1. DFT-Guided Discovery of Hybrid Catalysts for C-C Bond Formation; 2. Synthesis of a Reported PDI Inhibitor

Eric Greve
Marquette University

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1. DFT-GUIDED DISCOVERY OF HYBRID CATALYSTS FOR C-C BOND FORMATION; 2. SYNTHESIS OF A REPORTED PDI INHIBITOR

by

Eric Greve, B.Sc.

A Dissertation Submitted to the Faculty of the Graduate School, Marquette University, in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

August 2020
ABSTRACT
1. DFT-GUIDED DISCOVERY OF HYBRID CATALYSTS FOR C-C BOND FORMATION; 2. SYNTHESIS OF A REPORTED PDI INHIBITOR

Eric Greve, B.Sc.
Marquette University, 2020

1. Dual amine/pi Lewis acid catalyst systems have been reported for intramolecular direct additions of aldehydes/ketones to unactivated alkynes and occasionally alkenes, but related intermolecular reactions are rare. We reasoned that bulky metal ligands and bulky amine catalysts could minimize catalyst poisoning and could facilitate certain examples of direct intermolecular additions of unactivated aldehydes/ketones to alkenes/alkynes. Density Functional Theory (DFT) ground state calculations on putative catalytic intermediates for alkyne versus organocatalyst complexation to the π-acid, and also the key carbon-carbon bond formation were used to prioritize ligand/organocatalyst combinations. Our calculations suggested that PyBOX-Pt(II) catalysts for alkene/alkyne activation could be combined with certain organocatalysts for aldehyde activation. With such combinations, alkene/alkyne coordination to the π-acid were calculated to be more exergonic than catalyst poisoning pathways. Consistent with the calculations, preformed enamines generated from the MacMillan imidazolidinone did not displace ethylene from a biscationic (t-Bu)PyBOX-Pt^{2+} complex. This novel catalytic system facilitated an intramolecular C-C bond formation with a formyl alkyne substrate, and modified conditions have recently extended this to an analogous intermolecular reaction. Investigations into alternative metal, ligand, organocatalyst, and substrate combinations are ongoing.

2. The enzyme protein disulfide isomerase (PDI) is essential for the correct folding of proteins and the activation of certain cell surface receptors, and is a promising target for the treatment of cancer and thrombotic conditions. A previous high-throughput screen identified the commercial compound STK076545 as a promising PDI inhibitor. To confirm its activity and support further biological studies, a resynthesis was pursued of the reported β-keto-amide with an N-alkylated pyridone at the α-position. Numerous conventional approaches were complicated by undesired fragmentations or rearrangements. However, a successful 5-step synthetic route was achieved using an aldol reaction with an α-pyridone allyl ester as a key step. An X-ray crystal structure of the final compound confirmed that the reported structure of STK076545 was achieved, however its lack of PDI activity and inconsistent spectral data suggest that the commercial structure was misassigned.
ACKNOWLEDGEMENTS

Eric Greve, B.Sc.

First, I would like to extend my utmost gratefulness to my advisor Chris Dockendorff, for his tremendous guidance, support, and dedication to my education, training, and professional development throughout my graduate career. I am extremely fortunate to have been afforded the opportunity to work in your lab and appreciate the consistent demand and independent initiative throughout this journey. I would like to thank all of my coworkers, past and present, in the Dockendorff lab. Each of you brought your own enthusiasm and personality that has made these past years terrific for our scientific development and great friendship. You have all provided such tremendous support as we celebrate the highs and push through the low times. I would also like to thank my past graduate colleagues from the University of Wisconsin-Madison, particularly Carlos and Gray. With your amazing friendship, we have grown to be incredibly resilient.

Next, I would like to express my thanks to my committee members Professors James Gardinier, Nicholas Reiter, and Chae Yi. Your support and insightful comments helped me further question my studies and extend my chemistry knowledge. I would like to extend additional gratitude to Dr. Yi for your constant guidance during our supergroup meetings. Thank you to Dr. Sheng Cai for your assistance with NMR studies and Dr. Sergey Lindeman for help with my X-ray studies.

I would like to thank my all of family, particularly my mother Susan, father Jeffrey, sister Larisa, mother-in-law Debra, father-in-law Arthur, aunt Sharon, brother-in-law Travis, and nieces Evelyn and Margaret. You all have been my rock through all of my life and I love all of you! I would like to give a special shout out to my Grandma Green. I miss your spirit every day and am sending you my love and thanks for all the support you have always given me. You always told all your friends, “I don’t get great-grandchildren, I get Ph.D.s!” This one’s for you grandma!

Finally, I would like to thank my spouse Dr. Felicia Mata-Greve. I could never have gotten to this point without you. Thank you for always believing in me and traveling on this rollercoaster of life together. I appreciate all of your patience during the long work days and look forward to our future adventures. My dog, Jackson, you will never read this, but thank you for being my cuddle buddy and never change!
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LIST OF ABBREVIATIONS

α………………………………..alpha
Ac………………………………acetyl
ACC……………………………N-amino cyclic carbamate
AcOH………………………….acetic acid
AIBN…………………………azobisisobutyronitrile
APCI…………………………atmospheric-pressure chemical ionization
Ar……………………………..aryl
atm…………………………..atmosphere(s)
β………………………………..beta
Bn……………………………..benzyl
Boc…………………………….tert-butylcarbonyl
br…………………………….broad (spectral)
Bu……………………………..butyl
ºC……………………………..degrees Celsius
¹³C…………………………..carbon 13
calcld………………………..calculated
CDI…………………………..carbonyl diimazole
cm⁻¹…………………………wavenumbers (reciprocal centimeters)
conc…………………………..concentrated
Cs₂CO₃………………………cesium carbonate
Cu(I)…………………………copper(I)
Cu(II)…………………………copper(II)
Cys…………………………..cysteine
d……………………………..days(s); doublet (spectral); deuterium (D)
dba…………………………...dibenzylideneacetone
DBU………………………….1,8-diazabicyclo[5,4,0]non-5-ene
DCC………………………….N,N-dicyclohexylcarbodiimide
DCE…………………………..dichloroethane
DCM………………………….dichloromethane
δ………………………………..delta, chemical shift in NMR
dd……………………………..doublet of doublets
ddd…………………………..doublet of doublets of doublets
DFT…………………………..density functional theory
DIBAL-H……………………diisobutylaluminum hydride
DIPEA……………………....diisopropylethylamine
DMAP………………………4-(dimethylamino)pyridine
DMF…………………………..dimethylformamide
DMP..........................Dess-Martin periodinane
DMSO..........................dimethylsulfoxide
dt...............................doublet of triplets
EDC............................1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG.............................electron donating group
ER...............................endoplasmic reticulum
ESI.............................electrospray ionization
Et...............................ethyl
Et$_2$O..........................diethyl ether
EtOAc..........................ethyl acetate
EtOH...........................ethanol
equiv............................equivalent(s)
EWG............................electron withdrawing group
$\gamma$..........................gamma
g...............................gram(s)
GC-MS..........................gas chromatography-mass spectrometry
Gly............................glycine
h...............................hour(s)
HAT............................hydrogen-atom transfer
HATU............................1-[Bis(dimethylamino)methylene]1-H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate
His.............................histidine
HMDS..........................hexamethyldisilazane
HOBt..........................hydroxybenzotriazole
HPLC..........................high performance liquid chromatography
HTS............................high throughput screen
Hz...............................Hertz
HRMS..........................high-resolution mass spectrum
IBX............................2-iodoxybenzoic acid
IR...............................infrared
J................................coupling constant (in NMR)
K$_2$CO$_3$........................potassium carbonate
L...............................liter(s)
LC-MS..........................Liquid Chromatography-Mass Spectrometry
LDA............................lithium diisopropylamine
LiHMDS........................lithium bis(trimethylsilyl)amide
LiTMP..........................lithium tetramethylpiperidine
$\mu$..............................micro
m...............................multiplet (spectral), meter(s), milli
M...............................moles per liter (molar)
$m$CPBA........................m-chloroperoxybenzoic acid
PyOX…………………………..pyridine oxazoline
Pyr…………………………..pyridine
q…………………………quartet (spectral)
RAMP…………………………(R)-1-amino-2-methoxypyrrolidine
Rt…………………………retention time (in chromatography)
s…………………………singlet (NMR); second(s)
SAMP…………………………(S)-1-amino-2-methoxypyrrolidine
SOCl₂……………………thionyl chloride
t…………………………triplet (spectra)
TBAB……………………tetra-n-butylammonium bromide
TBS………………………….tert-butyldimethylsilyl
TEA………………………….triethylamine
t-Bu……………………..tert-butyl
TFA………………………….trifluoroacetic acid
THF………………………….tetrahydrofuran
TMS………………………….trimethylsilyl, tetramethylsilane (NMR)
TLC………………………….thin layer chromatography
µL…………………………microliter(s)
CHAPTER 1

INTRODUCTION

1.1 Introduction to Alpha Alkylations and Alkenylations of Carbonyl Compounds

The alpha functionalization of carbonyl compounds, a fundamental organic transformation, is important for the synthesis complex molecule synthesis in pharmaceuticals and natural products. The resulting products of these reactions are saturated alkylated carbonyl compounds or either α,β or β,γ unsaturated carbonyl compounds (Figure 1.1.1).

![Figure 1.1.1](image)

The α-alkylated moieties discussed above are found in many natural products. One example of an α-alkylated product is (S,S,S)-serricornin, a female-produced sex pheromone generated by the cigarette beetle Lasioderma serricorne (Figure 1.1.2A). This beetle is a serious pest of cured tobacco leaves. Another example is Nicolaou et al. synthesis of the side chain for zaragozic acid A (Figure 1.1.2B). The zaragozic acid class
of natural products inhibits squalene synthase, the enzyme responsible for the biosynthesis of cholesterol. Inhibition of this enzyme has implications in the treatment of coronary heart disease. Both syntheses formed hydrazone intermediates from an ketone or aldehyde and performed α-alkylation by treatment of hydrazone intermediates with LDA and alkyl iodide reactants. In the synthesis of the side chain of zaragozic acid, removal of the hydrazine auxiliary and subsequent Wittig olefination on the resulting aldehyde yielded the α,β-unsaturated ester.

**Figure 1.1.2** Examples of natural products synthesized utilizing α-alkylation reactions

Natural products and biologically active compounds containing β,γ unsaturated moieties have also been reported (**Figure 1.1.3**). One example is euphalalicin, which has been shown to be an inhibitor of P-glycoprotein, a transporter responsible for the efflux of drug-like molecules from cells. Multiple types of cancer lines overexpress this transporter, leading to multidrug resistance and subsequent failure of chemotherapy.\(^5\) Another example is Trictostatin A, which is a known inhibitor of histone deacetylase and found to be active in studies of cancer, lupus, malaria, and several other disease.\(^6\)-\(^7\) Macquarimcin A was isolated from Micromonospora chalcea by researchers at Abbott in 1995.\(^8\) Later, it was found to be a selective inhibitor of membrane-bound neutral phingomyelinase that exhibits anti-inflammatory activity.\(^9\)
Figure 1.1.3 Examples of natural products with $\alpha,\beta$ or $\beta,\gamma$ unsaturated moieties

<table>
<thead>
<tr>
<th>Euphosalicin</th>
<th>Trichostatin A</th>
<th>Macquarimicin A</th>
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<tr>
<td><img src="image1" alt="Euphosalicin" /></td>
<td><img src="image2" alt="Trichostatin A" /></td>
<td><img src="image3" alt="Macquarimicin A" /></td>
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Conventionally in industry, carbonyl alkylation or alkenylation involves generation of metal enolates followed by the addition of an alkyl halide (Figure 1.1.4A). In these cases, both the carbonyl nucleophile and alkylating agent electrophile are preactivated. While this method can be effective and is frequently utilized, this approach bears several drawbacks. First, stoichiometric strong metal bases, such as lithium diisopropylamine, are required to preform the metal enolate. In order to avoid self-condensation, the enolate formation may also need to take place under cryogenic conditions. Secondly, unsymmetrical ketones pose challenges in controlling regioselectivity and restraining overalkylation to di- or trisubstituted products. The alkyl halides reagents are significantly more expensive than their corresponding olefins, which are frequently used in the preparation of terminal alkyl halides.$^{10-11}$ Finally, activated enolate nucleophiles and alkyl halide electrophiles form stoichiometric metal halides and conjugate acids of the bases as byproducts.

Complementary strategies to the alkylation via an enolate are instead to either use an aza-enolate or silyl enol ether. An aza-enolate is formed when an imine is treated with LDA, or another strong base equivalent, to generate a nitrogen equivalent of an enolate (Figure 1.1.4B).$^{12}$ Silyl enol ethers can be prepared from carbonyl compounds by silylation of the corresponding enolate anions (Figure 1.1.4C).$^{13}$ These can be particularly useful for alkylation of unsymmetrical ketones as it is often possible to generate the less-
substituted silyl enol ether under conditions of kinetic control (i.e. LDA, low temperature), and the more-substituted silyl enol ether by equilibration using a weaker base such as triethylamine at elevated temperature. Alkylation with an electrophile, such as an alkyl halide, affords the corresponding alkylated carbonyl. One advantage with silyl enol ethers is that they can be alkylated with tertiary alkyl halides, using a strong Lewis acid to generate a tertiary carbocation electrophile.

**Figure 1.1.4** $\alpha$-Alkylation via an enolate (A), aza-enolate (B), and silyl enol ether (C)

A)  

\[
\text{enolate} \quad \xrightarrow{\text{THF, -78 °C}} \quad \text{desired product} \quad \xrightarrow{\text{byproducts}}
\]

B)  

\[
\text{aza-enolate} \quad \xrightarrow{\text{THF, -78 °C}} \quad \text{desired product}
\]

C)  

\[
\text{silyl enol ether} \quad \xrightarrow{\text{OTMS, TEA, DMF 130 °C}} \quad \text{silyl enol ether}
\]

An alternative $\alpha$-alkylation strategy is the Stork enamine alkylation (**Figure 1.1.5**). An aldehyde or ketone is condensed with a secondary amine to generate a nucleophilic enamine intermediate, which is alkylated upon treatment with an alkyl halide or Michael acceptor. The Stork enamine reaction affords monoalkylation with high regioselectivity at the less hindered $\alpha$ carbon under less basic conditions. After hydrolysis with acid, the desired alkylated aldehyde or ketone is generated; however, a stoichiometric amount of conjugate acid of the base is also produced.
A variety of methods exist for $\alpha$-alkenylation alpha of carbonyl compounds; however, many of these methods also require pre-activation of one or more coupling partners (Figure 1.1.1). Methods (A) also uses a stoichiometric amount of base to generate a metal enolate, followed by reaction with a pre-activated alkene using a transition metal catalyst (i.e. Pd or Ni). Method (B), as with method (A), requires pre-activation of both reactants and utilizes a metal catalyst. Finally, method (C) only requires pre-activation of the alkene coupling partner as the carbonyl is activated catalytically with an organocatalyst to generate the enamine nucleophile. All of these outlined methods have the common disadvantage that one or both reaction partners must be pre-activated. Accessing these activated substrates can be both inefficient and uneconomical. In the synthesis of a complex intermediate or natural product, activation of one or both substrates would also add an additional unnecessary complication to the synthesis.

Given the inherent value of compounds containing an alkylated or unsaturated carbonyl moiety, there have been great efforts in the development of efficient $\alpha$-alkylation/alkenylation reactions to access these structures. Currently, there are few/no examples of intermolecular reactions direct addition reactions that don’t use pre-activated coupling partners or sensitive catalysts. The development of catalytic methods for the direct additions of unactivated carbonyl-based nucleophiles to unactivated alkenes and alkynes would permit efficient and economical access to valuable intermediates and final compounds from relatively inexpensive starting materials and perfect atom economy (Figure 1.1.6).
1.2 Metal Catalyzed Cross Coupling Reactions

Transition metal catalysts (Pd and Ni) are commonly used to generate $\alpha,\beta$ or $\beta,\gamma$-unsaturated compounds via cross coupling reactions between enolates or enolate derivatives and activated alkenes (e.g. alkenylhalides, boronic esters, triflates, etc.). The reaction starts with oxidative addition of an activated alkene to the metal (Figure 1.2.1).

Transmetalation occurs with intermediate I and the enolate or enolate derivative, with loss of the leaving group (X) to generate intermediate II. Finally, reductive elimination affords the unsaturated compound and regenerates the metal catalyst. In a few cases, a catalytically generated enamine can be used instead of an enolate. Despite the need for using a pre-activated electrophile, cross coupling reactions remain a powerful tool to form these carbon-carbon bonds.
The first $\alpha$-alkenylation of an enolate was reported by Rathke and Millard in 1977 using NiBr$_2$ to couple lithium ester enolates and vinyl bromides; however, a stoichiometric amount of NiBr$_2$ was required to achieve optimum yields (Figure 1.2.2A).$^{16}$ There were no examples of nickel catalyzed $\alpha$-alkenylation under mild reaction conditions, until 2015, when Helquist and co-workers reported a Ni-catalyzed alkenylation of ketone enolates (Figure 1.2.2B).$^{17}$

**Figure 1.2.2 $\alpha$-Alkenylation via (A) stoichiometric NiBr$_2$ and (B) catalytic Ni(cod)$_2$**

![Chemical structures](image)

Ligand screening led to the investigation of $N$-heterocyclic carbenes (NHCs), which demonstrated the ability to retain the Ni in solution throughout the course of the reaction. Under the optimized reaction conditions, alkenylation without migration or cis/trans isomerization was achieved on aryl, cyclic, and aliphatic ketones coupled with alkyl or aryl vinyl bromides.$^{17}$

Besides nickel, palladium has been more commonly used to facilitate the alpha vinylation of amide, ester, and ketone enolates. For example, in 2007, Huang and co-workers first reported the coupling of vinyl bromides, vinyl triflates, and vinyl tosylates to 3-methoxyindole using [Pd(P$^3$Bu$_3$)Br]$_2$ as a catalyst (Figure 1.2.3).$^{18}$ The vinyl tosylates, prepared from ketones, proved to be effective coupling partners with a vinyl halide equivalent. While the oxindole was selected as a model substrate due to its abundance in
biological compounds, \(^{19-21}\) cyclic and acyclic aryl ketone and piperidine ester enolates were also shown to react with vinyl bromides and triflates in 48-95% yield. \(^{18}\)

**Figure 1.2.3** Pd-Catalyzed \(\alpha\)-Alkenylation of 3-Methoxyindole

\[
\begin{align*}
\text{Me} & \quad \text{(1 eq.)} \\
\text{Pd(PrBu}_{3}\text{Br)}_2 \text{ (2.5 mol%)} & \quad \text{LiHMDS (2.5 eq.)} \\
\text{PhMe, 80 °C, 48 h, 56-89 %}
\end{align*}
\]

Despite various attempts by Barriault to use the sodium enolate of 2,2,-dimethylcyclohexanone and perform a palladium catalyzed alkenylation under milder reaction conditions, the reaction afforded only 28% yield, \(^{22}\) which suggested the need for improved conditions. \(^{23}\) Since zinc enolates had been shown to be effective in related \(\alpha\)-arylation reactions, \(^{24}\) Helquist and Cosner reported in 2011 the use of a zinc enolate in a series of palladium catalyzed alkenylations and dienylations in the synthesis of Trichostatin A (Figure 1.2.4). \(^{25}\) The coupling was found to be very ligand dependent, with Pd(db)\(_2\) and the electron-rich, sterically demanding alkyl phosphine 1,1'-bis(di-tert-butylphosphino)ferrocene (dtbpf) ligand giving the best results. Additionally, no isomerization in the cross-coupled product was observed under the mild reaction conditions. \(^{25}\) Overall, nickel has been shown to be a low cost alternative to palladium in these cross-coupling reactions; yet, nickel and palladium catalyzed \(\alpha\)-alkenylation reactions still suffer from the need to preform enolates using strong bases.

**Figure 1.2.4** Example of Helquist and Cosner’s Pd-catalyzed ketone zinc enolate \(\alpha\)-alkenylation reaction

\[
\begin{align*}
\text{Me} & \quad \text{(1 eq.)} \\
\text{Pd(db)\(_2\) (4 mol%)} & \quad \text{dtbpf (4 mol%)} \\
\text{THF, 22 °C}
\end{align*}
\]
1.3 Aminocatalysis for α-Functionalization of Aldehydes/Ketones

An important intermediate for these α-alkylation reactions is a carbanion equivalent (i.e. enolate, azaenolate, metal enamide, etc) that is typically generated prior to the C-C bond forming step and requires a stoichiometric reagent. Processes where a nucleophile is generated in situ and catalytically have the inherent advantage of being more atom economical. A particularly useful strategy for catalytic in situ generation of nucleophiles involves the transformation of carbonyl containing substrates into enamine intermediates via a Lewis basic primary or secondary amine catalyst. In contrast to the Stork enamine reaction, the basis of enamine catalysis is a reversible and catalytic generation of enamines which undergo addition reactions with various electrophiles (X = Y) (Figure 1.3.1A). After hydrolysis of the resulting iminium ion (iv), the α-substituted carbonyl product is generated.26-28

Figure 1.3.1 (A) General catalytic cycle for alpha functionalization reactions via enamine catalysis. (i-ii) Condensation between an amine and carbonyl compound to form an enamine via an iminium ion intermediate; (iii) Nucleophilic addition of the enamine to an electrophile; (iv) Hydrolysis of the iminium ion. (B) Features of primary amine catalysis versus secondary amine catalysis.

This enamine mechanism is analogous to type I aldolases seen in Nature to accomplish aldol reactions.29 Nature’s aldolases have provided inspiration for chemists in the development of small molecule catalysts. The first direct asymmetric aldol reaction
catalyzed by proline was the Hajos-Parrish-Eder-Sauer-Wiechert cyclization reported in 1971.\textsuperscript{30-33} This enamine-catalyzed asymmetric aldol reaction method has since been extensively studied to extend the substrate scope, optimize the selectivity, and improve the utility of these aminocatalysts.\textsuperscript{34} Besides the addition to aldehyde electrophiles in aldol reactions, amine-catalyzed ketone activation has been reported for asymmetric Michael additions, Mannich-type reactions, and Diels-Alder reactions.\textsuperscript{26-28, 35} Secondary amines, such as chiral pyrrolidines or imidazolines, are highly utilized structural motifs for aminocatalysts over primary amines.\textsuperscript{26, 28} Due to the inherent structural constraints, secondary amine catalysts tend to be ineffective when bulkier intermediates (e.g., $\alpha$-branched aldehyde/ketone substrates or $Z$-enamines) are involved (Figure 1.3.1B). The development of chiral primary amines, particularly vicinal diamine scaffolds, has proven to be effective for asymmetric catalysis with sterically hindered aldehydes and $\alpha$-branched aldehydes.\textsuperscript{36}

1.4 Diastereoselective Intermolecular Alpha Alkylations

Although $\alpha$-alkylation via derived enolates has been shown to be a viable method with ketones, it is not particularly useful with aldehydes, and enantioselective versions of these reactions would be desirable. For both aldehydes and ketones, the use of azaenolates has been generally more effective in terms of reactivity, product yield, and regioselectivity. Furthermore, azaenolates also provide a means for incorporation of a nitrogen-based chiral auxiliary to achieve asymmetric reactions. In 1976, Enders developed (S)- and (R)-1-amino-2-methoxypyrrolidine hydrazine (SAMP/RAMP) auxiliaries that have been widely used for asymmetric $\alpha$-alkylation of ketones and aldehydes (Figure 1.4.1).\textsuperscript{37}
Although the asymmetric alkylation of SAMP/RAMP hydrazones has been employed in many natural product syntheses, the removal of the auxiliary is most often achieved using one of two harsh approaches: ozonolysis or quarternization with methyl iodide followed by hydrolysis with 3-4 M HCl. These methods limit substrate scopes due to functional group incompatibility, and require the use of auxiliaries that often can’t be recycled.

Not until 2008, when Coltart and Lim reported the use of chiral N-amino cyclic carbamate (ACC) auxiliaries, did broadly useful alternatives to the SAMP/RAMP-based auxiliaries appear. In contrast to the SAMP/RAMP auxiliaries, ACC auxiliaries have these notable advantages: easier introduction into and removal from ketones, rapid deprotonation of the hydrazones, and alkylation does not require extreme cryogenic conditions. While ACC hydrazone formation can typically occur by condensation of the ACC auxiliary and the ketone under mild refluxing conditions in the presence of 10 mol% p-TsOH x H₂O by refluxing in dichloromethane, chiral nonracemic \(\alpha\)-hydroxy ketone derivatives require a combination of pyridinium p-toluenesulfonate (PPTS) (5 mol%) and MgSO₄ to avoid epimerization. After alkylation, the ACC hydrazones

Figure 1.4.1 Enantioselective \(\alpha\)-alkylation via SAMP chiral auxiliary

![Diagram of SAMP chiral auxiliary alkylation]

Figure 1.4.2: Enantioselective \(\alpha\)-alkylation via ACC chiral auxiliary

![Diagram of ACC chiral auxiliary alkylation]
readily undergo hydrazone exchange in the presence of $\rho$-TsOH $\times$ H$_2$O in a 4:1 mixture of acetone and water without any detectable epimerization.$^{42}$ A significant benefit of the ACC auxiliaries over the SAMP/RAMP auxiliaries is recovery of the unmodified auxiliary by liberating the hydrazone with NH$_2$OH $\times$ HCl in the presence of 20 mol% $\rho$-TsOH $\times$ H$_2$O.$^{41}$ However, for applications using asymmetric ketones, mixtures of the E- and Z-hydrazones are formed and necessary to separate by chromatography or crystallization prior to the alkylation step.

**Figure 1.4.3** $\alpha$-Alkenylation of aldehydes with vinyl iodonium triflate salts

MacMillan and co-workers reported several methods that utilize an amine co-catalyst to activate an aldehyde, rather than pre-forming an enolate using a strong base.$^{43-44}$ In addition to being used for a cross aldol reaction, the chiral amine co-catalysts were found to facilitate enantioselective couplings of the intermediate enamine and pre-functionalized alkenes. In 2012, MacMillan reported the first $\alpha$-alkenylation of aldehydes with vinyl iodonium triflate salts (**Figure 1.4.3**).$^{45}$ In this synergistic catalysis approach, the aldehyde becomes activated using a chiral imidazolidinone organocatalyst to form a chiral enamine, which reacts with a highly electrophilic alkenylcopper(III) intermediate. After reductive elimination to furnish an $\alpha$-alkenyl iminium and a copper(I) salt, regeneration of the organocatalyst is accomplished through hydrolysis of the $\alpha$-alkenyl iminium. The substrate scope included both alkyl- and arylidonium electrophiles with yields ranging from 70–90% and most ee’s above 95%. This reaction suffered from requiring catalyst
loadings of 20–30% CuBr when using an internal or branched linear vinyl iodonium triflate salt.

MacMillan reported a similar α-alkenylation of aldehydes in 2013 using boronic acids and a similar bulky imidazolidinone organocatalyst catalyst (Figure 1.4).46 One significant difference is that the iodonium salts used Cu(I) as a co-catalyst, while the boronic acids used the less sensitive Cu(II) co-catalyst. The substrate scope was similar for both systems and the boronic acid coupling method had slightly poor yields and enantioselectivity. Additionally, 30 mol% Cu(OAc)$_2$ and 20 mol% organocatalyst were reported for all substrates. In contrast to the RAMP/SAMP or ACC approaches, these enantioselective α-alkenylation occur under catalytic and mild, room temperature conditions facilitated by dramatically lowering the HOMO-LUMO gap. However, these coupling routes require the use of expensive alkenyboronic acids and modest quantities of a co-catalyst copper salt.

**Figure 1.4.4 α-Alkenylation of aldehydes with boronic acids**

\[
\text{H}_2\text{C}_6\text{H}_4\text{OH} + \text{HO-CH} = \text{C}_6\text{H}_5\text{B} \rightarrow \text{H}_2\text{C}_6\text{H}_4\text{OH} + \text{HO-CH} = \text{C}_6\text{H}_5\text{B} \]

**1.5 Alkene Functionalization via Nucleometalation**

There would be substantial advantages in the use of simple unactivated olefins as alkylating agents. A general activation mode for the coupling of simple ketones and olefins still remains in development, yet catalytic alkene functionalizations have been present in the chemical industry since the mid-20$^{th}$ century. In 1959, Wacker Chemie developed a
Pd-catalyzed process for the oxidation of ethylene to acetaldehyde. While the stoichiometric oxidation of ethylene by Pd(II) salts was known since the 19th century, the Wacker oxidation owes its success to the ability to regenerate the Pd catalyst using cocatalytic CuCl₂ and molecular oxygen (Figure 1.5.1). The reaction proceeds through the π-Lewis acidic palladium coordinating to ethylene, which activates ethylene for the net addition of hydroxide and Pd across the C-C double bond to yield a β-hydroxyethyl-Pd(II) intermediate.

**Figure 1.5.1**: Palladium catalyzed Wacker oxidation of ethylene to acetaldehyde

\[
\begin{align*}
\text{H}_2\text{C}=\text{CH}_2 & \quad + \quad \text{H}_2\text{O} \\
\text{[Pd/Cu]} & \quad \frac{1}{2} \text{O}_2 \\
\rightarrow & \quad \text{H}_3\text{C} & \quad \text{O}
\end{align*}
\]

This hydroxypalladation step has been the subject of extensive mechanistic research and controversy over whether the reaction proceeds by a cis- or trans-hydroxypalladation pathway. After the discovery of the Wacker oxidation, numerous research groups have demonstrated that Pd(II) can facilitate the addition of several nucleophiles to alkenes (i.e. oxypalladation, aminopalladation, and carbopalladation) (Figure 1.5.2). The Wacker oxidation demonstrates the utility of π-Lewis acids for activating olefins.

**Figure 1.5.2**: Nucleopalladation examples: **A)** alcohol cyclization, **B)** carboxylic acid cyclization, **C)** aminoarylation and **D)** oxidative amination
Vitagliano and co-workers reported the first class of dicationic Pd(II) and Pt(II) PNP complexes of simple alkenes, which undergo stoichiometric reactions with oxygen or nitrogen nucleophiles. After nucleophilic attack by water or anilines, the $\sigma$–alkyl intermediates are notably stable towards $\beta$–H elimination, a result of the lack of an available adjacent coordination site in these tridentate systems. These dicationic olefin complexes were found to be much more activated towards nucleophilic addition than the neutral species, and no nucleophilic attack on the coordinated olefin was observed in monocationic complexes containing the isoelectronic and isostructural complexes with pyridine replaced with arene (i.e. PCP) \(\text{(Figure 1.5.3).}\)

\textbf{Figure 1.5.3} Displacement of an olefin coordinated to a Pd-PCP complex by oxygen and nitrogen-based nucleophiles

Vitagliano and co-workers also reported a catalytic hydrovinylation reaction, where electron-rich alkenes can attack Pt-coordinated ethylene to generate stabilized carbocation intermediates, which undergoes a series of 1,2-hydride shifts to generate the olefinic product \(\text{(Figure 1.5.4).}\) Unfortunately, other Pt-coordinated ethylene complexes, i.e. propene and 1-butene, were not reactive. This substrate scope limitation allowed a catalytic reaction to be achievable and prevented successive oligomerization.
Figure 1.5.4 Codimerization of ethylene and 2-methyl-2-butene via a Pt(II)-PNP complex

Inspired by Vitagliano’s reports, Gagné and co-workers investigated PNP-Pd(II) complexes capable of performing stoichiometric polyolefin cascade reactions to form a variety of polycycles. These reactions were proposed to proceed through a carbocation intermediate with β-H elimination inhibited due to the lack of an open cis coordination site. Pt(triphos)\(^{2+}\) was also found to be an effective cyclization initiator. However, the development of a catalytic cyclization was not achievable via the resulting bulky (triphos)Pt-alkyl\(^+\) complexes because protonolysis (protodemetalation) required strong acids not compatible with polyene substrates. Gagné and co-workers found that platinum(II)-PyBOX (pyridine-2,6-bisoxazoline) complexes were capable of promoting catalytic cyclization/protonation reactions of a variety of polyenes, generating polycyclic products with good yields (49-93%) and diastereoselectivities (Figure 1.5.5).

Figure 1.5.5 Pt(II) catalyzed enantioselective cyclization/protonation of polyenes

1.6 Pi Acid Catalyzed Intramolecular Additions to Alkenes/Alkynes

Activation of alkenes or alkynes with the use of π-Lewis acid metal catalysts has also been utilized for alpha functionalization of carbonyl compounds. This avoids the use
of pre-activated coupling partners. There are numerous examples of intramolecular reactions using \( \pi \)-acids to facilitate the addition of enol/enolate nucleophiles to unactivated C-C bonds, but very few intermolecular reactions. A review by Enders and coworkers specifically discusses these Conia-ene type intramolecular addition reactions.\(^{66}\) In a Conia-ene reaction, the alkene/alkyne is activated by coordination to the \( \pi \)-acid. Enol or enolate formation followed by attack on the activated unsaturated C-C metal complex gives a metal-alkyl intermediate. Protodemetalation or \( \beta \)-hydride elimination then affords the cyclized product (Figure 1.6.1).

**Figure 1.6.1** Mechanism for the \( \pi \)-Lewis acid catalyzed Conia-ene reaction

![Mechanism for the \( \pi \)-Lewis acid catalyzed Conia-ene reaction](image)

Palladium(II) has been shown to be an effective \( \pi \)-acid to catalyze oxidative alkylation of unactivated olefins with highly reactive carbon nucleophiles, such as malonate anions or silyl enol ethers.\(^{67-68}\) Hydroalkylation of less reactive alkenyl alkyl ketones can occur thermally via the Conia-ene reaction without a metal catalyst, but may require temperatures in excess of 350 °C.\(^{69}\) Widenhoefer and co-workers first reported Pd-catalyzed intramolecular hydroalkylation reactions of 3-butenyl- \( \beta \)-diketones and \( \beta \)-keto esters (Figure 1.6.2).\(^{54-55}\) The hydroalkylation tolerated substitution at the terminal acyl carbon atom, enolic carbon atom, and the terminal olefinic carbon (38-89%), but not at the allylic and homoallylic positions.

**Figure 1.6.2** Palladium(II) catalyzed hydroalkylation of 3-butenyl \( \beta \)-diketones

![Palladium(II) catalyzed hydroalkylation of 3-butenyl \( \beta \)-diketones](image)
The mechanism of the hydroalkylation was studied through a series of deuterium-labeling experiment, which were in agreement with a mechanism involving an outer-sphere attack on the pendant enol on the palladium-complexed olefin I to form a palladium cyclohexyl intermediate II (Figure 1.6.3). Migration of the palladium via a series of β-hydride elimination/addition steps (III to V) followed by protonolysis of a palladium enolate VI regenerates the palladium catalyst and yields 2-acylcyclohexanones.

**Figure 1.6.3** Proposed mechanism for the Pd(II) catalyzed intramolecular hydroalkylation

While 3-butenyl β-diketones and 3-butenyl β-keto esters undergo selective hydroalkylation in the presence of palladium(II), Widenhoefer and co-workers found that 4-pentenyl β-diketones and some 4-pentenyl β-keto esters underwent selective oxidative alkylation in the presence of PdCl₂(CH₃CN)₂ to form cyclohexanone derivatives (Figure 1.6.4). The catalytic oxidative alkylation was achieved via a CuCl₂ co-catalyst under an oxygen atmosphere. In contrast to the hydroalkylation of 3-butenyl β-dicarbonyls, palladium-catalyzed oxidative alkylation of 4-pentenyl β-diketones tolerated substitution along the 4-pentenyl chain. Palladium-catalyzed hydroalkylation could not be extended to the 4-pentenyl β-dicarbonyl compounds, due to the observed migration of the palladium
to form a palladium enolate complex that undergoes protonolysis. Thus, the palladium enolate complex needs to be formed prior to olefin displacement from a palladium olefin intermediate.

**Figure 1.6.4** Pd(II) catalyzed oxidative alkylation of 4-pentenyl \(\beta\)-diketones

![Reaction Scheme](image)

Widenhoefer sought to circumvent this issue with palladium by finding a suitable transition metal complex that would catalyze hydroalkylation through a pathway involving nucleophilic attack on a metal-olefin complex followed directly by protonolysis of the resulting metal-alkyl intermediate. Pt(II) complexes were found to be a suitable choice, since Pt(II)-alkyl complexes are more stable with respect to \(\beta\)-hydride elimination but can undergo protonolysis more easily.\(^{71}\) Since lanthanide Lewis acids are known to catalyze the addition of \(\beta\)-dicarbonyl compounds to Michael acceptors,\(^{72}\) EuCl\(_3\) was employed as a Lewis acid co-catalyst and was found to improve yields for the hydroalkylation of 4-pentenyl \(\beta\)-dicarbonyl compounds from 45 to 64% (**Figure 1.6.5**).\(^{73}\) While these intermolecular hydroalkylation reactions catalyzed by Pd(II) and Pt(II) complexes are not generalizable beyond yielding 2-acylcyclohexanone compounds, they do demonstrate the ability of group 10 metals to act as \(\pi\)-acids to activate olefins towards attack by carbon nucleophiles.

**Figure 1.6.5** Pt(II) catalyzed hydroalkylation of 4-pentenyl \(\beta\)-diketones

![Reaction Scheme](image)
In Widenhoefer’s reported hydroalkylation reactions, the substrates were limited to those containing activated methylene units, such as β-diketones and β-keto esters. However, simple ketones remain challenging substrates for performing hydroalkylation of unactivated alkenes, because they possess a less acidic C-H bond and a significantly lower enol/ketone equilibrium constant than β-diketones and β-keto esters. While Widenhoefer and co-workers did report a few examples of palladium-catalyzed intramolecular hydroalkylation of alkenes with α-alkyl or aryl ketones, these reactions require stoichiometric or substoichiometric CuCl₂ as an oxidant and either trimethylsilylchloride or HCl to facilitate ketone enolization. More recently, gold complexes were demonstrated to be efficient catalysts for the addition of enol equivalents to unactivated alkynes, and can promote the enolization of ketones. In 2011, Che and co-workers found that Au(I) complexes efficiently catalyze the direct intramolecular hydroalkylation of unactivated alkenes with simple ketones (Figure 1.6).

Figure 1.6 Au(I) catalyzed intermolecular hydroalkylation of simple α-ketones

This Au(I) catalyzed hydroalkylation also goes through an exo-trig cyclization pathway, similar to Widenhoefer’s hydroalkylation reactions on 4-pentenyl β-diketones. Using their optimal reaction conditions with the absence of additives, alkenyl alkyl and aryl ketones provided new five- and six-membered rings in excellent yields (71-99%) and good diastereoselectivity. This process was also applied to the synthesis of bicyclic ketones. When an alkyl ketone was treated with a catalytic amount of [IPrAuCl]/AgClO₄ and D₂O/toluene at 90 ºC for several hours, deuterium incorporation at the α-position of
the ketone was observed. Yet, no deuterium exchange occurred in the absence of the gold catalyst, which supported their hypothesis that the gold complex facilitates enolization of these α-ketones. However, no examples of substrates without geminal diesters, geminal diethers, or an N-tosyl moiety were reported.

Figure 1.6.7 Enantioselective Au(I) catalyzed intramolecular α-alkenylation

Toste and coworkers went on to develop an asymmetric version of their gold catalyzed intramolecular reaction with alkynes, but enantioselectivity was not achieved. This was presumably due to linear nature of Au(I)-alkyne complexes. However, a Pd(II) catalyst with a chiral SEGPHOS ligand with substituents projected towards the β-ketoester yielded ~90% ee for most substrates (Figure 1.6.7).\(^80\)

After these initial reports for π-acid catalyzed Conia-ene reactions, the next major advancement involved utilization of two catalysts, with each catalyst activating a different coupling partner. In these systems, the π-acid activates the unsaturated C-C bond and an organocatalyst activates the carbonyl compound via an enamine intermediate. This dual activation by two independent catalysts makes this a dual catalytic system, which allowed for the substrate scope to be include alkynyl aldehydes and ketones as opposed to limited to only 1,3-dicarbonyl compounds.

Dixon and Kirsch reported in 2008 that either a copper\(^81\) or gold\(^82\) catalyst respectively with an amine organocatalyst could cyclize formyl alkynes in a non-asymmetric fashion. Shortly after, Michelet reported a similar reaction using InCl\(_3\) as the
\(\pi\)-acid (Figure 1.6.8),\(^{83}\) Michelet’s cyclization used an alpha-branched aldehyde, versus Dixon’s and Kirsch’s non-alpha branched substrates, thus resulting in the generation of an all carbon quaternary center since the \(\beta,\lambda\)-unsaturated product cannot isomerize to the \(\alpha,\beta\)-alkene.

**Figure 1.6.8** InCl\(_3\) catalyzed intramolecular Conia-ene like reaction with formyl alkyne

\[
\begin{align*}
\text{InCl}_3 & \quad \text{20 mol}\% \\
(Cy)(i-Pr)NH & \quad \text{20 mol}\% \\
\text{DCE, 100 °C} & \quad \text{89%}
\end{align*}
\]

Attempts to develop an enantioselective version of this reaction with InCl\(_3\) was not very successful, as reactions gave both poor yields and enantioselectivities.\(^{84}\) Cu(I) instead proved to be an effective catalyst with high yields and enantioselectivities possible (Figure 1.6.9). The chiral phosphine ligand served two purposes: 1) in situ reduction of Cu(II) to Cu(I) instead of using air sensitive Cu(I) complexes, 2) the bulky tert-butyl substituents gave better enantioselectivity. Cyclohexylamine was found to be the optimal organocatalyst for its ability to form an enamine with alpha branched aldehydes compared to bulkier, secondary amines or linear primary amine organocatalysts.

**Figure 1.6.9** Cu(I) catalyzed enantioselective intramolecular reaction with formyl alkyne

\[
\begin{align*}
\text{Cu(OTf)} & \quad \text{5 mol}\% \\
\text{Ligand} & \quad \text{7.5 mol}\% \\
\text{Dioxane} & \quad \text{88% 93.5/6.5 er}
\end{align*}
\]

Unfortunately, the formyl alkyne substrate scope is apparently limited to the bulkier diester substituents on the alkyne tether to give enantioselective reactions. These
intramolecular $\alpha$-alkenylation reactions with dual catalysts demonstrated that $\pi$-acid catalysts were compatible in a reaction mixture with Lewis basic amine co-catalysts.

1.7 Methodology for Intermolecular Additions to Alkenes/Alkynes

In both the formation of metal enolates and the Stork enamine reaction, there is the requirement of using activated alkyl halide electrophiles. Additionally, only primary alkyl halides react effectively in most alkylation reactions. There is a substantial economic advantage in the use of simple unactivated olefins as alkylating agents. However, due to the unfavorable thermodynamics and kinetics, the addition of a metal enolate to a simple olefin requires complexation with a metal salt. For example, Nakamura and co-workers in 2004 were able to overcome this challenge by generating a zinc enamide intermediate from the corresponding $N$-aryl imine (Figure 1.7.1). The zinc enamide reacts smoothly with terminal alkenes in carbometalation reactions to generate $\gamma$-zincated imine intermediates. The organozinc intermediates can be quenched to yield a ketone or can react further with electrophiles in subsequent C-C bond formation reactions. While the use of these highly reactive zinc enamides demonstrates a possibility for the utilization of unactivated terminal olefins, the zinc enamide formation still requires the use of lithium diisopropylamine and $n$-butyl lithium.

![Figure 1.7.1 α-Alkylation of ketones by addition of zinc enamides to olefins](image)

Alternatively, free radical reactions in organic synthesis are a useful approach for the construction of C-C and C-X (X = H or heteroatom) bonds. Several high oxidation state
metal ions, such as Mn(III), Ce(IV), Ag(II), and Pb(IV), have been found to be effective for the generation of α-keto radicals and subsequent addition to alkenes.\textsuperscript{88-89} While most reports require stoichiometric quantities of metal reagent, two methods using catalytic AgNO\textsubscript{3} or Mn(OAc)\textsubscript{3} and respective reoxidants Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} or KMnO\textsubscript{4} were found to be effective for the addition of α-keto radicals to alkenes.\textsuperscript{90-91} Molecular oxygen would be the most desirable candidate for catalyst regeneration. In 2000, Ishii and co-workers found Mn(II)/Co(II) to be a novel catalyst system for the radical addition of ketones to alkenes using molecular oxygen as a reoxidant.\textsuperscript{92} Under the optimal reaction conditions, cyclic and aliphatic ketones were added to oct-1-ene or isopropenyl acetate in decent yields (61-85%) (Figure 1.7.2). An interesting observation was noted for the addition of cyclohexanone to styrene, which did not yield the expected product, but rather a six-membered cyclic peroxide. It was hypothesized that the stability of the intermediate benzyl radical preferentially reacted with O\textsubscript{2} rather than undergoing a radical termination step.

While this novel catalytic method provides an alternative route for α-alkylation of cyclic ketones, there are several drawbacks, i.e. limited regioselectivity for unsymmetrical linear ketones and limited functional group tolerance.

\textbf{Figure 1.7.2} Mn(II)/Co(II) catalyzed radical addition of ketones to oct-1-ene (A), isopropenyl acetate (B) or styrene (C) to yield the respective α-alkylated ketones or cyclic peroxide.

\[
\begin{align*}
\text{KOAc} & \quad \text{(1.3)} \\
\text{Ph} & \quad \text{AcOH, N\textsubscript{2}O\textsubscript{2} (1:1)} \\
80 \degree C, 10 \text{ h} & \quad 82-85\% \\
\end{align*}
\]

Due to success for the intramolecular hydroalkylation and oxidative alkylation of alkenyl β-diketones catalyzed by PdCl\textsubscript{2}(CH\textsubscript{3}CN)\textsubscript{2}, Widenhoefer and Wang looked to extend similar reaction conditions for the addition of stabilized β-diketone nucleophiles to
ethylene and propylene. Initially, the reaction of 2,4-nonanodione with ethylene (15 psi) in the presence of catalytic Pd(II) and stoichiometric CuCl$_2$ yielded a 36:64 mixture of alkene:alkane (Figure 1.7.3A). By increasing the ethylene pressure to 200 psi, both the efficiency and selectivity increased leading to exclusive formation of the alkenylation product as a separable mixture of $E$ and $Z$ isomers.

This improved selectivity is likely due to the increased rate of olefin displacement relative to protonolysis. The optimized reaction conditions were utilized on other unsymmetrical and symmetrical β-dicarbonyls (59-86% yields). Similar to the above mentioned intramolecular hydroalkylations of 4-pentenyl β-diketones, ethylene hydroalkylation catalyzed with a Pt(II) complex yielded only the α-alkylation product and no detectable amount of the alkene (Figure 1.7.3B). However, extending the palladium-catalyzed alkylation to propylene required additional activation of the β-diketones with stoichiometric EuCl$_3$ and led to the formation of furan byproducts, formed via palladium-catalyzed cyclization of the initially formed 4-allyl-2,6-dimethyl-3,5-heptanedione (Figure 1.7.4).
Similar to intermolecular additions to alkenes, the analogous intermolecular additions to alkynes are also rare and typically limited to the more reactive 1,3-dicarbonyl substrates. In 2007, Nakamura and coworkers reported a In(OTf)$_3$ catalyzed addition of alkynes to a β-ketoester. The In(OTf)$_3$ is proposed to activate both the β-ketoester and the alkyne. The Nakamura lab later developed a diastereoselective version of this intermolecular reaction (Figure 1.7.5). Although, this example required pre-forming an enamine with a chiral amine and an extra hydrolysis step at the completion of the reaction.

**Figure 1.7.5** Nakamura’s diastereoselective intermolecular addition of a β-ketoester to alkyne

The structure of the chiral auxiliary was crucial for obtaining higher enantioselectivity. Auxiliaries containing more sterically demanding groups (t-Bu, s-Bu, or i-Pr) afforded similar ee values of 91, 94, and 89% respectively, while smaller substituents were less selective and afforded ee’s of ~70%. The methoxy group on the chiral auxiliary was found to be more crucial as removal of this group resulted in a similar overall yield, but the ee dropped to 12%. This was hypothesized to be due to a 5-membered ring structure that forms between the methoxy group, nitrogen, and the metal center. Although this sequence was high yielding and highly enantioselective, this method suffers from being limited to 1,3-dicarbonyl compounds and is not catalytic with respect to the amine. Similarly to the Enders SAMP/RAMP hydrazone alkylation reaction, the chiral auxiliary needs to be hydrolyzed in a separate step.

An alternative non-asymmetric Nakamura reaction was reported by Xi and coworkers in 2013 (Figure 1.7.6). A synergistic gold/gallium catalyzed intermolecular
reaction was achieved where gold activates the alkyne and undergoes nucleophilic attack by a gallium generated enolate. This synergistic catalyst system was required as control experiments with only gold or gallium individually gave <5% yields.

Figure 1.7.6 Synergistic Au/Ga catalyzed intermolecular $\alpha$-alkenylation reaction

The main drawback for many of these intermolecular reactions is the requirement of readily enolized $\beta$-dicarbonyl substrates. A rare example of the direct addition of unactivated ketones to unactivated alkenes or alkynes was reported by Dong and coworkers.\textsuperscript{99-100} This method utilizes a bifunctional ligand that acts as both an organocatalyst and a directing group. This ligand in combination with the bulky electron rich N-heterocyclic carbene (NHC) ligand IMes for Rh facilitated a highly atom economical reaction capable of coupling inexpensive coupling partners such as simple olefins and alkynes. It was also discovered that 10 mol % TsOH$\cdot$H$_2$O promoted enamine formation. Using their optimized conditions, alkylation with ethylene or other terminal olefins on cyclopentanones, substituted in the 3 position, tolerated a range of functional groups, including secondary amides, malonates, and aliphatic esters with competitive alkylation sites (Figure 1.7.7). The reaction was regioselective for the less-hindered 5 position of cyclohexanone and selective for mono alkylated products.

Using a similar catalytic system, the Dong lab has also reported a method for $\alpha$-alkenylation of ketones.\textsuperscript{100} While Dong’s reports demonstrate that a bifunctional precatalyst strategy may be promising, significant disadvantages include the required elevated temperatures, air free (glovebox) reaction conditions, and up to 50 mol% of the
amine catalyst for the addition to alkynes. Additionally, only terminal olefins were effective and provided the linear products.

**Figure 1.7.7** Rh(I)-catalyzed direct addition of ketones to ethylene

\[
\begin{array}{c}
\text{O} \\
\text{R} \\
\end{array}
+ \quad \text{H}_2\text{C} = \text{CH}_2
\]

(300 psi)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\end{array}
\]

[\text{Rh(coe)}_2\text{Cl}]_2 (2.5 mol\%)

IMes (5 mol\%)

TsOH–H\_2O (10 mol\%)

toluene, 130 °C, 48 h

\[
\begin{array}{c}
\text{O} \\
\text{R} \\
\end{array}
\]

52-96%

Another synergistic catalyst system for \(\alpha\)-alkylation of aldehydes using alkenes was reported by MacMillan and coworkers in 2017 (**Figure 1.7.8**).\(^{101}\) This method employed the use of three synergistic catalytic processes: photoredox, enamine, and hydrogen-atom transfer (HAT). A bulky organocatalyst activates the aldehyde via an enamine and concurrent irradiation of the iridium photocatalyst with visible light produces an excited-state Ir(III) complex.

**Figure 1.7.8** Intermolecular \(\alpha\)-alkylation of aldehydes using synergistic photoredox, enamine, and hydrogen-atom transfer catalysis

A variety of substituted aldehydes and a variety of electron-rich and electron-deficient vinyl arenes were tolerated and gave 50–94% yields and typically 90% ee. Examination of reactivity with simple, less reactive olefins found terminal olefins to be less
reactive, while $\pi$-nucleophilic 1,1-disubstituted olefins (i.e. methylenecyclopentane) gave a moderate yield of 47% and 88% ee. Overall, this multicatalytic process facilitated both intra- and intermolecular aldehyde coupling with simple olefins for the construction of cyclic and acyclic products.

Although there are numerous methods available for the addition of aldehydes/ketones to alkenes/alkynes, they have significant limitations, particularly with regard to substrate scope. An ideal reaction would proceed through a catalytically generated nucleophile capable of adding to a $\pi$-acid activated unsaturated C-C bond in an intermolecular fashion using an air stable and functional group tolerant catalyst system. To overcome these challenges in the previously described methods, a Lewis acid/Lewis base catalyst system has been proposed via the following two approaches: (1) bifunctional catalyst systems, where the two discrete catalytic sites are tethered together in a single molecule, and (2) bulky dual catalysts with binding pockets selective for smaller alkynes/alkenes over bulkier amines/enamines. The design, synthesis, and study of both systems will be discussed in this dissertation.
CHAPTER 2

Bifunctional Group 10 Metals and Cu(I) Catalysts for Additions of Aldehydes and Ketones to Alkenes/Alkynes

2.1 Introduction to Bifunctional Catalysis

Though there are a substantial number of reports using dual catalysts for intramolecular additions of unactivated carbonyl compounds to alkynes and several for the additions to alkenes, intermolecular variants of these addition reactions are rather scarce. It is first important to define what is intended when referring to “dual” versus “bifunctional” catalysts. A dual catalytic system is one with two distinct catalysts that are separate molecules, and each catalyst activates a different substrate (Figure 2.1.1). After both substrates are activated by separate catalysts, the reaction proceeds. One challenge in a dual catalytic system is ensuring that the two catalysts are compatible. Instead of the catalysts activating each substrate, they could interact with each other during the course of the reaction. This possible unproductive catalyst poisoning interaction, which we will refer to as self-quenching or poisoning, is one limitation of using a dual catalyst strategy.

In contrast, a bifunctional catalyst possesses two more-or-less independent catalytic sites on a single molecule. The activation of the substrates proceeds in the same manner as with dual catalysts. However, since the two catalytic components are tethered together, it allows for the possibility of using two catalysts which may not be compatible in a dual catalyst system due to self-quenching. One disadvantage of intermolecular reactions with dual catalysts is that they may be entropically unfavorable. A bifunctional catalyst has the potential to overcome this challenge by allowing the substrates to react via an "pseudo-intramolecular" transition state. This is because each catalytic component is tethered together within a single molecule, causing the intermediate after the key bond formation to be a macrocycle (Figure 2.1.1). Improved reactivity may also result due to
the catalyst scaffold positioning each activated substrate in a geometrical orientation that is at an optimal orientation and distance for the desired reaction to occur. However, bifunctional catalysts are less flexible than a dual catalyst and the tether could be a hindrance for reactivity if the activated substrates are in the wrong orientation.

**Figure 2.1.1** General depiction of dual versus bifunctional catalysis

Bifunctional catalysis is a rare strategy in organic chemistry,\textsuperscript{102,103} but presented here are several representative examples. In Nature, type II aldolases catalyze asymmetric aldol reactions; a Zn\textsuperscript{2+} cofactor coordinated to three histidine residues polarizes the carbonyl donor through coordination, and a tyrosine residue (Tyr-113) activates the aldehyde acceptor by donating a proton to stabilize the developing charge.\textsuperscript{29} (Figure 2.1.2A) Other synthetically useful examples include Shibasaki’s report of a phosphine oxide/aluminum Lewis acid catalyst for asymmetric cyanosilylations (Figure 2.1.2B),\textsuperscript{104} and Wang’s amino acid-derived catalyst for asymmetric Michael\textsuperscript{105} (Figure 2.1.2C), aldol,\textsuperscript{106} and Diels-Alder reactions.\textsuperscript{107} Each of these examples consist of a Lewis
acidic metal to activate an electrophile tethered to a Brønsted or Lewis base that is capable of activating a nucleophile. This general bifunctional catalyst approach has been extended in the design of bifunctional catalysts described below.

**Figure 2.1.2** Select Examples of Bifunctional Lewis Acid/Organo Catalysts: A) Type II Aldolase; B) Shibasaki’s Cyanosilylation Catalyst; C) Wang’s Michael Reaction Catalyst

In 2020, Luo and coworkers reported an arene-containing chiral primary amine/palladium synergistic catalyst for an asymmetric allylic alkylation of β-keto esters or 1,3-diketones. The primary amine served as the organocatalyst to activate the carbonyl via enamine formation, while the arene acted as a σ-ligand for Pd, essentially forming in situ a bifunctional catalyst. This enhanced the reaction rate and reversed the chiral induction when compared to nonarene aliphatic derivatives (**Figure 2.1.3**). Vinylethylene carbonates or vinylepoxides were used to access the alcohol derivatives via a zwitterionic Pd-allyl intermediate. Their catalytic system was also capable of coupling with N-aryl carbamates to afford N-allylic aniline adducts with good yield and high enantioselectivity.

**Figure 2.1.3** Amine/Palladium synergistic catalysis for asymmetric allylic alkylation
A final example of a bifunctional catalyst system was reported by Dong and coworkers (previously discussed in Chapter 1). The bifunctional ligand, 7-azaindoline, was found to activate the ketone \( \alpha \)-C-H bonds via enamine formation, while the linked pyridyl directing group facilitated oxidative addition of a low-valent Rh(I) metal into the resulting enamine C-H bond, giving a metal hydride species (Figure 2.1.4 a-b). A model complex using 2-indanone, \([\text{Rh(ethylene)}_2\text{Cl}_2]\), 7-azaindoline, and PMe\(_3\) were used to obtain a crystal structure of an intermediate after enamine C-H bond insertion. The rhodium catalyst also serves to activate the olefin via coordination to the metal. Subsequent Ru-H migratory insertion (c) and reductive elimination (d) yields the alkylated enamine, which undergoes hydrolysis to regenerate the catalyst (e).

**Figure 2.1.4** Proposed catalytic cycle of Dong’s bifunctional catalyst. (a) Enamine formation; (b) Oxidative addition of enamine C-H bond; (c) Migratory insertion into olefin; (d) Reductive elimination to form new C-C bond; (e) Enamine hydrolysis.
These examples demonstrate how a bifunctional catalyst approach can be utilized to facilitate several important transformations. Further examples of bifunctional catalysts can be seen in reviews by Trost, Feng, Shibasaki, and Xiao. Designing a bifunctional catalyst requires careful consideration of each component (Lewis acid, Lewis base, ligand, additives, etc) during the development of an active catalyst. In the sections to follow we describe our approach in the design and synthesis of bifunctional catalysts.

2.2 Design and Prioritization of Bifunctional Lewis Acid/Lewis Base Catalysts for Additions of Aldehydes/Ketones to Alkenes or Alkynes using DFT

When designing these bifunctional catalysts, there are three critical components: amine organocatalyst, π-Lewis acid metal, and the “tether” (scaffold) between catalyst sites. Each need to be finely tuned to fulfill their individual task, while still cooperatively functioning with the other two components. Our proposed catalytic cycle starts with a late electrophilic, π acidic transition metal (i.e. Cu(I), Ni(II), Pd(II), Pt(II)) complexed to a bidentate or tridentate ligand with a pendant amine organocatalyst A (Figure 2.2.1). The pendant amine of A undergoes condensation with a ketone/aldehyde to form an enamine, and the olefin is activated via coordination to the metal (intermediate I). Nucleophilic attack of the enamine on the activated coordinated olefin would forms metal-alkyl intermediate II. Hydrolysis of the imine/iminium intermediate and protodemetalation or β-hydride elimination of the metal-alkyl intermediate yields the respective α-alkylated or α-alkenylated product and regenerates the active catalyst A. The β-hydride elimination option would require a co-oxidant to regenerate the active M(II) catalyst.

The pendant amine organocatalyst that activates the ketone or aldehyde via the formation of an enamine could be either a primary or secondary amine, which would alter the nucleophilicity and steric environment around the amine. Additionally, acyclic or cyclic
secondary amines may be utilized. Cyclic amines contain a more rigid structure, which could be advantageous in maintaining a strict geometry around the enamine. Acyclic amines provide more flexibility during macrocyclization and can be synthetically easier to diversify via substitution reactions; however, the additional flexibility may decrease the macrocyclization C-C bond reaction rate. Any intermolecular catalyst-catalyst interaction between an amine on one catalyst and a Lewis acidic site on another must be either geometrically impossible, rapidly reversible, and/or sterically disfavored.

**Figure 2.2.1** Proposed catalytic cycle of bifunctional Lewis acid/Lewis base catalysts

The \( \pi \)-Lewis acid metal is required to activate the alkene for an outer sphere attack by the enamine nucleophile. After nucleophilic attack, the subsequent metal-alkyl intermediate II requires the metal to be capable of undergoing protodemetalation or \( \beta \)-hydride elimination (with a co-oxidant) to regenerate the active catalyst and achieve catalytic turnover (**Figure 2.2.1**). Furthermore, the catalyst needs to be moisture tolerant, since the catalytic cycle mentioned above also includes the generation of enamine/iminium intermediates and their necessary hydrolysis. These limitations suggest
the use of late transition metals such as Ni, Pd, Pt, Cu, Ag, Au, that also have
demonstrated the ability to coordinate and activate alkenes and alkynes.

While the amine organocatalyst and π-Lewis acid metal are critical to activate the
respective aldehyde/ketone and alkene/alkyne starting materials, the structure of the
scaffold itself is also critical, which includes the “spacer” between the catalytic sites. The
Lewis acid and Lewis base sites need to be close enough to enable carbon-carbon bond
formation, but far enough away to prevent self-quenching. A suitable chelating section of
the precatalyst scaffold needs to act as a ligand for the π-acidic metal capable of activating
an alkene (or alkyne). When the alkene/alkyne coordinates to the metal, its reactive π*-orbital
is on the opposite face of the alkene from the metal. Thus, the precatalyst
scaffold requires the alkene or alkyne to be sandwiched between the metal and the
pendant enamine to facilitate an anti-addition. The spacer between the chelating section
and the amine organocatalyst needs to position the amine far enough away from the
metal, while minimizing steric interactions with the coordinated alkene or alkyne.

Since the synthesis of these complex precatalysts has been the rate-limiting step
in our research endeavors, we have turned towards a computational approach to help
prioritize our precatalyst designs. The presumed structures before and after C-C bond
formation are optimized using density functional theory (DFT), and the free energy change
between the ground state optimized structures is calculated (Figure 2.2.1). We assume
that the C-C bond formation step needs to be exergonic for catalysis to be achieved, and
this step may also be the rate-determining step. Such computational rational design
approaches are currently rare, but are becoming increasingly promising tools for catalyst
discovery.\textsuperscript{113}

We believe our proposed precatalysts are ideal for this computational approach
because the coordination geometries around our group 10 and 11 metals of interest are
well understood and can be effectively modeled using current DFT functionals and basis sets. Additionally, in our bifunctional catalyst systems the C-C bond formation step is an intramolecular macrocyclization, and macrocycle ring strain can be effectively estimated via DFT calculations\textsuperscript{114} to prioritize our precatalyst scaffolds.

2.3 Design of Bifunctional Cu(I) Catalysts for Direct Additions of Carbonyl Compounds to Alkynes

Our general strategy to approach developing bifunctional catalysts for the direct addition to alkenes and alkynes was conducted in a similar fashion: i) design bifunctional catalysts guided by DFT calculations, ii) synthesize the most promising precatalysts, iii) screen the precatalysts using a variety of alkenes/alkynes and ketones/aldehydes. This bifunctional Cu(I) catalyst project was spearheaded by Jacob Porter and our novel catalyst design strategy and initial efforts at the identification of an active catalyst led to the publication of a report titled “DFT-assisted design and evaluation of bifunctional copper(I) catalysts for the direct intermolecular addition of aldehydes and ketones to alkynes.”\textsuperscript{115} A brief summary of these studies with emphasis on aspects I contributed towards are described here.

In designing our catalyst system, we first sought to explore Lewis acid and ligand combinations that would be suitable for alkyne activation. Based on the literature precedent for intramolecular reactions with formyl alkyne substrates, alkyne 2.1 and intramolecular reaction conditions reported by Michelet\textsuperscript{84, 116} were selected as a model reaction system (Figure 2.3.1). Lewis acids previously reported for additions of carbonyl compounds to alkynes\textsuperscript{80-83, 95-97, 116-118} or alkenes\textsuperscript{93, 119} were screened. The Group 11 salts Cu(I), Au(I), and Ag(I) resulted in the highest yields. Due to previous reports of Cu(I) catalysts in Conia-ene type reactions, we decided to proceed with a Cu(I) system to determine if a ligand could accelerate the reaction. Several different ligands (H-dpa, (R,R)-
Ph-BOX, and 1,10 phenanthroline) were screened with the Cu(I) salt (CH$_3$CN)$_4$CuBF$_4$ and resulted in a decrease in reactivity. We hypothesize this may be due to 2:1 ligand:metal binding or other complex binding modes that do not leave a vacant coordination site on Cu for alkyne activation.$^{115}$

**Figure 2.3.1** Intramolecular (Conia-ene) reaction screen

Prior to proceeding with our strategy to build novel bifunctional catalysts, we wanted to rule out the possibility of using dual catalyst conditions for intermolecular reactions that were productive for intramolecular reactions. An NMR study was performed using a (2,2'-dipyridylamine)CuOTf complex to determine whether an electron-rich enamine intermediate could displace a coordinated alkyne and simply act as a competing ligand for the π-acid (Figure 2.3.2).$^{115}$ After addition of phenylacetylene to the Cu(I) complex, a downfield shift from 3.07 ppm to 4.01 ppm was observed in the $^1$H NMR signal for the alkyne proton of phenylacetylene. This is consistent with the formation of Cu-alkyne complex 2.3. Upon addition of the enamine derived from cyclohexanone and pyrrolidine, the signal for the uncoordinated alkyne reappeared at 3.07 ppm. Additionally, evidence for enamine coordination to the metal was observed as the vinyl enamine proton shifts upfield from 4.29 ppm to 3.99 ppm, suggesting that coordination of the enamine to the metal is highly favored over alkyne coordination. Subsequent formation of 1,2-addition product 2.4 was observed, which presumably forms via addition of a Cu-acetylide to a transient iminium ion. Variations of this transformation were recently reported by Larsen$^{120}$ and Ma.$^{121}$ With our hypothesis of a dual catalyst strategy being problematic with thus
sought after the design of a Cu(I) bifunctional catalyst that would not suffer from competitive displacement of coordinated alkynes by an enamine.

**Figure 2.3.2**: Enamine displacement of alkyne from (2,2'-dipyridylamine)Cu(I) complex and 1,2 addition to enamine/iminium ion

In 2016, Dockendorff and coworkers reported heterocycle based bifunctional catalysts for cross aldol reactions. We chose those bifunctional catalyst scaffold templates to be repurposed for additions of carbonyl compounds to alkynes. Based on the results of our Lewis acid study that found Group 11 Cu(I), Ag(I), and Au(I) salts to give the best yields in an intramolecular Conia-ene reaction, and reports of Cu(I) catalyzed intramolecular additions of aldehydes to alkynes by Michelet, we hypothesized that a bifunctional Cu(I) catalyst could promote an intermolecular reaction if the alkyne could be coordination at a suitable orientation and distance from the enamine moiety (**Figure 2.3.3**). Additionally, we hypothesized that a tridentate ligand moiety would be necessary to promote 1:1 ligand:metal binding as opposed to more complex binding modes (2:1 or 2:2; ligand:metal binding) that could be catalytically inactive. A tridentate ligand could adopt a favorable distorted tetrahedral Cu(I) geometry when coordinated to the alkyne. Inclusion of a central heterocycle closest to the organocatalyst portion of the bifunctional catalyst we hypothesized could also act as a hemilabile ligand and relieve ring strain of the macrocyclic intermediate formed after C-C bond formation by dissociating from the metal.
DFT calculations were implemented to help us prioritize our precatalyst scaffolds and limit the number of precatalysts synthesized. Geometry optimizations and ground state energies were computed for complexes before (2.5) and after (2.6 or 2.7) C-C bond formation (Figure 2.3.3). We hypothesized that an energetically unfavorable C-C bond formation step would preclude catalysis, thus more exergonic catalyst systems for this step were prioritized. A series of calculations were performed to evaluate different organocatalyst moieties (pyrrolidine, N-methyl, and N-benzyl), heterocyclic portions (imidazole, oxazole, and thiazole), and the eastern ligation portion of the catalyst (phenolate, quinoline, and phosphine based ligands). The addition of the enamine to the alkyne could proceed in a syn or anti fashion to generate cis or trans adduct intermediates and for almost all cases the trans isomer was found to be energetically unfavorable.

The thiazole-based catalyst was identified as the most exergonic for C-C bond formation. We hypothesized that sterically hindered amines may avoid intermolecular poisoning of a metal center on a second catalyst molecule; however, a bulkier amine would also slow the rate of enamine formation. Catalysts with the N-benzyl amine (−3.8 kcal/mol) was prioritized as it was found to be more energetically favorable than the N-methyl (−2.9 kcal/mol) or pyrrolidine (−2.1 kcal/mol), with the lower favorability of the pyrrolidine presumed to be due to the increase in strain on the macrocycle intermediate. Although the pyrrolidine varieties were computed to not be as energetically favorable as the N-benzyl amine, the C-C bond formation step was still found to be exergonic. A precatalyst with a
pyrrolidine as a Lewis base was still of interest to us due to its established effectiveness as an organocatalyst, particularly with other bifunctional systems. DFT calculations on variations of the eastern ligating portion of the $N$-benzyl catalyst ($R_3$) showed a significant improvement in $\Delta G$ with the quinoline ($-10.2$ kcal/mol) over the phenolate ligand ($-3.4$ kcal/mol). This increase in exergonicity for the C-C bond formation step is believed to be attributed to the Cu(I) species with the quinoline being cationic versus the neutral Cu(I) with the phenolate. The reduction in electron density around Cu(I) allows for more sigma donation from the coordinated alkyne, resulting in it being more electrophilic and C-C bond formation predicted to be more favorable. The phosphine-based ligand ($-10.3$ kcal/mol, $R^1 = \text{Me}, R^3 = \text{C}$) was comparable the quinoline ($R^3 = \text{B}$), but attempts to synthesize this ligand failed due to decomposition of the phosphine via oxidation during purification.

### 2.4 Synthesis of Pyrrolidine Based Precatalysts for Cu(I)

After using DFT calculations to prioritize the tridentate thiazole bifunctional catalysts, our next objective was to develop modular syntheses to access the desired heterocyclic precatalysts with either the pyrrolidine (Scheme 2.4.1) or N-benzyl amine (Scheme 2.4.2) as the Lewis base moiety. Starting with Boc-L-proline (2.8), EDC coupling with threonine methyl ester 2.9, followed by DMP oxidation, yielded known dipeptidyl ketone 2.11 in good yield. Heating with Lawesson’s reagent provided the thiazole 2.12, followed by reduction of the ester with sodium borohydride and catalytic sodium triacetoxyborohydride. Mesylation of primary alcohol 2.13 followed by addition of sodium azide generated azide 2.14, which was reduced with hydrogen and catalytic palladium on carbon. The resulting primary amine 2.15 could be combined in a modular fashion with a variety of aldehydes using reductive amination conditions to generate final precatalysts (2.16a-d) after Boc removal.
Reductive amination of the quinoline-based precatalysts in THF was complicated by the prominent formation of the bis-alkylated products which were not easily separable by column chromatography. Stepwise attempts to reduce the pre-formed imine with sodium borohydride yielded identical results. The use of acetic acid as a solvent was discovered to suppress the formation of the overalkylated byproduct, though reactions with these substrates were difficult to push to completion. A sulfonic acid resin (Amberlyst 15\textsuperscript{®}) was effective for both Boc removal and trapping the final diamine products, which allowed impurities to be washed away and the desired products released in high purity after basification with ammonia in methanol. The analogous N-benzyl-based precatalysts (2.17a-d) were synthesized by Jacob Porter using a similar synthetic route starting from \(N\)-Boc glycine (Figure 2.4.1).\textsuperscript{115}
2.5 Reaction Screening with Cu(I) and Thiazole-based Precatalysts

With a focused library of precatalysts in hand, we proceeded to test them in a variety of reaction screens with Cu(I) salts \((\left(\text{CH}_3\text{CN}\right)_4\text{CuBF}_4)\), utilizing GC-MS to analyze each reaction. For an initial solvent screen, cyclopentanone was selected due to its well-established reactivity for enamine formation.\(^{125-126}\) Internal alkynes (1-phenyl-1-propyne or 2-hexyne) were chosen as initial substrates due to the possibility that terminal alkynes may form undesired copper-acetylide species (Figure 2.5.1). Reactions with polar solvents (DMSO, DMF, and MeCN) gave no reaction at 50 °C. It is plausible that the coordinating nature of these solvents prevented interaction of the metal salt with the substrates. Chloroform and toluene also showed only starting material after 24 h at 50 °C. Nitromethane and THF produced an unknown, undesired byproduct that was also present in a control reaction run in THF where the 2-hexyne had been omitted. DCE and dioxane led to consumption of cyclopentanone, but gave complex, intractable mixtures of products.

**Figure 2.5.1** Solvent screen with N-benzyl-thiazole precatalyst and Cu(I)

![Figure 2.5.1](image)

Given the use of DCE in the known analogous intramolecular carbocyclization reactions, we explored additional substrates in this solvent with our library of precatalysts (Figure 2.5.2). This screening showed that phenol-based precatalysts (2.16b–d and 2.17b–d) were inactive under the reaction conditions. Quinoline-based precatalysts (such as 2.16a and 2.17a) showed complex mixtures of products. Analysis of these mixtures showed that GC-MS peaks were common amongst reactions with shared substrates. For
example, reactions 2-hexyne and all of the carbonyl substrates yielded a set of common byproducts that did not correspond to any desired products nor their derivatives, such as multiple alkenylation products, as determined by GC-MS and $^1$H NMR of scaled up reactions. No GC-MS peaks were identified that were unique to a specific set of substrates, which would have suggested a unique and potentially desirable reaction.

**Figure 2.5.2 General reaction screen in DCE**

Based on the GC-MS data, we believe that the products formed under these conditions are primarily due to carbonyl-carbonyl or alkyne-alkyne coupling reactions. GC-MS evidence for aldol self-condensation products was obtained in some cases, most notably when phenylacetaldehyde was used as the carbonyl compound. A second prominent byproduct seen via GC-MS for reactions that contained phenylacetylene was 1,4-diphenylbutadiyne, presumably via a Glaser coupling.127 The presence of this byproduct in these samples was confirmed by comparison of the GC-MS traces to that of a commercial sample of 1,4-diphenylbutadiyne. Additionally, select reactions were run with AgBF$_4$ as the metal salt instead of (CH$_3$CN)$_4$CuBF$_4$, and no reactions were observed in any of these cases. A range of acidic additives (4-nitrophenol, benzoic acid, $p$TsOH, acetic acid, and TFA) or a non-coordinating base (2,6-di-tert-butylpyridine) were additionally tested for the addition of cyclopentanone to 2-hexyne and found to result in no observable reaction in any case.
To ensure that we could detect desired product formation, a control reaction was run to confirm that trace amounts of desired product could be detected in our crude reaction mixtures via GC-MS. An authentic sample of product from the addition of acetone to phenylacetylene (2.18) was synthesized according to a protocol reported by Trofimov.\textsuperscript{128} Two parallel reactions were set up containing acetone and phenylacetylene substrates, and one reaction was doped with the positive control (2.17) at 5 mol\% (Figure 2.5.2). After stirring at 50 °C for 24 h, both reactions were analyzed via GC-MS. The positive control was detected in the reaction that was doped and it was not detected in the undoped reaction.

**Figure 2.5.3** X-ray structure of a 2:2 complex of 2.17a and AgBF$_4$

Although the DFT calculations were promising for the tridentate thiazole precatalysts with Cu(I), no desired product was afforded for the addition of an aldehyde or ketone to an alkyne. X-ray and NMR studies were carried out to investigate the lack of reactivity of this catalyst system. While we were unable to obtain single crystals of any Cu(I) complex with our precatalysts, Jacob Porter obtained a Ag(I) crystal with a 2:2 ligand to metal stoichiometry (Figure 2.5.3).\textsuperscript{115} One key observation was that neither Ag(I) atom coordinated to all three of the desired coordinating groups of the precatalyst, namely the
quinoline, thiazole, and the secondary amine proximal to the quinoline. Additionally, coordination of the $N$-benzylamine, instead of the quinoline, to Ag(I) was observed and could provide an explanation for the lack of reactivity of this catalyst class as the $N$-benzylamine is required to serve as the organocatalyst.

2.6 Design and DFT Prioritization of Bifunctional Catalysts for Additions of Ketones/Aldehydes to Alkenes

In tandem with our studies on Cu(I) bifunctional catalyst aimed to promote $\alpha$-alkenylation using alkynes, we also sought after a complementary strategy focused on $\alpha$-alkylations of carbonyl compounds with alkenes. The general strategy was consistent in that we first utilized DFT calculations to guide our bifunctional catalyst design prior to precatalyst synthesis and reaction screening. Our novel bifunctional design with a meta-substituted benzene spacer and initial efforts at identification of an active catalyst led to the publication of a report titled “DFT-assisted design and evaluation of bifunctional amine/pyridine-oxazoline metal catalysts for additions of ketones to unactivated alkenes and alkynes.” A summary of these studies and additional complementary DFT calculations are described here.

**Figure 2.6.1** General bifunctional catalyst design for intermolecular addition of unactivated aldehydes/ketones to unactivated olefins
Prior to the selection of potential catalysts for more detailed DFT calculations, bifunctional catalyst scaffolds were initially visualized using physical, hand-held models and on the computer using software such as Avogadro, which was also used for simple molecular mechanics minimization of the structures. This prescreening was used to observe whether the organocatalyst tether could position the activated aldehyde/ketone (via enamine formation) \textit{anti} to a complexed olefin, to permit its nucleophilic addition (\textbf{Figure 2.6.1}). We reasoned that the square planar coordination geometry of Group 10 transition metals could be ideal for providing access to coordinated olefin’s \(\pi^*\)-orbitals, while at the same time minimizing accessible geometries for poisoning by other functional groups. Precatalysts featuring oxazoline ligands were initially chosen due to the excellent precedent for oxazolines in Pd(II) catalysts promoting asymmetric Wacker-type oxidations.\textsuperscript{130} Our initial goal was to determine a suitable oxazoline-based bidentate ligand and organocatalyst tether combination predicted to promote nucleophilic addition to the olefin. The organocatalyst tether variables we considered included: attached position to \(\pi\)-acid moiety; tether length; and \(1^\circ\) and \(2^\circ\) amines.

Logical initial tether placements were either at the 3-position on the pyridine or the 4-position on the oxazoline (\textbf{Figure 2.6.1}). In our first scaffold design, a 3-substituted pyridine would space the tether further away from the metal than being at the 2-position. To minimize steric interactions between the coordinated olefin and an atom at the 2-position, a 3-substituted pyridazine was utilized rather than a pyridine. In the design for a tether on the oxazoline, an aryl substituent was utilized to again minimize any steric interactions with a coordinated olefin and position the organocatalyst an appropriate distance from the metal center. Using physical models to examine hypothetical transition states for the C-C bond forming step and ensure a favorable geometry of the enamine
with respect to $\pi^*$-orbitals of the coordinated olefins, the most promising two scaffolds 2.19 and 2.26 were optimized using DFT (Figure 2.6.2).

**Figure 2.6.2** Example of key olefin complex and iminium adduct intermediates before and after C-C bond formation optimized using DFT

The presumed intermediate structures before and after C-C bond formation were optimized using DFT, and the free energy changes between the ground state optimized structures were calculated (Figure 2.6.4). When performing the DFT calculations, conformational sampling was used to increase the probability of obtaining the ground state energy of a global minimum instead of a local minimum. This approach was used for each alkene complex, but not on the adduct intermediates due to their conformational constraint. A total of 9 different conformations were sampled for each enamine complex we report. These 9 conformations arise from all permutations resulting from 120° rotation of the $\text{C}^1\text{C}^2\text{C}^3\text{C}^4$ and $\text{C}^2\text{C}^3\text{C}^4\text{N}^5$ dihedral angles (Figure 2.6.3). Representative examples of their relative $G_{298}$ (kcal/mol) are provided below for conformers of 2.20-complex. In parentheses are the Gibbs free energies relative to the lowest energy conformer 2.20i.

Assuming that the C-C bond formation step needs to be exergonic for catalysis to be achieved, catalyst systems with more exergonic C-C bond formation were considered to be more promising. Depending on the face of the enamine that undergoes nucleophilic
addition to the olefin, the iminium adduct intermediate could be an $E$- or $Z$-iminium macrocycle adduct. Overall, the $Z$-iminium adducts were found to generally be lower in energy.

**Figure 2.6.3** Conformational sampling of DFT optimized 2.20-complex. Computed energies in Hartree and their ($\Delta G$) in kcal/mol relative to the lowest conformer 2.20h.

DFT calculations of the Pd(II)-ethylene complex and iminium adduct after C-C bond formation indicated that the free energy change was favorable for both the pyridyl- and pyridazine-oxazoline bifunctional precatalysts. Variations of both precatalysts were also calculated (Figure 2.6.4). Oxazoline 2.21 and nonplanar ligands 2.22 and 2.23 were all found to be less exergonic than 2.19. There was only a marginal energy difference between ligands 2.22 and 2.23; however, the 2-methyl substituted pyridyl 2.23 has the
added benefit of ethylene coordination to palladium *cis* to the oxazoline being 2.9 kcal/mol favored over the *trans* position, while *cis* coordination in 2.22 was found to only be 1.2 kcal/mol lower in energy than *trans* coordination (Figure 2.6.4).

**Figure 2.6.4** DFT calculations of bifunctional PyOX and pyridazine-oxazoline precatalysts

Decreasing the steric interactions by using pyridazine 2.26 rather than pyridine 2.28 was seen to be beneficial. Shortening the amine tether by one methylene unit in 2.29 had the dramatic effect of making the C-C bond formation very endergonic due to a high enthalpic penalty (+17.5 kcal/mol) due to ring strain. This confirmed our hypothesis that the amine tether length was crucial when designing these bifunctional precatalysts. Incorporation of geminal dimethyls on precatalysts 2.25 and 2.31 resulted in the
calculation of a more exergonic reaction. This was surprising, as the Thorpe-Ingold effect is a kinetic, not a thermodynamic, effect. The adduct formation for secondary acyclic precatalysts 2.20 and 2.27 and cyclic amine precatalysts 2.24(R) and 2.30 were more exergonic than their respective primary amines.

With the strong dependence on the tether length observed in the pyridazine system, we sought to test the effect of the tether length and position of substitution on the aryl ring in precatalyst 2.20 (Table 2.6.1). Having the tether in the meta position was the most favored, confirming our hypothesis using 3D models. Positioning the tether in the ortho position (entry 1, ΔG^2 = –16.8 kcal/mol) seems reasonable given its comparable thermodynamics to the meta position (entry 2, ΔG^2 = –18.8 kcal/mol), however this would place the amine or enamine in close enough proximity to poison the metal. This phenomenon was observed when performing DFT optimization on the enamine adding to the Pd(II) center and displacing ethylene to give the "quenched" structures (Table 2.6.1).

Table 2.6.1 DFT calculations on bifunctional PyOX precatalysts with varying tether length and position on the aryl ring

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine Tether Location</th>
<th>n</th>
<th>Quenched ΔG^1 (kcal/mol)</th>
<th>Adduct ΔG^2 (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ortho</td>
<td>1</td>
<td>–19.9</td>
<td>–16.9</td>
</tr>
<tr>
<td>2</td>
<td>meta</td>
<td>1</td>
<td>–8.3</td>
<td>–18.8</td>
</tr>
<tr>
<td>3</td>
<td>para</td>
<td>1</td>
<td>–1.6</td>
<td>–12.6</td>
</tr>
<tr>
<td>4</td>
<td>meta</td>
<td>0</td>
<td></td>
<td>–11.8</td>
</tr>
<tr>
<td>5</td>
<td>meta</td>
<td>2</td>
<td></td>
<td>–19.9</td>
</tr>
</tbody>
</table>

When the tether is in the ortho position, the addition of the enamine to the metal is calculated to be more favorable than the desired addition to ethylene (entry 1, ΔG^1 = –
19.9 kcal/mol vs $\Delta G^2 = -16.9$ kcal/mol). Moving the tether to the meta or para position (entries 2, 3) results in the desired adduct formation to be at least 10 kcal/mol more favorable than intramolecular quenching. As the length of the alkyl chain increases, the C–C bond formation is calculated to become more exergonic. A tethered ethylamine (entry 2) was found to be ideal. A shorter chain length (entry 4, $\Delta G^2 = -11.8$ kcal/mol) is less exergonic, and a catalyst with a longer chain length (entry 5, $\Delta G^2 = -19.9$ kcal/mol) is calculated to be most favorable for this transformation, but will likely lead to self-quenching via amine–metal coordination. Overall, these preliminary DFT calculations led us to prioritize the catalyst of entry 2 (Table 2.6.1) as our lead scaffold to study in further detail.

Table 2.6.2 DFT calculations of bifunctional PyOX precatalysts with varying counter ion and pyridyl substituents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Counter Ion (X)</th>
<th>Substituent (Y)</th>
<th>R</th>
<th>$\Delta G^2$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>H</td>
<td>Me</td>
<td>-18.8</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>H</td>
<td>Me</td>
<td>-19.9</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>H</td>
<td>Me</td>
<td>-20.5</td>
</tr>
<tr>
<td>4</td>
<td>PF$_6$</td>
<td>H</td>
<td>Me</td>
<td>-30.8</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>-17.2</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>F</td>
<td>H</td>
<td>-17.2</td>
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<tr>
<td>7</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>-18.5</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>Br</td>
<td>H</td>
<td>-19.0</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>OMe</td>
<td>H</td>
<td>-15.0</td>
</tr>
</tbody>
</table>

We sought to study the effect of the metal counter ion $X$ and the electronics of the pyridyl ring (substituent $Y$) on the C–C bond forming step (Table 2.6.2). More weakly coordinating counterions result in more exergonic calculated reactions (entries 1–4), though it should be emphasized that solvent effects, particularly with the cationic metals
under study here, may be difficult to quantify using these calculations. The weaker sigma donors yield more electrophilic metal centers, which in turn are expected to generate a more electrophilic ethylene complex that should provide more exergonic reactions. Although not as prominent, this trend was also observed for 4-substituted pyridyl precatalysts. Electron-withdrawing substituents (entries 7–8) yielded a more exergonic calculated C–C bond formation, and the electron-donating methoxy group (entry 9) resulted in a less exergonic reaction, though fluoride (entry 6, ΔG = −17.2 kcal/mol) was calculated to be equivalent to hydrogen (entry 5) with the use of a cationic palladium catalyst.

**Figure 2.6.5** A) DFT calculations of metal-ethylene complexes and adducts after C-C bond formation; B) DFT optimized structures using Cu(I)

<table>
<thead>
<tr>
<th>Metal</th>
<th>ΔG_{298} (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni(II)</td>
<td>-16.8</td>
</tr>
<tr>
<td>Pd(II)</td>
<td>-18.8</td>
</tr>
<tr>
<td>Pt(II)</td>
<td>-17.5</td>
</tr>
<tr>
<td>Cu(I)</td>
<td>28.5</td>
</tr>
</tbody>
</table>

These ligands were designed to provide square planar coordination geometries with group 10 transition metals. This geometry allows the coordinated alkene to be “sandwiched” between the metal and the appended enamine intermediate, providing access to the π*-orbitals on the alkene. Coordination of an alkene in this fashion, cis to the oxazoline and proximal to the organocatalyst tether, was found to be 3.0 kcal/mol more favorable than the trans coordination. When using a group 11 metal, such as Cu(I) (Figure
2.6.5A), the ethylene complex takes on a distorted tetrahedral coordination geometry, thus positioning the alkene π*-orbitals much further away from the enamine (Figure 2.6.5B).

The macrocyclization for Cu(I) with precatalyst 2.28 was calculated to be very endergonic, in contrast to the group 10 metals, confirming the this PyOX scaffold is not well suited for Cu(I).

*Figure 2.2.6* Estimation of transition state energy for C–C bond formation by DFT calculations of structures with fixed distances between enamine and ethylene. Values are normalized to the complex in its most stable conformation prior to C–C bond formation (which is set to G = 0 kcal/mol)

While these ground state DFT calculations are used to screen our precatalysts for exergonicity of the C–C bond forming step, the activation energy for this step also determines the catalyst viability. Given the computationally intensive nature of calculating these transition states, we sought to estimate the activation energy by fixing the distance between the new C–C bond formed between the ethylene carbon (C1) and enamine (C2), optimizing the geometries of the molecule, and calculating the resulting energies (*Figure*...
2.6.6). The free energies reported are with respect to the lowest energy conformation of the ethylene complex (Figure 2.6.3). The free energy barrier for C–C bond formation was estimated to be 7.4 kcal/mol, with 4.1 kcal/mol of that energy arising from the organocatalyst tether changing from an extended conformation (C1–C2 = 9.035 Å) to a more closed conformation (C1–C2 = 5.065 Å). This energy barrier should be low enough to overcome at elevated temperatures.

2.7 Synthesis of Bifunctional PyOx Precatalyst

After our initial DFT prioritization, we pursued the synthesis of the bifunctional precatalyst 2.20. Retrosynthetically, we surmised the oxazoline ring formation of 2.32 would be a natural disconnect for the synthesis of precatalyst 2.20 (Scheme 2.7.1). Alcohol 2.33 could be generated by an amide coupling of carboxylic acid 2.34 and amino alcohol 2.35. The amino alcohol was envisioned to arise via a Sharpless aminohydroxylation of the respective substituted styrene 2.36.131 With this retrosynthetic analysis, we recognized that the late stage peptide coupling would potentially enable more efficient access to precatalyst modifications on the eastern end.

Scheme 2.7.1 Retrosynthesis of precatalyst 2.20

In the forward direction (Scheme 2.7.2), the Boc protection of the primary amine 2.37 using Boc anhydride and triethylamine gave the desired carbamate 2.38 in good yield. While earlier stage reactions used commercially available 2-(3-bromophenyl)ethanamine, 2.37 was subsequently prepared more cheaply via reduction
of nitrile 2.44 using LiAlH₄ (Scheme 2.7.3). A Suzuki cross-coupling of aryl bromide 2.38 with 2,4,6-trivinylcyclotriboroxane-pyridine, prepared according to the literature, generated the substituted styrene 2.36. Sharpless asymmetric aminohydroxylation of on styrene 2.36 using (DHQD)₂PHAL, K₂OsO₄(OH)₄ and in situ generated benzyl N-chloro-N-sodiocarbamate afforded the carbobenzyloxy-protected amino alcohol 2.40 in 40% yield, with a predicted absolute stereochemistry of (R) when using the (DHQD)₂PHAL ligand. This enantioselectivity arises via an asymmetric induction. The main disadvantage to this route was the low yield in the aminohydroxylation step from the lack of regioselectivity, though regioisomer 2.39 was separable via flash chromatography. The hydrogenolysis of 2.40 was carried out using Pd/C and H₂ (3.5 bar) in MeOH to yield amino alcohol 2.35 in excellent yield. HATU amide coupling of various picolinic acids with amino alcohol 2.35 provided amides 2.41a-c in reasonable yields.

Scheme 2.7.2 1st Generation synthesis of PyOx based precatalyst

Oxazoline formation proceeded smoothly using DeoxoFluor® to afford compounds 2.42a-c. Unfortunately, N-methylation of 2.42a using NaH and iodomethane yielded a
mixture of mono- and bis-alkylated products, which were not separable via flash chromatography. Subjection of the mono- and bis-alkylated crude material to Boc deprotection using Amberlyst® 15 still yielded a mixture. To avoid these issues, we chose to test alternative N-methylation reaction conditions. The use of the weaker base potassium hydroxide in dimethyl sulfoxide demonstrated spot-to-spot conversion to the desired monoalkylated product with no bisalkylated byproduct evident via LC-MS (not shown).

While this first-generation synthesis of these PyOx bifunctional catalyst scaffolds provided a proof of concept, there were several drawbacks. First, the key Sharpless asymmetric aminohydroxylation was low yielding. Second, the late stage N-methylation using sodium hydride yielded inseparable overalkylated byproduct. Although this overalkylation problem was solved using potassium hydroxide, there was still concern over epimerization of the chiral oxazoline. Finally, the Suzuki cross coupling with 2,4,6-trivinylcyclotriboroxane-pyridine was not reliable, producing a wide range of conversions (25-90%).

To address the drawbacks from the first generation PyOx synthesis, several modifications were made. Rather than using a Sharpless asymmetric aminohydroxylation to access the key amino alcohol, we opted to utilize a styrene epoxidation/azide ring-opening sequence. Additionally, the N-methylation was implemented earlier in the synthesis. While this avoids the possibility of overalkylation, it does preclude any late stage modifications to the organocatalyst amine tether. Finally, potassium vinyltrifluoroborate, rather than the 2,4,6-trivinylcyclotriboroxane-pyridine complex, was used in the Suzuki cross coupling.

Utilizing the same first two synthetic steps in (Scheme 2.7.2), the BOC protected amine 2.38 can be made on a 10 g scale. At this stage, we decided to N-methylate 2.38 using potassium hydroxide and iodomethane in dimethyl sulfoxide to yield 2.45 in excellent
yield. Suzuki coupling of aryl bromide 2.45 with potassium vinyltrifluoroborate\(^{136}\) generated the substituted styrene 2.46, with more consistent results compared to vinyl triboroxine–pyridine complex. Subsequent epoxidation of styrene 2.46 with mCPBA followed by regioselective ring-opening with sodium azide in hot water gave azido alcohol 2.48 in 66% over two steps. While this synthetic route yields racemic material, optically active catalysts could optionally be generated from via asymmetric epoxidation methods. The current styrene epoxide opening method using sodium azide and hot water has been shown to give clean inversion of stereochemistry.\(^{137}\) Reduction of 2.48 using Pd/C under \(\text{H}_2\) afforded amino alcohol 2.49 in excellent yield. EDC amide coupling with picolinic acid followed by oxazoline formation using DeoxoFluor\(^{8138-139}\) proceeded smoothly to afford 2.51. Finally, Boc removal using excess trifluoroacetic acid (TFA) yielded the final precatalyst 2.20.

**Scheme 2.7.3** 2\(^{\text{nd}}\) generation synthesis of PyOx based precatalyst

![Scheme 2.7.3](image-url)
2.8 Intermolecular Reaction Screening using Bifunctional PyOx Catalyst

With the synthesized precatalyst 2.20 in hand, we proceeded to test it in a variety of reaction screens for the direct additions of ketones to alkenes and alkynes, using GC-MS to analyze each reaction. Cyclopentanone was selected due to its well-established reactivity for enamine formation.\(^\text{140}\) Additionally, methyl acetoacetate was chosen for its frequent use in alkene hydroalkylation reactions. Ethylene, 4-(4-fluorophenyl)-1-butene, and 6-phenyl-2-hexyne were chosen as representative electrophiles in the reactions (Tables 2.8.1 and 2.8.2); the aromatic handles were included with several substrates to facilitate product identification. Due to its polar, non-coordinating nature, nitromethane was used for all reactions; less polar solvents are often unable to dissolve the cationic metal salts of interest. For metal salts with halide counterions, the metal/precatalyst solution was reacted with 1 or 2 equivalents of AgBF\(_4\), and the resulting silver halide salts were filtered off prior to the addition of substrates.

Results from a representative metal salt screen with precatalyst 2.20, cyclopentanone, and either 4-(4-fluorophenyl)-1-butene (2.52) or ethylene (2.53) are given in Table 2.8.1. All reactions with ethylene (entries 1–16) produced no detectable desired products such as 2.54 or 2.55 via GC-MS, as confirmed by analysis of low concentrations of the positive control 2-ethyl-cyclopentanone (2.55, \(R^1, R^2 = H\)) added to a sample reaction mixture. Similarly, when we used 4-(4-fluorophenyl)-1-butene 2.52 (entries 1–16), no desired adducts were detected and only starting material peaks were prominent in the GC-MS traces.
Table 2.8.1 Screening of group 10 metal salts in reactions with cyclopentanone

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Result with:</th>
<th>2.52</th>
<th>2.53b</th>
</tr>
</thead>
<tbody>
<tr>
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<td>NiCl₂·6H₂O/AgBF₄</td>
<td>A</td>
<td>A</td>
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</tr>
<tr>
<td>2</td>
<td>NiI₂/AgBF₄</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ni(OAc)₂·4H₂O</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂(DME)/AgBF₄</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ni(OTf)₂</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pd(CH₃CN)₂(BF₄)₂</td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pd(CH₃CN)₂Cl₂/AgBF₄</td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Pt(DMSO)₂Cl₂/AgBF₄</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pt(DMSO)₂Cl₂/AgBF₄</td>
<td>A</td>
<td>A</td>
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<tr>
<td>11</td>
<td>Pt(DMSO)₂Cl₂/2AgBF₄</td>
<td>A</td>
<td>A</td>
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<tr>
<td>12</td>
<td>Pt(DMSO)₂Cl₂/2AgBF₄</td>
<td>A</td>
<td>A</td>
<td></td>
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<tr>
<td>13</td>
<td>AgBF₄</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>none</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Pd(CH₃CN)₄(BF₄)₂</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Pd(CH₃CN)₂Cl₂/AgBF₄</td>
<td>C</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

a Precatalyst 2.20 (2 mg, 0.007 mmol) was dissolved in NO₂Me (0.3 mL) and added to the respective metal salt (0.007 mmol) in a 1.5 mL HPLC vial. The alkene (0.070 mmol) and cyclopentanone (0.070 mmol) were added as solutions in NO₂Me (0.100 mL). The vials were heated at 50 ºC for 24 h, and analyzed directly via GC-MS. b Reactions were flushed with ethylene and stirred at 50 ºC for 24 h at 50 psi in a pressure flask. c Results: A: No reaction; B: trace amount of alkene dimerization; C: alkene oligomerization observed. d No precatalyst was used.

Olefin isomerization products and trace amounts of dimerization products were found in samples with 2.52 and palladium metals (entries 7–8). Precatalyst 2.20 appears to suppress olefin oligomerization, as control reactions without 2.20 (entries 15–16) had nearly complete consumption 2.52 and conversion to alkene dimer and trimers, as detected by GC-MS. In the case of ethylene, a peak with a mass corresponding to octene was detected in the GC-MS. Pt(II) and Pd(II) salts are known to promote the polymerization of alkenes.¹⁴¹⁻¹⁴³ A reaction screen for the addition of cyclopentanone to 6-phenyl-2-hexyne was also performed, but also yielded only peaks for the starting materials in the GC-MS.
Table 2.8.2 Screening of group 10 metal salts in reactions with methyl acetoacetate

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Metal</th>
<th>Temperature (ºC)</th>
<th>Result with:</th>
<th>2.52</th>
<th>2.53&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2.56</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂(DME)/AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ni(OTf)₂</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pd(CH₃CN)₄(BF₄)₂</td>
<td>50</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>Pd(CH₃CN)₂Cl₂/AgBF₄</td>
<td>50</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pt(DMSO)₂Cl₂/AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pt(DMSO)₂I₂/AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pt(DMSO)₂Cl₂/2AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>Pt(DMSO)₂I₂/2AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>AgBF₄</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<tr>
<td>10</td>
<td>–</td>
<td>50</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pt(DMSO)₂Cl₂/AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pt(DMSO)₂I₂/AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Pt(DMSO)₂Cl₂/2AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Pt(DMSO)₂I₂/2AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>15&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pt(DMSO)₂Cl₂/AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>16&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pt(DMSO)₂I₂/AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>17&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pt(DMSO)₂Cl₂/2AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>18&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pt(DMSO)₂I₂/2AgBF₄</td>
<td>90</td>
<td>-</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Precatalyst 2.20 (2 mg, 0.007 mmol) was dissolved in NO₂Me (0.3 mL) and added to the respective metal salt (0.007 mmol) in a 1.5 mL HPLC vial. The alkene or alkyne (0.070 mmol) and methyl acetoacetate (0.070 mmol) were added as solutions in NO₂Me (0.100 mL). The vials were heated at 50 ºC for 24 h, and analyzed directly via GC-MS. <sup>b</sup>Reactions were flushed with ethylene and stirred at 50 ºC for 24 h at 50 psi in a pressure flask. <sup>c</sup>Results: A: No reaction; B: trace amount of olefin dimerization; C: a peak with a mass corresponding to octene was present in the GC-MS; D: alkyne dimerization and trimerization observed. <sup>d</sup>Precatalyst 2.20 was not added to these reaction vials.

Due to the limited solubility of some of the nickel metal salts and Pd(OAc)₂ with our precatalyst in NO₂Me, we chose to exclude these metal salts in our additional screens. Mixtures of methyl acetoacetate with ethylene (2.53), 4-(4-fluorophenyl)-1-butene (2.52), or 6-phenyl-2-hexyne (2.56) were screened with precatalyst 2.20 and either palladium or platinum metal salts (Table 2.8.2). Similar results were obtained as in the screens using cyclopentanone. Only starting material peaks were present in the GC-MS, except when using palladium with 4-(4-fluorophenyl)-1-butene (column 4), where trace amounts of isomerized alkene and dimerization products were detected. Due to the observed lack of
reactivity, platinum monocationic and biscationic metal salt systems were tested at 90 ºC for the addition of methyl acetoacetate to either ethylene or 6-phenyl-2-hexyne (2.56). In the absence of precatalyst 2.20, ethylene presumably underwent oligomerization, as a peak with a mass corresponding to octene was detected by GC-MS (entries 15–18). Additionally, 6-phenyl-2-hexyne in the absence of 2.20 underwent dimerization and trimerization. With the incorporation of precatalyst 2.20, the alkyne dimers and trimers were completely suppressed when using 6-phenyl-2-hexyne, but a detectable amount of octene was present when using ethylene.

**Table 2.8.3 Additive screen with methyl acetoacetate**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-nitrophenol</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>benzoic acid</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>p-TsOH</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>acetic acid</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>2,6-di-tert-butylpyridine</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Precatalyst 2.20 (1 mg, 0.0035 mmol) and Pd(CH$_3$CN)$_4$BF$_4$ (0.0035 mmol) were dissolved in NO$_2$Me (0.05 mL) in a 1.0 mL test tube. Methyl acetoacetate (0.035 mmol) and the additive (0.0035 mmol) were added as solutions in NO$_2$Me (0.100 mL). The samples were heated at 50 ºC for 24 h, aliquots were taken for analysis directly via GC-MS, and the samples were heated at 90 ºC for an additional 24 h and analyzed directly via GC-MS. Reactions were flushed with ethylene and stirred under 50 psi in a pressure flask. NR = no reaction.

A range of additives was additionally tested for the addition of methyl acetoacetate to ethylene, along with the non-coordinating base 2,6-di-tert-butylpyridine (Table 2.8.3). These reactions were initially run at 50 ºC for 24 h, and allowed to cool to room temperature before ~50 µL aliquots were taken for GC-MS analysis, then the temperature was increased to 90 ºC for an additional 24 h. No reactions were observed with any of the additives after heating at 50 or 90 ºC. Despite promising DFT calculations, we were unable to obtain formation of any desired product from the addition of an enamine to an alkene.
via our PyOX bifunctional catalyst. Without this promising hit, we aimed to rationalize this lack of reactivity through NMR experiments and X-ray crystallography.

2.9 NMR Experiments with Pd(II)-PyOX Complexes and Attempted Crystallizations

In parallel with our efforts to screen our bifunctional PyOX precatalyst 2.20 under different reaction conditions, we attempted to obtain single crystals of various Pd(II) and Pt(II) complexes. Crystallization trials were run via slow diffusion using nitromethane, 1:1 nitromethane: benzene, or acetonitrile as the strong solvent and diethyl ether or pentane as the weak solvent. Unfortunately, our attempts were unsuccessful. To further probe the dynamics of the PyOX precatalyst with the metal salt, $^1$H NMR spectra were obtained in CD$_3$NO$_2$ before and after the addition of 1 equivalent of Pd(CH$_3$CN)$_2$Cl$_2$ to bifunctional precatalyst 2.20 (Figure 2.9.1).

**Figure 2.9.1** $^1$H NMR (CD$_3$NO$_2$, 300 MHz) spectra of PyOX precatalyst 2.20 (B) and its Pd(II) complex (A)

In the presence of Pd(II), all of the ligand peaks broaden significantly. Furthermore, the organocatalyst alkyl tether peaks have a downfield shift (Figure 2.9.1A). Broadening
of the precatalyst peaks upon addition of Pd(CH$_3$CN)$_2$Cl$_2$ is consistent with slow exchange between two or more complexes. The broadening and shifting of the aminoethyl peaks (the 4 methylene protons originally at 2.8 ppm, and the methyl protons at 2.3 ppm, Figure 2.9.1B) suggests an undesirable interaction between the metal and the amine, presumably in an intermolecular fashion.

**Figure 2.9.2** $^1$H NMR (CD$_3$NO$_2$, 300 MHz) spectra of Boc-protected PyOX precatalyst 2.51 (B) and its Pd(II) complex (A)

![NMR spectra of Boc-protected precatalyst and its Pd(II) complex](image)

A $^1$H NMR spectrum of the Boc-protected precatalyst 2.51 in the presence of Pd(CH$_3$CN)$_2$Cl$_2$ was also obtained (Figure 2.9.2). The ligand peaks remain sharp and downfield shifts are observed for the pyridyl and oxazoline protons after addition of Pd(II) (Figure 2.9.2A), while the aminoethyl and methyl protons at 3.4 and 2.9 ppm are not shifted. The noticeable difference in NMR signals between the carbamate 2.51 and precatalyst amine 2.20 upon the addition of Pd(II) is consistent with the amine (but not the carbamate) participating in undesirable intermolecular coordination with the metal, which may also occur under the reaction conditions and preclude substrate binding and activation. To the carbamate 2.51 and Pd(CH$_3$CN)$_2$Cl$_2$ (1 eq.) was added AgBF$_4$ (1 eq.) as a solution in CD$_3$NO$_2$, and the solution was shaken for 1 h and filtered through a PTFE
syringe filter, before a stock solution of cyclopentene (1 eq.) in CD$_3$NO$_2$ was added. Relative to a control sample without catalyst, there were no observed changes in the $^1$H NMR for the cyclopentene peaks. This indicated that a Pd–alkene complex did not form to a significant degree, though reactions on transiently-coordinated ligands are possible.

Despite the lack of reactivity from our PyOX or tridentate thiazole bifunctional catalysts, we learned valuable information to improve on our precatalyst design. The PyOX bifunctional catalyst had observable interactions from $^1$H NMR between the organocatalyst and $\pi$-acid, yet demonstrated evidence for Pd(II) coordination when the organocatalyst was Boc protected. The N-benzylamine for the tridentate thiazole precatalyst also had undesired coordination of the N-benzylamine to the Ag metal as evident from the X-ray crystal structure. We thus sought to utilize the tridentate strategy from the thiazole precatalyst and apply it to the existing bifunctional PyOX system or similar pincer ligands for group 10 metals. We hypothesize a tridentate ligand will establish a well-defined 1:1 metal:ligand complex and minimize undesired intermolecular interactions between the organocatalyst and $\pi$-acid.

2.10 DFT Calculations of Tridentate Bifunctional Catalysts

Examination of the X-ray structures of several pincer complexes suggested that a well-defined tridentate system may be promising scaffolds to contain binding pockets selective for smaller alkenes and alkynes over bulkier amines/enamines. The “Lockamine”-type NNN-ligands (derivatives of the “Nickamine-type” catalysts) reported by Hu$^{144}$ phenyl-bis(oxazoline) pincer ligand (PheBOX)$^{145-146}$ and pyridyl-bis(oxazoline) (PyBOX)$^{147-148}$ pincer ligand are examples of scaffolds that could meet these criteria. Our interest in using pincer complexes stemmed from the relevant precedent for alkene activation with group 10 metals, particularly Gagné’s iPr-PyBOX-Pt complexes.$^{65,149}$ We
thus sought to combine such pincer scaffolds with our pendant organocatalyst moiety previously designed for the bifunctional PyOX scaffold.

Table 2.10.1 DFT calculations of bifunctional PyBOX/PheBOX catalysts for propylene coordination (\(\Delta G_1, 2.61\)) and C-C bond formation (\(\Delta G_2, 2.62-2.65\))

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Y</th>
<th>(n (\pm))</th>
<th>(\Delta G_1) (kcal/mol)(a)</th>
<th>C-C Bond Formation: (\Delta G_2) (kcal/mol)(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni</td>
<td>N</td>
<td>2</td>
<td>0.6</td>
<td>-21.0</td>
</tr>
<tr>
<td>2</td>
<td>Pd</td>
<td>N</td>
<td>2</td>
<td>-4.2</td>
<td>-21.8</td>
</tr>
<tr>
<td>3</td>
<td>Pt</td>
<td>N</td>
<td>2</td>
<td>-7.5</td>
<td>-19.7</td>
</tr>
<tr>
<td>4</td>
<td>Ni</td>
<td>C</td>
<td>1</td>
<td>10.2</td>
<td>11.6</td>
</tr>
<tr>
<td>5</td>
<td>Pt</td>
<td>C</td>
<td>1</td>
<td>9.0</td>
<td>10.6</td>
</tr>
</tbody>
</table>

\(a\)Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent.

With these tridentate complexes, either a monocationic ("Lockamine"-type NNN ligands and PheBOX ligands) or dicationic (PyBOX ligands) complex intermediate could be formed \((2.61, \text{Table 2.10.1})\). Monocationic complexes possess the following advantages: they are more functional group tolerant (they should not react with alcohols or water) and the intermediate neutral alkyl-metal intermediate will be more susceptible to a subsequent protodemetallation that would be required for catalyst turnover. In the presence of water, the protodemetallation would ideally occur, but a stoichiometric amount of acid as a proton source may be needed. In contrast, an olefin in a dicationic metal complex has enhanced electrophilic character and is more activated towards nucleophilic addition than the respective monocationic species. However, the biscationic character also enhances the electrophilic character and hardness of the metal center, which can
lead to the soft olefin ligand being displaced by harder ligands and/or nucleophiles in an unproductive fashion.\textsuperscript{58}

DFT calculations were utilized to assist in understanding the impact the electronic environment around the Lewis acid has on the energetics for alkene coordination, C-C bond formation, and undesired intramolecular quenching in order to prioritize between the PyBOX, PheBOX, and Lockamine precatalyst scaffolds. The coordination of propylene to Ni(II), Pd(II), and Pt(II) bifunctional PyBOX (entries 1–3) and PheBOX (entries 4 and 5) complexes, and the subsequent intramolecular C-C bond formations with enamine nucleophiles, were calculated using DFT (Table 2.10.1). Alkene coordination was found to be favorable for Pd- and Pt-PyBOX complexes (entries 2 and 3), but significantly unfavorable for the PheBOX complexes (entries 4 and 5). Four possible diastereomeric adduct intermediates 2.62–2.65 can be formed as a result of linear or branched addition to propylene and the formation of an \(E\)- or \(Z\)-iminium ion. C-C bond formation is consistently favorable with bifunctional PyBOX catalysts (entries 1-3) and more exergonic for the branched addition (2.62 and 2.63) than linear addition (2.64 and 2.65), while the bifunctional PheBOX complexes (entries 4 and 5) are calculated to have unfavorable C-C bond formation, suggesting that they may not be suitable catalysts.

Table 2.10.2 DFT Calculations of bifunctional Lockamine catalysts for propylene coordination (\(\Delta G_1\), 2.67) and C-C bond formation (\(\Delta G_2\), 2.68–2.71)

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>(\Delta G_1) (kcal/mol)\textsuperscript{a}</th>
<th>(\Delta G_2) (kcal/mol)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni</td>
<td>13.3</td>
<td>7.3</td>
</tr>
<tr>
<td>2</td>
<td>Pt</td>
<td>−2.9</td>
<td>12.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent.
The coordination of propylene and subsequent C-C bond formation in Ni(II) and Pt(II) bifunctional Lockamine complexes were also calculated (Table 2.10.2). The C-C bond formation is slightly favored for 2.69 with Ni (entry 1), but may be irrelevant with propylene coordination being extremely unfavorable (13.3 kcal/mol), as observed with the Ni-PheBOX monocationic catalyst. In contrast to Ni, the Pt-Lockamine catalyst (entry 2) has favorable energetics for propylene complexation (−2.9 kcal/mol), but suffers from the same unfavorable C-C bond formation seen with the Pt-PheBOX catalyst.

**Table 2.10.3** DFT calculations of propylene coordination (ΔG₁, 2.73) and C-C bond formation (ΔG₂, 2.74–2.77) of Pt in PyBOX- and PheBOX-based complexes with EDGs and EWGs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y</th>
<th>X</th>
<th>n (+)</th>
<th>ΔG₁ (kcal/mol)</th>
<th>C-C Bond Formation: ΔG₂ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.73</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>N</td>
<td>H</td>
<td>2</td>
<td>−7.5</td>
<td>−19.7, −23.9, −17.2, −16.2</td>
</tr>
<tr>
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<td>N</td>
<td>OMe</td>
<td>2</td>
<td>−6.6</td>
<td>−17.5, −22.4, −15.6, −14.0</td>
</tr>
<tr>
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<td>N</td>
<td>NMe₂</td>
<td>2</td>
<td>−6.2</td>
<td>−14.6, −17.6, −12.3, −12.2</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>H</td>
<td>1</td>
<td>9.0</td>
<td>10.6, 8.4, 15.6, 17.2</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>Cl</td>
<td>1</td>
<td>ND b</td>
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<tr>
<td>6</td>
<td>C</td>
<td>NO₂</td>
<td>1</td>
<td>9.0</td>
<td>8.1, 4.6, 12.2, 13.4</td>
</tr>
</tbody>
</table>

*Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent. DFT energies have not been determined for this entry.*

The bifunctional PyBOX precatalysts showed the most promise with favorable energetics for propylene complexation and C-C bond formation, but these highly electrophilic metals may have limited functional group tolerance (i.e. react with alcohols or water). To decrease the electrophilicity of the biscationic PyBOX-based complexes, electron donating groups (EDGs) (X = OMe, NMe₂) were placed in the 4-position of the
pyridyl ligand (entries 1-3, Table 2.10.3). The EDGs attenuated the energetics of propylene complexation and C-C bond formation, but both steps were still exergonic. This feature could potentially promote higher turnover frequency if the overall energy profile became narrower as a result of these attenuated energetics, and may give improved functional group tolerance over the analogous biscationic catalysts without EDGs.

In contrast to the bifunctional PyBOX scaffold, monocationic PheBOX and Lockamine scaffolds suffered from endergonic C-C bond formation and propylene coordination for the bifunctional Ni-Lockamine. To increase the electrophilicity of the monocationic Pt in PheBOX complexes, electron withdrawing groups (EWGs) (X = Cl, NO$_2$) were placed in the 4-position of the phenyl ligand (entries 4-6, Table 2.10.3). The EWGs were calculated to have little impact on propylene coordination, and the C-C bond formation is predicted to be less endergonic, but still unfavorable. The monocationic Ni-Lockamine complex suffered from poor coordination to propylene, while the C-C bond formation in the Pt-Lockamine complex was calculated to be very endergonic (Table 2.10.2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>X</th>
<th>$\Delta G_1$ (kcal/mol)$^a$</th>
<th>C-C Bond Formation: $\Delta G_2$ (kcal/mol)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\Delta G_1$ (2.79)</td>
<td>$\Delta G_2$ (2.80–2.83)</td>
</tr>
<tr>
<td>1</td>
<td>Ni</td>
<td>H</td>
<td>13.3</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td>Ni</td>
<td>OMe</td>
<td>8.9</td>
<td>5.8</td>
</tr>
<tr>
<td>3</td>
<td>Pt</td>
<td>NMe$_2$</td>
<td>–2.9</td>
<td>10.5</td>
</tr>
<tr>
<td>4</td>
<td>Pt</td>
<td>H</td>
<td>–1.2</td>
<td>3.4</td>
</tr>
</tbody>
</table>

$^a$Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent.
EDGs (X = OMe) and EWGs (X = NO₂) were added para to the central amine in an effort to promote propylene coordination and C-C bond formation in the respective bifunctional Ni- and Pt-Lockamine complexes (Table 2.10.4). The EDGs (entry 2 vs 1) only provided a marginal improvement, although still endergonic, on propylene coordination, but had a negative influence on C-C bond formation. The Pt-Lockamine complex with EWGs (entry 4 vs 3) resulted in slightly less favorable propylene coordination; however, C-C bond formation became much more favorable, but still not exergonic.

**Table 2.10.5** DFT calculations of intramolecular enamine quenching ($\Delta G_2$) in bifunctional PyBOX and PheBOX catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Y</th>
<th>$n$ (+)</th>
<th>Propylene Coordination (2.84): $\Delta G_1$ (kcal/mol)</th>
<th>Enamine Quenching: $\Delta G_2$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni</td>
<td>N</td>
<td>2</td>
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<td>-18.5</td>
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<td>Pd</td>
<td>N</td>
<td>2</td>
<td>-4.2</td>
<td>-24.6</td>
</tr>
<tr>
<td>3</td>
<td>Pt</td>
<td>N</td>
<td>2</td>
<td>-7.5</td>
<td>-24.9</td>
</tr>
<tr>
<td>4</td>
<td>Ni</td>
<td>C</td>
<td>1</td>
<td>9.0</td>
<td>6.1</td>
</tr>
<tr>
<td>5</td>
<td>Pt</td>
<td>C</td>
<td>1</td>
<td>10.2</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Calculated using the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent.

A concern with these bifunctional catalysts is the potential of an enamine to irreversibly add to the metal in an intramolecular fashion. This would prevent the productive olefin coordination required for the desired reaction. The bifunctional PyBOX catalysts, predicted to be the most promising for propylene coordination and C-C bond formation, were found to be very exergonic for intramolecular enamine quenching (Table 2.10.5, entries 1–3). Enamine quenching in the bifunctional PheBOX catalysts was
calculated to not be problematic (entries 4–5), but these systems were not predicted to be promising catalysts due to unfavorable propylene coordination and C-C bond formation.

Bifunctional Lockamine-Ni catalysts exhibited similar results to the bifunctional PheBOX catalysts, having both unfavorable intramolecular enamine quenching and propylene coordination. Using Pt with the bifunctional Lockamine complex had the benefit of favorable energetics of propylene coordination, but the intramolecular enamine quenching is slightly favorable in some cases, depending on if it is the E-2.90 or Z-iminium 2.91 adduct (Figure 2.10.1).

![Figure 2.10.1 Intramolecular enamine quenching in bifunctional Lockamine catalysts. Energies are tabulated relative to 2.89.](image)

A bifunctional catalysts system with calculated favorable energetics for propylene coordination and C-C bond formation, but unfavorable intramolecular enamine quenching has yet to be found. Intramolecular enamine quenching could be a complication with these bifunctional catalysts, but we hypothesize that the enamine (or amine) is too far to complex directly with the metal without substantial structural reorganization (i.e. unfavorable transition state). When designing these catalysts, our goal was to position the organocatalyst far enough away to avoid the amine or enamine from poisoning the metal. Examination of the optimized DFT structures does indicate the enamine is substantial distance (>6Å) away from the metal center (Figure 2.10.2). In summary, these DFT calculations prioritized the bifunctional PyBOX scaffold over the PheBOX or Lockamine
due to its more favorable energetics for propylene coordination and C-C bond formation. The next step was to determine whether the bifunctional PyBOX scaffold would experimentally result in desired reactivity, unlike the analogous PyOX scaffold, for the addition of an aldehyde/ketone to an alkene or alkyne. Further results and discussion of this approach are given in Chapter 3.

**Figure 2.10.2** Examples of DFT optimized Pt-propylene complexes in bifunctional A) PyBOX; B) PheBOX; and C) Lockamine catalysts
3.1 Introduction to Dual Catalysis with Group 10 metal-PyBOX Complexes

Our previous unsuccessful attempts at adding aldehydes and ketones to alkenes and alkynes using a Pd/Pt(II)-PyOX or Cu(I) systems to activate unsaturated electrophiles led us to explore alternatives catalytic systems. A dual catalyst system was originally avoided due to the potential for the Lewis acid and Lewis basic catalytic sites to poison each other. The desired alkene activation via coordination to the \( \pi \)-acid metal would be in competition with direct coordination of the amine co-catalyst or enamine. Initially inspired by reports from Gagne\(^{65,149}\) that utilized a Pt-PyBOX complex for activation of alkenes, we hypothesized that it might be possible to adapt this system into a dual catalytic system suitable for additions of carbonyl compounds to alkenes or alkynes (Figure 3.1). Additionally, our previous DFT studies on tridentate bifunctional scaffolds suggested the PyBOX scaffold would result in more exergonic alkene complexation to group 10 metals than alternative tridentate scaffolds (“Lockamine” and PheBOX). We hypothesized that a dual catalytic approach could be an improvement over our previously tested bifunctional PyOX and Cu(I) systems in that 1) tridentate PyBOX ligands have been established to form stable rigid structures with group 10 metals, 2) facile synthesis of tridentate ligands or utilizing commercially available ligands, 3) variation of the \( \pi \)-acid and organocatalyst can be varied and optimized independently from each other. We hypothesize that substituents on the oxazoline ligands could be modulated to form a well-defined binding pocket in addition to using bulkier organocatalysts could prevent catalyst poisoning of the \( \pi \)-acid by the enamine and/or organocatalyst. A summarization of some of the work
discussed here resulted in a publication titled “Computationally-guided investigation of dual amine/pi Lewis acid catalysts for direct additions of aldehydes and ketones to unactivated alkenes and alkynes.”

Figure 3.1 Proposed dual catalytic approach for the addition of carbonyl compounds to alkenes using PheBOX and PyBOX scaffolds.

The proposed dual catalytic reaction as given in Figure 3.1 would proceed very similarly to the bifunctional catalyst systems (Chapter 2). An amine co-catalyst would activate an aldehyde or ketone via enamine formation (and loss of water), while the alkene/alkyne would be activated by the π-acidic metal via coordination. Outer sphere attack of the enamine on the coordinated alkene/alkyne would generate an organometallic intermediate (Figure 3.1, middle). Subsequent iminium hydrolysis and protodemetalation would yield the alkylation product and regenerates the active catalyst. In both the bifunctional and dual catalytic systems, we hypothesized that the branched alkylation products would be selectively formed, which is consistent with an outer sphere attacks of nucleophiles on alkenes coordinated to group 10 metals.

In the design of pincer ligands with selective binding pockets, analogs with varied substituents were explored. We hypothesized that pincer ligands with larger substituents...
(R' and R") would be more selective for binding alkenes and alkynes over amine co-catalysts or bulkier enamines due to steric constraints. Substituents at R' and R" could also be varied to selectively recognize terminal alkenes or 1,2-disubstituted E-alkenes by sterically blocking 2, 3, or 4 quadrants around the coordination site. Ligands with $C_2$-symmetry or ligands with one open quadrant may have bulky substituents that extend far enough out to affect the approach of a prochiral or chiral enamine to permit enantioselective reactions. Initially, terminal alkenes and alkynes were tested with ketones and aldehydes and several secondary amine co-catalysts, including pyrrolidine, proline, Jørgensen’s pyrrolidine, and MacMillan’s imidazolidinone (Figure 3.2). We hypothesize that the bulkier amines, such as Jørgensen’s pyrrolidine or MacMillan’s imidazolidinone, will be less prone to direct coordination and poisoning of the metal.

**Figure 3.2** Common organocatalysts for enamine reactions.

![Common organocatalysts for enamine reactions](image)

The final component to consider with these tridentate systems is the electronics around the metal. As previously discussed with the analogous bifunctional pincer scaffolds, the PyBOX ligands could be used to form biscationic complexes with an alkene or alkyne, which are more active towards nucleophilic addition. However, this enhanced electrophilic character and hardness on the metal center can lead to softer alkene and alkyne ligands being displaced by harder ligands and/or nucleophiles. Addition of electron withdrawing or donating groups to the pyridine moiety of the ligand, or using more electron rich pyridyl-bis(imidazoline) ligands, would allow us to tune the electrophilicity and strength of the coordinated alkene or alkyne. Syntheses of PheBOX and PyBOX complexes with varied substituents have been reported for other applications, and it was found that
asymmetric cyclopropanations of olefins were affected by the electronics of 4-substituted PyBOX ruthenium catalysts.\textsuperscript{155}

Our initial studies focused on a Pt-PyBOX complex to take advantage of the fact that platinum-olefin complexes are more stable than with other group 10 metals, which would assist with spectroscopic studies (e.g. NMR) on potential intermediates. Additionally, the protodemetalation of Pt(II) intermediates is known to be more facile than with analogous palladium complexes.\textsuperscript{156} However, nickel provides the great advantage of being approximately 3600x cheaper than platinum at current prices. We additionally wished to explore other transition metals with PyBOX ligands as potential Lewis acid catalysts.

### 3.2 DFT Optimization of Dual Catalyst Combinations

In order to study our proposed dual catalytic system before extensive reaction screening, we again used DFT calculations to computationally explore ligand, metal, and organocatalyst combinations that would minimize the likelihood of the competing Lewis acidic and Lewis basic catalysts from poisoning each other. In addition to performing DFT calculations on the C-C bond formation step, we also turned our attention towards comparing the Gibbs free energies of alkene and alkyne complexation between different metals (i.e. Ni, Pt, and Pd) with variable ligands and electronic environments (Figure 3.2.1). We hypothesized that even if the C-C bond formation was exergonic for a particular scaffold, an endergonic alkene or alkyne complexation could also be a factor inhibiting catalytic activity, i.e. the complete catalytic cycle should ultimately be considered. Complexation to the \(\pi\)-acid in our dual catalyst systems is especially important; the pincer complexes needs to have a selective binding pocket favoring coordination of smaller alkenes/alkynes, while blocking coordination of bulkier aminocatalysts or enamines.
Through comparing the Gibbs free energies of alkene, alkyne, aminocatalyst, and enamine coordination to the pincer complexes with varying steric and electronic environments, we sought to identify suitable catalyst combinations that could promote alkene/alkyne coordination and subsequent nucleophilic addition of the enamine to the coordinated olefin, while avoiding poisoning of the metal by the organocatalyst.

Figure 3.2.1 Key intermediates in our proposed dual catalytic approach

The first set of DFT calculations were performed to predict how changes in the electronic environment around the \( \pi \)-acid would effect propylene/acetylene coordination and C-C bond formation: the presence of an electron-donating group (EDG) \( X = \text{NMe}_2 \) at the 4-position of the pyridine; flanking oxazoline versus imidazoline ligands; and bis-methyl or isopropyl substituents on the oxazolines or imidazolines (Table 3.2.1). The addition of the enamine derived from acetone and pyrrolidine was used for our initial studies, with Ni(II) and Pt(II) catalyst complexes. For our DFT calculations, structures were again visualized and underwent a pre-optimization with molecular mechanics in Avogadro before geometries were further optimized and energies were calculated using DFT via Gaussian 09 software. Propylene complexation was found to be unfavorable with the bulky tetramethyl-substituted nickel complexes (entries 1–3), whereas acetylene complexation was favorable (entry 2). The relatively less sterically congested isopropyl-substituted nickel complexes also led to favorable propylene and acetylene complexation (entries 4–
6). With the platinum complexes, propylene complexation was found to be favorable for the tetramethyl-, isopropyl-, and tertbutyl-complexes (entries 7–14).

Table 3.2.1 DFT calculations of alkene complexation and iminium adduct formation

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<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>Y</th>
<th>Propylene complexation, ΔG₁ (kcal/mol)</th>
<th>or (acetylene) ΔG₂ (kcal/mol)</th>
<th>Enamine addition ΔG₂ (kcal/mol)</th>
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<td>Me</td>
<td>H</td>
<td>O</td>
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<td>O</td>
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<td>NH</td>
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<td>Me</td>
<td>H</td>
<td>O</td>
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<td>-21.2 (–44.6)</td>
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<td>H</td>
<td>NH</td>
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</tr>
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<td>H</td>
<td>O</td>
<td>-2.3</td>
<td>-16.1</td>
<td></td>
</tr>
</tbody>
</table>

*All calculations used the functional B3PW91 and basis set LANL2DZ for metals, and the basis set cc-pVDZ for all other atoms. DCM was the solvent. †Values in parentheses are for acetylene. ‡ΔG = –11.5 (entry 11) and –3.7 (entry 13) for 5-phenyl-1-pentyne complexation.

C-C bond formations to give the iminium adduct intermediates 3.3 were calculated to be exergonic for both Ni²⁺ and Pt²⁺ in all cases. The electron-donating group (EDG) dimethylamine (entries 1, 4, 7, 10, and 13) was found to have a beneficial effect on alkene coordination with platinum (e.g. entries 10 vs. 11), which initially led us to prioritize its use in our calculations in Table 3.2.1. However, it attenuated the favorable free energy changes of the enamine addition (C-C bond formation), which is not surprising considering the alternate direction of electron flow between the two steps. For synthetic simplicity, we
used the unsubstituted PyBOX complexes in our screening experiments (*vide infra*). The more electron rich pyridine-bis(imidazoline) systems gave relatively less favorable energetics for iminium adduct formation and propylene complexation (entries 3, 6, 9, and 12).

In the design of PyBOX ligands with selective binding pockets, the substituents (R, R') on the oxazolines can be varied to selectively recognize smaller alkenes or alkynes, while making bulkier enamine organocatalysts less prone to direct coordination and metal poisoning (*Figure 3.2.1*). Any interaction between the organocatalyst and Lewis acid should also be rapidly reversible. Another possible concern is that the metal could also be poisoned via aldehyde/ketone binding, instead of the alkene/alkyne; however, we were primarily interested in studying Pt or Pd systems, and presumed that this interaction was more likely for the harder, more oxophilic Ni(II) salts. This notion is consistent with some of DFT calculations that we have performed on coordination of carbonyls to group 10 metal complexes. For our subsequent calculations, the 4-NMe$_2$-PyBOX scaffold was selected due to its improved energetics for propylene binding. We considered a variety of secondary amine co-catalysts, including pyrrolidine, $\alpha$-methyl-L-proline, Jørgensen’s pyrrolidine 3.8$^{152}$ and MacMillan’s $t$-Bu-imidazolidinone 3.9$^{44}$ DFT calculations were performed on combinations of PyBOX, organocatalyst, alkene (propylene and ethylene), and metal (Ni, Pd, Pt) to determine the energetics of alkene coordination versus poisoning of the metal via organocatalyst coordination (*Table 3.2.2*).

As expected, pyrrolidine was calculated to fit into the binding pocket of all complexes and had very favorable (though undesired) metal coordination (*Table 3.2.2*, column 8). While the bulkier $\alpha$-methyl-L-proline had diminished energetics for coordination, it was also predicted to have favorable coordination with every system (column 9), and coordination via the carboxylate is also possible (not calculated). The
most promising organocatalysts were predicted to be Jørgensen’s pyrrolidine 2.6 and MacMillan’s imidazolidinone 2.7.

Table 3.2.2 DFT calculations for desired alkene/alkyne vs undesired amine coordination

<table>
<thead>
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<th>Entry</th>
<th>M</th>
<th>R</th>
<th>R’</th>
<th>X</th>
<th>Basis Set</th>
<th>Intermolecular Poisoning, $\Delta G_1$ (kcal/mol)</th>
<th>Coordination, $\Delta G_2$ (kcal/mol)</th>
</tr>
</thead>
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<td>Me</td>
<td>NMe₂</td>
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<td>−15.8</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>Ni</td>
<td>i-Pr</td>
<td>H</td>
<td>NMe₂</td>
<td>cc-pVDZ</td>
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<td>1.5</td>
</tr>
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<td>Def2-</td>
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<td>1.5</td>
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<tr>
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<td>Me</td>
<td>NMe₂</td>
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<td>NMe₂</td>
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<td>−20.2</td>
<td>1.5</td>
</tr>
<tr>
<td>19²</td>
<td>Pt</td>
<td>i-Bu</td>
<td>H</td>
<td>NMe₂</td>
<td>cc-pVDZ</td>
<td>−2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>20</td>
<td>Pt</td>
<td>i-Bu</td>
<td>H</td>
<td>NMe₂</td>
<td>Def2-</td>
<td>5.4</td>
<td>1.5</td>
</tr>
<tr>
<td>21²</td>
<td>Pt</td>
<td>i-Bu</td>
<td>H</td>
<td>NMe₂</td>
<td>cc-pVDZ</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>22</td>
<td>Pt</td>
<td>i-Bu</td>
<td>H</td>
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<td>cc-pVDZ</td>
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<tr>
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<td>Ph</td>
<td>H</td>
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<td>−26.3</td>
<td>1.5</td>
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<tr>
<td>24²</td>
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<td>Ph</td>
<td>H</td>
<td>NMe₂</td>
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<td>−10.0</td>
<td>1.5</td>
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<tr>
<td>25</td>
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<td>i-Bu</td>
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<td>H</td>
<td>cc-pVDZ</td>
<td>−0.3</td>
<td>1.5</td>
</tr>
<tr>
<td>26²</td>
<td>Pt</td>
<td>i-Bu</td>
<td>H</td>
<td>H</td>
<td>cc-pVDZ</td>
<td>−0.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*Calculations used the functional B3PW91, basis set LANL2DZ for metals, and basis set cc-pVDZ for all other atoms, and DCM as solvent, unless otherwise noted. *An UltraFine integration grid was used instead of the default Gaussian 09 FineGrid. NA = Not available—the calculation did not converge. *NO₂Me used as the solvent.
Lewis acid poisoning by these organocatalysts was calculated to be unfavorable with the bulkiest PyBOX systems (i.e. those with bis-\(t\)-Bu or tetramethyl substituents: entries 1, 4, 5, 8, 10, 13, and 18, columns 10 and 11). Coordination of propylene and ethylene in these systems was typically favored, with some exceptions, most notably the bulkier Ni complexes (entries 1, 3, and 4). Taking into account both organocatalyst poisoning and olefin coordination, the DFT calculations predicted MacMillan’s organocatalyst with \((4\text{-NMe}_2\text{-}t\text{-Bu-PyBOX})\text{Pt}^{2+}\) to be the most promising combination, due to the calculated endergonic coordination of the organocatalyst \(2.9\) \(+2.0\) kcal/mol) and the exergonic coordination of propylene \((-4.2\) kcal/mol) and ethylene \((-7.1\) kcal/mol) (Table 3.2.2, entry 18; Figure 3.2.2).

**Figure 3.2.2** Optimized structures for optimal combinations from Table 3.2.2 (entry 18). Propylene coordination to the Pt\(^{2+}\) complex (left) is calculated by DFT to be favorable, and organocatalyst coordination (right) unfavorable.

\[
\Delta G = -4.2\text{ kcal/mol} \quad \Delta G = 2.0\text{ kcal/mol}
\]

Wheeler recently noted that the default Gaussian09 (75,302) grids can result in errors greater than 5 kcal/mol in relative free energies for several systems.\(^{157}\) Thus, we repeated our calculations using a finer (99,590) grid size for several intermediates (Table 3.2.2, entries 15, 19, and 24) and found the grid size to have relatively modest effects; importantly, it did not change the promising energetics of \((t\text{-Bu-PyBOX})\text{Pt}^{2+}\) and
MacMillan's organocatalyst for use in the desired reaction (entry 18). The diastereomeric "poisoned" complex composed of the enantiomeric (t-Bu-PyBOX)Pt$^{2+}$ and 2.9 was calculated to be insignificantly slightly lower in energy (+2.1 kcal/mol versus +2.0 kcal/mol in entry 18).

For select entries of interest, additional DFT calculations were made by performing a single-point correction using the larger basis set Def2-QZVPP in an attempt to increase the accuracy of these predicted energies (Table 3.2.2, entries 3, 5, 16, and 20). In the case of the (i-Pr-PyBOX)-Ni$^{2+}$ complex, the complexation of ethylene and propylene was no longer exergonic (entry 3). However, the calculations on the i-Pr- and (t-Bu-PyBOX)-Pt$^{2+}$ complexes found relatively minor differences between basis sets for ethylene and propylene complexation, but organocatalyst 3.8 poisoning of the (t-Bu-PyBOX)-Pt$^{2+}$ complex was now computed to be unfavorable (+5.4 kcal/mol) and similar to poisoning by organocatalyst 3.9 (+5.3 kcal/mol) (entry 20). Additionally, DFT calculations were performed taking into consideration alternative solvents. This became important since the bis-cationic PyBOX-metal complexes were found to have poor solubility in less polar solvents. Using NO$_2$Me instead of DCM as the solvent (entries 17 and 21), the energies of alkene complexation were computed to be significantly different. Propylene was no longer computed to be exergonic for complexation to the (t-Bu-PyBOX)-Pt$^{2+}$ complex (entry 21, column 13). However, complexation of a terminal alkyne (5-phenyl-1-pentyne) or internal alkyne (6-phenyl-2-hexyne) to the (t-Bu-PyBOX)-Pt$^{2+}$ complex were found to still be exergonic (Table 3.2.2, column 14). Additionally, coordination of MeCN to the (t-Bu-PyBOX)-Pt$^{2+}$ was computed to be $-15.3$ kcal/mol when using the PCM solvation model with DCM. This suggests that using a coordinating solvent could also act as a competing ligand for the π-acid.
In addition to the organocatalysts or solvent acting as competing ligands for the π-acid, the electron-rich enamine intermediates could also coordinate competitively, as observed with our previously reported Cu(I)-phenylacetylene complex (Figure 2.6.2). We hypothesized that a bulkier enamine would coordinate less favorably to the sterically congested π-acidic metal than a smaller alkene. To test this hypothesis, we performed ground state DFT calculations for the addition of enamines 3.10 or 3.11 to the (t-Bu-PyBOX)-Pt$^{2+}$ ethylene complex (Figure 3.2.3). The bulkier enamine derived from 3.9 and phenylacetaldehyde (3.10) was calculated to be very endergonic (+11.8 kcal/mol) for the displacement of ethylene, while displacement with the smaller pyrrolidine-derived enamine (3.11) was found to be exergonic (−2.3 kcal/mol). This result suggested that a reaction using the smaller pyrrolidine would be unlikely. However, a catalytic reaction using the bulkier imidazolidinone organocatalyst may be feasible as neither the imidazolidinone organocatalyst, nor its enamine intermediate, were predicted to have more favorable interactions with the Pt$^{2+}$ complex than ethylene.

### 3.3 Synthesis and NMR Studies of PyBOX-Pt Complexes

Based on our DFT calculations, we decided to pursue the synthesis of Pt complexes from the tetramethyl- and t-Bu-PyBOX ligands 3.16a–b (Scheme 3.3.1). While the NMe$_2$ substitution at the 4-position of the PyBOX was calculated to be slightly more
exergonic for ethylene complexation and C-C bond formation, we did not see any significant advantage of this ligand, which requires a lengthier synthesis. Therefore, we proceeded to prepare the parent PyBOX ligands. Treatment of 2,6-pyridinedicarboxylic acid with oxalyl chloride afforded 3.14 in excellent yield. Coupling of 3.14 with 2-amino-2-methyl-1-propanol or L-tert-leucinol yielded 3.15a–b. Oxazoline formation using Deoxo-Fluor\textsuperscript{138-139} proceeded smoothly to yield PyBOX ligands 3.16a–b. The Pt(II) precatalyst from ligand 3.17a was prepared according to a protocol adapted from that reported by Gagné.\textsuperscript{65} Treatment of 3.16a with Pt(DMSO)\textsubscript{2}I\textsubscript{2}, prepared from a procedure reported by Vos,\textsuperscript{158} and one equivalent of AgBF\textsubscript{4} at 70 °C, yielded the cationic complex 3.17a in 88% yield. Elevated temperatures were found to be crucial for successful complexation. Attempts to isolate the cationic Pt(II) precatalyst from ligand 3.16b were unsuccessful.

Prior to screening dual catalytic reactions, we wanted to confirm via NMR that the optimal organocatalyst 3.9 identified in our DFT calculations (Figure 3.2.3) would not effectively compete with ethylene for complexation. For all of our NMR experiments and reaction screens, we generated the bis-cationic (t-Bu-PyBOX)Pt\textsuperscript{2+} ethylene complex in situ by heating a solution of 3.17a with one equivalent of AgBF\textsubscript{4} in CD\textsubscript{3}NO\textsubscript{2} at 40 °C for 1 h, and filtering off the silver salts using a syringe filter before bubbling ethylene into the solution. A downfield shift in the \textsuperscript{1}H NMR signal for ethylene was observed, from 5.39 ppm
to 5.47 ppm in CD$_3$NO$_2$, which is consistent with the formation of Pt-ethylene complex 3.18 (Figure 3.3.1). To the ethylene complex was added one equivalent of organocatalysts 3.8, 3.9, or MacMillan's imidazolidinone organocatalyst 3.19 (Figure 3.3.1). Upon the addition of 3.8 and 3.19, ethylene shifted back upfield to its original position in the $^1$H NMR, thus suggesting coordination of these organocatalysts is highly favored over ethylene coordination. However, when 3.9 was added, the $^1$H NMR peak for ethylene did not shift completely back to its original position and only shifted from 5.47 ppm to 5.44 ppm. This is consistent with at least a measurable fraction of ethylene binding to the platinum complex in the presence of the bulkier t-Bu imidazolidinone 3.9.

Figure 3.3.1 NMR study of the displacement of ethylene with pyrrolidine and imidazolidinone (3.9) organocatalysts

These findings are in agreement with our DFT calculations, as coordination of 3.8 to 3.17a was computed to be −0.2 kcal/mol, versus ethylene complexation (defined as 0 kcal/mol), while coordination of 3.9 to 3.17a was computed to be +6.0 kcal/mol (Table 3.2.2, entry 26). Therefore, 3.9 could be promising for use as an organocatalyst that does not poison the metal center. Additionally, in situ formation of the parent PyBOX-Pt(II) complex was confirmed via mass spectroscopy. After heating the solution of 3.17a with one equivalent of AgBF$_4$ in nitromethane at 40 ºC for 1 h, excess MeCN was added prior to using a direct inject LC-MS method with electrospray ionization. The m/z of 282.60 corresponds to the PyBOX-Pt(II)-MeCN complex (M$^{2+}$/2). With the results of these DFT calculations and spectroscopic characterizations in hand, we began reaction screening
using MacMillan’s imidazolidinone organocatalyst and t-Bu-PyBOX-Pt as the Lewis acid catalyst.

### 3.4 Dual Catalyst Intermolecular Reaction Screening with t-Bu-PyBOX-Pt Complex

With our DFT calculations predicting that the combination of a bulky t-Bu-PyBOX-Pt metal complex coupled with a bulky imidazolidinone organocatalyst would prevent catalyst poisoning and promote alkene/alkyne binding, we set out to screen a variety of alkenes/alkynes and carbonyl substrates for an intermolecular addition reaction. Although the majority of our calculations were performed on coordination of small alkenes (ethylene and propylene) to save on computational time, a selection of larger unsaturated alkyne substrates (Table 3.2.2, column 14) and 4-phenyl-1-butene (−6.0 kcal/mol) were also computed to have favorable energies of complexation to a t-Bu-PyBOX-Pt metal complex. We wished to gather further evidence for alkene or alkyne complexes with these larger substrates (Scheme 3.4.1), whose resulting addition products would provide easier UV detection and isolation. To accomplish this, reaction screens were set up in CD$_3$NO$_2$ to permit observation of alkene/alkyne binding via NMR. We were limited in choice of solvent to nitromethane, due to the insolvability of the in situ generated bis-cationic t-Bu-PyBOX-Pt(II) complex in less polar solvents.

**Scheme 3.4.1 Addition of enamines to Pt-PyBOX alkene/alkyne complexes**

A) AgBF$_4$ (1 eq)  
CD$_3$NO$_2$, 30 °C 1 h  
B) Alkene (3.21 bubbled; 3.22: 1eq)  
Alkyne (3.23-3.26: 1 eq)  
C) Enamine (3.27 or 3.28: 1 eq)  
Products?
Upon the addition of alkenes/alkynes 3.22–3.26 to the \textit{in situ} generated (\textit{t}-Bu-PyBOX)-Pt(II) complex 3.17a (see chapter 5 for details) in CD$_3$NO$_2$, there were no observed $^1$H NMR shifts for the PyBOX ligand protons or the protons in any of the substrates (Scheme 3.4.1). While this result doesn’t rule out the possibility of catalytic activity, it does suggest that the abundance of bound alkene or alkyne is small enough that it is not detectable by $^1$H NMR. Following $^1$H NMR analysis, preformed enamine 3.27 was added as a solution in CD$_3$NO$_2$ and samples were again analyzed by $^1$H NMR. After the addition of enamine 3.27, no observed displacement of ethylene was observed and no chemical shifts were observed in either the ligand or enamine for any of the samples. These results align with our DFT calculations (Figure 3.2.3) that predicted enamine 3.27 to have unfavorable energetics of catalyst poisoning (+11.8 kcal/mol).

\textbf{Scheme 3.4.2} Reaction screening with stoichiometric Pt complex 3.17a

The samples were heated at 80 °C for 24 h (50 psi of ethylene with 3.21) and analyzed directly via GC-MS, which indicated no detectable alkylation or alkenylation reactions. For comparative purposes, analogous reactions were also run with less hindered enamine 3.28. The samples immediately turned brown upon addition of enamine 3.28. We hypothesized that 3.28 underwent a redox reaction with the bis-cationic PyBOX-Pt(II) complex to generate a stabilized radical cation intermediate. In any regard, enamine 3.28 was found experimentally to have undesirable interactions with 3.17a, which was predicted by our DFT calculations (–2.3 kcal/mol, Figure 3.2.3). We hypothesize that the
lack of reactivity of 3.18 with 3.27 may be due to 3.27 being stabilized by conjugation and make C-C bond formation less favorable. Unfortunately, we were unable to isolate less stabilized enamines formed from butyraldehyde and the bulky imidazolidinone organocatalyst 3.9.

With the lack of success when using a preformed stabilized enamine, we next tested our prioritized dual catalytic system for the direct addition of aldehydes/ketones to alkenes and alkynes. Ethylene was selected due to its observed coordination to our PyBOX-Pt(II) complex, and 6-phenyl-2-hexyne (3.29) was chosen as a representative alkyne substrate (Scheme 3.4.2). The samples were heated at 80 ºC for 24 h (50 psi for samples with ethylene) and analyzed directly via GC-MS. Only starting material was detected for all samples. The lack of desired products for the reactions with ethylene was confirmed by comparison to the GC trace of commercially available 2-ethylhexanal.

**Scheme 3.4.3 Reaction screening using acetal substrate**

![Reaction screening using acetal substrate](image)

While our reaction screening afforded no detectable desired alkylation products, there was the possibility that we were forming the intermediate PyBOX-Pt-alkyl* complexes and unable to detect these intermediates via GC-MS. Such complexes may require an acid or proton shuttle to facilitate protonolysis.65 We screened a range of additives, including proton donors and bulky bases, for the addition of n-hexanal to ethylene using stoichiometric Pt-complex 3.17a and organocatalyst 3.9 (Table 3.4.1).
After 20 h, the reactions were analyzed via GC-MS. For all of the additives except water, only a trace amount of aldol self-condensation byproduct from \( n \)-hexanal was detected, in addition to unreacted substrates.

### Table 3.4.1 Additive screening for direct addition of hexanal to ethylene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Result(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>benzoic acid</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>( p )-TsO-H(_2)O</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>acetic acid</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>4-nitrophenol</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>Ph(_2)NH</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>2,6-di-tert-butylpyridine</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>A</td>
</tr>
</tbody>
</table>

\(^a\)NR = no reaction detected by GC-MS. A = trace amount of aldol condensation byproduct from \( n \)-hexanal was detected.

### 3.5 Dual Catalyst Intramolecular Reaction Screening

We next tested our dual catalytic system for the carbocyclization of formyl alkyne 3.31 to determine whether the C-C bond formation could alternatively proceed in an intramolecular fashion (Table 3.5.1). Gratifyingly, reaction screening performed by Jacob Porter found that alkyne 3.31 cyclized to afford enal 3.32 in 84% NMR yield when initially using 50 mol% of the t-Bu-PyBOX-Pt complex and organocatalyst 3.9 (entry 1). Other less hindered organocatalysts were tested and found to have negligible activities (entries 2–4). This finding was in agreement with our DFT predictions and \(^1\)H NMR experiments that these would have favorable coordination with the \( \pi \)-Lewis acid and outcompete the binding of an alkene/alkyne substrate.
Table 3.5.1 Intramolecular reactions with formyl alkyne 3.31

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid(s)</th>
<th>Lewis acid(s) (mol%)</th>
<th>Organocatalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.17a, AgBF₄</td>
<td>50</td>
<td>3.9 (50 mol%)</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>3.17a, AgBF₄</td>
<td>50</td>
<td>3.8 (50 mol%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>3.17a, AgBF₄</td>
<td>50</td>
<td>cyclohexylamine (50 mol%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>3.17a, AgBF₄</td>
<td>50</td>
<td>pyrrolidine (50 mol%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>3.16a, Pd(CH₃CN)₄(BF₄)₂</td>
<td>50</td>
<td>3.9 (50 mol%)</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>AgBF₄</td>
<td>50</td>
<td>3.9 (50 mol%)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>0</td>
<td>none</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>3.17a, AgBF₄</td>
<td>50</td>
<td>none</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>0</td>
<td>none</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>3.17a</td>
<td>50</td>
<td>3.9 (50 mol%)</td>
<td>11</td>
</tr>
</tbody>
</table>

a) Reactions were performed with screening procedure A, unless otherwise noted. See Experimental Section for details.

b) Reaction screening procedure B was used.
c) Yields measured (n = 1) by ¹H NMR with pentachloroethane as an internal standard; NR = No desired product detected by GC-MS.

This specific cyclization reaction was also reported by Kirsch using (PPh₃)AuSbF₆ and diisopropylamine catalysts, and we prepared an authentic sample of the product 3.32 using a Cu(OTf)₂, BINAP, and cyclohexylamine catalyst system reported by Michelet.

Switching to a palladium(II) precatalyst generated in situ from 3.16a and Pd(CH₃CN)₄(BF₄)₂, was found to be less effective with only a 13% yield (entry 5). Additionally, all control reactions had either negligible (<5%) or no detectible 3.32 when any combination of precatalyst 3.17a or organocatalyst 3.9 were omitted from the reaction mixture (entries 6–9). Interestingly, the reaction still produced some desired product when run without the addition of AgBF₄ to pre-form the bis-cationic platinum complex (entry 10). We presume that the alkyne is capable of displacing the iodide ligand (or the iodide binding is quite reversible), allowing the reaction to proceed to some extent (11% NMR yield). With a positive intramolecular reaction in hand, we next chose to test lower catalyst loadings to
optimize the reaction (Table 3.5.2). For these studies, reactions were run in CD$_3$NO$_2$ in order to measure NMR yields in situ to achieve the most accurate measurement of yield without potentially degrading the enal product. Yields were measured by $^1$H NMR using pentachloroethane as an internal standard.

Table 3.5.2 Catalyst loading studies for intramolecular reaction with formyl alkyne 3.31

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>32 (%)$^b$</th>
<th>33 (%)$^b$</th>
<th>32+33$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>29</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>32</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>46</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>79</td>
<td>0</td>
<td>79</td>
</tr>
</tbody>
</table>

$^a$Reactions were performed using intramolecular reaction screening procedure C. $^b$Yields measured (n = 1) by $^1$H NMR using pentachloroethane as an internal standard.

This procedure differs from our initial studies (Table 3.5.1) where samples were filtered through a silica plug before adding the internal standard and subsequent measurement of the yield by $^1$H NMR. These in situ measurements showed peaks consistent with exocyclic alkene 3.33, which isomerized to the more stable alkene 3.32 over the 24 h reaction time. Exocyclic alkene 3.33 was never observed when crude reaction mixtures were first filtered through a silica plug before analysis. Yields are reported as the sum of products of the desired C-C bond formation (3.32 + 3.33). Lower catalyst loadings of 1 and 5 mol% (entries 1 and 2) produced similar results (34 and 39% yields respectively). Raising the catalyst loading to 10% (entry 3) produced a significant increase in yield to 51%. The optimal result came from a metal catalyst loading of 20 mol% (entry 4, 79% yield of enal 3.32), which is comparable to the 84% yield when using a 50 mol% catalyst loading (Table 3.5.1).
Up to this point, all reactions were run at elevated temperatures with an in situ generated bis-cationic complex generated from Pt complex 3.17a. We next explored the effect of temperature on reactions using either the bis- or mono-cationic Pt complexes that previously showed reactivity (Table 3.5.1). The reaction run at ambient temperature with Pt complex 3.17a (20 mol%) and organocatalyst 3.9 (20 mol%) resulted in only trace formation of enal 3.32 and exocyclic alkene 3.33 (Table 3.5.3, entry 1). However, raising the temperature to 70 °C gave a 62% yield for the sum of both isomers (entry 2). When 3.17a was treated with 1 equivalent of AgBF$_4$ to generate the bis-cationic complex in situ prior to the addition of formyl alkyne 3.31, the reaction proceeded to quantitative yield at ambient temperature (entry 3).

![Diagram](image)

**Table 3.5.3** Temperature and counterion study for intramolecular reaction with 3.31

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Temperature (°C)</th>
<th>3.32 (%)</th>
<th>3.33 (%)</th>
<th>3.32+3.33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_4$, I</td>
<td>22</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>BF$_4$, I</td>
<td>70</td>
<td>50</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>3$^a$</td>
<td>(BF$_4$)$_2$</td>
<td>22</td>
<td>63</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>4$^a$</td>
<td>(BF$_4$)$_2$</td>
<td>70</td>
<td>79</td>
<td>0</td>
<td>79</td>
</tr>
</tbody>
</table>

$^a$Prior to the addition of formyl alkyne 3.31, complex 3.17a was dissolved in CD$_3$NO$_2$ (0.250 mL). This solution was transferred to an aluminum foil wrapped 1.5 mL HPLC vial containing AgBF$_4$. The solution was placed in an oil bath heated to 60 °C before being syringe filtered into another 1.5 mL HPLC vial. Addition of the substrate 3.31 and organocatalyst 3.9 followed. $^b$Yields measured (n = 1) by $^1$H NMR using pentachloroethane as an internal standard.

Reacting the pre-formed bis-cationic complex at 70 °C led to full conversion of alkyne 3.31 exclusively to enal 3.32 (entry 4). Formation of the more stable alkene 3.32 after 24 h was presumably due to isomerization of 3.33 at the elevated temperature. This study demonstrated that catalyst turnover was possible, and pre-generation of the highly reactive bis-cationic platinum complex was not necessary to achieve a catalytic reaction.
We had previously limited our choice of solvent to the polar non-coordinating solvent nitromethane due to the lack of solubility of the bis-cationic platinum complex formed after treatment with AgBF₄.

### Table 3.5.4 Solvent study for intramolecular reaction with 3.31

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>32 (%)</th>
<th>33 (%)</th>
<th>32+33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1²</td>
<td>CD₂Cl₂</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2³</td>
<td>THF-d₆</td>
<td>14(33)</td>
<td>7 (0)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>3³</td>
<td>CD₃CN</td>
<td>7 (14)</td>
<td>5 (6)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>4⁴</td>
<td>DMSO-d₆</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5⁴</td>
<td>CDCl₃</td>
<td>34 (46)</td>
<td>13 (14)</td>
<td>47 (60)</td>
</tr>
<tr>
<td>6ᵃᵇ</td>
<td>CD₃NO₂</td>
<td>50</td>
<td>12</td>
<td>62</td>
</tr>
</tbody>
</table>

*²Reaction only run for 24 h. ³Reaction heated to 70 °C. ⁴Yields measured (n = 1) by ¹H NMR using pentachloroethane as an internal standard. ⁵Yields in parenthesis measured after 48 h.

Given our observed catalytic activity of mono-cationic Pt complex 3.17a, Jacob Porter screened the intramolecular reaction in alternative deuterated solvents to allow direct measurement of ¹H NMR yields (Table 3.5.4). Interestingly, the reaction was found to tolerate a variety of less polar and/or coordinating solvents (entries 2, 3, and 5). Chloroform was demonstrated to be a promising solvent (entry 5) as a yield of 60% could be achieved after 48 h, which was comparable to nitromethane (62%) after 24 h. Jacob also explored the effect of changing the steric bulk on the alkyl substituents of the PyBOX ligand (Table 3.5.5). The t-Bu-PyBOX ligand (entry 1) gave a yield of 53%. This was slightly lower than previously observed (Table 3.5.3, entry 4) perhaps due to the decrease in reaction time. Less sterically hindered i-Pr- and Ph-PyBOX complexes also promoted productive reactions at 71% and 54% yields respectively (entries 2 and 3). Although our previously discussed calculations predicted that combination of organocatalyst 3.9 and (t-
Bu-PyBOX)-Pt(II) complex 3.17a would be preferred for favorable ethylene binding, in this intramolecular addition to an alkyne, less sterically hindered PyBOX complexes were tolerated.

### Table 3.5.5 PyBOX ligand study for intramolecular reaction on 3.31

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>32 (%)b</th>
<th>33 (%)b</th>
<th>32+33 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-Bu</td>
<td>40</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>50</td>
<td>21</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>42</td>
<td>12</td>
<td>54</td>
</tr>
</tbody>
</table>

*aPrior to the addition of formyl alkyne 3.31, the Pt-PyBOX complex was dissolved in CD$_3$NO$_2$ (0.250 mL). This solution was transferred to an aluminum foil wrapped 1.5 mL HPLC vial containing AgBF$_4$. The solution was placed in an oil bath heated to 60 ºC before being syringe filtered into another 1.5 mL HPLC vial. Addition of the substrate 3.31 and organocatalyst 3.9 followed. bYields measured by $^1$H NMR using pentachloroethane as an internal standard, as an average of two runs.

#### 3.6 Intermolecular Direct Alpha Alkenylation of Aldehydes with Terminal Alkynes

With new evidence that *in situ* pre-formation of the bis-cationic Pt-PyBOX complex was not necessary for catalytic activity in an intramolecular reaction (Table 3.5.3), we decided to revisit whether a direct intermolecular alpha alkenylation of an aldehyde could be achieved. We hypothesized that the monocationic Pt$^{2+}$ complex could be more tolerant and less readily poisoned in our intermolecular reaction system. To directly compare to the intramolecular reaction, nitromethane was selected as a solvent for initial testing. A non-alpha branched aldehyde, hexanal 3.34, compatible with organocatalyst 3.9 and terminal alkyne, 5-phenyl-1-pentyne 3.35, were chosen for our model system. We hypothesized alkyne coordination to the Pt-PyBOX complex would be favored for a terminal over internal alkyne. Jacob Porter discovered that when aldehyde 3.34 and terminal alkyne 3.35 were reacted with the mono-cationic Pt complex 3.17a in the
presence of organocatalyst 3.9, enal 3.36 was obtained in 19% yield as determined by $^1$H NMR (Scheme 3.6.1). Isolation and characterization of the resulting enal gave $^1$H/$^{13}$C NMR, HMBC, and HR-MS spectral data consistent with the structure 3.36. A $^1$H–$^1$H NOE experiment is still pending to support the alkene isomer depicted. We were surprised to find that the carbon-carbon bond formation had occurred at the terminal carbon of the alkyne to give the anti-Markovnikov product, which rapidly isomerized to afford 3.36. There were no observable proton peaks for the unisomerized $\beta,\gamma$-unsaturated aldehyde when monitoring the reaction by $^1$H NMR. We postulate that the bulky alkyl groups on the ligand and organocatalyst prevent addition to the internal alkyne carbon.

Scheme 3.6.1 Direct intermolecular addition of aldehyde 3.34 to alkyne 3.35

With enal 3.36 in hand, we were elated to have identified an intermolecular direct addition of an unactivated aldehyde to an unactivated alkyne. However, Jacob Porter’s preliminary solvent screen did not result in any yields above that of the catalyst loading, even after extended reaction time (72 h). We presumed these non-catalytic reactions may be due to the active catalyst not turning over after the first cycle, or catalyst degradation during the reaction. In an effort to generate catalytic turnover, we performed a screen of a wide variety of additives (Table 3.6.1). Acetonitrile was initially chosen as the solvent for the additive study due to its optimal yield in Table 3.6.3. CDCl$_3$ was selected as the solvent for a more extensive additive screen for both cost savings and to determine if catalytic
turnover would be enhanced with an acid additive in a less polar solvent. For these intermolecular reaction screens, 3.17 and chloroform were added to 1.5 mL HPLC vials before the addition of alkyne 3.35, aldehyde 3.34, organocatalyst, and NMR or GC standard as stock solutions. Vials were sealed and heated in an oil bath. In situ $^1$H NMR analysis was performed on crude mixtures. Prior to GC-MS analysis, samples were sent through a silica plug and eluted with DCM. Both the organocatalyst and $\pi$-Lewis acid were necessary to achieve an appreciable yield (Table 3.6.1, entries 9, 11, and 12). In the absence of the organocatalyst, the detectable yield may be attributed to addition via the enol tautomer of $n$-hexanal. Testing of several protic acid additives (entries 3–5, 10, and 14–16) showed that mild acids such as AcOH (entries 3 & 14) or benzoic acid (entry 15) were not found to promote catalyst turnover (Table 3.6.1).

Triflate containing additives were tested (entries 7 and 22–24), yet these additives were found to have no beneficial effects. Use of the stronger acid TFA gave NMR yields of 41% and 71% in MeCN and chloroform respectively (entries 4 and 10). Unfortunately, these reactions were found to generate a mixture of the desired product 3.36 and the aldol condensation byproduct 3.37, with alkene and aldehyde protons overlapping in the $^1$H NMR spectra (within 0.01 ppm), necessitating the use of GC to determine product ratios. In several reaction mixtures, there was a third aldehyde peak observed in $^1$H NMR not attributed to the starting material 3.34 or enal 3.36. This trace product was typically observed in <1%. When using TFA and the organocatalyst without Pt catalyst 17a, this byproduct was observed in 17% yield (entry 14). Attempted isolation of this unknown aldehyde afforded exclusively the self-aldol condensation byproduct 3.37. We hypothesize that the third aldehyde peak observed during our reaction monitoring was the aldol addition product that undergoes dehydration during its isolation.
Table 3.6.1 Additive screening for direct intermolecular addition of aldehyde 3.34 to 3.35

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (1 eq)</th>
<th>Solvent</th>
<th>3.34 (%)</th>
<th>3.36 + 3.37 (%) 24 h (48 h)$^d$</th>
<th>GC Ratio 3.36:3.37</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>CD$_3$CN</td>
<td>16 (29)</td>
<td>99:1</td>
<td>6.2:1</td>
</tr>
<tr>
<td>2$^b$</td>
<td>none</td>
<td>CD$_3$CN</td>
<td>6</td>
<td></td>
<td>1.6:1</td>
</tr>
<tr>
<td>3</td>
<td>AcOH</td>
<td>CD$_3$CN</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>CD$_3$CN</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>pTsOH</td>
<td>CD$_3$CN</td>
<td>&lt;5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>TBAI</td>
<td>CD$_3$CN</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ga(OTf)$_3$</td>
<td>CD$_3$CN</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>CDCl$_3$</td>
<td>54 (36)</td>
<td>8 (13)</td>
<td>99:1</td>
</tr>
<tr>
<td>9$^c$</td>
<td>none</td>
<td>CDCl$_3$</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
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<td>CDCl$_3$</td>
<td>8 (0)</td>
<td>71 (85)</td>
<td>0.1:1</td>
</tr>
<tr>
<td>11$^c$</td>
<td>TFA</td>
<td>CDCl$_3$</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12$^d$</td>
<td>TFA</td>
<td>CDCl$_3$</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13$^{c,d}$</td>
<td>TFA</td>
<td>CDCl$_3$</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>AcOH</td>
<td>CDCl$_3$</td>
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<td>17</td>
<td>1.2:1</td>
</tr>
<tr>
<td>15</td>
<td>benzoic acid</td>
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<td>45</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4-nitrobenzoic acid</td>
<td>CDCl$_3$</td>
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<td>19</td>
<td>2.1:1</td>
</tr>
<tr>
<td>17</td>
<td>NaTFA</td>
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<td>23 (16)</td>
<td>31 (30)</td>
<td></td>
</tr>
<tr>
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<td>CDCl$_3$</td>
<td>39</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>19$^b$</td>
<td>NaTFA</td>
<td>CDCl$_3$</td>
<td>83</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>pTsOH</td>
<td>CDCl$_3$</td>
<td>69</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>TBAI</td>
<td>CDCl$_3$</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Ga(OTf)$_3$</td>
<td>CDCl$_3$</td>
<td>36</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>In(OTf)$_3$</td>
<td>CDCl$_3$</td>
<td>5</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>N(nBu)$_2$OTf</td>
<td>CDCl$_3$</td>
<td>82</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>H$_2$O</td>
<td>CDCl$_3$</td>
<td>89</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>t-BuOH</td>
<td>CDCl$_3$</td>
<td>83</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>PhOH</td>
<td>CDCl$_3$</td>
<td>82</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>4-nitrophenol</td>
<td>CDCl$_3$</td>
<td>80</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>HFIP</td>
<td>CDCl$_3$</td>
<td>80</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Complex 3.17a was dissolved in solvent (0.2 mL) in a 1.5 mL HPLC vial before 3.35 was added via microsyringe. 3.34, organocatalyst 3.9, additive, and pentachloroethane were added as individual solutions in solvent (50 µL). The reactions were heated at 55 ºC for 48 h. Hexanal in CD$_3$CN was added via syringe pump at 8 uL/h for 24 h. $^b$No t-butyl-imidazolidinone organocatalyst added. $^c$No tBu-PyBOX-Pt complex added. $^d$Reaction yields (n = 1) measured by $^1$H NMR using pentachloroethane as an internal standard.
Key entries were repeated and analyzed using GC-MS to determine the ratios between enals 3.36 and 3.37, as $^1$H NMR could not easily provide that information. GC yields with these additives will also be acquired and those experiments are in progress. In the absence of an acid additive, the reaction in CD$_3$CN without an additive (entry 1) gave a 6.2:1 ratio of desired product 3.36 to 3.37, while chloroform (entry 8) gave exclusively enal 3.36. The acid additives (entries 3–5, 10, and 14–16) promoted the formation of aldol byproduct 3.37, with the strongest acid, TFA (entry 10), having the greatest effect. The increase in combined yield of both enals is attributed to the increase in conversion to the aldol condensation enal 3.37. In an effort to diminish the formation of enal 3.37, $n$-hexanal was added to the reaction via slow addition over the 24 h. This method was found to neither be beneficial for overall yield nor increase selectivity towards the desired product (entry 2).

In an effort to avoid promotion of the aldol condensation byproduct, alternative additives were explored. We hypothesized that an iodide source, such as TBAI (entries 6 and 21), would assist in regeneration of the stable complex 17a after protodemetalation. However, this additive did not produce an increase in reaction yield in MeCN and completely shut down the reaction in chloroform. Interestingly, H$_2$O and alcohol additives (entries 25–29) also did not promote a catalytic reaction. $^1$H NMR yields for both enals combined were 7–12% for with these alcohols, compared to the control yield of 8% in the absence of any additive (entry 8). It is currently inconclusive whether these additives are tolerated for the intermolecular reaction, and the determined $^1$H NMR yields are attributed to exclusively the aldol product. GC yields will be obtained to determine the composition for this set of reactions.
We next sought to determine the effect of the organocatalyst on both the reaction yield and selectivity for the direct addition product 3.36. Prior to identification of the aldol condensation product, an organocatalyst screen had been performed and analyzed by $^1$H NMR (Table 3.6.2). Less bulky indoline, cyclohexylamine, and pyrrolidine organocatalysts (entries 6–9) were found to give no measurable improvement over the control reaction without an organocatalyst (entry 1). Interestingly, $N$-ethylaniline (entry 4) was found to facilitate the reaction and gave a 10% combined yield, while the bulkier secondary amine $N$-$i$-$Pr$-cyclohexylamine (entry 5) gave no appreciable yield. MacMillan’s $t$-Bu-imidazolidinone was found to still produce the highest yield amongst all screened organocatalysts (entry 2). After identification of enal 3.37, the most promising organocatalysts (entries 2–4) were rescreened and analyzed via GC-MS to determine the ratio between enals 3.36 and 3.37. While there was some observed variation in yield between screens, the overall trend was consistent. We presume that some of this
variability can be attributed to the modest solubility of 17a in MeCN. MacMillan’s t-Bu-imidazolidinone (entry 2) gave the highest yield of direct addition product 3.36, while not promoting the formation of the aldol condensation product 3.37 to a greater degree than either Jorgensen’s pyrrolidine 3.8 or N-ethylaniline (entries 3–4).

**Table 3.6.3** Solvent study for direct addition of aldehyde 3.34 to alkyne 3.35

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>DCM</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>chloroform</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>NO₂Me</td>
<td>4</td>
</tr>
</tbody>
</table>

*Complex 3.17a was dissolved in solvent (0.25 mL) in a 1.5 mL HP-LC vial before 3.35 was added via microsyringe. 3.34, organocatalyst 3.9, and pentachloroethane were added as individual solutions in solvent (50 µL). The reactions were heated at 55 ºC for 48 h. Yields (n = 1) measured by GC-MS using hexamethylbenzene as an internal standard. Reaction run at 22 ºC.*

We also repeated the solvent screen to accurately determine the yield of direct addition product 3.36 using GC-MS, in contrast to our preliminary screen that was monitored via 1H NMR. All solvents gave lower yields (2–6 %) than the previous screen, but the overall trend was similar with MeCN and DCE (entries 2 and 6) affording the highest yields of 6%, though the reactions were not repeated to determine if these differences are statistically significant (**Table 3.6.3**). Interestingly, CDCl₃ (entry 4) gave minimal reactivity for the intermolecular reaction but was a suitable solvent for the intramolecular reaction.

We most recently performed a combinatorial metal salt and ligand study with our lead organocatalyst 3.9 in an effort to identify alternative lead catalyst systems. Several
platinum metal salts were tested in combination with a variety of bidentate and tridentate ligands (Table 3.6.4), and analyzed by GC-MS. The coordinating solvents acetonitrile and tetrahydrofuran were chosen for reactions in an effort to create homogenous solutions with many of the more poorly soluble metal salts.

![Diagram](image)

**Table 3.6.4** Combinatorial screen of Pt salts and ligands for intermolecular reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Pt(DMSO)Cl₂&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Pt(DMSO)I₂&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ziese’s Dimer&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Ptl₂&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MeCN</td>
<td>THF</td>
<td>MeCN</td>
<td>THF</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>7.2</td>
<td>7.6</td>
<td>5.1</td>
<td>6.9</td>
</tr>
<tr>
<td>2</td>
<td>(S)-iPrQuinox</td>
<td>3.7</td>
<td>8.3</td>
<td>3.3</td>
<td>7.1</td>
</tr>
<tr>
<td>3</td>
<td>BIPY</td>
<td>0.1</td>
<td>1.0</td>
<td>5.6</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>4,4’-dimethoxyBIPY</td>
<td>0.3</td>
<td>0.9</td>
<td>6.7</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>iPr-BOX</td>
<td>4.2</td>
<td>6.2</td>
<td>5.1</td>
<td>7.9</td>
</tr>
<tr>
<td>6</td>
<td>(Dimethyl)-i-Pr-PHOX</td>
<td>0.8</td>
<td>1.8</td>
<td>7.5</td>
<td>5.8</td>
</tr>
<tr>
<td>7</td>
<td>(R)-BINAP</td>
<td>2.4</td>
<td>5.4</td>
<td>8.0</td>
<td>5.6</td>
</tr>
<tr>
<td>8</td>
<td>Xantphos</td>
<td>&lt;0.1</td>
<td>2.6</td>
<td>0.8</td>
<td>2.9</td>
</tr>
<tr>
<td>9</td>
<td>(S,S)-DACH-phenyl Trost</td>
<td>0.6</td>
<td>0.6</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>10</td>
<td>iPr-PyBOX</td>
<td>11.2</td>
<td>10.5</td>
<td>19.0</td>
<td>13.9</td>
</tr>
<tr>
<td>11</td>
<td>tBu-PyBOX</td>
<td>6.6</td>
<td>8.9</td>
<td>8.9</td>
<td>9.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Metal salt, ligand, and solvent (0.3 mL) were heated at 55 °C for 1 h before 3.35 was added via syringe. Then 3.34, 3.39, and hexamethylbenzene were added as stock solutions in solvent (25 µL) and the solutions were heated at 55 °C for 24 h. <sup>b</sup>Gy yields determined using hexamethylbenzene as an internal standard. <sup>c</sup>Reactions were heated to 100 °C.

Interestingly, reactions with all metal salt/ligand combinations resulted in nearly exclusive formation of desired product 3.36. No detectable aldol condensation byproduct 3.37 and only a trace amount of a GC peak with a mass corresponding to the aldol addition product 3.38 were observed. Overall, Ziese’s dimer was only found to facilitate the direct addition product and gave a 5% yield when using i-Pr-PyBOX as a ligand in THF. Oxazoline-based ligands (entries 6, 10, and 11) and BINAP (entry 7) with Pt(DMSO)₂I₂ gave yields above the control reaction with Pt(DMSO)₂I₂ and without any ligand (entry 1).
The direct addition reaction was found to not tolerate elevated temperature as a selection of ligands screened in cyclopentylmethyl ether (CPME) at 100 °C all had negligible yields. The analogous metal salt Pt(DMSO)$_2$Cl$_2$ afforded consistently lower yields, which was expected due to the presence of the stronger coordinating chloride and DMSO ligands. Interestingly, the i-Pr-PyBOX ligand gave better yields than t-Bu-PyBOX with most of the platinum salts and the highest yield of 19% with Pt(DMSO)$_2$I$_2$ (entry 10, column 5).

Although a labile platinum source, such as Pt(DMSO)$_2$I$_2$, has been reported as being necessary when pre-forming Pt-PyBOX complexes, we hypothesized that the DMSO may be a source of catalyst poisoning when the catalyst is formed in situ. PtI$_2$ and Pt(MeCN)$_2$Cl$_2$ were screened as alternative metal salts to omit DMSO. Pt(MeCN)$_2$Cl$_2$ gave <1% yield of desired product 3.37 and no ligand combination with PtI$_2$ improved upon the control sample in the absence of a ligand (entry 1). We presumed that the decrease in reactivity of PtI$_2$ from Pt(DMSO)$_2$I$_2$ was the result of its extremely poor solubility. In an effort to combat this issue, Pt(PhCN)$_2$I$_2$ (3.39) was prepared and screened in acetonitrile with or without i-Pr-PyBOX and found to only have a 5% yield for both reactions. [Rh(COD)Cl]$_2$, Rh(COD)$_2$BF$_4$, [Rh(C$_2$H$_4$)Cl]$_2$, and [Ir(COD)Cl]$_2$ were also screened in combination with the t-Bu- and i-Pr-PyBOX in MeCN and afforded no desired direct addition product. Co and Ru metal salts will also be considered for future screens.

With i-Pr-PyBOX, Pt(DMSO)$_2$I$_2$, and organocatalyst 3.9 identified as our lead combination for the direct addition reaction, preliminary studies were performed to further explore the reaction dependence on the Lewis acid and organocatalyst. Several control reactions were performed varying the loading of each catalyst (Table 3.6.5). The variability between the 19% yield achieved in Table 3.6.4 (entry 10) and the 6% yield achieved here in Table 3.6.5 (entry 3) demonstrates the variability with this reaction. The direct addition reaction requires both organocatalyst and Pt metal salt, as omitting either gave no yield (entries 1–2).
Table 3.6.5 Catalyst loading screen for direct addition of aldehyde 3.34 to alkyne 3.35

As previously observed when heating samples in CPME at 100 °C (Table 3.6.4, column 7), the reaction yield decreased to 2% at 80 °C in MeCN (Table 3.6.5, entry 4). Increasing the metal/ligand loading to 1 equivalent resulted in a marginal increase to 9% (entry 5). However, increasing the organocatalyst loading to 1 equivalent gave a 34% yield (entry 6). This result was promising as a catalytic reaction was promoted with respect to the metal salt, albeit with limited turnover. We hypothesized that enamine formation and/or reactivity could be problematic or could be rate-limiting. In an effort to combat this, 4 Å mol sieves were added to the reaction, but resulted in only a 1% yield (entry 8).

3.7 Current/Future Work with Intermolecular Additions of Aldehydes to Alkynes

It was initially believed to be promising that TFA promoted some catalytic turnover, however that system has now been identified to instead promote the aldol condensation product. As a result of testing extensive ligand/metal combinations, a i-Pr-PyBOX-Pt
complex was found to afford higher yields than when using a t-Bu-PyBOX ligand. Ligand screening has been mostly limited to commercially available ligands. In order to fully explore the dependence on the steric environment of the ligand, more extensive PyBOX ligand screening is required, specifically a Me-PyBOX scaffold (Figure 3.7.1). If these less sterically demanding ligands are shown to still be tolerated, then internal alkynes may be reactive. However, this could pose a new challenge to control the regioselectivity for the new C-C bond formation.

**Figure 3.7.1** Future dual catalyzed additions of carbonyl compounds to alkynes/alkenes

![Diagram of dual catalyzed additions](image)

Although the PyBOX ligand sterics have been shown to affect the yield, the dependence on the organocatalyst was demonstrated to be a limiting factor on catalytic turnover. A wider range of amines will be explored in an attempt to optimize the reaction and generate substantial catalytic turnover. The bulky t-butyl imidazolidinone organocatalyst currently used restricts the substrate scope to non-alpha branched aldehyde substrates. An alternative organocatalyst capable of enamine formation with ketones and alpha-branched aldehydes is highly desirable. With chiral metal complexes and/or organocatalysts, asymmetric additions to alpha-branched aldehydes/ketones could be performed to generate a chiral all carbon quaternary center, and the resulting $\beta_{\gamma}$-unsaturated alkene would not be able to isomerize. Additionally, the reaction tolerance to other functional groups (i.e. free alcohols and protected amines) present in the substrates
will be examined. Preliminary data from the additive screen already suggests that alcohols may be tolerated.

Once catalytic turnover can be achieved, lower catalyst and substrate loadings will be explored. In order for these reactions to be broadly useful, it will be necessary to reduce the amount of expensive platinum catalyst needed. Additionally, initial studies used 5 equivalents of alkyne substrate, and the effect of reducing the amount of alkyne has yet to be explored. A reaction that only requires one equivalent of alkyne would of course be desirable, and might be critical if performing a macrocyclization reaction.

After obtaining optimized conditions for catalytic turnover with a more versatile organocatalyst that can facilitate enamine formation with a wider range of carbonyl substrates for additions to alkynes, our ideal reaction would facilitate the addition of carbonyl compounds to alkenes. We presume that the addition to alkenes will be more challenging than to alkynes, thus leading us to focus first on the optimization for additions to alkynes. Once we have an optimized system in hand, these conditions will be used to study an intramolecular addition to alkene substrates prior to attempting an intermolecular reaction. Additionally, we will attempt to transfer these conditions over to our bifunctional PyBOX system that will be further discussed in chapter 4. With these goals in mind, we are elated to report what is, to our knowledge, the first direct intermolecular anti-Markovnikov addition of an unactivated aldehyde to an unactivated terminal alkyne.

3.8 Future Work with Bifunctional PyBOX Catalyst

Although we had identified a dual catalyst system that promoted the intermolecular addition of an aldehyde to terminal alkyne, we still sought to develop a bifunctional catalyst system. If the dual catalyst approach remains restricted to the use of a bulky imidazolidinone organocatalyst, then the substrate scope would be limited to non-alpha-
branched aldehydes. We hypothesized that a bifunctional catalyst utilizing a PyBOX ligand moiety may be capable of enamine formation with alpha-branched aldehydes and ketones, while still preventing undesired coordination of the organocatalyst to the π-acid. We designed a PyBOX bifunctional catalyst based on our analogous design discussed in Chapter 2 (Figure 3.8.1).

**Figure 3.8.1** Dual vs bifunctional catalysis for intermolecular addition of carbonyl compounds to alkenes or alkynes

We hypothesized that a tridentate system would create a more well-defined binding pocket and undesired intermolecular interactions may be precluded due to incorporation of a third ligand around the Lewis acid. With the promising DFT calculations performed on propylene complexation and C-C bond formation, Jacob Porter and I successfully synthesized bifunctional PyBOX precatalyst 3.42 (Scheme 3.8.1). This synthesis utilized the key amino alcohol 2.57 previously synthesized for the PyOX-based precatalyst. The synthesis of the PyBOX-based precatalyst began with Fischer esterification of 2,6-pyridinedicarboxylic acid to afford monoester 3.37. EDC amide coupling with 2-amino-2-methyl-1-propanol gave amide 3.38 in 70% yield. Ester hydrolysis followed by EDC amide coupling of carboxylic acid 3.39 with amino alcohol 2.57 yielded bis-amide 3.40. As seen previously with the PyOX precatalyst synthesis, the alcohol of 2.57 further reacted with the picolinic acid moiety to generate an ester. Hydrolysis of this
ester byproduct was performed with the crude mixture using LiOH in 1:1 H₂O:THF to regenerate exclusively bis-amide 3.40. Oxazoline formation with Deoxo-Fluor® and subsequent Boc deprotection with TFA afforded the desired PyBOX precatalyst 3.42.

Scheme 3.8.1 Synthesis of bifunctional PyBOX precatalyst

A single crystal of the PyBOX bifunctional ligand with Pd(MeCN)₄(BF₄)₂ was obtained via slow diffusion in a 1:1 nitromethane:benzene solution by Jacob Porter. The structure of the X-ray crystal structure showed the precatalyst binding to Pd in a tridentate fashion along with a molecule of MeCN to give a square planar Pd complex (Figure 3.8.2). This X-ray structure gave evidence that complexation of the PyBOX precatalyst 3.42 to the Lewis acid occurred in a fashion consistent with our models, and there was no evidence for organocatalyst coordination to the Lewis acid. With this result, Jacob screened the bifunctional PyBOX catalyst for the intermolecular addition of aldehyde 3.34 to alkyne 3.35 (Scheme 3.8.2). In situ ¹H NMR analysis indicated the desired product had formed in 5% yield in CD₂Cl₂ at 30 ºC, although GC-MS analysis needs to be performed to confirm this to be enal 3.36 and not the aldol product.
Figure 3.8.2 X-ray crystal structure of precatalyst 3.42 bound to Pd

Overall, this suggests that the N-methylamine moiety on the bifunctional catalyst may be functioning to some degree as an organocatalyst. Due to the extremely limited supply of this bifunctional catalyst due to its challenging and lengthy synthesis, further screening will only be performed after further studies with the dual catalyst system. One pertinent control reaction to confirm that the catalyst is operating in a bifunctional manner is to test the Boc-protected PyBOX 3.41.

Scheme 3.8.2 Intermolecular addition of aldehyde 3.34 to alkyne 3.35 using in situ generated bifunctional PyBOX catalyst 3.43

Additionally, results from the combinatorial Lewis acid and ligand screen for the dual catalyst system suggest that it may not be necessary to use AgBF₄ to form monocationic PyBOX complexes. Depending on results from the dual catalyst screening, several variations of the bifunctional system will be considered (Figure 3.8.3). The lack of potential self-quenching in the bifunctional system could permit less-hindered ligand and
organocatalyst moiety combinations to be used. This may permit an increased substrate scope that may not be otherwise possible with our dual catalytic systems.

**Figure 3.8.3** Future plans for bifunctional PyBOX catalysis

PyBOX variations

organocatalyst variations

tether length

1) Pt(DMSO)$_2$$_2$. AgBF$_4$
solvent

2) $\text{R}_1^1 \text{R}_2^2 + \text{R}_5^5 \text{R}_6^6 \rightarrow$ branched or
$
\alpha, \beta$ or $\beta, \gamma$ unsaturated carbonyl products

alkenes or alkynes

ketone or $\alpha$-branched carbonyl compounds

$\text{R}_3^3: \text{CH}_2\text{R}_4^4$ or H
CHAPTER 4

Route Exploration and Synthesis of the Reported Structure of the Pyridone-based PDI Inhibitor STK076545

4.1 Introduction to Protein Disulfide Isomerase

Protein disulfide isomerase (PDI) is a key enzyme that catalyzes the oxidation-reduction and isomerization of disulfide bonds and serves as a necessary chaperone for protein folding.\(^{160}\) PDI is composed of four thioredoxin domains \(a, b, b',\) and \(a'\) and a 19 amino acid linker termed \(x\) between domains \(b'\) and \(a'\) (Figure 4.1.1) that are all attached in a U-shaped configuration. Thioredoxins are proteins that facilitate the reduction of other proteins. Both domains \(a\) and \(a'\) contain an active site Cys-Gly-His-Cys motif responsible for the oxidoreductase activity. Oxidized PDI exists in an open state with a more exposed hydrophobic area with potential substrate binding at the non-catalytic \(b\) and \(b'\) domains, the \(b'\) domain being the principle substrate binding domain.

![Figure 4.1.1 Crystal structure of oxidized hPDI (4EL1)\(^{161}\)](image)

Although primarily localized in the endoplasmic reticulum with its ER-retaining KDEL sequence at its C-terminus, PDI can be released onto the surface of endothelial and platelet cells, where it acts to promote effective coagulation via mechanisms presently...
under study. For these reasons, PDI inhibitors are of significant interest both for the treatment of cancer\textsuperscript{162} and the prevention of thrombosis.\textsuperscript{163} Several animal models of thrombosis have demonstrated that targeting cell surface PDI with antibodies or small molecules blocks both platelet accumulation and fibrin generation.\textsuperscript{164-168} Previously reported PDI antagonists suffer from poor selectivity, irreversibility, and/or low potency.\textsuperscript{169-172}

### 4.2 Identification and Activity of Novel Inhibitors of PDI

In an effort to identify novel inhibitors of PDI with more suitable therapeutic properties, a high-throughput screen was performed by Flaumenhaft and co-workers on approximately 5,000 bioactive small molecules.\textsuperscript{166} From their insulin-based turbidimetric assay, they identified 18 PDI inhibitory compounds representative of 13 separate chemical scaffolds, including 3 flavonols. Flavonols are a class of flavonoids found in high abundance in various fruits and vegetables. Of the identified flavonols, quercetin-3-rutinoside (rutin) was the most potent and inhibited PDI in a dose-dependent manner. Rutin was found to bind and reversibly inhibit PDI, while showing minimal activity towards other extracellular thiol isomerases present in the vasculature.

To further understand the structure activity relationship of rutin, common metabolites and other analogs were evaluated on their ability to inhibit PDI (Table 4.2.1). This study demonstrated that inhibitory activity against PDI for these flavonols was restricted to those with a 3-O-glycoside linkage. From this class, isoquercetin advanced to a phase II clinical trial to evaluate its efficacy to reduce hypercoagulability in cancer patients. There were 28 patients (cohort A) who received 500 mg of isoquercetin daily, while 29 patients (cohort B) took 1000 mg daily (Figure 4.2.1). After 56 days, isoquercetin was found to decrease D-dimer plasma concentrations, a biomarker for venous
thromboembolic disease, by a median of 22% in cohort B, while cohort A (500 mg) had a
nonsignificant median change in D-dimer of +9.90%.\textsuperscript{173} However, the high dose and highly
variable patients responses are drawbacks of isoquercertin.

\textbf{Table 4.2.1 Structure activity relationship for flavonols}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Compound Name} & \textbf{R\textsuperscript{1}} & \textbf{R\textsuperscript{2}} & \textbf{R\textsuperscript{3}} & \textbf{R\textsuperscript{4}} & \textbf{IC\textsubscript{50} (\mu M)} \textsuperscript{(95\% confidence interval)} \\
\hline
Quercertin & H & OH & OH & OH & >100 \\
Tamarixetin & H & OH & OCH\textsubscript{3} & OH & >100 \\
Isorhamnetin & H & OCH\textsubscript{3} & OH & OH & >100 \\
Diosmetin & H & OH & OCH\textsubscript{3} & H & >100 \\
Hyperoside & H & OH & OH & Galactose & 5.9 (2.9–12.5) \\
Isoquercertin & H & OH & OH & Glucose & 7.1 (4.3–12.0) \\
Quercertin-3-glucuronide & H & OH & OH & Glucuronic acid & 5.9 (3.5–10.1) \\
Rutin & H & OH & OH & Rutinose & 6.1 (1.1–10.7) \\
Datiscin & OH & H & H & Rutinose & 8.8 (3.2–24.3) \\
\hline
\end{tabular}
\end{table}

To seek additional PDI inhibitors, a second high-throughput screen was performed
on 348,505 compounds from the Molecular Libraries Small Molecule Repository.\textsuperscript{174} Two
series of PDI inhibitors, represented by bepristats 1a and 2a (Figure 4.2.2) were found to
bind to the hydrophobic pocket of the b’ domain.\textsuperscript{168} A commercial compound called
STK076545 was also identified from the high-throughput screen to be a reasonably potent
hit for the inhibition of PDI, and had an attractive structure for medicinal chemistry studies
relative to other hits.
The commercial supply of STK076545 was soon depleted, and we were unable to secure additional quantities, so we immediately endeavored to synthesize it. The work described here has been submitted for publication with the title “Route exploration and synthesis of the reported pyridone-based PDI inhibitor STK076545.” Its structure proved to be deceptively simple, and this chapter describes several pitfalls that were encountered prior to its successful synthesis.

4.3 Conventional Routes for Accessing β-Keto Amides

Methods for preparing β-keto amides have been pursued for at least a century. The most obvious approach to β-keto amides is via amide couplings between β-keto acids and amines, which also permits late stage diversification for medicinal chemistry studies (Figure 4.3.1, approach 'a'). However, this approach may be complicated by the limited...
stability of the \( \beta \)-keto acid starting materials, which can undergo decarboxylation (step 'b'). Alternatively, Meldrum’s acid can be C-acylated, then aminolysis affords a \( \beta \)-keto amide, but limited to \( \alpha \)-unsubstituted substrates.\(^{176}\) Direct aminolysis of \( \beta \)-keto esters\(^{177}\) or \( \beta \)-keto thioesters\(^{178}\) at high temperature is possible (approach 'c'), but can be compromised by competing enamine formation. Aminolysis reactions catalyzed with DMAP,\(^{179}\) enzymes,\(^{180}\) or transition metals\(^{181-182}\) have also been reported. Alternatively, addition of a ketone or enamine to an isocyanate have also been reported (approach 'd'). Cross Claisen-like condensations of esters with amide enolates have been reported (approach 'e'),\(^{183-184}\) or alternatively an aldol reaction between a pyridone-containing amide and a benzaldehyde (Ar = Ph for STK076545) could be envisaged (step 'f'), followed by alcohol oxidation (step 'h').

**Figure 4.3.1** Retrosynthetic strategies for accessing the \( \beta \)-keto amide in STK076545 (Ar = Ph, \( R^1 = -\text{CH}_2\text{CH}_2\text{NEt}_2 \)).
Other approaches involving a late stage addition of the pyridone are possible, but these were not initially considered since we were first interested in exploring amide structure-activity relationships (SARs), and the presence of a basic tertiary amine on the amide side chain of STK076045 could complicate a late stage halogenation/pyridone N-alkylation reaction. It remained to be determined how the presence of an α-pyridone could affect the steps outlined in Figure 4.3.1. Herein, we report our explorations of these routes, culminating in a successful 5-step synthesis of the reported structure of STK076545.

4.4 Synthesis of the reported structure of STK076545

4.4.1 Proceeding via a β-Keto Carboxylic Acid

The initial synthetic route we envisioned to access STK076545 (Figure 4.3.1, approach ‘a’) involved N-alkylation of 2-pyridone with bromo-β-keto ester 4.2, followed by ester hydrolysis and amide coupling (Scheme 4.4.1). Alkylation of 2-pyridone with 4.2 proceeded smoothly using conditions previously reported using a bromomalonate. Both the N-alkylated 4.3 and O-alkylated 4.4 products were isolated, in 47% and 9% yield respectively. 4.3 and 4.4 were readily distinguishable based on their $^{13}$C NMR chemical shifts for the $\alpha$-carbon, with the O-alkylated product 4.4 being assigned based on the more downfield $\alpha$-carbon peak at 75.9 ppm. In this paper, all alkylations of 2-pyridone gave N-alkylation as the major product, though the O-alkylated products were sometimes observed in trace amounts. Unfortunately, the hydrolysis of ester 4.3 under acidic (H$_2$SO$_4$) or basic conditions (NaOH, LiOH, or Me$_3$SnOH) all resulted in decarboxylation of carboxylic acid intermediate 4.6 to yield ketone 4.5, despite careful attempted isolations using buffered aqueous media.
Direct coupling of alkali metal carboxylate salts has been shown by Batey and coworkers to be a useful strategy with unstable carboxylic acids. Attempts at a tandem ester hydrolysis of 4.3 with NaOH or LiOH followed by peptide coupling with carboxylate 4.7 were not fruitful. Alternatively, the decarboxylation product 4.5 was synthesized on a larger scale via N-alkylation of 2-pyridone with 2-bromoacetophenone. Subsequent carboxylation using MgCl₂ and NaI with CO₂ also gave no detectable amount of carboxylate 4.8 or carboxylic acid 4.6 after an acidic workup.

In an effort to access carboxylic acid 4.6 under milder conditions, the analogous benzyl ester intermediate 4.13 was synthesized in four steps (Scheme 4.4.2). First, 1,3-dicarbonyl 10 was prepared from acetophenone and dimethylcarbonate using NaH in 98% yield. ZnO-catalyzed transesterification of 4.10 afforded benzyl alcohol 4.11. Next, monohalogenation of 4.11 with NBS catalyzed by Amberlyst-15®, followed by reaction with 2-pyridone yielded α-substituted-β-keto ester 4.13 in 66% yield over two steps. Benzyl removal from ester 4.13 via palladium-catalyzed hydrogenation also resulted in
decarboxylation. In addition, $^1$H NMR analysis of the crude product indicated the ketone was reduced to afford benzyl alcohol 4.14. Efforts to reduce the ketone prior to ester hydrolysis were not successful (Scheme 4.4.8).

### Scheme 4.4.2 Synthesis and deprotection of benzyl ester 4.13

**4.4.2 Enolate Formation and Reactivity of Benzylic Ketone Intermediate**

Instead of proceeding through a carboxylic acid intermediate, we envisioned installation of the amide via reaction of an enolate with a suitable isocyanate, or CDI followed by addition of an amine to the intermediate acylimidazole (Figure 4.3.1, approach ‘d’). To identify suitable conditions for enolate formation with ketone 4.5, LDA, LiHMDS, and NaH were screened as bases (Table 4.4.1). Reactions were quenched at $-78 \, ^{\circ}\text{C}$ or $20 \, ^{\circ}\text{C}$ using $\text{D}_2\text{O}$, and crude samples were analyzed via $^1$H NMR. Based on our screen, it was found that all reactions occurring at $20 \, ^{\circ}\text{C}$ facilitated enolate formation (entries 3-5), while no deuterium incorporation occurred when quenching the samples at $-78 \, ^{\circ}\text{C}$ (entries 1-2). The observed deuterium incorporation over 100% is within the systematic error associated with $1\text{H}$ NMR analysis, the scale used to weigh NaH, and microsyringe in preparation of LDA.
Table 4.4.1 Enolate formation from ketone 4.5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Base (eq.)</th>
<th>T (ºC) Addition of Base</th>
<th>T (ºC) Addition of D₂O</th>
<th>% Deuterium Incorporation⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1.05</td>
<td>–78</td>
<td>–78</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>1.05</td>
<td>–78</td>
<td>–78</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>1.05</td>
<td>–78</td>
<td>20</td>
<td>117</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>1.05</td>
<td>–78</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>1.2</td>
<td>20</td>
<td>20</td>
<td>134</td>
</tr>
</tbody>
</table>

⁵ Deuterium incorporation was determined via ¹H NMR.

The enolate from ketone 4.5 was next formed using LDA at 20 ºC and reacted with CDI or urea intermediate 4.16, synthesized from CDI and N,N-diethylethylenediamine (Scheme 4.4.3). There was no observable reaction with either electrophile, even after heating at 70 ºC. We then tested commercially available tert-butyl isocyanate as a model isocyanate for reaction screening. When LDA was used as a base, no desired product was observed. Rather, urea byproduct 4.18 formed from the addition of diisopropylamine to tert-butyl isocyanate was detected via LC-MS.
Switching to NaH as the base and heating the reaction at 100 °C for 2 h in toluene yielded amide 4.19 in 15% yield. Efforts to synthesize the desired isocyanate from N,N-diethylethylenediamine and triphosgene, or reacting diethylamine with 2-bromoethyl isocyanate, were both troublesome. With this synthetic route being low yielding and having the limitation of only producing secondary amides, we chose to seek an alternative route.

### 4.4.3 Direct Aminolysis of β-Keto Ester

Another common synthetic approach to access amides is via direct aminolysis of esters (Figure 4.3.1, approach ‘c’). Starting from β-keto ester 3, we first tested a Ag(I)-catalyzed aminolysis (Scheme 4.4.4). Rather than observing conversion to the desired β-keto amide, reaction monitoring via LC-MS when using condition A showed masses associated with ester 4.21 and amide 4.24 (Scheme 4.4.5). Similarly, when heating ester 4.3 with N,N-diethyethylenediamine in toluene at 80 °C with or without DMAP, the same decomposition peaks were present. Ester 4.21 was isolated when using conditions B and correlated with the mass peak observed via LC-MS. Ag(I)/DBU and DMAP were found to both accelerate the conversion to 4.21 in a few hours, in comparison to the reaction heated in toluene that proceeded slowly over 24 h. We hypothesize that the β-keto ester decomposes via a retro Claisen-like condensation mechanism. The amine (or nucleophilic catalyst) could add to the ketone, followed by collapse of the tetrahedral intermediate 4.22 and cleavage of the C-C bond to produce ester 4.21 (Scheme 4.4.5).

Štefane and Polanc reported a method to prepare β-keto amides from β-keto esters that proceeds via a 1,3,2-dioxaborinane intermediate. Reacting β-keto ester 4.3 with boron trifluoride etherate afforded the boron complex 4.20b in 82% yield (Scheme 4.4.4).
Unfortunately, subsequent treatment of \textbf{4.20b} with \textit{N,N}-diethylethylenediamine also resulted in decomposition to ester \textbf{4.21} after only 1 h, and complete decomposition after 24 h. Interestingly, when starting from \textit{\beta}-keto ester \textbf{4.10} which does not have the pyridone substituent in the \textit{\alpha} position, the preparation of the boron complex \textbf{4.20a} and treatment with \textit{N,N}-diethylethylenediamine cleanly afforded \textit{\beta}-keto amide \textbf{4.22}.

**Scheme 4.4.5 Proposed retro Claisen-like Condensation decomposition**

\[ \text{Scheme 4.4.4 Direct aminolysis attempts with \textit{\beta}-keto esters} \]

\[ \text{Scheme 4.4.5 Proposed retro Claisen-like Condensation decomposition} \]
4.4.4 Late Stage Pyridone Formation

Incorporation of the pyridone at the end of the synthesis was briefly considered. Attempts at $\alpha$-bromination of 4.22 were found to be unsuccessful, which we hypothesized would be challenging due to the presence of the basic tertiary amine. Alternatively, we proposed synthesizing $\alpha$-amino-ketone 4.30 and performing a condensation reaction with 2H-pyran-2-one to access the pyridone (Scheme 4.4.6), a strategy that has been previously reported for the preparation of $N$-substituted pyridones.$^{193}$ First, oxime 4.25 was synthesized from diethylmalonate.$^{194}$ Palladium-catalyzed hydrogenation of 4.25 and subsequent Boc protection of the intermediate amine afforded 4.27. Direct aminolysis of diester 4.27 with $N,N$-diethylethlenediamine yielded diamide 4.28. Then, acylation of 4.28 with benzoyl chloride in the presence of magnesium ethoxide provided $\beta$-keto-amide 4.29 in 44% yield.$^{195}$

Boc removal from 4.29 proceeded smoothly; unfortunately, the resulting $\alpha$-amino-ketone 4.30 was not isolatable and underwent intermolecular condensation to form 4.31 as evident from LC-MS analysis and crude $^1$H NMR. Due to the instability of 4.30 and our interest in exploring amide structure-activity relationships, we sought a more modular and robust method.

Scheme 4.4.6 Attempted synthesis of $\alpha$-amino-ketone 4.30 for late stage pyridone formation
4.4.5 Late Stage C-C Coupling

Inspired by our observed retro Claisen-like reaction that occurred with a β-keto ester substrate, we examined the feasibility of performing an aldol addition, Claisen-like condensation, or acylation with intermediates 4.34a-b (Scheme 4.4.7). Thus, installation of the C2-C3 bond would occur after amide formation and minimize the possibility of decarboxylation. Synthesis of 4.34a-b began with N-alkylation of 2-pyridone with ethyl bromoacetate followed by ester hydrolysis, affording the previously reported carboxylic acid 4.32. Amide coupling with either N,N-diethylethylenediamine 4.32a or PMB-protected amine 4.33b yielded amides 4.34a-b. We prepared the PMB-protected amide 4.27b in an effort to avoid competitive deprotonation of the amide proton during enolization reactions. Extensive efforts with various electrophiles (aldehyde, ester, or acid chloride 4.35a-c) bases (NaOMe, NaH, and LDA), and temperatures (0–160 °C) were all unfruitful (Table 4.4.2).

![Scheme 4.4.7 Synthesis of α-pyridone-amides 4.33a-b](image)

Identification of the aldol adduct as a possible intermediate provided inspiration to access alcohol 4.39, which would not undergo decarboxylation during ester hydrolysis (Scheme 4.4.8). Starting from benzyl esters 4.12 or 4.13, we attempted to either protect or reduce the benzylic ketone. Efforts to protect the ketone using ethylene glycol and catalytic p-TsOH with triethyl orthoformate and 4 Å mol sieves or a Dean–Stark trap resulted in no conversion. Alternatively, an attempt to reduce the ketone with DIBAL-H
resulted in pyridone reduction, as suggested by the crude $^1$H NMR spectrum. Switching to NaBH$_4$ produced benzyl ester 4.38, which we presume proceeds via a similar retro-aldol reaction as observed previously.

### Table 4.4.2 C2-C3 coupling screening on amide 4.33-b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>R</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature (ºC)</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.34a</td>
<td>H</td>
<td>NaOMe</td>
<td>PhMe</td>
<td>111</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4.34a</td>
<td>H</td>
<td>NaH</td>
<td>PhMe</td>
<td>111</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4.34a</td>
<td>H</td>
<td>NaOMe</td>
<td>none</td>
<td>140 – 160</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>4.34b</td>
<td>H</td>
<td>NaH</td>
<td>none</td>
<td>130</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4.34b</td>
<td>OMe</td>
<td>LDA</td>
<td>THF</td>
<td>-78 → RT</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>4.34b</td>
<td>Cl</td>
<td>LDA</td>
<td>THF</td>
<td>0 → RT</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>4.34b</td>
<td>Cl</td>
<td>LDA</td>
<td>THF</td>
<td>0 → -78 → 40</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$All reactions were monitored via LCMS and $^1$H NMR.

### Scheme 4.4.8 Attempted protection and reduction of benzylic ketones 4.12 and 4.13

#### 4.4.6 Protected Benzylic Alcohol Route

To access benzylic alcohols that could be converted to ketones late in the synthesis, we prepared bromohydrins 4.42a-b from the respective methyl and benzyl cinnamates using NBS and I$_2$ as a catalyst (Scheme 4.4.9). This also installed alpha
halides for pyridone alkylations. Under standard 2-pyridone alkylation conditions, epoxide 4.43 was exclusively formed. To circumvent this issue, the TBS- or MOM-protected bromohydrins 4.44a-b were synthesized. It was found that the use of 2,6-lutidine as base was critical, as alternative bases such as DIPEA favored epoxidation over alcohol protection. However, subjecting the TBS- or MOM-protected bromohydrin to pyridone alkylation conditions afforded only alkene 4.45 in <20% yield. Alternatively, the acetyl-protected alcohol 4.46 was synthesized using acetic anhydride and catalytic DMAP. N-alkylation of 2-pyridone using 4.46 afforded what was initially presumed to be the desired product 4.47a and alkene 4.48a in 18% and 9% yield respectively (Scheme 9). Due to the low yields, we screened alternative solvents (acetone) and bases (Cs\_2CO\_3) in an effort to increase the yield and selectivity; however, the yield of 4.47 was not improved.

Moving forward with the synthesis, methyl ester and acetate hydrolysis proceeded smoothly to yield the presumed carboxylic acid 4.49a (Scheme 4.4.10). At that time, we did not suspect any issues and completed the synthetic sequence to yield 4.57, which was initially thought to be STK076545 (Scheme 4.4.11). N,N-diethylthelyenediamine was used directly for the peptide coupling to prepare 4.52; however, the subsequent alcohol
oxidation was unsuccessful when using DMP, PDC, IBX, or Bobbitt’s salt under basic (2,6-lutidine) or acidic (silica gel) conditions.\(^\text{198}\)

**Scheme 4.4.10** N-alkylation of 2-pyridone with acetyl-protected bromohydrin

Instead, ethanolamine was TBS-protected to afford 4.51 and then used in an amide coupling using HATU with carboxylic acid 4.49 to yield 4.53 in 91% yield. DMP oxidation of the alcohol proceeded smoothly to afford ketone 4.54, followed by TBS removal using HCl. In a one-pot reaction, alcohol 4.55 underwent a mesylation followed by a substitution with diethylamine. The final product was treated with HCl to furnish the HCl salt 4.57 in 28% yield over 2 steps.

**Scheme 4.4.11** Synthesis of the incorrect regioisomer of STK076545

However, analogs 4.55 and 4.57 were both found to be inactive in a PDI activity assay measuring the reduction of insulin (cleavage of its disulfide bonds). Obtained X-ray crystal structures of 4.48b and 4.49b revealed that the pyridone was in the benzylic
position (Scheme 4.4.10). A distinct difference between 4.49a and the X-ray structure of 4.49b is the relative stereochemistry between the hydroxyl and pyridone substituents. We propose that cyclic acetoxonium ion intermediate 4.50 is formed, similar to that proposed for the Prévost and Woodward dihydroxylation reactions, and 2-pyridone then attacks the benzylic carbon. Since we started with (E)-methyl cinnamate, the anti addition of water to the intermediate rac-bromonium ion results in a racemic mixture of bromohydrins 4.46.

Formation of the proposed acetoxonium ion intermediate 4.50 and subsequent pyridone alkylation would result in inversion of both stereocenters and generate 4.47b. Ester hydrolysis of 4.47b then yielded acid 4.49b, with its relative stereochemistry confirmed by the X-ray crystal structure (Scheme 4.4.10).

**Scheme 4.4.12 Alkylation and attempted benzylic bromination**

\[
\text{4.21} \xrightarrow{1) \text{LiHMDS, THF, } -78 \, ^\circ \text{C}} \xrightarrow{2) \text{BnBr, THF, } -78 \rightarrow 0 \, ^\circ \text{C}} 68\% \quad \text{4.58} \xrightarrow{\text{NBS, AIBN, MeCN, } 55\,^\circ \text{C}} 80\% \quad \text{4.59}
\]

4.4.7 Aldol Addition to Ethyl and Allyl Esters

To circumvent the unexpected rearrangement through the acetoxonium ion intermediate, we planned to perform the N-alkylation prior to installation of the alcohol/ketone functionality. Inspired by Easton and co-workers’ use of NBS and AgNO₃ to generate hydroxy-α-amino acid derivatives, we sought to access a benzylic bromide intermediate from 4.58 (Scheme 4.4.12). Ester 4.21 was reacted with LiHMDS to generate an enolate, followed by alkylation with benzyl bromide to afford 4.58. Subsequent treatment with NBS and AIBN in MeCN yielded no bromination at the benzylic position. The m/z peak observed in the LC-MS trace confirmed the presence of a brominated
product, but the crude $^1$H NMR spectrum suggested that bromination occurred on the pyridone.

### Scheme 4.4.13 Aldol reactions with $\alpha$-pyridone ester 21

Alternatively, benzaldehyde was used instead of benzyl bromide to react with the enolate generated from ester 4.21 to access the benzylic alcohol directly (Scheme 4.4.13). Using identical conditions (LiHMDS and 0 °C), the elimination product 4.60 was generated. Hydrolysis of ester 4.60 yielded carboxylic acid 4.61, which X-ray crystallography confirmed to be the alkene to be the Z alkene. With LDA being more commonly used in the literature for aldol addition reactions with esters, we switched our base to LDA (Scheme 4.4.13). Quenching the reaction at –78 °C was found to be critical to avoid generation of the elimination product and give the desired alcohol 4.62. Unfortunately, ester hydrolysis with LiOH yielded the elimination product 4.60 again. In an effort to avoid generation of this undesired alkene, we synthesized the TBS-protected alcohol 4.63. This route was unfruitful as ester hydrolysis or cleavage using LiOH, Me$_3$SnOH, or LiI all resulted in the generation of 4.60.

In order to access the carboxylic acid under milder conditions, we instead synthesized allyl ester 4.64 (Scheme 4.4.14). First, 2-pyridone was alkylated with allyl chloroacetate to yield allyl ester 4.64, and subsequent aldol addition using benzaldehyde
afforded alcohol 4.65. By increasing the amount of benzaldehyde from 1 to 2 equivalents, we were able to nearly double the yield to 82% for this reaction. Allyl removal with Pd(PPh₃)₄ produced carboxylic acid 4.66. Amide coupling and subsequent DMP oxidation of alcohol 4.67 successfully produced the final β-keto-amide product 4.68 with the reported structure of STK076545. Alcohol analog 4.67 and the final compound 4.68 were both tested in the insulin reduction assay and found to be inactive. We obtained an X-ray crystal structure corroborating the structure of 4.68 (Figure 5.6.1). Interestingly, the ¹H and ¹³C NMR spectra do not match that of the batch received from the commercial supplier. This confirms that the structure of the active PDI-inhibiting compound was misassigned.

Scheme 4.4.14 Successful allyl ester route to STK076545

In conclusion, several conventional methods for forming β-keto amides resulted in fragmentation of pyridone-containing intermediates, such as retro-Claisen-like and retroaldol reactions. Efforts to instead proceed via an acetyl protected bromohydrin resulted in a rearrangement that we propose proceeds via an acetoxonium ion intermediate. Alternatively, we successfully synthesized the reported structure of STK076545 via a 5-step synthetic route proceeding through allyl ester 4.64. This strategy should prove to be broadly useful in accessing β-keto amides, particularly with an electron-withdrawing α-substituent such as N-pyridone. Unexpectedly, neither the final compound (4.68) nor
several of its precursors were found to inhibit protein disulfide isomerase, and its $^1$H and $^{13}$C NMR spectra do not match those of the active commercial compound STK076545. It is not uncommon for complex natural products to have misassigned structures which require correction after more detailed synthetic and spectroscopic studies.\textsuperscript{202} However, it is often taken for granted that simpler commercial small molecules are provided in high purity and with structures as advertised, which is not always the case.\textsuperscript{203} Our results here highlights the importance of resynthesis and structure validation of active compounds prior to embarking on medicinal chemistry campaigns. Current efforts in our lab are ongoing to elucidate the correct structure of the commercially supplied compound that may have useful PDI inhibitory activity.
CHAPTER 5

Experimental Procedures and Characterization of Compounds

5.1 General Information: Synthesis, Characterization, and Reaction Screening

All reagents and solvents were purchased from commercial vendors and used as received, unless otherwise noted. Nitromethane was distilled and stored over 4 Å molecular sieves prior to use. A Vacuum Atmospheres Co. Omni-Lab glovebox was used for weighing out air sensitive materials, as noted in the detailed protocols. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane (1H δ 0), CDCl3, (13C δ 77.16), CD3CN (1H δ 1.94), CD3OD (1H δ 3.31, 13C δ 49.00), or CD3NO2 (1H δ 4.33). NMR data are reported as follows: chemical shifts, multiplicity (obs = obscured, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. NMR data was processed using MestReNova software. Flash chromatography was performed using Biotage SNAP cartridges filled with 40–60 µm silica gel, or C18 reverse phase columns (Biotage® SNAP Ultra C18 or Isco Redisep® Gold C18Aq) on Biotage Isolera systems, with photodiode array UV detectors. Analytical thin layer chromatography (TLC) was performed on Agela Technologies glass plates with 0.25 mm silica gel with F254 indicator. Visualization was accomplished with UV light (254 nm) and aqueous potassium permanganate (KMnO4) stain followed by heating, unless otherwise noted. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS
method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 x 4.6 mm, 3 µm particle size, 110 Å pore size); column temperature 40 °C; 5 µL of sample in MeOH or CH₃CN at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25–95% CH₃CN/H₂O (both with 0.1% formic acid) over 5 min., then 95% CH₃CN/H₂O for 2 min. Purity was measured by UV absorbance at 210 or 254 nm. Gas chromatography/mass spectrometry (GC-MS) was performed with either an Agilent Technologies 6850 GC with 5973 MS detector, and Agilent HP-5S or Phenomenex Zebron ZB-5MSi Guardian columns (30 m, 0.25 mm ID, 0.25 µm film thickness), or a Shimadzu 2010 Plus GC with an AQC-20i auto injector and QP2010 SE MS detector, and Shimadzu SH-5Rxi-4SiMS column (30 m, 0.25 mm ID, 0.25 µm film thickness). High-resolution mass spectra were obtained at the University of Wisconsin-Milwaukee Mass Spectrometry Laboratory with a Shimadzu LCMS-IT-TOF with ESI and APCI ionization, or at the University of Cincinnati Environmental Analysis Service Center with an Agilent 6540 LCMS with accurate mass Q-TOF. IR spectra were obtained as a thin film on ZnSe plates using a Thermo Scientific Nicolet iS5 spectrometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter at λ = 589 nm, with a 10 mL cell with 10 cm path length. Specific rotations are reported as follows: [α]_D^TºC (c = g/100 mL, solvent). A VWR® Analog vortex mixer fitted with a 5 x 5” sample box with divider was used to shake reaction screening samples at 20 °C. Cis-[Pt(DMSO)] was prepared using a previously reported procedure. ⁵⁸

5.2 General Information: Density Functional Theory Calculations

Initial complexes were drawn within the Avogadro²⁰⁴ molecular visualization program and subjected to preliminary optimization with molecular mechanics using the auto-optimization feature (force field set to UFF, 4 steps per update, and steepest descent
algorithm). For alkene and alkyne complexes, as well as enamine and amine poisoned structures, conformational sample was utilized by submitting multiple starting point coordinates of the same complex varying tether positions and/or complexation orientations. This was utilized to ensure a higher probability of obtaining an optimized geometry for the global minimum. The resulting coordinates were added to the Gaussian 09 input file. All reported geometries were then optimized and energies were calculated by DFT using the B3PW91 functional\textsuperscript{31} and the basis sets LANL2DZ\textsuperscript{32} for all metals and cc-pVDZ for other atoms, using the PCM solvation model with dichloromethane, and the default FineGrid integration grid unless otherwise noted. Enthalpies and free energies were calculated at 298.15 K using unscaled harmonic vibrational frequencies. Subsequent calculations performed of different precatalysts/substrates used previously obtained optimized coordinates as starting points when performing variations and preoptimizations in Avogadro. All calculations were performed with Gaussian09 on the Père cluster at Marquette University.

5.3 Bifunctional Catalyst Reaction Screening Protocols

5.3.1 General Procedure for Cu(I) Intramolecular Carbocyclization Screens

The procedure used was adopted from the protocol reported by Michelet.\textsuperscript{124} First, a stock solution was made by adding formyl alkyne 2.1 (200 mg, 0.790 mmol) and cyclohexylamine (0.018 mL, 0.16 mmol) to a 4 mL vial with stir bar containing DCE (2.0 mL). After 10 min., 0.2 mL of this solution which contained formyl alkyne 2.1 (0.020 g, 0.079 mmol) and cyclohexylamine (1.8 \mu L, 0.016 mmol), was added to a 1.5 mL HPLC vial, which contained a solution of the ligand (0.012 mmol) and metal salt (0.012 mmol) in DCE (0.15 mL). The vials were capped and shaken for 16 h. The reaction mixtures were filtered through silica plugs in Pasteur pipets, eluted with EtOAc (~2 mL), and condensed.
Yields of 2.2 were measured by \textsuperscript{1}H NMR in CDCl\textsubscript{3} using pentachloroethane as an internal standard. Reactions using Cu(I) metal salts followed the same general procedure, however sample vials were set up in the glovebox and shaken on the benchtop.

5.3.2 General Procedure for Cu(I) Intermolecular Reaction Screens

Alkyne and carbonyl stock solutions were made first by mixing the alkyne (0.65 mmol) with solvent (0.75 mL) in a 1.5 mL HPLC vial. Carbonyl compounds (0.155 mmol) were mixed with solvent (0.6 mL) in a 1.5 mL HPLC vial. The vials were sealed and Ar was bubbled through the solutions for 10 min before they were brought into the glovebox. In the glovebox, a ligand 2.25a and (CH\textsubscript{3}CN)\textsubscript{4}CuBF\textsubscript{4} stock solution was made by weighing (CH\textsubscript{3}CN)\textsubscript{4}CuBF\textsubscript{4} (0.035 g, 0.109 mmol) into a 20 mL scintillation vial, followed by addition of 2.25a (0.042 g, 0.109 mmol) as a solution in solvent (10.5 mL). To separate HPLC vials, 0.5 mL of this stock solution containing 2.25a (2.0 mg, 0.005 mmol) and (CH\textsubscript{3}CN)\textsubscript{4}CuBF\textsubscript{4} (1.7 mg 0.005 mmol) was added followed by the respective addition of the alkyne stock solution (0.15 mL, 0.130 mmol) and carbonyl stock solution (0.10 mL, 0.026 mmol). If additives (0.005 mmol) were used, they were added at this point as a stock solution in solvent (0.1 mL). The reaction vials were removed from the glovebox, sealed with parafilm, and heated in a sand bath at 50 °C without stirring for 16 h. After heating, the samples were directly analyzed by GC-MS. GC-MS method (see General Information for further details): 50 °C to 100 °C over 2 min., then hold at 100 °C for 2 min, ramp to 280 °C over 18 min, then hold at 280 °C for 8 min. 2 \mu L injection volume.
5.3.3 General Procedure for PyOX Intermolecular Reaction Screens

Complex 2.28 (2 mg, 0.0070 mmol) and metal salt (0.0070 mmol) were dissolved in NO₂Me (0.3 mL) in an oven-dried 1.5 mL HPLC vial. The alkene (0.070 mmol) and carbonyl (0.070 mmol) substrates were added as individual stock solutions in NO₂Me (0.1 mL). Vials were then capped and heated at 50 ºC for 24 h. Reactions using ethylene were bubbled with ethylene and stirred at 50 ºC for 24 h under ethylene (50 psi) in a pressure flask. After heating, all samples were directly analyzed by GC-MS.

5.4 Dual Catalyst Reaction Screening Protocols

5.4.1 General Procedures for Intramolecular Reactions

Procedure A: Complex 3.17a (2.0 mg, 0.003 mmol) was dissolved in CH₃NO₂ (250 µL) in a 1.5 mL HPLC vial. This solution was transferred to a separate aluminum foil wrapped 1.5 mL HPLC vial containing AgBF₄ (1.0 mg, 0.0046 mmol). The vial was capped and placed in an oil bath heated to 50 °C for 30 min. The solution was filtered through a 22 µM PTFE syringe filter into another 1.5 mL HPLC vial containing substrate 3.31 (2.0 mg, 0.006 mmol) dissolved in CH₃NO₂ (100 µL). Lastly, organocatalyst (3.8, 3.9, cyclohexylamine, or pyrrolidine) (0.003 mmol) was added as a solution in CH₃NO₂ (100 µL). The reaction was placed in an oil bath and heated at 70 ºC for 16 h. The crude reaction mixtures were loaded onto silica gel plugs made from Pasteur pipettes containing ~4 cm silica gel and eluted with EtOAc (5 mL), then condensed and redissolved with CDCl₃. Analyses were performed by ¹H NMR using pentachloroethane as an internal standard.

Procedure B: Ligand 3.16a (5.0 mg, 0.015 mmol) was dissolved with CH₃NO₂ (500 µL) in a 1.5 mL HPLC vial. The solution was transferred to a separate 1.5 mL HPLC
vial containing (CH$_3$CN)$_4$Pd(BF$_4$)$_2$ (7.0 mg, 0.030 mmol). The solution turned yellow and homogeneous before being transferred to a 1.5 mL HPLC vial containing substrate 3.31 dissolved in CH$_3$NO$_2$ (200 µL). Lastly, organocatalyst 3.9 (4.0 mg, 0.015 mmol) was added as a solution in CH$_3$NO$_2$ (200 µL). The reaction was placed in an oil bath and heated at 70 °C for 16 h. The crude reaction mixture was loaded onto a silica gel plug made from a Pasteur pipette containing ~4 cm silica gel and eluted with EtOAc (5 mL), then condensed and redissolved with CDCl$_3$. Analysis was performed by $^1$H NMR using pentachloroethane as an internal standard.

**Procedure C:** Complex 3.17a (5 mg, 0.008 mmol), was added to a 1.5 mL HPLC vial followed by CD$_3$NO$_2$ (0.5 mL). This solution was transferred to a separate aluminum foil-wrapped 1.5 mL HPLC vial containing AgBF$_4$ (2 mg, 0.012 mmol). The solution was placed in an oil bath heated to 50 °C for 1 h, then filtered through a 22 µm PTFE syringe filter into a 1.5 mL HPLC vial. The solution of the metal complex (1, 5, 10, and 20 mol%) was added to separate 1.5 mL HPLC vials, then diluted up to 0.4 mL with CD$_3$NO$_2$. A solution of 3.31 (5 mg, 0.022 mmol) and pentachloroethane (3 µL, 0.022 mmol) in 0.1 mL CD$_3$NO$_2$ was then added. Lastly, the samples were transferred to a final 1.5 mL HPLC vial containing the organocatalyst 3.9 (1 mg, 0.004 mmol). The samples were placed in an oil bath heated to 70 °C for 24 h before being directly analyzed by $^1$H NMR to measure yield using pentachloroethane as an internal standard.

**Procedure D:** Complex 3.17a (0.003 mmol) were added to 1.5 mL HPLC vials followed by CD$_3$NO$_2$ (0.250 mL). The solutions were transferred to separate aluminum foil-wrapped 1.5 mL HPLC vials containing AgBF$_4$ (1 mg, 0.004 mmol). The reactions were placed in an oil bath heated to 60 °C for 1 h before being syringe filtered. Formyl alkyne 3.31 (3 mg, 0.014 mmol) and pentachloroethane (2 µL, 0.014 mmol) were then added
together as a solution in CD$_3$NO$_2$ (0.1 mL). Lastly, organocatalyst 3.9 (0.001 g, 0.003 mmol) was added as a solution in CD$_3$NO$_2$ (0.1 mL). The reactions were placed in an oil bath heated to 70 °C or left at 20 °C for 24 h before being analyzed by $^1$H NMR using pentachloroethane as an internal standard.

5.4.2 Intermolecular Reaction Screening with Pre-formed Bis Catonic Pt Complex

Complex 3.17a (1.0 mg, 0.0014 mmol) was dissolved in NO$_2$Me (0.3 mL) in an oven-dried 1.5 mL HPLC vial under N$_2$. Next, a 0.028 M solution of AgBF$_4$ in nitromethane (50 µL, 0.0014 mmol) was added via syringe. The vial was wrapped in aluminum foil and heated at 30–40 °C for 1 h. The white precipitate was filtered off by passing the solution through a PTFE syringe filter into another oven dried 1.5 mL HPLC vial. If ethylene was used, ethylene gas was bubbled through the solution for 5 min. The alkene/alkyne (0.014 mmol), aldehyde/ketone/acetal (0.0014–0.014 mmol), organocatalyst/enamine 3.9, 3.19, 3.27, or 3.28 (0.00035–0.0014 mmol), and additive (0.00035 mmol) were respectively added as solutions in NO$_2$Me (50 µL). Vials were either sealed and heated in a sand bath at 80 °C or placed in a pressure tube and stirred under ethylene (50 psi) at 80–90 °C for 20–24 h. Crude reaction mixtures were analyzed directly by GC-MS.

5.4.3 General Screening Procedure for Intermolecular Direct Addition Reaction of Aldehyde 3.34 to Alkyne 3.35

Complex 3.17a (4.1 mg, 0.00677 mmol) or the combination of a ligand (0.00677 mmol) plus metal salt (0.00677 mmol) were dissolved/suspended in solvent (0.3 mL) in an oven-dried 1.5 mL HPLC vial. If the metal plus ligand mixture was not homogenous, the mixture was heated at 55 °C for 1 h and allowed to cool to 20 °C. 5-phenyl-1-pentyne 3.35 (20.6 µL, 0.135 mmol) was added via microsyringe. Next, stock solutions of hexanal 3.34
in solvent (25 uL, 0.0271 mmol), organocatalyst in solvent (25 uL, 0.00542 mmol), and pentachloroethane in solvent (25 uL, 0.0271 mmol) were respectively added. The vials were capped, sealed with parafilm wax, and heated in an oil bath at 55 °C for 24 h. After 24 h, the reactions were analyzed by \(^1\)H NMR using pentachloroethane as an internal standard. Then solutions were sent through a silica plug (2 cm) in a pipette, eluted with DCM (4 mL), diluted to a total volume of 10 mL and analyzed by GC-MS. Samples analyzed exclusively by GC-MS used hexamethylbenzene as an internal standard instead of pentachloroethane.

5.5 Synthetic Experimental Procedures

5.5.1 Synthesis of Bifunctional Precatalysts for Cu(I)

![Image of the molecular structure of the product](image)

**Tert-butyl 2-{{(2S,3R)-3-hydroxy-1-methoxy-1-oxobutan-2-yl}carbamoyl}pyrrolidine-1-carboxylate (2.10)**. N-Boc-L-proline (2.8) (5.38 g, 24.5 mmol) and L-threonine methyl ester, HCl salt 2.9 (4.16 g, 24.5 mmol) were added to a 1.0 L flask with stir bar and sealed under N\(_2\). DCM (400 mL), HOBT (4.13 g, 27.0 mmol), TEA (8.60 mL, 61.7 mmol), and EDC HCl (5.17 g, 27.0 mmol) were sequentially added and the reaction was stirred for 20 h. LC-MS analysis confirmed complete conversion. The reaction was washed with half saturated NaHCO\(_3\) (2 x 200 mL) and 0.2 N HCl (2 x 200 mL). The combined aqueous washes were extracted with DCM (2 x 100 mL). The combined organics were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated to afford amide 2.10 as a colorless oil (5.91 g, 73%). The crude product was pushed forward without further
purification. This compound has been previously reported and characterized (CAS# 80897-23-0). $^1$H NMR (300 MHz, CDCl$_3$) δ 4.58 (dd, $J = 9.0, 2.6$ Hz, 1H), 4.36–4.26 (m, 2H), 3.77 (d, $J = 1.7$ Hz, 3H), 3.48–3.39 (m, 2H), 1.80–2.35 (m, 4H), 1.47 (s, 9H), 1.19 (d, $J = 6.4$ Hz, 3H).

![Tert-butyl 2-[[2S]-1-methoxy-1,3-dioxobutan-2-yl]carbamoyl]pyrrolidine-1-carboxylate (2.11)](image)

**Tert-butyl 2-[[2S]-1-methoxy-1,3-dioxobutan-2-yl]carbamoyl]pyrrolidine-1-carboxylate (2.11).** Alcohol 2.10 (5.91 g, 17.9 mmol) was added to a 1 L round bottom flask with stir bar followed by DCM (300 mL) and Dess-Martin periodinane (8.35 g, 19.7 mmol). The flask was sealed with a septum, flushed with N$_2$, and stirred for 3 h. H$_2$O (0.322 mL, 17.9 mmol) was added and the reaction stirred for an additional 3 h. LC-MS analysis confirmed complete conversion. The reaction was poured on to a 10% Na$_2$S$_2$O$_3$ solution (400 mL) and stirred for 45 min until both layers turned clear. The organic layer was separated, washed with saturated NaHCO$_3$ (2 x 100 mL) and brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude yellow oil was dissolved in DCM and purified via flash chromatography (100 g SiO$_2$ cartridge; 0–80 % EtOAc/hexanes) to afford ketone 2.11 as a yellow oil (4.60 g, 78%). This compound has been previously reported and characterized (CAS# 1027049-00-8).
Methyl 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-2-yl}-5-methyl-1,3-thiazole-4-carboxylate (2.12). Ketone 2.11 (4.59 g, 14.0 mmol) was added to a 250 mL flask with stir bar followed by anhydrous THF (150 mL). The headspace was purged with N₂ before Lawesson's Reagent (8.46 g, 20.9 mmol) was added. The flask was fitted with a reflux condenser and sealed under N₂ before being heated to reflux for 18 h. LC-MS analysis confirmed complete conversion. The reaction was condensed to an oil, dissolved in EtOAc (250 mL) and washed with saturated NaHCO₃ (2 x 250 mL). The aqueous washes were extracted with EtOAc (100 mL), and the combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude red oil was adsorbed onto SiO₂ (25 g) and purified via flash chromatography (100 g SiO₂ cartridge; 0–40% EtOAc/hexanes) to afford 2.12 as an orange oil (3.46 g, 76%). This compound has been previously reported and characterized (CAS# 838853-22-8): ¹H NMR (300 MHz, CDCl₃) δ 5.15 (d, J = 13.8 Hz, 1H), 3.93 (s, 3H), 3.65–3.37 (m, 2H), 2.45–2.12 (m, 2H), 2.00–1.84 (m, 2H), 1.55–1.30 (m, 9H).

Tert-butyl 2-[4-(hydroxymethyl)-5-methyl-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (2.13). Ester 2.12 (3.43 g, 10.5 mmol), sodium triacetoxyborohydride (0.112 g, 0.525 mmol), and sodium borohydride (0.898 g, 23.1 mmol) were added to a 100 mL oven-dried flask with stir bar and sealed under N₂ before anhydrous THF (30 mL) was added. The
reaction stirred for 5 min, then anhydrous methanol (1.70 mL, 42.0 mmol) was added over 15 min. The reaction was heated to 35 °C for 16 h. LC-MS analysis confirmed complete conversion. The reaction was diluted with EtOAc (30 mL) and quenched with saturated NH₄Cl. The layers were separated and the aqueous layer was extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layers were washed with brine and concentrated to afford alcohol 2.13 as a yellow oil (2.65 g, 85%). The crude material was moved forward without purification. [α]D^25 −78.36 (0.573, DCM); TLC Rf: 0.57 (90:10 DCM:MeOH); 1H NMR (300 MHz, CDCl₃) δ 5.15–5.03 (m, 1H), 4.62 (s, 3H), 3.56–3.39 (m, 2H), 2.40–2.37 (m, 2H), 2.28–2.17 (m, 1H), 1.94–1.89 (m, 2H), 1.47–1.34 (m, 9H); 13C NMR is complicated due to rotamers. 13C NMR (75 MHz, CDCl₃) 172.4, 171.5, 154.8, 154.4, 150.8, 150.7, 128.7, 128.5, 80.2, 59.4, 58.9, 58.1, 47.0, 46.6, 34.1, 32.9, 28.5, 28.4, 24.0, 23.2, 11.1; IR (film) 3377, 2975, 1698, 1388, 1366, 1165, 770 cm⁻¹; HRMS (ESI⁺) calcd for C₁₄H₂₂N₂O₃S [M+H]⁺ 299.1424, found 299.1405.

**Tert-butyl 2-[4-(azidomethyl)-5-methyl-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (2.14)**. Alcohol 2.13 (2.12 g, 7.11 mmol) was added to a 250 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (50 mL) was added followed by mesyl chloride (0.660 mL, 8.53 mmol) and triethylamine (1.12 mL, 8.61 mmol). The reaction was stirred at room temperature for 24 h. LC-MS analysis confirmed complete conversion. The DCM was removed under vacuum and the crude oil dissolved with anhydrous DMF (50 mL). Sodium azide (0.544 g, 8.53 mmol) was added in one portion and the reaction stirred for 16 h. The reaction was diluted with ether (250 mL) and washed with water (3 x 250 mL).
The aqueous layers were extracted with ether (2 x 100 mL). The combined organics were
washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude
orange oil was dissolved with minimal DCM and purified via flash chromatography (25 g
SiO$_2$ cartridge; 0–20% EtOAc/hexanes) to afford azide 2.14 as a yellow oil (1.73 g, 75%).

$[\alpha]_D^{25}$ -86.52 (0.620, DCM); TLC $R_f$: 0.40 (80:20 hexane:EtOAc); $^1$H NMR (300 MHz,
CDCl$_3$) $\delta$ 5.12–5.03 (m, 1H), 4.33 (s, 2H), 3.55–3.44 (m, 2H), 2.42 (s, 3H), 2.26–2.21 (m,
2H), 1.94–1.92 (m, 2H), 1.48–1.36 (m, 9H); $^{13}$C NMR is complicated due to rotamers. $^{13}$C
NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 171.2, 154.6, 154.2, 146.0, 145.7, 131.0, 130.8, 80.1,
80.0, 59.3, 58.8, 47.5, 46.9, 33.8, 32.5, 28.4, 28.3, 23.9, 23.1, 11.2; IR (film) 2976, 2093,
1695, 1384, 1166, 1113, 769 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{14}$H$_{21}$N$_5$O$_2$S [M+H]$^+$ 324.1489,
found 324.1457.

**Tert-butyl 2-[4-(aminomethyl)-5-methyl-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate**
(2.15). Azide 2.14 (1.63 g, 5.05 mmol) was added to a 250 mL pressure flask with stir bar
followed by methanol (50 mL). The flask was purged with Ar then 10% Pd/C (0.537 g,
0.505 mmol) was added. The reaction flask was attached to a Parr hydrogenator,
evacuated, and backfilled with hydrogen x 3. The reaction was stirred vigorously under 3
bar of hydrogen for 16 h. LC-MS analysis confirmed complete conversion. The reaction
mixture was passed through a pad of Celite, then concentrated to afford amine 2.15 as a
colorless oil (1.30 g, 87%). The crude product was used directly without further purification.

$[\alpha]_D^{25}$ -83.71 (0.653, DCM); TLC $R_f$: 0.39 (90:10 DCM:MeOH); $^1$H NMR (300 MHz, CDCl$_3$)
$\delta$ 5.15–5.01 (m, 1H), 3.79 (s, 2H), 3.57–3.39 (m, 3H), 2.37 (s, 3H), 3.57–3.39 (m, 3H).
2.37 (s, 3H), 2.28–2.21 (m, 2H), 1.95–1.92 (m, 2H), 1.67 (br s, 2H), 1.49–1.35 (m, 9H); 
$^{13}$C NMR is complicated due to rotamers. $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.7, 171.1, 154.8, 154.4, 152.8, 152.5, 126.6, 126.5, 80.1, 59.5, 59.0, 47.0, 46.5, 39.8, 34.0, 32.9, 28.6, 28.4, 23.9, 23.2, 11.1; IR (film) 3356, 3301, 2974, 1694, 1385, 1164, 1113, 770 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{14}$H$_{23}$N$_3$O$_2$S [$M+H]^+$ 298.1584, found 298.1548.

![Chemical Structure](image)  

2.16a

{[5-Methyl-2-(pyrrolidin-2-yl)-1,3-thiazol-4-yl]methyl}[(quinolin-8-yl)methyl]amine (2.16a). Amine 2.15 (0.200 g, 0.576 mmol) was added to a 25 mL oven-dried flask with stir bar followed by glacial acetic acid (5.0 mL). Next, quinoline-8-carbaldehyde (0.128 g, 0.777 mmol) and sodium triacetoxyborohydride (0.180, 0.847 mmol) were added. The vial was purged with N$_2$ and allowed to stir for 16 h. LC-MS analysis confirmed complete conversion. The reaction was neutralized with saturated NaHCO$_3$ and brought to pH ~9. The aqueous solution was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude dark orange oil was dissolved with DCM (50 mL), and Amberlyst$^\circledR$ 15 ion exchange resin (4 g) was added. The solution was stirred with the resin for 16 h. Analysis by LC-MS confirmed that the desired product had completely bound to the resin. The resin was filtered and washed with DCM (50 mL) and MeOH (50 mL). The washed resin was placed in a 50 mL round bottom flask with 3.5 N ammonia in methanol (30 mL) and stirred for 16 h. After 16 h, the resin was filtered and washed with 3.5 N ammonia in MeOH until no further material was eluted, as detected by TLC. The combined washes were concentrated
and the crude oil dissolved in DCM and purified via flash chromatography (5 g SiO₂; 0–27% 0.5N NH₃ in MeOH:DCM) to afford **2.16a** as a pale yellow oil (75 mg, 32%). [α]D25 -37.73 (0.273, DCM); TLC Rf = 0.16 (90:10 MeOH:DCM); ¹H NMR (400 MHz, CDCl₃) δ 8.91 (dd, J = 4.2, 1.8 Hz, 1H), 8.14 (dd, J = 8.3, 1.8 Hz, 1H), 7.75–7.67 (m, 2H), 7.49 (dd, J = 8.3, 6.9 Hz, 1H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H), 4.49–4.39 (m, 3H), 3.85 (s, 2H), 3.10 (ddd, J = 10.0, 7.2, 5.3, 1H), 3.01 (ddd, J = 10.0, 7.6, 6.5 Hz, 1H), 2.53 (br s, 2H), 2.32 (s, 3H), 2.29–2.18 (m, 1H), 1.99–1.72 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 150.4, 149.5, 147.0, 138.4, 136.4, 128.9, 128.4, 127.9, 127.0, 126.4, 121.0, 49.9, 50.4, 47.0, 33.9, 25.6, 11.3; IR (film) 3301, 2919, 1498, 1445, 828, 792 cm⁻¹; HRMS (ESI⁺) calcd for C₁₉H₂₂N₄S [M+H]⁺ 339.1638, found 339.1607.

**2.16b**

2-[[[[5-Methyl-2-(pyrrolidin-2-yl)-1,3-thiazol-4-yl]methyl]amino]methyl]phenol (2.16b). Amine 2.15 (0.195 g, 0.655 mmol) was added to a 100 mL oven-dried flask with stir bar followed by anhydrous THF (30 mL). Next, salicylaldehyde (0.088 g, 0.720 mmol) and sodium triacetoxyborohydride (0.167 g, 0.786 mmol) were added. The vial was purged with N₂ and stirred for 16 h. LC-MS analysis confirmed complete conversion. The reaction was quenched with saturated NH₄Cl and basified with saturated NaHCO₃. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was dissolved with DCM (50 mL), and Amberlyst® 15 ion exchange resin (4 g) was added. The solution was stirred with the resin for 16 h. Analysis by LC-MS confirmed that the
desired product had completely bound to the resin. The resin was filtered and washed with DCM (50 mL) and MeOH (50 mL). The washed resin was placed in a 50 mL round bottom flask with 3.5 N ammonia in methanol (30 mL) and was stirred for 16 h. After 16 h, the resin was filtered and washed with 3.5 N ammonia in MeOH until no further material was eluted, as determined by TLC. The combined washes were concentrated to give a brown oil, dissolved in DCM, and purified via flash chromatography (10 g SiO$_2$; 0–12% 0.5N NH$_3$ in MeOH/DCM) to afford **2.16b** as a colorless oil (119 mg, 60%). [$\alpha$]$^2$$^5$ -45.04 (2.280, DCM); TLC $R_f$ = 0.19 (90:10 DCM:MeOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.16 (td, $J$ = 8.0, 1.7 Hz, 1H), 6.94 (dd, $J$ = 7.4, 1.5 Hz, 1H), 6.83 (dd, $J$ = 8.1, 1.1 Hz, 1H), 6.76 (td, $J$ = 7.4, 1.2 Hz, 1H), 4.45 (dd, $J$ = 8.0, 5.4 Hz, 1H), 3.93 (s, 2H), 3.74 (s, 2H), 3.17–2.97 (m, 2H), 2.26–2.22 (m, 4H), 1.98–1.74 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.8, 158.3, 148.4, 128.9, 128.7, 128.6, 122.3, 119.0, 116.4, 49.8, 51.4, 47.0, 45.0, 3.9, 25.6, 11.0; IR (film) 3290, 2920, 1589, 1490, 1474, 1456, 1256, 754 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{16}$H$_{21}$N$_3$OS [M+H]$^+$ 304.1478, found 304.1452.

4-Chloro-2-[[[5-methyl-2-(pyrrolidin-2-yl)-1,3-thiazol-4-yl]methyl]amino)methyl]phenol (2.16c). Prepared as described for **2.16b**. Compound purified via flash chromatography (10 g SiO$_2$; 0–12% 0.5N NH$_3$ in MeOH/DCM) to afford **2.16c** as a yellow oil (101 mg, 43%). [$\alpha$]$^2$$^5$ -39.46 (0.147, DCM); TLC $R_f$ = 0.33 (90:10 DCM:MeOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.81 - 6.87 (m, 2H), 6.73 (dd, $J$ = 8.0, 2.0 Hz, 1H), 5.52 (br s, 2H), 4.47 (dd, $J$ = 7.6, 5.4 Hz, 1H), 3.90 (s, 2H), 2.73 (s, 2H), 3.19–2.99 (m, 2H), 2.27–2.21 (m,
4H), 1.99–1.81 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.1, 159.2, 148.0, 133.9, 129.4, 129.2, 120.8, 119.0, 116.7, 59.7, 50.8, 46.9, 44.8, 33.9, 25.5, 11.1; IR (film) 2923, 1585, 1447, 1237, 1081, 902 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{16}$H$_{20}$N$_3$OSCl $[M+H]^+$ 338.1088, found 338.1058.

![Image](2.16d)

**2,4-Di-tert-butyl-6-((((5-methyl-2-(pyrrolidin-2-yl)-1,3-thiazol-4-yl)methyl)amino)methyl)phenol (2.16d).** Prepared as described for 2.16b. Compound purified via flash chromatography (10 g SiO$_2$; 0-7% 0.5N NH$_4$ in MeOH/DCM) to afford 2.16d as a colorless oil (91 mg, 48%). $[a]_D^{25}$ -30.41 (1.207, DCM); TLC $R_f$ = 0.48 (90:10 DCM:MeOH); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.22 (d, $J$ = 1.8 Hz, 1H), 6.82 (d, $J$ = 1.8 Hz, 1H), 4.46 (dd, $J$ = 7.7, 5.4 Hz, 2H), 3.91 (s, 2H), 3.75 (s, 2H), 3.17–3.01 (m, 2H), 2.28–2.20 (m, 4H), 1.90 (m, 3H), 1.42 (s, 9H), 1.28 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 174.5, 154.8, 148.7, 140.4, 135.9, 128.9, 123.6, 123.0, 121.7, 59.7, 52.4, 47.0, 45.1, 35.0, 34.2, 34.0, 31.8, 29.7, 25.6, 11.2; IR (film) 3276, 3251, 1480, 1485, 1443, 1236, 877, 820 cm$^{-1}$; HRMS (ESI$^+$) calcd for C$_{24}$H$_{37}$N$_3$OS $[M+H]^+$ 416.2730, found 416.2709.
5.5.2 Synthesis of Bifunctional PyOX Precatalyst

2-(3-bromophenyl)ethanamine (2.45). This was prepared using a procedure described by Saha and coworkers.\textsuperscript{132} LiAlH\textsubscript{4} (3.04 g, 80.0 mmol) was added to a 250 mL oven-dried flask with stir bar and sealed under N\textsubscript{2}. Anhydrous THF (100 mL) was added, and the flask was cooled to –5 °C in an ice/salt bath. Concentrated H\textsubscript{2}SO\textsubscript{4} (3.9 g, 40 mmol) was added dropwise by syringe, and the resulting mixture was stirred at –5 °C for 1 h. A solution of 3-bromo-benzeneacetonitrile (9.80 g, 50.0 mmol) in dry THF (5.0 mL) was added dropwise, the flask was removed from the ice bath when the addition was complete, and the reaction was stirred at room temperature for 1 h. The reaction was then cooled back to –5 °C and quenched by the addition of 1:1 THF:H\textsubscript{2}O (12.4 mL). Et\textsubscript{2}O (50 mL) was added, followed by aqueous NaOH (3.6 M, 24.4 mL). The mixture was filtered through Celite, and the solids were washed well with additional Et\textsubscript{2}O (6 x 50 mL). Water (100 mL) was added and the phases were separated, and the organic phase was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated to afford amine 2.45 as a yellow oil (8.97 g, 90\%). This compound has been previously reported and characterized (CAS# 58971-11-2). IR (thin film): 3363, 3284, 2932, 2863, 1656, 1592, 1565, 1472, 1425, 1372, 1323, 775, 690, 664 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.36–7.29 (m, 2H), 7.20–7.10 (m, 2H), 2.96 (t, \( J = 6.9 \) Hz, 2H), 2.72 (t, \( J = 6.9 \) Hz, 2H), 1.19 (br s, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 142.3, 131.9, 130.1, 129.4, 127.6, 122.6, 43.4, 39.8.
tert-butyl N-[2-(3-bromophenyl)ethyl]carbamate (2.46). Amine 2.45 (8.93 g, 44.6 mmol) was added to a 250 mL oven-dried round bottom flask with stir bar and sealed under N₂. Anhydrous THF (70 mL) and TEA (12.4 mL, 89.0 mmol) were added and the reaction mixture was stirred for 15 min at 0 °C before Boc anhydride (10.7 g, 49.1 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h, then it was diluted with DCM (100 mL) and H₂O (100 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated. The crude yellow oil dissolved in DCM and purified via flash chromatography (340 g SiO₂ column, 0–20% EtOAc/hexanes) to afford 2.46 as a clear yellow oil (11.0 g, 82%). This compound has been previously reported and characterized (CAS# 153732-25-3). TLC Rᵣ = 0.70 (50:50 EtOAc:Hexanes); IR (thin film): 3343, 2976, 2931, 1687, 1596, 1567, 1508, 1474, 1426, 1365, 1343, 1269, 1247, 1162, 777, 692, 670 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37–7.34 (m, 2H), 7.20–7.10 (m, 2H), 4.59 (br s, 1H), 3.36 (q, J = 6.9 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.9, 141.5, 132.0, 130.2, 129.6, 127.6, 122.7, 79.5, 41.7, 36.0, 28.5.

2,4,6-trivinylcyclotriboroxane-pyridine. To an oven dried 1.0 L round bottom flask, trimethyl borate (55.0 mL, 0.448 mol) and anhydrous THF (120 mL) were added. An
addition funnel was attached, and the solution was purged with N\textsubscript{2} and cooled to -78 °C. Vinylmagnesium bromide (310 mL of a 0.7 M solution in THF, 0.217 mmol) was cannula transferred to the addition funnel, added dropwise over the course of 3 h, and the reaction was stirred at -78 °C for an additional 2 h. An aqueous 1M HCl solution (109 mL) was added dropwise over the course of 20 min. The solution was allowed to warm to 20 °C. Brine (100 mL) was added, and the solution was extracted with Et\textsubscript{2}O (3 x 100 mL), and the combined extracts were washed with water (100 mL), brine (100 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under vacuum to 250 mL. The Et\textsubscript{2}O solution was treated with pyridine (44.0 mL, 0.546 mmol) and stirred at 20 °C for 16 h. The solvents were evaporated under reduced pressure to give a pale yellow oil. Kugelrohr distillation under reduced pressure (100-135 °C, 0.5 Torr) gave the desired product as a pale yellow solid (5.65 g, 33%). The \textsuperscript{1}H NMR data obtained was in agreement with that reported in the literature.\textsuperscript{133} \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textdelta 8.82–8.79 (m, 2H), 8.02–7.97 (tt, J =1.6 Hz, J = 7.7 Hz, 2H), 7.61–7.56 (m, 2H), 6.03–6.00 (m, 6H), 5.84–5.78 (m, 3H).

![N-[2-(3-ethenylphenyl)ethyl]carbamate](image)

**tert-butyl N-[2-(3-ethenylphenyl)ethyl]carbamate (2.44).** A 250 mL oven-dried flask with stir bar was covered in tin-foil was equipped with a reflux condenser and sealed under Ar. Aryl bromide 2.46 (5.27 g, 17.6 mmol), ethylene glycol dimethyl ester (100 mL), tetrakis(triphenylphosphine)palladium(0) (406 mg, 0.351 mmol), potassium carbonate (2.91 g, 21.1 mmol), H\textsubscript{2}O (25 mL), and 2,4,6-trivinylcyclotriboroxane-pyridine complex (2.00 g, 8.33 mmol) were sequentially added. The reaction mixture was stirred and heated at reflux in an oil bath for 48 h, then cooled to ambient temperature. Distilled H\textsubscript{2}O (20 mL)
was added, and the resulting mixture was filtered. The filtrate was extracted with Et$_2$O (4 x 25 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (100 g SiO$_2$ column, 0–50% EtOAc/hexanes) to afford 2.44 as a clear yellow oil (3.75 g 86%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.28–7.23 (m, 3H), 7.10–7.08 (m, 1H), 6.69 (dd, $J = 17.6, 10.9$ Hz, 1H), 5.74 (dd, $J = 17.6, 0.8$ Hz, 1H), 5.24 (dd, $J = 10.9, 0.8$ Hz, 1H), 4.57 (br s, 1H), 3.39–3.37 (m, 2H), 2.79 (t, $J = 6.7$ Hz, 2H), 1.44 (s, 9H).

![Chemical structure](image)

**benzyl N-[(1R)-1-[[3-(2-[(tert-butoxy)carbonyl]amino)ethyl]phenyl]-2-hydroxyethyl] carbamate (2.47); benzyl N-[(2R)-2-[[3-(2-[(tert-butoxy)carbonyl]amino)ethyl]phenyl]-2-hydroxyethyl] carbamate (2.48).** In a 500 mL flask with stir bar, a solution of tert-butyl carbamate (6.14 g, 40.6 mmol) in $^0$PrOH (55 mL) was sequentially treated with a freshly prepared solution of NaOH (1.70 g, 42.5 mmol) in H$_2$O (110 mL) and tert-butylhypochlorite (4.42 g, 40.7 mmol). After stirring for 30 min, the solution was cooled to 0 °C and a solution of (DHQD)$_2$PHAL (467 mg, 0.600 mmol) in $^0$PrOH (55 mL) was added. Then, a solution of the 2.44 (3.30 g, 13.3 mmol) in $^0$PrOH (110 mL) was added followed by the addition of K$_2$OsO$_2$(OH)$_4$ (147 mg, 0.400 mmol). After stirring at 0 °C for 7 h, the green solution became a pale yellow. Saturated aqueous sodium sulfite (50 mL) was added, and the reaction was stirred for 20 min. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude product was taken up in DCM and purified via flash chromatography (340 g
SiO₂ column, 35–45% EtOAc/hexanes) to afford the desired regioisomer 2.48 as a white solid (2.21 g, 40%) and the undesired regioisomer 2.47 as a white solid (2.22 g, 40%).

**2.48**: ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.23 (m, 6H), 7.13–7.07 (m, 3H), 5.86 (br s, 1H), 5.08 (s, 2H), 4.79 (br s, 1H), 4.67 (br s, 1H), 3.81–3.77 (m, 2H), 3.37–3.31 (m, 2H), 2.94 (br s, 1H), 2.78–2.68 (m, 2H), 1.37 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 156.1, 139.7, 139.5, 136.4, 128.9, 128.6, 128.5, 128.4, 128.3, 127.1, 124.8, 79.4, 67.0, 66.4, 57.0, 41.6, 36.4, 28.9, 28.5.

**2.47**: ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.29 (m, 6H), 7.23–7.20 (m, 2H), 7.13–7.11 (m, 1H), 5.23 (br s, 1H), 5.11 (s, 2H), 4.84–4.83 (m, 1H), 4.57 (br s, 1H), 3.60–3.54 (m, 1H), 3.37–3.29 (m, 3H), 2.78 (t, J = 6.8 Hz, 2H), 1.41 (s, 9H).

**tert-butyl N-(2-{3-[(1R)-1-amino-2-hydroxyethyl]phenyl}ethyl)carbamate (2.43).** In a 250 mL flask with stir bar, 2.47 (2.10 g, 5.07 mmol) and MeOH (100 mL) were added. The headspace was flushed with N₂ before Pd/C (539 mg, 0.507 mmol) was added. The flask was sealed, and evacuated under house vacuum and flushed three times with H₂. The reaction mixture was stirred at 20 °C for 3 hours under H₂ (3.5 bar). The reaction mixture was filtered through a Celite plug, and the filtrate was condensed down under vacuum to afford amino alcohol 2.43 as a yellow oil (1.41 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.27 (m, 1H), 7.20–7.15 (m, 2H), 7.12–7.10 (m, 1H), 4.58 (br s, 1H), 4.03 (dd, J = 7.9, 4.5 Hz), 3.74 (dd, J = 10.8 Hz, 4.5 Hz), 3.56 (dd, J = 10.8, 7.9 Hz), 3.39-3.36 (m, 2H), 2.80 (t, J = 6.8 Hz), 2.05 (br s, 2H), 1.42 (s, 9H).
tert-butyl N-\{2-[(1R,4S)-1-[(4-chloropyridin-2-yl)formamido]-2-hydroxyethyl]phenyl\}ethylcarbamate (2.49b). Amino alcohol 2.43 (0.305 g, 1.09 mmol) and 4-chloropicolinic acid (0.156 g, 0.990 mmol) were added to a 50 mL oven-dried flask with stir bar sealed under N₂. Anhydrous DCM (30 mL), HOBT (0.161 g, 1.219 mmol), DIPEA (207 uL, 1.19 mmol), and HATU (0.452 g, 1.19 mmol) were sequentially added. The reaction mixture was stirred under N₂ for 16 h. A 50% saturated NaHCO₃ solution (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 20 mL) and EtOAc (2 x 20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was taken up in DCM and purified via flash chromatography (50 g SiO₂, 20–100% EtOAc/hexanes) to afford amide 2.49b as a yellow oil (0.345 g, 83%). \(^1\)H NMR (400 MHz, CD₃CN) \(\delta\) 8.68 (d, \(J = 8.1\) Hz, 1H), 8.56–8.53 (m, 1H), 7.59–7.55 (m, 1H), 7.27–7.17 (m, 3H), 7.11–7.09 (m, 1H), 5.35 (br s, 1H), 5.11–5.05 (m, 1H), 3.88–3.78 (m, 2H), 3.46–3.41 (m, 1H), 3.25–3.17 (m, 2H), 2.27–2.22 (m, 1H), 1.37–1.34 (m, 9H). \(^{13}\)C NMR (100 MHz, CD₃CN) \(\delta\) 163.6, 156.8, 152.5, 150.7, 146.3, 141.4, 140.7, 129.4, 128.8, 128.2, 127.5, 125.6, 123.2, 79.1, 66.0, 56.4, 42.4, 36.7, 28.6.
tert-butyl N-2-{3-[(4R)-2-(4-methylpyridin-2-yl)-4,5-dihydro-1,3-oxazol-4-yl]phenyl} ethyl)carbamate (2.50b). Alcohol 2.49b (0.329 g, 0.784 mmol) was added to a 25 mL with stir bar under N₂. Anhydrous DCM (10 mL) was added, the solution was cooled to –20 °C in a dry ice/MeOH/H₂O bath, and Deoxofluor® (163 uL, 0.885 mmol) was added dropwise over 5 min. The reaction mixture was stirred at –20 °C for 2 h. The reaction was allowed to warm to 20 °C before quenching with saturated NaHCO₃ (10 mL). The aqueous layer was extracted with DCM (3 x 15 mL), and the combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was taken up in DCM and purified via flash chromatography (10 g SiO₂, 3–10% MeOH/DCM) to afford oxazoline 2.50b as a clear and colorless oil (205 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ 8.64 (dt, J = 5.3, 0.6 Hz, 1H) 8.20 (dt, J = 2.0, 0.6 Hz, 1H), 7.45 (ddd, J = 5.3, 2.0, 0.6 Hz, 1H), 7.33–7.29 (m, 1H), 7.19–7.14 (m, 3H), 5.45 (dd, J = 10.3, 9.7 Hz, 1H), 4.92 (dd, J = 10.3, 8.6 Hz, 1H), 4.66 (br s, 1H), 4.40 (dd, J = 9.7, 8.6 Hz, 1H), 3.40–3.31 (m, 2H), 2.82–2.78 (m, 2H), 1.42 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 162.9, 155.9, 150.6, 147.9, 144.9, 141.7, 139.7, 129.1, 128.3, 127.2, 126.0, 124.9, 124.7, 79.2, 75.5, 70.3, 41.7, 36.1, 28.4.

tert-butyl N-[2-(3-bromophenyl)ethyl]-N-methylcarbamate (2.53). Carbamate 2.45 (10.8 g, 35.8 mmol) and powdered KOH (3.01 g, 53.7 mmol) were added to a 50 mL oven-
dried flask with stir bar and sealed under N₂. Anhydrous DMSO (20 mL) was added and the solution was stirred at 20 °C for 5 min. Then methyl iodide (3.34 mL, 53.7 mmol) was slowly added and the reaction mixture was stirred at 20 °C for 48 h. Aqueous NH₄Cl (25%, 450 mL) was added and the product was extracted with EtOAc (4 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was taken up in DCM and purified via flash chromatography (340 g SiO₂ column, 0–20% EtOAc/hexanes) to afford carbamate 2.53 as a clear yellow oil (9.8 g, 87%). This compound has been previously reported and characterized (CAS# 153732-25-3). TLC Rₓ = 0.84 (50:50 EtOAc:Hexanes); IR (thin film): 2974, 2929, 1688, 1596, 1568, 1475, 1424, 1390, 1364, 1214, 1232, 772, 693, 664 cm⁻¹; Note: some peaks are broadened/doubled due to carbamate rotamers. ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.33 (m, 2H), 7.18–7.09 (m, 2H), 3.42 (t, J = 6.9 Hz, 2H), 2.87–2.78 (m, 5H), 1.44–1.38 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.6, 141.7, 131.9, 130.1, 129.4, 127.7, 122.5, 79.5, 50.5, 34.3, 33.8, 28.4.

**tert-butyl N-[2-(3-ethenylphenyl)ethyl]-N-methylcarbamate (2.54).** A solution of potassium vinyltrifluoroborate (2.10 g, 15.7 mmol), PdCl₂ (53.2 mg, 0.30 mmol), PPh₃ (236 mg, 0.90 mmol), Cs₂CO₃ (14.7 g, 45.0 mmol), and aryl bromide 2.53 (4.71 g, 15.0 mmol) in THF/H₂O (9:1) (30 mL) was heated at 85 °C under an Ar atmosphere in a 15 mL sealed pressure tube. The reaction mixture was stirred at 85 °C for 22 h, then cooled to 20 °C and diluted with H₂O (45 mL) followed by extraction with DCM (3 x 150 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered,
and concentrated. The crude product was taken up in DCM and purified via flash chromatography (100 g SiO$_2$, 0–10% EtOAc/hexanes) to afford olein 2.54 as a clear yellow oil (3.51 g, 90%). R$_f$ = 0.70 (50:50); IR (thin film): 2975, 2930, 1690, 1632, 1602, 1582, 1480, 1451, 1422, 1391, 1364, 1163, 1133, 905, 878, 798, 771, 713 cm$^{-1}$; Note: some peaks are broadened/doubled due to carbamate rotamers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33–7.07 (m, 4H), 6.69 (dd, $J$ = 17.6, 10.9 Hz, 1H), 5.74 (d, $J$ = 17.6 Hz, 1H), 5.21 (d, $J$ = 10.9 Hz, 1H), 3.42 (t, $J$ = 7.0 Hz, 2H), 2.84–2.79 (m, 5H), 1.44–1.39 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 155.7, 139.6, 137.8, 136.9, 128.7, 128.5, 126.9, 124.3, 113.9, 79.3, 50.9, 35.0, 34.6, 28.4. HRMS (ESI$^+$): m/z [M+Na]$^+$ calcd for C$_{16}$H$_{23}$NO$_3$Na: 284.1626; found 284.1621.

![Image](https://example.com)

**tert-butyl N-methyl-N-[2-[3-(oxiran-2-yl)phenyl]ethyl]carbamate (2.55).** Olefin 2.54 (1.03 g, 3.92 mol) was added to a 25 mL oven-dried flask with stir bar and sealed under N$_2$. Anhydrous DCM (15 mL) was added and the solution was cooled to 0 °C. mCPBA (1.26 g, 5.11 mmol) was slowly added, and the reaction mixture was stirred at 0 °C for 3 h. The solution was allowed to warm to 20 °C and stirred for an additional 16 h. The reaction mixture was diluted with hexanes (200 mL), washed with 50% saturated NaHCO$_3$ (3 x 50 mL) and brine (50 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude pale yellow oil was taken up in DCM and purified via flash chromatography (100 g SiO$_2$, 0–20% EtOAc/hexanes) to afford epoxide 2.55 as a colorless oil (940 mg, 75%). TLC R$_f$ = 0.77 (50:50 EtOAc:Hexanes); IR (thin film): 2975, 2930, 1687, 1480, 1451, 1391, 1364, 1161, 1132, 879, 792, 771, 702 cm$^{-1}$; Note: some peaks are broadened/doubled.
due to carbamate rotamers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30–7.25 (m, 1H), 7.14–7.08 (m, 3H), 3.84 (dd, $J = 4.1$, 2.6 Hz, 1H), 3.42 (t, $J = 7.6$ Hz, 2H), 3.14 (dd, $J = 5.5$, 4.1 Hz, 1H), 2.83–2.78 (m, 6H), 1.44–1.39 (m, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 155.7, 139.6, 137.8, 136.9, 128.7, 128.5, 126.9, 124.3, 113.9, 79.3, 50.9, 35.0, 34.6, 28.5. HRMS (ESI$^+$): m/z [M+Na]$^+$ calcd for C$_{16}$H$_{23}$NO$_3$Na: 300.1576; found: 300.1570.

tert-butyl N-[2-[3-(1-azido-2-hydroxyethyl)phenyl]ethyl]-N-methylcarbamate (2.56).

Epoxide 2.55 (715 mg, 2.58 mmol) and H$_2$O (12 mL) were added to a 25 mL flask. To the stirred suspension was added sodium azide (504 mg, 7.75 mmol) and the reaction mixture was heated at 60 °C for 32 h. The flask was cooled to 20 °C, and H$_2$O (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were washed with brine (40 mL) and concentrated. The crude product was taken up in DCM and purified via flash chromatography (100 g SiO$_2$, 0–60% EtOAc/hexanes) to afford azide 2.55 as a colorless oil (533 mg, 71%). TLC R$_f$ = 0.62 (50:50 EtOAc:Hexanes); IR (thin film): 3425, 2976, 2931, 2868, 2096, 1667, 1482, 1451, 1428, 1393, 1365, 1249, 1161, 1134, 876, 792, 771, 706 cm$^{-1}$; Note: some peaks are broadened/doubled due to carbamate rotamers. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32–7.30 (m, 1H), 7.23–7.12 (m, 3H), 4.63 (t, $J = 6.2$ Hz, 1H), 3.75 (m, 2H), 3.44–3.42 (m, 2H), 2.83–2.78 (m, 5H), 2.66–2.51 (br s, 1H), 1.38 (br s, 9H) $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 155.8, 140.0, 136.8, 129.3, 129.1, 129.0, 127.8, 125.3, 79.5, 67.7, 66.5, 50.8, 50.1, 34.5, 34.0, 28.5. HRMS (ESI$^+$): m/z [M+Na]$^+$ calcd for C$_{16}$H$_{24}$N$_4$O$_3$Na: 343.1746; found: 343.1741.
tert-butyl $N$-[2-[3-(1-amino-2-hydroxyethyl)phenyl]ethyl]-$N$-methylcarbamate (2.57). Azide 8 (503 mg, 1.57 mmol) and MeOH (100 mL) were added to a 50 mL flask with stir bar. The headspace was flushed with $N_2$ for 5 minutes before Pd/C (167 mg, 0.157 mmol) was added. The flask was sealed and purged with $H_2$. The reaction mixture was stirred at 20 °C for 4 h under a positive pressure of $H_2$ using a balloon. The reaction mixture was filtered through a Celite plug, and the filtrate was concentrated to afford amine 2.57 as a colorless oil (442 mg, 96%). IR (thin film): 3355, 3297, 2974, 2929, 2865, 1686, 1481, 1451, 1392, 1364, 1305, 1248, 1215, 1162, 1133, 1049, 877, 823, 794, 771, 706 cm$^{-1}$; Note: some peaks are broadened/doubled due to carbamate rotamers. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.30–7.09 (m, 5H), 4.02 (dd, $J = 7.9$, 4.4 Hz, 1H), 3.72 (dd, $J = 10.7$, 4.4 Hz, 1H), 3.55 (dd, $J = 10.7$, 7.9 Hz, 1H), 3.44 –3.41 (m, 2H), 2.83–2.80 (m, 5H), 1.38 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.8, 143.2, 139.6, 128.9, 128.1, 127.2, 124.5, 79.4, 68.2, 57.4, 50.8, 34.6, 34.1, 28.5. HRMS (ESI$^+$): m/z [M+H]$^+$ calcd for C$_{16}$H$_{27}$N$_2$O$_3$: 295.2022; found: 295.2016.

**tert-butyl $N$-[2-(3-hydroxy-1-[(pyridin-2-yl)formamido]ethyl)phenyl]ethyl]-$N$-methylcarbamate (2.58).** Amine 2.57 (450 mg, 1.53 mmol) was added to a 100 mL oven-dried flask with stir bar and sealed under N2. Anhydrous DCM (30 mL), picolinic acid (190
mg, 1.53 mmol), HOBt (370 mg, 2.29 mmol), EDC-HCl (440 mg, 2.29 mmol), and DIPEA (523 μL, 3.06 mmol) were sequentially added and the reaction mixture was stirred at 20 ºC for 16 h. After 16 h, the reaction was concentrated under reduced pressure and taken up into EtOAc (100 mL) before being washed with H₂O (2 x 30 mL), saturated NaHCO₃ (2 x 30 mL), and brine (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude oil was taken up in DCM and purified via flash chromatography (50 g SiO₂, 0-8% MeOH:DCM) to yield a mixture of amide 2.58 and an ester byproduct formed from additional reaction of the primary alcohol with picolinic acid. This byproduct was easily converted back to 2.58 by redissolving the crude mixture in H₂O:THF (1:3) (32 mL) and adding LiOH-H₂O (25.7 mg, 0.613 mmol), then stirring at 20 ºC for 30 min. The aqueous layer was extracted with DCM (4 x 20 mL), and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated to afford exclusively amide 2.58 as a pale yellow oil (432 mg, 71% over 2 steps). TLC Rᵣ = 0.78 (90:10 DCM:MeOH); IR (thin film): 3385, 2974, 2930, 1665, 1591, 1570, 1516, 1484, 1465, 1433, 1393, 1365, 1164, 1135 cm⁻¹; Note: some peaks are broadened/doubled due to carbamate rotamers. ¹H NMR (300 MHz, CDCl₃) δ 8.77 (br s, 1H), 8.57 (d, J = 4.7 Hz, 1H), 8.19 (dd, J = 7.8 Hz, 0.8 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 7.30–7.04 (m, 5H), 5.22 (dt, J = 7.6, 4.8 Hz, 1H), 3.99 (t, J = 4.8 Hz, 2H), 3.41–3.39 (m, 2H), 2.84–2.81 (m, 7H), 1.38–1.34 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 164.7, 149.8, 148.3, 139.7, 139.5, 137.5, 129.2, 128.9, 128.6, 127.5, 126.4, 125.0, 122.5, 79.5, 66.8, 56.1, 50.8, 49.9, 34.5, 28.5; HRMS (ESI⁺): m/z [M+H]⁺ calcd for C₂₂H₃₀N₃O₄: 400.2236; found: 400.2231.
**tert-butyl N-methyl-N-[2-(3-[2-(pyridin-2-yl)-4,5-dihydro-1,3-oxazol-4-yl]phenyl]ethyl)carbamate (2.59).** Amide 10 (413 mg, 1.03 mmol) was added to a 50 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (15 mL) was added and the solution was cooled to −20 °C in a dry ice/MeOH/H₂O bath. Deoxofluor® (226 μL, 1.23 mmol) was added dropwise, and the mixture was stirred at −20 °C for 1 h. After 1 h, the reaction mixture was allowed to warm up to 20 °C and the mixture was stirred for an additional 1 h. The reaction was quenched with saturated NaHCO₃ (10 mL) and water (10 mL), and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was taken up in DCM and purified via flash chromatography (25 g SiO₂, 0–6% MeOH/DCM) to afford oxazoline 2.59 as an orange oil (346 mg, 88%).

TLC Rᵣ = 0.62 (90:10 DCM:MeOH); IR (thin film): 2974, 2929, 1687, 1640, 1477, 1441, 1391, 1363, 1308, 1248, 1164, 1134, 1099, 1043, 964, 878, 799, 772, 744, 706 cm⁻¹; Note: some peaks are broadened/doubled due to carbamate rotamers. ¹H NMR (400 MHz, CDCl₃) δ 8.76–8.74 (m, 1H), 8.17, (d, J = 7.9 Hz, 1H), 7.81 (td, J = 7.9, 1.7 Hz, 1H), 7.44 (ddd, J = 7.4, 5.0, 1.0 Hz, 1H), 7.31–7.29 (m, 1H), 7.19–7.10 (m, 3H), 5.44 (dd, J = 10.1, 8.7 Hz, 1H), 4.90 (dd, J = 10.1, 8.7 Hz, 1H), 4.38 (t, J = 8.7 Hz, 1H), 3.41 (m, 2H), 2.9–2.7 (m, 5H), 1.43–1.39 (br s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 164.0, 155.7, 149.9, 146.8, 142.1, 140.0, 136.8, 129.1, 128.4, 127.4, 125.9, 124.9, 124.4, 79.4, 75.4, 70.4, 51.0, 34.7, 34.2, 28.5; HRMS (ESI⁺): m/z [M+H]⁺ calcd for C₂₂H₂₆N₃O₃: 382.2131; found: 382.2125.
methyl(2-{3-[2-(pyridin-2-yl)-4,5-dihydro-1,3-oxazol-4-yl]phenyl}ethyl)amine  (2.28).

Carbamate 2.59 (157 mg, 0.142 mmol) was added to a 50 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (15.0 mL) was added, followed by dropwise addition of TFA (15.0 mL, 20.6 mmol). The reaction mixture was stirred for 10 min at 20 ºC. After 10 min, the reaction mixture was added dropwise into saturated NaHCO₃ (400 mL). The aqueous layer was extracted with DCM:MeOH (9:1) (5 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was taken up in DCM and purified via flash chromatography (12 g C18 cartridge, 0–80% 0.5 N NH₃ in MeOH/H₂O) to afford amine 2.28 as a colorless oil (64 mg, 55%). TLC Rₚ = 0.04 (90:10 DCM:MeOH); IR (thin film): 3394, 3056, 2934, 2801, 1640, 1583, 1570, 1471, 1441, 1362, 1248, 1102, 1043, 958, 801, 745, 706; ¹H NMR (300 MHz, CDCl₃) δ 8.75 (d, J = 4.8 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.46–7.42 (m, 1H), 7.32–7.27 (m, 1H), 7.19-7.14 (m, 3H), 5.44 (dd, J = 10.1, 8.7 Hz, 1H), 4.90 (dd, J = 10.1, 8.7 Hz, 1H), 4.44 (t, J = 8.7 Hz, 1H), 2.84–2.80 (m, 4H), 2.42 (s, 3H), 1.11 (br s, 1H);

¹³C NMR (75 MHz, CDCl₃) δ 163.9, 149.9, 146.8, 142.1, 140.8, 136.8, 129.0, 128.2, 127.3, 125.9, 124.8, 124.4, 75.4, 70.4, 53.3, 36.5, 36.6; HRMS (ESI⁺): m/z [M+H]⁺ calcd for C₁₁H₂₀N₃O: 282.1606; found: 282.1601.
5.5.3 Synthesis of PyBOX-Pt Complexes and Preformed Enamines

![Pyridine-2,6-dicarbonyl dichloride (3.14)](image)

**Pyridine-2,6-dicarbonyl dichloride (3.14):** 2,6-pyridinedicarboxylic acid (5.00 g, 29.9 mmol) was added to a 100 mL oven-dried flask with stir bar and sealed under N\(_2\). Anhydrous DCM (45.0 mL) was added via syringe and the suspension was cooled to 0 °C. Then oxalyl chloride (5.6 mL, 66.2 mmol) and anhydrous DMF (2 drops, ~20 µL) were sequentially added via syringe. The reaction mixture was warmed to 20 °C and stirred for 24 h vented into a saturated NaHCO\(_3\), at which point the solution became a homogenous pale yellow solution. Excess oxalyl chloride and solvent were removed under vacuum to afford 3.14 as an off-white solid (6.07 g, 99%). This compound has been previously reported and characterized (CAS# 3739-94-4). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.25–8.14 (m, 3H); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 165.4, 148.0, 139.4, 127.7.

![N2,N6-Bis[(2S)-1-hydroxy-2,2-dimethylpropyl]-2,6-pyridinedicarboxamide (15a)](image)

**N2,N6-Bis[(2S)-1-hydroxy-2,2-dimethylpropyl]-2,6-pyridinedicarboxamide (15a):** L-tert-leucinol (398 mg, 3.40 mmol) and TEA (0.50 mL, 3.59 mmol) were added to a 25 mL oven-dried flask with stir bar and sealed under N\(_2\). Anhydrous DCM (15 mL) was added and the solution was cooled to 0 °C in an ice bath before a solution of 3.14 (0.330 g, 1.62 mmol) in anhydrous DCM (3.0 mL) was added via syringe dropwise over 5 min. The reaction mixture was removed from the ice bath and stirred for 16 h at 20 °C. The reaction mixture was diluted with DCM (15 mL) and washed with saturated NaHCO\(_3\) (3 x 10 mL)
and H₂O (10 mL). The organic layer was dried over anhydrous Na₂SO₄, and concentrated. The crude off-white solid was taken up in DCM and purified via flash chromatography (25 g SiO₂ column, 0–10% i-PrOH/DCM) to afford **3.15a** as a white solid (514 mg, 87%). This compound has been previously reported and characterized (CAS# 1112149-02-6). ^1^H NMR (300 MHz, CDCl₃) δ (8.29 d, J = 7.9 Hz, 2H), 8.06 (d, J = 9.2 Hz, 2H), 8.01 (t, J = 7.9 Hz, 1H), 4.01–3.95 (m, 4H), 3.78–3.70 (m, 2H), 2.96 (t, J = 4.6 Hz, 2H), 1.05 (s, 18H); ^1^C NMR (75 MHz, CDCl₃) δ 164.4, 148.7, 139.4, 125.2, 63.2, 60.0, 34.1, 27.1.

**3.15a**

**N₂,N₆-Bis(2-hydroxyl-1,1-dimethylethyl)-2,6-pyridinedicarboxamide (3.15b):** 2-amino-2-methyl-1-propanol (6.00 mL, 62.9 mmol) and TEA (9.20 mL, 66.0 mmol) were added to a 250 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (50 mL) was added, an addition funnel was attached, the apparatus was purged with N₂ for 10 min, and cooled to 0 ºC in an ice bath. A solution of **3.14** (6.10 g, 29.9 mmol) in anhydrous DCM (45 mL) was added dropwise to the reaction via the addition funnel over the course of 1 h at 0 ºC. The reaction was diluted with DCM (100 mL), and washed with saturated NaHCO₃ (3 x 50 mL) and H₂O (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude yellow oil was taken up in DCM and purified via flash chromatography (100 g SiO₂ column, 0–10% i-PrOH/DCM) to afford **3.15b** as a pale yellow oil (1.88 g, 20%). This compound has been previously reported and characterized (CAS# 211050-32-7). ^1^H NMR (300 MHz, CDCl₃) δ 8.31 (d, J = 7.8 Hz, 2H), 8.08 (br s, 2H), 8.04 (t, J = 7.8 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.71 (d, J = 6.1 Hz, 4H), 1.47 (s, 12H); ^1^C NMR (75 MHz, CDCl₃) δ 163.3, 148.8, 139.5, 124.7, 70.7, 55.5, 24.2.
2,6-Bis[(4R)-4-tert-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (3.16a): Diol 15a (490 mg, 1.34 mmol) was added to a 25 mL oven-dried flask with stir bar and sealed under N2. Anhydrous DCM (15 mL) was added and the solution was cooled to –20 °C in a dry ice/MeOH:H₂O bath. Deoxo-Fluor® (519 uL, 2.82 mmol) was added dropwise over 5 min. The reaction mixture was stirred at –20 °C for 2 h, removed from the bath, and stirred an additional 10 h at 20 °C. The reaction was monitored via TLC (9:1 DCM:MeOH), which indicated complete conversion. The reaction was quenched with saturated NaHCO₃ (5 mL) and water (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude residue was taken up in DCM and purified via flash chromatography (25 g SiO₂ column, 0–1% MeOH/EtOAc) to afford 3.16a as a white solid (320 mg, 73%). This compound has been previously reported and characterized (CAS# 118949-63-6). Rᵣ = 0.86 (9:1 DCM:MeOH); ¹H NMR (300 MHz, CDCl₃) δ 8.25 (d, J = 7.9 Hz, 2H), 7.86 (t, J = 7.9 Hz, 1H), 4.48 (dd, J = 8.8, 10.3 Hz, 2H), 4.33 (dd, J = 8.4, 8.8 Hz, 2H), 4.11 (dd, J = 8.4, 10.3 Hz, 2H), 0.97 (s, 18H); ¹³C NMR (75 MHz, CDCl₃) 162.3, 147.0, 137.2, 125.9, 76.5, 69.6, 34.1, 26.1.
2,6-Bis(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-pyridine (3.16b): Diol 15b (410 mg, 1.33 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (10.0 mL) was and the solution was cooled to -20 °C in a dry ice/MeOH/H₂O bath. Deoxo-Fluor® (527 uL, 2.72 mmol) was added dropwise over 2 min, removed from the bath, and stirred an addition 2 h at 20 °C. LC-MS analysis indicated complete conversion. The reaction was quenched with saturated NaHCO₃ (10 mL) and diluted with EtOAc (70 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (15 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was taken up in DCM and purified via flash chromatography (10 g SiO₂ column, 0–100% EtOAc/hexanes) to afford 3.16b as a yellow oil (0.260 g, 72%). This compound has been previously reported and characterized (CAS# 131864-69-2). ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 7.9 Hz, 2H), 7.85 (t, J = 7.9 Hz, 1H), 4.22 (s, 4H), 1.40 (s, 12H).

(t-Bu)-PyBOX-Ptl(BF₄) (3.17a): PyBOX ligand 3.16a (25.0 mg, 0.0721 mmol), Pt(DMSO)₂I₂ (41.0 mg, 0.0685 mmol), and anhydrous DCM (10 mL), were sequentially added to a 25 mL oven dried pressure tube with stir bar. The tube was sealed and the solution was heated to 70 °C in an oil bath for 15 min to give a red homogenous solution. Next, AgBF₄ (14.0 mg, 0.0685 mmol) was added in one portion. The tube was sealed and
heated to 70 °C for 12 h. After 12 h, a white precipitate had formed and the solution was filtered through a PTFE syringe filter and concentrated to give a red oil. The oil was taken up into DCM (1.0 mL), and diethyl ether (15.0 mL) was rapidly added to precipitate the product. The supernatant was removed via pipette and the solid was dried under vacuum to afford 3.17a as an orange solid (47.0 mg, 88%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.80 (t, $J$ = 8.1 Hz, 1H), 8.14 (d, $J$ = 8.1 Hz, 2H), 5.22 (dd, $J$ = 2.1, 9.6 Hz, 2H), 4.95 (dd, $J$ = 8.3 Hz, 9.6 Hz, 2H), 4.31 (dd, $J$ = 2.1, 8.3 Hz, 2H), 1.11 (s, 18H). $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$ 175.5, 143.4, 142.9, 128.6, 77.2, 71.4, 35.6, 26.9; Anal. calcd (found) for C$_{19}$H$_{27}$BF$_4$IN$_3$O$_2$Pt, 1: C, 30.91 (27.57); H, 3.69 (3.44); N, 5.69 (4.46). LC-MS (direct injection): m/z = 651.05.

![3.19](image)

(5S)-2,2,3-Trimethyl-5-(phenylmethyl)-4-imidazolidinone (3.19): To a 4 mL vial, (5S)-(-)-2,2,3-trimethyl-5-(phenylmethyl)-4-imidazolidinone hydrochloride (104.4 mg, 0.410 mmol) was dissolved in H$_2$O (0.5 mL) and DCM (3 mL) was added. Then a 5 w/w% solution of NaOH was added until the solution was basic (pH 14). The mixture was shaken, the organic layer was separated, and the aqueous layer was extracted with DCM (4 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and condensed under vacuum to afford 3.19 as a colorless oil (76.2 mg, 85%). This compound has been previously reported and characterized (CAS# 132278-63-8). $^1$H NMR (300 MHz, CD$_3$NO$_2$) $\delta$ 7.34-7.21 (m, 5H), 3.70 (dd, $J$ = 8.7, 3.9 Hz, 1H), 3.13 (dd, $J$ = 14.1, 3.9 Hz, 1H), 2.76-2.69 (m, 4H), 1.96 (br s, 1H), 1.25 (s, 3H), 1.24 (s, 3H).
In a 5 mL oven-dried flask with stir bar, 2-phenylacetaldehyde (27.5 mg, 0.217 mmol) was added to a solution of (2S,5S)-5-benzyl-2-tert-butyl-3-methyl-imidazolidin-4-one (47.4 mg, 0.217 mmol) in anhydrous toluene (2.00 mL) in the presence of pTsOH (0.4 mg, 1 mol%). 4 Å mol sieves were added, a simple distillation apparatus was attached, and the system was purged with N₂ for 10 min. The mixture was heated at reflux for 4 h under a positive pressure of N₂, and approximately 1 mL of toluene was allowed to distill over. After 4 h, the reaction mixture turned a yellow color and the solution was cooled to room temperature. The reaction mixture was filtered through a cotton plug into an oven dried 20 mL scintillation vial and concentrated to yield a yellow oil. The crude oil was purified using flash chromatography (10 g SiO₂ column, 0–40% EtOAc/hexanes w/ 1% TEA) to afford 3.27 as a white solid (40.0 mg, 57%). This compound has been previously reported and characterized (CAS# 1289555-78-7). ¹H NMR (400 MHz, CD₃NO₂) δ 7.46 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.0 Hz, 1H), 7.13 (t, J = 7.2 Hz, 2H), 6.95 (m, 3H), 6.69 (d, J = 14.3 Hz, 1H), 4.83 (d, J = 14.3 Hz, 1H), 4.50 (s, 1H), 3.91 (dd, J = 8.0, 4.5 Hz, 1H), 3.27 (dd, J = 13.8, 4.5 Hz, 1H), 2.99 (m, 4H), 1.09 (s, 9H); ¹³C (100 MHz, CD₃NO₂) δ 173.4, 141.4, 141.0, 140.6, 131.6, 130.3, 130.2, 128.5, 126.0, 125.8, 103.3, 89.8, 67.3, 41.3, 38.8, 32.3, 27.2.
Styrylpyrrolidine (3.28): Phenylacetaldehyde (390 mg, 3.25 mmol) and 4 Å molecular sieves (3.9 g) were added to a 25 mL oven-dried flask with stir bar and sealed under N2. Anhydrous CHCl₃ (8.0 mL) was added and the solution was cooled to 0 ºC in an ice bath before pyrrolidine (320 uL, 3.90 mmol) was added dropwise. The reaction mixture was stirred at 0 ºC for 2 h. After 2 h, the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 24 h. After 24 h, the solution was filtered through a PTFE syringe filter into an oven dried 25 mL round bottom flask and condensed under vacuum to yield a pale yellow oil. The crude oil was distilled using a Kugelrohr apparatus under high vacuum to afford 3.28 as an orange oil (323 mg, 57%), bp 190-200 ºC/ 0.1 mmHg. This compound has been previously reported and characterized (CAS# 6908-73-2). ¹H NMR (300 MHz, CDCl₃) δ 7.19-7.16 (m, 4H), 7.04 (d, J = 13.8 Hz, 1H), 6.92 (m, 1H), 5.08 (d, J = 13.8 Hz, 1H), 3.24-3.20 (m, 4H), 1.92-.188 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 140.2, 135.9, 128.6, 123.3, 122.9, 97.3, 49.1, 25.4.
5.5.4 Synthesis of STK076545

Ethyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (4.3); ethyl 3-oxo-3-phenyl-2-(pyridin-2-yloxy)propanoate (4.4). A suspension of 2-hydroxypyridone (163 mg, 1.72 mmol), tetrabutylammonium bromide (59.5 mg, 0.184 mmol), and potassium carbonate (765 mg, 55.3 mmol) in acetone (6.0 mL) was heated to 40 °C and stirred for 30 min. Ethyl-2-bromo-3-oxo-3-phenylpropanoate (500 mg, 1.84 mmol) was added and the suspension was stirred at 40 °C for 30 min before being cooled to 20 °C. A solution of acetic acid (160 µL, 2.79 mmol) in water (2.0 mL) was added slowly, and the mixture was stirred for 15 min. The resulting mixture was diluted with H₂O (2.0 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude orange oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂ column, 0–60% EtOAc/hexanes) to afford pyridone 4.3 as a yellow oil (229 mg, 47%) and 4.4 as a yellow oil (44 mg, 9%).

4.3: R_f = 0.25 (50:50 EtOAc:hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 7.3 Hz, 2H), 7.64–7.58 (m, 2H), 7.51–7.46 (m, 3H), 7.37–7.33 (m, 1H), 6.62 (d, J = 8.7 Hz, 1H), 6.22–6.18 (m, 1H), 4.31–4.28 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.9, 166.6, 161.4, 140.6, 136.4, 134.8, 134.0, 129.4, 129.2, 120.2, 106.4, 62.8, 59.2, 14.1; LC-MS t_R = 3.96; m/z = 285.75 (M+H); 4.4: ¹H NMR (400 MHz, CDCl₃) δ 8.11–8.05 (m, 3H), 7.63–7.58 (m, 2H), 7.51–7.46 (m, 2H), 6.98–6.92 (m, 2H), 6.68 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.7, 166.6, 161.3, 146.5, 139.3, 133.9, 129.4, 128.7, 118.3, 111.4, 76.0, 62.2, 14.1; LC-MS t_R = 2.86; m/z = 285.75 (M+H).
1-(2-Oxo-2-phenylethyl)-1,2-dihydropyridin-2-one (4.5). 2-hydroxypyridine (0.263 g, 2.76 mmol) and Cs$_2$CO$_3$ (1.63 g, 5.02 mmol) were added to a 15 mL oven-dried flask with stir bar and sealed under N$_2$. Anhydrous DMF (5.0 mL) was added and the suspension was stirred at 20 °C for 30 min before 2-bromoacetophenone (0.500 g, 2.51 mmol) was added and the suspension was stirred for an additional 1 h at 20 °C. A solution of glacial acetic acid (210 uL, 3.77 mmol) in H$_2$O (2 mL) was slowly added and the mixture was stirred until it turned clear and stopped bubbling (~10 min). The mixture was diluted with H$_2$O (5 mL) and EtOAc (40 mL) and the layers were separated. The organic layer was washed with water (3 x 15 mL) and the combined aqueous layers were extracted with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude yellow solid was dissolved in DCM and purified via flash chromatography (50 g SiO$_2$ column, 0–100% EtOAc/hexanes) to afford pyridone 4.5 as a white crystalline solid (0.411 g, 77%). This compound has been previously reported and characterized (CAS# 952-75-0).$^{205}$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02–8.00 (m, 2H), 7.62 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.51–7.47 (m, 1H), 7.40–7.35 (m, 1H), 7.23–7.21 (m, 1H), 6.59 (d, $J = 9.2$ Hz, 1H), 6.21 (td, $J = 6.7$, 1.3 Hz, 1H), 2.21 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.4, 162.5, 140.2, 138.4, 134.7, 134.1, 129.0, 128.2, 120.8, 106.1, 54.4.
Methyl 3-oxo-3-phenylpropanoate (4.10). NaH (3.7 g, 60% in mineral oil, 92 mmol) and dimethyl carbonate (5.9 g, 66 mmol) were added to a 250 mL oven-dried flask with stir bar. A reflux condenser and addition funnel were attached, the apparatus was sealed and flushed with N₂, and anhydrous toluene (33 mL) was added under N₂. After the mixture was heated to reflux, a solution of acetophenone (3.80 mL, 32.4 mmol) in toluene (17 mL) was added dropwise over 0.5 h. The reaction solution turned orange with the formation of a white precipitate. After the evolution of hydrogen ceased (~15 min), the reaction was cooled to 20 ºC. Glacial acetic acid (10 mL) was added dropwise and a heavy pasty solid separated. Ice-cold water was slowly added until the solid dissolved completely, and the reaction mixture was diluted with EtOAc (200 mL). The organic layer was separated, washed with H₂O (200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was dissolved in DCM and purified via flash chromatography (100 g SiO₂ column, 0–25% EtOAc/hexanes) to afford ester 4.10 as an orange oil (5.65 g, 98%). This compound has been previously reported and characterized (CAS# 614-27-7).\(^{206}\)\(^{1}\)H NMR (300 MHz, CDCl₃) δ 12.51 (s, 0.22 H), 7.94 (m, 2H), 7.78 (m, 0.44 H), 7.76-7.58 (m, 0.44 H), 7.62-7.58 (m, 1 H), 7.50-7.40 (m, 2.7 H), 5.68 (s, 0.22 H), 4.01 (s, 2H), 3.80 (s, 0.65 H), 3.75 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 192.5, 173.6, 171.6, 168.0, 136.0, 133.9, 133.4, 131.4, 128.9, 128.64, 128.6, 126.2, 87.1, 52.6, 51.5, 45.8.
Benzyl 3-oxo-3-phenylpropanoate (4.11). A 25 mL round bottom flask was charged with methyl 3-oxo-3-phenylpropanoate (1.05 g, 5.91 mmol), benzyl alcohol (6.10 mL, 59.1 mmol), ZnO (96.0 mg, 1.18 mmol) and anhydrous toluene (5 mL). The flask was fitted with a short-path distillation head and heated in an oil bath set at 110 °C, distilling the methanol formed during the reaction. After 24 h, LC-MS analysis of the reaction mixture showed complete consumption of the starting material. The reaction mixture was filtered through a plug of Celite and concentrated. The crude residue was dissolved in DCM and purified via flash chromatography (100 g SiO$_2$ column, 0–20% EtOAc/hexanes) to afford benzyl ester 4.11 as a light orange oil (1.43 g, 95%). This compound has been previously reported and characterized (CAS# 63888-22-2).\textsuperscript{207} This compound exists as a mixture of tautomers in CDCl$_3$ (10:1 keto:enol). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 12.50 (s, enol), 7.94 (d, $J = 8.0$ Hz, enol), 7.90 (d, $J = 8.0$ Hz, 2H), 7.77 (d, $J = 7.9$ Hz, enol), 7.59 (t, $J = 7.5$ Hz, 1H), 7.48 – 7.28 (m, 7H), 5.73 (s, enol), 5.25 (s, enol), 5.19 (s, 2H), 4.04 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 192.4, 167.5, 135.4, 133.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 67.3, 46.1.

Benzyl 2-bromo-3-oxo-3-phenylpropanoate (4.12). In a 100 mL flask with stir bar, ester 11 (1.00 g, 3.93 mmol), N-bromosuccinimide (0.735 g, 4.13 mmol), and Amberlyst-15 (2.89 g) in ethyl acetate (30 mL) were stirred at 20 °C for 2.5 h. After completion of the reaction, as indicated by LC-MS, the reaction mixture was filtered and washed with EtOAc (2 x 20 mL). The combined organic filtrates were dried over anhydrous Na$_2$SO$_4$, and
concentrated. The crude product was dissolved in DCM and purified via flash chromatography (50 g SiO₂ column, 0–20% EtOAc/hexanes) to afford alkyl bromide 4.12 as a light yellow oil (1.20 g, 92%). This compound has been previously reported and characterized (CAS# 845733-96-2).¹¹ H NMR (400 MHz, CDCl₃) δ 7.94–7.92 (m, 2H), 7.58 (m, 1H), 7.43 (m, 2H), 7.30–7.23 (m, 5H)¹³C NMR (100 MHz, CDCl₃) δ 188.0, 165.1, 134.6, 134.3, 133.3, 129.2, 128.9, 128.6, 128.6, 128.4, 68.8, 46.4.

**Benzyl 3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenyl-propanoate (4.13).** A suspension of 2-hydroxypyridone (212 mg, 2.23 mmol), tetrabutylammonium bromide (65.4 mg, 0.203 mmol), and potassium carbonate (0.841 g, 6.09 mmol) in acetone (4.0 mL) was heated to 40 °C and stirred for 30 min. Then, bromide 4.12 (676 mg, 2.03 mmol) in acetone (0.5 mL) was added. The suspension was stirred at 40 °C for 30 min and cooled to 20 °C before a solution of acetic acid (232 uL, 4.06 mmol) in water (2.0 mL) was added slowly. The resulting mixture was stirred for 15 min before it was diluted with H₂O (5.0 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude dark orange oil was dissolved in DCM and purified via flash chromatography (50 g SiO₂, 0–50% EtOAc/hexanes) to afford pyridone 4.13 as a colorless oil (496 mg, 70%).¹¹ H NMR (400 MHz, CDCl₃) δ 8.07–8.04 (m, 2H), 7.64 (s, 1H), 7.60 (tt, J = 7.4, 1.2 Hz, 1H), 7.48–7.44 (m, 3H), 7.35–7.26 (m, 6H), 6.61 (d, J = 9.2 Hz, 1H), 6.18 (td, J = 6.8 Hz, 1.3 Hz, 1H), 5.25 (s, 2H).¹³C NMR (100 MHz, CDCl₃) δ 191.7, 166.5, 161.4, 140.7, 136.4, 134.8, 134.6, 133.9, 129.4, 129.2, 128.7, 128.7, 128.4, 120.3, 106.4, 68.3, 59.4; LC-MS tᵣ = 3.72; m/z = 348.10 (M+H).
1-(2-Hydroxy-2-phenylethyl)-1,2-dihydropyridin-2-one (4.14). To a 15 mL flask with stir bar, 4.13 (33.5 mg, 0.096 mmol) and MeOH (3.0 mL) were added. The flask headspace was flushed with N\(_2\) before 10\% Pd/C (10.3, 0.0096 mmol) was added. The flask was flushed with H\(_2\) and stirred under H\(_2\) (1 atm) at 20 °C for 1 h. After 1 h, the reaction mixture was filtered through Celite, condensed under vacuum and analyzed via LC-MS and \(^1\)H NMR, which indicated conversion to alcohol 4.14. \(^1\)H NMR of the crude product showed signals for alkyl protons at 4.36, 3.89, and 5.01 ppm, consistent with published data. This compound has been previously reported and characterized (CAS# 69914-21-2).\(^{208}\) \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 7.43–7.39 (m, 2H), 7.39–7.33 (m, 3H), 7.29–7.26 (m, 2H), 6.56 (d, \(J = 8.5\) Hz, 1H), 6.30 (td, \(J = 6.7\), 1.2 Hz, 1H), 5.01 (dd, \(J = 8.8\), 3.8 Hz, 1H), 4.36 (dd, \(J = 13.1\), 3.8 Hz, 1H), 3.89 (dd, \(J = 13.1\), 8.8 Hz, 1H). 215.75; LC-MS \(t_R\) = 1.68; m/z = 215.75 (M+H).

\(N\)-(2-(Diethylamino)ethyl)-1H-imidazole-1-carboxamide (4.16). In a 4 mL oven-dried vial, 1,1-carbonyl diimidazole (205 mg, 1.26 mmol) was added with stir bar and sealed under N\(_2\). Anhydrous THF (1.2 mL) was added and the solution was cooled to 0 °C in an ice bath. A solution of \(N,N\)-diethylethlenediamine (97.9 mg, 0.842 mmol) in anhydrous DCM (0.6 mL) was added dropwise over 10 min and the solution was stirred at 20 °C for 1.5 h. Next, the solvent was removed via vacuum and the crude product was loaded on to
Celite and purified via flash chromatography (12 g C18, MeOH/H2O gradient) to afford urea 4.16 as a yellow oil (93.7 mg, 53%). This compound has been previously reported (CAS# 698388-51-1).\(^{209}\) \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 8.18 (s, 1H), 7.45–7.42 (m, 1H), 7.09–7.07 (m, 2H), 3.46 (t, \(J = 6.1\) Hz, 2H), 2.66 (t, \(J = 5.6\) Hz, 2H), 2.61–2.51 (m, 4H), 1.06–0.97 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 149.1, 136.1, 130.3, 130.1, 116.1, 51.3, 46.8, 38.2, 11.8; LC-MS \(t_R = 1.01\); m/z = 210.80 (M+H).

\[\text{N-Tert-butyl-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenyl propanamide (4.19).}\]

In a 4 mL oven-dried vial with a stir bar, \(t\)-butylisocyanate (7.0 mg, 0.071 mmol) and NaH (60% w/w in mineral oil, 4.7 mg, 0.118 mmol) were mixed in anhydrous toluene (0.5 mL) under N₂ at 20 °C. Then, ketone 4.5 (10.0 mg, 0.047 mmol) was added in one portion and the mixture was heated at 100 °C for 2 h. After 2 h, the reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and condensed to a yellow residue. The crude product was purified via flash chromatography (10 g SiO₂, 0–100% EtOAc/hexanes) to afford amide 4.19 as a yellow oil (2.2 mg, 15%) and recovered ketone 4.5 (8.0 mg, 80%). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.98 (d, \(J = 8.0\) Hz, 2H), 7.74–7.72 (m, 1H), 7.56–7.52 (m, 1H) 7.43–7.36 (m, 3H), 7.31 (s, 1H), 6.85 (br. s., 1H), 6.61 (d, \(J = 9.0\) Hz, 1H), 6.29 (t, \(J = 6.8\) Hz, 1H). LC-MS \(t_R = 2.96\); m/z = 313.15 (M+H).
2,2-Difluoro-6-methoxy-4-phenyl-2H-1λ³,3,2λ⁴-dioxaborinine (4.20a). To an oven-dried 20 mL vial, 10 (0.420 g, 2.36 mmol) and a stir bar were added and the vial was purged with N₂ for 10 min. Then, anhydrous toluene (10 mL) and boron trifluoride etherate (0.58 mL, 4.71 mmol) were sequentially added. The reaction mixture was stirred at 20 °C for 20 h. The reaction mixture was then concentrated to ~1/3 of its volume and cooled to ~30 °C in a dry ice MeOH/H₂O cooling bath. The precipitated material was filtered off and washed with 5:1 petroleum ether/EtOAc (5 mL), yielding the boron complex 4.20a as a yellow solid (307 mg, 58%). ¹H NMR (300 MHz, CDCl₃) δ 7.96–7.92 (m, 2H), 7.63–7.57 (m, 1H), 7.51–7.46 (2H), 6.03 (s, 1H), 4.12 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.6, 176.3, 134.0, 132.0, 129.0, 127.9, 83.2, 56.1.

Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (4.21). To an oven-dried 1.0 L round bottom flask charged with a stir bar, NaH (60% in mineral oil, 1.99 g, 49.9 mmol) was suspended in anhydrous DMF (100 mL) and cooled to 0 °C in an ice bath under N₂. To the NaH suspension, a solution of 2-hydroxypyridine (4.07 g, 42.1 mmol) in anhydrous DMF (200 mL) was slowly added. The resulting solution was stirred for 1 h at 0 °C before ethyl bromoacetate (4.3 mL, 38 mmol) was added and the mixture was stirred at 20 °C for 1.5 h. The reaction was quenched with saturated NH₄Cl (40 mL) and the product was
extracted with DCM (3 x 150 mL). The combined organic extracts were washed with water (7 x 200 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (100 g SiO$_2$, 0–100 % EtOAc/hexanes) to yield ester 4.21 as a pale yellow oil (3.62 g, 53%). This compound has been previously reported and characterized (CAS# 80056-43-5). $^{196}$ R$_f$: 0.74 (DCM/MeOH 9:1). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40–7.34 (m, 1H), 7.24–7.21 (m, 1H), 6.61–6.58 (m, 1H), 6.23–6.18 (m, 1H), 4.64 (s, 2H), 4.24 (q, 2H, $J$ = 7.1 Hz), 1.29 (t, 3H, $J$ = 7.1 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 167.8, 162.5, 140.3, 138.0, 121.0, 121.0, 106.2, 61.9, 50.5, 14.2.

$N$-[2-(Diethylamino)ethyl]-3-oxo-3-phenylpropanamide (4.22). In a 15 mL oven-dried flask with stir bar, $N$,$N$-diethylethlenediamine (167.0 mg, 1.438 mmol) was added and sealed under N$_2$. Anhydrous MeCN (5.0 mL) and 4.20a (250 mg, 1.11 mmol) were added, and the reaction mixture was stirred at 20 °C for 4 h. After 4 h, an aliquot was removed, condensed under reduced pressure, and dissolved in CDCl$_3$ to monitor the reaction via $^1$H NMR. The reaction mixture was condensed under vacuum, dissolved in EtOAc (30 mL), washed with H$_2$O (2 x 10 mL), dried over MgSO$_4$, filtered, and condensed under vacuum to yield complex 4.22 as a pale yellow oil (283 mg, 82%). The crude oil (259 mg, 0.834 mmol), sodium acetate (0.342 g, 4.17 mmol), ethanol (5.0 mL), and H$_2$O (5.0 mL) were refluxed for 8 h. TLC analysis (10% MeOH/DCM) of the reaction mixture indicated the starting material was consumed. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (30 mL) and washed with water (2 x 10 mL). The combined aqueous layers were saturated with NaCl and extracted with 9:1 DCM:MeOH.
(5 x 10 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated. The crude oil was purified by flash chromatography (10 g SiO$_2$, 0–10% MeOH/DCM) to yield amide 4.22 as a pale yellow oil (147 mg, 67%). R$_f$: 0.50 (9:1 DCM:MeOH); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J = 7.4$ Hz, 2H), 7.61-7.57 (m, 1H) 7.50-7.45 (m, 2H), 3.96 (s, 2H), 3.48 (q, $J = 5.5$ Hz, 2H), 2.79-2.73 (m, 6H), 1.14 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 195.2, 178.2, 136.4, 133.8, 128.8, 128.7, 51.5, 47.0, 46.5, 36.5, 10.5; LC-MS t$_R$ = 1.06; m/z = 263.15 (M+H).

1,3-Diethyl 2-(hydroxyimino)propanedioate (4.25). To a 250 mL oven-dried flask with stir bar, NaOH (1.32 g, 33.0 mmol) was dissolved in glacial acetic acid (10 mL) at 0 ºC in an ice bath under constant stirring. A solution of diethyl malonate (8.01 g, 50.0 mmol) in glacial acetic acid (2.8 mL) was added dropwise over 5 min and the mixture was stirred for 30 min at 0 ºC. Then a solution of sodium nitrite (6.90 g, 100.0 mmol) in water (55 mL) was added dropwise over 1.5 h via an addition funnel. After the addition of the sodium nitrite solution was completed, the addition funnel was replaced with a septum fitted with an empty balloon. The reaction mixture was allowed to warm to 20 ºC and stirred for 16 h. The reaction mixture was saturated with NaCl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with a 1:1 mixture of saturated NaHCO$_3$ and brine (6 x 50 mL) until the pH of the aqueous layer was basic (pH 8–9). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude colorless liquid was dissolved in DCM and purified via flash chromatography (100g SiO$_2$, 0–60% EtOAc/hexanes) to afford 4.25 as a clear and colorless oil (2.10 g, 22%). This compound
has been previously reported and characterized (CAS# 6829-41-0). Rf: 0.41 (50:50 EtOAc:hexanes); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 10.13 (br s, 1H), 4.41 (q, \(J = 7.1\) Hz, 2H), 4.36 (q, \(J = 7.1\) Hz, 2H), 1.37 (t, \(J = 7.1\) Hz, 3H), 1.35 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 160.6, 160.1, 144.3, 62.9, 62.7, 14.1.

1,3-Diethyl 2-aminopropanedioate (4.26). Hydroxyimino 4.25 (1.73 g, 9.15 mmol) and EtOH (8.0 mL) were added to a 25 mL pressure tube with stir bar. The headspace was purged with N\(_2\) before 10% Pd/C (97.3 mg, 0.092 mmol) was quickly added. The reaction flask was attached to a Parr hydrogenator, evacuated, and backfilled with hydrogen x 3. The reaction was stirred vigorously under H\(_2\) (3 bar) for 2.5 h. LCMS and TLC analysis indicated complete conversion. The reaction mixture was filtered through a Celite plug using MeOH and concentrated to afford amino malonate 4.26 as a clear yellow oil (1.51 g, 94%). This compound has been previously reported and characterized (CAS# 6829-40-9). Rf: 0.79 (9:1 DCM:MeOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.29–4.20 (m, 4H), 3.80 (s, 1H), 1.91 (br s, 2H), 1.30 (t, \(J = 7.1\) Hz, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.7, 62.1, 58.7, 14.1.

\[\text{O} \quad \text{O} \quad \text{O} \quad \text{NH}_2 \]

4.26

1,3-Diethyl 2-\{[(tert-butoxy)carbonyl]amino\}propanedioate (4.27). Amino malonate 4.26 (1.45 g, 8.28 mmol) was added to a 50 mL flask with stir bar and sealed under N\(_2\).
Anhydrous THF (10 mL) and TEA (2.3 mL, 16.5 mmol) were added and the solution was cooled to 0 °C in an ice bath. BOC anhydride (2.00 g, 9.16 mol) was added and the reaction mixture was allowed to warm to 20 °C and stirred for 16 h. TLC analysis (50:50 EtOAc:hexanes; vanillin and ninhydrin stains) indicated complete conversion. DCM (50 mL) and H2O (30 mL) were added. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na2SO4, filtered, and concentrated. The crude yellow oil was dissolved in DCM and purified via flash chromatography (100 g SiO2, 0–60% EtOAc/hexanes) to afford 4.27 as a clear and colorless oil (2.00 g, 88%). This compound has been previously reported and characterized (CAS# 102831-44-7). Rf: 0.70 (50:50 EtOAc:hexanes; vanillin stain); 1H NMR (300 MHz, CDCl3) δ 5.58 (d, J = 7.6 Hz, 1H), 4.94 (d, J = 7.6 Hz, 1H), 4.33–4.21 (m, 4H), 1.45 (s, 9H), 1.30 (t, J = 7.1 Hz, 6H); 13C NMR (75 MHz, CDCl3) δ 166.8, 154.9, 80.7, 62.6, 57.7, 53.4, 28.3, 14.1.

**Tert-butyl N-[bis([2-(diethylamino)ethyl]carbamoyl)methyl]carbamate (4.28).** Boc protected amino malonate 4.27 (712 mg, 2.59 mmol), N,N-diethylethylenediamine (2.40 g, 20.7 mmol), and xylenes (5.0 mL) were added to a 25 mL oven-dried flask with stir bar. The flask was fitted with a reflux condenser, sealed under N2, and refluxed for 24 h. LCMS analysis indicated near complete conversion with some mixed amide-ester intermediate. The reflux condenser was replaced with a short path distillation condenser and xylenes and excess N,N-diethylethylenediamine were distilled off under ambient pressure. The crude oil was adsorbed onto Celite and purified via flash chromatography (12 g C18, 0–
95% MeOH/H₂O w/ 0.1% NH₄OH) to afford diamide 4.28 as a pale yellow oil (396 mg, 37%). ¹H NMR (300 MHz, CDCl₃) δ 7.42 (br s, 2H), 6.01 (br s, 1H), 4.63 (s, 1H), 3.29 (m, 4H), 2.55–2.49 (m, 12H), 1.45 (s, 9H), 1.01 (t,  J = 7.1 Hz, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 155.8, 80.7, 58.2, 51.2, 46.9, 37.7, 28.4, 12.0.

**Tert-butyl N-(1-[[2-(diethylamino)ethyl]carbamoyl]-2-oxo-2-phenylethyl)carbamate (4.29).** Magnesium (15.0 mg, 0.616 mmol) and CCl₄ (150 µL) were added to a 10 mL oven-dried flask with stir bar and sealed under N₂. Ethanol (74.6 µL, 1.28 mmol) was added dropwise at 20 ºC and the reaction was stirred for 20 min at 20 ºC. Then diethyl ether (0.5 mL) as added, a reflux condenser was attached, and the reaction mixture was refluxed for 1.5 h. After cooling to 20 ºC, a solution of diamide 4.28 (128 mg, 0.308 mmol) in EtOH (0.5 mL) was added dropwise. Then diethyl ether (0.5 mL) was added and the reaction mixture was stirred at room temperature for 1 h before benzoyl chloride (17.5 µL, 0.150 mmol) was added dropwise. LCMS analysis indicated incomplete conversion so additional benzoyl chloride (15.0 µL, 0.130 mmol) was added dropwise and the reaction mixture was stirred an additional 30 min. Saturated NaHCO₃ (5 mL) was added and the mixture was extracted with EtOAc (3 x 8 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was taken up into DCM and purified via flash chromatography (10 g SiO₂, 0–10% MeOH/DCM) to afford β-keto-amide 4.29 as an off white solid (46 mg, 44%). Rf: 0.54 (9:1 DCM:MeOH); ¹H NMR (300 MHz, CDCl₃) δ 8.10 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 6.20 (d,  J = 6.1 Hz, 1H), 5.75 (d,  J = 6.1 Hz, 1H), 3.30 (q,  J = 5.6 Hz, 2H), 2.58–2.54 (m, 6H), 1.44 (s, 9H), 1.03 (t,  J = 7.0 Hz, 6H); ¹³C NMR (75
MHz, CDCl₃) δ 193.7, 166.4, 155.3, 134.7, 134.1, 129.7, 128.7, 80.7, 60.9, 51.2, 46.9, 37.0, 28.3, 11.5.

2-(2-Oxo-1,2-dihydropyridin-1-yl)acetic acid (4.32). Ester 4.21 (3.59 g, 19.8 mmol) and EtOH:H₂O (1:1, 60 mL) were added to a 250 mL oven-dried flask with stir bar and cooled to 0 °C. A 1 N aqueous solution of LiOH (40 mL, 40 mmol) was added and the solution was stirred for 2 h at 20 °C. After 2 h, ethanol was removed under vacuum and 2 M HCl was added to the aqueous solution to reach a pH ~ 6. Next, the solution was concentrated down to dryness and the crude solid was dissolved with DCM and purified via flash chromatography (50 g SiO₂, 0–10% MeOH/DCM w/ 0.1% formic acid) to afford 4.32 as a white powder (2.04 g, 67%). This compound has been previously reported and characterized (CAS# 56546-36-2).¹⁹⁶ ¹H NMR (400 MHz, acetone-d₆) δ 7.62–7.60 (m, 1H), 7.46–7.42 (m, 1H), 6.41–6.25 (m, 1H), 6.26–6.21 (m, 1H), 4.71 (s, 2H).

[2-(Diethylamino)ethyl][(4-methoxyphenyl)methyl]amine (4.33b). To a 100 mL oven-dried flask with stir bar, N,N-diethylethylenediamine (1.25 g, 10.6 mmol) was added and the flask was sealed under N₂. i-PrOH (25 mL) was added and the flask was cooled to 0 °C. Then, p-anisaldehyde (1.58 mL, 12.8 mmol) was added dropwise, and the reaction
was slowly warmed to 20 °C and stirred for 16 h. MeOH (20 mL) was added, the solution was cooled to 0 °C, and NaBH₄ (1.69 g, 44.7 mmol) was added in portions over 1 h. The solution was stirred for an additional 1 h, while warmed to 20 °C. A solution of 10% NaOH in H₂O (25 mL) was added and the resulting mixture was extracted with DCM (3 x 40 mL). The combined organic layers were washed with a 10% aqueous solution of NaI (50 mL). The organic layers were dried over Na₂SO₄, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM (5 mL) and ether (10 mL), cooled to 0 °C, and a 4 M HCl solution in 1,4-dioxane (5.6 mL, 22.4 mmol) was added dropwise. The white precipitate was filtered and washed with DCM and diethyl ether to yield an off-white solid. This was dissolved in water (30 mL), cooled to 0 °C, and the solution was basified with NaOH (to pH ~ 9). The resulting mixture was extracted with DCM (3 x 40 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated to afford amine 4.33b as a yellow oil (1.86 g, 74% yield). This compound has been previously reported (CAS# 65875-40-3).²¹⁰ Rf = 0.57 (9:1 DCM:MeOH); ¹H NMR (300 MHz, CDCl₃) δ 7.23 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 2.66 (t, J = 6.2 Hz, 2H), 2.55 (t, J = 6.2 Hz, 2H), 2.49 (q, J = 7.1 Hz, 4H), 0.99 (t, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 158.6, 132.8, 129.3, 113.8, 55.3, 53.5, 52.7, 47.1, 46.9, 11.9; LC-MS tᵣ = 0.89; m/z = 236.90 (M+H).

![Image of 4.34a](image)

**N-[2-(Diethylamino)ethyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide** (4.34a).

Carboxylic acid 4.32 (37.0 mg, 0.242 mmol) was added to an oven-dried 50 mL flask with stir bar and sealed under N₂. To the suspension, anhydrous DCM (4.0 mL), HOBt (69.4
mg, 0.363 mmol), DIPEA (62.0 uL, 0.362 mmol), and N,N-diethylenediamine (33.7 mg, 0.290 mmol) were sequentially added. The reaction mixture was stirred for 5 min at 20 ºC before EDC-HCl (69.4 mg, 0.362 mmol) was added in one portion. The reaction mixture was stirred at 20 ºC for 48 h. Monitoring via LC-MS showed conversion to the desired product. The solvent was removed under vacuum and the residue was dry loaded using Celite and purified via flash chromatography (12 g C18, 0-95% MeOH/H₂O gradient w/ 0.1% NH₄OH) to afford amide 4.34a as a pale yellow oil (21 mg, 35%). ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.38 (m, 2H), 6.61 (d, J = 9.0 Hz, 1H), 6.24 (td, J = 1.3, 6.7 Hz, 1H), 4.56 (s, 2H), 3.30 (q, J = 5.7 Hz, 2H), 2.57–2.50 (m, 7H), 0.99 (t, J = 7.1 Hz, 6H); ¹³C NMR (75 MHz, CD₃OD) δ 168.1, 163.6, 141.5, 139.8, 139.7, 119.3, 107.2, 52.0, 51.2, 46.9, 36.6, 10.3; LC-MS t<sub>R</sub> = 0.99; m/z = 251.80 (M+H).

N-[2-(Diethylamino)ethyl]-N-[(4-methoxyphenyl)methyl]-2-(2-oxo-1,2-dihydropyridin-1-yl)acetamide (4.34b). Carboxylic acid 4.32 (0.300 g, 19.6 mmol) was added to an oven dried 50 mL flask with stir bar and sealed under N₂. Anhydrous DCE (20.0 mL) was added, and the resulting mixture was cooled to 0 ºC using an ice bath before EDC-HCl (0.563, 29.4 mmol), amine 4.34b (0.300 g, 19.6 mmol), and DMAP (23.9 mg, 1.96 mmol) were added. The reaction was allowed to warm up to 20 ºC and stirred under N₂ for 16 h. The resulting solution was washed with 1 M NaOH (10 mL). The aqueous layer was extracted with DCM (2 x 5 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was dissolved with DCM and purified via flash chromatography (12 g C18, 0–95% MeOH/H₂O
with 0.1% NH₄OH) to afford amide 4.34b as a colorless oil (213 mg, 29%). The ¹H and ¹³C NMR are complicated due to rotamers. ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.24 (m, 3H), 7.20–7.18 (m, 1H), 6.93–6.91 (m, 1H), 6.85–6.82 (m, 1H), 6.58–6.54 (m-1H), 6.22–6.16 (m, 1H), 4.89 (s, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 4.59 (s, 1H), 3.80–3.77 (s, 3H), 3.46–3.37 (m, 2H), 2.64–2.45 (m, 6H), 1.03–0.95 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.0, 166.7, 162.5, 162.4, 159.2, 159.0, 140.0, 140.0, 138.9, 138.7, 129.5, 129.1, 128.2, 127.9, 120.4, 114.3, 114.0, 105.8, 105.7, 55.3, 55.2, 51.5, 51.3, 50.3, 49.7, 49.4, 48.9, 47.5, 47.4, 45.6, 45.3, 45.2, 12.0; LC-MS tᵣ = 1.43; m/z = 371.95 (M+H).

Benzyl 2-bromo-3-hydroxy-3-phenylpropanoate (4.42a). To a 25 mL flask with stir bar, benzyl cinnamate (477 mg, 2.00 mmol), NBS (427 mg, 2.40 mmol) and MeCN:H₂O (4:1) (10 mL) were added and the solution was cooled to 0 ºC. Iodine (50.8 mg, 0.200 mmol) was added and the mixture was stirred for 72 h. The reaction mixture was washed with 10 % aq. sodium thiosulfate (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in DCM and purified by flash chromatography (50 g SiO₂, 0–100% EtOAc/hexanes) to afford bromohydrin 4.42a as a colorless liquid (276 mg, 41%). This compound has been previously reported (CAS# 1332928-50-3).²¹¹ Rᵣ = 0.47 (50:50 EtOAc:hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.37 (m, 10H), 5.20 (s, 2H), 5.07 (dd, J = 5.5, 8.2 Hz, 1H), 4.41 (d, J = 8.2 Hz, 1H), 3.26 (br d, J = 5.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 169.3, 139.0, 134.9, 128.9, 128.7, 128.7, 128.3, 127.0, 75.3, 68.0, 47.8.
Methyl 2-bromo-3-hydroxy-3-phenylpropanoate (4.42b). The procedure for the synthesis of bromohydrin 4.42a was used with the following modifications: methyl trans-cinnamate (1.62 g, 10.0 mmol) was used instead of benzyl trans-cinnamate, NBS (2.14 g, 12.0 mmol), MeCN:H₂O (4:1) (50 mL), and iodine (254 mg, 1.00 mmol). The crude product was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–40% EtOAc/hexanes) to afford bromohydrin 4.42b as an off-white solid (1.45 g, 56%). This compound has been previously reported (CAS# 90841-69-3).¹⁹⁷ Rᵣ = 0.38 (70:30 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.38 (m, 5H), 5.06 (dd, J = 5.3, 8.4 Hz, 1H), 4.37 (d, J = 8.4 Hz, 1H), 3.79 (s, 3H), 3.28 (d, J = 5.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 139.0, 128.9, 128.7, 127.1, 75.3, 53.3, 47.5.

Benzyl 3-phenyloxirane-2-carboxylate (4.43). In a 4 mL oven-dried vial with stir bar, a suspension of 2-hydroxyprydone (6.8 mg, 0.072 mmol), tetrabutylammonium bromide (1.9 mg, 0.0060 mmol), and ground potassium carbonate (24.7 mg, 0.179 mmol) in acetone (0.5 mL) was heated at 40 °C for 30 min. A solution of the bromohydrin 4.42a (20.0 mg, 0.0597 mmol) in acetone (0.2 mL) was added dropwise over 5 min and the mixture was stirred at 40 °C for 30 min. The reaction mixture was monitored via LCMS and TLC (50:50 EtOAc:hexanes) and stained with PAA. Saturated NH₄Cl (1 mL) and H₂O (1 mL) were added the solution was stirred for 10 min. The resulting solution was diluted
with H$_2$O (5 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were
dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude pale yellow oil was
dissolved in DCM and purified by flash chromatography (5 g SiO$_2$, 0–100% 
EtOAc/hexanes) to yield pyridone 4.43 as a colorless oil (11.4 mg, 75%). This compound 
has been previously reported and synthesized (CAS# 144667-57-2).

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.55 (d, $J = 1.7$ Hz, 1H), 4.11 (d, $J = 1.7$ Hz, 1H), 5.25 (m, 2H), 7.25-7.40 (m, 10H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 168.2, 135.1, 135.0, 129.2, 128.8, 128.8, 128.7, 
126.0, 67.6, 58.2, 56.9.

Methyl 2-bromo-3-[(tert-butyldimethylsilyl)oxy]-3-phenylpropanoate (4.44a).
Bromohydrin 4.42a (70.0 mg, 0.209 mg) was added to a 4 mL oven-dried vial with stir bar 
and sealed under N$_2$. Anhydrous DCM (1.0 mL), 2.6-lutidine (92.0 uL, 0.794 mmol) and 
TBSOTf (72.0 uL, 0.314 mmol) were sequentially added and the solution was stirred at 20 °C for 2 h. TLC analysis (50:50 EtOAc:hexanes) indicated consumption of starting 
material. The reaction was quenched with the slow addition of saturated NaCl (2 mL), and 
the mixture was stirred for 15 min. The aqueous layer was extracted with ether (2 x 10 mL), and the organic layer was washed with brine (5 mL), dried over anhydrous Na$_2$SO$_4$, 
filtered, and condensed. The crude yellow oil was dissolved in DCM and purified by flash 
chromatography (25 g SiO$_2$, 0–20% EtOAc/hexanes) to yield 4.44a as a pale yellow oil 
(277 mg, 77%). This compound has been previously reported and synthesized (CAS# 175722-72-2). $^{213}$ R$_f$ = 0.68 (70:30 hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31–
7.38 (m, 5H), 4.98 (d, $J = 9.8$ Hz, 1H), 4.21 (d, $J = 9.8$ Hz, 1H), 3.81 (s, 3H), 0.79 (s, 9H),
Methyl 2-bromo-3-(methoxymethoxy)-3-phenylpropanoate (4.44b). Bromohydrin 4.42a (100 mg, 0.386 mmol) was added to a 4 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (1.0 mL) was added and the solution was cooled to 0 ºC. Then, 2,6-lutidine (67.4 uL, 0.579 mmol) was added followed by dropwise addition of methoxychloromethane (44 uL, 0.579 mmol). The solution was stirred at 0 ºC for 1 h, allowed to warm up to 20 ºC, and then stirred for 16 h under N₂. After 16 h, the reaction was diluted with EtOAc (15 mL) and washed with saturated aq. NaHCO₃ (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude yellow oil was dissolved in DCM and purified by flash chromatography (5 g SiO₂, 0–40% EtOAc/hexanes) to yield 4.44b as a colorless oil (78 mg, 66%). Rf: 0.59 (70:30 hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.35 (m, 5H), 5.00 (d, J = 10.1 Hz, 1H), 4.54–4.45 (m, 2H), 4.33 (d, J = 10.1 Hz, 1H), 3.85 (s, 3H), 3.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 136.9, 129.1, 128.7, 128.6, 128.4, 128.4, 127.1, 94.8, 78.7, 56.1, 53.1, 47.3.
**Methyl 3-(acetyloxy)-2-bromo-3-phenylpropanoate (4.46).** Bromohydrin 4.42b (3.28 g, 12.6 mmol) was added to a 50 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DCM (20.0 mL), acetic anhydride (1.34 mL, 14.3 mmol) and DMAP (61.8 mg, 0.506 mmol) were sequentially added. The solution was stirred at 20 ºC for 16 h. TLC analysis (50:50 hexanes:EtOAc) confirmed consumption of starting material. The reaction mixture was poured into ice cold H₂O (100 mL), and extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude pale yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–20% EtOAc/hexanes) to yield 4.46 as a colorless oil (3.55 g, 93%). This compound has been previously reported and synthesized (CAS# 59339-56-9).²¹⁴ Rᵣ = 0.73 (50:50 EtOAc:hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.35 (m, 5H), 6.11 (d, J = 9.9 Hz, 1H), 4.50 (d, J = 9.9 Hz, 1H), 3.81 (s, 3H), 2.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 168.8, 168.3, 136.0, 129.3, 128.6, 128.0, 75.6, 53.3, 46.1, 20.9.

**Methyl 2-(acetyloxy)-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (4.47b); methyl (2Z)-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoate (4.48b).** 2-Hydroxypyridine (3.55 g, 37.4 mmol) and Cs₂CO₃ (8.11 g, 24.9 mmol) were added to a 250 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DMF (75 mL) was
added and the suspension was heated at 50 °C for 1 h, then cooled to 20 °C. A solution of alkyl bromide 4.46 (7.50 g, 24.9 mmol) in anhydrous DMF (20 mL) was added and the reaction mixture was stirred at 20 °C for 16 h. The reaction was quenched with saturated aq. NH₄Cl (75 mL), diluted with EtOAc (500 mL), and washed with H₂O (6 x 200 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. The resulting crude yellow oil was dissolved in DCM and purified by flash chromatography (100 g SiO₂, 0–100% EtOAc/hexanes) to yield 4.47b as a waxy off-white solid (1.98 g, 25%) and 4.48b as an off-white solid (0.60 g, 9%). 4.47b: ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.47 (m, 2H), 7.39–7.38 (m, 3H), 7.27–7.25 (m, 1H), 7.05 (d, J = 7.1 Hz, 1H), 6.87 (d, J = 5.1 Hz, 1H), 6.60 (d, J = 9.7 Hz, 1H), 6.02 (t, J = 6.7 Hz, 1H), 5.89 (d, J = 7.1 Hz, 1H), 3.65 (s, 3H), 2.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 167.9, 162.2, 139.4, 135.9, 134.6, 129.5, 129.3, 129.1, 120.7, 105.8, 71.3, 57.2, 53.0, 20.7; LC-MS tᵣ = 5.50; m/z = 255.75 (M+H). 4.48b: ¹H NMR (400 MHz, CDCl₃) δ 7.47–7.40 (m, 7H), 7.12 (ddd, J = 6.8, 2.1, 0.7 Hz, 1H), 6.66–6.63 (m, 2H), 6.27 (td, J = 6.8, 1.2 Hz, 1H), 3.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 161.8, 151.1, 140.6, 137.5, 131.2, 129.5, 129.2, 126.6, 122.1, 115.8, 105.9, 52.0; LC-MS tᵣ = 4.25; m/z = 255.75 (M+H).

2-Hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (4.49b). To a 50 mL flask with stir bar, acetate 4.47b (1.98 g, 6.28 mmol), THF (48 mL), H₂O (12 mL), and LiOH-H₂O (580 mg, 13.8 mmol) were sequentially added and the reaction was stirred at 20 °C for 30 min. Analysis via LC-MS indicated complete conversion. THF was removed under vacuum before a 1M HCl solution was added dropwise until the pH reached ~ 1.
The solution was concentrated, the crude product was dry loaded using Celite, and purified via flash chromatography (12 g C18, 0–95% 0.5 N NH₃ in MeOH/H₂O) to afford carboxylic acid 4.49b as an off-white solid (1.49 g, 92%). ¹H NMR (400 MHz, DMSO-d6) δ 7.49–7.47 (m, 3H), 7.37–7.29 (m, 4H), 6.43–6.40 (m, 2H), 6.15 (t, J = 6.7 Hz, 1H), 4.66 (d, J = 5.0 Hz, 1H). ¹³C NMR (100 MHz, DMSO-d6) δ 173.2, 161.2, 139.7, 137.6, 136.8, 129.3, 128.6, 128.1, 119.2, 105.0, 70.4, 58.2; LC-MS tᵣ = 3.34; m/z = 258.05 (M–H).

(2-Aminoethoxy)(tert-butyl)dimethylsilane (4.51). Ethanolamine (2.07 g, 33.9 mmol) was added to a 25 mL oven-dried flask with stir bar and sealed under N₂. Imidazole (4.61 g, 67.8 mmol) and anhydrous DCM (30 mL) were added before a solution of TBSCl (5.11 g, 33.9 mmol) in anhydrous DCM (5 mL) was added dropwise over 10 min via syringe pump at 20 °C. The solution was allowed to stir at 20 °C for 1 h. Next, the solution was diluted with DCM (150 mL) and washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered, and concentrated to give amine 4.51 as a pale yellow oil (4.77 g, 80%). This compound has been previously reported and synthesized (CAS# 101711-55-1).²¹⁵ ¹H NMR (CDCl₃, 400 MHz) δ 3.63 (t, J = 5.2 Hz, 2H), 2.77 (t, J = 5.2 Hz, 2H), 1.47, (br s, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 65.5, 44.5, 26.1, 18.5, -5.2.
**N-{2-[(Tert-butyldimethylsilyl)oxy]ethyl}-2-hydroxy-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (4.53).** To an oven-dried 50 mL round bottom flask, acid 4.49 (420 mg, 1.62 mmol), amine 4.51 (568 mg, 3.24), anhydrous DMF (10 mL), and anhydrous DCE (10 mL) were added. Next, NMM (356 uL, 3.24 mmol) was added via syringe and HATU (739 mg, 1.94 mmol) was added in one portion. The reaction mixture was stirred at 20 ºC for 16 h under N\textsubscript{2}. After 16 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with H\textsubscript{2}O (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and condensed under vacuum to yield a crude yellow oil. The crude oil was purified by flash chromatography (25 g SiO\textsubscript{2}, 0–100% EtOAc/hexanes) to afford amide 4.53 as a colorless oil (620 mg, 91%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.44–7.40 (m, 1H), 7.35–7.30 (m, 7H), 6.81 (br s, 1H), 6.68 (d, \( J = 9.1 \) Hz, 1H), 6.25 (t, \( J = 7.3 \) Hz, 1H), 6.00 (s, 1H), 4.84 (s, 1H), 3.66–3.53 (m, 2H), 3.42–3.30 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 170.9, 164.9, 140.6, 139.2, 135.0, 128.7, 128.6, 128.4, 121.6, 107.7, 74.5, 71.5, 61.8, 41.6, 26.0, 18.4, -5.3; LC-MS \( t_{R} = 5.74; m/z = 417.00 \) (M+H).
**N-{2-[(Tert-butyldimethylsilyl)oxy]ethyl}-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (4.54).** Alcohol 4.53 (205 mg, 0.492 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N₂. Anhydrous DCM (10 mL) and DMP (251 mg, 0.592 mmol) were added and the reaction was stirred at 20 °C for 2 h under N₂. A 10% Na₂S₂O₃ aqueous solution (10 mL) was added and the biphasic mixture was stirred for 20 min until the two layers became clear. The aqueous layer was separated and the organic layer was washed with saturated NaHCO₃ (2 x 5 mL). The combined aqueous layers were extracted with EtOAc (1 x 10 mL) and the combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂, 0–80% EtOAc/hexanes) to afford ketone 4.54 as an off-white solid (170 mg, 83%). 

$^1$H NMR (400 MHz, CDCl₃) δ 7.38–7.26 (m, 7H), 6.93 (d, J = 7.0 Hz, 1H), 6.85 (s, 1H), 6.52 (d, J = 9.1 Hz, 1H), 6.08 (t, J = 6.7 Hz, 1H), 3.64–3.60 (m, 2H), 3.43–3.25 (m, 2H), 0.80 (s, 9H), -0.04 (s, 6H); $^{13}$C NMR (100 MHz, CDCl₃) δ 189.8, 162.4, 159.4, 140.2, 135.5, 130.7, 130.2, 130.0, 129.7, 119.7, 106.5, 64.3, 61.3, 41.5, 25.9, 18.2, -5.4; LC-MS tᵣ = 6.09; m/z = 414.95 (M+H).
**N-(2-Hydroxyethyl)-2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (4.55).** To a 100 mL flask charged with a stir bar, silyl ether 4.54 (100 mg, 0.241 mmol) and MeOH (10.0 mL) were added. Then a 2% aqueous HCl in MeOH solution (10.0 mL) was added, and the reaction was stirred for 1 h at 20 ºC. The solution was concentrated, dry loaded on to Celite, and purified via flash chromatography (12 g C18, 0–40% MeOH/H$_2$O) to afford alcohol 4.55 as a colorless oil (56.7 mg, 78%). LC-MS $t_R = 3.64$; m/z = 300.85 (M+H). This intermediate was used directly in the next step.

**Diethyl(2-[2-oxo-3-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamido]ethyl}) azanium chloride (4.57).** Alcohol 4.55 (40.0 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under Ar. Anhydrous MeCN (4.0 mL), DIPEA (22.8 uL, 0.133 mmol), and MsCl (30.9 uL, 0.400 mmol) were respectively added and the solution was stirred at 20 ºC for 24 h. Analysis via TLC confirmed conversion to the mesylate. Freshly distilled diethylamine (275 uL, 2.66 mmol) stored over 4 Å mol sieves was added and the reaction was heated at 70 ºC for 16 h under Ar. The reaction was concentrated, dry loaded using Celite, and purified via flash chromatography (10 g C18, MeOH/H$_2$O gradient w/ 0.1% formic acid) to afford the free base of amine 4.57 as an off-
white powder (11.0 mg, 28%). \( R_f = 0.61 \) (95:5 DCM:MeOH); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \)

8.61 (s, 1H), 8.03 (s, 1H), 7.51–7.49 (m, 3H), 7.41 (ddd, \( J = 8.8, 6.6, 1.9 \) Hz, 1H), 7.37–7.35 (m, 2H), 6.90 (dd, \( J = 7.1, 1.7 \) Hz, 1H), 6.55 (d, \( J = 8.8 \) Hz, 1H), 6.15 (td, \( J = 6.6, 1.2 \) Hz, 1H), 6.07 (s, 1H), 4.73–4.70 (m, 1H), 4.26–4.22 (m, 1H), 3.86–3.58 (m, 6H), 1.36–1.24 (m, 6H). This compound had poor solubility in chloroform and MeOH. The HCl salt was formed prior to \(^{13}\)C NMR analysis. The product was taken up into minimal H\(_2\)O and 0.5 mL of 1M HCl was added. The solution was lyophilized to afford a yellow oil. \(^{13}\)C NMR (75 MHz, D\(_2\)O) \( \delta \) 170.4, 164.2, 155.1, 143.0, 136.5, 131.0, 131.0, 130.4, 129.9, 129.8, 118.9, 109.2, 64.8, 64.6, 49.7, 45.5, 41.9, 13.3, 10.6; LC-MS \( t_R = 1.61 \); m/z = 356.40 (M+H).

Ethyl 2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (4.58). In a 20 mL oven-dried vial with stir bar, HMDS (1.90 mL, 9.11 mmol) and anhydrous THF (9.0 mL) were added under N\(_2\). The solution was cooled to 0 °C in an ice bath before \( n \)-butyl lithium (5.43 mL of a 1.6 M solution in hexanes, 8.69 mmol) was added dropwise over 10 min. The solution was cooled to –78 °C before a solution of ester 4.21 (1.50 g, 8.28 mmol) in anhydrous THF (25.0 mL) was added dropwise. The solution was stirred at –78 °C for 1 h under N\(_2\) before benzylbromide (985 uL, 8.28 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, allowed to warm up to 0 °C, quenched with saturated NH\(_4\)Cl (10 mL), and diluted with EtOAc (50 mL). The organic layer was separated, washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The crude material was dissolved in DCM and purified via flash chromatography (100 g SiO\(_2\), 0–40%
EtOAc/hexanes) to afford **4.58** as a colorless oil (1.52 g, 68%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.28–7.18 (m, 4H), 7.11–7.08 (m, 2H), 7.03 (dd, $J = 6.9, 1.5$ Hz, 1H), 6.50 (d, $J = 9.2$ Hz, 1H), 6.03 (td, $J = 6.8, 1.3$ Hz, 1H), 5.41 (dd, $J = 9.7, 5.6$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.50 (m, 1H), 3.33 (m, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.5, 162.2, 139.6, 136.5, 136.1, 129.1, 128.7, 127.1, 120.8, 105.6, 61.9, 61.2, 36.3, 14.1; LC-MS $t_R = 4.67$; m/z = 271.90 (M+H).

![4.60](image)

**Ethyl (2Z)-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoate (4.60).** The procedure for the synthesis of **4.58** was followed using HMDS (392 mg, 2.43 mmol), anhydrous THF (9.0 mL), $n$-butyl lithium (1.45 mL of a 1.6 M solution in hexanes, 2.32 mmol), **4.21** (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL), and benzaldehyde (0.247 mL, 2.43 mmol) instead of benzylbromide. After workup, the product was dissolved in DCM and purified via flash chromatography (25 g SiO$_2$, 0–50% EtOAc/hexanes) to afford alkene **4.60** as an off-white solid (272 mg, 46%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.83 (s, 1H), 7.43 (ddd, $J = 9.0, 6.6, 2.0$ Hz, 1H), 7.33–7.26 (m, 3H), 7.20–7.18 (m, 2H), 6.96 (dd, $J = 6.7, 1.8$ Hz, 1H), 6.67 (d, $J = 8.7$ Hz, 1H), 6.18 (td, $J = 6.7, 1.0$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.31 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 163.4, 162.4, 140.8, 137.7, 137.4, 131.4, 130.5, 130.2, 129.9, 128.9, 121.8, 106.8, 62.0, 14.1. LC-MS $t_R = 6.06$; m/z = 269.80 (M+H).
(2Z)-2-(2-Oxo-1,2-dihydropyridin-1-yl)-3-phenylprop-2-enoic acid (4.61). To a 15 mL flask with stir bar, ester 4.60 (136 mg, 0.504 mmol), THF (6.0 mL), H₂O (1.5 mL), and LiOH·H₂O (25.4 mg, 0.604 mmol) were added and the solution was stirred at 20 ºC for 12 h. THF was removed under vacuum before a 1M HCl solution was added dropwise until the pH reached ~ 1. The solution was concentrated under vacuum and the crude product was dry loaded using Celite and purified via flash chromatography (12 g C18, 0–75% MeOH/H₂O w/ 0.1% formic acid) to afford carboxylic acid 4.61 as an off-white solid (108 mg, 89%). ¹H NMR (400 MHz, CD₃OD) δ 7.94 (s, 1H), 7.65 (ddd, J = 9.1, 6.7, 2.0 Hz, 1H), 7.39–7.30 (m, 4H), 7.20–7.18 (m, 2H), 6.67 (d, J = 9.1 Hz, 1H), 6.42 (td, J = 6.7, 1.0 Hz, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 166.2, 164.8, 143.6, 140.0, 139.0, 133.1, 131.7, 131.6, 130.9, 130.1, 121.6, 109.4; LC-MS tₘ = 4.17; m/z = 241.75 (M+H).

Ethyl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (4.62). In a 100 mL oven-dried flask with stir bar, diisopropylamine (309 μL, 2.21 mmol) and anhydrous THF (35.0 mL) were added via syringe under N₂. The solution was cooled to –78 ºC in a dry ice/acetone bath before n-butyl lithium (1.38 mL of a 1.6 M solution in hexanes, 2.21 mmol) was added dropwise over 10 min. The solution was allowed to stir for 30 min before a solution of 4.21 (400 mg, 2.21 mmol) in anhydrous THF (3.0 mL) was added dropwise
over 5 min. The heterogenous solution was stirred at −78 °C for 1 h before benzaldehyde (0.247 mL, 2.43 mmol) was added, and the solution was stirred at −78 °C for 2 h. The reaction was quenched at −78 °C via the addition saturated aq. NH₄Cl (15 mL) and diluted with EtOAc (75 mL). The organic layer was separated, washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude material was dissolved in DCM and purified via flash chromatography (50 g SiO₂, 0–100% EtOAc/hexanes) to afford alcohol **4.62** as a colorless oil (307 mg, 48%). The NMR spectra are complex due to diastereomers. **¹H NMR (300 MHz, CDCl₃)** δ 7.59 (dd, J = 6.8, 1.3 Hz, 1H), 7.26–7.15 (m, 12H), 6.80 (dd, J = 6.8, 1.5 Hz, 1H), 6.39 (d, J = 9.1 Hz, 1H), 6.28 (d, J = 9.1 Hz, 1H), 6.05 (td, J = 6.7, 1.2 Hz, 1H), 5.86 (td, J = 6.7 Hz, 1.2 Hz, 1H), 5.81 (d, J = 4.3 Hz, 1H), 5.63 (d, J = 4.3 Hz, 1H), 5.45 (d, J = 7.5 Hz, 1H), 4.74 (d, J = 7.5 Hz, 1H), 4.22–4.16 (m, 4H), 1.24–1.19 (m, 6H); **¹³C NMR (75 MHz, CDCl₃)** δ 169.4, 168.2, 162.9, 162.3, 140.2, 140.1, 139.5, 138.9, 138.5, 137.9, 128.4, 128.3, 127.8, 126.4, 125.9, 120.3, 119.7, 105.9, 105.6, 73.5, 72.1, 67.5, 63.5, 62.1, 62.1, 60.4, 21.1, 14.2, 14.1, 14.0; LC-MS tᵣ = 4.78, 4.92; m/z = 287.80 (M+H).

**Ethyl 3-[(tert-butyldimethylsilyl)oxy]-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenyl propanoate (4.63).** The procedure for the synthesis of **4.44a** was used with the following modifications: **4.62** (153 mg, 0.533 mmol), DCM (6.0 mL), 2,6-lutidine (74.4 uL, 0.639 mmol) and TBSOTf (147 uL, 0.639 mmol) were used. The crude oil was dissolved in DCM and purified via flash chromatography (25 g SiO₂, 0–50% EtOAc/hexanes) to yield **4.63** as a pale yellow oil (187 mg, 87%). **¹H NMR (300 MHz, CDCl₃)** δ 8.20 (dd, J = 6.9, 1.4 Hz,
1H), 7.87 (dd, J = 6.9, 1.4 Hz, 1H), 7.56–7.38 (m, 11H), 6.62 (d, J = 9.2 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 6.44–6.39 (m, 1H), 6.33–6.28 (m, 1H), 6.12 (d, J = 7.2 Hz, 1H), 5.87 (d, J = 3.9 Hz, 1H), 5.44 (d, J = 7.2 Hz, 1H), 4.59–4.51 (m, 1H), 4.45–4.33 (m, 3H), 1.53 (t, J = 7.1 Hz, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.13 (s, 9H), 1.11 (s, 9H), 0.29 (s, 3H), 0.25 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H). 13C NMR (75 MHz, CDCl₃) δ 169.0, 168.5, 162.2, 161.8, 139.6, 139.5, 139.4, 139.3, 138.7, 136.6, 128.3, 128.2, 128.2, 128.2, 127.0, 126.4, 120.4, 119.7, 105.4, 104.5, 75.6, 75.4, 62.1, 61.9, 61.7, 61.5, 25.8, 25.8, 18.1, 18.1, 14.2, 14.1, –4.4, –4.6, –5.3, –5.5; LC-MS tᵣ = 6.95; m/z = 401.95 (M+H).

Prop-2-en-1-yl 2-(2-oxo-1,2-dihydropyridin-1-yl)acetate (4.64). NaH (60% dispersion in mineral oil, 1.77 g, 46.3 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under N₂. Anhydrous DMF (125 mL) was added and the suspension was cooled to 0 °C in an ice bath. A solution of 2-hydroxypyridine (4.00 g, 42.1 mmol) in anhydrous DMF (25.0 mL) was slowly added and stirred for 1 h at 0 °C. Allyl chloroacetate (5.98 mL, 50.5 mmol) was added and the mixture was stirred at 20 °C for 12 h. The reaction was quenched with saturated NH₄Cl (200 mL) and diluted with EtOAc (750 mL). The organic layer was washed with water (6 × 200 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–85% EtOAc/hexanes) to afford pyridone 4.64 as a pale yellow oil (3.40 g, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.30 (ddd, J = 9.2, 6.7, 2.1 Hz, 1H), 7.20 (ddd, J = 6.7, 2.1, 0.7 Hz, 1H), 6.49 (ddd, J = 9.2, 1.4, 0.7 Hz, 1H), 6.13 (td, J = 6.7, 1.4 Hz, 1H), 5.82 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.25 (dq, J = 17.2 1.5 Hz, 1H), 5.17
Prop-2-en-1-yl 3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoate (4.65). In an oven-dried 100 mL flask with stir bar, anhydrous THF (50.0 mL) and diisopropylamine (1.55 mL, 11.0 mmol) were added via syringe under N₂. The solution was cooled to –78 °C before n-butyl lithium (6.90 mL of a 1.6 M solution in hexanes, 11.0 mmol) was added dropwise over 5 min. The solution was stirred for 30 min before a solution of ester 4.64 (1.94 g, 10.0 mmol) in anhydrous THF (8.0 mL) was added dropwise over 5 min and stirred at –78 °C for 1 h. Benzaldehyde (1.53 mL, 15.1 mmol) was added and the resulting solution was stirred at –78 °C for 2 h. The reaction was quenched at –78 °C with saturated aq. NH₄Cl and diluted with EtOAc (200 mL) and H₂O (10 mL). The layers were separated and the organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The crude yellow oil was dissolved in DCM and purified via flash chromatography (100 g SiO₂, 0–70% EtOAc/hexanes) to afford alcohol 4.65 as a yellow oil (2.45 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.43 (d, J = 7.9 Hz, 1H), 7.27–7.22 (m, 13H), 6.71 (dd, J = 6.8, 1.5 Hz, 1H), 6.46 (d, J = 9.1 Hz, 1H), 6.40 (d, J = 8.8 Hz, 1H), 6.09 (td, J = 6.8, 1.3 Hz, 1H), 5.94–5.81 (m, 3H), 5.73 (s, 2H), 5.57 (d, J = 7.9 Hz, 1H), 5.34–5.20 (m, 4H), 4.72–4.64 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 167.9, 163.1, 162.4, 140.3, 140.2, 139.4, 138.7, 138.5, 137.9, 131.4, 131.3, 128.5, 128.4, 128.4, 128.0,
126.4, 125.9, 120.5, 120.0, 119.1, 119.0, 106.0, 105.8, 73.7, 72.1, 68.0, 66.6, 66.6, 64.0;
LC-MS \( t_R = 4.40, 4.53 \); m/z = 299.75 (M+H).

3-Hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanoic acid (4.66). Alcohol 4.65 (1.90 g, 0.264 mmol) and Pd(PPh\(_3\))\(_4\) (12.2 mg, 0.0106 mmol) were added to a 500 mL oven-dried flash with stir bar and sealed under N\(_2\). Anhydrous THF (6.0 mL) and morpholine (24.2 \( \mu \)L, 0.277 mmol) were added via syringe and the reaction was stirred at 20 °C for 30 min. After 30 min, analysis via LC-MS indicated consumption of starting material. The reaction mixture was concentrated, dry loaded using Celite, and purified using flash chromatography (30 g C18, 0–95% MeOH/H\(_2\)O w/ 0.1% formic acid) to afford carboxylic acid 4.66 as a yellow oil (1.20 g, 73%). \(^1\)H NMR (400 MHz, CD\(_3\)OD) \( \delta \) 8.10 (d, \( J = 6.5 \) Hz, 1H), 7.44 (d, \( J = 6.5 \) Hz, 1H), 7.36–7.15 (m, 10H), 6.37 (d, \( J = 9.0 \) Hz, 1H), 6.30–6.27 (m, 1H), 6.14–6.10 (m, 1H), 5.73 (d, \( J = 3.8 \) Hz, 1H), 5.45 (d, \( J = 7.9 \) Hz, 1H), 5.30 (d, \( J = 7.9 \) Hz, 1H). LC-MS \( t_R = 3.74, 3.88 \); m/z = 259.75 (M+H).

\[ \text{N-[2-(Diethylamino)ethyl]-3-hydroxy-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenylpropanamide (4.67). Carboxylic acid 4.66 (886 mg, 3.42 mmol) was added to a 500 mL oven-dried flask with stir bar and sealed under N}_2\text{. Anhydrous DCM (150 mL), HATU (1.95} \]
g, 5.13 mmol), DIPEA (655 uL, 3.76 mmol), and $N,N$-diethylenediamine (624 uL, 4.44 mmol) were sequentially added and the solution was stirred at 20 ºC for 12 h. After 12 h, the reaction was concentrated under vacuum, dry loaded using Celite, and purified via flash chromatography (30 g C18, 0–95% MeOH/H$_2$O w/ 0.1% formic acid) to afford amide 4.67 as an off-white waxy solid (918 mg, 75%). m.p. 75–77 ºC; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 7.44 (dd, $J = 6.9, 1.5$ Hz, 1H), 7.34 (ddd, $J = 9.0, 6.7, 2.0$ Hz, 1H), 7.28–7.26 (m, 2H), 7.24–7.19 (m, 3H), 6.36 (dd, $J = 9.0, 0.6$ Hz, 1H), 6.14 (td, $J = 6.7, 1.3$ Hz, 1H), 5.39 (d, $J = 9.5$ Hz, 1H), 5.19 (d, $J = 9.5$ Hz, 1H), 3.79–3.73 (m, 1H), 3.64–3.57 (m, 1H), 3.38–3.22 (m, 6H), 1.31 (t, $J = 7.3$ Hz, 6H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 171.8, 164.4, 142.5, 141.1, 140.0, 129.5, 129.4, 128.0, 120.5, 108.4, 73.4, 67.3, 53.0, 49.1, 35.7, 9.2. LC-MS t$_R$ = 1.07, 1.32; m/z = 357.95 (M+H).

$N$-[2-(Diethylamino)ethyl]-3-oxo-2-(2-oxo-1,2-dihydropyridin-1-yl)-3-phenyl propanamide (4.68). Alcohol 4.67 (47.5 mg, 0.133 mmol) was added to a 20 mL oven-dried vial with stir bar and sealed under N$_2$. Anhydrous DCM (6.0 mL) and DMP (84.5 mg, 0.199 mmol) were sequentially added and the reaction mixture was stirred at 20 ºC for 1 h. After 1 h, H$_2$O (2.7 uL, 0.15 mmol) was added via microsyringe. The reaction solution was stirred at 20 ºC for 48 h before being quenched with saturated Na$_2$S$_2$O$_3$ (3 mL). The product was extracted with DCM (3 x 10 mL) and concentrated. The crude product was dissolved in DCM and purified via flash chromatography (12 g SiO$_2$, 0–20% MeOH/DCM) to afford ketone 4.68 as an off-white solid (11.7 mg, 25%). R$_f$ = 0.71 (80:20 DCM:MeOH); m.p. 124–129 ºC; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (d, $J = 7.1$ Hz, 2H), 7.65 (dd, $J = 6.8$,
1.7 Hz, 1H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 1H), 7.40–7.34 (m, 2H), 6.60 (d, $J = 9.2$
Hz, 1H), 6.24 (td, $J = 6.8$, 1.3 Hz, 1H), 3.39–3.28 (m, 2H), 2.57–2.48 (m, 6H), 0.96 (t, $J =$
7.2 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 192.0, 165.2, 162.0, 140.7, 137.4, 135.0, 134.3,
129.1, 128.8, 119.9, 106.2, 61.6, 51.1, 46.7, 37.4, 11.5; LC-MS $t_R = 1.57$; m/z = 356.20
(M+H).
5.6. X-ray Crystallographic Structures and Sample Preparation

**Figure 5.6.1: X-ray structures of 4.48b, 4.49b, 4.61, and 4.68**

**4.48b**

**4.49b**

**4.61**

**4.68**

**4.48b Preparation and Structure Description:** Colorless prism crystals were obtained via slow evaporation in a saturated solution of 4.48b in EtOAc. The trans-cinnamic acid residue is essentially planar with 2-pyridinone group almost perpendicular (dihedral angle 85°) to it.

**4.49b Preparation and Structure Description:** Colorless thin plates were obtained via slow cooling 4.49b (30 mg) in MeOH (0.5 mL). The compound represents a C2(S), C3(S)
diastereomer (crystallizing as a racemate). The molecule has a staggered conformation along the bond C2-C3.

4.61 Preparation and Structure Description: Colorless tablets were obtained via slow cooling 4.61 (40 mg) in MeOH (0.5 mL). The cinnamic acid residue has trans-configuration with the double bond and carboxy groups well-conjugated (dihedral angle O=C-C=C 169.6°). The styrene moiety is also conjugated (dihedral angle between benzene ring and double bond 8.1°). The pyridinone group is rotated out of conjugation (dihedral angle C-N-C=C 74.8°).

4.68 Preparation and Structure Description: Colorless prisms were obtained by slow evaporation of 4.68 (3 mg) in DCE:Dioxane (300 uL). The groups around the central tertiary carbon atom are arranged in a propeller-like order, with two α-carbonyl groups oriented anti relative to C-H bond and pyridinone carbonyl – syn (possibly – because of attraction between the carbonyl and acidic C-H group, although modern rules do not recognize 5-membered H-bonded rings). The amide group is in trans-conformation. The terminal NEt₂ group is orientationally disordered over two positions with equal population. The nearby phenyl group is also disordered, as a consequence.
5.7 NMR Spectra

5.7.1 NMR Spectra of Bifunctional Catalyst Synthesis

$^1$H NMR of 2.12 (300 MHz, CDCl$_3$)
$^{1}{H}$ NMR of 2.13 (300 MHz, CDCl$_3$)

$^{13}{C}$ NMR of 2.13 (75 MHz, CDCl$_3$)
$^{1}H$ NMR of 2.14 (300 MHz, CDCl$_3$)

$^{13}C$ NMR of 2.14 (100 MHz, CDCl$_3$)
$^1$H NMR of 2.15 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 2.15 (100 MHz, CDCl$_3$)
$^1$H NMR of 2.16a (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2.16a (100 MHz, CDCl$_3$)
$^1$H NMR of 2.16b (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2.16b (100 MHz, CDCl$_3$)
$^1$H NMR of 2.16c (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2.16c (100 MHz, CDCl$_3$)
$^1$H NMR of 2.16d (300 MHz, CDCl$_3$)

$^{13}$C NMR of 2.16d (75 MHz, CDCl$_3$)
$^1$H NMR of 2.38 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 2.38 (75 MHz, CDCl$_3$)
$^1$H NMR of 2.36 (300 MHz, CDCl$_3$)

[Chemical structure image of 2.36]
$^1$H NMR of **2.39** (400 MHz, CDCl$_3$)

![NMR spectrum of 2.39](image)
\( ^1H \text{ NMR of 2.40 (400 MHz, CDCl}_3 \) 

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{CbzN} & \quad \text{OH} \\
\text{Boc} & \quad \text{H}
\end{align*}
\]

\[2.40\]

\( ^{13}C \text{ NMR of 2.40 (100 MHz, CDCl}_3 \) 

\[
\begin{align*}
\text{C} & \quad \text{N} \\
\text{Boc} & \quad \text{H}
\end{align*}
\]

\[2.40\]
$^1$H NMR of 2.35 (400 MHz, CDCl$_3$)
$^1$H NMR of 2.41b (400 MHz, CD$_3$CN)

$^{13}$C NMR of 2.41b (100 MHz, CD$_3$CN)
$^1$H NMR of 2.42b (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2.42b (100 MHz, CDCl$_3$)
$^1$H NMR of 2.45 (300 MHz, CDCl$_3$)

$^13$C NMR of 2.45 (750 MHz, CDCl$_3$)
$^1$H NMR of 2.46 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 2.46 (75 MHz, CDCl$_3$)
$^1H$ NMR of 2.47 (300 MHz, CDCl$_3$)

$^{13}C$ NMR of 2.47 (75 MHz, CDCl$_3$)
$^1$H NMR of 2.48 (300 MHz, CDCl$_3$)

$^13$C NMR of 2.48 (75 MHz, CDCl$_3$)
$^1$H NMR of 2.49 (300 MHz, CDCl$_3$)

$^1$H NMR of 2.49 (75 MHz, CDCl$_3$)

$^{13}$C NMR of 2.49 (75 MHz, CDCl$_3$)
$^1$H NMR of 2.50 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 2.50 (75 MHz, CDCl$_3$)
$^1$H NMR of 2.51 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 2.51 (75 MHz, CDCl$_3$)
**$^1$H NMR of 2.20 (300 MHz, CDCl$_3$)**

**$^{13}$C NMR of 2.20 (75 MHz, CDCl$_3$)**
5.7.2 NMR Spectra for PyBOX-Pt Complex, Organocatalyst, and Enamine Synthesis

$^{13}$C NMR of 3.14 (300 MHz, DMSO-$d_6$)
$^1$H NMR of 3.15a (300 MHz, CDCl$_3$)

$^{13}$C NMR of 3.15a (75 MHz, CDCl$_3$)
$^1$H NMR of 3.15b (300 MHz, CDCl$_3$)

$^13$C NMR of 3.15b (75 MHz, CDCl$_3$)
$^1$H NMR of 3.16a (300 MHz, CDCl$_3$)

$^{13}$C NMR of 3.16a (75 MHz, CDCl$_3$)
$^1$H NMR of 3.16b (300 MHz, CDCl$_3$)
\[ ^1H \text{NMR of 3.17a (400 MHz, CDCl}_3 \text{)} \]

\[ ^1H \text{NMR of 3.19 (300 MHz, CDCl}_3 \text{)} \]
$^1$H NMR of 3.27 (400 MHz, CD$_3$NO$_2$)

$^{13}$C NMR of 3.27 (100 MHz, CD$_3$NO$_2$)
**\(^1\)H NMR of 3.28 (300 MHz, CDCl\(_3\))**

![\(^1\)H NMR spectrum of 3.28]

**\(^13\)C NMR of 3.28 (75 MHz, CDCl\(_3\))**

![\(^13\)C NMR spectrum of 3.28]
5.7.3 NMR Spectra for Synthesis of STK076545

\[ ^1\text{H NMR of 4.3 (400 MHz, CDCl}_3\text{)} \]

\[ ^{13}\text{C NMR of 4.3 (100 MHz, CDCl}_3\text{)} \]
$^1$H NMR of 4.4 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.4 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.5 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.5 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.10 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.10 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.11 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.11 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.12 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.12 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.13 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.13 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.14 (400 MHz, CD$_3$OD)

4.14 (crude)
$^1$H NMR of 4.16 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.16 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.19 (300 MHz, CDCl$_3$)
$^1$H NMR of 4.20a (300 MHz, CDCl$_3$)

13C NMR of 4.20a (75 MHz, CDCl$_3$)
$^1$H NMR of 4.21 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.21 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.22 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.22 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.25 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.25 (75 MHz, CDCl$_3$)
**$^1$H NMR of 4.26 (300 MHz, CDCl$_3$)**

![NMR spectrum](image)

**$^{13}$C NMR of 4.26 (75 MHz, CDCl$_3$)**

![NMR spectrum](image)
$^1$H NMR of 4.27 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.27 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.28 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.28 (75 MHz, CDCl$_3$)
$^{1}H$ NMR of 4.29 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.29 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.32 (400 MHz, acetone-$d_6$)
$^1$H NMR of 4.33b (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.33b (75 MHz, CDCl$_3$)
$^1$H NMR of 4.34a (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.34a (75 MHz, CD$_3$OD)
$^1$H NMR of 4.34b (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.34b (75 MHz, CDCl$_3$)
$^1$H NMR of 4.35 (300 MHz, CDCl$_3$)
$^1$H NMR of 4.42a (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.42a (75 MHz, CDCl$_3$)
$\text{H NMR of } 4.42b (300 \text{ MHz, CDCl}_3)$

$\text{C NMR of } 4.42b (75 \text{ MHz, CDCl}_3)$
$^1$H NMR of 4.43 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.43 (75 MHz, CDCl$_3$)
\(^1\)H NMR of 4.44a (300 MHz, CDCl\(_3\))

\(^1^3\)C NMR of 4.44a (75 MHz, CDCl\(_3\))
$^1$H NMR of **4.44b** (300 MHz, CDCl$_3$)

$^{13}$C NMR of **4.44b** (75 MHz, CDCl$_3$)
$^1$H NMR of 4.46 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.46 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.47b (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.47b (100 MHz, CDCl$_3$)
$^1$H NMR of 4.48b (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.48b (100 MHz, CDCl$_3$)
$^1$H NMR of 4.49 (400 MHz, DMSO-$d_6$)

$^{13}$C NMR of 4.49 (100 MHz, DMSO-$d_6$)
$^1$H NMR of 4.51 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.51 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.53 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.51 (100 MHz, CDCl$_3$)
\(^{1}H\) NMR of 4.54 (400 MHz, CDCl\(_3\))

\(^{13}C\) NMR of 4.54 (100 MHz, CDCl\(_3\))
$^1$H NMR of 4.57 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.57 (75 MHz, D$_2$O)
$^1$H NMR of 4.58 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.58 (75 MHz, CDCl$_3$)
$^1$H NMR of 4.60 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.60 (100 MHz, CDCl$_3$)
$^1$H NMR of 4.61 (400 MHz, CD$_3$OD)

$^{13}$C NMR of 4.61 (100 MHz, CD$_3$OD)
$^1$H NMR of 4.62 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.62 (75 MHz, CDCl$_3$)
$^{1}$H NMR of 4.63 (300 MHz, CDCl$_3$)

$^{13}$C NMR of 4.63 (75 MHz, CDCl$_3$)
H NMR of 4.64 (400 MHz, CDCl₃)

13C NMR of 4.64 (100 MHz, CDCl₃)
**$^1$H NMR of 4.65 (400 MHz, CDCl$_3$)**

![NMR spectrum of 4.65 (400 MHz)](image)

**$^{13}$C NMR of 4.65 (100 MHz, CDCl$_3$)**

![NMR spectrum of 4.65 (100 MHz)](image)
$^{1}H$ NMR of 4.66 (400 MHz, CD$_3$OD)
**$^1$H NMR of 4.67 (400 MHz, CD$_3$OD)**

![H NMR spectrum of 4.67](image)

**$^{13}$C NMR of 4.67 (100 MHz, CD$_3$OD)**

![C NMR spectrum of 4.67](image)
$^{1}H$ NMR of 4.67 (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4.67 (100 MHz, CDCl$_3$)


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