

DISSERTATION

LIGAND AND REACTION DEVELOPMENT IN THE RHODIUM(III)-CATALYZED C–H
ACTIVATION-MEDIATED SYNTHESIS OF N-HETEROCYCLES

Submitted by

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In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

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Fort Collins, Colorado

Summer 2013

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ABSTRACT

LIGAND AND REACTION DEVELOPMENT IN THE RHODIUM(III)-CATALYZED C–H ACTIVATION-MEDIATED SYNTHESIS OF N-HETEROCYCLES

Described herein are the development of new directing groups and new ligands for Rh(III)-catalyzed, multi-component synthesis of nitrogen containing heterocycles. The amide directing group was found to be an effective coupling partner for the synthesis of isoquinolones. Mechanistic experiments suggested the possibility to activate alkenyl C–H bonds for the synthesis of pyridones. During these studies, development of a new cyclopentadienyl ligand (Cp^t) for C–H activation allowed for enhanced regioselectivity in the alkyne insertion event. Oxime directing groups were found to provide pyridines when coupled with alkynes. Again the Cp^t ligand impacted the alkyne migratory insertion event. This ligand is also effective in controlling the migratory insertion of alkenes in the synthesis of dihydroisoquinolones. An enantioselective synthesis of dihydroisoquinolones was discovered using a strept(avidin)-based artificial metalloenzyme providing enhanced reactivity, regioselectivity, and enantioselectivity. This artificial metalloenzyme is also effective for controlling the enantioselective synthesis of γ -lactams from diazo compounds and benzamides.

ACKNOWLEDGEMENT

I need to start by thanking my advisor, Professor Tomislav Rovis, for creating an amazing environment for me to develop as a chemist. His excitement for science is contagious and I am grateful to count myself among the infected. Tom's mentorship has taught me that with excitement, passion, generosity, and hard work anything can be accomplished. I cannot imagine a better graduate school experience.

I want to thank the Rovis Group, past and present. The open and friendly environment in conjunction with the depth of scientific understanding has made this a tremendous place to develop as a scientist. I specifically want to thank Derek Dalton for solving X-ray crystal structures, Kyle Ruhl for helping me finish the diazo paper, and Kerem "Oz" Ozboya for being helpful and supportive even while I was ...difficult.

I would also like to thank Professor Thomas R. Ward. When Tom and Tom started the metalloenzyme collaboration he invited me to spend three months in Basel, Switzerland to learn as much as I could about artificial metalloenzymes. Tom has been extremely supportive, helpful in teaching me about this new area of research, and a great resource when considering research options outside of classical organic chemistry.

I would also like to thank Professor Christopher J. Douglas. I was late in becoming a chemistry major and had no research experience. Chris not only gave me the opportunity to do research, but he helped me find something I was excited about. He was patient in dealing with my shortcomings and help point me in the right direction.

I, of course, need to thank my family. They have been eternally supportive of all my educational endeavors, providing me with the resources and support to become who I am today. Finally, I need to thank my wife Erin. She has been incredibly supportive, loving, and patient. She has

even agreed to move to Los Angeles, which she describes as the “worst place on the planet”. She is truly amazing and I can’t imagine doing this without her.

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Chapter 1

Rhodium(III)-Catalyzed C–H Activation of Benzamides for the Synthesis of Nitrogen Containing Heterocycles

1.1 Late Transition Metal Catalyzed C–H Activation

1.1.1 Introduction

The ability to synthesize complex molecules from simple starting materials is an over arching goal in organic synthesis. Furthermore, environmental and economic factors necessitate methods that are catalytic with high levels of selectivity and reactivity. This is particularly important in the field of nitrogen containing heterocycle synthesis, as nearly 70% of the top 200 drugs on the market today contain this motif (Figure 1.1).¹ As a consequence, numerous research groups have employed a variety of multi-component reactions to access these cores.^{2,3,4} Processes involving C–H activation can potentially provide complementary routes to desired nitrogen containing heterocycles without unwanted pre-activation elements.

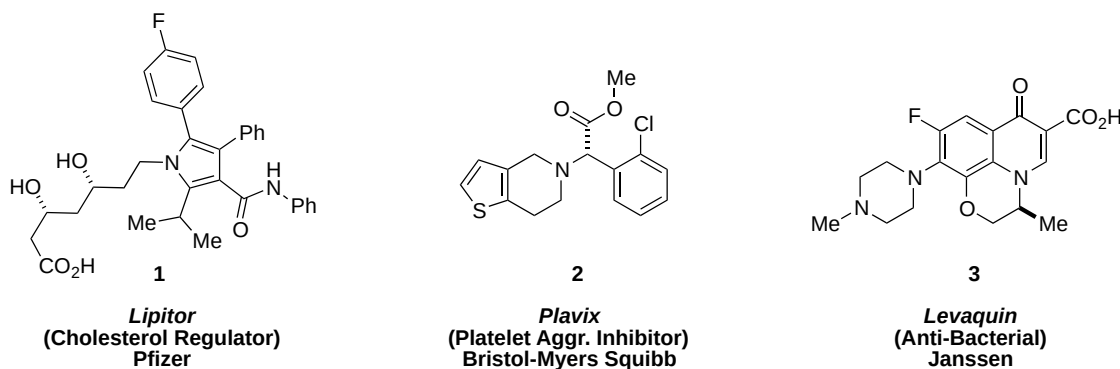
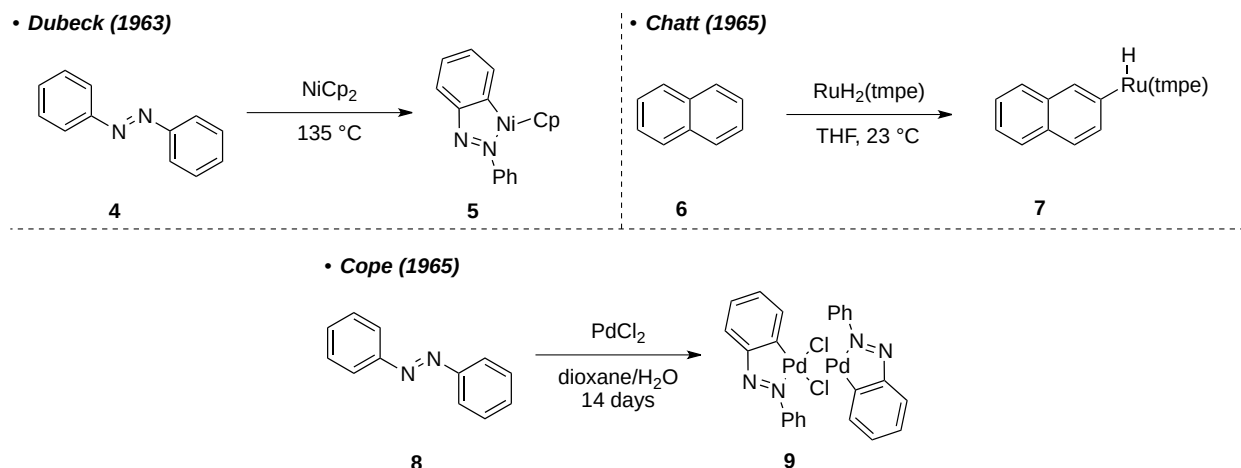


Figure 1.1 Common Drugs Containing N-Heterocycles

Functionalization of C–H bonds is an attractive approach to build molecular complexity because they are ubiquitous in molecules. Direct manipulation of unactivated C–H bonds is difficult because their chemical strength (90-100 kcal/mol) makes them kinetically inert. Seminal reports by Dubeck,⁵ Chatt,⁶ and Cope⁷ demonstrated that it is possible to cleave C–H bonds with transition metals (Scheme 1.1). Activation of C–H bonds can be categorized by whether a discrete C–M bond is formed. Examples where

a discrete C–H bond is not formed include cytochrome p450 metal-oxo catalyzed C–H oxidation,⁸ and metal catalyzed carbenoid and nitrenoid C–H insertions.^{9,10} Our work is centered on the formation of a direct C–M. There are two basic mechanisms for this activation, oxidative addition and electrophilic metallation.



Scheme 1.1 Seminal Reports of C–H Activation

1.1.2 Oxidative Pathway

In 1965, Chatt found that ruthenium (0) will undergo oxidative addition into the C–H bonds of naphthalene **6** to generate a hydrido ruthenium complex **7** (Scheme 1.1).⁶ Since this report, numerous groups have explored how this activation occurs.¹¹ Mechanistically, oxidative addition into C–H bonds is understood to occur with an initial interaction between the electron rich C–H σ -orbital and an electron poor d-orbitals on the metal. This is followed by a second interaction whereby the electrons in the filled d-orbital of the metal donate into the empty C–H σ^* -orbital. In this step the C–H bond is cleaved forming a new C–M and M–H bond with an increase in the net oxidation state of the metal (Figure 1.2). The requirement of a strong interaction between the metal and the C–H bond is manifested in less sterically hindered C–H bonds being activated preferentially over more hindered bonds, even if the more hindered bond has a weaker bond dissociation energy. Electron rich metals proposed to activate C–H bonds via this mechanism including; Zr^{II} , Ru^0 , Rh^{I} , and Ir^{I} .¹²

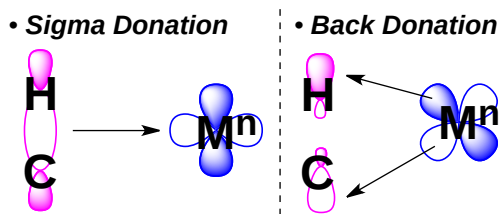
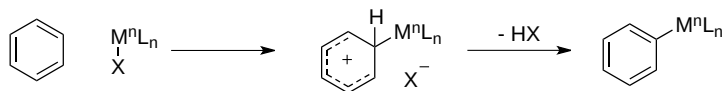


Figure 1.2 Mechanism for Oxidative Addition C–H Activation

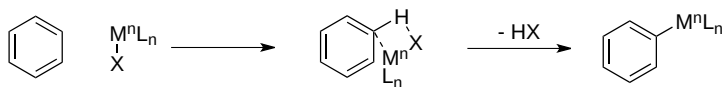
1.1.3 Electrophilic Mechanistic Pathway

An alternative approach to activate C–H bonds is to use a highly electrophilic metal. The overall outcome of this reaction is the conversion of a C–H bond to a C–M bond without a net change in the oxidation state of the metal. This mechanistic pathway is possible because an X-type ligand acts as a base in the transformation. As with oxidative addition C–H activations, chemoselectivity for the C–H activation favors the less hindered C–H bond. Metals understood to undergo this type of mechanism are generally electron poor and include Pd^{II}, Pt^{II}, Rh^{III}, Ir^{III}, Co^{III} and Ru^{II}. There are three proposed mechanistic pathways by which electrophilic C–H activation is believed to occur; (1) a S_EAr mechanism proceeding through a Wheland intermediate, similar to electrophilic aromatic substitution, followed by rapid deprotonation, or (2) a sigma-bond metathesis, or (3) a concerted metallation-deprotonation (CMD) involving an agostic interaction between the metal and the C–H bond (Figure 1.3). In the context of recent catalytic C–H activation reactions, the S_EAr and CMD mechanism have received increased attention in the form of mechanistic and computational studies.

• ***S_EAr Mechanism***



• ***Sigma Bond Metathesis***



• ***Concerted-Metallation Deprotonation (CMD)***

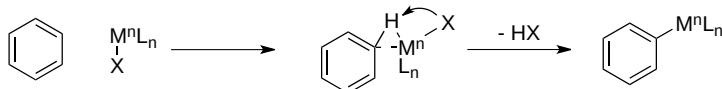
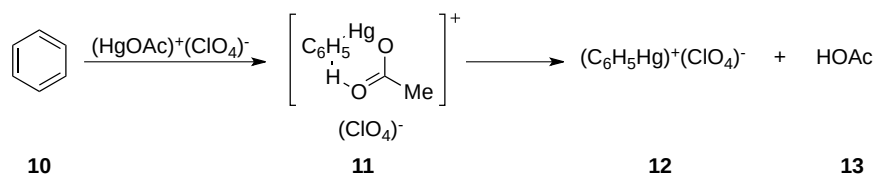


Figure 1.3 Mechanisms for Electrophilic C–H Activation

1.1.4 Concerted Metallation Deprotonation and S_EAr Mechanistic Studies

Mechanistic studies exploring the nuances of arene metallation predate transition metal catalysis, having been initially studied in the mercuration of arenes.^{13–16} Using extensive mechanistic experiments, Brown and Kresge proposed the arene mercuration proceeds through a concerted 6-membered transition state containing the C–H bond of the arene, mercury, and an acetate ligand. In the transition state **11**, the C–H bond is deprotonated by the mercury ligated acetate to form a new C–Hg bond with loss of acetic acid (Scheme 1.2). While very little was understood about the interaction between the arene and mercury, kinetic studies found that electron rich arenes were favored over electron poor, and proteo arenes are favored over deutero arenes with a kinetic isotope effect (KIE) value of 6.

• ***Transition State Proposed by Brown and Kresge***



Scheme 1.2 Proposed Mechanism for Arene Mercuration

This type of mechanism was re-explored by Ryabov in the stoichiometric cyclopalladation of N,N-dimethylbenzylamine using Pd(OAc)₂.¹⁷ Ryabov found that electron-rich arenes proceed more rapidly than electron-poor and the reaction had a KIE value of 2.2. The mechanistic hypothesis proposed is similar to that of Brown and Kresge where the acetate facilitates deprotonation via a 6-membered

transition state. Additionally, Ryabov suggests the electronic preference is suggestive of a buildup in positive charge present in the Wheland intermediate of a S_EAr mechanism (Figure 1.4).

Nearly 20 years later, the nature of the C–H activation event was re-examined using DFT calculations.¹⁸

In contrast to the hypothesis by Ryabov, Davies and Macgregor suggest that an agostic interaction between the C–H bond and Pd is operative, rather than a Wheland intermediate in the same system. However, the calculations do support the hypothesis that C–H activation proceeds through an acetate containing 6-membered transition state (Figure 1.4). Using this modified model, the KIE value and Hammett plot were calculated and closely fit the experimental data obtained by Ryabov.

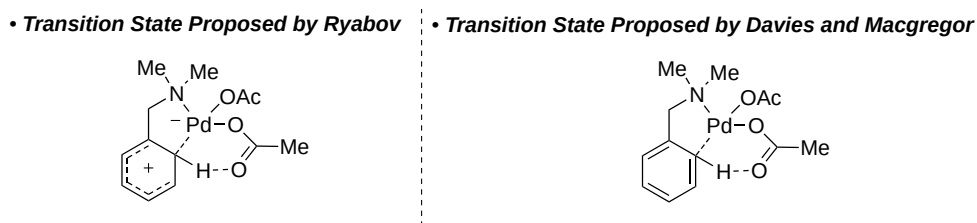


Figure 1.4 Two Mechanistic Hypotheses for Arene Metallation

Additional calculations by Davies and MacGregor suggest that $\text{Ir}^{\text{III}}\text{Cp}$ complexes metallate *N,N*-dimethylbenzylamine via a (CMD) mechanism in a fashion similar to $\text{Pd}(\text{OAc})_2$.¹⁹ In fact, the CMD transition state was found to be lower in energy than an oxidative mechanism or a 4-membered transition state mechanism (Figure 1.5). Interestingly, there was no evidence for an agostic interaction in the 6-membered transition state, although depending on the ligands and base used, an agostic interaction is likely present in other systems.

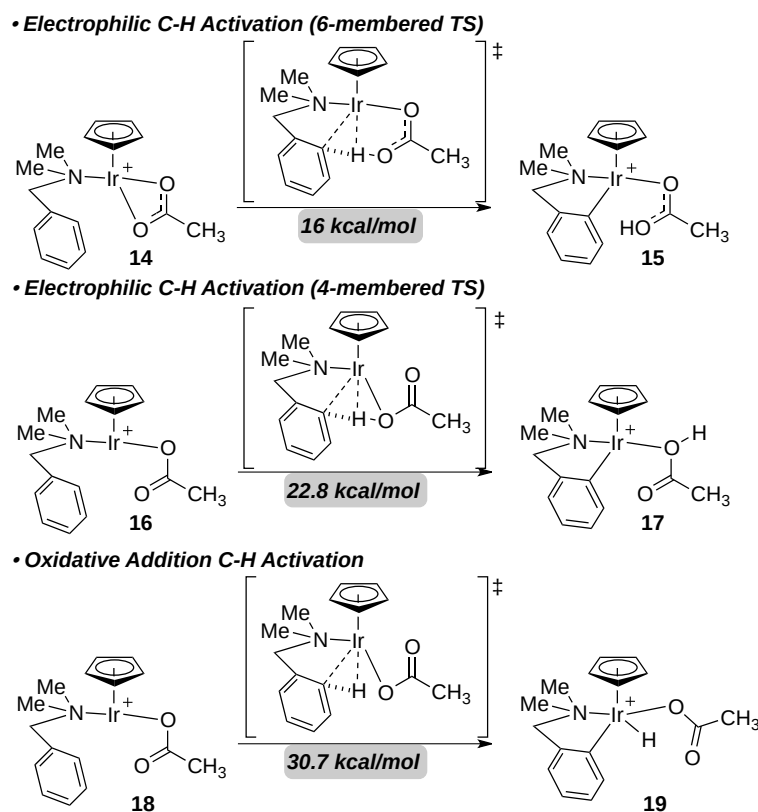


Figure 1.5 Three Proposed Mechanisms for Iridium Catalyzed C–H Activation

The groups of Fagnou and Echavarren proposed an acetate facilitated CMD mechanism in the *catalytic* arylation of arenes.²⁰⁻²² These research groups were drawn to this mechanistic hypothesis because of the lack of an electronic preference in the C–H activation event. These reports have been followed by numerous DFT calculations that support a CMD mechanism being operative in many Pd(II) catalyzed C–H activations. Unfortunately, generalized trends are difficult to conclude because of the large dependence on the ligands, base, and arene.²³

1.1.5 Directing Groups

As mentioned before, C–H activation usually occurs at the least hindered C–H bond. Independent of mechanism, the regioselectivity of the C–H activation event is frequently controlled using directing groups. Directing groups contain a Lewis basic atom (nitrogen, phosphorus, or oxygen) that acts as a ligand for the metal. This ligand places the metal in proximity to one C–H bond, resulting in a 5 or 6 membered metallacycle in an event referred to as cyclometallation (Figure 1.6). A wide range of directing

groups has been explored including: amides, amines, pyridines, acids, alcohols, imines, oximes, and ketones.²⁴⁻²⁶ In the synthesis of heterocycles using cyclometallated intermediates, the directing group also acts as a coupling partner, and is ultimately incorporated in the annulated product. Consequently this group plays an important role in the types of heterocycles accessible using this approach.

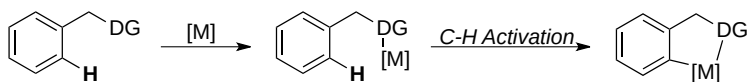


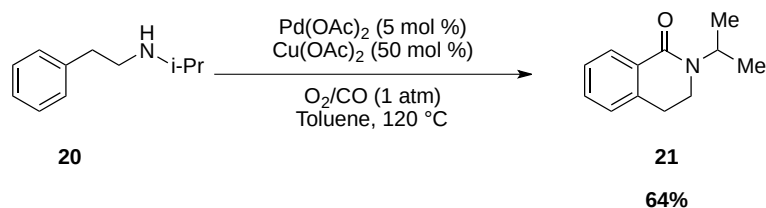
Figure 1.6 Cyclometallation via C–H Activation

1.1.6 Multi-Component Synthesis of Heterocycles Using Pd(II) C–H Activation

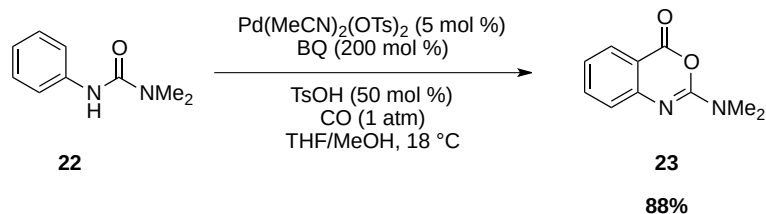
Upon accessing these cyclometallated intermediates, the resultant C–M bonds can be functionalized to introduce a wide range of functional groups ranging from new C–C bonds to C–Heteroatom bonds.^{24,25,27}

Carbonylation reactions have been the primary means of accessing heterocyclic motifs using Pd catalyzed C–H activation. In 2004 Orito and coworkers found that benzylic and homo-benzylic amines can be coupled with carbon monoxide under Pd(OAc)₂ catalysis to access γ - and δ - benzolactams in high yield (Scheme 1.3).²⁸ Lloyd-Jones and Booker-Milburn expanded this reaction to encompass protected anilines, allowing access to cyclic imidates under mild conditions (Scheme 1.3).²⁹ In related work, Yu and coworkers found that benzoic acid derivatives were suitable coupling partners for carbonylation reactions, allowing cyclic anhydrides to be accessed, which would ultimately be opened under the reactions conditions to produce di-acids in good yields. (Scheme 1.3).³⁰

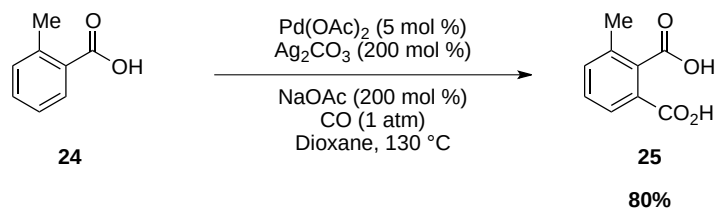
•Orito (2004)



•Lloyd-Jones and Booker-Milburn (2009)



•Yu (2008)

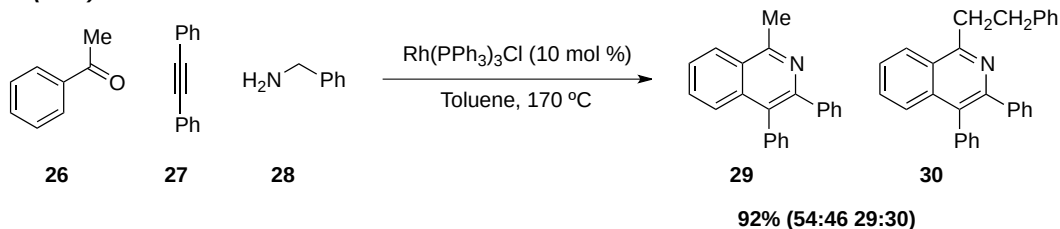


Scheme 1.3 Palladium(II)-Catalyzed Heterocycle Synthesis

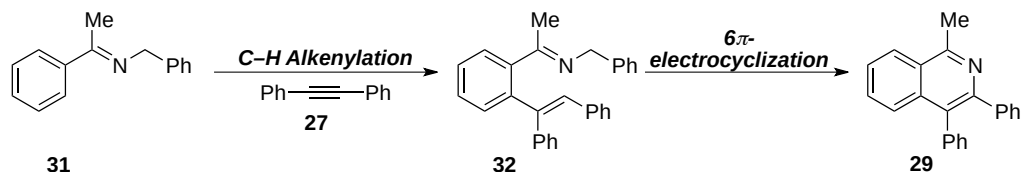
1.1.7 Rhodium(I) Catalyzed Heterocycle Synthesis

Rhodium(I) salts are effective catalysts for the synthesis of nitrogen containing heterocycles.²⁴ Early work by Jun and coworkers demonstrated that acetophenone **26**, diphenyl acetylene **27**, and benzyl amine **28** can be coupled in the presence of $\text{Rh}(\text{PPh}_3)\text{Cl}$ to provide isoquinoline adducts **29** and **30** in good yield (Scheme 1.4).³¹ The reaction is proposed to proceed through an alkenylated intermediate **32** that can undergo a 6π -electrocyclization, followed by elimination of toluene. The authors found the desired product is isolated with an additional isoquinoline **30**, which bears homo-benzyl group instead of a methyl group adjacent to nitrogen. Odom and coworkers used this reactivity in tandem with the titanium-catalyzed hydroamination of en-yne to access similar adducts.³²

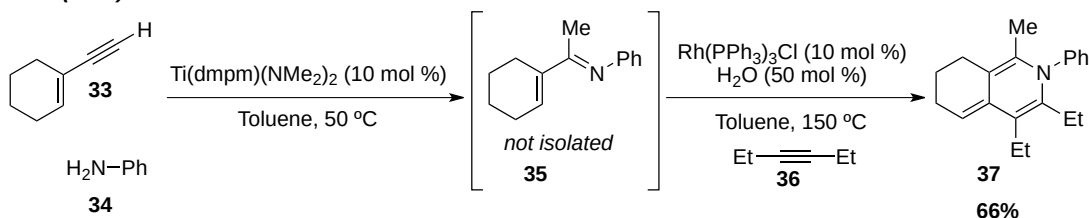
• Jun (2003)



Proposed Mechanism



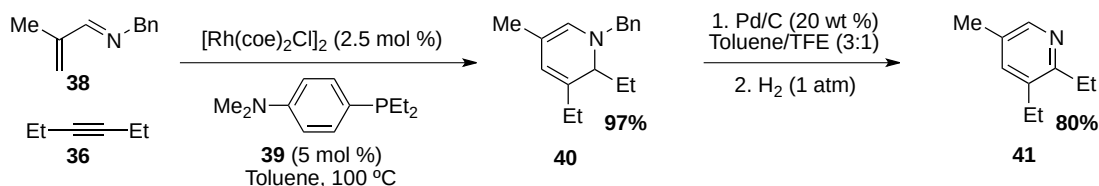
• Odom (2004)



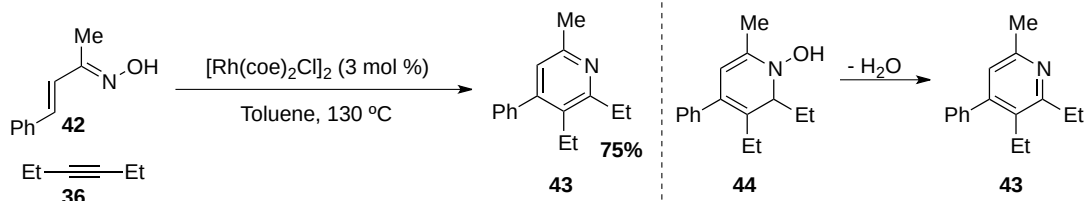
Scheme 1.4 Rhodium(I)-Catalyzed Heterocycle Synthesis

While exploring the alkenylation of α,β -unsaturated imines, Bergman and coworkers found when 3-hexyne **36** was used in lieu of terminal alkynes an undesired dihydro-pyridine product **40** was isolated (Scheme 1.5).³³ Upon treatment of dihydro-pyridine **40** with Pd/C under air, followed by deprotection, the desired pyridine **41** adduct can be isolated.³⁴ This transformation is quite broad, tolerating a wide range of alkynes and imine substitution patterns. Cheng found that this process can proceed in a single step when an oxime directing group is employed.³⁵ This reaction is understood to proceed via imine alkenylation, followed by 6π -electrocyclization to access a similar dihydropyridine. Upon dehydration across the C–N bond, the desired product is obtained (Scheme 1.5).

• **Bergman and Ellman (2008)**



• **Cheng (2008)**



Scheme 1.5 Rhodium(I)-Catalyzed Pyridine Synthesis

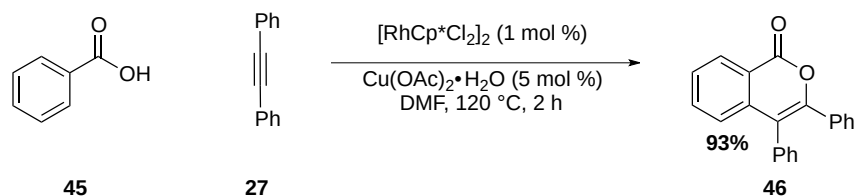
1.1.8 Rhodium(III) Catalyzed Heterocycle Synthesis

In a seminal report by Satoh and Miura, benzoic acids were coupled to alkynes to provide isocoumarins using $[\text{RhCp}^*\text{Cl}_2]_2$ and catalytic $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (Scheme 1.6).^{36,37} Later, they found 2-phenyl benzimidazole can be coupled to alkynes to provide a 6-member nitrogen containing heterocycles but with 2 equivalents of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (Scheme 1.6).³⁸ In both cases the reaction tolerates a wide range of substitution patterns on the arene and alkyne. When unsymmetrical alkynes are used the desired product was found with greater than 10:1 ratio of regioisomers. Mechanistically, the authors hypothesize the metal catalyst coordinates to the directing group to facilitate cyclometallation forming a 5-membered rhodacycle. After alkyne coordination, migratory insertion can occur to generate a 7-membered rhodacycle, which upon reductive elimination generates the desired product and a rhodium(I) species which is oxidized by $\text{Cu}(\text{OAc})_2$ to regenerate the active catalyst. Unfortunately, there is no experimental evidence to support this mechanism (Scheme 1.6).

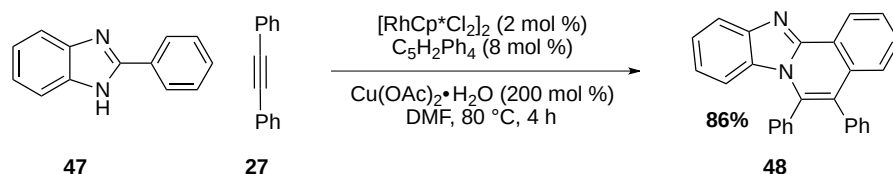
Concurrently, Fagnou demonstrated that *N*-aryl acetamides could be coupled with alkynes to provide uniquely substituted indoles in high yield and >10:1 regioselectivity (Scheme 1.6).^{39,40} Jones found that isoquinolines could be prepared from *N*-methyl imines when stoichiometric amounts of rhodium were used. Electronically, the reaction favors electron-rich imines, leading Jones to propose the C–H activation

occurs through a S_EAr mechanism (Scheme 1.6). A catalytic variant of this reaction was developed independently by Fagnou and Miura where the imine is substituted with either a proton or a labile tert-butyl group (Scheme 1.6).^{41,42} Mechanistic experiments by Fagnou demonstrate that a 6π -intermediate is not operative toward achieving product. Instead, they proposed a similar mechanism as proposed by Miura where migratory insertion across the alkyne provides a 7-membered metallocycle that can undergo reductive elimination with loss of isobutene (Scheme 1.6).

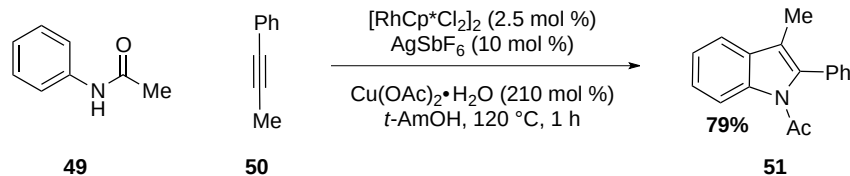
• *Miura and Satoh (2007)*



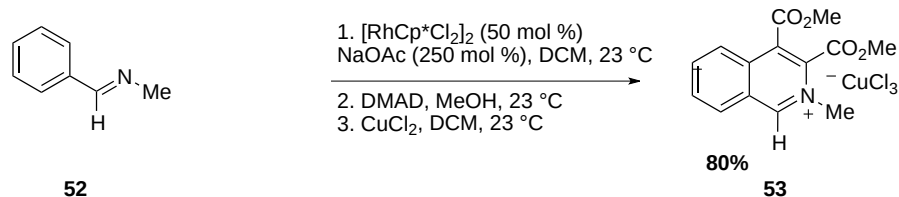
• *Miura and Satoh (2008)*



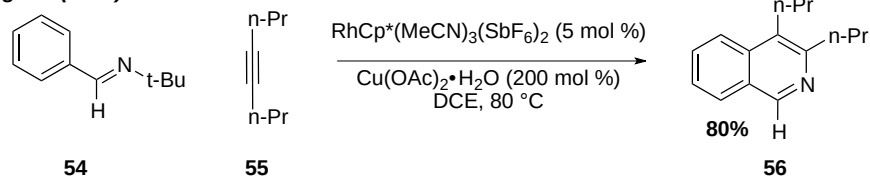
• *Fagnou (2008)*



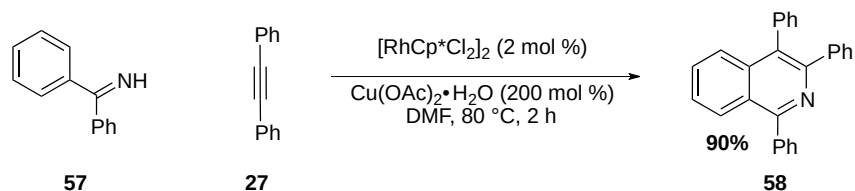
• *Jones (2008)*



• *Fagnou (2009)*



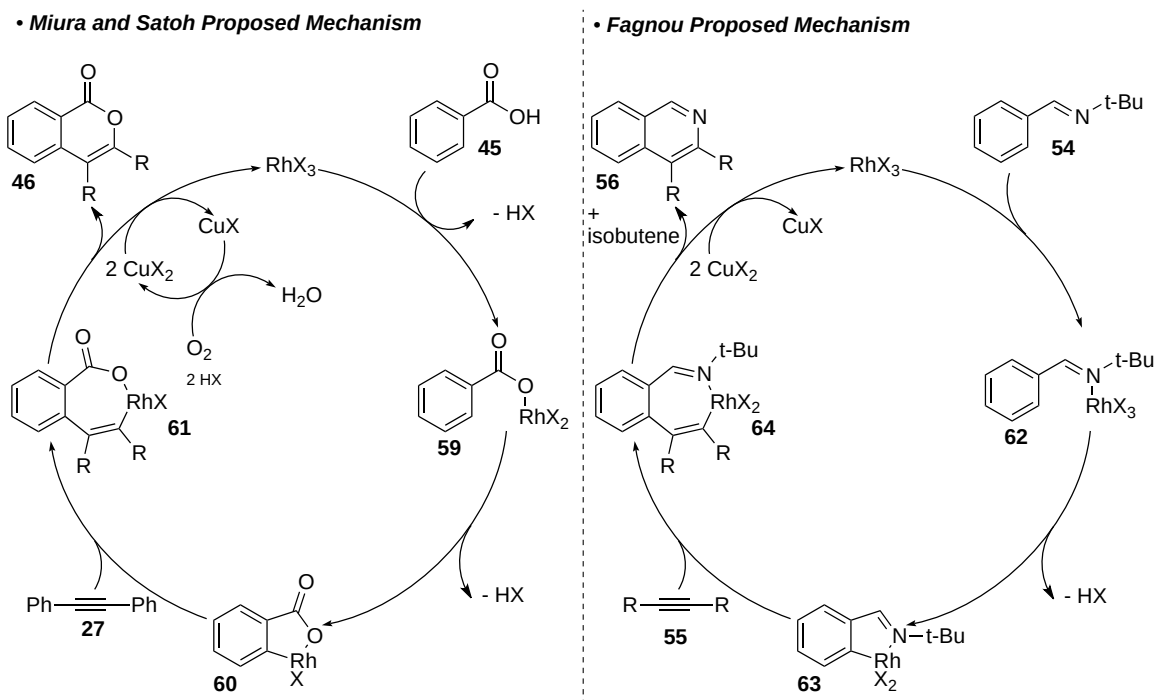
• *Miura and Satoh (2009)*



Scheme 1.6 Rhodium(III)-Catalyzed Heterocycle Synthesis

As opposed to the previously developed chemistry, where the directing group is exclusively used to control regioselectivity of the C–H activation; here the directing group is also a coupling component for heterocycles synthesis. Consequently, use of directing groups that give useful products is an important

advance. Evaluation of the directing groups reveals most contain a reasonably acidic N–H or O–H bond. We were initially interested in determining if the N–H bonds of amides would be sufficiently acidic for this family of reactivity. Our end goal was to provide the community with a new method for accessing ubiquitous nitrogen containing heterocyclic motifs.



Scheme 1.7 Proposed Mechanisms for Rhodium(III)-Catalyzed Heterocycle Synthesis

1.2 Results

1.2.1 Reaction Development for the Rh(III) Catalyzed Synthesis of Isoquinolones

In previous studies, our group has accessed indolizidine and quinolizidine scaffolds in high yield and enantioselectivity from the Rh(I) catalyzed [2+2+2] cycloaddition (Scheme 1.8). While the scope is broad, the reaction requires the alkene to be tethered to the isocyanate to diminish pyridone formation.⁴³ Unfortunately, this requirement limits the types of heterocyclic motifs accessible using this method. Mechanistic studies suggest the reaction proceeds through a 5-membered rhodium(III) metallacycle (Figure 1.7). We imagined a similar metallo-heterocycle could be accessed through a different mechanistic manifold, allowing access a broader range of heterocycles. Interrogation of the proposed 5-membered rhodacycle suggested that a similar metallocycle could be accessed from an amide directed C–

H activation (Figure 1.7). The benefit of this approach is that the π -component can be exchanged to provide a wide range of heterocycles.

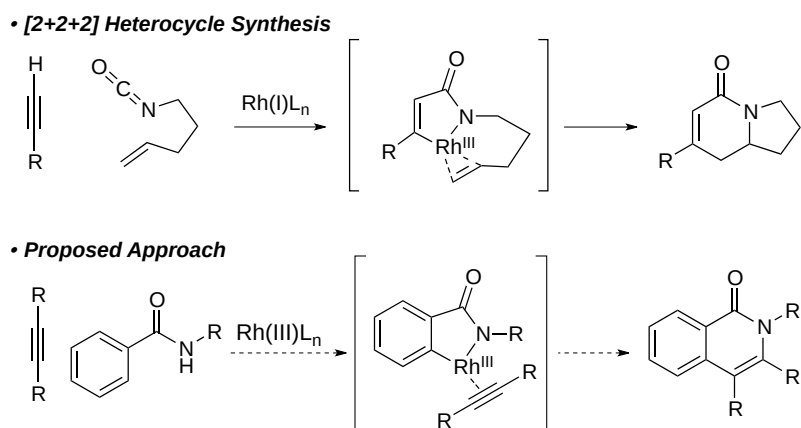
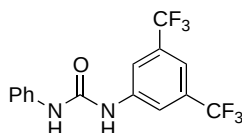


Figure 1.7 Proposed Metallocyclic Intermediates

Similar metallacycles to the one we hoped to functionalize have been proposed as intermediates in Rh(III) and Pd(II) catalyzed C–H activation reactions.^{30,36,38,41,44,45} We initially attempted to couple *N*-phenyl benzamide **65** with 1-octyne **66** in the presence of catalytic Pd(OAc)₂ and Cu(OAc)₂ as a stoichiometric oxidant (Table 1.1). When the reaction was conducted at 60 °C in DMF, only starting material was observed (Table 1.1, entry 1). We speculated that the N–H bond was not acidic enough to facilitate the C–H activation, consequently a thiourea **68** was added in the hope of increasing the acidity of the N–H bond of the amide, but again no product was observed.⁴⁶ Even a thiourea additive in the presence of a weak base failed to provide product (Table 1.1, entries 2-4). Complete deprotonation of the amide with NaH also did not give the desired product (Table 1.1, entry 5).

Table 1.1 Pd(II)-Catalyzed Isoquinolone Synthesis

Entry	Additive	Temp (°C)	Solvent	Yield (%) ^b
1	-	60	DMF	0
2	thiourea 68	60	DMF	0
3	thiourea 68 CsF (200 mol %)	60	DMF	0
4	thiourea 68 CsF (200 mol %)	110	Toluene	0
5	NaH (100 mol %)	100	1,4 dioxane	0

Reaction Conditions: **65** (1 equiv), **66** (1.5 equiv)^b Starting Material obtained in all reactions^c Thiourea **68** =

Since Pd(II) did not afford product, we shifted our focus to Rh(III) catalysts. [RhCp*Cl₂]₂ was used as a precatalyst, as per precedent of Fagnou,^{39,41} and Miura and Satoh.^{36-38,47} We tested this catalyst in the coupling of *N*-Me-benzamide to 1-phenyl-1-butyne to potentially provide isoquinolones. We were concerned about the acidity of the N–H bond being incompatible with the reaction. Consequently the sodium salt of amide **69** was used in our initial studies.

The reaction of sodium amidate **69** with 1-phenyl-1-butyne **70** in presence of catalytic [RhCp*Cl₂]₂ (2.5 mol %), catalytic AgSbF₆ (10 mol %), and Cu(OAc)₂•H₂O as the stoichiometric oxidant in toluene at 120 °C provided the desired product in 23% yield with greater than 19:1 regioisomeric ratio favoring isoquinolone **71** over **72** (Table 1.2, entry 1). Upon exclusion of AgSbF₆ the yield increased to 55% (Table 1.2, entry 2). A brief screen of solvents failed to increase yields (Table 1.2, entries 3-5).

Table 1.2 Sodium Amide Optimization

Entry	Additive	Solvent	Yield (%)	rr
1	AgSbF ₆ (10 mol %)	Toluene	23	>10:1
2	-	Toluene	55	>10:1
3	-	DMF	< 5	>10:1
4	-	1,4 dioxane	0	-
5	-	DCE	< 5	>10:1

Reaction Conditions: **69** (1 equiv), **70** (1.25 equiv), 0.1 M, 16 hours. Yield determined after chromatography. Regioisomeric Ratio (rr) determined from crude ¹H NMR favoring **71**.

With success using sodium amide **69** as a starting material, we explored using amide **73** in the reaction. An amide would be a superior starting material because it does not require an additional step to prepare. We initiated our studies by coupling *N*-methyl benzamide **73** with diphenyl acetylene **27**, catalyzed by [RhCp*Cl₂]₂ in the presence of AgSbF₆, with stoichiometric Cu(OAc)₂•H₂O as an oxidant in a variety of solvents at 110 °C. We were pleased to find that toluene provides the desired isoquinolone **74** in 23% yield (Table 1.3, entry 1). Dichloroethane provided slightly enhanced yield (Table 1.3, entry 2), but dimethylformamide and 1,4 dioxane gave lower yields (Table 1.3, entry 3-4). The best result was obtained using *t*-amyl alcohol with the product isolated in 65% yield after 12 h (Table 1.3, entry 5). Decreasing the reaction concentration did not have a substantial impact on the reaction yield (Table 1.3, entries 6-7). In contrast, increased reaction concentration afforded product in decreased yield (Table 1.3, entry 8).

Table 1.3 Solvent Optimization

Entry	Solvent	Molarity (M)	Yield (%)
1	Toluene	0.16	23
2	DMF	0.16	50
3	DCE	0.16	60
4	1,4 dioxane	0.16	60
6	<i>t</i> -AmOH	0.16	65
7	<i>t</i> -AmOH	0.10	64
8	<i>t</i> -AmOH	0.05	62
9	<i>t</i> -AmOH	0.25	38

Reaction Conditions: **73** (1 equiv), **27** (1.25 equiv), 16 hours. Yield determined after chromatography.

We explored the impact the oxidant had on the reaction (Table 1.4). Catalytic $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ under an atmosphere of O_2 afforded product in only 19% yield (Table 1.4, entry 2). We speculated the decreased yield with catalytic $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was an artifact of $\text{Cu}(\text{OH})_2$ being an ineffective oxidant for $[\text{RhCp}^*\text{Cl}_2]_2$. Indeed, with $\text{Cu}(\text{OH})_2$ was used as an oxidant, less than 5% yield of **74** is observed (Table 1.4, entry 3). Use of two electron oxidants, frequently used as oxidants in Pd(II) catalyzed C–H activation reactions,⁴⁸ provided product in decreased yield by comparison to single electron oxidants (Table 1.4, entry 4-5). Interestingly, replacing $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ with $\text{Cu}(\text{OTf})_2$ completely shut down the reaction (Table 1.4, entry 6). However, by adding pivalic acid and K_2CO_3 or sodium acetate to the reaction the yields were recovered (Table 1.4, entries 7 and 11). Under these conditions, when the $\text{Cu}(\text{OTf})_2$ is removed, again no product is observed (Table 1.4, entry 8). Addition of non-carboxylate bases, $\text{KO}t\text{-Bu}$ or Et_3N , in the presence of $\text{Cu}(\text{OTf})_2$ did not result in product formation (Table 1.4, entries 9-10). These experiments suggest the reaction is dependent on a single electron oxidant and weak carboxylate base. Sanford and coworkers propose a photocatalyst can provide a single-electron oxidation of Pd(III) to Pd(IV) in the presence of an oxidative quencher.⁴⁹ We wondered whether a $\text{Ru}(\text{bpy})_3\text{Cl}_2$ photocatalyst

could oxidize Rh(I) to Rh(III) in the presence of O₂ or benzoyl-peroxide. Unfortunately in both cases, only starting material was observed (Table 1.4, entries 12-13).

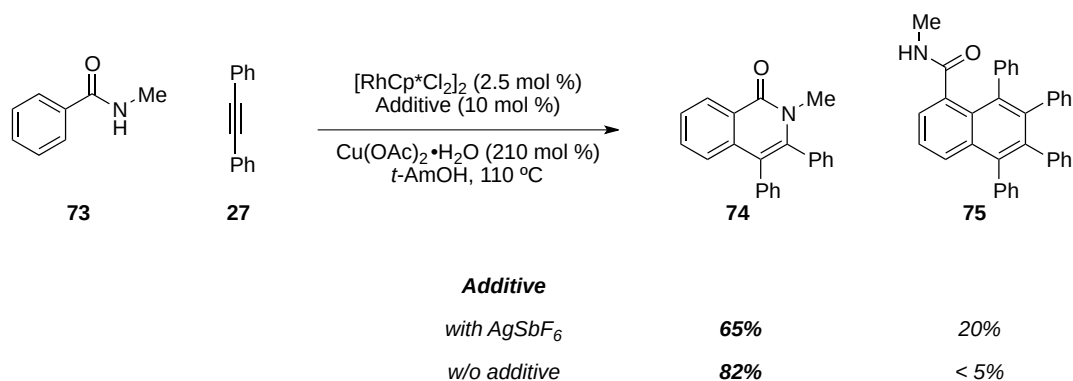
Table 1.4 Oxidant Optimization

Reaction scheme: N-methylbenzamide (**73**) + diphenylacetylene (**27**) $\xrightarrow[\text{Oxidant, } t\text{-AmOH, } 110\text{ }^\circ\text{C}]{[\text{RhCp}^*\text{Cl}_2]_2 (2.5\text{ mol } \%), \text{AgSbF}_6 (10\text{ mol } \%)}$ Naphthalene derivative (**74**)

Entry	Oxidant	Yield (%)
1	Cu(OAc) ₂ •H ₂ O (210 mol %)	65
2	Cu(OAc) ₂ •H ₂ O (20 mol %), O ₂ (1atm)	19
3	Cu(OH) ₂ (200 mol %)	< 5
4	PhI(OAc) ₂ (100 mol %)	13
5	Benzoquinone (100 mol %)	0
6	Cu(OTf) ₂ (210 mol %)	0
7	Cu(OTf) ₂ (210 mol %), K ₂ CO ₃ (250 mol %), PivOH (50 mol %)	63
8	K ₂ CO ₃ (250 mol %), PivOH (50 mol %)	0
9	Cu(OTf) ₂ (210 mol %), Et ₃ N (500 mol %)	0
10	Cu(OTf) ₂ (210 mol %), KOt-Bu (250 mol %)	0
11	Cu(OTf) ₂ (210 mol %), NaOAc (200 mol %)	63
12	Ru(bpy) ₃ Cl ₂ (2 mol %), NaOAc (200 mol %), 26 W Light	0
13	Ru(bpy) ₃ Cl ₂ (2 mol %), NaOAc (200 mol %), (BzO) ₂ (200 mol %), 26 W Light	0

Reaction Conditions: **73** (1 equiv), **27** (1.25 mol %), 0.16 M, 16 hours. Yield determined after chromatography

With the yield of our desired product topping out at 65%, we explored the mass balance of the reaction. A naphthalene side product **75** was isolated in 20% yield as a significant portion of the mass balance (Scheme 1.8). Upon removal of AgSbF₆, formation of the naphthalene side product is diminished, allowing the desired product to be isolated in 82% yield (Scheme 1.8). A hypothesis for this observation will be discussed later.



Scheme 1.8 Impact of AgSbF_6 Additive

A series of late transition metal pre-catalysts salts were screened to determine their ability to catalyze this reaction (Table 1.5). Addition of sub-stoichiometric PPh_3 had a detrimental effect, with decreased yields and conversions observed (Table 1.5, entry 2). When the catalyst is ligated with an electron deficient triazolium carbene, substantially decreased yields are observed, even over extended reaction times. (Table 1.5, entry 3). A screen of different halogens on rhodium revealed chloride to be the best, followed by iodide and bromine (Table 1.5, entries 1, 4-5). Use a pre-generated cationic catalyst gave product in 56% yield (Table 1.5, entry 6). A survey of different metals revealed iridium to be incompatible with this reaction (Table 1.5, entry 9). Surprisingly, $[\text{Ru}(\text{cymene})\text{Cl}_2]_2$ was an effective catalyst, although the reaction appears to be air sensitive (Table 1.5, entry 10). When the atmosphere was exchange for argon, enhanced yields were observed (Table 1.5, entry 11).

Table 1.5 Precatalyst Screen

Entry	Precatalyst	Yield (%)
1	[RhCp*Cl ₂] ₂	82
2 ^a	[RhCp*Cl ₂] ₂	50
3	RhCp*Cl ₂ • 76	10 ^b
4	[RhCp*Br ₂] ₂	34
5	[RhCp*I ₂] ₂	45
6 ^c	[RhCp*(MeCN) ₃](SbF ₆) ₂	56
7	[RhTpCl ₂] ₂	0
8	[RhTpCl ₂] ₂	0
9	[IrCp*Cl ₂] ₂	0
10	[Ru(cymene)Cl ₂] ₂	50
11 ^d	[Ru(cymene)Cl ₂] ₂	70
12	[RuCp*Cl] ₄	0

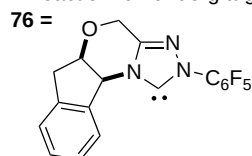
Reaction Conditions: **73** (1 equiv), **27** (1.25 mol %), 0.16 M, 16 hours

^a Additive (PPh₃) (10 mol %)

^b Reaction time extended to 48 hours

^c Catalyst Loading (5 mol %)

^d Reaction run under argon atmosphere



Ideal conditions in hand, the reaction was tested with a variety of amides (Table 1.6). The amides were prepared in a single step from the corresponding acid chloride and amine. *Para*-substituted amides are well tolerated in the reaction (Table 1.6, entries 1-5). Interestingly amides bearing an aldehyde do not undergo decarbonylation (Table 1.6, entry 5). Aryl substituents are tolerated on the nitrogen of the amide, providing product in high yield with no observed indole formation (Table 1.6, entry 6). Small alkyl substituents fare well in the reaction (Table 1.6, entry 7), however more sterically bulky *cyclo*-hexyl or *tert*-butyl substituents are not tolerated, resulting in isolation of starting material (Table 1.6, entries 8-9).

Meta-substituents provide product in modest yield and high regioselectivity (>10:1) (Table 1.6, entry 10-11). The reaction favors C–H activation *para*- to the substituent, presumably due to sterics disfavoring C–H activation *ortho*- to the substituent. Extended aryl amides also fare well in the reaction, again as a single regioisomer (Table 1.6, entry 13).

Table 1.6 Amide Scope

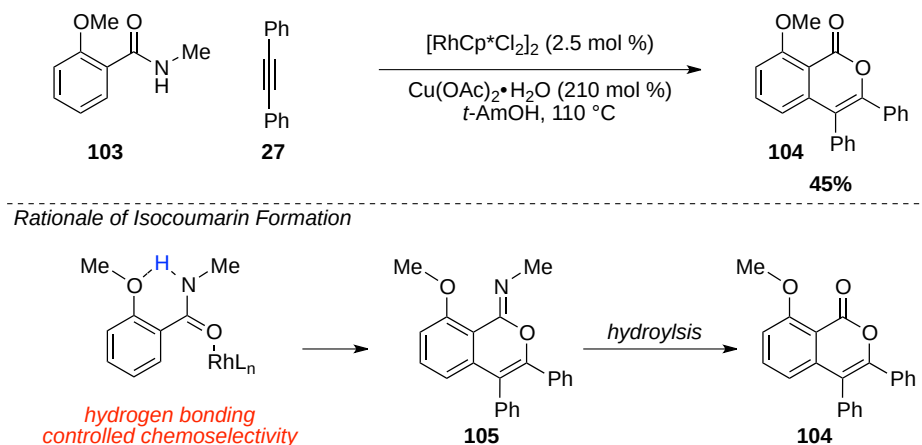
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		98	8		0
2		82	9		0
3		95	10		80 ^a
4		82	11		65 ^a
5		61	12		42
6		65	13		78 ^a
7		58			

Reaction Conditions: Amide (1 equiv), Alkyne (1.25 mol %), 0.16 M, 16 hours. Yield determined after chromatography. Unless otherwise stated, all regioselectivities were greater than 19:1

^a 10:1 regioselectivity

In select cases, the isocoumarin adduct was isolated from the reaction. Specifically, when a methoxy group is placed at the *ortho*- position of the amide, isocoumarin **104** is isolated in 45% yield (Scheme 1.9). When the *ortho*- substituent is changed to a methyl group, selectivity for the desired isoquinolone

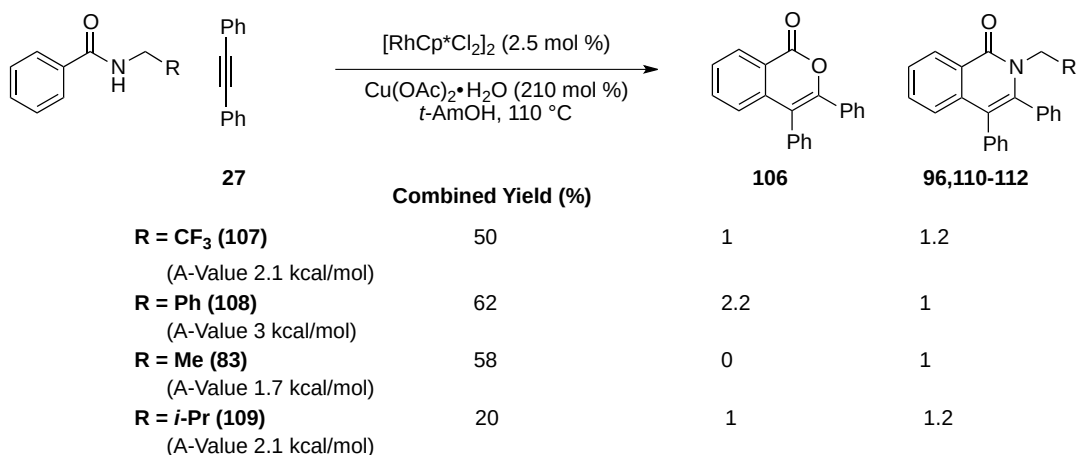
product is recovered, with no observed isocoumarin product. We imagine the formation of the isocoumarin adduct in this case is an artifact of the amides ability to form a stabilizing hydrogen bond between the oxygen of the methoxy group and the amide. This interaction would favor chelation of rhodium by the oxygen of the amide and consequently form the imidate intermediate **105**, which can be hydrolysed under the reaction conditions to give isocoumarin **104** (Scheme 1.9).



Scheme 1.9 Impact of *ortho*-Substitution

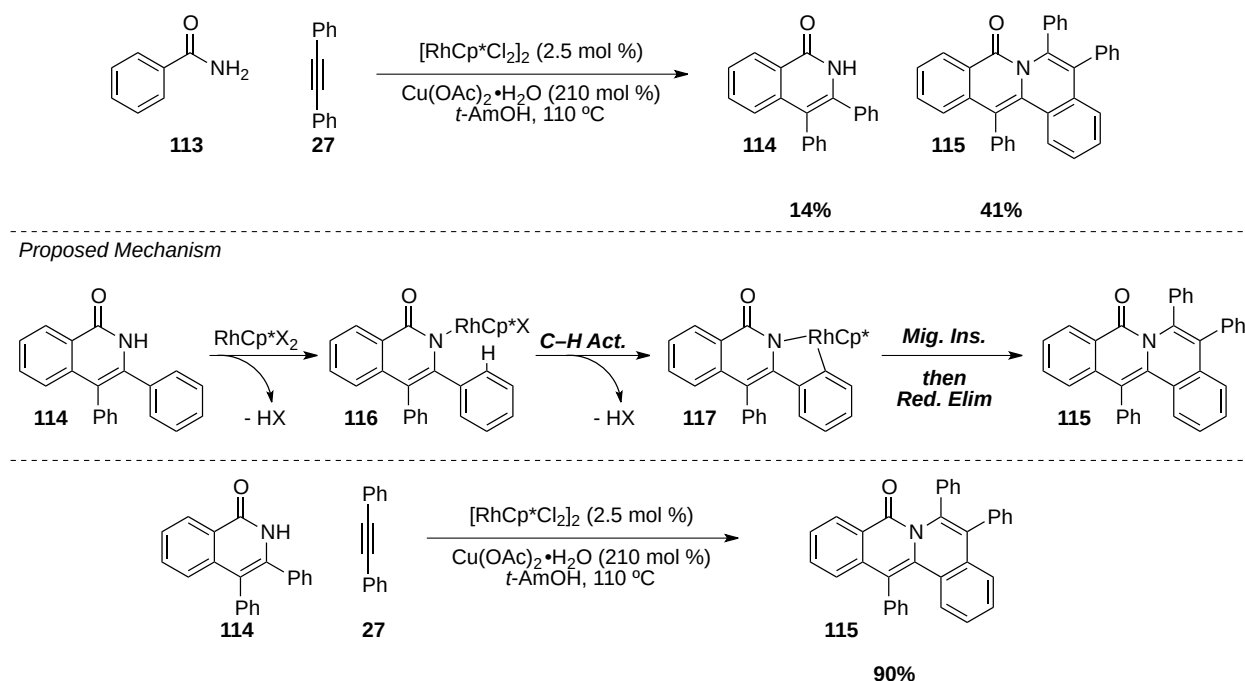
Substitution on nitrogen also controlled the distribution of isoquinolone and isocoumarin adducts. When methyl is replaced with 2,2,2-trifluoroethyl, a 1.2:1 ratio of isoquinolone **110** to isocoumarin **106** is isolated in 50% combined yield. With benzyl substitution, the ratio moves to 1:2.2 favoring the isocoumarin adduct **106**. We imagine the formation of the isocoumarin product is a result of both steric and electronic effects. In both cases, a larger group off the nitrogen disfavors chelation of rhodium. A-values were used to approximate the steric bulk of a given substituent. An A-value is the energy difference between the two chair cyclohexane conformations bearing a particular functional group. Comparison of A-values reveals $-\text{CF}_3$ to be slightly larger than $-\text{Me}$ (2.1 kcal/mol and 1.7 kcal/mol respectively), and Ph to be significantly larger than Me (3.0 kcal/mol). To support this claim, *N*-isobutyl benzamide was prepared and when submitted to the reaction conditions the product mixture favored isoquinolone in a 1.2:1 ratio with a 20% combined yield. Based on these experiments, we proposed steric

effects have a larger influence than electronics in controlling the distribution of products, although electron deficient substrates participate more readily in the reaction (Scheme 1.10).



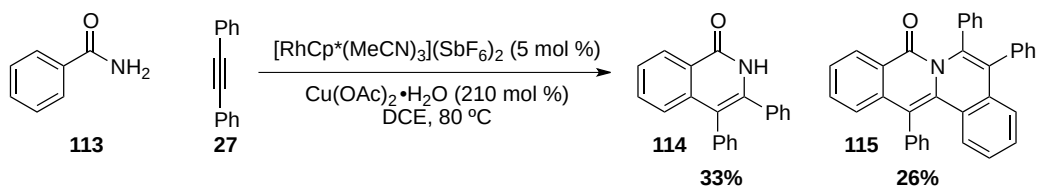
Scheme 1.10 Impact of Substitution on Nitrogen

When primary benzamide **113** was submitted to the reaction conditions a mixture of the desired isoquinolone **114** adduct is observed with an unwanted side product arising from a secondary C–H activation event **115** (Scheme 1.11). We hypothesized the desired product initially formed is metallated with an active Rh(III) species. This species can facilitate a second C–H activation to form a new metallacycle **117**, which upon migratory insertion and reductive elimination forms lactam **115**. This was confirmed when the isolated isoquinolone **114** was submitted to the reaction conditions and lactam **115** was formed in 90% yield (Scheme 1.11).



Scheme 1.11 Product Distribution with Primary Benzamides

In an effort to optimize the reaction for the desired lactam, a range of solvents were screened. While all solvents gave a mixture of products favoring the tetracyclic product **115**, DCE was found to be the most favorable with the desired product **114** formed in 33% yield with the tetracyclic product **11** formed in 26% yield. Unfortunately, further attempts to optimize this reaction failed to provide superior results and this direction of research was abandoned (Scheme 1.12).



Scheme 1.12 Ideal Conditions for Primary Amides

The scope of amides also included heteroaromatic compounds bearing non-basic heteroatoms (Table 1.7). By comparison to simple aryl amides, heteroaromatic compounds had disparate levels of reactivity, which required the use of two sets of reaction conditions. While 3-substituted heterocycles would proceed in the reaction with our standard conditions (Table 1.7, entries 1, 5-8), generally 2-substituted heterocycles required a more reactive cationic catalyst (Table 1.7, entries 2-4). Regardless of catalyst, the reaction

proceed in high yield with high levels of regioselectivity for both the C–H activation and the alkyne insertion. When nicotinic acid derivative **121** was used under the reaction conditions only trace amounts of product formation were observed. Presumably, the basic nitrogen can coordinate to either the rhodium catalyst or the copper oxidant to stifle reactivity.

Table 1.7 Heterocyclic Amide Scope

Entry	Amide	Conditions	Product	Yield (%)	
1		A		126	86
2		B		127	55
3		B		128	63
4		B		129	87
5		A		130	62
6		A		131	82
7		A		132	93
8		A or B		133	0

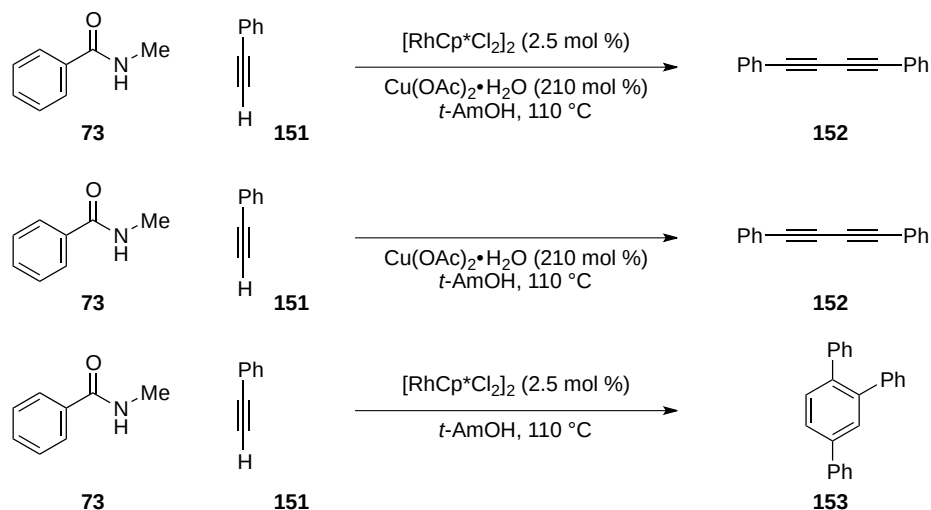
Reaction Conditions: Amide (1 equiv), Alkyne (1.25 equiv), 0.16M, 16 hours. Yields determined after chromatography. When 1-phenyl-1-butyne was used regioselectivity was >10:1.

Conditions A: Catalyst = [RhCp*Cl₂]₂ (2.5 mol %)

Conditions B: Catalyst = [RhCp*(MeCN)₃](SbF₆) (5 mol %)

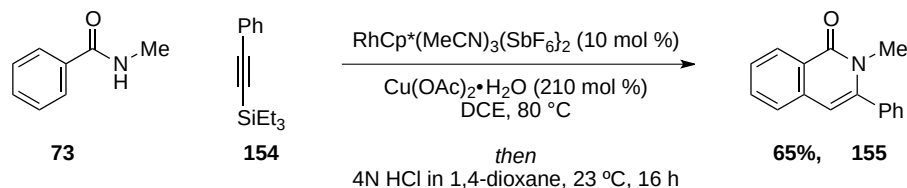
The scope of the alkynes was explored in coupling with *N*-methyl benzamide **73** (Table 1.8). Electron rich and electron deficient di-aryl alkynes fare well in the reaction with electron rich alkynes providing product in enhanced yield by comparison to electron poor alkynes (Table 1.8, entries 1-2). Symmetrical di-alkyl alkynes give product in low yield under the standard reaction conditions; however, when the oxidant was changed to Ag₂CO₃, the desired product was isolated in 50% yield (Table 1.8, entry 3). Unsymmetrical alkynes fare well in the reaction, generally providing product with high regioselectivity (>19:1) (Table 1.8, entries 4-9). When aryl/alkyl unsymmetrical alkynes are used, the aryl group sits adjacent to the nitrogen of the isoquinolone. Increasing the size of the alkyl group results in decreased regioselectivity (10:1) (Table 1.8, entry 8). Silyl protected propargyl alcohols tolerate the reaction conditions and provide product in high yield and excellent regioselectivity (Table 1.8, entry 6). While propionates fail to provide product under these reaction conditions, the di-ethyl acetal fares well with high yield excellent regioselectivity (Table 1.8, entry 7). Unsymmetrical di-alkyl alkynes also provide isoquinolone product in superb yield and regioselectivity (Table 1.8, entry 9). In contrast to aromatic substituted alkynes, with di-alkyl alkynes most sterically encumbering group lies adjacent to the aromatic ring. The origin of the regioselectivity will be explored later.

Attempts to use terminal alkynes resulted exclusively in dimerization of the alkyne in a copper catalyzed Glaser coupling to give the di-yne **152** adduct which did not partake in the reaction (Scheme 1.13). When rhodium was removed from the reaction mixture the Glaser coupling still occurred. However, when copper was removed from the reaction, trimerization of alkyne **153** was observed with no di-yne product.



Scheme 1.13 Products Observed Using Terminal Alkynes

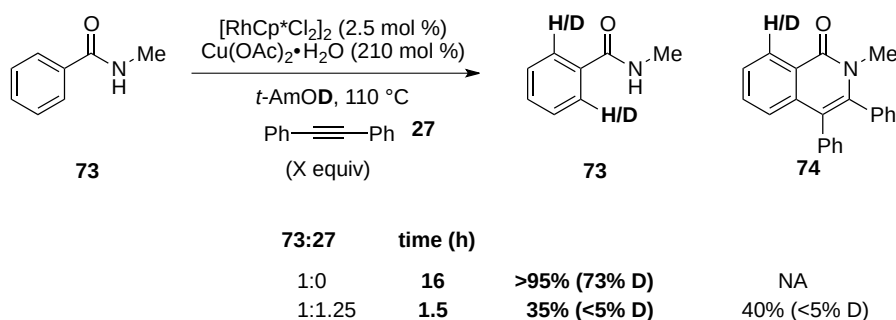
To obtain isoquinolones from terminal alkynes, we tried different conditions with silyl protected alkynes. While TMS protected alkynes failed to provide product, TES-protected phenyl acetylene provided silyl isoquinolone product **150** when the cationic catalyst was used in DCE. Unfortunately the reaction provided a mixture of the desired product and the deprotected product under the reaction conditions. However, if the crude material is treated with 4N HCl in dioxane at 23 °C the unprotected product can be isolated. These two step can be combined when 4N HCl in dioxane is added to the reaction vessel after 16 hours to obtain the desired product in 62% yield (Scheme 1.14).



Scheme 1.14 TES-Protected Alkynes

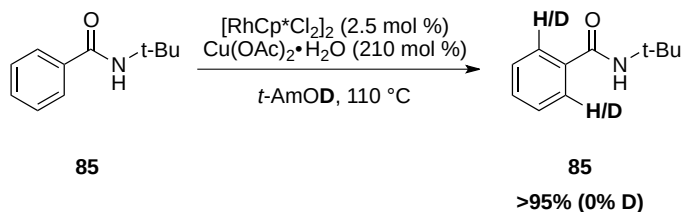
1.2.2 Mechanistic Studies

We initially wanted to probe the reversibility of the C–H activation event. When benzamide **73** is submitted to the reaction conditions in the absence of alkyne using d_1 -tAmOD, after 16 hours 73% deuterium incorporation is observed at the *ortho*-positions. However, when the same reaction is conducted with 1 equivalent of diphenylacetylene, after 1.5 hours, the starting material is isolated with no deuterium incorporation, and the product is obtained with no observable deuterium incorporation. These experiments support C–H activation being irreversible under the standard reaction conditions (Scheme 1.15).



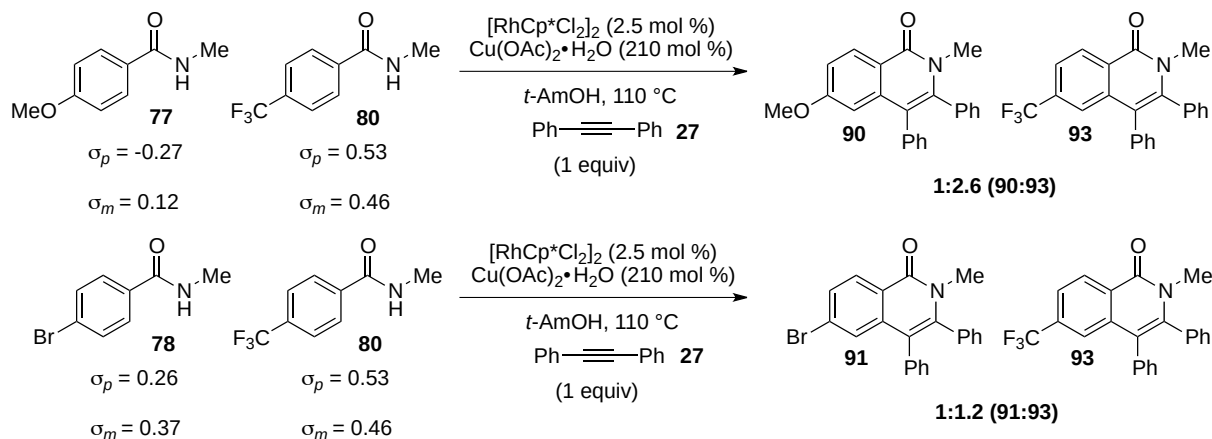
Scheme 1.15 C–H Activation Reversibility

Similar mechanistic experiments illuminated why sterically bulky amides do not provide product under the current reaction conditions. When *N*-t-Bu benzamide was submitted to the reaction condition with d_1 -t-AmOH and without alkynes, no deuterium incorporation was observed. This experiment suggest that sterically bulky amides are not efficient directing groups for Rh(III)-catalyzed C–H activation (Scheme 1.16). We can also assume that the amide metallates at nitrogen for the C–H activation rather than the oxygen.



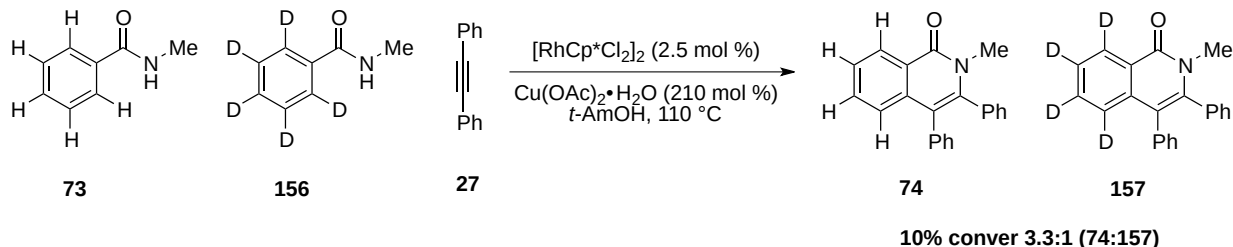
Scheme 1.16 Sterically Bulky Amides

Based on this precedent, we explored the mechanistic nuances of this reaction to find evidence for C–H activation occurring through a CMD mechanism. During optimization, we found the reaction only proceeds in the presence of a carboxylate base, which is weakly coordinating. While this supports the possibility for a 6-membered transition state, it does not preclude the presence of a Wheland intermediate. A series of competition experiments were utilized to understand more about this event. When equimolar amounts of benzamide **77** and **80** are run in the presence of the $[\text{RhCp}^*\text{Cl}_2]_2$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and 1 equivalent of diphenyl acetylene **27**, the more electron deficient substrate is favored 2.6:1 (**90:93**). These results suggest that an arenium intermediate is not involved in the C–H activation event; however, it does not suggest whether N–H or C–H activation is the turnover limiting step. A second competition experiment between *p*-Br and *p*-CF₃ benzamides (**78** and **80** respectively) was used because of their unique electron properties, quantified by their Hammett values. In this reaction if disparate amounts of the two products are isolated, based on the *para*- Hammett values, the experiment would support N–H bond activation as being turnover limiting. However, if similar amounts of the two products are isolated C–H activation would be turnover limiting because of the similar σ_m Hammett values. After conducting the experiment, nearly equimolar amounts of the two products were isolated, suggesting C–H activation as the turnover-limiting step in the reaction (Scheme 1.17).



Scheme 1.17 Probe of Amide Electronics

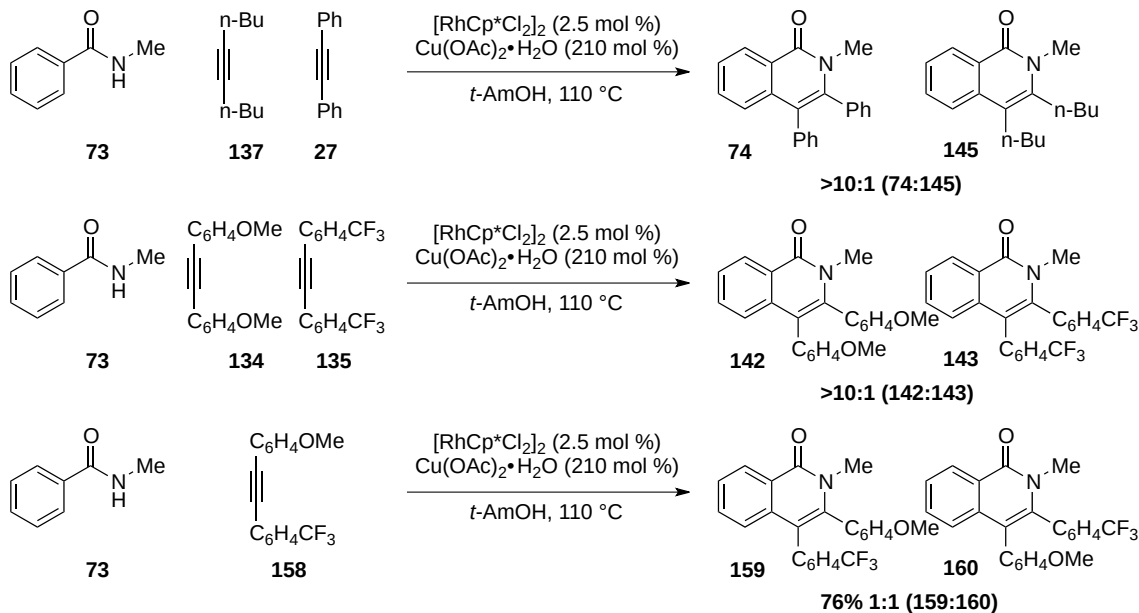
As further support, a competition experiment between D_5 -*N*-methylbenzamide **156** and H_5 -*N*-methylbenzamide **73** was conducted. When the overall amide concentration is the same as the standard reaction conditions and the reaction is stopped after 10 minutes, the proteo-product **74** is favored at a 3.3:1 ratio with 10% overall conversion. This further supports the that C–H activation is the turnover limiting step of the reaction, proceeding through a CMD mechanism facilitated by acetate (Scheme 1.18)



Scheme 1.18 KIE Competition Experiment

Competition experiments were used to learn about the subsequent steps of the mechanism. When 5-decyne and diphenylacetylene were run in competition under the standard reaction conditions, product from the diphenylacetylene was the only observed product **47**, suggesting the reaction favors aryl alkynes. The reaction also prefers more electron rich alkynes, as determined by a competition between an electron rich di-aryl alkyne **134** and an electron poor di-aryl alkyne **135** resulting in exclusive formation of the product derived from the more electron rich alkyne **142**. Finally, to determine if the alkyne migratory insertion had any electronic preference, a differentially substituted alkyne was utilized which bear an

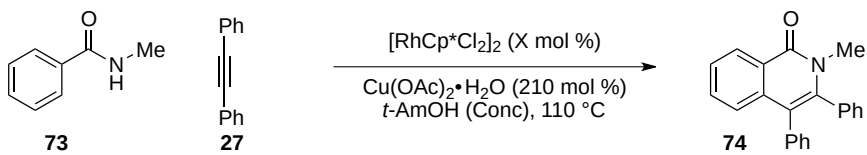
electron-donating group on one arene and an electron-withdrawing group on the other. After the reaction was complete a 1:1 mixture of products was observed, suggesting the reaction does not have an electronic preference during the migratory insertion event (Scheme 1.19).



Scheme 1.19 Alkyne Competition Experiments

1.2.3 Precatalyst Loading and Alkyne Inhibition

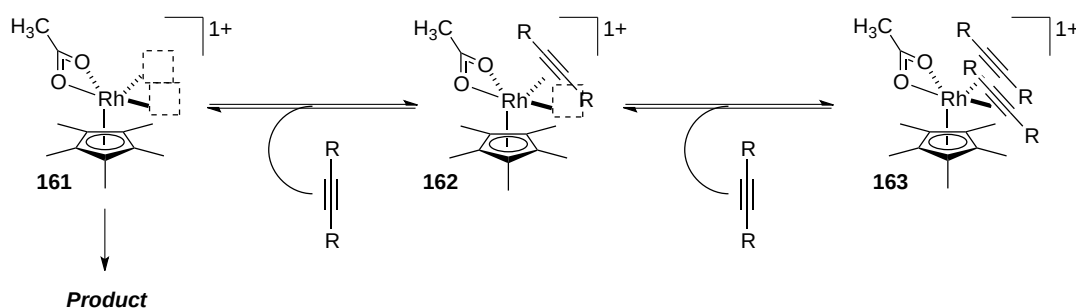
We were interested in decreasing the precatalyst loading of the reaction. Initially we decreased the catalyst loading to 0.5 mol % and found the yield decreased to 4%. Concentration of the reaction was increased to provide reaction conditions with the same molarity by comparison to catalyst but again the yield decreased even further. With decreased catalyst loading the substrate/catalyst ratio is significantly greater, and we thus speculated that substrate inhibition was the source of decreased yield. Batch-wise addition of amide did not enhance yield, however when alkyne was added in three batches the product was isolated in a diminished 68% yield when the reaction is performed on gram scale (Table 1.9).

Table 1.9 Precatalyst Loading


Entry	Catalyst Loading	Conc. (M)	Modification	Yield (%)
1	2.5 mol %	0.16	-	82
2	0.5 mol %	0.16	-	40
3	0.5 mol %	0.80	-	35
4	0.5 mol %	0.16	Amide batch addition	40
5	0.5 mol %	0.16	Alkyne batch addition	68

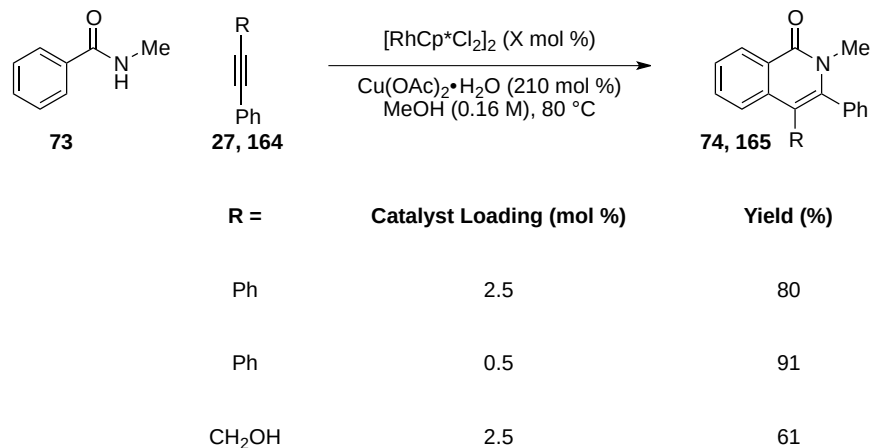
Reaction Conditions: **73** (1 equiv), **27** (1.25 equiv), 0.16 M. Yield determined after chromatography. Batch addition = 20% of the total amount added over 2 hours.

Studies in catalyst loading suggest that the alkyne is acting as an inhibitor in the reaction. Preliminary kinetic studies further support reaction inhibition and increased catalyst loadings. This is consistent with the kinetic information reports by the Fagnou group in the Rh(III) catalyzed synthesis of indoles.⁴⁰ Fagnou concludes that alkyne inhibition comes from coordination of one or two equivalents of alkyne to the rhodium salt prior to rate limiting C–H activation. We speculate that since the turnover limiting step is C–H activation in our system that a similar mode of inhibition may be occurring (Figure 1.8).

Proposed Mode of Alkyne Inhibition**Figure 1.8** Potential Mode of Alkyne Inhibition

A strategy to minimize this inhibition could lead to lower catalyst loading. We imagined this off-cycle inhibition could be precluded if a more coordinating solvent was employed to compete with the alkyne for free coordination sites. We were pleased to find that MeOH was a competent solvent for the reaction,

providing product in 80% yield with 2.5 mol % catalyst loading. Gratifyingly, when the catalyst loading was decreased to 0.5 mol %, the product was isolated in 90% yield without batch-wise addition. On gram scale, similar efficacies were observed (Scheme 1.20). The solvent changed also made it possible for simple unprotected propargyl alcohols to be incorporated in the reaction in 62% yield and >10:1 regioselectivity. (Scheme 1.20)



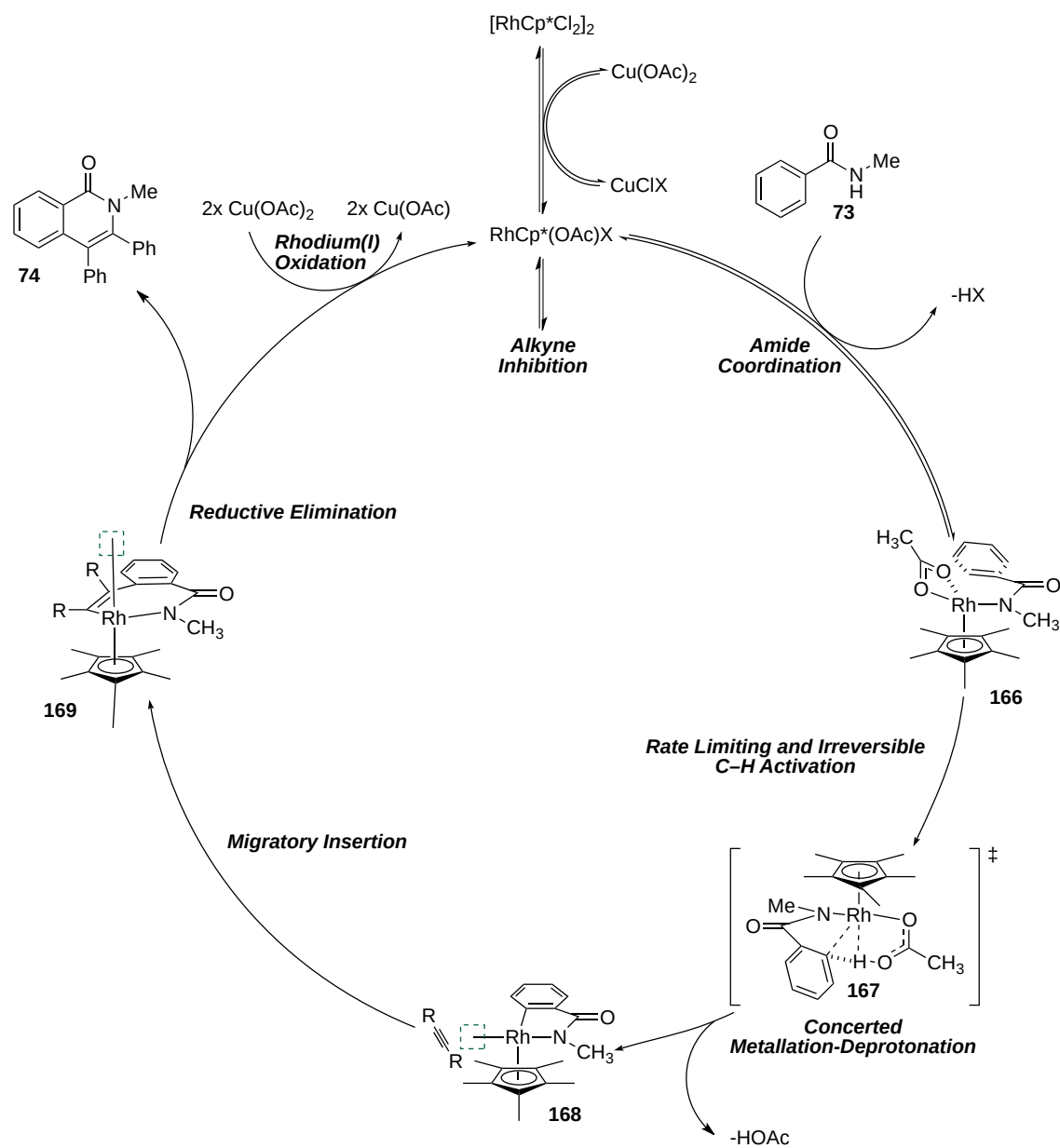
Scheme 1.20 Impact of Solvent of Precatalyst Loading

Based on these experiments, we proposed the reaction proceeds through the following mechanism. The rhodium dimer can decompose to the rhodium monomer with ligand exchange from copper to form a rhodium acetate complex. Metallation of the amide with loss of an X-type ligand can generate a rhodium amidate **166**. As the acetate ligand goes from κ^2 to κ^1 , a coordination site is made available which can form an agostic interaction with the *ortho* C–H bond to facilitate the C–H activation proceeding through a CMD mechanism **167** to generate the cyclometallated product **168**. Our mechanistic studies suggest this step is turnover limiting and irreversible. Coordination of the alkyne, followed by reductive elimination, leads too a 7-membered metallocycle **169**, which upon reductive elimination forms the desired isoquinolone and a Rh(I) complex which is oxidized to a Rh(III) complex with two equivalents of Cu(OAc)₂ (Scheme 1.21).

We speculate the undesired naphthalene adduct **75** is formed from intermediate **169**. If the amide dissociates from rhodium, the alkenyl arm can swing around and undergo activation at the *meta*-position.

After migratory insertion of the alkyne and reductive elimination naphthalene **75** would be formed. We speculate the cationic conditions favor amide dissociation.

Our rationale for the regioselectivity of migratory insertion depends on the substitution pattern of the alkyne. When an aryl group is present, we propose the aryl group sits adjacent to rhodium for electronic reasons. However, when di-alkyl alkynes are used there are no electron-biasing factors and simple sterics control the regioselectivity. We imagine the overall energy of the system is lower when the steric bulk of the alkyne and the bulk of the Cp* ligand are distant from one another.

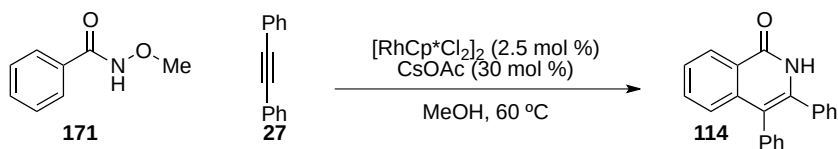


Scheme 1.21 Proposed Mechanism

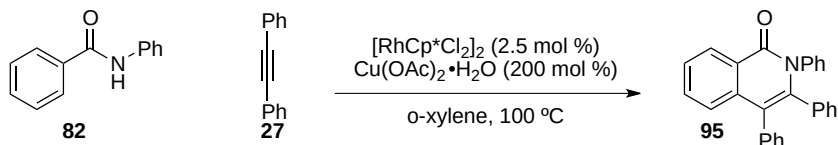
1.3 Concurrent Work

While preparing a manuscript based on this work,⁵⁰ concurrent work was reported by Fagnou.⁵¹ In this work benzhydroxamic acids were used as the substrate. Fagnou found that the N–O bond would act as an internal oxidant, eliminating the need for an external oxidant. While in review, Satoh and Miura reported an isoquinolone synthesis very similar to ours using an external oxidant.⁵² Their reaction was largely explored using *N*-aryl amides and did not contain mechanistic experiments. Li conducted a similar study and reported it shortly after ours was published.⁵³ As with Satoh and Miura, the paper focuses on *N*-aryl amides. Our success using ruthenium catalyst (unpublished) was replicated by Ackerman nearly a year later using identical conditions (Scheme 1.22).⁵⁴

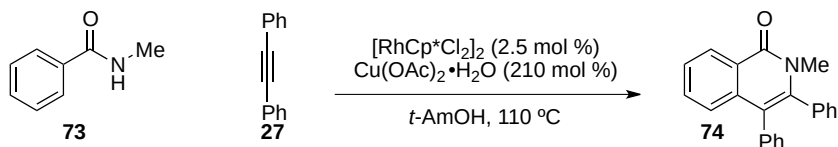
• Fagnou (Submitted March 26, 2010; Published April 30, 2010)



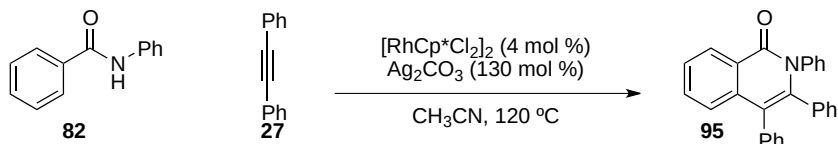
• Satoh and Miura (Submitted April 28, 2010; Published June 12, 2010)



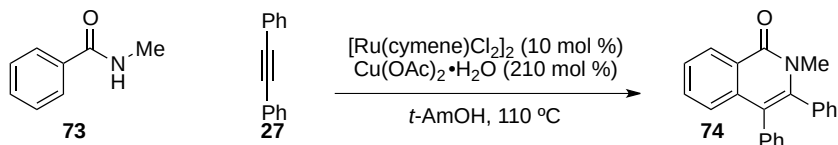
• Rovis (Submitted May 3, 2010; Published July 13, 2010)



• Li (Submitted August 23, 2010; Published October 5, 2010)



• Ackerman (Submitted March 18, 2011; Published May 24, 2011)

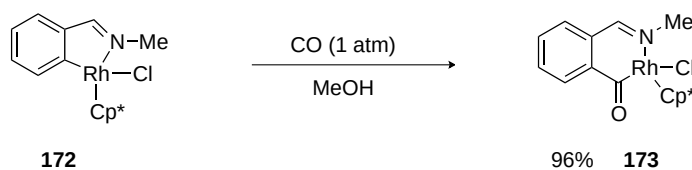


Scheme 1.22 Concurrent Work

1.4 Carbonylation to Access Phthalimides

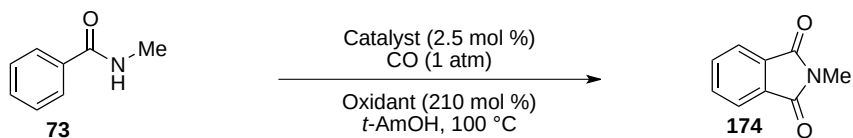
We were interested in exploring coupling partners beyond alkynes. Jones and coworkers found that carbon monoxide can undergo migratory insertion with Rh(III) metallacycle **172** to provide a new 6-membered metallacycle (Scheme 1.23).⁵⁵ We speculated that the same process could occur with the 5-membered metallacycle **173** we proposed as a key intermediate in our isoquinolone synthesis.

• Jones (2010)



Scheme 1.23 Stoichiometric Carbonylation

We were pleased to find when reaction condition similar to our isoquinolone synthesis were used under 1 atmosphere of CO, the desired phthalimide **174** was observed in 7% yield (Table 1.10, entry 1). We initiated our optimization screening a swath of different oxidants. Most oxidants failed to provide the desired product except for silver based oxidants, with AgOAc and Ag₂CO₃ giving product in 7% and 5% yield respectively (Table 1.10, entry 2-3). A brief solvent and concentration screen gave **174** in slightly increased yields (Table 1.10, entry 13-14). A large increase in yield was observed when the neutral catalyst was exchanged for a cationic variant. In the best case, the desired product was formed in 45% yield with Ag₂CO₃ over 16 hours (Table 1.10, entry 16). Extending the reaction time to 36 hours gave further enhancement, delivering the desired product in 66% yield with the rest of the mass balance being unreacted starting material (Table 1.10, entry 19). At this point, the project was continued by Dr. Ya Du who further optimized the reaction and explored the substrate scope.⁵⁶

Table 1.10 Optimization of Phthalimide

Entry	Precatalyst	Oxidant	Concentration (M)	Yield (%) ^a
1	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ •H ₂ O	0.16	7
2	[RhCp*Cl ₂] ₂	AgOAc	0.16	7
3	[RhCp*Cl ₂] ₂	Ag ₂ CO ₃	0.16	5
4	[RhCp*Cl ₂] ₂	BQ	0.16	0
5	[RhCp*Cl ₂] ₂	CeSO ₄	0.16	0
6	[RhCp*Cl ₂] ₂	K ₂ S ₂ O ₈	0.16	0
7	[RhCp*Cl ₂] ₂	tBuO ₂ Bz	0.16	0
8	[RhCp*Cl ₂] ₂	FeCl ₃	0.16	0
9	[RhCp*Cl ₂] ₂	Mn(OAc) ₃	0.16	0
10	[RhCp*Cl ₂] ₂	Ag ₂ O	0.16	0
11	[RhCp*Cl ₂] ₂	PhI(OAc) ₂	0.16	0
12	[RhCp*Cl ₂] ₂	Pyridine <i>N</i> -Oxide	0.16	0
13	[RhCp*Cl ₂] ₂	AgOAc	0.3	14
14	[RhCp*Cl ₂] ₂	Ag ₂ CO ₃	0.3	4
15 ^b	[RhCp*(MeCN) ₃](SbF ₆) ₂	AgOAc	0.3	18
16 ^b	[RhCp*(MeCN) ₃](SbF ₆) ₂	Ag ₂ CO ₃	0.3	45
17 ^b	[RhCp*(MeCN) ₃](SbF ₆) ₂	Cu(OAc) ₂ •H ₂ O	0.3	2
18 ^{b,c}	[RhCp*(MeCN) ₃](SbF ₆) ₂	Ag ₂ CO ₃	0.3	45
19 ^{b,d}	[RhCp*(MeCN) ₃](SbF ₆) ₂	Ag ₂ CO ₃	0.3	70 (66) ^e

Reaction Conditions: 73 (1 equiv), Reaction time: 16 h

^a Yields Determined by GC/MS (Internal Standard = 1,3,5 trimethoxybenzene)

^b Catalyst Loading (5 mol %)

^c CO Bubbled through the reaction

^d Reaction time 38 h

^e Isolated Yield

1.5 Alkenes as Coupling Partners

We imagined that alkenes could be used in lieu of alkynes or carbon monoxide to provide the dihydroisoquinoline motif from simple amides and alkenes. Unfortunately previous examples with

rhodium (III) catalysis exclusively provided *ortho*-olefination. Indeed, under our reaction condition, when the alkyne is replaced with styrene the undesired mono-*ortho*-olefination product is formed in 80% yield (Table 1.11). Further optimization revealed the cationic catalyst to be superior to the neutral variant. The cationic rhodium species is capable of catalyzing the olefination reaction at temperatures as low as 23 °C. Unfortunately, even under the mildest conditions, only β -hydride elimination occurs. Switching to acidic conditions does not preclude β -hydride at 80 °C, but does eliminate the need for a copper based oxidant while providing the olefinated product in quantitative yield.

Table 1.11 Olefination Optimization

73 **175** $\xrightarrow[\text{Additive (210 mol \%)}]{\text{Solvent, Temp}}$ **176**

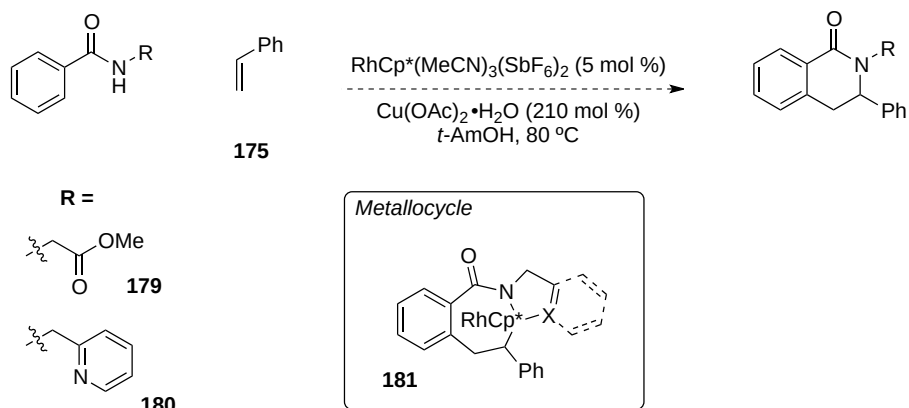
PRECATALYST A
 $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol %)

PRECATALYST B
 $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ (5 mol %)

Entry	Precatalyst	Additive	Solvent	Temperature (°C)	Yield (%)
1	A	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	<i>t</i> -AmOH	110	80
2	B	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	<i>t</i> -BuOH	80	90
3	B	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	Acetone	55	81
4	B	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	Acetone	23	45
5 ^a	B	PivOH ^b	DCE	80	99

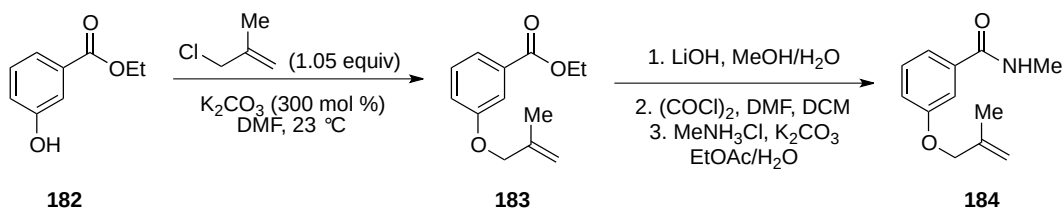
Reaction Conditions: **73** (1 equiv); **170** (1.1 equiv); 0.2M
^a methyl acrylate (**177**) was used instead of styrene (Product = **178**)
^b Additive (500 mol %)

To achieve the cyclized product, the unwanted β -hydride elimination had to be disfavored by comparison to reductive elimination. We imagined the β -hydride elimination occurs from either the 7-membered metallacycle, or the adduct after migratory insertion with ligand exchange of the amide. We imagined if a second coordinating group is added to the amide, it should occupy the free coordination site where β -hydride elimination occurs (Scheme 1.24). Unfortunately, ester **179** and pyridine **180** coordinating groups fail to provide any product. Presumably the coordinating group occupies the open coordination site irreversibly, failing to allow for the requisite open coordination site required for C–H activation (Scheme 1.24).



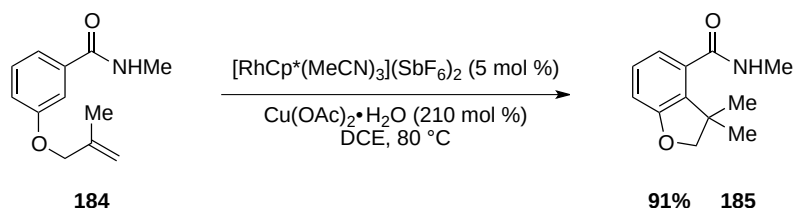
Scheme 1.24 Attempts to Avoid β -Hydride Elimination

In a further attempt to dissuade β -hydride elimination we imagined eliminating the β -hydrogen. Unfortunately, exogenous alkenes bearing substituents failed to provide product under our reaction conditions. An alternative was to tether the alkene to the *meta*-position of the arene. Upon activating of the adjacent C–H bond and migratory insertion, the intermediate 7-membered metallocycle can be formed which would be unable to undergo β -hydride elimination, and therefore should proceed to reductively eliminate. The starting material was prepared from allylation of *m*-hydroxyethylbenzoate **182** with 3-chloro-2-methyl-1-propene to provide the desired ester. Upon saponification, conversion to the acid chloride, and amination, the desired amide **184** can be accessed in 65% yield (Scheme 1.25).



Scheme 1.25 Tethered-Substrate Synthesis

To our surprise, when amide **184** was submitted to the reaction conditions, the desired dihydroisoquinolone was not observed but rather protonation of the 7-membered metallocycle to give *ortho*-alkylated amide **185** in 91% yield. We screened a variety of solvents and bases to qualitatively determine if reductive elimination would occur under different conditions. Unfortunately, in all cases either starting material and/or protonation are observed (Scheme 1.26).



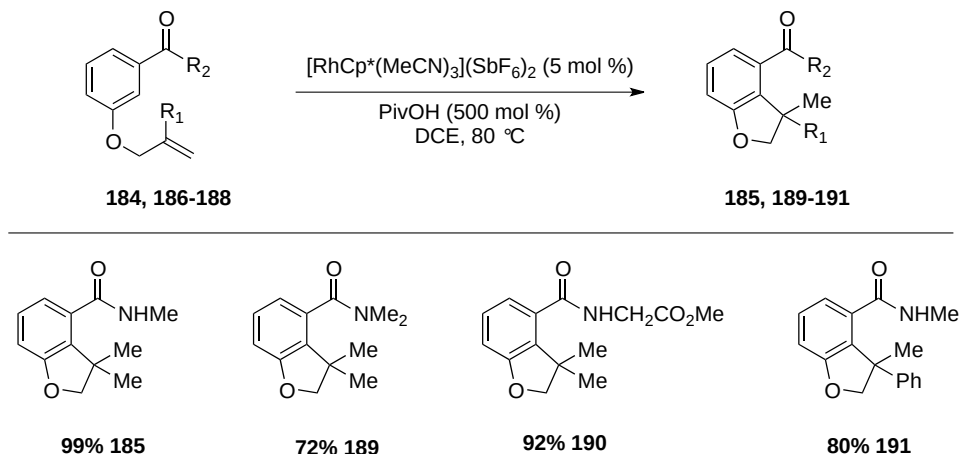
QUALITATIVE SCREEN:

Solvent : Acetone, Toluene, Dioxane, *t*AmOH, THF, DMF, H₂O, Hexanes, EtOAc, MeCN

Bases: Pyridine, 2,6-lutidine, Li₂CO₃, K₂CO₃

Scheme 1.26 Attempts of Preclude Protonation

Since reductive elimination does not occur there is no change in the oxidation state of the metal. As a consequence the exogenous oxidant might not be necessary to achieve the same reactivity. Indeed, when excess pivalic acid is added to the reaction, the protonation product **185** is isolated in 99% yield. We found the alkylation of amides to be interesting and briefly explored the scope. A screen of different directing groups revealed primary and secondary amides, and esters all provide product. Further modifications to the alkene provide product in good yield. At this point, the project was transferred to Dr. Tyler Davis, who has further explored the scope and possibilities of this reactivity (Scheme 1.27).



Scheme 1.27 Tethered-Alkene Scope

1.6 Conclusion

In conclusion we have developed a methodology to construct heterocycles through C–H activation. We first studied the synthesis of isoquinolones from the coupling of alkynes and benzamides. The reaction can tolerate a wide range of amides and alkynes. Unsymmetrical alkynes and meta substituted amides

provide product in high regioselectivity. Mechanistic experiments suggests the C–H activation proceeds through a CMD mechanism facilitated by an acetate base. The alkyne insertion event favors electron rich alkynes and aromatic alkynes. Similar conditions also provide access to phthalimides using a carbonylation reaction. Attempts to access dihydroisoquinolones from alkenes failed because of unwanted β -hydride elimination. In the event that β -hydride elimination cannot occur, protonation occurs rather than reductive elimination.

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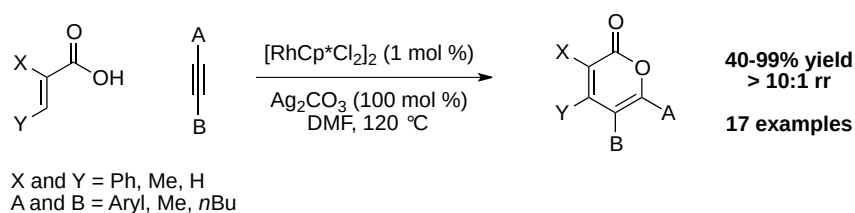
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Chapter 2

Ligand Development to Control the Regioselectivity of Migratory Insertion in Amide-Directed Rh(III)-Catalyzed C–H Activation Reactions

2.1 Introduction

After demonstrating that $[\text{RhCp}^*\text{Cl}_2]_2$ is capable of coupling benzamides and alkynes to access isoquinolones, we shifted our attention to the synthesis of monocyclic heterocycles mediated by the activation of non-aromatic C–H bonds. Our previous mechanistic studies suggested that Rh(III) catalyzed C–H activation proceeds via concerted metallation-deprotonation (CMD). Since positive charge does not need to be stabilized in this transition state, we hypothesized that alkenyl C–H bonds could undergo a similar process. Nonetheless, activation of alkenyl C–H bonds with Rh(III) salts are rare, with the only report being the coupling of acrylic acids and alkynes described by Miura and Satoh.¹ The conditions tolerate α and β substitution on the acid with a variety of symmetrical alkynes. Examples using unsymmetrical alkynes gave a mixture of regioisomeric products in a 10:1 ratio favoring the aromatic group adjacent to nitrogen (Scheme 2.1).



Scheme 2.1 Previous Catalytic Activation of Alkenyl C–H Bonds

We sought to couple acrylamides with alkynes to access polysubstituted-pyridones under Rh(III) catalysis. Our proposed approach is a departure from previous methodologies to synthesize substituted pyridones. The most common method is the [2+2+2] cycloaddition of alkynes and isocyanates catalyzed by Co(I),²⁻⁶ Ni(0),⁷⁻¹¹ Rh(I),¹²⁻¹⁹ or Ru(II).^{20,21} Mechanistically, the reaction is understood to proceed via oxidative cyclization between the isocyanate, one equivalent of alkyne, and a metal catalyst to generate a 5-membered metallacycle. Migratory insertion across a second equivalent of alkyne followed by

reductive elimination furnishes the desired product and the active catalyst. The oxidative cyclization and migratory insertion frequently occur with high levels of regioselectivity, predominately favoring one substitution pattern (Figure 2.1).

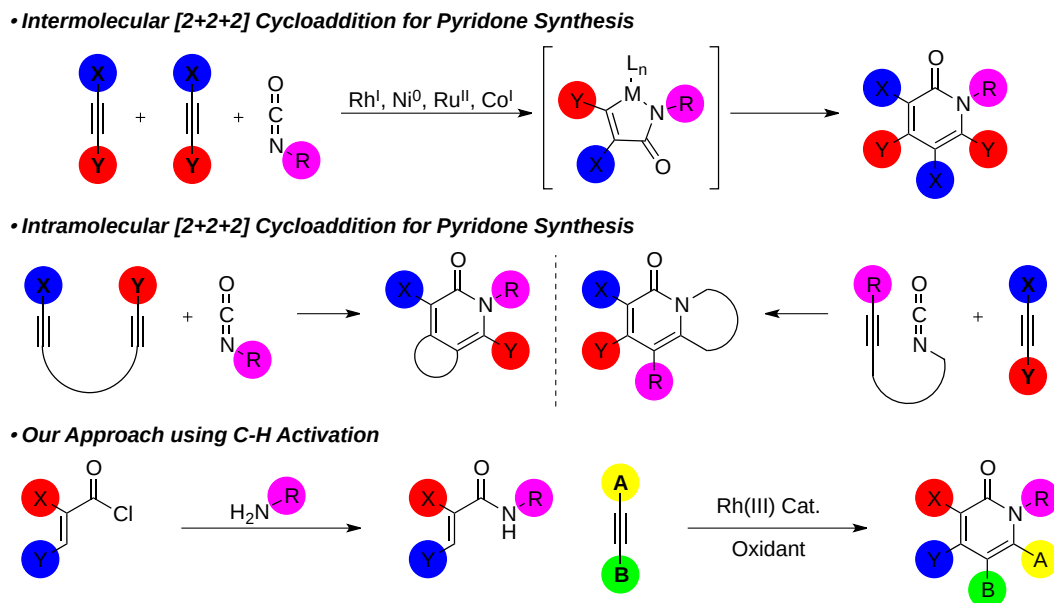


Figure 2.1 Comparison of Metal-Catalyzed Pyridone Syntheses

The fully 3-component reaction suffers from indiscriminate alkyne insertion; consequently a statistical mixture of products is observed when two different alkynes are used. Accordingly, practical application of this method can only couple one alkyne and one isocyanate. To circumvent this issue, researchers have explored tethering two of the components together. This strategy allows for a broader range of substitution patterns, but unfortunately gives less common cyclic products. In contrast, our approach would allow for substitution to be controlled through choice of readily accessible acrylamide and alkyne. The acrylamide can be accessed through a simple coupling reaction between an amine and acryl chloride (Figure 2.1).

2.2 Results

2.2.1 Initial Optimization

We initiated our studies coupling acrylamide **192** with 1-phenyl-1-butyne **70** in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in *t*-AmOH to provide pyridone adducts **193** and **194** in a 5:1 ratio of

regioisomers in 30% yield (Table 2.1, entry 1). Reaction optimization was initially conducted with the goal of increasing the yield. At 110 °C, DCE provided the desired products in 85% yield and 6:1 regioselectivity (Table 2.1, entry 5). Unfortunately, attempts to decrease the temperature below the boiling point substantially decreased the yield (Table 2.1, entry 6). Chlorinated solvents with higher boiling points did provide product in good yields, but we elected to abandon the approach due to solvent toxicity (Table 2.1, entry 8). With ideal conditions not yet in hand, a more reactive cationic catalyst was attempted. While we had previously observed that cationic catalysts can lead to unwanted naphthalene side products, this pathway is not of concern when using acrylamides due to the absence of an adjacent C–H bond. We were pleased to find the cationic catalyst provides the desired product in 90% yield and 5:1 ratio of regioisomers at 95 °C (Table 2.1, entry 10). Decreasing the temperature to 60 °C still gave high yield and a marginal increase in regioselectivity (Table 2.1, entry 12). In a final attempt to increase regioselectivity, the reaction was performed in acetone at 23 °C. Unfortunately, after 30 hours, only 20% yield of the desired product was obtained with no increase in the regioselectivity (Table 2.1, entry 13).

Table 2.1 Optimization of Pyridone Synthesis

Entry	Precatalyst	Solvent	Temp (°C)	Yield (%)	Regioisomer Ratio
1	[RhCp*Cl ₂] ₂	<i>t</i> -AmOH	110	30	7.8:1
2	[RhCp*Cl ₂] ₂	Toluene	110	5	nd
3	[RhCp*Cl ₂] ₂	1,4-Dioxane	110	12	nd
4	[RhCp*Cl ₂] ₂	DMF	110	30	nd
5	[RhCp*Cl ₂] ₂	DCE	110	85	7.8:1
6	[RhCp*Cl ₂] ₂	DCE	80	10	nd
7	[RhCp*Cl ₂] ₂	PhCl	110	0	nd
8	[RhCp*Cl ₂] ₂	TCE	110	75	8:1
9	[RhCp*Cl ₂] ₂	DCE	95	57	6:1
10 ^a	[RhCp*(MeCN) ₃](SbF ₆) ₂	DCE	95	90	5:1
11 ^a	[RhCp*(MeCN) ₃](SbF ₆) ₂	DCE	80	90	6:1
12 ^a	[RhCp*(MeCN) ₃](SbF ₆) ₂	DCE	60	86	6:1
13 ^a	[RhCp*(MeCN) ₃](SbF ₆) ₂	Acetone	23	20	7:1

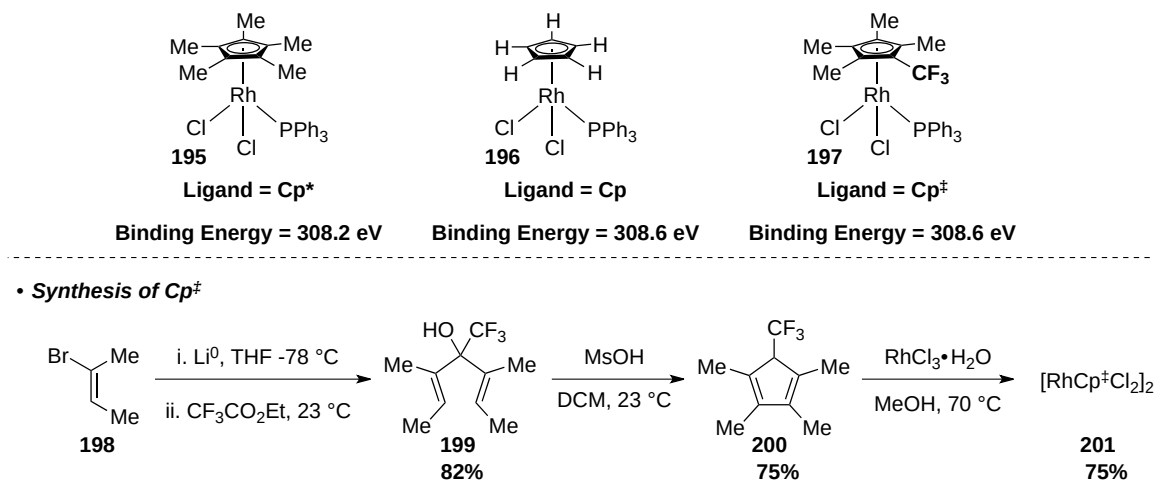
Reaction Conditions: **192** (1 equiv), **70** (1.1 equiv), Catalyst (2.5 mol %), Cu(OAc)₂·H₂O (210 mol %), Solvent (0.16 M). Regioselectivity determined by ¹H NMR.

^a Catalyst Loading is 5 mol %

In an attempt to further increase the regioselectivity of the alkyne insertion, we considered the use of modified cyclopentadienyl ligands. Methodical ligand development has not yet been explored in Rh(III) C–H activation reactions. In nearly all cases the classic Cp* ligand is used. The one exception is the activation of aldehyde C–H bonds, where a tetraphenylcyclopentadiene ligand is used.²² We prepared three unique ligands to probe the impact that electronics, ancillary coordinating groups, and sterics have on the regioselectivity of the alkyne insertion.

In the early 1990's Gassman examined the impact trifluoromethyl groups had on cyclopentadienyl ligands in Rh(III) complexes.²³ Gassman found the cyclopentadienyl ligand in RhCp*Cl₂(PPh₃) **195** had a inner

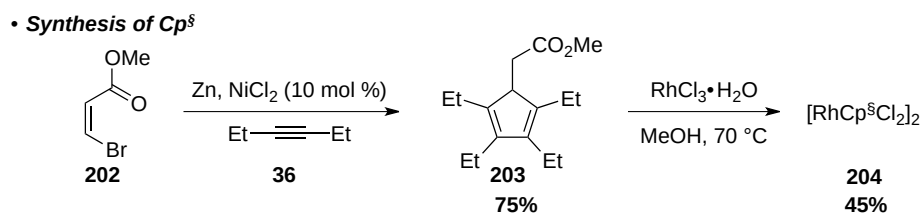
shell electron binding energy of 308.2 eV, while $\text{RhCpCl}_2(\text{PPh}_3)$ **196** had an inner shell electron binding energy of 308.6 eV suggesting Cp^* binds more strongly than Cp , presumably due to the impact of the electron donating methyl substituents. When one of the methyl groups is replaced with a trifluoromethyl group ($\text{Cp}^\ddagger$) the inner shell binding energy shifts to 308.6 eV for $\text{RhCp}^\ddagger\text{Cl}_2(\text{PPh}_3)$ **197**. These values support that $\text{Cp}^\ddagger$ is more electron deficient than Cp^* and similar electronically to Cp . The ligand was prepared, based on a procedure by Gassman, in two steps from 2-bromo-2-butene **198** and ethyl trifluoroacetate (Scheme 2.2). The $\text{Cp}^\ddagger$ complex can be ligated to rhodium by refluxing with $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ in MeOH for 24 hours.



Scheme 2.2 Electronic Impact on Cp Binding

We imagined a Cp ligand containing a ligating group could give enhanced levels of regioselectivity because it can provide steric bulk to the unoccupied coordination site. Careful selection of the ligating group was essential. If the ligand coordinates too strongly the reactivity of the catalyst will be inhibited because the ligand will always fill one coordination site on the metal. Examination of the literature revealed that amines and quinolones containing cyclopentadienyl ligands are frequently employed at ligating groups to facilitate transfer hydrogenation reactions.^{24,25} X-ray crystallography suggested that bond between the ligating group and the metal is strong and essentially irreversible. We speculated that a weaker coordinating group might have a more labile bond. Inspired by the weak coordinating ability of esters in C–H activation reactions, we elected to use an methyl ester as a coordinating group.²⁶ This ligand

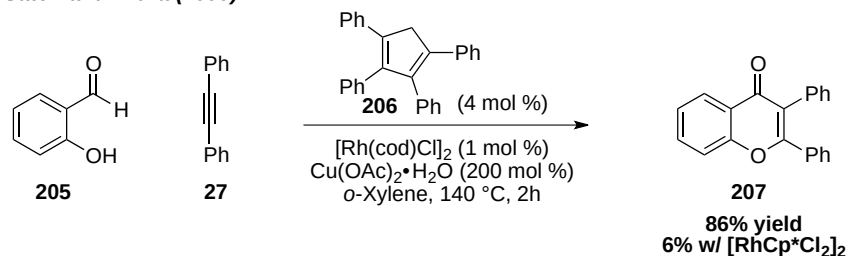
(Cp^s) was prepared in one steps from 3-hexyne and 3-bromo-ethylacrylate under Ni(0) catalysis and was ligated to rhodium using the standard conditions (Scheme 2.3).



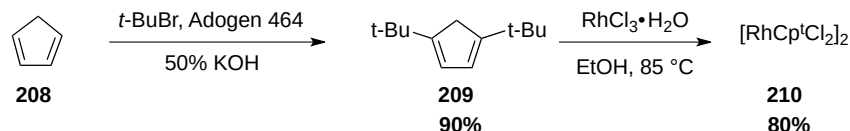
Scheme 2.3 Synthesis of Weakly-Coordinating Cp Ligand

Finally, a bulky ligand was selected with the hope that sterics would control the regioselectivity of the reaction. Previous work by Satoh and Miura found that tetraphenylcyclopentadiene (Cp^{Ph4}) **206** with [Rh(cod)Cl]₂ catalyzes that the coupling of salicylaldehyde **205** and diphenyl acetylene **27** at elevated temperatures (Scheme 2.3).²² Unfortunately, the existence of a discrete RhCp^{Ph4} was not established, making the impact of this ligand more nebulous. As an alternative, we selected 1,3 di-*tert*-butyl cyclopentadiene (Cp^t) **209** as a sterically bulky ligand for the reaction. The neutral rhodium complex had previously been prepared for inorganic studies.²⁷ This ligand can be prepared in one step from cyclopentadiene and *tert*-butyl bromide under basic conditions in the presence of a phase transfer catalyst.²⁸ The steric bulk of the ligand necessitated higher temperature to prepare the desired rhodium catalyst **210** (Scheme 2.3).

• *Satoh and Miura (2009)*

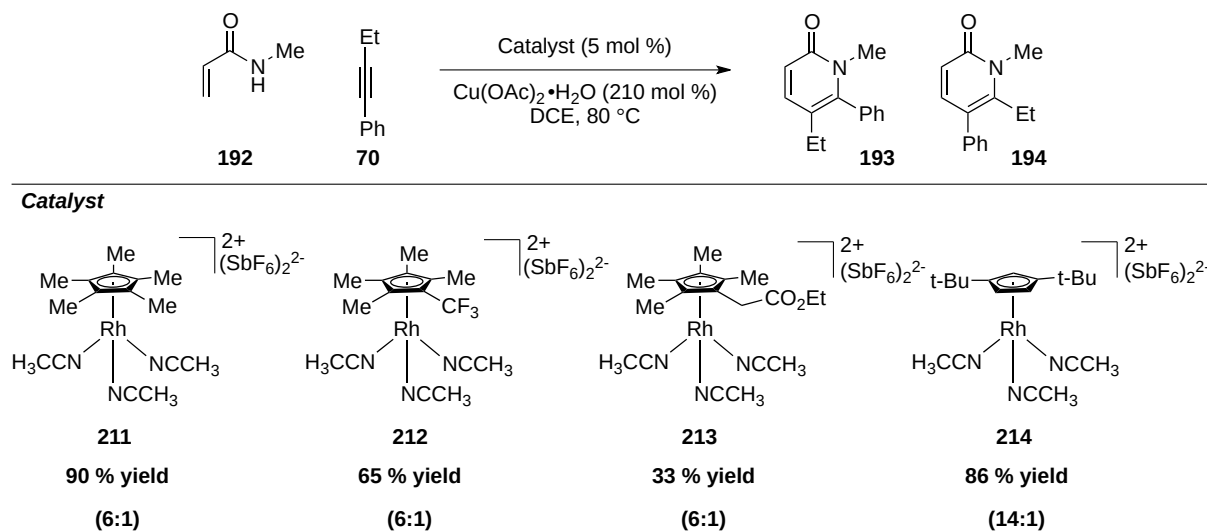


• *Synthesis of Cp^t*



Scheme 2.4 Sterically Bulky Cp Ligands

The cationic variants of all the rhodium salts were prepared by treating the neutral catalyst with AgSbF_6 in CH_3CN .²⁹ When submitted to the previously optimized conditions, the electron deficient **212** ($\text{Cp}^\ddagger$) provided product in 50% yield without enhanced regioselectivity. Switching to the coordinating ligand **213** (Cp^s) furnished product in 33% yield, but again without increased regioselectivity. Mimicking the metal/ligand conditions used by Satoh and Miura (CH_2Ph_4 with $[\text{Rh}(\text{cod})\text{Cl}]_2$) failed to provide any product, even at elevated temperatures. In contrast, sterically bulky **214** (Cp^t) gave the desired product in 86% yield with substantially improved regioselectivity (14:1) (Scheme 2.5). Having achieved excellent regioselectivity, we screened the Cp^* and Cp^t metal complexes with a variety amides and alkynes.

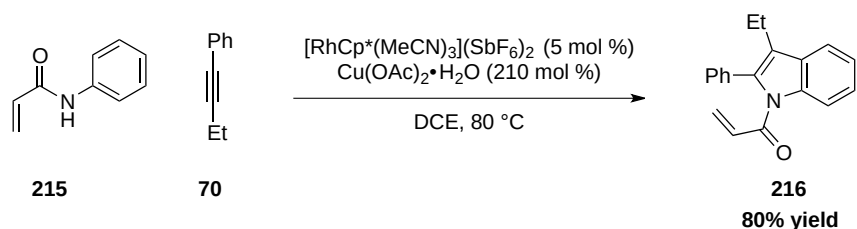


Scheme 2.5 Impact of Ligand on Alkyne Migratory Insertion

2.2.2 Substrate Scope

The scope of the amide component is quite broad with a variety of substitution patterns tolerated (Table 2.2). Replacing the methyl group on nitrogen with ethyl still results in excellent levels of regioselectivity when **214** (Cp^t) is used (Table 2.2, entry 2). Further increase in the steric bulk with an alanine methyl ester derivative gives the desired product in high yield (Table 2.2, entry 3). More bulky substitution (*tert*-butyl) does not afford product. When an aromatic group is placed on nitrogen the desired pyridone adduct is not observed. Instead, C–H activation occurred on the aromatic ring to provide the indole product **216** in excellent yield (Scheme 2.6). A variety of substitution patterns are tolerated on the alkene component of the acrylamide. Alkyl substitution at the α -position results in pyridone **230** in modest regioselectivity. However, upon use of **214** (Cp^t) the regioselectivity increases to 8.3:1 (Table 2.2, entry 4). Alkyl substitution at the β -position decreases the effectiveness of Cp^t with only a modest increase in regioselectivity (Table 2.2, entries 5-7). All attempts with longer alkyl substituents required elevated temperatures and extended times to obtain trace product formation. Diene based acrylamides also fail to give any desired product. We were interested in determining whether the pyridone motif would form in the presence of *N*-Acetyl enamine. Prior work by Fagnou demonstrated *N*-Acetyl enamine and alkynes form pyrrole products in high yield and regioselectivity.³⁰ We were pleased to find that pyridone is

formed preferentially in high yield and excellent regioselectivity (Table 2.2, entry 8). Presumably this is due to the preference for a 5-membered rhodacycle by comparison to the 6-membered rhodacycle. Strongly electron-withdrawing groups at the β -position produce product in good yield, with regioselectivity that can be improved with use of **214** (Cp^t) (Table 2.2, entry 9). We found that the steric bulk of Cp^t was not necessary to obtain product in high regioselectivity when an aromatic substituent is located at the β -position (Table 2.2, entries 10-11). Furthermore, ferrocene based acrylamides fare well under the reaction conditions (Table 2.2, entry 12). When Cp^t is used with cinnamides, the regioselectivity of the alkyne insertion decreases from 19:1 to 8:1. Unfortunately, when the alkene is moved out of conjugation, activation of the alkenyl C–H bond is not observed.



Scheme 2.6 Undesired Indole Synthesis

Table 2.2 Acrylamide Scope

Reaction scheme showing the synthesis of products **193, 228-238** from acrylamide derivatives (**192, 217-227**) and alkyne **70** under the following conditions: Catalyst (5 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (210 mol %), DCE, 80 °C. The yield and regio-selectivity are indicated for each product.

Entry	Product	Cp*	Cp ^t	Entry	Product	Cp*	Cp ^t
1		90 % (6:1)	86 % (14:1)	7		60 % (3.8:1)	82 % (4.6:1)
2		85 % (5:1)	78 % (15:1)	8		—	85 % (>19:1)
3		76 % (>19:1)	—	9		75 % (6.8:1)	65 % (>19:1)
4		98 % (5:1)	98 % (8.3:1)	10		74 % (>19:1)	78 % (8.1:1)
5		85 % (3.3:1)	82 % (4.8:1)	11 ^a		85 % (>19:1)	—
6		75 % (3.6:1)	69 % (4.6:1)	12 ^b		85 % (>19:1)	—

Reaction Conditions: acrylamide (1 equiv), **70** (1.1 equiv), Catalyst (2.5 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (210 mol %), Solvent (0.16 M). Regioselectivity determined by ^1H NMR.

Cp^t = $[\text{RhCp}^t(\text{MeCN})_3](\text{SbF}_6)_2$

Cp* = $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$

^a Reaction Time was extended to 48h

^b F_c = Ferrocene

The scope of alkynes was explored on the parent system with both Cp* and Cp^t. (Table 2.3) Propiolates are well tolerated under the reaction conditions with enhanced regioselectivity observed with Cp^t (Table 2.3, entry 1). Variation of the substituents steric bulk resulted in product formation with modest levels of regioselectivity (Table 2.3, entries 2 and 5). Protected propargyl alcohols and amines provide product

with lower levels of regioselectivity by comparison to their simple alkyl counterparts. Fortunately the regioselectivity can be increased with use of **214** (Cp^h) (Table 2.3, entry 3-4). En-yne also provide product in high levels of regioselectivity when **214** (Cp^h) is used rather than **211** (Cp*) (Table 2.3, entry 6). Di-alkyl alkynes with sterically different groups give pyridones in high regioselectivity with Cp*; however, if the steric bulk of the two groups are not sufficiently different, the reaction is essentially unselective independent of ligand (Table 2.3, entry 7-8). As previously observed, terminal alkynes are not tolerated under the reaction conditions due to dimerization. Silyl protected phenyl acetylene provides product in high yield and modest regioselectivity (Table 2.3, entry 9). Unfortunately, Cp^t results in product with decreased regioselectivity.

Table 2.3 Alkyne Scope

				yield (regio-selectivity)			
Entry	Product	Cp*	Cp ^t	Entry	Product	Cp*	Cp ^t
1 ^a		62 % (4.7:1)	50 % (>19:1)	6		60 % (4.8:1)	79 % (16:1)
2		78 % (11:1)	—	7		74 % (11:1)	—
3		65 % (2.5:1)	58 % (4.8:1)	8		52 % (1.2:1)	60% (1:1.2)
4		69 % (2.1:1)	56 % (7.2:1)	g ^b		53 % (5.8:1)	55% (2.7:1)
5		77 % (5:1)	81 % (12.3:1)				

Reaction Conditions: **192** (1 equiv), alkyne (1.1 equiv), Catalyst (2.5 mol %), Cu(OAc)₂•H₂O (210 mol %), Solvent (0.16 M). Regioselectivity determined by ¹H NMR.

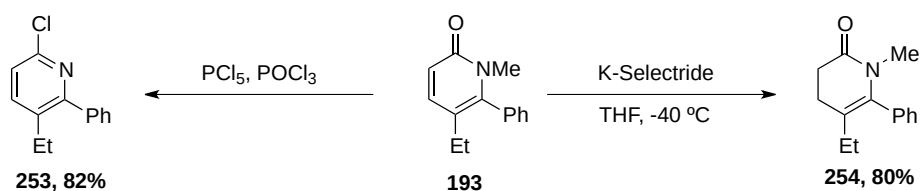
Cp^t = [RhCp^t(MeCN)₃](SbF₆)₂

Cp* = [RhCp*(MeCN)₃](SbF₆)₂

^a 2 equivalents of alkyne

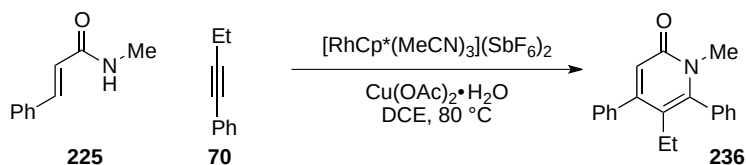
^b 10 mol% catalyst used

These pyridone products can be easily derivitized to increasingly interesting products (Scheme 2.7). Upon treatment with POCl₃ and PCl₅ the pyridone product **193** can be converted to an α-chloro pyridine **253**. Upon treatment with K-selectride the pyridone can undergo a 1,4 reduction to form differentially substituted dihydropyridones **254**.



Scheme 2.7 Product Derivatization

We endeavored to scale the reaction while decreasing the loading of both the rhodium precatalyst and copper oxidant (Table 2.4). We were pleased to find that decreasing the copper loading to 20 mol % did not result in a substantial loss in yield of the desired pyridone. Decreasing the catalyst loading to 1 mol % decreased the yield to 15%. Presuming alkyne inhibition was the source of decreased turnovers. Upon portion-wise addition of the alkyne, with 1 mol % catalyst the yield increased to 37%. Increasing the catalyst loading while making the reaction more dilute with portionwise addition did not increase the yield. Increasing the reaction concentration with portionwise addition resulted in slightly increased yield, presumably due to enhanced interactions between the amide and rhodium catalyst. Using the same conditions with 2 mol % catalyst loading on gram scale resulted in product formation in 69% yield. Interestingly, when copper is removed completely, under an atmosphere of O₂ in the presence of NaOAc, the desired product is formed in 40% yield (Table 2.4, entry 7). Using pivalic acid under an ambient atmosphere provides product in 50% yield (Table 2.4, entry 8). Attempts to enhance this yield through the use of pyridine additives, as demonstrated by Stoltz, did not result in increased yield.³¹ Finally, using the polyoxometalate employed as an oxidant by Sanford for sp³ olefination failed to provide useful yields (Table 2.4, entry 9).³²

Table 2.4 Precatalyst and Oxidant Loading

Entry	Scale (mmol)	Catalyst Loading (mol %)	Conc. (M)	Oxidant Loading (mol %)	Yield (%)
1	0.22	5	0.3	20	86
2	0.22	1	0.3	20	15
3 ^a	0.22	1	0.3	20	37
4 ^a	0.22	2.5	0.15	20	35
5 ^a	0.22	1	0.6	20	45
6 ^a	6.22	2	0.6	20	69
7 ^b	0.22	5	0.3	0	40
8 ^c	0.22	5	0.3	0	50
9 ^d	0.22	5	0.3	5	5

Reaction Conditions: **225** (1 equiv), **70** (1.1 equiv), 16 h.

^a Portion-wise addition of alkyne.

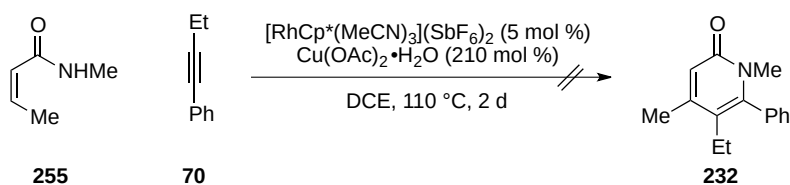
^b Run under an atmosphere of O₂ with 4 equiv of NaOAc

^c Run under an ambient atmosphere with PivOH (20 mol %)

^d Oxidant = H₄[PMo₁₁VO₄₀], 100 mol % NaOAc

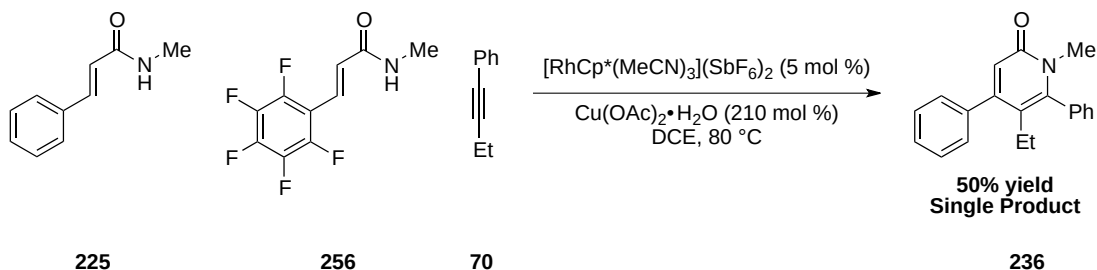
2.2.3 Mechanistic Studies

During our studies we suspected the reaction proceeded via a CMD C–H activation. Alternatively, one could imagine the reaction proceeding through a rhodium catalyzed 4+2 cycloaddition, or an electrophilic C–H activation where positive charge would form adjacent to the amide. In the latter two cases, the substrate would not necessarily require a cis- relationship between the C–H bond and the amide. To test this hypothesis, the amide derived from angelic acid was prepared. When amide **255** was submitted to the reaction conditions for extended reaction times, the desired product was not observed, suggesting these other mechanistic pathways may not be operative (Scheme 2.8).



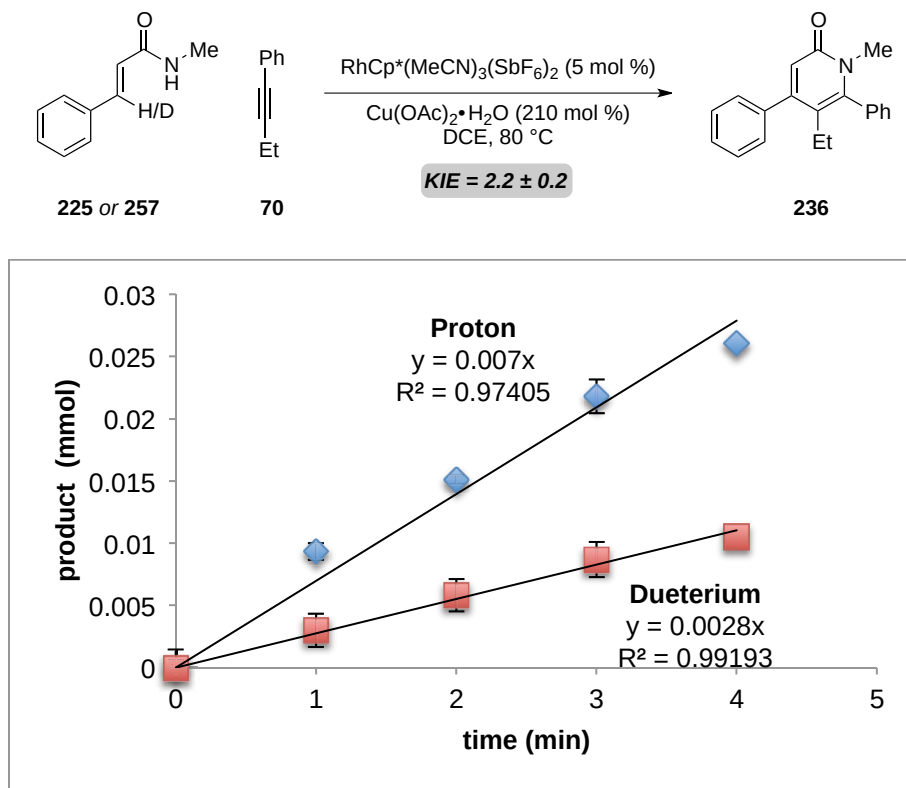
Scheme 2.8 Acrylamide Geometry

We gleaned mechanistic insights through the use of competition experiments, kinetic isotope studies, and initial rates experiments. An initial competition experiment between pentafluoro-cinnamyl amide **256** and cinnamyl amide **223** provided the cinnamyl pyridone **234** in 50% yield with no observed pentafluoro-cinnamyl pyridone. (Scheme 2.9) If this process is mechanistically similar to our isoquinolone formation, the product containing a pentafluorophenyl group would be expected because of the increased acidity of the C–H bond. To determine whether C–H activation is the turnover-limiting step, kinetic isotope studies were employed.



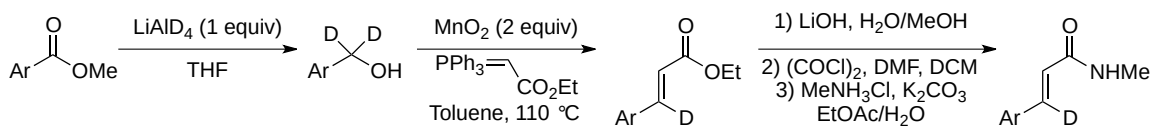
Scheme 2.9 Acrylamide Competition Experiment

We began by exploring if a kinetic isotope effect is present with the parent cinnamyl amide **218**. Using initial rate kinetics, a KIE value of 2.2 ± 0.2 was observed for amide **218**, sitting at the edge between a primary and secondary kinetic isotope effect (Scheme 2.10). In comparison to the KIE value found for the isoquinolone synthesis of 3.3 ± 0.2 , the value is low. This result in conjunction with the competition experiment, suggests that the mechanism has more nuances. We elected to obtain a Hammett plot to help illuminate these subtleties.



Scheme 2.10 Cinnamide Initial Rate KIE Study

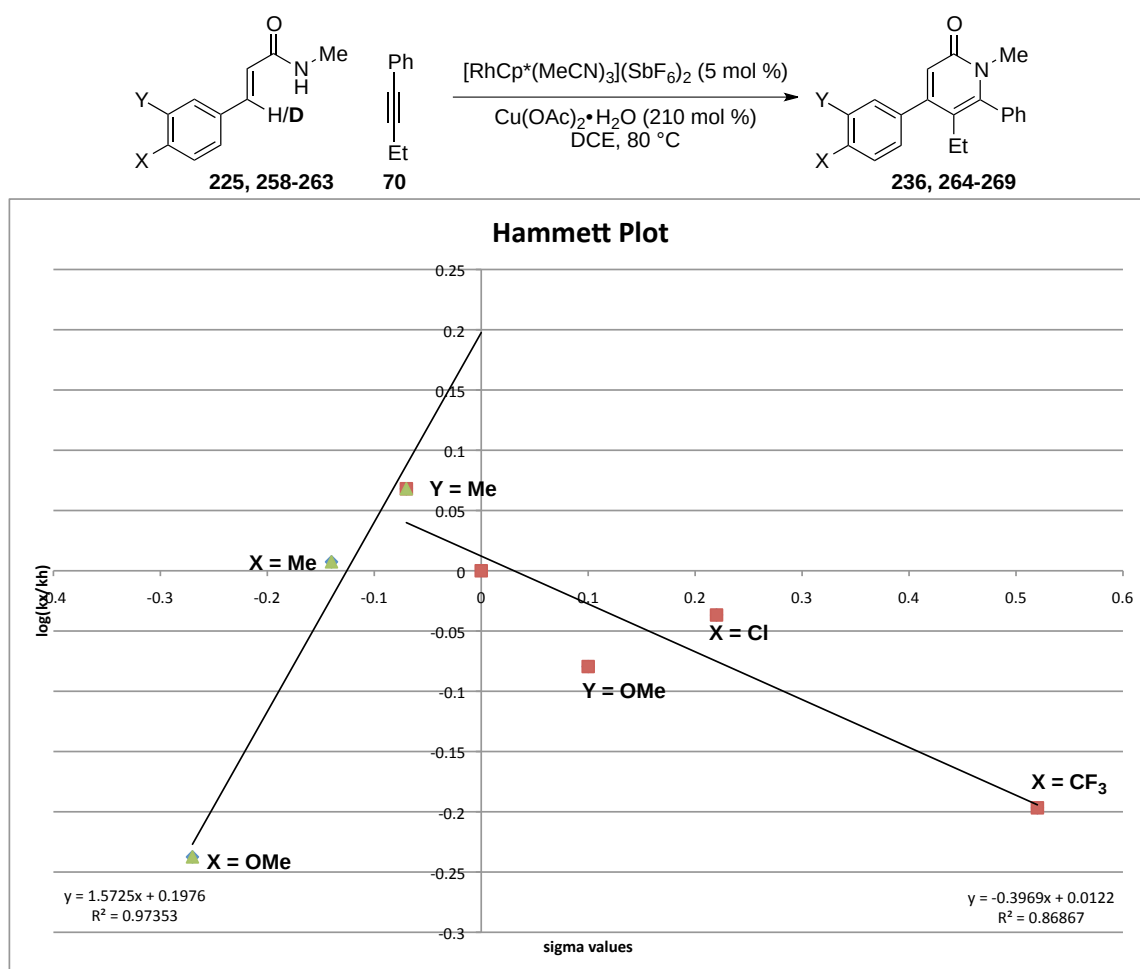
Seven substrates with electronically different characteristics were prepared in five steps (Scheme 2.11). The desired substituted methyl benzoate was reduced using LiAlD_4 to generate the desired d_2 -benzyl alcohol. Upon treatment with MnO_2 and Wittig reagent, the alcohol was oxidized to d_1 -aldehyde which can immediately proceed in a Wittig reaction to generate the desired α,β -unsaturated ester. After saponification and amination, the desired substrate is prepared with deuterium located exclusively at the β -position. The proteo-amide is prepared in an analogous fashion from the proteoaldehyde.



Scheme 2.11 Starting Material Synthesis

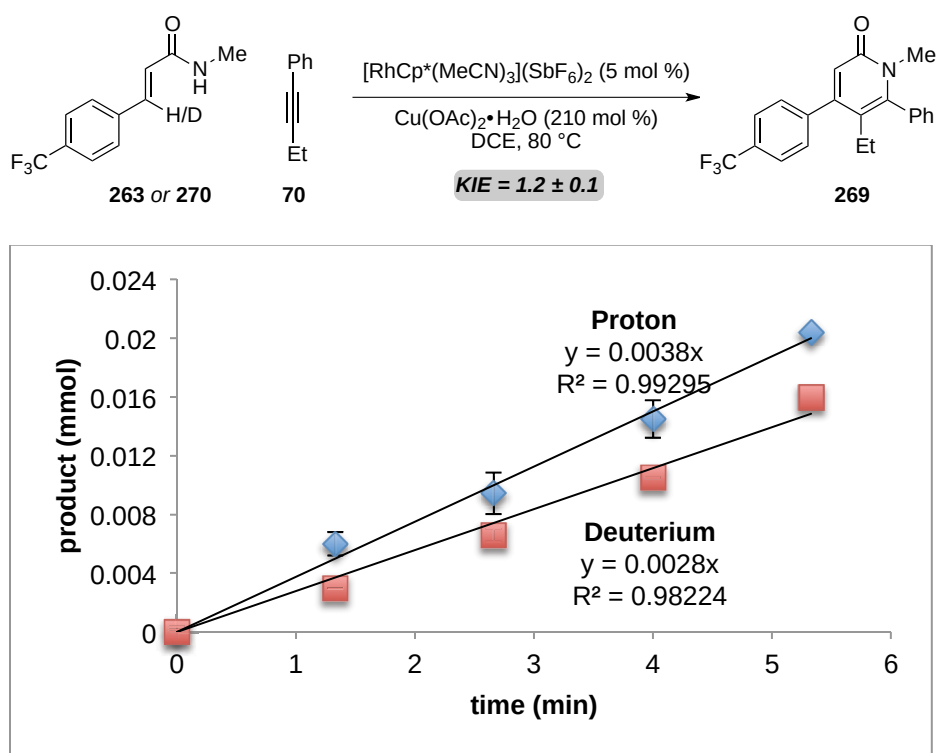
Initial rate kinetics was performed thrice on each substrate. Substrates bearing electron-donating substituents proceed in the reaction significant more slowly than more electron neutral substituent (Scheme 2.12). However, as electron withdrawing substituents are placed on the aromatic ring, the

reaction rate slows, reaching a minimum with *p*-trifluoromethyl cinnamide **263**. The bisecting nature of these plots is indicative of a mechanistic change. When C–H activation proceeds through a CMD mechanism and is turnover limiting, the reaction would proceed most quickly with electron poor substrates and have a positive Hammett plot slope. This trend would suggest that the left side of the Hammett plot is consistent with C–H activation as the turnover limiting step. When reductive elimination occurs, there is a net oxidation of the substrate and a reduction in the metal. Reductive elimination occurs most rapidly with electron deficient metals and electron rich substrates. A negative slope in the Hammett plot would be observed if reductive elimination was the turnover-limiting event. Since the right side of the Hammett plot has a negative slope, it is possible that reductive elimination is turnover limiting in this regime. This potential mechanistic dichotomy could be manifested in differential KIE values.

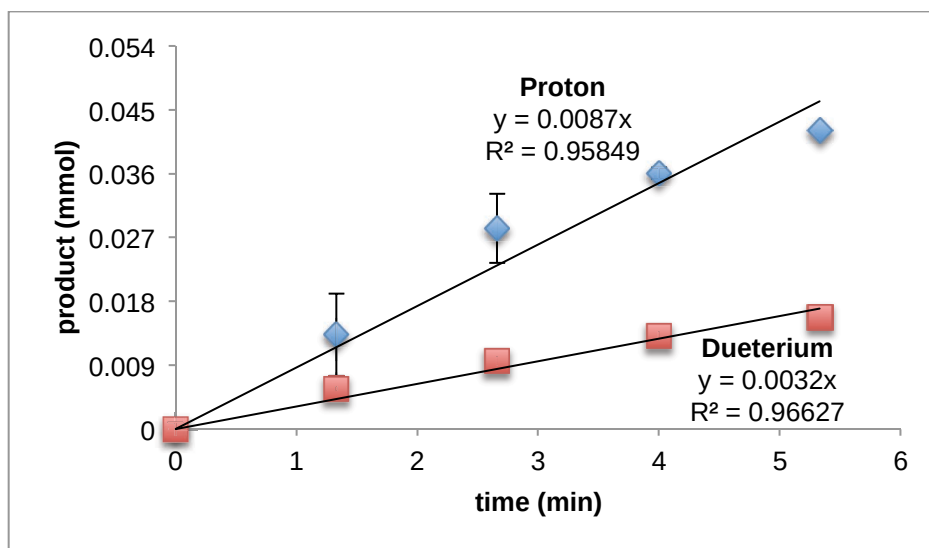
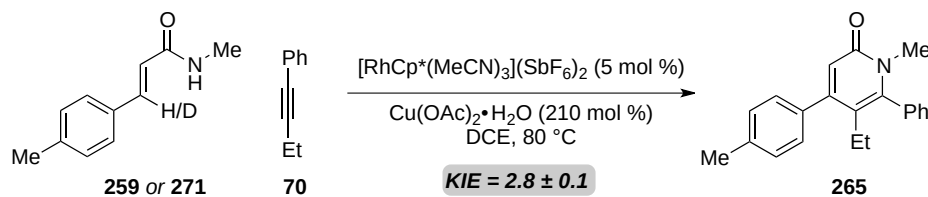


Scheme 2.12 Hammett Study of Cinnamides

The potential for KIE dichotomy was probed using *p*-methyl cinnamide **258** and *p*-trifluoromethyl cinnamide **262**. If reductive elimination is the turnover-limiting step for electron poor substrates, then electron deficient amide **262** should give very small KIE values. Accordingly, if C–H activation is the turnover limiting step for electron rich substrates, then electron rich amide **258** should give a KIE values larger than 2. Using initial rate kinetics a KIE value of 1.2 was found with the electron poor amide **262** (Scheme 2.13), and a KIE value of 2.8 was observed from electron rich substrate **258** (Scheme 2.14).

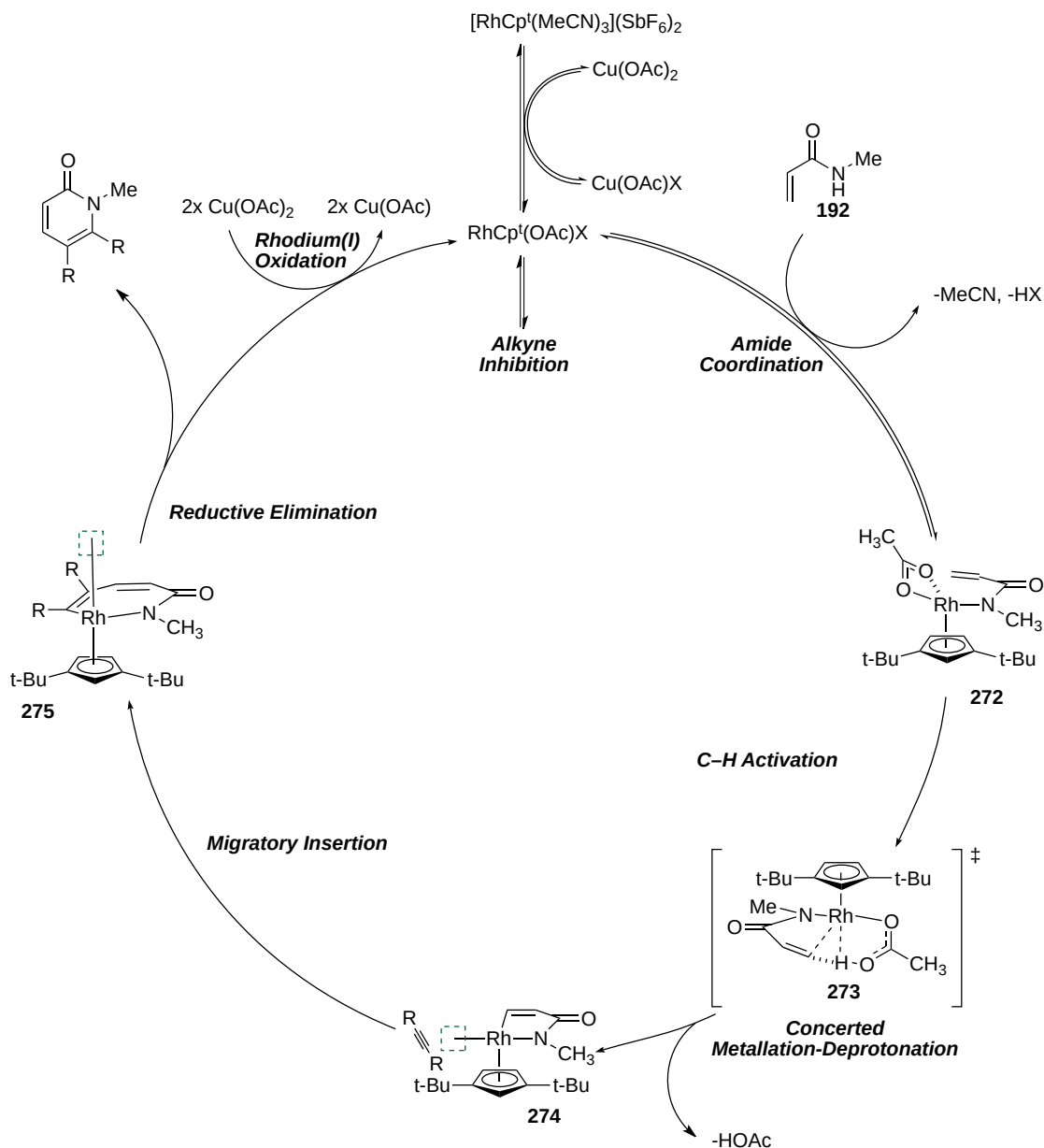


Scheme 2.13 Initial KIE for Electron-Poor Cinnamide



Scheme 2.14 Initial KIE for Electron-Poor Cinnamide

These results support the following mechanism (Scheme 2.15). The rhodium precatalyst coordinates to the acrylamides to form a rhodium amidate **272**. Under the aegis of acetate, C–H activation occurs presumably via a CMD mechanism to generate a 5-membered rhodacycle **274**. After alkyne coordination, migratory insertion can occur to generate a 7-membered metallocycle. Upon reductive elimination the desired pyridone is formed and a Rh(I) complex, which can undergo oxidation to Rh(III) to complete the catalytic cycle. Hammett and KIE studies suggest two mechanisms are potentially operative. When electron rich substrates are used, evidence suggests that C–H activation is the turnover limiting step; however, use of electron poor substrates appear to have a step after C–H activation as the turnover limiting step, presumably reductive elimination.

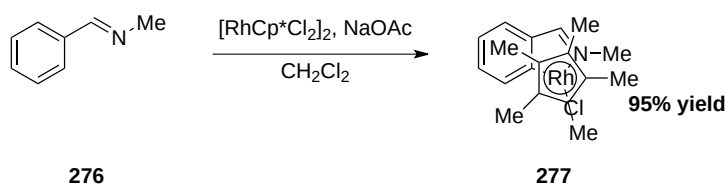


Scheme 2.15 Proposed Mechanism

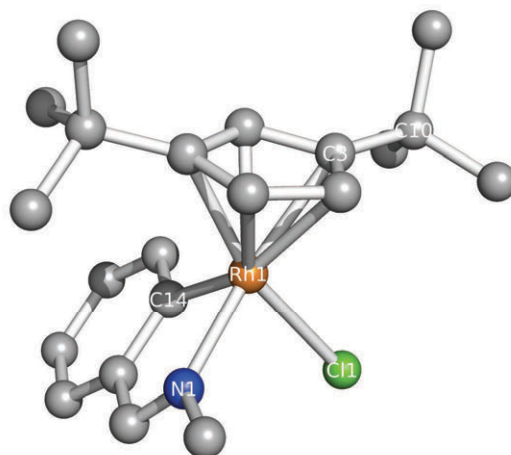
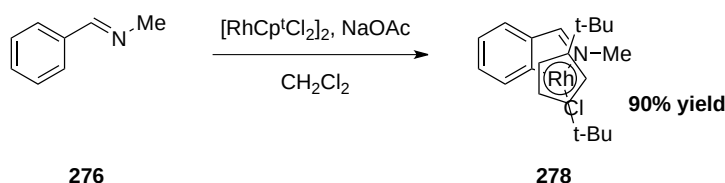
2.2.4 Regioselectivity of Alkyne Insertion

Attempts at isolating the 5-membered or 7-membered metallocycle as a means for rationalizing the regioselectivity were fruitless. Jones has previously isolated a 5-membered rhodacycle **277** from N -methyl benzaldehyde imine **276** and $[\text{RhCp}^*\text{Cl}_2]_2$.³³ To glean insight into the impact of the ligand on the metallocycle, we prepared a similar metallocycle **278** using $[\text{RhCp}^*\text{Cl}_2]_2$. Upon recrystallization, a crystal suitable for single crystal X-ray crystallography was obtained.

• Jones (2008)



• Our Work



Scheme 2.16 Crystal Structure of Cp^t Metallocycle

An evaluation of the bond lengths and angles of **278** by comparison to Jones structure **277** suggests a possible source of the enhanced regioselectivity (Table 2.5). As expected, the distance between the centroid of the Cp ligand and rhodium is longer within structure **278** than in the structure **277**. In most cases the bond lengths are longer with **278** than with **277** except for the Rh–N bond distance. The shorter bond distance suggests a greater degree of sigma donation potentially an artifact of a less electron rich metal center. Again the bond angles are similar in most cases. The exception is the $\text{C}_2\text{--Rh--Cl}$ bond angle which is substantially larger with Cp^t complex **278** by comparison to Cp^* complex **277**. This carbon bears the steric bulk of the *tert*-butyl group and sits almost directly over the Rh–Cl bond (Table 2.5). It is

possible that the steric bulk has a repulsive interaction with the Cl ligand, which causes the increase in bond angle.

Table 2.5 Bond Lengths and Angles

	Complex 277 (Cp*)	Complex 278 (Cp ^t)
Cp Centroid to Rh₁	1.834 Å	1.845 Å
Rh₁–Cl₁	2.384 Å	2.399 Å
Rh₁–N₁	2.095 Å	2.08 Å
Rh₁–C₁₄	2.029 Å	2.031 Å
C₁₀–C₃–Rh₁	127.05 °	130.09 °
C₃–Rh₁–Cl₁	90.09 °	98.03 °
C₁₄–Rh₁–Cl₁	85.47 °	85.69 °
N₁–Rh₁–Cl₁	86.69 °	87.84 °
N₁–Rh₁–C₁₄	78.67 °	78.76 °

Information gleaned from the x-ray crystal structure in conjunction with the regioselectivity trends observed when Cp* is used by comparison to Cp^t give an indication as to the source of enhanced regioselectivity. In the synthesis of isoquinolones, the aromatic group sits adjacent to rhodium in the metallacycle with high levels of regioselectivity. Pyridones using Cp* provide product with much lower selectivity for reasons that are not immediately clear. Nonetheless, when Cp^t is used as a ligand the steric environment changes substantially. If one of the *tert*-butyl groups is placed over the open coordination site to minimize steric interactions the second site can be expected to sit over the 6-position of the metallacycle (Figure 2.2). In this model there appears to be less steric interaction with the substituent adjacent to rhodium and greater steric interaction with the substituent at the 6-position of the metallacycle (opposite end of the alkyne). If a late transition state is present for alkyne migratory insertion, steric interactions would be minimized at the 6-position resulting in enhanced levels of regioselectivity. The impact of Cp^t is not uniform over all substitution patterns, suggesting the *tert*-butyl groups might be in slightly different position depending on acrylamide substitution pattern.

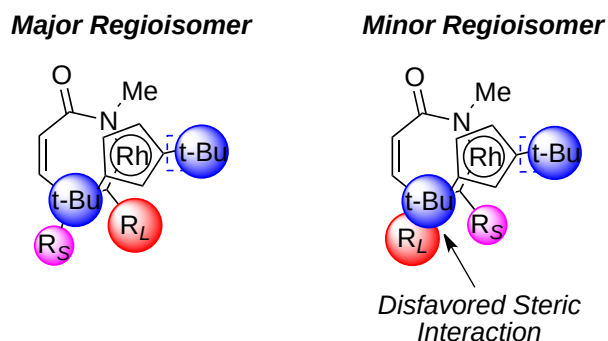
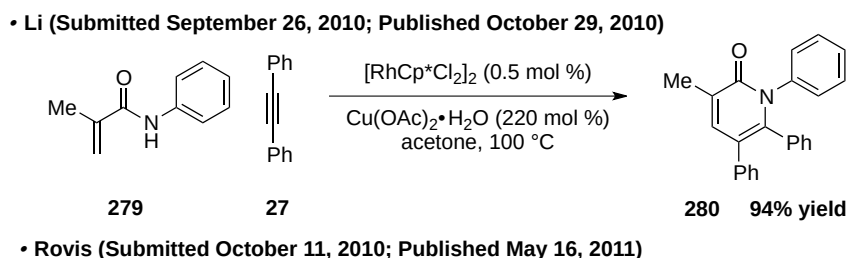


Figure 2.2 Rationale for Regioselectivity

2.2.5 Concurrent Work

During our investigation and submission of the material described in this chapter,³⁴ Xingwei Li and coworkers describe a similar Rh(III) catalyzed synthesis of pyridones from acrylamides and alkynes.^{35,36} In contrast to our approach, Li's condition tolerate aromatic substitution on nitrogen without undesired indole formation. Unfortunately their conditions are not tolerant of β -substitution on the acrylamide. As we observed, when unsymmetrical alkynes were used, only modest levels of regioselectivity were observed (Scheme 2.17).

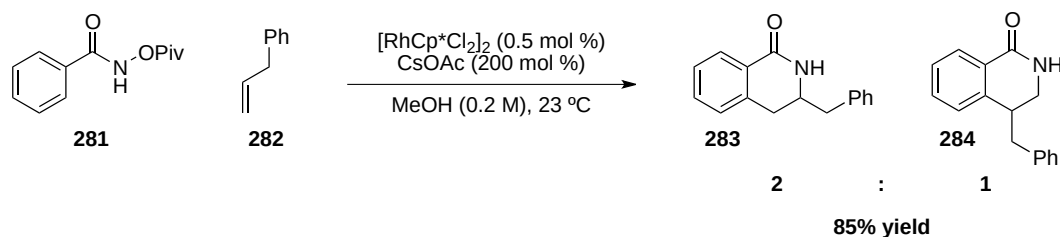


Scheme 2.17 Concurrent Work

2.3 Cp^t Impact on Dihydroisoquinolone Synthesis

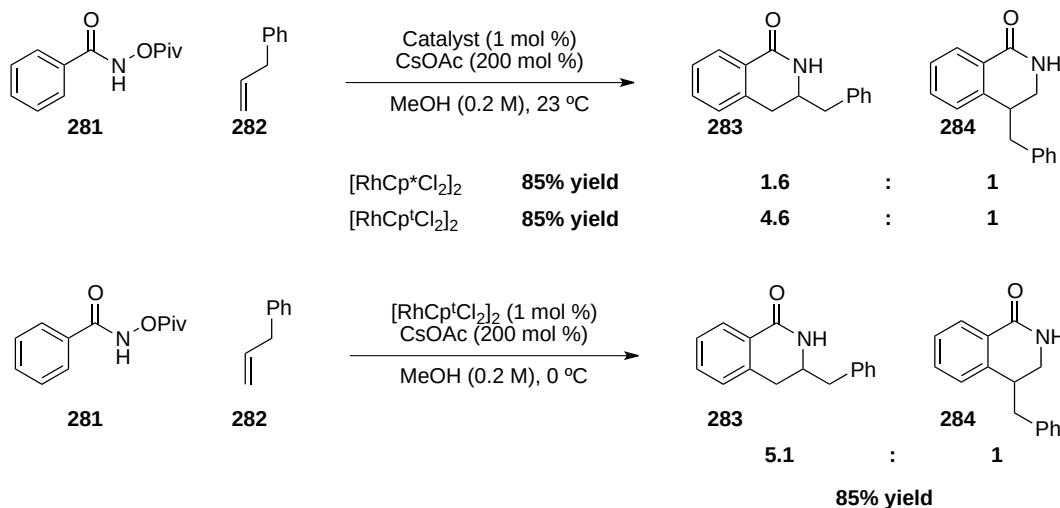
In light of the success using Cp^t to control the regioselectivity of alkyne insertion, we explored the impact Cp^t has on the regioselectivity of alkene insertion. Recently Fagnou and Glorius demonstrated that alkenes can be coupled to *O*-Pivaloyl benzhydroxamic acids to provide dihydroisoquinolones in high yield.^{37,38} While styrene and dienes provide product with high levels of regioselectivity, Fagnou found that allyl benzene gave a much lower level of regioselectivity (2:1 ratio of regioisomers) (Scheme 2.18). We were interested in the impact the Cp^t ligand could have on this reaction.

• Fagnou (2011)



Scheme 2.18 Dihydroisoquinolone Report by Fagnou

In our hands, $[\text{RhCp}^*\text{Cl}_2]_2$ coupled benzhydroxamic acid **281** and allylbenzene **282** to provide dihydroisoquinolones **283** and **284** as a 1.6:1 ratio of regioisomers in 85% yield (Scheme 2.19). When the same reaction was conducted with $[\text{RhCp}^t\text{Cl}_2]_2$ the yield remained the same but the regioselectivity increased to 4.6:1 (Scheme 2.19). We were pleased to find when the temperature was decreased to 0 °C, the regioselectivity was further increased to 5.1:1 without a loss in yield. (Scheme 2.19).



Scheme 2.19 Impact of Cp^t on Alkene Migratory Insertion

Pleased by this trend, we explored the impact on regioselectivity with a variety of alkenes (Table 2.6). Cp^t was effective in increasing the regioselectivity for homo-allylbenzene from 2.3:1 with Cp^* to 14:1 (Table 2.6, entry 1). Increasing the length of the alkyl chain did not diminish the ability of Cp^t to increase the regioselectivity (Table 2.6, entry 2). When the aryl group is electron rich the regioselectivity increased from 1.6:1 to 9.4:1 when the Cp^t catalyst is used (Table 2.6, entry 3). When allyl-benzene is rendered electron poor, the ability of Cp^t to increase the regioselectivity is decreased (Table 2.6, entry 4). γ,δ -

Unsaturated esters containing a stereocenter provide product as a 1:1 ratio of diastereomers with Cp^t effectively increase the regioselectivity (Table 2.6, entry 5). The steric bulk of Cp^t is also effective toward increasing the regioselectivity of simple alkyl alkenes, with 1-decene providing product with 15:1 regioselectivity with Cp^t (Table 2.6, entries 6). Finally, when protected allylic alcohol **291** was used with Cp^* , regioisomer **A** was favor in a 2:1 ratio. Switching to Cp^t inverted the regioselectivity, favoring the opposite regioisomer **B** in a 3:1 ratio (Table 2.6, entry 7). We speculated the reversal in selectivity is an artifact of electronics.

Table 2.6 Alkene Scope

Entry	Alkene	Product	Cp^* ^a	Cp^t ^b
1 ^c		292:293	95%	90%
	285		2.3:1	14:1
2 ^c		294:295	85%	85%
	286		1.6:1	8:1
3 ^c		296:297	68%	60%
	287		1.6:1	9.4:1
4 ^c		298:299	70%	71%
	288		1.3:1	5.5:1
5 ^{c,d}		300:301	92%	92%
	289		1.2:1	7.2:1
6 ^e		302:303	92%	91%
	290		2.4:1	15:1
7 ^e		304:305	88%	80%
	291		1:2	3:1

Reaction Conditions: **281** (1 equiv), alkene (1.1 equiv), 0.2M, 16h.

^aYields determined by GC/MS

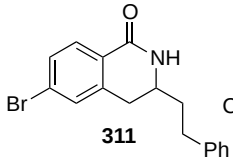
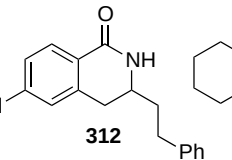
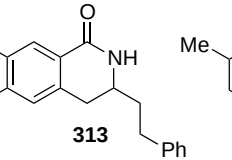
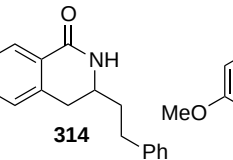
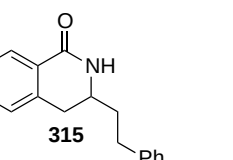
^bYields determined after column chromatography

^cRegioselectivity determined by GC/MS

^d1:1 ratio of diastereomers

^eRegioselectivity determined by ¹H NMR

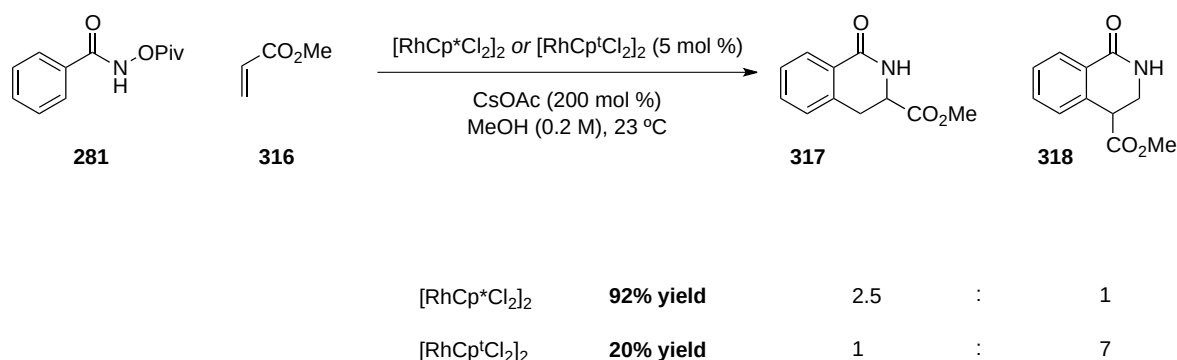
A variety of amides were tested in the coupling with homo-allyl-benzene to determine the impact aromatic substitution had on the ligands ability to control regioselectivity (Figure 2.3). Electronics did not have a large impact on the regioselectivity, with electron poor and electron rich giving an unselective reaction, while Cp^t increased the regioselectivity, with selectivity's ranging from 5.6:1 to 7:1 (Figure 2.3). Placement of a methyl group at the *meta*- position furnished poor selectivity with Cp^* , but was increase to greater than 10:1 after Cp^t .

									
311		312		313		314		315	
Cp^*	Cp^t	Cp^*	Cp^t	Cp^*	Cp^t	Cp^*	Cp^t	Cp^*	Cp^t
88%	85%	87%	81%	97%	98%	95%	95%	90%	91%
1:1	6:1	1.6:1	7:1	1:1	6:1	3:1	11:1	1:1	5.6:1

Reaction Conditions: See Table 2.18

Figure 2.3 Hydroxamic Acid Scope

Fagnou also found that acrylates also provide product with low levels of regioselectivity. When the catalyst was exchanged for $[\text{RhCp}^t\text{Cl}_2]_2$ catalyst loadings were substantially decreased, but the regioselectivity of the reaction switches favoring the 4-substituted with a 7:1 ratio of regioisomers in 20% yield. Increasing the catalyst loading and temperature did not have an impact on the yield. The remainder of the mass balance in the reaction with $[\text{RhCp}^t\text{Cl}_2]_2$ is *ortho*-olefination and starting material. Regioselectivity of the alkene insertion was confirmed by GC/MS. It appears that electron deficient alkenes do not tolerate the bulky electron poor nature of the Cp^t ligand.



Scheme 2.20 Impact with Acrylates

2.4 Conclusion

We have developed a 2-pyridone synthesis from the coupling of acylamides and alkynes. Using the standard Cp* ligand, low to modest levels of regioselectivity are observed for the alkyne insertions. After screen ligands to probe the impact of electronics, sterics, and coordinating group ability, we found that Cp^t gave enhanced levels of regioselectivity in the vast majority of examples. During our mechanistic investigation we found that Cu(OAc)₂ loading could be decreased without a detrimental effect on the reaction. Further studies suggest the presence a mechanistic dichotomy depending on the electronic character of the acylamide. We found that this ligand is also effective for alkene migratory insertion in the synthesis of dihydroisoquinolones. Use of a crystal structure and regioselectivity trends allow us to propose a preliminary model for the source of increased regioselectivity.

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Chapter 3

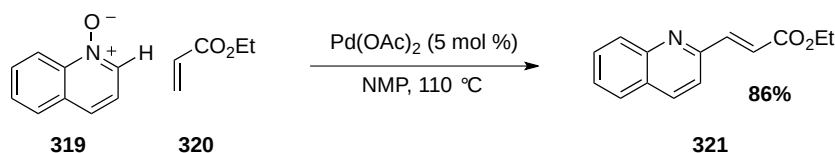
Oximes as Coupling Partners for the Synthesis of Pyridines and Isoquinolines

3.1 Introduction

3.1.1 N–O Bonds as Internal Oxidants

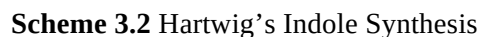
Oximes are common directing groups in C–H activation reactions.¹ Due to their stability, they are an ideal directing group for metal catalyzed oxidation,^{2,3} amination,⁴ halogenation,⁵ and olefination of C–H bonds.⁶ A frequently overlooked component of this directing group is the weak N–O bond (55 kcal/mol). We imagined this weak bond could serve as an oxidant in Rh(III) catalyzed C–H activation reactions. We hoped to showcase this potential in the coupling of α,β -unsaturated oximes and alkynes to access poly-substituted pyridines.

The use of internal oxidants has become increasingly prevalent in the field of metal catalyzed C–H activation.⁷ The approach benefits from not requiring the addition of a stoichiometric terminal oxidant, and frequently features high levels of selectivity in C–H activation event. Early reports by Wu and Cui showed that quinoline-*N*-oxide **319** will direct C–H olefination with subsequent reduction of the N–O bond (Scheme 3.1).⁸ Mechanistic studies suggest that upon olefination, the resultant Pd(0) species is oxidized by the quinoline *N*-oxide to generate an active Pd(II) catalyst and the reduced quinoline **321**. Mechanistic evidence suggests that oxidation does not necessarily occur with substrate fidelity, as exogenous quinoline *N*-oxides are also reduced.



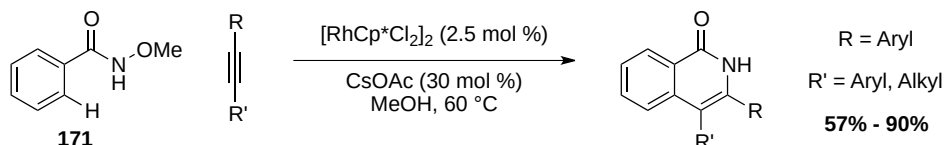
Scheme 3.1 Internal Oxidant in Pd(II)-Catalyzed Olefination

Independently, Hartwig demonstrated the N–O bonds of oximes to be effective oxidants for the palladium catalyzed intramolecular amination of arenes to provide indoles (Scheme 3.2).⁹ Contrary to the previous example, Hartwig proposes oxidation of the Pd(0) catalyst through reduction of the N–O bond to generate

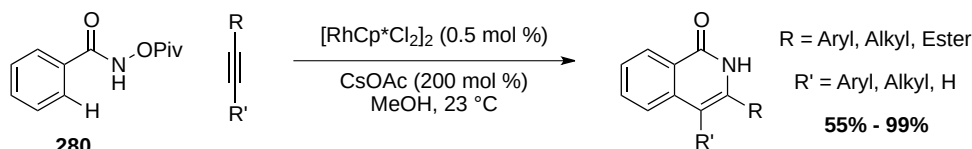


O-pivaloyl benzhydroxamic acid **280** with alkenes to afford the dihydroisoquinolone motif (Scheme 3.4).^{11,13} Glorius proposes that coordination of the pivaloyl oxygen to the open coordination site precludes β -hydride elimination rendering reductive elimination the only viable pathway.

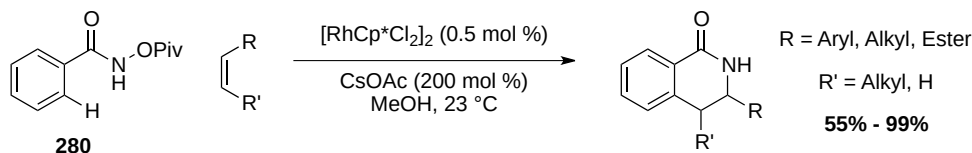
• **Fagnou (2010) - 1st Generation System**



• **Fagnou (2011) - 2nd Generation System**



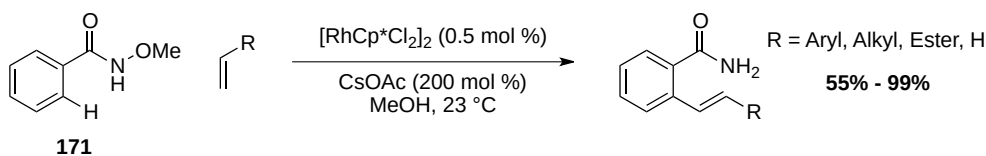
• **Fagnou and Glorius (2011)**



Scheme 3.4 Internal Oxidants Using Rh(III)-Catalyzed C–H Activation

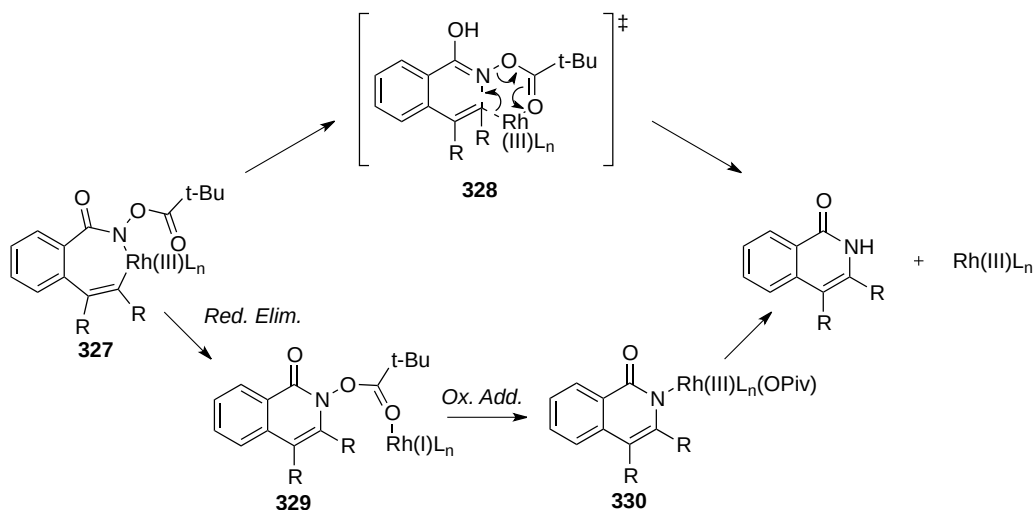
Based on this proposal, Glorius found that O–Me benzhydroxamic acids and alkenes can be coupled to give clean *ortho*-olefination rather than dihydroisoquinolone formation (Scheme 3.5).¹³ Using redox free directing groups for Rh(III) catalyzed olefination generally resulted in a mixture of mono and bis olefination products. When an internal oxidant is employed, however, only mono-olefination is possible.¹⁴⁻¹⁶ This approach is effective for a variety of electron deficient alkenes and substituted benzhydroxamic acids.

• **Glorius (2011)**



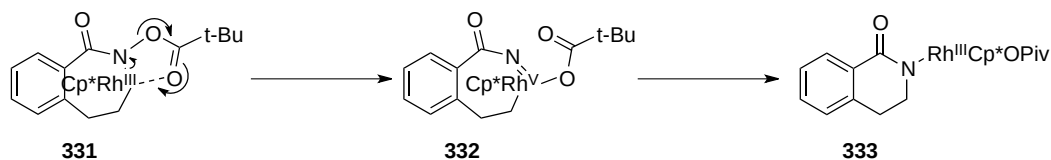
Scheme 3.5 Internal Oxidant for Rh(III)-Catalyzed Olefination

Early mechanistic experiments by Fagnou indicated that exogenous N–O bonds are not reduced during the course of the reaction. Consequently, Fagnou proposed two possible mechanisms to rationalize this observation: either the C–N bond formation/N–O bond cleavage occurs in a concerted 6-membered transition state **318** yielding the product and a rhodium complex at the appropriate oxidation state, or reductive elimination occurs to generate a Rh(I) complex bound to the oxygen of the hydroxamic acid (Scheme 3.6). This Rh(I) complex can rapidly undergo oxidative addition into the N–O bond providing the observed product and a rhodium complex at the appropriate oxidation state. DFT calculations of the two possible mechanisms indicate the latter pathway is more viable under the reaction conditions.



Scheme 3.6 Mechanistic Possibilities Proposed by Fagnou

Xia and coworkers performed DFT calculations to elucidate the mechanism for dihydroisoquinolone formation (Scheme 3.7). These studies suggest that after alkene migratory insertion, the OPiv group migrates to rhodium via a 5-membered transition state to form a Rh(V) nitrene **332**, which rapidly undergoes reductive elimination to form a rhodium amidate **333**.¹⁷ After protonation with acetic acid, the desired product is furnished with release of an active Rh(III) complex.

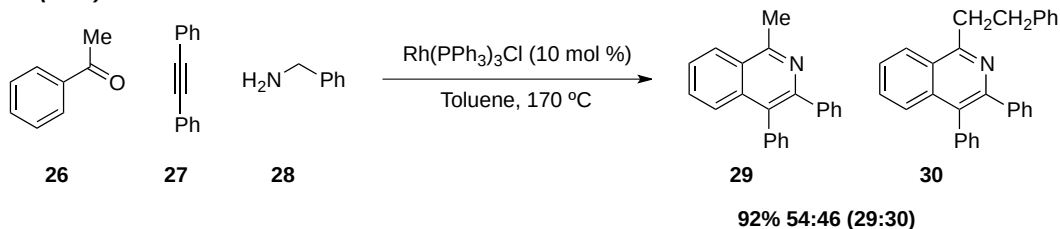


Scheme 3.7 Mechanistic Possibilities Proposed by Xia

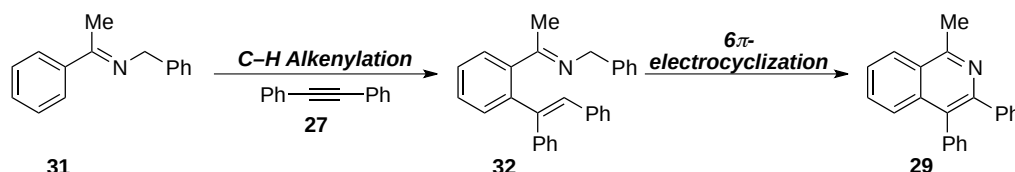
3.1.2 Synthesis of Pyridines and Isoquinolones using C–H Activation

Pyridine and isoquinoline scaffolds have previously been accessed using Rh(I) catalyzed C–H activation. In an early report Jun and coworkers demonstrated that imine derivatives of acetophenone can be coupled to alkynes to access isoquinolines in high yield.¹⁸ Mechanistically, the reaction is understood to proceed via C–H olefination to generate an *ortho*-alkenyl imine. Upon 6 π -electrocyclization and subsequent oxidation the desired product is generated in high yield. Bergman and coworkers expanded on this work to synthesize pyridines with excellent regioselectivity.¹⁹ Mechanistically, a dihydropyridine intermediate **40** is the product of the Rh(I) catalyzed C–H activation; however an additional two steps are required to generate the desired pyridine. Cheng and coworkers were able to eliminate these additional steps by using an α,β -unsaturated oxime to generate pyridines in high yield but modest regioselectivity.²⁰

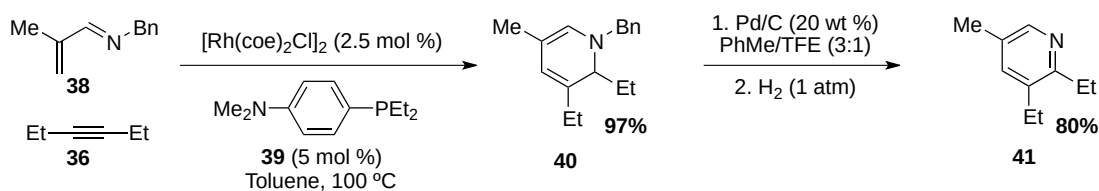
• Jun (2003)



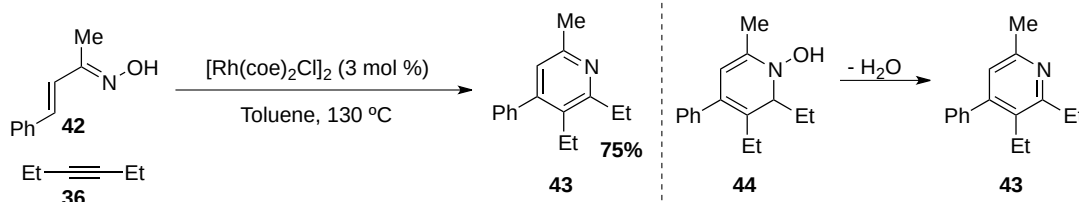
Proposed Mechanism



• Bergman and Ellman (2008)



• Cheng (2008)

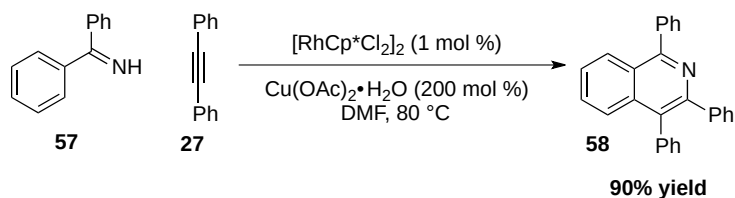


Scheme 3.8 Rh(I)-Catalyzed Pyridine Syntheses

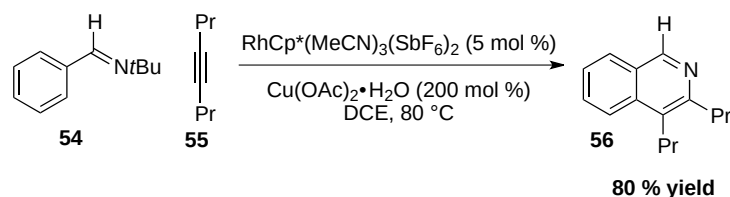
We envisioned a Rh(III) catalyzed C–H activation would be an attractive approach to access pyridine and isoquinolines motifs. Seminal work by Satoh and Miura describes the coupling of imines derived from benzophenone with diphenylacetylene (Scheme 3.9).²¹ Unfortunately, this approach also provided the undesired 1,2 addition products when aldimines were used. Fagnou and coworkers expanded on this work by coupling *tert*-butyl aldimines with di-alkyl alkynes (Scheme 3.9).²² This reaction is understood to be mechanistically distinct from the Rh(I) catalyzed syntheses. After electrophilic C–H activation to form a 5-membered rhodacycle, migratory insertion across the alkyne can form a 7-membered rhodacycle. Upon reductive elimination the desired product is generated and a Rh(I) intermediate is formed, which is

oxidized to generate an active catalytic species. Unfortunately, both reactions are limited in terms of imine, alkyne, and require an external oxidant.

•*Miura and Satoh (2009)*



•*Fagnou (2009)*



Scheme 3.9 Rh(III)-Catalyzed Isoquinoline Syntheses

3.2 Results

3.2.1 Reaction Optimization

We began our studies with the goal of preparing pyridines from α,β -unsaturated oximes and unsymmetrical alkynes. The essential feature of our plan was to employ the N–O bond of the oxime as an internal oxidant. We imagined that using an internal oxidant would tolerate a broader range of starting materials than current Rh(III) methods to access isoquinolines. Based on our previous experience with alkene C–H activation, we speculated the regioselectivity of the alkyne insertion would be problematic and imagined a sterically bulky Cp ligand could provide greater control over the insertion event. After a synthesis of pyridines was optimized, we believed similar conditions could be translated to the efficient synthesis of isoquinolines.

Our studies began by testing an oxime ester **334**, an oxime ether **335**, and a free oxime **336** in conditions similar to Fagnou's 1st generation isoquinolone synthesis. When the oxime starting materials are stirred with 1-phenyl-1-butyne **70** in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ and CsOAc in *i*-PrOH, only the oxime ester **324** and the unprotected oxime **326** provided the desired pyridine products (**327** and **328**) in modest yield

as a 1:1 ratio of regioisomers (Table 3.1). The oxime ether did not furnish any product, with the remainder of the mass balance being unreacted starting material.

Table 3.1 Optimization of Oxime Substituent

Reaction scheme: Oxime 70 (a cyclohexene ring with a Me group and an N-R group) reacts with ethynyl phenyl ether (Ph-C≡C-Et) in the presence of [RhCp*Cl₂]₂ (2.5 mol %), CsOAc (50 mol %), and iPrOH at 70 °C to yield two regioisomers, 337 and 338. Structure 337 has a Me group at position 1, an N-Ph group at position 2, and an Et group at position 3. Structure 338 has a Me group at position 1, an N-Et group at position 2, and a Ph group at position 3.

Entry	R =	Yield (%)	Regioselectivity
1	OAc (334)	35	1:1
2	OMe (335)	< 5	-
3	OH (336)	35	1:1

Reaction Conditions: Oxime (1 equiv), (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

We initially focused our efforts toward increasing the yield of the desired product. When DCE is used as a solvent, less than 5% of the desired product is formed (Table 3.2 entry 1). Switching to a cationic catalyst did not increase the yield (Table 3.2, entry 2). The reaction worked much better with MeOH as a solvent, with the products isolated in 50% yield as a 1.2:1 ratio of regioisomers (Table 3.2 entry 3). Removal of CsOAc decreased the yield, but did not substantially alter the regioselectivity (Table 3.2, entry 4). Removal of the catalyst prevented reactivity, evidence that an uncatalyzed [4+2] reaction is not operative under these conditions (Table 3.2, entry 5). Finally, using a cationic catalyst under polar protic conditions furnished product in modest yield, as a 1:1 ratio of regioisomers (Table 3.2, entry 6).

Table 3.2 General Optimization

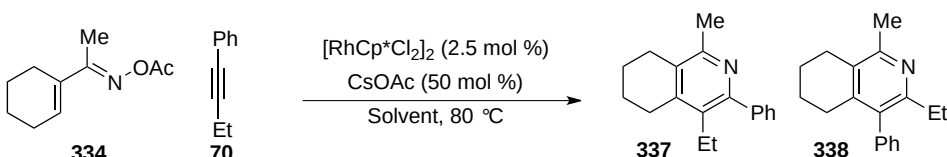
Entry	Precatalyst	Base	Solvent	Yield (%)	Regioselectivity
1	[RhCp*Cl ₂] ₂	CsOPiv (100 mol %)	DCE	< 5	–
2 ^a	RhCp*(MeCN) ₃ (SbF ₆) ₂	CsOPiv (100 mol %)	DCE	< 5	–
3	[RhCp*Cl ₂] ₂	CsOAc (100 mol %)	MeOH	50	1.2:1
4	[RhCp*Cl ₂] ₂	–	MeOH	17	1.1:1
5	–	CsOAc (100 mol %)	MeOH	0	–
6 ^a	RhCp*(MeCN) ₃ (SbF ₆) ₂	CsOAc (50 mol %)	MeOH	20	1:1

Reaction Conditions: **334** (1 equiv), **70** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

^a Catalyst Loading is 5 mol %

The initial screen suggested that solvent played an important role in the outcome of the reaction. A screen of solvents revealed that non-polar and polar aprotic solvents do not afford product in high yields. Toluene, however, provided product with enhanced regioselectivity by comparison to reactions run in MeOH (Table 3.3, entry 1). The best yields were observed with 2,2,2-trifluoroethanol (TFE), although the regioselectivity under these conditions remained low (Table 3.3, entry 2). We speculated the regioselectivity could be increased without a substantial loss in yield if a mixed solvent system was used. Unfortunately, mixtures of toluene with TFE or AcOH resulted in low yield and low regioselectivity (Table 3.3, entries 7-8). We wondered if the absence of water in toluene was the source of enhanced regioselectivity. Unfortunately, when the reaction is run in TFE with molecular sieves, an increase in the regioselectivity is not observed (Table 3.3, entry 9). In fact, the presence of a substantial quantity of water has no impact on the regioselectivity of the reaction, with the pyridines **337** and **338** isolated in high yields (Table 3.3, entries 10-11).

Table 3.3 Solvent Optimization

			
Entry	Solvent	Yield (%)	Regioselectivity
1	Toluene	20	3:1
2	TFE	80	1.2:1
3	THF	< 5	-
4	DMF	< 5	-
5	HFIP	< 5	-
6	EtOAc	12	2:1
7	Toluene/AcOH (4:1)	< 5	-
8	Toluene/TFE (4:1)	10	1.4:1
9	TFE 3Å M.S	55	1.2:1
10	TFE/H ₂ O (1:4)	80	1.2:1
11	Pabst Blue Ribbon	82	1.2:1

Reaction Conditions: **334** (1 equiv), **70** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

We next examined a variety of bases and temperatures, in the hope of increasing the regioselectivity. Initially decreasing the reaction temperature to 60 °C resulted in decreased yields but had no impact on the regioselectivity (Table 3.4, entry 1). A screen of different bases revealed K₂CO₃ to be ideal, with enhanced yields but no impact on the regioselectivity (Table 3.4, entry 3). All other bases provided product but with decreased yield. Other metal catalysts gave inferior results (Table 3.4, entries 5-6). Indenyl based catalyst failed to provide superior results (Table 3.4, entry 7). Increasing the temperature to 80 °C afforded product in enhanced yield, with the best conditions being K₂CO₃ in TFE with [RhCp*Cl₂]₂ providing product in 90% yield as a 1.2:1 ratio of regioisomers (Table 3.4, entry 10).

Table 3.4 Precatalyst and Base Screen

Entry	Precatalyst	Base	Temperature (°C)	Yield (%)	Regioselectivity
1	[RhCp*Cl ₂] ₂	CsOAc	60	40	1.2:1
2	[RhCp*Cl ₂] ₂	CsOPiv	60	62	1.2:1
3	[RhCp*Cl ₂] ₂	K ₂ CO ₃	60	70	1.2:1
4	[RhCp*Cl ₂] ₂	NaOAc	60	35	1.2:1
5	[IrCp*Cl ₂] ₂	CsOAc	60	0	–
6 ^a	[Ru(cymene)Cl ₂] ₂	CsOAc	80	< 5	–
7 ^b	[Rh(Indene)Cl ₂] ₂	CsOAc	80	23	1.2:1
8	[RhCp*Cl ₂] ₂	Cs ₂ CO ₃	23	19	1.2:1
9	[RhCp*Cl ₂] ₂	Cs ₂ CO ₃	80	50	1.2:1
10	[RhCp*Cl ₂] ₂	K ₂ CO ₃	80	90	1.2:1

Reaction Conditions: **334** (1 equiv), **70** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

^a Catalyst Loading is 10 mol %

^b Indene = 1,2,3-trimethyl-indene

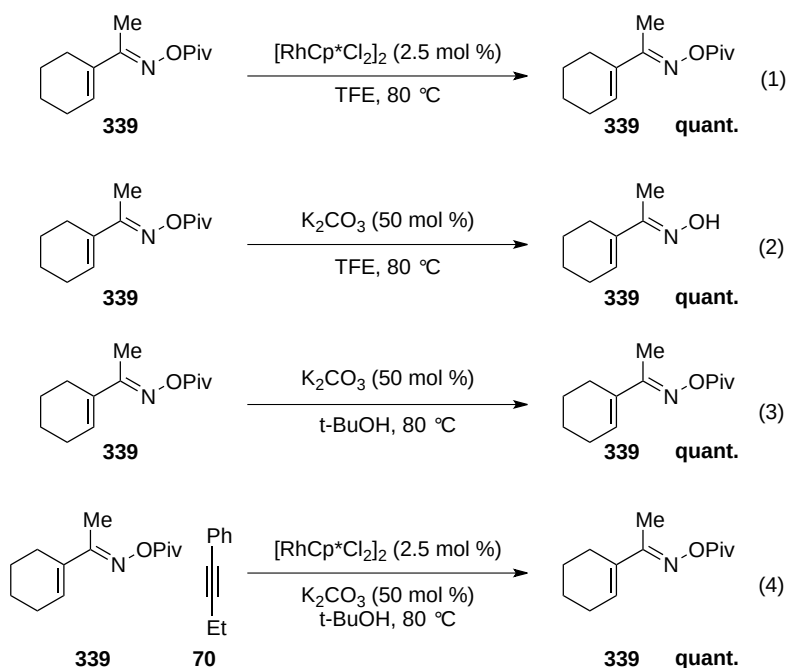
Still displeased with the levels of regioselectivity, we explored the impact of the ester substitution on the regioselectivity of alkyne insertion (Table 3.5). Using the optimized conditions, a variety of esters with different steric and electronic characteristics were explored. Bulky *tert*-butyl **339**, *iso*-butyl **340**, and *cyclo*-hexyl **341** esters provided product in 80-85% yield but had no impact on regioselectivity (Table 3.5, entries 1-3). Benzoyl esters also worked well but again afforded no increase in regioselectivity (Table 3.5, entry 4). Finally, exchange of the oxime for a Boc-hydrazine **343** failed to produce any product, with exclusive isolation of the starting materials (Table 3.5, entry 5). The inability of the ester substituent to have any impact on the reaction suggested that a feature of the reaction was not understood.

Table 3.5 Oxime-Ester Optimization

Entry	R =	Yield (%)	Regioselectivity
1	339	85	1.2:1
2	340	85	1.2:1
3	341	80	1.2:1
4	342	80	1.2:1
5	343	—	—

Reaction Conditions: Oxime (1 equiv), **70** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ^1H NMR.

A series of control experiments were employed to learn about the mechanistic nuances of the reaction (Scheme 3.10). We suspected that hydrolysis of the ester might occur during the reaction. When the pivaloyl protected oxime was stirred in TFE with catalytic $[\text{RhCp}^*\text{Cl}_2]_2$ in the absence of alkyne, the starting material is isolated in quantitative yield (Scheme 3.10, (1)). When the same oxime is stirred with K_2CO_3 in the absence to $[\text{RhCp}^*\text{Cl}_2]_2$ and alkyne, however, the unprotected oxime is observed after 5 minutes (Scheme 3.10, (2)). We suspected that trifluoroethanolysis of the oxime ester occurs after deprotonation of the solvent. To test this hypothesis, the solvent was exchanged for *t*-BuOH. Presumably *t*-BuOH serves as a poor nucleophile and the alcoholysis of the ester will be slow. We were pleased to find when the pivaloyl oxime was stirred with K_2CO_3 in *t*-BuOH at 80 °C, the starting material was isolated with very little decomposition to the unprotected oxime (Scheme 3.10, (3)). Under the same conditions with the rhodium catalyst and alkyne, no product was isolated. These experiments led us to speculate that the unprotected oxime is essential for the reaction to proceed (Scheme 3.10, (3)). A ^1H NMR study of the reaction revealed in our original system the oxime is completely deprotected in under 5 minutes and product formation occurred after this event.



Scheme 3.10 Control Experiments of Oxime-Ester Decomposition

With this insight, we re-examined the reaction using the simple unprotected oxime. Under the condition previously attempted the desired product was isolated in 90% yield with 1:1.2 ratio of regioisomers (Table 3.6, entry 1). Contrary to our previous attempts, the temperature can be decreased to 45 °C with minimal loss in yield and similar levels of regioselectivity (Table 3.6, entry 2). Use of CsOAc as a base results in decreased yield and addition of water to the reaction does not have a detrimental effect (Table 3.6, entry 3). Given the current levels of regioselectivity, we screened a variety of cyclopentadienyl ligands to determine their impact on the regioselectivity. Electron deficient ligands failed to increase the regioselectivity, and had a detrimental effect on yield (Table 3.6, entry 4). Use of the sterically bulky, Cp^t complex gave enhanced regioselectivity (4:1) (Table 3.6, entry 5). Unfortunately, moving to an even more bulky ligand, di-*tert*-hexylcyclopentadienyl (Cp^Ψ), did not provide further enhancement in the regioselectivity (Table 3.6, entry 7). In a final attempt to optimize for regioselectivity, a 1,2-diphenyl-3,4,5-trimethyl cyclopentadienyl complex was prepared. Presumably, the aromatic groups would sit perpendicular to Cp ligand and communicate the steric bulk to the metal center. Unfortunately, this ligand

failed to increase the regioselectivity (Table 3.6, entry 8). Given the increase in selectivity with Cp^t, we initiated an exploration of the substrate scope.

Table 3.6 Oxime Precatalyst Optimization

Reaction scheme: Oxime **336** (1-methyl-2-(cyclohex-1-en-1-yl)ethan-1-one oxime) reacts with alkyne **50** (1-phenyl-2-methyl-1,2,3,4,5-pentamethyl-1,3-diene) in the presence of a catalyst (2.5 mol %), K₂CO₃ (200 mol %), in TFE at a given temperature to produce two regioisomeric products, **344** and **345**, which are 1,2,3,4,5-pentamethyl-1,3-diene derivatives with a phenyl group and a methyl group at different positions on the diene system.

Entry	Precatalyst	Temperature (°C)	Yield (%)	Regioselectivity
1	[RhCp [*] Cl ₂] ₂	80	90	2:1
2	[RhCp [*] Cl ₂] ₂	45	87	2:1
3 ^a	[RhCp [*] Cl ₂] ₂	45	65	2:1
4	[RhCp ^t Cl ₂] ₂	45	20	1:1
5	[RhCp ^t Cl ₂] ₂	45	87	1:4
6 ^b	[RhCp ^t Cl ₂] ₂	45	83	1:2
7	[RhCp ^w Cl ₂] ₂	45	20	1:2
8	[RhCp ^o Cl ₂] ₂	45	80	1:2

Reaction Conditions: **336** (1 equiv), **50** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

^a CsOAc used as a base

^b Reaction run in MeOH

3.2.2 Substrate Scope

We tested a variety of oximes with [RhCp^{*}Cl₂]₂ and [RhCp^tCl₂]₂ to determine the impact each ligand has on the regioselectivity of the reaction. In all cases similar yields were obtained with both catalyst. When alkyl substitution was located at the β-position of the α,β-unsaturated oxime, Cp^{*} was essentially unselective (Table 3.7, entries 1 and 3). Use of Cp^t, however, increased the regioselectivity. The reaction favors placing the larger group of the alkyne away from the nitrogen of the pyridine. When the β-position lacks substitution Cp^{*} is mildly selective, and Cp^t can only marginally increase the regioselectivity (Table 3.7, entry 2). Finally, placing electron-withdrawing groups at the β-position results in greater regioselectivity with the smaller group adjacent to the electron-withdrawing group (Table 3.7, entries 4-5).

Table 3.7 Alkyl-Oxime Scope

Entry	Oxime	Products		Yield (%)	
				Cp*	Cp ^t
1	 346	 347	 348	80% (1:1) (347:348)	83% (1:4) (347:348)
2	 349	 350	 351	87% (1:2) (350:351)	85% (1:2.6) (350:351)
3	 352	 353	 354	92% (1.2:1) (353:354)	93% (1:3.4) (353:354)
4	 355 R = C(O)NMe ₂	 356	 357	72% (6.6:1) (356:357)	74% (1:1) (356:357)
5	 358	 359	 360	92% (10:1) (359:360)	68% (1:1) (359:360)

Reaction Conditions: oxime (1 equiv), **50** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography.

Regioselectivity determined by ¹H NMR.

Cp* = [RhCp*Cl₂]₂

Cp^t = [RhCp^tCl₂]₂

When an aryl group is located at the β-position, the ligand was effective toward reversing the regioselectivity (Table 3.8). When Cp* is used, selectivity favored the aromatic group being adjacent to nitrogen (Table 3.8, entries 1,2, and 4). When Cp^t is used, however, the selectivity is reversed favoring

the smallest group adjacent to nitrogen (Table 3.8, entries 2 and 4). Additionally, we were pleased to find aldoximes tolerated under the reaction conditions using symmetrical alkynes at slightly elevated temperatures (Table 3.8, entry 3).

Table 3.8 Aryl Oxime Scope

Entry	Oxime	Products	Yield (%) Cp*	Yield (%) Cp ^t
1	 361	 362 363	75% (4:1) (362:363)	70% (1:1) (362:363)
2	 364	 365 366	80% (3.5:1) (365:366)	83% (1:3.4) (365:366)
3 ^a	 367	 368	45%	
4	 369	 370 371	92% (3.1:1) (370:371)	93% (1:3.3) (370:371)

Reaction Conditions: oxime (1 equiv), **27** or **50** (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

Cp* = [RhCp*Cl₂]₂

Cp^t = [RhCp^tCl₂]₂

^a Reaction run at 80 °C

A variety of alkynes were screened to determine the effect the substitution has the regioselectivity (Table 3.9). Protected propargyl alkynes provide product in high yield but modest regioselectivity (Table 3.9, entry 1). The selectivity is enhanced when cyclopropyl substitution is located on phenyl acetylene (Table

3.9, entry 2). Highly electron-withdrawing groups gave even higher levels of selectivity with good yield (Table 3.9, entry 3). When an electron-withdrawing group is placed off the aromatic ring, there is no discernible effect on regioselectivity (Table 3.9, entry 4). Alkynes bearing coordinating groups, such as pyridine, fare well in the reaction, although in lower levels of regioselectivity (Table 3.9, entry 5). Symmetrical di-aryl and di-alkyl alkynes are also tolerated in good yield (Table 3.9, entries 6 and 7).

Table 3.9 Alkyne Scope

Entry	Alkyne	Products	Yield (%)
1	 138	 372 373	80 (2.5:1)
2	 240	 374 375	81 (4.4:1)
3	 239	 376 377	89 (5:1)
4	 378	 379 380	85 (3.5:1)
5	 381	 382 383	66 (2.5:1)
6	 27	 384	89
7	 137	 385	65

Reaction Conditions: **369** (1 equiv), alkyne (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

We were pleased to find that unsymmetrical di-alkyl alkynes fare very well in this reaction, providing product with high levels of regioselectivity and excellent yields (Table 3.10). Almost all cases the

regioselectivity is greater than 10:1 with high yields. The most sterically demanding group is placed away from the nitrogen of the pyridine. The regioselectivity was confirmed by NOESY 2D-NMR.

Table 3.10 Di-alkyl Alkyne Scope

Entry	Alkyne	Products	Yield (%)
1	 141	 386 387	95 (10:1)
2	 388	 389 390	71 (9:1)
3	 391	 392 393	95 (11:1)
4	 394	 395 396	89 (12:1)
5	 397	 398 399	0

Reaction Conditions: **369** (1 equiv), alkyne (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

We next explored the ligand effect in regards to isoquinolone formation (Table 3.11). We elected to explore these substrates using unsymmetrical aryl-alkyl alkynes because the regioselectivity appears to be most impacted by the steric bulk of the Cp ligand. The oxime derived from acetophenone coupled well with 1-phenyl-1-butyne in excellent yield and excellent levels of regioselectivity (Table 3.11, entry 1). This trend held for a variety of aryl oximes where the C–H activation occurs on a phenyl ring, and in all cases the yield and regioselectivity remained high (Table 3.11, entries 2 and 3). Interestingly, pyridyl

oximes are well tolerated in the reaction, providing product in high yield and high regioselectivity (Table 3.11, entries 4 and 5). Additionally, the oxime derived from nicotinic acid **403** undergoes C–H activation *para*- to the nitrogen (Table 3.11, entry 4). We rationalize that a metal is potentially coordinating the pyridine increasing its steric demand, causing activation to occur at the less kinetically acidic position. Other heteroaromatic substrates provide product in high yield, but with variable levels of regioselectivity (Table 3.11, entries 6-9). Generally Cp* favors the aryl group next to the nitrogen of pyridine, while Cp^t favors the opposite regioisomer.

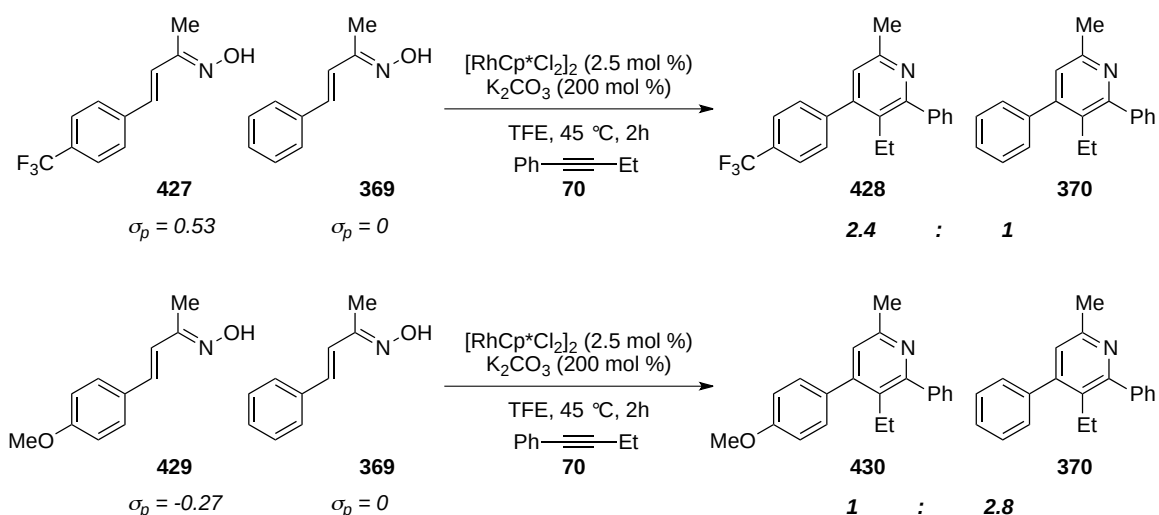
Table 3.11 Isoquinoline Scope

400-408	50 and 70	409-426		
Entry	Products	Yield (%)		
		Cp*	Cp ^t	
1	 409	 410	94 % (10:1)	n/d
2	 411	 412	86 % (15:1)	n/d
3	 413	 414	87 % (10:1)	n/d
4	 415	 416	70 % (10:1)	n/d
5	 417	 418	72 % (10:1)	n/d
6	 419	 420	92 % (2.1:1)	90 % (1:9.2)
7	 421	 422	93% (10:1)	95 % (1:2.5)
8	 423	 424	88 % (3.7:1)	90% (3.4:1)
9	 425	 426	98 % (4:1)	96% (1:2.1)

Reaction Conditions: oxime (1 equiv), alkyne (1.1 equiv), 0.1 M, 16 h. Yields determined after column chromatography. Regioselectivity determined by ¹H NMR.

3.2.3 Mechanistic Experiments

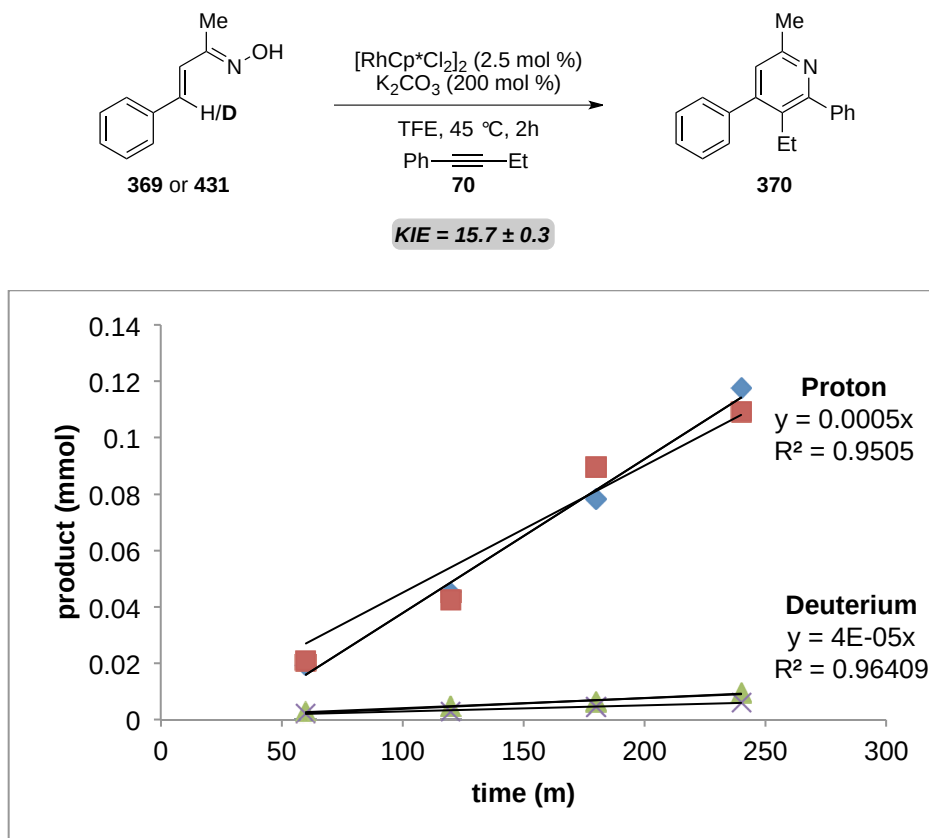
Mechanistic studies were employed to glean insight into the nuances of the reaction. A series of competition experiments were used to determine the electronic preference of the rhodium catalyst. When electronically deficient alkenyl oxime **427** was run in competition with the electronically neutral oxime **369**, the electronic deficient pyridine product **428** was favored at a 2.4:1 ratio (Scheme 3.11). When the same reaction was run with an electron rich oxime **429** in competition with an electron neutral oxime **369**, the electron neutral pyridine **370** was formed preferentially at a 2.8:1 ratio. These experiments suggest the anomalies observed in the pyridone synthesis are not present in this reaction. Furthermore, these experiments support that preferential reactivity of the most electron deficient substrate is consistent with a CMD mechanism.



Scheme 3.11 Oxime Competition Experiments

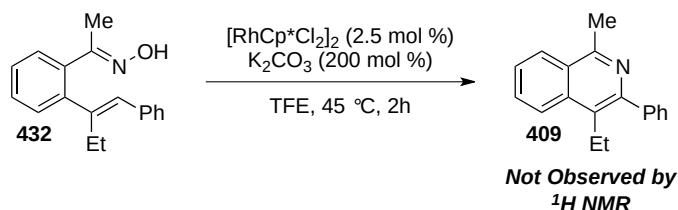
The electronic preference of the reaction could be the artifact of two possible mechanisms, a rhodium catalyzed [4+2] hetero Diels-Alder type reaction, or a C–H activation mediated mechanism. If C–H activation is turnover limiting, a primary kinetic isotope effect should be observed. If the 4+2 event is turnover limiting, however, a secondary kinetic isotope effect would be expected. After performing initial rate kinetic analysis of the proteo and deuterio substrate, a strong primary kinetic isotope value of 15.7 ± 0.3 is observed. This value, in collaboration with the necessity for a carboxylate base, suggests the

reaction proceeds through rate limiting CMD mechanism (Scheme 3.12). This exceptionally high KIE values is consistent with the high value observed by Fagnou in the synthesis of isoquinolones. The large value suggests a high degree of linearity in the deprotonation event. This artifact might be a point of commonality in internal redox Rh(III) pathways.



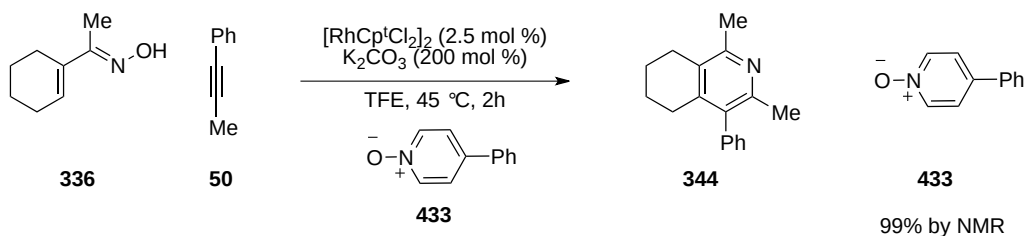
Scheme 3.12 Oxime Initial Rate KIE Study

Presumably after the C–H activation event, protonation of the resultant metallacycle would form an $\alpha,\beta,\gamma,\delta$ unsaturated oxime, which could undergo a thermal 6π -electrocyclization to generate a dihydropyridine, which upon elimination of H_2O would generate the desired product. To test the possibility of this mechanism, the olefinated product was independently generated on the aromatic substrate. When submitted to the reaction conditions, the unreacted starting material was isolated, suggesting this intermediate is not present in the catalytic cycle (Scheme 3.13).



Scheme 3.13 Test for 6 π -Electrocyclization

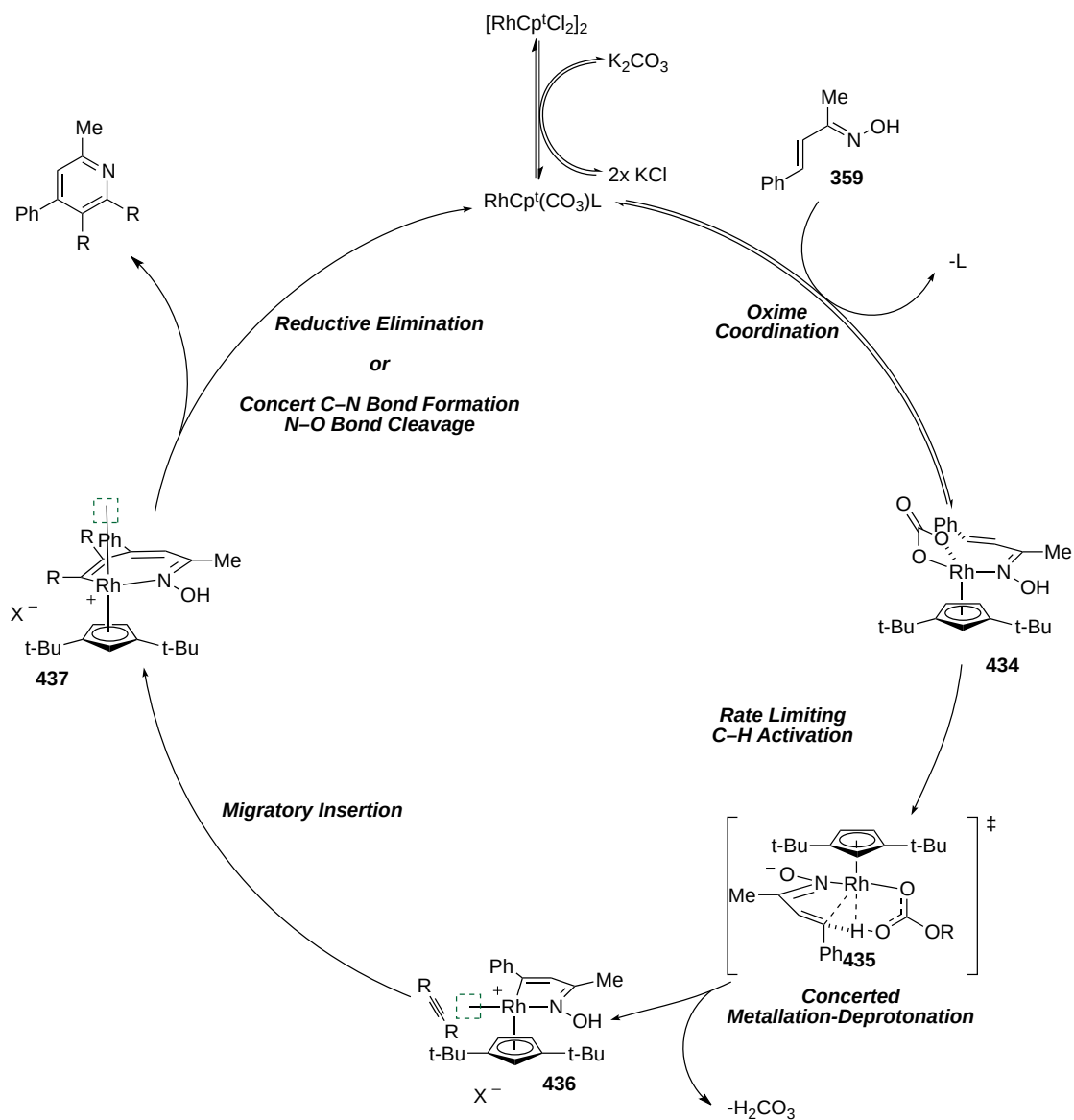
In the absence of the electrocyclization mechanism, the most plausible pathway involves reductive elimination to generate a Rh(I) complex and pyridine *N*-oxide **433**, which can oxidize the Rh(I) complex to generate the active catalyst and the desired pyridine. Presumably, this could occur without substrate specificity. We imagined this possibility could be tested if an exogenous pyridine *N*-oxide were added to the reaction. If the exogenous pyridine *N*-oxide is reduced, we can assume that the oxidation is indiscriminate. When the reaction was run, however, none of the exogenous pyridine *N*-oxide was reduced (Scheme 3.14). This suggests that the oxidation occurs from the same substrate as reductive elimination.



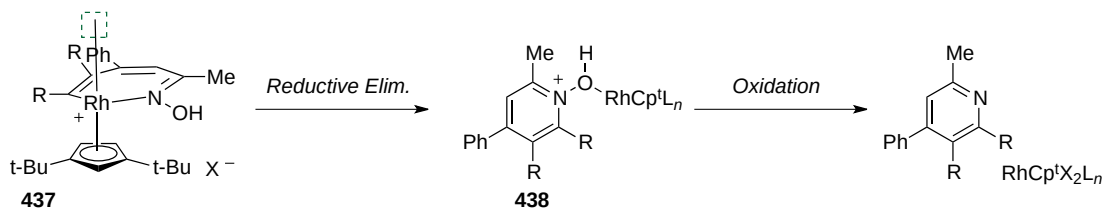
Scheme 3.14 Probe of Exogenous Oxidant

Based on these mechanistic studies, we proposed the reaction proceeds through the following mechanism (Scheme 3.15). The rhodium dimer decomposes to a rhodium monomer with chlorides replaced with carbonate ligands. This species can coordinate one equivalent of oxime to generate intermediate **434**. Calculations by Fagnou suggest that neutral complexes have a lower barrier to undergo CMD mediated C–H activation.¹² Presumably this is the reason why free oximes perform better by comparison to *O*-acetyl oximes and oxime ethers. Upon deprotonation of the oxime, carbonate facilitated C–H activation can occur to generate a 5-membered rhodacycle, which upon coordination and migratory insertion of the alkyne generates a 7-membered rhodacycle. From our control experiments we can assume there is no

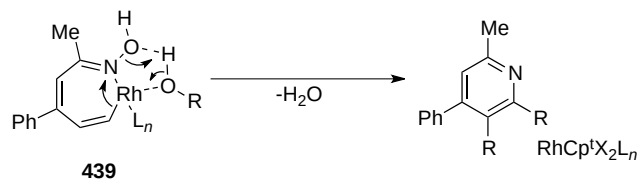
substrate crossover during oxidation after reductive elimination. We imagine that reductive elimination could occur to generate a Rh(I) complex that is bound to the oxygen of the resultant pyridine *N*-oxide, which can undergo rapid oxidation to generate the desired pyridine and Rh(III) catalyst. Alternatively, the product-forming event could be a concerted C–N bond formation N–O bond cleavage rather than reductive elimination. In this case there would be no net change in oxidation state of the metal and would easily account for the lack of substrate crossover.



Reductive Elimination



Concerted C-N Bond Formation/N-O Bond Cleavage

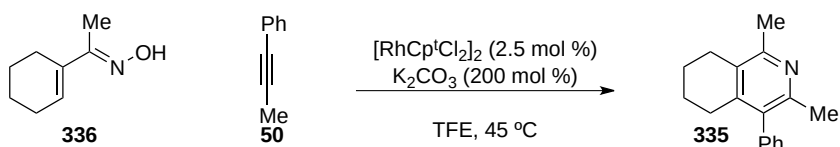


Scheme 3.15 Proposed Mechanism

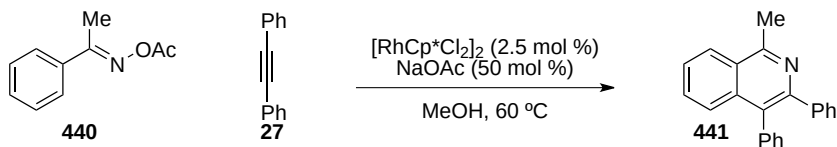
3.3 Concurrent Work

During review and resubmission of our work²³ the groups of Chiba,²⁴ Fagnou,¹² and Li²⁵ published the synthesis of isoquinolones for aryl oximes and alkynes. Chiba used an OAc oxime and found a variety of alkynes provided isoquinolones in high yield and regioselectivity. Fagnou proposed that the oxime become deprotected under the reaction conditions and the free oxime is the active starting material. Li used the insight by Fagnou to synthesize isoquinolones from free oximes. In none of these cases was a sterically bulky cyclopentadienyl ligand used to control regioselectivity. Chiba published the synthesis of pyridines from oximes and alkynes after our report.²⁶

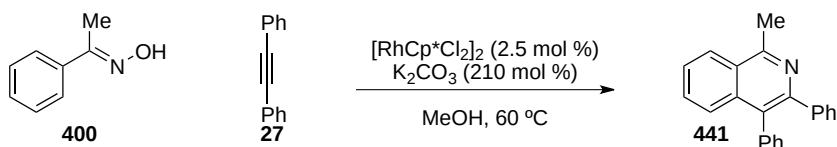
• **Rovis** (Submitted October 11, 2010; Published September 21, 2011)



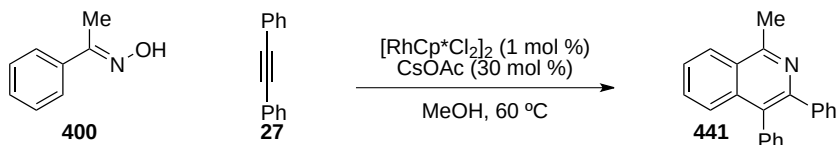
• **Chiba** (Submitted October 16, 2010; Published November 17, 2010)



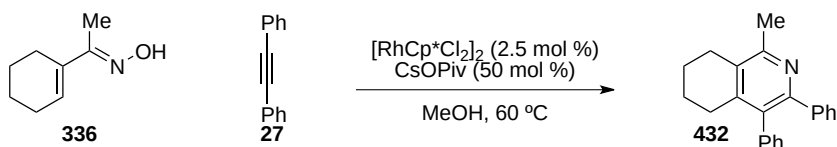
• **Fagnou** (Submitted February 5, 2011; Published March 31, 2011)



• **Li** (Submitted November 24, 2010; Published March 10, 2011)



• **Chiba** (Submitted September 1, 2011; Published October 25, 2011)



Scheme 3.16 Concurrent Work

3.4 Conclusion

In conclusion, we found that the N–O bond of oximes can act as an internal oxidant in the synthesis of pyridines and isoquinolines. Optimization studies suggest that the reaction proceeds when the oxime is unprotected. Using the standard Cp* ligand provides product with very low regioselectivity in many cases. Use of our previously developed *di*-tert-butyl cyclopentadienyl ligand enhanced the regioselectivity in the case of pyridines. In isoquinolines the regioselectivity is diminished and occasionally reversed. Mechanistic studies suggest the reaction proceeds via C–H activation, migratory insertion, and a complex reductive elimination where either the resulting pyridine N-oxide oxidizes the resultant Rh(I) species without substrate crossover, or via a concerted C–N bond formation N–O bond cleavage with no discrete Rh(I) intermediate formed.

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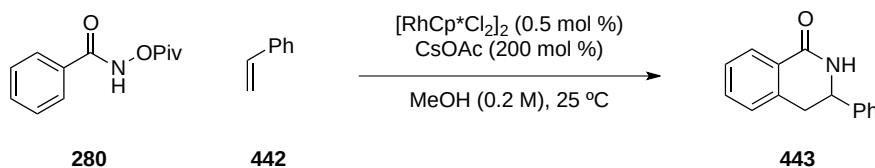
Chapter 4

Artificial Metalloenzymes as a Catalyst Scaffold for Rhodium(III)-Catalyzed C–H Activation

4.1 Introduction

Achieving enantiomeric induction in Rh(III)-catalyzed C–H activation reactions is a persistent problem. Recent reports by Fagnou¹ and Glorius² demonstrate that *O*-pivaloyl benzhydroxamic acids can be coupled to alkenes providing dihydroisoquinolones in high yield under ambient conditions (Scheme 4.1). Given our interest in ligand controlled Rh(III)-catalyzed C–H activation reactions, we endeavored to render this transformation asymmetric. Our previous mechanistic studies suggested that exogenous chiral phosphine and carbene ligands would be incompatible with this reaction because of the need for all three available coordination sites. An alternative approach would be to utilize a chiral cyclopentadienyl ligand.³

•Fagnou and Glorius (2011)



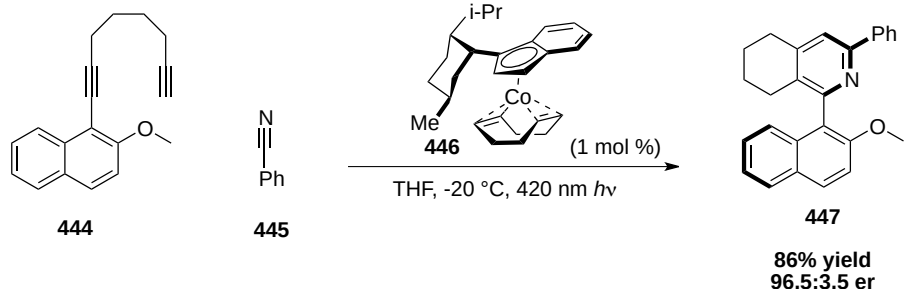
Scheme 4.1 Fagnou and Glorius Synthesis of Dihydroisoquinolones

4.1.1 Chiral Cyclopentadienyl Ligands

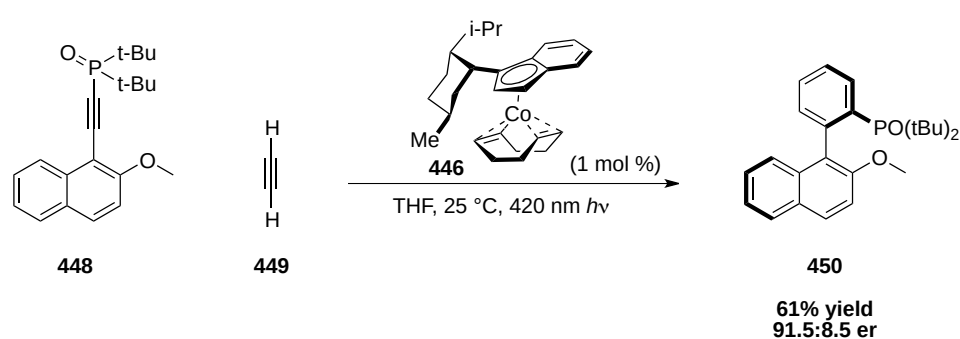
A survey of the literature revealed the vast majority of reported chiral cyclopentadienyl complexes bear coordinating groups to obtain good levels of enantioselectivity.⁴⁻⁹ Unfortunately, our need for three coordination sites prohibits the use of these ligands. An alternative approach uses a chiral cyclopentadienyl ligand lacking a coordinating moiety. A remarkably small number of single point chiral cyclopentadienyl ligated late transition metal complexes capable of inducing high levels of enantioselectivity have been reported. The most effective system is the cobalt catalyzed [2+2+2] cycloaddition of alkynes and nitriles to generate atropisomeric benzene and pyridine products (Scheme 4.2).¹⁰⁻¹² The authors found that menthyl containing indenyl ligands were most effective toward inducing asymmetry. The reaction provided 2-naphthyl pyridine and 2-naphthyl benzene products in high yield and

greater than 91.5:8.5 *er*. Unfortunately, other examples of single point chiral cyclopentadienyl ligands on late transition metals failed to provide acceptable levels of enantioselectivity for a variety of reactions.³

• **Heller and Gutnov**



• **Heller and Gutnov**



Scheme 4.2 Previous Effective Chiral Cyclopentadienyl Ligands

4.1.2 Artificial Metalloenzymes

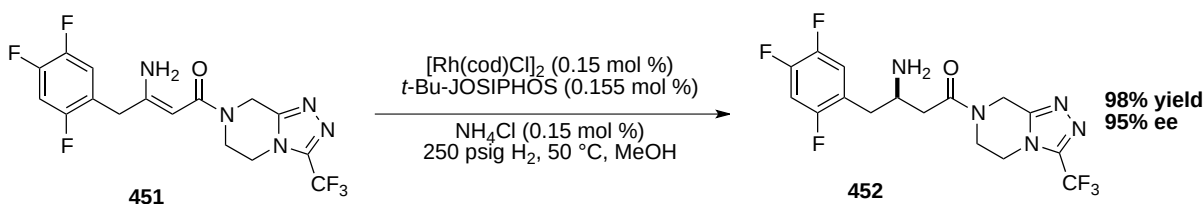
Due to the dearth of precedent for chiral cyclopentadienyl ligands to render transformations asymmetric, we imagined an alternative system where the metal catalyst is docking to a chiral supramolecular scaffold to induce asymmetry. Bio-catalysis has been resurgent largely due to the attractiveness of the process.¹³⁻¹⁶

These catalysts can be expressed in large quantities from *E. coli* in a single step and the catalysts are biodegradable, satisfying the two fundamental tenets of an environmentally friendly process. More importantly, these proteins are extremely effective toward catalyzing specific transformations with high catalyst turnover and excellent enantioselectivity. In spite of these benefits, broader adoption of biocatalysis has been slow because of high substrate specificity and the relatively small number of transformations they can catalyze.

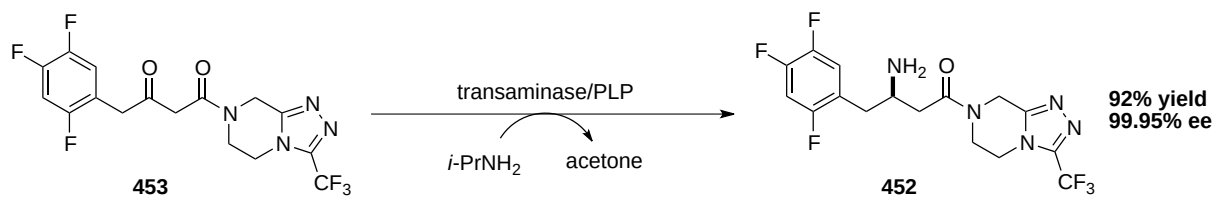
The issue of enhanced substrate scope has been largely mitigated thanks to the power of directed evolution.¹⁷⁻¹⁹ Pioneering work by Arnold and coworkers demonstrated that issues of enzyme stability, solvent tolerance, and substrate scope could be resolved using this method.²⁰⁻²² In directed evolution, mutations are introduced into an enzyme and their activity is tested. Mutants that respond favorably to the mutation are carried into another round of directed evolution. This process continues until a mutant is achieved with the appropriate activity.

This concept is utilized in the industrial synthesis of Sitagliptin (Januvia[®]) (Scheme 4.3).²³ The first generation synthesis involved an enantioselective rhodium catalyzed hydrogenation of enamine **451** to provide the penultimate intermediate **452**.²⁴ While this process won the 2006 President Green Chemistry Challenge Award for its low catalyst loading, adoption of this protocol for manufacturing scale required additional purification steps at the cost of overall yield. The process group at Merck teamed with the directed evolution group at Codexis to evolve a superior solution, in the form of a transaminase enzyme. The starting enzyme was a (*R*)-selective transaminase ATA-117 capable of catalyzing the transamination of small ketones with relative ease. Unfortunately, this mutant had poor activity with the desired substrate. After 11 rounds of directed evolution, a mutant was found that tolerated large quantities of organic solvents, stable at 45 °C, functioned at high concentrations, and provided the product in 92% yield with 99.95% *ee* with no metal contamination (Scheme 4.3).

• 2nd Generation Approach



• 3rd Generation Approach

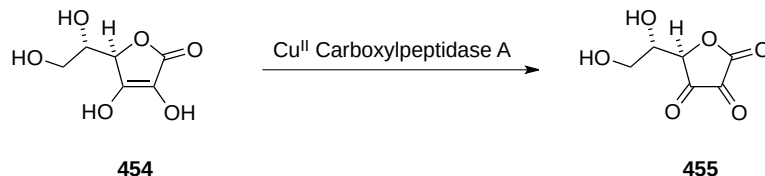


Scheme 4.3 Engineered Transaminase

While this approach can solve problems of substrate tolerance and enzyme stability, it has not been effective in broadening the types of transformations catalyzed by enzymes. In contrast, transition metal catalysis has been extensively explored for a bevy of useful transformations. A burgeoning direction of research is combining the power and specificity of bio-catalysis with the litany of reactions catalyzed by transition metals.²⁵⁻²⁷ The over-arching goal is to create a catalyst with the benefits of both transition metal and bio-catalysis. To achieve these synergistic properties, a reliable method for linking the metal to the enzyme is required. There are three basic strategies to anchor the metal catalyst to the enzyme; dative, covalent, and supramolecular anchoring.

Dative anchoring is where the metal is ligated by the heteroatoms of the polypeptide. Pioneering work by Kaiser found that when the natural zinc cofactor in carboxypeptidase A is replaced with copper the enzymes natural activity is suppressed in favor of ascorbate oxidation (Scheme 4.4).²⁸ Since this report, the dative anchoring has been used to develop effective catalyst for Diels-Alder reactions,²⁹ hydrogenations,³⁰ hydroformylations,³¹⁻³³ and oxidations.³⁴⁻³⁶

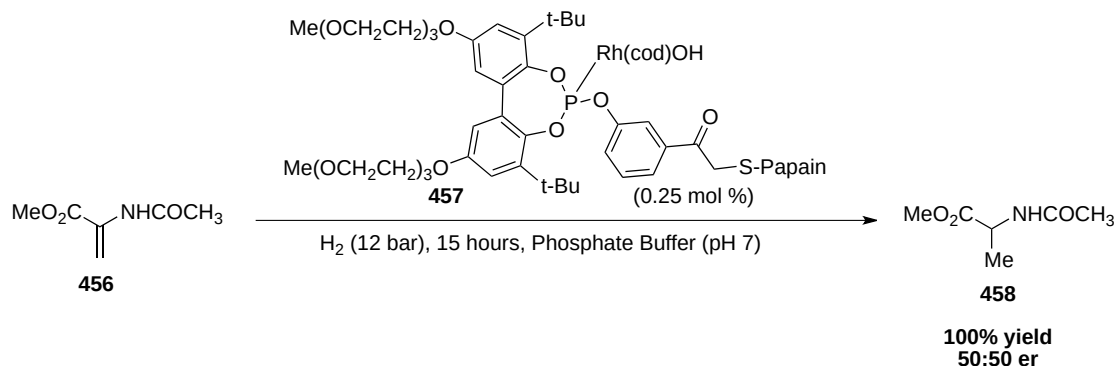
• **Kaiser (1976)**



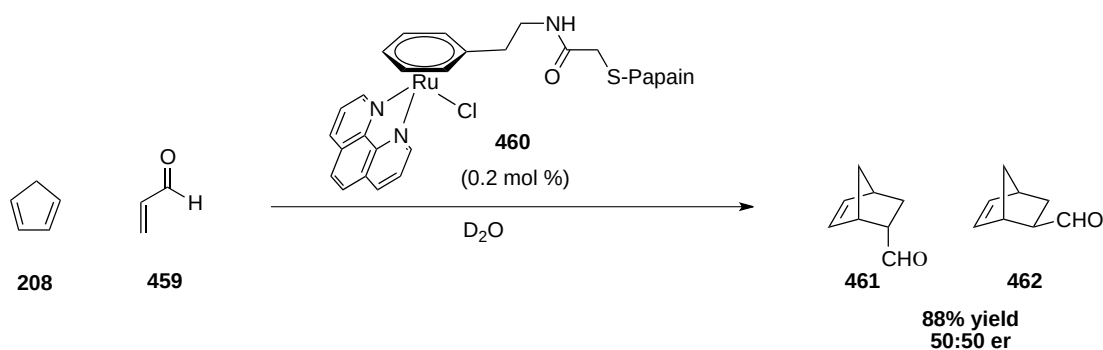
Scheme 4.4 Artificial Metalloenzyme Catalyzed Oxidation of Ascorbate

An alternative approach is to covalently link the metal complex to the enzyme.²⁵ This can be achieved through reacting a nucleophilic side chain (usually cysteine) with the electrophilic component of a metal ligand. This tactic is based on the early work of Kaiser where papain, a cysteine protease, is covalently linked to bromoacetyl-functionalized flavin generating an enzyme capable of oxidizing dihydronicotinamide.³⁷ This report has inspired the development of papain metalloenzymes for hydrogenation and Diels-Alder reactions (Scheme 4.5).^{38,39} While a degree of rate enhancement is observed in both cases, the complexes lack the ability to induce asymmetry. De Vries argues the flexibility inherent to a single covalent linker diminishes the ability of the protein to induce asymmetry. Indeed, Lu and workers found that two covalent linkages in a myoglobin based oxidation catalyst gave superior enantioselectivity by comparison to a single covalent bond.^{40,41} The assumption is that two covalent bonds localize the metal in a single location within the enzyme providing a single geometry in the oxidation transition state.

• *de Vries (2005)*



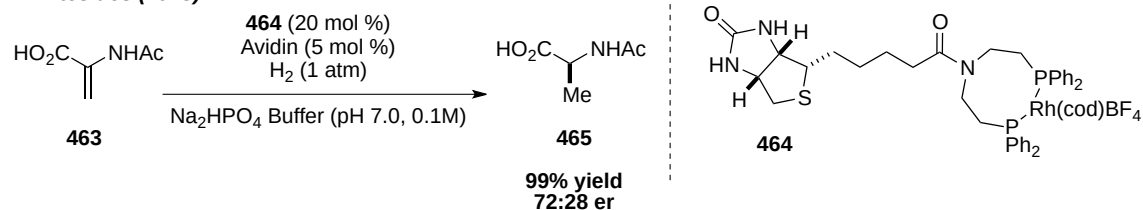
• *Salmain (2010)*



Scheme 4.5 Papain Based Artificial Metalloenzymes

Supramolecular anchoring is achieved through binding the metal to a co-factor for which the protein has a high affinity. This approach was pioneered by Whitesides in 1978 using the unusually strong interaction between biotin and avidin to dock a rhodium catalyst for the asymmetric hydrogenation of protected α -acetamidoacrylic acid **463** (Scheme 4.6).⁴² Since this initial report, the use of other guests as ligands for enzyme anchoring have been used, including porphyrins and antibodies.²⁵

• *Whitesides (1978)*



Scheme 4.6 Avidin Based Metalloenzyme for Hydrogenation

4.1.3 Biotin-(strept)avidin Artificial Metalloenzyme Technology

We selected the supramolecular docking system as the starting point for our development of an artificial metalloenzyme. The biotin-(strept)avidin system was selected because streptavidin has an affinity for biotin at 10^{14} L/mol (Figure 4.1). This level of affinity makes the coordination of the metal bound biotin essentially irreversible. (Strept)avidin is a 16.1 kDa protein expressed by *Streptomyces Avidinii*. The secondary structure of the protein is largely anti-parallel β -sheets which coil forming the β -barrel found in the tertiary structure.⁴³ (Strept)avidin is typically observed as a tetramer and used as such in most biotechnology applications. Biotin binds inside the β -barrel with the carboxylate residue sitting at the surface. The tetramer is capable of binding four equivalents of biotin, with two of the biotin moieties sitting within 30 Å of one another. This enzyme has been particularly popular in the field of biotechnology because of its high affinity for substrates bearing a biotin tag.⁴⁴ Furthermore, the enzyme has exceptional stability to higher temperatures (T_m = 112.2 °C fully ligated in phosphate buffer or T_m = 75.5 °C unligated in phosphate buffer) and organic solvents.⁴⁵

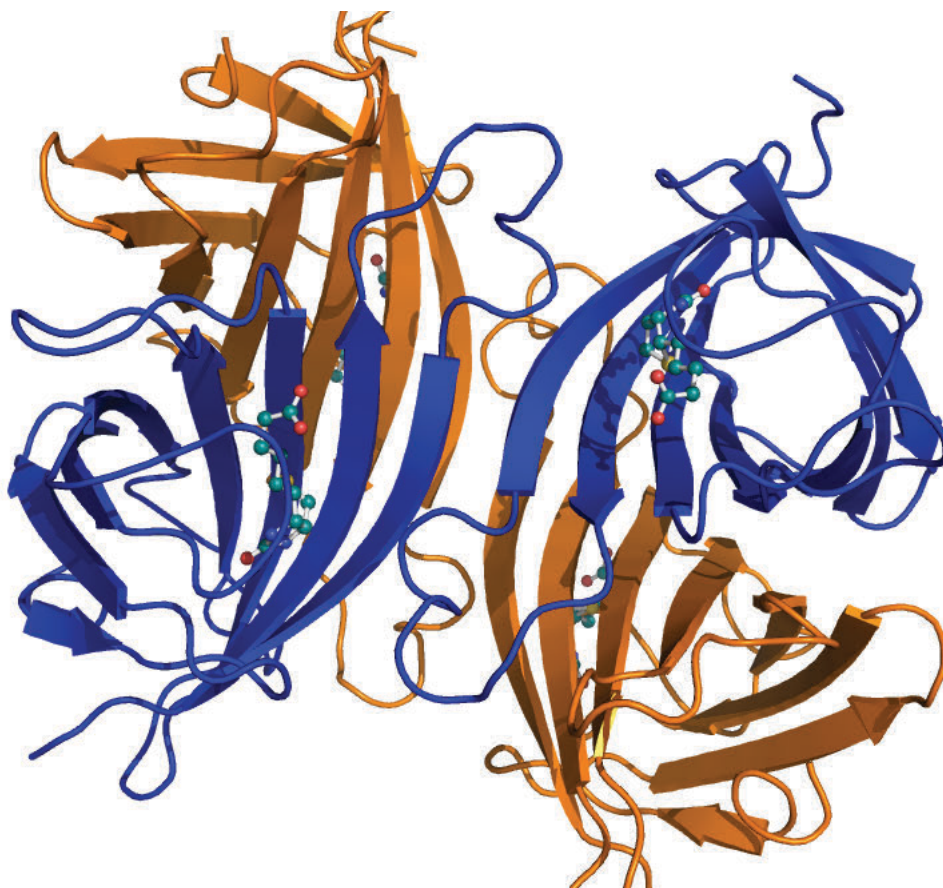
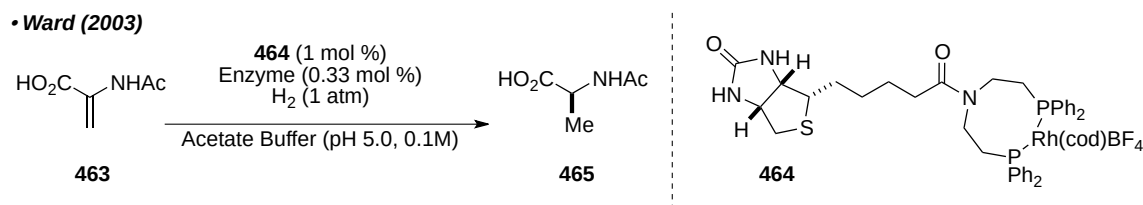


Figure 4.1 Streptavidin Tetramer Loaded with Biotin

After the initial report by Whitesides in 1978, the biotin-strept(avidin) technology for use in artificial metalloenzymes was overlooked until 2003 when Ward reexamined the reduction of α -acetamidoacrylic acid (Table 4.1).⁴⁶ Ward found that replacing avidin with streptavidin resulted in a substantial increase in the enantiomeric ratio (*er*) from 68.5:31.5 to 96:4 using **464**, the same ligand utilized by Whitesides and coworkers. The *er* can be further enhanced to 98:2 by replacing serine at position 112 with glycine.

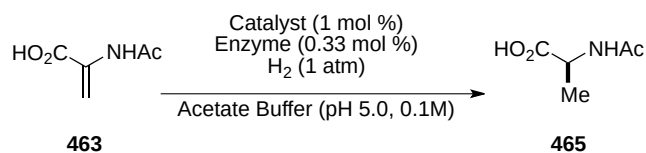
Table 4.1 Streptavidin Based Metalloenzyme for Hydrogenation

Entry	Enzyme	Yield (%)	e.r
1	Avidin	90	68.5:31.5
2	(Strept)avidin	99	96:4
3	SAV-S112G	99	98:2

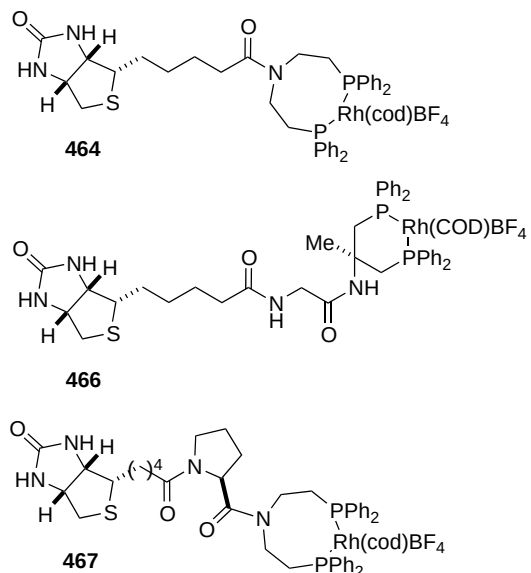
Ward has used two different approaches to increase the yield and enantioselectivity of a given reaction: genetic modification and chemo-optimization.⁴⁷ Chemo-optimization involves modification of the chemical component linking biotin to the metal catalyst. Genetic optimization involves introducing different amino acid residues into specific positions in the protein to modify the chemical space in the active site. Ward found that chemo-optimization generally has a greater impact on the enantioselectivity of the reaction than genetic modification. Using this systematic approach, Ward explored the impact biotinylated linkers and (Strept)avidin mutants have on the selectivity of the reaction. When a longer linker **466** is used with avidin the opposite major enantiomer can be accessed, providing product in 90:10 *er* (Table 4.2, entry 2).⁴⁸ Alternatively, the opposite enantiomer of the product can be accessed in 93:7 *er* using a chiral proline linker **467** and *wild-type* streptavidin (Table 4.2, entry 3).⁴⁹ The enzyme can also play a role in rate enhancement. Kinetic evaluation of the catalyst bound to streptavidin (**464** $\subset$ SAV) by comparison to the unbound catalyst **464** revealed **464** $\subset$ SAV to be 2.95x more reactive than free **464**.⁵⁰

Table 4.2 Impact of Mutations and Biotin-Linker on the Hydrogenation of Acrylic Acids

• Ward (2005)

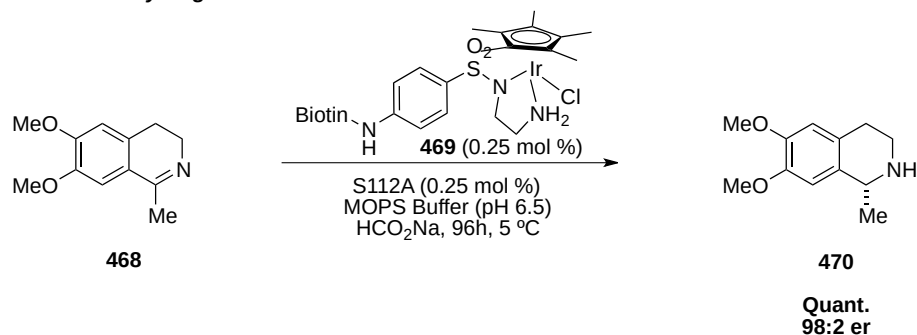


Entry	Catalyst	Enzyme	Yield (%)	e.r
1	464	S112G	84	98:2
2	466	Avidin	80	10:90
3	467	SAV	100	7:93

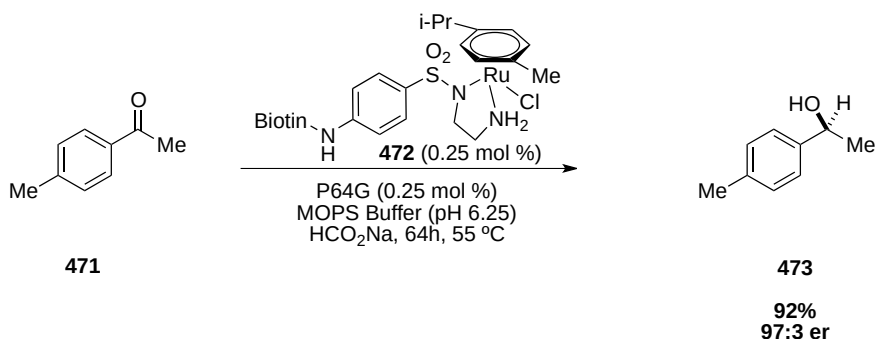


Since these initial reports, the methodology has been expanded to transfer hydrogenation of imines,^{51,52} alcohol oxidation,⁵³ ketone reduction,^{54,55} Tsuji-Trost allylation,⁵⁶ sulfide oxidation,⁵⁷ and olefin metathesis (Scheme 4.7).^{58,59} While the linkers and metal catalyst change in each case, the fundamental approach to optimize for enantioselectivity and yield remain the same.

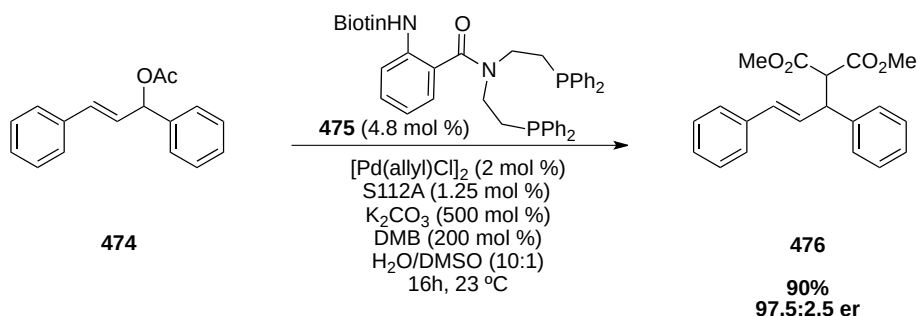
• *Imine Transfer Hydrogenation*



• *Ketone Reduction*



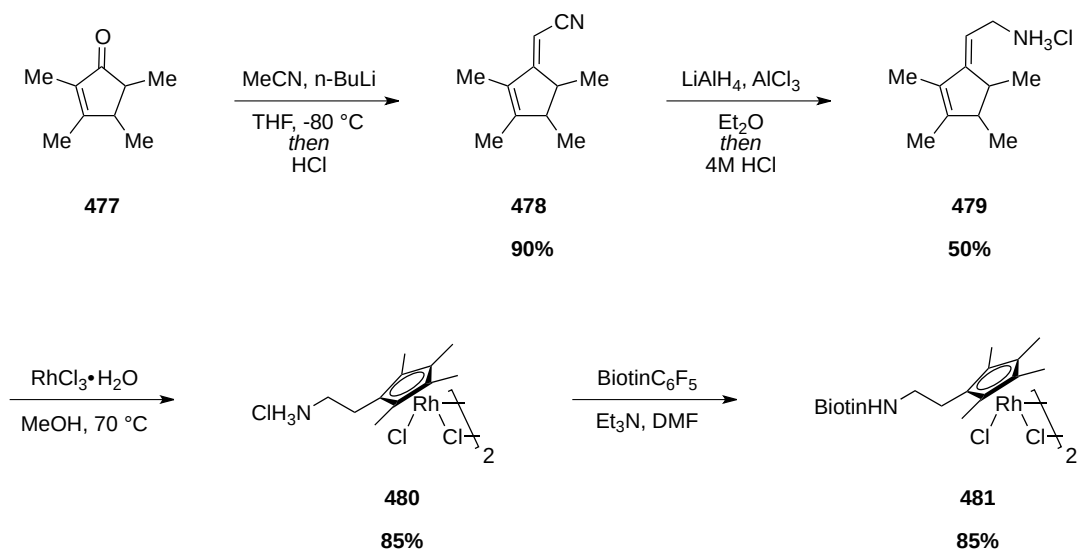
• *Tsuji-Trost Allylation*



Scheme 4.7 Examples of Transformations Catalyzed by Streptavidin Based Metalloenzymes

In the transfer hydrogenation of imines, the biotinylated ligand complexes to the metal through a diamine ligand. Ward and coworkers were interested in linking the metal through the Cp* or arene ligand to allow for a broader array of ligands to occupy the available coordination sites. A graduate student in the Ward group, Mr. Jeremy Zimbron, prepared a biotinylated Rh(III) complex for transfer hydrogenation reactions.⁶⁰ The synthesis of the Rh(III) amine complex can be achieved in four steps using a literature procedure.⁶¹ The [RhCp*^{C₂H₄NH₂}Cl₂]₂ complex can be coupled to activated biotin under basic conditions to provide the desired [RhCp*^{biotin}Cl₂]₂ **481** complex (Scheme 4.8). It was at this juncture that we entered

into a collaboration with the Ward Group to apply the biotin-(strept)avidin artificial metalloenzyme technology to the asymmetric synthesis of dihydroisoquinolones mediated by Rh(III) C–H activation.



Scheme 4.8 Synthesis of **481**

4.2 Results

4.2.1 Optimization

Since aqueous conditions are required to maintain the protein's stability, we initially probed the desired reaction's tolerance for aqueous medium. We were pleased to find the coupling of *O*-pivaloyl benzhydroxamic acid **281** with styrene **442** in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ and CsOAc proceeds well in a 1:1 mixture of MeOH/H₂O in >20:1 regioselectivity and 90% yield (Table 4.3, entry 2). The fraction of water could be increased to 80% without any substantial loss in reactivity (Table 4.3, entry 3). As with the synthesis of pyridines, the reaction tolerates impurities, apparent when the reaction is run in Pabst Blue Ribbon Beer (Table 4.3, Entry 4).

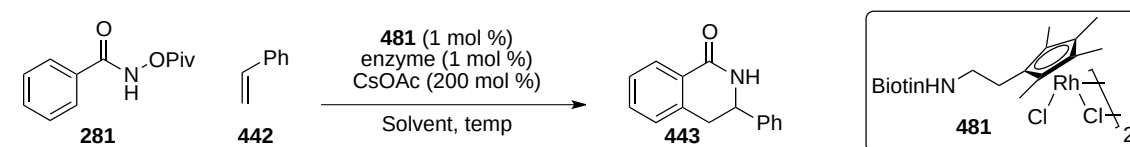
Table 4.3 Reaction Tolerance of Aqueous Conditions

Entry	Solvent	Yield (%)
1	MeOH	92
2	H ₂ O/MeOH (1:1)	94
3	H ₂ O/MeOH (4:1)	93
4	Pabst Blue Ribbon	93

Reaction Conditions: **280** (1 equiv), **442** (1.1 equiv), 0.2 M, 16 h

Having established the reaction will tolerate aqueous conditions, $[\text{RhCp}^*\text{Cl}_2]_2$ **481** was prepared according to the procedure provided by Mr. Zimbron. When submitted to the reaction conditions in the absence of enzyme, the catalyst affords the desired product in 45% yield (Table 4.4, entry 1). Introduction of *wild-type* (strept)avidin (WT SAV) inhibited the reaction with only starting material observed (Table 4.4, entry 2). Increasing the temperature to 45 °C or 55 °C failed to produce product **443** (Table 4.4, entries 3 and 4). Changing the solvent to a 1:1 ratio of MeOH/H₂O to increase the solubility of the starting material provides the desired product in 5% yield with 52.5:47.5 *er* (Table 4.4, entry 5). Exchange of the serine residue for an alanine at position 112 provided the product in slightly increased yield, but as a racemic mixture (Table 4.4, entry 6). Use of NaOAc, instead of CsOAc, did not provide substantial increase in yield or *er* (Table 4.4, entry 7). Finally, using avidin (AVI) gave product in low yield and low enantioselectivity (Table 4.4, entry 9). The reluctance of these conditions to provide product forced us to reconsider the role the enzyme has on the reaction.

Table 4.4 Initial Screen with Metalloenzymes



Entry	Enzyme	Solvent	Temperature (°C)	Yield (%)	er
1	–	H ₂ O/MeOH (4:1)	23	45	–
2	WT SAV	H ₂ O/MeOH (4:1)	23	0	–
3	WT SAV	H ₂ O/MeOH (4:1)	45	0	–
4	WT SAV	H ₂ O/MeOH (4:1)	55	0	–
5	WT	H ₂ O/MeOH (1:1)	55	5	52.5:47.5
6	S112A	H ₂ O/MeOH (1:1)	55	10	50:50
7 ^a	WT	H ₂ O/MeOH (1:1)	55	10	55:45
8 ^a	S112K	H ₂ O/MeOH (1:1)	55	0	–
9 ^a	AVI	H ₂ O/MeOH (1:1)	55	5	51:49

Reaction Conditions: **281** (1 equiv), **442** (10 equiv), 0.05 M, 64 hours

^a NaOAc used as base

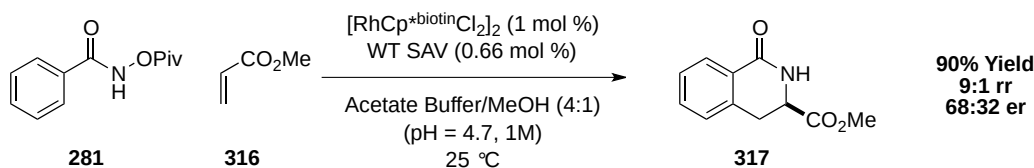
Previous mechanistic experiments indicated that three coordination sites are required for catalyst activity in C–H activation reactions.⁶² We speculated that in the presence of a protein, the basic components of the peptide could coordinate to the metal and shutdown catalysis. We hypothesized that buffered acidic conditions might preclude unwanted coordination events and help facilitate the reaction. Since acetate is essential for the concerted metallation-deprotonation (CMD) C–H activation, acetic acid buffers were screened in the reaction (Table 4.5). Using a 4:1 mixture of acidic acid buffer (pH=4.7 at 1M) and MeOH at 55 °C, the desired product is provided in substantially enhanced yield but with no enantioselectivity (Table 4.5, entry 1). Modification of the buffer concentration afforded a mild increase in yield, but again with no enantioselectivity (Table 4.5, entry 2). Finally, decreasing the reaction temperature and increasing the reaction time allowed for product to be accessed in nearly quantitative yield, but with no enantioselectivity (Table 4.5, entry 4).

Table 4.5 Acidic Reaction Conditions

Entry	Enzyme	Solvent	Temperature (°C)	Yield (%)	er
1	WT SAV	Acetate Buffer/MeOH (pH 4.7, 1M)	55	65	50:50
2	WT SAV	Acetate Buffer/MeOH (pH 4.7, .05M)	55	74	50:50
3	WT SAV	Acetate Buffer/MeOH (pH 4.7, .025M)	55	75	50:50
4	WT SAV	Acetate Buffer/MeOH (pH 4.7, .68M)	23	99	50:50

Reaction Conditions: **280** (1 equiv), **442** (10 equiv), 0.05M

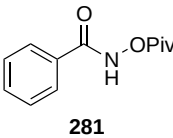
Our goal in using styrene as a coupling partner was to use steric interactions to induce enantioselectivity. Unfortunately this approach only provided racemic product. Given the large number of hydrogen bonding residues present in an enzyme, if a Lewis basic atom was present in the alkene, hydrogen bonding to the enzyme could occur helping to provide some level of enantioselectivity. When methyl acrylate **316** was used instead of styrene, high yields were observed with improved regioselectivity and for the first time, modest levels of enantioselectivity were observed (68:32 er) (Scheme 4.9).

**Scheme 4.9** Methyl Acrylate as the Alkene

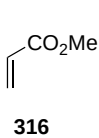
Upon arrival at the University of Basel for a three-month internship in the group of Professor Thomas R. Ward, further reaction optimization was undertaken. In the group's previous studies of (strept)avidin based transfer hydrogenation catalysts they found a half loaded (2 equivalents of metal to (strept)avidin) tetramer afforded superior enantioselectivity (96.5:3.5 er) by comparison to a fully loaded (4 equivalents of metal to (strept)avidin tetramer) (strept)avidin tetramer (94:6 er).⁵¹ Presumably this was an artifact of the close proximity of the two metal centers. A study was performed to determine if the same effect was present in our system (Table 4.6). When the streptavidin tetramer was loaded with 1 equivalent of

[RhCp*^{biotin}Cl₂]₂ (1/4 of the tetramer loaded) the desired product was observed in 95% yield, with 8:1 regioselectivity, and 69:31 *er* (Table 4.6, entry 1). Addition of an additional equivalent of metal catalyst (1/2 of the tetramer loaded) again gives product in 95% yield, with 8:1 regioselectivity, and 68:32 *er* (Table 4.6, entry 2). Additional equivalents of metal to fully load the catalyst did not have a significant impact on the yield nor enantioselectivity of the reaction (Table 4.6, entries 3-4). These studies suggest the chemistry occurring around the metal center is not impacted by the adjacent metal center.

Table 4.6 Impact of Partial Streptavidin Loading



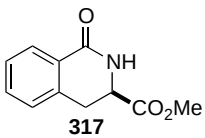
281



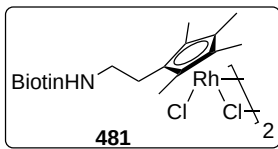
316

481 (X mol %)
WT SAV (X mol %)

Acetate Buffer/MeOH
(pH 4.7, 0.5 M)
23 °C, 40 h



317

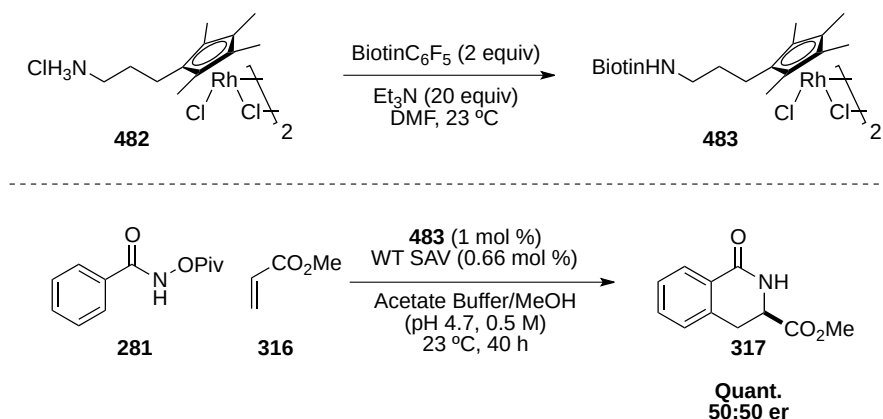


481

Entry	Enzyme Loading	Tetramer Loading	Yield (%)	Regioselectivity	<i>er</i>
1	2.0 mol %	1/4	95	8:1	69:31
2	1.5 mol %	2/4	95	8:1	68:32
3	1.0 mol %	3/4	95	8:1	68:32
4	0.5 mol %	4/4	95	8:1	68:32

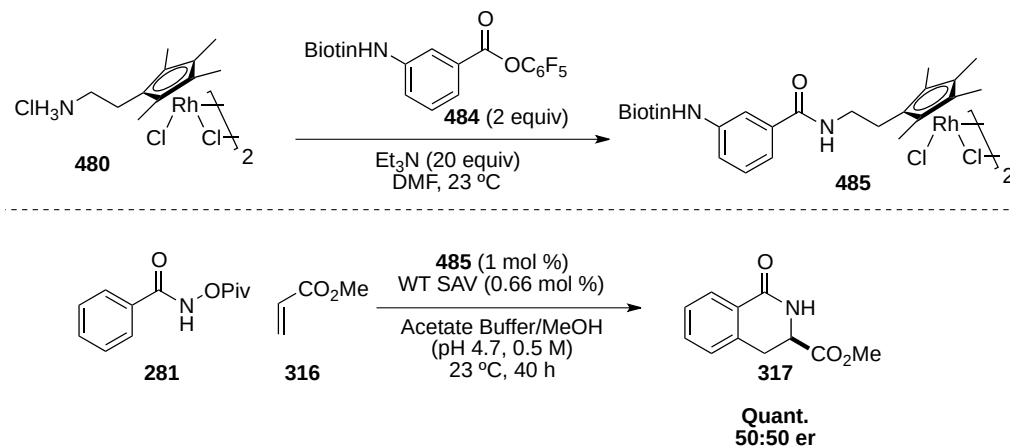
Reaction Conditions: **281** (1 equiv), **316** (10 equiv), 0.05 M

After finding the loading of the metal cofactor in the enzyme does not provide differential levels of enantioselectivity or yield, we modified the linker with the goal of increasing the enantioselectivity. To probe to potential of modified linkers, we sought to increase the carbon tether length from two carbons to three. Previously, Ikariya and coworkers prepared a three-carbon linker for use as a transfer hydrogenation catalyst.⁶³ Using the same approach we were able to access the desired rhodium complex in good yield (Scheme 4.10). Upon treatment of **482** with pentafluorophenylbiotin in DMF with Et₃N a mixture of the desire product and the cyclized product was observed. Under our current mechanistic understanding, we believed the cyclized complex would be completely unreactive under the reaction conditions and would not negatively impact the enantioselectivity. Consequently, when **483** is submitted to the reaction conditions the desired product was observed in high yield but without any enantioselectivity.



Scheme 4.10 Impact of Longer Linkers on Enantioselectivity

We hypothesized the extended linker was too flexible to allow for good enantio-induction. With the goal of rigidifying the linker, we prepared a rhodium complex containing a *m*-amino benzoic acid linker. This complex was prepared by coupling **480** with the activated BiotinNHC₆H₄CO₂C₆F₅ **484** to generate **485** in good yield. Unfortunately, when submitted to the reaction conditions, the desired product was observed in high yield but with no enantioselectivity. We speculate that elongated linkers fail to provide enantioselectivity because they move the metal center too far from the protein. Efforts to prepare a shortened linker were met with failure.



Scheme 4.11 Amino-Benzoic Acid Derived Linker

With the goal of increasing enantioselectivity, a variety of mutants were tested under our previously optimized reaction conditions. Prior to this screen, a docking study was performed to determine the approximate location of the metal within the active site. This was achieved by initial Hartree-Fock energy

minimization of the biotinylated rhodium complex $\text{RhCp}^{\text{biotin}}(\text{OAc})_2$. The energy-minimized model was docked into the crystal structure of streptavidin. The biotin moiety of the metal catalyst was superimposed onto biotin in the crystal structure. At this point the dihedral angles of the bonds in the linker connecting biotin to the metal Cp complex were rotated to minimize steric interactions with the protein surface. The resulting model suggested that serine at position 112, leucine at position 124, and lysine at position 121 to be closest to the metal center. In the later case, residue K121 closest to the metal in our model is from the opposite streptavidin monomer to the one binding the metal (monomer signified with an A or B) (Figure 4.2).

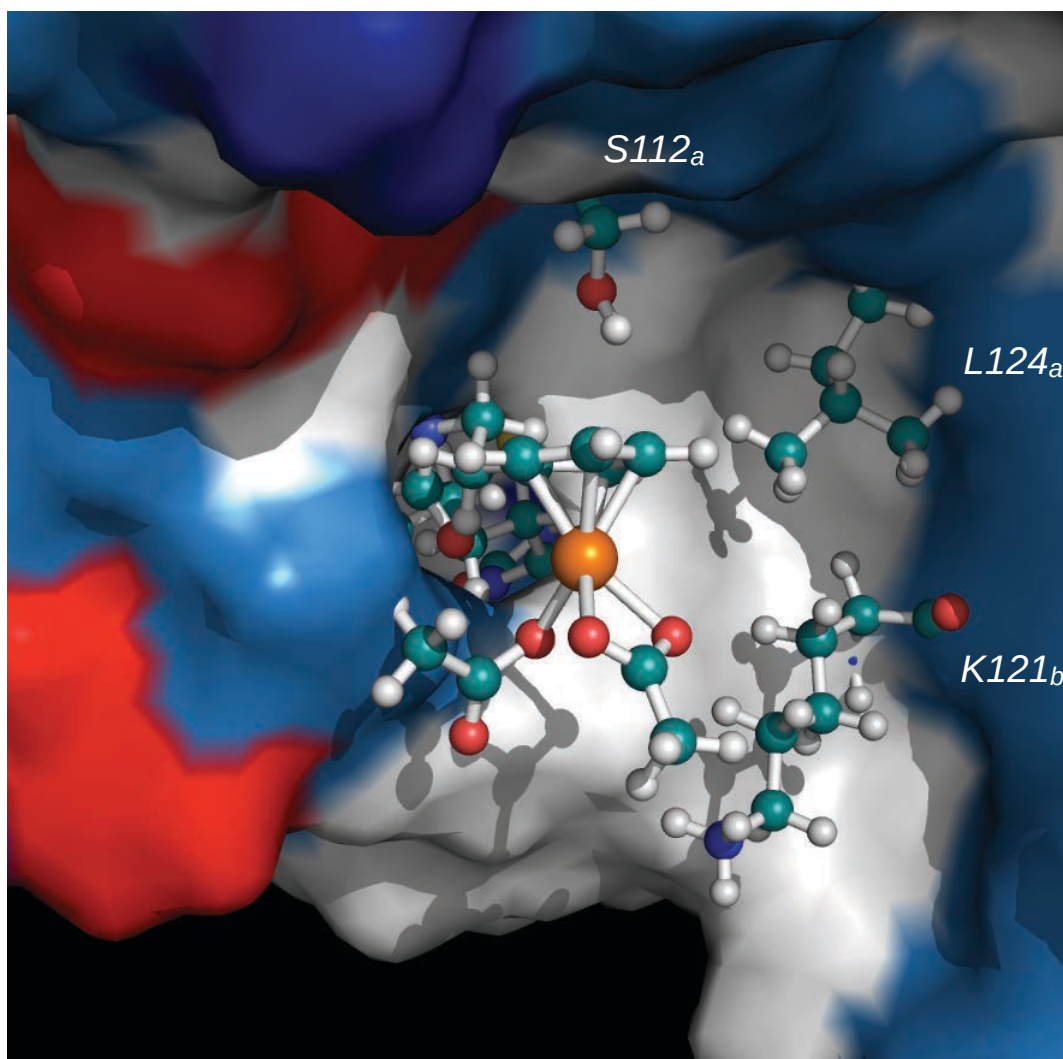


Figure 4.2 Model of the Active Site

We initially screened a broad range of mutants at position 112, and a more narrow collection of mutants at positions 121 and 124 (Table 4.7). Coordinating residues, such as histidine and cysteine, failed to provide appreciable amounts of product (Table 4.7, entries 2, 5, 7, and 11). Aromatic residues, such as tyrosine and phenylalanine, provided product in high yield with no loss in enantioselectivity (Table 4.7, entries 4, 10, and 13). Bulky hydrophobic residues also fare well, but with decreased levels of enantioselectivity (Table 4.7, entries 6, and 9). The only mutation to provide increased enantioselectivity was L124Y, which provided product in 95% yield and 70:30 *er* (Table 4.7, entry 16).

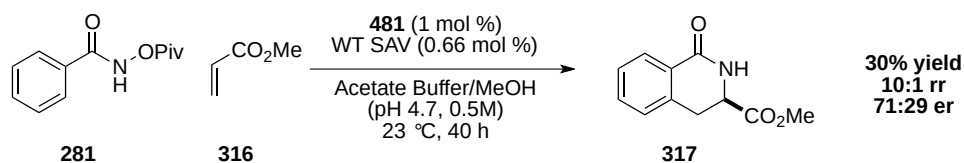
Table 4.7 Impact of Mutations of Enantioselectivity

Entry	Mutant	Yield (%)	Regioselectivity	<i>er</i>
1	S112A	95	9:1	68:32
2	S112C	< 5	—	—
3	S112E	95	3:1	61:39
4	S112F	95	8:1	68:32
5	S112H	< 5	—	—
6	S112L	95	10:1	68:32
7	S112M	< 5	—	—
8	S112R	95	8:1	52:48
9	S112V	95	8:1	63.5:36.5
10	S112Y	95	8:1	68:32
11	K121H	< 5	—	—
12	K121G	< 5	—	—
13	K121F	95	8:1	68:32
14	L124A	95	8:1	65.5:34.5
15	K124K	95	8:1	57:43
16	L124Y	95	8:1	70:30

Reaction Conditions: **281** (1 equiv), **316** (10 equiv), 0.05 M

The inability of the mutants to have a substantial impact on enantioselectivity under the current reaction conditions suggested that control experiments were necessary to confirm that isomerization of the product was not occurring over the course of the reaction. When the reaction is run on larger scale and aliquots were taken periodically over the course of the reaction, the enantioselectivity remains constant over the course of the reaction precluding racemization as a possible source of the low enantioselectivity.

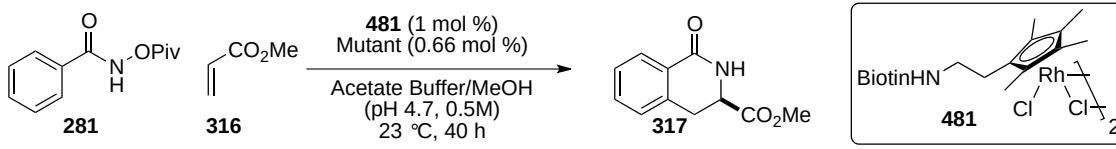
After evaluation of the conditions, we considered the alkene concentration in the reaction. Under the early optimized conditions 10 equivalents of methyl acrylate were used to assure that any alkene concentration loss due to evaporation over the course of the reaction would not diminish the yield. When the concentration of alkene was decreased to 1.1 equivalent the yield decreased to 30%, with a mild enhancement in regioselectivity to 10:1 from 8:1, and a moderate jump in enantioselectivity to 71:29 from 68:32 (Scheme 4.12).



Scheme 4.12 Decreased Alkene Loading

Pleased by the mild increase in enantioselectivity, we re-evaluated mutants at position S112 that did not decrease enantioselectivity in our previous screen (Table 4.8). We were pleased to find that S112A provides product in low yield but good levels of regioselectivity and 73.5:26.5 *er* under the new conditions (Table 4.8, entry 1). The previous screen also revealed aromatic residues to be effective mutants. Introduction of phenylalanine or tyrosine at position S112 (S112F, S112Y) gave product in low yield, variable regioselectivity, but significantly increased enantioselectivity with S112Y affording product with 81.5:18.5 *er* (Table 4.8, entry 3)

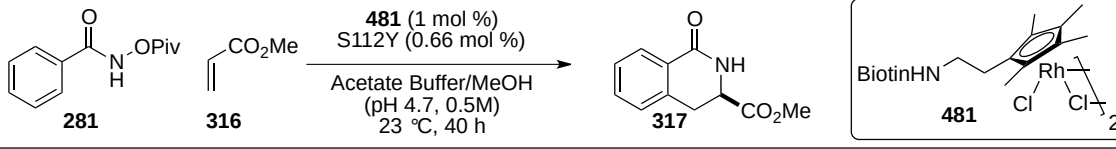
Table 4.8 Limited Mutant Screen at Low Alkene Concentration

				
Entry	Mutant	Yield (%)	Regioselectivity	er
1	S112A	30	10:1	73.5:26.5
2	S112F	35	6:1	80:20
3	S112Y	27	12:1	81.5:18.5

Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv), 0.05 M

To enhance the enantioselectivity, further reaction optimization was utilized (Table 4.9). An evaluation of the overall concentration revealed the reaction to perform best at 0.5 M (Table 4.9, entry 2). We were pleased to find that increasing the pH to 5.9 results in a marked increase in *er* (86:14) (Table 4.9, entry 4). Modification of the buffer concentration revealed the greatest *er* observed of 88:12 (Table 4.9, entry 5).

Table 4.9 Impact of pH and Concentration of Enantioselectivity

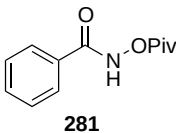
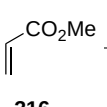
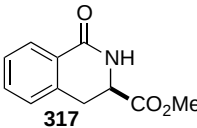
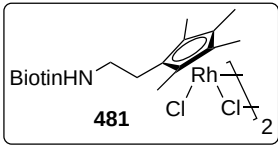
						
Entry	pH	Conc. of Buffer (M)	Overall Conc. (M)	Yield(%)	Regioselectivity	er
1	4.7	1	0.005	20	12:1	76.5:23.5
2	4.7	1	0.05	27	12:1	81.5:18.5
3	4.7	1	0.5	30	12:1	80:20
4	5.9	1	0.05	20	12:1	86:14
5	5.9	0.7	0.05	27	12:1	88:12

Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv)

To assure that another mutant would not give enhanced enantioselectivity under the new reaction conditions, we screened a wide range of mutants at positions S112, K121, and L124. Since we were only interested in the effect on enantioselectivity, decreased reaction times were used, and yields were not collected. Mutations at position S112 seemed to have the greatest impact on the enantioselectivity with aromatic residues universally increasing the enantioselectivity by comparison to *wild-type* streptavidin

(Table 4.10, entries 1, 4, and 15). Side chains containing non-aromatic sterically bulky groups did not have the same beneficial effect of the large aromatic residues (Table 4.10, entries 7, 9, 14, 20). Coordinating residues (histidine, cysteine, and methionine), were poorly reactive and prohibiting the ability to obtain useful data (Table 4.10, entries 3, 6, and 10). Polar amino acid substitutions universally resulted in decreased levels of enantioselectivity (Table 4.10, entries 11, 12). Interestingly, alterations to positions K121, L124, or P49 failed to provide a level of enhanced selectivity (Table 4.10, entries 16-23).

Table 4.10 Full Mutant Screen Under Optimized Conditions

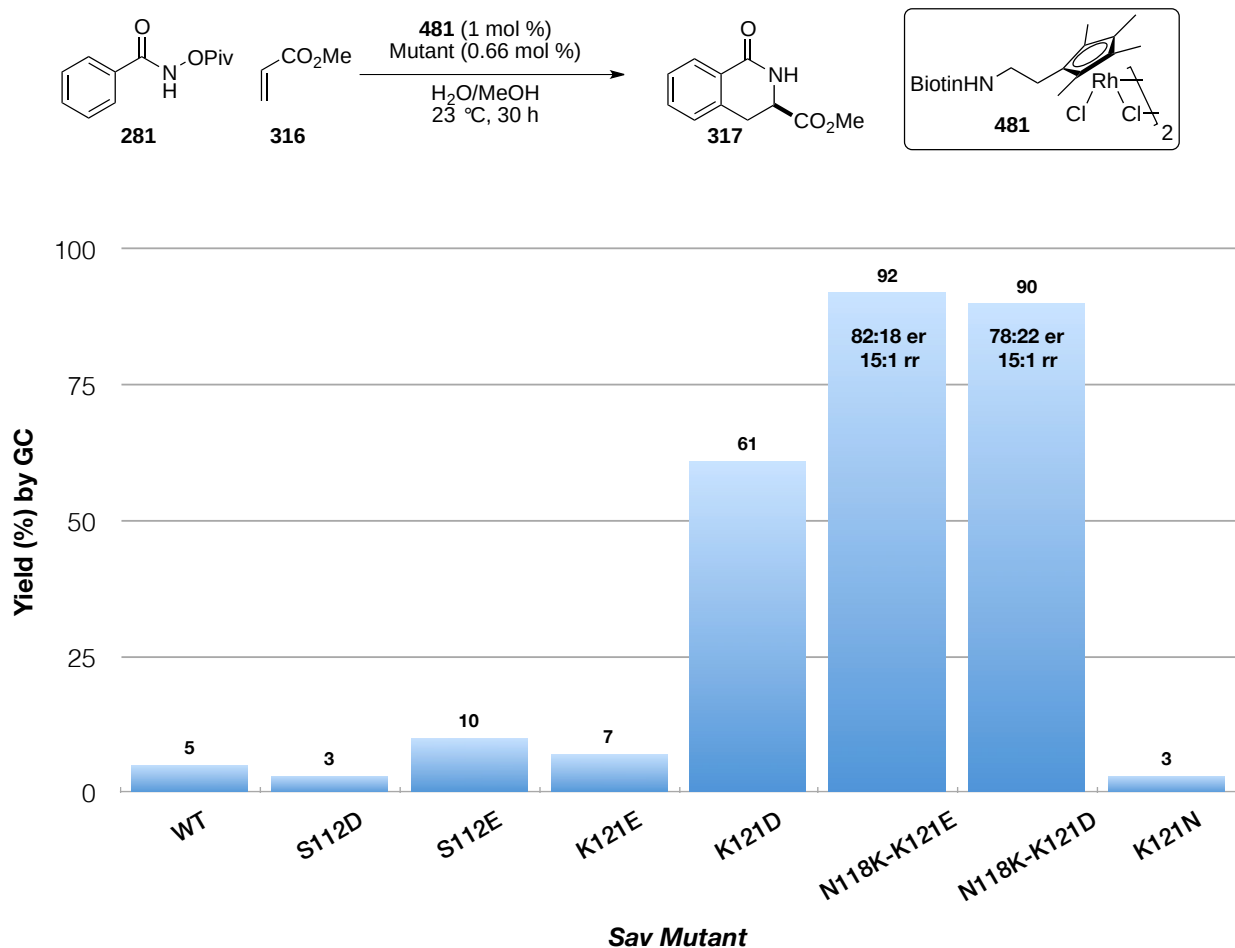
 281  316 481 (1 mol %) Mutant (0.66 mol %) Acetate Buffer/MeOH (pH 5.9, 0.7M) 23 °C, 18 h  317  481			
Entry	Mutant	Regioselectivity	er
1	WT SAV	9:1	72:28
2	S112A	8:1	75:25
3	S112C	–	–
4	S112F	10:1	86.5:13.5
5	S112G	10:1	50:50
6	S112H	–	–
7	S112I	10:1	64:36
8	S112K	10:1	46:54
9	S112L	10:1	50:50
10	S112M	–	–
11	S112N	10:1	62:38
12	S112Q	10:1	50:50
13	S112T	10:1	73:27
14	S112V	10:1	62:38
15	S112W	10:1	85.5:14.5
16	K121H	10:1	50:50
17	K121F	12:1	62:38
18	K121N	10:1	66:34
19	L124F	10:1	50:50
20	L124V	10:1	70:30
21	L124K	10:1	60:40
22	L124Y	10:1	67:33
23	P47G	10:1	60:40

Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv)

At this point, we had identified a mutant that gives promising levels of enantioselectivity but the yields were far from acceptable. We shifted our attention toward finding a solution for the low yields.

Mechanistic studies by Fagnou suggested that C–H activation is turnover limiting in the synthesis of isoquinolones.¹ Furthermore, these studies suggest the C–H activation event occurs through an acetate assisted (CMD) mechanism, similar to what we observed in our Rh(III) catalyzed C–H activation mediated heterocycles synthesis. Since the rate of the reaction is controlled by the C–H activation event, which involves a carboxylate base, we reasoned that if a carboxylate base was introduced into the active site of the enzyme, the rate of the reaction might be increased, which could result in enhanced yields. Thankfully, nature possesses two carboxylate containing amino acids, glutamic and aspartic acid.

We began by preparing four mutants that contain aspartic or glutamic acid at position S112 and K121. To determine if the presence of the carboxylate impacts reactivity, the reaction medium was changed to 4:1 H₂O/MeOH. Under these reaction conditions *wild-type* streptavidin provides product in 5% yield and 71:29 *er* (Scheme 4.13). Introduction of aspartic or glutamic acid at position S112 did not have a substantial impact on reactivity. Again glutamic acid did not have a beneficial impact at position K121. We were pleased to find that aspartic acid at position 121 did have an advantageous effect with the desired product observed in 61% yield. Examination of carboxylate containing mutants in Ward mutant library provided a double mutant, which contains glutamic acid at position 121, and lysine at position 118 (N118K-K121E). When submitted to the reaction conditions, N118K-K121E provided product in an astonishing 92% yield. Further evaluation of the reaction revealed 15:1 regioselectivity and 82:18 *er*. When glutamic acid was replaced with aspartic acid (N118K-K121D) similarly high yields are observed but with lower *er* (78:22). As a control experiment asparagine was introduced at position 121 (K121N). Electronically this residue should be similar to an acid but be completely incapable of facilitating the CMD event. When submitted to the reaction conditions, K121N provided product in less than 5% yield (Scheme 4.13). Attempts at generating mutants with different amino acids at position N118 were unsuccessful because of difficulty generating the mutated plasmids required for protein expression.

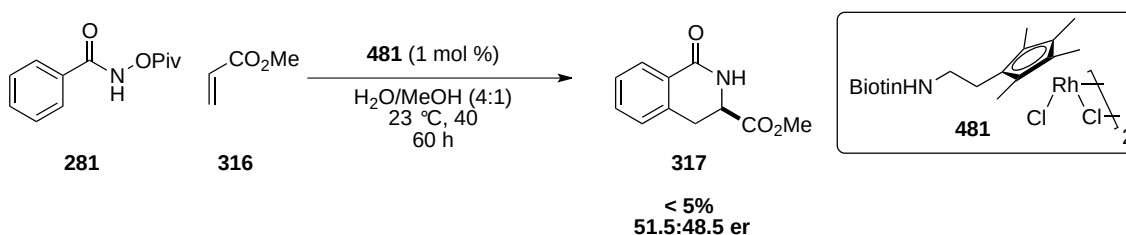


Scheme 4.13 Screen of Carboxylate-Containing Mutants Under Buffer-Free Conditions

Kinetic experiments were used to lend further evidence for the role the carboxylate base plays in the reaction. Early initial rate kinetic studies gave irreproducible results because of the heterogeneous nature of the reaction. An alternative approach to glean kinetic insight is to track the enantioselectivity of the reaction. In a previous study, Ward found the relative activity of the free rhodium complex (*free*) by comparison to the streptavidin bound rhodium complex (*bound*) could be determined by monitoring the enantioselectivity as the amount of the biotinylated rhodium complex is increased beyond the number of free binding sites in streptavidin.⁵⁰ The degree of protein acceleration by comparison to the free biotinylated catalyst can be calculated by (eq 1):

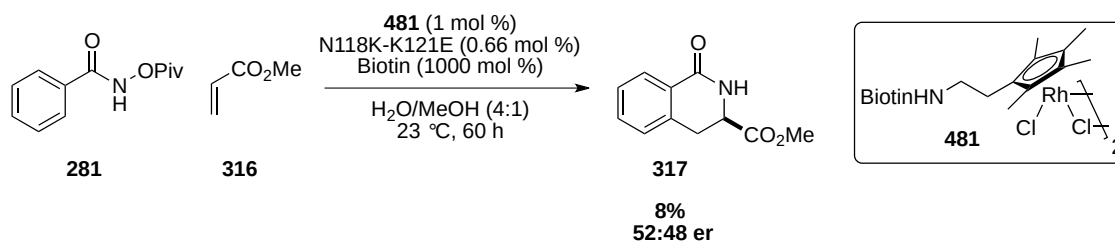
$$\%(\text{R})_{\text{calculated}} = \frac{k_{\text{bound}} \cdot \mu_{\text{bound}} \cdot \%(\text{R})_{\text{bound}} + k_{\text{free}} \cdot \mu_{\text{free}} \cdot \%(\text{R})_{\text{free}}}{k_{\text{bound}} \cdot \mu_{\text{bound}} + k_{\text{free}} \cdot \mu_{\text{free}}}$$

where k_{bound} and k_{free} are the rate constants for the streptavidin bound rhodium complex (k_{bound}) and the free rhodium complex (k_{free}), μ_{bound} and μ_{free} are the number of protein bound rhodium complex (μ_{bound}) and the number of free complexes (μ_{free}), and $\%(R)_{bound}$ and $\%(R)_{free}$ is the percentage of (R) enantiomer delivered with the streptavidin bound rhodium complex ($\%(R)_{bound}$) and the unbound rhodium complex ($\%(R)_{free}$). When amide **281** and alkene **316** were submitted to MeOH/H₂O (1:4) in the presense of [RhCp*^{biotin}Cl₂]₂ without exogenous acetate base added, the reaction provides a trace amount of product in 51.5:48.5 *er* giving the value required for $\%(R)_{free}$ (Scheme 4.14).



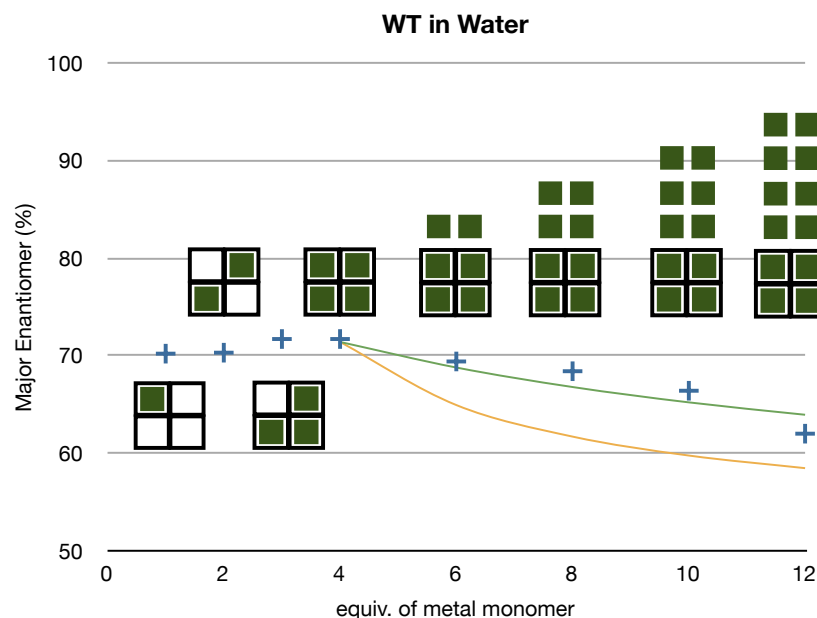
Scheme 4.14 *Er* Under Streptavidin Free Conditions

An additional control experiment needed is to determine if alternative coordination modes are available for the biotinylated rhodium complex to streptavidin that might result in an unexpected induction of asymmetry. Upon dissolving the enzyme N118K-K121E in H₂O, excess biotin (10 equivalents) was added to the reaction and allowed to stir for 10 minutes. This event ensures that all sites capable of binding the rhodium catalyst are filled with biotin. After introduction of the rhodium catalyst **481**, amide **281**, and alkene **316** and stirring for 60h, the desired product is observed in 8% yield, 6:1 *rr*, and 52:48 *er*. This experiment suggests there are no secondary interactions between the rhodium catalyst **481** and the enzyme that might result in asymmetric induction (Scheme 4.15).



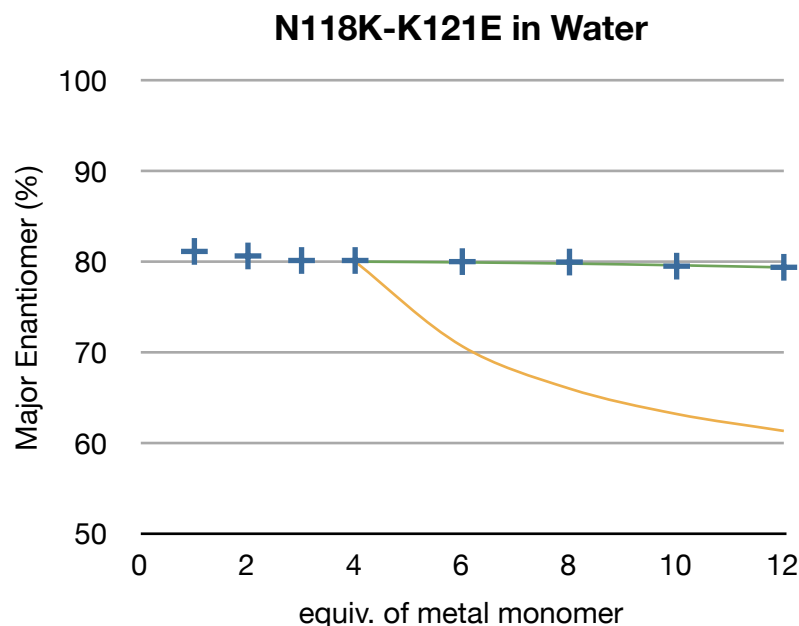
Scheme 4.15 Control Experiment of Secondary Coordination

Control experiments in hand, the initial study was conducted to determine the relative rates of rhodium complex **481** and **481** $\subset$ WT-SAV. 1, 2, 3, and 4 equivalents of rhodium catalyst **481** were added to completely fill WT-SAV (first four data points in Scheme 4.16) then 6, 8, 10, and 12 equivalents were added. This ensured that in the final data point there is 2x as much **481** by comparison to bound catalyst (**481** $\subset$ WT-SAV). We observed that as more unbound catalyst was present the *er* decreased. Using equation 4.1, if $k_{free}=k_{bound}$ then the observed % (*er*) would match the orange line in Scheme 4.16. Qualitatively, the bound catalyst is more reactive than the unbound catalyst because the observed %(*R*) (blue cross) is greater than the %(*R*) (orange line) predicted if the complexes were equally reactive. This amount can be quantified if $k_{free} = 1$ and $k_{bound} = X$. Performing least square minimization we find the bound complex is 3x more reactive than the free catalyst with an equation that fits the observed data with an $R^2 = .92$ (green line). Presumably the hydrophobic pocket of streptavidin has increased affinity for the starting materials than the overall reaction solution (Scheme 4.16).



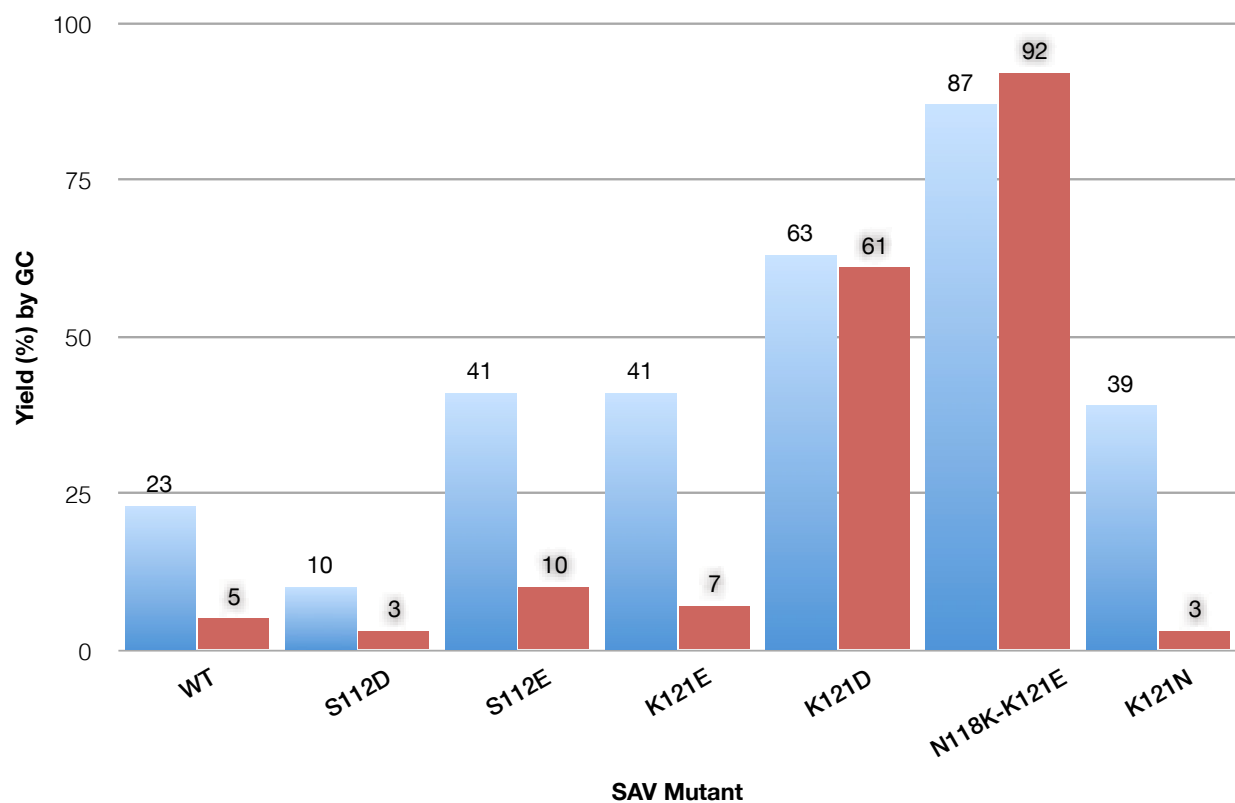
Scheme 4.16 Rate Analysis of (**481** $\subset$ WT-SAV) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ WT-SAV) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst

The same approach was used to evaluate the relative rates of **481** and **481** $\subset$ N118K-K121E. In contrast to marked decrease in *er* observed when using WT-SAV, N118K-K121E does not have a substantial decrease in *er* when excess **481** is added to the reaction. As before, the observed *er* is much greater than what would be expected if the bound and free complexes were equally reactive. Using least mean squares, we can determine the bound catalyst is 92x more reactive than the free catalyst. Since the assumptions built into the two sets of reaction conditions are the same, the relative reactivity of the two bound complexes can be compared. These studies suggest that **481** $\subset$ N118K-K121E is over 30x more reactive than **481** $\subset$ WT-SAV (Scheme 4.17). Furthermore, internal KIE studies found that **481** $\subset$ N118K-K121E has a KIE value of 4.8 support for the C–H activation favoring the weaker C–H bond.



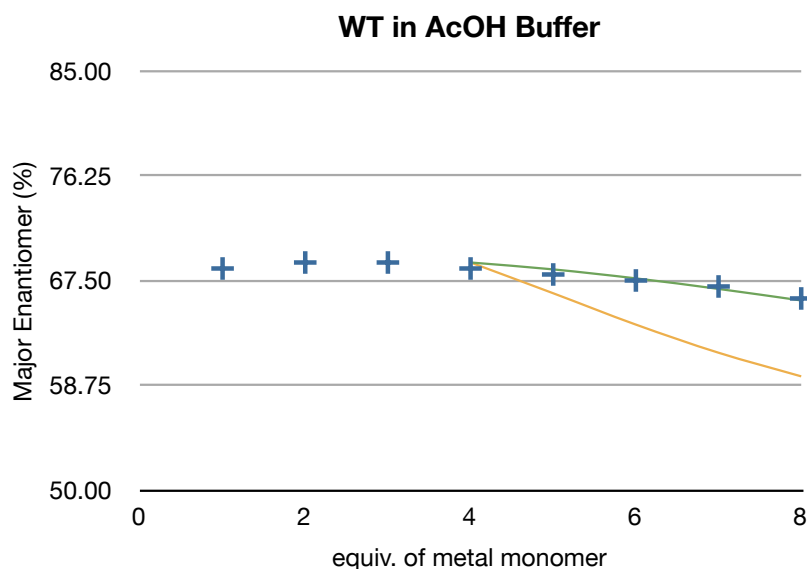
Scheme 4.17 Rate Analysis of (**481** $\subset$ N118K-K121E) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ N118K-K121E) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst

We were curious how the acetate containing mutants would fare when run in the presence of acetate buffer (Scheme 4.18). Interestingly, K121D and N118K–K121E continue to be the most efficient mutants providing product in nearly identical yield to the reactions run in water. The other mutants, which afforded low yields when run in water, gave low to modest yield but never reached the level of efficiency found using N118K–K121E (Scheme 4.18). These results suggest a specific base is involved in the C–H activation event for N118K–K121E and K121D, while all other mutants require the acetate base provide by the solvent to achieve modest conversion.



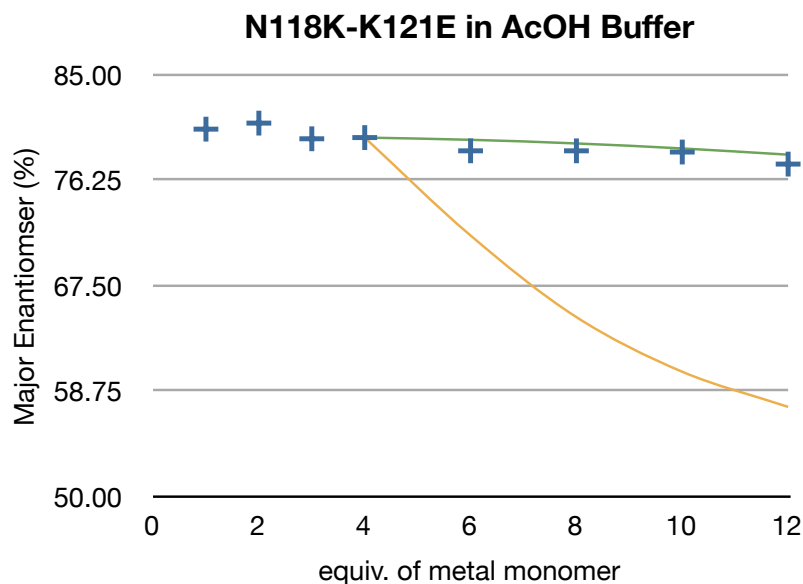
Scheme 4.18 Performance of Mutants Under Different Conditions Blue Bars = Acetate Buffer; Red Bars = H₂O

The same kinetic analysis was performed on **481** $\subset$ WT-SAV in the presense of acetate buffer. Under these conditions the enzyme bound complex is nearly 5x more reactive than the unbound rhodium catalyst. As before, we attribute the rate enhancement to affinity of the starting material for the hydrophobic pocket of the enzyme (Scheme 4.19).



Scheme 4.19 Rate Analysis of (**481** $\subset$ WT-SAV) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ WT-SAV) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst

When the same analysis was performed on **481** $\subset$ N118K-K121E in the presence of acetate buffer, the bound complex was found to be approximately 60x more reactive than **481** (Scheme 4.20). The observed %(*R*) decreased more than was observed in water, presumably because the acetate buffer allows for the reaction to occur outside the enzyme, but the metal bound complex is still substantially more reactive. When compared to **481** $\subset$ WT-SAV, **481** $\subset$ N118K-K121E is at least 12x more reactive. This value further supports the rate enhancement being more than just an artifact of the hydrophobic pocket or the presence of an acetate source, but rather the specific location of the carboxylate residue. In many ways this mimics the catalytic triads used in nature to lower the activation energy of a give step. Consequently, we have termed the interaction present in our system a catalytic metallo-dyad (Figure 4.3).



Scheme 4.20 Rate Analysis of (**481** $\subset$ N118K-K121E) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ N118K-K121E) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst

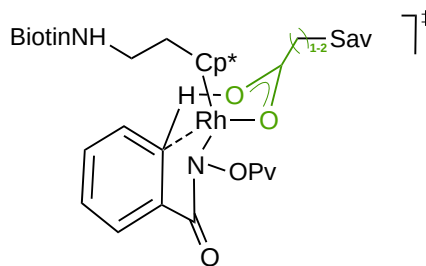
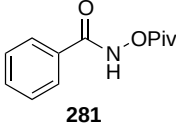


Figure 4.3 Proposed C–H Activation Transition State

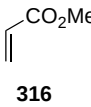
Overlooked using the artificial metalloenzyme complex is the catalyst loading. While the weight percent loading of rhodium is low (5 wt %), the loading of the enzyme is quite high at 216 wt% with extended reaction times (Table 4.11). At 55 °C, the reaction is done is less than 12 hours with degradation of the *er* to 78:22. However, upon decreasing the temperature to 37 °C, after 12 hours, full conversion is observed with increased levels of enantioselectivity (81.5:18.5). We were interested in decreasing the catalyst loading on this highly reactive mutant. When the enzyme loading is decreased to 21.6 wt% (0.066 mol % enzyme), the desired product is provided in high yield, with equivalent regioselectivity and

enantioselectivity after 10 days at 23 °C. Increasing the temperature to 37 °C, the reaction is complete after 24 hours in quantitative yield at 80:20 *er* (Table 4.11).

Table 4.11 Decreased Catalyst Loading

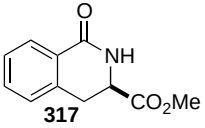


281

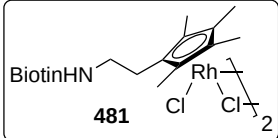


316

$\xrightarrow[\text{H}_2\text{O/MeOH, temperature, time}]{\text{481 (X mol \%), N118K-K121E (X mol \%)}}$



317



481

Entry	481 Loading (mol %)	Enzyme Loading (mol %, WT%)	Temperature (°C)	Time (h)	Yield (%)	<i>er</i>
1	1	0.66, 216	23	36	92	82:18
2	1	0.66, 216	55	<12	99	78:22
3	1	0.66, 216	37	<12	99	81.5:18.5
4	0.1	0.066, 21.6	37	24	99	80:20
5	0.1	0.066, 21.6	23	240	82	82:18

Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv)

With a highly reactive mutant in hand, we shifted our attention back to enantioselectivity. Mutations at position K121 and N118 were required for the metal to be sufficiently reactive for catalysts. Evaluation of a PyMol interpretation of the mutated active site suggested mutations at position S112 to have the greatest impact on enantioselectivity because of their proximity to the metal (Figure 4.4).

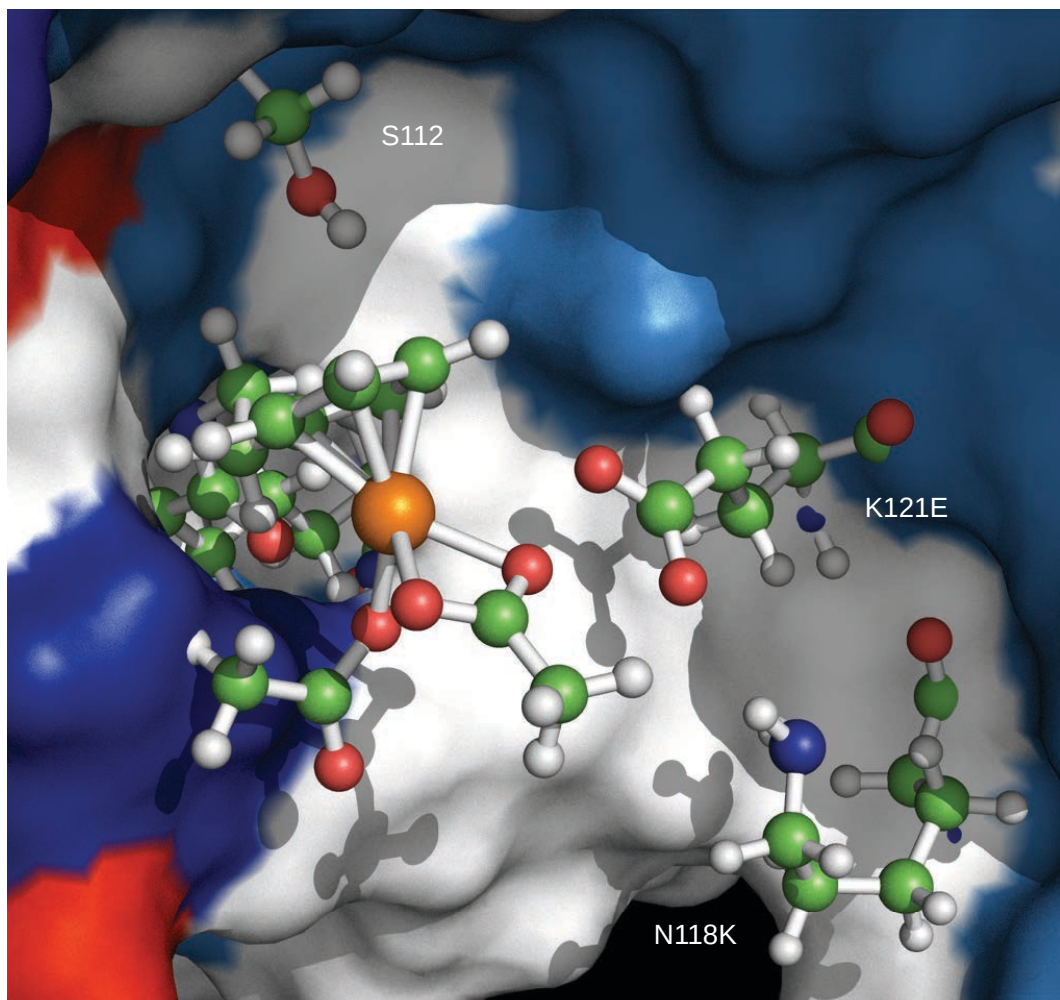


Figure 4.4 Model of N118K-K121E

In our previous mutant screen, we found the introduction of aromatic residues at position S112 to give the highest levels of enantioselectivity with tyrosine (S112Y) providing product with 88:12 er. We endeavored to produce three new mutants that could potentially give high levels of reactivity and enantioselectivity, S112Y-K121D, S112Y-K121E, and S112Y-N118K-K121E. When triple mutant S112Y-N118K-K121E is run in reaction medium lacking acetate buffer, the desired product is observed in 15% yield, 15:1 regioselectivity, and an enhanced 91:9 er. Double mutant S112Y-K121D provided product in slightly enhanced yield and regioselectivity and 90:10 er. The most promising results came when S112Y-K121E was used, with 80% yield, 20:1 regioisomeric ratio, and 90:10 er. This mutant appeared to form higher order enzyme aggregates under the reaction conditions leading to greater enzyme

insolubility. This can be overcome when the reaction is run in a 0.7 M MOPS buffer set to pH=5.9, where the yield is now 95%, with 19:1 regioselectivity, and 91:9 er. Unfortunately attempts at lowering the catalyst loading with increased temperature only provided product in 30% yield, 19:1 regioselectivity, and 89:11 er.

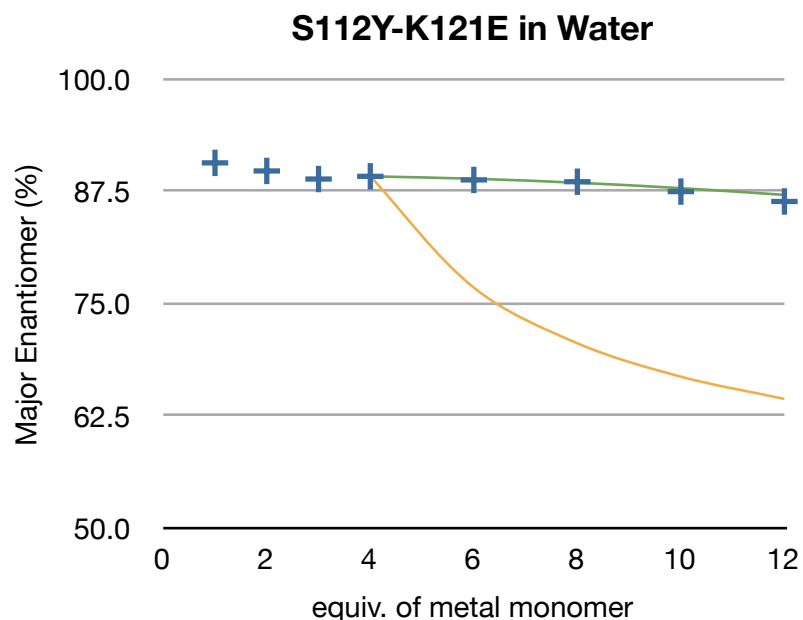
Table 4.12 Screen of Double Mutants

Entry	Mutant	Yield (%)	Regioselectivity	er
1	S112Y-N118K-K121E	15	15:1	91:9
2	S112Y-K121D	30	20:1	90:10
3	S112Y-K121E	80	20:1	90:10
4	S112Y-K121E	95	19:1	91:9
5 ^a	S112Y-K121E	30	19:1	89:11

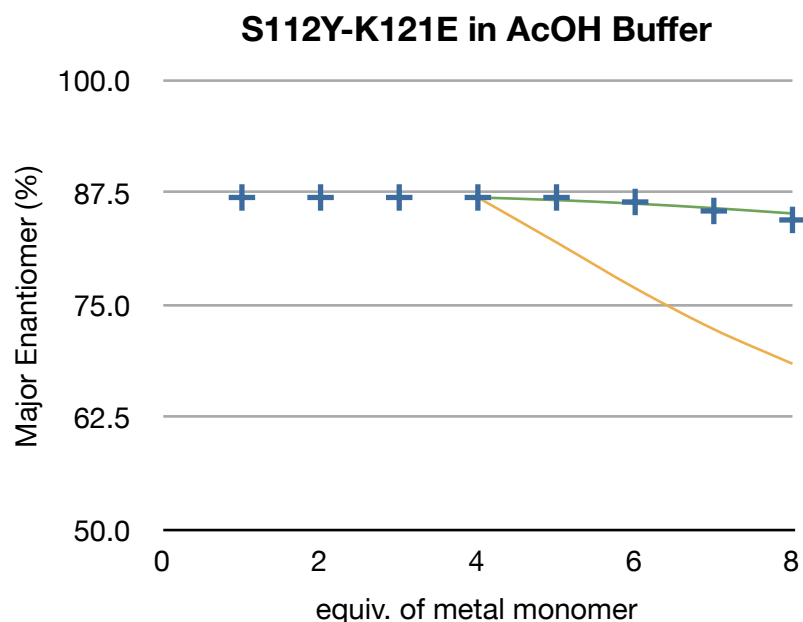
Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv), 0.05 M

^a **481** (0.1 mol %), Mutant (0.066 mol %), 37 °C

We were interested in how this new mutant compared to WT and N118K-K121E. Performing the same kinetic analysis we used for the previous mutants we found that **481** $\subset$ S112Y-K121E to be 34x more reactive than the **481** when the reaction was conducted in water. This information supports that **481** $\subset$ S112Y-K121E is 11x more reactive the **481** $\subset$ WT-SAV, but 3x less reactive that **481** $\subset$ S112Y-K121E (Scheme 4.21). When the same experiments are conducted using acetic acid buffer (pH = 5.9; M = 0.7), the **481** $\subset$ S112Y-K121E is nearly 20x more reactive than the **481** (Scheme 4.22). Under these conditions, **481** $\subset$ S112Y-K121E is 5x more reactive than **481** $\subset$ WT-SAV. By comparison to **481** $\subset$ N118K-K121E, **481** $\subset$ S112Y-K121E is approximately 3x less reactive. These experiments support the relative reactivities of the complexes are the same, regardless of reaction medium.



Scheme 4.21 Rate Analysis of (**481** $\subset$ S112Y-K121E) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ S112Y-K121E) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst



Scheme 4.22 Rate Analysis of (**481** $\subset$ S112Y-K121E) v. **481**. Blue Cross = Observed % Major Enantiomer. Yellow Line = Predicted % Major Enantiomer if (**481** $\subset$ S112Y-K121E) and **481** are equally active. Green Line = Least Mean Squared fit for data points. Divided Box = Streptavidin Tetramer. Green Box = Biotinylated Catalyst

4.2.2 Substrate Scope

With optimal conditions in hand, we explored the scope of the reaction (Table 4.13). A variety of *para*-substituents fare well in the reaction with good levels of enantioselectivity. In all cases the regioselectivity of the alkene insertion was greater than 10:1. There was no obvious trend in yield. Generally, halogen substituents provided product in good yield and good levels of enantioselectivity (Table 4.13, entries 1 and 4). The best enantioselectivity was observed with a *para*-nitro substituent, providing product in 93:7 *er* (Table 4.13, entry 5). *Meta*-substituents provide product in good yield in >10:1 regioselectivity in the C–H activation event, high levels of enantioselectivity (Table 4.13, entry 6-8).

Table 4.13 Amide Scope

Entry	Product	Yield (%)	Regioselectivity	er
1		64	14:1	88:12
2		10	19:1	87:13
3		25	16:1	84:16
4		95	40:1	89:11
5		30	32:1	93:7
6		87	15:1	89:11
7		40	30:1	82:18
8		80	22:1	89:11

Reaction Conditions: Amide (1 equiv), (**316** 1.1 equiv) (0.05 M)

We also explored the scope of tolerated alkenes (Table 4.14). Larger alkyl acrylates fared well in the reaction, providing product in high yield and excellent enantioselectivity (Table 4.14, entry 2). Benzyl acrylates provide product in high yield, but low enantioselectivity (Table 4.14, entry 3). While methyl vinyl ketone gave product in very enantioselectivity, the yield was quite high (Table 4.14, entry 4). Attempting to use styrene under the optimized conditions again failed to afford any enantioselectivity, although the yield was high (Table 4.14, entry 5). We speculated the addition of a heteroatom might

furnish a degree of enantioselectivity. Regrettably, use of 4-vinyl pyridine failed to product any product. Finally, when a 1,1 disubstituted alkene is submitted to the reaction conditions, no desired product is formed (Table 4.14, entry 6).

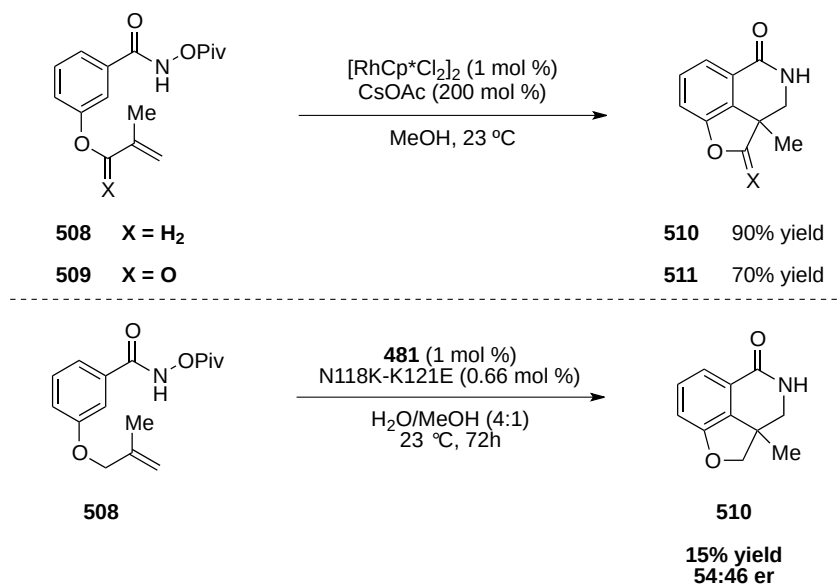
Table 4.14 Alkene Scope

Entry	Product	Yield (%)	Regioselectivity	er
1	 317	95	15:1	91:9
2	 503	70	36:1	90:10
3	 504	61	15:1	73:27
4	 505	95	10:1	56:44
5	 506	95	50:1	50:50
5	 507	0	-	-

Reaction Conditions: **281** (1 equiv), alkenes (1.1 equiv), (0.05 M)

Given the modest levels of selectivity observed using exogenous alkenes, we explored the use of tethered alkenes. In our previous studies we found a variety of different directing groups resulted in the formation of protonation of the 7-membered metallocycle rather than reductive elimination (Chapter 1). We imagined the use of the N–O internal oxidant might present the possibility for reductive elimination. Indeed, when an olefin is tethered to the *meta*-position, a tricyclic core, bearing a quaternary carbon, is formed in excellent yield using the conditions pioneered by Fagnou (Scheme 4.23). When amide **508** is submitted to the artificial metalloenzyme conditions using mutant N118K-K121E, the desired product is

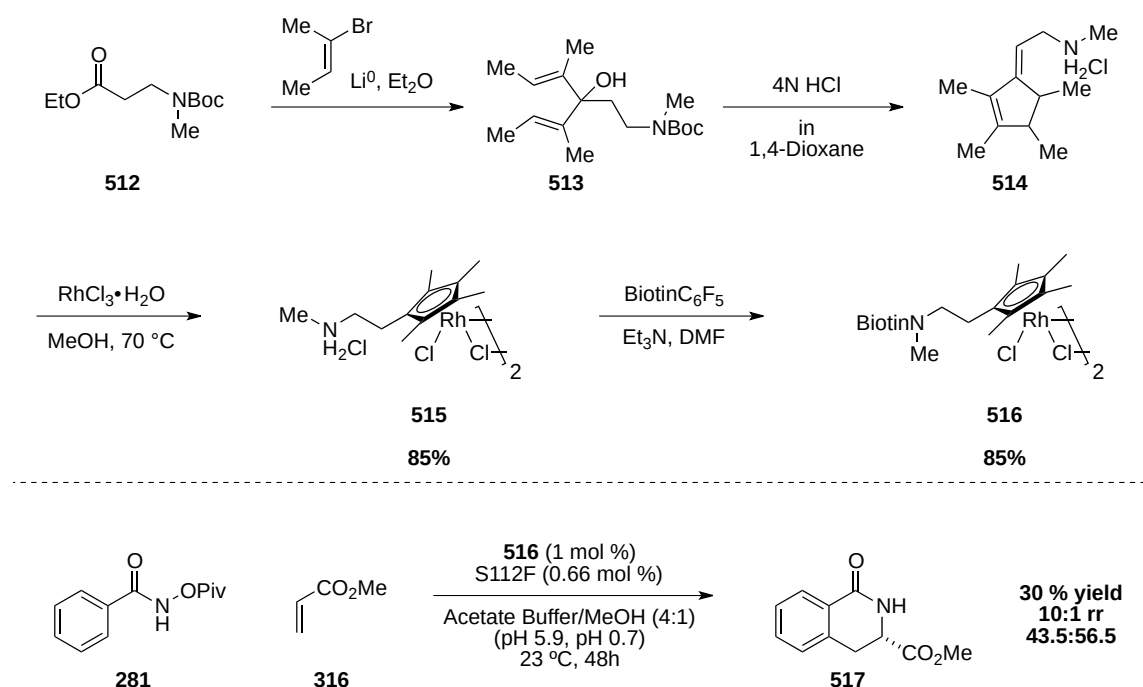
isolated in 15% yield with 54:46 *er*. Unfortunately all further attempts to optimize this reaction failed to produce increased yields.



Scheme 4.23 Impact of Tethered Alkenes

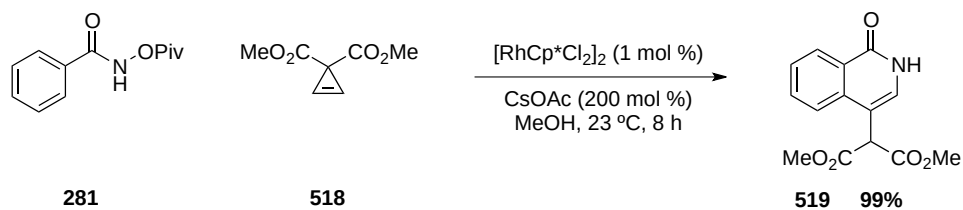
Inspired by these efforts, we were curious if the enzyme could control the regioselectivity of the C–H activation event when substituent is placed at the *meta*-position. Unfortunately, after a wide swath of mutants was tested, we found the metalloenzyme does not have a large impact on the regioselectivity of the C–H activation.

The previous studies by Ward suggested that modifying the linker might allow access to the opposite enantiomer. We speculated that adding an alkyl group to the nitrogen of the amide might modify the position of the complex and provide access to the opposite enantiomer. Using complex **516** with mutant S112F, we were pleased to find the desired product could be accessed in 30% yield and 56.5:43.5 *er* (Scheme 4.24).



Scheme 4.24 Alkylated Amide Tethers

We were curious how cyclopropenes would fare in the reaction. We initially explored the use of cyclopropene **518**, bearing two ester groups. Unfortunately under enzyme free conditions the resulting product opens to form an isoquinolone adduct **519** in excellent yield. Interestingly, this product provides isoquinolones with the opposite regioselectivity typically observed using terminal alkynes (Scheme 4.25).¹

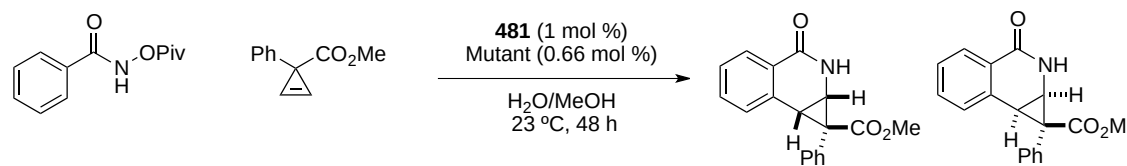


Scheme 4.25 Activated Cyclopropanes

When one of the ester groups is replaced with a phenyl moiety, the unwanted opening reaction is eliminated and the desired cyclized product is isolated in 80% yield as a 1.4:1 ratio of diastereomers. The diastereomers are presumably derived from a non-selectivity migratory insertion across the two faces to the cyclopropene. When this reaction is conducted using **481** $\subset$ N118K-K121E, the yield remains, with

>10:1 regioselectivity and 89:11 *er* (Table 4.15, entry 2). Moving to **481** $\subset$ S112Y-K121E, the yield and regioselectivity remain high, but the *er* decreases to 83:11 (Table 4.15, entry 3).

Table 4.15 Metalloenzyme Catalyzed Coupling with Cyclopropenes



Entry	Mutant	Regioselectivity	Yield (%)	<i>er</i>
1	-	1.4:1	80	50:50
2	N118K-K121E	10:1	80	89:11
3	S112Y-K121E	10:1	60	83:11

Reaction Conditions: **281** (1 equiv), **520** (1.1 equiv), 0.5 M

4.2.3 Calculations and New Ligand Design

A crystal structure of **481** $\subset$ N118K-K121D was obtained to elucidate more about the active site of the enzyme. The mutant N118K-K121D, expressed by myself, was crystallized by Tillmann Heinisch, a coworker in the Ward group at the University of Basel, and soaked in a solution of **481** to obtain the desired crystalline complex, which was collected and solved by Tillman Heinisch. Upon solving the structure, good resolution was found for the enzyme and rhodium center, but the location of the ligands around the metal were nebulous. Maurus Schmid, a computational chemistry graduate student in the Ward Group, generated two enantiomers of the axially chiral rhodium metallocycle, and performed energy minimization after docking these structures into the crystal structure. After comparing the two enantiomers of the metallocycle in the enzyme, we found the distance between the acetate residue and the open coordination site was quite different. In structure **A** the distance is 2.99 angstroms, while structure **B** has a difference of 4.90 angstroms (Figure 4.5). If alkene migratory insertion occurs with the steric bulk pointed away from Cp* ligand, then the major enantiomer observed in our reaction is derived from structure **A**. The calculations suggest the location of the metal is partially controlled by an interaction between the tyrosine residue and the Cp* ligand.

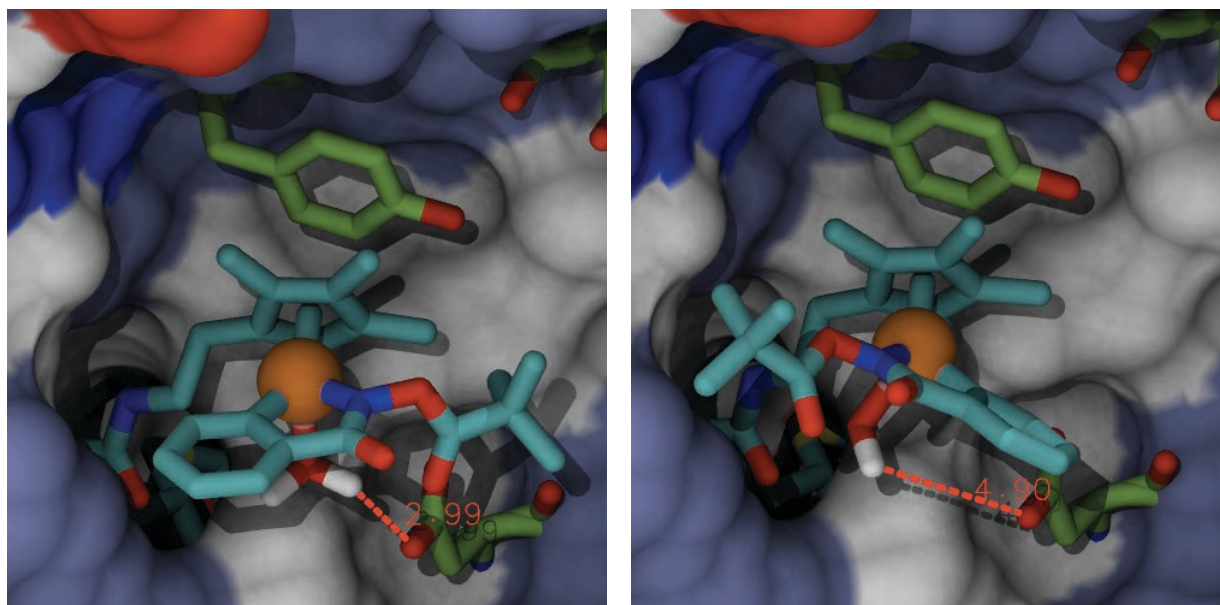
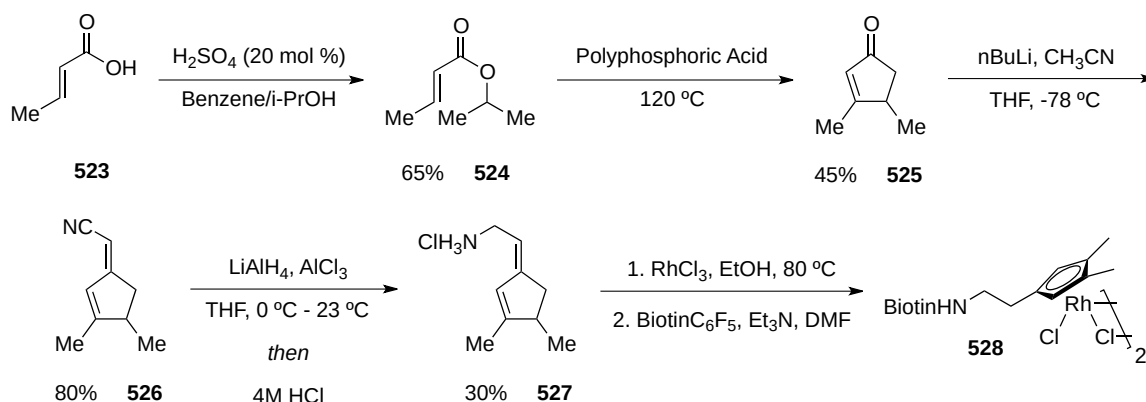


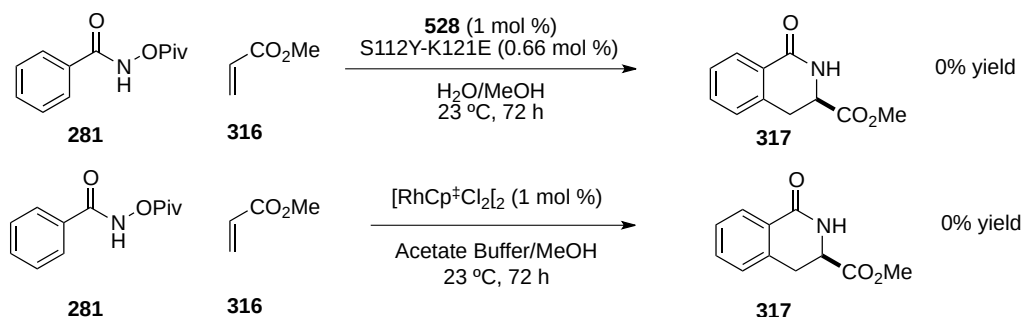
Figure 4.5 Calculations for Acetate Distance in **481** $\subset$ N118K-K121D. Left Figure (Structure A); Right Figure (Structure B)

If we assume that tyrosine is electron rich, and Cp* is electron poor, then a less electron rich Cp ligand would strengthen this interaction and potentially give enhanced enantioselectivity. As such, a *di*-methyl Cp ligand was prepared. This ligand was can be prepared in 4 steps from crotonic acid **523** and isopropanol. After 3,4 di-methyl cyclopentadienone **525** was accessed, the same procedure was used to afford ammonium complex **527** in good yield. The biotinylation was achieved using 3 equivalents of Et₃N rather than 20 equivalents to preclude cyclization of the amine on to rhodium. When the biotinylated metal complex **528** was complexed with S112Y-K121E, no product formation was observed. Using the same complex in the absence of enzyme, but in the presence of an acetate buffer also failed to afford the desired product.

Ligand Synthesis



Reactions



Scheme 4.26 Impact of Less Electron-Rich Ligands

We speculated the Cp ligand was not electron rich enough to facilitate the reaction. Attempting the same reaction with less electron rich $[\text{RhCp}^+\text{Cl}_2]_2$ ligands failed to provide appreciable amounts of product (Scheme 4.26). In our previous work we found the $\text{Cp}^\dagger$ ligand works well with non-polarized olefins (Chapter 2). It is possible that this complex has a less electron rich metal center and is not able to undergo migratory insertion with electron poor olefins.

4.3 Isoquinolone Synthesis

We were curious if alkynes would work in the presence of the metalloenzyme to potentially control regioselectivity. Our studies began by attempting coupling 1-phenyl-1-propene **50** with benzhydroxamic acid **281** to provide isoquinolone **529**. Initial attempts using the **481** $\subset$ WT SAV complex with acetate buffer failed to provide the desired product (Table 4.16, entry 1). Even elevated temperatures and prolonged reaction times failed to furnish the desired product. Interestingly, using **481** $\subset$ N118K-K121E

provided isoquinolone in 92% yield. Upon removal of acetate buffer the yield remained high in 24 hours (Table 4.16).

Table 4.16 Metalloenzyme Catalyzed Synthesis of Isoquinolones

Entry	Mutant	Buffer	Regioselectivity	Yield (%)
1	WT	AcOH (pH=5.9, 0.7M)	-	0%
2	S112Y	AcOH (pH=5.9, 0.7M)	-	0%
3	N118K-K121E	AcOH (pH=5.9, 0.7M)	50:1	92%
4	N118K-K121E	H ₂ O	50:1	92%

Reaction Conditions: **281** (1 equiv), **50** (1.1 equiv), 0.05 M

We wanted to elucidate the need for an internal acetate residue. In previous studies in the synthesis of isoquinolones, we found evidence the alkyne had an inhibitory impact on the reaction (Chapter 1). The kinetic studies with dihydroisoquinolones suggested the hydrophobic nature of the active site has a high affinity for hydrophobic substrates. If the alkyne has a high affinity for the active site, the local concentration of alkyne would be quite high and could potentially shut down reactivity. Using **481** = N118K-K121E, we varied the concentration of alkyne and found the reaction yield was decreased at increased reaction concentrations, suggesting that an inhibitory effect might be in play (Figure 4.27).

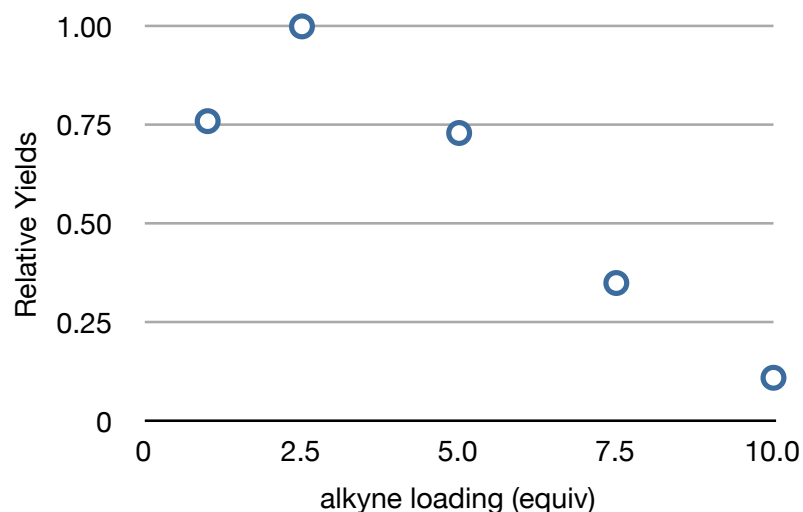
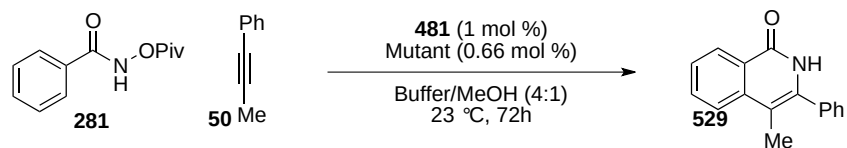


Figure 4.27 Impact of Alkyne Loading on Reaction Yield

The role of the acetate residue can be attributed to its ability to occupy coordination sites on the metal. With one site occupied, the bi-dentate amide can occupy the other two sites and create a saturated metal center. When the amide goes from bi-dentate to mono-dentate, a free coordination site is opened to facilitate C–H activation. In the absence of the acetate residue the alkyne can fill the free coordination site and shut down reactivity. Based on this hypothesis monodentate ligand should also be ineffective. Indeed, use of methyl benzamides or oximes failed to provide any of our desired products (Figure 4.6).

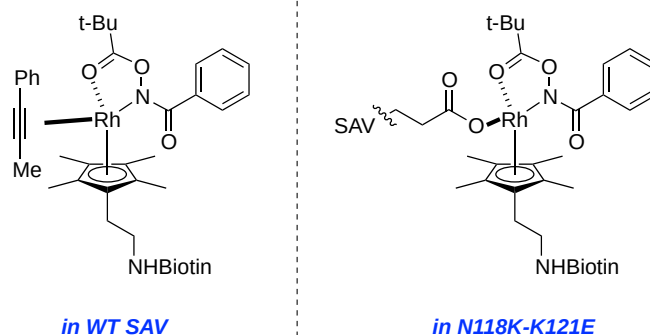


Figure 4.6 Hypothesis of Carboxylate Role in the Isoquinolone Synthesis

4.4 Attempts with Cell-Free Lysate

We attempted to catalyze the synthesis of dihydroisoquinoline **317** using unpurified protein. The benefit of this approach is mutants can be screened in 8 days rather than the 21 days required under our current expression/purification system. Initial attempts using the WT-SAV in a 4:1 mixture of Acetate Buffer (pH = 4.7, Concentration = 0.7 M) failed to provide product (Table 4.17, entry 1). To preclude inhibition by other proteins, we heated a solution of the cell free lysate to 70 °C at 10 minutes; unfortunately this failed to provide any desired product (Table 4.17, entry 2). Previous studies by Dr. Yvonne Wilson in Prof. Thomas R. Wards group found that glutathione had an inhibitory impact on SAV-based transfer-hydrogenation reactions. Fortunately, addition of azodicarbonamide allowed for increased yields to be observed. Unfortunately, addition of excess azodicarbonamide to our reaction failed to provide any desired product (Table 4.17, entry 3). Finally, addition of excess methyl acrylate as an electrophile to react with free thiols did not result in any product formation (Table 4.17, entry 4). Given that three coordination sites are required for reactivity, we speculate the cell free lysate contains a compound that is coordinating to the metal and inhibiting catalysis.

Table 4.17 Screen of Cell Free Lysate

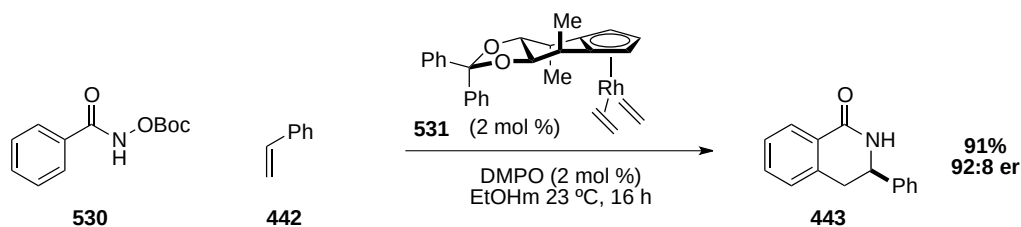
Entry	Modification to Standard Conditions	Yield (%)
1	none	0
2	Preheat Aqueous Solution with Cell Free Lysate and Remove Solid Precipitate	0
3	Add Azodicarbonamide (10 equiv)	0
4	Use Excess 316 (50 equiv)	0

Reaction Conditions: **281** (1 equiv), **316** (1.1 equiv), 0.05 M. Reaction ran using WT-SAV Cell Free Lysate

4.5 Concurrent Work

While our research was in progress, Cramer and coworkers investigated the use of chiral cyclopentadienyl ligands for the Rh(III)-catalyzed synthesis of isoquinolones (Scheme 4.28). Cramer used a tartrate-based ligand to obtain excellent levels of enantioselectivity with sterically bulky alkenes. Our report⁶⁴ and Cramer's⁶⁵ report were published back-to-back in *Science*.

• Cramer

**Scheme 4.28** Concurrent Work

4.6 Conclusion

In conclusion, our group in collaboration with Prof. Thomas R. Ward at the University of Basel have developed an artificial metalloenzyme capable of catalyzing Rh(III)-mediated C–H activation processes. This catalyst has been showcased in the enantioselective synthesis of dihydroisoquinolones. During our studies we found the introduction of aspartic or glutamic acid into the active site resulted in a more active complex. This interaction is also capable of insulating the reactivity of the rhodium complex in the synthesis of isoquinolones.

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Chapter 5

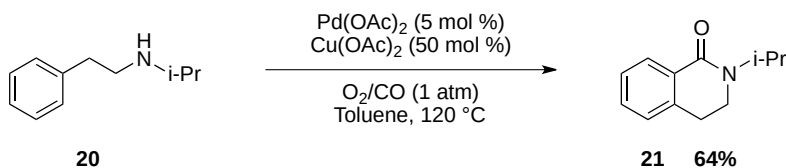
Coupling Benzamides and Diazo Compounds To Form γ -Lactams via Rhodium(III)-Catalyzed C–H Activation

5.1 Introduction

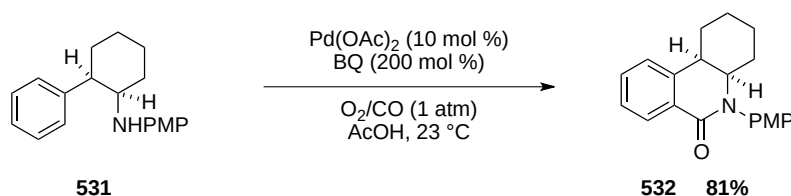
Our studies into the use of artificial metalloenzymes as a catalyst scaffold for rhodium(III) C–H activation led us to consider other nitrogen containing heterocycles which have a stereogenic carbon.¹ To the best of our knowledge, dihydroisoquinolone is the only heterocyclic motif accessible using Rh(III)-catalyzed C–H activation that contains a stereogenic center.^{2,3} We focused our efforts toward the development of a method to access γ -lactams from benzamides and diazo esters, where the diazo compound acts as a 1-carbon coupling partner.

Carbonylation of C–H bonds, catalyzed by electrophilic metals, represents the vast majority of coupling reactions involving 1-carbon components (Scheme 5.1). Pioneering work by Orito and coworkers found homo-benzyl amines can be coupled with CO under Pd(II) catalysis at elevated temperatures to provide lactams in high yield.^{4,5} Gaunt found similar products can be accessed under ambient conditions with a stoichiometric oxidant.⁶ Yu and coworkers found carbonylation reactions to be an effective method for accessing anhydrides, which quickly decompose to di-carboxylic acid.⁷ Only in rare cases were they able to access the intermediate anhydride. When the carboxylic acid directing group is changed to an electron-deficient amide, carbonylation of sp^3 C–H bonds is possible, providing access to phthalimides in excellent yield.⁸ Furthermore, use of a tertiary alcohol directing group provides lactones when a Pd(II) catalyst bearing an amino acid ligand is employed.⁹

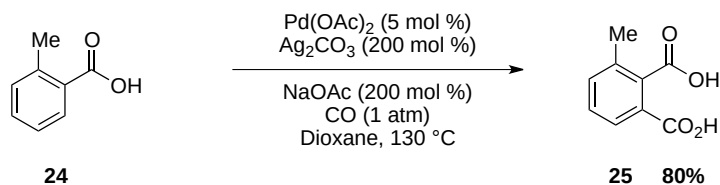
•Orito (2004)



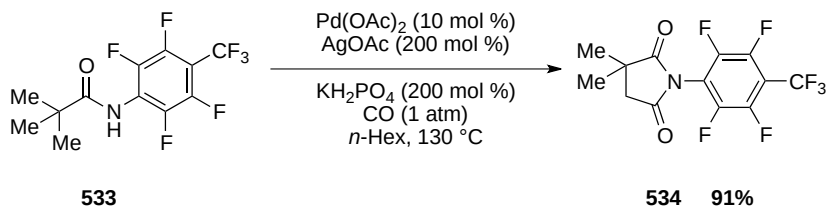
•Gaunt (2011)



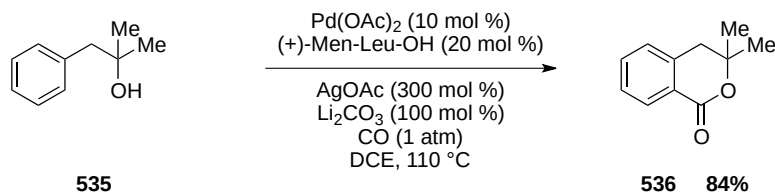
•Yu (2008)



•Yu (2010)



•Yu (2011)

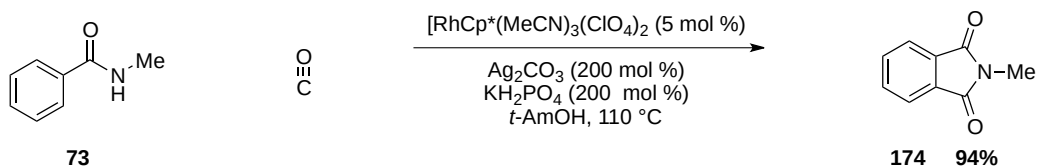


Scheme 5.1 Pd(II)-Catalyzed Carbonylation Reactions

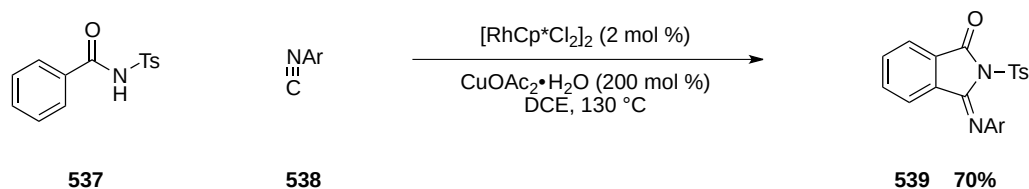
Examples of C–H carbonylation under the aegis of Rh(III) catalysts are rare. Previously, we found amides could be coupled with carbon monoxide providing phthalimides in good yield (Scheme 5.2).¹⁰ Unfortunately, this approach could not be expanded to other directing groups. Concurrent work by Zhu and Falck found isocyanides to be competent coupling partners in an analogous reaction (Scheme 5.2).¹¹

Mechanistically these reactions are understood to occur via a similar mechanism (Scheme 5.2). Metallation of the amide provides the rhodium amidate **166**. This intermediate can undergo an acetate facilitated CMD C–H activation to generate a 5-membered rhodacycle **540**, presumably similar to the metallacycle proposed in our isoquinolone synthesis. In previous studies 1,2-migratory insertion across a π -component (alkene and alkyne) can provide a 7-membered metallocycle. In this case the 1,1-migratory insertion occurs across carbon monoxide or an isocyanide to furnish a 6-membered metallacycle. Upon reductive elimination the desired product is formed along with a Rh(I) species that can be reoxidized with a stoichiometric oxidant to complete the catalytic cycle.

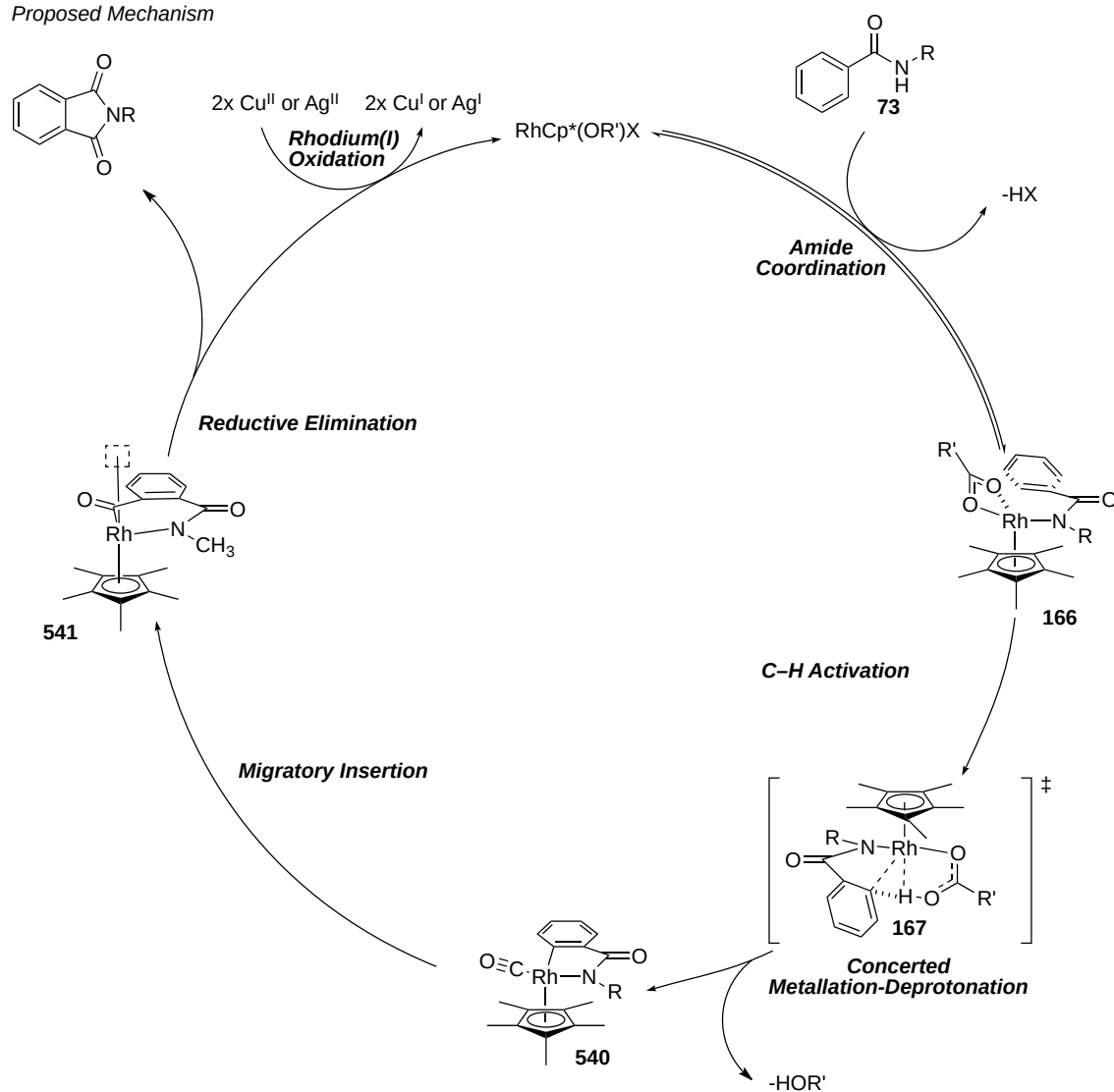
• **Rovis (2011)**



• **Zhu and Falck (2011)**



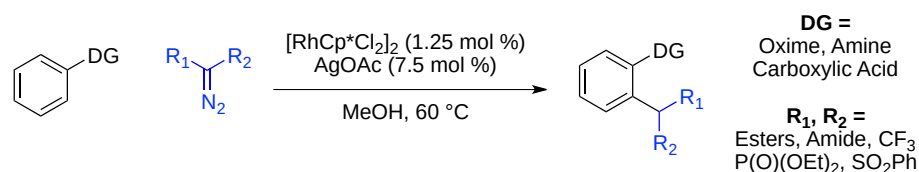
Proposed Mechanism



Scheme 5.2 Rh(III)-Catalyzed Coupling with 1-carbon Components

We were interested in expanding this work to encompass other one-carbon components with carbenic character. Recently Yu and coworkers found acceptor/acceptor diazo esters could be coupled with various directing group containing arenes to provide *o*-substituted products in high yield (Scheme 5.3).¹² Directing groups tolerated using this method include: oximes ethers, 2° amines, and carboxylic acids. It is proposed this mechanism proceeds via C–H activation to generate a 5-membered rhodacycle, which upon de-nitrogenative metallocarbenoid formation and migratory insertion forms a 6-membered ring. This intermediate can undergo protonation to generate the desired product and a Rh(III) complex which can re-enter the catalytic cycle.

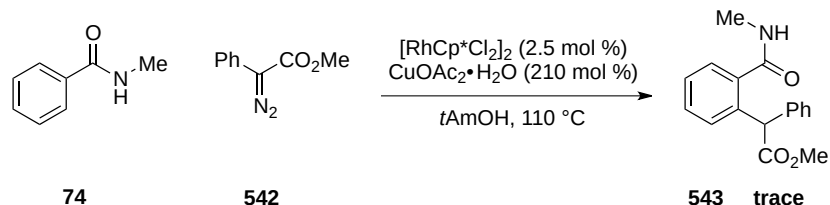
• Yu (2012)



Scheme 5.3 Yu's *ortho*- Functionalization with Diazo Compounds

5.2 Results

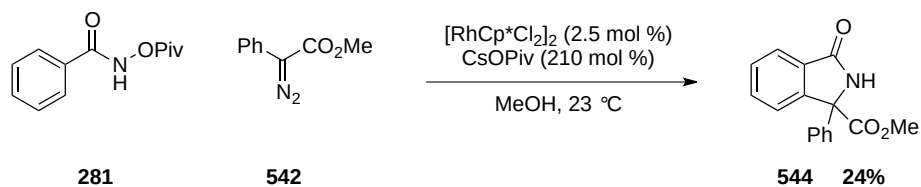
Our goal was take a simple amide starting material and a donor/acceptor diazo-compound, which in the presence of a Rh(III) catalyst and an oxidant would provide the desire γ -lactam. We began our studies using N-methylbenzamide **74** and α -phenyl methyl diazo ester **542** with [RhCp*Cl₂]₂ and stoichiometric Cu(OAc)₂•H₂O in *t*-AmOH at 110 °C, but unfortunately these conditions did not provide any desired product (Scheme 5.4). An examination of the crude reaction mixture revealed decomposition of the diazo ester and a small amount of the undesired *o*-functionalized product **543**. This experiment pointed toward a potential problem with our system. Copper salts are known to decompose diazo esters at elevated temperatures, which will make the development of this reaction difficult. Additionally, the absence of a cyclized product suggests the alkyl rhodium complex rapidly undergoes protonation, similar to our observations with the tethered alkenes (Chapter 1).



Scheme 5.4 Initial Attempt with a Mono-dentate Amide

In the examples described by Yu and coworkers, monodentate directing groups all universally result in protonation. Fagnou and Glorius found bidentate directing groups preclude β -hydride elimination in the synthesis of dihydroisoquinolones.^{2,3} We imagined that this type of directing group could stabilize the resulting metallocycle and prevent protonation. Furthermore, using a substrate containing an internal oxidant would eliminate the need for an exogenous copper based oxidant, which should diminish degradation of the diazoester substrate.

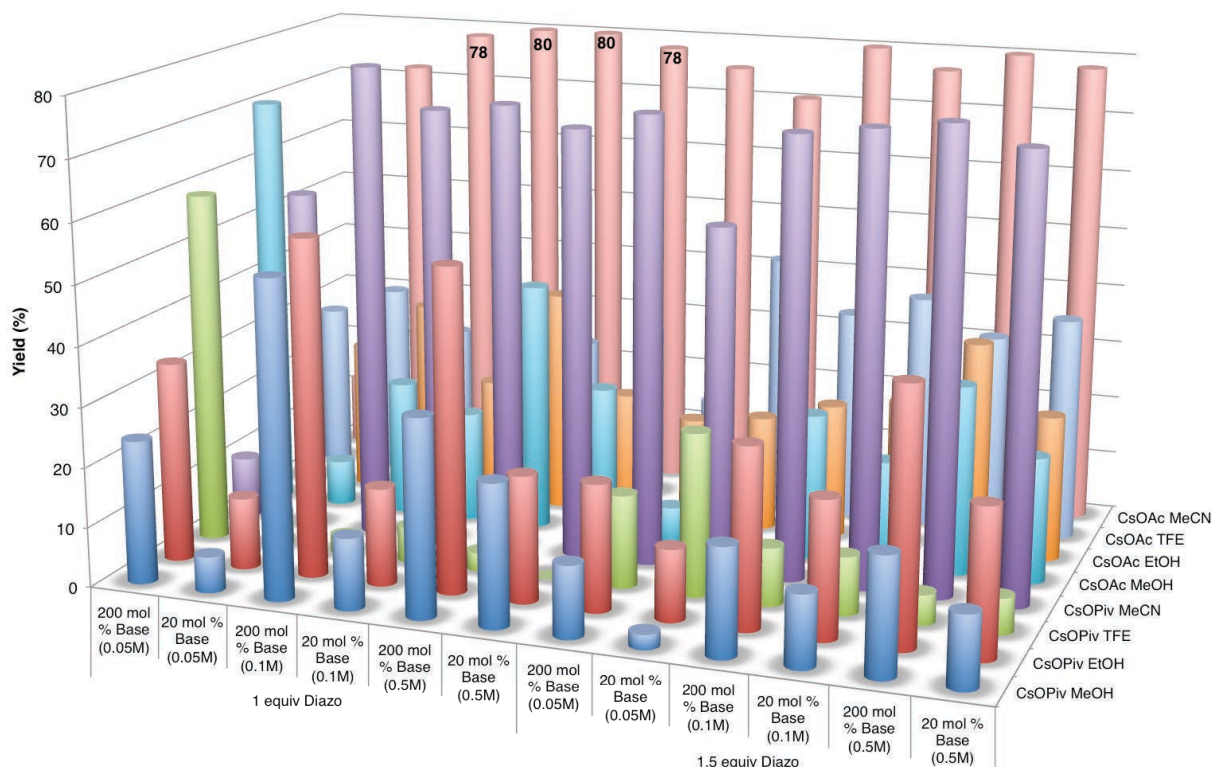
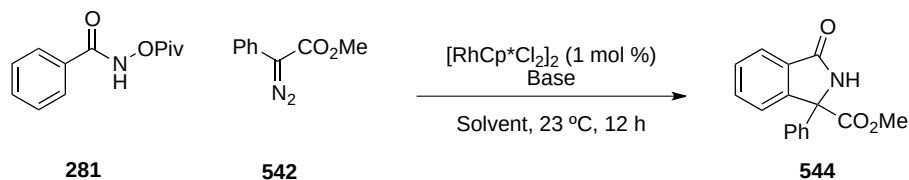
Initial studies using ethyl diazo acetate resulted in exclusive dimerization of the ester. This unwanted pathway was avoided when donor/acceptor diazoesters were used. We were pleased to find when *O*-pivaloylbenzhydroxamic acid **281** is stirred with α -phenyl methyl diazo acetate **542** in MeOH in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ and stoichiometric CsOPiv at 23°C , the desired γ -lactam product **544** is observed in 24% yield (Scheme 5.5). The remainder of the mass balance constituted methanolysis of amide **281**.



Scheme 5.5 Initial Attempt with a Benzhydroxamic Acid

In lieu of typical low-through put reaction optimization, this reaction was optimized using a 96-well reaction vessel (Scheme 5.6). In these reactions the catalyst and temperature were kept constant while the base, solvent, and stoichiometry were varied. MeOH, EtOH, $\text{CF}_3\text{CH}_2\text{OH}$, and MeCN were screened as solvents at different concentrations. CsOAc and CsOPiv were screened as bases with varying stoichiometries. Finally two different amounts of diazo ester were screened. In the presence of an internal

standard, the desired product formation was quantified using HPLC (Scheme 5.6). Universally MeCN gave enhanced yield by comparison to polar protic solvents. CsOAc provided product in slightly enhanced yield by comparison to CsOPiv. Furthermore, there was no benefit to using super stoichiometric amounts of base, as 20 mol % gave high yields. We found that diazo ester stoichiometry did not have an impact on the yield. As determined by this screen our ideal conditions were amide **281** (1 equiv), diazo compound **542** (1.1 equiv), with CsOAc (20 mol %) and $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol %) in MeCN (0.1 M) for 3 hour provides product in 81% yield. The catalyst loading can be decreased to 1 mol % with no loss in yield. We were further pleased to find the catalyst loading can be further decreased to 0.4 mol % when the reaction is conducted on gram scale, with the product purified via recrystallation in 75% yield.



Scheme 5.6 96-Well Optimization

Ideal conditions in hand, we explored a variety of amide substitution patterns (Table 5.1). A wide variety of *p*-substituted amides furnished the desired product in high yield. Specifically, halogens, ethers, and nitro-groups worked well in the reaction (Table 5.1, entries 2, 3, and 5). The type of substituent at the *m*-position played an important role in the regioselectivity of the C–H activation event. When *m*-methyl benzhydroxamic acid **309** was used, C–H activation occurred exclusively para to the methyl group, presumably to avoid disfavored steric interactions (Table 5.1, entry 8). When a methoxy group was placed at the *meta* position, however, a 1.1:1 ratio of C–H activation regioisomers was observed (Table 5.1, entry 7). A 2:1 ratio of C–H activation regioisomers was observed when 3-naphthyl benzamide was used. (Table 5.1, entry 9). In contrast, the electron donating tetrahydronaphthyl benzhydroxamic acid gave the desired

product as a single regioisomer, again with activation occurring at the less hindered position (Table 5.1, entry 10). We attribute the decrease in regioselectivity in selected case to be an artifact of the increased acidity of the C–H bond *ortho*- to the substituent. Increasing the acidity of the C–H bond overpowers the steric bias of the C–H activation, giving a mixture of *ortho*- and *para*- products. Highly electron rich, Gallic acid-derived amide provided at elevated temperatures (Table 5.1, entries 11). Finally, thiophene based amides provide product in good yield (Table 5.1, entry 12). Unfortunately, alkene based amides failed to provide any desired product.

Table 5.1 Amide Scope

$\text{R-Ph-CO-NH-OPiv} + \text{Ph-CO}_2\text{Me-N}_2 \xrightarrow[\text{CH}_3\text{CN, 23 } ^\circ\text{C}]{[\text{RhCp}^*\text{Cl}_2]_2 (1 \text{ mol } \%), \text{CsOAc (20 mol \%)}} \text{R-Ph-CO-NH-Ph-CO}_2\text{Me}$

281, 306, 308-310, 545-551 **542** **544, 552-562**

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		81 %	7a,b		74%
2		84 %	8		97%
3		99 %	9 ^c		68 %
4		79%	10		94%
5		88%	11 ^a		87%
6		74 %	12 ^a		50 %

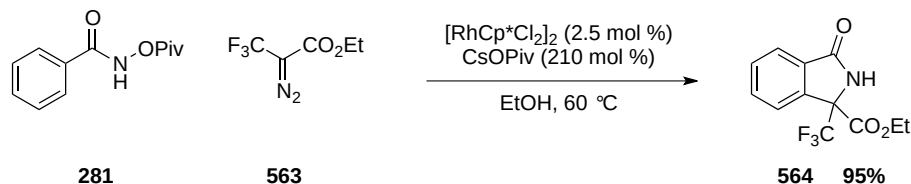
Reaction Conditions: Amide (1 equiv), **542** (1.2 equiv), 0.1M

^a Reaction Conducted at 60 °C

^b Isolated in a 1.1:1 ratio of regioisomers

^c Isolated in a 2:1 ratio of regioisomers

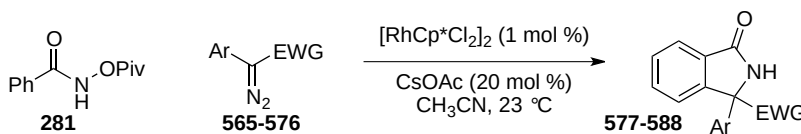
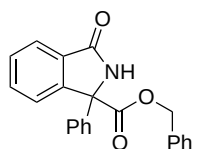
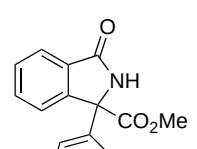
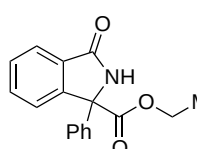
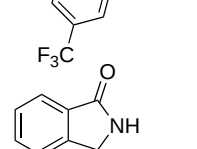
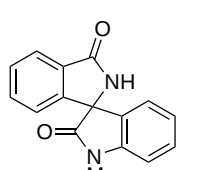
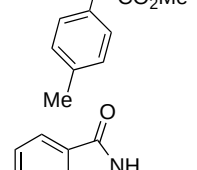
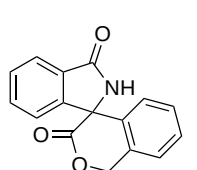
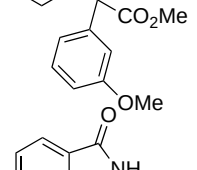
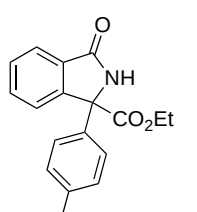
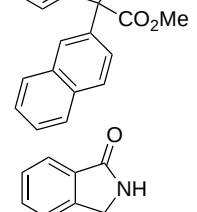
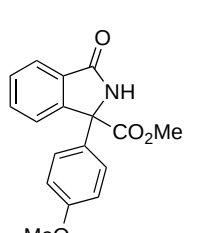
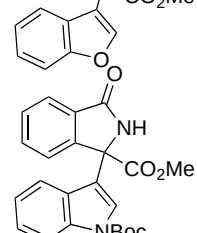
We were curious if acceptor/acceptor diazo esters would provide the desired product in the reaction. Since we were interesting in accessing heterocycles containing stereogenic carbons, an unsymmetrical diazo ester was prepared. When benzhydroxamic acid **281** and trifluoromethyl diazo ester **563** were reacted under our current condition, very little product was formed. Thankfully, changing the solvent to EtOH in the presence of super-stoichiometric CsOAc provided the desired lactam **564** in 95% yield (Scheme 5.7).



Scheme 5.7 Acceptor/Acceptor Diazo Compound

With the help of a junior graduate student, Kyle E. Ruhl, we found a broad range of donor/acceptor diazo compounds are tolerated with reasonable scope. A variety of ester substituents are tolerated in good yield (Table 5.2, entries 1 and 2). Cyclic diazo esters and amides gave spiro compounds in high yields (Table 5.2, entries 3 and 4). Unfortunately, diazo compounds bearing an alkene underwent cyclization to provide a pyrazole rather than forming the desired product.¹³ Substitution on the aromatic ring is well tolerated. While electron-poor amides provide the desired product within 3 hours under the standard reaction conditions (Table 5.2, entries 2-6), electron-rich substrates were far more sluggish and required elevated temperatures and prolonged reaction times (Table 5.2, entries 7 and 11). We were pleased to find that electron rich heteroaryl diazo esters also provided the corresponding products, albeit in lower yields (Table 5.2, entries 11 and 12).

Table 5.2 Donor/Acceptor Diazo Compound Scope

					
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		577 95 %	7		583 97%
2		578 96 %	8a		584 84%
3		579 64 %	9		585 71 %
4		580 80%	10		586 98%
5		581 94%	11a		587 37%
6a		582 86 %	12a		588 27 %

Reaction Conditions: **281** (1 equiv), Diazo (1.2 equiv), 0.1M

^a Reaction Conducted at 60 °C

Attempts to broaden the scope of the electron-withdrawing group to amides and phosphonates provided product in low yield. In contrast, 1-phenyl-2,2,2-trifluoro diazo- ethane **589**, as described by Davies and

co-workers,¹⁴ delivered the desired trifluoro-lactam adducts in excellent yield under ambient conditions (Figure 5.1). Electron-withdrawing groups on the aromatic ring provided product in high yields and reaction time under 4 hours (**596**, **599**, **600**). Consistent with our previous observation, electron-rich aromatic groups provided substantially lower product yields even at high temperatures (**597**).

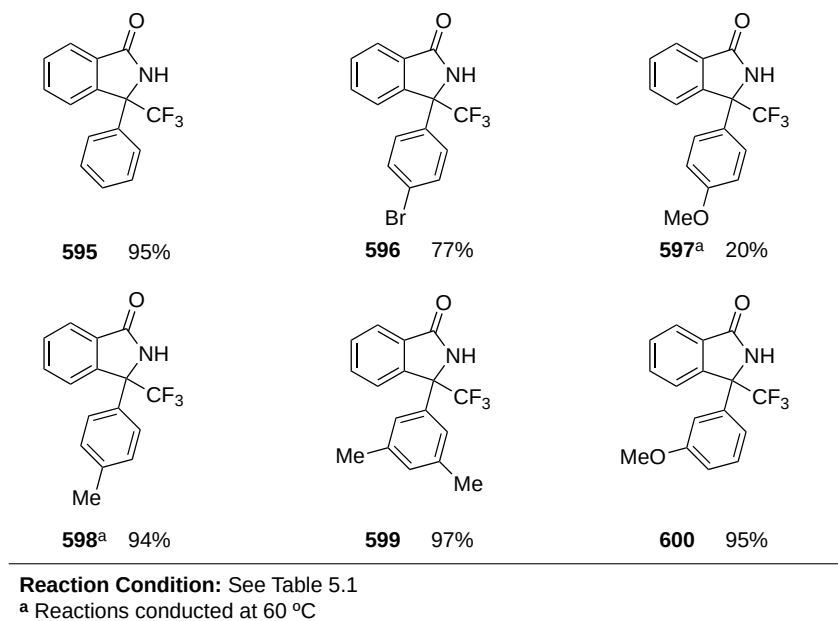


Figure 5.1 Trifluoromethyl Substituted Diazo Scope

Given the volatility of the trifluoromethyl substituted diazo-compounds, we explored *in situ* generation of the diazo compound from tosyl hydrazones (Table 5.3). When generating the diazo for isolation, Bamford-Stevens conditions were used resulting in a red solution when the reaction was complete. Under these conditions water was generated, an additive known not to inhibit the reaction; consequently we explored similar conditions. When all the reactants were mixed in acetonitrile or MeOH with addition of 2 equivalents of KOH, the reaction turned deep red, but no desired product was observed (Table 5.3, entries 1 and 3). Increasing the reaction temperature to 60 °C again did not furnish any desired product (Table 5.3, entries 2 and 4). Exchanging the base to NaOMe failed to afford the desired product in MeOH or CH₃CN (Table 5.3, entries 5 and 6). In all cases, the reactions turned deep red, but only starting material was observed. TLC of reaction confirmed the desired diazo was generated, but no product was formed. We speculated that a small amount of the hydrazone was coordinating to the rhodium catalyst

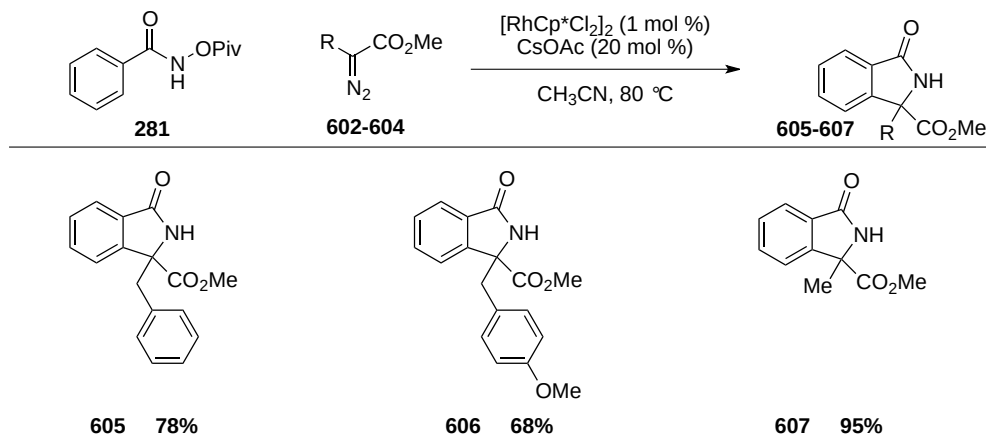
and inhibiting its ability to catalyze the reaction. Consequently, we tested if delayed addition of $[\text{RhCp}^*\text{Cl}_2]_2$, CsOAc, and **281** would result in product formation. Unfortunately at elevated temperatures delayed addition failed to provide product. Our current hypothesis is the *p*-methyl sulfinate, generated upon formation of the desired diazo, is coordinating to the catalyst and rendering it ineffective. Indeed, Jones found that sulfinates are strong ligands for RhCp^* complexes, which can only be removed with HCl.¹⁵

Table 5.3 Attempts for *in situ* Diazo Generation

Entry	Base	Solvent	Temperature (°C)	Yield (%)
1	KOH (2 equiv)	CH ₃ CN	23	0
2	KOH (2 equiv)	CH ₃ CN	60	0
3	KOH (2 equiv)	MeOH	23	0
4	KOH (2 equiv)	MeOH	60	0
5	NaOMe (2 equiv)	MeOH	60	0
6	NaOMe (2 equiv)	CH ₃ CN	60	0
7 ^a	KOH (2 equiv)	CH ₃ CN	60	0
8 ^a	KOH (2 equiv)	MeOH	60	0

Reaction Conditions: **281** (1 equiv), **601** (1.1 equiv), 0.1 M
^a **281**, $[\text{RhCp}^*\text{Cl}_2]_2$, and CsOAc were added after 1 hour

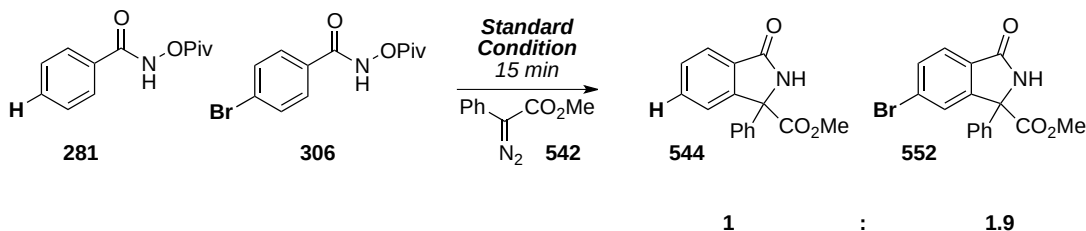
After additional optimization, simple acceptor diazo compounds are incorporated to provide lactams at elevated temperatures (Scheme 5.8). Kyle and I found that electron rich and electron poor benzyl substitution provide product in good yield. Simply alkyl substitution also gives product in good yield.



Scheme 5.8 Acceptor Diazo Scope

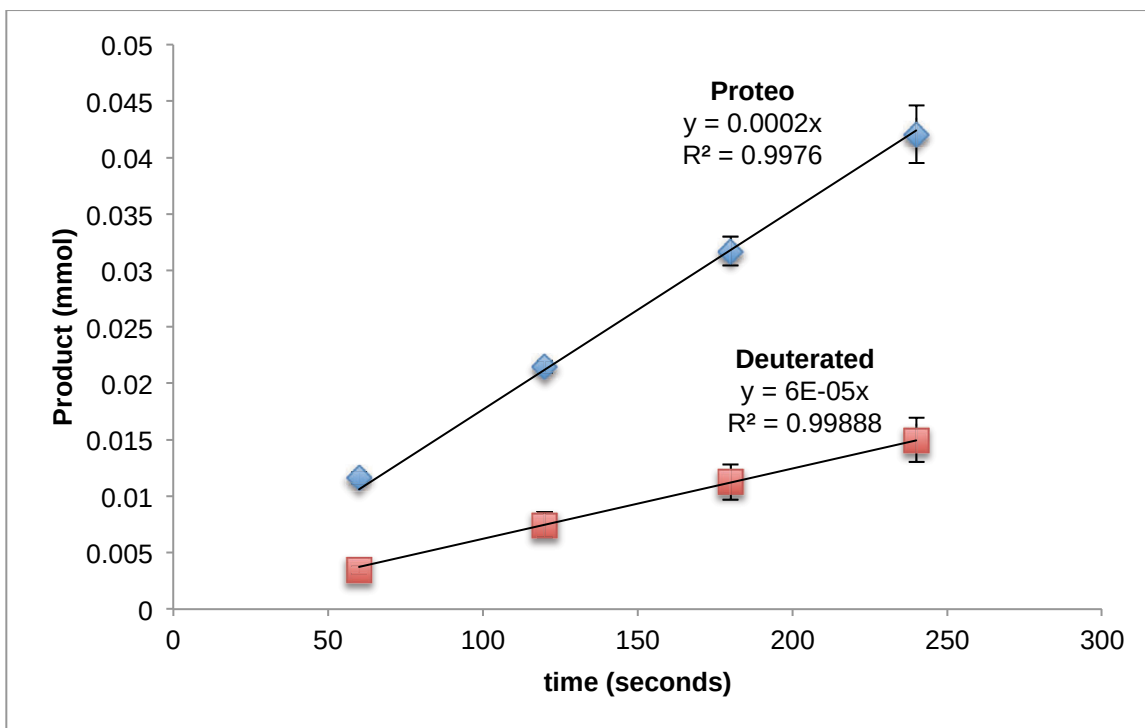
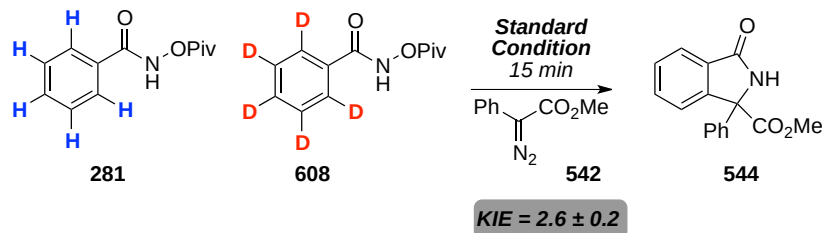
5.3 Mechanistic Experiments

Competition experiments were used to determine the electronic preference of the reaction. When p-bromobenzamide **306** was run in competition with the unsubstituted amide **281** the reaction favors the electron deficient amide **552** in a 1.9:1 ratio (Scheme 5.9). This experiment suggests that C–H activation favors the more acid C–H bond indicative of a CMD C–H activation.



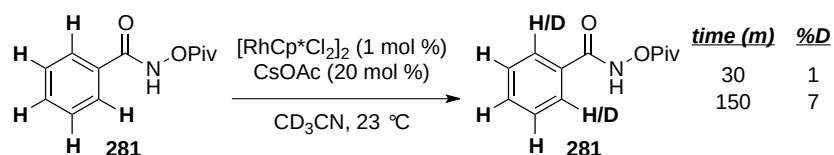
Scheme 5.9 Amide Competition Experiment

An initial rate kinetic isotope study revealed a KIE value of 2.6 ± 0.2 (Scheme 5.10). Together these studies suggest C–H activation occurs via a concerted-metalation deprotonation (CMD) mechanism, and the C–H activation does not proceed through a Wheland intermediate. These experiments are consistent with the observation that reactions involving substrates bearing more electron donating groups are sluggish.



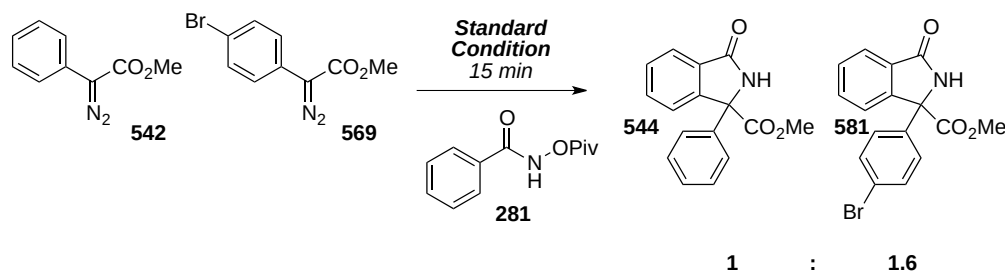
Scheme 5.10 Initial Rate KIE Study

Removing the diazo compound and running the reaction in the presence of MeCN-d₃ allowed us to determine the reversibility of the C–H activation event (Scheme 5.11). After 15 min, <1% deuterium incorporation at the ortho positions was observed, as determined by ¹H NMR analysis. After 150 min, the degree of deuterium incorporation increased to 7%. These results suggest C–H activation is largely irreversible on the time scale of the reaction, which is consistent with previous reports by Fagnou and Glorius.^{2,3}



Scheme 5.11 C–H Activation Reversibility

A competition experiment was used to determine the preference of the reaction for electronically different donor/acceptor diazo compounds (Scheme 5.12). Kyle and I found that when methyl *p*-bromophenyl diazo acetate **569** was used in competition with **542**, the electron-deficient substrate was favored 1.6:1 after 15 min. These results suggest migratory insertion or reductive elimination favors the more electron-deficient substrate. Since reductive elimination should favor a more electron-rich substrate, it is reasonable to surmise migratory insertion favors an electron-deficient diazo substrate because of its increased electrophilicity.

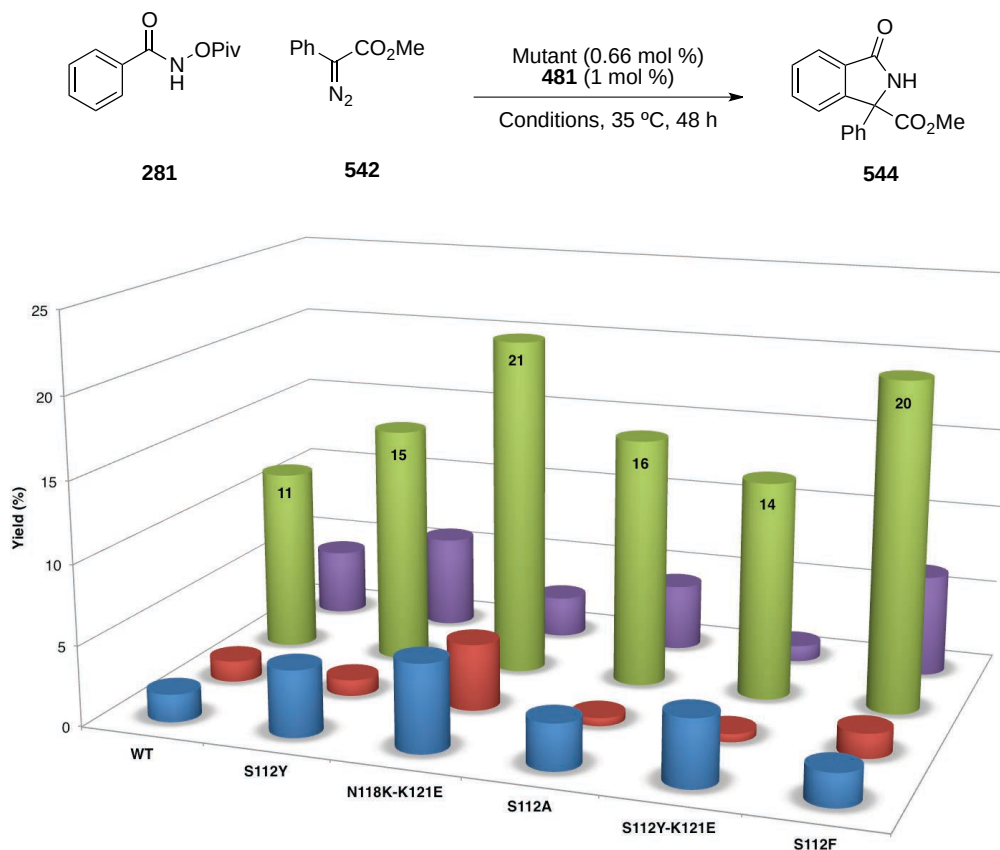


Scheme 5.12 Diazo Compound Competition Experiment

5.4 Artificial Metalloenzyme Catalyzed Reaction

Having achieved our goal to find a new heterocycle that can be prepared using Rh(III) C–H activation, we began screening metalloenzymes to render the transformation asymmetric (Scheme 5.13). In the asymmetric synthesis of isoquinolones, we found success using enzymes, which contain carboxylate residues proximal, the metal center to achieve good levels of reactivity, and aromatic residues at position S112 to achieve good levels of enantioselectivity. We screened the reaction against six different mutants, WT, S112A, N118K-K121E, S112Y, S112Y-K121E, S112F. All the mutants were screened with 4 different reactions conditions, MeOH with acetate buffer and water, and CH₃CN with acetate buffer and water. After allowing the reaction to stir at 35 °C for 48 hours, the desired product was observed in low

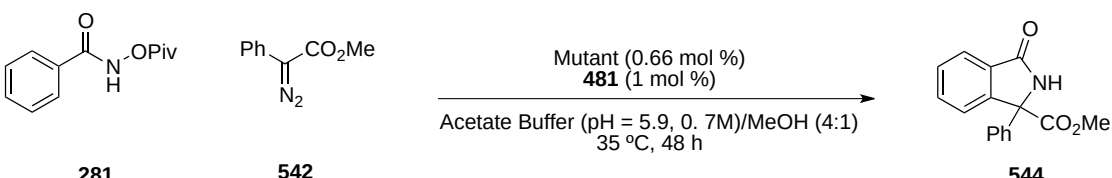
yields in all cases. A 4:1 ratio of acetate buffer and MeOH provided the highest yields (Scheme 5.13, green bars), with the best mutants being N118K-K121E, and S112F giving yields of 21% and 20%.



Scheme 5.13 Initial Screen with Artificial Metalloenzymes. Blue Bars = MeOH/H₂O (1:4); Red Bars = CH₃CN/H₂O (1:4); Green Bars = MeOH/Acetate Buffer (pH = 5.9, 0.7 M) (1:4); Purple Bars = CH₃CN/Acetate Buffer (pH = 5.9, 0.7 M) (1:4)

The enantioselectivity of all the mutants were determined under the best reaction conditions (Table 5.4). *Wild-type* and S112A gave the lowest levels of enantioselectivity. As we observed with the dihydroisoquinolone synthesis, placing an aromatic group at position S112 gave a substantial increase in enantioselectivity (Table 5.4, entries 2 and 6) with the S112F furnishing product in 75:25 er. Interestingly, addition of an acetate residue near the active site did not give a more reactive mutant, with N118K-K121E giving product in modest er but only 5% increase in yield. The best results were found using S112Y-K121E which gave product in 14% yield and 78:22 er (Table 5.4, entry 5).

Table 5.4 Enantioselectivity with Diazo Compounds

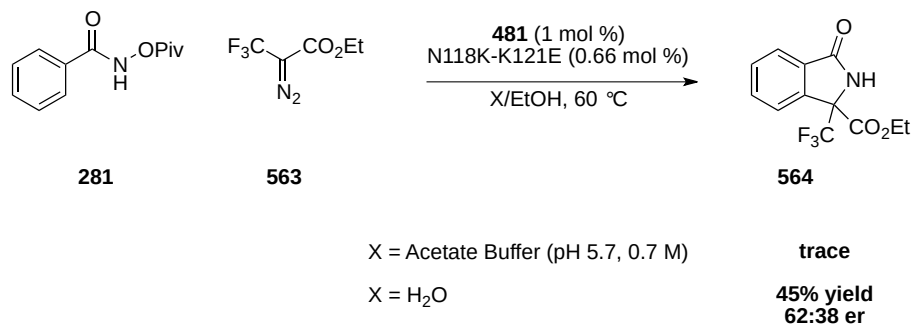
			
281	542		544
Entry	Mutant	er	Yield (%)
1	WT	68:32	11
2	S112Y	73:27	15
3	N118K-K121E	71:29	21
4	S112A	64:36	16
5	S112Y-K121E	78:22	14
6	S112F	75:25	20

Reaction Conditions: **281** (1 equiv), **542** (1 equiv), 0.05 M, All Yields and er's determined by HPLC v. and DTBP

We were perplexed by the low yields obtained under the reaction conditions. A brief screen of the pH of the acetate buffer revealed basic conditions to be superior to acid conditions, again contrary to our previous observations. Analysis of the reaction mixture by GC/MS found that acidic conditions accelerate the decomposition of our diazo starting material. In contrast under basic conditions, the diazo decomposed more slowly, but benzhydroxamic acid **281** decomposes under these reactions conditions. Interestingly, when the diazo is removed, very little benzhydroxamic acid decomposition is observed. These results suggest the diazo ester helps facilitate the decomposition of **281**. This suggested that batchwise addition of diazoester might allow for increased yields of the desired product. Unfortunately, batchwise addition failed to provide enhanced yields.

After re-examining the system, we realized that trifluoromethyl diazo ester **563** did not result in amide decomposition, even in the presence of a polar protic solvent (Scheme 5.7). This result suggested that acceptor/acceptor diazo esters might be more amenable to the conditions required for metalloenzyme catalysis. When **563** was submitted to a reaction mixture containing **481**, N118K-K121E, and **281** in a 4:1 mixture of acetate buffer and EtOH, trace formation of the desire product was formed. However, when

the acetate buffer was removed, the desired product can be observed in 45% yield with 62:38 er (Scheme 5.14).



Scheme 5.14 Enantioselective Coupling with Acceptor/Acceptor Diazo Esters

5.4 Conclusion

In conclusion, we have found that diazo-compounds can served as coupling partners to provide γ -lactams in excellent yields under mild conditions. A variety of amide substitution patterns are tolerated, and a wide range of acceptor/acceptor, acceptor, and donor/acceptor diazo compounds can be used by modifying the reaction conditions. The reaction is also amenable to metalloenzyme catalysis, albeit in modest yield and enantioselectivity. Issues of starting material decomposition can be averted when acceptor/acceptor diazo compounds are used.

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Portions of this work are reported in:

Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, 135, 5364.

Appendix 1

Rhodium(III)-Catalyzed C–H Activation of Benzamides for the Synthesis of Nitrogen Containing Heterocycles

General Methods

All reactions were carried out in 1 dram sealed vials under an atmosphere of air with magnetic stirring in an aluminum-heating block without drying or degassing of the vial. *t*-Amyl alcohol was purchased from Sigma-Aldrich and used without further purification. Column chromatography was performed on SiliCycle® Silica Flash® 40-63µm 60A. Thin Layer chromatography was performed on SiliCycle® 250 µm 60A plates. Visualization was accomplished with UV light (254 nm), KMnO₄, and CAM.

¹H NMR and ¹³C NMR spectra were recorded on a Varian 400 MHz or Varian 300 MHz spectrometers at ambient temperature. ¹H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (Hz). ¹³C NMR are reported as the following: chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec. Infrared spectra (IR) were obtained on Bruker Tensor 27 FT-IR spectrometer. Regioselectivity was determined from nOe spectroscopy. For compounds lacking significant nOe's, the regioselectivities were assigned based on the shift of the N-methyl peak and correlation with known compounds.

Catalyst Synthesis

The following catalysts were purchased from Sigma-Alrich and used as received:

Pd(OAc)₂, [Ru(cymene)₂Cl₂], and [RhCp*Cl]₄.

The following catalyst were prepare for literature procedures:

[RhCp*Cl₂]₂,¹ RhCp*Cl₂•**76**,² [RhCp*Br₂]₂,³ [RhCp*I₂]₂,³ [RhCp*(MeCN)₃](SbF₆)₂,⁴ [RhTpCl₂]₂,⁵ and [RhTp'Cl₂]₂.⁵

Synthesis of Alkynes

Alkynes **27**, **66**, **70**, **137**, **139**, **140**, **141** were purchased from Aldrich Chemical Co. and used without further purification. Alkyne **138** was prepared by a typical TBS-protection of the corresponding alcohol, which was purchased from Aldrich Chemical Company. Alkynes **134**, **135**, **136**, **158** were prepared according to literature method.⁶ **154** was prepared according to a literature method.⁷

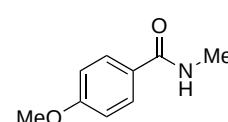
Synthesis of Amides

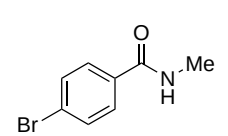
Amides **73**, **82**, **108**, and **113** were purchased from Aldrich Chemical Co. and used without further purification. Amide **103** and **179** were prepared according to literature precedent.^{8,9} All other amides were prepared from the corresponding acid chloride and amine hydrochloride salt.

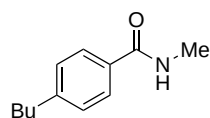
General Procedure of Amide Synthesis

To a round bottom flask charged with a magnetic stir bar was added the acid chloride (1 equiv), potassium carbonate (2 equiv), and ether (1 M). To the reaction mixture was added the amine hydrochloride salt in one portion. The flask was capped with a septum and the reaction was allowed to stir. After 12 hours the reaction was quenched with 1 M HCl and extracted with ether (3 x 30 ml), washed with brine and dried over MgSO₄, and concentrated *in vacuo* to yield a white solid (50% - 95%). This amide was directly submitted to the reaction without further purification.

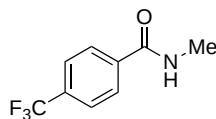
Amide Characterization

 **4-methoxy-N-methylbenzamide (77):** ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.19 (m, 2H), 7.12-7.06 (m, 2H), 5.88 (s, br, 1H), 2.88 (s, 1.5H), 2.86 (s, 1.5H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 136.5, 135.9, 130.8, 129.7, 129.6, 125.6, 26.5, 19.7.

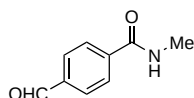
 **4-bromo-N-methylbenzamide (78):** ¹H NMR (400 MHz, CDCl₃) δ 7.57-7.54 (m, 2H), 7.47-7.45 (m, 2H), 6.33 (s, br, 1H), 2.92 (s, 1.5H), 2.91 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 133.3, 131.7, 128.4, 125.9, 26.9.



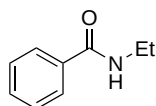
4-butyl-*N*-methylbenzamide (79): ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, 2H, $J=8$ Hz), 7.12 (d, 2H, $J=8$ Hz), 6.33 (s, br, 1H), 2.91 (s, 1.5H), 2.90 (s, 1.5H), 2.55 (t, 2H, $J=7.6$ Hz), 1.52 (q, 2H, $J=7.6$ Hz) 1.27 (m, 2H), 0.84 (t, 3H, $J=7.2$ Hz) ; ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 146.6, 131.9, 128.5, 126.8, 35.4, 33.3, 26.7, 22.2, 13.8.



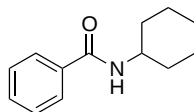
***N*-methyl-4-(trifluoromethyl)benzamide (80):** ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, br, 2H, $J=7.6$ Hz), 7.60 (d, br, 2H, $J=7.6$ Hz), 6.30 (s, br, 1H), 2.96 (s, 1.5H), 2.95 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 137.8, 133.1 (q), 127.2, 125.6, 125.5, 26.9.



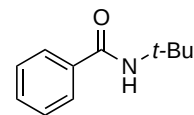
4-formyl-*N*-methylbenzamide (81): ^1H NMR (400 MHz, CDCl_3) δ 10.05 (s, 1H), 7.90 (m, 4H, $J=7.6$ Hz), 6.27 (s, br, 1H), 3.03 (s, 1.5H), 3.02 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 167.0, 139.7, 138.1, 129.8, 127.5, 26.9.



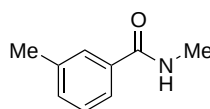
***N*-ethylbenzamide (83):** ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, br, 2H, $J=7.2$ Hz), 7.44-7.33 (m, 3H), 6.51 (s, br, 1H), 3.43 (m, 2H), 1.19 (t, 3H, $J=7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 134.8, 131.1, 128.4, 126.8, 34.9, 14.8.



***N*-cyclohexylbenzamide (84):** ^1H NMR (400 MHz, CDCl_3) δ 7.75-7.72 (m, 2H), 7.47-7.37 (m, 3H), 6.02 (m, br, 1H), 3.98-3.92 (m, 1H), 2.02-1.98 (m, 2H), 1.73 (dt, $J = 13.4, 3.8$ Hz, 2H), 1.65-1.60 (m, 1H), 1.45-1.35 (m, 2H), 1.26-1.15 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 135.1, 131.17, 131.14, 128.45, 128.43, 126.80, 126.78, 48.6, 33.2, 25.5, 24.9.



***N*-(*tert*-butyl)benzamide (85):** ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, 2H), 7.35 (m, 3H), 5.90 (s, br, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 135.9, 131.0, 128.4, 126.7, 51.5, 28.8.



***N*,3-dimethylbenzamide (86):** ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 0.4$ Hz, 1H), 7.51 (td, $J = 4.3, 1.3$ Hz, 1H), 7.28-7.24 (m, 2H), 2.97 (m, 3H), 2.35 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.47, 168.42, 138.35, 138.32, 134.6, 132.0, 128.3, 127.6, 123.73, 123.73, 26.8, 21.3.

3-methoxy-*N*-methylbenzamide (87): ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.23 (m, 3H), 7.00-6.98 (m, 1H), 6.25 (s, br, 1H), 3.81 (s, 3H), 2.98 (s, 1.5H), 2.97 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃) δ 168.1, 159.7, 136.1, 129.5, 118.5, 117.5, 112.2, 55.4, 26.8.

***N*,2-dimethylbenzamide (88):** ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.19 (m, 2H), 7.13-7.09 (m, 2H), 5.9 (s, br, 1H), 2.88 (s, 1.5H), 2.87 (s, 1.5H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 136.5, 135.9, 130.9, 129.7, 126.6, 125.6, 26.532, 19.7.

***N*-methyl-2-naphthamide (89):** ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.72 (m, 4H), 7.41 (m, 2H), 6.60 (s, br, 1H), 2.95 (s, 1.5H), 2.94 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃) δ 168.4, 134.6, 132.6, 131.8, 128.8, 128.3, 127.7, 127.5, 127.3, 126.6, 123.6 26.9.

***N*-(2,2,2-trifluoroethyl)benzamide (107):** ¹H NMR (400 MHz, CDCl₃) δ 7.80-7.77 (m, 2H), 7.57-7.51 (m, 1H), 7.48-7.42 (m, 2H), 6.44-6.40 (m, 1H), 4.11 (qd, *J* = 9.1, 6.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 133.6, 133.1, 132.2, 128.75, 128.73, 128.65, 127.08, 127.06, 126.98, 125.5, 122.7, 41.1 (q).

***N*-isobutylbenzamide (109):** ¹H NMR (400 MHz, CDCl₃) δ 7.75-7.73 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.37 (m, 2H), 3.26 (dd, *J* = 6.8, 6.1 Hz, 2H), 1.88 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 134.9, 131.2, 128.5, 126.8, 47.3, 28.6, 20.1.

***N*-(pyridin-2-ylmethyl)benzamide (180):** ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.87-7.84 (m, 2H), 7.69 (s, br, 1H), 7.69-7.62 (m, 1H), 7.49-7.44 (m, 1H), 7.42-7.38 (m, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.19-7.16 (m, 1H), 4.72 (d, *J* = 4.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 156.3, 148.9, 136.8, 134.4, 131.4, 122.4, 122.1, 44.7.

General Procedure for the Synthesis of Heteroaryl *N*-methyl Carboxamides

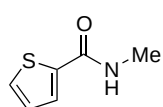
Amides **118** and **119** were prepared from the corresponding acid chloride as described prior. Amides **120**, **123**, and **125** were prepared from the corresponding carboxylic acids, which were purchased from Sigma

Aldrich Chemical Co. without further purification. Amides **121**, **122**, **124** were prepared from the corresponding methyl ester pyrrole or indole using the following procedure

A round bottom flask with a stir bar was charge with methyl ester (1 equiv), KOtBu (1.25 equiv), 18-crown-6 (10 mol %), Hexanes (1.6 M), and DMSO (0.8 M) under argon. The mixture was stirred for 5 minutes before adding MeI (3 equiv). When the reaction was complete as determined by TLC (generally 20 minutes) water was added and the mixture stirred for 5 minutes. The mixture was extracted with EtOAc (3 x 20 ml), washed with 10% LiCl, washed with brine, dried over MgSO₄, and concentrated to yield the desired alkylated product. This crude product was then dissolved in THF (1 M). LiOH (5 equiv) was added followed by enough water to dissolve the LiOH (generally equal to the amount of THF). The mixture was heated to reflux for 6 hours before allowing the reaction to cool. The mixture acidified using 2N HCl to pH 1. The mixture was extracted with EtOAc (3 x 20 ml), washed with brine, dried over MgSO₄ and concentrated to yield the product as a solid.

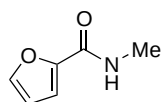
The following procedure was used to convert all heteroaryl carboxylic acids to their corresponding *N*-methyl carboxamide.

A round bottom flask with a stir bar was charged with carboxylic acid (1 equiv), EDC•HCl (1.2 equiv), HOBT (0.3 equiv), and MeNH₃Cl (1.05 equiv). The flask was sealed with a septum and placed under vacuum and then flushed with argon. MeCN (0.8 M) was added to the flask under argon and the solution was allowed to stir. After 5 minutes the Et₃N (1.05 equiv) was added and the reaction was allowed to stir until consumption of the carboxylic acid was observed (generally 1.5 hours). H₂O was added to the reaction mixture and then was extracted with EtOAc (3 x 20 ml) followed by washing with Brine, dried over MgSO₄, and concentrated to yield the desired product as a solid.

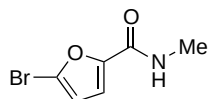


***N*-methylthiophene-2-carboxamide (118):** ¹H NMR (400 MHz, CDCl₃) δ 7.52 (m, 1H), 7.35 (m, 1H), 6.96 (m, 1H), 6.85 (s, br, 1H), 2.88 (s, 1.5H), 2.87 (s, 1.5H); ¹³C NMR (100

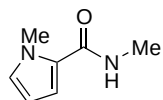
MHz, CDCl₃) δ 162.9, 139.0, 129.7, 128.0, 127.6, 26.7.



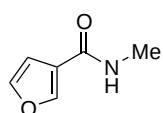
N-methylfuran-2-carboxamide (119): ^1H NMR (300 MHz, CDCl_3) δ 7.41 (dd, 1H, $J=0.9$ Hz), 7.10 (m, 1H), 6.49 (m, 1H), 6.36 (s, br, 1H) 2.98 (s, 1.5H), 2.97 (s, 1.5H).



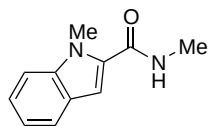
N-methylfuran-2-bromo-4-carboxamide (120): ^1H NMR (400 MHz, CDCl_3) δ 6.98 (d, 1H, $J=3.6$ Hz), 6.48 (s, br, 1H), 6.36 (d, 1H, $J=3.2$ Hz), 2.92 (s, 1.5H), 2.91 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 158.1, 149.8, 124.3, 116.3, 114.2, 26.1.



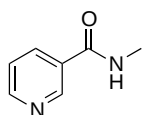
N,1-dimethyl-1H-pyrrole-2-carboxamide (121): ^1H NMR (400 MHz, CDCl_3) δ 6.65 (m, 1H), 6.50 (m, 1H), 6.10 (s, br, 1H), 6.02 (m, 1H), 3.88 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.8, 127.7, 117.6, 111.4, 107.1, 36.5, 26.0.



N-methylfuran-3-carboxamide (123): ^1H NMR (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.33 (s, 1H), 6.62 (s, br, 1H), 2.85 (s, 1.5H), 2.84 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.6, 144.6, 143.6, 122.5, 108.3, 26.2.



N,1-dimethyl-1H-indole-2-carboxamide (124): ^1H NMR (400 MHz, CDCl_3) δ 7.58 (m, 1H), 7.31 (m, 2H), 7.12 (m, 1H), 6.77 (s, 1H), 6.22 (s, br, 1H) 4.03 (s, 3H), 2.99 (s, 1.5H), 2.98 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 163.5, 132.4, 126.2, 124.2, 121.9, 120.6, 110.3, 103.7, 31.7, 26.6.



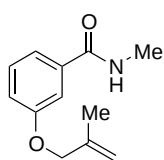
N-methylnicotinamide (125): ^1H NMR (400 MHz, CDCl_3) δ 8.94 (d, $J = 2.1$ Hz, 1H), 8.65-8.64 (m, 1H), 8.09 (dt, $J = 7.9, 2.0$ Hz, 1H), 7.35-7.32 (m, 1H), 2.98 (dd, $J = 4.8, 1.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 151.9, 147.7, 135.2, 130.3, 123.5, 26.8.

General Synthesis of Tethered Alkene Amides

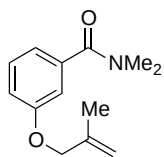
3-hydroxyethylbenzoate **182** (1 equiv) and K_2CO_3 (3 equiv) was placed in a flask containing a stirbar and dissolved in DMF (0.5 M). After stirring for 5 minutes, 1-chloro-2-methyl-3-propene was added rapidly and the mixture was stirred at 23 °C. After 16 hours the reaction mixture was diluted with Et_2O (50 ml) and 10% LiCl (50 ml). The organic layer was collected, and the aqueous layer was washed 3x with Et_2O (3 x 25 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated

in vacuo. The crude product was purified via column chromatography (4:1 Hexanes/EtOAc) to provide **183** as a white solid (70% yield).

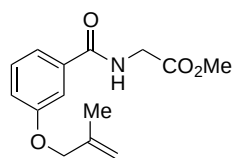
183 was added to a vial and dissolved in MeOH (0.2 M). The mixture was treated with 15% LiOH (0.2 M) and stirred at 23 °C until the reaction was deemed complete by TLC (usually less than 3 hours). Upon completion, the mixture was diluted with EtOAc. The organic layer was removed and the aqueous layer was acidified with Conc. HCl until the pH reached 1. The aqueous layer was washed 5 times with EtOAc. The organic fractions were collected, washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was dissolved in DCM (0.2 M) and stirred. After 5 minutes (COCl₂)₂ (1.5 equiv) was added followed by 2 drops of DMF and the reaction was allowed to stir for 3 hours. Upon completion, the reaction was concentrated *in vacuo* to provide a viscous light orange oil. The oil was dissolved in EtOAc (0.2 M). The desired amine (1 equiv) and K₂CO₃ (2 equiv) was added to this mixture, followed by H₂O (0.4 M). After 4 hours the reaction was diluted with H₂O and the organic layer was extracted. The aqueous layer was extracted with EtOAc thrice, and the combined organic fractions were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified via column chromatography (1:1 Hexanes/EtOAc) to provide the desired amide.



N-methyl-3-((2-methylallyl)oxy)benzamide (184): ¹H NMR (CDCl₃) δ 7.36 (dd, *J* = 2.4, 1.7 Hz, 1H), 7.31 (m, 1H), 7.04 (ddd, *J* = 8.0, 2.6, 1.2 Hz, 1H), 5.03 (d, *J* = 40.4 2H), 4.47 (s, 2H), 3.01 (d, *J* = 4.9 Hz, 3H), 1.83 (s, 3H); ¹³C NMR (CDCl₃) δ 168.0, 158.9, 140.5, 136.0, 129.5, 118.6, 118.1, 113.2, 112.9, 71.8, 26.8, 19.4; **MS (M+1)** Calc. 205.1; Found 206.1; **IR (thin film)** 1636, 1541, 1237, 711, 692 cm⁻¹; **TLC** (1:1 Hexane/EtOAc) R_f = .20.



N,N-dimethyl-3-((2-methylallyl)oxy)benzamide (186): ¹H NMR (CDCl₃) δ 7.30-7.27 (m, 1H), 6.97-6.93 (m, 3H), 5.08-4.98 (m, 2H), 4.43 (s, 2H), 3.06-2.97 (m, 6H), 1.81 (s, 3H); ¹³C NMR (CDCl₃) δ 171.3, 158.6, 140.5, 137.5, 129.4, 119.3, 116.1, 113.2, 112.8, 71.8, 19.3; **MS (M+1)** Calc. 219.1; Found 220.1; **IR (thin film)** 1636, 1393, 1268, 751, 692 cm⁻¹; **TLC** (1:1 Hexane/EtOAc) R_f = .20.



methyl 2-(3-((2-methylallyl)oxy)benzamido)acetate (187): ^1H NMR (CDCl_3) δ

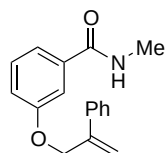
7.38-7.37 (m, 1H), 7.32-7.30 (m, 2H), 7.05 (dd, $J = 6.3, 2.9$ Hz, 1H), 5.08-4.97 (m,

2H), 4.45 (s, 2H), 4.21 (d, $J = 5.1$ Hz, 2H), 3.77 (s, 3H), 1.80 (s, 3H); ^{13}C NMR

(CDCl_3) δ 170.4, 167.2, 158.9, 140.4, 135.0, 129.6, 119.0, 118.6, 113.3, 113.0, 71.8, 52.5, 41.7, 19.4; **MS**

(M+1) Calc. 263.1; Found 264.1; **IR (thin film)** 1741, 1683, 1208, 714, 688 cm^{-1} ; **TLC** (1:1

Hexane/EtOAc) $R_f = .33$.



N-methyl-3-((2-phenylallyl)oxy)benzamide (188): ^1H NMR (CDCl_3) δ 7.46-7.24 (m,

8H), 7.07-7.04 (m, 1H), 6.19 (s, br, 1H), 5.60-5.44 (m, 2H), 4.91 (s, 2H), 2.98 (d, $J = 4.9$

Hz, 3H); ^{13}C NMR (CDCl_3) δ 168.0, 158.8, 142.7, 138.1, 136.1, 129.6, 128.5, 128.0,

126.0, 119.0, 118.3, 115.1, 113.3, 69.9, 26.8; **MS (M+1)** Calc. 267.1; Found 268.1; **IR (thin film)** 1636,

1541, 1487, 1049, 778 cm^{-1} ; **TLC** (1:1 Hexane/EtOAc) $R_f = .18$.

General Procedure for Rhodium Catalyzed Isoquinolone Synthesis

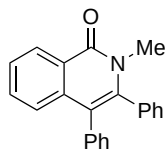
A one-dram vial with a stir bar was charged with amide (0.22 mmol, 1 equiv), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.46 mmol, 210 mol %), and $[\text{Cp}^*\text{RhCl}_2]_2$ (0.0055 mmol, 2.5 mol %). If the alkyne is a solid, it was added (0.275 mmol, 1.25 equiv) followed by 1.5 ml of *t*-amyl alcohol. If the alkyne is a liquid, 1.5 ml of *t*-amyl alcohol was added followed by the alkyne (0.275, 1.25 equiv). The vial was sealed and placed into a 110 $^\circ\text{C}$ heating block for 16 h. The reaction was allowed to cool and poured into a separatory funnel with excess dichloromethane and extracted twice with 10% NH_4OH in saturated NH_4Cl . The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. The residue was dissolved in 1 ml of dichloromethane and loaded onto a column of silica gel and eluted with a suitable solution of ethyl acetate and hexanes (typically 1:4). Evaporation of solvent afforded the product.

General Procedure of 7.4 mmol Scale Reaction

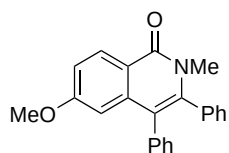
To a 100 ml round bottom equipped with a stir bar and reflux condenser was added benzamide (7.4 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (14.8 mmol), and $[\text{Cp}^*\text{RhCl}_2]_2$ (0.5 mol %) followed by 50 ml of *t*-amyl alcohol.

The flask was heated to 110 °C (oil bath temperature) and allowed to stir at this temperature for 30 minutes. Diphenyl acetylene (2.47 mmol) was added at this stage and then again after 2.5 hours and 5 hours (3 portions for 7.4 mmol total). After the final addition of alkyne, the reaction mixture was allowed to reflux for 10 hours. The reaction was allowed to cool and then poured into a separatory funnel with excess dichloromethane and extracted twice with 10% NH₄OH in saturated NH₄Cl. The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. The residue was recrystallized from ethyl acetate to yield pure product as a white solid (68% yield).

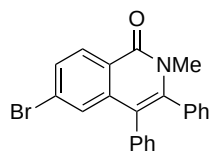
Characterization of Isoquinolone Products:



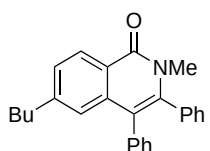
2-methyl-3,4-diphenylisoquinolin-1(2H)-one (74): According to the general procedure, the desired isoquinolone was isolated as a white solid (82%): **R_f** = .69 (2:1 Hexanes/EtOAc); **mp** 225 – 227 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.49 (d, 1H, *J* = 7.5 Hz), 7.43 (q, 2H, *J* = 7.2 Hz), 7.19 – 7.05 (m, 10H), 6.99 (d, 1H, *J* = 6.4 Hz), 3.29 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 162.7, 141.2, 137.1, 136.5, 135.0, 132.0, 131.5, 129.9, 128.3, 128.0, 127.9, 127.8, 126.7, 126.6, 125.3, 124.9, 118.8, 34.3; **IR (thin film)** 1646, 1443 1130, 718, 757, 703 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 312.1383; found 312.1385.



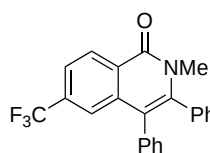
6-methoxy-2-methyl-3,4-diphenylisoquinolin-1(2H)-one (90): According to the general procedure, the desired isoquinolone was isolated as a white solid (98%): **R_f** = .54 (2:1 Hexanes/EtOAc); **mp** 206 – 210 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.45 (d, 1H, *J* = 8.8 Hz), 7.23 – 7.02 (m, 11H), 6.49 (d, 1H, *J* = 2.4 Hz), 3.66 (s, 3H), 3.30 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 162.7, 142.1, 139.4, 136.7, 135.4, 131.7, 130.2, 130.1, 128.3, 128.1, 127.0, 119.2, 118.7, 115.6, 107.2, 55.4, 34.3; **IR (Thin Film)** 1637, 1610, 1483, 1415, 1284, 1230, 1143, 724 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 342.1489; found 342.1492.



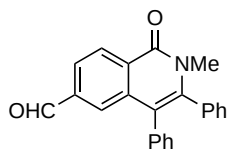
6-bromo-2-methyl-3,4-diphenylisoquinolin-1(2H)-one (91): According to the general procedure, the desired isoquinolone was isolated as a white solid (82%): $R_f = .83$ (2:1 Hexanes/EtOAc); **mp** 262 – 264 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.37 (d, 1H, $J = 8.8$ Hz), 7.55 (d, 1H, $J = 8.4$ Hz), 7.26 – 6.99 (m, 11H), 6.49 (d, 1H, $J = 2.4$ Hz), 3.30 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.5, 142.9, 138.9, 135.8, 134.9, 131.6, 130.1, 129.9, 128.6, 128.5, 128.3, 127.9, 127.7, 127.3, 123.8, 118.1, 34.6; **IR (Thin Film)** 1649, 1593, 1442, 1323, 1026, 930, 783, 705 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 390.0488; found 390.0493.



6-butyl-2-methyl-3,4-diphenylisoquinolin-1(2H)-one (92): According to the general procedure, the desired isoquinolone was isolated as a white solid (95%): $R_f = .66$ (2:1 Hexanes/EtOAc); **mp** 134 – 137 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.44 (d, 1H, $J = 8.4$ Hz), 7.31 (dd, 1H, $J = 8$ Hz, $J = 1.2$ Hz), 7.23 – 7.02 (m, 10H), 6.9 (s, 1H), 3.31 (s, 3H), 2.56 (t, 2H, 8 Hz), 1.50 (q, 2H, $J = 7.6$ Hz), 1.25 (q, 2H, $J = 7.6$ Hz), 0.84 (t, 3H, $J = 7.6$ Hz) ; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.9, 147.7, 141.4, 137.4, 136.8, 135.4, 131.8, 130.2, 128.3, 128.2, 128.1, 127.7, 126.9, 124.7, 123.2, 119.0, 36.2, 34.4, 33.5, 22.5, 14.0 ; **IR (Thin Layer)** 2925, 2920, 1650, 1614, 1481, 1327, 699 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 368.2009; found 368.2013.



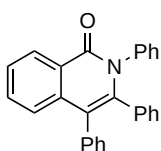
2-methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinolin-1(2H)-one (93): According to the general procedure, the desired isoquinolone was isolated as a white solid (82%): $R_f = .71$ (2:1 Hexanes/EtOAc); **mp** 173-177 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.64 (d, 1H, $J = 8.4$ Hz), 7.66 (dd, 1H, $J = 8.4$ Hz, $J = 0.8$ Hz), 7.41 (s, 1H), 7.23 – 7.15 (m, 6H), 7.10 (m, 2H), 7.02 (m, 2H), 3.35 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.2, 143.1, 137.4, 135.6, 134.8, 134.0, 133.7, 131.6, 129.2, 128.7, 128.4, 127.5, 127.1, 122.7, 118.8, 34.8 ; **IR (Thin Film)** 1653, 1592, 1494, 1317, 1257, 1169, 1124, 1074, 943, 841, 788, 697 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 380.1257; found 380.1269.



2-methyl-1-oxo-3,4-diphenyl-1,2-dihydroisoquinoline-6-carbaldehyde (94):

According to the general procedure, the desired isoquinolone was isolated as a yellow solid (61%) : $R_f = .28$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ

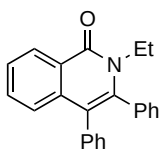
9.91 (s, 1H), 8.62 (d, 1H, $J=8$ Hz), 7.90 (dd, 1H, $J=8.4$ Hz, $J=1.2$ Hz), 7.58 (d, 1H, $J=0.8$ Hz), 7.18 (m, 5H), 7.05 (m, 5H), 3.31 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 192.1, 162.1, 142.7, 138.5, 137.5, 135.6, 134.5, 131.4, 129.7, 129.2, 129.0, 128.5, 128.4, 128.3, 128.2, 127.3, 124.8, 118.7, 34.6; **IR (Thin Film)** 1683, 1647, 1556, 1493, 1342, 1177, 802, 703 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 340.1332; found 340.133.



2,3,4-Triphenyl-1(2H)-isoquinolone (95): Known Compound.¹⁰ $^1\text{H NMR}$ (400 MHz,

CDCl_3) δ 8.52 (m, 1H), 7.54-7.44 (m, 3H), 7.20-7.00 (m, 10m), 6.82 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.6, 141.0, 139.4, 137.6, 136.3, 134.7, 132.5, 131.6, 131.0,

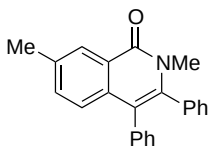
129.28, 128.5, 128.2, 127.9, 127.5, 127.1, 127.0, 126.9, 126.8, 125.6, 125.5, 118.8.



2-ethyl-3,4-bis(phenyl)isoquinolin-1(2H)-one (96): According to the general procedure,

upon workup the desired isoquinolone was isolated as a white solid (58%): $R_f = .43$ (2:1 Hexanes/EtOAc); **mp** 221-224 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.52 (dd, 1H, $J = 8$ Hz,

$J = 1.6$ Hz), 7.48 (m, 2H), 7.23-7.11 (m, 10H) 7.02 (m, 1H), 3.92 (q, 2H, $J = 6.8$), 1.14 (t, 3H, $J=6.8$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.2, 141.3, 137.4, 136.8, 135.0, 132.2, 131.7, 130.4, 128.3, 128.1, 128.0, 127.9, 127.9, 126.9, 126.7, 125.5, 119.2, 41.5, 14.3 ; **IR (Thin Film)** 1642, 1588, 1481, 1325, 1072, 758, 705 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 326.1539; found 326.1539.

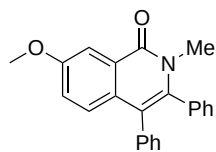


2,7-dimethyl-3,4-diphenylisoquinolin-1(2H)-one (99): According to the general

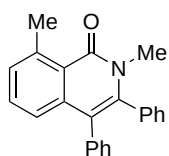
procedure, upin workup the desired isoquinolone was isolated as a white sold (80%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.35 (s, 1H), 7.33 (d, $J = 8.1$, 1H), 7.17 (m, 8H), 7.06

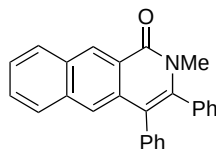
(m, 3H), 3.33 (s, 3H), 2.48 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.7, 140.2, 136.66, 136.62, 135.1, 134.9, 133.5, 131.5, 130.0, 128.12, 128.08, 127.8, 127.3, 126.7, 125.3, 124.8, 118.8, 34.3, 21.4.



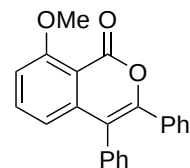
7-methoxy-2-methyl-3,4-diphenylisoquinolin-1(2H)-one (100): According to the general procedure, upon workup 49 mg (65%) of the desired isoquinolone was isolated as a white solid: $R_f = .54$ (2:1 Hexanes/EtOAc); **mp** 186-191 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.93 (d, 1H, $J=2$ Hz), 7.23-7.03 (m, 12H), 3.93 (s, 3H), 3.34 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 158.8, 139.1, 136.8, 135.3, 131.7, 131.5, 130.4, 128.3, 128.2, 128.1, 127.3, 126.9, 126.3, 122.7, 119.0, 107.7, 55.9, 34.1; **IR (Thin Film)** 2925, 1641, 1590, 1498, 1443, 1353, 1254, 1027, 833, 790, 728, 699 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 342.1491; found 342.1489.



2,8-dimethyl-3,4-diphenylisoquinolin-1(2H)-one (101): According to the general procedure, upon workup 30 mg (42%) of the desired isoquinolone was isolated as a white solid: $R_f = .71$ (2:1 Hexanes/EtOAc); **mp** 218-222 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.32 (t, 1H, $J=3.6$ Hz), 7.23 – 6.94 (m, 12H), 3.27 (s, 3H), 3.00 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.7, 141.9, 141.4, 139.1, 137.4, 135.5, 131.8, 131.4, 130.0, 128.3, 128.2, 128.2, 126.8, 123.9; 34.5, 24.6. **IR (Thin Layer)** 2926, 1645, 1594, 1440, 1306, 810, 787, 752, 701 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 326.1539; found 326.1541.

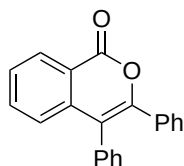


2-methyl-3,4-diphenylbenzo[glisoquinolin-1(2H)-one (102): According to the general procedure, upon workup 61 mg (78%) of the desired isoquinolone was isolated as a yellow solid: $R_f = .81$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.14 (s, 1H), 8.06 (m, 1H), 7.71 (m, 1H) 7.57 (s, 1H), 7.47 (m, 2H), 7.22-7.10 (m, 10H), 3.4 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.5, 140.3, 137.0, 135.4, 135.3, 133.9, 132.0, 131.8, 130.3, 129.5, 129.4, 129.2, 128.33, 128.3, 128.2, 128.1, 128.0, 127.0, 126.1, 124.3, 123.8, 119.0, 34.4; **IR (Thin Layer)** 2924, 1654, 1624, 1492, 1167, 698 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 362.1539; found 362.1543.

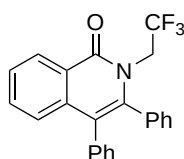


8-methoxy-3,4-diphenyl-1H-isochromen-1-one (104): According to the general procedure, the desired isoquinolone was isolated as a white solid (37%): $R_f = .21$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45 (t, 1H, $J = 8$ Hz), 7.32 (m, 3H), 7.24 (m, 2H), 7.15 (m, 5H), 6.90 (d, 1H, $J=8.4$ Hz), 6.63 (dd, 1H, $J=8.4$ Hz, $J=0.8$ Hz) 3.98 (s, 3H); ^{13}C

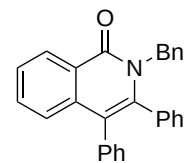
NMR (100 MHz, CDCl₃) δ 161.7, 158.8, 151.4, 141.8, 135.3, 124.9, 132.9, 131.3, 129.1, 128.9, 128.8, 128.7, 127.9, 127.7, 121.2, 117.5, 116.4, 109.9, 109.3, 56.4, 29.7; **HRMS (ESI)** m/e calcd (M+H) 329.1172; found 329.1174.



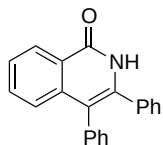
3,4-diphenyl-1H-isochromen-1-one (106): This compound has already been reported¹¹ the ¹H NMR has been included: ¹H NMR (400 MHz, CDCl₃) δ 8.35 (dd, 1H, $J=8$ Hz, $J=0.8$ Hz), 7.58 (m, 1H), 7.47 (m, 1H), 7.35 (m, 3H), 7.28 (m, 2H), 7.20 (m, 6H).



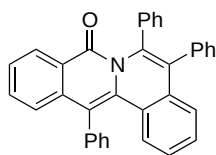
3,4-diphenyl-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one (110): According to the general procedure, the desired isoquinolone was isolated as an off white solid with inseparable starting material: $R_f = .10$ (20:1 Hexanes/EtOAc); See spectrum for ¹H NMR (400 MHz, CDCl₃); ¹³C NMR (100 MHz, CDCl₃); **IR (thin film)** 1654, 1603, 1541, 1262, 1158, 763 cm⁻¹; **HRMS (ESI)** m/e calcd (M+H) 380.1257 ; found 380.1257.



2-benzyl-3,4-diphenylisoquinolin-1(2H)-one (108): According to the general procedure, the desired isoquinolone was isolated as an off white solid (62%): $R_f = .60$ (2:1 Hexanes/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 8.55 (m, 1H), 7.50 (m, 2H), 7.19 (s, 1H), 7.15 (m, 8H), 7.00 (m, 4H), 6.83 (m, 3H) 5.14 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 141.3, 137.7, 137.3, 136.4, 134.3, 132.2, 131.5, 130.4, 128.2, 128.2, 128.1, 127.8, 127.5, 126.9, 126.9, 126.8, 126.7, 126.6, 125.5, 119.4, 49.0; **IR (thin film)** 2925, 1725, 1650, 1492, 1443, 1324, 1074, 700 cm⁻¹; **HRMS (ESI)** m/e calcd (M+H) 388.1696 ; found 388.1696.

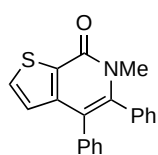


3,4-diphenylisoquinolin-1(2H)-one (114): According to the general procedure, the desired isoquinolone was isolated as an off white solid (33%); ¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 8.46-8.44 (m, 1H), 7.57 (ddd, $J = 8.3, 7.0, 1.4$, 1H), 7.48 (td, $J = 7.5, 1.0$, 1H), 7.34 (dd, $J = 8.2, 0.5$, 1H), 7.32-7.27 (m, 3H), 7.27-7.21 (m, 5H), 7.18-7.16 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 138.6, 137.0, 135.7, 135.0, 132.6, 131.8, 129.2, 128.6, 128.35, 128.31, 127.45, 127.27, 126.6, 125.6, 125.1, 117.2.



5,6,13-triphenyl-8H-isoquinolino[3,2-a]isoquinolin-8-one (115): According to the general procedure, the desired isoquinolone was isolated as an off white solid (26%);

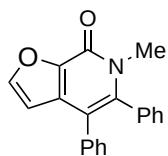
¹H NMR (400 MHz, CDCl₃) δ 8.23 (dd, *J* = 7.9, 1.0, 1H), 7.61-7.48 (m, 7H), 7.44-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.18-7.09 (m, 7H), 7.07-7.04 (m, 5H), 6.86 (ddd, *J* = 8.5, 6.7, 1.8, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 138.5, 137.1, 133.7, 133.0, 132.25, 132.12, 131.4, 129.6, 129.01, 128.81, 128.4, 128.1, 127.9, 127.57, 127.43, 127.11, 126.92, 126.76, 126.64, 126.41, 126.26, 125.79, 125.61, 125.51.



6-methyl-4,5-diphenylthieno[2,3-c]pyridin-7(6H)-one (126): According to the general procedure, upon workup the desired isoquinolone was isolated as a white solid (86%); **R_f** = .63 (2:1 Hexanes/EtOAc); **mp** 232-235 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.53 (d, 1H, *J* = 5.2 Hz), 7.18 (m, 3H), 7.08 (m, 5H) 7.00 (m, 2H), 6.83 (d, 1H, *J* = 5.2 Hz), 3.33 (s, 3H); **¹³C NMR**

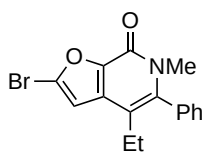
(100 MHz, CDCl₃) δ 158.8, 145.5, 142.2, 136.9, 134.6, 132.7, 130.6, 130.1, 128.9, 128.4, 128.3, 127.9, 126.8, 124.7, 117.7, 98.3, 34.3; **IR (Thin Film)** 3072, 1639, 1579, 1492, 1440, 779, 760, 699 cm⁻¹ ;

HRMS (ESI) *m/e* calcd (M+H) 318.0947; found 318.0947.



6-methyl-4,5-diphenylfuro[2,3-c]pyridin-7(6H)-one (137): According to the general procedure, the desired isoquinolone was isolated as a white solid (55%); **R_f** = .22 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.66 (d, 1H, *J*=2 Hz), 7.26 – 7.18 (m,

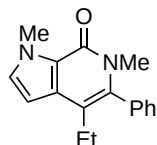
2H), 7.08 (m, 5H), 6.96 (m, 2H), 6.41 (d, 1H, *J*=2 Hz) , 3.34 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 153.6, 148.0, 142.2, 141.4, 136.1, 134.6, 133.4, 131.6, 130.3, 130.1, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 126.7, 114.9, 107.2, 34.2 ; **IR (Thin Film)** 1674, 1557, 1492, 1020, 780, 714 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 302.1176; found 302.117.



2-bromo-4-ethyl-6-methyl-5-phenylfuro[2,3-c]pyridin-7(6H)-one (128):

According to the general procedure, the desired isoquinolone was isolate as a pale while solid (63%); **R_f** = .28 (2:1 Hexanes/EtOAc); **¹H NMR** (300 MHz, CDCl₃) δ 7.50 (m, 3H), 7.25 (m, 2H), 6.69 (s, 1H), 3.27 (s, 3H), 2.25 (q, 2H, *J*=7.5 Hz), 1.01 (t, 3H, *J*=7.5 Hz); **¹³C NMR** (100 MHz, CDCl₃) 152.2, 142.9, 141.2, 134.6, 134.5, 131.4, 129.3, 129.1, 129.0, 113.4, 108.0,

33.8, 22.7, 14.8; **IR (Thin Film)** 2968, 1673, 1558, 1495, 1259, 1079, 924, 709 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 332.0281; found 332.0281.



4-ethyl-1,6-dimethyl-5-phenyl-1H-pyrrolo[2,3-c]pyridin-7(6H)-one (129): According

to the general procedure, the desired isoquinolone was isolate as a white solid (87%): $R_f =$

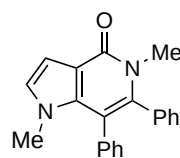
.18 (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.46 (m, 3H), 7.27 (m, 2H),

7.03 (d, 1H, $J=3$ Hz), 6.32 (d, 1H, $J=3$ Hz), 4.23 (s, 3H), 3.22 (s, 3H), 2.30 (q, 2H, $J=7.5$ Hz), 1.05 (t, 3H,

$J=7.5$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 155.9, 136.2, 135.9, 131.4, 131.2, 129.8, 128.7, 128.3, 122.4,

115.5, 100.4, 35.9, 33.2, 22.7, 14.9; **IR (Thin Film)** 2965, 1652, 1579, 1488, 705 cm^{-1} ; **HRMS (ESI)** m/e

calcd (M+H) 267.1492; found 267.1497.



1,5-dimethyl-6,7-diphenyl-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (130): According to

the general procedure, the desired isoquinolone was isolated as a white solid (63%): $R_f =$

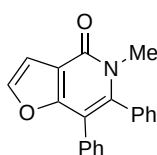
.08 (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.18 – 7.05 (m, 10H), 6.90

(d, 1H, $J = 2.8$ Hz), 6.71 (d, 1H, $J=3.2$ Hz), 3.29 (s, 3H), 3.01 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ

159.8, 140.6, 136.8, 135.6, 135.2, 131.8, 130.1, 128.1, 128.0, 127.9, 127.7, 127.2, 115.6, 104.2, 36.1, 33.9

; **IR (Thin Film)** 1638, 1544, 1444, 1071, 740, 716 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 315.1492;

found 315.1485.



5-methyl-6,7-diphenylfuro[3,2-c]pyridin-4(5H)-one (131): According to the general

procedure, upon workup the desired isoquinolone was isolated as a white solid (82%) : $R_f =$

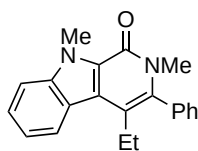
.46 (2:1 Hexanes/EtOAc); **mp** 235-240 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.41 (d, 1H,

$J = 1.6$ Hz), 7.23 (m, 2H), 7.19 (s, 1H) 7.12 (m, 5H), 7.02 (m, 3H), 3.31 (s, 3H); $^{13}\text{C NMR}$ (100 MHz,

CDCl_3) δ 159.7, 158.3, 143.5, 134.2, 132.7, 130.6, 130.1, 128.7, 128.4, 127.9, 127.1, 114.7, 107.5, 34.5 ;

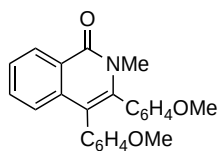
IR (Thin Film) 1658, 1556, 1493, 1440, 1306, 1169, 795, 743, 717, 696 cm^{-1} ; **HRMS (ESI)** m/e calcd

(M+H) 302.1176; found 302.1177.



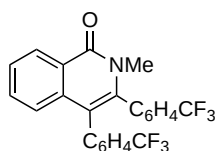
4-ethyl-2,9-dimethyl-3-phenyl-2,9-dihydro-1H-pyrido[3,4-b]indol-1-one (132):

According to the general procedure, the desired isoquinolone was isolate as a yellow solid (93%): $R_f = .21$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.09 (doublet of triplets, 1H, $J=8.4$ Hz, $J=9$ Hz), 7.52 (m, 5H), 7.31 (m, 3H), 4.43 (s, 3H), 3.33 (s, 3H), 2.67 (q, 2H, $J=7.5$ Hz), 1.20 (t, 3H, $J=7.5$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.3, 141.2, 136.2, 135.6, 129.8, 128.8, 128.5, 126.8, 126.1, 123.3, 123.1, 121.3, 120.0, 117.1, 110.1, 33.9, 31.4, 22.8, 14.7; **IR (Thin Film)** 2976, 1649, 1559, 1474, 1410, 1292, 1154, 913, 741, 707 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 317.1648; found 317.1647.



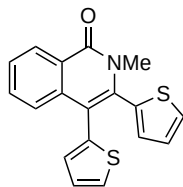
2-methyl-3,4-bis(4-(methoxy)phenyl)isoquinolin-1(2H)-one (142): According to

the general procedure, upon workup the desired isoquinolone was isolated as a white solid (94%): $R_f = .65$ (2:1 Hexanes/EtOAc); **mp** 204-206 $^{\circ}\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.52 (d, 1H, $J = 8$ Hz), 7.47 (m, 2H), 7.15 (m, 2H) 7.00 (d, 2H, $J = 8.4$ Hz), 6.94 (d, 2H, $J = 8.4$ Hz), 6.74 (m, 4H), 3.74 (s, 6H), 3.33 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 158.3, 151.9, 141.5, 137.7, 132.7, 132.1, 131.3, 131.2, 137.9, 127.8, 126.6, 125.5, 118.9, 113.8, 113.6, 55.2, 34.5, 29.9; **IR (Thin Film)** 2925, 1648, 1612, 1510, 1326, 1290, 1247, 1174, 1029, 808, 781 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 372.1595; found 372.1595.



2-methyl-3,4-bis(4-(trifluoromethyl)phenyl)isoquinolin-1(2H)-one (143):

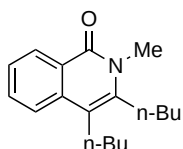
According to the general procedure, upon workup the desired isoquinolone was isolated as a semi-solid (50%): $R_f = .36$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.54 (m, 1H), 7.54 (m, 4H), 7.46 (d, 2H, $J=7.6$ Hz), 7.24 (m, 2H), 7.16 (d, 2H, $J=7.6$ Hz), 7.03 (m, 1H), 3.30 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.7, 140.1, 138.3, 136.5, 132.7, 132.0, 131.2, 130.5, 129.5, 128.3, 127.5, 125.7 (q), 125.3 (q), 125.2, 117.9, 34.6; **IR (Thin Film)** 2924, 1651, 1407, 1325, 1166, 1124, 1068, 1020, 832, 776 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 448.1131; found 448.1129.



2-methyl-3,4-di(thiophen-2-yl)isoquinolin-1(2H)-one (144): According to the general procedure, upon workup the desired isoquinolone was isolated as a yellow solid (50%):

R_f = .32 (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.45 (d, 1H, J = 7.6 Hz), 7.47 (m, 2H), 7.27 (m, 2H) 7.20 (m, 1H), 6.87 (m, 3H), 6.77 (m, 1H), 3.74 (s, 6H), 3.38

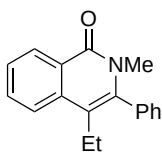
(s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.6, 137.1, 136.9, 136.2, 134.9, 132.3, 130.1, 129.7, 127.8, 127.7, 127.3, 126.7, 126.6, 126.5, 126.4, 125.4, 125.1, 114.2, 34.2; **IR (Thin Film)** 2925, 1650, 1339, 1226, 1117, 1032, 777, 700 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 372.1595; found 372.1595.



3,4-dibutyl-2-methylisoquinolin-1(2H)-one (145): This is a known compound.¹² Only

NMR data are shown here. The reaction was run with Ag_2CO_3 purchased from Sigma Aldrich Chemical Company and stored in a glove box. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ

8.48-8.43 (m, 1H), 7.65-7.63 (m, 2H), 7.45-7.39 (m, 1H), 3.66 (s, 3H), 2.75-2.69 (m, 4H), 1.61-1.43 (m, 8H), 1.03-0.93 (m, 6H).

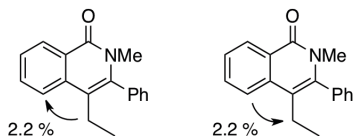


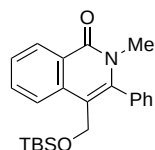
4-ethyl-2-methyl-3-phenylisoquinolin-1(2H)-one (146): According to the general

procedure, upon workup 47 mg (82%) of the desired isoquinolone was isolated as a pale yellow solid: R_f = .38 (2:1 Hexanes/EtOAc); **mp** 131-132 $^\circ\text{C}$; $^1\text{H NMR}$ (400 MHz,

CDCl_3) δ 8.48 (d, 1H, J = 8.0 Hz), 7.67-7.62, 7.45-7.40 (m, 4H) 7.23 – 7.18 (m, 2H), 3.16 (s, 3H), 2.37 (q, 2H, J = 7.2 Hz). .98 (t, 3H, J = 7.2 Hz) ; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.4, 140.1, 136.0, 135.6, 132.0, 129.1, 129.0, 128.7, 128.4, 126.3, 125.7, 123.1, 116.6, 34.0, 21.6, 14.8; **IR (Thin Film)** 2968, 1648, 1613, 1487, 1333, 1055, 762, 703 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 264.1383; found 264.1392.

NOE:





4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-3-phenylisoquinolin-1(2H)-one

(147): According to the general procedure, upon workup the desired isoquinolone was

isolated as a light orange semi-solid (67%): $R_f = .44$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400

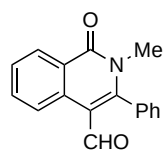
MHz, CDCl_3) δ 8.47 (d, 1H, $J = 8$ Hz), 7.84 (d, 1H, $J = 4$ Hz), 7.66 (m, 1H), 7.47 (m, 4H), 7.30 (m, 2H),

4.39 (s, 2H), 3.23 (s, 3H), .79 (s, 9H), .1 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.1, 142.7, 136.6,

134.7, 132.3, 129.6, 129.2, 128.9, 128.2, 126.7, 125.7, 124.1, 114.2, 60.0, 34.4, 26.0, 18.5 ; **IR (Thin**

Film) 2928, 2360, 1654, 1488, 1326, 1252, 1050, 836, 764, 700 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H)

380.204; found 308.2038.



2-methyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carbaldehyde (148): According

to the general procedure, upon workup the desired isoquinolone was isolated as a white

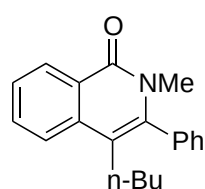
solid (78%): $R_f = .38$ (2:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.45 (s, 1H),

9.16 (d, 1H, $J=8.4$ Hz), 8.47 (dd, 1H, $J=8$ Hz, $J=.4$ Hz), 7.76 (m, 1H), 7.55 (m, 4H), 7.36 (m, 2H) 3.28

(s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 191.4, 157.4, 133.9, 133.3, 132.0, 130.4, 129.6, 129.4, 128.0,

127.9, 125.5, 124.6, 34.2; **IR (Thin Layer)** 2360, 1653, 1485, 1367, 1313, 764, 728 cm^{-1} ; **HRMS (ESI)**

m/e calcd (M+H) 264.1019; found 264.1020.



4-butyl-2-methyl-3-phenylisoquinolin-1(2H)-one (149): According to the general

procedure, upon workup the desired isoquinolone was isolated inseparable mixture of

isomers as a white solid (70%). An inseparable olefin isomer impurity was removed

by refluxing in ethanol with RhCl_3 for 12 hours: $R_f = .48$ (2:1 Hexanes/EtOAc); mp 85-87 $^\circ\text{C}$; See spectra

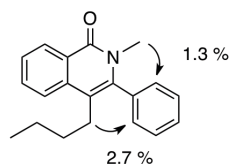
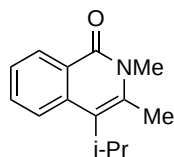
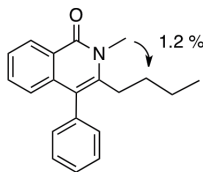
for its $^1\text{H NMR}$ (400 MHz, CDCl_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.1, 162.4, 141.0, 140.3, 137.5,

136.3, 135.6, 131.9, 131.7, 130.9, 129.2, 128.9, 128.7, 128.3, 127.6, 127.5, 126.3, 125.8, 125.6, 124.9,

123.9, 123.2, 117.7, 115.4, 34.1, 32.5, 31.4, 31.2, 30.6, 30.5, 28.1, 22.7, 22.5 ; **IR (Thin Layer)** 2956,

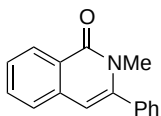
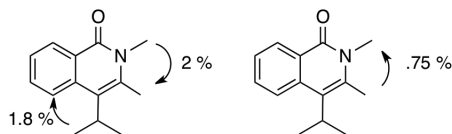
1650, 1613, 1487, 1415, 1333, 1072, 772, 703 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 292.1696; found

292.1697.

NOE: Major Regioisomer**NOE: Minor Regioisomer**

4-isopropyl-2,3-dimethylisoquinolin-1(2H)-one (150): According to the general procedure, upon workup the desired isoquinolone was isolated as a white solid (64%):

$R_f = .30$ (2:1 Hexanes/EtOAc); **mp** 106-109 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.42 (dd, 1H, $J=8$ Hz, $J=1.2$ Hz), 7.80 (d, 1H, $J=8.4$ Hz), 7.54 (m, 1H), 7.34 (m, 1H), 3.58 (s, 3H), 3.52 (m, 1H), 2.39 (s, 3H), 1.37 (d, 6H, $J=7.6$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.6, 135.6, 131.3, 129.0, 128.6, 128.4, 125.3, 119.2, 98.3, 36.6, 31.7, 29.7, 21.7, 17.5; **IR (Thin Layer)** 2959, 2927, 1645, 1485, 1340, 1036, 772, 701 cm^{-1} ; **HRMS (ESI)** m/e calcd (M^+) 216.1383; found 216.138.

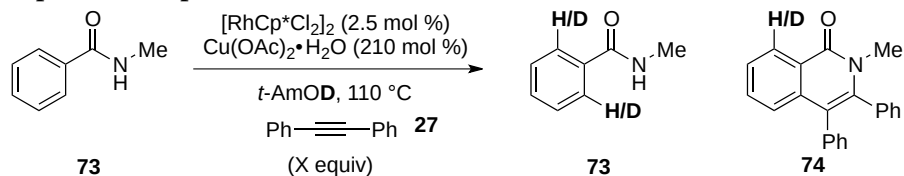
NOE:

2-methyl-3-phenylisoquinolin-1(2H)-one (155): A 1 dram vial was charged with a stirbar, **73** (0.2 mmol), $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ (0.02 mmol, 10 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.42 mmol, 210 mol %), and DCE (2 mL). After 15 seconds **154** (0.22 mmol, 1.1 equiv)

was added. The vial was sealed and stirred at 80 °C for 16 hours before being allowed to cool to 23 °C over 1 hour. The vial was opening and 4N HCl in 1,4-dioxane was added (2 mL). After stirring for an additional 16 hours, the reaction diluted with EtOAc (4 mL) and extracted twice with 10% NH_4OH in saturated NH_4Cl . The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. The residue was dissolved in 1 mL of dichloromethane and loaded onto a column of silica gel and eluted with a suitable solution of ethyl acetate and hexanes (typically 1:4). Evaporation of solvent afforded the product as a white solid (65%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.45-8.43 (m, 1H), 7.64-7.60 (m, 1H), 7.49-7.44 (m, 5H), 7.42-7.38 (m, 2H), 6.44 (s, 1H), 3.41 (s, 3H) $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ

163.3, 143.9, 136.34, 136.19, 132.2, 128.90, 128.75, 128.67, 128.60, 127.8, 126.76, 126.57, 125.8, 107.5, 98.6, 34.1.

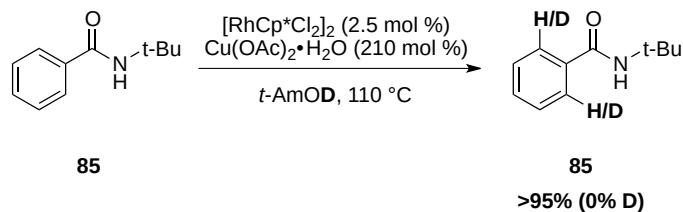
Deuterium Incorporation Experiments:



73:27	time (h)		
1:0	16	>95% (73% D)	NA
1:1.25	1.5	35% (<5% D)	40% (<5% D)

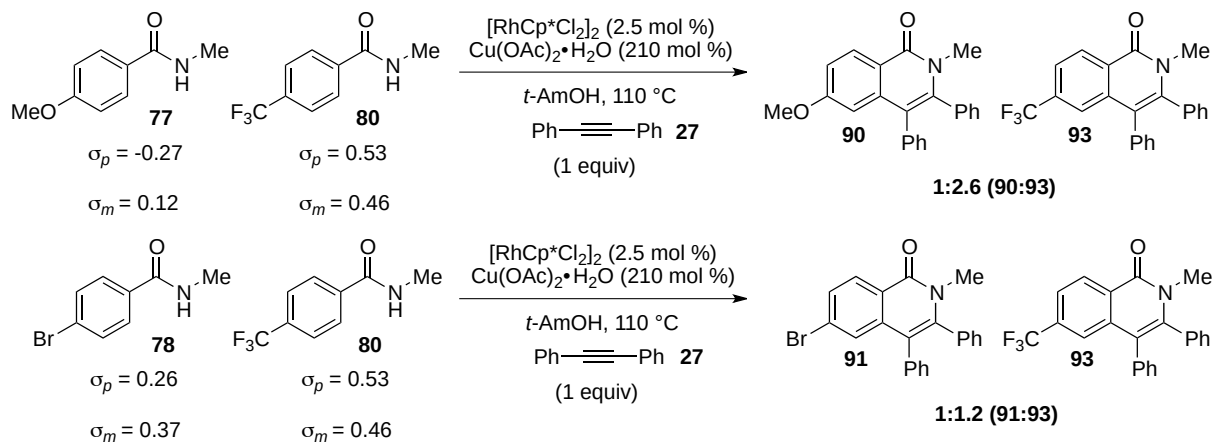
A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), $[\text{RhCp}^*\text{Cl}_2]_2$ (3.4 mg, 0.0055 mmol, 2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (90 mg, 0.46 mmol, 210 mol%), and a stir bar. $t\text{-AmOD}$ (1.5 ml, generated by agitating $t\text{-AmOH}$ with D_2O in a 1:10 ratio, then drying over MgSO_4) was added and the mixture stirred at 110 °C. After 16 hours the reaction mixture was cooled and diluted with CH_2Cl_2 . The solution was extracted with 10% NH_4OH in sat. NH_4Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO_4 , and concentrated to yield the deuterated amide in 95% yield and 73% deuterium incorporation at the two ortho positions as judged by ^1H NMR.

A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), **27** (50 mg, 0.275 mmol, 1.25 equiv), $[\text{RhCp}^*\text{Cl}_2]_2$ (3.4 mg, 0.0055 mmol, 2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (90 mg, 0.46 mmol, 210 mol%), and a stir bar. $t\text{-AmOD}$ (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH_2Cl_2 . The solution was extracted with 10% NH_4OH in sat. NH_4Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO_4 , and concentrated. The amide was purified away from the isoquinolone to reveal unobservable deuterium incorporation. This experiment suggests that under the reaction conditions C–H insertion is essentially irreversible.



A 1 dram vial was charged with benzamide **85** (39 mg, 0.22 mmol, 1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), and a stir bar. tAmOD (1.5 ml) was added and the mixture stirred at 110 °C. After 16 hours the reaction mixture was cooled and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated to yield the starting material in quantitative yield, with <5% deuterium incorporation as judged by ¹H NMR.

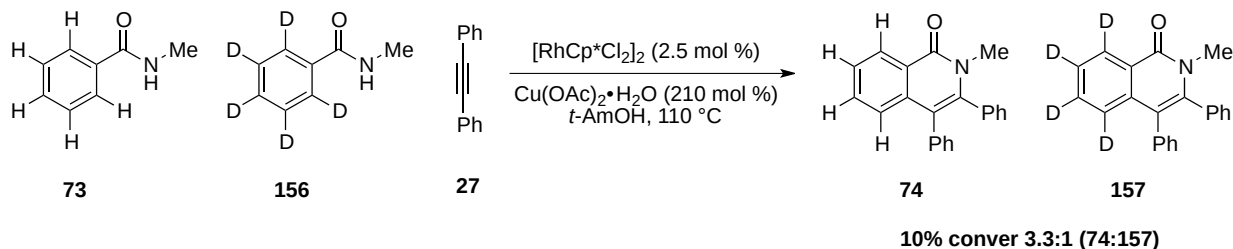
Competition Experiments



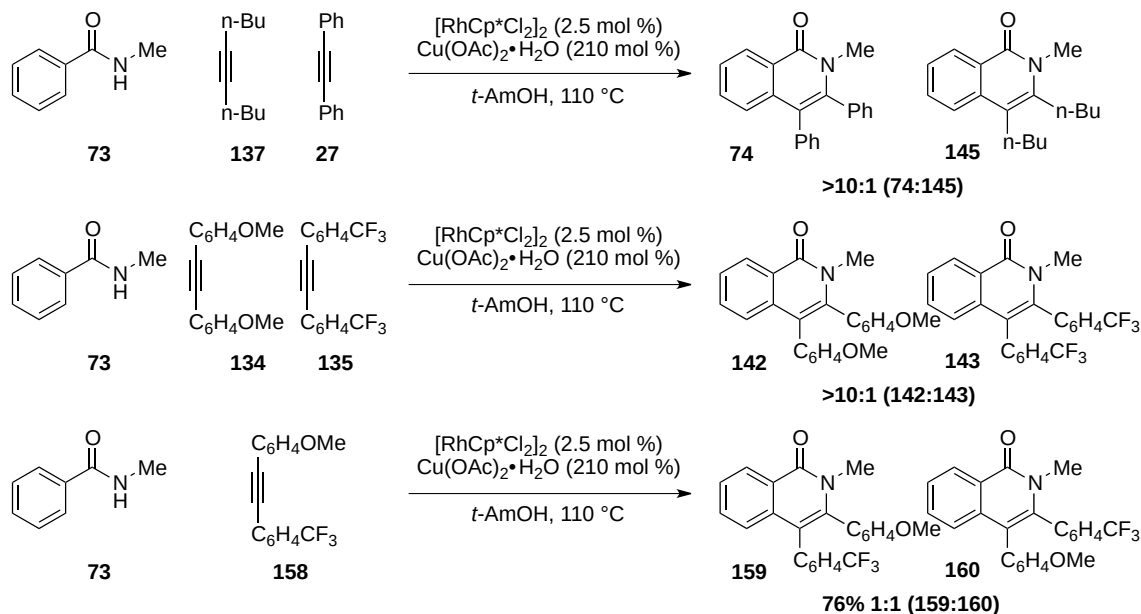
A 1 dram vial was charged with benzamide **77** (30 mg, 0.22 mmol, 1 equiv), **80** (50 mg, 0.22 mmol, 1 equiv), **27** (0.22 mmol, 1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar and tAmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. ¹H NMR revealed a 2.6:1 ratio of products **93** to **90**.

A 1 dram vial was charged with benzamide **78** (30 mg, 0.22 mmol, 1 equiv), **80** (50 mg, 0.22 mmol, 1 equiv), **27** (0.22 mmol, 1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg,

0.46 mmol, 210 mol%), a stir bar, and *t*AmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. ¹H NMR revealed a 1.2:1 ratio of products **93** to **91**.



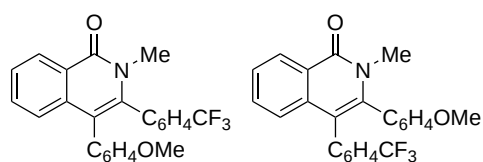
A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), **156** (50 mg, 0.22 mmol, 1 equiv), **27** (0.44 mmol, 2 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂·H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar, and *t*AmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 10 minutes, the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. ¹H NMR revealed 10% conversion and a 3.3:1 ratio of products **74** to **157**.



A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), **74** (50 mg, 0.22 mmol, 1 equiv), **145** (0.22 mmol, 1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂·H₂O (90

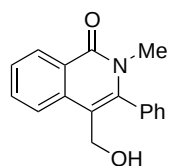
mg, 0.46 mmol, 210 mol%), a stir bar, and tAmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. ¹H NMR revealed a >10:1 ratio of products **74** to **145**.

A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), **134** (50 mg, 0.22 mmol, 1 equiv), **135** (0.22 mmol, 1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar, and tAmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. ¹H NMR revealed a >10:1 ratio of products **142** to **143**.



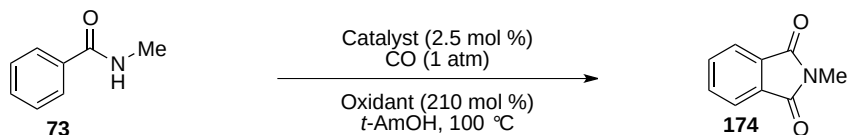
3-(4-methoxyphenyl)-2-methyl-4-(4-(trifluoromethyl)phenyl)isoquinolin-1(2H)-one (159); 4-(4-methoxyphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)isoquinolin-1(2H)-one (160);

A 1 dram vial was charged with benzamide **73** (30 mg, 0.22 mmol, 1 equiv), **158** (50 mg, 0.275 mmol, 1.25 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar, and tAmOH (1.5 ml) was added and the mixture stirred at 110 °C. After 2 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. After purification by column chromatography, the desired products were isolated as a 1:1 ratio of regioisomers as a white solid (76%): **R_f** = .15, .25 (2:1 Hexanes/EtOAc); For its spectra see ¹H NMR (400 MHz, CDCl₃); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 159.6, 139.9, 136.7, 132.6, 132.4, 132.1, 131.2, 130.6, 128.2, 128.0, 127.2, 127.0, 125.7, 125.5, 125.4, 125.3, 128.2, 125.0, 114.0, 113.8, 55.4, 36.8, 34.7, 29.9, 24.9, 23.6; **IR (Thin Film)** 2932, 1651, 1612, 1512, 1324, 1126 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 410.1362; found 410.137.



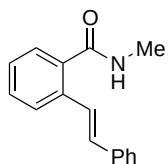
4-(hydroxymethyl)-2-methyl-3-phenylisoquinolin-1(2H)-one (165): A 1 dram vial was charged with benzamide **73** (0.20 mmol, 1 equiv), **164** (0.22 mmol, 1.1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar, and MeOH (1.5 ml) was added and the mixture stirred at 60 °C. After 16 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. After purification by column chromatography, the desired products were isolated as a 1:1 ratio of regioisomers as a white solid (76%): ¹H NMR (400 MHz, CDCl₃) δ 8.48 (dd, J = 8.1, 1.0, 1H), 7.93 (d, J = 8.1, 1H), 7.52-7.45 (m, 5H), 7.39 (tt, J = 7.4, 1.5, 2H), 4.46 (s, 2H), 3.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 143.1, 135.9, 134.3, 132.5, 131.3, 129.19, 129.08, 129.01, 128.5, 128.2, 126.82, 126.78, 125.4, 123.5, 114.0, 59.3, 34.2, 26.8.

General Procedure for Carbonylation of N-Me Benzamide



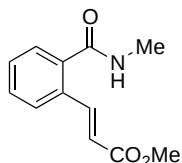
A 16 x 200 mm test tube is charged with a stirbar, **73** (0.22 mmol, 1 equiv), [RhCp*(MeCN)₃](SbF₆)₂ (0.011 mmol, 5 mol %), Ag₂CO₃ (0.462 mmol, 210 mol %), and *t*-AmOH (0.3 M). The test tube was fitted with a 14/20 septum and the vial was sparged with CO. After 5 minutes sparging was stopped and the tube was placed under an atmosphere of CO and placed in a heating block at 110 °C. After 16 hours the tube was allowed to cool to 23 °C over 30 minutes. The solvent was removed and the product was purified by column chromatography to provide **174** as a white solid in 66% yield. ¹H and ¹³C NMR spectra matched the commercial sample purchased from Sigma Aldrich Co.

Intermolecular Olefination



(E)-N-methyl-2-styrylbenzamide (176): A 1 dram vial was charged with benzamide **74** (0.20 mmol, 1 equiv), **175** (0.22 mmol, 1.1 equiv), [RhCp*Cl₂]₂ (3.4 mg, 0.0055 mmol, 2.5 mol%), Cu(OAc)₂•H₂O (90 mg, 0.46 mmol, 210 mol%), a stir bar, and *t*-BuOH (1.5

ml) was added and the mixture stirred at 80 °C. After 18 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. After purification by column chromatography, the desired products were isolated as a light yellow solid (90%): ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.51-7.45 (m, 3H), 7.45-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.29-7.25 (m, 2H), 7.04 (d, *J* = 16.2 Hz, 1H), 5.81-5.79 (m, 1H), 3.04-2.99 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 137.0, 135.62, 135.43, 131.39, 131.36, 130.2, 128.7, 128.0, 127.58, 127.45, 126.8, 126.2, 125.9, 26.8.



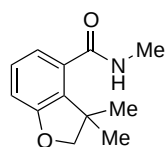
(E)-methyl 3-(2-(methylcarbamoyl)phenyl)acrylate (178): A 1 dram vial was charged with benzamide **74** (0.20 mmol, 1 equiv), **177** (0.22 mmol, 1.1 equiv), [RhCp*(MeCN)₃](SbF₆)₂ (8.3 mg, 0.01 mmol, 5 mol%), PivOH (0.02 mmol, 20 mol%), a stir bar, and DCE (1.5 ml) was added and the mixture stirred at 80 °C. After 18 hours

the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. After purification by column chromatography, the desired products were isolated as a light yellow solid (99%): ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, *J* = 16.0 Hz, 1H), 7.47-7.35 (m, 4H), 6.36 (d, *J* = 16.0 Hz, 1H), 3.77 (s, 3H), 3.00 (d, *J* = 4.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 166.9, 142.0, 137.1, 132.7, 131.3, 130.3, 129.8, 128.5, 127.5, 127.1, 126.8, 120.4, 51.8, 26.9.

General Procedure for Intramolecular Olefination

A 1 dram vial was charged with benzamide (0.20 mmol, 1 equiv), [RhCp*(MeCN)₃](SbF₆)₂ (8.3 mg, 0.01 mmol, 5 mol%), PivOH (1.00 mmol, 500 mol%), a stir bar, and DCE (1.5 ml) was added and the mixture

stirred at 80 °C. After 18 hours the reaction mixture was allowed to cool and diluted with CH₂Cl₂. The solution was extracted with 10% NH₄OH in sat. NH₄Cl (3 x 15 ml), washed with brine (1 x 15 ml), dried over MgSO₄, and concentrated. After purification by column chromatography, the desired products were isolated as a light colored solid.

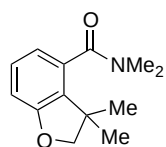


N,3,3-trimethyl-2,3-dihydrobenzofuran-4-carboxamide (185): ¹H NMR (CDCl₃) δ

7.13-7.08 (m, 1H), 6.83 (d, *J* = 7.8 Hz, 2H), 4.16 (s, 2H), 2.96 (d, *J* = 4.9 Hz, 3H), 1.43 (s, 7H); ¹³C NMR (CDCl₃) δ 169.5, 160.3, 133.8, 133.6, 128.2, 118.9, 111.7, 85.2, 42.9,

26.6, 25.9; **MS (M+1)** Calc. 205.1; Found 206.1; **IR (thin film)** 3059, 1637, 1533, 1438, 1264, 983 cm⁻¹;

TLC (1:1 Hexane/EtOAc) R_f = .40.



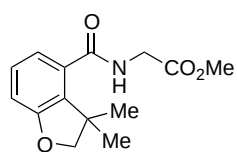
N,N,3,3-tetramethyl-2,3-dihydrobenzofuran-4-carboxamide (189): ¹H NMR (CDCl₃)

δ 7.12-7.08 (m, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.16 (s, 2H), 3.09 (s, 3H), 2.83 (s, 3H), 1.33 (s, 6H); ¹³C NMR (CDCl₃) δ 170.0, 160.0, 132.9, 131.9,

128.33, 128.31, 128.17, 118.9, 118.25, 118.23, 118.18, 111.7, 110.30, 110.28, 85.2, 84.8, 42.6, 39.1, 34.5,

25.9; **MS (M+1)** Calc. 219.1; Found 220.1; **IR (thin film)** 1659, 1458, 1395, 1264, 993 cm⁻¹; **TLC** (1:1

Hexane/EtOAc) R_f = .37.



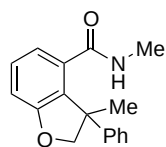
methyl 2-(3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamido)acetate (190):

¹H NMR (CDCl₃) δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.18 (d, *J* = 5.4 Hz, 2H), 4.16 (s, 2H), 3.77 (s, 3H); ¹³C

NMR (CDCl₃) δ 170.2, 168.9, 160.4, 134.3, 132.6, 128.28, 128.26, 119.19, 119.17, 112.2, 85.3, 52.4,

43.0, 41.5, 25.9; **MS (M+1)** Calc. 263.1; Found 264.1. **IR (thin film)** 1750, 1652, 1521, 1436, 992, 804

cm⁻¹; **TLC** (1:1 Hexane/EtOAc) R_f = .44.



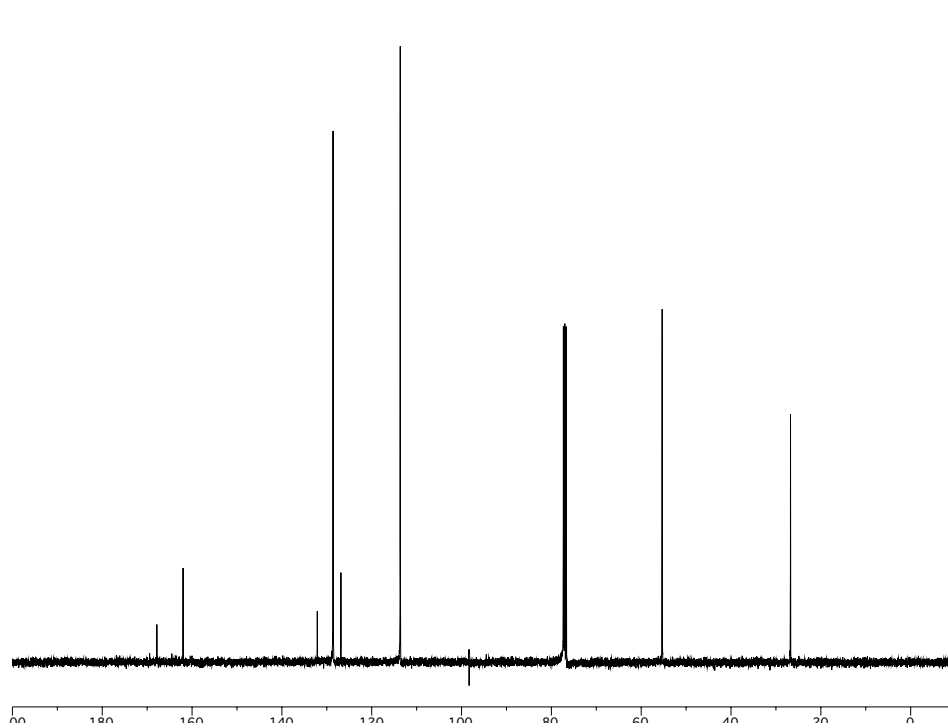
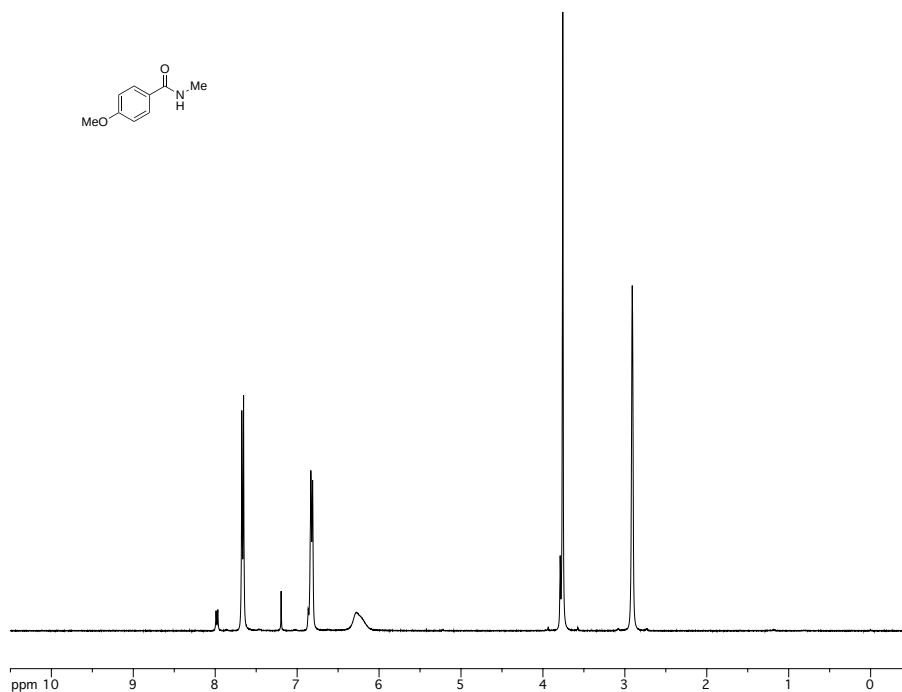
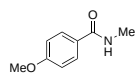
N,3-dimethyl-3-phenyl-2,3-dihydrobenzofuran-4-carboxamide (191): ^1H NMR

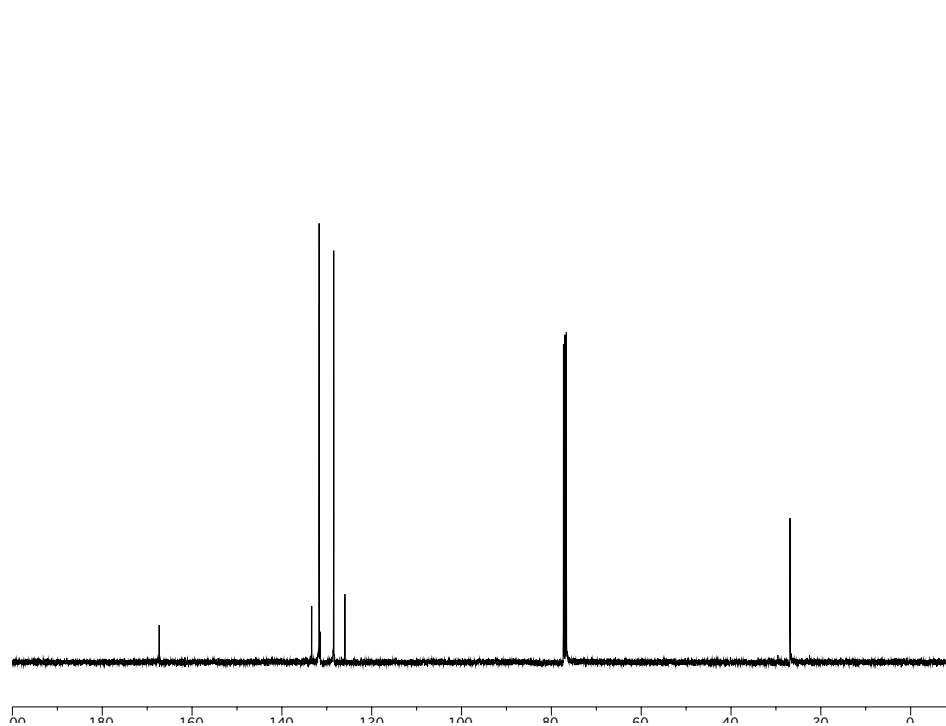
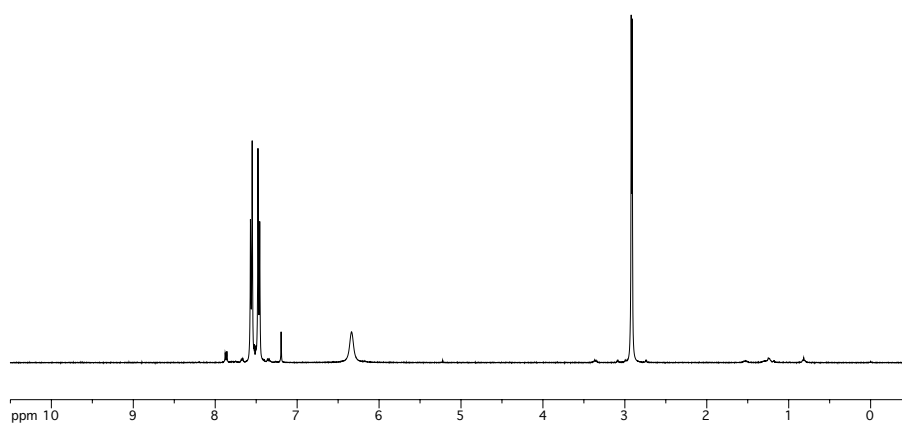
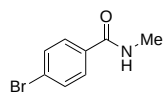
(CDCl_3) δ 7.33-7.18 (m, 6H), 6.96-6.93 (m, 2H), 4.99 (dt, $J = 1.4, 0.7$ Hz, 1H), 4.47 (dd,

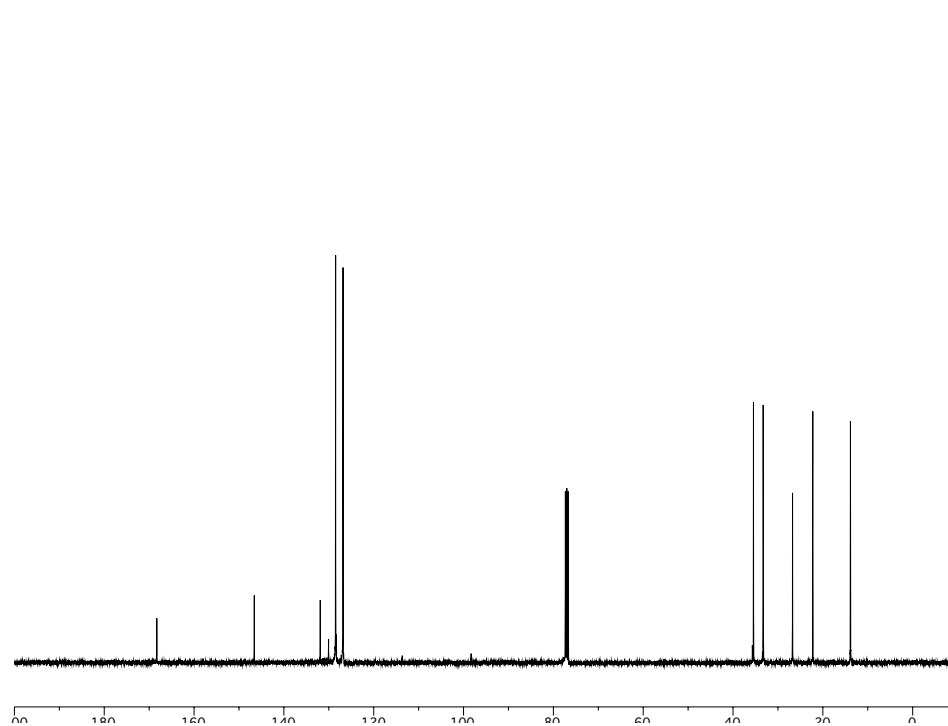
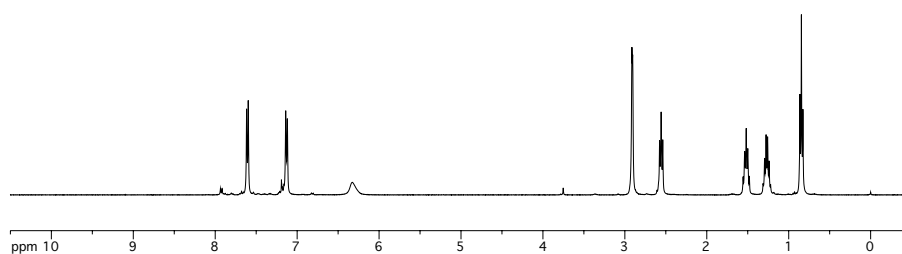
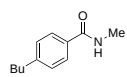
$J = 37.5, 8.6$ Hz, 2H), 2.46 (d, $J = 4.9$ Hz, 3H), 1.85 (s, 3H); ^{13}C NMR (CDCl_3) δ 168.5,

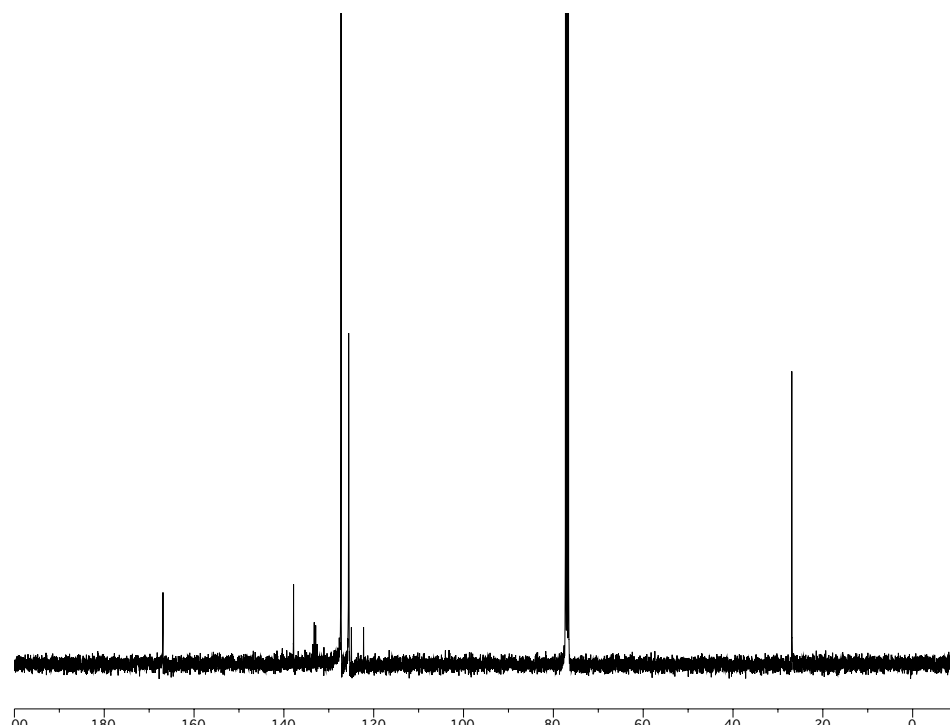
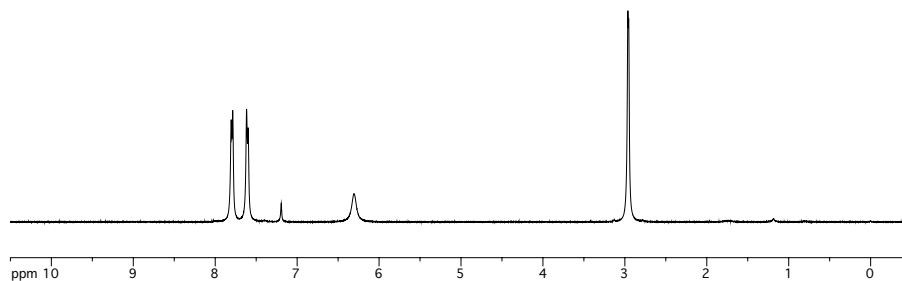
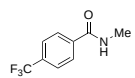
160.3, 145.9, 133.8, 132.8, 129.0, 126.7, 120.4, 111.8, 87.1, 50.0, 26.1, 24.0; **MS (M+1)** Calc. 267.1;

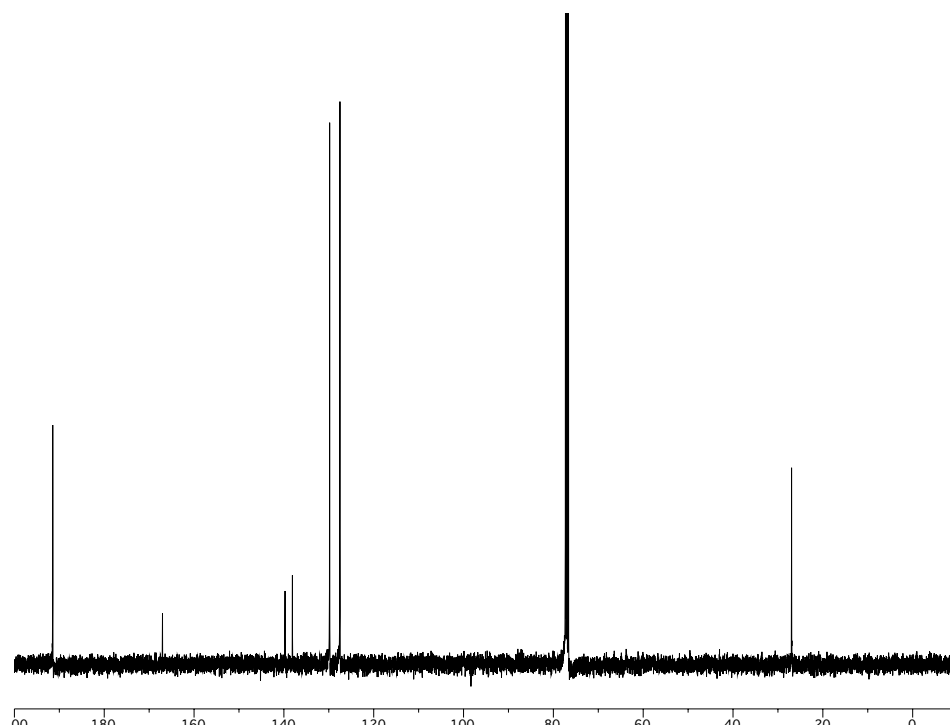
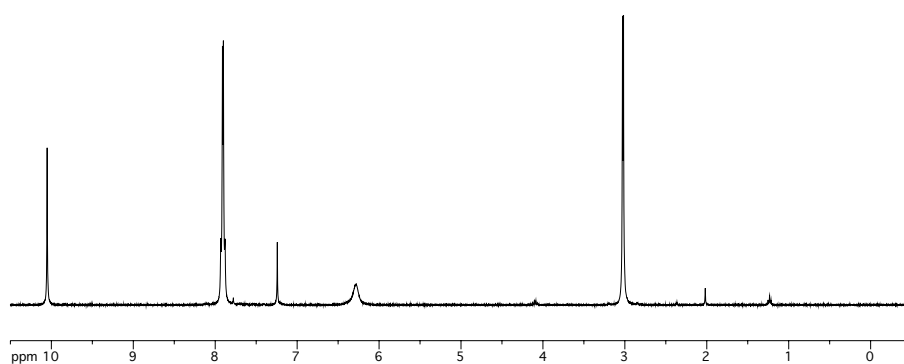
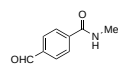
Found 268.1; **IR (thin film)** 3059, 1637, 1533, 1438, 1264, 983 cm^{-1} ; **TLC** (1:1 Hexane/EtOAc) $R_f = .38$.

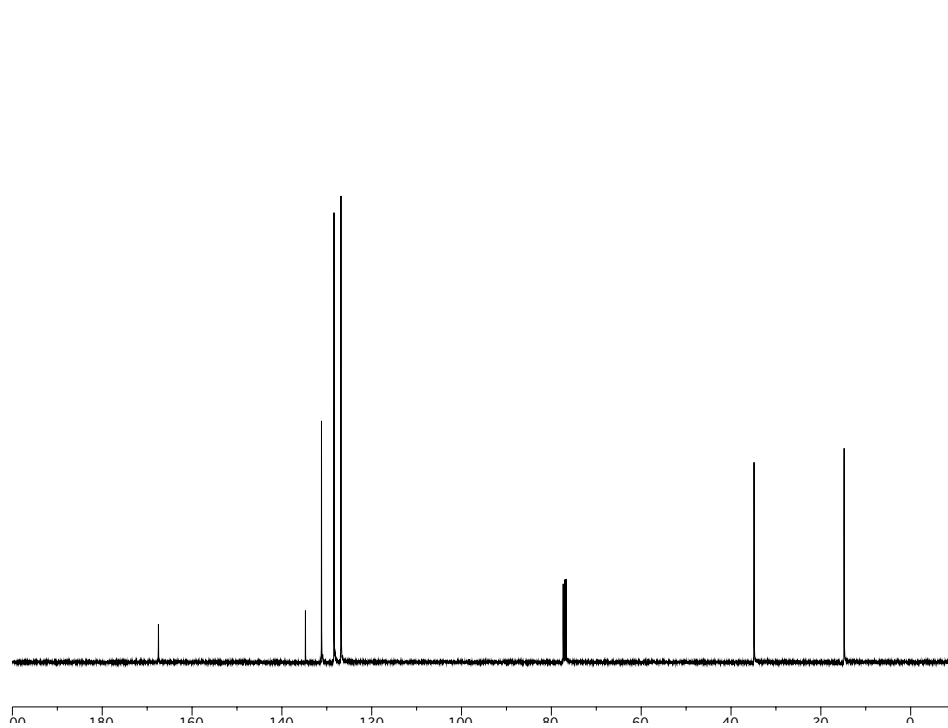
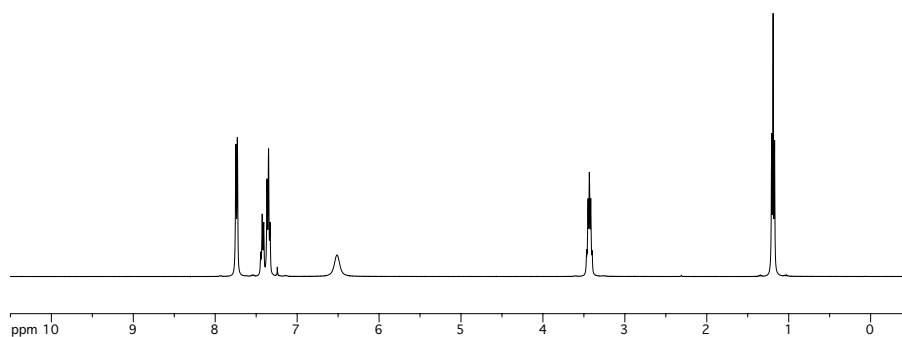


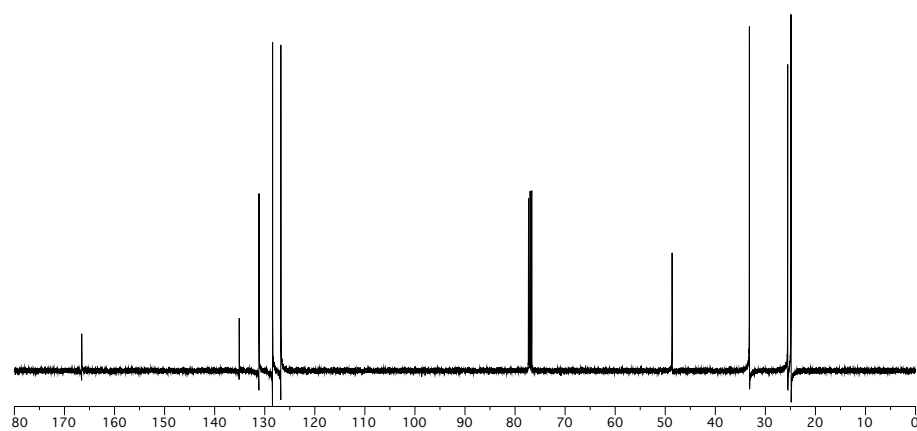
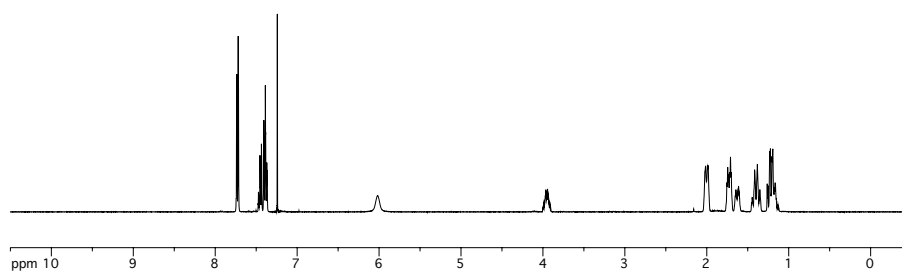
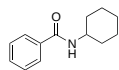


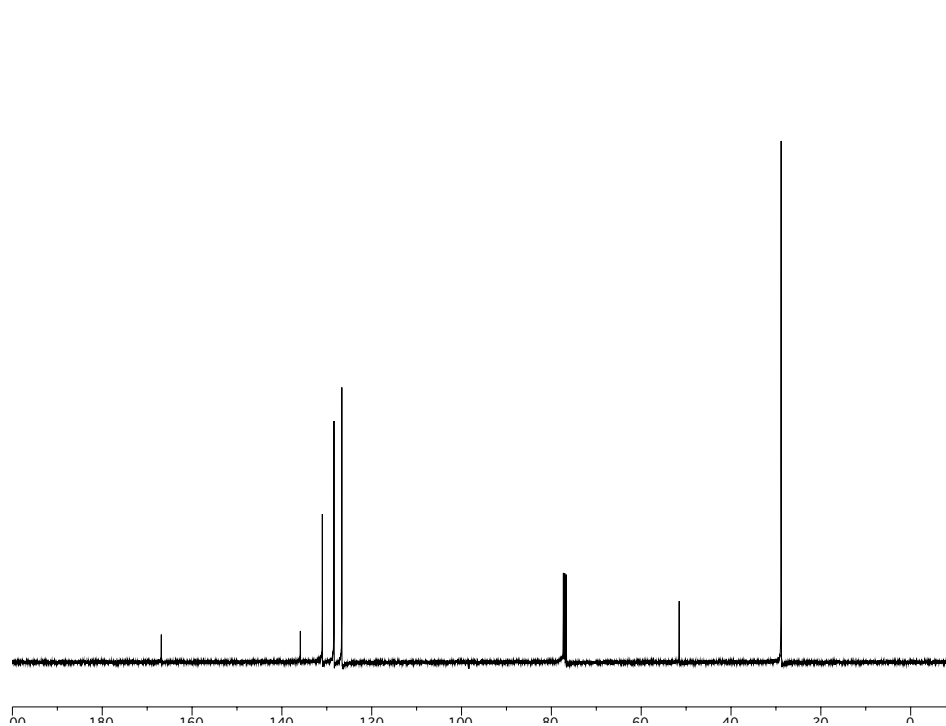
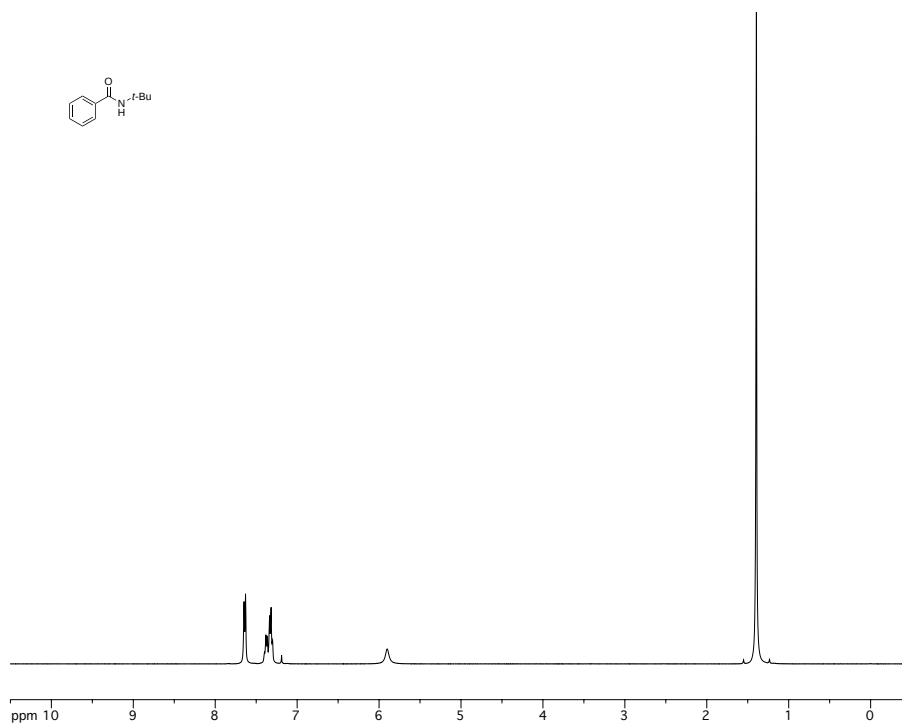


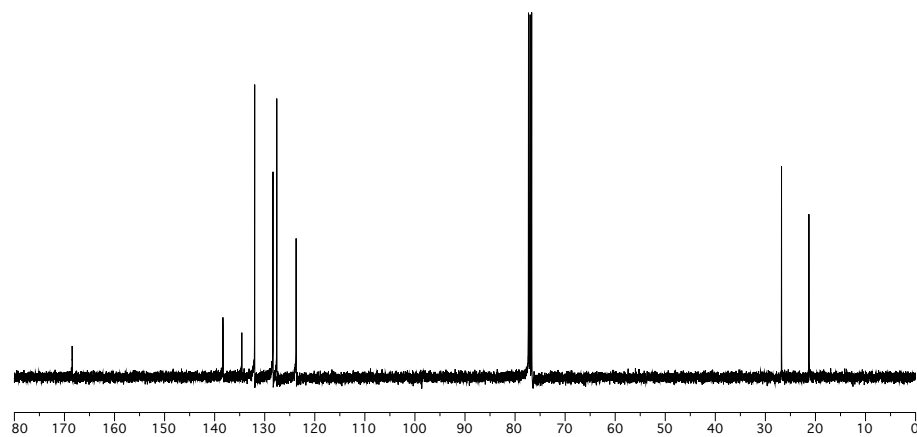
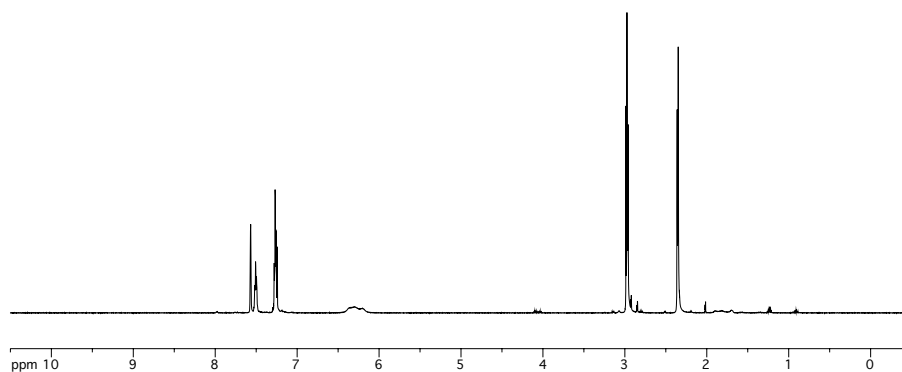
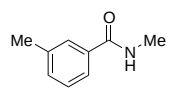


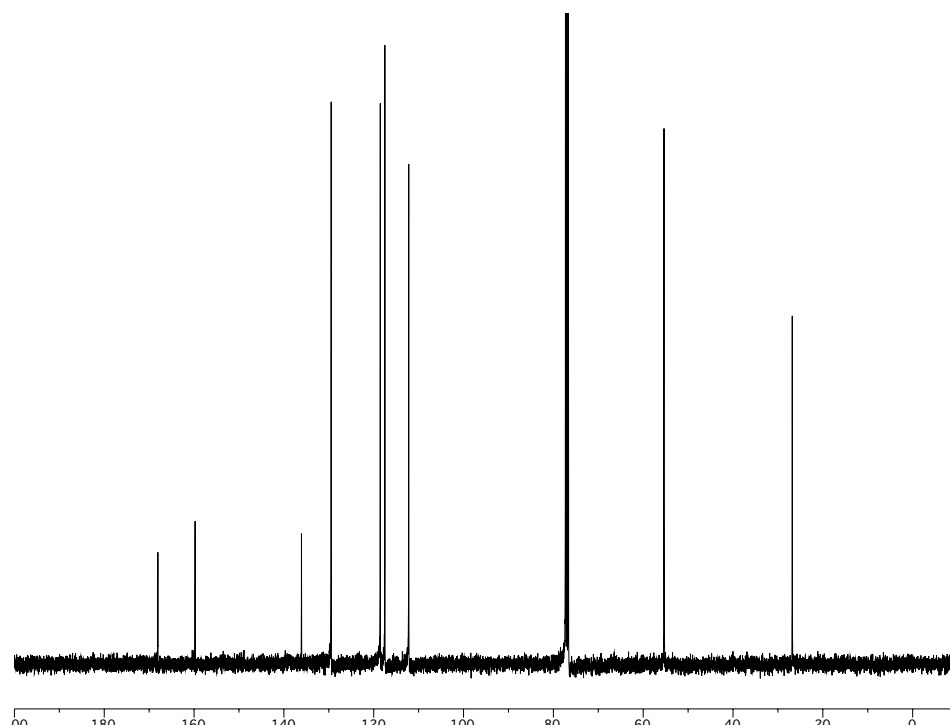
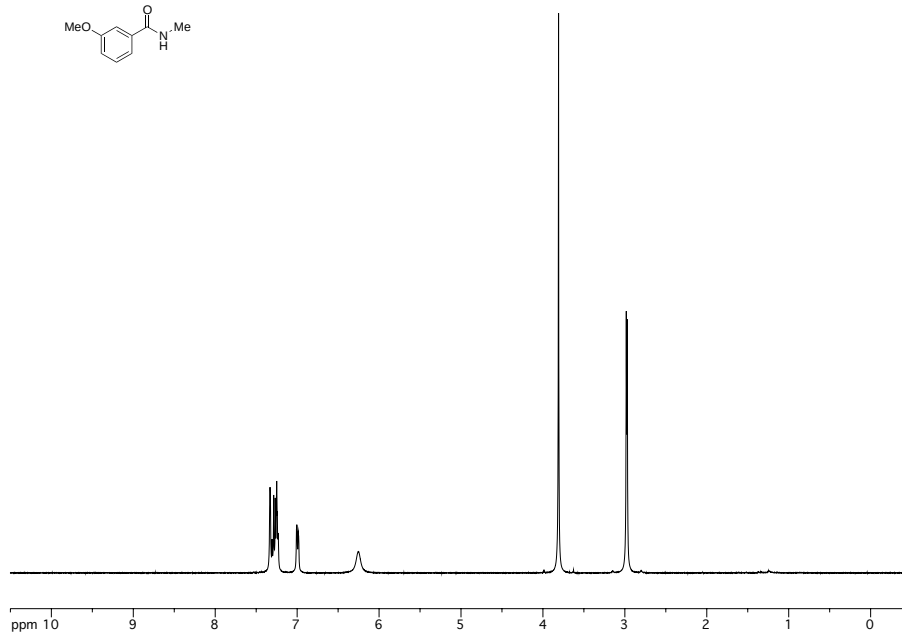
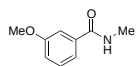


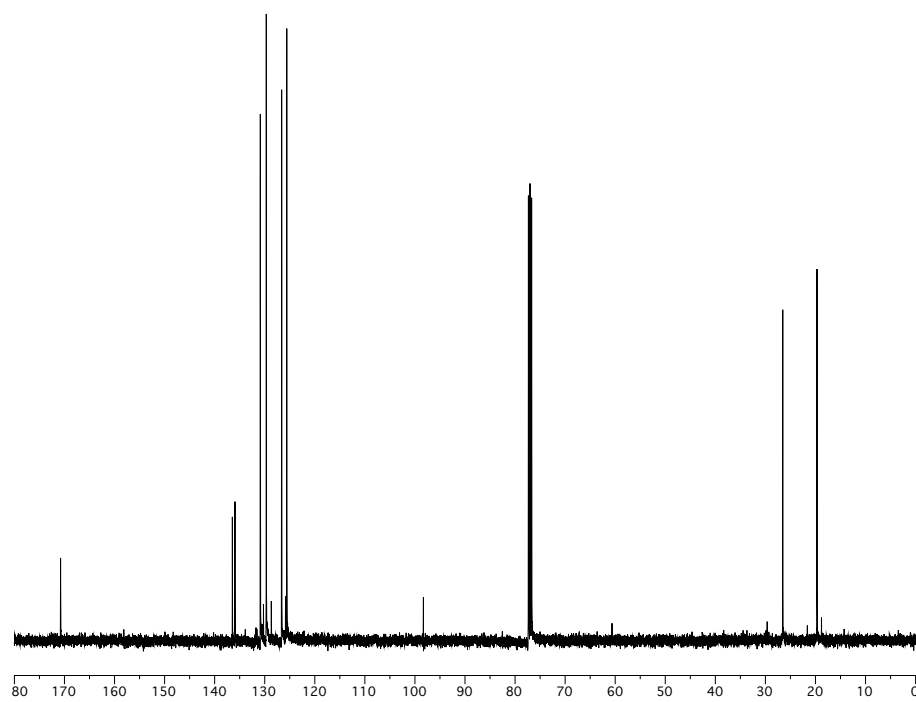
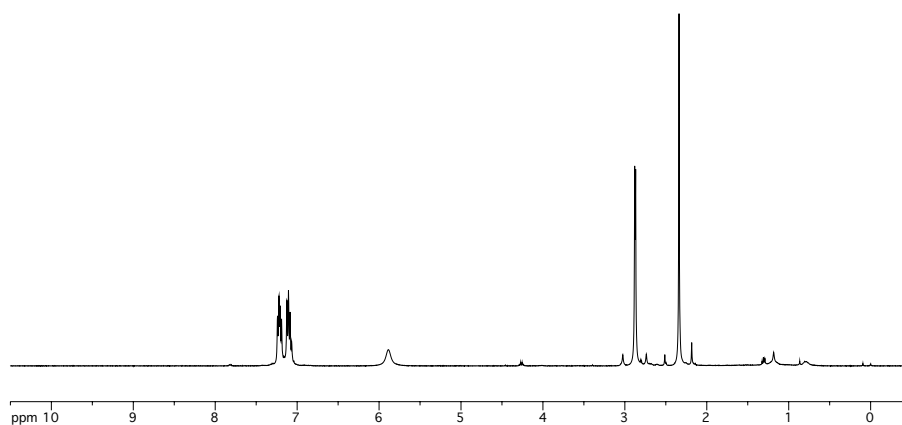


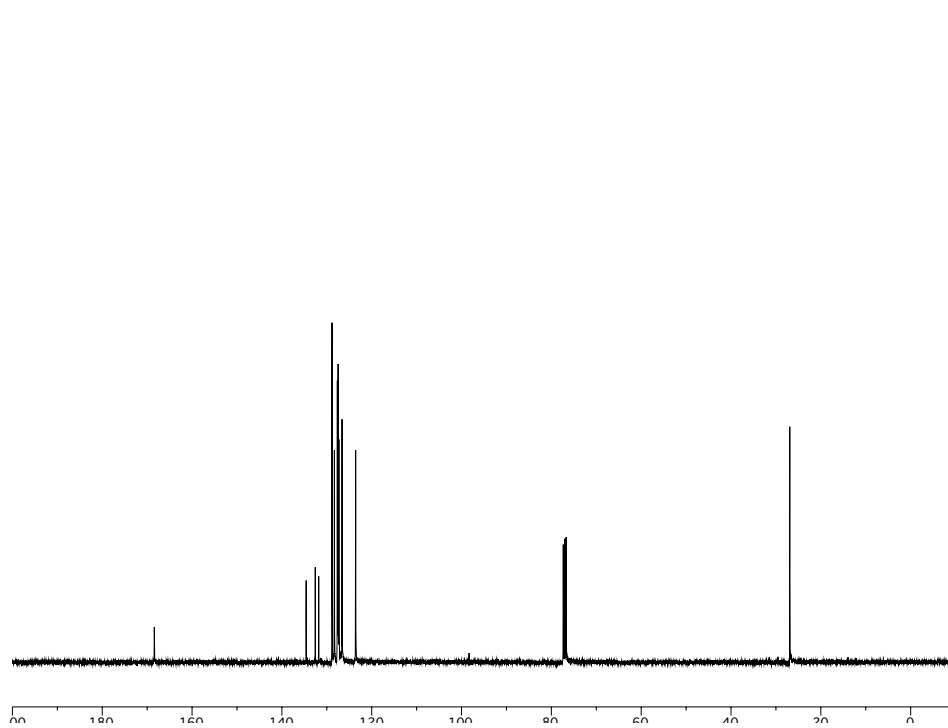
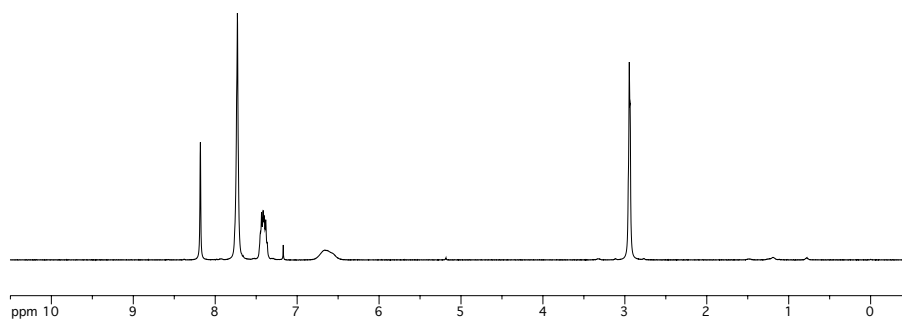
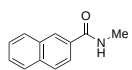


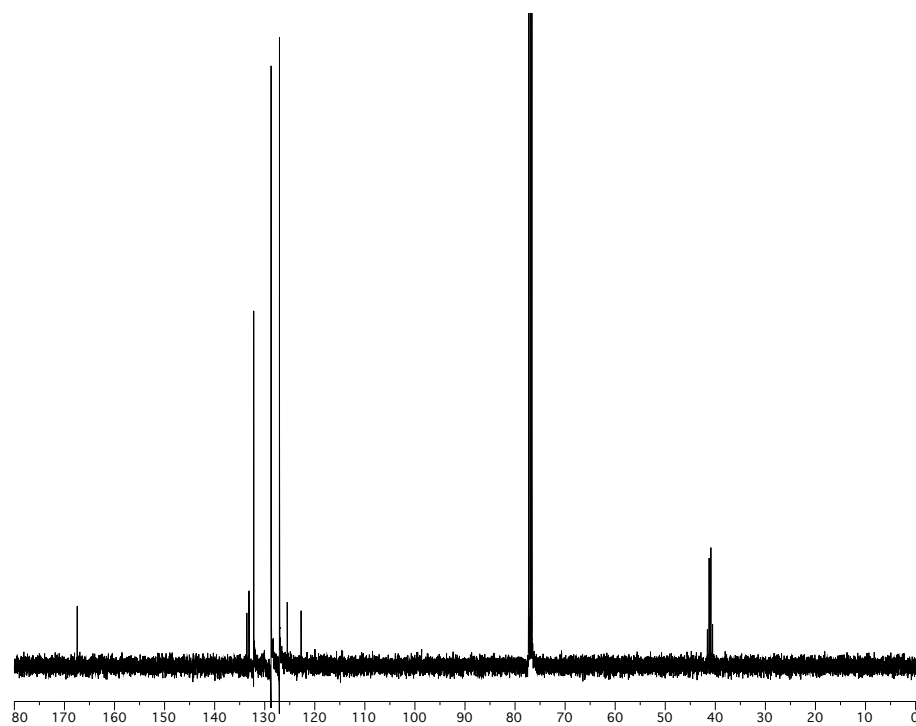
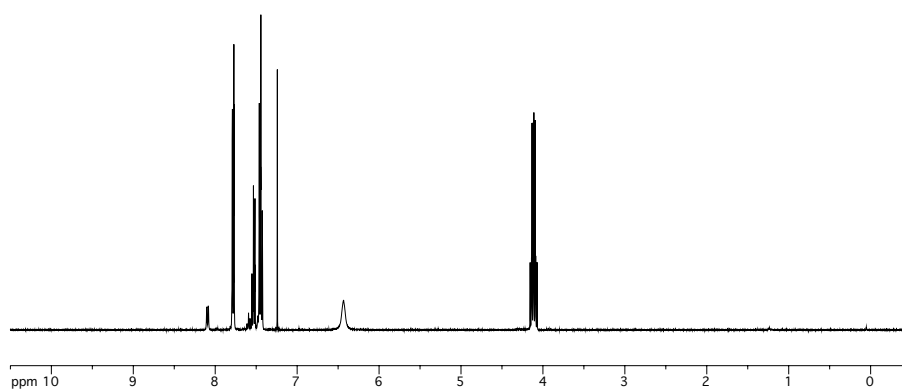
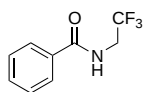


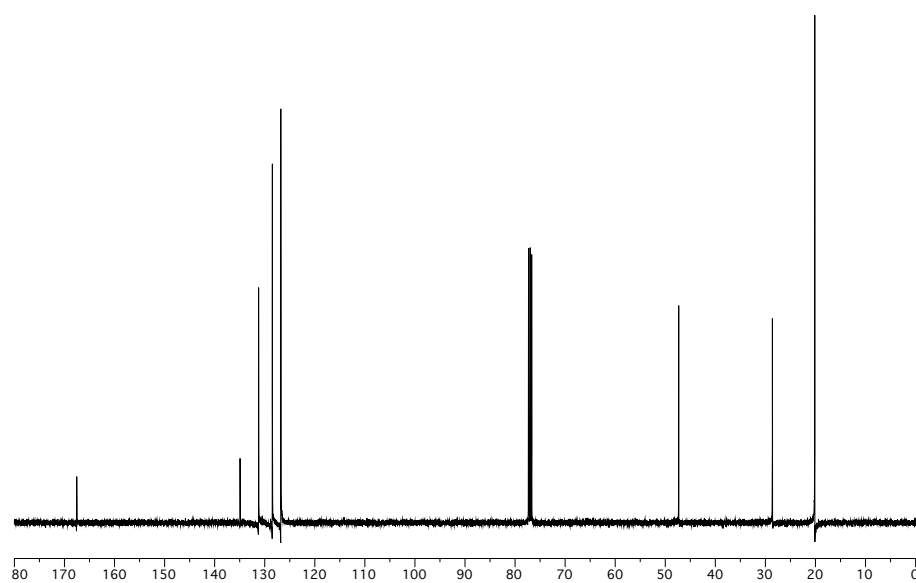
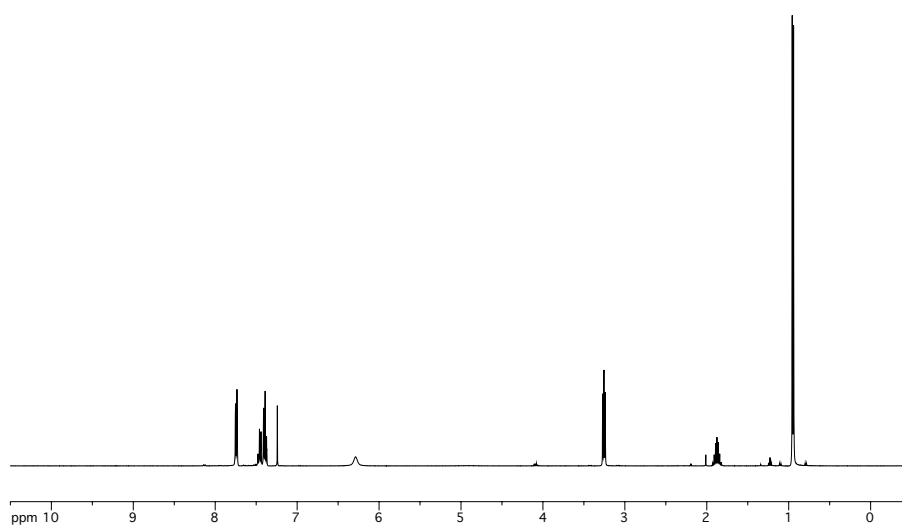
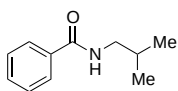


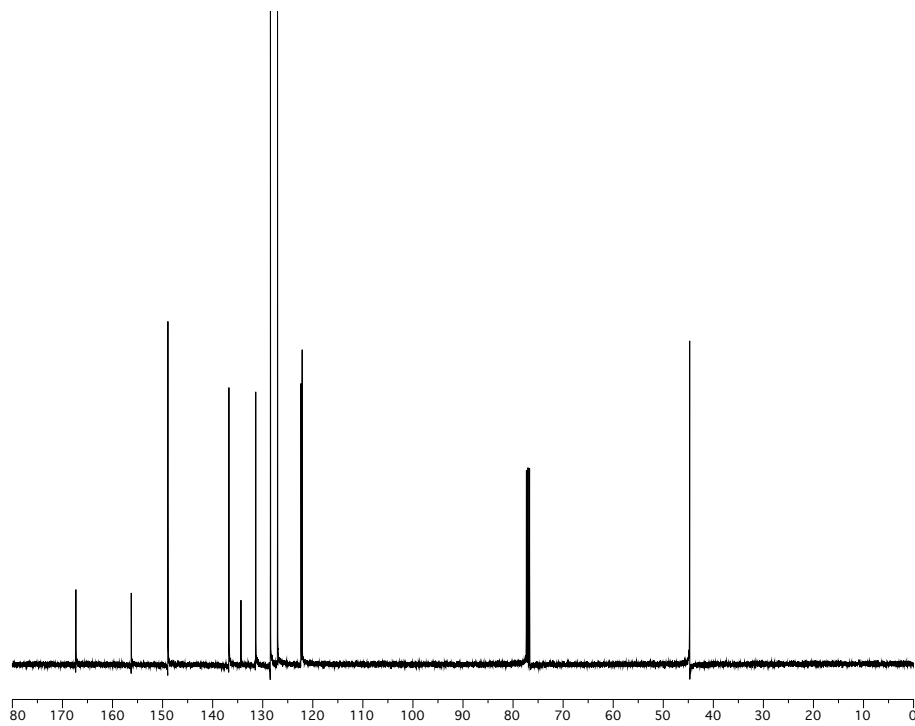
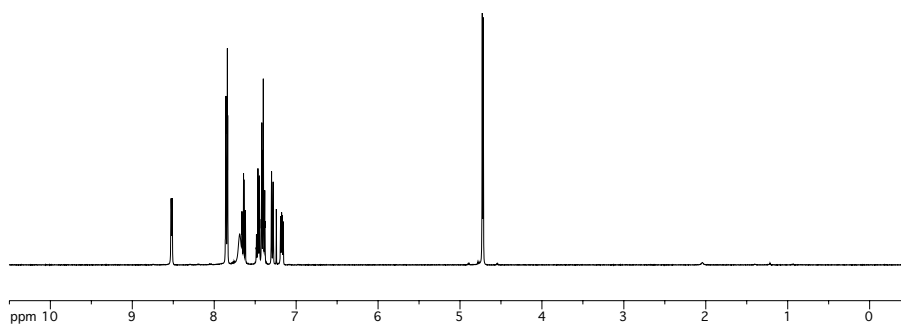
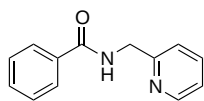


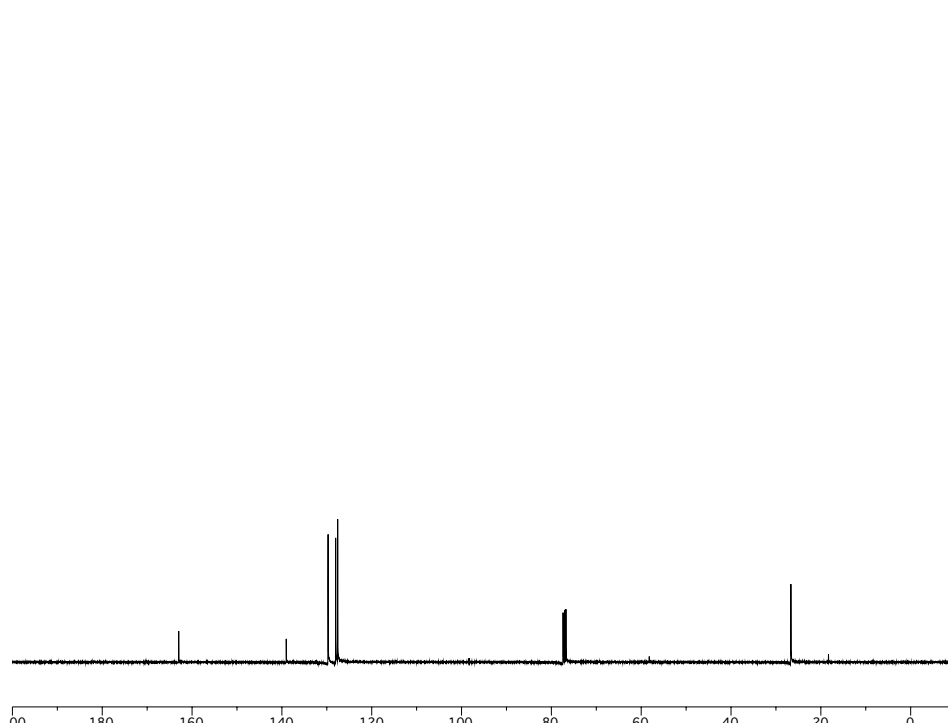
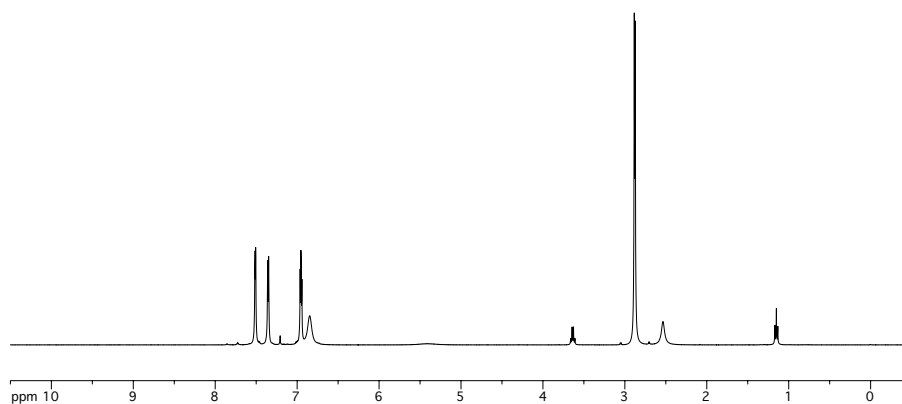
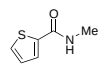


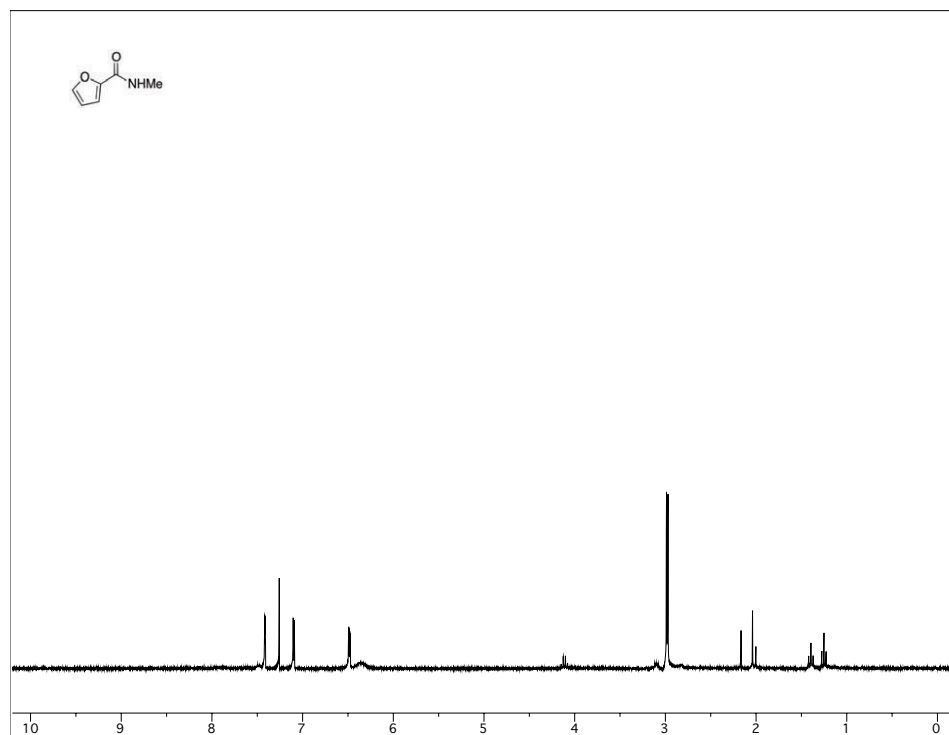


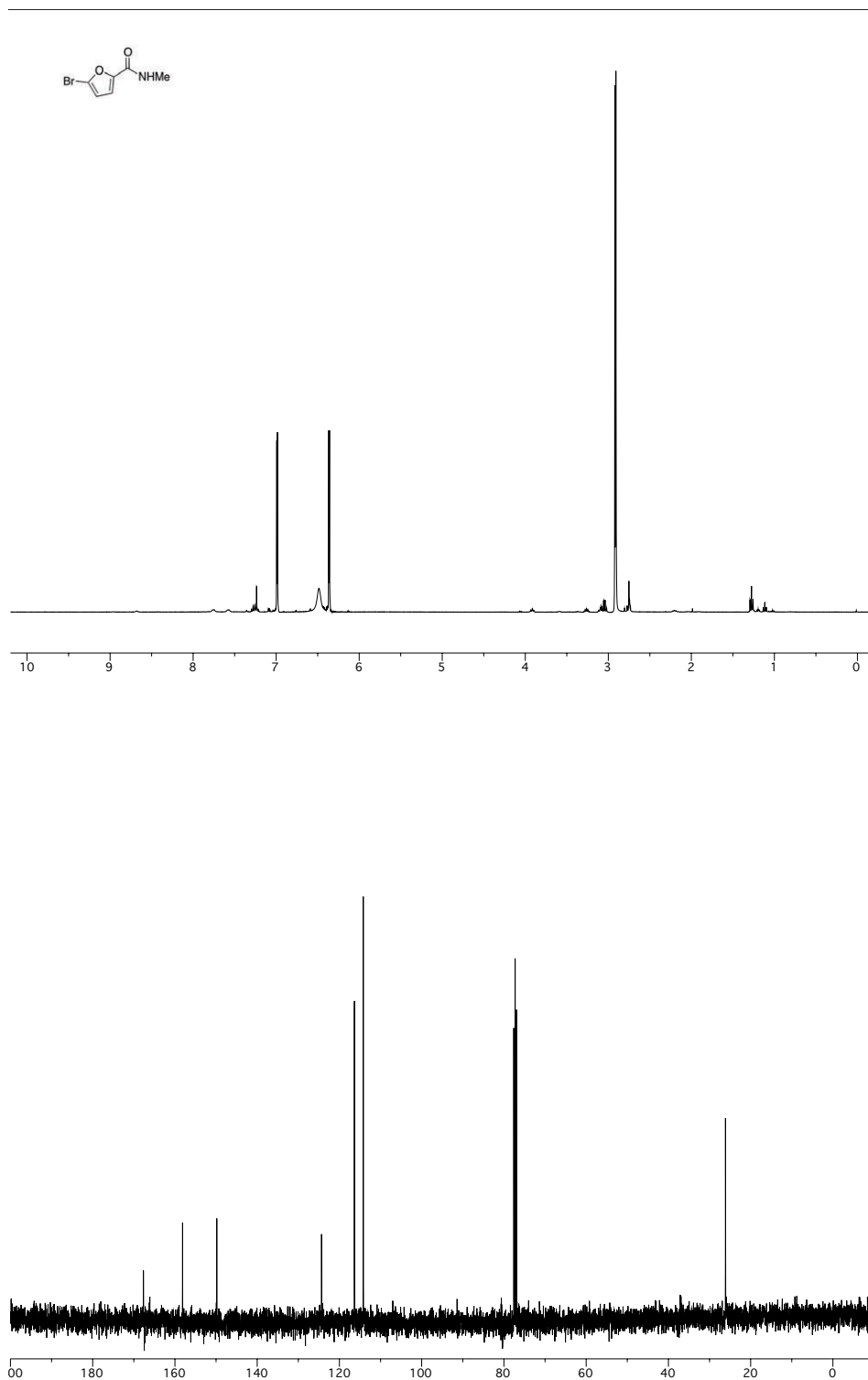


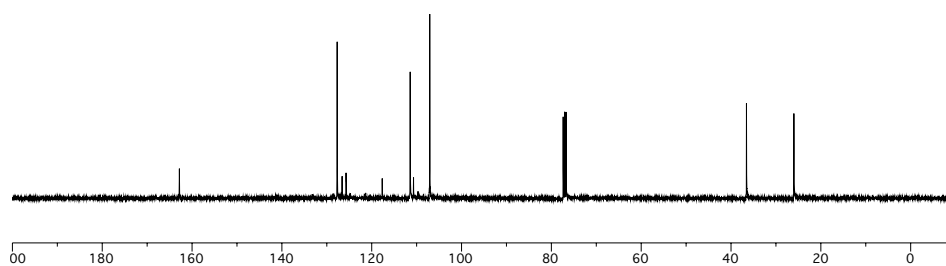
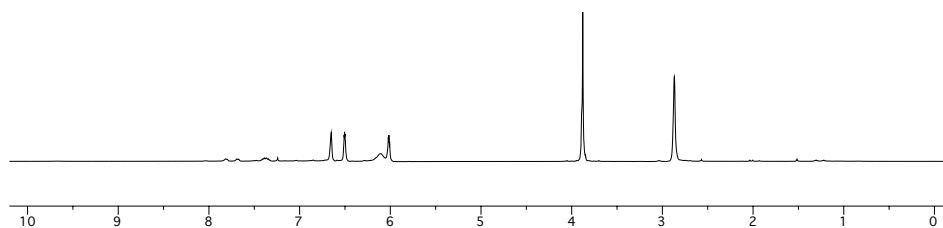
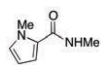


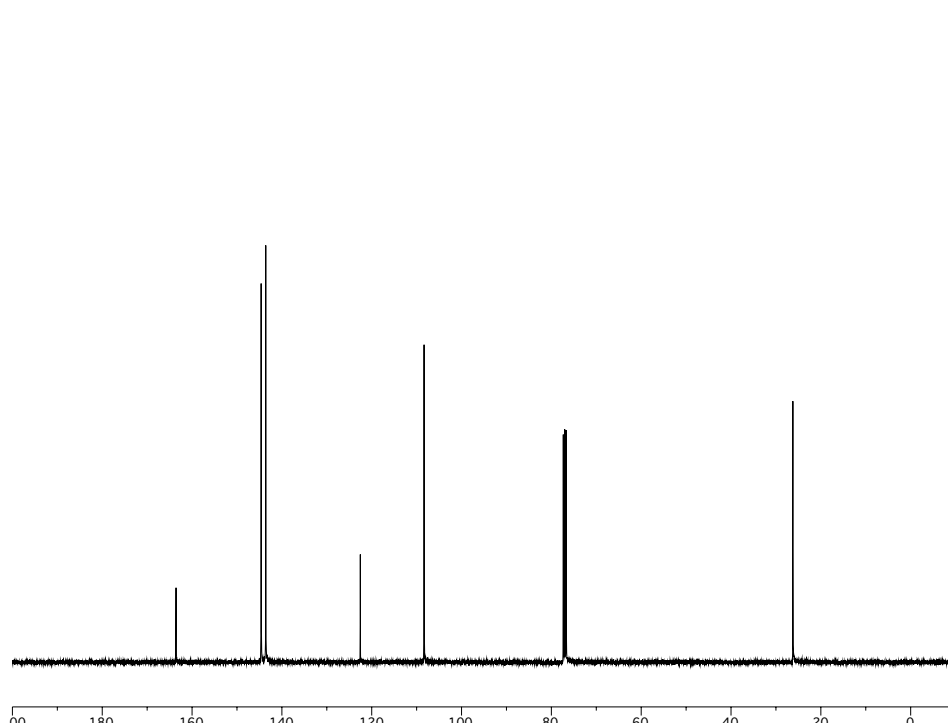
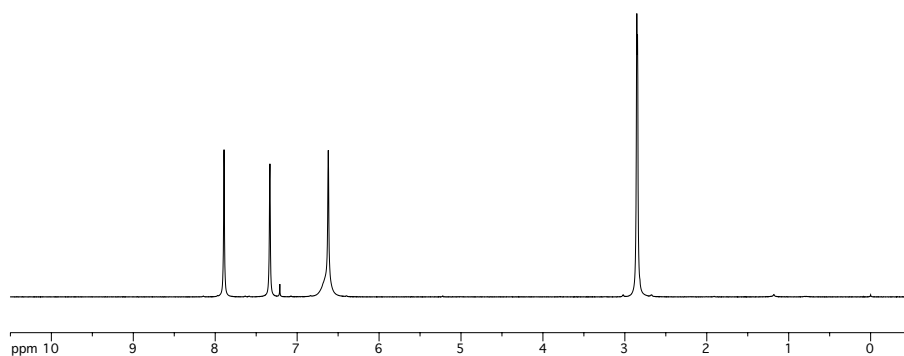


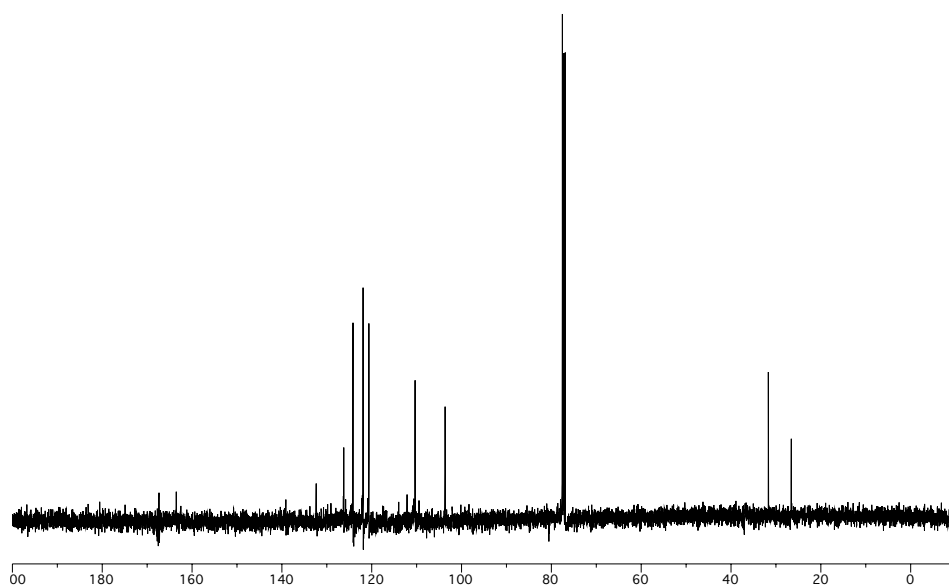
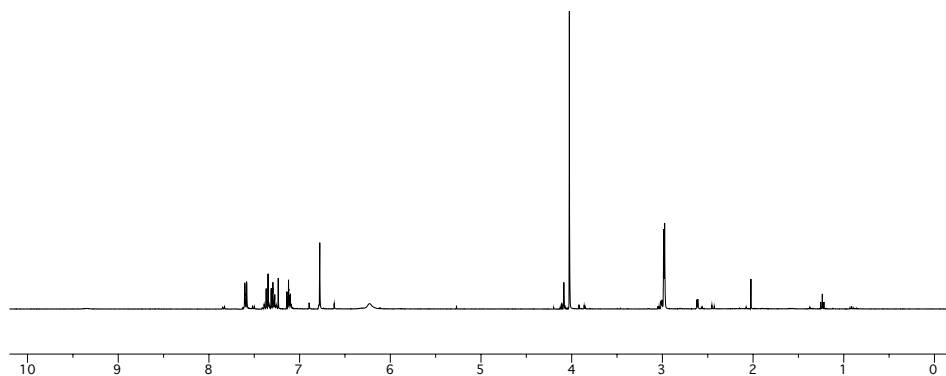
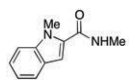


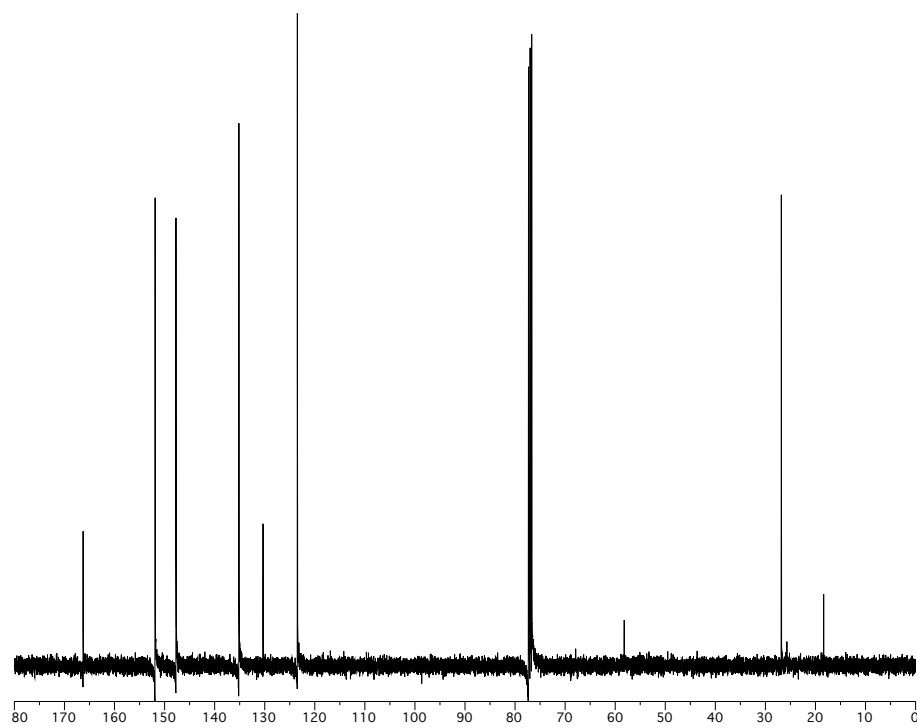
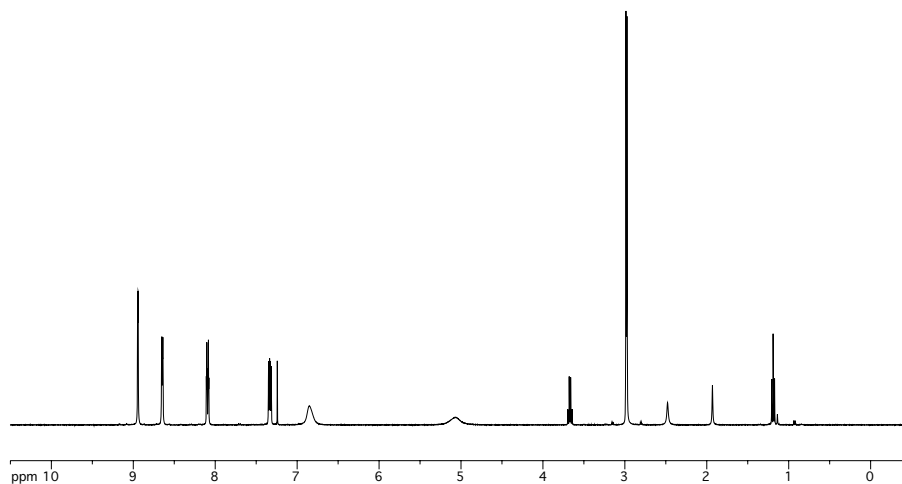


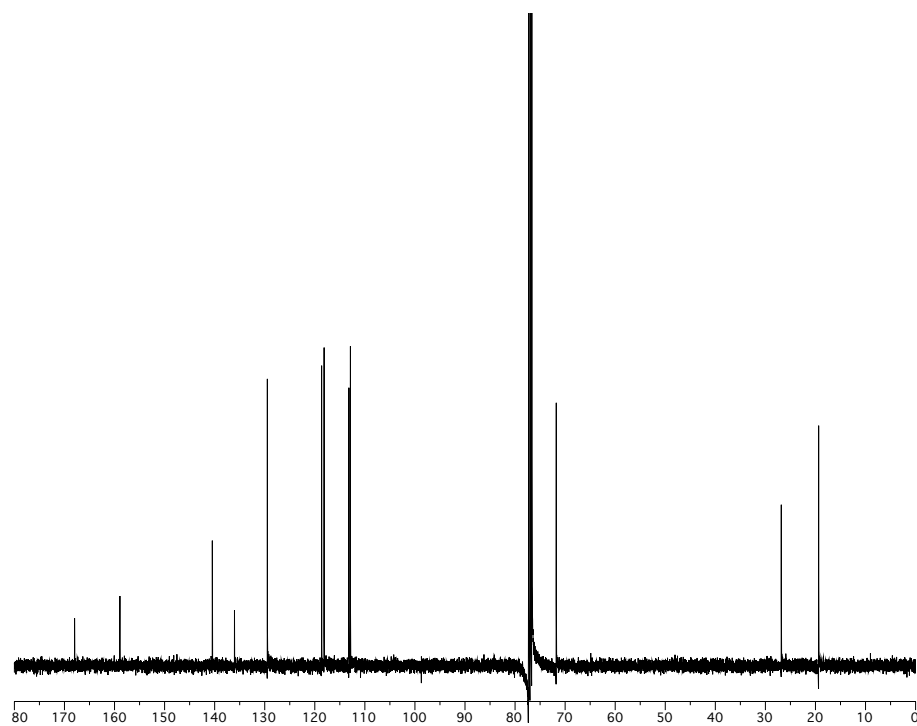
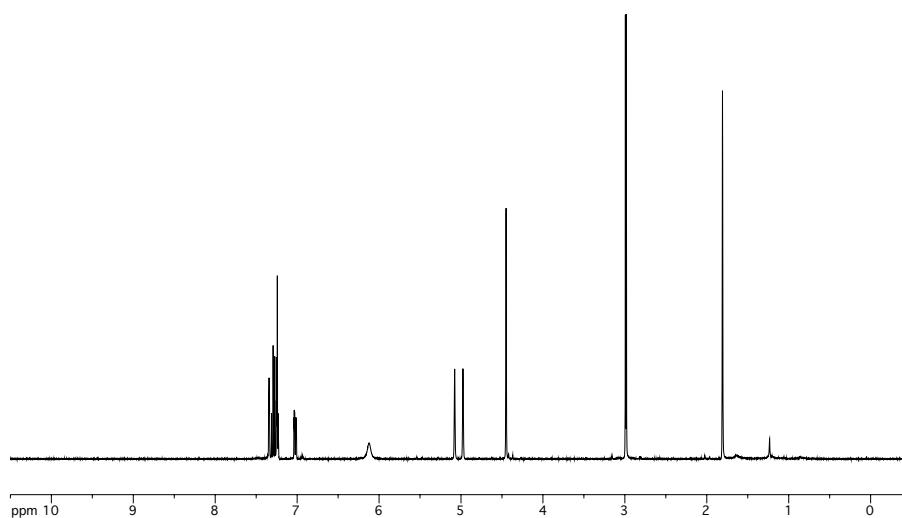
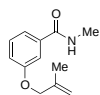


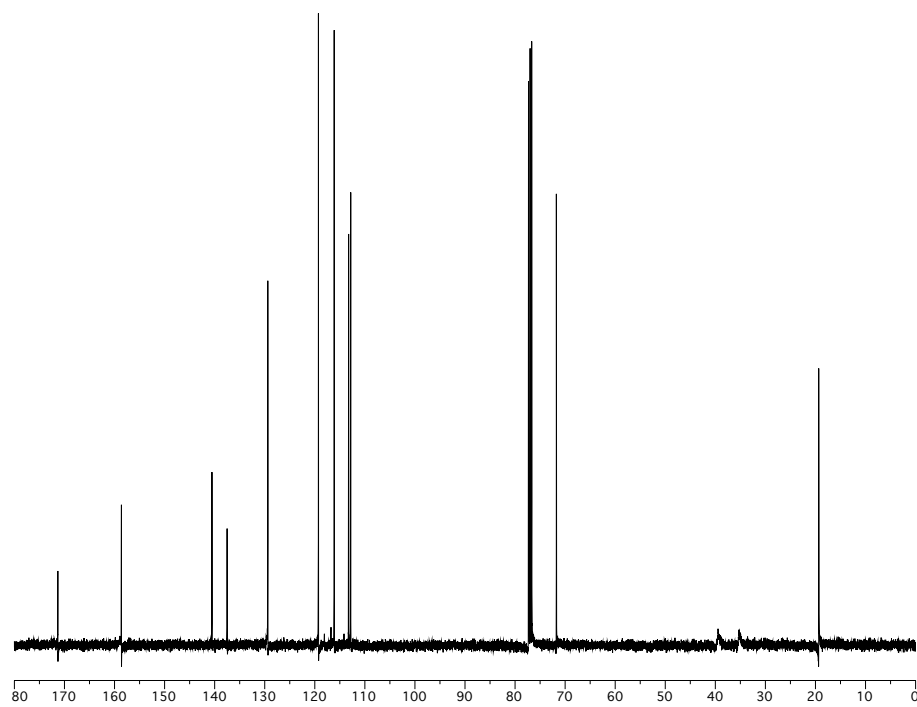
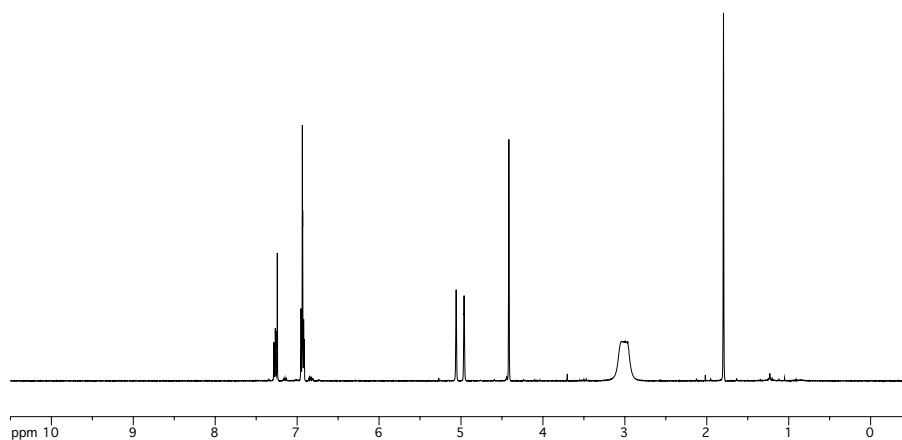
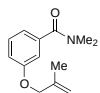


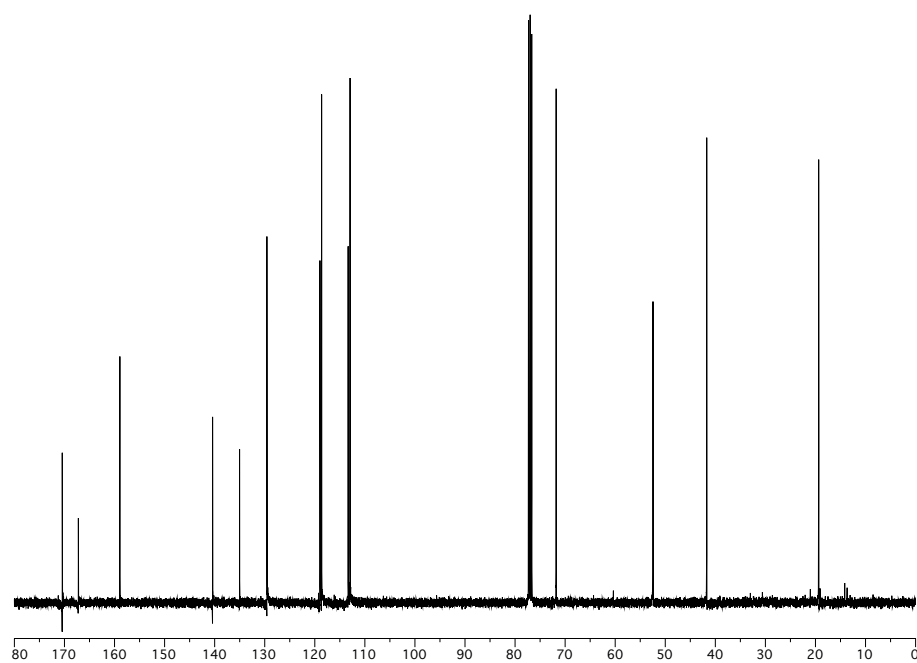
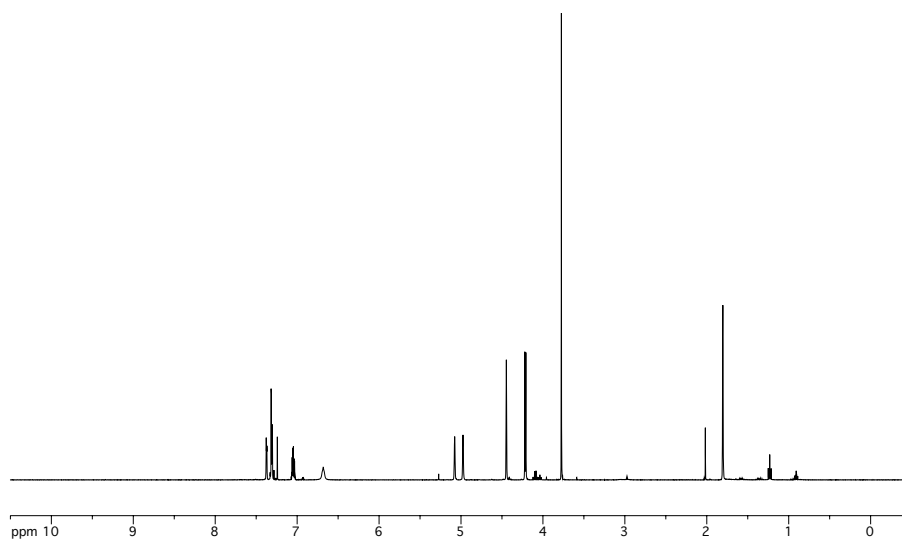
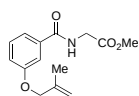


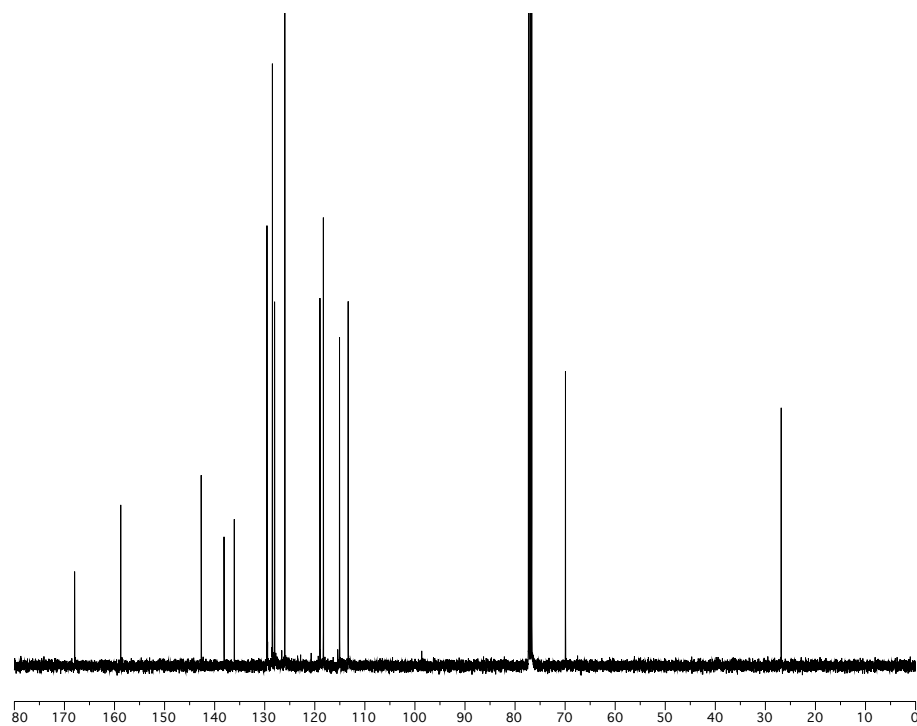
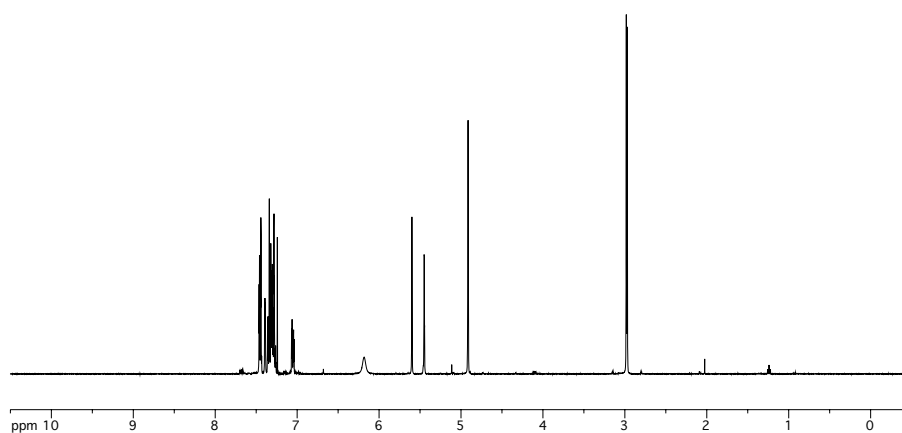


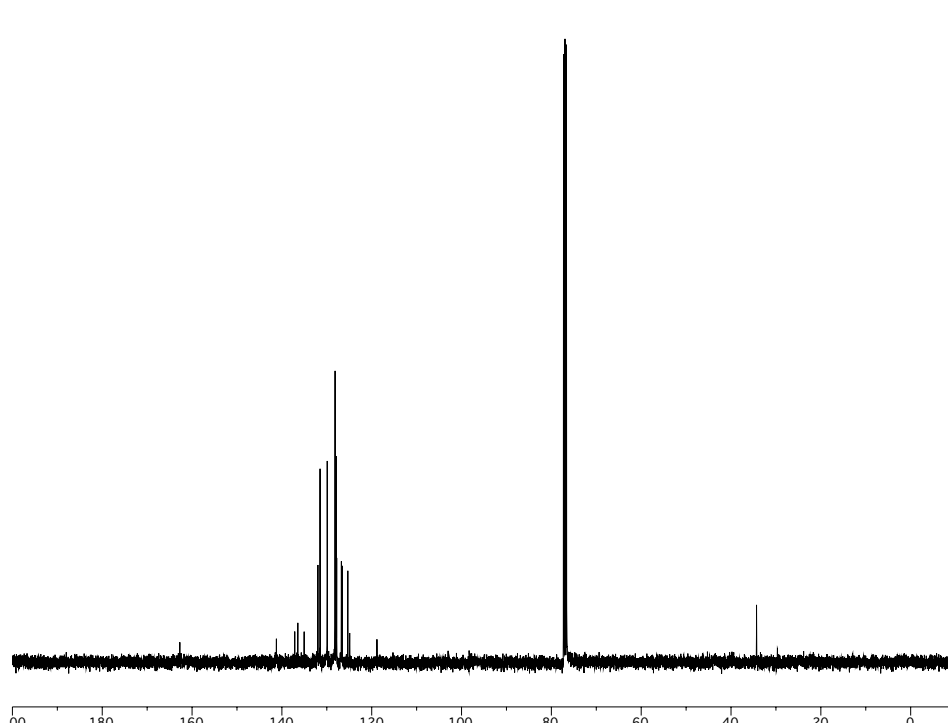
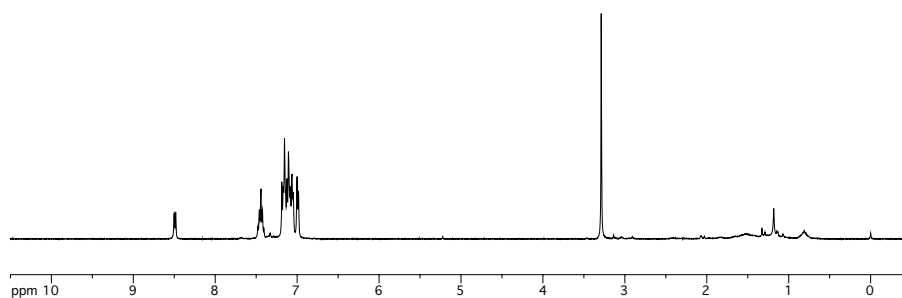


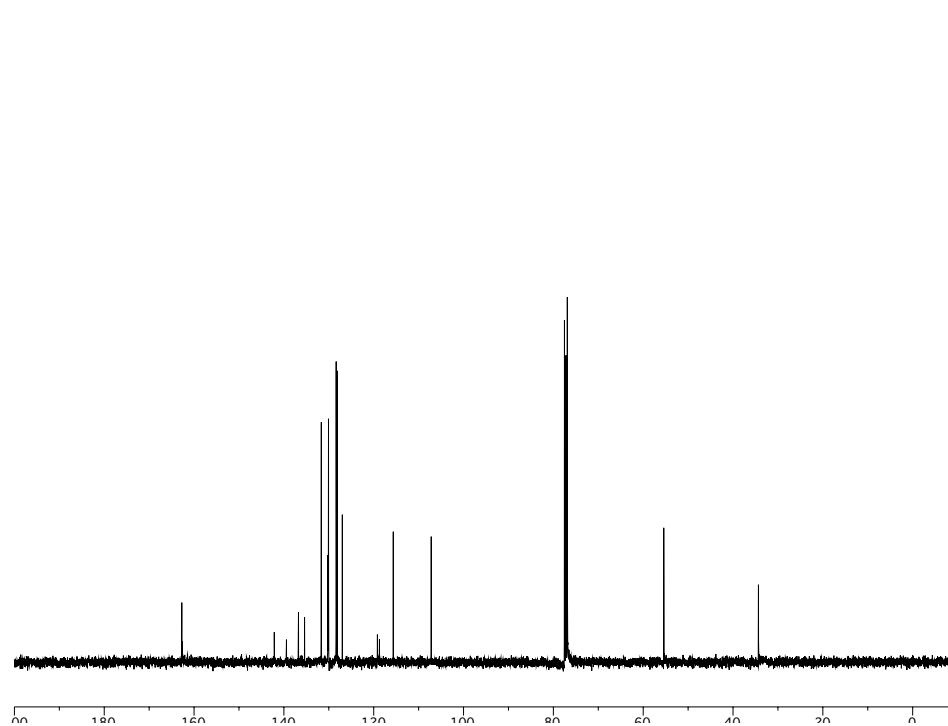
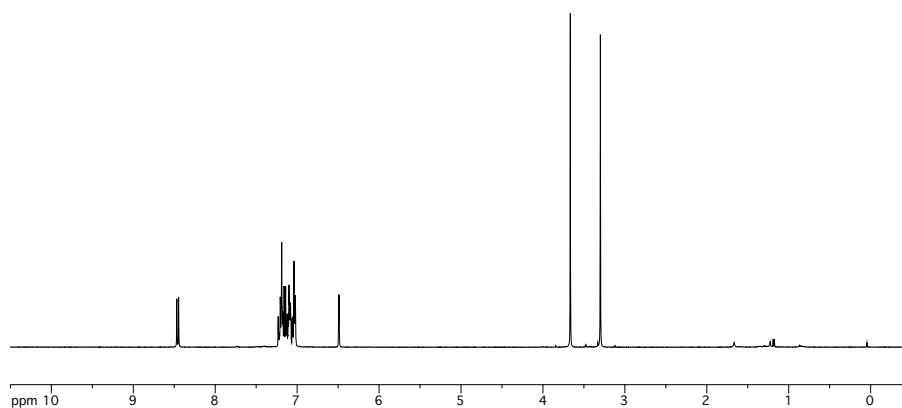
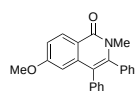


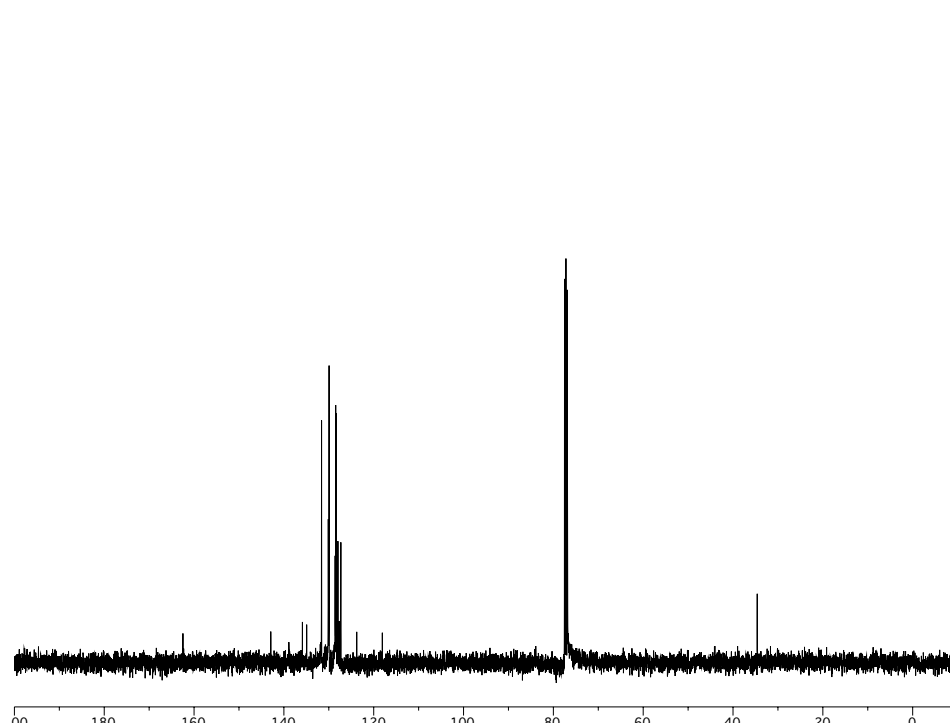
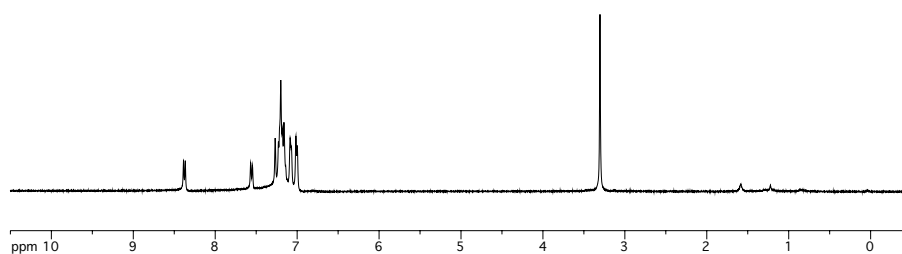
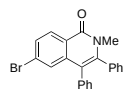


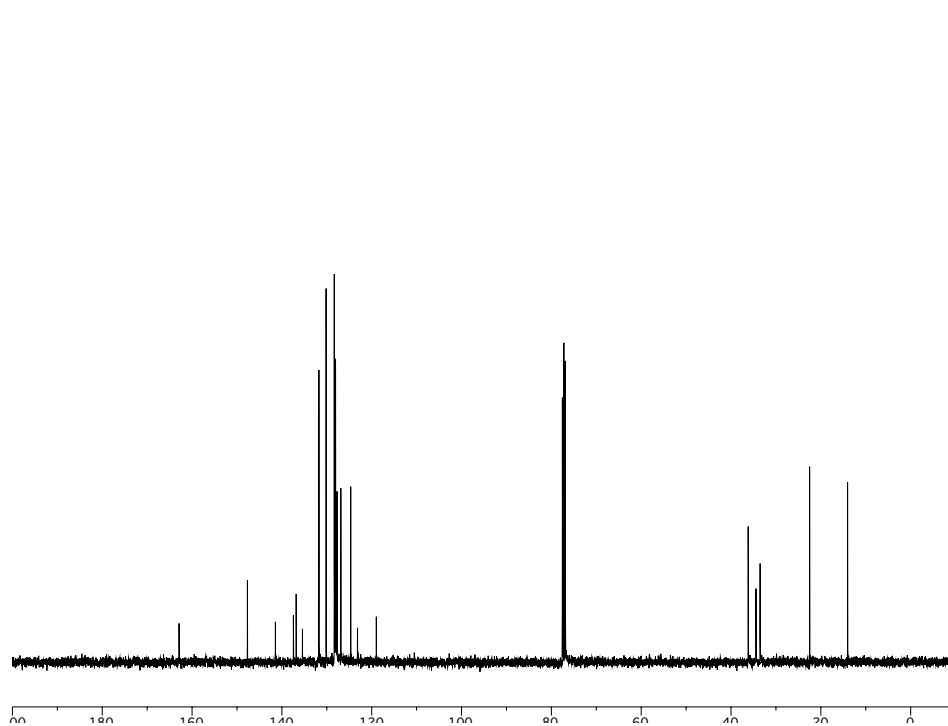
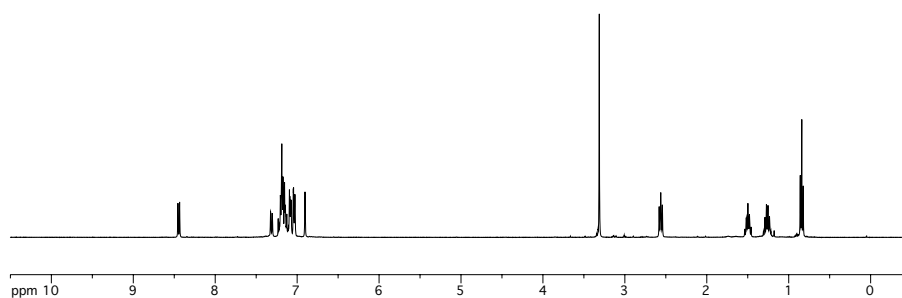
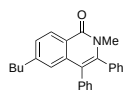


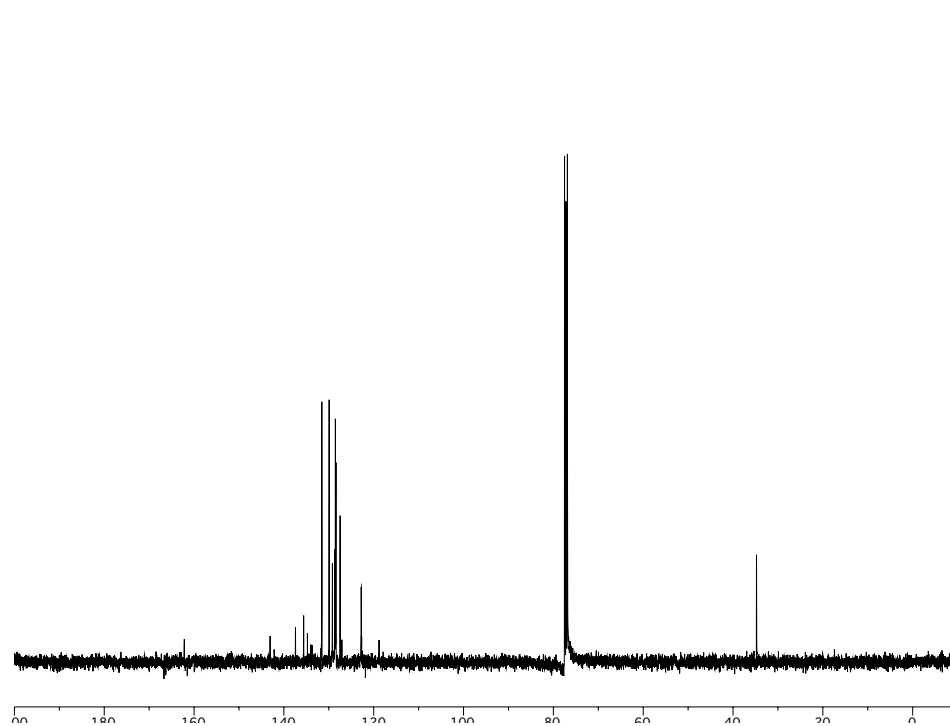
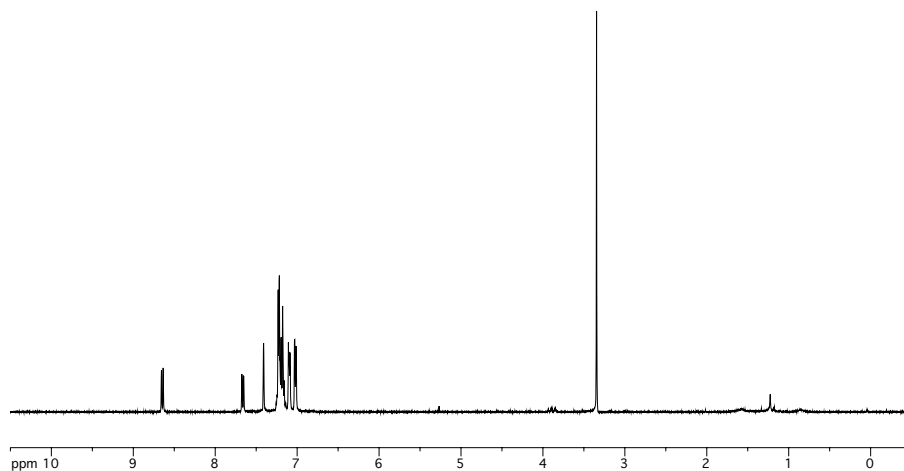
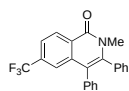


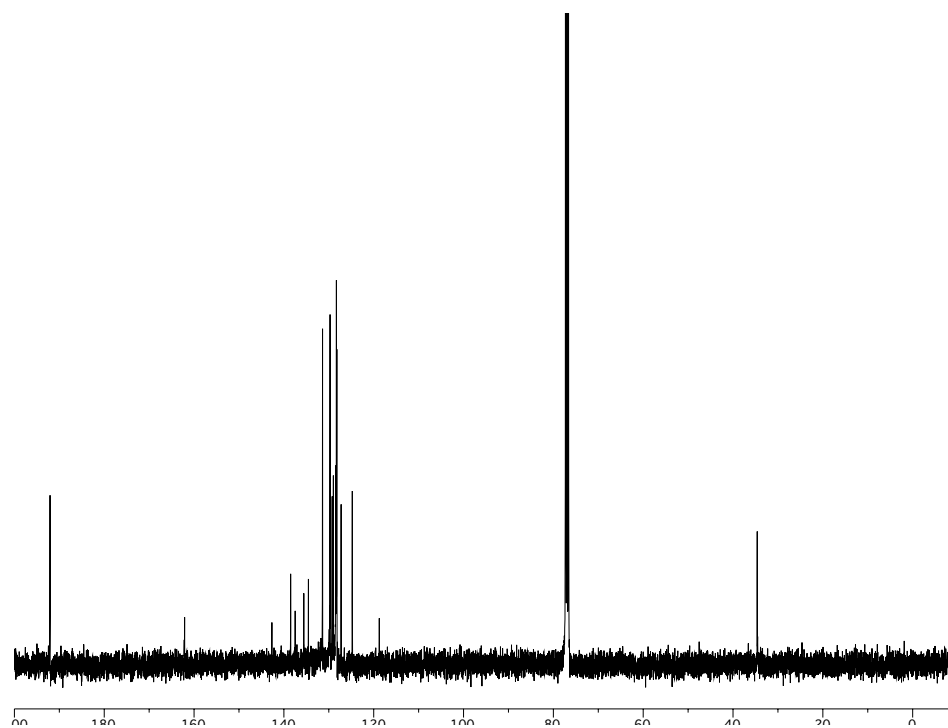
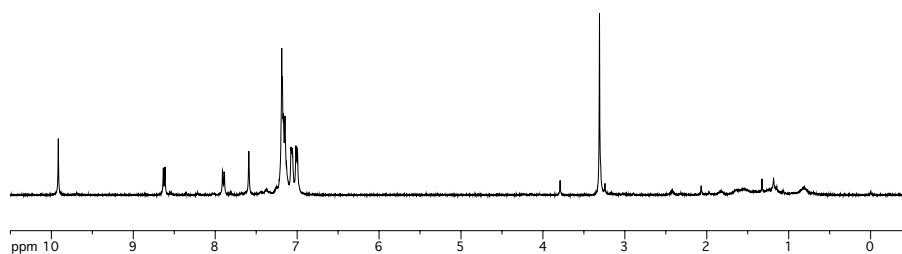
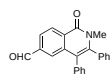


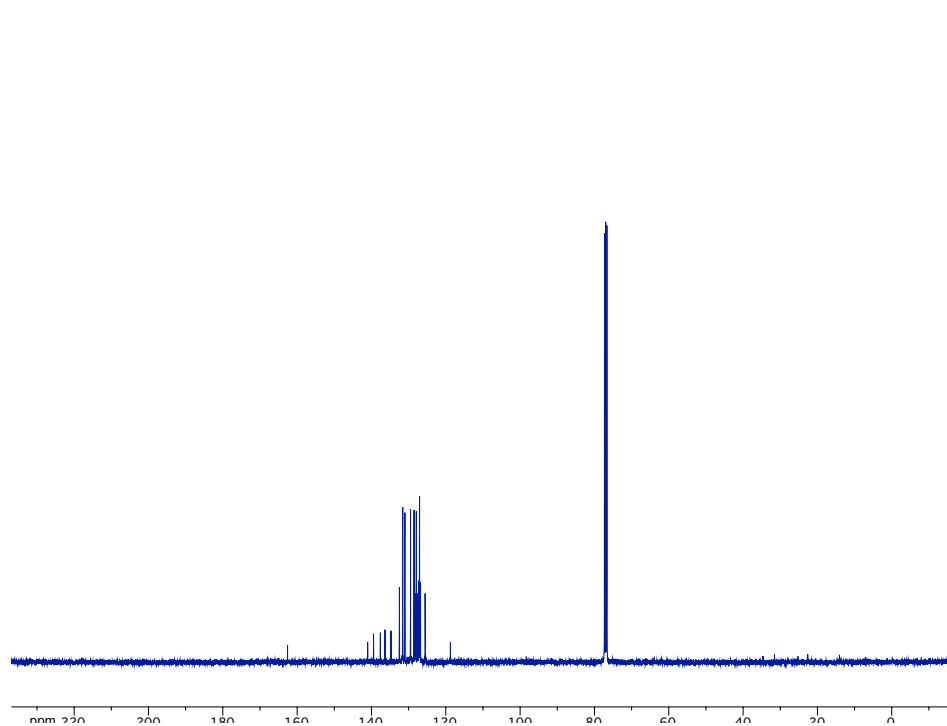
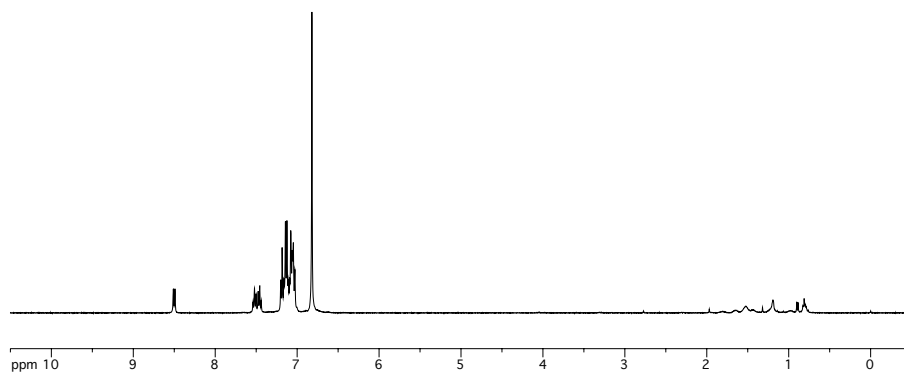


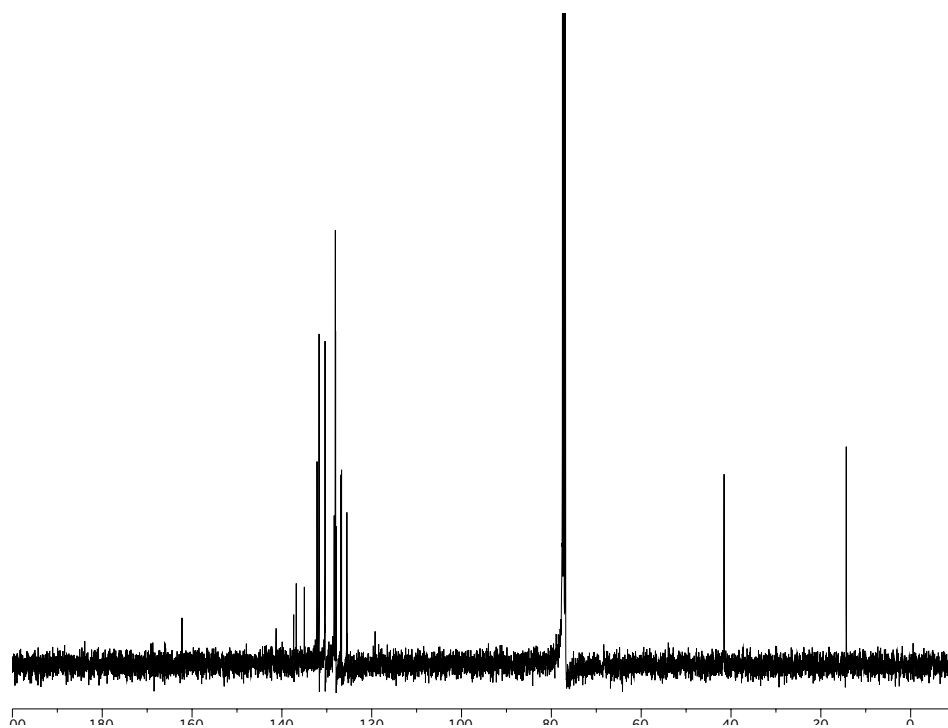
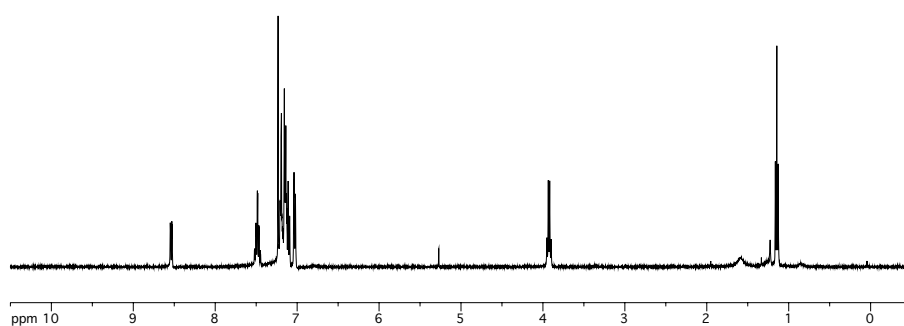


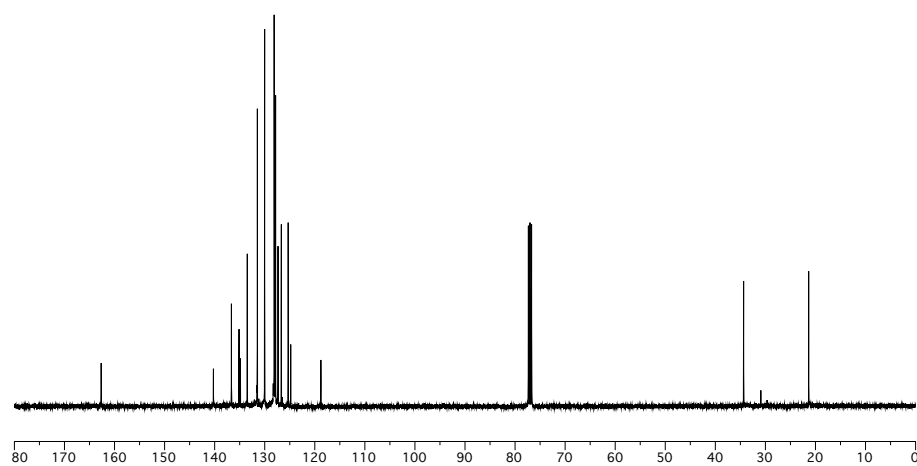
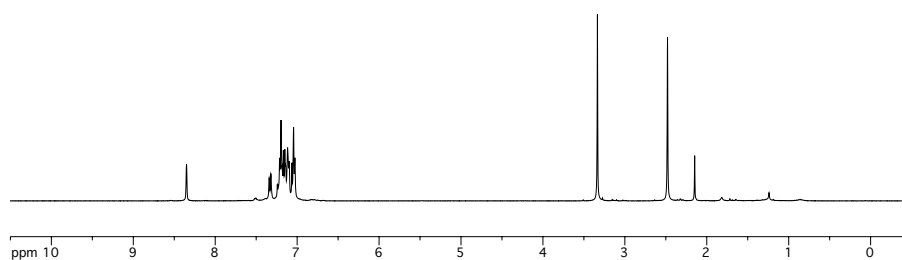
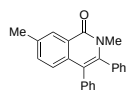


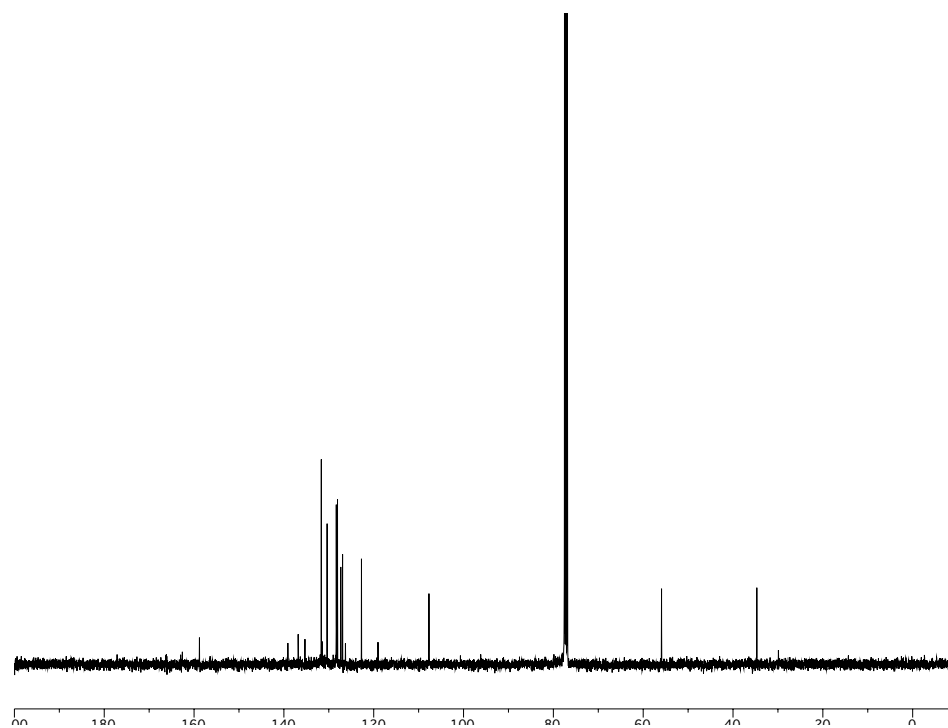
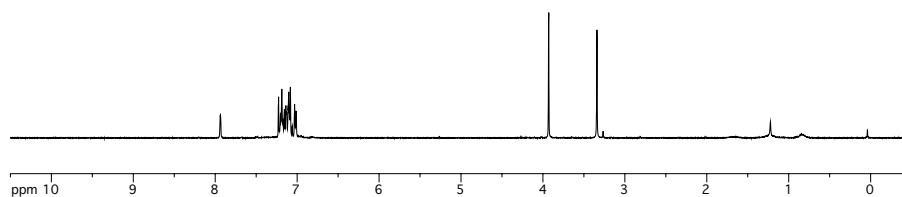
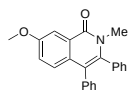


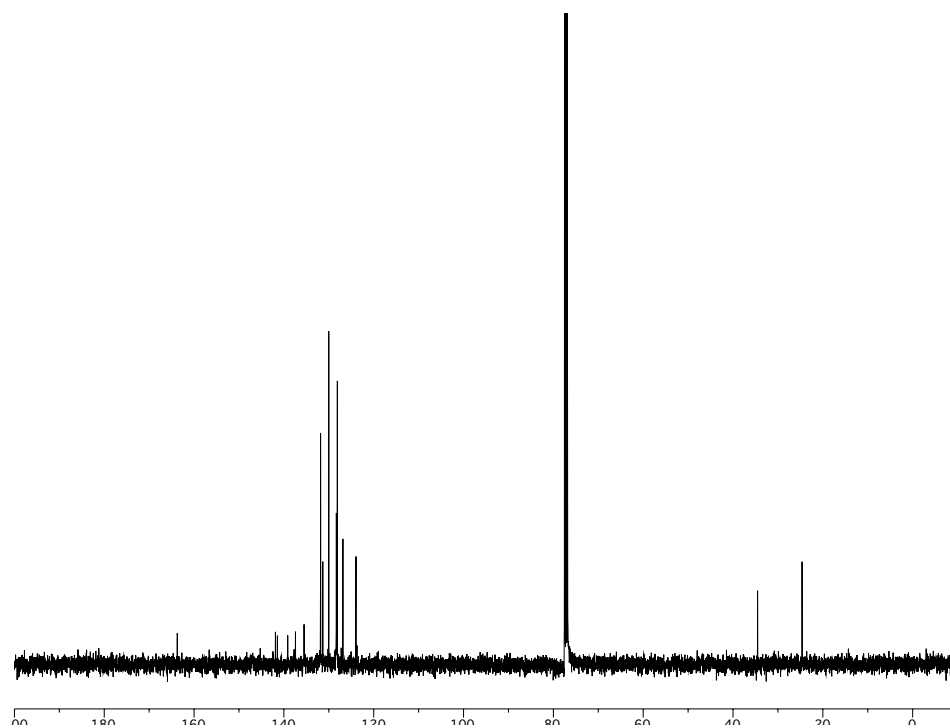
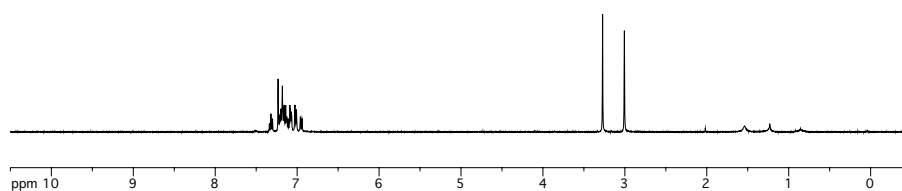
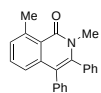


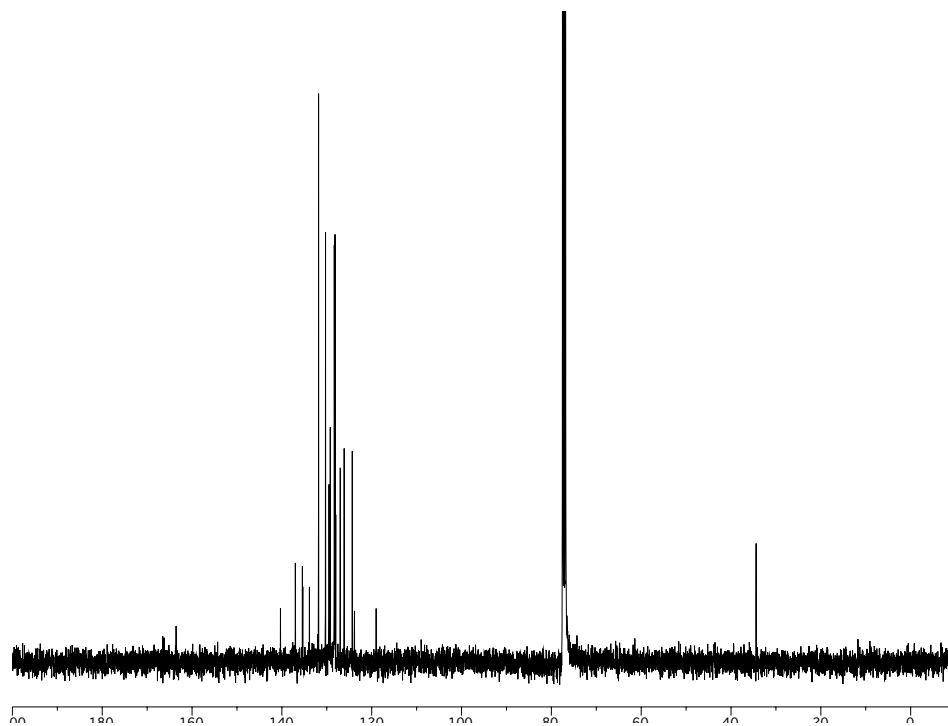
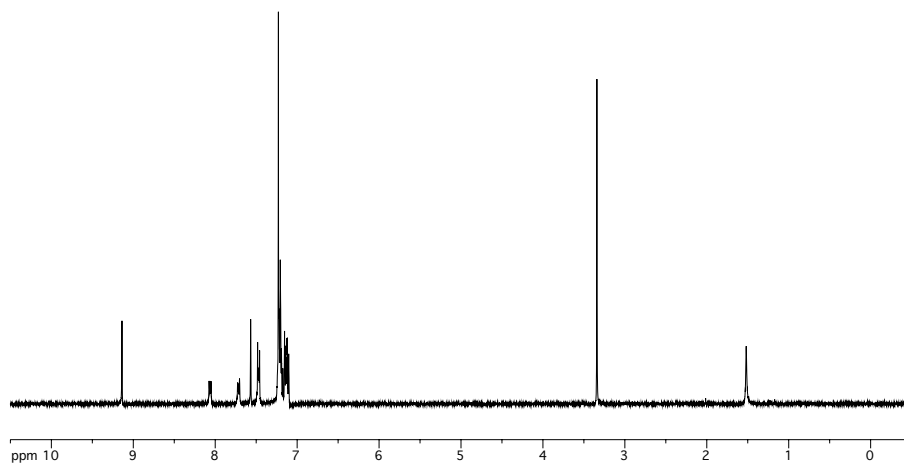
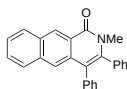


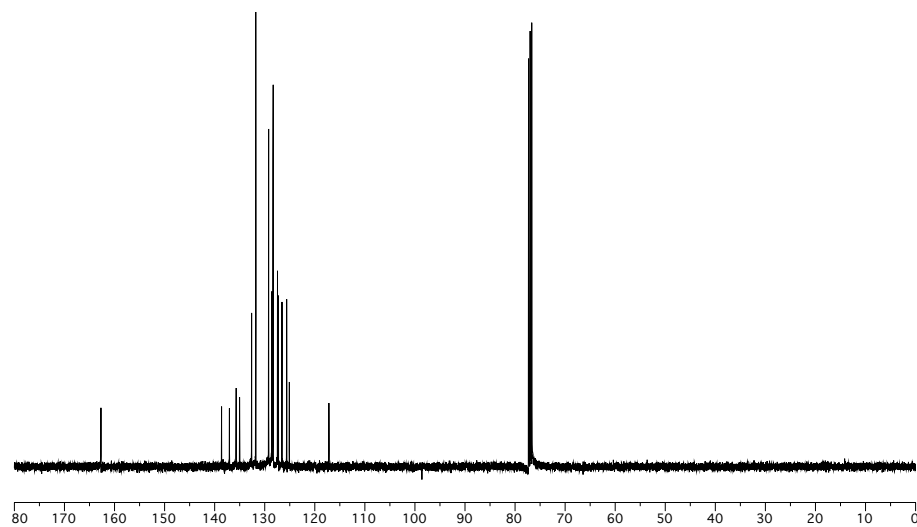
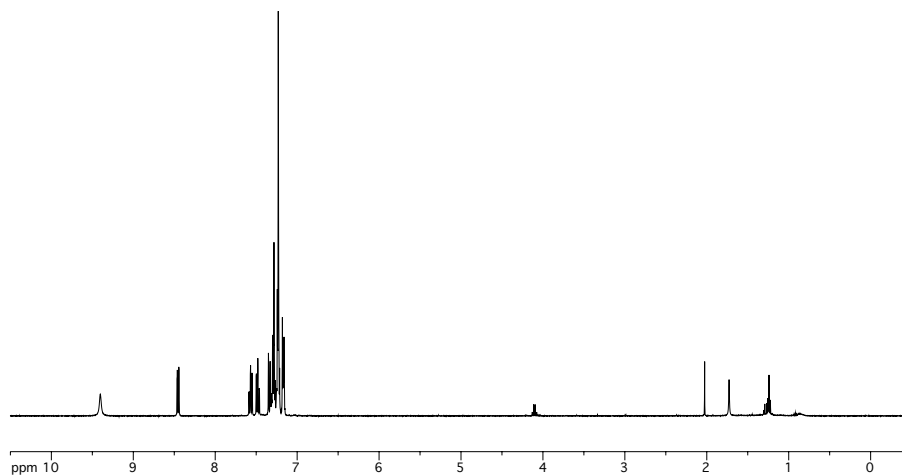


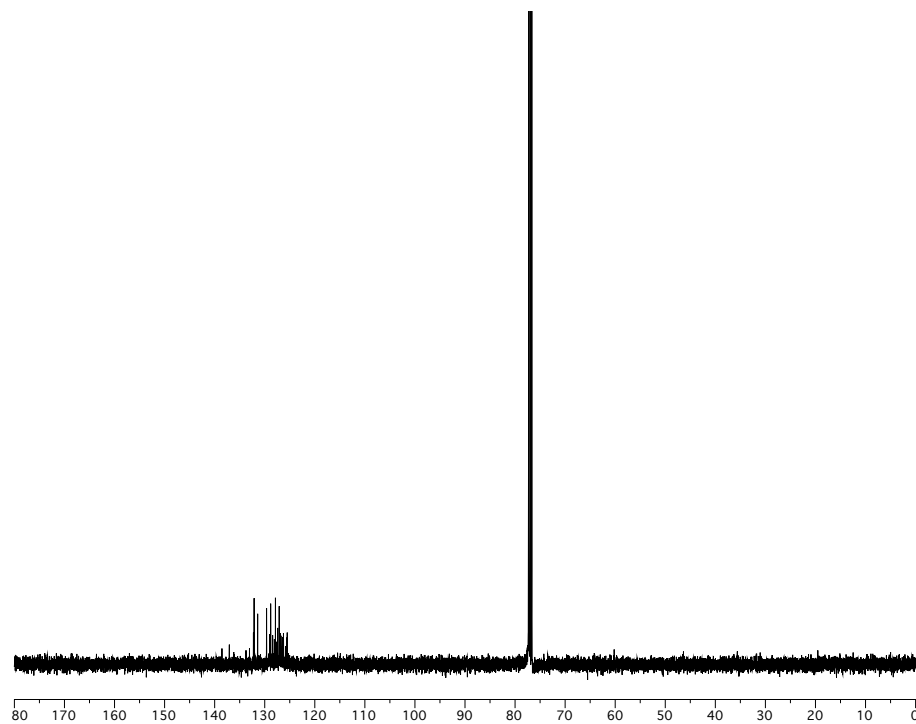
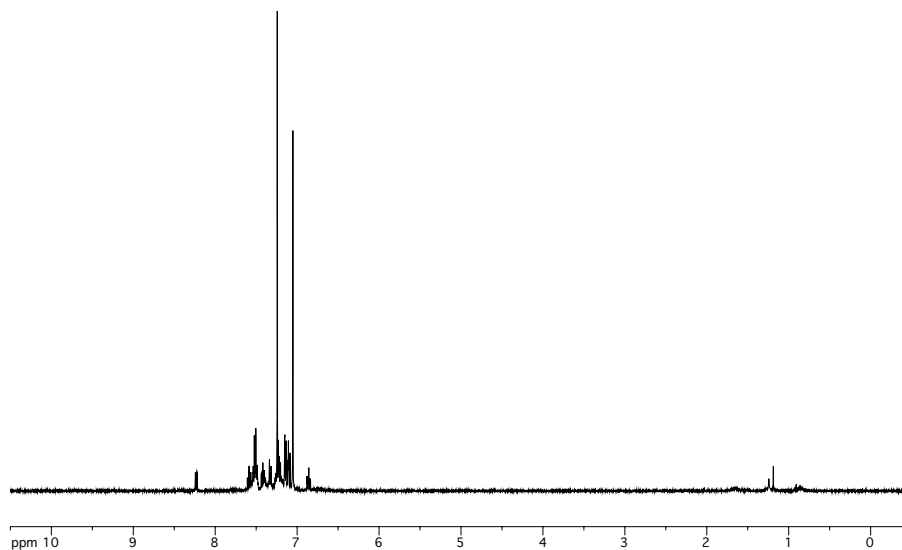
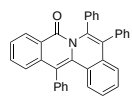


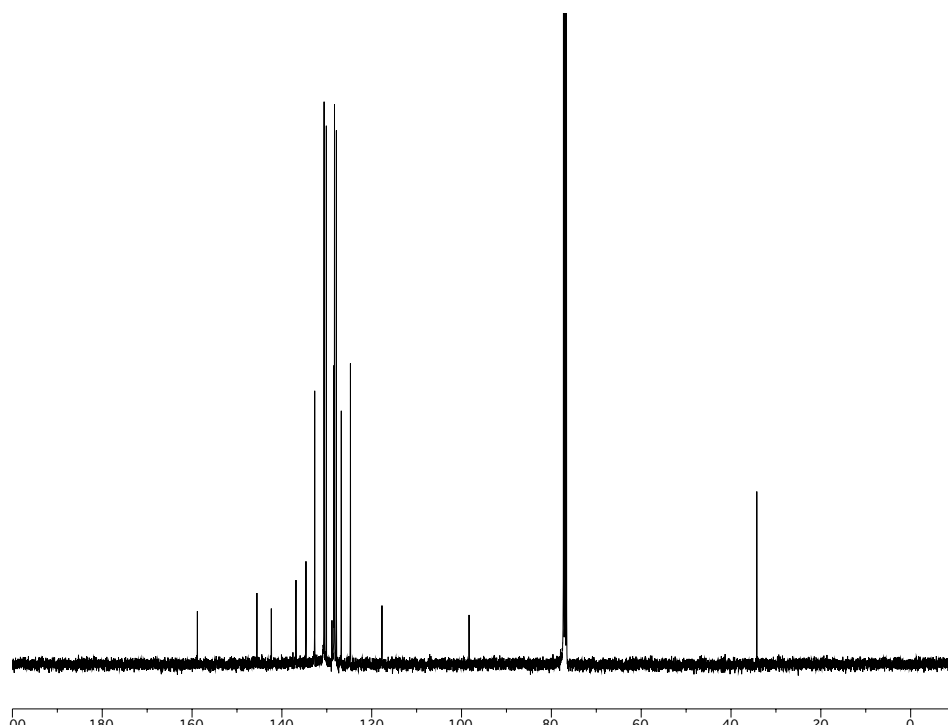
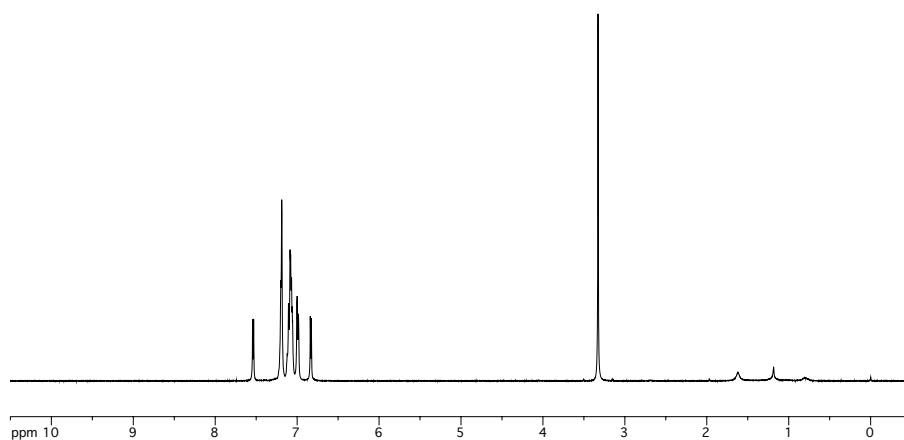


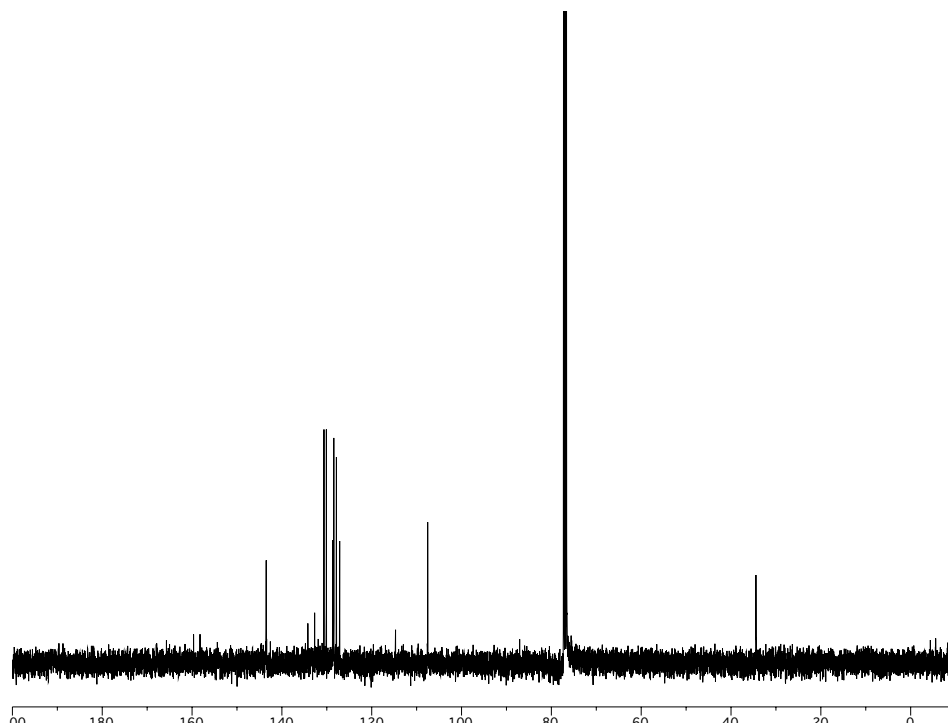
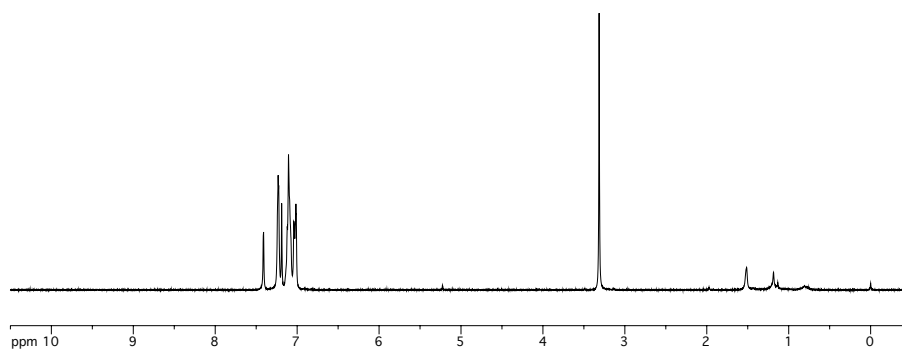


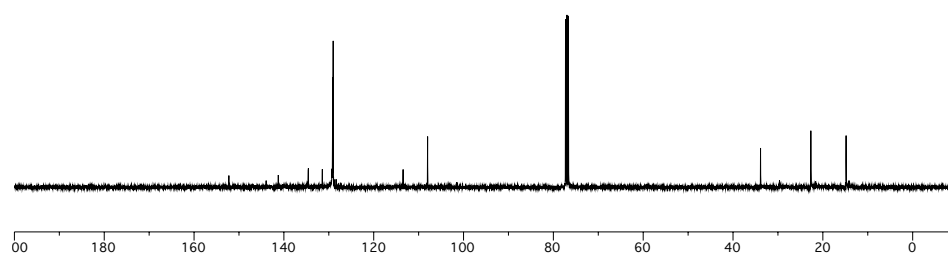
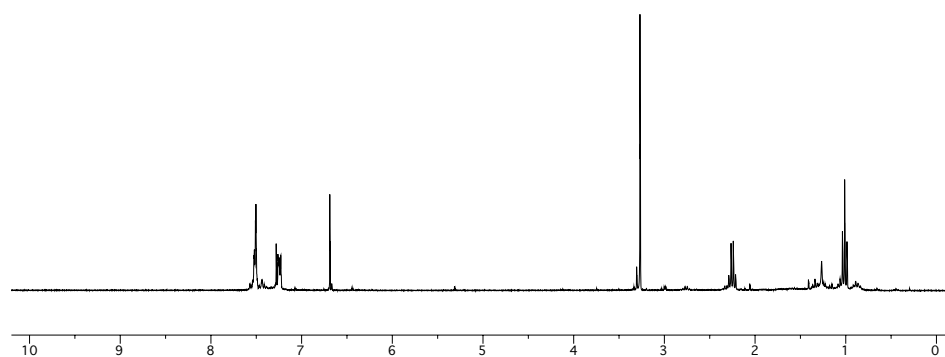
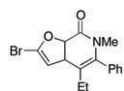


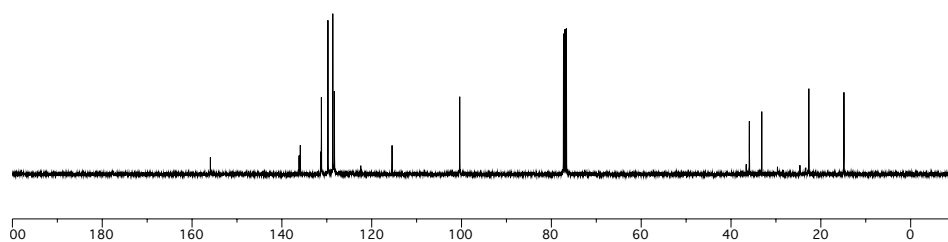
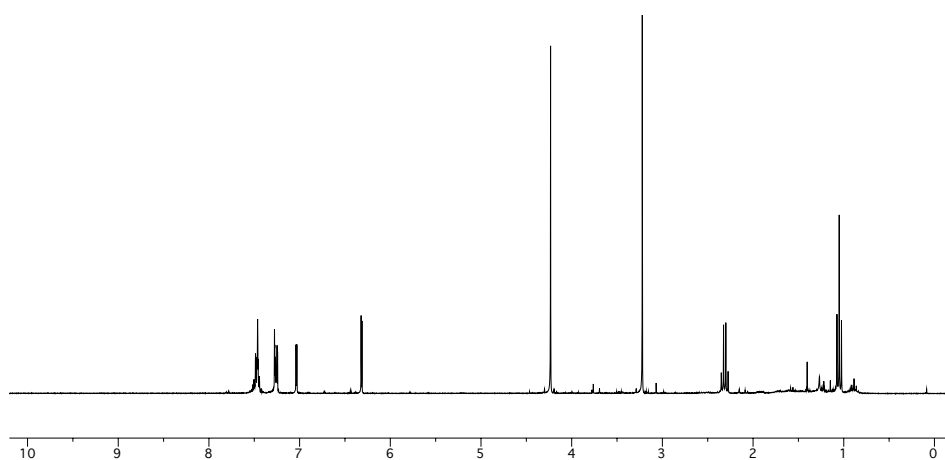


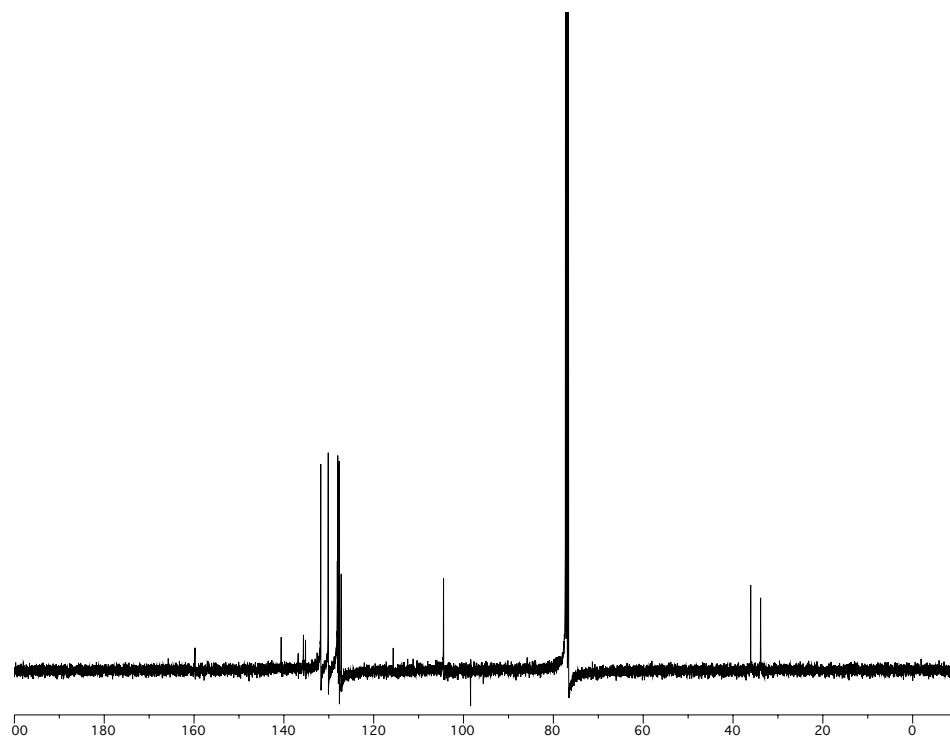
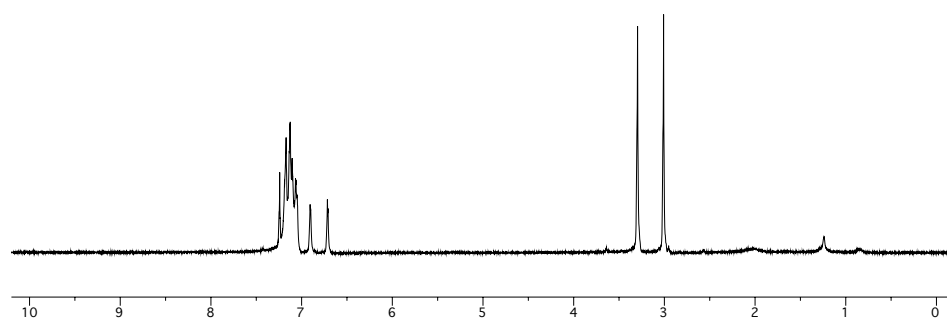


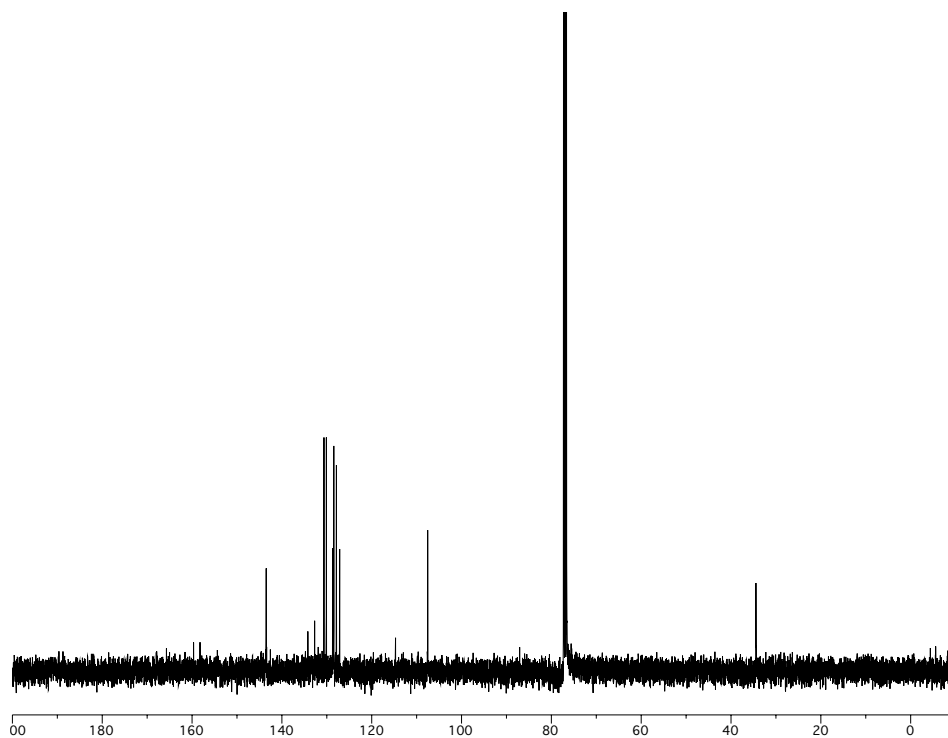
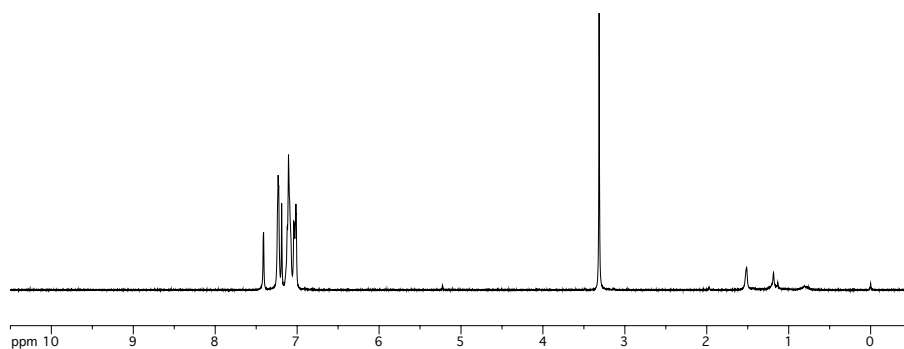


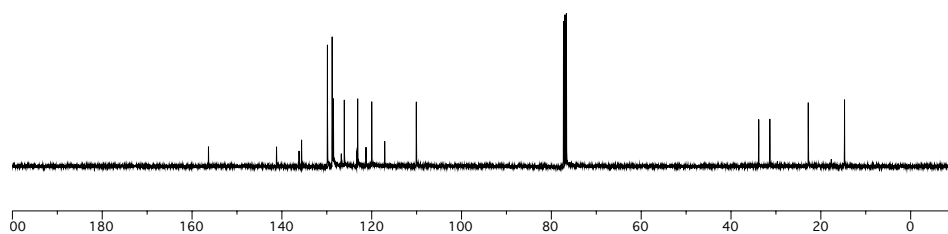
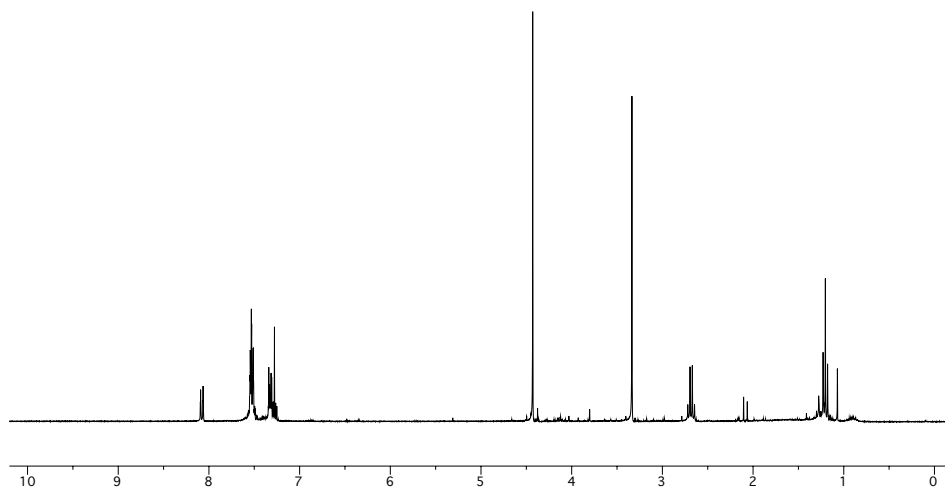
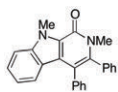


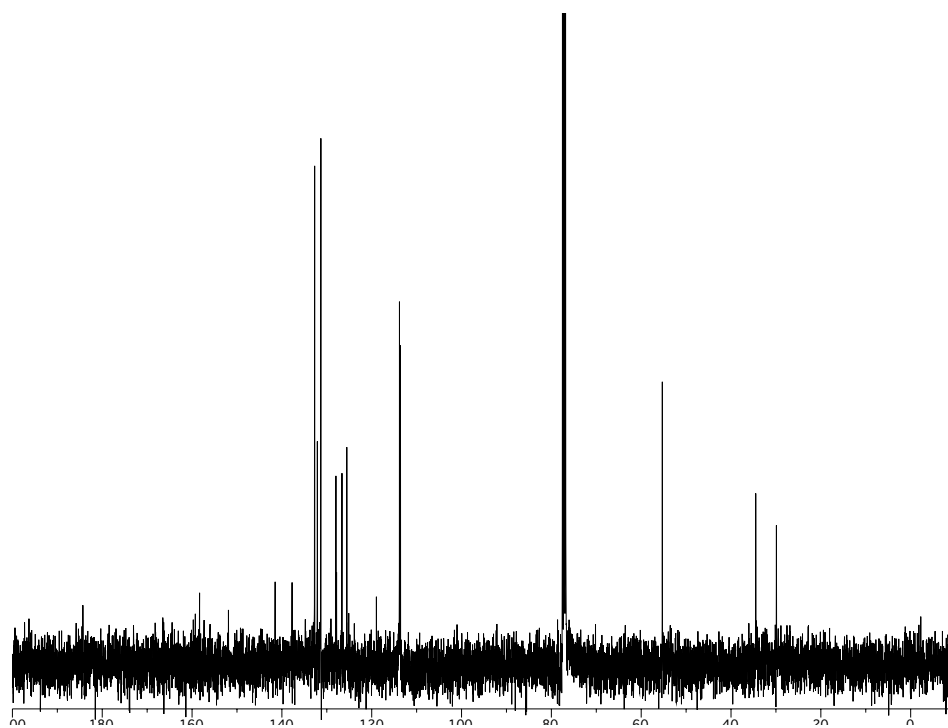
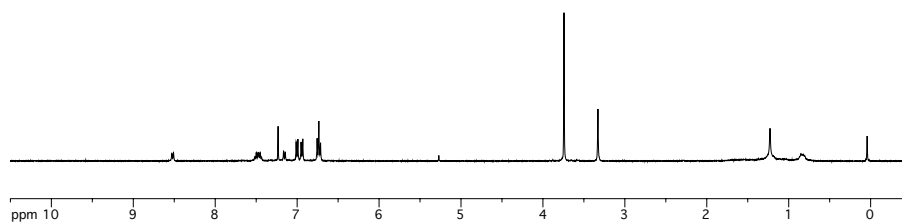
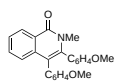


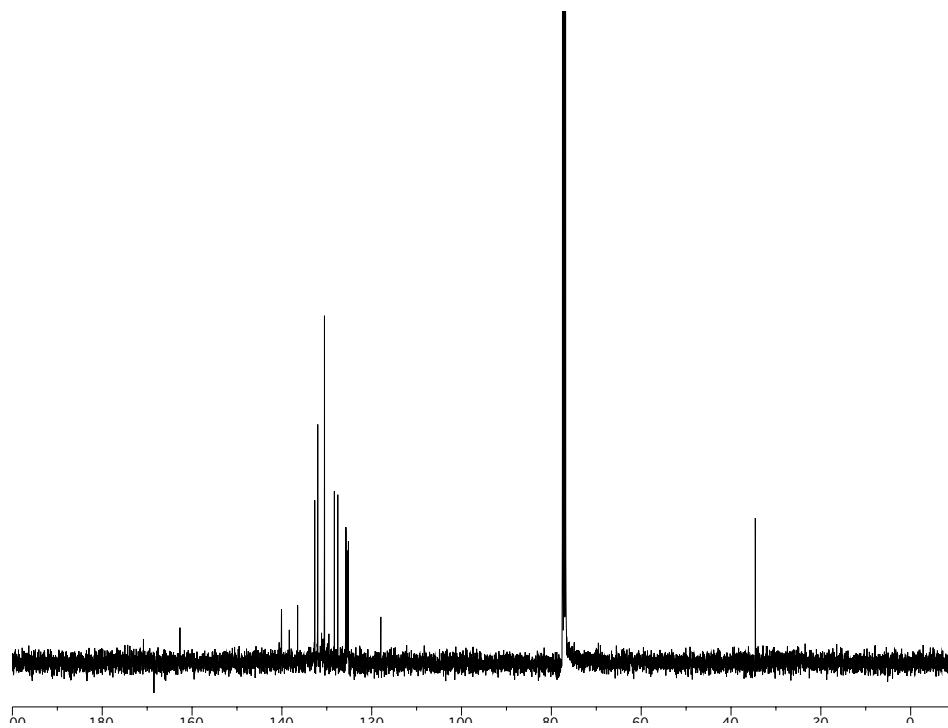
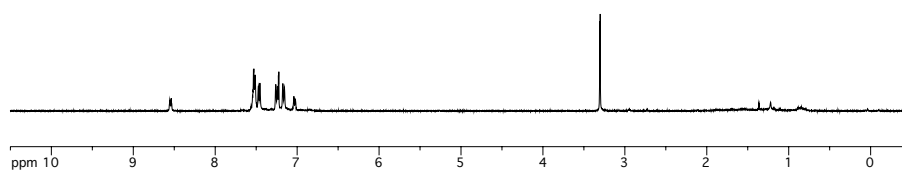
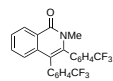


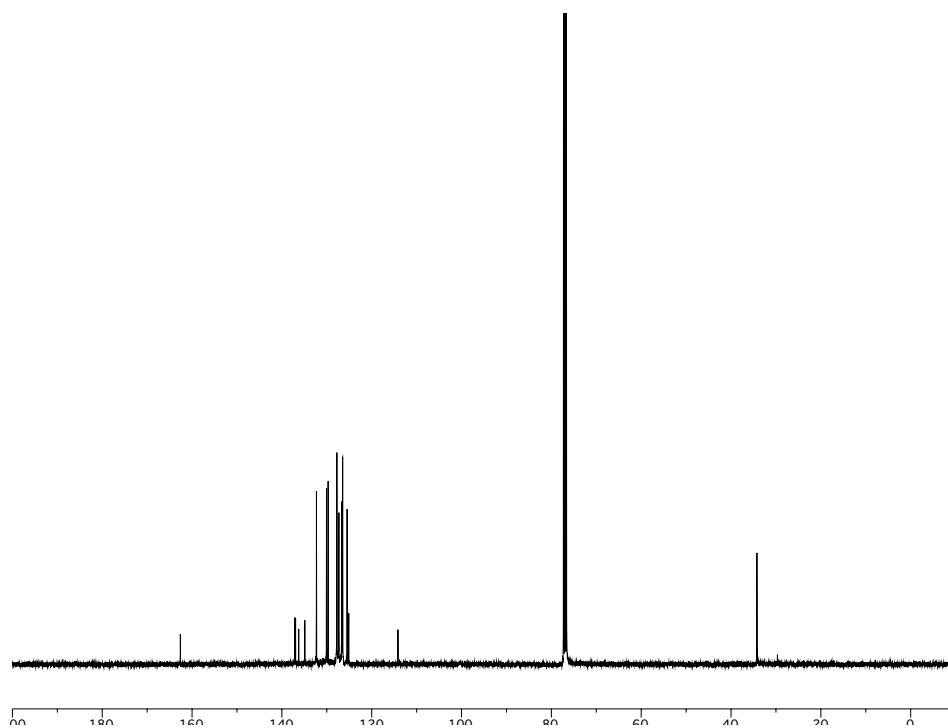
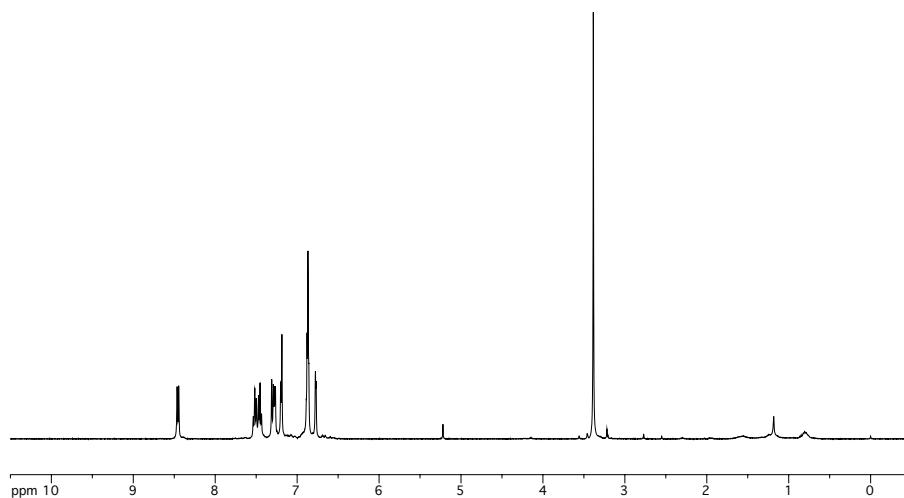


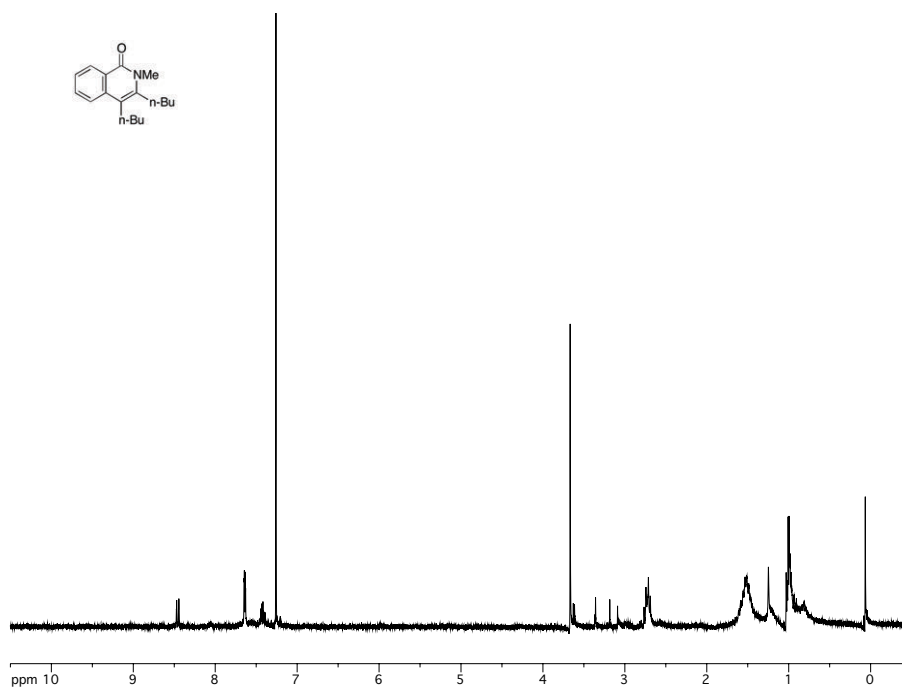


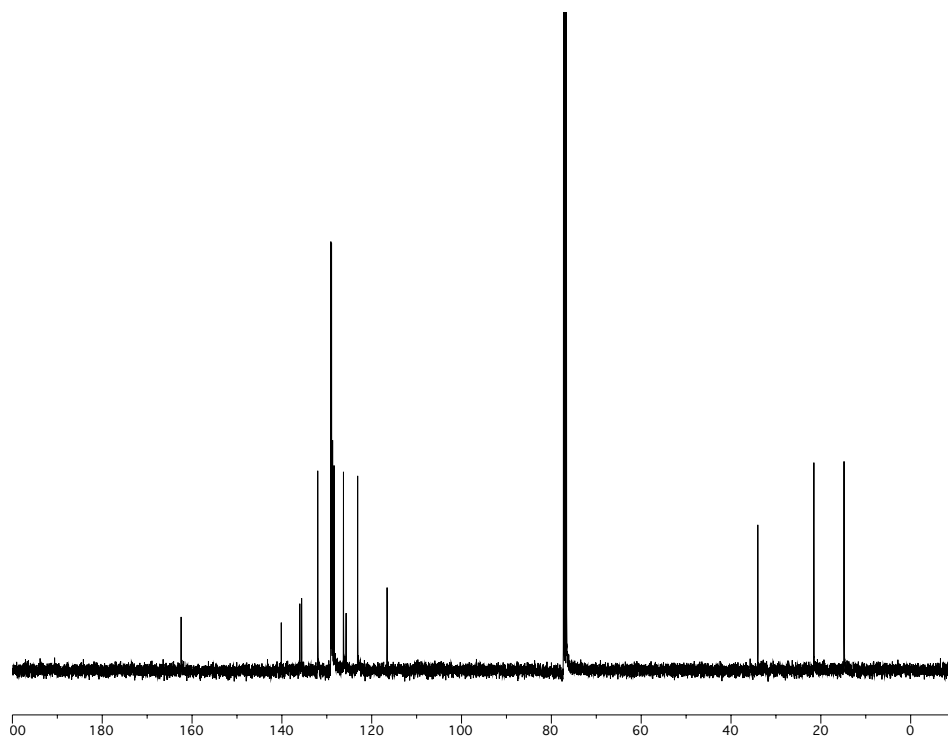
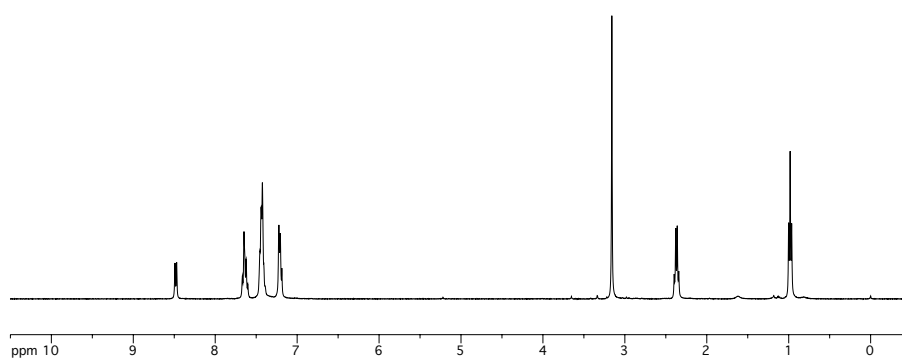
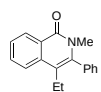


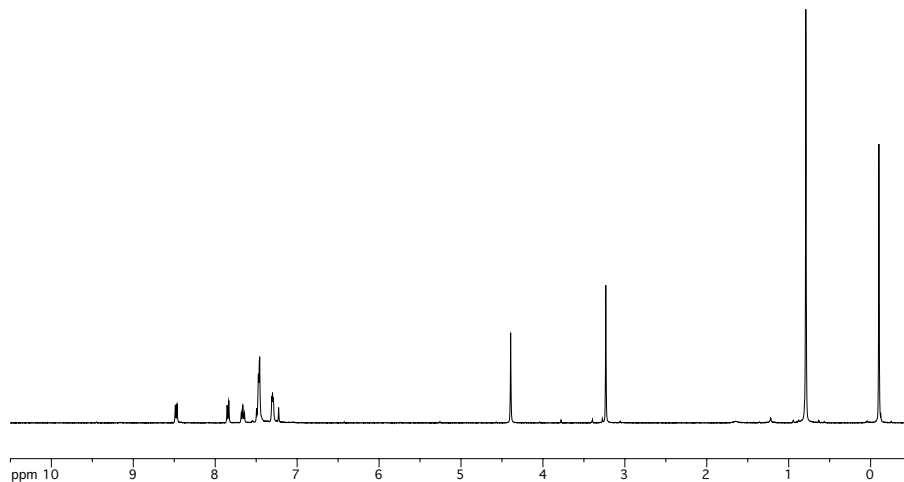


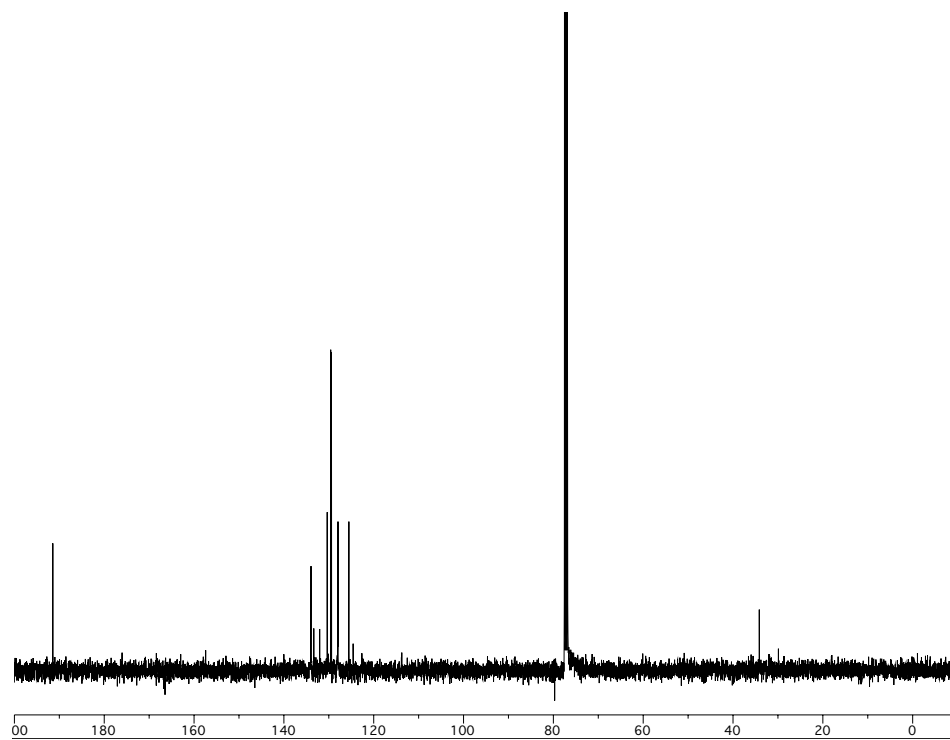
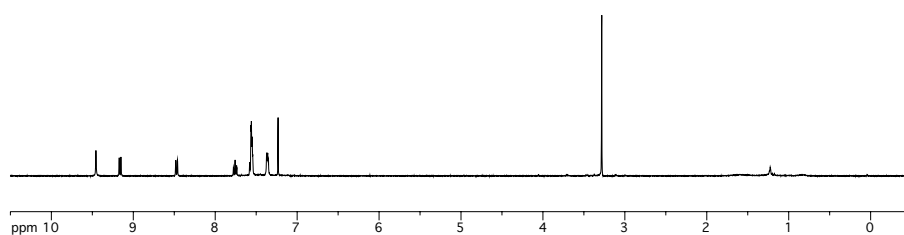


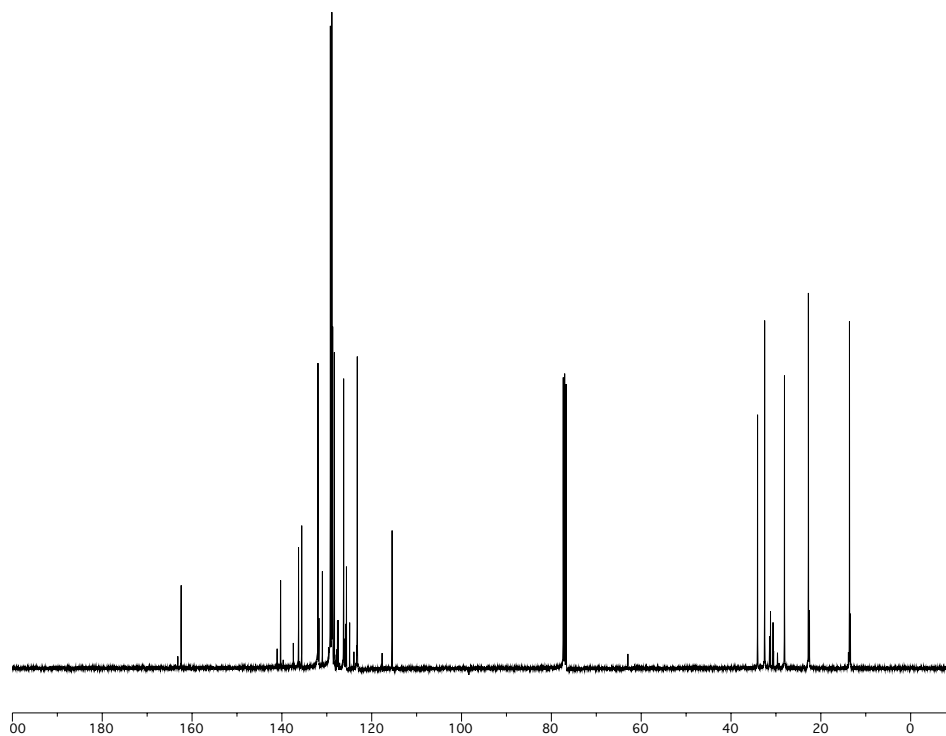
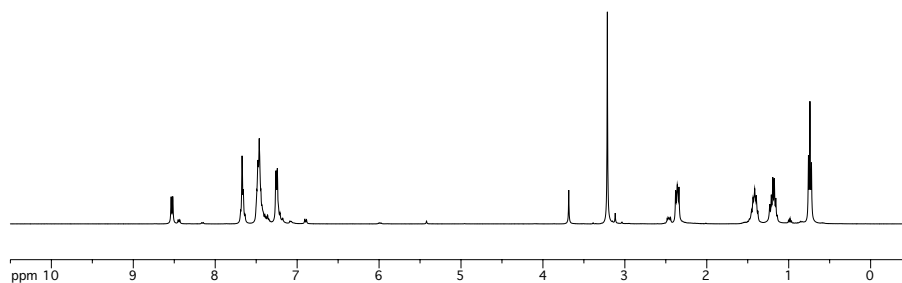


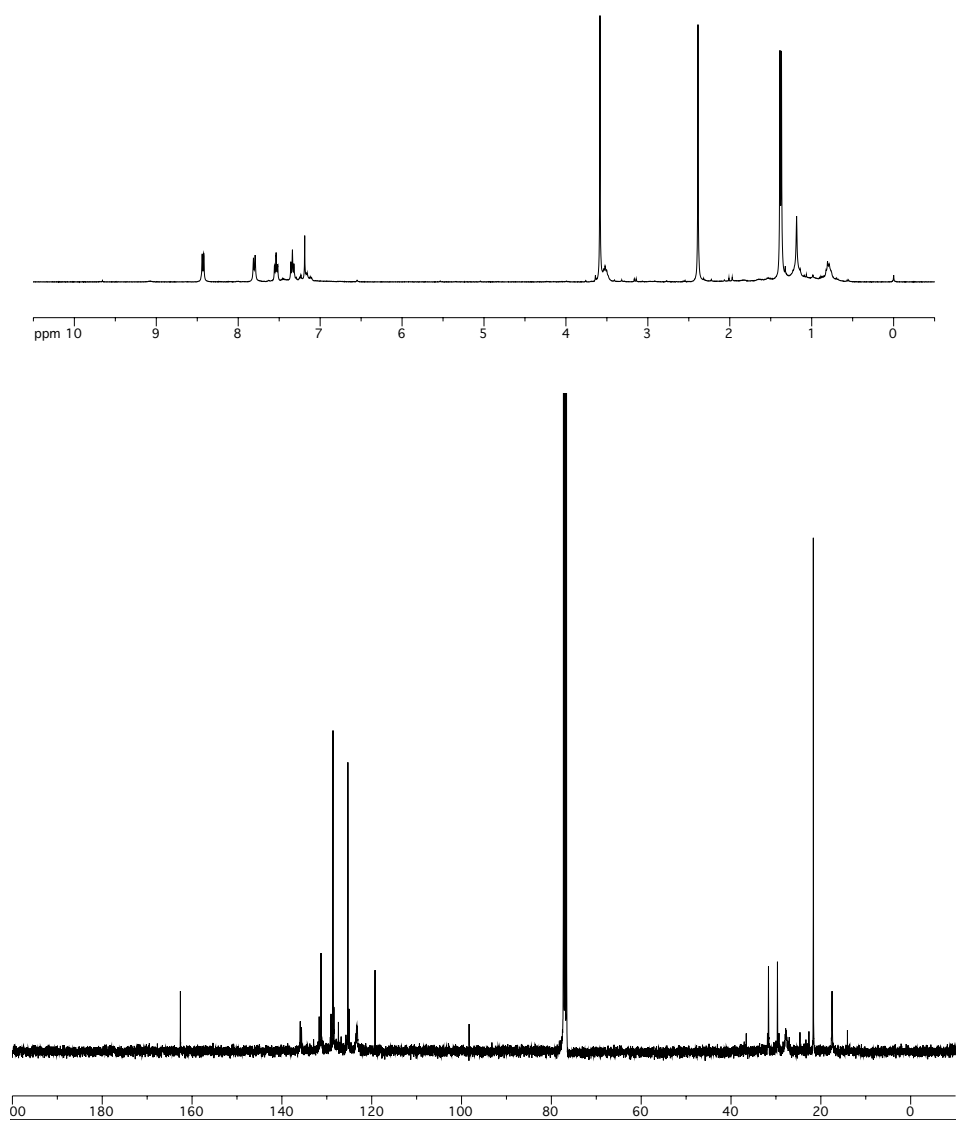


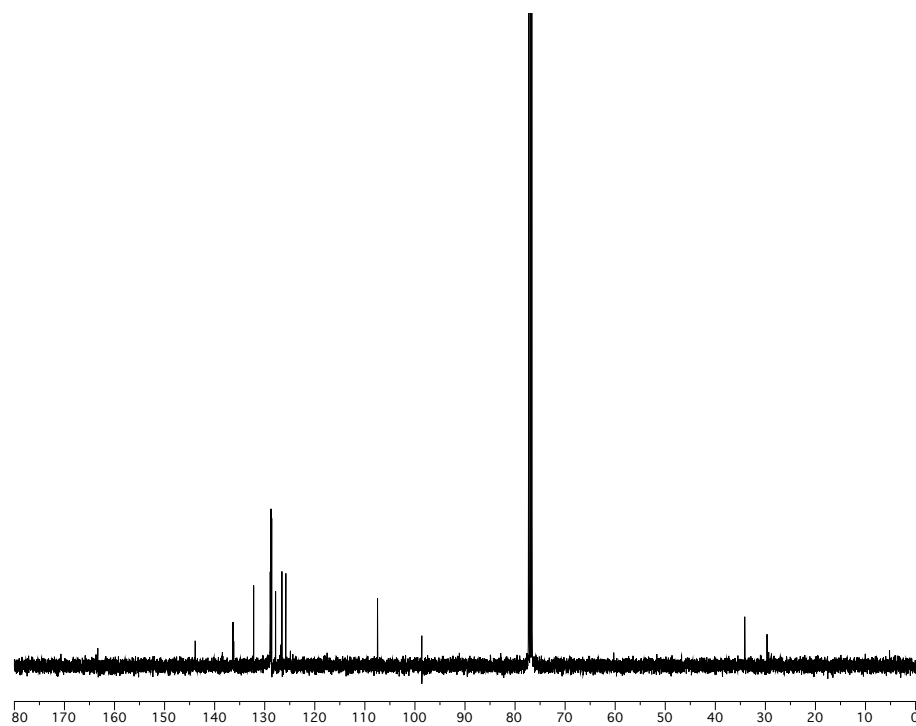
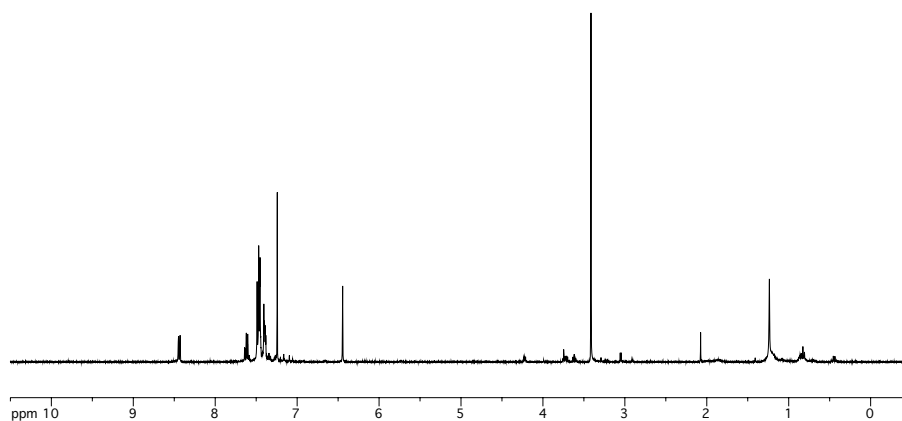
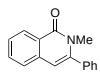


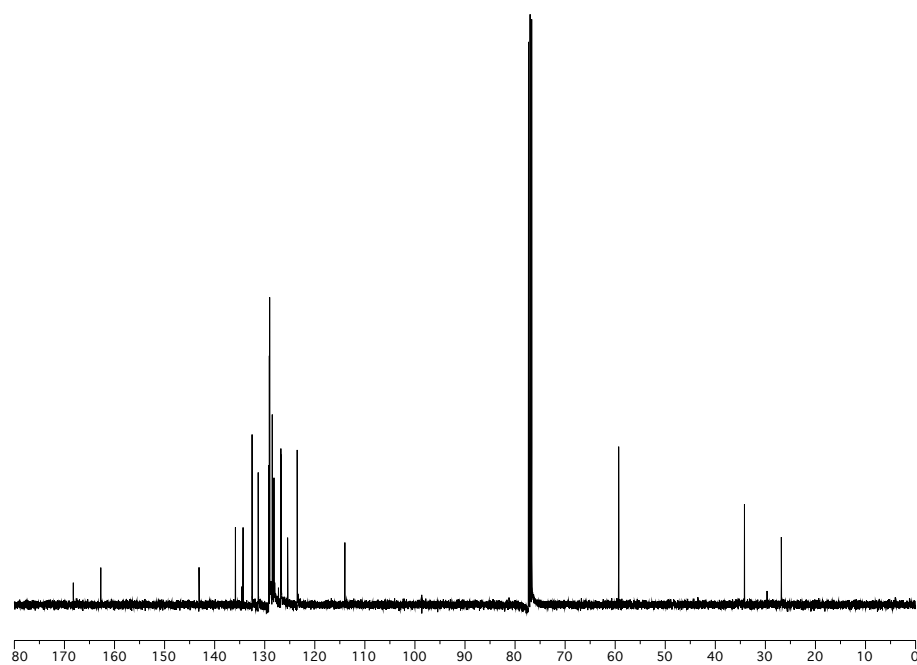
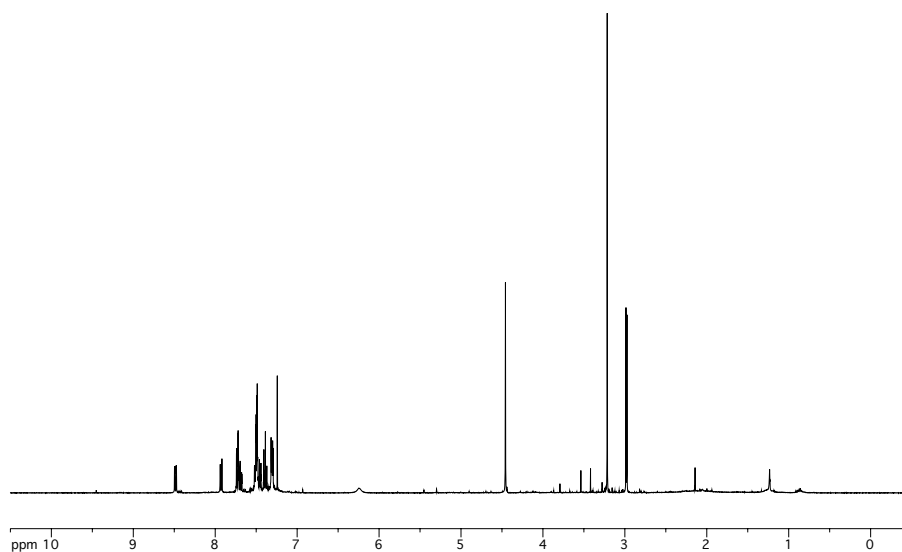
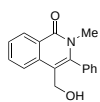


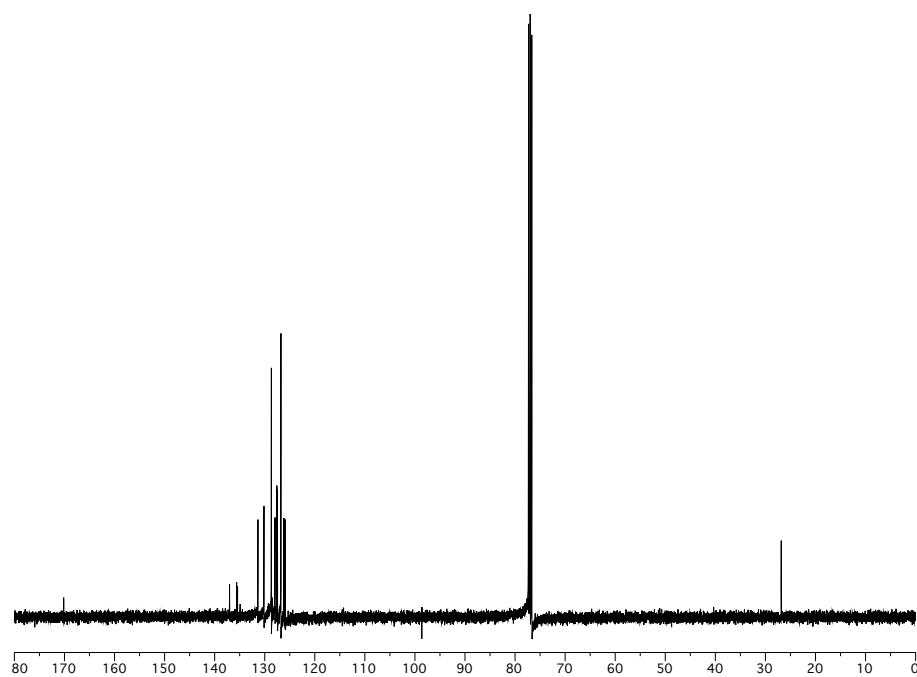
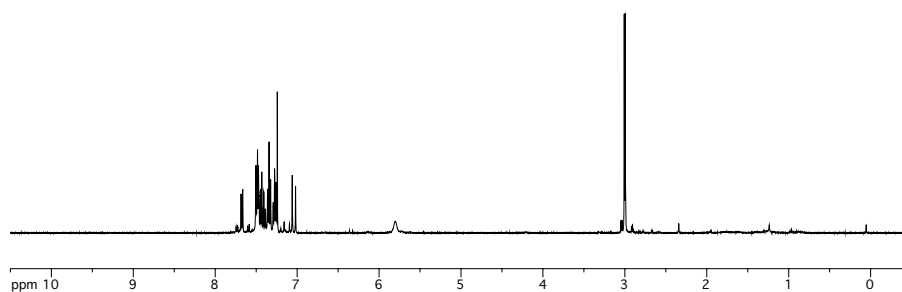
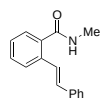


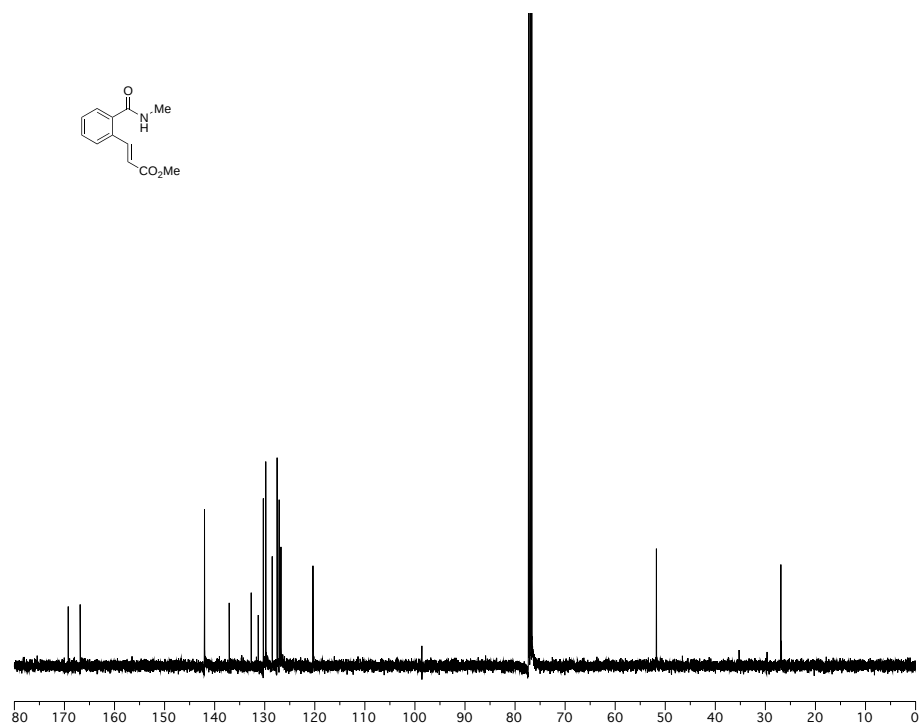
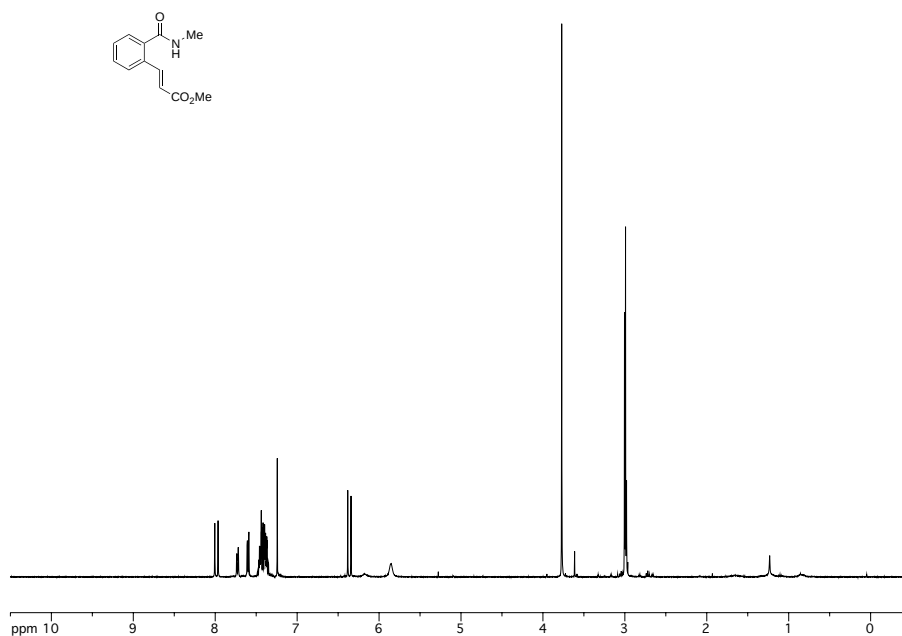


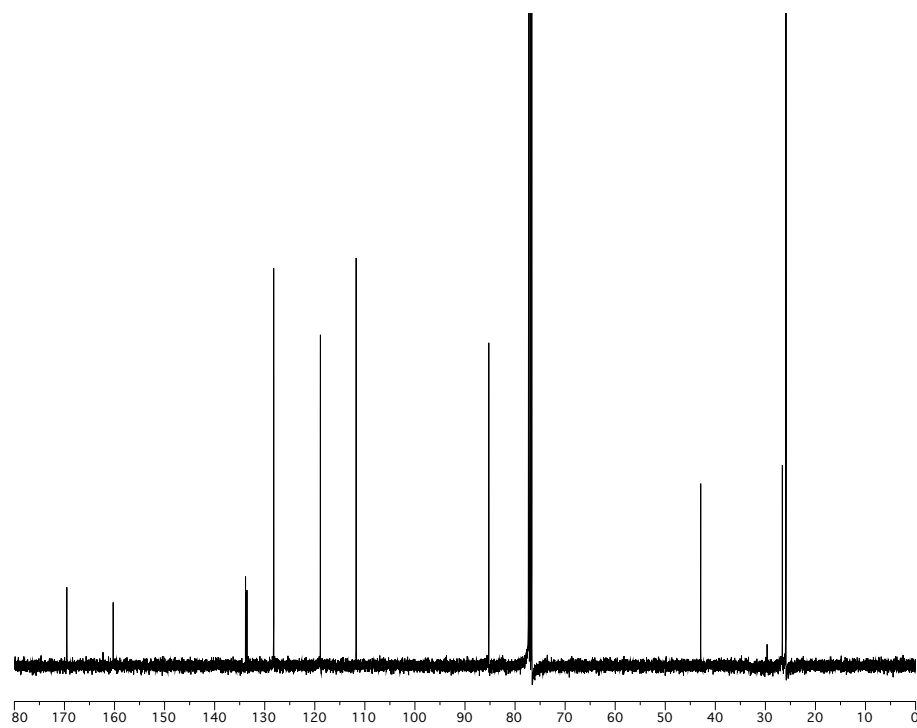
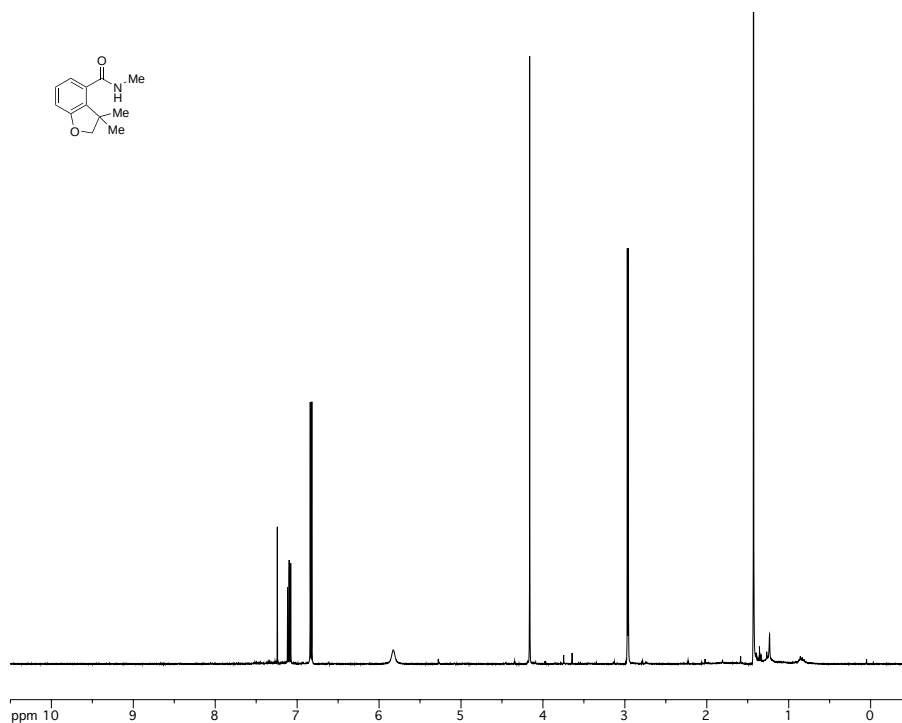


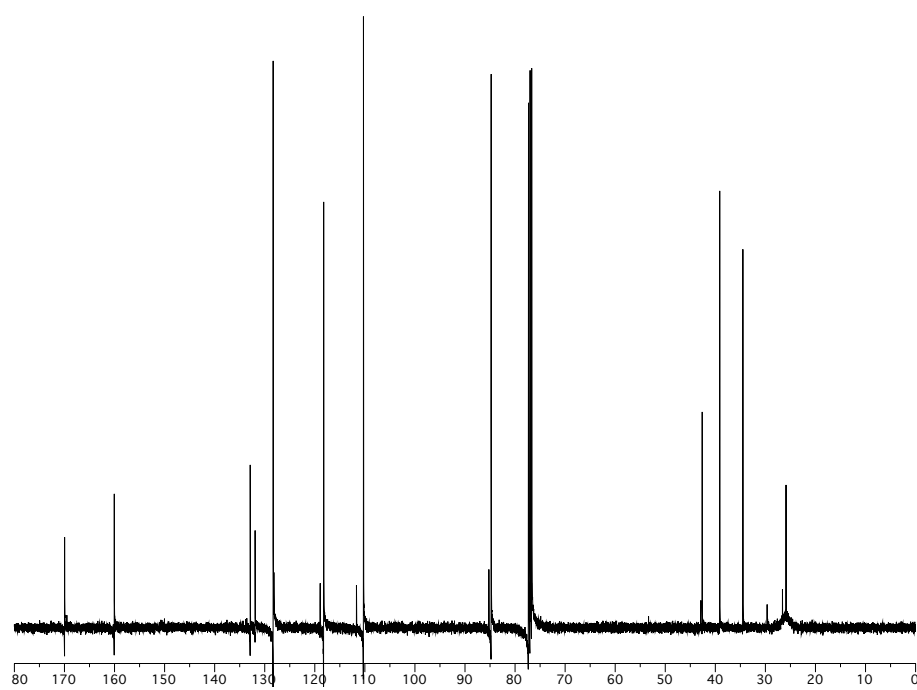
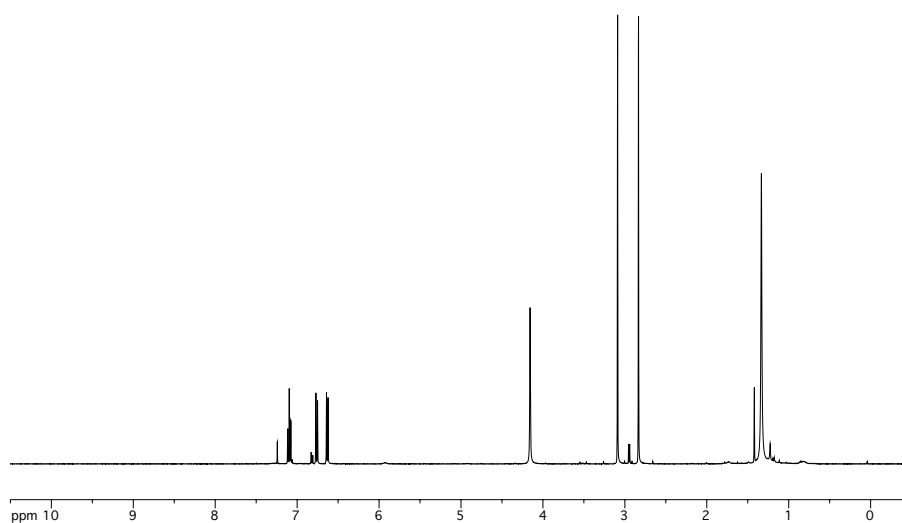
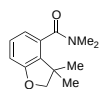


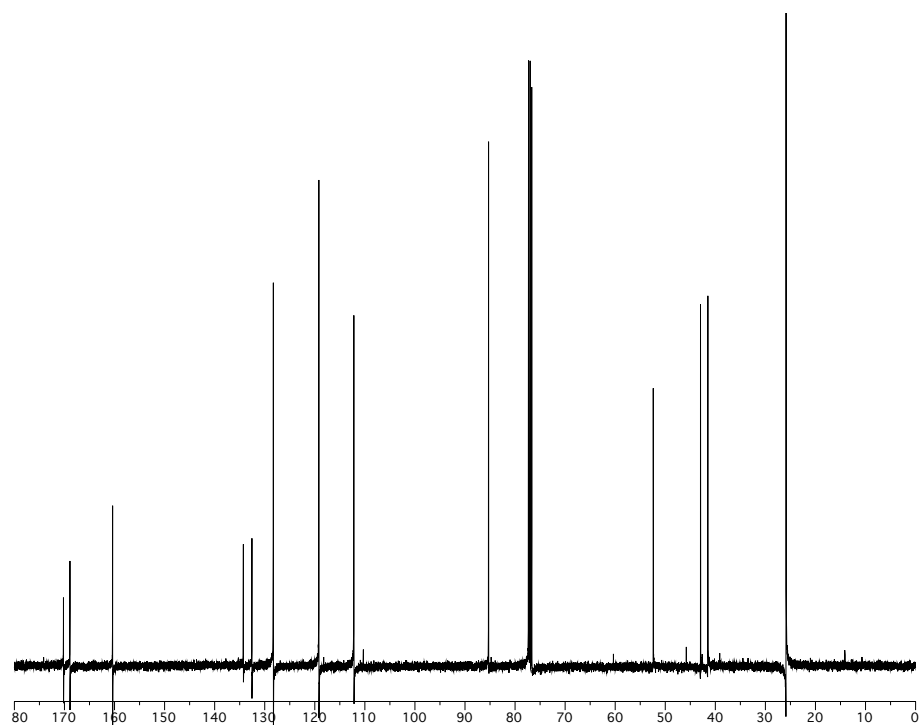
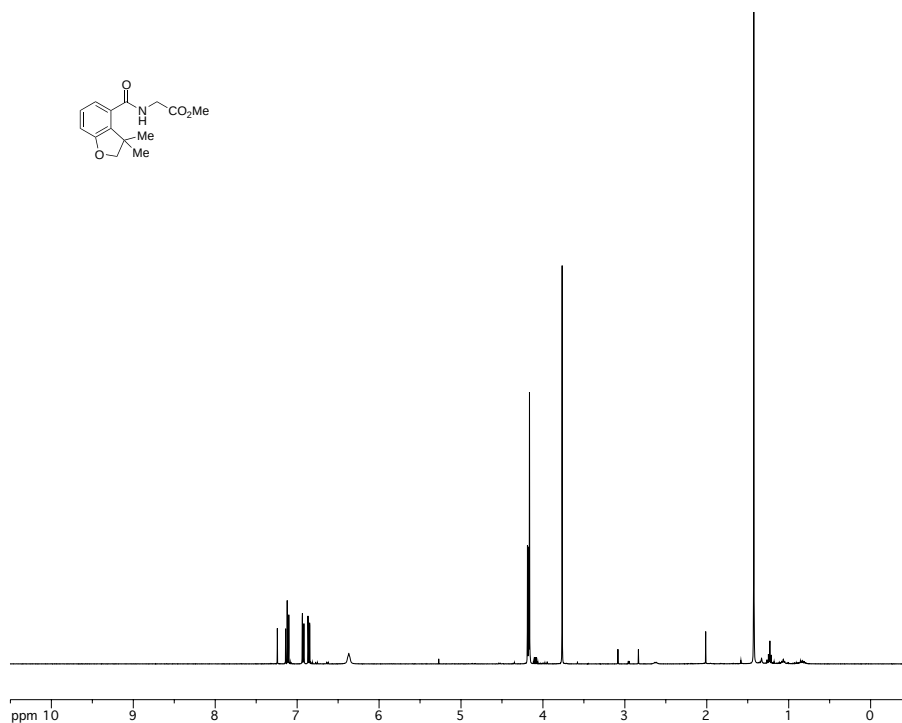


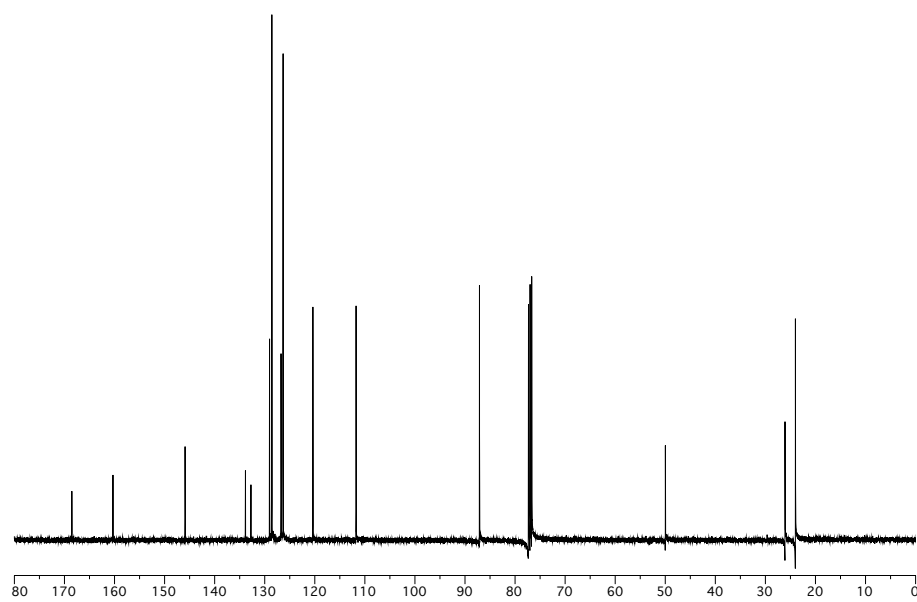
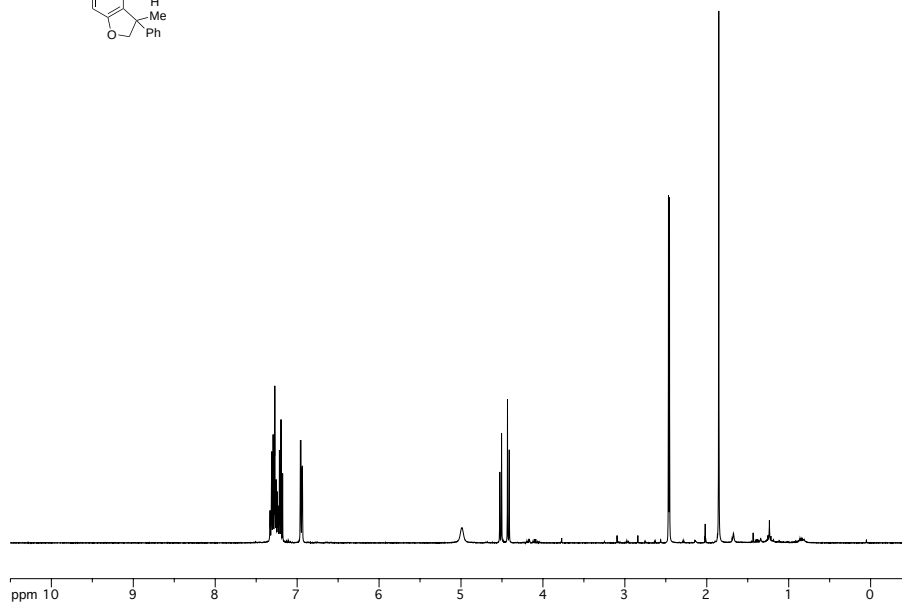
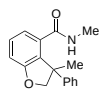












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Appendix 2

Ligand Development to Control the Regioselectivity of Migratory Insertion in Amide Directed Rh(III)-Catalyzed C–H Activation Reactions

General Methods

All reactions were carried out in 1.5 dram sealed vials under an atmosphere of air with magnetic stirring in an aluminum-heating block without drying or degassing of the vial. ACS grade 1,2 dichloroethane was purchased from Fischer Scientific and used without further purification. Column chromatography was performed on SiliCycle® Silica Flash® 40-63µm 60A. Thin Layer chromatography was performed on SiliCycle® 250 µm 60A plates. Visualization was accomplished with UV light (254 nm), KMnO₄, and CAM.

¹H NMR and ¹³C NMR spectra were recorded on a Varian 300 and 400 MHz spectrometers at ambient temperature. ¹H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (Hz). ¹³C NMR are reported as the following: chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec. Infrared spectra (IR) were obtained on Bruker Tensor 27 FT-IR spectrometer. The regioselectivity of di-alkyl determined from nOe spectroscopy. Regioselectivities were assigned based on the shift of the N-methyl peak and correlation with known compounds.

Catalyst Synthesis

[RhCp*Cl₂]₂ and [RhCp[†]Cl₂]₂ were prepared from literature procedures.^{1,2}

[RhCp[§]Cl₂]₂ was prepared from RhCl₃•H₂O and **203**, which can be accessed in one step from commercially available starting materials.³ The following procedure was used to couple **203** with RhCl₃•H₂O:

A 25 ml sealed tube was charged with a stirbar, $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ (0.1 mmol) and MeOH (2 ml). This solution was stirred for 2 minutes before **203** (0.12 mmol) was added in a single portion. The vessel was sealed the placed in an oil bath set to 70 °C. After 24 hours the vessel was allowed to cool to 23 °C before being further cooled to -20 °C overnight. The resulting suspension was filtered and washed with Et_2O to provide a dark red/brown solid.

^1H NMR (400 MHz, CDCl_3) δ 3.68 (s, 3H), 3.49 (s, 2H), 2.4-2.2 (m, 8H), 1.19-1.14 (m, 6H), 1.08 (t, J = 7.7, 6H).

$[\text{RhCp}^*\text{Cl}_2]_2$ was prepared from $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ and **209**, which can be accessed in one step from commercially available starting materials.⁴ A procedure described by Kong and Jin was used to prepare the catalyst.⁵

^1H NMR (400 MHz, CDCl_3) δ 5.64 (s, 2H), 5.35 (s, 1H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 108.67, 108.58, 82.43, 82.34, 81.24, 81.16, 31.1, 30.0.

All cationic catalysts were prepared from a procedure outlined by White and coworkers.⁶

Alkyne Synthesis

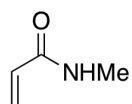
Alkynes **70**, **140**, **141**, **239**, **242**, **243** were purchased from Sigma Aldrich Company and used without further purification. Alkyne **138** was prepared by a typical TBS-protection of the corresponding alcohol, which was purchased from Aldrich Chemical Company. **154**,⁷ **240**,⁸ and **241**⁹ was prepared via literature procedure.

Amide Synthesis

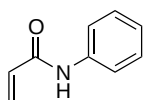
Amides **192**, **221**, **222**, and **224** were prepared from the corresponding acid chloride via a literature procedure.¹⁰ All other amides were prepared from the corresponding carboxylic acid using the general procedure:

To a flame dried round bottom flask charged with a magnetic stir bar under argon was added the carboxylic acid (1 equiv), amine (1.05 equiv), HOBt (0.3 equiv), EDC (1.2 equiv) and acetonitrile (2 M). To the reaction mixture was added triethylamine (1.05 equiv) over 5 minutes at room temperature. The reaction was allowed to stir under the reaction was complete as indicated by TLC. The reaction was concentrated *in vacuo* before dissolving in dichloromethane and washed with water (2 x 20 ml), brine (1 x 20 ml) dried over MgSO₄, and concentrated *in vacuo* and purified via column chromatography.

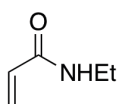
Acrylamide Characterization



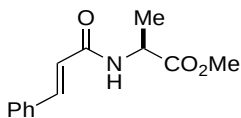
N-methylacrylamide (192): ¹H NMR (400 MHz, CDCl₃) δ 6.22 (dd, 1H, *J*=16.8 Hz, *J*=1.6 Hz), 6.08 (dd, 1H, *J*=16 Hz, *J*=10.4 Hz), 5.95 (s, br, 1H), 5.58 (dd, 1H, *J*=10 Hz, *J*=1.6 Hz), 2.85 (s, 1.5H), 2.84 (s, 1.5H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 130.7, 126.0, 26.2.



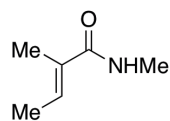
N-phenylacrylamide (215): ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 16.8 Hz, 1H), 6.29-6.22 (m, 1H), 5.73 (dd, *J* = 10.1, 1.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 163.6, 137.72, 137.70, 131.2, 129.0, 127.7, 124.5, 120.03, 119.95.



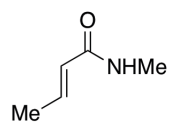
N-ethylacrylamide (217): ¹H NMR (400 MHz, CDCl₃) δ 6.6 (s, br, 1H), 6.13 (m, 2H), 6.08 (dd, 1H, *J*=16 Hz, *J*=10.4 Hz), 5.52 (dd, 1H, *J*=9.6 Hz, *J*=2 Hz), 3.27 (m, 2H), 1.09 (t, 3H, *J*=4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 131.1, 125.6, 34.3, 14.5.



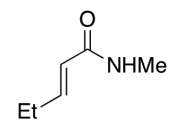
(S)-methyl 2-cinnamidopropanoate (218): ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, 1H, *J*=15.6 Hz, *J*=1.2 Hz), 7.47-7.43 (m, 2H), 7.36-7.29 (m, 3H), 6.49-6.41 (m, 1H), 4.74 (q, 1H, *J*=7.6 Hz), 3.73 (d, 3H, rotamer), 1.45 (dd, 3H, rotamer, *J*=4.4 Hz, *J*=7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 141.6, 134.6, 130.4, 129.7, 129.0, 128.8, 128.2, 127.8, 120.1, 52.5, 48.1, 18.5.



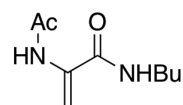
(E)-N,2-dimethylbut-2-enamide (220): ^1H NMR (400 MHz, CDCl_3) δ 6.40 (dq, 1H, $J=6.8$ Hz), 5.7 (s, br, 1H), 2.85 (s, 1.5H), 2.84 (s, 1.5H), 1.82 (s, 3H), 1.72 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 131.6, 130.4, 26.4, 13.8, 12.3.



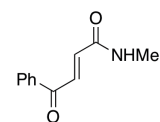
(E)-N-methylbut-2-enamide (221): ^1H NMR (400 MHz, CDCl_3) δ 6.77 (dt, 1H, $J=14$ Hz, $J=6.8$ Hz), 5.71 (dd, 1H, $J=13.6$ Hz, $J=1.6$ Hz), 5.41 (s, br, 1H), 2.80 (s, 1.5H), 2.79 (s, 1.5H), 1.77 (dd, 3H, $J=6.8$ Hz, $J=1.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 139.6, 124.8, 26.2, 17.6.



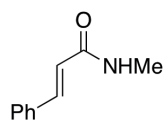
(E)-N-methylpent-2-enamide (222): ^1H NMR (400 MHz, CDCl_3) δ 6.81 (dt, 1H, $J=6.4$ Hz, $J=15.6$ Hz), 5.67 (dt, 1H, $J=15.6$ Hz, $J=1.6$ Hz), 5.45 (s, br, 1H), 2.81 (s, 1.5H), 2.80 (s, 1.5H), 2.13 (dq, 2H, $J=7.2$ Hz, $J=1.2$ Hz), 0.98 (t, 3H, $J=7.6$ Hz). ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 145.9, 122.3, 26.2, 25.0, 12.4.



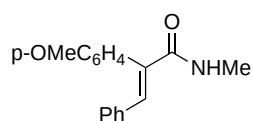
2-acetamido-N-butylacrylamide (223): ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, br, 1H), 6.39 (s, 1H), 6.18 (s, br, 1H), 5.13 (s, 1H), 3.32 (m, 2H), 2.09 (s, 1.5H), 2.08 (s, 1.5H), 1.52 (m, 2H), 1.33 (m, 2H), 0.91 (dt, 3H, $J=7.2$ Hz, $J=1.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 169.0, 163.8, 134.4, 100.1, 39.8, 31.4, 24.7, 19.9, 13.6.



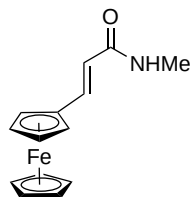
(E)-N-methyl-4-oxo-4-phenylbut-2-enamide (224): ^1H NMR (400 MHz, CDCl_3) δ 7.95 (m, 3H), 7.54 (m, 1H), 7.43 (m, 2H), 6.90 (d, 1H, $J=14.8$ Hz), 2.92 (s, 1.5H), 2.90 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.6, 164.6, 136.8, 134.9, 133.7, 133.0, 128.8, 26.7.



N-methylcinnamamide (225): ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, 1H, 15.6 Hz), 7.40 (m, 2H), 7.26 (m, 3H), 6.35 (dd, 1H, $J=16$ Hz, $J=4$ Hz), 5.9 (s, br, 1H), 2.88 (s, 1.5H), 2.87 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 140.7, 134.8, 129.5, 128.7, 127.7, 120.5, 26.5.



(E)-2-(4-methoxyphenyl)-N-methyl-3-phenylacrylamide (226): ^1H NMR (400 MHz, CDCl_3) δ 7.81 (s, 1H), 7.14-7.11 (m, 5H), 7.00-6.93 (m, 4H), 5.6 (s, br, 1H), 3.83 (s, 3H), 2.83 (s, 1.5H), 2.82 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 159.6, 136.7, 135.1, 133.9, 131.1, 130.8, 128.3, 128.1, 55.2, 26.9.



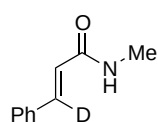
(E)-3-(ferrocene)-N-methylacrylamide (227): ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, 1H, $J=15.2$), 5.99 (dd, 1H, $J=15.6$ Hz, $J=3.2$ Hz), 4.42 (s, 2H), 4.32 (s, 2H), 4.11 (s, 5H), 2.89 (s, 1.5H), 2.88 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 140.9, 128.3, 117.5, 79.4, 780.24, 69.6, 69.4, 68.2, 36.3.

Amide Synthesis for Kinetic Studies

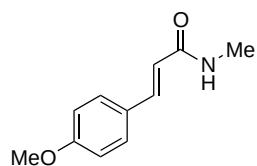
A 50 ml flask was charged with a stir-bar and flame dried under vacuum and cooled under argon. The flask was charged with benzaldehyde- α - d_1 (1 equiv, 5 mmol) and ethyl 2-(triphenylphosphoranylidene)acetate (1.1 equiv, 5.5 mmol). The mixture was dissolved in dichloromethane (.33 M, 15 ml) and allowed to stir at 21 °C. After the reaction was determined to be complete by TLC the mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography (9:1 Hex/EtOAc) to yield the desired α,β unsaturated ethyl ester (75% yield).

A 25 ml flask was charged with a stir-bar and flame dried under vacuum and cooled under argon. The flask was charged with methylamine hydrochloride (2 equiv, 7 mmol) and dissolved in dichloromethane. The flask was cooled to 0 °C and Me_3Al (2M in Toluene, 2 equiv, 7 mmol) was added dropwise over 30 min. The flask was allowed to stir for an additional 2h at 0 °C before the α,β unsaturated ethyl ester (1 equiv, 3.5 mmol) was added dropwise over 15 min. The resulting solution was allowed to warm to 21 °C and stir overnight. The solution was cooled 0 °C and H_2O was added dropwise until methane loss ceased. A saturated solution of sodium potassium tartrate was added to the mixture and allowed to stir for 1h. The solution was extracted with dichloromethane (3 x 20 ml), washed with brine (1 x 20 ml), dried over

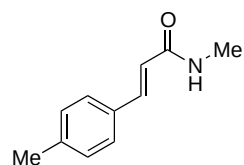
MgSO₄, and concentrated *in vacuo*. The resulting residue was purified via column chromatography (EtOAc) to yield the desired amide as a white solid (50% yield).



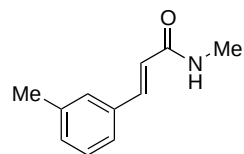
d1-N-methylcinnamamide (257): ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.46 (m, 2H), 7.37-7.32 (m, 3H), 6.37 (t, *J* = 2.0 Hz, 1H), 5.66-5.64 (m, 1H), 2.93 (d, *J* = 4.9 Hz, 3H).
¹³C NMR (100 MHz, CDCl₃) δ 166.5, 134.7, 129.6, 128.8, 127.7, 120.3, 26.5.



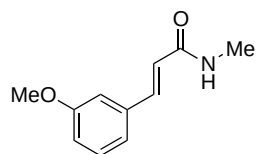
(E)-3-(4-methoxyphenyl)-N-methylacrylamide (258): ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, *J* = 15.6, 1H), 7.42 (d, *J* = 8.7, 2H), 6.86 (dd, *J* = 8.7, 1.2, 2H), 6.24 (d, *J* = 15.6, 1H), 5.65-5.63 (m, 1H), 3.81 (s, 3H), 2.92 (d, *J* = 4.9, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 160.8, 140.5, 129.3, 127.5, 118.0, 114.2, 98.6, 55.3, 26.5.



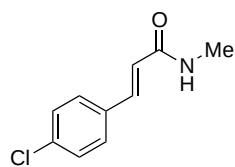
(E)-N-methyl-3-(p-tolyl)acrylamide (259): ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 15.6, 1H), 7.36 (d, *J* = 8.1, 2H), 7.14 (d, *J* = 8.0, 2H), 6.34 (d, *J* = 15.6, 1H), 5.79-5.76 (m, 1H), 2.92 (d, *J* = 4.9, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 140.8, 139.9, 132.0, 129.5, 127.7, 119.4, 26.5, 21.4.



(E)-N-methyl-3-(m-tolyl)acrylamide (260): ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 15.6, 1H), 7.28 (d, *J* = 4.5, 2H), 7.25-7.21 (m, 1H), 7.14 (d, *J* = 7.4, 1H), 6.36 (d, *J* = 15.6, 1H), 2.93 (d, *J* = 4.9, 3H), 2.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 140.9, 138.4, 134.7, 130.4, 128.6, 128.4, 124.8, 120.3, 26.5, 21.3.



(E)-3-(3-methoxyphenyl)-N-methylacrylamide (261): ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 15.6, 1H), 7.27 (d, *J* = 7.9, 1H), 7.07 (d, *J* = 7.6, 1H), 7.00 (s, 1H), 6.89-6.86 (m, 1H), 6.36 (d, *J* = 15.6, 1H), 5.67-5.64 (m, 1H), 3.80 (s, 3H), 2.93 (d, *J* = 4.9, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 159.8, 140.7, 136.2, 129.8, 120.8, 120.3, 115.3, 112.9, 55.2, 26.5.

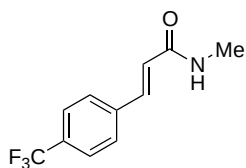


(E)-3-(4-chlorophenyl)-N-methylacrylamide (262): ^1H NMR (400 MHz, CDCl_3)

δ 7.55 (d, J = 15.6, 1H), 7.40-7.36 (m, 2H), 7.31-7.27 (m, 2H), 6.36 (d, J = 15.6,

1H), 5.87 (dd, J = 1.5, 1.0, 1H), 2.92 (d, J = 4.9, 3H); ^{13}C NMR (100 MHz, CDCl_3)

δ 166.3, 139.4, 135.4, 133.3, 121.1, 26.5.

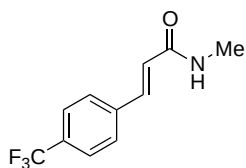


(E)-N-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (263): ^1H NMR (400

MHz, CDCl_3) δ 7.64-7.54 (m, 5H), 6.46 (dd, J = 15.6, 1.7, 1H), 2.93 (t, J = 4.9,

3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.98, 165.93, 139.2, 138.21, 138.20, 128.8,

127.83, 127.71, 126.6, 125.78, 125.74, 125.70, 125.67, 122.9, 26.6.

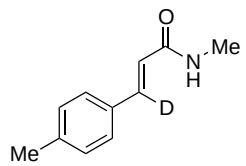


d_1 -(E)-N-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (270): ^1H NMR (400

MHz, CDCl_3) δ 7.62-7.54 (m, 4H), 6.45 (s, 1H), 5.88 (dd, J = 1.3, 0.4, 1H), 2.94

(d, J = 4.9, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 138.16, 138.15, 132.04,

131.94, 128.60, 128.48, 127.8, 125.78, 125.74, 125.70, 125.67, 125.2, 122.8, 26.6.



(E)-N-methyl-3-(p-tolyl)acrylamide (271): ^1H NMR (400 MHz, CDCl_3) δ 7.36

(d, J = 8.0, 2H), 7.15-7.12 (m, 2H), 6.34 (s, br, 1H), 2.92 (d, J = 4.9, 3H), 2.33 (d, J

= 3.1, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 139.8, 132.0, 129.5, 127.7,

119.4, 26.5, 21.4.

General procedure for rhodium catalyzed pyridone synthesis: A 1.5 dram vial with a stir bar was charged with freshly purified amide (0.22 mmol, 1 equiv), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.46 mmol, 210 mol %), and $\text{RhCp}^*(\text{MeCN})_3(\text{SbF}_6)_2$ or $\text{RhCp}^l(\text{MeCN})_3(\text{SbF}_6)_2$ (0.011 mmol, 5 mol %). If the alkyne is a solid, it was added (0.24 mmol, 1.1 equiv) followed by 0.75 ml of dichloroethane. If the alkyne is a liquid, 0.75 ml of dichloroethane was added followed by the alkyne (0.24 mmol, 1.1 equiv). The vial was sealed and placed into a 80 °C heating block for 8-16 h. The reaction was allowed to cool and poured into a separatory funnel with excess ethyl acetate and extracted twice with 10% NH_4OH . The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. Regioselectivities were determined

from diagnostic N-Me shifts, and by GC/MS of the crude reaction mixture. The residue was dissolved in 1 ml of dichloromethane and loaded onto a column of silica gel and eluted with a suitable solution of ethyl acetate and hexanes (typically 1:1 EtOAc/Hexanes). Evaporation of solvent afforded the product.

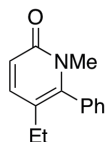
192 and **217** were stored as 0.88 M solutions in DCE. When these substrates were used the solids were added followed by 0.25 mL of the amide solution. The total volume remained 0.75 mL.

General procedure for rhodium catalyzed pyridone synthesis with catalytic $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$: A 16 mL test-tube with a stir bar was charged with freshly purified amide (0.22 mmol, 1 equiv), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.022 mmol, 20 mol %), $\text{RhCp}^*(\text{MeCN})_3(\text{SbF}_6)_2$ (0.011 mmol, 5 mol %), 0.75 mL of dichloroethane, and 1-phenyl-1-butyne (.24 mmol, 1.1 equiv) sequentially. The vial was capped with a septum penetrated by a needle and placed into a 80 °C heating block for 16 h. The reaction was allowed to cool and poured into a separatory funnel with excess ethyl acetate and extracted twice with 10% NH_4OH . The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. The residue was dissolved in 1 mL of dichloromethane and loaded onto a column of silica gel and eluted with a suitable solution of ethyl acetate and hexanes (typically 1:1 EtOAc/Hexanes). Evaporation of solvent afforded the product.

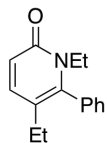
General Procedure of 6.22 mmol scale reaction: To a 50 mL round bottom equipped with a stir bar was added amide (6.22 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.244 mmol), and $\text{RhCp}^*(\text{MeCN})_3(\text{SbF}_6)_2$ (2.0 mol %) followed by 10.5 mL of dichloroethane. The flask was heated to 80 °C (sand bath temperature) and allowed to stir at this temperature. 1-phenyl-1-butyne (6.22 mmol) was added portionwise at 0, 1, 3, 5, and 8 hours (5 portions for 6.22 mmol total). After the final addition of alkyne, the reaction mixture was allowed to reflux for 14 hours. The reaction was allowed to cool and then poured into a separatory funnel with excess ethyl acetate and extracted twice with 10% NH_4OH in saturated NH_4Cl . The organic portion was extracted once with brine, dried over magnesium sulfate, and concentrated. The residue was purified via flash chromatography (EtOAc) to yield the product with unreacted starting material. The yield of the

desired product was determined use ^1H NMR integration of the diagnostic methyl peaks to determine the ratio. This ratio consequently was applied to the semi-pure yield (69% yield).

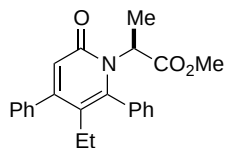
Characterization of Pyridone Products



5-ethyl-1-methyl-6-phenylpyridin-2(1H)-one (193): According to the general procedure, the desired pyridone was isolated as a yellow oil (90%, Cp* 6.8:1 rs, Cp^l 14:1): **R_f** = .24 (2:1 Hexanes/EtOAc); ^1H NMR (400 MHz, CDCl₃) δ 7.48-7.31 (m, 3H), 7.29 (d, 1H, J = 8.8 Hz, major), 7.23 (d, 1H, J = 0.8 Hz, minor), 7.18-7.16 (m, 2H), 6.62 (d, 1H, J = 8.8 Hz, major), 6.50 (d, 1H, J =9.2 Hz, minor), 3.62 (s, 3H), 3.17 (s, 3H), 2.59 (q, 2H, J = 7.6 Hz, minor), 2.03 (q, 2H, J = 7.6 Hz, major), 1.10 (td, 3H, J = 7.6 Hz, J = 0.8 Hz minor), 0.92 (td, 3H, J = 7.6 Hz, J = 0.8 Hz major); ^{13}C NMR (100 MHz, CDCl₃) δ 170.2, 163.1, 148.5, 145.9, 141.4, 139.2, 134.4, 130.8, 129.3, 128.86, 128.81, 128.7, 128.4, 127.3, 120.3, 120.3, 116.7, 40.2, 39.3, 34.2, 31.5, 29.6, 26.2, 24.4, 23.9; **IR (thin film)** 2966, 1653, 1162, 735, 705 cm⁻¹; **HRMS (ESI)** m/e calcd (M+H) 214.1226; found 214.1231.

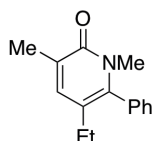


1,5-diethyl-6-phenylpyridin-2(1H)-one (228): According to the general procedure, the desired pyridone was isolated as a yellow oil (85%, Cp* 5:1 rs, Cp^l 15:1): **R_f** = .24 (2:1 Hexanes/EtOAc); ^1H NMR (400 MHz, CDCl₃) δ 7.43 (m, 3H), 7.25-7.20 (m, 3H), 6.56 (d, 1H, J =9.2 Hz, major), 6.43 (d, 1H, J =9.6, minor), 4.14 (q, 2H, J =6.8 Hz, minor), 3.72 (q, 2H, J =6.8 Hz, major), 2.55 (q, 2H, J =7.2 Hz, minor), 1.95 (q, 2H, J =10 Hz, major), 1.32 (t, 3H, J =6.4 Hz, minor), 1.04 (t, 3H, J =6.8, major), 0.89 (t, 3H, J =7.2 Hz, major); ^{13}C NMR (100 MHz, CDCl₃) δ 162.8, 162.0, 147.9, 145.6, 141.4, 140.4, 139.4, 134.4, 134.1, 129.4, 129.17, 129.12, 129.0, 128.79, 128.74, 128.4, 127.2, 120.3, 120.1, 117.3, 41.3, 39.3, 24.5, 23.2, 15.3, 14.3, 14.2, 14.0; **IR (thin film)** 2969, 1655, 1584, 1541, 733 cm⁻¹; **HRMS (ESI)** m/e calcd (M+H) 228.1383; found 228.1387.



(S)-methyl 2-(5-ethyl-2-oxo-4,6-diphenylpyridin-1(2H)-yl)propanoate

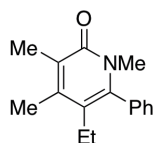
(229): According to the general procedure, the desired pyridone was isolated as a off-white solid (85%, Cp^t 15:1): **R_f** = .56 (EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.43 (m, 3H), 7.32 (m, 4H), 7.26 (m, 3H), 6.39 (s, 1H), 4.15 (q, 1H, *J*=6.8 Hz), 3.66 (s, 3H), 1.97 (q, 2H, *J*=7.6 Hz), 1.46 (d, 3H, *J*=6.8 Hz), 0.5 (t, 3H, *J*=7.2 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ 170.4, 160.8, 154.8, 145.9, 139.0, 134.5, 129.2, 129.2, 128.5, 128.1, 127.9, 127.8, 120.5, 119.5, 56.6, 52.3, 22.3, 14.8.; **IR (thin film)** 1749, 1658, 1221, 1084, 703 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 362.1751; found 362.176.



5-ethyl-1,3-dimethyl-6-phenylpyridin-2(1H)-one (230): According to the general

procedure, the desired pyridone was isolated as a off-white solid (98%, Cp* 5:1 rs, Cp^t 8.3:1): **R_f** = .43 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.46 (m, 3H), 7.12

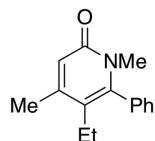
(m, 3H), 3.58 (s, 3H, minor), 3.13 (s, 3H, major), 2.52 (q, 2H, *J*=7.6 Hz, minor), 2.14 (s, 3H, major), 2.08 (s, 3H, minor), 1.97 (q, 2H, *J*= 7.6 Hz, major), 1.05 (t, 3H, *J*=7.6 Hz, minor), 0.88 (t, 3H, *J*=7.6 Hz, major); **¹³C NMR** (100 MHz, CDCl₃) δ 163.7, 162.8, 145.4, 143.1, 139.6, 139.1, 138.2, 134.7, 129.4, 128.9, 128.8, 128.7, 128.3, 128.0, 127.1, 125.4, 119.6, 119.5, 46.6, 43.9, 34.3, 31.6, 24.5, 23.7, 20.9, 17.3, 15.9, 15.4, 13.3; **IR (thin film)** 2926, 1651, 1602, 1557, 764 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 228.1383; found 228.1384.



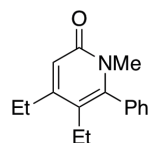
5-ethyl-1,3,4-trimethyl-6-phenylpyridin-2(1H)-one (231): According to the general procedure, the desired pyridone was isolated as a yellow oil (85%, Cp* 3.3:1 rs, Cp^t

4.8:1): **R_f** = .44 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.43 (m, 3H), 7.19

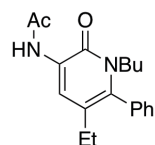
(dd, 2H, *J*=7.6 Hz, *J*=1.6 Hz, major), 7.12 (dd, 2H, *J*=8.0 Hz, *J*=1.6 Hz, minor), 3.63 (s, 3H, minor), 3.16 (s, 3H), 2.39 (q, 2H, *J*=7.6 Hz, minor), 2.20 (s, 6H, major), 2.15 (s, 3H, minor), 2.12 (q, 2H, *J*=7.2 Hz, major), 1.77 (s, 3H, minor), 1.01 (t, 3H, *J*=7.6 Hz, minor), 0.88 (t, 3H, *J*=7.6 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ 163.2, 162.3, 145.3, 145.1, 144.2, 142.4, 138.9, 135.4, 130.2, 128.88, 128.83, 128.63, 128.5, 127.1, 125.3, 122.7, 121.2, 119.9, 34.5, 31.7, 29.6, 24.1, 22.5, 18.1, 16.1, 14.9, 13.3, 13.2, 13.0; **IR (thin film)** 2929, 1636, 1585, 1491, 764 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 242.1539; found 242.1542.



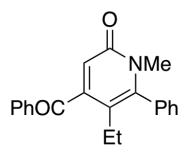
5-ethyl-1,4-dimethyl-6-phenylpyridin-2(1H)-one (232): According to the general procedure, the desired pyridone was isolated as a off-white solid (75%, Cp* 3.6:1 rs, Cp^t 4.6:1); **R_f** = .16 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.46 (m, 3H, major), 7.38 (m, 3H, minor), 7.20 (dd, 2H, *J*=8.4 Hz, *J*=1.6 Hz, major), 7.12 (dd, 2H, *J*=8.4 Hz, *J*=1.6 Hz, minor), 6.48 (s, 1H, major), 6.39 (s, 1H, minor), 3.60 (s, 3H, minor), 3.12 (s, 3H, major), 2.42 (q, 2H, *J*=7.2 Hz, minor), 2.22 (s, 3H, major), 2.08 (q, 2H, *J*=7.2 Hz, major), 1.77 (s, 3H, minor), 1.03 (t, 3H, *J*=7.6 Hz, minor), 0.86 (t, 3H, *J*=7.2 Hz, major); **¹³C NMR** (100 MHz, CDCl₃) δ 163.2, 162.4, 150.3, 147.8, 145.7, 142.06, 142.02, 137.9, 134.9, 130.0, 128.9, 128.8, 128.6, 127.4, 120.4, 118.9, 116.3, 107.1, 34.0, 31.2, 24.2, 21.9, 21.3, 19.6, 14.7, 12.8; **IR (thin film)** 2967, 1655, 1583, 1348, 707 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 228.1383; found 228.1383.



4,5-diethyl-1-methyl-6-phenylpyridin-2(1H)-one (233): According to the general procedure, the desired pyridone was isolated as a yellow oil (82%, Cp* 3.8:1 rs, Cp^t 4.6:1); **R_f** = .16 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.49 (m, 3H, major), 7.22 (dd, 2H, *J*=7.6 Hz, *J*=2.0 Hz, major), 6.55 (s, 1H, major), 3.63 (s, 3H, minor), 3.15 (s, 3H, major), 2.56 (q, 2H, *J*=7.2 Hz), 2.13 (q, 2H, *J*=7.2 Hz), 1.25 (t, 3H, *J*=7.6 Hz), 0.87 (t, 3H, *J*=7.6 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ 162.8, 155.7, 145.8, 135.0, 128.9, 128.8, 128.6, 120.2, 116.8, 34.0, 29.6, 25.0, 21.3, 15.1, 13.3; **IR (thin film)** 2966, 1653, 1532, 1488, 766, 706 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 242.1539; found 242.1541.



N-(1-butyl-5-ethyl-2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)acetamide (234): According to the general procedure, the desired pyridone was isolated as a yellow oil (85%, Cp* >19:1, rotamers); **R_f** = .73 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) Mixture of rotamers see spectra; **¹³C NMR** (100 MHz, CDCl₃) δ 172.0, 165.8, 161.0, 136.0, 132.5, 131.5, 128.8, 128.6, 128.1, 127.1, 127.0, 126.2, 125.1, 124.5, 118.0, 109.4, 46.6, 39.1, 31.9, 31.0, 25.2, 20.2, 20.0, 19.5, 19.4, 15.2, 15.0, 13.74, 13.7; **IR (thin film)** 2961, 1645, 1630, 1287, 696 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 313.1911; found 313.1912.



4-benzoyl-5-ethyl-1-methyl-6-phenylpyridin-2(1H)-one (235): According to the

general procedure, the desired pyridone was isolated as a red solid (75%, Cp* 6.8:1 rs,

Cp^t >19:1): **R_f** = .16 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.88 (dd, 2H,

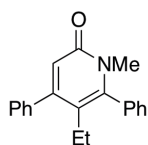
J=8.4 Hz, *J*=1.2 Hz), 7.56 (tt, 1H, *J*=7.2 Hz, *J*=1.2 Hz), 7.43 (m, 5H), 7.20 (m, 2H), 6.47 (s, 1H), 6.43 (s,

1H), 3.63 (s, 3H, minor), 3.16 (s, 3H, major), 2.02 (q, 2H, *J*=7.6 Hz), 0.66 (t, 3H, *J*=7.6 Hz); **¹³C NMR**

(100 MHz, CDCl₃) δ 195.4, 161.6, 150.5, 148.1, 135.5, 134.2, 134.1, 130.1, 129.3, 129.1, 128.7, 128.5,

117.8, 117.7, 34.5, 21.7, 15.6; **IR (thin film)** 2969, 1652, 1568, 1262, 727 cm⁻¹; **HRMS (ESI)** *m/e* calcd

(M+H) 318.1489; found 318.149.



5-ethyl-1-methyl-4,6-diphenylpyridin-2(1H)-one (236): According to the general

procedure, the desired pyridone was isolated as a yellow solid (85%, Cp* 17.6:1 rs): **R_f** =

.16 (2:1 Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.41 (m, 3H), 7.22 (m, 3H), 7.05

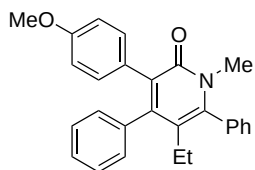
(m, 4H), 6.45 (s, 1H), 3.62 (s, 3H, minor), 3.14 (s, 3H, major), 2.51 (q, 2H, *J*=7.2 Hz, minor), 1.99 (q, 2H,

J=7.6 Hz, major), 1.04 (t, 3H, *J*=7.2 Hz, minor), 0.49 (t, 3H, *J*=7.6 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ

162.2, 154.5, 153.3, 149.0, 146.6, 139.1, 134.9, 131.0, 129.0, 128.9, 128.7, 128.1, 127.9, 127.8, 119.6,

119.5, 117.0, 34.2, 31.5, 24.3, 22.0, 14.9, 13.0; **IR (thin film)** 2968, 1655, 1523, 1074, 750 cm⁻¹; **HRMS**

(ESI) *m/e* calcd (M+H) 290.1539; found 290.1543.



5-ethyl-3-(4-methoxyphenyl)-1-methyl-4,6-diphenylpyridin-2(1H)-one (237):

According to the general procedure, the desired pyridone was isolated as a off-

white solid (This reaction did not react complication, as a consequence the

starting material could not be completely removed from the product) (85%, Cp* >19:1): **R_f** = .53 (EtOAc);

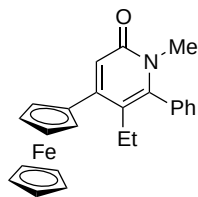
¹H NMR (400 MHz, CDCl₃) δ 7.44 (m, 3H), 7.27 (dd, 2H, *J*=8.4 Hz, *J*=2.0 Hz), 7.10 (m, 3H), 6.97 (m,

4H), 6.59 (d, 2H, *J*=8.8 Hz), 3.64 (s, 3H), 3.19 (s, 3H), 1.92 (q, 2H, *J*=7.2 Hz), 0.49 (t, 3H, *J*=7.6 Hz); **¹³C**

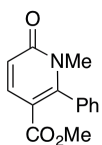
NMR (100 MHz, CDCl₃) δ 162.0, 157.8, 151.2, 145.0, 138.1, 136.7, 135.3, 138.1, 136.7, 135.2, 132.6,

131.7, 131.0, 130.2, 129.2, 129.1, 128.9, 128.8, 128.7, 128.3, 128.1, 127.6, 126.7, 119.3, 114.9, 112.8,

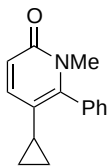
55.0, 34.8, 22.8, 15.0; **IR (thin film)** 1632, 1442, 1245, 912, 703 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 396.1958; found 396.1966 .



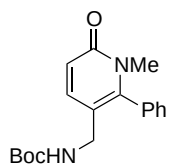
5-ethyl-1-methyl-4-ferrocene-6-diphenylpyridin-2(1H)-one (238): According to the general procedure, the desired pyridone was isolated as a red solid (85%, Cp* >19:1); R_f = .28 (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42 (m, 3H), 7.17 (m, 2H), 7.06 (s, 1H), 4.42 (t, 2H, $J=1.6$ Hz), 4.26 (t, 2H, $J=1.6$ Hz), 4.15 (s, 5H), 3.09 (s, 3H), 2.15 (q, 2H, $J=7.6$ Hz), 0.59 (t, 3H, $J=7.6$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.3, 151.7, 145.8, 135.1, 129.0, 128.8, 128.7, 119.9, 70.3, 69.8, 69.4, 68.6, 34.1, 22.0, 15.2; **IR (thin film)** 1648, 1562, 1229, 821, 705 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 398.1212; found 398.1209.



1-methyl-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxylate (244): According to the general procedure, the desired pyridone was isolated as a yellow oil (62%, Cp* 4.7:1 rs, Cp* >19:1); R_f = .24 (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88 (d, 1H, $J=10$ Hz), 7.44 (m, 3H), 7.14 (m, 2H), 6.63 (d, 1H, $J=9.6$ Hz), 6.54 (d, 1H, $J=9.6$ Hz), 3.58 (s, 3H, minor), 3.47 (s, 3H, major+minor), 3.15 (s, 3H, major); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.0, 163.0, 154.3, 134.6, 129.2, 128.7, 128.6, 127.4, 118.1, 51.7, 34.2; **IR (thin film)** 2924, 1728, 1662, 1117, 704 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 244.0968; found 244.0971.



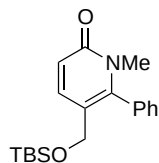
5-cyclopropyl-1-methyl-6-phenylpyridin-2(1H)-one (245): According to the general procedure, the desired pyridone was isolated as a yellow oil (78%, Cp* 11:1); R_f = .30 (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45-7.39 (m, 3H), 7.31-7.29 (m, 1H), 7.24-7.19 (m, 3H), 6.92 (d, 1H, $J=5.6$ Hz), 6.51 (d, 1H, $J=5.6$ Hz), 3.73 (s, 3H, minor), 3.16 (s, 3H, major), 1.24-1.19 (m, 1H), 0.85-0.78 (m, 1H), 0.55-0.51 (m, 2H), 0.39-0.37 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.6, 147.1, 146.4, 141.8, 139.0, 137.1, 134.5, 129.2, 139.0, 128.8, 126.7, 121.6, 119.0, 119.0, 118.2, 34.3, 32.3, 13.5, 11.7, 10.5, 7.26; **IR (thin film)** 1659, 1585, 1534, 829, 721 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 226.1226; found 226.1230.



tert-butyl ((1-methyl-6-oxo-2-phenyl-1,6-dihydropyridin-3-yl)methyl)carbamate

(246): According to the general procedure, the desired pyridone was isolated as a yellow

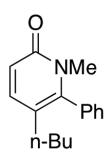
oil (65%, Cp* 2.5:1; 58%, Cp^t 4.8:1); **R_f** = .28 (EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.45-7.42 (m, 4H), 7.17-7.13 (m, 2H), 6.56 (d, 1H, *J*=8.8 Hz, major), 6.43 (d, 1H, *J*=8.8 Hz, minor), 4.76 (s, br, 1H, minor), 4.49 (s, br, 1H, major), 4.20 (d, 2H, *J*=5.6 Hz, minor), 3.67 (d, 2H, *J*=5.6 Hz, major), 3.57 (s, 3H, minor), 3.12 (s, 3H, major), 1.36 (s, 9H, minor), 1.34 (s, 9H, major); **¹³C NMR** (100 MHz, CDCl₃) δ 162.8, 155.5, 147.3, 141.0, 140.3, 133.3, 129.4, 129.3, 129.2, 128.7, 128.4, 127.7, 119.4, 115.7, 40.7, 34.1, 28.3; **IR (thin film)** 1709, 1656, 1583, 1168, 731, 704 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 315.1703; found 315.1711.



5-(((tert-butyldimethylsilyl)oxy)methyl)-1-methyl-6-phenylpyridin-2(1H)-one (247):

According to the general procedure, the desired pyridone was isolated as a yellow oil

(69%, Cp* 2.1:1; 58%, Cp^t 7.2:1); **R_f** = .33 (EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.61-7.59 (m, 2H), 7.50-7.42 (m, 1H), 7.41-7.35 (m, 1H), 7.36-7.29 (m, 2H), 6.73 (d, 1H, *J*=9.2 Hz, major), 6.71 (d, 1H, *J*=9.2 Hz, minor), 4.58 (s, 2H, minor), 4.14 (s, 2H, major), 3.82 (s, 3H, minor), 3.30 (s, 3H, major), 0.96 (s, 9H, minor), 0.91 (s, 9H, major), 0.06 (s, 6H, minor), 0.00 (s, 6H, major); **¹³C NMR** (100 MHz, CDCl₃) δ 168.7, 152.2, 148.9, 146.9, 145.7, 143.8, 139.0, 135.1, 135.0, 134.9, 134.7, 134.6, 134.5, 134.3, 134.2, 134.0, 133.1, 127.2, 125.3, 124.8, 123.3, 67.1, 65.4, 39.7, 37.0, 31.4, 31.2, 23.8; **IR (thin film)** 1741, 1589, 1461, 1070, 836 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 330.1884; found 330.1890.

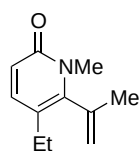


5-butyl-1-methyl-6-phenylpyridin-2(1H)-one (248): According to the general procedure, the

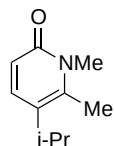
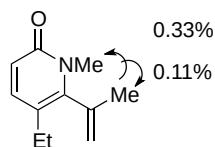
desired pyridone was isolated as a yellow oil (81%, Cp* 5:1, Cp^t 12.3:1); **R_f** = .20 (2:1

Hexanes/EtOAc); **¹H NMR** (400 MHz, CDCl₃) δ 7.41 (m, 3H), 7.21 (m, 1H), 7.12 (m, 2H), 6.54 (d, 1H, *J*=9.2 Hz, major), 6.43 (d, 1H, *J*=9.2 Hz, minor), 3.56 (s, 3H, minor), 3.13 (s, 3.13, major), 1.97 (t, 2H, *J*=8.0 Hz); 1.24 (m, 2H, major + minor), 1.07 (sextet, 2H, *J*=7.6 Hz, major), 0.7 (t, 3H, *J*=7.6 Hz, major + minor); **¹³C NMR** (100 MHz, CDCl₃) δ 163.5, 162.7, 147.5, 136.1, 141.4, 141.1, 139.3, 134.4, 129.5, 128.9, 128.7, 127.2, 120.4, 119.1, 119.0, 118.7, 116.7, 34.2, 32.9, 31.7, 30.8, 30.6, 30.3,

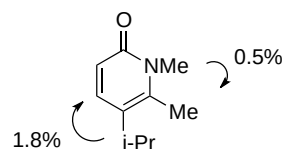
22.3, 22.1, 13.6, 13.4; **IR (thin film)** 2956, 1656, 1543, 830, 766 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 242.1539; found 242.1544.

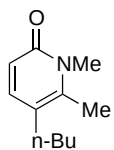


5-ethyl-1-methyl-6-(prop-1-en-2-yl)pyridin-2(1H)-one (249): According to the general procedure, the desired pyridone was isolated as a yellow oil (60%, Cp* 4.8:1; 79%, Cp^t 16:1); $R_f = .25$ (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.16 (d, 1H, $J=5.6$ Hz), 6.44 (d, 1H, $J=5.2$ Hz), 5.37 (t, 1H, $J=1.6$ Hz), 4.97 (t, 1H, $J=1.6$ Hz), 3.52 (s, 3H, minor), 3.40 (s, 3H, major), 2.26 (m, 2H), 1.91 (t, 3H, $J=1.6$ Hz), 1.01 (t, 3H, $J=7.2$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.7, 147.1, 140.8, 138.4, 119.3, 118.5, 117.9, 116.5, 32.7, 24.2, 22.9, 15.9; **IR (thin film)** 1661, 1585, 1540, 1084, 830 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 178.1226; found 178.1229.

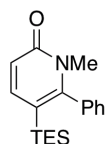


5-isopropyl-1,6-dimethylpyridin-2(1H)-one (250): According to the general procedure, the desired pyridone was isolated as a yellow oil (74%, Cp* 11:1); $R_f = .16$ (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.34 (d, 1H, $J=9.6$ Hz), 6.65 (d, 1H, $J=9.2$ Hz), 3.65 (s, 3H, minor), 3.6 (s, 3H, major), 2.96 (septet, 1H, $J=9.2$ Hz), 2.36 (s, 3H), 1.16 (d, 6H, $J=6.8$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.7, 147.1, 141.9, 137.6, 117.0, 98.5, 32.0, 28.5, 22.9, 19.5, 15.8; **IR (thin film)** 1659, 1461, 1414, 1159, 829 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 166.1226; found 166.1229.



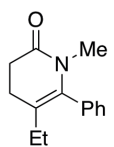


5-butyl-1,6-dimethylpyridin-2(1H)-one (251): According to the general procedure, the desired pyridone was isolated as a yellow oil (74%, Cp* 11:1): R_f = .25 (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.06 (d, 1H, J =9.2 Hz, major), 7.04 (d, 1H, J =9.2 Hz, minor), 6.35 (m, 1H), 3.51 (s, 3H), 3.48 (s, 3H), 2.32 (t, 2H, J =8.0 Hz), 2.32 (s, 3H, major), 2.01 (s, 3H, minor), 1.53-1.07 (m, 4H, major and minor), 0.95-8.82 (m, 3H, major and minor); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) see spectra; **IR (thin film)** 1766, 1661, 1460, 1198, 826 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 180.1383; found 180.1381.



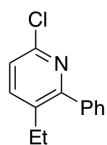
1-methyl-6-phenyl-5-(triethylsilyl)pyridin-2(1H)-one (251): According to the general procedure, the desired pyridone was isolated as a yellow oil (61%, Cp* 3.8:1 rs, Cp^t 3:1): R_f = .30 (EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45 (m, 4H), 7.22 (m, 2H), 6.66 (d, 1H, J =8.8 Hz), 3.70 (s, 3H, minor), 3.20 (s, 3H, major), 0.78 (t, 6H, J =7.6 Hz), 0.27 (q, 9H, J =8.0 Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.8, 151.6, 141.2, 132.7, 126.5, 125.9, 125.4, 125.1, 124.6, 114.6, 30.6, 4.3, 3.8, 1.7, .00; **IR (thin film)** 2924, 1656, 1512, 1171, 826 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 300.1778; found 242.1542.

Product Elaboration



5-ethyl-1-methyl-6-phenyl-3,4-dihydropyridin-2(1H)-one (254): A flame-dried 50 ml flask with a stir bar under argon was charged with pyridine **193** (.5 mmol, 1 equiv) and dry THF (15 ml). The reaction was cooled to -35 °C and 1M L-Selectride in THF was added dropwise over 15 minutes. The reaction was allowed to stir for 2 hrs at -35 °C before warming to 0 °C and stirring for 1 hr. At 0 °C brine (2 ml) was added. After 20 min 30% H_2O_2 (5 ml) and then NaOH (2 ml of 3M). The reaction was extracted with ether (3 x 10 ml), washed with brine (10 ml), dried over MgSO_4 , and concentrated *in vacuo*. The crude mixture was purified via column chromatography (1:1 Hexanes/EtOAc) to yield the desire product as a yellow oil (80%) R_f = .20 (2:1 Hexanes/EtOAc); ^1H (400 MHz, CDCl_3) δ 7.32-7.27 (m, 3H), 7.09 (m, 2H), 3.15 (s, 3H), 2.64 (s, 3H), 2.50 (m, 2H), 2.25 (m, 2H),

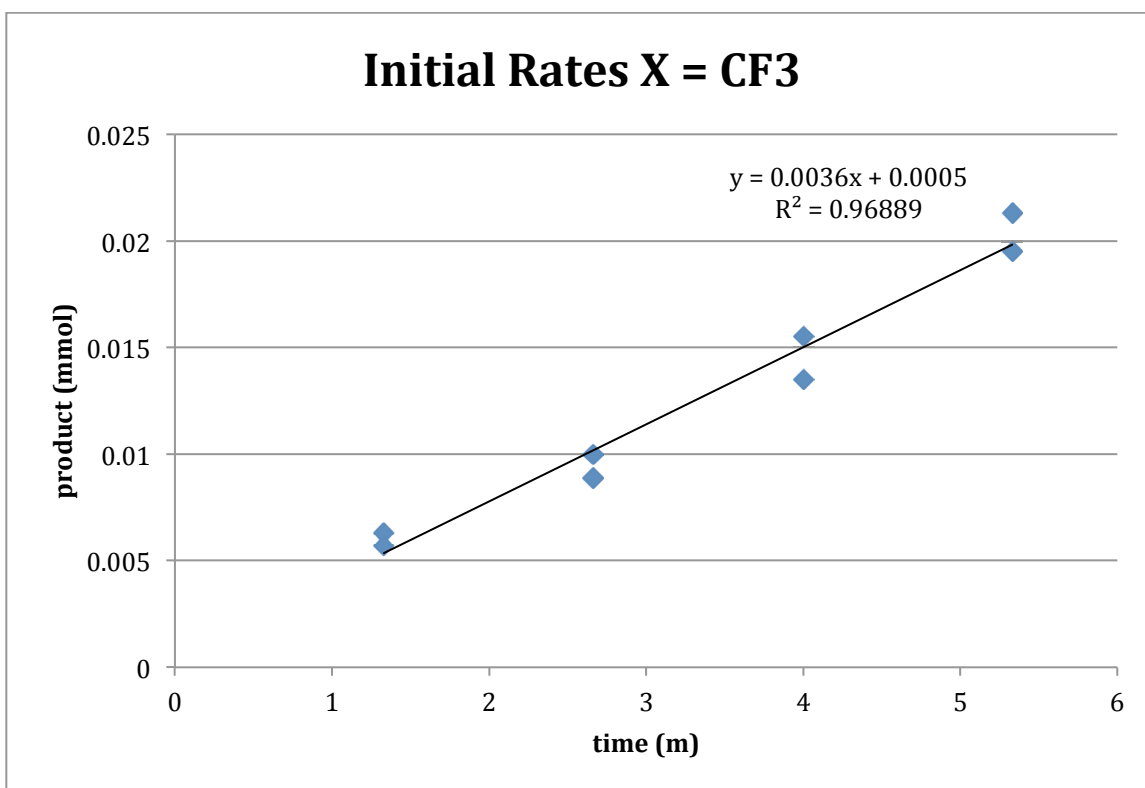
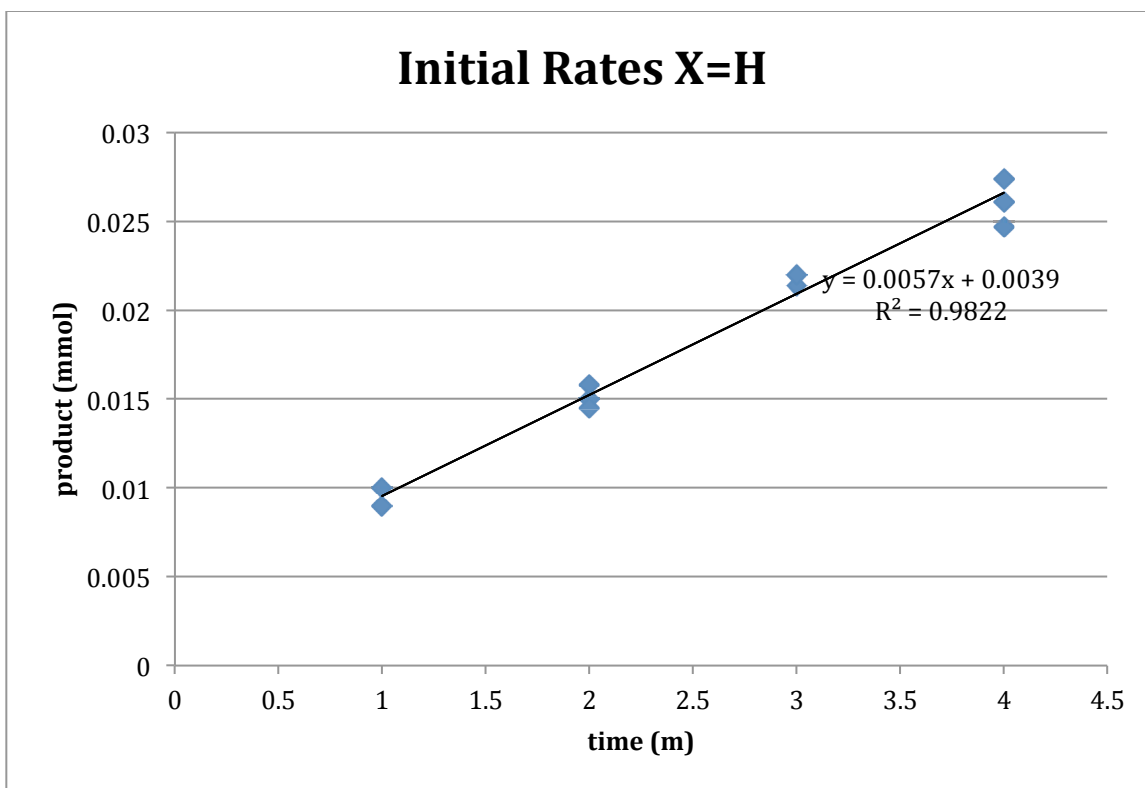
1.85 (q, 2H, $J=7.6$ Hz), 0.934 (t, 3H, $J=7.6$ Hz minor), 0.86 (t, 3H, $J=7.6$ Hz, major); ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 135.4, 134.9, 129.5, 128.5, 128.4, 128.3, 127.9, 121.1, 71.9, 47.8, 35.0, 31.7, 31.4, 27.5, 25.9, 24.2, 23.7, 18.5, 12.9; HRMS (ESI) m/e calcd (M+H) 216.1383; found 216.1388.

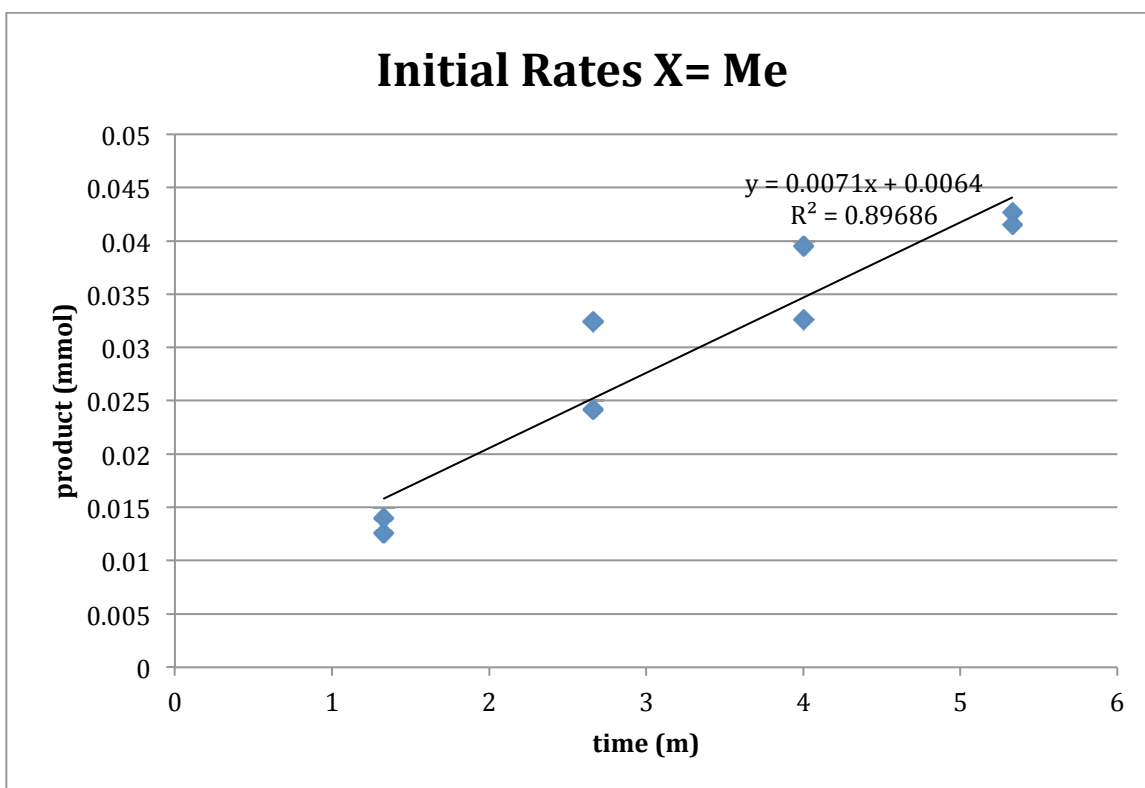
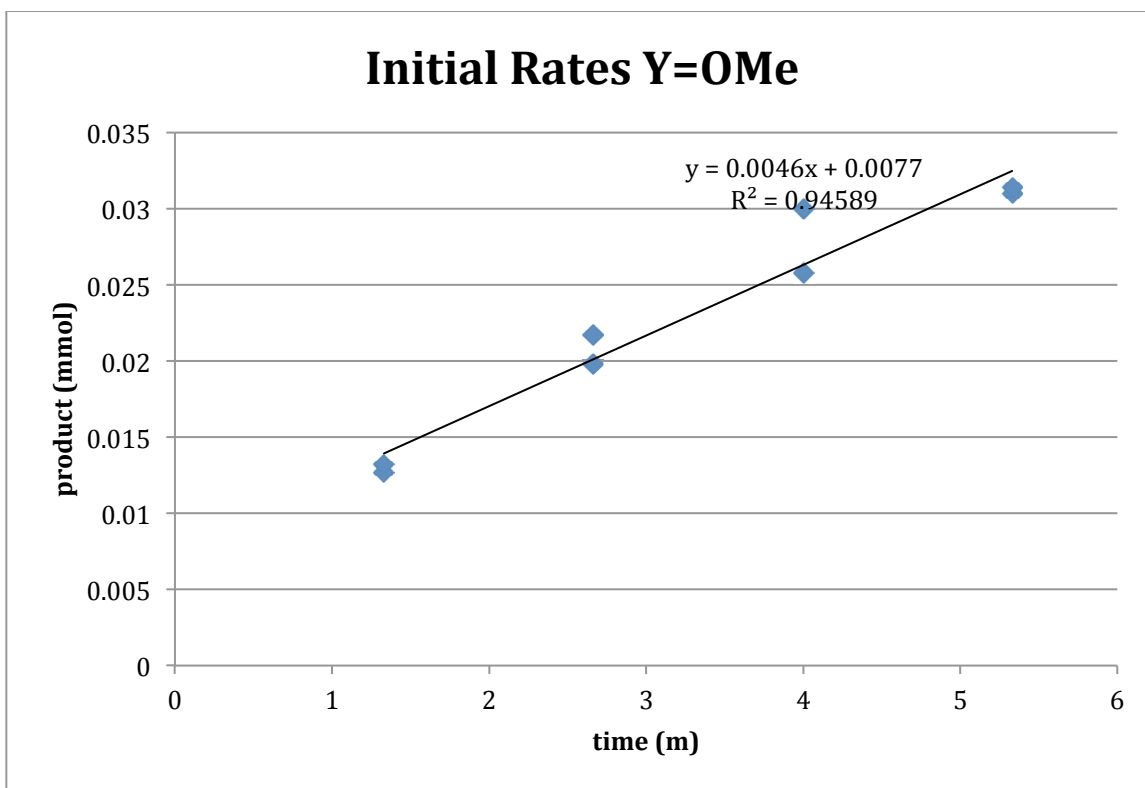


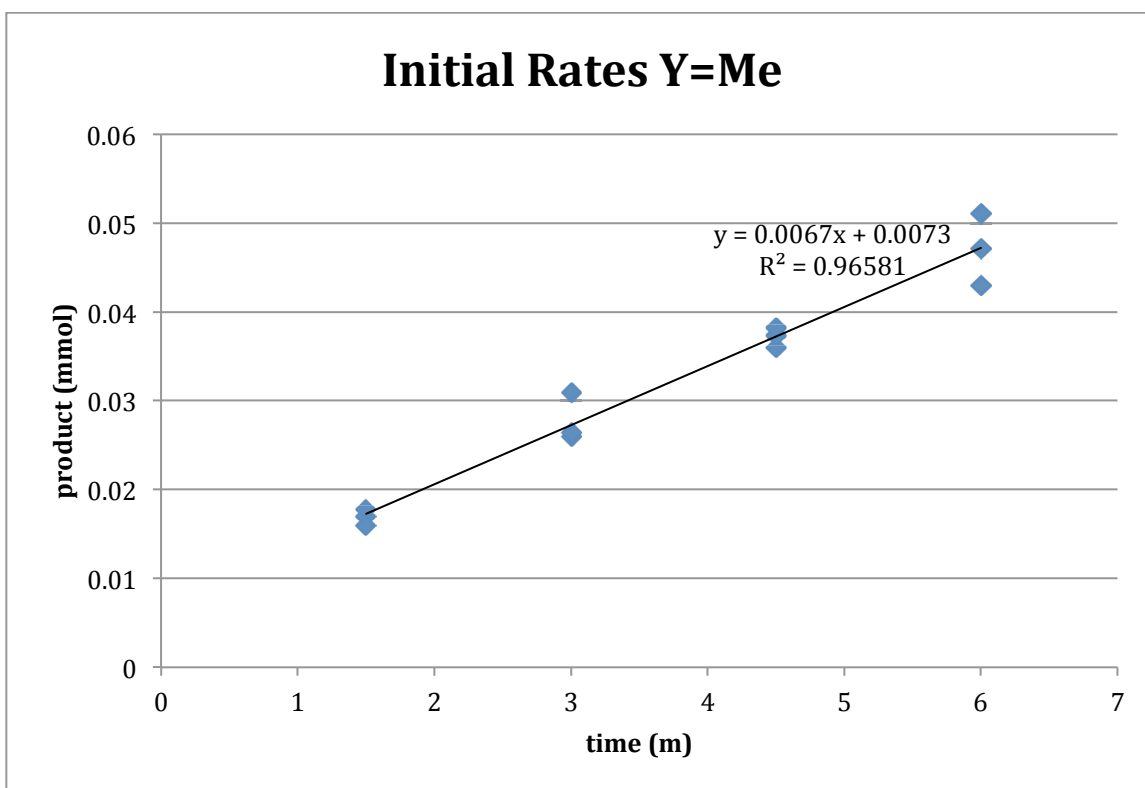
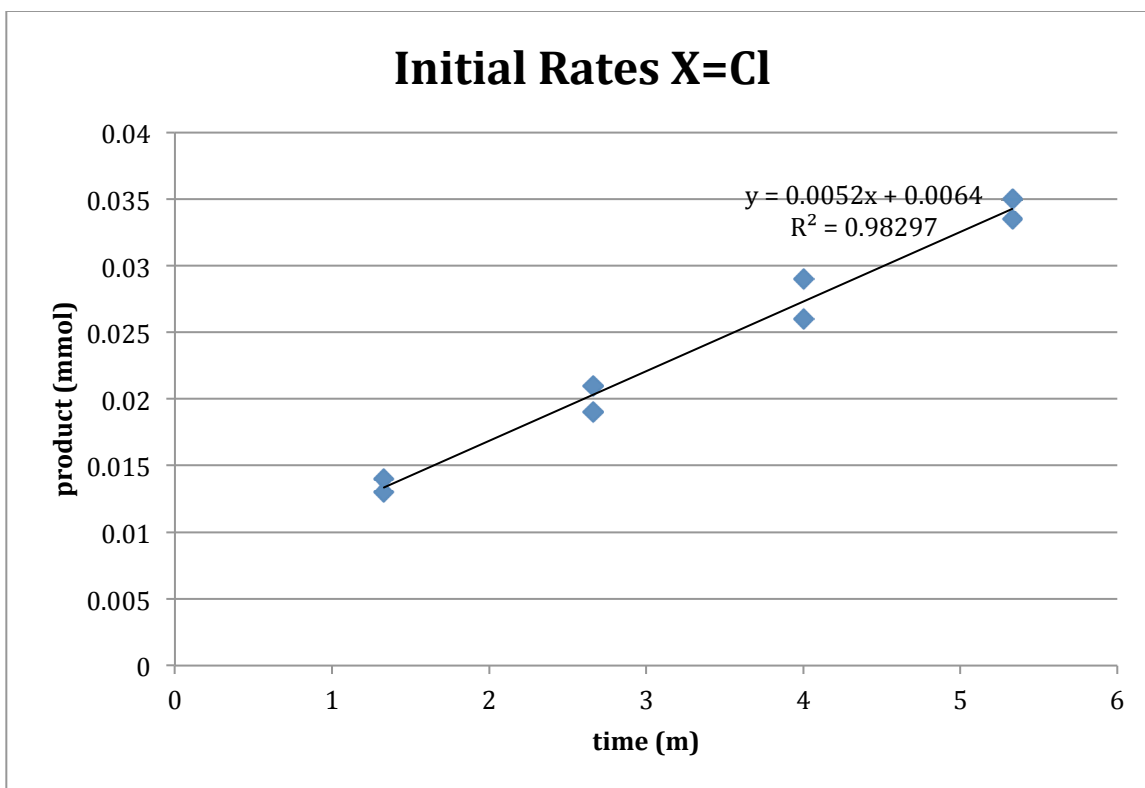
6-chloro-3-ethyl-2-phenylpyridine (253): A 25 ml vial with a stir bar was charged pyridone **193** (.15 mmol, 1 equiv), PCl_5 (.15 mmol, 1 equiv), and 1.25 ml. The vial was sealed and warmed to reflux. After 24 h reaction was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified via column chromatography in neutral silica (9:1 Hexanes/EtOAc).to yield the product as a yellow oil (90%). $R_f = .31$ (9:1 Hexanes/EtOAc/EtOAc); ^1H (400 MHz, CDCl_3) δ 7.57 (m, 1H), 7.41 (m, 5H), 7.23 (m, 1H), 2.62 (q, 2H, $J=7.2$ Hz), 1.11 (t, 3H, $J=7.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 161.6, 158.8, 147.8, 140.1, 139.6, 139.1, 135.7, 128.9, 128.8, 128.4, 128.3, 129.2, 128.1, 122.7, 121.1, 28.4, 24.8, 15.1, 13.9; IR (thin film) 2863, 1656, 1639, 1511, 700 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 218.0731; found 218.073.

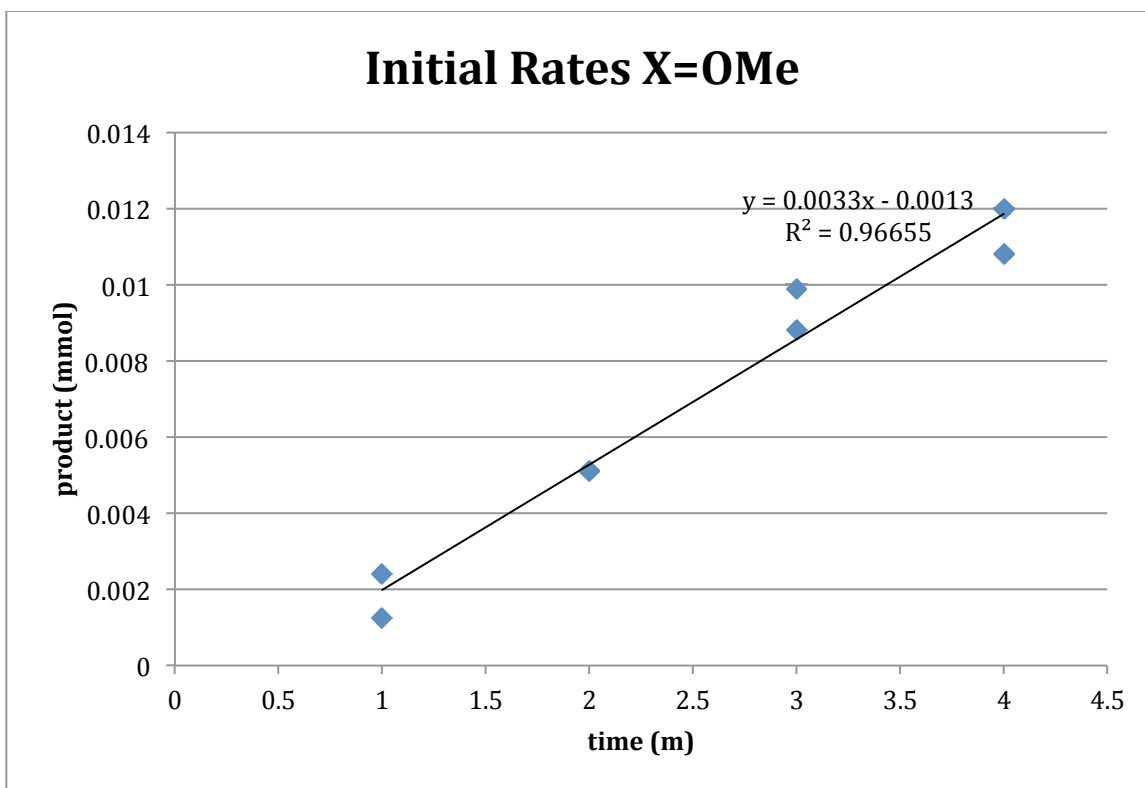
Kinetic Studies

A 1.5 dram vial was charged with a stir-bar, *N*-methyl cinnamamide or *D-N*-methyl cinnamamide (.22 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (.46 mmol), and 1,3,5 trimethoxy-benzene (.22 mmol). The vial was fitted with a septa and charged with dichloroethane (.50 ml). 1-phenyl-1-butyne (.22 mmol) was added to the reaction solution and the vial was placed into an 80 $^\circ\text{C}$ heating block and stirred for 5 min. A separate vial was charged with $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ (5 mol %), .25 ml of dichloroethane, and .15 ml of acetone to yield a bright yellow solution. This solution was added to the reaction vessel in the heating block. 0.1 ml aliquots were taken every minute for 4 minutes (after 1,2,3,and 4 minutes), diluted with ethyl acetate and extracted with 10 % NH_4OH in H_2O . The aliquots were interpreted using GC/MS.









Metallocycle formation 278

Rhodacycle **278** was formed following the procedure outlined by Jones and coworkers.¹¹

¹H NMR (400 MHz, CDCl₃) δ 8.00-7.98 (m, 1H), 7.92 (d, J = 7.8, 1H), 7.46-7.44 (m, 1H), 7.09-7.05 (m, 1H), 7.00-6.97 (m, 1H), 5.25-5.23 (m, 3H), 4.01-3.99 (m, 3H), 1.18-1.16 (m, 9H), 1.02-1.02 (m, 9H).

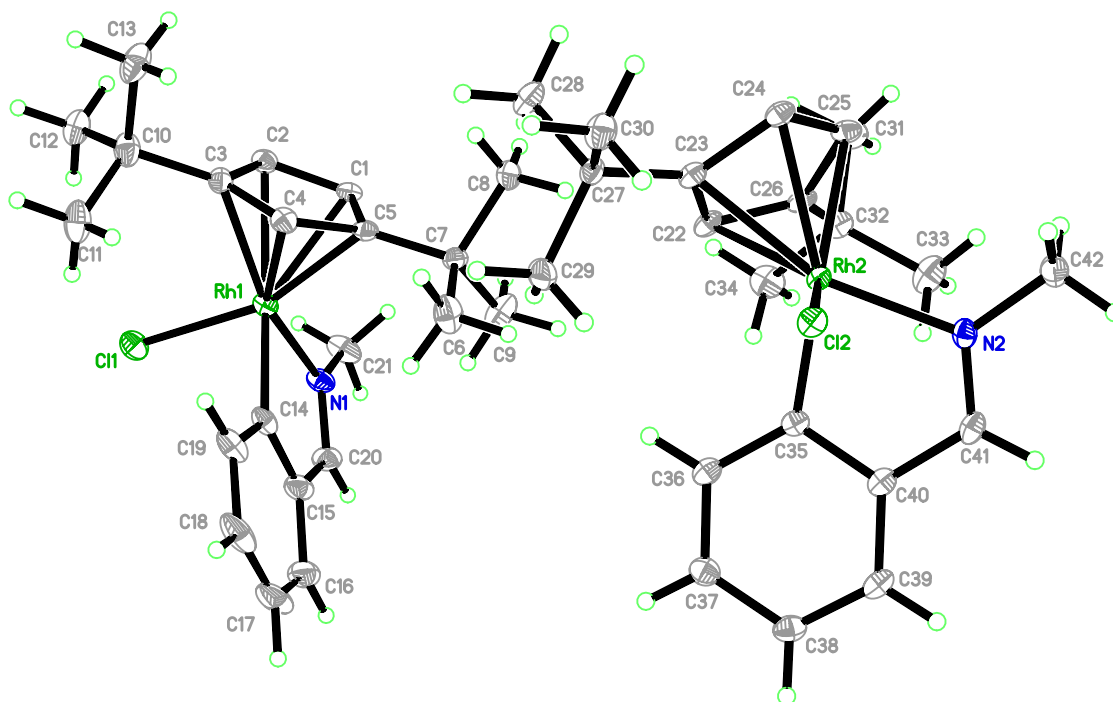


Table S2.1. Crystal data and Structure Refinement

Identification code	rovis167_0m	
Empirical formula	$\text{C}_{21} \text{H}_{29} \text{Cl N Rh}$	
Formula weight	433.81	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P-1$	
Unit cell dimensions	$a = 11.7956(12)$ Å	$\alpha = 85.713(5)^\circ$.
	$b = 12.3940(12)$ Å	$\beta = 81.671(6)^\circ$.
	$c = 13.9527(14)$ Å	$\gamma = 80.615(5)^\circ$.
Volume	$1988.5(3)$ Å ³	
Z	4	
Density (calculated)	1.449 Mg/m^3	
Absorption coefficient	0.995 mm^{-1}	

F_{000}	896
Crystal size	0.07 x 0.06 x 0.05 mm ³
Theta range for data collection	1.67 to 30.58°.
Index ranges	-16 ≤ h ≤ 16, -17 ≤ k ≤ 17, -19 ≤ l ≤ 19
Reflections collected	44475
Independent reflections	12069 [$R_{\text{int}} = 0.0578$]
Completeness to theta = 30.58°	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9519 and 0.9318
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12069 / 0 / 447
Goodness-of-fit on F^2	1.042
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0519$, $wR_2 = 0.1073$
R indices (all data)	$R_1 = 0.1003$, $wR_2 = 0.1324$
Largest diff. peak and hole	2.566 and -1.227 e.Å ⁻³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å² $\times 10^3$) for Rovis167_0m. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	8631(3)	8306(3)	2697(3)	22(1)
C(2)	9356(4)	8521(3)	3360(3)	26(1)
C(3)	9523(4)	7552(3)	4014(3)	26(1)
C(4)	8943(4)	6742(3)	3702(3)	25(1)
C(5)	8347(3)	7202(3)	2904(3)	23(1)

C(6)	7414(5)	5552(3)	2770(3)	41(1)
C(7)	7752(3)	6601(3)	2257(3)	24(1)
C(8)	8616(4)	6302(5)	1357(3)	48(1)
C(9)	6675(4)	7324(4)	1961(4)	45(1)
C(10)	10347(4)	7365(4)	4776(3)	35(1)
C(11)	9819(5)	6729(4)	5669(3)	45(1)
C(12)	10627(4)	8448(4)	5056(4)	40(1)
C(13)	11473(4)	6675(4)	4324(4)	49(1)
C(14)	6434(4)	7246(3)	4877(3)	28(1)
C(15)	5277(4)	7759(4)	4847(3)	33(1)
C(16)	4335(5)	7261(4)	5301(4)	44(1)
C(17)	4539(6)	6262(5)	5782(4)	57(2)
C(18)	5673(6)	5745(4)	5825(3)	51(2)
C(19)	6592(5)	6241(3)	5395(3)	36(1)
C(20)	5169(4)	8795(4)	4311(3)	33(1)
C(21)	6109(4)	10168(4)	3374(3)	40(1)
C(22)	8015(3)	3268(3)	350(3)	23(1)
C(23)	8880(3)	2355(3)	491(3)	22(1)
C(24)	9316(3)	1912(3)	-452(3)	23(1)
C(25)	8691(3)	2523(3)	-1146(3)	23(1)
C(26)	7848(3)	3380(3)	-655(3)	23(1)
C(27)	9402(3)	2053(3)	1426(3)	22(1)
C(28)	10241(4)	2879(4)	1483(3)	35(1)

C(29)	8467(4)	2133(4)	2308(3)	34(1)
C(30)	10081(4)	898(3)	1432(3)	32(1)
C(31)	7982(4)	4930(3)	-1867(3)	37(1)
C(32)	7125(4)	4345(3)	-1147(3)	26(1)
C(33)	6249(4)	3964(4)	-1685(3)	39(1)
C(34)	6503(4)	5143(3)	-390(3)	36(1)
C(35)	5812(3)	2068(3)	765(3)	20(1)
C(36)	5501(3)	2465(3)	1691(3)	24(1)
C(37)	4393(4)	2457(3)	2175(3)	27(1)
C(38)	3549(4)	2056(3)	1757(3)	28(1)
C(39)	3820(4)	1682(3)	844(3)	26(1)
C(40)	4941(3)	1677(3)	350(3)	22(1)
C(41)	5326(4)	1240(3)	-584(3)	23(1)
C(42)	6857(4)	814(3)	-1879(3)	29(1)
Cl(2)	7575(1)	-14(1)	680(1)	23(1)
Cl(1)	7467(1)	9110(1)	5614(1)	35(1)
N(1)	6124(3)	9110(3)	3912(2)	28(1)
N(2)	6383(3)	1264(2)	-942(2)	22(1)
Rh(2)	7401(1)	1815(1)	-40(1)	17(1)
Rh(1)	7634(1)	8124(1)	4168(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for Rovis167_0m.

		C(14)-C(15)	1.414(6)
		C(14)-Rh(1)	2.025(4)
C(1)-C(2)	1.413(6)	C(15)-C(16)	1.406(6)
C(1)-C(5)	1.460(5)	C(15)-C(20)	1.434(6)
C(1)-Rh(1)	2.228(4)	C(16)-C(17)	1.367(8)
C(2)-C(3)	1.458(5)	C(17)-C(18)	1.394(8)
C(2)-Rh(1)	2.284(4)	C(18)-C(19)	1.374(7)
C(3)-C(4)	1.429(6)	C(20)-N(1)	1.289(5)
C(3)-C(10)	1.523(6)	C(21)-N(1)	1.460(5)
C(3)-Rh(1)	2.210(4)	C(22)-C(23)	1.418(5)
C(4)-C(5)	1.435(5)	C(22)-C(26)	1.436(6)
C(4)-Rh(1)	2.181(4)	C(22)-Rh(2)	2.180(4)
C(5)-C(7)	1.522(6)	C(23)-C(24)	1.454(6)
C(5)-Rh(1)	2.164(4)	C(23)-C(27)	1.519(5)
C(6)-C(7)	1.519(5)	C(23)-Rh(2)	2.206(4)
C(7)-C(9)	1.521(6)	C(24)-C(25)	1.404(5)
C(7)-C(8)	1.526(6)	C(24)-Rh(2)	2.270(4)
C(10)-C(12)	1.524(6)	C(25)-C(26)	1.469(6)
C(10)-C(11)	1.534(6)	C(25)-Rh(2)	2.241(4)
C(10)-C(13)	1.536(7)	C(26)-C(32)	1.530(5)
C(14)-C(19)	1.392(5)	C(26)-Rh(2)	2.175(3)

C(27)-C(30)	1.522(5)	C(5)-C(1)-Rh(1)	68.2(2)
C(27)-C(29)	1.527(6)	C(1)-C(2)-C(3)	107.2(3)
C(27)-C(28)	1.548(5)	C(1)-C(2)-Rh(1)	69.6(2)
C(31)-C(32)	1.546(5)	C(3)-C(2)-Rh(1)	68.3(2)
C(32)-C(33)	1.513(6)	C(4)-C(3)-C(2)	108.0(3)
C(32)-C(34)	1.525(6)	C(4)-C(3)-C(10)	125.7(4)
C(35)-C(36)	1.395(5)	C(2)-C(3)-C(10)	125.5(4)
C(35)-C(40)	1.414(5)	C(4)-C(3)-Rh(1)	69.9(2)
C(35)-Rh(2)	2.031(4)	C(2)-C(3)-Rh(1)	73.9(2)
C(36)-C(37)	1.382(6)	C(10)-C(3)-Rh(1)	130.1(3)
C(37)-C(38)	1.397(6)	C(3)-C(4)-C(5)	108.9(3)
C(38)-C(39)	1.365(6)	C(3)-C(4)-Rh(1)	72.1(2)
C(39)-C(40)	1.398(6)	C(5)-C(4)-Rh(1)	70.1(2)
C(40)-C(41)	1.432(6)	C(4)-C(5)-C(1)	106.4(3)
C(41)-N(2)	1.279(5)	C(4)-C(5)-C(7)	127.2(3)
C(42)-N(2)	1.459(5)	C(1)-C(5)-C(7)	125.3(3)
Cl(2)-Rh(2)	2.3995(9)	C(4)-C(5)-Rh(1)	71.4(2)
Cl(1)-Rh(1)	2.4045(12)	C(1)-C(5)-Rh(1)	73.0(2)
N(1)-Rh(1)	2.050(3)	C(7)-C(5)-Rh(1)	130.2(3)
N(2)-Rh(2)	2.079(3)	C(6)-C(7)-C(9)	109.3(4)
		C(6)-C(7)-C(5)	111.0(3)
C(2)-C(1)-C(5)	109.5(3)	C(9)-C(7)-C(5)	110.7(3)
C(2)-C(1)-Rh(1)	74.0(2)	C(6)-C(7)-C(8)	108.5(4)

C(9)-C(7)-C(8)	109.7(4)	C(22)-C(23)-C(27)	124.7(4)
C(5)-C(7)-C(8)	107.6(3)	C(24)-C(23)-C(27)	126.6(3)
C(3)-C(10)-C(12)	111.0(4)	C(22)-C(23)-Rh(2)	70.1(2)
C(3)-C(10)-C(11)	109.9(4)	C(24)-C(23)-Rh(2)	73.4(2)
C(12)-C(10)-C(11)	110.8(4)	C(27)-C(23)-Rh(2)	130.9(3)
C(3)-C(10)-C(13)	107.2(4)	C(25)-C(24)-C(23)	108.3(3)
C(12)-C(10)-C(13)	108.9(4)	C(25)-C(24)-Rh(2)	70.8(2)
C(11)-C(10)-C(13)	109.0(4)	C(23)-C(24)-Rh(2)	68.7(2)
C(19)-C(14)-C(15)	116.7(4)	C(24)-C(25)-C(26)	108.4(3)
C(19)-C(14)-Rh(1)	129.4(4)	C(24)-C(25)-Rh(2)	73.0(2)
C(15)-C(14)-Rh(1)	113.9(3)	C(26)-C(25)-Rh(2)	68.19(19)
C(16)-C(15)-C(14)	121.4(4)	C(22)-C(26)-C(25)	106.4(3)
C(16)-C(15)-C(20)	124.5(5)	C(22)-C(26)-C(32)	126.2(4)
C(14)-C(15)-C(20)	114.2(4)	C(25)-C(26)-C(32)	126.2(4)
C(17)-C(16)-C(15)	119.5(5)	C(22)-C(26)-Rh(2)	70.9(2)
C(16)-C(17)-C(18)	120.1(4)	C(25)-C(26)-Rh(2)	73.0(2)
C(19)-C(18)-C(17)	120.3(5)	C(32)-C(26)-Rh(2)	130.7(3)
C(18)-C(19)-C(14)	122.0(5)	C(23)-C(27)-C(30)	111.8(3)
N(1)-C(20)-C(15)	116.2(4)	C(23)-C(27)-C(29)	111.3(3)
C(23)-C(22)-C(26)	109.1(4)	C(30)-C(27)-C(29)	108.4(3)
C(23)-C(22)-Rh(2)	72.1(2)	C(23)-C(27)-C(28)	106.4(3)
C(26)-C(22)-Rh(2)	70.6(2)	C(30)-C(27)-C(28)	109.0(3)
C(22)-C(23)-C(24)	107.7(3)	C(29)-C(27)-C(28)	109.9(4)

C(33)-C(32)-C(34)	109.8(4)	C(35)-Rh(2)-N(2)	78.65(15)
C(33)-C(32)-C(26)	111.5(3)	C(35)-Rh(2)-C(26)	109.11(14)
C(34)-C(32)-C(26)	109.7(3)	N(2)-Rh(2)-C(26)	108.06(13)
C(33)-C(32)-C(31)	109.9(4)	C(35)-Rh(2)-C(22)	97.28(15)
C(34)-C(32)-C(31)	108.9(3)	N(2)-Rh(2)-C(22)	143.41(13)
C(26)-C(32)-C(31)	106.9(3)	C(26)-Rh(2)-C(22)	38.51(14)
C(36)-C(35)-C(40)	116.9(3)	C(35)-Rh(2)-C(23)	119.23(15)
C(36)-C(35)-Rh(2)	129.1(3)	N(2)-Rh(2)-C(23)	161.69(14)
C(40)-C(35)-Rh(2)	113.7(3)	C(26)-Rh(2)-C(23)	64.10(14)
C(37)-C(36)-C(35)	120.8(4)	C(22)-Rh(2)-C(23)	37.72(14)
C(36)-C(37)-C(38)	121.5(4)	C(35)-Rh(2)-C(25)	146.55(14)
C(39)-C(38)-C(37)	119.1(4)	N(2)-Rh(2)-C(25)	100.38(14)
C(38)-C(39)-C(40)	119.9(4)	C(26)-Rh(2)-C(25)	38.81(14)
C(39)-C(40)-C(35)	121.8(4)	C(22)-Rh(2)-C(25)	63.48(15)
C(39)-C(40)-C(41)	123.9(4)	C(23)-Rh(2)-C(25)	62.80(14)
C(35)-C(40)-C(41)	114.2(4)	C(35)-Rh(2)-C(24)	157.03(16)
N(2)-C(41)-C(40)	117.4(4)	N(2)-Rh(2)-C(24)	124.03(14)
C(20)-N(1)-C(21)	120.4(4)	C(26)-Rh(2)-C(24)	63.20(14)
C(20)-N(1)-Rh(1)	116.9(3)	C(22)-Rh(2)-C(24)	62.78(14)
C(21)-N(1)-Rh(1)	122.5(3)	C(23)-Rh(2)-C(24)	37.89(15)
C(41)-N(2)-C(42)	121.1(3)	C(25)-Rh(2)-C(24)	36.25(14)
C(41)-N(2)-Rh(2)	115.7(3)	C(35)-Rh(2)-Cl(2)	86.10(10)
C(42)-N(2)-Rh(2)	122.8(3)	N(2)-Rh(2)-Cl(2)	85.32(8)

C(26)-Rh(2)-Cl(2)	161.16(11)	C(4)-Rh(1)-C(2)	63.03(14)
C(22)-Rh(2)-Cl(2)	131.01(10)	C(3)-Rh(1)-C(2)	37.82(14)
C(23)-Rh(2)-Cl(2)	99.10(9)	C(1)-Rh(1)-C(2)	36.47(14)
C(25)-Rh(2)-Cl(2)	127.31(10)	C(14)-Rh(1)-Cl(1)	87.81(12)
C(24)-Rh(2)-Cl(2)	98.46(9)	N(1)-Rh(1)-Cl(1)	85.69(10)
C(14)-Rh(1)-N(1)	78.78(16)	C(5)-Rh(1)-Cl(1)	162.23(11)
C(14)-Rh(1)-C(5)	103.71(15)	C(4)-Rh(1)-Cl(1)	127.53(11)
N(1)-Rh(1)-C(5)	109.58(14)	C(3)-Rh(1)-Cl(1)	98.00(11)
C(14)-Rh(1)-C(4)	97.31(16)	C(1)-Rh(1)-Cl(1)	132.52(10)
N(1)-Rh(1)-C(4)	146.62(15)	C(2)-Rh(1)-Cl(1)	101.41(11)
C(5)-Rh(1)-C(4)	38.58(14)		
C(14)-Rh(1)-C(3)	123.90(16)		
N(1)-Rh(1)-C(3)	156.99(14)		
C(5)-Rh(1)-C(3)	64.38(15)		
C(4)-Rh(1)-C(3)	37.98(15)		
C(14)-Rh(1)-C(1)	139.50(15)		
N(1)-Rh(1)-C(1)	98.10(14)		
C(5)-Rh(1)-C(1)	38.80(13)		
C(4)-Rh(1)-C(1)	63.43(14)		
C(3)-Rh(1)-C(1)	62.75(15)		
C(14)-Rh(1)-C(2)	160.06(16)		
N(1)-Rh(1)-C(2)	119.17(14)		
C(5)-Rh(1)-C(2)	63.59(15)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Rovis167_0m. The anisotropic displacement factor exponent takes the form: $-2p^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	18(2)	24(2)	22(2)	-1(2)	4(2)	-5(2)
C(2)	24(2)	26(2)	26(2)	-1(2)	0(2)	0(2)
C(3)	24(2)	27(2)	25(2)	-5(2)	-5(2)	2(2)
C(4)	25(2)	20(2)	27(2)	-2(2)	-2(2)	5(2)
C(5)	16(2)	24(2)	25(2)	-2(2)	1(2)	0(2)
C(6)	65(4)	28(2)	34(3)	0(2)	-11(2)	-18(2)
C(7)	20(2)	27(2)	24(2)	1(2)	-2(2)	-4(2)
C(8)	40(3)	77(4)	34(3)	-26(3)	1(2)	-27(3)
C(9)	44(3)	33(2)	64(3)	-1(2)	-27(3)	-8(2)
C(10)	41(3)	33(2)	32(3)	-5(2)	-13(2)	4(2)
C(11)	64(4)	36(2)	38(3)	3(2)	-26(3)	-3(2)
C(12)	46(3)	37(2)	42(3)	-5(2)	-19(2)	-7(2)
C(13)	42(3)	47(3)	60(4)	-14(3)	-28(3)	9(2)
C(14)	41(3)	22(2)	20(2)	-3(2)	2(2)	-7(2)
C(15)	36(3)	32(2)	32(3)	-10(2)	6(2)	-13(2)

C(16)	41(3)	53(3)	41(3)	-17(2)	8(2)	-23(2)
C(17)	84(5)	60(3)	35(3)	-14(3)	22(3)	-55(3)
C(18)	96(5)	33(2)	26(3)	-2(2)	9(3)	-31(3)
C(19)	56(3)	27(2)	23(2)	-1(2)	4(2)	-6(2)
C(20)	23(2)	36(2)	37(3)	-8(2)	2(2)	1(2)
C(21)	43(3)	32(2)	35(3)	9(2)	7(2)	10(2)
C(22)	21(2)	19(2)	32(2)	5(2)	-8(2)	-9(2)
C(23)	19(2)	20(2)	27(2)	1(2)	-6(2)	-6(2)
C(24)	21(2)	20(2)	29(2)	2(2)	-4(2)	-9(2)
C(25)	20(2)	24(2)	27(2)	4(2)	1(2)	-9(2)
C(26)	18(2)	19(2)	31(2)	5(2)	-4(2)	-8(2)
C(27)	19(2)	23(2)	24(2)	-2(2)	-7(2)	-1(2)
C(28)	29(3)	39(2)	42(3)	0(2)	-15(2)	-12(2)
C(29)	29(3)	48(3)	23(2)	0(2)	-6(2)	-1(2)
C(30)	31(3)	30(2)	35(3)	0(2)	-14(2)	3(2)
C(31)	39(3)	27(2)	41(3)	13(2)	-1(2)	-5(2)
C(32)	27(2)	21(2)	31(2)	8(2)	-6(2)	-4(2)
C(33)	44(3)	32(2)	45(3)	12(2)	-23(2)	-8(2)
C(34)	35(3)	30(2)	40(3)	5(2)	-7(2)	9(2)
C(35)	20(2)	16(2)	23(2)	4(2)	-4(2)	-3(2)
C(36)	21(2)	20(2)	30(2)	1(2)	-7(2)	-2(2)
C(37)	26(2)	26(2)	28(2)	-2(2)	-1(2)	-1(2)
C(38)	22(2)	26(2)	36(3)	-2(2)	0(2)	-2(2)

C(39)	21(2)	22(2)	38(3)	2(2)	-10(2)	-5(2)
C(40)	21(2)	16(2)	28(2)	3(2)	-8(2)	-2(2)
C(41)	26(2)	18(2)	28(2)	3(2)	-14(2)	-3(2)
C(42)	34(3)	30(2)	25(2)	-3(2)	-5(2)	-8(2)
Cl(2)	25(1)	18(1)	24(1)	4(1)	-6(1)	-5(1)
Cl(1)	39(1)	32(1)	31(1)	-9(1)	0(1)	-2(1)
N(1)	26(2)	26(2)	27(2)	1(1)	3(2)	3(2)
N(2)	28(2)	20(2)	18(2)	2(1)	-7(2)	-6(1)
Rh(2)	17(1)	16(1)	18(1)	2(1)	-5(1)	-4(1)
Rh(1)	24(1)	19(1)	22(1)	1(1)	-1(1)	-1(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Rovis167_0m.

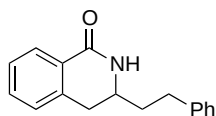
	x	y	z	U(eq)
H(6A)	8098	5071	2915	61
H(6B)	7018	5200	2358	61
H(6C)	6911	5723	3362	61
H(8A)	9331	5925	1551	72
H(8B)	8756	6958	978	72
H(8C)	8304	5836	977	72

H(9A)	6322	6937	1542	67
H(9B)	6889	7981	1624	67
H(9C)	6135	7512	2529	67
H(11A)	9121	7160	5962	67
H(11B)	10364	6573	6129	67
H(11C)	9642	6054	5477	67
H(12A)	10980	8822	4492	60
H(12B)	11152	8309	5532	60
H(12C)	9925	8895	5322	60
H(13A)	11309	5981	4163	73
H(13B)	12023	6558	4779	73
H(13C)	11789	7053	3746	73
H(16)	3579	7610	5275	53
H(17)	3920	5925	6080	69
H(18)	5809	5062	6147	61
H(19)	7343	5895	5451	44
H(20)	4451	9216	4256	40
H(21A)	5324	10538	3403	60
H(21B)	6430	10057	2710	60
H(21C)	6562	10605	3657	60
H(28A)	10839	2812	935	52
H(28B)	10585	2727	2071	52
H(28C)	9819	3610	1477	52

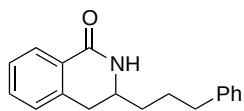
H(29A)	8060	2869	2337	50
H(29B)	8821	1937	2887	50
H(29C)	7931	1641	2255	50
H(30A)	9563	380	1412	48
H(30B)	10441	754	2013	48
H(30C)	10666	830	876	48
H(31A)	7557	5523	-2213	55
H(31B)	8417	4419	-2318	55
H(31C)	8503	5212	-1516	55
H(33A)	5725	3596	-1234	58
H(33B)	6646	3469	-2165	58
H(33C)	5821	4585	-1995	58
H(34A)	6009	5720	-694	55
H(34B)	7064	5449	-105	55
H(34C)	6043	4762	106	55
H(36)	6045	2738	1986	28
H(37)	4206	2726	2792	33
H(38)	2812	2043	2097	34
H(39)	3261	1432	550	32
H(41)	4827	950	-916	28
H(42A)	6266	521	-2137	44
H(42B)	7495	241	-1798	44
H(42C)	7122	1382	-2318	44

Dihydroisoquinolone Synthesis Using Cp^t

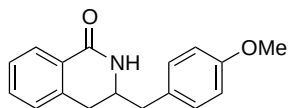
283 and **284** had previously been characterized by Fagnou.¹² All reactions were conducted according to the procedure outline by Fagnou, with [RhCp^tCl₂]₂ used in place of [RhCp^{*}Cl₂]₂. The regioselectivity of the alkene insertion was determined by GC/MS and ¹H NMR, while the yield for reactions catalyzed by [RhCp^{*}Cl₂]₂ was determined by GC/MS. The yield of reaction catalyzed by [RhCp^tCl₂]₂ was determined by isolation after column chromatography.



3-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (292): The product was isolated in 90% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (dd, J = 7.7, 1.4, 1H), 7.47-7.43 (m, 1H), 7.35 (td, J = 7.6, 1.2, 1H), 7.29-7.25 (m, 2H), 7.19-7.14 (m, 4H), 6.35-6.34 (m, 1H), 3.73 (ddd, J = 12.5, 4.3, 0.7, 1H), 3.43 (ddd, J = 12.5, 4.6, 3.2, 1H), 2.87 (dt, J = 7.3, 3.7, 1H), 2.75-2.68 (m, 1H), 2.61 (ddd, J = 14.0, 9.0, 6.9, 1H), 2.06-1.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.0, 142.7, 141.3, 132.1, 128.59, 128.47, 128.25, 128.20, 128.14, 128.11, 128.08, 127.17, 127.04, 126.6, 126.0, 125.6, 44.0, 37.4, 34.8, 33.4, 31.4.

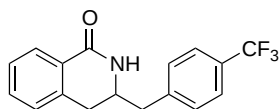


3-(3-phenylpropyl)-3,4-dihydroisoquinolin-1(2H)-one (294): The product was isolated in 85% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.05-8.03 (m, 1H), 7.42 (td, J = 7.5, 1.3, 1H), 7.33 (t, J = 7.2, 1H), 7.27-7.23 (m, 1H), 7.18-7.12 (m, 4H), 6.51 (d, J = 1.7, 1H), 3.68 (dd, J = 12.4, 4.3, 1H), 3.35 (dt, J = 12.2, 3.9, 1H), 2.82 (t, J = 3.3, 1H), 2.59 (t, J = 6.9, 2H), 1.75-1.68 (m, 3H), 1.61 (dtd, J = 12.5, 6.7, 3.2, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 142.9, 141.9, 132.1, 128.33, 128.31, 128.27, 128.11, 127.94, 127.07, 127.01, 125.8, 44.1, 37.8, 35.8, 32.9, 29.2.



3-(4-methoxybenzyl)-3,4-dihydroisoquinolin-1(2H)-one (296): The product was isolated in 60% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 7.5, 1H), 7.41 (td, J = 7.4, 1.3, 1H), 7.37-7.33 (m, 1H), 7.07 (t, J = 5.5, 1H), 7.03 (d, J = 8.5, 2H), 6.85-6.80 (m, 2H), 6.13-6.13 (m, 1H), 3.78 (s, 3H), 3.57 (dd, J = 12.4, 4.1, 1H), 3.27

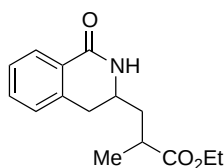
(ddd, $J = 12.4, 4.4, 2.9$, 1H), 3.03-3.01 (m, 1H), 2.93-2.83 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 158.2, 142.4, 132.2, 131.0, 130.13, 130.02, 128.2, 127.9, 127.22, 127.09, 114.3, 113.9, 98.7, 55.2, 42.9, 40.1, 38.9.



3-(4-(trifluoromethyl)benzyl)-3,4-dihydroisoquinolin-1(2H)-one

(298): The product was isolated in 71% yield. ^1H NMR (400 MHz,

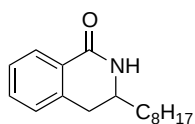
CDCl_3) δ 8.09 (dd, $J = 7.3, 1.8$, 1H), 7.52 (t, $J = 6.0$, 2H), 7.43-7.34 (m, 2H), 7.21 (d, $J = 8.0$, 2H), 7.00-6.98 (m, 1H), 6.29-6.28 (m, 1H), 3.63 (ddd, $J = 12.5, 4.1, 0.9$, 1H), 3.26 (ddd, $J = 12.6, 4.8, 2.7$, 1H), 3.12-3.05 (m, 1H), 3.00 (t, $J = 8.0$, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 143.1, 141.6, 132.2, 129.4, 128.3, 128.0, 127.5, 127.1, 125.48, 125.44, 125.41, 43.1, 39.75, 39.61.



ethyl 2-methyl-3-(1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)propanoate

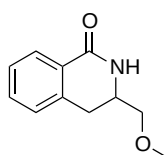
(300): The product was isolated in 92% yield. ^1H NMR is a mixture of

diastereomers. See Spectra; ^{13}C NMR (100 MHz, CDCl_3) δ 176.3, 175.9, 165.92, 165.78, 142.6, 141.9, 132.4, 132.0, 128.34, 128.16, 128.06, 127.92, 127.46, 127.37, 127.27, 126.8, 60.50, 60.47, 45.1, 43.3, 37.6, 37.4, 37.10, 37.07, 35.8, 18.01, 17.95, 14.30, 14.24.



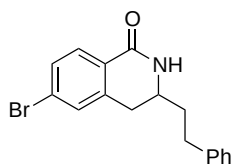
3-octyl-3,4-dihydroisoquinolin-1(2H)-one (302): The product was isolated in

91% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.05-8.03 (m, 1H), 7.43 (td, $J = 7.5, 0.5$, 1H), 7.32 (t, $J = 7.5$, 1H), 7.18 (d, $J = 7.5$, 1H), 6.65 (d, $J = 2.1$, 1H), 3.69 (dd, $J = 12.4, 4.4$, 1H), 3.38 (dd, $J = 10.1, 6.2$, 1H), 2.80 (t, $J = 3.8$, 1H), 1.65 (t, $J = 6.8$, 2H), 1.29-1.18 (m, 13H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.2, 143.3, 132.0, 128.04, 128.00, 126.94, 126.92, 44.0, 37.9, 33.3, 31.8, 29.57, 29.45, 29.2, 27.3, 22.6, 14.1.

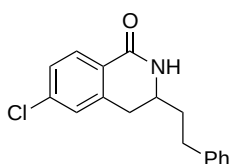


3-(methoxymethyl)-3,4-dihydroisoquinolin-1(2H)-one (304): The product was

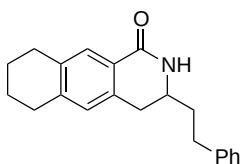
isolated in 80% yield as a mixture of regioisomers.



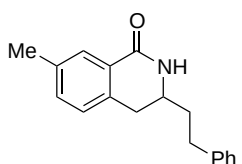
6-bromo-3-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (311): The product was isolated in 85% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92 (d, J = 8.3, 1H), 7.48 (dd, J = 8.3, 1.9, 1H), 7.33 (d, J = 1.9, 1H), 7.30-7.26 (m, 2H), 7.20-7.14 (m, 3H), 6.59 (d, J = 2.5, 1H), 3.70 (ddd, J = 12.6, 4.3, 1.2, 1H), 3.43 (ddd, J = 12.6, 4.6, 3.4, 1H), 2.84 (dt, J = 7.2, 3.6, 1H), 2.75-2.68 (m, 1H), 2.61 (ddd, J = 14.0, 9.0, 6.9, 1H), 2.05-1.97 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.4, 144.6, 140.9, 130.5, 129.9, 128.6, 128.2, 127.01, 126.86, 126.2, 43.8, 37.2, 34.5, 33.3.



6-chloro-3-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (312): The product was isolated in 85% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.00 (d, J = 8.3, 1H), 7.33-7.24 (m, 3H), 7.18 (q, J = 8.4, 4H), 6.28 (d, J = 1.3, 1H), 3.73-3.69 (m, 1H), 3.45-3.41 (m, 1H), 2.86-2.83 (m, 1H), 2.70 (dd, J = 9.2, 6.1, 1H), 2.63 (dd, J = 8.8, 7.1, 1H), 2.06-1.98 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 191.2, 144.5, 140.9, 138.3, 129.9, 128.6, 128.2, 127.5, 127.0, 126.2, 43.8, 37.3, 34.5, 33.3, 29.7.

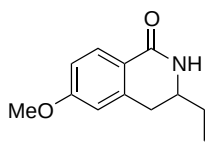


3-phenethyl-3,4,6,7,8,9-hexahydrobenzo[g]isoquinolin-1(2H)-one (313): The product was isolated in 98% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.28-7.24 (m, 3H), 7.19-7.15 (m, 4H), 6.87 (s, 1H), 3.68 (ddd, J = 12.4, 4.3, 1.2, 1H), 3.42-3.38 (m, 1H), 2.78 (s, 4H), 2.72-2.59 (m, 3H), 2.03-1.97 (m, 2H), 1.78 (s, 4H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 166.5, 141.9, 141.5, 139.6, 136.2, 128.7, 128.43, 128.35, 128.27, 127.5, 126.0, 125.3, 44.2, 37.0, 34.8, 33.5, 29.7, 28.9, 22.99, 22.89.

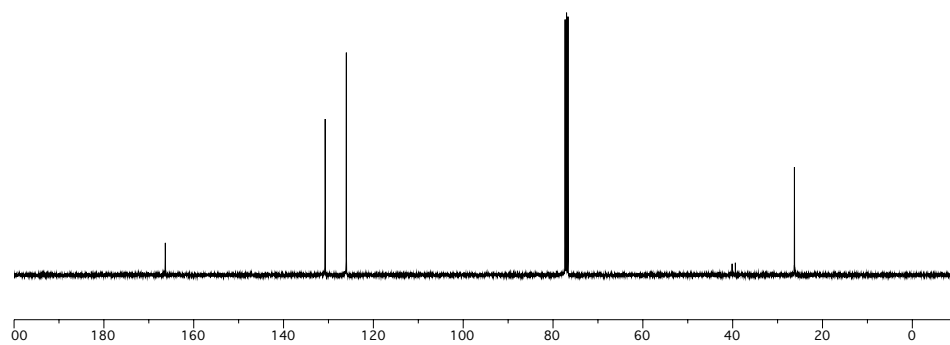
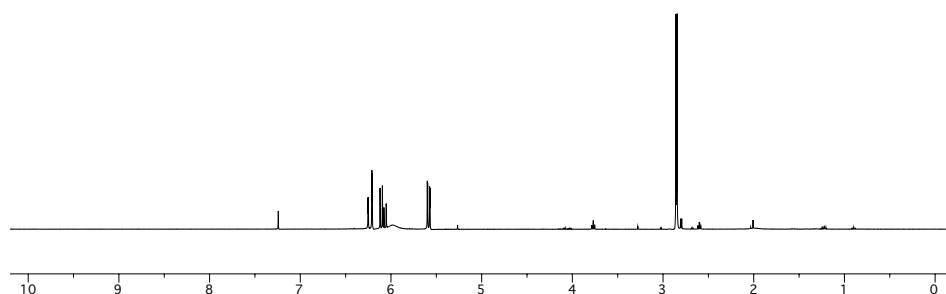


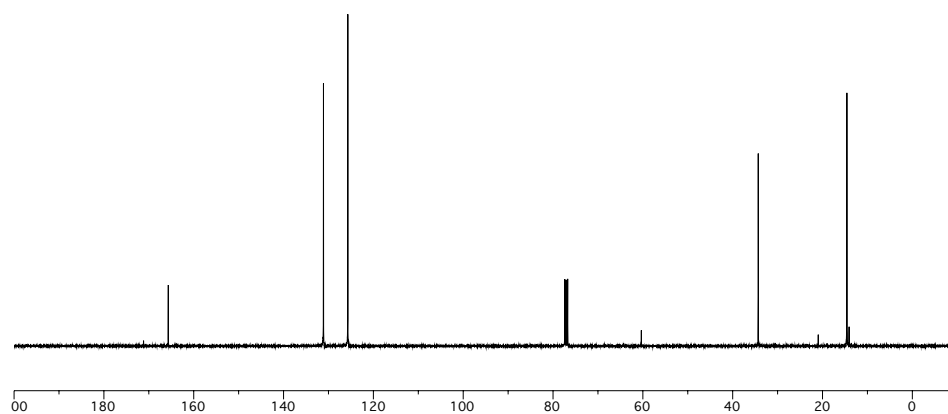
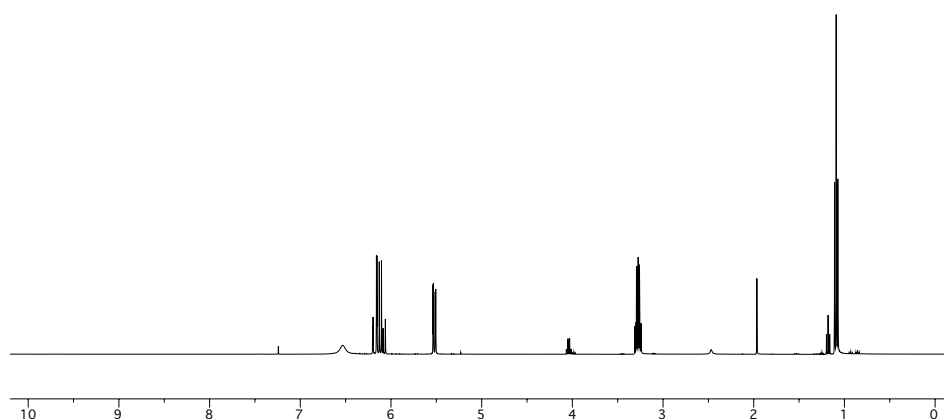
7-methyl-3-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (314): The product was isolated in 95% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.89 (s, 1H), 7.28-7.24 (m, 4H), 7.19-7.14 (m, 4H), 7.08 (d, J = 7.7, 1H), 6.50 (s, 1H), 3.70 (ddd, J = 12.4, 4.4, 1.2, 1H), 3.43-3.39 (m, 1H), 2.83 (t, J = 3.4, 1H), 2.65 (ddd, J = 25.8, 8.8, 6.9, 2H), 2.36 (d, J = 3.8, 3H), 2.01-1.97 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ

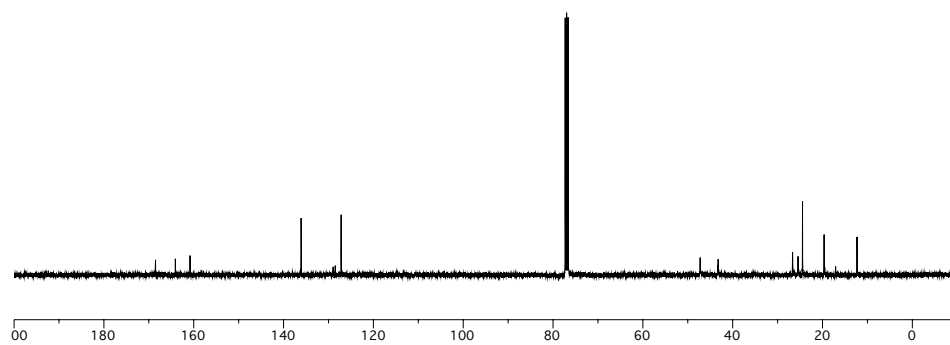
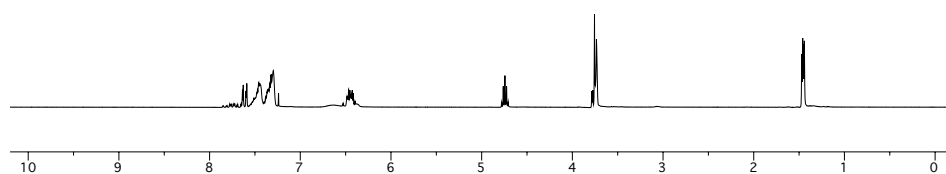
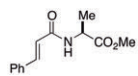
166.3, 141.4, 139.8, 136.9, 132.9, 128.56, 128.51, 128.45, 128.34, 128.25, 127.8, 127.0, 126.0, 44.2, 37.0, 34.8, 33.4, 21.0.

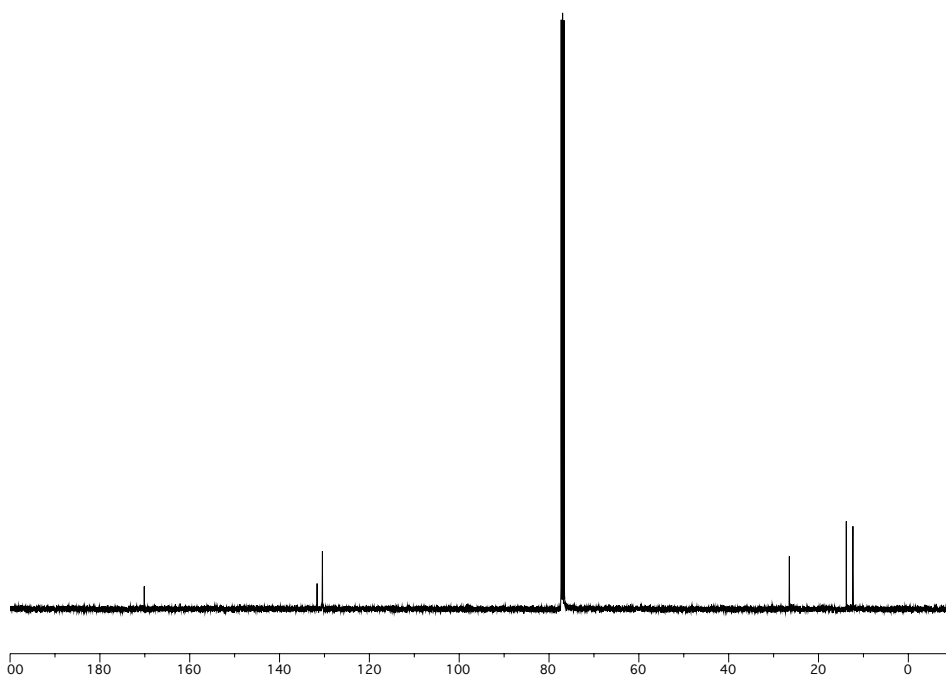
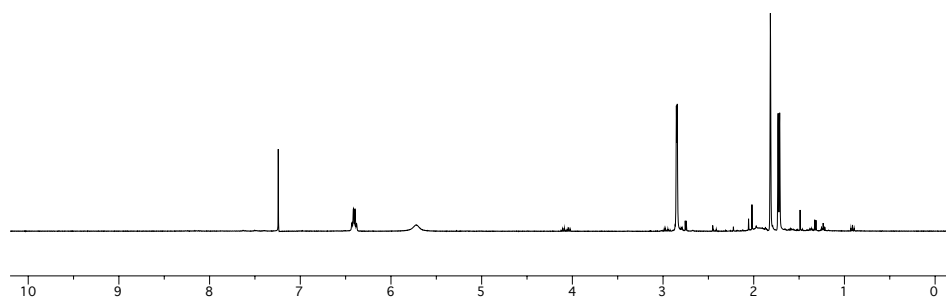


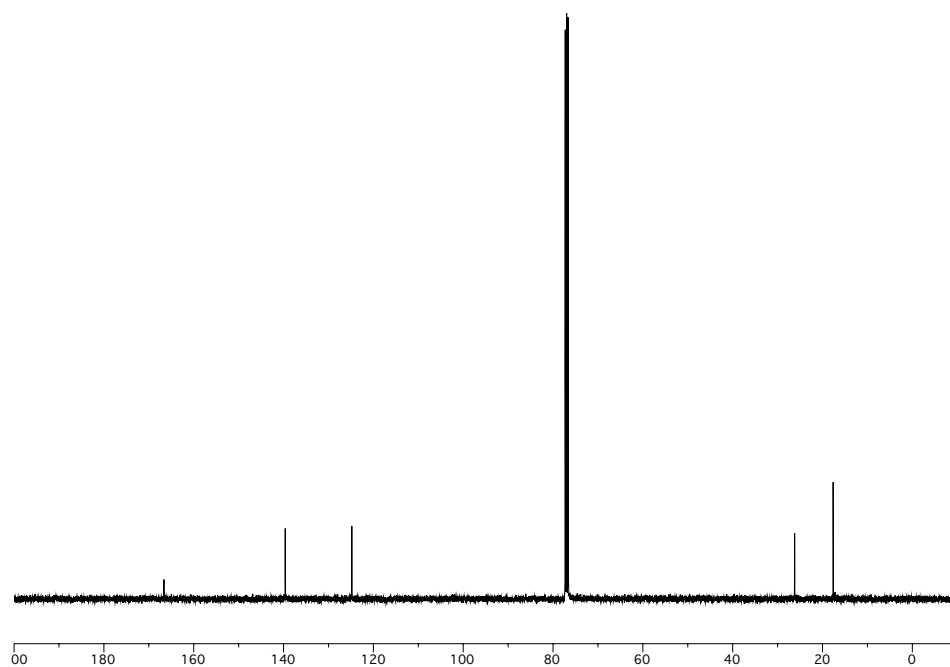
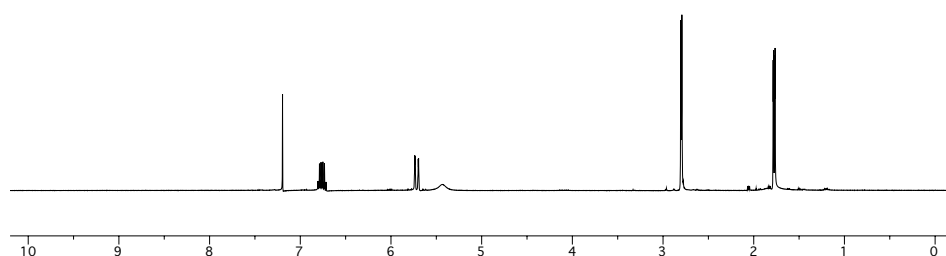
6-methoxy-3-phenethyl-3,4-dihydroisoquinolin-1(2H)-one (315): The product was isolated in 91% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 8.6$, 1H), 7.26 (t, $J = 7.8$, 2H), 7.19-7.14 (m, 3H), 6.85 (dd, $J = 8.6$, 2.5, 1H), 6.39-6.39 (m, 1H), 3.83 (s, 3H), 3.70 (ddd, $J = 12.4$, 4.3, 0.9, 1H), 3.40 (ddd, $J = 12.4$, 4.4, 3.4, 1H), 2.81 (t, $J = 3.6$, 1H), 2.67 (ddd, $J = 23.5$, 9.2, 6.5, 2H), 2.06-1.98 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.1, 162.5, 144.9, 141.3, 130.3, 128.5, 128.3, 126.0, 120.9, 112.37, 112.22, 55.4, 44.0, 37.7, 34.6, 33.4.

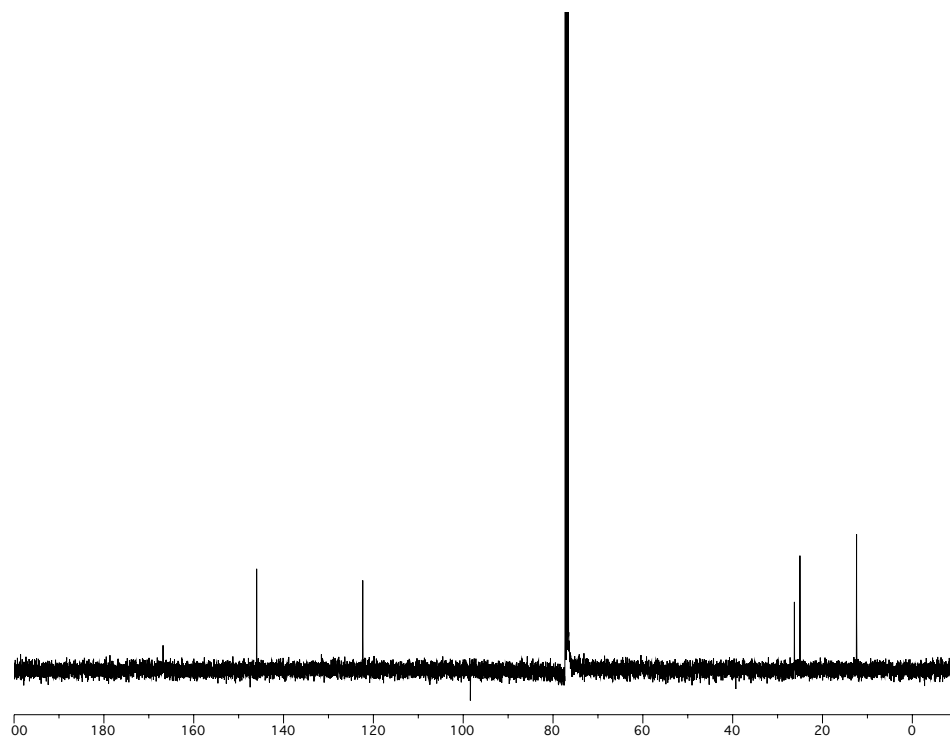
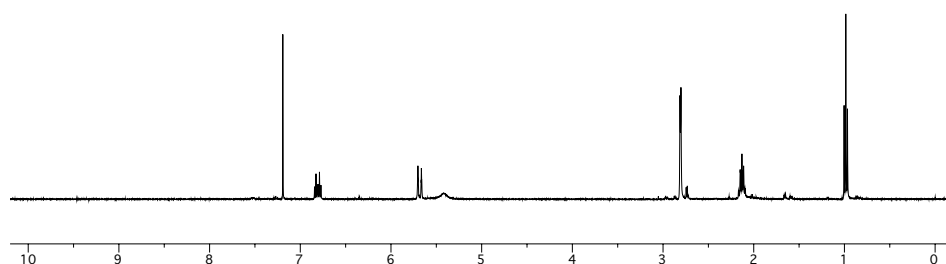


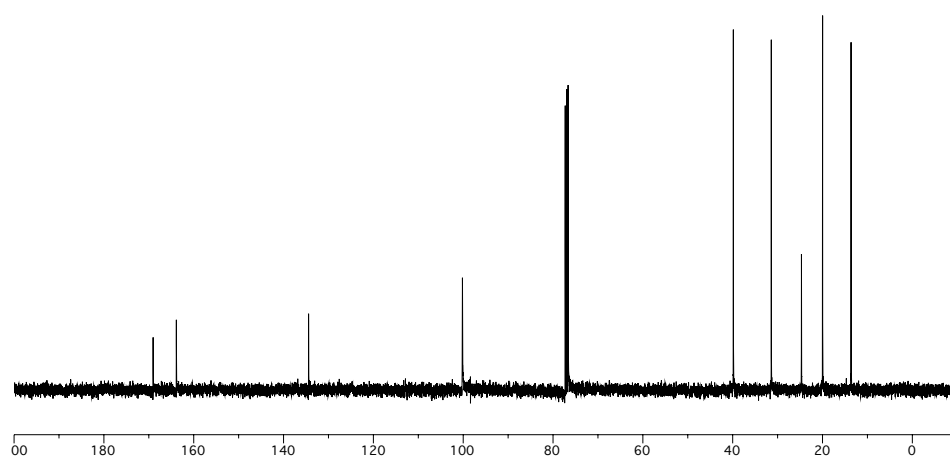
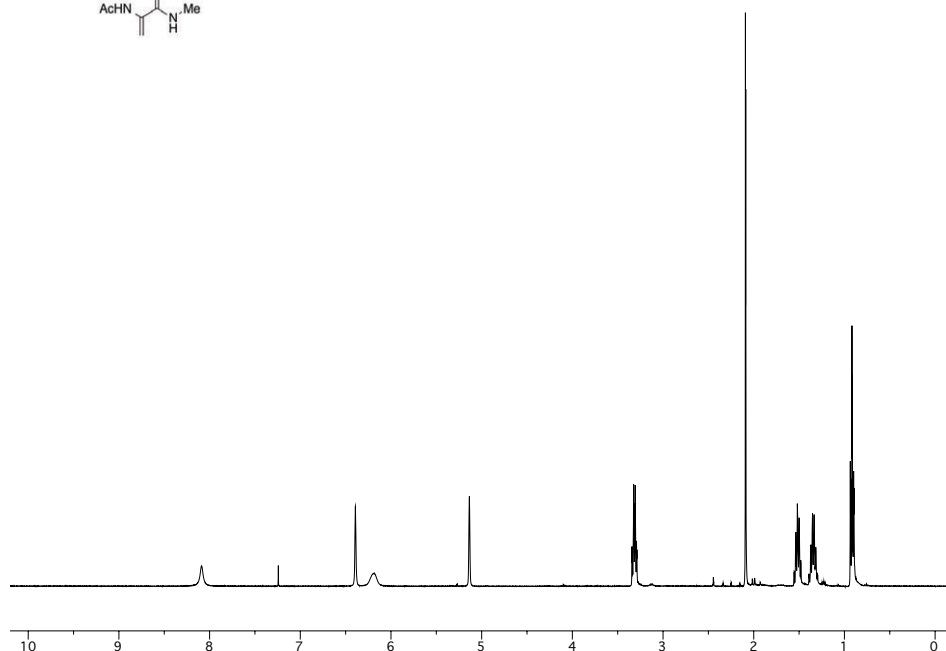
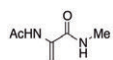


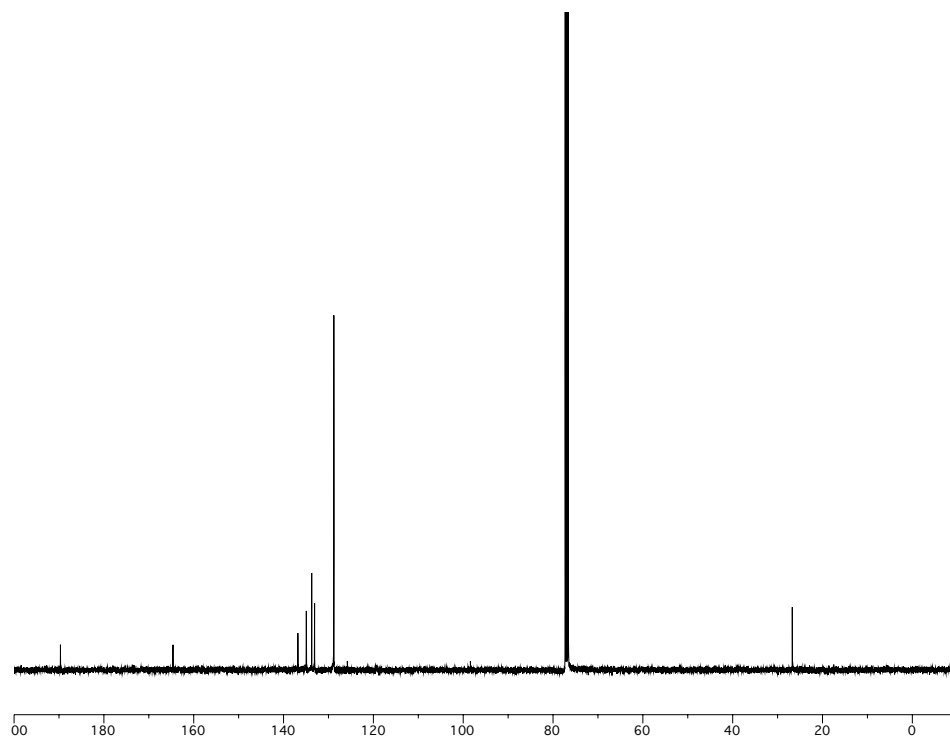
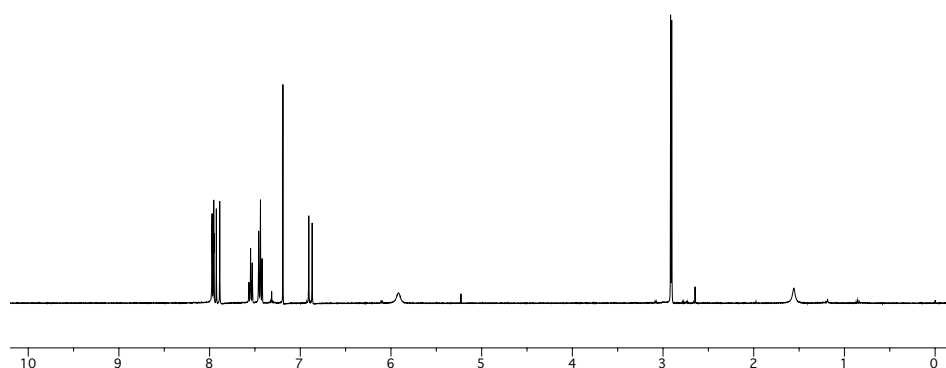
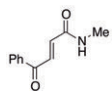


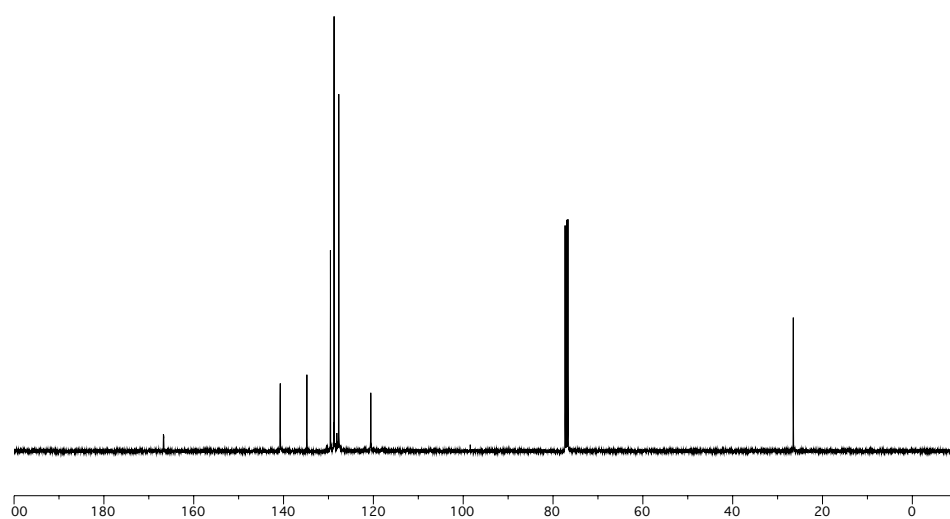
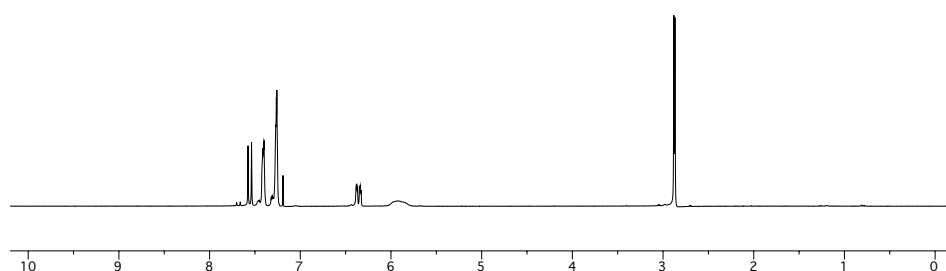


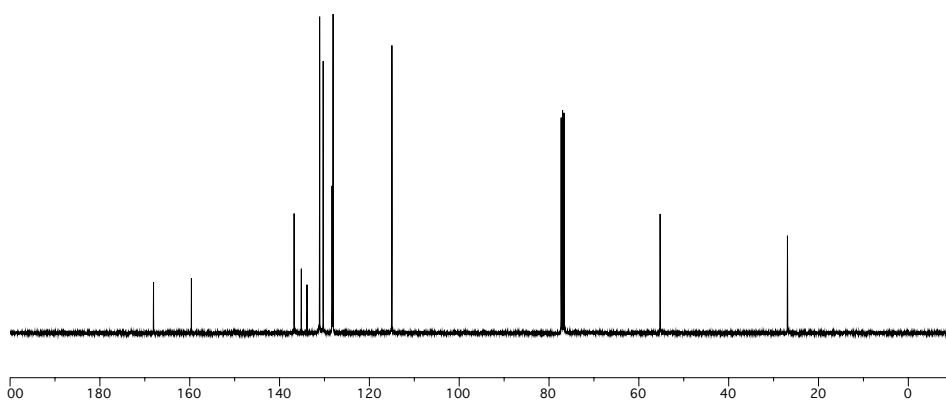
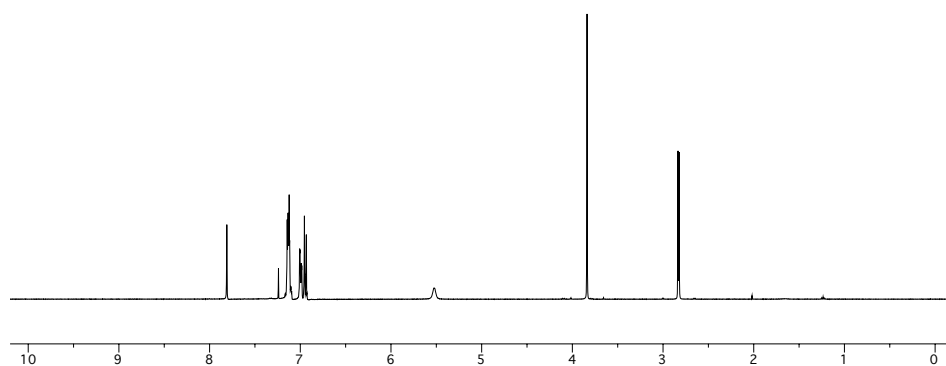
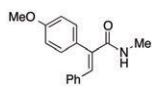


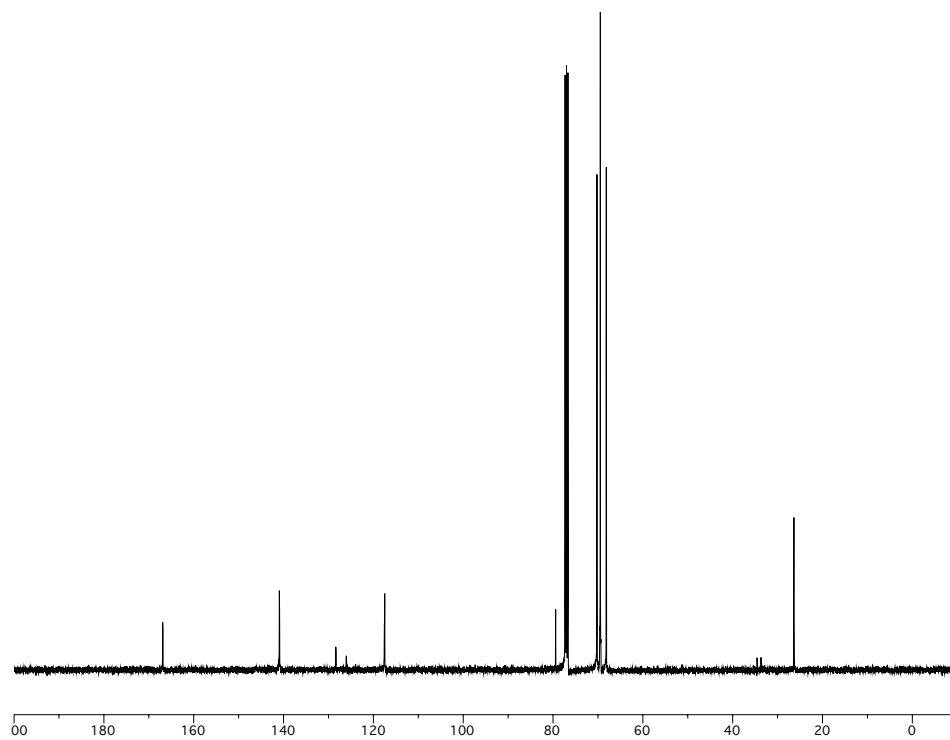
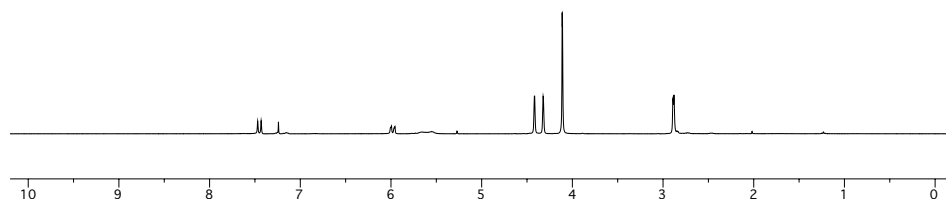
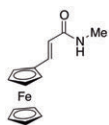


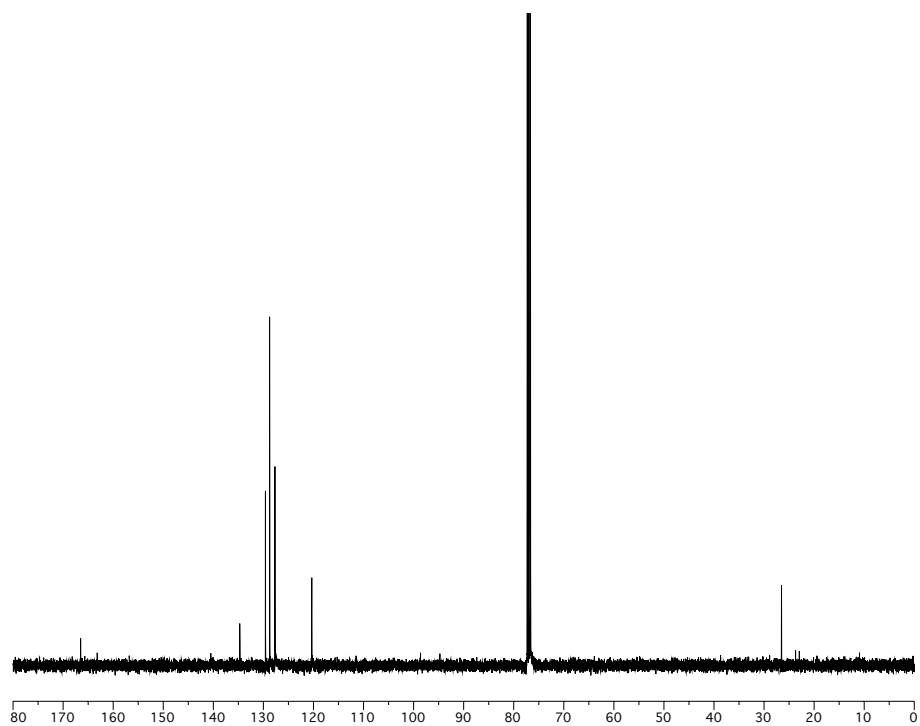
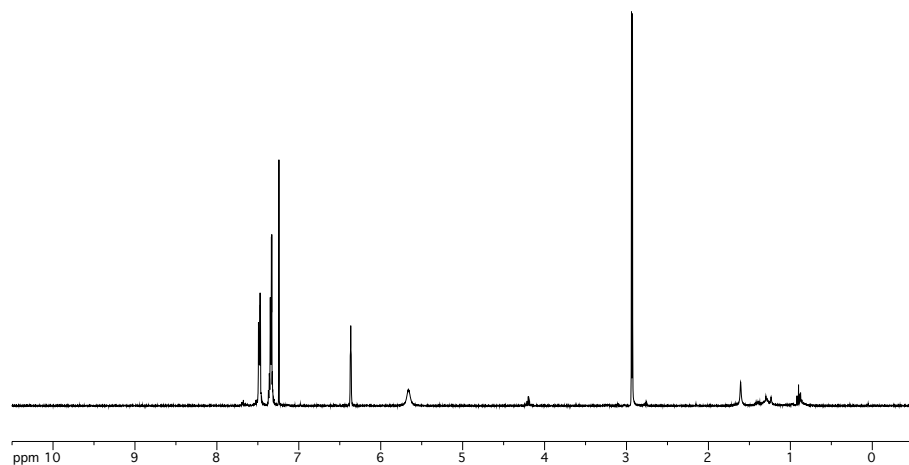


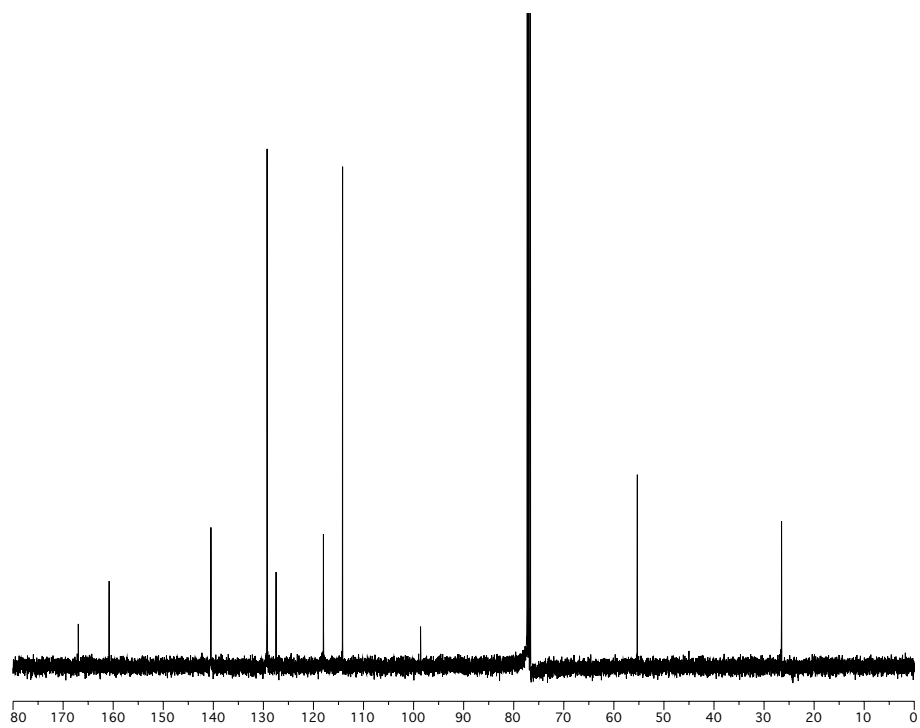
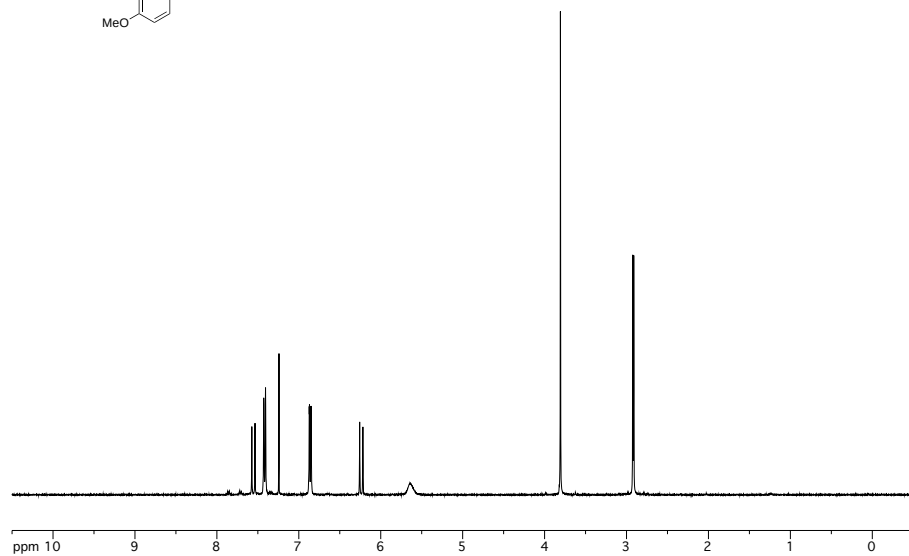
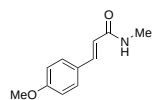


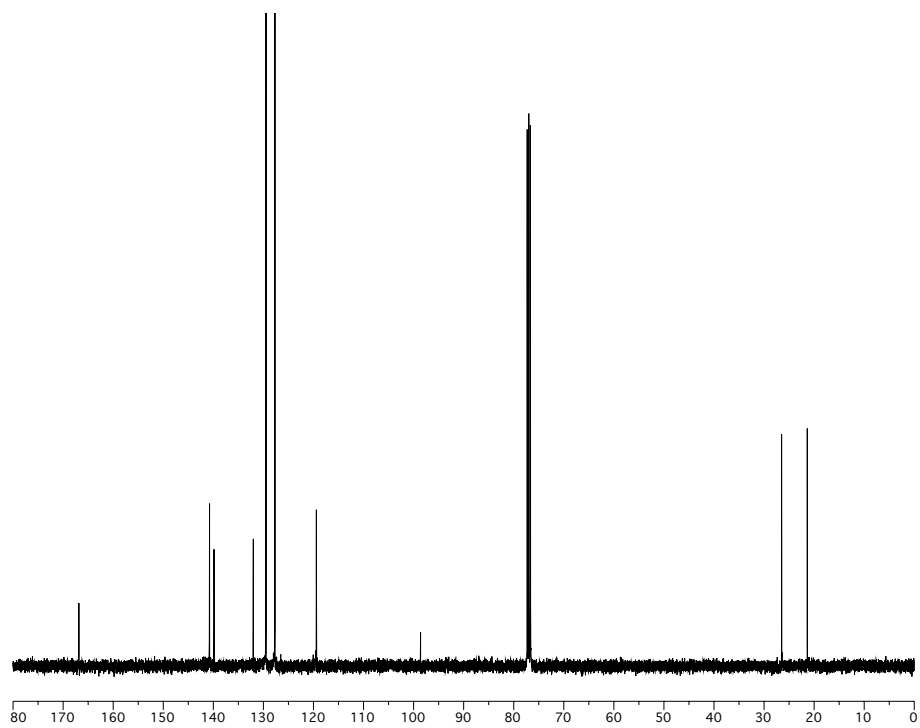
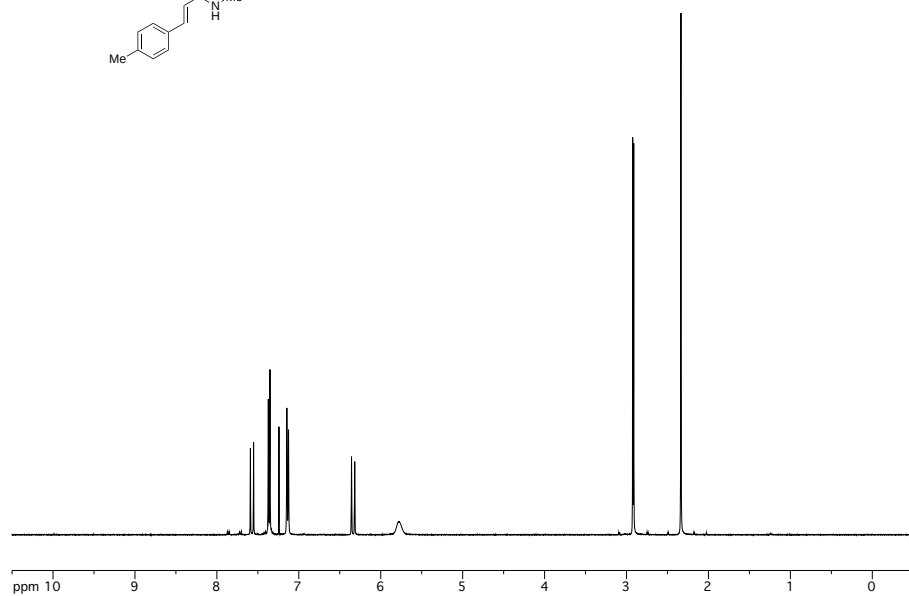
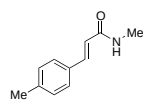


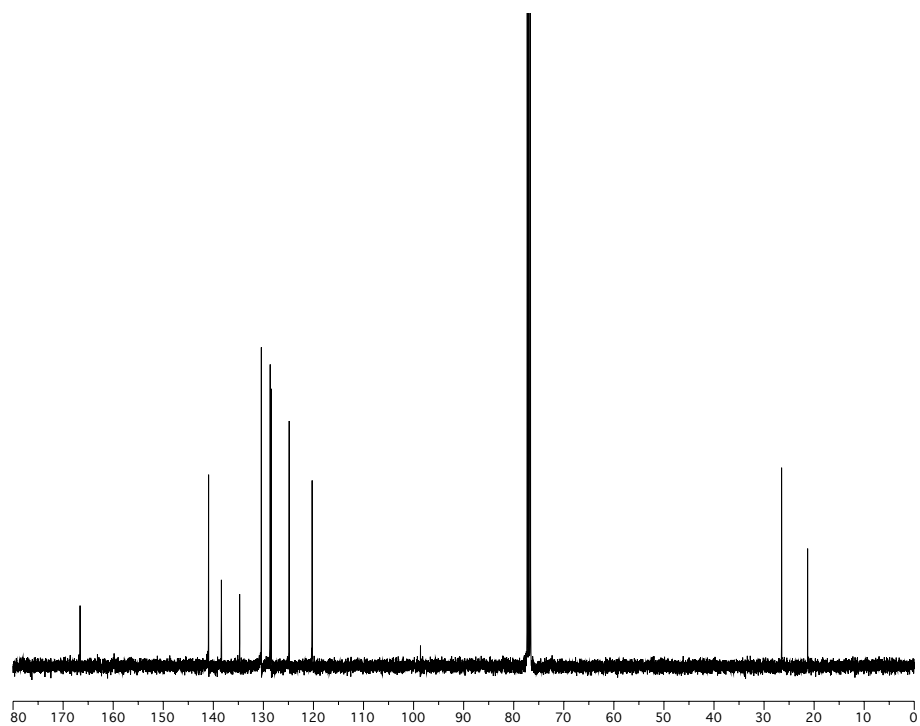
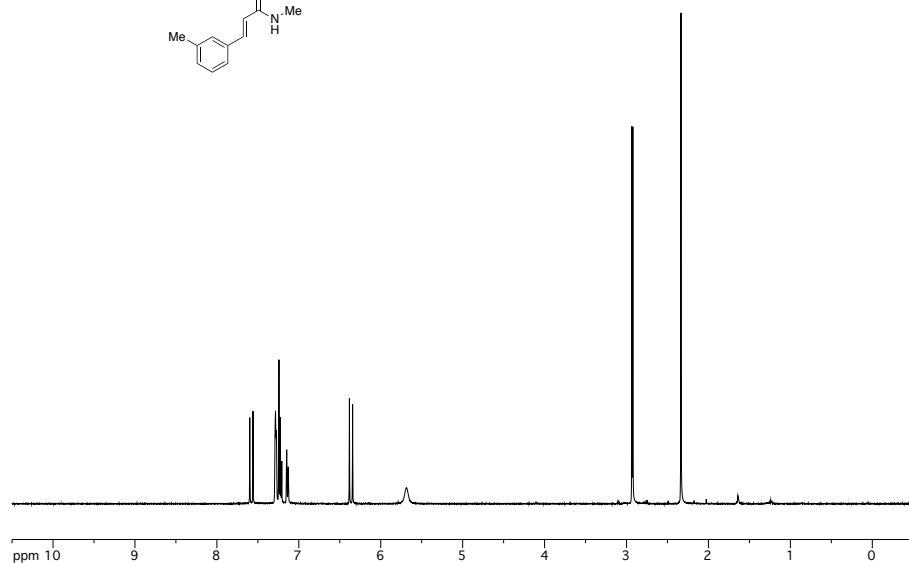
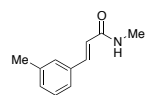


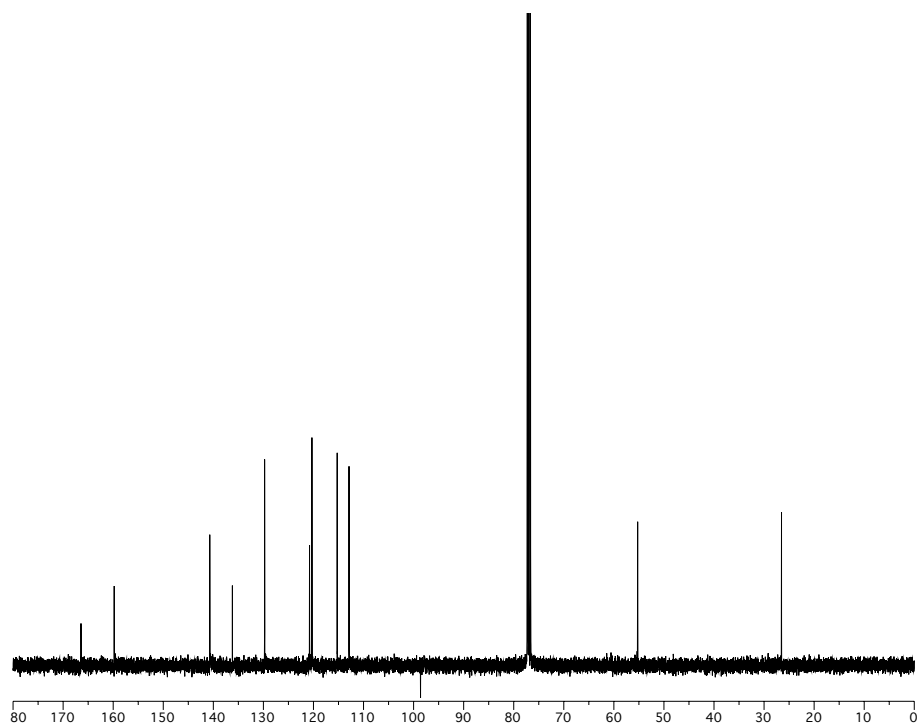
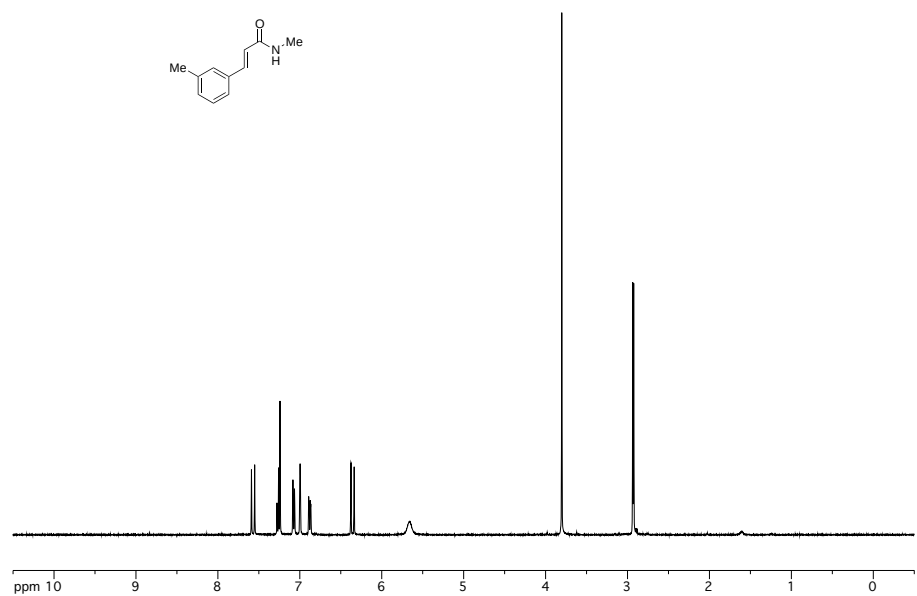


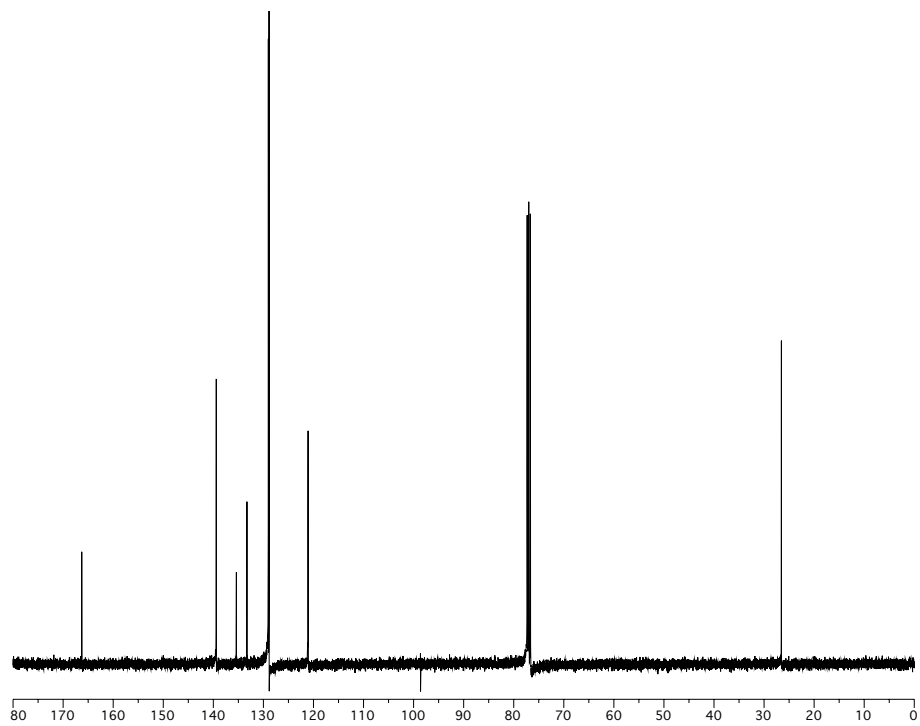
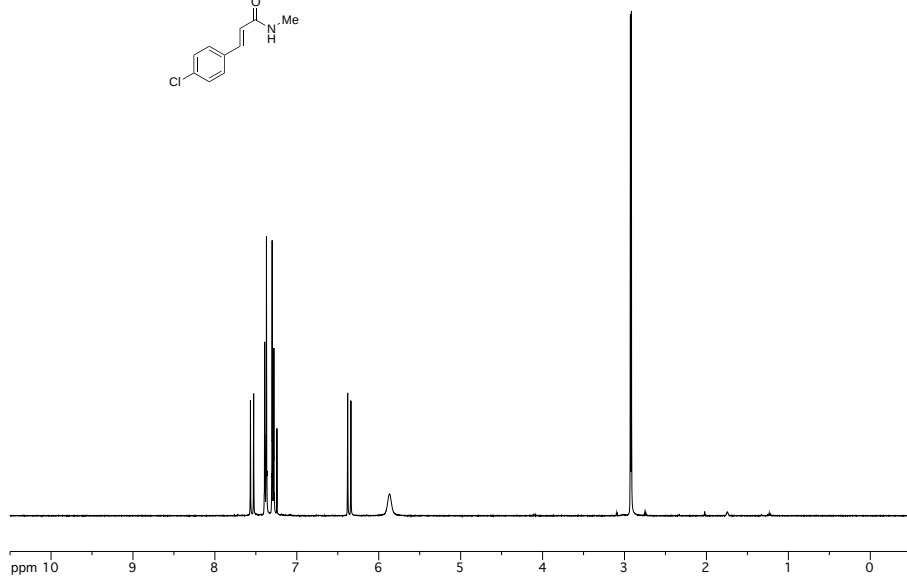
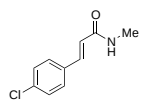


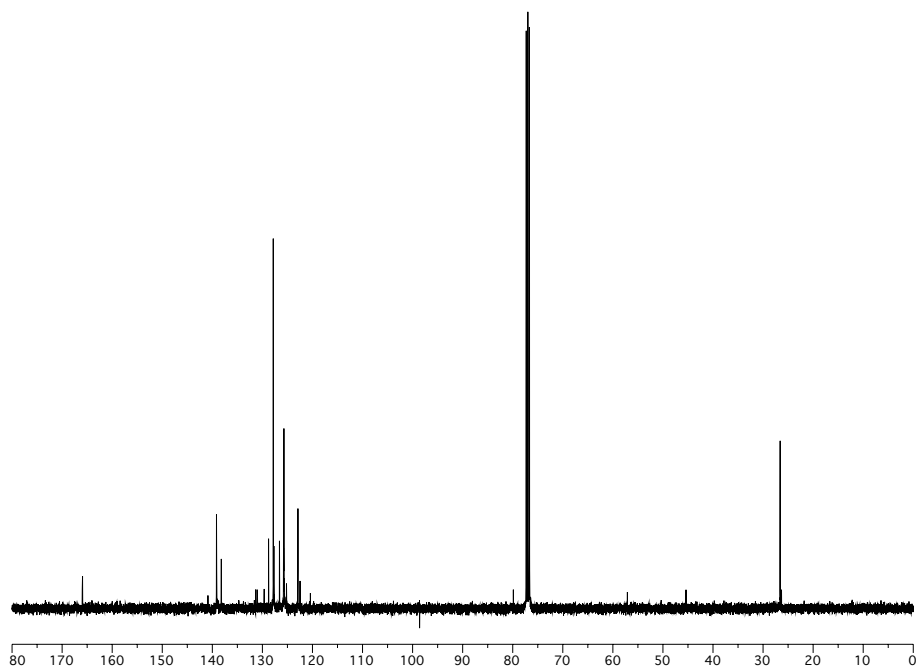
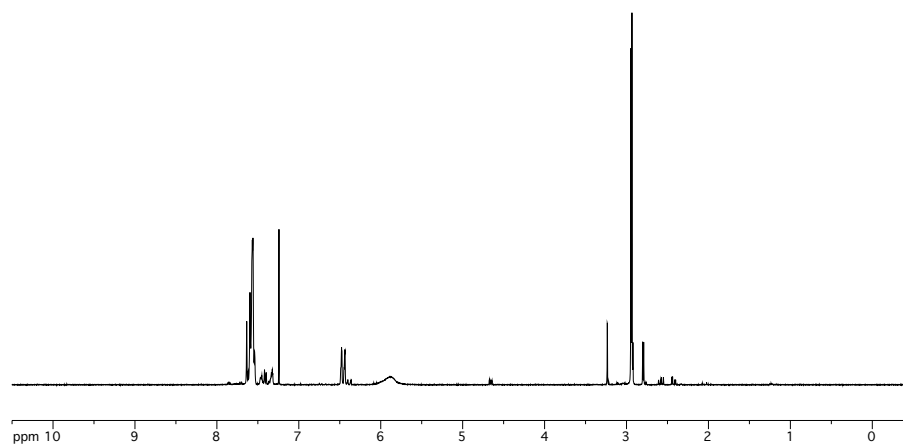
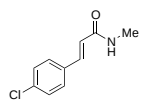


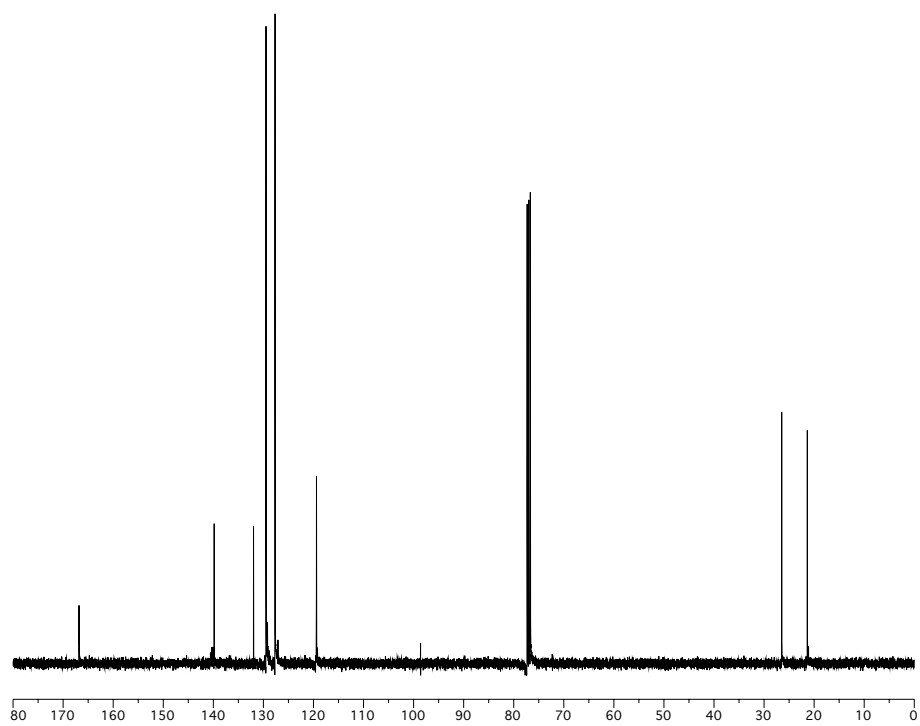
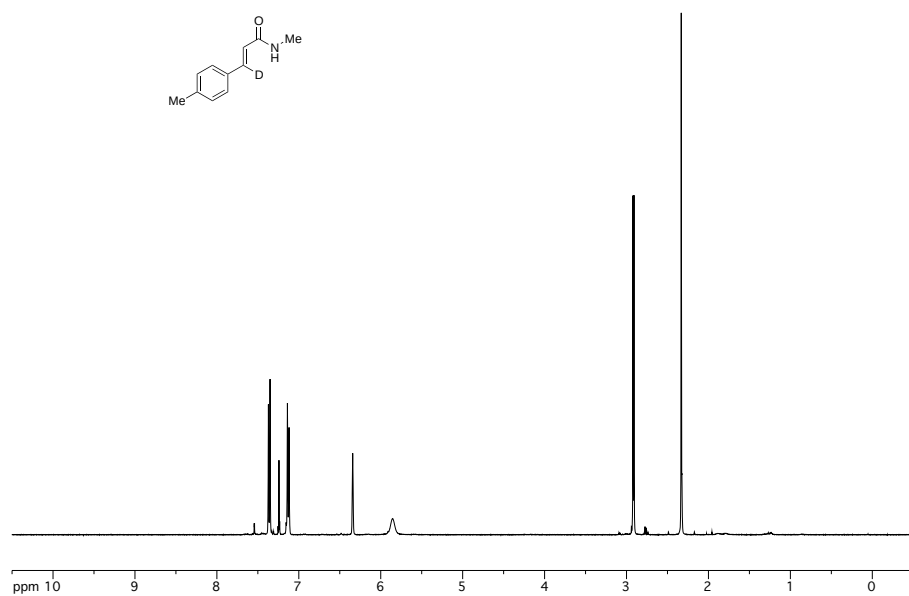
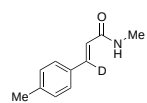


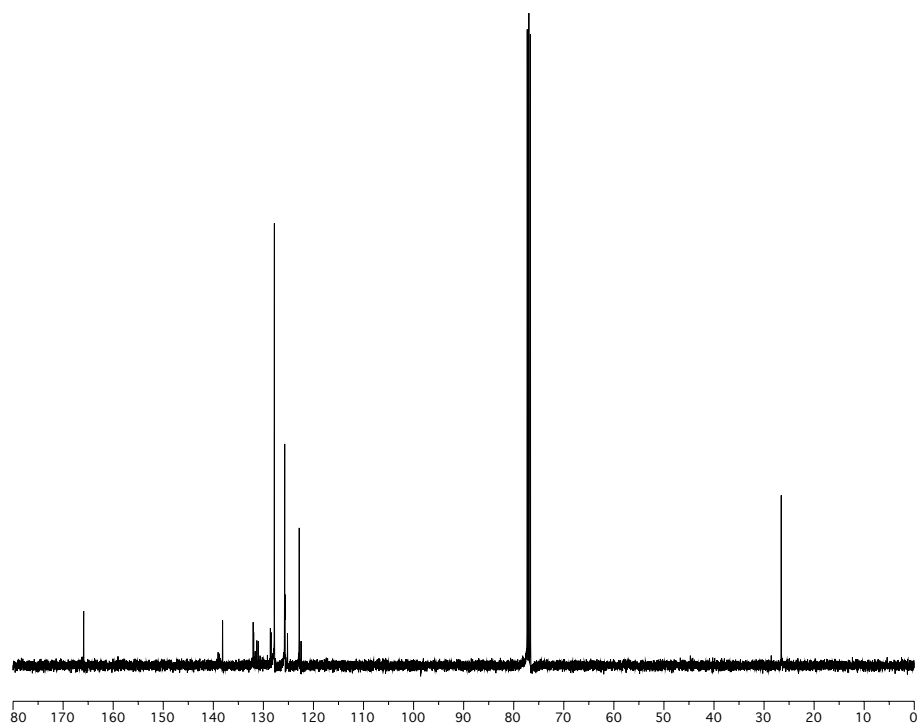
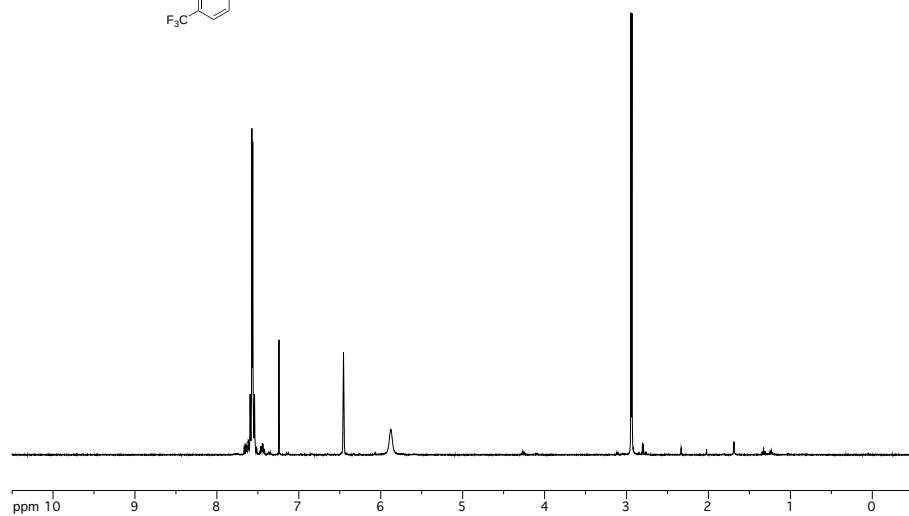
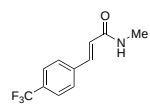


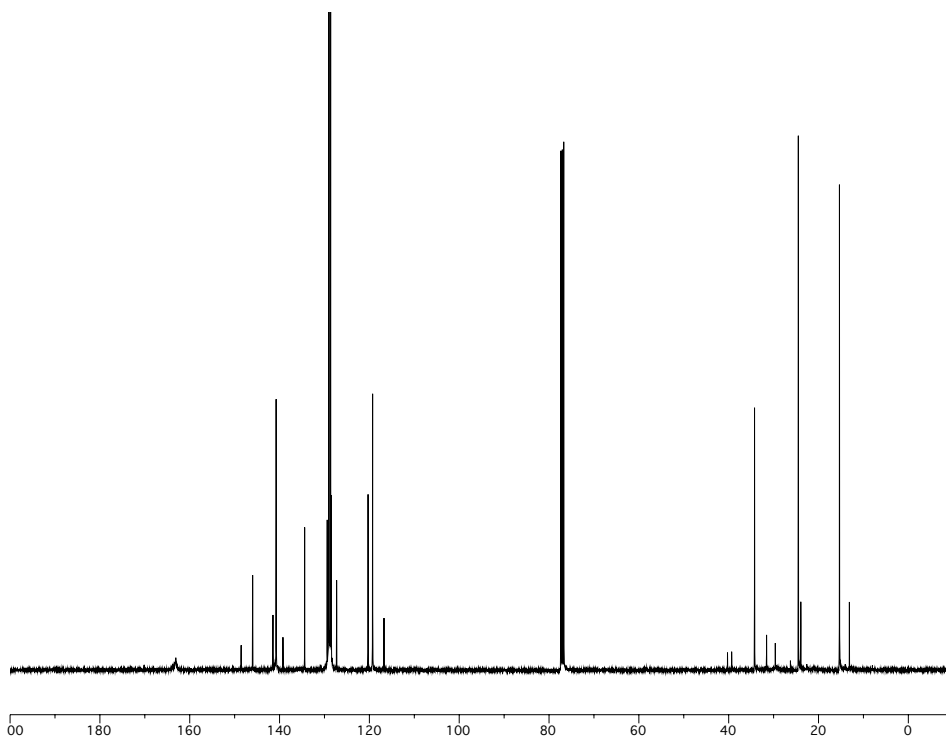
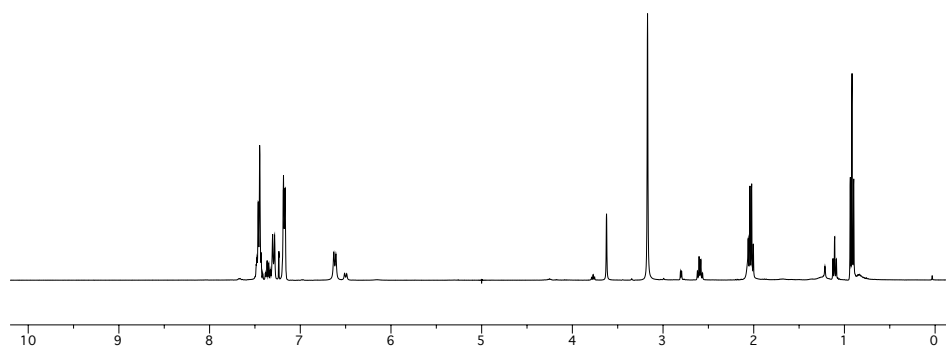


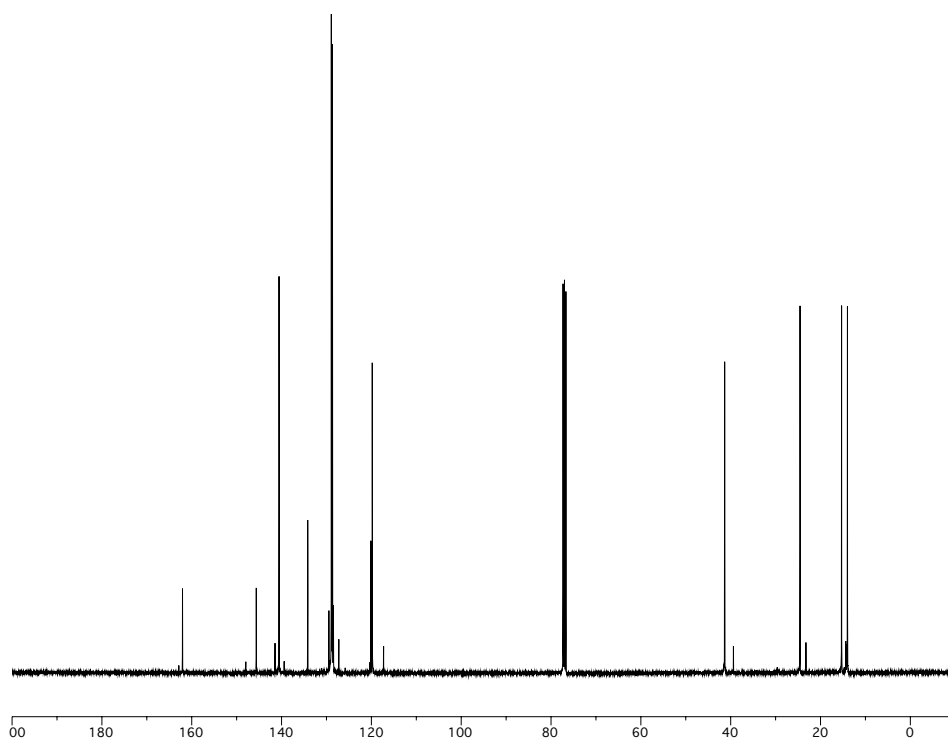
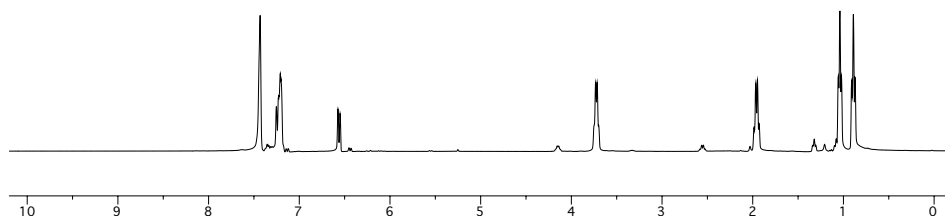


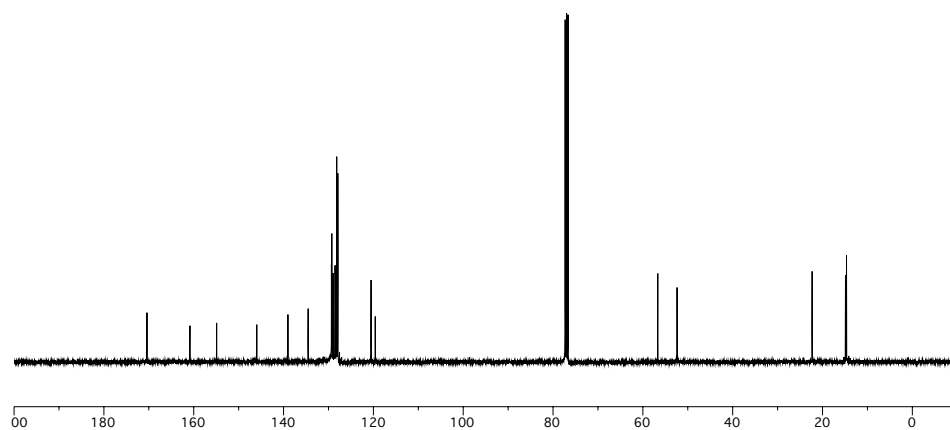
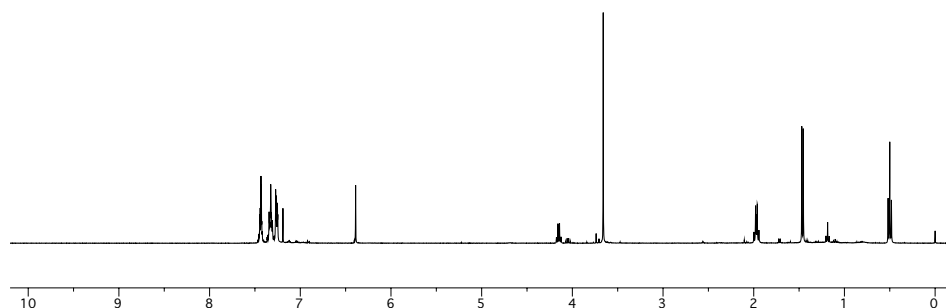
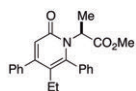


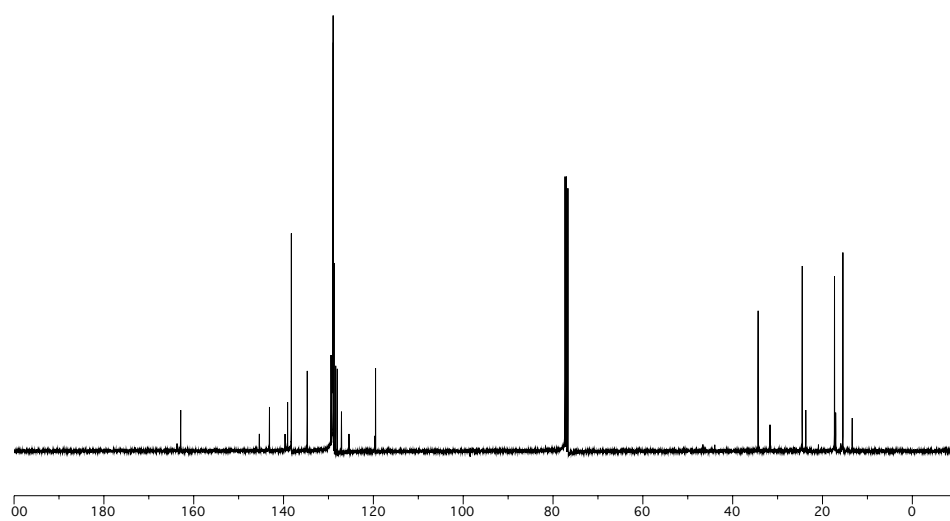
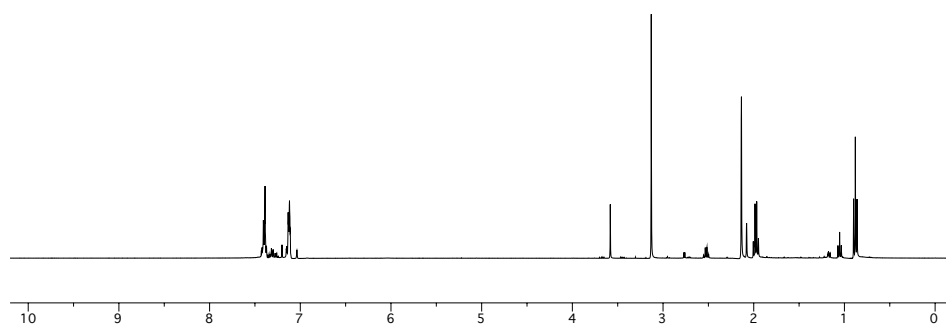


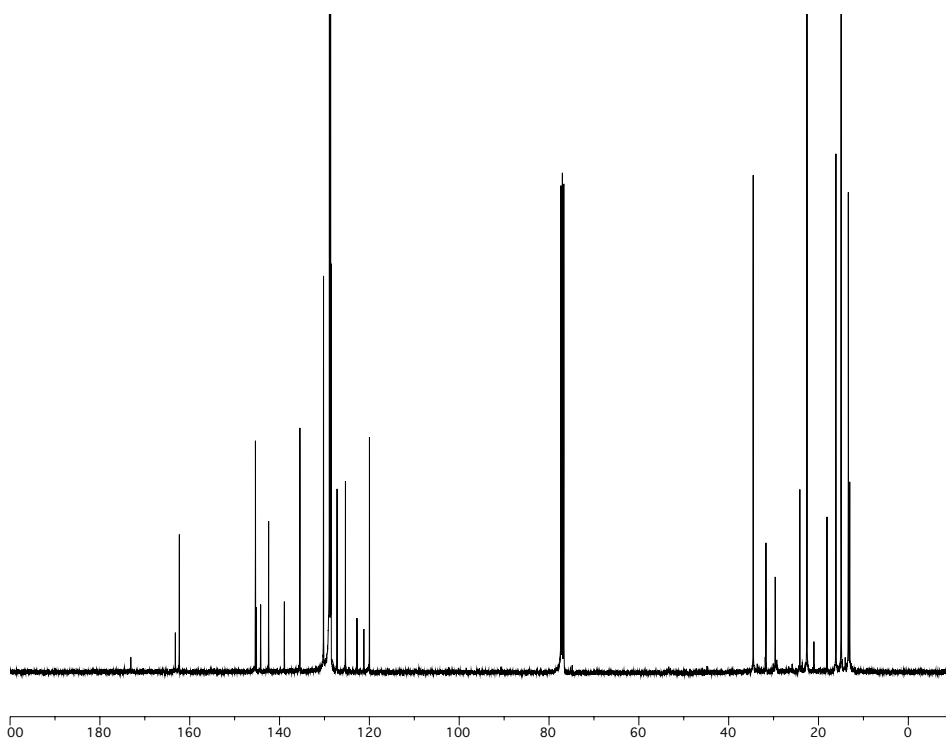
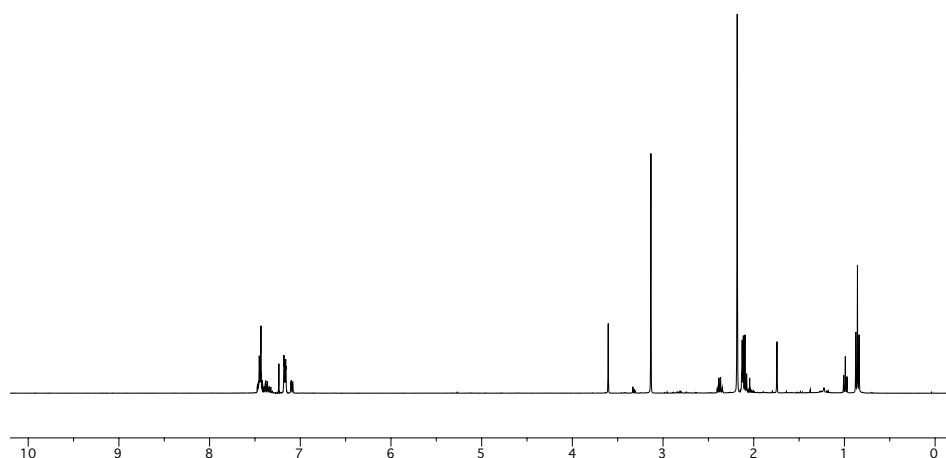


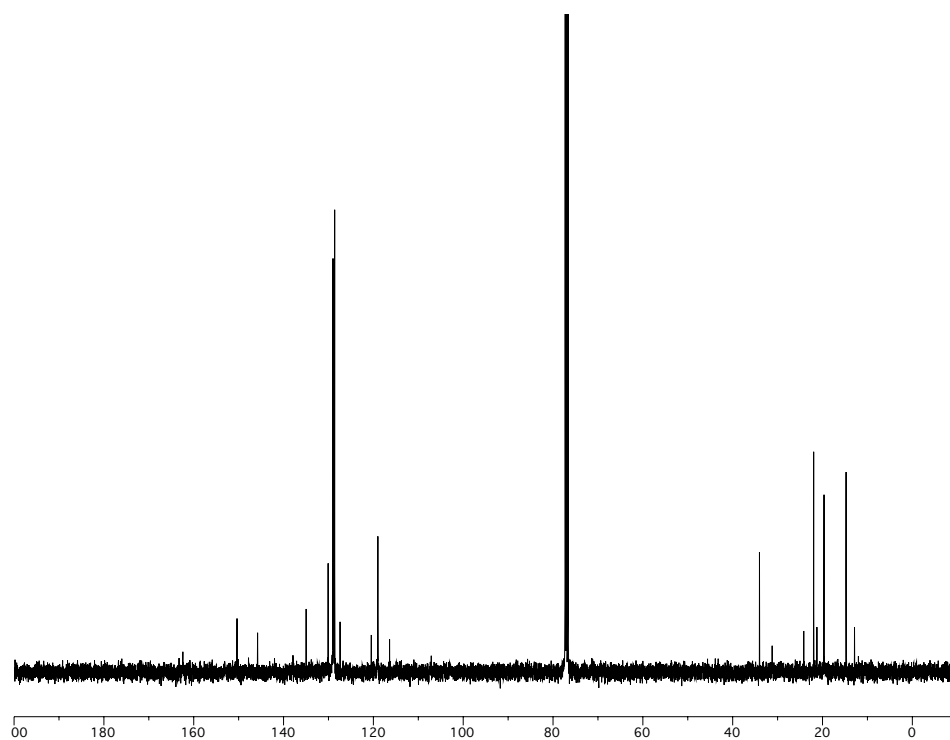
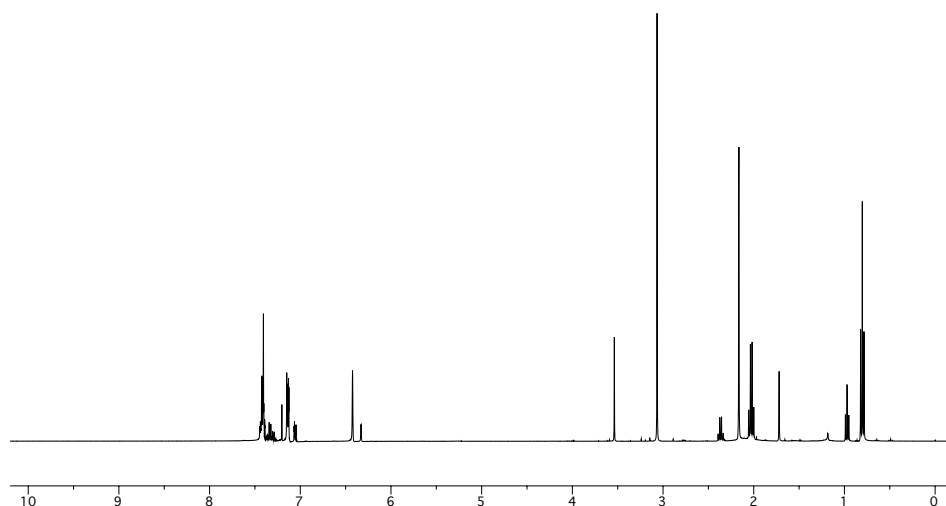


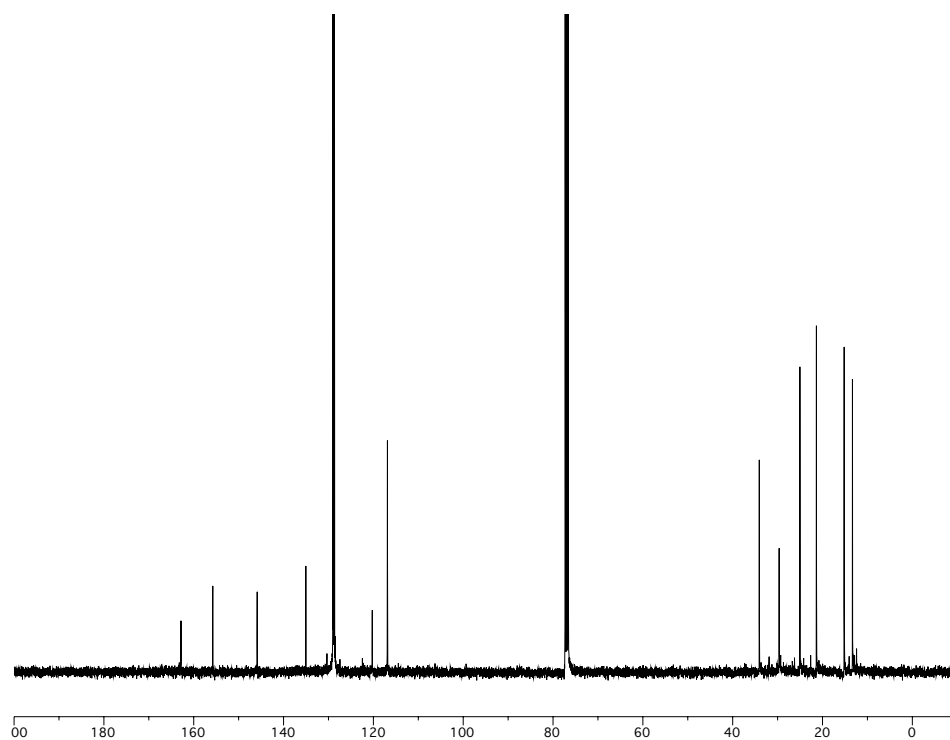
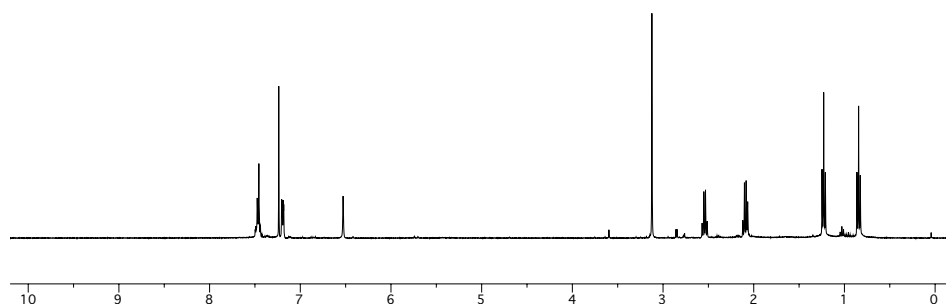


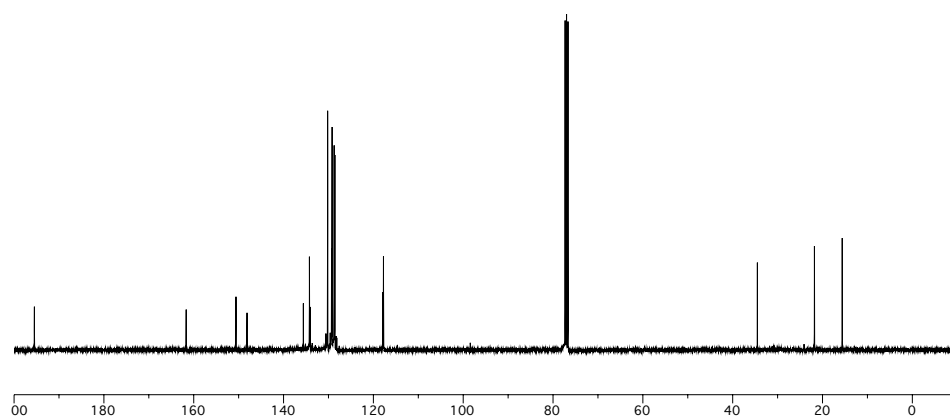
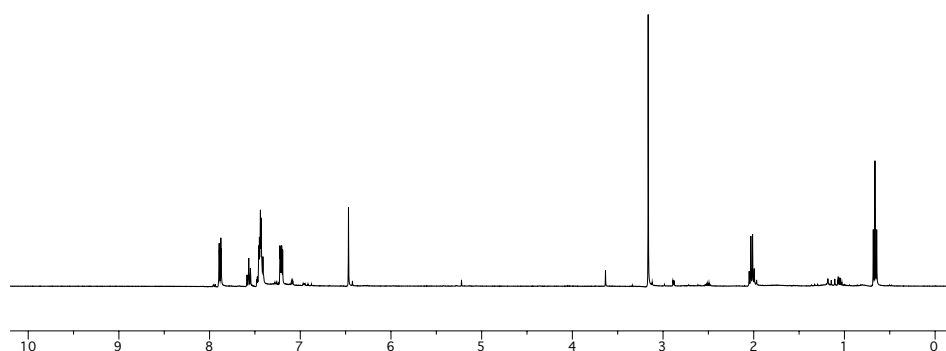
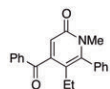


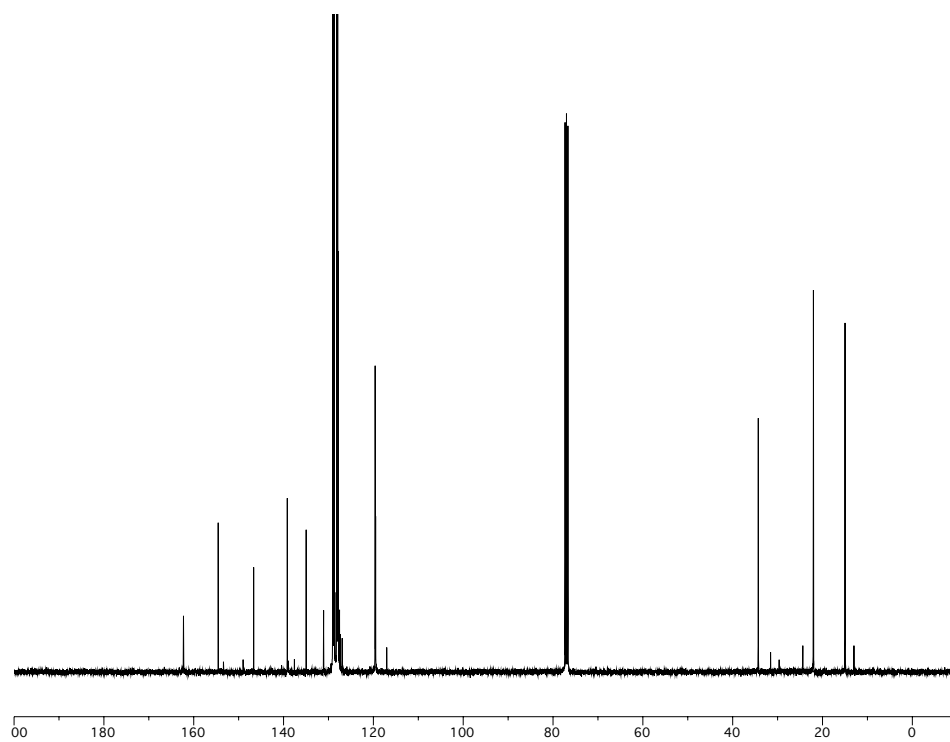
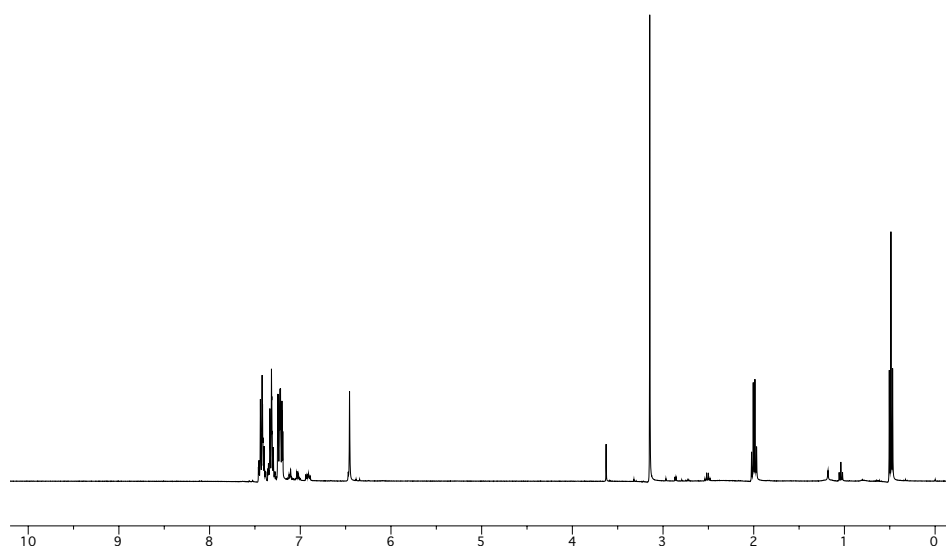


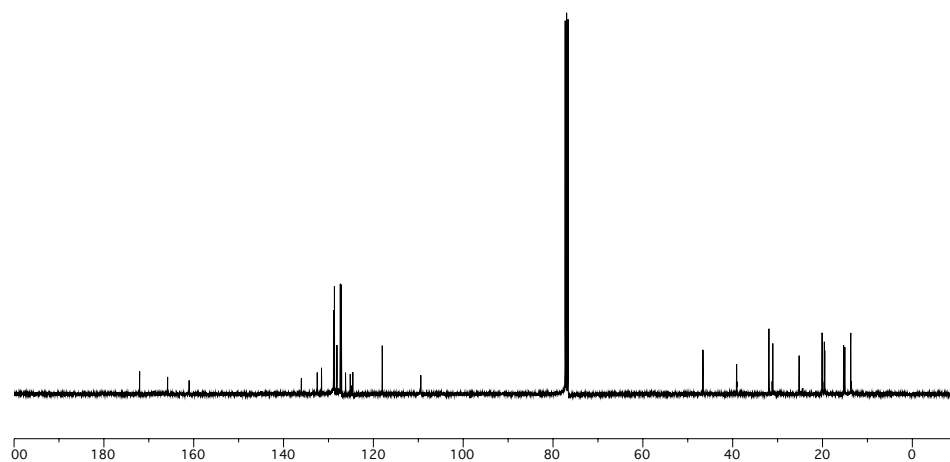
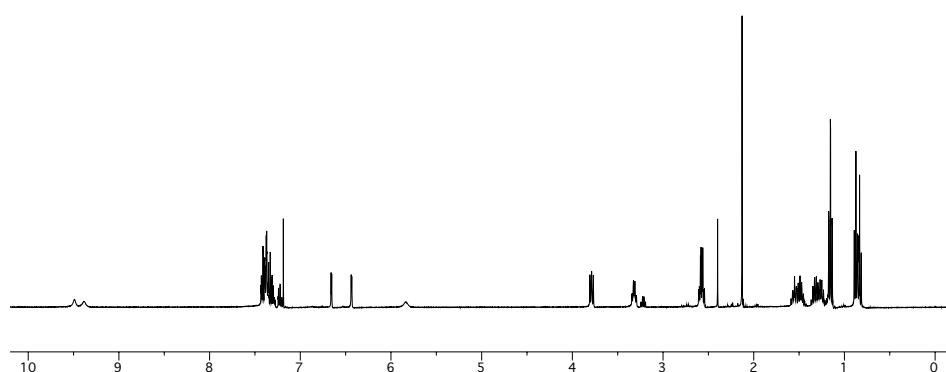
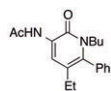


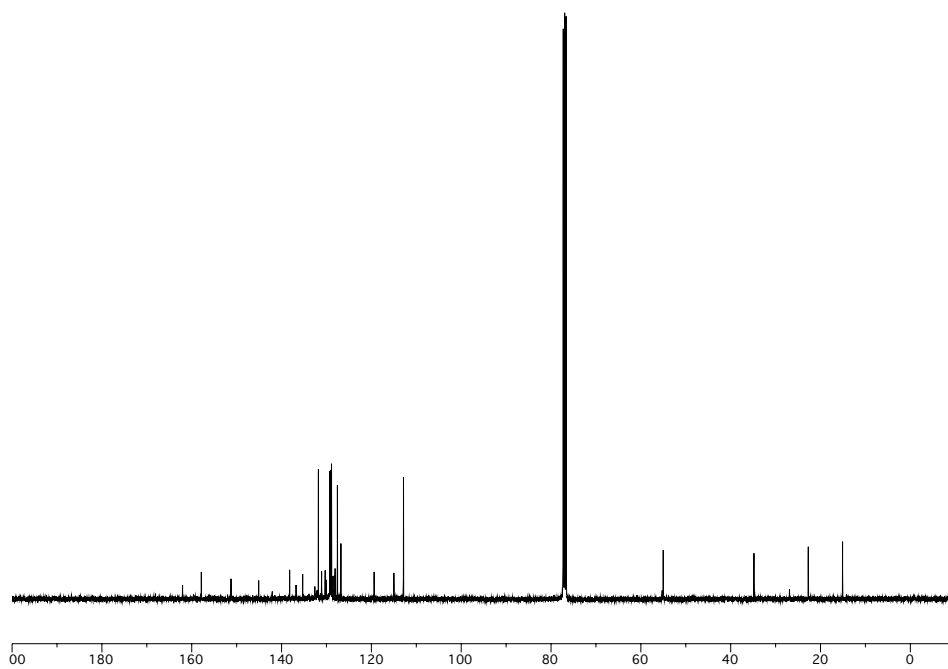
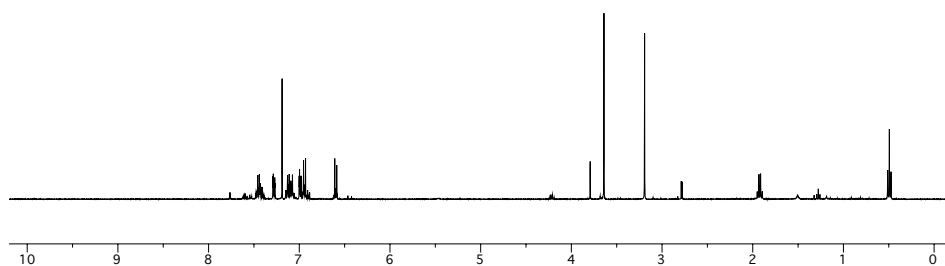
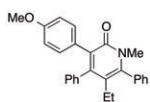


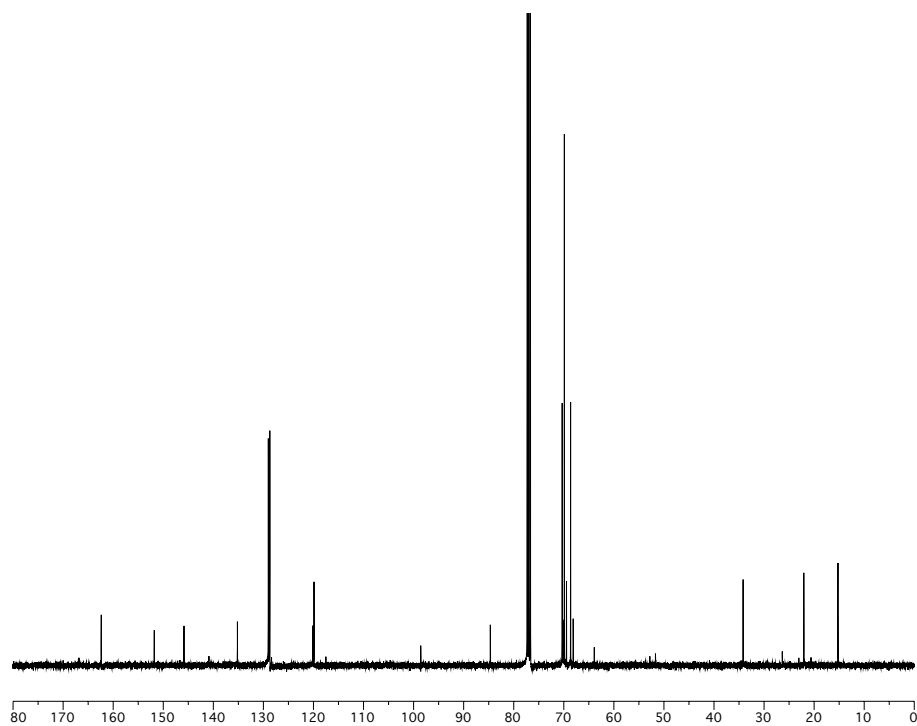
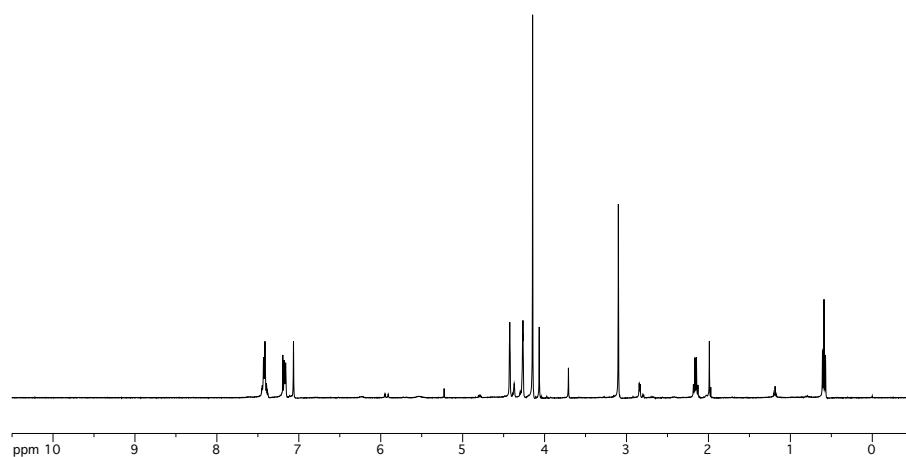
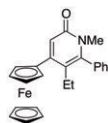


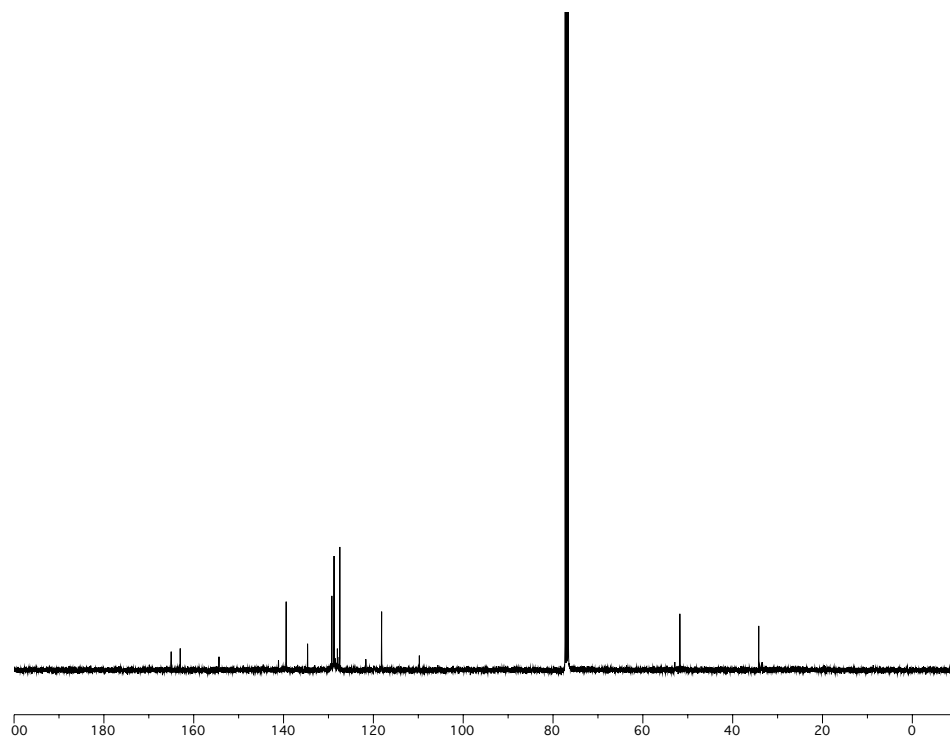
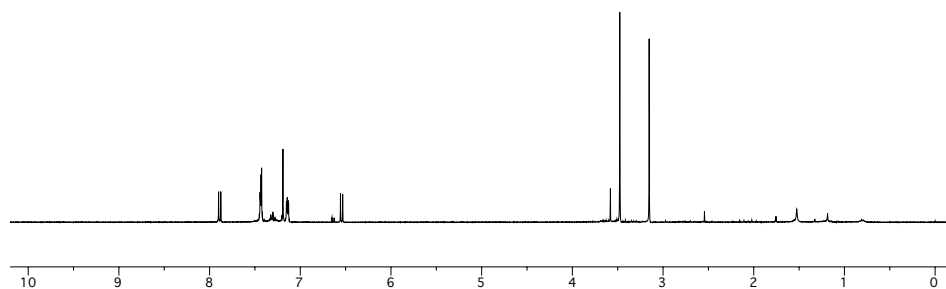


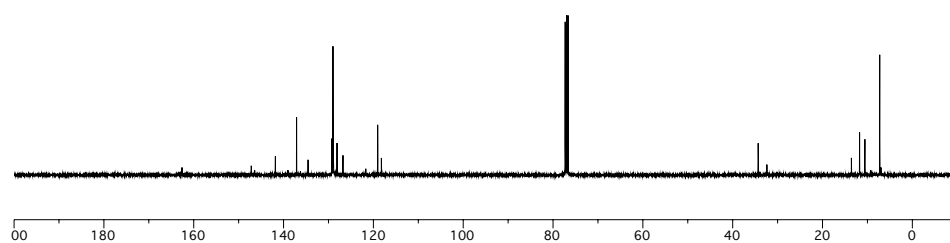
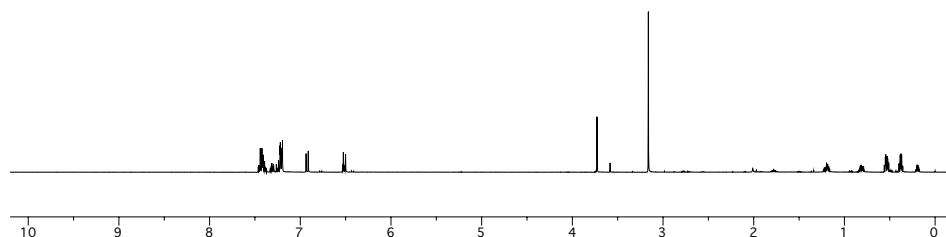
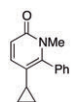


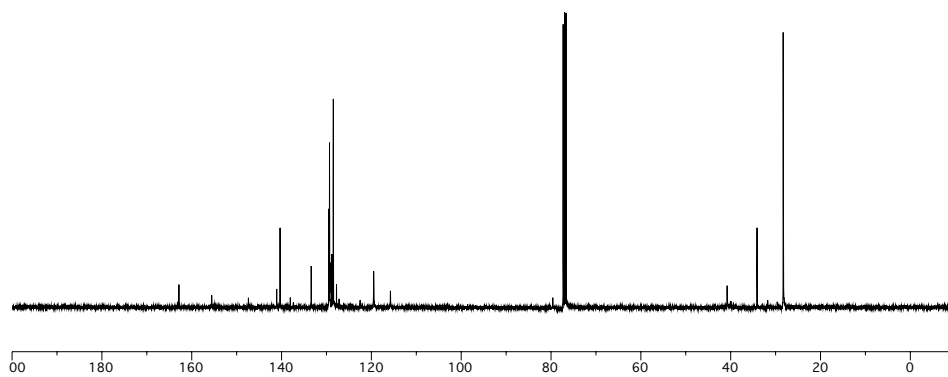
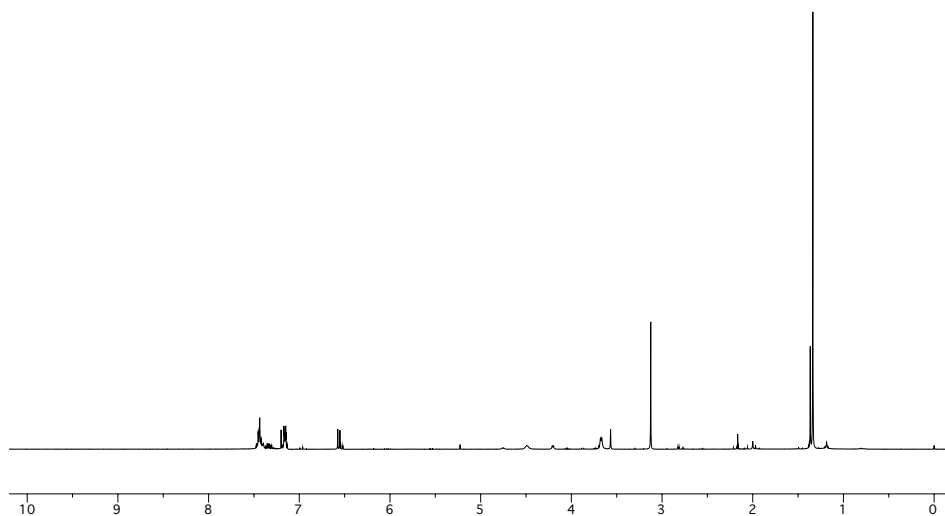
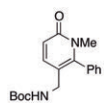


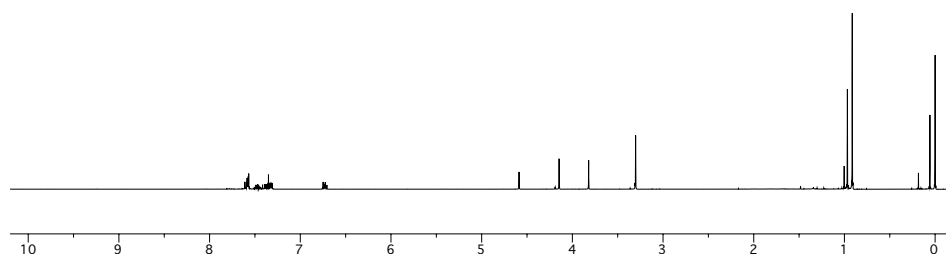


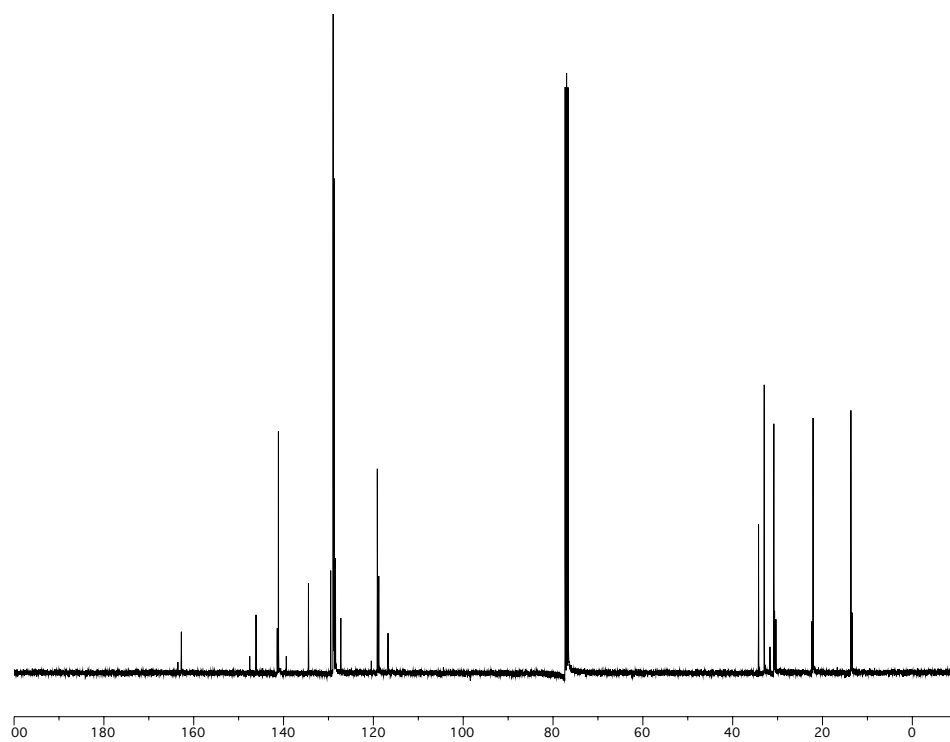
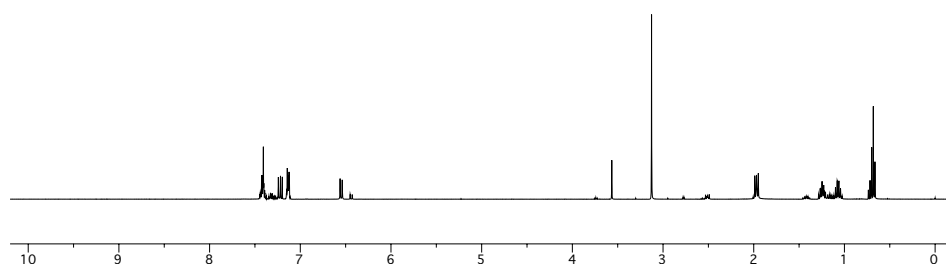


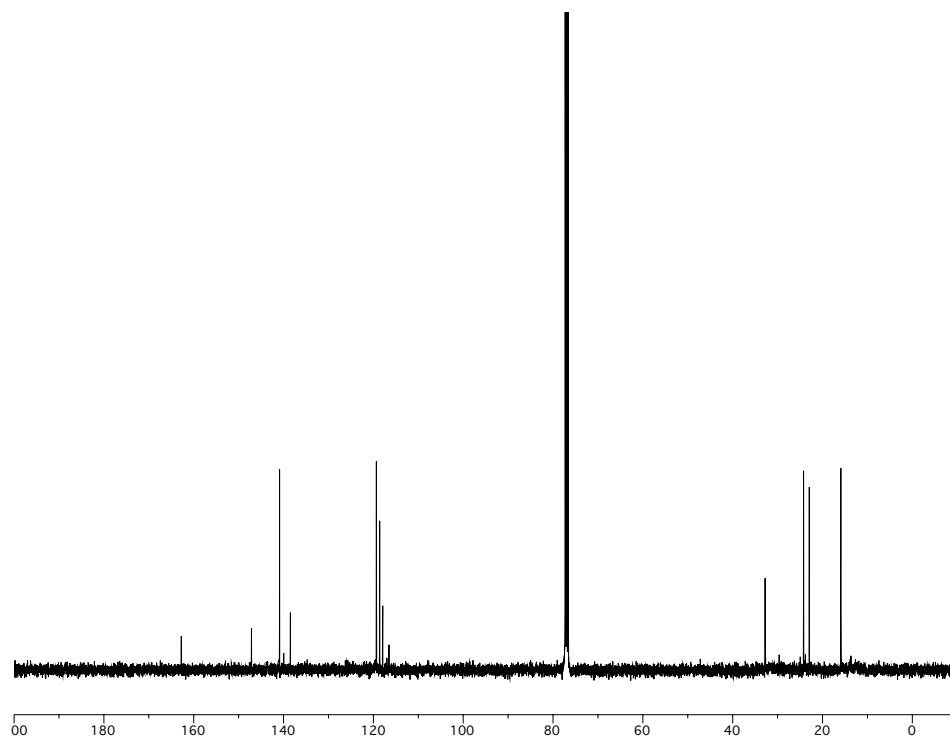
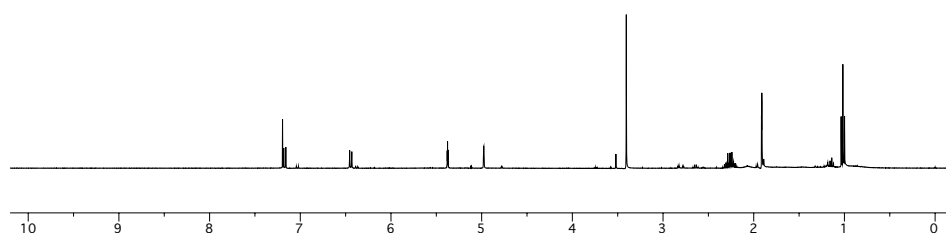


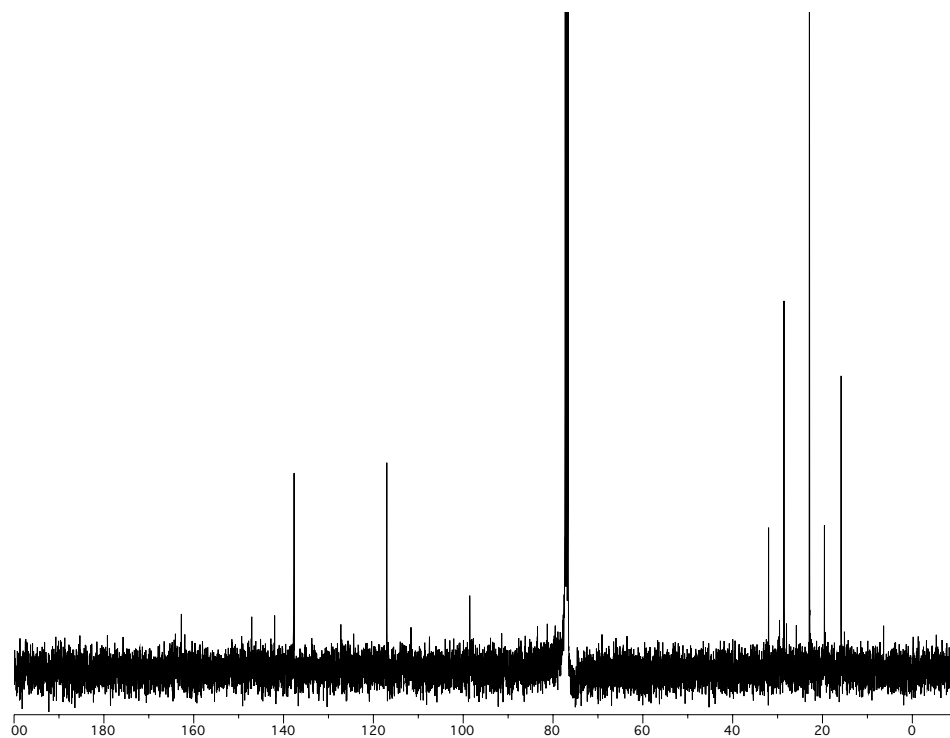
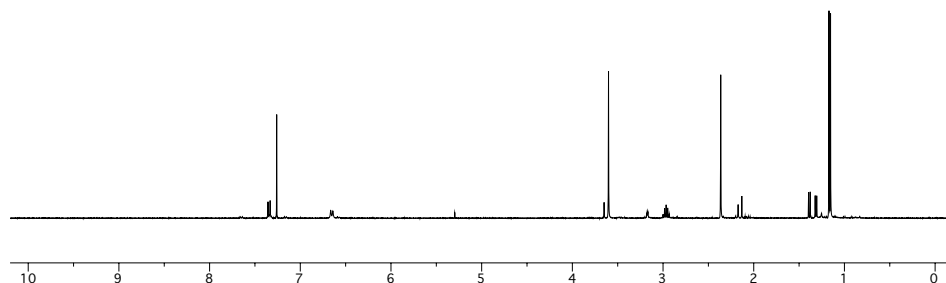


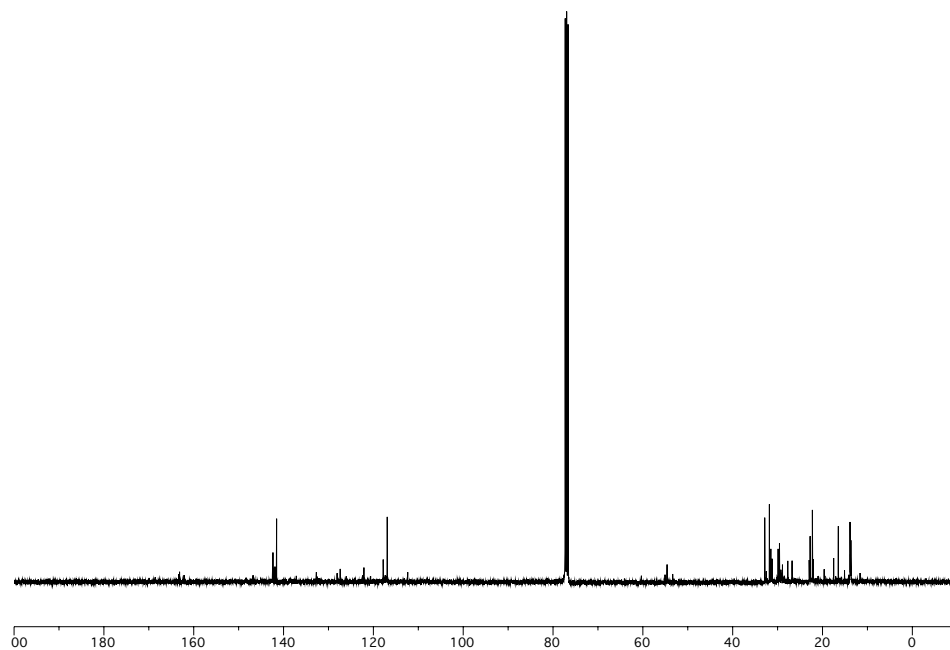
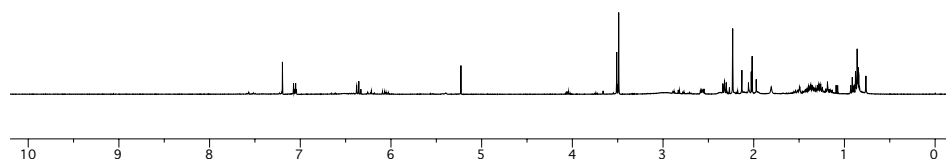


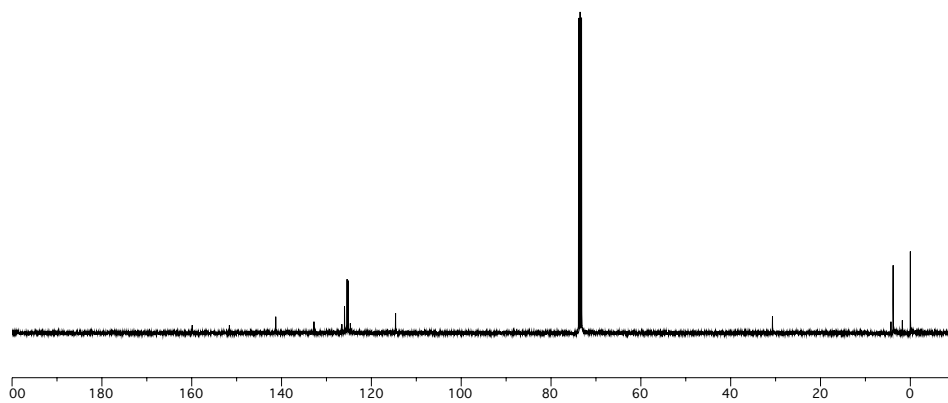
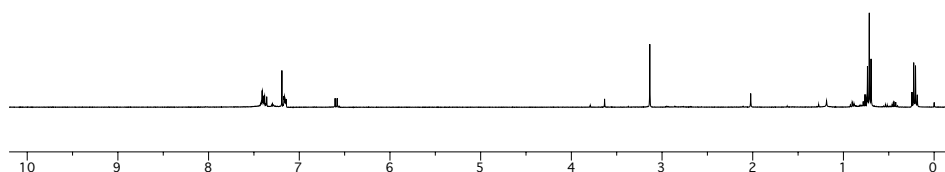


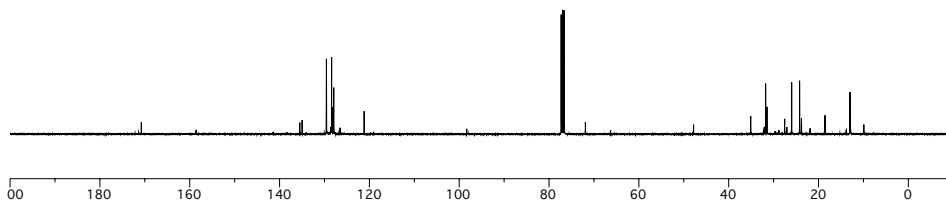
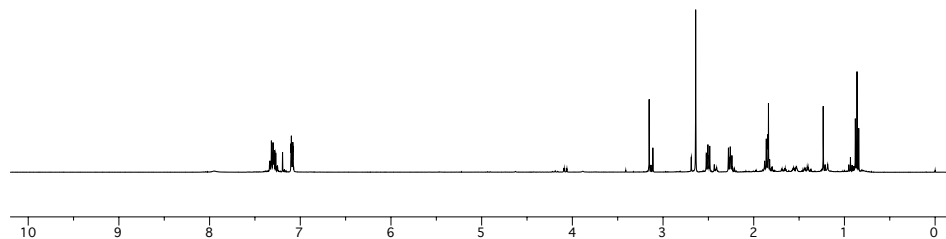


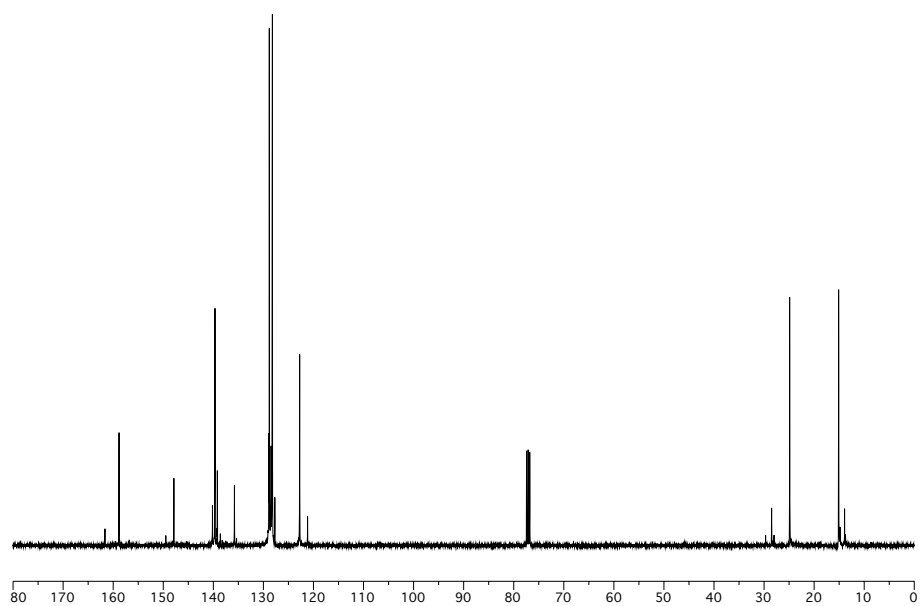
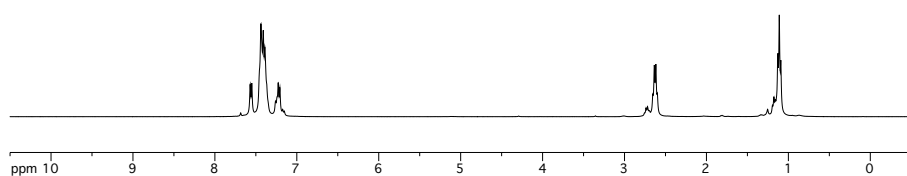


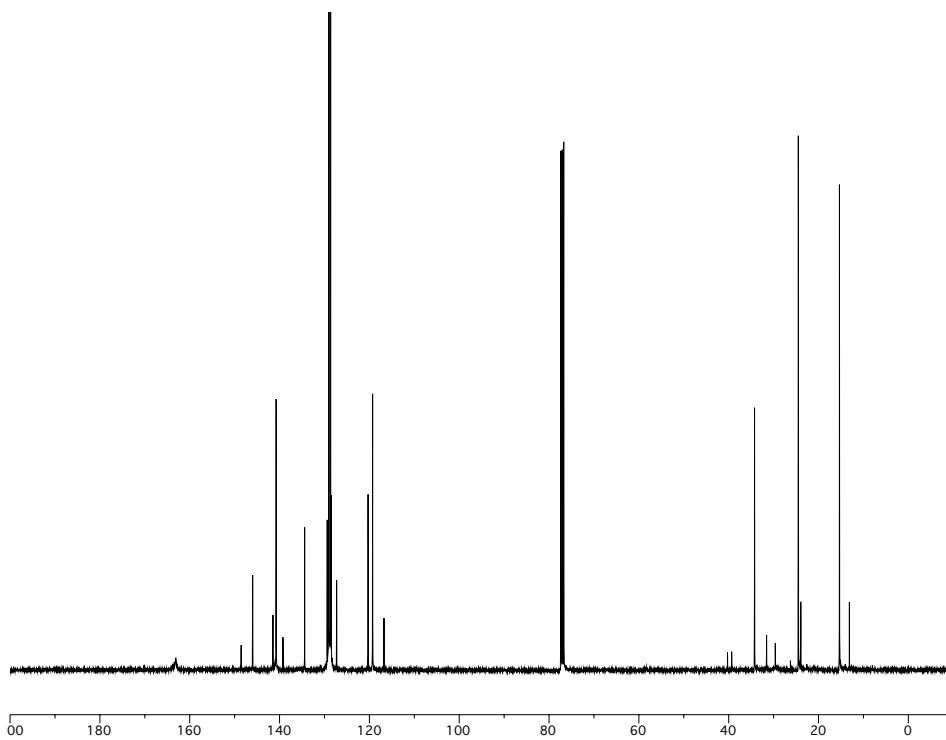
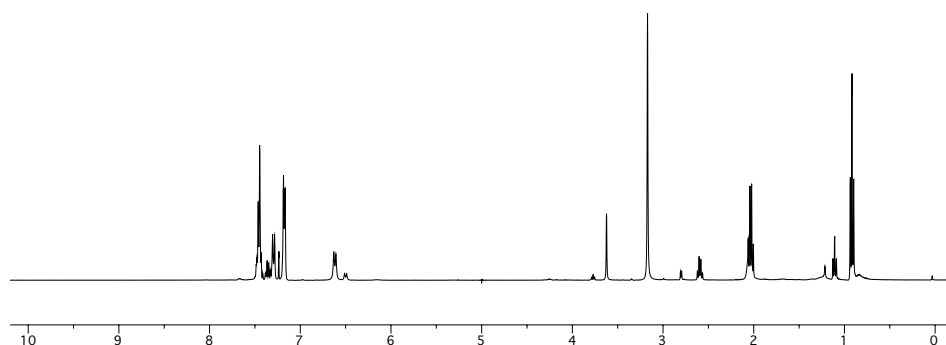


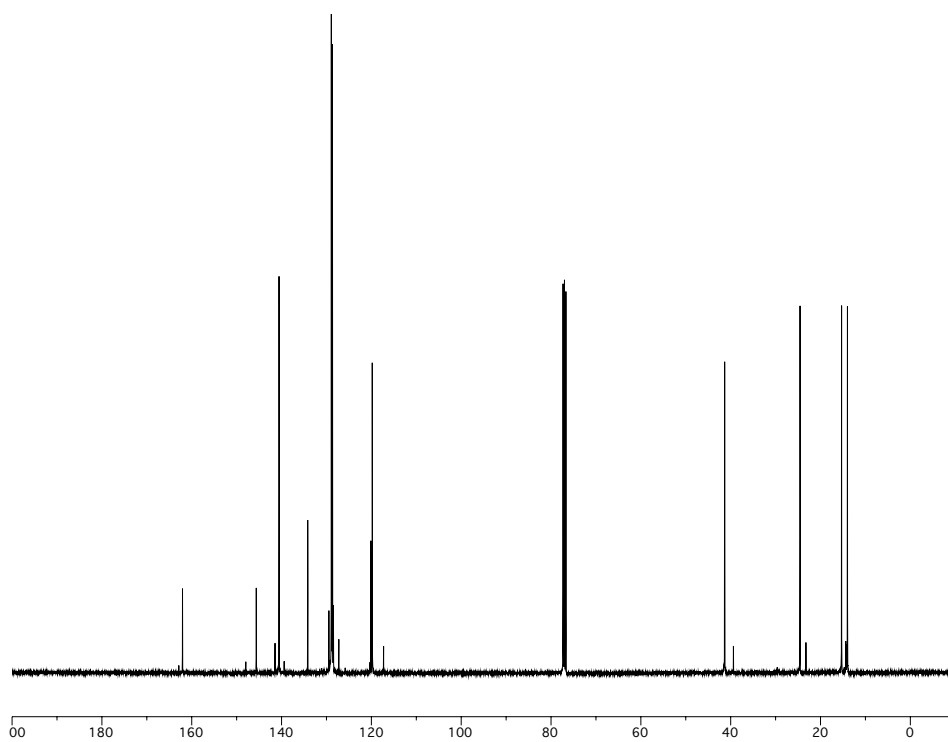
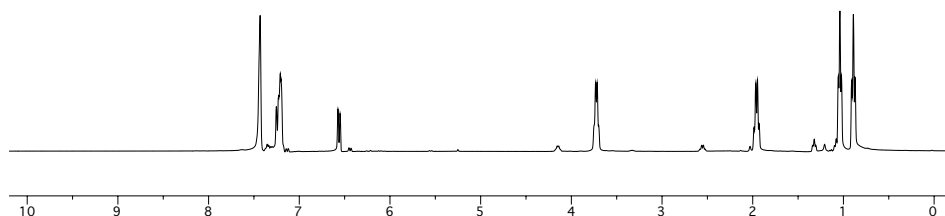


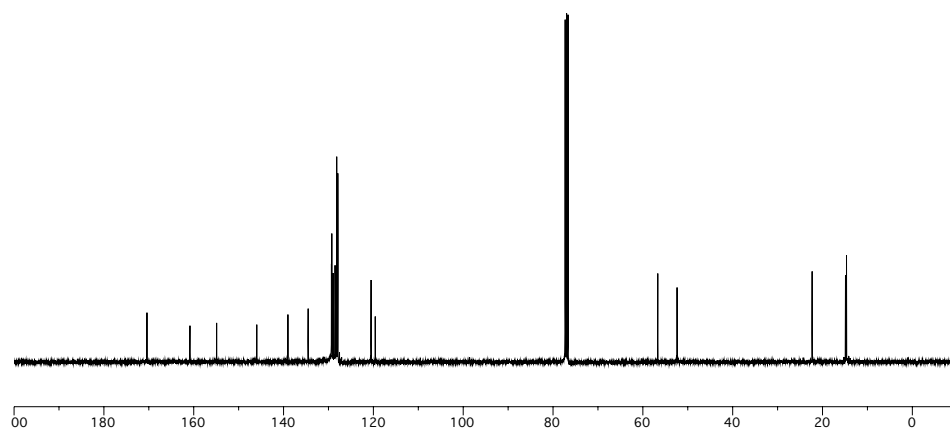
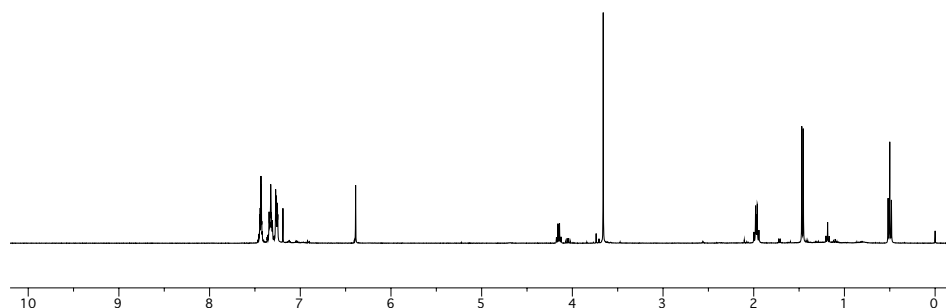
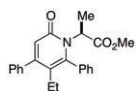


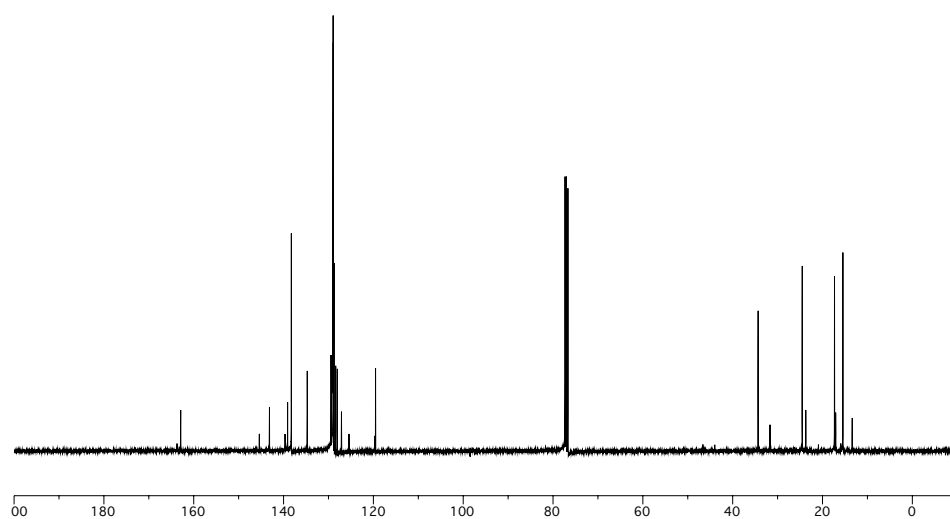
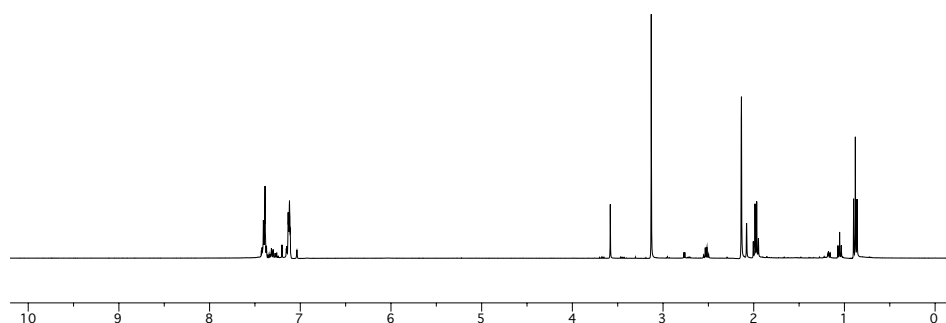


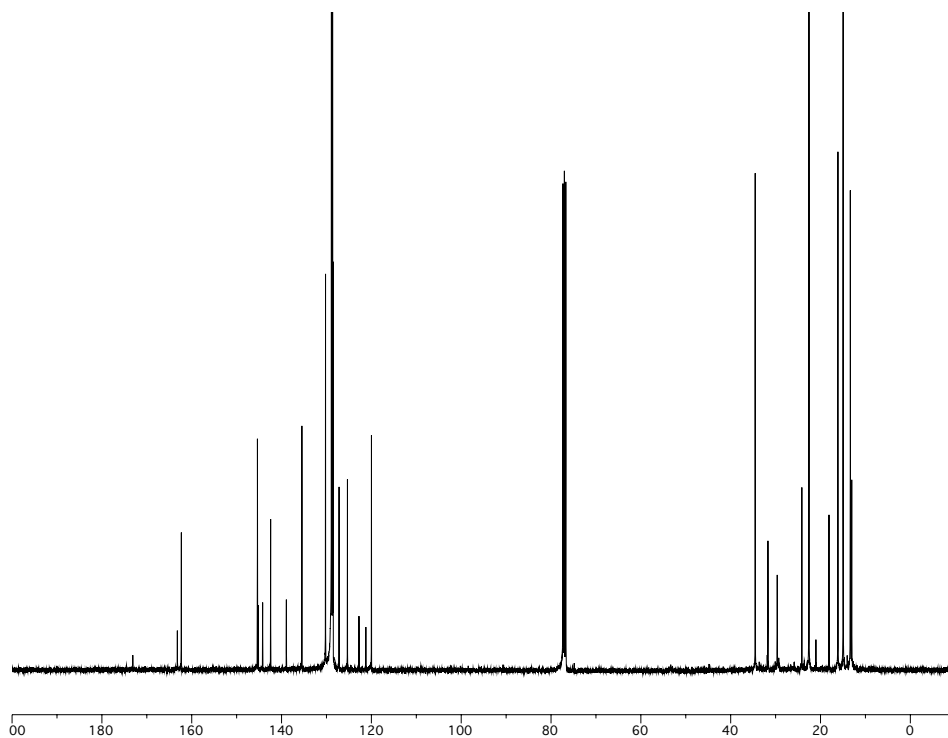
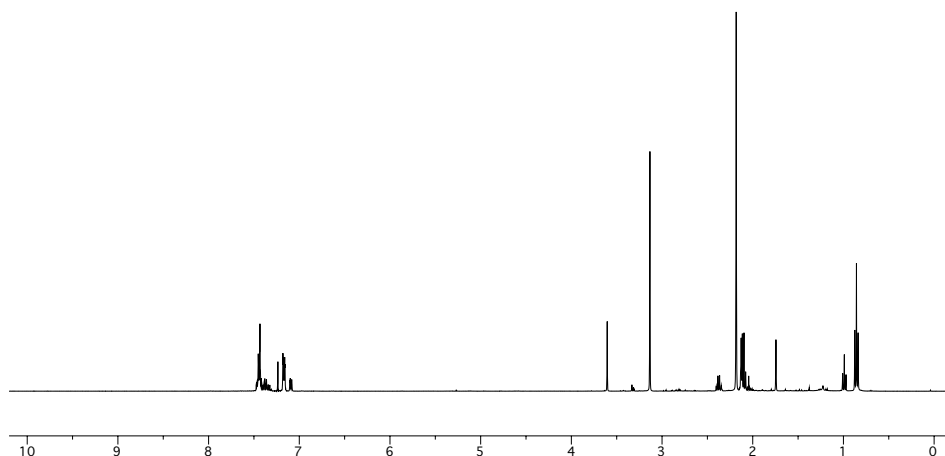


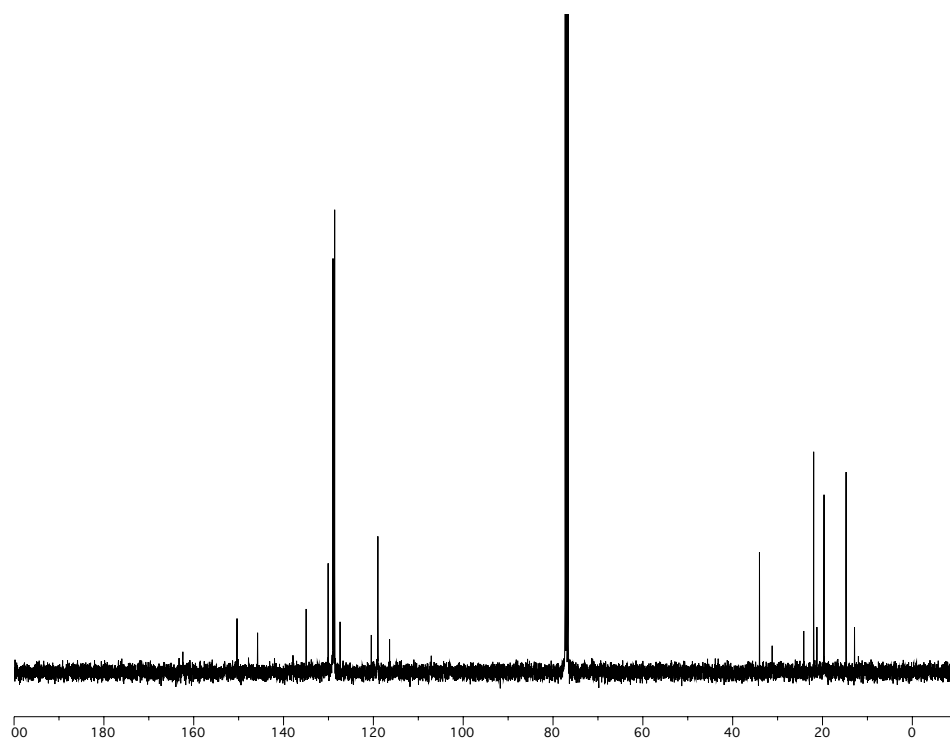
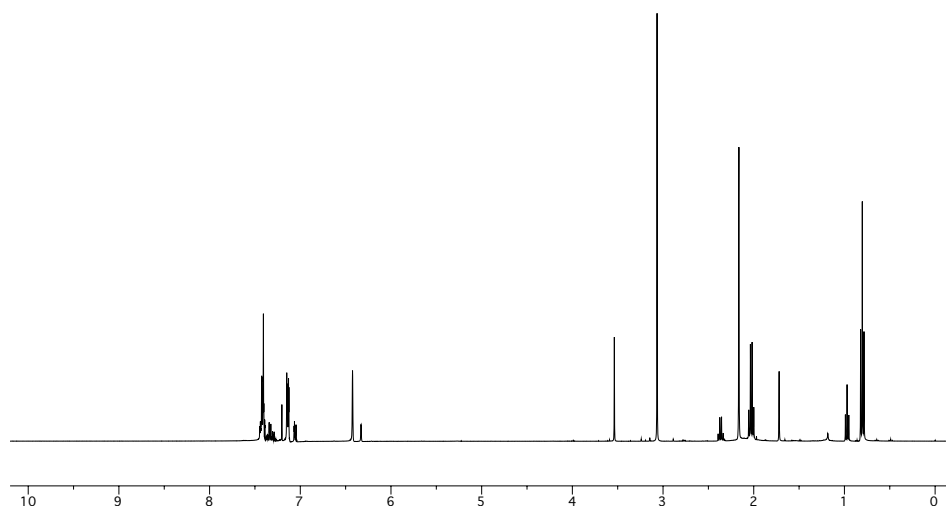


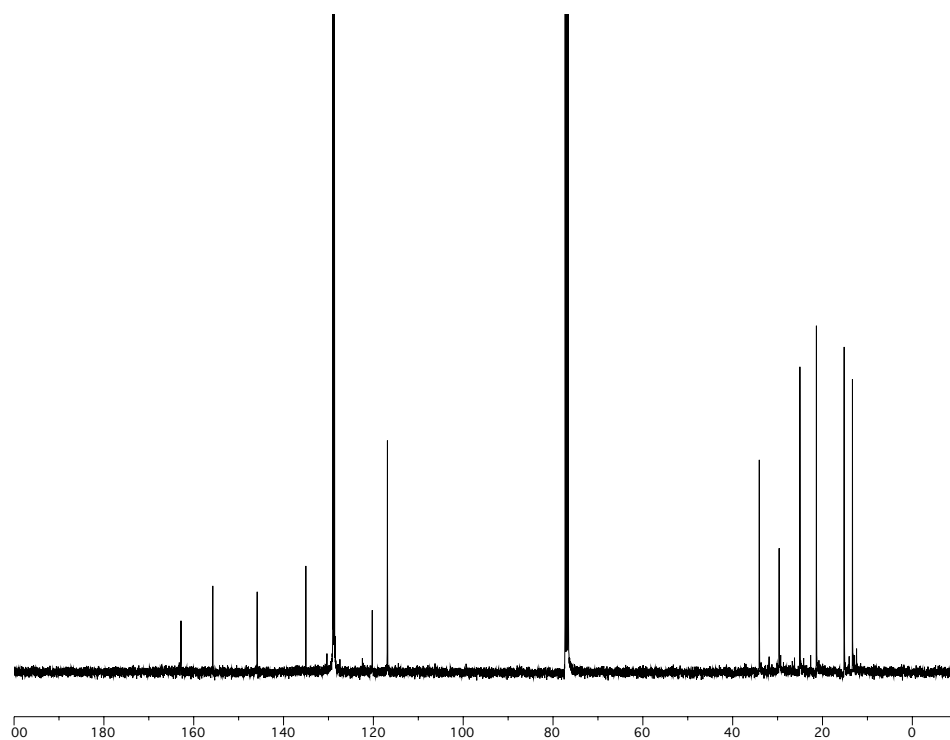
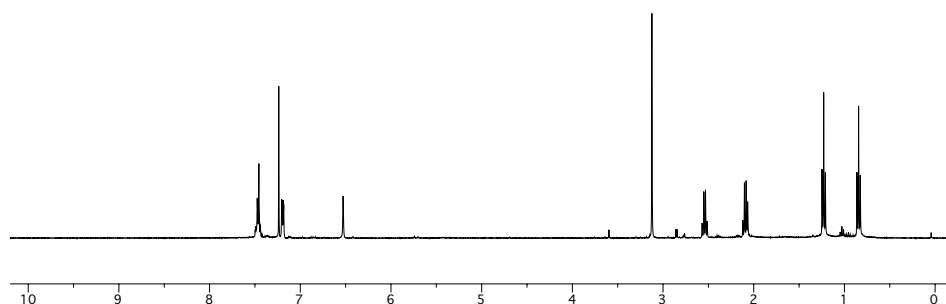


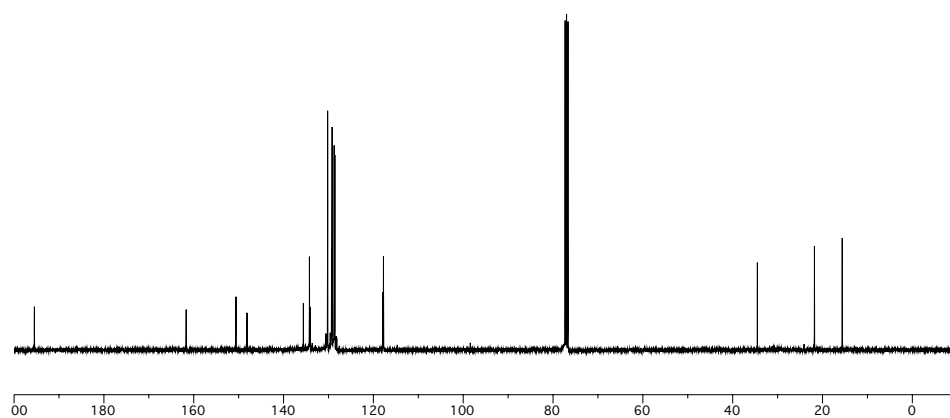
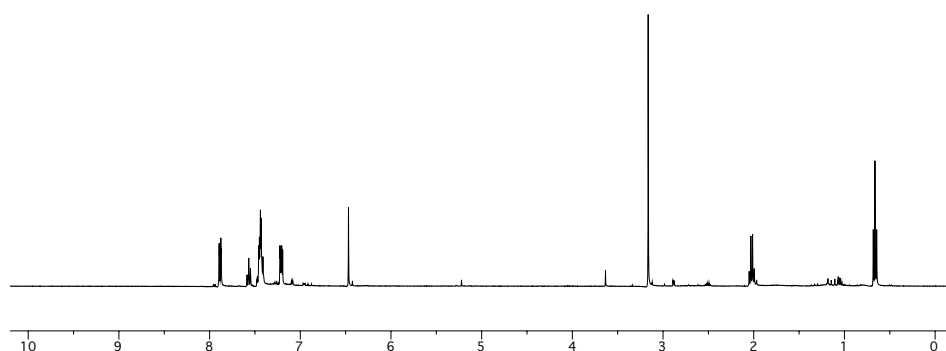
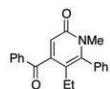


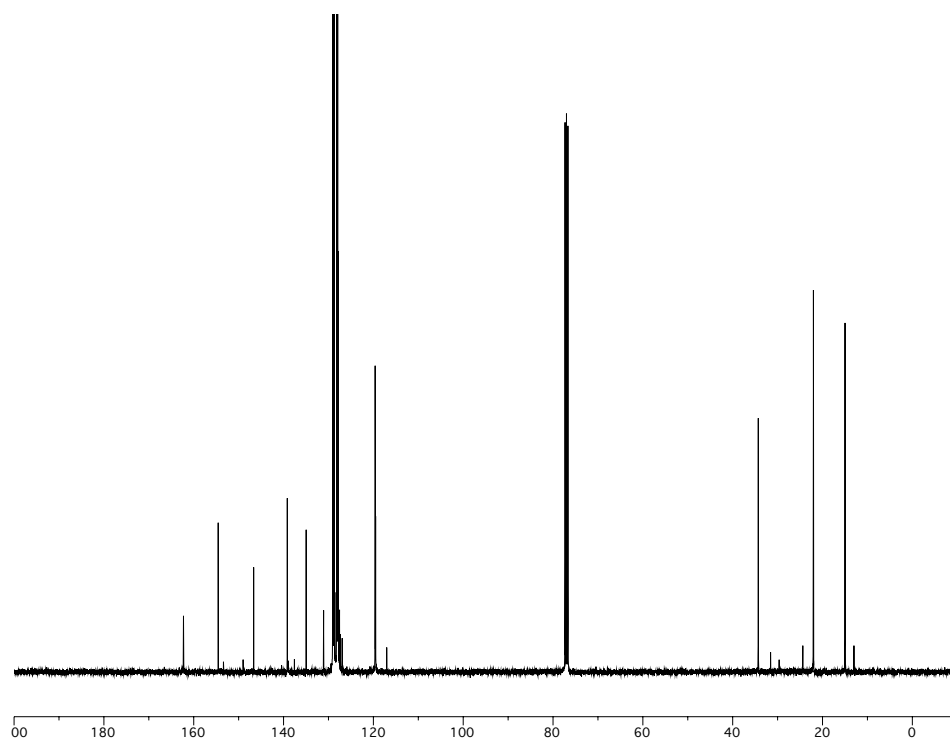
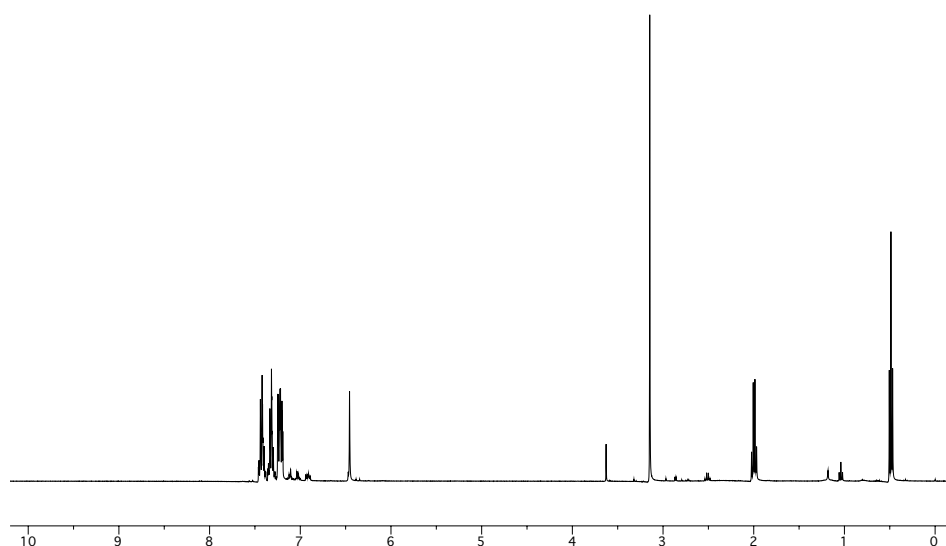


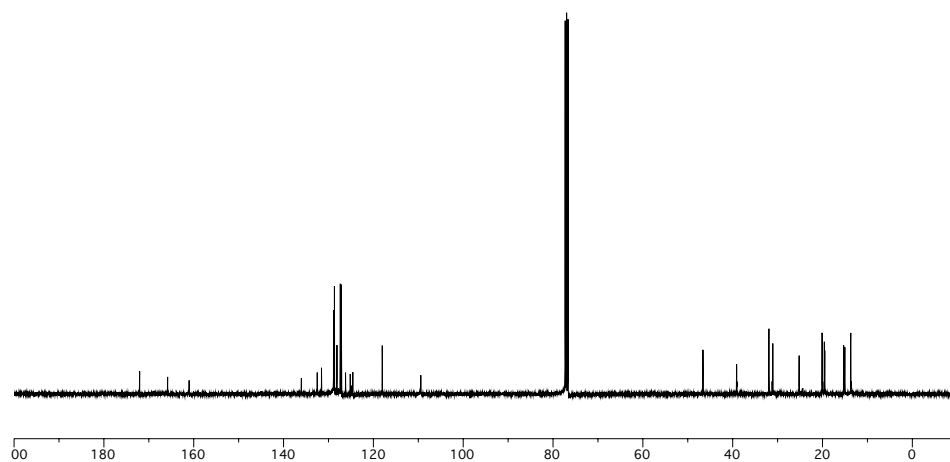
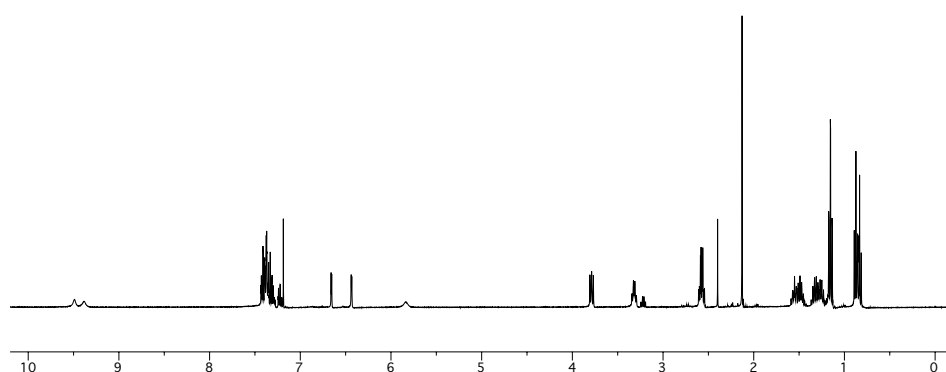
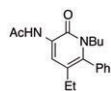


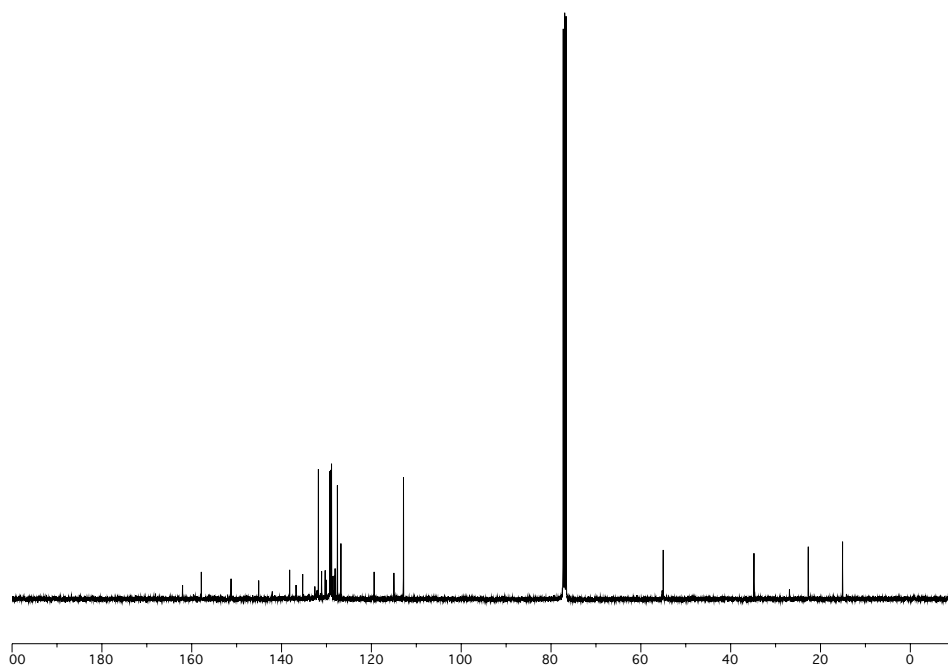
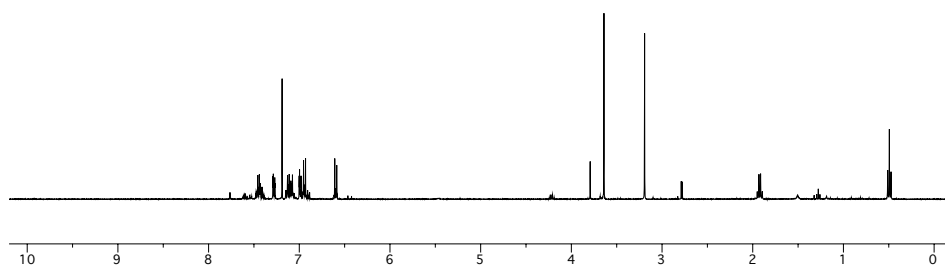
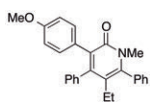


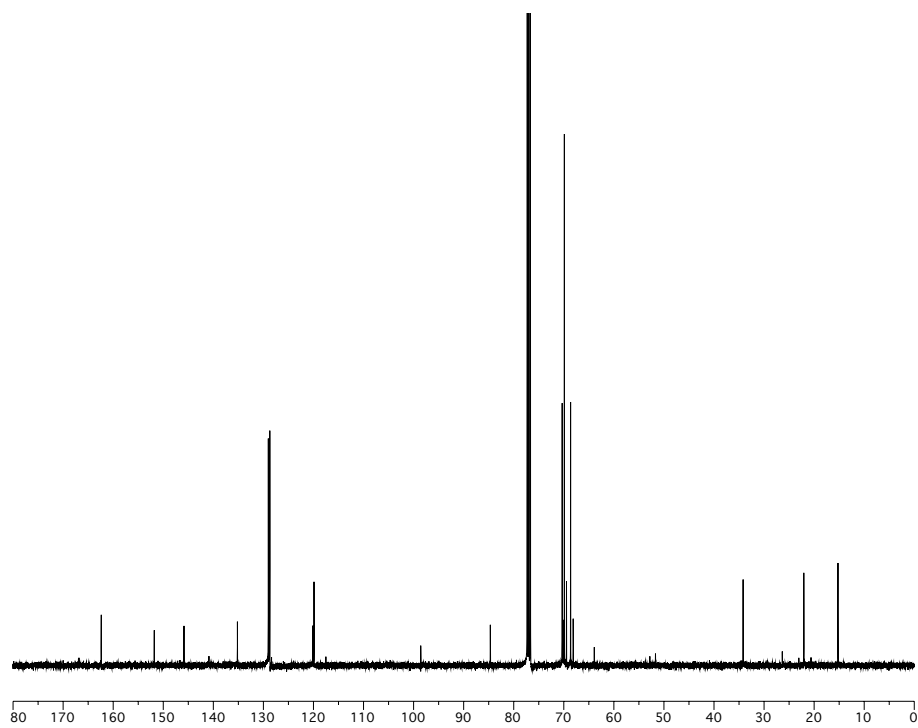
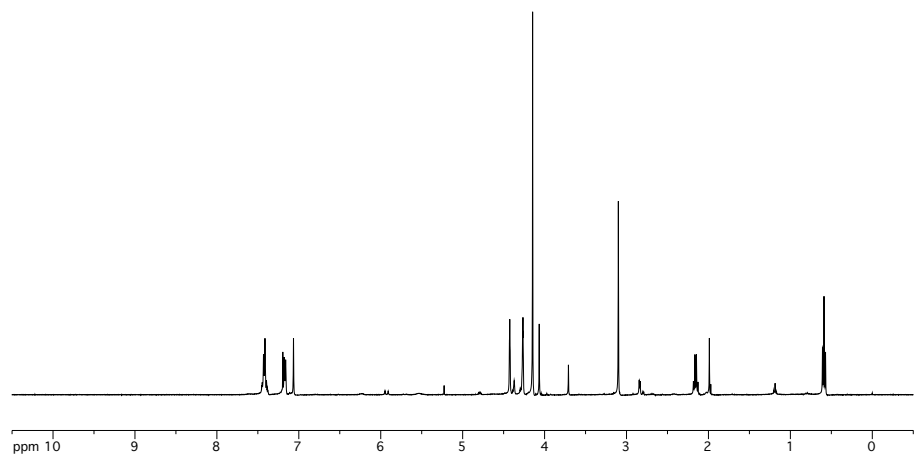
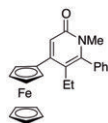


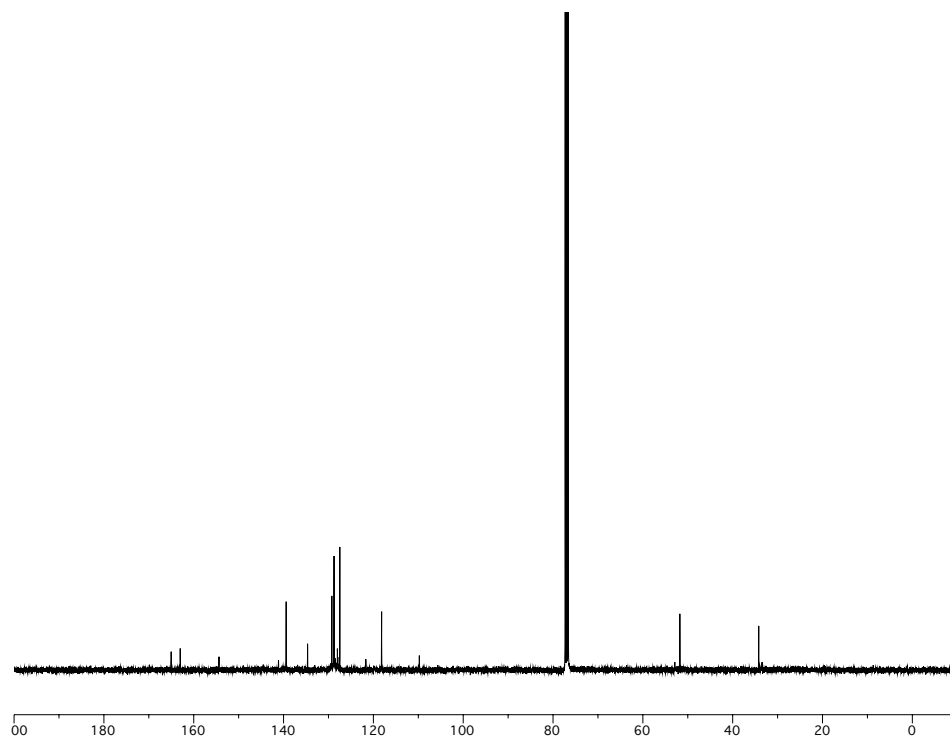
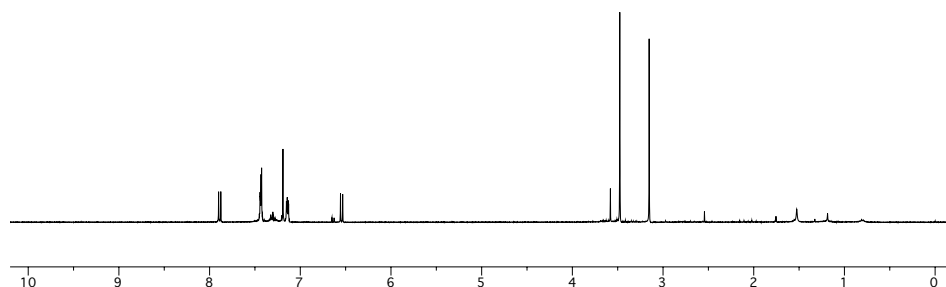


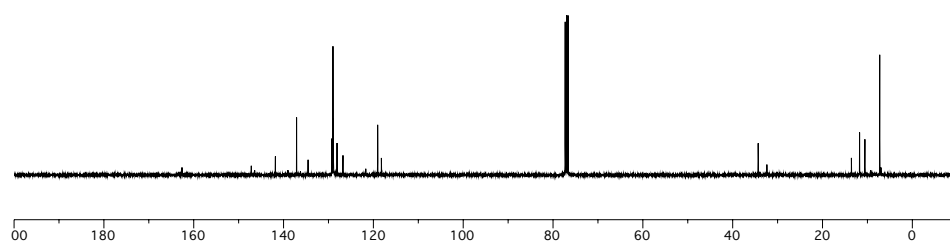
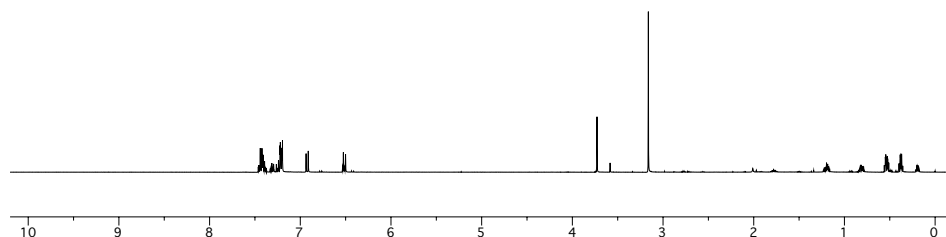
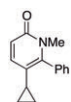


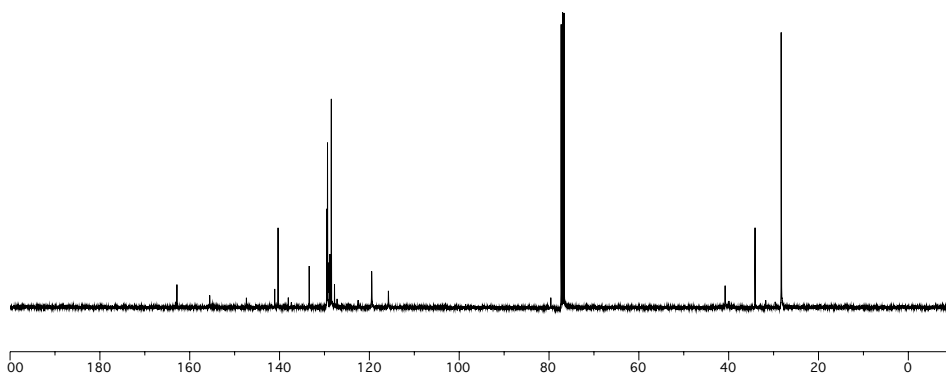
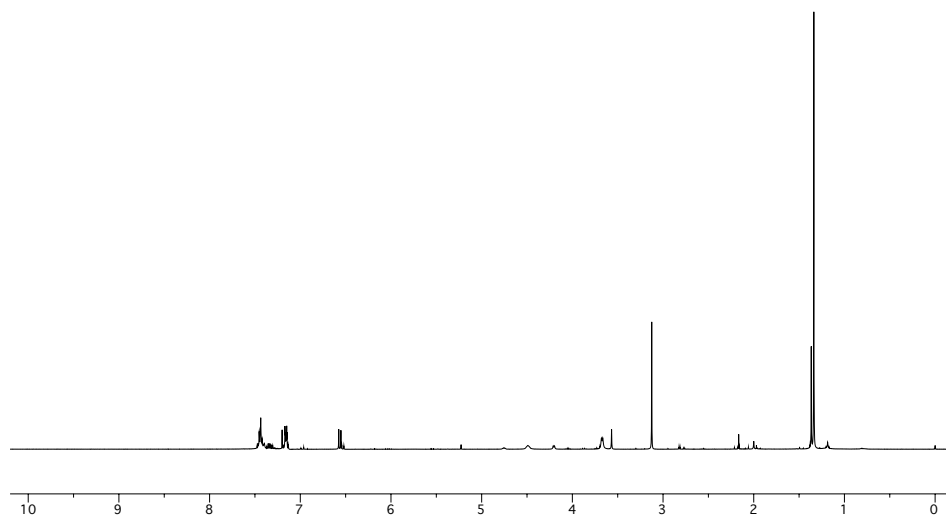
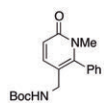


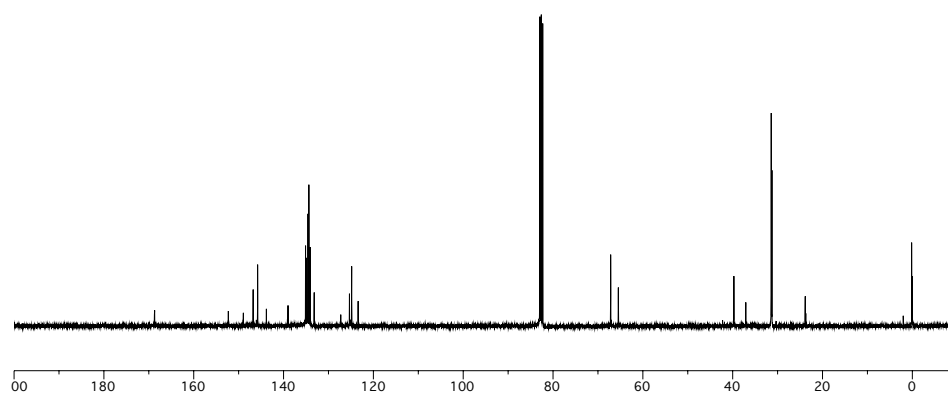
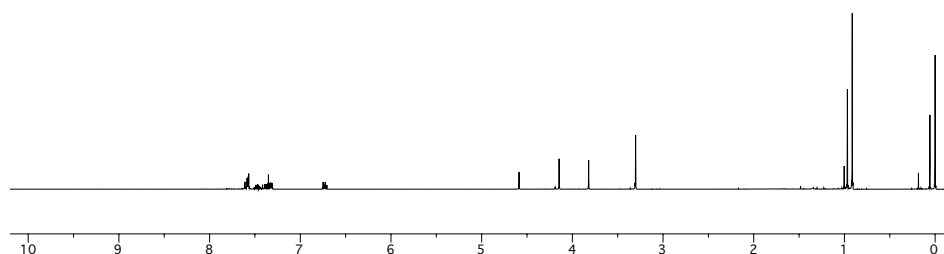
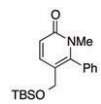


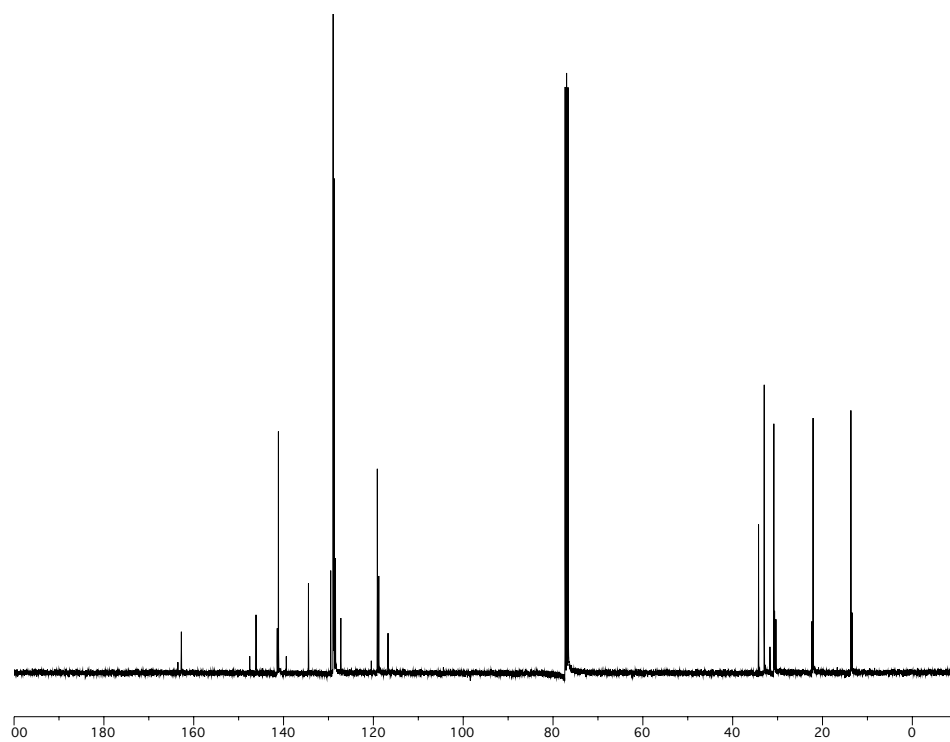
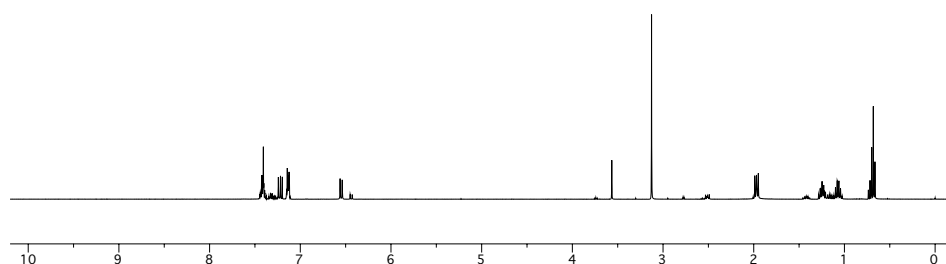


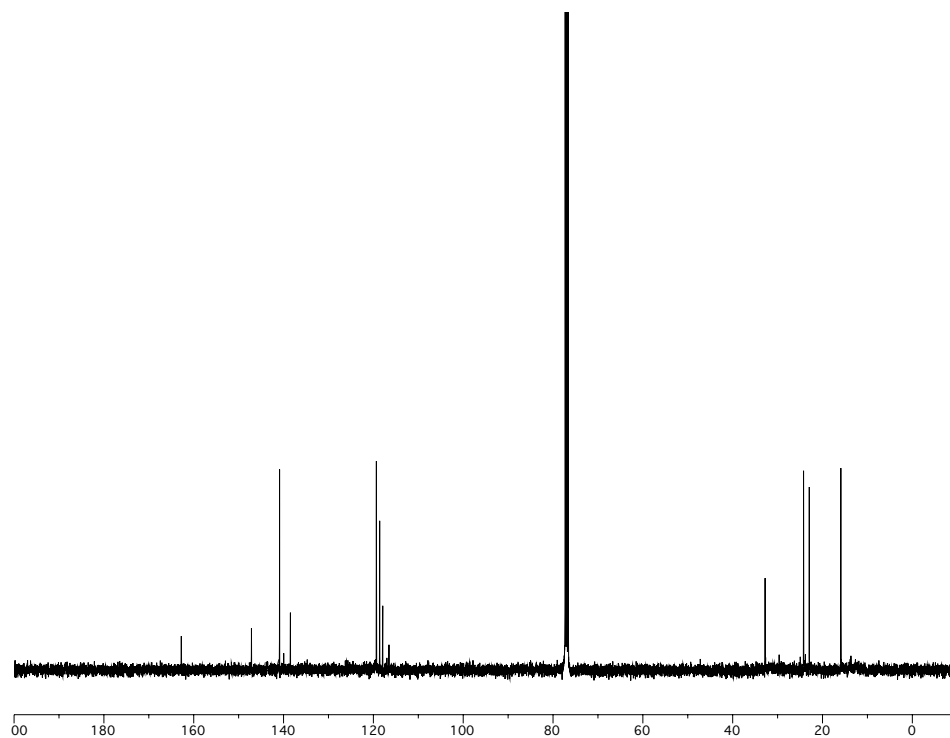
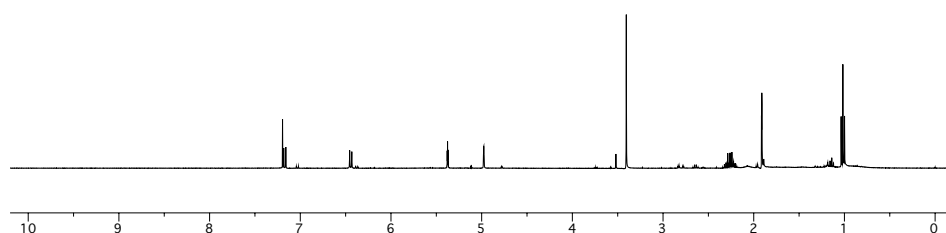


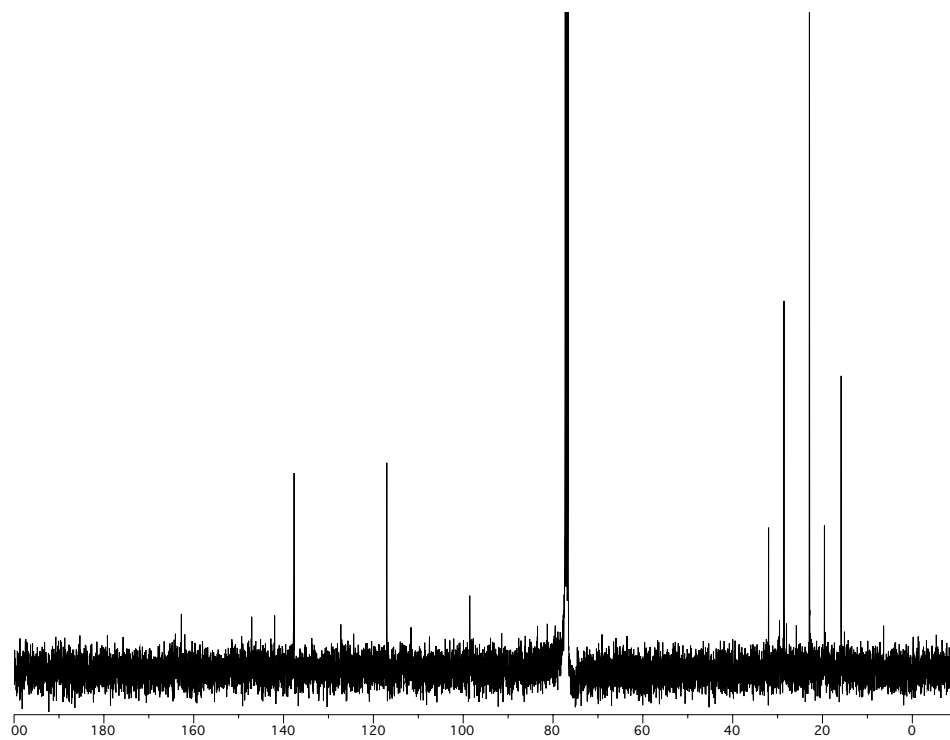
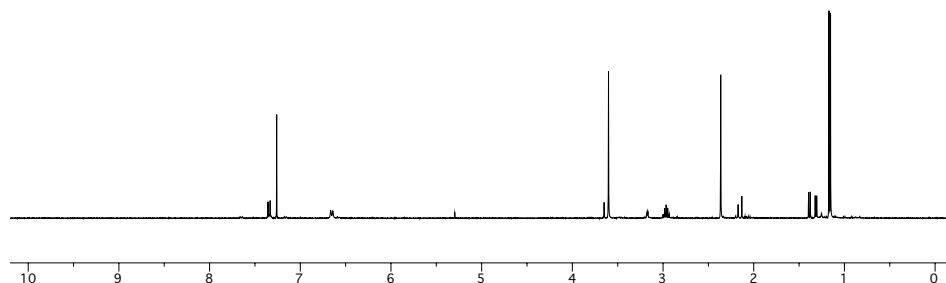


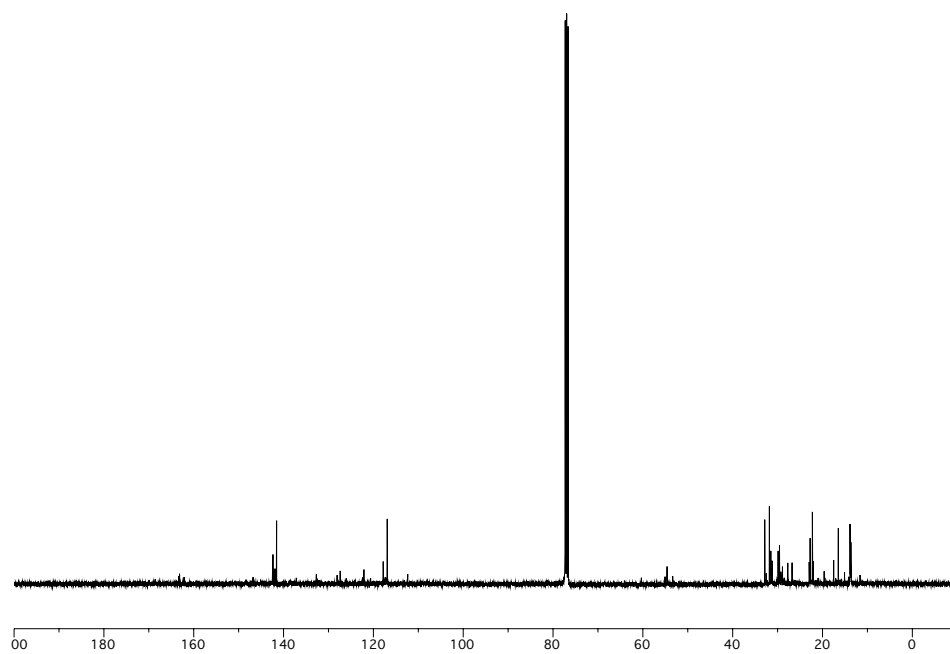
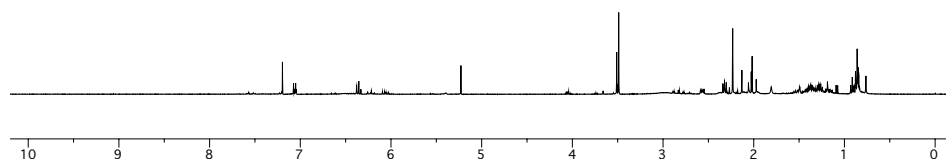


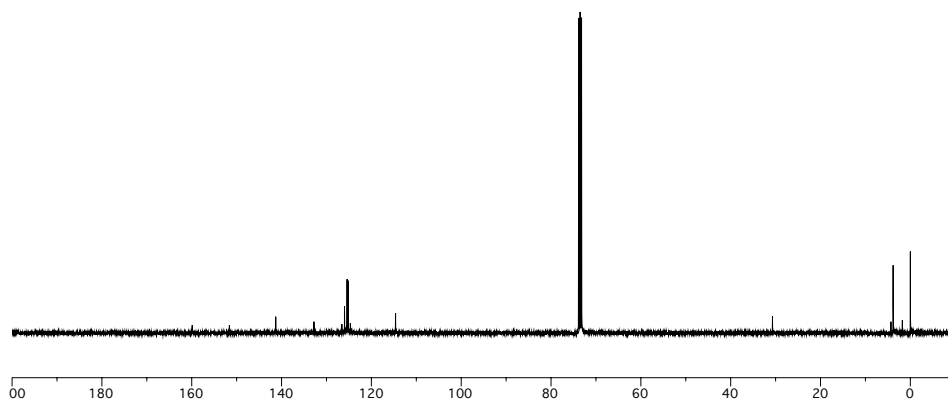
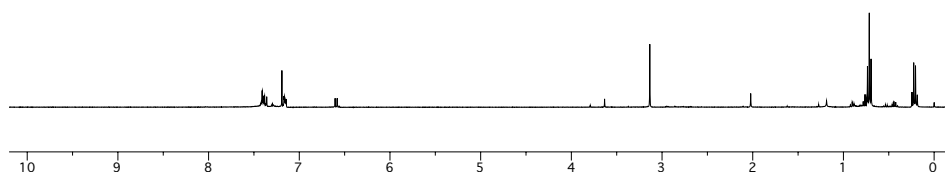


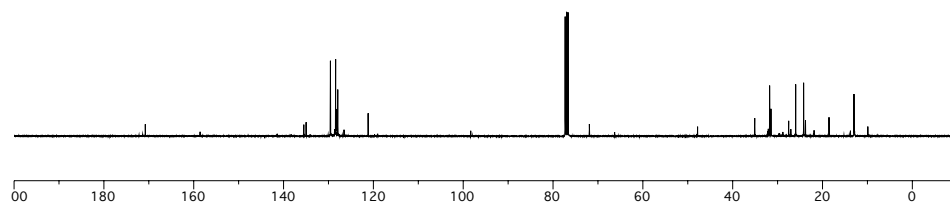
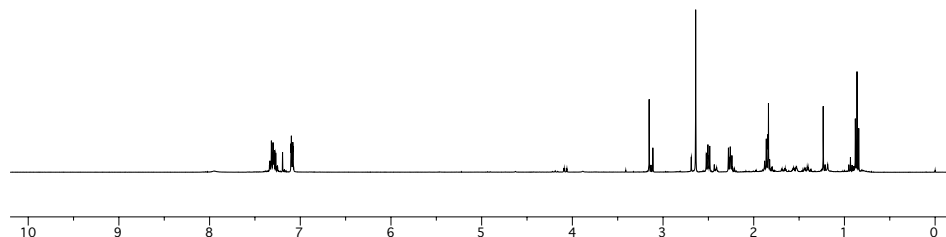


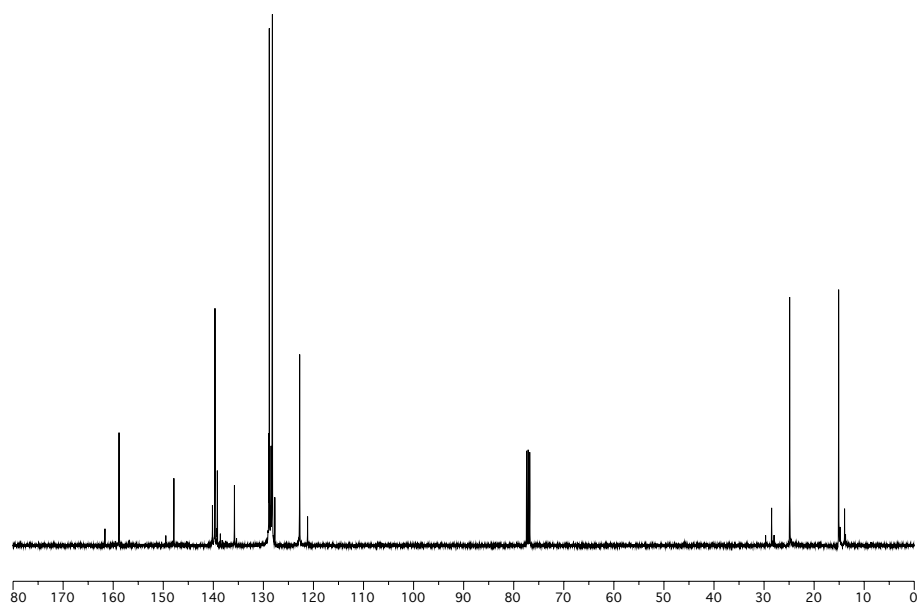
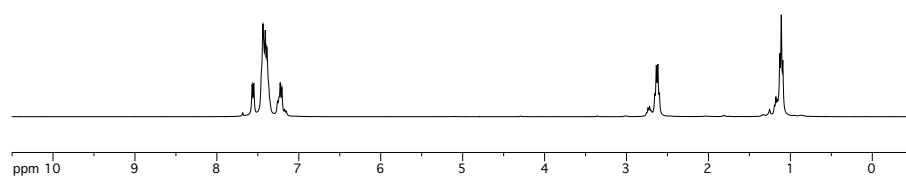


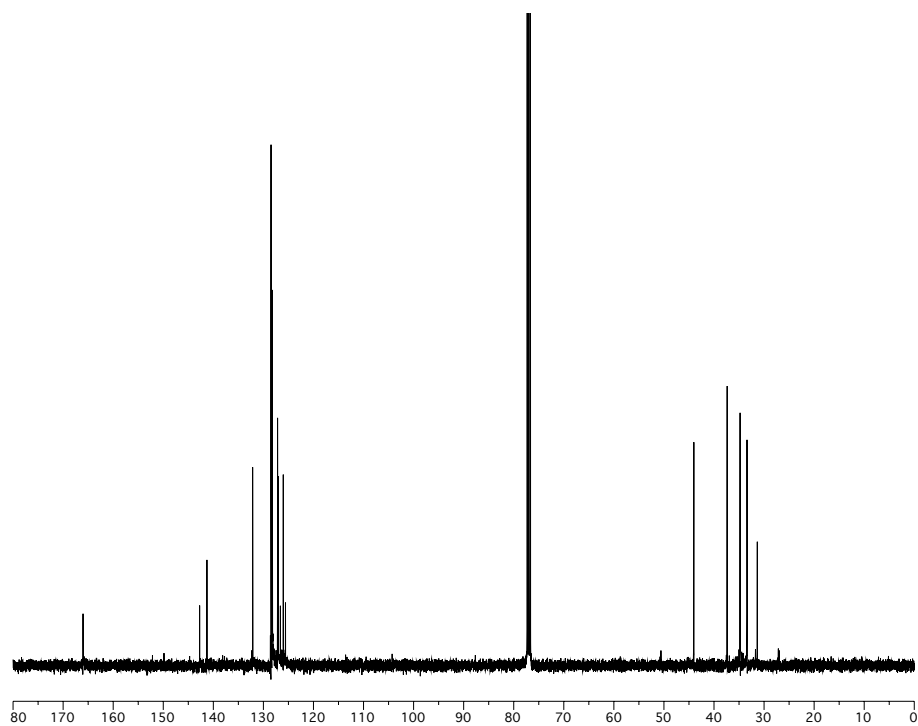
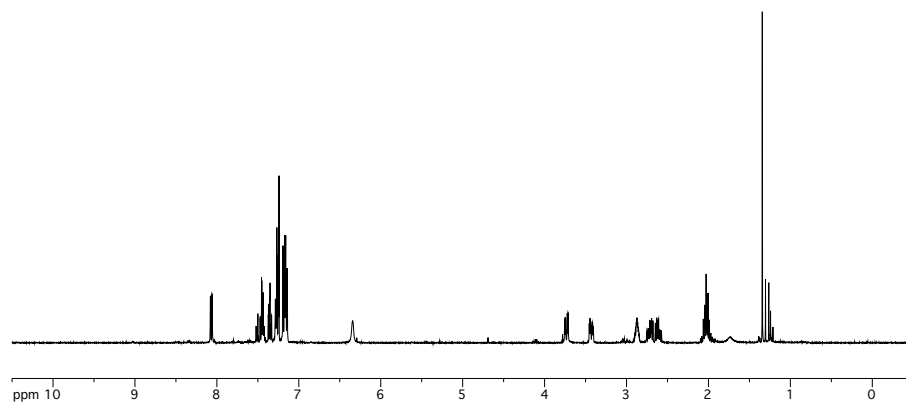
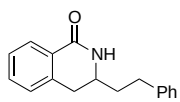


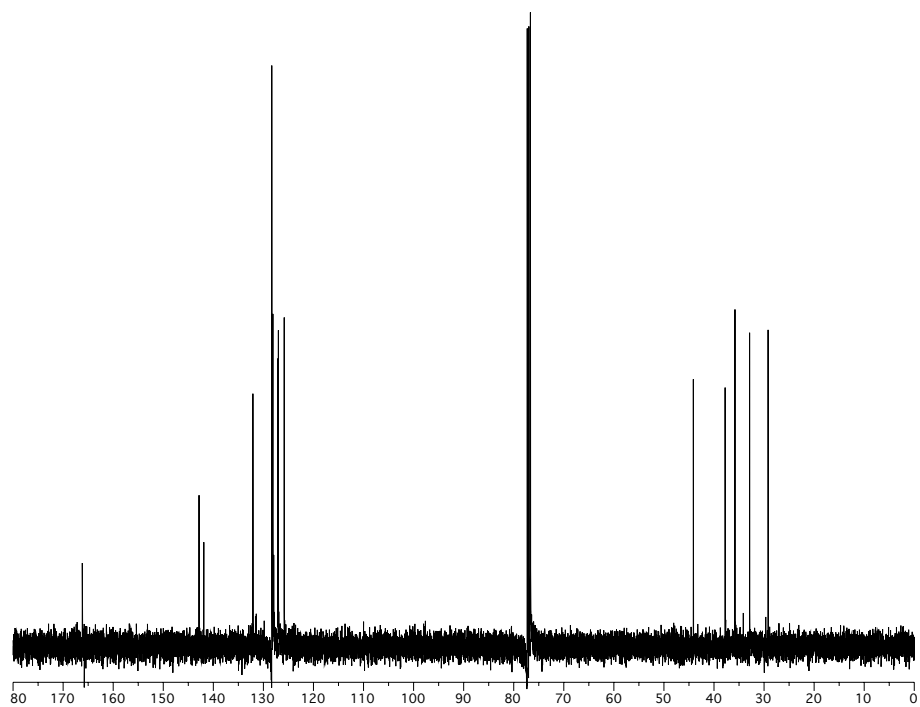
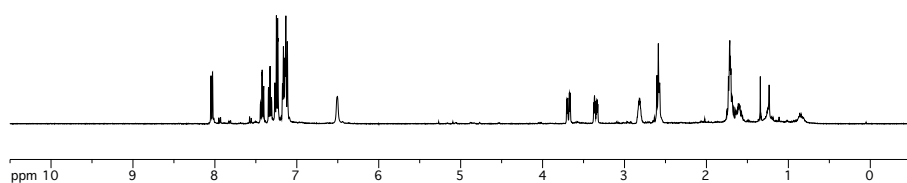
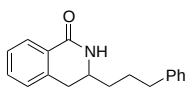


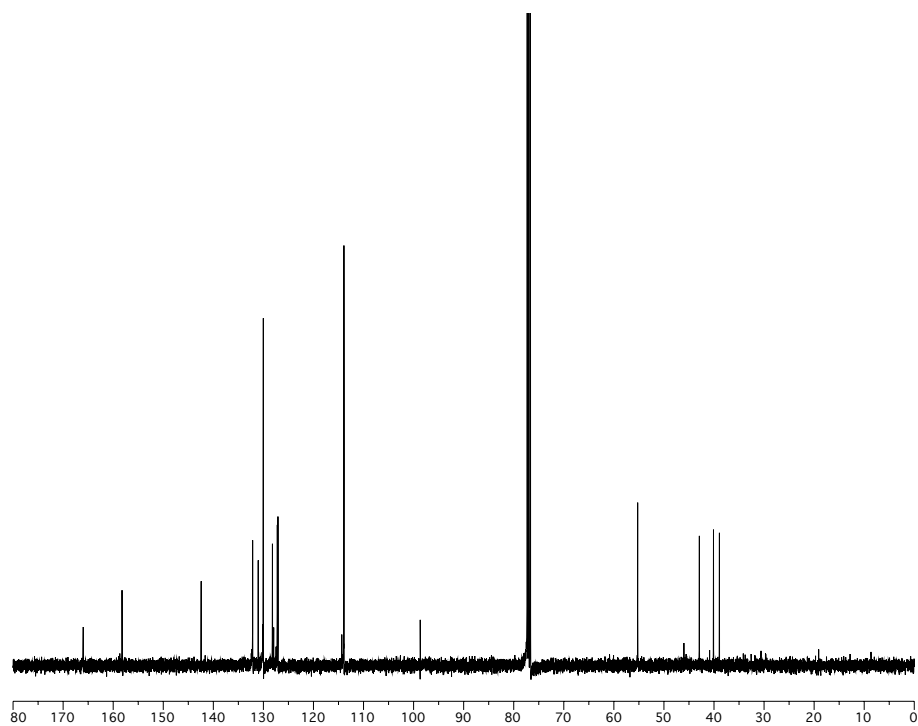
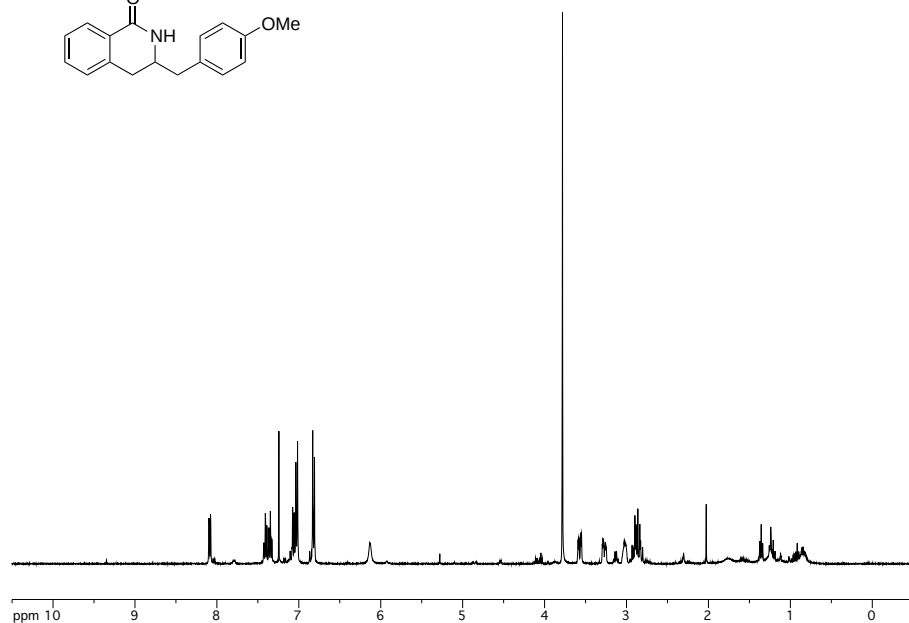
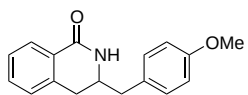


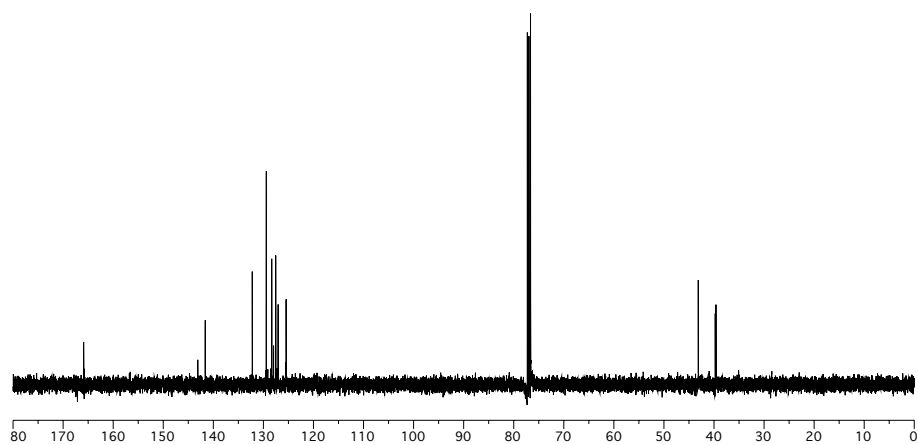
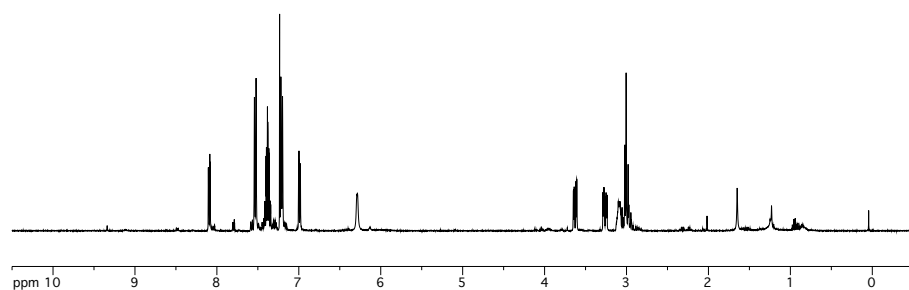
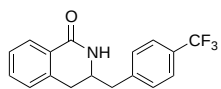


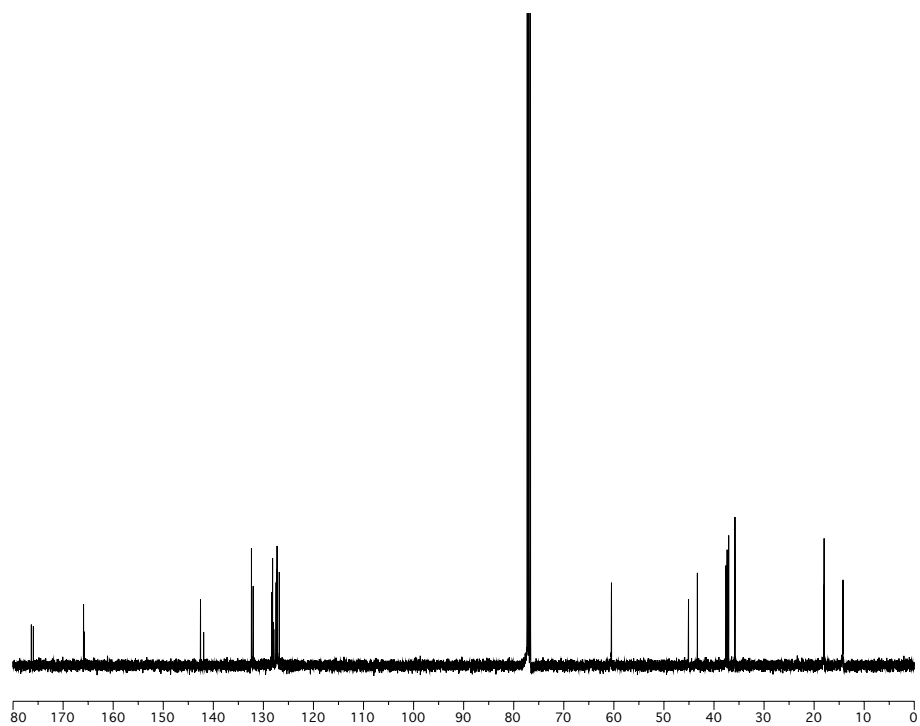
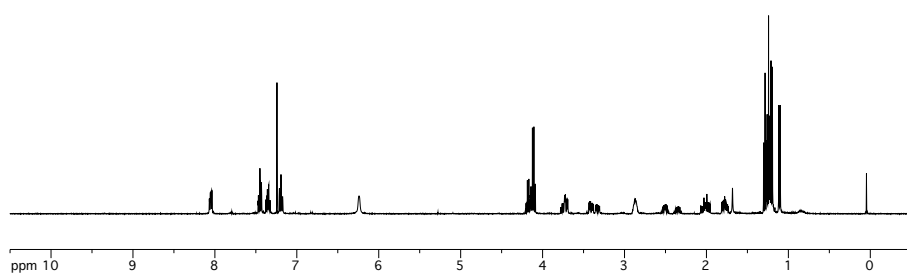
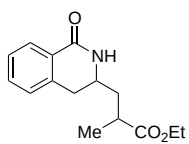


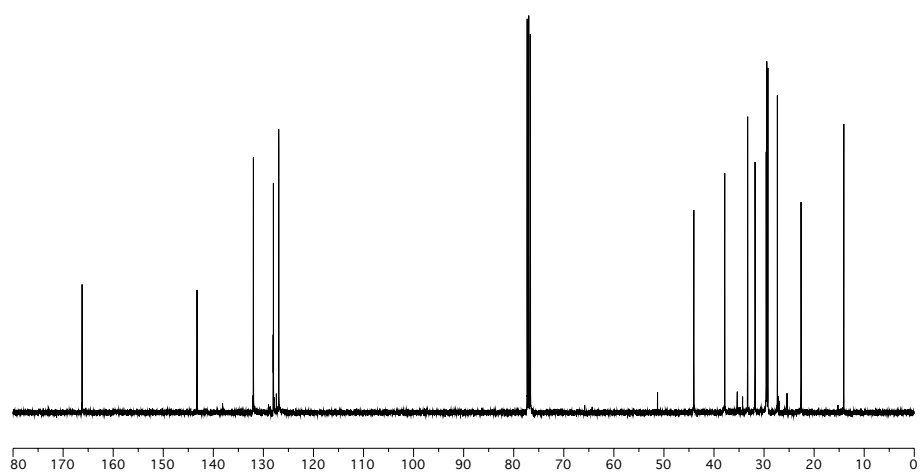
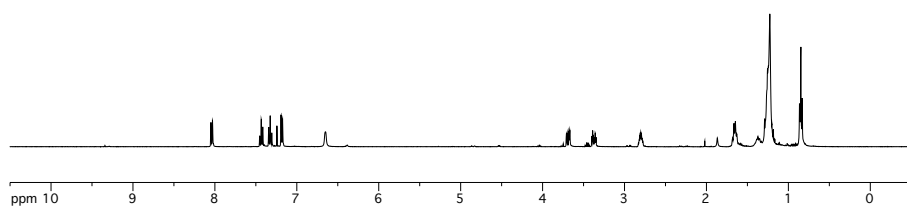
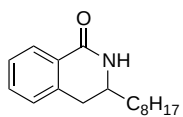


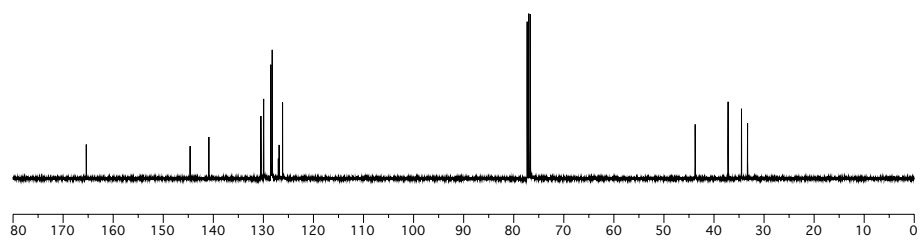
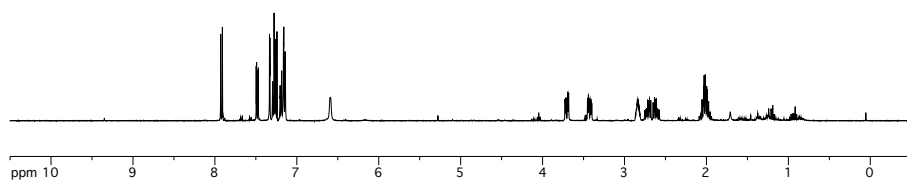
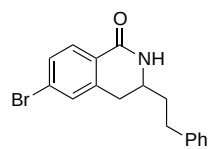


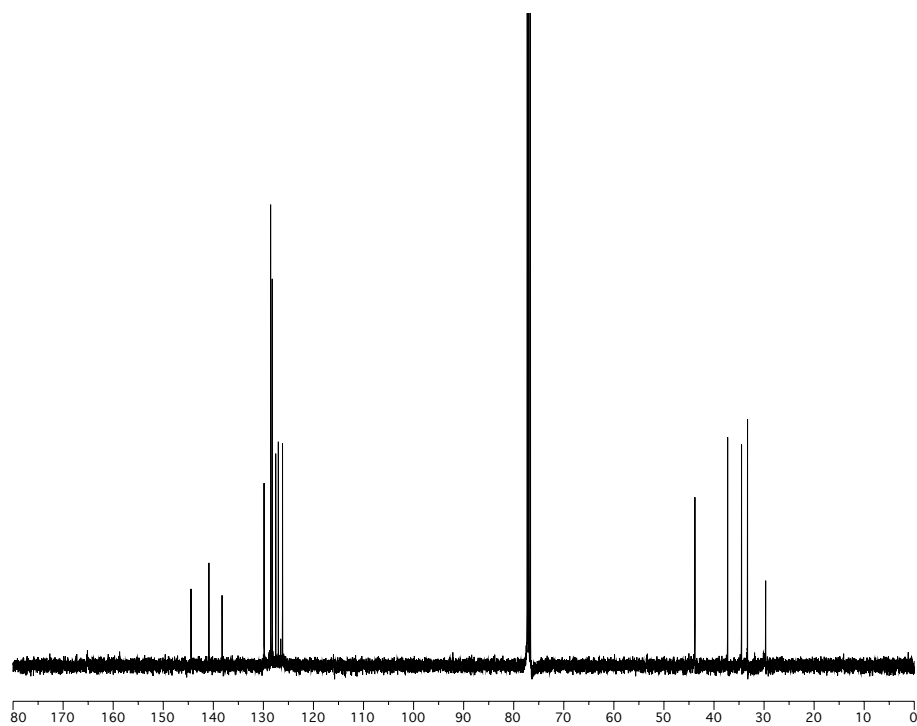
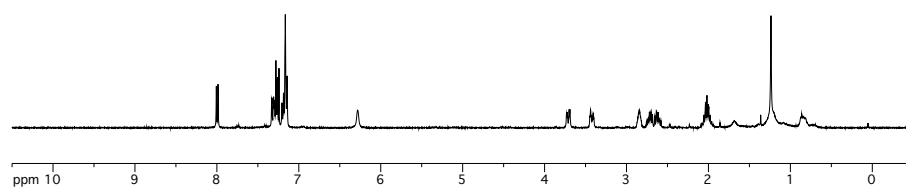
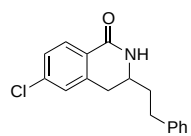


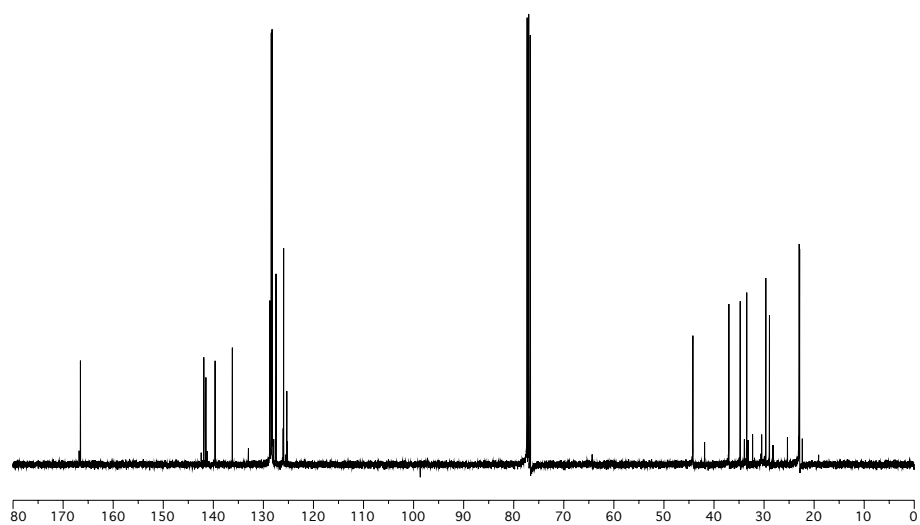
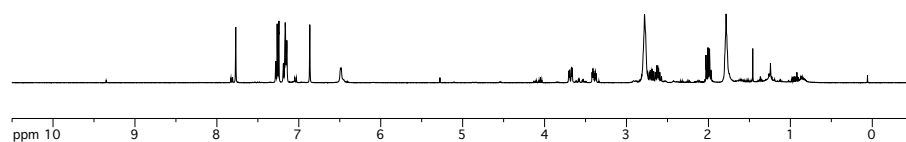
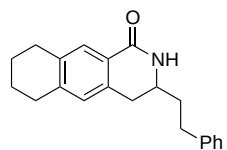


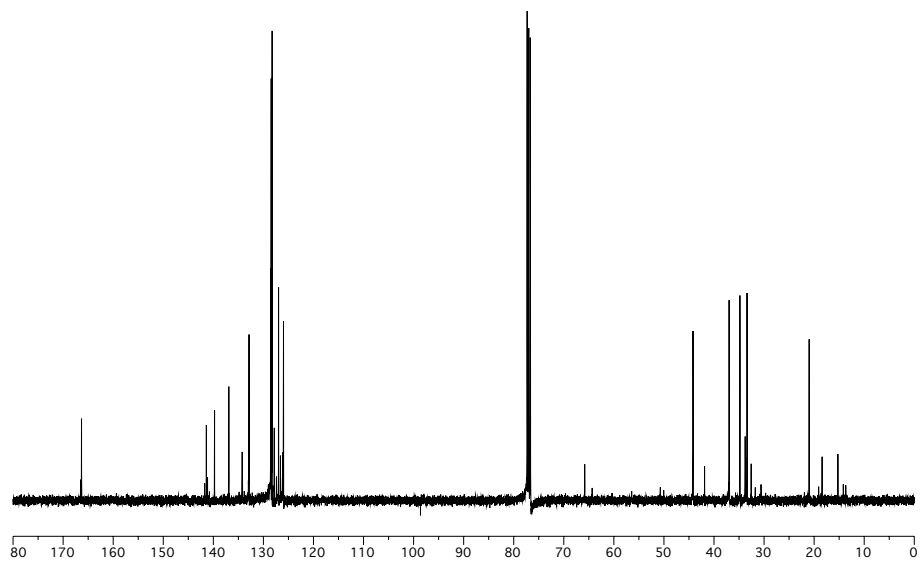
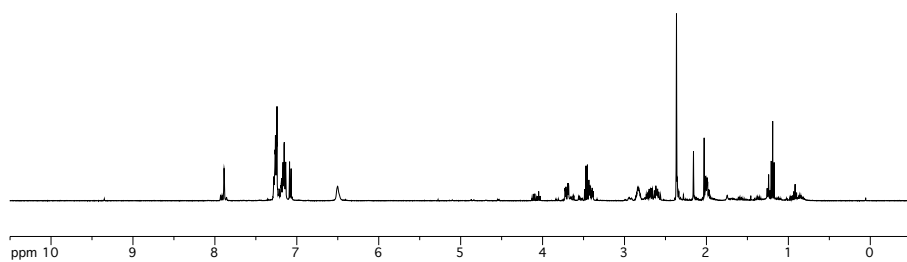
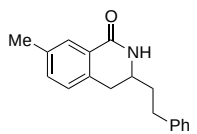


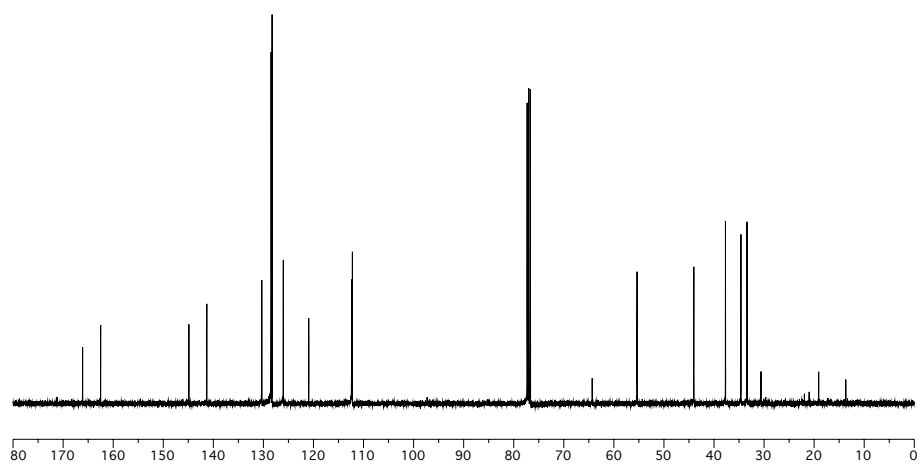
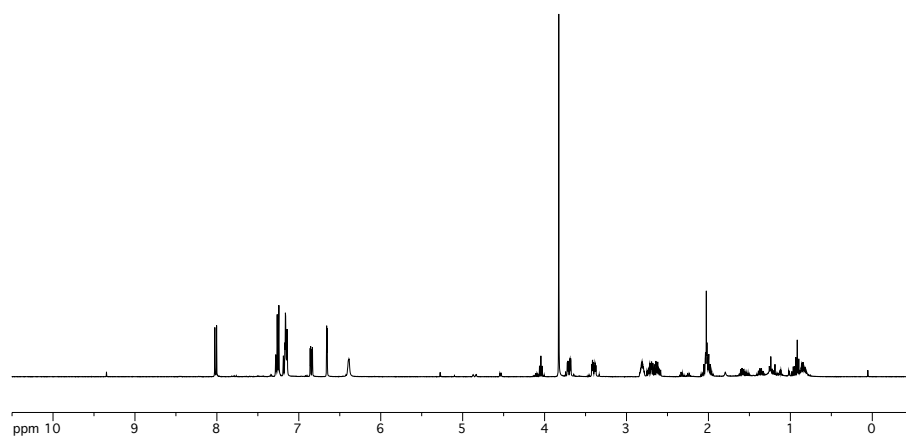
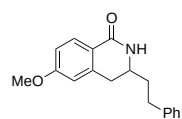












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Appendix 3

Oximes as Coupling Partners for the Synthesis of Pyridines and Isoquinolines

General Methods

All reactions were carried out in 1.5 dram sealed vials under an atmosphere of air with magnetic stirring in an aluminum-heating block without drying or degassing of the vial. ACS grade 2,2,2-trifluoroethanol was purchased from Sigma Aldrich Chemical Company and used without further purification. Column chromatography was performed on SiliCycle® Silica Flash® 40-63µm 60A. Thin Layer chromatography was performed on SiliCycle® 250 µm 60A plates. Visualization was accomplished with UV light (254 nm), KMnO₄, and CAM.

¹H NMR and ¹³C NMR spectra were recorded on a Varian 300 and 400 MHz spectrometers at ambient temperature. ¹H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (Hz). ¹³C NMR are reported as the following: chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec. Infrared spectra (IR) were obtained on Bruker Tensor 27 FT-IR spectrometer. Regiomer ratios were determined by GC/MS, with absolute regiochemistry determined by NOESY, analogy to complementary substrates, or previously reported ¹H NMR.

Catalyst Synthesis

[RhCp^ΨCl]₂ was prepared from the following procedure.

Freshly cracked cyclopentadiene (1 equiv) was added to a 23 °C solution of KOH (50% aqueous) (40 equiv KOH), 3-bromo-3-methyl-propane (5 equiv), and Adogen 464 (1 gram/mol of KOH). The solution was stirred and heated to 60 °C for 2 hours then warmed 100 °C. After 2 addition hours more 3-bromo-3-methyl-propane (5 equiv) was added and allowed to stir. After 2 hours the solution was cooled to 23 °C, washed with pentane (3 x 50 ml), dried over MgSO₄, and concentrated *in vacuo*. The crude product was

purified via column chromatography followed by vacuum distilled to provide the 1,3-di-*tert*-amyl-cyclopentadiene in low yield (5-10%).

1,3-di-*tert*-amyl-cyclopentadiene added to a stirring solution of EtOH and RhCl₃•H₂O and heated to 80 °C for 96 hours. Upon cooling to -20 °C, the heterogenous solution was filtered and washed with Et₂O to furnish the desired product in low yield (5-10%).

[RhCp⁰Cl₂]₂ was prepared from the following procedure:

The cyclopentadiene ligand was prepared as described by Taki and coworkers.¹

1,2-di-phenyl-3,4,5-trimethyl-cyclopentadiene added to a stirring solution of EtOH and RhCl₃•H₂O and heated to 80 °C for 48 hours. Upon cooling to -20 °C, the heterogenous solution was filtered and washed with Et₂O to furnish the desired product (45%).

Alkyne Synthesis

Alkynes **27**, **50**, **70**, **137**, **140**, **141**, **239**, **397** were purchased from Sigma Aldrich Company and used without further purification. Alkyne **138** was prepared by a typical TBS-protection of the corresponding alcohol, which was purchased from Aldrich Chemical Company. **378**,² **381**,³ **388**,⁴ **394**⁴ were prepared via literature procedure.

General Procedure for Synthesis of Oximes

All oximes were generated from the corresponding ketone or aldehyde. A 50 ml flask was charged with a stirbar, ketone or aldehyde (1 equiv), NH₂OH•HCl (1.2 equiv), NaOAc (1.2 equiv), and ethanol (.4 M). The flask was placed into an 80 °C oil bath and stirred until the reaction was complete as determined by TLC. The flask was removed from the oil bath and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in CH₂Cl₂ and H₂O (4:1). The mixture was extracted with CH₂Cl₂ trice, washed with Na₂CO₃ twice. The organic layer was washed with brine, dried over

MgSO₄, and concentrated *in vacuo*. The residue was purified via silica gel column chromatography (2:1 Hex/EtOAc) to yield pure oxime as a mixture of isomers.

α,β Unsaturated Oxime Characterization

(*E*)-1-(cyclohex-1-en-1-yl)ethanone oxime (336): ¹H NMR (300 MHz, CDCl₃) δ 6.20 (m, 1H), 2.27-2.23 (comp m, 2H), 2.19-2.16 (comp m, 2H), 2.02 (s, 3H), 1.66-1.58 (comp m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 134.2, 130.2, 25.9, 24.3, 22.3, 21.9, 9.8.

(3*E*,4*E*)-hex-4-en-3-one oxime (346): Isolated as a 1:1 mixture of isomers. ¹H NMR (400 MHz, CDCl₃) δ 6.08 (dd, *J* = 6.1, 1.4 Hz, 1H), 6.03 (d, *J* = 1.3 Hz, 1H), 2.54-2.46 (m, 2H), 2.42-2.34 (m, 2H), 1.91-1.88 (m, 3H), 1.87-1.81 (m, 5H), 1.13-1.02 (m, 7H); ¹³C NMR (100 MHz, CDCl₃) δ 132.0, 128.1, 124.7, 21.6, 19.2, 16.3, 15.8, 14.9, 8.4.

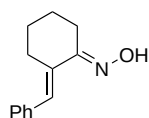
(*E*)-3-methylbut-3-en-2-one oxime (349): ¹H NMR (400 MHz, CDCl₃) δ 5.41 (t, *J* = 0.7 Hz, 1H), 5.31 (t, *J* = 1.2 Hz, 1H), 2.11 (s, 3H), 1.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 140.8, 117.5, 19.2, 10.1.

(2*E*,3*E*)-non-3-en-2-one oxime (352): ¹H NMR (400 MHz, CDCl₃) δ 6.07 (d, *J* = 0.8 Hz, 2H), 2.14 (q, *J* = 6.7 Hz, 2H), 1.97 (s, 3H), 1.41 (dt, *J* = 14.5, 7.2 Hz, 2H), 1.28-1.27 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.1, 134.2, 124.5, 116.5, 30.2, 28.80, 28.75, 26.0, 19.9, 11.4, 7.0.

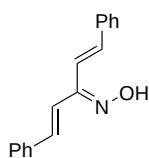
(2*E*,4*E*)-4-(hydroxyimino)-*N,N*-dimethylpent-2-enamide (355): ¹H NMR (300 MHz, MeOH) δ 7.17 (dd, *J* = 15.7, 1.0 Hz, 1H), 6.82-6.77 (m, 1H), 3.18 (s, 3H), 3.02 (s, 3H), 2.02 (s, 3H).

(2*E*,4*E*)-1,1,1-trifluorooct-2-en-4-one oxime (358): Isolated as a 2.3:1 mixture of oximes isomers. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (dd, *J* = 16.6, 2.1 Hz, 1H minor), 6.76 (dd, *J* = 16.3, 2.0 Hz, 1H, major), 6.13 (dd, *J* = 16.6, 6.3 Hz, 1H, minor), 6.04 (dt, *J* = 17.8, 9.7 Hz,

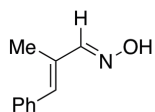
1H, major), 2.53 (t, $J = 7.8$ Hz, 2H, major), 2.41 (t, $J = 7.7$ Hz, 2H, minor), 1.58-1.47 (m, 2H, major and minor), 1.39 (dt, $J = 14.7, 7.2$ Hz, 2H, major and minor), 0.94 (td, $J = 7.3, 3.5$ Hz, 3H, major and minor); ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 153.4, 134.41(q, major), 127.05, 126.87, 126.80, 124.94 (q, minor), 124.38, 124.24, 123.1, 122.8, 122.44, 122.40, 121.70, 121.55, 120.7, 120.3, 120.0, 119.6, 40.4, 39.1, 30.4, 28.9, 28.1, 23.9, 22.8, 22.3, 13.65, 13.60



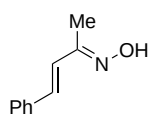
(1E,2E)-2-benzylidenecyclohexanone oxime (361): ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.32 (m, 5H), 6.93 (s, 1H), 2.71-2.66 (m, 4H), 1.76-1.64 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 127.1, 125.5, 124.6, 26.4, 22.39, 22.28, 20.7.



(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one oxime (364): ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.54 (m, 2H), 7.52-7.50 (m, 2H), 7.41-7.32 (m, 8H), 7.13 (d, $J = 17.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 137.8, 136.3, 136.1, 135.4, 129.1, 128.76, 128.72, 128.63, 128.57, 127.36, 127.22, 127.0, 121.9, 116.7.



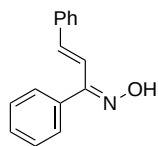
(1E,2E)-2-methyl-3-phenylacrylaldehyde oxime (367): ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, br, 1H), 7.84 (s, 1H), 7.27 (m, 5H), 6.62 (s, 1H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.1, 136.7, 136.2, 131.7, 129.2, 128.3, 127.6, 13.0.



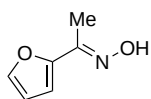
(2E,3E)-4-phenylbut-3-en-2-one oxime (369): ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.45 (m, 2H), 7.34 (dd, $J = 8.0, 6.6$ Hz, 3H), 6.87 (d, $J = 7.2$ Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 136.3, 133.4, 128.4, 127.5, 126.8, 125.7, 9.7.

Aryl Oxime Characterization

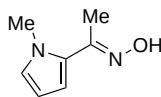
Aryl oximes **400**,⁵ **401**,⁵ **403**,⁶ **404**,⁶ **405**,⁷ **406**,⁵ **407**,⁸ **408**⁹ were prepared according to literature procedures.



(1E,2E)-chalcone oxime (402): Prepared using the general procedure. ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, J = 16.6 Hz, 1H), 7.46-7.34 (m, 5H), 7.31-7.21 (m, 3H), 6.74 (d, J = 16.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 139.7, 136.1, 134.7, 129.21, 129.17, 128.70, 128.68, 128.56, 128.42, 128.38, 128.33, 128.30, 127.5, 117.0



(E)-1-(furan-2-yl)ethanone oxime (407): Prepared using the general procedure. ^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, J = 1.8, 0.7 Hz, 1H), 6.64 (dd, J = 3.4, 0.7 Hz, 1H), 6.44 (dd, J = 3.4, 1.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.1, 147.4, 143.6, 111.2, 110.0, 11.1.

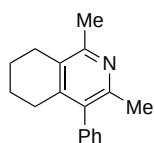


(E)-1-(1-methyl-1H-pyrrol-2-yl)ethanone oxime (408): Prepared using the general procedure. ^1H NMR (400 MHz, CDCl_3) δ 6.65 (t, J = 2.2 Hz, 1H), 6.44 (dd, J = 3.8, 1.8 Hz, 1H), 6.11 (dd, J = 3.8, 2.6 Hz, 1H), 3.80 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.2, 128.5, 126.9, 112.5, 107.3, 37.9, 12.9.

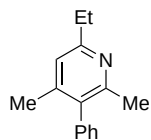
General Procedure for Pyridine and Isoquinoline Synthesis

A 1.5 dram vial was charged with a stirbar, free oxime (1 equiv), $[\text{RhCp}^*\text{Cl}_2]_2$ or $[\text{RhCp}^t\text{Cl}_2]_2$ (2.5 mol %), and K_2CO_3 (2 equiv). TFE was added followed by alkyne (1.1 equiv). The reaction was sealed, warmed to 45 °C, and stirred until the reaction was complete as determined by TLC. Once complete the reaction was allowed to cool to room temperature and transferred to a 25 ml round bottom flask with excess CH_2Cl_2 . Residual solvent was removed and the residue was purified via silica gel column chromatography.

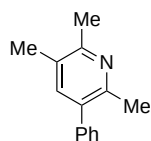
1,3-dimethyl-4-phenyl-5,6,7,8-tetrahydroisoquinoline (345): This compound was previously characterized by Cheng and co-workers.¹⁰ ^1H NMR is provided. (Cp^* 2:1, 87%; Cp^t 1:4, 82%).



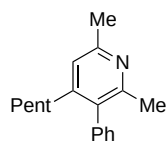
^1H NMR (400 MHz, CDCl_3) δ 7.42-7.40 (m, 2H), 7.38-7.31 (m, 1H), 7.11 (dd, J = 8.2, 1.3 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.47 (s, 3H), 2.29 (t, J = 6.3 Hz, 2H), 2.19 (s, 3H), 1.78 (ddd, J = 6.6, 5.5, 5.3 Hz, 2H), 1.66-1.62 (m, 2H).



6-ethyl-3,4-dimethyl-2-phenylpyridine (348): A 1.5 dram vial was charged with a stirbar, free oxime (1 equiv), $[\text{RhCp}^*\text{Cl}_2]_2$ or $[\text{RhCp}^t\text{Cl}_2]_2$ (.025 mol %), and K_2CO_3 (2 equiv). TFE was added followed by alkyne (1.1 equiv). The reaction was sealed, warmed to 80 °C, and stirred until the reaction was complete as determined by TLC. Once complete the reaction was allowed to cool to room temperature and transferred to a 25 ml round bottom flask with excess CH_2Cl_2 . Residual solvent was removed and the residue was purified via silica gel column chromatography. Regioselectivity confirmed by analogy. (Cp^* 1:1, 80%; Cp^t =4:1, 83%). R_f = .18 (9:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.48-7.41 (m, 4H, major), 7.39-7.35 (m, 4H, minor), 7.16 (d, J = 1.5 Hz, 1H, major), 7.16-7.14 (m, 1H, minor), 6.97 (s, 1H, minor), 6.93 (s, 1H, major), 2.81 (q, J = 7.6, 3H, major), 2.80 (q, J = 7.6, 3H, minor) 2.33 (s, 3H, minor), 2.26 (s, 3H, major), 2.18 (s, 3H, minor), 2.02 (s, 3H, major), 1.33 (t, J = 7.6 Hz, 3H, major), 1.32 (t, J = 7.6 Hz, 3H, minor); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 161.2, 159.9, 158.0, 155.2, 146.8, 145.7, 141.5, 139.1, 134.2, 129.14, 129.08, 128.6, 128.0, 127.4, 127.0, 126.7, 121.9, 120.6, 31.03, 30.96, 23.4, 20.27, 20.15, 15.8, 14.27, 14.19. **IR (thin film)** 2969, 1592, 1462, 1071, 761, 702 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 212.1434; found 212.1432.



2,3,5-trimethyl-6-phenylpyridine (351): Prepared using the general procedure and isolated as a viscous orange liquid. (Cp^* 2:1, 87%; Cp^t =1:4, 85%). R_f = .10 (9:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (dd, J = 8.3, 1.4 Hz, 1H, minor), 7.45-7.41 (m, 3H, major), 7.38-7.36 (m, 1H, minor), 7.31 (dt, J = 6.5, 1.6 Hz, 2H, major), 7.28 (s, 1H), 2.54 (s, 3H, major), 2.52 (s, 1H, minor), 2.47 (s, 3H, major), 2.30 (s, 1H, minor), 2.29 (s, 3H, major), 2.27 (s, 1H, minor); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 152.4, 149.3, 137.5, 137.1, 136.1, 131.8, 127.1, 126.47, 126.41, 125.87, 125.68, 125.48, 124.9, 124.5, 20.0, 19.57, 19.48, 16.7, 16.06, 15.95. **IR (thin film)** 2966, 1553, 1431, 1073, 746 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 198.1277; found 198.1280.



2,6-dimethyl-4-pentyl-3-phenylpyridine (354): Prepared using the general procedure

and isolated as a viscous orange liquid. Regiochemistry determined by analogy. (Cp* 1:1.2, 92%; Cp^t = 3.4:1, 93%). R_f = .15 (9:1 Hexanes/EtOAc); ¹H NMR (400 MHz,

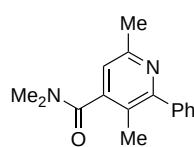
CDCl₃) δ 7.44-7.39 (m, 3H), 7.38-7.33 (m, 2H), 7.15-7.12 (m, 2H), 6.92 (s, 1H), 2.54 (s, 3H), 2.29-2.24

(m, 2H), 2.23 (s, 3H), 1.44-1.35 (m, 6H), 1.20-1.11 (m, 5H), 0.79 (dd, *J* = 8.3, 5.7 Hz, 3H); ¹³C NMR

(100 MHz, CDCl₃) δ 153.3, 152.9, 152.0, 148.5, 147.5, 136.2, 131.1, 126.8, 126.5, 125.8, 125.4, 124.8,

124.5, 119.6, 118.3, 30.7, 30.3, 28.9, 27.3, 21.6, 21.0, 19.9, 19.6, 11.39, 11.22. **IR (thin film)** 2928, 1592,

1458, 1008, 703 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 254.1903; found 254.1907.



N,N,3,6-tetramethyl-2-phenylisonicotinamide (356): According to the general

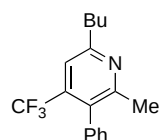
procedure, the desired pyridine was isolated as a yellow oil (Cp* 6.6:1, 72%; Cp^t = 1:1,

74%) ¹H NMR (400 MHz, CDCl₃) δ 7.47-7.45 (m, 5H), 6.98 (s, 1H), 3.16 (s, 3H),

2.92 (s, 3H), 2.59 (s, 3H), 2.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 159.3, 155.8, 146.0, 128.9,

128.2, 128.0, 123.2, 118.4, 38.2, 34.4, 30.0, 24.1, 16.0; **IR (thin film)** 1640, 1442, 1072, 760, 697 cm⁻¹;

HRMS (ESI) *m/e* calcd (M+H) 255.1492; found 255.1493.



6-butyl-2-methyl-3-phenyl-4-(trifluoromethyl)pyridine (3j): According to the general

procedure, the desired pyridine was isolated as a yellow oil (Cp* 10:1, 72%; Cp^t = 1:1,

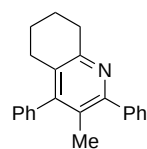
68%); ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.40 (m, 5H), 7.35 (s, 1H), 2.86 (t, *J* = 7.9

Hz, 2H), 2.36 (d, *J* = 1.6 Hz, 3H), 1.73 (dtd, *J* = 9.9, 7.8, 5.6 Hz, 2H), 1.41 (dd, *J* = 15.0, 7.4 Hz, 2H),

0.95 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 160.3, 140.1, 137.6 (q), 129.1, 128.25,

128.15, 125.3, 125.0, 117.22, 117.16, 37.9, 32.0, 22.5, 15.67, 15.64, 13.9; **IR (thin film)** 2961, 1593,

1445, 1251, 764 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 294.1467; found 294.1464.

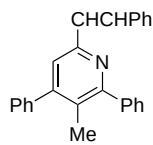


3-methyl-2,4-diphenyl-5,6,7,8-tetrahydroquinoline (362): This compound was previously

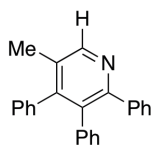
characterized by Cheng and co-workers.⁵ Provided is a ¹H NMR. (Cp* 4:1, 75%; Cp^t = 1:1,

70%). ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.35 (m, 8H), 7.16-7.13 (m, 2H), 3.01 (t, *J* =

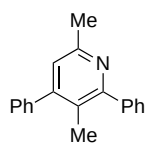
6.4 Hz, 2H), 2.36 (t, J = 6.4 Hz, 2H), 1.91 (s, 3H), 1.89-1.86 (m, 2H), 1.72 (qd, J = 6.1, 2.6 Hz, 2H).



3-methyl-2,4-diphenyl-6-styrylpyridine (365): Prepared using the general procedure and isolated as a viscous orange liquid. Regiochemistry determined by analogy (Cp^* 3.5:1, 77%; Cp^t =1:3.4, 76%). R_f = .15 (9:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.67-7.05 (m, 18H), 2.46 (s, 3H, minor), 2.19 (s, 3H, major). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.6, 152.6, 151.2, 141.3, 140.1, 139.5, 136.87, 136.77, 133.8, 132.1, 130.2, 129.23, 129.18, 128.97, 128.94, 128.83, 128.70, 128.69, 128.63, 128.40, 128.36, 128.22, 128.15, 128.04, 127.98, 127.96, 127.87, 127.84, 127.81, 127.29, 127.09, 127.04, 126.98, 126.91, 120.9, 120.3, 17.9. **IR (thin film)** 2925, 1579, 1449, 1074, 699 cm^{-1} ; **HRMS (ESI)** m/e calcd ($\text{M}+\text{H}$) 348.1747; found 348.1743.

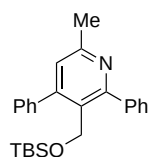


5-methyl-2,3,4-triphenylpyridine (368): A 1.5 dram vial with a stir bar was charged with K_2CO_3 (0.11 mmol, 0.5 equiv), and $[\text{RhCp}^*\text{Cl}_2]_2$ (0.0055 mmol, 2.5 mol %). The 2,2,2 trifluoroethanol (1.5 ml) was added followed by oxime (.24 mmol, 1.1 equiv) and alkyne (.22 mmol, 1 equiv). The vial was sealed and placed into a 80 °C heating block for 24 h. The reaction was concentrated *in vacuo*. The residue was dissolved in 1 ml of dichloromethane and loaded onto a neutral column of silica gel and eluted with a suitable solution of ethyl acetate and hexanes (typically 20:1 EtOAc/Hexanes with 1% Et_3N). Evaporation of solvent afforded the product. (45%); R_f = .60 (9:1 Hexanes/EtOAc w/ 5% Et_3N); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.82 (s, 1H), 7.46 (m, 3H), 7.39-7.35 (m, 6H), 7.17-7.16 (m, 4H), 7.03-7.00 (2H), 2.36 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 155.6, 149.3, 140.7, 138.09, 138.04, 134.6, 131.1, 129.7, 129.1, 127.7, 127.5, 127.2, 126.1, 17.7; **IR (thin film)** 1640, 1442, 1072, 760, 697 cm^{-1} ; **HRMS (ESI)** m/e calcd ($\text{M}+\text{H}$) 322.159; found 322.1597.



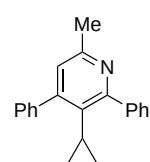
3,6-dimethyl-2,4-diphenylpyridine (370): According to the general procedure, the desired pyridine was isolated as a yellow oil (Cp^* 3.1:1, 91%; Cp^t =1:3.3, 90%). R_f = .25 (9:1 Hexanes/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.54-7.35 (m, 11H, minor), 7.24-7.20 (m, 3H, major), 7.18-7.14 (m, 3H, major), 7.06-7.03 (m, 5H, major), 2.61 (s, 3H, major), 2.60 (s, 3H,

minor), 2.39 (s, 3H, major), 2.14 (s, 3H, minor); ^{13}C NMR (100 MHz, CDCl_3) δ 159.2, 156.25, 156.14, 154.8, 151.0, 149.1, 141.4, 140.1, 139.5, 138.5, 132.3, 130.47, 130.34, 129.21, 129.16, 129.05, 128.93, 128.7, 128.29, 128.21, 128.13, 127.97, 127.92, 127.80, 127.70, 127.68, 127.64, 127.1, 126.7, 125.1, 122.8, 121.7, 24.22, 24.12, 23.9, 17.5. **IR (thin film)** 1586, 1493, 1073, 700 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 260.1434; found 260.1438.



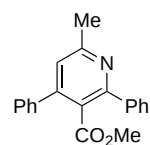
3-(((tert-butyldimethylsilyl)oxy)methyl)-6-methyl-2,4-diphenylpyridine (372):

According to the general procedure, the desired pyridine was isolated as a yellow oil (80%, 2.5:1); R_f = .78 (9:1 Hexanes/EtOAc w/ 5% Et_3N); ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, 1H, $J=8.0$ Hz, $J=2.0$ Hz), 7.72 (m, 2H), 7.65-7.60 (m, 4H), 7.45-7.21 (m, 5H), 4.80 (s, 2H), 4.66 (s, 2H), 4.49 (s, 2H), 2.85 (s, 3H), 2.83 (s, 3H), 2.82 (s, 3H), 1.07 (s, 9H, major), 1.03 (s, 9H, minor), .13 (s, 6H, minor). 0.00 (s, 6H, major); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 162.7, 162.5, 158.3, 146.5, 145.1, 136.6, 135.8, 135.3, 135.1, 134.8, 134.1, 133.87, 133.83, 133.7, 133.5, 133.4, 133.2, 133.0, 132.7, 129.1, 128.6, 71.6, 67.9, 65.4, 31.8, 31.6, 30.2, 30.0, 29.8, 24.0, 0.5, 0.0; **IR (thin film)** 2927, 2360, 1588, 1252, 699 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 390.2248; found 390.2249.



3-cyclopropyl-6-methyl-2,4-diphenylpyridine (374):

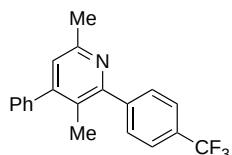
According to the general procedure, the desired pyridine was isolated as a yellow oil 81%, 4.4:1; R_f = .23 (19:1 Hexanes/EtOAc w/ 1% Et_3N); ^1H NMR (400 MHz, CDCl_3) δ 7.93-7.91 (m, 2H), 7.75-7.62 (m, 8H), 7.31 (s, 1H), 2.86 (s, 3H), 2.26-2.22 (m, 1H), 0.65-0.62 (m, 2H), 0.03-0.13 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 1604, 155.1, 152.3, 141.2, 139.9, 129.8, 128.9, 128.4, 127.5, 127.2, 127.0, 122.1, 23.7, 12.8, 9.9, 9.6; **IR (thin film)** 1586, 1493, 1072, 753, 700 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 286.159; found 286.1597.



methyl 6-methyl-2,4-diphenylnicotinate (376):

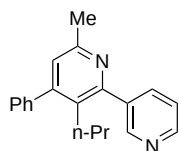
According to the general procedure, the desired pyridine was isolated as a yellow oil (89%, 5:1); R_f = .15 (19:1 Hexanes/EtOAc w/ 1% Et_3N); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (dd, J = 7.8, 1.7 Hz, 2H), 7.37-7.31 (m,

8H), 7.19 (s, 1H), 7.09 (s, 1H), 3.37 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 159.0, 156.4, 148.8, 139.8, 138.3, 128.99, 128.94, 128.84, 128.74, 128.64, 128.61, 128.53, 128.46, 128.34, 128.28, 128.21, 127.84, 127.76, 125.6, 122.32, 122.27, 52.1, 24.6; IR (thin film) 1730, 1587, 1266, 1107, 699 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 303.1259; found 303.1262.



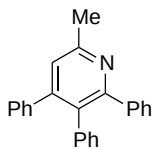
3,6-dimethyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)pyridine (379): According to the general procedure, the desired pyridine was isolated as a yellow oil (85%, 3.5:1); $R_f = .76$ (9:1 Hexanes/EtOAc w/ 5% Et_3N); ^1H NMR (400 MHz, CDCl_3)

δ 7.64-7.56 (m, 3H), 7.39-7.32 (m, 4H), 7.28-7.25 (m, 2H), 6.99 (s, 1H), 2.51 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 155.2, 151.4, 144.92, 144.91, 139.7, 132.6, 130.8, 129.66, 129.51, 129.07, 128.93, 128.67, 128.61, 128.38, 128.21, 127.94, 127.87, 127.84, 127.5, 126.4, 125.6, 125.25, 125.21, 125.17, 125.13, 125.10, 124.99, 124.96, 123.42, 123.32, 121.9, 24.0, 17.3. HRMS (ESI) m/e calcd (M+H) 328.1307 found 328.1308.



6-methyl-4-phenyl-3-propyl-2,3'-bipyridine (382): According to the general procedure, the desired pyridine was isolated as a yellow oil. (66%, 2.5:1); $R_f = .76$ (9:1 Hexanes/EtOAc w/ 5% Et_3N); ^1H NMR (400 MHz, CDCl_3) δ 8.76 (s, 1H), 8.65 (d, $J =$

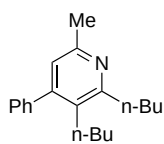
3.8 Hz, 1H), 7.85 (dt, $J = 7.8, 1.8$ Hz, 1H), 7.47-7.39 (m, 4H), 7.32 (dd, $J = 7.9, 1.6$ Hz, 2H), 7.04 (s, 1H), 2.60 (s, 3H), 2.55-2.51 (m, 2H), 1.13-1.07 (m, 2H), 0.50 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.6, 155.7, 155.0, 151.6, 149.4, 148.6, 139.7, 136.7, 131.0, 128.36, 128.31, 127.8, 124.3, 123.2, 30.7, 23.87, 23.67, 13.9; IR (thin film) 1671, 1446, 1103, 749, 701 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 289.1699; found 289.1696.



6-methyl-2,3,4-triphenylpyridine (384): According to the general procedure, the desired pyridine was isolated as a white solid (89%); $R_f = .35$ (19:1 Hexanes/EtOAc w/ 1% Et_3N);

^1H NMR (400 MHz, CDCl_3) δ 7.27-7.25 (m, 3H), 7.21-7.17 (m, 6H), 7.08-7.02 (m, 5H), 6.85 (dd, $J = 7.8, 1.7$ Hz, 2H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 157.7, 156.7, 139.5,

137.7, 131.7, 131.4, 129.86, 129.82, 129.2, 127.8, 127.6, 127.25, 127.18, 126.4, 123.3, 24.2; **IR (thin film)** 1671, 1446, 1103, 749, 701 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 322.159; found 322.159.



2,3-dibutyl-6-methyl-4-phenylpyridine (385): According to the general procedure, the

desired pyridine was isolated as a yellow oil. (65%); $R_f = .76$ (9:1 Hexanes/EtOAc w/ 5%

Et_3N); **^1H NMR** (400 MHz, CDCl_3) 7.34-7.28 (m, 3H), 7.18-7.16 (m, 2H), 6.72 (s, 1H),

2.76-2.72 (m, 2H), 2.42 (s, 3H), 2.42 (q, $J = 2.7$ Hz, 5H), 1.66-1.60 (m, 2H), 1.39 (dd, $J = 15.0, 7.4$ Hz,

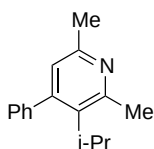
2H), 1.24 (ddd, $J = 13.7, 6.7, 3.5$ Hz, 3H), 1.12-1.07 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.66 (q, $J = 6.7$ Hz,

3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 160.4, 154.1, 150.5, 140.5, 130.0, 128.9, 128.43, 128.39, 128.21,

128.15, 128.02, 127.6, 127.3, 123.2, 122.1, 41.5, 35.2, 33.1, 32.80, 32.66, 28.0, 26.7, 23.9, 23.1, 22.8,

19.1, 14.02, 13.97, 13.53, 13.44; **IR (thin film)** 1671, 1446, 1103, 749, 701 cm^{-1} ; **HRMS (ESI)** m/e calcd

(M+H) 282.2210 found 282.2216.



2-isopropyl-3,6-dimethyl-4-phenylpyridine (386): According to the general procedure,

the desired pyridine was isolated as an off white solid (73%, 10.8:1); $R_f = .70$ (9:1

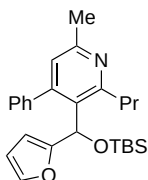
Hexanes/EtOAc w/ 5% Et_3N); **^1H NMR** (400 MHz, CDCl_3) δ 7.30 (m, 3H), 7.13 (dd, 2H,

$J=8.0$ Hz, $J=2.0$ Hz), 6.69 (s, 1H), 3.11 (septet, 1H, $J=7.6$ Hz), 2.60 (s, 3H), 2.41 (s, 3H), 1.12 (d, 6H,

$J=7.2$ Hz); **^{13}C NMR** (100 MHz, CDCl_3) δ 156.3, 153.5, 150.5, 141.3, 135.2, 128.3, 127.9, 127.2, 122.5,

28.7, 24.3, 23.7, 21.4; **IR (thin film)** 2959, 1587, 1444, 1073, 777 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H)

226.159; found 226.1591.



2-(((tert-butyldimethylsilyl)oxy)(furan-2-yl)methyl)-6-methyl-4-phenyl-3-

propylpyridine (388): According to the general procedure, the desired pyridine was

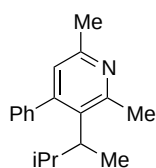
isolated as a yellow oil (71%, 9:1); $R_f = .4$ (9:1 Hexanes/EtOAc); Regiochemistry

assigned via analogy; **^1H NMR** (400 MHz, CDCl_3) δ 7.79-7.75 (m, 5H), 7.66 (s, 1H),

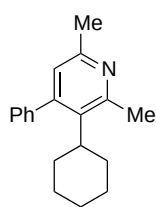
6.75 (dd, $J = 3.2, 1.8$ Hz, 1H), 6.59 (d, $J = 3.2$ Hz, 1H), 6.36 (s, 1H), 3.38-3.17 (m, 2H), 2.94 (s, 3H), 1.98

(s, 2H), 1.24 (t, $J = 7.3$ Hz, 3H), 1.19 (s, 7H), 0.10 (d, $J = 35.8$ Hz, 5H); **^{13}C NMR** (100 MHz, CDCl_3) δ

168.6, 162.5, 161.6, 147.0, 145.0, 134.6, 133.58, 133.55, 133.3, 126.9, 115.8, 111.8, 103.93, 103.92, 72.6, 43.3, 31.31, 31.16, 29.7, 28.8, 23.5, 19.9, 0.6; **IR (thin film)** 2959, 1587, 1444, 1073, 777 cm^{-1} ; **HRMS (ESI)** m/e calcd (M+H) 422.2504; found 422.251.

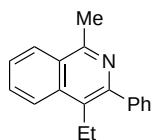


2,6-dimethyl-3-(3-methylbutan-2-yl)-4-phenylpyridine (392): According to the general procedure, the desired pyridine was isolated as a yellow oil (95%, 11:1); $R_f = .4$ (9:1 Hexanes/EtOAc); Regiochemistry assigned via analogy; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.41 (m, 3H), 7.23 (m, 2H), 6.81 (s, 1H), 3.05 (m, 1H), 2.68 (s, 3H), 2.52 (s, 3H), 1.4-1.3 (m, 5H), 0.90 (m, 3H), 0.76 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.5, 153.6, 141.4, 134.4, 128.75, 128.70, 128.5, 128.16, 127.98, 127.40, 127.27, 122.5, 37.8, 34.1, 29.7, 24.5, 23.8, 21.4, 20.0, 14.1.

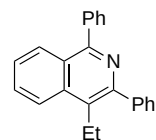


3-cyclohexyl-2,6-dimethyl-4-phenylpyridine (395): According to the general procedure, the desired pyridine was isolated as a yellow oil (89%, 12:1); $R_f = .4$ (9:1 Hexanes/EtOAc); Regiochemistry assigned via analogy; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42 (m, 3H), 7.23 (m, 2H), 6.81 (s, 1H), 2.84-2.80 (m, 1H), 2.75 (s, 3H), 2.53 (s, 3H), 1.81-1.65 (m, 8H), 1.13 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.4, 153.6, 150.9, 141.5, 134.5, 128.4, 128.2, 127.9, 127.3, 122.8, 40.8, 31.9, 31.3, 27.2, 26.9, 26.0, 24.86, 24.72, 23.8.

Characterization of Isoquinolones

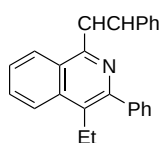


4-ethyl-1-methyl-3-phenylisoquinoline (409): According to the general procedure with the addition of 2 equiv. of $\text{CF}_3\text{CO}_3\text{CH}_2\text{CF}_3$, the desired pyridine was isolated as an off white solid (94%, >10:1 rr). Cheng and coworkers previously prepared this compound.¹⁰ Included is the $^1\text{H NMR}$.



4-ethyl-1,3-diphenylisoquinoline (411): According to the general procedure, the desired pyridine was isolated as a yellow solid (86%, >15:1 rr). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.19-8.15 (m, 2H), 7.78-7.72 (m, 3H), 7.62 (dt, $J = 8.1, 1.6$ Hz, 2H), 7.58-7.46 (m, 6H), 7.45-7.40 (m, 1H), 3.13 (q, $J = 7.5$ Hz, 2H), 1.37 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ

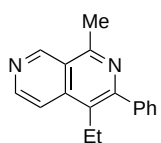
158.2, 151.1, 141.8, 139.9, 136.0, 130.29, 130.17, 130.07, 129.88, 129.4, 128.50, 128.41, 128.32, 128.26, 128.20, 128.15, 128.07, 127.4, 126.2, 125.9, 123.9, 21.9, 15.7 ; **HRMS (ESI)** *m/e* calcd 309.1517 (M⁺) ; found 309.1522.



4-ethyl-3-phenyl-1-styrylisoquinoline (413): According to the general procedure, the

desired pyridine was isolated as a yellow solid (87%, >10:1 rr). **¹H NMR** (400 MHz, CDCl₃) δ 8.45 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 15.6 Hz, 1H),

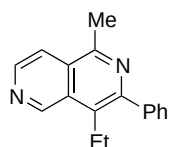
7.95 (d, *J* = 15.6 Hz, 1H), 7.75 (ddd, *J* = 9.4, 6.0, 1.5 Hz, 1H), 7.69-7.61 (m, 5H), 7.54-7.37 (m, 5H), 7.34-7.29 (m, 2H), 3.08 (q, *J* = 7.5 Hz, 2H), 1.31 (dd, *J* = 9.6, 5.4 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 152.0, 151.3, 142.0, 137.2, 135.9, 135.6, 129.67, 129.55, 129.46, 129.38, 128.61, 128.42, 128.23, 128.01, 127.96, 127.45, 127.39, 127.32, 126.3, 125.9, 125.1, 124.2, 123.2, 21.9, 15.7; **HRMS (ESI)** *m/e* calcd 335.1674 (M⁺); found 335.1681.



6-ethyl-3-methyl-5-phenyl-1,4-naphthyridine (415): According to the general

procedure, the desired pyridine was isolated as an off white solid (73%, 10:1); **R_f** = .3 (19:1 Hexanes/EtOAc w/ 1% Et₃N); **¹H NMR** (400 MHz, CDCl₃) δ 8.77 (d, *J* = 5.0 Hz,

1H), 7.83 (d, *J* = 5.8 Hz, 1H), 7.51-7.41 (m, 5H), 3.05 (s, 3H), 2.96 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.1, 154.5, 151.5, 146.6, 140.8, 138.7, 133.4, 128.9, 128.3, 128.0, 127.7, 116.84, 116.81, 21.7, 21.2, 15.5, 11.6; **IR (thin film)** 1570, 1441, 1385, 720, 701 cm⁻¹; **HRMS (ESI)** *m/e* calcd (M+H) 249.1386; found 249.1392.

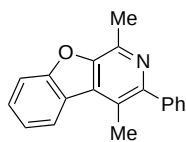


7-ethyl-4-methyl-6-phenyl-1,5-naphthyridine (417): According to the general

procedure, the desired pyridine was isolated as an off white solid (86%, 10:1); **R_f** = .3 (19:1 Hexanes/EtOAc w/ 1% Et₃N); **¹H NMR** (400 MHz, CDCl₃) δ 9.59 (s, 1H), 8.72 (d,

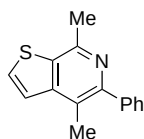
1H, *J*=6.0 Hz), 7.89 (dd, 1H, *J*=6.0 Hz, *J*=0.8 Hz), 7.52-7.42 (m, 5H), 3.10 (q, 2H, *J*=7.6 Hz), 2.96 (s, 3H), 1.32 (t, 3H, *J*=7.6 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ 155.6, 152.3, 149.8, 143.7, 140.7, 129.1,

128.2, 127.8, 117.9, 21.8, 20.9, 16.3; **IR (thin film)** 2959, 1587, 1444, 1073, 777 cm^{-1} ; **HRMS (ESI)** m/e calcd ($\text{M}+\text{H}_3$) 251.1543; found 251.1544.



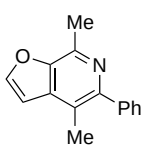
1,4-dimethyl-3-phenylbenzofuro[2,3-c]pyridine (419): According to the general procedure, the desired pyridine was isolated as a yellow solid (Cp^* 2.1:1 92% / Cp^t 1:9.2 90%). **^1H NMR** (400 MHz, CDCl_3) δ 7.59-7.51 (m, 4H), 7.49-7.44 (m, 1H),

7.40 (dt, $J = 6.2, 1.7$ Hz, 2H), 7.08 (td, $J = 7.6, 0.9$ Hz, 1H), 6.95 (ddd, $J = 7.9, 1.3, 0.6$ Hz, 1H), 2.86 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 156.8, 151.9, 149.5, 148.4, 140.9, 139.9, 137.4, 129.7, 129.35, 129.25, 128.99, 128.96, 128.94, 128.88, 128.81, 128.64, 128.32, 128.14, 127.9, 127.5, 123.8, 123.5, 123.17, 123.10, 123.02, 122.86, 122.70, 112.3, 112.0, 22.1, 18.6, 16.7. **HRMS (ESI)** m/e calcd 274.1226 ($\text{M}+\text{H}$); found 274.1228.



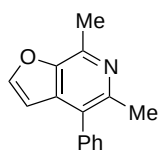
4,7-dimethyl-5-phenylthieno[2,3-c]pyridine (421): According to the general procedure, the desired pyridine was isolated as a yellow solid (Cp^* 10:1 93% / Cp^t 1:2.5 95%). **^1H NMR** (400 MHz, CDCl_3) δ 7.59 (d, $J = 5.4$ Hz, 1H), 7.46-7.44 (m, 2H), 7.38-7.36 (m, 4H),

7.31-7.29 (m, 1H), 2.74 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 152.1, 149.6, 145.9, 140.8, 134.0, 130.9, 129.69, 129.63, 128.5, 128.1, 127.4, 122.8, 122.1, 23.3, 16.6. **HRMS (ESI)** m/e calcd 240.0846 ($\text{M}+\text{H}$); found 240.0841.



4,7-dimethyl-5-phenylfuro[2,3-c]pyridine (423): According to the general procedure, the desired pyridine was isolated as a yellow solid (88%, 2.7:1 rr). **^1H NMR** (400 MHz, CDCl_3) δ 7.73 (d, $J = 2.2$ Hz, 1H), 7.52 (dd, $J = 8.2, 1.3$ Hz, 2H), 7.44 (dd, $J = 8.2, 6.7$ Hz,

2H), 7.38-7.36 (m, 1H), 6.82 (d, $J = 2.2$ Hz, 1H), 2.77 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 150.8, 149.7, 147.5, 147.22, 147.09, 140.9, 140.5, 139.6, 134.4, 129.53, 129.49, 128.4, 128.1, 127.37, 127.28, 127.0, 121.1, 105.9, 105.5, 22.2, 18.48, 18.45, 16.2; **HRMS (ESI)** m/e calcd 224.107 ($\text{M}+\text{H}$) ; found 224.1067.



5,7-dimethyl-4-phenylfuro[2,3-c]pyridine (424): According to the general procedure,

the desired pyridine was isolated as a yellow solid (90%, 2.4:1 rr). **¹H NMR** (400 MHz,

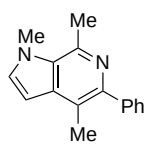
CDCl₃) δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.52-7.43 (m, 2H), 7.42-7.35 (m, 3H), 6.52 (d, *J* = 2.1

Hz, 1H), 2.77 (s, 3H), 2.52 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 150.8, 149.7, 149.2, 147.5, 147.21,

147.09, 140.9, 140.5, 139.6, 137.7, 134.4, 133.9, 129.61, 129.52, 129.49, 129.40, 128.52, 128.43, 128.1,

127.36, 127.27, 126.9, 121.0, 105.9, 105.5, 22.2, 18.5, 16.2; **HRMS (ESI)** *m/e* calcd 224.107 (M+H);

found 224.1067.



1,4,7-trimethyl-5-phenyl-1H-pyrrolo[2,3-c]pyridine (425): According to the general

procedure, the desired pyridine was isolated as a yellow solid (Cp* 98% 4:1 / Cp^t 96%

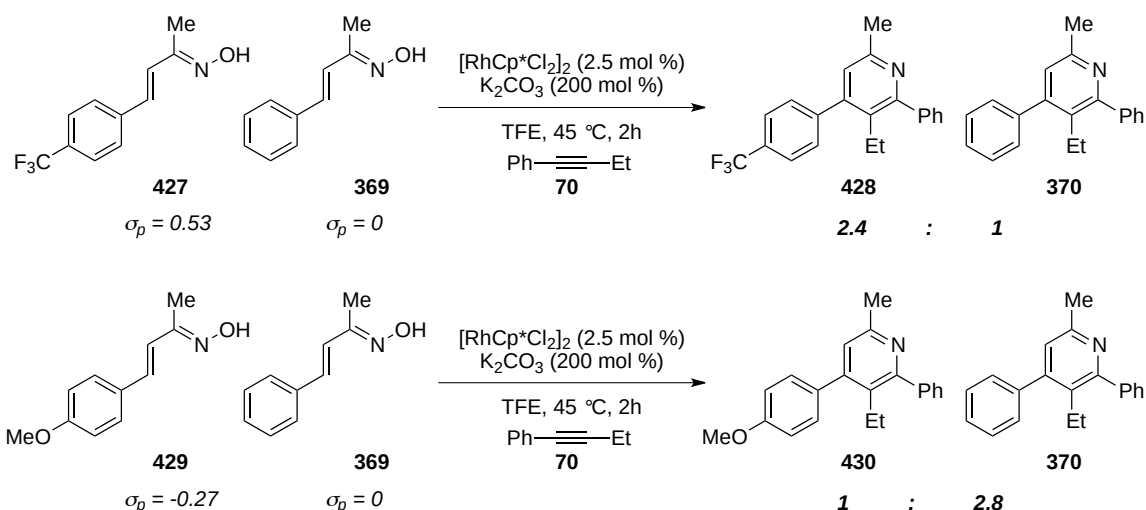
1:2.1). **¹H NMR** (400 MHz, CDCl₃) δ 7.48-7.42 (m, 2H), 7.41-7.35 (m, 3H), 7.01 (d, *J* =

3.0 Hz, 1H), 6.12 (d, *J* = 3.0 Hz, 1H), 4.06 (s, 3H), 2.98 (s, 3H), 2.48 (s, 3H); **¹³C NMR** (100 MHz,

CDCl₃) δ 142.3, 140.5, 138.7, 135.2, 133.6, 133.2, 131.0, 129.8, 128.2, 127.9, 126.90, 126.78, 126.1,

99.8, 99.5, 36.76, 36.74, 22.6, 21.7, 15.6. **HRMS (ESI)** *m/e* calcd 237.1386 (M+H); found 237.1381.

Internal Competition Experiment



A 1.5 dram vial is charged with **427** (0.3 mmol), **369** (0.3 mmol), K_2CO_3 (200 mol %), 1,3,5 trimethoxybenzene (0.3 mmol), and TFE (3 ml). 1-phenyl-1-butyne **70** (0.3 mmol) was added to this

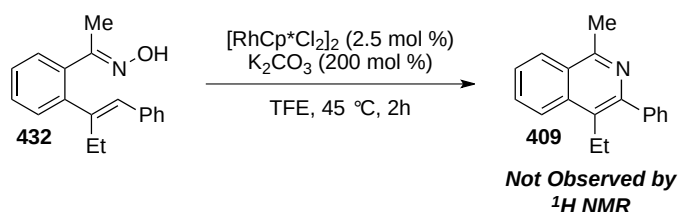
solution and the flask was sealed and placed into 45 °C aluminium heating block. After 2 hours the reaction was allowed to cool, and the reaction was interpreted by GC/MS.

A 1.5 dram vial is charged with **429** (0.3 mmol), **369** (0.3 mmol), K₂CO₃ (200 mol %), 1,3,5 trimethoxybenzene (0.3 mmol), and TFE (3 ml). 1-phenyl-1-butyne **70** (0.3 mmol) was added to this solution and the flask was sealed and placed into 45 °C aluminium heating block. After 2 hours the reaction was allowed to cool, and the reaction was interpreted by GC/MS.

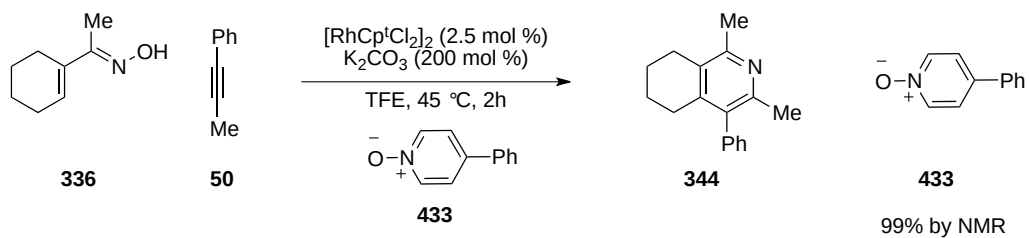
KIE Experiments

A 1.5 dram vial was charged with a stir-bar, (3E)-4-phenylbut-3-en-2-one oxime or D-(3E)-4-phenylbut-3-en-2-one oxime (.22 mmol), K₂CO₃ (.44 mmol), and 1,3,5 trimethoxy-benzene (.22 mmol). The vial was fitted with a septa and charged with 2,2,2-trifluoroethanol (2.2 ml). 1-phenyl-1-butyne (.22 mmol) was added to the reaction solution and the vial was placed into a 45 °C heating block and stirred for 5 min. A separate vial was charged with [RhCp*Cl₂]₂ (2.5 mol %) and .25 ml of 2,2,2-trifluoroethanol to yield a bright yellow solution. This solution was added to the reaction vessel in the heating block. 0.1 ml aliquots were taken every 60 seconds for 4 minutes (after 60, 120, 180, 240 seconds), diluted with ethyl acetate and were interpreted using GC/MS. Aliquots were collected ever 4 min for D-(3E)-4-phenylbut-3-en-2-one oxime

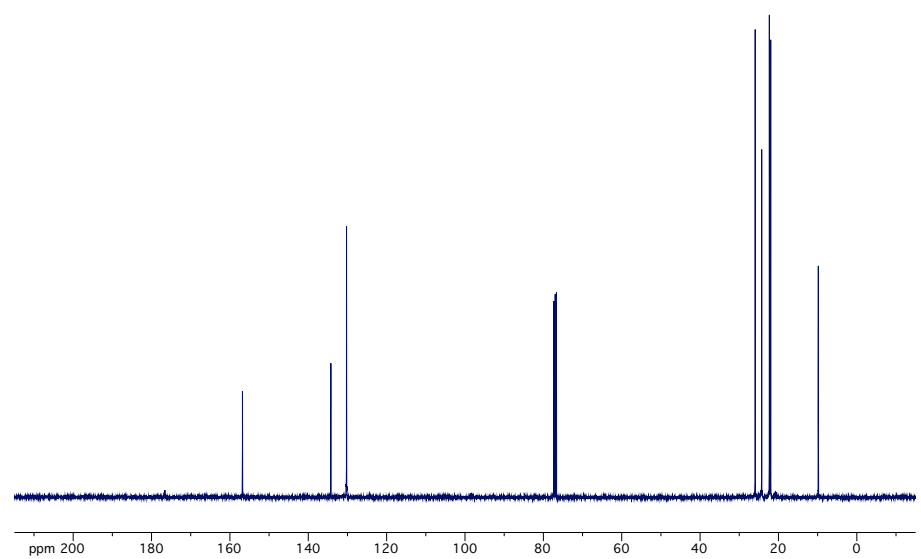
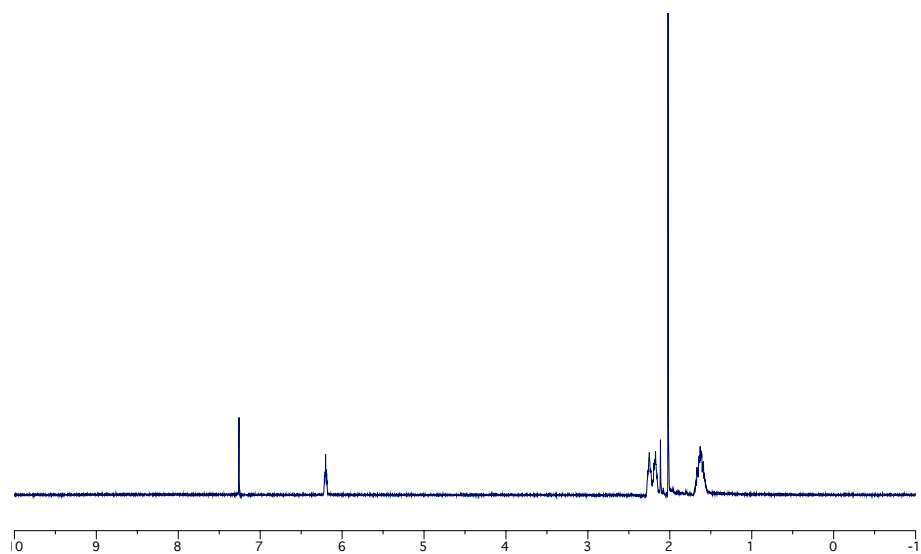
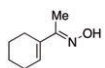
Mechanistic Experiments

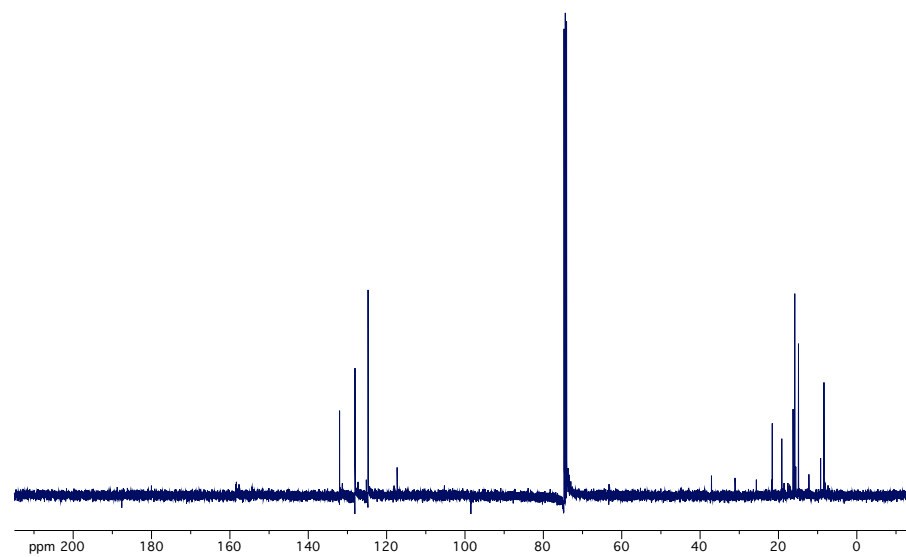
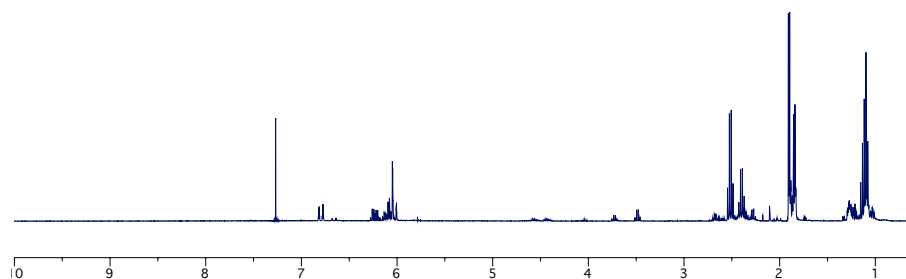
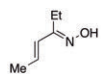


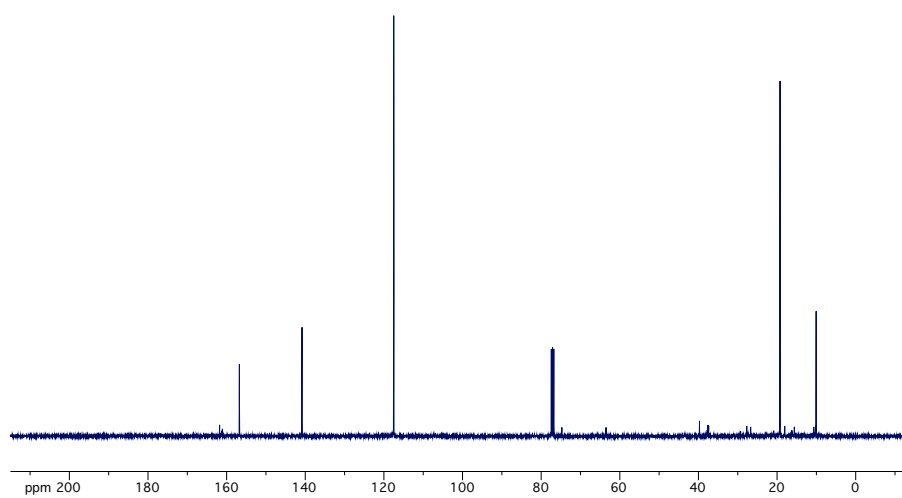
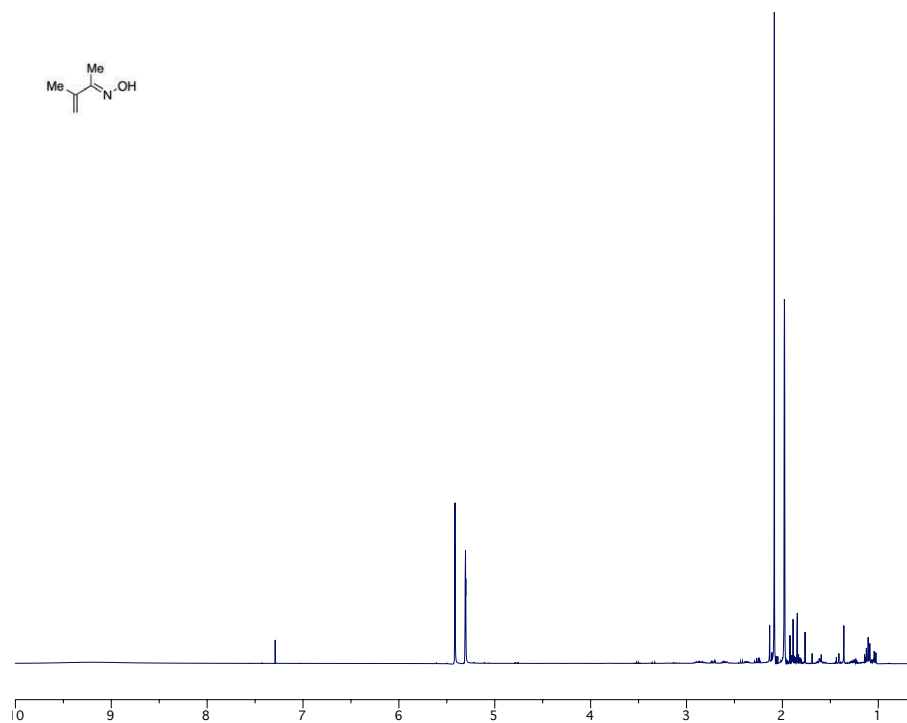
431 was prepared as described by Cheng and coworkers,¹⁰ and submitted to the standard reaction conditions, then concentrated *in vacuo*. None of the desired **409** was observed.

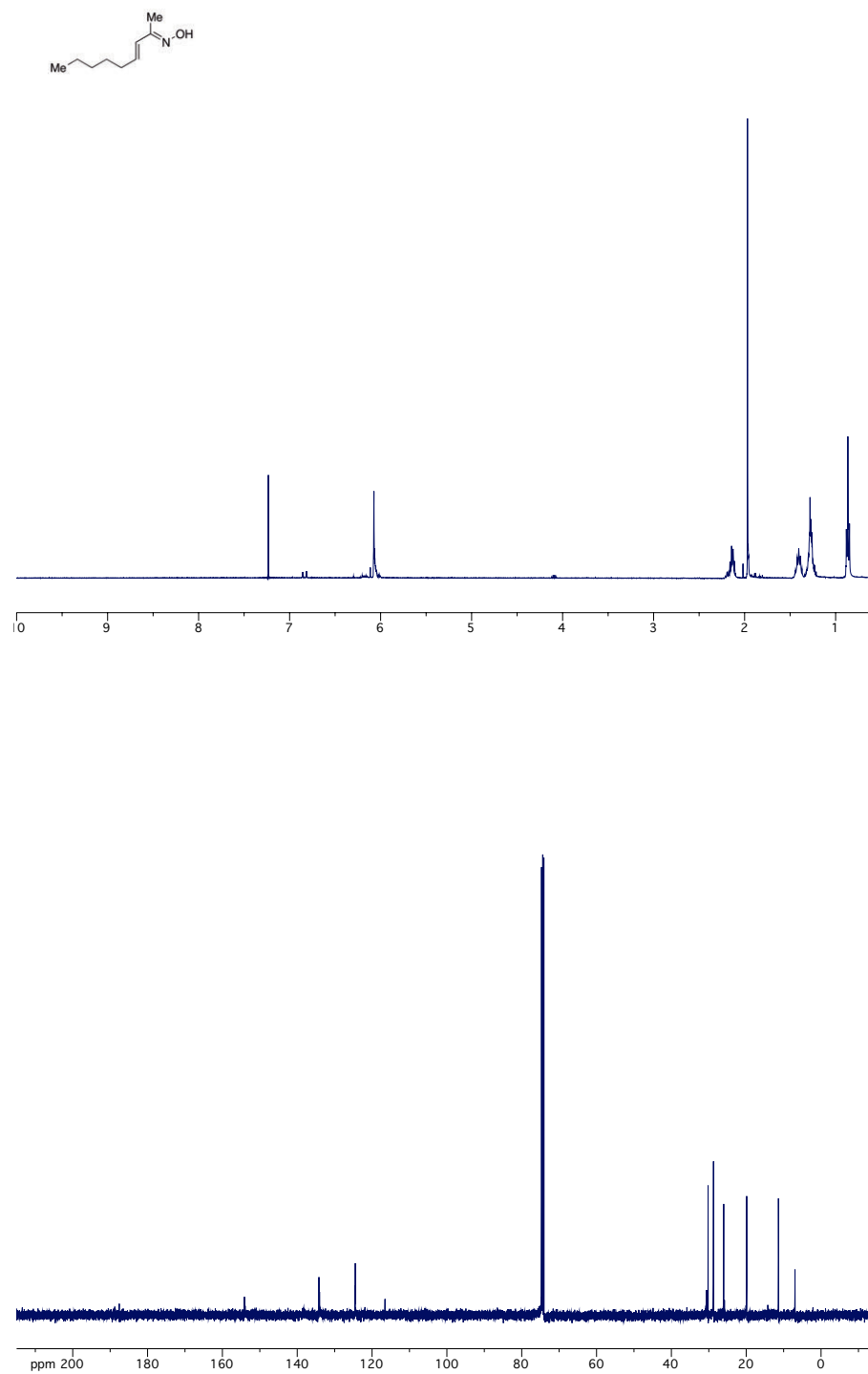


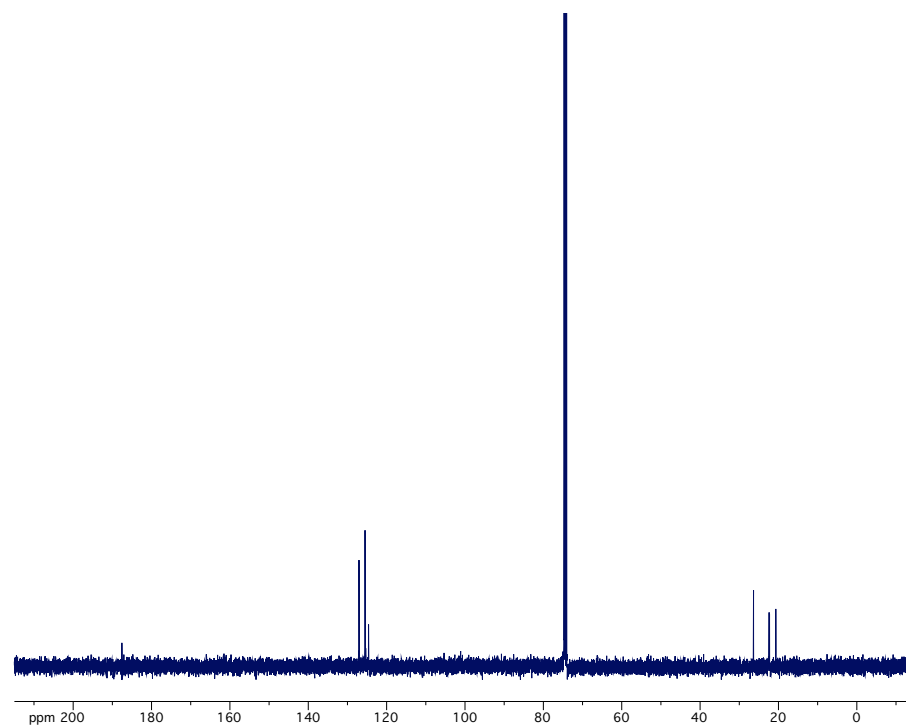
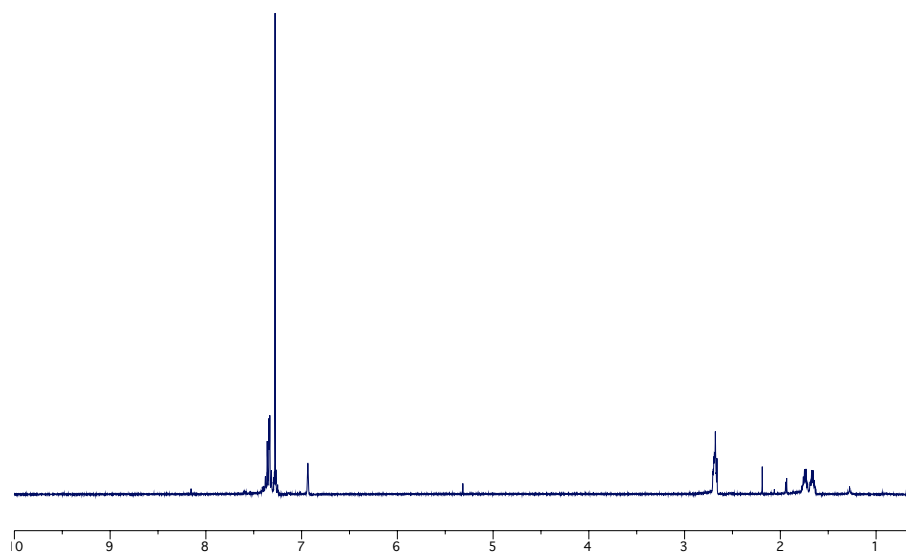
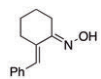
A 1.5 dram vial is charged with **336** (0.3 mmol), K_2CO_3 (200 mol %), 1,3,5 trimethoxybenzene (0.3 mmol), and TFE (3 ml). 1-phenyl-1-butyne (100 mol %), and 4-phenyl pyridine *N*-oxide **433** (0.3 mmol) was added to this solution and the flask was sealed and placed into 45 °C aluminium heating block. After 4 hours the reaction was allowed to cool and was concentrated *in vacuo*. The crude NMR revealed product formation with no reduced pyridine *N*-oxide.

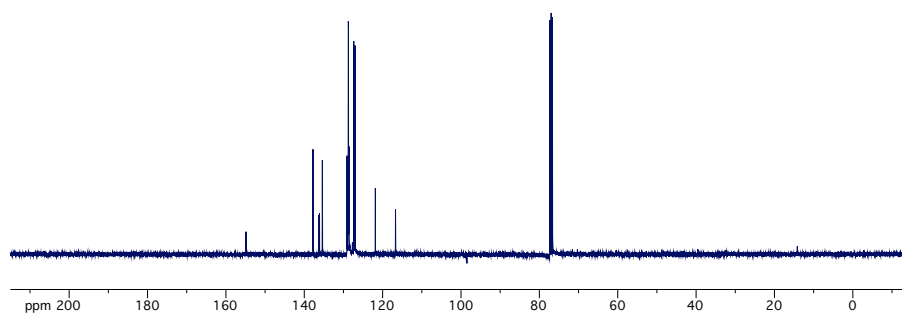
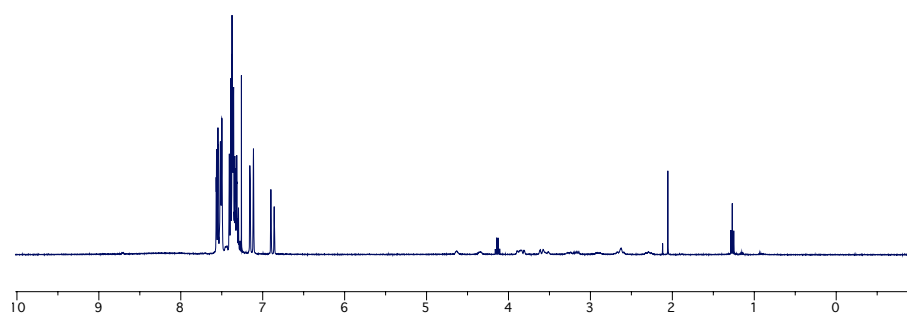
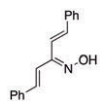


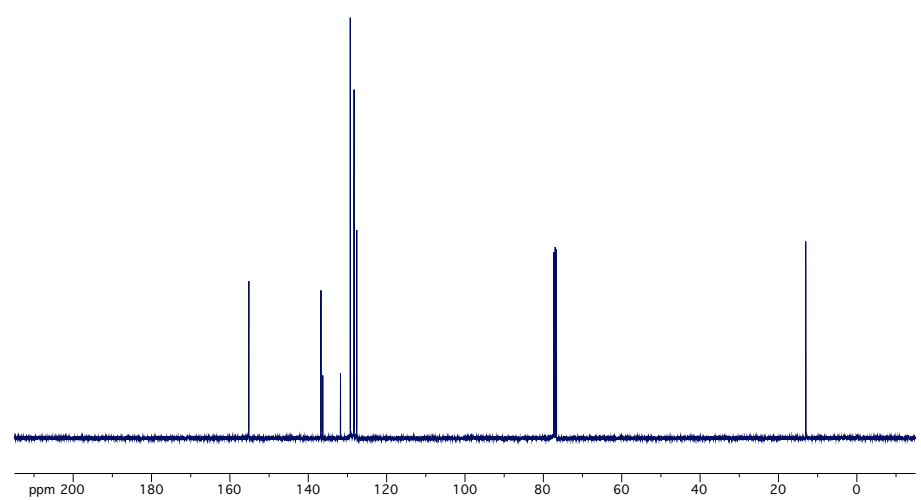
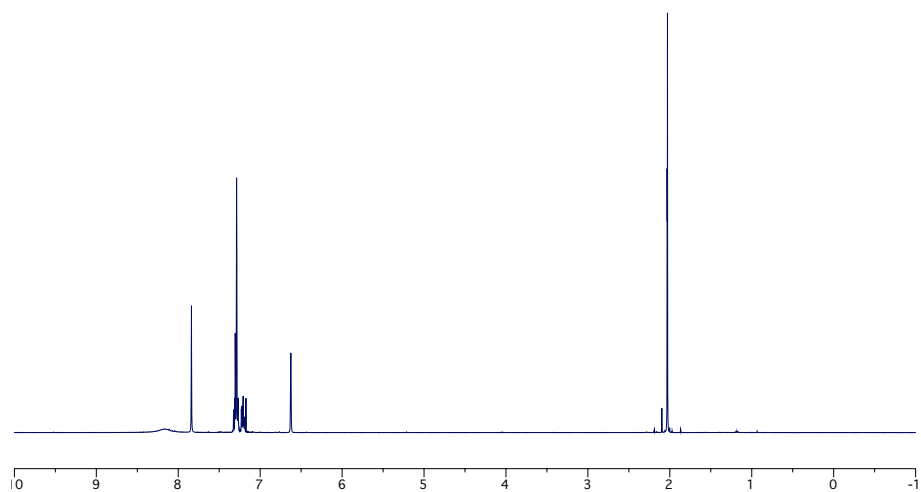
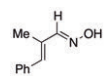


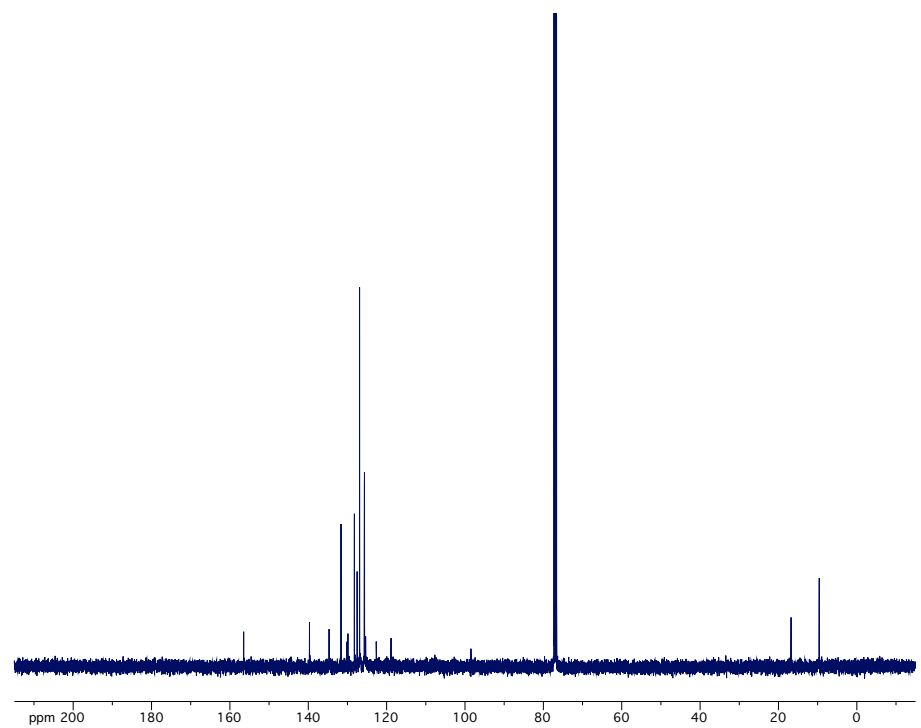
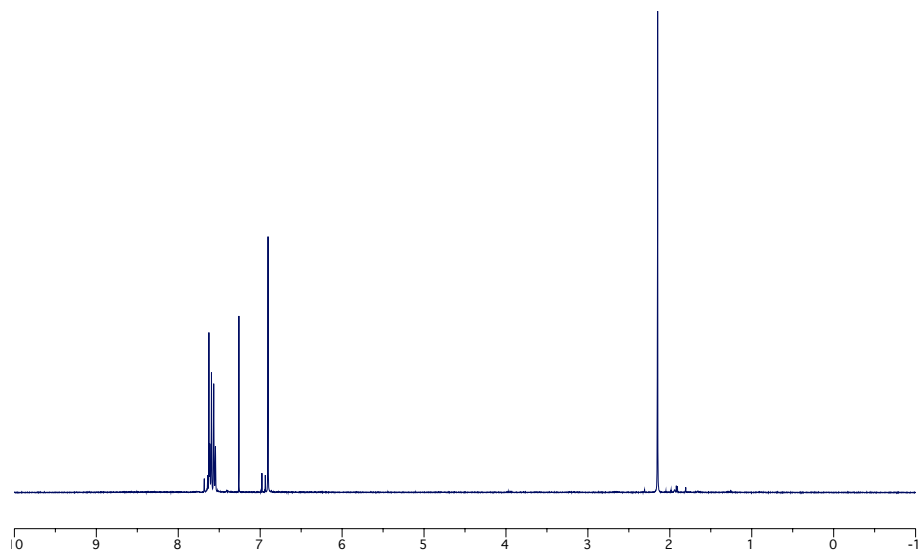
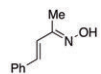


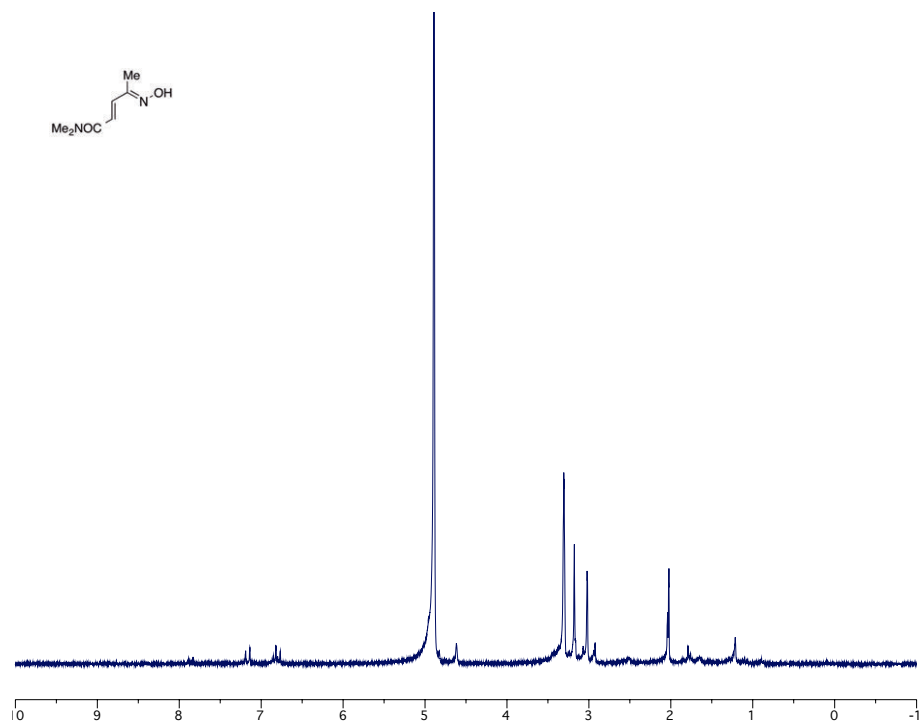


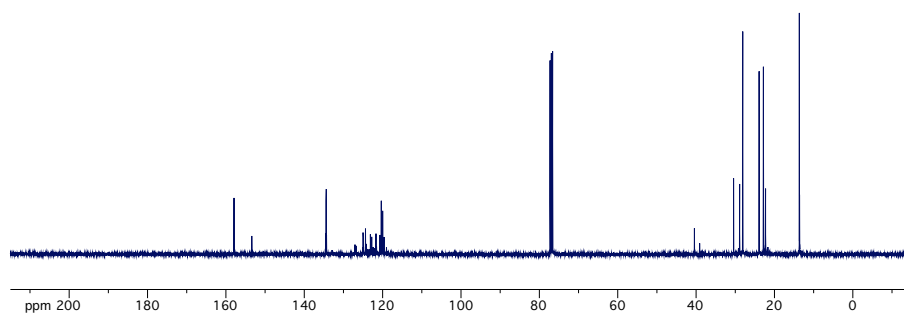
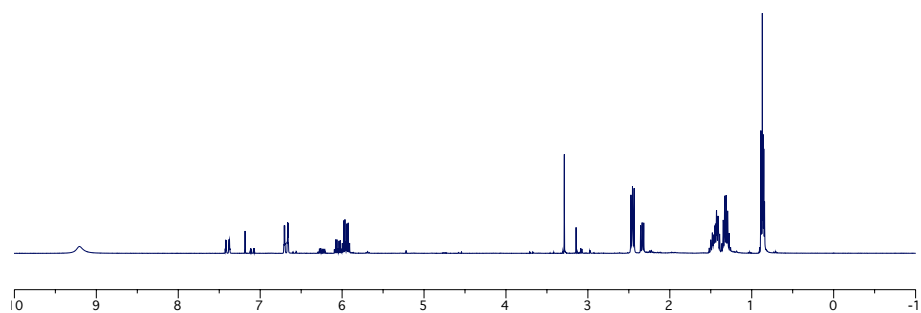
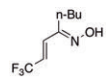


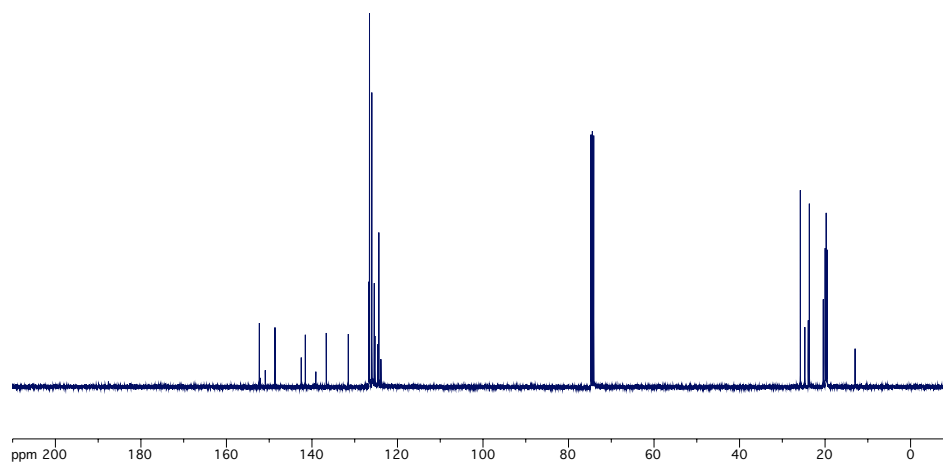
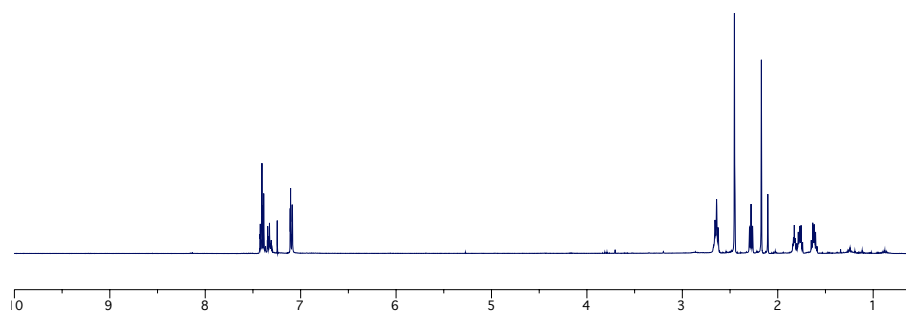
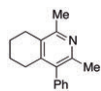


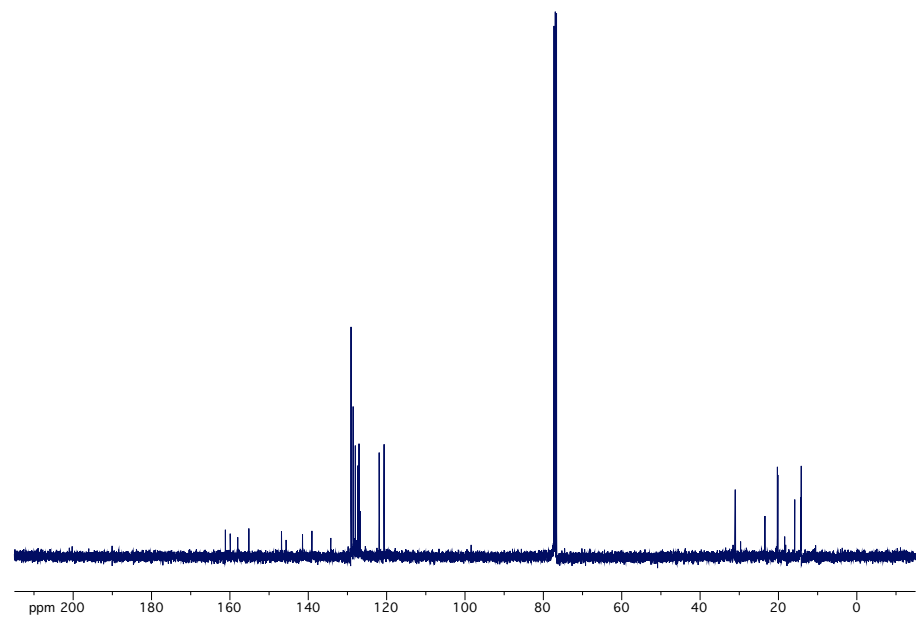
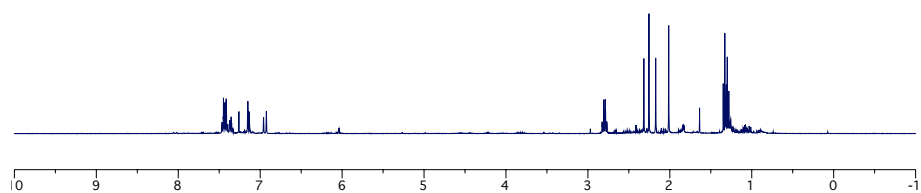


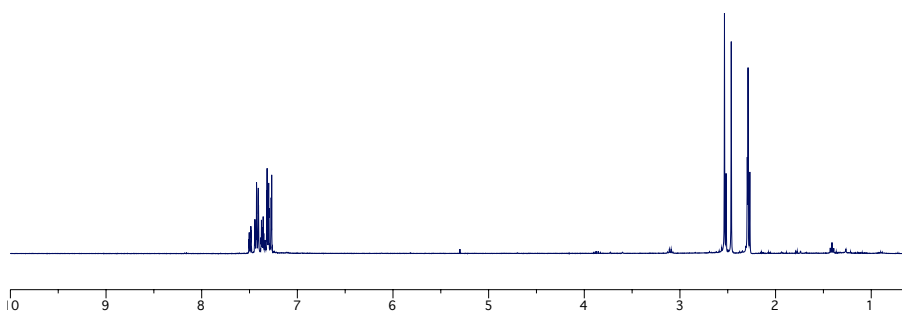


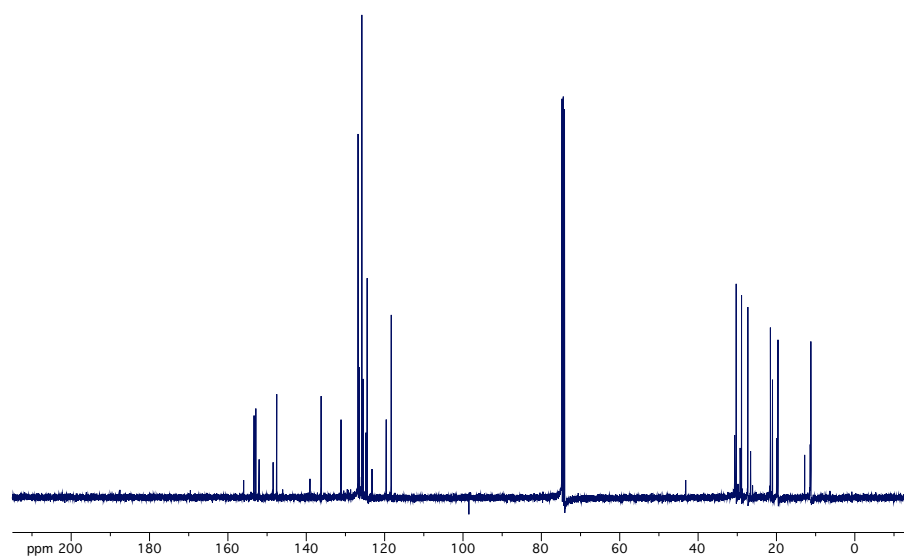
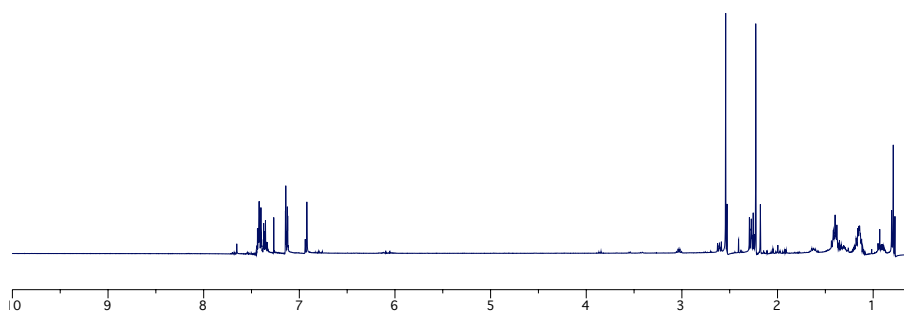
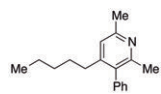


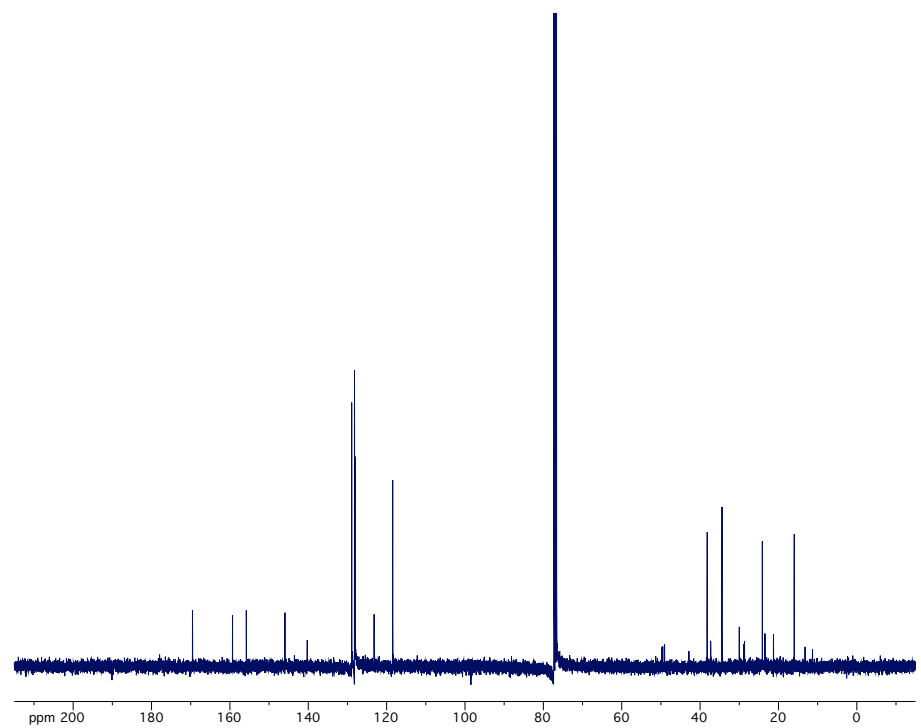
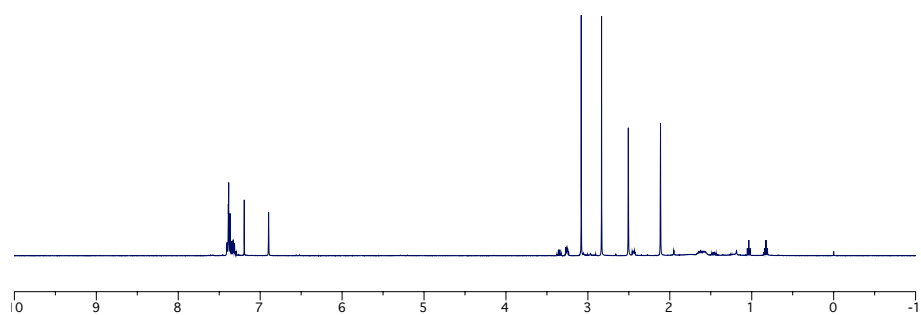
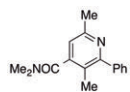


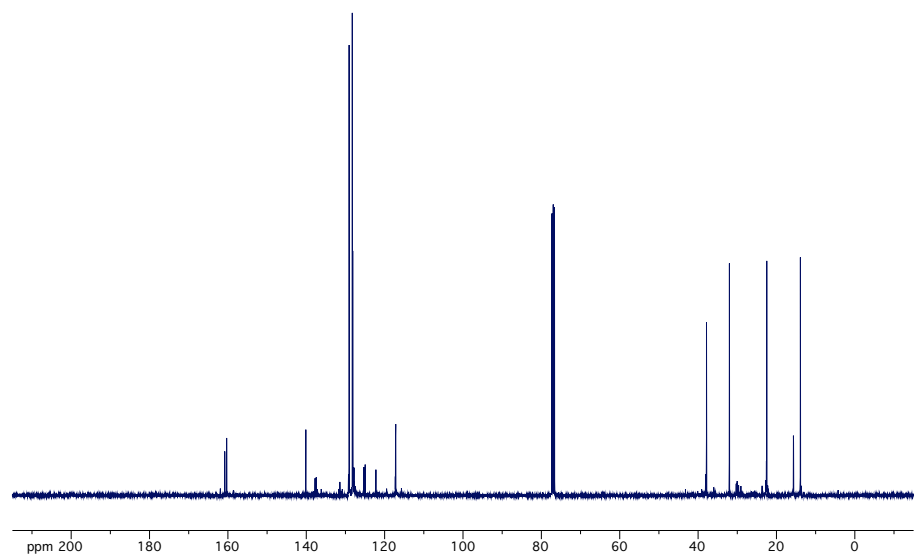
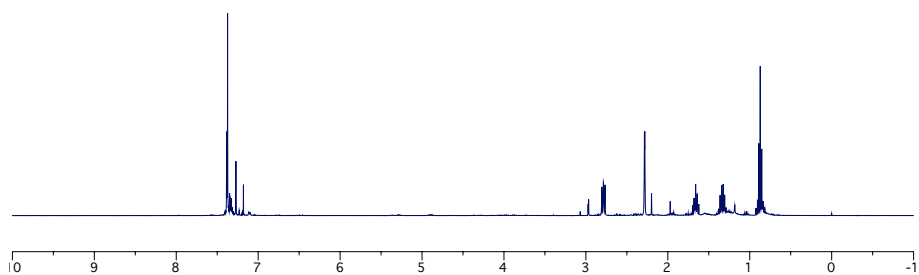
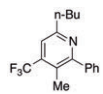


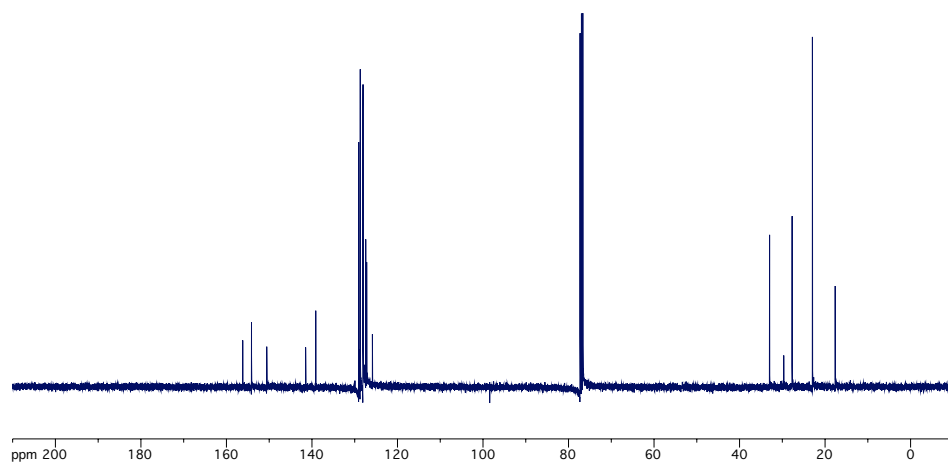
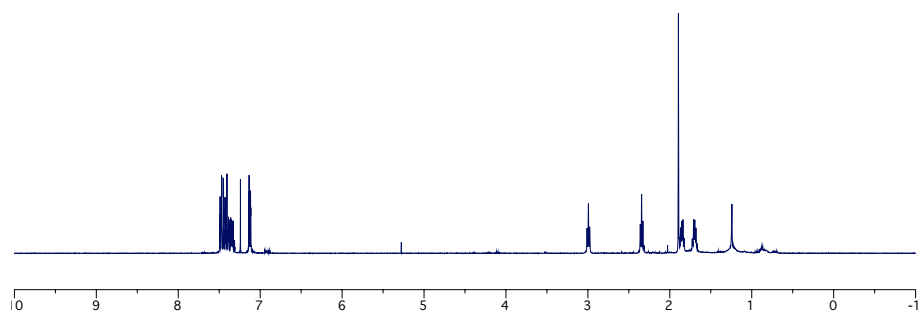


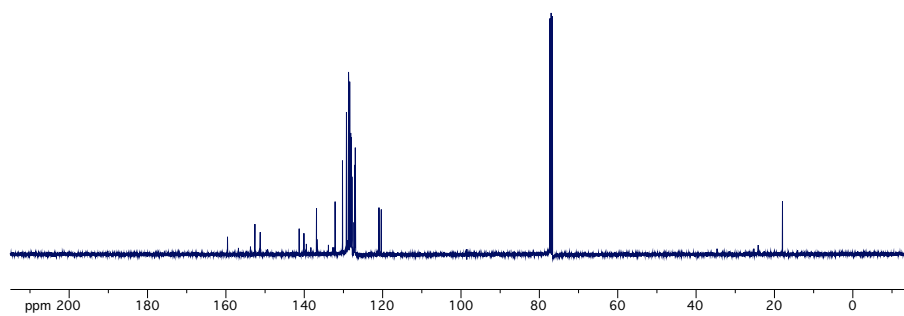
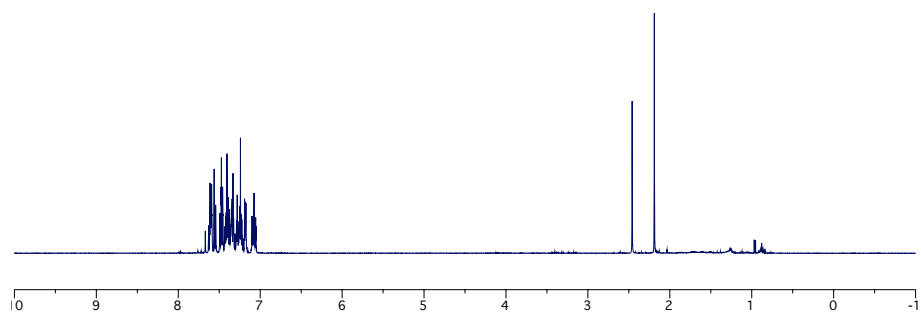
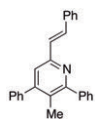


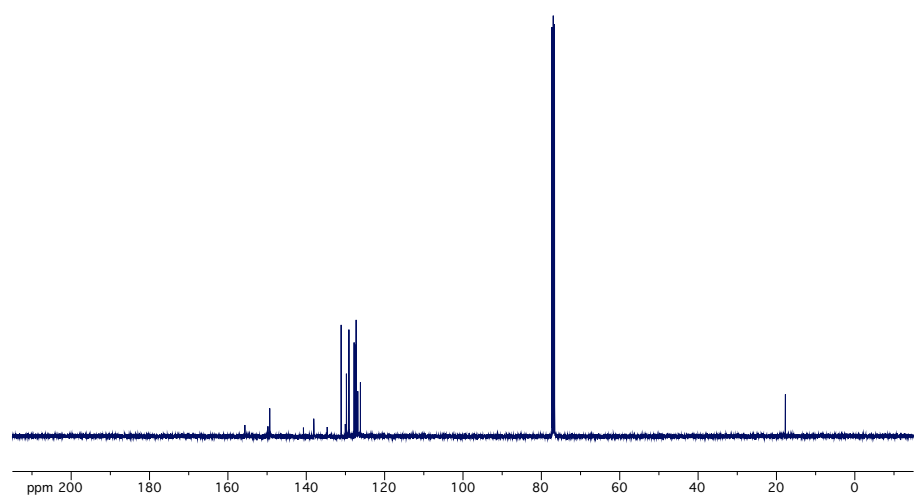
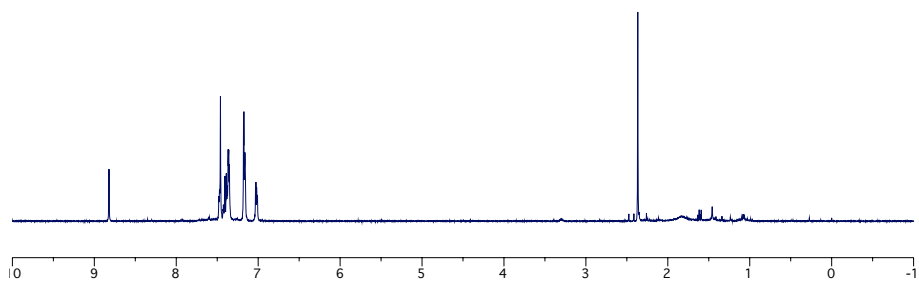
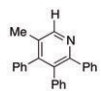


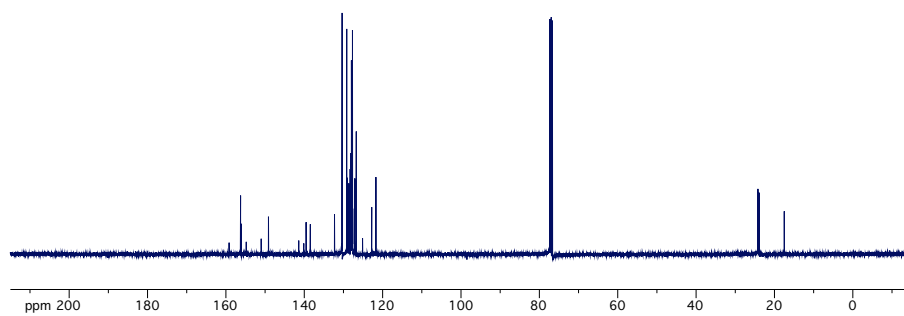
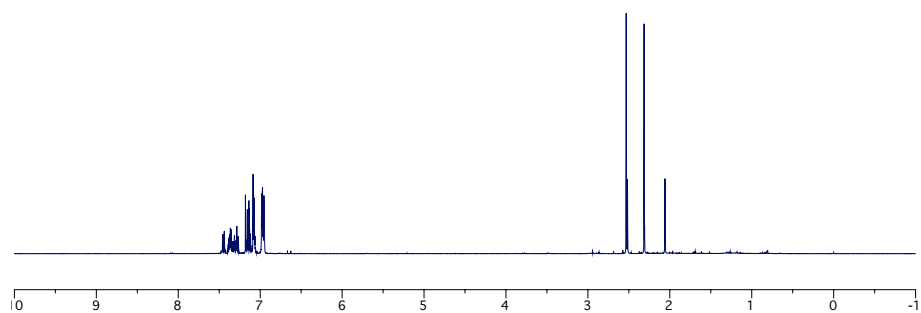


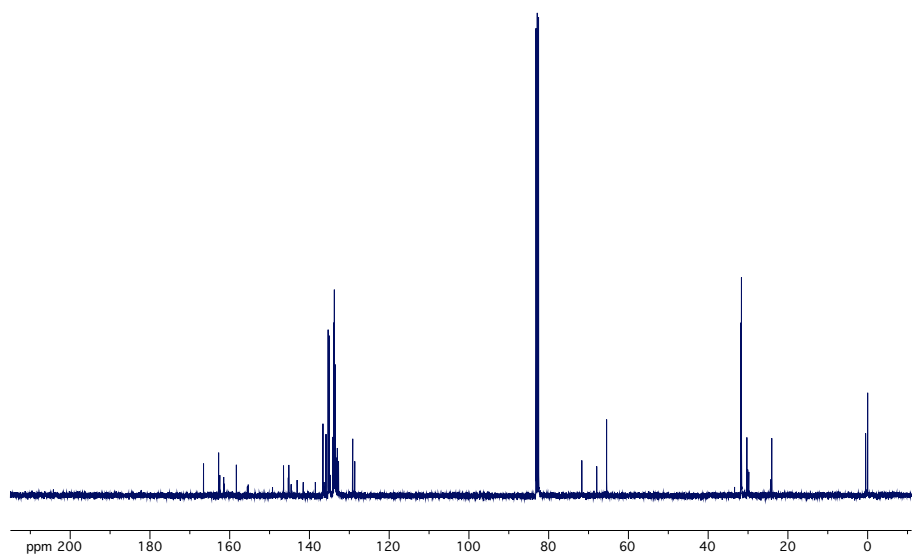
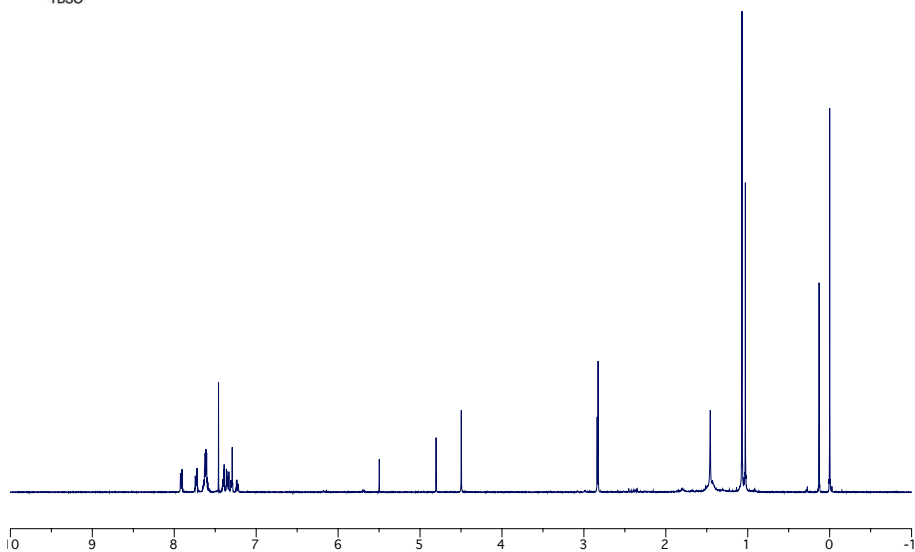


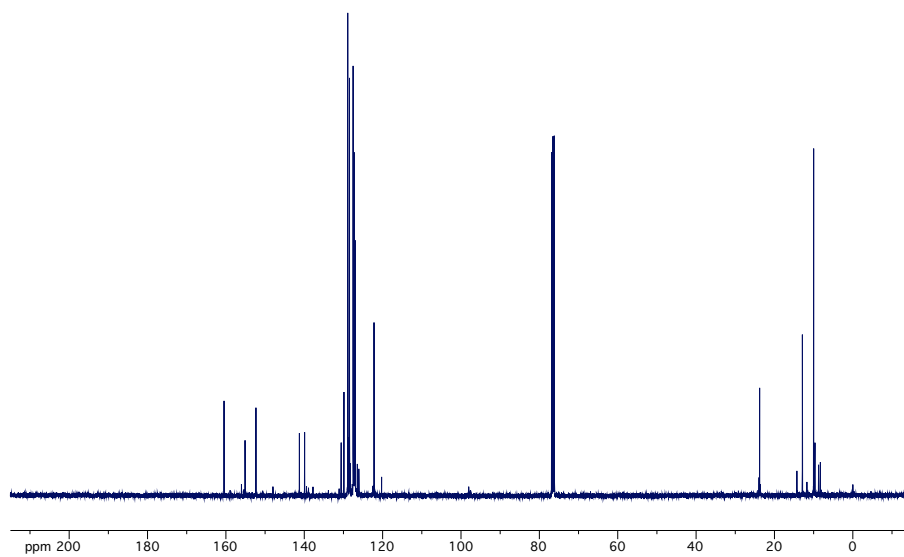
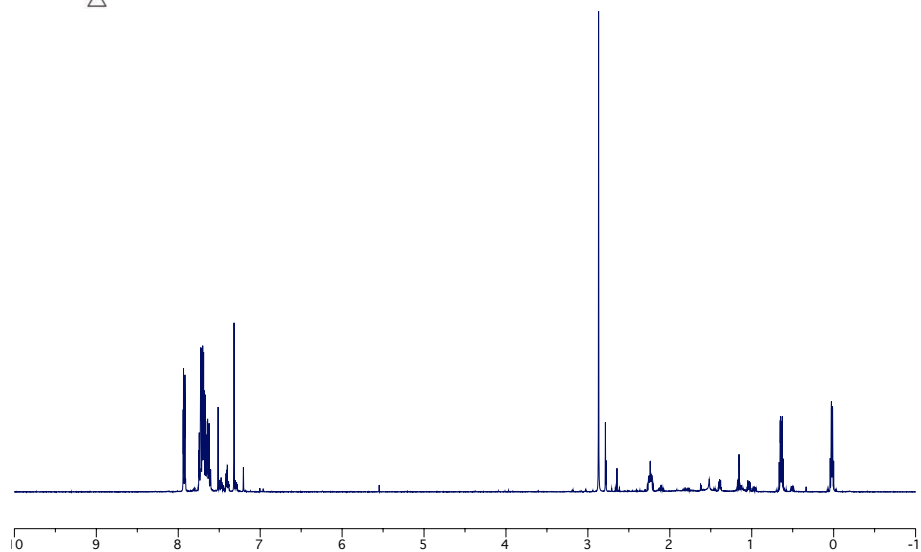
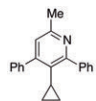


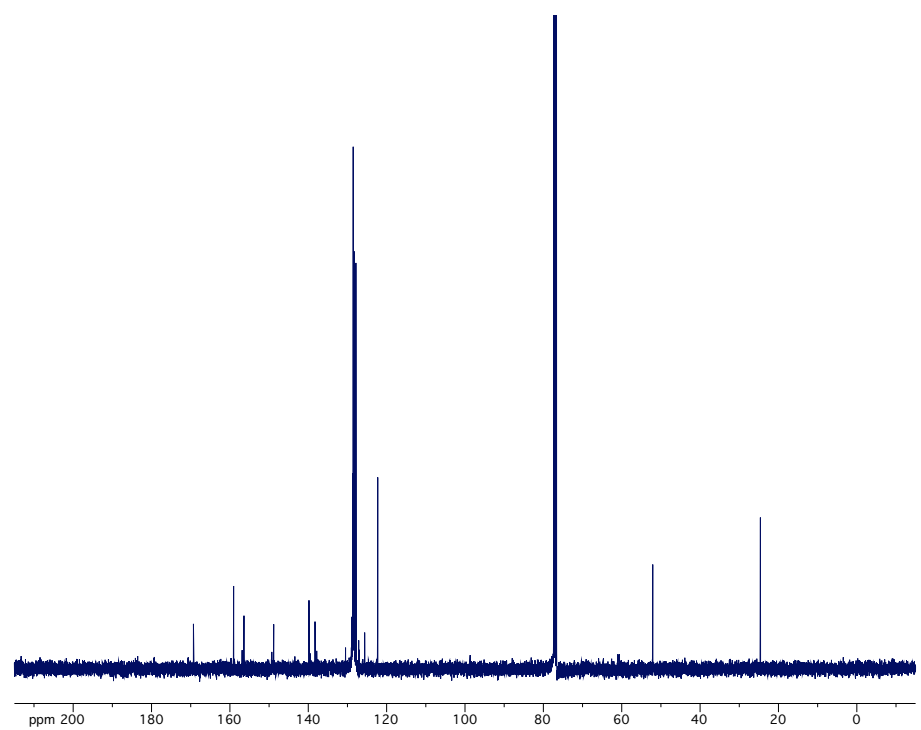
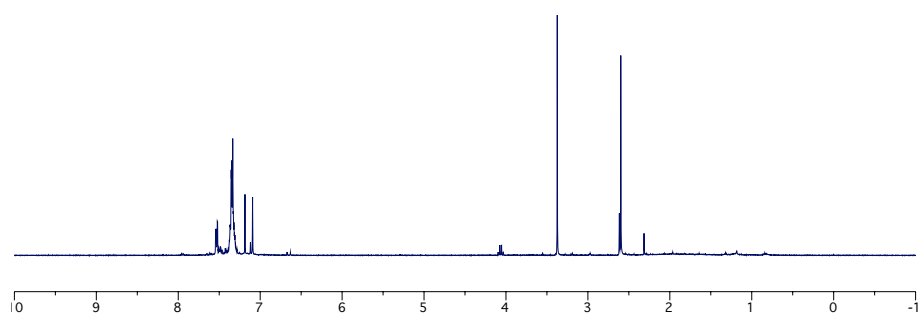


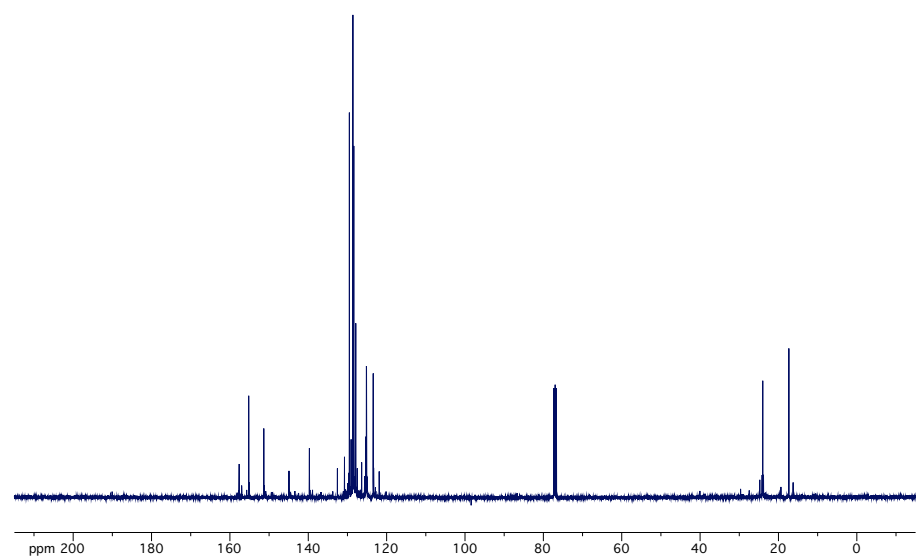
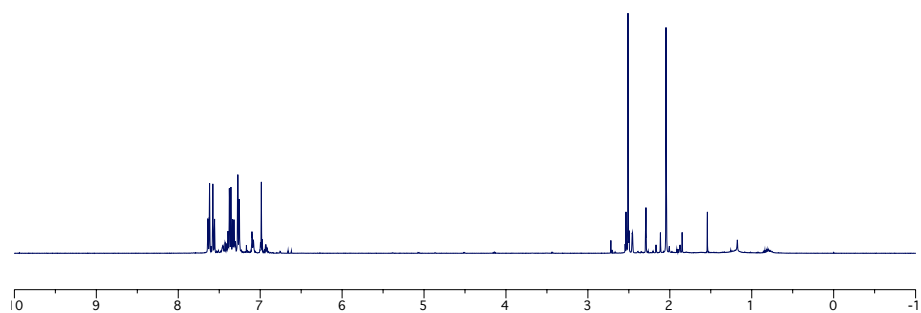
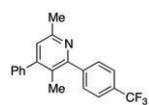


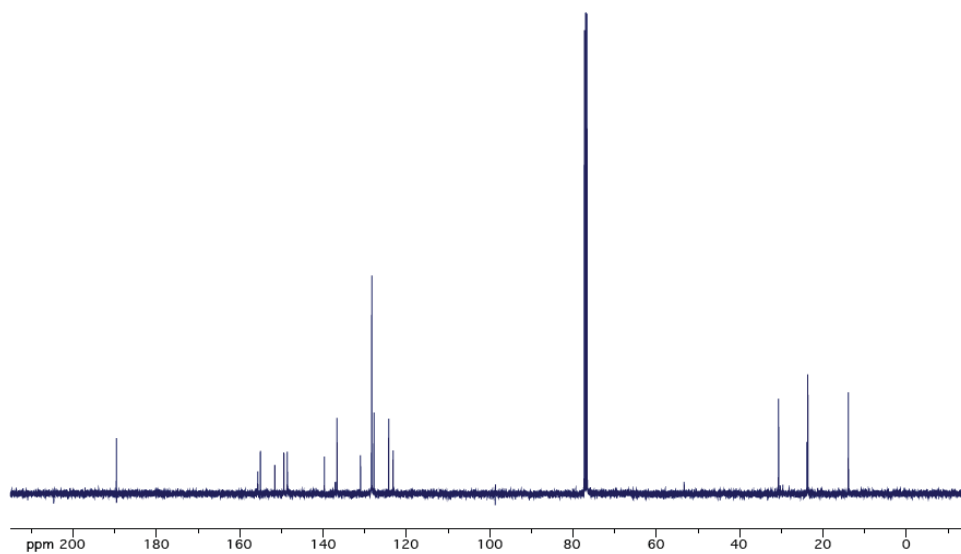
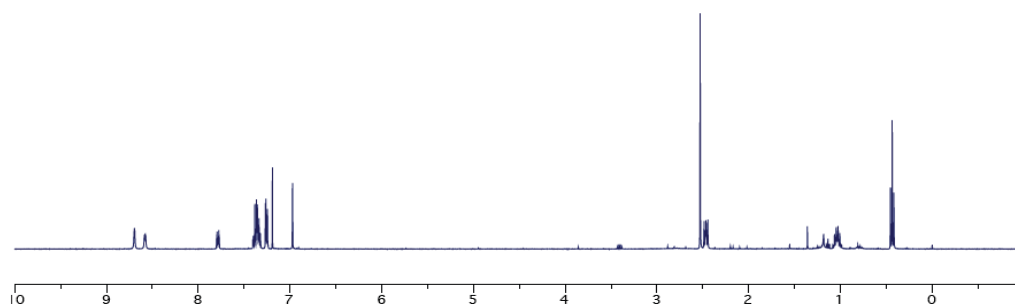
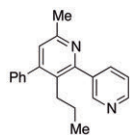


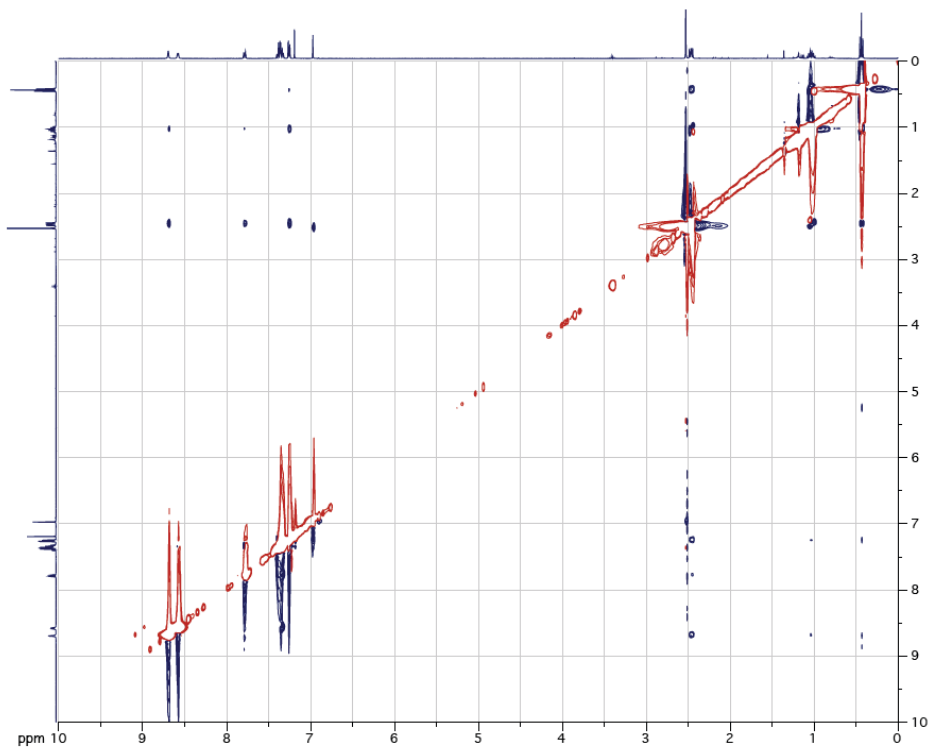


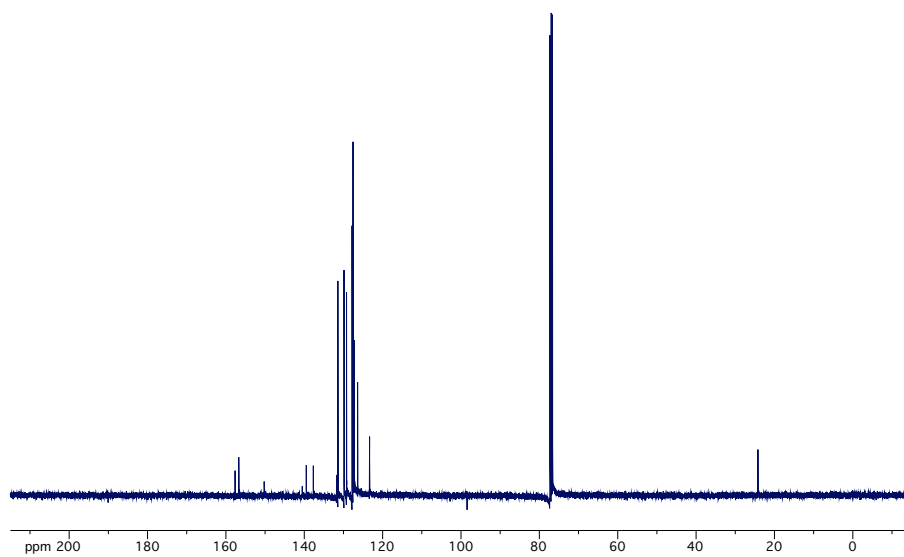
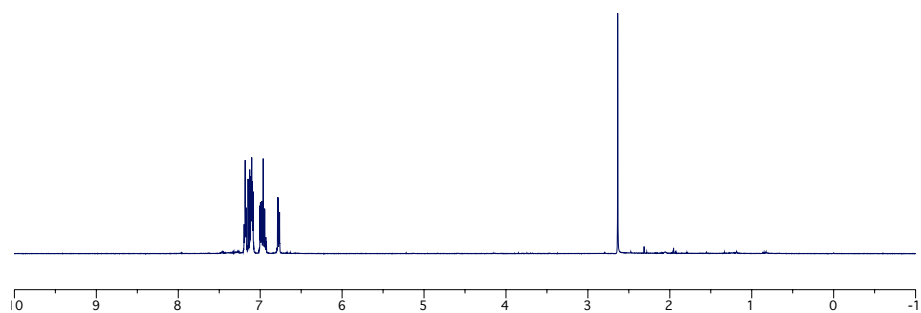


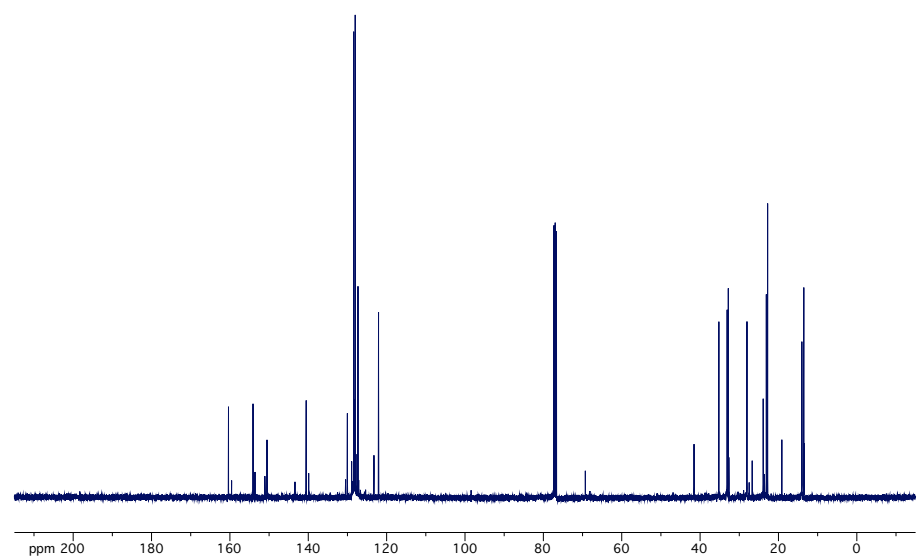
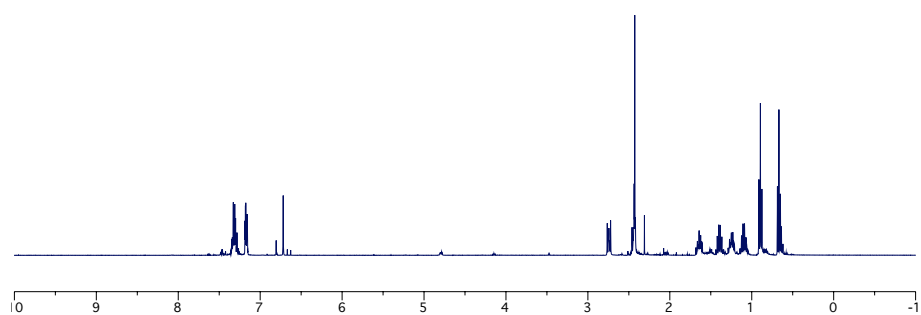
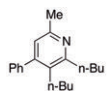


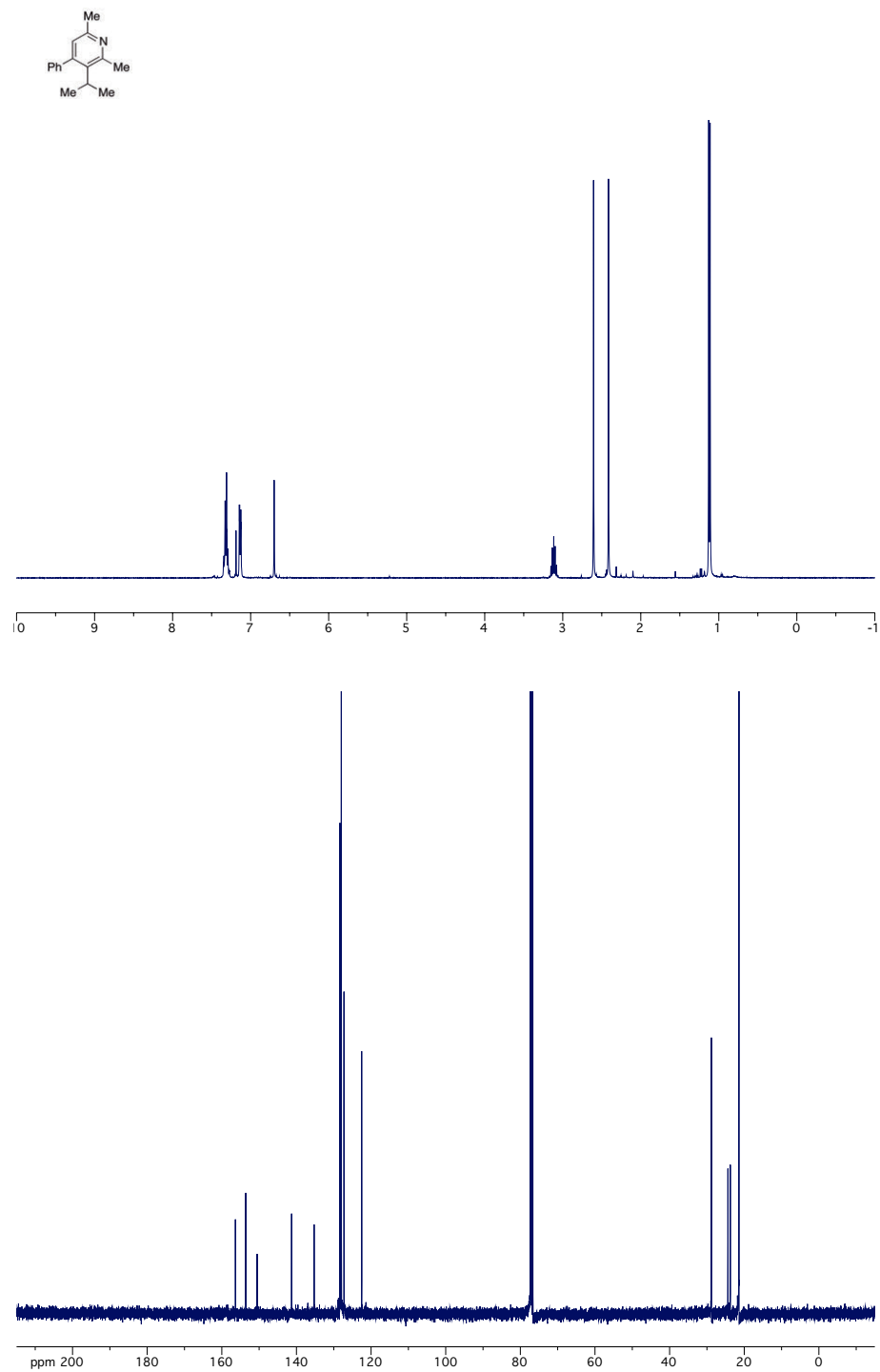


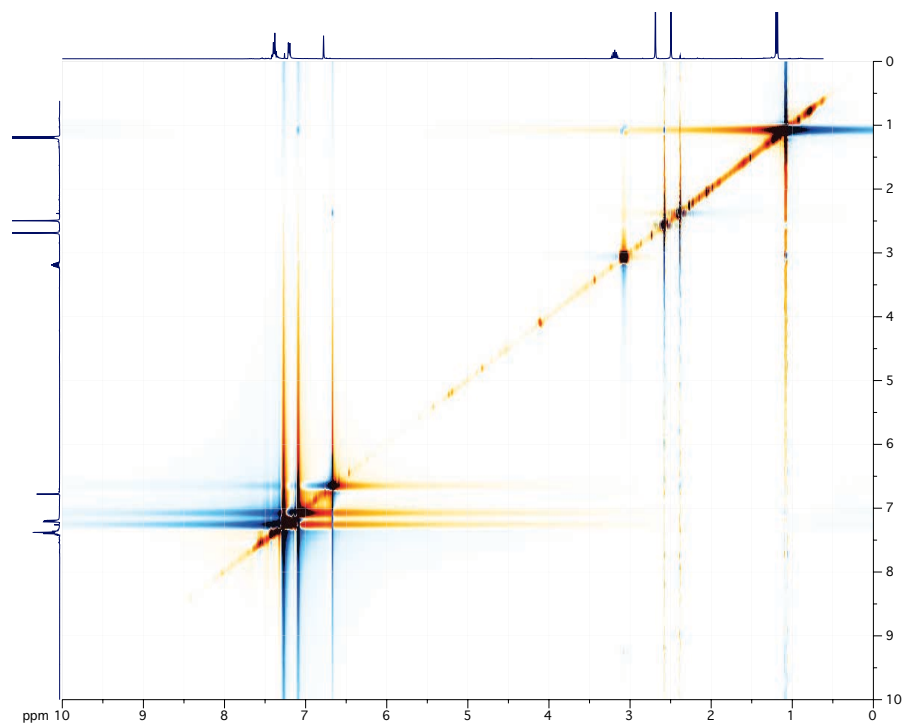


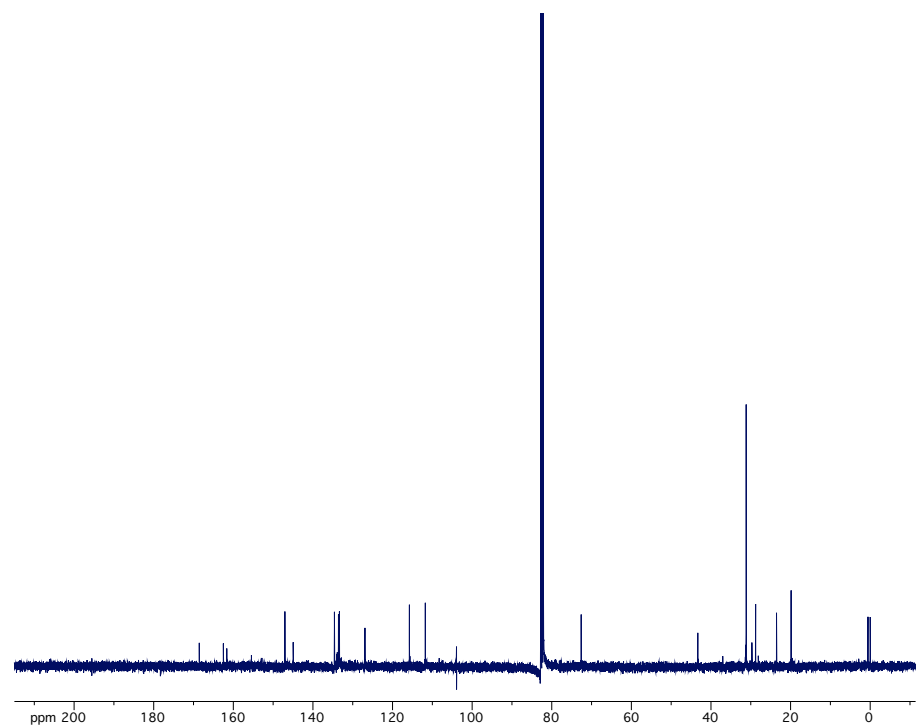
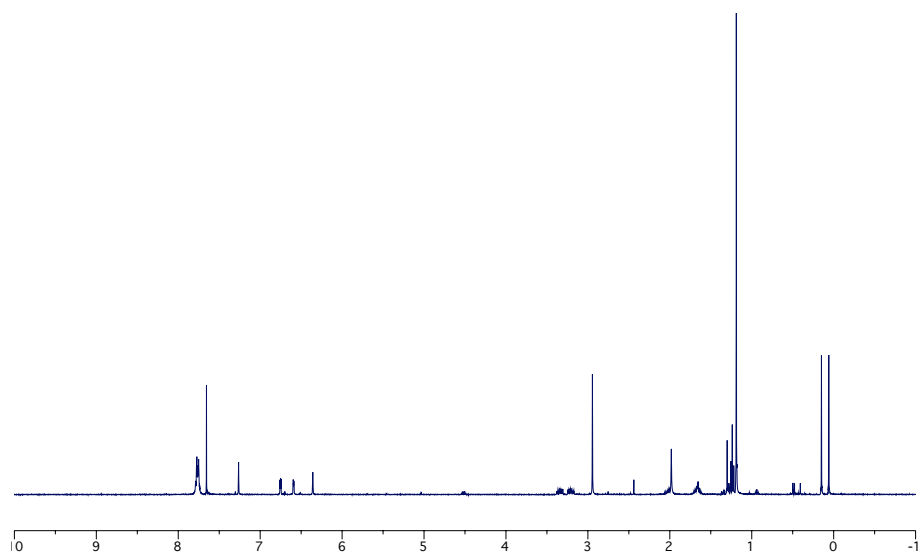
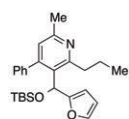


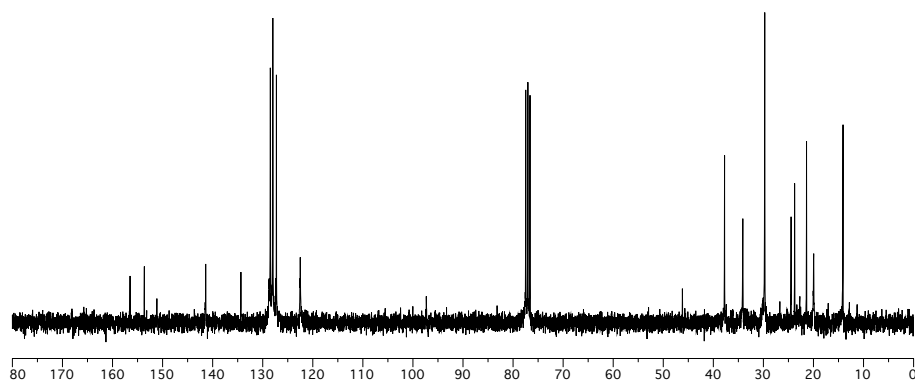
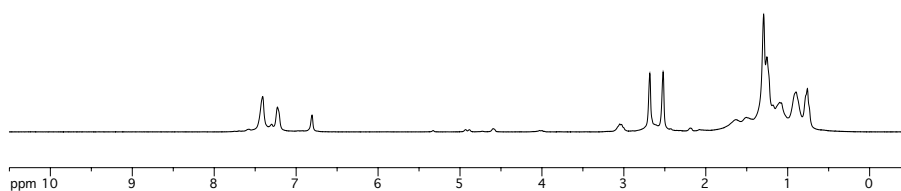
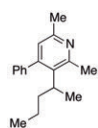


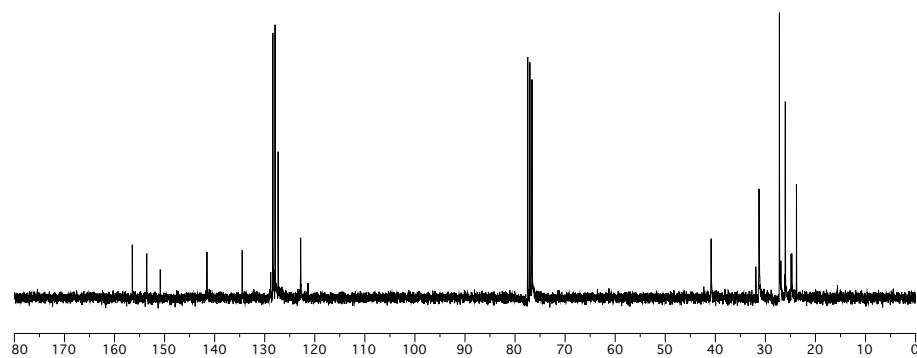
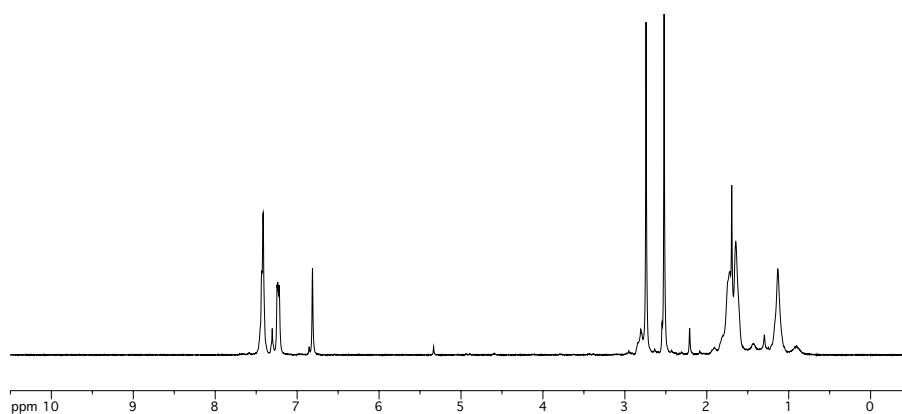
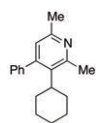


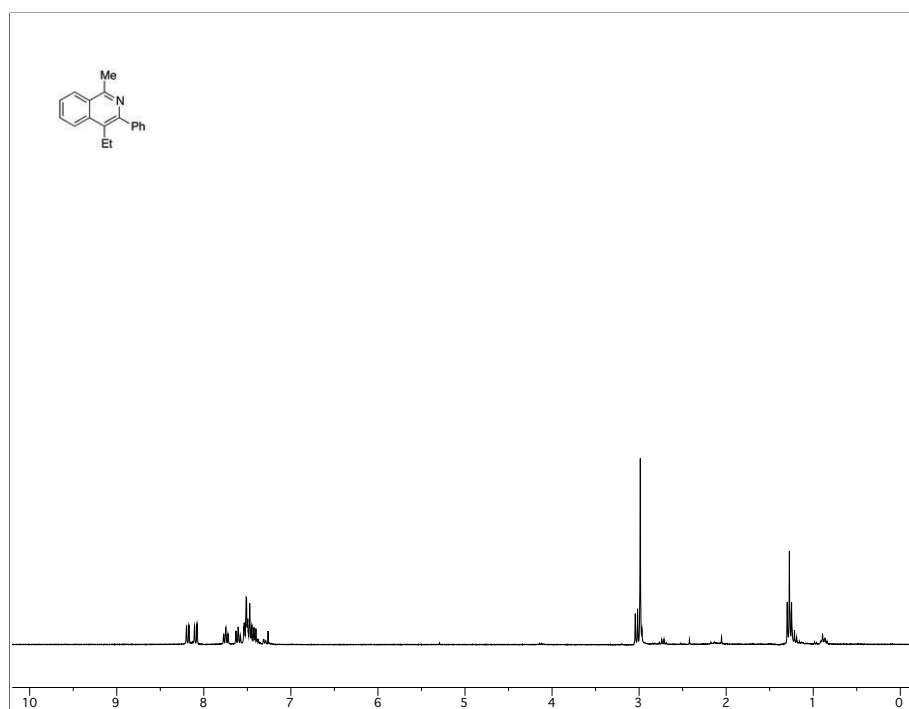


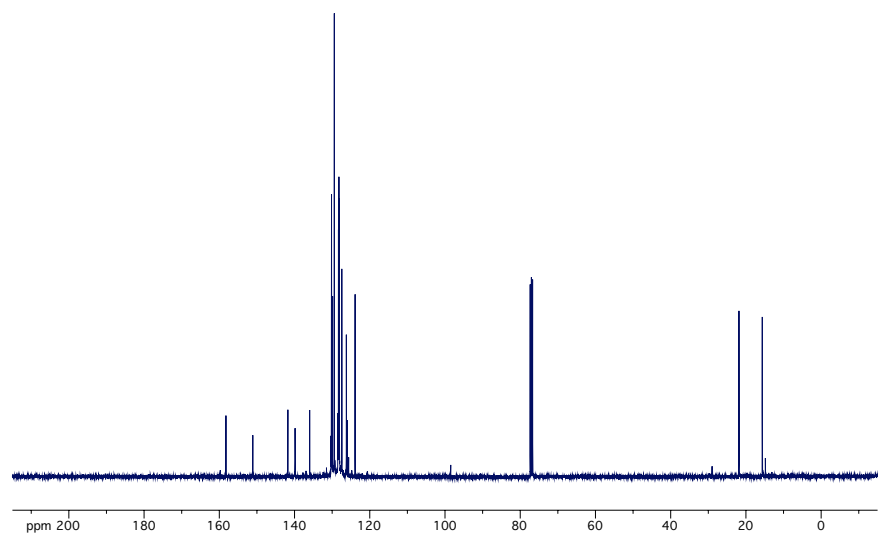
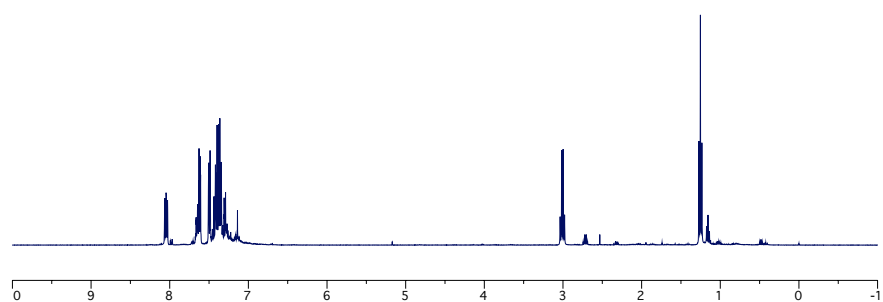


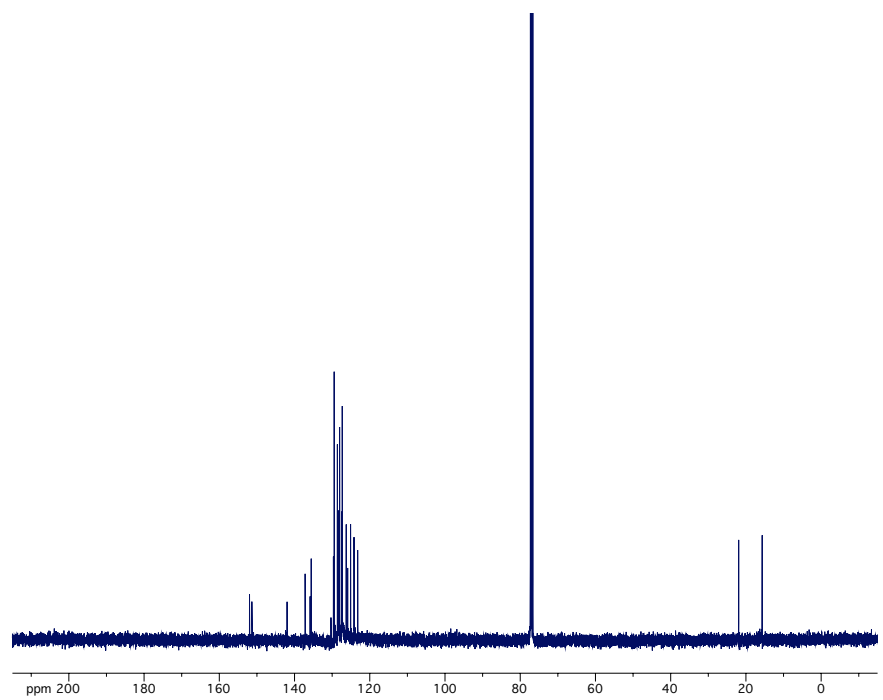
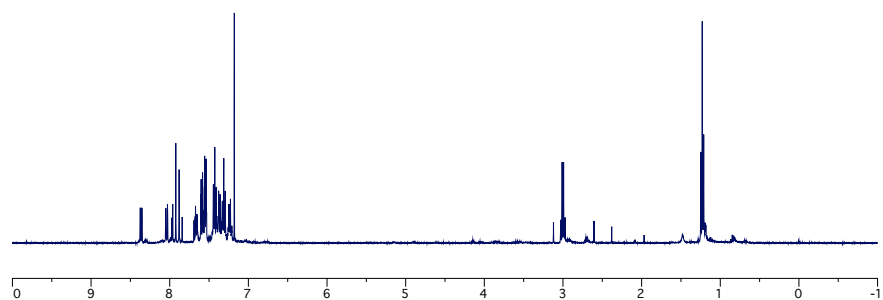
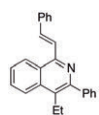


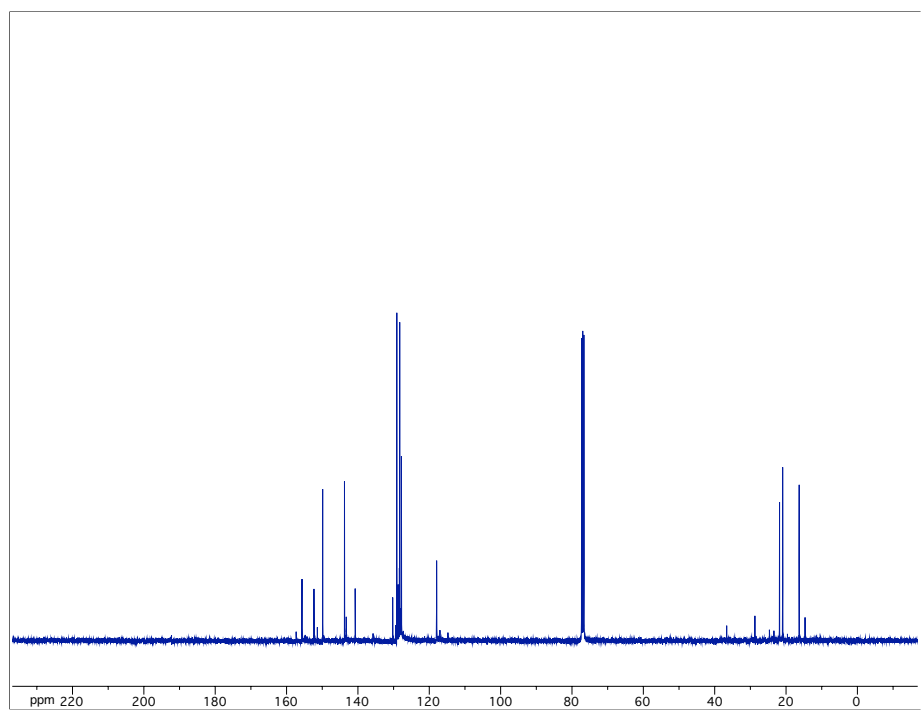
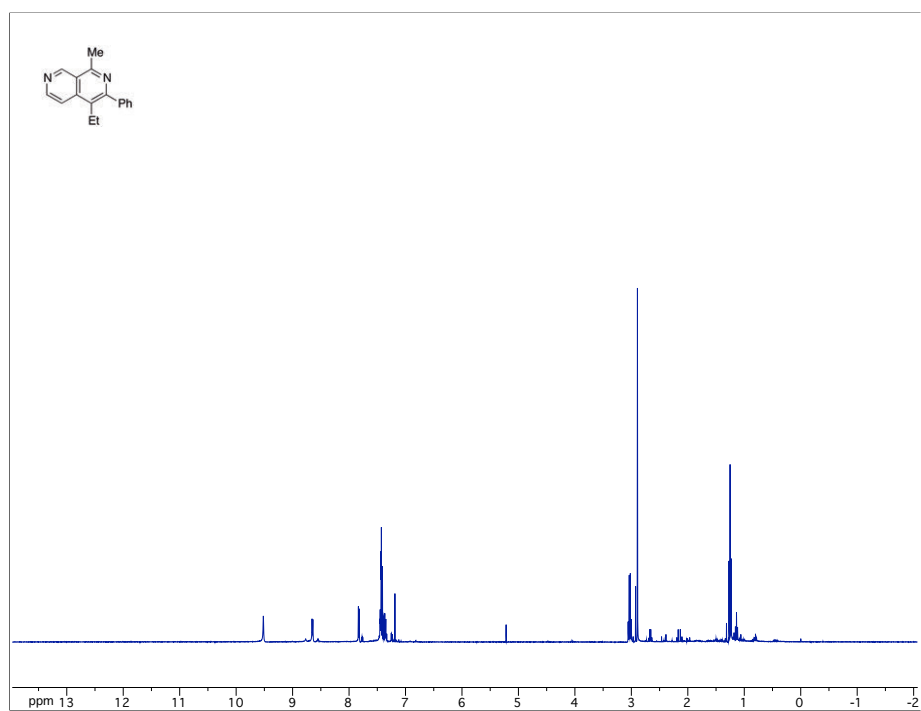


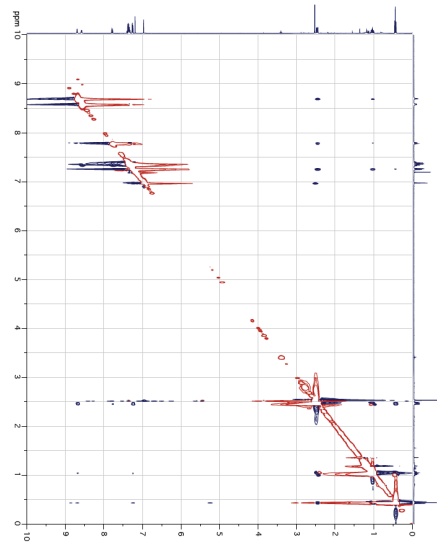


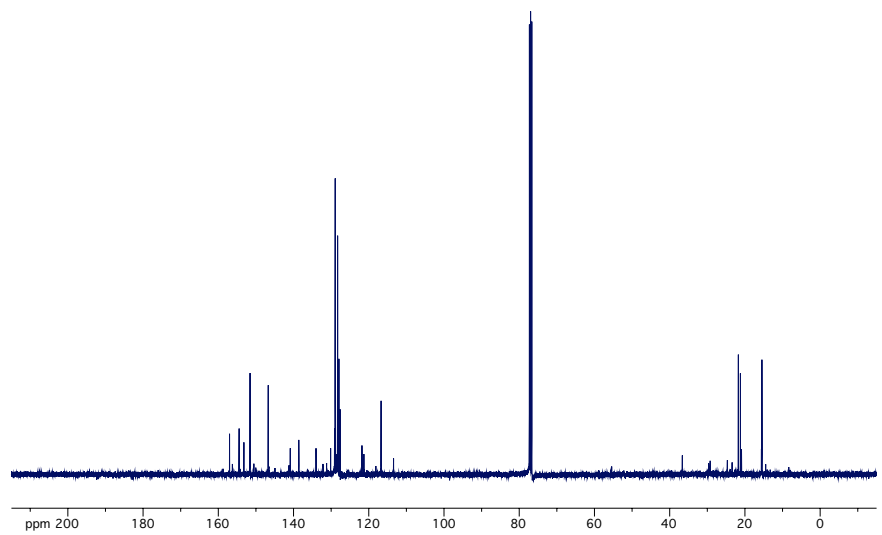
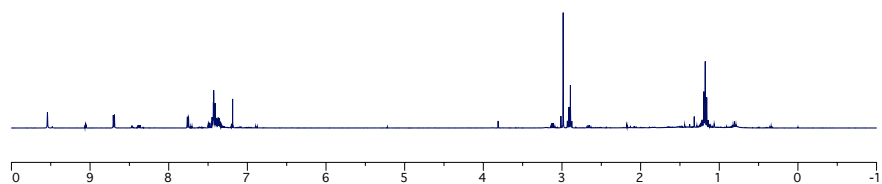
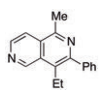


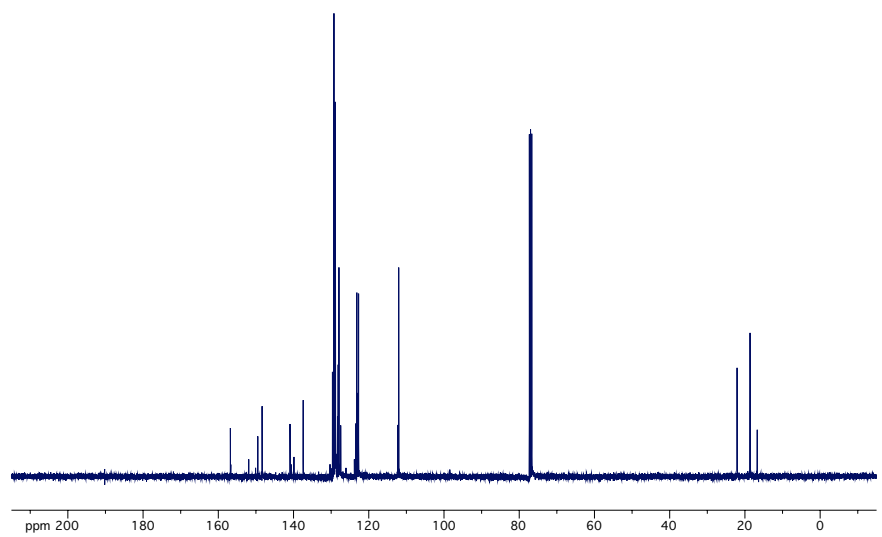
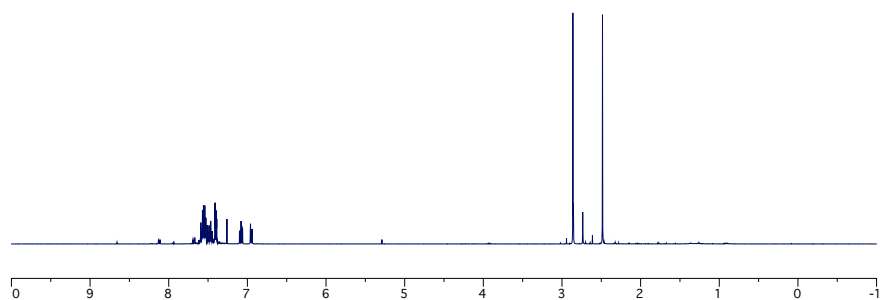
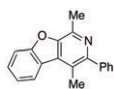


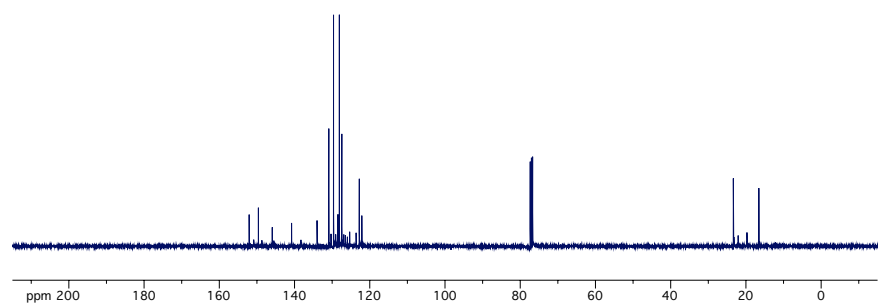
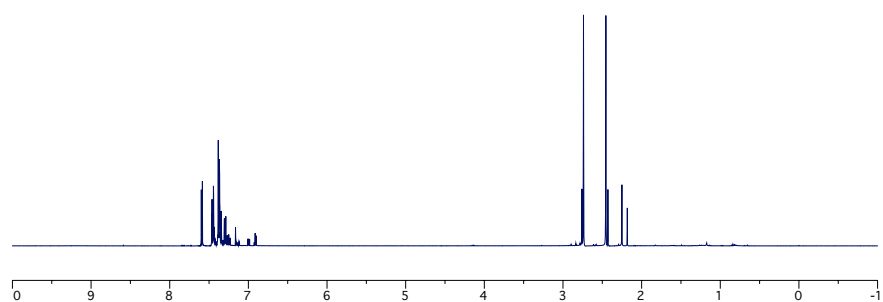


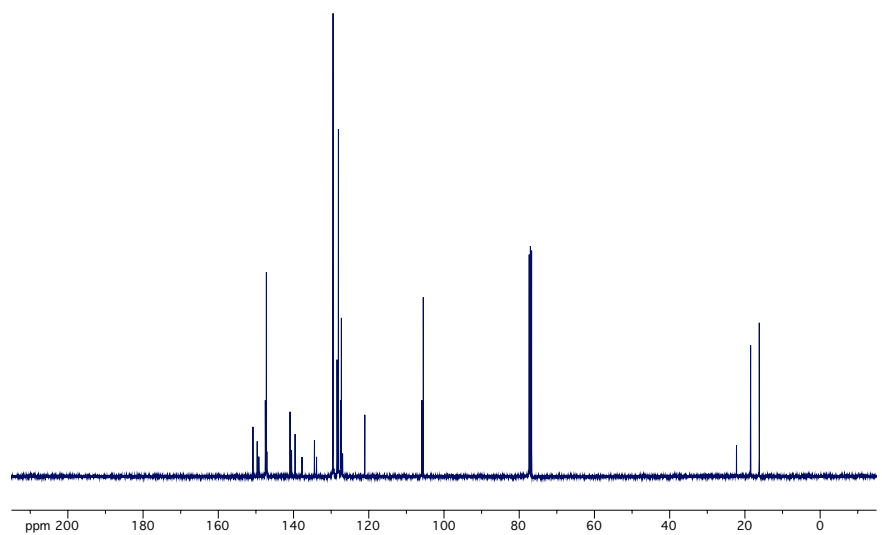
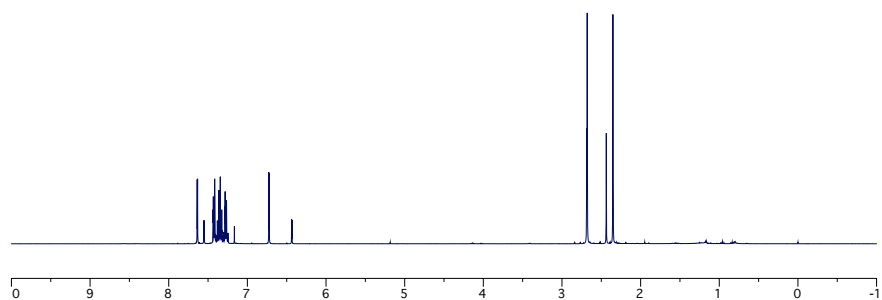


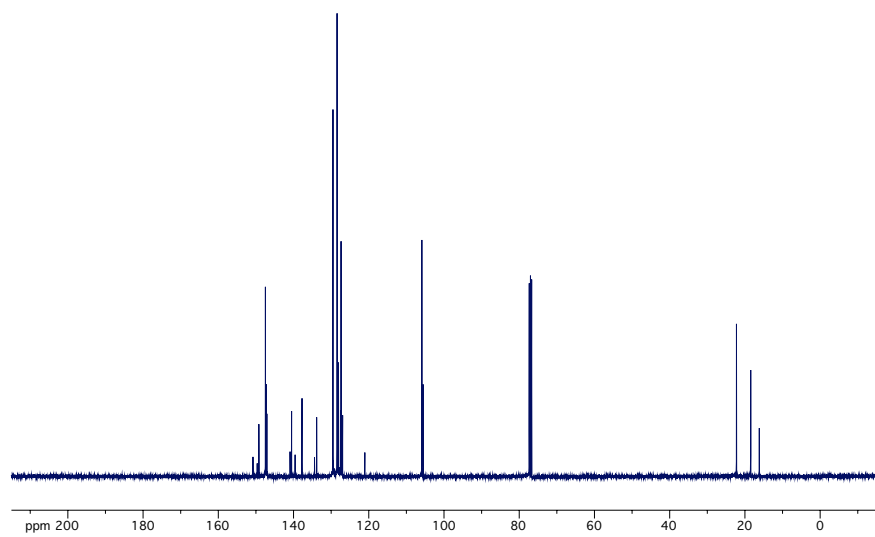
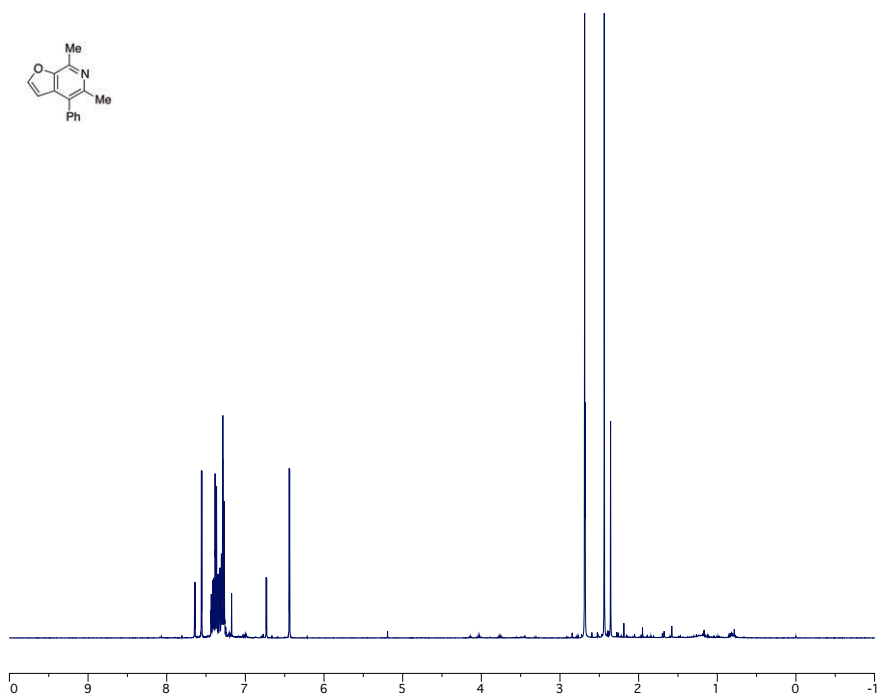


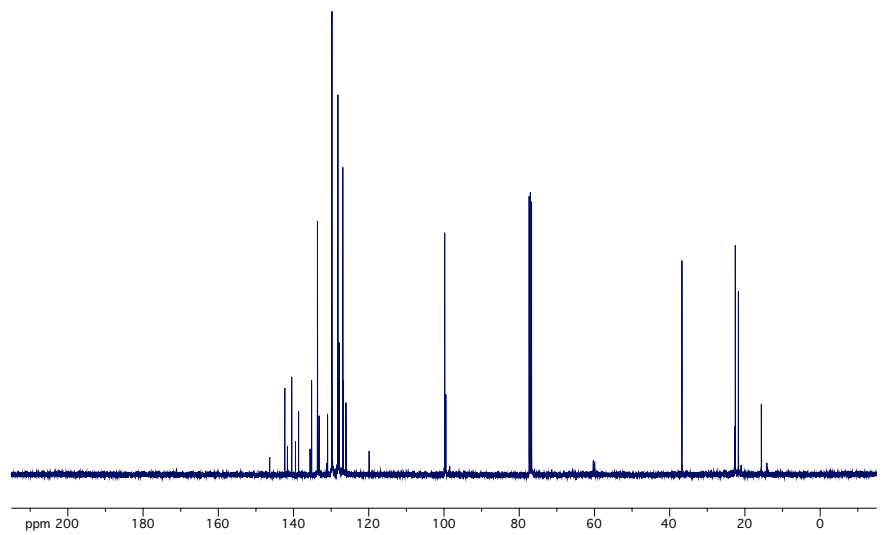
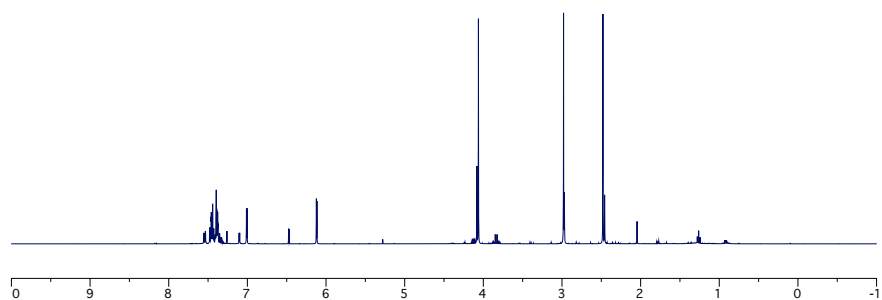












Appendix References

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Appendix 4

Artificial Metalloenzymes as a Catalyst Scaffold for Rhodium(III)-Catalyzed C–H Activation

General Methods

All reactions were carried out in 0.5 dram sealed vials under an atmosphere of air with magnetic stirring without drying or degassing of the vial. HPLC grade MeOH was purchased from VWR and used without further purification. Column chromatography was performed on SiliCycle® Silica Flash® 40-63µm 60A. Thin Layer chromatography was performed on SiliCycle® 250 µm 60A plates. Visualization was accomplished with UV light (254 nm), KMnO₄, and CAM.

¹H NMR and ¹³C NMR spectra were recorded on a Varian 400 MHz spectrometers at ambient temperature. ¹H NMR data are reported as the following: chemical shift in parts per million (δ, ppm) from chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (Hz). ¹³C NMR are reported as the following: chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Conversions and regioselectivities were determined by GC with a calibrated internal standard (1,3,5 trimethoxybenzene). Mass spectra were obtained on a Fisons VG Autospec. Infrared spectra (IR) were obtained on Bruker Tensor 27 FT-IR spectrometer. Enantiomeric ratio was determined by Chiral HPLC.

Site-Directed Mutagenesis

A pET11b plasmid containing the gene encoding for streptavidin fused with a T7-tag was used as a template for PCR (this plasmid was a generous gift from Prof. Paolo Santambrogio, University of Milan). Primers were designed following the method described by Zheng et al. and tested in silico to minimize hairpin formation.¹ Primers were obtained from Microsynth. PCR reactions of 50 µL total volume contained 5 – 25 ng of template plasmid, forward and reverse primers (300 nM each, Microsynth), dNTPs (0.1 mM each, Stratagene), DMSO (5 %), Pfu buffer (1 ×, Stratagene), polymerase Pfu turbo (3.75 U, Stratagene). The cycle conditions were: initial denaturation (95 °C, 5 min), followed by 16 cycles of

denaturation (1 min at 95 °C), annealing (1 min at 50 – 60 °C, depending on the primers used), elongation (10 min at 68 °C). The final elongation was performed at 68 °C for 1 h. PCR products were analysed by gel electrophoresis (1 % agarose). The initial DNA template was digested by DpnI (1 h at 37 °C, New England Biolabs). 5 µl of PCR product were used to transform chemically competent XL1-blue *E. coli* cells (produced in-house). Plasmids were purified using a Wizard Plus SV Miniprep DNA purification System (Promega) and were sequenced either by Starseq or Microsynth.

Production of Recombinant Streptavidin

Chemically competent BL21(DE3)pLysS *E. coli* cells (produced in-house) were transformed by the plasmids containing the desired mutations. Transformed cells were plated on LB- Lennox agar plates containing ampicillin (50 µg/mL, AppliChem), chloramphenicol (34 µg/mL, AppliChem) and glucose (2 % w/v), and incubated overnight at 37 °C. The culture medium (300 mL total, 20 g/L bactotryptone (BD), 1.3 g/L Na₂HPO₄, 1 g/L KH₂PO₄, 8 g/L NaCl, 15g/L bacto yeast extract (Merck) containing ampicillin (50 µg/mL), chloramphenicol (34 µg/mL), and glucose (2% w/v) was inoculated with a single colony. This preculture was incubated overnight on an orbital shaker (37 °C, 250 rpm). The fermentation was performed in a 30 L fermenter (NLF22, Bioengineering). The culture medium (20 L) containing ampicillin (50 µg/mL), chloramphenicol (34 µg/mL) and glucose (0.4 % w/v) was inoculated with the whole preculture. To avoid the formation of inclusion bodies, cells were grown at 20 °C, 30 °C or 37 °C, depending on the mutant. When an OD₆₀₀ of 2 – 3 was reached the expression of streptavidin was induced by addition of isopropyl β-D-1- thiogalactopyranoside (final concentration 0.4 mM, AppliChem). The cells were harvested 3 - 4 h after induction (expression at 30 °C and 37 °C) or after overnight expression (20 °C) by centrifugation (3600 × g, 10 min, 4 °C). The supernatant was discarded and the pellet was frozen at -20 °C until it was thawed for purification. Protein expression was confirmed by SDS-PAGE analysis.

Protein Purification

The pellet was thawed and resuspended in Tris-HCl buffer (20 mM, pH 7.4, 500-1000 ml / 150 - 450 g pellet). DNase I (2 - 3 mg, Roche) and phenylmethylsulfonyl fluoride (to a final concentration of 1 mM, AppliChem) were added and the resuspended cells were incubated at RT under vigorous shaking until the mixture became less viscous. The sample was dialyzed against 6 M guanidinium hydrochloride (Acros), pH 1.5 at room temperature for 24 hours. Two further dialysis steps were performed (20 mM Tris-HCl, pH 7.4, 4 °C, followed by 50 mM Na₂CO₃, pH 9.8, 0.5 M NaCl, 4°C) to prepare the proteic extract for affinity chromatography. The proteic extract was centrifuged (18 000 × g, 30 min, 4 °C) to remove cell debris. The supernatant was filtered (Whatman paper filter) and applied to a 2- iminobiotin sepharose column (Affiland) equilibrated at pH 9.8 (50 mM Na₂CO₃, 0.5 M NaCl). Pure streptavidin was eluted with 1% acetic acid, immediately dialyzed against Tris- buffer (10 mM Tris-HCl, pH 7.4) for 24 h at 4 °C, followed by distilled water for 24 h and finally two times against mQ-water for 24 h at 4 °C. The purified protein solution was frozen at -80 °C, lyophilized, and the lyophilized protein stored at 4 °C. The molecular weight of the purified protein was assessed by ESI-MS.

Auto-Dock Calculations

Auto-Dock calculations were conducted as described by Morris.²

Starting Amides

Pivaloyl protected hydroxamic acids were prepared as described by Guimond³ and Fagnou⁴.

Starting Materials

All alkenes and alkynes were purchased from Sigma-Aldrich and used without further purification.

Synthesis of [RhCp*^{biotin}Cl₂]₂ (481) and (483)

[RhCp*(CH₂CH₂NH₃Cl)Cl₂]₂ was prepared from a known literature procedure.⁵

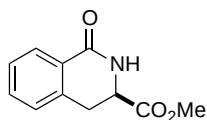
[RhCp*(CH₂CH₂CH₂NH₃Cl)Cl₂]₂ was prepared from a known literature procedure.⁶

$[(\eta^5\text{C}_5\text{Me}_4\text{CH}_2)_2\text{NH}_3)\text{RhCl}_2]_2\text{Cl}_2$ (200 mg, 0.296 mmol) was suspended in DMF (20 mL) and biotin pentafluorophenyl ester (231 mg, 0.562 mmol) and Et_3N (0.831 mL, 5.920 mmol) were added. The compounds rapidly dissolved to give a dark red solution. It was left to stir at RT overnight. The solvent was removed and the reddish solid was suspended in hexane. The solid was filtrated and washed with hexane (3*15 mL) then with dichloromethane (4*15 mL) to afford 284 mg of brown-red powder (85% yield). ^1H NMR (500 MHz, DMSO) δ 7.93 (t, J = 6.0 Hz, 2H), 6.36 (d, J = 33.2 Hz, 4H), 4.30 – 4.27 (m, 2H), 4.12 – 4.09 (m, 2H), 3.22 (dd, J = 13.4, 6.9 Hz, 4H), 3.09 – 3.05 (m, 2H), 2.80 (dd, J = 12.4, 5.0 Hz, 2H), 2.55 (d, J = 12.4 Hz, 2H), 2.26 (t, J = 6.9 Hz, 4H), 2.02 (t, J = 7.4 Hz, 4H), 1.68 (s, 12H), 1.64 (s, 12H), 1.80 – 1.25 (m, 12H). ^{13}C NMR (126 MHz, DMSO) δ 172.06 (2C), 162.68 (2C), 100.47 (5C), 99.07 (5C), 96.72 (2C), 61.01 (2C), 59.15 (2C), 55.37 (2C), 40.89 (2C), 39.66 (2C), 35.06 (2C), 28.19 (2C), 26.00 (2C), 25.07 (2C), 24.13 (2C), 8.70 (4C), 8.59 (4C). HR-MS (ESI-MS, pos): m/z = 1091.1294 $[\text{M}-\text{Cl}]^+$; calcd. $\text{C}_{42}\text{H}_{64}\text{Cl}_4\text{N}_6\text{O}_4\text{Rh}_2\text{S}_2$, 1126.1294.

General Synthesis for Dihydroisoquinolone

A 0.5 dram flask is charged with an oven dried stir bar and the appropriate tetrameric strept(avidin) mutant (0.66 mol %, 6.6×10^{-5} mmol, 4.3 mg). The solution was dissolved in deionized water (160 μL) and allowed to stir for 2 minutes. A solution of $[\text{RhCp}^{\text{biotin}}\text{Cl}_2]_2$ (1 μL of a solution in DMSO (0.1 M, 1 mol %, 0.11 mg)) was added to the solution and stirred at 500 rpm. After 5 minutes, a solution of pivaloyl protected hydroxamic acid in MeOH (.25M solution, 40 μL , 1 equiv., 2.12 mg) was added to the reaction and stirred for 30 seconds. After alkene was added (1 equiv, 0.9 mg) the reaction is sealed and allowed to stir at 23 °C. After 36 hours the reaction is quenched with 400 μL of ethyl acetate and a 50 μL solution of 1,3,5 trimethoxybenzene in ethyl acetate (0.2M). The reaction is allowed to stir for 10 minutes (1000 rpm) before 200 μL of the organic layer was removed. Yield and diastereoselectivity was determined via GC, enantioselectivity was determined by HPLC.

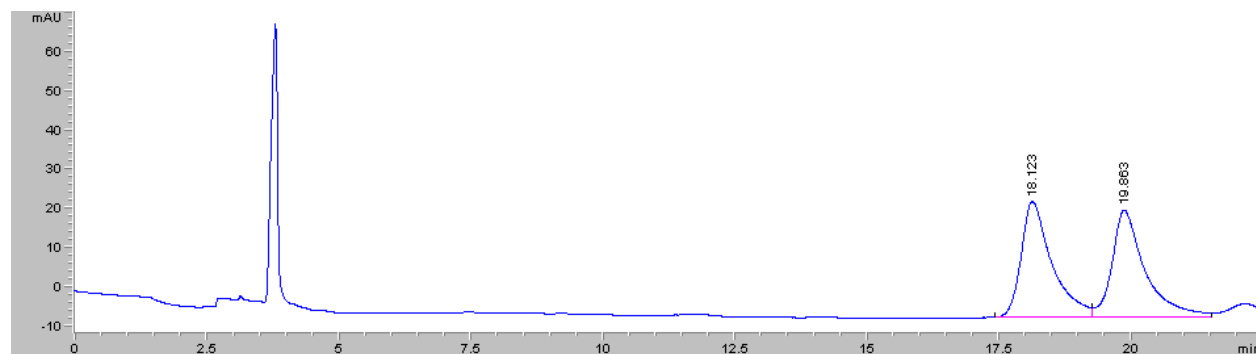
Characterization and HPLC traces for Dihydroisoquinolone



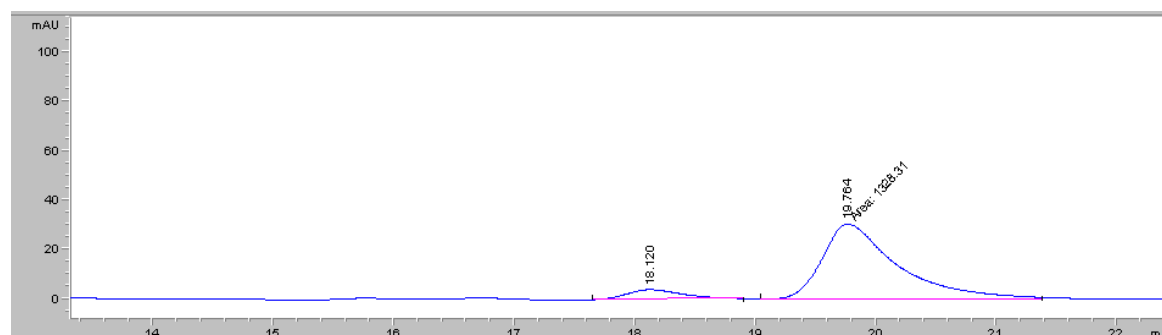
methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (317): This compound

have been previously reported. Absolute configuration determined by HPLC trace of enantiopure sample. Included is the ^1H NMR. ^1H (400 MHz, CDCl_3) δ 8.08 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.49-7.45 (m, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.24 (d, $J = 7.5$ Hz, 1H), 6.50 (s, 1H), 4.41 (ddd, $J = 10.0, 5.1, 1.9$ Hz, 1H), 3.80 (s, 3H), 3.33 (dd, $J = 15.7, 5.1$ Hz, 1H), 3.21 (dd, $J = 15.7, 10.0$ Hz, 1H).

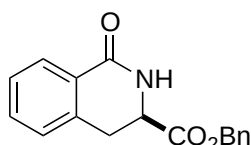
Chiral HPLC: IA Column; 90:10 Hexane/iPrOH.



#	Time	Area	Height	Width	Area (%)	Symmetry
1	18.12	1213	29.7	0.589	50.053	0.537
2	19.863	1210	27.4	0.6269	49.947	0.524



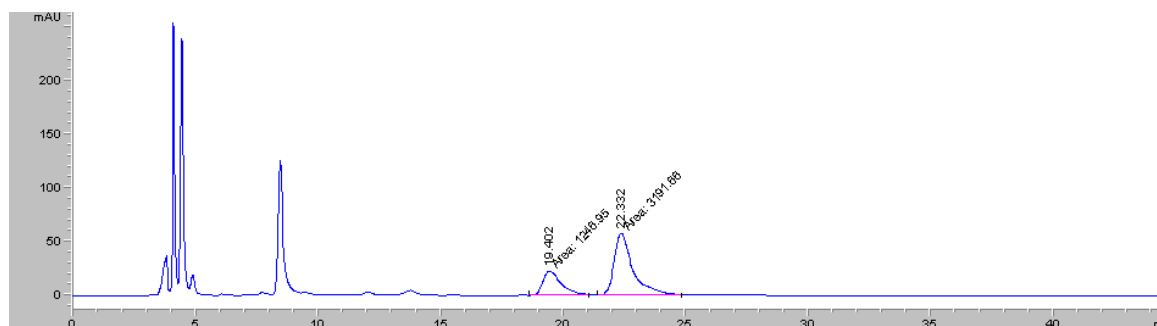
#	Time	Area	Height	Width	Area (%)	Symmetry
1	18.12	127.6	3.9	0.4911	8.764	0.689
2	19.764	1328.3	30.5	0.7267	91.23	0.587



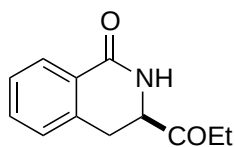
(R)-benzyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (504): ^1H -

NMR (400 MHz; CDCl_3): δ 8.07 (dd, $J = 7.7, 1.1$ Hz, 1H), 7.46 (td, $J = 7.5, 1.4$ Hz, 1H), 7.39-7.34 (m, 4H), 7.31-7.29 (m, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 6.46 (d,

$J = 0.4$ Hz, 1H), 5.25-5.21 (m, 2H), 4.43 (ddd, $J = 9.9, 5.1, 1.9$ Hz, 1H), 3.37-3.18 (m, 2H). ^{13}C NMR (101 MHz; cdcl_3): δ 170.2, 165.1, 136.1, 134.8, 132.5, 132.0, 128.68, 128.67, 128.60, 128.46, 128.37, 128.30, 128.18, 127.58, 127.40, 124.1, 122.2, 67.7, 53.2, 31.2. IR (Thin Film) 2364, 2084, 1639, 1286, 724 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 282.1125; found 282.113. Chiral HPLC: IA Column; 90:10 Hexane/iPrOH.



#	Time	Area	Height	Width	Area (%)	Symmetry
1	19.402	1247	22.8	0.9118	28.093	0.515
2	22.332	3191.7	58.4	0.9105	71.907	0.559

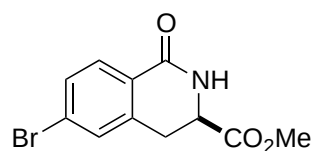
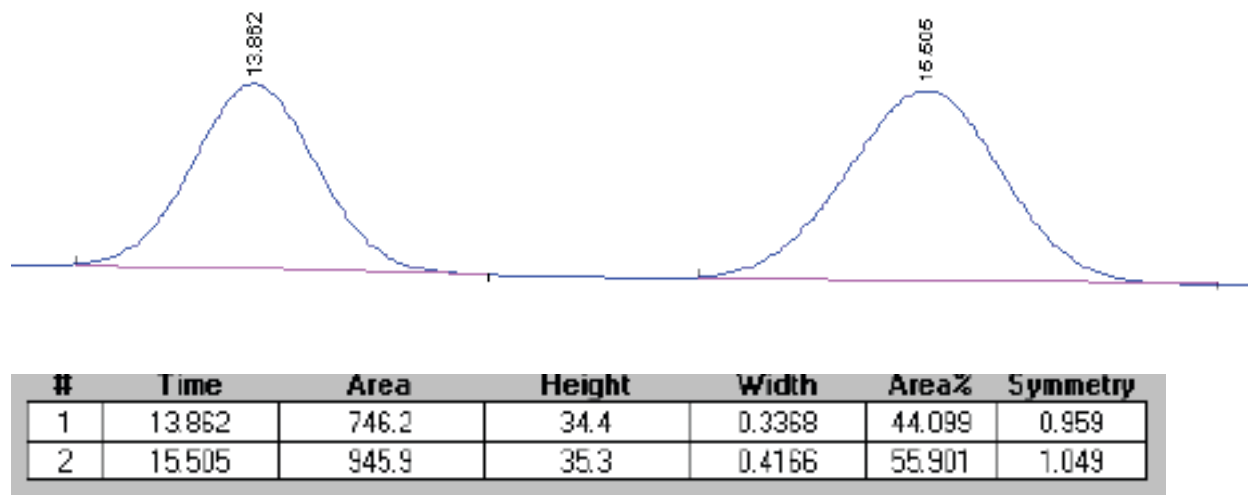


(R)-3-propionyl-3,4-dihydroisoquinolin-1(2H)-one (505): ^1H NMR (400 MHz,

CDCl_3) δ 8.07 (d, $J = 7.4$ Hz, 1H), 7.48 (td, $J = 7.5, 1.1$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.26 (t, $J = 5.3$ Hz, 1H), 6.97 (s, 1H), 4.37 (dd, $J = 10.7, 4.2$ Hz, 1H), 3.32

(dd, $J = 15.3, 4.7$ Hz, 1H), 3.13 (dd, $J = 15.2, 11.1$ Hz, 1H), 2.69-2.50 (m, 2H), 1.12 (t, $J = 7.2$ Hz, 3H).

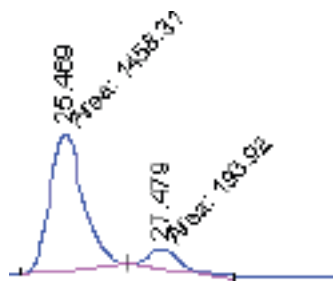
^{13}C NMR (400 MHz, CDCl_3) δ 203.9, 162.4, 133.5, 130.0, 126.1, 125.6, 125.1, 124.8, 56.8, 29.4, 28.6, 4.84, 4.83. IR (Thin Film) 1719, 1668, 1466, 1144, 801 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 204.1019; found 204.1023. *Chiral HPLC*: IC Column; 80:20 Hexane/iPrOH



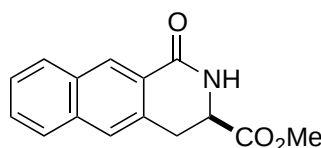
(R)-methyl 6-bromo-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

(490): ^1H -NMR (400 MHz; CDCl_3): δ 7.96 (d, J = 8.3 Hz, 1H), 7.54 (dd, J = 8.3, 1.1 Hz, 1H), 7.44 (s, 1H), 6.73 (s, 1H), 4.43 (ddd, J = 9.1, 5.3, 1.8 Hz, 1H), 3.88-3.78 (m, 3H), 3.37-3.19 (m, 2H). ^{13}C NMR (101 MHz; CDCl_3): δ 170.4, 164.5, 137.9, 131.0, 130.4, 129.9, 127.3, 53.03, 52.85, 30.7. IR (Thin Film) 1709, 1672, 1458, 1436, 771 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 283.9917; found 283.9920. *Chiral HPLC*: IA Column; 90:10 Hexane/iPrOH

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#	Time	Area	Height	Width	Area%	Symmetry
1	25.469	1458.3	30.3	0.8012	88.263	0.765
2	27.479	193.9	4	0.8152	11.737	0.543

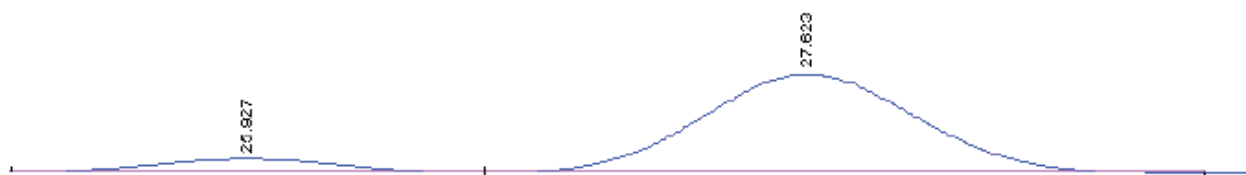


(R)-methyl 1-oxo-1,2,3,4-tetrahydrobenzo[glisoquinoline-3-carboxylate

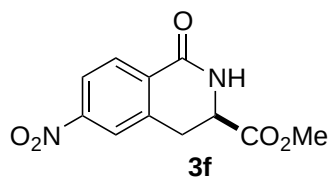
(497): This compound have been previously reported. Included is the

^1H NMR. ^1H NMR (400 MHz; CDCl_3): δ 8.63 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.6 Hz, 2H), 7.53 (td, J = 17.1, 8.0 Hz, 3H), 6.75 (s, 1H), 3.78 (d, J = 2.5 Hz, 4H), 3.52-3.47 (m, 1H), 3.36 (d, J = 9.4 Hz, 1H). *Chiral HPLC*: IA Column; 90:10 Hexane/iPrOH.

ENANTIOENRICHED



#	Time	Area	Height	Width	Area%	Symmetry
1	25.927	277	6.9	0.4968	10.817	1.005
2	27.623	2284.2	50.1	0.7039	89.183	0.943

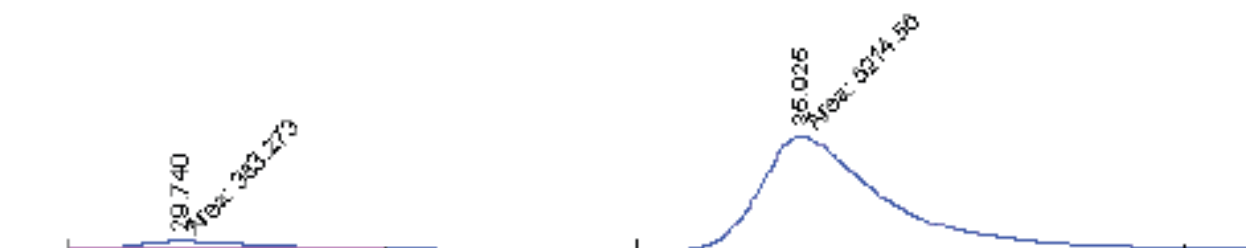


(R)-methyl 6-nitro-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

(494): $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.41-8.35 (m, 1H), 8.25-8.13 (m, 1H), 7.53-7.38 (m, 1H), 6.47-6.43 (m, 1H), 4.38 (ddd, $J = 9.5, 5.2, 2.2$ Hz, 1H), 3.74 (q, $J = 1.7$ Hz, 3H), 3.43-3.37 (m, 1H), 3.25 (dd, $J = 16.0, 9.5$ Hz, 1H). ^{13}C NMR (101 MHz; cdcl_3): δ 170.0, 137.6, 131.5, 129.8, 129.1, 128.3, 126.4, 125.1, 123.8, 122.65, 122.57, 52.7, 31.0. IR (Thin Film) 1740, 1677, 1527, 820, 749 cm^{-1} ; HRMS (ESI) m/e calcd (M+H) 251.0662; found 251.0657.

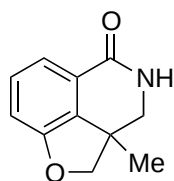
Chiral HPLC: IA Column; 90:10 Hexane/iPrOH

ENANTIOENRICHED



#	Time	Area	Height	Width	Area%	Symmetry
1	29.74	383.3	4.3	1.4815	6.847	0.545
2	35.925	5214.5	59	1.4722	93.153	0.47

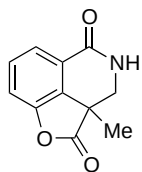
Tethered Alkenes



2a-methyl-3,4-dihydro-2H-furo[4,3,2-de]isoquinolin-5(2aH)-one (510): ^1H NMR

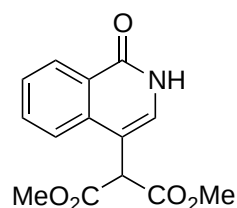
(400 MHz, CDCl_3) δ 7.35 (d, $J = 7.7$, 1H), 7.25 (d, $J = 3.2$, 1H), 6.92 (d, $J = 7.9$, 1H),

6.65 (t, $J = 0.5$, 1H), 4.51 (d, $J = 8.5$, 1H), 4.28 (d, $J = 8.5$, 1H), 3.69 (d, $J = 11.8$, 1H), 3.48 (dd, $J = 11.7$, 4.5, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 65.6, 157.1, 136.6, 129.4, 125.2, 117.9, 113.2, 84.1, 51.5, 39.6, 22.5.



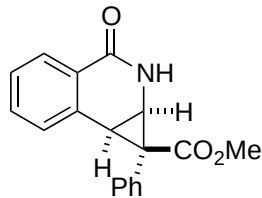
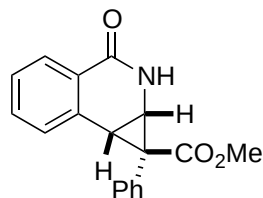
2a-methyl-3,4-dihydro-2H-furo[4,3,2-de]isoquinoline-2,5(2aH)-dione (511): ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, $J = 7.8$, 1H), 7.25-7.23 (m, 5H), 6.97 (d, $J = 8.0$, 1H), 6.06-6.05 (m, 1H), 3.98 (d, $J = 12.0$, 1H), 3.72 (d, $J = 4.2$, 3H), 3.28 (dd, $J = 12.2$, 4.7, 1H).

Cyclopropenes



dimethyl 2-(1-oxo-1,2-dihydroisoquinolin-4-yl)malonate (519): ^1H NMR (400 MHz, CDCl_3) δ 8.47 (dd, $J = 8.0$, 1.1, 1H), 7.71 (d, $J = 6.9$, 1H), 7.62 (d, $J = 8.1$, 1H), 7.57 (d, $J = 28.7$, 1H), 7.35 (s, 1H), 4.95 (s, 1H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 163.5, 136.4, 133.0, 128.8, 128.1, 127.0, 126.1, 122.3,

108.8, 53.1, 51.2.



(1R,1aR,7bR)-methyl 3-oxo-1-phenyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[c]isoquinoline-1-carboxylate (521) and (1R,1aS,7bS)-methyl 3-oxo-1-phenyl-1a,2,3,7b-tetrahydro-1H-

cyclopropa[c]isoquinoline-1-carboxylate (522): ^1H NMR (400 MHz, CDCl_3) δ See Spectra

Isoquinolones:

Isoquinolone **529** was previously prepared by Fagnou.⁴

Relative Rates of Bound and Unbound Catalyst

The following stock solutions were prepared:

Enzyme in H_2O - (43 mg in 1.6 ml, 6.6×10^{-2} M)

$[\text{RhCp}^*\text{biotin}\text{Cl}_2]_2$ in DMSO - (20 mg in 177.0 μl , 0.1 M)

Pivaloyl benzhydroxamic acid in MeOH - (100 mg in 1887 μl , 0.28 M)

Stir bars were added to 8 vials (0.5 dram). Each flask was charged with 200 µl of the enzyme solution. A rhodium solution was charged to each vial in various amounts (0.33 µl, 0.66 µl, 1.00 µl, 1.33 µl, 2.00 µl, 2.66 µl, 3.33 µl, 4 µl, all at 0.1 M). The vials were allowed to stir for 5 minutes. Each flask was then charged with 40 µl of the benzhydroxamic acid solution and 1.1 µl of methyl acrylate. The vials were sealed and allowed to stir. After 24 h the vials were diluted with 200 µl of ethyl acetate and allowed to stir for an additional 10 minutes. The ethyl acetate phase was transferred to a vial and the er was determined by chiral HPLC.

The data was fit the following equation:

$$\% (R)_{\text{calculated}} = \frac{k_{\text{bound}} \cdot \mu_{\text{bound}} \cdot \% (R)_{\text{bound}} + k_{\text{free}} \cdot \mu_{\text{free}} \cdot \% (R)_{\text{free}}}{k_{\text{bound}} \cdot \mu_{\text{bound}} + k_{\text{free}} \cdot \mu_{\text{free}}}$$

where:

k_{bound} = rate constant for reaction with protein

k_{free} = rate constant for reaction without protein

μ_{bound} = % of bound complexes

μ_{free} = % of free complexes

$\% (R)_{\text{bound}}$ = % (R) produced by bound complex

$\% (R)_{\text{free}}$ = % (R) produced by free complex

The fitting was performed using Equation Solver in Microsoft Excel program

Table S4.1 Raw Data for Kinetic Experiments with WT-SAV

	WT in AcOH				WT in H2O	
	Equiv of Metal	<i>er</i>			Equiv of Metal	<i>er</i>
Observed	1	68.5		Observed	1	70.2
	2	69			2	70.3
	3	69			3	71.7
	4	68.5			4	71.7
	5	68.0			6	69.4
	6	67.5			8	68.4
	7	67			10	66.4
	8	66			12	62
Best Fit	1			Best Fit	1	
	2				2	
	3				3	
	4	69			4	71.4
	5	68.42424 24242424			6	68.77837 83783784
	6	67.67441 86046512			8	66.78095 23809524
	7	66.79558 01104972			10	65.20851 06382979
	8	65.83333 33333333			12	63.93846 15384615
Equally Reactive	1			Equally Reactive	1	
	2				2	
	3				3	
	4	69			4	71.4
	5	66.43243 24324324			6	64.93333 33333333
	6	63.81818 18181818			8	61.7
	7	61.47169 81132075			10	59.76
	8	59.5			12	58.46666 66666667

Table S4.2 Raw Data **for** Kinetic Experiments with N118K-K121E

	N118K-K121E in AcOH				N118K-K121E in H2O	
	Equiv of Metal	er			Equiv of Metal	er
Observed	1	80.5		Observed	1	81.125
	2	81			2	80.625
	3	79.7			3	80.125
	4	79.8			4	80.125
	6	78.7			6	80
	8	78.7			8	79.95
	10	78.6			10	79.5
	12	77.6			12	79.375
Best Fit	1			Best Fit	1	
	2				2	
	3				3	
	4	79.8			4	80
	6	79.61490 68322981			6	79.91869 91869919
	8	79.31147 54098361			8	79.78417 26618705
	10	78.89696 96969697			10	79.59785 5227882
	12	78.38095 23809524			12	79.36170 21276596
Equally Reactive	1			Equally Reactive	1	
	2				2	
	3				3	
	4	79.8			4	80
	6	71.67272 72727273			6	70.66666 66666667
	8	64.9			8	66
	10	60.36521 73913044			10	63.2
	12	57.45			12	61.33333 33333333

Table S4.3 Raw Data for Kinetic Experiments with S112Y-K121E

	S112Y-K121E in AcOH				S112Y-K121E in H2O	
	Equiv of Metal	er			Equiv of Metal	er
Observed	1	89.7		Observed	1	90.7
	2	89.7			2	89.8
	3	89.1			3	88.9
	4	88.3			4	89.2
	6	87.5			6	88.8
	8	85.3			8	88.6
	10	83			10	87.5
	12	81.4			12	86.4
Best Fit				Best Fit		
	1				1	
	2				2	
	3				3	
	4	88.3			4	89.2
	6	86.90218 97810219			6	88.92846 71532847
	8	84.78623 85321101			8	88.48461 53846154
	10	82.20127 38853503			10	87.88085 10638298
	12	79.39302 3255814			12	87.13333 33333333
Equally Reactive	1			Equally Reactive	1	
	2				2	
	3				3	
	4	88.3			4	89.2
	6	77.85454 54545455			6	76.8
	8	69.15			8	70.6
	10	63.32173 91304348			10	66.88
	12	59.575			12	64.4

HABA Titrations

The following stock solutions were prepared:

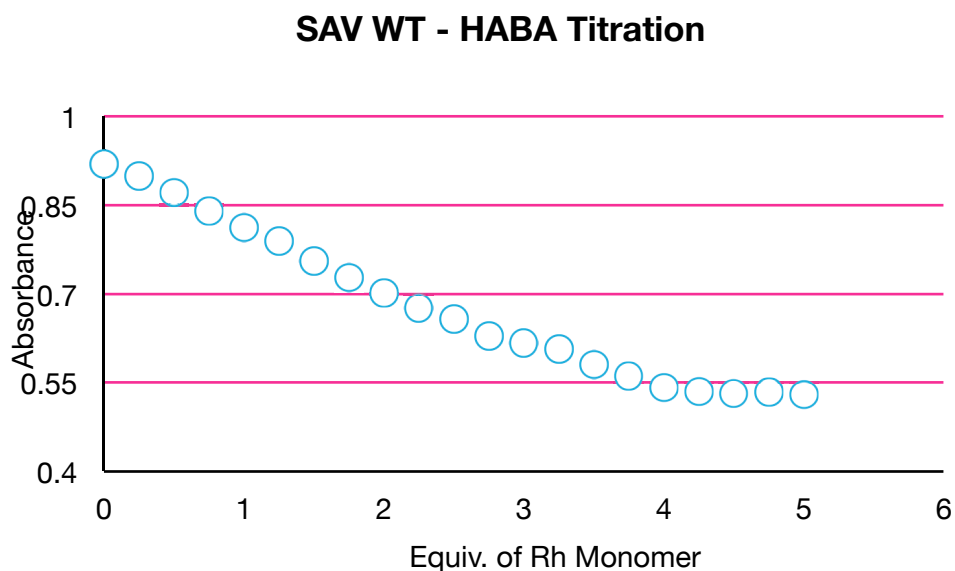
[RhCp*^{biotin}Cl₂]₂ in DMSO - 9.6×10^{-4} M (5.41 mg in 10 ml, 0.47 mM)

WT Sav in H₂O - 8.0×10^{-6} M (5.25 mg in 10 ml, 8.0 mM)

HABA in H₂O - 9.6×10^{-3} M (23.2 mg in 10 ml, 9.5 mM)

A cuvette is charged with 2.4 ml (8.0 mM) of protein solution and 0.5 ml of the HABA solution. UV absorbance was taken at 500 nm. 5 μ l of the rhodium solution (0.47 mM) was added to the cuvettes and turned 10 times and a UV absorbance was taken. This was repeated 20 times to develop a titration curve.

HABA Titration

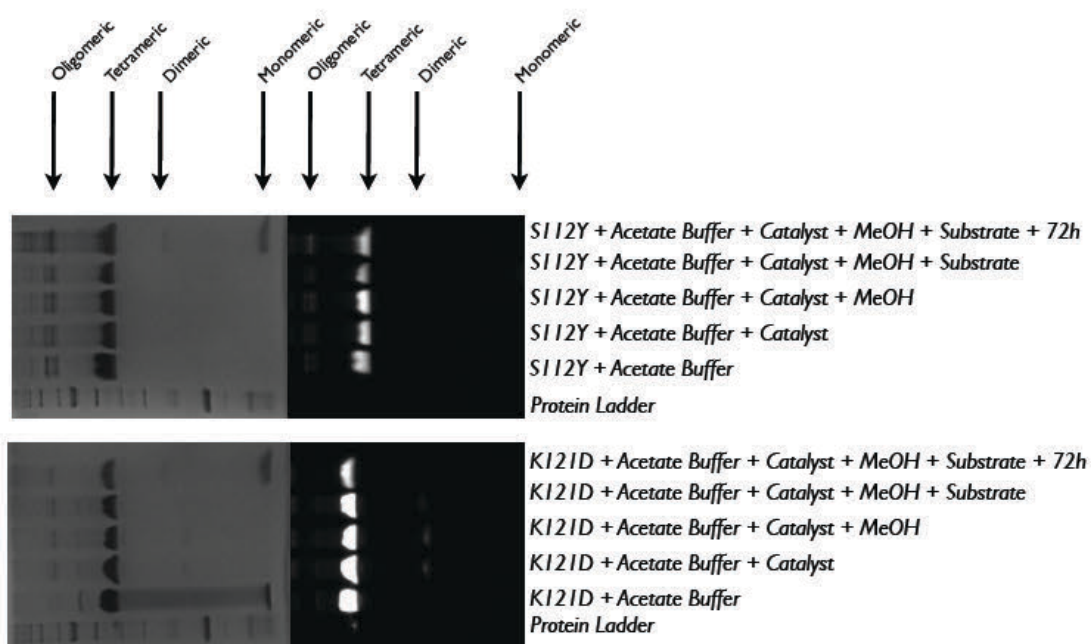


SDS-Page Analysis of the Reaction

It is well established that non-denatured, active streptavidin can be detected by SDS-PAGE using biotinylated fluorescein (B4F) as a specific marker. The same SDS-PAGE gels can also be stained with comassie-blue to visualize all proteins, right. Under non-denaturing conditions, streptavidin migrates primarily as an active tetramer, although the protein also has a known tendency to aggregate to form

oligomers (in some cases, dimers and monomers of streptavidin are also commonly detected as minor, active species).

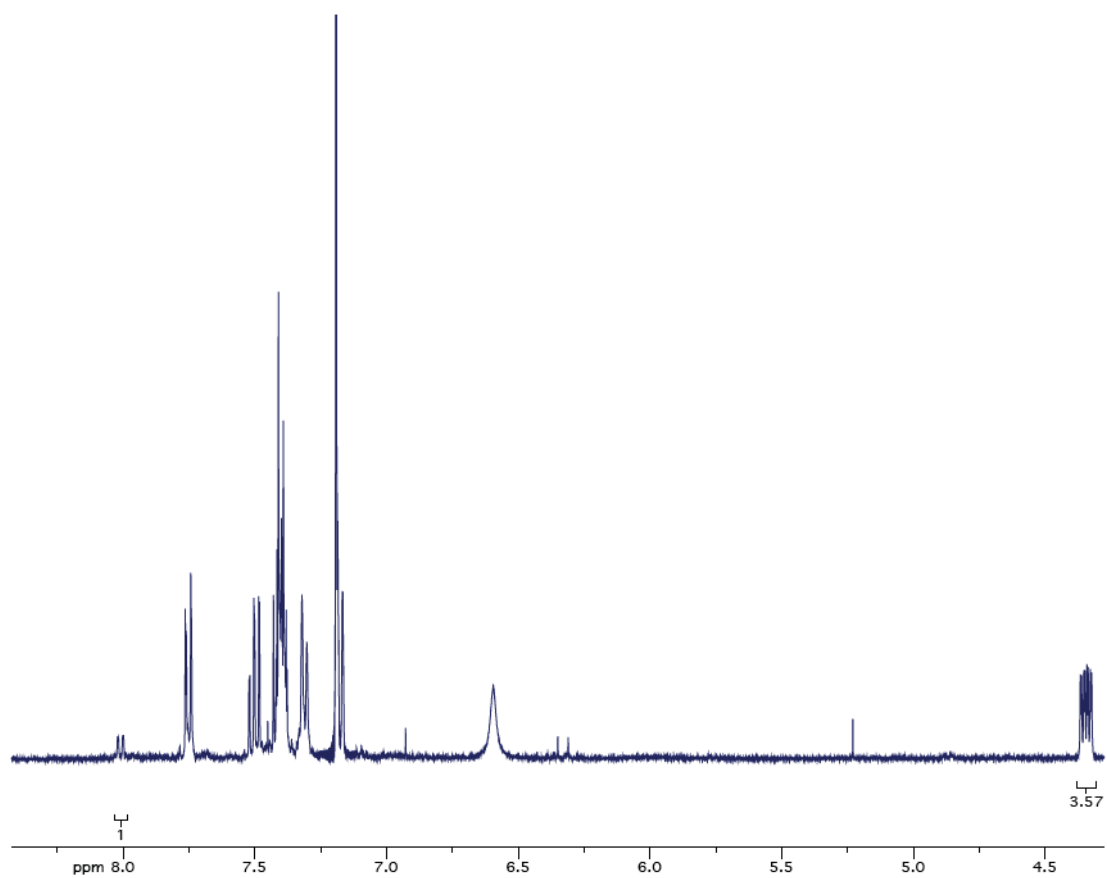
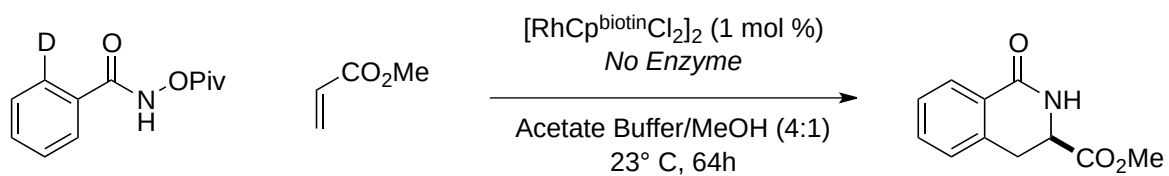
In this present study, under catalytic conditions the reaction mixture formed a suspension; upon microcentrifugation at 14'000rpm this suspension could be separated into a pellet and a clear supernatant. The pellet contained trace active streptavidin (Non- Denatured Pellet), which was able to bind biotinylated fluorescein. These figures show that as each solvent and compound is added to the reaction, the SAV mutant stays largely as the active tetramer, dimer, or oligomer. Further studies indicate that the precipitate in these reactions is largely starting material.

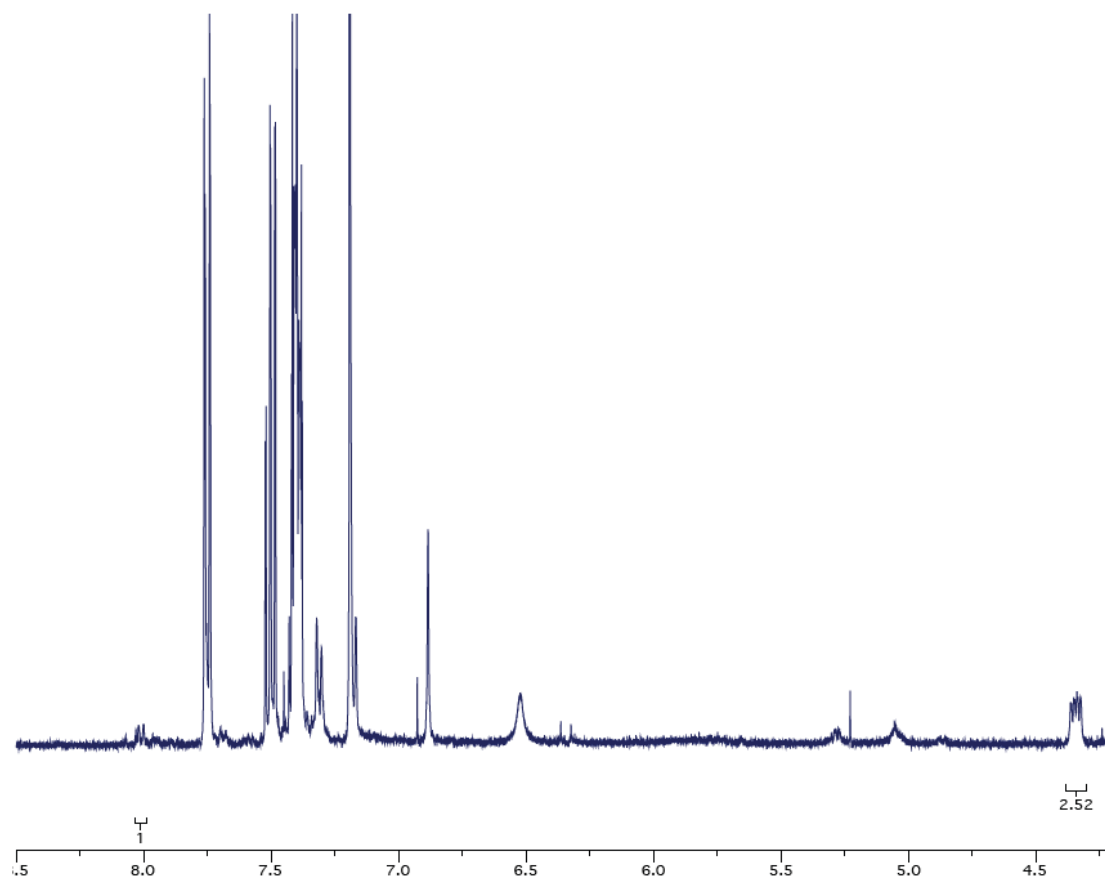
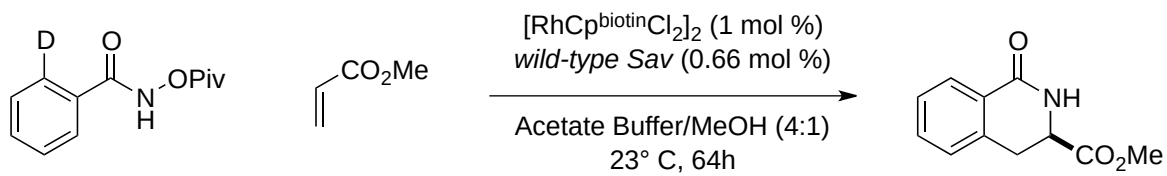


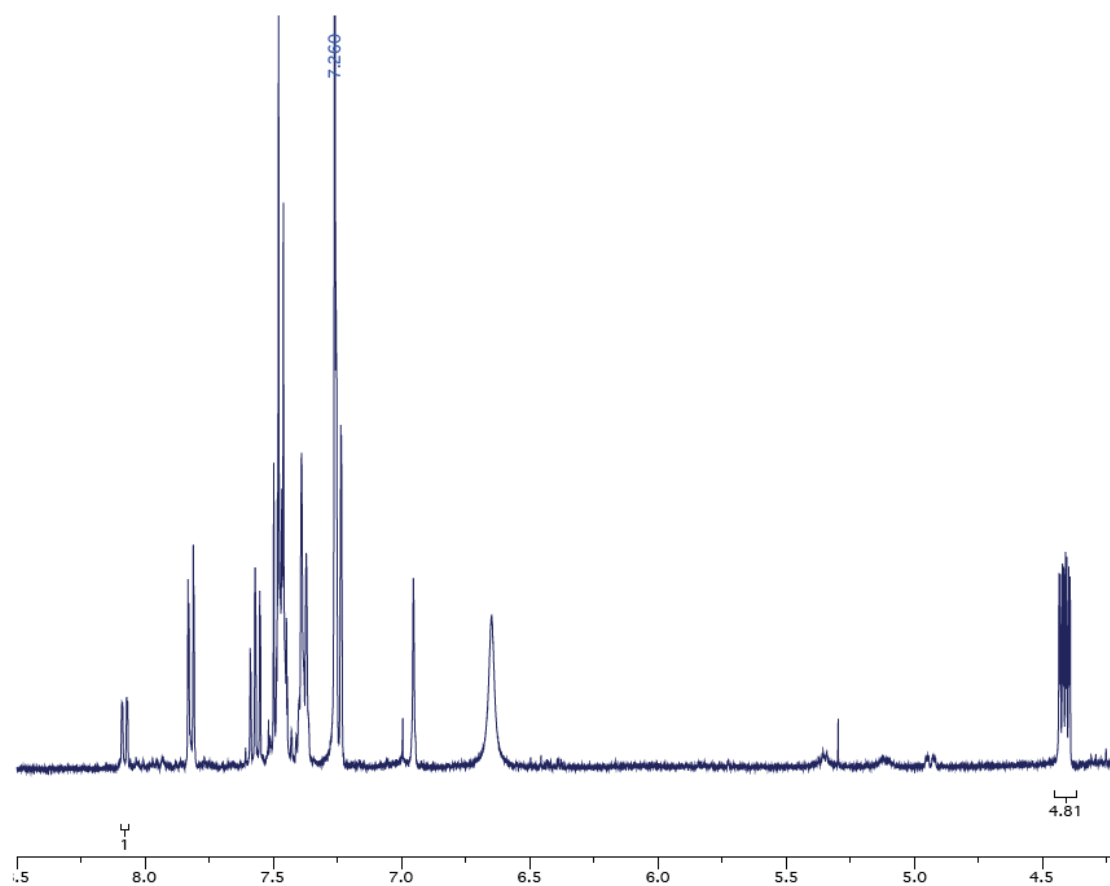
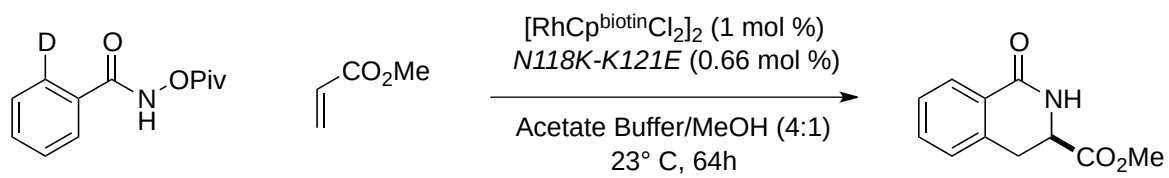
SDS-Page Gels.

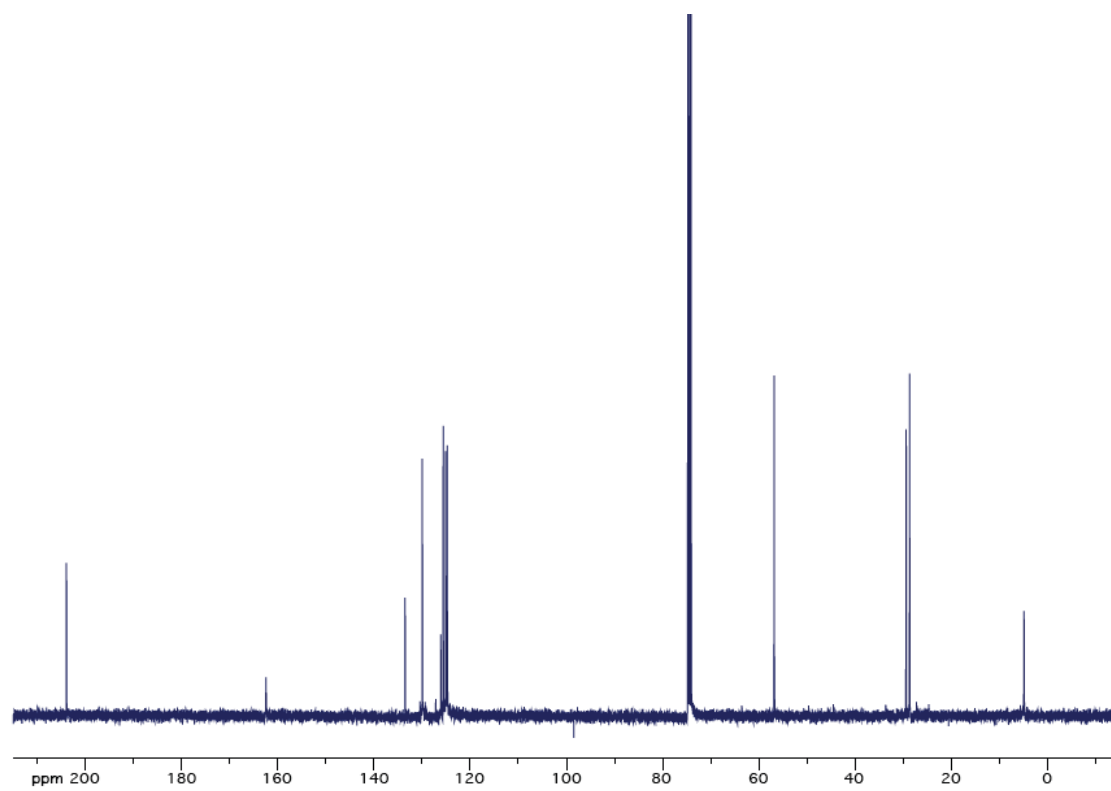
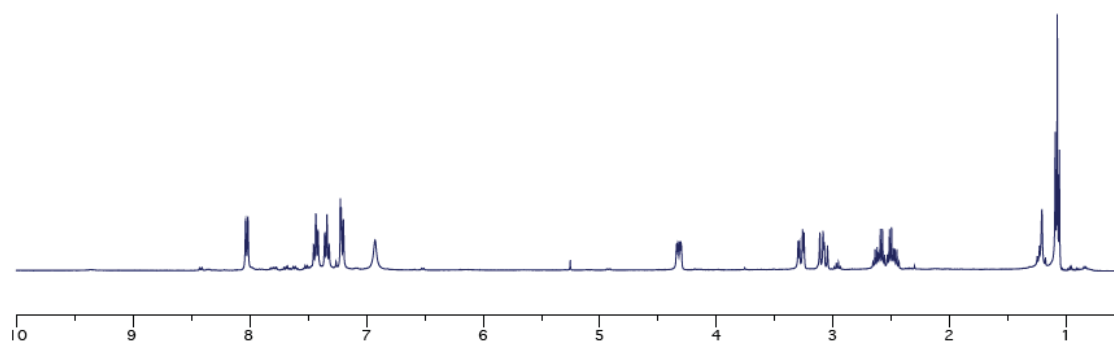
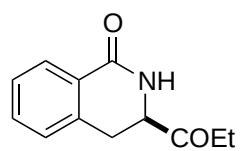
Right - B4F Stain, Left - Coomassie Stain

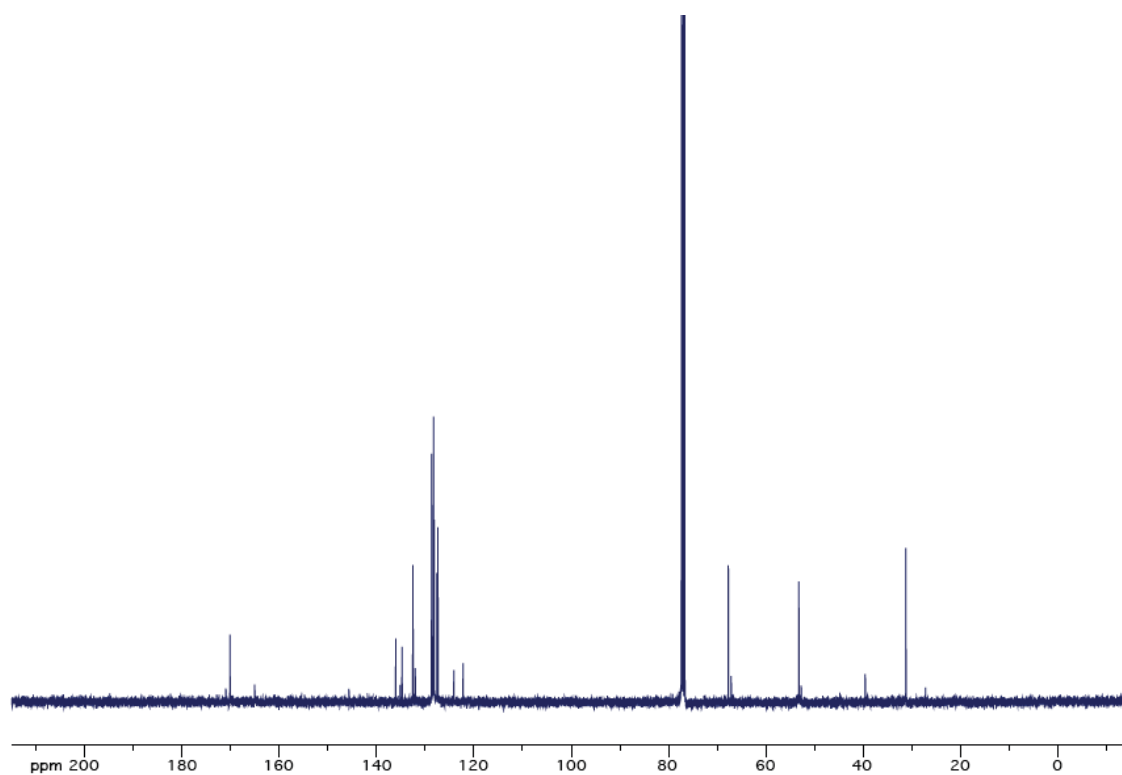
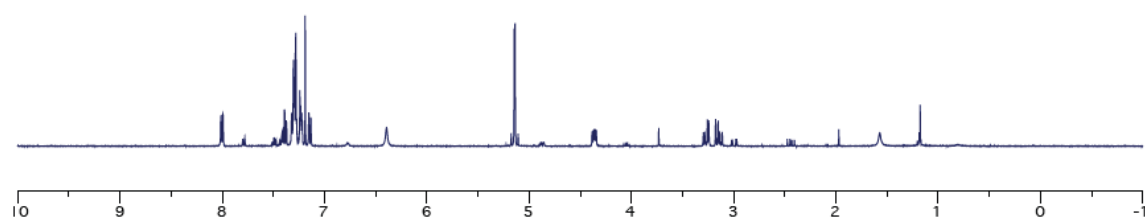
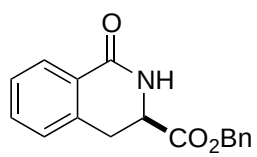
Kinetic Isotope Effect Raw Data

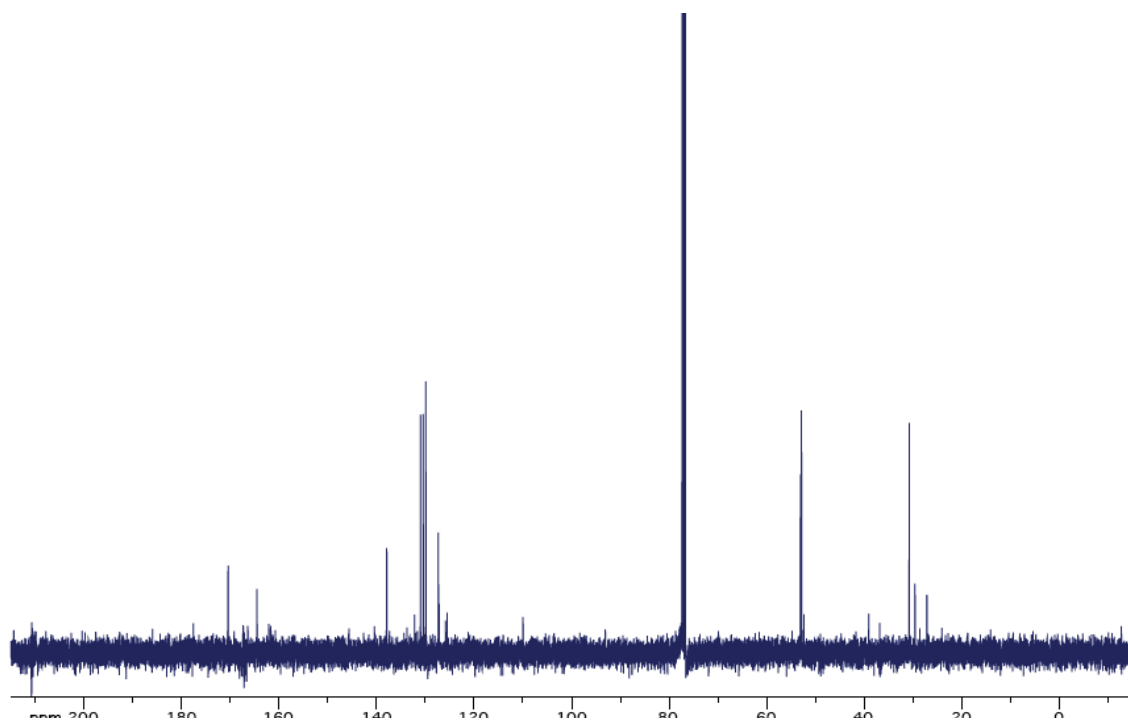
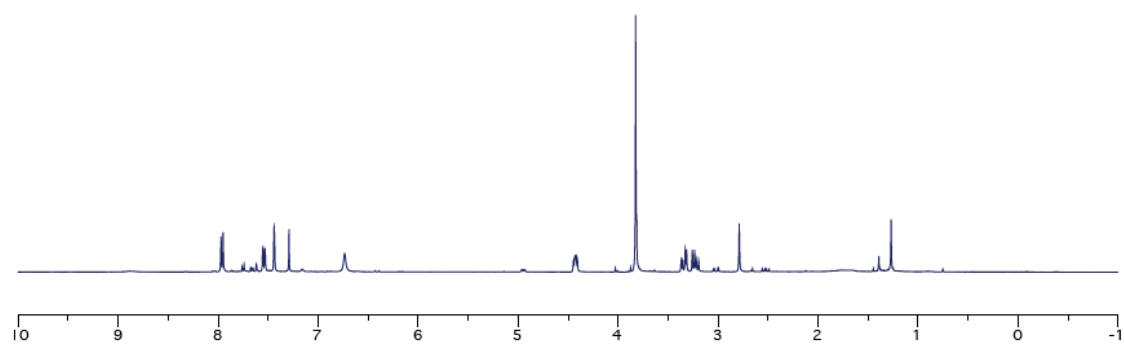
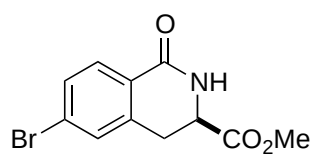


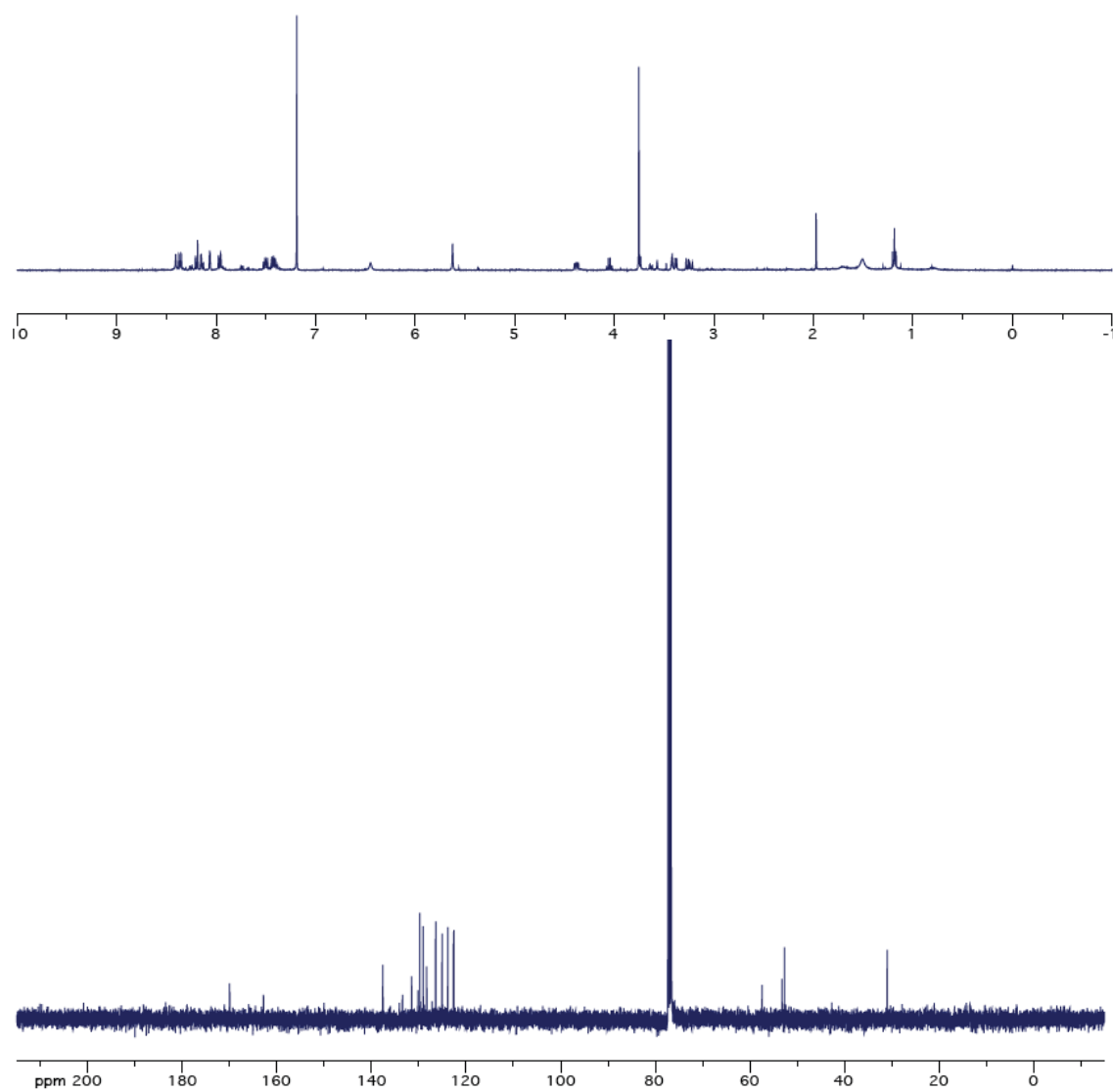
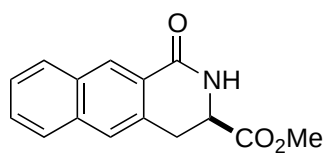


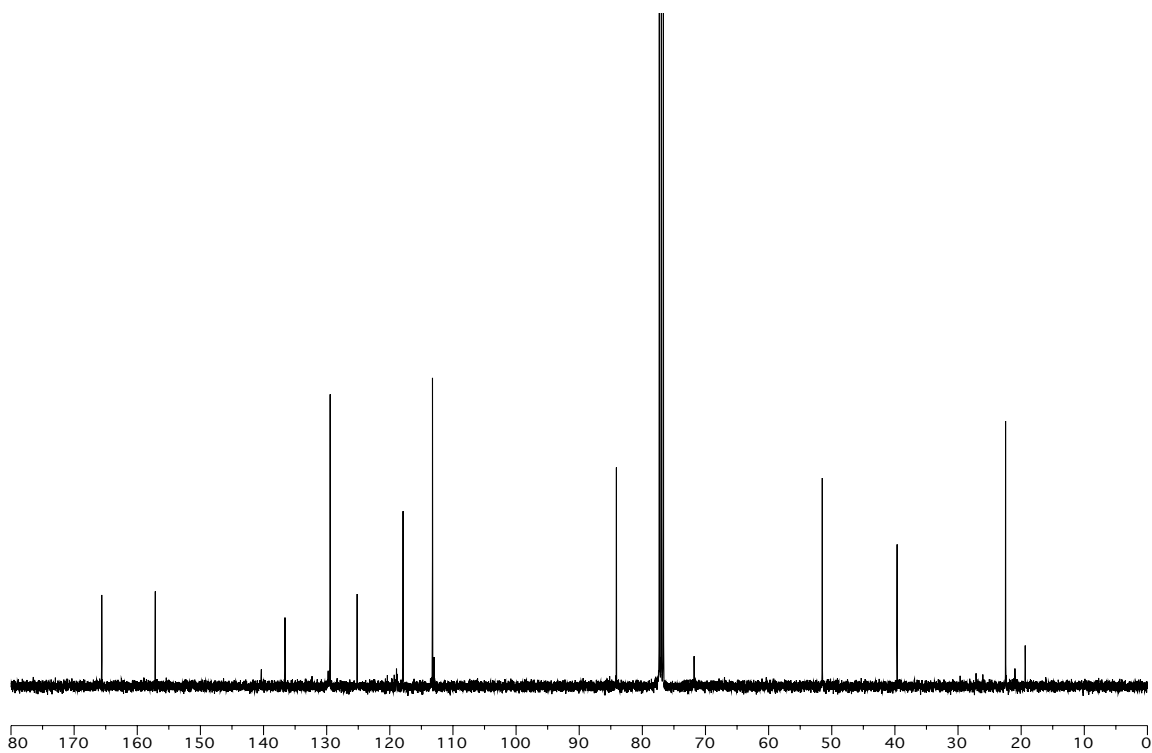
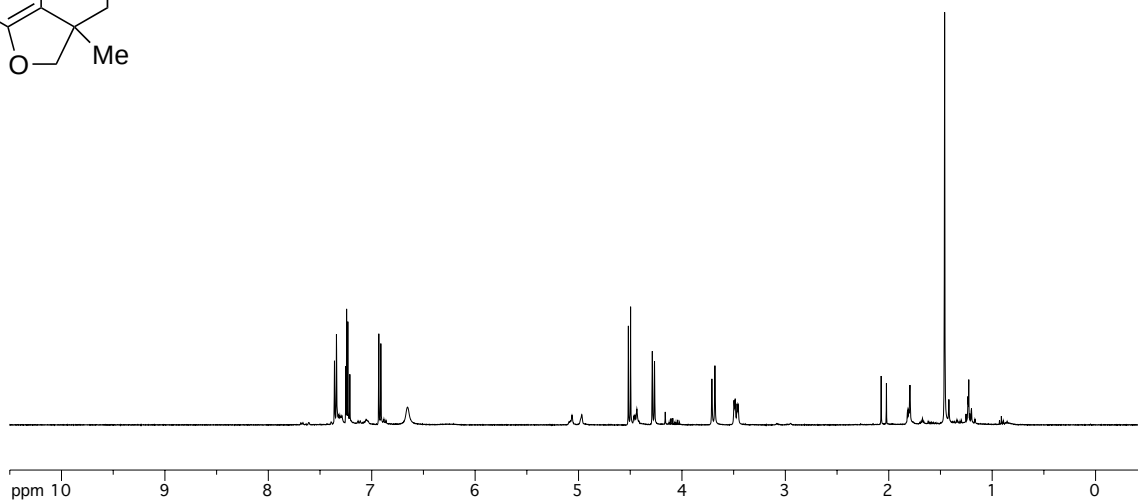
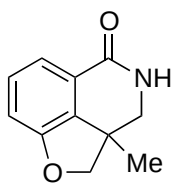


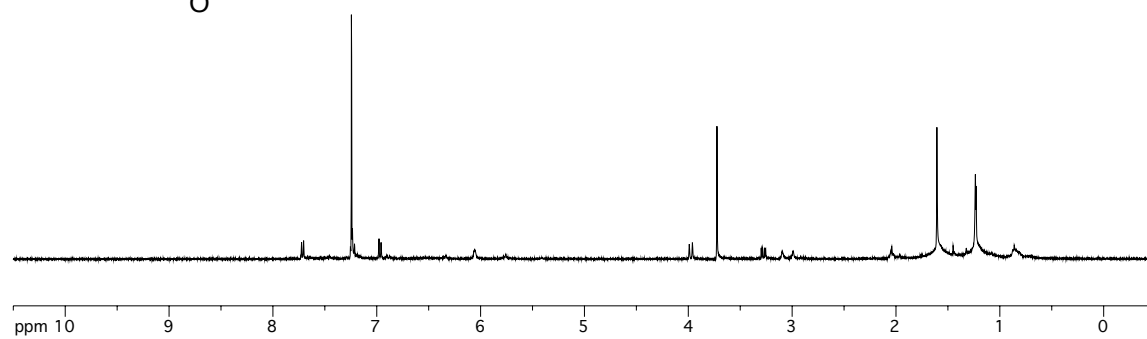
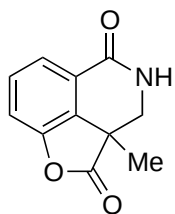


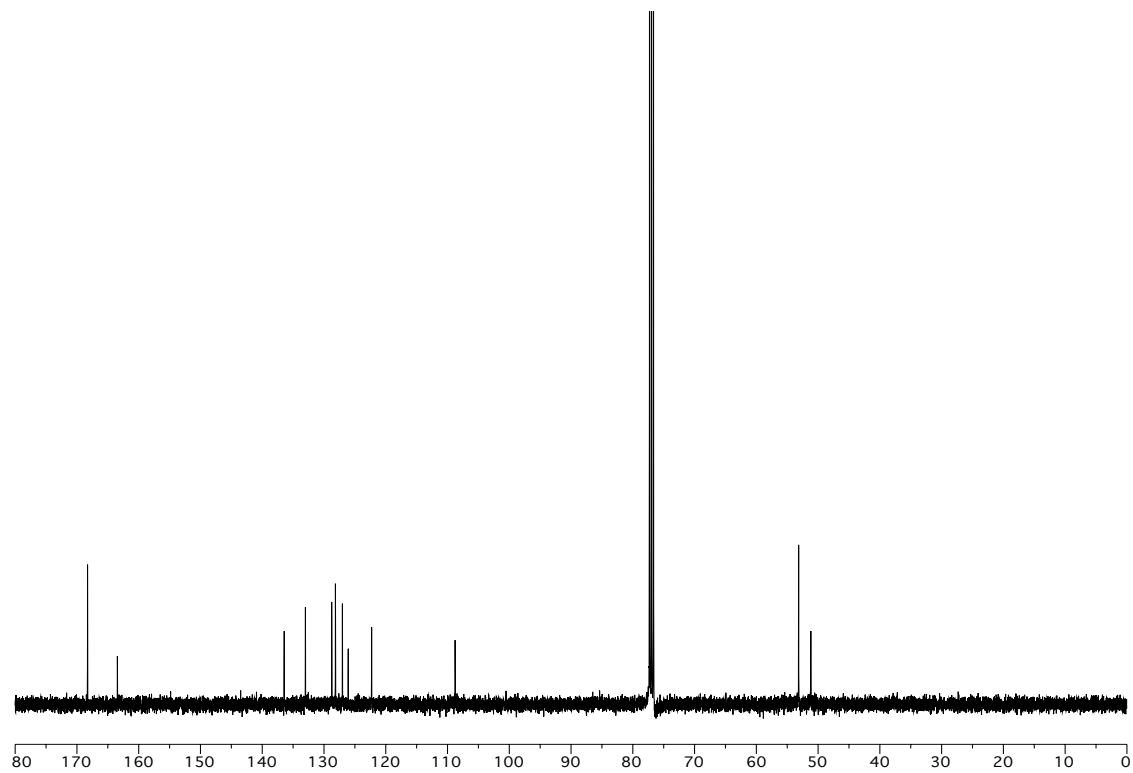
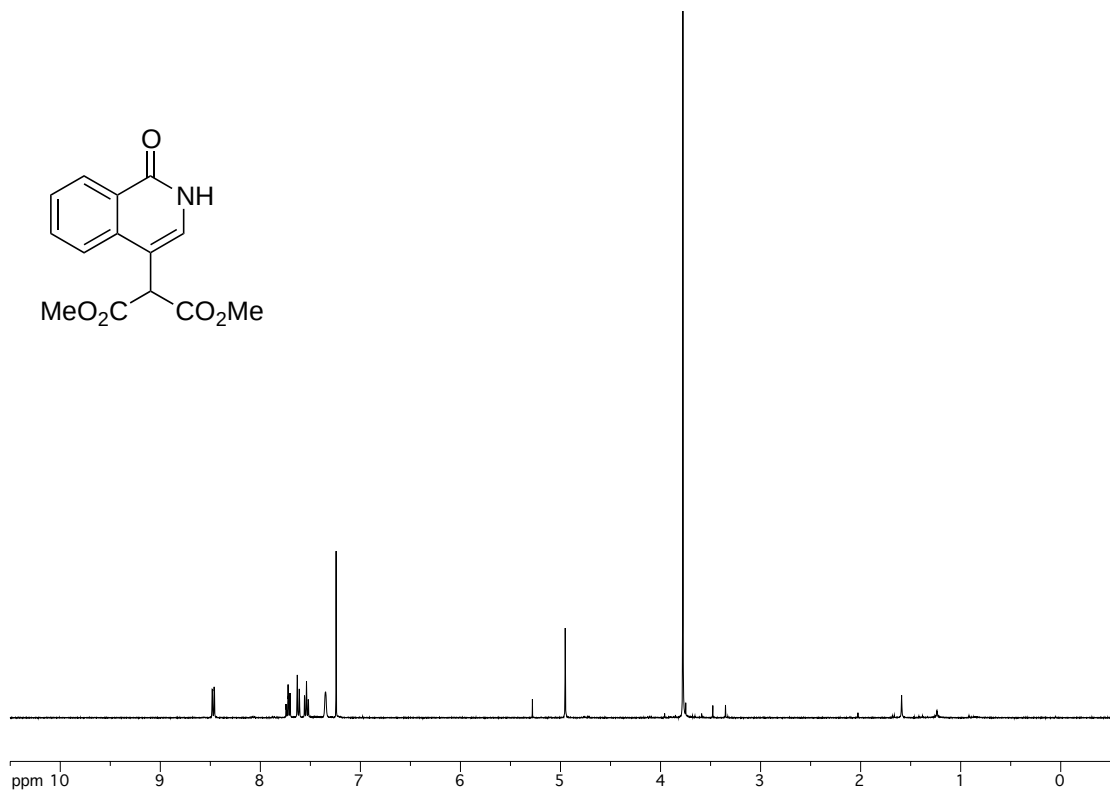
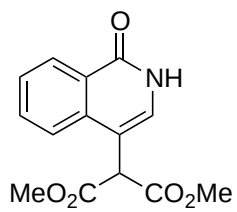


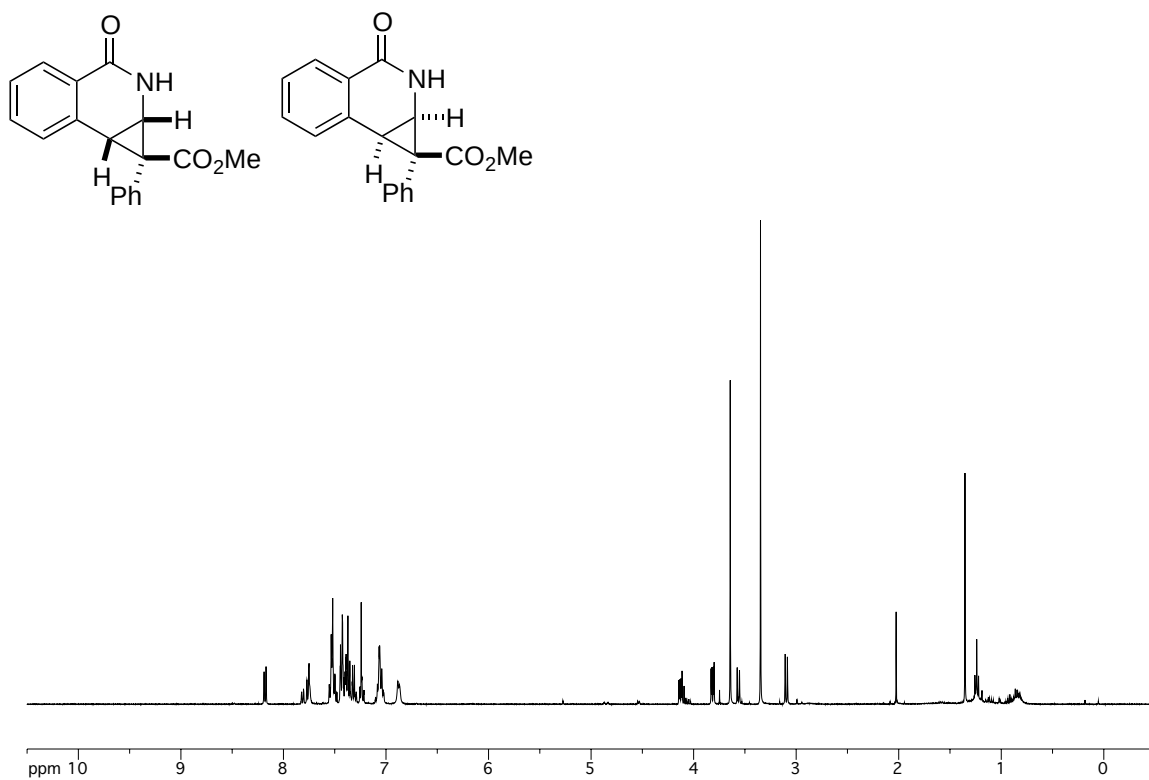












Appendix References

- (1) Zheng, L; Baumann, U.; Reymond, J.-L. *Nucleic Acids Res.* **2004**, 32, e115.
- (2) G. M. Morris *et al.* *J. Comput. Chem.* **2009**, 30, 2785.
- (3) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, 133, 2350.
- (4) Guimond, N.; Gorelsky, S. I. ; Fagnou, K. *J. Am. Chem. Soc.* **2011**, 133, 6449.
- (5) Reiner, T.; Jantke, D.; Raba, A.; Marziale, A. N.; Eppinger, J. *J. Organomet. Chem.* **2009**, 694, 1934.
- (6) Ito, M.; Tejima, N.; Yamamura, M.; Endo, Y.; Ikariya, T. *Organometallics* **2010**, 29, 1886.

Appendix 5

Coupling Benzamides and Diazo Compounds To Form γ -Lactams via Rhodium(III)-Catalyzed C–H Activation

General Methods

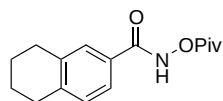
All reactions were carried out in 1.5 dram sealed vials under an atmosphere of air with magnetic stirring in an aluminum-heating block without drying or degassing of the vial. Column chromatography was performed on SiliCycle® Silica Flash® 40-63 μ m 60A. Thin Layer chromatography was performed on SiliCycle® 250 μ m 60A plates. Visualization was accomplished with UV light (254 nm), KMnO₄, and CAM.

¹H NMR and ¹³C NMR spectra were recorded on a Varian 300 and 400 MHz spectrometers at ambient temperature. ¹H NMR data are reported as the following: chemical shift in parts per million (δ , ppm) from chloroform (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets) and coupling constant (Hz). ¹³C NMR are reported as the following: chemical shifts are reported in ppm from CDCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisons VG Autospec. Infrared spectra (IR) were obtained on Bruker Tensor 27 FT-IR spectrometer.

General Procedure for the Synthesis of Pivaloyl-Benzhydroxamic Acids

All pivaloyl protected benzhydroxamic acids were prepared as described by Fagnou and Guimond.¹ Protected hydroxamic acids were previously reported.^{1,2,3,4}

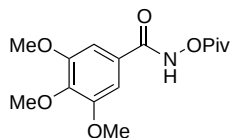
***N*-(pivaloyloxy)-5,6,7,8-tetrahydronaphthalene-2-carboxamide (310):** ^1H NMR



(400 MHz, CDCl_3) δ 9.29 (s, b, 1H), 7.52 (m, 2H), 7.13 (d, $J = 7.8$ Hz, 1H), 2.79 (m, 4H), 1.81 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.1, 167.1, 142.7,

137.8, 129.5, 128.2, 127.9, 124.2, 38.4, 29.5, 29.2, 27.0, 22.82, 22.74.

3,4,5-trimethoxy-*N*-(pivaloyloxy)benzamide (550): ^1H NMR (400 MHz, CDCl_3)



δ 9.21 (s, b, 1H), 7.05 (s, 2H), 3.89 (m, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.8, 153.3, 125.9, 104.7, 60.9, 56.3, 38.5, 27.0.

Trifluoromethyl Diazo-Compounds

A flamed-dried 250 ml round bottom flask was cooled under vacuum and placed under an argon atmosphere. The flask was then charged with the appropriate aryl bromide (10 mmol), dissolved in anhydrous THF (100 mL, 0.1 M) and chilled to -78°C . $n\text{-BuLi}$ (1.6 M in hexane, 6.6 mL, 10.5 mmol) was slowly added drop-wise over 10 minutes and stirred for an additional 10 minutes. Trifluoromethyl Weinreb ketone (10.5 mmol) was then slowly added via syringe and the mixture was allowed to stir at -78°C for two hours. The dry-ice/acetone bath was removed then replaced with an ice bath and the reaction was stirred for an additional 30 minutes. The reaction was quenched with sat. NH_4Cl solution (30 mL) and 1 M HCl (30 mL) followed by extraction of the aqueous layer with Et_2O (3x40 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated *in vacuo* (some volatile CF_3 -ketones were concentrated with a chilled water bath). The crude clear-yellow oil was then vacuum distilled ($100\text{--}125^\circ\text{C}$ at 1-2 torr) to afford the clean trifluoromethyl ketones in 60-70% yield.

The ketone was converted to the diazo compound as described by Davies.⁵

General Procedure A for Iso-Indolone Synthesis

A 1.5 dram vial was charged with a stirbar, amide (0.25 mmol, 1 equiv), [RhCp*Cl₂]₂ (0.0025 mmol, 1 mol %), and Cs₂CO₃ (0.05 mmol, 20 mol %). The mixture was dissolved in CH₃CN (2.5 mL, 0.1M) and stirred. After 2 minutes the vial was charged with the diazo compound (0.25 mmol, 1 equiv) and then sealed. After 3 hours the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography. Some compounds contain a small amount of pivalic acid after the initial column. This can be removed by placing the residue on a small plug of silica gel and eluting with 2:1 Hexane/EtOAc with 1% Et₃N.

General Procedure A for Iso-Indolone Synthesis (1 gram scale)

A 1.5 dram vial was charged with a stirbar, amide (5 mmol, 1 equiv), [RhCp*Cl₂]₂ (0.025 mmol, 0.5 mol %), and Cs₂CO₃ (1 mmol, 20 mol %). The mixture was dissolved in CH₃CN (50 mL, 0.1M) and stirred. After 2 minutes the vial was charged with the diazo compound (5 mmol, 1 equiv) and then sealed. After 3 hours the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via recrystallization with EtOAc/Hexanes.

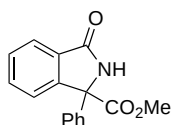
General Procedure B for Iso-Indolone Synthesis

A 1.5 dram vial was charged with a stirbar, amide (0.25 mmol, 1 equiv), [RhCp*Cl₂]₂ (0.0025 mmol, 1 mol %), and Cs₂CO₃ (0.05 mmol, 20 mol %). The mixture was dissolved in CH₃CN (2.5 mL, 0.1M) and stirred. After 2 minutes the vial was charged with the diazo compound (0.25 mmol, 1 equiv), sealed, and warmed to 60 °C. After the reaction was complete as determined by TLC the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography. Some compounds contain a small amount of pivalic acid after the initial column. This can be removed by placing the residue on a small plug of silica gel and eluting with 2:1 Hexane/EtOAc with 1% Et₃N.

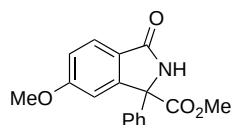
General Procedure C for Iso-Indolone Synthesis

A 1.5 dram vial was charged with a stirbar, amide (0.25 mmol, 1 equiv), [RhCp*Cl₂]₂ (0.0025 mmol, 1 mol %), and Cs₂CO₃ (0.05 mmol, 20 mol %). The mixture was dissolved in CH₃CN (2.5 mL, 0.1M) and stirred. After 2 minutes the vial was charged with the diazo compound (0.25 mmol, 1 equiv), sealed, and warmed to 80 °C. After the reaction was complete as determined by TLC the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography. Some compounds contain a small amount of pivalic acid after the initial column. This can be removed by placing the residue on a small plug of silica gel and eluting with 2:1 Hexane/EtOAc with 1% Et₃N.

Product Characterization

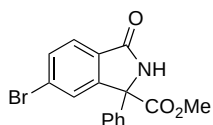


methyl 3-oxo-1-phenylisoindoline-1-carboxylate (544): The product was isolated as an off-white solid in 81% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. When the reaction is performed on gram scale, **3a** is isolated in 75% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.86-7.84 (m, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.59 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 (td, *J* = 7.4, 1.0 Hz, 1H), 7.39-7.33 (m, 5H), 7.25 (s, 1H), 3.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 169.6, 145.2, 138.2, 132.5, 130.4, 129.3, 129.1, 128.8, 125.37, 125.27, 123.8, 70.6, 53.4; **IR (thin film)** 1743, 1703, 1244, 1018, 688 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 268.09; found 268.1; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).



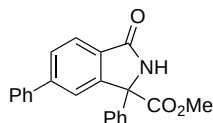
methyl 6-methoxy-3-oxo-1-phenylisoindoline-1-carboxylate (552): The product was isolated as an off-white solid in 84% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.37-7.34 (m, 5H), 7.15 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.94 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 169.4, 163.4, 147.6, 138.3, 129.1, 128.8, 125.38, 125.20, 115.9, 110.2, 70.3, 55.8, 53.4; **IR (thin**

film) 1747, 1699, 1443, 1249, 1098 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 298.1; found 298.1; **R_f** = 0.11 (1:1 Hexane/Ethyl Acetate).



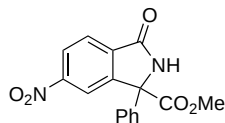
methyl 6-bromo-3-oxo-1-phenylisoindoline-1-carboxylate (553): The product was isolated as an off-white solid in 99% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl

Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.84 (d, J = 1.4 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 1H), 7.40-7.34 (m, 5H), 7.21 (s, 1H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.3, 168.6, 146.9, 137.5, 132.8, 129.28, 129.23, 129.08, 128.6, 127.3, 125.24, 125.19, 70.3, 53.6; **IR (thin film)** 1706, 1606, 1154, 1114, 839 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 345.0; found 345.0; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).



methyl 3-oxo-1,6-diphenylisoindoline-1-carboxylate (554): The product was isolated as an off-white solid in 79% yield following general procedure A. The

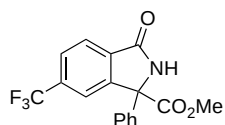
purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.91-7.88 (m, 2H), 7.74 (dd, J = 7.9, 1.3 Hz, 1H), 7.60-7.57 (m, 2H), 7.48-7.32 (m, 8H), 7.04 (s, 1H), 3.84 (d, J = 1.9 Hz, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.7, 169.3, 145.9, 139.9, 138.1, 129.1, 128.82, 128.77, 128.5, 128.1, 127.4, 125.3, 124.06, 123.86, 70.5, 53.4; **IR (thin film)** 1703, 1615, 1155, 1116, 844 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 344.1; found 344.2; **R_f** = 0.19 (1:1 Hexane/Ethyl Acetate).



methyl 6-nitro-3-oxo-1-phenylisoindoline-1-carboxylate (555): The product was isolated as an yellow solid in 88% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl

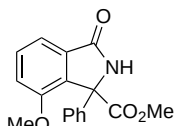
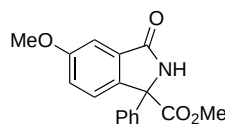
Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.85 (ddd, J = 7.5, 1.1, 0.8 Hz, 1H), 7.71 (dt, J = 7.7, 0.9 Hz, 1H), 7.59 (td, J = 7.5, 1.3 Hz, 1H), 7.52 (td, J = 7.4, 1.1 Hz, 1H), 7.38-7.33 (m, 5H), 7.01 (s, 1H), 3.84 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.8, 169.5, 145.2, 138.2, 132.6, 130.3, 129.3, 129.1, 128.8, 125.35,

125.28, 123.8, 70.6, 53.4; **IR (thin film)** 1703, 1611, 1242, 1152, 1113 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 313.1; found 313.1; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).



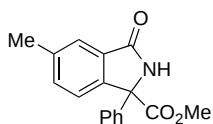
methyl 3-oxo-1-phenyl-6-(trifluoromethyl)isoindoline-1-carboxylate (556): The product was isolated as an off-white solid in 74% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl

Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.95-7.94 (m, 2H), 7.77 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.36 (d, J = 7.5 Hz, 5H), 7.24 (s, 1H), 3.85 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.1, 168.2, 145.7, 137.2, 134.4 (q), 133.6, 129.36, 129.20, 126.72, 126.68, 126.65, 125.2, 124.5, 122.57, 122.53, 70.8, 53.7; **¹⁹F NMR** (376 MHz; CDCl_3): δ -62.4; **IR (thin film)** 1742m 1703, 1612, 1245, 1128 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 336.1; found 336.1; **R_f** = 0.28 (1:1 Hexane/Ethyl Acetate).



methyl 5-methoxy-3-oxo-1-phenylisoindoline-1-carboxylate (557): The products were isolated as an off-white solid in 74% yield in a 1.1:1 ratio is regioisomers favoring **1g** following

general procedure B. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. Under these conditions the two isomers were inseparable. **¹H NMR** (400 MHz, CDCl_3) δ 7.56 (d, J = 8.5 Hz, 1H), 7.46-7.44 (m, 2H), 7.36-7.27 (m, 10H), 7.19 (s, 1H), 7.11 (dd, J = 8.5, 2.5 Hz, 1H), 7.02 (dd, J = 5.9, 3.0 Hz, 2H), 3.83 (s, 3H, major), 3.80 (s, 3H, major), 3.78 (s, 3H, minor), 3.72 (s, 3H, minor); **¹³C NMR** (100 MHz, CDCl_3) δ 170.21, 170.10, 169.8, 169.52, 169.41, 163.7, 160.9, 155.4, 138.4, 137.3, 136.5, 132.0, 131.2, 129.0, 128.7, 128.34, 128.21, 126.5, 126.1, 125.4, 120.8, 116.0, 115.7, 106.4, 70.5, 70.3, 55.79, 55.72, 53.32, 53.16; **IR (thin film)** 1742, 1702, 1606, 1491, 1155 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 298.1; found 298.1; **R_f** = 0.17 (1:1 Hexane/Ethyl Acetate).

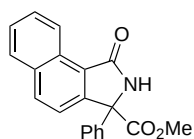
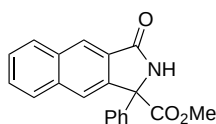


methyl 5-methyl-3-oxo-1-phenylisoindoline-1-carboxylate (558): The product

was isolated as an off-white solid in 97% yield following general procedure A. The

purification for performed via flash chromatography using 1:1 Hexanes/Ethyl

Acetate. **¹H NMR** (400 MHz, CDCl₃) δ 7.63 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.34-7.31 (m, 5H), 6.89 (s, 1H), 3.85-3.81 (m, 3H), 2.42 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 170.0, 169.6, 142.5, 139.6, 138.4, 133.6, 130.5, 129.1, 128.7, 125.3, 125.0, 124.0, 70.4, 53.4, 21.3; **IR (thin film)** 1743, 1702, 1450, 1243, 1112 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 282.1; found 282.1; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).

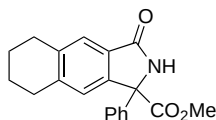


methyl 3-oxo-1-phenyl-2,3-dihydro-1H-benzo[f]isoindole-1-

carboxylate (559): The products were isolated as an off-white

solid in 68% yield in a 2:1 ratio is regioisomers favoring **1i**

following general procedure B. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. Under these conditions the two isomers were inseparable. **¹H NMR** (400 MHz, CDCl₃) δ 8.12 (s, 1H), 8.05-7.99 (m, 2H), 7.96-7.86 (m, 3H), 7.60-7.52 (m, 3H), 7.44-7.39 (m, 3H), 7.37-7.30 (m, 5H), 7.16-7.14 (m, 1H), 6.94 (s, 1H), 3.85 (s, 3H, major), 3.82 (s, 3H, minor); **¹³C NMR** (100 MHz, CDCl₃) δ 170.2, 169.0, 139.9, 138.9, 135.5, 133.3, 131.4, 129.5, 129.12, 129.01, 128.96, 128.90, 128.82, 128.63, 128.09, 127.99, 127.7, 127.04, 126.93, 126.80, 126.6, 125.4, 124.9, 124.5, 119.5, 70.4, 53.5; **IR (thin film)** 1741, 1701, 1608, 1156, 1113 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 318.1; found 318.1; **R_f** = 0.19 (1:1 Hexane/Ethyl Acetate)

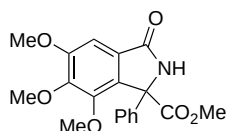


methyl 3-oxo-1-phenyl-2,3,5,6,7,8-hexahydro-1H-benzo[f]isoindole-1-

carboxylate (560): The product was isolated as an off-white solid in 94% yield

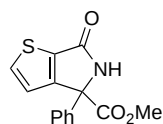
following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl₃) δ 7.52 (s, 1H), 7.35-7.29 (m, 6H), 6.89 (d, *J* = 9.2 Hz, 1H), 3.84-3.77 (m, 3H), 2.88-2.76 (m, 4H), 1.78-1.73 (m, 4H); **¹³C NMR** (100 MHz, CDCl₃) δ 170.2, 169.9, 142.8, 142.4, 139.0, 138.7, 129.09, 129.02, 128.6, 127.7, 125.55, 125.45, 125.35, 124.1, 70.3, 53.3,

30.2, 29.5, 22.76, 22.71; **IR (thin film)** 1737, 1699, 1433, 1152, 1006 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 322.1; found 322.1; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).



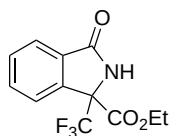
methyl 5,6,7-trimethoxy-3-oxo-1-phenylisoindoline-1-carboxylate (561): The product was isolated as an off-white solid in 87% yield following general procedure

B. Column chromatography was prepared Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.33-7.28 (m, 5H), 7.13 (s, 1H), 6.90 (s, 1H), 3.90 (s, 3H), 3.90-3.86 (m, 4H), 3.86-3.81 (m, 5H), 3.46 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.6, 169.4, 155.9, 149.6, 146.5, 137.1, 131.8, 128.45, 128.41, 126.2, 125.3, 101.6, 70.2, 60.8, 60.2, 56.3, 53.3; **IR (thin film)** 1745, 1701, 1347, 1238, 1099 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 358.1; found 358.1; **R_f** = 0.11 (1:1 Hexane/Ethyl Acetate).



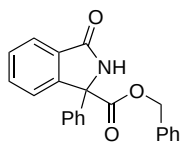
methyl 6-oxo-4-phenyl-5,6-dihydro-4H-thieno[2,3-c]pyrrole-4-carboxylate (562): The product was isolated as an off-white solid in 50% yield following general procedure B.

Column chromatography was prepared 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.68 (dd, J = 4.8, 0.9 Hz, 1H), 7.41-7.32 (m, 5H), 7.24 (d, J = 0.9 Hz, 1H), 7.07 (s, 1H), 3.80 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.2, 165.0, 155.5, 137.2, 136.2, 134.2, 129.13, 128.93, 125.3, 122.7, 69.8, 53.5; **IR (thin film)** 1742, 1697, 1435, 1253, 1155 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 374.1; found 374.1; **R_f** = 0.22 (1:1 Hexane/Ethyl Acetate).



ethyl 3-oxo-1-(trifluoromethyl)isoindoline-1-carboxylate (564): The product was isolated as an off-white solid in 50% yield following general procedure C. Column chromatography was prepared 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ

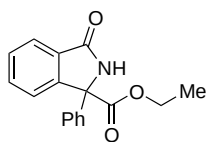
7.88-7.85 (m, 2H), 7.68-7.59 (m, 2H), 7.28 (s, 1H), 4.32 (q, J = 7.1, 2H), 1.32 (q, J = 7.2, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.8, 164.1, 137.3, 133.1, 131.3, 130.9, 124.9, 124.4, 124.1, 121.3, 68.6 (q), 63.9, 13.8.



benzyl 3-oxo-1-phenylisoindoline-1-carboxylate (577): The product was isolated as

an off-white solid in 95% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3)

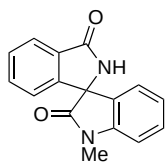
δ 7.83 (d, $J = 7.2$ Hz, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.55 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.4, 1.0$ Hz, 1H), 7.33-7.24 (m, 11H), 5.23 (d, $J = 3.0$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.7, 169.2, 145.2, 138.1, 134.6, 132.5, 130.4, 129.3, 128.75, 128.61, 125.3, 123.8, 70.7, 68.3; **IR (thin film)** 1704, 1613, 1228, 1008, 743 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 344.1; found 344.1; $R_f = 0.48$ (1:1 Hexane/Ethyl Acetate).



ethyl 3-oxo-1-phenylisoindoline-1-carboxylate (578): The product was isolated as

an off-white solid in 96% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3)

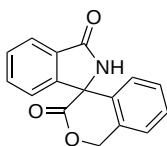
δ 7.83 (dt, $J = 7.5, 1.0$ Hz, 1H), 7.69 (dt, $J = 7.7, 0.8$ Hz, 1H), 7.57 (td, $J = 7.5, 1.3$ Hz, 1H), 7.49 (td, $J = 7.4, 1.1$ Hz, 1H), 7.38-7.30 (m, 5H), 7.20 (s, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 1.28-1.22 (m, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.6, 169.3, 145.4, 138.4, 132.5, 130.4, 129.22, 129.04, 128.7, 125.36, 125.26, 123.8, 70.6, 62.7, 14.0; **IR (thin film)** 1704, 1613, 1469, 1239, 1025, 749 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 282.1; found 282.1; $R_f = 0.41$ (1:1 Hexane/Ethyl Acetate).



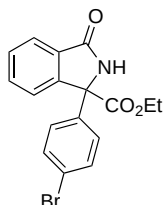
1-methylspiro[indoline-3,1'-isoindoline]-2,3'-dione (579): The product was isolated as

an off-white solid in 64% yield following general procedure B. Column chromatography was prepared Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, DMSO) δ 8.98 (s, 1H), 7.84-7.82 (m,

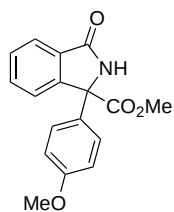
1H), 7.74 (dd, $J = 6.2, 1.3$ Hz, 1H), 7.50 (dtd, $J = 14.0, 7.1, 1.3$ Hz, 2H), 7.43-7.38 (m, 1H), 7.20 (d, $J = 7.8$ Hz, 1H), 7.03-6.94 (m, 2H), 7.03-6.94 (m, 3H), 3.21 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, DMSO) δ 173.9, 170.54, 170.52, 145.9, 144.5, 132.9, 132.1, 131.6, 130.6, 129.6, 128.6, 127.8, 127.6, 124.1, 123.73, 123.60, 122.19, 122.15, 109.9, 67.1, 27.2; **IR (thin film)** 1692, 1096, 978, 840 748 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 265.1; found 265.1; $R_f = 0.13$ (1:1 Hexane/Ethyl Acetate).



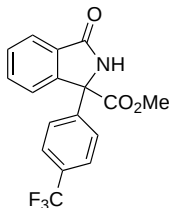
spiro[isochroman-4,1'-isoindoline]-3,3'-dione (580): The product was isolated as an off-white solid in 50% yield following general procedure B. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, DMSO) δ 9.42 (s, 1H), 7.73 (dt, J = 4.4, 2.2 Hz, 1H), 7.54-7.41 (m, 5H), 7.31 (s, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.12 (d, J = 15.6 Hz, 1H), 5.73 (d, J = 15.7 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, DMSO) δ 170.4, 168.9, 147.4, 133.2, 132.8, 131.07, 130.97, 130.1, 129.22, 129.14, 125.6, 125.4, 124.2, 123.2, 70.8, 64.7; **IR (thin film)** 1751, 1697, 1471, 1397, 1231 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 266.1; found 266.0; R_f = 0.18 (1:1 Hexane/Ethyl Acetate).



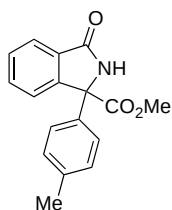
ethyl 1-(4-bromophenyl)-3-oxoisindoline-1-carboxylate (581): The product was isolated as an off-white solid in 94% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (dd, J = 7.4, 0.8 Hz, 1H), 7.66 (dd, J = 7.6, 0.7 Hz, 1H), 7.58 (td, J = 7.5, 1.2 Hz, 1H), 7.51 (td, J = 7.4, 0.9 Hz, 1H), 7.46-7.44 (m, 2H), 7.28-7.25 (m, 2H), 4.27 (t, J = 7.1 Hz, 2H), 1.26 (q, J = 6.9 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.6, 169.0, 144.9, 137.5, 132.7, 132.2, 130.3, 129.4, 127.2, 125.1, 123.9, 122.9, 70.1, 62.9, 14.0; **IR (thin film)** 1704, 1469, 1238, 1099, 1010 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 360.0; found 360.0; R_f = 0.48 (1:1 Hexane/Ethyl Acetate).



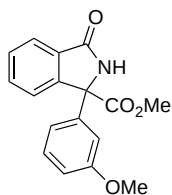
methyl 1-(4-methoxyphenyl)-3-oxoisindoline-1-carboxylate (582): The product was isolated as an off-white solid in 86% yield following general procedure B. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.57 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (td, J = 7.4, 0.9 Hz, 1H), 7.26-7.24 (m, 2H), 7.24-7.22 (m, 2H), 6.86-6.82 (m, 2H), 6.71-6.68 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.0, 169.2, 159.8, 145.5, 132.5, 130.2, 129.2, 126.72, 126.70, 125.2, 123.8, 114.4, 55.3, 53.4; **IR (thin film)** 1701, 1511, 1253, 1180, 1030 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 298.1; found 298.1; R_f = 0.25 (1:1 Hexane/Ethyl Acetate).



methyl 1-(4-trifluoromethylphenyl)-3-oxoisindoline-1-carboxylate (583): The product was isolated as an off-white solid in 97% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.85-7.83 (m, 2H), 7.70-7.68 (m, 1H), 7.62-7.53 (m, 6H), 3.83 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.1, 169.4, 144.6, 142.1, 132.9, 131.2, 130.9, 130.3, 129.7, 126.25, 126.14, 126.10, 126.07, 126.03, 125.98, 125.04, 125.00, 124.1, 122.3, 70.3, 67.0, 53.7; **IR (thin film)** 1707, 1414, 1248, 1070, 754 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 336.1; found 336.1; R_f = 0.45 (1:1 Hexane/Ethyl Acetate).

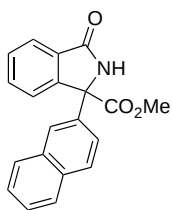


methyl 1-(4-methylphenyl)-3-oxoisindoline-1-carboxylate (584): The product was isolated as an off-white solid in 84% yield following general procedure B. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83-7.80 (m, 1H), 7.69-7.67 (m, 1H), 7.56 (td, J = 7.5, 1.2 Hz, 1H), 7.49 (td, J = 7.4, 0.8 Hz, 1H), 7.23-7.21 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.98-6.97 (s, br, 1H), 3.81 (s, 3H), 2.30 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.00, 169.98, 169.42, 169.40, 145.35, 145.34, 138.8, 135.3, 132.5, 130.4, 129.76, 129.74, 129.2, 128.7, 127.5, 125.29, 125.23, 125.13, 125.07, 123.8, 70.4, 53.4, 27.0; **IR (thin film)** 1703, 1468, 1246, 1020, 750 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 282.1; found 282.1; R_f = 0.34 (1:1 Hexane/Ethyl Acetate).



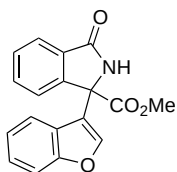
methyl 1-(3-methoxyphenyl)-3-oxoisindoline-1-carboxylate (585): The product was isolated as an off-white solid in 71% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83-7.81 (m, 1H), 7.72-7.69 (m, 1H), 7.57 (td, J = 7.6, 1.2 Hz, 1H), 7.49 (td, J = 7.4, 1.0 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 6.96 (ddd, J = 7.8, 1.8, 0.8 Hz, 1H), 6.90 (t, J = 2.1 Hz, 1H), 6.84 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.73, 169.57, 160.0, 145.0, 139.7, 132.6, 130.30, 130.19, 129.3, 125.3, 123.8, 117.5, 113.8, 111.5, 70.5,

67.0, 55.3, 53.4; **IR (thin film)** 1704, 1602, 1257, 1022, 749 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 298.1; found 298.1; **R_f** = 0.34 (1:1 Hexane/Ethyl Acetate).



methyl 1-(naphthalen-2-yl)-3-oxoisindoline-1-carboxylate (586): The product was isolated as an off-white solid in 98% yield following general procedure A. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3)

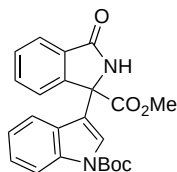
δ 7.86 (dt, J = 7.9, 0.8 Hz, 1H), 7.83-7.78 (m, 4H), 7.72 (dt, J = 7.7, 0.9 Hz, 1H), 7.58 (td, J = 7.5, 1.3 Hz, 1H), 7.54-7.48 (m, 3H), 7.38 (dd, J = 8.6, 2.0 Hz, 1H), 6.81 (s, 1H), 3.87 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.8, 169.4, 145.3, 135.4, 133.08, 132.97, 132.7, 130.3, 129.39, 129.22, 128.2, 127.6, 126.87, 126.79, 125.4, 124.5, 123.9, 122.8, 53.5; **IR (thin film)** 1702, 1468, 1242, 1022, 909 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 318.1; found 318.2; **R_f** = 0.32 (1:1 Hexane/Ethyl Acetate).



methyl 1-(benzofuran-3-yl)-3-oxoisindoline-1-carboxylate (587): The product was isolated as an off-white solid in 23% yield following general procedure B. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3)

δ 7.91 (dd, J = 6.6, 1.5 Hz, 1H), 7.73-7.71 (m, 1H), 7.65 (s, 1H), 7.58 (quintetd, J = 7.3, 1.4 Hz, 2H), 7.46 (d, J = 8.3 Hz, 1H), 7.27 (ddd, J = 8.4, 6.2, 2.2 Hz, 1H), 7.16-7.13 (m, 2H), 6.96 (s, 1H), 3.83 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.45, 169.40, 155.6, 143.9, 143.0, 132.8, 130.6, 129.8, 125.1, 124.70, 124.68, 124.1, 123.3, 119.9, 118.5, 111.9, 65.2, 29.7, 27.1; **IR (thin film)** 1703, 1453, 1246, 1115, 748 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 308.1; found 308.1; **R_f** = 0.41 (1:1 Hexane/Ethyl Acetate).

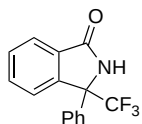
tert-butyl 3-(1-(methoxycarbonyl)-3-oxoisindolin-1-yl)-1H-indole-1-carboxylate



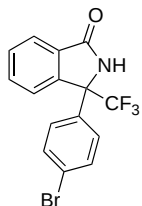
(588): The product was isolated as an off-white solid in 26% yield following general procedure B. Column chromatography was prepared 1:1 Hexanes/Ethyl Acetate. **¹H**

NMR (400 MHz, CDCl_3) δ 7.91 (dd, J = 6.6, 1.4 Hz, 1H), 7.76-7.74 (m, 1H), 7.58 (ddd, J = 8.6, 7.2, 1.4 Hz, 2H), 7.53 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.13 (dd, J = 6.0, 0.8 Hz, 2H), 6.87 (s, 1H), 3.82 (s, 3H), 1.64 (s, 9H); **¹³C NMR** (100 MHz, CDCl_3) δ 169.8, 169.3, 144.0, 132.7, 130.8, 129.7,

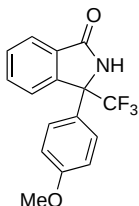
125.02, 124.93, 124.3, 124.1, 123.2, 119.1, 117.6, 115.6, 84.6, 66.1, 53.6, 28.1; **IR (thin film)** 1707, 1453, 1372, 1238, 1153 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 407.2; found 407.2; **R_f** = 0.42 (1:1 Hexane/Ethyl Acetate).



3-phenyl-3-(trifluoromethyl)isoindolin-1-one (595): The product was isolated as an yellow solid in 90% yield following general procedure A. The purification for performed via flash chromatography using 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.92-7.90 (m, 1H), 7.68-7.56 (m, 5H), 7.41-7.36 (m, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 170.8, 143.1, 133.8, 132.9, 131.3, 130.1, 129.3, 128.99, 128.91, 126.64, 126.62, 126.1, 124.5, 124.3, 123.3, 68.7 (q); **¹⁹F NMR** (376 MHz; CDCl_3): δ -73.0; **IR (thin film)** 1711, 1470, 1258, 1174, 939 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 278.1; found 278.0; **R_f** = 0.4 (1:1 Hexane/Ethyl Acetate)

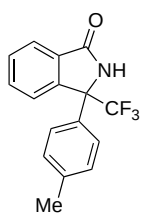


3-(4-bromophenyl)-3-(trifluoromethyl)isoindolin-1-one (596): The product was isolated as an yellow solid in 80% yield following general procedure A. The purification for performed via flash chromatography using 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.92-7.89 (m, 1H), 7.62 (ddd, J = 9.7, 7.4, 1.6 Hz, 2H), 7.57-7.50 (m, 3H), 7.42 (d, J = 8.7 Hz, 2H); **¹³C NMR** (100 MHz, CDCl_3) δ 171.2, 148.2, 133.13, 133.04, 132.26, 132.24, 132.21, 130.4, 128.22, 128.20, 124.7, 124.1, 123.8, 122.6; **¹⁹F NMR** (376 MHz; CDCl_3): δ -72.8; **IR (thin film)** 1708, 1255, 1172, 934, 804 cm^{-1} ; **MS (ESI)** m/e calcd (M+H) 356.1; found 356.0; **R_f** = 0.39 (3:1 Hexane/Ethyl Acetate).



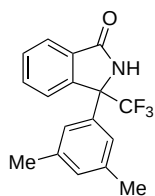
3-(4-methoxyphenyl)-3-(trifluoromethyl)isoindolin-1-one (597): The product was isolated as an yellow solid in 20% yield following general procedure B. The purification for performed via flash chromatography using 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl_3) δ 7.81 (dd, J = 7.4, 1.1 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J = 3.8 Hz, 2H), 7.49 (dd, J = 7.4, 4.3 Hz, 1H), 7.41 (d, J = 8.9 Hz, 2H), 6.80-6.78 (m, 2H), 3.69 (s, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 170.2, 160.0, 143.2, 132.7, 131.2, 129.9, 127.94, 127.92, 127.90, 126.1, 125.6, 124.4, 124.1,

123.3, 114.2, 68.5, 68.2, 67.9, 67.6, 55.2; **¹⁹F NMR** (376 MHz; CDCl₃): δ -73.4; **IR (thin film)** 1704, 1516, 1260, 1172, 1085 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 308.1; found 308.1; **R_f** = 0.55 (1:1 Hexane/Ethyl Acetate).



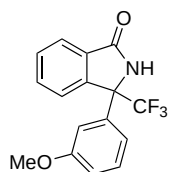
3-(4-methylphenyl)-3-(trifluoromethyl)isoindolin-1-one (598): The product was isolated as an yellow solid in 94% yield following general procedure B. The purification for performed via flash chromatography using 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl₃) δ 7.89 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.64-7.55 (m, 3H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.17 (t,

J = 5.8 Hz, 2H), 6.67-6.65 (m, 1H), 2.33-2.31 (m, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 169.7, 139.4, 138.9, 132.9, 130.0, 129.7, 126.3, 124.5, 124.2, 21.0; **¹⁹F NMR** (376 MHz; CDCl₃): δ -73.0; **IR (thin film)** 1712, 1470, 1318, 1258, 1171cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 292.3; found 292.1; **R_f** = 0.33 (3:1 Hexane/Ethyl Acetate).



3-(3,5-dimethylphenyl)-3-(trifluoromethyl)isoindolin-1-one (599): The product was isolated as an yellow solid in 97% yield following general procedure A. The purification for performed via flash chromatography using 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400

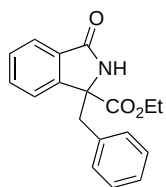
MHz, CDCl₃) δ 7.89 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.64-7.55 (m, 3H), 7.13 (d, *J* = 0.3 Hz, 2H), 7.00 (t, *J* = 0.7 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 169.9, 143.4, 138.7, 133.7, 132.9, 130.97, 130.92, 130.0, 126.2, 124.43, 124.23, 124.11, 124.09, 123.4, 21.4; **¹⁹F NMR** (376 MHz; CDCl₃): δ -72.6; **IR (thin film)** 1710, 1468, 1267, 1158, 958 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 306.3; found 306.1; **R_f** = 0.38 (3:1 Hexane/Ethyl Acetate).



3-(3-methoxyphenyl)-3-(trifluoromethyl)isoindolin-1-one (600): The product was isolated as an yellow solid in 95% yield following general procedure A. The purification for performed via flash chromatography using 2:1 Hexanes/Ethyl Acetate. **¹H NMR** (400

MHz, CDCl₃) δ 7.89 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.63-7.56 (m, 3H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.14 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.08 (s, 1H), 6.90 (ddd, *J* = 8.3, 2.5, 0.7 Hz, 1H), 6.82 (d, *J* = 5.4 Hz, 1H); **¹³C NMR**

(100 MHz, CDCl₃) δ 169.8, 159.9, 135.3, 132.9, 130.1, 124.5, 124.2, 118.64, 118.61, 114.0, 113.13, 113.11, 55.3; **¹⁹F NMR** (376 MHz; CDCl₃): δ -72.8; **IR (thin film)** 1713, 1605, 1470, 1261, 1176 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 308.3; found 308.0; **R_f** = 0.24 (3:1 Hexane/Ethyl Acetate).



ethyl 1-benzyl-3-oxoisindoline-1-carboxylate (605): The product was isolated as an

off-white solid in 78% yield following general procedure C. Column chromatography

was prepared 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz, CDCl₃) δ 7.81 (d, *J* = 7.7

Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.62 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 0.9 Hz,

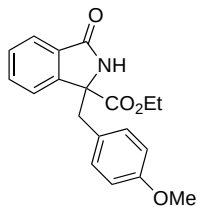
1H), 7.28-7.23 (m, 3H), 7.14-7.12 (m, 2H), 6.60 (s, br, 1H), 4.13 (qq, *J* = 10.5, 7.1 Hz, 2H), 3.73 (d, *J* =

13.4 Hz, 1H), 2.95 (d, *J* = 13.4 Hz, 1H), 1.19 (q, *J* = 7.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 170.0,

169.6, 145.0, 134.5, 132.5, 130.8, 129.7, 129.3, 128.6, 127.6, 123.9, 123.3, 68.7, 45.1, 14.0; **IR (thin**

film) 1700, 1467, 1248, 738, 699 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 295.1; found 295.1; **R_f** = 0.40 (1:1

Hexane/Ethyl Acetate).



ethyl 1-(4-methoxybenzyl)-3-oxoisindoline-1-carboxylate (606): The product was

isolated as an off-white solid in 68% yield following general procedure C. Column

chromatography was prepared 1:1 Hexanes/Ethyl Acetate. **¹H NMR** (400 MHz,

CDCl₃) δ 7.78 (t, *J* = 7.7 Hz, 2H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 1.0

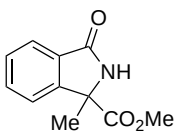
Hz, 1H), 7.06-7.03 (m, 2H), 6.81-6.78 (m, 2H), 6.29 (s, 1H), 4.18-4.09 (m, 2H), 3.76 (s, 3H), 3.69 (d, *J* =

13.5 Hz, 1H), 2.86 (d, *J* = 13.6 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 170.1,

169.3, 159.1, 145.1, 132.4, 130.8, 129.3, 126.5, 123.9, 123.3, 114.0, 68.8, 62.3, 55.2, 44.4, 14.0; **IR (thin**

film) 1701, 1611, 1513, 1248, 1034 cm⁻¹; **MS (ESI)** *m/e* calcd (M+H) 326.1 ; found 326.1; **R_f** = 0.26 (1:1

Hexane/Ethyl Acetate).



methyl 1-methyl-3-oxoisindoline-1-carboxylate (607): The product was isolated as

an off-white solid in 68% yield following general procedure C. Column

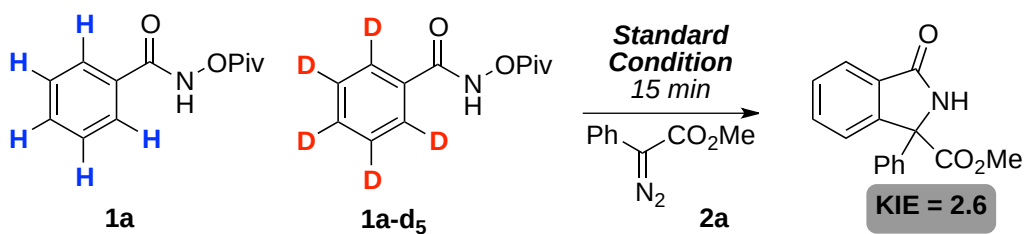
chromatography was prepared 1:1 Hexanes/Ethyl Acetate. ^1H NMR (400 MHz,

CDCl_3) δ 7.81-7.79 (m, 2H), 7.66 (dd, $J = 7.7, 0.7$, 1H), 7.59 (t, $J = 7.5$, 1H), 4.19-4.15 (m, 2H), 1.79 (s,

3H), 1.26-1.23 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.3, 132.5, 132.0, 130.5, 129.1, 128.6, 127.3,

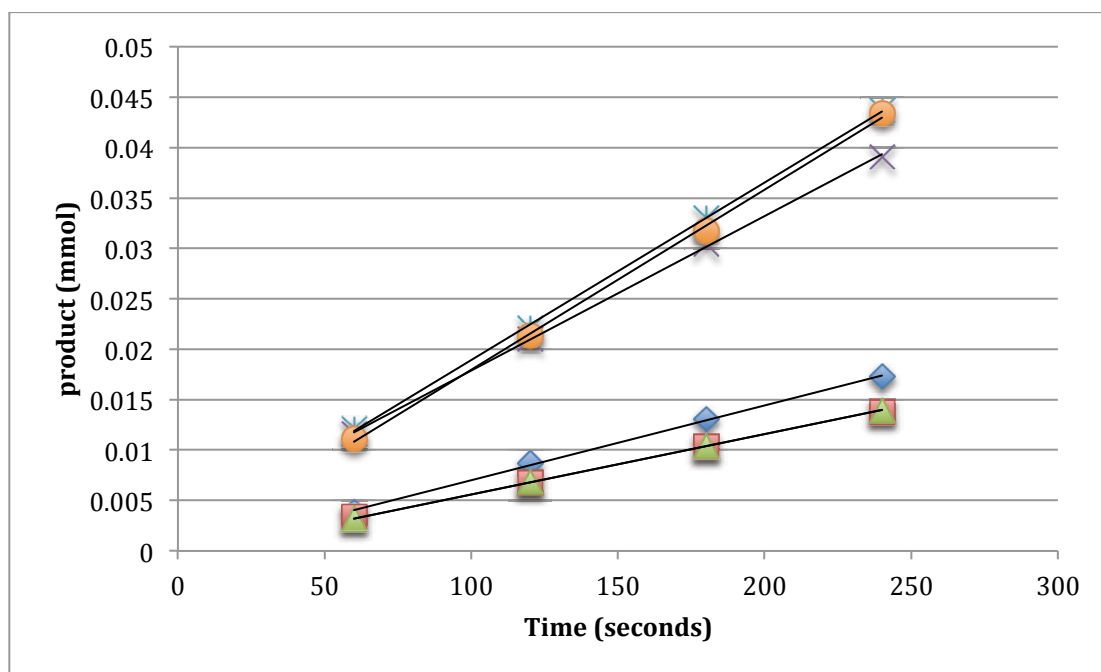
123.8, 123.0, 98.6, 64.4, 62.4, 25.5, 14.0.

- Kinetic Isotope Study (B)

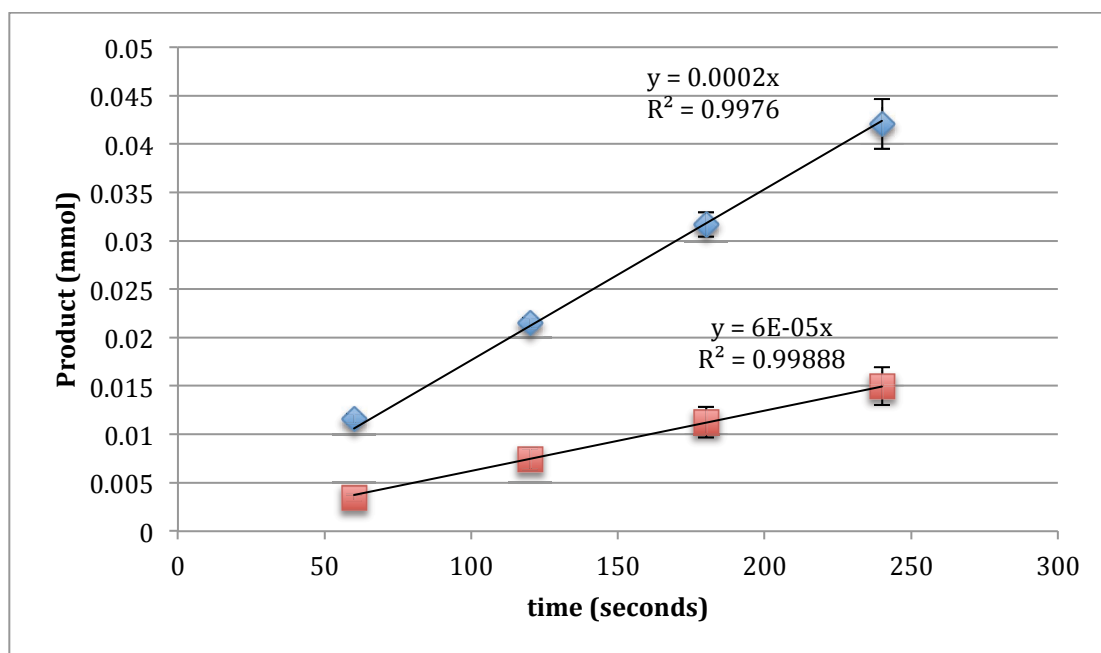


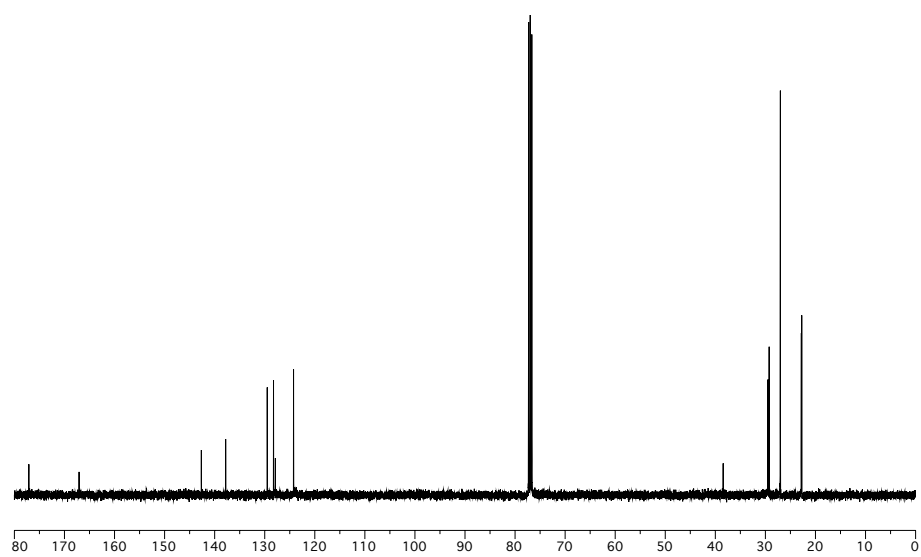
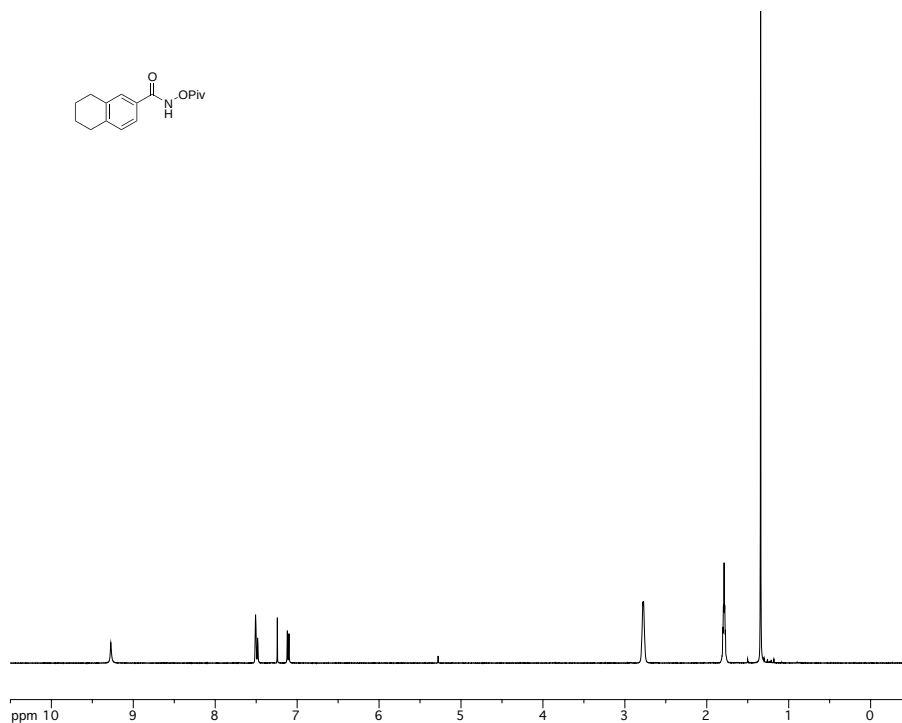
A 1.5 dram vial was charged with a stirbar, amide **1a** or **1a'** (0.25 mmol, 1 equiv), trimethoxybenzene (0.25 mmol, 1 equiv) and Cs_2CO_3 (0.05 mmol, 20 mol %). The mixture was dissolved in CH_3CN (2.5 mL, 0.1M) and stirred. After 3 minutes diazocompound **2a** (0.25 mmol, 1 equiv) was added. After stirring for 10 minutes a solution of $[\text{RhCp}^*\text{Cl}_2]_2$ (0.0025 mmol, 1 mol %) in DCM (50 μL) was added. Aliquotes were taken every 60 seconds and quenched with 50 μL of $\text{CF}_3\text{CO}_2\text{H}$ in DCM (400 μL). The reaction mixture was analyzed using GC/MS.

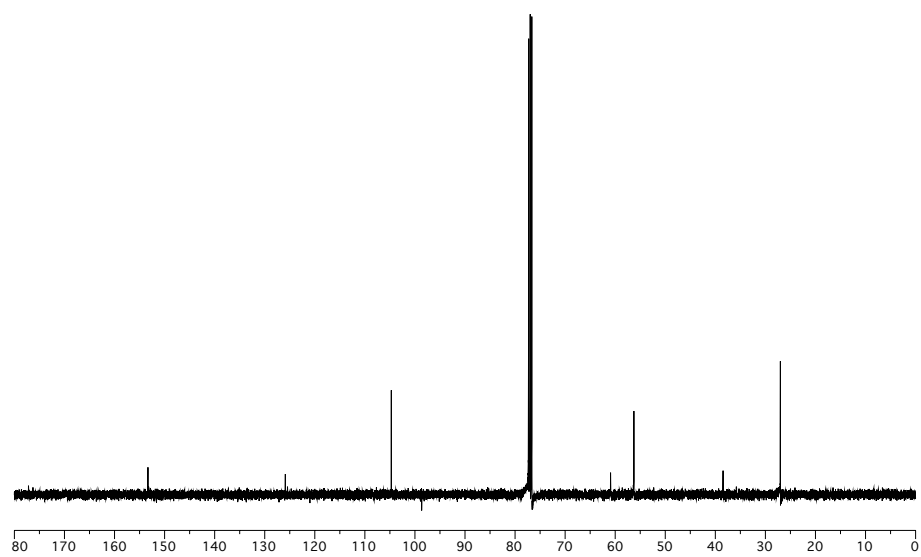
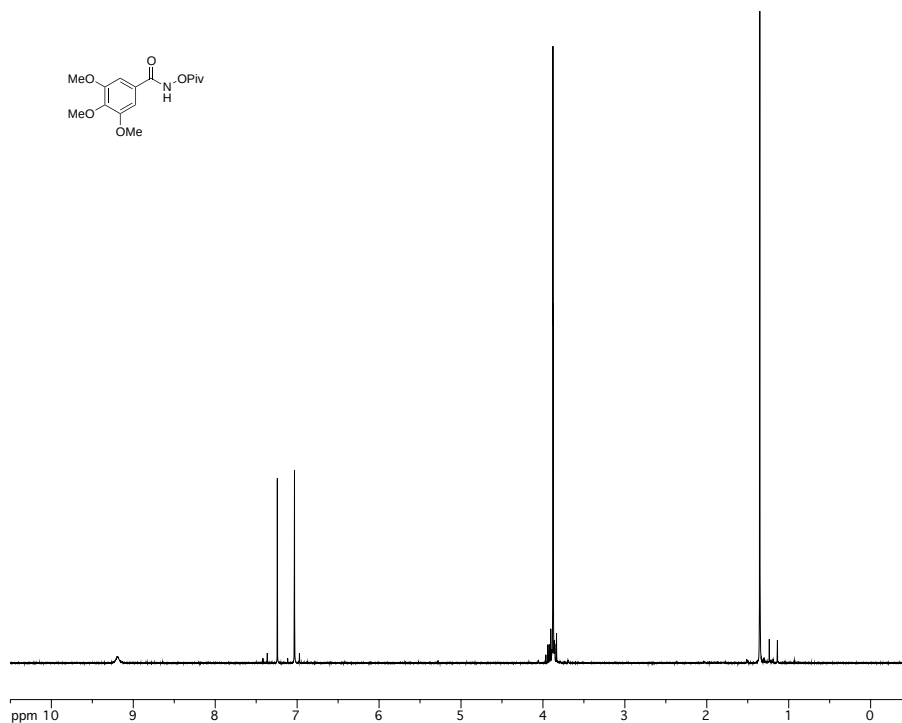
RESULTS FOR INDIVIDUAL RUNS

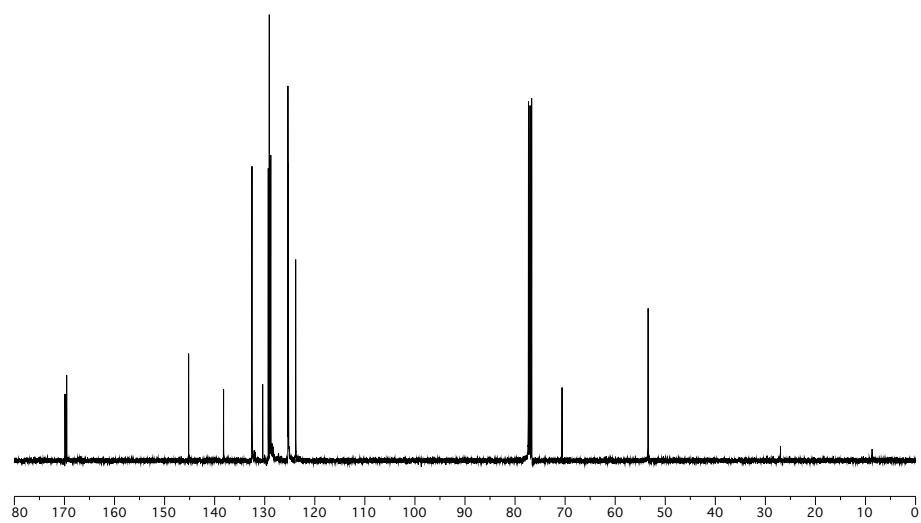
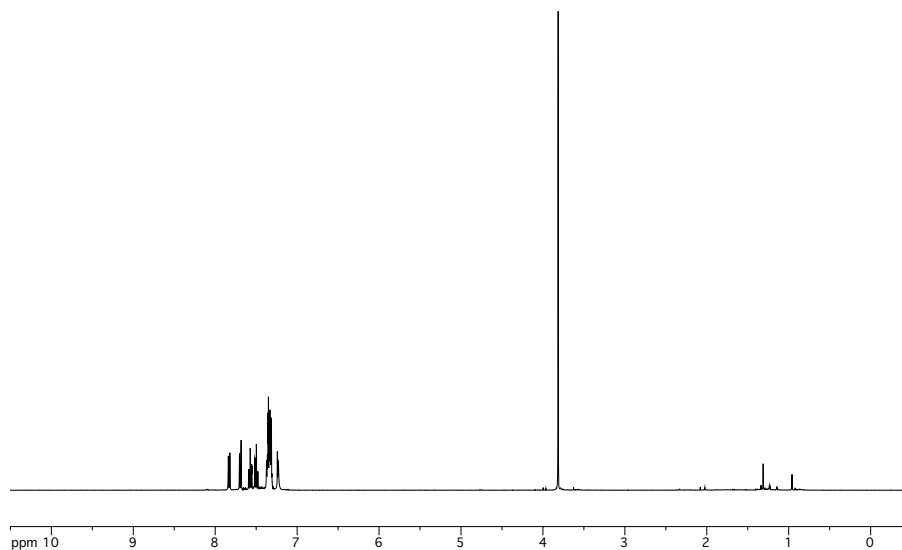
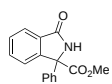


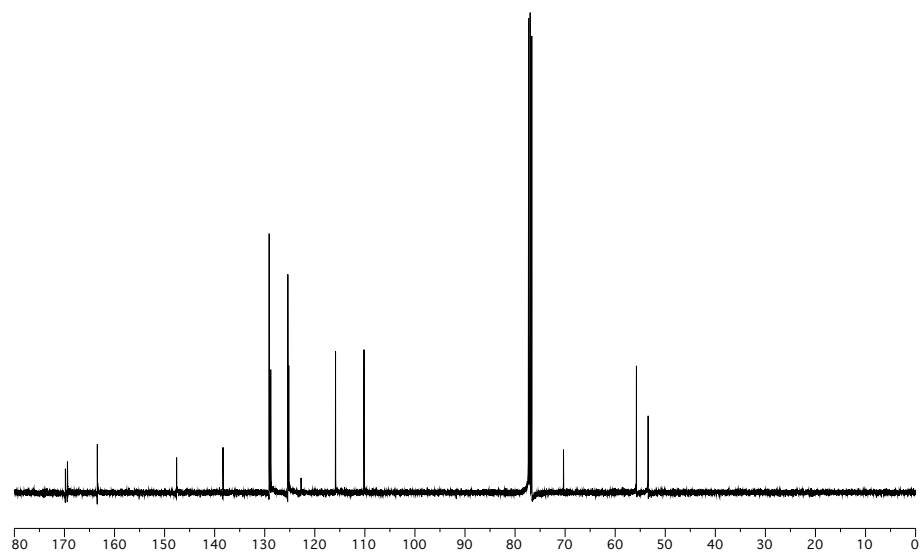
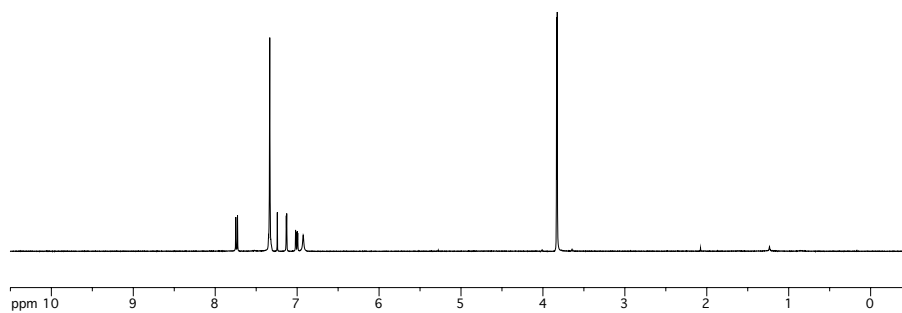
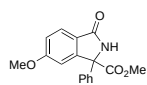
AVERAGES

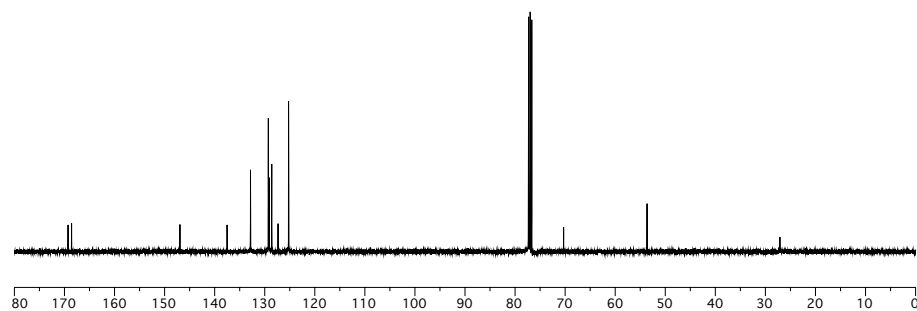
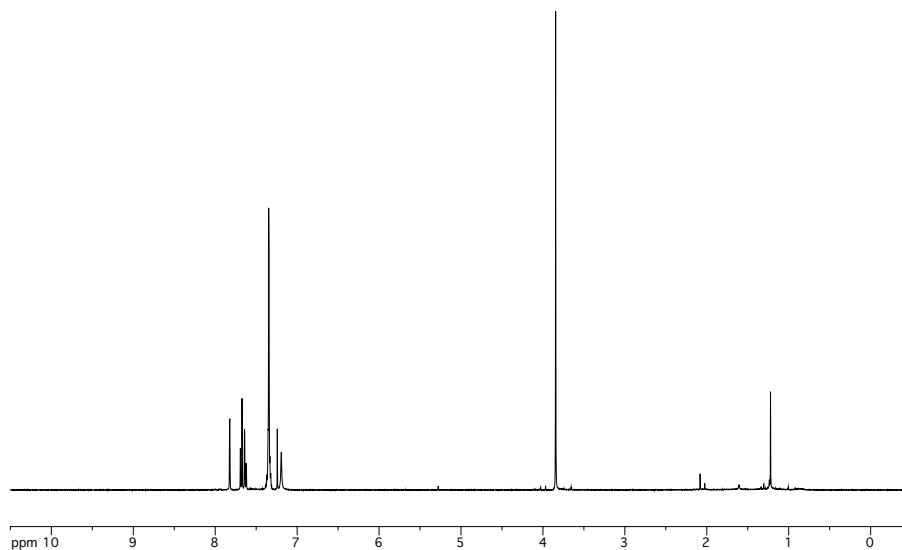
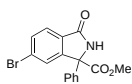


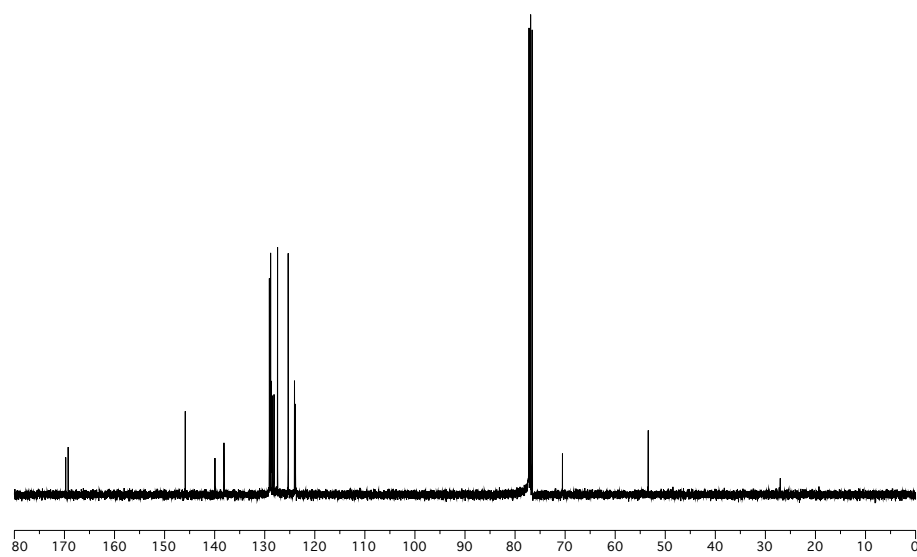
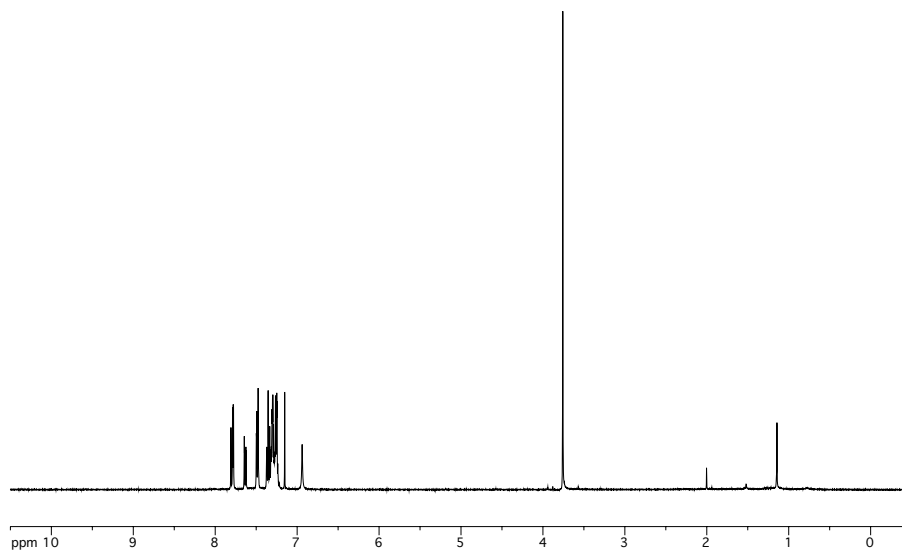
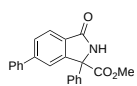


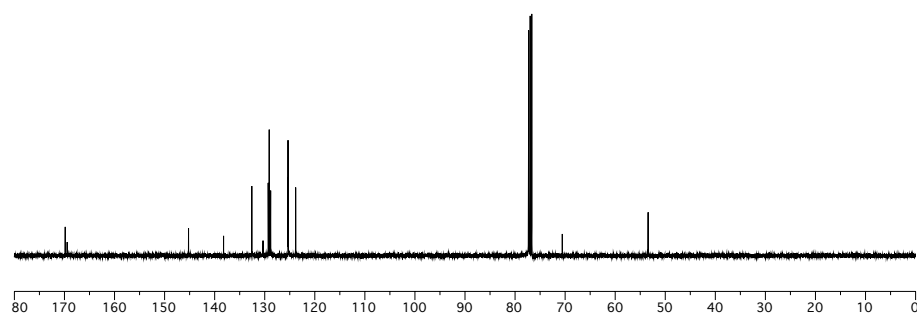
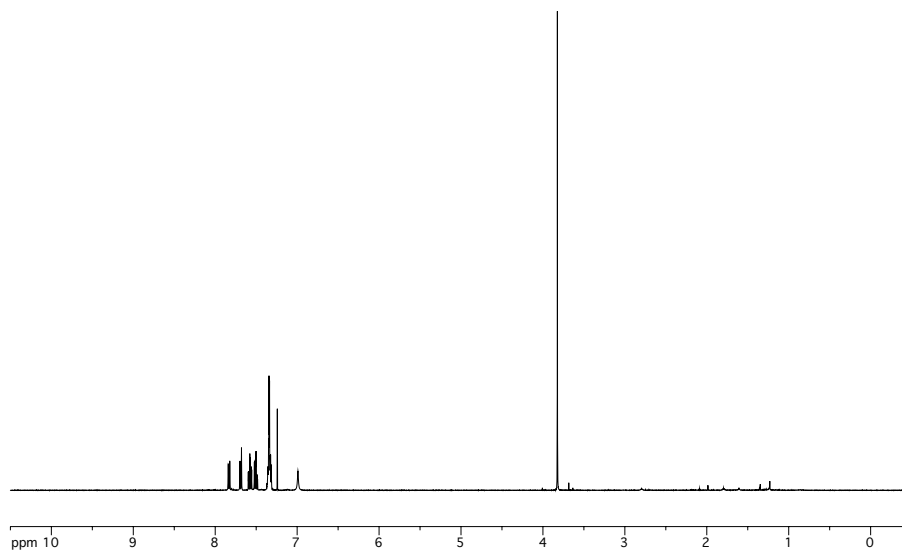
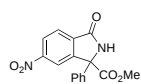


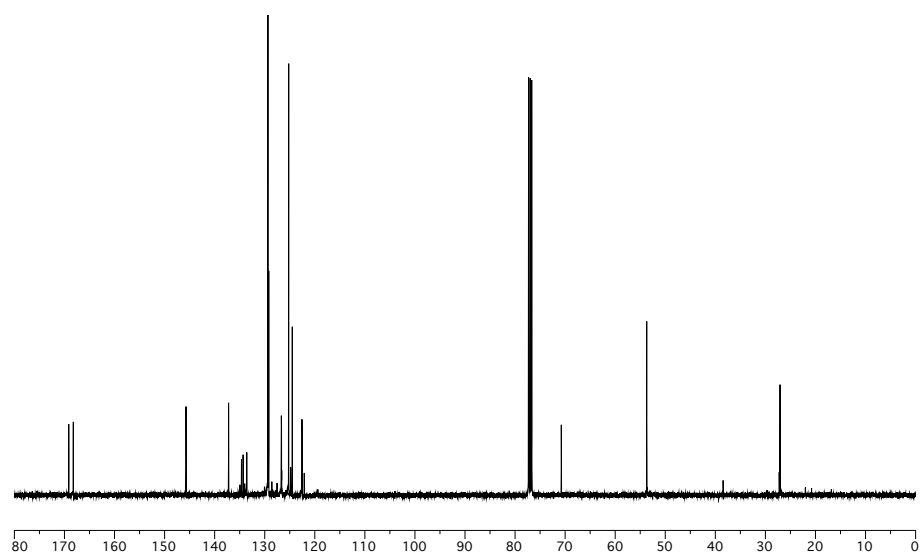
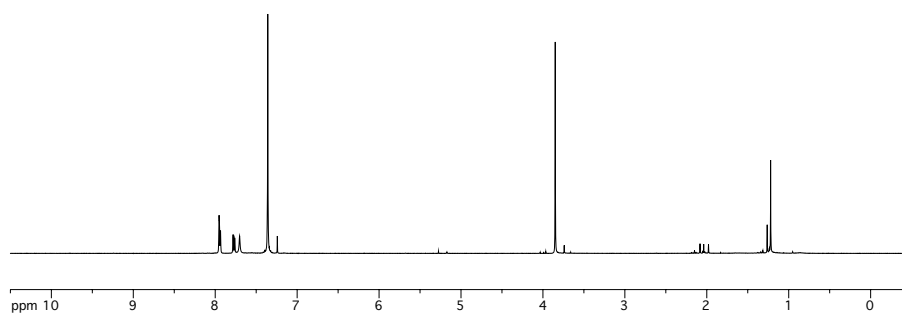
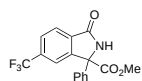


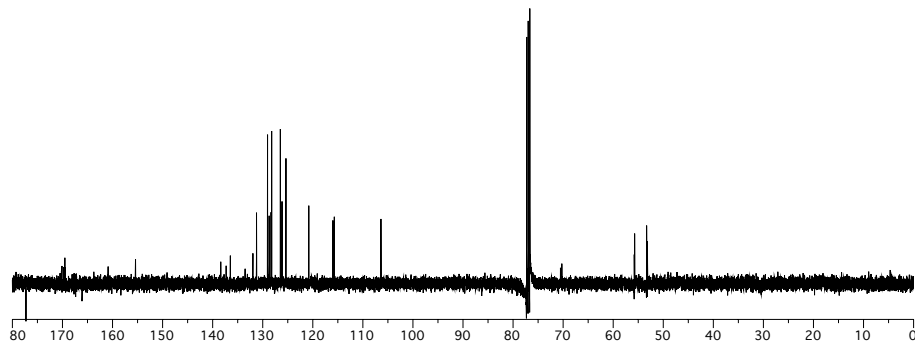
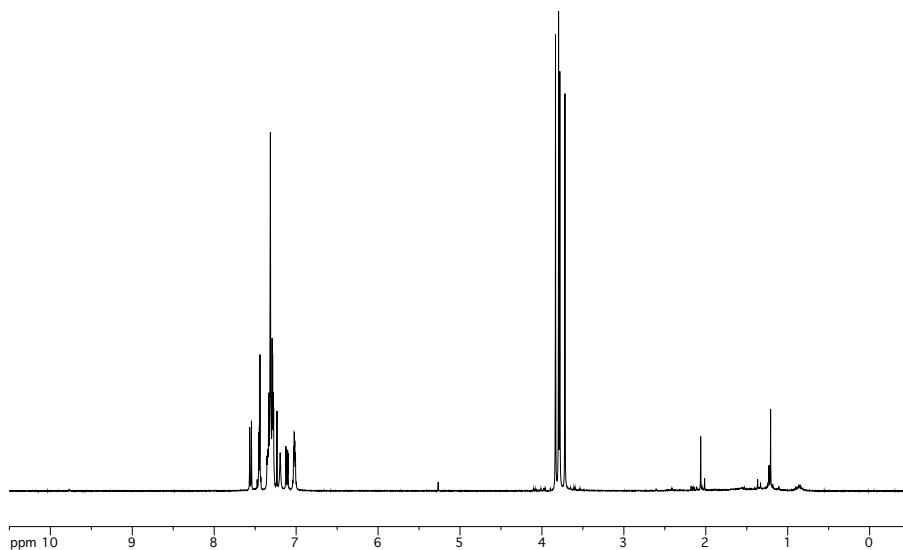
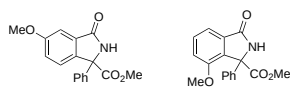


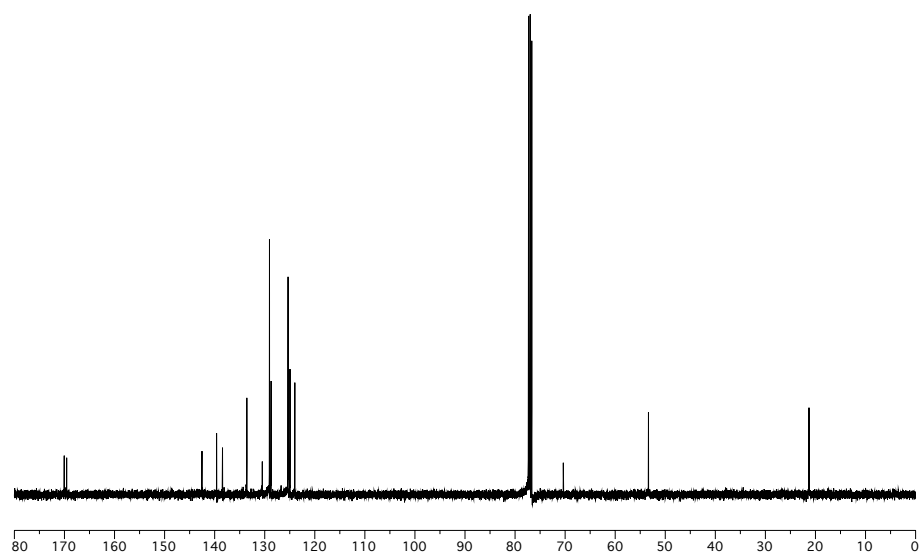
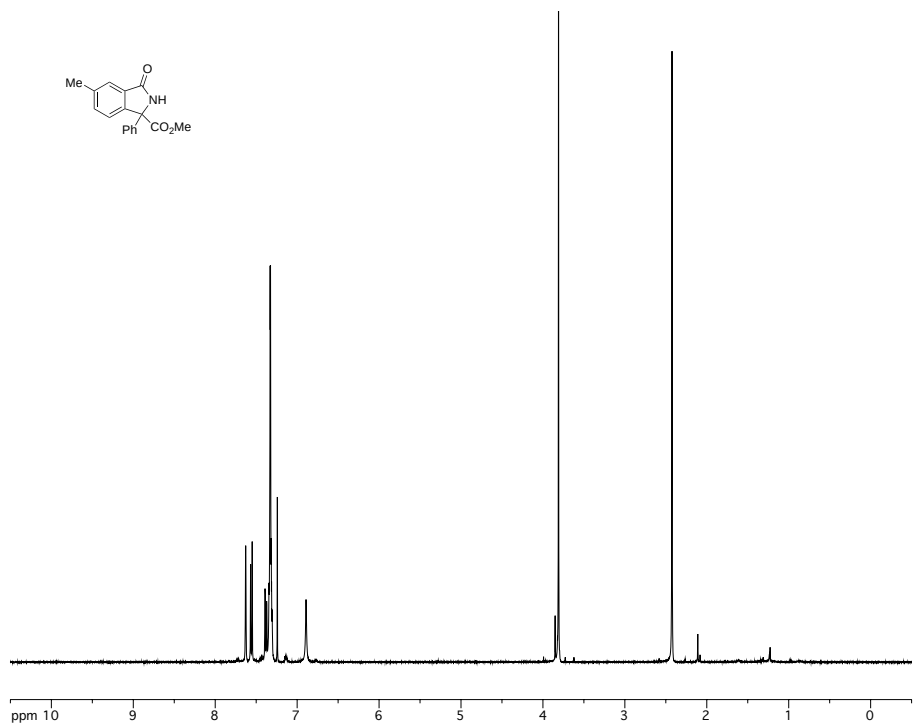


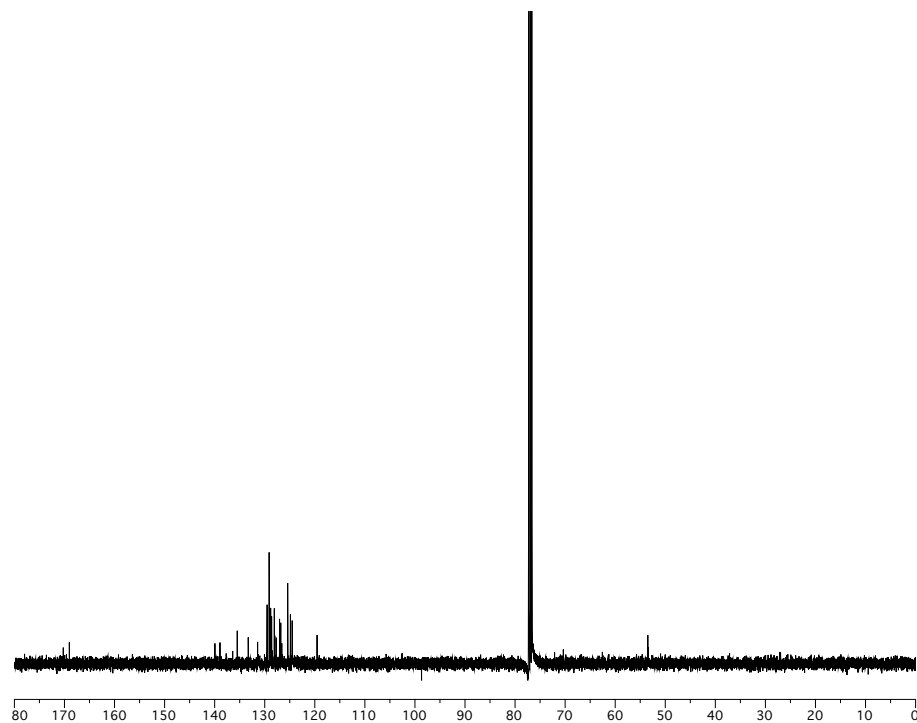
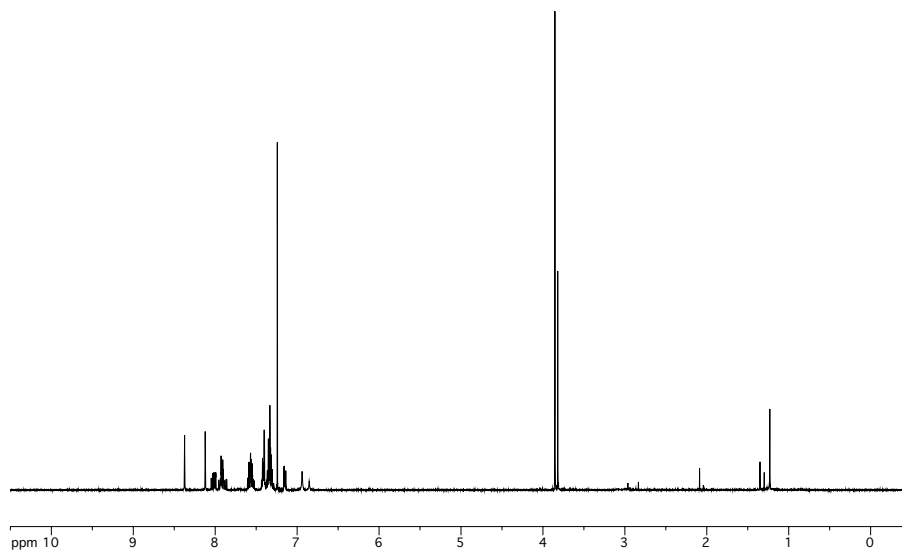
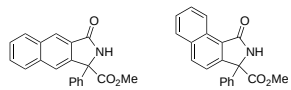


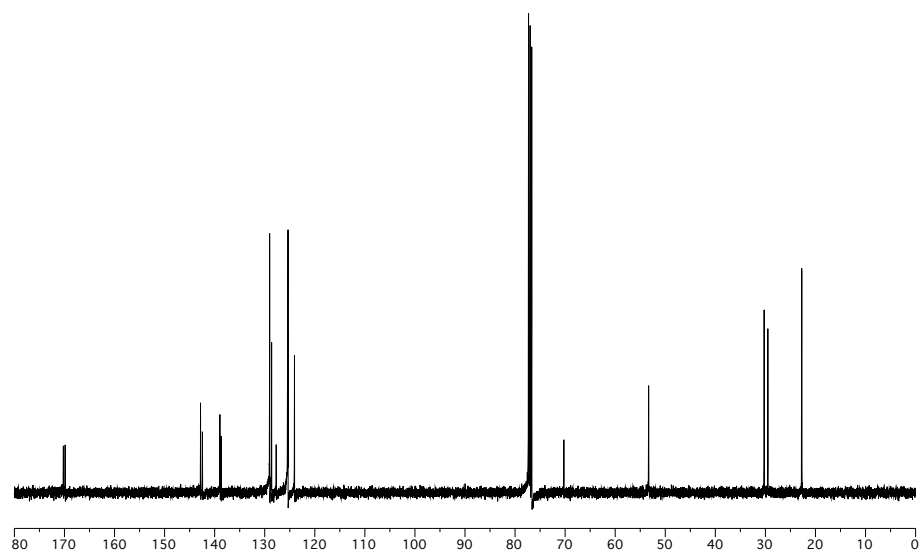
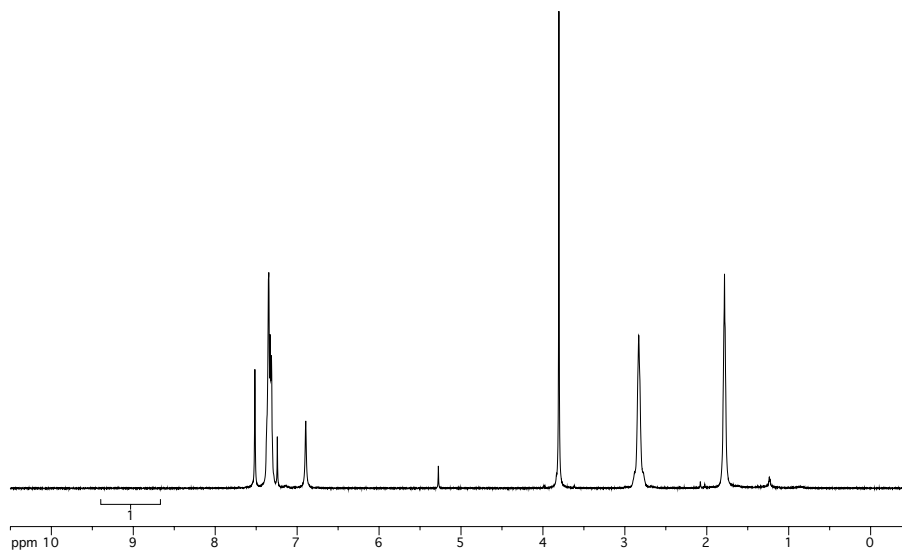
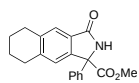


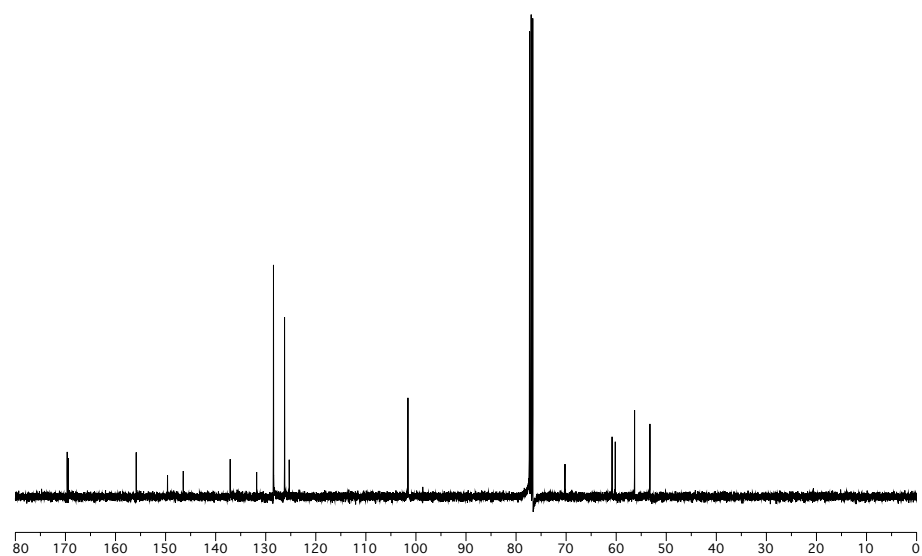
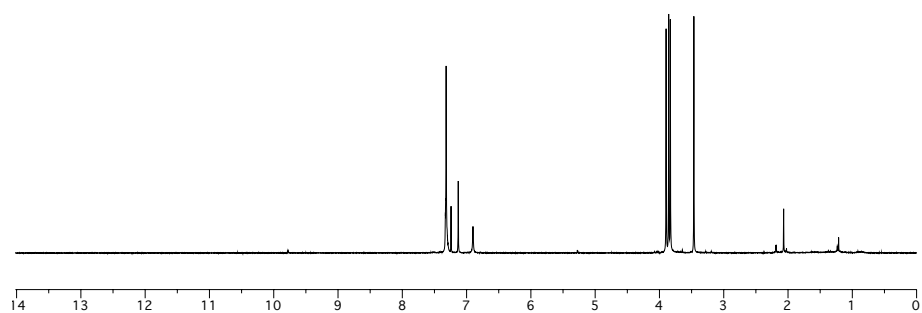
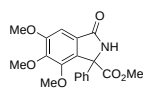


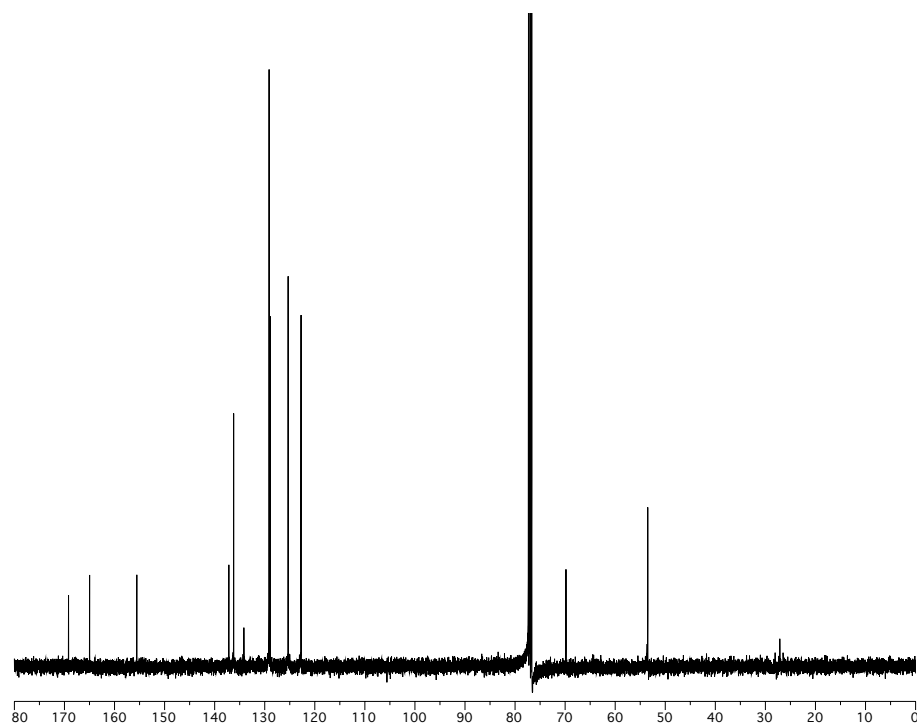
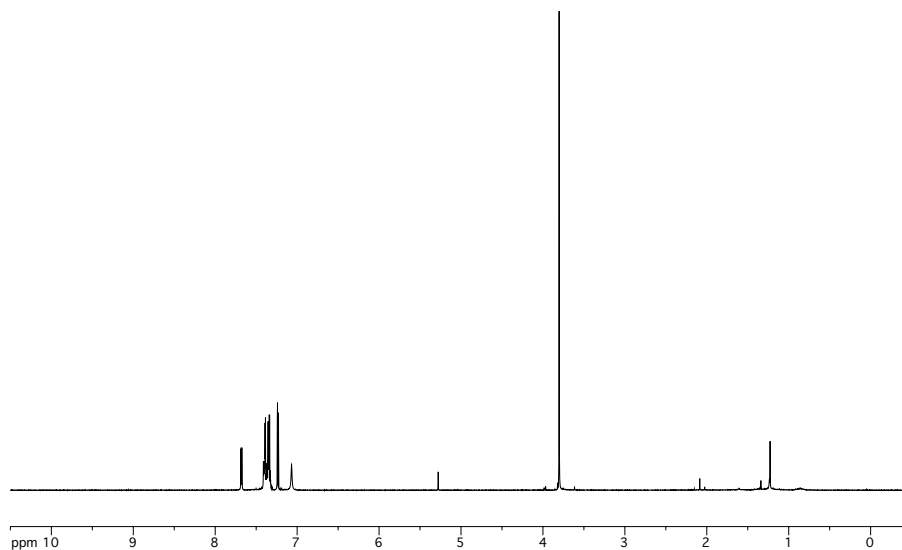
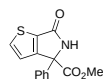


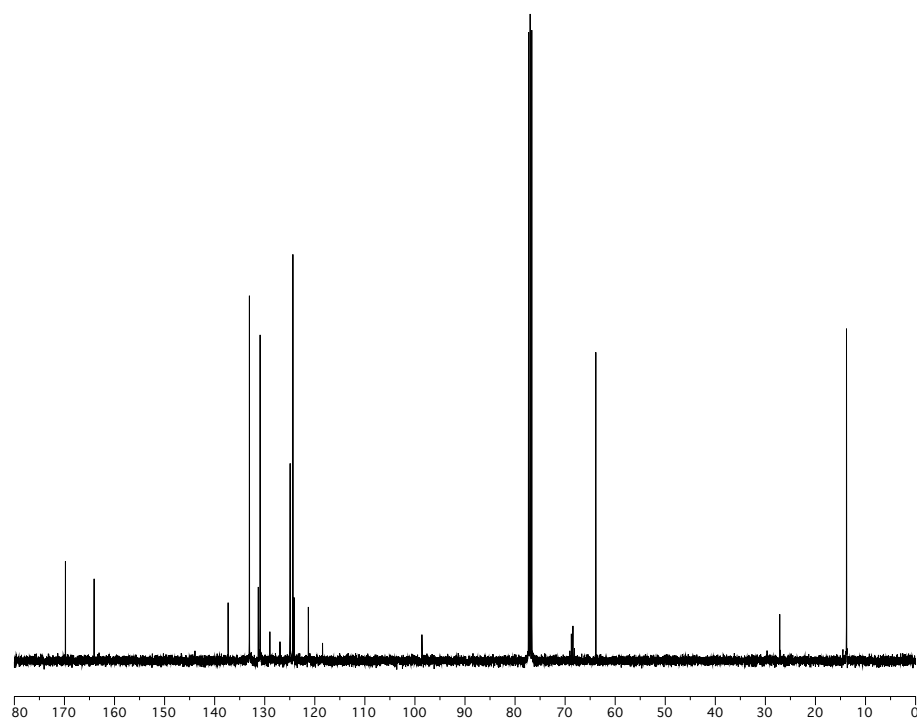
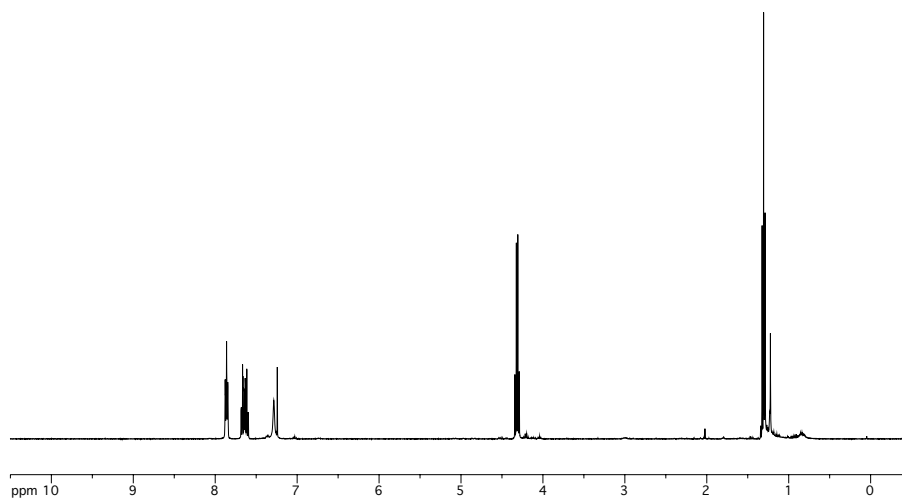
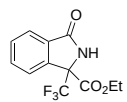


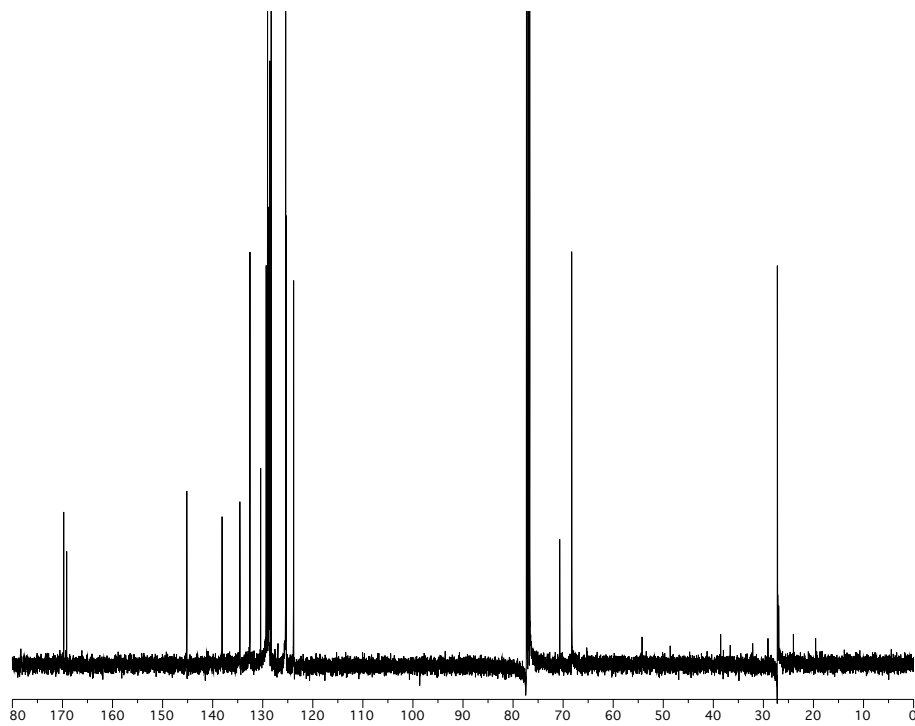
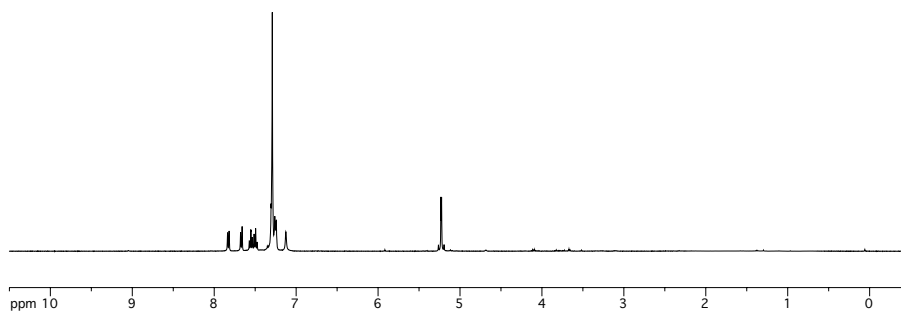
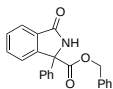


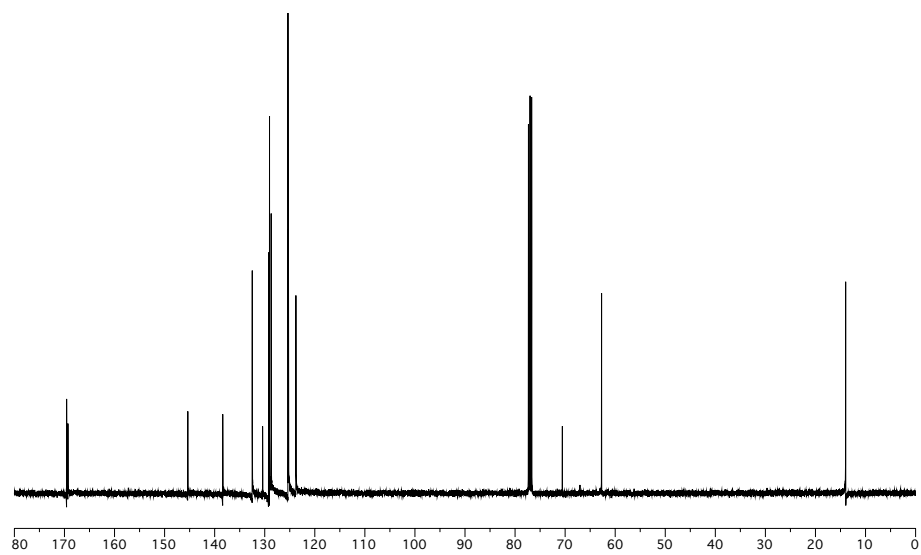
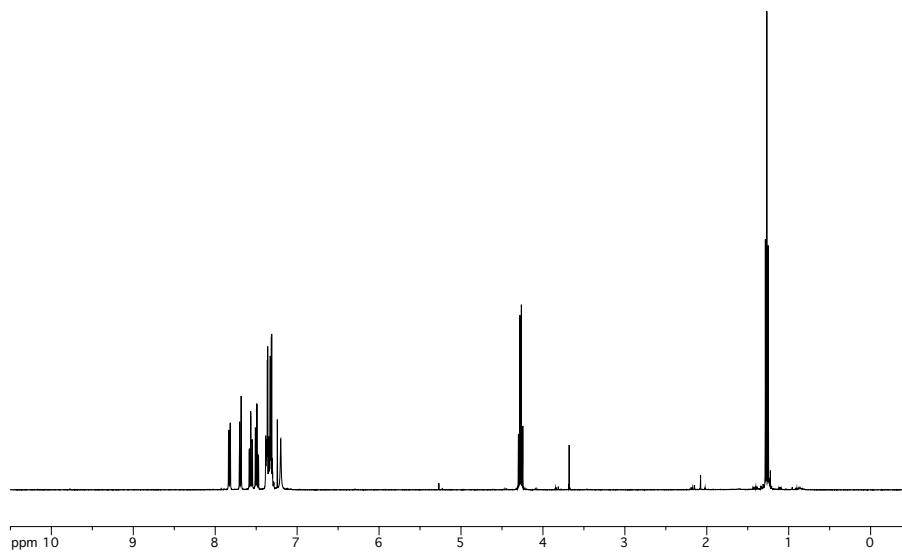
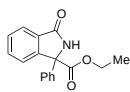


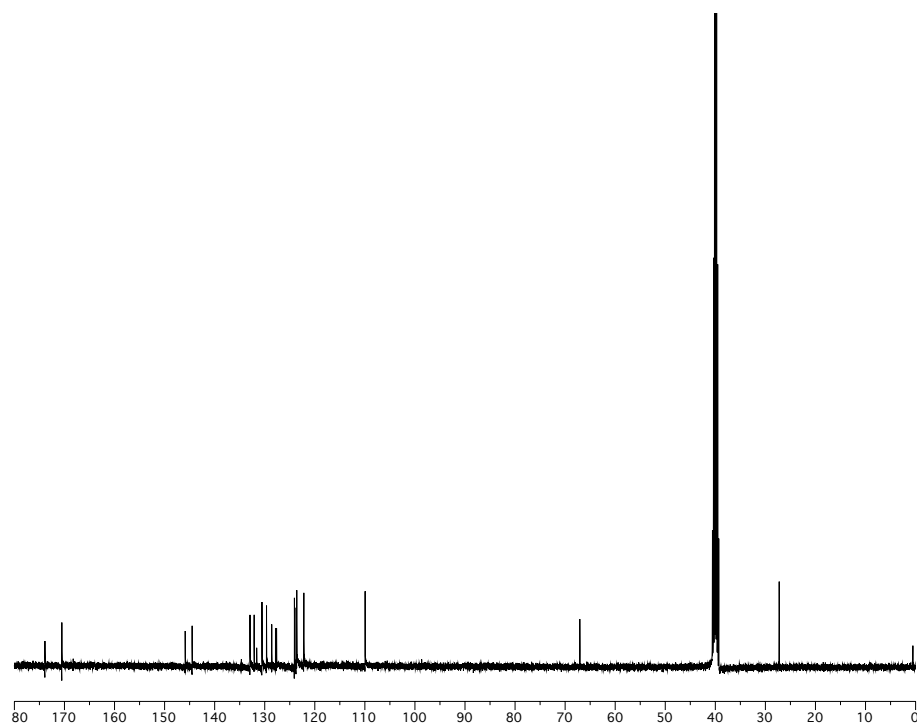
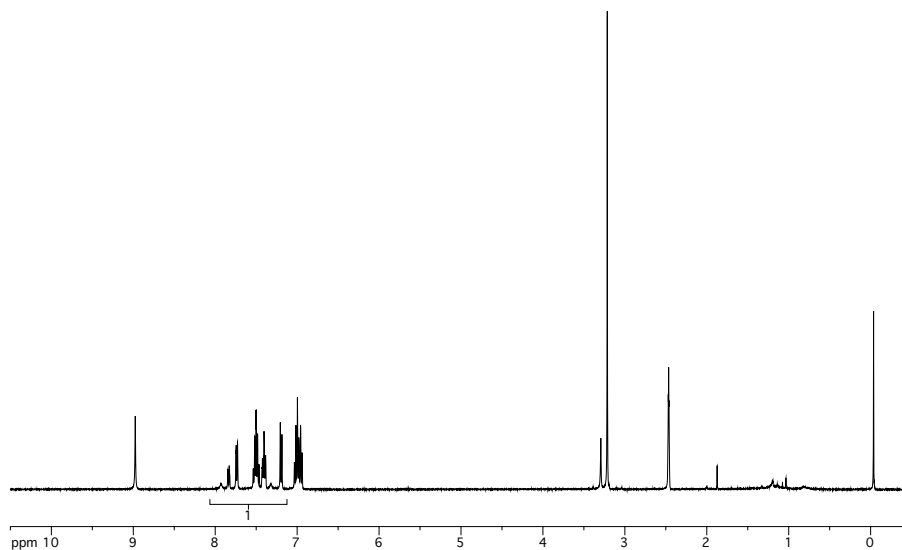
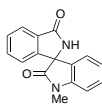


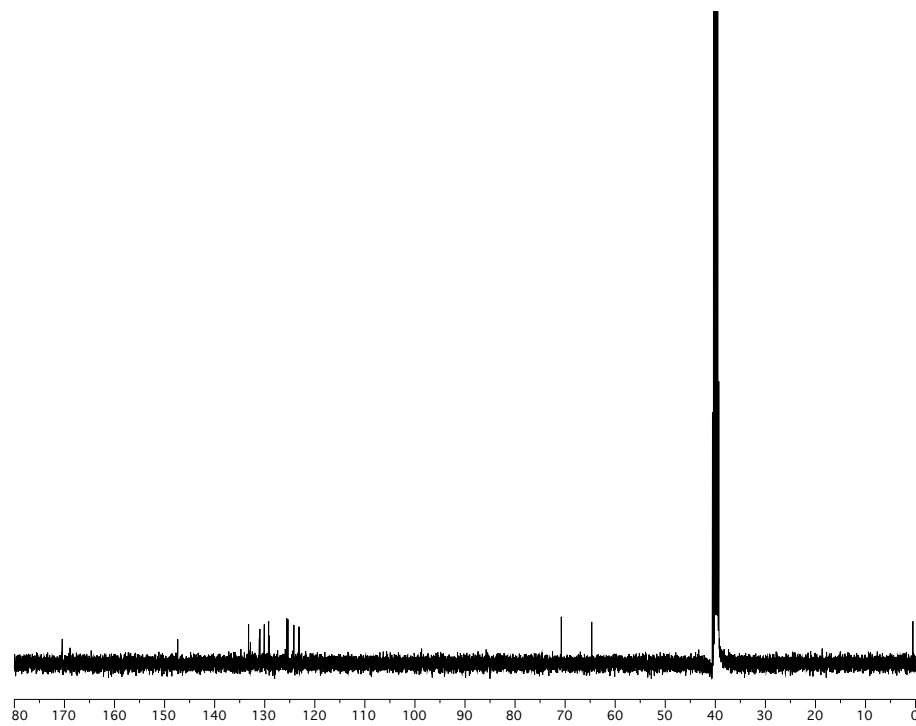
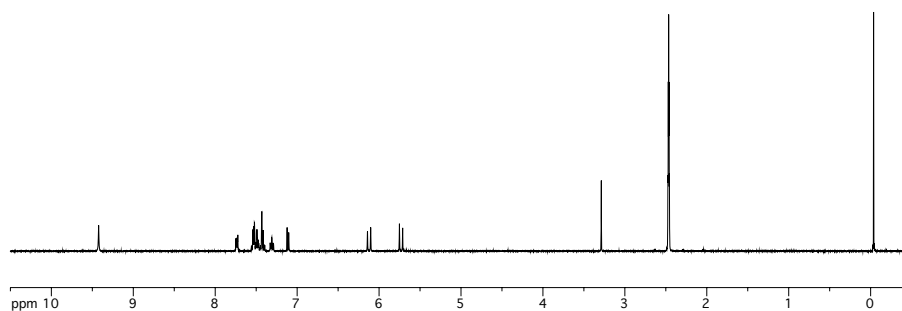
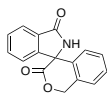


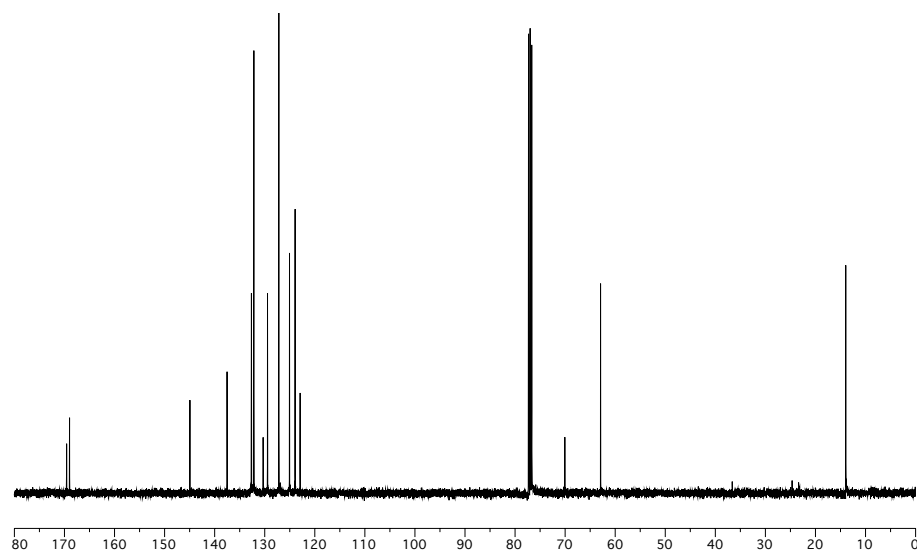
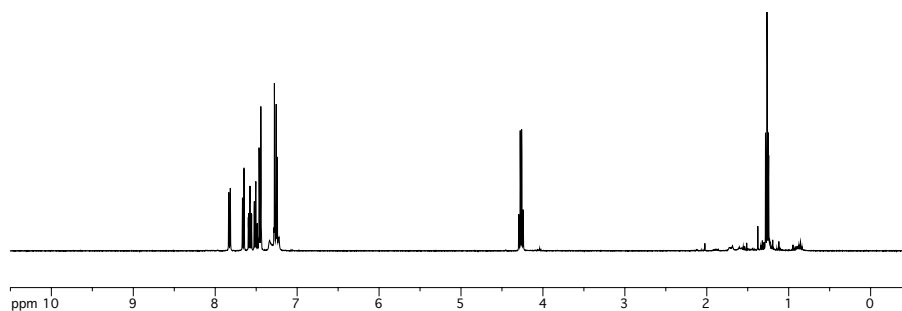
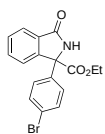


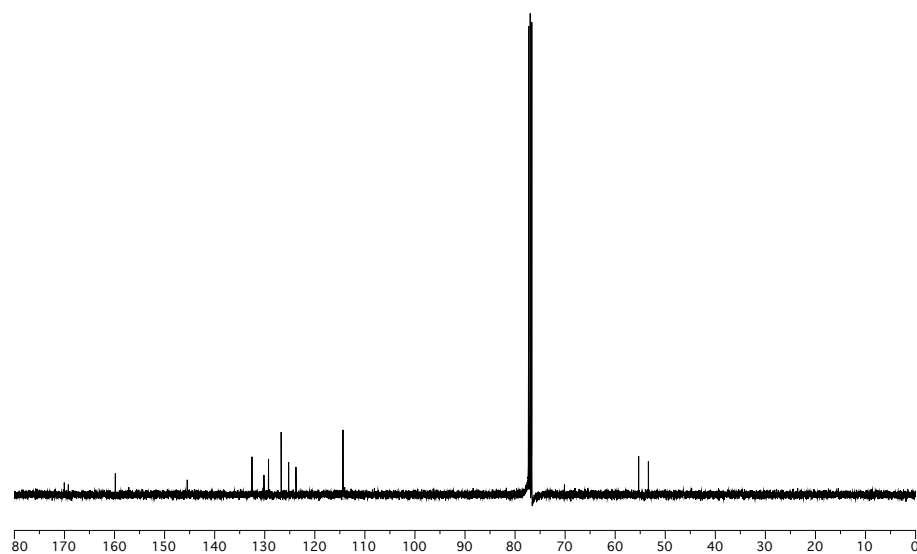
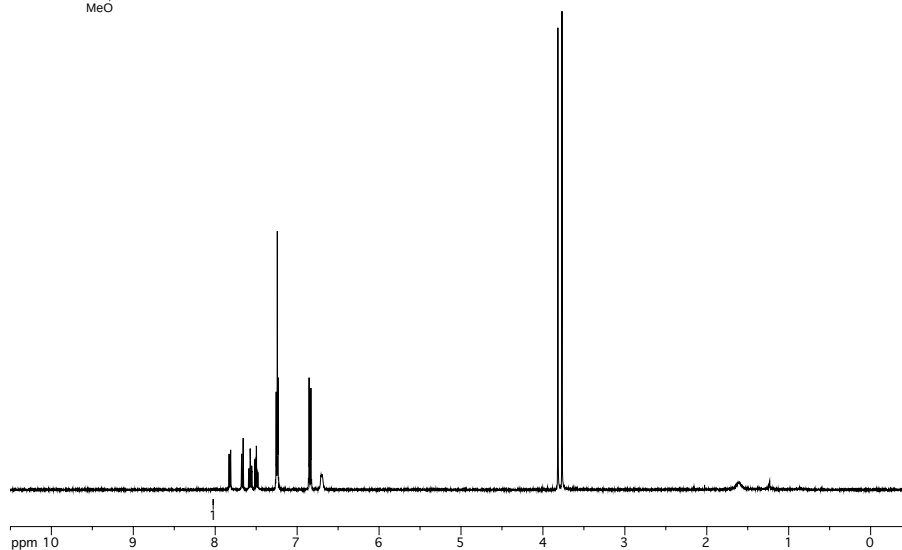
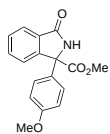


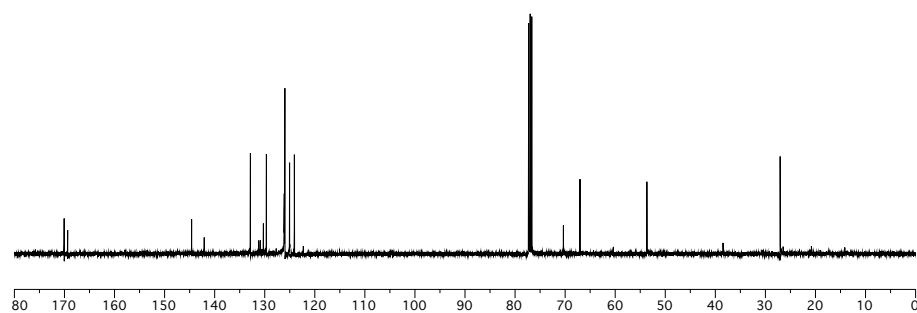
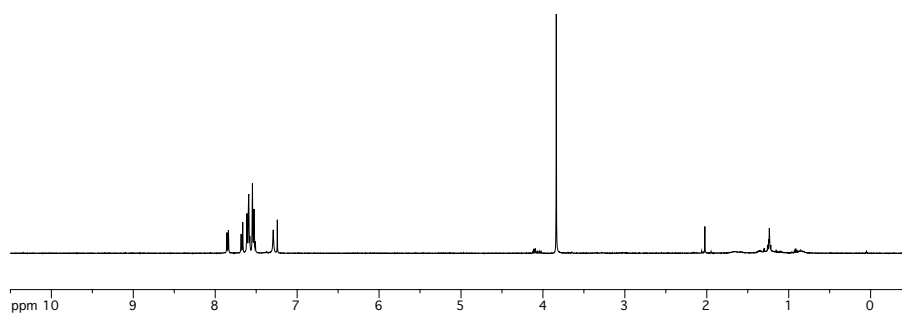
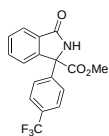


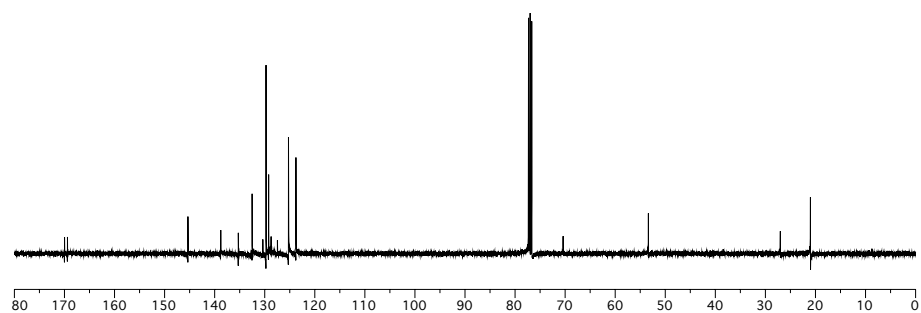
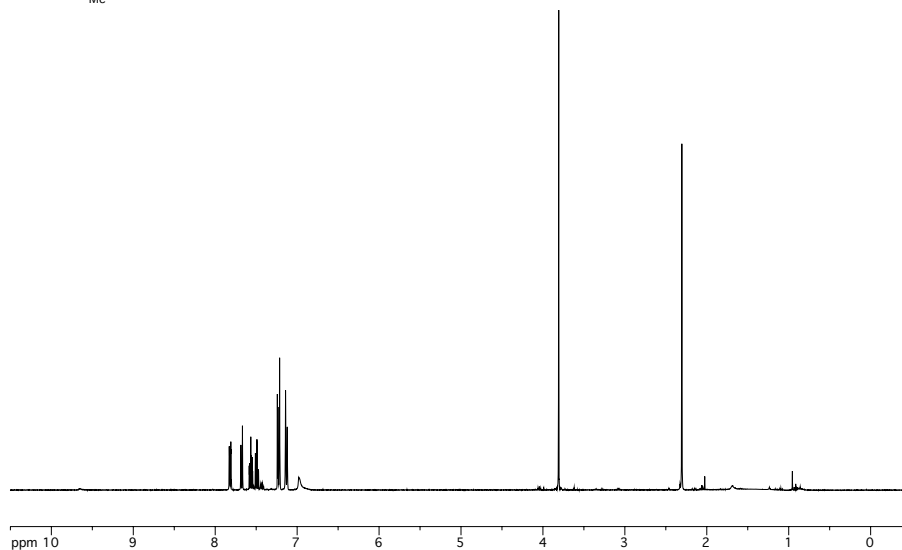
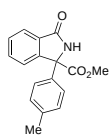


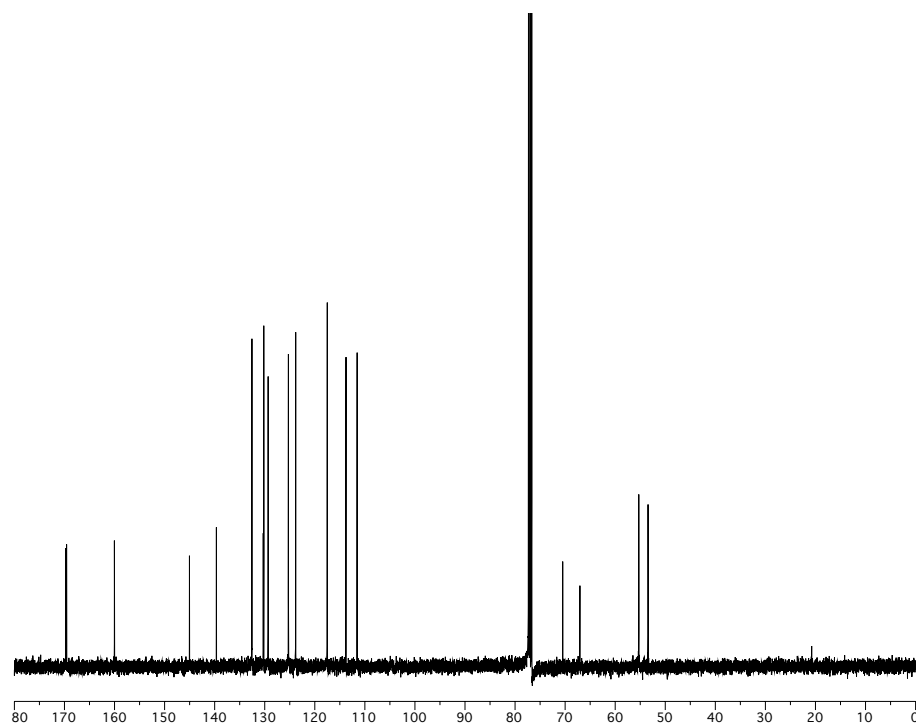
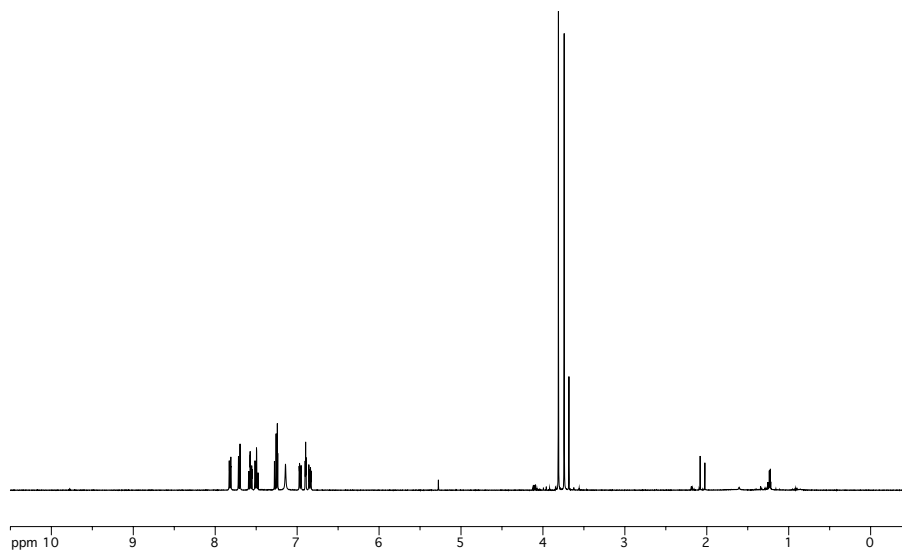
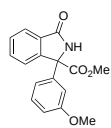


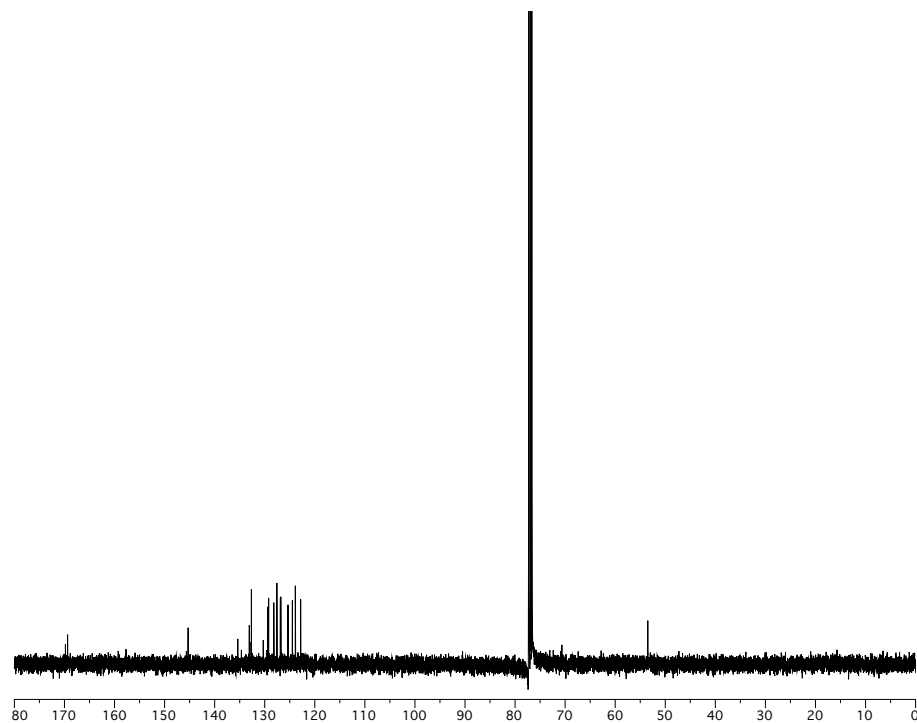
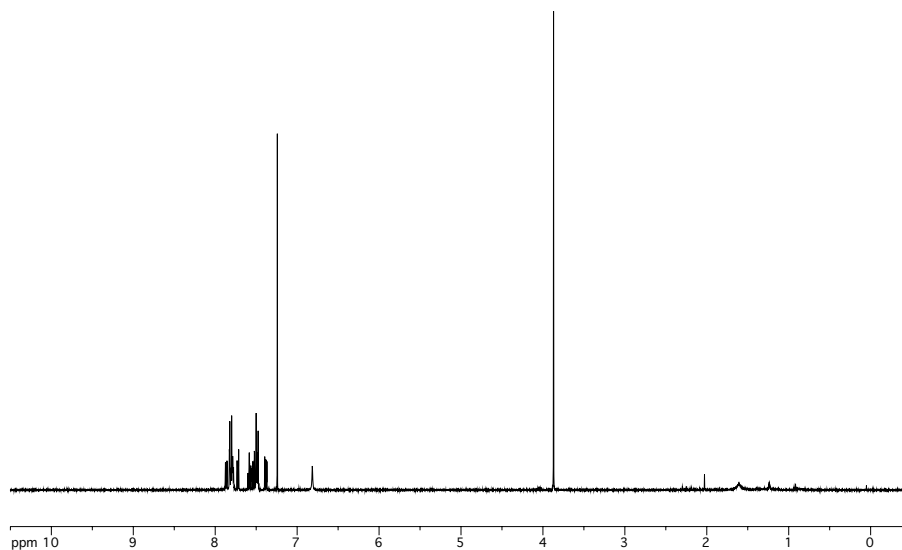
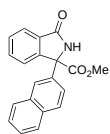


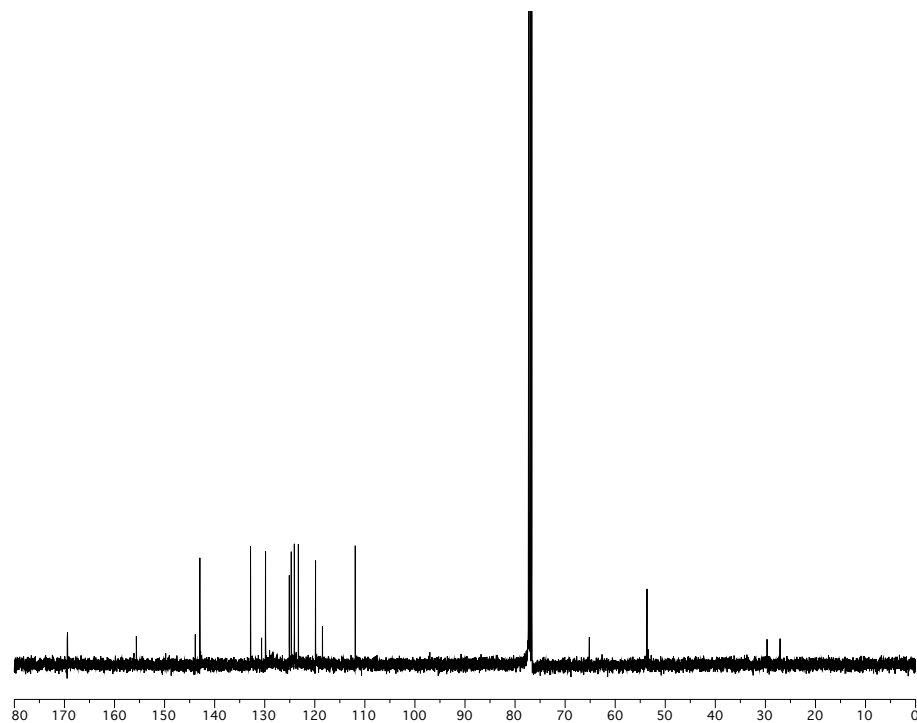
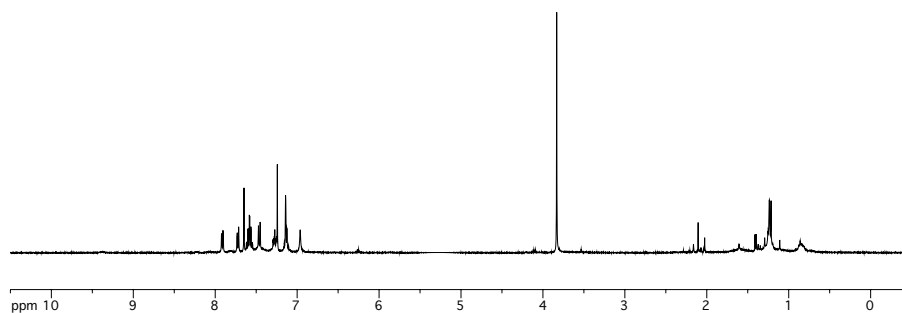
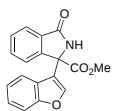


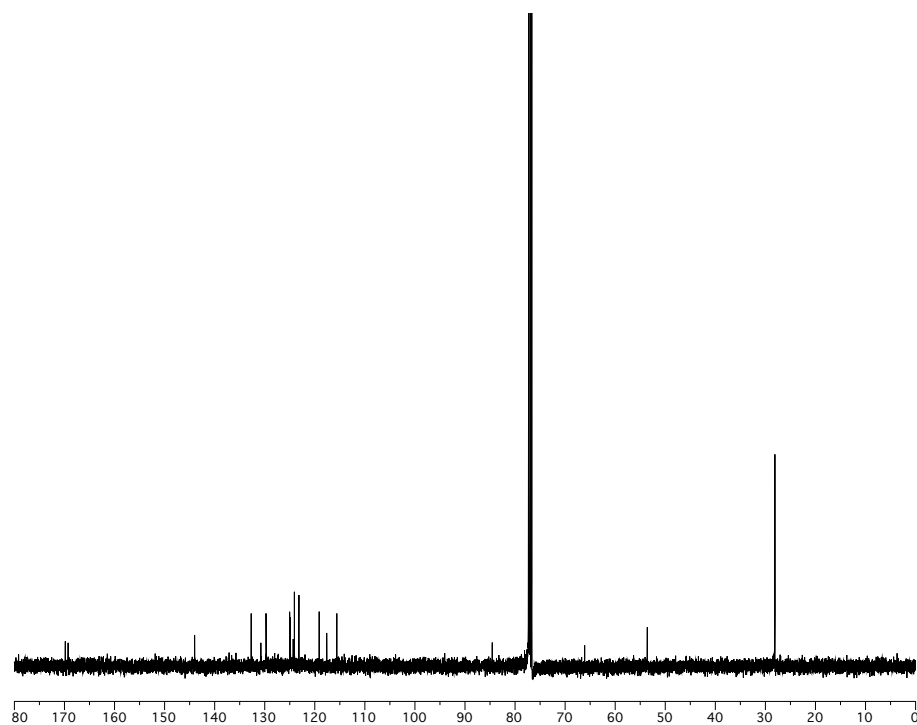
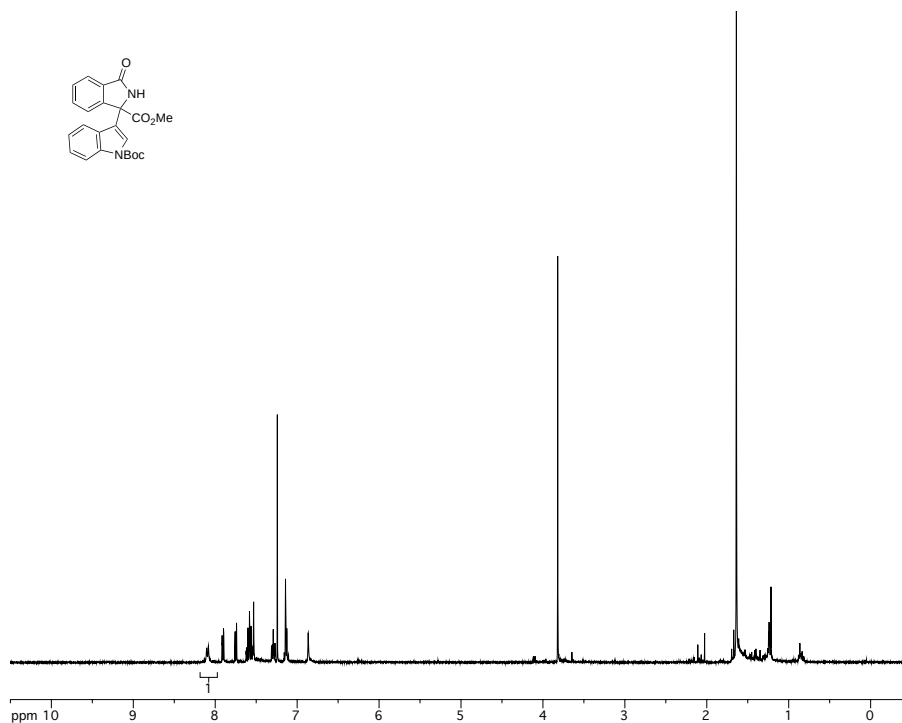
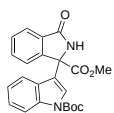


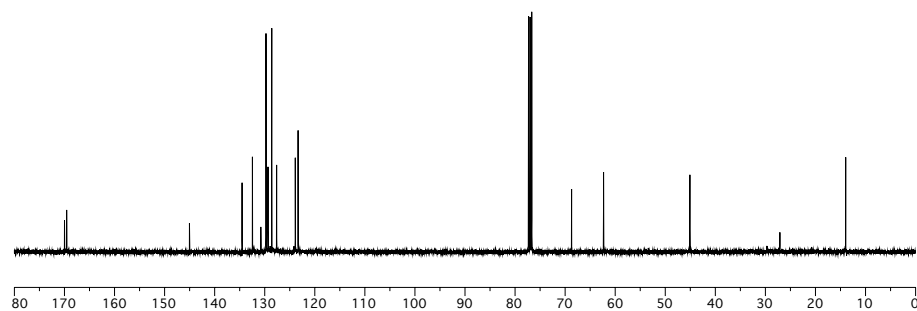
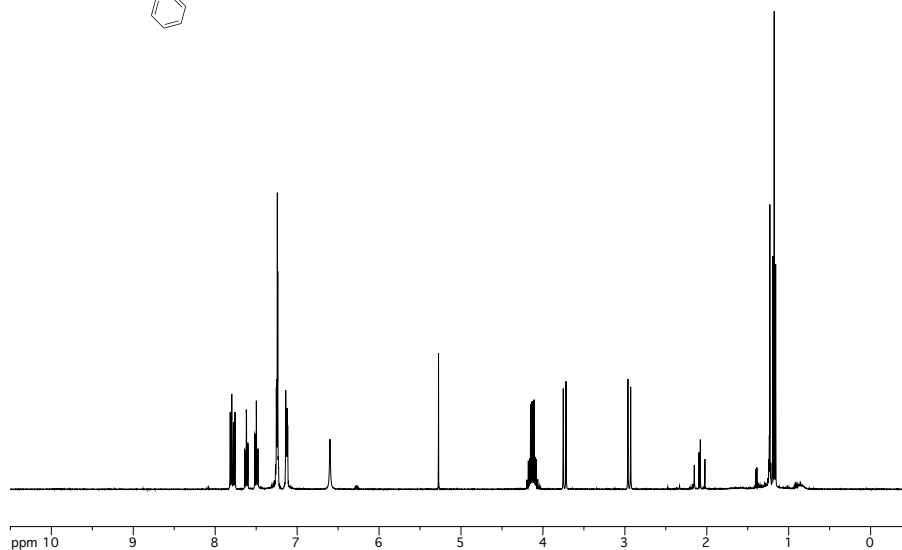
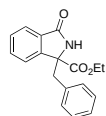


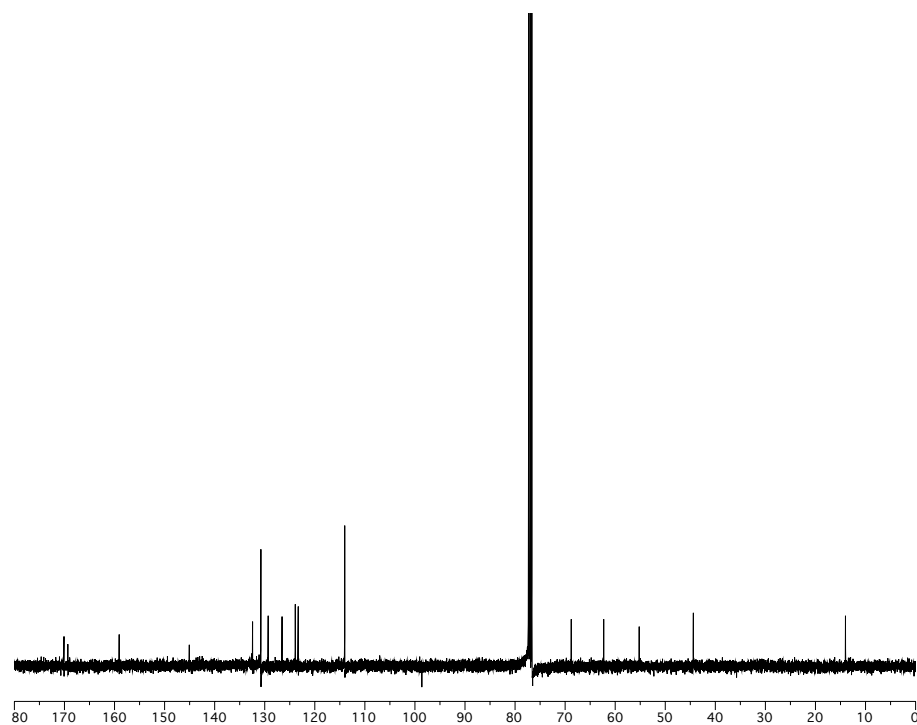
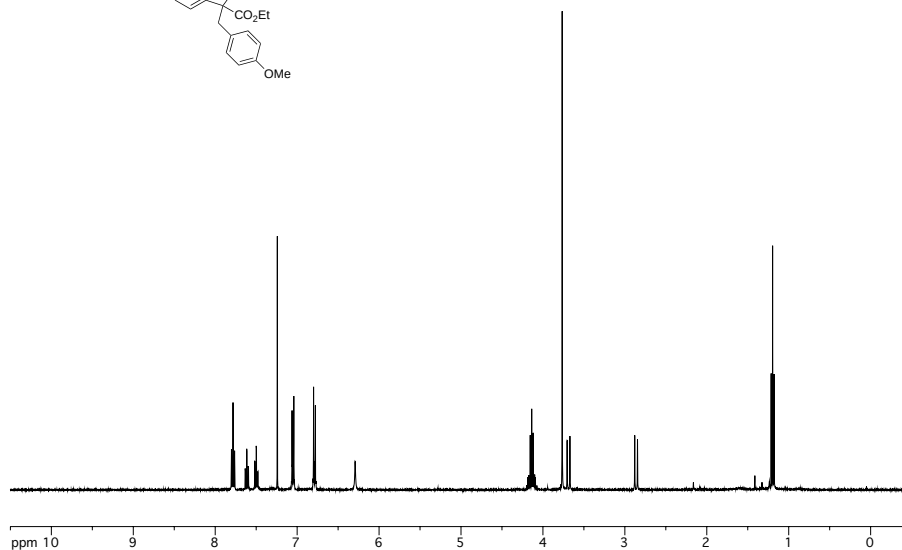
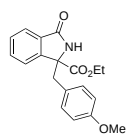


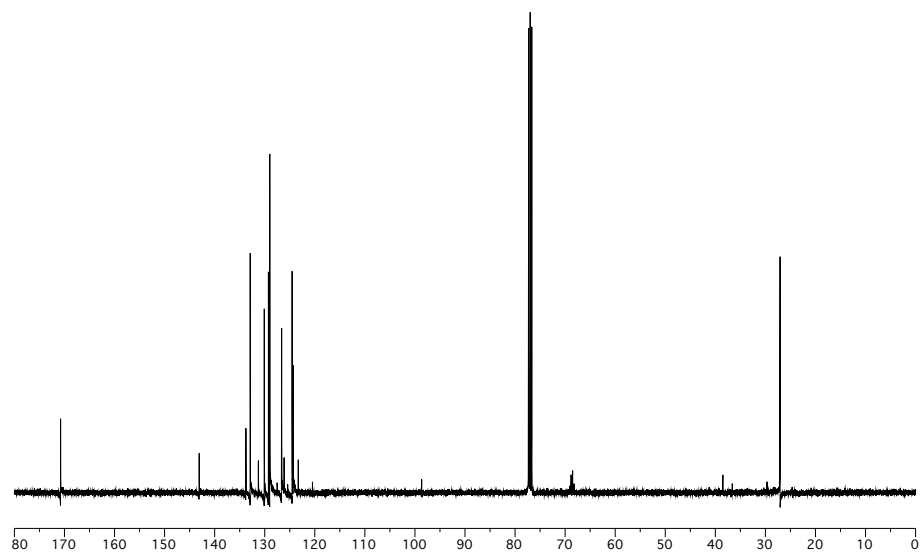
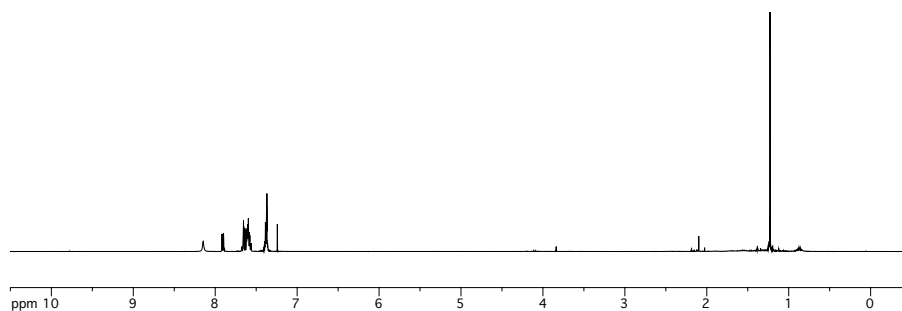


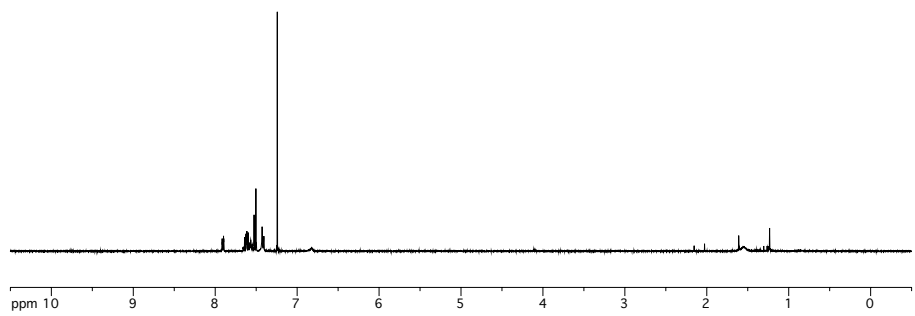
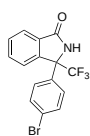
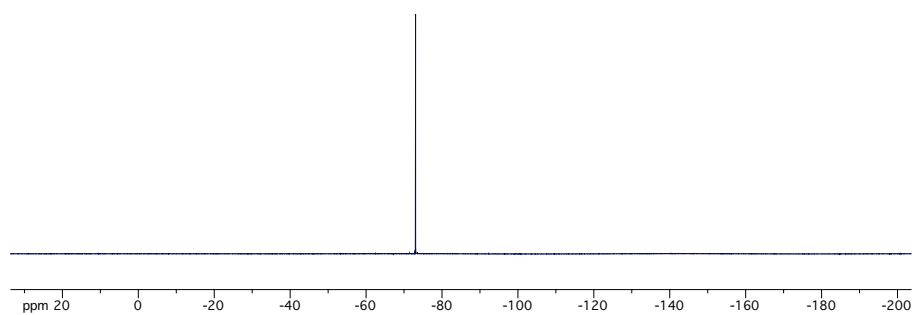


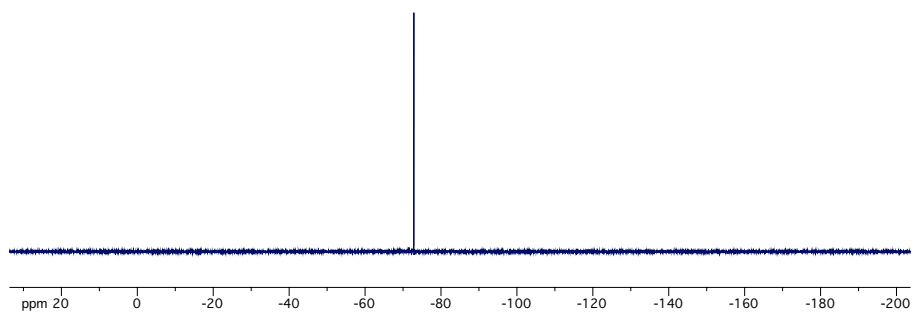
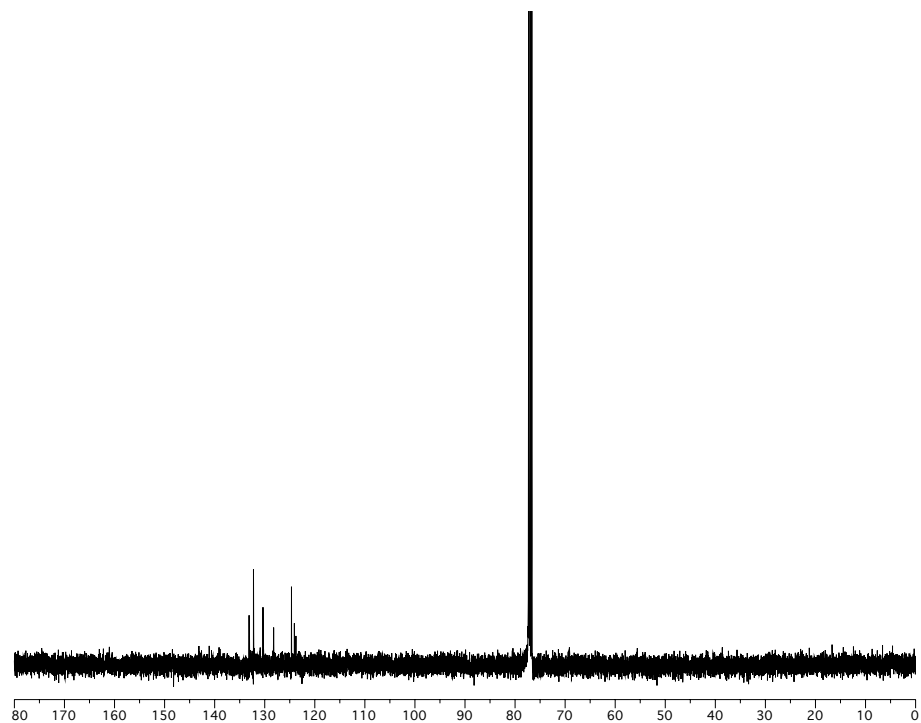


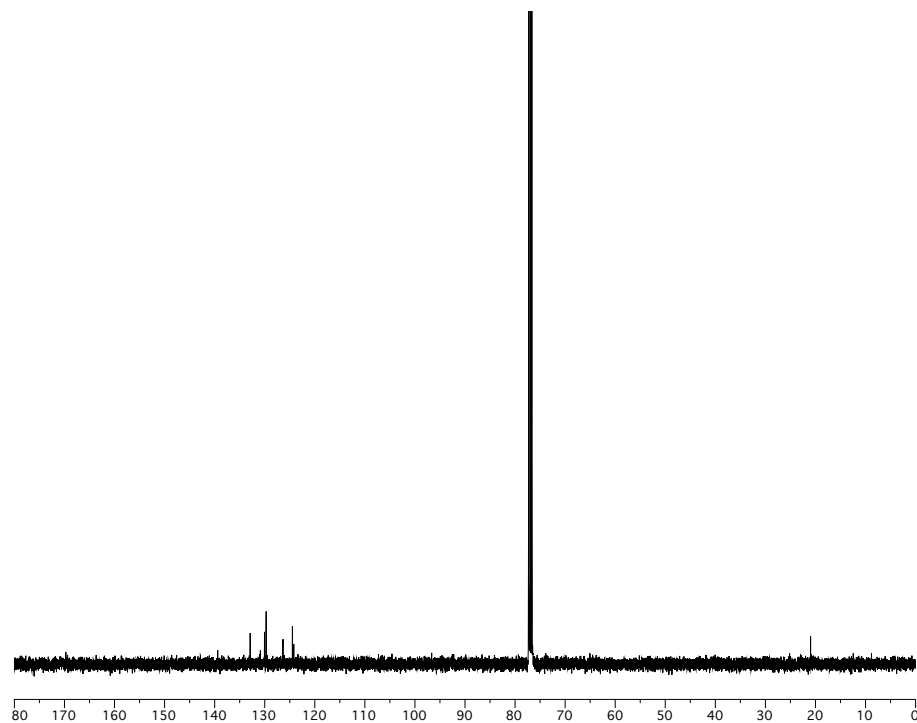
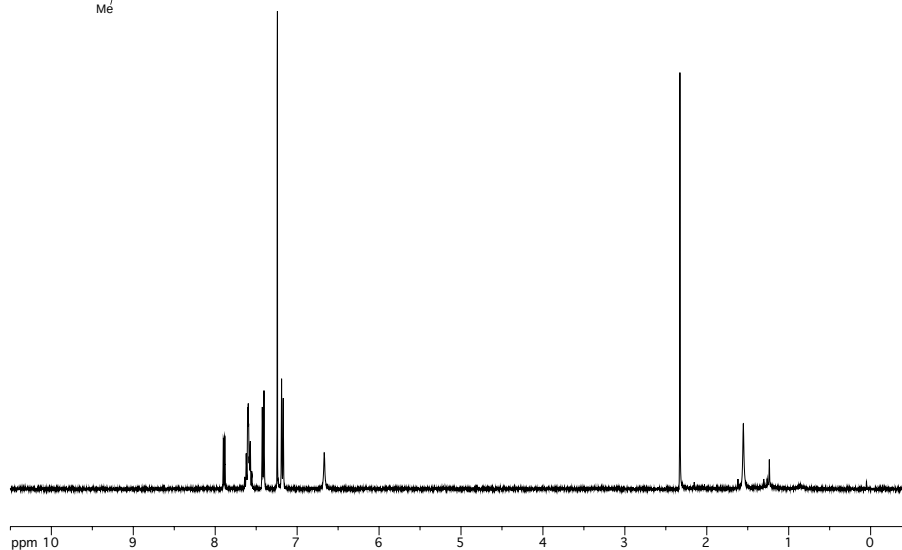
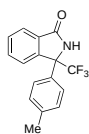


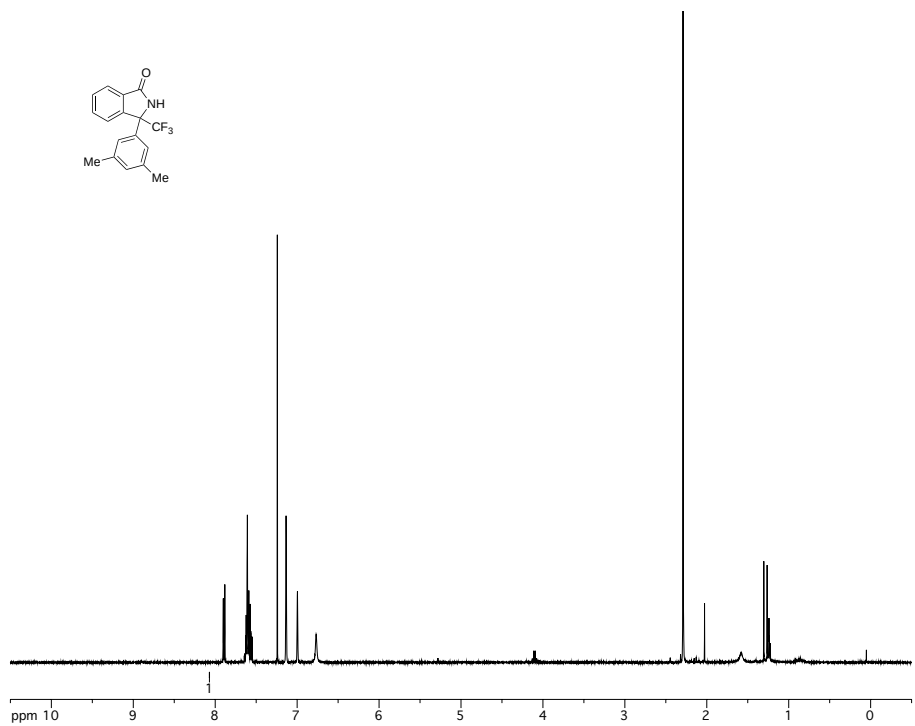
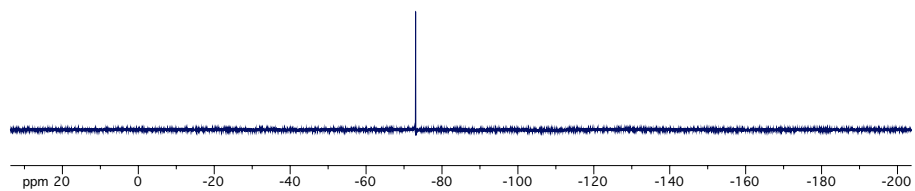


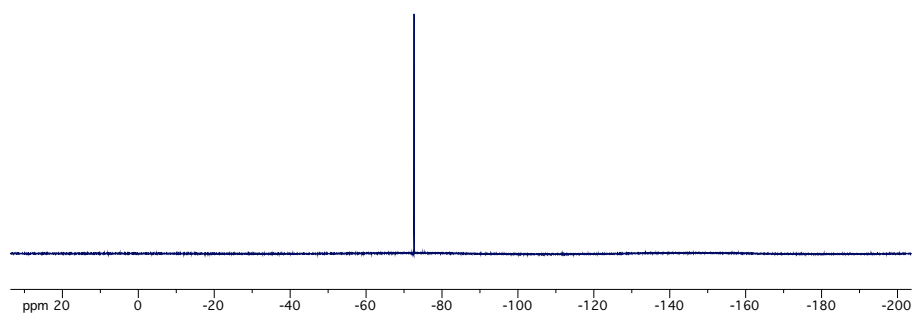
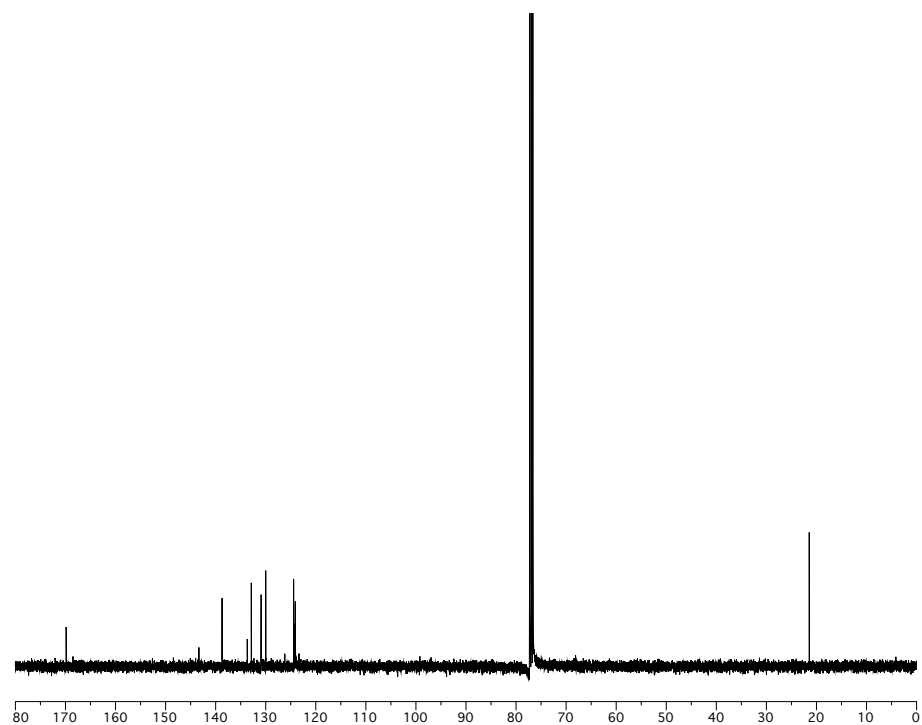


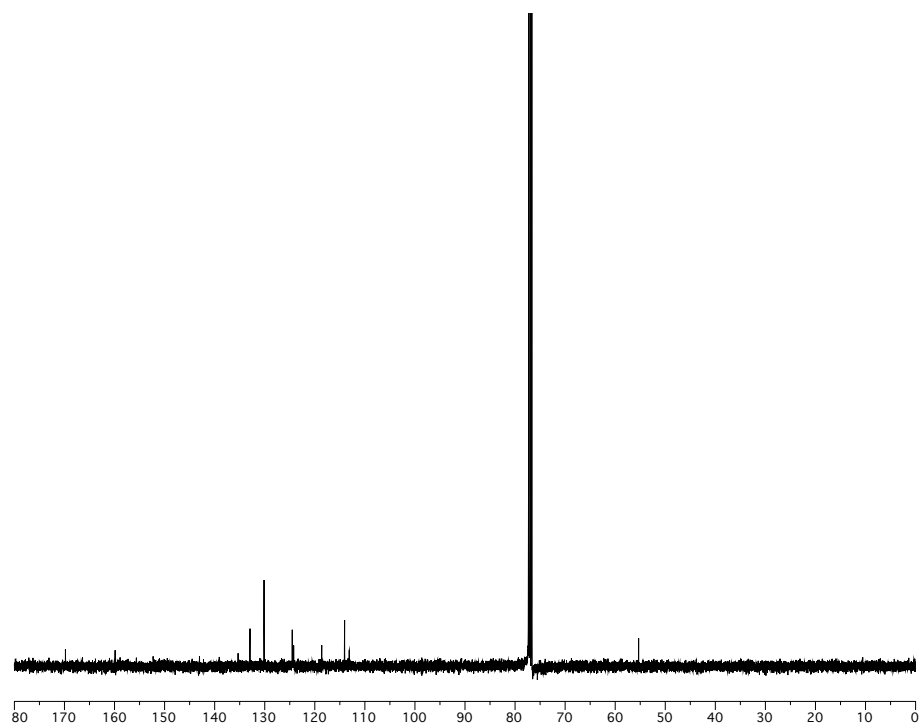
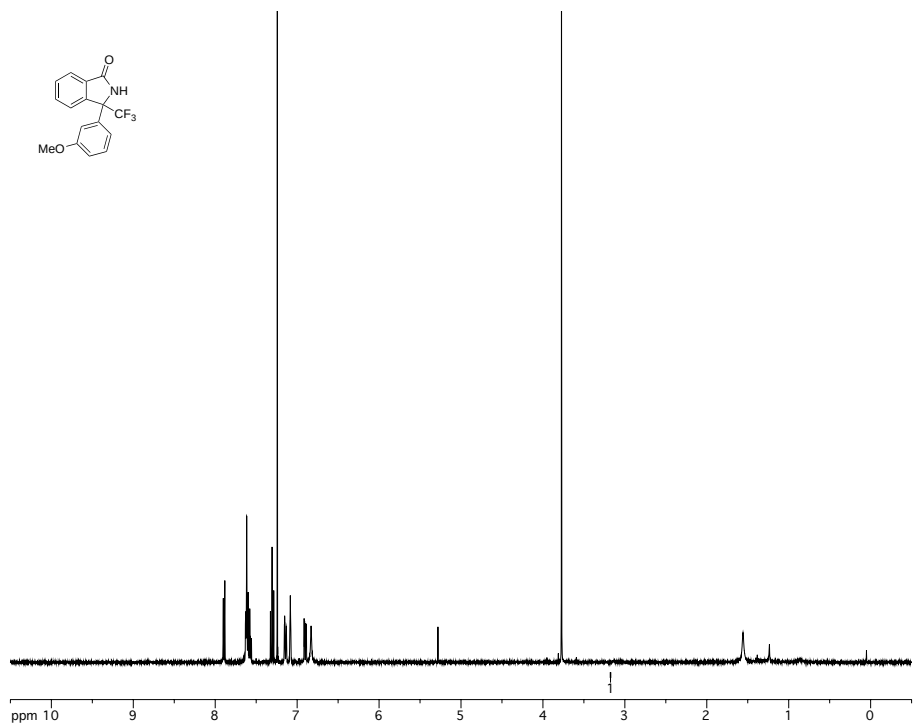


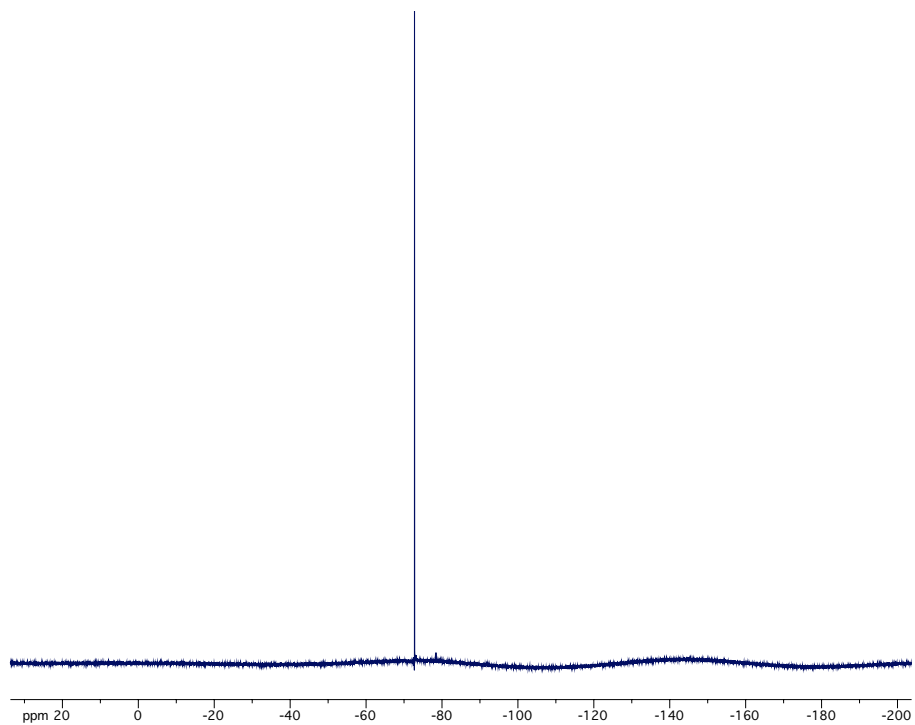


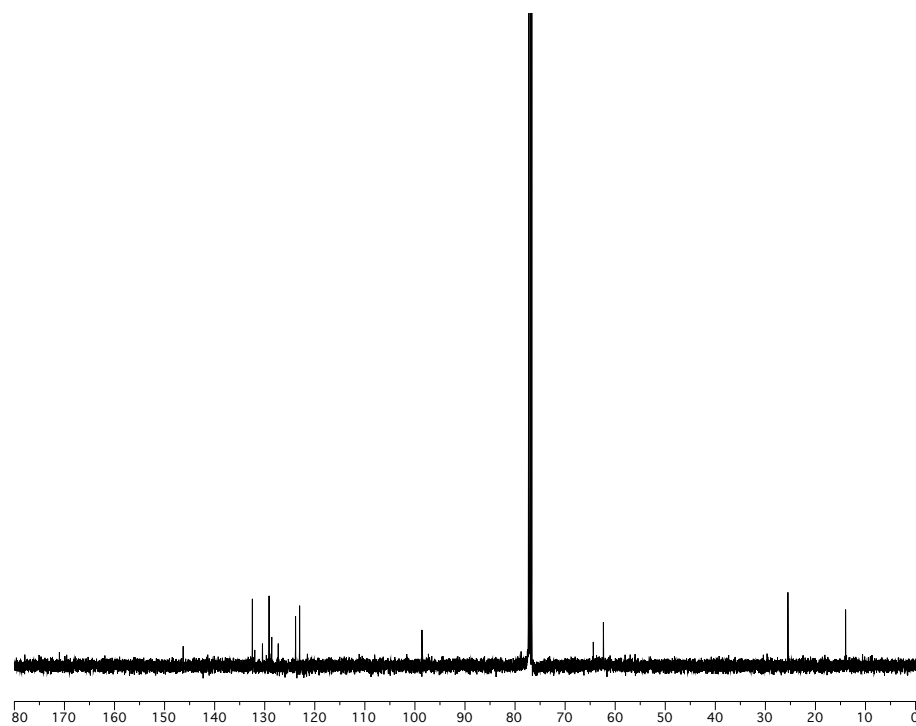
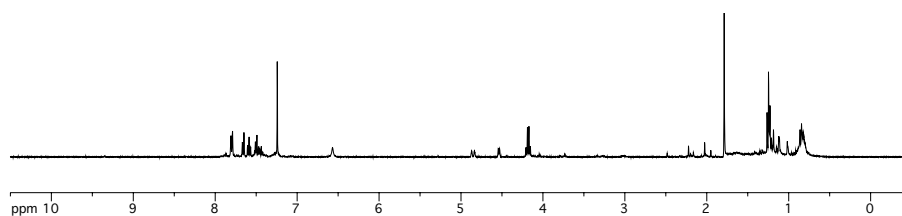
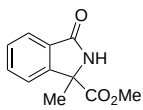












Appendix References

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