THESIS

THE DEVELOPMENT OF LIGANDS FOR C–H FUNCTIONALIZATION UTILIZING AMINO ACID DERIVED DIRECTING GROUPS

Submitted by

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ABSTRACT

THE DEVELOPMENT OF LIGANDS FOR C–H FUNCTIONALIZATION UTILIZING AMINO ACID DERIVED DIRECTING GROUPS

The functionalization of unreactive bonds has become a focus of new reaction methodology. The foremost difficulty lies within achieving high levels of chemo-, regio-, and stereoselectivity without the need for molecular complexity. The aim of my project was to develop a catalyst system that could direct a C–H functionalization by forming a transient covalent attachment to a simple substrate and release the substrate after the transformation. I have developed two asymmetric catalysts for the C–H acetoxylation of sp^3 and sp^2 bonds. The sp^3 C–H acetoxylation occurs with high levels of diastereoselectivity, demonstrating the compatibility of this idea for enantioselective C–H functionalization.

In the course of my asymmetric ligand development, I engineered a stereoretentive synthesis for the formation of quaternary asymmetric amino amides. The straightforward synthesis involves facile, high yielding conversion of L-proline into a broad scope of differentially substituted amides with excellent enantioselectivity.

Furthermore, my exploration into amino acid derived ligands has uncovered a new method for C–C bond formation. The coupling of aryl substrates, originating from aryl sulfonamides, with olefins in a Heck-type transition metal catalyzed process has been discovered from examining serine scaffolds. This transformation may become a useful addition to the arsenal of C–C bond forming reactions.

Acknowledgements

I would first like to thank Eric for being a fantastic mentor during my time at Colorado State University. It's been very exciting to be a part of a brand new start up lab, and I want to thank him for letting me be a part of it. I also want to thank him for being so understanding in recent months with the tough decisions I've had to make.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Acac	acetylacetonate
Ac_2O	acetic anhydride
Bu	butyl
Bn	benzyl
Boc	*t*-butoxy carbonyl
Boc_2O	di-*t*-butyl dicarbonate
BQ	benzoquinone
CAN	cerric ammonium nitrate
Cp	cyclopentaldienyl anion
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	day
Dba	dibenzylideneacetone
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMP	Dess Martin periodinane
DMSO	dimethylsulfoxide
Dppe	1,2-bisdiphenylphosphinoethane
DMAP	4-dimethylaminopyridine

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
HOBt	hydroxybenzotriazole
h	hour
IPA	isopropyl alcohol
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	meta-chloroperbenzoic acid
Mes	mesityl, (2,4,6-trimethyl phenyl)
min	minute
Ms	methane sulfonyl
MTPA	α-methoxy,α-trifluoromethyl phenyl acetic acid
Ns	4-nitrophenyl sulfonyl
PGME	phenyl glycine methyl ester
Ph	phenyl
PTSA	*p*-toluene sulfonic acid
TBS	tert-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxy radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Ts	*p*-toluene sulfonyl

Chapter 1

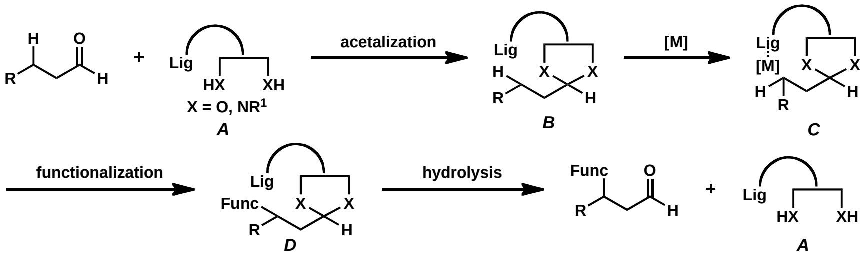
C–H Functionalization

Carbon-hydrogen bond functionalization, particularly in the formation of new carbon-carbon and carbon-heteroatom bonds, is a primary focus of modern methodological studies.[1] The development of new reactions relying on C–H functionalization is widely pursued in an effort to construct complex molecules from those with a low degree of functionality. Our research will exploit a transient directing group to accomplish the C–H functionalization of simple substrates without the necessity for a high degree of initial functionality within the molecule.

1.1 Research Objectives

Recent demonstrations of C–H bond functionalization involve an internalized ligating group to achieve high levels of chemo- and regioselectivity.[1] Our methodology will focus on the development of a ligand (**A**) that contains a heteroatom ligating group that can transiently attach to a substrate with a low degree of functionality (Scheme 1.1.1). We endeavor to attach the ligand to an aldehyde substrate through an acetal linkage. The acetalization component of the ligand will condense onto an aldehyde to afford a substrate-ligand adduct (**B**). The internal ligating group can then coordinate a metal (**C**) and place it in position to perform a C–H functionalization (**D**). Upon hydrolysis, the functionalized product will be released and the ligand regenerated. We will demonstrate the utility of this methodology with respect to the current examples of C–H functionalization.

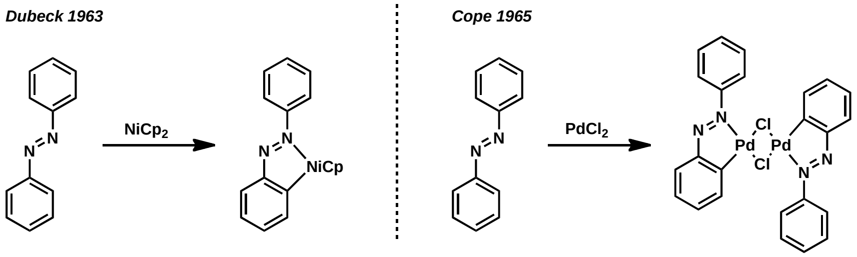
Scheme 1.1.1



1.2 Recent Examples of C–H Functionalization

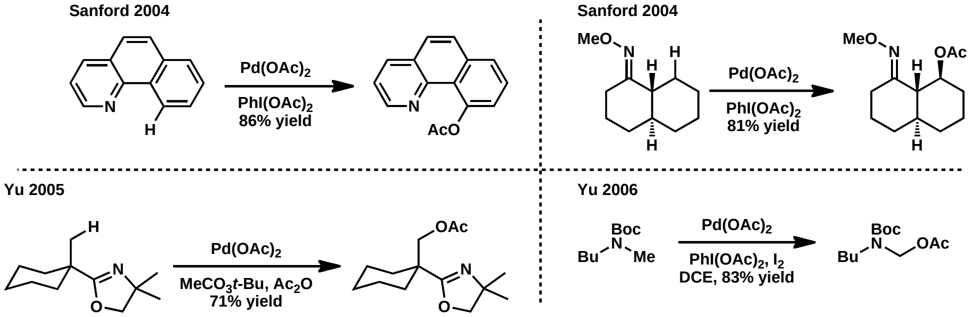
Directed C–H bond activation was first accomplished in the 1960s, when both Dubeck and Cope discovered the cyclometallation product of azobenzene (Scheme 1.2.1).[2,3] Since this discovery, remarkable work has advanced the application of C–H activation to catalysis and functionalization. In the course of these advances, much insight into the mechanism of C–H activation has been achieved leading to the progression of reaction development.

Scheme 1.2.1



Directed C–H bond functionalization via Pd^{II}/Pd^{IV} catalysis has been widely explored in recent years by numerous groups.[1] Carbon-oxygen bond formation has been one of the most widely explored areas of C–H functionalization. In 2004, Sanford and coworkers showed that 7,8-benzoquinoline would undergo acetoxylation in the presence of catalytic palladium and stoichiometric iodobenzene diacetate (Scheme 1.2.2).[4] A variety of directing groups have mediated C–H functionalization in these aromatic systems. Mechanistically, a Pd^{II}/Pd^{IV} catalytic cycle was envisioned featuring initial C–H activation followed by oxidation and reductive elimination (*vide supra*). Additionally, Sanford and coworkers discovered the same transformation can be induced in the functionalization of *sp*^{3} C–H bonds (Scheme 1.2.2).[5] In rigid systems, 2° C–H bonds undergo acetoxylation diastereoselectively, suggesting that either C–H activation or reductive elimination proceeds stereoselectively.

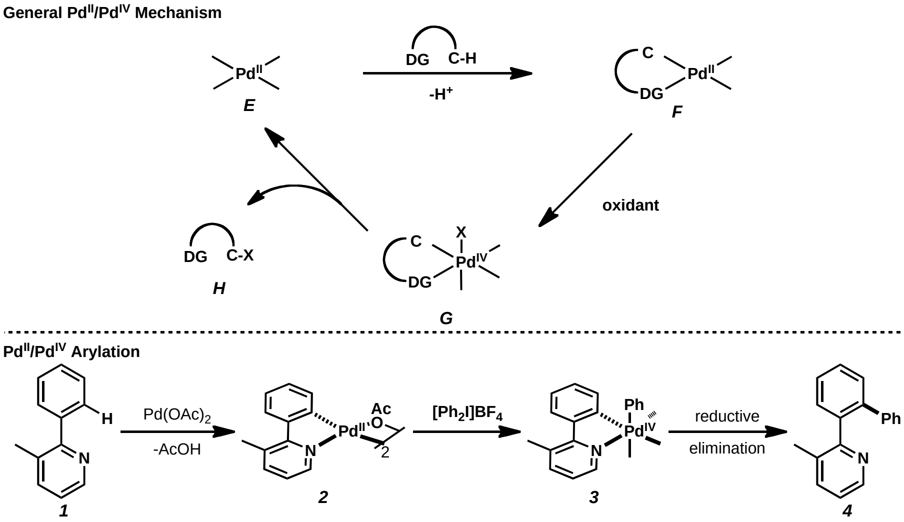
Scheme 1.2.2



Similarly, Yu and coworkers have demonstrated oxazolines to be competent directing groups in these transformations.[6] In the presence of catalytic palladium (II) and *tert*-butyl peracetate in acetic anhydride, the acetoxylated product was afforded in 71% yield (Scheme 1.2.2). The mechanism is presumed to follow that outlined by Sanford and coworkers. Further investigations revealed a dual role for Ac_2O, both assisting in the oxidation to palladium (IV) and regeneration of the $Pd(OAc)_2$ catalyst. Changing the solvent to propionic or isobutyric anhydride afforded the corresponding carboxylate product. Similarly, they have observed IOAc to be a competent oxidant in these transformations, generated *in situ* from I_2 and $PhI(OAc)_2$.[7] Boc-protected methyl amines were acetoxylated at the 1° C–H bond in the presence of catalytic $Pd(OAc)_2$ and IOAc in 83% yield.

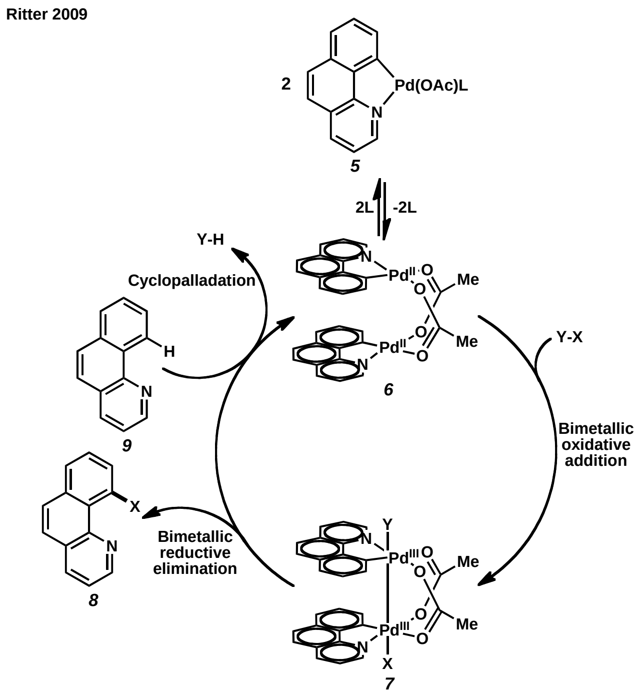
In the first proposed mechanism, it is envisioned that an internal ligating group directs the palladium to undergo C–H activation to form the palladacycle (**F**) (Scheme 1.2.3). Subsequent oxidation to Pd^{IV} (**G**) followed by reductive elimination affords the acetoxylated product (**H**) in 86% yield.[4] These Pd^{IV} complexes have been isolated and well-studied in comparable reductive eliminations.[8] Dissociation to the products is thought to occur through a pre-dissociation of a ligand, or a direct reductive elimination. This mechanism was demonstrated in a C-C bond forming arylation reaction executed by Sanford and coworkers.[9] Cyclometallation of **1** *via* $Pd(OAc)_2$ afforded palladacycle **2**, which upon treatment with a diaryliodonium salt oxidized Pd^{II} to Pd^{IV} (**3**). Reductive elimination from the Pd^{IV} species formed the new carbon-carbon bond of product **4** and regenerated the palladium catalyst. This mechanism is thought to be applicable to all C–H oxidation reactions.

Scheme 1.2.3


General Pd^II/Pd^IV Mechanism
Pd^II
E
DG C-H
-H+
C
DG
Pd^II
F
oxidant
X
C
DG
Pd^IV
G
DG C-X
H
Pd^II/Pd^IV Arylation
H
N
1
Pd(OAc)2
-AcOH
Ac
O
Pd^II
N
2
2
[Ph2I]BF4
Ph
Pd^IV
N
3
reductive
elimination
Ph
N
4

Recently, new mechanistic evidence has suggested that a bimetallic Pd^{III}/Pd^{III} or Pd^{II}/Pd^{IV} species may be the active catalyst.[10] The mechanistic hypothesis is shown in Scheme 1.2.4. Upon cyclometallation, two palladacycles (**5**) dimerize to form intermediate **6**. This species can undergo a bimetallic oxidative addition to form a Pd^{III}-Pd^{III} bond (**7**). A bimetallic reductive elimination can occur to release the functionalized product (**8**) and regenerate the catalyst. This reductive elimination is thought to occur via a 1,1-concerted reductive elimination. Ritter and coworkers have compiled extensive kinetic and mechanistic work to support this hypothesis. The rate-determining step (RDS) of this transformation is highly dependent on the strength of the oxidant. In the case of $PhI(OAc)_2$, the RDS of acetoxylation is C–H activation, negating the significance of a Pd^{III}-Pd^{III} dimer versus the conventional Pd^{II}/Pd^{IV} catalytic cycle. In the case of *N*-chlorosuccinimide, however, the RDS of chlorination is the oxidative step, where the mechanistic support for a Pd^{III}-Pd^{III} dimer materialized. If it is assumed that two Pd atoms are required to come together to form a dimeric species in the RDS, the reaction should be second order in palladium. If the catalyst resting state is dimeric and the RDS is dimeric in palladium the reaction should be first order in palladium. Because the catalyst resting state is in equilibrium between monomeric and dimeric species, the kinetic data revealed that the reaction is 1.5 order in palladium. These bimetallic high oxidation state species have been isolated and characterized and have shown kinetic competency in C–H functionalization reactions.

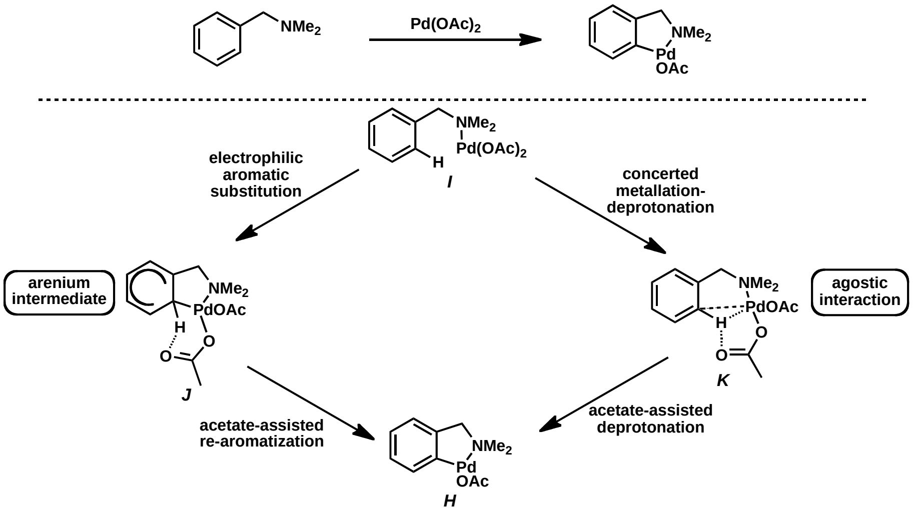
Scheme 1.2.4


Ritter 2009
2
Pd(OAc)L
N
5
2L
-2L
Y-H
Cyclopalladation
H
N
9
N
Pd^{II}
O
O
Me
O
O
Me
Pd^{II}
N
6
Y-X
Bimetallic oxidative addition
X
N
8
Bimetallic reductive elimination
Y
Pd^{III}
Me
Pd^{III}
Me
X
7

While the mechanism of oxidation in these transformations has been well-studied, the mechanism of the cyclometallation step requires additional explanation. In the context of directed C–H activation, three possible pathways have been postulated: oxidative addition, σ-bond metathesis and electrophilic activation.[11-13] C–H activation via palladium is thought to occur by either an electrophilic aromatic substitution mechanism or through an agostic interaction leading to a concerted metallation-deprotonation (CMD) event (Scheme 1.2.5).[11] In both cases, directing group coordination places the metal in position to undergo C–H activation. The electrophilic aromatic substitution reaction involves the formation of the arenium intermediate **J**, with subsequent re-aromatization via base-assisted deprotonation. While this mechanism cannot be unambiguously discredited, recent computational studies by Davies and coworkers suggest that an agostic C–H bond interaction for the initiation of activation is most probably followed by a CMD event.[13] Investigations with **10** and $Pd(OAc)_2$ suggest that initiation occurs via displacement of one η^2 acetate arm with the C–H bond to afford the 6-membered agostic intermediate **K**.

Fagnou and coworkers have also investigated the mechanism of acetate-assisted C–H activation.[14] It was found that acetate derivatives were essential for the realization of the reaction, which supports the agostic interaction-CMD mechanism. Additionally, they observed large kinetic isotope effects consistent with hydrogen abstraction during the rate-determining step. Lastly, they observed that electron poor aromatics outcompete electron rich systems in direct competition, which is contradictory with an electrophilic aromatic substitution mechanism. All of these observations suggest that the mechanism of C–H activation more closely aligns with a CMD event, rather than electrophillic aromatic substitution.

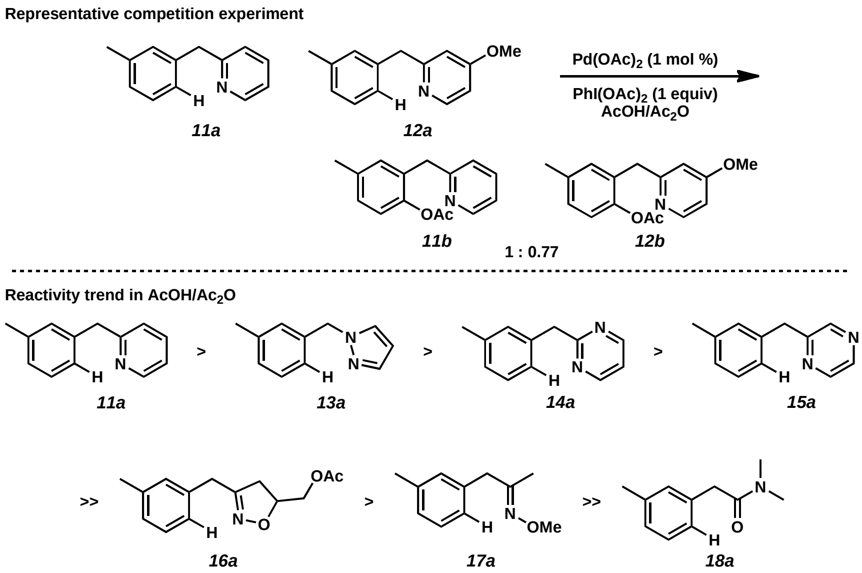
Scheme 1.2.5


NMe$_2$
Pd(OAc)$_2$
NMe$_2$
Pd
OAc
NMe$_2$
Pd(OAc)$_2$
H
I
electrophilic aromatic substitution
concerted metallation-deprotonation
arenium intermediate
NMe$_2$
PdOAc
H
O
O
J
NMe$_2$
PdOAc
H
O
O
K
agostic interaction
acetate-assisted re-aromatization
acetate-assisted deprotonation
NMe$_2$
Pd
OAc
H

The directing groups in these transformations can play an important role in the rate of functionalization. Sanford and coworkers have further investigated nitrogen based directing group ability.[15] Utilizing benzylpyridine derivatives and optimized reaction conditions, competition studies were conducted and revealed that directing groups with electron donating substituents reacted preferentially (Scheme 1.2.6, **11a** and **12a**). Subsequently, individual kinetic studies were conducted on the substrates, and revealed that electron-withdrawing substituents on the pyridine ring enhanced the reaction rate for acetoxylation. Presumably, a more basic pyridine will bind palladium (II) preferentially over a less basic pyridine. C–H activation, however, occurs more rapidly with a less basic pyridine as a directing group, reducing the amount of electron density around the palladium species. In addition to substituent effects, competition studies were conducted between different directing groups to ascertain the reactivity and revealed that more basic directing groups reacted preferentially (Scheme 1.2.6). Based on the data, a relative reactivity trend in Ac_2O/AcOH was compiled and ranked directing groups in terms of reactivity with the pyridine **11a** being most reactive and amide **18a** being least reactive.

Individual studies were conducted on the substrates, revealing that all of the directing groups (**11a-18a**) were competent for directing C–H functionalization.

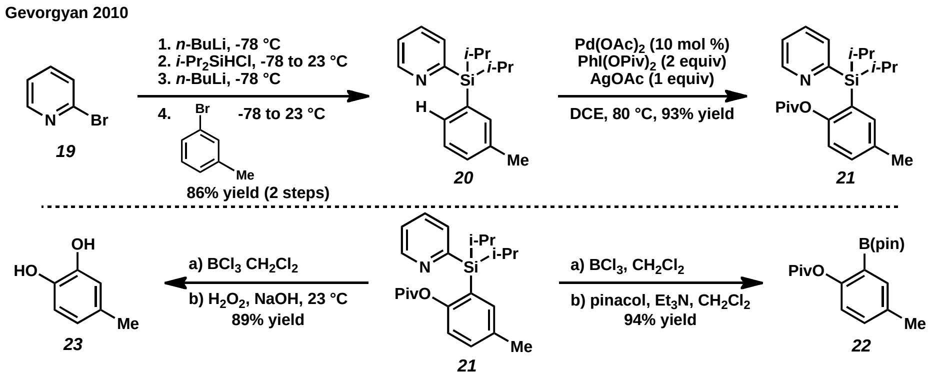
Scheme 1.2.6


Representative competition experiment
11a
12a
Pd(OAc)2 (1 mol %)
PhI(OAc)2 (1 equiv)
AcOH/Ac2O
11b
12b
1 : 0.77
Reactivity trend in AcOH/Ac2O
11a
13a
14a
15a
16a
17a
18a

1.3 Convertible Directing Groups

A limitation inherent in traditional directed C–H functionalization is the difficulty of removal of the required directing group. There have been recent examples of these processes occurring in high yield. Gevorgyan and coworkers used silicon-tethered pryidine directing groups to promote C–H pivaloxylation and acetoxylation via palladium catalysis with oxidation via a hypervalent iodine species (Scheme 1.3.1).[16] By treating 2-bromopyridine (**19**) with *n*-butyllithium and diisopropylsilyl chloride, followed by *n*-butyllithium and 3-bromotoluene they attached the pyridinediisopropylsilyl directing group in two steps with good yield. Treatment of **20** with pivaloxylation conditions afforded **21** in excellent yield, while treatment with PhI(OAc)$_2$ afforded the corresponding acetoxylated product in 88% yield. The addition of AgOAc in the functionalization reaction provided higher yields, presumably by increasing the concentration of Pd(OAc)$_2$ in solution.[17] From the functionalized product, the silicon-tethered directing group was removed and the functional group transformed in one pot to reveal a variety of different compounds. Treatment with borontrichloride followed by pinacol afforded the pinacolborane derivative (**22**) in excellent yield, which can be further derivatized in Suzuki couplings. Alternatively, treatment with borontrichloride followed by oxidizing conditions afford the catechol derivative (**23**). Furthermore, they were able to replace the directing group with H by treatment with AgF in MeOH in 93% yield. This method provides a selective high yielding four-step C–H oxidation via a transformable directing group.

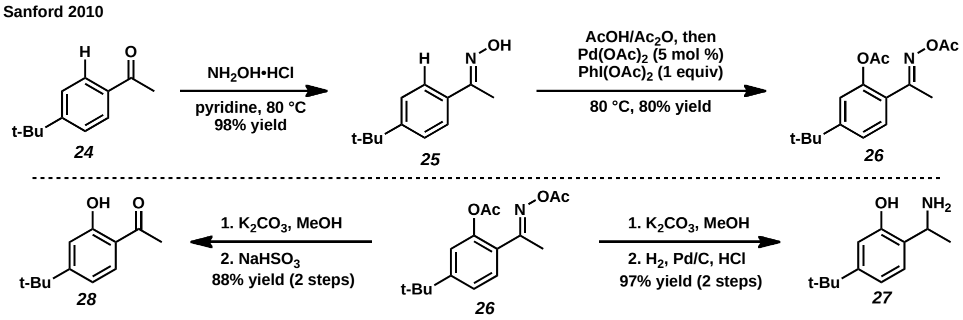
Scheme 1.3.1



Gevorgyan 2010
19
1. n-BuLi, -78 °C
2. i-Pr2SiHCl, -78 to 23 °C
3. n-BuLi, -78 °C
4. -78 to 23 °C
86% yield (2 steps)
20
Pd(OAc)2 (10 mol %)
PhI(OPiv)2 (2 equiv)
AgOAc (1 equiv)
DCE, 80 °C, 93% yield
21
a) BCl3 CH2Cl2
b) H2O2, NaOH, 23 °C
89% yield
23
a) BCl3, CH2Cl2
b) pinacol, Et3N, CH2Cl2
94% yield
22

Sanford and coworkers developed an alternative method using another convertible directing group.[18] They found *O*-acetyl oximes to be competent directing groups in the acetoxylation of aryl sp^2 C–H bonds as well as sp^3 C–H bonds (Scheme 1.3.2). In one step in high yield, ketone **24** was converted to the corresponding oxime (**25**). Treatment with an AcOH/Ac_2O mixture, presumably to make the *O*-acetyl oxime, followed by treatment with $Pd(OAc)_2$ and $PhI(OAc)_2$ afforded the desired acetoxylated product (**26**) in good yield. *O*-acetyl oximes are easily transformable directing groups, and after removal of the acetate, different chemical modifications afforded a diverse number of products. Treatment with hydrogenation conditions afforded the corresponding primary amine (**27**), while treatment with sodium bisulfite provided the original ketone (**28**). This method provides a highly selective four-step procedure to generate acetoxylated *sp*^{2} and *sp*^{3} C–H bonds in good yield.[19]

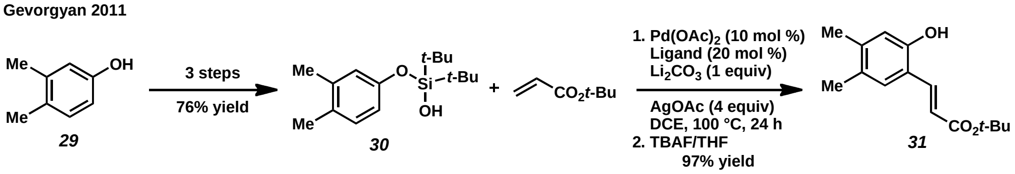
Scheme 1.3.2



Sanford 2010
24
$NH_2OH•HCl$
pyridine, 80 °C
98% yield
25
$AcOH/Ac_2O$, then
$Pd(OAc)_2$ (5 mol %)
$PhI(OAc)_2$ (1 equiv)
80 °C, 80% yield
26
28
1. K_2CO_3, MeOH
2. $NaHSO_3$
88% yield (2 steps)
26
1. K_2CO_3, MeOH
2. H_2, Pd/C, HCl
97% yield (2 steps)
27

Gevorgyan and coworkers also developed a C–H alkenylation reaction with a directing group that can be easily removed (Scheme 1.3.3).[20] Using an ortho silanol directing group, they were able to effect *sp*^{2} alkenylation, which upon treatment with TBAF revealed the functionalized product devoid of the necessary directing group. In three steps, which can be performed semi-one-pot, phenol **29** was converted to silanol **30** in good yield. The C–H alkenylation reaction was effected under palladium catalysis with an amino acid derived ligand developed by Yu and coworkers.[21] Upon completion of the functionalization, treatment with TBAF in a semi-one-pot reaction afforded product **31** in excellent yield. This method provided a five-step process in two pots to provide C–H alkenylation products with excellent selectivity.[22]

Scheme 1.3.3

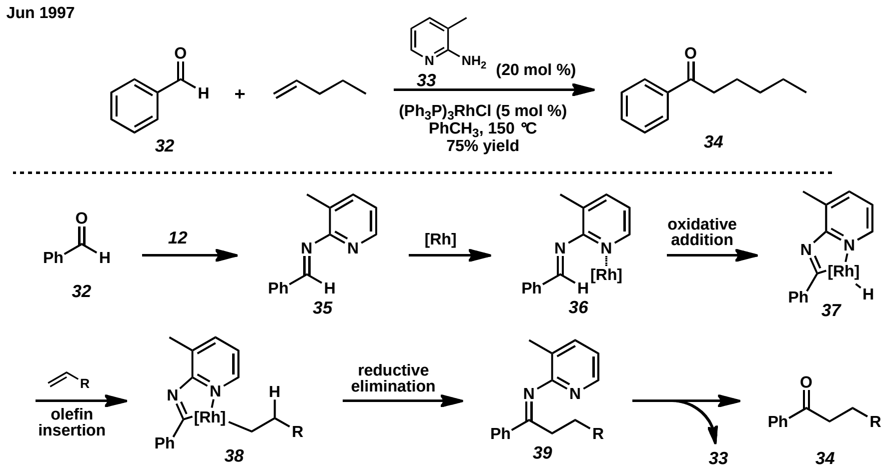


Gevorgyan 2011
29
3 steps
76% yield
30
+
1. $Pd(OAc)_2$ (10 mol %)
Ligand (20 mol %)
Li_2CO_3 (1 equiv)
AgOAc (4 equiv)
DCE, 100 °C, 24 h
2. TBAF/THF
97% yield
31

1.4 Transient Directing Group Scaffolds

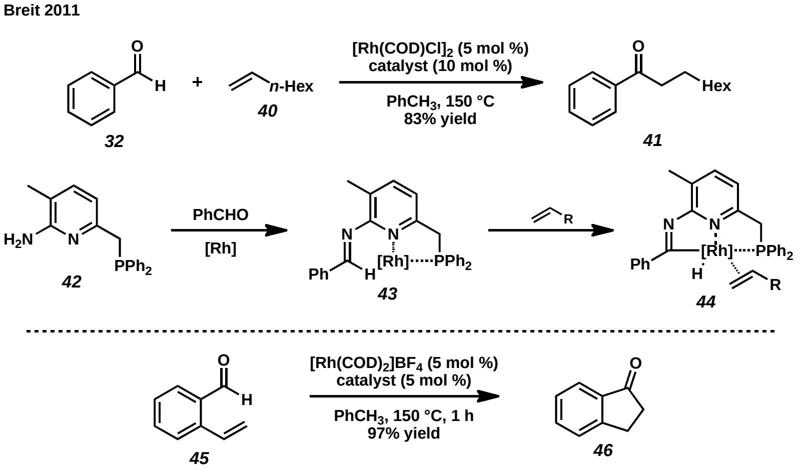
While there have been a few examples of easily convertible directing groups, these methods still require several steps to both install and remove the necessary functionality for high levels of selectivity in each substrate. The goal of our research is to accomplish directed C–H functionalization with an *in situ* removable directing group. In a few demonstrated chelation-assisted transformations a directing group is attached to the desired substrate to form a transient reactive intermediate, which can then undergo some kind of functionalization. Jun and coworkers reported a chelation-assisted hydroacylation of benzaldehyde with a picoline catalyst (**33**) (Scheme 1.4.1).[23] In this transformation, an internal directing group is prepared *in situ* to enable C–H activation. Treatment of benzaldehyde with 1-pentene in the presence of catalytic rhodium and 2-amino-3-picoline (**33**) afforded the hydroacylated product in 75% yield. Jun and coworkers proposed that **33** condenses onto benzaldehyde to give imine **35** (Scheme 1.4.1). Coordination to imine **35** by rhodium gives amino-rhodium species **36**, which is converted to 5-membered rhodacycle **37** via oxidative C–H activation. Olefin insertion to give rhodacycle **38** followed by reductive elimination affords hydroacylated intermediate **39**. Hydrolysis then provides desired hydroacylated product **34** and regenerates the directing ligand. Although the same transformation can be effected without the picoline additive, its use prevents an undesired decarbonylation reaction.

Scheme 1.4.1


Jun 1997
O
H
+
N
NH2
(20 mol %)
33
(Ph3P)3RhCl (5 mol %)
PhCH3, 150 °C
75% yield
32
O
34
O
Ph
H
32
12
N
N
Ph
H
35
[Rh]
N
N
[Rh]
Ph
H
36
oxidative
addition
N
N
[Rh]
Ph
H
37
R
olefin
insertion
N
N
[Rh]
H
R
Ph
38
reductive
elimination
N
N
Ph
R
39
33
O
Ph
R
34

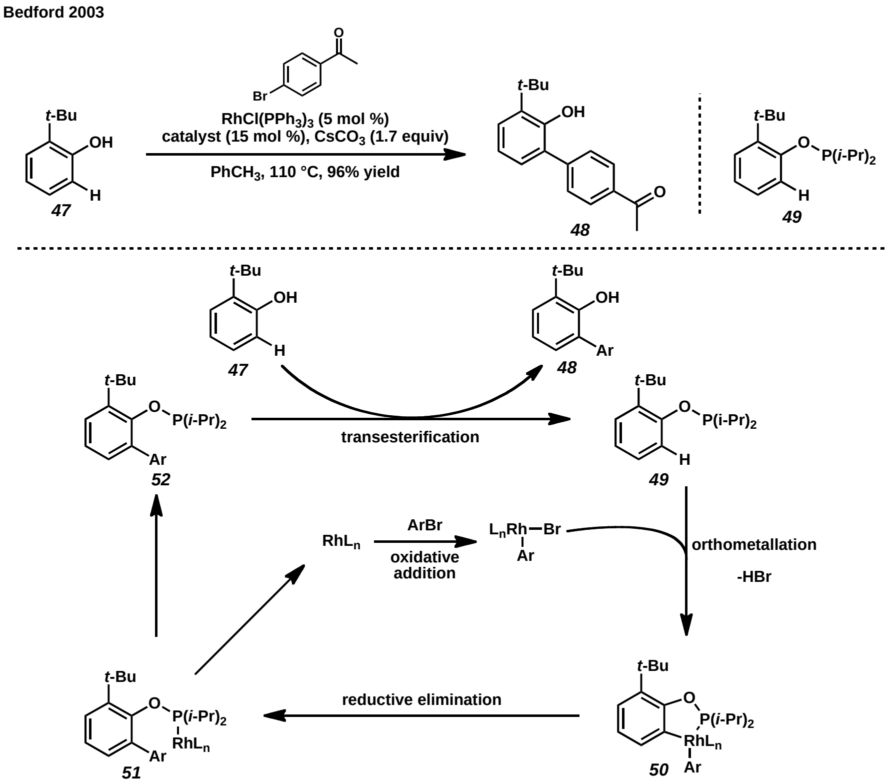
Breit and coworkers employed a bifunctional strategy towards the hydroacylation of aryl aldehydes (Scheme 1.4.2).[24] In this method, a picoline catalyst containing a pendant phosphine (**42**) was utilized to direct hydroacylations. This design allows bidentate-coordination between the catalyst and the metal. As a result, a lower catalyst loading was achieved while maintaining high reactivity by generating a higher effective concentration of activated substrate **44**. Using this catalyst, a hydroacylation of benzaldehyde with 1-octene was achieved in 83% yield. An intramolecular hydroacylation was also promoted with this catalyst system, converting **45** to cyclized **46** in excellent yield. In general, intramolecular hydroacylation suffers from complications with polymerization and decarbonylation. This transformation was effected with low catalyst loadings and high yield with the bifunctional catalyst.

Scheme 1.4.2


Breit 2011
O
H
+
n-Hex
32
40
[Rh(COD)Cl]2 (5 mol %)
catalyst (10 mol %)
PhCH3, 150 °C
83% yield
O
Hex
41
H2N
N
PPh2
42
PhCHO
[Rh]
N
N
Ph
H
[Rh]·····PPh2
43
R
N
N
Ph
H
[Rh]·····PPh2
R
44
O
H
45
[Rh(COD)2]BF4 (5 mol %)
catalyst (5 mol %)
PhCH3, 150 °C, 1 h
97% yield
O
46

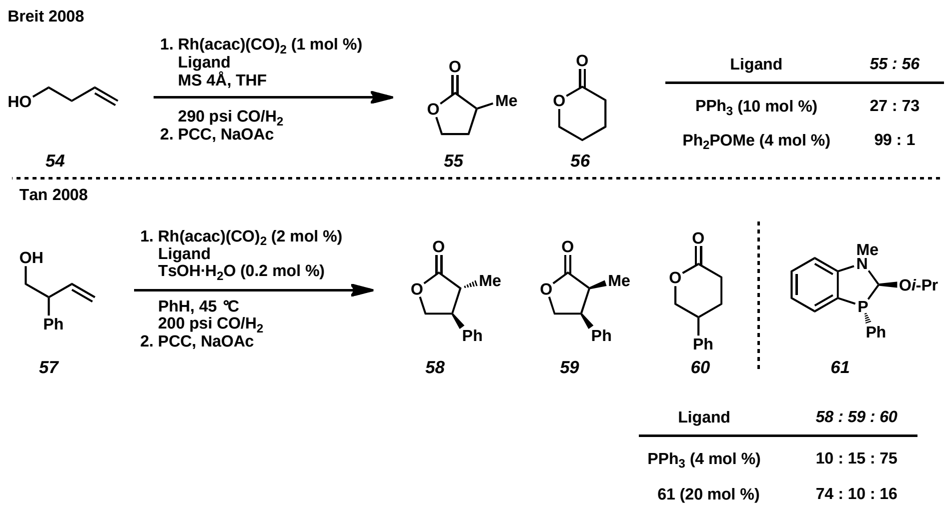
Bedford and coworkers demonstrated a C–H arylation using a transient directing group.[25] In this method, a rhodium-catalyzed ortho-arylation of phenols was described using a phosphinite directing group (Scheme 1.4.3). Mechanistically, it was proposed that the rhodium (I) species undergoes an oxidative addition of an aryl bromide to generate **53**. When coordinated to the rhodium (III) complex, **49** can then undergo an orthometallation to give rhodacycle **50**. Reductive elimination provides the arylated phosphinite product (**52**). Upon a transesterifcation process, a new substrate exchanges with the arylated phosphinite to release the cross-coupled product (**48**). The use of the phosphinite catalyst provided a single arylated product, ortho to the phenol. One limitation of this chemistry is the need for a bulky *t*-butyl group at the other ortho position to achieve high yields. Decreasing the steric bulk of this position provided lower yields, and with no ortho substitution, no product was isolated.

Scheme 1.4.3


Bedford 2003
Br
O
t-Bu
OH
H
47
RhCl(PPh3)3 (5 mol %)
catalyst (15 mol %), CsCO3 (1.7 equiv)
PhCH3, 110 °C, 96% yield
48
P(i-Pr)2
49
Ar
52
transesterification
RhLn
ArBr
oxidative addition
LnRh—Br
orthometallation
-HBr
reductive elimination
50
51

Breit and coworkers have also used this concept in hydroformylation reactions, where they employed a phosphinite catalyst to promote desired reactivity.[26] With triphenylphosphine as an external directing group, hydroformylation of **54** was observed under rhodium catalysis to give lactols, which afforded lactones **55** and **56** upon oxidation (Scheme 1.4.4). Good selectivity for the linear hydroformylation product (**56**) was observed under these conditions. When triphenylphosphine was exchanged for the phosphinite ligand, however, the hydroformylation reaction proceeded with excellent selectivity for the branched product (**55**). Breit and coworkers proposed that the alcohol substrate exchanges with methoxy group, as a ligand on phosphorous, generating an internal phosphine-directing group. This intermediate directed the hydroformylation of **54** with enhanced reactivity to give the branched product (**55**) in excellent selectivity. Tan and coworkers employed a similar model to achieve high regio- and diastereoselectivity in hydroformylation reactions (Scheme 1.4.4).[27] In their system, hydroformylation occured in the presence of an external phosphine catalyst to give linear product **60** in good selectivity. Introduction of a specialized phosphine catalyst (**61**), which can undergo ligand exchange with the alcohol substrate (**57**), allowed a now internal phosphine catalyst to direct hydroformylation to give the branched product (**58**) in good regio- and diastereoselectivity (Scheme 1.4.4).

Scheme 1.4.4

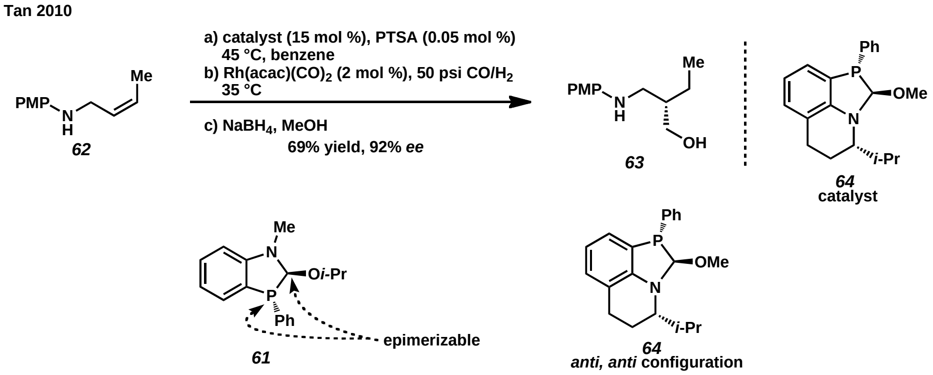

Breit 2008
1. Rh(acac)(CO)$_2$ (1 mol %)
Ligand
MS 4Å, THF
290 psi CO/H$_2$
2. PCC, NaOAc
HO
O
Me
54
55
56
Tan 2008
1. Rh(acac)(CO)$_2$ (2 mol %)
Ligand
TsOH·H$_2$O (0.2 mol %)
PhH, 45 °C
200 psi CO/H$_2$
2. PCC, NaOAc
OH
Ph
N
Me
P
O*i*-Pr
57
58
59
60
61

Ligand	*55 : 56*
PPh$_3$ (10 mol %)	27 : 73
Ph$_2$POMe (4 mol %)	99 : 1

Ligand	*58 : 59 : 60*
PPh$_3$ (4 mol %)	10 : 15 : 75
61 (20 mol %)	74 : 10 : 16

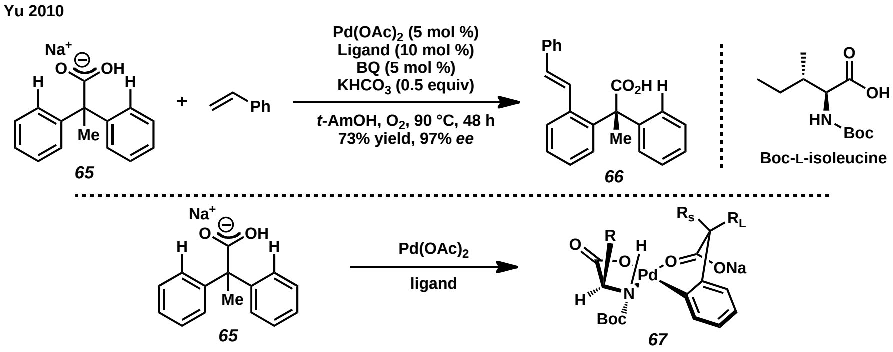
Tan and coworkers have recently developed a new enantioselective hydroformylation using a transient directing group scaffold.[28] In comparison to their original catalyst, the new scaffold contains an additional non-epimerizable stereocenter (Scheme 1.4.5). In catalyst **61**, both stereocenters are epimerizable under the reaction conditions, preventing any high degree of stereoinduction. In catalyst **64**, however, the stereocenter with the isopropyl group is permanently set, preserving the stereochemical integrity of the other stereocenters, as they maintain an *anti*, *anti* configuration in order to prevent *syn*-pentane interactions. Using this catalyst, Tan and coworkers obtained the hydroformylated product **(63)** in good yield and high enantioselectivity. Rational catalyst design of this nature to incorporate stereoselectivity may be very important in the development of enantioselective C–H functionalization.

Scheme 1.4.5


Tan 2010
a) catalyst (15 mol %), PTSA (0.05 mol %) 45 °C, benzene
b) Rh(acac)(CO)$_2$ (2 mol %), 50 psi CO/H$_2$ 35 °C
c) NaBH$_4$, MeOH
69% yield, 92% *ee*
PMP
N
H
Me
62
63
OH
Ph
P
OMe
N
i-Pr
64
catalyst
Me
N
O*i*-Pr
P
Ph
epimerizable
61
64
anti, anti configuration

Yu and coworkers have recently developed a carboxylic acid directed C–H olefination reaction.[29] Subjecting achiral **65** to catalytic Pd(OAc)$_2$, BQ, KHCO$_3$ and an amino acid ligand in the presence of O$_2$ afforded the desymmeterized olefinated product (**66**) in 97% *ee* (Scheme 1.4.6). The amino acid, Boc-L-isoleucine, acts as a ligand on palladium to perform a diastereoselective C–H activation to generate **67**. Migratory insertion into the olefin and β-hydride elimination afforded olefinated product **66** and Pd^0. Reoxidation via BQ and O$_2$ afforded the active Pd^{II} catalyst. This example demonstrates that rational ligand design and reaction development can generate enantiopure products from simple achiral starting materials without the need for molecular complexity.

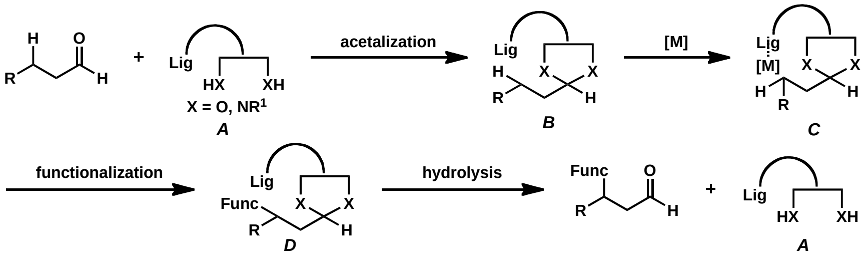
Scheme 1.4.6


Yu 2010
Na+
O
OH
H
H
Me
65
+
Ph
Pd(OAc)2 (5 mol %)
Ligand (10 mol %)
BQ (5 mol %)
KHCO3 (0.5 equiv)
t-AmOH, O2, 90 °C, 48 h
73% yield, 97% ee
Ph
CO2H H
Me
66
O
OH
HN
Boc
Boc-L-isoleucine
Pd(OAc)2
ligand
R
RS
RL
O
O
H
Pd
O
ONa
H
N
Boc
67

1.5 Research Objectives Revisited

In an effort to unify the power of directed C–H activation with chelate-assisted functionalization, we aim to develop C–H activation methodology mediated by a transient directing group. We envision designing a ligand that has both an acetalization component and an attached ligating group (Scheme 1.5.1). The acetalization component will condense onto a carbonyl substrate, forming a covalently bound intermediate with an internal directing group. The tethered ligating group will then direct metal-catalyzed functionalization to a remote carbon-hydrogen or carbon-carbon bond. Hydrolysis of the ligand will reveal the functionalized product and regenerate the free ligand. Proposed to be catalytic in both ligand and metal, this functionalization will generate molecular complexity in rapid fashion without the need for additional directing group removal steps. With proper design, the scaffold will be able to direct a C–H functionalization with high regio- and stereoselectivity.

Scheme 1.5.1


acetalization
[M]
functionalization
hydrolysis
Lig
HX
XH
X = O, NR1
A
B
C
D
Func
R
H
O
[M]

1.6 References and Notes

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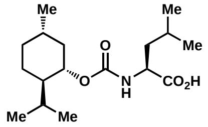

(+)menthyl(O_2C)-Leu-OH

[22] These conditions work well for very electron rich aromatic systems, but the yields decrease significantly when employing electron-deficient aromatics. Furthermore, only activated olefins are utilized in these transformations.

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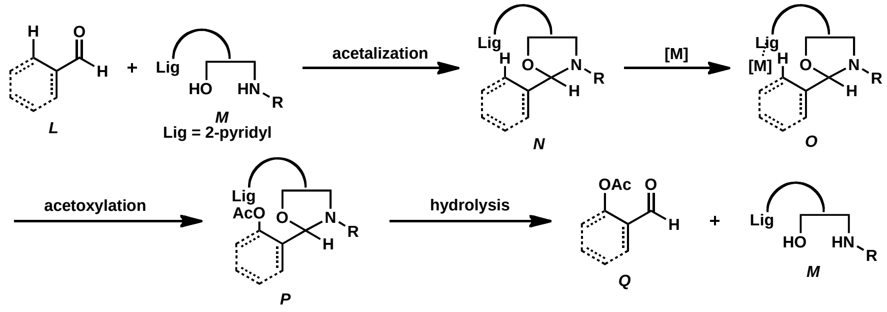
Chapter 2

Acetoxylation of *sp*^{2} and *sp*^{3} C–H Bonds

In an effort to unify the power of directed C–H functionalization with chelate-assisted functionalization, we aimed to develop a C−H acetoxylation of *sp*^{2} and *sp*^{3} C–H bonds mediated by a transient directing group (Scheme 2.0.1). We envisioned a ligand that has both an acetalization component and a ligating group. Based on work by Sanford[1] and Yu,[2] we imagined using an oxazoline or pyridyl ligating group to direct a metal-catalyzed functionalization of a remote C−H bond. The acetalization component needs to condense onto an aldehyde, therefore we envisioned using a combination of an alcohol or acid and amine or amide (**M**), which would afford substrate-ligand adduct **N**. Treatment with acetoxylation conditions would afford functionalized intermediate **P**. Subsequent hydrolysis of the ligand would reveal the functionalized product (**Q**), and regenerate the free ligand. Proposed to be catalytic in both ligand and metal, this method would require synchronization of initial acetalization, functionalization, and transacetalization.

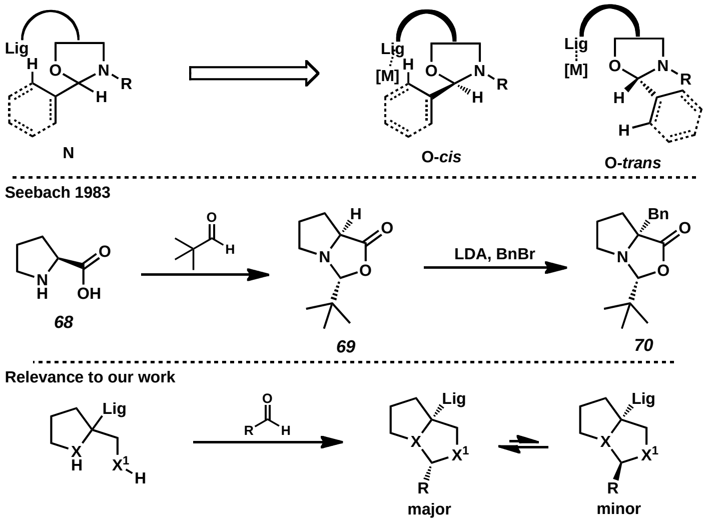
Scheme 2.0.1. General Concept



2.1 Ligand Synthesis

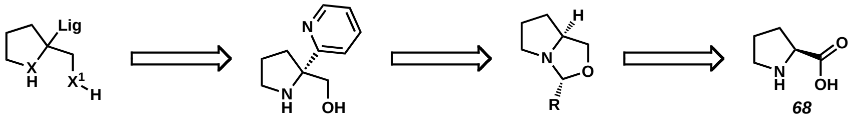
Our initial studies began with ligand design and synthesis. We imagined an amino alcohol could serve as the acetalization component, which should readily condense onto an aldehyde forming an *N,O*-acetal. For a ligating group, an oxazoline or 2-pyridyl moiety would be straightforward to install, and these have already been demonstrated as competent directing groups in C–H acetoxylation.[1-2] What remained to be determined was the structural alignment of the ligand. Based on our hypothesis, the formation of our substrate ligand adduct **N**, can occur with a *cis* or *trans* relationship between the substrate to be functionalized and the ligating group (Scheme 2.1.1). If the **O-*cis*** isomer were obtained, the relationship between the ligating group and substrate would allow for C–H functionalization. If the **O-*trans*** isomer were obtained, however, the ligating group and substrate would not be in proximity to promote a directed functionalization. Literature precedent revealed that [3.3.0] systems can provide high levels of the desired stereoselectivity. Seebach has demonstrated self-reproduction of chirality using amino acids to build structurally complex unnatural amino acids (Scheme 2.1.1).[3] L-Proline (**68**) was condensed onto pivaldehyde to afford **69** as a single diastereomer. Alkylation with benzyl bromide afforded **70**, again as a single diastereomer, with a *cis* relationship between the α-substituent and the alkyl group of the acetal. We believed we could exploit this method to achieve a *syn* relationship between our ligating group and substrate. In the event that trace amounts of the *anti* isomer is generated, it should be unreactive to functionalization conditions, and isomerization would presumably yield the *syn* diastereomer.

Scheme 2.1.1. Formulation of Our Approach


Lig
H
O
N
R
H
N
Lig
[M]
H
O
N
R
H
O-*cis*
Lig
[M]
O
N
R
H
H
O-*trans*
Seebach 1983
O
H
N
H
OH
68
H
O
N
O
69
LDA, BnBr
Bn
O
N
O
70
Relevance to our work
Lig
X
H
X1
H
O
R
H
Lig
X
X1
R
major
Lig
X
X1
R
minor

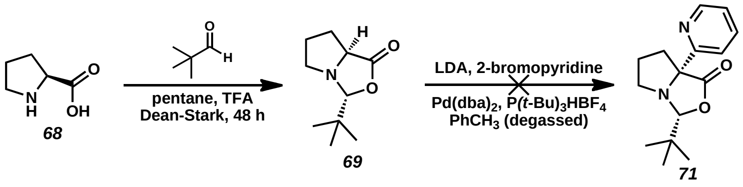
We imagined this [3.3.0] system could be used, yielding high levels of diastereoselectivity[3] and providing a rigid ligand scaffold. With these concepts in hand, we designed our ligand retrosynthesis from (*S*)-proline (Scheme 2.1.2). Installation of the directing group could be accomplished upon protection of the amino acid; deprotection and reduction of the acid would afford the desired ligand.

Scheme 2.1.2. Ligand Retrosynthesis


Lig
X
H
X1
H
N
N
H
OH
H
N
O
R
N
H
OH
O
68

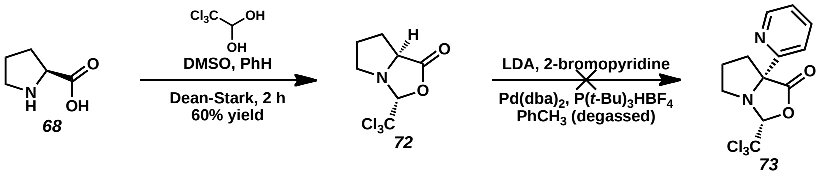
Employing Seebach's acetalization/alkylation chemistry, the *N,O*-acetal (**69**) was formed as a single diastereomer (Scheme 2.1.3).[3] Acetal **69** was unstable under air, and rapidly decomposed to the starting materials. An attempted arylation using Hartwig's enolate coupling chemistry[4] was unsuccessful at generating the desired pyridine ligand.

Scheme 2.1.3. Initial Ligand Synthesis


pentane, TFA
Dean-Stark, 48 h
LDA, 2-bromopyridine
Pd(dba)$_2$, P(t-Bu)$_3$HBF$_4$
PhCH$_3$ (degassed)
68
69
71

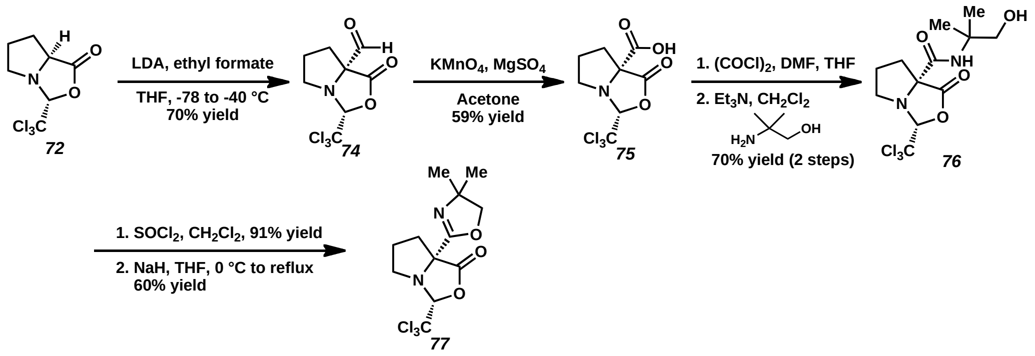
Realizing that compound **69** would be difficult to alkylate, we looked to find different condensation conditions that would render a more stable *N,O*-acetal. Following a revised Seebach procedure,[3] chloral hydrate could be condensed with proline (Scheme 2.1.4). Using these conditions we obtained **72** as a single diastereomer in 60% yield. Treatment with arylation conditions, however, proved unsuccessful to generate the pyridine ligand (**73**).

Scheme 2.1.4. A Revised Route


DMSO, PhH
Dean-Stark, 2 h
60% yield
LDA, 2-bromopyridine
Pd(dba)$_2$, P(t-Bu)$_3$HBF$_4$
PhCH$_3$ (degassed)
68
72
73

We expected using an oxazoline ligating group, rather than a pyridine, would better facilitate ligand synthesis. Alkylation with ethyl formate afforded the desired aldehyde as a stable isolable compound (Scheme 2.1.5). Several conditions were tried to oxidize the aldehyde to the acid,[5] with $KMnO_4$ being the most successful oxidant.[6] Treating **75** with oxalyl chloride afforded the corresponding acid chloride, which upon treatment with an amino alcohol afforded the desired amide. We investigated several procedures to transform the amide into the corresponding oxazoline.[7] Although we were able to generate the alkyl chloride in good yield, the base induced cyclization to afford the oxazoline was not reproducible.

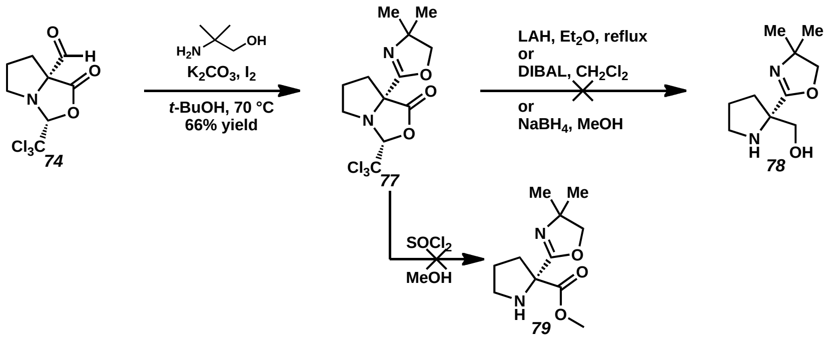
Scheme 2.1.5. Synthesis of an Oxazoline Ligating Group



72
LDA, ethyl formate
THF, -78 to -40 °C
70% yield
74
KMnO4, MgSO4
Acetone
59% yield
75
1. (COCl)2, DMF, THF
2. Et3N, CH2Cl2
H2N OH
70% yield (2 steps)
76
1. SOCl2, CH2Cl2, 91% yield
2. NaH, THF, 0 °C to reflux
60% yield
77

Ultimately, we employed an *in situ* oxidation/cyclization of the aldehyde to produce the corresponding oxazoline.[8] Treatment of aldehyde **74** with 2,2-dimethyl-1-aminoethanol, base and iodine afforded oxazoline **77** in one step in good yield (Scheme 2.1.6). To generate the amino alcohol ligand directly, we treated oxazoline **77** with a variety of different reducing agents, but were unable to isolate any of the desired product. Additionally, we tried to generate the methyl ester by treatment with anhydrous HCl in methanol, but were unsuccessful.

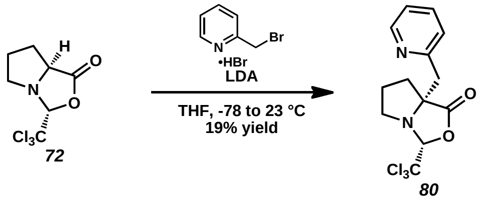
Scheme 2.1.6. Attempted Cleavage of the *N*,*O*-acetal



74
H2N OH
K2CO3, I2
t-BuOH, 70 °C
66% yield
77
LAH, Et2O, reflux
or
DIBAL, CH2Cl2
or
NaBH4, MeOH
78
SOCl2
MeOH
79

Believing the oxazoline to be too sensitive to *N,O*-acetal cleavage conditions, we thought a pryidine ligating group might be more robust and provide us with a ligand. Eager to install this ligating group to test our original hypothesis, we tried a standard alkylation procedure using 2-bromomethyl pyridine hydrobromide (Scheme 2.1.7). The alkylation was successful in installing the pyridine directing group to generate **80** in modest yield. Several different bases were examined in an effort to improve the yield of the alkylation, but were unsuccessful.

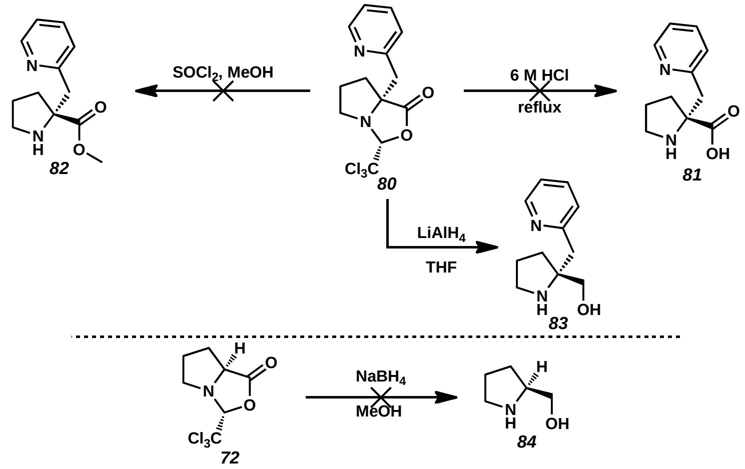
Scheme 2.1.7. Installation of a Pyridyl Ligating Group



Base	yield
LDA	19%
KHMDS	0%
LiHMDS	0%

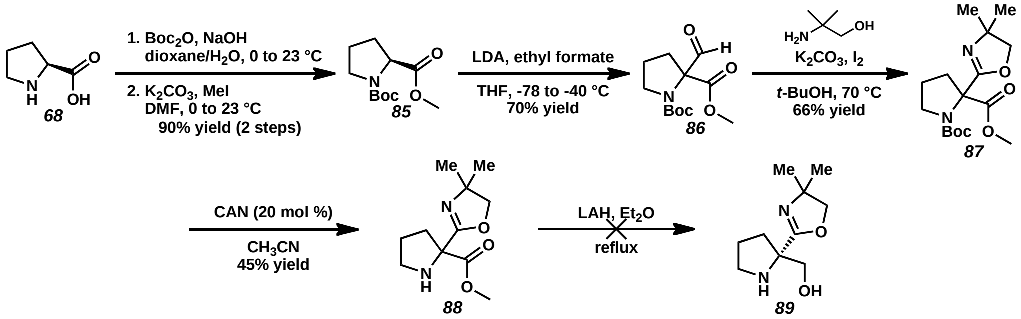
Treatment with typical acid hydrolysis conditions, however, did not afford the desired amino acid (**81**) (Scheme 2.1.8). Believing the existence of pyridine and acid moieties to be problematic, we tried to bypass the intermediate by generating the methyl ester (**82**) using anhydrous HCl and methanol, but again were unsuccessful. In an attempt to generate amino alcohol **83** directly we treated **80** with $LiAlH_4$ to reduce the acetal, but only observed decomposition of the starting material. Furthermore, treating **72** with a reducing agent failed to afford amino alcohol **84**, indicating that the *N,O*-acetal could not be cleaved under reductive conditions.

Scheme 2.1.8. Hydrolysis of the *N,O*-acetal



As the ligand synthesis via the *N,O*-acetal was proving unsuccessful, we considered that protecting the amine and carboxylic acid independently would provide a more successful approach. Formation of the *t*-butyl carbamate with subsequent esterification afforded (*S*)-Boc-proline methyl ester **85** (Scheme 2.1.9). To install the oxazoline, **85** was formylated with ethyl formate. Treatment with oxidative conditions and the amino alcohol afforded the desired oxazoline (**87**) in good yield. After trying several deprotection conditions[9] the Boc group was removed with catalytic CAN in CH_3CN.[10] Treatment with LAH to reduce the methyl ester, however, failed to provide any amino alcohol ligand, again demonstrating the high reactivity of the oxazoline moiety in our system.

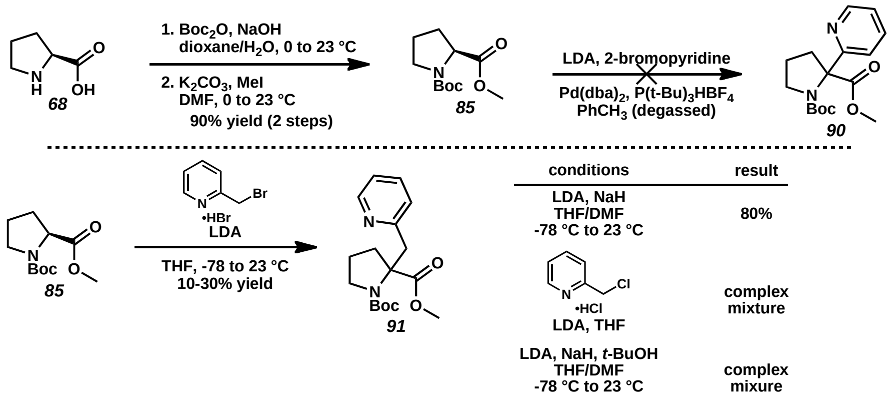
Scheme 2.1.9. A Revised Synthesis of an Oxazoline Ligand



68
1. Boc$_2$O, NaOH dioxane/H$_2$O, 0 to 23 °C
2. K$_2$CO$_3$, MeI DMF, 0 to 23 °C
90% yield (2 steps)
85
LDA, ethyl formate
THF, -78 to -40 °C
70% yield
86
H$_2$N OH
K$_2$CO$_3$, I$_2$
t-BuOH, 70 °C
66% yield
87
CAN (20 mol %)
CH$_3$CN
45% yield
88
LAH, Et$_2$O
reflux
89

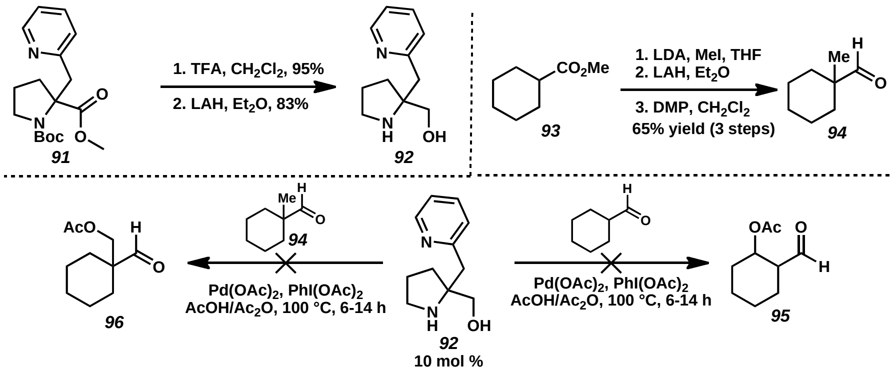
Believing a pyridine to be much more robust to the deprotection steps, we again sought to install this ligating moiety. Treatment with the arylation conditions was still unsuccessful, most likely due to the steric bulk of the protecting groups. Installing the methyl pyridine to generate **91** was low-yielding under several different conditions (Scheme 2.1.10). We attributed this yield to the low solubility of the electrophile salt and the super stoichiometric amount of LDA needed to neutralize the electrophile, which resulted in the competitive addition of LDA into the bromomethyl pyridine. We developed a procedure of neutralizing the electrophile outside of the main reaction with NaH (washed) in DMF at 0 °C. The addition of this suspension enolate improved the yield of **91**.

Scheme 2.1.10. Revised synthesis of a pyridyl ligand


68
1. Boc$_2$O, NaOH dioxane/H$_2$O, 0 to 23 °C
2. K$_2$CO$_3$, MeI DMF, 0 to 23 °C
90% yield (2 steps)
85
LDA, 2-bromopyridine
Pd(dba)$_2$, P(t-Bu)$_3$HBF$_4$ PhCH$_3$ (degassed)
90
85
•HBr
LDA
THF, -78 to 23 °C
10-30% yield
91
conditions
result
LDA, NaH THF/DMF -78 °C to 23 °C
80%
•HCl
LDA, THF
complex mixture
LDA, NaH, t-BuOH THF/DMF -78 °C to 23 °C
complex mixure

The removal of the Boc group was straightforward and occurred in high yield. Initial reduction of the methyl ester with DIBAL was unsuccessful (Scheme 2.1.11). Treatment of **91** with LAH, however, afforded the desired ligand (**92**) in good yield. The stability of **92** to air and water was not high, and led to its decomposition to a red oil. Limited handling in open atmosphere was necessary to use the ligand in further experiments. With the ligand in hand, functionalization was attempted, although initially unsuccessful. Treating cyclohexanecarboxaldehyde with a catalytic amount of ligand and acetoxylation conditions was ineffective at generating acetoxylated product **95** (Scheme 2.1.11). Rather than trying to functionalize a 2° *sp*^{3} C–H bond, which has proven difficult,[11] we synthesized aldehyde **94** which contains a 1° *sp*^{3} C–H bond. Treatment of this aldehyde with catalytic amounts of ligand and acetoxylation conditions was also unsuccessful.

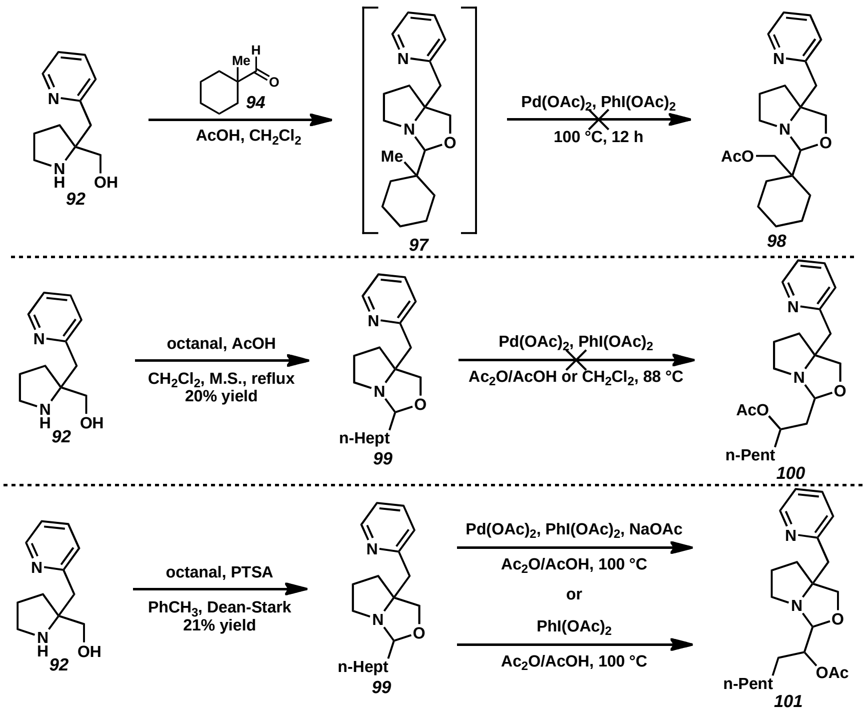
Scheme 2.1.11. Initial attempts at catalytic functionalization



1. TFA, CH2Cl2, 95%
2. LAH, Et2O, 83%
91
92
CO2Me
93
1. LDA, MeI, THF
2. LAH, Et2O
3. DMP, CH2Cl2
65% yield (3 steps)
94
Pd(OAc)2, PhI(OAc)2
AcOH/Ac2O, 100 °C, 6-14 h
96
95
92
10 mol %

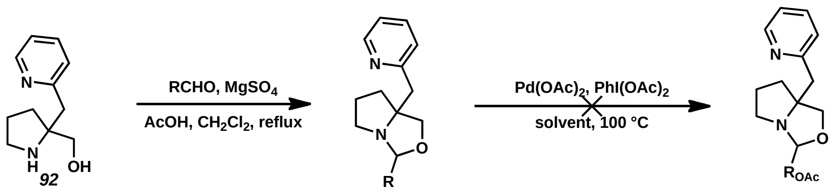
Realizing that the synchronization of acetalization, functionalization, and transacetalization was extremely challenging, we sought to study the system in a stoichiometric sense. This approach afforded the opportunity to study the nature of the *N,O*-acetal and the competency of our ligand for C–H functionalization. We first tried a one-pot, two-step procedure treating the aldehyde (**94**) and ligand **92** with AcOH in CH_2Cl_2, followed by treatment with acetoxylation conditions, but no functionalized ligand adduct was isolated (Scheme 2.1.12). Condensation onto octanal resulted in a highly labile *N,O*-acetal (**99**). When subjected to typical functionalization conditions, no desired acetoxylation product **100** was observed. Interestingly, when **99** was exposed to functionalization conditions at 100 °C, we observed acetoxylation of the α-position (to the acetal). Upon treating the substrate with stoichiometric oxidant in the absence of palladium we still observed the acetoxylated product; the product therefore likely arises from an enamine-catalyzed acetoxylation.[12] Treatment of octanal with acetoxylation conditions afforded no α-acetoxylation product.

Scheme 2.1.12. Attempts at stoichiometric functionalization


92
94
AcOH, CH$_2$Cl$_2$
97
Pd(OAc)$_2$, PhI(OAc)$_2$
100 °C, 12 h
98
octanal, AcOH
CH$_2$Cl$_2$, M.S., reflux
20% yield
99
Pd(OAc)$_2$, PhI(OAc)$_2$
Ac$_2$O/AcOH or CH$_2$Cl$_2$, 88 °C
100
octanal, PTSA
PhCH$_3$, Dean-Stark
21% yield
Pd(OAc)$_2$, PhI(OAc)$_2$, NaOAc
Ac$_2$O/AcOH, 100 °C
or
PhI(OAc)$_2$
Ac$_2$O/AcOH, 100 °C
101

We believed the enamine induced processes were occurring as a result of *N,O*-acetal lability. To slow down these processes with aliphatic aldehydes we employed α-disubstituted aldehydes (Table 2.1.1). After condensation of the ligand with an aldehyde, each substrate-ligand adduct was treated to acetoxylation conditions. All of the substrates independent of solvent resulted in a complex mixture of products that could not be deconvoluted.

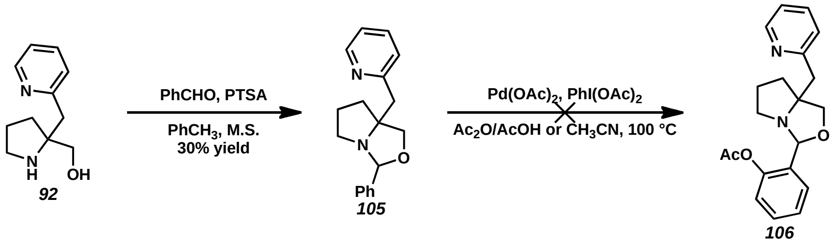
Table 2.1.1. Examination of α-substituted aldehydes


92
RCHO, MgSO$_4$
AcOH, CH$_2$Cl$_2$, reflux
Pd(OAc)$_2$, PhI(OAc)$_2$
solvent, 100 °C

aldehyde	yield	funct. conditions	result
i-PrCHO	31%	DCE, 16 h	complex mixture
i-BuCHO	20%	DCE 16 h	complex mixture
CyCHO	31%	Ac$_2$O/AcOH, 12 h	complex mixture
		CH$_3$CN, 17 h	complex mixture
		PhCH$_3$, 17 h	complex mixture

Lastly, due to our unsuccessful acetoxylation attempts with aliphatic aldehydes, we turned to functionalize aromatic aldehydes (Scheme 2.1.13). Condensation of the ligand (**92**) onto benzaldehyde afforded **105** in moderate yield. Treatment with acetoxylation conditions, however, was unsuccessful at providing functionalized products.

Scheme 2.1.13. Attempted functionalization of benzaldehyde

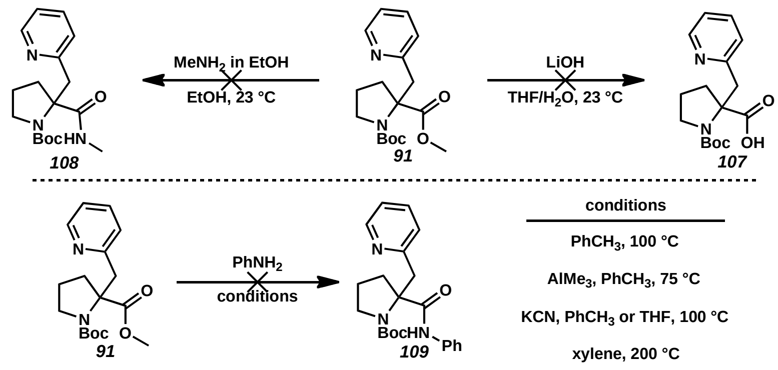


While we have been able to synthesize the desired ligand scaffolds and condense them onto aldehydes, the products of these condensations have shown to be rather unstable. Seemingly the instability of the acetal may lend satisfactorily to the transacetalization we hope to achieve. If the linkage is too labile however, oxidative side products may dominate the reactions, and prevent the desired C–H functionalization.

2.2 Acetoxylation of Isobutyraldehyde

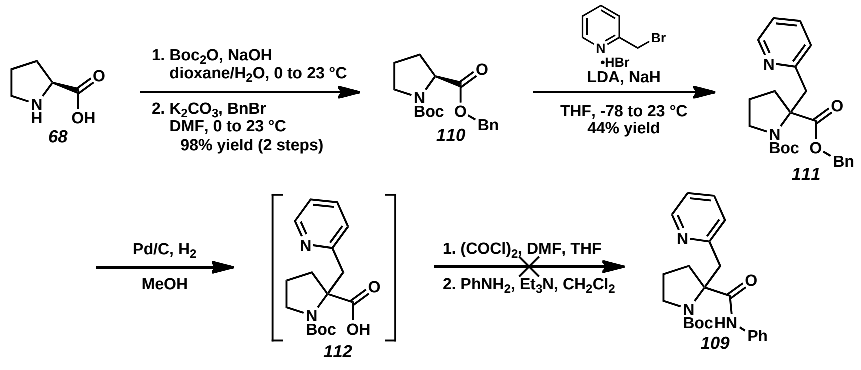
We attributed our difficulty in effecting functionalization to the lability of the *N*,*O*-acetal and attempted to find a more stable acetalization component. Literature accounts show that when amino amides were condensed onto aromatic aldehydes, the resulting *N*,*N*-aminal was a stable, isolable product.[13] We sought to convert protected amino ester **91** to the amide via the carboxylic acid; however, saponification was unsuccessful (Scheme 2.2.1). Direct conversion to the methyl amide (**108**) via methylamine was ineffective. Exposing the methyl ester to aniline in toluene at 100 °C did not afford any of the phenyl amide product (**109**). Likewise, heating to 200 °C in xylene, or treating with KCN in toluene or THF were ineffective at generating the desired amide. We also tried to generate the aluminum amide, but this was also ineffective at displacing the methyl ester.

Scheme 2.2.1. Conversion to an amino amide


MeNH2 in EtOH
EtOH, 23 °C
LiOH
THF/H2O, 23 °C
108
91
107
PhNH2
conditions
109
conditions
PhCH3, 100 °C
AlMe3, PhCH3, 75 °C
KCN, PhCH3 or THF, 100 °C
xylene, 200 °C

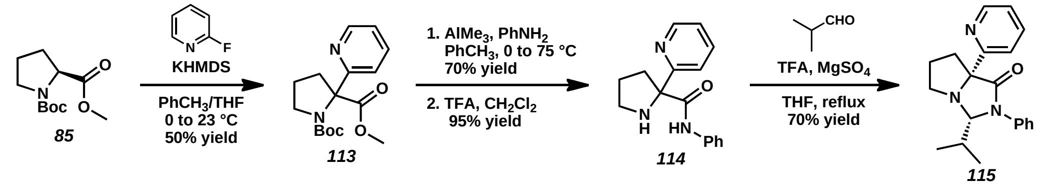
The installation of an amide from the methyl ester appeared to be an impractical route to an amino amide. Rather than employing a saponification of the methyl ester, we imagined using a hydrogenation of a benzyl ester to generate the desired acid. Formation of the benzyl ester occurred in high yield, and alkylation with 2-bromomethyl pyridine installed the ligating group (Scheme 2.2.2). Hydrogenation with Pd/C and H_2 appeared to afford the desired carboxylic acid. Any attempt to convert the acid into the amide, however, was unsuccessful.

Scheme 2.2.2. An alternative approach to an amino amide


68
1. Boc2O, NaOH
dioxane/H2O, 0 to 23 °C
2. K2CO3, BnBr
DMF, 0 to 23 °C
98% yield (2 steps)
110
•HBr
LDA, NaH
THF, -78 to 23 °C
44% yield
111
Pd/C, H2
MeOH
112
1. (COCl)2, DMF, THF
2. PhNH2, Et3N, CH2Cl2
109

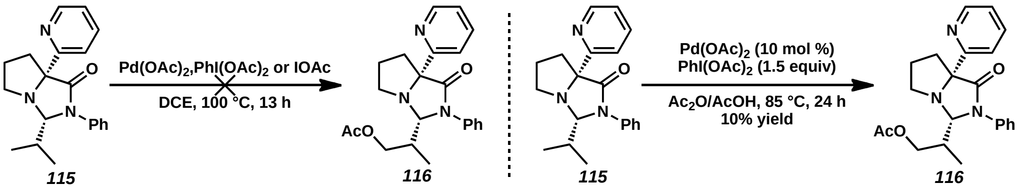
Troubled by the difficulty of generating the amino amide ligand with the methyl pyridine ligating group, we began to examine a new ligating group. We imagined that a pyridine directly attached to the [3.3.0] system may be successful. By changing the conformational flexibility of the system, differential activity may be imparted, and may enable us to convert the methyl ester into the desired amide. Nucleophilic aromatic substitution with **85** afforded the arylated product (**113**) (Scheme 2.2.3). Treatment with trimethylaluminum and aniline directly afforded the desired amide.[14] Deprotection with TFA proceeded with high yield to provide amino amide ligand **114**. Isolation of this compound proceeded smoothly and decomposition was not observed under ambient conditions. Condensation onto isobutyraldehyde afforded **115** in good yield as a stable *N,N*-aminal.

Scheme 2.2.3. Generation of an amino amide



Initial attempts at acetoxylation were unsuccessful, using either $PhI(OAc)_2$ or IOAc as the stoichiometric oxidant at 100 °C in DCE (Scheme 2.2.4). When reacted under Sanford's original conditions with catalytic $Pd(OAc)_2$ and stoichiometric $PhI(OAc)_2$ in $AcOH/Ac_2O$ at 85 °C, monoacetoxylated product **116** was observed in 10% isolated yield, observed as a single diastereomer. In the absence of palladium no reaction was observed, suggesting that the transformation was a palladium-catalyzed C–H acetoxylation. Initial optimization attempts revealed that as temperature increased, an increase in the ratio of product to starting material was observed, with the highest ratio occurring at 85 °C, but still only providing 10% yield. Above 100 °C, only iminium-catalyzed products and decomposition products were observed.

Scheme 2.2.4. Initial acetoxylation of isobutyraldehyde

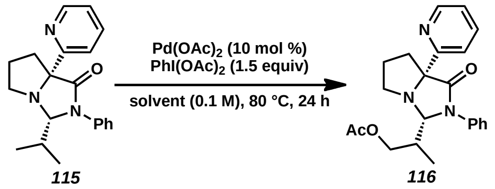


Pd(OAc)$_2$,PhI(OAc)$_2$ or IOAc
DCE, 100 °C, 13 h
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, 85 °C, 24 h
10% yield
N
O
N
N
Ph
AcO
115
116
115
116

temp °C	115 : 116
110	1.0 : 0
70	5.9 : 1
75	6.0 : 1
80	2.8 : 1
85	2.7 : 1 (10% yield)

We began the optimization of the acetoxylation reaction by a solvent screen. As seen in Table 2.2.1, when the reaction was run in any solvent but AcOH/Ac$_2$O, no product was observed. Yu and coworkers found that Ac$_2$O was essential for regenerating the active palladium catalyst.[2] Attempts with various mixed solvent systems with Ac$_2$O again provided no product. Mixed solvent systems with AcOH yielded no product with DCE or PhCH$_3$, but did provide a small amount of product when using CH$_3$CN. Believing AcOH and Ac$_2$O to be essential to the reaction, we tried adding multiple equiv of each to reactions run in DCE, PhCH$_3$ and CH$_3$CN, but no product was observed.

Table 2.2.1. Solvent screen

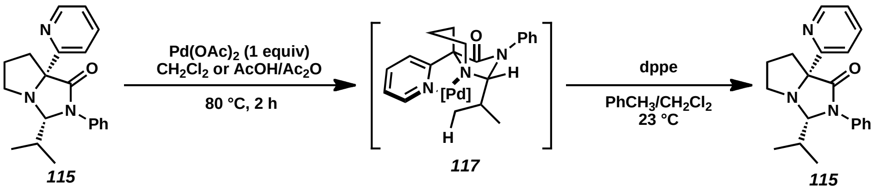


Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
solvent (0.1 M), 80 °C, 24 h
N
O
N
N
Ph
AcO
115
116

solvent	115 : 116	solvent (1:1)	115 : 116	solvent (1:1)	115 : 116
DCE	1.0 : 0	DCE:Ac$_2$O	1.0 : 0	DCE:AcOH	1.0 : 0
PhCH$_3$	1.0 : 0	PhCH$_3$:Ac$_2$O	1.0 : 0	PhCH$_3$:AcOH	1.0 : 0
PhH	1.0 : 0	PhH:Ac$_2$O	1.0 : 0	CH$_3$CN:AcOH	6.0 : 1
CH$_3$CN	1.0 : 0	CH$_3$CN:Ac$_2$O	1.0 : 0		
CH$_2$Cl$_2$	1.0 : 0	CH$_2$Cl$_2$:Ac$_2$O	1.0 : 0		

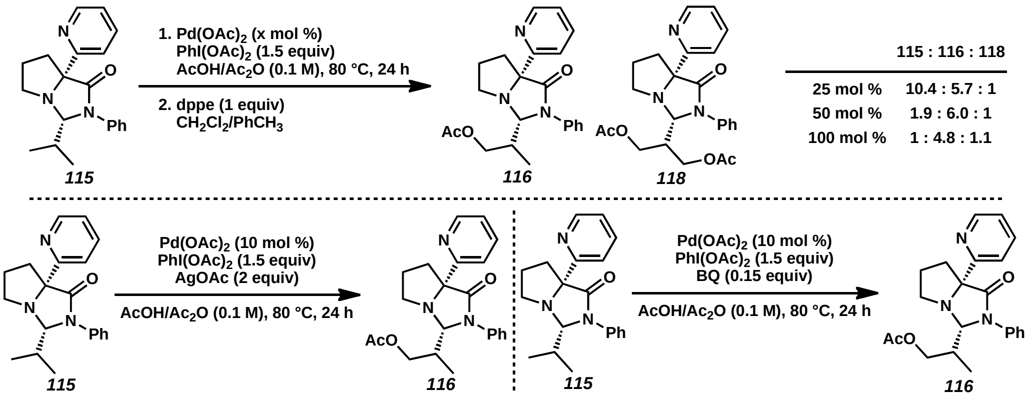
In an attempt to isolate a putative C–H activated palladacycle, we treated the isobutyraldehyde substrate (**115**) with stoichiometric palladium in the absence of oxidant (Scheme 2.2.5). Subsequent treatment with diphenylphosphinoethane (dppe) released the starting material. Based on this result, we believe that the palladium coordinated to the substrate in a bi-dentate fashion to afford **117**, but based on ^{1}H NMR, no C–H activation was observed.

Scheme 2.2.5. Generation of a palladacycle



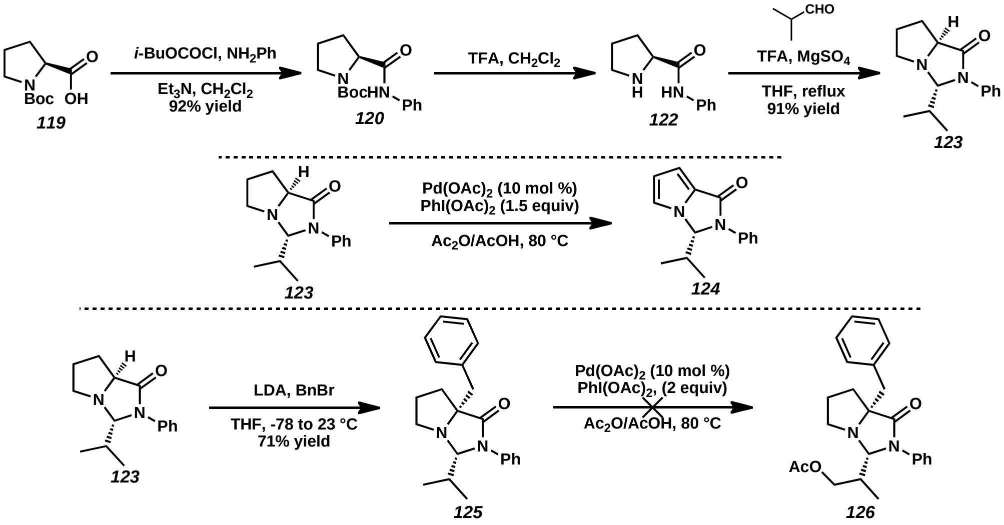
The low levels of conversion in these reactions were curious to us. Treatment with stoichiometric palladium and the addition of oxidant gave near complete consumption of starting material, affording the major product as the monoacetoxylated compound (**116**) and the minor as the diacetoxylated product (**118**) (Scheme 2.2.6). Due to these findings and low catalyst loading providing only a small amount of desired product (<10%), we examined the catalytic turnover of the palladium catalyst. Increasing the catalyst loading of palladium to 25 mol % followed by treatment with dppe afforded an increase in the ratio of product to starting material, suggesting less than two catalytic turnovers. Indeed, when catalyst loading was increased to 50 mol %, over 75% conversion of the starting material was observed. We postulated that the low turnover may be due to the formation of PdI_2 which is inactive in acetoxylation reactions.[15] Treatment of **115** with two equiv of AgOAc in the presence of acetoxylation conditions, however, failed to improve the turnover number. We attribute the low conversion to the incredibly strong binding of the ligand to palladium. It is interesting to note, however, despite the high catalyst loadings, the product was isolated with high diastereoselectivity, speaking to the high selectivity of the C–H functionalization. Further optimization found 50 mol % $Pd(OAc)_2$ with 1.8 equiv of oxidant for 24 h to yield 66% of **116** in 10 to1 dr and 13% of the diacetoxylated product (**118**).

Scheme 2.2.6. Catalyst turnover


1. Pd(OAc)$_2$ (x mol %)
PhI(OAc)$_2$ (1.5 equiv)
AcOH/Ac$_2$O (0.1 M), 80 °C, 24 h
2. dppe (1 equiv)
CH$_2$Cl$_2$/PhCH$_3$
115 : 116 : 118
25 mol % 10.4 : 5.7 : 1
50 mol % 1.9 : 6.0 : 1
100 mol % 1 : 4.8 : 1.1
N
O
N
Ph
AcO
OAc
115
116
118
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
AgOAc (2 equiv)
AcOH/Ac$_2$O (0.1 M), 80 °C, 24 h
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
BQ (0.15 equiv)
AcOH/Ac$_2$O (0.1 M), 80 °C, 24 h

In order to learn more about the directing capability of our scaffold, we tried to establish that the pyridine-ligating group was essential for functionalization. In our system it is possible that the pyrrolidine nitrogen, phenyl amide or pyridine could be directing the functionalization. The role of the pyridyl group could be determined by removing it and observing the outcome. Formation of the phenyl amide via mixed anhydride chemistry and subsequent deprotection allowed us to generate amino amide **122** (Scheme 2.2.7). Condensation onto isobutyraldehyde afforded the desired *N*,*N*-aminal. With no pyridyl ligating group we expected that functionalization could not occur. Rather than no reaction, however, we observed oxidation of the pyrrolidine ring to the corresponding pyrrole (**124**), necessitating the presence of a α-substituent. We installed a benzyl group at the α-position to mimic the size of the ligating group, without the nitrogen. When subjected to the functionalization conditions, no acetoxylation was observed, suggesting that the pyridine-ligating group is essential for the C–H acetoxylation in our system.

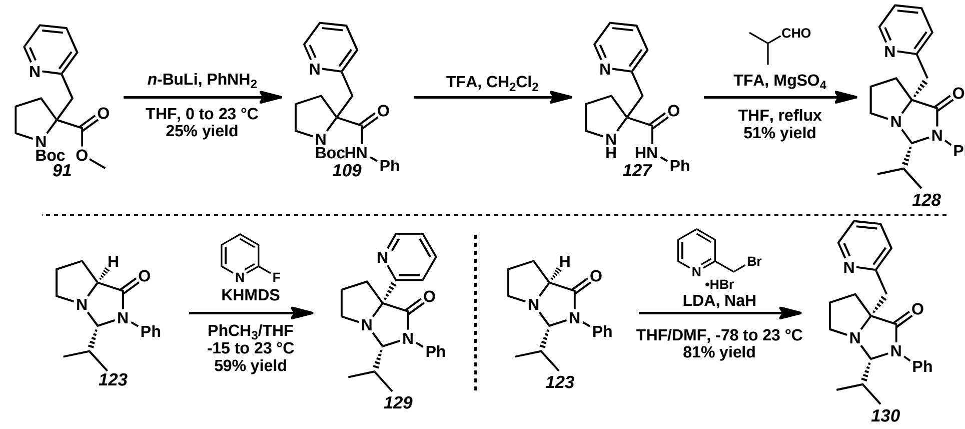
Scheme 2.2.7.



119
i-BuOCOCl, NH_2Ph
Et_3N, CH_2Cl_2
92% yield
120
TFA, CH_2Cl_2
122
CHO
TFA, $MgSO_4$
THF, reflux
91% yield
123
$Pd(OAc)_2$ (10 mol %)
$PhI(OAc)_2$ (1.5 equiv)
Ac_2O/AcOH, 80 °C
124
LDA, BnBr
THF, -78 to 23 °C
71% yield
125
$Pd(OAc)_2$ (10 mol %)
$PhI(OAc)_2$, (2 equiv)
Ac_2O/AcOH, 80 °C
126

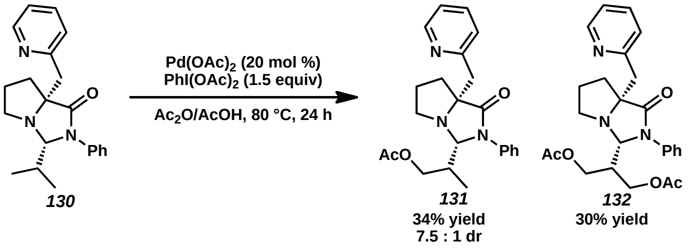
Encouraged by our ligand design providing stoichiometric C–H acetoxylation with high selectivity, we imagined changing the connectivity of the pyridine ligating group to our acetalization component by adding a methylene linker. This new scaffold would likely allow for greater conformational flexibility, and thereby likely impart differential reactivity. Despite all of our unsuccessful attempts to convert methyl ester **91** to phenyl amide **109**, we eventually treated the ester with phenyl amide to afford the desired product in modest yield. Subsequent deprotection afforded the amino amide ligand, which could be condensed onto isobutyraldehyde to afford test substrate **128**. Ultimately, we realized we could use our synthesis of **125** (*vide supra*) to synthesize the amino amide scaffolds stereoselectively (Scheme 2.2.8). Subjecting **123** to the appropriate base and electrophile afforded both **129** and **130** in good yield with complete diastereoselectivity.

Scheme 2.2.8. Asymmetric ligand synthesis


91
n-BuLi, PhNH$_2$
THF, 0 to 23 °C
25% yield
109
TFA, CH$_2$Cl$_2$
127
CHO
TFA, MgSO$_4$
THF, reflux
51% yield
128
123
KHMDS
PhCH$_3$/THF
-15 to 23 °C
59% yield
129
123
•HBr
LDA, NaH
THF/DMF, -78 to 23 °C
81% yield
130

Treating substrate **130** with acetoxylation conditions afforded a nearly 1 : 1 mixture of mono- and diacetoxylated products (Scheme 2.2.9). The addition of a methylene linker to the pryidine ligating group dramatically increased the reactivity of the functionalization event. Decreasing the catalyst loading and equiv of oxidant resulted in incomplete conversion to product. Increasing the number of equiv of oxidant resulted in higher amount of diacetoxylated product (**132**). When the acetoxylation was run at lower temperatures, limited conversion to monoacetoxylated product **131** was observed.

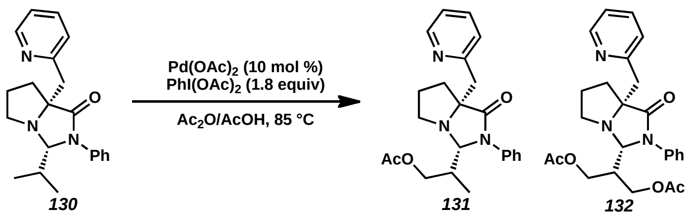
Scheme 2.2.9. Acetoxylation of isobutyraldehyde


130
Pd(OAc)$_2$ (20 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, 80 °C, 24 h
131
34% yield
7.5 : 1 dr
132
30% yield

conditions	*130 : 131 : 132*
Pd(OAc)$_2$ (10 mol %) PhI(OAc)$_2$ (1.0 equiv)	2.7 : 1.5 : 1.0
Pd(OAc)$_2$ (10 mol %) PhI(OAc)$_2$ (2.0 equiv) 80 °C 24 h	5.8 : 1.0 : 0
Pd(OAc)$_2$ (10 mol %) PhI(OAc)$_2$ (1.0 equiv) 40 °C 24 h	0 : 1.0 : 1.9

Analysis of the length of reaction was done to determine the extent of diacetoxylation as a function of time, as well as decomposition. At 8 h, good conversion to monoacetoxylated product was observed (Scheme 2.2.10). With longer reaction times, the conversion appeared to decrease, suggesting that decomposition of the products may be occurring.

Scheme 2.2.10. Time screen for acetoxylation

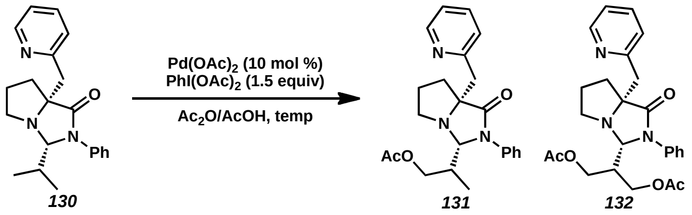


Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.8 equiv)
Ac$_2$O/AcOH, 85 °C
N
O
N
N
Ph
AcO
OAc
130
131
132

time (h)	*130 : 131 : 132*
8	1 : 4.2 : 2.8
10	1 : 3.4 : 2.5
16	1 : 3.4 : 4.0
18	1 : 2.3 : 2.3

Upon optimization we found that changing the temperature of the reaction affected both the amount of diacetoxylated product and the diastereoselectivity of the monoacetoxylated product (Scheme 2.2.11). At 55 °C after 24 h 41% of the monoacetoxylated product was observed with 10 : 1 dr, with only 13% diacetoxylated product. Upon increasing the temperature to 70 °C, after 13 h 48% of the monoacetxoylated product was observed with 5.9 : 1 dr, and 19% diacetoxylated product was isolated.

Scheme 2.2.11



Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, temp
N
O
N
N
Ph
AcO
OAc
130
131
132

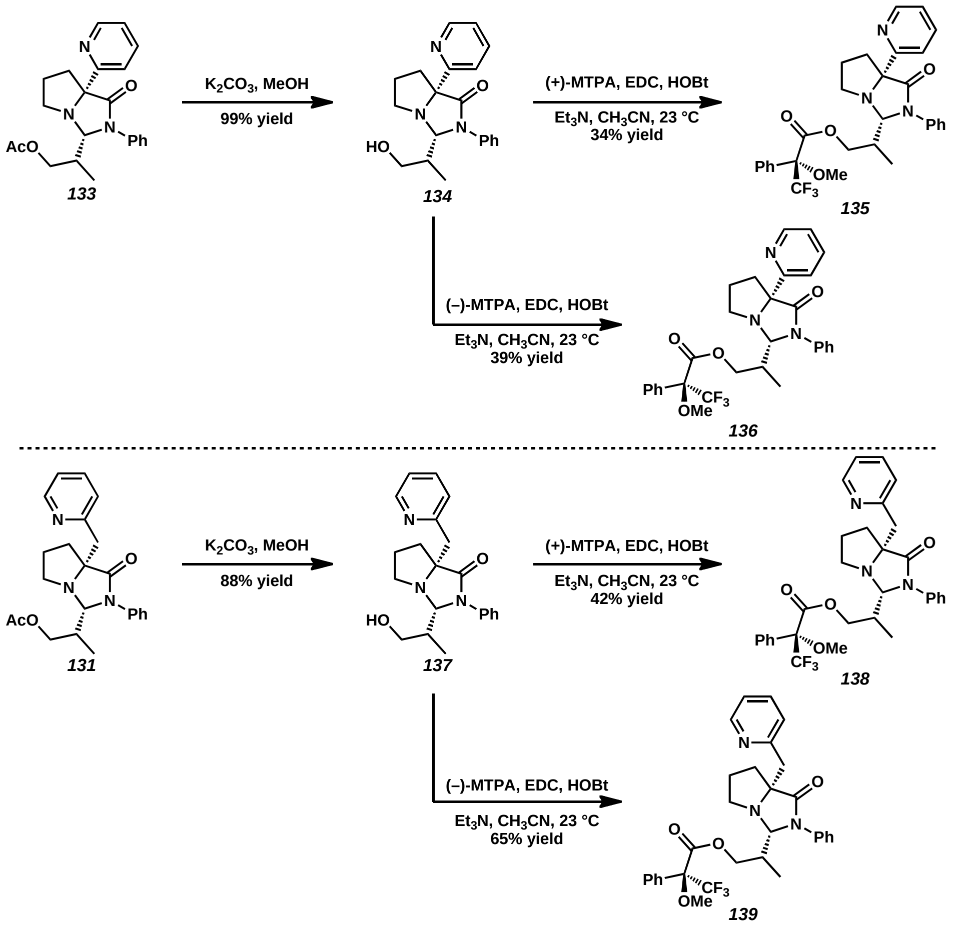
time (h)	temp (°C)	*131 : 132* (%)	dr
24	55	41 : 13	10 : 1
13	70	48 : 19	5.9 : 1

2.3 Determination of Absolute Configuration

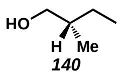
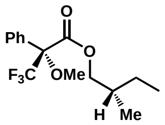
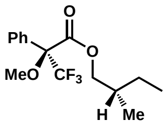
Our observation of high levels of diastereoselectivity in the monoacetoxylation of substrates **116** and **131** is a promising entrance into the possibility of asymmetric C–H functionalization. In order to understand the mode of selectivity, however, we needed to determine which methyl of the isopropyl group was being functionalized. Due to our asymmetric ligand synthesis and highly diastereoselective functionalization reaction, we should be generating a single enantiomeric product. We imagined a chiral shift reagent may be able to tell us the absolute configuration of the new stereocenter generated through functionalization.[16] Seebach and coworkers have used Mosher's acid as a chiral shift reagent to determine the absolute configuration of primary alcohols.[17] We imagined coupling the functionalized products with both enantiomers and comparing the ^{19}F NMR shifts to literature data.

Treatment of asymmetric **133** with K_2CO_3 in MeOH afforded the primary alcohol in excellent yield (Scheme 2.3.1). The coupling reaction with both (+)- and (–)-MTPA mediated by EDC and HOBt afforded esters **135** and **136** as single diastereomers, reinforcing the highly stereoselective synthesis of our substrates. Treatment of **131** with the same sequence of conditions afforded esters **138** and **139** as single diastereomers. The low conversion to the esters was attributed to the low reactivity of the substrates. When increasing the catalyst loading of HOBt to almost one equiv, the reaction proceeded in greater than 50% yield. The optical rotation of the remaining starting material was compared to that of the original starting mixture and found to be the same, indicating that a kinetic resolution process was not occurring. The literature precedence by Seebach suggested that when the (*S*)-alcohol is coupled with (*S*)-MTPA, the ^{19}F NMR peak shifts further upfield than that of the (*S*)-alcohol when coupled with the (*R*)-MTPA acid (Scheme 2.3.1). In ester **136**, the (*S*)-MTPA adduct had a downfield shift relative to the (*R*)-MTPA adduct. Similarly, ester **139** from the coupling with (*S*)-MTPA had a downfield shift relative to the (*R*) adduct. This data suggests that the pro-*S* methyl is selectively functionalized under acetoxylation conditions.

Scheme 2.3.1. Determination of absolute configuration

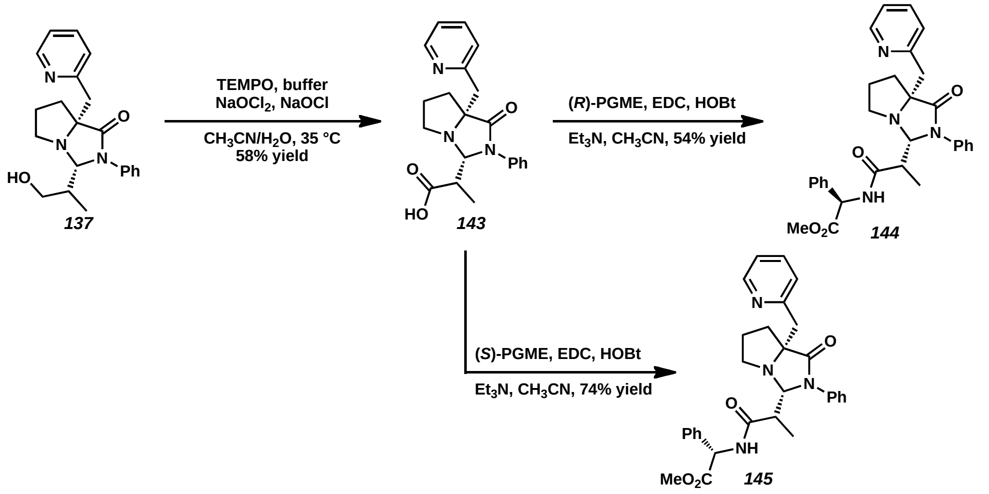


K2CO3, MeOH
99% yield
(+)-MTPA, EDC, HOBt
Et3N, CH3CN, 23 °C
34% yield
(–)-MTPA, EDC, HOBt
Et3N, CH3CN, 23 °C
39% yield
K2CO3, MeOH
88% yield
(+)-MTPA, EDC, HOBt
Et3N, CH3CN, 23 °C
42% yield
(–)-MTPA, EDC, HOBt
Et3N, CH3CN, 23 °C
65% yield
133
134
135
136
131
137
138
139

alcohol	Ester (*R*)-(+)-MTPA	Ester (*S*)(–)-MTPA
 ***140***	 ***141*** (δ)^{19}F = -72.10 ppm	 ***142*** (δ)^{19}F = -72.12 ppm
134	***135*** (δ)^{19}F = -72.081 ppm	***136*** (δ)^{19}F = -72.079 ppm
135	***138*** (δ)^{19}F = -72.18 ppm	***139*** (δ)^{19}F = -72.16 ppm

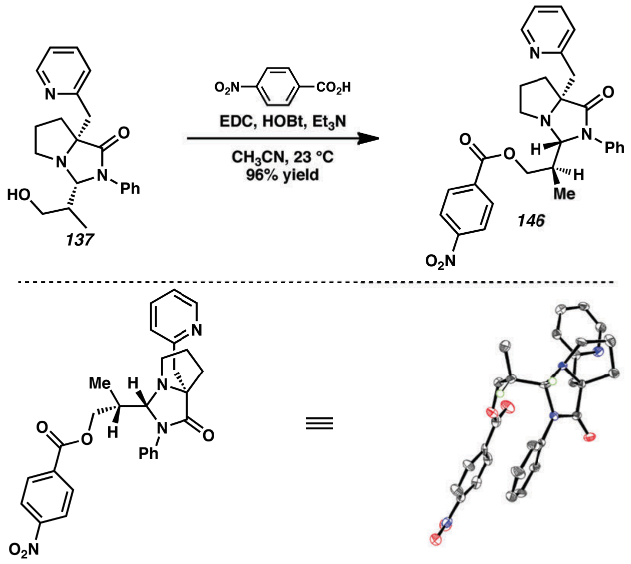
Eager to have additional evidence to support our findings of the absolute configuration, we imagined converting the primary alcohol to an acid, in order to have a α-stereocenter which may provide corroboration to our previous findings. Oxidation of the primary alcohol to the corresponding acid occurred via a mild bleach procedure (Scheme 2.3.2).[18] Peptide coupling with (*R*)-PGME and (*S*)-PGME afforded the corresponding amides. If an (*S*),(*S*) relationship is established between the PGME and new stereocenter, the aminal proton should be better shielded by the phenyl ring of the PGME.[19] If an (*R*),(*R*) relationship is established, the aminal proton should be relatively less shielded, and appear further downfield than in the (*S*)-PGME amide. A shift of 4.73 ppm was observed for amide **144**, while a shift of 4.49 ppm was observed for amide **145**, again supporting that the pro-*S* methyl is selectively functionalized.

Scheme 2.3.2. Another analysis of absolute configuration


TEMPO, buffer
NaOCl$_2$, NaOCl
CH$_3$CN/H$_2$O, 35 °C
58% yield
(*R*)-PGME, EDC, HOBt
Et$_3$N, CH$_3$CN, 54% yield
(*S*)-PGME, EDC, HOBt
Et$_3$N, CH$_3$CN, 74% yield
137
143
144
145

Ultimately, we sought out an X-ray crystal structure to confirm the absolute stereochemistry of the new stereocenter. While an X-ray structure cannot provide the absolute configuration on its own, the use of a chiral starting material as a template provides a known stereocenter from which to set the remaining stereocenters. Coupling with *p*-nitrobenzoic acid afforded ester **145** (Scheme 2.3.3). The compound was crystallized and afforded the X-ray structure. From the structure it is clear to see that the pro-*S* methyl is selectively functionalized under the acetoxylation conditions, which is consistent with the evidence provided by the esters and amides.

Scheme 2.3.3. X-ray crystal analysis

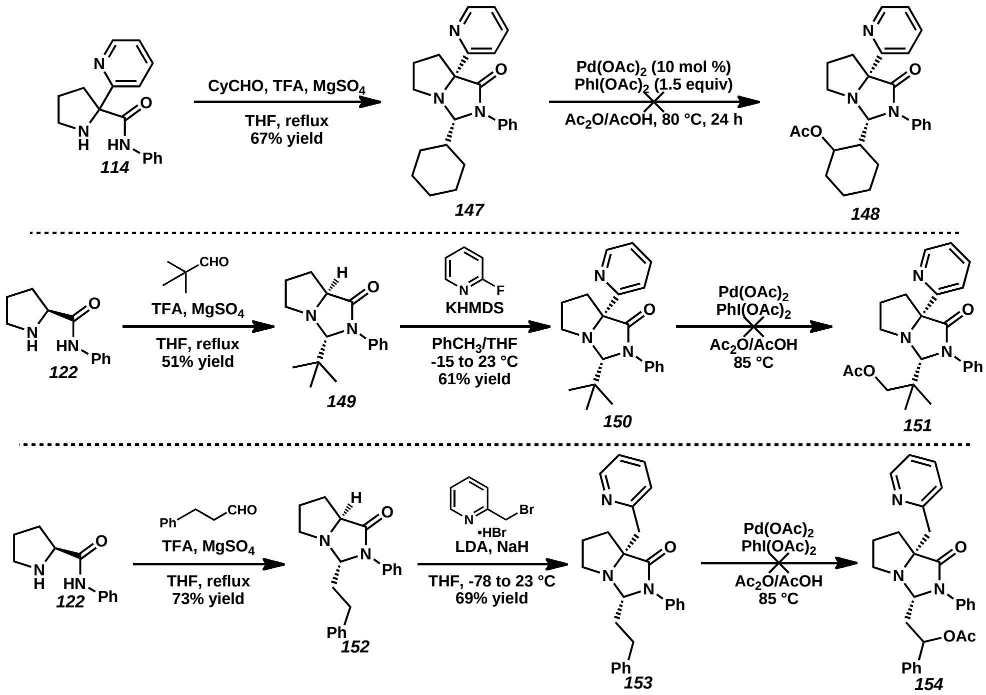


The acetoxylation of *sp*^{3} C–H bonds in both **115** and **130** occurs with high levels of diastereoselectivity. While we have not been able to achieve the functionalization of 2° C–H bonds, the high levels of selectivity observed thus far may translate into an asymmetric C–H functionalization reaction, if the appropriate conditions are realized. The ligand synthesis from a chiral starting material is straightforward and is conducted with what we believe to be high levels of stereoretention.

2.4 Other Attempts at *sp*^{3} C–H Functionalization

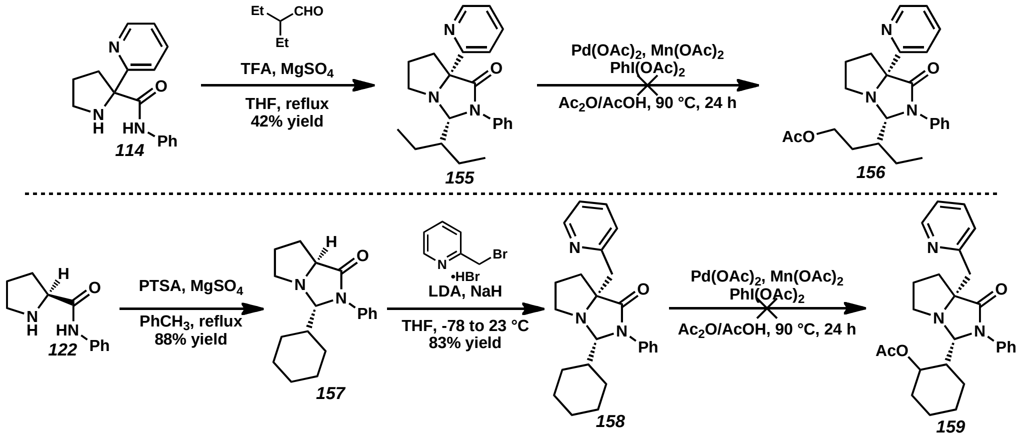
In addition to the functionalization of isobutyraldehyde, we have attempted the acetoxylation of several other aliphatic aldehydes. Condensation of ligand **114** onto cyclohexanecarboxaldehyde afforded *N,N*-aminal **147** as a single diastereomer (Scheme 2.4.1). Treatment of this substrate with acetoxylation conditions, however, did not afford any of the desired functionalized product. We attribute this lack of reactivity to the difficulty of activating 2° C–H bonds, and that the appropriate geometry for functionalization may not be possible in our system. Knowing that *t*-Bu groups in general are easy to activate, we imagined installing pivaldehyde as the aldehyde to be activated.[20] Condensation onto pivaldehyde afforded the aminal as a single diastereomer. Alkylation with 2-fluoropyridine afforded test substrate **150** in modest yield. Treatment of the more sterically hindered substrate with functionalization conditions, however, resulted in no acetoxylated product. We imagine that the steric interaction between a *t*-butyl methyl and the phenyl amide prevents functionalization. We also synthesized the hydrocinnamaldehyde derivative **153**. After condensation with amino amide **122**, alkylation provided a single diastereomer of **152**. Treatment with acetoxylation conditions, however, did not afford any of the benzylic acetate. The conformationally flexible nature of the hydrocinnamaldehyde likely contributes to the lack of functionalization.

Scheme 2.4.1. Other substrates for acetoxylation


CyCHO, TFA, MgSO$_4$
THF, reflux
67% yield
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, 80 °C, 24 h
114
147
148
TFA, MgSO$_4$
THF, reflux
51% yield
KHMDS
PhCH$_3$/THF
-15 to 23 °C
61% yield
Pd(OAc)$_2$
PhI(OAc)$_2$
Ac$_2$O/AcOH
85 °C
122
149
150
151
TFA, MgSO$_4$
THF, reflux
73% yield
•HBr
LDA, NaH
THF, -78 to 23 °C
69% yield
Pd(OAc)$_2$
PhI(OAc)$_2$
Ac$_2$O/AcOH
85 °C
122
152
153
154

Corey and coworkers have previously reported a diastereoselective *sp*^{3} C–H acetoxylation reaction of 2° C–H bonds.[21] In order to achieve this reactivity, as 2° C–H bonds are very unreactive to these electrophillic activation conditions, they added Mn(OAc)$_2$ as an activator for the C–H functionalization reaction. Presumably manganese acts as a Lewis acid to activate the palladium for C–H activation. We imagined this might allow acetoxylation of our unreactive substrates. We generated pyridine **155** from amino amide **114** and ethylbutyraldehyde in good yield and as a single diastereomer (Scheme 2.4.2). Subjecting pyridine **155** to Corey's acetoxylation conditions, however, afforded none of the desired product, and only starting material was recovered. We also generated aminal **158** from a condensation with amino amide **122** and cyclohexanecarboxaldehyde, followed by an alkylation with 2-bromomethyl pyridine as a single diastereomer. Treatment with the acetoxylation conditions, however, afforded none of the acetoxylated product.

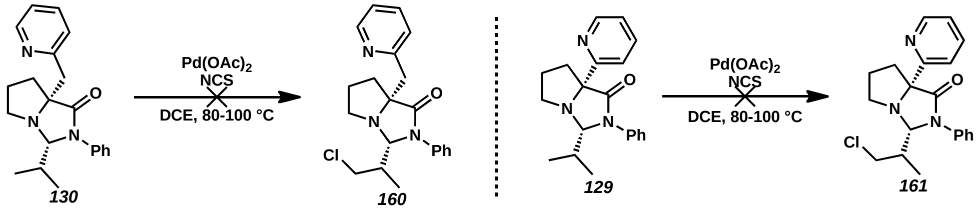
Scheme 2.4.2. Acetoxylation of 2 ° C–H bonds



Et
CHO
Et
TFA, MgSO$_4$
THF, reflux
42% yield
Pd(OAc)$_2$, Mn(OAc)$_2$
PhI(OAc)$_2$
Ac$_2$O/AcOH, 90 °C, 24 h
N
O
N
H
HN
Ph
114
155
AcO
156
PTSA, MgSO$_4$
PhCH$_3$, reflux
88% yield
Br
•HBr
LDA, NaH
THF, -78 to 23 °C
83% yield
Pd(OAc)$_2$, Mn(OAc)$_2$
PhI(OAc)$_2$
Ac$_2$O/AcOH, 90 °C, 24 h
H
122
157
158
159

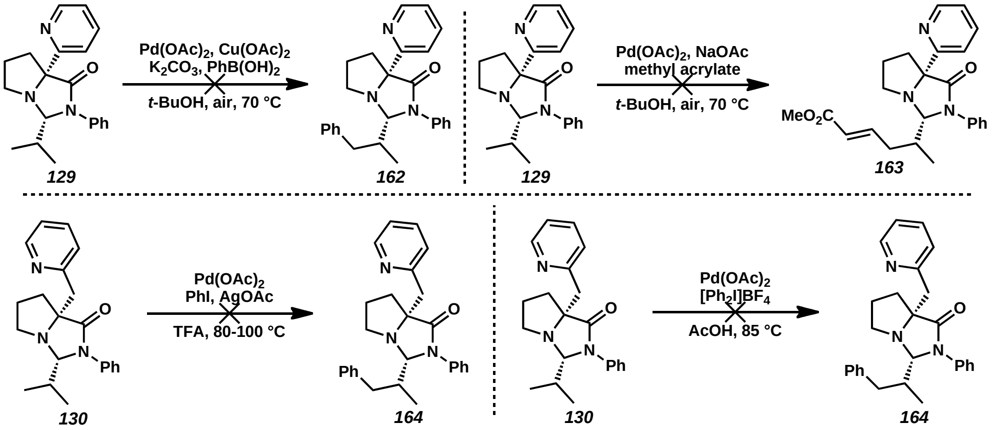
Besides acetoxylation we tried a number of different carbon-heteroatom and carbon-carbon bond formations utilizing substrates **129** and **130**. There have been numerous examples of C–Cl bond formation using electrophillic chlorine sources, such as NCS.[22] Subjecting pyridine **129** or pyridine **130** to NCS under palladium catalysis, however, afforded none of the carbon-chlorine bond formed products and only led to decomposition (Scheme 2.4.3). We believe that NCS may not be a strong enough oxidant to reach a higher valent Pd^{III} or Pd^{IV} species, and therefore only decomposes the substrate through other oxidative processes.

Scheme 2.4.3. ***sp*^{3} C–H chlorination**


Pd(OAc)$_2$
NCS
DCE, 80-100 °C
130
160
Pd(OAc)$_2$
NCS
DCE, 80-100 °C
129
161

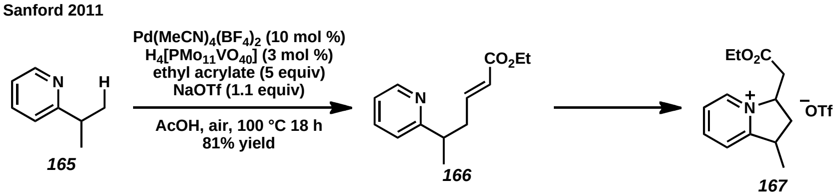
We also tried several carbon-carbon bond forming functionalization reactions under palladium catalysis. Yu and coworkers[23] demonstrated that Suzuki-type coupling can occur with catalytic palladium and PhB(OH)$_2$ with Cu(OAc)$_2$ and air acting to reoxidize Pd^0 to Pd^{II} (Scheme 2.4.4). When these conditions were employed with pyridines **129** and **130**, no arylated product was observed from the reaction. Additionally, we tried to perform a Heck-type coupling under palladium catalysis, but again no olefination product was isolated. Daugulis and coworkers have developed arylation conditions utilizing PhI under palladium catalysis.[24] Mechanistically, they envisioned an oxidation from Pd^{II} to Pd^{IV} via PhI, followed by reductive elimination to give the new carbon-carbon bond. Subjecting pyridine **130** to these conditions, however, generated none of the desired arylated product. Likewise, utilizing Sanford's diaryliodonium chemistry,[25] arylated pyridine **164** was not isolated from the reaction.

Scheme 2.4.4. Other *sp*^{3} C–H functionalizations


Pd(OAc)$_2$, Cu(OAc)$_2$
K$_2$CO$_3$, PhB(OH)$_2$
t-BuOH, air, 70 °C
129
162
Pd(OAc)$_2$, NaOAc
methyl acrylate
t-BuOH, air, 70 °C
129
163
Pd(OAc)$_2$
PhI, AgOAc
TFA, 80-100 °C
130
164
Pd(OAc)$_2$
[Ph$_2$I]BF$_4$
AcOH, 85 °C
130
164

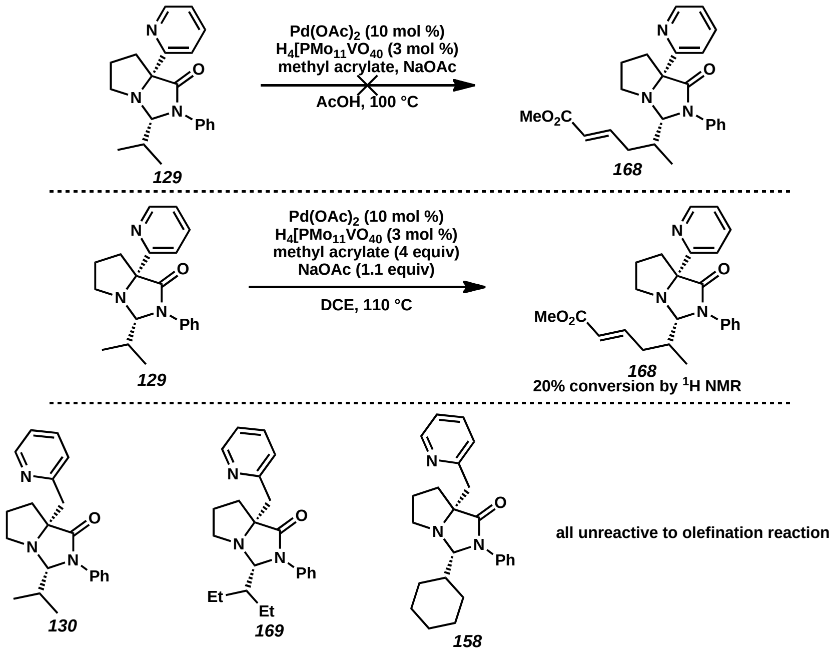
Sanford and coworkers have recently developed a new olefination reaction using a polyoxometalate co-catalyst (Scheme 2.4.5).[26] Subjecting 2-ethylpyridine to $Pd(MeCN)_4(BF_4)_2$ and $H_4[PMo_{11}VO_{40}]$ in the presence of ethyl acrylate and air in AcOH affords the olefinated intermediate (**165**). Pyridine can then act as a nucelophile and add into the Michael acceptor to form pyridinidum salt **166**. While the role of the polyoxometalate is not entirely clear, it is believed that it is involved in the reoxidation of Pd^0 to Pd^{II} to regenerate the active catalyst. It may also be involved in the C–H activation step, activating the palladium salt for cyclometallation.

Scheme 2.4.5. Olefination of *sp*^{3} C–H bonds



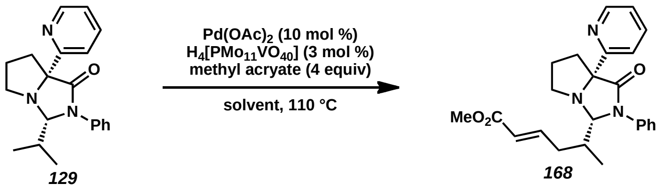
We imagined we may be able to utilize this chemistry for our *sp*^{3} C–H functionalization reactions. Subjecting pyridine **129** to similar conditions in AcOH at 100 °C afforded none of the olefinated product (**168**) (Scheme 2.4.6). Treatment with the same conditions in DCE at 110 °C, however, afforded almost 20% conversion to olefinated product **168** as confirmed by LCMS. Interestingly, when we subjected pyridines **130**, **169**, and **158** to the same conditions, no reaction was observed. While pryidines **158** and **169** have not been reactive to any functionalization conditions, pyridine **130** normally shows enhanced reactivity relative to pyridine **129**. Clearly each oxidation system is influenced by subtle structural effects.

Scheme 2.4.6. Initial olefination of isobutyraldehyde


Pd(OAc)$_2$ (10 mol %)
H$_4$[PMo$_{11}$VO$_{40}$ (3 mol %)
methyl acrylate, NaOAc
AcOH, 100 °C
129
168
Pd(OAc)$_2$ (10 mol %)
H$_4$[PMo$_{11}$VO$_{40}$ (3 mol %)
methyl acrylate (4 equiv)
NaOAc (1.1 equiv)
DCE, 110 °C
129
168
20% conversion by ^{1}H NMR
130
169
158
all unreactive to olefination reaction

With the initial reactivity realized, we sought to begin optimization of the reaction (Table 2.4.1). Increasing the equiv of NaOAc decreased the percent conversion of the transformation. Running the same reaction in *t*-AmOH afforded none of the olefinated product, and only starting material was recovered. In CH_3CN nearly identical conversion was observed compared to that in DCE. Changing the base to Na_2CO_3 and adding NaOPiv only resulted in a trace amount of product formation. Changing the base to K_2CO_3 with no NaOPiv additive provided none of the desired product. When the reaction was run in CF_3CH_2OH, 23% conversion to olefinated product was observed. When the reaction was run in DMF, however, no olefinated product **168** was isolated. In Sanford's work, it was noted that Pd(OAc)$_2$ provided higher conversion to product when acac was used as a ligand. These conditions, however, were unsuccessful at providing any of the functionalized product with our substrate. Furthermore, we hypthesized adding just 1 equiv of AcOH might promote the reaction further, but again this was unsuccessful at improving the conversion.

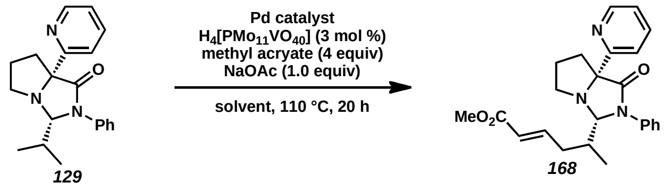
Table 2.4.1. Optimization of solvent and base



entry	solvent	base	additive	% conversion
1	DCE	NaOAc (2 equiv)	none	18
2	t-AmOH	NaOAc (2 equiv)	none	0
3	CH_3CN	NaOAc (2 equiv)	none	17
4	DCE	Na_2CO_3 (1 equiv)	NaOPiv (0.2 equiv)	trace
5	DCE	K_2CO_3 (1 equiv)	none	0
6		NaOAc (1.1 equiv)	none	23
7	DMF	NaOAc (1.1 equiv)	none	0
8	DCE	NaOAc (1.0 equiv)	acac (10 mol %)	0
9	CF_3CH_2OH	NaOAc (1.0 equiv)	AcOH (1.0 equiv)	trace

We next examined our palladium catalyst, eager to see if an alternative catalyst would enhance the conversion. Utilizing the very electrophillic catalyst that Sanford and coworkers used, we saw no improvement in conversion to **168** in either CF_3CH_2OH or DCE (Table 2.4.2). With $Pd(OAc)_2$ nearly 30% conversion was observed to product **168** using 1 equiv of NaOAc. Employing $PdCl_2$ afforded none of the product, and $Pd(TFA)_2$ only converted 14% of the starting material to the olefinated product. Rather than adding acac to the reaction, we used the F_6 version of $Pd(acac)_2$ and observed only 11% conversion to the product in CF_3CH_2OH. It may follow that the H_6 version being more basic may enhance the reaction relative to the F_6 variant.

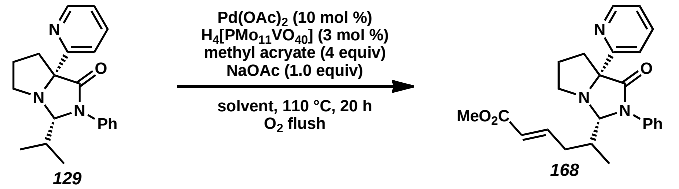
Table 2.4.2. Optimization of palladium catalyst


Pd catalyst
H4[PMo11VO40] (3 mol %)
methyl acryate (4 equiv)
NaOAc (1.0 equiv)
solvent, 110 °C, 20 h
129
168

entry	catalyst	solvent	% conversion
1	$Pd(CH_3CN)_4(BF_4)_2$	CF_3CH_2OH	20
2	$Pd(CH_3CN)_4(BF_4)_2$	DCE	18
3	$Pd(OAc)_2$	DCE	28
4	$PdCl_2$	DCE	0
5	$Pd(TFA)_2$	DCE	14
6	$Pd(acac\text{-}F_6)_2$	CF_3CH_2OH	11

Lastly we sought to examine the reoxidation step of the transformation, to ascertain whether or not this was hindering the conversion. Presumably, the polyoxometalate is partially responsible for the reoxidation of Pd^0 to Pd^{II} with the assistance of oxygen. We thought that our reaction conditions (run in a sealed vial under ambient air) may not be oxygen rich enough to regenerate the active catalyst. We found that if we flush the vial with pure oxygen before sealing, we see an increase in the conversion to product **168** (Scheme 2.4.7). In CF_3CH_2OH we see greater than 30% conversion to product, although in DCE we see less than 20% conversion to product **168**.

Scheme 2.4.7. Addition of O_2 for conversion


Pd(OAc)2 (10 mol %)
H4[PMo11VO40] (3 mol %)
methyl acryate (4 equiv)
NaOAc (1.0 equiv)
solvent, 110 °C, 20 h
O2 flush
129
168

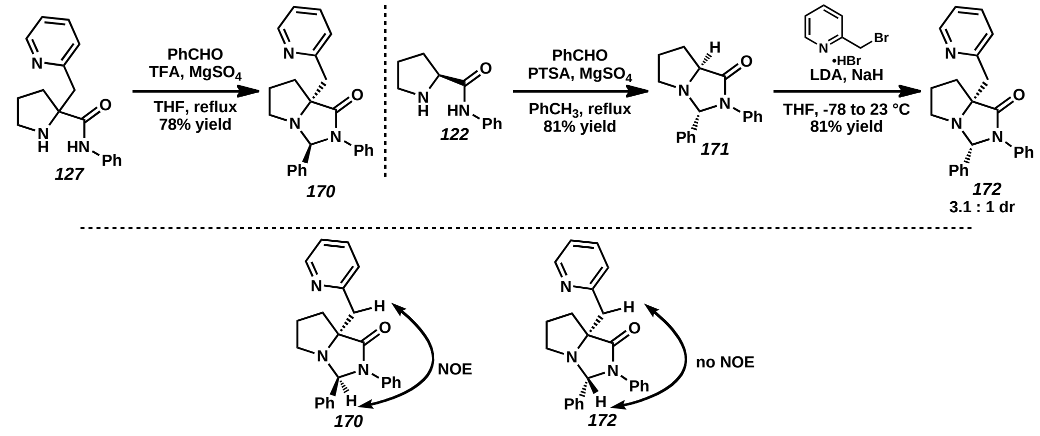
CF_3CH_2OH	33% conversion
DCE	18% conversion

The olefination reaction is the only functionalization other than acetoxylation that has been successful with our model substrates. The reaction has not been fully optimized, with 33% conversion being the best observed. Part of the low conversion may be due to exceptional binding of the substrate to the palladium catalyst, preventing turnover, as longer reaction times do not improve the conversion. It is apparent that CF_3CH_2OH gives the best conversion of all the solvents employed in this transformation. Further optimization of this reaction is required before synchronization of functionalization and acetalization can be attempted, although the mild reaction conditions may lend satisfactory results.

2.5 Acetoxylation of *sp*^{2} C–H Bonds

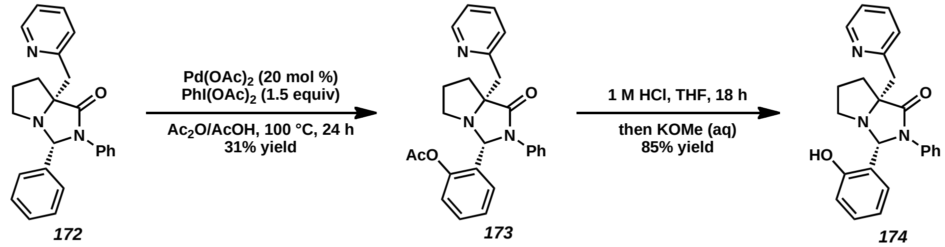
Due to our success in the stoichiometric functionalization of the isobutyraldehyde substrates we decided to examine the functionalization of aromatic aldehydes. Condensing racemic amino amide **127** onto benzaldehyde afforded the desired *N,N*-aminal (**170**, Scheme 2.5.1). Alternatively, we synthesized the test substrate via our asymmetric ligand synthesis, which afforded a mixture of diastereomers, the minor of which corresponded to condensation product **170**. An NOE analysis of the diastereomers revealed the major product of the alkylation to be the syn diastereomer. Conversely, the condensation reaction provided only the anti diastereomer, showing an NOE between the acetal proton and a benzylic proton.

Scheme 2.5.1. Synthesis of a benzaldehyde ligand adduct



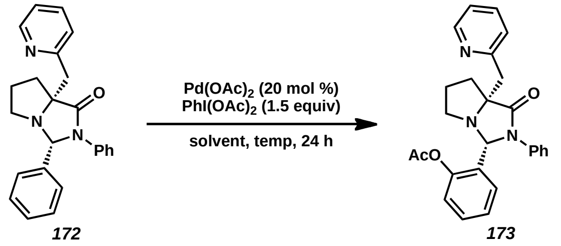
With the desired substrate in hand, we subjected **172** to acetoxylation conditions and were delighted to isolate 31% of the apparent functionalized product (Scheme 2.5.2). Treatment with aqueous acid followed by Claisen's alkali afforded the phenol product in good yield, confirming the identity of an aryl acetate. A brief solvent screen was conducted with $PhCH_3$, CH_2Cl_2, DCE and CH_3CN, all affording the desired acetoxylated product in less than 10% yield. In alcohol solvent, such as MeOH, IPA or *t*-AmOH, no product was observed from the reaction. These results speak to the necessity of the AcOH/Ac_2O solvent combination.

Scheme 2.5.2. Initial acetoxylation of benzaldehyde


Pd(OAc)2 (20 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 100 °C, 24 h
31% yield
1 M HCl, THF, 18 h
then KOMe (aq)
85% yield
N
O
N
N
Ph
AcO
HO
172
173
174

A combined solvent and temperature screen began our optimization of the acetoxylation reaction. At 100 °C, either AcOH or a combined AcOH/CH_2Cl_2 solvent mixture provided less than 10% of the desired product (Table 2.5.1). Ac_2O alone provided no acetoxylated product. At 23 °C there was no reaction in the mixed solvent system. Warming to 80 °C provided 50% of the desired product in a mixed solvent system, although heating to 90 °C caused a decrease in yield, presumably due to increased decomposition. Treatment with functionalization conditions in AcOH provided 25% yield but again lost effectiveness at higher temperatures.

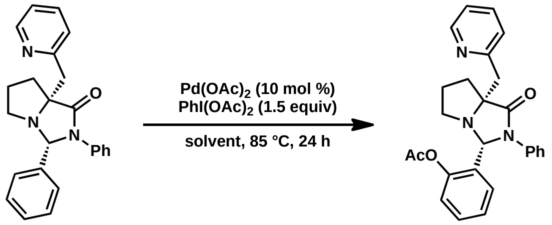
Table 2.5.1. Solvent screen


Pd(OAc)2 (20 mol %)
PhI(OAc)2 (1.5 equiv)
solvent, temp, 24 h
N
O
N
N
Ph
AcO
172
173

solvent	temp (°C)	yield	solvent	temp (°C)	yield
AcOH	100	<10%	AcOH:Ac_2O	80	50
Ac_2O	100	0%	AcOH	80	25
AcOH:CH_2Cl_2	100	<10%	AcOH:Ac_2O	90	36
AcOH:Ac_2O	23	0%	AcOH	90	18

Optimization continued with further probing the solvent composition and concentration. AcOH/Ac_2O as a solvent provided much higher levels of conversion and yield as compared to AcOH alone (Table 2.5.2). Moving from 0.05 M to 0.1 M provided a dramatic increase in yield, but increasing the concentration even more showed a decrease in yield. Presumably higher concentrations lead to higher levels of decomposition. While conversion noticeably improved, yield did not.

Table 2.5.2. Solvent concentration screen

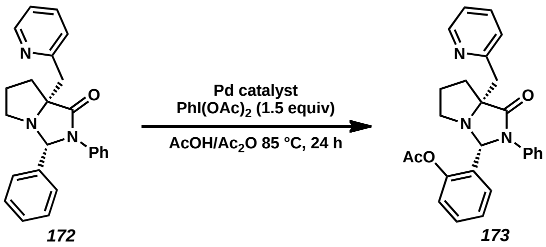


172 *173*

solvent	concentration (M)	*172 : 173*	yield (%, crude)
Ac_2O/AcOH	0.05	1.0 : 2.0	40
Ac_2O/AcOH	0.1	1.0 : 3.0	62
Ac_2O/AcOH	0.2	1.0 : 8.3	50
AcOH	0.05	2.3 : 1.0	12
AcOH	0.1	1.3 : 1.0	18
AcOH	0.2	1 : 1	27

An examination of catalyst type and loading next directed our efforts towards optimization. Utilizing $PdCl_2$ afforded a lower conversion than $Pd(OAc)_2$ at the same catalyst loading (Scheme 2.5.3). The use of $Pd(TFA)_2$ provided even less product, and the formation of an oxidized side product was becoming more obvious (*vide infra*). As $Pd(OAc)_2$ appeared to be the most effective catalyst, different loadings were examined. From our results, it is evident that the reaction is sensitive to catalyst loading, with 10 mol % being the most effective concentration.

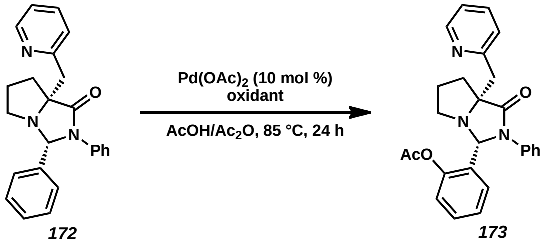
Scheme 2.5.3. Effect of palladium catalyst



Pd catalyst (mol %)	*172 : 173*
$PdCl_2$ (10)	1.0 : 1.5
Pd(TFA)$_2$ (10)	1.2 : 1.0
Pd(OAc)$_2$ (5)	1.7 : 1
Pd(OAc)$_2$ (10)	1.0 : 8.0
Pd(OAc)$_2$ (15)	1.0 : 2.0

We sought to examine the effect of the oxidant on yield and the formation of the oxidized side product. Increasing the equiv of PhI(OAc)$_2$ to 2 afforded higher conversion to the acetoxylated product (Scheme 2.5.4). Increasing to 3 equiv, however, began to lead to decomposition pathways and an increased amount of formation of an oxidized side product. Changing the oxidant to a perester[2a] provided only a small amount of product **173**. Using a stronger oxidant like Oxone only resulted in decomposition of the starting material and no conversion to functionalized product.

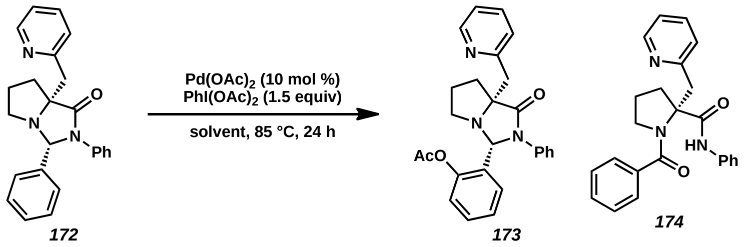
Scheme 2.5.4. Effect of oxidant on acetoxylation



entry	oxidant	yield (%)
1	PhI(OAc)$_2$ (1.5 equiv)	62
2	PhI(OAc)$_2$ (2 equiv)	65
3	PhI(OAc)$_2$ (3 equiv)	41
4		<10
5	oxone	decomp

We eventually identified the oxidized side product as amide **174** (Table 2.5.3). We screened a range of conditions to ascertain the mechanism of amide formation. Under our typical acetoxylation conditions, a 4.6 : 1 ratio of product **173** and amide **174** was observed. Increasing the concentration to 0.4 M increased the formation of amide **174**, where a <2 : 1 ratio of **173** to **174** was observed. Functionalization in AcOH at 0.4 M afforded only the acetoxylated product, and none of the oxidized amide was observed. Treatment with acetoxylation conditions in only Ac$_2$O now afforded amide **174** in a 1.1 : 1 ratio to functionalized product, albeit with low conversion. Under atypical functionalization conditions with the addition of PivOH as the acetate source and K_2CO_3 as the corresponding base in CH_2Cl_2, only the oxidized amide product was afforded. Furthermore, in highly acidic TFA, only the formation of the amide was observed; no acetoxylated product was isolated.

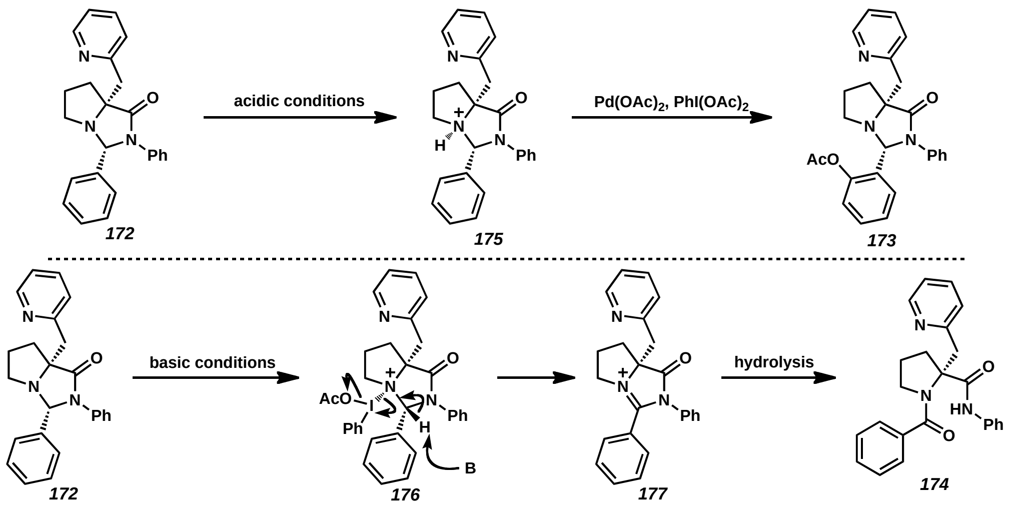
Table 2.5.3. Formation of an oxidized byproduct



entry	conditions	*173 : 174*
1	Ac_2O/AcOH, 0.1 M	4.6 : 1
2	Ac_2O/AcOH, 0.4 M	1.7 : 1
3	AcOH, 0.4 M	1 : 0
4	K_2CO_3, PivOH, CH_2Cl_2, 0.1 M	0 : 1
5	Ac_2O, 0.1 M	1 : 1.1
6	TFA, 0.1 M	0 : 1

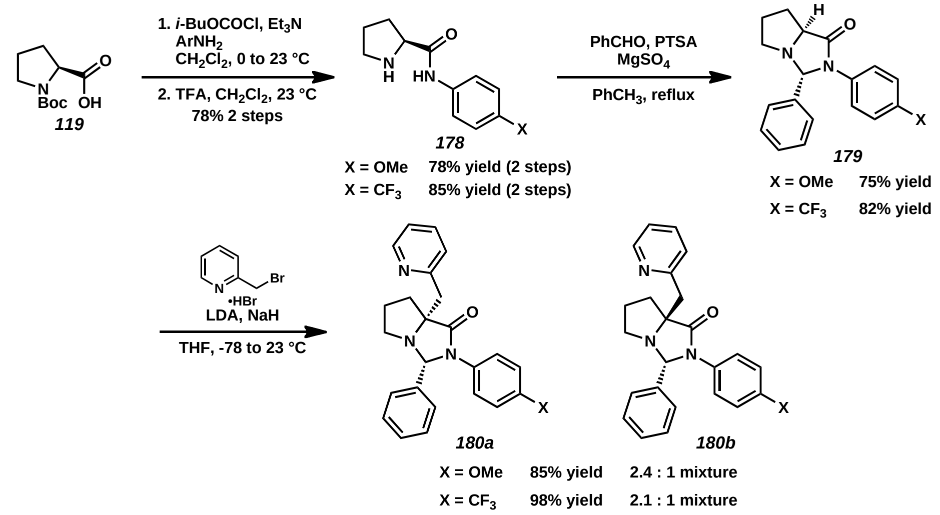
Based on these results, we believed the rate of formation of the amide byproduct was directly dependent on the acidity of the functionalization conditions. Under acidic conditions, the pyrrolidine nitrogen is protonated and the pyridyl directs the acetoxylation to the phenyl ring of the aminal (Scheme 2.5.5). Conversely, if the conditions are neutral, or even basic, the pyrrolidine nitrogen is not protonated and can attack $PhI(OAc)_2$ to generate ammonium intermediate **176**. Deprotonation to eliminate PhI and acetate anion occurs to form iminium **177**. Hydrolysis of the iminium reveals the oxidized amide. Under our conditions in Table 2.5.3, the pattern appears to follow our proposed mechanism. In entry 6, however, treatment with a much more acidic TFA should result in the formation of acetoxylated product if the pyrrolidine nitrogen is protonated. We attribute this contradiction to the formation of a much stronger oxidant $PhI(TFA)_2$, which can perform the oxidation to the amide in a much more facile manner.

Scheme 2.5.5. Possible mechanism of aminal oxidation


acidic conditions
Pd(OAc)2, PhI(OAc)2
172
175
173
basic conditions
hydrolysis
172
176
177
174

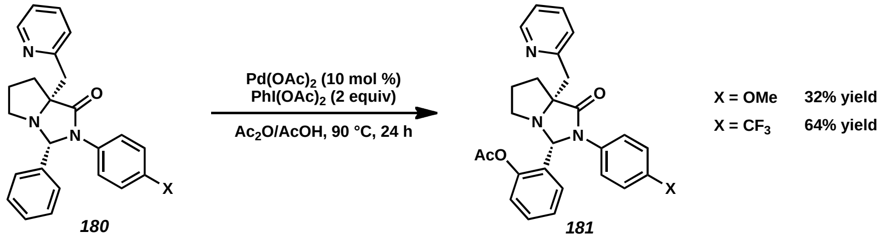
Interested in learning more about this oxidative transformation, we sought to electronically modify the amide component of our ligand to see its effect on the rate of acetoxylation and aminal oxidation. We imagined using both an electron rich aromatic amide and an electron poor aromatic amide. Starting from L-Boc proline we generated the amide bond and deprotected the pyrrolidine nitrogen for both **178-OMe** and **178-CF$_3$** in good yield (Scheme 2.5.6). Condensation onto benzaldehyde afforded the corresponding *N,N*-aminals in good yield. Alkylation with 2-bromopyridine afforded **180-OMe** and **180b-OMe** in a 2.4 : 1 mixture of diastereomers. Likewise alkylation of **179-CF$_3$** afforded a 2.1 : 1 mixture of diasteromers in excellent yield.

Scheme 2.5.6. Synthesis of electronically different amides


119
1. i-BuOCOCl, Et3N ArNH2 CH2Cl2, 0 to 23 °C
2. TFA, CH2Cl2, 23 °C 78% 2 steps
178
X = OMe 78% yield (2 steps)
X = CF3 85% yield (2 steps)
PhCHO, PTSA MgSO4
PhCH3, reflux
179
X = OMe 75% yield
X = CF3 82% yield
•HBr LDA, NaH
THF, -78 to 23 °C
180a
180b
X = OMe 85% yield 2.4 : 1 mixture
X = CF3 98% yield 2.1 : 1 mixture

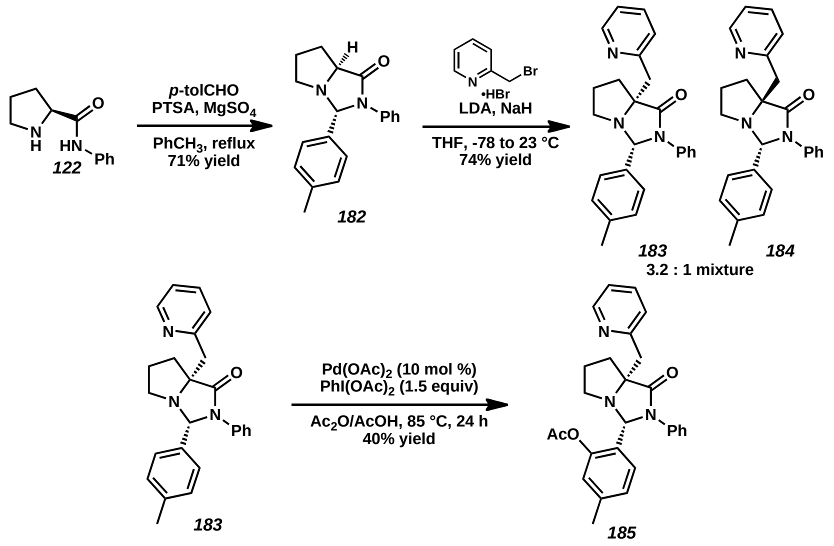
We subjected both differentially substituted amides to our standard acetoxylation conditions. The monoacetoxylation of **180-OMe** occurred in 32% yield with a large degree of aminal oxidation and decomposition (Scheme 2.5.7). The very electron rich nature of the amide makes the aminal center much more prone to oxidation. Monoacetoxylation of **180-CF$_3$** occurred much more smoothly in 64% yield. The occurrence of aminal oxidation was much less prevalent, likely due to the now more electron deficient nature of the aminal center.

Scheme 2.5.7. Acetoxylation of electronically modified amides


180
Pd(OAc)2 (10 mol %) PhI(OAc)2 (2 equiv)
Ac2O/AcOH, 90 °C, 24 h
181
X = OMe 32% yield
X = CF3 64% yield

Expanding the substrate scope, we condensed amino amide **122** onto *p*-tolualdehyde to afford aminal **182** in good yield (Scheme 2.5.8). Alkylation with 2-bromomethyl pyridine afforded a 3.2 : 1 mixture of syn to anti diastereomers. Treatment of the syn diastereomer with acetoxylation conditions afforded acetate **185** in modest yield.

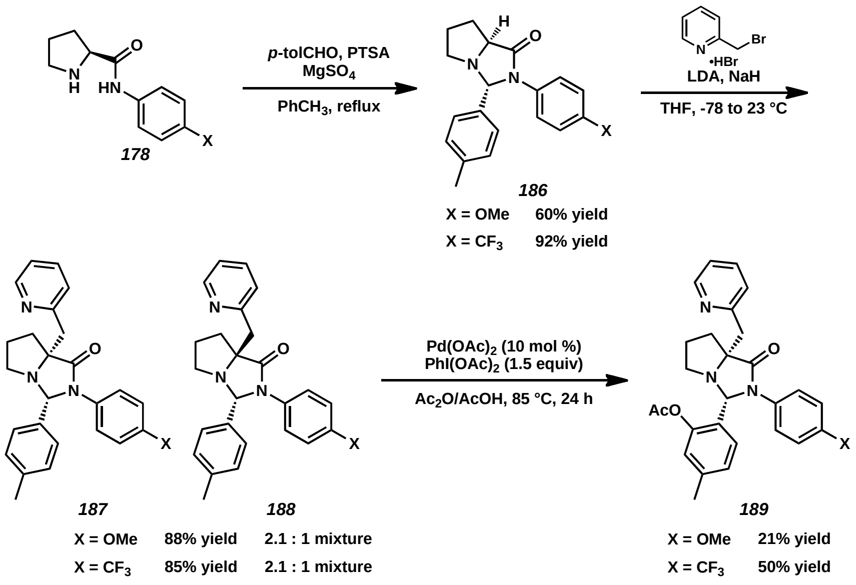
Scheme 2.5.8. Acetoxylation of *p*-tolualdehyde



122
p-tolCHO
PTSA, MgSO4
PhCH3, reflux
71% yield
182
•HBr
LDA, NaH
THF, -78 to 23 °C
74% yield
183
184
3.2 : 1 mixture
183
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
40% yield
185

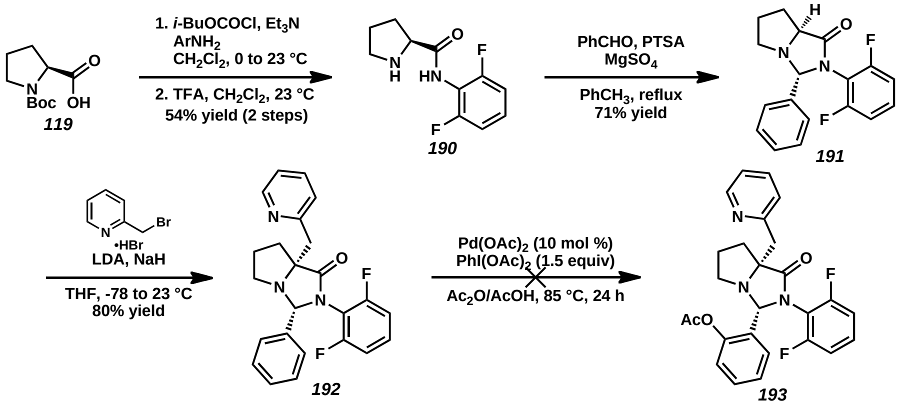
We imagined by utilizing the *p*-methoxyphenyl amide and *p*-tolualdehyde as the substrate to functionalize that the aminal center would be very sensitive to oxidation, even under our typical conditions. Condensing amino amides **178-OMe** and **178-CF$_3$** onto *p*-tolualdehyde afforded aminals **186-OMe** and **186-CF$_3$** in good yield (Scheme 2.5.9). Alkylation with 2-bromomethyl pryidine afforded pyridines **187** and **188** in a 2.1 : 1 mixture of diastereomers for both *p*-OMe and *p*-CF$_3$. Acetoxylation of the syn diastereomer (**187-OMe**) with our typical functionalization conditions afforded the desired product in 21% yield, and the amide byproduct in 19% yield. Conversely, treatment of **187-CF$_3$** with acetoxylation conditions afforded the desired product in 50% yield, with only 14% of the amide product isolated.

Scheme 2.5.9. Further extension of substrate scope


178
p-tolCHO, PTSA
MgSO4
PhCH3, reflux
186
X = OMe 60% yield
X = CF3 92% yield
•HBr
LDA, NaH
THF, -78 to 23 °C
187
188
X = OMe 88% yield 2.1 : 1 mixture
X = CF3 85% yield 2.1 : 1 mixture
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
AcO
189
X = OMe 21% yield
X = CF3 50% yield

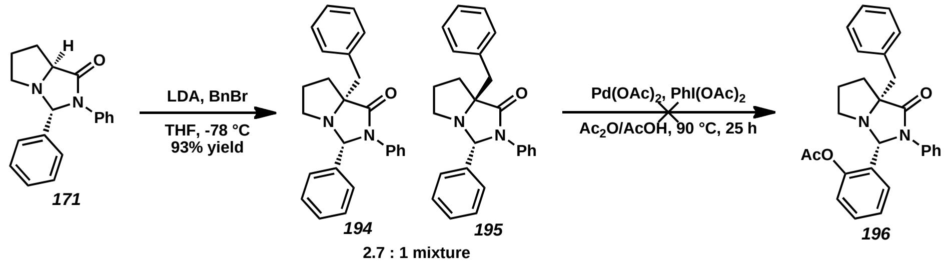
Based on the degree of aminal oxidation we imagined further decreasing the electron rich nature of the aminal center by using a more electron deficient amide. Coupling with 2,6-difluoroaniline and deprotection afforded amino amide **190** (Scheme 2.5.10). Condensation with benzaldehyde afforded aminal **191** in good yield. Alkylation with 2-bromomethyl pyridine afforded **192** as a single diastereomer. This enhancement of selectivity could be attributed to the electron deficient nature of the amide. Interestingly, treating pyridine **192** with acetoxylation conditions afforded none of the desired functionalized product. This may be due to activation of one of the C-F bonds or coordination to the palladium.

Scheme 2.5.10. Synthesis of the 2,6-difluorophenyl amide


1. i-BuOCOCl, Et3N ArNH2 CH2Cl2, 0 to 23 °C
2. TFA, CH2Cl2, 23 °C
54% yield (2 steps)
119
190
PhCHO, PTSA MgSO4
PhCH3, reflux
71% yield
191
•HBr
LDA, NaH
THF, -78 to 23 °C
80% yield
192
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
193

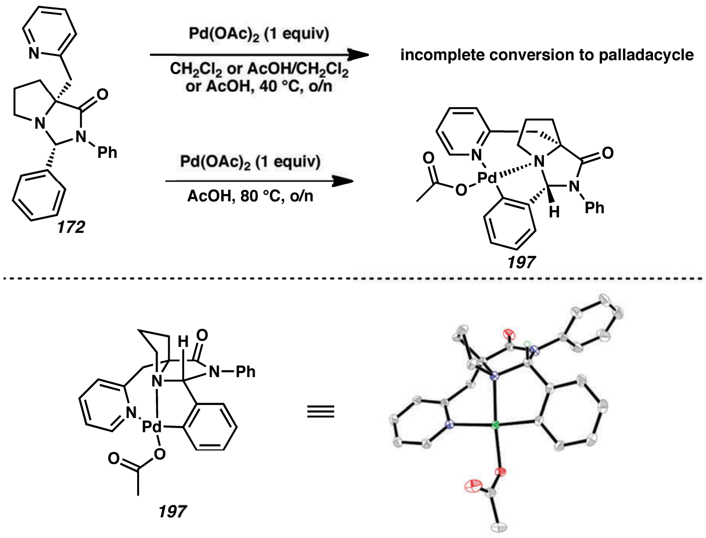
Seeking to establish the validity of the pyridyl ligating group directing the functionalization reaction, we wanted to remove the pyridyl group and observe if any functionalization could occur in its absence. From substrate **171** we were able to install a benzyl group via alkylation to generate a mixture of diastereomers (Scheme 2.5.11). We believed the benzyl group would have the same steric component as the pyridyl, without the nitrogen ligating component. We subjected the mixture of diastereomers to standard acetoxylation conditions. No acetoxylated product was observed from the reaction, and only aminal oxidized byproducts were observed other than starting material. This result establishes the necessity of the pyridyl ligating group for acetoxylation.

Scheme 2.5.11. Installation of a benzyl group


171
LDA, BnBr
THF, -78 °C
93% yield
194
195
2.7 : 1 mixture
Pd(OAc)2, PhI(OAc)2
Ac2O/AcOH, 90 °C, 25 h
196

Lastly we were interested in examining the potential for isolation of a palladacycle. Treating substrate **172** with stoichiometric palladium in CH_2Cl_2, CH_2Cl_2/AcOH or just AcOH at 40 °C overnight afforded incomplete conversion to a complex that by ^{1}H NMR appeared to be the palladacycle (Scheme 2.5.12). Treating substrate **172** with palladium in AcOH at 80 °C for 2 h afforded the same structure with complete conversion. We were able to crystallize the complex and obtain an X-ray crystal structure. From the structure it is obvious that the pyridyl and pyrrolidine nitrogen are coordinated to palladium. A palladium-carbon bond is also observed at the ortho position of the desired aryl ring. The syn orientation between the pyridyl group and aminal group allows for the desired C–H activation.

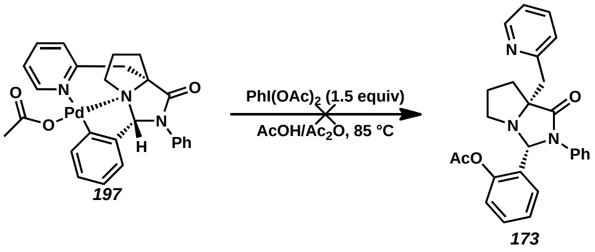
Scheme 2.5.12. Generation of a palladacycle



172
Pd(OAc)₂ (1 equiv)
CH₂Cl₂ or AcOH/CH₂Cl₂ or AcOH, 40 °C, o/n
incomplete conversion to palladacycle
Pd(OAc)₂ (1 equiv)
AcOH, 80 °C, o/n
197
197

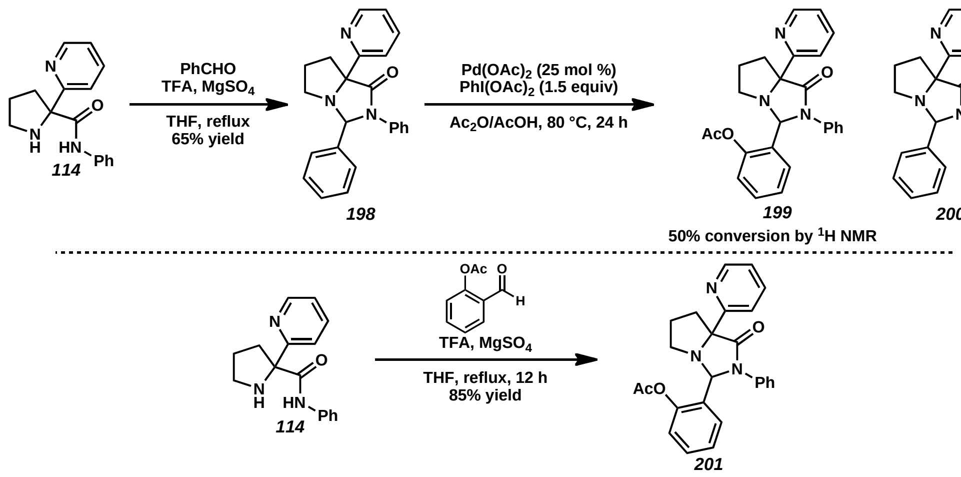
While we had isolated and characterized palladacycle **197**, we were not sure of its kinetic competency in these acetoxylation reactions. Subjecting the palladacycle to stoichiometric oxidant in AcOH/Ac_2O at 85 °C, followed by treatment with dppe, afforded none of the desired acetoxylated product **273** (Scheme 2.5.13). If the oxidation was proceeding via a Pd^{III}-Pd^{III} dimer, the size of the ligand may prevent this metal-metal bond formation, thereby inhibiting product formation. To circumvent this, we imagined adding an additional 5 mol % palladium that may be able to then form the dimeric metal species upon oxidation. Indeed, upon workup with dppe, we observed a small amount of the functionalized product (**173**). This low conversion may indicate that the isolated palladacycle is not an active intermediate under our reaction conditions. Much more exploration into these complexes is necessary to understand more about the mechanism of functionalization.

Scheme 2.5.13. Examination of the kinetic competency of the palladacycle



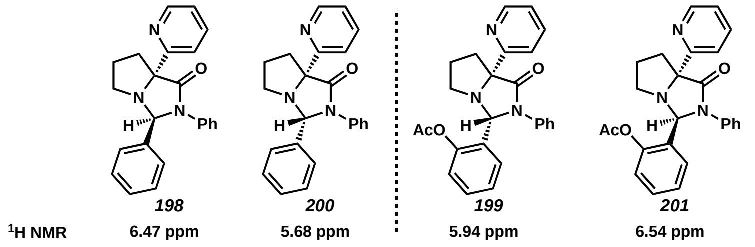
Based on the success of our acetoxylation of *sp*^{2} C–H bonds using substrate ligand adduct **172**, we imagined we may be able to impart similar reactivity with ligand **114**. Racemic **114** was condensed with benzaldehyde in THF to afford *N*,*N*-aminal **198** of unknown stereochemistry (Scheme 2.5.14). While we were easily able to determine the relative stereochemistry of substrate **172** with NOE data, this substrate did not allow for an analogous analysis. We therefore subjected **198** to the functionalization conditions, believing that based on all of our data, the anti diastereomer would not functionalize under our conditions. Treatment with catalytic palladium and stoichiometric oxidant in AcOH/Ac_2O afforded a new product resembling the desired monoacetoxylated product (**199**). The reaction also afforded a new compound that contained no acetate, but appeared similar in structure to the starting aminal (**198**). We compared product **199** to the condensation product (**201**) of acetoxylated benzaldehyde and ligand **114**, which did not afford the same product by ^{1}H NMR.

Scheme 2.5.14. Functionalization of benzaldehyde with a new ligand


PhCHO
TFA, MgSO4
THF, reflux
65% yield
Pd(OAc)2 (25 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 80 °C, 24 h
114
198
199
200
50% conversion by 1H NMR
TFA, MgSO4
THF, reflux, 12 h
85% yield
114
201

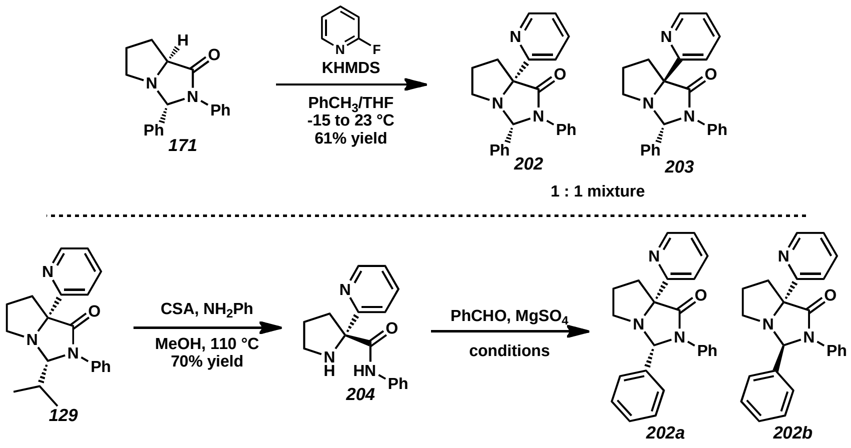
We conducted a ^{1}H NMR analysis of the aminal protons of each substrate in order to determine the stereochemistry of each. We found that the aminal shifts of both condensation products **198** and **201** were similar and downfield at 6.5 ppm (Scheme 2.5.15). In contrast, the shift of the aminal proton of acetate product **199** was much further upfield at 5.94 ppm. The unknown product of the functionalization reaction appeared to be the opposite diastereomer of **198** with a ^{1}H NMR shift of 5.64 ppm. Based on this large difference in shift, we believed that the condensation reactions were providing the anti diastereomer of the *N,N*-aminal. Under the functionalization conditions however, we believed that the anti diastereomer was isomerizing and then functionalization was occurring, affording **199**. The appearance of the syn diastereomer (**200**) confirmed the isomerization event under acetoxylation conditions.

Scheme 2.5.15. ^{1}H NMR analysis of aminal protons


198
200
199
201
1H NMR
6.47 ppm
5.68 ppm
5.94 ppm
6.54 ppm

Perplexed by the formation of the anti diastereomer via condensation, we imagined we could synthesize the desired substrate in a similar manner to the above ligand syntheses. Subjecting aminal **171** to alkylation conditions with 2-fluoropryidine, however, did not afford a single diastereomer, but rather a 1 : 1 mixture of syn (**202**) to anti (**203**) asymmetric pryidines (Scheme 2.5.16). We again turned to the condensation reaction to ascertain whether we could obtain the syn diastereomer selectively. In our original conditions and with PTSA in $PhCH_3$, we only observed the anti diastereomer. Based on the functionalization conditions providing isomerization, we imagined that the addition of AcOH might lead to the syn diastereomer preferentially. Indeed, when AcOH was used as the acid catalyst in the condensation of asymmetric **204** and benzaldehyde, we observed greater than a 4 : 1 mixture of syn to anti. Increasing the ratio of AcOH : $PhCH_3$ (1 : 5) led to a 6.3 : 1 mixture of syn to anti, and using a 1 : 1 ratio of $PhCH_3$ to AcOH afforded a 6 to 1 ratio. When run on scale, we observed a 4 : 1 ratio of syn to anti in 90% yield.

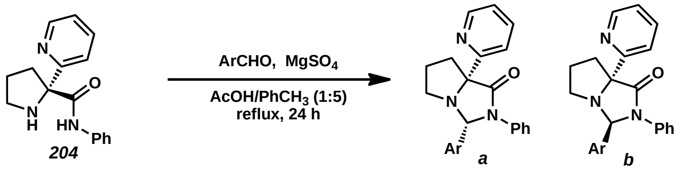
Scheme 2.5.16. Obtaining the syn diastereomer selectively

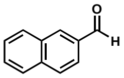


acid	solvent	temp (°C), time (h)	*a : b*
TFA (10 mol %)	THF	72, 18 h	0 : 1.0
PTSA (5 mol %)	$PhCH_3$	110, 24 h	0 : 1.0
AcOH (1 M)	$PhCH_3$	110 °C, 24 h	4.3 : 1.0
AcOH (0.5 M)	$PhCH_3$	110 °C, 24 h	6.3 : 1.0
AcOH (0.1 M)	$PhCH_3$	110 °C, 24 h	6.0 : 1.0

We therefore synthesized the corresponding syn diasteromers selectively using AcOH in the condensation reactions (Table 2.5.4). Utilizing electron neutral benzaldehyde, the syn diastereomer was obtained in a 4 : 1 ratio in good yield. More electron rich *p*-tolualdehyde afforded aminal **205** as a 6 : 1 ratio of syn to anti diastereomers. The *m*-tolualdehyde aminal was synthesized with slightly less selectivity in the ratio of syn to anti. Interestingly, the *o*-tolualdehyde derivative when condensed with the chiral ligand still afforded the anti diastereomer (**207b**) in a 1.5 : 1 ratio in good yield. We attribute this reversal in selectivity to the more sterically hindered nature of the aldehyde, inhibiting the syn condensation. Electron deficient *p*-Cl benzaldehyde was much less selective for the isomerization of the anti to syn diastereomer, providing only a 3.8 : 1 ratio for syn. Conversely, the 2-naphthyl derivative provided the highest level of syn to anti selectivity, with greater than 7 : 1 ratio.

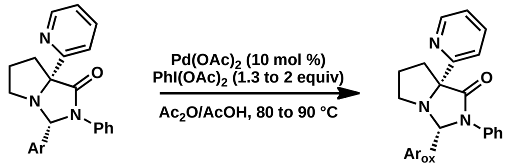
Table 2.5.4. Expanding aminal substrate scope

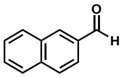


ArCHO	product	dr (*a* : *b*)	yield (%)	ArCHO	product	dr (*a* : *b*)	yield (%)
Ph	202	4.0 : 1	89	*p*-OMe	208	5.8 : 1	78
p-Me	205	6.0 : 1	86	*p*-Cl	209	3.8 : 1	67
m-Me	206	5.8 : 1	76	 O H	210	7.3 : 1	80
o-Me	207	1 : 1.5	87				

Subjecting the syn diastereomers to the functionalization conditions required lower temperatures and less equiv of oxidant for completion of the reaction as compared to ligand substrate adduct **172**. In most cases, the starting material was completely consumed (Table 2.5.5). When a 4 : 1 ratio of **202** was treated with the functionalization conditions, a 55% yield of monoacetoxylated product was isolated. An additional 6% of diacetoxylated product was also observed. Likewise, subjecting the *p*-tolualdehyde derivative to the functionalization conditions resulted in moderate yield of monoacetoxylated product and 16% yield of diacetoxylated product. The *m*-tolualdehyde derivative was completely selective for the less hindered ortho position in good yield. Furthermore, the *o*-tolualdehyde derivative was completely selective for sp^2 C–H functionalization in excellent yield. Subjecting electron rich *p*-anisaldehyde derivative **208** to milder acetoxylation conditions provided the functionalized product (**215**) in good yield, with less than 10% diacetoxylated product. Lastly, the 2-naphthyl derivative was completely selective for the less hindered position, and afforded acetoxylated arene **217** in 58% yield.

Table 2.5.5. Acetoxylation of syn diastereomers

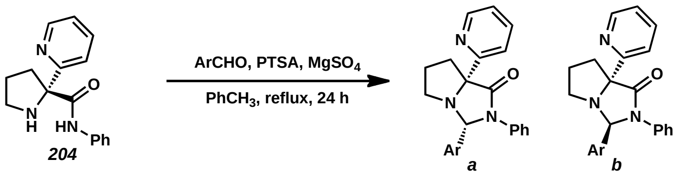


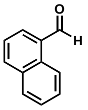
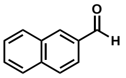
ArCHO	product	yield (%) Ar_{ox}	ArCHO	product	yield (%) Ar_{ox}
Ph	211	55^a	*p*-OMe	215	37^c
p-Me	212	47^b	*p*-Cl	216	39
m-Me	213	72		217	58
o-Me	214	85			

[a] 6% yield diacetoxylated product. [b] 16% diacetoxylated product.
[c] 9% diacetoxylated product

Interested in examining the difference in yield between utilizing the syn or anti diastereomer in acetoxylation reactions, we sought to synthesize a few anti diastereomers (Table 2.5.6). Condensation with benzaldehyde using PTSA and toluene afforded the anti diastereomer as the only product in good yield. Using the more electron rich *p*-tolualdehyde afforded a mixture of diastereomers in a 1 : 3 ratio. Condensation with *m*-tolualdehyde was less selective, affording a 1 : 5 mixture of **206** as syn to anti diastereromers. Electron rich *p*-anisaldehyde afforded a 4 : 1 mixture of anti to syn diastereomers in moderate yield. Finally, condensation with 1 and 2-naphthyl aldehydes provided only the anti diastereomers (**218** and **210**) in good yield.

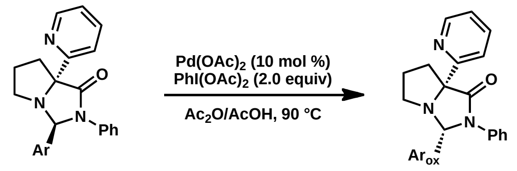
Table 2.5.6. Synthesis of the anti diastereomers

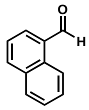
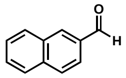


ArCHO	product	dr (*a* : *b*)	yield (%)	ArCHO	product	dr (*a* : *b*)	yield (%)
Ph	202	0 : 1.0	87		218	0 : 1.0	85
p-Me	205	1 : 3.0	83				
m-Me	206	1 : 5.0	82				
p-OMe	208	1 : 3.9	69		210	0 : 1.0	72

We subjected the diastereomeric mixtures to standard acetoxylation conditions utilizing two equiv of oxidant for 24 h. Functionalization of the electron neutral benzaldehyde derivative provided 42% yield of the monoacetoxylated product (**211**) and less than 5% of the diacetoxylated product (Table 2.5.7). Using the syn diastereomer provided a 13% higher yield than the corresponding anti diastereomer. The remaining starting material was isolated as a 2 : 1 mixture of syn and anti diastereomers. Utilizing derivative **205** provided nearly a 1 : 1 mixture of mono- to diacetoxylated products, displaying much higher reactivity. *m*-Tolualdehyde derivative **206** was selectively functionalized at the less hindered ortho position, with no recovered starting material. Employing the more electron rich *p*-anisaldehyde derivative **208** provided only a moderate amount of product, with the mass balance consisting of decomposition. This is most likely due to the very electron rich nature of the starting aminal. Conversely, 1-naphthyl derivative **218** was completely unreactive under the acetoxylation conditions and afforded no product. The 2-naphthyl derivative, however, was cleanly functionalized at the less sterically hindered position to give acetoxylated product **217** in good yield.

Table 2.5.7. Acetoxylation of anti diastereomers



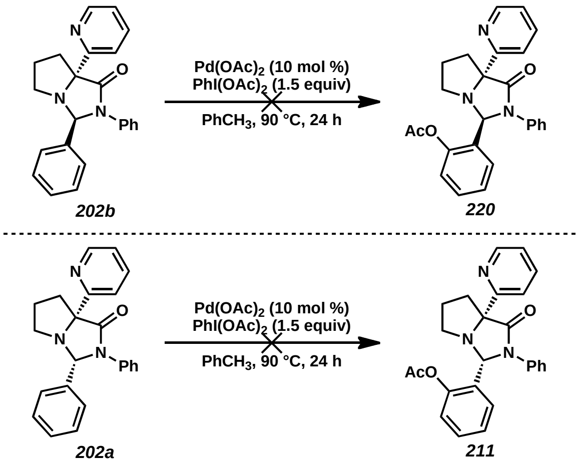
ArCHO	product	yield (%) Ar$_{ox}$	ArCHO	product	yield (%) Ar$_{ox}$
Ph	211	42		219	no rxn
p-Me	212	31 (28)[a]			
m-Me	213	51			
p-OMe	215	23[b]		217	44

[a] yield in parentheses corresponds to observed diacetoxylated product.
[b] Run at 80 °C for 20 h.

We attributed the low mass recovery of some of the above transformations to the isomerization event necessary for the syn diastereomer to form in order for functionalization to occur. During the isomerization event, the substrate may be more prone to oxidative decomposition, resulting in loss of starting material and/or product. Utilizing the syn diastereomers rather than the anti isomers prevented the unnecessary isomerization event and decreased the amount of oxidative decomposition, thereby giving higher yields of the corresponding acetoxylated products.

We believed that in the functionalization reactions utilizing anti diastereomers, that the anti isomer was first isomerizing to the syn diastereomer and then undergoing functionalization. Subjecting anti **202b** to acetoxylation conditions in PhCH$_3$, we observed no acetoxylated product, and only saw the formation of aminal oxidized byproducts (Scheme 2.5.17). In PhCH$_3$ the anti diastereomer cannot isomerize to syn **202a**, therefore functionalization cannot occur. When syn **202a** was subjected to the same conditions, however, no acetoxylated product was observed. For this particular transformation it seems essential that AcOH/Ac$_2$O be present for functionalization to occur; therefore, it is very difficult to find conditions in which the anti diastereomer cannot isomerize to the syn. Additionally, in all functionalization reactions utilizing the anti diastereomer, syn isomeric starting material was observed. Treating a 4 : 1 mixture of syn **202** to PTSA in refluxing $PhCH_3$ (conditions that typically provide the anti diastereomer) for 5 days afforded complete isomerization of anti **202b** to syn, and not the reverse. Based on this result, it is unlikely that the syn diastereomer could isomerize to the anti and then undergo functionalization. Furthermore, we have not observed any of anti acetoxylated **220** in any of the functionalization reactions.

Scheme 2.5.17.

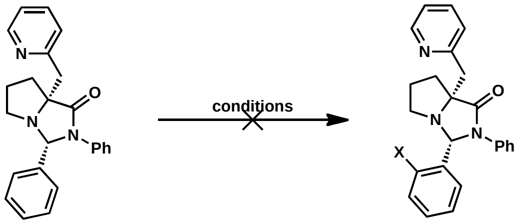


The acetoxylation of *sp*^{2} C–H bonds has been relatively straightforward. The substrate scope for this transformation has been much more extensive than that of *sp*^{3} C–H bond functionalization in our system. For that reason we anticipated that the synchronization of functionalization and transacetalization may be most feasible with aromatic aldehydes.

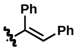
2.6 Other Attempts at Functionalization of *sp*^{2} C–H Bonds

We have tried additional functionalization reactions with substrate **172** (Table 2.6.1). In an attempt to form a carbon-carbon bond, we employed catalytic palladium and silver acetate in the presence of iodobenzene, but observed none of the desired arylated product.[24] Furthermore, we treated **172** with Sanford's diaryliodonium conditions, but were unable to isolate any of the functionalized product. We also tried to employ an electrophillic rhodium catalyst in the presence of an acetate source and diphenyl acetylene, but we did not observe any of the olefinated product.[28]

Table 2.6.1. Other *sp*^{2} C–H functionalization reactions



172

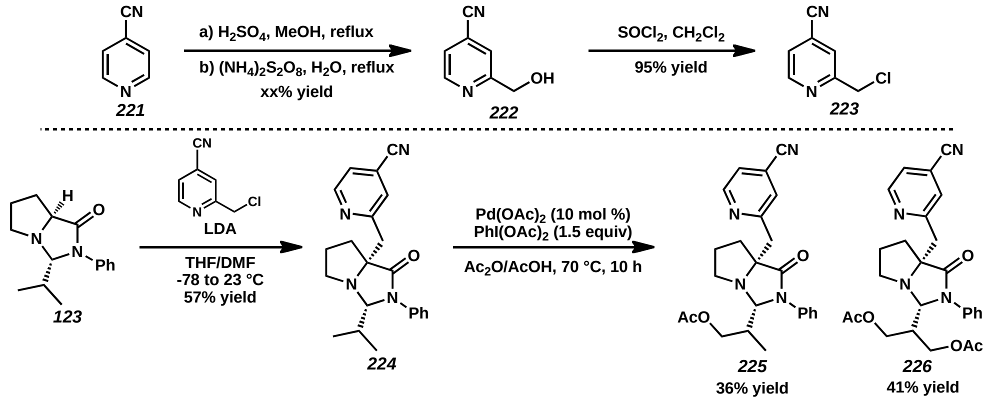
entry	conditions	X
1	$Pd(OAc)_2$, PhI AgOAc, AcOH 130 °C, 48 h	Ph
2	$Pd(OAc)_2$, $[Ph_2I]BF_4$ AcOH, 85 °C, 24 h	Ph
3	$RhCp^*(MeCN)_3[SbF_6]_2$ PivOH, PhCCPh $PhCH_3$, 24 h	 Ph Ph

While we have not observed any other transformation other than C–H acetoxylation, there are numerous other transformations and conditions that should be examined. Specifically, the olefination chemistry developed by Sanford and coworkers, which has been successful in our *sp*^{3} C–H olefination reaction, has not been examined in the context of *sp*^{2} C–H bond functionalization in our system. A non-directed version has been developed by Ishii and coworkers, which may prove successful with our ligand-substrate adduct.[29]

2.7 Electronic Modification of Ligating Groups

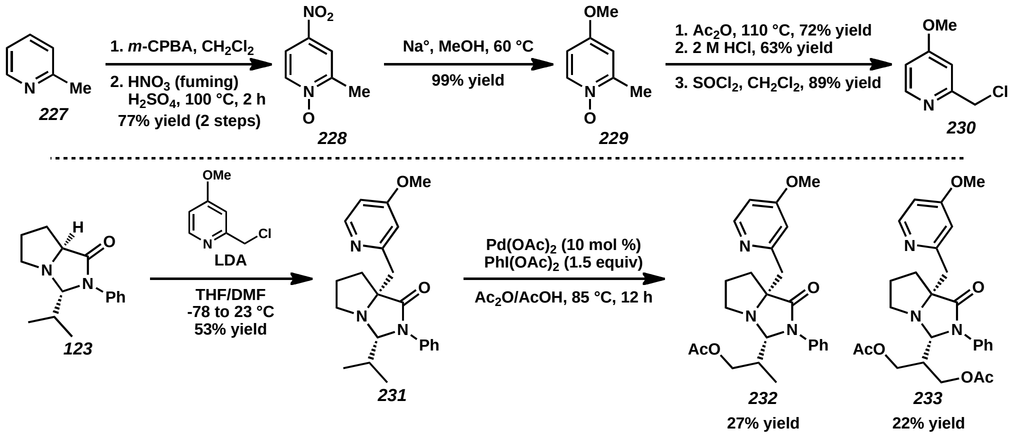
We imagined electronic and steric differentiation of the pyridyl ligating group may render differential reactivity. Synthesis of the *p*-CN pyridyl was straightforward, with hydroxymethylation[30] of cyanopyridine followed by chlorination to afford the pyridyl chloride (**223**) (Scheme 2.7.1). Installation of the ligating group via alkylation afforded substrate **224**. Treatment with acetoxylation conditions afforded a mixture of 41% diacetoxylated to 36 % monoacetoxylated product. We attributed this increase in reactivity to the electron deficient nature of the pyridyl ligating group, which should increase the rate of C–H activation, presumably the rate-determining step.

Scheme 2.7.1. Installation of an electron deficient pyridine


a) H2SO4, MeOH, reflux
b) (NH4)2S2O8, H2O, reflux
xx% yield
SOCl2, CH2Cl2
95% yield
221
222
223
LDA
THF/DMF
-78 to 23 °C
57% yield
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 70 °C, 10 h
123
224
225
36% yield
226
41% yield

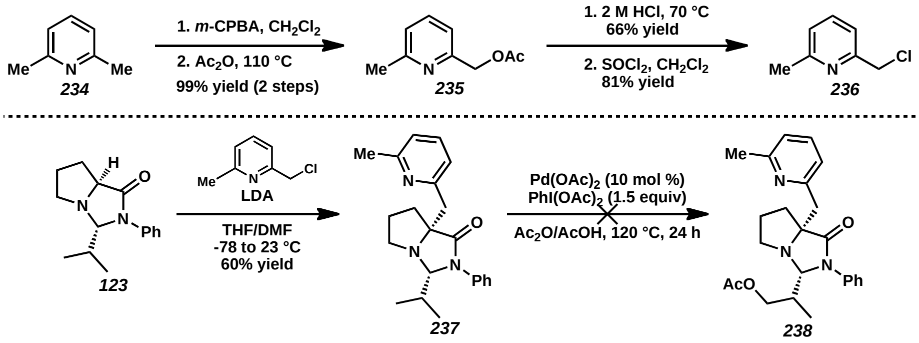
Conversely, we sought to make the pyridyl ligating group more electron rich to observe the effect on the product distribution of functionalization. Construction of the ligating group began with the conversion of 2-methylpyridine into the *p*-NO_2-pyridine *N*-oxide via an *m*-CPBA oxidation followed by nitration to afford **228** (Scheme 2.7.1). Conversion of the *p*-NO_2 group into the *p*-OMe pyridine via nucleophilic aromatic substitution afforded **229** in excellent yield. Rearrangement in Ac_2O followed by cleavage of the resultant acetate, and conversion of the benzylic alcohol into the corresponding chloride afforded **230** in good yield over 3 steps.[31] Alkylation of **123** with the benzylic chloride afforded the substrate in moderate yield. Upon treatment with functionalization conditions afforded 27% monoacetoxylated and 22% yield diacetoxylated product, with 16% of starting material recovered. With a much more electron rich directing group, the C–H activation step is presumably slower, due to the much more electron richness of the coordinated palladium.

Scheme 2.7.1. Installation of an electron rich pyridine ligating group


227
1. m-CPBA, CH2Cl2
2. HNO3 (fuming)
H2SO4, 100 °C, 2 h
77% yield (2 steps)
228
Na°, MeOH, 60 °C
99% yield
229
1. Ac2O, 110 °C, 72% yield
2. 2 M HCl, 63% yield
3. SOCl2, CH2Cl2, 89% yield
230
123
LDA
THF/DMF
-78 to 23 °C
53% yield
231
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 12 h
232
27% yield
233
22% yield

With the addition of the methylene spacer between the pyridyl ligating group and the [3.3.0] system we had observed increased diacetoxylation. We attributed this increased reactivity to the high conformational flexibility imparted by this structure. In an effort to tune this reactivity, we imagined generating a more sterically hindered pyridine which might provide more controlled levels of selectivity. Synthesis of the 6-methylpyridyl ligand began from 2,6-dimethylpyridine, which was converted into the *N*-oxide and then rearranged in Ac_2O to afford the benzylic acetate (**235**) (Scheme 2.7.3). Removal of the acetate and conversion of the resultant alcohol into the chloride afforded pyridine **236**. Alkylation with **123** afforded pyridine **237** in good yield. Treatment with acetoxylation conditions, however, afforded no functionalized product, even after prolonged reaction times at 120 °C. Presumably the pyridyl ligating site is now too sterically hindered to coordinate the palladium effectively to promote acetoxylation.

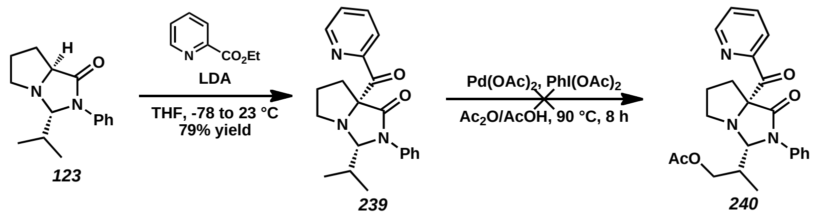
Scheme 2.7.3. Installation of sterically hindered pyridine



Me
N
Me
234
1. m-CPBA, CH2Cl2
2. Ac2O, 110 °C
99% yield (2 steps)
Me
N
OAc
235
1. 2 M HCl, 70 °C
66% yield
2. SOCl2, CH2Cl2
81% yield
Me
N
Cl
236
H
O
N
N
Ph
123
Me
N
Cl
LDA
THF/DMF
-78 to 23 °C
60% yield
Me
N
O
N
N
Ph
237
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 120 °C, 24 h
Me
N
O
N
N
Ph
AcO
238

We also imagined restricting the flexibility of the directing group by substituting the benzyl position of the pyridine ligand. We envisaged this could provide higher levels of diastereoselectivity as well as prohibiting the amount of diacetoxylated product. We also believed we could tune the electronic nature of the pyridyl with the group we were to install at the benzylic position. We installed an electron withdrawing carbonyl at the benzylic position by alkylating **123** with 2-ethylpicolinate in good yield (Scheme 2.7.4). Treatment of pyridine **239** with acetoxylation conditions, however, afforded none of the desired product. We attributed this inactivity to the likely chelation of palladium between the pyridyl nitrogen and the oxygen of the newly installed carbonyl.

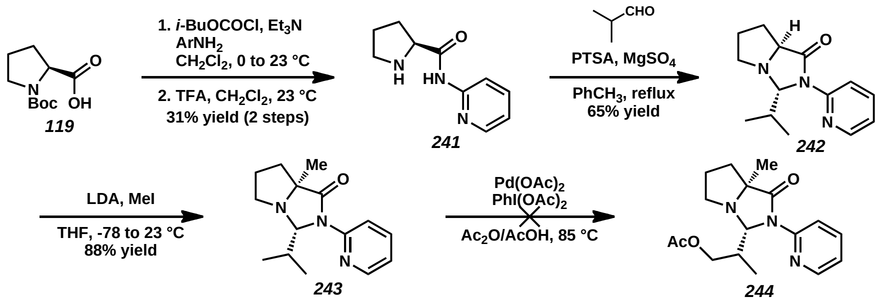
Scheme 2.7.4. Installation of conformationally restricted pyridine



H
O
N
N
Ph
123
N
CO2Et
LDA
THF, -78 to 23 °C
79% yield
N
O
O
N
N
Ph
239
Pd(OAc)2, PhI(OAc)2
Ac2O/AcOH, 90 °C, 8 h
N
O
O
N
N
Ph
AcO
240

Additionally, we tried modifying the position of the ligating group on our scaffold as well as its electronics. From **119** we were able to synthesize amino amide **241** with a pyridyl ligating group on the amide (Scheme 2.7.5). Condensation onto isobutyraldehyde afforded aminal **242** in good yield. We chose to alkylate the α-position with methyl iodide to avoid any oxidation of the pyrrolidine ring. Treating substrate **243** with acetoxylation conditions, however, was unsuccessful at generating any of the functionalized product. The palladium catalyst may be bound tightly between the pyridyl nitrogen, pyrrolidine nitrogen and even the amide, which could prevent C–H functionalization.

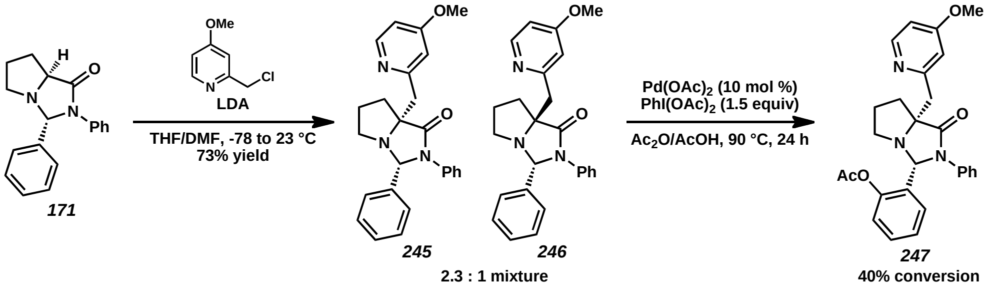
Scheme 2.7.5. Repositioning the ligating group



119
1. *i*-BuOCOCl, Et$_3$N
ArNH$_2$
CH$_2$Cl$_2$, 0 to 23 °C
2. TFA, CH$_2$Cl$_2$, 23 °C
31% yield (2 steps)
241
PTSA, MgSO$_4$
PhCH$_3$, reflux
65% yield
242
LDA, MeI
THF, -78 to 23 °C
88% yield
243
Pd(OAc)$_2$
PhI(OAc)$_2$
Ac$_2$O/AcOH, 85 °C
244

Along with examining electronically modified pyridines in *sp*^{3} C–H acetoxylation, we tested the functionalization of *sp*^{2} C–H bonds using the same ligating groups. Alkylation with **230** afforded a 2.3 : 1 mixture of syn to anti diastereomers (Scheme 2.7.6). Treatment of the mixture with functionalization conditions provided only 40% conversion to the monoacetoxylated product (**247**), with the mass balance containing mostly starting material.

Scheme 2.7.6. Acetoxylation of *sp*^{2} C–H bonds



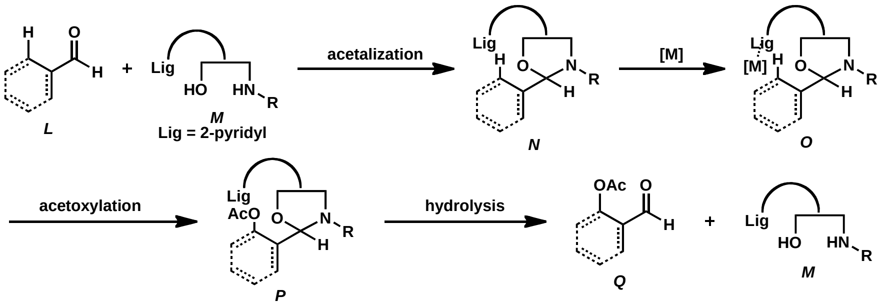
171
LDA
THF/DMF, -78 to 23 °C
73% yield
245
246
2.3 : 1 mixture
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, 90 °C, 24 h
247
40% conversion

Based on the results of electronically modifying the pyridyl ligating group, it appears that using a slightly more electron deficient ligating group, such as *p*-CN pyridyl may promote C–H functionalization reactions more readily than the electron rich *p*-OMe pyridyl. Very little investigation into the effects of these different pyridyl ligating groups has been done, and may eventually expand the types of C–H functionalization possible on these substrates.

2.8 Synchronization of Functionalization and Transacetalization

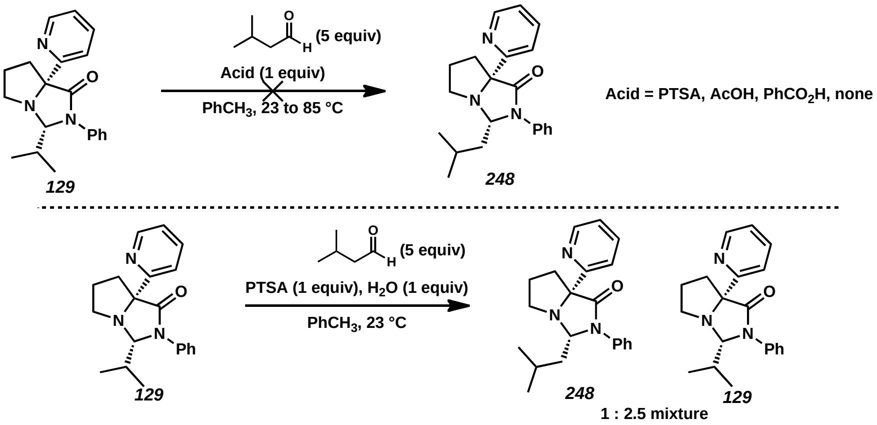
Thus far we have synthesized a ligand capable of condensing onto an aldehyde in a stereoselective fashion. We have also been able to perform a functionalization of the *sp*^{2} and *sp*^{3} C–H bonds of the aldehyde substrate when it is bound to our scaffold. In order to achieve our desired transformation (Scheme 2.8.1) we need to be able to synchronize the functionalization of the aldehyde with transacetalization. Having studied the functionalization independently, we now sought to study the transacetalization aspect of our general hypothesis and eventually see if we could achieve synchronization of the two processes.

Scheme 2.8.1. Revisiting the general concept of transacetalization and functionalization



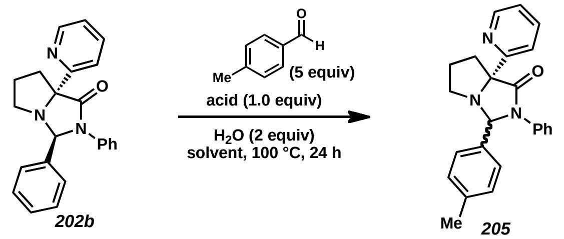
We began this study of transacetalization independent of the functionalization conditions. We wanted to first examine the general ability of the substrate-ligand adduct to exchange with exogenous aldehyde. Subjecting pyridine **129** to various acids in toluene in the presence of superstoichiometric isovaleraldehyde afforded none of the desired exchange product (Scheme 2.8.2). Treating with PTSA in toluene at room temperature provided a small amount of the exchange product (**248**).

Scheme 2.8.2. Initial exchange of isobutyraldehyde


(5 equiv)
Acid (1 equiv)
PhCH$_3$, 23 to 85 °C
Acid = PTSA, AcOH, PhCO$_2$H, none
129
248
(5 equiv)
PTSA (1 equiv), H$_2$O (1 equiv)
PhCH$_3$, 23 °C
129
248
129
1 : 2.5 mixture

We next tried to exchange aromatic aldehydes employing similar conditions with a variety of solvents (Table 2.8.1). In toluene at 100 °C we observed almost 75% conversion to exchange product **205** as a mixture of diastereomers. Treating with PTSA in THF afforded 75% conversion to the exchange product. In MeOH, near complete exchange was observed with both PTSA and CSA in 24 h. Employing *t*-AmOH as the solvent also provided high levels of conversion with CSA, with slightly diminished reactivity with PTSA. Reactions run in isopropanol and *t*-butanol afforded less exchange product **205**. In AcOH, with no additional acid we saw greater than 75% conversion to the exchange product, which was a promising lead for the acetoxylation reaction, as AcOH is a necessary solvent. Running the exchange reaction in a mixed solvent of AcOH/Ac$_2$O, however, afforded none of the exchange product, and only provided isomerization.

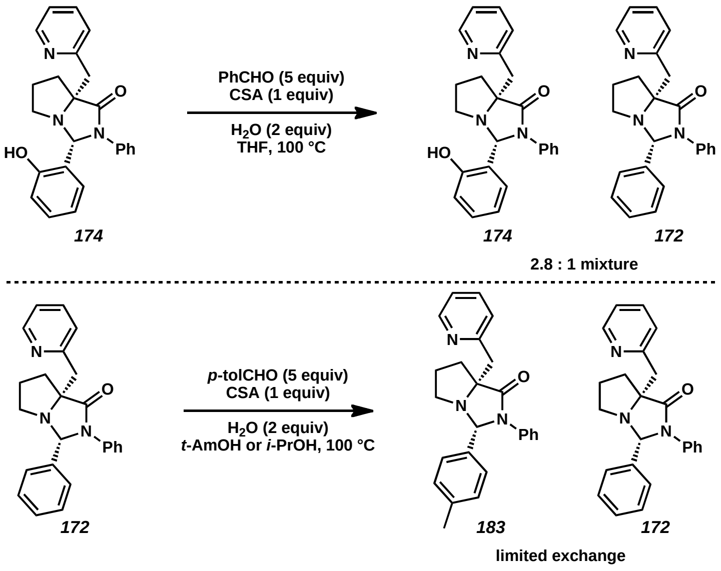
Table 2.8.1. Exchange of aromatic aldehydes


Me
(5 equiv)
H
O
acid (1.0 equiv)
H_2O (2 equiv)
solvent, 100 °C, 24 h
N
O
N
N
Ph
202b
205
Me

entry	acid	solvent	*202 : 205*	entry	acid	solvent	*202 : 205*
1	CSA	$PhCH_3$	1 : 2.8	6	PTSA	*t*-AmOH	1 : 7.0
2	PTSA	THF	1 : 3.0	7	CSA	*i*-PrOH	1 : 3.8
3	PTSA	MeOH	1 : 11.3	8	CSA	*t*-BuOH	1 : 5.1
4	CSA	MeOH	1 : 11.0	9	-	AcOH	1 : 3.5
5	CSA	*t*-AmOH	1 : 11.5	10	-	AcOH/Ac_2O	1 : 0

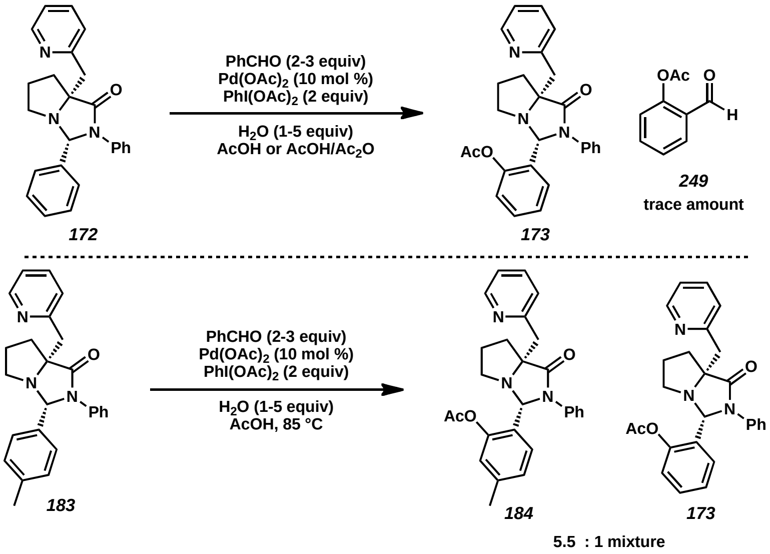
We also tried to employ exchange conditions to substrate **174** (Scheme 2.8.3). Treating functionalized **174** with benzaldehyde and CSA in THF afforded a small amount of exchange product **172**. Additionally, we treated **172** with *p*-tolualdehyde and CSA in alcoholic solvents, but observed only minimal exchange. Furthermore, in AcOH only a trace amount of the exchange product was observed, illustrating the limited exchangeability of this ligand-substrate adduct.

Scheme 2.8.3. Exchange of functionalized product


PhCHO (5 equiv)
CSA (1 equiv)
H_2O (2 equiv)
THF, 100 °C
HO
N
O
N
N
Ph
174
174
172
2.8 : 1 mixture
p-tolCHO (5 equiv)
CSA (1 equiv)
H_2O (2 equiv)
t-AmOH or *i*-PrOH, 100 °C
172
183
172
limited exchange

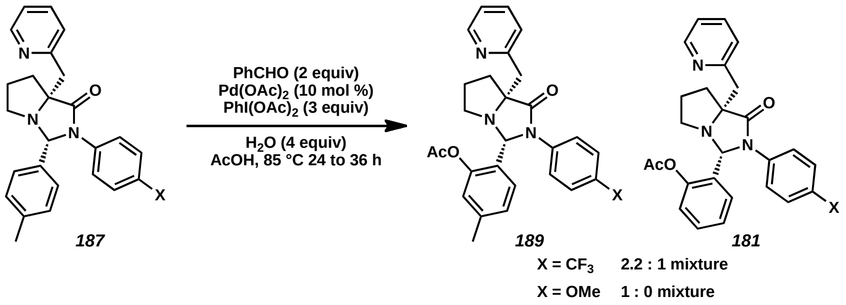
After testing the exchangeability of our ligand-substrate adducts independent of functionalization conditions, we sought to test the synchronization of functionalization and transacetalization with our scaffold. Treating pyridine **172** with acetoxylation conditions with additional benzaldehyde and water afforded functionalized product **173** with only limited amounts of acetoxylated salicyaldehyde (Scheme 2.8.4). We believed the exchange of benzaldehyde for **249** was very slow under these conditions. Additionally, we tried to exchange benzaldehyde with substrate **183** under the acetoxylation conditions. We observed a very small amount of the functionalized exchange product under these conditions.

Scheme 2.8.4. Initial attempts at synchronizing transacetalization with functionalization


PhCHO (2-3 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (2 equiv)
H2O (1-5 equiv)
AcOH or AcOH/Ac2O
172
173
249
trace amount
PhCHO (2-3 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (2 equiv)
H2O (1-5 equiv)
AcOH, 85 °C
183
184
173
5.5 : 1 mixture

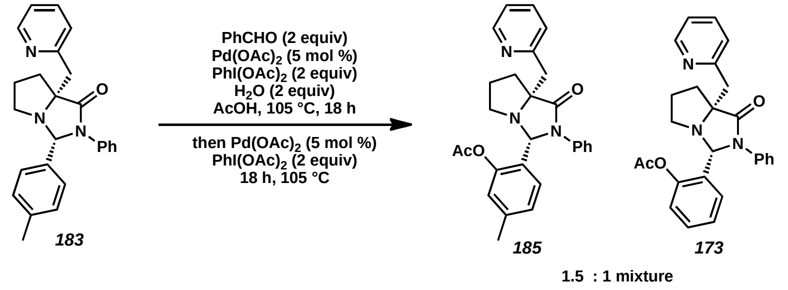
With our limited success with substrate **183**, we sought to examine the electronically modified phenyl amide substrates (Scheme 2.8.5). Subjecting tolualdehyde substrate **187-CF$_3$** to benzaldehyde and functionalization conditions afforded a 2.2 : 1 mixture of acetoxylated **189-CF$_3$** to functionalized exchange product **181-CF$_3$**. Treating the *p*-OMe variant with acetoxylation conditions and benzaldehyde afforded none of the acetoxylated exchange product (**181-OMe**), but good exchange was observed. We attributed this lack of reactivity to the oxidatively sensitive aminal center.

Scheme 2.8.5. Electronically modified pyridines for synchronization


PhCHO (2 equiv)
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (3 equiv)
H$_2$O (4 equiv)
AcOH, 85 °C 24 to 36 h
N
O
N
X
AcO
187
189
181
X = CF$_3$ 2.2 : 1 mixture
X = OMe 1 : 0 mixture

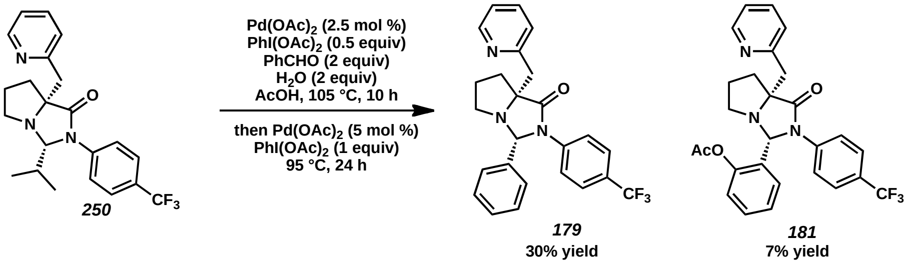
We envisioned that using a two-step addition of catalyst and oxidant might provide higher levels of conversion to the functionalized exchange product. Treating **183** with benzaldehyde, catalyst and oxidant in AcOH at 105 °C for 18 h, followed by more catalyst and oxidant afforded a 1.5 : 1 mixture of **185** to **173** (Scheme 2.8.6). We increased the temperature of the reaction in an effort to see higher levels of exchange, likely trading off for more decomposition.

Scheme 2.8.6. Small amounts of synchronization


PhCHO (2 equiv)
Pd(OAc)$_2$ (5 mol %)
PhI(OAc)$_2$ (2 equiv)
H$_2$O (2 equiv)
AcOH, 105 °C, 18 h
then Pd(OAc)$_2$ (5 mol %)
PhI(OAc)$_2$ (2 equiv)
18 h, 105 °C
N
O
Ph
AcO
183
185
173
1.5 : 1 mixture

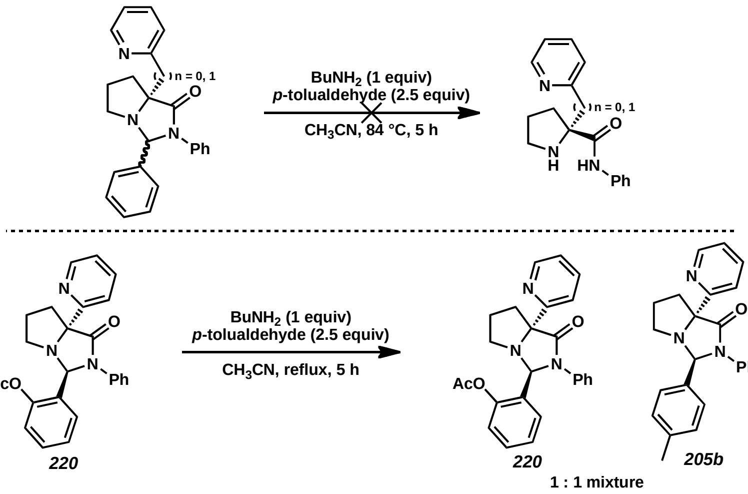
Next we sought to examine the synchronization of functionalization and transacetalization utilizing our isobutyraldehyde ligand adduct **250**. Although exchanging with another aliphatic aldehyde may be unsuccessful, we imagined using an aromatic exchange aldehyde. Treating **250** with benzaldehyde, catalyst and oxidant, again in a two step procedure afforded 30% yield of the exchange product (**179-CF$_3$**) and 7% yield of the activated exchange product (**181-CF$_3$**) (Scheme 2.8.7).

Scheme 2.8.7. Synchronization of aliphatic and aromatic aldehydes


Pd(OAc)$_2$ (2.5 mol %)
PhI(OAc)$_2$ (0.5 equiv)
PhCHO (2 equiv)
H$_2$O (2 equiv)
AcOH, 105 °C, 10 h
then Pd(OAc)$_2$ (5 mol %)
PhI(OAc)$_2$ (1 equiv)
95 °C, 24 h
250
179
30% yield
181
7% yield

While we had observed some synchronization of functionalization and transacetalization, we wanted to improve the yield of the functionalized exchange product. A literature example showed transacetalization of aminals using an amine in the reaction.[32] We tried this reaction on substrates **129** and **172** with no observed free ligand or exchange product (Scheme 2.8.8). Interestingly, when we used anti isomer **220** in the reaction, we observed good exchange and a small amount of free ligand. While we were unable to use additional amine in the functionalization conditions, due to immediate acetalization, we believed using the anti isomer of **220** may exhibit improved transacetalization.

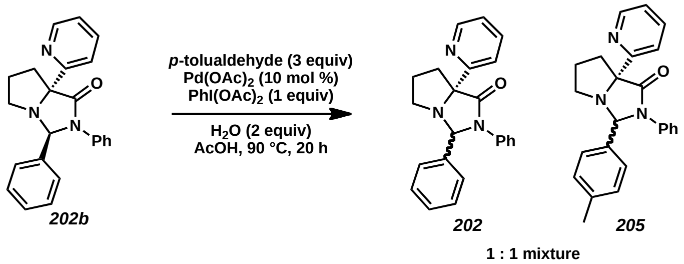
Scheme 2.8.8. Attempted ligand hydrolysis/exchange


n = 0, 1
BuNH$_2$ (1 equiv)
p-tolualdehyde (2.5 equiv)
CH$_3$CN, 84 °C, 5 h
n = 0, 1
BuNH$_2$ (1 equiv)
p-tolualdehyde (2.5 equiv)
CH$_3$CN, reflux, 5 h
220
220
205b
1 : 1 mixture

Based on these results, we hypthesized that using **202b** as the starting ligand adduct might facilitate transacetalization and thereby functionalization. Treating anti **202b** with *p*-

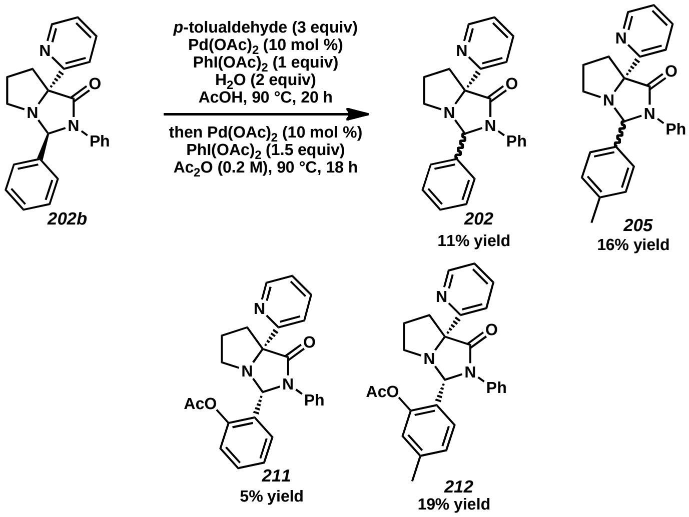
tolualdehyde, catalyst and oxidant afforded a 1 : 1 mixture of exchange product to starting material, but no functionalization of either substrate was observed (Scheme 2.8.9).

Scheme 2.8.9. Another attempt at synchronization


p-tolualdehyde (3 equiv)
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1 equiv)
H$_2$O (2 equiv)
AcOH, 90 °C, 20 h
202b
202
205
1 : 1 mixture

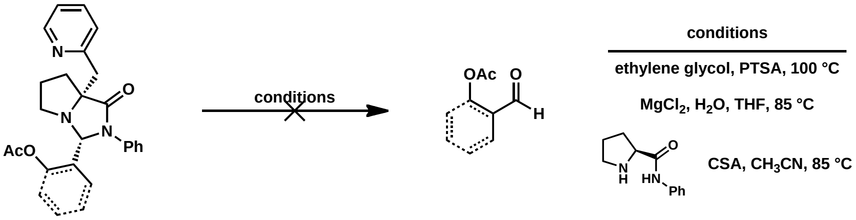
We turned to our two-step procedure in order to improve the yield of the functionalized exchange product. Treating anti **202b** with *p*-tolualdehyde, catalyst and oxidant for 20 h at 90 °C, followed by the addition of more catalyst, oxidant and Ac$_2$O afforded 16% yield of the exchange product (**205**) and 19% yield of the functionalized exchange product (**212**) (Scheme 2.8.10). It is likely that the first step induces the transacetalization, and the addition of more catalyst and oxidant in the second step performs the functionalization. While not the ideal synchronized process, this reaction still demonstrates that exchange and functionalization can occur under similar reactions conditions to afford functionalized exchange product.

Scheme 2.8.10. Successful transacetalization and functionalization


p-tolualdehyde (3 equiv)
Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1 equiv)
H$_2$O (2 equiv)
AcOH, 90 °C, 20 h
then Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O (0.2 M), 90 °C, 18 h
202b
202
11% yield
205
16% yield
211
5% yield
212
19% yield

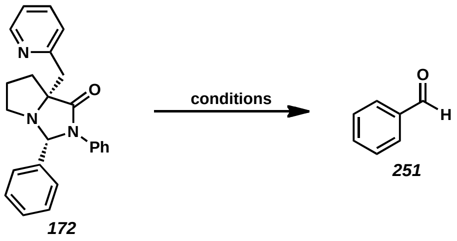
Lastly, we sought to remove the ligand independent of the functionalization conditions. Treating any functionalized product with Lewis acids or exchange acetal components afforded none of the desired acetoxylated aldehyde in either aromatic or aliphatic cases (Scheme 2.8.11). Removing the ligand from the activated isobutyraldehyde proved exceedingly difficult, presumably because elimination could occur to form an acrolein byproduct.

Scheme 2.8.11. Removal of the ligand from functionalized products



We then turned our attention to removing the ligand from aromatic aldehydes, as we could actually isolate the product without elimination. We imagined testing the unactivated product first, as it should be easier to remove the ligand from **251**. Treating **172** with amino amide **122** and acid afforded a complex mixture of products (Table 2.8.2). We imagined that silica gel was weakly acidic enough to possibly remove the ligand, and we had observed slight decomposition when purifying these *N*,*N*-aminals by chromatography. At 85 °C in MeOH however, we only observed recovered starting material. We then tried a reductive cleavage using NaBH$_4$, which also only afforded starting material. Using a stronger reducing agent like LAH reduced the amide to the secondary amine, forming a very labile aminal. Treatment with aqueous acid cleaved the aminal to afford benzaldehyde in 25% yield.

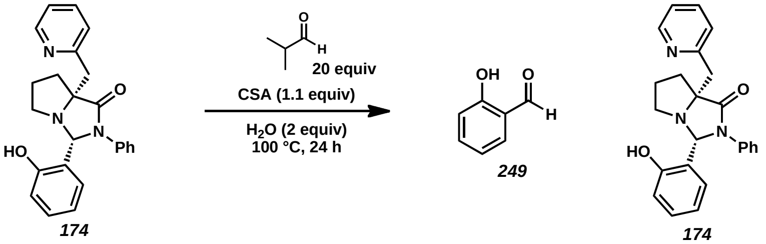
Table 2.8.2. Conditions for ligand removal



entry	conditions	result
1	*122*, CSA CH_3CN	complex mix
2	silica, MeOH H_2O, 85 °C	*172*
3	$NaBH_4$, MeOH 80 °C	*172*
4	LAH, THF 1 M $KHSO_4$	25% yield

Rather than finding an acetal component which could exchange with the ligand and condense onto the desired aldehyde, we endeavored to use a sacrificial aldehyde which could condense with the ligand and free the desired aldehyde. Again we turned to aromatic aldehydes, as these substrates would avoid elimination and reduce the complexity of the product mixture. Additionally, we used substrate **174** as it was afforded from acetate **173** upon exposure to acid. Using isobutyraldehyde as the sacrificial aldehyde we observed less than 15% liberation of aldehyde as based on crude ^{1}H NMR (Scheme 2.8.12). Changing the solvent to THF afforded much higher conversion (nearly 40%). Using CH_3CN and dioxane as the solvent also increased the conversion of observed salicyladehyde.

Scheme 2.8.12. Transacetalization for ligand removal

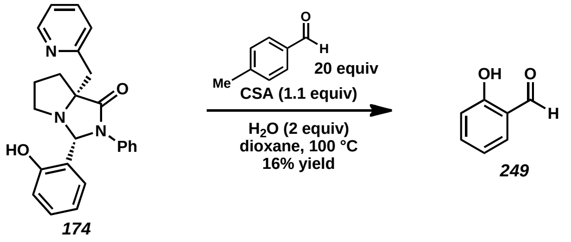


entry	conditions	*174 : 249*
1	MeOH (0.1 M)	6.6 : 1
2	THF (0.4 M)	1.6 : 1
3	CH_3CN (0.25 M)	1.7 : 1
4	dioxane (0.25 M)	1.4 : 1

Based on the success of ligand cleavage with isobutyraldehyde, we imagined that using a more electron rich aromatic aldehyde may push the conversion higher. Treating **174** with *p*-tolualdehyde and acid in dioxane afforded nearly 50% conversion by crude ^{1}H NMR (Scheme

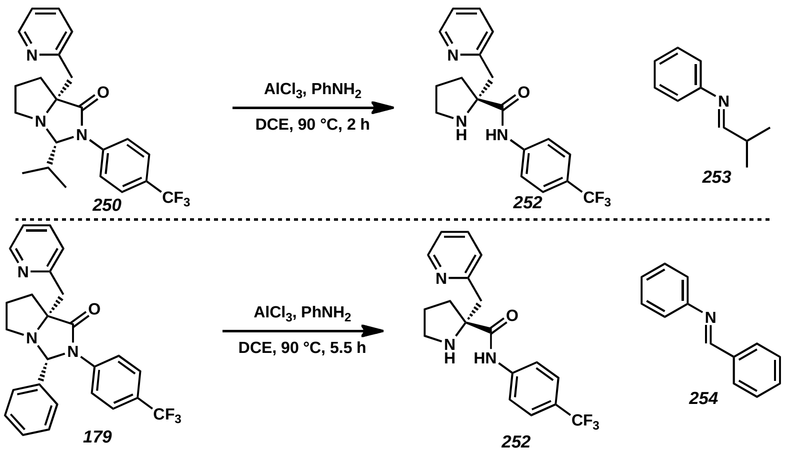
2.8.13). Analysis by GC, however, showed only a 16% yield of salicylaldehyde. We attribute this discrepancy to decomposition under the reaction conditions. Furthermore, we tried a more electron rich *p*-anisaldehyde as the sacrificial component, but could not improve the yield of **249**.

Scheme 2.8.13. Exchange with aromatic aldehydes


N
O
N
N
Ph
HO
174
O
H
Me
20 equiv
CSA (1.1 equiv)
H2O (2 equiv)
dioxane, 100 °C
16% yield
OH
O
H
249

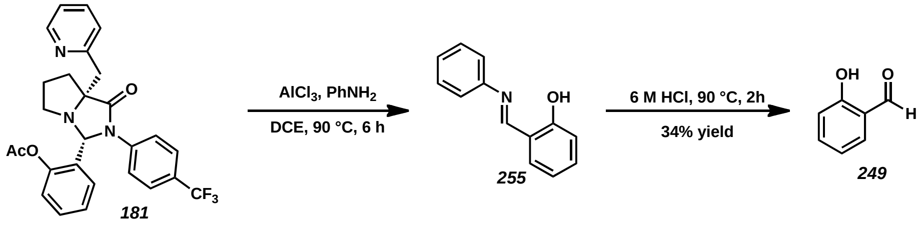
Rather than exchanging an aldehyde or acetal component to free the ligand, we thought we could use a transamidation reaction.[33] The reaction should create an unstable aminal center, which could fall apart, yielding the transamidated free ligand and the corresponding imine. Interestingly, when we subjected substrate **250** to $AlCl_3$ and aniline in DCE we observed near full conversion to the corresponding free ligand and aniline derived imine **253** (Scheme 2.8.14). While this is not the transamidation product, it still releases the desired ligand and a cleavable imine. Likewise, we could perform this cleavage reaction on **179** to afford the free ligand and imine **254**.

Scheme 2.8.14. Transamidation conditions for ligand removal


N
O
N
N
CF3
250
AlCl3, PhNH2
DCE, 90 °C, 2 h
N
O
N
H
HN
CF3
252
N
253
N
O
N
N
CF3
179
AlCl3, PhNH2
DCE, 90 °C, 5.5 h
N
O
N
H
HN
CF3
252
N
254

Subjecting the functionalized isobutyraldehyde ligand adduct to the reaction conditions afforded a complex mixture, most likely due to side elimination reactions. Subjecting **181-CF_3** to the conditions, however, afforded the phenol imine product (**255**) (Scheme 2.8.15). Cleavage of the imine with aqueous acid afforded salicylaldehyde in 34% over two steps, with 23% recovery of the starting imine.

Scheme 2.8.15. Successful removal of the ligand



We are now able to perform transacetalization with our ligand under acidic alcoholic conditions. We can also remove the ligand after functionalization using Lewis acidic conditions and a sacrificial amine. Furthermore, we can combine these two processes under our modified acetoxylation conditions and generate a functionalized exchange product. While this process is not yet ideal, it is an initial lead which demonstrates the feasibility of our original hypothesis.

2.9 Conclusions

We have endeavored to combine a regio- and stereoselective functionalization with a removable directing group *in situ*, without the need for extra steps for removal of a ligating group. We have shown the asymmetric development of ligands that can condense onto an aromatic or aliphatic aldehyde and be isolated as a stable aminal. We have shown a highly diastereoselective sp^3 C–H acetoxylation reaction that generates a single enantiomer. We have also shown that changing the connectivity of the ligating group can impart differential reactivity. Furthermore, we have demonstrated regioselective sp^2 C–H acetoxylation, again with differential reactivity dependent on ligating group connectivity. Finally, we have shown that synchronization of transacetalization and functionalization is possible with our scaffold. While we have only displayed modest amounts of this synchronization, the development of new reactions and modification of the scaffold should ultimately lead to the realization of this idea.

2.10 References and Notes

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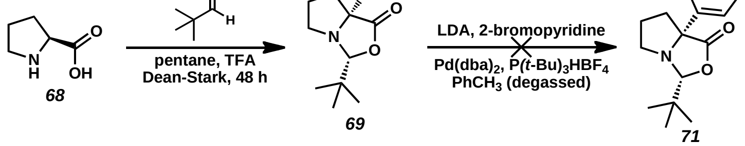
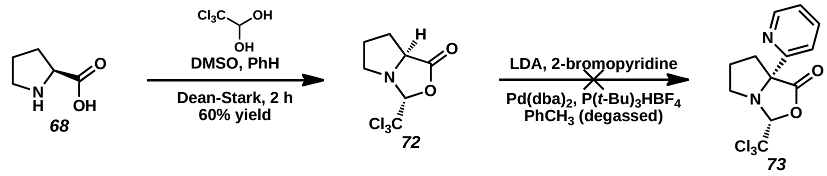
2.11 Experimental Procedures and Characterization

Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, *N*,*N*-dimethylformamide, dichloromethane, hexanes, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH_2. 2-Fluoropyridine was freshly distilled before use. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Gelest (Morrisville, PA), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), Mallinckrodt Chemicals (Phillipsburg, NJ), Spectrum (Gardena, CA) Fischer Scientific (Fair Lawn) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to either *p*-anisaldehyde or $KMnO_4$ solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), a Varian Inova 400 (at 400 MHz), or a Varian 400 MR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on either a Varian Inova 400 (at 100 MHz), a Varian Mercury 300 (at 75 MHz), or a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with either a Nicolet Magna FTIR 760, a Nicolet 380 FTIR, or a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.



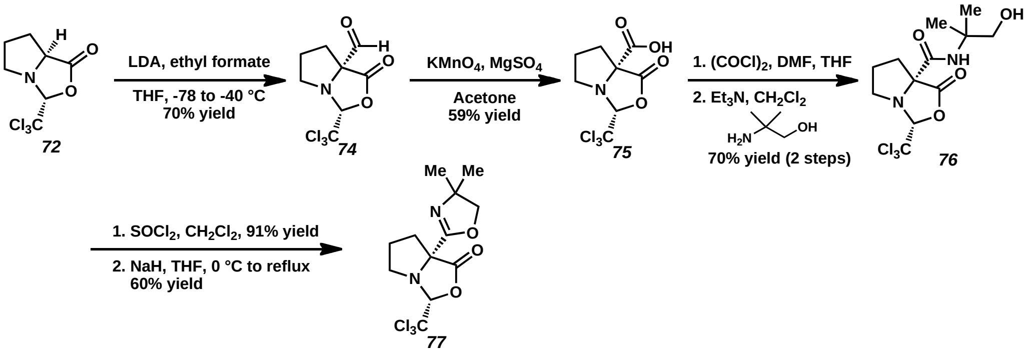
Acetal 69: To a suspension of L-proline (1.09g, 8.69 mmol) and pentane (35 mL) was added pivaladehyde (4.83 mL, 43.5 mmol) and TFA (13μL). The suspension was reflulxed for 48 h, with azeotropic removal of water. The clear reaction mixture was concentrated to afford **69** (1.31 g, 82% yield) as a clear oil.

Pyridine 71: To a solution of diisopropylamine (0.240 mL, 1.67 mmol) and tolune (degassed) (1.00 mL) was added *n*-BuLi (1.00 mL, 1.61 mmol, 1.6 M in hexanes) at -78 °C. The solution was stirred at -78 °C for 5 min, then at 0 °C for 10 min. A solution of **69** (250 mg, 1.24 mmol) in toluene (degassed) (2.00 mL) was added to the solution at 0 °C, and stirred for 20 min. To a solution of Pd(dba)$_2$ (36.0 mg, 0.062 mmol) and P(*t*-Bu)$_3$HBF$_4$ (18.0 mg, 0.062 mmol) in toluene (degassed) (1.00 mL) was added 2-bromopyridine (0.120 mL, 1.24 mmol). To this solution was added the enolate solution. The reaction was stirred at 23 °C overnight. The reaction was concentrated under reduced pressure with no product formation by ^{1}H NMR.



Acetal 72: L-proline (7.00 g, 60.8 mmol) and chloral hydrate (16.6 g, 100 mmol) and DMSO (4.00 mL) were refluxed in benzene (203 mL) for 2 h with azeotropic removal of water. The cooled solution was washed with sat. aqueous NaHCO$_3$ (4 x 75 mL), dried over MgSO$_4$ and concentrated yielding a yellow-orange solid. The product was decolorized over a small plug of silica (5 cm x 5 cm) to yield **72** (8.60 g, 58% yield, R$_f$ = 0.29 in 9:1 hexanes:EtOAc) as a light orange solid.

Pyridine 73: To a solution of diisopropylamine (0.180 mL, 1.25 mmol) and toleune (degassed) (1.00 mL) was added *n*-BuLi (0.750 mL, 1.21 mmol, 1.6 M in hexanes) at -78 °C. The solution was stirred at -78 °C for 5 min, then at 0 °C for 10 min. A solution of **72** (249 mg, 1.02 mmol) in toluene (degassed) (2.00 mL) was added to the solution at 0 °C, and stirred for 20 min. To a solution of Pd(dba)$_2$ (27.0 mg, 0.046 mmol) and P(*t*-Bu)$_3$HBF$_4$ (13.0 mg, 0.046 mmol) in toluene (degassed) (1.00 mL) was added 2-bromopyridine (0.0900 mL, 0.927 mmol). To this solution was added the enolate solution. The reaction was stirred at 23 °C overnight. The reaction was concentrated under reduced pressure with no product formation by ^{1}H NMR.



72
LDA, ethyl formate
THF, -78 to -40 °C
70% yield
74
KMnO4, MgSO4
Acetone
59% yield
75
1. (COCl)2, DMF, THF
2. Et3N, CH2Cl2
70% yield (2 steps)
76
1. SOCl2, CH2Cl2, 91% yield
2. NaH, THF, 0 °C to reflux
60% yield
77

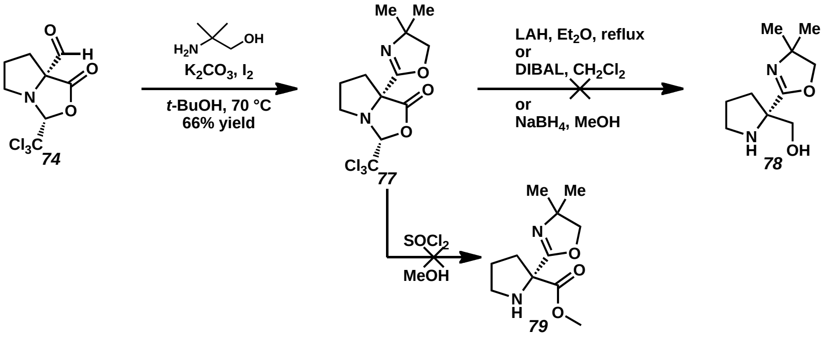
Aldehyde 74: To a solution of diisopropylamine (1.79 mL, 12.7 mmol) and THF (15.4 mL) at -78 °C was added *n*-BuLi (4.9 mL, 12.3 mmol, 2.5 M in hexanes). Stirred for 5 min at -78 °C then warmed to 0 °C for 10 min. To this solution at -78 °C was added a solution of **72** (2.01 g, 8.18 mmol) in THF (8.00 mL) dropwise. This solution was stirred for 30 min at -78 °C. Ethyl formate (2.64 mL, 32.7 mmol) was added slowly at -78 °C. The reaction was allowed to warm to -40 °C over 45 min, then stirred for 10 min at -40 °C. Citric acid (10%, 20 mL) was added slowly. The aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated yielding an orange oil. The crude product was purified via chromatography (7:1 to 7:3 hexanes:EtOAc) yielding **74** (1.62 g, 70% yield, R_f = 0.40 in 1:1 hexanes:EtOAc).

Acid 75: To a solution of **74** (1.25 g, 4.59 mmol), MgSO$_4$ (0.912 g, 7.57 mmol), and acetone (77.0 mL) was added KMnO$_4$ (1.02 g, 6.43 mmol) portionwise over 45 min. The reaction was stirred at 23 °C for an additional 30 min. The solvent was removed under reduced pressure. The remaining brown residue was extracted with hot water (3 x 15 mL). The extract was filtered and decolorized with $NaSO_3$ and extracted with $CHCl_3$ (3 x 15 mL). The aqueous layer was concentrated to 30 mL and acidified to pH ~4 with 1 M HCl. The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated yielding **75** (0.778 g, 59% yield, R_f = 0.2 in 1:1 hexanes:EtOAc) as a white solid.

Acid chloride: To a solution of **75** (0.603 g, 2.09 mmol) in THF (10.5 mL) at 0 °C was added oxalyl chloride (0.912 mL, 10.5 mmol) and DMF (2 drops). The reaction was stirred for 5 min at 0 °C, then 1 h at 23 °C. The reaction mixture was concentrated under reduced pressure and concentrated from benzene (3 x 20 mL) yielding acid chloride (0.528 g, 82% yield, R_f = 0.78 in 1:1 hexanes:EtOAc) as a yellow solid.

Amide 76: To a solution of 3-amino-3-methyl propanol (0.659 mL, 6.88 mmol) Et_3N (0.725 mL, 5.16 mmol) and CH_2Cl_2 (7.50 mL) at 0 °C was added a solution of acid chloride (0.528 g, 1.72 mmol) in CH_2Cl_2 (8.6 mL) dropwise. The reaction was stirred for 10 min at 0 °C, then at 23 °C for 1 h. The reaction was quenched with 0.5 M HCl (17 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4 and cocnetrated yielding **76** (0.616 g, 99% yield, R_f = 0.60) as an amber oil (yellow amorphous solid under vacuum).

Oxazoline 77: To **76** (0.692 g, 1.93 mmol) in CH_2Cl_2 (14.1 mL) at 0 °C was added $SOCl_2$ (1.93 mL, 26.5 mmol) dropwise. The reaction was stirred at 0 °C for 10 min, then warmed to 23 °C and stirred for 2 h. The reaction was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (2 20 mL). The organics were washed with brine (20 mL) dried over Na_2SO_4 and concentrated to afford the corresponding alkyl chlorde (0.661 g, 91% yield, R_f = 0.62 in 1:1 hexanes:EtOAc). To a suspension of NaH (washed in hexanes) (0.112 g, 2.81 mmol), in THF (5.00 mL) was added the alkyl chloride (0.529 g, 1.40 mmol) in THF (6.20 mL) at 0 °C. The suspension was stirred at 0 °C for 10 min, then warmed to 23 °C. The reaction was heated to reflux (after adding 3 drops *t*-BuOH) for 26 h. The reaction was cooled and quenched with sat. aq. NH_4Cl (5 mL) and the aqueous layer extracted with EtOAc (2 x 10 mL). The organic layers were washed with brine (15 mL) dried over Na_2SO_4 and concentrated. The crude residue was purified via chromatography (7:3 to 1:1 hexanes:EtOAc) to afford **77** (0.285 g, 60% yield, R_f = 0.38 in 1:1 hexanes:EtOAc) as a light brown solid.



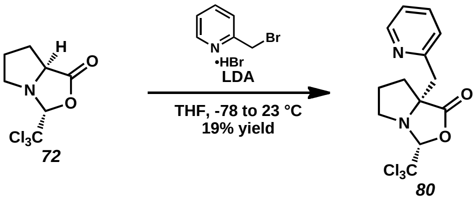
Oxazoline 77: To a solution of **74** (100 mg, 0.367 mmol) in *t*-BuOH (3.70 mL) was added 3-amino-3-methyl propanol (38.7 μL, 0.404 mmol) at 23 °C. The reaction was stirred at 23 °C for 1 h. K_2CO_3 (152 mg, 1.10 mmol) and I_2 (186 mg, 0.734 mmol) were added at 23 °C. The reaction was heated to 70 °C for 18 h. The reaction was quenched with Na_2SO_3 until I_2 color gone. The aqueous was extracted with ether (3 x 10 mL). The organics were washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated. The crude mixture was purified via chromatography (6:1 to 7:3 hexanes:EtOAc) to afford **77** (49.6 mg, 40% yield, R_f = 0.38 in 1:1 hexanes:EtOAc) as a light brown solid.

Ester 79: At 0 °C $SOCl_2$ (0.927 mL, 12.7 mmol) was added slowly to MeOH (2.50 mL). This solution was stirred at 0 °C for 5 min, then **77** (0.433 g, 1.27 mmol) in MeOH (2.50 mL) was added slowly. The reaction was warmed to 23 °C and stirred for 5 d. The solution was concentrated under reduced pressure, the crude residue redissolved in MeOH and concentrated. The residue was taken up in H_2O and neutralized to pH 7 with 1 M NaOH. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (15 mL) dried over $MgSO_4$ and concentrated under reduced pressure. No product was formed by ^1H NMR.

Amino Alcohol 78: To a solution of LAH (51.1 mg, 1.35 mmol) in Et_2O (0.500 mL) was added **77** (70.3 mg, 0.207 mmol) in THF (1.00 mL) and Et_2O (0.500 mL) at 0 °C. The reaction was heated to reflux overnight. The reaction was cooled to 0 °C and H_2O (51.1 μL), 15% NaOH (51.1 μL) and H_2O (153 μL) were added sequentially. The mixture was stirred for 1 h, forming a white precipitate. The precipitate was filtered with EtOAc and the organic layer dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.

Amino Alcohol 78: To a solution of **77** (62.6 mg, 0.184 mmol) in CH_2Cl_2 (1.00 mL) at -78 °C was added DIBAL (0.368 mL, 0.368 mmol, 1.0 M in hexanes) dropwise. The reaction was stirred at -78 °C for 2 h. The reaction was quenched with EtOH. To the mixture was added sat. aq. Rochelle's salt and EtOAc. The mixture was stirred overnight. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.

Amino Alcohol 78: To a solution of **77** (49.5 mg, 0.146 mmol) in MeOH (4.90 mL) at 23 °C was added $NaBH_4$ (9.7 mg, 0.256 mmol). The reaction was stirred overnight at 23 °C. The reaction was quenched with sat. aq. NH_4Cl and the solvent removed under reduced pressure. The aqueous layer was extracted with EtOAc (2 x 5 mL), the organic layers dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.

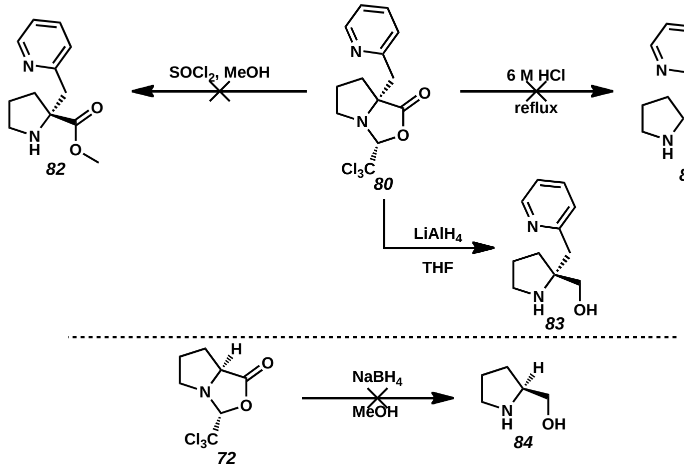


Base	yield
LDA	19%
KHMDS	0%
LiHMDS	0%

Pyridine 80: To a solution of diisopropylamine (0.65 mL, 4.62 mmol) in THF (1.00 mL) at -78 °C was added *n*-BuLi (1.81 mL, 4.53 mmol, 2.5 M in hexanes). The solution was stirred for 10 min at -78 °C. This solution was added to a solution of 2-bromomethylpyridine hydrobromide (0.433g, 1.71 mmol) in THF (1.00 mL) at -78 °C. To this suspension was added **72** (0.500 g, 2.05 mmol) in THF (4.00 mL) at -78 °C. The reaction was stirred at -78 °C for 1.5 h. The reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude mixture was purified via chromatography (4:1 to 2:3 hexanes:EtOAc) to afford **80** (0.114 g, 26% yield, R_f = 0.29 in 1:1 hexanes:EtOAc) as a yellow solid.

Pyridine 80: To a suspension of 2-bromomethylpyridine hydrobromide (0.519 g, 2.05 mmol) in THF (1.00 mL) at -78 °C was added KHMDS (409 mg, 2.05 mmol) in THF (1.78 mL). To a solution of KHMDS (0.961 g, 4.82 mmol) in THF (4.20 mL) was added **72** (1.00 g, 4.09 mmol) as a solution in THF (5.00 mL). The electrophile solution was added to the enolate slowly at -78 °C. The reaction was stirred at -78 °C for 1.5 h. The reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated. No product was observed by ^1H NMR.

Pyridine 80: To a solution of HMDS (1.46 mL, 6.87 mmol) in THF (3.00 mL) at -78 °C was added *n*-BuLi (2.71 mL, 6.77 mmol, 2.5 M in hexanes). The solution was stirred for 10 min at -78 °C. This solution was added to a solution of 2-bromomethylpyridine hydrobromide (0.517 g, 2.05 mmol) in THF (1.00 mL) at -78 °C. To this suspension was added **72** (1.00 g, 4.09 mmol) in THF (4.00 mL) at -78 °C. The reaction was stirred at -78 °C for 1.5 h. The reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated. No product was observed by ^1H NMR.



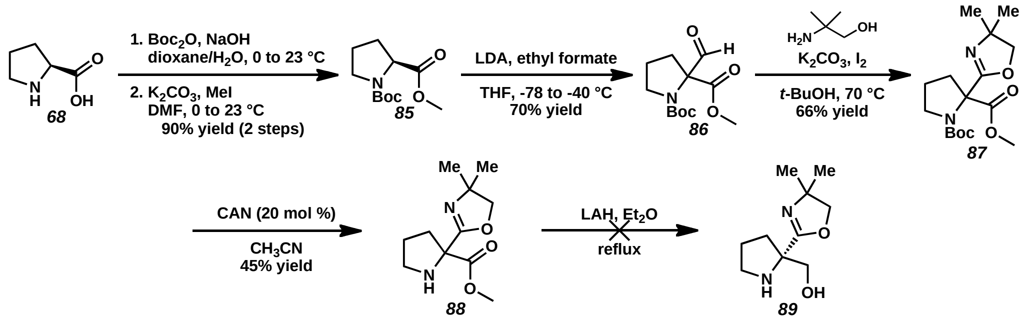
Acid 81: HCl (2.89 mL, 2.0 M) was added to **80** (0.114 g, 0.340 mmol) and heated to reflux for 1 h. The reaction mixture was filtered and extracted with CH_2Cl_2 (3 x 5 mL). The aqueous layer was concentrated under reduced pressure. No product was observed by ^1H NMR.

Ester 82: $SOCl_2$ (0.490 mL, 6.78 mmol) was added to MeOH (1.00 mL) at 0 °C and stirred for 5 min at 0 °C. To this solution was added **80** (0.228 g, 0.678 mmol) in MeOH (2.00 mL) at 0 °C. the reaction was warmed to 23 °C and stirred overnight. The mixture was concentrated under reduced pressure. The residue was dissolved in H_2O, neutralized with 10% NaOH and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.

Amino alcohol 83: To a suspension of LAH (14.6 mg, 0.385 mmol) in THF (0.500 mL) was added **80** (56.5 mg, 0.257 mmol) in THF (1.50 mL) at 0 °C. The mixture was warmed to 23 °C and stirred for 3 h. The reaction was quenched with H_2O, acidified with 10% H_2SO_4 and stirred for 15 min. The mixture was filtered and the aqueous layer extracted with EtOAc (3 x 5 mL).

The combined organic layers were washed with brine (10 mL) dried over $MgSO_4$ and concentrated. No product was observed by ^1H NMR.

Prolinol 84: To a solution of $NaBH_4$ (27.0 mg, 0.716 mmol) in MeOH (5.00 mL) was added **72** (100 mg, 0.409 mmol) in MeOH (8.00 mL) at 23 °C. The reaction was stirred at 23 °C for 19 h. The reaction was quenched with acetone (2.70 mL) at 0 °C and stirred for 10 min. The solvent was removed under reduced pressure. The residue was taken up in H_2O, then extracted with CH_2Cl_2 (2 x 10 ml). The organic layers were dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.


68
1. Boc₂O, NaOH
dioxane/H₂O, 0 to 23 °C
2. K₂CO₃, MeI
DMF, 0 to 23 °C
90% yield (2 steps)
85
LDA, ethyl formate
THF, -78 to -40 °C
70% yield
86
K₂CO₃, I₂
t-BuOH, 70 °C
66% yield
87
CAN (20 mol %)
CH₃CN
45% yield
88
LAH, Et₂O
reflux
89

Ester 85: To a solution of (*S*)-proline (**68**) (15.0 g, 130 mmol) in aq. NaOH (1 M, 261 mL) and dioxane (65.2 mL) at 0 ˚C was added Boc_2O (33.1 g, 154 mmol) portionwise over 20 min. The resulting mixture was stirred at 0 ˚C for 30 min, then allowed to warm to 23 ˚C and stirred overnight. The organic solvent was removed in vacuo. The remaining aqueous solution was acidified to pH ~2 with 1 M $KHSO_4$. The aqueous solution was extracted with $CHCl_3$ (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to afford carbamate (28.0 g, 99% yield, R_f = 0.17 in 1:1 hexanes/EtOAc) as a white solid.

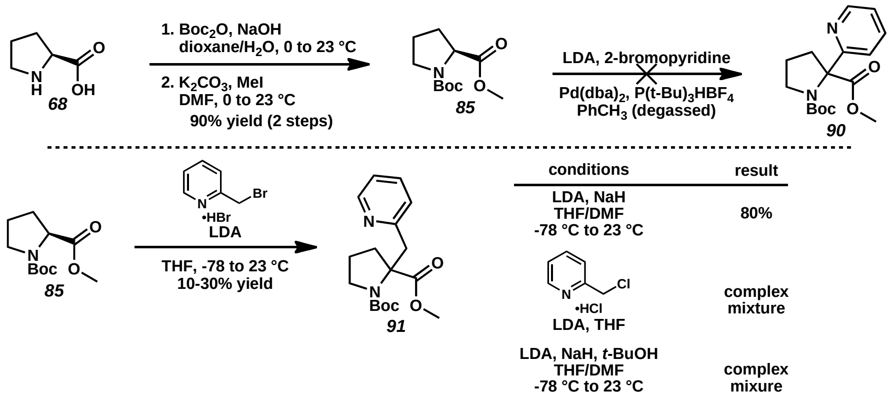
To the carbamate (2.00 g, 9.29 mmol) in DMF (9.30 mL) was added K_2CO_3 (1.41 g, 10.2 mmol) at 0 °C. The suspension was stirred 10 min at 0 °C, then MeI (1.20 mL, 18.6 mmol) was added at 0 °C and stirred for an additional 30 min at 0 °C, then 3 h at room temperature. The reaction mixture was filtered, then partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude mixture was purified via flash chromatography (1:3 EtOAc:hexanes) to give **85** (2.09 g, 98% yield, R_f = 0.60 in 1:1 EtOAc:hexanes) as a clear oil.

Aldehyde 86: To a solution of diisopropylamine (0.365 mL, 2.60 mmol) in THF (2.00 mL) at -78 °C was added *n*-BuLi (1.01 mL, 2.52 mmol, 2.5 M in hexanes). The mixture was stirred for 10 min at -78 °C. To this solution was added **85** (0.385 g, 1.68 mmol) in THF (2.80 mL) at -78 °C. The reaction was stirred an additional 30 min at -78 °C, at which time ethyl formate (0.543 mL, 6.72 mmol) was added at -78 °C. The reaction was warmed to -30 °C over 6 h. The reaction was quenched with citric acid (10 mL, 10%). The aqueous was extracted with EtOAc (2 x 10 mL). The organic layers were washed with brine (15 mL), dried over Na_2SO_4 and concentrated. The crude mixture was purified via flash chromatography (6:1 to 7:3 hexanes:EtOAc) to afford **86** (0.303 g, 70% yield, R_f = 0.50 in 1:1 hexanes:EtOAc) as a clear oil.

Oxazoline 87: To a solution of **86** (303 mg, 1.18 mmol) in *t*-BuOH (11.8 mL) was added 3-amino-3-methyl propanol (125 μL, 1.30 mmol) at 23 °C and stirred for 1 h. K_2CO_3 (489 mg, 3.54 mmol) and I_2 (599 mg, 2.36 mmol) were added to the reaction at 23 °C, then heated to 70 °C for 18 h. Na_2SO_3 was added until the I_2 color had disappeared. The aqueous was extracted with Et_2O (3 x 15 mL). The organic layers were washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (4:1 to 3:2 hexanes:EtOAc) to afford **87** (0.254 g, 67% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a light yellow solid.

Amine 88: To a solution of **87** (211 mg, 0.645 mmol) in CH_3CN (2.60 mL) was added CAN (70.8 mg, 0.129 mmol) and refluxed for 2 h. Additional CAN (94.7 mg, 0.173 mmol) was added and refluxed overnight. The mixture was concentrated under reduced pressure. The residue was suspended between sat. aq. $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated. The crude mixture was purified via flash chromatography (1:1 hexanes:EtOAc to 90:5:5 EtOAc:MeOH:Et_3N) to afford **88** (66.7 mg, 46% yield, $R_f = 0.0$ in 1:1 hexanes:EtOAc) as a yellow oil.

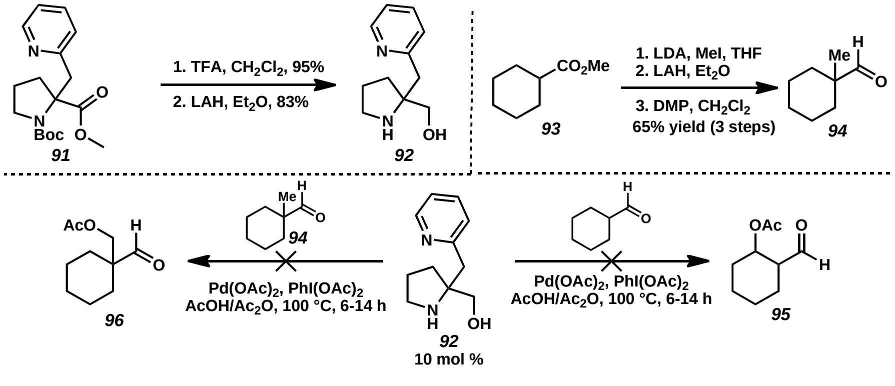
Amino alcohol 89: To a solution of LAH (28.0 mg, 0.737 mmol) in Et_2O (2.00 mL) was added **88** (66.7 mg, 0.295 mmol) in Et_2O (1.00 mL) at 0 °C. The reaction was stirred at 23 °C overnight. The reaction was cooled to 0 °C and H_2O (28.0 μL), 15% NaOH (28.0 μL) and H_2O (84.0 μL) were added sequentially. The mixture was stirred for 1 h, forming a white precipitate. The precipitate was filtered with EtOAc and the organic layer dried over Na_2SO_4 and concentrated. No product was observed by ^1H NMR.


68
1. Boc2O, NaOH
dioxane/H2O, 0 to 23 °C
2. K2CO3, MeI
DMF, 0 to 23 °C
90% yield (2 steps)
85
LDA, 2-bromopyridine
Pd(dba)2, P(t-Bu)3HBF4
PhCH3 (degassed)
90
85
•HBr
LDA
THF, -78 to 23 °C
10-30% yield
91
conditions
result
LDA, NaH
THF/DMF
-78 °C to 23 °C
80%
•HCl
LDA, THF
complex
mixture
LDA, NaH, t-BuOH
THF/DMF
-78 °C to 23 °C
complex
mixure

Pyridine 90: To a solution of diisopropylamine (75.1 μL, 0.535 mmol) in toluene (degassed) (1.00 mL) at -78 °C was added *n*-BuLi (0.210 mL, 0.515 mmol, 2.5 M in hexanes). After stirring for 10 min at -78 °C, **85** (100 mg, 0.436 mmol) in toluene (degassed) (1.50 mL) was added at -78 °C and stirred for 20 min at 0 °C. This solution was added to $Pd(dba)_2$ (11.4 mg, 0.0198 mmol), $P(t\text{-}Bu)_3HBF_4$ (5.7 mg, 0.0198 mmol) and 2-bromopyridine (38.7 μL, 0.396

mmol) in toluene (degassed) (0.500 mL) at 23 °C and stirred overnight. The solvent was removed under reduced pressure. No product was observed by ^{1}H NMR.

Pyridine 91: To a solution of freshly distilled diisopropylamine (479 μL, 3.41 mmol) in THF (4 mL) at -78 ˚C was added *n*-BuLi (1.7 mL, 1.9 M in hexanes, 3.27 mmol). The solution was stirred for 10 min at -78 ˚C, at which time **85** (750 mg, 3.27 mmol) in THF (4.2 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To NaH (327 mg, 8.18 mmol) (which was first washed with hexanes (2 x 1.5 mL)), in DMF (7.0 mL) at 0 ˚C was added 2-bromomethyl pyridine hydrobromide (690 mg, 2.73 mmol). The suspension was stirred at 0 ˚C for 30 min at which time it was added quantitatively, with additional DMF (1.2 mL), to the enolate solution at -78 ˚C. The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched with H_2O (20 mL) slowly at first at 23 ˚C. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (1:3 to 3:7 EtOAc/Hexanes eluent) to afford **91** (0.684 g, 78% yield, R_f = 0.33 in 1:1 EtOAc:hexanes) as a yellow solid.


91
1. TFA, CH2Cl2, 95%
2. LAH, Et2O, 83%
92
93
1. LDA, MeI, THF
2. LAH, Et2O
3. DMP, CH2Cl2
65% yield (3 steps)
94
96
94
Pd(OAc)2, PhI(OAc)2
AcOH/Ac2O, 100 °C, 6-14 h
92
10 mol %
Pd(OAc)2, PhI(OAc)2
AcOH/Ac2O, 100 °C, 6-14 h
95

Amino alcohol 92: To a solution of **91** (44.6 mg, 0.139 mmol) in CH_2Cl_2 (0.300 mL) at 23 °C was added TFA (214 μL, 2.78 mmol). The reaction was stirred at 23 °C for 1 h. The solvent was removed under reduced pressure. The crude residue was neutralized with sat. aq. $NaHCO_3$.

The aqueous layer was extracted with $CHCl_3$ (3 x 5 mL), the organic layers dried over Na_2SO_4 and concentrated to afford amine (35.3 mg, 99% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a brown solid.

To a solution of LAH (147 mg, 3.87 mmol) in Et_2O (7.00 mL) was added amine (341 mg, 1.55 mmol) in Et_2O (8.50 mL) at 0 °C. The reaction was stirred at 23 °C for 1 h. The reaction was cooled to 0 °C and H_2O (147 μL), 15% NaOH (147 μL) and H_2O (441 μL) were added sequentially. The mixture was stirred for 1 h, forming a white precipitate. The precipitate was filtered with EtOAc and the organic layer dried over Na_2SO_4 and concentrated. The crude mixture was purified via flash chromatography (90:5:5 EtOAc:Et_3N:MeOH) to afford **92** (0.246 g, 83% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a clear oil, which began to turn yellow over exposure to air.

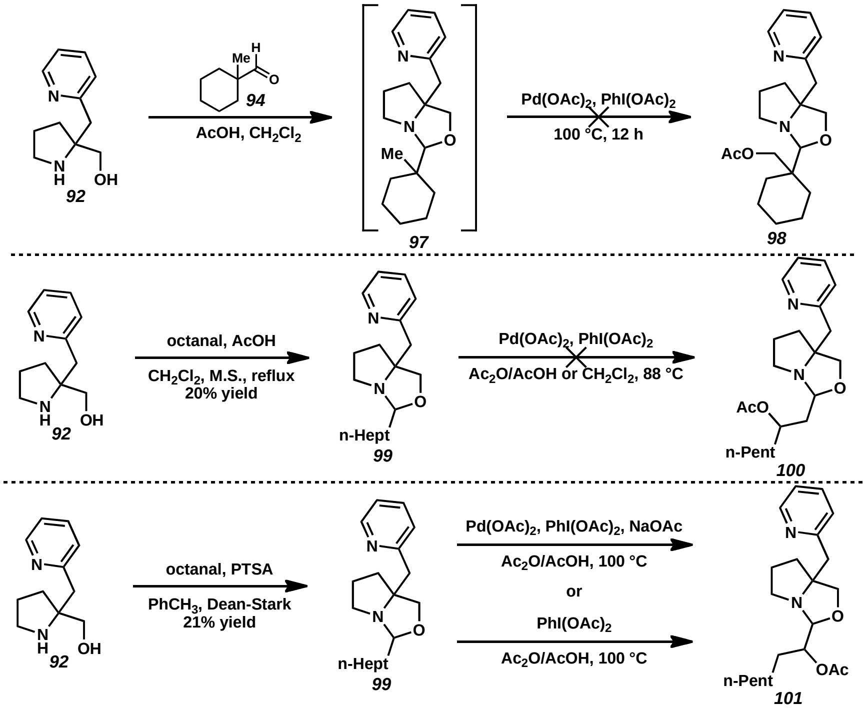
Aldehyde 94: To a solution of diisopropylamine (6.13 mL, 43.3 mmol) in THF (32.0 mL) at -78 °C was added *n*-BuLi (26.1 mL, 41.7 mmol, 1.6 M in hexanes). The solution was stirred at -78 C for 5 min, then at 0 °C for 10 min. To this solution at -78 °C was added **93** (5.00 mL, 35.3 mmol). The reaction was stirred at 0 °C for 1 h. To this solution at 0 °C was added MeI (2.0 mL, 32.1 mmol) dropwise. The reaction was stirred at 0 °C for an additional 30 min, then quenched with H_2O (15 mL). The aqueous layer was extracted with ether (4 x 30 mL). The combined organic layers were washed with HCl (50 mL, 10%), brine (50 mL) and H_2O (50 mL), dried over Na_2SO_4 and concentrated to afford the **94a** (4.60 g, 83% yield, Rf = 0.71 in 1:9 hexanes:EtOAc) as a yellow oil.

To a suspension of LAH (1.67 g, 44.1 mmol) and THF (50.0 mL) at 0 °C was added **94a** (4.60 g, 29.4 mmol) in THF (10.0 mL). The reaction was warmed to 23 °C and stirred for 1.5 h. The reaction was cooled to 0 °C and H_2O was added until bubbling stopped. H_2SO_4 (1.00 mL, 10%)

was added and stirred for 15 min. The mixture was filtered with EtOAc and the organic layer was washed with brine. The aqueous layer was extracted with EtOAc, the combined organic layers dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (9:1 to 6:1 hexanes:EtOAc) to afford **94b** (3.54 g, 94% yield, $R_f = 0.17$ in 9:1 hexanes:EtOAc) as a clear oil.

To a stirring solution of DMP (3.69 g, 8.59 mmol) in CH_2Cl_2 (40.0 mL) was added **94b** (0.999 g, 7.81 mmol) as a solution in CH_2Cl_2 (20.0 mL). The reaction was stirred at 23 °C for 1 h. Ether was added to the mixture, which was then added to NaOH (50 mL, 1 M) and stirred for 10 min. The ether layer was washed with 1 M NaOH and H_2O. The organic layer was dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (6:1 hexanes:ether) to afford **95** as a clear oil.

General procedure for functionalization: Aldehyde (1 equiv), ligand **92** (10 mol %), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.1 equiv) and $AcOH/Ac_2O$ (1:1, 0.12 M) were combined in a vial and stirred at 100 °C for the allotted time. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. No functionalized aldehydes were observed by ^1H NMR.


92
94
Me
H
O
AcOH, CH$_2$Cl$_2$
97
Pd(OAc)$_2$, PhI(OAc)$_2$
100 °C, 12 h
98
AcO
octanal, AcOH
CH$_2$Cl$_2$, M.S., reflux
20% yield
99
n-Hept
Pd(OAc)$_2$, PhI(OAc)$_2$
Ac$_2$O/AcOH or CH$_2$Cl$_2$, 88 °C
100
n-Pent
octanal, PTSA
PhCH$_3$, Dean-Stark
21% yield
Pd(OAc)$_2$, PhI(OAc)$_2$, NaOAc
Ac$_2$O/AcOH, 100 °C
or
PhI(OAc)$_2$
Ac$_2$O/AcOH, 100 °C
101
OAc
N
H
OH
O

Acetate 98: To **92** (27.7 mg, 0.219 mmol) and **94** (42.1 mg, 0.219 mmol) in CH$_2$Cl$_2$ (2.20 mL) was added AcOH (2.0 μL) and heated to 100 °C for 7 h. The reaction was concentrated under reduced pressure, then concentrated from toluene (2 x 2 mL). To Pd(OAc)$_2$ (4.9 mg, 0.0219 mmol) and PhI(OAc)$_2$ (106 mg, 0.329 mmol) was added the crude residue in CH$_2$Cl$_2$ (2.20 mL) and AcOH (2.0 μL) and heated to 100 °C for 12 h. The solvent was removed under reduced pressure. No functionalized product was observed by ^{1}H NMR.

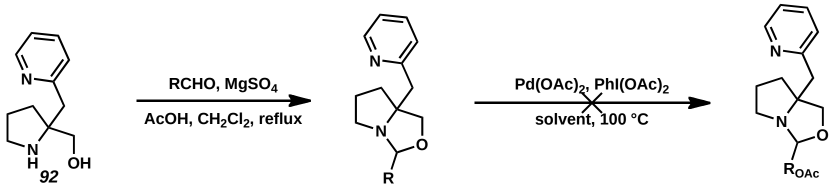
Acetal 99: To a solution of **92** (0.189 g, 0.983 mmol) in CH$_2$Cl$_2$ (9.83 mL) and 4 Å molecular sieves was added octanal (0.184 mL, 1.18 mmol) and AcOH (5.6 μL, 0.0983 mmol) and heated to reflux overnight. The reaction was washed with sat. aq. NaHCO$_3$, dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified via flash chromatography (7:3 to 1:1 hexanes:EtOAc) to afford **99** (59.8 mg, 20% yield, R$_f$ = 0.20 in 1:1 hexanes:EtOAc) as a clear oil.

Acetate 100: To $Pd(OAc)_2$ (2.2 mg, 9.89 μmol) and $PhI(OAc)_2$ (35.0 mg, 0.109 mmol) was added **99** (29.9 mg, 0.0989 mmol) and Ac_2O/AcOH (1:1, 0.800 mL). The mixture was heated to 88 °C for 13 h. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. No functionalized aldehydes were observed by ^1H NMR.

Acetal 99: To a solution of **92** (180 mg, 0.937 mmol) in toluene (4.00 mL) was added PTSA (3.6 mg, 0.0187 mmol) and octanal (0.190 mL, 1.22 mmol). The reaction was heated to reflux with azeotropic removal of water overnight. The reaction was washed with sat. aq. $NaHCO_3$ (2 x 10 mL) and dried over $MgSO_4$ and concentrated to afford **99** (60.6 mg, 21% yield, $R_f = 0.20$ in 1:1 hexanes:EtOAc) as a clear oil.

Acetate 101: To $Pd(OAc)_2$ (1.1 mg, 4.96 μmol) and $PhI(OAc)_2$ (17.6 mg, 0.0546 mmol) was added **99** (15.0 mg, 0.0496 mmol), NaOAc (2.0 mg, 0.0248 mmol) and Ac_2O/AcOH (1:1, 0.400 mL). The mixture was heated to 100 °C for 13 h. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Acetate **101** was observed by crude ^1H NMR.

Acetate 101: To $PhI(OAc)_2$ (17.6 mg, 0.0546 mmol) was added **99** (15.0 mg, 0.0496 mmol) and AcOH/Ac_2O (1:1, 0.400 mL) and heated to 100 °C for 4 h. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Acetate **101** was observed by crude ^1H NMR.


N
H
OH
92
RCHO, MgSO$_4$
AcOH, CH$_2$Cl$_2$, reflux
N
N
O
R
Pd(OAc)$_2$, PhI(OAc)$_2$
solvent, 100 °C
N
N
O
R$_{OAc}$

aldehyde	yield	funct. conditions	result
i-PrCHO	31%	DCE, 16 h	complex mixture
i-BuCHO	20%	DCE 16 h	complex mixture
CyCHO	31%	Ac_2O/AcOH, 12 h	complex mixture
		CH_3CN, 17 h	complex mixture
		$PhCH_3$, 17 h	complex mixture

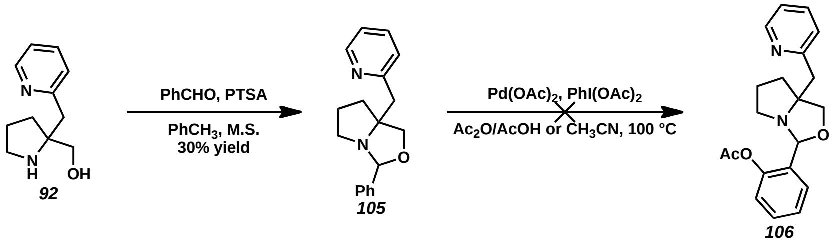
General procedure for forming acetals: To **92** (1 equiv) in CH_2Cl_2 (0.1 M) was added aldehyde (1.3 equiv) and AcOH (0.1 equiv) and the reaction heated to reflux overnight. The reaction was washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated.

Acetal 102: 31% yield, $R_f = 0.20$ in 1:1 hexanes:EtOAc

Acetal 103: 20% yield, $R_f = 0.22$ in 1:1 hexanes:EtOAc

Acetal 104: 31% yield, $R_f = 0.25$ in 1:1 hexanes:EtOAc

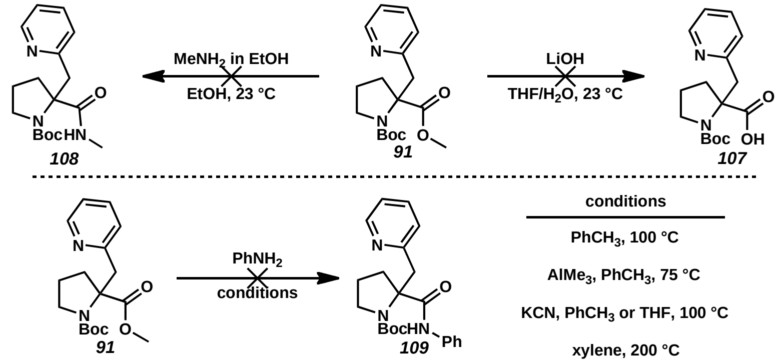
General procedure for acetoxylation: To acetal (1.0 equiv) was added $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.6 equiv) and solvent (0.12 M) and stirred at 100 °C for the allotted time. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. No acetoxylated product was observed by ^{1}H NMR.


N
H
OH
92
PhCHO, PTSA
PhCH$_3$, M.S.
30% yield
N
N
O
Ph
105
Pd(OAc)$_2$, PhI(OAc)$_2$
Ac$_2$O/AcOH or CH$_3$CN, 100 °C
N
N
O
AcO
106

Acetal 105: To a solution of **92** (0.100 g, 0.520 mmol) in toluene (2.10 mL) and 4 Å molecular sieves was added benzaldehyde (68.4 μL, 0.677 mmol) and PTSA (2.0 mg, 0.0104 mmol) and heated to reflux overnight. The reaction was washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 to 7:3

hexanes:EtOAc) to afford **105** (19.3 mg, 13% yield, R_f = 0.22 in 1:1 hexanes:EtOAc) as a clear oil.

Acetate 106: To acetal **105** (13.7 mg, 0.0489 mmol) was added $Pd(OAc)_2$ (1.1 mg, 4.90 μmol) $PhI(OAc)_2$ (17.3 mg, 0.0538 mmol) and $AcOH/Ac_2O$ or CH_3CN (1:1, 0.400 mL) and stirred at 100 °C for 14 h. The reaction was filtered through a plug of glass wool and diluted with pentane. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. No acetoxylated product was observed by ^{1}H NMR.


MeNH₂ in EtOH
EtOH, 23 °C
LiOH
THF/H₂O, 23 °C
108
91
107
PhNH₂
conditions
91
109
conditions
PhCH₃, 100 °C
AlMe₃, PhCH₃, 75 °C
KCN, PhCH₃ or THF, 100 °C
xylene, 200 °C

Methyl amide 108: To $MeNH_2$ (0.12 mL, 8.0 M in ethanol) was added **91** (100 mg, 0.312 mmol) in EtOH (1.20 mL) at 23 °C. The reaction was stirred at 23 °C overnight. The solvent was removed under reduced pressure. No product was observed by ^{1}H NMR.

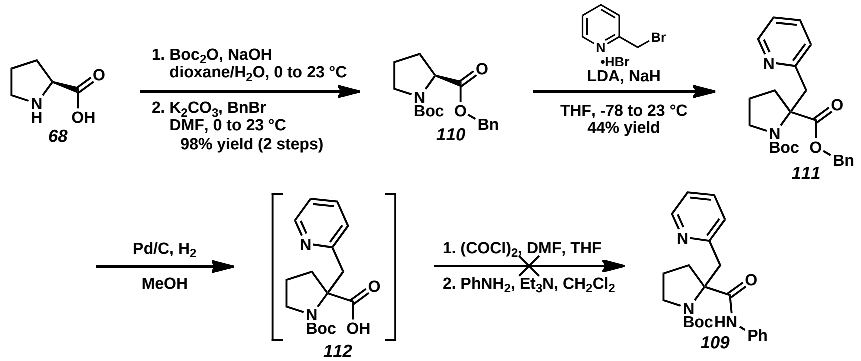
Acid 107: To **91** (1.37 g, 4.28 mmol) in THF (8.56 mL) and H_2O (4.30 mL) was added LiOH (103 mg, 4.28 mmol). The reaction was stirred at 23 °C overnight. The solvent was removed under reduced pressure. The solution was acidified to pH 2 with 1 M HCl. The aqueous was extracted with EtOAc (3 x 20 mL), the organic layers dried over Na_2SO_4 and concentrated. No product was observed by ^{1}H NMR.

Phenyl amide 109: To a solution of aniline (50.6 μL, 0.555 mmol) in toluene (2.00 mL) at 0 °C was added $AlMe_3$ (0.280 mL, 2.0 M in toluene) dropwise over 15 min. Stirred for 1 h at 23 °C. To this solution was added **91** (84.6 mg, 0.264 mmol) in toluene (2.00 mL) at 23 °C. The reaction was heated to 75 °C for 18 h. The reaction was poured slowly into a mixture of conc. HCl (1.3 M), ice and EtOAc (1 M). The aqueous layer was extracted with EtOAc (3 x 10 mL), the organics dried over $MgSO_4$ and concentrated. No product formation by ^{1}H NMR.

Phenyl amide 109: **91** (25.0 mg, 0.0781 mmol), aniline (35.0 μL, 0.390 mmol) and toluene (1.60 mL) were combined in a sealed vial and heated to 100 °C for 24 h. The solvent was removed under reduced pressure. No product formation by ^{1}H NMR.

Phenyl amide 109: To **91** (30.0 mg, 0.0937 mmol) and KCN (0.6 mg, 3.37 μmol) in toluene or THF (0.900 mL) was added aniline (42.0 μL, 0.468 mmol) at 23 °C. The mixture was heated to 100 °C overnight. The solvent was removed under reduced pressure. No product formation by ^{1}H NMR.

Phenyl amide 109: **91** (25.0 mg, 0.0781 mmol) aniline (35.0 μL, 0.390 mmol) and xylene (0.800 mL) were combined in a 2-dram vial and heated to 250 °C overnight. The solvent was removed under reduced pressure. No product formation by ^{1}H NMR.

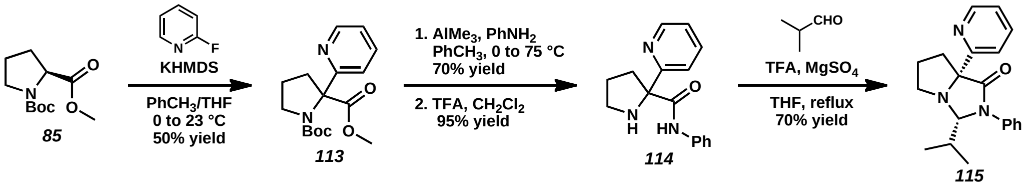

68
1. Boc2O, NaOH
dioxane/H2O, 0 to 23 °C
2. K2CO3, BnBr
DMF, 0 to 23 °C
98% yield (2 steps)
110
•HBr
LDA, NaH
THF, -78 to 23 °C
44% yield
111
Pd/C, H2
MeOH
112
1. (COCl)2, DMF, THF
2. PhNH2, Et3N, CH2Cl2
109

Ester 110: To **119** (2.00 g, 9.29 mmol) in DMF (18.6 mL) was added K_2CO_3 (1.41 g, 10.2 mmol) at 0 °C. The suspension was stirred 10 min at 0 °C, then BnBr (2.20 mL, 13.9 mmol) was added at 0 °C and stirred for an additional 30 min at 0 °C, then 3 h at room temperature. The reaction mixture was filtered, then partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude mixture was purified via flash chromatography (1:3 EtOAc:hexanes) to give **110** (2.83 g, 99% yield, $R_f = 0.25$ in 4:1 EtOAc:hexanes) as a clear oil.

Pyridine 111: To a solution of freshly distilled diisopropylamine (246 μL, 1.75 mmol) in THF (2.00 mL) at -78 ˚C was added *n*-BuLi (0.730 mL, 2.3 M in hexanes, 1.68 mmol). The solution was stirred for 10 min at -78 ˚C, at which time **110** (512 mg, 1.68 mmol) in THF (2.20 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To NaH (168 mg, 4.19 mmol) (which was first washed with hexanes (2 x 1.0 mL)), in DMF (3.20 mL) at 0 ˚C was added 2-bromomethyl pyridine hydrobromide (354 mg, 1.39 mmol). The suspension was stirred at 0 ˚C for 30 min at which time it was added quantitatively, with additional DMF (1.0 mL), to the enolate solution at -78 ˚C. The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched with H_2O (10 mL) slowly at first at 23 ˚C. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (1:3 to 3:7 EtOAc/Hexanes eluent) to afford **111** (0.227 g, 41% yield, $R_f = 0.35$ in 1:1 EtOAc:hexanes) as a yellow oil.

Acid 112: To **111** (325 mg, 0.820 mmol) in MeOH (3.30 mL) was added Pd/C (33.0 mg). The flask was flushed with H_2, then an H_2 balloon was fitted until the reaction was complete by TLC. The reaction mixture was filtered through celite with MeOH. The organics were concentrated to afford **112** (0.296 g) by crude ^{1}H NMR.

Amide 109: To **112** (240 mg, 0.793 mmol) in THF (4.00 mL) was added $(COCl)_2$ (0.346 mL, 3.96 mmol) and DMF (4 drops) at 0 °C. After 5 min the reaction was warmed to 23 °C and stirred for 1 h. The solvent was removed and concentrated from benzene (2 x 5 mL). To aniline (0.289 mL, 3.17 mmol) and triethylamine (0.334 mL, 2.38 mmol) in CH_2Cl_2 (3.40 mL) at 0 °C was added the acid chloride in CH_2Cl_2 (4.00 mL). The reaction, black in color, was stirred at 23 °C for 1h. The reaction was washed with $KHSO_4$ (10 mL, 1 M), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL) sequentially. The organic layer was dried over Na_2SO_4 and concentrated. No product was observed via crude ^1H NMR.

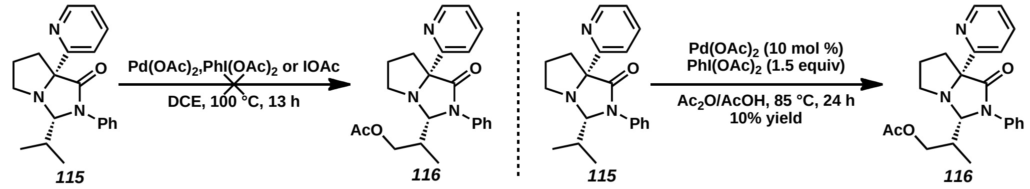


Pyridine 113: To a solution of **85** (1.58 g, 6.90 mmol) and 2-fluoropryidine (0.590 mL, 6.90 mmol) in $PhCH_3$ (23.0 mL) at 0 °C was added KHMDS (13.8 mL, 6.90 mmol, 0.5 M in THF) dropwise over 1 h. The reaction was stirred for 1 h at 0 °C, then 23 °C for 24 h. The reaction was filtered through a plug of silica gel and concentrated. The crude residue was purified via flash chromatography (4:1 to 3:1 hexanes:EtOAc) to afford **113** (1.03g, 48% yield, R_f = 0.38 in 1:1 hexanes:EtOAc) as a yellow oil.

To a solution of aniline (644 μL, 7.07 mmol) in toluene (3.40 mL) at 0 °C was added $AlMe_3$ (3.50 mL, 2.0 M in toluene) dropwise over 15 min. Stirred for 1 h at 23 °C. To this solution was added **113** (1.03 g, 3.37 mmol) in toluene (6.70 mL) at 23 °C. The reaction was heated to 75 °C for 18 h. The reaction was poured slowly into a mixture of conc. HCl (1.3 M), ice and EtOAc (1 M). The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (7:3 to 3:2 hexanes:EtOAc) to afford amide (0.857 g, 69% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as thick yellow oil.

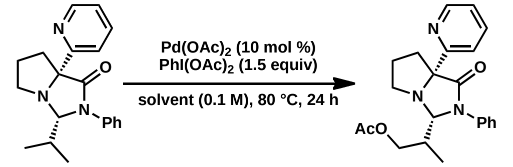
Amino amide 114: To amide (0.857 g, 2.33 mmol) in CH_2Cl_2 (4.70 mL) at 23 °C was added TFA (3.60 mL, 46.6 mmol). The reaction was stirred for 1 h at 23 °C. The solvent was removed under reduced pressure. The crude residue was neutralized with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 15 mL), dried over Na_2SO_4 and concentrated to afford **114** (623 mg, 99% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a pale yellow solid.

Aminal 115: To **114** (100 mg, 0.374 mmol), $MgSO_4$ (67.5 mg, 0.561 mmol) and isobutyraldehyde (44.4 μL, 0.486 mmol) in THF (4.00 mL) was added TFA (5.8 μL, 0.0748 mmol) at 23 °C. The reaction was heated to reflux overnight. The solvent was removed under reduced pressure. The residue was taken up in sat. aq. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (7:3 to 3:2 hexanes:EtOAc with 1% Et_3N) to afford **115** (103 mg, 86% yield, R_f = 0.31 in 1:1 hexanes:EtOAc) as a light beige solid.



115
Pd(OAc)2,PhI(OAc)2 or IOAc
DCE, 100 °C, 13 h
116
115
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
10% yield
116

temp °C	115 : 116
110	1.0 : 0
70	5.9 : 1
75	6.0 : 1
80	2.8 : 1
85	2.7 : 1 (10% yield)

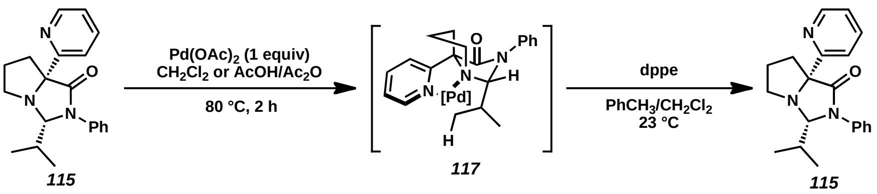


Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
solvent (0.1 M), 80 °C, 24 h

115 **116**

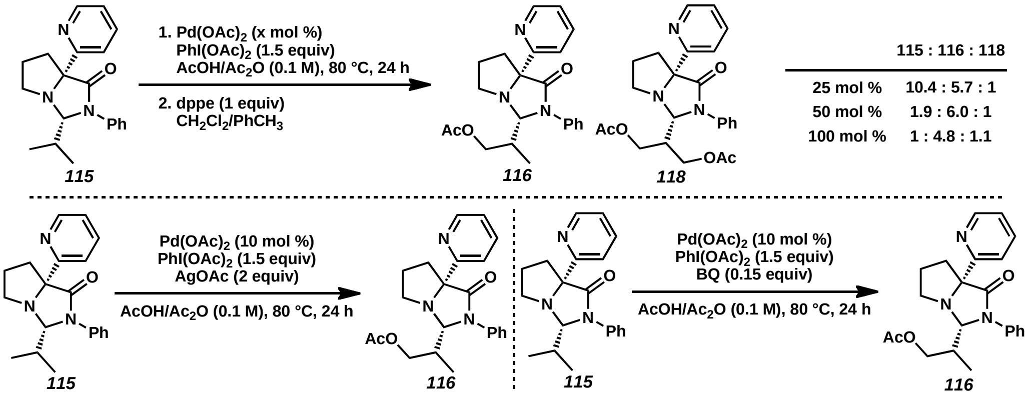
solvent	115 : 116	solvent (1:1)	115 : 116	solvent (1:1)	115 : 116
DCE	1.0 : 0	DCE:Ac_2O	1.0 : 0	DCE:AcOH	1.0 : 0
$PhCH_3$	1.0 : 0	$PhCH_3$:Ac_2O	1.0 : 0	$PhCH_3$:AcOH	1.0 : 0
PhH	1.0 : 0	PhH:Ac_2O	1.0 : 0	CH_3CN:AcOH	6.0 : 1
CH_3CN	1.0 : 0	CH_3CN:Ac_2O	1.0 : 0		
CH_2Cl_2	1.0 : 0	CH_2Cl_2:Ac_2O	1.0 : 0		

General procedure for acetoxylation: $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.5 equiv) and **115** (1 equiv) were combined with solvent (0.1 M) in a 2-dram vial and heated to the noted temperature for the allotted time. The reaction was neutralized with sat. aq. $NaHCO_3$. The aqueous was extracted with CH_2Cl_2 (3x), the organics dried over Na_2SO_4 and concentrated. Ratios were assigned by crude ^{1}H NMR.



Pd(OAc)2 (1 equiv)
CH2Cl2 or AcOH/Ac2O
80 °C, 2 h
dppe
PhCH3/CH2Cl2
23 °C
[Pd]
N
O
Ph
H
115
117
115

To **115** (10.0 mg, 0.0311 mmol) and $Pd(OAc)_2$ (7.0 mg, 0.0311 mmol) was added Ac_2O/AcOH (1:1, 0.300 mL) in a 2-dram vial, and the reaction was heated to 80 °C for 24 h. The solvent was removed by azeotropic evaporation from heptanes (3 x 2 mL). The residue was treated with dppe (12.4 mg, 0.0311 mmol) and CH_2Cl_2/toluene (1:1, 0.311 mL) at 23 °C for 24 h. The solvent was removed under reduced pressure. ^{1}H NMR revealed the product to be **115**.



1. Pd(OAc)2 (x mol %)
PhI(OAc)2 (1.5 equiv)
AcOH/Ac2O (0.1 M), 80 °C, 24 h
2. dppe (1 equiv)
CH2Cl2/PhCH3
115 : 116 : 118
25 mol % 10.4 : 5.7 : 1
50 mol % 1.9 : 6.0 : 1
100 mol % 1 : 4.8 : 1.1
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
AgOAc (2 equiv)
AcOH/Ac2O (0.1 M), 80 °C, 24 h
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
BQ (0.15 equiv)
AcOH/Ac2O (0.1 M), 80 °C, 24 h
AcO
OAc
Ph
115
116
118
115
116
115
116

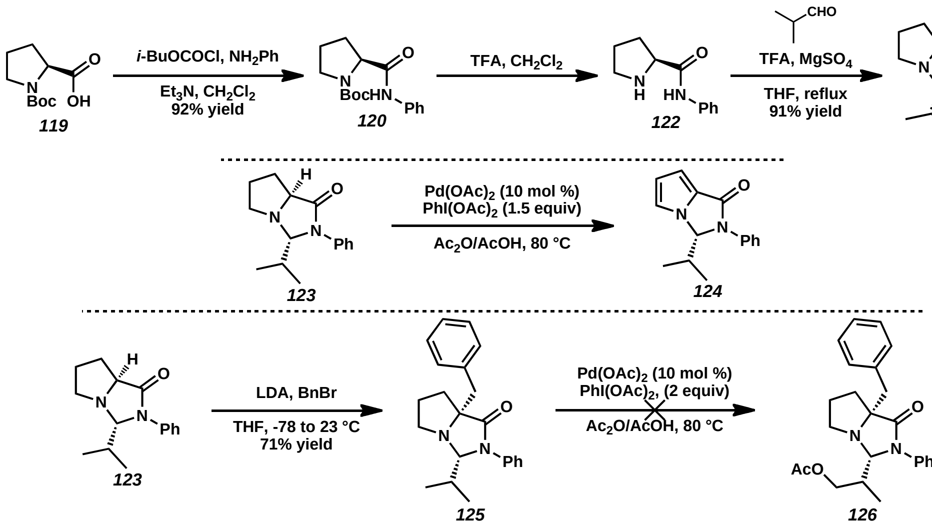
General procedure for acetoxylation: **115** (1 equiv), $Pd(OAc)_2$ (25-100 mol %) and $PhI(OAc)_2$ (1.5 equiv) were combined with AcOH/Ac_2O (1:1, 0.1 M) and heated to 80 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). The residue was treated with 1,2-bis(diphenylphosphino)ethane (1 equiv) in $PhCH_3$/CH_2Cl_2 (1:1, 0.1 M) and stirred overnight at 23 ˚C. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (4:1 → 3:1 hexanes/acetone eluent) to afford acetate **116** and diacetate **118**.

Pyridine **116** (200 mg, 0.622 mmol), $Pd(OAc)_2$ (69.8 mg, 0.311 mmol), and $PhI(OAc)_2$ (351 mg, 1.10 mmol) were dissolved in AcOH (3.10 mL) and Ac_2O (3.10 mL) in a round-bottomed flask. The flask was capped and heated to 85 ˚C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 15 mL). The residue was treated with 1,2-bis(diphenylphosphino)ethane (249 mg, 0.622 mmol) in $PhCH_3/CH_2Cl_2$ (1:1, 6.20 mL) and stirred overnight at 23 ˚C. The solvent was removed by rotary evaporation, and the crude residue was purified by flash chromatography (4:1 → 3:1 hexanes/acetone eluent) to afford acetate **120** (156 mg, 66% yield, $R_f = 0.45$ in 1:1 hexanes/acetone) as a light yellow oil and diacetate **121** (36.0 mg, 13% yield, $R_f = 0.43$ in 1:1 hexanes/acetone) as a light yellow oil.

Acetate 120: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.6 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.46-7.37 (comp m, 4H), 7.24-7.18 (comp m, 2H), 4.77 (d, *J* = 3.4 Hz, 1H), 3.80 (dd, *J* = 6.5, 3.1 Hz, 2H), 3.53 (dt, *J* = 10.7, 6.4 Hz, 1H), 3.05 (dt, *J* = 11.1, 5.7 Hz, 1H), 2.52 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.39 (dt, *J* = 13.3, 6.7 Hz, 1H), 2.14-1.83 (comp m, 3H), 1.82 (s, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.6, 149.3, 136.7, 136.5, 129.1, 126.2, 124.1, 122.2, 120.6, 98.4, 84.6, 77.6, 65.5, 59.4, 38.9, 36.2, 25.6, 20.7, 14.0; IR (film) 3061, 2967, 1735, 1701, 1497, 1408, 1237 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{22}H_{26}N_3O_3]^+$: 380.1969, found 380.1970.

Diacetate 121: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.75-7.67 (comp m, 2H), 7.47-7.39 (comp m, 4H), 7.23-7.19 (comp m, 2H), 5.02 (d, *J* = 3.9 Hz, 1H), 4.12 (dd, *J* = 11.3, 7.3 Hz, 1H), 4.04 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.95 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.85 (dd, *J* = 11.3, 7.3 Hz, 1H), 3.53 (dt, *J* = 10.6, 6.5 Hz, 1H), 3.04 (dt, *J* = 11.1, 5.8 Hz, 1H), 2.56 (dt, *J* =

13.3, 6.8 Hz, 1H), 2.40 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.30 (dddd, *J* = 7.2, 5.5, 3.9, 1.7 Hz, 1H), 2.03 (s, 3H), 2.02-1.97 (m, 1H), 1.89-1.85 (m, 1H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.4, 161.6, 149.4, 136.5, 136.2, 129.1, 126.4, 123.7, 122.3, 120.5, 80.5, 77.8, 62.0, 61.4, 59.1, 41.0, 38.9, 25.7, 20.8, 20.7; IR (film), 2961, 1738, 1703, 1588, 1226, 1039, 753, 697 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{28}N_3O_5]^+$: 438.2023, found 438.2023.



119
i-BuOCOCl, NH2Ph
Et3N, CH2Cl2
92% yield
120
TFA, CH2Cl2
122
CHO
TFA, MgSO4
THF, reflux
91% yield
123
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 80 °C
124
LDA, BnBr
THF, -78 to 23 °C
71% yield
125
Pd(OAc)2 (10 mol %)
PhI(OAc)2, (2 equiv)
Ac2O/AcOH, 80 °C
126

Amide 120: To a solution of **119** (2.50 g, 11.6 mmol) in CH_2Cl_2 (38.7 mL) at 0 ˚C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and triethylamine (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 ˚C, aniline (1.16 mL, 12.8 mmol) was added, and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was washed sequentially with aq. $KHSO_4$ (1 M, 50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 ˚C, and filtered to afford amide **120** (3.32 g, 98% yield, R_f = 0.52 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.

Amino amide 122: To a solution of amide **120** (3.32 g, 11.4 mmol) in CH_2Cl_2 (22.8 mL) at 23 ˚C was added TFA (17.6 mL, 228 mmol). The solution was stirred at 23 ˚C for 1 h, and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide **122** (2.20 g, 99% yield, R_f = 0.05 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.

Aminal 123: To a solution of amino amide **122** (1.50 g, 7.88 mmol) in $PhCH_3$ (26.3 mL) at 23 ˚C was added isobutyraldehyde (1.10 mL, 11.8 mmol), $TsOH{\cdot}H_2O$ (75.0 mg, 0.394 mmol), and $MgSO_4$ (1.40 g, 11.8 mmol). The suspension was heated to reflux and stirred overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL), and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford aminal **123** (1.75 g, 91% yield, R_f = 0.48 in 1:1 hexanes/EtOAc) as a light yellow solid, which was sufficiently pure to be taken on to the next step.

Aminal 123: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.1 Hz, 1H), 4.63 (app. s, 1H), 3.95 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.31-3.26 (m, 1H), 2.77 (app. q, *J* = 7.8 Hz, 1H), 2.23-2.15 (m, 1H), 2.06-1.97 (m, 1H), 1.90-1.86 (m, 1H), 1.84-1.78 (comp m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 136.8, 129.1, 125.7, 123.4, 87.9, 66.4, 58.5, 31.3, 28.9, 25.1, 18.4, 14.6; IR (film) 2963, 3053, 1683, 1504, 1411, 758, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{15}H_{20}N_2ONa]^+$: 267.1468, found 267.1468.

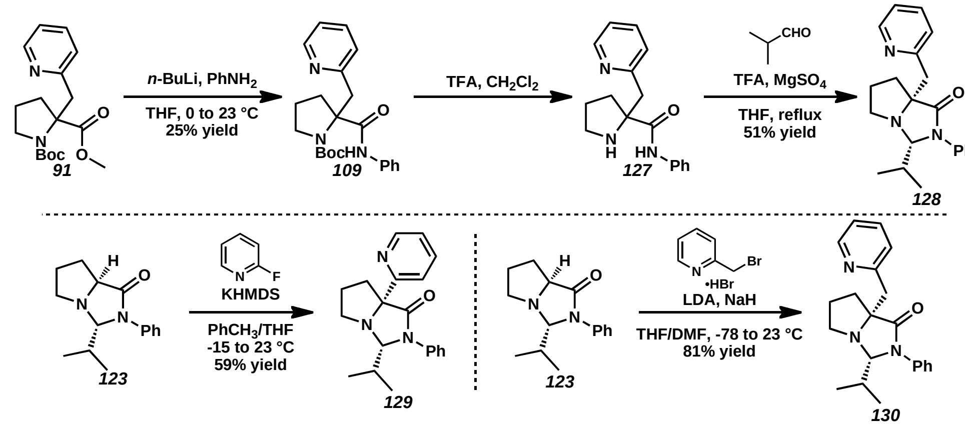
Pyrrole 124: **123** (10.0 mg, 0.0409 mmol), $Pd(OAc)_2$ (0.9 mg, 4.09 μmol) and $PhI(OAc)_2$ (19.8 mg, 0.0614 mmol) in $AcOH/Ac_2O$ (1:1, 0.400 mL) were heatd to 80 °C overnight. The solvent was removed by azeotropic removal with heptanes (3 x 5 mL). ^{1}H NMR revealed the pyrrole (**124**).

Aminal 125: To a solution of freshly distilled diisopropylamine (167 μL, 1.19 mmol) in THF (5.00 mL) at -78 ˚C was added *n*-BuLi (0.460 mL, 2.5 M in hexanes, 1.15 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **123** (200 mg, 0.818 mmol) in THF (3.20 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. Benzyl bromide (256 μL, 1.64 mmol) was added at -78 ˚C, and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was quenched with water (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (9:1 to 4:1 hexanes/EtOAc eluent) to afford aminal **125** (195 mg, 71% yield, R_f = 0.74 in 4:1 hexanes/EtOAc) as a white amorphous solid.

Aminal 125: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.36 (comp m, 6H), 7.30-7.20 (comp m, 4H), 4.48 (d, *J* = 2.8 Hz, 1H), 3.06 (ABq, *J* = 13.6 Hz, Δν = 76.8 Hz, 2H), 2.73-2.72 (comp m, 2H), 2.08-2.02 (m, 1H), 1.89-1.78 (comp m, 2H), 1.56-1.49 (m, 1H), 1.34-1.32 (m, 1H), 0.93 (d, *J* = 1.1 Hz, 3H), 0.72 (d, *J* = 3.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 137.6, 136.5, 131.0, 129.0, 127.9, 126.4, 126.1, 124.4, 86.9, 75.0, 58.8, 42.8, 34.5, 30.8, 24.8, 18.5, 14.8; IR (film) 3029, 2964, 1700, 1498, 1409, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{22}H_{27}N_2O]^+$: 335.2118, found 335.2120.

Acetate 126: Aminal **125** (20.0 mg, 0.0598 mmol), $Pd(OAc)_2$ (1.3 mg, 5.98 μmol), and $PhI(OAc)_2$ (28.9 mg, 0.0897 mmol) were dissolved in $AcOH/Ac_2O$ (1:1, 0.600 mL) in a scintillation vial. The vial was heated to 80 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (2 x 10 mL). Water (10 mL) was added to the residue, and the mixture was neutralized with solid Na_2CO_3 until pH ~9. The mixture was extracted with

CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Only starting material was observed by ^{1}H NMR.



n-BuLi, PhNH2
THF, 0 to 23 °C
25% yield
TFA, CH2Cl2
CHO
TFA, MgSO4
THF, reflux
51% yield
Boc
91
BocHN
109
127
128
KHMDS
PhCH3/THF
-15 to 23 °C
59% yield
123
129
•HBr
LDA, NaH
THF/DMF, -78 to 23 °C
81% yield
123
130

Amide 109: To aniline (210 μL, 2.35 mmol) in THF (15.4 mL) at -78 °C was added *n*-BuLi (0.85 mL, 2.5M in hexanes, 2.14 mmol). Stirred 10 min at -78 °C, then warmed to 0 °C. To this solution was added quickly **91** (684 mg, 2.14 mmol) in THF (6.00 mL) at 0 °C. The reaction was stirred 10 min at 0 °C, then quenched with H_2O (25 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organics were washed with brine (40 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (1:4 to 7:13 EtOAc:hexanes) to afford **109** (286 mg, 35% yield, R_f = 0.33 in 1:1 EtOAc:hexanes) as a red oil.

Amino amide 127: To **109** (286 mg, 0.75 mmol) in CH_2Cl_2 (1.50 mL) was added TFA (1.20 mL, 15.0 mmol) at room temperature. Stirred for 1 h at room temperature, then the solvent was removed. The residue was quenched with sat. aq. $NaHCO_3$ solution until pH 9, then the aqueous was extracted with CH_2Cl_2 (3 x 15 mL). Organics dried over Na_2SO_4 and concentrated to afford **127** (162 mg, 77% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a brown oil with no further purification necessary.

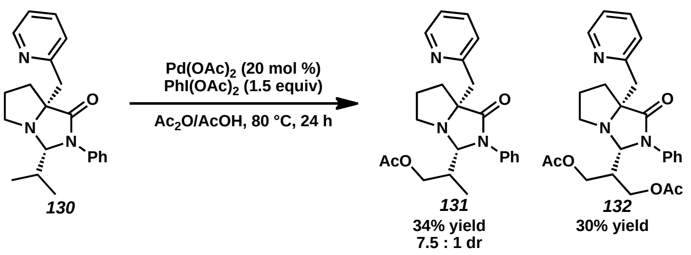
Aminal 128: To **127** (108 mg, 0.384 mmol) in THF (3.80 mL) was added isobutyraldehyde (53.0 μL, 0.576 mmol), TFA (6.0 μL, 0.0768 mmol) and $MgSO_4$ (69.3 mg, 0.576 mmol) at 23 °C. The suspension was refluxed overnight. Upon cooling, the reaction was quenched with sat. aq. $NaHCO_3$ solution (10 mL). The aqueous was extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (3:1 to 7:3 hexanes:EtOAc) to give **128** (65.6 mg, 51% yield,R_f = 0.74 in 40:1 EtOAc/MeOH) as a light brown solid.

Pyridine 129: To a solution of aminal **123** (500 mg, 2.04 mmol), 2-fluoropyridine (176 μL, 2.04 mmol) in $PhCH_3$ (10.2 mL) at -15 ˚C was added KHMDS (408 mg, 2.04 mmol) in THF (4.10 mL) slowly over 1 h. Upon completion of addition, the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction was filtered over a pad of silica (5 x 5 cm, 100 mL EtOAC eluent) and concentrated. The crude product was purified by flash chromatography (3:1 → 1:1 hexanes/EtOAc eluent) to afford pyridine **129** (385 mg, 59% yield, 148 mg recovered **123**: 83% yield, corrected, R_f = 0.31 in 1:1 hexanes/EtOAc) as a light beige solid.

Pyridine 129: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 3.7 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.64 (td, *J* = 7.7, 1.5 Hz, 1H), 7.41-7.34 (comp m, 4H), 7.21-7.13 (comp m, 2H), 4.64 (d, *J* = 3.1 Hz, 1H), 3.44 (dt, *J* = 10.9, 6.7 Hz, 1H), 3.03 (dt, *J* = 11.2, 5.7 Hz, 1H), 2.48 (app. t, *J* = 7.0 Hz, 2H), 1.93-1.81 (comp m, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.55 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 162.2, 149.4, 136.6, 136.0, 129.0, 126.1, 124.3, 121.8, 120.8, 86.4, 77.7, 59.1, 38.8, 31.1, 25.6, 18.4, 15.1; IR (film) 2962, 1701, 1587, 1497, 1407, 752 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{20}H_{24}N_3O]^+$: 322.1914, found 322.1914.

Pyridine 130: To a solution of freshly distilled diisopropylamine (177 μL, 1.30 mmol) in THF (3.00 mL) at -78 ˚C was added *n*-BuLi (0.480 mL, 2.5 M in hexanes, 1.20 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **123** (295 mg, 1.20 mmol) in THF (3.10 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (121 mg, 60% dispersion in mineral oil, 3.00 mmol, washed 2 x 1.0 mL with hexanes) in DMF (5.00 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (255 mg, 1.00 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.10 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched by slow addition of H_2O (20 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 35 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford pyridine **130** (272 mg, 81% yield, R_f = 0.74 in 40:1 EtOAc/MeOH) as a beige solid.

Pyridine 130: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 3.8 Hz, 1H), 7.62 (t, *J* = 6.8 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.40-7.34 (comp m, 4H), 7.23-7.19 (m, 1H), 7.15 (t, *J* = 5.6 Hz, 1H), 4.47 (d, *J* = 2.8 Hz, 1H), 3.27 (ABq, *J* = 13.2 Hz, Δν =18.5 Hz, 2H), 2.76 (app. s, 2H), 2.19-2.06 (comp m, 2H), 1.78-1.74 (m, 1H), 1.64-1.57 (m, 1H), 1.49-1.45 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.58 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 158.1, 148.8, 136.4, 129.0, 126.1, 125.3, 124.4, 121.5, 98.3, 86.4, 74.9, 58.4, 45.4, 34.9, 30.6, 24.7, 18.4, 14.3; IR (film) 2969, 2870, 1676, 1600, 1524, 1443, 755 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{21}H_{25}N_3ONa]^+$: 358.1890, found 358.1894.



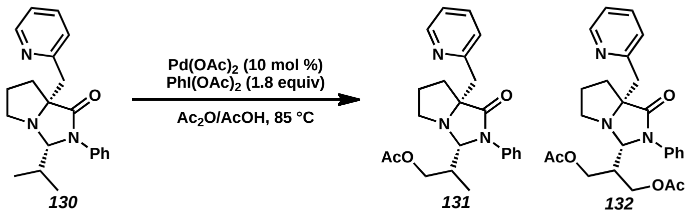
130

131
34% yield
7.5 : 1 dr

132
30% yield

conditions	*130 : 131 : 132*
$Pd(OAc)_2$ (10 mol %) $PhI(OAc)_2$ (1.0 equiv)	2.7 : 1.5 : 1.0
$Pd(OAc)_2$ (10 mol %) $PhI(OAc)_2$ (2.0 equiv) 80 °C 24 h	5.8 : 1.0 : 0
$Pd(OAc)_2$ (10 mol %) $PhI(OAc)_2$ (1.0 equiv) 40 °C 24 h	0 : 1.0 : 1.9

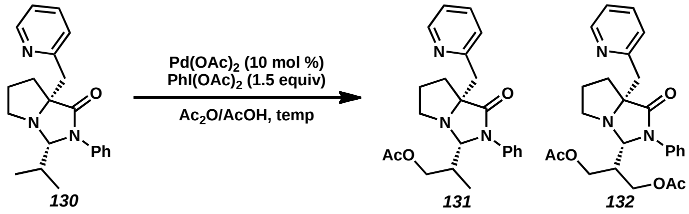
General procedure for acetoxylation: **130** (1 equiv), $Pd(OAc)_2$ (10-20 mol %) and $PhI(OAc)_2$ (1.0-1.5 equiv) in $AcOH/Ac_2O$ was heated to 40-80 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (3:1 → 1:1 hexanes/acetone eluent) to afford acetate **131** (R_f = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate **132** (R_f = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid. Ratios were determined by crude ^{1}H NMR.



130 ***131*** ***132***

time (h)	*130 : 131 : 132*
8	1 : 4.2 : 2.8
10	1 : 3.4 : 2.5
16	1 : 3.4 : 4.0
18	1 : 2.3 : 2.3

General procedure for acetoxylation: **130** (1 equiv), $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ (1.8 equiv) in $AcOH/Ac_2O$ was heated to 85 °C for the allotted time. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Ratios were determined by crude ^{1}H NMR.



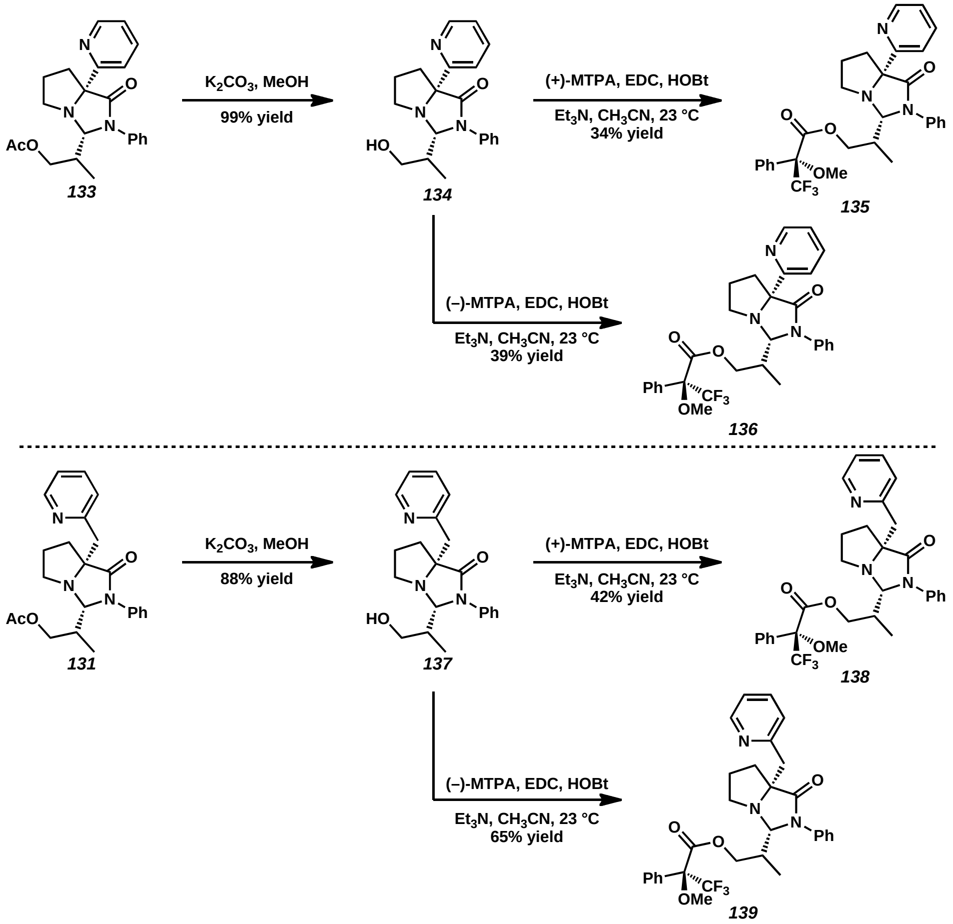
130 ***131*** ***132***

time (h)	temp (°C)	*131 : 132* (%)	dr
24	55	41 : 13	10 : 1
13	70	48 : 19	5.9 : 1

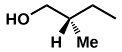
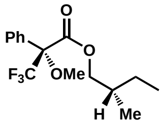
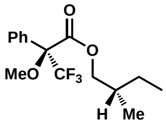
General procedure for acetoxylation: **130** (1 equiv), $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ (1.5 equiv) in $AcOH/Ac_2O$ was heated to 55-70 °C for 13-24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (3:1 to 1:1 hexanes/acetone eluent) to afford acetate **131** (R_f = 0.48 in 1:1 hexanes/acetone) as a light yellow amorphous solid and diacetate **132** (R_f = 0.35 in 1:1 hexanes/acetone) as a light yellow amorphous solid.

Acetate 131: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45-7.34 (comp m, 5H), 7.22 (tt, *J* = 6.8, 1.8 Hz, 1H), 7.15 (ddd, *J* = 7.4, 5.0, 1.0 Hz, 1H), 4.54 (d, *J* = 3.5 Hz, 1H), 3.83 (d, *J* = 6.3 Hz, 2H), 3.23 (ABq, *J* = 13.2 Hz, Δν = 35.9 Hz, 2H), 2.92-2.85 (m, 1H), 2.83-2.77 (m, 1H), 2.23-2.07 (comp m, 2H), 1.93 (s, 3H), 1.85 (qd, *J* = 6.6, 3.5 Hz, 1H), 1.68-1.53 (comp m, 2H), 0.83 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 170.7, 157.9, 148.9, 136.5, 135.9, 129.0, 126.3, 125.1, 124.3, 124.0, 121.7, 84.4, 74.9, 65.0, 58.2, 45.6, 36.3, 35.3, 24.7, 20.9, 14.0; IR (film) 3061, 2967, 2881, 1736, 1699, 1594, 1499, 1236, 754 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{23}H_{28}N_3O_3]^+$: 394.2125, found 394.2126.

Diacetate 132: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.1 Hz, 1H), 7.62 (td, *J* = 7.6, 1.5 Hz, 1H), 7.43-7.35 (comp m, 5H), 7.23-7.21 (m, 1H), 7.15 (dd, *J* = 6.8, 5.4 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 1H), 3.94 (dd, *J* = 13.6, 6.1 Hz, 4H), 3.23 (ABq, *J* = 13.2 Hz, Δν = 33.8 Hz, 2H), 2.93-2.84 (m, 1H), 2.80-2.73 (m, 1H), 2.22-2.08 (comp m, 2H), 1.66-1.57 (comp m, 2H), 2.02 (s, 3H), 1.92 (s, 3H), 1.99-1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 170.5, 170.4, 157.6, 149.0, 136.1, 135.9, 129.1, 126.6, 125.1, 124.0, 121.8, 80.3, 75.0, 61.9, 60.8, 57.9, 45.5, 41.0, 35.6, 24.7, 20.79, 20.76; IR (film) 2965, 1739, 1702, 1593, 1409, 1226 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{29}N_3O_5Na]^+$: 474.1999, 474.1997.



N
O
N
N
Ph
AcO
133
K_2CO_3, MeOH
99% yield
HO
134
(+)-MTPA, EDC, HOBt
Et_3N, CH_3CN, 23 °C
34% yield
Ph
OMe
CF_3
135
(–)-MTPA, EDC, HOBt
Et_3N, CH_3CN, 23 °C
39% yield
136
131
K_2CO_3, MeOH
88% yield
137
(+)-MTPA, EDC, HOBt
Et_3N, CH_3CN, 23 °C
42% yield
138
(–)-MTPA, EDC, HOBt
Et_3N, CH_3CN, 23 °C
65% yield
139

alcohol	Ester (*R*)-(+)-MTPA	Ester (*S*)(–)-MTPA
 *140*	 *141* $(\delta)^{19}F$ = -72.10 ppm	 *142* $(\delta)^{19}F$ = -72.12 ppm
134	*135* $(\delta)^{19}F$ = -72.081 ppm	*136* $(\delta)^{19}F$ = -72.079 ppm
135	*138* $(\delta)^{19}F$ = -72.18 ppm	*139* $(\delta)^{19}F$ = -72.16 ppm

Alcohol 134: To a solution of acetate **133** (127 mg, 0.335 mmol) in MeOH (3.30 mL) was added K_2CO_3 (92.5 mg, 0.669 mmol) at 23 ˚C, and the resulting mixture was stirred 24 h. The reaction was partitioned between water (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over Na_2SO_4 and

concentrated in vacuo to afford alcohol **134** (113 mg, 99% yield, R_f = 0.34 in 1:1 hexanes/acetone) as a white solid. The alcohol was sufficiently pure to be taken on to the next step.

Alcohol 134: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.9 Hz, 1H), 7.78-7.73 (comp m, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.27-7.22 (comp m, 2H), 4.72 (d, *J* = 3.5 Hz, 1H), 3.60 (dd, *J* = 12.1, 1.1 Hz, 2H), 3.44 (dt, *J* = 11.1, 6.7 Hz, 1H), 3.33 (dd, *J* = 12.1, 5.8 Hz, 1H), 3.09 (dt, *J* = 11.3, 5.8 Hz, 1H), 2.56 (dt, *J* = 13.2, 6.9 Hz, 1H), 2.33 (dt, *J* = 13.2, 6.7 Hz, 1H), 1.91 (app. quintet, *J* = 6.7 Hz, 2H), 1.82-1.78 (m, 1H), 1.04 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 160.8, 148.2, 137.1, 136.3, 129.2, 126.7, 124.9, 122.8, 121.8, 86.4, 78.2, 61.6, 58.1, 38.8, 37.6, 25.4, 13.9; IR (film) 3333, 2964, 1701, 1591, 1407, 751 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{20}H_{24}N_3O_2]^+$: 338.1863, found 138.1871.

Ester 135: To a solution of alcohol **134** (48.7 mg, 0.144 mmol), (+)-MTPA (33.8 mg, 0.144 mmol), EDC (33.2 mg, 0.173 mmol), HOBt (6.6 mg, 0.0432 mmol) in CH_3CN (1.40 mL) at 23 ˚C was added Et_3N (21.3 μL, 0.152 mmol). The reaction was stirred overnight at 23 ˚C. The solvent was removed, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester **135** (27.0 mg, 34% yield, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.

Ester 135: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.3 Hz, 1H), 7.74-7.65 (comp m, 2H), 7.47-7.30 (comp m, 9H), 7.26-7.16 (comp m, 2H), 4.70 (d, *J* = 5.3 Hz, 1H), 4.19-4.11 (comp m, 2H), 3.52-3.44 (m, 1H), 3.44 (s, 3H), 2.96 (dt, *J* = 10.5, 6.5 Hz, 1H), 2.59-2.52 (m, 1H), 2.44-2.37 (m, 1H), 2.03-1.94 (comp m, 2H), 1.92-1.82 (m, 1H), 0.79 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 166.1, 161.84, 161.82, 149.4, 136.9, 136.5, 132.1, 129.6, 129.2, 128.4, 127.3, 126.5, 124.4, 122.2, 120.7, 83.4, 77.9, 68.1, 58.5, 55.3, 55.2, 38.4, 25.6, 13.8; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.18; IR (film) 2968, 1748, 1705, 1588, 1169, 1122, 696 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{30}H_{30}F_3N_3O_4Na]^+$: 576.2081, found 576.2069.

Ester 136: To a solution of alcohol **134** (53.2 mg, 0.158 mmol), (–)-MTPA (36.9 mg, 0.158 mmol), EDC (36.3 mg, 0.189 mmol), HOBt (7.2 mg, 0.0473 mmol) in CH_3CN (1.60 mL) at 23 ˚C was added Et_3N (23.3 μL, 0.166 mmol). The reaction was stirred overnight at 23 ˚C. The solvent was removed by rotary evaporation, and the residue was partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester **136** (33.7 mg, 39% yield, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.

Ester 136: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 1H), 7.75-7.66 (comp m, 2H), 7.43-7.29 (comp m, 9H), 7.26-7.15 (comp m, 2H), 4.70 (d, *J* = 5.4 Hz, 1H), 4.28 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.02 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.46-3.41 (m, 1H), 3.43 (d, *J* = 0.7 Hz, 3H), 2.93 (dt, *J* = 10.5, 6.5 Hz, 1H), 2.58-2.51 (m, 1H), 2.43-2.36 (m, 1H), 2.03-1.93 (comp m, 2H), 1.91-1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 166.2, 161.9, 149.3, 136.9, 136.6, 132.2, 129.6, 129.2, 128.4, 127.2, 126.5, 124.7, 124.4, 122.3, 121.9, 120.7, 83.2, 77.6, 68.1, 58.4, 55.3, 38.4, 38.3, 25.6, 13.9; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.16; IR (film) 2969, 1749, 1708, 1588, 1273, 1169, 1023 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{30}H_{30}F_3N_3O_4Na]^+$: 576.2081, found 576.2080.

Alcohol 137: To a solution of acetate **131** (118 mg, 0.300 mmol) in MeOH (3.00 mL) at 23 °C was added K_2CO_3 (83.0 mg, 0.600 mmol), and the resulting mixture was stirred overnight. The reaction was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford alcohol **137** (93.1 mg, 88% yield, R_f = 0.34 in 1:1 hexanes/acetone) as a white solid, which was sufficiently pure to be taken on to the next step.

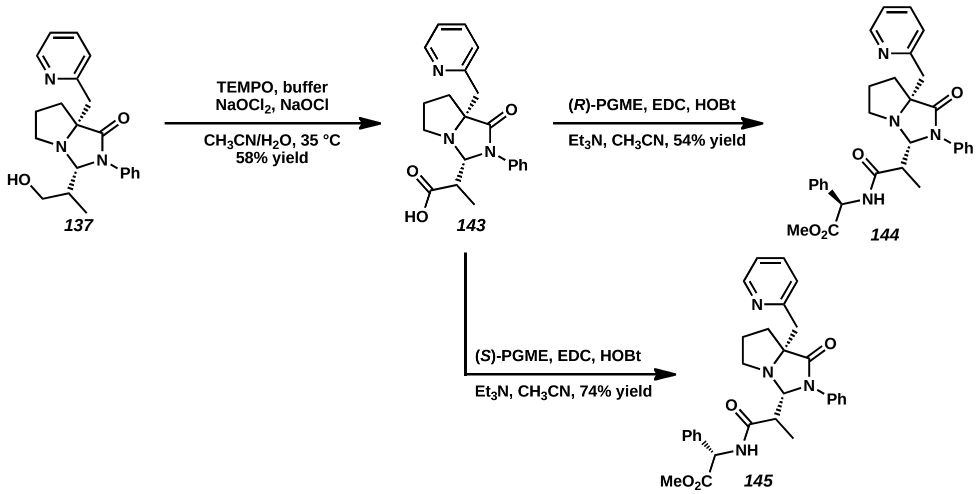
Alcohol 137: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.41-7.35 (comp m, 2H), 7.30-7.28 (comp m, 3H), 7.26-7.21 (m, 1H), 7.16 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H), 4.51 (d, *J* = 3.4 Hz, 1H), 3.71 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.35 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.26 (ABq, *J* = 13.2 Hz, Δν = 12.8 Hz, 2H), 2.82-2.77 (m, 1H), 2.72-2.65 (m, 1H), 2.16-2.11 (m, 1H), 2.01-1.94 (m, 1H), 1.82-1.74 (m, 1H), 1.65-1.54 (m, 1H), 1.38-1.31 (m, 1H), 0.97 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 156.8, 149.0, 136.2, 129.2, 126.7, 125.2, 124.9, 123.7, 121.7, 86.5, 74.4, 62.0, 57.7, 45.1, 37.7, 34.3, 24.6, 14.1; IR (film) 3332, 2961, 1696, 1594, 1476, 753, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{21}H_{26}N_3O_2]^+$: 352.2020, found 352.2024.

Ester 138: To a solution of alcohol **137** (45.0 mg, 0.128 mmol), (*R*)-(+)-MTPA (30.0 mg, 0.128 mmol), EDC (29.4 mg, 0.154 mmol), HOBt (6.0 mg, 0.0380 mmol) in CH_3CN (1.30 mL) at 23 ˚C was added Et_3N (19.0 μL, 0.134 mmol). The reaction was stirred 24 h at 23 ˚C. The solvent was removed, and the residue partitioned between water (10 mL) and EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester **138** (30.5 mg, 42% yield, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.

Ester 138: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 4.9, 0.9 Hz, 1H),7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.42-7.34 (comp m, 8H), 7.26-7.21 (comp m, 3H), 7.11 (ddd, *J* = 7.4, 5.0, 1.0 Hz, 1H), 4.40 (d, *J* = 4.7 Hz, 1H), 3.95 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.86 (dd, *J* = 10.8, 7.5 Hz, 1H), 3.43 (d, *J* = 0.9 Hz, 3H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.06 (d, *J* = 13.2 Hz, 1H), 3.05-3.01 (m, 1H), 2.77 (dt, *J* = 11.4, 5.7 Hz, 1H), 2.16-2.05 (comp m, 2H), 1.73-1.66 (comp m, 2H), 1.43-1.37 (m, 1H), 0.65 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 166.0, 157.9, 149.1, 149.0, 136.4, 136.0, 132.2, 129.6, 129.2, 128.3, 127.2, 126.8, 125.0, 124.9, 121.8, 83.7, 75.2, 67.3, 57.7, 55.2, 46.0, 37.9, 36.4, 24.7, 13.9; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.081; IR (film) 2967, 1749, 1704, 1592, 1169, 1024, 720, 698 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{31}H_{33}F_3N_3O_4]^+$: 568.2418, found 568.2420.

Ester 139: To alcohol **137** (70.6 mg, 0.201 mmol), (*S*)-(–)-MTPA (47.0 mg, 0.201 mmol), EDC (46.2 mg, 0.241 mmol), HOBt (27.7 mg, 0.0181 mmol) in CH_3CN (2.00 mL) at 23 ˚C was added Et_3N (29.6 μL, 0.211 mmol). The reaction was stirred 24 h at 23 ˚C. The solvent was removed, and the residue dissolved in water (10 mL) and EtOAc (10 mL). The organic layer was separated, then dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford ester **139** (74.5 mg, 65% yield, R_f = 0.52 in 1:1 hexanes/acetone) as a white solid.

Ester 139: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.43-7.32 (comp m, 8H), 7.26-7.21 (comp m, 3H), 7.12 (ddd, *J* = 7.4, 5.0, 0.9 Hz, 1H), 4.41 (d, *J* = 4.9 Hz, 1H), 4.03 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.82 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.43 (d, *J* = 0.8 Hz, 3H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.07 (d, *J* = 13.2 Hz, 1H), 2.97 (dt, *J* = 11.3, 7.0 Hz, 1H), 2.71 (dt, *J* = 11.3, 5.7 Hz, 1H), 2.17-2.06 (comp m, 2H), 1.71-1.61 (comp m, 2H), 1.48-1.39 (m, 1H), 0.65 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 166.1, 157.9, 149.1, 136.5, 136.0, 132.2, 129.6, 129.2, 128.3, 127.22, 127.21, 126.7, 124.9, 121.8, 83.6, 75.1, 67.5, 57.6, 55.2, 46.0, 38.0, 36.2, 24.7, 13.9; ^{19}F NMR (300 MHz, $CDCl_3$) δ -72.079; IR (film) 3063, 2967, 2881, 1749, 1703, 1592, 1170, 735 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{31}H_{33}F_3N_3O_4]^+$: 568.2418, found 568.2421.


TEMPO, buffer
NaOCl$_2$, NaOCl
CH$_3$CN/H$_2$O, 35 °C
58% yield
(*R*)-PGME, EDC, HOBt
Et$_3$N, CH$_3$CN, 54% yield
(*S*)-PGME, EDC, HOBt
Et$_3$N, CH$_3$CN, 74% yield
N
O
Ph
HO
NH
MeO$_2$C

137

143

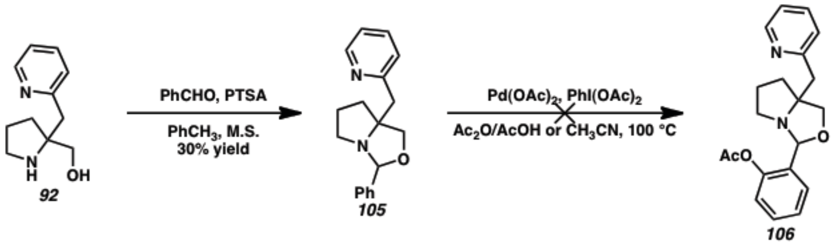
144

145

Acid 143: To **137** (122 mg, 0.347 mmol) in CH_3CN (1.70 mL) with TEMPO (3.8 mg, 0.0243 mmol), NaH_2PO_4/Na_2HPO_4 buffer (1.30 mL, 0.67 M) and $NaOCl_2$ (78.5 mg, 0.694 mmol) at 35 °C was added NaOCl (9.0 μL, 6.94 μmol, 6% solution in H_2O) slowly over 1 h. The reaction was stirred at 35 °C overnight (10 h). Upon cooling to 23 °C, water was added and the solution set to pH 8 with 1 M NaOH. The mixture was poured into sat. aq. Na_2SO_3 and stirred for 30 min. EtOAc was added and separated. The aqueous layer was acidified to pH 2 with 1 M $KHSO_4$ then extracted with EtOAc (2 x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:3 to 1:1 hexanes:acetone) to afford **143** (74.0 mg, 58% yield, R_f = 0.1 in 1:1 hexanes:acetone) as a white amorphous solid.

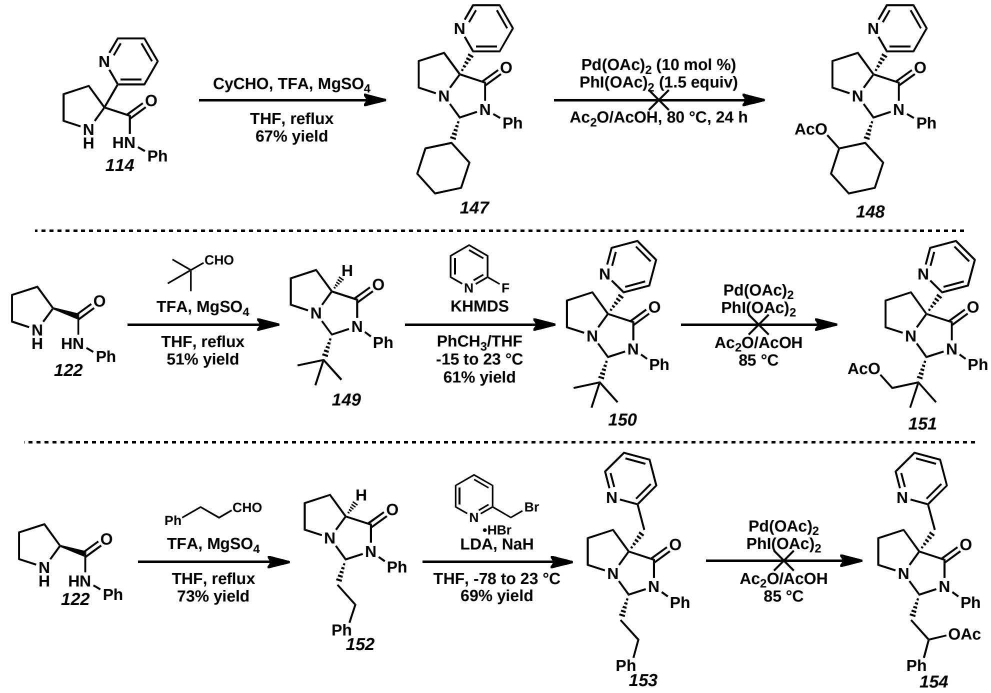
Amide 145: To acid **143** (24.5 mg, 0.0670 mmol), (*S*)-(+)-PGME (13.5 mg, 0.0670 mmol), EDC (16.7 mg, 0.0871 mmol), HOBt (10.3 mg, 0.0670 mmol) in CH_3CN (0.700 mL) at 23 ˚C was added Et_3N (19.3 μL, 0.137 mmol). The reaction was stirred 24 h at 23 ˚C. The solvent was removed, and the residue dissolved in water (10 mL) and EtOAc (10 mL). The organic layer was separated, then dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford amide **145** (18.4 mg, 54% yield, R_f = 0.55 in 1:1 hexanes/acetone) as a white solid.

Amide 144: To acid **143** (38.1 mg, 0.104 mmol), (*R*)-(-)-PGME (21.0 mg, 0.104 mmol), EDC (26.0 mg, 0.136 mmol), HOBt (16.0 mg, 0.104 mmol) in CH_3CN (1.00 mL) at 23 ˚C was added Et_3N (30.0 μL, 0.214 mmol). The reaction was stirred 24 h at 23 ˚C. The solvent was removed, and the residue dissolved in water (10 mL) and EtOAc (10 mL). The organic layer was separated, then dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford amide **144** (39.4 mg, 74% yield, R_f = 0.54 in 1:1 hexanes/acetone) as a white solid.



To a solution of alcohol **137** (87.2 mg, 0.248 mmol), *p*-nitrobenzoic acid (45.6 mg, 0.273 mmol), EDC (57.0 mg, 0.298 mmol), HOBt (38.0 mg, 0.248 mmol) in CH_3CN (2.50 mL) at 23 °C was added Et_3N (38.0 μL, 0.273 mmol). The reaction was stirred at 23 °C for 3 d. The volatile organic solvent was removed, and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford benzoate **146** (119 mg, 96% yield, R_f = 0.47 in 1:1 hexanes/acetone) as a white solid. The solid was crystallized by a layering technique with CH_2Cl_2 and hexanes.

Ester 146: ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 5.0, 0.9 Hz, 1H), 8.31-8.21 (comp m, 2H), 8.07-7.99 (comp m, 2H), 7.72 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.39-7.29 (comp m, 4H), 7.25-7.20 (comp m, 2H), 4.59 (d, *J* = 3.4 Hz, 1H), 3.99 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.93 (dd, J = 10.9, 8.0 Hz, 1H), 3.34 (ABq, J = 13.2 Hz, $\Delta\nu$ = 67.7 Hz, 2H), 3.10 (dt, J = 11.5, 7.3 Hz, 1H), 2.88 (dt, J = 11.4, 5.7 Hz, 1H), 2.14 (app. t, J = 7.2 Hz, 2H), 2.01-1.95 (m, 1H), 1.79-1.69 (comp m, 2H), 0.93 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 164.2, 157.3, 150.4, 148.2, 137.0, 136.1, 135.5, 130.5, 129.2, 126.6, 125.5, 124.3, 123.4, 122.3, 84.1, 75.2, 66.2, 57.8, 44.9, 36.4, 35.9, 24.7, 14.3; [IR (film) 2968, 1723, 1721, 1527, 1276, 1103, 720 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{28}H_{29}N_4O_5]^+$: 500.2132, found 500.2137; mp 110-116 °C.



114
CyCHO, TFA, MgSO4
THF, reflux
67% yield
147
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 80 °C, 24 h
148
122
TFA, MgSO4
THF, reflux
51% yield
149
KHMDS
PhCH3/THF
-15 to 23 °C
61% yield
150
Pd(OAc)2
PhI(OAc)2
Ac2O/AcOH
85 °C
151
122
TFA, MgSO4
THF, reflux
73% yield
152
•HBr
LDA, NaH
THF, -78 to 23 °C
69% yield
153
Pd(OAc)2
PhI(OAc)2
Ac2O/AcOH
85 °C
154

General procedure for condensation: To amino amide (1 equiv) in THF (0.1 M) was added aldehyde (1.3 equiv), TFA (10 mol %) and $MgSO_4$ (1.5 equiv) at 23 °C. The reaction was heated to reflux overnight. Upon cooling, sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3x) and the organic layers dried over Na_2SO_4 and concentrated. The crude residue was purified via column chromatography (4:1 to 1:1 hexanes:EtOAc) to afford the pure aminal.

Aminal 147: 67% yield, R_f = 0.25 in 1:1 hexanes:EtOAc

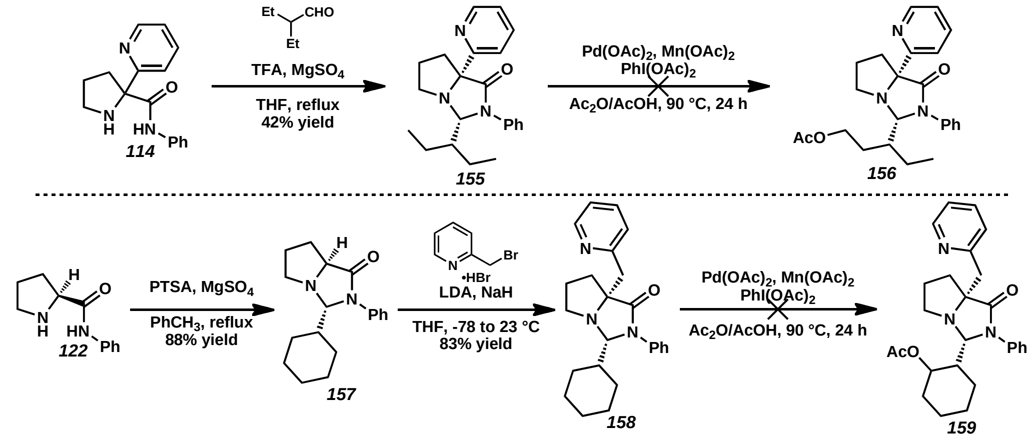
Aminal 149: 51% yield, R_f = 0.30 in 1:1 hexanes:EtOAc

Aminal 152: 73% yield, R_f = 0.35 in 1:1 hexanes:EtOAc

Pyridine 150: To a solution of aminal **149** (809 mg, 3.13 mmol), 2-fluoropyridine (269 μL, 3.13 mmol) in $PhCH_3$ (10.4 mL) at -15 ˚C was added KHMDS (625 mg, 3.13 mmol) in THF (6.30 mL) slowly over 1 h. Upon completion of addition, the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction was filtered over a pad of silica (5 x 5 cm, 100 mL EtOAC eluent) and concentrated. The crude product was purified by flash chromatography (3:1 to 1:1 hexanes/EtOAc eluent) to afford pyridine **150** (244 mg, 23% yield, R_f = 0.25 in 1:1 hexanes/EtOAc) as a light beige solid.

Pyridine 153: To a solution of freshly distilled diisopropylamine (552 μL, 3.93 mmol) in THF (4.40 mL) at -78 ˚C was added *n*-BuLi (1.51 mL, 2.5 M in hexanes, 3.77 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **152** (1.16 g, 3.77 mmol) in THF (5.00 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (377 mg, 60% dispersion in mineral oil, 9.42 mmol, washed 2 x 2.0 mL with hexanes) in DMF (8.00 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (795 mg, 3.14 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.40 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched by slow addition of H_2O (20 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 35 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (1:3 to 2:3 hexanes/EtOAc eluent) to afford pyridine **153** (865 mg, 69% yield, R_f = 0.18 in 1:1 hexanes:EtOAc) as a light orange solid.

General procedure for acetoxylation: Pyridine (1 equiv), $Pd(OAc)_2$ (10-50 mol %) and $PhI(OAc)_2$ (1.5-2.0 equiv) were combined in $AcOH/Ac_2O$ (1:1, 0.1 M) in a 2-dram vial and heated to 80-85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Crude ^1H NMR revealed no product formation.



114
Et
CHO
Et
TFA, MgSO4
THF, reflux
42% yield
155
Pd(OAc)2, Mn(OAc)2
PhI(OAc)2
Ac2O/AcOH, 90 °C, 24 h
AcO
156
122
PTSA, MgSO4
PhCH3, reflux
88% yield
157
Br
•HBr
LDA, NaH
THF, -78 to 23 °C
83% yield
158
Pd(OAc)2, Mn(OAc)2
PhI(OAc)2
Ac2O/AcOH, 90 °C, 24 h
AcO
159

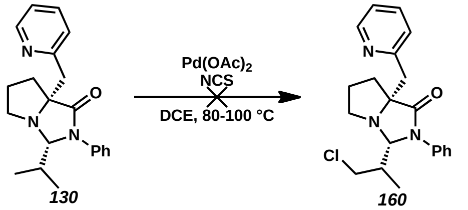
General procedure for condensation: To amino amide (1 equiv) in THF or toluene (0.1 M) was added aldehyde (1.3 equiv), TFA (10 mol %) or PTSA (5 mol %) and $MgSO_4$ (1.5 equiv) at 23 °C. The reaction was heated to reflux overnight. Upon cooling, sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (3x) and the organic layers dried over Na_2SO_4 and concentrated. The crude residue was purified via column chromatography (4:1 to 1:1 hexanes:EtOAc) to afford the pure aminal.

Aminal 155: 42% yield, $R_f = 0.25$ in 1:1 hexanes:EtOAc

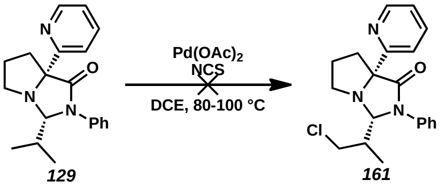
Aminal 157: 88% yield, $R_f = 45$ in 1:1 hexanes:EtOAc

Pyridine 158: To a solution of freshly distilled diisopropylamine (337 μL, 2.40 mmol) in THF (3.70 mL) at -78 ˚C was added *n*-BuLi (0.920 mL, 2.5 M in hexanes, 2.31 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **157** (654 mg, 2.30 mmol) in THF (4.00 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (230 mg, 60% dispersion in mineral oil, 5.75 mmol, washed 2 x 2.0 mL with hexanes) in DMF (6.00 mL) at 0 ˚C was added 2-bromomethylpyridine hydrobromide (485 mg, 1.92 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.70 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched by slow addition of H_2O (20 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 35 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (1:3 to 3:2 hexanes/EtOAc eluent) to afford pyridine **158** (865 mg, 83% yield, R_f = 0.18 in 1:1 hexanes:EtOAc) as a light yellow solid.

General procedure for acetoxylation: Pyridine (1 equiv), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (1.2 equiv) and $PhI(OAc)_2$ (4.0 equiv) were combined in $AcOH/Ac_2O$ (1:1, 0.1 M) in a 2-dram vial and heated to 90 °C for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptanes (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. Crude ^{1}H NMR revealed no product formation.

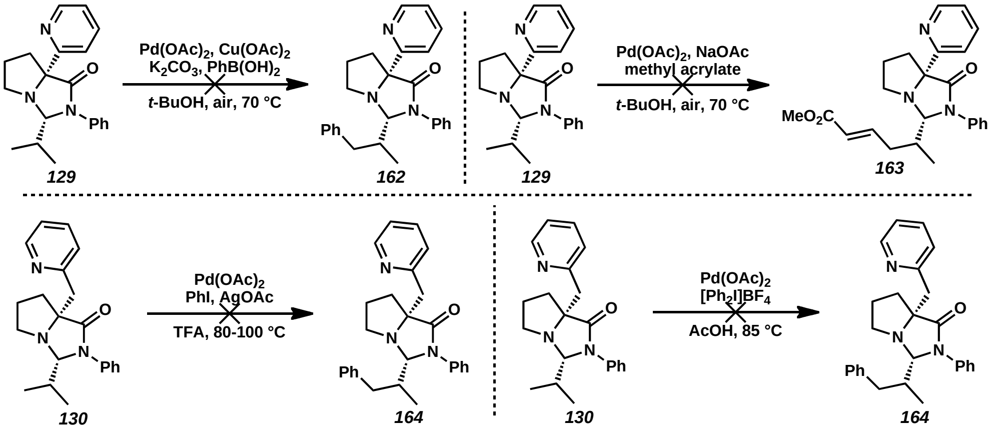


130 160

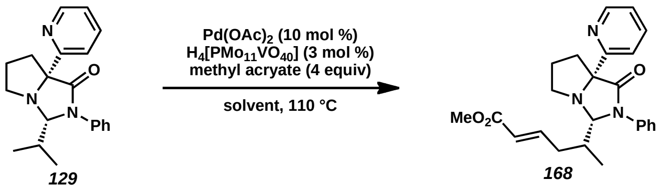


129 161

General procedure for chlorination: Pyridine (1 equiv), $Pd(OAc)_2$ (10-50 mol %) and NCS (1-2 equiv) were combined in DCE in a 2-dram vial and heated to 80-100 °C for 24 h. Solvent was removed under reduced pressure. Crude ^1H NMR revealed no product formation.

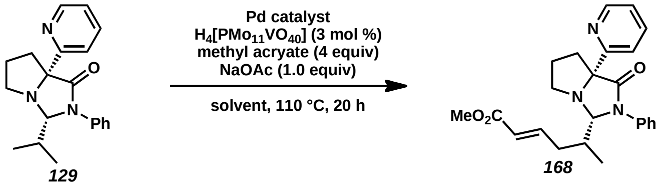

Pd(OAc)2, Cu(OAc)2
K2CO3, PhB(OH)2
t-BuOH, air, 70 °C
129
162
Pd(OAc)2, NaOAc
methyl acrylate
t-BuOH, air, 70 °C
129
163
MeO2C
Pd(OAc)2
PhI, AgOAc
TFA, 80-100 °C
130
164
Pd(OAc)2
[Ph2I]BF4
AcOH, 85 °C
130
164
N
O
Ph

General procedure for olefination: Pyridine (1 equiv), $Pd(OAc)_2$ (10 mol %), $H_4[PMo_{11}VO_{40}]$ (3 mol %), methyl acrylate (4 equiv) and NaOAc (1.1 equiv) were combined in AcOH or DCE (0.1 M) in a 2-dram vial and heated to 110 °C for 24 h. The reaction was filtered through a plug of celite with CH_2Cl_2 and the solvent was removed under reduced pressure. Product ratios determined by crude ^1H NMR.


Pd(OAc)$_2$ (10 mol %)
H$_4$[PMo$_{11}$VO$_{40}$] (3 mol %)
methyl acryate (4 equiv)
solvent, 110 °C
N
O
N
N
Ph
MeO$_2$C
129
168

entry	solvent	base	additive	% conversion
1	DCE	NaOAc (2 equiv)	none	18
2	t-AmOH	NaOAc (2 equiv)	none	0
3	CH_3CN	NaOAc (2 equiv)	none	17
4	DCE	Na_2CO_3 (1 equiv)	NaOPiv (0.2 equiv)	trace
5	DCE	K_2CO_3 (1 equiv)	none	0
6		NaOAc (1.1 equiv)	none	23
7	DMF	NaOAc (1.1 equiv)	none	0
8	DCE	NaOAc (1.0 equiv)	acac (10 mol %)	0
9	CF_3CH_2OH	NaOAc (1.0 equiv)	AcOH (1.0 equiv)	trace

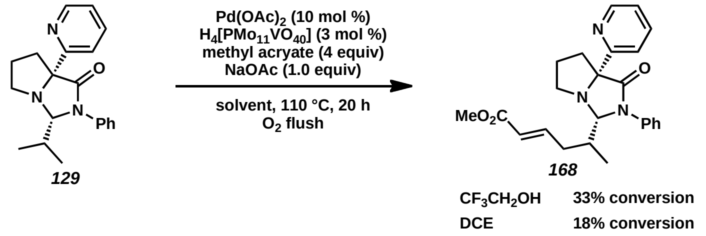
General procedure for olefination: Pyridine (1 equiv), Pd(OAc)$_2$ (10 mol %), H$_4$[PMo$_{11}$VO$_{40}$] (3 mol %), methyl acrylate (4 equiv), additive (0-1.0 equiv) and base (1-2 equiv) were combined in solvent (0.1 M) in a 2-dram vial and heated to 110 °C for 24 h. The reaction was filtered through a plug of celite with CH$_2$Cl$_2$ and the solvent was removed under reduced pressure. Product ratios determined by crude ^{1}H NMR.


Pd catalyst
H$_4$[PMo$_{11}$VO$_{40}$] (3 mol %)
methyl acryate (4 equiv)
NaOAc (1.0 equiv)
solvent, 110 °C, 20 h
N
O
N
N
Ph
MeO$_2$C
129
168

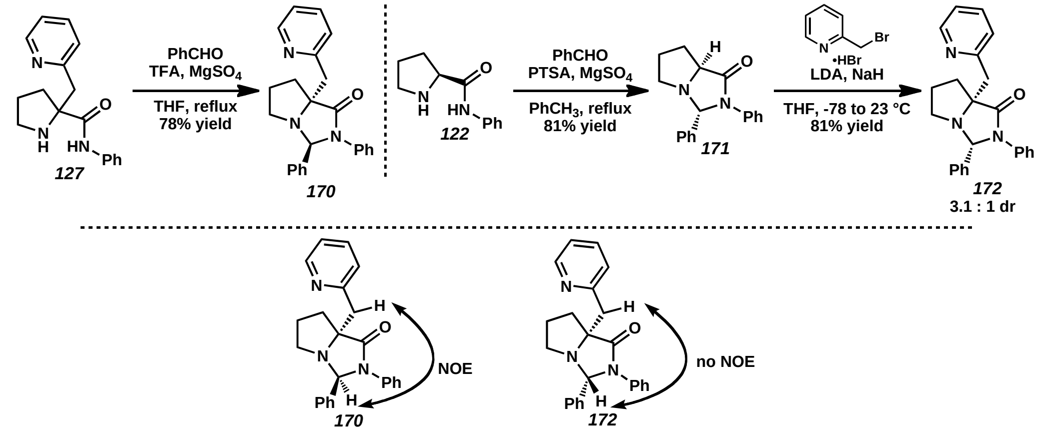
entry	catalyst	solvent	% conversion
1	$Pd(CH_3CN)_4(BF_4)_2$	CF_3CH_2OH	20
2	$Pd(CH_3CN)_4(BF_4)_2$	DCE	18
3	$Pd(OAc)_2$	DCE	28
4	$PdCl_2$	DCE	0
5	$Pd(TFA)_2$	DCE	14
6	Pd(acac-F$_6$)$_2$	CF_3CH_2OH	11

General procedure for olefination: Pyridine (1 equiv), palladium catalyst (10 mol %), H$_4$[PMo$_{11}$VO$_{40}$] (3 mol %), methyl acrylate (4 equiv), and NaOAc (1.0 equiv) were combined in

DCE or CF_3CH_2OH (0.1 M) in a 2-dram vial and heated to 110 °C for 24 h. The reaction was filtered through a plug of celite with CH_2Cl_2 and the solvent was removed under reduced pressure. Product ratios determined by crude ^1H NMR.


Pd(OAc)2 (10 mol %)
H4[PMo11VO40] (3 mol %)
methyl acryate (4 equiv)
NaOAc (1.0 equiv)
solvent, 110 °C, 20 h
O2 flush
129
168
MeO2C
CF3CH2OH 33% conversion
DCE 18% conversion

General procedure for olefination: Pyridine (1 equiv), $Pd(OAc)_2$ (10 mol %), $H_4[PMo_{11}VO_{40}]$ (3 mol %), methyl acrylate (4 equiv), and NaOAc (1.0 equiv) were combined in DCE or CF_3CH_2OH (0.1 M) in a 2-dram vial fitted with a septum. The vial was flushed with O_2 from a balloon, then sealed and heated to 110 °C for 20 h. The reaction was filtered through a plug of celite with CH_2Cl_2 and the solvent was removed under reduced pressure. Product ratios determined by crude ^1H NMR.


PhCHO
TFA, MgSO4
THF, reflux
78% yield
127
170
122
PhCHO
PTSA, MgSO4
PhCH3, reflux
81% yield
171
•HBr
LDA, NaH
THF, -78 to 23 °C
81% yield
172
3.1 : 1 dr
NOE
170
no NOE
172

Pyridine 170: To **127** (71.3 mg, 0.253 mmol) in THF (2.50 mL) was added PhCHO (33.3 μL, 0.329 mmol), TFA (3.9 μL, 0.12 mmol) and $MgSO_4$ (61.0 mg, 0.507 mmol) at 23 °C. The suspension was refluxed overnight. Upon cooling, the reaction was quenched with sat. aq.

$NaHCO_3$ solution (10 mL). The aqueous was extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:4 to 1:1 EtOAc:hexanes) to give **170** (73.6 mg, 78% yield, R_f = 0.21 in 40:1 EtOAc:MeOH) as a light brown solid.

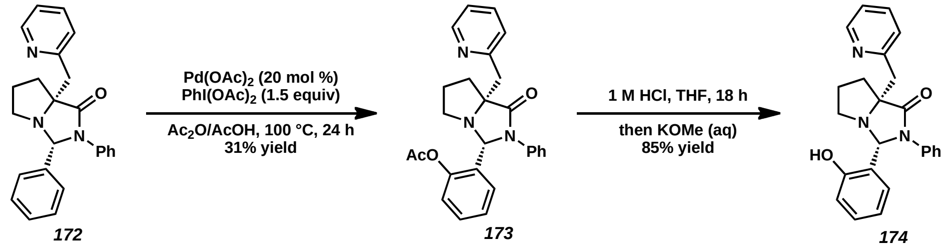
Aminal 171: To a solution of amino amide **122** (1.50 g, 7.90 mmol) in $PhCH_3$ (26.3 mL) at 23 ˚C was added benzaldehyde (1.00 mL, 10.2 mmol), $TsOH·H_2O$ (75.0 mg, 0.395 mmol), and $MgSO_4$ (1.40 g, 11.8 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The dark brown residue was purified by flash chromatography (7:3 hexanes/EtOAc eluent) to afford aminal **171** (1.77 g, 81% yield, R_f = 0.24 in 1:1 hexanes/EtOAc) as a light brown solid.

Aminal 171: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.36-7.25 (comp m, 7H), 7.11-7.07 (m, 1H), 5.67 (s, 1H), 4.03 (app. t, *J* = 6.6 Hz, 1H), 3.46-3.41 (m, 1H), 2.88 (app. q, *J* = 8.3 Hz, 1H), 2.20 (app. q, *J* = 8.3 Hz, 2H), 1.92-1.87 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 139.6, 137.9, 129.3, 129.2, 128.7, 126.2, 125.3, 121.3, 83.8, 64.5, 56.2, 27.7, 25.0; IR (film) 2969, 3032, 1699, 1598, 1498, 1384, 757 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for ($M+H^+$) $[C_{18}H_{19}N_2O]^+$: 279.1492, found 279.1492.

Pyridine 172: To a solution of freshly distilled diisopropylamine (933 μL, 6.60 mmol) in THF (8.00 mL) at -78 ˚C was added *n*-BuLi (2.60 mL, 2.5 M in hexanes, 6.40 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **171** (1.77 g, 6.40 mmol) in THF (7.90 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (638 mg, 60% dispersion in mineral oil, 15.9 mmol, washed 2 x 1.5 mL with hexanes) in DMF (14.0 mL) at 0 ˚C was added 2-bromomethylpyridine hydrobromide (1.34 g, 5.30 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.90 mL DMF). The reaction mixture was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (40 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **172** (1.38 g, 71% yield, R_f = 0.46 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **172b** (458 mg, 23% yield, R_f = 0.21 in 40:1 EtOAc/MeOH) as a light beige solid.

Pyridine 172: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.6 Hz, 1H), 7.53 (app. t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 2H), 7.18-7.13 (comp m, 4H), 7.07 (t, *J* = 8.1 Hz, 2H), 6.89-6.88 (comp m, 2H), 5.44 (s, 1H), 3.20 (ABq, *J* = 13.1 Hz, Δν = 80.5 Hz, 2H), 3.18-3.14 (m, 1H), 2.99 (dt, *J* = 11.2, 5.7 Hz, 1 H), 2.33-2.26 (m, 1H), 2.23-2.16 (m, 1H), 1.83-1.76 (m, 1H), 1.63-1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 157.8, 148.6, 140.1, 137.0, 135.8, 128.7, 128.3, 128.2, 127.0, 125.4, 125.3, 122.5, 121.5, 83.1, 75.1, 55.8, 45.2, 35.5, 24.6; IR (film) 3052, 2968, 1702, 1592, 1499, 1391, 747, 702 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1732.

Pyridine 172b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.0 Hz, 1H), 7.50 (td, *J* = 7.7, 1.7 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20-7.15 (comp m, 6H), 7.11-7.09 (comp m, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 5.34 (s, 1H), 3.48 (d, *J* = 13.1 Hz, 1H), 3.12 (d, *J* = 13.1 Hz, 1H), 2.57-2.50 (m, 1H), 2.45-2.36 (comp m, 2H), 2.10 (dt, *J* = 12.7, 6.1 Hz, 1H), 1.66-1.60 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 157.6, 149.1, 137.5, 136.1, 134.3, 128.5, 128.42, 128.40, 128.2, 124.9, 124.6, 122.1, 121.7, 78.5, 75.0, 51.2, 46.2, 35.8, 24.5; IR (film) 2967, 1707, 1591, 1377, 1301, 746, 703 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H)$^+$ [$C_{24}H_{24}N_3O$]$^+$: 370.1914, found 370.1917.

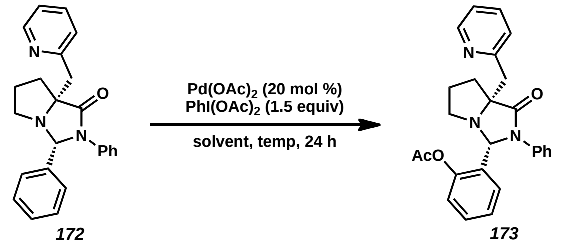


Acetate 173: Pyridine **172** (50.0 mg, 0.141 mmol), Pd(OAc)$_2$ (6.3 mg, 0.0283 mmol), and PhI(OAc)$_2$ (68.0 mg, 0.211 mmol) were dissolved in AcOH (0.700 mL) and Ac$_2$O (0.700 mL) in a round-bottomed flask. The flask was capped and heated to 100 ˚C for 24 h. The reaction was filtered through a plug of silicaand the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate **173** (18.9 mg, 31% yield, R$_f$ = 0.50 in 1:1 hexanes/acetone) as a beige solid.

Acetate 173: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.47 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.52 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.45 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30-7.25 (comp m, 4H), 7.14 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.10-7.06 (comp m, 2H), 7.01 (td, *J* = 7.6, 0.8 Hz, 1H), 6.85-6.81 (comp m, 2H), 5.80 (s, 1H), 3.17 (dt, *J* = 10.3, 6.2 Hz, 1 H), 3.08 (s, 2H), 2.95 (dt, *J* = 10.2, 6.6 Hz, 1H), 2.38 (s, 3H), 2.21 (app. t, *J* = 7.2 Hz, 2H), 1.71-1.62, (m, 1H), 1.37-1.28 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.8, 168.7, 157.3, 148.9, 148.3, 137.3, 135.8, 132.0, 129.0, 128.9, 126.6, 126.0, 125.9, 124.9, 122.8, 121.5, 120.7, 98.4, 77.7, 75.0, 57.4, 44.5, 34.7, 24.7, 21.1; IR (film) 3062, 2966, 1767, 1702, 1497, 1385, 1199 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H$^+$) [$C_{26}H_{26}N_3O_3$]$^+$: 428.1969, found 428.1976.

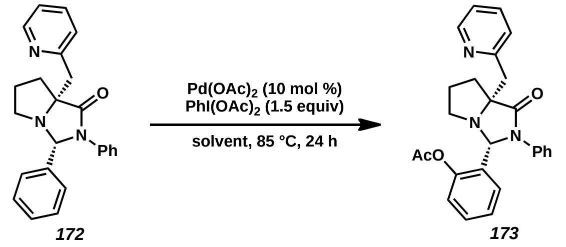
Phenol 174: Acetate **173** (122 mg, 0.284 mmol) was dissolved in aq. HCl (1 M, 2.80 mL) and THF (5.70 mL), and the resulting solution was heated to reflux overnight. Upon cooling the reaction was quenched with solid Na_2CO_3 until pH ~9-10. The mixture was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was taken up in ether (20 mL) and extracted with Claisen's alkali (17.5 g KOH dissolved in 12.5 mL H_2O, then 37.5 mL MeOH added, 3 x 15 mL). The combined aqueous layers were acidified to pH ~9-10 and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford phenol **174** (98.0 mg, 89% yield, R_f = 0.42 in 1:1 acetone:hexanes) as a beige solid.

Phenol 174: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29-7.25 (m, 1H), 7.23-7.20 (comp m, 3H), 7.17-7.10 (comp m, 2H), 7.06-7.04 (comp m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.65 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.57 (td, *J* = 7.4, 1.0 Hz, 1H), 5.34 (s, 1H), 3.32 (ABq, *J* = 14.1 Hz, Δν = 93.0 Hz, 2H), 3.10 (dt, *J* = 12.4, 8.0 Hz, 1H), 2.99 (ddd, *J* = 12.4, 7.9, 4.6 Hz, 1H), 2.38-2.24 (comp m, 2H), 2.16-2.07 (m, 1H), 1.95-1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 157.5, 156.8, 149.2, 136.6, 135.8, 130.7, 130.6, 128.9, 127.0, 125.7, 124.9, 122.0, 119.7, 118.7, 117.8, 82.0, 74.5, 50.8, 43.0, 33.1, 23.9; IR (film) 3061, 2965, 1699, 1597, 1499, 1399, 755 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{24}N_3O_2]^+$: 386.1863, found 386.1865.


Pd(OAc)$_2$ (20 mol %)
PhI(OAc)$_2$ (1.5 equiv)
solvent, temp, 24 h
N
O
N
N
Ph
AcO
172
173

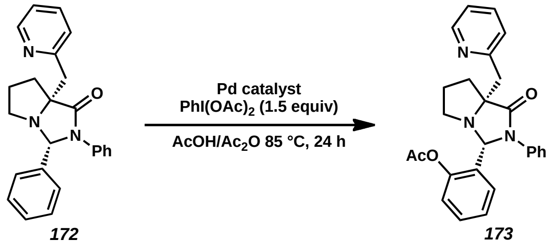
solvent	temp (°C)	yield	solvent	temp (°C)	yield
AcOH	100	<10%	AcOH:Ac$_2$O	80	50
Ac$_2$O	100	0%	AcOH	80	25
AcOH:CH$_2$Cl$_2$	100	<10%	AcOH:Ac$_2$O	90	36
AcOH:Ac$_2$O	23	0%	AcOH	90	18

General procedure for acetoxylation: Pyridine **172** (1 equiv), Pd(OAc)$_2$ (20 mol %), PhI(OAc)$_2$ (1.5 equiv) in solvent (0.1 M) were heated to 80-100 °C for 24 h. The reaction was filtered through a plug of silicaand the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent).


Pd(OAc)$_2$ (10 mol %)
PhI(OAc)$_2$ (1.5 equiv)
solvent, 85 °C, 24 h
N
O
N
N
Ph
AcO
172
173

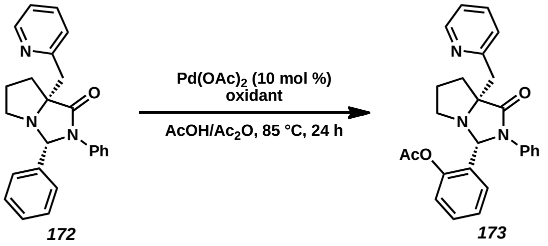
solvent	concentration (M)	*172 : 173*	yield (%, crude)
Ac$_2$O/AcOH	0.05	1.0 : 2.0	40
Ac$_2$O/AcOH	0.1	1.0 : 3.0	62
Ac$_2$O/AcOH	0.2	1.0 : 8.3	50
AcOH	0.05	2.3 : 1.0	12
AcOH	0.1	1.3 : 1.0	18
AcOH	0.2	1 : 1	27

General procedure for acetoxylation: Pyridine **172** (1 equiv), Pd(OAc)$_2$ (10 mol %), PhI(OAc)$_2$ (1.5 equiv) in solvent (0.05-0.2 M) were heated to 85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The yields were calculated based on the crude mass recovery.


N
O
N
N
Ph
172
Pd catalyst
PhI(OAc)$_2$ (1.5 equiv)
AcOH/Ac$_2$O 85 °C, 24 h
N
O
N
N
Ph
AcO
173

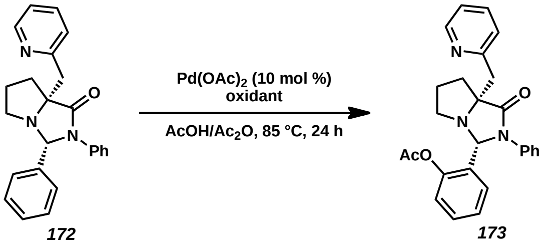
Pd catalyst (mol %)	*172 : 173*
$PdCl_2$ (10)	1.0 : 1.5
$Pd(TFA)_2$ (10)	1.2 : 1.0
$Pd(OAc)_2$ (5)	1.7 : 1
$Pd(OAc)_2$ (10)	1.0 : 8.0
$Pd(OAc)_2$ (15)	1.0 : 2.0

General procedure for acetoxylation: Pyridine **172** (1 equiv), palladium catalyst (5-15 mol %), PhI(OAc)$_2$ (1.5 equiv) in AcOH/Ac$_2$O (0.2 M) were heated to 85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The product ratios were determined by crude ^{1}H NMR.


N
O
N
N
Ph
172
Pd(OAc)$_2$ (10 mol %)
oxidant
AcOH/Ac$_2$O, 85 °C, 24 h
N
O
N
N
Ph
AcO
173

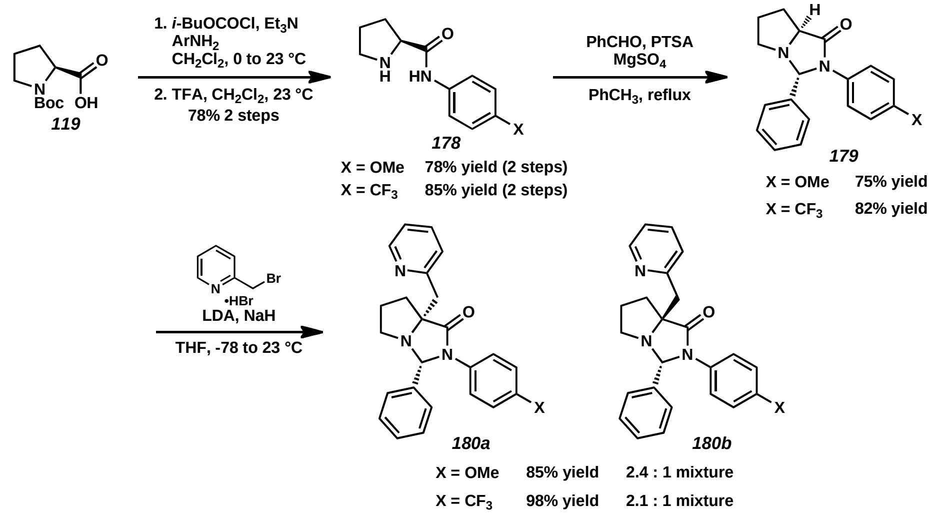
entry	oxidant	yield (%)
1	PhI(OAc)$_2$ (1.5 equiv)	62
2	PhI(OAc)$_2$ (2 equiv)	65
3	PhI(OAc)$_2$ (3 equiv)	41
4		<10
5	oxone	decomp

General procedure for acetoxylation: Pyridine **172** (1 equiv), Pd(OAc)$_2$ (10 mol %), oxidant (1.5 -3 equiv) in AcOH/Ac$_2$O (0.2 M) were heated to 85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The yields were calculated based on the crude mass recovery.


N
O
N
N
Ph
172
Pd(OAc)$_2$ (10 mol %)
oxidant
AcOH/Ac$_2$O, 85 °C, 24 h
N
O
N
N
Ph
AcO
173

entry	oxidant	yield (%)
1	PhI(OAc)$_2$ (1.5 equiv)	62
2	PhI(OAc)$_2$ (2 equiv)	65
3	PhI(OAc)$_2$ (3 equiv)	41
4		<10
5	oxone	decomp

General procedure for acetoxylation: Pyridine **172** (1 equiv), Pd(OAc)$_2$ (10 mol %), PhI(OAc)$_2$ (1.5 equiv) in solvent (0.2 M) were heated to 85 °C for 24 h. Upon cooling, the solvent was removed by azeotropic removal with heptanes (3 x 15 mL). The product ratios were determined by crude ^{1}H NMR. In entry 4, K_2CO_3 (1 equiv) and PivOH (20 mol %) were added to the reaction with the other reagents.



119
1. *i*-BuOCOCl, Et$_3$N
ArNH$_2$
CH$_2$Cl$_2$, 0 to 23 °C
2. TFA, CH$_2$Cl$_2$, 23 °C
78% 2 steps
178
X = OMe 78% yield (2 steps)
X = CF$_3$ 85% yield (2 steps)
PhCHO, PTSA
MgSO$_4$
PhCH$_3$, reflux
179
X = OMe 75% yield
X = CF$_3$ 82% yield
•HBr
LDA, NaH
THF, -78 to 23 °C
180a
180b
X = OMe 85% yield 2.4 : 1 mixture
X = CF$_3$ 98% yield 2.1 : 1 mixture

Aminal 179-OMe: To a solution of (*S*)-*N*-Boc proline (0.500 g, 2.32 mmol) in CH_2Cl_2 (11.6 mL) at 0 ˚C was added isobutyl chloroformate (0.334 mL, 2.56 mmol) and Et_3N (0.359 mL, 2.56 mmol). After stirring for 20 minutes at 0 ˚C, *p*-anisidine (315 mg, 2.56 mmol) was added, and the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction mixture was washed sequentially with aq. $KHSO_4$ (1 M, 15 mL), sat. aq. $NaHCO_3$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (5 mL), cooled to 0 ˚C and filtered to afford amide (750 mg, 99% yield, R_f = 0.41 in 1:1 hexanes/EtOAc) as a light beige solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide (3.72 g, 11.6 mmol) in CH_2Cl_2 (23.2 mL) at 23 ˚C was added TFA (18.0 mL, 232 mmol). The resulting solution was stirred at 23 ˚C for 1 h, and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9-10. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2

(3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide (2.03 g, 79% yield, R_f = 0.0 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amino amide (250 mg, 1.14 mmol) in $PhCH_3$ (5.70 mL) at 23 ˚C was added benzaldehyde (0.150 mL, 1.48 mmol), $TsOH{\cdot}H_2O$ (11.0 mg, 0.0578 mmol), and $MgSO_4$ (205 mg, 1.70 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The dark brown residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford aminal **179-OMe** (264 mg, 75% yield R_f = 0.22 in 1:1 hexanes/EtOAc) as a light yellow solid.

Aminal 179-OMe: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (comp m, 6H), 6.83-6.78 (comp m, 3H), 5.56 (s, 1H), 4.07 (t, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 3.42 (dt, *J* = 9.6, 5.3 Hz, 1H), 2.92-2.86 (m, 1H), 2.23-2.17 (comp m, 2H), 1.93-1.87 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 157.0, 139.6, 130.4, 128.9, 128.5, 126.2, 123.5, 114.2, 84.4, 64.4, 56.2, 55.3, 27.6, 24.8; IR (film) 2966, 1513, 1248, 1031, 831, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{21}N_2O_2]^+$: 309.1598, found 309.1595.

Pyridine 180-OMe: To a solution of freshly distilled diisopropylamine (484 µL, 3.45 mmol) in THF (4.10 mL) at -78 ˚C was added *n*-BuLi (1.32 mL, 2.5 M in hexanes, 3.31 mmol). The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **179-OMe** (1.02 g, 3.31 mmol) in THF (7.00 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (331 mg, 60% dispersion in mineral oil, 8.27 mmol, washed 2 x 1.5 mL with hexanes) in DMF (9.10 mL) at 0 ˚C was added 2-

(bromomethyl)pyridine hydrobromide (697 mg, 2.76 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 2.00 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (30 mL) at 23 ˚C, and the mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **180a-OMe** (663 mg, 60% yield, R_f = 0.38 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **180b-OMe** (278 mg, 25% yield, R_f = 0.22 in 40:1 EtOAc/MeOH) as a yellow oil.

Pyridine 180a-OMe: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dt, *J* = 4.4, 1.5 Hz, 1H), 7.51 (td, *J* = 7.7, 1.9 Hz, 1H), 7.17-7.11 (comp m, 7H), 6.83 (dd, *J* = 7.8, 1.7 Hz, 2H), 6.76-6.72 (comp m, 2H), 5.30 (s, 1H), 3.69 (s, 3H), 3.36 (d, *J* = 13.2 Hz, 1H), 3.10-3.03 (comp m, 2H), 2.96 (ddd, *J* = 11.4, 6.5, 5.0 Hz, 1H), 2.30 (ddd, *J* = 13.5, 8.2, 5.5 Hz, 1H), 2.15 (dt, *J* = 13.3, 7.6 Hz, 1H), 1.83-1.76 (m, 1H), 1.66-1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 158.1, 157.2, 148.9, 140.1, 135.6, 129.7, 128.24, 128.20, 127.3, 125.3, 124.8, 121.4, 114.0, 83.7, 75.0, 55.30, 55.27, 45.6, 35.6, 24.6; IR (film) 2958, 1700, 1589, 1513, 1249, 749, 702 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{26}N_3O_2]^+$: 400.2020, found 400.2024.

Pyridine 181b-OMe: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.52 (td, *J* = 7.7, 1.9 Hz, 1H), 7.26-7.08 (comp m, 6H), 6.89-6.85 (comp m, 2H), 6.73-6.69 (comp m, 2H), 5.30 (s, 1H), 3.71 (s, 3H), 3.49 (d, *J* = 13.1 Hz, 1H), 3.13 (d, *J* = 13.1 Hz, 1H), 2.54 (td, *J* = 9.1, 6.7 Hz, 1H), 2.44-2.37 (comp m, 2H), 2.14-2.05 (m, 1H), 1.68-1.59 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 177.4, 157.6, 156.7, 136.1, 134.4, 128.54, 128.47, 128.2, 124.7, 123.7, 121.7, 113.8, 78.8, 75.1, 55.3, 51.1, 46.2, 35.9, 24.6; IR (film) 2961, 1703, 1512, 1248, 1032, 830, 702 cm^{-1}; HRMS (ESI^{+}) *m/z* calc'd for $(M+H)^{+}$ $[C_{25}H_{26}N_3O_2]^{+}$: 400.2020, found 400.2016.

Aminal 179-CF$_3$: To a solution of (*S*)-*N*-Boc proline (2.50 g, 11.6 mmol) in CH_2Cl_2 (33.2 mL) at 0 ˚C was added isobutyl chloroformate (1.67 mL, 12.8 mmol) and Et_3N (1.80 mL, 12.8 mmol). After stirring for 20 minutes at 0 ˚C, *p*-trifluoromethylaniline (1.59 mL, 12.8 mmol) was added and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was washed sequentially with aq. $KHSO_4$ (1 M, 50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 ˚C and filtered to afford amide (4.44 g, 89% yield, R_f = 0.59 in 1:1 hexanes/EtOAc) as a light beige solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide (3.70 g, 10.3 mmol) in CH_2Cl_2 (20.7 mL) at 23 ˚C was added TFA (15.9 mL, 207 mmol). The solution was stirred at 23 ˚C for 1 h, at which point the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide (2.57 g, 96% yield, R_f = 0.00 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amino amide (948 mg, 3.70 mmol) in $PhCH_3$ (18.3 mL) at 23 ˚C was added benzaldehyde (0.482 mL, 4.80 mmol), $TsOH\cdot H_2O$ (34.9 mg, 0.184 mmol), and $MgSO_4$ (663 mg, 5.50 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The dark brown residue was purified by flash chromatography (4:1 → 7:3 hexanes/EtOAc eluent) to afford aminal **179-CF$_3$** (1.04 g, 82% yield, R_f = 0.45 in 1:1 hexanes/EtOAc) as a light yellow solid.

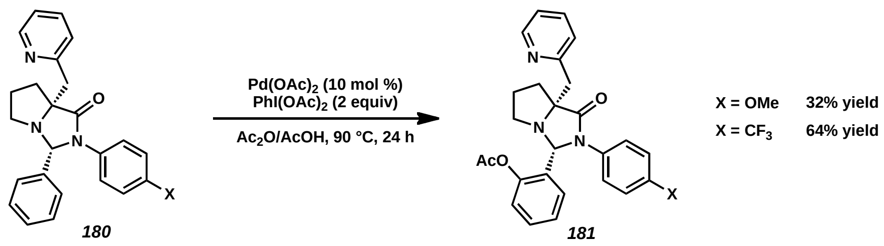
Aminal 179-CF$_3$: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.40-7.34 (comp m, 3H), 7.33-7.28 (comp m, 2H), 5.74 (s, 1H), 4.03 (t, *J* = 6.7 Hz, 1H), 3.47 (dt, *J* = 9.6, 5.0 Hz, 1H), 2.87 (app. q, *J* = 8.6 Hz, 1H), 2.22 (dt, *J* = 8.1, 6.6, 2H), 1.95-1.87 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.5, 140.8, 138.6, 129.2, 128.8, 126.1 (q, *J* = 3.8 Hz), 125.8, 120.0, 83.1, 64.2, 56.0, 27.4, 24.8; IR (film) 3034, 2971, 1711, 1615, 1522, 1380, 1327, 1124 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H)$^+$ [$C_{19}H_{19}F_3N_2O$]$^+$: 347.1366, found 347.1365.

Pyridine 180-CF$_3$: To a solution of freshly distilled diisopropylamine (634 μL, 4.50 mmol) in THF (4.8 mL) at -78 ˚C was added *n*-BuLi (1.73 mL, 2.5 M in hexanes, 4.30 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **179-CF$_3$** (1.50 g, 4.30 mmol) in THF (6.00 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (433 mg, 60% dispersion in mineral oil, 10.8 mmol, washed 2 x 1.5 mL with hexanes) in DMF (8.80 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (913 mg, 3.60 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 2.00 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H$_2$O (30 mL) at 23 ˚C, and the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **180a-CF$_3$** (1.04 g, 66% yield, R_f = 0.58 in 40:1

EtOAc/MeOH) as a beige solid and pyridine **180b-CF$_3$** (498 mg, 32% yield, R$_f$ = 0.19 in 40:1 EtOAc/MeOH) as a light beige solid.

Pyridine 180a-CF$_3$: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (dd, *J* = 4.9, 0.8 Hz, 1H), 7.55-7.47 (comp m, 5H), 7.22-7.19 (comp m, 3H), 7.17-7.14 (m, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.8 Hz, 2H), 5.49 (s, 1H), 3.19 (ABq, *J* = 13.2 Hz, Δν = 69.6 Hz, 2H), 3.21 (dt, *J* = 11.1, 6.8 Hz, 1H), 3.00 (dt, *J* = 11.4, 5.8 Hz, 1H), 2.31-2.19 (comp m, 2H), 1.84-1.74 (m, 1H), 1.65-1.55 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 175.4, 157.3, 148.3, 140.12, 140.11, 139.5, 136.2, 128.6, 125.9 (q, *J* = 3.8 Hz), 125.5, 125.2, 121.7, 121.4, 82.6, 75.1, 56.0, 44.8, 35.6, 24.6; IR (film) 3063, 2967, 1710, 1614, 1326, 1122 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+Na)$^+$ [C$_{25}$H$_{22}$F$_3$N$_3$ONa]$^+$: 460.1607, found 460.1614.

Pyridine 181b-CF$_3$: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.50 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.52 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.24-7.21 (comp m, 4H), 7.17-7.14 (comp m, 3H), 7.09-7.07 (comp m, 2H), 5.32 (s, 1H), 3.50 (d, *J* = 13.2 Hz, 1H), 3.12 (d, *J* = 13.2, 1H), 2.54 (td, *J* = 9.0, 6.9 Hz, 1H), 2.46-2.37 (comp m, 2H), 2.16-2.10 (m, 1H), 1.70-1.62 (comp m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.9, 149.1, 140.7, 136.1, 133.8, 128.8, 128.5, 128.2, 125.6 (q, *J* = 3.8 Hz), 124.5, 121.8, 121.4, 78.5, 74.9, 51.3, 46.3, 36.0, 24.5; IR (film) 2967, 1713, 1614, 1324, 1166, 1119, 844, 703 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H)$^+$ [C$_{25}$H$_{23}$F$_3$N$_3$O]$^+$: 438.1788, found 438.1793.



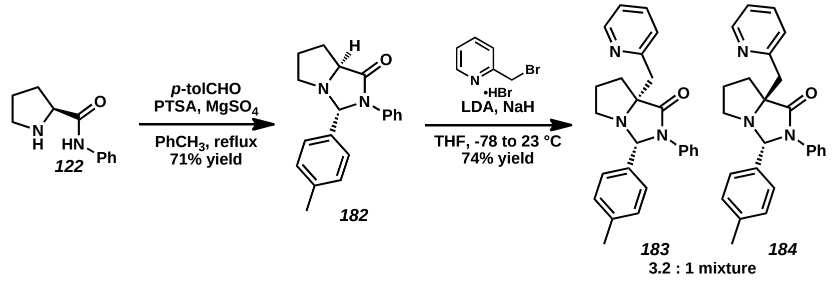
Acetate 181-OMe: Pyridine **180-OMe** (200 mg, 0.501 mmol), $Pd(OAc)_2$ (11.2 mg, 0.0501 mmol), and $PhI(OAc)_2$ (161 mg, 0.501 mmol) were dissolved in AcOH (3.50 mL) and Ac_2O (3.50 mL) in a round-bottomed flask. The flask was capped and heated to 95 ˚C for 8 h, at which time $PhI(OAc)_2$ (161 mg, 0.501 mmol) was added. The reaction was stirred an additional 16 h at 95 ˚C. Upon cooling the solvent was removed by azeotropic evaporation with heptanes (3 x 15 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (17:3 to 4:1 hexanes/acetone eluent) to afford acetate **181-OMe** (73.4 mg, 32% yield, R_f = 0.30 in 1:1 hexanes/acetone) as a light yellow residue.

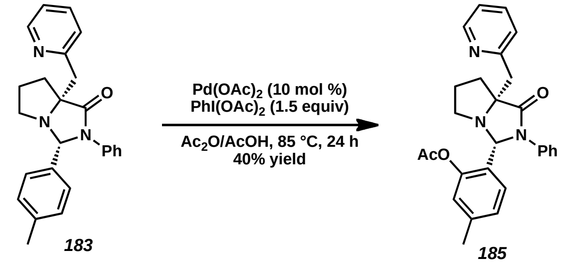
Acetate 181-OMe: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.45 (td, *J* = 7.7, 1.9 Hz, 1H), 7.38-7.34 (comp m, 2H), 7.26-7.22 (m, 1H), 7.11-7.06 (comp m, 2H), 6.99 (td, *J* = 7.6, 1.1 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.81-6.74 (comp m, 3H), 5.70 (s, 1H), 3.72 (s, 3H), 3.14-3.05 (comp m, 3H), 2.93 (dt, *J* = 10.5, 6.4 Hz, 1H), 2.34 (s, 3H), 2.27-2.15 (comp m, 2H), 1.75-1.61 (m, 1H), 1.42-1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 168.7, 157.3, 156.8, 148.9, 148.6, 135.6, 132.0, 130.3, 129.0, 126.9, 126.0, 125.7, 122.7, 121.4, 114.1, 77.7, 75.0, 57.0, 55.3, 44.9, 34.8, 24.7, 21.1; IR (film) 2959, 1766, 1513, 1249, 1199, 832 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{28}N_3O_4]^+$: 458.2074, found 458.2080.

Acetate 181-CF$_3$: Pyridine **180-CF$_3$** (300 mg, 0.686 mmol), $Pd(OAc)_2$ (15.4 mg, 0.0686 mmol), and $PhI(OAc)_2$ (221 mg, 0.686 mmol) were dissolved in AcOH (3.50 mL) and Ac_2O (3.50 mL) in a round-bottomed flask. The flask was capped and heated to 95 ˚C for 12 h, at which time $PhI(OAc)_2$ (221 mg, 0.686 mmol) was added. The reaction was stirred an additional 12 h at 95 ˚C. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 15 mL).

Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate **181-CF$_3$** (218 mg, 64% yield, R_f = 0.53 in 1:1 hexanes/acetone) as a light yellow residue.

Acetate 181-CF$_3$: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.6 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.47 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30 (td, *J* = 8.4, 1.6 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.10 (dd, *J* = 6.9, 5.4 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.71 (dd, *J* = 7.8, 1.3 Hz, 1H), 5.80 (s, 1H), 3.21 (dt, *J* = 10.2, 6.1 Hz, 1H), 3.08 (ABq, *J* = 13.2 Hz, Δν =12.2 Hz, 2H), 2.95 (dt, *J* = 10.2, 6.7 Hz, 1H), 2.39 (s, 3H), 2.26-2.19 (comp m, 2H), 1.71-1.64 (m, 1H), 1.38-1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 168.7, 156.9, 148.9, 148.2, 140.3, 136.0, 131.5, 129.3, 128.6, 126.22, 126.16, 126.1 (q, *J* = 3.8 Hz), 125.9, 123.1, 121.6, 119.9, 77.6, 75.0, 57.6, 44.3, 34.8, 24.7, 21.1; IR (film) 2968, 1768, 1712, 1379, 1326, 1199, 843, 736 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{25}F_3N_3O_3]^+$ 496.1843, found 496.1843.


122
p-tolCHO
PTSA, MgSO4
PhCH3, reflux
71% yield
182
•HBr
LDA, NaH
THF, -78 to 23 °C
74% yield
183
184
3.2 : 1 mixture


183
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
40% yield
185

To a solution of amide **122** (684 mg, 3.60 mmol) in $PhCH_3$ (17.9 mL) at 23 ˚C was added *p*-tolualdehyde (0.553 mL, 4.67 mmol), $TsOH{\cdot}H_2O$ (34.2 mg, 0.180 mmol) and $MgSO_4$ (562 mg, 4.67 mmol). The mixture was heated to reflux and stirred 16 h. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (7:3 → 3:2 hexanes/EtOAc eluent) to afford aminal **182** (764 mg, 73% yield, R_f = 0.34 in 1:1 hexanes/EtOAc) as a beige solid.

Aminal 182: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.31-7.26 (comp m, 2H), 7.21-7.14 (comp m, 4H), 7.11-7.07 (m, 1H), 5.65 (s, 1H), 4.03 (t, *J* = 6.7 Hz, 1H), 3.42 (dt, *J* = 9.7, 5.1 Hz, 1H), 2.86 (app. q, *J* = 8.5 Hz, 1H), 2.31 (s, 3H), 2.20 (app. q, *J* = 7.3 Hz, 2H), 1.92-1.85 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 138.3, 137.8, 136.5, 129.7, 128.9, 125.9, 124.9, 121.0, 83.5, 64.3, 55.9, 27.4, 24.8, 21.1; IR (film) 2967, 1701, 1498, 1382, 757, 691 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{19}H_{21}N_2O]^+$: 293.1648, found 293.1650.

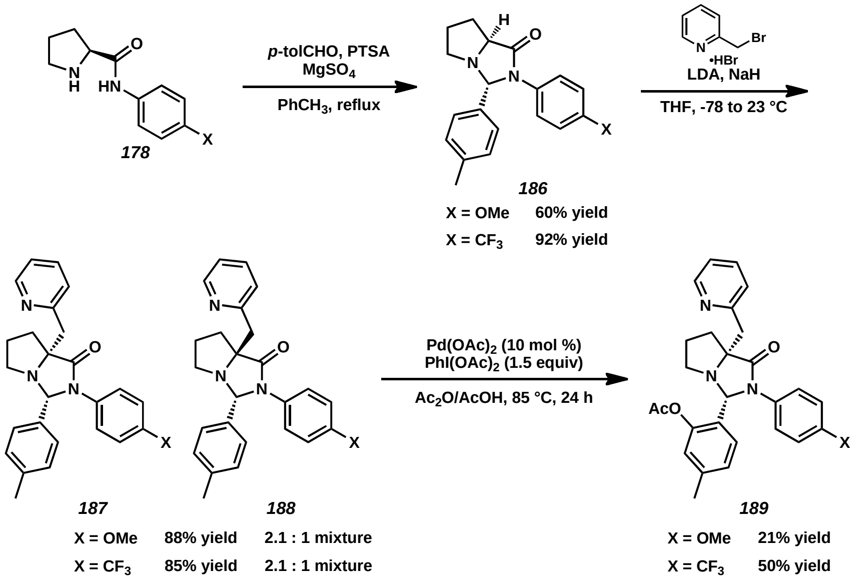
To a solution of freshly distilled diisopropylamine (354 μL, 2.52 mmol) in THF (4.00 mL) at -78 ˚C was added *n*-BuLi (0.970 mL, 2.5 M in hexanes, 2.42 mmol). The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **182** (707 mg, 2.42 mmol) in THF (4.10 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (242 mg, 60% dispersion in mineral oil, 6.05 mmol, washed with 2 x 1.5 mL hexanes) in DMF (7.00 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (510 mg, 2.02 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.10 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (30 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **183** (545 mg, 71% yield, R_f = 0.40 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **184** (210 mg, 27% yield, R_f = 0.09 in 40:1 EtOAc/MeOH) as a light beige solid.

Pyridine 183: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.51 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.15-7.12 (m, 1H), 7.10-7.04 (comp m, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.40 (s, 1H), 3.19 (ABq, *J* = 13.2 Hz, Δν = 88.2 Hz, 2H), 3.13-3.07 (m, 1H), 2.96 (dt, *J* = 11.3, 5.8 Hz, 1H), 2.32-2.26 (m, 1H), 2.26 (s, 3H), 2.17 (dt, *J* = 13.7, 7.0 Hz, 1H), 1.83-1.72 (m, 1H), 1.62-1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 158.0, 148.8, 137.9, 137.2, 137.0, 135.5, 129.0, 128.7, 127.0, 125.4, 125.3, 122.6, 121.3, 82.9, 75.0, 55.6, 45.4, 35.4, 24.6, 21.1; IR (film) 3048, 2965, 2878, 1701, 1592, 1499, 1387, 754, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{26}N_3O]^+$: 384.2070, found 384.2068.

Pyridine 184: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.8, 0.9 Hz, 1H), 7.50 (td, *J* = 7.7, 1.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.19-7.15 (comp m, 3H), 7.04-6.96 (comp m, 7H), 5.31 (s, 1H), 3.48 (d, *J* = 13.1 Hz, 1H), 3.12 (d, *J* = 13.1 Hz, 1H), 2.55 (dt, *J* = 9.6, 7.6 Hz, 1H), 2.44-2.37 (comp m, 2H), 2.25 (s, 3H), 2.10 (dt, *J* = 12.6, 6.1 Hz, 1H), 1.66-1.59 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 157.6, 149.1, 138.3, 137.5, 136.0, 131.3, 128.9, 128.4, 128.3, 124.8, 124.6, 122.2, 121.7, 78.4, 75.0, 51.1, 46.2, 35.8, 24.5, 21.1; IR (film) 3047, 2967, 2870, 1707, 1597, 1501, 1379, 734, 694 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{25}N_3ONa]^+$: 406.1890, found 406.1895.

Acetate 185: Pyridine **183** (100 mg, 0.261 mmol), $Pd(OAc)_2$ (5.9 mg, 0.0261 mmol), and $PhI(OAc)_2$ (168 mg, 0.522 mmol) were dissolved in AcOH (1.30 mL) and Ac_2O (1.30 mL) in a round-bottomed flask. The flask was capped and heated to 90 ˚C, and stirred for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 15 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate **185** (51.3 mg, 45% yield, $R_f = 0.44$ in 1:1 hexanes/acetone) as a light yellow residue.

Acetate 185: ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, J = 4.1, 0.7 Hz, 1H), 7.54-7.44 (comp m, 3H), 7.29-7.23 (comp m, 2H), 7.10-7.04 (comp m, 2H), 6.93-6.89 (comp m, 2H), 6.81 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 5.74 (s, 1H), 3.12 (dt, J = 10.3, 6.2 Hz, 1H), 3.08 (s, 2H), 2.92 (dt, J = 10.3, 6.6 Hz, 1H), 2.36 (s, 3H), 2.29 (s, 3H), 2.20 (app. t, J = 7.2 Hz, 2H), 1.69-1.62 (m, 1H), 1.34-1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 168.8, 157.5, 148.7, 148.5, 139.3, 137.4, 135.5, 128.93, 128.85, 126.9, 126.5, 125.8, 124.9, 123.3, 121.3, 120.7, 98.5, 77.6, 74.9, 57.2, 44.7, 34.6, 24.7, 21.1 21.0; IR (film) 2925, 1767, 1703, 1383, 1200, 753, 692 cm^{-1}; HRMS (ESI$^+$) m/z calc'd for $(M+H)^+$ $[C_{27}H_{28}N_3O_3]^+$: 442.2125, found 442.2130.


178
p-tolCHO, PTSA
MgSO4
PhCH3, reflux
186
X = OMe 60% yield
X = CF3 92% yield
•HBr
LDA, NaH
THF, -78 to 23 °C
187
188
X = OMe 88% yield 2.1 : 1 mixture
X = CF3 85% yield 2.1 : 1 mixture
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
AcO
189
X = OMe 21% yield
X = CF3 50% yield

Aminal 186-OMe: To a solution of amide **178** (500 mg, 2.27 mmol) in $PhCH_3$ (11.3 mL) at 23 ˚C was added *p*-tolualdehyde (0.348 mL, 2.95 mmol), $TsOH{\cdot}H_2O$ (21.6 mg, 0.114 mmol) and $MgSO_4$ (410 mg, 3.40 mmol). The mixture was heated to reflux and stirred 16 h. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (7:3 → 3:2 hexanes/EtOAc eluent) to afford aminal **186-OMe** (439 mg, 60% yield, R_f = 0.30 in 1:1 hexanes/EtOAc 1 % Et_3N) as a beige solid.

Pyridine 187: To a solution of freshly distilled diisopropylamine (199 μL, 1.42 mmol) in THF (2.8 mL) at -78 ˚C was added *n*-BuLi (0.540 mL, 2.5 M in hexanes, 1.36 mmol). The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **186-OMe** (439 mg, 1.36 mmol) in THF (4.00 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (136 mg, 60% dispersion in mineral oil, 3.40 mmol, washed with 2 x 1.0 mL hexanes) in DMF (5.80 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (287 mg, 1.13 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.00 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (30 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **187-OMe** (206 mg, 54% yield, R_f = 0.40 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **188-OMe** (90.4 mg, 31% yield, R_f = 0.09 in 40:1 EtOAc/MeOH) as a light beige solid.

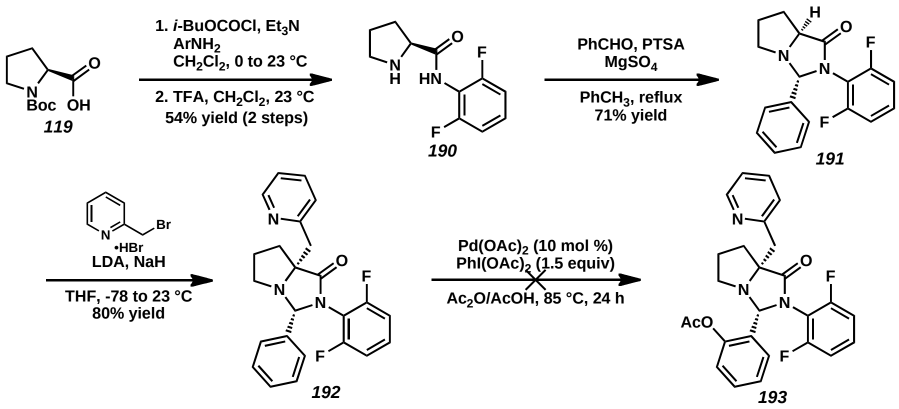
Acetate 189-OMe: Pyridine **187-OMe** (15.0 mg, 0.0363 mmol), $Pd(OAc)_2$ (0.8 mg, 3.63 μmol), and $PhI(OAc)_2$ (17.5 mg, 0.0544 mmol) were dissolved in AcOH (0.180 mL) and Ac_2O (0.180 mL) in a round-bottomed flask. The flask was capped and heated to 90 ˚C, and stirred for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (17:3 → 4:1 hexanes/acetone eluent) to afford acetate **189-OMe** (3.8 mg, 21% yield, R_f = 0.40 in 1:1 hexanes/acetone) as a light yellow residue.

Aminal 186-CF$_3$: To a solution of amide **178** (500 mg, 1.93 mmol) in $PhCH_3$ (9.70 mL) at 23 ˚C was added *p*-tolualdehyde (0.297 mL, 2.52 mmol), $TsOH{\cdot}H_2O$ (18.4 mg, 0.0968 mmol) and $MgSO_4$ (350 mg, 2.90 mmol). The mixture was heated to reflux and stirred 16 h. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography (7:3 to 3:2 hexanes/EtOAc eluent) to afford aminal **186-CF$_3$** (645 mg, 92% yield, R_f = 0.40 in 1:1 hexanes/EtOAc 1 % Et_3N) as a beige solid.

Pyridine 187-CF$_3$: To a solution of freshly distilled diisopropylamine (262 μL, 1.86 mmol) in THF (4.00 mL) at -78 ˚C was added *n*-BuLi (0.720 mL, 2.5 M in hexanes, 1.79 mmol). The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **186-CF$_3$** (645 mg, 1.79 mmol) in THF (5.00 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (179 mg, 60% dispersion in mineral oil, 4.47 mmol, washed with 2 x 1.0 mL hexanes) in DMF (8.00 mL) at 0 ˚C was added 2-

(bromomethyl)pyridine hydrobromide (377 mg, 1.49 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.00 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (30 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **187-CF₃**(387 mg, 70% yield, R_f = 0.45 in 40:1 EtOAc/MeOH) as a beige solid and pyridine **188-CF₃** (183 mg, 15% yield, R_f = 0.15 in 40:1 EtOAc/MeOH) as a light beige solid.

Acetate 189-OMe: Pyridine **187-CF₃** (15.0 mg, 0.0332 mmol), $Pd(OAc)_2$ (0.7 mg, 3.32 μmol), and $PhI(OAc)_2$ (16.1 mg, 0.0498 mmol) were dissolved in AcOH (0.170 mL) and Ac_2O (0.170 mL) in a round-bottomed flask. The flask was capped and heated to 90 ˚C, and stirred for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (17:3 to 4:1 hexanes/acetone eluent) to afford acetate **187-CF₃** (8.8 mg, 50% yield, R_f = 0.45 in 1:1 hexanes/acetone) as a light yellow residue.



119
1. i-BuOCOCl, Et3N
ArNH2
CH2Cl2, 0 to 23 °C
2. TFA, CH2Cl2, 23 °C
54% yield (2 steps)
190
PhCHO, PTSA
MgSO4
PhCH3, reflux
71% yield
191
•HBr
LDA, NaH
THF, -78 to 23 °C
80% yield
192
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 24 h
193

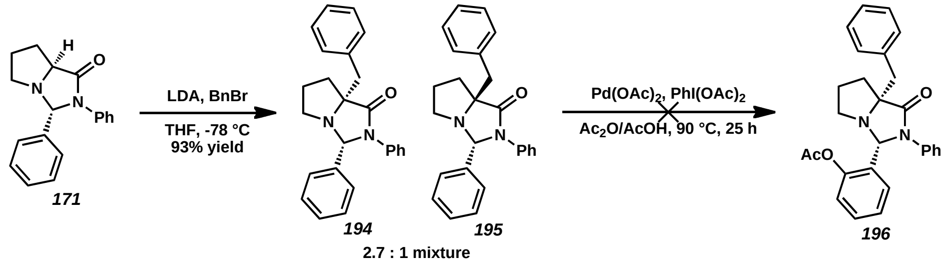
Aminal 191: To a solution of (*S*)-*N*-Boc proline (500 mg, 2.32 mmol) in CH_2Cl_2 (15.5 mL) at 0 ˚C was added isobutyl chloroformate (0.334 mL, 2.56 mmol) and Et_3N (0.359 mL, 2.56 mmol). After stirring for 20 minutes at 0 ˚C, 2,6-difluoroaniline (0.275 mL, 2.56 mmol) was added and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was washed sequentially with aq. $KHSO_4$ (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a pale brown solid. The crude solid was suspended in hexanes (15 mL), cooled to 0 ˚C and filtered to afford amide (736 g, 97% yield, R_f = 0.59 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amide (736 g, 2.26 mmol) in CH_2Cl_2 (4.50 mL) at 23 ˚C was added TFA (3.50 mL, 45.1 mmol). The solution was stirred at 23 ˚C for 1 h, at which point the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide **190** (284 mg, 56% yield, R_f = 0.00 in 1:1 hexanes/EtOAc) as a white solid, which was sufficiently pure to be taken on to the next step.

To a solution of amino amide **190** (283 mg, 1.25 mmol) in $PhCH_3$ (8.30 mL) at 23 ˚C was added benzaldehyde (0.164 mL, 1.63 mmol), $TsOH·H_2O$ (11.9 mg, 0.0625 mmol), and $MgSO_4$ (226 mg, 1.88 mmol). The suspension was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The dark brown residue was purified by flash chromatography (4:1 to 7:3 hexanes/EtOAc eluent) to afford aminal **191** (304 mg, 77% yield, R_f = 0.45 in 1:1 hexanes/EtOAc) as a light yellow solid.

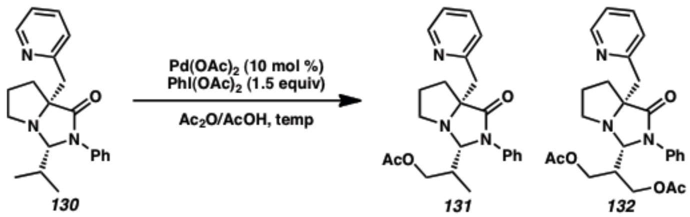
Pyridine 192: To a solution of freshly distilled diisopropylamine (233 μL, 1.66 mmol) in THF (2.00 mL) at -78 ˚C was added *n*-BuLi (0.640 mL, 2.5 M in hexanes, 1.59 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal **191** (500 g, 1.59 mmol) in THF (3.30 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (160 mg, 60% dispersion in mineral oil, 3.98 mmol, washed 2 x 1.5 mL with hexanes) in DMF (4.30 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (335 mg, 1.33 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.00 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (20 mL) at 23 ˚C, and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (2:3 hexanes/EtOAc eluent) to afford pyridine **192** (428 g, 80% yield, R_f = 0.58 in 40:1 EtOAc/MeOH) as a light yellow amorphous solid.

Acetate 193: Pyridine **192** (25.0 mg, 0.0617 mmol), $Pd(OAc)_2$ (1.4 mg, 6.17 μmol), and $PhI(OAc)_2$ (29.8 mg, 0.0925 mmol) were dissolved in AcOH (0.310 mL) and Ac_2O (0.310 mL) in a round-bottomed flask. The flask was capped and heated to 90 ˚C, and stirred for 24 h. Upon cooling, the solvent was removed by azeotropic evaporation with heptane (3 x 5 mL). Water (10 mL) was added, and the mixture was treated with solid Na_2CO_3 until pH ~9. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. No acetoxylated product was observed by crude ^{1}H NMR.



Aminal 194: To a solution of freshly distilled diisopropylamine (146 μL, 1.04 mmol) in THF (4.00 mL) at -78 ˚C was added *n*-BuLi (0.400 mL, 2.5 M in hexanes, 1.01 mmol). The solution was stirred for 10 min at -78 ˚C, at which time **171** (250 mg, 0.720 mmol) in THF (3.20 mL) was added, and the resulting solution was stirred for an additional 30 min at -78 ˚C. Benzyl bromide (225 μL, 1.44 mmol) was added at -78 ˚C, and the reaction was warmed to 23 ˚C, and stirred overnight. The reaction was quenched with water (10 mL). The aqueous was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (7:1 hexanes:EtOAc to 4:1 hexanes:EtOAc) to afford **194:195** as a 2.7 : 1 ratio of inseparable diastereomers (225 mg, 85% yield, R_f = 0.29 in 4:1 hexanes:EtOAc) as a white amorphous solid.

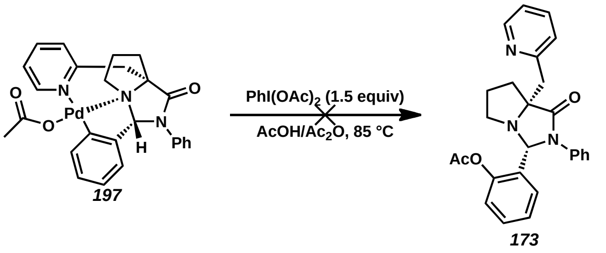
Aminal 194: ^{1}H NMR (400 MHz, $CDCl_3$) (see NMR spectrum for details); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 174.9, 140.1, 137.5, 137.4, 137.1, 136.7, 134.5, 131.1, 130.4, 128.7, 128.4, 128.38, 128.24, 128.17, 128.1, 127.8, 127.3, 126.7, 126.3, 125.4, 125.0, 122.9, 122.6, 83.4, 78.6, 75.7, 75.4, 55.1, 51.1, 44.0, 43.2, 36.1, 35.7, 24.7, 24.6; IR (film) 3031, 2965, 2877, 1704, 1599, 1497, 1385, 700 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{25}H_{25}N_2O]^+$: 369.1961, found 369.1968.



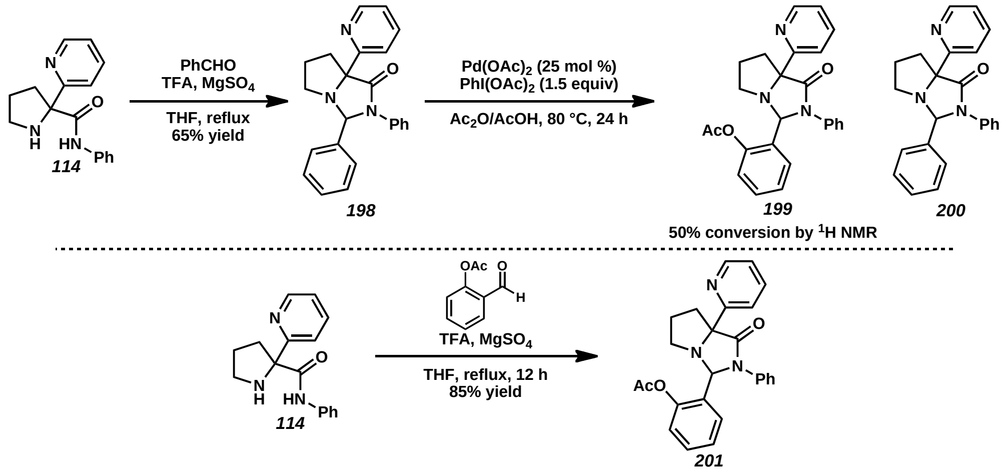
time (h)	temp (°C)	*131 : 132* (%)	dr
24	55	41 : 13	10 : 1
13	70	48 : 19	5.9 : 1

Pyridine **172** (10.0 mg, 0.0271 mmol) and $Pd(OAc)_2$ (6.1 mg, 0.0271 mmol) were dissolved in AcOH (0.270 mL) in a scintillation vial. The vial was sealed and heated to 85 ˚C for 1 h. The reaction was cooled to 23 ˚C, and the organic solvent was removed azeotropically with heptane (3 x 5 mL) to afford palladacycle **197** (17.9 mg, 99% yield) as a light brown solid. The solid was crystallized by a layering technique with CH_2Cl_2 and hexanes.

Palladacycle 197: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 5.5, 1.4 Hz, 1H), 7.85 (td, *J* = 7.7, 1.4 Hz, 1H), 7.43-7.37 (comp m, 5H), 7.09-6.96 (comp m, 4H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 5.43 (s, 1H), 4.51 (d, *J* = 14.5 Hz, 1H), 3.60 (d, *J* = 14.5 Hz, 1H), 3.55 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.83-2.75 (m, 1H), 2.61 (dd, *J* = 12.2, 7.6 Hz, 1H), 2.04 (s, 3H), 1.98-1.84 (m, 1H), 1.82-1.71 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 154.3, 151.7, 146.7, 146.3, 138.5, 134.0, 133.3, 129.4, 128.9, 128.7, 127.4, 126.5, 124.3, 124.2, 123.7, 93.3, 75.8, 62.2, 46.7, 33.6, 24.6; IR (film) 3051, 2970, 1712, 1598, 1402, 730, 702 cm^{-1}; mp 250 °C dec.


197
PhI(OAc)$_2$ (1.5 equiv)
AcOH/Ac$_2$O, 85 °C
173
AcO
Ph
Pd
N
O
H

Acetate 173: To palladacycle **197** (14.5 mg, 0.0271 mmol) in AcOH/Ac$_2$O (1:1, 0.270 mL) was added PhI(OAc)$_2$ (13.1 mg, 0.0406 mmol) and heated to 85 °C overnight. Upon cooling to 23 °C, dppe (21.6 mg, 0.0541 mmol) was added and the mixture stirred overnight at 23 °C. The solvent was removed via azeotropic removal with heptanes (3 x 10 mL). No acetoxylated product was observed by crude ^{1}H NMR.

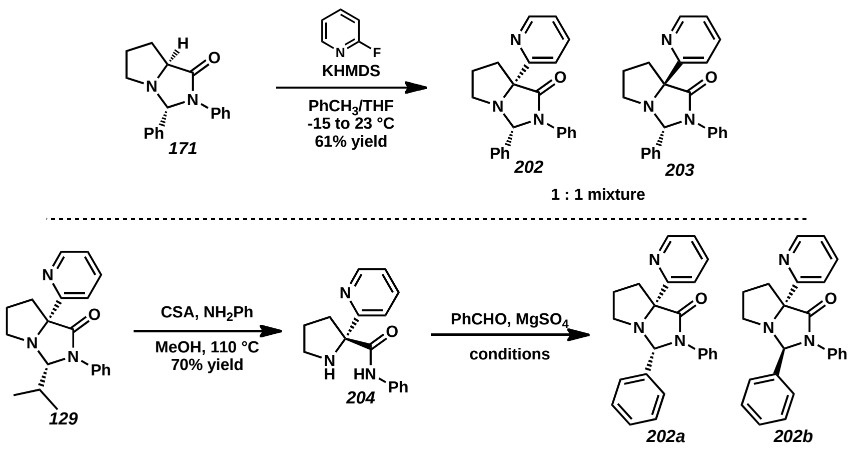

114
PhCHO
TFA, MgSO$_4$
THF, reflux
65% yield
198
Pd(OAc)$_2$ (25 mol %)
PhI(OAc)$_2$ (1.5 equiv)
Ac$_2$O/AcOH, 80 °C, 24 h
199
200
50% conversion by ^{1}H NMR
114
OAc
TFA, MgSO$_4$
THF, reflux, 12 h
85% yield
201
AcO
Ph
HN
N
H
O

Aminal 198: To a solution of amino amide **114** (100 mg, 0.374 mmol) in THF (3.70 mL) at 23 °C was added benzaldehyde (49.2 μL, 0.486 mmol), TFA (5.8 μL, 0.0748 mmol) and MgSO$_4$ (67.5 mg, 0.561 mmol). The suspension was heated to 75 °C for 12 h. Upon cooling to 23 °C, the solution was quenched with sat. aq. NaHCO$_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by column chromatography (7:3 to 1:1 hexanes/EtOAc eluent) to afford aminal **198** (85.8 mg, 65% yield, R$_f$ = 0.10 in 1:1 hexanes:EtOAc) as a beige solid.

Acetate 199: Pyridine **198** (10.0 mg, 0.0281 mmol), $Pd(OAc)_2$ (1.6mg, 7.03 μmol), and $PhI(OAc)_2$ (13.6 mg, 0.0422 mmol) were dissolved in AcOH (0.140 mL) and Ac_2O (0.140 mL) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 80 °C for 24 h. Upon cooling, CH_2Cl_2 (10 mL) and water (10 mL) were added and the mixture was neutralized with Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude ^{1}H NMR showed 50% conversion to acetate **199**.

Aminal 201: To a solution of amino amide **114** (50 mg, 0.187 mmol) in THF (1.87 mL) at 23 °C was added acetylated salicylaldehyde (39.9 mg, 0.243 mmol), TFA (1.4 μL, 0.0187 mmol) and $MgSO_4$ (33.8 mg, 0.281 mmol). The suspension was heated to 75 °C for 12 h. Upon cooling to 23 °C, the solution was quenched with sat. aq. $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (7:3 to 1:1 hexanes/EtOAc eluent) to afford acetate **201** (65.6 mg, 85% yield, R_f = 0.50 in EtOAc) as a beige solid.

Aminal 201: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.69-7.62 (comp m, 2H), 7.33-7.17 (comp m, 6H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.07-7.02 (comp m, 3H), 6.54 (s, 1H), 2.83 (dt, *J* = 13.5, 8.9 Hz, 1H), 2.74 (td, *J* = 9.5, 6.7 Hz, 1H), 2.59-2.55 (m, 1H), 2.42 (ddd, *J* = 12.9, 8.4, 4.0 Hz, 1H), 2.35 (s, 3H), 1.90-1.79 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 169.4, 160.3, 149.7, 149.3, 137.8, 136.4, 129.6, 129.0, 128.5, 126.9, 125.6, 124.7, 123.3, 122.4, 121.8, 120.9, 77.9, 72.6, 50.1, 36.0, 24.7, 20.8; IR (film) 2967, 1766, 1711, 1587, 1369, 1198, 753 cm^{-1}; HRMS (ESI^{+}) *m/z* calc'd for $(M+Na)^{+}$ $[C_{25}H_{23}N_{3}O_{3}Na]^{+}$: 436.1632, found 436.1632.



H
O
N
N
Ph
Ph
171
N
F
KHMDS
PhCH3/THF
-15 to 23 °C
61% yield
202
203
1 : 1 mixture
129
CSA, NH2Ph
MeOH, 110 °C
70% yield
H
HN
204
PhCHO, MgSO4
conditions
202a
202b

acid	solvent	temp (°C), time (h)	*a : b*
TFA (10 mol %)	THF	72, 18 h	0 : 1.0
PTSA (5 mol %)	$PhCH_3$	110, 24 h	0 : 1.0
AcOH (1 M)	$PhCH_3$	110 °C, 24 h	4.3 : 1.0
AcOH (0.5 M)	$PhCH_3$	110 °C, 24 h	6.3 : 1.0
AcOH (0.1 M)	$PhCH_3$	110 °C, 24 h	6.0 : 1.0

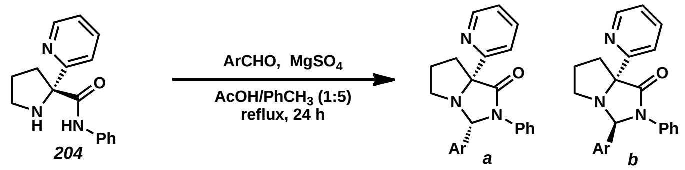
Pyridine 202: To a solution of aminal **171** (585 mg, 2.10 mmol), 2-fluoropyridine (181 μL, 2.10 mmol) in $PhCH_3$ (7.01 mL) at -15 ˚C was added KHMDS (419 mg, 2.10 mmol) in THF (4.20 mL) slowly over 1 h. Upon completion of addition, the reaction was allowed to warm to 23 ˚C and stirred overnight. The reaction was filtered over a pad of silica (5 x 5 cm, 100 mL EtOAC eluent) and concentrated. The crude product was purified by flash chromatography (3:1 to 1:1 hexanes/EtOAc eluent) to afford a 1 to 1 mixture of diastereomers of pyridine **202** (459 mg, 61% yield, $R_f = 0.10$ in 1:1 hexanes/EtOAc) as a light beige solid.

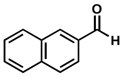
Pyridine 202: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.53-7.48 (comp m, 4H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.20-7.15 (comp m, 5H), 7.10-7.04 (comp m, 2H), 5.68 (s, 1H), 3.48 (dt, *J* = 10.6, 6.4 Hz, 1H), 3.20 (dt, *J* = 10.6, 6.6 Hz, 1H), 2.70 (dt, *J* = 13.2, 7.6 Hz, 1H), 2.57 (ddd, *J* = 13.4, 7.4, 6.2 Hz, 1H), 2.04-1.91 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 161.1, 149.2, 139.74, 139.69, 137.2, 136.0, 128.8, 128.3, 128.2, 127.0, 125.2, 122.1, 121.9, 121.0, 83.2, 77.9, 56.7, 37.6, 25.2; IR (film) 2966, 1704, 1587, 1495, 1382, 1299, 753, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{23}H_{21}N_3ONa]^+$: 378.1577, found 378.1574.

Amino Amide 204: To pyridine **129** (750 mg, 2.33 mmol) in a screw cap vial with Teflon cap was added CSA (542 mg, 2.33 mmol), NH_2Ph (106 μL, 1.17 mmol) and MeOH (4.66 mL). The reaction was heated to 110 °C for 24 h. Upon cooling, the reaction mixture was concentrated. To the residue was added sat. aq. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (3:1 to 3:2 hexanes/EtOAc eluent) to afford amino amide **204** (874 mg, 70% yield (97% yield borsm) $R_f = 0.05$ in 1:1 hexanes/EtOAc) as a beige solid.

Amide 204: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (bs, 1H), 8.47 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.89 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.69 (td, *J* = 7.8, 1.8 Hz, 1H), 7.61-7.58 (comp m, 2H), 7.31-7.26 (comp m, 2H), 7.19 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 7.08-7.03 (m, 1H), 4.29 (bs, 1H), 3.19 (dt, *J* = 10.3, 7.0 Hz, 1H), 3.11 (ddd, *J* = 10.3, 6.9, 5.6 Hz, 1H), 2.81 (ddd, *J* = 12.6, 6.9, 5.6 Hz, 1H), 2.11 (dt, *J* = 12.6, 7.9 Hz, 1H), 1.91-1.72 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 173.2, 160.3, 147.4, 138.0, 136.7, 128.8, 123.8, 122.5, 122.4, 119.1, 74.2, 47.1, 39.1, 26.9; IR (film) 3262, 2968, 2869, 1682, 1601, 1516, 1441, 1312, 751, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{16}H_{18}N_3O]^+$: 268.1444, found 268.1445.

General procedure for condensation reaction: To amide **204** (1 equiv) in $PhCH_3$ or THF (0.1 M) was added benzaldehyde (1.3 equiv), $MgSO_4$ (1.5 equiv) and acid (amount indicated) and refluxed overnight. Upon cooling, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Product ratios were determined by crude ^1H NMR.



ArCHO	product	dr (*a* : *b*)	yield (%)	ArCHO	product	dr (*a* : *b*)	yield (%)
Ph	202	4.0 : 1	89	*p*-OMe	208	5.8 : 1	78
p-Me	205	6.0 : 1	86	*p*-Cl	209	3.8 : 1	67
m-Me	206	5.8 : 1	76		210	7.3 : 1	80
o-Me	207	1 : 1.5	87				

General procedure for condensation reaction: To amide **204** (1 equiv) in $PhCH_3$ or THF (0.1 M) was added benzaldehyde (1.3 equiv), $MgSO_4$ (1.5 equiv) and acid (amount indicated) and refluxed overnight. Upon cooling, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Product ratios were determined by crude ^1H NMR.

Pyridine 205: According to the general procedure, amino amide **204** (120 mg, 0.449 mmol), *p*-tolualdehyde (69.0 μL, 0.584 mmol), $MgSO_4$ (81.1 mg, 0.674 mmol), and $PhCH_3$/AcOH (5:1, 2.99 mL) were heated to 110 °C for 24 h. Aminal **205** was isolated as a 6.0:1 mixture of diastereomers (143 mg, 86 % yield, R_f = 0.53 in 40:1 EtOAc:MeOH eluent) as a beige solid. The major diastereomer could be further purified for characterization analysis.

Pyridine 205: ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.56 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.50 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45-7.42 (comp m, 2H), 7.25-7.21 (comp m, 2H), 7.12-7.04 (comp m, 4H), 7.00 (d, *J* = 7.9 Hz, 2H), 5.63 (s, 1H), 3.42 (dt, *J* = 10.7, 6.5 Hz, 1H), 3.18 (dt, *J* = 10.7, 6.5 Hz, 1H), 2.72-2.57 (comp m, 2H), 2.25 (s, 3H), 2.03-1.89 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 161.2, 149.2, 138.0, 137.1, 136.8, 136.0, 129.1, 128.7, 126.9, 125.2, 122.3, 121.9, 121.0, 83.1, 77.9, 56.4, 37.5, 25.2, 21.1; IR (film) 2925, 1707, 1598, 1499, 1381, 1313, 753, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{24}N_3O]^+$: 370.1914, found 370.1915.

Pyridine 206: According to the general procedure, amino amide **204** (150 mg, 0.561 mmol), *m*-tolualdehyde (85.7 μL, 0.729 mmol), $MgSO_4$ (101 mg, 0.842 mmol), and $PhCH_3$/AcOH (5:1, 3.74 mL) were heated to 110 °C for 24 h. Aminal **206** was isolated as a 5.8:1 mixture of diastereomers (157 mg, 76% yield, R_f = 0.53 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

Pyridine 206: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.8, 0.7 Hz, 1H), 7.53-7.44 (comp m, 4H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.10-7.03 (comp m, 3H), 6.98-6.94 (comp m, 2H), 5.63 (s, 1H), 3.49 (dt, *J* = 10.5, 6.2 Hz, 1H), 3.19 (dt, *J* = 10.5, 6.6 Hz, 1H), 2.70 (dt, *J* = 13.3, 7.6 Hz, 1H), 2.55 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.19 (s, 3H), 2.01-1.93 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 161.2, 149.1, 139.6, 138.0, 137.3, 135.9, 128.9, 128.7, 128.2, 127.6, 125.1, 122.0, 121.9, 121.0, 83.3, 78.0, 56.9, 37.7, 25.3, 21.3; IR (film) 2924, 1707, 1587, 1496, 1381, 1300, 752, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1732.

Pyridine 207: According to the general procedure, amino amide **204** (102 mg, 0.382 mmol), *o*-tolualdehyde (57.6 μL, 0.496 mmol), $MgSO_4$ (69.0 mg, 0.573 mmol), and $PhCH_3$/AcOH (5:1, 2.55 mL) were heated to 110 °C for 24 h. Aminals **207a** and **207b** were isolated as a 1:1.5 mixture of inseparable diastereomers (123 mg, 87% yield, R_f = 0.58 in 40:1 EtOAc:MeOH eluent).

Pyridine 207a (syn): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.31-6.94 (comp m, 8H), 6.73-6.64 (comp m, 2H), 5.91 (s, 1H), 3.67 (dt, *J* = 9.6, 5.2 Hz, 1H), 3.18 (td, *J* = 8.8, 6.9 Hz, 1H), 2.87-2.73 (m, 1H), 2.57 (s, 3H), 2.35 (ddd, *J* = 13.2, 7.9, 5.3 Hz, 1H), 2.01-1.90 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 161.1, 148.8, 138.0, 136.6, 135.7, 135.5, 130.6, 128.8, 128.3, 127.7, 126.2, 124.6, 121.6, 120.8, 120.5, 79.9, 77.7, 57.5, 38.3, 25.1, 19.4; IR (film) 3061, 2968, 1710, 1598, 1498, 1375, 1303, 748, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3O_3Na]^+$: 392.1733, found 392.1735.

Pyridine 207b (anti): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dt, *J* = 4.7, 1.4 Hz, 1H), 7.72-7.65 (comp m, 2H), 7.30-7.14 (comp m, 7H), 7.04-6.95 (comp m, 3H), 6.61 (s, 1H), 2.84 (dt, *J* = 13.2, 8.8 Hz, 1H), 2.76 (td, *J* = 9.4, 6.8 Hz, 1H), 2.62 (s, 3H), 2.51-2.42 (comp m, 2H), 1.86-1.79 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 160.3, 149.7, 137.1, 136.6, 132.4, 130.6, 128.4, 128.3, 127.9, 125.4, 122.3, 121.6, 120.7, 77.7, 75.0, 50.5, 36.3, 24.8, 19.0; IR (film) 2968, 1711, 1597, 1367, 1321, 747, 694 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1730.

Pyridine 208: According to the general procedure, amino amide **204** (109 mg, 0.408 mmol), *p*-anisaldehyde (64.5 μL, 0.530 mmol), $MgSO_4$ (73.7 mg, 0.612 mmol), and $PhCH_3$/AcOH (5:1, 2.72 mL) were heated to 110 °C for 24 h. Pyridine **208** was isolated as a 5.8:1 mixture of diastereomers (123 mg, 78% yield, R_f = 0.50 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

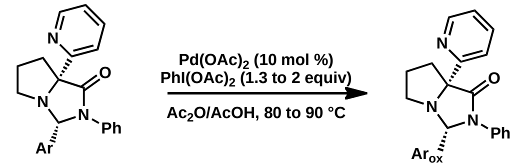
Pyridine 208: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.3 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.51 (td, *J* = 7.7, 1.6 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.13-7.04 (comp m, 4H), 6.71 (d, *J* = 8.6 Hz, 2H), 5.62 (s, 1H), 3.72 (s, 3H), 3.42 (dt, *J* = 10.7, 6.5 Hz, 1H), 3.17 (dt, *J* = 10.8, 6.4 Hz, 1H), 2.73-2.54 (comp m, 2H), 2.06-1.89 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 161.2, 159.4, 149.2, 137.1, 136.0, 131.9, 128.7, 128.3, 125.2, 122.4, 121.9, 121.0, 113.7, 82.9, 77.9, 56.3, 55.2, 37.5, 25.2; IR (film) 2958, 1707, 1587, 1384, 1248, 753, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{24}H_{24}N_3O_2]^+$: 386.1863, found 386.1849.

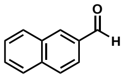
Pyridine 209: According to the general procedure, amino amide **204** (106 mg, 0.397 mmol), *p*-chlorobenzaldehyde (72.4 mg, 0.515 mmol), $MgSO_4$ (71.7 mg, 0.596 mmol), and $PhCH_3$/AcOH (5:1, 2.65 mL) were heated to 110 °C for 24 h. Pyridine **209** was isolated as a 3.8:1 mixture of diastereomers (104 mg, 67% yield, R_f = 0.57 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

Pyridine 209: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.7 Hz. 1H), 7.51 (d, J = 3.7 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 1H), 7.16-7.07 (comp m, 6H), 5.65 (s, 1H), 3.49 (dt, *J* = 10.6, 6.3 Hz, 1H), 3.17 (dt, *J* = 10.6, 6.6 Hz, 1H), 2.70 (dt, *J* = 13.3, 7.5 Hz, 1H), 2.57-2.54 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.02-1.94 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 161.0, 149.2, 138.3, 137.0, 136.1, 128.9, 128.5, 128.4, 125.4, 122.1, 122.0, 120.8, 82.6, 77.9, 56.8, 37.6, 25.3; IR (film) 2959, 2360, 1707, 1597, 1382, 1089, 753 cm^1; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{23}H_{21}N_3OCl]^+$: 390.1368, found 390.1370.

Pyridine 210: According to the general procedure, amino amide **204** (101 mg, 0.378 mmol), 2-naphthaldehyde (76.7 mg, 0.491 mmol), $MgSO_4$ (68.2 mg, 0.567 mmol), and $PhCH_3$/AcOH (5:1, 2.52 mL) were heated to 110 °C for 24 h. Pyridine **210** was isolated as a 7.3:1 mixture of diastereomers (123 mg, 80% yield, R_f = 0.50 in 40:1 EtOAc:MeOH eluent). The major diastereomer could be further purified for characterization analysis.

Pyridine 210: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.7 Hz, 1H), 7.76-7.73 (m, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.66-7.65 (m, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.45-7.35 (comp m, 4H), 7.22 (t, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 6.9 Hz, 2H), 5.82 (s, 1H), 3.49 (dt, *J* = 10.6, 6.4 Hz, 1H), 3.26 (dt, *J* = 10.7, 6.5 Hz, 1H), 2.74 (dt, *J* = 13.3, 7.6 Hz, 1H), 2.64-2.57 (m, 1H), 2.08-1.92 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 161.2, 149.2, 137.13, 137.08, 133.2, 132.8, 128.8, 128.6, 127.9, 127.6, 126.4, 126.2, 126.1, 125.3, 124.4, 122.2, 121.9, 120.9, 83.5, 78.0, 56.6, 37.7, 25.3; IR (film) 2967, 1707, 1597, 1499, 1380, 1317, 749 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+Na)$^+$ [$C_{27}H_{23}N_3ONa$]$^+$: 428.1733, found 428.1729.



ArCHO	product	yield (%) Ar_{ox}	ArCHO	product	yield (%) Ar_{ox}
Ph	211	55[a]	*p*-OMe	215	37[c]
p-Me	212	47[b]	*p*-Cl	216	39
m-Me	213	72		217	58
o-Me	214	85			

[a] 6% yield diacetoxylated product. [b] 16% diacetoxylated product.
[c] 9% diacetoxylated product

Representative acetoxylation procedure: Pyridine **202** (84.7 mg, 0.238 mmol), $Pd(OAc)_2$ (5.3 mg, 0.0238 mmol), and $PhI(OAc)_2$ (115 mg, 0.357 mmol) were dissolved in AcOH (1.76 mL) and Ac_2O (1.76 mL) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 80 °C for 15.5 h, at which time $PhI(OAc)_2$ (38.3 mg, 0.119 mmol) was added. The reaction was heated at 85 °C for an additional 9.5 h. Upon cooling, CH_2Cl_2 (10 mL) and water (10 mL) were added and the mixture was neutralized with Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude residue was purified by flash chromatography (4:1 → 7:3 hexanes/acetone eluent) to afford acetate **211** (54.2 mg, 55% yield (61% borsm), R_f = 0.45 in 1:1 hexanes/acetone) as a beige solid and the corresponding diacetate (6.7 mg, 6% yield, R_f = 0.26 in 1:1 hexanes/acetone) as a beige solid.

Acetate 212: According to the general procedure, pyridine **205** (125 mg, 0.338 mmol), $Pd(OAc)_2$ (7.6 mg, 0.0338 mmol), $PhI(OAc)_2$ (109 mg, 0.338 mmol) and $AcOH/Ac_2O$ (1:1, 3.38 mL) were stirred at 85 °C for 8 h. $PhI(OAc)_2$ (32.7 mg, 0.101 mmol) was added, and the mixture stirred an additional 10.5 h at 85 °C. Acetate **212** was isolated as a beige solid (68.2 mg, 47% yield, R_f = 0.50 in 1:1 hexanes/acetone) and diacetate product was isolated as a beige solid (26.0 mg, 16% yield, R_f = 0.27 in 1:1 hexanes/acetone).

Acetate 212: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.58-7.55 (comp m, 2H), 7.38-7.30 (comp m, 3H), 7.28-7.23 (m, 1H), 7.08-7.00 (comp m, 2H), 6.90 (d, *J* = 0.6 Hz, 1H), 6.68-6.60 (comp m, 2H), 5.89 (s, 1H), 3.53 (dt, *J* = 9.9, 5.8 Hz, 1H), 3.15 (dt, *J* = 9.9, 7.1 Hz, 1H), 2.73 (dt, *J* = 13.2, 7.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 1.98-1.85 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.0, 161.0, 148.9, 148.5, 139.3, 137.5, 135.9, 128.8, 127.1, 126.3, 123.2, 121.7, 121.1, 120.4, 77.8, 77.6, 57.5, 38.1, 25.2, 21.1, 21.0; IR (film) 2968, 1766, 1708, 1497, 1373, 1200, 733, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{26}H_{25}N_3O_3Na]^+$: 450.1788, found 450.1796.

Diacetate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.72-7.76 (m, 1H), 7.53-7.47 (comp m, 3H), 7.25-7.19 (comp m, 3H), 7.17-7.11 (m, 1H), 7.07-7.01 (m, 1H), 6.76 (s, 2H), 5.98 (s, 1H), 3.35 (dt, *J* = 10.6, 6.6 Hz, 1H), 3.12 (dt, *J* = 10.6, 6.5 Hz, 1H), 2.69-2.50 (comp m, 2H), 2.28 (s, 3H), 2.07-1.89 (comp m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 168.4, 160.7, 149.3, 149.0, 139.7, 136.9, 135.9, 128.74, 128.68, 124.8, 121.8, 121.3, 120.8, 119.8, 119.6, 75.3, 56.6, 39.1, 25.0, 21.2, 21.0; IR (film) 2968, 1769, 1709, 1371, 1181, 1045, 753, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{28}H_{27}N_3O_5Na]^+$: 508.1843, found 508.1852.

Acetate 213: According to the general procedure, pyridine **206** (124 mg, 0.336 mmol), $Pd(OAc)_2$ (7.5 mg, 0.0336 mmol), $PhI(OAc)_2$ (162 mg, 0.504 mmol), and $AcOH/Ac_2O$ (1:1, 3.36 mL) were stirred at 80 °C for 15.5 h. $PhI(OAc)_2$ (54.1 mg, 0.168 mmol) was added, and the reaction stirred at 85 °C for an additional 9.5 h. Acetate **213** (104 mg, 72% yield, R_f = 0.48 in 1:1 hexanes/acetone) was isolated as a beige solid .

Acetate 213: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.60-7.57 (comp m, 2H), 7.36-7.24 (comp m, 4H), 7.08-7.04 (m, 1H), 7.00 (ddd, *J* = 7.1, 4.9, 1.5 Hz, 1H), 6.95 (d, *J* = 1.2 Hz, 2H), 6.53 (s, 1H), 5.87 (s, 1H), 3.56 (dt, *J* = 9.7, 5.7 Hz, 1H), 3.16-3.10 (m, 1H), 2.75 (dt, *J* = 13.3, 7.9 Hz, 1H), 2.38 (s, 3H), 2.38-2.32 (m, 1H), 1.91 (s, 3H), 1.97-1.90 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.1, 161.2, 148.7, 146.4, 137.7, 135.7, 135.2, 130.6, 129.4, 128.9, 127.6, 124.7, 122.4, 121.7, 121.1, 120.2, 77.8, 77.7, 57.5, 38.1, 25.2, 21.1, 20.6; IR (film) 3061, 2968, 1762, 1709, 1496, 1378, 1190, 755, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{26}H_{26}N_3O_3]^+$: 428.1969, found 428.1974.

Acetate 214: According to the general procedure, pyridines **207a** and **207b** (123 mg, 0.333 mmol), $Pd(OAc)_2$ (7.5 mg, 0.0333 mmol), $PhI(OAc)_2$ (107 mg, 0.333 mmol) and $AcOH/Ac_2O$ (1:1, 3.33 mL) were stirred at 85 °C for 10 h. $PhI(OAc)_2$ (53.6 mg, 0.167 mmol) was added, and the reaction stirred an additional 10.5 h at 85 °C. Acetate **214** (128 mg, 85% yield, R_f = 0.42 in 1:1 hexanes/acetone) was isolated as a beige solid. The ^{1}H NMR spectrum featured highly broadened peaks, complicating characterization. Acetate **214** was therefore hydrolyzed to the phenol for characterization analysis.

Acetate 214: HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{26}H_{25}N_3O_3Na]^+$: 450.1788, found 450.1786.

Phenol 214b: Acetate **214** (33.7 mg, 0.0789 mmol) was dissolved in aq. HCl (1 M, 0.789 mL) and THF (1.47 mL), and the resulting solution was heated to reflux overnight. Upon cooling the reaction was quenched with solid Na_2CO_3 until pH ~9. The mixture was then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford phenol **214b** (14.1 mg, 46% yield, R_f = 0.28 in 1:1 hexanes/acetone) as a light yellow oil.

Phenol 214b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (bs, 1H), 8.67 (dt, *J* = 4.8, 1.4 Hz, 1H), 7.77-7.75 (comp m, 2H), 7.29-7.24 (m, 1H), 7.23-7.19 (comp m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.95-6.90 (comp m, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 3.18 (dt, *J* = 12.5, 8.0 Hz, 1H), 3.08 (ddd, *J* = 12.4, 7.8, 4.4 Hz, 1H), 2.73-2.65 (comp m, 2H), 2.23-2.16 (m, 1H), 1.99-1.91 (m, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.1, 148.5, 138.5, 136.9, 135.2, 130.7, 128.8, 128.0, 127.8, 122.9, 122.0, 121.3, 117.8, 116.8, 78.8, 50.9, 44.9, 34.8, 25.0, 19.4; IR (film) 3061, 2959, 1709, 1586, 1471, 1397, 1123, 749, 702 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3O_2Na]^+$: 408.1682, found 408.1690.

Acetate 215: According to the general procedure, pyridine **208** (123 mg, 0.319 mmol), $Pd(OAc)_2$ (7.2 mg, 0.0319 mmol), $PhI(OAc)_2$ (134 mg, 0.415 mmol) and $AcOH/Ac_2O$ (1:1, 3.19 mL) were stirred at 80 °C for 13 h. $PhI(OAc)_2$ (51.4 mg, 0.160 mmol) was added, and the mixture was stirred for an additional 5 h at 85 °C. Acetate **215** was isolated as a beige solid (73.1 mg, 37% yield, R_f = 0.40 in 1:1 hexanes/acetone), as well as the corresponding diacetoxylation product (14.0 mg, 9% yield, R_f = 0.23 in 1:1 hexanes/acetone) as a beige solid.

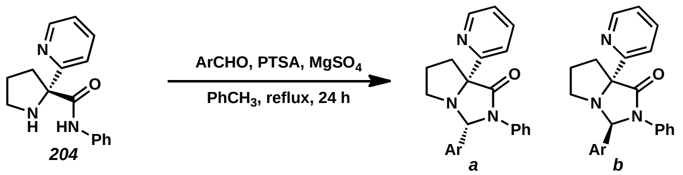
Acetate 215: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.58-7.54 (comp m, 2H), 7.41-7.33 (comp m, 2H), 7.30-7.23 (m, 2H), 7.09-7.01 (comp m, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.35 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.85 (s, 1H), 3.70 (s, 3H), 3.52 (dt, *J* = 9.9, 5.9 Hz, 1H), 3.14 (dt, *J* = 9.9, 7.1 Hz, 1H), 2.73 (dt, *J* = 13.3, 7.8 Hz, 1H), 2.44-2.38 (m, 1H), 2.40 (s, 3H), 1.98-1.86 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 168.8, 161.1, 159.9, 149.5, 148.9, 137.5, 135.9, 128.8, 128.0, 124.8, 123.3, 121.8, 121.0, 120.5, 111.1, 108.7, 77.8, 77.5, 57.3, 55.4, 38.0, 25.2, 21.1; IR (film) 2922, 1765, 1708, 1501, 1375, 1201, 753 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{26}H_{25}N_3O_4Na]^+$: 466.1737, found 466.1734.

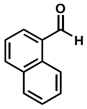
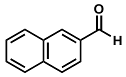
Acetate 216: According to the general procedure, pyridine **209** (104 mg, 0.267 mmol), $Pd(OAc)_2$ (6.0 mg, 0.0267 mmol), $PhI(OAc)_2$ (172 mg, 0.534 mmol) and $AcOH/Ac_2O$ (1:1, 2.67 mL) were stirred at 90 °C for 24 h with acetate **216** isolated as a beige solid (47.0 mg, 39% yield (51% borsm), R_f = 0.48 in 1:1 hexanes/acetone).

Acetate 216: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.56-7.53 (comp m, 2H), 7.44-7.37 (comp m, 2H), 7.30-7.24 (comp m, 2H), 7.13 (d, *J* = 1.8 Hz, 2H), 7.04 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.89 (s, 1H), 3.56 (dt, *J* = 9.8, 5.8 Hz, 1H), 3.14 (dt, *J* = 9.7, 7.2 Hz, 1H), 2.75 (dt, *J* = 13.3, 7.8 Hz, 1H), 2.42 (s, 3H), 2.36 (ddd, *J* = 13.2, 7.5, 5.7 Hz, 1H), 2.02-1.90 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.4, 160.8, 148.9, 137.3, 136.0, 134.0, 129.9, 129.0, 128.1, 125.6, 125.0, 123.3, 122.0, 121.9, 121.0, 120.3, 77.8, 57.6, 38.1 25.2, 21.0; IR (film) 2959, 1769, 1701, 1598, 1376, 1193, 754, 692 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{25}H_{22}N_3O_3ClNa]^+$: 470.1242, found 470.1247.

Acetate 217: According to the general procedure, pyridine **210** (123 mg, 0.303 mmol), $Pd(OAc)_2$ (6.8 mg, 0.0303 mmol), $PhI(OAc)_2$ (127 mg, 0.394 mmol) and $AcOH/Ac_2O$ (1:1, 3.03 mL) were stirred at 80 °C for 13 h. $PhI(OAc)_2$ (48.8 mg, 0.151 mmol) was added, and the reaction was stirred at 85 °C for an additional 5 h. Acetate **217** was isolated as a beige solid (81.5 mg, 58% yield, R_f = 0.43 in 1:1 hexanes/acetone).

Acetate 217: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.72-7.69 (comp m, 3H), 7.58 (s, 1H), 7.42-7.37 (m, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.29-7.24 (comp m, 3H), 7.18 (s, 1H), 7.15 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.08-7.02 (comp m, 2H), 6.78 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 6.04 (s, 1H), 3.67 (dt, J = 9.5, 5.5 Hz, 1H), 3.24-3.18 (m, 1H), 2.82 (dt, J = 13.3, 8.0 Hz, 1H), 2.46 (s, 3H), 2.33 (ddd, J = 13.2, 7.7, 5.4 Hz, 1H), 2.01-1.91 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.1, 161.1, 148.6, 146.3, 138.0, 135.7, 133.0, 130.5, 129.7, 128.9, 127.9, 127.0, 126.7, 125.8, 124.6, 121.5, 120.9, 120.3, 120.0, 79.4, 77.9, 57.9, 38.4, 25.2, 21.2; IR (film) 2968, 1763, 1708, 1376, 1198, 752 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H)$^+$ $[C_{29}H_{26}N_3O_3]^+$: 464.1969, found 464.1969.



ArCHO	product	dr (*a* : *b*)	yield (%)	ArCHO	product	dr (*a* : *b*)	yield (%)
Ph	202	0 : 1.0	87		218	0 : 1.0	85
p-Me	205	1 : 3.0	83				
m-Me	206	1 : 5.0	82		210	0 : 1.0	72
p-OMe	208	1 : 3.9	69				

Aminal 202b: According to the general procedure, aminal **202b** was isolated as a beige solid (87% yield).

Aminal 205b: According to the general procedure, aminal **205b** was isolated as a beige solid (143 mg, 83% yield, R_f = 0.19 in EtOAc).

Aminal 205b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 7.69-7.60 (comp m, 2H), 7.33-7.30 (comp m, 2H), 7.24-7.17 (comp m, 5H), 7.08 (d, J = 7.8 Hz, 2H), 7.07-7.02 (m, 1H), 6.44 (s, 1H), 2.85-2.77 (comp m, 2H), 2.59-2.54 (m, 1H), 2.50-2.44 (m, 1H), 2.29 (s, 3H), 1.93-1.80 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 176.0, 160.2, 149.6, 138.5, 137.9, 136.6, 131.3, 129.0, 128.5, 128.4, 124.7, 122.4, 122.1, 121.1, 78.2, 78.0, 50.5, 36.2, 25.0, 21.2; IR (film) 2967, 1709, 1597, 1377, 1303, 752, 693 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for (M+H)$^+$ $[C_{24}H_{24}N_3O]^+$: 370.1914, found 370.1917.

Aminal 206b: According to the general procedure, aminal **206b** was isolated as a beige solid (109 mg, 82% yield, R_f = 0.50 in 9:1 CH_2Cl_2/MeOH).

Aminal 206b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 0.7 Hz, 1H), 7.69-7.58 (comp m, 2H), 7.32 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.23-7.20 (comp m, 4H), 7.14-7.02 (comp m, 4H), 6.42 (s, 1H), 2.85-2.77 (comp m, 2H), 2.55 (ddd, *J* = 9.3, 5.8, 3.5 Hz, 1H), 2.50-2.44 (m, 1H), 2.29 (s, 3H), 1.92-1.81 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 176.0, 160.1, 149.6, 138.1, 137.9, 136.6, 134.3, 129.5, 129.4, 128.4, 128.1, 125.5, 124.8, 122.4, 122.0, 121.1, 78.3, 78.0, 50.5, 36.2, 25.0, 21.3; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3ONa]^+$: 392.1733, found 392.1738.

Aminal 207b: According to the general procedure, aminal **207b** was isolated as a beige solid (166 mg, 88% yield, R_f = 0.59 in 40:1 EtOAc/MeOH).

Aminal 208b: According to the general procedure, aminal **208b** was isolated as a beige solid (135 mg, 69% yield, R_f = 0.52 in 9:1 CH_2Cl_2/MeOH).

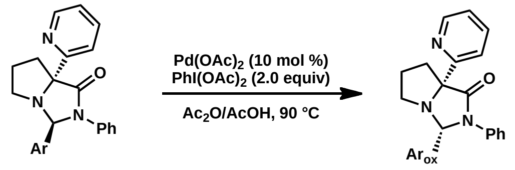
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.69-7.59 (comp m, 3H), 7.32-7.29 (comp m, 2H), 7.23 (d, *J* = 8.4 Hz, 4H), 7.06-7.02 (m, 1H), 6.82-6.79 (comp m, 2H), 6.42 (s, 1H), 3.76, (s, 3H), 2.85-2.77 (comp m, 2H), 2.58 (ddd, *J* = 9.4, 6.0, 3.7, 1H), 2.50-2.44 (m, 1H), 1.93-1.81 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 159.7, 149.6, 137.8, 136.7, 129.9, 128.7, 128.5, 128.3, 126.3, 124.8, 122.4, 122.2, 121.1, 113.7, 82.9, 78.0, 55.1, 50.4, 36.2, 25.0; HRMS (ESI^+) *m/z* calc'd for $(M+Na)^+$ $[C_{24}H_{23}N_3O_2Na]^+$: 408.1682, found 408.1684.

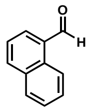
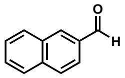
Aminal 218: According to the general procedure, aminal **218** was isolated as a beige solid (262 mg, 85% yield, R_f = 0.63 in EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dt, *J* = 4.7, 1.4 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.76-7.74 (comp m, 2H), 7.69 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.57 (td, *J* = 7.5, 1.0 Hz,1H), 7.33-7.16 (comp m, 8H) 7.04-7.00 (m, 1H), 2.89 (dt, *J* = 13.2, 8.8 Hz, 1H), 2.78 (td, *J* = 9.6, 6.8 Hz, 1H), 2.53-2.47 (m, 1H), 2.40-2.34 (m, 1H), 1.88-1.75 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 160.4, 149.6, 138.4, 136.7, 133.7, 131.5, 129.6, 129.0, 128.7, 128.5, 127.0, 126.1, 126.0, 124.63, 124.60, 123.5, 122.5, 121.7, 121.2, 78.2, 75.2, 50.4, 36.1, 24.7; IR (film) 2967, 1710, 1597, 1499, 1368, 1301 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{24}N_3O]^+$: 406.1914, found 406.1914.

Aminal 210b: According to the general procedure, aminal **210b** was isolated as a beige solid (174 mg, 72% yield, R_f = 0.22 in EtOAc).

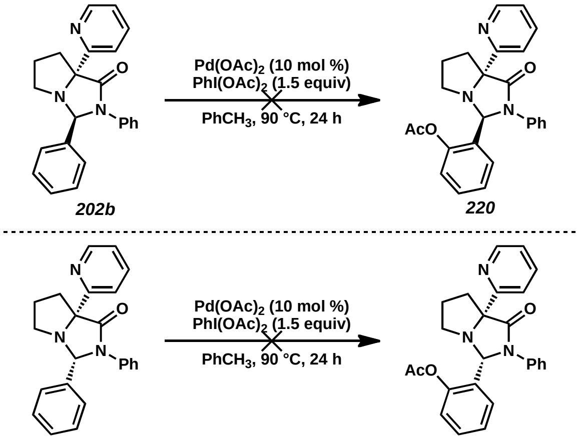
Aminal 210b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.87 (s, 1H), 7.81-7.74 (comp m, 3H), 7.72-7.64 (comp m, 2H), 7.48-7.46 (comp m, 2H), 7.40-7.39 (comp m, 3H), 7.23-7.17 (comp m, 3H), 7.03-7.00 (m, 1H), 6.66 (s, 1H), 2.90-2.82 (comp m, 2H), 2.58-2.47 (comp m, 2H), 1.92-1.82 (comp m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ176.1, 160.1, 149.6, 137.8, 136.7, 133.3, 132.9, 132.0, 128.7, 128.5, 128.1, 127.6, 126.6, 126.4, 125.5, 124.9, 122.5, 122.1, 121.2, 78.5, 78.1, 50.6, 36.2, 25.1; HRMS (ESI$^+$) *m/z* calc'd for $(M+H)^+$ $[C_{27}H_{24}N_3O]^+$: 406.1914, found 406.1902.



ArCHO	product	yield (%) Ar_{ox}	ArCHO	product	yield (%) Ar_{ox}
Ph	211	42		219	no rxn
p-Me	212	31 (28)[a]			
m-Me	213	51			
p-OMe	215	23[b]		217	44

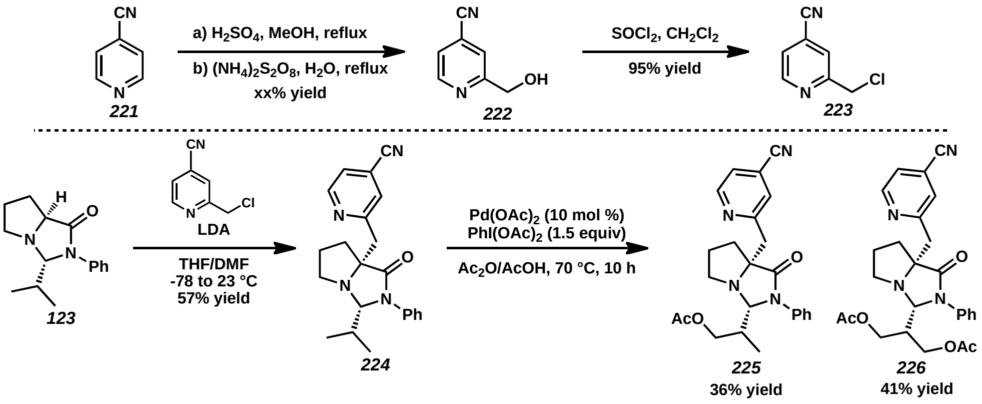
[a] yield in parentheses corresponds to observed diacetoxylated product.
[b] Run at 80 °C for 20 h.

General acetoxylation procedure: Pyridine (1 equiv), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (2 equiv) were dissolved in $AcOH/Ac_2O$ (1:1, 0.1 M) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 90 °C for 24 h. Upon cooling, CH_2Cl_2 (10 mL) and water (10 mL) were added and the mixture was neutralized with Na_2CO_3 until pH ~9. The mixture was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. To the crude mixture was added heptane (10 mL) and concentrated to ensure removal of residual Ac_2O. The crude residue was purified by flash chromatography (4:1 → 7:3 hexanes/acetone eluent) to afford acetates **211-217** in the yields indicated.



202b *220* *202a* *211*

General procedure for functionalization: Pyridine (1 equiv), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (2 equiv) were dissolved in toluene (0.1 M) in a 2-dram vial. The vial was sealed with a Teflon cap and heated to 90 °C for 24 h. Upon cooling, the solvent was removed. No acetoxylated product was observed by crude ^{1}H NMR.



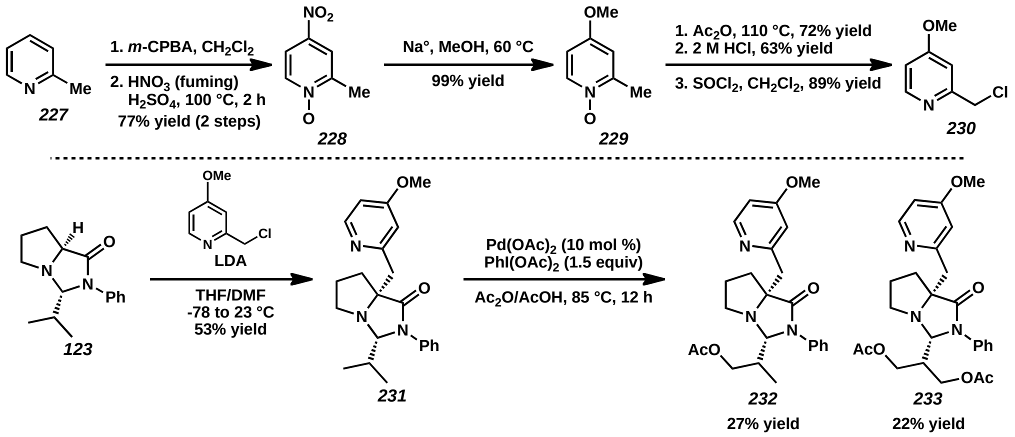
221
a) H2SO4, MeOH, reflux
b) (NH4)2S2O8, H2O, reflux
xx% yield
222
SOCl2, CH2Cl2
95% yield
223
123
LDA
THF/DMF
-78 to 23 °C
57% yield
224
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 70 °C, 10 h
225
36% yield
226
41% yield

Pyridine 224: 4-cyanopyridine (2.00 g, 19.2 mmol) and H_2SO_4 (0.200 mL, conc.) were refluxed in MeOH (28.6 mL) for 30 min. $(NH_4)_2S_2O_8$ (7.01 g, 30.7 mmol) in H_2O (12.8 mL) was added to the solution over 30 min at reflux. The reaction was refluxed an additional 1 h. After cooling to 23 °C, the resultant precipitate was filtered, and the sovent was removed under reduced pressure. The residue was neutralized with sat. aq. Na_2CO_3. The aqueous was extracted with $CHCl_3$ (4 x 30 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (2:3 hexanes:EtOAc to EtOAc) to afford **222** (994 mg, 39% yield, R_f = 0.15 in 1:1 hexanes:EtOAc) as a beige solid.

To pyridine (990 mg, 7.38 mmol) in CH_2Cl_2 (29.5 mL) at 23 °C was added $SOCl_2$ (0.639 mL, 8.86 mmol) slowly. The reaction was stirred for 1 h at 23 °C. The reaction was quenched with sat. aq. Na_2CO_3, then the aqueous was extracted with CH_2Cl_2 (40 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford pyridine **223** (1.07 g, 95% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a red oil.

To diisopropylamine (0.250 mL, 1.78 mmol) in THF (5.20 mL) at -78 °C was added *n*-BuLi (0.690 mL, 1.72 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **123** (750 mg, 3.07 mmol) in THF (7.00 mL) was added at -78 °C and stirred for 30 min. To this solution was added pyridine **223** (225 mg, 1.47 mmol) in DMF (2.90 mL) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with

H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (3:2 to 1:1 hexanes:EtOAc) to afford pyridine **224** (250 mg, 57% yield, $R_f = 0.22$ in 1:1 hexanes:EtOAc) as a yellow solid.


227
1. m-CPBA, CH2Cl2
2. HNO3 (fuming) H2SO4, 100 °C, 2 h
77% yield (2 steps)
228
Na°, MeOH, 60 °C
99% yield
229
1. Ac2O, 110 °C, 72% yield
2. 2 M HCl, 63% yield
3. SOCl2, CH2Cl2, 89% yield
230
123
LDA
THF/DMF
-78 to 23 °C
53% yield
231
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 85 °C, 12 h
232
27% yield
233
22% yield

Pyridine 230: To **227** (1.00 mL, 10.1 mmol) in CH_2Cl_2 (25.3mL) was added *m*-CPBA (4.54 g, 20.3 mmol) at 23 °C. The reaction was capped and stirred at 23 °C overnight. The suspension was washed with NaOH (3 x 10 ml, 10% aq.). The aqueous was extracted with CH_2Cl_2 (5 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford the *N*-oxide (1.06 g, 95% yield, $R_f = 0.0$ in 1:1 hexanes:EtOAc) as a yellow oil.

To *N*-oxide (1.06 g, 9.67 mmol) in conc. H_2SO_4 (3.70 mL) at 0 °C was added fuming HNO_3 (3.3 mL) dropwise. The mixture was heated to 100 °C for 2 h. The reaction was cooled to 23 °C, then neutralized with sat. aq. Na_2CO_3. The aqueous was extracted with CH_2Cl_2 (4 x 20 mL) and dried over Na_2SO_4 and concentrated to afford pyridine **228** (1.34 g, 90% yield, $R_f = 0.0$ in 1:1 hexanes:EtOAc) as a yellow solid.

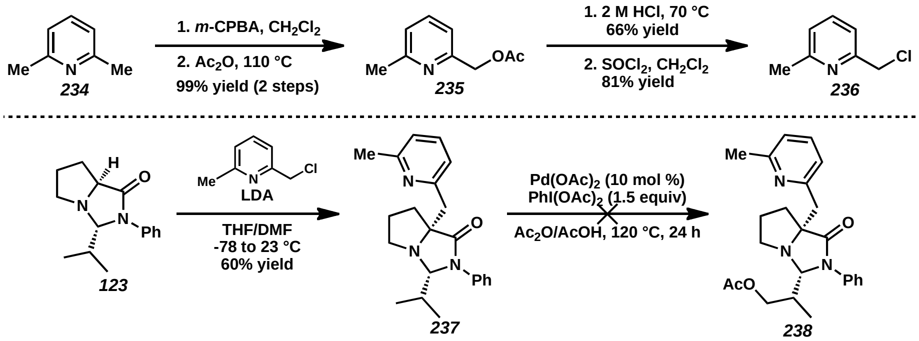
To **228** (3.00 g, 19.5 mmol) in MeOH (194 mL) at 60 °C was added a solution of Na° (0.460 g, 19.9 mmol) in MeOH (62.0 mL). The reaction was stirred 20 min at 60 °C, then cooled to 23 °C. The solvent was removed under reduced pressure. The residue was taken up in H_2O (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated to afford **229** (2.79 g, 99% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as an orange oil.

N-oxide (19.5 mmol) and Ac_2O (7.50 mL) were heated to 110 °C for 2 h. The reaction was cooled to 23 °C, then neutralized with sat. aq. Na_2CO_3. The aqueous was extracted with CH_2Cl_2 (4 x 75 mL). The organic layers were dried over Na_2SO_4 and concentrated to afford pyridine (2.53 g, 72% yield, R_f = 0.20 in 1:1 hexanes:EtOAc) as an orange oil.

Pyridine (2.53, 14.0 mmol) in HCl (17.5 mL, 2 M (aq)) was heated to 70 °C for 2 h. The mixture was cooled to 23 °C, then quenched with sat. aq. Na_2CO_3. The aqueous was extracted with CH_2Cl_2 (4 x 20 mL). The organics were dried over Na_2SO_4 and concentrated to afford the product (1.23 g, 63% yield) as a light yellow solid.

To pyridine (1.23 g, 8.82 mmol) in CH_2Cl_2 (34.0 mL) at 23 °C was added $SOCl_2$ (0.763 mL, 10.6 mmol) slowly. The reaction was stirred for 1 h at 23 °C. The reaction was quenched with sat. aq. Na_2CO_3, then the aqueous was extracted with CH_2Cl_2 (40 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford pyridine **230** (1.24 g, 89% yield, R_f = 0.45 in 1:1 hexanes:EtOAc) as a red oil.

Pyridine 231: To diisopropylamine (0.625 mL, 4.45 mmol) in THF (7.30 mL) at -78 °C was added *n*-BuLi (1.72 mL, 4.29 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **123** (750 mg, 3.07 mmol) in THF (8.00 mL) was added at -78 °C and stirred for 30 min. To this solution was added pyridine **230** (580 mg, 3.68 mmol) in DMF (7.40 mL) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:4 to 3:7 hexanes:EtOAc) to afford pyridine **231** (599 mg, 53% yield, R_f = 0.20 in 1:1 hexanes:EtOAc) as a yellow solid.



Me
N
Me
234
1. m-CPBA, CH2Cl2
2. Ac2O, 110 °C
99% yield (2 steps)
Me
N
OAc
235
1. 2 M HCl, 70 °C
66% yield
2. SOCl2, CH2Cl2
81% yield
Me
N
Cl
236
H
O
N
N
Ph
123
Me
N
Cl
LDA
THF/DMF
-78 to 23 °C
60% yield
Me
N
O
N
N
Ph
237
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O/AcOH, 120 °C, 24 h
Me
N
O
N
N
Ph
AcO
238

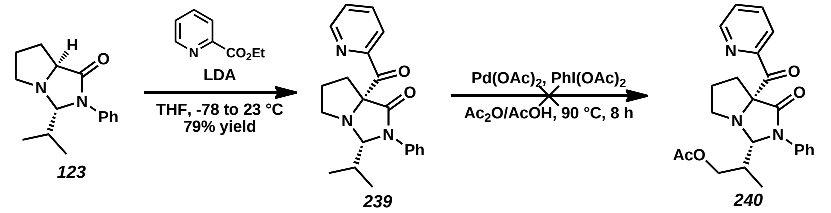
Pyridine 236: To **234** (1.00 mL, 8.59 mmol) in CH_2Cl_2 (21.5 mL) was added *m*-CPBA (3.85 g, 17.2 mmol) at 23 °C. The reaction was capped and stirred at 23 °C overnight. The suspension was washed with NaOH (3 x 10 ml, 10% aq.). The aqueous was extracted with CH_2Cl_2 (5 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford the *N*-oxide (1.47 g, 99% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a yellow oil.

N-oxide (8.59 mmol) and Ac_2O (3.3 mL) were heated to 110 °C for 2 h. The reaction was cooled to 23 °C, then neutralized with sat. aq. Na_2CO_3. The aqueous was extracted with CH_2Cl_2 (4 x 20 mL). The organic layers were dried over Na_2SO_4 and concentrated to afford pyridine **235** (1.71 g, 99% yield, R_f = 0.75 in 40:1 EtOAc:MeOH) as a yellow oil.

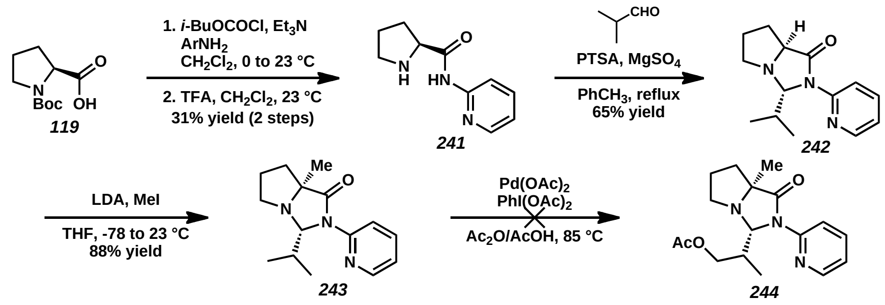
Pyridine **235** (1.71, 8.59 mmol) in HCl (10.7 mL, 2 M (aq)) was heated to 70 °C for 2 h. The mixture was cooled to 23 °C, then quenched with sat. aq. Na_2CO_3. The aqueous was extracted with CH_2Cl_2 (4 x 20 mL). The organics were dried over Na_2SO_4 and concentrated to afford the product (697 mg, 66% yield) as a light yellow solid.

To pyridine (697 mg, 5.66 mmol) in CH_2Cl_2 (23.6 mL) at 23 °C was added $SOCl_2$ (0.490 mL, 6.79 mmol) slowly. The reaction was stirred for 1 h at 23 °C. The reaction was quenched with sat. aq. Na_2CO_3, then the aqueous was extracted with CH_2Cl_2 (40 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford pyridine **236** (648 mg, 81% yield, $R_f = 0.70$ in 1:1 hexanes:EtOAc) as an orange oil.

Pyridine 237: To diisopropylamine (0.287 mL, 2.04 mmol) in THF (4.00 mL) at -78 °C was added *n*-BuLi (0.790 mL, 1.96 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **123** (400 mg, 1.64 mmol) in THF (5.90 mL) was added at -78 °C and stirred for 30 min. To this solution was added pyridine **236** (278 mg, 1.96 mmol) in DMF (3.90 mL) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:4 to 3:7 hexanes:EtOAc) to afford pyridine **237** (343 mg, 60% yield, $R_f = 0.20$ in 1:1 hexanes:EtOAc) as a yellow solid.



Pyridine 239: To diisopropylamine (0.417 mL, 2.96mmol) in THF (6.60 mL) at -78 °C was added *n*-BuLi (1.15 mL, 1.96 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **123** (500 mg, 2.04 mmol) in THF (7.00 mL) was added at -78 °C and stirred for 30 min. To this solution was added 2-ethylnicotinate (0.414 mL, 3.07 mmol) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:4 to 1:3 hexanes:EtOAc) to afford pyridine **240** (233 mg, 79% yield, $R_f = 0.40$ in 1:1 hexanes:EtOAc) as a yellow solid.

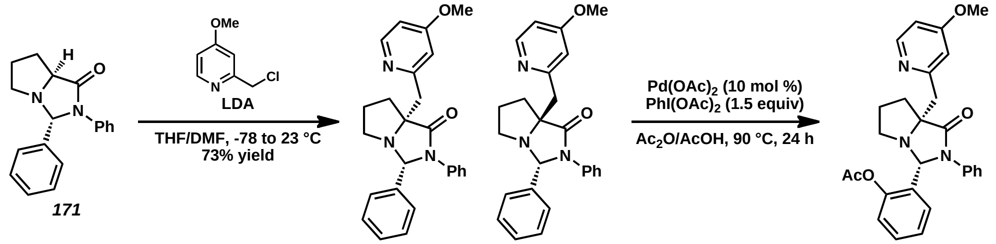

119
1. i-BuOCOCl, Et3N
ArNH2
CH2Cl2, 0 to 23 °C
2. TFA, CH2Cl2, 23 °C
31% yield (2 steps)
241
PTSA, MgSO4
PhCH3, reflux
65% yield
CHO
242
LDA, MeI
THF, -78 to 23 °C
88% yield
243
Pd(OAc)2
PhI(OAc)2
Ac2O/AcOH, 85 °C
244
Me
AcO

Aminal 243: To **119** (2.00 g, 9.29 mmol) in CH_2Cl_2 (31.0 mL) at 0 °C was added *i*-BuOCOCl (1.34 mL, 10.2 mmol) and Et_3N (1.44 mL, 10.2 mmol). The suspension was stirred at 0 °C for 15 min, at which time 2-aminopyridine (962 mg, 10.2 mmol) was added at 0 °C. The reaction was warmed to 23 °C and stirred overnight. The reaction was washed with 1 M $KHSO_4$ (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL) sequentially. Dried over Na_2SO_4 and concentrated to afford the amide (1.09 g, 40% yield, R_f = 0.40 in 1:1hexanes:EtOAc) as a white solid.

To the amide (1.09 g, 3.73 mmol) in CH_2Cl_2 (7.40 mL) at 23 °C was added TFA (5.70 mL, 74.5 mmol). The reaction was stirred for 1 h at 23 °C. The solvent was removed under reduced pressure. The residue was neutralized with solid Na_2CO_3. H_2O was added, and then the aqueous was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were dried over Na_2SO_4 and concentrated to afford amide **241** (559 mg, 78% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as an orange oil.

To **241** (559 mg, 2.92 mmol) in toluene (14.6 mL) was added isobutyraldehyde (0.400 mL, 4.38 mmol), PTSA (27.8 mg, 0.146 mmol) and $MgSO_4$ (528 mg, 4.38 mmol) and the suspension heated to reflux overnight. Upon cooling, sat. aq. $NaHCO_3$ (20 mL) was added. The aqueous was extracted with EtOAc (3 x 20 mL). The organics were dried over Na_2SO_4 and concentrated. The crude residue was purfied via flash chromatography (4:1 hexanes:EtOAc) to afford **242** (466 mg, 65% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a light yellow oil.

To diisopropylamine (0.387 mL, 2.76 mmol) in THF (4.00 mL) at -78 °C was added *n*-BuLi (1.06 mL, 2.66 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **242** (466 mg, 1.90 mmol) in THF (5.50 mL) was added at -78 °C and stirred for 30 min. To this solution was added MeI (0.237 mL, 3.80 mmol) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:4 hexanes:EtOAc) to afford pyridine **243** (434 mg, 88% yield, R_f = 0.70 in 1:1 hexanes:EtOAc) as a yellow oil.



171

245 *246*

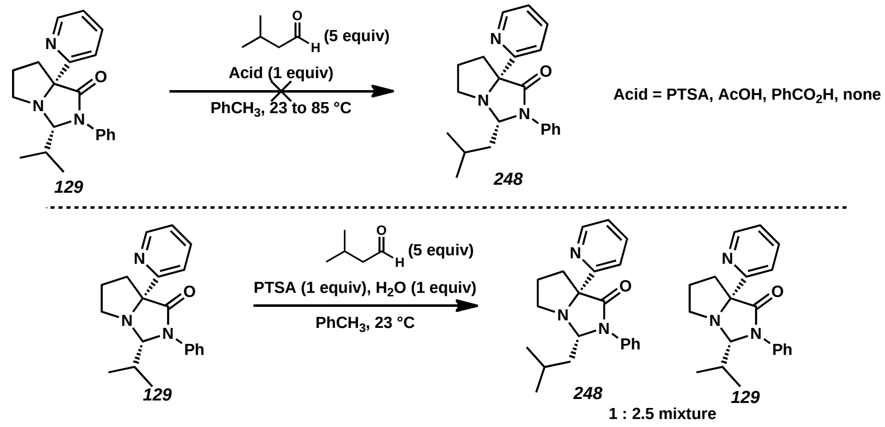
2.3 : 1 mixture

247

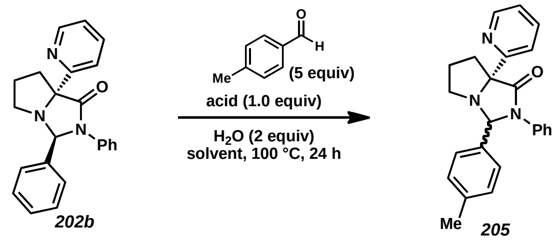
40% conversion

Pyridine 245: To diisopropylamine (0.384 mL, 2.73 mmol) in THF (5.50 mL) at -78 °C was added *n*-BuLi (1.05 mL, 2.64 mmol, 2.5 M in hexanes) slowly. The reaction was stirred at -78 °C for 10 min, then aminal **171** (524 mg, 1.88 mmol) in THF (7.00 mL) was added at -78 °C and stirred for 30 min. To this solution was added pyridine **236** (356 mg, 2.26 mmol) in DMF (4.50 mL) at -78 °C. The solution was warmed to 23 °C and stirred overnight. The reaction was quenched with H_2O (10 mL). The aqueous was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (1:7 to 3:7 hexanes:acetone) to afford pyridine **245** (551 mg, 73% yield, R_f = 0.51 in 1:1 hexanes:acetone) as an amorphous yellow solid.

Acetate 247: Pyridine **245** (15.0 mg, 0.0376 mmol), $Pd(OAc)_2$ (0.8 mg, 3.76 μmol) and $PhI(OAc)_2$ (18.1 mg, 0.0563 mmol) were heated in $AcOH/Ac_2O$ (1:1, 0.380 mL) to 90 °C for 24 h. The solvent was removed by azeotropic removal with heptanes (3 x 10 mL). Crude ^1H NMR revealed 40% conversion to product, with no purification.

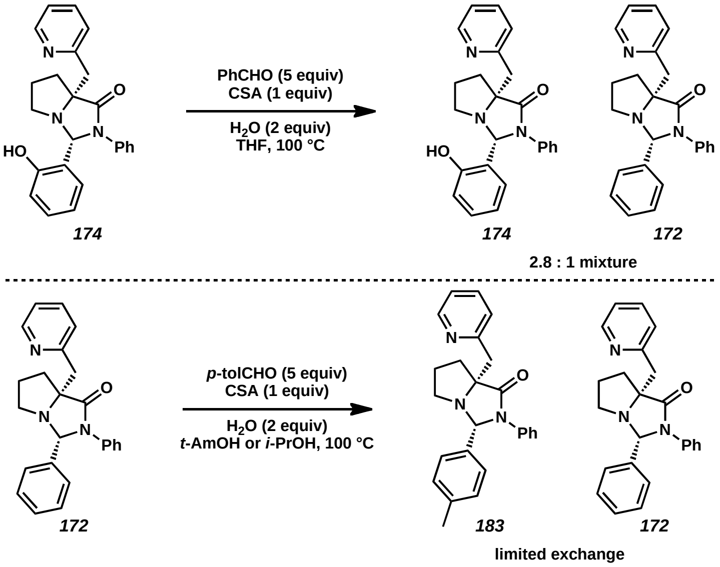

(5 equiv)
Acid (1 equiv)
PhCH3, 23 to 85 °C
Acid = PTSA, AcOH, PhCO2H, none
129
248
(5 equiv)
PTSA (1 equiv), H2O (1 equiv)
PhCH3, 23 °C
129
248
129
1 : 2.5 mixture

General exchange procedure: Pyridine **129** (1 equiv), isovaleraldehyde (5 equiv), acid (1 equiv) and H_2O (1 equiv) were combined in toluene (0.1 M) and heated to the temperature indicated for the time indicated. Solvent was removed under reduced pressure. Analysis by crude ^1H NMR afforded exchange ratios.

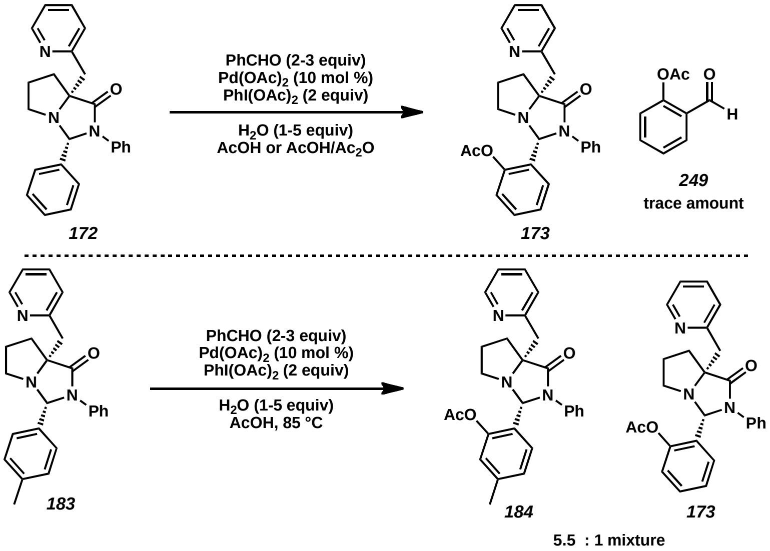

Me
(5 equiv)
acid (1.0 equiv)
H2O (2 equiv)
solvent, 100 °C, 24 h
202b
205

entry	acid	solvent	*202 : 205*	entry	acid	solvent	*202 : 205*
1	CSA	$PhCH_3$	1 : 2.8	6	PTSA	*t*-AmOH	1 : 7.0
2	PTSA	THF	1 : 3.0	7	CSA	*i*-PrOH	1 : 3.8
3	PTSA	MeOH	1 : 11.3	8	CSA	*t*-BuOH	1 : 5.1
4	CSA	MeOH	1 : 11.0	9	-	AcOH	1 : 3.5
5	CSA	*t*-AmOH	1 : 11.5	10	-	$AcOH/Ac_2O$	1 : 0

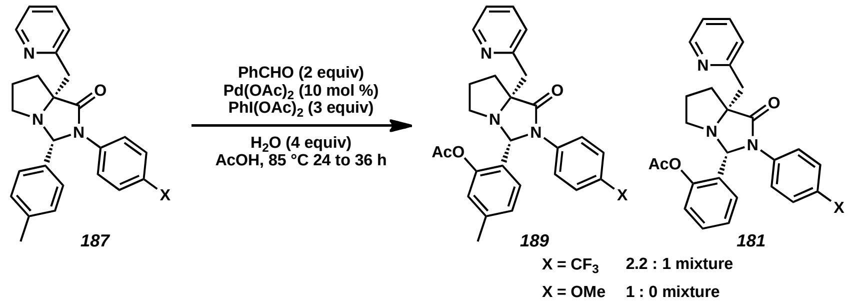
General exchange procedure: Pyridine **202b** (1 equiv), *p*-tolualdehyde (5 equiv), acid (1 equiv) and H_2O (2 equiv) were combined in solvent (0.1 M) and heated to 100 °C for 24 h. The solvent was removed under reduced pressure. Analysis by crude ^{1}H NMR afforded exchange ratios.


PhCHO (5 equiv)
CSA (1 equiv)
H2O (2 equiv)
THF, 100 °C
174
174
172
2.8 : 1 mixture
p-tolCHO (5 equiv)
CSA (1 equiv)
H2O (2 equiv)
t-AmOH or i-PrOH, 100 °C
172
183
172
limited exchange

General exchange procedure: Pyridine (1 equiv), benzaldehyde (5 equiv), CSA (1 equiv) and H_2O (2 equiv) were combined in solvent (0.5 M) and heated to 100 °C for 24 h. The solvent was removed under reduced pressure. Analysis by crude ^{1}H NMR afforded exchange ratios.

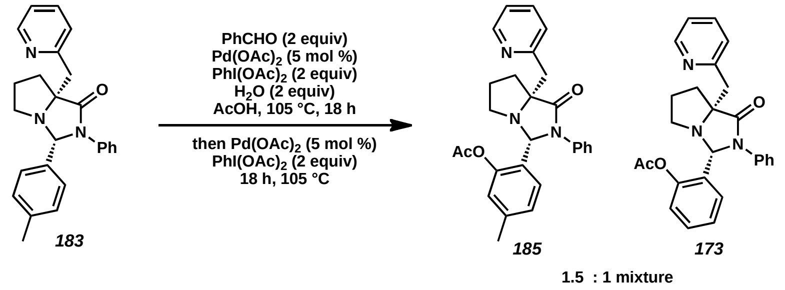

PhCHO (2-3 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (2 equiv)
H2O (1-5 equiv)
AcOH or AcOH/Ac2O
172
173
249
trace amount
PhCHO (2-3 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (2 equiv)
H2O (1-5 equiv)
AcOH, 85 °C
183
184
173
5.5 : 1 mixture

General procedure for synchronization: Pyridine (1 equiv), PhCHO (2 equiv), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2 equiv) and H_2O (5 equiv) were combined in AcOH or $AcOH/Ac_2O$ (1:1) (0.2 M) and heated to 85 °C for 24 h. The solvent was removed via azeotropic removal with heptanes (3 x 10 mL). Analysis by crude ^1H NMR afforded exchange ratios.



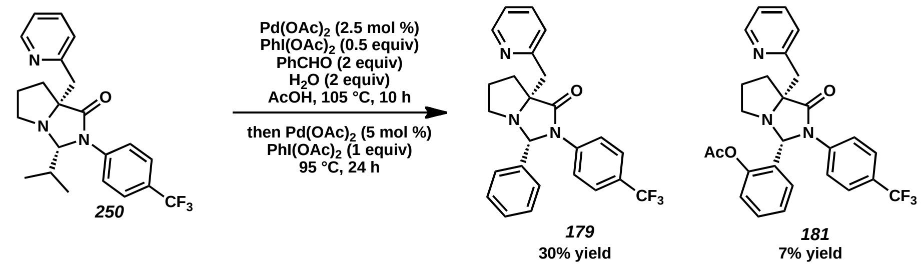
PhCHO (2 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (3 equiv)
H2O (4 equiv)
AcOH, 85 °C 24 to 36 h
187
189
181
AcO
X
X = CF3 2.2 : 1 mixture
X = OMe 1 : 0 mixture

General procedure for synchronization: Pyridine (1 equiv), PhCHO (2 equiv), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (3 equiv) and H_2O (4 equiv) were combined in AcOH (0.1 M) and heated to 85 °C for 24-36 h. The solvent was removed via azeotropic removal with heptanes (3 x 10 mL). Analysis by crude ^1H NMR afforded exchange ratios.



PhCHO (2 equiv)
Pd(OAc)2 (5 mol %)
PhI(OAc)2 (2 equiv)
H2O (2 equiv)
AcOH, 105 °C, 18 h
then Pd(OAc)2 (5 mol %)
PhI(OAc)2 (2 equiv)
18 h, 105 °C
183
185
173
Ph
AcO
1.5 : 1 mixture

General procedure for synchronization: Pyridine (1 equiv), PhCHO (2 equiv), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (2 equiv) and H_2O (2 equiv) were combined in AcOH (0.1 M) and heated to 105 °C for 18 h. Then $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (2 equiv) were added and heated to 105 °C for an additional 18 h. The solvent was removed via azeotropic removal with heptanes (3 x 10 mL). Analysis by crude ^1H NMR afforded exchange ratios.

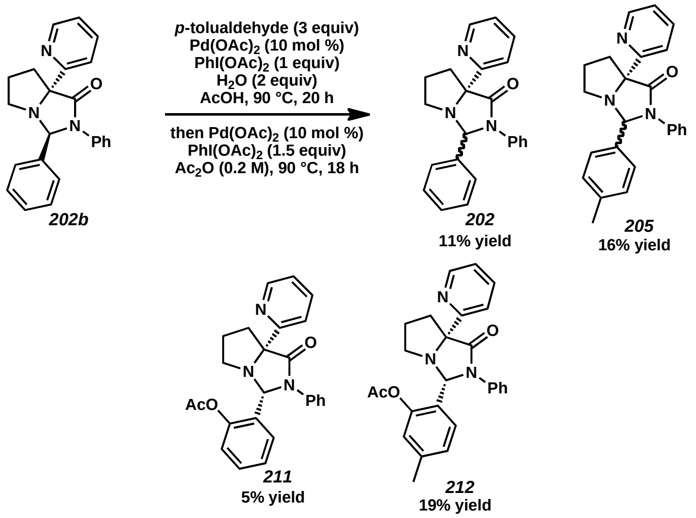


Pyridine 250: To a solution of amino amide **178-CF_3** (1.00 g, 3.87 mmol) in $PhCH_3$ (19.4 mL) at 23 ˚C was added isobutyraldehyde (0.530 mL, 5.81 mmol), $TsOH\cdot H_2O$ (37.0 mg, 0.194 mmol), and $MgSO_4$ (0.700 g, 5.81 mmol). The mixture was heated to reflux overnight. Upon cooling to 23 ˚C, the solution was quenched with sat. aq. $NaHCO_3$ (20 mL), and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography (4:1 hexanes/EtOAc eluent) to give the aminal (1.12 g, 92% yield, R_f = 0.49 in 1:1 hexanes/EtOAc) as a light yellow oil.

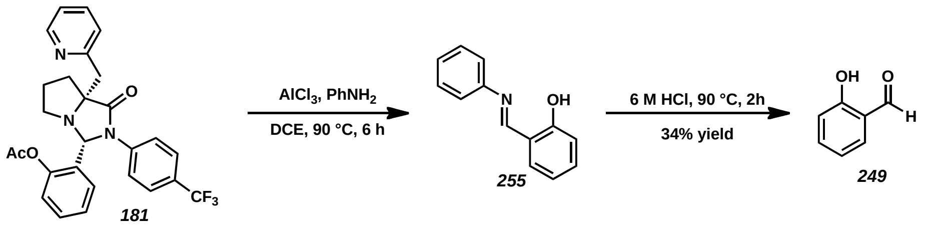
To a solution of freshly distilled diisopropylamine (516 μL, 3.68 mmol) in THF (5.00 mL) at -78 ˚C was added *n*-BuLi (1.41 mL, 2.5 M in hexanes, 3.52 mmol) dropwise. The solution was stirred for 10 min at -78 ˚C, at which time a solution of aminal (1.10 g, 3.52 mmol) in THF (6.80 mL) was added, and the resulting mixture was stirred for an additional 30 min at -78 ˚C. To a suspension of NaH (368 mg, 60% dispersion in mineral oil, 9.19 mmol, washed 2 x 1.5 mL) in DMF (10.0 mL) at 0 ˚C was added 2-(bromomethyl)pyridine hydrobromide (775 mg, 3.06 mmol). The suspension was stirred at 0 ˚C for 30 min, at which time it was added to the enolate solution at -78 ˚C (flask rinsed with additional 1.80 mL DMF). The suspension was warmed to 23 ˚C and stirred overnight. The reaction was quenched slowly with H_2O (25 mL) at 23 ˚C, and the resulting mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 35 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography (7:3 → 1:1 hexanes/EtOAc eluent) to afford pyridine **250** (905 mg, 73% yield, $R_f = 0.21$ in 1:1 hexanes/EtOAc) as a light yellow solid.

Pyridine 250: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.65-7.59 (comp m, 3H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.15 (ddd, *J* = 7.4, 5.0, 1.0 Hz, 1H), 4.53 (d, *J* = 3.0 Hz, 1H), 3.24 (ABq, *J* = 12.2 Hz, Δν = 20.5 Hz, 2H), 2.82-2.75 (comp m, 2H), 2.20-2.15 (m, 1H), 2.10-2.03 (m, 1H), 1.79 (septet of doublets, *J* = 6.8, 3.0 Hz, 1H), 1.65-1.54 (m, 1H), 1.51-1.42 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.55 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 157.9, 148.8, 139.6, 135.8, 126.1 (q, *J* = 3.8 Hz), 125.2, 123.8, 121.6, 85.9, 74.8, 58.5, 45.4, 35.0, 30.5, 24.6, 18.3, 14.3; IR (film) 2966, 1704, 1614, 1325, 1124, 845, 748 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $(M+Na)^+$ $[C_{22}H_{25}N_3OF_3Na]^+$: 426.1764, found 426.1766.

Acetate 181: Pyridine **250** (100 mg, 0.248 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0124 mmol), $PhI(OAc)_2$ (80.0 mg, 0.248 mmol), PhCHO (50.0 μL, 0.496 mmol), and H_2O (18.0 μL, 0.992 mmol) were dissolved in AcOH (2.50 mL) in a scintillation vial. The vial was capped and heated to 105 °C for 10 h. The reaction was cooled to 95 °C and $Pd(OAc)_2$ (5.6 mg, 0.0248 mmol) and $PhI(OAc)_2$ (160 mg, 0.496 mmol) were added, and the reaction was stirred for another 24 h at 95 °C. Upon cooling, the solvent was removed, and the resulting mixture was neutralized with solid Na_2CO_3 and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford pyridine **179-CF$_3$** (33.0 mg, 30% yield) and acetate **181-CF$_3$** (8.6 mg, 7% yield).


p-tolualdehyde (3 equiv)
Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1 equiv)
H2O (2 equiv)
AcOH, 90 °C, 20 h
then Pd(OAc)2 (10 mol %)
PhI(OAc)2 (1.5 equiv)
Ac2O (0.2 M), 90 °C, 18 h
202b
202
11% yield
205
16% yield
211
5% yield
212
19% yield
N
O
Ph
AcO

Acetate 212: Pyridine **202b** (63.4 mg, 0.178 mmol), $Pd(OAc)_2$ (4.0 mg, 0.0178 mmol), $PhI(OAc)_2$ (57.3 mg, 0.178 mmol), *p*-tolualdehyde (63.0 μL, 0.534 mmol), and H_2O (6.4 μL, 0.356 mmol) were dissolved in AcOH (0.890 mL) in a 2-dram vial. The vial was capped and heated to 90 °C for 20 h. $Pd(OAc)_2$ (4.0 mg, 0.0178 mmol), $PhI(OAc)_2$ (86.0 mg, 0.267 mmol) and Ac_2O (0.890 mL) were added and the reaction heated for an additional 18 h at 90 °C. Upon cooling, the solvent was removed and the resulting mixture was neutralized with solid Na_2CO_3 and water (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (4:1 hexanes/acetone eluent) to afford pyridine **202** (7.0 mg, 11% yield), acetate **211** (3.6 mg, 5% yield), pyridine **205** (10.8 mg, 16% yield) and acetate **212** (14.1 mg, 19% yield).


AlCl3, PhNH2
DCE, 90 °C, 6 h
6 M HCl, 90 °C, 2h
34% yield
181
255
249
N
O
AcO
CF3
OH
H

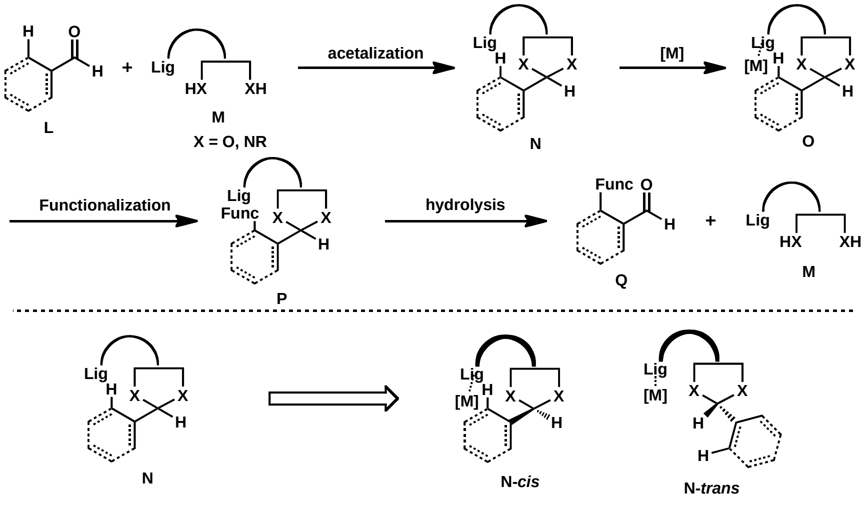
To a solution of phenol **181** (76.0 mg, 0.198 mmol) and $AlCl_3$ (66.9 mg, 0.502 mmol) in DCE (1.30 mL) at 23 °C was added $PhNH_2$ (69.0 μL, 0.753 mmol). The resulting mixture was heated to 90 °C and stirred for 8 h. Upon cooling, the reaction mixture was poured into water, and sat. Rochelle's salt (10 mL) was added. The aqueous was extracted with EtOAc (3 x 15 mL), the organics washed with brine (20 mL) and dried over Na_2SO_4 and concentrated. To the crude mixture was added aq. HCl (6 M, 2.50 mL) and heated to 70 °C for 3 h. Upon cooling, the mixture was poured into water and the aqueous extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated to afford a mixture of salicylaldehyde (**249**) (9.3 mg, 38% yield) and imine **255** (5.2 mg, 13% yield).

Chapter 3

Alternative Ligand Scaffolds

In addition to our acetoxylation of *sp*^{2} and *sp*^{3} C-H bonds using an amino amide scaffold, we have synthesized alternative ligand scaffolds that we imagined could perform our desired chelate-assisted functionalization (Scheme 3.0.1). Examining our desired reaction profile, we wanted to design a scaffold that contains both an acetalization component and a ligating group. The acetalization component can condense onto an aldehyde to generate the substrate ligand adduct. Upon treatment with a transition metal, the ligating group can coordinate the metal and place it in position to undergo functionalization of an unreactive bond. Finally, hydrolysis will release the functionalized product and regenerate the ligand. Again we envisioned a *cis* relationship between the ligating group and the substrate to ensure the close proximity needed to induce the desired functionalization.

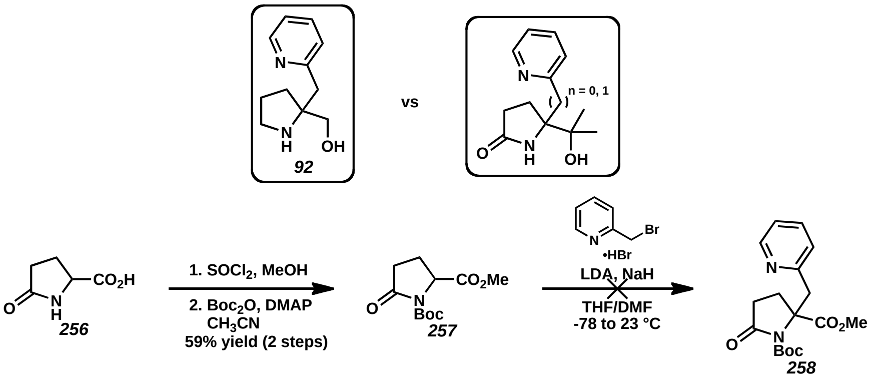
Scheme 3.0.1. General Concept



3.1 Examining Amino Acid Derived Scaffolds

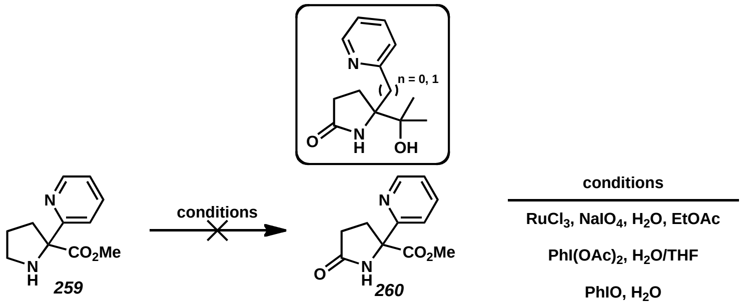
Our first entry into examining alternative scaffolds began with derivatization of our proline scaffold. Our original amino alcohol (**92**) scaffold proved much too labile to perform the desired chemistry (Scheme 3.1.1). We anticipated that by changing the electronics of the condensation components we might be able to introduce more stability into the *N*,*O*-acetal. By changing the amine into an amide and the primary alcohol into a tertiary alcohol, we envisioned a much more robust acetal. From pyroglutamic acid we converted acid **256** to the methyl ester, followed by amide protection to afford **257** in two steps. Alkylation with 2-bromomethyl pyridine, however, was unsuccessful in affording **258**.

Scheme 3.1.1. Acetalization component redesign


92
vs
n = 0, 1
256
1. SOCl$_2$, MeOH
2. Boc$_2$O, DMAP
CH$_3$CN
59% yield (2 steps)
257
•HBr
LDA, NaH
THF/DMF
-78 to 23 °C
258

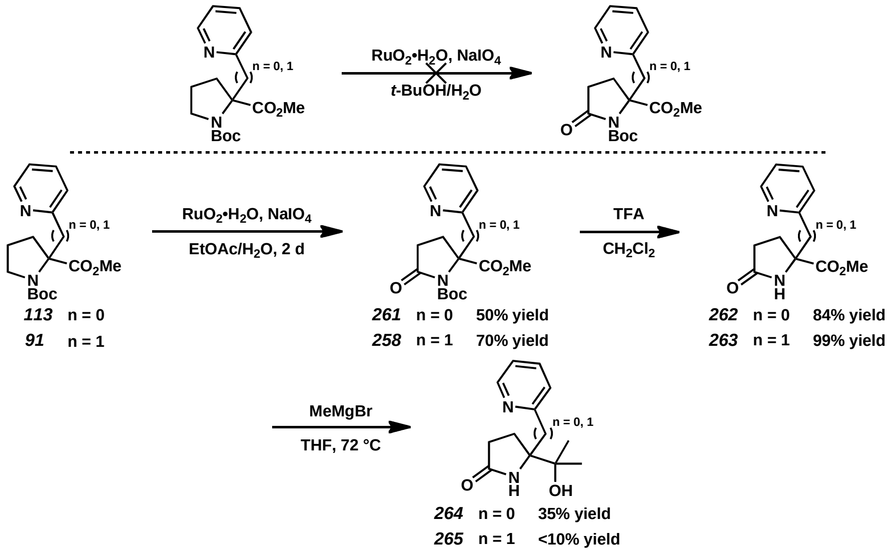
Unable to install the ligating group after the amide was in place, we conceptualized first installing the pyridyl ligating group, then oxidizing the amine to the amide. We treated substrate **259** with several oxidizing conditions but were unable to isolate the desired amide (Scheme 3.1.2). In most cases we observed a single oxidation to form a hemiacetal, which could then form the aldehyde, preventing any further oxidation.

Scheme 3.1.2. Initial attempted oxidation to the amide


n = 0, 1
259
conditions
260
conditions
RuCl$_3$, NaIO$_4$, H$_2$O, EtOAc
PhI(OAc)$_2$, H$_2$O/THF
PhIO, H$_2$O

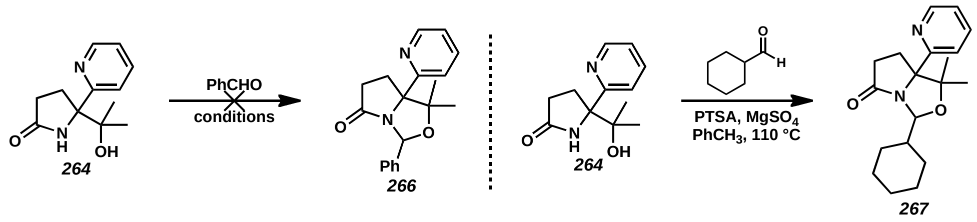
We next attempted the oxidation of the amine to the amide on the protected substrate. When **113** or **91** was reacted with RuO_2 and $NaIO_4$ in a miscible *t*-BuOH/H_2O mixture none of the desired amide was generated (Scheme 3.1.3). Using a two-phase solvent system, however, afforded amide **261** in 50% yield and amide **258** in 70% yield.[1] Deprotection afforded amide **262** in 84% yield, and amide **263** in quantitative yield. Treatment of amide **263** with MeMgBr afforded the tertiary alcohol (**264**) in moderate yield. Under identical conditions, amide **263** afforded the desired alcohol **265** in less than 10% yield. Employing MeLi instead of MeMgBr did not improve the conversion to alcohol **265**.

Scheme 3.1.3. Oxidation of pyrrolidine to pyrrolidinone


n = 0, 1
CO₂Me
Boc
RuO₂•H₂O, NaIO₄
t-BuOH/H₂O
RuO₂•H₂O, NaIO₄
EtOAc/H₂O, 2 d
TFA
CH₂Cl₂
113 n = 0
91 n = 1
261 n = 0 50% yield
258 n = 1 70% yield
262 n = 0 84% yield
263 n = 1 99% yield
MeMgBr
THF, 72 °C
OH
264 n = 0 35% yield
265 n = 1 <10% yield

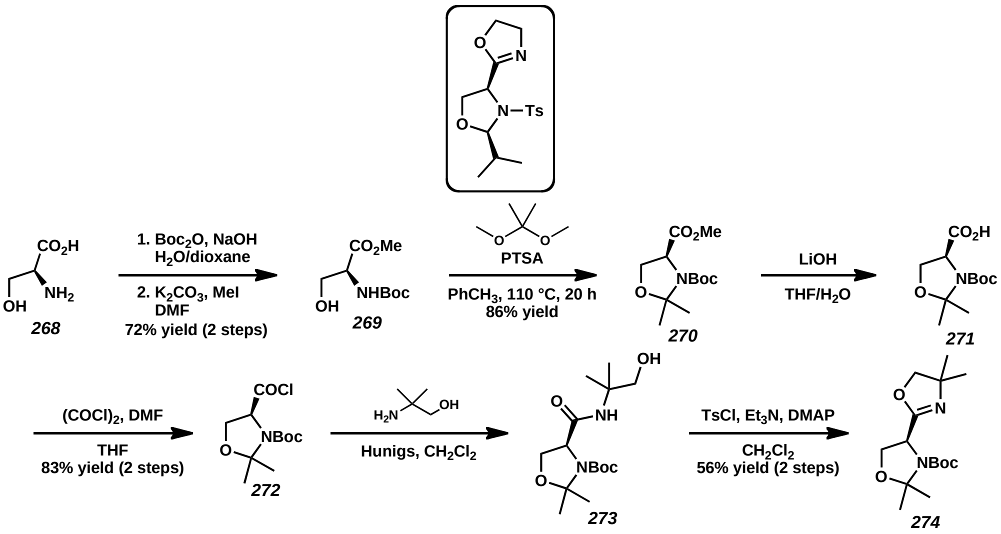
With amide alcohol **264**, we attempted to condense the ligand onto different aldehydes. Any attempted condensation with aromatic aldehydes was unsuccessful at producing the *N,O*-acetal (Scheme 3.1.4). Ligand **264** did condense with aliphatic aldehydes in the presence of PTSA and $MgSO_4$ to afford *N,O*-acetal **267**. Due to the difficulty of the synthesis of the ligand, we abandoned this ligand scaffold for the amino amide scaffold.

Scheme 3.1.4. Attempted condensation of the amide alcohol


264
PhCHO
conditions
266
264
PTSA, $MgSO_4$
$PhCH_3$, 110 °C
267

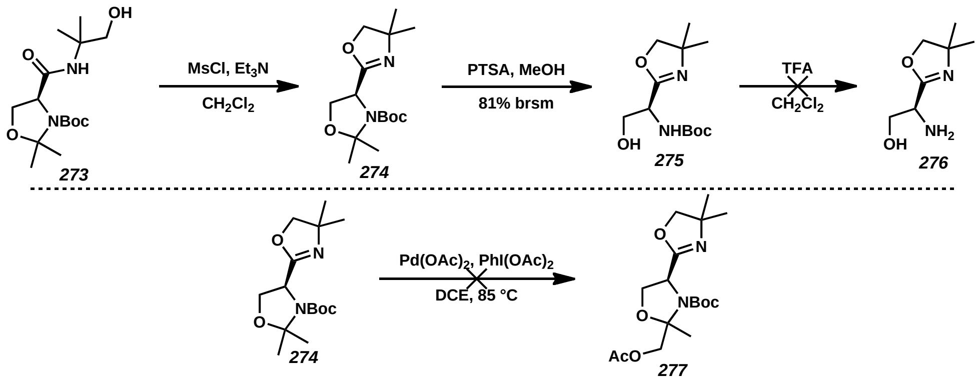
As an alternative we began investigating a scaffold based on L-serine. We imagined using the amino alcohol as the acetalization component, while converting the acid moiety into an oxazoline-ligating group (Scheme 3.1.5). Based on Seebach's work with amino acids, we believed we would achieve a *syn* relationship between the ligating group and aldehyde substrate.[2] From **268** we introduced a Boc protecting group and converted the acid into corresponding methyl ester **269**. Protecting the acetalization components with an acetonide allowed us to manipulate methyl ester **270**. Saponification in quantitative yield followed by conversion into the acid chloride afforded **272**. Treatment of the acid chloride with 2,2-dimethyl-1-aminoethanol afforded amide **273** in quantitative yield. Protecting the alcohol TsCl generated the tosylate, which quickly closed down under the basic conditions to afford oxazoline **274**.

Scheme 3.1.5. Oxazoline scaffold from serine


268
1. Boc_2O, NaOH
H_2O/dioxane
2. K_2CO_3, MeI
DMF
72% yield (2 steps)
269
PTSA
$PhCH_3$, 110 °C, 20 h
86% yield
270
LiOH
THF/H_2O
271
$(COCl)_2$, DMF
THF
83% yield (2 steps)
272
Hunigs, CH_2Cl_2
273
TsCl, Et_3N, DMAP
CH_2Cl_2
56% yield (2 steps)
274

To confirm product **274** by ^{1}H NMR, which proved difficult due to methyl rotamers, we imagined using a slightly different procedure to generate the oxazoline product. Treating amide alcohol **273** with MsCl and Et_3N afforded product **274**, which we believed to be the oxazoline (Scheme 3.1.6). Removal of the acetonide generated amino alcohol **275**. Removal of the amine protecting group with TFA, however, did not afford amino alcohol **276**. This was likely due to the propensity of alcohols to act as nucleophiles during this reaction. Rather than continue to pursue the deprotection of the amine, we attempted to examine the functionalization potential of **274**. Treatment with $Pd(OAc)_2$ and $PhI(OAc)_2$ in DCE afforded none of the desired acetoxylated product (**277**).

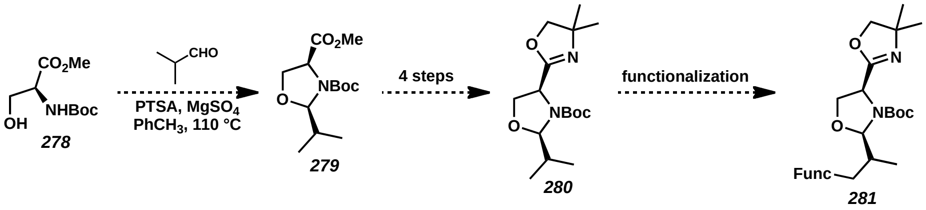
Scheme 3.1.6. Another route to the oxazoline



Due to unsuccessful formation of **276**, we discontinued our examination of this ligand. Based on our work with the amino amide ligand in Chapter 2, it is probable that a more straightforward synthesis of this ligand substrate adduct could be achieved (Scheme 3.1.7). Rather than forming an acetonide to protect the amino alcohol component, **278** could be condensed onto the aldehyde to be functionalized. This would eliminate the need for further manipulation after the oxazoline is installed. If the protecting group proved problematic due to its size, presumably a different protecting group could be installed prior to condensation.

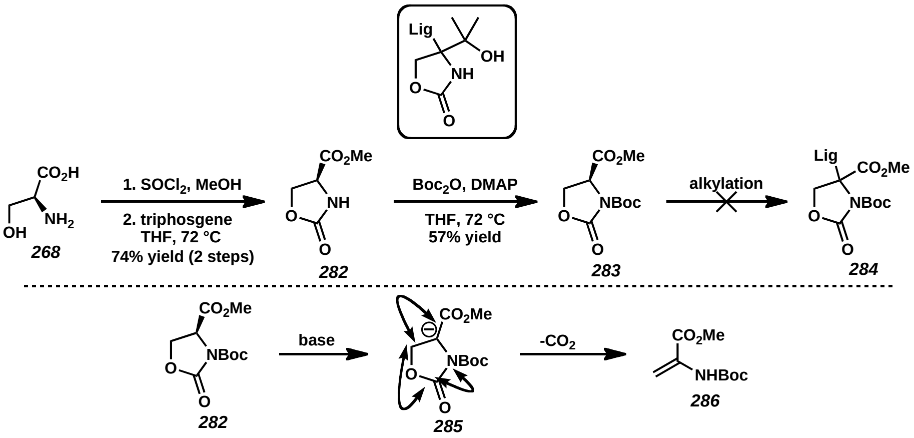
Subjecting acetal **280** to functionalization conditions could yield the desired functionalized product.

Scheme 3.1.7. Possible route to the desired ligand


CO2Me
NHBoc
OH
278
CHO
PTSA, MgSO4
PhCH3, 110 °C
CO2Me
NBoc
O
279
4 steps
O
N
NBoc
O
280
functionalization
O
N
NBoc
O
Func
281

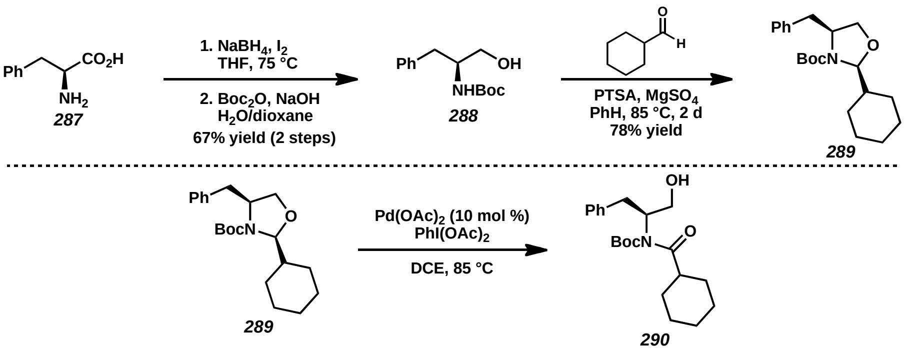
In the synthesis of oxazoline **276** we imagined one of the difficulties to be the steric bulk of the Boc protecting group, which could inhibit both condensation and functionalization. Alternatively, we imagined locking the amino alcohol as an oxazolidinone, installing the ligating group α to the methyl ester, and then forming the alcohol to generate ligand **284** (Scheme 3.1.8). Formation of the methyl ester followed by synthesis of the oxazolidinone afforded **282**. We imagined that protection of the amine would be necessary for alkylation, so we installed a Boc group to give **283**. Any attempts at alkylation, however, afforded none of the desired product. We attributed this to the propensity of anion **285** to liberate CO_2 before alkylation, leading to decomposition product **286**.

Scheme 3.1.8. Attempted synthesis of an oxazolidinone ligand


Lig
OH
NH
O
O
CO2H
NH2
OH
268
1. SOCl2, MeOH
2. triphosgene
THF, 72 °C
74% yield (2 steps)
CO2Me
NH
O
O
282
Boc2O, DMAP
THF, 72 °C
57% yield
CO2Me
NBoc
O
O
283
alkylation
Lig
CO2Me
NBoc
O
O
284
CO2Me
NBoc
O
O
282
base
CO2Me
NBoc
O
O
285
-CO2
CO2Me
NHBoc
286

Rather than installing a heterocylic directing group, which has shown to involve numerous steps for ligand synthesis, we envisioned using Yu's work with Boc ligating groups.[3] Starting from L-phenylalanine, we reduced the acid to the corresponding alcohol, then protected the amine to afford amino alcohol **288** (Scheme 3.1.9). Condensation onto cyclohexanecarboxaldehyde afforded *N*,*O*-acetal **289** in good yield. Treatment with acetoxylation conditions, however, only afforded amide **290** via an oxidation of the acetal center. Subjecting **289** to just PhI(OAc)$_2$ also afforded **290** as the only product. Presumably the Boc group cannot direct the functionalization under these conditions; therefore, the uncatalyzed oxidation is the only transformation that takes place.

Scheme 3.1.9. Ligand design based on phenylalanine

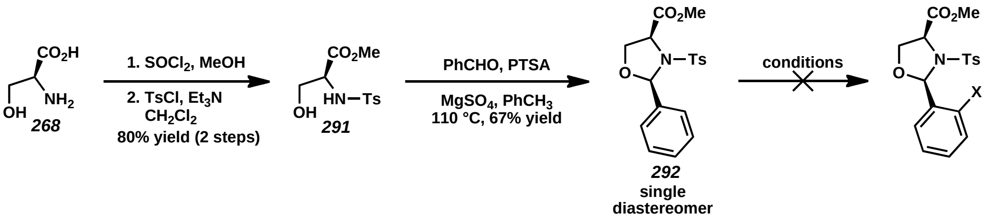

Ph
CO2H
NH2
287
1. NaBH4, I2
THF, 75 °C
2. Boc2O, NaOH
H2O/dioxane
67% yield (2 steps)
Ph
OH
NHBoc
288
O
H
PTSA, MgSO4
PhH, 85 °C, 2 d
78% yield
Ph
BocN
O
289
Ph
BocN
O
289
Pd(OAc)2 (10 mol %)
PhI(OAc)2
DCE, 85 °C
OH
Ph
BocN
O
290

While none of these ligands has shown any success in a C–H functionalization reaction, further exploration is needed. With an improved synthesis of serine derived oxazoline **280**, functionalization may be successful. Additionally, we have already demonstrated that the *N*,*O*-acetal can be easily cleaved with PTSA in MeOH. Furthermore, the amide alcohol ligand derivatives have not been examined fully and may exhibit potential for C–H functionalization.

3.2 Serine Derived Scaffolds for C–C Bond Formation

We have examined amino acid scaffolds with traditional cyclic heteroatom ligating groups for C–H functionalization. We also sought to examine non-cyclic heteroatom ligating groups on the L-serine acetalization framework. We began with a carboxylic acid ligating group. Treating L-serine with anhydrous HCl in MeOH followed by TsCl and Et_3N afforded the *N*-Ts methyl ester (**291**) (Scheme 3.2.1). Condensation onto benzaldehyde generated *N,O*-acetal **292** as a single diastereomer. We reacted the methyl ester under functionalization conditions to ascertain the directing group ability of the methyl ester. Treatment with $PhB(OH)_2$ in the presence of $Pd(OAc)_2$, K_2CO_3, benzoquinone, and $Cu(OAc)_2$ afforded an unknown product with no acetal.[4] Acetoxylation of **292** under our standard conditions resulted in recovered starting material.[5] Additionally, subjecting **292** to PhI in the presence of $Pd(OAc)_2$ and K_2CO_3 resulted in decomposition of the starting material.[6]

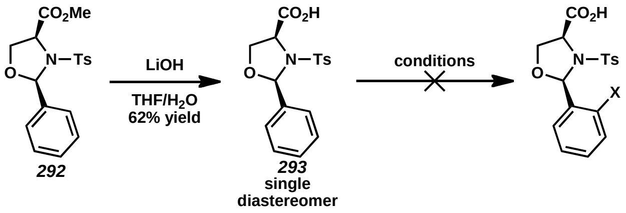
Scheme 3.2.1. Attempted functionalization of benzaldehyde


CO2H
NH2
OH
268
1. SOCl2, MeOH
2. TsCl, Et3N
CH2Cl2
80% yield (2 steps)
CO2Me
HN−Ts
OH
291
PhCHO, PTSA
MgSO4, PhCH3
110 °C, 67% yield
CO2Me
N−Ts
O
292
single
diastereomer
conditions
CO2Me
N−Ts
O
X

conditions	X	result
$Pd(OAc)_2$, K_2CO_3, BQ $Cu(OAc)_2$, $PhB(OH)_2$ *t*-AmOH, 90 °C	Ph	no acetal
$Pd(OAc)_2$, $PhI(OAc)_2$ $AcOH/Ac_2O$, 85 °C	OAc	SM
$Pd(OAc)_2$, PhI, K_2CO_3 *t*-AmOH, 90 °C	Ph	decomp

We wanted to examine the success of a carboxylic acid ligating group for C–H functionalization as demonstrated by Yu and coworkers.[7] Saponification of the methyl ester to the corresponding acid **293** occurred in good yield (Scheme 3.2.2). Treatment of **293** to a variety of functionalization conditions afforded none of the desired C–C bond formation. Only cleavage of the acetal was observed, with no recovered starting material.

Scheme 3.2.2. Acid directed functionalization reactions

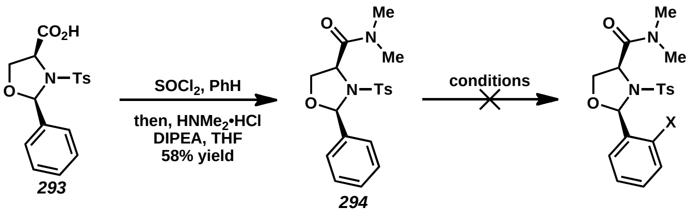


292 **293** single diastereomer

conditions	X	result
$Pd(OAc)_2$, $[Ph_2I]BF_4$ AcOH, 80 °C	Ph	no acetal
$Pd(OAc)_2$, K_2HPO_4 $Cu(OAc)_2$, BQ, $PhB(OH)_2$ *t*-BuOH, 100 to 120 °C	Ph	no acetal
$Pd(OAc)_2$, methyl acrylate $Cu(OAc)_2$, DMF 100 to 120 °C	CO_2Me	no acetal
$Pd(OAc)_2$, K_2HPO_4 $Cu(OAc)_2$, BQ $PhBF_3K$, *t*-BuOH 100 to 120 °C	Ph	no acetal

We were able to convert acid **293** directly into the dimethylamide to probe its directing group ability (Scheme 3.2.3). Functionalization conditions utilizing a diaryliodonium salt resulted in no observed arylated product.[7] Treatment with acetoxylation conditions resulted in complete recovery of starting material. Utilizing $RhCl(PPh_3)_3$ and methyl acrylate resulted in no observed olefinated product, with only starting material being recovered.[8]

Scheme 3.2.3. Generation of a dimethyl amide ligating group

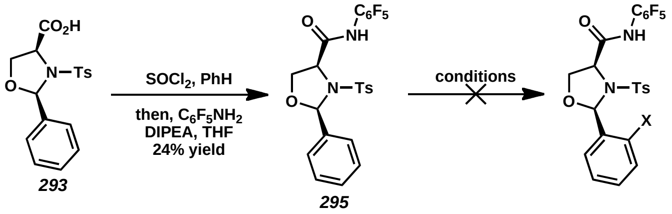


293 **294**

conditions	X
$Pd(OAc)_2$ $[Ph_2I]BF_4$ AcOH, 80 °C	Ph
$Pd(OAc)_2$ $PhI(OAc)_2$ $AcOH/Ac_2O$, 85 °C	OAc
$RhCl(PPh_3)_3$ methyl acrylate $PhCH_3$, 150 °C	CO_2Me

Yu and coworkers have demonstrated very electron poor aryl amides to be effective directing groups for C–H olefination.[9] We converted acid **293** into the pentafluorophenyl amide (**295**) in modest yield (Scheme 3.2.4). Employing Yu's conditions afforded none of the desired olefinated product and only resulted in decomposition. Additionally, subjecting **295** to $PhB(OH)_2$ under palladium catalysis only decomposed the starting material.

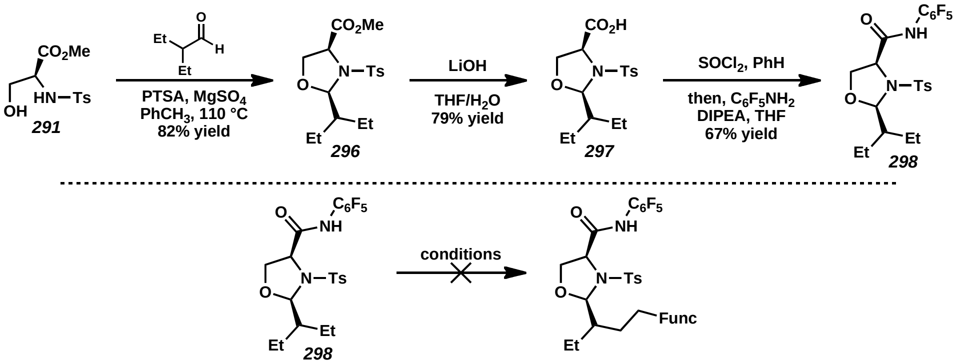
Scheme 3.2.4. Installation of a pentafluorophenyl amide ligating group


CO_2H
N−Ts
O
293
$SOCl_2$, PhH
then, $C_6F_5NH_2$
DIPEA, THF
24% yield
C_6F_5
O
NH
N−Ts
O
295
conditions
C_6F_5
O
NH
N−Ts
O
X

conditions	X	result
$Pd(OAc)_2$, benzyl acrylate LiCl, $Cu(OAc)_2$, DMF 100 to 110 °C	CO_2Bn	decomp
$Pd(OAc)_2$, K_2CO_3 $Cu(OAc)_2$, BQ, $PhB(OH)_2$ *t*-BuOH, 100 °C	Ph	decomp

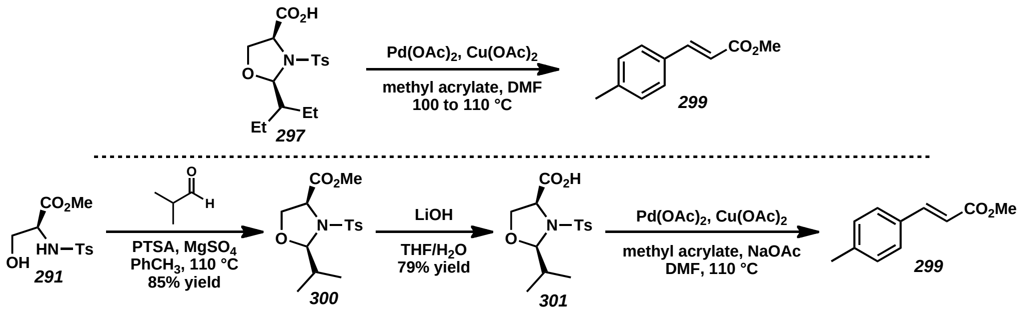
We wanted to investigate *sp*^{3} C–H functionalization with amide or acid ligating groups. Condensing **291** with 2-ethylbutyraldehyde afforded *N,O*-acetal **296** in good yield (Scheme 3.2.5). Saponification of the methyl ester afforded acid **297**, which was converted into the electron deficient amide (**298**) via the acid chloride. Under functionalization conditions, substrate **298** produced none of the desired product and only resulted in decomposition.

Scheme 3.2.5. Attempted functionalization of *sp*^{3} C–H bonds


CO_2Me
HN−Ts
OH
291
Et
O
H
Et
PTSA, $MgSO_4$
$PhCH_3$, 110 °C
82% yield
CO_2Me
N−Ts
O
Et
Et
296
LiOH
THF/H_2O
79% yield
CO_2H
N−Ts
O
Et
Et
297
$SOCl_2$, PhH
then, $C_6F_5NH_2$
DIPEA, THF
67% yield
C_6F_5
O
NH
N−Ts
O
Et
Et
298
C_6F_5
O
NH
N−Ts
O
Et
Et
298
conditions
C_6F_5
O
NH
N−Ts
O
Func
Et

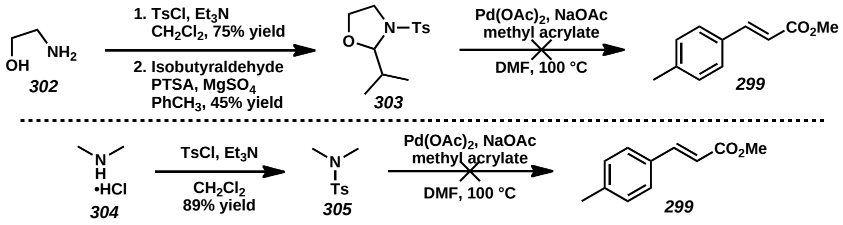
We subjected carboxylic acid **297** to a variety of functionalization conditions with no success. When we subjected **297** to $Pd(OAc)_2$, $Cu(OAc)_2$, and methyl acrylate in DMF at 110 °C, however, we observed the formation of olefin **299** in modest conversion (Scheme 3.2.6). We imagined that the product arose from a coupling between the *p*-tolyl moiety of the *N*-Ts and methyl acrylate. This transformation was also possible utilizing substrate **301**, which was synthesized in a similar fashion. Treating **301** with Pd(OAc)$_2$, Cu(OAc)$_2$, methyl acrylate and NaOAc afforded the olefin product in modest yield.

Scheme 3.2.6. Formation of C–C bond under palladium catalysis


CO2H
N–Ts
O
Et
Et
297
Pd(OAc)2, Cu(OAc)2
methyl acrylate, DMF
100 to 110 °C
CO2Me
299
CO2Me
HN–Ts
OH
291
O
H
PTSA, MgSO4
PhCH3, 110 °C
85% yield
CO2Me
N–Ts
O
300
LiOH
THF/H2O
79% yield
CO2H
N–Ts
O
301
Pd(OAc)2, Cu(OAc)2
methyl acrylate, NaOAc
DMF, 110 °C
CO2Me
299

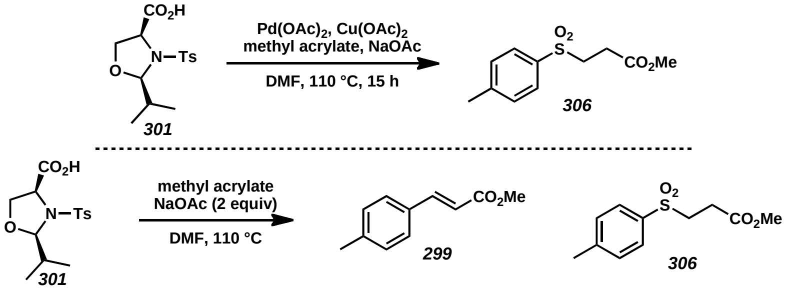
We ran control experiments to ascertain information about the transformation. Treating **297** or **301** to the reaction conditions in the absence of palladium afforded none of the coupled product, suggesting that the transformation was a palladium catalyzed event. We also removed the carboxylic acid to determine its ligating role in this reaction. From aminoethanol (**302**) tosylation of the amine and then condensation onto isobutyraldehyde provided *N,O*-acetal **303** (Scheme 3.2.7). Treatment of **303** with the coupling conditions afforded none of the olefin product. Additionally, *N,N*-dimethyltoluenesulfonamide was subjected to the reaction conditions, but furnished none of the desired product. We believed the role of the carboxylic acid to be essential for this transformation.

Scheme 3.2.7. Control experiments for C–C bond formation


NH2
OH
302
1. TsCl, Et3N
CH2Cl2, 75% yield
2. Isobutyraldehyde
PTSA, MgSO4
PhCH3, 45% yield
N–Ts
O
303
Pd(OAc)2, NaOAc
methyl acrylate
DMF, 100 °C
CO2Me
299
N
H
•HCl
304
TsCl, Et3N
CH2Cl2
89% yield
N
Ts
305
Pd(OAc)2, NaOAc
methyl acrylate
DMF, 100 °C
CO2Me
299

We sought to examine this transformation further by optimization. Treating **301** with the conditions and copper afforded a new product, resulting from sulfinate addition into the Michael acceptor (Scheme 3.2.8). We examined the role of copper in this reaction and the corresponding product distribution. Treating **301** with $Pd(OAc)_2$ and 2 equiv of $Cu(OAc)_2$ gave 10% of olefin product **299** and 4% of sulfone product **306**. Running the reaction in the absence of $Cu(OAc)_2$ affords 15% yield of the olefin product and 32% of the sulfone product. Changing the catalyst to $Pd(dba)_2$, a source of Pd^0, and in the absence of $Cu(OAc)_2$, the reaction conditions afforded only 8% yield of the olefin product and 43% yield of the sulfone product. In the absence of Pd^{II}, it is apparent that the nucleophilic addition into methyl acrylate is the dominant transformation.

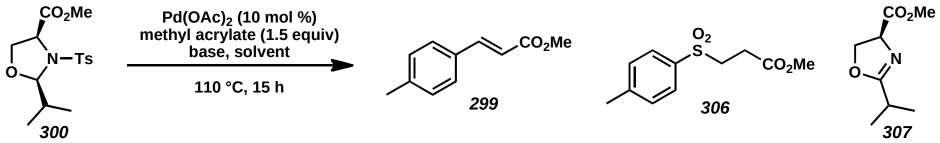
Scheme 3.2.8. Initial optimization yields a new product



Pd (10 mol %)	$Cu(OAc)_2$	yield (%) *299 : 306*
$Pd(OAc)_2$	2.0 equiv	10 : 4
$Pd(OAc)_2$	none	15 : 32
$Pd(dba)_2$	none	8 : 43

We next investigated solvent optimization and different bases (Table 3.2.1). We decided to employ methyl ester **300** for optimization purposes, as using the corresponding acid likely resulted in additional decomposition pathways and lower yields due to the acidic proton. Employing the reaction conditions in DMF for 15 h afforded 35% of olefin product **299** and 32% of sulfone product **306**. Employing different solvents afforded only trace amounts of product. Modifying the base to K_2CO_3 resulted in the formation of a new product, oxazoline **307**. In DMF, 36% of the olefin product and 45% of the oxazoline product was observed, with no sulfone product. In CH_3CN, equal amounts of olefin and sulfone products were obtained, with the majority of the product arising from oxazoline **307**.

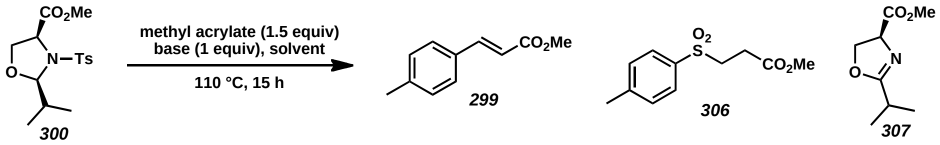
Table 3.2.1. Base and solvent screen



base	solvent	yield (%) *299 : 306 : 307*
NaOAc (2 equiv)	DMF	35 : 32 : 0
NaOAc (2 equiv)	*t*-AmOH	trace
NaOAc (2 equiv)	CH_3CN	none
NaOAc (2 equiv)	DCE	none
K_2CO_3 (1 equiv)	DMF	36 : 0 : 45
K_2CO_3 (1 equiv)	CH_3CN	15 : 15 : 46

We continued our optimization examining the palladium catalyst, base and solvent (Table 3.2.2). Treating substrate **300** with $Pd(OAc)_2$ and K_2CO_3 in DMSO afforded 26% of olefin **299** and 41% of oxazoline **307**. Modifying the palladium catalyst to $Pd(dba)_2$, a source of Pd^0, afforded only 10% of sulfone product when K_2CO_3 was employed in CH_3CN. When K_2HPO_4 or Na_2CO_3 were employed, no products were isolated. It was apparent that a source of Pd^{II} was necessary for the formation of olefin **299**. Employing $PdCl_2$ in DMF, 17% of the olefin product and 40% of the oxazoline product were isolated, with no observable sulfone. Employing the same conditions in DMSO afforded 87% yield of the olefin product and 72% of the oxazoline product. It seemed evident that the oxazoline product and olefin were arising from the same starting material. Employing Na_2CO_3 or K_2HPO_4 provided less than 30% of the olefin product, with no sulfone or oxazoline isolated from the reaction. The use of a more soluble palladium catalyst, $PdCl_2(CH_3CN)_2$ or $PdCl_2(PPh_3)_2$, did not lead to an improvement in yield, with only 53% and 38% of olefin product isolated, respectively.

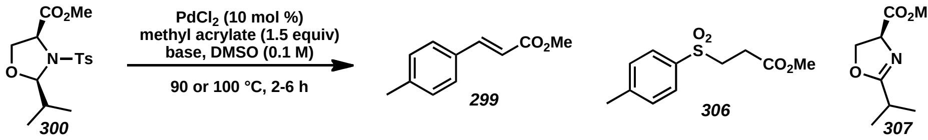
Table 3.2.2. Catalyst and base screen



Pd (10 mol %)	base	solvent	yield (%) *299 : 306 : 307*
$Pd(OAc)_2$	K_2CO_3	DMSO	26 : 0 : 41
$Pd(dba)_2$	K_2CO_3	CH_3CN	0 : 10 : 0
$Pd(dba)_2$	K_2HPO_4	CH_3CN	0 : 0 : 0
$Pd(dba)_2$	Na_2CO_3	CH_3CN	0 : 0 : 0
$PdCl_2$	K_2CO_3	DMF	17 : 0 : 40
$PdCl_2$	K_2CO_3	DMSO	87 : 0 : 72
$PdCl_2$	Na_2CO_3	DMSO	29 : 0 : 0
$PdCl_2$	K_2HPO_4	DMSO	10 : 0 : 0
$PdCl_2(CH_3CN)_2$	K_2CO_3	DMSO	53 : 0 : 51
$PdCl_2(PPh_3)_2$	K_2CO_3	DMSO	38 : 0 : 54

We wanted to further investigate the role of base in this transformation. While NaOAc and K_2CO_3 appeared to work well in most reactions, several different salts of the acetate or carbonate bases did not work at all. Using $KHCO_3$ as the base, we obtained 33% yield of the olefin product and 40% yield of oxazoline **307** (Table 3.2.3). Employing hydroxide salts like barium and calcium resulted in no reaction. After increasing the equiv of NaOAc we observed an improvement in yield of olefin product to 71%, with nearly 50% of the oxazoline product. KOAc also functioned well in this transformation, providing almost 60% yield of the olefin product when 2 equiv were used. LiOAc also afforded nearly 60% yield of the olefin, with a comparable amount of oxazoline product. Employing different carbonate bases gave mixed results, with strong bases causing decomposition and weaker salts providing no reaction. The use of different carboxylate salts was mostly ineffective, with sodium pivalate providing the greatest yield at 54%.

Table 3.2.3. Extensive examination of bases

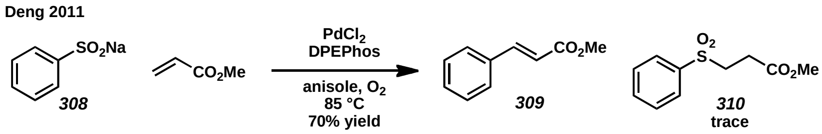


base	yield (%) *299 : 306 : 307*	base	yield (%) *299 : 306 : 307*
$KHCO_3$ (2 equiv)	33 : 0 : 40	LiOAc (2 equiv)	59 : 0 : 52
$Ba(OH)_2$ (0.5 equiv)	none	Cs_2CO_3 (1 equiv)	complex
$Ca(OH)_2$ (0.5 equiv)	none	Li_2CO_3 (1 equiv)	none
NaOAc (4 equiv)	71 : 0 : 46	*t*-$BuCO_2Na$ (2 equiv)	54 : 0 : 43
KOAc (2 equiv)	59 : 0 : 37	Cl_3CCO_2Na (2 equiv)	10 : 0 : 0
KOAc (1.5 equiv)	46 : 0 : 41	$PhCO_2Na$ (2 equiv)	29 : 0 : 9

We began assembling our evidence to get a mechanistic picture of the coupling reaction. It was evident that a Pd^{II} salt was the active catalyst, as Pd^0 catalysts were ineffective at generating olefin product **299**. $PdCl_2$ was the best palladium catalyst examined, while DMSO was the most effective solvent. There also appeared to be a significant dependence on the type of base used in the reaction. It seemed essential that either an acetate anion or potassium cation be present for significant product formation. Additionally, we had not confirmed whether olefin **299** and oxazoline **307** were originating from the same starting material.

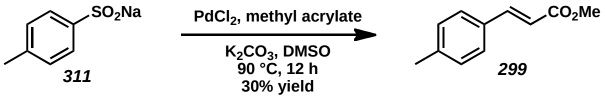
We examined the literature for any background information that could help us understand the transformation. There have been some examples of C–S bond activation of sulfones via nickel catalysis[10] and sulfonyl chlorides via palladium catalysis.[11] One such example demonstrates the C–S bond activation of a sulfonamide via a Kumada coupling with nickel. More recently, Deng and coworkers discovered a desulfitative Heck reaction employing sodium sulfinates and activated olefins to generate coupled olefin products (Scheme 3.2.9).[12] Treating **308** with methyl acrylate under palladium catalysis and O_2 afforded the olefin product and only trace amounts of sulfone **310**. The sulfinate adds into Pd^{II} with loss of SO_2 to afford the activated Pd^{II} species. Migratory insertion followed by β-hydride elimination afforded the olefin product in good yield. The use of oxygen as a terminal oxidant was essential for regenerating the Pd^{II} catalyst.

Scheme 3.2.9. Desulfitative Heck reaction



Based on this example, we imagined we might be generating the sulfinate salt, which could then undergo the desulfitative Heck coupling to afford the olefin product. Subjecting sodium sulfinate **311** to our reaction conditions only afforded 30% yield of the coupled olefin product, suggesting that our reaction was not going through a discrete sodium sulfinate (Scheme 3.2.10).

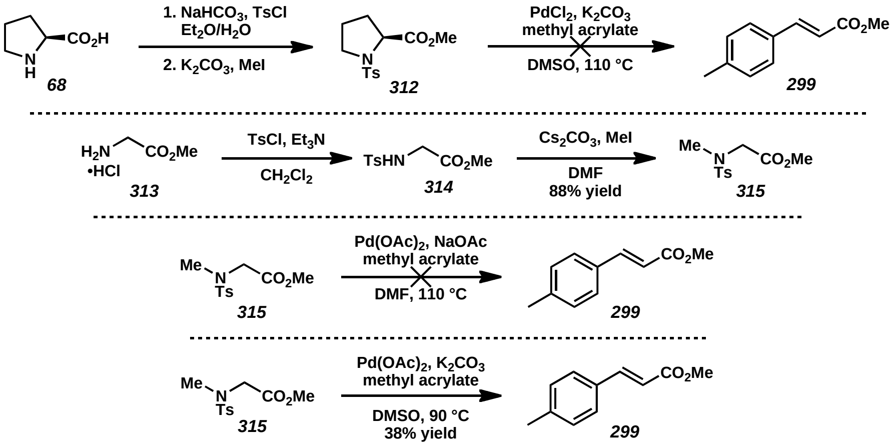
Scheme 3.2.10



We wanted to further investigate the structural aspects that were necessary for the coupling reaction to occur. Starting from L-proline, the amine was tosyl protected and subsequent esterification afforded the methyl ester (**312**) (Scheme 3.2.11). Subjecting **312** to the reaction conditions afforded none of the desired olefin product. We also wanted to examine the elimination of the cyclic structure, and ascertain its role in the coupling reaction. We tosylated glycine methyl ester to afford **314**. Methylation with MeI and Cs_2CO_3 afforded acyclic substrate **315**. Treating this substrate with the reaction conditions containing NaOAc afforded none of the coupled product. Under the same conditions with K_2CO_3 as the base, however, product **299** was isolated in 38% yield. It is interesting that the proline derivative is unreactive under our coupling conditions, while the parent substrate, cyclic **300**, affords product in up to 90% yield.

Additionally, acyclic product **315** is converted to the coupled product in nearly 40% yield. Evidently there are structural aspects to this transformation that have yet to be elucidated.

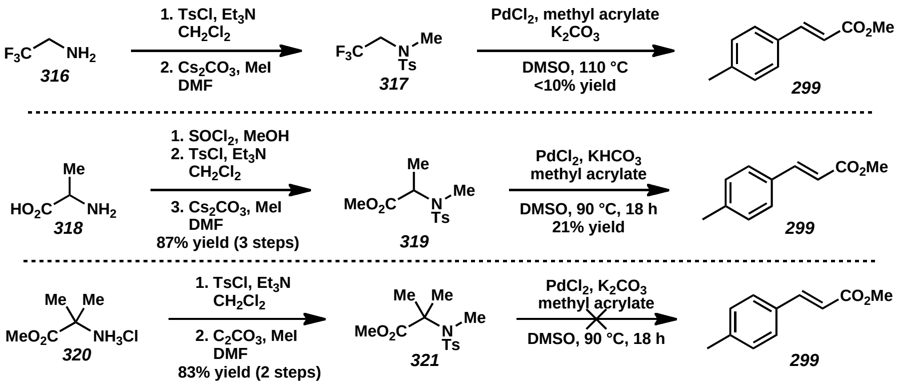
Scheme 3.2.11. Synthesis of additional substrates



68
1. NaHCO3, TsCl
Et2O/H2O
2. K2CO3, MeI
312
PdCl2, K2CO3
methyl acrylate
DMSO, 110 °C
299
313
TsCl, Et3N
CH2Cl2
314
Cs2CO3, MeI
DMF
88% yield
315
Pd(OAc)2, NaOAc
methyl acrylate
DMF, 110 °C
299
315
Pd(OAc)2, K2CO3
methyl acrylate
DMSO, 90 °C
38% yield
299

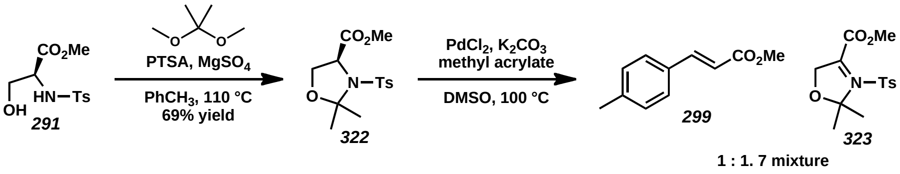
Based on the conversion of glycine derived substrate **315** to olefin **299**, we sought to examine the role of the methyl ester. Treating amine **316** with TsCl followed by alkylation afforded the tertiary amine (**317**) (Scheme 3.2.12). Reacting substrate **317** with the coupling conditions afforded less than 10% yield of the olefin product, demonstrating the necessity of the methyl ester, potentially as a ligating group. Similarly, we sought to examine a more sterically hindered alanine derived substrate. Subjecting **318** to anhydrous HCl in MeOH, followed by tosylation and alkylation with MeI afforded substrate **319**. Subjecting **319** to the coupling conditions afforded only 21% yield of the olefin product, signifying a decrease in reactivity, likely due to the α-methyl group. Furthermore, we wanted to eliminate the possibility of the generation of a sulfinate salt. Methyl alanine methyl ester hydrochloride was reacted with TsCl and subsequent methylation with MeI afforded sulfonamide **321**. Employing coupling conditions, however, afforded none of the desired olefin product. This result may signify that the mechanism of the coupling reaction proceeds through a sulfinate salt, although the increased steric hinderance cannot be discredited.

Scheme 3.2.12. Further structural evaluation


F3C NH2
316
1. TsCl, Et3N CH2Cl2
2. Cs2CO3, MeI DMF
F3C N Me Ts
317
PdCl2, methyl acrylate K2CO3
DMSO, 110 °C <10% yield
CO2Me
299
Me
HO2C NH2
318
1. SOCl2, MeOH
2. TsCl, Et3N CH2Cl2
3. Cs2CO3, MeI DMF
87% yield (3 steps)
Me
MeO2C N Me Ts
319
PdCl2, KHCO3 methyl acrylate
DMSO, 90 °C, 18 h 21% yield
CO2Me
299
Me Me
MeO2C NH3Cl
320
1. TsCl, Et3N CH2Cl2
2. C2CO3, MeI DMF
83% yield (2 steps)
Me Me
MeO2C N Me Ts
321
PdCl2, K2CO3 methyl acrylate
DMSO, 90 °C, 18 h
CO2Me
299

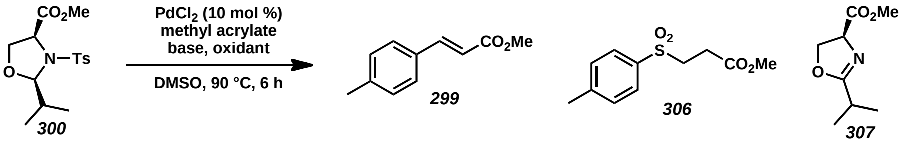
We speculated that the reaction could be initiated by an elimination of the sulfinate salt, followed by a desulfitative Heck coupling as demonstrated by Deng and coworkers. To further probe this pathway, we imagined generating acetonide **322** to the conditions (Scheme 3.2.13). With no acetal proton available for elimination to form the oxazoline, we imagined the reaction could not occur if it were proceeding via an elimination of the sulfinate. Treating acetonide **322** with the coupling conditions afforded a 1 to 1.7 mixture of coupled product to oxazoline **323**. It is possible that an elimination via the α-proton occurs first, followed by isomerization to the oxazoline **323**. This result again indicates that the reaction may be proceeding through an elimination to a sulfinate.

Scheme 3.2.13. Formation of an acetonide


CO2Me
OH HN–Ts
291
O O
PTSA, MgSO4
PhCH3, 110 °C 69% yield
CO2Me
O N–Ts
322
PdCl2, K2CO3 methyl acrylate
DMSO, 100 °C
CO2Me
299
CO2Me
O N–Ts
323
1 : 1. 7 mixture

Wanting to improve the yield of this transformation, we examined catalyst turnover more closely. Based on the work by Deng and coworkers, we imagined that the addition of a terminal oxidant might assist the conversion of Pd^0 to the active Pd^{II} species. Employing K_2CO_3 or KOAc in the presence of air afforded low conversion to olefin and sulfone products, with significant oxazoline formation (Table 3.2.4). Employing K_2CO_3 or KOAc in the presence of $Cu(OAc)_2$ afforded only a small amount of olefin product, and in the absence of base there was no reaction. Using K_2CO_3 and benzoquinone afforded a complex mixture of products, while employing KOAc afforded almost 50% yield of olefin product **299**. Utilizing KOAc in the presence of an oxygen balloon and catalytic $Cu(OAc)_2$ afforded a 63% yield of the olefin product. Removal of $Cu(OAc)_2$ and only using an oxygen balloon afforded 67% of the desired olefin product, with 30% of the isolated oxazoline. Treating **300** with catalytic amounts of BQ, $NaNO_2$ or AgOAc in the presence of KOAc afforded less than a 40% yield of the desired olefin product.

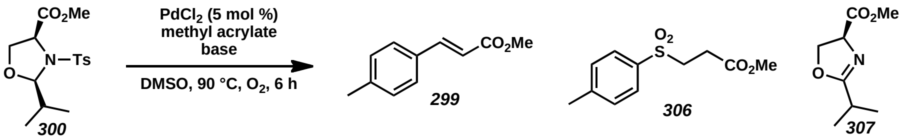
Table 3.2.4. Additional optimization of C–C bond formation



base	oxidant	yield (%) *299 : 306 : 307*	base	oxidant	yield (%) *299 : 306 : 307*
K_2CO_3 (1 equiv)	air	18 : 5 : 54	KOAc (2 equiv)	O_2 balloon $Cu(OAc)_2$ (20 mol %)	63 : 0 : 4
KOAc (2 equiv)	air	25 : 38 : 39	KOAc (2 equiv)	O_2 balloon	67 : 0 : 29
K_2CO_3 (1 equiv)	$Cu(OAc)_2$ (2 equiv)	18 : 7 : 0	KOAc (2 equiv)	BQ (25 mol %)	36 : 0 : 35
none	$Cu(OAc)_2$ (2 equiv)	none	KOAc (2 equiv)	$NaNO_2$ (25 mol %)	27 : 0 : 7
KOAc (2 equiv)	$Cu(OAc)_2$ (2 equiv)	20 : 0 : 0	KOAc (2 equiv)	AgOAc (25 mol %)	27 : 16 : 29
K_2CO_3	BQ (1 equiv)	complex			
KOAc	BQ (1 equiv)	47 : 31 : 63			

Continuing with our optimization we wanted to reduce the catalyst loading for the coupling reaction, and based on the results in Table 3.2.4 the use of O_2 should increase catalyst turnover. Utilizing 3 equivialents of NaOAc afforded 92% yield of the olefin product and only 18% of the oxazoline product (Table 3.2.5). Reducing the amount of base to 1.5 equiv afforded only 52% yield of the olefin product, with no byproducts. Utilizing Na_2CO_3 with catalytic AcOH afforded a 70% yield of the desired product. Additionally, we found that using pulverized NaOAc gave a 90% yield of the desired olefin product.

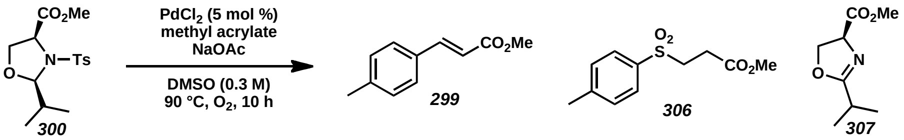
Table 3.2.5. Reducing catalyst loading



base	yield (%) *299 : 306 : 307*
NaOAc (3 equiv)	92 : 0 : 18
NaOAc (1.5 equiv)	52 : 0 : 0
Na_2CO_3 (1.5 equiv) AcOH (10 mol %)	70 : 0 : 7
NaOAc (3 equiv) (pulverized)	89: 0 : 0

Throughout our optimization, we found that the yields of the corresponding products was inconsistent from reaction to reaction. We ground the NaOAc to make it more soluble and therefore reactive in the coupling reaction. We also tried slow addition of base, which still provided inconsistent results. Furthermore, we were concerned with the oxygen transfer to the reaction vessel, and attempted to modify the mode of oxygen transfer to increase consistency, but were unsuccessful. Lastly, we set up replicate experiments to test the reliability of the transformation (Table 3.2.6). At 1 and 2 equiv of NaOAc, the yields of olefin **299** and oxazoline **307** were relatively constant. Increasing to 3 and 4 equiv of NaOAc, however, afforded very inconsistent results. We attribute this irregularity to the possible rate of elimination of the sulfinate salt. With small amounts of base only small amounts of the sodium sulfinate can be generated, which leads to consistent conversion to product. Larger amounts of base can eliminate the sulfinate quickly, which may lead to other decomposition byproducts rather than the olefin product.

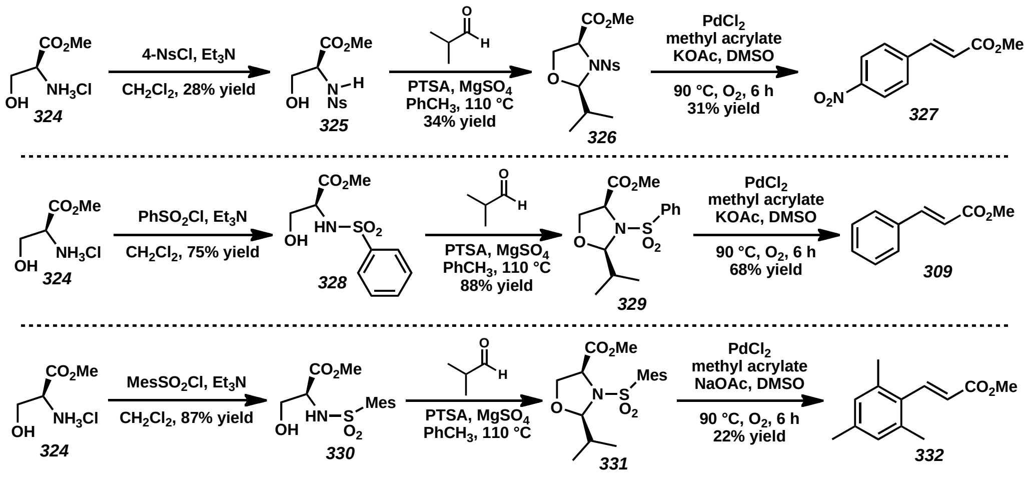
Table 3.2.6. Examination of reaction consistency



equivalents NaOAc	yield (%) *299 : 306 : 307*	equivalents NaOAc	yield (%) *299 : 306 : 307*
1.0	44 : 0 : 8	3.0	18 : 22 : 12
1.0	44 : 0 : 2	3.0	65 : 0 : 12
2.0	62 : 0 : 13	4.0	54 : 5 : 0
2.0	62 : 0 : 5	4.0	76 : 0 : 13

Based on our results we believed that the reaction was occurring via a controlled elimination of the sulfinate salt and then undergoing a desulfitative Heck reaction as demonstrated by Deng and coworkers. Further examination of this transformation and structural analysis is necessary to confirm the sulfinate mechanism. We imagined we could expand the substrate scope, however, which thus far has been limited to activated olefins and a limited number of sulfinate salts. We began our scope evaluation with electron deficient *p*-NO_2-sulfonylchloride to form sulfonamide **325** (Scheme 3.2.14). Condensation onto isobutyraldehyde afforded *N,O*-acetal **326**. Treatment with the coupling conditions afforded the coupled product in 31% yield. Additionally, we utilized benzene sulfonyl chloride to generate sulfonamide **328**. Condensation onto isobutyraldehyde afforded substrate **329**, which when subjected to the coupling conditions afforded the desired olefin in 68% yield. Furthermore, we wanted to determine if we could exploit this coupling to form hindered C–C bonds. Coupling with mesitylene sulfonylchloride to from sulfonamide **330** occurred in good yield. Condensation with isobutyraldehyde afforded the desired acetal, that when subjected to the coupling conditions afforded the desired olefin product in 22% yield.

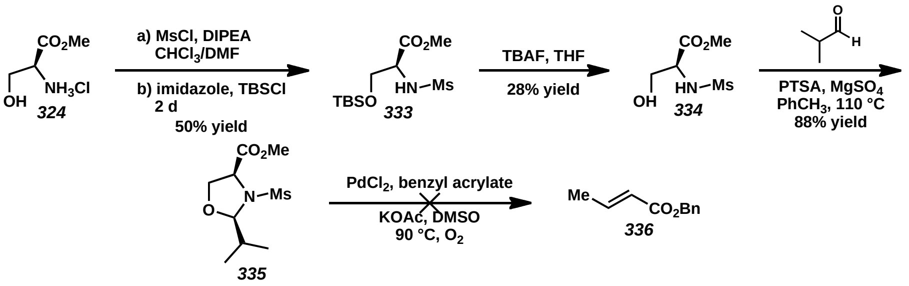
Scheme 3.2.14. Expansion of substrate scope



CO2Me
NH3Cl
OH
324
4-NsCl, Et3N
CH2Cl2, 28% yield
N–H
Ns
325
PTSA, MgSO4
PhCH3, 110 °C
34% yield
NNs
326
PdCl2
methyl acrylate
KOAc, DMSO
90 °C, O2, 6 h
31% yield
O2N
327
PhSO2Cl, Et3N
CH2Cl2, 75% yield
HN–SO2
328
PTSA, MgSO4
PhCH3, 110 °C
88% yield
Ph
329
PdCl2
methyl acrylate
KOAc, DMSO
90 °C, O2, 6 h
68% yield
309
MesSO2Cl, Et3N
CH2Cl2, 87% yield
Mes
330
PTSA, MgSO4
PhCH3, 110 °C
331
PdCl2
methyl acrylate
NaOAc, DMSO
90 °C, O2, 6 h
22% yield
332

Ultimately, we envisioned our substrate scope extending to triflates, which when utilized in our coupling conditions could install a trifluormethyl group, a functional group of great interest recently. We began with the mesyl derivative to test the feasibility of this reaction with non-aryl coupling partners (Scheme 3.2.15). To install the methane sulfonamide we employed a two-step procedure to generate the sulfonamide and TBS-protect the alcohol.[13] Removal of the TBS group afforded amino alcohol **334**. Condensation onto isobutyraldehyde afforded the desired acetal, that when subjected to the coupling conditions only resulted in decomposition.

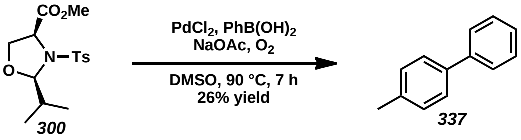
Scheme 3.2.15. Attempted coupling of a methane sulfonamide



CO2Me
NH3Cl
OH
324
a) MsCl, DIPEA
CHCl3/DMF
b) imidazole, TBSCl
2 d
50% yield
TBSO
HN–Ms
333
TBAF, THF
28% yield
334
PTSA, MgSO4
PhCH3, 110 °C
88% yield
N–Ms
335
PdCl2, benzyl acrylate
KOAc, DMSO
90 °C, O2
Me
CO2Bn
336

We imagined that performing a Heck reaction with a methyl-Pd^{II} species might prove difficult. Instead we envisioned performing a desulfitative Suzuki coupling, which should prove more facile. Subjecting **300** to our coupling conditions in the presence of $PhB(OH)_2$ afforded phenyl toluene (**337**) in moderate yield (Scheme 3.2.16). Further optimization of this transformation needs to be examined to determine its feasibility in coupling with methane or triflouromethane sulfonamides.

Scheme 3.2.16. Coupling with boronic acids

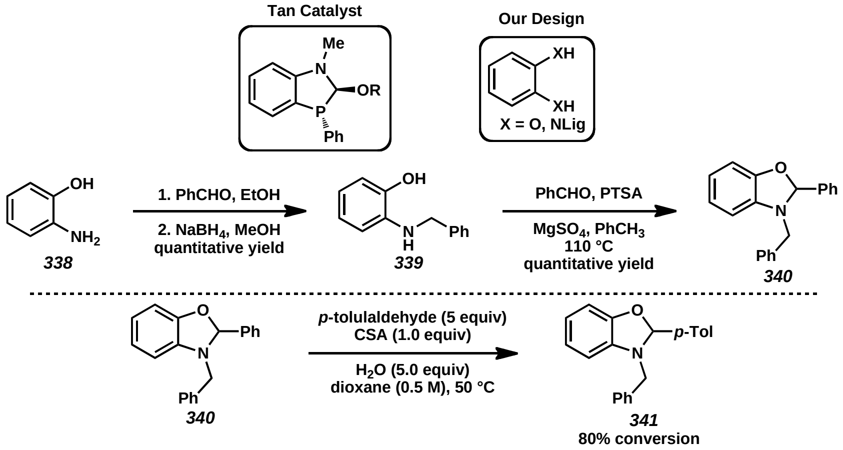


While attempting to develop a methodology to perform C–H functionalization reactions with a transient directing group, we have discovered a relatively unexplored transformation. The extent of this new method to form C–C bonds is not yet known, but could extend to simple methyl or trifluoromethyl Heck couplings with olefins or Suzuki couplings with boronic acids. More investigation into the scope of this transformation could lead to higher utility and mechanistic insight.

3.3 Non-Amino Acid Derived Scaffolds

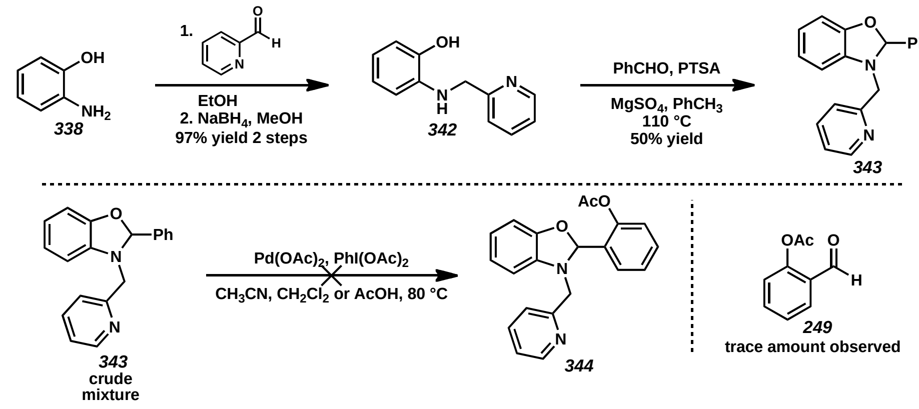
Looking more closely at the work done with transient directing groups, we re-examined our approach. Tan and coworkers have used aromatic amino phosphines as acetalization components.[14] We imagined using amino alcohol acetalization components in a similar manner. In our design, we envisioned installing the directing group on the amine component, either directly attached to the aromatic ring, or benzylic to the aromatic ring (Scheme 2.3.1). Before installing a directing group we wanted to determine the feasibility of the condensation reaction and transacetalization. Amino phenol **338** was condensed with benzaldehyde to form the corresponding imine, then reduced to the secondary amine with $NaBH_4$ to afford **339** in quantitative yield over 2 steps. Condensation of amino phenol **339** with benzaldehyde afforded the *N*,*O*-acetal in quantitative yield. The product was not stable to silica gel chromatography, speaking to its high lability. We also wanted to examine the exchangeability of this framework. Treating **340** with *p*-tolualdehyde with CSA and H_2O in dioxane overnight at 50 °C afforded 80% conversion to exchange product **341**.

Scheme 3.3.1. New catalyst design


Tan Catalyst
Me
N
OR
P
Ph
Our Design
XH
XH
X = O, NLig
OH
NH2
338
1. PhCHO, EtOH
2. NaBH4, MeOH
quantitative yield
OH
N
H
Ph
339
PhCHO, PTSA
MgSO4, PhCH3
110 °C
quantitative yield
O
Ph
N
Ph
340
O
Ph
N
Ph
340
p-tolulaldehyde (5 equiv)
CSA (1.0 equiv)
H2O (5.0 equiv)
dioxane (0.5 M), 50 °C
O
p-Tol
N
Ph
341
80% conversion

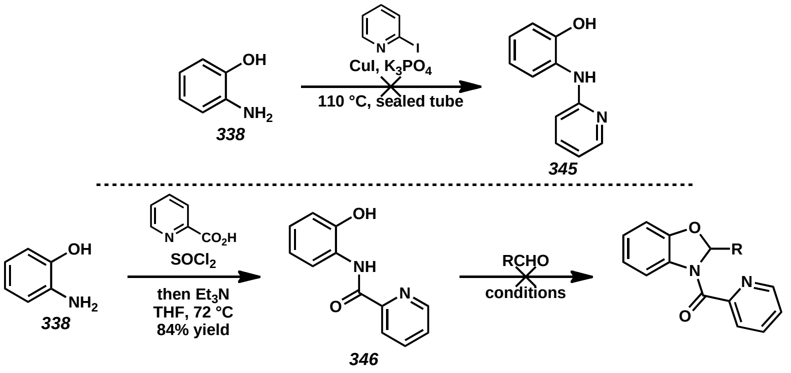
Encouraged by these preliminary experiments we sought to install a ligating group to examine the possibility of functionalization of the desired C–H bond. From amino phenol **338** we were able to form the corresponding imine with 2-pyridinecarboxaldehyde (Scheme 3.3.2). Treatment with $NaBH_4$ afforded amino phenol **342** in 97% yield over two steps. Condensation with benzaldehyde only proceeded to 50% conversion to afford *N,O*-acetal **344**. When the crude mixture was reacted under acetoxylation conditions, a complex mixture of products, with observed trace amounts of acetoxylated benzaldehyde were obtained.

Scheme 3.3.2. Attempts at acetoxylation


OH
NH2
338
1.
O
H
N
EtOH
2. NaBH4, MeOH
97% yield 2 steps
OH
N
H
N
342
PhCHO, PTSA
MgSO4, PhCH3
110 °C
50% yield
O
Ph
N
N
343
O
Ph
N
N
343
crude
mixture
Pd(OAc)2, PhI(OAc)2
CH3CN, CH2Cl2 or AcOH, 80 °C
AcO
O
N
N
344
OAc
O
H
249
trace amount observed

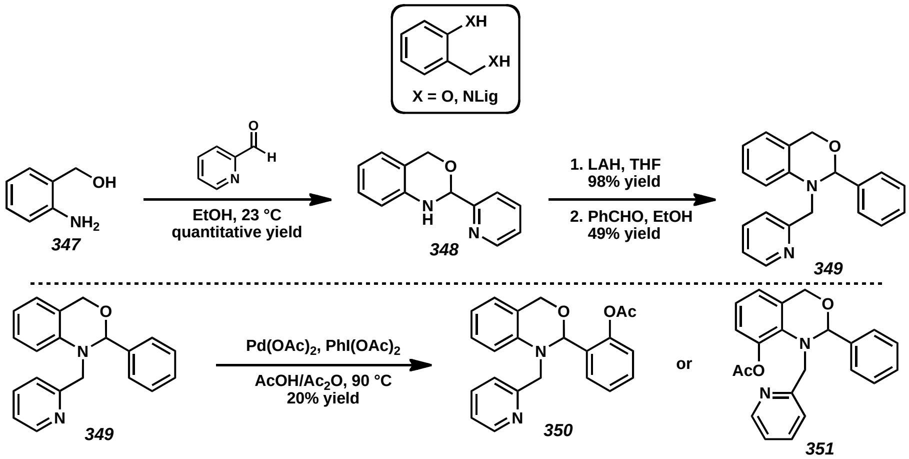
We were concerned about the conformational flexibility of substrate ligand adduct **343** and its inability to direct C–H functionalization regioselectively. We sought to inhibit this flexibility by attaching the pyridyl ligating group directly to the nitrogen via Buchwald's arylation chemistry.[15] Coupling with iodopyridine and amino phenol **338** was unsuccessful (Scheme 3.3.3). Alternatively we imagined installing a carbonyl moiety at the benzylic position to reduce flexibility of the ligating group. Amide coupling with picolinic acid afforded amide **346**. Unfortunately, condensation with aromatic or aliphatic aldehydes was unsuccessful at generating the desired substrate ligand adduct. Additionally, substitution of the 2-pyridyl ligating group for any other amide did not improve the condensation onto any aldehyde.

Scheme 3.3.3. Altering pyridyl connectivity


OH
NH2
338
N
I
CuI, K3PO4
110 °C, sealed tube
OH
NH
N
345
OH
NH2
338
N
CO2H
SOCl2
then Et3N
THF, 72 °C
84% yield
OH
NH
O
N
346
RCHO
conditions
O
R
N
O
N

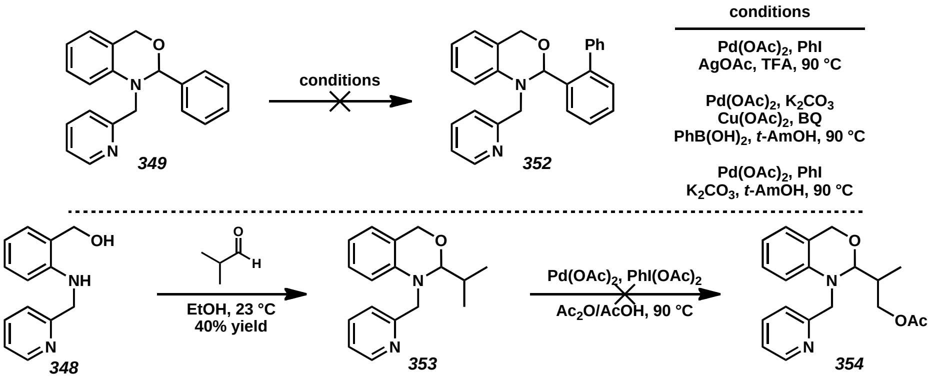
Next we sought to alter the connectivity of the acetalization components and positioning of the ligating group. Starting from amino alcohol **347**, we formed *N,O*-acetal **348** via condensation with 2-pyridylcarboxaldehyde (Scheme 3.3.4).[16] Treatment with LAH afforded the hydroamination product, followed by condensation with benzaldehyde to afford *N,O*-acetal **349** in good yield, which was stable to chromatography. Subjecting **349** to acetoxylation conditions afforded an acetoxylated product in 20% yield, but it was unclear whether the desired C–H bond had been activated to afford **350**, rather than acetate **351**. We subjected the product of the acetoxylation to an exchange reaction with benzaldehyde, but no salicylaldehyde or acylated salicylaldehyde was observed in the reaction mixture.

Scheme 3.3.4. Altering the connectivity of acetalization components


XH
XH
X = O, NLig
OH
NH2
347
O
H
N
EtOH, 23 °C
quantitative yield
O
N
H
N
348
1. LAH, THF
98% yield
2. PhCHO, EtOH
49% yield
O
N
N
349
O
N
N
349
Pd(OAc)2, PhI(OAc)2
AcOH/Ac2O, 90 °C
20% yield
O
OAc
N
N
350
or
O
N
AcO
N
351

We next tried to form a C–C bond via C–H functionalization utilizing substrate ligand adduct **349** (Scheme 3.3.5). Treating **349** with PhI in the presence of palladium and silver resulted in decomposition with no observable product **352**. Treatment with $PhB(OH)_2$ in the presence of palladium, copper, K_2CO_3 and benzoquinone only resulted in recovery of starting material. Likewise, coupling with PhI in the presence of palladium and K_2CO_3 only provided recovered staring material. We also wanted to investigate the functionalization of sp^3 C–H bonds using ligand **348**. Condensation onto isobutyraldehyde afforded *N,O*-acetal **353** in moderate yield, again stable to chromatography. Subjecting **353** to acetoxylation conditions, however, resulted only in decomposition.

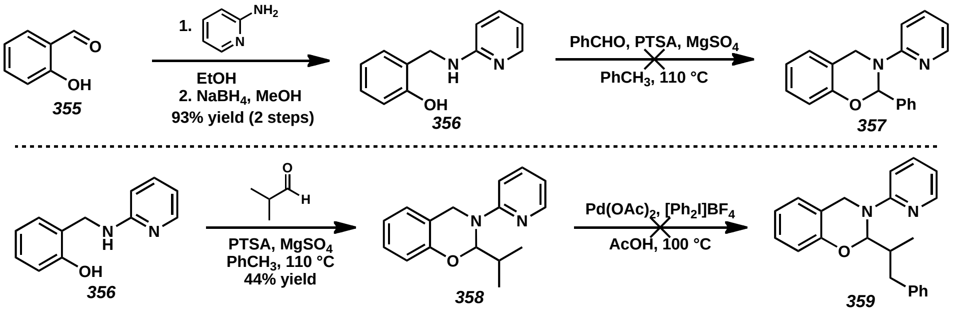
Scheme 3.3.5. Other C–H functionalization reactions



349
conditions
352
Ph
conditions
Pd(OAc)2, PhI
AgOAc, TFA, 90 °C
Pd(OAc)2, K2CO3
Cu(OAc)2, BQ
PhB(OH)2, t-AmOH, 90 °C
Pd(OAc)2, PhI
K2CO3, t-AmOH, 90 °C
OH
NH
348
EtOH, 23 °C
40% yield
353
Pd(OAc)2, PhI(OAc)2
Ac2O/AcOH, 90 °C
354
OAc

Lastly, we sought to alter the positioning of the alcohol and amine components. From amino alcohol **355** we installed the ligating group in two steps in excellent yield (Scheme 3.3.6). Condensation onto benzaldehyde, however, did not occur to afford *N,O*-acetal **357**. We then condensed the ligand onto isobutyraldehyde to afford *N,O*-acetal **358**. Subjecting **358** to palladium and a diaryliodonium salt to perform a C–H arylation was unsuccessful and resulted in decomposition.

Scheme 3.3.6. Alteration of acetalization components



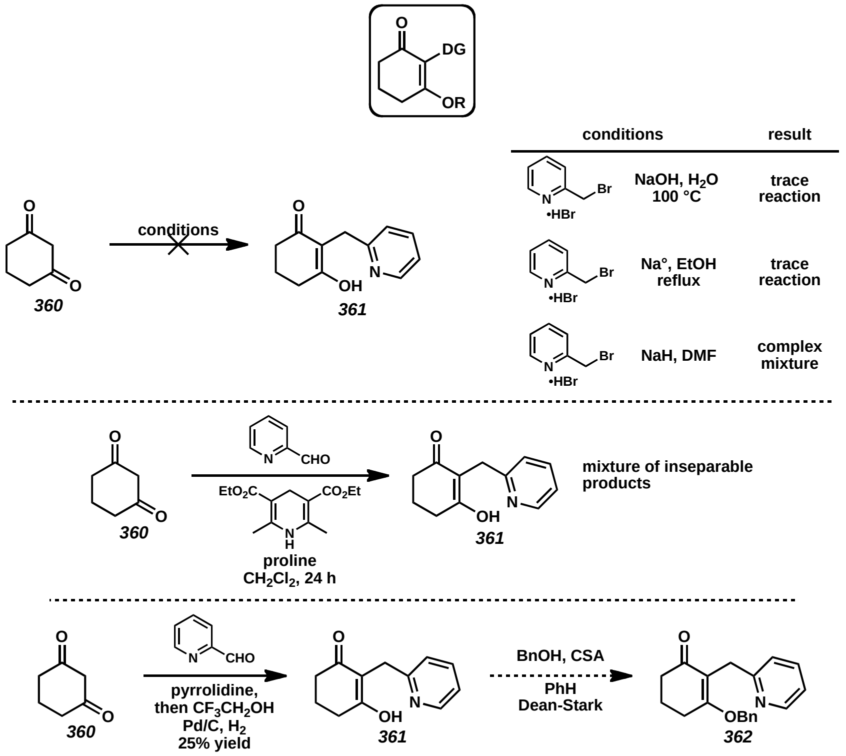
355
1.
NH2
EtOH
2. NaBH4, MeOH
93% yield (2 steps)
356
PhCHO, PTSA, MgSO4
PhCH3, 110 °C
357
Ph
356
PTSA, MgSO4
PhCH3, 110 °C
44% yield
358
Pd(OAc)2, [Ph2I]BF4
AcOH, 100 °C
359
Ph

The problems associated with these non-amino acid derived ligands mostly lie with the instability of the *N,O*-acetal or poor regioselectivity of the functionalization. Using the aryl ring as the backbone lends several possible sp^2 C–H bonds to be functionalized. Alteration of the aryl ring by placing substituents in the ortho positions may resolve the issue of regioselectivity, but could result in other complications, particularly ease of ligand synthesis.

3.4 Redesigning Substrate-Ligand Relationship

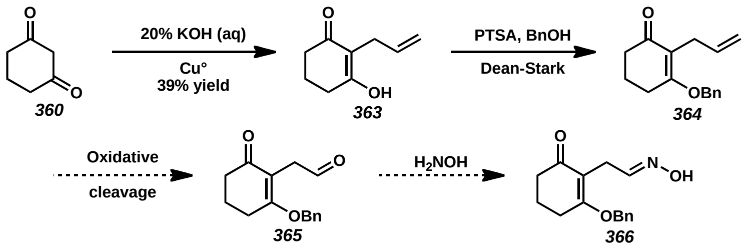
We wondered if a different substrate ligand relationship may facilitate reaction development. Rather than the ligand coordinating through an aldehyde, we envisioned forming the substrate ligand adduct via an ether linkage. Employing a vinylogous ester scaffold, we may achieve good levels of exchangeability with C–H functionalization (Scheme 3.4.1). We first sought to install the ligating group via alkylation. Treatment of dione **360** with 2-bromomethyl pyridine under various conditions did not afford the desired enol product. We attempted a Knovenagel condensation followed by *in situ* reduction with the Hanztch ester to give the enol product.[17] We were able to form the desired product, but it was inseparable from the byproducts of the reaction. Employing a two-step Knovenagel/hydrogenation procedure afforded the desired enol product (**361**).[18] From this product, formation of the vinylogous ester with BnOH and Dean-Stark conditions should be possible to achieve the desired test substrate.

Scheme 3.4.1. Installation of a pyridyl ligating group


DG
OR
conditions
result
•HBr
Br
NaOH, H₂O 100 °C
trace reaction
Na°, EtOH reflux
trace reaction
NaH, DMF
complex mixture
conditions
360
361
CHO
EtO₂C
CO₂Et
proline
CH₂Cl₂, 24 h
mixture of inseparable products
pyrrolidine,
then CF₃CH₂OH
Pd/C, H₂
25% yield
BnOH, CSA
PhH
Dean-Stark
362

Because of the difficulties associated with installing a pyridyl ligating group, we elected to examine other ligating groups. Installation of an allyl group via alkylation occurred in moderate yield (Scheme 3.4.2).[19] Esterification with BnOH under Dean-Stark conditions afforded the benzyl ester. Oxidative cleavage and condensation with hydroxyl amine would generate the oxime ligand (**366**).

Scheme 3.4.2. Installation of an oxime ligating group


360
20% KOH (aq)
Cu°
39% yield
363
PTSA, BnOH
Dean-Stark
364
Oxidative
cleavage
365
H₂NOH
366
OBn
OH

These initial ligand syntheses for alcohol exchange need more synthetic exploration. Upon synthesis of **366**, both exchangeability and directing group capability should be examined.

Furthermore, the exploration of other ligating groups may improve ligand synthesis and/or exchangeability of alcohol substrates.

3.5 Conclusions

Our investigations into ligands for C–H functionalization have revealed *N,O* acetals as promising scaffolds. Modulating the ligating groups have exhibited promising results. These studies suggest that further investigations into the serine derived scaffold could be beneficial. These explorations have also revealed new reactivity, which upon further examination may be advantageous to the synthetic community.

3.6 References and Notes

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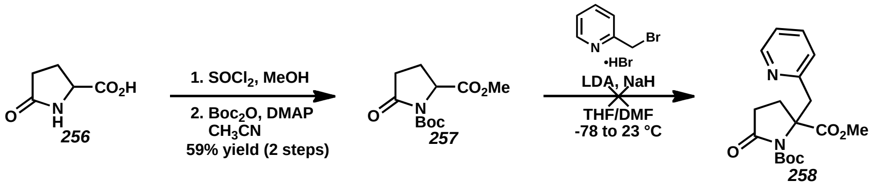
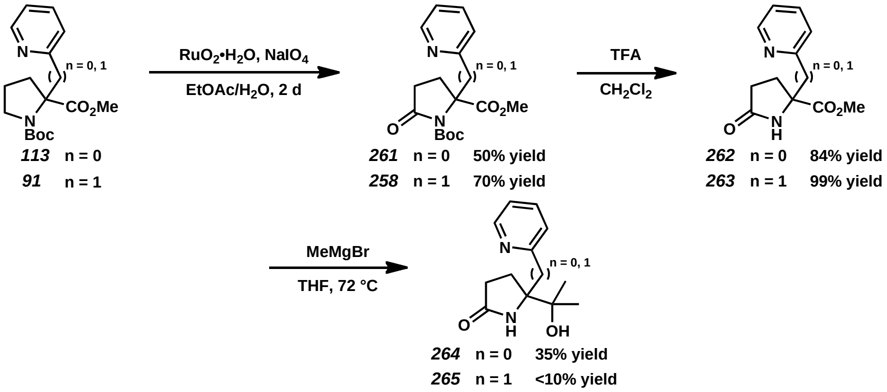
3.7 Experimental Procedures

Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, *N*,*N*-dimethylformamide, dichloromethane, hexanes, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH_2. 2-Fluoropyridine was freshly distilled before use. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Gelest (Morrisville, PA), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), Mallinckrodt Chemicals (Phillipsburg, NJ), Spectrum (Gardena, CA) Fischer Scientific (Fair Lawn) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to either *p*-anisaldehyde or $KMnO_4$ solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), a Varian Inova 400 (at 400 MHz), or a Varian 400 MR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on either a Varian Inova 400 (at 100 MHz), a Varian Mercury 300 (at 75 MHz), or a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with either a Nicolet Magna FTIR 760, a Nicolet 380 FTIR, or a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.



To **256** (500 mg, 3.87 mmol) in MeOH (3.90 mL) at 0 °C was added $SOCl_2$ (0.390 mL, 5.34 mmol) slowly. Stirred an additional 5 min at 0 °C, then 23 °C overnight. $NaHCO_3$ (77.4 mg) was added, then the mixture was filtered through celite. The celite was washed with hot MeOH (3 x 15 mL). The organic solvent was removed under reduced pressure to afford the methyl ester (554 mg, 99% yield) as a murky yellow oil, with no further purification.

To methyl ester (19.1 mmol) and DMAP (468 mg, 3.83 mmol) in CH_3CN (19.1 mL) was added Boc_2O (4.22 g, 19.3 mmol) at 23 °C. The reaction was stirred at 23 °C overnight, at which point the solvent was removed under reduced pressure. To the residue was added 1 M $KHSO_4$ and EtOAc. The aqueous layer was extracted with EtOAc (3 x 20 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (1:1 hexanes:EtOAc) to afford **257** (2.75 g, 59% yield, R_f = 0.30 in 1:1 hexanes:EtOAc) as a white solid.



n = 0, 1
CO2Me
Boc
113 n = 0
91 n = 1
RuO2•H2O, NaIO4
EtOAc/H2O, 2 d
261 n = 0 50% yield
258 n = 1 70% yield
TFA
CH2Cl2
262 n = 0 84% yield
263 n = 1 99% yield
MeMgBr
THF, 72 °C
OH
264 n = 0 35% yield
265 n = 1 <10% yield

To $RuO_2•H_2O$ (4.3 mg, 0.0325 mmol) and $NaIO_4$ (4.30 mL, 10% aq) was added **113** (100 mg, 0.325 mmol) in EtOAc (1.60 mL) at 23 °C. The reaction was stirred for 2 d at 23 °C. IPA was added and stirred at 23 °C for 2 h. The black precipitate was filtered and washed with EtOAc. The organics were washed with brine (2 x 10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (3:1 to 1:1 hexanes:EtOAc) to afford **261** (59.3 mg, 57% yield, R_f = 0.25 in 1:1 hexanes:EtOAc) as a beige solid.

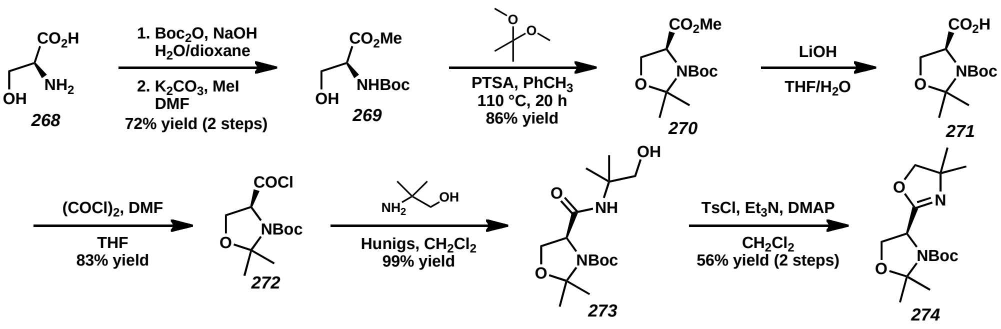
To **261** (59.3 mg, 0.185 mmol) in CH_2Cl_2 (0.400 mL) was added TFA (0.29 mL, 3.70 mmol). The reaction was stirred at 23 °C for 1 h. The solvent was removed under reduced pressure. The residue was neutralized with sat. aq. $NaHCO_3$. The aqueous was extracted with CH_2Cl_2 (3 x 10 mL). The organics were dried over Na_2SO_4 and concentrated to afford **262** (34.0 mg, 84% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a beige solid.

To **262** (34.0 mg, 0.154 mmol) in THF (1.50 mL) was added MeMgBr (0.160 mL, 0.471 mmol, 3.0 M in Et_2O) at 0 °C. The reaction was warmed to 23 °C and then refluxed for 3 h. Sat. aq. $NaHCO_3$ was added upon completion. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (40:1 to 19:1 EtOAc:MeOH) to afford **264** (11.7 mg, 35% yield, R_f = 0.10 in 40:1 EtOAc:MeOH) as a beige solid.

To $RuO_2{\bullet}H_2O$ (4.2 mg, 0.0312 mmol) and $NaIO_4$ (4.20 mL, 10% aq) was added **113** (100 mg, 0.312 mmol) in EtOAc (1.60 mL) at 23 °C. The reaction was stirred for 2 d at 23 °C. IPA was added and stirred at 23 °C for 2 h. The black precipitate was filtered and washed with EtOAc. The organics were washed with brine (2 x 10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (3:1 to 1:1 hexanes:EtOAc) to afford **258** (104 mg, 70% yield, R_f = 0.20 in 1:1 hexanes:EtOAc) as a beige solid.

To **258** (72.1 mg, 0.216 mmol) in CH_2Cl_2 (0.400 mL) was added TFA (0.332 mL, 4.31 mmol). The reaction was stirred at 23 °C for 1 h. The solvent was removed under reduced pressure. The residue was neutralized with sat. aq. $NaHCO_3$. The aqueous was extracted with CH_2Cl_2 (3 x 10 mL). The organics were dried over Na_2SO_4 and concentrated to afford **263** (51.5 mg, 99% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as a beige solid.

To **262** (51.5 mg, 0.220 mmol) in THF (2.20 mL) was added MeMgBr (0.220 mL, 0.673 mmol, 3.0 M in Et_2O) at 0 °C. The reaction was warmed to 23 °C and then refluxed for 3 h. Sat. aq. $NaHCO_3$ was added upon completion. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified via flash chromatography (40:1 to 19:1 EtOAc:MeOH) to afford **265** in less than 10% yield as a beige solid.


CO2H
NH2
OH
268
1. Boc2O, NaOH
H2O/dioxane
2. K2CO3, MeI
DMF
72% yield (2 steps)
CO2Me
NHBoc
OH
269
PTSA, PhCH3
110 °C, 20 h
86% yield
CO2Me
NBoc
O
270
LiOH
THF/H2O
CO2H
NBoc
O
271
(COCl)2, DMF
THF
83% yield
COCl
NBoc
O
272
NH2
OH
Hunigs, CH2Cl2
99% yield
OH
O
NH
NBoc
O
273
TsCl, Et3N, DMAP
CH2Cl2
56% yield (2 steps)
O
N
NBoc
O
274

To a solution of **268** (0.500 g, 4.76 mmol) in dioxane (4.76 mL) and 1 M NaOH (9.52 mL) at 0 °C was added Boc_2O (1.23 g, 5.62 mmol) portionwise over 5 min. The reaction was stirred an additional 30 min at 0 °C, then 23 °C overnight. The organic solvent was removed under reduced pressure. The aqueous was acidified to pH 2 with 1 M $KHSO_4$. The aqueous was extracted with $CHCl_3$ (3 x 20 mL). The organics were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford Boc-serine (1.11 g, 99% yield) as a thick clear oil.

To Boc-serine (4.76 mmol) in DMF (4.76 mL) at 0 °C was added K_2CO_3 (724 mg, 5.24 mmol) and stirred for 10 min at 0 °C. To this solution was added MeI (0.59 mL, 9.52 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min, the at 23 °C for 3 h. The reaction was filtered, the filtrate suspended between H_2O and EtOAc. The organic layer was washed with brine (2 x 15 mL), dried over Na_2SO_4 and concentrated to afford **269** (0.860 g, 72% yield, R_f = 0.39 in 1:1 hexanes:EtOAc) as an amber oil.

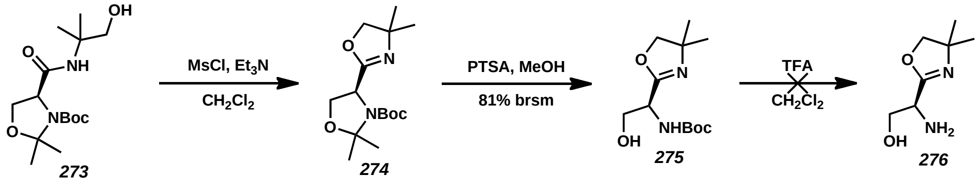
To **269** (0.804 g, 3.67 mmol) in toluene (16.0 mL) at 23 °C was added dimethoxy propane (1.18 mL, 9.54 mmol) and PTSA (13.9 mg, 0.0734 mmol). The flask was fitted with a short path distillation apparatus, and heated to reflux until 4 mL had been collected. More dimethoxy propane (0.45 mL, 3.67 mmol) and PTSA (7.0 mg, 0.037 mmol) were added. Another 4 mL of solvent was distilled off. The reaction was then fitted with a condenser and refluxed overnight. Upon cooling to 23 °C, sat. aq. $NaHCO_3$ was added. The aqueous was extracted with EtOAc (2 x 10 mL). The organics were washed with brine, dried over Na_2SO_4 and concentrated to afford **270** (0.817 g, 86% yield, $R_f = 0.65$ in 1:1 hexanes:EtOAc) as an orange oil.

To a solution of **270** (0.817 g, 3.16 mmol) in THF (6.32 mL) and H_2O (3.16 mL) was added LiOH (75.6 mg, 3.16 mmol) and stirred overnight at 23 °C. The residue was acidified to pH 2 with 1 M $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organics were dried over Na_2SO_4 and concentrated to afford **271** (0.809 g, 99% yield) as a clear oil.

To a solution of **271** (0.809 g, 3.30 mmol) in THF (16.5 mL) at 0 °C was added $(COCl)_2$ (1.44 mL, 16.5 mmol) and DMF (5 drops). The reaction was stirred at 0 °C for 5 min, then 23 °C for 1 h. The solvent was removed, and the residue concentrated from benzene (3 x 10 mL) to afford **272** (0.774 g, 83% yield) as a yellow solid.

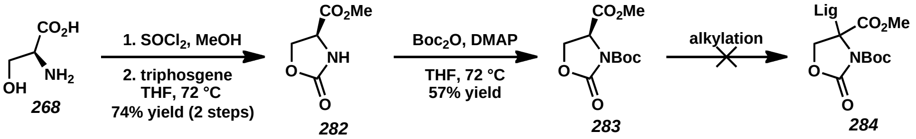
To a solution of amino alcohol (1.06 mL, 11.1 mmol), DIPEA (1.93 mL, 11.1 mmol) and CH_2Cl_2 (12.0 mL) at 0 °C was added **272** (0.774 g, 2.77 mmol) in CH_2Cl_2 (13.9 mL). The reaction was stirred at 0 °C for 10 min, then 23 °C overnight. The reaction was washed with 0.5 M HCl. The aqueous was extracted with CH_2Cl_2 (2 x 15 mL). The combined organics were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford **273** (0.756 g, 99% yield) as a yellow amorphous solid.

To a solution of **273** (0.756 g, 2.39 mmol) in CH_2Cl_2 (9.08 mL) and Et_3N (0.696 mL, 4.99 mL) and DMAP (27.7 mg, 0.227 mmol) was added TsCl (0.433 g, 2.27 mmol) at 23 °C. The combined organics were washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4 and concentrated. The crude residue was prufied via flash chromatography (3:2 to 1:1 hexanes:EtOAc) to afford **274** (0.424 g, 56% yield, R_f = 0.29 in 1:1 hexanes:EtOAc) as a beige solid.



OH
O
NH
NBoc
O
273
MsCl, Et3N
CH2Cl2
O
N
NBoc
O
274
PTSA, MeOH
81% brsm
O
N
OH
NHBoc
275
TFA
CH2Cl2
O
N
OH
NH2
276

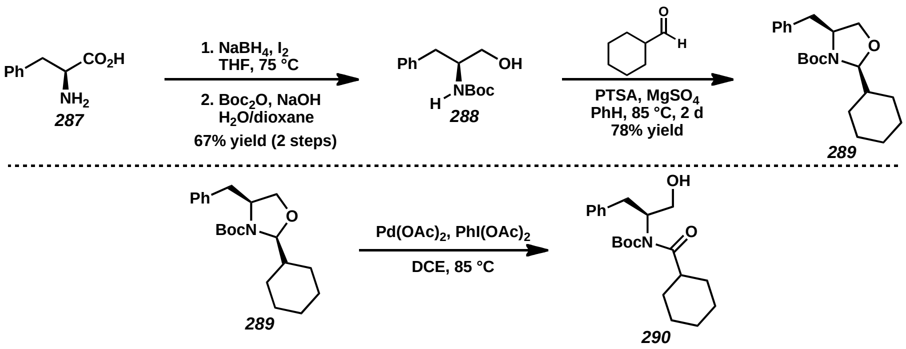
To a solution of **274** (100 mg, 0.335 mmol) in MeOH was added PTSA (24.2 mg, 0.127 mmol) at 23 °C and stirred for 18 h. Sat. aq. $NaHCO_3$ was added under pH 9. MeOH was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organics were dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (19:1 to 9:1 CH_2Cl_2:MeOH) to afford **275**.



CO2H
NH2
OH
268
1. SOCl2, MeOH
2. triphosgene
THF, 72 °C
74% yield (2 steps)
CO2Me
NH
O
O
282
Boc2O, DMAP
THF, 72 °C
57% yield
CO2Me
NBoc
O
O
283
alkylation
Lig
CO2Me
NBoc
O
O
284

To serine methyl ester (100 mg, 0.643 mmol) in THF (5.4 mL) was added triphosgene (191 mg, 0.643 mmol) in THF (1.0 mL). The mixture was refluxed for 4 h, at which point the solvent was removed under reduced pressure. The crude mixture was purified over silica (1:1 to 3:2 hexanes:EtOAc) to afford **282** (68.8 mg, 74% yield) as a white solid.

To **282** (50 mg, 0.345 mmol) in THF (1.7 mL) was added Boc_2O (113 mg, 0.517 mmol) and DMAP (4.2 mg, 0.0345 mmol) at 23 °C. The mixture was refluxed for 1 h, at which time the solvent was removed. The crude residue was purified over silica (48.4 mg, 57% yield).

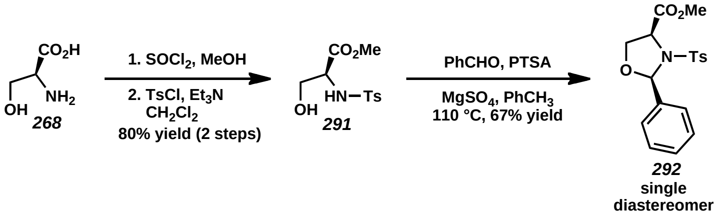


To $NaBH_4$ (275 mg, 7.27 mmol) in THF (10.1 mL) was added **287** (500 mg, 3.03 mmol) at 23 °C. I_2 (768 mg, 3.03 mmol) was added in THF (2.0 mL) slowly. The mixture was heated to reflux upon ceasing of bubbling for 18 h. After cooling to 23 °C, MeOH was added until the solution was clear. The solvent was removed under reduced pressure. 20% aq. KOH (8 mL) was added and the mixture stirred for 4 h. The aqueous was extracted with CH_2Cl_2 (3 x 10 mL), the organics dried over Na_2SO_4 and concentrated to afford amino alcohol (0.443 g, 97% yield).

To a solution of amino alcohol (0.443 g, 2.93 mmol) in dioxane (3.0 mL) and 1 M NaOH (5.9 mL) at 0 °C was added Boc_2O (0.754 g, 3.46 mmol) portionwise over 5 min. The reaction was stirred an additional 30 min at 0 °C, then 23 °C overnight. The organic solvent was removed under reduced pressure. The aqueous was acidified to pH 2 with 1 M $KHSO_4$. The aqueous was extracted with $CHCl_3$ (3 x 20 mL). The organics were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford **288** (0.504 g, 69% yield) as a white solid.

To **288** (100 mg, 0.398 mmol) in benzene (4.0 mL) was added cyclohexanecarboxaldehyde (0.053 mL, 0.438 mmol), PTSA (1.1 mg, 5.97 μmol) and $MgSO_4$ (71.8 mg, 0.597 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (9:1 to 4:1

hexanes:EtOAc) to afford **289** (107 mg, 78% yield, R_f = 0.75 in 4:1 hexanes:EtOAc) as a white solid.

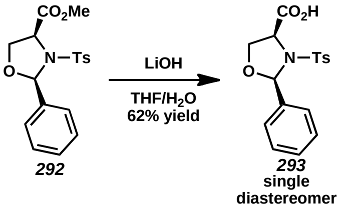


CO2H
NH2
OH
268
1. SOCl2, MeOH
2. TsCl, Et3N
CH2Cl2
80% yield (2 steps)
CO2Me
HN−Ts
OH
291
PhCHO, PTSA
MgSO4, PhCH3
110 °C, 67% yield
CO2Me
N−Ts
O
292
single
diastereomer

To **268** (7.5 g, 71.4 mmol) in MeOH (143 mL) at 0 °C was added $SOCl_2$ (26.0 mL, 357 mmol) slowly. Stirred an additional 5 min at 0 °C, then 23 °C overnight. The solvent was removed and the solid residue concentrated from Et_2O (3 x 50 mL) to afford the methyl ester (9.19 g, 83% yield).

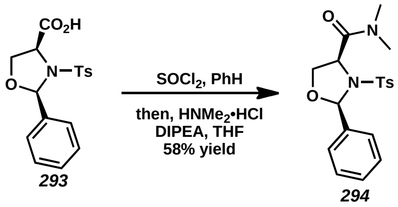
To methyl ester (2.0 g, 12.9 mmol) in CH_2Cl_2 at 0 °C was added Et_3N (4.38 mL, 30.9 mmol). Stirred for 5 min at 0 °C, the TsCl (2.70 g, 14.1 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford **291** (3.03 g, 86% yield) as a beige solid.

To **291** (1.50 g, 5.49 mmol) in toluene (27.4 mL) was added benzaldehyde (0.720 mL, 7.14 mmol), PTSA (52.2 mg, 0.274 mmol) and $MgSO_4$ (991 mg, 8.23 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **292** (931 mg, 47% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a white solid.

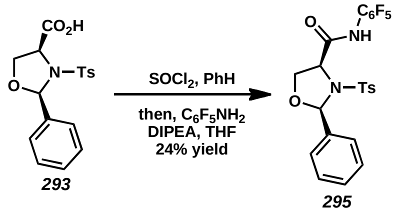


CO2Me
N−Ts
O
292
LiOH
THF/H2O
62% yield
CO2H
N−Ts
O
293
single
diastereomer

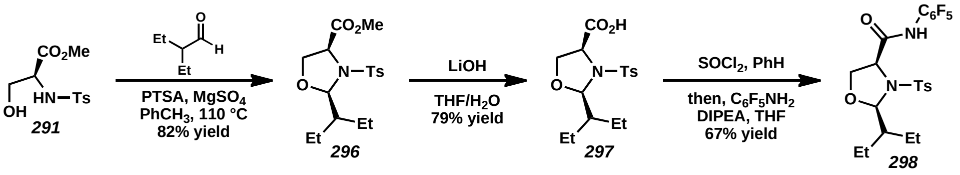
To a solution of **292** (0.856 g, 2.37 mmol) in THF (4.7 mL) and H_2O (2.4 mL) was added LiOH (56.7 mg, 2.37 mmol) and stirred overnight at 23 °C. The residue was acidified to pH 2 with 1 M $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organics were dried over Na_2SO_4 and concentrated to afford **293** (0.624 g, 76% yield) as a white solid.



To **293** (367 mg, 1.06 mmol) in PhH (5.3 mL) was added $SOCl_2$ (0.768 mL, 10.6 mmol) at 23 °C, then heated to 60 °C for 1 h. The solvent was removed and concentrated from PhH (3 x 10 mL). To the crude residue was added THF (5.3 mL), DIPEA (0.561 mL, 3.22 mmol) and NMe_2H•HCl (172 mg, 2.11 mmol) at 23 °C and then stirred overnight at 23 °C. The reaction was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford **294** (211 mg, 54% yield, R_f = 0.23 in 1:1 hexanes:EtOAc) as a beige amorphous solid.



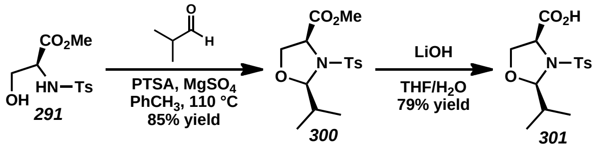
To **293** (250 mg, 0.720 mmol) in PhH (3.6 mL) was added $SOCl_2$ (0.524 mL, 7.20 mmol) at 23 °C, then heated to 60 °C for 1 h. The solvent was removed and concentrated from PhH (3 x 10 mL). To the crude residue was added THF (3.6 mL), DIPEA (0.263 mL, 1.51 mmol) and $C_6F_5NH_2$ (0.138 mL, 0.756 mmol) at 23 °C and then stirred overnight at 23 °C. The reaction was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford **295** (89 mg, 24% yield, $R_f = 0.25$ in 4:1 hexanes:EtOAc) as a yellow solid.


CO2Me
HN—Ts
OH
291
Et
O
H
Et
PTSA, MgSO4
PhCH3, 110 °C
82% yield
CO2Me
N—Ts
O
Et
Et
296
LiOH
THF/H2O
79% yield
CO2H
N—Ts
O
Et
Et
297
SOCl2, PhH
then, C6F5NH2
DIPEA, THF
67% yield
O
C6F5
NH
N—Ts
O
Et
Et
298

To **291** (1.00 g, 3.66 mmol) in toluene (18.3 mL) was added 2-ethylbutyraldehyde (0.809 mL, 6.59 mmol), PTSA (34.8 mg, 0.183 mmol) and $MgSO_4$ (661 mg, 5.49 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **296** (1.07 g, 82% yield, $R_f = 0.75$ in 1:1 hexanes:EtOAc) as a white solid.

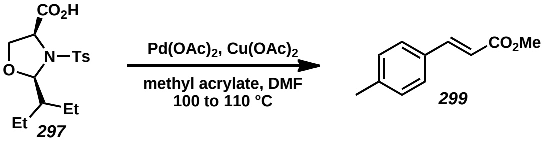
To a solution of **296** (1.06 g, 3.00 mmol) in THF (6.0 mL) and H_2O (3.0 mL) was added LiOH (71.8 mg, 3.00 mmol) and stirred overnight at 23 °C. The residue was acidified to pH 2 with 1 M $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organics were dried over Na_2SO_4 and concentrated to afford **297** (0.925 g, 90% yield) as a yellow solid.

To **297** (195 mg, 0.571 mmol) in PhH (2.9 mL) was added $SOCl_2$ (0.416 mL, 5.71 mmol) at 23 °C, then heated to 60 °C for 1 h. The solvent was removed and concentrated from PhH (3 x 10 mL). To the crude residue was added THF (2.9 mL), DIPEA (0.209 mL, 1.20 mmol) and $C_6F_5NH_2$ (0.125 mL, 0.685 mmol) at 23 °C and then stirred overnight at 23 °C. The reaction was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford **298** (195 mg, 67% yield, $R_f = 0.34$ in 4:1 hexanes:EtOAc) as an orange oil.

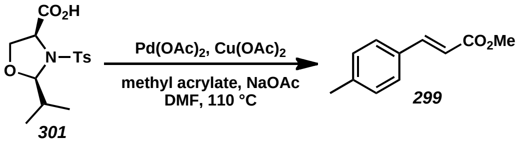

CO2Me
HN−Ts
OH
291
PTSA, MgSO4
PhCH3, 110 °C
85% yield
CO2Me
N−Ts
O
300
LiOH
THF/H2O
79% yield
CO2H
N−Ts
O
301

To **291** (1.58 g, 5.78 mmol) in toluene (28.9 mL) was added isobutyraldehyde (0.792 mL, 8.67 mmol), PTSA (55.0 mg, 0.289 mmol) and $MgSO_4$ (1.04 g, 8.67 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **300** (1.17 g, 62% yield, R_f = 0.75 in 4:1 hexanes:EtOAc) as a white solid.

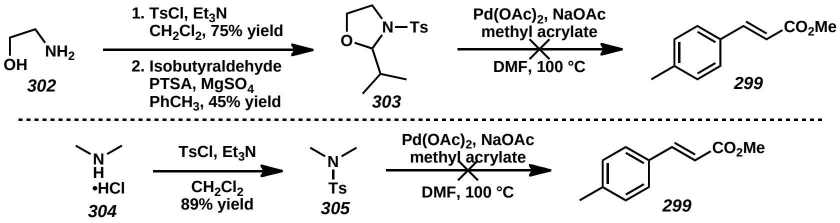
To a solution of **300** (217 mg, 0.663 mmol) in THF (1.3 mL) and H_2O (0.7 mL) was added LiOH (15.9 mg, 0.663 mmol) and stirred overnight at 23 °C. The residue was acidified to pH 2 with 1 M $KHSO_4$. The aqueous layer was extracted with EtOAc (3 x 15 mL), the combined organics were dried over Na_2SO_4 and concentrated to afford **301** (0.206 g, 99% yield) as a white solid.


CO2H
N−Ts
O
Et
Et
297
Pd(OAc)2, Cu(OAc)2
methyl acrylate, DMF
100 to 110 °C
CO2Me
299

297 (50 mg, 0.146 mmol), $Pd(OAc)_2$ (3.3 mg, 0.0146 mmol) methyl acrylate (19.8 μL, 0.220 mmol) and $Cu(OAc)_2$ (53.2 mg, 0.293 mmol) were combined in DMF (0.1.5 mL) and heated to 110 °C for 8 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated.


CO2H
N−Ts
O
301
Pd(OAc)2, Cu(OAc)2
methyl acrylate, NaOAc
DMF, 110 °C
CO2Me
299

301 (20 mg, 0.0638 mmol), Pd(OAc)$_2$ (1.4 mg, 6.38 μmol), Cu(OAc)$_2$ (23.2 mg, 0.128 mmol), methyl acrylate (8.6 μL, 0.0957 mmol) and NaOAc (10.5 mg, 0.128 mmol) were combined in DMF (0.64 mL) and heated to 110 °C for 24 h. Sat. aq. NaHCO$_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na$_2$SO$_4$ and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299** (1.1 mg, 10% yield) as a clear oil.



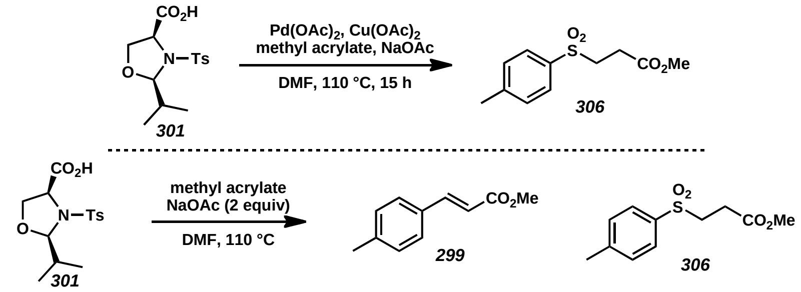
OH
NH2
302
1. TsCl, Et3N
CH2Cl2, 75% yield
2. Isobutyraldehyde
PTSA, MgSO4
PhCH3, 45% yield
O
N−Ts
303
Pd(OAc)2, NaOAc
methyl acrylate
DMF, 100 °C
CO2Me
299
N
H
•HCl
304
TsCl, Et3N
CH2Cl2
89% yield
N
Ts
305
Pd(OAc)2, NaOAc
methyl acrylate
DMF, 100 °C
CO2Me
299

To **302** (0.250 mL, 4.14 mmol) in CH$_2$Cl$_2$ (13.8 mL) at 0 °C was added Et$_3$N (0.689 mL, 4.97 mmol). Stirred for 5 min at 0 °C, the TsCl (0.869 mg, 4.56 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M KHSO$_4$, sat. aq. NaHCO$_3$ and brine sequentially. The organic layer was dried over Na$_2$SO$_4$ and concentrated to afford sulfonamide (0.672 g, 75% yield) as a light yellow oil.

To sulfonamide (0.672 g, 3.12 mmol) in toluene (20.8 mL) was added isobutyraldehyde (0.427 mL, 4.68 mmol), PTSA (29.7 mg, 0.156 mmol) and MgSO$_4$ (0.564 g, 4.68 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. NaHCO$_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **303** (381 mg, 45% yield, $R_f = 0.75$ in 4:1 hexanes:EtOAc) as a yellow oil.

To **304** (500 mg, 6.13 mmol) in CH$_2$Cl$_2$ (20.4mL) at 0 °C was added Et$_3$N (2.07 mL, 14.7 mmol). Stirred for 5 min at 0 °C, the TsCl (1.30 g, 6.74 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1

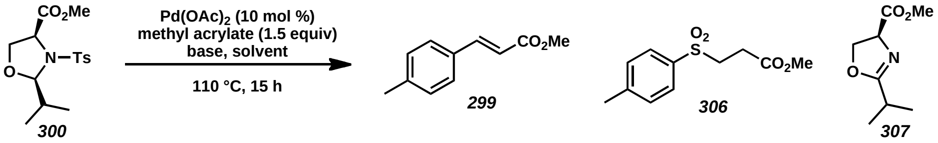
M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide **305** (1.09 g, 89% yield) as a light yellow solid.



CO2H
N–Ts
O
301
Pd(OAc)2, Cu(OAc)2
methyl acrylate, NaOAc
DMF, 110 °C, 15 h
O2
S
CO2Me
306
CO2H
N–Ts
O
301
methyl acrylate
NaOAc (2 equiv)
DMF, 110 °C
CO2Me
299
O2
S
CO2Me
306

Pd (10 mol %)	$Cu(OAc)_2$	yield (%) *299 : 306*
$Pd(OAc)_2$	2.0 equiv	10 : 4
$Pd(OAc)_2$	none	15 : 32
$Pd(dba)_2$	none	8 : 43

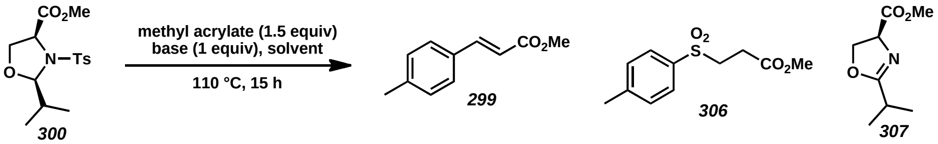
General coupling procedure: Acetal (1 equiv), palladium (10 mol %), $Cu(OAc)_2$ (2 equiv), NaOAc (2 equiv), methyl acrylate (1.5 equiv) and DMF (0.1 M) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299** and **306** in the yields indicated.



CO2Me
N–Ts
O
300
Pd(OAc)2 (10 mol %)
methyl acrylate (1.5 equiv)
base, solvent
110 °C, 15 h
CO2Me
299
O2
S
CO2Me
306
CO2Me
N
O
307

base	solvent	yield (%) *299 : 306 : 307*
NaOAc (2 equiv)	DMF	35 : 32 : 0
NaOAc (2 equiv)	t-AmOH	trace
NaOAc (2 equiv)	CH_3CN	none
NaOAc (2 equiv)	DCE	none
K_2CO_3 (1 equiv)	DMF	36 : 0 : 45
K_2CO_3 (1 equiv)	CH_3CN	15 : 15 : 46

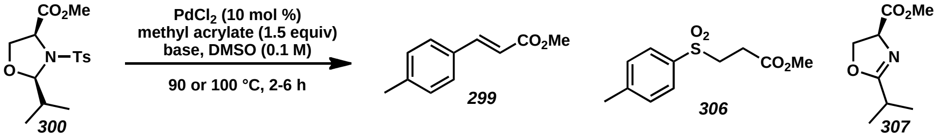
General coupling procedure: Acetal (1 equiv), $Pd(OAc)_2$ (10 mol %), base (1-2 equiv), methyl acrylate (1.5 equiv) and solvent (0.1 M) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.



CO_2Me
N–Ts
O
300
methyl acrylate (1.5 equiv)
base (1 equiv), solvent
110 °C, 15 h
CO_2Me
299
O_2
S
CO_2Me
306
CO_2Me
N
O
307

Pd (10 mol %)	base	solvent	yield (%) *299 : 306 : 307*
$Pd(OAc)_2$	K_2CO_3	DMSO	26 : 0 : 41
$Pd(dba)_2$	K_2CO_3	CH_3CN	0 : 10 : 0
$Pd(dba)_2$	K_2HPO_4	CH_3CN	0 : 0 : 0
$Pd(dba)_2$	Na_2CO_3	CH_3CN	0 : 0 : 0
$PdCl_2$	K_2CO_3	DMF	17 : 0 : 40
$PdCl_2$	K_2CO_3	DMSO	87 : 0 : 72
$PdCl_2$	Na_2CO_3	DMSO	29 : 0 : 0
$PdCl_2$	K_2HPO_4	DMSO	10 : 0 : 0
$PdCl_2(CH_3CN)_2$	K_2CO_3	DMSO	53 : 0 : 51
$PdCl_2(PPh_3)_2$	K_2CO_3	DMSO	38 : 0 : 54

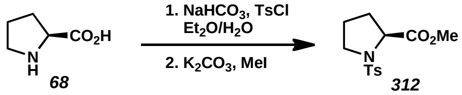
General coupling procedure: Acetal (1 equiv), palladium (10 mol %), base (1 equiv), methyl acrylate (1.5 equiv) and solvent (0.1 M) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.



CO_2Me
N–Ts
O
300
$PdCl_2$ (10 mol %)
methyl acrylate (1.5 equiv)
base, DMSO (0.1 M)
90 or 100 °C, 2-6 h
CO_2Me
299
O_2
S
CO_2Me
306
CO_2Me
N
O
307

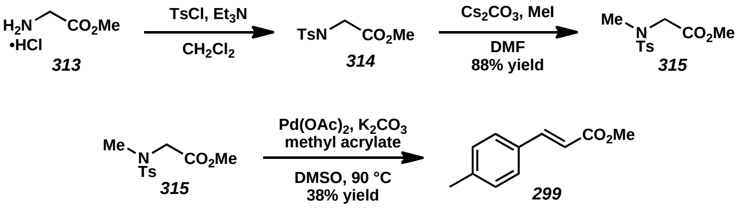
base	yield (%) *299 : 306 : 307*	base	yield (%) *299 : 306 : 307*
$KHCO_3$ (2 equiv)	33 : 0 : 40	LiOAc (2 equiv)	59 : 0 : 52
$Ba(OH)_2$ (0.5 equiv)	none	Cs_2CO_3 (1 equiv)	complex
$Ca(OH)_2$ (0.5 equiv)	none	Li_2CO_3 (1 equiv)	none
NaOAc (4 equiv)	71 : 0 : 46	*t*-$BuCO_2Na$ (2 equiv)	54 : 0 : 43
KOAc (2 equiv)	59 : 0 : 37	Cl_3CCO_2Na (2 equiv)	10 : 0 : 0
KOAc (1.5 equiv)	46 : 0 : 41	$PhCO_2Na$ (2 equiv)	29 : 0 : 9

General coupling procedure: Acetal (1 equiv), $PdCl_2$ (10 mol %), base (0.5-4 equiv), methyl acrylate (1.5 equiv) and DMSO (0.1 M) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 2-6 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.


CO2H
N
H
68
1. NaHCO3, TsCl
Et2O/H2O
2. K2CO3, MeI
CO2Me
N
Ts
312

To **68** (500 mg, 4.34 mmol) in sat. aq. $NaHCO_3/Et_2O$ (21.7 mL) was added TsCl (1.24 g, 6.51 mmol) at 23 °C. The reaction was stirred at 23 °C overnight. The reaction was acidified to pH 2 with 3 M HCl. The aqueous was extracted with EtOAc (3 x 15 mL). The organics were dried over Na_2SO_4 and concentrated to afford tosyl protected proline (1.07 g, 92% yield) as a white solid.

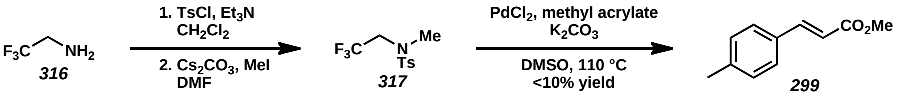
To protected proline (500 mg, 1.86 mmol) in DMF (3.71 mL) at 23 °C was added K_2CO_3 (282 mg, 2.04 mmol). After stirring for 10 min at 23 °C, MeI (0.231 mL, 3.71 mmol) was added. The reaction was stirred at 23 °C overnight. The reaction was partitioned between H_2O and EtOAc. The organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to afford **312** (447 mg, 85% yield) as a white solid.


H2N
•HCl
CO2Me
313
TsCl, Et3N
CH2Cl2
TsN
CO2Me
314
Cs2CO3, MeI
DMF
88% yield
Me
N
Ts
CO2Me
315
Me
N
Ts
CO2Me
315
Pd(OAc)2, K2CO3
methyl acrylate
DMSO, 90 °C
38% yield
CO2Me
299

To **313** (5.0 g, 39.8 mmol) in CH_2Cl_2 (39.8 mL) at 0 °C was added Et_3N (13.4 mL, 95.6 mmol). Stirred for 5 min at 0 °C, the TsCl (8.35 g, 43.8 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide **314** (9.01 g, 93% yield) as a light yellow solid.

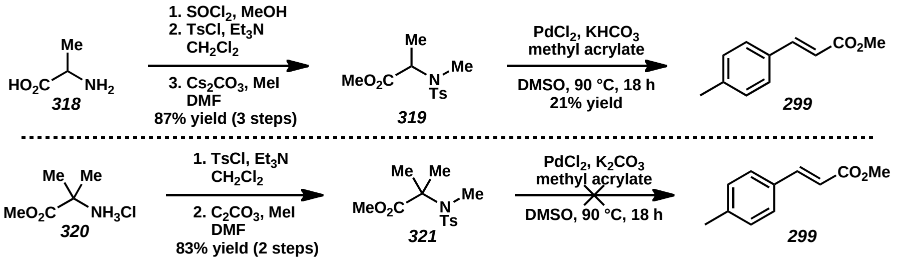
To **314** (500 mg, 2.06 mmol) in DMF (4.1 mL) at 23 °C was added Cs_2CO_3 (737 mg, 2.26 mmol). After stirring for 10 min at 23 °C, MeI (0.192 mL, 3.08 mmol) was added. The reaction was stirred at 23 °C overnight. The reaction was partitioned between H_2O and EtOAc. The organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to afford **315** (464 mg, 88% yield, R_f = 0.54 in 1:1 hexanes:EtOAc) as a yellow oil.

Sulfonamide **315** (20 mg, 0.0777 mmol), $PdCl_2$ (1.4 mg, 7.77 μmol) K_2CO_3 (10.7 mg, 0.0777 mmol), methyl acrylate (10.5 μL, 0.117 mmol) and DMSO (0.78 mL) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 12 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299** (5.2 mg, 38% yield).



To **316** (250 mg, 1.85 mmol) in CH_2Cl_2 (9.2 mL) at 0 °C was added Et_3N (0.622 mL, 4.43 mmol). Stirred for 5 min at 0 °C, the TsCl (387 mg, 2.03 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide (412 mg, 88% yield) as a white solid.

To the sulfonamide (412 mg, 1.63 mmol) in DMF (3.3 mL) at 23 °C was added Cs_2CO_3 (583 mg, 1.79 mmol). After stirring for 10 min at 23 °C, MeI (0.152 mL, 2.44 mmol) was added. The reaction was stirred at 23 °C overnight. The reaction was partitioned between H_2O and EtOAc. The organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to afford **317** (358 mg, 82% yield) as a white solid.


1. SOCl2, MeOH
2. TsCl, Et3N
CH2Cl2
3. Cs2CO3, MeI
DMF
87% yield (3 steps)
Me
HO2C
NH2
318
MeO2C
N
Me
Ts
319
PdCl2, KHCO3
methyl acrylate
DMSO, 90 °C, 18 h
21% yield
CO2Me
299
Me
Me
MeO2C
NH3Cl
320
1. TsCl, Et3N
CH2Cl2
2. C2CO3, MeI
DMF
83% yield (2 steps)
321
PdCl2, K2CO3
methyl acrylate
DMSO, 90 °C, 18 h
299

To **318** (1.0 g, 11.2 mmol) in MeOH (44.9 mL) at 0 °C was added $SOCl_2$ (4.09 mL, 56.1 mmol) slowly. Stirred an additional 5 min at 0 °C, then 23 °C overnight. The solvent was removed and the solid residue concentrated from Et_2O (3 x 50 mL) to afford the methyl ester (1.59 g, 99% yield) as a white solid.

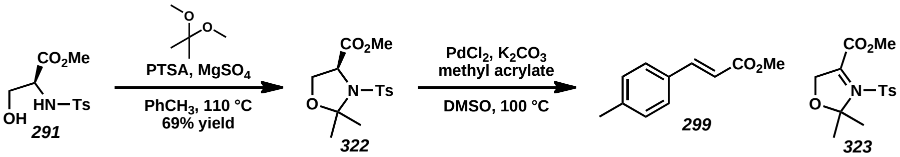
To the methyl ester (500 mg, 3.58 mmol) in CH_2Cl_2 (17.9 mL) at 0 °C was added Et_3N (1.21 mL, 8.60 mmol). Stirred for 5 min at 0 °C, the TsCl (751 mg, 3.94 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide (1.00 g, 99% yield) as a clear oil.

To the sulfonamide (3.58 mmol) in DMF (7.2 mL) at 23 °C was added Cs_2CO_3 (1.28 g, 3.94 mmol). After stirring for 10 min at 23 °C, MeI (0.446 mL, 7.16 mmol) was added. The reaction was stirred at 23 °C overnight. The reaction was partitioned between H_2O and EtOAc. The organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to afford **319** (843 mg, 87% yield) as a yellow oil.

Sulfonamide **319** (20 mg, 0.0737 mmol), $PdCl_2$ (1.3 mg, 7.37 μmol) $KHCO_3$ (7.8 mg, 0.0737 mmol), methyl acrylate (9.9 μL, 0.111 mmol) and DMSO (0.74 mL) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 12 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299** (2.7 mg, 21% yield).

To the methyl ester **320** (400 mg, 2.60 mmol) in CH_2Cl_2 (13.0 mL) at 0 °C was added Et_3N (0.915 mL, 6.51 mmol). Stirred for 5 min at 0 °C, the TsCl (546 mg, 2.86 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide (586 mg, 83% yield) as a white solid.

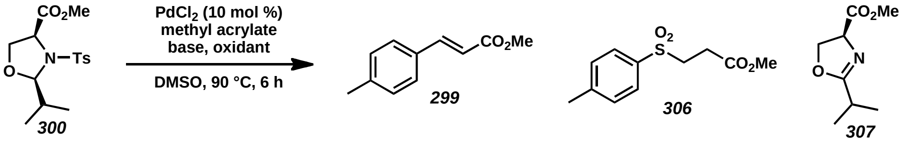
To the sulfonamide (371 mg, 1.29 mmol) in DMF (2.6 mL) at 23 °C was added Cs_2CO_3 (462 mg, 1.42 mmol). After stirring for 10 min at 23 °C, MeI (0.161 mL, 2.58 mmol) was added. The reaction was stirred at 23 °C overnight. The reaction was partitioned between H_2O and EtOAc. The organic layer was washed with brine (2 x 10 mL), dried over Na_2SO_4 and concentrated to afford **321** (371 mg, 99% yield) as a yellow oil.



1 : 1. 7 mixture

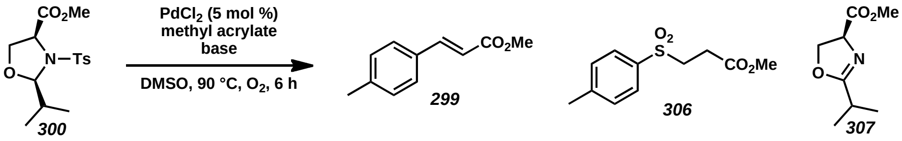
To sulfonamide **291** (328 mg, 1.20 mmol) in toluene (12.0 mL) was added dimethoxypropane (0.221 mL, 1.80 mmol), PTSA (11.4mg, 0.0600 mmol) and $MgSO_4$ (0.289 g, 2.40 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **322** (259 mg, 69% yield, $R_f = 0.72$ in 1:1 hexanes:EtOAc) as a yellow oil.

Acetal **322** (20 mg, 0.0638 mmol), $PdCl_2$ (1.1 mg, 6.38 μmol) K_2CO_3 (8.8 mg, 0.0638 mmol), methyl acrylate (8.6 μL, 0.0957 mmol) and DMSO (0.64 mL) were combined in a 2-dram vial and capped. The reaction was heated to 110 °C for 12 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299** and **323** in a 1 : 1.7 mixture.


CO2Me
N–Ts
O
300
PdCl2 (10 mol %)
methyl acrylate
base, oxidant
DMSO, 90 °C, 6 h
CO2Me
299
O2
S
CO2Me
306
CO2Me
N
O
307

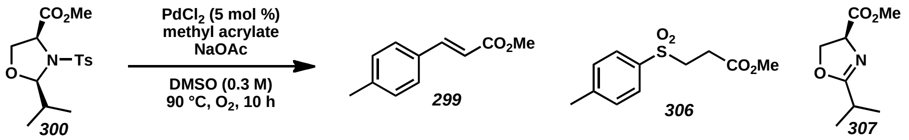
base	oxidant	yield (%) *299 : 306 : 307*	base	oxidant	yield (%) *299 : 306 : 307*
K_2CO_3 (1 equiv)	air	18 : 5 : 54	KOAc (2 equiv)	O_2 balloon $Cu(OAc)_2$ (20 mol %)	63 : 0 : 4
KOAc (2 equiv)	air	25 : 38 : 39	KOAc (2 equiv)	O_2 balloon	67 : 0 : 29
K_2CO_3 (1 equiv)	$Cu(OAc)_2$ (2 equiv)	18 : 7 : 0	KOAc (2 equiv)	BQ (25 mol %)	36 : 0 : 35
none	$Cu(OAc)_2$ (2 equiv)	none	KOAc (2 equiv)	$NaNO_2$ (25 mol %)	27 : 0 : 7
KOAc (2 equiv)	$Cu(OAc)_2$ (2 equiv)	20 : 0 : 0	KOAc (2 equiv)	AgOAc (25 mol %)	27 : 16 : 29
K_2CO_3	BQ (1 equiv)	complex			
KOAc	BQ (1 equiv)	47 : 31 : 63			

General coupling procedure: Acetal **300** (1 equiv), $PdCl_2$ (10 mol %), base (1-2 equiv), methyl acrylate (1.5 equiv), oxidant (0.25-2 equiv) and DMSO (0.1 M) were combined in a 2-dram vial and capped. Those reactions with O_2 were fitted with a septum and an O_2 balloon. The reaction was heated to 90 °C for 6 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.


CO2Me
N–Ts
O
300
PdCl2 (5 mol %)
methyl acrylate
base
DMSO, 90 °C, O2, 6 h
CO2Me
299
O2
S
CO2Me
306
CO2Me
N
O
307

base	yield (%) *299 : 306 : 307*
NaOAc (3 equiv)	92 : 0 : 18
NaOAc (1.5 equiv)	52 : 0 : 0
Na_2CO_3 (1.5 equiv) AcOH (10 mol %)	70 : 0 : 7
NaOAc (3 equiv) (ground)	89: 0 : 0

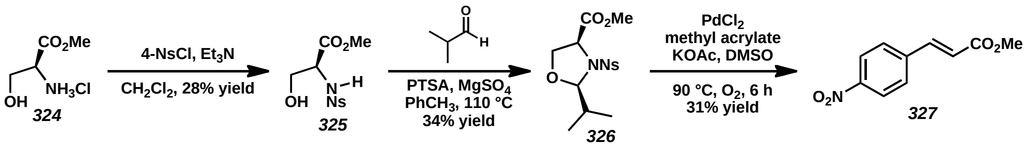
General coupling procedure: Acetal **300** (1 equiv), $PdCl_2$ (5 mol %), base (1.5-3 equiv), methyl acrylate (1.5 equiv), and DMSO (0.1 M) were combined in a 2-dram vial and were fitted with a septum and an O_2 balloon. The reaction was heated to 90 °C for 6 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.



CO2Me
N−Ts
O
300
PdCl2 (5 mol %)
methyl acrylate
NaOAc
DMSO (0.3 M)
90 °C, O2, 10 h
CO2Me
299
O2
S
CO2Me
306
CO2Me
N
O
307

equivalents NaOAc	yield (%) *299 : 306 : 307*	equivalents NaOAc	yield (%) *299 : 306 : 307*
1.0	44 : 0 : 8	3.0	18 : 22 : 12
1.0	44 : 0 : 2	3.0	65 : 0 : 12
2.0	62 : 0 : 13	4.0	54 : 5 : 0
2.0	62 : 0 : 5	4.0	76 : 0 : 13

General coupling procedure: Acetal **300** (1 equiv), $PdCl_2$ (5 mol %), NaOAc (1-4 equiv), methyl acrylate (1.5 equiv), and DMSO (0.3 M) were combined in a 2-dram vial and were fitted with a septum and an O_2 balloon. The reaction was heated to 90 °C for 10 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **299**, **306**, and **307** in the yields indicated.

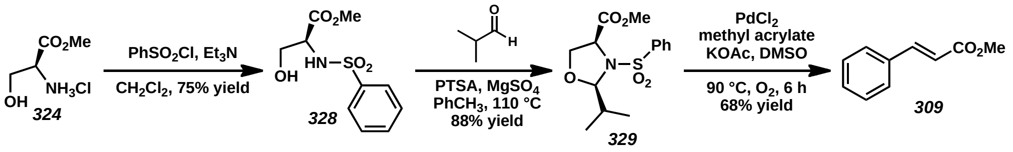


CO2Me
OH
NH3Cl
324
4-NsCl, Et3N
CH2Cl2, 28% yield
CO2Me
OH
N−H
Ns
325
O
H
PTSA, MgSO4
PhCH3, 110 °C
34% yield
CO2Me
NNs
O
326
PdCl2
methyl acrylate
KOAc, DMSO
90 °C, O2, 6 h
31% yield
O2N
CO2Me
327

To the methyl ester **324** (500 mg, 3.21 mmol) in CH_2Cl_2 (16.1 mL) at 0 °C was added Et_3N (1.08 mL, 7.71 mmol). Stirred for 5 min at 0 °C, the 4-NsCl (783 mg, 3.54 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide (274 mg, 24% yield) as a yellow solid.

To sulfonamide **325** (0.274 g, 0.90 mmol) in toluene (18.0 mL) was added isobutyraldehyde (0.123 mL, 1.35 mmol), PTSA (8.6 mg, 0.045 mmol) and $MgSO_4$ (0.163 g, 1.35 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **326** (109 mg, 35% yield, $R_f = 0.55$ in 1:1 hexanes:EtOAc) as a yellow oil.

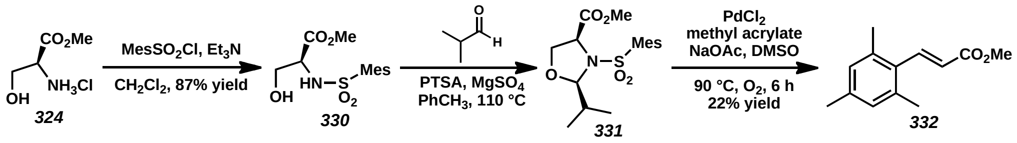
Acetal **326** (20 mg, 0.0558 mmol), $PdCl_2$ (1.0 mg, 5.58 μmol), K_2CO_3 (7.7 mg, 0.0558 mmol), methyl acrylate (7.5 μmol, 0.0837 mmol), and DMSO (0.56 mL) were combined in a 2-dram vial and capped. The reaction was heated to 100 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **327** (3.6 mg, 31% yield).


CO2Me
NH3Cl
OH
324
PhSO2Cl, Et3N
CH2Cl2, 75% yield
CO2Me
HN–SO2
OH
328
O
H
PTSA, MgSO4
PhCH3, 110 °C
88% yield
CO2Me
N–S
Ph
O2
O
329
PdCl2
methyl acrylate
KOAc, DMSO
90 °C, O2, 6 h
68% yield
CO2Me
309

To the methyl ester **324** (750 mg, 4.82 mmol) in CH_2Cl_2 (24.1 mL) at 0 °C was added Et_3N (1.63 mL, 11.6 mmol). Stirred for 5 min at 0 °C, the $PhSO_2Cl$ (0.679 mL, 5.30 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide **328** (932 mg, 75% yield) as a yellow fluffy solid.

To sulfonamide **328** (0.932 g, 3.60 mmol) in toluene (23.9 mL) was added isobutyraldehyde (0.492 mL, 5.39 mmol), PTSA (34.2 mg, 0.180 mmol) and $MgSO_4$ (0.649 g, 5.39 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **329** (996 mg, 88% yield) as a beige solid.

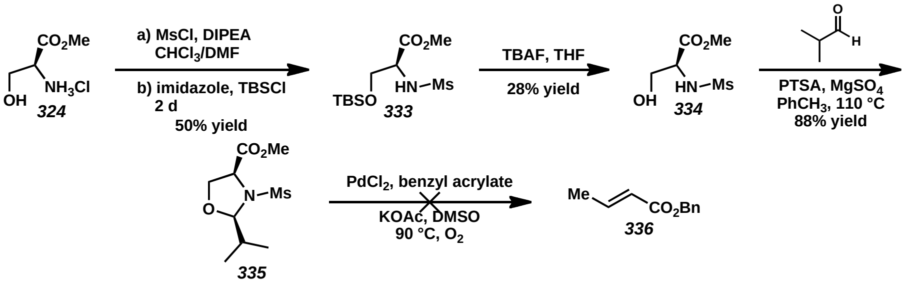
Acetal **329** (40 mg, 0.128 mmol), $PdCl_2$ (2.3 mg, 0.0128 mmol), KOAc (25.2 mg, 0.256 mmol), methyl acrylate (17.3 μL, 0.192 mmol), and DMSO (1.28 mL) were combined in a 2-dram vial and capped. The reaction was heated to 100 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **309** (14.0 mg, 68% yield).



To the methyl ester **324** (500 mg, 3.21 mmol) in CH_2Cl_2 (16.1mL) at 0 °C was added Et_3N (1.08 mL, 7.71 mmol). Stirred for 5 min at 0 °C, the $MesSO_2Cl$ (0.773 g, 3.54 mmol) was added. The reaction was stirred for an additional 1 h at 0 °C, then 23 °C overnight. The crude mixture was washed with 1 M $KHSO_4$, sat. aq. $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4 and concentrated to afford sulfonamide **330** (846 mg, 87% yield) as a white solid.

To sulfonamide **330** (0.846 g, 2.81mmol) in toluene (14.0 mL) was added isobutyraldehyde (0.384 mL, 4.21 mmol), PTSA (26.7 mg, 0.140 mmol) and $MgSO_4$ (0.507 g, 4.21 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **331** (411 mg, 41% yield) as a beige solid.

Acetal **331** (40 mg, 0.113 mmol), $PdCl_2$ (1.0 mg, 5.63 μmol), NaOAc (27.8 mg, 0.339 mmol), methyl acrylate (15.3 μL, 0.170 mmol), and DMSO (0.38 mL) were combined in a 2-dram vial and capped. The reaction was heated to 100 °C for 15 h. Sat. aq. $NaHCO_3$ was added to the crude reaction mixture. The aqueous was extracted with EtOAc (2 x 2 mL), the organics washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was plugged on silica (4:1 hexanes:EtOAc) to afford **332** (5.1 mg, 22% yield).

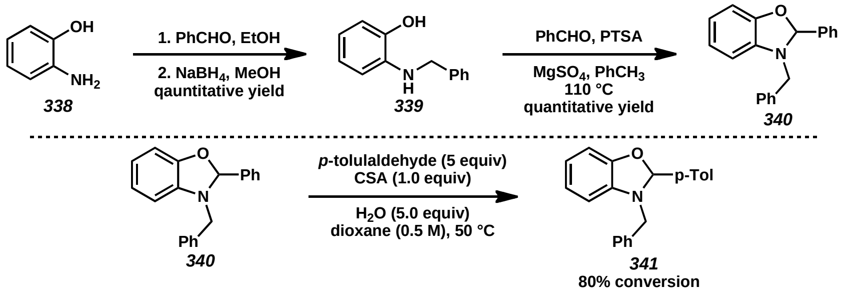

CO2Me
NH3Cl
OH
324
a) MsCl, DIPEA
CHCl3/DMF
b) imidazole, TBSCl
2 d
50% yield
CO2Me
HN–Ms
TBSO
333
TBAF, THF
28% yield
CO2Me
HN–Ms
OH
334
O
H
PTSA, MgSO4
PhCH3, 110 °C
88% yield
CO2Me
N–Ms
O
335
PdCl2, benzyl acrylate
KOAc, DMSO
90 °C, O2
Me
CO2Bn
336

To the methyl ester **324** (500 mg, 3.21 mmol) in DMF/$CHCl_3$ (3.82 mL) at -78 °C was added DIPEA (1.40 mL, 8.04 mmol) and MsCl (0.299 mL, 3.86 mmol). The reaction was warmed to 0 °C and stirred for 2 h. Then imidazole (875 mg, 12.9 mmol) and TBSCl (581 mg, 3.86 mmol) were added at 0 °C. The reaction was stirred at 23 °C for 48 h. The reaction was quenched with 5% $NaHCO_3$, the aqueous layer extracted with Et_2O. The organics were washed with 5% citric acid, H_2O, 5% $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford sulfonamide **333** (492 mg, 49% yield) as a white solid.

To sulfonamide **333** (492 mg, 1.58 mmol) in THF (10.5 mL) was added TBAF (3.16 mL, 3.16 mmol, 1.0 M in THF) at 23 °C. The reaction was stirred at 23 °C for 2 h. The reaction was quenched with H_2O. The aqueous was extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4

and concentrated. The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to afford **334** (87.0 mg, 28% yield).

To sulfonamide **334** (87 mg, 0.441 mmol) in toluene (4.4 mL) was added isobutyraldehyde (60.4 μL, 0.662 mmol), PTSA (4.2 mg, 0.0221 mmol) and $MgSO_4$ (79.7 mg, 0.662 mmol). The suspension was refluxed overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated to afford **335** (91.6 mg, 83% yield).

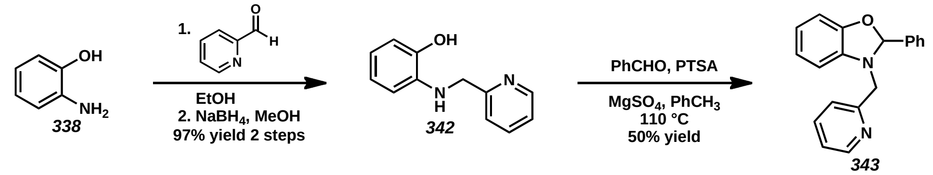

OH
NH2
338
1. PhCHO, EtOH
2. NaBH4, MeOH
qauntitative yield
OH
N
H
Ph
339
PhCHO, PTSA
MgSO4, PhCH3
110 °C
quantitative yield
O
Ph
N
Ph
340
O
Ph
N
Ph
340
p-tolulaldehyde (5 equiv)
CSA (1.0 equiv)
H2O (5.0 equiv)
dioxane (0.5 M), 50 °C
O
p-Tol
N
Ph
341
80% conversion

To **338** (1.0 g, 9.16 mmol) in EtOH (9.2 mL) was added PhCHO (0.94 mL, 9.26 mmol) at 23 °C. Stirred overnight at 23 °C. The solvent was removed under reduced pressure, and the crude residue concentrated from PhH (3 x 10 mL) to afford the acetal (1.84 g, 99% yield) as a beige solid.

To the acetal (1.5 g, 7.61 mmol) in MeOH (23.0 mL) was added $NaBH_4$ (575 mg, 15.2 mmol) over 10 min. After 5 min, the reaction was complete and quenched with sat. aq. NH_4Cl. Water was added to dissolve the salts. The aqueous layer was extracted with EtOAC (3 x 15 mL). The organics were washed with brine, dried over Na_2SO_4 and concentrated to afford **339** (1.60 g, 99% yield) as a brown solid.

339 (250 mg, 1.26 mmol) was mixed with benzaldehyde (0.165 mL, 1.63 mmol), PTSA (12.0 mg, 0.0628 mmol) and $MgSO_4$ (227 mg, 1.88 mmol) in toluene (12.6 mL) and refluxed overnight. Sat. aq. $NaHCO_3$ was added to the cooled reaction. The aqueous was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated to afford **340** in quantitative yield.

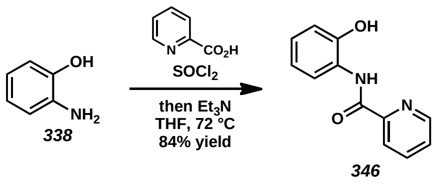
340 (50 mg, 0.174 mmol), *p*-tolualdehyde (0.103 mL, 0.870 mmol), CSA (40.4 mg, 0.174 mmol) and H_2O (15.7 μL, 0.870 mmol) were combined in dioxane (0.35 mL) and heated to 50 °C overnight. The solvent was removed and analyzed by ^1H NMR.



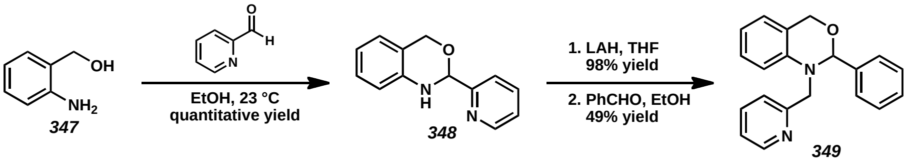
To **338** (1.0 g, 9.16 mmol) in EtOH (9.2 mL) was added 2-pyridinecarboxaldehyde (0.884 mL, 9.26 mmol) at 23 °C. Stirred overnight at 23 °C. The solvent was removed under reduced pressure, and the crude residue concentrated from PhH (3 x 10 mL) to afford the acetal in quantitative yield.

To the acetal (9.16 mmol) in MeOH (27.8 mL) was added $NaBH_4$ (693 mg, 18.3 mmol) over 10 min. After 5 min, the reaction was complete and quenched with sat. aq. NH_4Cl. Water was added to dissolve the salts. The aqueous layer was extracted with EtOAC (3 x 15 mL). The organics were washed with brine, dried over Na_2SO_4 and concentrated to afford **342** (1.77 g, 97% yield) as a brown solid.

339 (1.0 mg, 4.99 mmol) was mixed with benzaldehyde (0.66 mL, 6.49 mmol), PTSA (47.5 mg, 0.250 mmol) and $MgSO_4$ (902 mg, 7.49 mmol) in toluene (20.0 mL) and refluxed overnight. Sat. aq. $NaHCO_3$ was added to the cooled reaction. The aqueous was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated to afford **343** as a mixture of product and starting material.


OH
NH2
338
N
CO2H
SOCl2
then Et3N
THF, 72 °C
84% yield
OH
NH
O
N
346

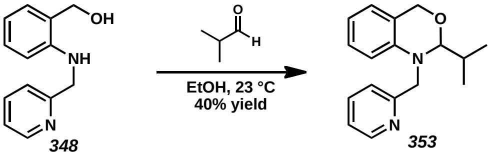
2-picolinic acid (1.13 g, 9.16 mmol) and $SOCl_2$ (3.4 mL) were combined in THF (6.5 mL) at 0 °C, then heated to 50 °C for 1 h. The solvent was removed under reduced pressure, and concentrated twice from THF (2 x 10 mL). The residue was dissolved in THF (11.2 mL), then **338** (1.0 g, 9.16 mmol) and Et_3N (1.93 mL, 13.7 mmol) was added at 0 °C. The reaction was refluxed overnight. The precipitate was filtered off, and the filtrate concentrated to afford **346** (1.64 g, 84% yield) as a brown solid.


OH
NH2
347
O
H
N
EtOH, 23 °C
quantitative yield
O
N
H
N
348
1. LAH, THF
98% yield
2. PhCHO, EtOH
49% yield
O
N
N
349

To **347** (1.0 g, 8.12 mmol) and 2-pyridinecarboxaldehyde (0.776 mL, 8.12 mmol) were combined in EtOH (8.1 mL) at 23 °C and stirred overnight. The solvent was removed under reduced pressure and the crude residue concentrated from PhH (3 x 10 mL) to afford **348** (1.80 g, 99% yield) as a red oil.

To the acetal (8.12 mmol) in THF (58.0 mL) at 0 °C was added LAH (339 mg, 8.93 mmol). The reaction was stirred at 23 °C for 2 h. The reaction was cooled to 0 °C and 0.339 mL H_2O, 0.339 mL 10% NaOH, and 1.02 mL H_2O were added sequentially. The solid was filtered off and the organic layer was dried over Na_2SO_4 and concentrated to give the amino alcohol (1.71 g, 98% yield) as a red oil.

The amino alcohol (250 mg, 1.20 mmol) and benzaldehyde (0.122 mL, 1.20 mmol) were combined in EtOH (1.2 mL) at 23 °C and stirred overnight. The solvent was removed under reduced pressure and the crude residue was concentrated from PhH (3 x 10 mL). The crude residue was purified via flash chromatography (7:3 hexanes:EtOAc) to give **349** (177 mg, 49% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a light yellow oil.



The amino alcohol (250 mg, 1.20 mmol) and isobutyraldehyde (0.160 mL, 1.75 mmol) were combined in EtOH (1.2 mL) at 23 °C and stirred overnight. The solvent was removed under reduced pressure and the crude residue was concentrated from PhH (3 x 10 mL). The crude residue was purified via flash chromatography (4:1 hexanes:EtOAc) to give **349** (129 mg, 40% yield, R_f = 0.60 in 1:1 hexanes:EtOAc) as a clear oil.

Appendix 1

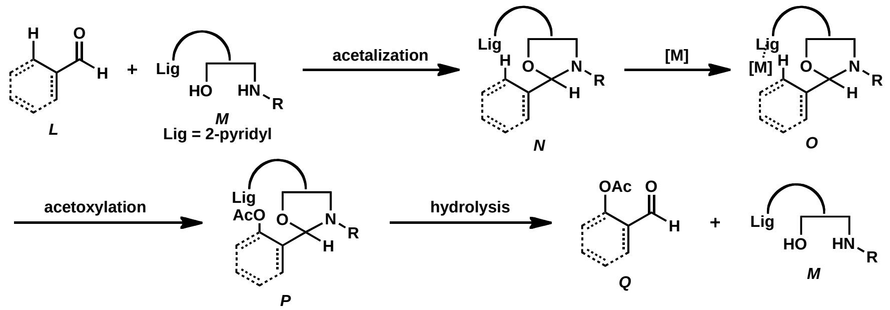
Synthesis of Asymmetric Amino Amides

The development of asymmetric syntheses is always of interest to the synthetic community. In particula the synthesis of chiral secondary amines has been utilized for many asymmetric organocatalyzed transformations.[1] The emergence of such methods has required the ease of synthesis of these chiral catalysts.

A1.1 Development of an Asymmetric Synthesis

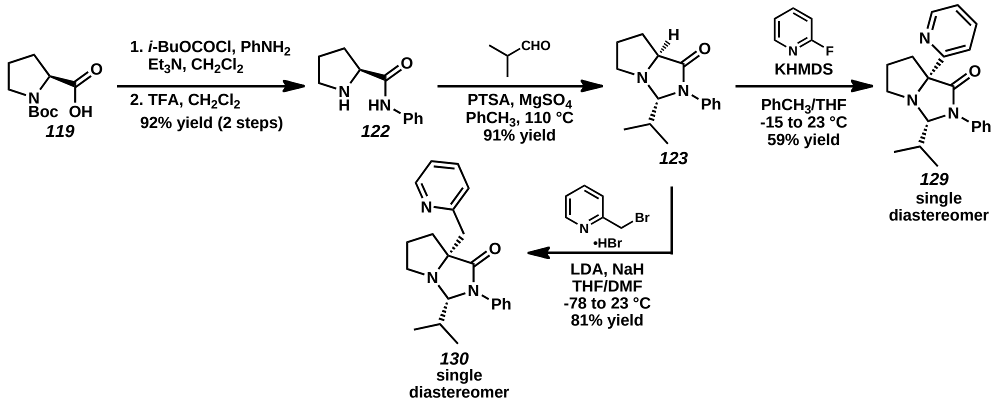
Our original project outline involved developing a ligand scaffold that could perform a functionalization of an unreactive C–H bond with high regio- and stereoselectivity. We envisioned utilizing a combination of an alcohol and amine as acetalization components to condense onto an aldehyde (Scheme A1.1.1). This ligand would also contain an internal ligating group that could coordinate a metal and direct a C–H acetoxylation. Upon functionalization, we envisioned hydrolysis would release the activated product and regenerate the ligand.

Scheme A1.1.1. **Revisiting the general concept**



In the course of our ligand development, we uncovered an asymmetric ligand synthesis (Scheme A1.1.2). From **119** we were able to form amino amide **122** in good yield. Condensation onto isobutyraldehyde afforded *N*,*N*-aminal in good yield as a single diastereomer. Arylation with 2-fluoropryidine afforded ligand substrate adduct **129** in good yield as a single diastereomer. Additionally, alkylation with 2-bromomethyl pyridine afforded **130** as a single diastereomer. Starting from a single enantiomer (L-proline) and considering the high diastereoselectivity, it can be assumed that the alkylated products are also single enantiomers.

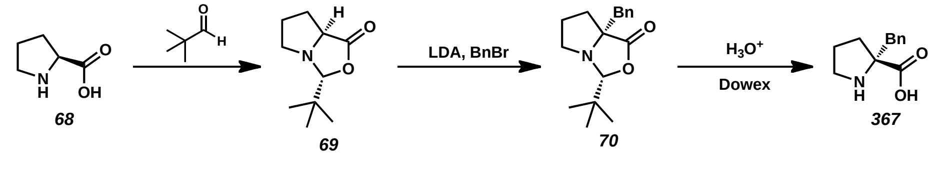
Scheme A1.1.2. Synthesis of ligands 129 and 130



119
1. *i*-BuOCOCl, PhNH$_2$ Et$_3$N, CH$_2$Cl$_2$
2. TFA, CH$_2$Cl$_2$
92% yield (2 steps)
122
CHO
PTSA, MgSO$_4$
PhCH$_3$, 110 °C
91% yield
123
KHMDS
PhCH$_3$/THF
-15 to 23 °C
59% yield
129
single diastereomer
•HBr
LDA, NaH
THF/DMF
-78 to 23 °C
81% yield
130
single diastereomer

A similar example of asymmetric synthesis was employed by Seebach and coworkers in 1983 in the generation of α-substituted amino acids.[2] L-Proline was condensed onto pivaldehyde to afford *N,O*-acetal **69** (Scheme A1.1.3). Alkylation with LDA and BnBr afforded α-substituted *N,O*-acetal **70** as a single diastereomer. Cleavage of the acetal was accomplished with aqueous acid, followed by purification with a Dowex column to afford amino acid **367** as a single enantiomer. Although this sequence provides a short, high yielding (>80% each step) synthesis of asymmetric amino acids, the intermediates are very unstable and difficult to work with. Additionally, the isolation and purification of the desired amino acid is not trivial.

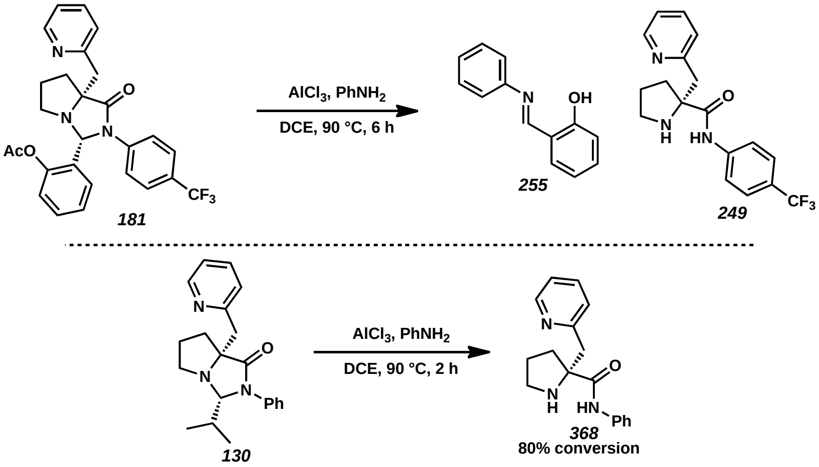
Scheme A1.1.3. Seebach's amino acid synthesis



Seebach 1983
68
69
LDA, BnBr
70
H$_3$O$^+$
Dowex
367

We find that our approach provides a quick straightforward synthesis of asymmetric *N,N*-aminals without unstable intermediates or nontrivial purification steps. The only remaining difficulty in our approach was the development of a high yielding cleavage procedure to release the enantioenriched amino amide. To liberate our activated product, we subjected acetoxylated **181** to transamidation conditions with complete conversion to **249** (Scheme A1.1.4).[3] We subjected our isobutyraldehyde-ligand adduct to the same conditions and observed 80% conversion to the free ligand (**368**).[4]

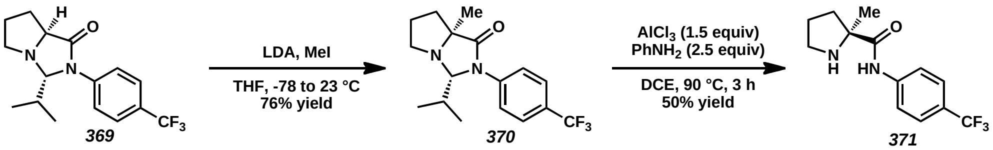
Scheme A1.1.4. Hydrolysis of ligands 181 and 130



AcO
181
$AlCl_3$, $PhNH_2$
DCE, 90 °C, 6 h
255
249
CF_3
130
Ph
$AlCl_3$, $PhNH_2$
DCE, 90 °C, 2 h
368
80% conversion

We began examining substrate scope and the feasibility of the $AlCl_3$ reaction conditions for hydrolysis of the *N*,*N*-aminal. Alkylation of aminal **369** with MeI afforded the α-substituted aminal in good yield (Scheme A1.1.5). Subjecting **370** to $AlCl_3$ and aniline in DCE for only 1 h afforded the product in 90% isolated yield. Extending the reaction time to 3 h resulted in a decrease of yield to 50%.

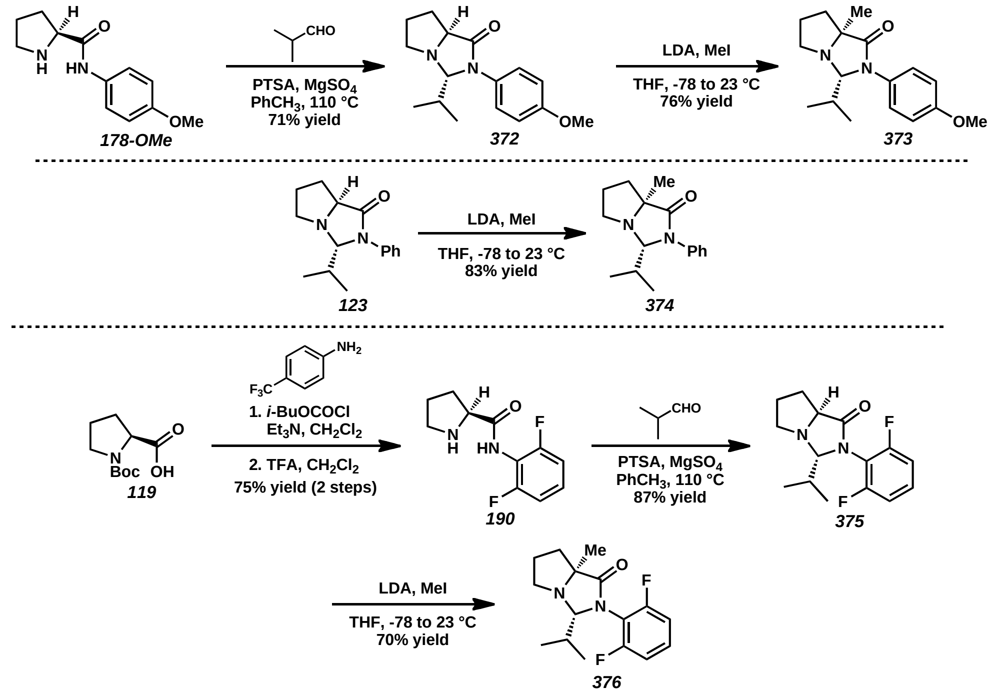
Scheme A1.1.5. Initial substrate synthesis and hydrolysis



369
LDA, MeI
THF, -78 to 23 °C
76% yield
370
$AlCl_3$ (1.5 equiv)
$PhNH_2$ (2.5 equiv)
DCE, 90 °C, 3 h
50% yield
371
CF_3
Me

Having discovered a cleavage method providing a 90% yield of the amino amide, we began to investigate substrate scope in terms of the amide component. Amino amide **178-OMe** was condensed onto isobutyraldehyde to afford aminal **372**, followed by alkylation with MeI afforded α-substituted aminal **373** in good yield and as a single diastereomer (Scheme A1.1.6). Using *N*,*N*-aminal **123**, we installed an α-methyl group to afford aminal **374**. Additionally, we wanted to explore the tolerance of the reaction with an electron deficient 2,6-difluorophenyl amide. Formation of amino amide **190** occurred in moderate yield. Formation of aminal **375** via condensation and α-alkylation with MeI occurred in decent yield.

Scheme A1.1.6. Initial substrate scope

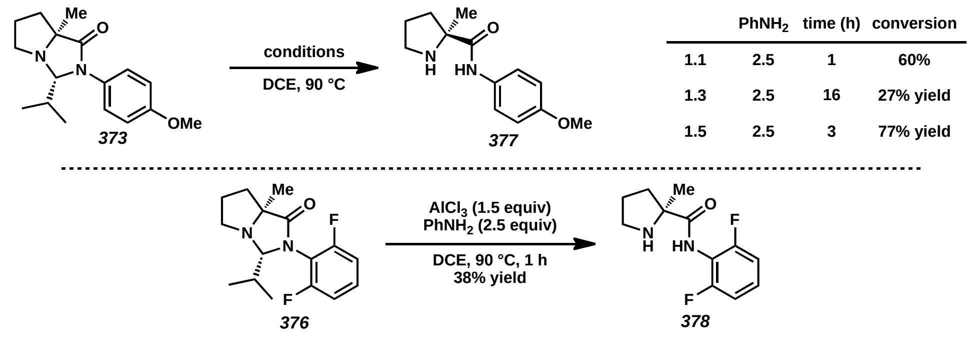

178-OMe
CHO
PTSA, MgSO4
PhCH3, 110 °C
71% yield
372
LDA, MeI
THF, -78 to 23 °C
76% yield
373
123
LDA, MeI
THF, -78 to 23 °C
83% yield
374
NH2
F3C
1. i-BuOCOCl
Et3N, CH2Cl2
2. TFA, CH2Cl2
75% yield (2 steps)
119
190
CHO
PTSA, MgSO4
PhCH3, 110 °C
87% yield
375
LDA, MeI
THF, -78 to 23 °C
70% yield
376

A1.2 Hydrolysis of Asymmetric *N*,*N*-aminals

Next we sought to examine how the electronics of the amide affected the hydrolysis of the aminal. Subjecting electron rich phenyl amide **373** to 1.1 equiv of $AlCl_3$ with aniline for 1 h afforded 60% conversion to amino amide **377** (Table A1.2.1). Increasing the amount of aluminum to 1.3 equiv for 16 h afforded less than 30% yield of amino amide **377**. When 1.5 equiv of $AlCl_3$ was employed for 3 h, a 77% isolated yield of the amino amide was observed.

We also subjected aminal **376** to hydrolysis conditions, and obtained a 38% yield of the desired amino amide, with no remaining starting material, suggesting a significant degree of decomposition.

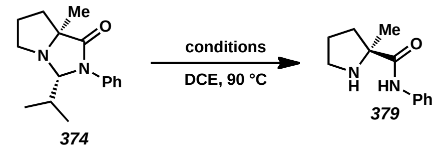
Table A1.2.1. Examining aluminum-mediated hydrolysis


Me
O
N
N
OMe
373
conditions
DCE, 90 °C
Me
O
N
H
HN
OMe
377
Me
O
N
N
F
F
376
AlCl3 (1.5 equiv)
PhNH2 (2.5 equiv)
DCE, 90 °C, 1 h
38% yield
Me
O
N
H
HN
F
F
378

	$PhNH_2$	time (h)	conversion
1.1	2.5	1	60%
1.3	2.5	16	27% yield
1.5	2.5	3	77% yield

While both electron rich and electron deficient α-methyl substituted aminals had undergone hydrolysis, we next aimed to examine the electron neutral phenyl amide under hydrolysis conditions (Table A1.2.2). Subjecting **374** to typical $AlCl_3$ conditions resulted in no reaction. Employing Al(O*i*-Pr)$_3$ as the Lewis acid also gave no reaction. Utilizing $AlCl_3$ and *p*-anisidine as the amine afforded nearly a 50% yield of the hydrolysis product. We attribute this reactivity to the electron rich nature of the *p*-OMe amine. Employing $FeCl_3$ and aniline generated the amino amide in 38% yield. Other Lewis acids such as $ZnCl_2$, $MgCl_2$, and $TiCl_4$ provided less than 10% of the hydrolyzed product. When $AlBr_3$ was employed with aniline, a 40% conversion to amino amide **379** was observed.[5]

Table A1.2.2. Hydrolysis of the electron neutral aminal

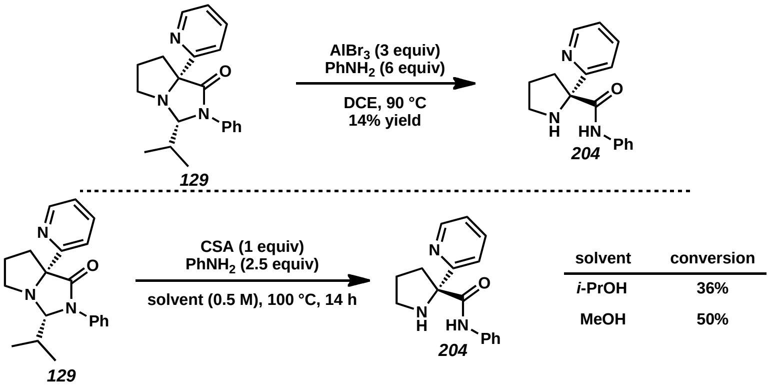


374 379

conditions	result
$AlCl_3$ (1.5 equiv), $PhNH_2$ (2.5 equiv), 1 h	no reaction
Al(O-*i*-Pr)$_3$, $PhNH_2$ (2.5 equiv), 1 h	no reaction
$AlCl_3$ (1.5 equiv), *p*-anisidine, 16 h	48% yield
$FeCl_3$ (1.25 equiv), $PhNH_2$ (2.5 equiv), 26 h	38% yield
$ZnCl_2$ (1.25 equiv), $PhNH_2$ (2.5 equiv), 26 h	no reaction
$MgCl_2$ (1.25 equiv), $PhNH_2$ (2.5 equiv), 26 h	<10% yield
$TiCl_4$ (1.25 equiv), $PhNH_2$ (2.5 equiv), 26 h	<10% yield
$AlBr_3$ (1.5 equiv), $PhNH_2$ (2.5 equiv), 3.5 h	40% conversion

The pyridyl-substituted aminals appeared to have less reactivity towards hydrolysis than the corresponding methyl substituted aminal.[6] Subjecting pryidine **129** to $AlBr_3$ and aniline in DCE afforded a 14% yield of the hydrolyzed product (Scheme A1.2.1). Taking a slightly different approach we subjected **129** to CSA and aniline in IPA or MeOH affording much better conversion to product (36 and 50%, respectively).[7]

Scheme A1.2.1. Hydrolysis of aminal 129

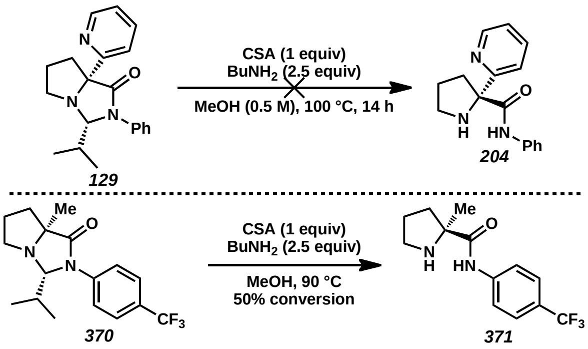


129 204 129 204

solvent	conversion
i-PrOH	36%
MeOH	50%

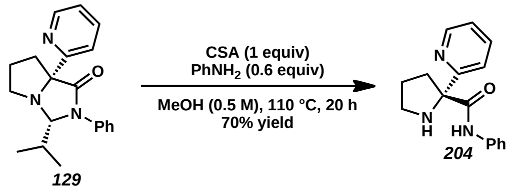
Purification of the amino amide proved difficult with the amount of aniline left in the reaction mixture.[8] We imagined using a volatile amine that could be removed upon workup. Treating **129** with CSA and butylamine resulted in no conversion to the desired amino amide (Scheme A1.2.2). When aminal **370** was subjected to the same conditions, however, almost 50% conversion to the desired product was observed.

Scheme A1.2.2. Hydrolysis of aminals with an amine catalyst


CSA (1 equiv)
BuNH$_2$ (2.5 equiv)
MeOH (0.5 M), 100 °C, 14 h
129
204
CSA (1 equiv)
BuNH$_2$ (2.5 equiv)
MeOH, 90 °C
50% conversion
370
371

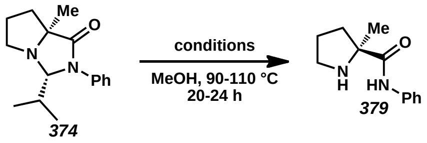
Rather than using a super-stoichiometric amount of aniline, we discovered that we could use aniline catalytically with CSA in MeOH at 110 °C, to afford 70% yield of the desired amino amide (Scheme A1.2.3). The remainder of the reaction mixture was recovered starting material.

Scheme A1.2.3. Hydrolysis of aminal 129


CSA (1 equiv)
PhNH$_2$ (0.6 equiv)
MeOH (0.5 M), 110 °C, 20 h
70% yield
129
204

We next explored the acid mediated hydrolysis of aminal **129** in our amino amide synthesis. Treating aminal **374** with stoichiometric CSA and catalytic aniline afforded nearly 90% conversion to the product with 75% isolated yield (Table A1.2.3). Reducing the amount of CSA to 50 mol % reduced the conversion to 50% of product **379**. Utilizing 1 equiv of CSA and only 25 mol % aniline in MeOH afforded 92% conversion to the amino amide product. At 90 °C, the same conditions only afforded 50% conversion to the desired product. Realizing that 1 equiv of acid was necessary, we wanted to optimize the reaction in terms of amine catalyst loading and concentration of the reaction. The use of 1 equiv of CSA and 50 mol % aniline in 0.5 M MeOH at 100 °C afforded 76% conversion to product. The conversion improved when the amount of aniline was decreased to 25 mol % at the same concentration. Modifying the acid to PTSA with 50 mol % aniline and a 0.5 M concentration in MeOH afforded 92% conversion to amino amide **379**. These results indicate that only 25 mol % aniline is necessary at high concentrations (0.5 M or greater).

Table A1.2.3. Acid and amine screen

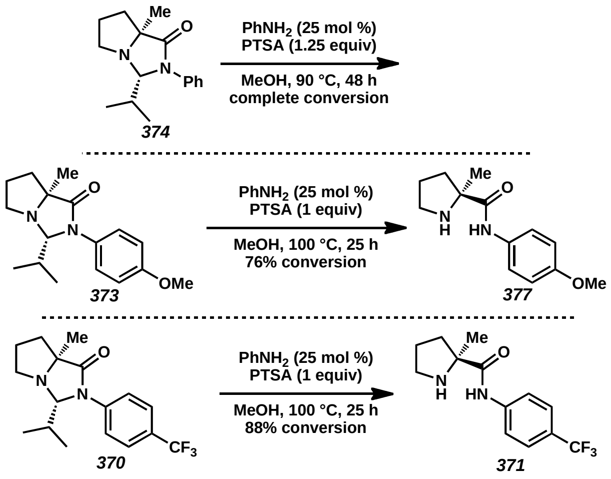


acid	$PhNH_2$	conversion (110 °C)
CSA (1 equiv)	0.6 equiv	86% (75% yield)
CSA (0.5 equiv)	0.6 equiv	50%
CSA (1 equiv)	0.25 equiv	92% (50% at 90 °C)

acid	$PhNH_2$	MeOH [M]	conversion (100 °C)
CSA (1 equiv)	0.5 equiv	0.5	76%
CSA (1 equiv)	0.25 equiv	0.5	84%
CSA (1 equiv)	0.5 equiv	0.25	77%
PTSA (1 equiv)	0.5 equiv	0.5	92%
PTSA (1 equiv)	0.5 equiv	0.25	81%
PTSA (1 equiv)	0.25 equiv	0.25	84%
PTSA (1 equiv)	0.25 equiv	0.5	91%

While we had achieved high levels of conversion, we had been unable to make the reaction proceed to completion. We imagined that the product might inhibit further hydrolysis by quenching the acid mediator. Treating aminal **374** with 1.25 equiv of PTSA and 25 mol % aniline in MeOH at 90 °C for 48 h gave complete conversion to amino amide **379** (Scheme A1.2.4). We began examining this hydrolysis reaction on electronically different amides. Treating electron rich aminal **373** with aniline and 1 equiv of acid afforded 76% conversion to the hydrolyzed product. Likewise, subjecting electron deficient aminal **370** to the same conditions afforded 88% conversion to amino amide **377**. Employing excess acid, such as 1.25 equiv of PTSA, should provide complete conversion to the hydrolyzed products.

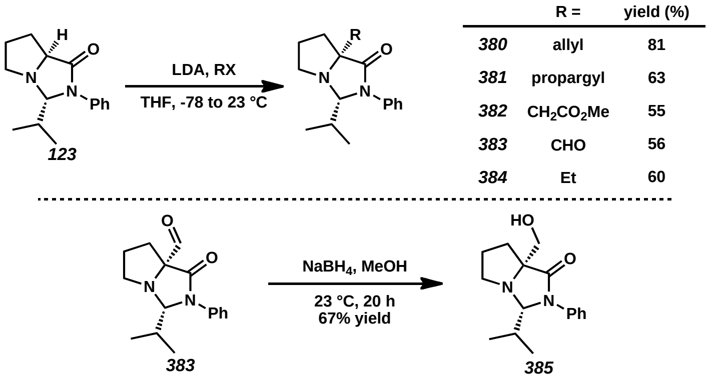
Scheme A1.2.4. Hydrolysis substrate scope


Me
O
N
N
Ph
374
PhNH$_2$ (25 mol %)
PTSA (1.25 equiv)
MeOH, 90 °C, 48 h
complete conversion
373
OMe
PhNH$_2$ (25 mol %)
PTSA (1 equiv)
MeOH, 100 °C, 25 h
76% conversion
H
HN
377
370
CF$_3$
PhNH$_2$ (25 mol %)
PTSA (1 equiv)
MeOH, 100 °C, 25 h
88% conversion
371

A1.3 Substrate Scope

We ultimately wanted to investigate the tolerance of α-substitution (Scheme A1.3.1). Treating aminal **123** with LDA and a variety of electrophiles allowed us to achieve a broad substrate scope in good yield. The aldehyde (**383**) could be reduced to the primary alcohol (**385**) via treatment with NaBH$_4$ in good yield.

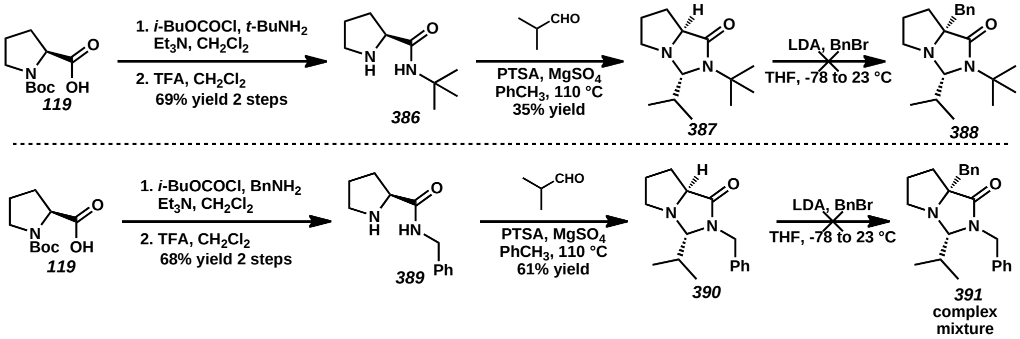
Scheme A1.3.1. α-Substitution substrate scope


H
O
N
N
Ph
123
LDA, RX
THF, -78 to 23 °C
R
383
NaBH$_4$, MeOH
23 °C, 20 h
67% yield
HO
385

	R =	yield (%)
380	allyl	81
381	propargyl	63
382	CH$_2$CO$_2$Me	55
383	CHO	56
384	Et	60

We also wanted to expand the scope of aryl amides to include alkyl amides. Formation of *t*-butyl amino amide **386** occurred in 69% yield in two steps (Scheme A1.3.2). Condensation onto isobutyraldehyde occurred in moderate yield to afford the desired aminal. Alkylation was unsuccessful, however, resulting in unreacted starting material. We attribute this lack of reactivity to the large steric bulk of the *t*-butyl group. We were also able to synthesize the benzyl amino amide in 2 steps in good yield. Condensation onto isobutyraldehyde afforded aminal **390** in good yield. Alkylation, however, was again unsuccessful and provided a complex mixture of products.[9]

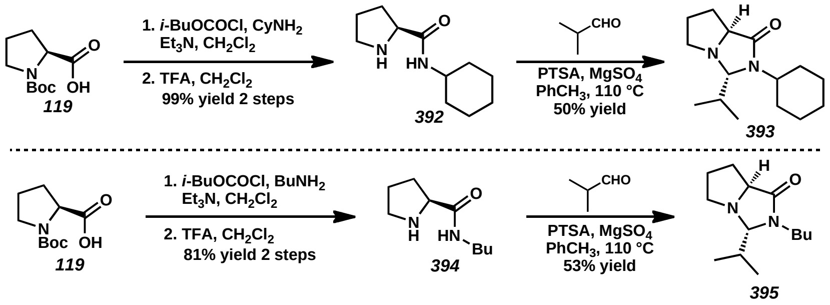
Scheme A1.3.2. Generating alkyl amides



N
Boc OH
119
1. *i*-BuOCOCl, *t*-BuNH$_2$
Et$_3$N, CH$_2$Cl$_2$
2. TFA, CH$_2$Cl$_2$
69% yield 2 steps
N
H
HN
O
386
CHO
PTSA, MgSO$_4$
PhCH$_3$, 110 °C
35% yield
H
O
N
N
387
LDA, BnBr
THF, -78 to 23 °C
Bn
O
N
N
388
N
Boc OH
119
1. *i*-BuOCOCl, BnNH$_2$
Et$_3$N, CH$_2$Cl$_2$
2. TFA, CH$_2$Cl$_2$
68% yield 2 steps
N
H
HN
Ph
389
CHO
PTSA, MgSO$_4$
PhCH$_3$, 110 °C
61% yield
H
O
N
N
Ph
390
LDA, BnBr
THF, -78 to 23 °C
Bn
O
N
N
Ph
391
complex
mixture

Rather than installing a *t*-butyl amide, we thought a cyclohexane amide may be less sterically hindered and function in the alkylation reaction (Scheme A1.3.3). Formation of the cyclohexane amide (**392**) followed by condensation onto isobutyraldehyde afforded aminal **393**. Likewise, we thought an *n*-butyl amide would also be significantly less sterically hindered. Formation of the butyl amide (**81**) occurred in good yield in two steps. Condensation onto isobutyraldehyde afforded aminal **53** in moderate yield. Alkylation of these two substrates with benzyl bromide would afford the desired α-substituted *N*,*N*-aminals.

Scheme A1.3.3. Less sterically hindered alkyl amides



N
Boc OH
119
1. *i*-BuOCOCl, CyNH$_2$
Et$_3$N, CH$_2$Cl$_2$
2. TFA, CH$_2$Cl$_2$
99% yield 2 steps
N
H
HN
O
392
CHO
PTSA, MgSO$_4$
PhCH$_3$, 110 °C
50% yield
H
O
N
N
393
N
Boc OH
119
1. *i*-BuOCOCl, BuNH$_2$
Et$_3$N, CH$_2$Cl$_2$
2. TFA, CH$_2$Cl$_2$
81% yield 2 steps
N
H
HN
Bu
394
CHO
PTSA, MgSO$_4$
PhCH$_3$, 110 °C
53% yield
H
O
N
N
Bu
395

A1.4 Determination of Enantiomeric Excess

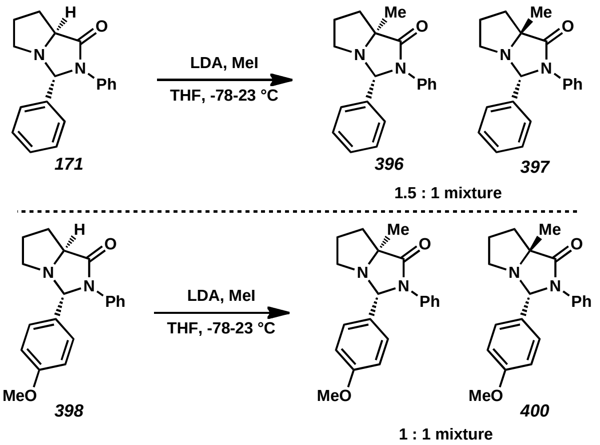
In order to determine the success of our asymmetric synthesis, we needed to examine the enantiomeric excess (*ee*) of the resultant amino amides. We have fully developed the asymmetric route to the amino amides, including hydrolysis. After developing a racemic route to the amino amides we were able to determine the *ee* by chiral HPLC. Method development on HPLC provided adequate separation between the two enantiomers. Analysis of asymmetric **379** revealed that a single enantiomer results from our synthesis.

The method we have developed for the synthesis of these asymmetric amino amides is both high yielding and decidedly stereorententive. The remaining substrates need to be hydrolyzed to reveal the asymmetric amino amides, and the corresponding racemate needs to be synthesized in order to determine the remaining *ee*'s.

A1.5 Generation of the Other Enantiomer from L-Proline

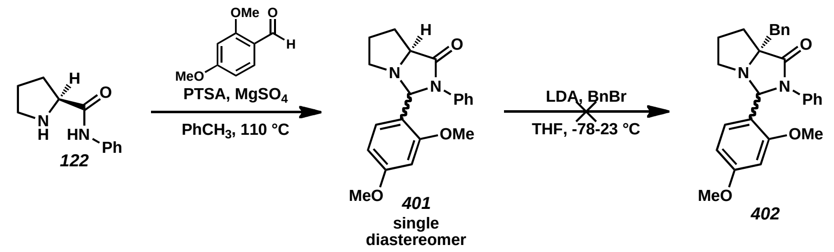
Besides retaining the stereochemistry of the L-proline starting material, we envisioned obtaining the other enantiomer via an anti-selective alkylation. Treating aminal **171** with LDA and MeI afforded a 1.5 : 1 mixture of syn to anti isomers (Scheme A1.5.1). Subjecting more electron rich aminal **398** to the same conditions afforded a 1 : 1 mixture of syn to anti isomers. It is evident that the more electron rich nature of the aminal favors more anti alkylation.

Scheme A1.5.1. Initial attempts at anti functionalization


H
O
N
N
Ph
171
LDA, MeI
THF, -78-23 °C
Me
396
397
1.5 : 1 mixture
MeO
398
400
1 : 1 mixture

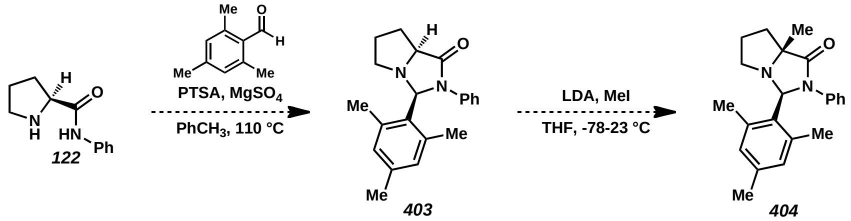
Based on this idea, we imagined employing an even more electron rich and more sterically hindered *N*,*N*-aminal. Condensation onto 2,4-dimethoxybenzaldehyde afforded the aminal (**401**) as a single diastereomer of unknown stereochemistry (Scheme A1.5.2). Alkylation of this aminal was unsuccessful utilizing LDA and benzyl bromide, only providing a complex mixture of products. It is likely that the highly electron rich nature of the aminal resulted in decomposition upon treatment with the alkylation conditions.

Scheme A1.5.2. Utilizing a more electron rich aromatic aldehyde


H
O
N
H
HN
Ph
122
OMe
O
H
MeO
PTSA, MgSO4
PhCH3, 110 °C
N
N
Ph
OMe
MeO
401
single
diastereomer
LDA, BnBr
THF, -78-23 °C
Bn
402

We were unable to determine if an anti alkylation would be favored under such conditions due to decomposition. The unidentified diastereomer of the condensation reaction was very intriguing, however. If the condensation reaction provided the anti diastereomer, then a syn alkylation would be more desirable to afford the other enantiomer of the amino amide. Condensation onto a sterically hindered aromatic aldehyde such as mesityl aldehyde may afford the anti diastereomer (**403**) (Scheme A1.5.3). If we could then perform a syn alkylation, we would obtain the desired enantiomer of the amino amide.

Scheme A1.5.3. Sequence for syn alkylation



A1.6 Conclusion

We have developed a highly stereoretentive method of substituted amino amide synthesis. The synthesis of *N*,*N*-aminals is straightforward with simple high yielding reactions. The hydrolysis of the aminal occurs with high yield, and because only a catalytic amount of amine is needed, is easy to purify via chromatography. The amino amide we have obtained thus far has shown to be a single enantiomer by HPLC analysis. The remaining aminal substrates will need to be hydrolyzed and then analyzed by HPLC in order to determine the *ee* of the corresponding amino amides.

A1.7 References and Notes

[1] MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107* 5471-5569.

[2] (a) Boes, M.; Naef, R.; Schweizer, W. B.; Seebach, D. *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398. (b) Sting, A. R.; Hoffman, M.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.

[3] Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035-4036.

[4] Transamination does not occur under these conditions. Presumably $AlCl_3$ acts as a Lewis acid, activating the aminal center for attack by the stoichiometric amine. Collapse of the aminal center to form the corresponding imine occurs to provide the free amino amide.

[5] Using Al(O*i*-Pr)$_3$ as a Lewis acid resulted in no reaction, suggesting that a much strong Lewis acid was needed. $AlCl_3$ provided trace amounts of reaction, so we examined $AlBr_3$ which is even stronger than $AlCl_3$.

[6] This may be due to some cooperative effect of the pyridyl nitrogen and the aluminum reagent.

[7] Li, D.; Zhang, Y.; Xia, C.; Guo, W. *Heterocycles* **2005**, *65*, 1829-1836. We abandoned the use of Lewis acids for hydrolysis due to their inconsistency across substrates and propensity to cause decomposition.

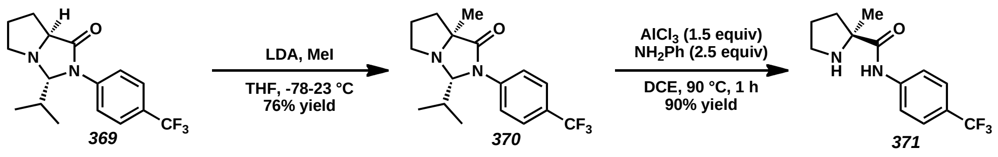
[8] Aniline could not be removed using any method other than column chromatography. Even with chromatography, the aniline generally eluted with the product.

[9] This mixture of products may be due to competitive deprotonation of a benzyl proton on the benzyl amide.

[10] Kelly, S.; Watts, J.; McKee, V.; Kelleher, F. *Tetrahedron* **2010**, *66*, 3525-3536. The authors stated that the reaction occurred in just 5 h. We found incomplete conversion, but by running the reaction for several days, near complete conversion could be obtained.

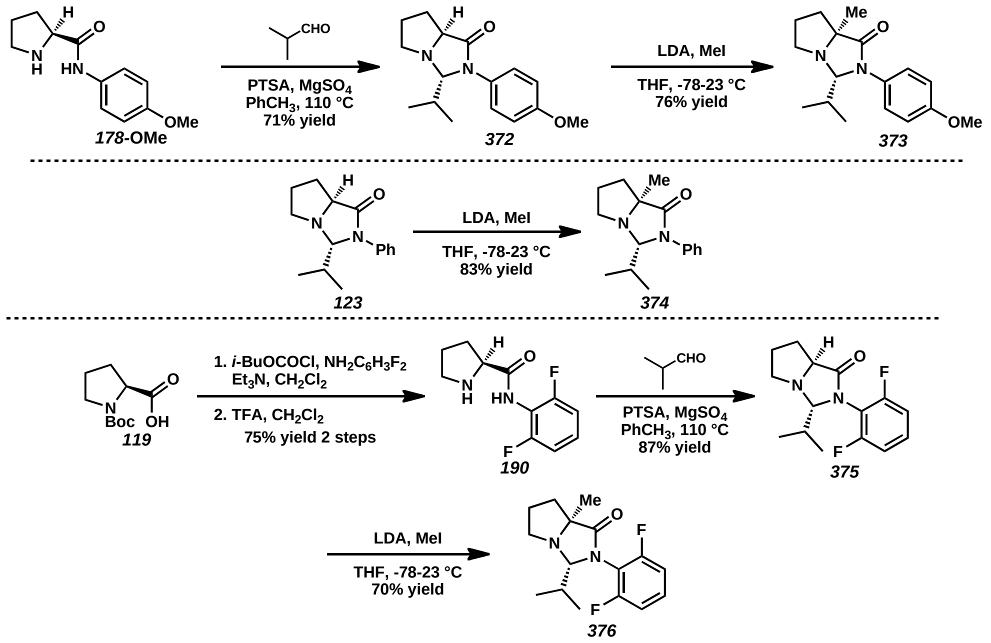
A1.8 Experimental procedures

Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Tetrahydrofuran, *N*,*N*-dimethylformamide, dichloromethane, hexanes, and toluene were purified by passing through activated alumina columns. Diisopropylamine was distilled over CaH_2. 2-Fluoropyridine was freshly distilled before use. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA), Sigma-Aldrich (St. Louis, MO), Gelest (Morrisville, PA), Oakwood Products (West Columbia, SC), Strem (Newburport, MA), Mallinckrodt Chemicals (Phillipsburg, NJ), Spectrum (Gardena, CA) Fischer Scientific (Fair Lawn) and TCI America (Portland, OR). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (Silicycle, Quebec City, Canada). Visualization was accomplished with UV light and exposure to either *p*-anisaldehyde or $KMnO_4$ solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz), a Varian Inova 400 (at 400 MHz), or a Varian 400 MR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on either a Varian Inova 400 (at 100 MHz), a Varian Mercury 300 (at 75 MHz), or a Varian 400 MR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on NaCl plates (film) with either a Nicolet Magna FTIR 760, a Nicolet 380 FTIR, or a Bruker Tensor 27. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.



General procedure for α-alkylation: To a solution of diisopropylamine (0.744 mL, 5.30 mmol) in THF (11.2 mL) at -78 °C was added *n*-BuLi (2.03 mL, 5.08 mmol, 2.5 M in hexanes). After stirring for 10 min at -78 °C, **369** (1.32 g, 4.24 mmol) was added in THF (10.0 mL) at – 78 °C. The reaction was stirred for 30 min at -78 °C. MeI (0.396 mL, 6.36 mmol) was added at -78 °C, at which time the reaction was warmed to 23 °C and stirred overnight. Water (10 mL) was added. The aqueous layer was extracted with EtOAc (3 x 20 mL). The organics were washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was purified via flash chromatography (7:1 to 4:1 hexanes:EtOAc) to afford **370** (1.06 g, 76% yield, R_f = 0.32 in 4:1 hexanes:EtOAc) as a yellow solid.

General procedure for hydrolysis via $AlCl_3$: To **370** (150 mg, 0.460 mmol) in DCE (2.30 mL) was added $AlCl_3$ (91.9 mg, 0.689 mmol) and aniline (0.105 mL, 1.15 mmol) in a 2-dram vial. The reaction was heated to 90 °C for 3 h. Upon cooling, the reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified over silica (7:3 to 1:1 hexanes:EtOAc) to afford **371** (62.3 mg, 50% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) as an orange oil.


178-OMe
CHO
PTSA, MgSO4
PhCH3, 110 °C
71% yield
372
LDA, MeI
THF, -78-23 °C
76% yield
373
123
LDA, MeI
THF, -78-23 °C
83% yield
374
119
1. i-BuOCOCl, NH2C6H3F2
Et3N, CH2Cl2
2. TFA, CH2Cl2
75% yield 2 steps
190
CHO
PTSA, MgSO4
PhCH3, 110 °C
87% yield
375
LDA, MeI
THF, -78-23 °C
70% yield
376

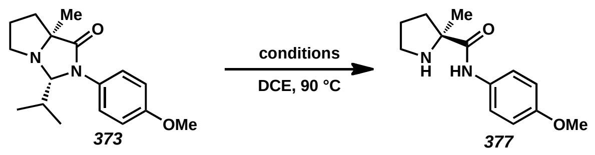
General procedure for aminal formation: **178-OMe** (826 mg, 3.75 mmol), isobutyraldehyde (0.513 mL, 5.63 mmol), PTSA (35.7 mg, 0.188 mmol) and $MgSO_4$ (677 mg, 5.63 mmol) were combined in toluene (25.0 mL) and heated to reflux overnight. The reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 20 mL), the organics dried over Na_2SO_4 and concentrated. The crude residue was purified over silica (3:1 to 7:3 hexanes:EtOAc) to afford **372** (733 mg, 71% yield, R_f = 0.24 in 1:1 hexanes:EtOAc) as a yellow solid.

Aminal 373: According to the general procedure, **373** (76% yield, R_f = 0.52 in 1:1 hexanes:EtOAc) as a yellow solid.

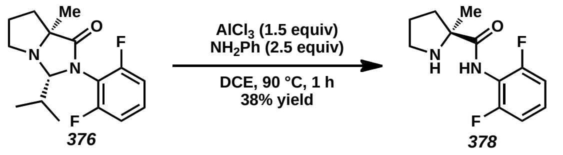
Aminal 374: According to the general procedure, **374** (83% yield, R_f = 0.32 in 4:1 hexanes:EtOAc) as a yellow solid.

Aminal 375: According to the general procedure, **375** (87% yield, R_f = 0.53 in 1:1 hexanes:EtOAc) as a white solid.

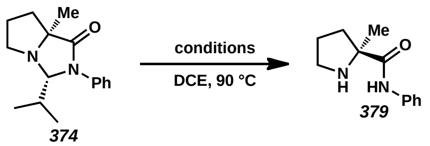
Aminal 376: According to the general procedure, **376** (70% yield, R_f = 0.62 in 1:1 hexanes:EtOAc) as a yellow solid.


Me
O
N
N
OMe
373
conditions
DCE, 90 °C
Me
O
N
H
HN
OMe
377

	NH_2Ph	time (h)	conversion
1.1	2.5	1	60%
1.3	2.5	16	27% yield
1.5	2.5	3	77% yield

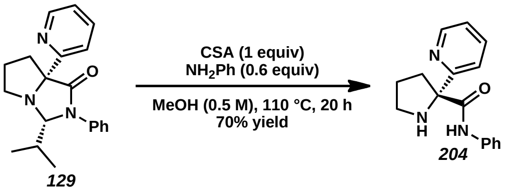

Me
O
N
N
F
F
376
$AlCl_3$ (1.5 equiv)
NH_2Ph (2.5 equiv)
DCE, 90 °C, 1 h
38% yield
Me
O
N
H
HN
F
F
378

Amide 378: According to the general procedure **378** (38% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) was isolated as a light brown solid.

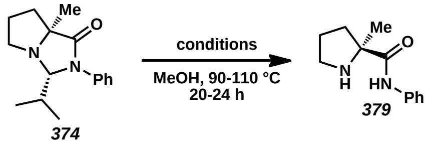

Me
O
N
N
Ph
374
conditions
DCE, 90 °C
Me
O
N
H
HN
Ph
379

conditions	result
$AlCl_3$ (1.5 equiv), NH_2Ph (2.5 equiv), 1 h	no reaction
Al(O-*i*-Pr)$_3$, NH_2Ph (2.5 equiv), 1 h	no reaction
$AlCl_3$ (1.5 equiv), *p*-anisidine, 16 h	48% yield
$FeCl_3$ (1.25 equiv), NH_2Ph (2.5 equiv), 26 h	38% yield
$ZnCl_2$ (1.25 equiv), NH_2Ph (2.5 equiv), 26 h	no reaction
$MgCl_2$ (1.25 equiv), NH_2Ph (2.5 equiv), 26 h	<10% yield
$TiCl_4$ (1.25 equiv), NH_2Ph (2.5 equiv), 26 h	<10% yield
$AlBr_3$ (1.5 equiv), NH_2Ph (2.5 equiv), 3.5 h	40% conversion

General procedure: **374** (1 equiv), Lewis acid (1.25-1.5 equiv), amine (2.5 equiv) and DCE were combined in a 2-dram vial and heated to 90 °C for the indicated time. Upon cooling, the reaction was quenched with H_2O. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated. The conversion was determined by crude ^{1}H NMR.


N
O
N
N
Ph
129
CSA (1 equiv)
NH_2Ph (0.6 equiv)
MeOH (0.5 M), 110 °C, 20 h
70% yield
N
O
N
H
HN
Ph
204

Representative procedure for acid hydrolsis: To pyridine **129** (750 mg, 2.33 mmol) in a screw cap vial with Teflon cap was added CSA (542 mg, 2.33 mmol), NH_2Ph (106 μL, 1.17 mmol) and MeOH (4.66 mL). The reaction was heated to 110 °C for 24 h. Upon cooling, the reaction mixture was concentrated. To the residue was added sat. aq. $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (3:1 to 3:2 hexanes/EtOAc eluent) to afford amino amide **204** (874 mg, 70% yield (97% yield borsm) R_f = 0.05 in 1:1 hexanes/EtOAc) as a beige solid.

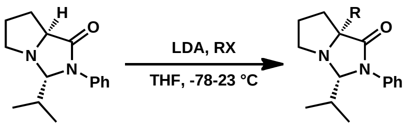


374 *379*

acid	NH_2Ph	conversion (110 °C)
CSA (1 equiv)	0.6 equiv	86% (75% yield)
CSA (0.5 equiv)	0.6 equiv	50%
CSA (1 equiv)	0.25 equiv	92% (50% at 90 °C)

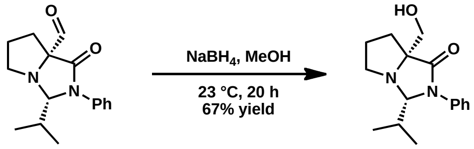
acid	NH_2Ph	MeOH [M]	conversion (100 °C)
CSA (1 equiv)	0.5 equiv	0.5	76%
CSA (1 equiv)	0.25 equiv	0.5	84%
CSA (1 equiv)	0.5 equiv	0.25	77%
PTSA (1 equiv)	0.5 equiv	0.5	92%
PTSA (1 equiv)	0.5 equiv	0.25	81%
PTSA (1 equiv)	0.25 equiv	0.25	84%
PTSA (1 equiv)	0.25 equiv	0.5	91%

According to the general procedure, the conversion to **379** was determined by ^{1} H NMR.



123

	R =	yield (%)
380	allyl	81
381	propargyl	63
382	CH_2CO_2Me	55
383	CHO	xx
384	Et	xx



383 *385*

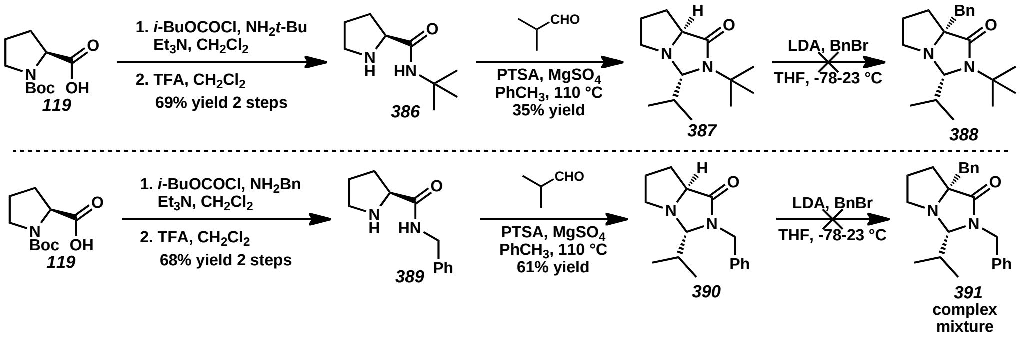
Aminal 380: According to the general procedure **380** (81% yield, R_f = 0.48 in 3:1 hexanes:EtOAc) was isolated as a light brown solid.

Aminal 381: According to the general procedure **381** (63% yield, R_f = 0.45 in 3:1 hexanes:EtOAc) was isolated as a light brown solid.

Aminal 382: According to the general procedure **382** (55% yield, R_f = 0.40 in 3:1 hexanes:EtOAc) was isolated as a light yellow oil.

Aminal 383: According to the general procedure **383** (xx% yield, R_f = 0.42 in 3:1 hexanes:EtOAc) was isolated as a light yellow solid.

Alcohol 385: According to the general procedure **385** (67% yield, R_f = 0.25 in 3:1 hexanes:EtOAc) was isolated as a light yellow solid.

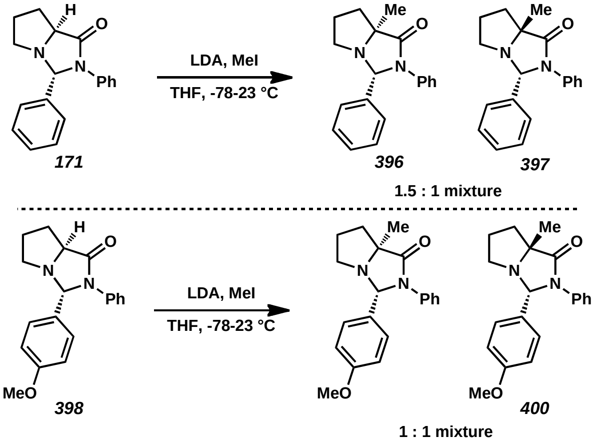

119
1. i-BuOCOCl, NH2t-Bu Et3N, CH2Cl2
2. TFA, CH2Cl2
69% yield 2 steps
386
CHO
PTSA, MgSO4
PhCH3, 110 °C
35% yield
387
LDA, BnBr
THF, -78-23 °C
388
119
1. i-BuOCOCl, NH2Bn Et3N, CH2Cl2
2. TFA, CH2Cl2
68% yield 2 steps
389
CHO
PTSA, MgSO4
PhCH3, 110 °C
61% yield
390
LDA, BnBr
THF, -78-23 °C
391
complex mixture

Representative procedure for amino amide formation: To a solution of (*S*)-*N*-Boc proline (750 mg, 3.48 mmol) in CH_2Cl_2 (17.4 mL) at 0 ˚C was added isobutyl chloroformate (0.501 mL, 3.83 mmol) and triethylamine (0.539 mL, 3.83 mmol). After stirring for 20 minutes at 0 ˚C, $BnNH_2$ (0.419 mL, 3.83 mmol) was added, and the reaction was warmed to 23 ˚C and stirred overnight. The reaction was washed sequentially with aq. $KHSO_4$ (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a pale brown solid. To a solution of crude amide in CH_2Cl_2 (6.97 mL) at 23 ˚C was added TFA (5.37 mL, 69.7 mmol). The solution was stirred at 23 ˚C for 1 h, and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and neutralized with solid Na_2CO_3 until pH ~9. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford amino amide **389** (482 mg, 68% yield, R_f = 0.00 in 1:1 hexanes/EtOAc) as a light brown solid, which was sufficiently pure to be taken on to the next step.

Aminal 390: According to the general procedure **390** (61% yield, R_f = 0.25 in 1:1 hexanes:EtOAc) was isolated as a light yellow solid.

Amide 386: According to the general procedure **386** (69% yield, R_f = 0.0 in 1:1 hexanes:EtOAc) was isolated as a white solid.

Aminal 387: According to the general procedure **387** (35% yield, R_f = 0.20 in 1:1 hexanes:EtOAc) was isolated as a light yellow solid.



171 *396* *397*

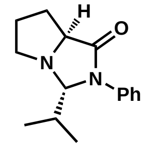
1.5 : 1 mixture

398 *400*

1 : 1 mixture

According to the general procedure. The product ratios were determined by crude ^{1}H NMR.

Appendix B: Spectra Associated with Chapter 2



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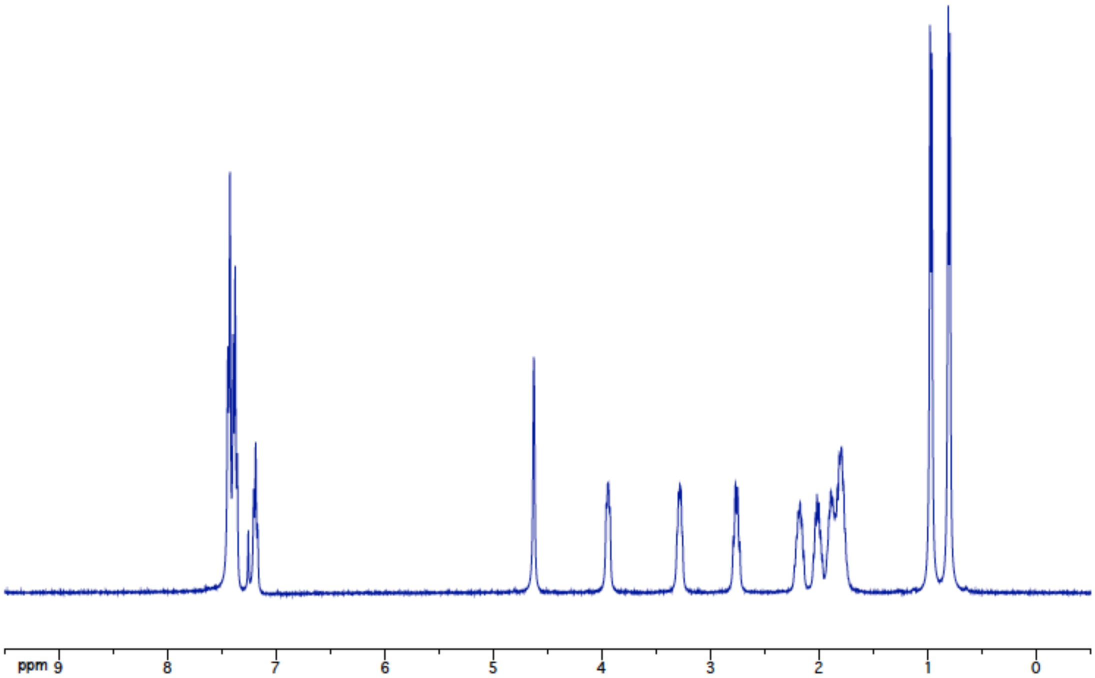

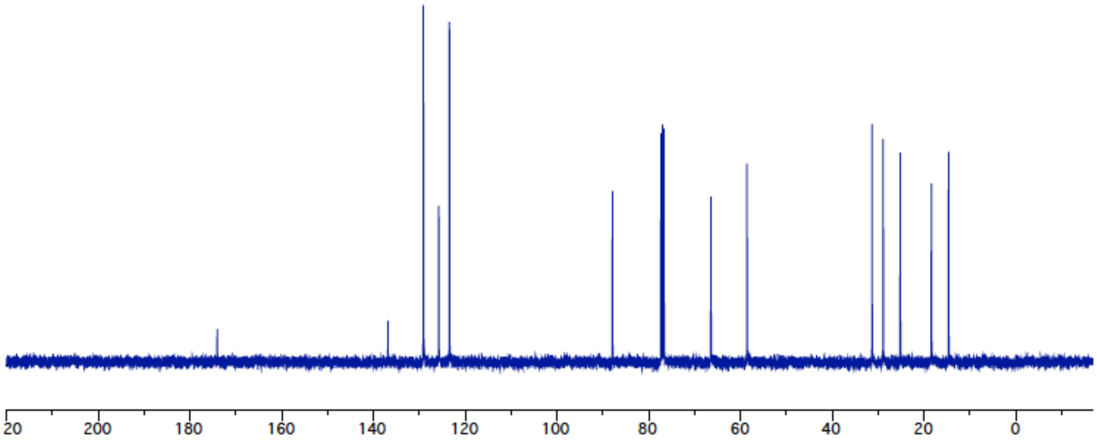

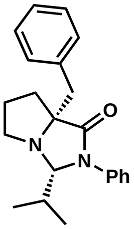

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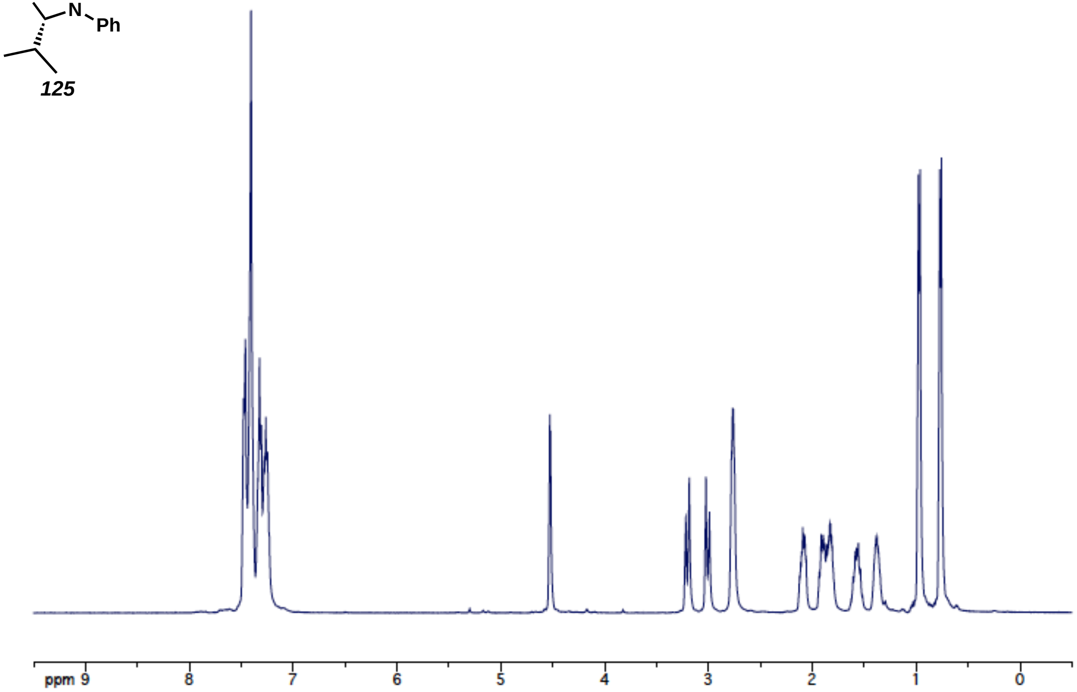

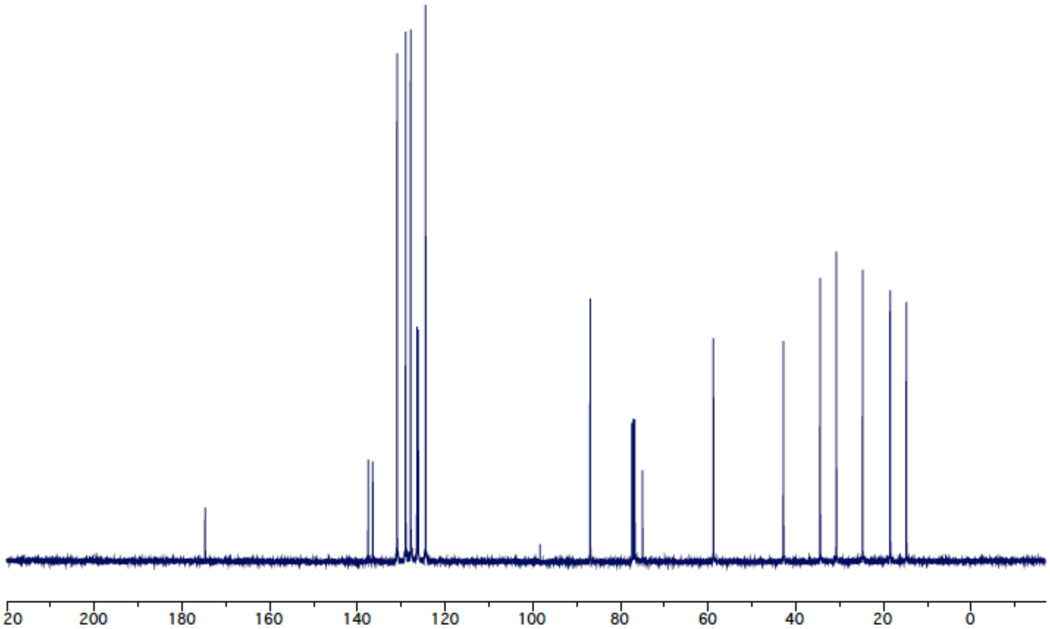

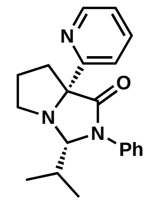

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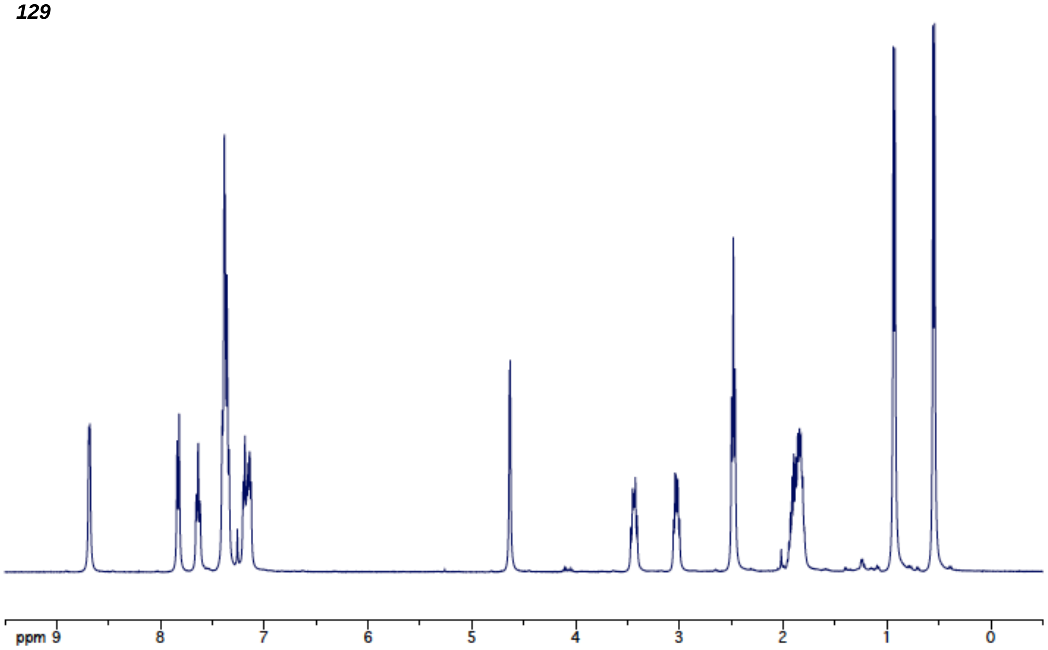

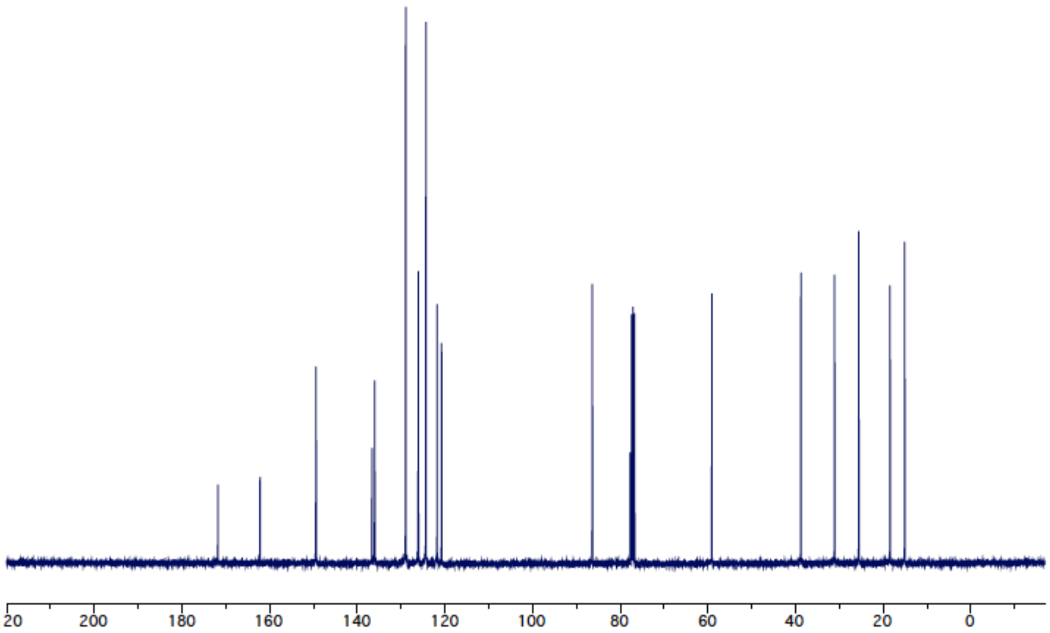

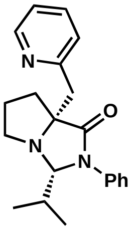

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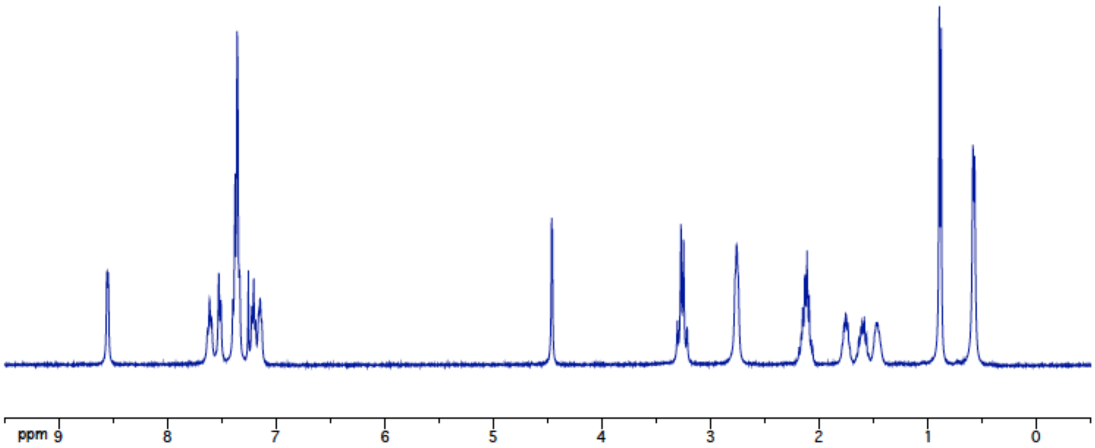

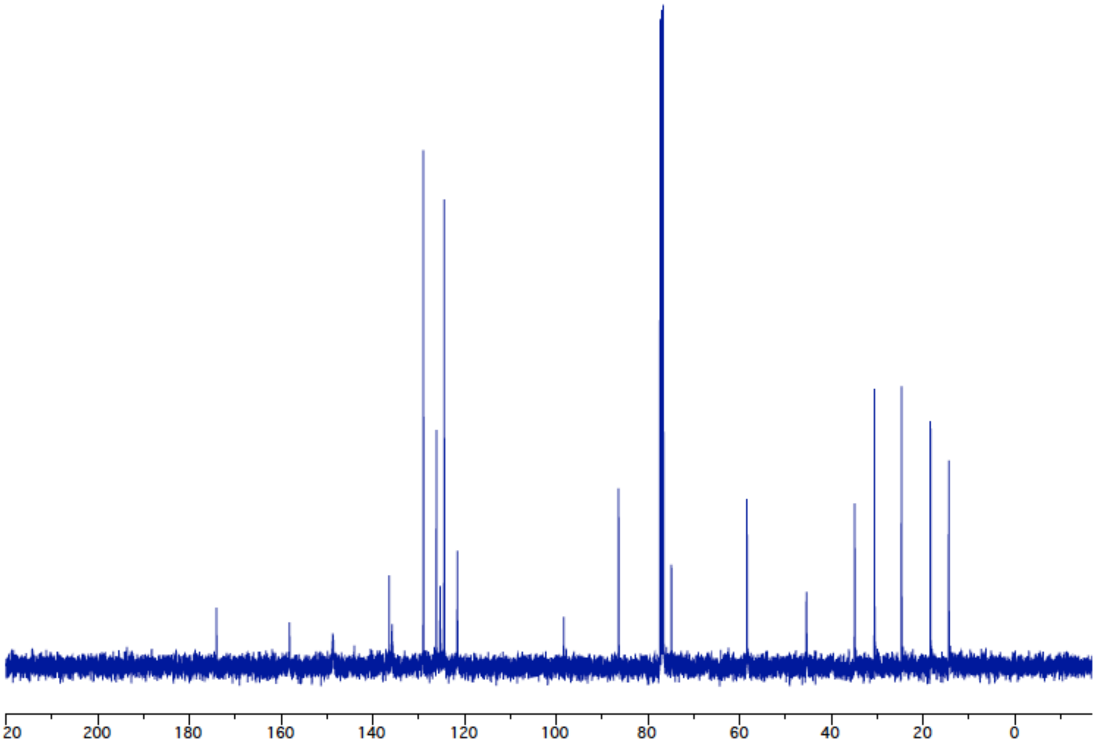

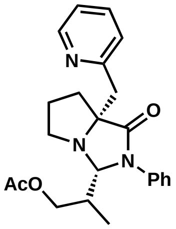
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N
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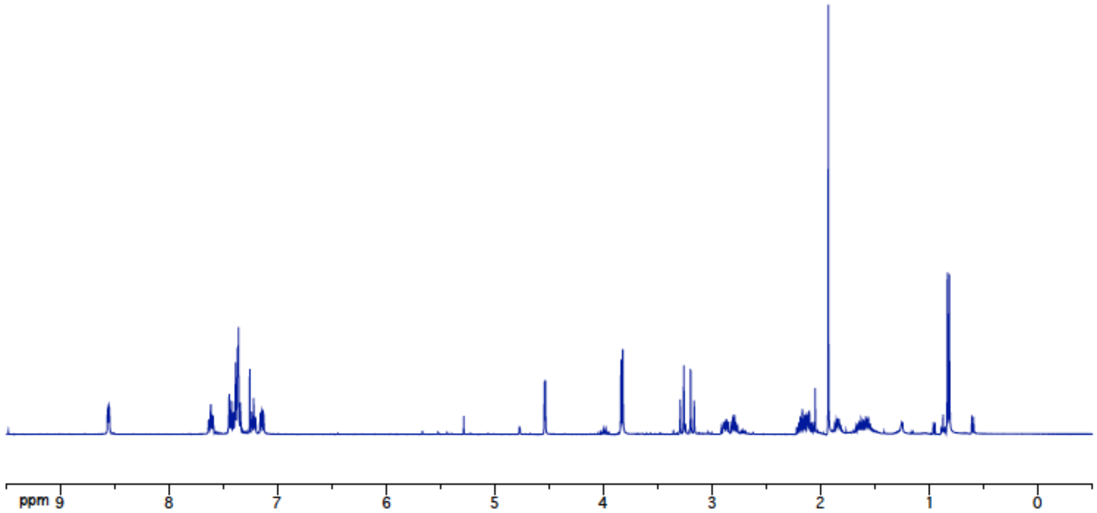
AcO

131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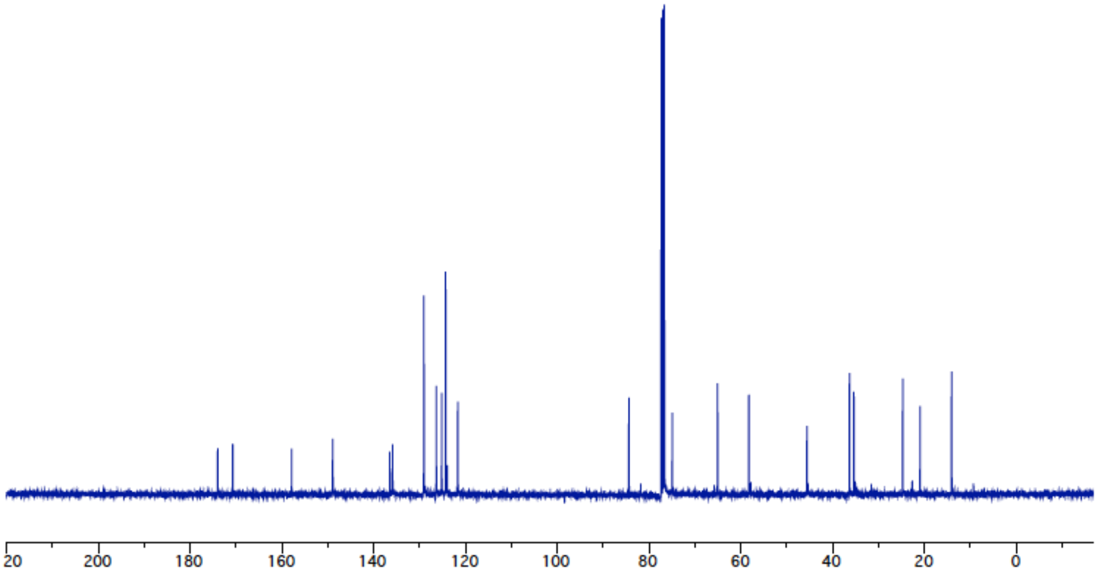
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20
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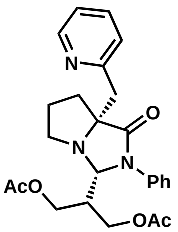
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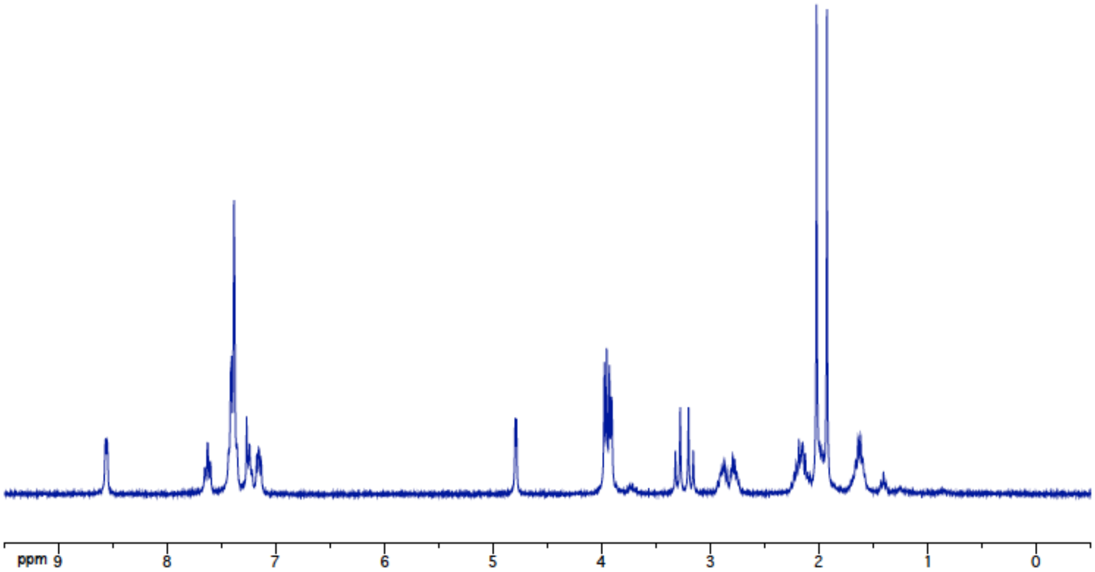
N
N
Ph
AcO
OAc

132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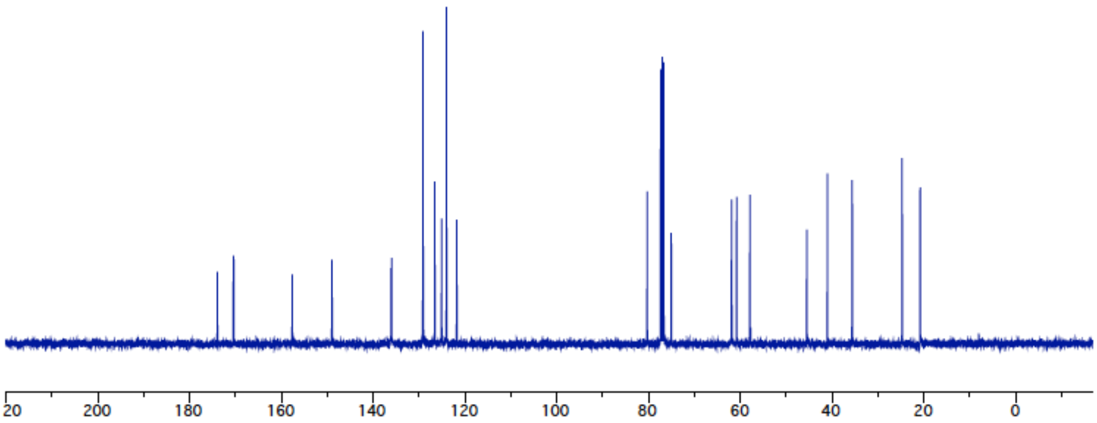
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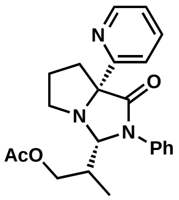
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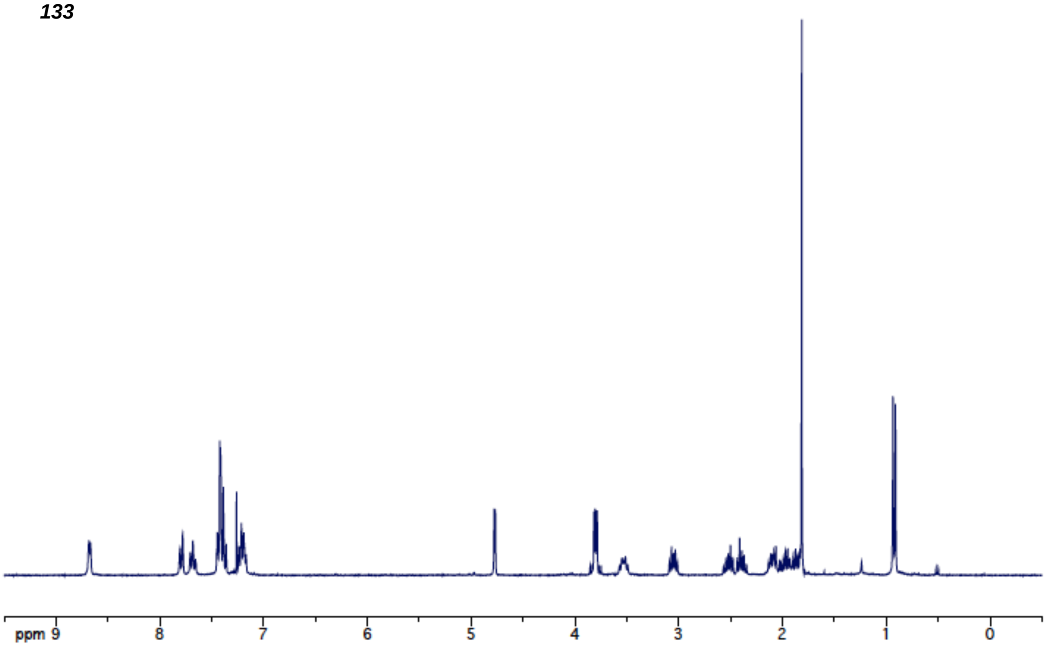
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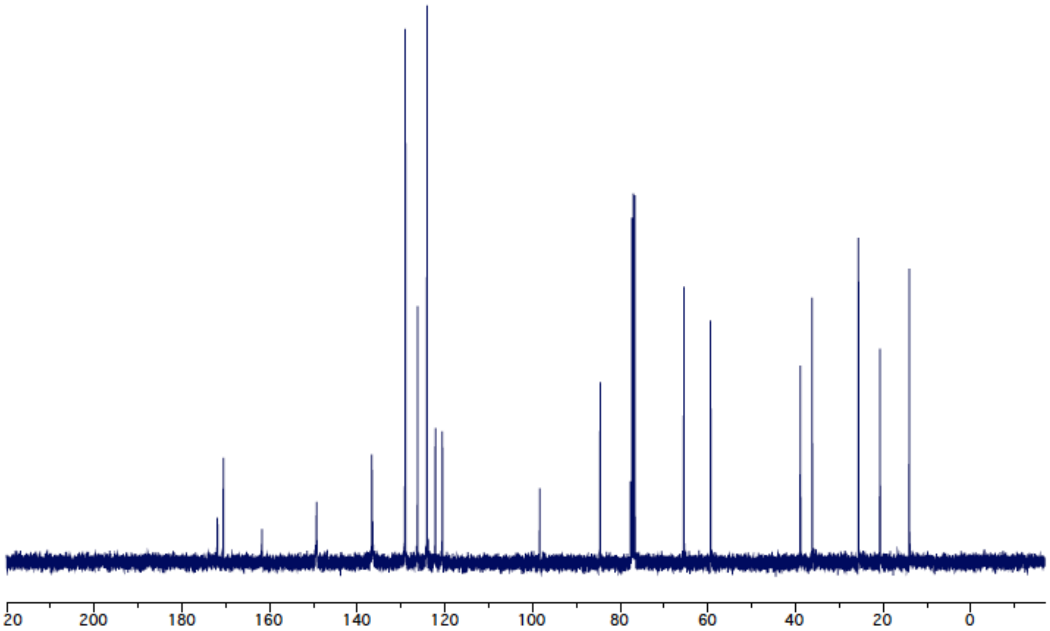
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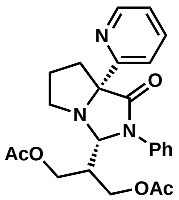
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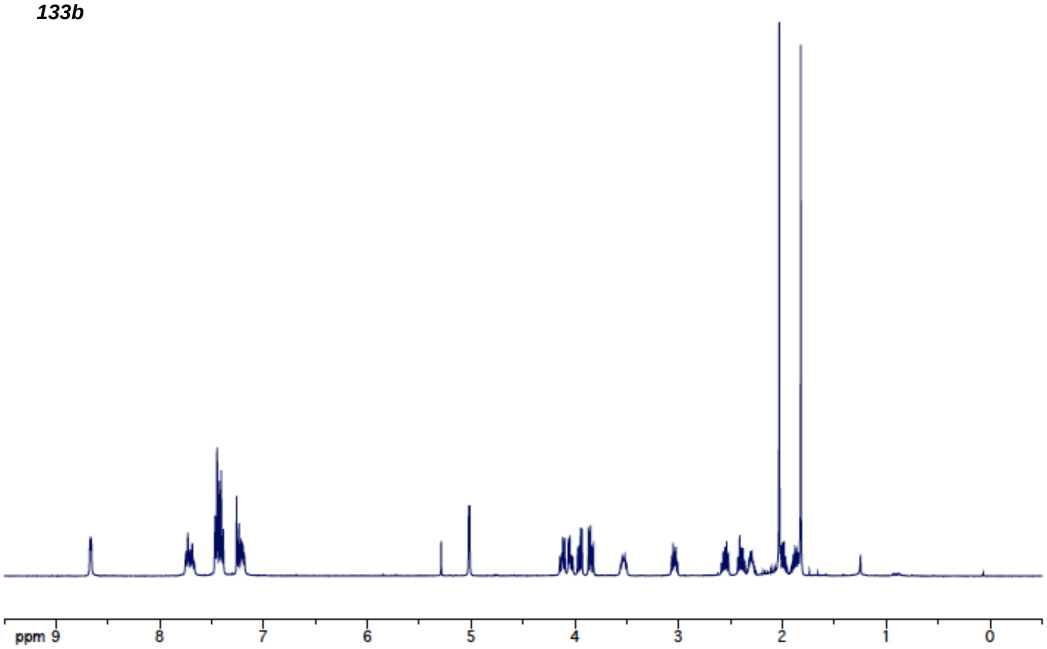
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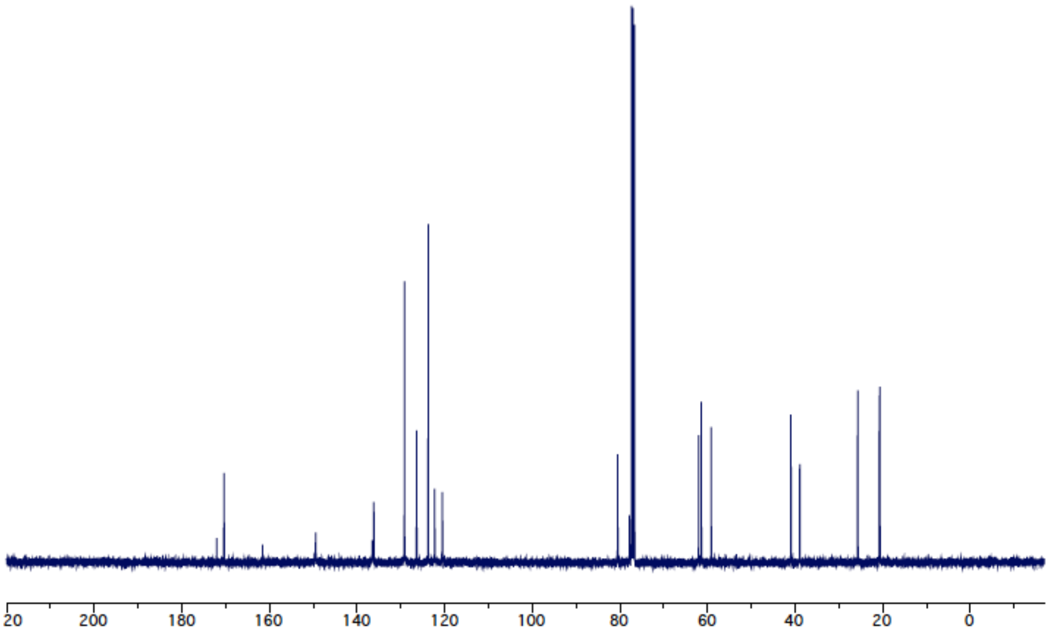
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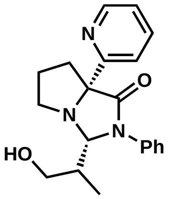

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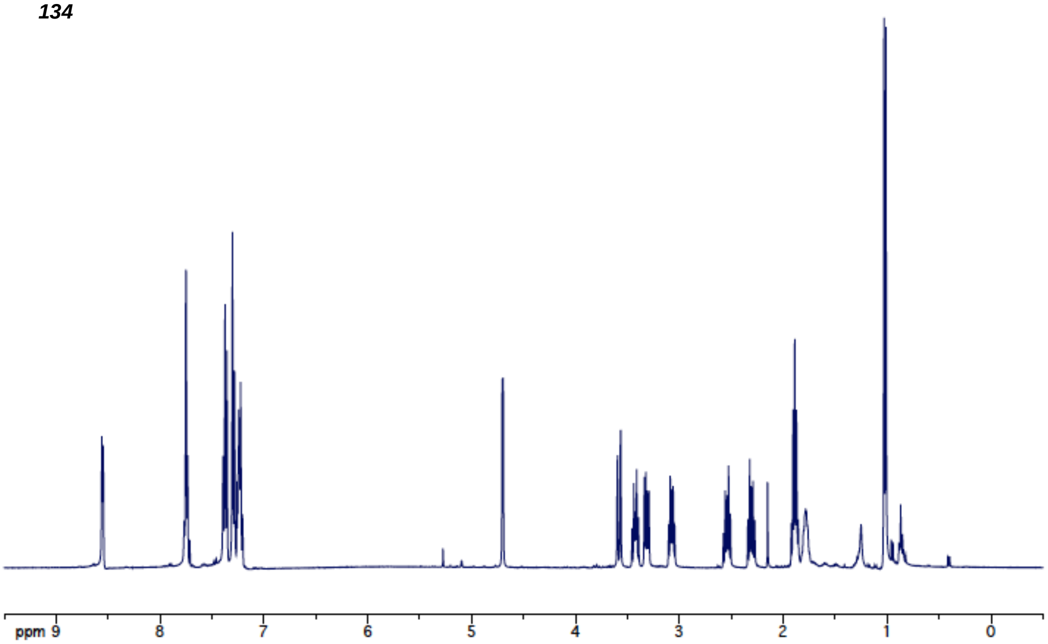

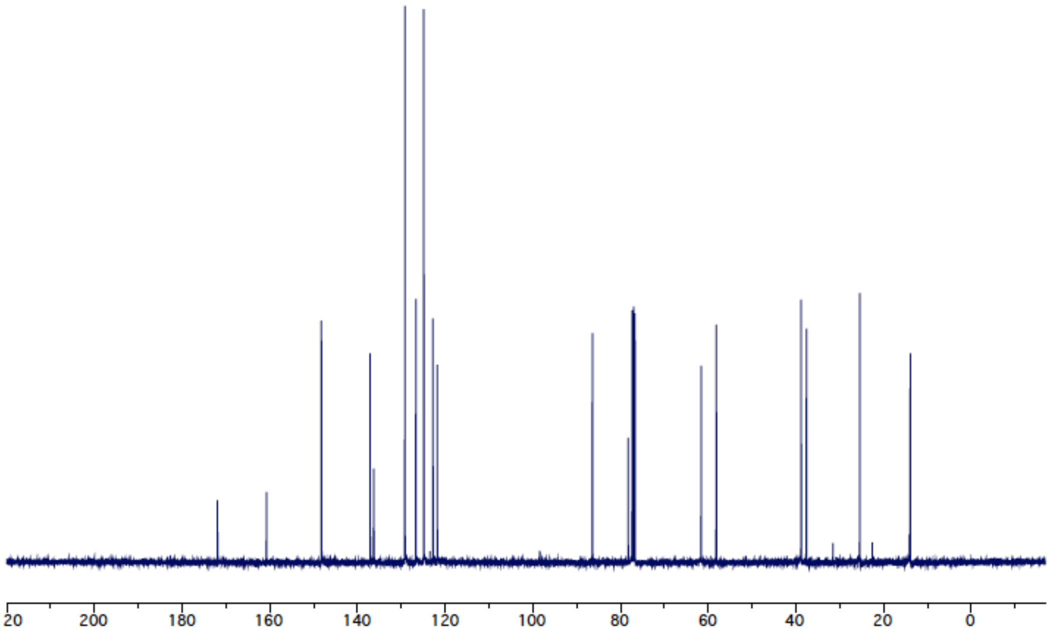

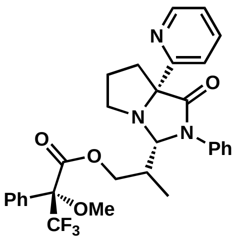
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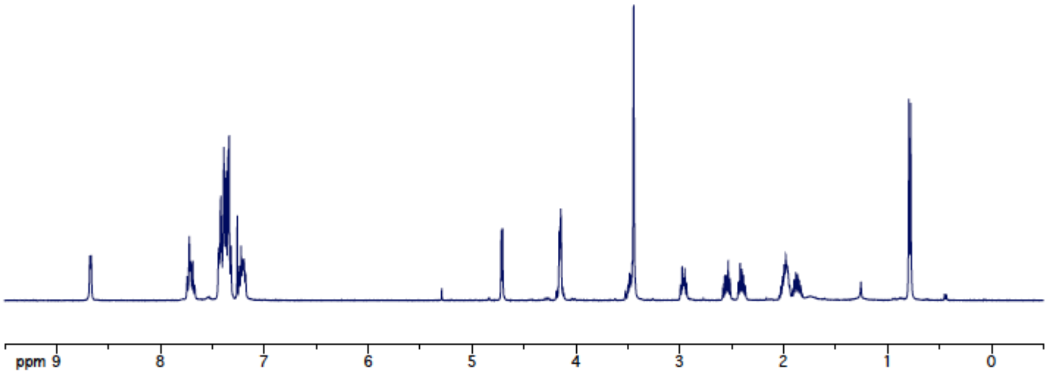
N
N
Ph
O
O
Ph
OMe
CF3

135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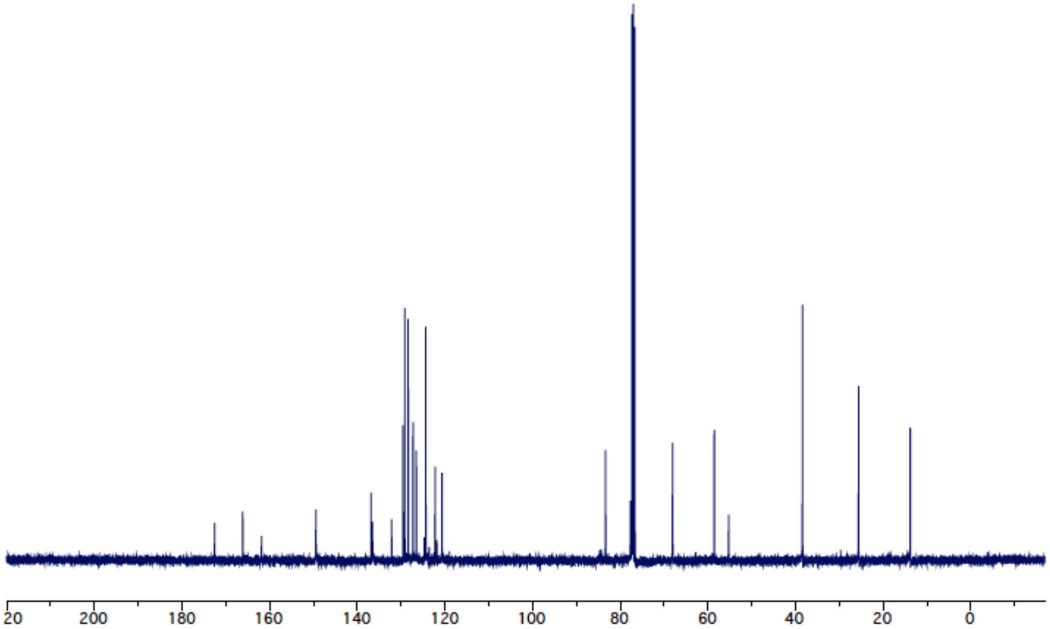
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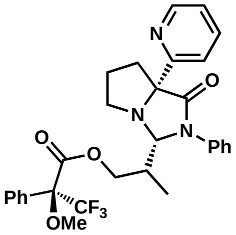
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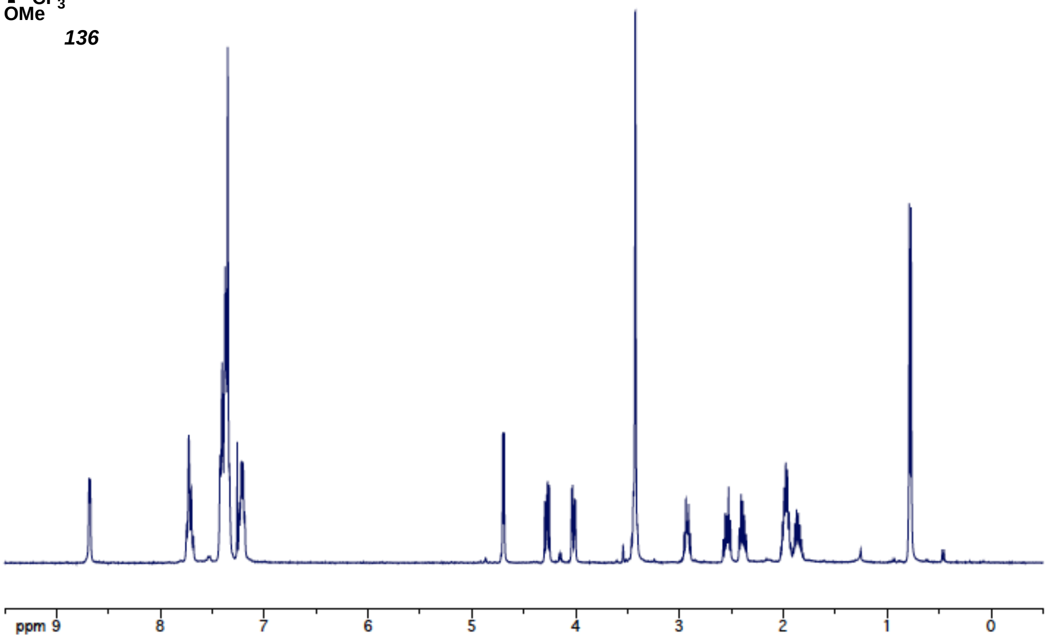
O
Ph
CF$_3$
OMe

136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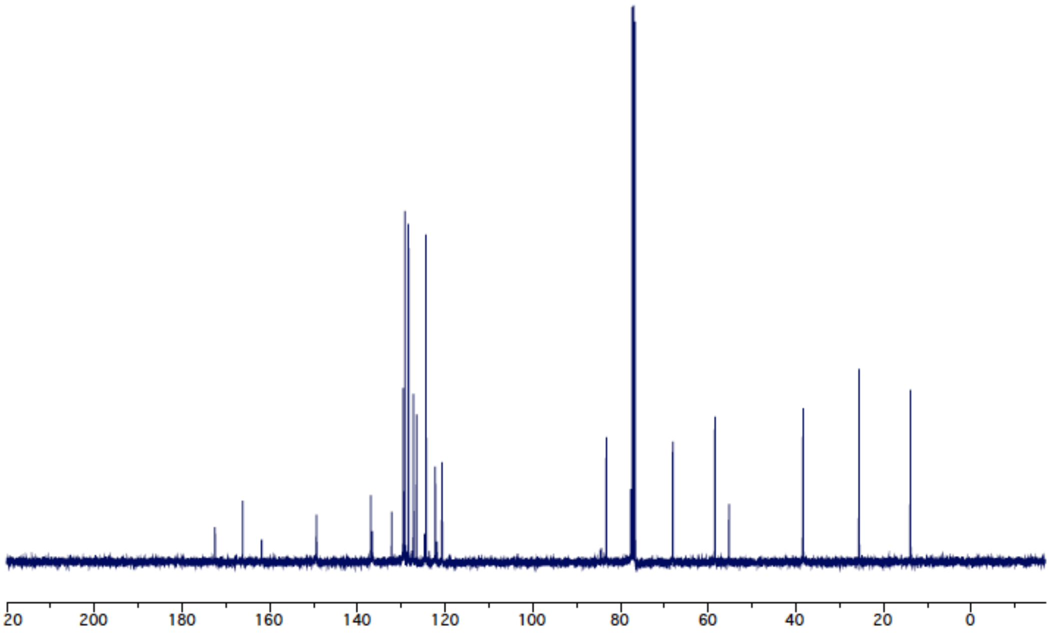
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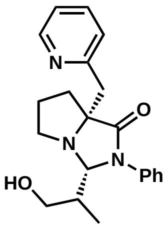
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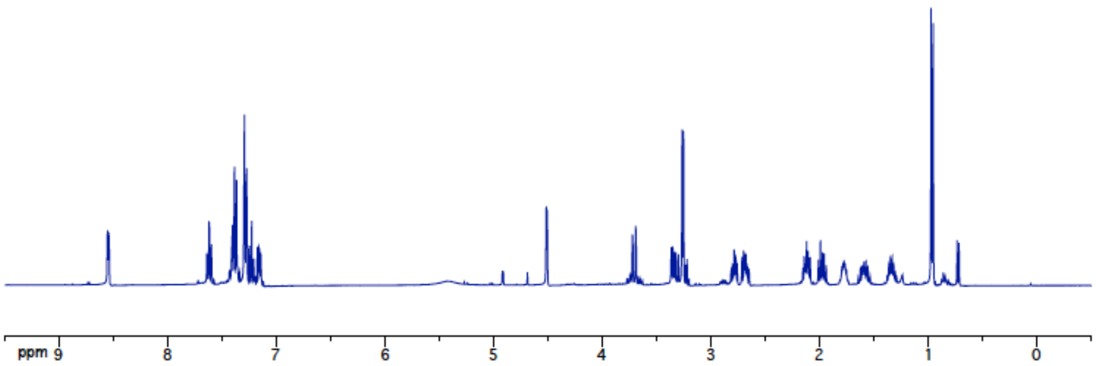
N
N
Ph
HO

137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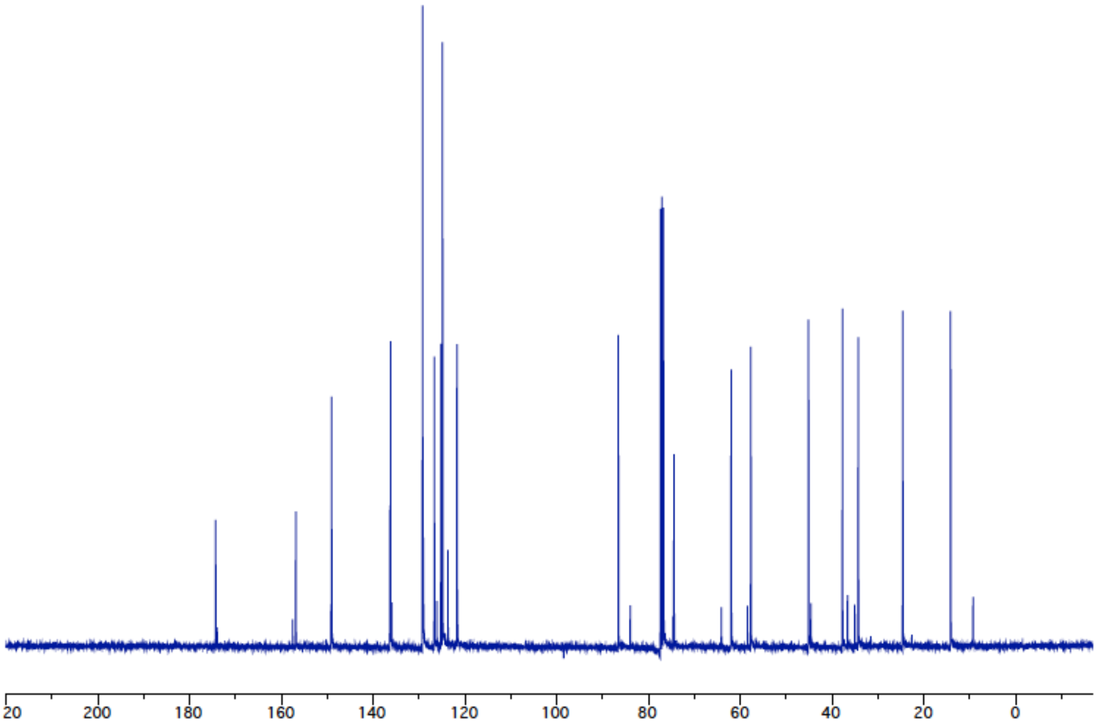
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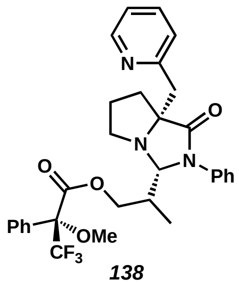
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N
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Ph
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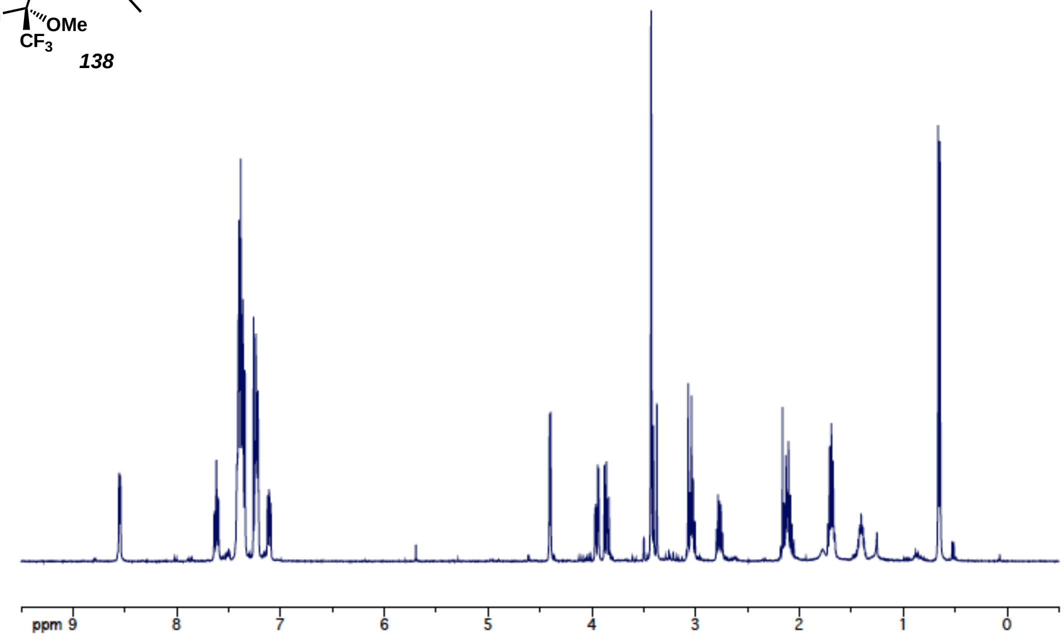
CF3

138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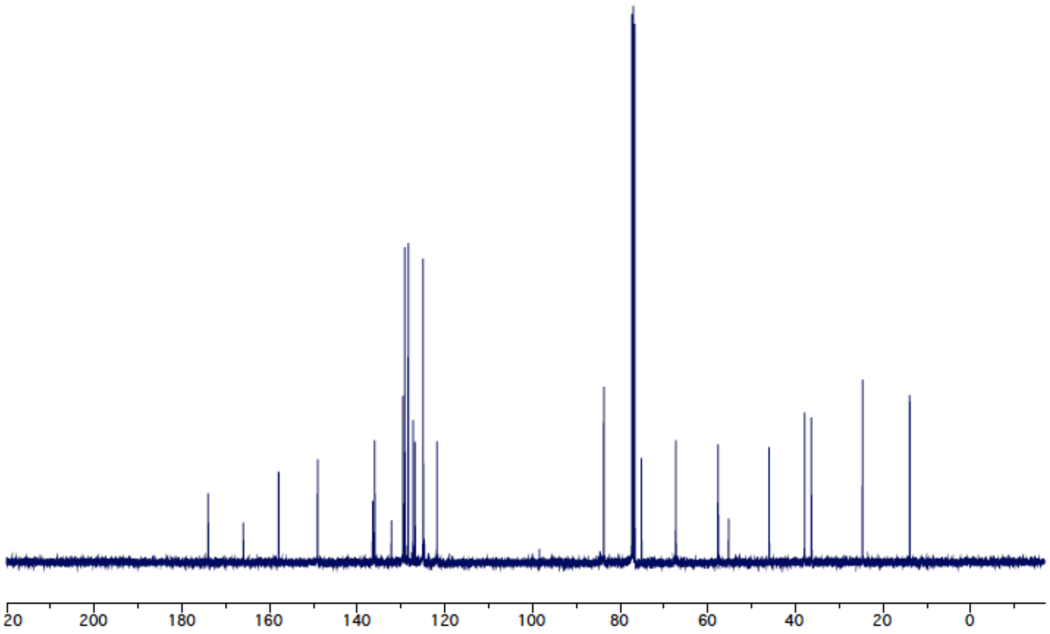
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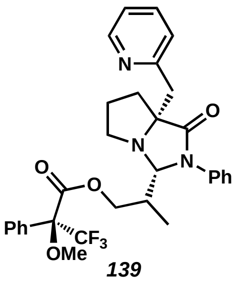
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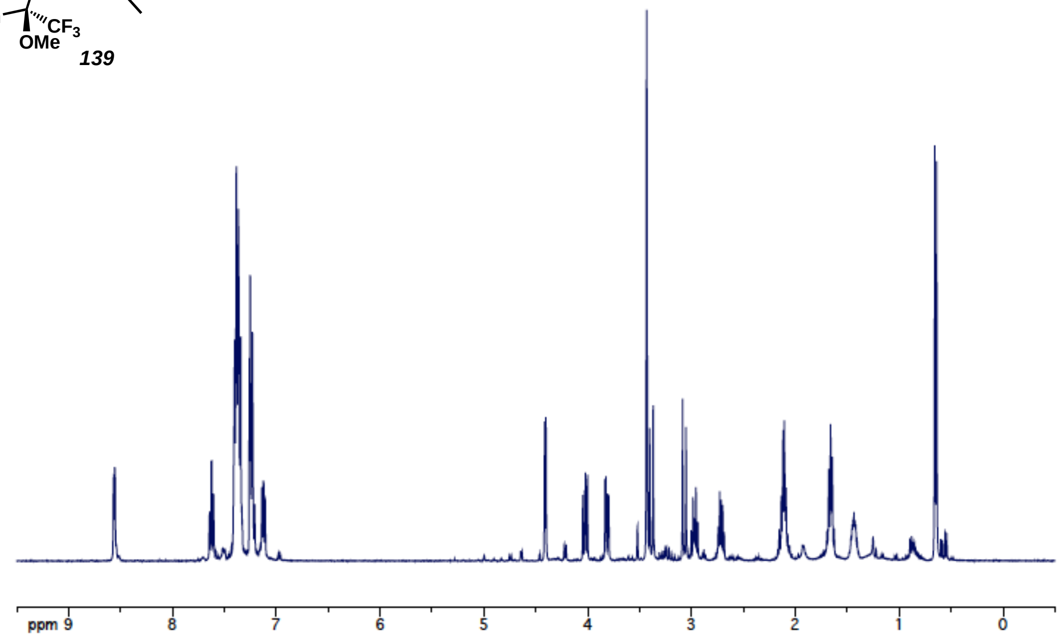
Ph
O
O
Ph
CF3
OMe

139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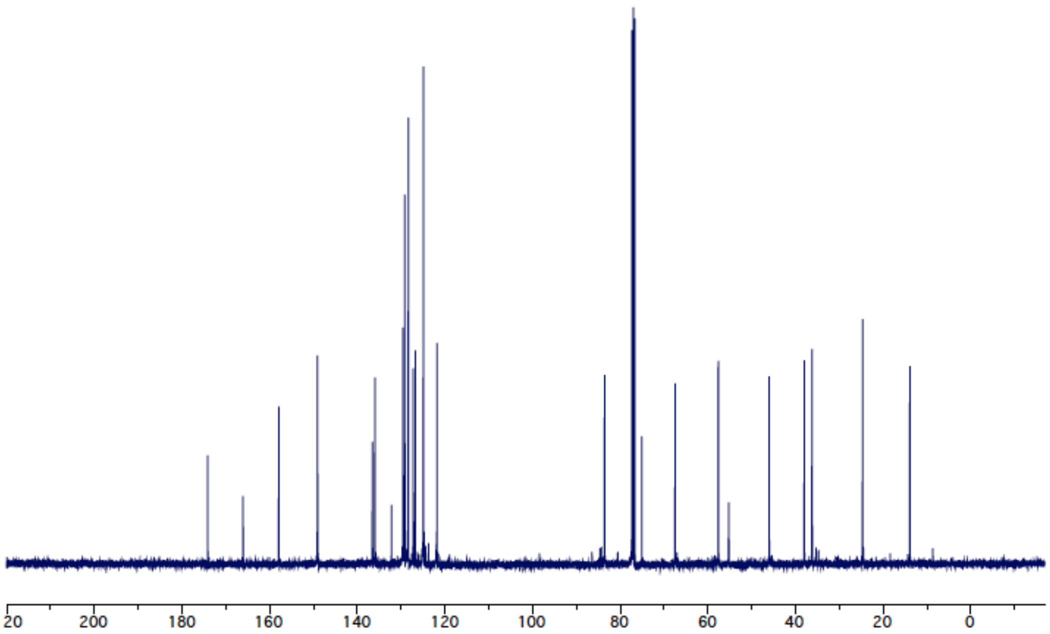
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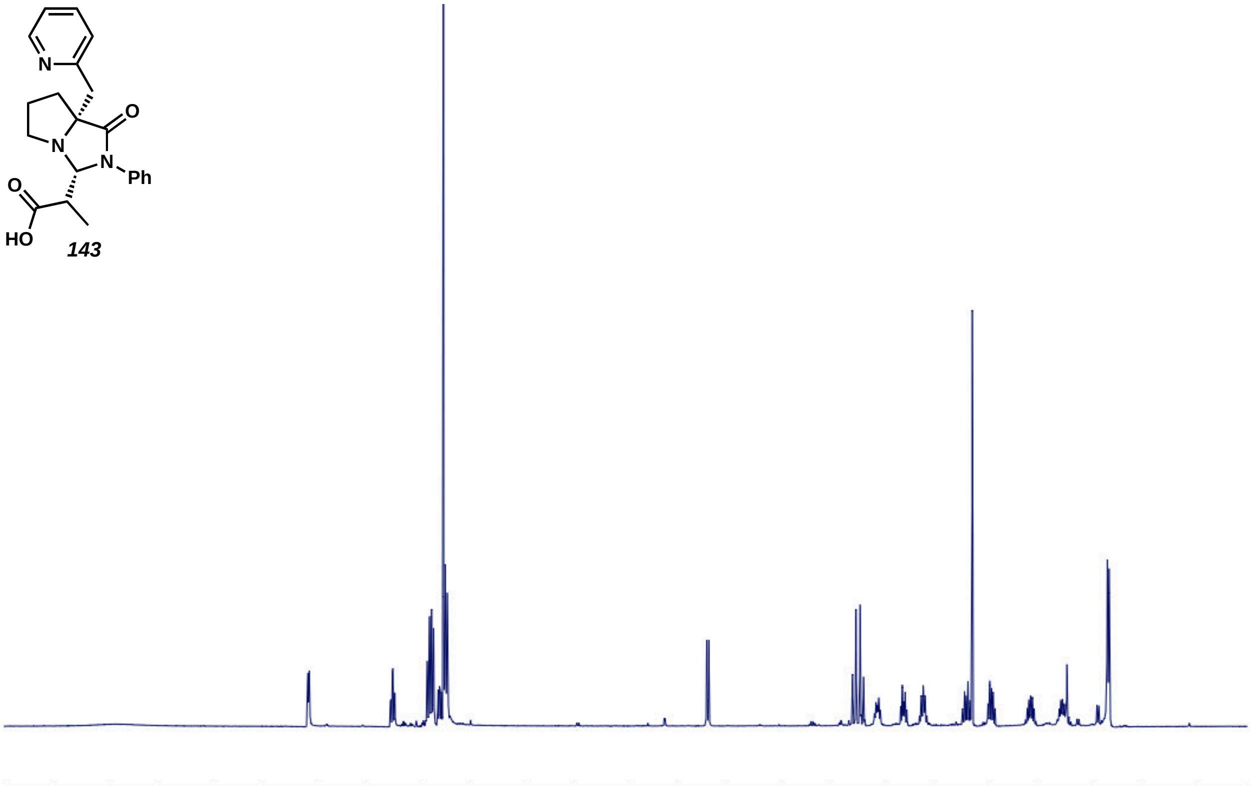
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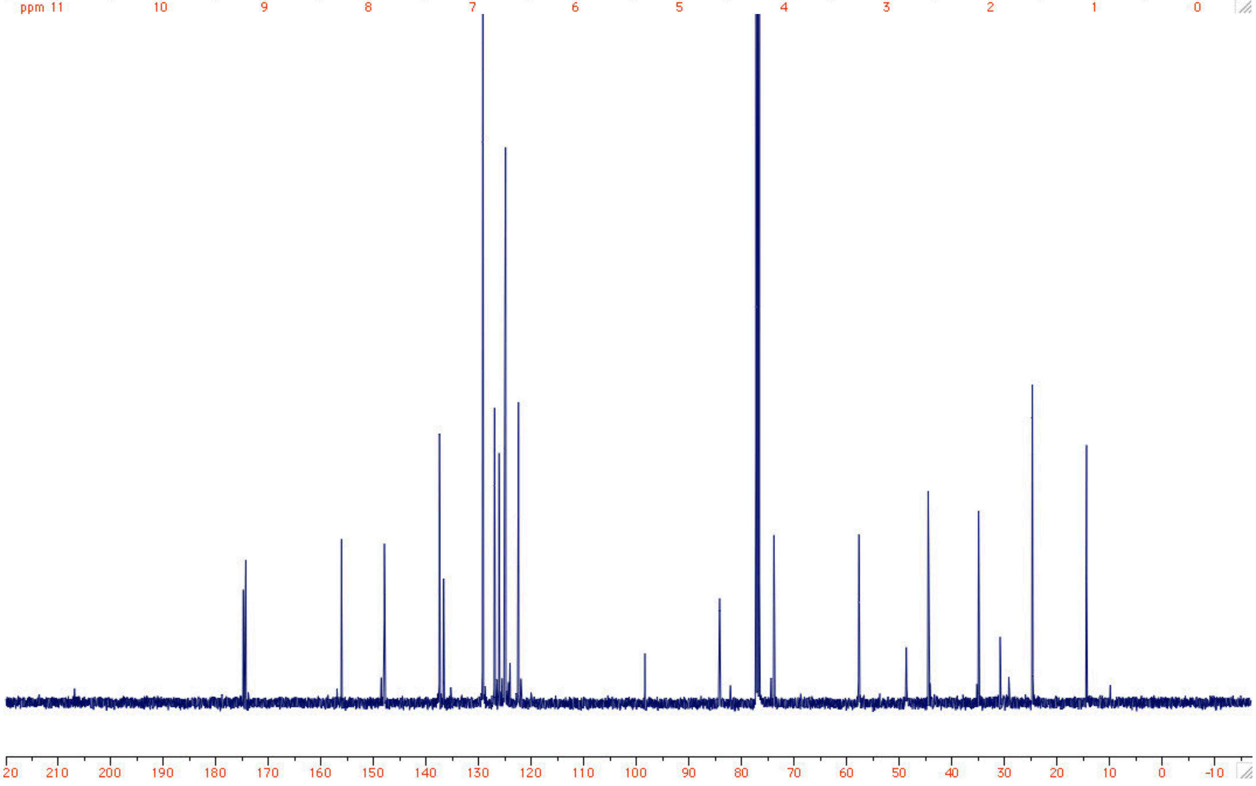
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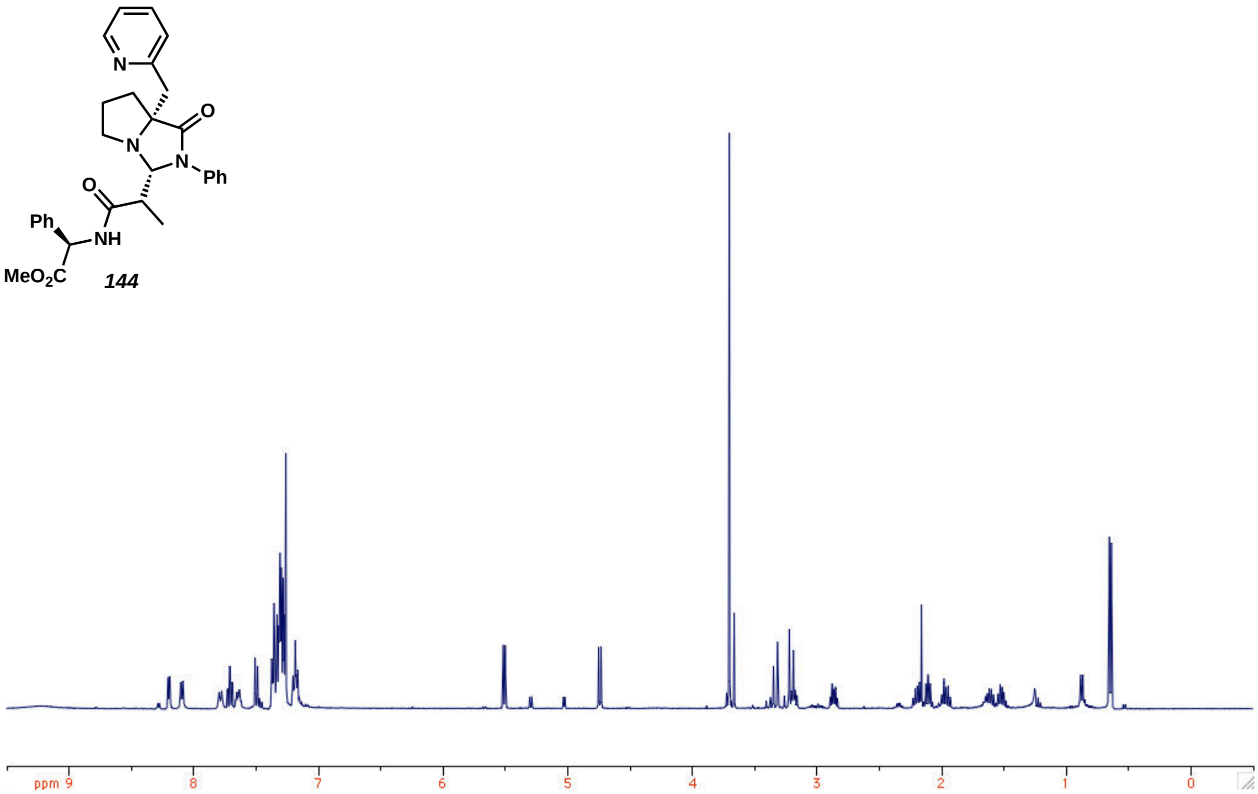
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NH
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144

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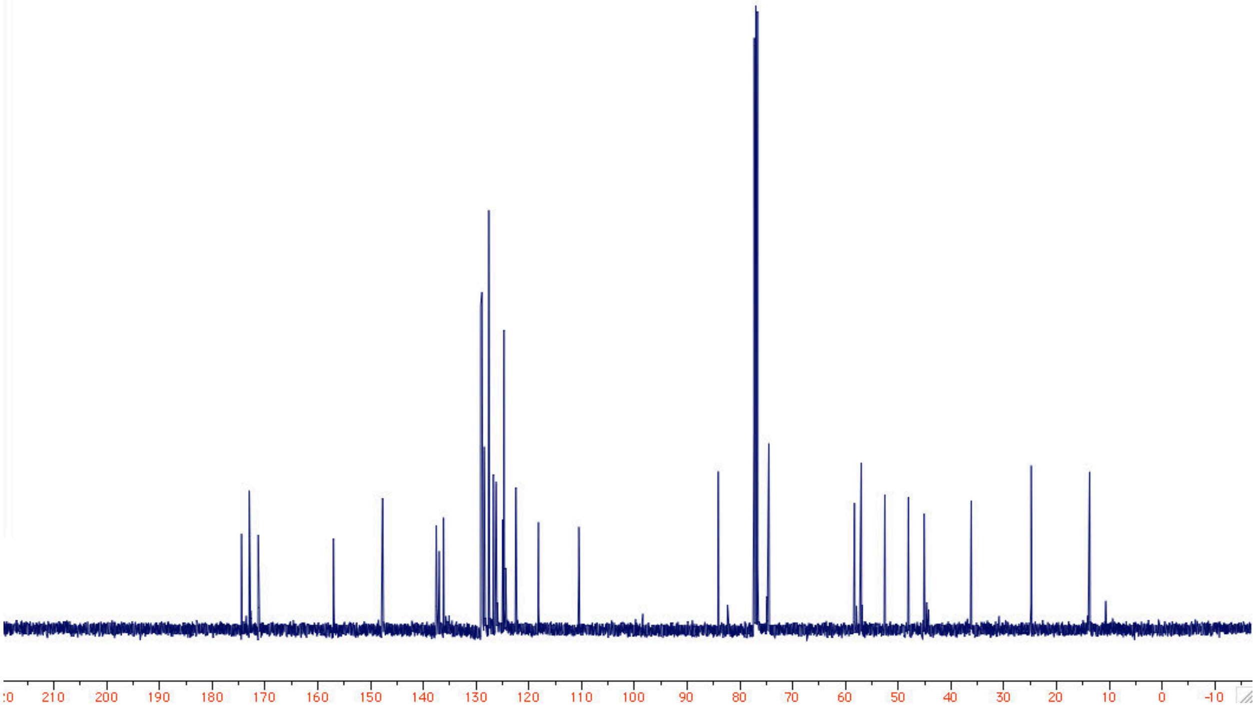
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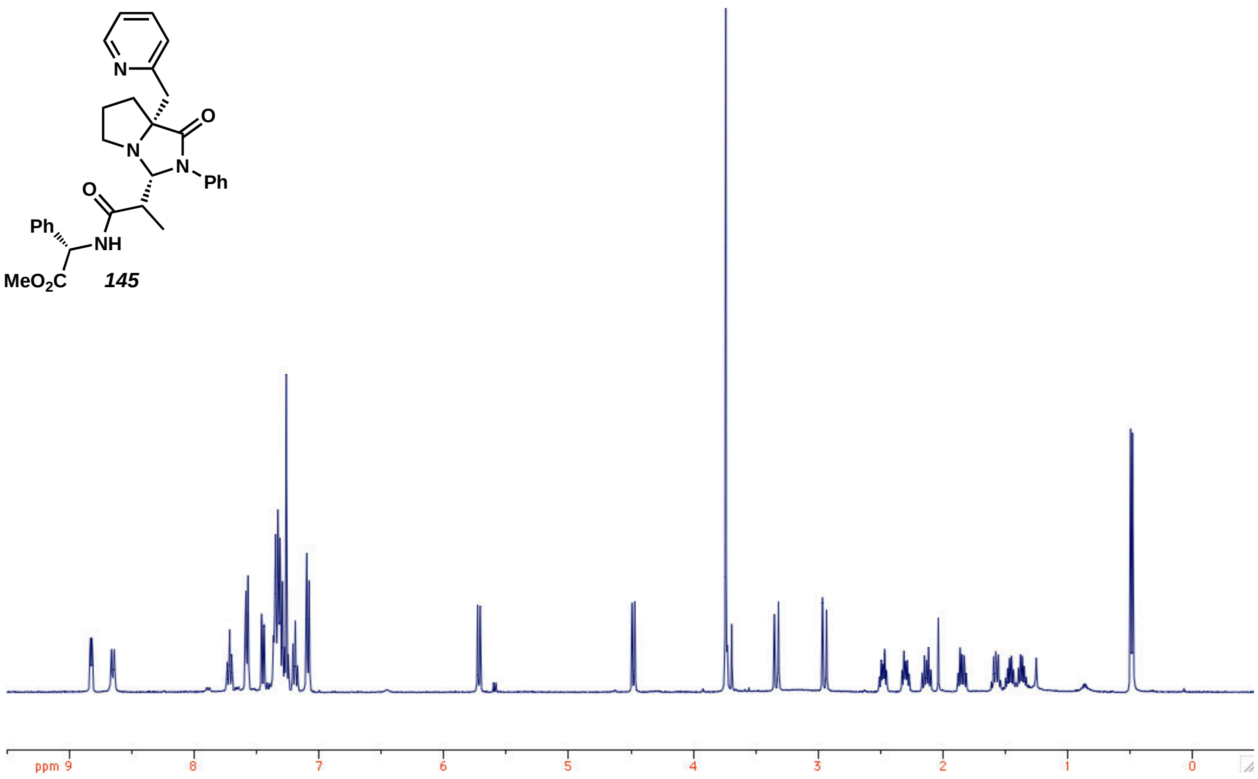

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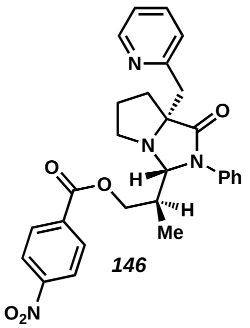
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H
H
Me
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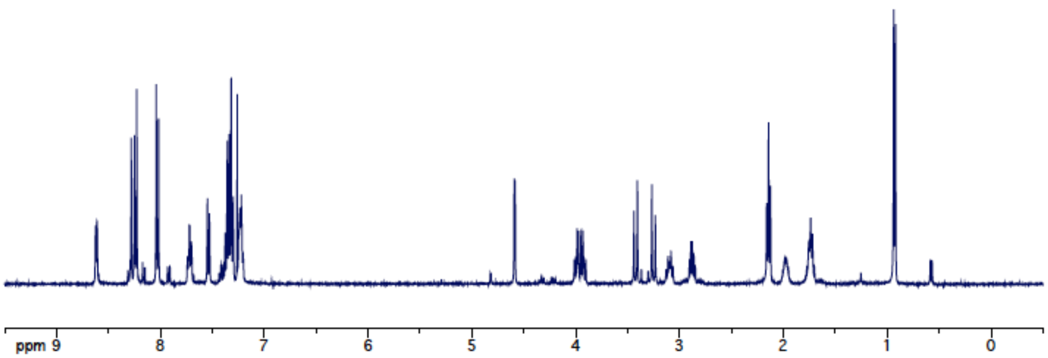
O
O₂N

146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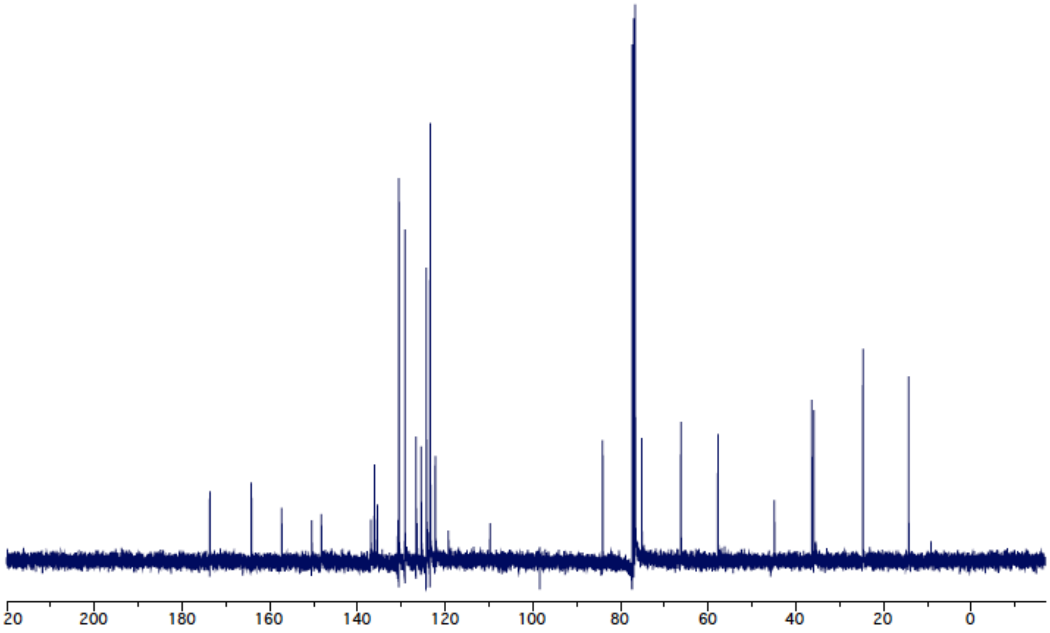
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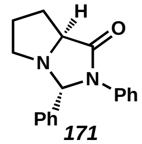
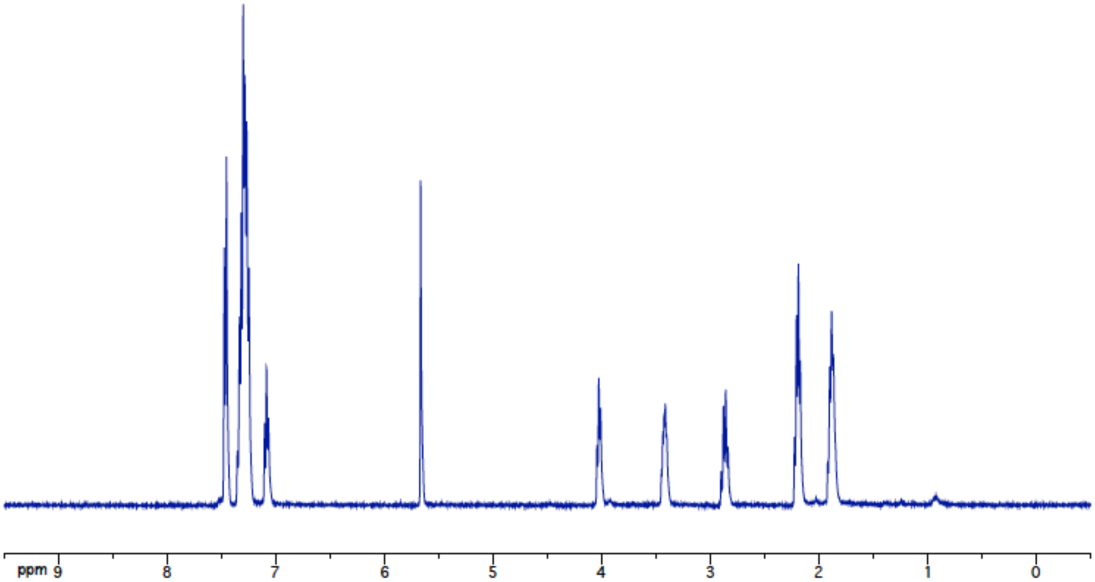

H
O
N
N
Ph
Ph

171


ppm
9
8
7
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5
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3
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1
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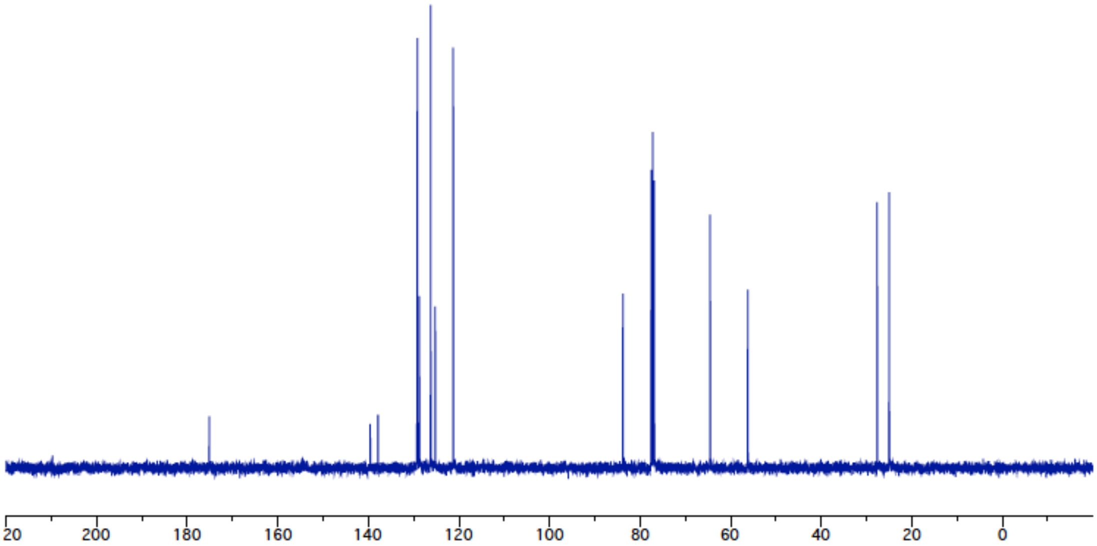
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200
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60
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20
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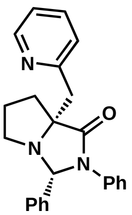
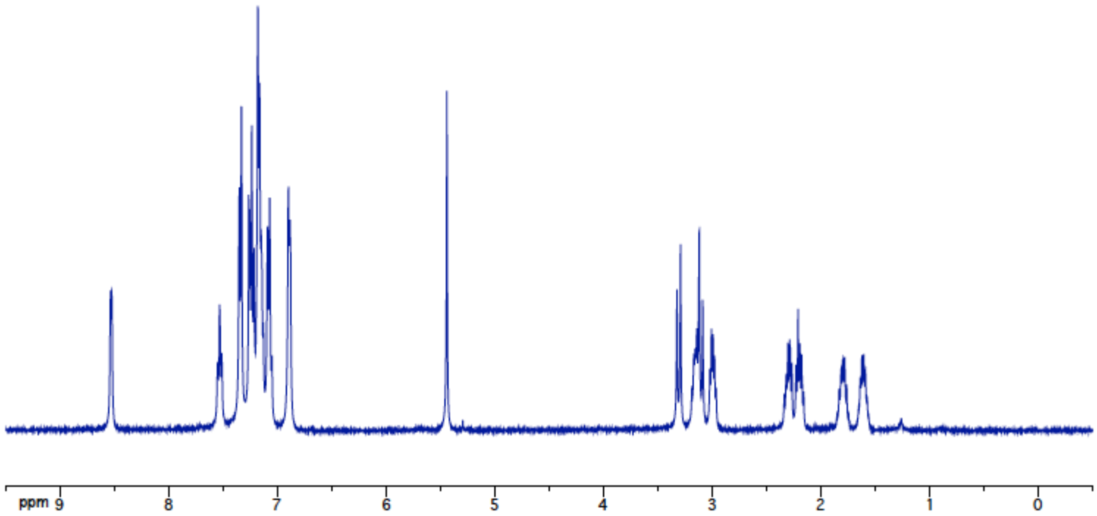

N
O
N
N
Ph
Ph

172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3
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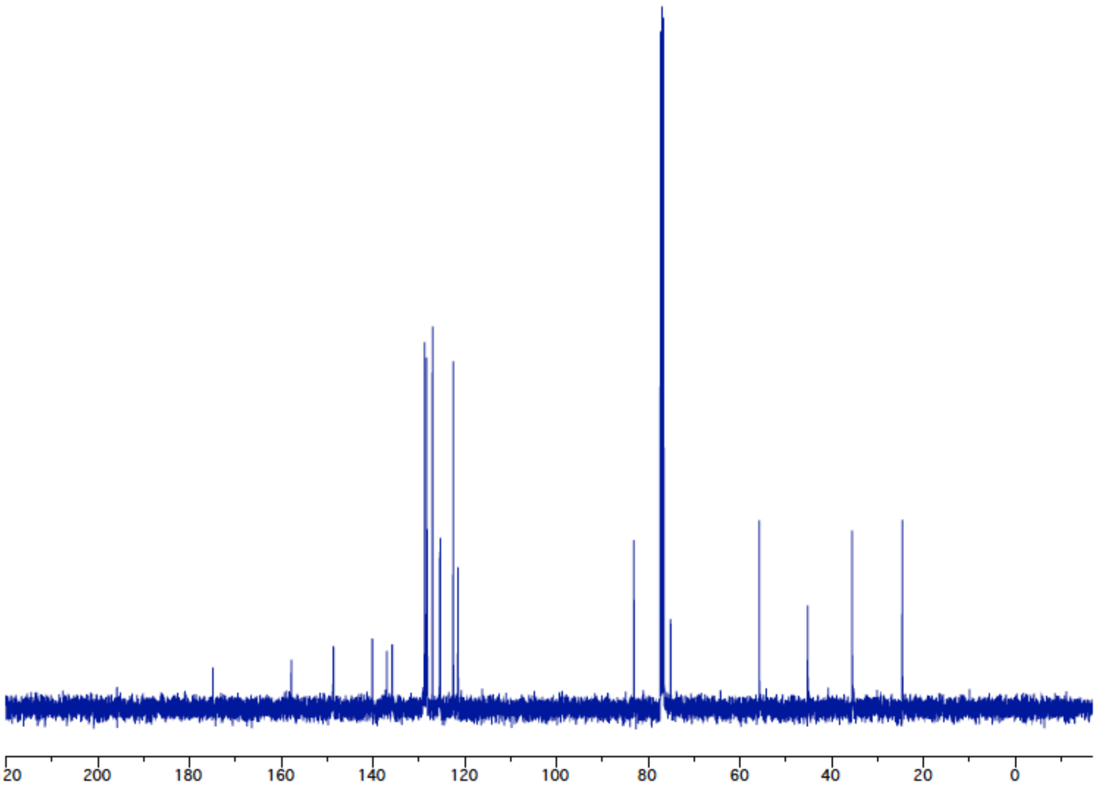
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200
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140
120
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80
60
40
20
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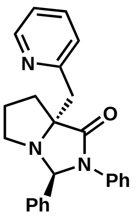
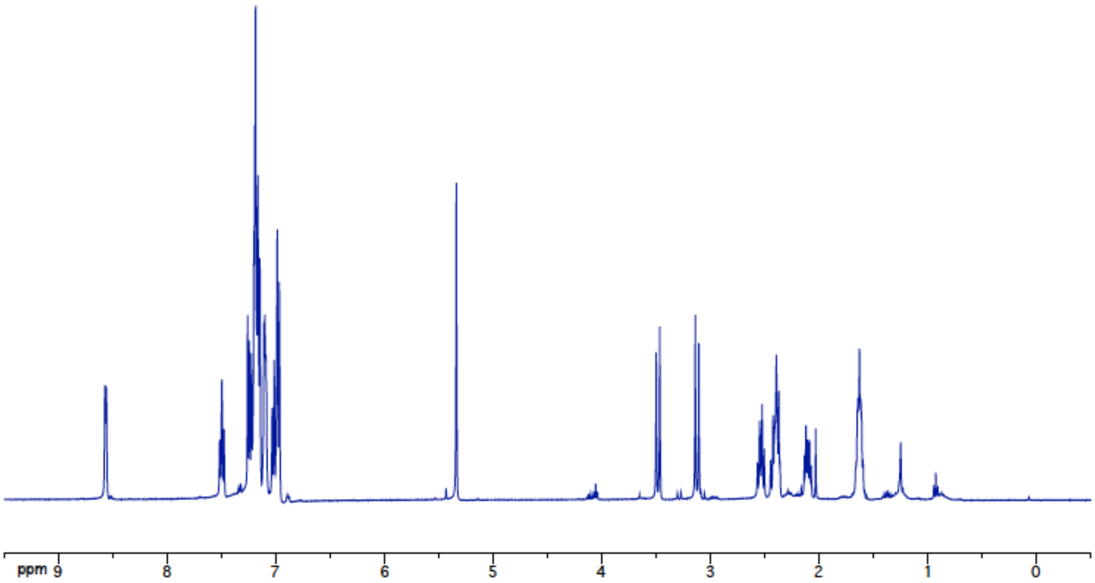

N
O
N
N
Ph
Ph

172b


ppm 9
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7
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3
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1
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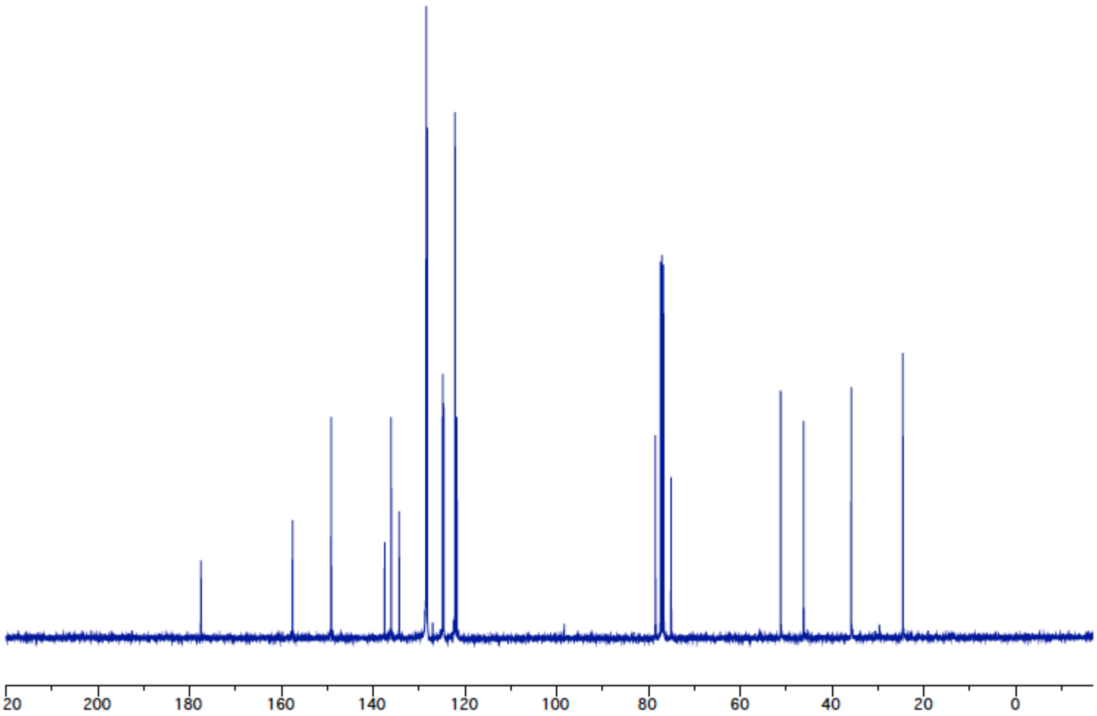
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200
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140
120
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80
60
40
20
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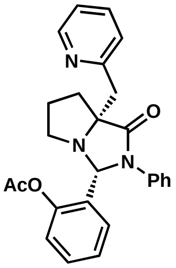
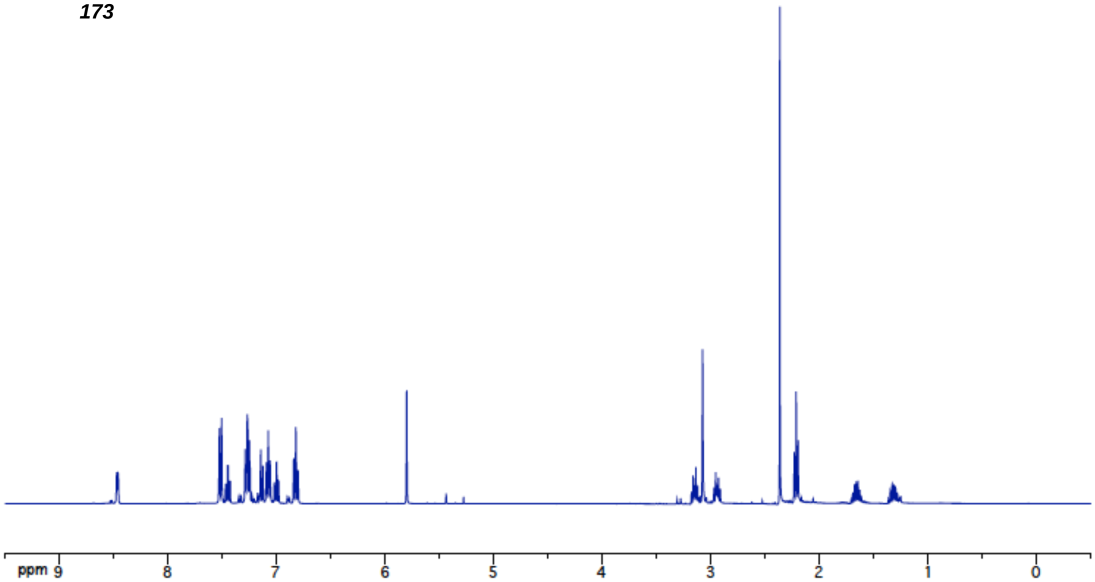

N
O
N
N
Ph
AcO

173


ppm 9
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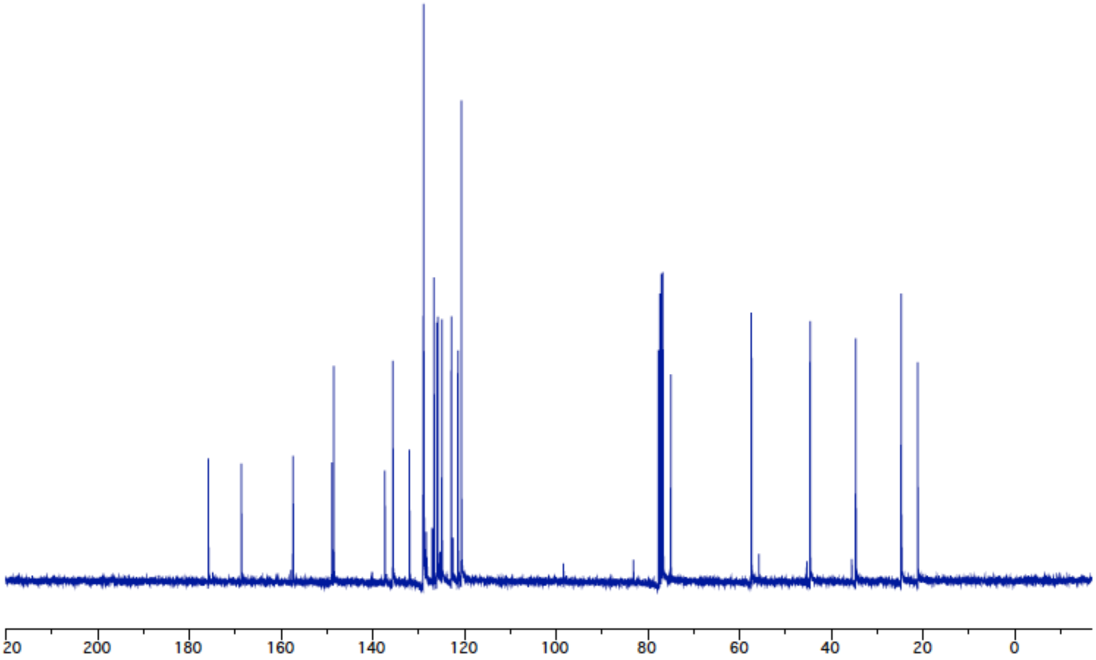
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140
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60
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20
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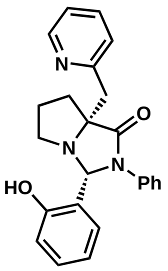
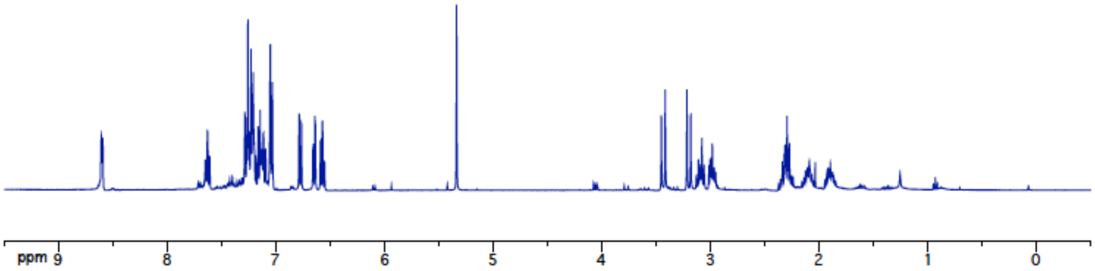

N
O
N
N
Ph
HO

174


ppm
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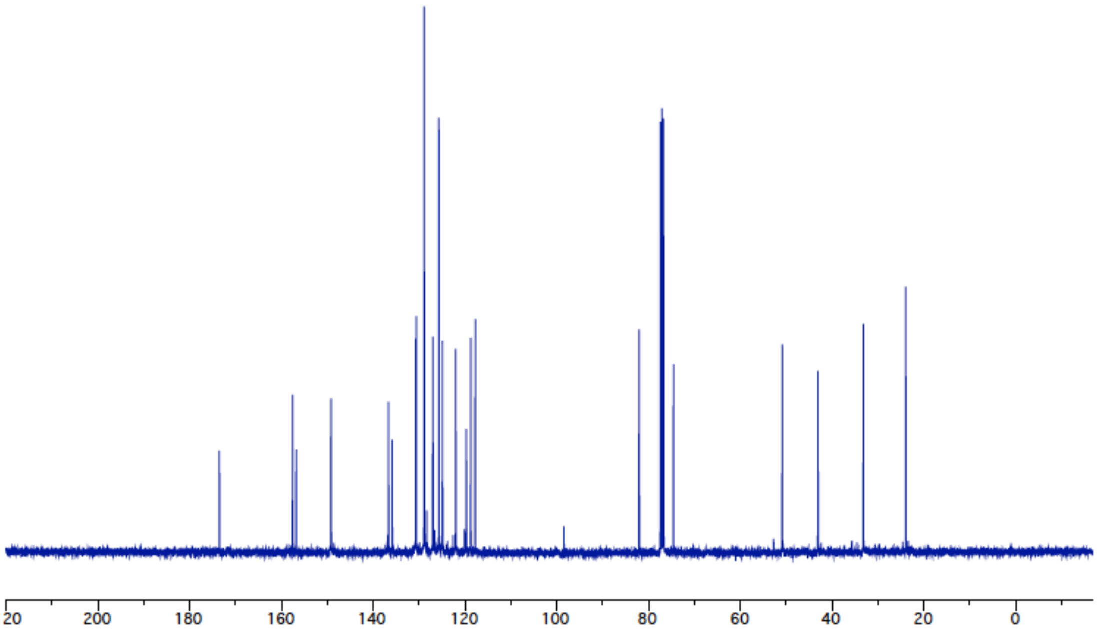
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140
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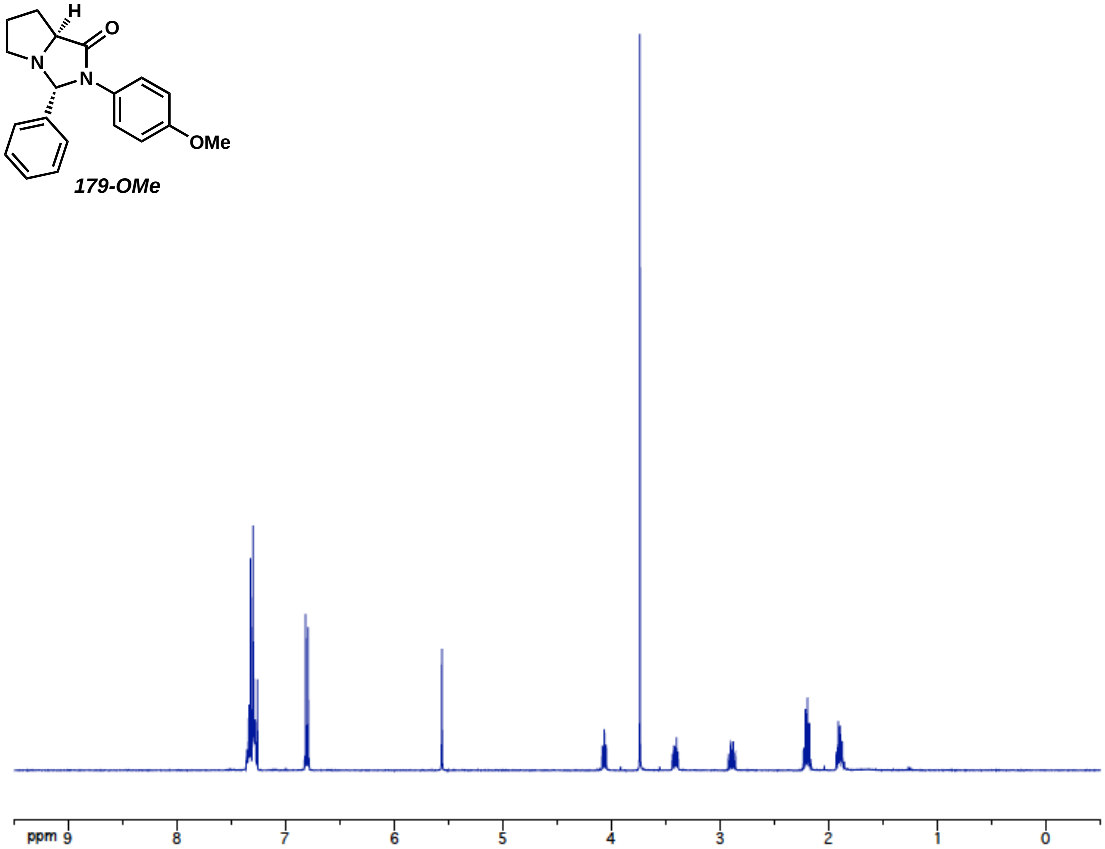
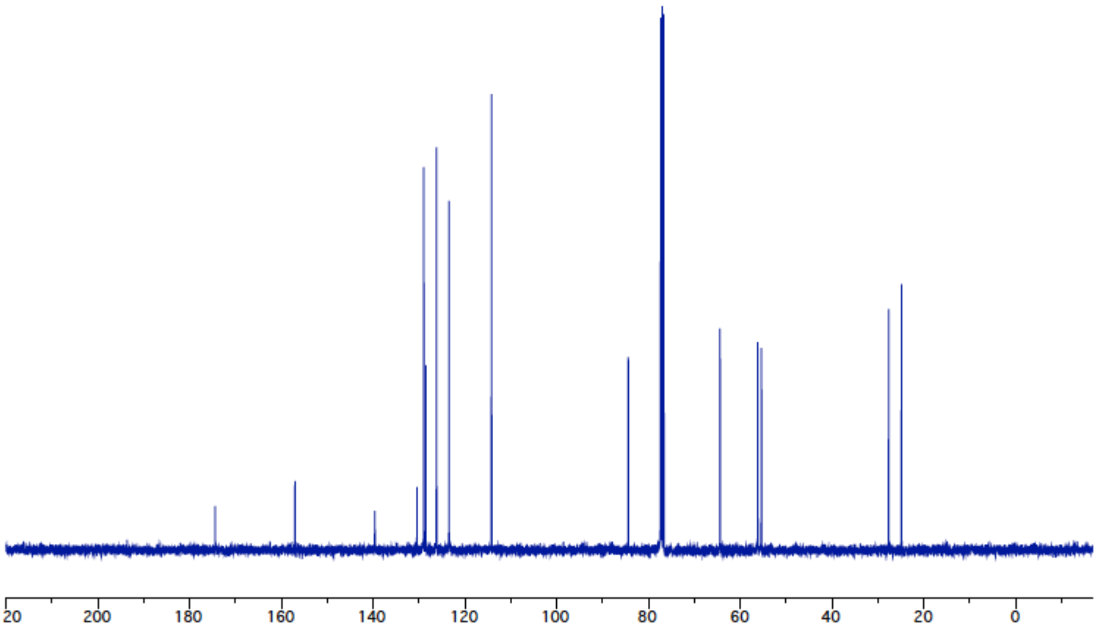
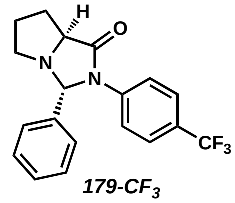
20
0

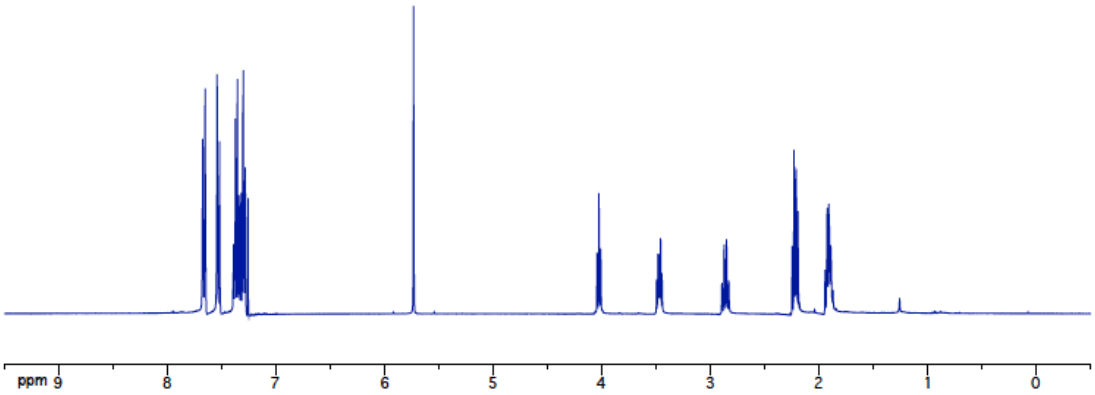


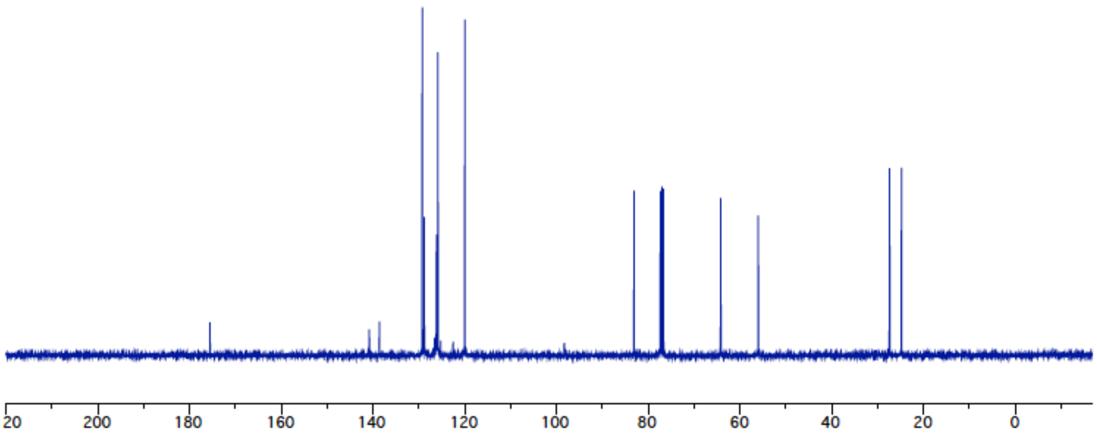
179-OMe

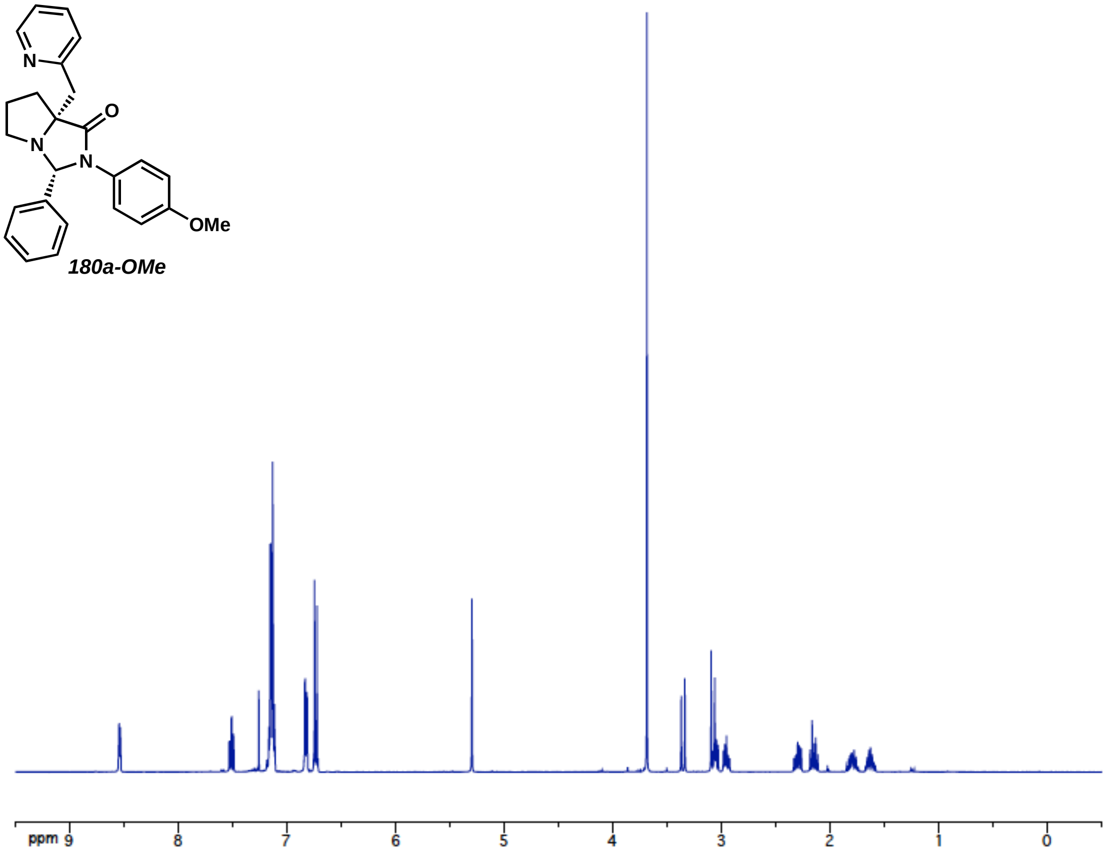




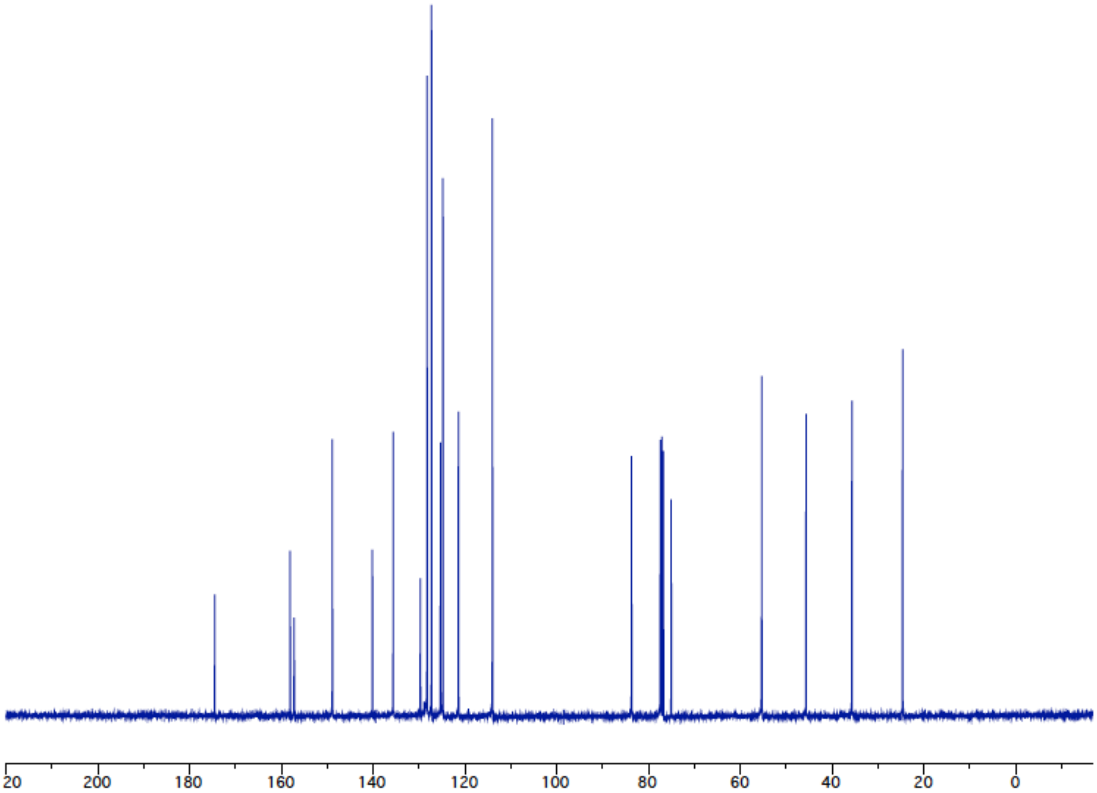
179-CF$_3$

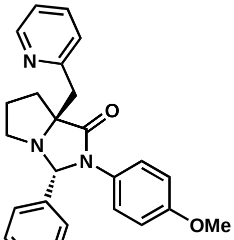




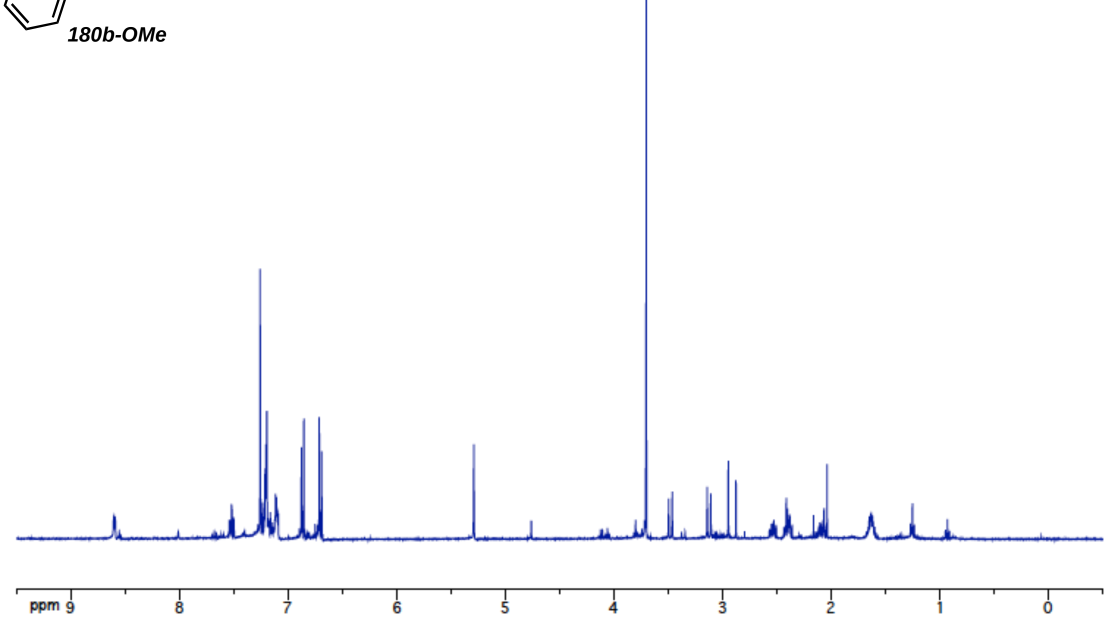


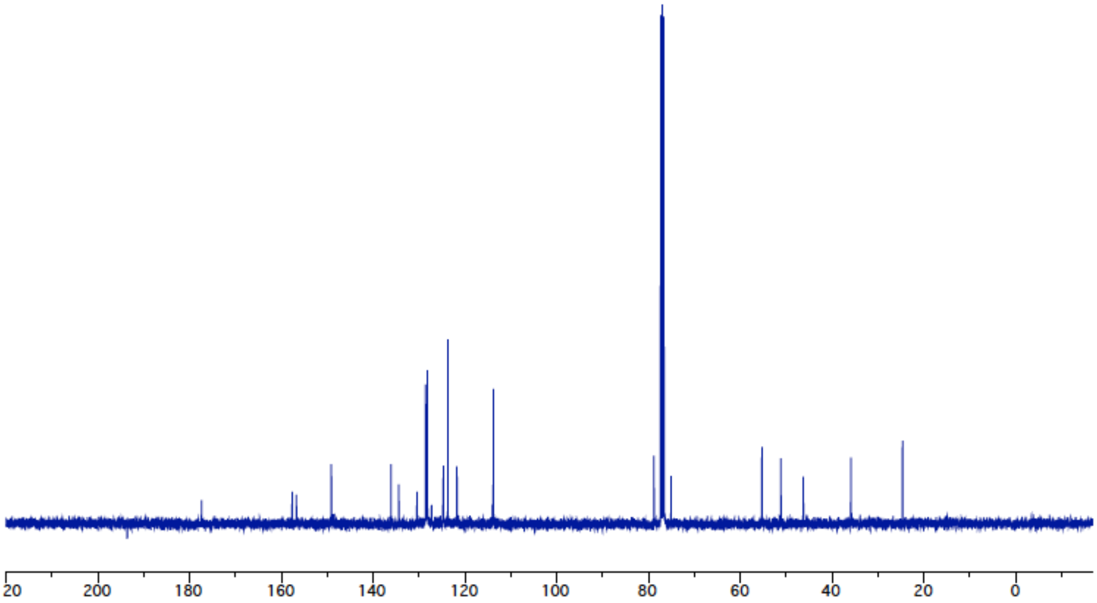
180a-OMe

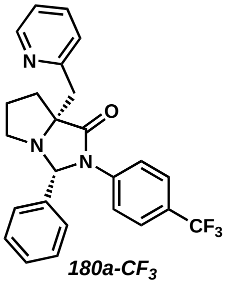




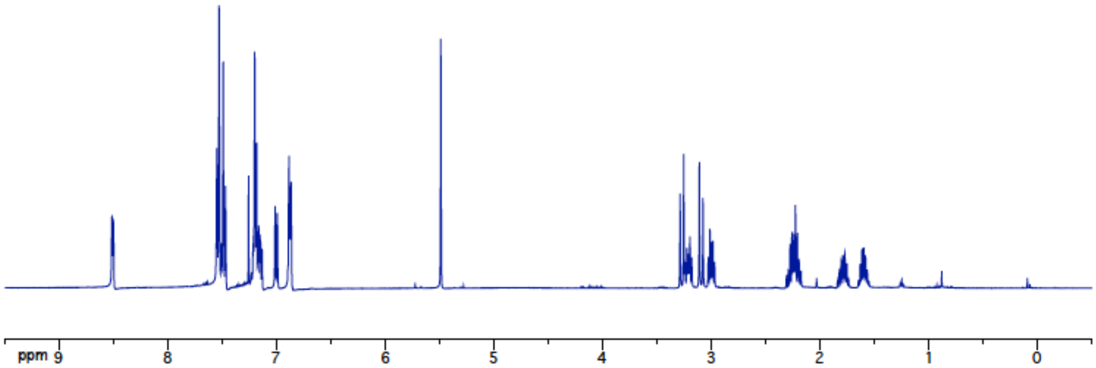
180b-OMe

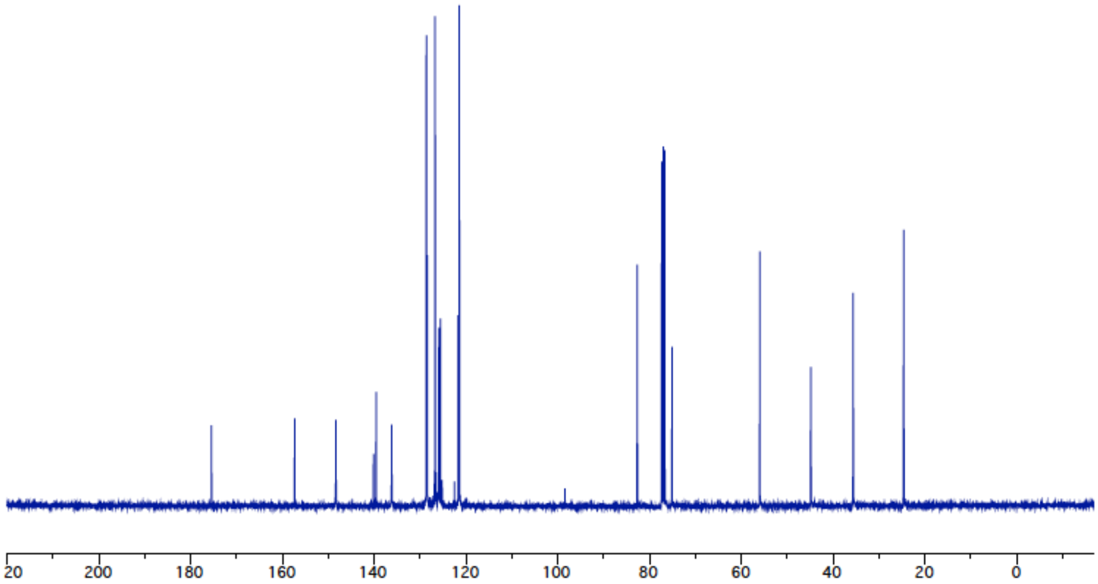


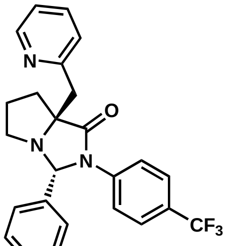




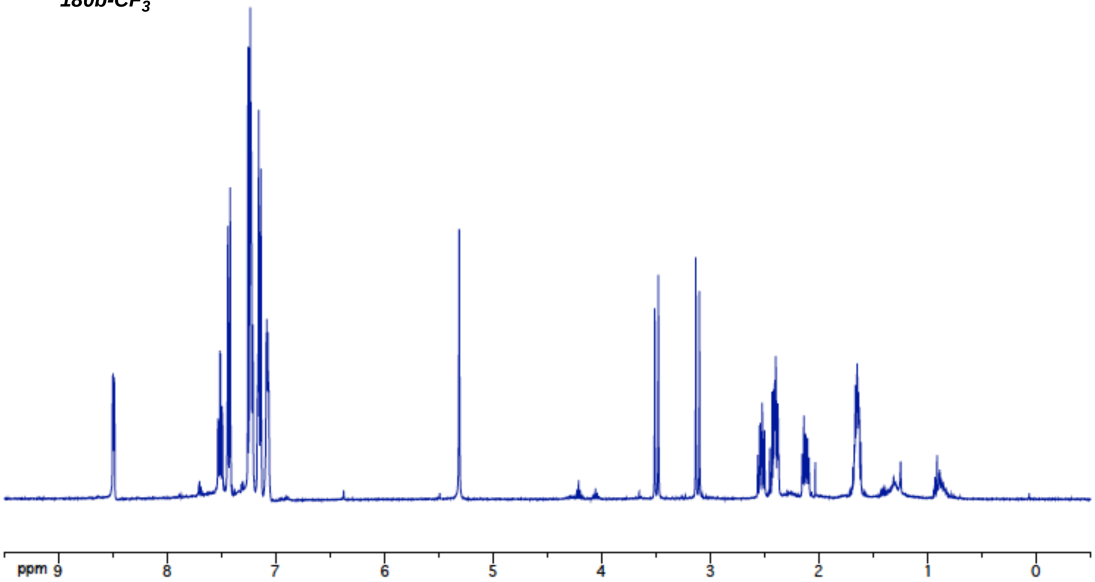
180a-CF$_3$

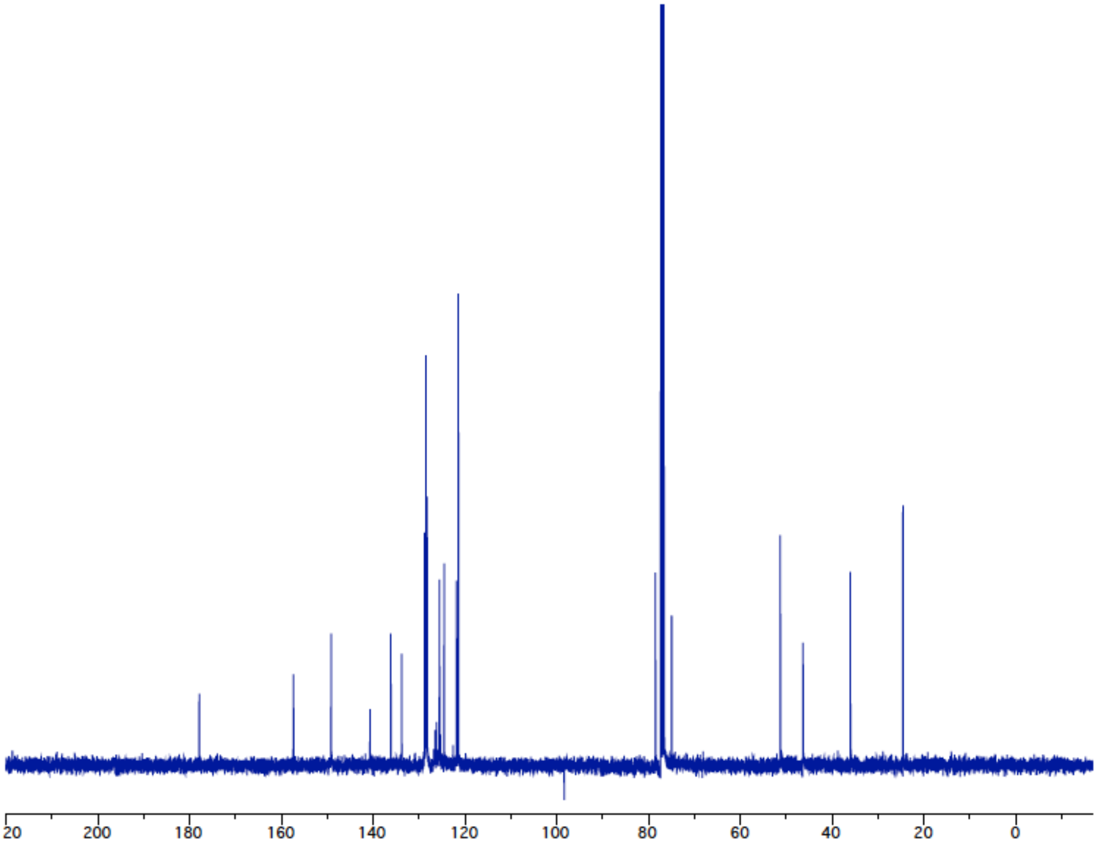


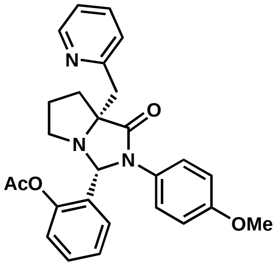




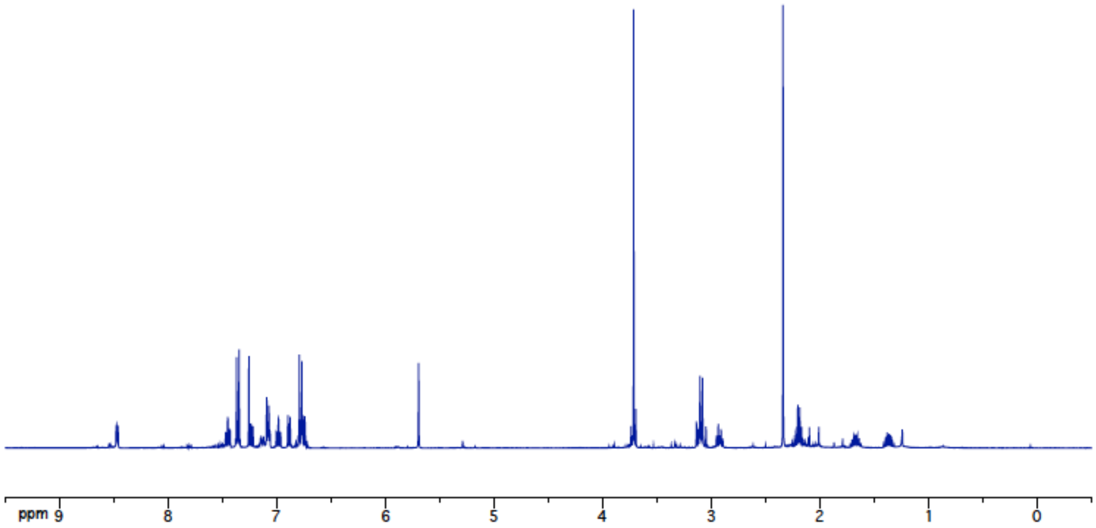
180b-CF_3

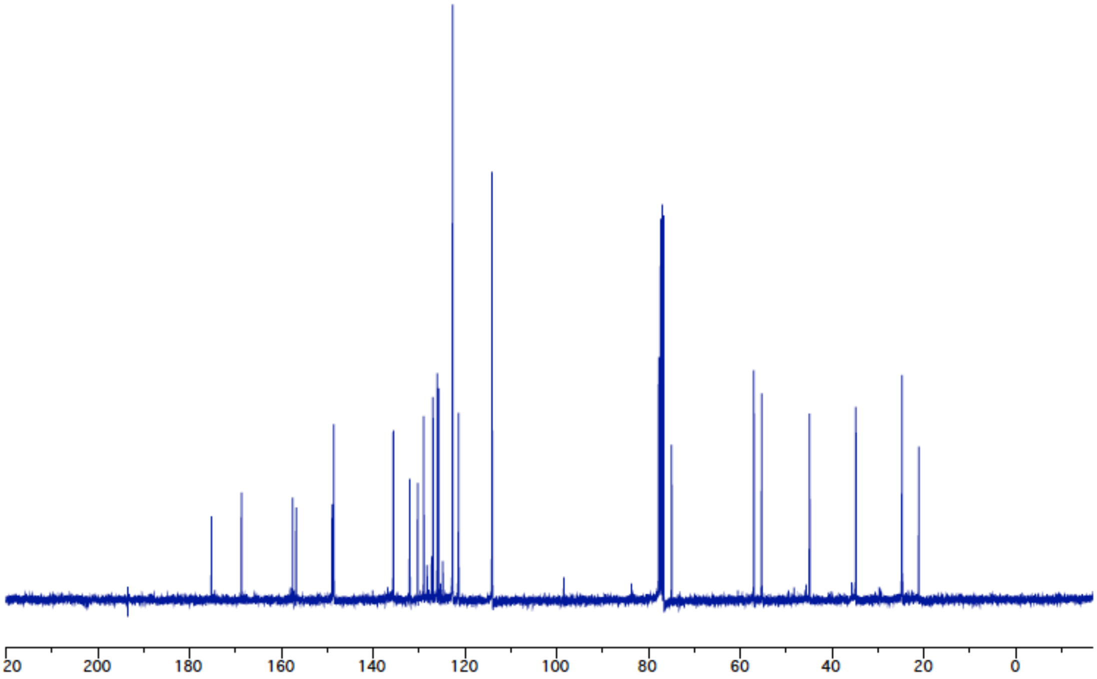


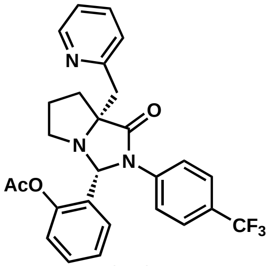



N
O
N
N
AcO
OMe

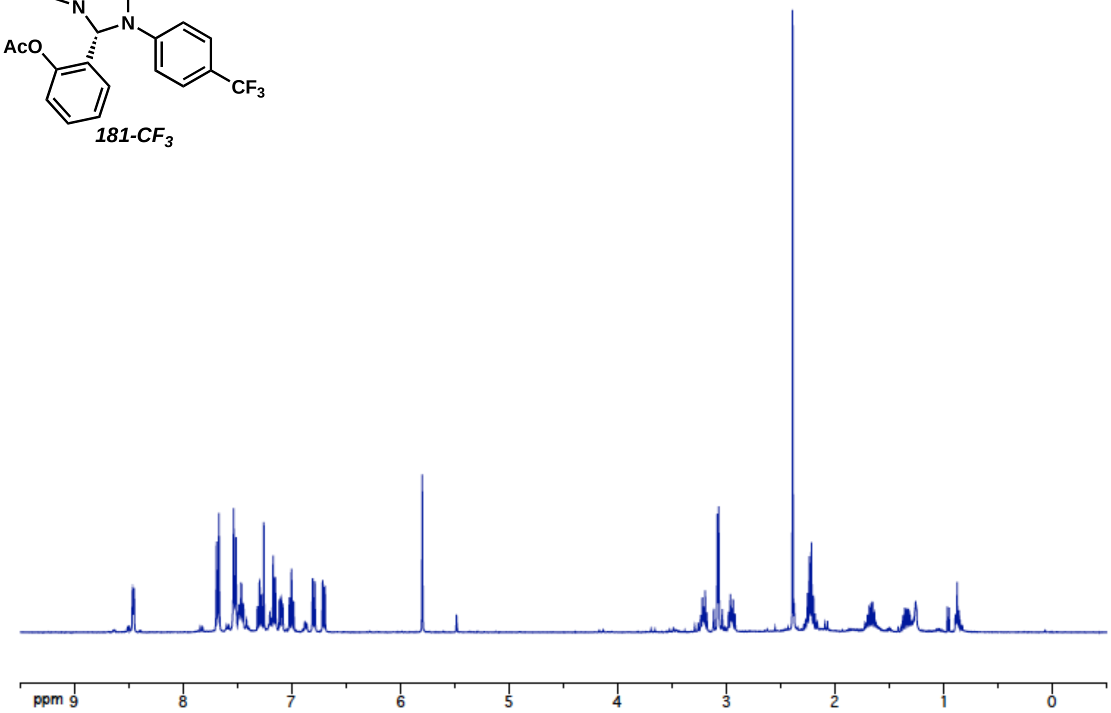
181-OMe

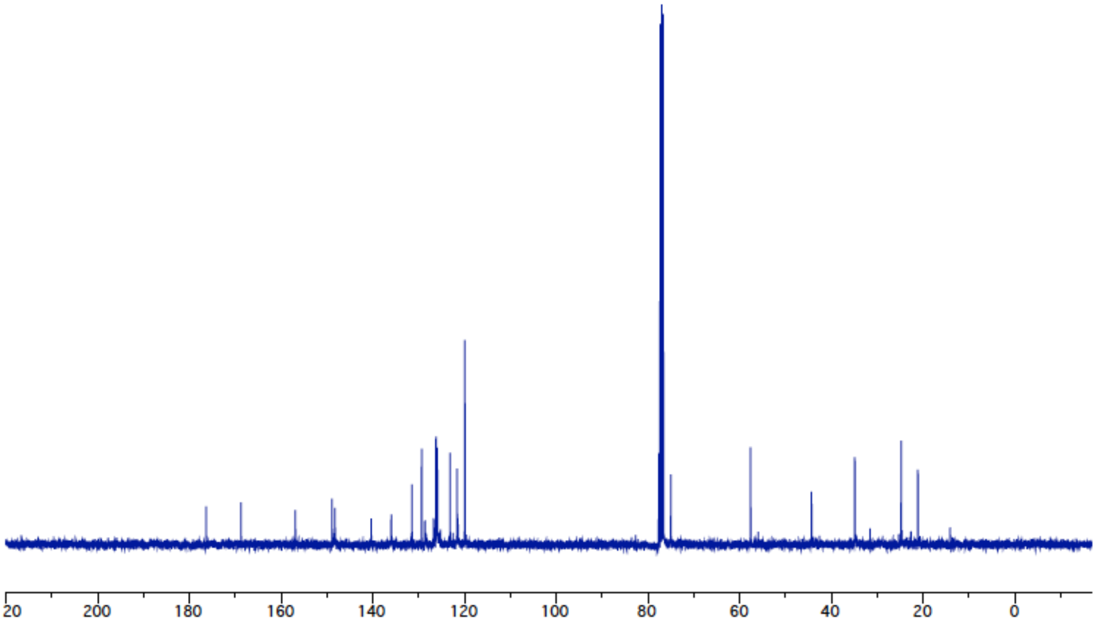

ppm 9
8
7
6
5
4
3
2
1
0

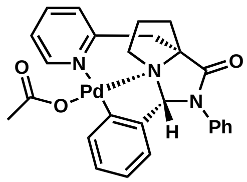

20
200
180
160
140
120
100
80
60
40
20
0


N
O
N
N
AcO
CF3

181-CF$_3$

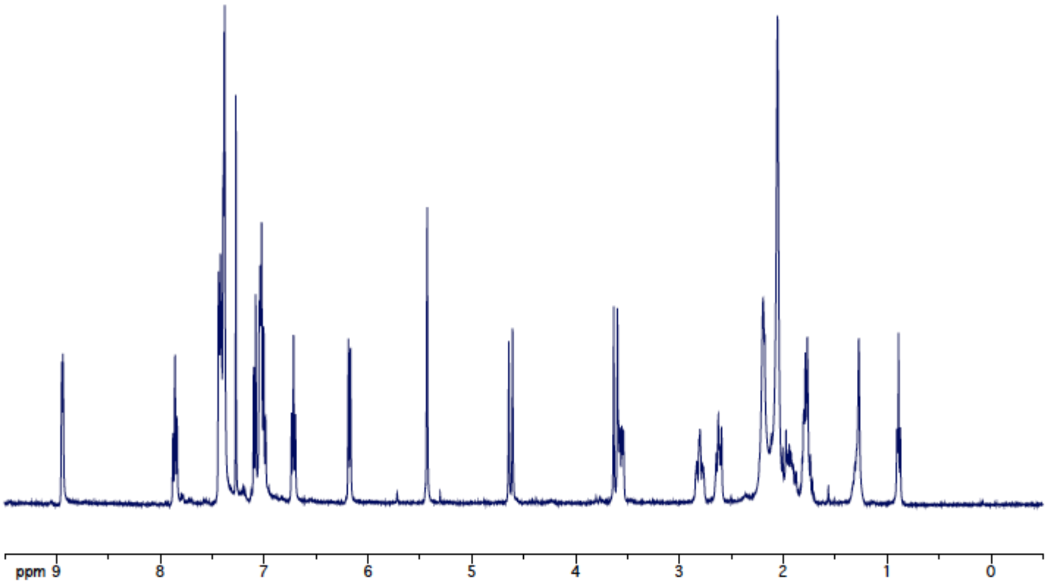

ppm 9
8
7
6
5
4
3
2
1
0


20
200
180
160
140
120
100
80
60
40
20
0

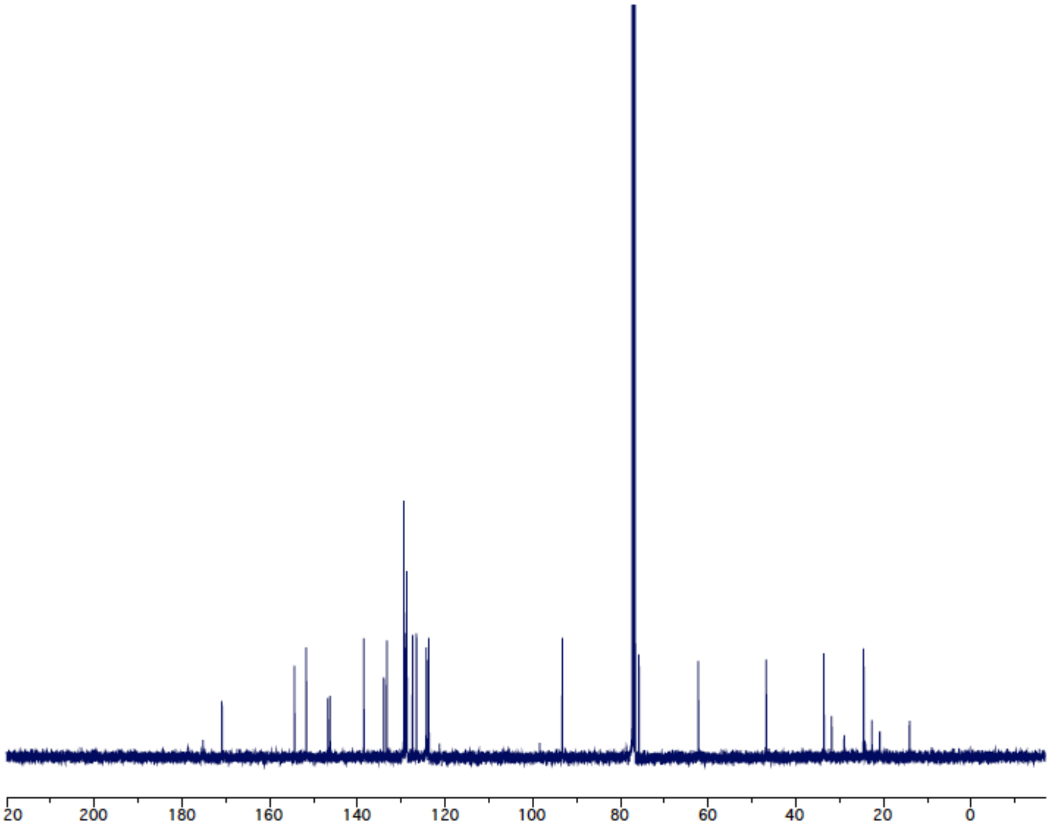


N
O
O
Pd
N
O
N
H
Ph

197



ppm 9
8
7
6
5
4
3
2
1
0



20
200
180
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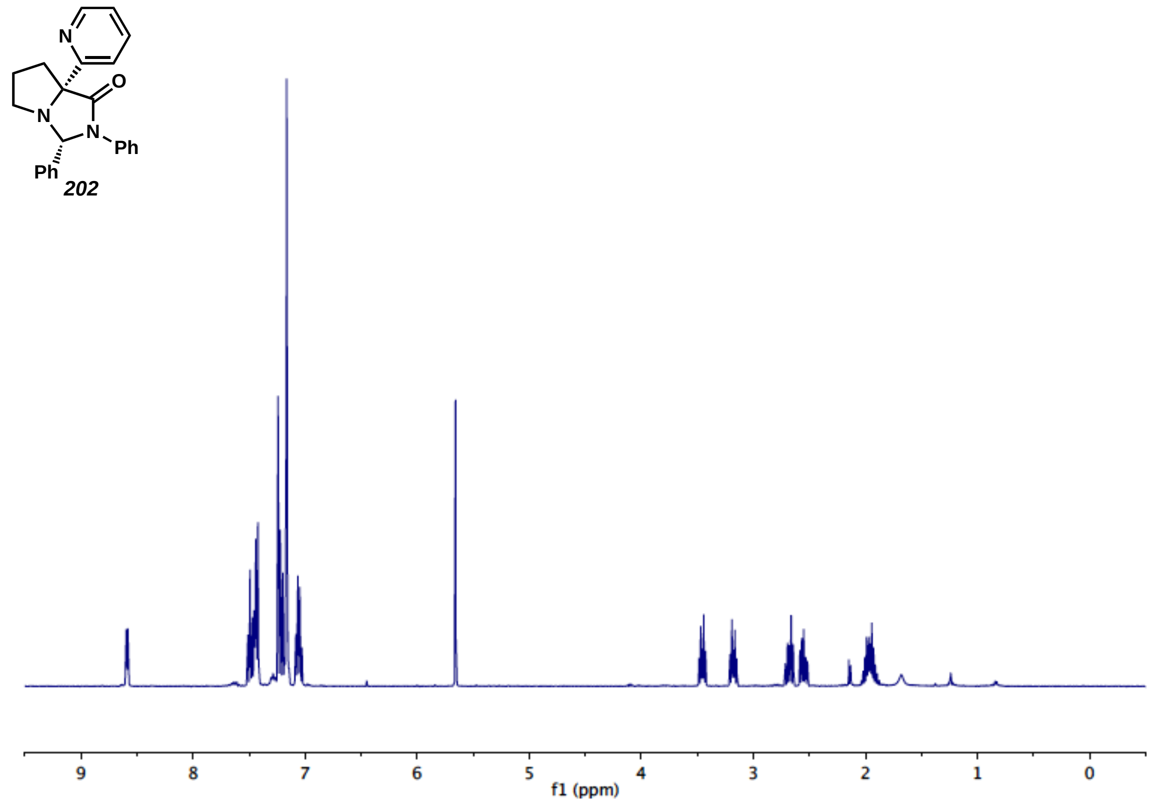
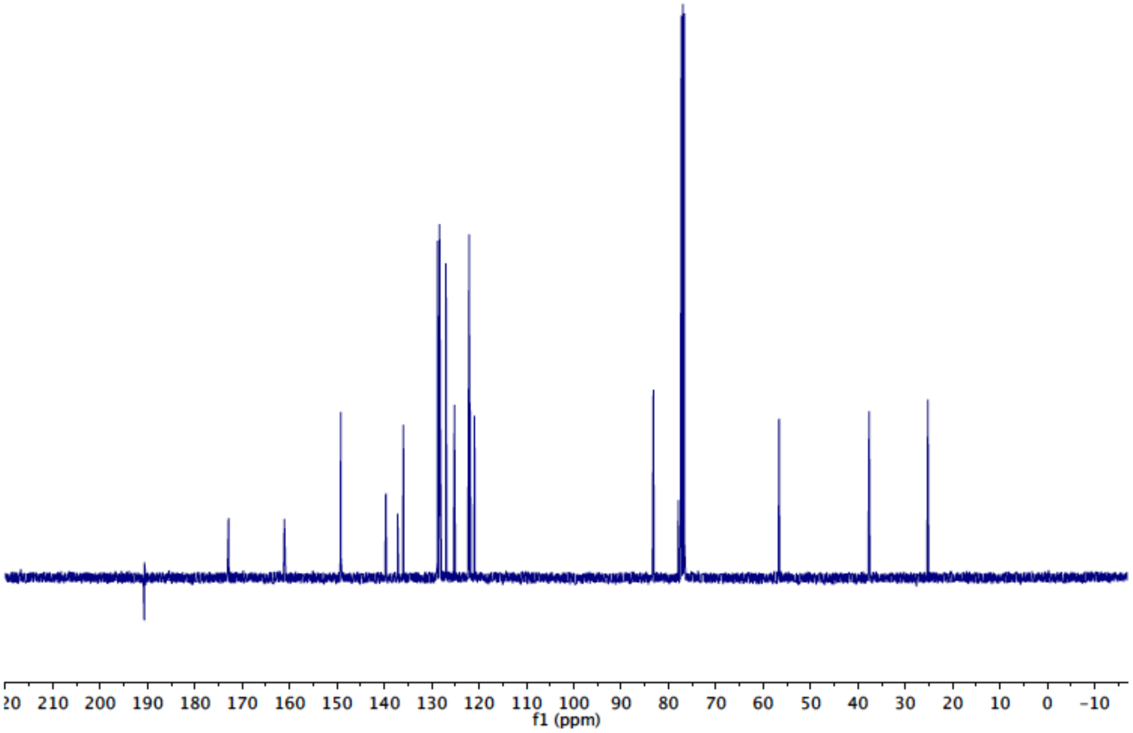
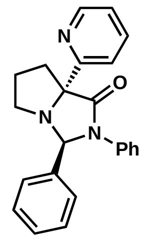
100
80
60
40
20
0


N
O
N
N
Ph
Ph

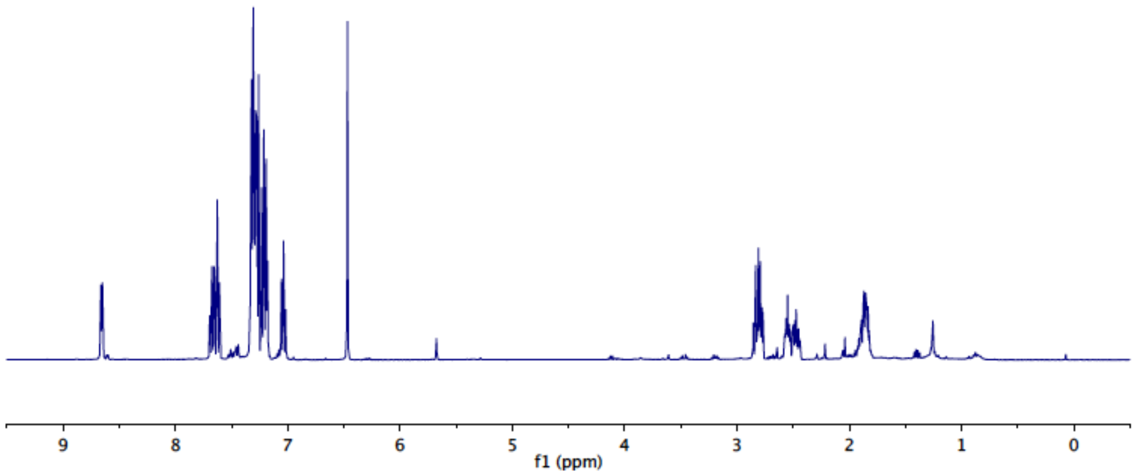
202

9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O
N
N
Ph

203


9
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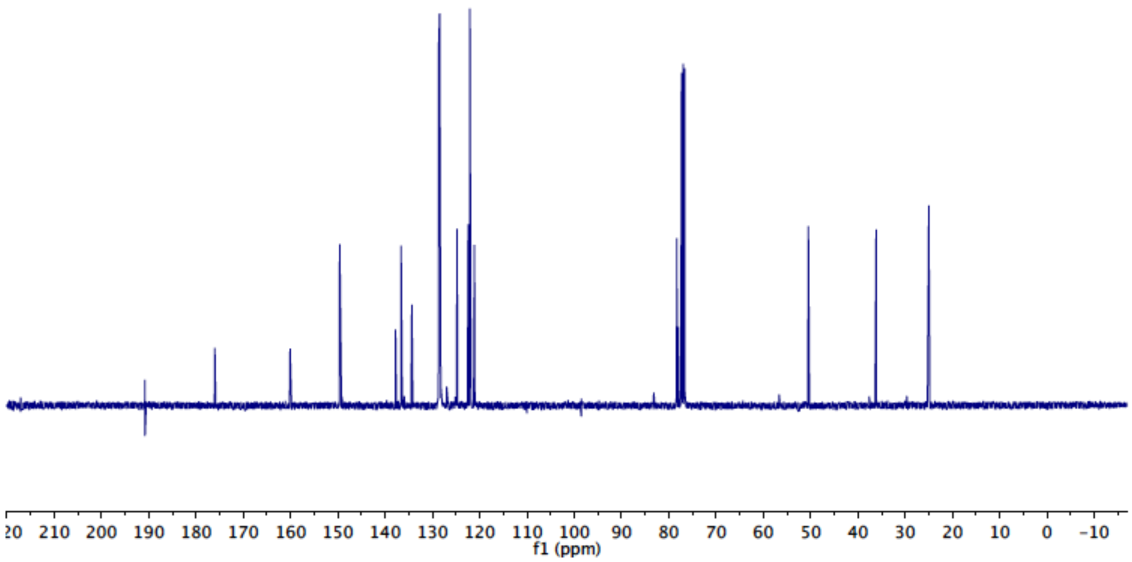
7
6
5
4
3
2
1
0
f1 (ppm)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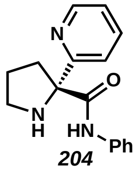
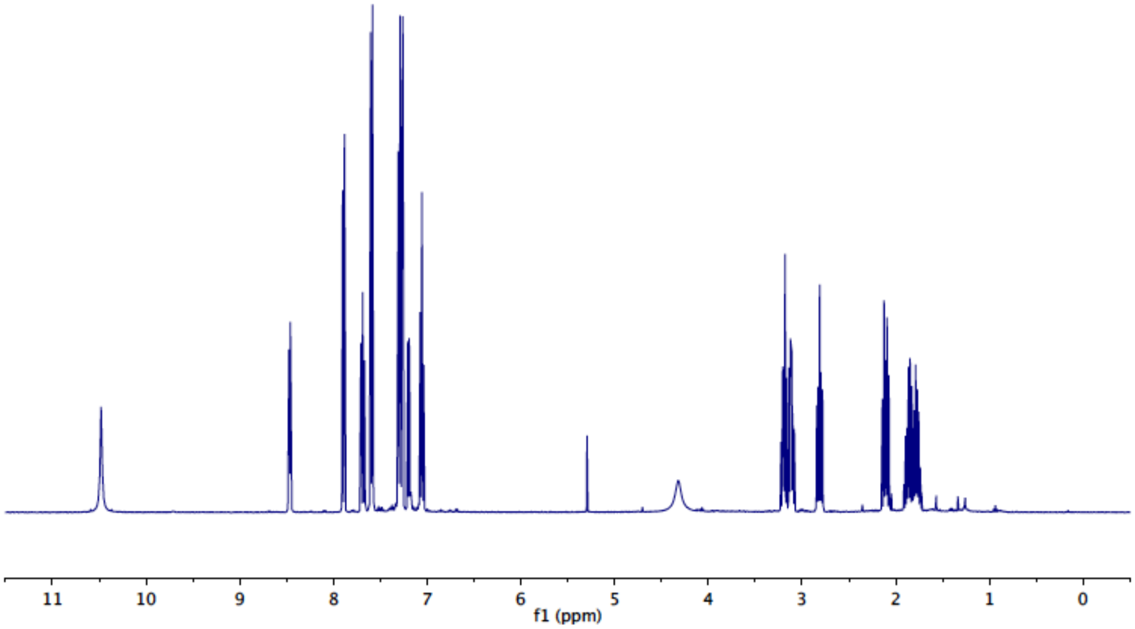
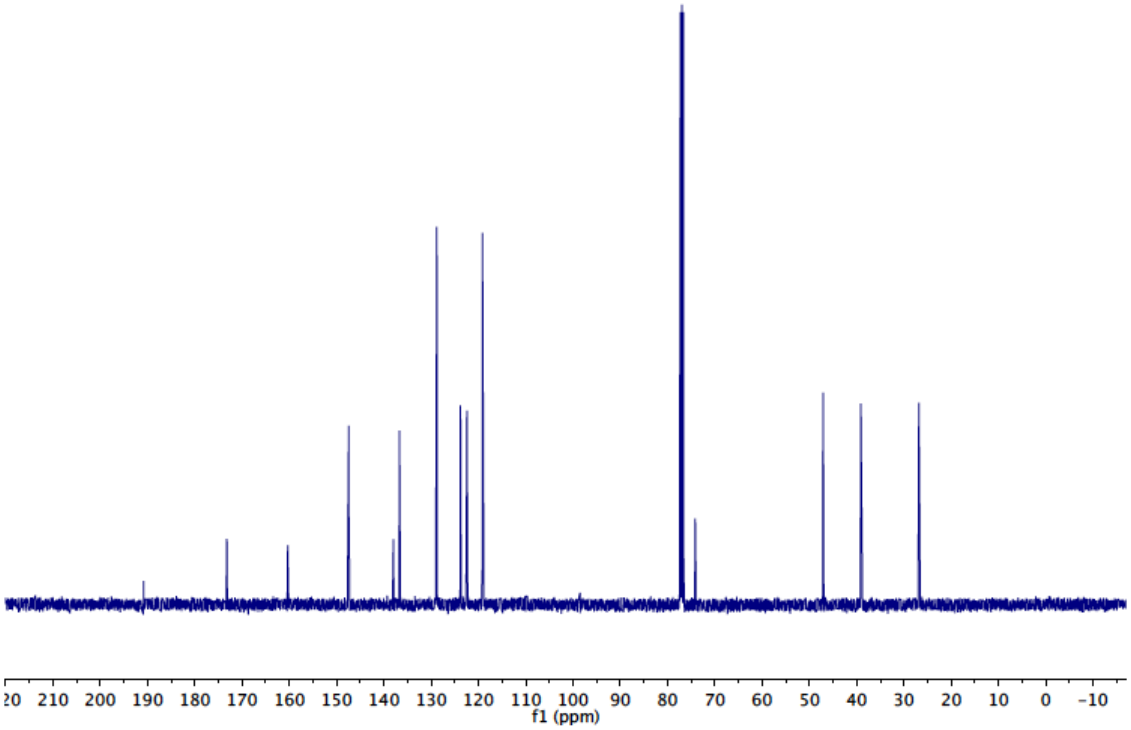
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


N
O
N
H
HN
Ph

204


11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
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150
140
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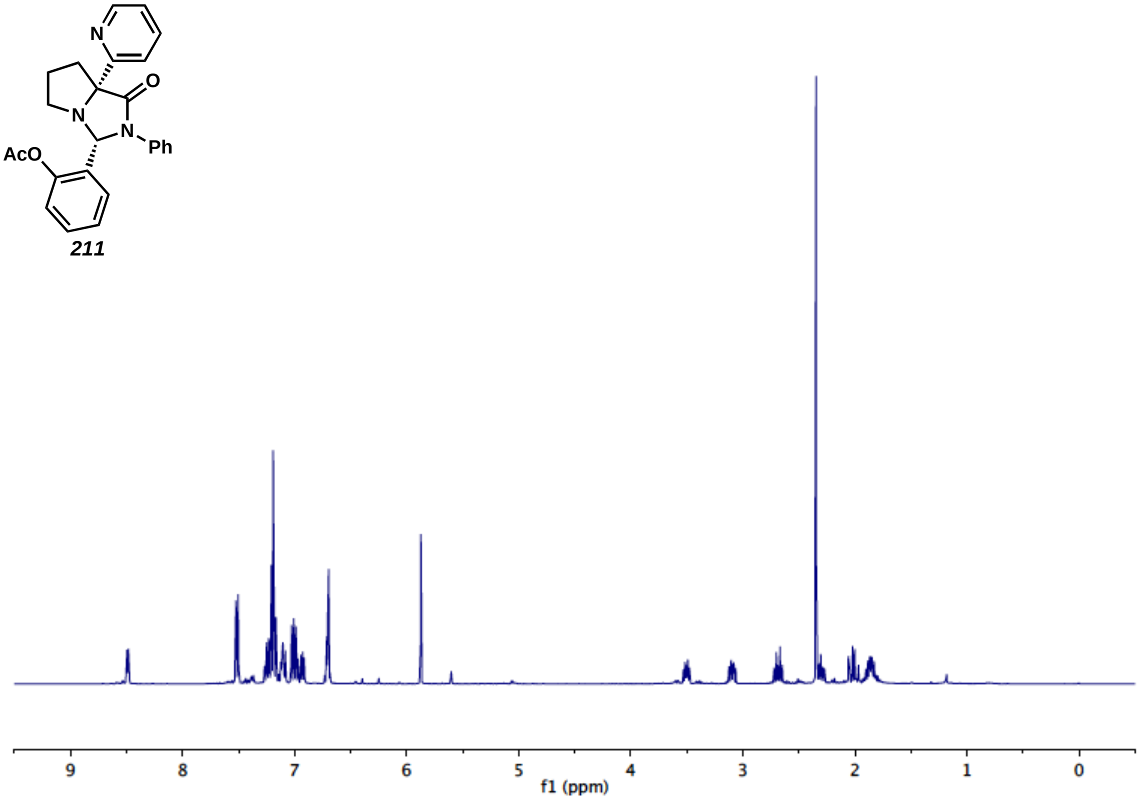
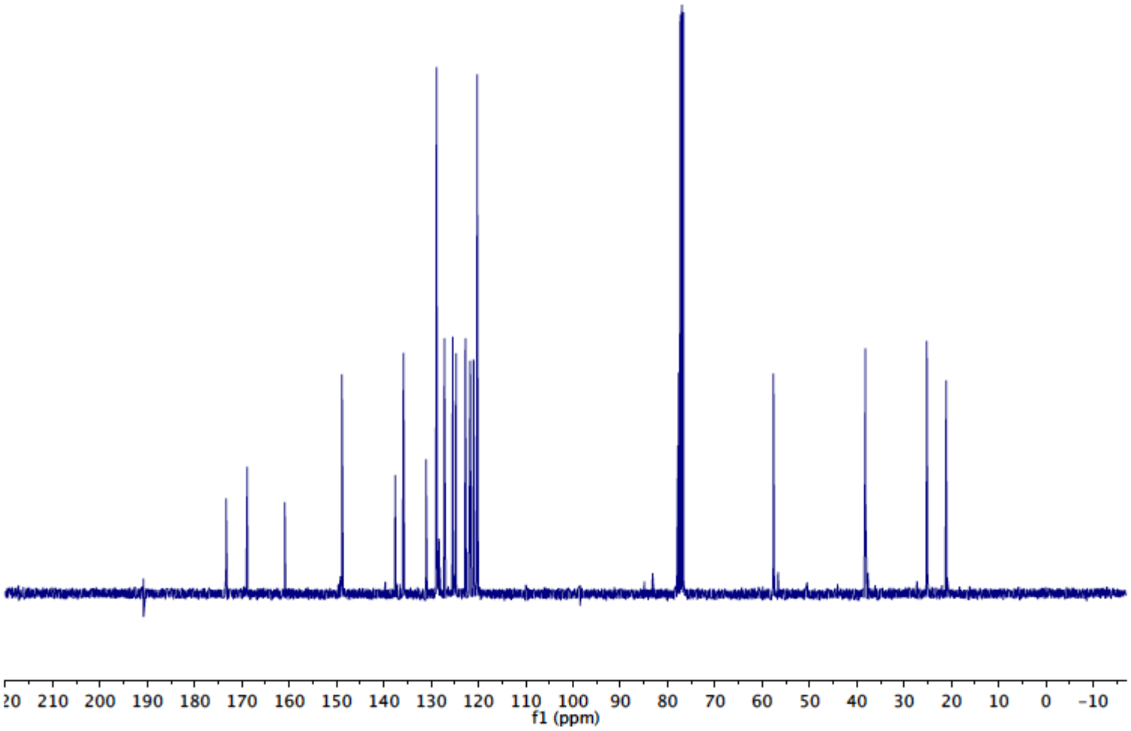
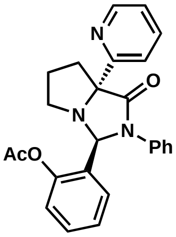
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
N
Ph
AcO

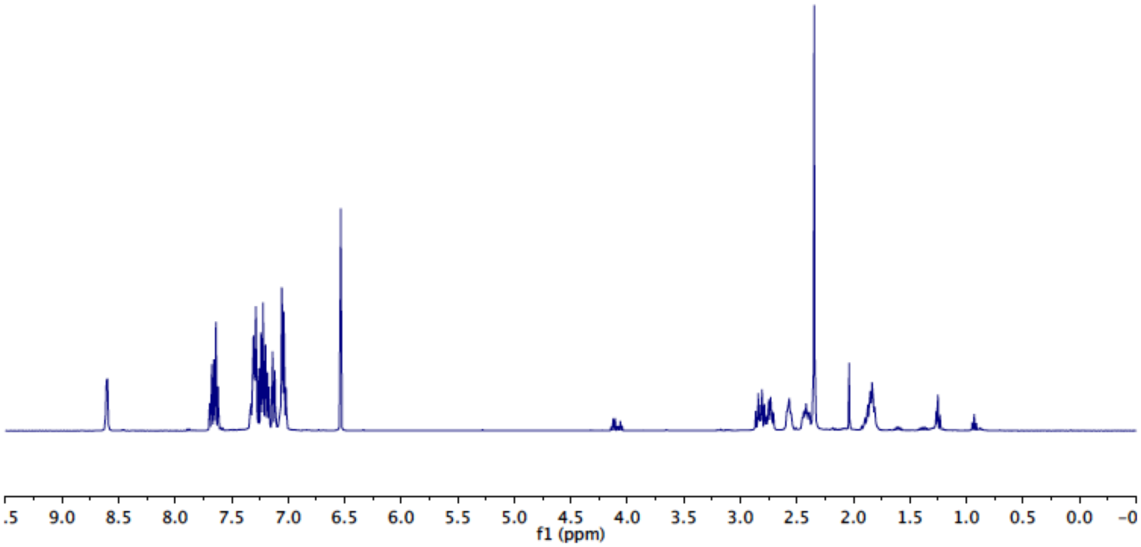
211

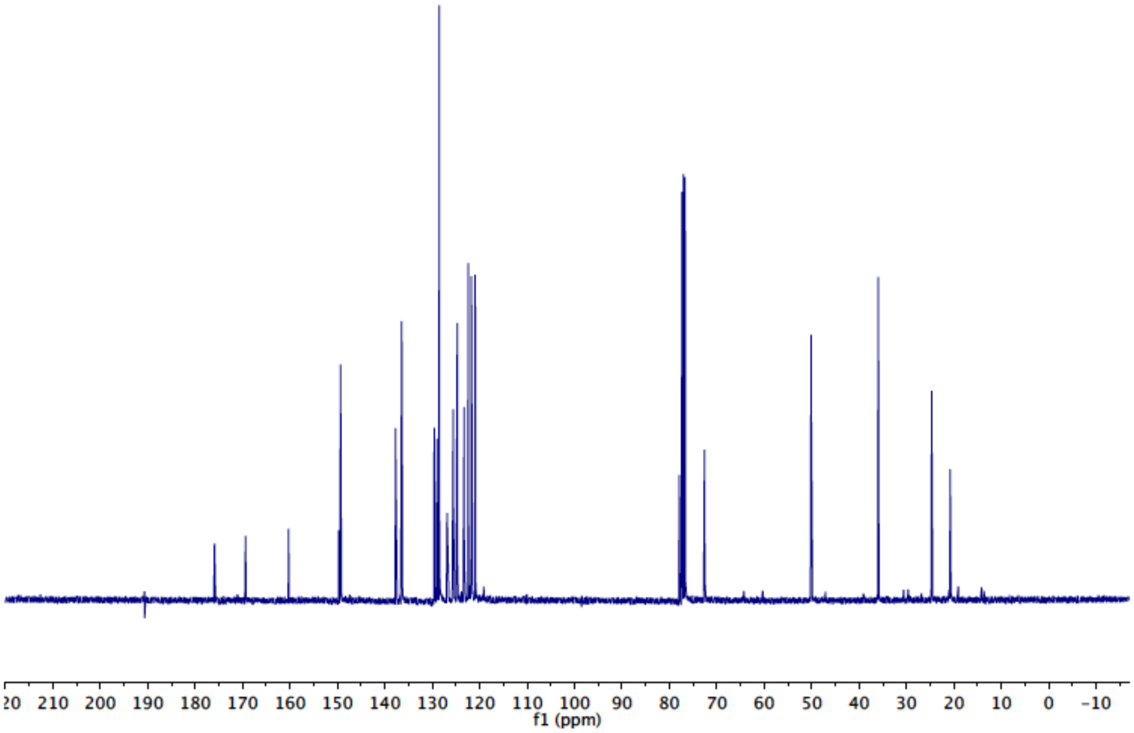
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

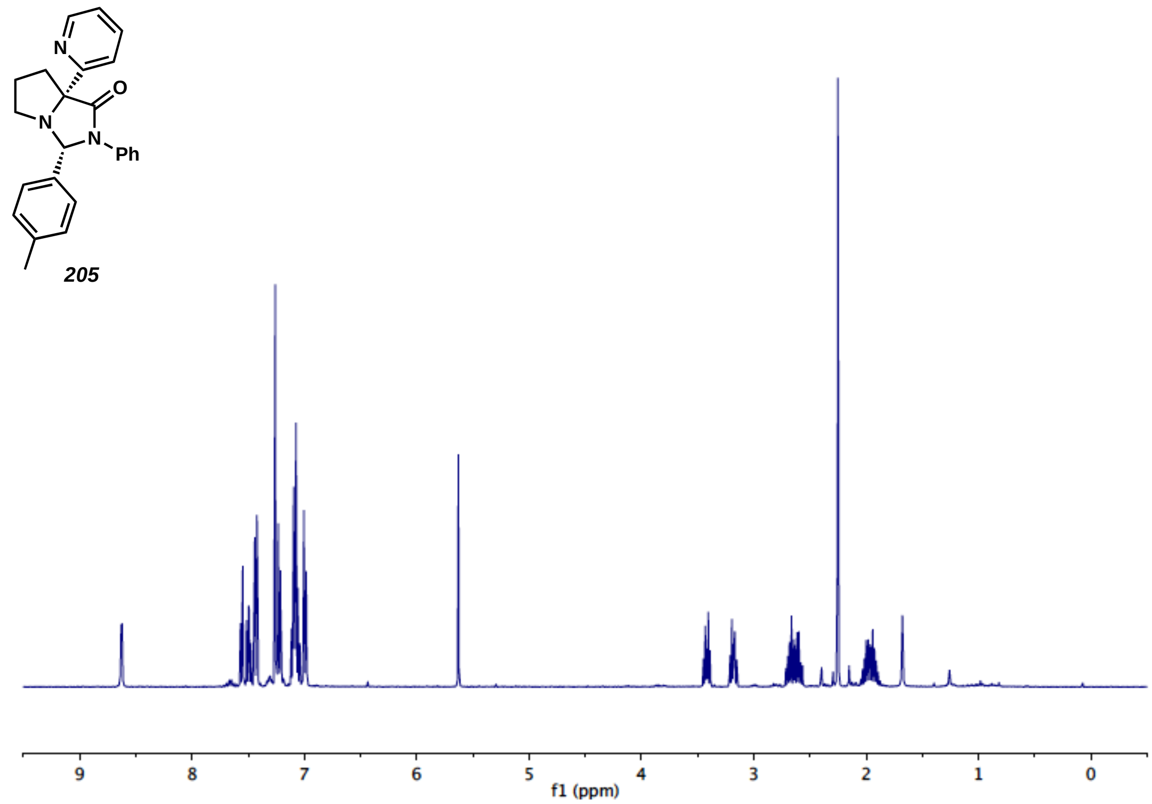

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O
N
N
Ph
AcO

201

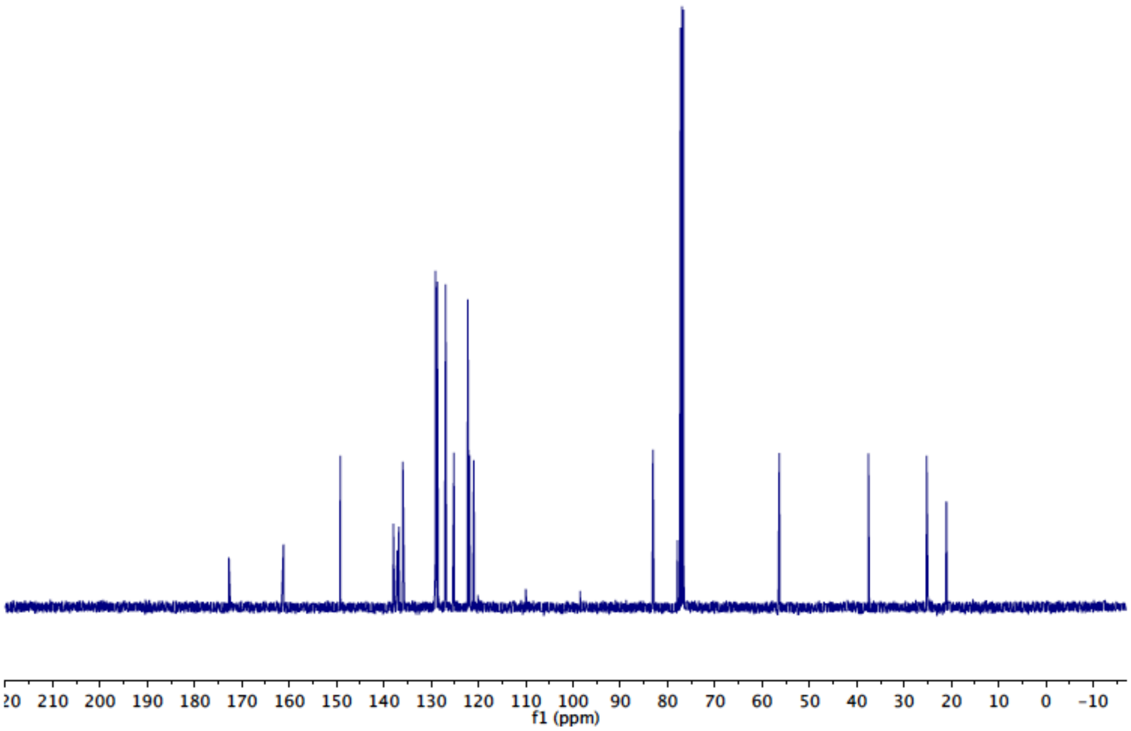

.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
–0
f1 (ppm)

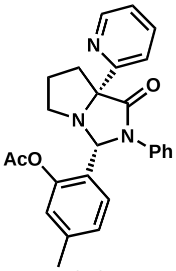

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
N
Ph

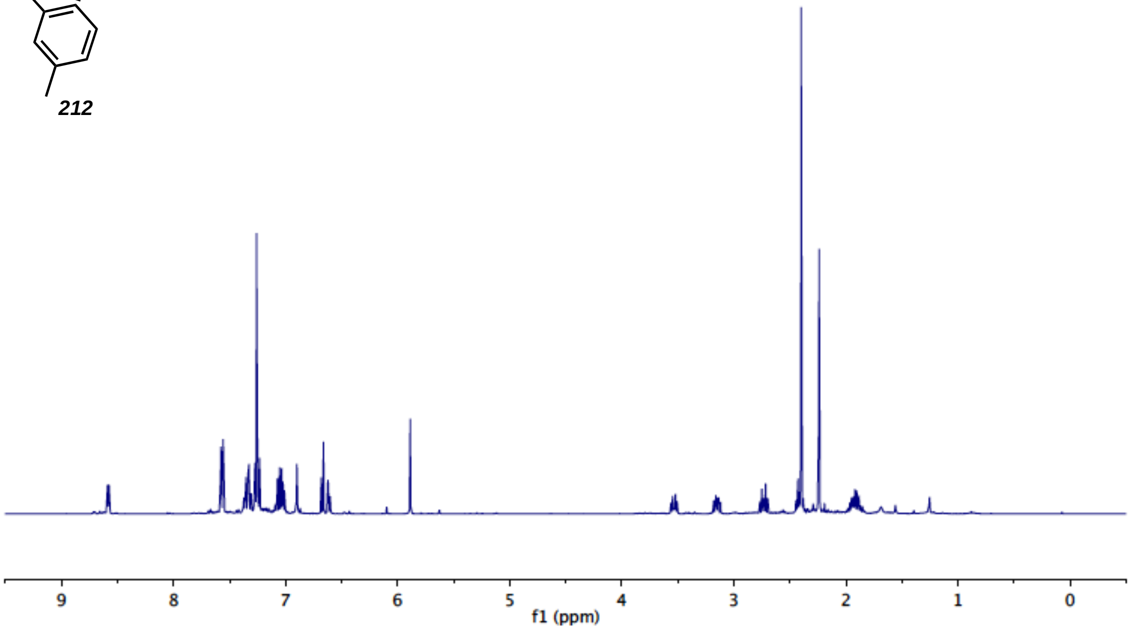
205

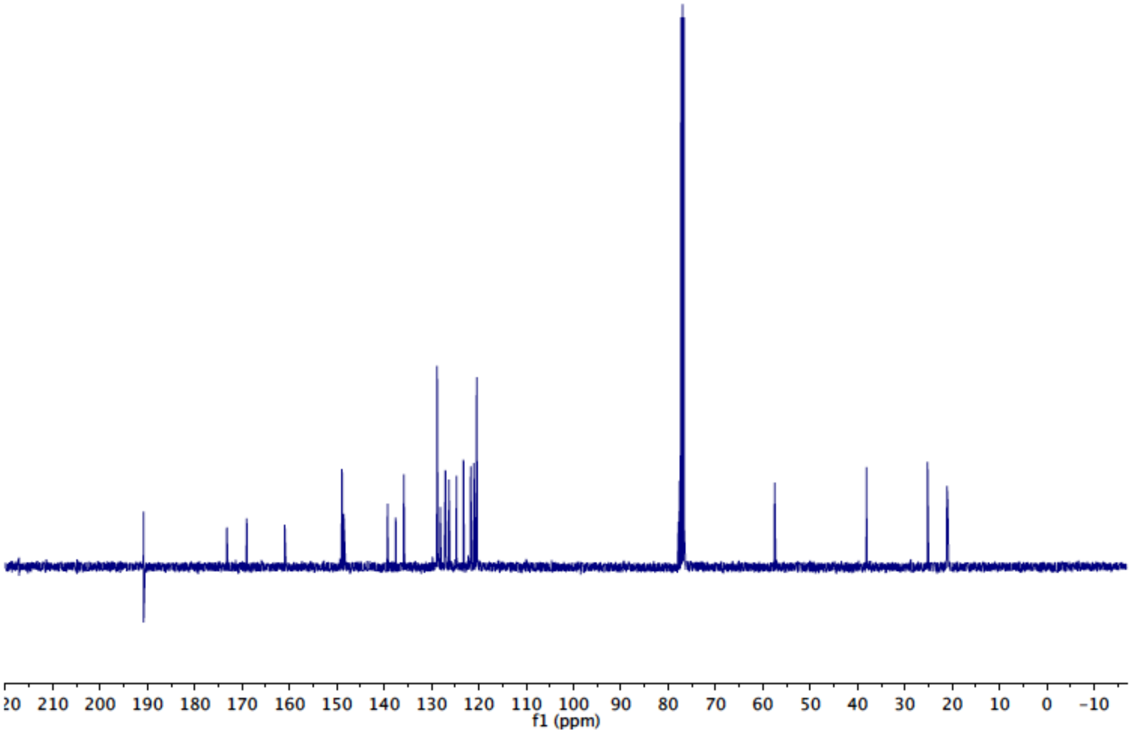
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

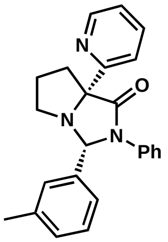

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
Ph
AcO

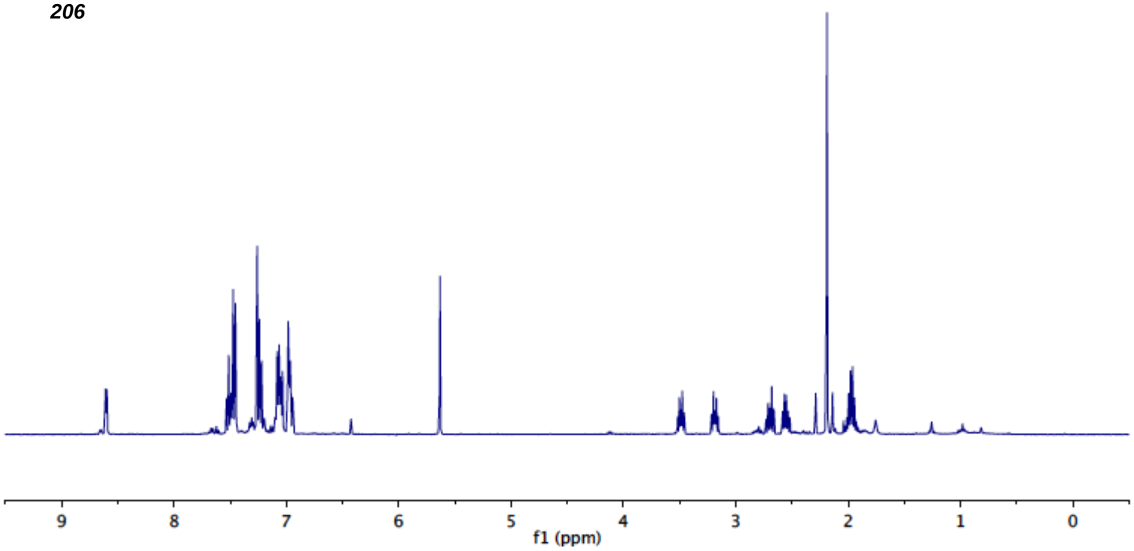
212

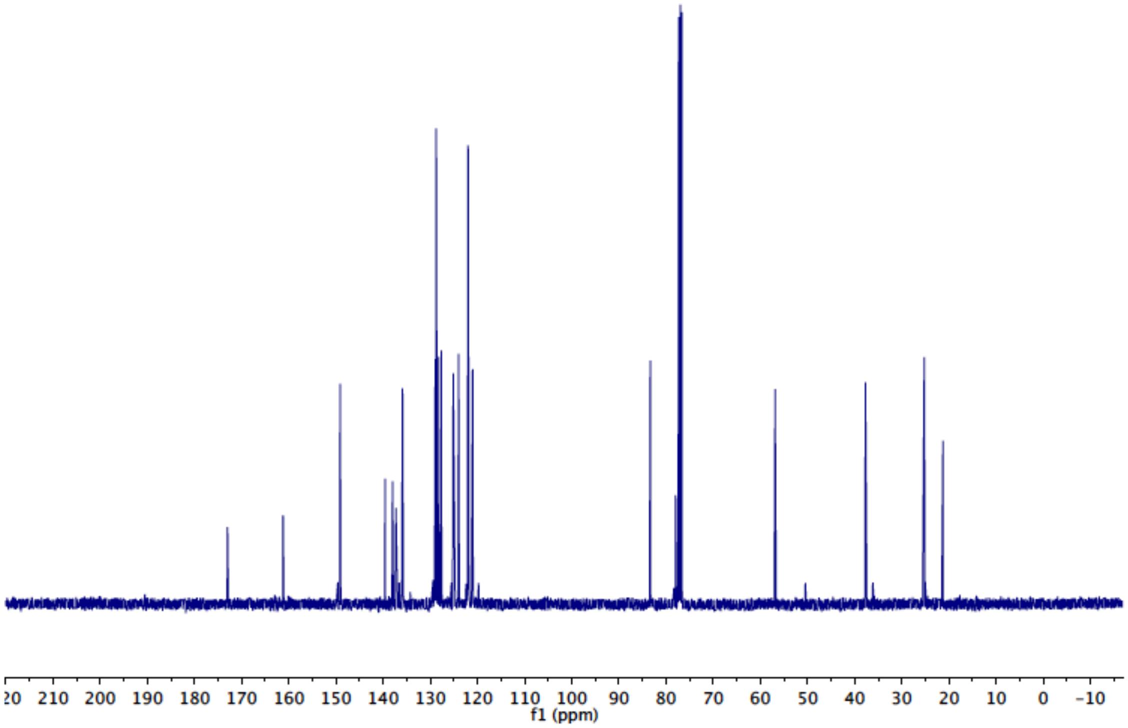

9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
N
Ph

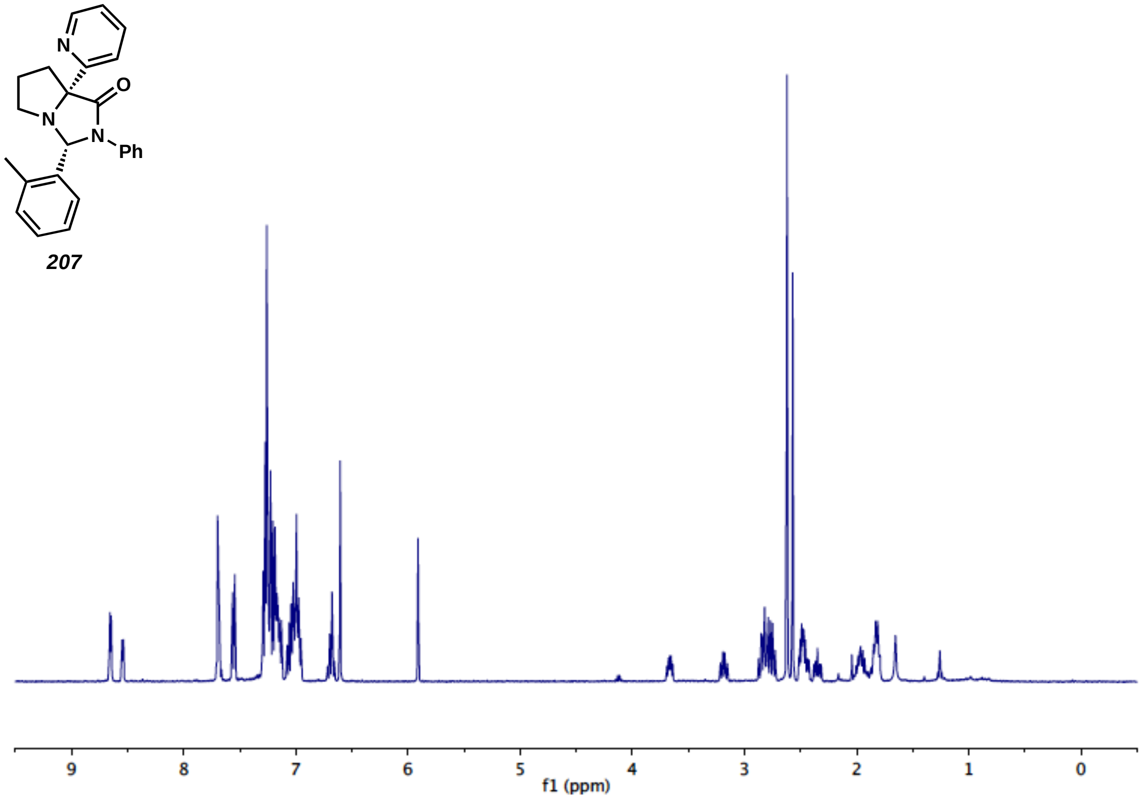
206

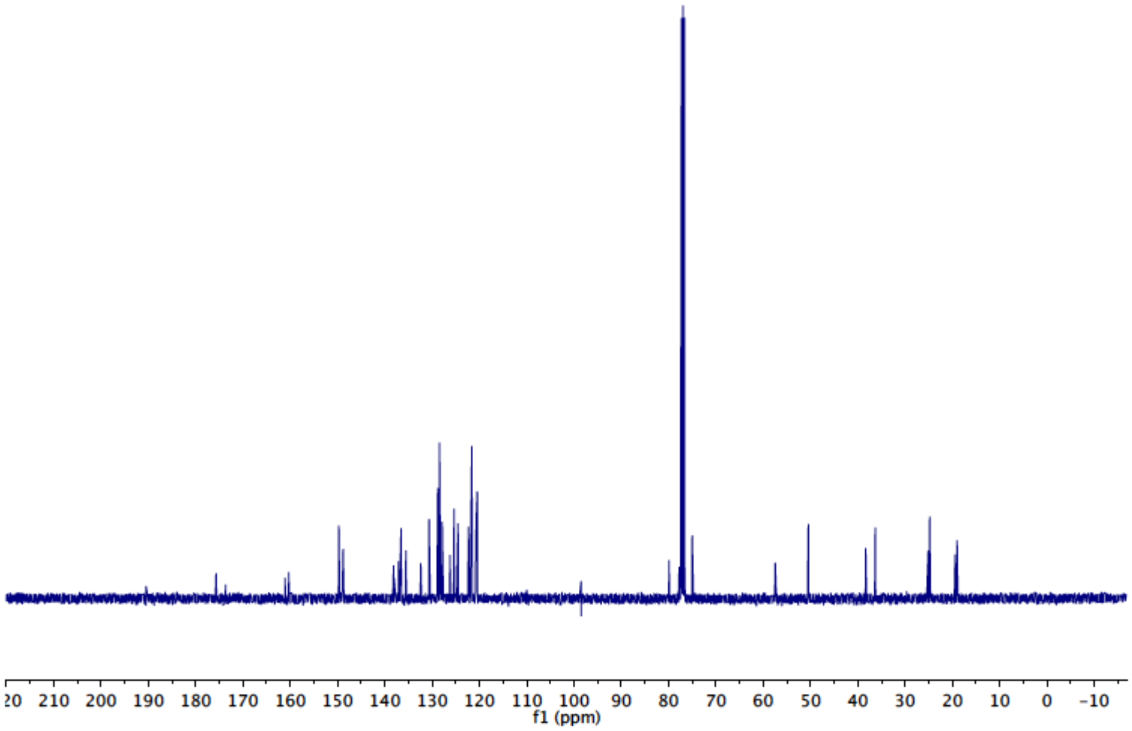

9
8
7
6
5
4
3
2
1
0
f1 (ppm)

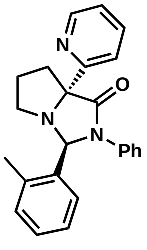

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

N
O
N
N
Ph

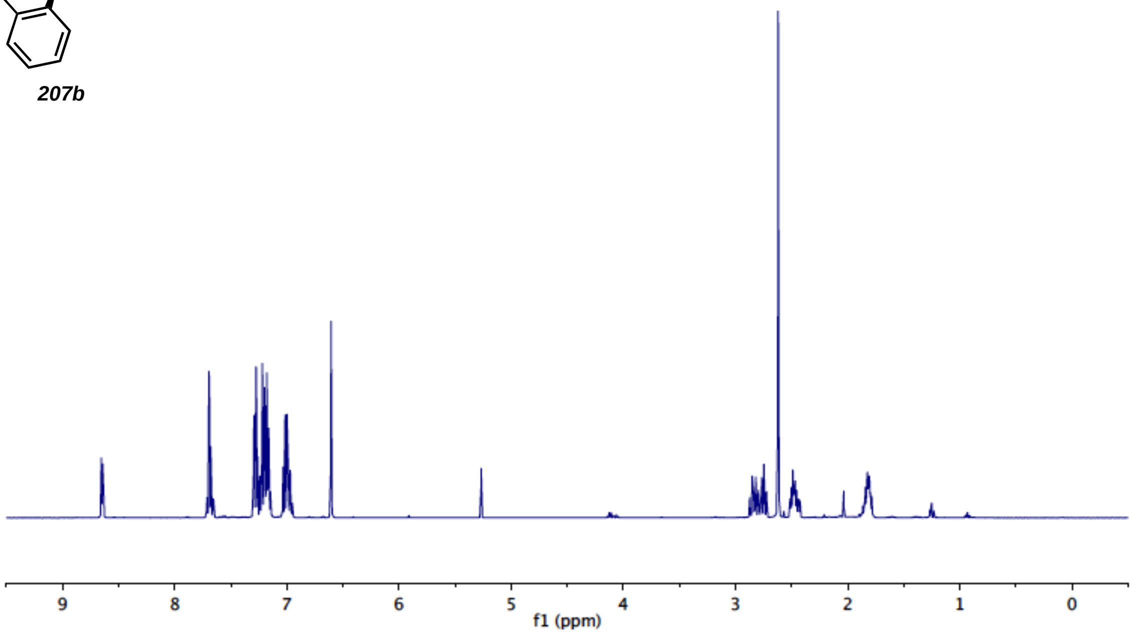
207

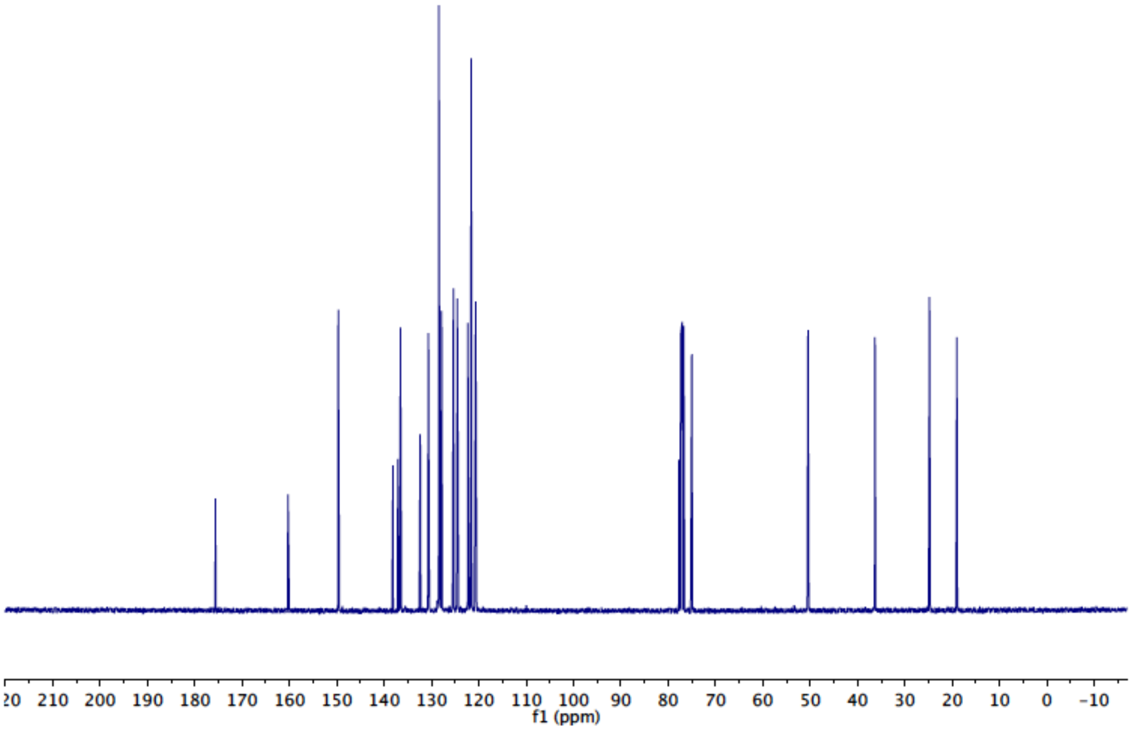

9
8
7
6
5
4
3
2
1
0
f1 (ppm)

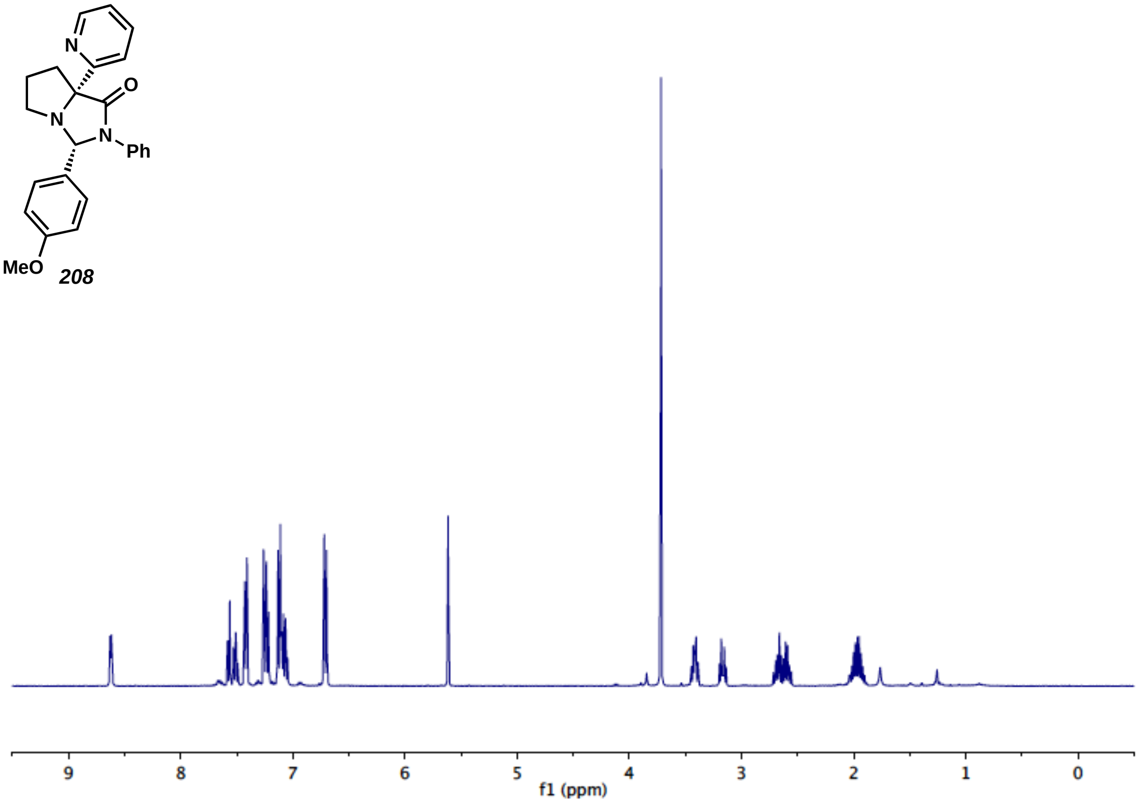

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



207b

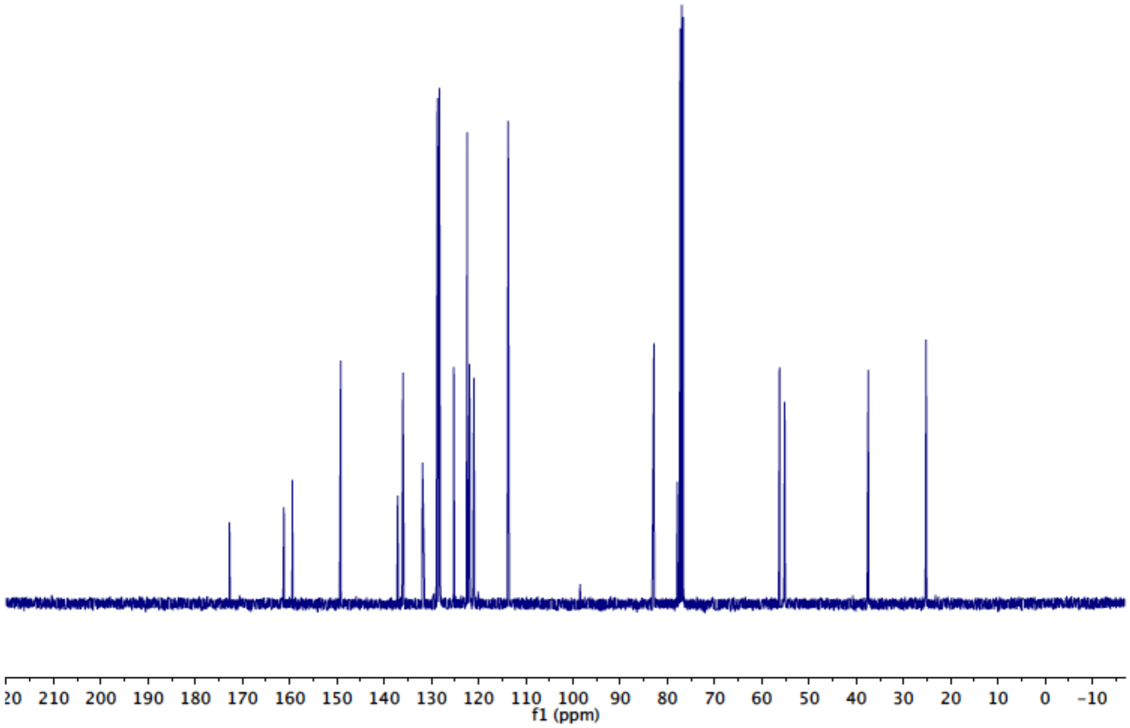

9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


N
O
N
N
Ph
MeO

208

9
8
7
6
5
4
3
2
1
0
f1 (ppm)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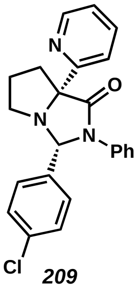
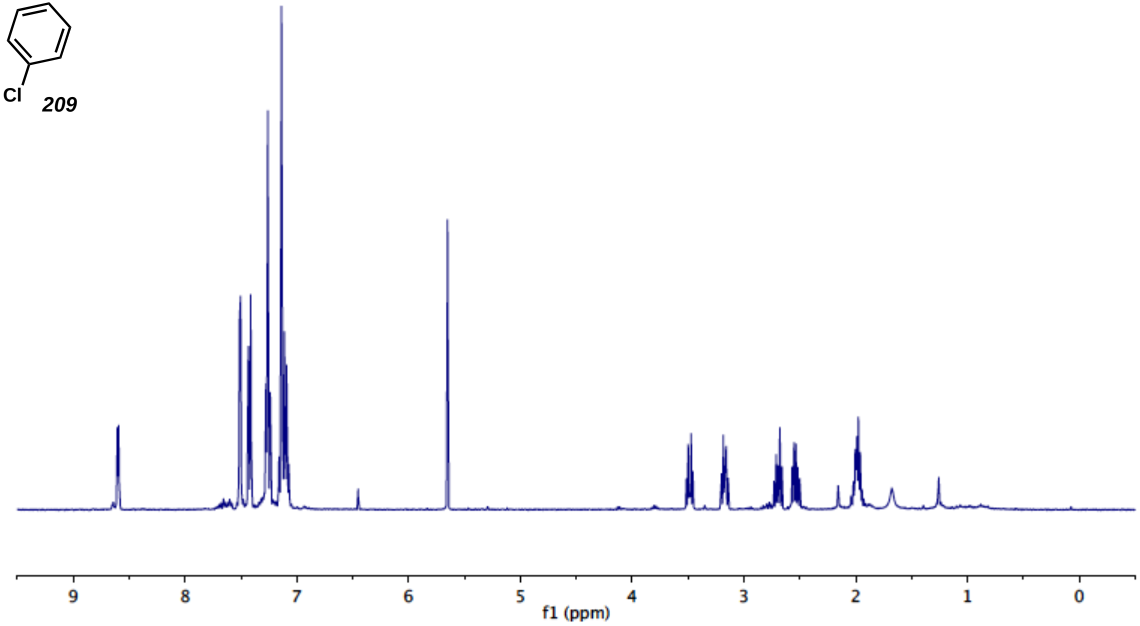
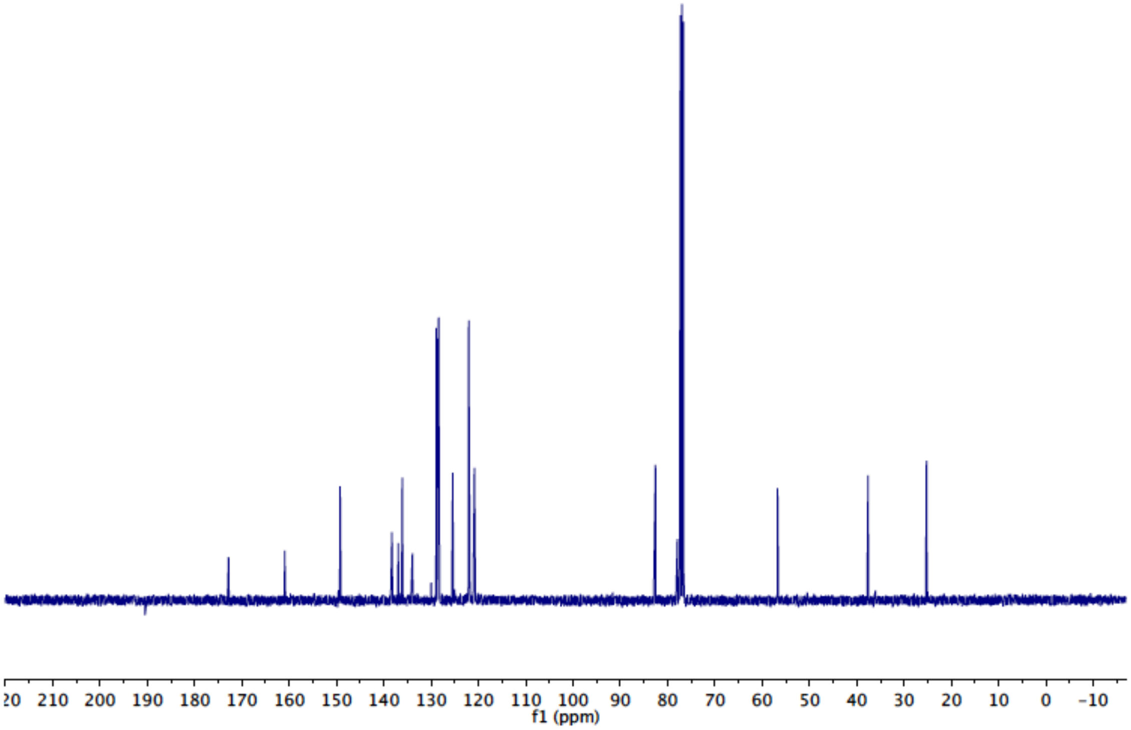
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O
N
N
Ph
Cl

209


9
8
7
6
5
4
3
2
1
0
f1 (ppm)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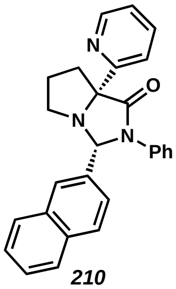
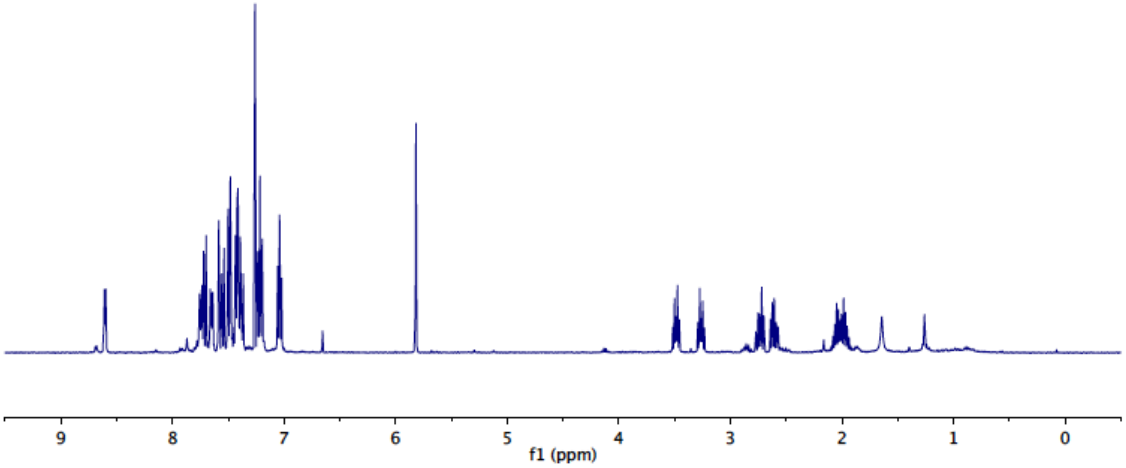
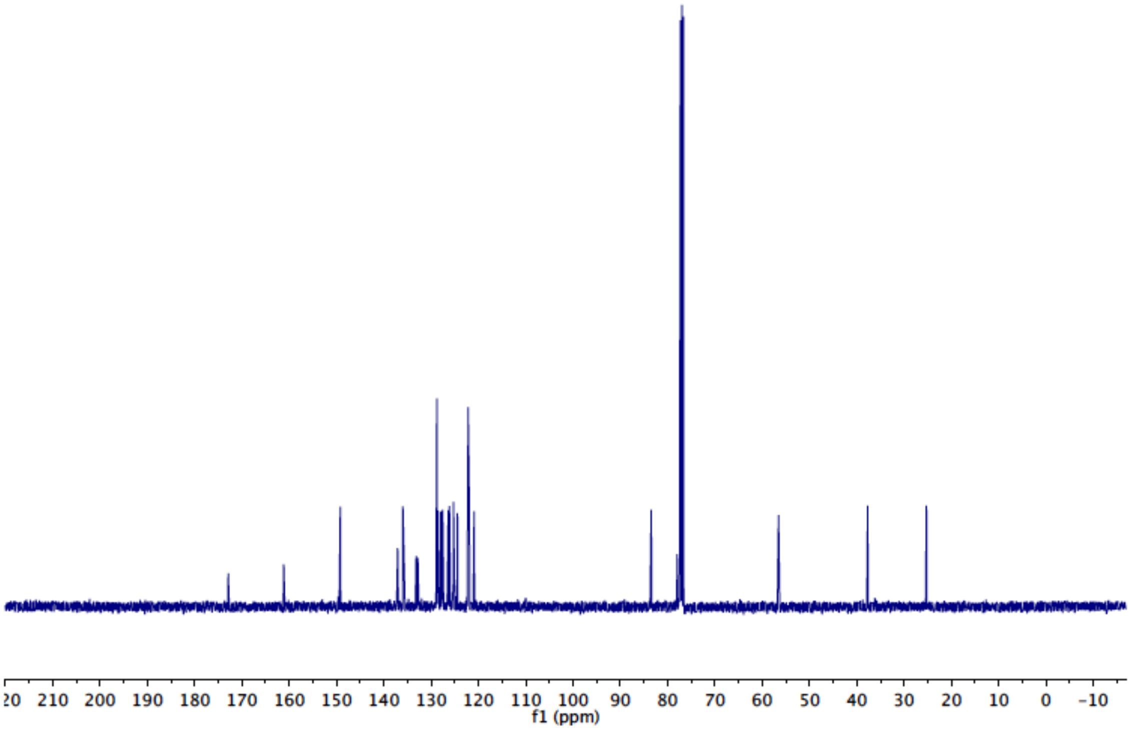
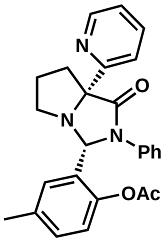
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O
N
N
Ph

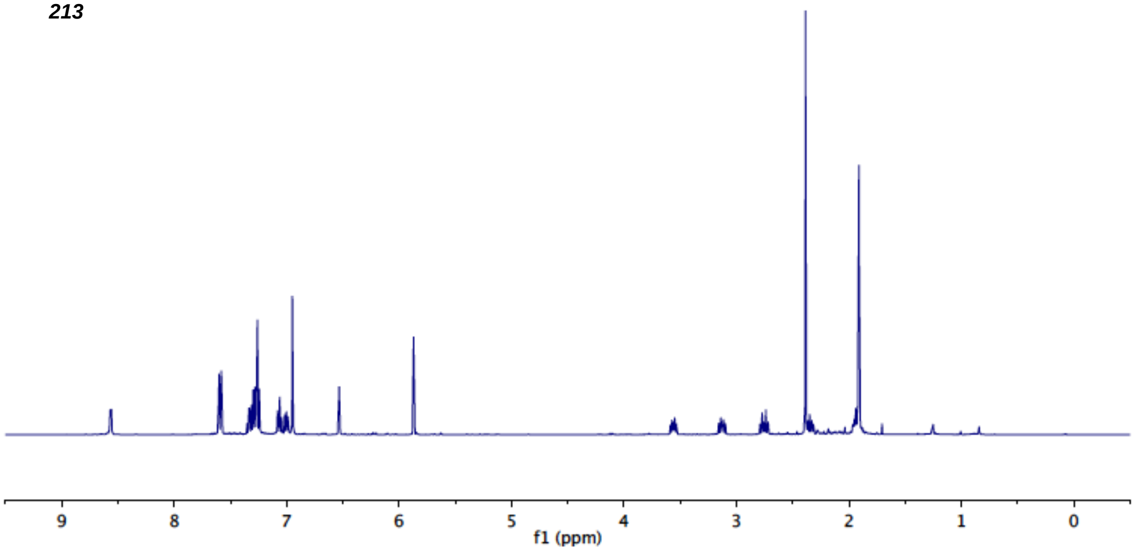
210

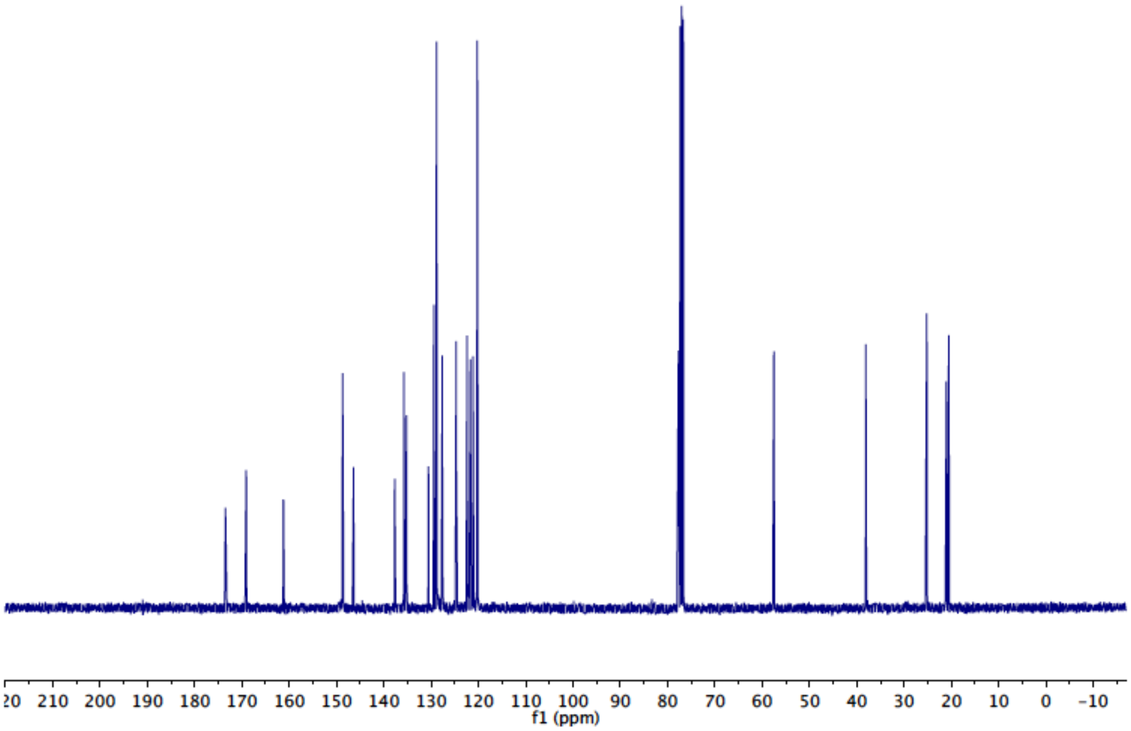

9
8
7
6
5
4
3
2
1
0
f1 (ppm)

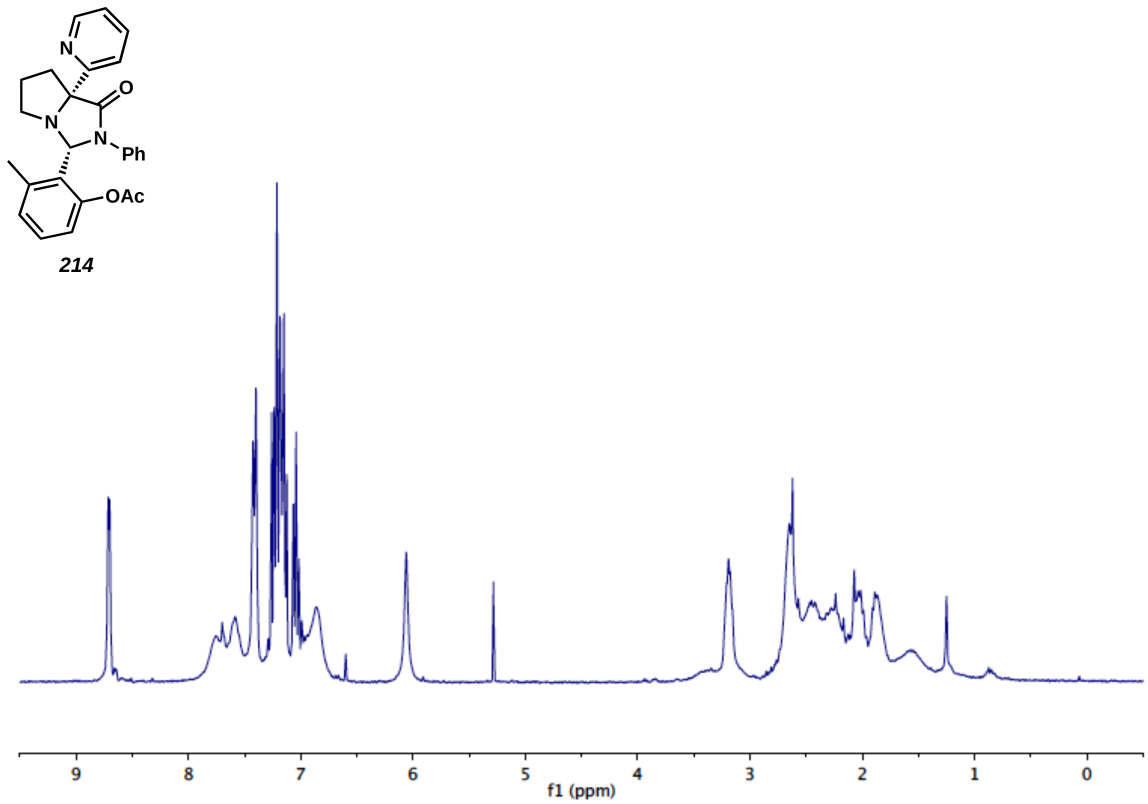

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
N
Ph
OAc

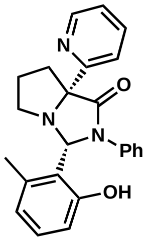
213


9
8
7
6
5
4
3
2
1
0
f1 (ppm)

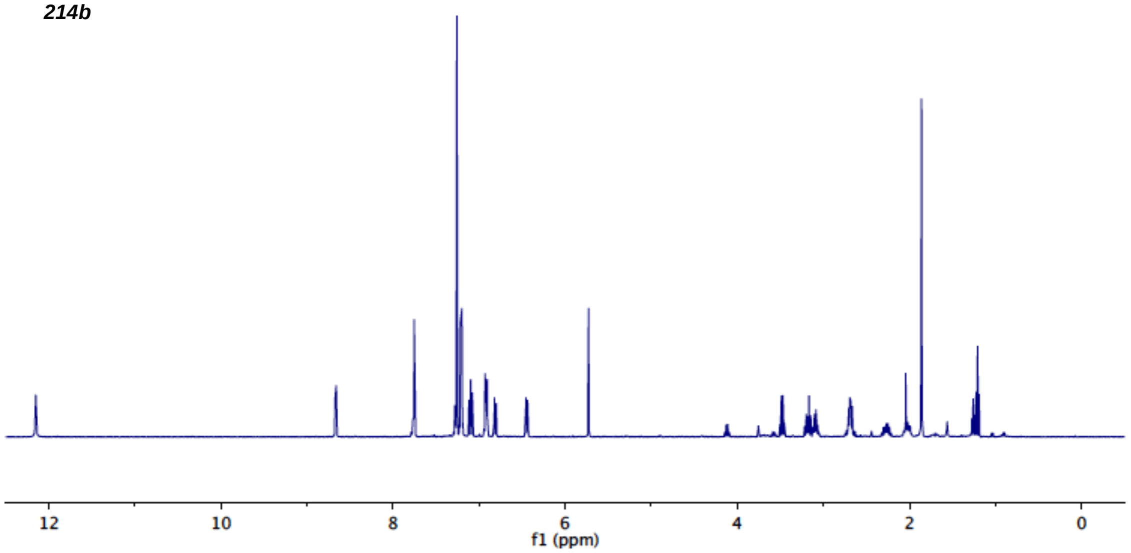

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

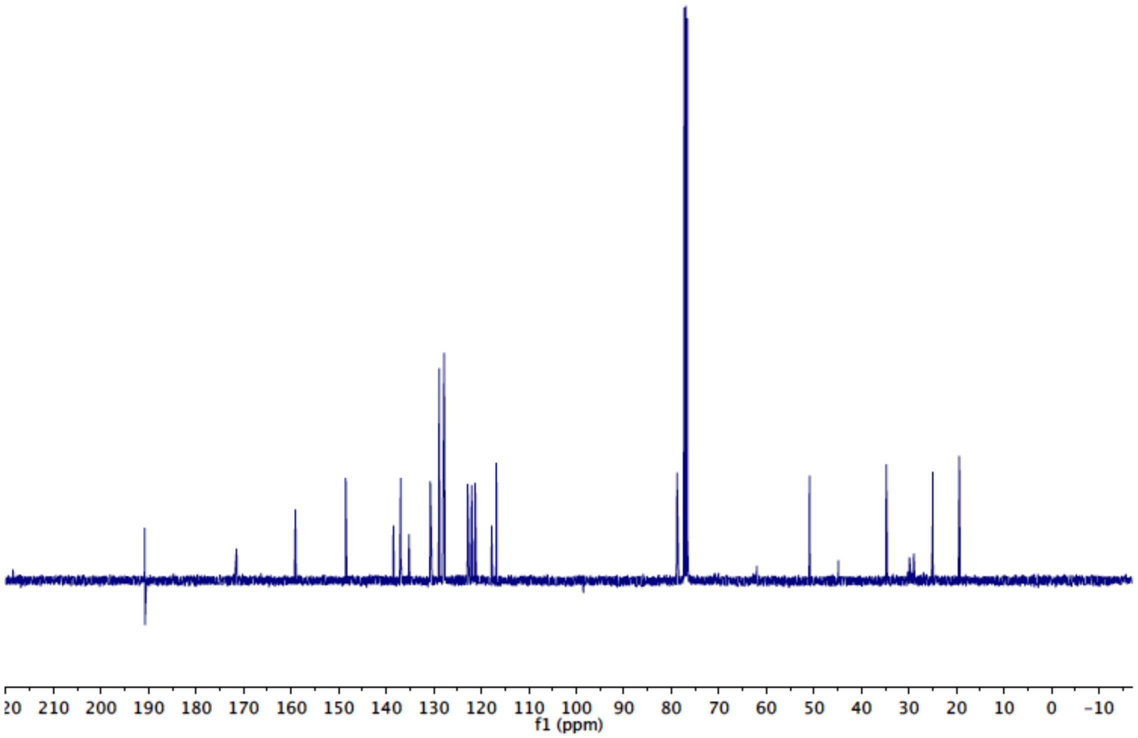


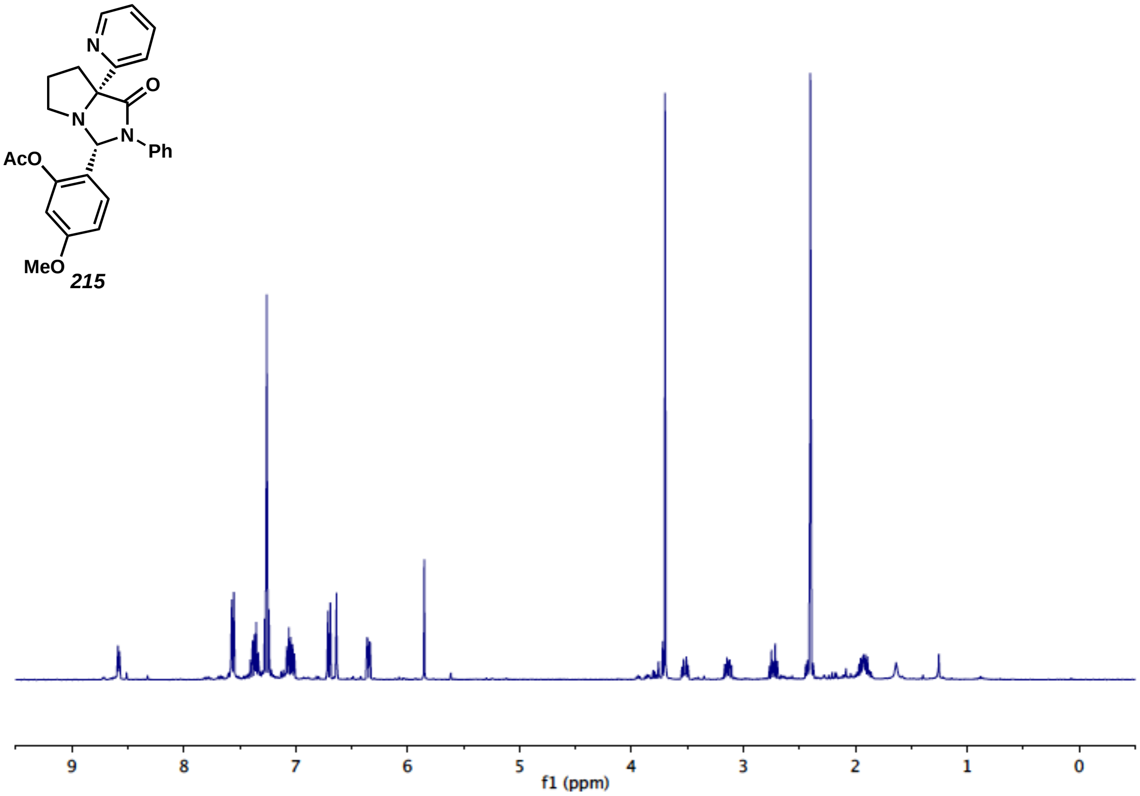
214


N
O
N
N
Ph
OH

214b

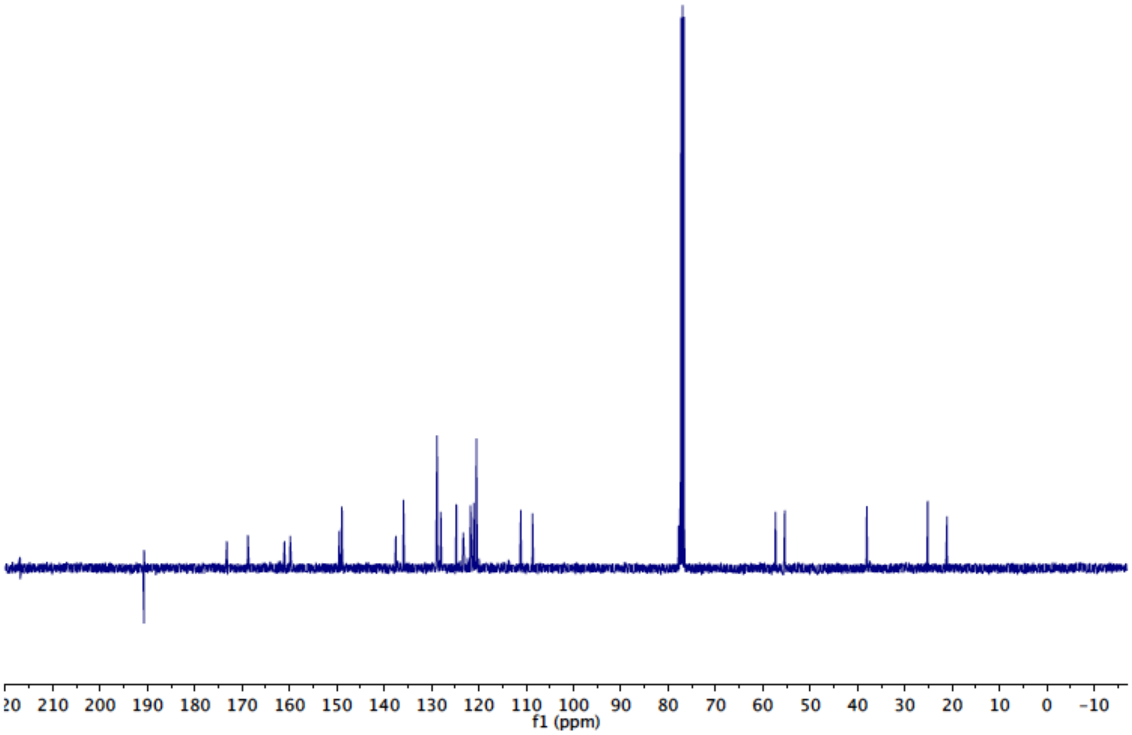

12
10
8
6
4
2
0
f1 (ppm)

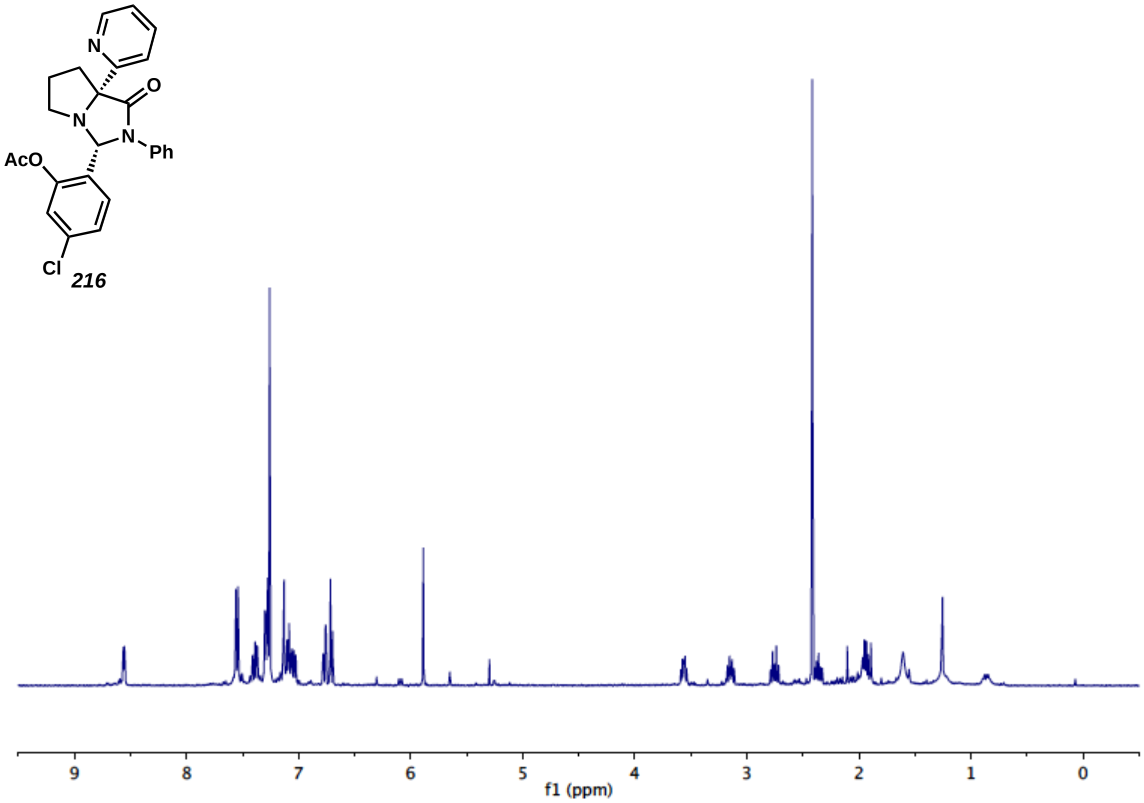

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)


N
O
N
N
Ph
AcO
MeO

215

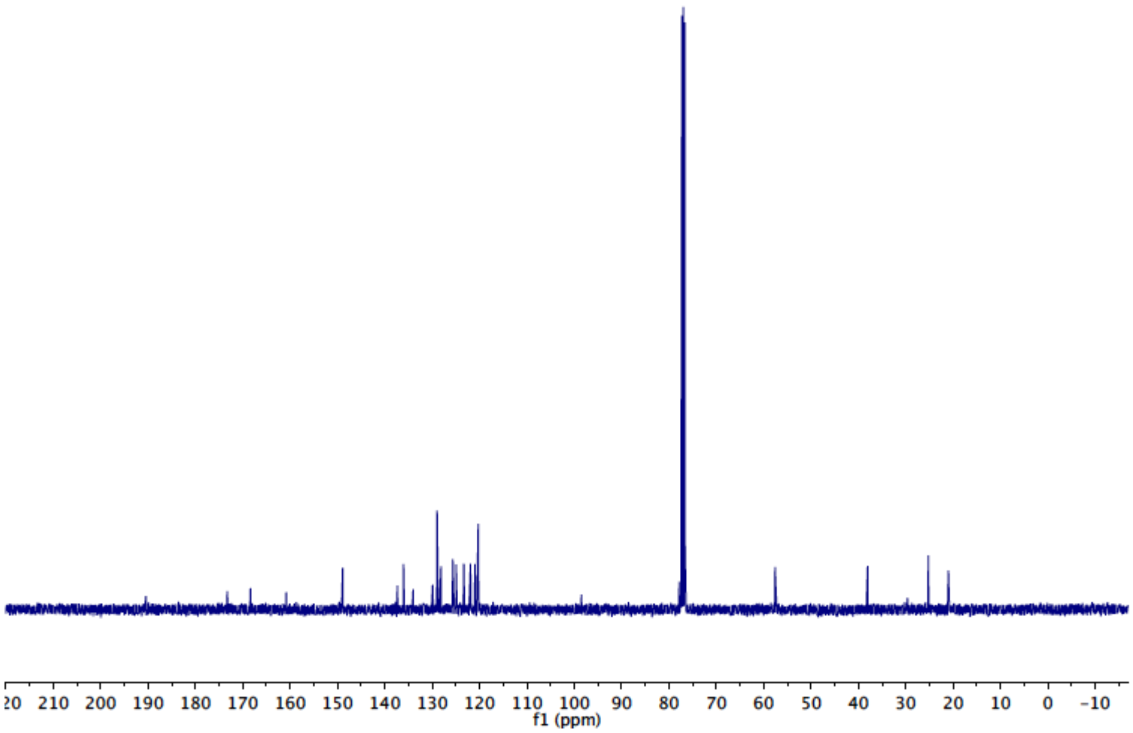
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
O
N
N
Ph
AcO
Cl

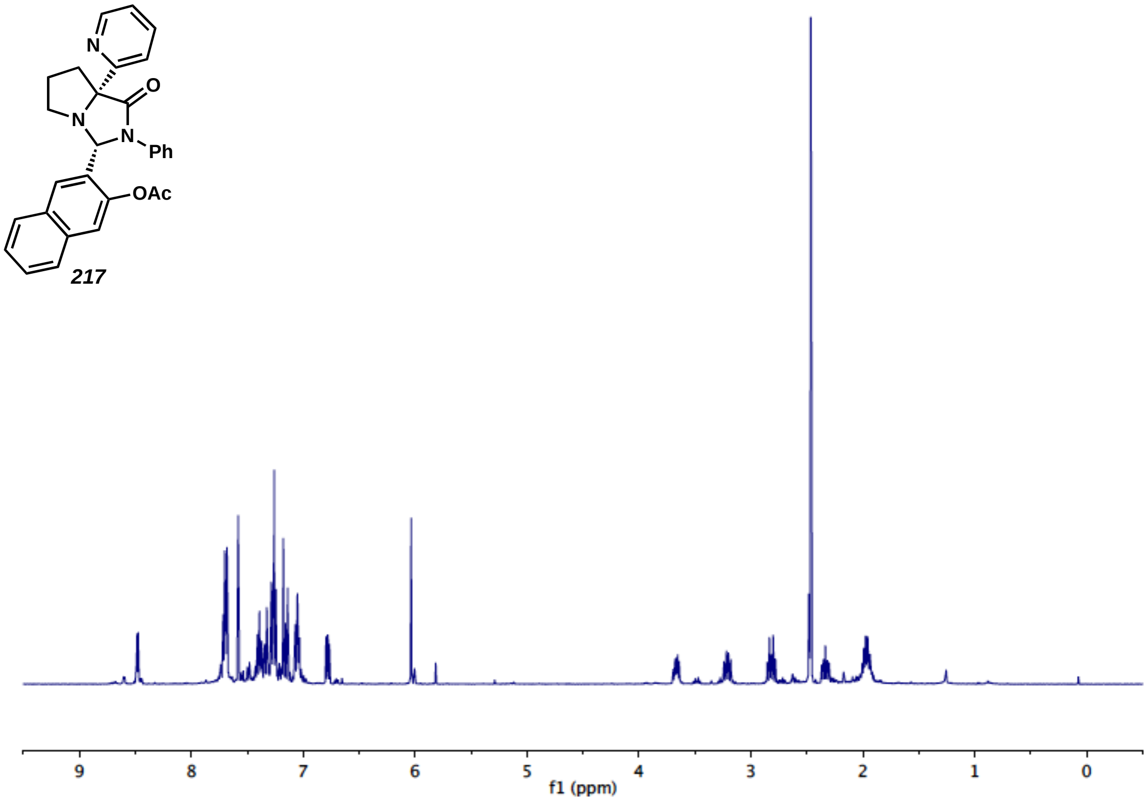
216

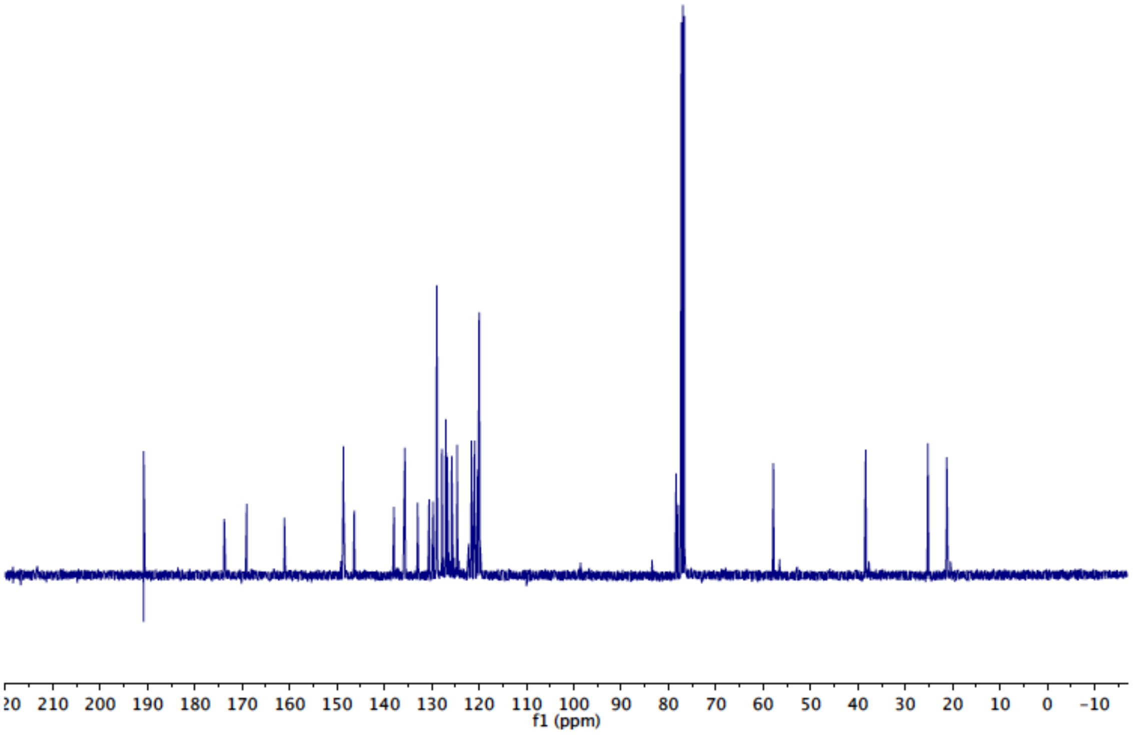
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

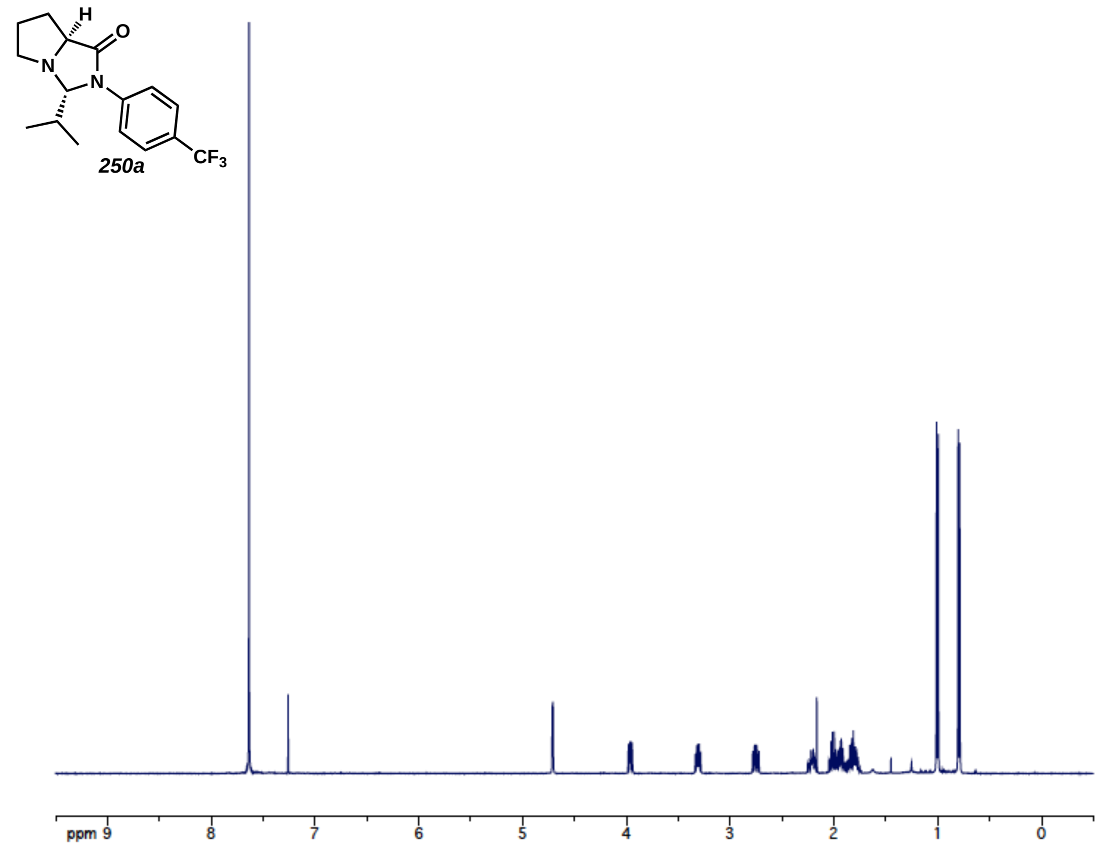

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

N
O
N
N
Ph
OAc

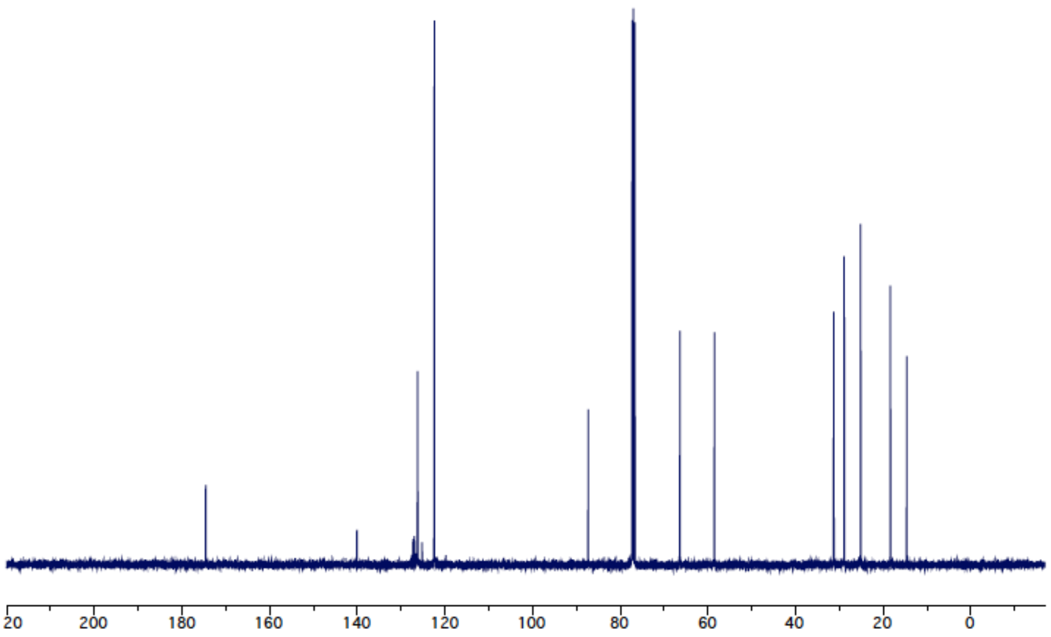
217

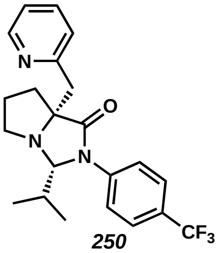

9
8
7
6
5
4
3
2
1
0
f1 (ppm)


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)

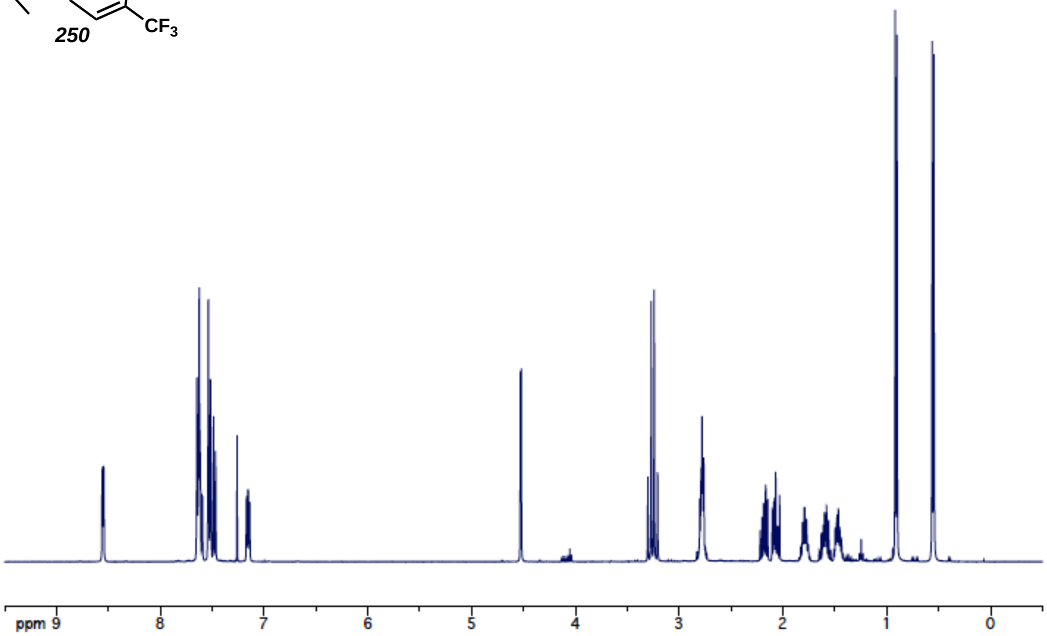


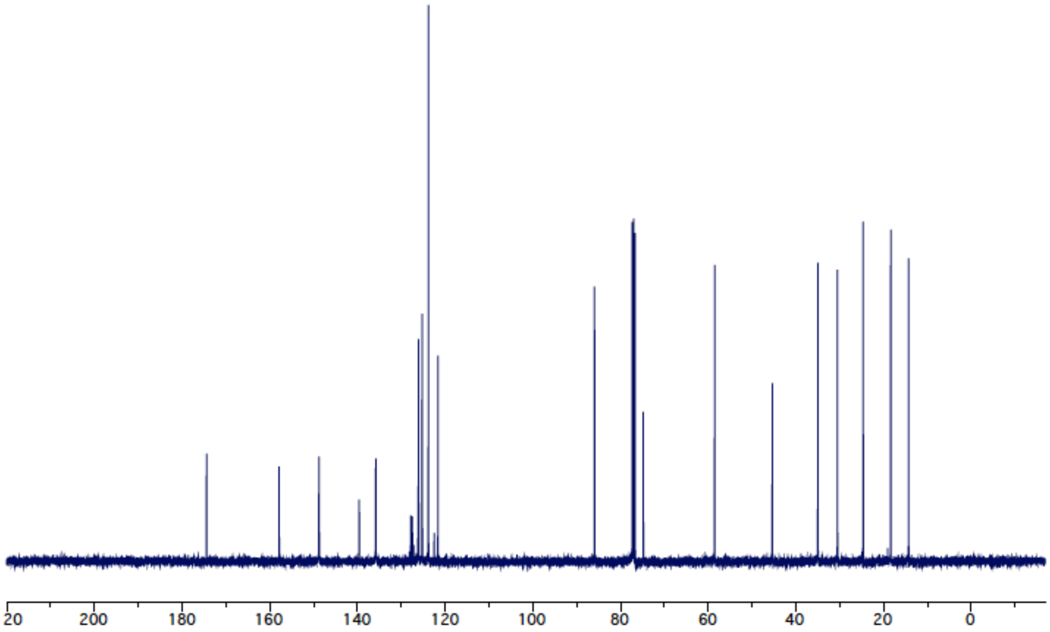
250a





250

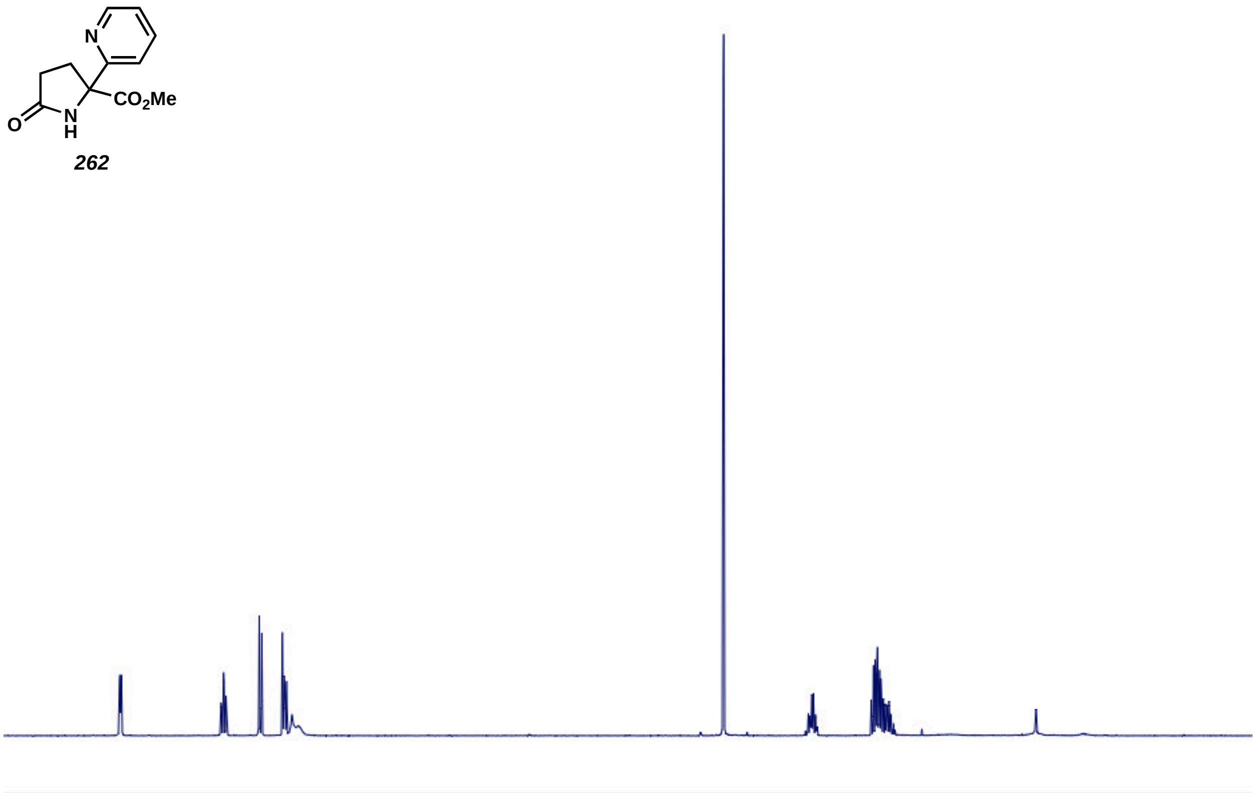


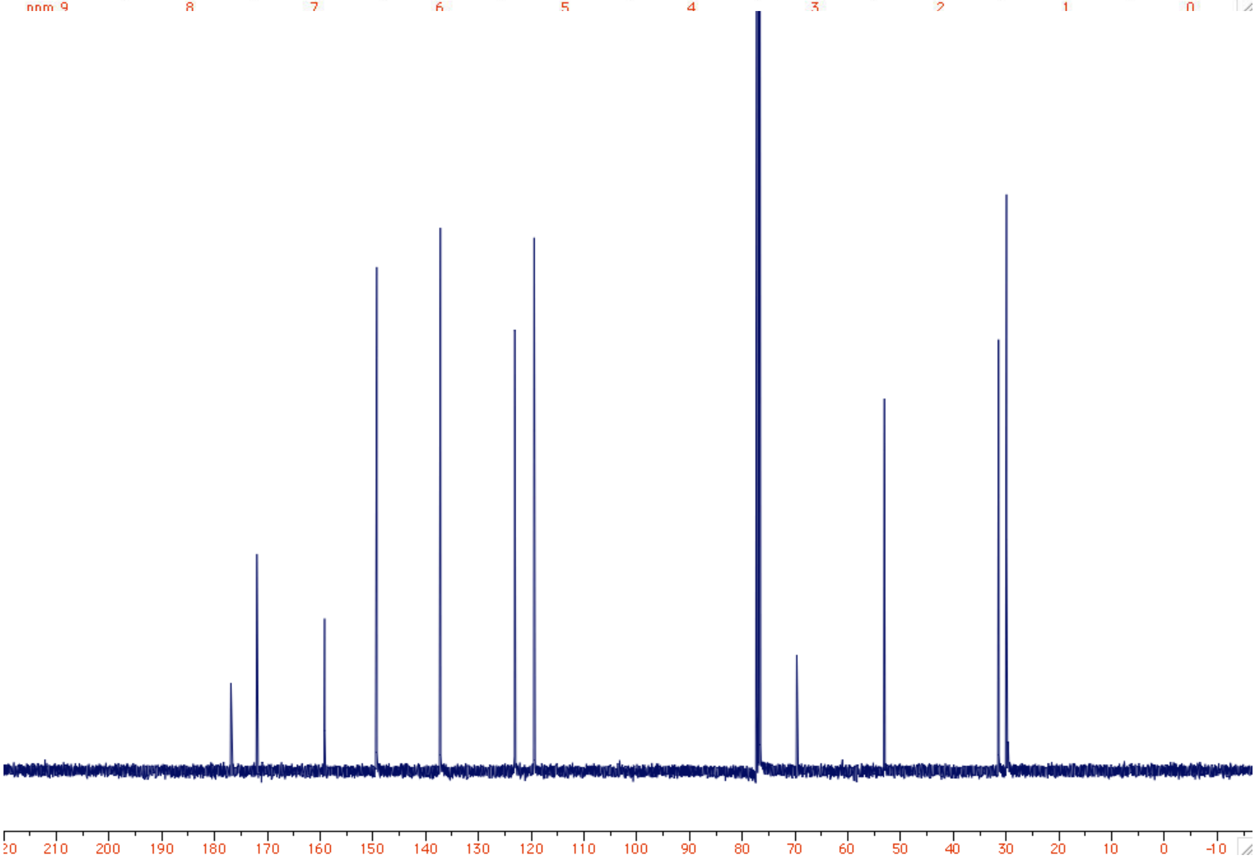


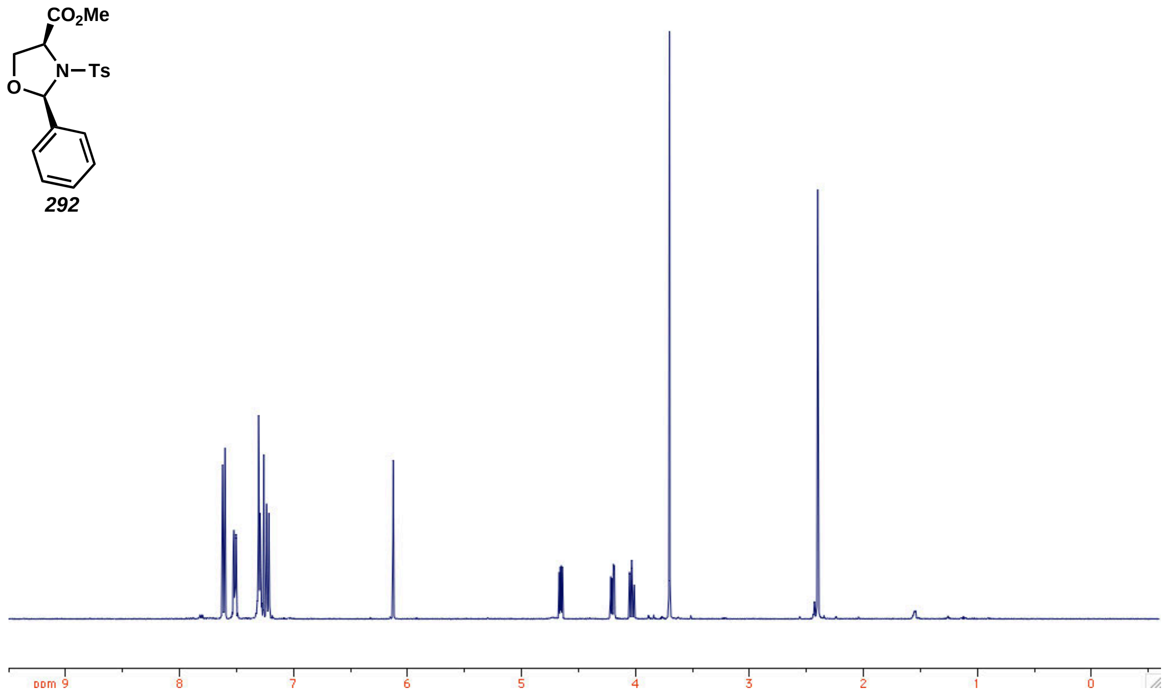
Appendix 3: Spectra Associated with Chapter 3

N
CO2Me
O
N
H

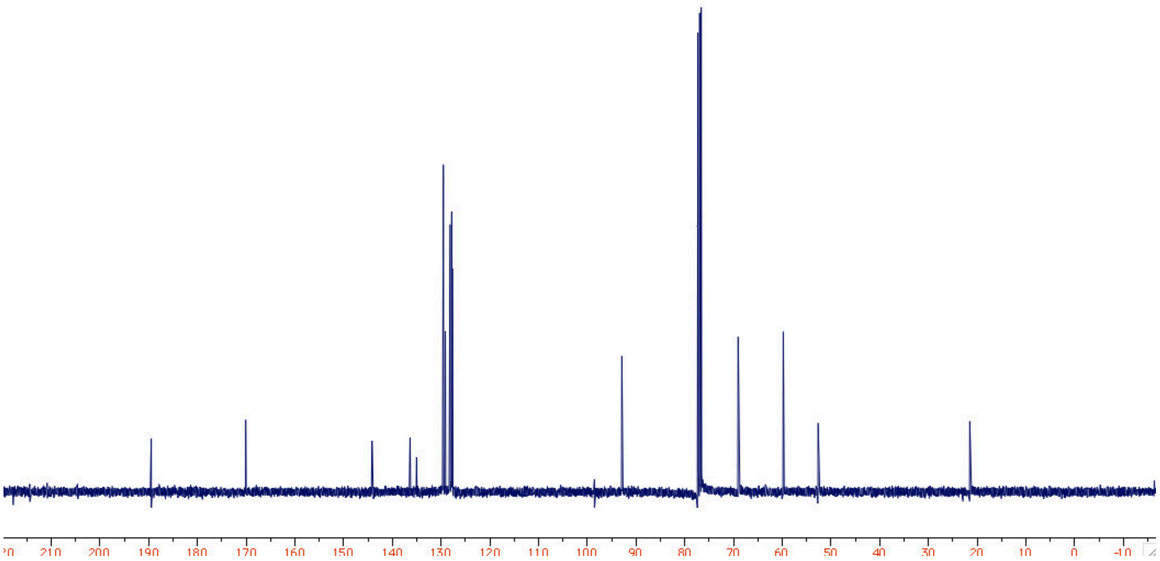
262


ppm 9
8
7
6
5
4
3
2
1
0


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

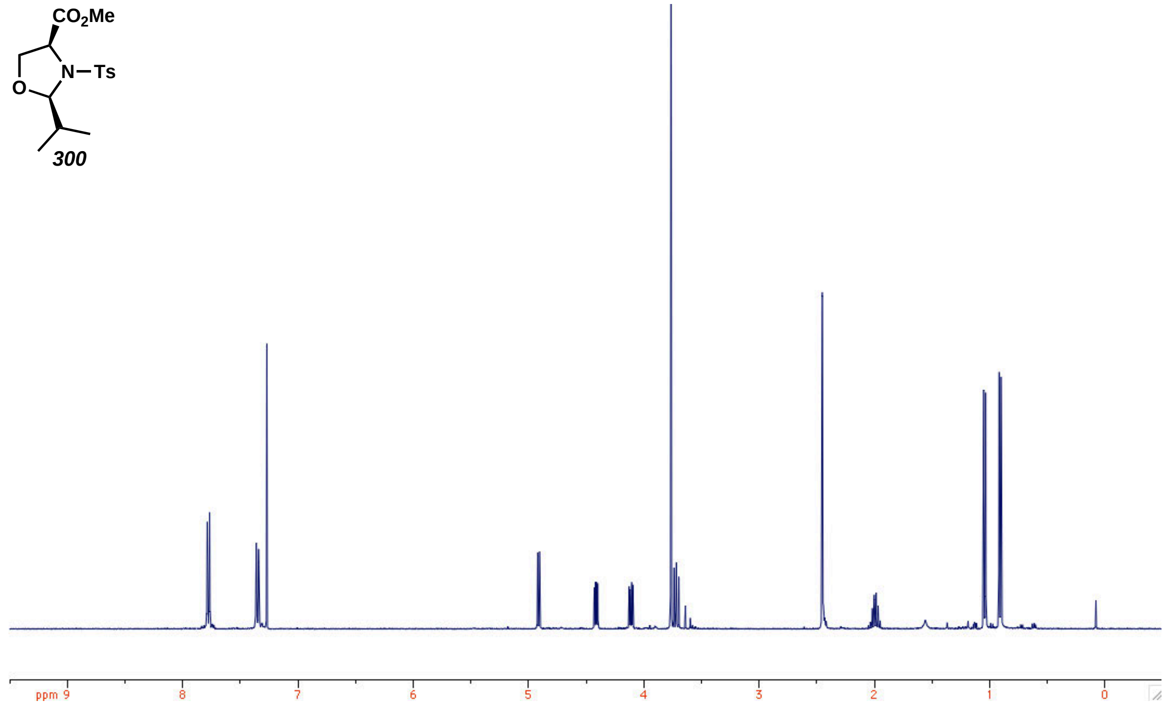

CO2Me
N−Ts
O
ppm 9
8
7
6
5
4
3
2
1
0

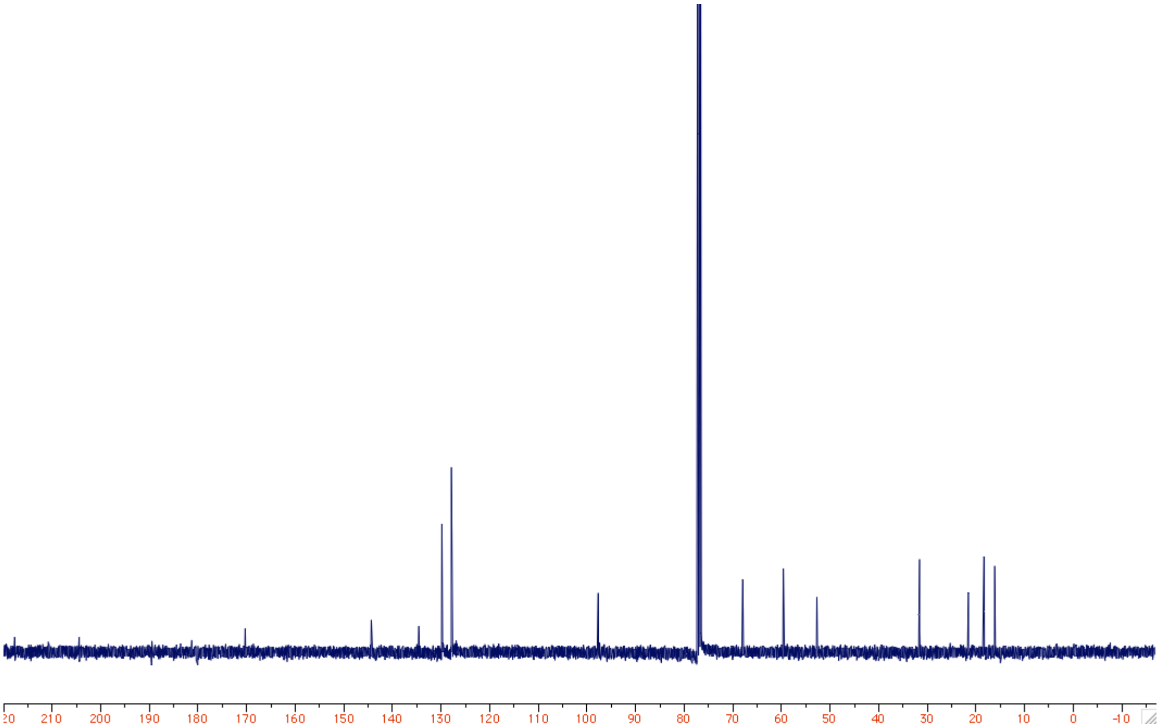
292

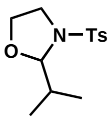

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

CO2Me
N–Ts
O

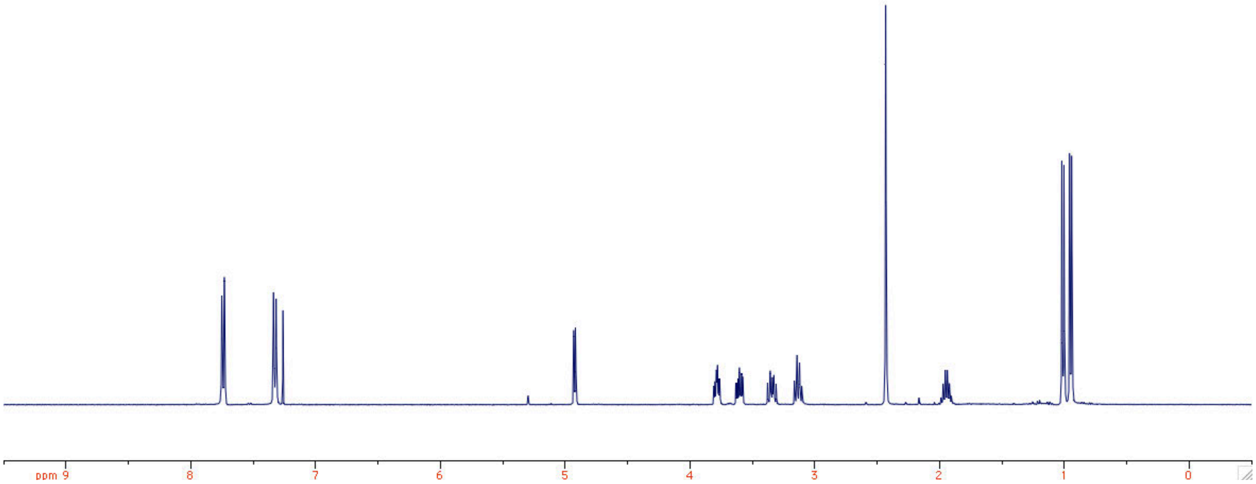
300

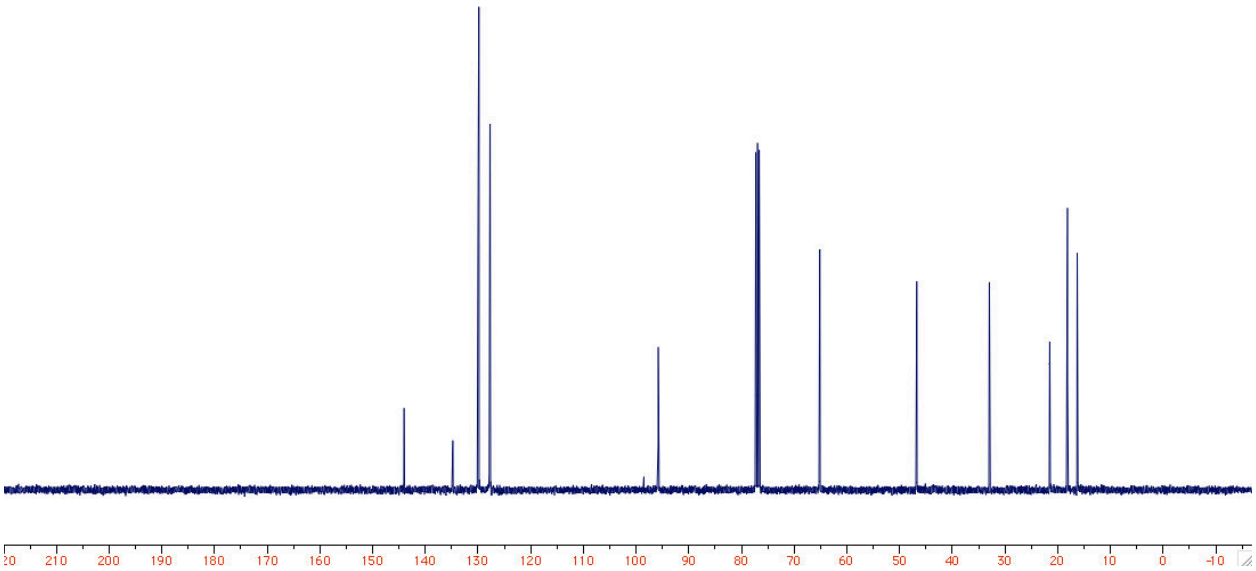

ppm 9
8
7
6
5
4
3
2
1
0

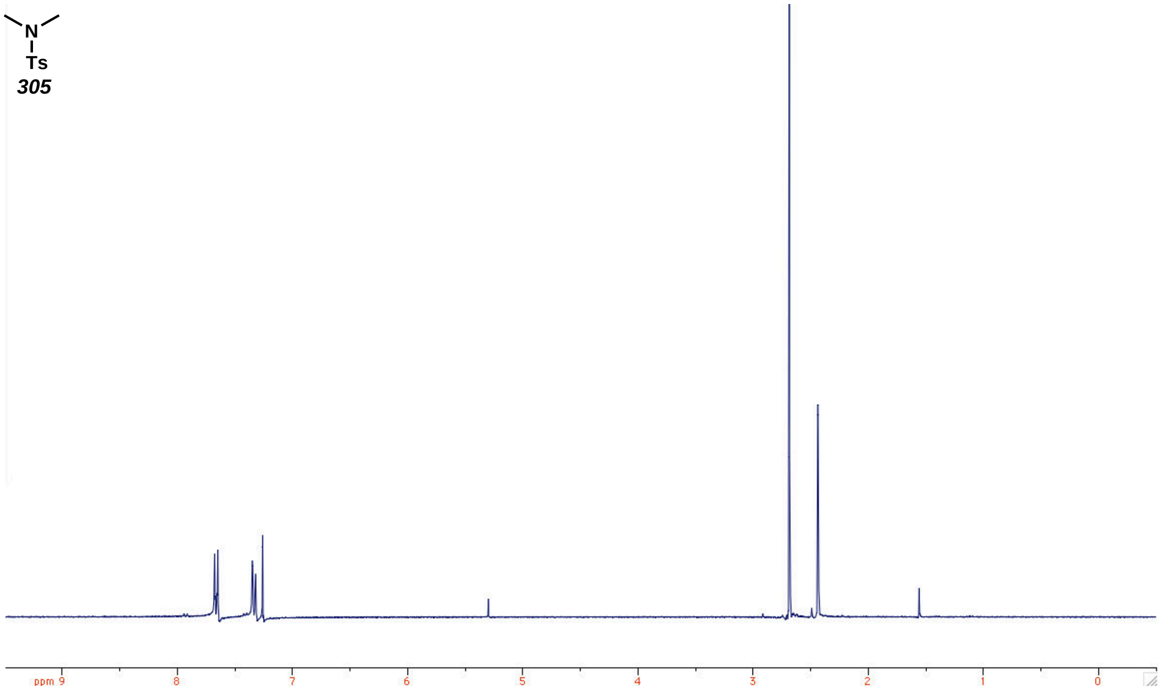

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
N
Ts

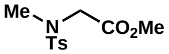
303


ppm 9
8
7
6
5
4
3
2
1
0

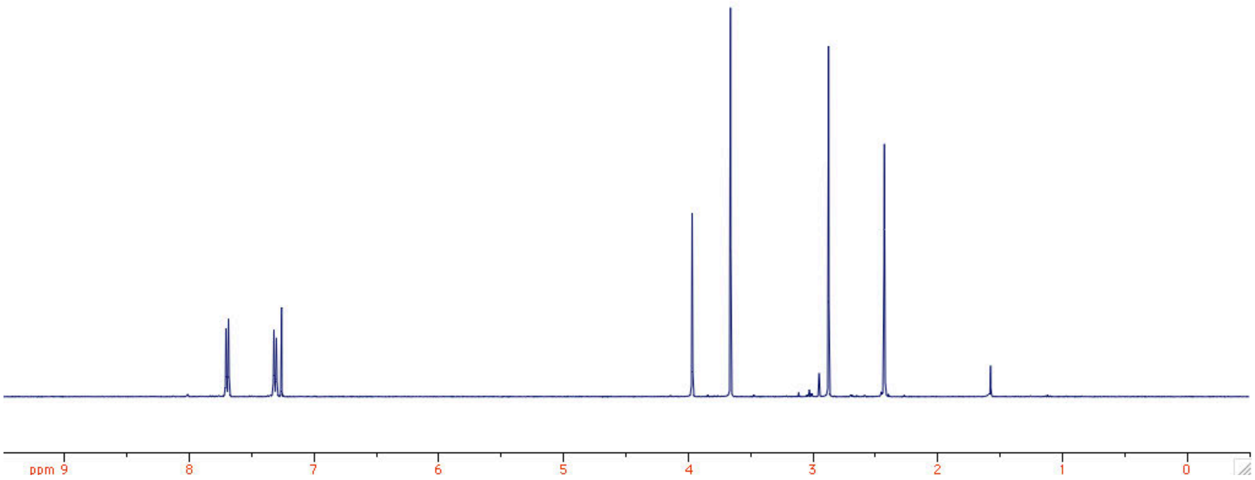

20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

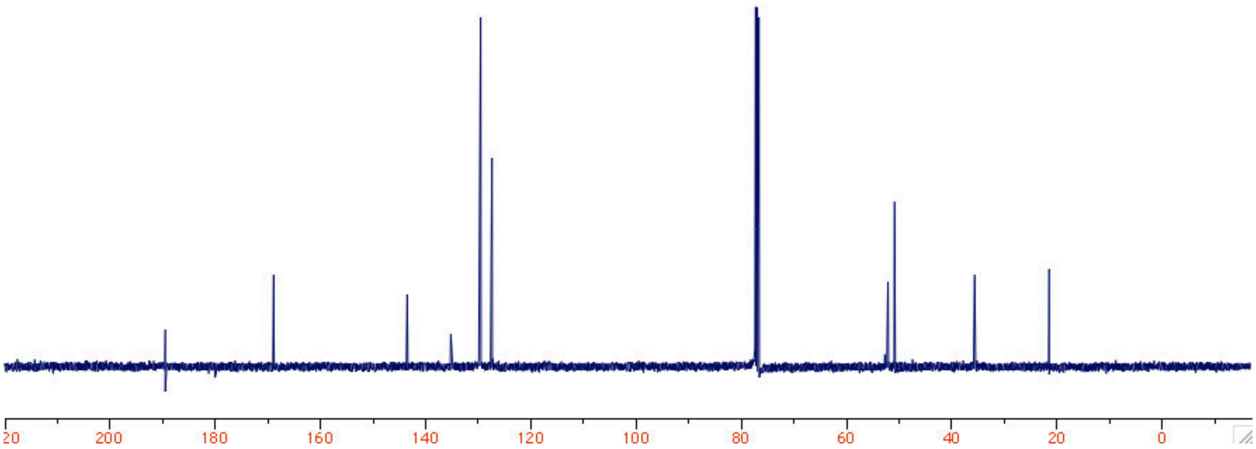


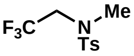
305


Me
N
Ts
CO2Me

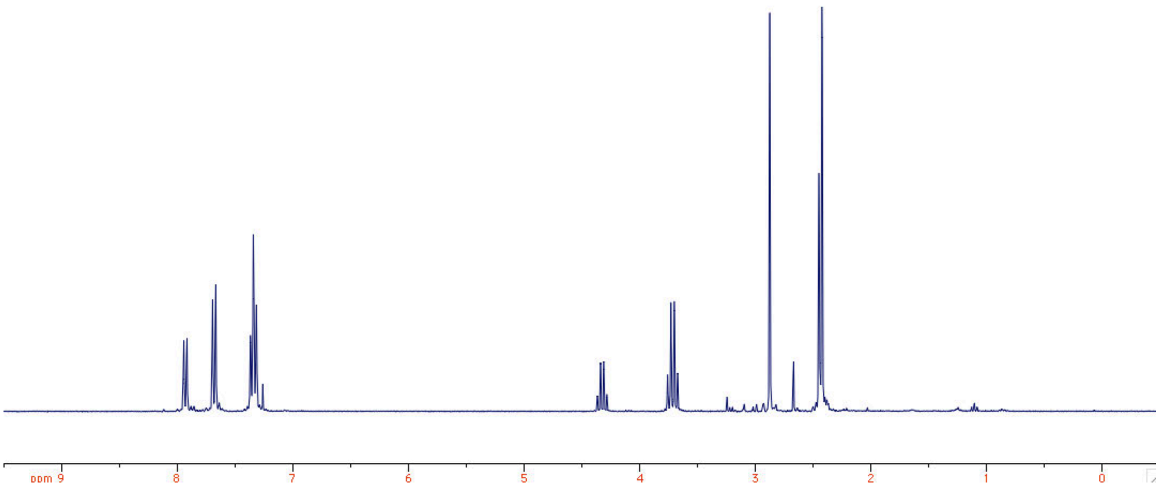
315

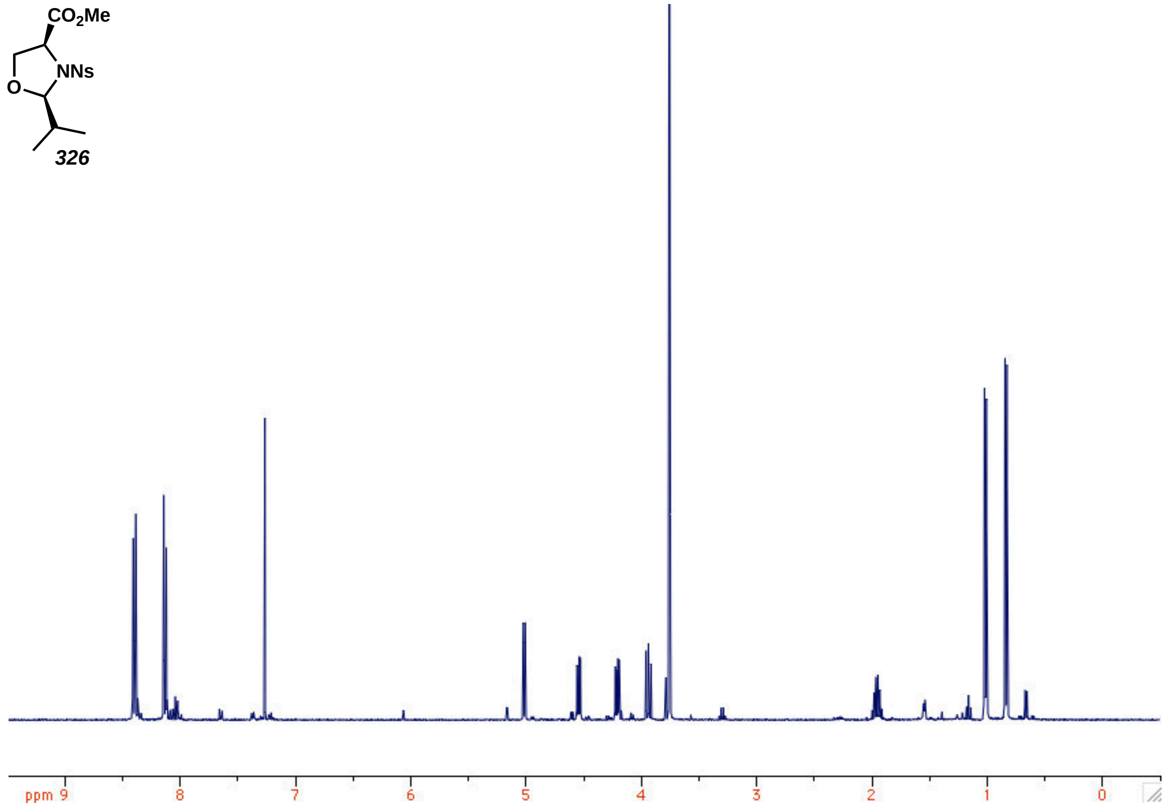

ppm 9
8
7
6
5
4
3
2
1
0


20
200
180
160
140
120
100
80
60
40
20
0



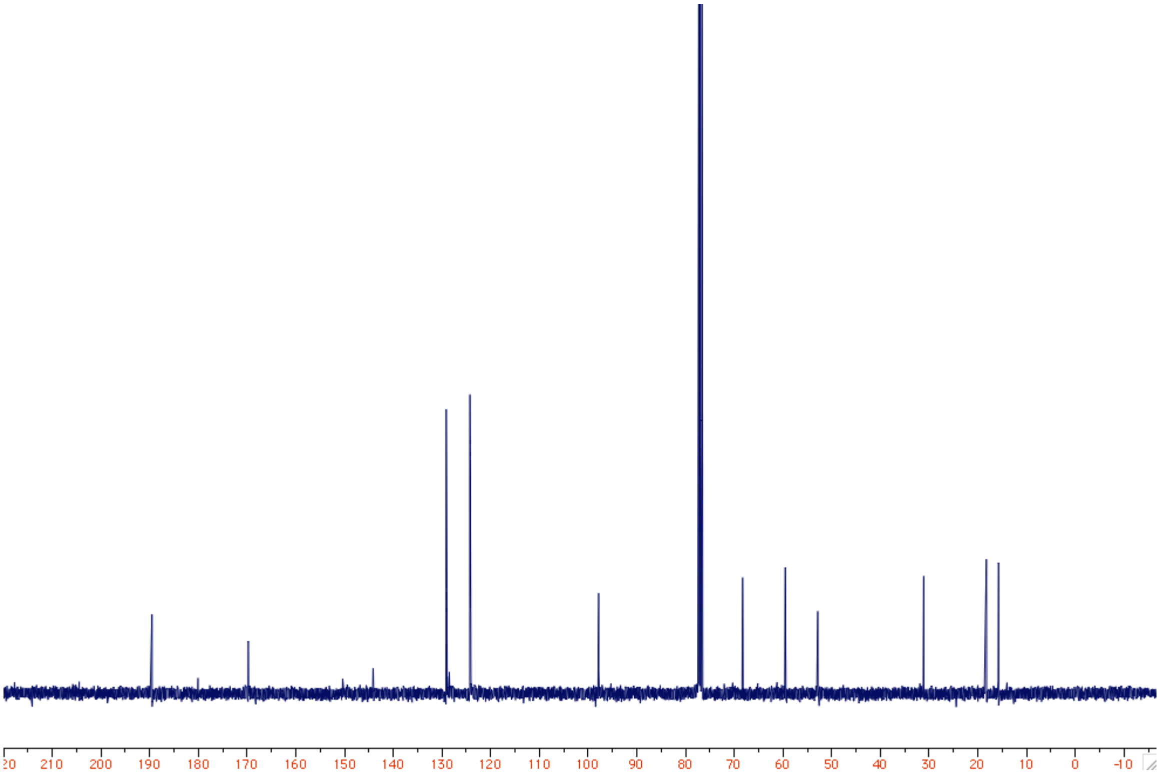
317

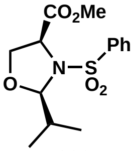



CO2Me
NNs
O

326

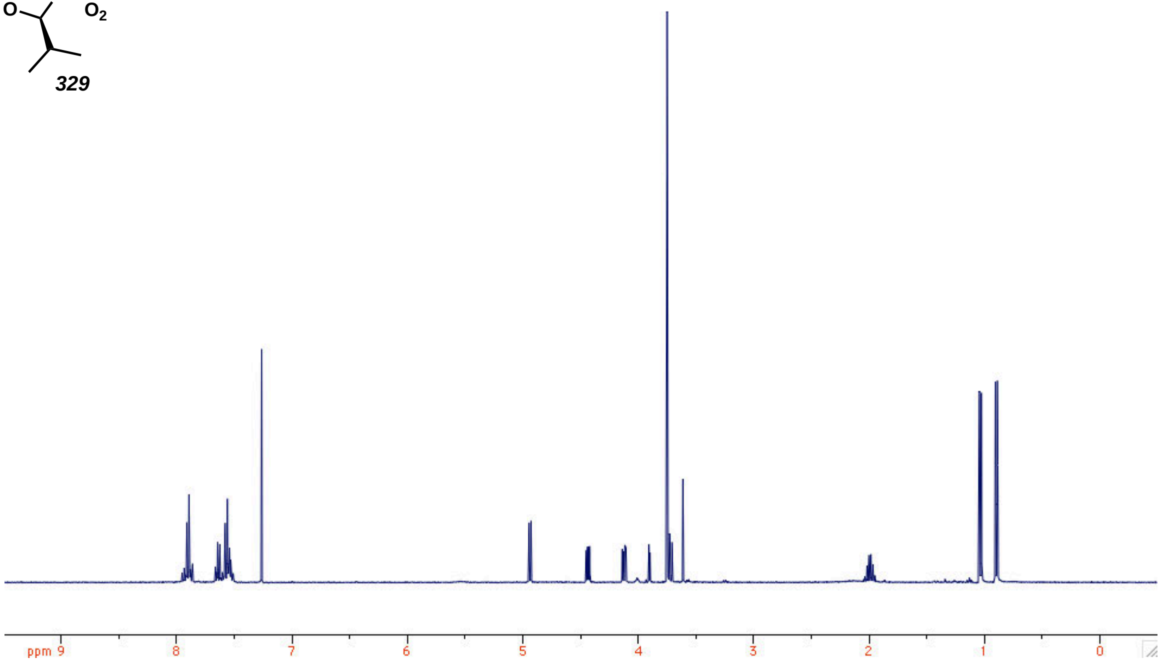
ppm 9
8
7
6
5
4
3
2
1
0


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

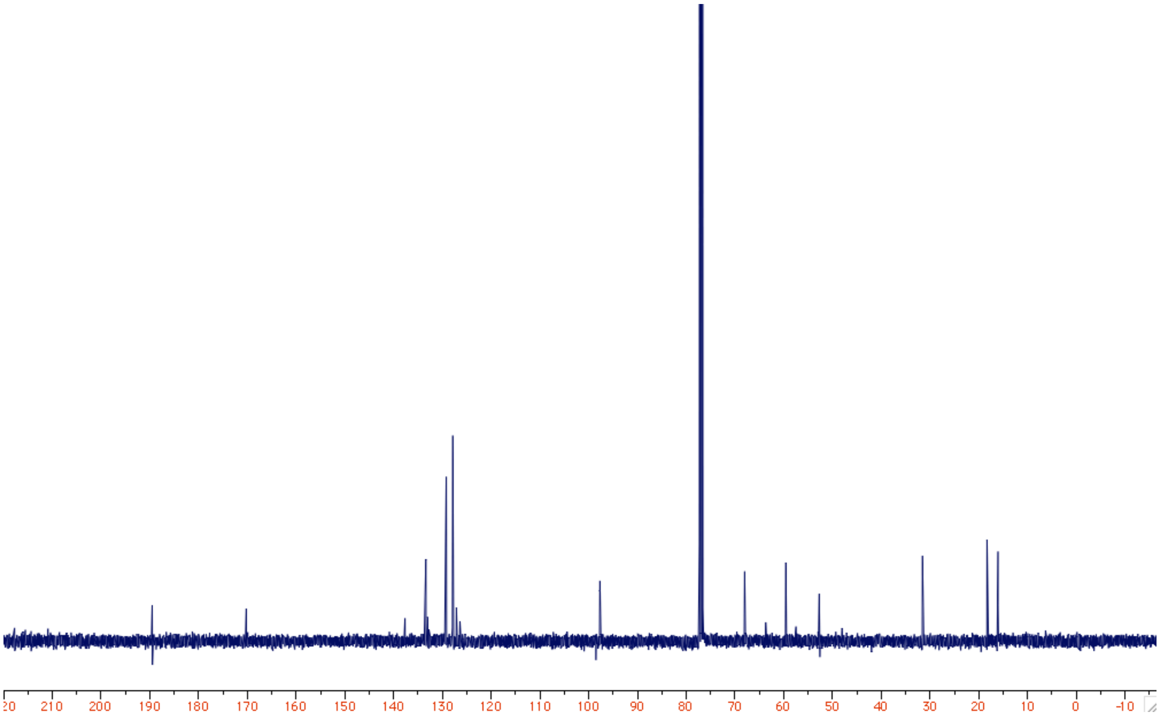


CO2Me
Ph
N
S
O2
O

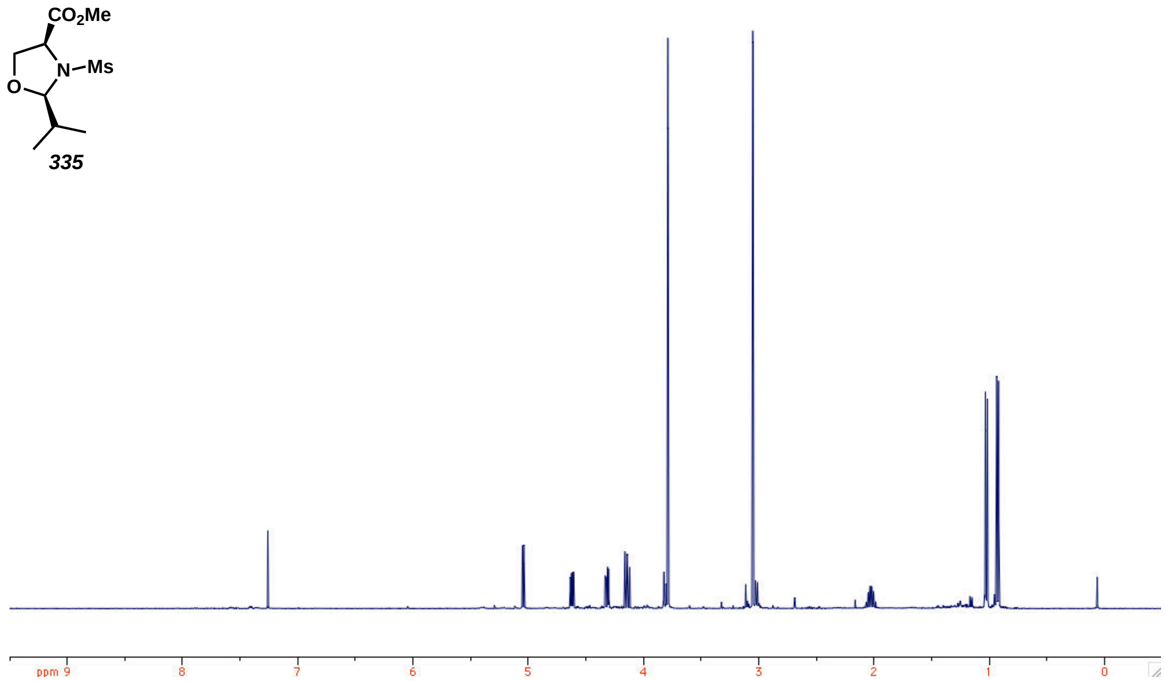
329



ppm 9
8
7
6
5
4
3
2
1
0

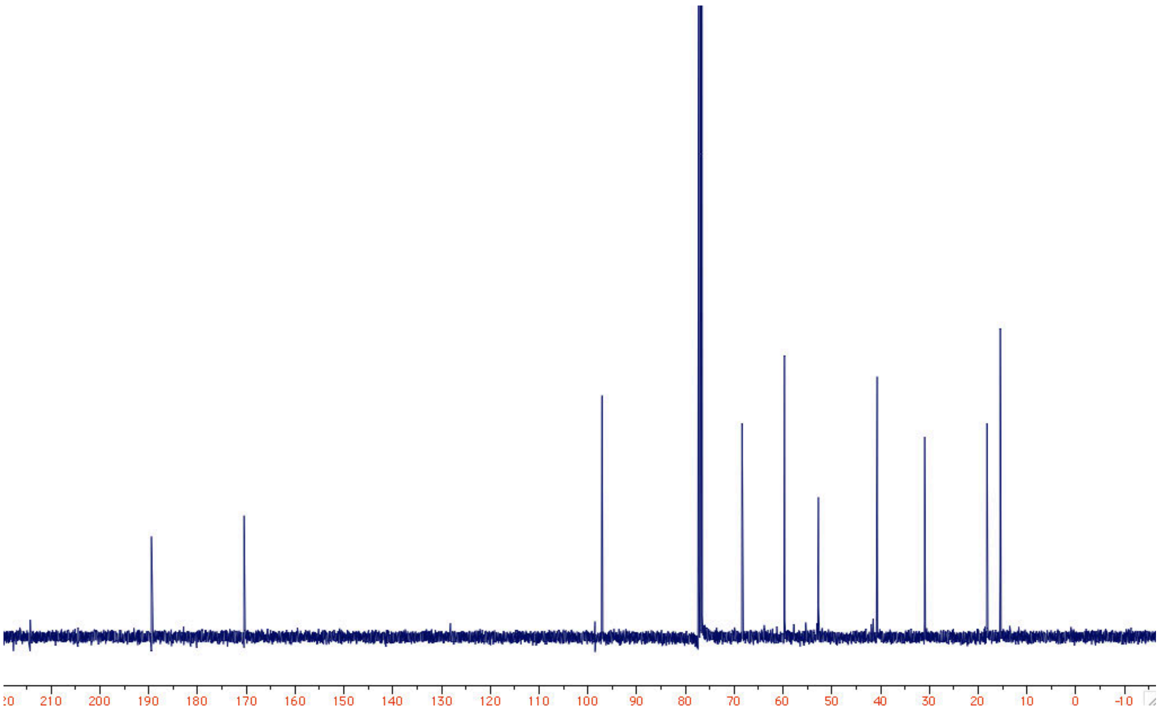


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



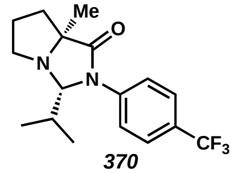
CO2Me
N
Ms
O
ppm 9
8
7
6
5
4
3
2
1
0

335

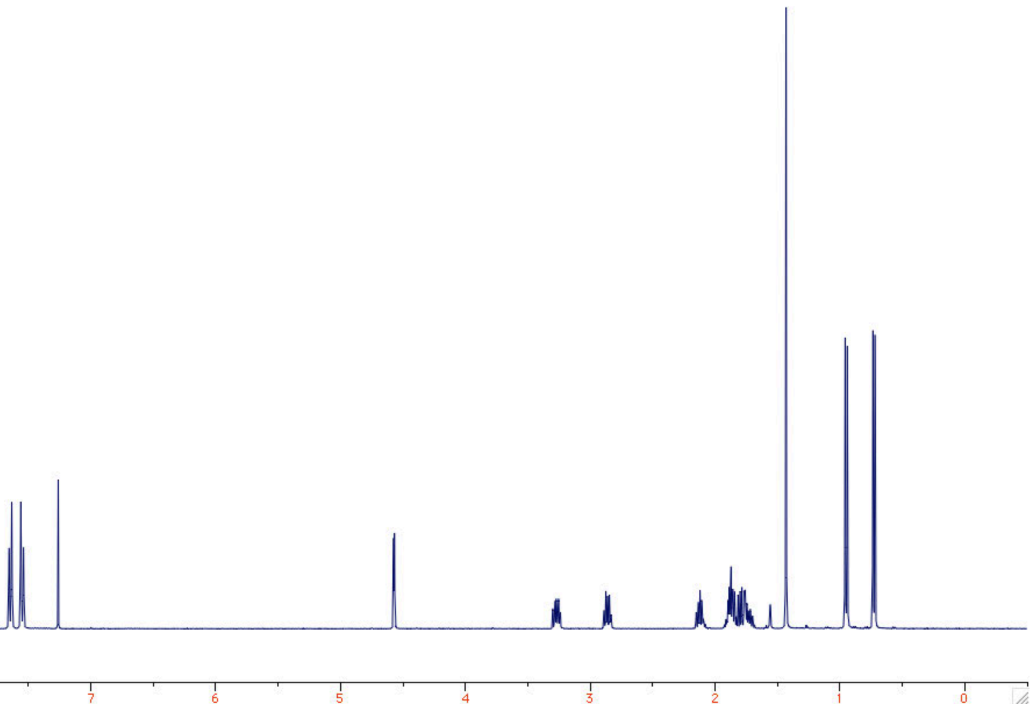


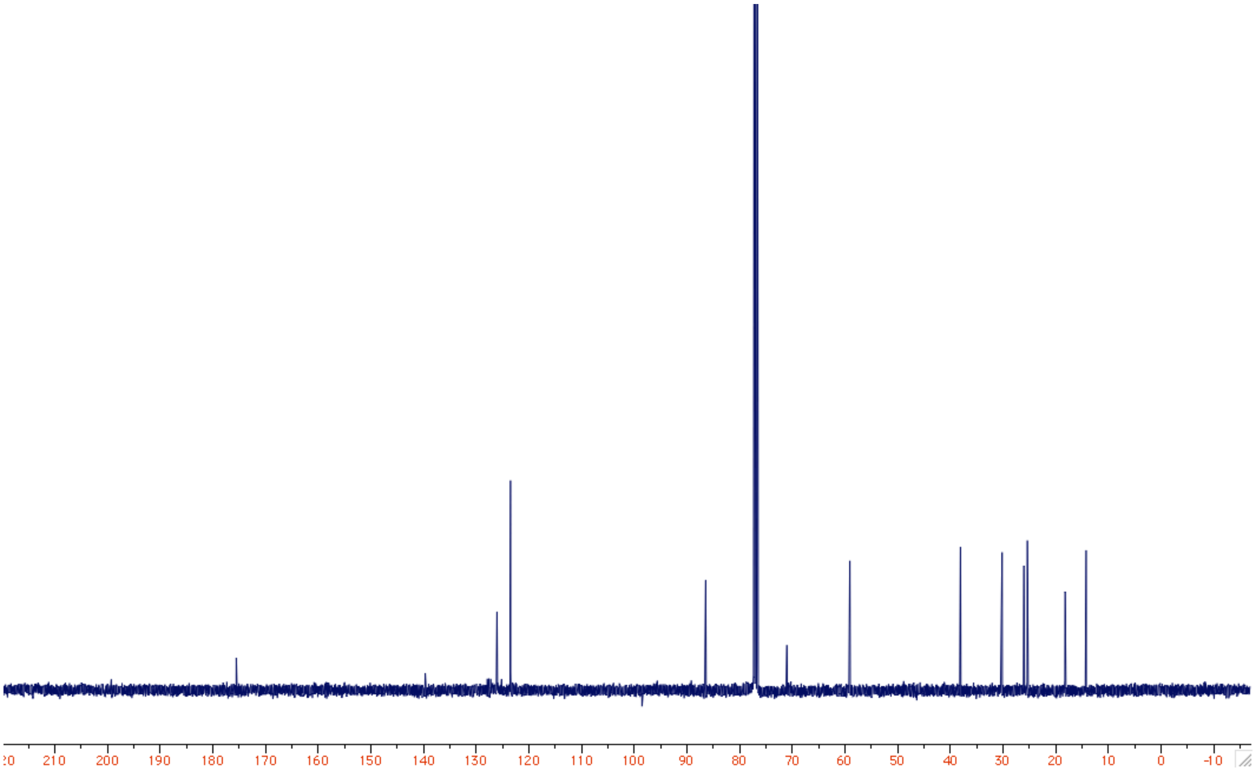
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Appendix 4: Spectra for Appendix 1


Me
O
N
N
CF3

370


ppm 9
8
7
6
5
4
3
2
1
0


20
210
200
190
180
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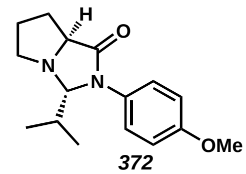
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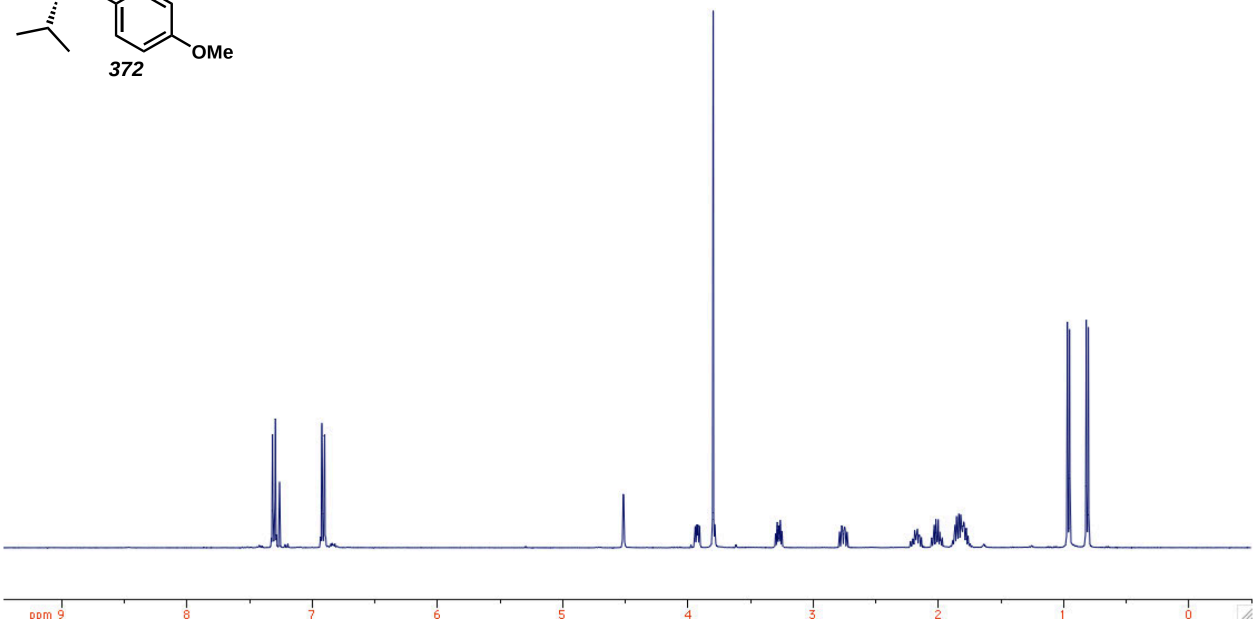
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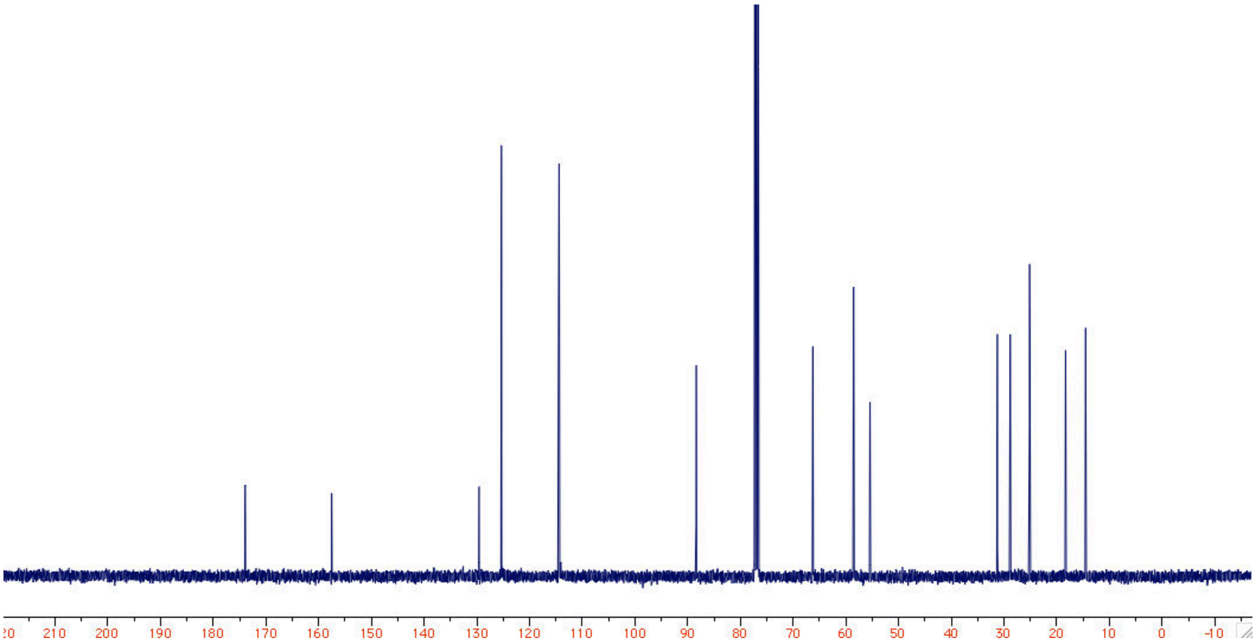
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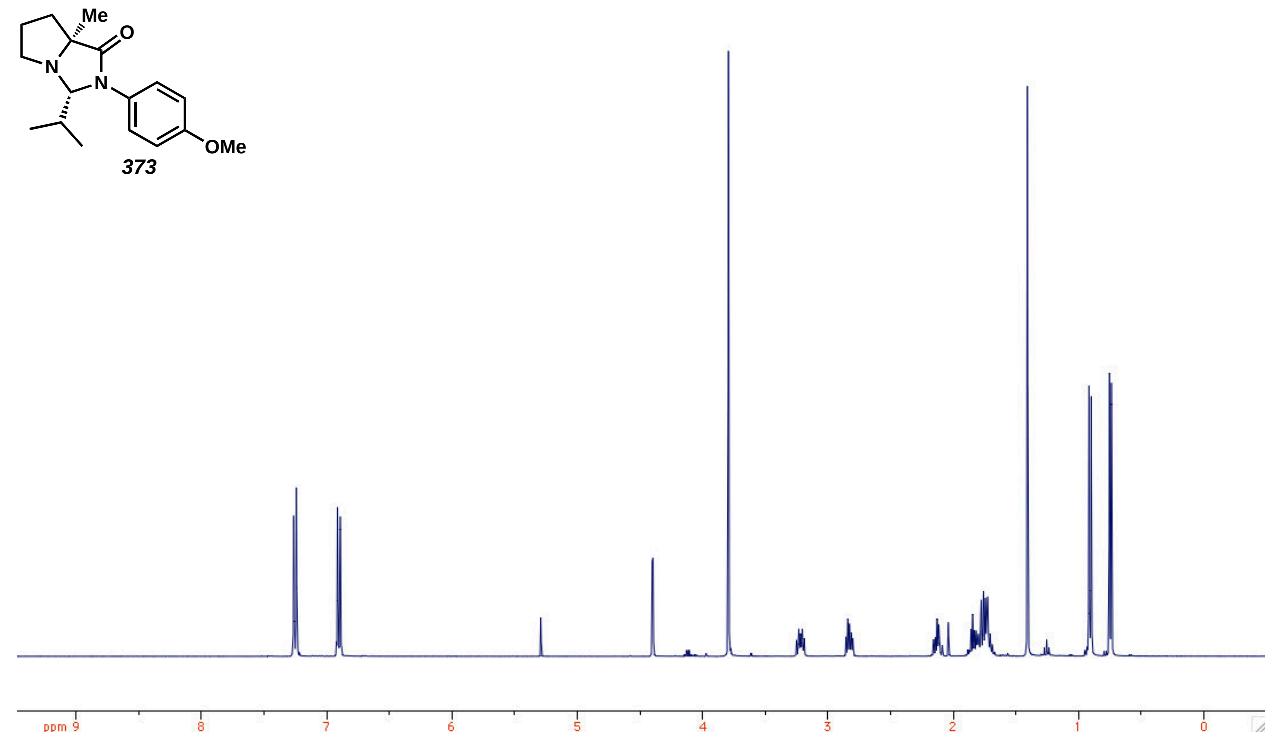
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373

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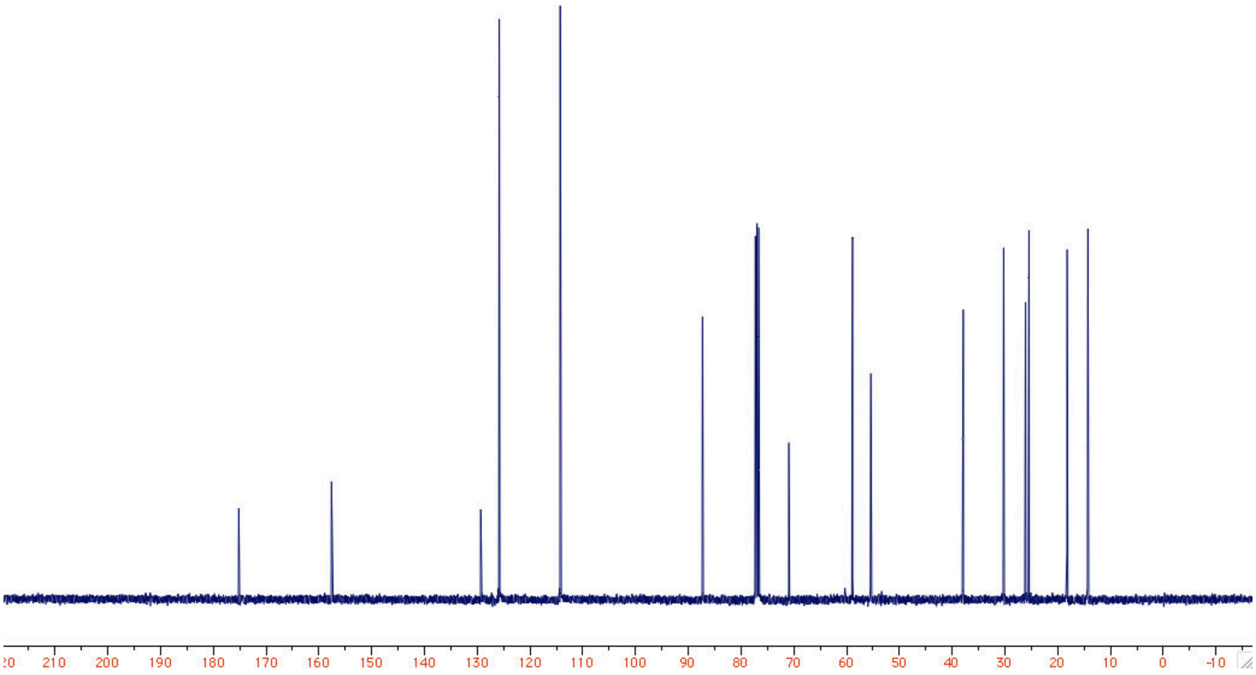
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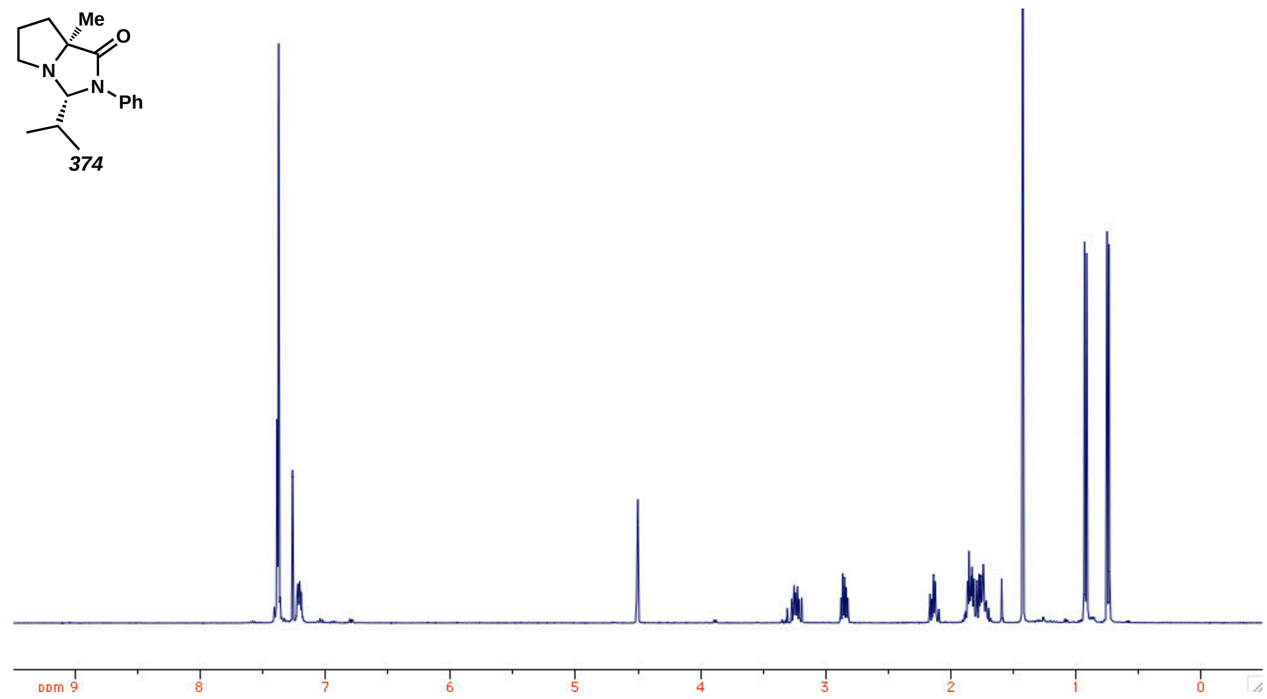
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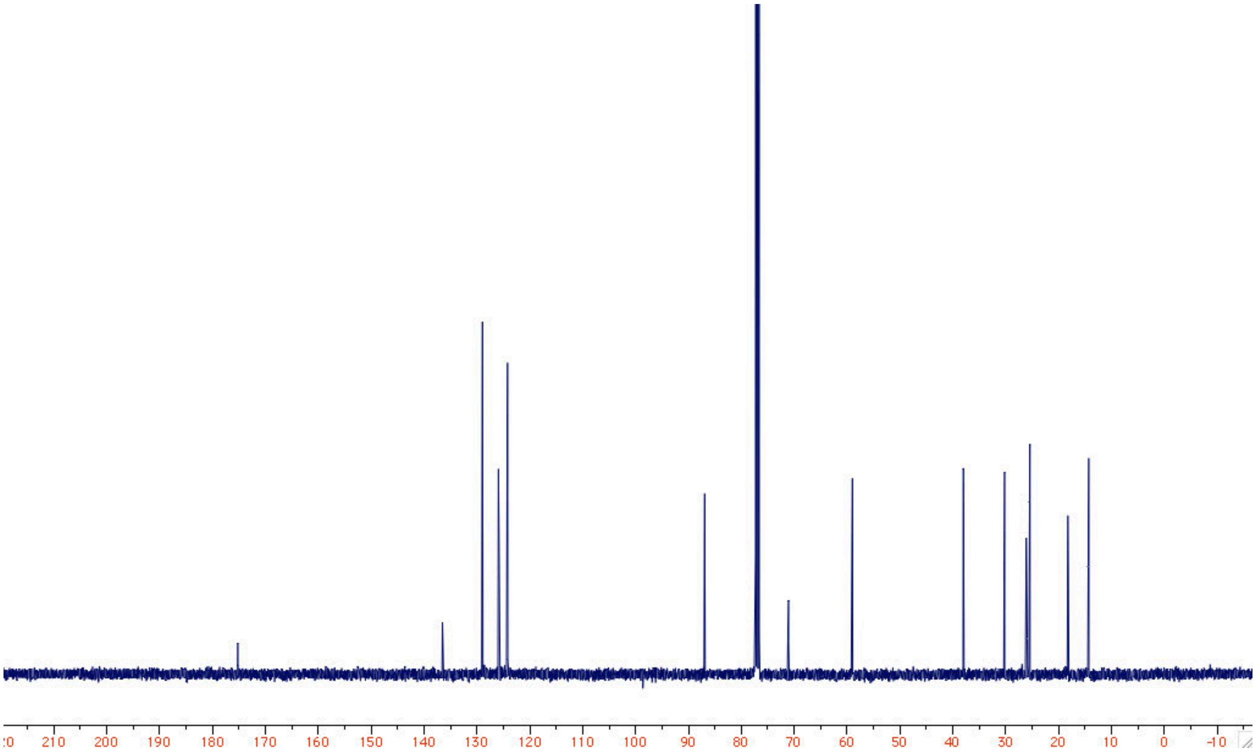
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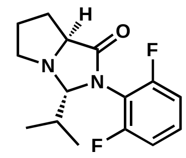
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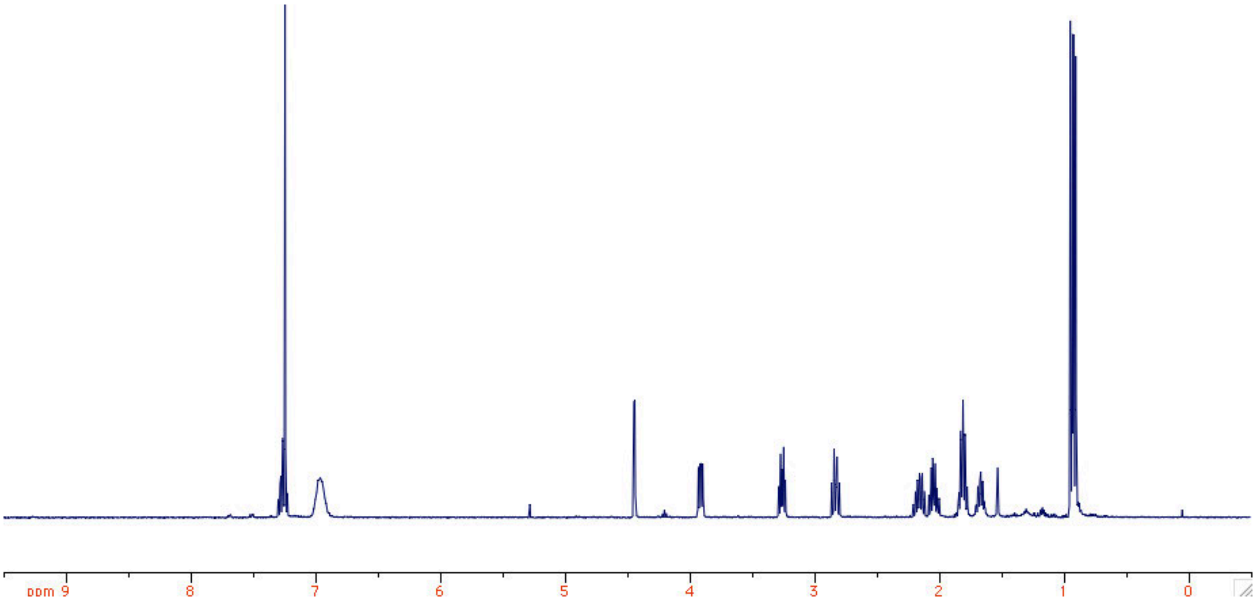
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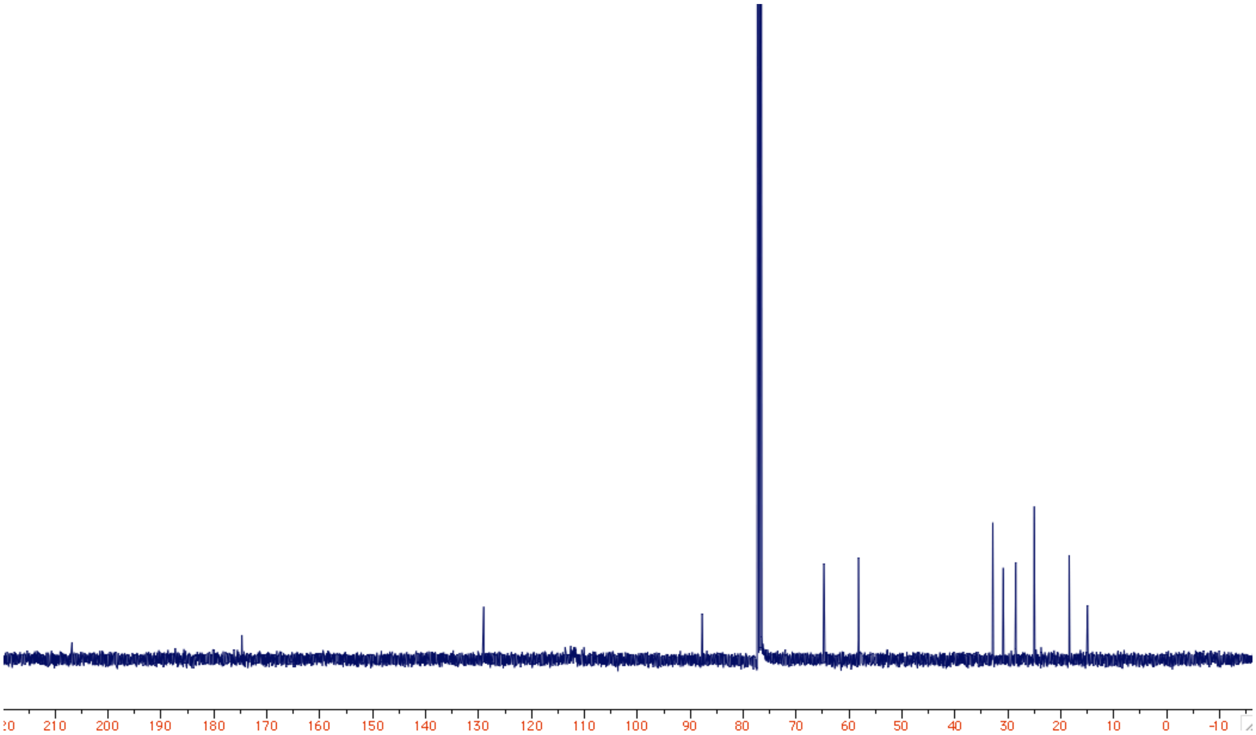
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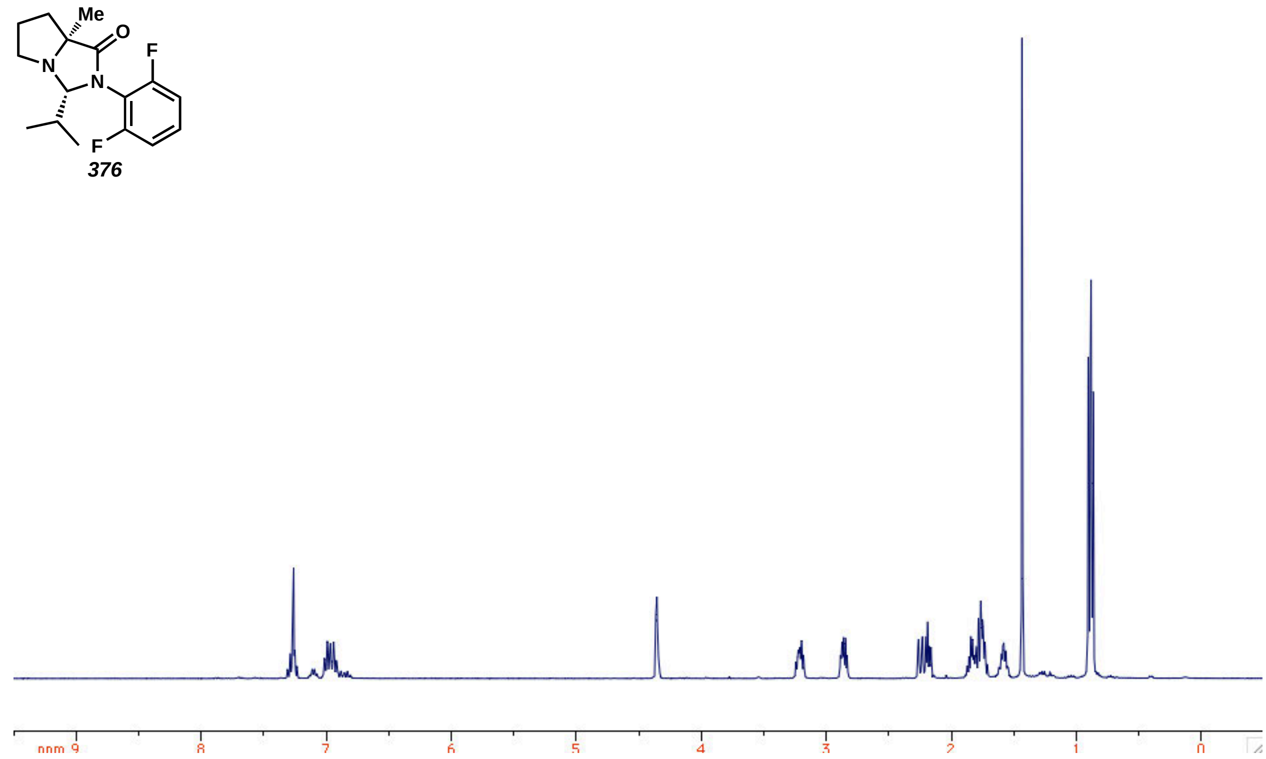
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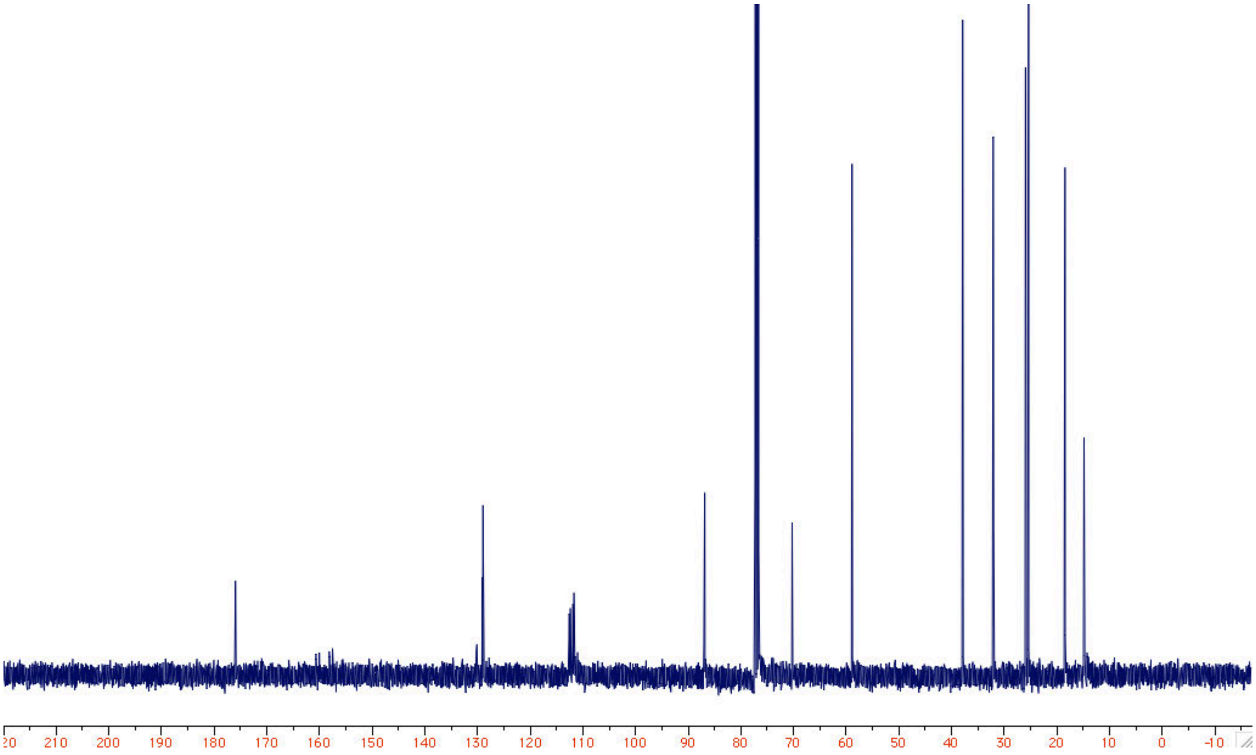
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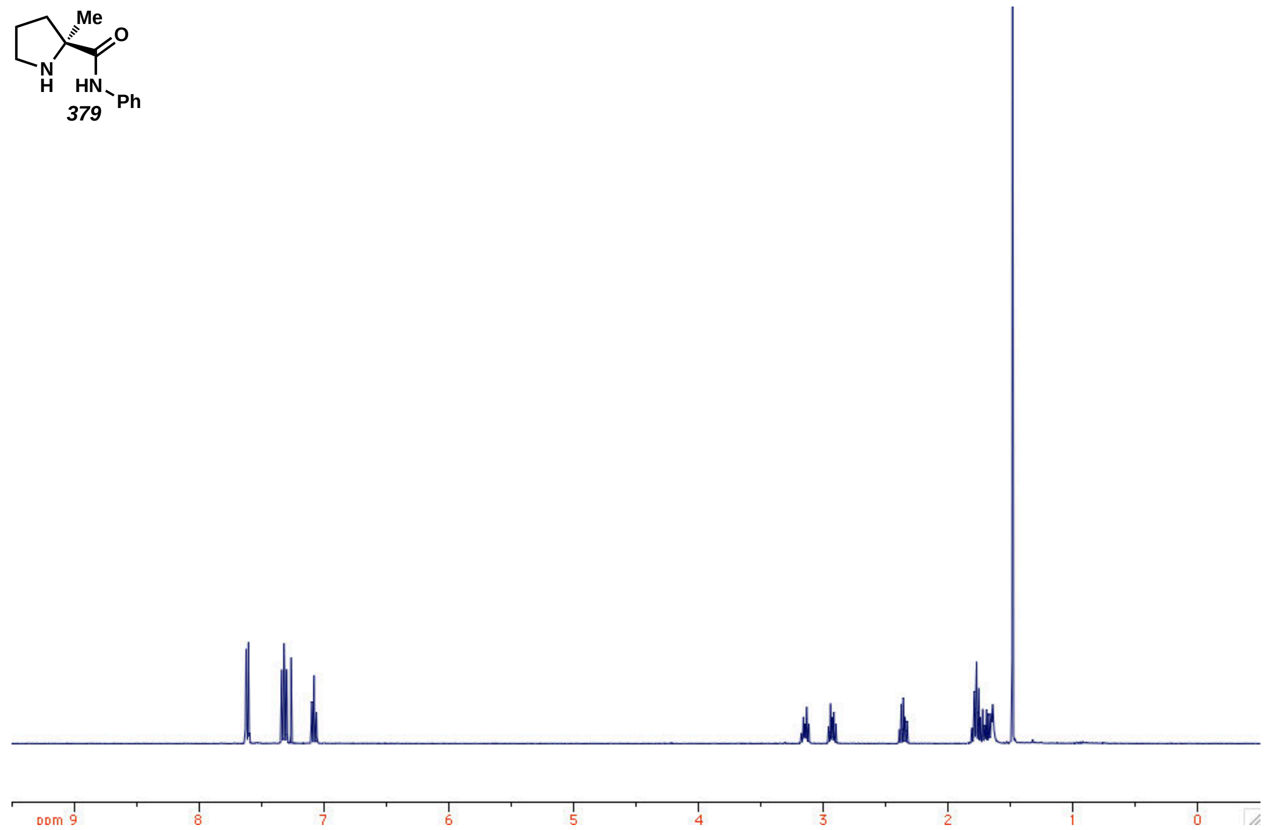
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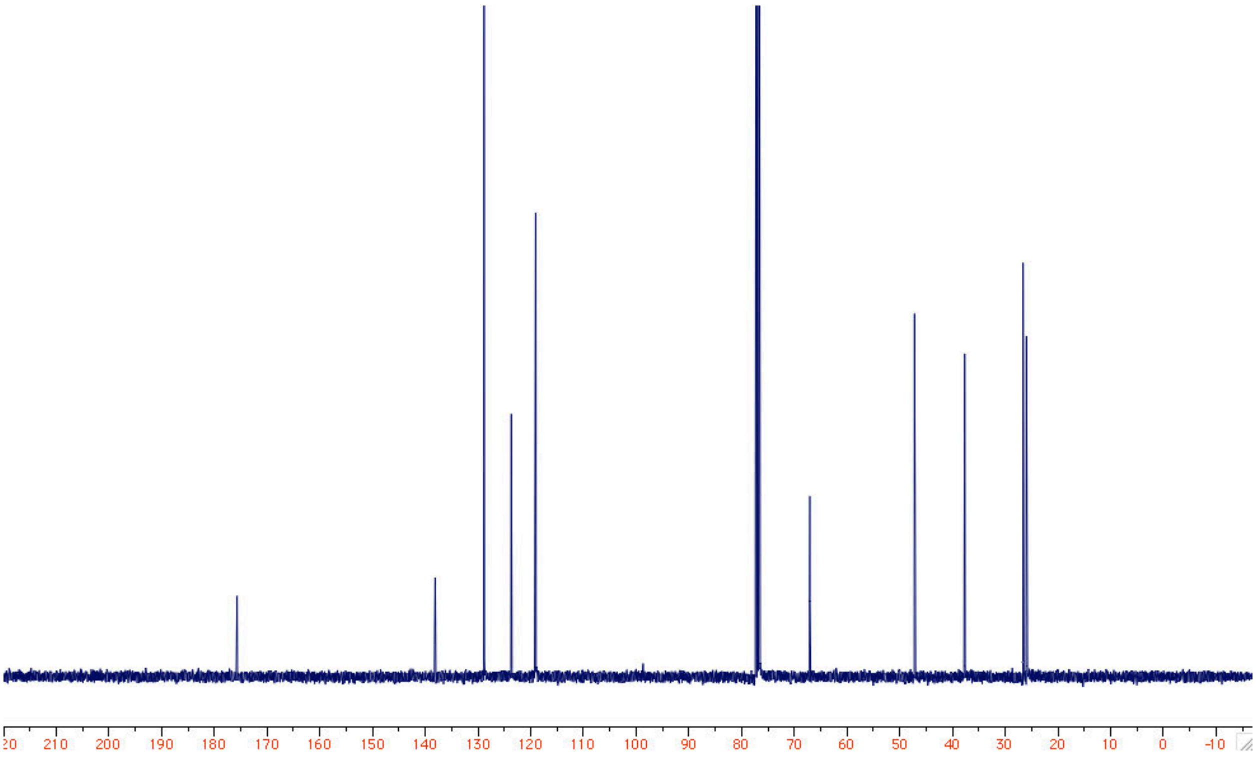
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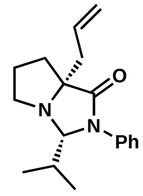
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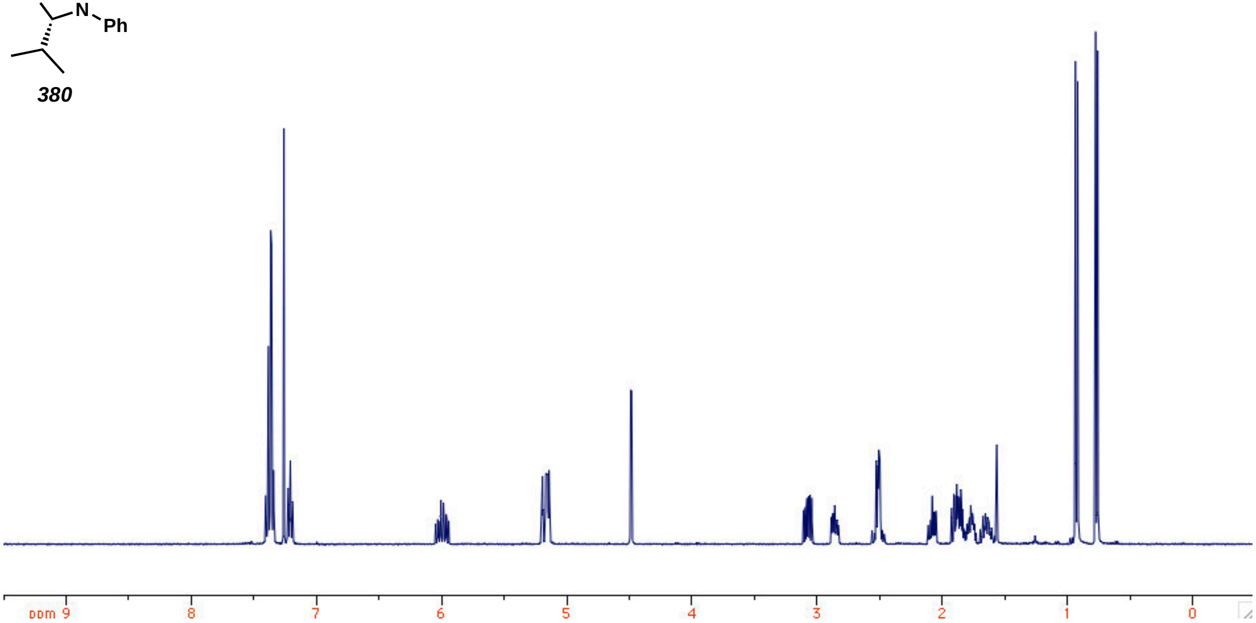
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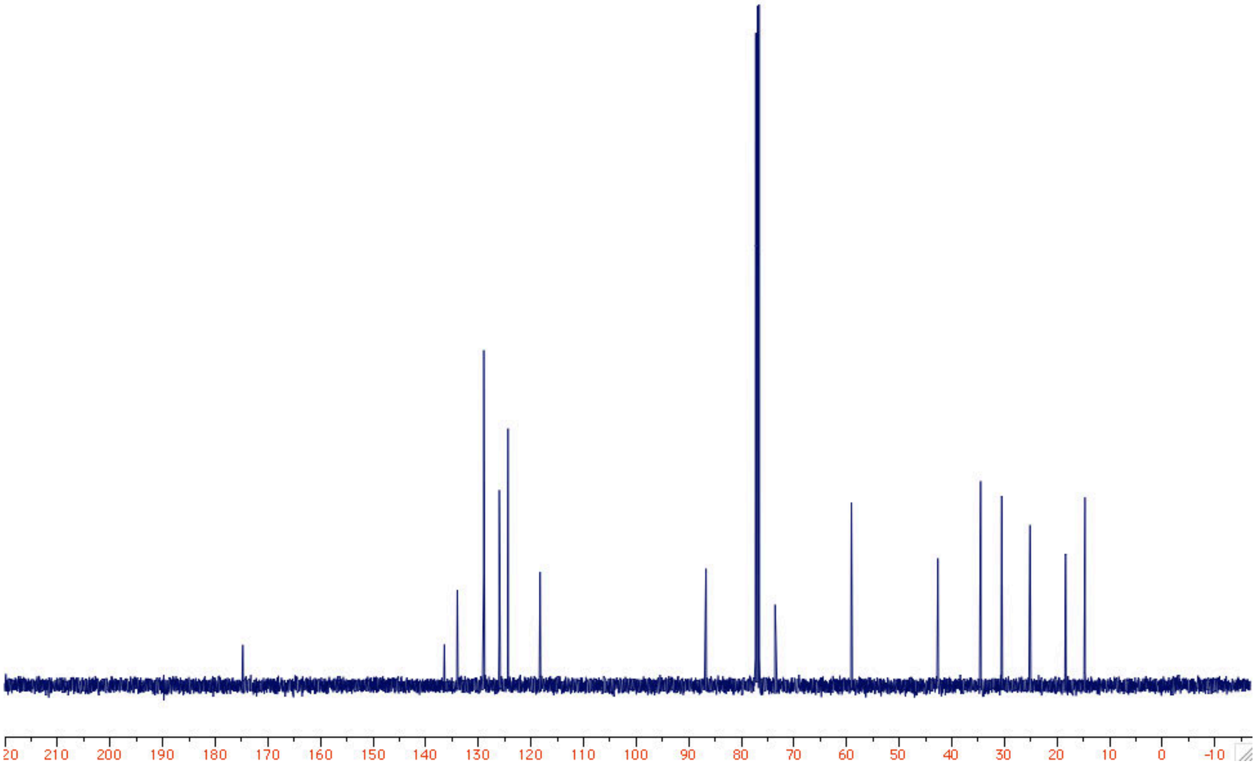
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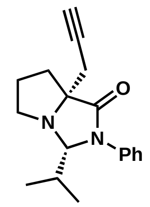
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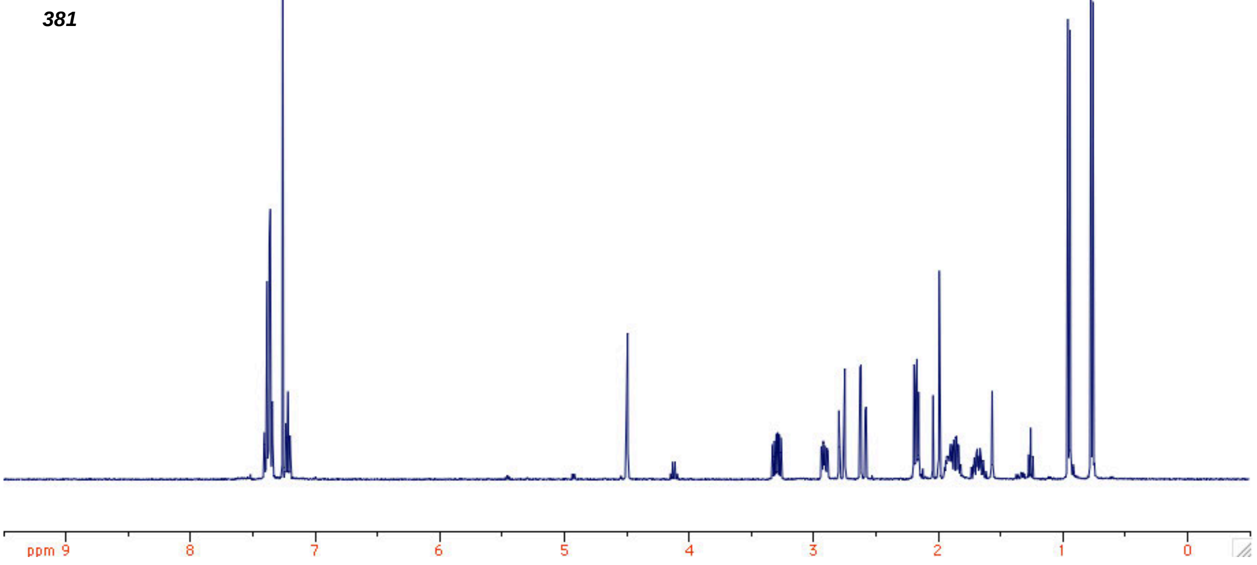
381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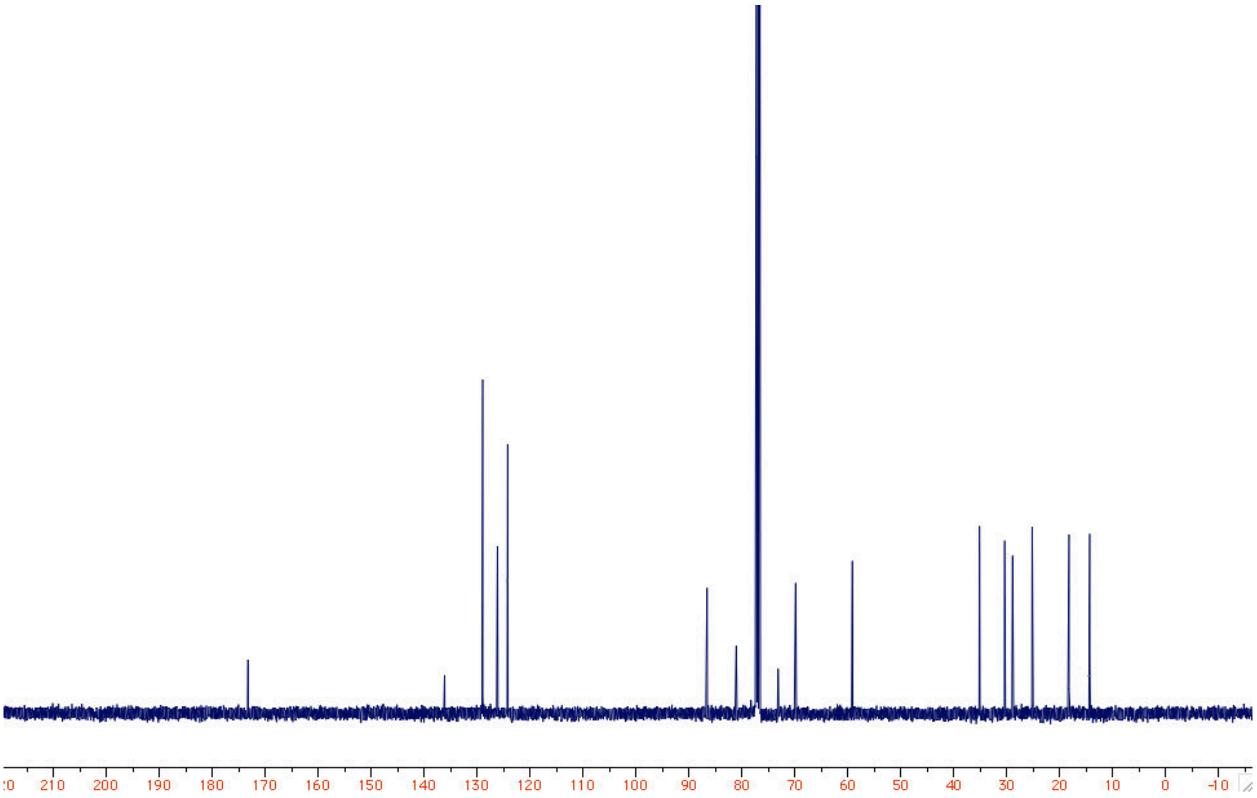
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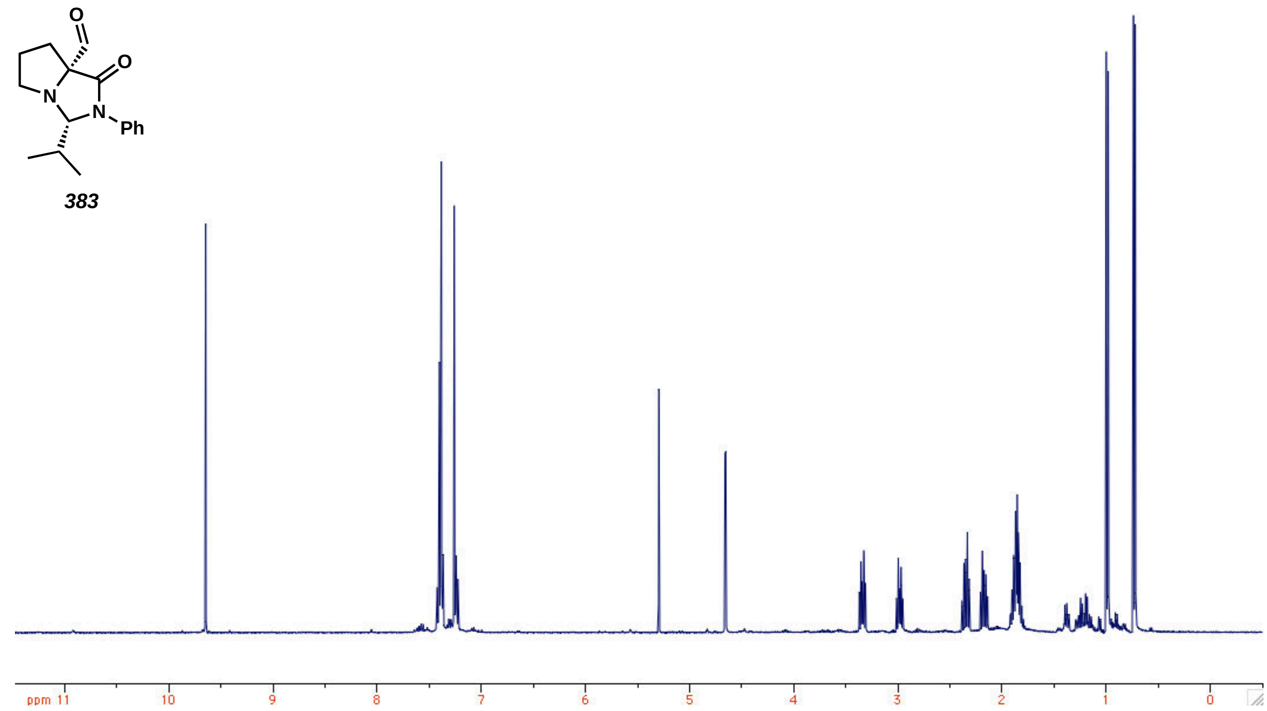
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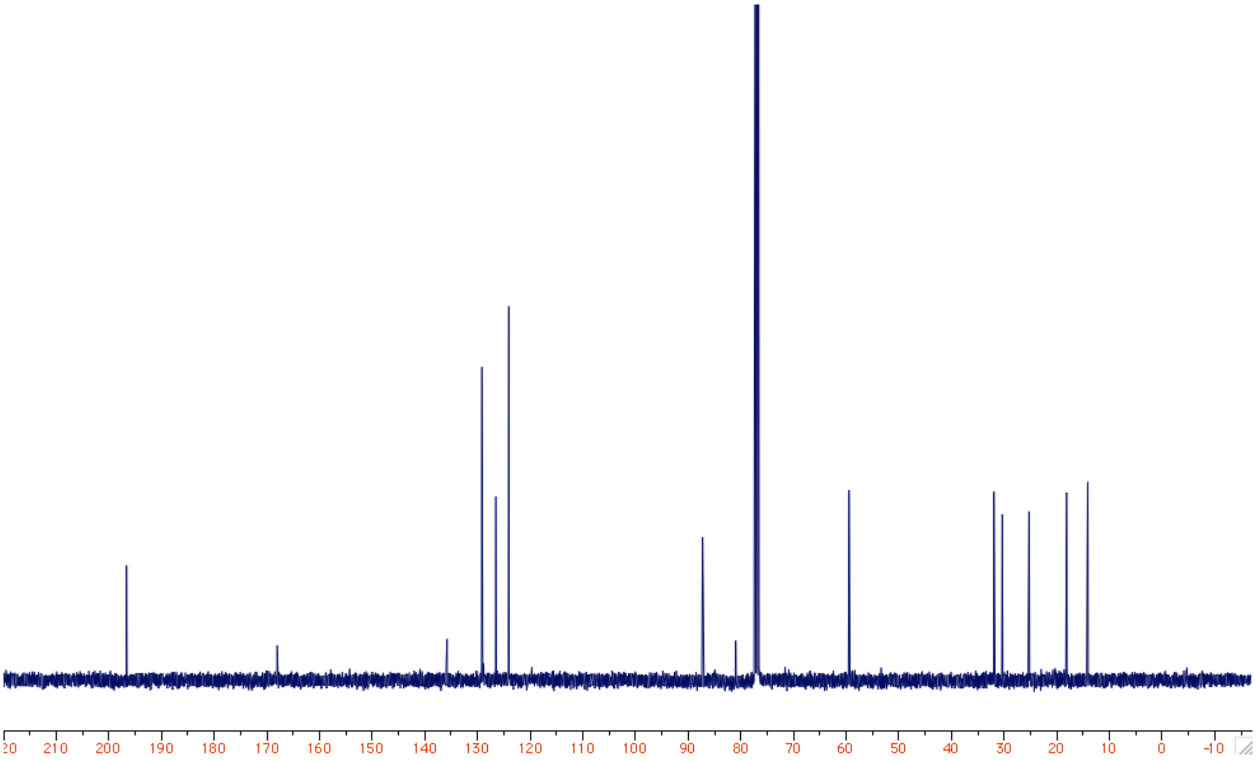
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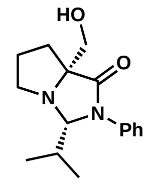
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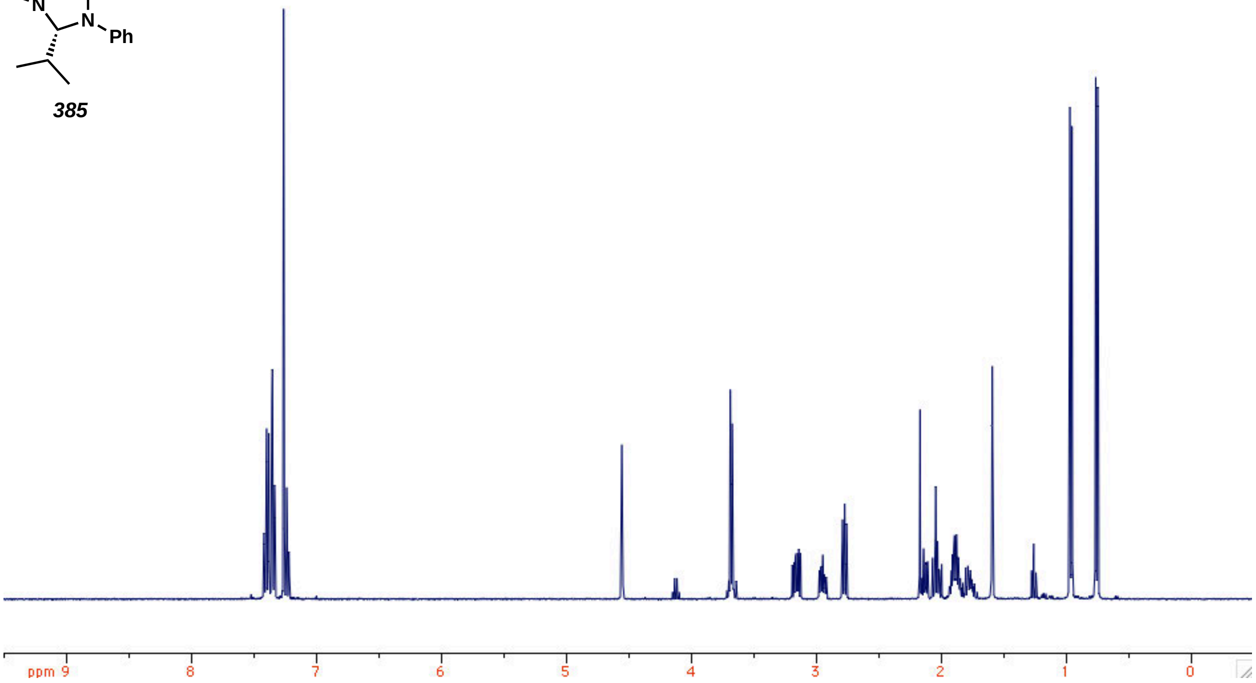
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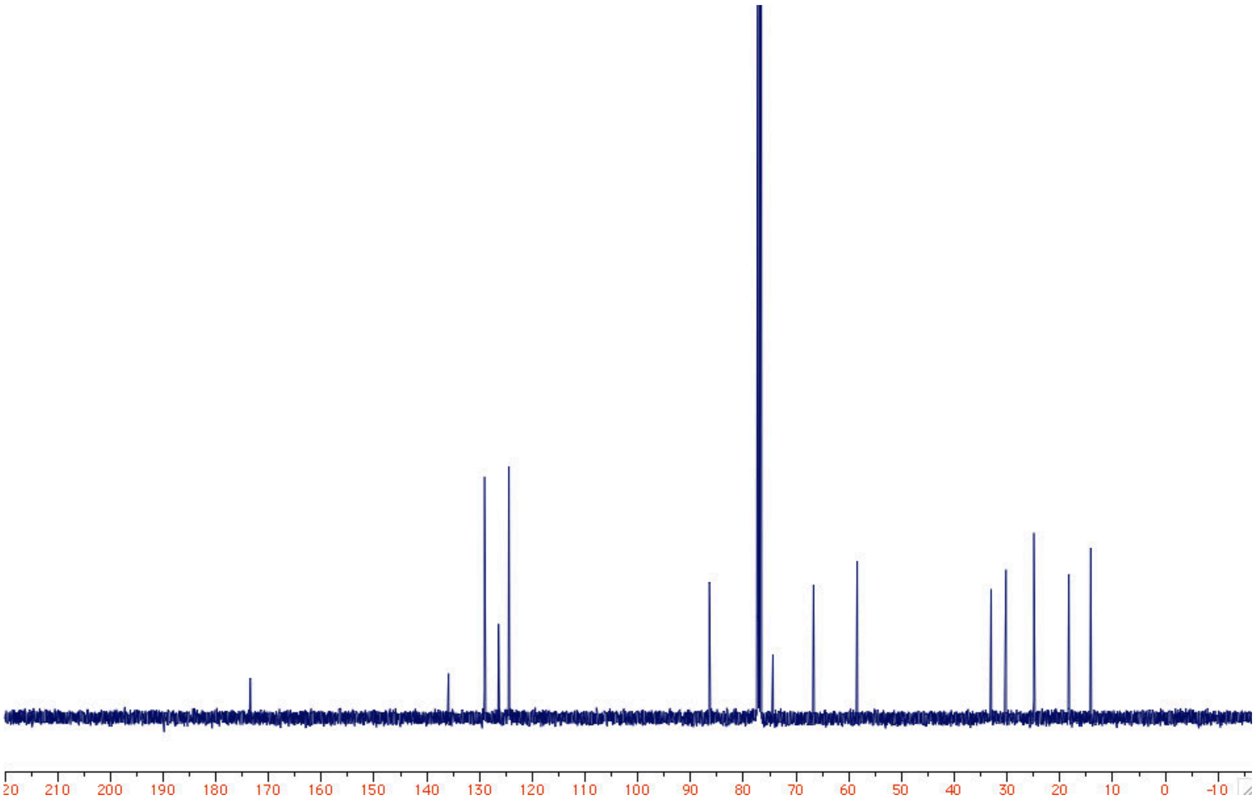
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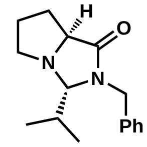

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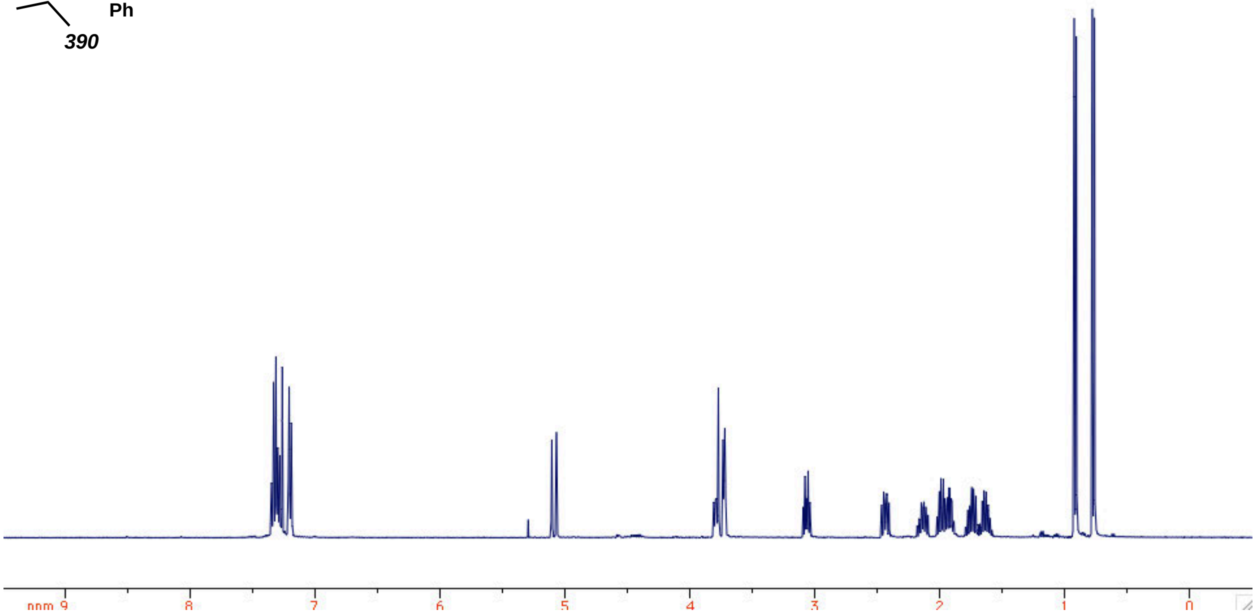
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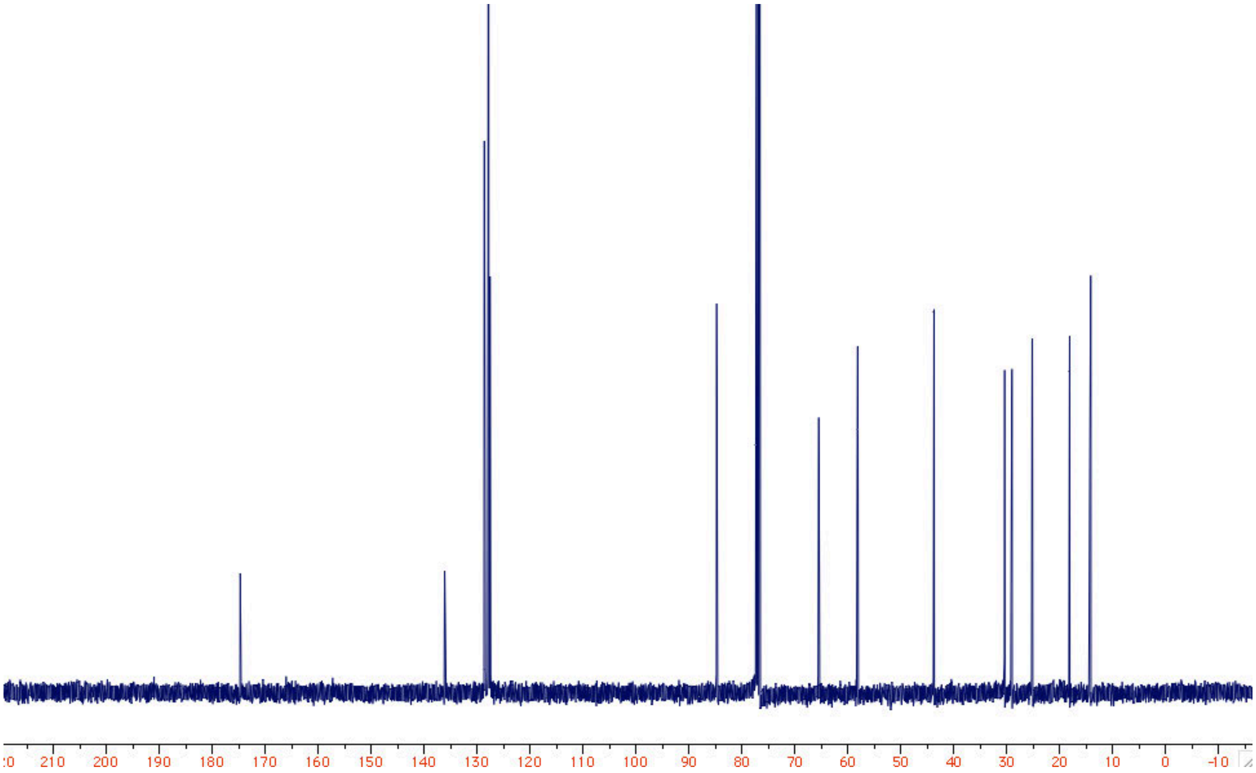
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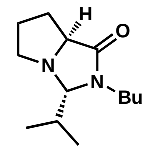
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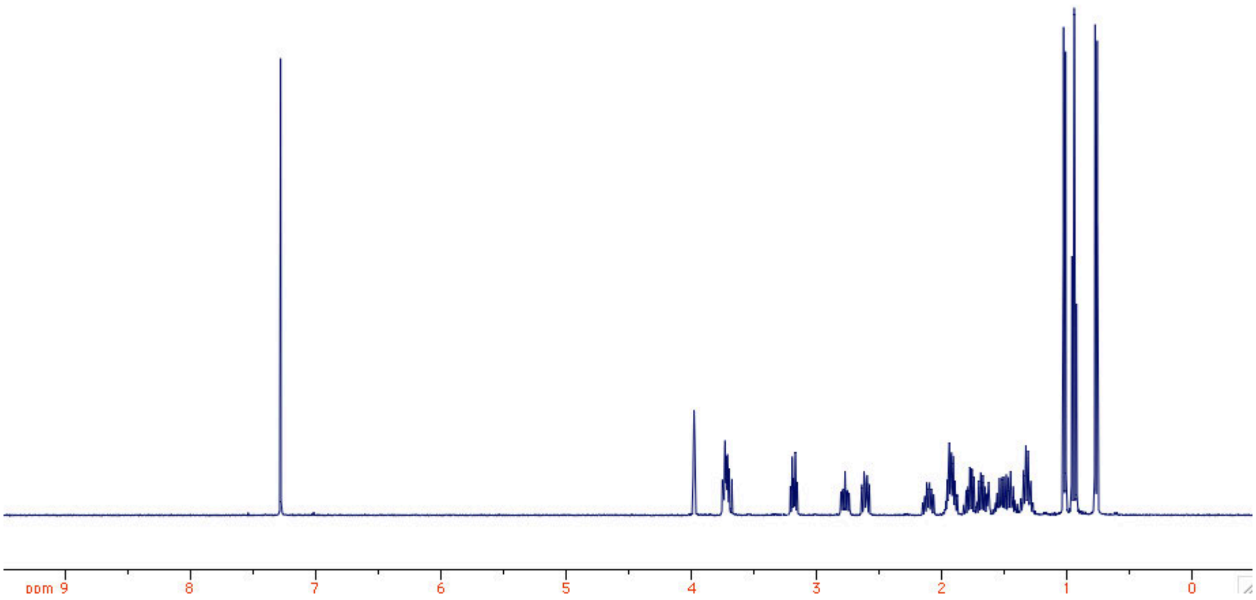
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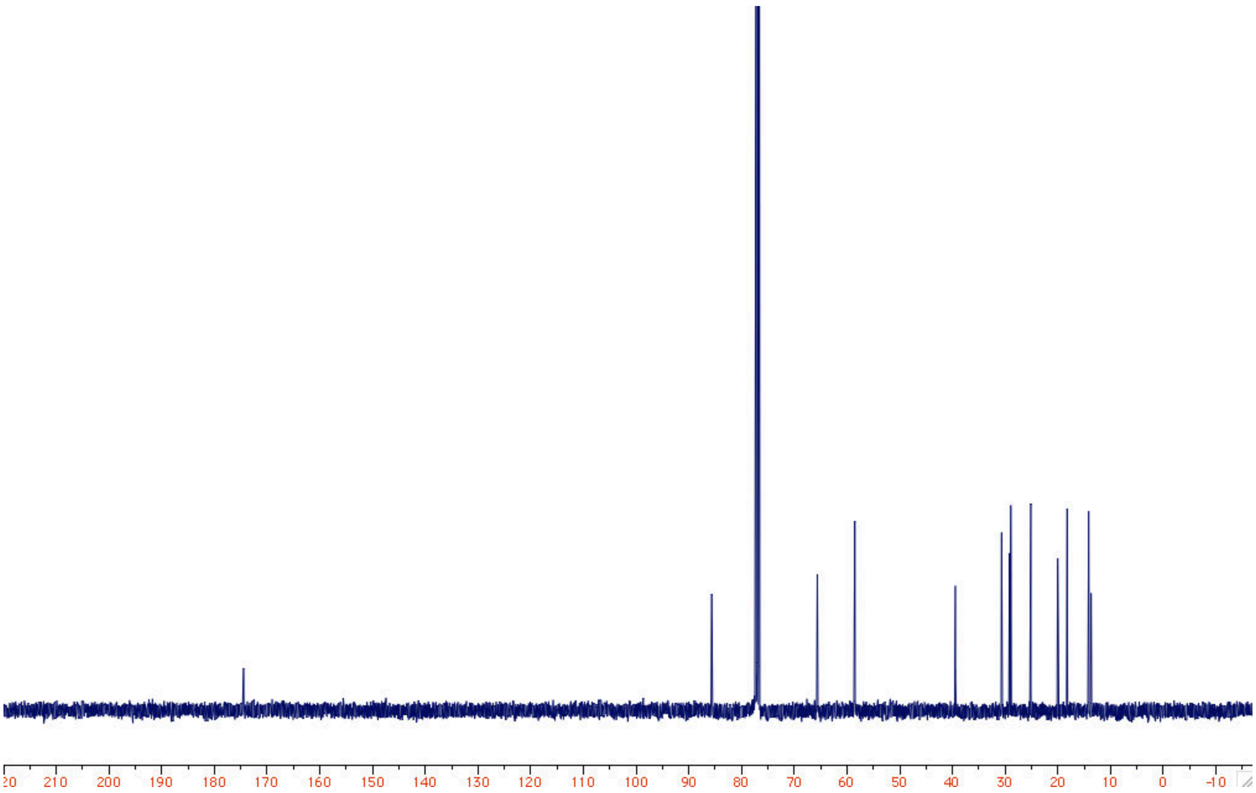
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