligand class, we were also

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curious if the reaction could be carried out in a diastereoselective fashion. If successful, this would be an important demonstration that, through the appropriate choice of ligand, either structural isomer of product can be obtained in a selective and predictable fashion.

**Scheme 3.14** Inspiration from Past Studies in the Tan Lab.

![Scheme 3.14](image)

### 3.4.1 Initial Investigations into Distal-Selectivity

We initiated our investigation with a small ligand screen using homoallylic alcohol substrate **3.54** bearing an allylic methyl substituent (Table 3.1). Using PPh₃ as a control ligand results in a modest preference for the distal product (46:54 rr) with minimal levels of diastereocntrol and only 30% conversion (Table 3.4, Entry 1). This result highlights the dual challenge of achieving high levels of selectivity and reactivity simultaneously for disubstituted olefins in hydroformylation. Performing the reaction with oxazolidine ligand **3.58** results in the selective formation of the distal product (19:81 rr) with good levels of diastereocntrol (76:24 dr) and a marked increase in conversion.
Notably, when compared to using first generation racemic scaffolding ligand 3.55 where the proximal lactone is formed in a 95:5 rr (Table 3.4, Entry 2), the regioselectivity is completely overturned in favor the distal lactone in the presence of oxazolidine ligand 3.58. A matched/mis-matched relationship exists in the hydroformylation reaction with chiral scaffolding ligand 3.46 when enantiopure substrates are used in the reaction, with (R)-3.54 being matched (Table 3.4, Entries 4 – 5). Due to the numerous amino alcohols available from the chiral pool for further diversification of the ligand backbone, our studies continued using enantiopure substrate (R)-3.54.

**Table 3.4 Preliminary Ligand Screen.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Conv (%)(^a)</th>
<th>rr (3.56:3.57)(^b)</th>
<th>dr (anti:syn)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rac-3.54</td>
<td>PPh(_3)</td>
<td>30</td>
<td>46:54</td>
<td>53:47</td>
</tr>
<tr>
<td>2</td>
<td>rac-3.54</td>
<td>3.55</td>
<td>quant.</td>
<td>95:5</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>rac-3.54</td>
<td>3.58</td>
<td>60</td>
<td>19:81</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>(S)-3.54</td>
<td>3.46</td>
<td>65</td>
<td>28:72</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td>(R)-3.54</td>
<td>3.46</td>
<td>87</td>
<td>9:91</td>
<td>88:12</td>
</tr>
</tbody>
</table>

\(^a\) Based on \(^1\)H NMR using mesitylene as an internal standard. \(^b\) Determined by achiral Gas Chromatography. \(^c\) Determined by \(^1\)H NMR in CD\(_3\)OD.
Having identified the matched isomer of substrate, the effect of pressure on the hydroformylation reaction was investigated. The pressure was increased incrementally from 60 psi to 400 psi (Table 3.5). While the regioselectivity was relatively unaffected by the change in pressure, the conversion increased slightly at higher pressures of syngas, with the system being most active at 400 psi. The effect of pressure is the most obvious when the diastereoselectivity is examined. An increased preference for the formation of the anti diastereomer of the $\delta$-lactone is observed at higher pressures, eventually reaching 88:12 dr at 400 psi (Table 3.5, Entry 4).

Table 3.5 Pressure Screen between ($R$)-3.54 and Ligand 3.46.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>Conv (%)$^a$</th>
<th>rr (3.56:3.57)$^b$</th>
<th>dr (anti:syn)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>77</td>
<td>9:91</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>79</td>
<td>10:90</td>
<td>83:17</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>85</td>
<td>16:84</td>
<td>83:17</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>87</td>
<td>9:91</td>
<td>88:12</td>
</tr>
</tbody>
</table>

$^a$ Based on $^1$H NMR using mesitylene as an internal standard. $^b$ Determined by achiral Gas Chromatography. $^c$ Determined by $^1$H NMR in CD$_3$OD.

To drive the consumption of starting material, a rhodium loading screen was undertaken (Table 3.6). As expected, higher conversions were observed as more rhodium catalyst was added to the reaction. While the regiochemical outcome of the reaction was relatively unaffected, increasing the amount of rhodium from 2 mol % to 4 mol % resulted in a decrease in diastereoselection, eventually reaching 80:20 dr at 4 mol % rhodium loading (Table 3.6, Entry 3). As more rhodium catalyst is added to the reaction,
an unselective background reaction is likely more prevalent, which leads to an observed erosion in regio- and diastereoselectivity.

Table 3.6 Rhodium Loading Screen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh loading (%)</th>
<th>Conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rr (3.56:3.57)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr (anti:sync)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2%</td>
<td>60</td>
<td>14:86</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>3%</td>
<td>85</td>
<td>16:84</td>
<td>83:17</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>78</td>
<td>17:83</td>
<td>80:20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on 1H NMR using mesitylene as an internal standard. <sup>b</sup> Determined by achiral Gas Chromatography. <sup>c</sup> Determined by 1H NMR in CD3OD.

Although better regio- and diastereoselectivities were obtained using 2 mol % rhodium catalyst (Table 3.6, Entry 1), further studies continued with 3 mol % rhodium loading, since it afforded the best balance of conversion and selectivity. We were optimistic that an evaluation of ligands would help us to further improve upon these results.

3.4.2 Optimization of the Scaffolding Ligand Structure

With the optimized conditions in hand, a broad ligand screen was undertaken. Due to the highly modular nature of this ligand design, a small library of ligands was synthesized to test for distal- and diastereoselectivity. Through the rational manipulation of various sites on the ligand structure, we were eager to learn how each modification affected the outcome of the hydroformylation reaction.
Having carried out optimization reactions with 3.46, we first probed how the electronics on phosphorus affected the reaction (Table 3.7). Keeping the l-valine oxazolidine backbone intact, ligands containing an electron-rich (3.59) and an electron-deficient (3.60) phosphine center were synthesized. While the electronics on phosphorus did not dramatically affect the regio- and diastereoselectivity in the reaction, the conversion increased going towards a more electron-deficient phosphine (Table 3.7, Entries 1 – 3). This observation is consistent with previous findings that electron deficient ligands accelerate hydroformylation through the more facile dissociation of CO, and subsequent olefin coordination.22 In order to probe the combination of electronics and sterics around the phosphorus center, both the ortho-OMe (3.61) and ortho-CF3 (3.62) ligands were tested (Table 3.7, Entries 4 – 5). While both ligands selectively formed the δ-lactone, attenuated conversions were observed in both cases when compared to the corresponding para-substituted ligands (Table 3.7, Entries 1 and 3). Although 3.61 and 3.62 afforded the δ-lactone selectively, 21:79 rr and 19:81 rr respectively, the diastereoselectivities in favor of the anti isomer were lower in the case of both ligands. In particular, a 51:49 dr was observed for ortho-CF3 ligand 3.62 (Table 3.7, Entry 5). Examination of the crude 1H NMR spectra after the hydroformylation reaction showed considerable amounts of the trans olefin isomer of 3.51. If the ligand is participating in isomerization of the starting material rather than hydroformylation, this could account for the low conversion; additionally, if the isomerized starting material is consumed during the course of the hydroformylation reaction a lower diastereomer ratio would be expected.

Electron-deficient ligand 3.60 afforded the best balance between reactivity and selectivity.

Table 3.7 Screen of Electronically and Sterically Modified Phosphines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv (%)</th>
<th><em>rr</em> (3.56:3.57)</th>
<th><em>dr</em> (anti:syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.59</td>
<td>65</td>
<td>14:86</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>3.46</td>
<td>87</td>
<td>9:91</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>3.60</td>
<td>94</td>
<td>11:89</td>
<td>92:8</td>
</tr>
<tr>
<td>4</td>
<td>3.61</td>
<td>52</td>
<td>21:79</td>
<td>74:26</td>
</tr>
<tr>
<td>5</td>
<td>3.62</td>
<td>52</td>
<td>19:81</td>
<td>51:49</td>
</tr>
</tbody>
</table>

* Based on 1H NMR using mesitylene as an internal standard. *b* Determined by achiral Gas Chromatography. *c* Determined by 1H NMR in CD3OD.

To further improve upon both the reactivity and selectivities, a variety of other modifications were made with respect to the phosphine unit using the L-valine oxazolidine backbone (Table 3.8). Based on the data obtained with ligand 3.60, we hypothesized that if one trifluoromethyl group is advantageous for reactivity, then making the phosphine more electron-deficient could further accelerate the reaction. Ligand 3.63, bearing two 3,5-bis(trifluoromethyl)phenyl groups appended to the phosphine, afforded attenuated regio- and diastereoselectivites (Table 3.8, Entry 1). Isomerized starting material was also observed in the crude reaction mixture, which can account for the decreased conversion and selectivities. Leighton and co-workers have demonstrated that a dibenzophosphole moiety serves as an active stoichiometric directing
group for branched selective hydroformylation. A ligand containing a
dibenzophosphole phosphine moiety (3.64) was synthesized but was not active under our
reaction conditions, resulting in 20% consumption of starting material (Table 3.8, Entry 2). We also considered that a bond rotation about the exocyclic C-N bond could have a
deleterious effect on the reaction by placing the phosphine away from the substrate-
binding site. To increase the probability of a positive interaction between the metal- and
substrate-binding sites, a 3,5-bis-(diphenylphosphino)benzene ligand (3.65) was designed.
While the regio- and diastereoselectivities did not improve, the conversion dropped to
60% (Table 3.8, Entry 3). An explanation for this observed attenuation in reactivity is
that adding an additional phosphine unit alters the phosphine-metal ratio, which increases
the probability of generating an inactive tris-phosphine ligated rhodium species.

To account for the additional phosphine unit present in the ligand, we also
decreased the ligand loading to 5 mol % 3.65 in the reaction so that the concentration of
phosphine relative to the rhodium catalyst was similar to our other ligand screens. Under
these conditions, 60% conversion, 13:87 rr, and 85:15 dr were observed, which is similar
to the results using 10 mol % 3.65 (Table 3.8, Entry 3). While the outcome of the reaction
was not improved when the amount of ligand 3.65 was lowered, the fact that the ligand
loading can be decreased by a factor of two, while still maintaining the same selectivities,
is a positive attribute. Due to the synthetic difficulty in synthesizing the 3,5-bis-
(diphenylphosphino)benzene compounds, we continued screening ligands with only one
phosphine unit present in the meta position.

Table 3.8 Altering the Phosphorous Center More Dramatically.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>rr (3.56:3.57)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>dr (anti: syn)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.63</td>
<td>72</td>
<td>19:81</td>
<td>72:28</td>
</tr>
<tr>
<td>2</td>
<td>3.64</td>
<td>20</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>3</td>
<td>3.65</td>
<td>60</td>
<td>15:85</td>
<td>87:13</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on <sup>1</sup>H NMR using mesitylene as an internal standard. <sup>b</sup>Determined by achiral Gas Chromatography. <sup>c</sup>Determined by <sup>1</sup>H NMR in CD<sub>3</sub>OD.

Due to the availability of amino acids, the substitution on the oxazolidine backbone was varied. Reducing the size of the substituent on the oxazolidine ring to a methyl group (3.66) resulted a 24:76 rr and 74:26 dr, which are lower selectivities when compared to the original L-valine derived catalyst 3.46 (Table 3.9, Entry 1). Additionally, only 55% conversion was obtained for L-alanine derived ligand 3.66. Ligand 3.67 containing a backbone derived from L-<i>tert</i>-leucine afforded similar regio- and diastereoselectivities (Table 3.9, Entry 3). Additionally, ligand 3.67 is more active than 3.46 or 3.66, giving 92% conversion in the hydroformylation reaction.
Table 3.9 Effect of Changing the Oxazolidine Backbone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv (%)a</th>
<th>rr (3.56:3.57)b</th>
<th>dr (anti:syn)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.66</td>
<td>55</td>
<td>24:76</td>
<td>74:26</td>
</tr>
<tr>
<td>2</td>
<td>3.46</td>
<td>87</td>
<td>9:91</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>3.67</td>
<td>92</td>
<td>9:91</td>
<td>87:13</td>
</tr>
</tbody>
</table>

a Based on 1H NMR using mesitylene as an internal standard. b Determined by achiral Gas Chromatography. c Determined by 1H NMR in CD3OD.

Increasing the size of the substituent on the oxazolidine backbone resulted in improved conversions and selectivities. Since these oxazolidine ligands exist as a mixture of diastereomers at the aza-orthoester stereocenter, it is possible that placing a larger substituent on the oxazolidine ring allows the ligand to access a conformation where the directed hydroformylation is favored. A subtle change in the diastereomer ratio of substrate-bound-ligand can favor the directed reaction pathway and lead to an improvement in reactivity and selectivity.

With the previous knowledge that phosphine electronics have a large effect on the reactivity (Table 3.10), they were altered for the ligand derived from L-tert-leucine. Consistent with previous observations, modifying the electronics on the phosphine moiety did not have a dramatic effect on the regio- or diastereoselectivity observed in the reaction. Additionally, electron-rich phosphine ligand 3.68 gave the lowest conversion (Table 3.10, Entry 1). While electron-deficient ligand 3.69 was still quite active (Table
3.10, Entry 3), the conversions and selectivities were similar to the corresponding neutral phosphine ligand 3.67.

**Table 3.10** Electronically Modified Phosphines with a 1-tert-leucine Oxazolidine Backbone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conv (%)a</th>
<th>( r (3.56:3.57)b )</th>
<th>dr (anti:syn)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.68</td>
<td>63</td>
<td>14:86</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>3.67</td>
<td>92</td>
<td>9:91</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>3.69</td>
<td>88</td>
<td>10:90</td>
<td>85:15</td>
</tr>
</tbody>
</table>

a Based on \(^1\)H NMR using mesitylene as an internal standard. b Determined by achiral Gas Chromatography. c Determined by \(^1\)H NMR in CD\(_2\)OD.

All of the aforementioned ligands exist as a mixture of diastereomers at the substrate-binding site relative to the amino acid-derived oxazolidine backbone. Due to the success of a rigid catalyst structure is diastereomerically pure (3.36) for the functionalization of 1,2-diol system, the synthesis of a phosphine ligand that exists as a single diastereomer was our ultimate goal. Attempts to synthesize the triarylphosphine analogue of organocatalyst 3.36 were unsuccessful; however, a single diastereomer of ligand was observed by \(^1\)H NMR when a gem-dimethyl group was placed on the methylene linker between the oxazolidine ring and the triaryl phosphine (3.70). Unsure which diastereomer of ligand was synthesized, a 1D nOe experiment was carried out to confirm the absolute stereochemistry (Figure 3.6). An nOe correlation exists between \( H_{(1)} \) and the \(-\text{OMe}\) substituent. Conversely, an nOe is observed between \( H_{(2)} \) and the isopropyl group on the
oxazolidine backbone. Thus, the absolute stereochemistry was confirmed to be *anti* between the isopropyl and –OMe substituents, which is the opposite relative stereochemistry observed in organocatalyst 3.36.

**Figure 3.6** Confirmation of Absolute Stereochemistry of 3.70 by nOe Correlations.

When ligand 3.70 was used in the hydroformylation reaction the δ-lactone was formed selectively in 18:82 rr and 82:18 dr in favor of the *anti* diastereomer (Scheme 3.15); however, only 29% conversion was observed. Based on this information, we posit that the *syn* configuration between the oxazolidine and aza-orthoester stereocenters should be the optimal diastereomer, but attempts to confirm this hypothesis by synthesizing such a ligand have been unsuccessful.

**Scheme 3.15** Hydroformylation of 3.54 with a Single Diastereomer of Ligand 3.70.
Through the rational manipulation of the electronics on the phosphine and the substituent on the oxazolidine backbone, two nearly equivalent distal-selective scaffolding ligands were identified (3.60 and 3.67, Scheme 3.16). Due to its ease of synthesis and strongest preference for the distal-lactone, we continued our studies with L-tert-leucine-derived ligand 3.67. Ligand 3.71, which is identical to 3.67 but lacks a substrate-binding site, was also tested in the hydroformylation. The reaction proceeds sluggishly (44% conversion), and the regio- and diastereoselectivities are comparable to utilizing PPh₃ as ligand. This demonstrates the importance of the substrate-binding site for both achieving high levels of selectivity and obtaining rate-acceleration in the reaction.

**Scheme 3.16** Two Optimal Ligands and Hydroformylation with Control Catalyst 3.71.

![Scheme 3.16](image)

The advantage of this ligand design is that a small library of ligands can be accessed efficiently. Although 3.67 was identified as the optimal ligand for this particular
substrate, the entire library of ligands is available for screening versus other substrates, and even other substrates classes, to ultimately obtain the optimal results.

3.4.3 Exploration of the Substrate Scope

Having identified the optimal ligand, the scope of the reaction was explored through the synthesis of a variety of enantiopure substrates. As demonstrated previously, 3.54 undergoes hydroformylation efficiently with good isolated yields and high levels of selectivity for the formation of the anti-distal lactone (Table 3.11, Entry 1). When trans olefin 3.72 participates in the reaction (Table 3.11, Entry 2), the δ-lactone is still formed selectively (20:80 rr), but the syn-isomer is observed as the major stereoisomer due to a hydrometallation transition state that minimizes A1,3-strain (vide infra).

Employing a substrate containing a large isopropyl substituent at the allylic position (3.73) results in a highly selective reaction, with the anti-δ-lactone formed in 5:95 rr and 91:9 dr (Table 3.11, Entry 3). The low isolated yield is attributed to incomplete conversion (72%) during the hydroformylation reaction. In the presence of 12 mol % PPh3 and 6 mol % Rh(acac)(CO)2 at 75 °C and 400 psi H2/CO, no appreciable conversion is observed for substrate 3.73. This highlights the difficulty in employing very sterically hindered olefin substrates in hydroformylation. Moreover, it demonstrates the significant rate-enhancement using ligand 3.67 over the control reaction with PPh3.
Table 3.11 Substrate Table for Distal- and Diastereoselective Hydroformylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>major product</th>
<th>rs&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HO Me Bu</td>
<td>O Bu</td>
<td>9:91</td>
<td>87:13</td>
<td>78%</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HO Me Bu</td>
<td>O Bu</td>
<td>20:80</td>
<td>32:68</td>
<td>52%</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HO Me Bu</td>
<td>O Bu</td>
<td>5:95</td>
<td>91:9</td>
<td>53%</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>O Ph</td>
<td>12:88</td>
<td>83:17</td>
<td>66%</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>O Ph-(p-OMe)</td>
<td>7:93</td>
<td>88:12</td>
<td>72%</td>
</tr>
<tr>
<td>6&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>O Ph-(p-Br)</td>
<td>13:87</td>
<td>89:11</td>
<td>62%</td>
</tr>
<tr>
<td>7&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>O Ph-(p-Cl)</td>
<td>12:88</td>
<td>87:13</td>
<td>68%</td>
</tr>
<tr>
<td>8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>O Ph-(m-CF&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>9:91</td>
<td>91:9</td>
<td>73%</td>
</tr>
<tr>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>O Me</td>
<td>O Ph-(m-OMe)</td>
<td>9:91</td>
<td>86:14</td>
<td>77%</td>
</tr>
<tr>
<td>10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>TBSO Pentyl</td>
<td>O Pentyl</td>
<td>15:85</td>
<td>89:11</td>
<td>50%</td>
</tr>
<tr>
<td>11&lt;sup&gt;f&lt;/sup&gt;</td>
<td>HO Ph</td>
<td>O Ph</td>
<td>16:84</td>
<td>-</td>
<td>80%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Regio- (proximal:distal lactones) and diastereoselectivities (anti: syn) were determined by GC or 1H NMR of the crude reaction mixture after PCC oxidation. b Isolated yield of combined distal lactone products. c (i) 10 mol % 3.67, 0.10 mol % p-TsOH, benzene; (ii) 3 mol % Rh(acac)(CO)<sub>2</sub>, 55 °C, 400 psi H<sub>2</sub>/CO, benzene; (iii) PCC, NaOAc, DCM. d Standard conditions except 20 mol % 3.67 and 6 mol % Rh(acac)(CO)<sub>2</sub> were used. e Standard conditions except 12 mol % 3.67 and 4 mol % Rh(acac)(CO)<sub>2</sub> were used. f Standard conditions except the hydroformylation was run at 35 °C using 5 mol % 3.67 and 2 mol % Rh(acac)(CO)<sub>2</sub>.
A variety of substrates containing an aryl substituent at the allylic position were also examined. Phenyl substituted substrate 3.74 underwent directed hydroformylation efficiently with high levels of selectivity (Table 3.11, Entry 4). Various electron-deficient and electron-rich \( \text{para} \)-substituted (Table 3.11, Entries 5 – 7) and \( \text{meta} \)-substituted (Table 3.11, Entries 8 – 9) aromatic substituents were well tolerated and afforded the \( \delta \)-lactones in a regio- and diastereoselective fashion. Highlighting the functional group tolerance of the reaction, a substrate bearing a silyl ether substituent gave the distal lactone (15:85 \( \text{rr} \)) in high levels of diastereoselectivity for the \( \text{anti} \) diastereomer (Table 3.11, Entry 10).

Subjecting terminal olefin substrate 3.81 to the hydroformylation conditions revealed that the inherent regiochemical preference is amplified in favor of the \( \delta \)-lactone. Under identical conditions using PPh\(_3\) as ligand, a 28:72 \( \text{rr} \) is obtained. Employing ligand 3.67, the six-membered lactone is isolated as the major product in 16:84 \( \text{rr} \). Given the inherent preference for terminal olefin 3.81 to form the distal lactone, it is surprising that, in the presence of ligand 3.67, the regioselectivity in favor of the \( \delta \)-lactone is not amplified higher. To explain this result, we hypothesize that the formation of the proximal isomer also proceeds through a directed pathway.

### 3.4.4 Proposed Model for Diastereoselectivity

The diastereoselectivity observed in the hydroformylation reaction correlates with the size of the substituent at the allylic position. The selective formation of the \( \text{anti} \) diastereomer of the \( \delta \)-lactone is attributed to the minimization of \( A_{1,3} \)-strain in the hydrometallation step of the reaction.

In the case of homoallylic alcohol substrate 3.54, which contains an allylic methyl substituent, the substrate prefers to adopt a conformation where the allylic substituent is
placed away from the butyl group of the olefin (Figure 3.7, Equation 1). This $A^{1,3}$-strain minimized transition state would, after hydroformylation and PCC oxidation, lead to the formation of anti-3.57. It is possible that the syn diastereomer arises from the transition state where $A^{1,3}$-strain is not minimized due to the steric interaction between the methyl and butyl substituents (Figure 3.7, Equation 2). However, due to the energetic penalty in adopting such an unfavorable conformation, it is also likely that the formation of syn-3.57 originates from an unselective background reaction.

**Figure 3.7** $A^{1,3}$-Strain Model for Observed Diastereoselectivity for Z-olefin 3.54.

In support of this hypothesis, the diastereoselectivity is amplified in favor of the anti diastereomer (91:9 dr) when a larger isopropyl substituent is placed in the allylic position (Table 3.11, Entry 3). To further demonstrate the effect of $A^{1,3}$-strain on diastereoselectivity, $E$-configured olefin substrate 3.72 affords the syn diastereomer as the major product (Figure 3.8, Equation 1). Notably, the magnitude of diastereoselection for the $E$-olefin in favor of the syn diastereomer (32:68 dr) is lower than that of the corresponding Z-olefin substrate 3.54 (87:13 dr) for the anti diastereomer. This result is
consistent with an energetic difference between the respective hydrogen (Figure 3.8, Equation 1) and butyl (Figure 3.7, Equation 1) groups interacting with the allylic methyl substituent on the substrate.

**Figure 3.8** A $^{13}$-Strain Model for Observed Diastereoselectivity for E-Olefin 3.72.

Based on this stereochemical model, increasing the size of both the allylic substituent and the vinylic group should further amplify the preference for the *anti*-δ-lactone. Attempts to synthesize such a substrate as the Z-olefin isomer were unsuccessful, presumably due to the steric repulsion between the two groups.

### 3.4.5 Probing the Importance of the Substrate Tether

A critical question for this new ligand class is where the regioselectivity in the hydroformylation reaction originates from. The preference for the δ-lactone over the γ-lactone is likely due to the formation of a less strained, larger metallacycle in the hydrometallation step during the catalytic cycle. The lowering of ring strain with
increased ring size is analogous to carbocycles that exhibit a drop in ring strain moving from 11 to 12-membered rings.

To further explore this question, the regioselective hydroformylation of allylic, homoallylic and bis-homoallylic alcohol substrates were investigated (Table 3.12). Allylic alcohol 3.82 undergoes hydroformylation with ligand 3.67 very efficiently (99% conversion) with a slight preference for the formation of the proximal product (Table 3.12, Entry 1). Employing PPh₃ rather than ligand 3.67 under identical conditions reveals a similar regiochemical preference for the proximal product (67:33 rr). Homoallylic alcohol 3.83 shows a significant preference for the distal δ-lactone product (21:79 rr) relative to the control reaction carried out with PPh₃, where a modest favorability for the proximal product exists (Table 3.12, Entry 2). Notably, the control reaction with PPh₃ is sluggish (40% conversion) compared to the corresponding reaction with 3.67 (84% conversion), which highlights the rate-accelerating affect using ligand 3.67. Bishomoallylic alcohol 3.84 exhibits minimal levels of regio-control for the distal product (Table 3.12, Entry 3). Interestingly, the reaction displays high conversion with ligand 3.67, which is in stark contrast to the control reaction using PPh₃. This result is most consistent with a directed reaction that is non-selective; however, an undirected reaction cannot be ruled out at this time.
Table 3.12 Importance of Substrate Tether Length.

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>proximal</th>
<th>distal</th>
<th>% conv&lt;sup&gt;a&lt;/sup&gt;</th>
<th>r&lt;sub&gt;b&lt;/sub&gt; (p:d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>HO&lt;sub&gt;3&lt;/sub&gt; Bn</td>
<td>O&lt;sub&gt;2&lt;/sub&gt; Bn</td>
<td>&gt; 99% (&gt; 99%)</td>
<td>58:42 (67:33)</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2</td>
<td>O&lt;sub&gt;2&lt;/sub&gt; Bn</td>
<td>O&lt;sub&gt;2&lt;/sub&gt; Bn</td>
<td>84% (40%)</td>
<td>21:79 (57:43)</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3</td>
<td>O&lt;sub&gt;2&lt;/sub&gt; Bn</td>
<td>HO&lt;sub&gt;3&lt;/sub&gt; Bn</td>
<td>89% (36%)</td>
<td>46:54 (59:41)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversion based on remaining starting material after the hydroformylation reaction using mesitylene as an internal standard. <sup>b</sup> Regioselectivities were determined by <sup>1</sup>H NMR. <sup>c</sup> Crude hydroformylation reaction was subjected to Pinnick oxidation. <sup>d</sup> Crude hydroformylation reaction was subjected to PCC oxidation. <sup>e</sup> No derivatization of the crude hydroformylation reaction was carried out. <sup>f</sup> Results in parentheses were run under identical conditions, except PPh<sub>3</sub> was used rather than 3.67.

These results demonstrate that the regiochemical outcome is dependent on the choice of tether length between the olefin and phosphine moiety, with homoallylic alcohols showing the highest degree of specificity. This is in contrast to proximal selective directing groups, which are generally more promiscuous with respect to substrate class.

### 3.5 Initial Enantioselective Results for the Asymmetric Hydroformylation of Homoallylic Alcohols

Recognizing that 3.67 contains a chiral backbone derived from t-<sup>tert</sup>-leucine, we investigated if any asymmetric induction could be observed in the reaction (Table 3.13). Employing homoallylic substrate 3.83 under the optimal conditions for diastereoselective
hydroformylation of homoallylic alcohols (Section 3.4), δ-lactone 3.86 was isolated in 19% ee. A pressure screen was carried out to see its effect on enantioselectivity. Decreasing the pressure from 400 psi to 100 psi afforded an increase in conversion, with full consumption of starting material observed when the reaction was run at 100 psi. While the regiochemical preference for the 3.86 was relatively unchanged, an increase in the enantioselectivity was observed at lower pressures. The highest level of asymmetric induction was observed at 100 psi, with the δ-lactone isolated in 37% ee (Table 3.13, Entry 3).24

**Table 3.13 Effect of Pressure on Enantioselectivity for 3.83.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>Conversion (%)a</th>
<th>rr (3.85:3.86)a</th>
<th>ee b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>84</td>
<td>21:79</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>94</td>
<td>29:71</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>quant</td>
<td>23:77</td>
<td>37</td>
</tr>
</tbody>
</table>


a Based on 1H NMR using 1,3,5-trimethoxybenzene as an internal standard. b Determined by high pressure liquid chromatography.

Under slightly modified reaction conditions with ligand 3.67, δ-lactone 3.86 is still formed selectively (17:83 rr) and in 34% ee (Scheme 3.17). It is interesting to note that the proximal lactone is isolated in 20% ee. Taken together with the hydroformylation of terminal olefin 3.81 (Table 3.11, Entry 11) and bishomoallylic alcohol 3.84 (Table

3.12, Entry 3), this further demonstrates that both the proximal and distal lactone products are formed via a directed pathway.

**Scheme 3.17** Determination of the Enantiomeric Excess for the Proximal Lactone.

A styrenyl substrate (3.87) was also tested in enantioselective hydroformylation using ligand 3.67. Based on $\eta^3$-coordination of the rhodium catalyst to the conjugated system, this substrate should possess an inherent preference to form the distal isomer; however, since it is also a 1,2-disubstituted alkene, it is likely less reactive than a corresponding terminal styrenyl substrate. Employing PPh$_3$ as ligand under the optimal conditions for diastereoselective hydroformylation affords the distal lactone selectively (25:75 $\text{rr}$). This inherent substrate selectivity is enhanced in the presence of ligand 3.67 to 15:85 $\text{rr}$ in favor of $\delta$-lactone 3.89 (Table 3.14, Entry 1). Under these conditions, 3.89 is isolated in 19% ee (Table 3.14, Entry 1). A pressure screen revealed that the regiochemical outcome is not strongly affected by the change in pressure, but slightly elevated conversions are observed at lower pressures. Whereas enantioselectivity and pressure exhibited an inverse relationship in the case of 3.83 (Table 3.13), lowering the pressure using styrenyl substrate 3.87 afforded the $\delta$-lactone in 12% ee (Table 3.14, Entry 3).
Table 3.14 Effect of Pressure on Enantioselectivity for Styrenyl Substrate 3.87.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>Conversion (%)</th>
<th>$rr\ (3.88:3.89)^a$</th>
<th>ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>55 (33)$^c$</td>
<td>15:85</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
<td>65</td>
<td>(25:75)$^c$</td>
<td>(--)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>63</td>
<td>18:82</td>
<td>12</td>
</tr>
</tbody>
</table>

$^a$ Based on $^1$H NMR using 1,3,5-trimethoxybenzene as an internal standard. $^b$ Determined by high pressure liquid chromatography. $^c$ Reaction run using PPh$_3$ as ligand rather than ligand 3.67.

In contrast to the diastereoselective hydroformylation of homoallylic alcohols bearing an allylic stereocenter, straight chain homoallylic alcohols afford low levels of enantioselectivity. In the case of diastereoselective hydroformylation, the selectivity is a result of a substrate-controlled mechanism (Section 3.4.4). Further supporting a substrate-controlled model for diastereoselectivity, a modest matched/mis-matched relationship is observed for homoallylic alcohol substrates bearing an allylic stereocenter for enantiopure substrates with ligand 3.46 (Table 3.4). This observation is consistent with low levels of enantioselectivity for straight chain homoallylic alcohols. The lack of adequate catalyst control in the hydroformylation reaction results in poor asymmetric induction for this substrate class. Modifications to the ligand scaffold should help alleviate these issues, particularly through the synthesis of the appropriate diastereomer of ligand to impart conformational rigidity on the hydrometallation transition state to allow for effective discrimination between the faces of the olefin.
3.6 Conclusions

In the hydroformylation of unactivated 1,2-disubstituted olefins, the challenge of directing to the distal olefinic carbon has gone relatively unaddressed. A highly tunable catalytic directing group has been developed. Through a rational design approach, a small library of ligands was synthesized to probe the effect of steric on the oxazolidine ring and the phosphine electronics on the hydroformylation reaction. Having identified 3.67 as the optimal ligand, it has been used to carry out the distal and diastereoselective hydroformylation of homoallylic alcohols bearing allylic stereocenters to afford anti-δ-lactone products. Altering the distance between the alcohol and olefin functionality revealed that homoallylic alcohols afforded the δ-lactone with the highest levels of regioselectivity. Although modest, ligand 3.67 can influence the stereochemical outcome of the reaction, affording δ-lactone product 3.86 in 37% ee. Together with previous examples of proximal-selective hydroformylation, these results begin to more fully address the challenge of controlling regioselectivity in hydroformylation.

3.7 Experimental Section

3.7.1 General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using Silicycle silica gel, SiliaFlash P60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed
solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). \(^1\)H, \(^{13}\)C, \(^{31}\)P, and \(^{19}\)F NMR were performed on either Varian Gemini 400 MHz, Varian Unity Inova 500 MHz, Varian Gemini 500 MHz, or Varian 600 MHz spectrometers. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. \(\text{C}_6\text{D}_6\) was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for \(^1\)H and \(^{13}\)C and external standard (neat \(\text{H}_3\text{PO}_4\)) for \(^{31}\)P NMR. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm\(^{-1}\). HRMS and X-ray crystal structure data were generated in Boston College facilities. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. An Agilent Technologies 7890A gas chromatography system equipped with a 7683B Series Injector was used to introduce samples into a J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 µm film thickness) or Supelco Gamma Dex 120 (30 m x 0.25 mm x 0.25 µm film thickness). Detection was by FID and data was worked up with Agilent Technologies GC ChemStation software. Retention times are reported in minutes. Hydroformylation was performed in an Argonaut Technologies Endeavor\textsuperscript{©} Catalyst Screening System using 1:1 \(\text{H}_2/\text{CO}\) supplied by Airgas, Inc.
3.7.2 Characterization of Ligands

The following compounds were synthesized according to literature procedures and matched all reported spectroscopic data: (3-bromophenyl)diphenylphosphane, 25 3-(diphenylphosphanyl)benzaldehyde, 26 bis(4-methoxyphenyl)phosphate oxide, 27 bis(4-(trifluoromethyl)phenyl)phosphine oxide, 28 bis(3,5-bis(trifluoromethyl)phenyl)phosphine oxide 29

General Procedure A (Reductive Amination): To a round-bottom flask containing 4 Å molecular sieves was added the 3-phosphino benzaldehyde (1 equivalent) and amino alcohol (1.5 – 1.7 equivalents) in THF (0.3 M relative to benzaldehyde). The solution was heated to 50 °C with vigorous stirring. After 6 hours, the molecular sieves were filtered off and the resulting mixture was concentrated to a viscous residue, which was dissolved in anhydrous methanol (0.3 M). The solution was cooled to 0 °C, sodium borohydride was added (3 equivalents), and the reaction was allowed to warm to room temperature over 2 hours. The methanol was removed under reduced pressure, the residue was diluted with dichloromethane (20 mL), and the reaction was quenched by the addition of water (10 mL) at 0 °C. The aqueous layer was extracted dichloromethane (2 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification by column chromatography afforded the title compound.

**General Procedure B (Ligand Closure):** $N,N$-dimethylformamide dimethylacetal (5 equivalents) was added to a solution of amino alcohol from the reductive amination (1 equivalent) in freshly distilled methanol (0.1 M relative to amino alcohol) and the reaction was stirred at room temperature for 3 hours. The volatiles were removed on high vacuum and the residue was re-dissolved in dry methanol (0.1 M). After stirring for 2 hours at room temperature, the volatiles were removed under vacuum. The crude residue was brought into the glovebox and extracted with dry, degassed pentane (2 x 15 mL). Removal of the pentane under vacuum afforded the title compound.

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

**2-((3-(diphenylphosphanyl)benzyl)amino)-2-methylpropan-1-ol.** Synthesized according to the General Procedure A for reductive amination. Imine formation was carried out with 3-(diphenylphosphanyl)benzaldehyde (500 mg, 1.72 mmol) and 2-amino-2-methylpropan-1-ol (250 mg, 2.97 mmol) in THF (9 mL). Reduction of the imine occurred in methanol (9 mL) with sodium borohydride (195 mg, 5.15 mmol). Purification by column chromatography (50% EtOAc/Hex containing 1% Et$_3$N) afforded the title compound as a colorless solid (469 mg, 76%).

**$^1$H NMR** (CDCl$_3$, 500 MHz) δ 7.28 – 7.35 (m, 12H), 7.26 – 7.27 (m, 1H), 7.13 – 7.16 (m, 1H), 3.63 (s, 2H), 3.30 (s, 2H), 1.10 (s, 6H); **$^{13}$C NMR** (CDCl$_3$, 126 MHz) δ 141.2 (d, $J_{C-P} = 7.6$ Hz), 137.6 (d, $J_{C-P} = 11.4$ Hz), 137.4 (d, $J_{C-P} = 10.5$ Hz), 133.9 (d, $J_{C-P} = 20.0$ Hz), 133.7 (d, $J_{C-P} = 23.8$ Hz), 132.5 (d, $J_{C-P} = 16.2$ Hz), 128.9, 128.8 (d, $J_{C-P} = 5.7$ Hz), 128.7, 128.6 (d, $J_{C-P} = 6.7$ Hz), 68.6, 54.2, 46.4, 24.4; **$^{31}$P NMR** (CDCl$_3$, 202 MHz) δ – 5.4; **IR:** 2967, 1476, 1433, 1051, 742, 694, 467
cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{23}\)H\(_{27}\)N\(_1\)O\(_1\)P\(_1\) [M+H]\(^+\): 364.1830, found: 364.1837.

3-(3-(diphenylphosphanyl)benzyl)-2-methoxy-4,4-dimethyloxazolidine. Synthesized according to the General Procedure B using \(N,N\)-dimethylformamide dimethylacetal (814 µL, 6.13 mmol) and 2-((3-(diphenylphosphanyl)benzyl)amino)-2-methylpropan-1-ol (446 mg, 1.23 mmol) in freshly distilled methanol (12 mL). The closure was cycled with anhydrous methanol (12 mL). Extraction with pentane (2 x 10 mL) and removal of pentane under vacuum afforded the title compound as a colorless solid (457 mg, 92%).

**\(^1\)H NMR** (C\(_6\)D\(_6\), 500 MHz) \(\delta\) 7.57 (d, 1H, \(J = 7.8\) Hz), 7.43 (dt, 4H, \(J = 7.8, 1.5\) Hz), 7.31 – 7.34 (m, 1H), 7.28 (d, 1H, \(J = 7.3\) Hz), 7.03 – 7.12 (m, 7H), 5.16 (s, 1H), 3.65 (d, 1H, \(J = 4.9\) Hz), 3.63 (d, 1H, \(J = 11.7\) Hz), 3.51 (d, 1H, \(J = 7.3\) Hz), 3.43 (d, 1H, \(J = 14.1\) Hz), 3.01 (s, 3H), 0.90 (s, 3H), 0.82 (s, 3H); **\(^{13}\)C NMR** (CDCl\(_3\), 101 MHz) \(\delta\) 140.2 (d, \(J_{C-P} = 6.9\) Hz), 137.5 (d, \(J_{C-P} = 9.2\) Hz), 137.0 (d, \(J_{C-P} = 10.7\) Hz), 134.2 (d, \(J_{C-P} = 19.8\) Hz), 133.9 (d, \(J_{C-P} = 19.1\) Hz), 133.3 (d, \(J_{C-P} = 19.8\) Hz), 129.4, 128.9, 128.7 (d, \(J_{C-P} = 6.7\) Hz), 128.6 (d, \(J_{C-P} = 6.7\) Hz), 128.6 (d, \(J_{C-P} = 6.9\) Hz), 112.2, 78.5, 59.5, 51.0, 47.1, 24.4, 22.9; **\(^{31}\)P NMR** (C\(_6\)D\(_6\), 202 MHz) \(\delta\) – 5.4; **IR**: 2965, 2877, 1726, 1476, 1433, 1387, 1323, 1245, 1092, 1076, 1039, 940, 743, 695, 495 cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{25}\)H\(_{29}\)N\(_1\)O\(_2\)P\(_1\) [M+H]\(^+\): 406.1936, found: 406.1918.

(S)-2-((3-(diphenylphosphanyl)benzyl)amino)-3-methylbutan-1-ol. A solution of (S)-2-amino-3-methylbutan-1-ol (1.97 g, 19.1 mmol) and 3-(diphenylphosphanyl)benzaldehyde (3.69 g, 12.7
mmol) in DCM (100 mL) was stirred at room temperature for 3 hours. Triethylamine (2.7 mL, 19 mmol) and NaBH(OAc)$_3$ (5.38 g, 25.4 mmol) were added to the flask and the reaction as allowed to stir at room temperature overnight. The reaction was partitioned between water (70 mL) and DCM (150 mL). The organic layer was washed with an additional portion of water (70 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1% Et$_3$N/EtOAc) to afford the title compound as a colorless oil (4.18 g, 88%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.27 – 7.35 (m, 13 H), 7.15 – 7.19 (m, 1H), 3.78 (d, 1H, $J$ = 13.0 Hz), 3.71 (d, 1H, $J$ = 13.5 Hz), 3.59 (dd, 1H, $J$ = 10.5, 4.0 Hz), 3.33 (dd, 1H, $J$ = 11.0, 4.0 Hz), 2.38 – 2.42 (m, 1H), 1.80 – 1.85 (m, 1H), 0.92 (d, 3H, $J$ = 7.0 Hz), 0.87 (d, 3H, $J$ = 7.0 Hz);

$^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 140.9 (d, $J_{C-P}$ = 7.9 Hz), 137.7 (d, $J_{C-P}$ = 11.2 Hz), 137.4 (d, $J_{C-P}$ = 2.2 Hz), 137.3, 133.9 (d, $J_{C-P}$ = 19.1 Hz), 133.7 (d, $J_{C-P}$ = 21.3), 132.6 (d, $J_{C-P}$ = 16.8 Hz), 128.9 (d, $J_{C-P}$ = 11.2 Hz), 128.9 (d, $J_{C-P}$ = 5.6 Hz), 128.7 (d, $J_{C-P}$ = 6.7 Hz), 63.9, 60.6, 51.4, 29.0, 19.8, 18.6; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 5.4; IR: 3367, 2957, 2872, 1586, 1476, 1434, 1180, 1092, 1042, 998, 788, 744, 696, 497 cm$^{-1}$;

HRMS (DART-TOF) calcd. for C$_{24}$H$_{29}$N$_1$O$_1$P$_1$ [M+H]$^+$: 378.1987, found: 378.1975; $\left[\alpha\right]_D^{20} = +3.86$ ($c$ = 0.680, CHCl$_3$, $l$ = 50 mm).

(4S)-3-(3-(diphenylphosphanyl)benzyl)-4-isopropyl-2-methoxyoxazolidine. Followed General Procedure B with (S)-2-((3-(diphenylphosphanyl)benzyl)amino)-3-methylbutan-1-ol (1.23 g, 3.28 mmol), freshly distilled methanol (32 mL) and $N,N$-dimethylformamide dimethylacetal (2.2 mL 16 mmol). Extraction with with pentane (2 x 20 mL) and removal of the volatiles were removed under vacuum yielded the pure product as a
colorless oil that exists as a 1:1 mixture of diastereomers (1.09 g, 80%). $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 7.58 (d, 0.5H, $J = 7.8$ Hz), 7.47 (d, 0.5H, $J = 7.8$ Hz), 7.40-7.37 (m, 4H), 7.33-7.27 (m, 1.5H), 7.20 (d, 0.5H, $J = 7.8$ Hz), 7.09-6.99 (m, 7H), 5.15 (s, 0.5H), 5.04 (s, 0.5H), 3.86 (dd, 0.5H, $J = 8.3$, 7.8 Hz), 3.83 (d, 0.5H, $J = 13.2$ Hz), 3.69 (dd, 0.5H, $J = 7.3$, 7.8 Hz), 3.64 (dd, 0.5H, $J = 7.8$, 5.9 Hz), 3.63 (d, 0.5H, $J = 10.0$ Hz), 3.54 (dd, 1H, $J = 14.7$, 13.2 Hz), 3.40 (d, 0.5H, $J = 14.2$ Hz), 3.01 (s, 1.5H), 2.95 (s, 1.5H), 2.94 – 2.90 (m, 0.5H), 2.44 (app q, 0.5H, $J = 7.3$ Hz), 1.56-1.49 (m, 1H), 0.74 (d, 1.5H, $J = 6.9$ Hz), 0.65 (d, 1.5H, $J = 3.4$ Hz), 0.63 (d, 1.5H, $J = 3.4$ Hz), 0.57 (d, 1.5H, $J = 6.9$ Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 139.6 (d, $J_{C,P} = 6.7$ Hz), 139.2 (d, $J_{C,P} = 6.7$ Hz), 137.2 – 137.5 (6 signals), 134.5 (d, $J_{C,P} = 9.5$ Hz), 134.3 (d, $J_{C,P} = 10.5$ Hz), 133.9 (d, $J_{C,P} = 20.0$ Hz), 132.9 (d, $J_{C,P} = 20.0$ Hz), 132.6 (d, $J_{C,P} = 19.1$ Hz), 129.6 (d, $J_{C,P} = 19.1$ Hz), 128.9, 128.7 (d, $J_{C,P} = 6.7$ Hz), 128.6 (d, $J_{C,P} = 13.4$ Hz), 114.6, 110.6, 68.4, 67.5, 66.0, 63.6, 57.0, 52.9, 51.4, 50.1, 31.1, 28.6, 20.4, 19.6, 17.7, 15.5; $^{31}$P NMR (C$_6$D$_6$, 202 MHz) $\delta$ – 5.4, – 5.5; IR: 3069, 2929, 2279, 1884, 1817, 1585, 1364, 1155, 1057, 744, 697, 494 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{26}$H$_{31}$N$_1$O$_2$P$_1$ [M+H]$^+$: 420.2092, found: 420.2099; $[\alpha]_D^{20} = + 34.7$ (c = 0.480, CHCl$_3$, l = 50 mm).

(3-bromophenyl)-bis-(4-methoxyphenyl)phosphine oxide. To a 100 mL, flame-dried, round-bottom flask in the glovebox was added bis(dibenzylideneacetone)palladium (317 mg, 0.552 mmol) and 1,3-bis-(diphenylphosphino)-propane (228 mg, 0.552 mmol). The flask was fitted with a dry reflux condenser, and the apparatus was brought out of the glovebox and placed under argon. Toluene (22 mL), bis(4-methoxyphenyl)phosphate oxide (4.00 g,
15.3 mmol), 1-bromo-3-iodobenzene (2.35 mL, 18.4 mmol), and Hunig’s base (3.37 mL, 19.3 mmol) were added to the flask successively. The reaction was heated to reflux overnight. After being cooled to room temperature, the crude mixture was partitioned between water (20 mL) and ethyl acetate (70 mL). The layers were separated and the aqueous layer was extracted with an additional portion of ethyl acetate (50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (2% Et₃N/EtOAc) to afford an off white solid (3.31 g, 52%). ¹H NMR ((CD₃)₂CO, 500 MHz) δ 7.81 (d, 1H, J = 11.7 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.65 (s, 1H), 7.61 (app dd, 4H, J = 11.3 Hz, 8.8 Hz), 7.46 – 7.50 (app dt, 1H, J = 7.8 Hz, 2.9 Hz), 7.09 (app dd, 4H, J = 8.8 Hz, 2.0 Hz), 3.87 (s, 6H); ¹³C NMR (CDCl₃, 126 MHz) δ 162.8 (d, J_C-P = 2.7 Hz), 136.5 (d, J_C-P = 101 Hz), 134.8 (d, J_C-P = 2.9 Hz), 134.4 (d, J_C-P = 10.5 Hz), 133.7 (d, J_C-P = 11.4 Hz), 130.6 (d, J_C-P = 8.6 Hz), 130.2 (d, J_C-P = 13.4 Hz), 123.4 (d, J_C-P = 112 Hz), 123.2 (d, J_C-P = 14.3 Hz), 114.3 (d, J_C-P = 13.4 Hz), 55.5; ³¹P NMR (CDCl₃, 202 MHz) δ + 27.5; IR: 1595, 1502, 1254, 1177, 1118, 802, 547 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₀H₁₅Br₁O₃P₁ [M+H]⁺: 417.0255, found: 417.0249.

(3-bromophenyl)-bis-(4-methoxyphenyl)phosphine. To a solution of (3-bromophenyl)bis(4-methoxyphenyl)-phosphine oxide (3.22 g, 7.72 mmol) in toluene (77 mL) was added triethylamine (5.90 mL, 42.5 mmol). The solution was cooled to 0 °C and trichlorosilane (3.90 mL, 38.6 mmol) was added slowly to the stirring solution. The flask
was fitted with a reflux condenser and the solution was heated to reflux overnight. The reaction was cooled to 0 °C and quenched by the addition of 30% NaOH (40 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and the combined organic layers were washed with an additional portion of water (30 mL). The organic layer was dried over MgSO₄, filtered, and concentrated to yield an opaque oil that was used in the next step without purification (3.00 g, 97%). 

**1H NMR** (CDCl₃, 500 MHz) δ 7.41 – 7.43 (m, 1H), 7.34 (d, 1H, J = 6.5 Hz), 7.24 – 7.27 (m, 5H), 7.16 – 7.18 (m, 1H), 6.90 (d, 4H, J = 8.5 Hz), 3.81 (s, 6H); **13C NMR** (CDCl₃, 126 MHz) δ 160.6, 142.3 (d, J_C-P = 15.3 Hz), 135.6 (d, J_C-P = 21.9 Hz), 135.5 (d, J_C-P = 19.1 Hz), 131.7 (d, J_C-P = 19.1 Hz), 131.4, 130.1 (d, J_C-P = 5.7 Hz), 127.6 (d, J_C-P = 7.6 Hz), 123.2 (d, J_C-P = 6.7 Hz), 114.6 (d, J_C-P = 8.6 Hz), 55.4; **31P NMR** (CDCl₃, 202 MHz) δ – 7.8; **IR**: 1596, 1500, 1255, 1179, 1120, 829, 548 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₀H₁₉BrO₂P₁ [M+H]⁺: 401.0306, found: 401.0291.

**3-(bis(4-methoxyphenyl)phosphino)benzaldehyde.** To a -78 °C solution of (3-bromophenyl)-bis-(4-methoxyphenyl)phosphine (3.23 g, 8.05 mmol) in THF (81 mL) was added n-BuLi (3.63 mL, 8.86 mmol, 2.44 M solution in hexane). After stirring at this temperature for 50 minutes, DMF (1.20 mL, 16.1 mmol) was added and the resulting solution was warmed to room temperature over 4 hours. The reaction was quenched by the addition of saturated ammonium chloride (60 mL) and extracted with ethyl acetate (150 mL). The organic layer was extracted with an additional portion of water (40 mL), dried over MgSO₄, filtered, and concentrated in
Purification of the crude reaction mixture on silica gel (15% EtOAc/Hex) afforded the title compound as a colorless oil (1.53 g, 57%).  

**¹H NMR** (CDCl₃, 500 MHz) δ 9.93 (s, 1H), 7.81 (d, 1H, J = 6.8 Hz), 7.74 (d, 1H, J = 6.8 Hz), 7.45 – 7.51 (m, 2H), 7.25 – 7.29 (m, 4H), 6.91 (d, 4H, J = 8.3 Hz), 3.82 (s, 6H);  

**¹³C NMR** (CDCl₃, 126 MHz) δ 192.4, 160.8, 141.1 (d, Jₐₚ = 13.4 Hz), 138.9 (d, Jₐₚ = 18.1 Hz), 136.5 (d, Jₐₚ = 4.8 Hz), 135.6 (d, Jₐₚ = 21.0 Hz), 134.8 (d, Jₐₚ = 19.1 Hz), 129.2 (d, Jₐₚ = 5.7 Hz), 129.0, 127.4 (d, Jₐₚ = 7.6 Hz), 114.6 (d, Jₐₚ = 8.6 Hz), 55.4;  

**³¹P NMR** (CDCl₃, 202 MHz) δ – 8.8;  

**IR**: 1698, 1594, 1498, 1287, 1250, 1178, 828 cm⁻¹;  


(5)-2-(((3-(bis(4-methoxyphenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol. To a flame-dried, round-bottom flask was added 3-(bis(4-methoxyphenyl)phosphino)benzaldehyde (700 mg, 2.09 mmol), (S)-2-amino-3-methylbutan-1-ol (323 mg, 3.14 mmol), and dichloromethane (21 mL). After the mixture was stirred at room temperature for 3.5 hours, triethylamine (.437 mL, 3.14 mmol) and NaBH(OAc)₃ (887 mg, 4.18 mmol) were added to the flask and the reaction was stirred at room temperature overnight. The mixture was diluted with water (25 mL) and extracted with dichloromethane (2 x 40 mL). The combined organics were dried over MgSO₄, filtered and concentrated. Silica gel chromatography (2% Et₃N/EtOAc) afforded a colorless oil (674 mg, 77%). 

**¹H NMR** (CDCl₃, 500 MHz) δ 7.21 – 7.28 (m, 7H), 8.11-7.14 (m, 1H), 6.89 (d, 4H, J = 8.3 Hz), 3.81 (s, 6H), 3.79 (d, 1H, J = 13.2 Hz), 3.73 (d, 1H, J = 13.2 Hz), 3.59 (dd, 1H, J = 10.8 Hz, 3.9 Hz), 3.34 (dd, 1H, J = 10.7 Hz, 6.8 Hz),
2.39 – 2.42 (m, 1H), 1.80 – 1.84 (m, 1H), 0.92 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 7.0 Hz); 13C NMR (CDCl3, 126 MHz) δ 160.5 140.7 (d, J_C-P = 6.7 Hz), 139.1 (d, J_C-P = 10.5 Hz), 135.5 (d, J_C-P = 21.0 Hz), 133.1 (d, J_C-P = 21.0 Hz), 132.0 (d, J_C-P = 16.2 Hz), 128.7 (d, J_C-P = 5.7 Hz), 128.5 (d, J_C-P = 11.5 Hz), 128.3, 114.4 (d, J_C-P = 7.6 Hz), 63.9, 60.5, 55.4, 51.4, 29.0, 19.8, 18.6; 31P NMR (CDCl3, 202 MHz) δ – 8.6; IR: 3346, 2955, 1593, 1496, 1245, 1176, 826, 531 cm⁻¹; HRMS (DART-TOF) calcd. for C26H33N1O3P1 [M+H]+: 438.2198, found: 438.2189; [α]D²⁰ = + 6.5 (c = 0.550, CHCl3, l = 50 mm).

(4S)-3-(3-(bis(4-methoxyphenyl)phosphino)benzyl)-4-isopropyl-2-methoxyoxazolidine. Followed General Procedure B using (S)-2-((3-(bis(4-methoxyphenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol (620 mg, 1.48 mmol), methanol (25 mL) and N,N-dimethylformamide dimethyl acetal (1.00 mL, 7.39 mmol). Extraction of the crude residue with dry, degassed pentane (2 x 15 mL) and removal of the volailes under vacuum afforded the title compound as a viscous oil that exists as a mixture of two diastereomers in a 1:1 ratio (618 mg, 90%). 1H NMR (C6D6, 500 MHz) δ 7.66 (d, 0.5H, J = 7.8 Hz), 7.54 (d, 0.5H, J = 7.8 Hz), 7.34 – 7.46 (m, 5H), 7.24 (d, 0.5H, J = 7.8 Hz), 7.12 – 7.19 (m, 1.5H), 6.72 – 6.76 (m, 4H), 5.24 (s, 0.5H), 5.12 (s, 0.5H), 3.91 (d, 0.5H, J = 12.7 Hz), 3.90 (d, 0.5H, J = 8.3 Hz), 3.74 (t, 0.5H, J = 7.6 Hz), 3.59 – 3.70 (m, 2H), 3.49 (d, 0.5H, J = 14.2 Hz), 3.24 (s, 6H), 3.09 (s, 1.5H), 3.02 (s, 1.5H), 2.97 – 3.00 (m, 0.5H), 2.52 (q, 0.5H, J = 7.3 Hz), 1.58 – 1.62 (m, 1H), 0.81 (d, 1.5H, J = 6.9 Hz), 0.71 (d, 1.5H, J = 6.9 Hz), 0.70 (d, 1.5H, J = 6.9 Hz), 0.63 (d, 1.5H, J = 6.9 Hz); 13C NMR (CDCl3, 126 MHz) δ 160.5, 160.4 (d, J_C-P = 2.7 Hz), 139.4 (d, J_C-P = 5.7 Hz),
139.0 (d, $J_{C,P} = 6.2$ Hz), 138.5 – 138.8 (4 lines), 135.3 – 135.5 (6 signals), 132.8 (d, $J_{C,P}$ = 9.5 Hz), 133.7 (d, $J_{C,P} = 9.5$ Hz), 132.2 (d, $J_{C,P} = 18.1$ Hz), 131.9 (d, $J_{C,P} = 19.1$ Hz), 129.2 (d, $J_{C,P} = 20.0$ Hz), 128.4 – 129.7 (7 signals), 114.4 – 114.5 (4 signals), 68.3, 67.4, 66.0, 63.5, 57.0, 55.4, 52.8, 51.4, 50.1, 31.1, 28.5, 20.3, 19.5, 17.6, 15.4; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ = 8.67, – 8.71; IR: 2954, 1592, 1496, 1244, 1176, 1029, 825, 529 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{28}$H$_{35}$N$_1$O$_4$P$_1$ [M+H]$^+$: 480.2304, found: 480.2286; $[\alpha]_D^{20}$ = +10.4 (c = 0.405, CDCl$_3$, l = 50 mm).

(3-bromophenyl)bis(4-(trifluoromethyl)phenyl)phosphine oxide. To a flame-dried, 25-mL, round-bottom flask in a dry box was added bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.50 g, 4.44 mmol), bis(dibenzylideneacetone)palladium (926 mg, 0.160 mmol), and 1,3-bis(diphenylphosphino)propane (660 mg, 0.160 mmol). The flask was brought out of the dry box and was placed under nitrogen. The flask was charged, successively, with toluene (5 mL), 3-bromo-1-iodobenzene (0.682 mL, 5.35 mmol), and N,N-diisopropylethylamine (1.01 mL, 5.62 mmol) and the reaction was heated to reflux overnight. The reaction was cooled to room temperature and was partitioned between water (20 mL) and DCM (40 mL). The aqueous layer was washed with an additional portion of DCM (40 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (20% EtOAc/Hex containing 1% Et$_3$N) to yield the title compound as colorless solid (1.91 g, 88%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.74 – 7.83 (m, 10H), 7.56 (dd, 1H, $J = 12.0$, 8.0 Hz), 7.39 (dt, 1H, $J = 8.0$, 3.5 Hz); $^{13}$C NMR (CDCl$_3$, 151 MHz) $\delta$
136.1 (d, $J_{C-P} = 3.1$ Hz), 135.7 (d, $J_{C-P} = 103.0$ Hz), 134.7 (d, $J_{C-P} = 10.7$ Hz), 134.6 (dq, $J_{C-P,F} = 32.8, 3.1$ Hz), 133.7 (d, $J_{C-P} = 103.0$ Hz), 132.7 (d, $J_{C-P} = 10.7$ Hz), 130.8 (d, $J_{C-P} = 13.0$ Hz), 130.6 (d, $J_{C-P} = 9.9$ Hz), 126.0 – 126.1 (m), 123.9 (d, $J_{C-P} = 15.3$ Hz), 123.6 (d, $J_{C-F} = 273$ Hz); $^{19}$F NMR (CDCl$_3$, 470 MHz) δ – 63.8; $^{31}$P NMR (CDCl$_3$, 202 MHz) δ + 25.3; IR: 3057, 1611, 1504, 1321, 1128, 1062, 836, 766, 685, 572 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{20}$H$_{13}$Br$_1$F$_6$O$_1$P$_1$ [M+H]$^+$: 492.9713, found: 492.9792.

(3-bromophenyl)bis(4-(trifluoromethyl)phenyl)phosphane. To a flame-dried flask was added (3-bromophenyl)bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.00 g, 2.03 mmol), Et$_3$N (1.57, 11.2 mmol), and toluene (20 mL). The solution was cooled to 0 °C and trichlorosilane was added dropwise. The flask was fitted with a reflux condenser and the reaction was heated to reflux overnight. The solution was cooled to room temperature, quenched by the addition of 30% NaOH (30 mL), and further diluted with water (10 mL). The aqueous layer was extracted with DCM (3 x 40 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (20% EtOAc/Hex) afforded the title compound as a colorless oil (932 mg, 95%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.63 (d, 4H, $J = 8.0$ Hz), 7.55 (d, 1H, $J = 8.0$ Hz), 7.45 (d, 1H, $J = 7.5$ Hz), 7.40 (t, 4H, $J = 8.0$ Hz), 7.21 – 7.22 (m, 2H); $^{13}$C NMR (CDCl$_3$, 151 MHz) δ 140.6 (d, $J_{C-P} = 13.7$ Hz), 137.9 (d, $J_{C-P} = 14.4$ Hz), 136.3 (d, $J_{C-P} = 22.0$ Hz), 133.8 (d, $J_{C-P} = 19.8$ Hz), 133.0, 132.5 (d, $J_{C-P} = 19.5$ Hz), 131.4 (q, $J_{C-P} = 33.0$ Hz), 130.5 (d, $J_{C-P} = 6.8$ Hz), 128.8 (d, $J_{C-P} = 24.8$ Hz), 125.6 – 125.6 (m), 125.2 (q, $J_{C-F} = 272$ Hz), 123.5 (d, $J_{C-P} = 8.4$ Hz); $^{19}$F NMR (CDCl$_3$, 470 MHz) δ – 62.9; $^{31}$P

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NMR (CDCl₃, 202 MHz) δ – 5.3; IR: 1606, 1396, 1166, 1106, 831, 781, 686 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₀H₁₃Br₁F₆P₁ [M+H]⁺: 476.9842, found: 476.9842.

3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzaldehyde. To a flame-dried, round-bottom flask was added (3-bromophenyl)-bis((4-trifluoromethyl)phenyl)phosphine (789 mg, 1.84 mmol) and THF (10 mL). The solution was cooled to –78 °C, n-BuLi (0.884 mL, 2.21 mmol, 2.50 M solution in hexane) was added dropwise, and the reaction was stirred for 30 minutes at this temperature. N,N-dimethylformamide (0.226 mL, 23.0 mL) was added to the solution and the cold bath was removed. The reaction continued to stir at room temperature for 2 hours and was quenched by the addition of water (10 mL). The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, a concentrated in vacuo. The crude reaction was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (371 mg, 47%). ¹H NMR (CDCl₃, 500 MHz) δ 9.98 (s, 1H), 7.92 (d, 1H, J = 7.3 Hz), 7.86 (d, 1H, J = 7.8 Hz), 7.64 (d, 4H, J = 7.8 Hz), 7.53 – 7.58 (m, 2H), 7.41 (t, 4H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 126 MHz) δ 191.8, 140.7 (d, J_C-P = 14.3 Hz), 139.6 (d, J_C-P = 19.1 Hz), 137.2 (d, J_C-P = 14.3 Hz), 137.0 (d, J_C-P = 6.7 Hz), 135.3 (d, J_C-P = 22.9 Hz), 134.1 (d, J_C-P = 20.2 Hz), 131.7 (q, J_C-F = 32.4 Hz), 130.8, 129.9 (d, J_C-P = 5.7 Hz), 125.7 – 125.9 (m), 124.0 (q, J_C-F = 273 Hz); ¹⁹F NMR (CDCl₃, 470 MHz) δ – 62.9; ³¹P NMR (CDCl₃, 202 MHz) δ – 6.1; IR: 3062, 2852, 2302, 1926, 1701, 1397, 1124, 1060, 1016, 794, 600 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₁H₁₄F₆O₁P₁ [M+H]⁺: 427.0687, found: 427.0683.
(S)-2-((3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)phenyl)phosphanyl)benzyl)amino)-3-methylbutan-1-ol. General Procedure A was followed using 3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzaldehyde (697 mg, 1.64 mmol) and (S)-2-amino-3-methylbutan-1-ol (253 mg, 2.45 mmol) and THF (9 mL). The imine was reduced in methanol (9 mL) with NaBH₄ (185 mg, 4.90 mmol). Silica gel chromatography (50% EtOAc/Hex containing 1% Et₃N) yielded the title compound as a colorless oil (737 mg, 50%).

**1H NMR** (CDCl₃, 500 MHz) δ 7.60 (d, 4H, J = 8.0 Hz), 7.31 – 7.41 (m, 7H), 7.18 (d, 1H, J = 7.5 Hz), 3.82 (d, 1H, J = 13.0 Hz), 3.74 (d, 1H, J = 13.5 Hz), 3.60 (dd, 1H, J = 11.0, 4.0 Hz), 3.35 (dd, 1H, J = 10.5, 6.5 Hz), 2.40 – 2.44 (m, 1H), 1.79 – 1.86 (m, 1H), 0.92 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 6.5 Hz);

**13C NMR** (CDCl₃, 126 MHz) δ 141.7 (d, Jₐ₁₈ = 14.5 Hz), 141.6 (d, Jₐ₁₈ = 8.4 Hz), 135.3 (d, Jₐ₁₈ = 10.7 Hz), 134.1 (d, Jₐ₁₈ = 23.7 Hz), 134.0 (d, Jₐ₁₈ = 19.8 Hz), 132.9 (d, Jₐ₁₈ = 17.6 Hz), 131.3 (q, Jₐ₁₈ = 32.8 Hz), 129.8, 129.4 (d, Jₐ₁₈ = 6.9 Hz), 125.5 – 125.7 (m), 124.2 (q, Jₐ₁₈ = 272 Hz), 64.1, 60.7, 51.3, 29.0, 19.7, 18.6; **19F NMR** (CDCl₃, 470 MHz) δ – 62.9; **31P NMR** (CDCl₃, 202 MHz) δ – 5.6; **IR**: 3059, 2931, 1606, 1396, 1165, 1126, 1060, 832, 700 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₆H₂₇F₆N₁O₁P₁ [M+H]⁺: 514.1735, found: 514.1753. [α]D²⁰ = +6.11 (c = 1.00, CHCl₃, l = 50 mm).
(4S)-3-(3-(bis(4-methoxyphenyl)phosphanyl)benzyl)-4-isopropyl-2-methoxyoxazolidine. General Procedure B was followed using (S)-2-((3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzyl)amino)-3-methylbutan-1-ol (737 mg, 1.44 mmol), N,N-dimethylformamide dimethylacetal (0.960 mL, 7.18 mmol), and 14 mL methanol.

Extraction with pentane (2 x 15 mL) and removal of the volatiles were removed under vacuum yielded the pure product as a colorless oil that exists as a 1:1 mixture of diastereomers (726 g, 91%). $^1$H NMR (C₆D₆, 500 MHz) δ 7.46 (d, 0.5H, $J = 8.0$ Hz), 7.42 (d, 0.5H, $J = 7.5$ Hz), 7.33 (d, 0.5H, $J = 7.0$ Hz), 7.02 – 7.23 (m, 10.5H), 5.08 (s, 0.5H), 4.99 (s, 0.5H), 3.86 (d, 0.5H, $J = 13.0$ Hz), 3.84 (dd, 0.5H, $J = 8.5$, 7.5 Hz), 3.69 (dd, 0.5H, $J = 8.0$, 7.5 Hz), 3.61 (dd, 0.5H, $J = 8.0$, 6.0 Hz), 3.60 (d, 0.5H, $J = 4.0$ Hz), 3.58 (dd, 0.5H, $J = 13.5$, 7.0 Hz), 3.52 (d, 0.5H, $J = 13.5$ Hz), 3.41 (d, 0.5H, $J = 14.5$ Hz), 2.96 (s, 1.5H), 2.95 (s, 1.5H), 2.42 (q, 1H, $J = 7.0$ Hz), 1.44 – 1.54 (m, 1H), 0.72 (d, 1.5H, $J = 7.0$ Hz), 0.62 (d, 1.5H, $J = 7.0$ Hz); $^{13}$C NMR (C₆D₆, 126 MHz) δ 146.9, 141.8 (d, $J_{C-P} = 14.7$ Hz), 141.7 (d, $J_{C-P} = 11.5$ Hz), 140.5 (q, $J_{C-F} = 2.3$ Hz), 135.0 (d, $J_{C-P} = 1.5$ Hz), 134.9 (d, $J_{C-P} = 1.5$ Hz), 134.3 (d, $J_{C-P} = 15.2$ Hz), 134.1 (d, $J_{C-P} = 14.4$ Hz), 133.7 (d, $J_{C-P} = 19.8$ Hz), 133.6 (d, $J_{C-P} = 15.9$ Hz), 133.5 (d, $J_{C-P} = 23.5$ Hz), 132.7 (d, $J_{C-P} = 11.3$ Hz), 132.5 (d, $J_{C-P} = 10.6$ Hz), 130.7 (d, $J_{C-P} = 33.4$ Hz), 129.9 (d, $J_{C-P} = 36.4$ Hz), 128.8 (d, $J_{C-P} = 7.6$ Hz), 128.7 (d, $J_{C-P} = 7.6$ Hz), 125.1 – 125.3 (6 signals), 124.3 (d, $J_{C-F} = 273$ Hz), 124.2 (d, $J_{C-F} = 273$ Hz), 114.8, 109.9, 68.4, 66.5, 65.4, 63.4, 56.5, 51.9, 50.5, 49.7, 30.5, 28.4, 19.5, 18.7, 16.9, 15.0; $^{19}$F NMR (CDCl₃, 470 MHz) δ – 62.7; $^{31}$P NMR
(CDCl₃, 202 MHz) δ – 5.8; IR: 2958, 2896, 1728, 1606, 1132, 1165, 1060, 956, 700, 514 cm⁻¹; [α]ₒ^2⁰ = + 38.7 (c = 1.00, CHCl₃, l = 50 mm).

**(3-(1,3-dioxolan-2-yl)phenyl)bis(2-methoxyphenyl)phosphine.** To a solution of 2-(3-bromophenyl)-1,3-dioxolane (1.46 g, 6.36 mmol) in THF (35 mL) at -78 °C was added tert-butyllithium (8.84 mL, 13.3 mmol, 1.51 M solution in pentane) over 5 minutes. The reaction was allowed to stir at -78 °C for 20 minutes and then warmed to -20 °C over 30 minutes. After being re-cooled to -78 °C, a solution of chlorobis(2-methoxyphenyl)phosphine (1.61 g, 5.72 mmol) in THF (15 mL) was added. The reaction was allowed to warm slowly to room temperature overnight and quenched by the addition of water (50 mL). The crude product was extracted with dichloromethane (2 x 70 mL), dried over Na₂SO₄, filtered, and concentrated. Purification on silica gel (20% EtOAc/Hex) afforded the title compound as a colorless solid (679 mg, 30%). **¹H NMR** (CDCl₃, 500 MHz) δ 7.46 (d, 1H, J = 7.8 Hz), 7.43 (d, 1H, J = 7.8 Hz), 7.31 – 7.34 (m, 3H), 7.22 (t, 1H, J = 7.3 Hz), 6.82 – 6.89 (m, 4H), 6.65 – 6.70 (m, 2H), 5.74 (s, 1H), 3.98 – 4.08 (m, 4H); **¹³C NMR** (CDCl₃, 126 MHz) δ 161.5 (d, J_C-P = 16.2 Hz), 137.9 (d, J_C-P = 7.6 Hz), 136.9 (d, J_C-P = 11.4 Hz), 135.0 (d, J_C-P = 17.2 Hz), 134.0 132.8 (d, J_C-P = 25.8 Hz), 130.3, 128.5 (d, J_C-P = 6.7 Hz), 126.7, 125.1 (d, J_C-P = 12.4 Hz), 121.2, 110.4 (d, J_C-P = 1.9 Hz), 104.1, 65.5, 55.9; **³¹P NMR** (CDCl₃, 202 MHz) δ – 27.5; IR: 1573, 1471, 1430, 1240, 1072, 1023, 795 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₃H₂₄O₄P₁ [M+H]^+: 395.1422, found: 395.1425.
3-(bis(2-methoxyphenyl)phosphino)benzaldehyde. To a 50-mL, round-bottom flask under argon was added (3-(1,3-dioxolan-2-yl)phenyl)bis(2-methoxyphenyl)phosphine (600 mg, 1.52 mmol) as a solution in THF (10 mL), followed by 3N hydrochloric acid (5.0 mL, 15.2 mmol, sparged with argon for 15 minutes prior to addition). The solution was heated to 50 °C for 2 hours with vigorous stirring. The reaction was cooled to 0 °C, basified by the addition of 6N sodium hydroxide to pH 12, and extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to a colorless solid which was used in the next step without purification (506 mg, 91%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 9.93 (s, 1H), 7.85 (d, 1H, $J$ = 7.8 Hz), 7.78 (d, 1H, $J$ = 7.3 Hz), 7.50 – 7.53 (m, 1H), 7.45 – 7.47 (m, 1H), 7.36 (dt, 2H, $J$ = 8.3 Hz, 1.5 Hz), 6.84 – 6.92 (m, 4H), 6.66 – 6.69 (m, 2H), 3.73 (s, 6H); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 192.6 161.6 (d, $J_{C-P}$ = 16.2 Hz), 139.9 (d, $J_{C-P}$ = 19.1 Hz), 138.9 (d, $J_{C-P}$ = 13.4 Hz), 136.5 (d, $J_{C-P}$ = 6.7 Hz), 136.2 (d, $J_{C-P}$ = 21.9 Hz), 134.0 (d, $J_{C-P}$ = 1.9 Hz), 130.8, 129.1 (d, $J_{C-P}$ = 3.8 Hz), 129.0 (d, $J_{C-P}$ = 5.7 Hz), 124.2 (d, $J_{C-P}$ = 12.4 Hz), 121.3, 110.5 (d, $J_{C-P}$ = 1.9 Hz), 55.9; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 27.1; IR: 1697, 1584, 1472, 1464, 1273, 794 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{21}$H$_{20}$O$_3$P$_1$ [M+H]$^+$: 351.1150, found: 351.1163.

(S)-2-((3-(bis(2-methoxyphenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol. Followed General Procedure A using 3-(bis(2-methoxyphenyl)phosphino)benzaldehyde (490 mg, 1.40 mmol), (S)-2-amino-3-methylbutan-1-ol (217 mg, 2.10 mmol), and THF (11 mL).
The generated imine was reduced with NaBH$_4$ (106 mg, 2.80 mmol) in dry methanol (11 mL). The title compound was isolated by silica gel chromatography (EtOAc containing 2% Et$_3$N) for afford a colorless solid (401 mg, 68%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.28 – 7.35 (m, 5H), 7.14 (t, 1H, $J = 6.8$ Hz), 6.89 (dd, 2H, $J = 8.3$ Hz, 5.0 Hz), 6.85 (t, 2H, $J = 7.3$ Hz), 6.66 – 6.68 (m, 2H), 3.77 (d, 1H, $J = 13.2$ Hz), 3.74 (s, 6H), 3.71 (d, 1H, $J = 13.2$ Hz), 3.58 (dd, 1H, $J = 10.8$ Hz, 3.9 Hz), 3.33 (dd, 1H, $J = 10.8$ Hz, 6.9 Hz), 2.38 – 2.42 (m, 1H), 1.79 – 1.83 (m, 1H), 0.90 (d, 3H, $J = 6.9$ Hz), 0.86 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 161.5 (d, $J_{C-P} = 16.2$ Hz), 140.4 (d, $J_{C-P} = 7.6$ Hz), 136.9 (d, $J_{C-P} = 10.5$ Hz), 134.1, 133.9, 133.8, 132.9 (d, $J_{C-P} = 18.1$ Hz), 130.4, 128.6 (d, $J_{C-P} = 6.7$ Hz), 125.3 (d, $J_{C-P} = 12.4$ Hz), 121.1, 110.4, 63.8, 60.5, 55.9, 51.4, 29.0, 19.8, 18.6; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 28.0; IR: 2957, 1471, 1430, 1241, 1042, 794 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{26}$H$_{33}$N$_1$O$_3$P$_1$ [M+H]$^+$: 438.2198, found: 438.2202.

(4S)-3-(3-(bis(2-methoxyphenyl)phosphino)benzyl)-4-isopropyl-2-methoxyoxazolidine. Synthesized according to General Procedure B using (S)-2-((3-(bis(2-methoxyphenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol (397 mg, 0.943 mmol), methanol (13 mL), and $N,N$-dimethylformamide dimethyl acetal (0.63 mL, 7.4 mmol). Extraction of the crude residue with 1:1 pentane:benzene (2 x 10 mL) and removal of the solvent under vacuum afforded the title compound as a viscous oil that is a mixture of two diastereomers in a 40:60 ratio (378 mg, 87%). $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 7.69 (d, 0.6H, $J = 7.8$ Hz), 7.56 (d, 0.4H, $J = 7.8$ Hz), 7.43 – 7.45 (m, 1H), 7.36 (d, 0.6H, $J = 7.3$ Hz), 7.26 (d, 0.4H, $J =$
7.3 Hz), 7.03 – 7.16 (m, 4.2H), 6.75 – 6.80 (m, 2.4H), 6.50 – 6.54 (m, 2.4H), 5.22 (s, 0.4H), 5.11 (s, 0.6H), 3.86 – 3.93 (m, 1.2H), 3.66 – 3.75 (m, 1.2H), 3.56 – 3.62 (m, 1.2H), 3.45 (d, 0.4H, J = 14.2 Hz), 3.22 (s, 3.6H), 3.20 (s, 2.4H), 3.03 (s, 1.2H), 2.98 (s, 1.8H), 2.94 – 2.97 (m, 0.6H), 2.50 (q, 0.4H, J = 7.3 Hz), 1.56 – 1.61 (m, 1H), 0.77 (d, 1.8H, J = 6.9 Hz), 0.69 (d, 1.2H, J = 6.9 Hz), 0.68 (d, 1.2H, J = 6.9 Hz), 0.61 (d, 1.8H, J = 6.9 Hz);

$^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 161.4 – 161.6 (4 signals), 139.1 (d, $J_{C-P}$ = 6.7 Hz), 138.7 (d, $J_{C-P}$ = 7.6 Hz), 136.7 (d, $J_{C-P}$ = 11.4 Hz), 136.4 (d, $J_{C-P}$ = 10.5 Hz), 135.0, 134.8 (d, $J_{C-P}$ = 6.7 Hz) 134.6, 133.8 – 134.0 (4 signals), 133.1 (d, $J_{C-P}$ = 20.0 Hz), 132.8 (d, $J_{C-P}$ = 20.0 Hz), 130.2 – 130.3 (3 signals), 129.7, 129.3, 128.3 – 128.5 (5 signals), 125.3 – 125.5 (4 signals), 121.1 (d, $J_{C-P}$ = 3.8 Hz), 114.4, 110.7, 110.4, 68.2, 67.5, 66.0, 63.5, 57.0, 55.9, 55.8 (2 signals), 52.9, 51.3, 50.2, 31.1, 28.4, 20.3, 19.5, 17.7, 15.4; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 26.3, – 26.5; IR: 2955, 1461, 1429, 1272, 1070, 1023, 753, 729 cm$^{-1}$;

HRMS (DART-TOF) calcd. for C$_{28}$H$_{35}$N$_{1}$O$_{4}$P$_{1}$ [M+H]$^+$: 480.2304, found: 480.2287; $|\alpha|_D^{20}$ = +10.4 (c = 0.470, CDCl$_3$, l = 50 mm).

(3-(1,3-dioxolan-2-yl)phenyl)bis(2-(trifluoromethyl)phenyl)phosphine. To a solution of 2-(3-bromophenyl)-1,3-dioxolane (1.12 g, 4.88 mmol) in THF (27 mL) at -78 °C was added tert-butyllithium (6.8 mL, 10.2 mmol, 1.50 M solution in pentane) over 5 minutes. The reaction was allowed to stir at -78 °C for 20 minutes and then warmed to -20 °C over 30 minutes. After being re-cooled to -78 °C, a solution of chlorobis(2-(trifluoromethyl)phenyl)phosphine (1.58 g, 4.44 mmol) in THF (6 mL) was added. The reaction was allowed to warm slowly to room temperature overnight and quenched by the addition of water (25 mL). The crude product was
extracted with ethyl acetate (2 x 60 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification on silica gel (15% EtOAc/Hex) afforded the title compound as a beige solid (624 mg, 30%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.73 (app dq, 2H, $J = 4.0$ Hz, 1.3 Hz), 7.29 – 7.48 (m, 8H), 7.08 (dt, 1H, $J = 7.3$ Hz, 1.5 Hz), 6.78 – 7.00 (m, 2H), 5.70 (s, 1H), 3.95 – 4.03 (m, 4H); $^{13}$C NMR (CDCl$_3$, 126 MHz) δ 138.7 (d, $J_{C-P} = 7.6$ Hz), 136.1, 135.7 (d, $J_{C-P} = 29.4$ Hz), 135.6 (d, $J_{C-P} = 7.6$ Hz), 134.9 (d, $J_{C-P} = 19.1$ Hz), 134.6 (d, $J_{C-F} = 31.5$ Hz, 5.7 Hz), 132.5 (d, $J_{C-P} = 25.8$ Hz), 131.8, 129.3, 129.1 (d, $J_{C-P} = 5.7$ Hz), 127.6, 127.0 (quintet, $J_{C-F} = 5.7$ Hz), 124.4 (d, $J_{C-F} = 275$ Hz), 103.7, 65.5; $^{31}$P NMR (CDCl$_3$, 202 MHz) δ –14.3 (septet, $J_{P-F} = 53$ Hz); $^{19}$F NMR (CDCl$_3$, 470 MHz) δ –57.4 (d, $J_{F-P} = 53$ Hz); IR: 1308, 1166, 1109, 1091, 1034, 769 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{23}$H$_{18}$F$_6$O$_2$P$_1$ [M+H]$^+$: 471.0949, found: 471.0955.

3-(bis(2-(trifluoromethyl)phenyl)phosphino)benzaldehyde. To a solution of 3-(1,3-dioxolan-2-yl)phenyl)bis(2-(trifluoromethyl)phenyl)phosphine (565 mg, 1.20 mmol) in THF (4 mL) was added 3 N hydrochloric acid (4 mL, sparged with nitrogen for 15 minutes). The resulting mixture was heated to 50 °C for 3 hours, cooled to 0 °C in an ice/water bath, basified by the addition of saturated aqueous NaHCO$_3$, and extracted with dichlormethane (2 x 20 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification on a short silica gel plug (20% EtOAc/Hex) afforded the title compound as a beige solid (437 mg, 85%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 9.94 (s, 1H), 7.90 (d, 1H, $J = 7.3$ Hz), 7.81 (dd, 2H, $J = 7.8$, 3.9 Hz), 7.68 (d, 1H, $J = 7.3$ Hz), 7.42 – 7.55 (m, 6H), 7.03 (dd, 2H, $J = 7.3$, 3.9 Hz); $^{13}$C NMR
(CDCl₃, 151 MHz) δ 192.0, 139.8 (d, J_C-P = 22.0 Hz), 127.6 (d, J_C-P = 16.1 Hz), 136.8 (d, J_C-P = 5.8 Hz), 136.0, 135.4 (d, J_C-P = 22.0 Hz), 134.8 (dq, J_C-P = 30.6, 4.6 Hz), 134.7 (d, J_C-P = 28.9 Hz), 132.0, 130.2, 129.7, 129.6 (d, J_C-P = 5.8 Hz), 127.2 – 127.4 (m, J_C-F, 5 signals), 124.5 (q, J_C-P = 275.6 Hz); ³¹P NMR (CDCl₃, 202 MHz) δ – 14.2 (septet, J_P = 52.9 Hz); ¹⁹F NMR (CDCl₃, 470 MHz) δ – 57.6 (d, J_F-P = 53 Hz); IR: 1308, 1166, 1109, 1091, 1034, 769 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₁H₁₄F₆O₁P₁ [M+H]^+: 427.0687, found: 427.0690.

(S)-2-(((3-(bis(2-(trifluoromethyl)phenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol. Followed General Procedure A using 3-(bis(2-(trifluoromethyl)phenyl)phosphino)benzaldehyde (515 mg, 1.21 mmol), and (S)-2-amino-3-methylbutan-1-ol (187 mg, 1.81 mmol) in THF (9 mL). The imine was reduced with NaBH₄ (137 mg, 3.63 mmol) in MeOH (12 mL). The title compound was isolated by silica gel chromatography (50% EtOAc/Hex containing 1% Et₃N) for afford a colorless oil (449 mg, 72%). ¹H NMR (CDCl₃, 500 MHz) δ 7.76 – 7.78 (m, 2H), 7.48 (t, 2H, J = 7.3 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.29 – 7.35 (m, 2H), 7.16 (d, 1H, J = 8.8 Hz), 7.00 – 7.03 (m, 3H), 3.78 (d, 1H, J = 13.2 Hz), 3.71 (d, 1H, J = 13.2 Hz), 3.57 (dd, 1H, J = 10.7 Hz, 3.9 Hz), 3.33 (dd, 1H, J = 10.7 Hz, 7.7 Hz), 2.36 – 2.40 (m, 1H), 2.01 (br s, 1H), 1.76 – 1.83 (m, 1H), 0.90 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.8 Hz); ¹³C NMR (CDCl₃, 151 MHz) δ 141.1 (d, J_C-P = 7.6 Hz), 136.1 (d, J_C-P = 1.7 Hz), 136.0 (d, J_C-P = 5.1 Hz), 135.7 (d, J_C-P = 5.1 Hz), 135.6 (d, J_C-P = 12.7 Hz), 134.6 (dq, J_C-F-P = 30.4 Hz, 4.5 Hz), 133.9 (d, J_C-P = 25.4 Hz), 132.4 (d, J_C-P = 18.7 Hz), 131.8, 129.3 (d, J_C-P = 11.5 Hz), 129.1 (d, J_C-P = 6.8 Hz), 127.0 (septet, J_C-F = 5.4 Hz), 120.5.
124.4 (q, $J_{C-F} = 275.2$ Hz), 63.8, 60.5, 51.2, 29.0, 19.8, 18.6; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 14.3 (septet, $J_{P-F} = 52$ Hz); $^{19}$F NMR (CDCl$_3$, 470 MHz) $\delta$ – 57.4 (d, $J_{F-P} = 53$ Hz); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.75 – 7.77 (m, 2H), 7.35 – 7.48 (m, 5H), 7.28 – 7.32 (m, 1H), 7.14 – 7.18 (m, 1H), 7.04 – 7.09 (m, 1H), 6.98 – 7.02 (m, 2H), 5.14 (s, 0.5H), 4.86 (s, 0.5H), 3.93 – 3.99 (m, 1H), 3.79 (dd, 1H, $J = 13.7, 3.9$ Hz), 3.70 – 3.74 (m, 2H), 3.07 – 3.09 (m, 0.5H), 3.05 (s, 1.5H), 3.03 (s, 1.5H), 2.74 (dd, 0.5H, $J = 15.1, 7.3$ Hz), 1.75 – 1.79 (m, 0.5H), 1.62 – 1.66 (m, 0.5H), 0.75 – 0.83 (m, 6H); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta$ 139.9 (d, $J_{C-P} = 6.7$ Hz), 139.6 (d, $J_{C-P} = 6.7$ Hz), 136.0, 135.9 (d, $J_{C-P} = 19.1$ Hz), 134.4 – 135.4 (8 signals), 133.1 (d, $J_{C-P} = 22.9$ Hz), 132.8 (d, $J_{C-P} = 21.9$ Hz), 131.7, 131.1 (d, $J_{C-P} = 25.8$ Hz), 129.3 (d, $J_{C-P} = 6.7$ Hz), 129.2, 128.9 (d, $J_{C-P} = 7.6$ Hz), 128.8 (d, $J_{C-P} = 7.6$ Hz), 127.0, 126.9 – 127.1 (m, 5 signals), 124.4 (dq $J_{C-F} = 275.6$ Hz), 114.6, 110.6, 68.5, 67.4, 66.0, 63.6, 57.1, 52.8, 51.3, 50.1, 30.1, 28.5, 20.3, 19.5, 17.6, 15.4; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 14.4 (septet, $J_{P-F} = 53$ Hz), – 14.3 (septet, $J_{P-F} = 53$ Hz); $^{19}$F NMR (CDCl$_3$, 470
MHz) \( \delta = 57.4 \) (d, \( J_{F,P} = 52.8 \) Hz), \( \delta = 57.3 \) (d, \( J_{F,P} = 52.8 \) Hz); \textbf{IR:} 2957, 1308, 1166, 1129, 1111, 1059, 769 \text{ cm}^{-1}; \textbf{HRMS} (DART-TOF) calcd. for \( \text{C}_{28}\text{H}_{29}\text{F}_{6}\text{N}_{1}\text{O}_{2}\text{P}_{1} \) [M+H]: 556.1840, found: 556.1855.

(3-(1,3-dioxolan-2-yl)phenyl)bis(3,5-bis(trifluoromethyl)phenyl)phosphine. To a solution of 2-(3-bromophenyl)-1,3-dioxolane (800 mg, 3.48 mmol) in THF (20 mL) at -78 °C was added \textit{tert}-butyllithium (4.6 mL, 7.30 mmol, 1.54 M solution in pentane) over 5 minutes. The reaction was allowed to stir at -78 °C for 20 minutes and then warmed to -20 °C over 30 minutes. After being re-cooled to -78 °C, a solution of bis(3,5-bis(trifluoromethyl)phenyl)chlorophosphine (1.55 g, 3.16 mmol) in THF (20 mL) was added. The reaction was allowed to warm slowly to room temperature overnight and quenched by the addition of water (30 mL). The crude product was extracted with dichloromethane (2 x 60 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification on silica gel (7% EtOAc/Hex) afforded the title compound as a colorless solid (416 mg, 21%).

\textbf{1H NMR} (CDCl$_3$, 500 MHz) \( \delta = 7.90 \) (s, 2H), 7.72 (s, 2H), 7.71 (s, 2H), 7.61 (d, 1H, \( J = 7.8 \) Hz), 7.55 – 7.58 (m, 1H), 7.46 – 7.49 (m, 1H), 7.26 – 7.29 (m, 1H), 5.81 (s, 1H), 4.01 – 4.08 (m 4H); \textbf{13C NMR} (CDCl$_3$, 126 MHz) \( \delta = 139.7 \) (d, \( J_{C-P} = 8.6 \) Hz), 139.6 (d, \( J_{C-P} = 18.1 \) Hz), 134.3 (d, \( J_{C-P} = 16.2 \) Hz), 133.2 (d, \( J_{C-P} = 2.9 \) Hz), 133.0 (d, \( J_{C-P} = 1.9 \) Hz), 132.9 (d, \( J_{C-P} = 10.5 \) Hz), 132.4, 132.2, 132.2 (dq, \( J_{C-F} = 33.6 \) Hz, 6.0 Hz), 129.7 (d, \( J_{C-P} = 6.7 \) Hz), 129.0, 123.4 (septet, \( J_{C-F} = 3.8 \) Hz), 122.9 (q, \( J_{C-F} = 273 \) Hz), 102.9, 65.3; \textbf{31P NMR} (CDCl$_3$, 202 MHz) \( \delta = 4.0 \); \textbf{19F NMR} (CDCl$_3$, 470 MHz) \( \delta = 63.1 \); \textbf{IR:} 1352, 1275,
1173, 1125, 1095, 897, 703, 682 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₅H₁₆F₁₂O₂P₁ [M+H]⁺: 607.0696, found: 607.0685.

3-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)benzaldehyde.

To a 50 – mL, round-bottom flask under argon was added (3-(1,3-dioxolan-2-yl)phenyl)bis(3,5-bis(trifluoromethyl)phenyl)phosphine (403 mg, 0.644 mmol) as a solution in THF (8 mL), followed by 3N hydrochloric acid (8.0 mL, 24.0 mmol, sparged with argon for 15 minutes prior to addition). The solution was heated to 50 °C for 2 hours with vigorous stirring. The reaction was cooled to 0 °C, basified by the addition of 6N sodium hydroxide to pH 12, and extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to a colorless solid which was used in the next step without purification (241 mg, 66%).

**¹H NMR** (CDCl₃, 500 MHz) δ 10.0 (s, 1H), 8.00 (d, 1H, J = 7.8 Hz), 7.94 (d, 2H), 7.89 – 7.91 (m, 1H), 7.72 (d, 2H, J = 6.8 Hz), 7.64 – 7.67 (m, 3H), 7.51 – 7.55 (m, 1H); **¹³C NMR** (CDCl₃, 126 MHz) δ 191.2, 139.2 (d, J_C-P = 16.2 Hz), 139.0 (d, J_C-P = 19.1 Hz), 135.2 (d, J_C-P = 25.8 Hz), 135.0, 133.4 (d, J_C-P = 21.0 Hz), 131.9 – 132.9 (8 signals), 130.5, 124.0, 123.1 (q, J_C-F = 273 Hz); **³¹P NMR** (CDCl₃, 202 MHz) δ – 4.7; **¹⁹F NMR** (CDCl₃, 470 MHz) δ – 63.1; **IR**: 1704, 1353, 1276, 1175, 1128, 1097, 897, 682 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₅H₁₆F₁₂O₂P₁ [M+H]⁺: 563.0434, found: 563.0428.
(S)-2-((3-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol. Synthesized according to General Procedure A using (S)-2-amino-3-methylbutan-1-ol (126 mg, 1.22 mmol), THF, (6 mL), and 3-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)benzaldehyde (456 mg, 0.811 mmol). Reduction of the imine was carried out with NaBH₄ (94 mg, 2.4 mmol) in anhydrous methanol (8 mL). The title compound was isolated by silica gel chromatography (50% EtOAc/Hex) for afford a colorless oil (402 mg, 76%).

**¹H NMR** (CDCl₃, 500 MHz) δ 7.90 (s, 2H), 7.72 (s, 2H), 7.70 (s, 2H), 7.48 (d, 1H, J = 7.8 Hz), 7.41 – 7.45 (m, 1H), 7.36 (d, 1H, J = 9.8 Hz), 7.16 – 7.19 (m, 1H), 3.84 (d, 1H, J = 13.2 Hz), 3.78 (d, 1H, J = 13.2 Hz), 3.61 (dd, 1H, J = 10.8 Hz, 4.4 Hz), 3.37 (33, 1H, J = 10.8 Hz, 6.9 Hz), 2.40 – 2.43 (m, 1H), 1.79 – 1.86 (m, 1H), 0.92 (d, 3H, J = 6.8 Hz), 0.88 (d 3H, J = 6.9 Hz); **¹³C NMR** (CDCl₃, 126 MHz) δ 142.3 (d, J_C-P = 8.6 Hz), 139.9 (d, J_C-P = 18.1 Hz), 134.2, 133.9, 133.1 – 133.3 (5 signals), 132.7 (q, J_C-F = 26.4 Hz), 132.6 (d, J_C-P = 9.5 Hz), 132.3, 130.8, 130.0 (d, J_C-P = 6.7 Hz), 123.4 (septet, d, J_C-F = 3.8 Hz), 123.2 (q, J_C-F = 273 Hz), 64.1, 60.8, 51.2, 29.0, 19.6, 18.6, 14.3; **³¹P NMR** (CDCl₃, 202 MHz) δ – 4.1; **¹⁹F NMR** (CDCl₃, 470 MHz) δ – 63.0; **IR**: 3391, 2961, 1353, 1277, 1181, 1132, 1043, 703 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₈H₂₅F₁₂N₁O₃P₁ [M+H]⁺: 650.1482, found: 650.1449; [α]D²⁰ = + 4.90 (c = 0.585, CHCl₃, l = 50 mm).
(4S)-3-(3-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)benzyl)-2-methoxyoxazolidine. Followed General Procedure B using N,N-dimethylformamide dimethyl acetal (0.30 mL, 2.3 mmol), THF (6 mL), and (S)-2-((3-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)benzyl)amino)-3-methylbutan-1-ol (300 mg, 0.462 mmol). Extraction of the crude residue with degassed pentane (2 x 10 mL) and removal of the solvent under varuum afforded a colorless oil which exists as a mixture of two diastereomers in a 1:1 ratio (299 mg, 93%).

**1H NMR** (C₆D₆, 500 MHz) δ 7.63 – 7.66 (m, 5.5H), 7.43 – 7.48 (m, 1H), 7.24 (d, 0.5H, J = 7.8 Hz), 7.03 – 7.09 (m, 3H), 5.03 (s, 0.5H), 4.97 (s, 0.5H), 3.81 – 3.85 (m, 1H), 3.69 – 3.71 (m, 0.5H), 3.57 – 3.61 (m, 1H), 3.47 – 3.53 (m, 1H), 3.34 (d, 0.5H, J = 15.1 Hz), 3.00 (s, 1.5H), 2.97 (s, 1.5H), 2.87 – 2.91 (m, 0.5H), 2.37 – 2.43 (m, 0.5H), 1.43 – 1.50 (m, 1H), 0.69 (d, 1.5H, J = 6.8 Hz), 0.62 (d, 1.5H, J = 6.8 Hz), 0.58 (d, 3H, J = 6.8 Hz);

**13C NMR** (CDCl₃, 126 MHz) δ 141.2 (d, J_C-P = 7.5 Hz), 141.1 (d, J_C-P = 7.6 Hz), 139.8 – 140.0 (5 signals), 134.4 (d, J_C-P = 22.0 Hz), 134.2 (d, J_C-P = 21.2 Hz), 133.3 (d, J_C-P = 19.5 Hz), 133.0, 132.5 (dq, J_C-F = 31.6 Hz, 6.1 Hz), 129.6 – 129.7 (4 signals), 123.6, 123.2 (q, J_C-F = 273 Hz), 115.0, 110.3, 69.0, 67.5, 66.0, 63.6, 57.1, 52.8, 51.4, 49.8, 31.3, 28.6, 20.2, 19.4, 17.6, 15.3; **31P NMR** (CDCl₃, 202 MHz) δ -4.5 (43%), -4.8 (57%); **HRMS** (DART-TOF) calcd. for C₃₀H₂₇F₁₂N₁O₂P₁ [M+H]⁺: 692.1588, found: 692.1581; [α]D²⁰ = +14.3 (c = 0.685, CDCl₃, l = 50 mm).

(S)-2-((3-(diphenylphosphanyl)benzyl)amino)propan-1-ol.

Carried out according to General Procedure A. The imine was
synthesized from 3-(diphenylphosphanyl)benzaldehyde (600 mg, 2.07 mmol) and (S)-2-aminopropan-1-ol (202 mg, 2.69 mmol) in tetrahydrofuran (7 mL). Reduction occurred in anhydrous methanol (7 mL) with sodium borohydride (235 mg, 6.21 mmol). Purification using silica gel chromatography (1% Et<sub>3</sub>N/EtOAc) afforded the title compound as a colorless oil (456 mg, 64%).  

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\text{H NMR (CDCl}_3, 500 \text{ MHz}) \delta 7.28 – 7.35 (m, 12H), 7.27 – 7.26 (m, 1H), 7.15 – 7.18 (m, 1H), 3.82 (d, 1H, } J = 13.2 \text{ Hz), 3.70 (d, 1H, } J = 13.2 \text{ Hz)}, 3.54 – 3.57 (m, 1H), 3.22 (dd, 1H, } J = 10.8, 6.9 \text{ Hz), 2.76 – 2.80 (m, 1H), 1.04 (s, 3H);}
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\text{C NMR (CDCl}_3, 101 \text{ MHz}) \delta 140.8 (d, } J_{C-P} = 7.6 \text{ Hz), 137.6 (d, } J_{C-P} = 11.5 \text{ Hz), 137.4 (d, } J_{C-P} = 10.7 \text{ Hz), 133.9 (d, } J_{C-P} = 19.8 \text{ Hz), 133.6 (d, } J_{C-P} = 22.9 \text{ Hz), 132.6 (d, } J_{C-P} = 16.8 \text{ Hz), 128.9, 128.8 (d, } J_{C-P} = 6.1 \text{ Hz), 128.7, 128.6 (d, } J_{C-P} = 6.7 \text{ Hz), 65.7, 53.9, 51.1, 17.4;}
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\text{P NMR (CDCl}_3, 202 \text{ MHz}) \delta – 5.4; \text{ IR: 3299, 2967, 2870, 1477, 1435, 1214, 1172, 1118m 1091, 1027, 998, 745, 726, 696, 541 cm}^{-1}; \text{ HRMS (DART-TOF) calcd. for C}_{22}\text{H}_{25}\text{N}_1\text{O}_1\text{P}_1 [\text{M+H}]: 350.1674, \text{ found: 350.1685; } [\alpha]_D^{20} = + 6.72 (c = 0.600, CHCl}_3, l = 50 \text{ mm}).
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**(4S)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxy-4-methylxazolidine.** Synthesized using General Procedure B with (S)-2-((3-(diphenylphosphanyl)benzyl)amino)propan-1-ol (355 mg, 1.03 mmol), freshly distilled methanol (15 mL) and N,N-dimethylformamide dimethylacetal (684 µL, 5.15 mmol). Extraction with pentane (2 x 10 mL) and removal of the volatiles under reduced pressure to afforded the title compound as a viscous oil as a 1:1 mixture of diastereomers (325 mg, 81 %).  

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\text{H NMR (C}_6\text{D}_6, 500 \text{ MHz}) \delta 7.64 (d, 0.5H, } J = 8.3 \text{ Hz), 7.50 (d, 0.5H, } J = 7.8 \text{ Hz), 7.41-7.44 (m, 4H), 7.30 – 7.34 (m, 1.5H),}
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7.20 (d, 0.5H, J = 7.8 Hz), 7.03 – 7.16 (m, 7H), 5.22 (s, 0.5H), 5.10 (s, 0.5H), 3.97 (t, 0.5H, J = 7.3 Hz), 3.75 (d, 0.5H, J = 13.2 Hz), 3.70 (dd, 0.5H, J = 7.6, 6.6 Hz), 3.59 (t, 1H, J = 13.7 Hz), 3.36 – 3.43 (s, 1.5H), 3.12 (s, 1.5H), 3.05 – 3.09 (m, 0.5H), 3.01 (s, 1.5H), 2.67 – 2.73 (m, 0.5H), 0.74 (d, 1.5H, J = 6.0 Hz), 0.70 (d, 1.5H, J = 6.0 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 139.3 (d, J_C-P = 7.6 Hz), 138.7 (d, J_C-P = 6.9 Hz), 137.1 – 137.6 (11 signals), 133.8 – 134.5 (8 signals), 132.7 (d, J_C-P = 19.0 Hz), 132.5 (d, J_C-P = 17.5 Hz), 128.9, 128.8 (d, J_C-P = 1.5 Hz), 128.7 (d, J_C-P = 6.1 Hz), 128.6 (d, J_C-P = 6.9 Hz), 113.5, 110.3, 72.8, 72.1, 56.8, 54.0, 53.3, 52.6, 50.8, 49.4, 17.3, 17.0; ³¹P NMR (C₆D₆, 202 MHz) δ – 5.4, – 5.5; IR: 2966, 2886, 1477, 1434, 1345, 1289, 1156, 744, 697, 495 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₄H₂₇N₁O₂P₁ [M+H⁺]: 392.1779, found: 392.1782; [α]D²⁰ = + 32.9 (c = 0.465, CHCl₃, l = 50 mm).

(S)-2-((3-(diphenylphosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol. Followed General Procedure A using (S)-2-amino-3,3-dimethylbutan-1-ol (884 mg, 7.54 mmol), 3-(diphenylphosphanyl)benzaldehyde (1.46 g, 5.03 mmol) and THF (18 mL). The imine was reduced with NaBH₄ (382 mg, 10.1 mmol) in anhydrous methanol (18 mL). Silica gel column chromatography (100 % EtOAc) to afford the title compound as a colorless oil (1.27 g, 64%). ¹H NMR (CDCl₃, 500 MHz) δ 7.28 – 7.34 (m, 13H), 7.17 – 7.18 (m, 1H), 3.83 (d, 1H, J = 13.2 Hz), 3.79 (d, 1H, J = 12.7 Hz), 3.60 (dd, 1H, J = 10.7, 4.9 Hz), 3.37 (dd, 1H, J = 10.7, 6.4 Hz), 2.30 – 2.32 (m, 1H), 0.90 (s, 9H); ¹³C NMR (CDCl₃, 126 MHz) δ 140.9 (d, J_C-P = 6.7 Hz), 137.8 (d, J_C-P = 11.5 Hz), 137.3 (d, J_C-P = 10.5 Hz), 133.9 (d, J_C-P = 20.0 Hz), 133.7 (d, J_C-P = 21.9 Hz), 132.7 (d,
18.1 Hz), 129.0, 128.9 (d, $J_{C,P} = 6.7$ Hz), 128.8, 128.7 (d, $J_{C,P} = 7.6$ Hz), 67.1, 60.2, 54.1, 34.6, 27.0; $^{31}\text{P NMR}$ (CDCl$_3$, 202 MHz) δ – 5.4; IR: 3338, 2952, 2867, 1476, 1434, 1413, 1091, 1043, 1026, 997, 788, 743, 695, 495 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{25}$H$_{31}$N$_1$O$_1$P$_1$ [M+H]$^+$: 392.2143, found: 394.2148; $[\alpha]_D^{20} = -0.873$ ($c = 0.655$, CHCl$_3$, $l = 50$ mm).

(4S)-4-(tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine. Synthesized according to General Procedure B with N,N-dimethylformamide dimethylacetal (2.00 mL, 14.9 mmol), (S)-2-((3-(diphenylphosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (1.17 g, 2.99 mmol) and methanol (30 mL). Extraction and removal of the volatiles under vacuum yielded a pale yellow oil that exists as a 1:1 mixture of diastereomers (1.10 g, 84%). $^1\text{H NMR}$ (C$_6$D$_6$, 500 MHz) δ 7.66 (d, 0.5H, $J = 7.3$ Hz), 7.59 (d, 0.5H, $J = 7.3$ Hz), 7.41 – 7.45 (m, 4H), 7.31 – 7.37 (m, 1H), 7.03 – 7.14 (m, 8H), 5.05 (s, 0.5H), 5.03 (s, 0.5H), 4.16 (d, 0.5H, $J = 13.6$ Hz), 3.90 – 3.93 (m, 0.5H), 3.82 (d, 0.5H, $J = 13.7$ Hz), 3.73 – 3.78 (m, 1H), 3.69 (dd, 0.5H, $J = 8.3$, 2.4 Hz), 3.61 (d, 1H, $J = 6.9$ Hz), 2.92 (s, 1.5H), 2.91 (s, 1.5H), 2.51 – 2.54 (m, 0.5H), 2.48 – 2.51 (m, 0.5H), 0.78 (s, 4.5H), 0.77 (s, 4.5H); $^{13}\text{C NMR}$ (CDCl$_3$, 101 MHz) δ 140.2 (d, $J_{C,P} = 6.1$ Hz), 140.0 (d, $J_{C,P} = 6.1$ Hz), 137.6 (d, $J_{C,P} = 10.7$ Hz), 137.4 (d, $J_{C,P} = 4.6$ Hz), 137.3 (d, $J_{C,P} = 3.8$ Hz), 137.1 (d, $J_{C,P} = 17.7$ Hz), 133.6 – 134.3 (7 signals), 132.9 (d, $J_{C,P} = 21.4$ Hz), 132.5 (d, $J_{C,P} = 22.1$ Hz), 129.3, 128.9 (d, $J_{C,P} = 6.9$ Hz), 128.8, 128.7 (d, $J_{C,P} = 6.9$ Hz), 128.4 (d, $J_{C,P} = 7.0$ Hz), 115.6, 110.5, 73.1, 68.5, 66.5, 65.4, 60.1, 53.0, 52.4, 52.3, 35.3, 33.8, 26.9, 26.4; $^{31}\text{P NMR}$ (C$_6$D$_6$, 202 MHz) δ – 5.6; IR: 2953, 2898, 1477, 1437, 1393, 1360, 1198, 1141, 213
(S)-2-((3-(bis(4-methoxyphenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol. Followed General Procedure A. Imine formation was carried out with (S)-2-amino-3,3-dimethylbutan-1-ol (216 mg, 1.84 mmol) and 3-(bis(4-methoxyphenyl)phosphino)benzaldehyde (322 mg, 0.920 mmol). The imine was reduced with NaBH₄ (104 mg, 2.76 mmol) in anhydrous methanol. Work-up and silica gel chromatography of the resulting crude residue (1% Et₃N/EtOAc) to gave the title compound as a colorless oil (172 mg, 41%).

^1H NMR (CDCl₃, 500 MHz) δ 7.20 – 7.28 (m, 7H), 7.11 – 7.14 (m, 1H), 6.88 (d, 4H, J = 8.8 Hz), 3.83 (d, 1H, J = 13.1 Hz), 3.80 (s, 6H), 3.78 (d, 1H, J = 12.8 Hz), 3.60 (dd, 1H, J = 10.7, 4.9 Hz), 3.38 (dd, 1H, J = 10.7, 5.9 Hz), 2.30 – 2.32 (m, 1H), 0.91 (s, 9H); ^13C NMR (CDCl₃, 151 MHz) δ 160.5, 140.8 (d, J_C-P = 6.9 Hz), 139.2 (d, J_C-P = 11.6 Hz), 135.5 (d, J_C-P = 20.8 Hz), 133.0 (d, J_C-P = 20.8 Hz), 132.1 (d, J_C-P = 17.3 Hz), 128.7 (d, J_C-P = 5.8 Hz), 128.4, 128.3, 114.4 (d, J_C-P = 6.9 Hz), 67.1, 60.2, 55.4, 54.1, 34.6, 27.5; ^31P NMR (CDCl₃, 202 MHz) δ – 8.6; IR: 3376, 2954, 2869, 1594, 1497, 1402, 1364, 1285, 1177, 1095, 1030, 827, 796, 531 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₇H₃₅N₁O₃P₁ [M+H]^+: 452.2355, found: 452.2373; [α]D^20 = −2.89 (c = 0.485, CHCl₃, l = 50 mm).
(4S)-3-(3-(bis(4-methoxyphenyl)phosphanyl)benzyl)-4-(tert-butyl)-2-methoxyoxazolidine. Synthesized according to General Procedure B using \( N,N \)-dimethylformamide dimethylacetal (254 \( \mu \)L, 1.91 mmol), and (S)-2-((3-(bis(4-methoxyphenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (172 mg, 0.381 mmol) in methanol (5.5 mL). Extraction in the glovebox with degassed pentane (2 x 10 mL) and removal of the volatiles under reduced pressure gave the title compound as a viscous oil (167 mg, 89 %). 

\[ \text{\(^1\text{H NMR}\)} (\text{\( \text{C}_6\text{D}_6\)}, 600 \text{ MHz}) \delta 7.70 \text{ (d, 0.6H, } J = 7.3 \text{ Hz}), 7.62 \text{ (d, 0.6H, } J = 7.8 \text{ Hz}), 7.37 - 7.47 \text{ (m, 5H), 7.12 - 7.20 \text{ (m, 1.8H), 6.73 - 6.76 \text{ (m, 4H), 5.10 \text{ (s, 0.6H), 5.08 \text{ (s, 0.4H), 4.22 \text{ (d, 0.4H, } J = 13.7 \text{ Hz), 3.93 \text{ (t, 0.4H, } J = 8.1 \text{ Hz), 3.87 \text{ (d, 0.4H, } J = 13.7 \text{ Hz), 3.75 - 3.81 \text{ (m, 1.2H), 3.70 \text{ (dd, 0.4H, } J = 8.3, 2.4 \text{ Hz), 3.65 \text{ (d, 1.2H, } J = 5.4 \text{ Hz), 3.24 \text{ (s, 3.6H), 3.23 \text{ (s, 2.4H), 2.95 \text{ (s, 3H), 2.56 \text{ (dd, 0.4H, } J = 7.8, 2.4 \text{ Hz), 2.52 \text{ (t, 0.6H, } J = 8.3 \text{ Hz), 0.81 \text{ (s, 5.4H), 0.79 \text{ (s, 3.6H); \(^{13}\text{C NMR\)} (\text{CDCl}_3, 151 \text{ MHz}) \delta 160.5, 139.9 \text{ (d, } J_{\text{C-P}} = 5.8 \text{ Hz), 139.8 \text{ (d, } J_{\text{C-P}} = 5.8 \text{ Hz), 138.8 \text{ (d, } J_{\text{C-P}} = 10.4 \text{ Hz), 138.5 \text{ (d, } J_{\text{C-P}} = 9.2 \text{ Hz), 135.5 \text{ (d, } J_{\text{C-P}} = 20.8 \text{ Hz), 135.4 \text{ (d, } J_{\text{C-P}} = 20.8 \text{ Hz), 135.1 \text{ (d, } J_{\text{C-P}} = 8.4 \text{ Hz), 133.6 \text{ (d, } J_{\text{C-P}} = 17.3 \text{ Hz), 133.1 \text{ (d, } J_{\text{C-P}} = 17.3 \text{ Hz), 132.2 \text{ (d, } J_{\text{C-P}} = 20.8 \text{ Hz), 131.8 \text{ (d, } J_{\text{C-P}} = 20.8 \text{ Hz), 128.5 - 128.8 \text{ (7 signals), 128.3 \text{ (d, } J_{\text{C-P}} = 8.1 \text{ Hz), 115.6, 114.4 \text{ (d, } J_{\text{C-P}} = 8.1 \text{ Hz), 110.5, 73.1, 68.5, 66.6, 65.4, 60.2, 55.4, 53.1, 52.4, 52.3, 35.3, 33.8, 26.8, 26.4; \(^{31}\text{P NMR\)} (\text{C}_6\text{D}_6, 202 \text{ MHz}) \delta = 8.7; \text{ IR: } 2952, 2900, 1593, 1496, 1461, 1304, 1283, 1244, 1094, 1063, 1030, 826, 796, 530 \text{ cm}^{-1}; \text{ HRMS (DART-TOF) calcd. for } \text{C}_{29}\text{H}_{37}\text{N}_{1}\text{O}_{4}\text{P} [\text{M+H}]^+: 494.2460, \text{ found: 494.2445; } [\alpha]_D^{20} = +20.8 \text{ (c = 0.570, CHCl}_3, \ell = 50 \text{ mm).} }\]
(S)-2-((3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol. Synthesized according to General Procedure A using (S)-2-amino-3,3-dimethylbutan-1-ol (125 mg, 1.07 mmol), THF (8 mL), and 3-(bis(4-(trifluoromethyl)phenyl)phosphanyl). Reduction of the imine was carried out with NaBH₄ (94 mg, 2.5 mmol) in anhydrous methanol (6 mL). After workup, the crude residue was purified by column chromatography (1% Et₃N/EtOAc) to afford the title compound as a colorless oil (218 mg, 50%).

**1H NMR** (CDCl₃, 500 MHz) δ 7.72 (s, 1H), 7.60 (d, 4H, J = 7.8 Hz), 7.35 – 7.41 (m, 5H), 7.31 (d 1H, J = 7.3 Hz), 7.19 (app t, 1H, J = 7.3 Hz), 3.88 (d, 1H, J = 13.2 Hz), 3.82 (d, 1H, J = 13.2 Hz), 3.61 – 3.64 (m, 1H), 3.37 – 3.40 (m, 1H), 2.32 (dd, 1H, J = 5.9, 4.9 Hz), 0.90 (s, 9H); **13C NMR** (CDCl₃, 151 MHz) δ 141.7 (d, J_C-P = 9.3 Hz), 135.3 (d, J_C-P = 10.4 Hz), 133.8 – 134.6 (6 signals), 133.0 (d, J_C-P = 18.5 Hz), 131.3 (q, J_C-F = 32.4 Hz), 129.8, 129.4 (d, J_C-P = 2.3 Hz), 124.2 (q, J_C-F = 273 Hz), 67.4, 60.4, 54.1, 34.6, 27.5; **31P NMR** (CDCl₃, 202 MHz) δ −5.6; **19F NMR** (CDCl₃, 470 MHz) δ −62.9; **IR**: 3415, 2958, 2870, 1477, 1396, 1323, 1127, 1107, 1060, 1016, 997, 832, 599 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₂₇H₂₇F₆N₁O₁P₁ [M+H]^+: 528.1891, found: 528.1874; [α]D²⁰ = +4.44 (c = 0.540, CHCl₃, l = 50 mm).
(4S)-3-(3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzyl)-4-(tert-butyl)-2-methoxyoxazolidine. Followed General Procedure B using N,N-dimethylformamide dimethyleacetal (256 µL, 1.90 mmol), (S)-2-(((3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (200 mg, 0.380 mmol), and methanol (6 mL). Extraction pentane (2 x 10 mL) and concentration under reduced pressure afforded the title compound as a viscous oil (198 mg, 92%).

$^1$H NMR (C$_6$D$_6$, 500 MHz) δ 7.57 (d, 0.6H, $J = 7.8$ Hz), 7.53 (d, 0.4H, $J = 7.8$ Hz), 7.41 (d, 0.4H, $J = 7.8$ Hz), 7.07 – 7.28 (m, 10.6H), 4.98 (s, 0.4H), 4.96 (s, 0.6H), 4.19 (d, 0.4H, $J = 13.7$ Hz), 3.88 (t, 0.4H, $J = 8.1$ Hz), 3.85 (d, 0.4H, $J = 13.7$ Hz), 3.76 (t, 0.6H, $J = 8.1$ Hz), 3.64 – 3.70 (m, 1.6H), 3.58 (d, 0.6H, $J = 8.1$ Hz), 2.90 (s, 1.2H), 2.87 (s, 1.8H), 2.52 (dd, 0.4H, $J = 7.8$, 2.4 Hz), 2.46 (dd, 0.6H, $J = 8.8$, 7.8 Hz), 0.74 (s, 3.6H), 0.73 (s, 5.4H);

$^{13}$C NMR (CDCl$_3$, 151 MHz) δ 141.7 – 142.0 (5 signals), 141.9 (d, $J_{C-P} = 5.8$ Hz), 140.9 (d, $J_{C-P} = 5.8$ Hz), 135.1 (d, $J_{C-P} = 10.4$ Hz), 134.8 (d, $J_{C-P} = 9.4$ Hz), 133.7 – 134.2 (8 signals), 133.2 (d, $J_{C-P} = 24.3$ Hz), 132.8 (d, $J_{C-P} = 24.3$ Hz), 131.2 (q, $J_{C-F} = 32.4$ Hz), 129.9, 129.8, 129.1 (d, $J_{C-P} = 9.3$ Hz), 128.9 (d, $J_{C-P} = 8.1$ Hz), 125.6, 124.2 (q, $J_{C-F} = 273$ Hz), 115.9, 110.3, 73.3, 68.5, 66.4, 65.4, 60.0, 53.0, 52.4, 52.2, 35.3, 33.8, 26.8, 26.3; $^{31}$P NMR (C$_6$D$_6$, 202 MHz) δ – 5.8;

$^{19}$F NMR (CDCl$_3$, 564 MHz) δ – 62.9 IR: 2956, 1606, 1477, 1396, 1320, 1164, 1124, 1106, 1059, 1016, 998, 831, 700, 599, 514 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{29}$H$_{31}$F$_6$N$_2$O$_2$P$_1$ [M+H]$^+$: 570.1997, found: 570.1985; [α]$_D^{20}$ = +16.4 (c = 0.475, CHCl$_3$, l = 50 mm).
(S)-2-((2-(3-(diphenylphosphino)phenyl)propan-2-yl)amino)-3-methylbutan-1-ol. Titanium ethoxide (1.25 mL, 5.92 mmol) was added to a solution of 1-(3-(diphenylphosphino)phenyl)ethanone (1.00 g, 3.29 mmol) and (S)-3-methyl-1-((triethylsilyl)oxy)butan-2-amine (715 mg, 3.29 mmol) in THF (6 mL) and heated to 60 °C under argon overnight. The reaction was cooled to room temperature and concentrated in vacuo. Titanium byproducts were distilled off under high vacuum on a Kugelrohr distillation apparatus. The remaining residue was suspended in ethyl acetate and filtered through a short plug of silica to afford the imine as a viscous orange oil (1.66 g, quantative), which was used directly in the next reaction without further purification.

To a solution of (S)-N-(1-(3-(diphenylphosphino)phenyl)ethylidene)-3-methyl-1-((triethylsilyl)oxy)butan-2-amine (1.66 g, 3.29 mmol) in tetrahydrofuran (22 mL) at 0 °C was added methyllithium (4.0 mL, 9.87 mmol, 2.50 M solution in diethoxymethane). The reaction was allowed to warm to room temperature overnight, quenched by the dropwise addition of water (20 mL), and extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (30% EtOAc/Hex containing 1% Et₃N) to afford the title compound as a colorless oil (428 mg, 32%).

**¹H NMR** (CDCl₃, 500 MHz) δ 7.41 – 7.45 (m, 2H), 7.28 – 7.34 (m, 11H), 7.14 (t, 1H, J = 7.3 Hz), 3.21 (dd, 1H, J = 10.5 Hz, 4.7 Hz), 3.16 (dd, 1H, J = 10.3 Hz, 4.4 Hz), 2.34 – 2.37 (m, 1H), 1.45-1.41 (m, 1H), 1.32 (s, 3H), 1.42 (s, 3H), 0.73 (d, 3H, J = 6.4 Hz), 0.72 (d, 3H, J = 6.8 Hz); **¹³C NMR** (CDCl₃, 126 MHz) δ148.3 (d, J_{C,P} = 6.7 Hz), 137.3 – 137.5 (4 signals), 137.2 (d, J_{C,P} = 11.4 Hz), 134.0 (d, J_{C,P} = 1.9 Hz), 133.8 (d, J_{C,P} = 1.9 Hz).
N.O

OMe

Me

Me

Me

Me

PPh₂

N

O

(4S)-3-(2-(3-(diphenylphosphino)phenyl)propan-2-yl)-4-isopropyl-2-methoxyoxazolidine. Synthesized according to General Procedure B using (S)-2-((2-(3-(diphenylphosphino)phenyl)propan-2-yl)amino)-3-methylbutan-1-ol (373 mg, 0.921 mmol), N,N-dimethylformamide dimethyl acetal (0.61 mL, 4.6 mmol) in anhydrous methanol (13 mL). After the completion of the reaction, the residue was extracted with dry, degassed pentane (2 x 10 mL), which was removed under vacuum to afford a colorless oil which is a single diastereomer (400 mg, 97%). \(^1\)H NMR (\(\text{C}_6\text{D}_6\), 500 MHz) \(\delta\) 7.54 – 7.57 (m, 2H), 7.27 – 7.34 (m, 13H), 7.15 – 7.18 (m, 1H), 5.02 (s, 1H), 3.88 (t, 1H, \(J = 7.8\) Hz), 3.71 – 3.74 (m, 1H), 3.00 – 3.04 (m, 1H), 2.92 (s, 3H), 1.60 – 1.65 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 0.86 (d, 3H, \(J = 6.8\) Hz), 0.82 (d, 3H, \(J = 6.9\) Hz); \(^{13}\)C NMR (CDCl₃, 126 MHz) \(\delta\) 148.7 (d, \(J_{C-P} = 6.7\) Hz), 137.5 (d, \(J_{C-P} = 10.5\) Hz), 136.7 (d, \(J_{C-P} = 10.5\) Hz), 134.0 (d, \(J_{C-P} = 5.7\) Hz), 133.8 (d, \(J_{C-P} = 5.7\) Hz), 132.6 (d, \(J_{C-P} = 21.9\) Hz), 132.2 (d, \(J_{C-P} = 18.1\) Hz), 128.9 (d, \(J_{C-P} = 3.0\) Hz), 128.7 (d, \(J_{C-P} = 6.7\) Hz), 128.3 (d, \(J_{C-P} = 6.7\) Hz), 127.5, 113.3, 68.6, 62.7, 59.3, 52.9, 33.3, 30.2, 24.0, 21.0, 18.5; \(^{31}\)P NMR (CDCl₃, 202 MHz) \(\delta\) – 5.1; IR: 2953, 1434, 1077, 1066, 1027, 743, 695, 498 cm⁻¹; HRMS (DART-TOF) calcd. for C₂₈H₃₅N₁O₂P₁ [M+H]⁺: 448.2405, found: 448.2390; \([\alpha]_d^{20}\) = – 22.4 (c = 0.660, CDCl₃, l = 50 mm).
(S)-4-(tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)oxazolidine. To a stirring suspension of (S)-2-((3-(diphenylphosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (383 mg, 0.979 mmol) and paraformaldehyde (44 mg, 1.5 mmol) in anhydrous toluene (25 mL) was added p-toluenesulfonic acid monohydrate (39 mg, 0.20 mmol). The solution was heated to reflux overnight with azeotropically removal of water. The reaction was cooled to room temperature and the volatiles were removed under reduced pressure. The remaining residue was diluted with chloroform (30 mL) and washed with saturated NaHCO$_3$ (15 mL). The aqueous layer was extracted with an additional portion of chloroform (30 mL), the combined organics were dried over MgSO$_4$, filtered, and concentrated in vacuo. Flash column chromatography (10% EtOAc/Hex) afforded the product as a colorless oil (203 mg, 51%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.27 – 7.36 (m, 13H), 7.19 (t, 1H, $J = 7.5$ Hz), 4.18 (d, 1H, $J = 5.9$ Hz), 4.00 (d, 1H, $J = 6.4$ Hz), 3.95 (t, 1H, $J = 8.3$ Hz), 3.79 (d, 1H, $J = 13.7$ Hz), 3.72 (d, 1H, $J = 13.2$ Hz), 3.50 (dd, 1H, $J = 8.8, 7.3$ Hz), 2.71 (t, 1H, $J = 7.3$ Hz), 0.82 (s, 9H); $^{13}$C NMR (CDCl$_3$, 151 MHz) $\delta$ 140.8, 137.5 (d, $J_{C-P} = 10.4$ Hz), 137.4 (d, $J_{C-P} = 9.3$ Hz), 134.1 (d, $J_{C-P} = 25.4$ Hz), 133.9 (d, $J_{C-P} = 18.5$ Hz), 132.6 (d, $J_{C-P} = 19.7$ Hz), 129.2 128.9, 128.7 (d, $J_{C-P} = 6.9$ Hz), 128.6 (d, $J_{C-P} = 6.9$ Hz), 87.2, 73.6, 66.7, 62.2, 34.6, 26.4; $^{31}$P NMR (CDCl$_3$, 202 MHz) $\delta$ – 5.5; IR: 2953, 2867, 1477, 1434, 1392, 1157, 1068, 1013, 913, 743, 696, 495 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{26}$H$_{31}$N$_1$O$_1$P$_1$ [M+H]$^+$: 404.2143, found: 404.2131; $[\alpha]_D^{20} = -6.43$ (c = 0.435, CHCl$_3$, l = 50 mm).
3.7.3 Substrate Syntheses and Characterization

The following compounds were synthesized according to literature procedures and matched all reported spectroscopic data: (S)-2-methyl-3-(trityloxy)propanal,\(^{30}\) 2-(((R)-4,4-dibromo-2-methylbut-3-en-1-yl)oxy)tetrahydro-2H-pyran,\(^{31}\) methyl (S)-2-(hydroxymethyl)-3-methylbutanoate,\(^{32}\) (R)-2-phenyloxirane,\(^{33}\) (R)-2-(4-chlorophenyl)oxirane,\(^{33}\) (R)-2-(4-bromophenyl)oxirane,\(^{34}\) (R)-2-(4-methoxyphenyl)oxirane,\(^{35}\) (R)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol,\(^{36}\) (R)-2-(3-(methoxy)phenyl)oxirane,\(^{33}\) (R,Z)-non-3-ene-1,2-diol.\(^{37}\)

\[
\text{(R,Z)-(((2-methyloct-3-en-1-yl)oxy)methanetriyl)tribenzene.}
\]

To a stirring suspension of (1-pentyl)triphenylphosphonium bromide (3.00 g, 7.26 mmol) in THF (30 mL) at \(-78^\circ C\) was added \(n\)-butyllithium (2.2 mL, 2.4 M solution in hexane). The reaction was stirred at \(-78^\circ C\) for 10 minutes and was then allowed to warm to 0 \(^\circ\)C over 25 minutes. The bright orange solution was recooled to \(-78^\circ C\) and (S)-2-methyl-3-(trityloxy)propanal (1.60 g, 4.84 mmol) was added as a solution in THF (5 mL). The reaction was quenched by the addition of water (20

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mL), extracted with Et₂O (3 x 40 mL), and the combined organic phases were dried over MgSO₄. Filtration and removal of the solvent under reduced pressure afforded a yellow residue, which was subjected to silica gel chromatography (15% DCM/Hex) to afford the title compound as a colorless oil (1.58 g, 85%). ¹H NMR (600 MHz, CDCl₃) δ 7.44 – 7.46 (m, 6H), 7.27 – 7.30 (m, 6H), 7.21 – 7.24 (m, 3H), 5.34 – 5.38 (m, 1H), 5.14 – 5.18 (m, 1H), 2.94 – 2.97 (m, 1H), 2.86 – 2.89 (m, 1H), 2.74 – 2.80 (m, 1H), 2.03 – 2.07 (m, 2H), 1.29 – 1.34 (m, 4H), 1.00 (d, 3H, J = 6.4 Hz), 0.90 (t, 3H, J = 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 144.7, 133.1, 130.3, 129.0, 127.9, 127.0, 86.4, 68.5, 33.0, 32.3, 27.5, 22.6, 18.4, 14.2; IR 2957, 2927, 2870, 1491, 1449, 1065, 1034, 774, 763, 705 cm⁻¹; HRMS (ESI⁺) calcd. for C₂₈H₃₂O₁Na₁ [M+Na⁺]: 407.2351, found: 407.2349; [α]D²⁰ = −39.4 (c = 0.420, CHCl₃, l = 50 mm).

(R,Z)-2-methyloct-3-en-1-ol. In a round-bottom flask p-toluenesulfonic acid monohydrate (635 mg, 3.34 mmol) and (R,Z)-((2-methyloct-3-en-1-yl)oxy)methanetriyl)tribenzene (3.21 g, 8.35 mmol) were stirred in dichloromethane (14 mL) and anhydrous methanol (10 mL) overnight. The volatiles were removed in vacuo and the residue was partitioned between saturated sodium bicarbonate (20 mL) and dichloromethane (40 mL). The aqueous layer was washed with an additional portion of dichloromethane (40 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (15% EtOAc/Hex), affording a colorless oil (743 mg, 62%). ¹H NMR (600 MHz, CDCl₃) δ 5.50 – 5.54 (m, 1H), 5.11 (dt, 1H, J = 11.2, 1.2 Hz), 3.48 (dd, 1H, J = 10.6, 5.9 Hz), 3.33 (dd, 1H, J = 10.6, 8.2 Hz), 2.68 – 2.73 (m, 1H), 2.02 – 2.12 (m, 2H), 1.42 (br s, 1H), 1.30 – 1.36 (m, 4H), 0.94 (d, 3H, J = 7.0 Hz), 0.89 (t, 3H, J
= 7.0 Hz); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 132.7, 132.1, 67.9, 35.0, 32.3, 27.6, 22.6, 17.2, 14.2; IR 3330, 2956, 2927, 2972, 1456, 1378, 1068, 1002, 990, 713, 607 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_9$H$_{19}$O$_1$ [M+H]$^+$: 143.1436, found: 143.1430; [α]$_D^{20}$ = + 11.8 (c = 0.805, CHCl$_3$, l = 50 mm).

(S,Z)-2-methyloct-3-en-1-ol. Same experimental procedure followed as (R,Z)-2-methyloct-3-en-1-ol and all spectral and analytical data are identical except for the optical rotation [α]$_D^{20}$ = −9.51 (c = 0.745, CHCl$_3$, l = 50 mm).

Methyl-(S)-3-methyl-2-((trityloxy)methyl)butanoate. Trityl chloride (3.00 g, 10.6 mmol), DMAP (74 mg, 0.59 mmol), methyl-(S)-2-(hydroxymethyl)-3-methylbutanoate (865 mg, 5.92 mmol), and dichloromethane (20 mL) were added to a round-bottom flask under nitrogen. Triethylamine (1.64 mL, 11.8 mmol) was added to the vigorously stirred solution slowly and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH$_4$Cl (30 mL) and extracted with dichloromethane (2 x 60 mL). The combined organics were washed with water (20 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a viscous oil (2.25 g, 98%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.42 (m, 6H), 7.27 – 7.31 (m, 6H), 7.21 – 7.24 (m, 3H), 3.73 (s, 3H), 3.33 (t, 1H, $J = 8.8$ Hz), 3.25 (dd, 1H, $J = 8.8$, 5.4 Hz), 2.39 – 2.44 (m, 1H), 1.86 – 1.90 (m, 1H), 0.89 (t, 3H, $J = 7.1$ Hz), 0.83 (d, 3H, $J = 6.5$ Hz), 0.76 (d, 3H, $J = 6.8$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.0, 144.2, 128.9, 127.9, 127.2, 86.8, 63.4, 53.5, 51.5, 28.1, 20.8, 20.7; IR 1961, 1736, 1491, 1448, 1221, 1195, 1079,
1033, 773, 763, 747, 633 cm\(^{-1}\); HRMS (ESI\(^{+}\)) calcd. for \(C_{26}H_{28}O_{3}Na\) \([M+Na]^{+}\): 411.1936, found: 411.1938; \([\alpha]_{D}^{20} = +14.3\ (c = 0.355, \text{CHCl}_3, l = 50 \text{ mm})\).

\((R)-3\text{-methyl-2-((trityloxy)methyl)butan-1-ol}\). To a suspension of lithium aluminum hydride (210 mg, 5.52 mmol) in THF (12 mL) at 0 °C was added a solution of methyl-(S)-3-methyl-2-((trityloxy)methyl)butanoate (1.43 g, 3.58 mmol) in THF (6 mL). The reaction was allowed to warm to room temperature overnight. After cooling to 0 °C, the reaction was quenched by the slow, drop-wise addition of water (2.5 mL). Anhydrous MgSO\(_4\) was added to the flask, and the slurry was filtered and concentrated under reduced pressure to afford the title compound as a viscous colorless oil (1.30 g, 98%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.45 (m, 6H), 7.29 – 7.33 (m, 6H), 7.23 – 7.26 (m, 3H), 3.72 – 3.76 (m, 1H), 3.65 – 3.70 (m, 1H), 3.38 (dd, 1H, \(J = 9.3, 3.9 \text{ Hz}\)), 3.19 (dd, 1H, \(J = 9.3, 7.3 \text{ Hz}\)), 2.42 (dd, 1H, \(J = 6.9, 4.9 \text{ Hz}\)), 1.72 – 1.77 (m, 1H), 1.59 – 1.62 (m, 1H), 0.83 (d, 3H, \(J = 6.9 \text{ Hz}\)), 0.76 (d, 3H, \(J = 6.8 \text{ Hz}\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 144.0, 128.8, 128.1, 127.3, 87.5, 65.3, 64.7, 47.2, 26.9, 20.5; IR 3428, 2957, 2974, 1490, 1338, 1219, 1153, 1065, 1031 1002, 762, 745, 704, 648 cm\(^{-1}\); HRMS (ESI\(^{+}\)) calcd. for \(C_{25}H_{28}O_{2}Na\) \([M+Na]^{+}\): 383,1987, found: 383.1990; \([\alpha]_{D}^{20} = +23.1\ (c = 0.170, \text{CHCl}_3, l = 50 \text{ mm})\).

\((S)-3\text{-methyl-2-((trityloxy)methyl)butanal}\). To a solution of oxalyl chloride (1.10 mL, 12.5 mmol) in DCM (31 mL) at –78 °C was added DMSO (2.20 mL, 31.3 mmol). After stirring at this temperature for 30 minutes a solution of \((R)-3\text{-methyl-2-((trityloxy)methyl)butan-1-ol}\) (2.26 g, 6.27 mmol) in DCM (6 mL) was added drop-wise. The reaction mixture was stirred at –78 °C for a
further 45 minutes before Et$_3$N (3.50 mL, 25.0 mmol) was added drop-wise to the solution. After 15 minutes, the mixture was warmed to 0 °C and quenched by the addition of water (30 mL) then extracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated NaHCO$_3$ (30 mL), brine (20 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford a yellow oil that was used in the next reaction immediately without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.66 (d, 1H, $J$ = 3.5 Hz), 7.36 – 7.39 (m, 6H), 7.24 – 7.26 (m, 6H), 7.20 – 7.22 (m, 3H), 3.35 (d, 2H, $J$ = 6.0 Hz), 2.26 – 2.30 (m, 1H), 2.05 – 2.08 (m, 1H), 0.85 (d, 3H, $J$ = 7.0 Hz), 0.77 (d, 3H, $J$ = 6.5 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 205.0, 143.9, 128.8, 128.0, 127.3, 87.1, 61.2, 59.0, 26.2, 20.7, 20.2.

(R,Z)-(((2-isopropyloct-3-en-1-yl)oxy)methanetriyl)tribenzene. To a suspension of (1-pentyl)triphenylphosphonium bromide (3.12 g, 7.56 mmol) in THF (40 mL) at -78 °C was added n-butyllithium (3.00 mL, 6.93 mmol, 2.30 M in pentane). The bright solution was stirred at -78 °C for 15 minutes, warmed to 0 °C over 30 minutes, and re-cooled to -78 °C. (S)-3-methyl-2-((trityloxy)methyl)butanal (2.26 g, 6.30 mmol) was added as a solution in THF (6 mL) and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of water (30 mL) and extracted with diethyl ether (2 x 60 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated. Silica gel chromatography (10% DCM/Hex) afforded the title compound as a colorless oil (1.98 g, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.46 (m, 6H), 7.27 – 7.30 (m, 6H), 7.20 – 7.23 (m, 3H), 5.47 – 5.52 (m, 1H), 5.21 – 5.26 (m, 1H), 2.97 – 3.04 (m, 2H), 2.46 – 2.49 (m, 1H), 2.05 – 2.08 (m, 2H), 1.84 – 1.89 (m, 1H), 1.31 – 1.35 (m, 4H), 0.90 (t, 3H, $J$ =
6.9 Hz), 0.77 (d, 3H, \(J = 6.9\) Hz), 0.74 (d, 3H, \(J = 6.8\) Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 144.7, 131.9, 129.6, 129.0, 127.8, 127.0, 65.6, 44.1, 32.3, 29.0, 27.7, 22.7, 21.1, 18.8, 14.3; IR 2955, 2925, 2870, 1490, 1448, 1068, 1032, 898, 762, 744, 632 cm\(^{-1}\); HRMS (ESI\(^+\)) calcd. for \(C_{30}H_{36}O_1Na\) [M+Na\(^+\)]\(^+\): 435.2664, found: 435.2659; \([\alpha]\)\(_D\)\(^{20}\) = −44.8 (c = 0.525, CHCl\(_3\), \(l = 50\) mm).

(R,Z)-2-isopropyloct-3-en-1-ol. A solution of glacial acetic acid (32 mL), water (3.5 mL), and (R,Z)-((2-isopropyloct-3-en-1-yl)oxy)methanetriyl)tribenzene (1.98 g, 4.80 mmol) was heated to 50 °C for 5 hours. The reaction was cooled to room temperature and the volatiles removed under reduced pressure. Trityl alcohol was precipitated out by the addition of hexane and filtered off. The organic layer was concentrated \textit{in vacuo} and the crude residue was subjected to column chromatography (7% EtOAc/Hex) to afford the title compound as a colorless oil (531 mg, 65%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.65 – 5.70 (m, 1H), 5.12 – 5.16 (m, 1H), 3.66 – 3.68 (m, 1H), 3.34 – 3.37 (m, 1H), 2.05 – 2.10 (m, 2H), 1.57 – 1.64 (m, 1H), 1.32 – 1.35 (m, 5H), 0.91 (d, 3H, \(J = 6.8\) Hz), 0.89 – 0.91 (m, 3H), 0.86 (d, 3H, \(J = 6.8\) Hz); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 134.9, 129.1, 64.9, 46.8, 32.2, 29.4, 27.8, 22.6, 21.0, 19.9, 14.2; IR 3331, 2956, 2927, 1465, 1214, 1060, 1034, 1013, 750, 668 cm\(^{-1}\); HRMS (DART-TOF) calcd. for \(C_{11}H_{23}O_1\) [M+H\(^+\)]\(^+\): 171.1749, found: 171.1747; \([\alpha]\)\(_D\)\(^{20}\) = −3.26 (c = 0.470, CHCl\(_3\), \(l = 50\) mm).

2-(((R)-2-methyloct-3-yn-1-yl)oxy)tetrahydro-2\(H\)-pyran. To a solution of 2-(((R)-4,4-dibromo-2-methylbut-3-en-1-yl)oxy)tetrahydro-2\(H\)-pyran (2.18 g, 6.64 mmol) in THF (50 mL) at −78 °C was added
\( n\text{-BuLi} \) (6.10 mL, 14.6 mmol, 2.40 M solution in hexane). The reaction was stirred at this temperature for 45 minutes and 1-iodobutane (3.80 mL, 33.3 mmol) was added. After warming the room temperature over 40 minutes, the reaction was heated to 55 °C for 3 hours. The reaction was cooled to room temperature, quenched by the addition of saturated aqueous \( \text{NH}_4\text{Cl} \) (30 mL), diluted further with water (5 mL), and extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over \( \text{MgSO}_4 \), filtered, and concentrated. Silica gel chromatography (3% EtOAc/Hex) afforded the title compound as a colorless oil that exists as a 1:1 mixture of diastereomers (1.04 g, 70%).

\(^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 4.65 (t, 0.5H, \( J = 3.4 \) Hz), 4.63 (t, 0.5H, \( J = 3.4 \) Hz), 3.84 – 3.91 (m, 1H), 3.73 (dd, 0.5H, \( J = 9.5, 6.1 \) Hz), 3.55 (dd, 0.5H, \( J = 9.5, 8.1 \) Hz), 3.50 – 3.51 (m, 1H), 3.45 (dd, 0.5H, \( J = 9.3, 6.4 \) Hz), 3.25 (dd, 0.5H, \( J = 9.5, 7.6 \) Hz), 2.66 – 2.70 (m, 1H), 2.14 (t, 2H, \( J = 6.9 \) Hz), 1.82 – 1.85 (m, 1H), 1.68 – 1.73 (m, 1H), 1.36 – 1.63 (m, 8H), 1.17 (d, 3H, \( J = 6.9 \) Hz), 0.89 (t, 3H, \( J = 7.3 \) Hz); \(^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \) 99.1, 98.8, 82.3, 82.2, 81.3, 81.2, 72.1, 72.0, 62.4, 622, 31.4, 31.3, 30.8, 30.7, 27.0, 26.9, 25.7, 22.1, 19.6, 19.5, 18.6, 18.5, 18.4, 13.8; \( \text{IR} \) 2933, 2812, 1123, 1061, 1034, 973 cm\(^{-1}\); \( \text{HRMS} \) (DART-TOF) calcd. for C\(_{14}\)H\(_{25}\)O\(_2\) [M+H]\(^+\): 225.1855, found: 225.1855.

\((\text{R})\text{-2-methyloct-3-yn-1-ol}\. \) To a round-bottom flask containing \( p\)-TsOH monohydrate (130 mg, 0.674 mmol) was added 2-((\(\text{R}\))-2-methyloct-3-yn-1-yl)oxy)tetrahydro-2H-pyran (1.51 g, 6.74 mmol) in anhydrous methanol (20 mL). The reaction was allowed to stir at room temperature until all starting material was consumed (approx. 3 hours). The solution was transferred to a separatory funnel, diluted with dichloromethane (40 mL) and washed with saturated aqueous
NaHCO₃ (15 mL). The layers were separated and the aqueous layer was extracted with an additional portion of dichloromethane (30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. Silica gel chromatography (15% EtOAc/Hex) afforded the title compound as a colorless oil (788 mg, 83%). ¹H NMR (600 MHz, CDCl₃) δ 3.53 (dd, 1H, J = 10.3, 5.6 Hz), 3.44 (dd, 1H, J = 10.3, 7.1 Hz), 2.62 – 2.65 (m, 1H), 2.16 (dt, 2H, J = 7.3, 2.2 Hz), 1.81 (br s, 1H), 1.45 – 1.49 (m, 2H), 1.35 – 1.44 (m, 2H), 1.13 (d, 3H, J = 7.1 Hz), 0.90 (t, 3H, J = 7.3 Hz); ¹³C NMR (151 MHz, CDCl₃) δ 82.9, 81.5, 67.3, 31.3, 29.8 22.1, 18.6, 17.5, 13.8; IR 3340, 2958, 2932, 2874, 1457, 1379, 1329, 1039, 1015 cm⁻¹; HRMS (DART-TOF) calcd. for C₉H₁₇O₁ [M+H]⁺: 141.1279, found: 141.1281; [α]D²⁰ = +15.2 (c = 1.13, CHCl₃, l = 50 mm).

(R,E)-2-methyloct-3-en-1-ol. A flame-dried, three-neck, round-bottom flask fitted with a dry ice condenser was charged with ammonia (7.2 mL) at −78 °C. Sodium metal (328 mg, 14.3 mmol) was added piece-wise at this temperature, upon which time the solution turned deep blue. The solution was allowed to stir while warming to −35 °C over 20 minutes and (R)-2-methyloct-3-yn-1-ol (0.500 g, 3.57 mmol) was added drop-wise as a solution in THF (4 mL). The reaction was allowed to stir for 3 hours at −30 °C and was quenched by the careful addition of solid NH₄Cl (approx 10 eq). The ammonia was allowed to evaporate and the reaction mixture was diluted with water (15 mL). Extraction with dichloromethane (2 x 30 mL), followed by drying over MgSO₄ and concentration in vacuo showed that trace amounts of starting material remained. The crude residue was re-subjected to the same reaction conditions and work-up procedure. Purification on a short plug of silica afforded the title compound as a colorless oil (419 mg, 83%). ¹H NMR (600 MHz, CDCl₃) δ 5.50
- 5.55 (m, 1H), 5.22 – 5.26 (m, 1H), 3.44 – 3.48 (m, 1H), 3.32 – 3.36 (m, 1H), 2.27 – 2.32 (m, 1H), 2.00 – 2.02 (m, 2H), 1.44 (br s, 1H), 1.26 – 1.37 (m, 4H), 0.97 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 7.0 Hz); \( ^{13}C \) NMR (151 MHz, CDCl\( _3 \)) \( \delta \) 132.7, 132.4, 67.5, 40.0, 32.5, 31.9, 22.4, 16.8, 14.1; IR 3340, 2957, 2924, 2972, 1457, 1378, 1034, 968 cm\(^{-1} \); HRMS (DART-TOF) calcd. for C\(_9\)H\(_{19}\)O\(_1\) [M+H]\(^+\): 143.1436, found: 143.1433; \([\alpha]_D\)\(^{20} = +17.8 \) (c = 0.920, CHCl\(_3\), \( l = 50 \) mm).

**General Procedure C (Preparation of Aryl Substrates):** To a suspension enantiopure aryloxirane (1 equiv) and CuCl(COD) (0.10 equiv) in THF (0.40 M) at – 78 °C was added (Z)-prop-1-en-1-ylmagnesium bromide (1.5 equiv, 1.0 M solution in THF). The reaction was allowed to warm to room temperature over 8 hours, quenched by the addition of water (15 mL), and extracted with EtOAc (2 x 40 mL). The combined organic phases were dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography (20% EtOAc/Hex) to afford the title compound.

\[
\begin{align*}
\text{(S,Z)-2-phenylpent-3-en-1-ol.} & \quad \text{Synthesized according to General Procedure C using (R)-2-phenyloxirane (1.64 mL, 19.3 mmol) to afford the title compound as a colorless oil (1.43 g, 46%)}. \\
\text{\( ^{1}H \) NMR} & \quad (500 MHz, CDCl\(_3 \)) \delta 7.31 – 7.34 (m, 2H), 7.22 – 7.27 (m, 3H), 5.71 – 5.74 (m, 1H), 5.59 – 5.64 (m, 1H), 3.85 – 3.90 (m, 1H), 3.79 – 3.81 (m, 1H), 3.70 – 3.73 (m, 1H), 1.70 (dd, 3H, J = 6.5, 1.5 Hz), 1.47 (br s, 1H); \text{\( ^{13}C \) NMR} (126 MHz, CDCl\(_3 \)) \delta 141.8, 130.2, 129.0, 128.0, 127.6, 126.9, 67.2, 46.3, 13.5; \text{IR} 3560, 3026, 1493, 1452, 1050, 757, 714, 699, \end{align*}
\]

668 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{11}\)H\(_{13}\) [M+H-H\(_2\)O]\(^+\): 145.1018, found: 145.1020; \(\lbrack \alpha \rbrack_\text{D}^{20} = + 164\) (\(c = 0.440\), CHCl\(_3\), \(l = 50\) mm).

(S,Z)-2-(4-methoxyphenyl)pent-3-en-1-ol. Synthesized according to General Procedure C using (R)-2-(4-methoxyphenyl)oxirane (795 mg, 5.29 mmol) to afford the title compound as a yellow oil (674 mg, 85%).

\(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.17 (d, 2H, \(J = 8.3\) Hz), 6.87 (d, 2H, \(J = 8.8\) Hz), 5.68 – 5.72 (m, 1H), 5.56 – 5.60 (m, 1H), 3.80 – 3.85 (m, 1H), 3.79 (s, 3H), 3.74 – 3.78 (m, 1H), 3.66 – 3.70 (m, 1H), 1.69 (dd, 3H, \(J = 6.8, 2.0\) Hz), 1.45 (br s, 1H); \(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 158.6, 133.7, 130.5, 128.9, 127.3, 114.4, 67.3, 55.5, 45.4, 13.5; IR 3394, 3011, 2934, 2836, 1610, 1511, 1464, 1248, 1178, 1036, 828, 703 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{12}\)H\(_{15}\)O\(_1\) [M+H-H\(_2\)O]\(^+\): 175.1123, found: 175.1127; \(\lbrack \alpha \rbrack_\text{D}^{20} = + 157\) (\(c = 0.450\), CHCl\(_3\), \(l = 50\) mm).

(S,Z)-2-(4-bromophenyl)pent-3-en-1-ol. Synthesized according to General Procedure C using (R)-2-(4-bromophenyl)oxirane (1.00 g, 5.02 mmol) to afford the title compound as a yellow oil (662 mg, 55%). \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44 (d, 2H, \(J = 8.3\) Hz), 7.13 (d, 2H, \(J = 8.3\) Hz), 5.70 – 5.75 (m, 1H), 5.54 – 5.58 (m, 1H), 3.81 – 3.84 (m, 1H), 3.76 – 3.79 (m, 1H), 3.70 (dd, 1H, \(J = 10.8, 7.3\) Hz), 1.68 (d, 3H, \(J = 6.9\) Hz), 1.47 (br s, 1H); \(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 140.9, 132.0, 129.7, 129.6, 128.1, 120.7, 67.0, 45.7, 13.5; IR 3362, 3016, 2930, 2874, 1487, 1377, 1214, 1072, 1052, 1010, 819, 785, 729, 668 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{11}\)H\(_{12}\)Br\(_1\) [M+H-H\(_2\)O]\(^+\): 223.0122, found: 223.0115; \(\lbrack \alpha \rbrack_\text{D}^{20} = + 133\) (\(c = 0.710\), CHCl\(_3\), \(l = 50\) mm).
(S,Z)-2-(4-chlorophenyl)pent-3-en-1-ol. Synthesized according to General Procedure C using (R)-2-(4-chlorophenyl)oxirane (1.88 g, 12.2 mmol) to afford the title compound as a yellow oil (700 mg, 30%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (d, 2H, $J = 8.3$ Hz), 7.18 (d, 2H, $J = 8.3$ Hz), 5.71 – 5.75 (m, 1H), 5.54 – 5.58 (m, 1H), 3.82 – 3.87 (m, 1H), 3.76 – 3.79 (m, 1H), 3.68 – 3.72 (m, 1H), 1.68 (d, 3H, $J = 6.8$ Hz), 1.48 (br s, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 140.4, 132.6, 129.7, 129.3, 129.0, 128.0, 67.1, 45.6, 13.5; IR 3362, 2932, 2875, 1491, 1092, 1048, 1014, 823, 735, 582 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{11}$H$_{23}$Cl$_1$ [M+H-H$_2$O]$^+$: 179.0628, found: 179.0634; $[\alpha]_D^{20}$ = +166 ($c = 0.870$, CHCl$_3$, $l = 50$ mm).

(R)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl 4-methylbenzenesulfonate. To a solution of (R)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol (3.00 g, 13.8 mmol) in anhydrous pyridine (59 mL) at 0 °C was added $p$-toluenesulfonyl chloride (2.90 g, 15.2 mmol). The reaction was stirred under nitrogen overnight while warming to room temperature. The reaction was quenched by the addition of water (20 mL) and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (20% EtOAc/Hex) to afford the title compound as a yellow oil (2.32 g, 44%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 (d, 2H, $J = 8.3$ Hz), 7.47 – 7.57 (m, 3H), 7.45 (d, 1H, $J = 7.6$ Hz), 7.32 (d, 2H, $J = 8.3$ Hz), 5.03 – 5.06 (m, 1H), 4.16 (dd, 1H, $J = 10.8$, 3.4 Hz), 4.04 (dd, 1H, $J = 10.5$, 8.1 Hz), 2.87 (br s, 1H), 2.43 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 145.2, 139.6, 132.6, 131.5 (q, $J_{C,F} = 32.4$ Hz), 130.2, 129.9, 129.4, 128.1, 125.5, 124.1 (q, $J_{C,F} = 273$ Hz), 123.3, 74.1, 71.6,
29.1; \textsuperscript{19}F NMR (470 MHz, CDCl\textsubscript{3}) \( \delta = 62.7 \); \textbf{IR} 3394, 3513, 1357, 1329, 1190, 1173, 1124, 1097, 1073, 974, 828, 811, 750, 703, 670, 662, 554 cm\textsuperscript{-1}; \textbf{HRMS} (DART-TOF) calcd. for \( C_{16}H_{19}F_{3}N_{1}O_{4}S_{1} \) [M+NH\textsubscript{4}]\textsuperscript{+}: 378.0987, found: 378.0979; \([\alpha]\)\textsubscript{D}\textsuperscript{20} = −33.6 (c = 0.780, CHCl\textsubscript{3}, l = 50 mm).

\textit{(R)-2-(3-(trifluoromethyl)phenyl)oxirane}. A solution of (R)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl 4-methylbenzenesulfonate (2.00 g, 5.39 mmol) in THF (9 mL) and 6 M aqueous NaOH (9 mL) was stirred vigorously at room temperature for 4 hours. The reaction was diluted with water (15 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo} to afford the pure epoxide as a colorless oil (1.00 g, 93%). \textbf{\textit{1H NMR}} (500 MHz, CDCl\textsubscript{3}) \( \delta = 7.55 – 7.57 \) (m, 1H), 7.54 (s, 1H), 7.46 – 8.47 (m, 2H), 3.92 (dd, 1H, \( J = 3.9, 2.5 \) Hz), 3.18 (dd, 1H, \( J = 5.4, 4.4 \) Hz), 2.89 (dd, 1H, \( J = 5.6, 2.7 \) Hz); \textbf{\textit{13C NMR}} (126 MHz, CDCl\textsubscript{3}) \( \delta = 139.0, 131.3 \) (q, \( J_{C-F} = 32.4 \) Hz), 129.2, 129.0, 125.2, 124.1 (q, \( J_{C-F} = 273 \) Hz), 122.5, 52.0, 51.5; \textbf{\textit{19F NMR}} (470 MHz, CDCl\textsubscript{3}) \( \delta = 62.8 \); \textbf{IR} 2956, 2924, 2365, 2359, 1329, 1165, 1126, 1099, 1073, 1031, 803 cm\textsuperscript{-1}; \textbf{HRMS} (DART-TOF) calcd. for \( C_{9}H_{8}F_{3}O_{1} \) [M+H]\textsuperscript{+}: 189.0527, found: 189.0531; \([\alpha]\)\textsubscript{D}\textsuperscript{20} = −3.39 (c = 0.860, CHCl\textsubscript{3}, l = 50 mm).

\textbf{(S,Z)-2-(3-(trifluoromethyl)phenyl)pent-3-en-1-ol.} Synthesized according to General Procedure C using (R)-2-(3-(trifluoromethyl)phenyl)oxirane (700 mg g, 3.72 mmol) to afford the title compound as a yellow oil (376 mg, 44%). \textbf{\textit{1H NMR}} (500 MHz, CDCl\textsubscript{3}) \( \delta = 7.44 – 7.50 \) (m, 4H), 5.75 – 5.79 (m, 1H), 5.58 – 5.63 (m, 1H), 3.91 – 3.96 (m, 1H), 3.81 (dd, 1H, \( J = 10.9, 6.4 \) Hz), 3.75 (dd, 1H, \( J = 7.3, 3.4 \) Hz), 1.70 (d, 3H, \( J = 6.9 \) Hz), 1.51 (br s, 1H); \textbf{\textit{13C}}
NMR (126 MHz, CDCl₃) δ 142.9, 131.4, 131.2 (q, J_C-F = 31 Hz), 129.3, 129.2, 128.5, 124.7, 124.3 (q, J_C-F = 273 Hz), 123.8, 67.0, 46.0, 13.5; ¹⁹F NMR (470 MHz, CDCl₃) δ –62.6; IR 3362, 1447, 1328, 1163, 1123, 1095, 802, 718, 702 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₂H₁₂F₃ [M+H-H₂O]⁺: 213.0891, found: 213.0892; [α]_D²⁰ = +108 (c = 0.515, CHCl₃, l = 50 mm).

**(S,Z)-2-(3-methoxyphenyl)pent-3-en-1-ol.** Synthesized according to General Procedure C using (R)-2-(3-(methoxy)phenyl)oxirane (630 mg, 4.20 mmol) to afford the title compound as a yellow oil (270 mg, 34%). ¹H NMR (500 MHz, CDCl₃) δ 7.25 (t, 1H, J = 7.8 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.77 – 6.80 (m, 2H), 5.70 – 5.74 (m, 1H), 5.57 – 5.62 (m, 1H), 3.85 – 3.87 (m, 1H), 3.80 (s, 3H), 3.78 – 3.82 (m, 1H), 3.71 – 3.73 (m, 1H), 1.70 (d, 3H, J = 6.9 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 160.1, 143.4, 130.1, 129.9, 127.7, 120.3, 114.0, 112.0, 67.1, 55.4, 46.3, 13.5; IR 3389, 2933, 2875, 1600, 1584, 1488, 1465, 1453, 1433, 1288, 1152, 1047, 778, 697 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₂H₁₅O₁ [M+H-H₂O]⁺: 175.1123, found: 173.1130; [α]_D²⁰ = +208 (c = 0.375, CHCl₃, l = 50 mm).

**(R,Z)-1-((4-methoxybenzyl)oxy)non-3-en-2-ol.** A round-bottom flask was charged with (R,Z)-non-3-ene-1,2-diol (200 mg, 1.26 mmol), dibutyltin oxide (430 mg, 1.71 mmol), and toluene (10 mL). The reaction was heated to reflux with azeotropic removal of water overnight. The reaction was cooled to room temperature and the Dean-Stark apparatus was removed. To the flask was added tetrabutylammonium iodide (650 mg, 1.76 mmol) and 4-methoxybenzyl chloride (276 mg, 1.76 mmol) and the reaction was heated to reflux for 4 hours. After cooling to room temperature, the reaction was quenched with water (10 mL) and extracted with DCM (2 x
30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by silica gel chromatography (12% EtOAc/Hex) afforded the title compound as a colorless oil (318 mg, 91%, contains 30% of an inseparable impurity). ¹H NMR (500 MHz, CDCl₃) δ 7.27 (d, 2H, J = 9.3 Hz), 6.88 (d, 2H, J = 8.3 Hz), 5.54 – 5.56 (m, 1H), 5.34 – 5.35 (m, 1H), 4.63 – 4.65 (m, 1H), 4.50 (m, 2H), 3.81 (s, 3H), 3.42 (dd, 1H, J = 9.5, 3.8 Hz), 3.33 (dd, 1H, J = 9.8, 8.3 Hz), 2.37 (br s, 1H), 2.02 – 2.12 (m, 2H), 1.24 – 1.38 (m, 6H), 0.88 (t, 3H, J = 7.1 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 158.7, 134.6, 129.7, 129.6, 127.9, 114.1, 74.0, 73.2, 67.1, 55.5, 31.6, 29.5, 28.1, 22.7, 14.2; IR 3448, 3007, 2955, 2927, 2856, 1612, 1586, 1513, 1464, 1247, 1174, 1100, 1074, 1036, 821, 756 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₇H₃₀N₁O₃ [M+NH₄]⁺: 296.2226, found: 296.2235; [α]D²₀ = −36.8 (c = 0.445, CHCl₃, l = 50 mm).

(R,Z)- tert-butyl(1-((4-methoxybenzyl)oxy)non-3-en-2-yl)oxy)dimethylsilane. To a 50-mL round-bottom flask was added (R,Z)-1-((4-methoxybenzyl)oxy)non-3-en-2-ol (318 mg, 1.14 mmol), 2,6-lutidine (0.33 mL, 2.9 mmol), and DCM (11 mL). The solution was cooled to 0 °C and TBSOTf (0.52 mL, 2.3 mmol) was added slowly over 3 minutes. The reaction was allowed to warm to room temperature over 90 minutes, quenched by the addition of saturated NH₄Cl (15 mL), and extracted with DCM (2 x 30 mL). The combined organics were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1% EtOAc/Hex) to afford the product as a colorless oil (301 mg, 67%). ¹H NMR (500 MHz, CDCl₃) δ 7.25 (app dd, 2H, J = 6.4, 2.0 Hz), 6.86 (app dd, 2H, J = 6.4, 2.0 Hz), 5.40 – 5.45 (m, 1H), 5.30 – 5.34 (m, 1H), 4.62 – 4.65 (m, 1H), 4.57 (d, 1H, J = 11.7 Hz), 4.50 (d, 1H, J = 11.7 Hz), 3.81 (s, 3H),
3.41 (dd, 1H, J = 10.0, 7.1 Hz), 3.33 (dd, 1H, J = 10.3, 4.9 Hz), 2.01 – 2.06 (m, 2H), 1.25 – 1.36 (m, 6H), 0.89 (s, 9H), 0.88 (t, 3H, J = 8.3 Hz), 0.070 (s, 3H), 0.056 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 159.2, 131.6, 131.0, 130.8, 129.3, 113.9, 75.0, 73.2, 68.9, 55.5, 31.8, 29.5, 28.2, 26.1, 22.7, 18.5, 14.2, -4.3, -4.4; IR 2955, 2928, 2855, 1513, 1463, 1248, 1172, 1120, 1091, 1039, 1006, 834, 776 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\textsubscript{23}H\textsubscript{39}O\textsubscript{2}Si\textsubscript{1} [M+H\textsubscript{-}H\textsubscript{2}O]\(^{+}\): 375.2719, found: 375.2718; \([\alpha]_D\)\textsuperscript{20} = -7.55 (c = 0.620, CHCl\textsubscript{3}, l = 50 mm).

\((R,Z)-2-((\text{tert-butyl} \text{dimethylsilyl})\text{oxy})\text{non-3-en-1-ol.}\) To a vigorously stirred solution of \((R,Z)-\text{tert-butyl}(1-(\text{4-methoxybenzyl})\text{oxy})\text{non-3-en-2-yl} \text{oxy})\text{dimethylsilane (150 mg, 0.38 mmol), DCM (6 mL), and water (1.5 mL) at 0 °C was added DDQ (106 mg). The reaction was allowed to warm to room temperature over 2 hours and was quenched by the addition of a 1:1:1 mixture of saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate:water (10 mL). The aqueous layer was extracted with DCM (2 x 30 mL) and the combined organic layers were dried over MgSO\textsubscript{4}. Filtration, and removal of the solvent \textit{in vacuo} afforded a crude residue which was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (87 mg, 84%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.44 – 5.49 (m, 1H), 5.26 – 5.30 (m, 1H), 4.51 – 4.55 (m, 1H), 3.40 (dd, 2H, J = 7.1, 5.6 Hz), 1.98 – 2.08 (m, 3H), 1.25 – 1.38 (m, 6H), 089 (s, 9H), 0.88 (t, 3H, J = 8.3 Hz), 0.081 (s, 3H), 0.058 (s, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 132.7, 129.9, 70.2, 66.9, 31.7, 29.5, 28.5, 26.0, 22.7, 18.3, 14.2, -4.0, -4.6; IR 3439, 2956, 2928, 2857, 1463, 1235, 1095, 1062, 1036, 1005, 835, 812 cm\(^{-1}\); HRMS
(DART-TOF) calcd. for C₁₅H₃₁O₁Si₁ [M+H-H₂O]⁺: 255.2144, found: 255.2140; [α]D²⁰ = + 3.99 (c = 0.315, CHCl₃, l = 50 mm).

(S)-2-phenylbut-3-en-1-ol. To a suspension of (R)-phenyloxirane (1.00 g, 8.32 mmol) and CuCl(COD) (172 mg, 0.84 mmol) in THF (12 mL) at –78 °C was added vinylmagnesium bromide (10.0 mL, 10.0 mmol, 1.0 M solution in THF). The reaction as allowed to warm to room temperature over 8 hours. The reaction was quenched by the addition of saturated NH₄Cl (30 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (872 mg, 71%). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.29 – 7.37 (m, 2H), 7.24 – 7.27 (m, 3H), 5.99 – 6.06 (m, 1H), 5.18 – 5.24 (m, 2H), 3.83 – 3.85 (m, 2H), 3.54 (q, 1H, J = 7.3 Hz), 1.53 (br s); \(^{13}\)C NMR (126 MHz, CDCl₃) δ 140.8, 138.4, 129.0, 128.2, 127.2, 117.3, 66.3, 52.7; IR 3355, 3028, 2876, 1493, 1453, 1054, 1029, 994, 918, 756, 700, 680 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C₁₀H₁₁ [M+H-H₂O]⁺: 131.0861, found: 131.0867; [α]D²⁰ = + 67.5 (c = 0.545, CHCl₃, l = 50 mm).

3.7.4 Characterization of Hydroformylation Products

Table 3.11– Substrate Table

General Hydroformylation Procedure. The Endeavor was charged with 500 µL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed into the wells. The Endeavor was sealed and purged with nitrogen (4×100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1×100 psi), stirring was started at 250 rpm, and
the Endeavor was heated to and held at 55 °C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H₂/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant reaction temperature of 55 °C and pressure of 400 psi H₂/CO for 15 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, and the benzene was removed in vacuo. A solution of mesitylene in chloroform-d (100 µL, 0.5408 M) was added. The conversion of the reaction was determined by ¹H NMR in chloroform-d with respect to remaining starting material. The solvent was removed under reduced pressure. The crude hydroformylation mixture was added, as a solution in dichloromethane (3 mL), to a scintillation vial containing pyridinium chlorochromate (128.7 mg, 0.597 mmol), sodium acetate (16.0 mg, .195 mmol), and 4 Å molecular sieves. The reaction was stirred for 12 hours at room temperature and eluted through a short plug of silica gel (100% Et₂O). The regio- and diastereoselectivities were determined by either GC or ¹H NMR.

**General Procedure D:** In a dry box, (R,Z)-2-methyloct-3-en-1-ol (28.4 mg, 0.200 mmol), (4S)-4-(tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (8.7 mg, 0.020 mmol), a p-toluenesulfonic acid in benzene (351 µL, 2.0 x 10⁻⁴ mmol, 5.7 x 10⁻⁴ M solution) were mixed in C₆D₆ (0.8 mL) and allowed to equilibrate in a sealed NMR tube for 3 hours at 45 °C. (Note: the appearance of free MeOH can be monitored by ¹H NMR.) The solution was concentrated in the dry box to remove the generated MeOH, the residue was re-dissolved in C₆D₆, and was allowed to equilibrate for an additional 3 hours at 45 °C before being concentrated again in the dry box. The resulting mixture was dissolved in benzene (3.5 mL), mixed with 3% Rh(acac)(CO)₂ (1.5 mg, 0.006 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.
**General Procedure E:** Same as General Procedure A, except 20% (4S)-4-((tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (17.3 mg, 0.040 mmol) and 6% Rh(acac)(CO)$_2$ (3.1 mg, 0.012 mmol) were used.

**General Procedure F:** Same as General Procedure A, except 12% (4S)-4-((tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (10.4 mg, 0.024 mmol) and 4% Rh(acac)(CO)$_2$ (2.1 mg, 0.008 mmol) were used.

**General Procedure G:** Same as General Procedure A, except 5% (4S)-4-((tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (4.4 mg, 0.010 mmol) and 2% Rh(acac)(CO)$_2$ (1.1 mg, 0.004 mmol) were used.

**Gas Chromatography Analysis Methods**

**GC Method A:** J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 µm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 2 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 3 min.

**GC Method B:** J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 µm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 1 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 6 min.

**GC Method C:** Supelco Gamma Dex 120 (30 m x 0.25 mm x 0.25 µm film thickness) 60 °C for 5 min, ramp 1 °C/min to 150 °C, 150 °C for 10 min, ramp 8 °C/min to a final temperature of 220 °C.

**GC Method D:** J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 µm film thickness): 140 °C for 6 min, ramp 40 °C/min to 220 °C, 220 °C for 5 min.

**GC Method E:** J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 µm film thickness): 140 °C for 3 min, ramp 8 °C/min to 220 °C, 220 °C for 10 min.
**GC Method F**: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 1 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 10 min

**Table 3.11, Entry 1**

(R,Z)-2-methyloct-3-en-1-ol was subjected to hydroformylation using General Procedure D. Achiral GC analysis using GC Method A afforded three peaks corresponding to each γ-lactone product (6.80 min and 7.93 min) and the combined δ-lactone products (8.47 min). The diastereoselectivity of the reaction was determined by ¹H NMR in CD₃OD. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

**Major product:**

(3R,5R)-3-butyl-5-methyltetrahydro-2H-pyran-2-one. Isolated as a colorless oil (27 mg, 78%). **GC Method A**: 8.47 min.; ¹H NMR (500 MHz, CDCl₃) δ 4.20 (dd, 1H, J = 10.8, 4.9 Hz), 3.89 (t, 1H, J = 10.8 Hz), 2.46 – 2.51 (m, 1H), 2.12 – 2.17 (m, 1H), 1.84 – 1.88 (m, 1H), 1.69 – 1.72 (m, 2H), 1.42 – 1.45 (m, 1H), 1.33 – 1.37 (m, 4H), 1.00 (d, 3H, J = 6.9 Hz), 0.91 (t, 3H, J = 7.1 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 175.4, 73.2, 37.5, 32.7, 31.2, 29.3, 27.0, 22.8, 17.2, 14.2; IR 2957, 2931, 2872, 1740, 1459, 1380, 1341, 1103, 1047, 1007, 725 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₀H₁₉O₂ [M+H]^+: 171.1380, found: 171.1384; [α]D²⁰ = −34.0 (c = 0.405, CHCl₃, l = 50 mm).

**Proof of Absolute Stereochemistry:**

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The absolute stereochemistry was confirmed by 1D nOe experiments between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-butyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-methyl substituent. See spectroscopic data for further details.

**Minor Products:**

![Chemical Structure](image)

**(3S,5R)-3-buty1-5-methyltetrahydro-2H-pyran-2-one.** GC Method A: 8.47 min.; \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.28 (dd, 1H, \(J = 11.3, 3.9\) Hz), 3.83 – 3.90 (m, 1H), 2.39 – 2.43 (m, 1H), 2.03 – 2.12 (m, 1H), 1.86 – 1.92 (m, 1H), 1.67 – 1.71 (m, 1H), 1.44 – 1.51 (m, 2H), 1.23 – 1.33 (m, 4H), 0.97 (d, 3H, \(J = 6.4\) Hz), 0.95 (t, 3H, \(J = 7.1\) Hz); \(^13C\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.2, 74.8, 40.4, 34.4, 31.5, 29.0, 28.8, 22.8, 17.6, 14.2; IR 2978, 2931, 2973, 1734, 1459, 1213, 1155, 1109, 1045, 749, 750 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{10}\)H\(_{19}\)O\(_2\) [M+H]: 171.1380, found: 171.1384; \([\alpha]_D^{20} = +3.4\) (c = 0.260, CHCl\(_3\), \(l = 50\) mm).

![Chemical Structure](image)

**anti-4-methyl-3-pentylidihydrofuran-2(3H)-one.** This compound has been synthesized previously in our laboratories and all spectroscopic data are in accordance.\(^21\) GC Method A: 6.80 min.
**syn-4-methyl-3-pentyldihydrofuran-2(3H)-one.** This compound has been synthesized previously in our laboratories and all spectroscopic data are in accordance.\(^1\) **GC Method A:** 7.93 min.

**GC Trace for the Determination of Regioselectivity**

![GC Trace Image]

**Table 3.11, Entry 2:**

(R,Z)-2-isopropylcoct-3-en-1-ol was subjected to hydroformylation using General Procedure E. Achiral GC analysis using GC Method B afforded three peaks corresponding to the γ-lactone product (12.19 min) and the combined δ-lactone products (13.68 min). The diastereoselectivity of the reaction was determined by chiral GC analysis using GC Method C to afford two signals, \(t_{\text{minor}} = 107.6\) min, \(t_{\text{major}} = 107.9\) min. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

**Major Product:**
(3R,5S)-3-butyl-5-isopropyltetrahydro-2H-pyran-2-one. Isolated as a colorless oil (22 mg, 57%). **GC Method B**: 13.68 min, **GC Method C**: 107.9 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.25 (dd, 1H, $J = 11.7, 4.9$ Hz), 3.98 – 4.02 (m, 1H), 2.39 – 2.41 (m, 1H), 1.81 – 1.85 (m, 2H), 1.74 – 1.79 (m, 1H), 1.56 – 1.61 (m, 2H), 1.30 – 1.40 (m, 4H), 0.94 (d, 3H, $J = 6.9$ Hz), 0.92 (d, 3H, $J = 7.3$ Hz), 0.90 (t, 3H, $J = 6.9$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.8, 70.2, 38.7, 37.6, 30.9, 29.9, 29.3, 28.5, 22.8, 20.2, 19.9, 14.1; **IR** 2957, 2932, 2873, 1746, 1467, 1390, 1370, 1245, 1165, 1151, 1114, 1071, 1031 cm$^{-1}$; **HRMS** (DART-TOF) calcd. for C$_{12}$H$_{23}$O$_2$ [M+H]$^+$: 199.1698, found: 199.1703; $[\alpha]_D^{20} = -58.6$ (c = 0.480, CHCl$_3$, $l$ = 50 mm).

**Minor Products:**

(3S,5S)-3-butyl-5-isopropyltetrahydro-2H-pyran-2-one. Isolated with (3R,5S)-3-butyl-5-isopropyltetrahydro-2H-pyran-2-one in an 88:12 ratio. **GC Method B**: 13.7 min, **GC Method C**: 107.6 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.32 (ddd, 1H, $J = 10.3, 5.1, 1.7$ Hz), 4.04 (dd, 1H, $J = 11.3, 9.0$ Hz), 2.39 – 2.41 (m, 1H), 2.04 – 2.10 (m, 1H), 1.74 – 1.85 (m, 2H), 1.56 – 1.61 (m, 1H), 1.30 – 1.40 (m, 6H), 0.94 (d, 3H, $J = 6.9$ Hz), 0.92 (d, 3H, $J = 7.3$ Hz), 0.90 (t, 3H, $J = 6.9$ Hz).
(3R,4R)-4-isopropyl-3-pentyldihydrofuran-2(3H)-one. GC Method B: 12.15 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.29 – 4.32 (m, 1H), 3.95 – 3.98 (m, 1H), 2.32 (q, 1H, $J$ = 6.5 Hz), 2.09 – 2.12 (m, 1H), 1.64 – 1.77 (m, 3H), 1.41 – 1.49 (m, 1H), 1.29 – 1.32 (m, 5H), 0.96 (d, 3H, $J$ = 7.0 Hz), 0.91 (d, 3H, $J$ = 7.1 Hz), 0.89 (t, 3H, $J$ = 6.8 Hz); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 180.1, 69.5, 46.4, 43.2, 32.0, 30.8, 30.6, 26.5, 22.6, 20.3, 19.2, 14.2.

(3R,4R)-4-isopropyl-3-pentyldihydrofuran-2(3H)-one. Not observed or isolated in any hydroformylation reaction (reactions carried out with ligand 3c and control reactions with PPh$_3$).
Table 3.11, Entry 3

(R,E)-2-methyloct-3-en-1-ol was subjected to hydroformylation using General Procedure D. Achiral GC analysis using GC Method A afforded three peaks corresponding to each γ-lactone product (6.80 min and 7.93 min) and the combined δ-lactone products (8.47 min). The diastereoselectivity of the reaction was determined by 1H NMR in CD3OD. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

**Major Product:**

![Chemical structure image]

(3S,5R)-3-butyl-5-methyltetrahydro-2H-pyran-2-one. Isolated as a colorless oil (18 mg, 52%). **GC Method A:** 8.47 min.; 1H NMR (500 MHz, CDCl3) δ 1H NMR (500 MHz, CDCl3) δ 4.28 (dd, 1H, J = 11.3, 3.9 Hz), 3.83 – 3.90 (m, 1H), 2.39 – 2.43 (m, 1H), 2.03 – 2.12 (m, 1H), 1.86 – 1.92 (m, 1H), 1.67 – 1.71 (m, 1H), 1.44 – 1.51 (m, 2H), 1.23 – 1.33 (m, 4H), 0.97 (d, 3H, J = 6.4 Hz), 0.95 (t, 3H, J = 7.1 Hz); 13C NMR (126 MHz, CDCl3) δ 174.2, 74.8, 40.4, 34.4, 31.5, 29.0, 28.8, 22.8, 17.6, 14.2; **IR** 2978, 2931, 2973, 1734, 1459, 1213, 1155, 1109, 1045, 749, 750 cm⁻¹; **HRMS** (DART-TOF) calcd. for
C₁₀H₁₉O₂ [M+H]⁺: 171.1380, found: 171.1384; [α]D²⁰ = + 3.4 (c = 0.260, CHCl₃, l = 50 mm).

**GC Trace for the Determination of Regioselectivity**

![GC Trace Image]

**Table 3.11, Entry 4**

(S,Z)-2-phenylpent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method D afforded three peaks corresponding to each γ-lactone product (7.67 min and 7.73 min) and the combined δ-lactone products (8.46 min). The diastereoselectivity of the reaction was determined by ¹H NMR in CDCl₃. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

**Major product:**

![Major Product Image]

**(3R,5S)-3-methyl-5-phenyltetrahydro-2H-pyran-2-one.** Isolated as a colorless semi-solid (25 mg, 66%). **GC Method D:** 8.46 min.; **¹H NMR** (500 MHz, CDCl₃) δ 7.35 – 7.38 (m, 2H), 7.25 – 7.30 (m, 3H), 4.33 – 4.41 (m, 2H), 3.28 – 3.32 (m, 1H), 2.82 – 2.86 (m, 1H), 2.28 – 2.34 (m, 1H), 1.95 – 2.02 (m, 1H), 1.31 (d, 3H, J = 6.8 Hz); **¹³C NMR**
(126 MHz, CDCl\textsubscript{3}) \( \delta \) 175.4, 140.6, 129.2, 127.6, 127.4, 72.3, 38.5, 34.6, 33.1, 16.8; \textbf{IR} 2973, 2935, 1742, 1380, 1214, 1161, 1117, 1080, 1054, 1033, 755, 701, 668 cm\textsuperscript{-1}; \textbf{HRMS} (DART-TOF) calcd. for C\textsubscript{12}H\textsubscript{15}O\textsubscript{2} [M+H]\textsuperscript{+}: 191.1072, found: 191.1067; \([\alpha]\textsubscript{D}\textsuperscript{20} = -25.1 (c = 0.255, CHCl\textsubscript{3}, \ell = 50 \text{ mm}).

\textit{Proof of Absolute Stereochemistry:}

The absolute stereochemistry was confirmed by 1D nOe experiments between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-methyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-aryl substituent. See spectroscopic data for further details.

\textit{Minor Products:}

\begin{center}
\includegraphics[width=0.3\textwidth]{minor_product.png}
\end{center}

(3\textit{S},5\textit{S})-3-methyl-5-phenyltetrahydro-2\textit{H}-pyran-2-one. \textbf{GC Method D}: 8.46 min.; \textbf{\(^1H\) NMR} (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.34 – 7.36 (m, 2H), 7.27 – 7.30 (m, 1H), 7.23 – 7.25 (m, 2H), 4.48 – 4.50 (m, 1H), 4.26 (dd, 1H, \( J \) = 11.3, 10.3 Hz), 3.25 – 3.31 (m, 1H), 2.69 – 2.74 (m, 1H), 2.27 – 2.33 (m, 1H), 1.99 (q, 1H, \( J \) = 12.7 Hz), 1.36 (d, 3H, \( J \) = 6.9 Hz); \textbf{\(^{13}C\) NMR} (126 MHz, CDCl\textsubscript{3}) \( \delta \) 174.1, 140.3, 129.1, 127.6, 127.3, 74.5, 40.4, 36.2, 35.8, 16.9.
**anti-3-ethyl-4-phenyldihydrofuran-2(3H)-one.** This compound has been synthesized previously in our laboratories and all spectroscopic data are in accordance.\(^\text{21}\)** GC Method D: 7.67 min.

![Image of anti-3-ethyl-4-phenyldihydrofuran-2(3H)-one]

**syn-3-ethyl-4-phenyldihydrofuran-2(3H)-one.** This compound has been synthesized previously in our laboratories and all spectroscopic data are in accordance.\(^\text{21}\)** GC Method D: 7.73 min.

**GC Trace for the Determination of Regioselectivity**

![GC Trace Image]

**Table 3.11, Entry 5**

\((S,Z)\)-2-(4-methoxyphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method B afforded two peaks corresponding to the combined γ-lactone products (18.16 min and 17.73 min) and the combined δ-lactone products (19.48 min). The diastereoselectivity of the reaction was determined by \(^1\text{H}\) NMR in CDCl\(_3\). Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

**Major product:**
(3R,5S)-5-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one. Isolated as a colorless solid (32 mg, 72%). GC Method B: 19.48 min; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.17 (d, 2H, $J$ = 8.8 Hz), 6.88 (d, 2H, $J$ = 8.8 Hz), 4.30 – 4.36 (m, 2H), 3.80 (s, 3H), 3.21 – 3.28 (m, 1H), 2.78 – 2.86 (m, 1H), 2.23 – 2.29 (m, 1H), 1.92 – 1.98 (m, 1H), 1.30 (d, 3H, $J$ = 6.7 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.4, 159.0, 132.5, 128.4, 114.5, 72.5, 55.5, 37.6, 34.7, 33.0, 16.9; IR 2936, 1740, 1612, 1308, 1278, 1248, 1214, 1161, 1084, 1055, 1033, 831, 750 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{13}$H$_{17}$O$_3$ [M+H]$^+$: 221.1178, found: 221.1184; $[\alpha]_D^{20}$ = -16.2 ($c$ = 0.420, CHCl$_3$, $l$ = 50 mm).

Proof of Absolute Stereochemistry:

The absolute stereochemistry was confirmed by 1D nOe experiments between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-methyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-aryl substituent. See spectroscopic data for further details.

Minor Products:
(3S,5S)-5-(4-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one. GC Method B: 19.48 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.10 (d, 2H, $J$ = 8.8 Hz), 6.82 (d, 2H, $J$ = 8.8 Hz), 4.45 (ddd, 1H, $J$ = 13.2, 5.1, 2.2 Hz), 4.19 (t, 1H, $J$ = 10.8 Hz), 3.80 (s, 3H), 3.20 – 3.26 (m, 1H), 2.66 – 2.71 (m, 1H), 2.23 – 2.29 (m, 1H), 1.84 (q, 1H, $J$ = 12.7 Hz), 1.34 (d, 3H, $J$ = 6.9 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.1, 159.1, 132.2, 128.3, 114.4, 74.7, 55.5, 39.6, 36.2, 35.9, 17.3.

(3R,4S)-3-ethyl-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one. GC Method B: 17.73 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.18 (d, 2H, $J$ = 8.8 Hz), 6.90 (d, 2H, $J$ = 8.8 Hz), 4.49 – 4.52 (m, 1H), 4.06 – 4.09 (m, 1H), 3.81 (s, 3H), 3.34 – 3.42 (m, 1H), 2.61 – 2.66 (m, 1H), 1.77 – 1.83 (m, 1H), 1.67 – 1.73 (m, 1H), 0.94 (t, 3H, $J$ = 7.6 Hz); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 178.4, 159.3, 130.4, 128.5, 114.7, 72.4, 55.5, 47.9, 46.6, 22.1, 11.2.
(3S,4S)-3-ethyl-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one. GC Method B: 18.16 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.08 (d, 2H, $J = 8.8$ Hz), 6.85 (d, 2H, $J = 8.3$ Hz), 4.55 (dd, 1H, $J = 9.3$, 5.9 Hz), 4.43 (dd, 1H, $J = 9.3$, 2.5 Hz), 3.80 (s, 3H), 3.65 – 3.69 (m, 1H), 2.67 – 2.72 (m, 1H), 1.61 – 1.66 (m, 1H), 1.07 – 1.12 (m, 1H), 0.90 (t, 3H, $J = 7.3$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 178.9, 130.8, 128.9, 128.1, 114.5, 73.0, 55.5, 46.5, 44.2, 19.4, 12.3.

GC Trace for the Determination of Regioselectivity

Table 3.11, Entry 6

(S,Z)-2-(4-bromophenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by $^1$H NMR in CDCl$_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

**Major product:**

![Chemical Structure](image-url)
(3R,5S)-5-(4-bromophenyl)-3-methyltetrahydro-2H-pyran-2-one. Isolated as a colorless solid (33 mg, 62%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.47 (d, 2H, $J = 8.3$ Hz), 7.12 (d, 2H, $J = 8.3$ Hz), 4.29 – 4.37 (m, 2H), 3.23 – 3.29 (m, 1H), 2.78 – 2.83 (m, 1H), 2.21 – 2.27 (m, 1H), 1.94 – 2.00 (m, 1H), 1.29 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.0, 139.5, 132.3, 129.1, 121.5, 71.9, 38.0, 34.6, 33.0, 16.9; IR 2973, 2936, 1743, 1490, 1361, 1160, 1117, 1074, 1056, 1034, 1009, 821, 752 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{12}$H$_{14}$BrO$_2$ [M+H]$^+$: 269.0177, found: 269.0187; $[\alpha]_D^{20} = -22.9$ (c = 0.640, CHCl$_3$, l = 50 mm).

Minor products:

(3S,5S)-5-(4-bromophenyl)-3-methyltetrahydro-2H-pyran-2-one. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (d, 2H, $J = 8.8$ Hz), 7.11 (d, 2H, $J = 8.8$ Hz), 4.46 – 4.49 (m, 1H), 4.22 (dd, 1H, $J = 11.5$, 9.5 Hz), 3.23 – 3.27 (m, 1H), 2.68 – 2.73 (m, 1H), 2.27 – 2.33 (m, 1H), 1.83 (q, 1H, $J = 12.4$ Hz), 1.35 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.9, 139.5, 132.3, 129.0, 121.5, 73.9, 39.9, 36.0, 35.7, 17.1.
(3R,4S)-4-(4-bromophenyl)-3-ethyldihydrofuran-2(3H)-one. ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, 2H, J = 8.3 Hz), 7.14 (d, 2H, J = 8.3 Hz), 4.52 (t, 1H, J = 8.8 Hz), 4.07 (t, 1H, J = 9.5 Hz), 3.37 – 3.43 (m, 1H), 2.62 – 2.66 (m, 1H), 1.78 – 1.84 (m, 1H), 1.67 – 1.72 (m, 1H), 0.93 (t, 3H, J = 7.6 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 177.8, 137.8, 132.5, 129.1, 121.9, 71.9, 47.9, 46.8, 22.2, 11.3.

![Chemical Structure](image_url)

(3S,4S)-4-(4-bromophenyl)-3-ethyldihydrofuran-2(3H)-one. ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, 2H, J = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 4.55 (dd, 1H, J = 9.3, 6.4 Hz), 4.40 (dd, 1H, J = 9.3, 2.0 Hz), 3.65 – 3.69 (m, 1H), 2.73 (dt, 1H, J = 8.3, 5.4 Hz), 1.61 – 1.66 (m, 1H), 1.01 – 1.08 (m, 1H), 0.90 (t, 3H, J = 7.3 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 178.3, 137.9, 132.3, 129.5, 121.8, 72.5, 46.3, 44.5, 19.4, 12.3.

**Table 3.11, Entry 7**

(S,Z)-2-(4-chlorophenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by ¹H NMR in CDCl₃. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

**Major Product:**
(3R,5S)-5-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one. Isolated as a colorless oil (30 mg, 68%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33 (d, 2H, $J = 8.3$ Hz), 7.19 (d, 2H, $J = 8.3$ Hz), 4.29 – 4.37 (m, 2H), 3.25 – 3.31 (m, 1H), 2.79 – 2.84 (m, 1H), 2.22 – 2.28 (m, 1H), 1.95 – 2.01 (m, 1H), 1.31 (d, 3H, $J = 6.8$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.0, 139.0, 133.4, 129.3, 128.7, 71.9, 37.9, 34.5, 32.9, 16.8; IR 2973, 2936, 1743, 1493, 1413, 1236, 1161, 1117, 1090, 1057, 1034, 827 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{12}$H$_{14}$ClO$_2$ [M+H]$^+$: 225.0682, found: 221.0689; [$\alpha$]$_{D}^{20} = -22.4$ (c = 0.500, CHCl$_3$, $l = 50$ mm).

Minor Products:

(3S,5S)-5-(4-chlorophenyl)-3-methyltetrahydro-2H-pyran-2-one. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.32 (dd, 2H, $J = 6.4$, 2.0 Hz), 7.16 (dd, 2H, $J = 6.4$, 2.0 Hz), 4.46 – 4.49 (m, 1H), 4.22 (dd, 1H, $J = 11.3$, 9.8 Hz), 3.23 – 3.29 (m, 1H), 2.67 – 2.73 (m, 1H), 2.27 – 2.32 (m, 1H), 1.82 (dd, 1H, $J = 24.9$, 12.7 Hz), 1.35 (d, 3H, $J = 7.3$ Hz); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 173.9, 138.9, 133.5, 129.3, 128.6, 74.0, 39.8, 36.0, 35.8, 17.2.
Proof of Absolute Stereochemistry:

The absolute stereochemistry was confirmed by 1D nOe experiments between the C(3) and C(5) hydrogen atoms. An nOe correlation is observed between these two hydrogen substituents. See spectroscopic data for further details.

\[ \text{(3R,4S)-4-(4-chlorophenyl)-3-ethyldihydrofuran-2(3H)-one.} \]

\( ^1\text{H NMR} \) (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.34 (d, 2H, \( J = 8.3 \) Hz), 7.20 (d, 2H, \( J = 8.3 \) Hz), 4.52 (t, 1H, \( J = 8.6 \) Hz), 4.08 (t, 1H, \( J = 9.3 \) Hz), 3.39 – 3.45 (m, 1H), 2.62 – 2.66 (m, 1H), 1.78 – 1.84 (m, 1H), 1.67 – 1.73 (m, 1H), 0.94 (t, 3H, \( J = 7.6 \) Hz); \n
\( ^{13}\text{C NMR} \) (126 MHz, CDCl\textsubscript{3}) \( \delta \) 177.9, 137.24, 133.9, 129.6, 128.8, 72.0, 47.9, 46.8, 22.2, 11.3.

\[ \text{(3S,4S)-4-(4-chlorophenyl)-3-ethyldihydrofuran-2(3H)-one.} \]

\( ^1\text{H NMR} \) (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.31 (dd, 2H, \( J = 6.4, 2.0 \) Hz), 7.10 – 7.11 (m, 2H), 4.56 (dd, 1H, \( J = 9.3, 5.9 \) Hz), 4.42 (dd, 1H, \( J = 9.3, 2.0 \) Hz), 3.68 – 3.72 (m, 1H), 2.71 – 2.78 (m, 1H), 1.62 – 1.68 (m, 1H), 1.03 = 1.09 (m, 1H), 0.91 (t, 3H, \( J = 7.3 \) Hz); \n
\( ^{13}\text{C NMR} \) (151 MHz, CDCl\textsubscript{3}) \( \delta \) 178.3, 137.4, 133.7, 129.3, 129.2, 72.6, 46.3, 44.4, 19.4, 12.3.

**Table 3.11, Entry 8**
(S,Z)-2-(3-trifluoromethylphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by \(^1\)H NMR in CDCl\(_3\). Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

**Major Product:**

(3R,5S)-3-methyl-5-(3-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-one. Isolated as a colorless oil (38 mg, 73%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, 1H, \(J = 7.8\) Hz), 7.45 – 7.49 (m, 3H), 4.34 – 4.41 (m, 2H), 3.33 – 3.40 (m, 1H), 2.82 – 2.87 (m, 1H), 2.27 – 2.33 (m, 1H), 1.99 – 2.05 (m, 1H) 1.30 (d, 3H, \(J = 6.9\) Hz); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 174.9, 141.6, 131.5 (q, \(J_{C-F} = 32\) Hz), 130.9, 129.7, 124.5, 124.1, 124.0 (q, \(J_{C-F} = 272\) Hz), 71.7, 38.4, 34.5, 32.9, 16.8; \(^19\)F NMR (470 MHz, CDCl\(_3\)) \(\delta\) – 62.7; IR 2977, 2939, 1745, 1382, 1162, 1121, 1059, 917, 805, 704, 664 cm\(^{-1}\); HRMS (DART-TOF) calcd. for C\(_{13}\)H\(_{14}\)F\(_3\)O\(_2\) [M+H]\(^+\): 259.0946, found: 259.0946; \([\alpha]_D^{20} = -16.4\) (c = 0.600, CHCl\(_3\), \(l = 50\) mm).

**Minor Products:**
(3S,5S)-3-methyl-5-(3-(trifluoromethyl)phenyl)tetrahydro-2H-pyran-2-one.  $^1$H NMR (500 MHz, CDCl$_3$) δ 7.55 (d, 1H, $J = 7.3$ Hz), 7.46 – 7.50 (m, 3H), 4.51 (ddd, 1H, $J = 13.7$, 5.4, 2.2 Hz), 4.27 (dd, 1H, $J = 11.3$, 9.8 Hz), 3.33 – 3.38 (m, 1H), 2.70 – 2.75 (m, 1H), 2.32 – 2.36 (m, 1H), 1.85 (m, 1H), 1.36 (d, 3H, $J = 6.9$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.7, 141.5, 131.4 (q, $J_{C-F} = 32$ Hz), 130.0, 129.7, 124.6, 124.2 (q $J_{C-F} = 273$ Hz), 124.1, 73.3, 40.2, 36.0, 35.7, 17.1; $^{19}$F NMR (470 MHz, CDCl$_3$) δ −62.7.

(3R,4S)-3-ethyl-4-(3-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one.  $^1$H NMR (500 MHz, CDCl$_3$) δ 7.58 (d, 1H, $J = 7.8$ Hz), 7.46 – 7.57 (m, 3H), 4.58 (t, 1H, $J = 8.6$ Hz), 4.13 (t, 1H, $J = 9.5$ Hz), 3.51 (app q, 1H, $J = 9.6$ Hz), 2.66 – 2.73 (m, 1H), 1.81 – 1.86 (m, 1H), 1.70 – 1.76 (m, 1H), 0.95 (t, 3H, $J = 7.3$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.6, 129.9, 131.8 (q, $J_{C-F} = 32$ Hz), 130.8, 130.0, 125.0, 124.4, 124.1 (q, $J_{C-F} = 272$ Hz), 71.9, 47.9, 47.1, 22.3, 11.2; $^{19}$F NMR (470 MHz, CDCl$_3$) δ −62.7.

(3S,4S)-3-ethyl-4-(3-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one.  $^1$H NMR (500 MHz, CDCl$_3$) δ 7.57 (d, 1H, $J = 7.8$ Hz), 7.48 (t, 1H, $J = 7.8$ Hz), 7.40 (s, 1H), 7.38 (d, 1H, $J = 7.8$ Hz), 4.60 (dd, 1H, $J = 9.3$, 6.4 Hz), 4.46 (dd, 1H, $J = 9.5$, 2.2 Hz), 3.78 – 3.81 (m, 1H), 2.76 – 2.81 (m, 1H), 1.62 – 1.66 (m, 1H), 1.00 – 1.06 (m, 1H), 0.93 (t, 3H,
$J = 7.3 \text{ Hz}$; $^{13}\text{C NMR}$ (126 MHz, CDCl$_3$) $\delta$ 178.1, 139.9, 131.4 ($q$, $J_{C-F} = 32 \text{ Hz}$), 130.8, 129.8, 124.9, 124.8, 124.0 ($q$, $J_{C-F} = 273 \text{ Hz}$), 72.3, 46.3, 44.9, 19.5, 12.2; $^{19}\text{F NMR}$ (470 MHz, CDCl$_3$) $\delta$ – 62.7.

**Table 3.11, Entry 9**

$(S,Z)$-2-(3-methoxyphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method E afforded three peaks corresponding to each γ-lactone product (10.36 min and 10.51 min) and the combined δ-lactone products (12.02 min). The diastereoselectivity of the reaction was determined by $^1\text{H NMR}$ in CDCl$_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

**Major Product:**

![Chemical Structure](image)

**(3R,5S)-5-(3-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one.** Isolated as a colorless solid (34 mg, 77%). **GC Method E:** 12.02 min.; $^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.24 – 7.28 (m, 1H), 6.77 – 6.83 (m, 3H), 4.33 – 4.38 (m, 2H), 3.81 (s, 3H), 3.25 – 3.28 (m, 1H), 2.80 – 2.85 (m, 1H), 2.26 – 2.32 (m, 1H), 1.96 – 2.00 (m, 1H), 1.30 (d, 3H, $J = 6.9 \text{ Hz}$); $^{13}\text{C NMR}$ (126 MHz, CDCl$_3$) $\delta$ 175.4, 160.2, 142.2, 132.2, 119.6, 113.7, 112.4, 72.2, 55.5, 38.5, 34.6, 33.0, 16.8; **IR** 2936, 1742, 1601, 1585, 1488, 1456, 1263, 1159, 1117, 1085, 1035, 781, 670 cm$^{-1}$; **HRMS** (DART-TOF) calcd. for C$_{13}$H$_{17}$O$_3$ [M$+$H]$^+$: 221.1178, found: 221.1172; $[\alpha]D^{20} = -13.1$ (c = 1.01, CHCl$_3$, l = 50 mm).
Minor Products:

(3S,5S)-5-(3-methoxyphenyl)-3-methyltetrahydro-2H-pyran-2-one. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27 – 7.30 (m, 1H), 6.77 – 6.83 (m, 3H), 4.49 (ddd, 1H, $J = 11.3, 5.4, 2.5$ Hz), 4.25 (dd, 1H, $J = 11.3, 10.3$ Hz), 3.80 (s, 3H), 3.22 – 3.27 (m, 1H), 2.67 – 2.73 (m, 1H), 2.27 – 2.32 (m, 1H), 1.83 – 1.91 (m, 1H), 1.35 (d, 3H, $J = 7.3$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 174.0, 160.2, 141.9, 130.2, 119.5, 113.5, 112.6, 74.4, 55.4, 40.4, 36.2, 35.8, 17.3.

(3R,4S)-3-ethyl-4-(3-methoxyphenyl)dihydrofuran-2(3H)-one. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29 (t, 1H, $J = 7.3$ Hz), 6.83 – 6.87 (m, 2H), 6.79 (s, 1H), 4.53 (t, 1H, $J = 8.6$ Hz), 4.12 (t, 1H, $J = 9.3$ Hz), 3.82 (s, 3H), 3.38 – 3.44 (m, 1H), 2.67 – 2.71 (m, 1H), 1.77 – 1.85 (m, 1H), 1.69 – 1.76 (m, 1H), 0.96 (t, 3H, $J = 7.3$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 178.3, 160.3, 140.4, 130.4, 119.7, 113.7, 112.8, 72.2, 55.5, 47.8, 47.3, 22.2, 11.2.
(3S,4S)-3-ethyl-4-(3-methoxyphenyl)dihydrofuran-2(3H)-one. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.23 (d, 1H, \(J = 7.8\) Hz), 6.82 (dd, 1H, \(J = 8.3, 2.4\) Hz), 6.75 (d, 1H, \(J = 7.8\) Hz), 6.69 (app t, 1H, \(J = 2.0\) Hz), 4.55 (dd, 1H, \(J = 9.3, 5.9\) Hz), 4.46 (dd, 1H, \(J = 9.3, 2.5\) Hz), 3.79 (s, 3H), 3.66 – 3.69 (m, 1H), 2.69 – 2.74 (m, 1H), 1.61 – 1.66 (m, 1H), 1.08 – 1.14 (m, 1H), 0.92 (t, 3H, \(J = 7.3\) Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 178.7, 160.1, 140.4, 130.2, 120.0, 113.9, 112.8, 72.7, 55.4, 46.4, 45.0, 22.8, 14.3.

**GC Trace for the Determination of Regioselectivity**

Table 3.11, Entry 10

(R,Z)-2-((tert-butyldimethylsilyl)oxy)non-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method F afforded four peaks corresponding to each \(\gamma\)-lactone product (18.26 min and 18.61 min) and each \(\delta\)-lactone product (18.97 min and 19.13 min). Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

**Major Product:**
(R,Z)-2-((tert-butyldimethylsilyl)oxy)non-3-en-1-ol. Isolated as a colorless oil (30.9 mg, 51%). **GC Method F**: 18.97 min.; **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 4.27 (dd, 1H, $J = 13.0$, 5.1 Hz), 4.10 – 4.15 (m, 1H), 2.72 – 2.78 (m, 1H), 1.96 – 2.01 (m, 1H), 1.85 – 1.89 (m, 1H), 1.72 – 1.75 (m, 1H), 1.45 – 1.50 (m, 1H), 1.27 – 1.34 (m, 7H), 0.88 (s, 9H), 0.87 (t, 3H, $J = 8.3$ Hz), 0.076 (s, 3H), 0.072 (s, 3H); **$^{13}$C NMR** (126 MHz, CDCl$_3$) $\delta$ 174.2, 73.3, 64.1, 36.0, 33.9, 31.8, 30.9, 26.4, 25.9, 23.0, 18.2, 14.2, -4.7; **IR** 2954, 2929, 2858, 1737, 1464, 1255, 1213, 1059, 1026, 1007, 837, 807, 778 cm$^{-1}$; **HRMS** (DART-TOF) calcd. for C$_{16}$H$_{33}$O$_3$Si$_1$ [M+H]$^+$: 301.2199, found: 301.2199; $[\alpha]_{D}^{20} = -9.7$ (c = 775, CHCl$_3$, l = 50 mm).

**Minor Products:**

(3S,5R)-5-((tert-butyldimethylsilyl)oxy)-3-pentyltetrahydro-2H-pyran-2-one. **GC Method F**: 19.13 min.; **$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ 4.21 (dd, 1H, $J = 11.0$, 2.7 Hz), 4.05 (dd, 1H, $J = 11.0$, 5.6 Hz), 2.34 – 2.39 (m, 1H), 2.24 – 2.29 (m, 1H), 1.85 – 1.90 (m, 1H), 1.54 – 1.60 (m, 2H), 1.29 – 1.33 (m, 7H), 0.88 (s, 9H), 0.87 (t, 3H, $J = 8.3$ Hz), 0.077 (s, 3H), 0.072 (s, 3H); **$^{13}$C NMR** (126 MHz, CDCl$_3$) $\delta$ 173.9, 72.9, 65.1, 38.2, 35.3, 31.9, 30.9, 26.6, 25.9, 22.7, 18.2, 14.2, -4.6.
(3R,4R)-4-((tert-butyldimethylsilyl)oxy)-3-hexyldihydrofuran-2(3H)-one.

**GC Method F:** 18.26 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.32 – 3.45 (m, 1H), 4.24 – 4.27 (m, 1H), 3.95 – 3.98 (m, 1H), 2.43 – 2.46 (m, 1H), 1.69 – 1.73 (m, 1H), 1.47 – 1.56 (m, 1H), 1.42 – 1.48 (m, 2H), 1.25 – 1.32 (m, 6H), 0.88 (s, 9H), 0.87 (t, 3H, $J = 8.3$ Hz), 0.082 (s, 3H), 0.066 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 177.8, 73.4, 73.3, 48.8, 31.8, 29.3, 28.4, 27.0, 25.8, 22.8, 18.0, 14.2, -4.4, -4.6.

(3S,4R)-4-((tert-butyldimethylsilyl)oxy)-3-hexyldihydrofuran-2(3H)-one.

**GC Method F:** 18.61 min.; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.51 – 4.53 (m, 1H), 3.83 (dd, 1H, $J = 11.3, 3.4$ Hz), 3.67 (dd, 1H, $J = 11.3, 2.9$ Hz), 2.69 – 2.71 (m, 1H), 2.31 – 2.36 (m, 1H), 1.94 – 1.98 (m, 1H), 1.85 – 1.87 (m, 1H), 1.29 – 1.41 (m, 7H), 0.89 (s, 9H), 0.87 (t, 3H, $J = 7.3$ Hz), 0.077 (s, 3H), 0.062 (s, 3H).

**GC Trace for the Determination of Regio- and Diastereoselectivity**
Table 3.11, Entry 11

(S)-2-phenylbut-3-en-1-ol was subjected to hydroformylation using General Procedure G. The regioselectivity of the hydroformylation reaction was determined by $^1$H NMR in CDCl$_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

(S)-5-phenyltetrahydro-2H-pyran-2-one. Isolated as a colorless solid (28 mg, 80%). This compound has been synthesized previously in our laboratories (in racemic form) and all spectroscopic data are in accordance.$^{21}$ $[\alpha]_D^{20} = + 25.1$ ($c = 0.520$, CHCl$_3$, $l = 50$ mm).

Table 3.12 – Importance of Substrate Tether

The following compounds have been synthesized previously and are in accordance with reported NMR spectra: (Z)-4-phenylbut-2-en-1-ol,$^{38}$ 5-phenylpent-3-yn-1-ol,$^{39}$ (Z)-6-phenylhex-4-en-1-ol,$^{40}$ 3-hydroxy-2-(2-phenylethyl)propionic acid,$^{41}$ 3-benzyldihydrofuran-2(3H)-one,$^{42}$ 3-benzyltetrahydro-2H-pyran-2-ol,$^{43}$ 3-benzyltetrahydro-2H-pyran-2-one.$^{44}$

---

General Procedure H: In a dry box, the appropriate alcohol substrate (0.200 mmol), (4S)-4-(tert-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyazolidine (8.7 mg, 0.020 mmol), a p-toluenesulfonic acid in benzene (351 µL, 2.0 x 10⁻⁴ mmol, 5.72 x 10⁻⁴ M solution) were mixed in C₆D₆ (0.8 mL) and allowed to equilibrate in a sealed NMR tube at 45 °C for 3 hours. (Note: the appearance of methanol can be monitored by ¹H NMR). The solution was concentrated in the dry box to remove the generated MeOH, the residue was redissolved in C₆D₆, and was allowed to equilibrate for an additional 4 hours at 45 °C before being concentrated again in the dry box. The appearance of free MeOH can be monitored by ¹H NMR. The resulting mixture was dissolved in benzene (3.5 mL), mixed with 3% Rh(acac)(CO)₂ (1.5 mg, 0.006 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

General Procedure I (Control reaction using PPh₃ as ligand): In a dry box, the appropriate alcohol substrate (0.200 mmol), triphenylphosphine (5.2 mg, 0.020 mmol), and Rh(acac)(CO)₂ (1.5 mg, 0.006 mmol) were mixed in benzene (3.5 mL). The resulting yellow solution was injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

Table 3.12, Entry 1

The reaction was carried out according to General Procedure H and I. Upon completion of the hydroformylation reaction, the benzene was removed in vacuo and internal standard (mesitylene in CDCl₃) was added to determine conversion, based on remaining starting material, by ¹H NMR. The mixture was concentrated on a rotary evaporator in a glass scintillation vial. To the vial was added a magnetic stir bar, acetonitrile (0.75 mL), water (0.75 mL), sodium phosphate (144 mg, 1.20 mmol), and 35% aqueous H₂O₂ (0.120
mL, 1.23 mmol). The reaction was cooled to 0 °C and a solution of sodium chlorite (tech.
grade, 80%, 138 mg, 1.2 mmol) in water (0.75 mL), was added dropwise. The reaction
was stirred and warmed to room temperature over 3 hours. The reaction as quenched by
the addition of sodium sulfite (spatula tip) and 1M aqueous HCl (3 mL). The reaction
was extracted with DCM (3 x 10 mL), dried over MgSO₄, filtered, and concentrated
under reduced pressure. The crude reaction was analyzed by H NMR in CDCl₃ to
determine the regioselectivity of the reaction.

**Table 3.12, Entry 2**

(Z)-5-phenylpent-3-en-1-ol. A round-bottom flask was charged
with Lindlar’s catalyst (330 mg) and purged with nitrogen. 5-
phenylpent-3-yn-1-ol (660 mg, 4.11 mmol) in MeOH (12.5 mL)
was added followed by quinoline (35 µL, 0.27 mmol). The flask was evacuated and
refilled with H₂ four times, fitted with a H₂ balloon, and stirred at room temperature
under H₂ for 2.5 h. The reaction was filtered through a plug of silica and concentrated.
Column chromatography (20% EtOAc/Hex) yielded a light yellow oil (495 mg, 76%). H NMR (500 MHz, CDCl₃) δ 7.28 – 8.31 (m, 2H), 7.18 – 7.21 (m, 3H), 5.74 – 5.79 (m, 1H),
5.51 – 5.56 (m, 1H), 3.71 (t, 2H, J = 6.6 Hz), 3.45 (d, 2H, J = 7.3 Hz), 2.44 – 2.48 (m,
2H), 1.44 (br s, 1H); C NMR (126 MHz, CDCl₃) δ 140.9, 131.6, 128.7, 128.5, 126.4,
126.2, 62.5, 33.8, 31.0; IR 3337, 3025, 2939, 2883, 1602, 1495, 1453, 1400, 1047, 738,
679, 621, 562 cm⁻¹; HRMS (DART-TOF) calcd. for C₁₁H₁₆O₁ [M+H-H₂O]⁺: 163.1123,
found: 163.1128.

The reaction was carried out according to General Procedure H and I. Upon completion
of the hydroformylation reaction, the benzene was removed *in vacuo* and internal
standard (mesitylene in CDCl$_3$) was added to determine conversion, based on remaining starting material, by $^1$H NMR. The regioselectivity of the reaction was determined at this point by comparison of the lactol peaks in the crude $^1$H NMR. The solvent was removed under reduced pressure. The crude hydroformylation mixture was added, as a solution in dichloromethane (3 mL), to a scintillation vial containing pyridinium chlorochromate (129 mg, 0.597 mmol), sodium acetate (16.0 mg, 0.195 mmol), and 4 Å molecular sieves. The reaction was stirred for 12 hours at room temperature, eluted through a short plug of silica gel (100% Et$_2$O), concentrated under reduced pressure, and subjected to silica gel chromatography (20% EtOAc/Hex). HPLC analysis of the δ-lactone was used to determine the enantioselectivity of the hydroformylation reaction.

3-phenyltetrahydrofuran-2-ol. Exists as a 1:1 mixture of diastereomers. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27 – 7.30 (m, 4H), 7.18 – 7.21 (m, 6H), 5.34 (t, 1H, $J$ = 3.7 Hz), 5.22 (t, 1H, $J$ = 2.4 Hz), 4.09 – 4.13 (m, 1H), 4.03 (dd, 1H, $J$ = 15.7, 7.3 Hz), 3.93 – 3.97 (m, 1H), 3.82 (dd, 1H, $J$ = 15.7, 7.3 Hz), 3.04 (d, 1H, $J$ = 2.9 Hz), 2.83 (d, 1H, $J$ = 2.9 Hz), 2.66 – 2.70 (m, 4H), 2.17 – 2.22 (m, 1H), 2.11 – 2.14 (m, 1H), 2.01 – 2.04 (m, 1H), 1.91 – 1.98 (m, 1H), 1.76 – 1.84 (m, 2H), 1.57 – 1.65 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.4, 142.0, 128.6, 128.5, 126.1, 126.0, 103.4, 98.4, 67.3, 67.1, 46.2, 44.0, 34.8, 34.4, 34.3, 30.7, 20.5, 29.1; IR 3394, 2930, 2858, 1496, 1454, 1118, 1029, 1012, 986, 908, 749, 699, 497 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{12}$H$_{15}$O$_1$ [M+H-H$_2$O]$^+$: 175.1123, found: 175.1118.

3-benzyltetrahydro-2H-pyran-2-one. PCC oxidation and chromatography (15% EtOAc/Hex) afforded the title compound as a colorless oil. All spectroscopic data for this compound are in accordance with previously
published reports.\textsuperscript{44} HPLC (OD-H, 0.50 mL/min, 5% $i$-PrOH, 95% hexane, 220 nm)

$t_{r_{\text{minor}}} = 23.2$ min and $t_{r_{\text{major}}} = 24.2$ min, 19\% ee.

![HPLC chromatogram](image)

### Table 3.12, Entry 3

The reaction was carried out according to General Procedure H and I. Upon completion of the hydroformylation reaction, the benzene was removed \textit{in vacuo} and internal standard (mesitylene in CDCl$_3$) was added to determine conversion, based on remaining starting material, by $^1$H NMR. The regioselectivity of the reaction was determined at this point by comparison of the lactol and aldehyde peaks in the crude $^1$H NMR.

**3-phenethyltetrahydro-2H-pyrano-2-ol.** Exists as a 1:1 mixture of diastereomers. \textsuperscript{1}$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 – 7.29 (m, 4H), 7.18 – 7.21 (m, 6H), 5.11 (d, 1H, $J = 2.5$ Hz), 4.48 (d, 1H, $J = 6.4$ Hz), 3.97 – 4.02 (m, 2H), 3.55 – 3.58 (m, 1H), 3.47 – 3.50 (m, 1H), 2.60 – 2.73 (m, 4H), 1.99 – 2.03 (m, 2H), 1.67 – 1.76 (m, 2H), 1.45 – 1.61 (m, 4H); \textsuperscript{13}$^1$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.6, 128.5, 125.9, 99.7, 94.0, 65.4, 60.0, 41.5, 39.4, 33.5, 33.2, 27.4, 25.5, 24.9, 23.8; IR 3387, 2933, 2855, 1496, 1454, 1273, 1130, 1072, 1027, 986, 903, 867, 577, 544 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{13}$H$_{17}$O$_1$ [M+H-H$_2$O]$^+$: 189.1279, found: 189.1284.
2-benzyl-6-hydroxyhexanal. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)

\[
\begin{align*}
9.65 (d, 1H, J = 5.0 \text{ Hz}), & \quad 7.25 – 7.30 (m, 2H), \quad 7.15 – 7.22 (m, 3H), \\
3.61 (t, 2H, J = 6.4 \text{ Hz}), & \quad 3.00 (dd, 1H, J = 14.1, 7.3 \text{ Hz}), \quad 2.74 (dd, 1H, J = 14.2, 6.8 \text{ Hz}), \\
2.62 – 2.64 (m, 1H), & \quad 1.35 – 1.67 (m, 6H); \quad ^{13}\text{C NMR} (126 MHz, CDCl\(_3\)) \delta 204.7, 138.9, \\
129.1, 128.7, 126.6, 62.7, 53.6, 35.2, 32.8, 28.4, 23.4; \quad \textbf{IR} \ 3027, 2935, 2861, 1703, 1454, \\
1406, 1210, 1170, 1072, 1053, 1030, 744, 699, 543 \text{ cm}^{-1}; \quad \textbf{HRMS} (\text{DART-TOF}) \text{ calcd. for} \\
\text{C}_{13}\text{H}_{17}\text{O}_2 [\text{M-H}]^+: 205.1229, \text{ found: 205.1227.}
\end{align*}
\]

### 3.7.5 Spectral Data

For published spectral data for Section 3.4: Distal- and Diastereoselective Hydroformylation of Homoallylic Alcohols, see the following link:

[http://pubs.acs.org/doi/suppl/10.1021/ja504247g](http://pubs.acs.org/doi/suppl/10.1021/ja504247g)

Spectral data for un-published ligands are included herein.
$^1$H NMR Spectrum for Amino Alcohol Precursor to Ligand 3.59

$^{13}$C NMR Spectrum for Amino Alcohol Precursor to Ligand 3.59
$^{31}$P NMR Spectrum for Amino Alcohol Precursor to Ligand 3.59

$^1$H NMR Spectrum for Ligand 3.59
$^{13}$C NMR Spectrum for Ligand 3.59

$^{31}$P NMR Spectrum for Ligand 3.59
$^1$H NMR Spectrum for Amino Alcohol Precursor to Ligand 3.60

$^{13}$C NMR Spectrum for Amino Alcohol Precursor to Ligand 3.60
$^3$P NMR Spectrum for Amino Alcohol Precursor to Ligand 3.60

$^{19}$F NMR Spectrum for Amino Alcohol Precursor to Ligand 3.60
$^1$H NMR Spectrum for Ligand 3.60

$^{13}$C NMR Spectrum for Ligand 3.60
$^{31}$P NMR Spectrum for Ligand 3.60

$^{19}$F NMR Spectrum for Ligand 3.60
\(^1\)H NMR Spectrum for Acetal Precursor to Ligand 3.61

\(^{13}\)C NMR Spectrum for Acetal Precursor to Ligand 3.61
$^{31}$P NMR Spectrum for Acetal Precursor to Ligand 3.61

$^1$H NMR Spectrum for Aldehyde Precursor to Ligand 3.61
$^{13}$C NMR Spectrum for Aldehyde Precursor to Ligand 3.61

$^{31}$P NMR Spectrum for Aldehyde Precursor to Ligand 3.61
$^1$H NMR Spectrum for Amino Alcohol Precursor to Ligand 3.61

$^{13}$C NMR Spectrum for Amino Alcohol Precursor to Ligand 3.61
$^{31}$P NMR Spectrum for Amino Alcohol Precursor to Ligand 3.61

$^1$H NMR Spectrum for Ligand 3.61
$^{13}$C NMR Spectrum for Ligand 3.61

$^{31}$P NMR Spectrum for Ligand 3.61
$^1$H NMR Spectrum for Acetal Precursor to Ligand 3.62

$^{13}$C NMR Spectrum for Acetal Precursor to Ligand 3.62
$^{31}\text{P}$ NMR Spectrum for Acetal Precursor to Ligand 3.62

$^{19}\text{F}$ NMR Spectrum for Acetal Precursor to Ligand 3.62
$^1$H NMR Spectrum for Aldehyde Precursor to Ligand 3.62

$^{13}$C NMR Spectrum for Aldehyde Precursor to Ligand 3.62
$^{31}$P NMR Spectrum for Aldehyde Precursor to Ligand 3.62

$^1$H NMR Spectrum for Amino Alcohol Precursor to Ligand 3.62
$^{13}$C NMR Spectrum for Amino Alcohol Precursor to Ligand 3.62

$^{31}$P NMR Spectrum for Amino Alcohol Precursor to Ligand 3.62
$^1$H NMR Spectrum for Ligand 3.62

$^{13}$C NMR Spectrum for Ligand 3.62
$^3$P NMR Spectrum for Ligand 3.62

$^{19}$F NMR Spectrum for Ligand 3.62
$^1$H NMR Spectrum for Acetal Precursor Ligand 3.63

$^{13}$C NMR Spectrum for Acetal Precursor Ligand 3.63
$^{31}$P NMR Spectrum for Acetal Precursor Ligand 3.63

$^{19}$F NMR Spectrum for Acetal Precursor Ligand 3.63
$^1$H NMR Spectrum for Aldehyde Precursor Ligand 3.63

$^{13}$C NMR Spectrum for Aldehyde Precursor Ligand 3.63
$^{31}$P NMR Spectrum for Aldehyde Precursor Ligand \textbf{3.63}

![Phosphorus NMR Spectrum](image)

$^{19}$F NMR Spectrum for Aldehyde Precursor Ligand \textbf{3.63}

![Fluorine NMR Spectrum](image)
$^1$H NMR Spectrum for Amino Alcohol Precursor Ligand 3.63

$^{13}$C NMR Spectrum for Amino Alcohol Precursor Ligand 3.63
$^{31}$P NMR Spectrum for Amino Alcohol Precursor Ligand 3.63

$^{19}$F NMR Spectrum for Amino Alcohol Precursor Ligand 3.63
$^1$H NMR Spectrum for Ligand 3.63

$^{13}$C NMR Spectrum for Ligand 3.63
$^{31}$P NMR Spectrum for Ligand 3.63

$^{1}$H NMR Spectrum for Ligand 3.64
$^{31}$P NMR Spectrum for Ligand 3.64

$^1$H NMR Spectrum for Ligand 3.65
$^{31}\text{P NMR Spectrum for Ligand 3.65}$

$^1\text{H NMR Spectrum for Amino Alcohol Precursor to Ligand 3.70}$
$^{13}$C NMR Spectrum for Amino Alcohol Precursor to Ligand 3.70

$^{31}$P NMR Spectrum for Amino Alcohol Precursor to Ligand 3.70
$^1$H NMR Spectrum for Ligand 3.70

$^{13}$C NMR Spectrum for Ligand 3.70
$^{31}$P NMR Spectrum for Ligand 3.70
Chapter 4: Silicon Nanowires as Photoelectrodes for Carbon Dioxide Fixation

4.1 Introduction

Carbon dioxide (CO$_2$) is present in the atmosphere as a part of the earth’s natural carbon cycle. Due to its abundance, minimal toxicity, and low cost, converting this C$_1$-feedstock into synthetically useful compounds is advantageous. In fact, many bulk chemicals are currently being produced routinely using CO$_2$ such as urea$^1$ (to make nitrogen fertilizers), salicylic acid,$^2$ and polycarbonate-based plastics.$^3,4$ Despite its utility in bulk chemical synthesis, it is difficult to activate such a thermodynamically and kinetically stable molecule (Scheme 4.1). High over-potentials are often needed to complete the multi-electron electrochemical reduction of CO$_2$. Additionally, poor product selectivity is often observed, often leading to a complex mixture of products.$^5$

Scheme 4.1 Products of Direct CO$_2$ Reduction and their Corresponding Overpotentials.

\[
\begin{align*}
\text{CO}_2 + \text{e}^- & \rightarrow \text{CO}_2^- \quad \text{E}^\circ = -1.90 \text{ V} \\
\text{CO}_2 + 2\text{H}^+ + 2\text{e}^- & \rightarrow \text{CO} + \text{H}_2\text{O} \quad \text{E}^\circ = -0.53 \text{ V} \\
\text{CO}_2 + 2\text{H}^+ + 2\text{e}^- & \rightarrow \text{HCO}_2\text{H} \quad \text{E}^\circ = -0.61 \text{ V} \\
\text{CO}_2 + 4\text{H}^+ + 4\text{e}^- & \rightarrow \text{HCHO} + \text{H}_2\text{O} \quad \text{E}^\circ = -0.48 \text{ V} \\
\text{CO}_2 + 6\text{H}^+ + 6\text{e}^- & \rightarrow \text{CH}_3\text{OH} + \text{H}_2\text{O} \quad \text{E}^\circ = -0.38 \text{ V} \\
\text{CO}_2 + 8\text{H}^+ + 8\text{e}^- & \rightarrow \text{CH}_4 + \text{H}_2\text{O} \quad \text{E}^\circ = -0.24 \text{ V}
\end{align*}
\]


A great deal of work has been done to overcome these challenges. The majority of these efforts have focused on the formation of fuels. The reduction of carbon dioxide by nickel and cobalt catalysts highlights the many challenges that plague the direct reduction of CO$_2$. A key step in the catalytic reduction of carbon dioxide is its ability to bind to a vacant coordination site on the reduced metal catalyst. Carbon dioxide is a linear molecule, which binds to a metal center through the electrophilic carbon atom. Upon coordination, carbon dioxide must go from a linear geometry to bent, which requires a significant energy input in the absence of protons. Additionally, the solubility of carbon dioxide in organic solvents is limiting for catalytic activation.

An alternative approach is to indirectly reduce carbon dioxide by incorporating it into organic molecules. Ideally, this would afford synthetically useful C$_1$-extended organic compounds. A prominent example of the indirect reduction of carbon dioxide is photosynthesis, which is a process that converts solar energy into chemical energy in two stages: the light and dark reactions (Figure 4.1). The light reaction begins when chlorophyll absorbs a photon, promoting an electron to a higher energy level. The excited electron goes through an electron transfer chain, thus causing a series of redox reactions. This creates a potential across the cell membrane, the energy from which is used to form the small molecule adenosine-5’-triphosphate (ATP). The final electron acceptor is NADP$^+$, which is converted to nicotinamide adenine dinucleotide phosphate (NADPH). In the light reactions, the energy harvested from light is stored in the chemical bonds of these two small molecules (Figure 4.1).

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ATP and NADPH then participate in the dark reactions (Calvin Cycle). In the first step, carbon dioxide is incorporated into ribulose-1,5-bis-phosphate (RuBP) to generate a β-keto carboxylic acid. This ultimately fragments to two molecules of 3-phosphoglycerate (3PG). Phosphoglycerate kinase catalyzes the phosphorylation of 3PG by a molecule of ATP to afford 1,3-bisphosphoglycerate, which is then reduced by NADPH to form glyceraldehyde 3-phosphate (GAP), a precursor to glucose and other sugars. An additional molecule of ATP is needed to regenerate RuBP so that it can sequester another molecule of carbon dioxide (Figure 4.1).

Photosynthesis is nature’s way of indirectly reducing CO₂. It employs two distinct cycles to separate the energy-harvesting process and the synthesis of sugar building blocks. By sequestering energy from sunlight, photosynthesis is able to overcome the thermodynamic challenges of directly reducing CO₂. Additionally, by incorporating carbon dioxide into the organic molecule prior to its reduction, it avoids

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producing a variety of oxidation states at the carbon center and allows for a high degree of selectivity.

Since both light and CO$_2$ are abundant, we were inspired by photosynthesis and sought to adapt the idea of indirect reduction of carbon dioxide to a laboratory setting. In doing so, we would sidestep the challenge of poor selectivity that is seen in the direct multi-electron reduction of carbon dioxide. However, devising a strategy in the laboratory to sufficiently separate the energy-harvesting and the carbon-carbon bond forming reactions is challenging.

4.2 Silicon Nanowires as Photoelectrodes for Carbon Dioxide Fixation

In a joint effort between the Tan and Wang (Boston College) groups, we sought to apply the concept of storing energy harvested from light in chemical bonds and utilizing it in organic transformations to access synthetically useful compounds. We first identified a reaction that had previously been carried out under solely electrochemical conditions: the carboxylation of ketones and aldehydes to form $\alpha$-hydroxyacids. The first example of electrocarboxylation of aromatic ketones was reported in 1960 by Wawzonek and Gunderson.\textsuperscript{9} In this seminal work, the carboxylation was carried out in a diaphragm cell using a platinum cathode and mercury anode. Under high constant operating potentials in the presence of CO$_2$, the authors propose the formation of a ketyl anion, which affords the desired benzilic acid and a number of side products. Further improving upon the substrate scope and selectivities in the reaction, Silvestri and co-workers utilized a diaphragmless cell with a sacrificial aluminum anode in $N,N$-dimethylformamide (DMF).

and tetrabutylammonium bromide (Bu₄NBr) as the supporting electrolyte. Under one atmosphere of CO₂ and an applied potential of −1.2 V, benzophenone (4.1) can be reduced and trap carbon dioxide to afford benzilic acid (4.2) in 75% yield (Scheme 4.2, Equation 1). This methodology was also extended to ketones bearing an aliphatic group. With an applied potential of −1.4 V and one atmosphere of carbon dioxide, 6-methoxy-2-acetonaphthalene (4.3) affords carboxylic acid 4.4 in 80% yield (Scheme 4.2, Equation 2).

Scheme 4.2 Silvestri’s Electrochemical Carboxylation of Aromatic Ketones.

![Scheme 4.2](image)

In order to adapt this reaction into a photoelectrochemical setting, a light-harvesting mechanism needed to be identified. Due to their ability to efficiently participate in charge separation, semi-conductors were explored for this purpose. Semi-conductors offer the advantage of being able to absorb light broadly in the visible range. The wavelength of light absorbed depends on the size of the semi-conductor’s band gap. When light hits the semi-conductor in the form of photons, electrons are promoted from the valence band (VB) to the conduction band (CB), leaving behind a hole. Hypothetically, upon coming into contact with an electrolytic solution, a flow of charge occurs between the semi-conductor and the solution. This generates a depletion

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layer in the semi-conductor near the semi-conductor/solution interface, which results in a bend in the band gap. The formation of such a depletion layer is important, since it ensures that the photogenerated charges are separated with high efficiencies when illuminated. As a result, semi-conductors have been employed as photoelectrodes for artificial photosynthesis in the form of photoelectrochemical (PEC) cells.\textsuperscript{11}

Taking inspiration from photosynthesis, we wondered if we could harvest energy from light and use it to perform the photoelectrochemical carboxylation of aromatic ketones to generate synthetically useful carboxylic acid products (Scheme 4.3). Similar to photosynthesis, we hoped that we could indirectly reduce CO\textsubscript{2} to avoid the generation carbon in a complex mixture of oxidation states.

**Scheme 4.3** The Key Carboxylation Steps in Photosynthesis and the Proposed PEC Carboxylation.

\textit{Carbon dioxide fixation in the Calvin Cycle (Photosynthesis)}

\[
\begin{align*}
\text{RuBP} & \xrightarrow{\text{CO}_2} \text{3PG} \\
\text{H}_2\text{O} & \rightarrow \text{3PG}
\end{align*}
\]

\textit{Proposed Photoelectrochemical Carboxylation of Aromatic Ketones}

\[
\begin{align*}
\text{CO}_2 \xrightarrow{h\nu} & \text{COOH} \\
\text{H}_2\text{O}^+ & \rightarrow \text{COOH}
\end{align*}
\]

4.2.1 Photoelectrochemical (PEC) Characterization of Silicon Nanowires (SiNWs)

Silicon nanowires (SiNWs) were identified as a suitable light-harvesting electrode because they are efficient at converting solar energy into electrical energy, easy to make, and stable under reductive conditions. We initially sought to determine the key characteristics of this photoelectrochemical system using SiNWs as a photoelectrode in the carboxylation of benzophenone (Scheme 4.4).

Scheme 4.4 General Reaction Scheme for the PEC Carboxylation of Benzophenone.

![Scheme 4.4](image)

We found the electrochemical potential of the solution to be – 0.12 V, which was determined by the Tafel technique in the dark (all potentials are relative to Ag/AgI/I reference, which is 0.60 V more positive than the saturated calomel electrode, SCE). The Fermi level of silicon was also determined to be 0.74 V (measured by the Mott-Schottky plot, see supporting information for further details). Taking this information together with the known doping levels of silicon (10[^15] cm[^3] B-doped; ρ: 10-20 Ωcm), the energetics of the benzophenone carboxylation system were constructed (Figure 4.2). When a potential is applied under dark conditions, a large degree of band bending (0.86 V in magnitude) exists on the surface, which creates a substantial depletion layer where photogenerated

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charges can be separated efficiently. When illuminated, the separated charges create a built-in field to help power the carboxylation reaction to form benzoic acid. Both n-type and p-type SiNWs with different doping levels were examined for this purpose, and moderately doped p-type SiNWs proved to be the most optimal photocathodes.

**Figure 4.2** Energetics of the p-type SiNWs System for Benzophenone Carboxylation.

This photoelectrochemical system exhibits other notable characteristics. In the dark, no photocurrent is detected for applied potentials up to – 2.4 V (Figure 4.3(a)). Under illumination conditions, high saturation current densities are observed at low negative applied potentials (31.1 mA cm$^{-2}$ at – 1.20 V), which suggests that light makes a significant contribution to the reaction (Figure 4.3(a)). Additionally, when the SiNWs are replaced by a Pt cathode under identical illumination and applied potential conditions, only 2.00 mA cm$^{-2}$ photocurrent was observed (Figure 4.3(a)). Notably, the saturation current density observed with SiNWs approaches the theoretical limit for Si under identical conditions (43.0 mA cm$^{-2}$),$^{13}$ which highlights the utility of SiNWs for high-efficiency PEC operations. The saturation current density also scales linearly with

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illumination intensity, which demonstrates that charge separation is effective (Figure 4.3(b)).

Figure 4.3 Photoelectrochemical characteristics of benzilic acid formation by p-type SiNWs. (a) SiNWs compared to other commonly used electrodes. (b) Photocurrent density versus voltage under different illumination conditions.

As demonstrated in Figure 4.3(a) SiNWs also exhibit a less-negative turn-on voltage (−0.52 V at > 1 mA/cm²) relative to both planar Si (−0.63 V) and Pt (−1.15 V, a commonly used electrode); however, SiNWs exhibit a lower saturation current density (32.1 mA/cm²) than planar Si (34.4 mA/cm²). Similar to previous reports, the high surface area of SiNWs may cause increased charge recombination at the semiconductor/solution interface.¹³a,¹⁴ This results in reduced saturation current densities, while not considering light-trapping mechanisms. However, increased charge recombination with SiNWs also suggests that the open-circuit potentials are lower, which would result in a more negative turn-on voltage relative to planar Si. This is not observed experimentally. To reconcile this data, we believe that the better performance is derived

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from the multifaceted nature of SiNWs, which results in improved charge transfer kinetics. The favorable charge transfer between SiNWs and benzophenone results in lower overpotentials.

This hypothesis is supported by experiments where both the saturation current densities ($J_{\text{sc}}$, Figure 4.4(a)) and the turn-on voltages ($V_{\text{on}}$, Figure 4.4(b)) were measured using SiNWs of different lengths ($L$ varying between 0 and 10 µm). The generated photocurrent ($J_{\text{sc}}$) is dependent on two conflicting factors: light absorption and charge recombination. The photocurrent should increase as the SiNWs get longer if light absorption is the determining factor, since longer SiNWs can absorb more light. Conversely, if the generated photocurrent was solely dependent on charge recombination, a decrease is predicted for longer SiNWs because they have more recombination sites. A monotonic decrease of $J_{\text{sc}}$ for shorter SiNWs ($0 < L < 6$ µm) is observed, because light absorption is relatively weak and charge recombination dominates (Figure 4.4(a)). For longer SiNWs ($L > 6$ µm), the effect of improved light absorption dominates, which leads to an increase of $J_{\text{sc}}$. In the range of $0 < L \leq 6$ µm, the turn-on voltage scales with $L$ monotonically (Figure 4.4(b)). Recombination-induced open-circuit potential reduction dominates for longer SiNWs ($L > 6$ µm), resulting in more negative turn-on potentials.
4.2.2  Mechanistic Investigations for the PEC Carboxylation of Aromatic Ketones

Having identified SiNWs as a suitable photoelectrode, we sought to elucidate the mechanism of the carboxylation reaction. A variety of control experiments were carried out using p-type SiNWs under illumination conditions. For these experiments, the volume of solvent and concentration of supporting electrolyte (Bu₄NBr) were kept constant. As shown in Figure 4.5 (left), under typical reaction conditions with CO₂ and benzophenone, the current density level plateaus at 29.4 mA/cm². In the absence of CO₂, the current density levels out at 14.6 mA/cm², which is approximately half of that observed when CO₂ is present in the reaction. This data supports a two-step single electron transfer mechanism, whereby the photogenerated electrons first reduce benzophenone to afford a ketyl radical anion. The second electron transfer, which is not observed in Figure 4.5, takes place after CO₂ fixation.
**Figure 4.5** (left) p-type SiNW Photoelectrode measured with or without CO\(_2\) or (right) without benzophenone substrate. As a reference, the trace for typical carboxylation is shown on the right in red.

Control experiments were also carried out in the absence of benzophenone (Figure 4.5, right). When benzophenone is not present in the reaction mixture, CO\(_2\) is directly reduced to afford carbon in a variety of oxidation states. The reaction competes with the desired CO\(_2\) fixation process and is undesired. Electrochemical side reactions with the solvent only occurs at extremely negative potentials (less than \(-2.1\) V) and do not result in photocurrent under photoelectrochemical conditions. In order to avoid the direct reduction of CO\(_2\), the operating potentials were limited to more positive than \(-1.2\) V, as indicated by the green shaded area in Figure 4.5 (right).

This photoelectrochemical data has allowed us to construct a proposed mechanism of action for the photoelectrochemical fixation of CO\(_2\) by benzophenone (Figure 4.6). In the presence of light, p-type SiNWs generate electrons in solution which, through a single electron transfer, reduce benzophenone (4.1) to the radical anion. The radical anion then traps a molecule of CO\(_2\). A second single electron transfer occurs at the carbon-centered radical to generate a carbanion, which can trap an additional molecule of
Upon aqueous workup, benzilic acid (4.2) is isolated. The aluminum counter-electrode removes the holes from the solution by providing electrons, resulting in net oxidation to produce Al³⁺, which dissolves in the reaction medium.¹⁵

**Figure 4.6** Mechanism of Action for PEC Carboxylation of Benzophenone.

It was important that high levels of selectivity could be obtained for the desired carboxylic acid product (4.2). Early in our studies, we anticipated other byproducts that could result from the reaction. These include secondary alcohol 4.5, resulting from the failure to trap CO₂, and diol 4.6, as a result of the carbanion trapping another molecule of ketone substrate (Scheme 4.5).

**Scheme 4.5** Possible Products Generated from the PEC Carboxylation of Benzophenone.

Under typical operating conditions (−1.20 V, 100 mW/cm² AM 1.5 illumination), benzophenone underwent carboxylation in the presence of 1 atmosphere of CO₂ at a

faradaic efficiency of 94% (Scheme 4.6). Importantly, 4.2 was isolated in 98% yield, which highlights the high degree of selectivity in this reaction for the desired product.

**Scheme 4.6** Photoelectrochemical Carboxylation of Benzophenone.

![Scheme 4.6](image)

The stability of the SiNWs photoelectrode towards degradation pathways, such as oxidation and photocorrosion, is of the utmost importance. Since the carboxylation is carried out under reducing conditions, oxidation decomposition pathways were less likely. The SiNWs photoelectrode was used in the carboxylation for four consecutive runs and no considerable difference in photoelectrochemical performance was observed (Figure 4.7). The rate, yield, and observed selectivities were reproduced over the course of each experiment, which is consistent with the SiNW photoelectrode remaining intact over time. The reaction yields for the α-hydroxy acid 4.2, as determined by $^1$H NMR spectroscopy (based on remaining starting material) were found to be > 98% (1st run), 97% (2nd run), 98% (3rd run), and 98% (4th run). A peak turn-over frequency (TOF) was estimated to be 25.8 s⁻¹, assuming that every Si surface atom is an active site.
4.2.3 Reaction Optimization and Substrate Scope

Under typical reaction conditions, a constant potential of $-1.2 \text{ V}$ is applied under illumination conditions. Carbon dioxide is bubbled through the solution with vigorous stirring for the duration of the reaction at room temperature. Using benzophenone as the aromatic ketone resulted in a 98% isolated yield of benzoic acid (Scheme 4.6).

To demonstrate the synthetic utility of the reaction, 2-acetyl-6-methoxynaphthalene (4.3) was employed as a substrate. Importantly, carboxylated product 4.4 is a precursor to the non-steroidal anti-inflammatory drug (NSAID) naproxen (Scheme 4.7). Under the same procedure used for benzophenone, 2-acetyl-6-methoxynaphthalene underwent the carboxylation and 4.4 was observed in a 97% $^1\text{H}$ NMR yield, and was isolated in 84% yield. No measureable amounts of byproducts were observed, which is confirmed by a calculated selectivity of 98% for 4.4. The success of this substrate in the photoelectrochemical carboxylation reaction indicated that the

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reduction potential for ketone substrates containing an aliphatic group could be reduced under the photoelectrochemical reaction conditions.

**Scheme 4.7** Synthesis of a Precursor to (+/-)-naproxen via PEC Carboxylation.

![Scheme 4.7](image)

The reaction was further extended to 4-isobutylacetophenone (4.9), where desired product 4.10 is a precursor to ibuprofen. Under the typical reaction conditions for both benzophenone and 2-acetyl-6-methoxynaphthalene, 73% conversion was observed, but only 9% of 4.10 was seen by $^1$H NMR (Scheme 4.8). The remaining mass balance was determined to be diol 4.12, which results from the failure to trap CO$_2$. The low levels of selectivity for the desired carboxylic acid product may be attributed to a generated ketyl radical that is less stable than the corresponding benzophenone radical. As a result, this ketyl radical may more readily dimerize with another molecule of substrate or fail to trap at all.

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Scheme 4.8 PEC Carboxylation of 4-isobutylacetophenone under Standard Conditions.

\[
\text{4.8} \quad \text{(+/-)-ibuprofen}
\]

In order to suppress formation of \(4.12\) and promote the carboxylation reaction, we sought to keep the concentration of \(4.9\) low relative to \(\text{CO}_2\). We carried out an experiment by slowly adding the substrate over the course of 8 hours. Complete conversion was obtained and \(4.10\) was observed in a 37\% \(^1\text{H}\) NMR yield, which was a considerable improvement (Scheme 4.9). Alcohol byproduct \(4.11\) accounted for 36\% of the generated products, with the remaining mass balance being attributed to diol \(4.12\).

Scheme 4.9 Slow Addition of Substrate to Favor the Carboxylation Reaction.

Another way to improve the selectivity for carboxylic acid \(4.10\) is by increasing the effective concentration of \(\text{CO}_2\) in the reaction. Under standard conditions, \(\text{CO}_2\) is bubbled through the reaction at room temperature. In order the increase the solubility of
CO₂, the reaction was carried out at 4 °C with constant bubbling of CO₂. Upon workup, 66% of 4.10 was observed by ¹H NMR, which is a drastic improvement relative to our previous reaction conditions. Although good ¹H NMR yields of 4.10 were obtained, the result was not reproducible. Depending on the flow rate of CO₂ during the course of the reaction, various amounts of the acetonitrile solvent would evaporate thus affecting the relative concentrations of reagents.

To address the reproducibility of the reaction, we developed a procedure that would keep the relative concentrations constant (Scheme 4.10). After all of the reagents were added to the reaction flask, the solution was saturated with CO₂ at 4 °C for 25 minutes. The gas inlet needle was then replaced with a balloon of CO₂ and potential was applied to the vessel with vigorous stirring at 4 °C. Following this procedure, 4.10 was isolated in 64% yield. When carried out at room temperature, this modified procedure also works for benzophenone and 2-acetyl-6-methoxynaphthalene, giving nearly identical results.

Scheme 4.10 Optimized Result for the PEC Carboxylation of 4-isobutylacetophenone.

The same carboxylation reaction has been carried out on benzophenone using graphite or mercury electrodes in the absence of light. The results obtained under our photoelectrochemical system are comparable to the electrochemical reactions, in terms of both yield and selectivity (Table 4.1). Notably, the photoelectrochemical reactions
utilizing SiNWs as the photocathode were carried out at potentials up to 670 mV less-negative than those reported using electrochemical means, with the difference in potential being explained by the contribution of light to the reaction. The use of SiNWs as photocathodes in the reactions demonstrates that the energy in solar light can be harnessed to promote the carboxylation of aromatic ketones under low applied potentials.

Table 4.1 Comparison of PEC Results and Electrochemical Literature Results.

<table>
<thead>
<tr>
<th>Product</th>
<th>Cathode (this work)</th>
<th>Selectivity (this work)</th>
<th>Yield(^a) (this work)</th>
<th>Cathode (Lit)</th>
<th>Selectivity(^d) (Lit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>SiNWs</td>
<td>100%</td>
<td>98%(^b)</td>
<td>Graphite</td>
<td>82%(^e)</td>
</tr>
<tr>
<td>4.4</td>
<td>SiNWs</td>
<td>100%</td>
<td>84%(^b)</td>
<td>Mercury</td>
<td>82%(^f)</td>
</tr>
<tr>
<td>4.10</td>
<td>SiNWs</td>
<td>64%</td>
<td>64%(^c)</td>
<td>Mercury</td>
<td>90%(^g)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of carboxylic acid product. \(^b\) Reaction run in acetonitrile at rt under 1 atm of CO\(_2\) with an applied potential of ~1.2 V. \(^c\) Standard conditions, except reaction was carried out at 4 °C with a constant applied potential of ~1.6 V. \(^d\) Reactions were done under constant current mode 10 mA cm\(^2\). \(^e\) Run in N-methylpyrrolidine at rt under 1 atm of CO\(_2\). \(^f\) Run in DMF at 0 °C under an atmosphere of CO\(_2\). \(^g\) Reaction carried out in at rt in DMF under 65 atm of CO\(_2\).

4.3 Conclusions

The harvesting of energy from light has proven to be extremely useful in the context of reactions such as water splitting and the direct reduction of CO\(_2\) for the production of fuels; however, the use of photoenergy for the synthesis of more complex molecular architectures is an underdeveloped area. Utilizing p-type SiNWs as a photocathode, the photoelectrochemical carboxylation of aromatic ketones has been developed to afford \(\alpha\)-hydroxy carboxylic acids. Due to the morphology of the SiNWs, electron transfer between the photocathode and the organic substrate is quite facile.
Under low constant applied potentials, it was found that light makes a significant contribution to the reaction. Utilizing low operating potentials also ensures that CO$_2$ is not directly reduced, which results in the suppression of byproduct formation and high levels of selectivity for the desired carboxylic acid product. Highlighting the synthetic utility of this method, two precursors to the NSAID compounds ibuprofen and naproxen were synthesized using CO$_2$, an abundant C$_1$ feedstock, and light, an crucial source of energy in nature.

4.4 Experimental Section

4.4.1 Tafel Plot: Investigation of Equilibrium Conditions

Figure 4.8 (a) Tafel plot of planar Si sample in a benzophenone solution; (b) Tafel plot of Si Nanowires sample in a benzophenone solution. All measurements were performed with 25 mM benzophenone in 0.1 M TBAB acetonitrile solution with CO$_2$ bubbling. Xe lamp light intensity 100 mW cm$^{-2}$ was calibrated by a Si diode under AM 1.5 irradiation condition. Scan rate was 0.1 mV/sec, and scan direction was from negative potential to positive potential. All the voltages are relative to reference electrode Ag/AgI/I$^-$. The equilibrium potential is the point at which the cathodic current density and the anodic one are equal. At this potential, the electrochemical potential of the electrolyte
solution aligns with the Fermi level of Si. As shown in Figure 4.8, the equilibrium potential of planar Si is $-0.120\ \text{V}$ in dark. When illuminated, the equilibrium potential shifts positively as a result of the photogenerated electron accumulation on the surface. Together with the Mott-Schottky plot (which will be discussed later), the energetic scheme of Si/ benzophenone junction can be generated.

Compared with planar samples, Si nanowires (NWs) exhibit more positive equilibrium potential in dark or under illumination. This suggests that it requires less applied potential in order for the benzophenone reduction to take place on Si NWs. Importantly, the difference between the equilibrium potentials in dark and under illumination is larger ($0.4\ \text{V}$) for Si NWs than for planar Si ($0.22\ \text{V}$). It indicates that a higher build-in potential is obtained on Si NWs. This is likely caused by improved light absorption by SiNWs.

### 4.4.2 Mott-Schottky Plot

In the reverse bias region, the space charge region capacitance ($C_{sc}$) of p-SiNWs can be described by the Mott-Schottky relation:

$$C_{sc}^{-2} = \frac{2}{A^2 q \varepsilon_0 \varepsilon N_A} \left( -V + V_{fb} - \frac{kT}{q} \right)$$

where $\varepsilon_0$ is the permittivity of free space; $\varepsilon$ is the dielectric constant of silicon; $V$ is the applied potential; $V_{fb}$ is the flat-band potential; $N_A$ is the dopant density of silicon; $A$ is the surface area of the electrode; $k$ is the Boltzmann constant; and $T$ is the temperature. The Mott-Schottky plots obtained at different frequencies are linear ($R^2 > 0.995$) and the flat-band potential is measured as $0.74\ \text{V}$ (all potentials refer to Ag/AgI/I$^-$ reference, which is $0.60\ \text{V}$ more positive than SCE, saturated calomel electrode).
Figure 4.9 Mott-Schottky plots of SiNW photoelectrode measured in CO$_2$/benzophenone system at different frequencies. All the measurements were carried out in dark. The dotted lines are linear fitting curves.

4.4.3 Photocurrents of Bulk Si Electrodes

Figure 4.10 (a) photocurrent density of planar Si electrode at different light intensities; (b) linear relationship of photocurrent density of the sample with light intensity at applied potential of -2.5 V (vs reference electrode). All measurements were performed with 25 mM benzophenone in 0.1 M NBu$_4$Br acetonitrile solution with CO$_2$ bubbling. Xe lamp was used as light source. All light intensity was calibrated by a Si diode under AM 1.5 irradiation condition.
The linear relationship between saturation photocurrents densities on planar Si and light intensities suggest effective electron transfer on the Si/ benzophenone junction. The photocurrent density of planar Si is slightly higher than Si NWs, which is due to the increased charge recombination on the larger surface area of Si NWs. But the turn-on potential is more negative than Si NWs. The turn-on photocurrent slope on Si NWs (68.7 mA cm$^{-2}$ V$^{-1}$) is also slightly lower than the planar Si (70.1 mA cm$^{-2}$ V$^{-1}$). This indicates improved electron transfer kinetics from multifaceted Si NWs to liquid electrolyte junction, leading to reduced overpotentials.

4.4.4  General Information

Unless otherwise noted, all reagents were obtained commercially and used without further purification. Flash column chromatography was performed using Silicycle SiliaFlash F60 silica gel and ACS grade solvents as received from Fisher Scientific. All reactions were performed with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC), unless otherwise noted. $^1$H and $^{13}$C NMR were performed on a Varian VNMRS 500 MHz spectrometer. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3 Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual solvent. Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR, equipped with a single crystal diamond ATR module, and values are reported in cm$^{-1}$. High resolution mass spectrometry (HRMS) data was generated as Boston College facilities.
**Procedure for Photocatalyst Fabrication**\(^{18}\): The preparation of SiNWs was reported previously. One prepared, the substrates containing SiNWs were immersed in HF (aqueous, 5\%) for 2 minutes and then dried in a stream of N\(_2\). Al (300nm) was then sputtered onto the backside of the substrates by radio frequency magnetron sputtering (AJA International, Orion 8, MA, USA). They were then annealed in Ar (flow rate: 5000 standard cubic centimeters per minute, SCCM) at 450 °C for 5 minutes. Afterword, tinned copper wires were fixed to the Al film by Ag epoxy (SPI supplies, PA, USA). Lastly, non-conductive hysol epoxy (Locite, OH, USA) was used to seal the entire substrate, except for the regions where SiNWs resided.

**General Procedure for Photoelectrochemical Reactions:** In a dry box, tetrabutylammonium bromide (0.644 g, 2.00 mmol), benzophenone (80.0 mg, 0.439 mmol), and acetonitrile (18 mL) were added to a flame-dried, three-neck, 25-mL round-bottom flask equipped with magnetic stir bar. One of the following was placed in each neck of the round-bottom flask: SiNWs working electrode, aluminum counter electrode, Ag/AgI/I\(_2\) reference electrode. The reaction vessel was brought out of the dry box and CO\(_2\) was bubbled through the solution with an oil bubbler outlet. A constant potential of \(-1.2\) V was applied to the reaction mixture and the generated reaction current was monitored during the course of the reaction. Light was shined onto the reaction, which was vigorously stirred overnight. Without illumination, the reaction current was negligible.

4.4.5 Preparation of Substrates for Photoelectrochemical Carboxylation

Benzophenone was obtained from Sigma-Aldrich and used without purification. 2-Acetyl-6-methoxynaphthalene was purchased from TCI America and was used without further purification.

1-(4-isobutylphenyl)ethanone. To a flame-dried, 250-mL, round-bottom flask was added AlCl$_3$ (9.38 g, 70.3 mmol) and CH$_2$Cl$_2$ (86 mL). The mixture was cooled to 0 °C, and acetyl chloride (5.00 mL, 70.3 mmol) and isobutylbenzene (10.0 mL, 63.9 mmol) were added, sequentially, to the flask. The reaction was stirred at this temperature for 90 minutes. The mixture was poured into a mixture of ice water and CH$_2$Cl$_2$ (150 mL). The two layers were partitioned in a separatory funnel and the organic layer was washed with water (70 mL) and brine (50 mL). The organic layer was dried over MgSO$_4$ filtered, and concentrated in vacuo. The title compound was distilled to purity using a Kugelrohr and was isolated as a colorless oil (10.7 g, 95%). $^1$H NMR ((CD$_3$)$_2$CO, 500 MHz) δ 7.89 (d, 2H, J = 8.3 Hz), 7.30 (3, 2H, J = 8.3 Hz), 2.55 (d, 2H, J = 7.3 Hz), 2.54 (s, 3H), 1.87 – 1.95 (m, 1H), 0.89 (d, 6H, J = 6.6 Hz); $^{13}$C NMR ((CD$_3$)$_2$CO, 125 MHz) δ 197.6, 148.2, 136.3, 130.3, 129.2, 45.9, 31.0, 26.8, 22.7; IR: 2956, 1680, 1605, 1357, 1265, 950, 596, 582 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{12}$H$_{17}$O$_1$ [M+H]$^+$: 177.1279, found: 177.1280.

4.4.6 Characterization of Products of Photoelectrochemical Carboxylation
**2-hydroxy-2,2-diphenylacetic acid.** To a flame-dried, three-neck, 25-mL, round-bottom flask equipped with magnetic stir bar was added tetrabutylammonium bromide (0.664 g, 2.00 mmol), benzophenone (0.22 M benzophenone in acetonitrile; 2.00 mL, 80.0 mg, 0.439 mmol) and acetonitrile (18 mL) in a dry box. One of the following was placed in each neck of the round-bottom flask: Si NWs working electrode, aluminum counter electrode, Ag/AgI/I⁻ reference electrode. The reaction vessel was brought out of the dry box and CO₂ was bubbled through the solution with an oil bubbler outlet. A potential -1.2 V was applied to the reaction mixture and a light was shined onto the reaction with vigorous stirring overnight. The crude reaction mixture was concentrated *in vacuo*, quenched with 6 N HCl (7.5 mL), and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the title compound as a colorless solid (98 mg, 98%).

**Assignments:**

- **1H NMR** ((CD₃)₂CO, 500 MHz) δ 7.49 – 7.52 (m, 4H), 7.29 – 7.37 (m, 6H);
- **13C NMR** ((CD₃)₂CO, 125 MHz) δ 175.3, 144.1, 128.7, 128.5, 128.3, 81.6; IR: 3394, 2865, 1715, 1243, 1175, 1053, 697 cm⁻¹;
- **HRMS** (DART-TOF) calcd. for C_{14}H_{11}O₂ [M+H-H₂O]⁺: 211.0759, found: 211.0758.

**2-hydroxy-2-(6-methoxynaphthalen-2-yl)propanoic acid.** To a flame-dried, three-neck, 25-mL, round-bottom flask equipped with magnetic stir bar was added tetrabutylammonium bromide (0.664 g, 2.00 mmol), 2-acetyl-6-methoxynaphthalene (0.0865 g, 0.432 mmol) and acetonitrile (20 mL) in a dry box. One of the following was placed in each neck of the round-bottom flask: Si NWs working electrode, aluminum counter electrode, Ag/AgI/I⁻ reference electrode. The reaction vessel was brought out of
the dry box and CO$_2$ was bubbled through the solution with an oil bubbler outlet. A potential – 1.2 V was applied to the reaction mixture and a light was shined onto the reaction with vigorous stirring overnight. The crude reaction mixture was concentrated \textit{in vacuo} to remove the acetonitrile solvent. To the crude reaction was added 6 N NaOH (3 mL). The aqueous layer was washed with diethyl ether (15 mL). After separating the two layers, the organic layer was washed with an additional portion of 6 N NaOH (3 mL). The organic layer was discarded and the combined aqueous layers were acidified to pH = 2 with concentrated HCl. This aqueous layer was washed with diethyl ether (2 x 30 mL) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated \textit{in vacuo} to afford the title compound as a colorless solid, which turns beige upon standing (89 mg, 84%). $^1$H NMR ((CD$_3$)$_2$CO, 500 MHz) $\delta$ 8.05 (d, 1H, $J = 1.5$ Hz) 7.77 – 7.82 (m, 2H), 7.69 – 7.71 (m, 1H), 7.28 (d, 1H, $J = 2.4$ Hz), 7.13 – 7.15 (m, 1H), 3.91 (s, 3H), 1.81 (s, 3H); $^{13}$C NMR (((CD$_3$)$_2$CO, 125 MHz) $\delta$ 176.5, 158.8, 139.8, 134.8, 130.3, 129.3, 127.3, 125.0, 124.5, 119.5, 106.2, 76.0, 55.5, 27.4; IR: 3410, 2940, 1724, 1605, 1266, 1132, 851 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{14}$H$_{13}$O$_3$ [M+H-H$_2$O]$^+$: 229.0865, found: 229.0872.

\begin{center}
\includegraphics[width=0.2\textwidth]{2-hydroxy-2-(4-isobutylphenyl)propanoic_acid.png}
\end{center}

**2-hydroxy-2-(4-isobutylphenyl)propanoic acid.** To a flame-dried, three-neck, 25-mL, round-bottom flask equipped with magnetic stir bar was added tetrabutylammonium bromide (0.664 g, 2.00 mmol) in a dry box. One of the following was placed in each neck of the round-bottom flask: Si NWs working electrode, aluminum counter electrode, Ag/AgI/I$^-$/ reference electrode. The reaction vessel was brought out of the glovebox and
was purged with CO$_2$ three times. Acetonitrile (20 mL) was added to the flask under an atmosphere of CO$_2$ and the flask was then brought into a cold room (4 °C) where CO$_2$ was bubbled through the solution. During the course of sparging the solution, 4-isobutylacetophenone (80.0 µL, 0.432 mmol) was brought out of the dry box and added to the reaction via syringe. Sparging with CO$_2$ was continued for an additional 20 minutes, after which time the inlet/outlet needles were replaced with a balloon of CO$_2$. A potential of −1.6 V was applied to the reaction mixture and a light was shined onto the reaction with vigorous stirring overnight. The crude reaction mixture was concentrated _in vacuo_ to remove the acetonitrile solvent. To the crude reaction was added 6 N HCl (8 mL). The aqueous layer was washed with diethyl ether (3 x 20 mL). The combined organic layers were washed with 6 N NaOH (3 x 6 mL) and the organic layer was discarded. The aqueous layer was acidified to pH = 2 using concentrated HCl. The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the organic layer was dried over MgSO$_4$, filtered, and concentrated _in vacuo_ to afford the title compound as a colorless solid (62 mg, 65%). $^1$H NMR ((CD$_3$)$_2$CO, 500 MHz) $\delta$ 7.53 (d, 2H, $J = 8.1$ Hz), 7.15 (d, 2H, $J = 8.1$ Hz), 2.47 (d, 2H, $J = 7.3$ Hz), 1.82 – 1.90 (m, 1H), 1.73 (s, 3H), 0.89 (d, 6H, $J = 6.6$ Hz); $^{13}$C NMR ((CD$_3$)$_2$CO, 125 MHz) $\delta$ 176.2, 142.0, 141.4, 129.4, 125.8, 75.9, 45.3, 30.7, 27.4, 22.5; IR: 3423, 2955, 2926, 2869, 1716, 1262, 1146, 1119 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{13}$H$_{17}$O$_3$ [M-H]$^-$: 221.1178, found: 221.1175.

**4.4.7 Characterization of Byproducts of Photoelectrochemical Carboxylation**

![Structure of byproduct](image)

328
Diphenylmethanol. Purchased from Sigma-Aldrich and analyzed by $^1$H NMR in acetone-$d_6$. $^1$H NMR ((CD$_3$)$_2$CO, 500 MHz) δ 7.44 (d, 4H, $J = 7.6$ Hz), 7.30 – 7.33 (m, 2H), 7.20 – 7.23 (m, 2H), 5.85 (d, 1H, $J = 3.7$ Hz), 4.87 (d, 1H, $J = 3.9$ Hz); $^{13}$C NMR ((CD$_3$)$_2$CO, 125 MHz) δ 146.5, 129.0, 127.7, 127.4, 76.2; IR: 3275, 1493, 1454, 1032, 1017, 762, 739 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{13}$H$_{11}$ [M+H-H$_2$O]$^+$: 167.0861, found: 167.0865.

![Chemical structure of Diphenylmethanol](image)

1,1,2,2-tetraphenylethane-1,2-diol. Purchased from Sigma-Aldrich and analyzed by $^1$H NMR in acetone-$d_6$. $^1$H NMR ((CD$_3$)$_2$CO, 500 MHz) δ 7.44 – 7.46 (m, 8H), 7.10 – 7.11 (m, 12H), 4.79 (s, 2H); $^{13}$C NMR ((CD$_3$)$_2$CO, 125 MHz) δ 147.0, 130.1, 127.4, 127.1, 84.1; IR: 3554, 3056, 1445, 1024, 741, 698 cm$^{-1}$; HRMS (DART-TOF) calcd. for C$_{26}$H$_{21}$O$_1$ [M+H-H$_2$O]$^+$: 349.1592, found: 349.1588.

![Chemical structure of 1,1,2,2-tetraphenylethane-1,2-diol](image)

1-(6-methoxynaphthalen-2-yl)ethanol. To a flame-dried, 15-mL, round-bottom flask was added NaBH$_4$ (134 mg, 3.00 mmol) and dry methanol (3.0 mL). The mixture was cooled to 0 °C and 2-Acetyl-6-methoxynaphthalene (500 mg, 2.50 mmol) was added to the flask, with stirring, as a solution in methanol (1.4 mL). After the addition was complete, the reaction was allowed to warm to room temperature over one hour. The reaction was quenched by the addition of 4 N HCl (10 mL), transferred to a separatory
funnel, and extracted with dichloromethane (60 mL). The organic layer was dried over MgSO₄, filtered, and concentrated to yield a colorless solid (420 mg, 83%). **¹H NMR** ((CD₃)₂CO, 500 MHz) δ **¹H NMR** ((CD₃)₂CO, 500 MHz) δ 7.78 (s, 1H), 7.77 (d, 1H, J = 2.2 Hz), 7.75 (s, 1H), 7.50 – 7.52 (m, 1H), 7.27 (d, 1H, J = 2.4 Hz), 7.12 – 7.14 (m, 1H), 4.96 – 5.01 (m, 1H), 4.21 (d, 1H, J = 3.9 Hz), 3.90 (s, 3H), 1.48 (s, 3H, J = 6.6 Hz); **¹³C NMR** ((CD₃)₂CO, 125 MHz) δ 158.5, 143.5, 134.9, 130.2, 129.8, 127.6, 125.7, 124.3, 119.5, 106.6, 70.1, 55.6, 26.2; **IR**: 3340, 2972, 1251, 1203, 760, 698 cm⁻¹; **HRMS** (DART-TOF) calcd. for C₁₃H₁₃O₁ [M+H-H₂O]⁺: 185.0966, found: 185.0970.

**1-(4-isobutylphenyl)ethanol.** To a flame-dried, 25-mL, round-bottom flask was added NaBH₄ (129 mg, 3.40 mmol) and methanol (4 mL). The mixture was cooled to 0 °C, followed by the addition of 1-(4-isobutylphenyl)ethanone (500 mg, 2.84 mmol) as a solution in methanol (1 mL). The reaction was allowed to warm to room temperature over one hour, quenched by the addition of 4 N HCl (10 mL), transferred to a separatory funnel, and washed with dichloromethane (70 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. Isolation of the title compound was carried out using silica gel column chromatography (20% EtOAc/Hex) to afford a colorless oil (429 mg, 84%). **¹H NMR** ((CD₃)₂CO, 500 MHz) δ 7.28 (d, 2H, J = 7.8 Hz), 7.10 (d, 2H, J = 8.1 Hz), 4.78 – 4.82 (m, 1H), 4.0 (d, 1H, J = 4.2 Hz), 2.45 (d, 2H, J = 7.3 Hz), 1.82 – 1.87 (m, 1H), 1.38 (d, 3H, J = 6.4 Hz), 0.89 (d, 6H, J = 6.6 Hz); **¹³C NMR** ((CD₃)₂CO, 125 MHz) δ 145.7, 140.7, 129.6, 126.1, 69.9, 45.7, 31.1, 26.3, 22.8; **IR**: 3342, 2954,
1094, 846, 799, 554 cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{12}H_{17}\) [M+H-H\(_2\)O]\(^+\): 161.1330, found: 161.1331.

![Chemical Structure](image)

**2,3-bis(4-isobutylphenyl)butane-2,3-diol** (isolated as a mixture of *meso* and *dl* compounds). Prepared by the method of Banik, *et al*.\(^{19}\)

\(^1\)H NMR ((CD\(_3\))\(_2\)CO, 500 MHz) \(\delta\) 7.23 (d, 4H, \(J = 8.3 \text{ Hz}\)), 7.07 (d, 4H, \(J = 8.1 \text{ Hz}\)), 6.95 (m, 8H), 4.07 (s, 2H), 3.92 (s, 2H), 2.42 – 2.44 (m, 8H), 1.81 – 1.86 (m, 4H), 1.51 (s, 6H), 1.50 (s, 6H), 0.87 – 0.89 (m, 24H); \(^13\)C NMR ((CD\(_3\))\(_2\)CO, 125 MHz) \(\delta\) 144.1, 143.5, 140.2, 140.0, 128.3, 128.2, 128.1, 128.0, 79.0, 78.7, 45.64, 46.63, 31.1, 31.0, 25.5, 25.2, 22.7, 22.6; **IR**: 3450, 2952, 1338, 1102, 1063, 1019, 907, 848, 798, 596 cm\(^{-1}\); **HRMS** (DART-TOF) calcd. for C\(_{24}H_{33}O_1\) [M+H-H\(_2\)O]\(^+\): 337.2531, found: 337.2519.

**4.4.8 Spectral Data**

Spectral data for substrates and PEC carboxylation products are included herein:

$^1$H NMR of 4.9

$^{13}$C NMR of 4.9
$^1$H NMR of 4.2

$^{13}$C NMR of 4.2
$^1$H NMR of 4.4

$^{13}$C NMR of 4.4
$^1$H NMR of 4.10

$^{13}$C NMR of 4.10
$^1$H NMR of 4.5

$^{13}$C NMR of 4.5
$^1$H NMR of 4.6

$^{13}$C NMR of 4.5
$^1$H NMR of the Secondary Alcohol By-Product of the PEC Reduction of 4.3

$^{13}$C NMR of the Secondary Alcohol By-Product of the PEC Reduction of 4.3
$^1$H NMR of 4.11

$^{13}$C NMR of 4.11
$^1$H NMR of 4.12

$^{13}$C NMR of 4.12