

**Development of Carbon–Carbon Sigma–Bond Activation with Rhodium
Catalysts**

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL OF
THE UNIVERSITY OF MINNESOTA

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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September 2011

ACKNOWLEDGEMENTS

First I would like to thank my advisor Chris Douglas for giving me the opportunity to be a part of his research group. I am excited to see the science that will come out of the group in the years to come, and I am very proud to have been a part of it.

I also would like to thank the Douglas group as a whole for creating a wonderful working environment. It was always a pleasure to come to work where I was able to discuss ideas and chemistry and learn from each and everyone in the group. I especially would like to thank Ashley Dreis and Giang Hoang for being great scientists and co-workers but even better friends.

I was given opportunities to grow not only as a scientist, but also as a teacher while in graduate school. I again have to thank Chris Douglas for allowing me to take advantage of these opportunities. First, I must thank Jane Wissinger, who served as a wonderful mentor while I served as Head Organic Teaching Assistant. Her enthusiasm for organic chemistry lab is contagious and inspiring. Secondly, I must acknowledge Sandra Olmsted, who allowed me to co-teach her organic chemistry course at Augsburg College. I am very lucky to have a mentor that I

could talk to and ask questions of while teaching a course for the first time.

Creighton University is a very special place to me, and the reason is because of the people. I had wonderful mentors while there including David Dobberpuhl, Julie Soukup, Gary Michels, Martin Hulce, and William Stephens. Dobs, Dr. Hulce, and Dr. Stephens were especially instrumental serving as both my academic and research advisors.

Finally, I must thank my family and girlfriend Anne. My Mom first suggested a career in chemistry over breakfast after telling me how excited I sound when I talk about my research projects. She has always been a source of support and encouragement in this endeavor and in everything that I do. My Dad has always been my hero and I have always wanted to be just like him. He taught me by his example what it means to work hard everyday, but at the same time to enjoy the people around you and tell jokes from time to time. My sister, Margy Jo, has always been there with for me with an encouraging note or helping our chemistry league softball team actually have a female. My brother, T.J., helped to show me how much fun you can have at college when I needed to relax and even helped serve as a test proctor for chemistry.

My girlfriend, Anne has been with me from the start of my time here at Minnesota. She has always supported me in this experience when I know at times it could not have been easy with the late nights, long hours, and Ally Lou. Thank you so much for your encouragement and perspective when I needed them most.

ABSTRACT OF THE DISSERTATION

Development of Carbon–Carbon Sigma–Bond Activation with Rhodium
Catalysts

By

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Doctor of Philosophy in Chemistry

University of Minnesota, Twin Cities, 2011

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Chapter 1. This chapter provides a review of the chemistry of metal catalyzed reactions involving normally unreactive sigma-bonds. Literature examples for a variety of methods to activate C–C and C–H sigma-bonds are discussed in detail. Particularly the preliminary work of Suggs and Jun in this field is presented.

Chapter 2. Presented herein is the development of an intermolecular and chemoselective method for C–C and C–H sigma-bond activation based on rhodium catalyst and solvent. The synthesis of substrates and optimization is presented. The results are given for a

variety of substrate ketones and alkenes. Finally, a discussion of the mechanism is presented.

Chapter 3. Presented herein is the development of an intramolecular carboacylation of alkynes with activated C–C sigma-bonds with rhodium catalysts. The synthesis of the substrates and optimization is presented. Results are presented with a number of substrates with various electronic groups. Mechanistic considerations are presented as well.

Chapter 4. Presented herein are the studies toward C–C sigma-bond activation with an organic co-catalyst. The synthesis of substrates and a number of investigations with them are presented. Finally, a discussion of future work in this project is presented.

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CHAPTER 1

1.1 Introduction

Carbon–carbon sigma-bond activation with a transition metal-catalyst has been a decades long challenge in the field of organometallic chemistry.¹ While there have been significant advances towards this end only a few examples have been done catalytically. Most examples required stoichiometric amounts of transition metal.² Recently, a number of publications have reported the catalytic carbon–carbon bond activation using various substrates and strategies, but often these approaches used aromatization³ or ring-strain relief⁴ as driving forces. To date, only the carbon–nitrile sigma-bond has been shown to be activated and lead to more complex products.⁵

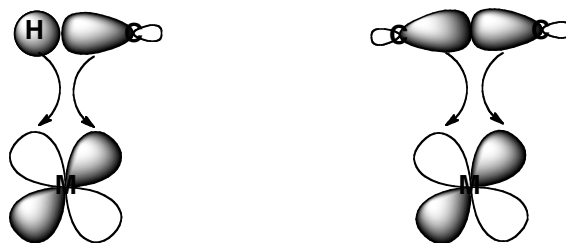
A great deal of work has been done on C–H activation processes including cyclometallation processes⁶, intermolecular C–H sigma-bond activation of aromatic C–H bonds⁷, and even insertion into a C–H bond of a saturated hydrocarbon⁸ which have all been landmarks in C–H activation. These metal complexes in homogenous media have lead to new reactivity enabling more efficient processes involving hydrocarbons.⁹ C–H bond activation is often the major competing pathway for unstrained C–C sigma-bond activation reactions. There are several factors contributing to the activation of C–H over C–C sigma-bond activation. First, it is often simply easier for the metal center to approach a C–H sigma-bond (sterics). Second, a statistical abundance of C–H bonds will always be prevalent with hydrocarbons. Finally, its postulated that the activation energy for oxidative addition of a metal to a C–C sigma-bond is higher than predicted for a C–H bond.¹⁰

Nevertheless, chemoselective C–C sigma-bond activation versus C–H is thermodynamically feasible based on a Hess' Law analysis using known M–C, M–H, C–C, and C–H bond dissociation energies. Examples specifically include M–C_{aryl} bonds, which are quite strong, particularly with iridium and rhodium metals, making substrates with these sp²–hybridized carbons with sigma-bonds good substrates for C–C sigma-bond activation.¹¹ It still does remain difficult to predict the effectiveness of substrates as steric effects can interfere with bond strength estimation in a certain metal-complex.

Theoretical calculations highlight another inherent problem with C–C sigma-bond activation and its three-centered nonpolar transition state.¹² Calculations for first-row (3d) transition metals show the activation energies for insertion into the C–C bond of ethane and the C–H bond of methane are 40-45 and 20-25 kcal mol⁻¹ respectively. The second row transition metals (4d) such as rhodium have much lower activation energies 13-27 kcal mol⁻¹ for C–C sigma-bond insertion while C–H activation lower as well (0-9 kcal mol⁻¹). This data suggests that the key difference is orbital directionality differences between C–H and C–C sigma-bonds in regards to the kinetic barrier for bond insertion (Scheme 1). In the oxidative addition of a C–H bond to a metal, the spherically symmetrical 1s orbital can bind to both the metal and carbon atom simultaneously. This is not possible with a C–C sigma-bond with the sp³–hybridized carbon atom having only one optimal binding direction, and in the course of the activation rotation occurs into a position no longer optimal for both

bonding directions. This suggests that bond insertion is greatly influenced by the different nature of C–H and C–C bonds and is independent of the metal involved.

Scheme 1. Orbital representation of C–H (left) and C–C (right) bonds in oxidative addition and the effect of orbital directionality

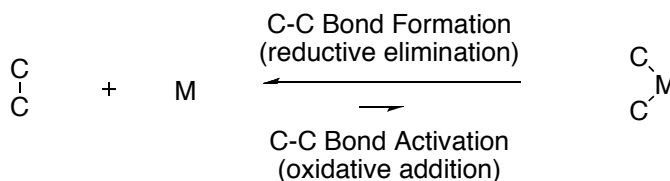


Despite the aforementioned factors, C–C sigma-bond activation is possible, particularly with specific substrate and catalyst design and considerations. Much like the recent surge in reaction discovery involving carbon–hydrogen sigma-bond activation,¹³ carbon–carbon sigma-bond activation has the ability to open even more new possibilities in retrosynthetic design and an ability to mechanistically study C–C sigma-bond activation. Not unlike a carbonyl functional group, a carbon–carbon sigma-bond when activated could allow for the direct completion of many synthetic transformations without the need for previously installing synthetic handles, i.e. halogens.

The major hindrance to this activation is that C–C activation (oxidative addition) has a reverse process (reductive elimination), and the oxidative addition and reductive elimination equilibrium lies towards oxidative addition (Scheme 2). This is due to the thermodynamically favored carbon–carbon sigma-bond, approximately (90

kcal/mol), versus the formation of two weaker metal–carbon bonds, (20-30 kcal/mol).¹⁴ The reductive elimination is therefore typically a thermodynamically downhill process, similar to other well known organometallic catalytic cycles.

Scheme 2. Carbon–Carbon Sigma-bond Activation Equilibrium with Metals

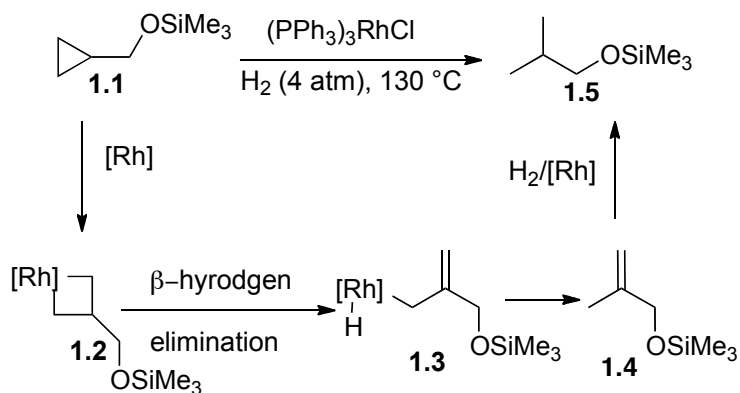


1.2 Precedence

Despite the thermodynamic disadvantage for carbon–carbon sigma-bond activation, researchers have devised ways to circumvent the problem. The majority of these methods overcome the inherent thermodynamic disadvantage by utilizing high energy starting materials such as strained rings or unstrained substrates that lead to the formation of stable metallacycles with via inherent molecular coordination possibilities. An interesting dimension to using strained–ring systems is the propensity to undergo a β –alkyl elimination versus the more common β –hydride elimination. Essentially, the strategy is to make C–C sigma-bond activation thermodynamically favorable by weakening the C–C bond used with strain and strengthening the M–C bonds formed with chelation.

The most common method for carbon–carbon sigma-bond activation is the use of a 3 or 4–membered carbon ring as the high energy starting material. Oxidative addition into these carbon–carbon sigma-bonds is favorable as the resulting 4 or 5–membered metallacycles are more stable than the starting substrates. Chirik and co-workers have shown this method with a cyclopropane derivative (**1.1**) using Wilkinson’s catalyst, which is able to directly insert into the carbon–carbon sigma-bond (Scheme 3).¹⁵ The Rh(I) catalyst activates the less hindered carbon–carbon sigma-bond regioselectively forming the 4–membered metallacycle (**1.2**), which undergoes a β –hydride elimination giving **1.3**. If under an inert N₂ atmosphere the final product, following reductive elimination, is the alkene (**1.4**), but if under H₂ pressure (4 atm) then hydrogenation of the alkene occurs giving **1.5**.

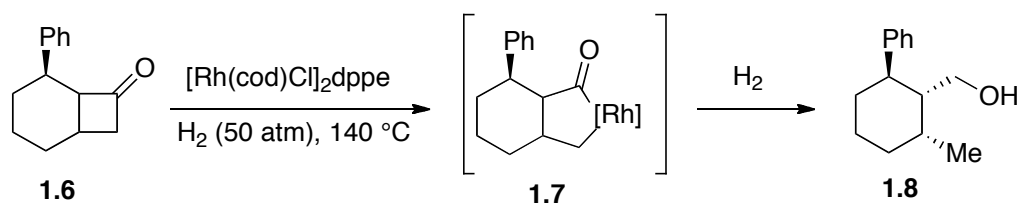
Scheme 3. Carbon–Carbon Sigma-bond Activation in a Cyclopropane Ring



They have also been able to perform this tandem carbon–carbon sigma-bond activation/hydrogenation with a number of functional groups in place of the silyl-protected alcohol. Furthermore, by using functional groups that are able to coordinate to the metal catalyst, they have shown that it is possible to activate the more hindered carbon–carbon sigma-bond of a functionalized cyclopropane.

Murakami and co-workers have developed a similar cyclobutanone (**1.6**) carbon–carbon sigma-bond activation complex (**1.7**), which proceeds both regioselectively and stereoselectively giving the alcohol **1.8** (Scheme 4).¹⁶ The Rh(I) catalyst again adds into the carbon–carbon sigma-bond (**1.7**) and following consecutive hydrogenolysis gives the alcohol **1.8**.

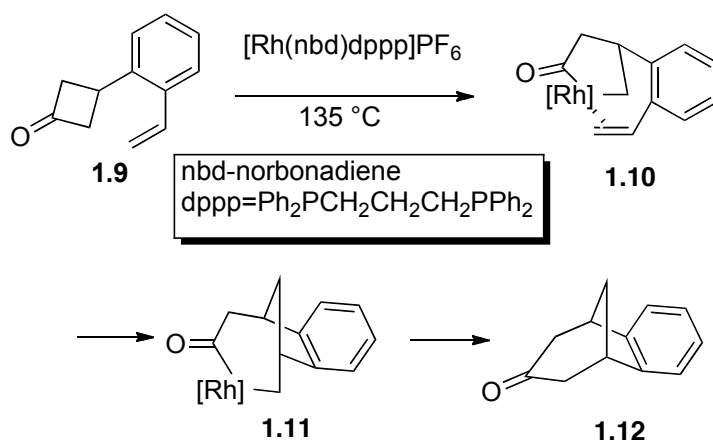
Scheme 4. Carbon–Carbon Sigma-bond Activation in a Cyclobutanone Ring



Another approach to cyclobutanone C–C sigma-bond activation and functionalization involves the intramolecular carboacylation of alkenes (Scheme 5).¹⁷ Cyclobutanone **1.9** undergoes bond activation to give metallacycle **1.10**. Migratory insertion of the alkene (**1.10**→**1.11**) followed by reductive elimination (**1.11**→**1.12**) gives [3.2.1] bicyclooctanone **1.12**. The conversion of the cyclobutanone **1.9** to a

bridged complex bridged ring system represents an increase in the molecular complexity with C–C activation.

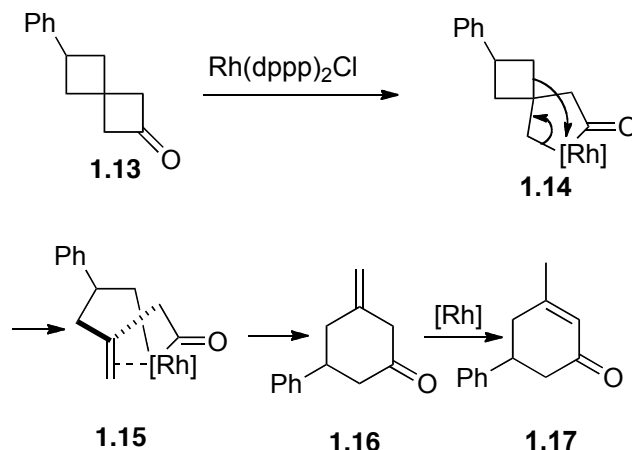
Scheme 5. Intramolecular Alkene Insertion into an Activated C–C Sigma-bond



β -Carbon or alkyl elimination is a novel carbon–carbon cleavage in organometallic chemistry. This transformation has been applied to carbon–carbon sigma-bond activation in a few recent examples with the driving force again being relief of ring strain and the formation of stable metallacycle intermediates.

An example of β -alkyl elimination is the strained spiro-cyclobutane system (**1.13**) developed by Murakami and Ito that undergoes consecutive carbon–carbon sigma-bond activation (Scheme 6).¹⁸ Initial oxidative insertion occurs forming the 5-membered metallacycle (**1.14**) followed by β -alkyl elimination to relieve the ring strain of the adjacent cyclobutane (**1.15**). After reductive elimination (**1.15** \rightarrow **1.16**), isomerization of the double bond results in the α,β -unsaturated cyclic ketone **1.17**.

Scheme 6. β -alkyl Elimination of a C–C Sigma-bond Activated Cyclobutane



The examples from this section have shown that C–C sigma-bond activation is possible in strained ring systems containing inherently weaker C–C sigma-bonds. However, these types of strained molecules are not common, and while these examples are interesting and informative, they are not that synthetically useful.

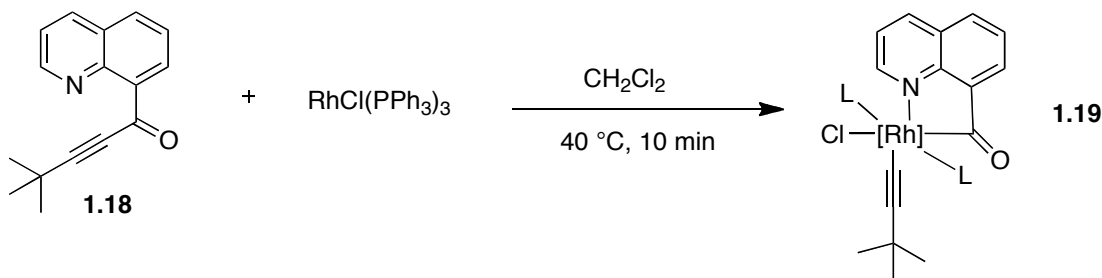
1.3 Substrate Directed Carbon–Carbon/Carbon–Hydrogen Bond Activation

1.3.1 Background

The ability to activate a carbon–carbon sigma-bond in an unactivated system, without strain is a daunting challenge. Using a chelating substrate to help direct and activate a particular carbon–carbon sigma-bond is a method developed by Suggs and Jun. One of the first reports from these scientists was the directed cleavage of a sp^2 – sp C–C sigma-bond adjacent to a ketone in a 8-acylquinolinyl substrate (Scheme 7).¹⁹

Treating Wilkinson's catalyst ($\text{RhCl}(\text{PPh}_3)_3$) with the 8-quinoliny ketone (**1.18**) in dichloromethane at 40 °C for 10 minutes turned an initially red solution, presumably a Rh(I) complex, to a yellow solution Rh(III). Treatment of the yellow solution with diethyl ether gave a solid yellow precipitate (**1.19**), the structure of which was assigned by various spectroscopic methods. Further evidence for the formation of **1.19** was given by treatment of the yellow solid with HCl, which gave *t*-butylacetylene in high yield.

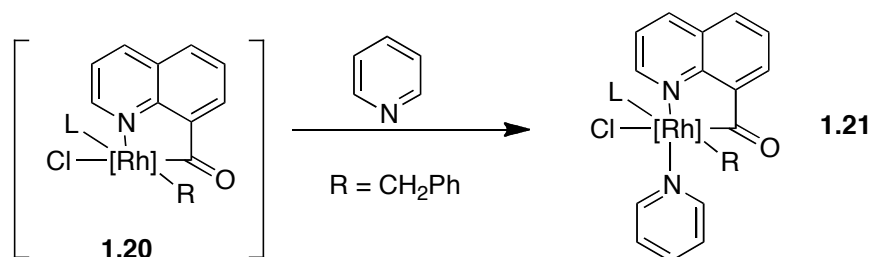
Scheme 7. Suggs and Jun's Substrate Directed sp^2 - sp C-C sigma-bond Activation



Following the work with alkyne substrates, a new Rh(I) metal catalyst was used giving more information on the effect that phosphine ligands may have on metallacycle formation.²⁰ From the work with alkynes it was known that acetylenic ketones are quite reactive with Wilkinson's catalyst¹⁹ and even can be cleaved by NaOH.²¹ Another Rh(I) source was therefore investigated, $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$. Within minutes, a benzyl ketone in benzene at room temperature will form an insoluble metal-chlorine complex (**1.20**). **1.20** can be coordinated with pyridine (excess) to

solubilize the pyridine-benzyl complex (Scheme 8). The pyridine complex can then be crystallized to the 6-coordinate structure (**1.21**) confirmed by x-ray diffraction. Important observations from this experiment were that no 6-membered ring metallacycle from benzyl C–H activation occurred, which was confirmed by deuterium labeling of the benzylic C–H’s. Also addition of phosphines to these metal-complexes (**1.20** and **1.21**) caused reductive elimination to starting acyl-ketones or when using Rh(I) metals with phosphines, i.e. Wilkinson’s catalyst, no metallacycle was observed at all.

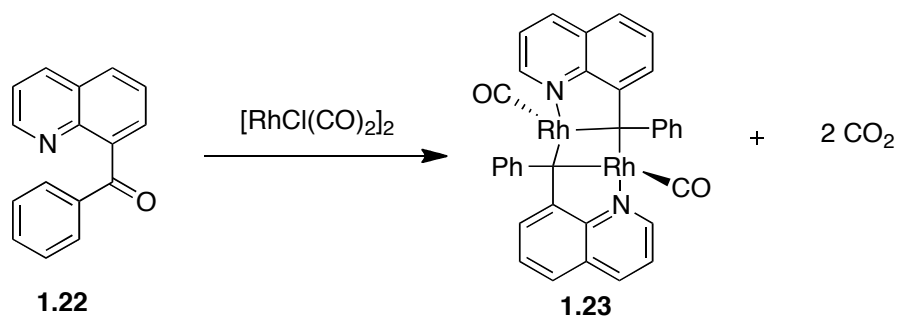
Scheme 8. C–C sigma-bond Activation Complex Formation Adjacent to Ketones



Another example of ligands on the Rh(I) source playing a role is shown in Scheme 9.²² When phenyl ketone **1.22** is mixed in benzene at room temperature with a Rh(I) with carbon monoxide ligands carbon dioxide and the metallacycle **1.23** is formed. The phenyl ketone is deoxygenated with this Rh(I) source, obviously making it not useful for new product formation. The previous two examples (Schemes 7 & 8) highlight the importance of the selection of the ancillary ligands either phosphines or

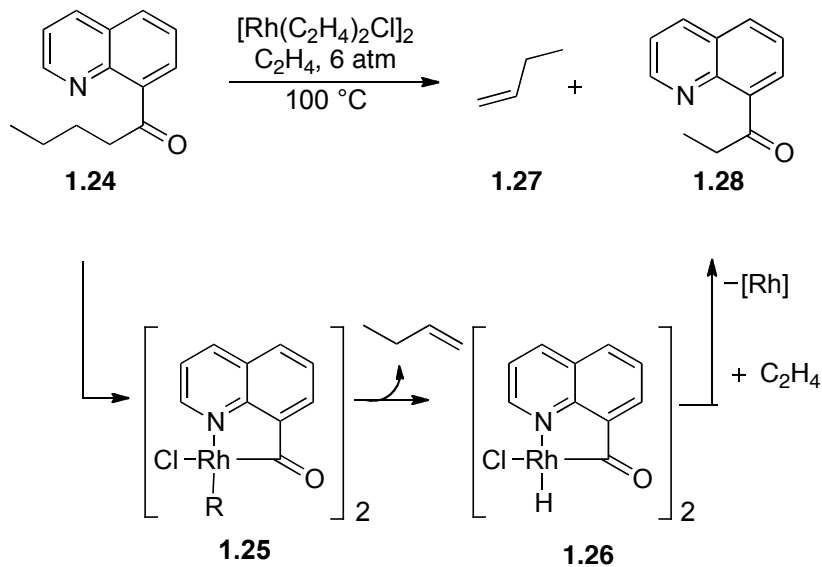
carbon monoxides on the rhodium metal as they can have a profound effect on the reactivity.

Scheme 9. Non-Productive CO₂ Formation by Rhodium Metal



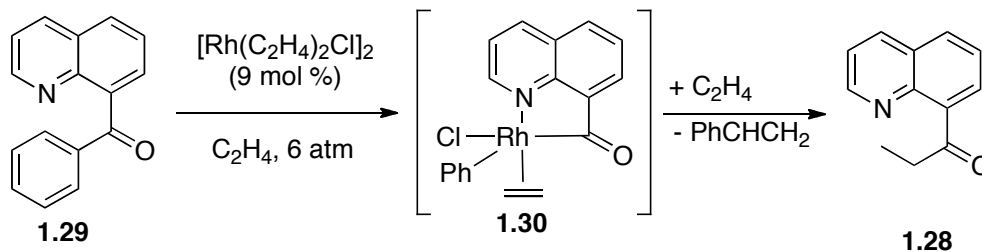
The next step was to develop a C–C sigma-bond activation process that was catalytic and formed new products from the carefully chosen substrates. An alkyl ketone (**1.24**) could undergo a catalytic process under 6 atm of ethylene (Scheme 10).²³ The chelating nitrogen of **1.24** directs the cyclometallation and this facilitates the oxidative addition of the Rh(I) catalytic complex giving the 5-membered metallacycle (**1.25**). After β–hydrogen elimination of **1.25**, alkene **1.27** and rhodium hydride **1.26** are formed. Intermediate **1.26** undergoes a migratory insertion with ethylene, followed by reductive elimination, resulting in product **1.28**. However, ethylene was the only alkene of these examples that was able to form new alkyl-ketones, indicating that reductive elimination is more facile than β-hydrogen elimination with all other alkenes in these rhodium-metallacycles.

Scheme 10. Suggs and Jun's Catalytic C–C Sigma-bond Activation System



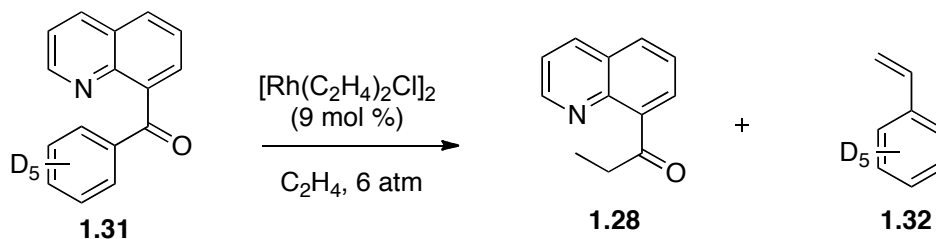
It was also interesting that no competing carbon–hydrogen bond insertion forming a 6–membered metallacycle took place for phenylketones such as **1.29** (Scheme 11), demonstrating a selective catalytic method. Substrate **1.29** after C–C sigma-bond activation forms the metallacycle **1.30** which has no β -hydrogens meaning the β -hydrogen elimination found in Scheme 10 is not possible. Instead a migratory insertion of ethylene to the phenyl ring takes place followed by β -hydrogen elimination producing styrene and the same ketone as before **1.28** (Schemes 10 & 11).

Scheme 11. Suggs and Jun's 8-acylquinoline Directed C–C Sigma-bond Activation System



To rule out a possible mechanism with benzyne formation instead of direct C–C bond activation, a fully deuterated phenyl ring in an 8-acylquinoline (**1.31**) was subjected to the catalytic conditions (Scheme 12). If the benzyne mechanism took place a benzyne-hydride (deuterium) complex would be formed and the deuterium could be incorporated into the ethylene after reductive elimination. However, spectroscopic analysis of the products showed no deuterium incorporation into product **1.28**, thus ruling out benzyne formation with the fully deuterated styrene (**1.32**) also being formed. Finally and surprisingly, Wilkinson's catalyst, despite having phosphines ligands and which had been previously been known to halt metallacycle formation, also allowed for the formation of **1.28** from **1.29**. This can be accounted for by noting the stronger $\text{M}-sp^2$ bonds present in intermediate **1.30**.²⁴

Scheme 12. Deuterium Labeling Studies



Suggs and Jun's discovered that the carbon undergoing activation will retain stereochemistry after activation. When a chiral center is α to the carbonyl carbon, carbon-carbon sigma-bond activation did not alter the chirality.²³ Thus leaving the potential to transfer stereochemical information to products following a migratory insertion.

1.4 Co-Catalyst Directed Carbon-Carbon Sigma-bond Activation

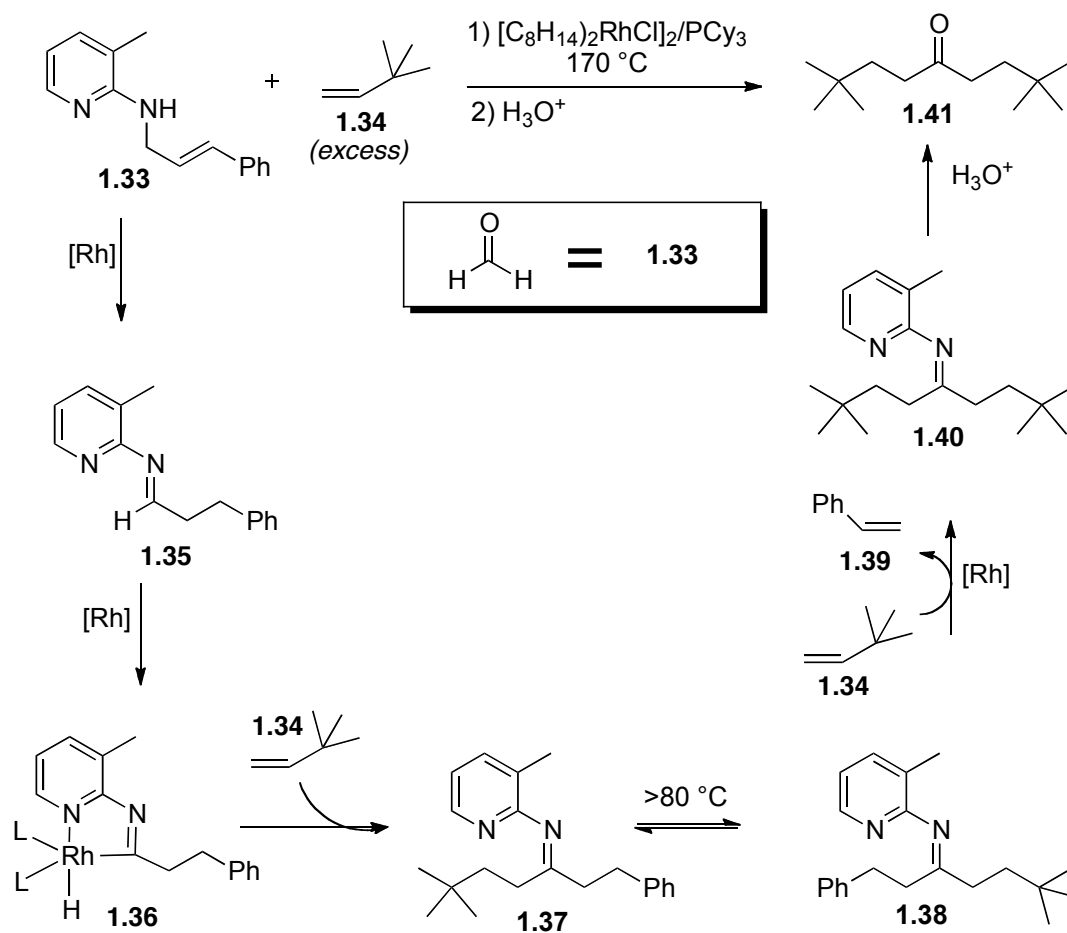
1.4.1 Background

While creative in its approach to activate and functionalize a carbon-carbon sigma-bond, the previous proposal required that the product also contain the chelating agent needed for the formation of the 5-membered metallacycle. Alternatively, using a chelating agent that also serves as a type of co-catalyst would be advantageous since the target materials not being restricted to molecules containing chelating moieties as

part of their structure. This exact type of method has been investigated by Jun and co-workers using an aldehyde, a secondary alcohol, and unstrained ketone substrates.

Initial work done by Jun and co-workers shows the utility of using an allylamine (**1.33**), as a masked form of formaldehyde (Scheme 13).²⁵ Following isomerization, **1.35** undergoes a carbon–hydrogen sigma-bond activation giving metallacycle **1.36**. In the presence of excess alkene **1.34**, migratory insertion readily occurs into the olefin giving the imine **1.37**. Activation of the C–C sigma-bond adjacent to the imine carbon of **1.38** allows for the formation of a metallacycle that directs the β –hydride elimination of **1.39** and a second insertion of the excess alkene **1.34** to give imine **1.40**. Hydrolysis completes the cycle, resulting in symmetrical ketone **1.41**.

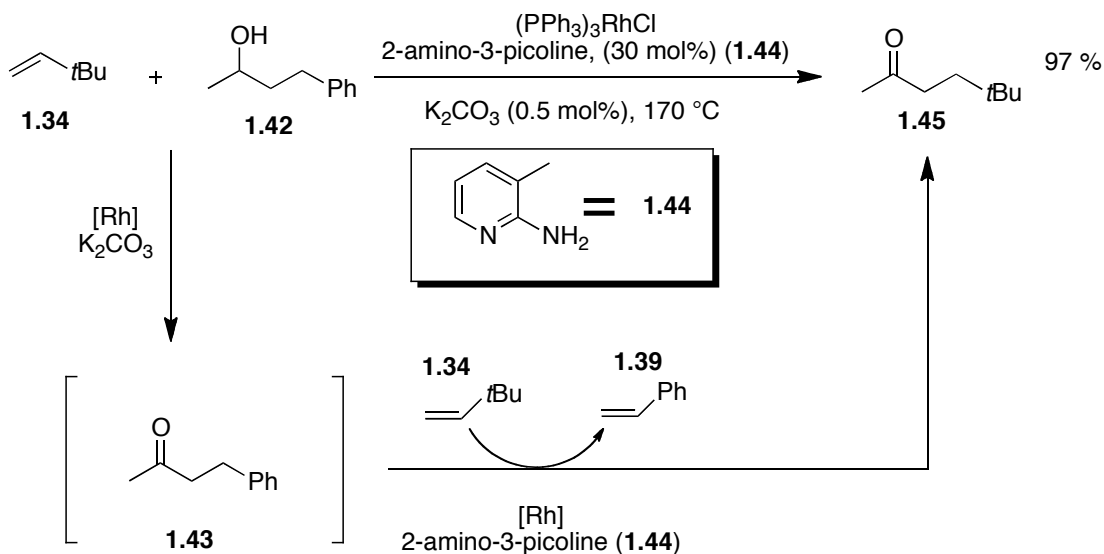
Scheme 13. Catalytic Cycle with Allylamine, an Addition of Formaldehyde Across Two Alkenes



Similar to the work with the formaldehyde equivalent allylamine in Scheme 13, using a *sec*-alcohol as a starting material also gave a C–C sigma-bond activation catalysis sequence (Scheme 14).²⁶ Starting with various *sec*-alcohols, a dual reaction sequence of transfer hydrogenation and C–C sigma-bond activation gave a ketone product. Alcohol **1.42** underwent transfer hydrogenation to give the ketone **1.43**,

which condensed with the amine-directing co-catalyst (**1.44**) before C–C activation. β -hydride elimination giving styrene (**1.39**) and subsequent coordination to alkene (**1.34**), migratory insertion, reductive elimination, and finally hydrolysis, regenerating **1.44**, gave the product ketone **1.45** in high yield. It is important to note that the methyl group of ketone **1.43** is unreactive under these reaction conditions.

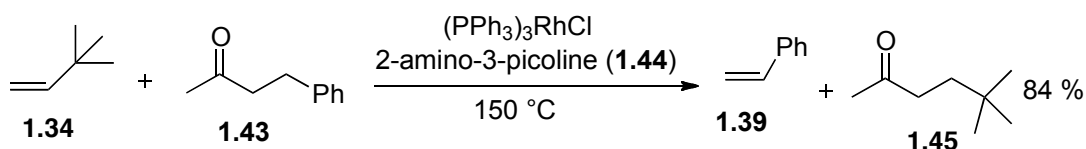
Scheme 14. C–C Sigma-Bond Activation with *sec*-Alcohols



Ketones are also able to be the starting materials for C–C sigma-bond activation with co-catalyst amines (Scheme 15).²⁷ The co-catalyst amine, 2-amino-3-picoline (**1.44**) along with Wilkinson's catalyst, $(\text{RhCl}(\text{PPh}_3)_3)$, gave the ketone **1.45** as the major product and trace styrene (**1.39**), a similar carbon–carbon sigma-bond

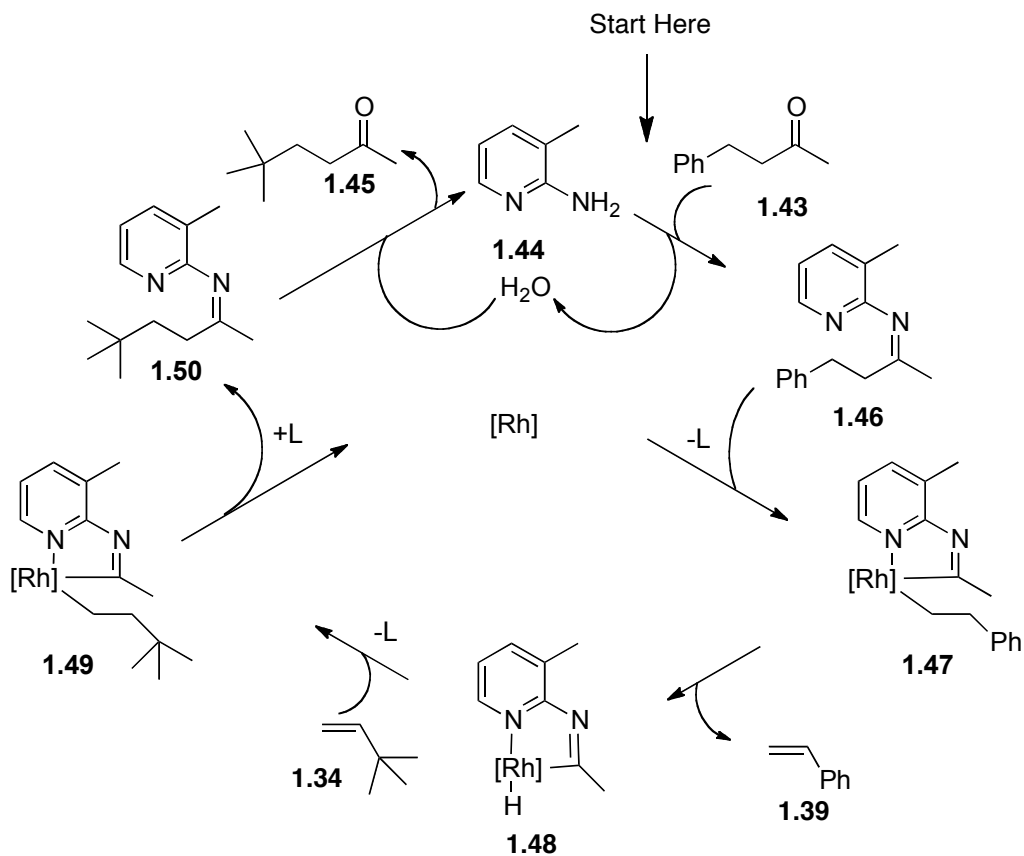
activation to Schemes 13 & 14. Again it is also worth noting that the methyl group of ketone **1.43** is not reactive toward C–C sigma-bond activation.

Scheme 15. Amine Co-Catalyst Directed C-C Sigma-bond Activation with Ketones



The catalytic cycle (Scheme 16) shows the role of the co-catalyst, similar catalytic cycles are proposed for reactions in Schemes 13 & 14 as well. 2-amino-3-picoline (**1.44**) condenses onto ketone **1.43** producing the imine **1.46** thus facilitating the formation of the 5-membered metallacycle **1.47** with rhodium. Following β -hydride elimination of styrene (**1.39**), migratory insertion of alkene **1.34** with the rhodium hydride species (**1.48**) gives metallacycle **1.49**. After reductive elimination from **1.49**, imine **1.50** is generated. Hydrolysis of **1.50** gives the newly substituted ketone **1.45** and the regeneration of the co-catalyst, 2-amino-3-picoline (**1.44**).

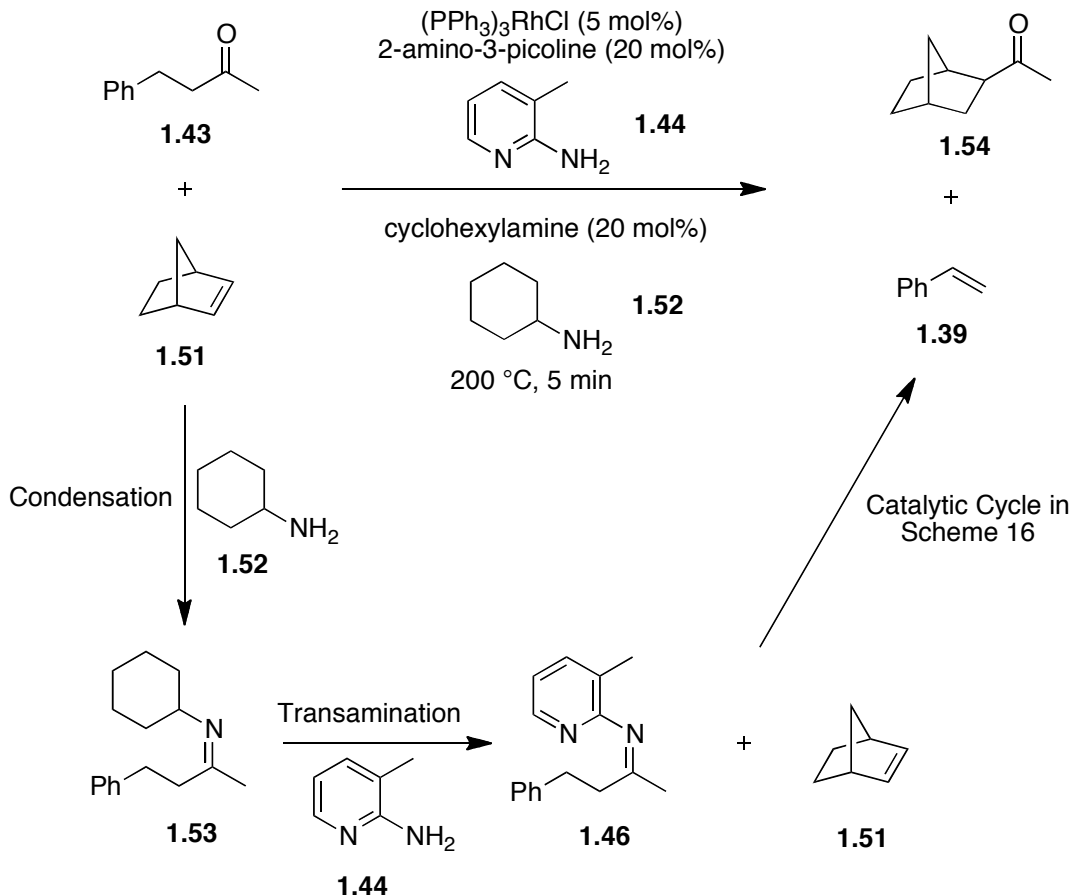
Scheme 16. Catalytic Cycle of C–C Sigma-bond Activation with an Amine Co-Catalyst



Jun's group also carefully examined more esoteric examples using C–C sigma-bond activation with the amine co-catalyst (**1.44**) that often revealed some mechanistic insight. One such study involved using another amine to help facilitate C–C sigma-bond activation in conjunction with the normally used amine co-catalyst, **1.44** in conjunction with a second amine, cyclohexylamine (**1.52**). Using benzylacetone (**1.43**), a known suitable starting material for these catalytic systems, and norbornene (**1.51**) an alkene without accessible β -hydrogens, these new

parameters were investigated (Scheme 17).²⁸ Under microwave irradiation, ketone **1.43** first condenses with cyclohexylamine **1.52**. This condensation, not deprotonation of **1.44** activating it toward condensation, is believed to occur as more basic secondary and tertiary amines did not enhance the reactivity. It was also found that the reaction proceeded much more smoothly with cyclohexylamine **1.52** than any other amine tested. Thus following an initial condensation, a transamination of *N*-cyclohexyl imine **1.53** with amine **1.44** gave the imine **1.46**. Finally in a series of steps similar to that shown in Scheme 16, hydroacylation of the alkene **1.51** gave a new ketone **1.54** and styrene (**1.39**). The authors noted an enhanced reactivity with microwave irradiation, most likely due to acceleration of the condensation steps of the catalytic cycle.

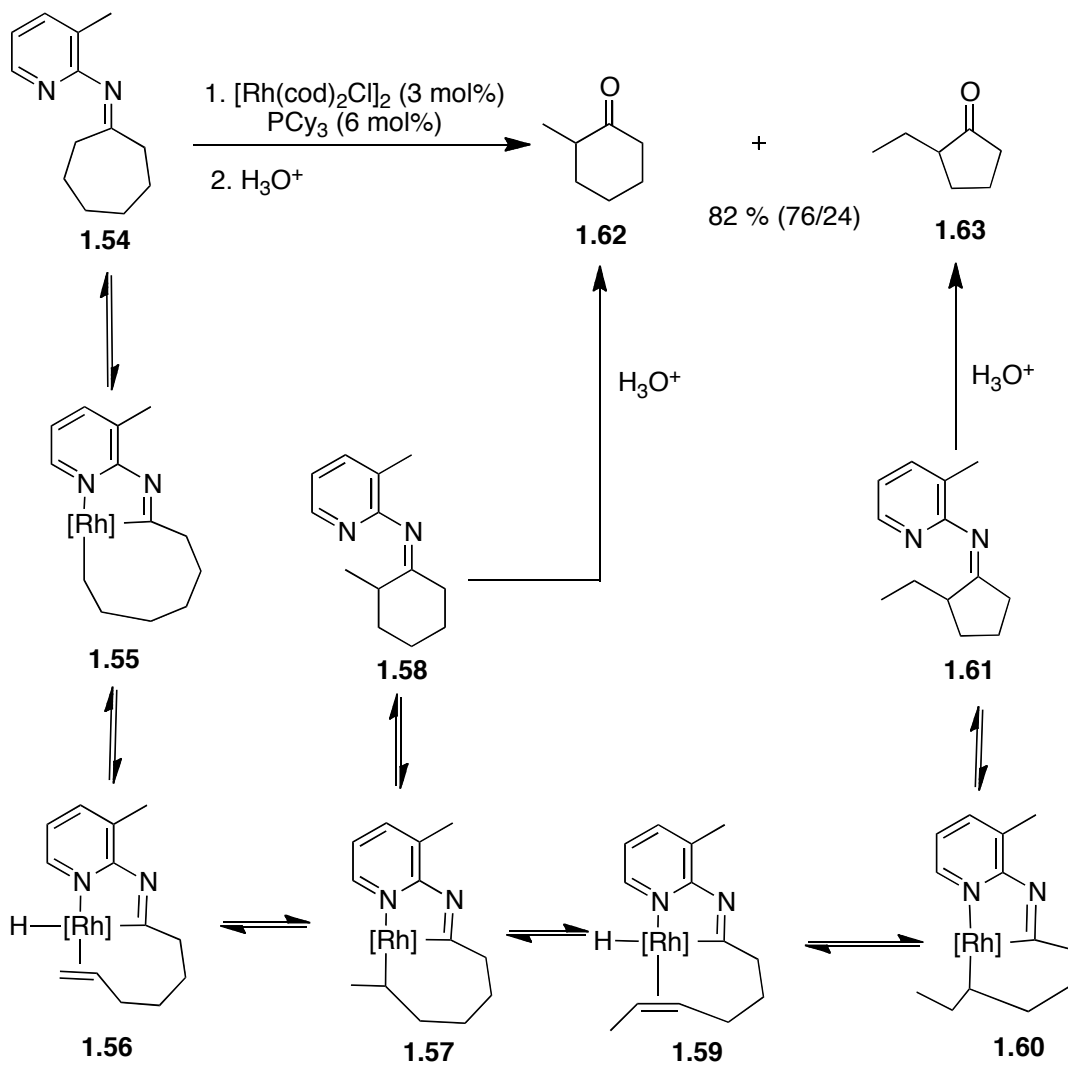
Scheme 17. Transamination and C–C Activation under Microwave Irradiation



Another interesting study done by Jun's group was investigating the possible skeletal rearrangements of cyclic ketones (Scheme 18).²⁹ The preformed imine **1.54** undergoes C–C sigma-bond activation (**1.55**) followed by β -hydride elimination giving rhodium hydride/alkene complex **1.56**. Migratory insertion gives a rhodium metallacycle (**1.57**) that has two competing pathways, one toward reductive elimination (**1.58**) and the other another β -hydride elimination to a more substituted

alkene (**1.59**). Imine **1.58** after hydrolysis gives the cyclohexanone **1.62**. The less likely pathway, based on product ratio, is migratory insertion of the rhodium hydride (**1.59**) to the metallacycle **1.60**, which after reductive elimination forms imine **1.61**. Hydrolysis of **1.61** with acid gave cyclopentanone (**1.63**) albeit in a lower amount than the more thermodynamically stable cyclohexanone **1.62**. This work highlights the effects that sterics and thermodynamics can play around the rhodium metallacycle and in product formation.

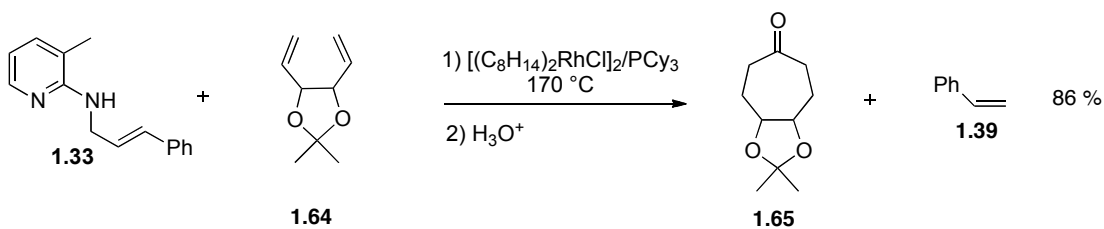
Scheme 18. C–C Sigma-Bond Activation and Ketone Rearrangement



In other work involving cyclic ketones, allylamine **1.33** (Scheme 13) can be a useful substitute for formaldehyde. As demonstrated in Scheme 19³⁰ using allylamine **1.33**, it is possible to facilitate the formation of a 7-membered ring via the catalytic

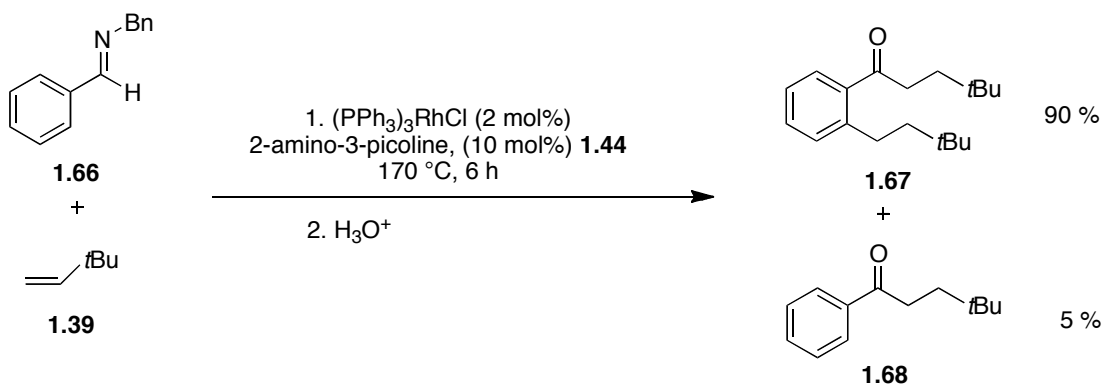
cycle in Scheme 13. Alkene **1.64** can enter the catalytic cycle twice undergoing two hydroacylation reactions, subsequently giving the ketone **1.65**.

Scheme 19. Ring Closure with a Masked Form of Formaldehyde



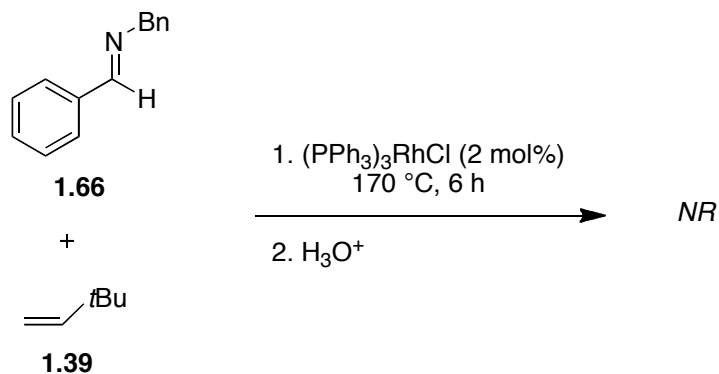
Finally, an example highlighting both the possibility of a potential C–C sigma-bond activation intermediate instead leading to C–H *ortho*-alkylation of a phenyl ring is shown in Scheme 20.³¹ The aldimine (**1.66**) was treated with Wilkinson’s catalyst, the amine co-catalyst (**1.44**), and an excess of alkene (**1.39**), but the predicted hydroacylation product **1.68** was not the major product. Instead the product of both a hydroacylation and *ortho*-alkylation was found (**1.67**) in high yield (90 %). This example shows that even with a co-catalyst in place for C–C activation that yet another C–H activation pathway (*ortho*-alkylation) can compete with a desired C–C activation.

Scheme 20. Hydroacylation and *ortho*-Alkylation Reaction Sequence



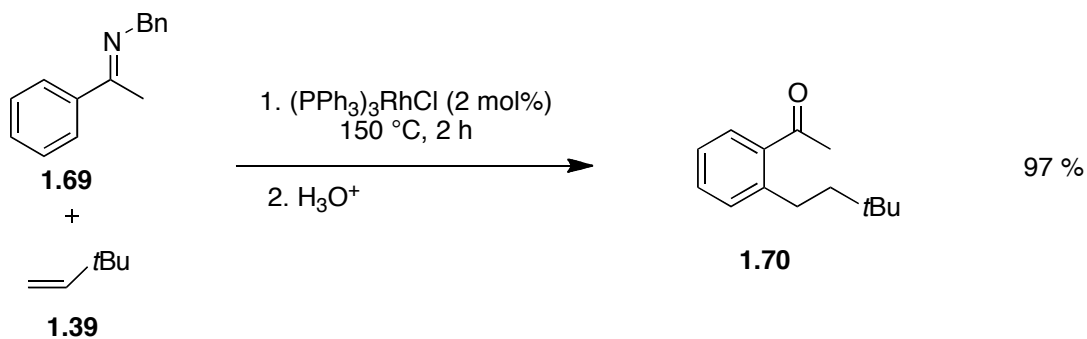
Curious to see which reaction in this 2-reaction cascade occurred first, the starting aldimine (**1.66**), Wilkinson's catalyst, and excess alkene (**1.39**) were combined in the absence of the amine co-catalyst, 2-amino-3-picoline (**1.44**). Under these conditions no product was formed (Scheme 21). Indicating that the starting aldimine (**1.66**) was not directing the rhodium metal to *ortho*-C–H activation and alkylation.

Scheme 21. Investigation into Aldimine (**1.66**) Leading to *ortho*-Alkylation



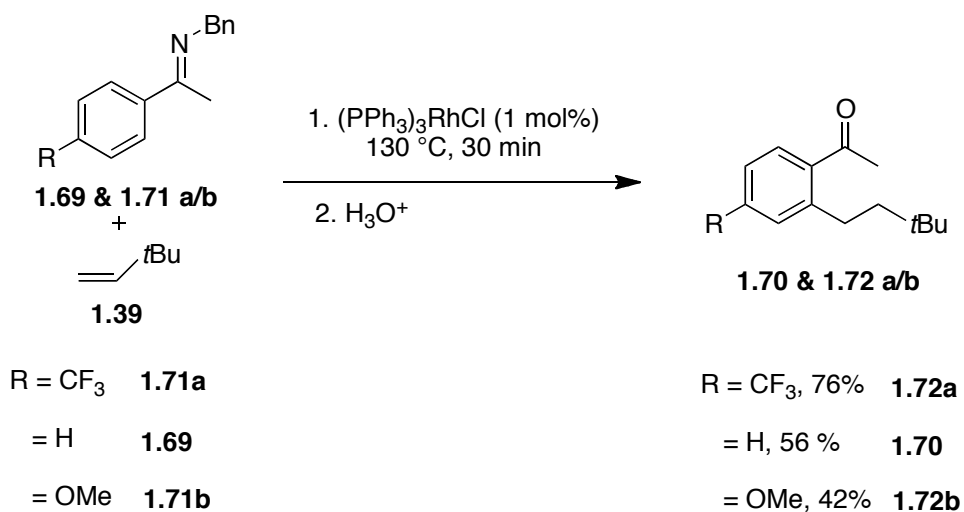
However, when the ketimine (**1.69**) of benzylamine and acetophenone was reacted with Wilkinson's catalyst and excess alkene (**1.39**) in the absence of the traditional amine co-catalyst (**1.44**) the *ortho*-alkylation product **1.70** was synthesized in high yield (97 %). These results show that the rhodium-catalyzed *ortho*-alkylation takes place after hydroacylation of aldimines with ketimines.

Scheme 22. Investigation into Ketimine (**1.69**) leading to *ortho*-alkylation



Following the detailed work on the sequence of the domino reactions in Scheme 21, the high reactivity of ketimines toward *ortho*-alkylation was exploited with various alkenes, but a study of the electronic effects on the *ortho*-alkylation was particularly enlightening. Taking various *para*-substituted ketimines (**1.69** & **1.71a/b**) with both electron-withdrawing and electron-donating groups, the reactivity was examined. It was found that ketimines with electron-withdrawing groups (**1.71a**) were much more reactive than ketimine with electron-donating groups (**1.71b**) giving the *ortho*-alkylation products **1.72a** and **1.72b** respectively.

Scheme 23. Electronic Effects on *ortho*-Alkylation of Ketimines



1.5 Research Goals

The relatively new field of catalytic transition metal carbon–carbon sigma-bond activation should prove useful to the modern synthetic organic chemist. This new type of transformation allows access to new and unusual disconnections in retrosynthetic analysis. The examples shown have varying degrees of utility for synthesis, but the preliminary work done so far shows a great deal of promise.

Our research began in earnest hoping to develop new reactivity in carbon–carbon sigma-bond activation. Two concurrent projects were undertaken towards this effort. The first project proposed uses a substrate–directed mode of activation using chelation potential in the starting materials to facilitate carbon–carbon sigma-bond activation. Based on the precedent shown by Suggs and Jun,³² we set out to develop an intermolecular addition of an activated carbon–carbon sigma-bond across an alkene substrate. Unlike the work of Suggs and Jun where an aryl or alkyl side chain of a ketone is often replaced with an alkyl side chain following β –hydrogen elimination, our newly developed method would initially focus on alkene substrates lacking the propensity to undergo β –hydrogen elimination. By avoiding elimination, this new method of addition to alkenes results in a net increase in molecular complexity.

The second project proposed again uses chelation to direct the metal catalyst, however, the chelating portion is in the form of a co-catalyst that could be removed

via hydrolysis leaving a product no longer dependent on starting materials with inherent chelation potential.

After careful review of the literature, research goals were laid out in earnest.

The Research Goals were to:

- 1) Develop an intermolecular catalytic method for C–C or C–H sigma-bond activation using inherent substrate directed chelation of metals.
- 2) Develop a catalytic method for C–C bond activation adjacent to ketones using an amine directing co-catalyst.

CHAPTER 2

2.1 Introduction

A major challenge in the development of carbon-carbon sigma-bond (C–C) activation is competitive activation and functionalization at C–H bonds,³³ which are typically more accessible to metal catalysts (Figure 1). As a result, catalytic C–C activation and functionalization is an under-developed strategy in synthetic organic chemistry.³⁴ We are aware of only a few prior studies in which competitive C–C and C–H activation pathways can be controlled. A series of papers from Nakao and Hiyama elegantly demonstrated that Ni-catalyzed aryl C–CN or *ortho*-C–H activation could be controlled by ligand or substrate choice.³⁵ In both cases, an alkyne was inserted into the activated bond. Jones studied competitive C–CN and C–H activation reactions in allyl cyanides.³⁶ Milstein has extensively studied C–C and C–H activation in toluene-based pincer systems.³⁷

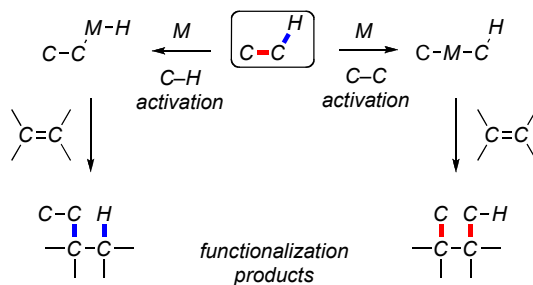


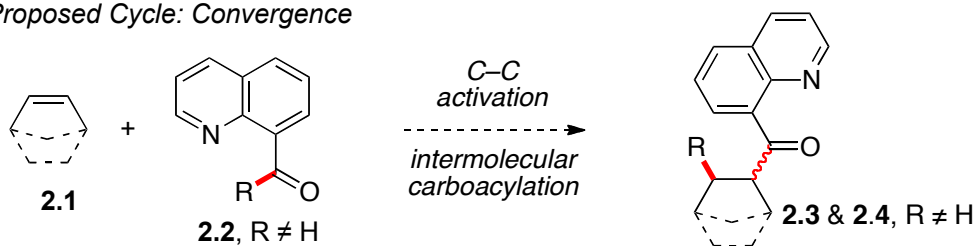
Figure 1. C–C and C–H Activation Reactions.

As organic substrates for C–C and C–H bond activation become more complex, controlling competing pathways becomes critically important. To that end, we are investigating direct inter- and intramolecular³⁸ alkene carboacylation with unstrained ketones via C–C activation. These investigations have led to the discovery that ketone C–C or *ortho*-C–H activation can be controlled by the appropriate choice of catalyst and solvent.

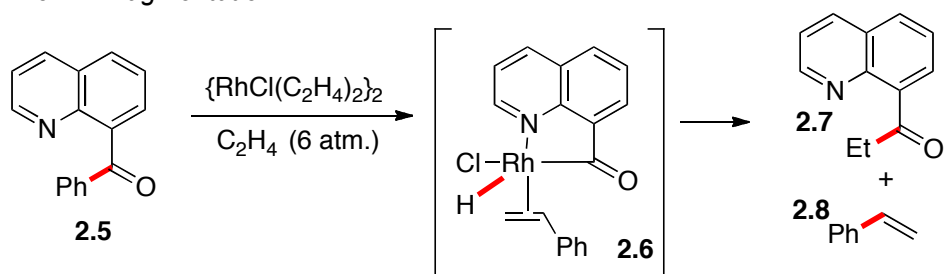
Our success with intramolecular carboacylation³⁸ led us to contemplate an intermolecular variant (**2.1** + **2.2** → **2.3** & **2.4**, Scheme 1) for convergent syntheses. Previously, C–C activation of **5** with $\{\text{RhCl}(\text{C}_2\text{H}_4)_2\}_2$ and excess C_2H_4 , yielded fragmentation products **2.7** and styrene (**2.8**) via a Rh–H intermediate (**2.6**).³⁹ This unusual hydroacylation provides good yield, but C_2H_4 was the only alkene capable of this reaction.⁴⁰

Scheme 1. Catalytic C–C Activation Reactions with 8-acylquinolines

Proposed Cycle: Convergence



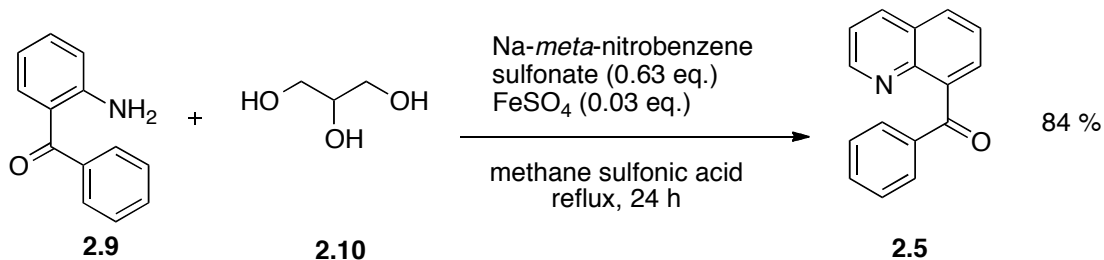
Known: Fragmentation



2.2 Substrate Synthesis

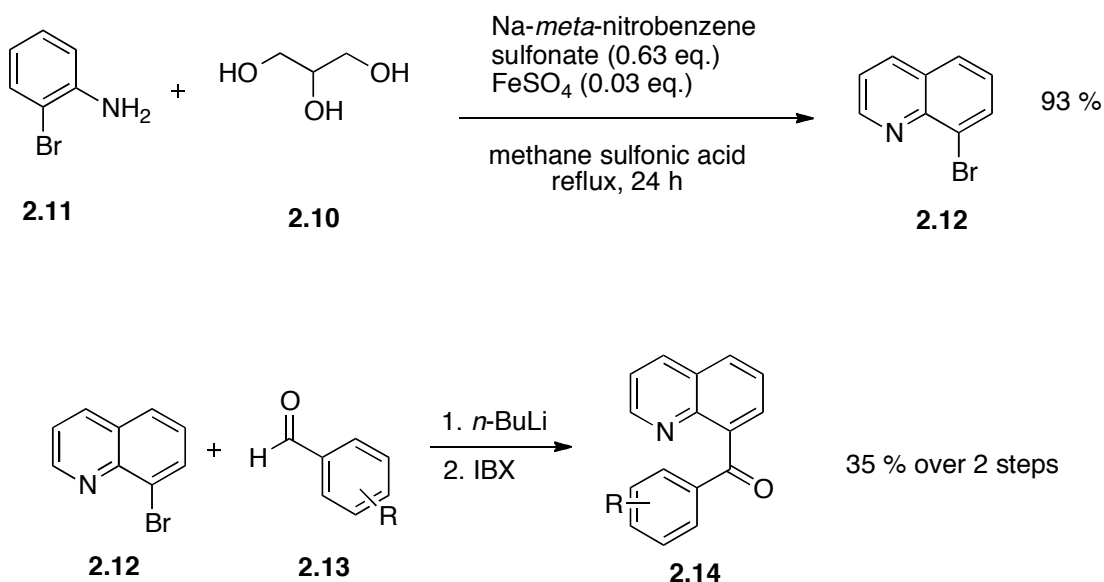
The initially proposed reaction to investigate carbon–carbon sigma-bond activation using a substrate–based chelation was done with substrate **2.5** and the alkene norbornene (Scheme 1). Norbornene was chosen because the resulting Rh-alkyl intermediate would not have sterically accessible syn-vicinal hydrides for β -hydride elimination.⁴¹ The 8-acylquinoline **2.5** was known in the literature, but the synthesis was not given. Therefore, an one–step synthesis was performed using the Skraup reaction (Scheme 2).⁴²

Scheme 2. Skraup Reaction with 2–Aminobenzophenone and Glycerol



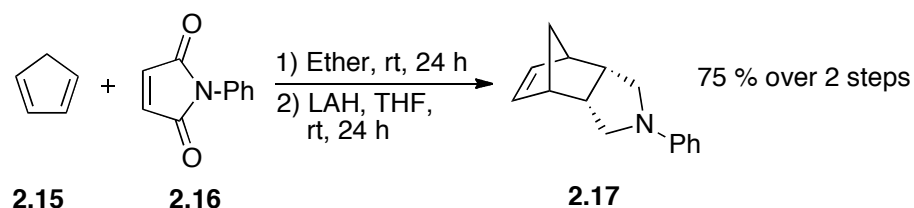
This reaction using 2-aminobenzophenone (**2.9**) and glycerol (**2.10**) in refluxing methanesulfonic acid with sodium-*meta*-nitrobenzene sulfonate and iron sulfonate gave over 84 % yield of the desired substrate **2.5**. It is also possible to prepare 8-acylquinoline substrates with differing substitution and functionality on the phenyl ring using 2-bromoaniline (**2.11**) to generate the 8-bromoquinoline (**2.12**) (Scheme 3).⁴³ Compound (**2.5**) can undergo a lithium-halogen exchange and the resulting carbanion can react with various substituted benzyl aldehydes (**2.14**). Subsequent oxidation of the resulting alcohol to the ketone gives the targeted substituted substrates (**2.14**).³⁸

Scheme 3. Skraup Reaction with 2-Bromoaniline and Glycerol and Synthesis of Functionalized 8-Acylquinolines



We chose [2.2.1] bicycloheptenes for this initial study to avoid intermediates with accessible *syn* β -hydrides. Another alkene substrate (**2.17**) with inaccessible β -hydrogens was synthesized in 75 % yield over 2 steps from a Diels–Alder reaction⁴⁴ of **2.15** and **2.16** followed by LAH reduction of the carbonyls (Scheme 4).⁴⁵

Scheme 4. Synthesis of Alkene **2.17**



Alkene compounds **2.18** and **2.19** are easily accessed by a route similar to that in Scheme 4, using maleic anhydride and cyclopentadiene (**2.15**) in a Diels–Alder reaction followed by LAH reduction (Figure 2).⁴⁶ Alkene **2.18** also had its hydroxyls derivatized as acetates, benzyl ethers, and silyl ethers groups to assess the impact of these functional groups on the proposed carboacylation. Regrettably, any protecting group on the hydroxyls was not combatable with the reactions conditions leading to no new products. The ketal **2.20** that previously has been successfully used in related hydroformylation reactions⁴⁷ was studied as well.

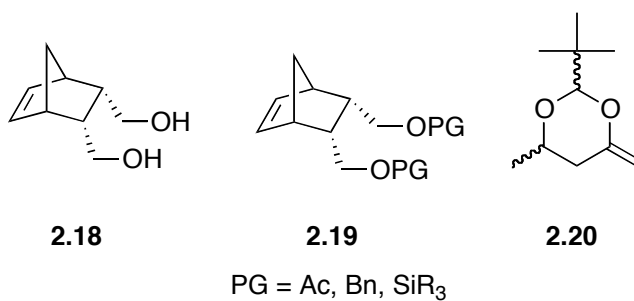
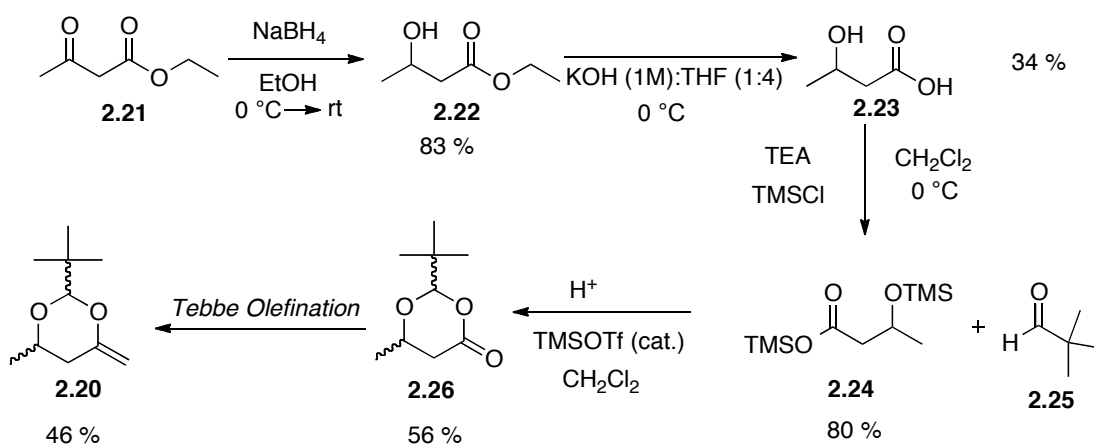


Figure 2. Alkene Derivatives for C–H Sigma-bond Functionalization

Alkene **2.20** was synthesized via a known route (Scheme 5) in which ethylacetoacetate (**2.21**) is selectively reduced (**2.22**) and then hydrolyzed (**2.23**). The silylated β -hydroxyacid **2.24** affords the compound for ketal formation with pivalaldehyde (**2.25**) to give lactone **2.26**, which after Tebbe olefination gives alkene **2.20**.⁴⁸ This alkene substrate did not prove useful, as it did not lead to products under any reaction conditions. This synthesis was performed by Chad Larson, a summer undergraduate researcher.

Scheme 5. Synthesis of Alkene **2.20**



2.3 Reaction Optimization and Results

We heated an equimolar amount of ketone **2.5** and norbornene (**2.27**) for 24 hrs with rhodium catalysts (Table 1). Although Wilkinson's catalyst was ineffective (entry 1), $\{\text{RhCl}(\text{C}_2\text{H}_4)_2\}_2$ provided formation of a new product, **2.29**.⁴⁹ This C–H activation is likely directed by the ketone oxygen.⁵⁰ In CH_3CN , the conversion decreased, but a small amount of carboacylation product **2.28** formed (entry 3). A switch to $\text{Rh}(\text{OTf})(\text{cod})_2$ provided higher conversion, but lower chemoselectivity (entry 5). A solvent screen (entries 6–9) showed that the product distribution depended on solvent, with THF providing complete selectivity for **2.28** (entry 9). It is remarkable that one can select exclusive C–C or C–H activation and functionalization by the appropriate choice of catalyst and solvent. The addition of phosphine ligands to the $\text{Rh}(\text{OTf})(\text{cod})_2/\text{THF}$ reactions decreased the yield without affecting the **2.28:2.29** ratio (entries 10 and 11). A related reaction involving intramolecular C–C sigma-bond activation was found to be inverse order in phosphines, collaborating this result.⁵¹ In all cases, **2.28** and **2.29** were obtained with good diastereocontrol (> 95:5 by ^1H NMR). Excess alkene (10 equiv.) did not improve yields for **2.28** and **2.29** with conditions in entries 9 and 2 respectively.

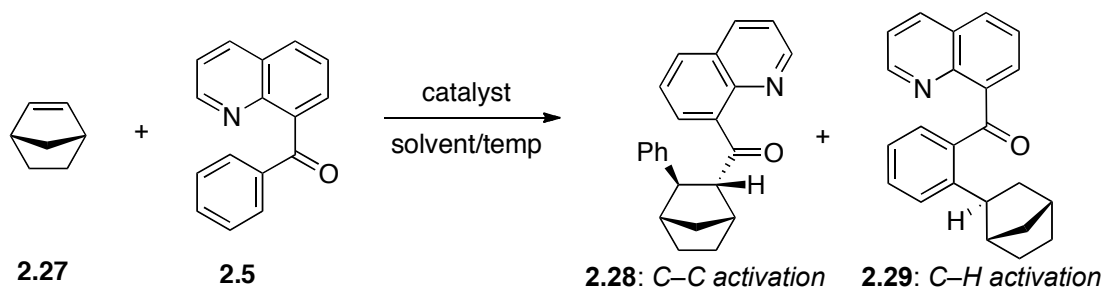


Table 1. Carboacylation and Hydroarylation with **2.5**

Entry	Catalyst ^[b]	Solvent	Temp	Yield, 2.28:2.29 ^[a]
1	RhCl(PPh ₃) ₃	PhCH ₃	130 °C	<10%, –
2	{RhCl(C ₂ H ₄) ₂ } ₂ ^[c]	PhCH ₃	130 °C	79% , 0:1
3	{RhCl(C ₂ H ₄) ₂ } ₂ ^[c]	CH ₃ CN	100 °C	35%, ~1:20
4	Rh(BF ₄)(cod) ₂	PhCH ₃	130 °C	38%, 1:6
5	Rh(OTf)(cod) ₂	PhCH ₃	130 °C	56%, 4:5
6	Rh(OTf)(cod) ₂	PhCF ₃	130 °C	44%, 1:5
7	Rh(OTf)(cod) ₂	(CH ₂ Cl) ₂	130 °C	62%, 1:7
8	Rh(OTf)(cod) ₂	CH ₃ CN	100 °C	41%, 5:3
9	Rh(OTf)(cod) ₂	THF	100 °C	50% , 1:0
10	Rh(OTf)(cod) ₂	THF ^[d]	100 °C	20%, 1:0
11	Rh(OTf)(cod) ₂	THF ^[e]	100 °C	12%, 1:0



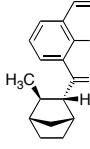
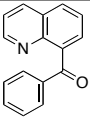

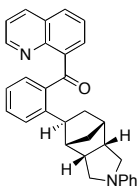
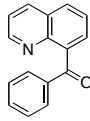
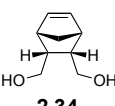
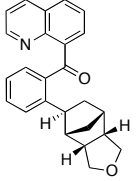
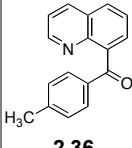

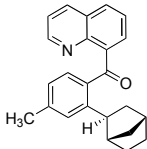
[a] Yields and ratios by ¹H NMR with internal standard [b] catalyst loadings 10 mol % unless otherwise noted. [c] 5 mol % catalyst used. [d] with 20 mol % PPh₃. [e] with 20 mol % P(*t*-Bu)₃. Legend: cod = 1,5-cyclooctadiene, THF = tetrahydrofuran, OTf = trifluoromethane sulfonate

We examined other 8-acyl quinolines with bridged cycloalkenes (Table 2).

We used the optimized conditions from Table 1 to examine substituent effects rather than re-optimize each substrate pair. Exchanging the 8-benzoyl group for acetyl (**2.30**),⁵² C–H activation products were avoided altogether, even when {RhCl(C₂H₄)₂}₂ is used in PhCH₃ (condition A). Using functionalized alkenes (**2.32**

and **2.34**) increased the propensity of **2.5** to undergo hydroarylation rather than carboacylation. Diol **2.34** underwent spontaneous cyclization to a tetrahydrofuran ring along with concurrent hydroarylation (**2.35**, Table 2).

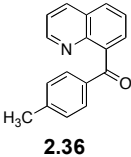

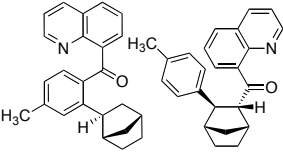
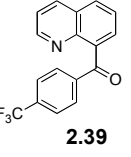

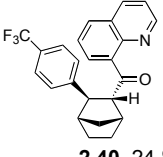
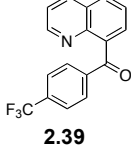
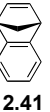
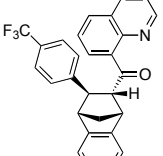
Table 2. Substrates with Conditions A

Quinoline	Alkene	Cond. ^[a]	Products/Yield ^[b]
 <p>2.30</p>	 <p>2.27</p>	A	 <p>2.31, 39 % (60%)</p>
 <p>2.5</p>	 <p>2.32</p>	A	 <p>2.33, 44% (65%)</p>
 <p>2.5</p>	 <p>2.34</p>	A	 <p>2.35, 41% (60%)</p>
 <p>2.36</p>	 <p>2.27</p>	A	 <p>2.37, 44 % (64%)</p>

[a] Condition A: $\{\text{RhCl}(\text{C}_2\text{H}_4)_2\}_2$, 5 mol %, PhCH_3 , 130 °C, 24 hr. [b] Yields after chromatography, (%) yields based on recovered starting material.

Alkenes **2.32** and **2.34** did not undergo carboacylation even with Rh(OTf)(cod)₂ in THF (condition B). By adding a *para* CH₃ group (**2.36**, Table 2), selectivity was complete for C–H activation with condition A, but condition B gave a ~1:1 mixture of **2.37** and **2.38** (Table 3). Changing the CH₃ group of **2.36** to CF₃ (**2.39**) suppressed the C–H activation pathway, suggesting that more electron-rich aryl ketones undergo C–H activation more readily under condition B. When alkene **2.41** was used, the yield was similar, but the diastereomer ratio of **2.42** decreased (~4:1, *anti:syn*).

Table 3. Substrates with Conditions B

Quinoline	Alkene	Cond. ^[a]	Products/Yield ^[b]
 <p>2.36</p>	 <p>2.27</p>	B	 <p>2.37 2.38</p> <p>30%, (66%), 2.37:2.38; 1:1</p>
 <p>2.39</p>	 <p>2.27</p>	B	 <p>2.40, 24 %</p>
 <p>2.39</p>	 <p>2.41</p>	B	 <p>2.42, 24 %</p>

[a] Condition B: Rh(OTf)(cod)₂ 10 mol %, THF, 100 °C, 24 hr. [b] Yields after chromatography, (%) yields based on recovered starting material.

Reactions were run with the substrates **2.43-2.48** (Figure 3) resulting from the reactions shown in Scheme 3. The initial work was done to see the effect of both electron-withdrawing and -donating functional groups on the phenyl ring with both conditions A and B (Tables 2 & 3). This work was carried out with undergraduate Todd Hyster. It was found that electron donating groups (**2.43-2.46**) increased the reactivity, possibly by facilitating the initial oxidative addition step into the aryl carbon-hydrogen sigma-bond. However, with the electron-donating groups multiple products were seen, showing greater reactivity but less selectivity for the desired single insertion C-H activation product **2.29**. The exception was the *para*-methyl (**2.43**), which when in the presence of excess alkene (**2.27**) gave a product with two equivalents of norbornene incorporated from the activation of both *ortho*-C-Hs. The electron-withdrawing groups on substrates **2.47** and **2.48** completely shut down the reaction.

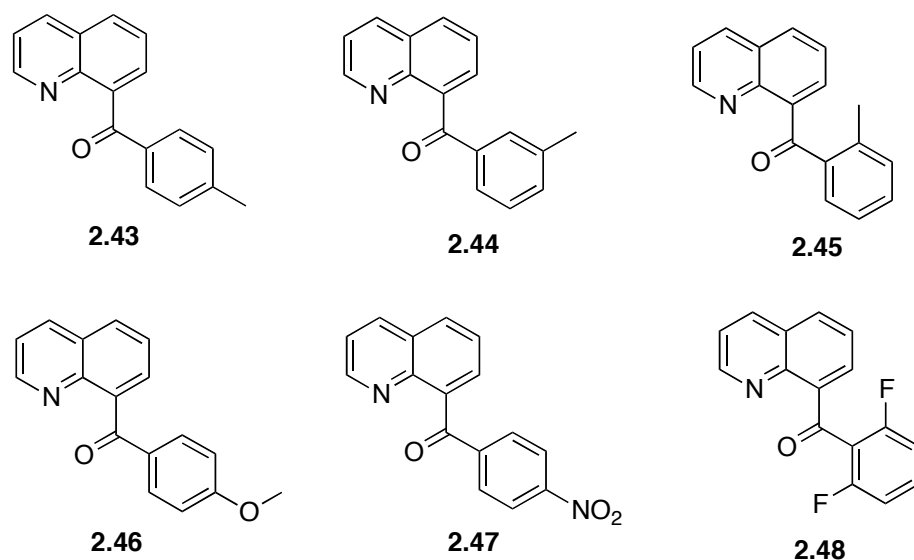


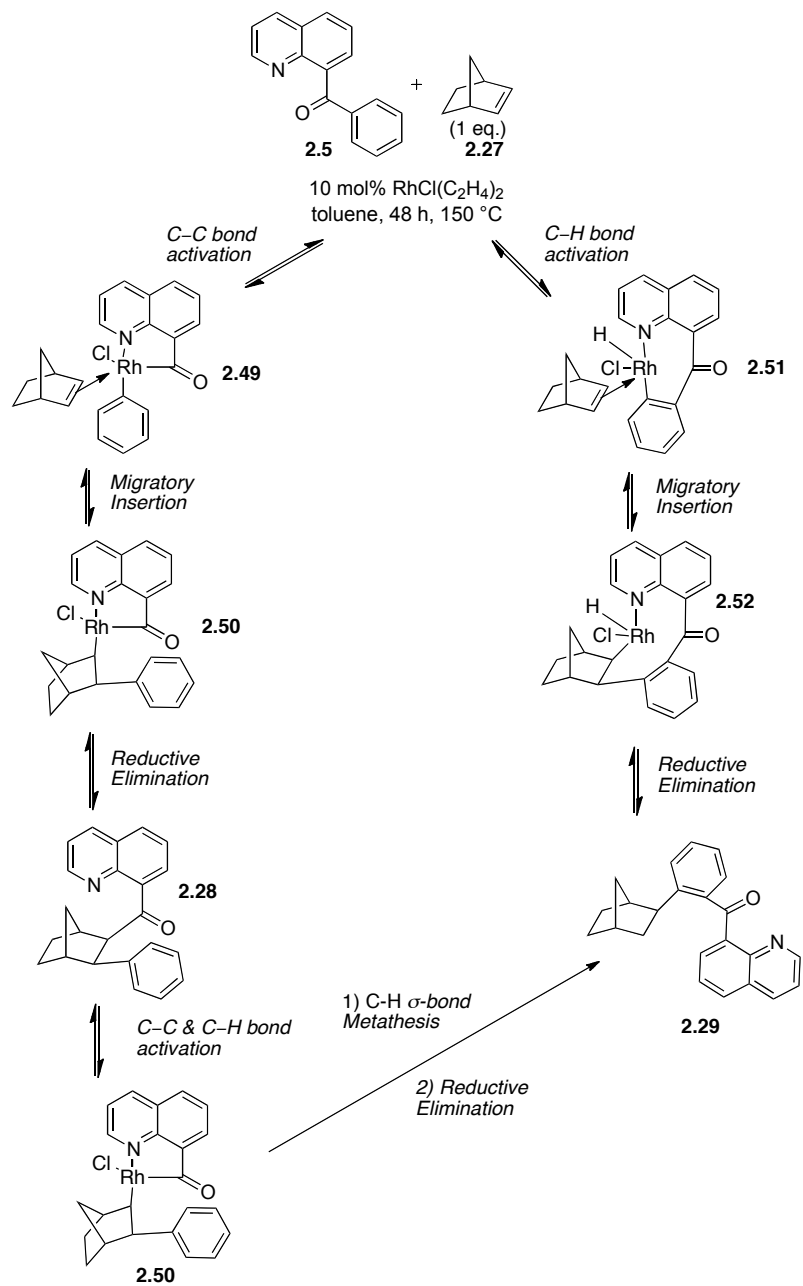
Figure 3. Functionalized Directing Substrates

2.4 Mechanistic Considerations

We initiated an elucidation of the mechanism of the C–H sigma-bond activation reaction catalytic cycle. Acylquinoline **2.5**, when submitted to the reaction conditions and norbornene (**2.27**), has given a product with a norbornene in the final product **2.29** at the *ortho*-aryl position. It was hypothesized that the C–C sigma-bond activation product (**2.28**) might be incorporated in the catalytic cycle leading to the C–H sigma-bond activation product **2.28**. Scheme 6 shows two hypothetical mechanisms for the resulting carbon–hydrogen sigma-bond activated product **2.29**. Following the C–H sigma-bond activation pathway, C–H sigma-bond activation gives the metallocycle **2.51** followed by the migratory insertion intermediate **2.52**. Reductive elimination results in the C–H activation product **2.29**. However, this does

not exclude the possibility of the C–C sigma-bond activation pathway. The C–C sigma-bond activation pathway has a metallocycle (**2.49**) formation step followed by migratory insertion (**2.50**). Reductive elimination gives the initially proposed alkene addition product **2.28** for C–C sigma-bond activation. However, because C–C sigma-bond activation could occur with **2.28** metallocycle **2.50** could be reformed and do further chemistry. Metallocycle could undergo σ -bond metathesis with an aryl C–H bond followed by reductive elimination to give the C–H activation product **2.29**.⁵³

Scheme 6. Proposed Mechanisms

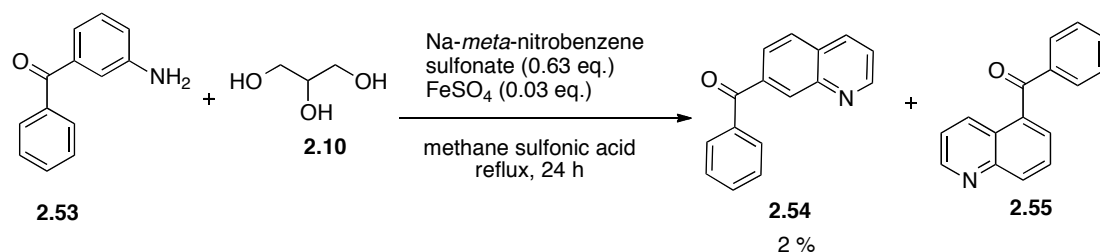


In an effort to probe the proposed mechanisms in Scheme 6 a number of experiments were designed. Compound **2.54** was utilized to look at the metallocycle being formed in the initial oxidative addition step with the [Rh](I) catalysts (Scheme 6). Both pathways proposed form 5-membered chelation mediated metallocycles, but with substrate **2.54** the nitrogen was not available to form a 5-membered metallocycle. If no insertion of norbornene (**2.27**) occurred to a C–H sigma-bond, then the C–C sigma-bond activation pathway might be an intermediate in the C–H sigma-bond activation catalytic cycle with 8-acylquinoline substrates. A final caveat of this experiment was to see whether carbon–hydrogen sigma-bond activation still occurs at the *ortho*-phenyl or possibly at the C–H bond adjacent the nitrogen of the quinoline ring, which had been shown previously.⁵⁴ The only bond activation when using **2.54** with conditions A was the insertion of an ethyl group at the C–H bond adjacent the nitrogen of the quinoline from ethylene present on the starting rhodium catalyst. These results lead to the need for more experimentation to reveal the catalytic cycle as these results were inconclusive with regard to the possible role of a C–C sigma-bond activated metallocycle intermediate (i.e. **2.49**) in a C–H sigma-bond activation catalytic cycle.

Scheme 7 shows the proposed Skraup reaction to give a 7-acylquinoline (**2.54**) instead of the 8-acylquinoline **2.5**. This reaction, unlike the previous Skraup reactions (Schemes 2 & 3), may lead to a potential mixture of regioisomers giving the 5-acylquinoline **2.55** as a possible by-product. This did not pose a major problem

despite the low yield, as this reaction was done on a large scale, and the subsequent reactions using this substrate were run at mmol scale.

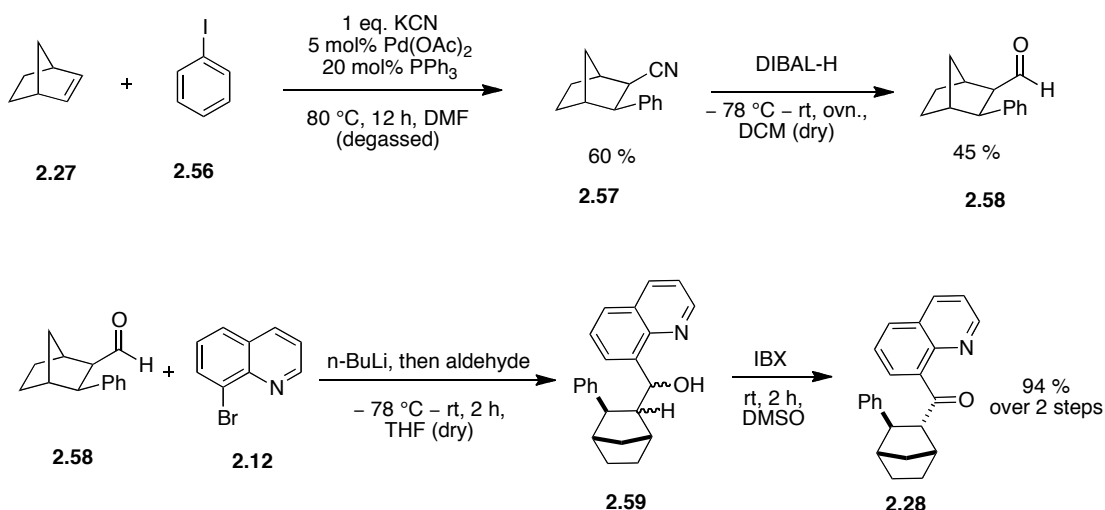
Scheme 7. Skraup Reaction Synthesis of 7-Acylquinoline **2.54**



Concurrent with the discovery of the presence of a C–C sigma-bond activation product (Table 1, entry 3), an independent synthesis of **2.28** (Scheme 8) was done to serve two purposes. First positive identification of the proposed product **2.28** in the spectra of crude reaction mixtures without a pure sample, and second we wished to test the interconversion of **2.28** and **2.29** proposed in Scheme 6 with {RhCl(C₂H₄)₂}₂. The synthesis began with the palladium-catalyzed addition of a phenyl ring and nitrile across norbornene (**2.27**) using iodobenzene (**2.56**) and potassium cyanide in degassed DMF (60 % yield, **2.57**).⁵⁵ Reduction of the resulting nitrile (**2.57**) with DIBAL-H gave the corresponding aldehyde (**2.58**) in 45 % yield.⁵⁶ Using 8-bromoquinoline (**2.12**), a lithium-halogen exchange with *n*-BuLi created the 8-lithioquinoline that was allowed to react with aldehyde (**2.58**) in dry THF, giving the

alcohol (**2.59**). Alcohol **2.59** was carried on without purification and oxidized with IBX⁵⁷ to give the proposed C–C sigma-bond activation product (**2.28**).

Scheme 8. Independent Synthesis of C–C sigma-bond Activation



Following the independent synthesis (Scheme 8), it was confirmed by nOe spectral analysis that the final product (**2.28**) from C–C sigma-bond activation under the optimized reaction conditions B (Table 1) and the independent synthesis product were a complete spectral match and were *trans* and not the expected *cis* product.⁵⁸ Presumably, an epimerization takes place facilitated by the quinoline nitrogen six atoms away from the ketone α -proton.⁵⁸ Finally, after obtaining both via C–C sigma-bond activation product independently and by the optimized reaction conditions, it was submitted to the C–H sigma-bond activation conditions to see if the equilibration of the carboacylation product **2.28** to the hydroarylation product **2.29** with

$\{\text{RhCl}(\text{C}_2\text{H}_4)_2\}_2$ in PhCH_3 is feasible (Scheme 6). Carbon–Carbon activation in 8-acyl quinolines is thought to be reversible,⁵⁹ and β -carbon elimination in norbornyl systems is also known,^{60,61} When (**2.28**) was subjected to these conditions, only recovered (**2.28**) was isolated leading us to believe that it is not in the C–H sigma-bond activation catalytic cycle (Scheme 6).

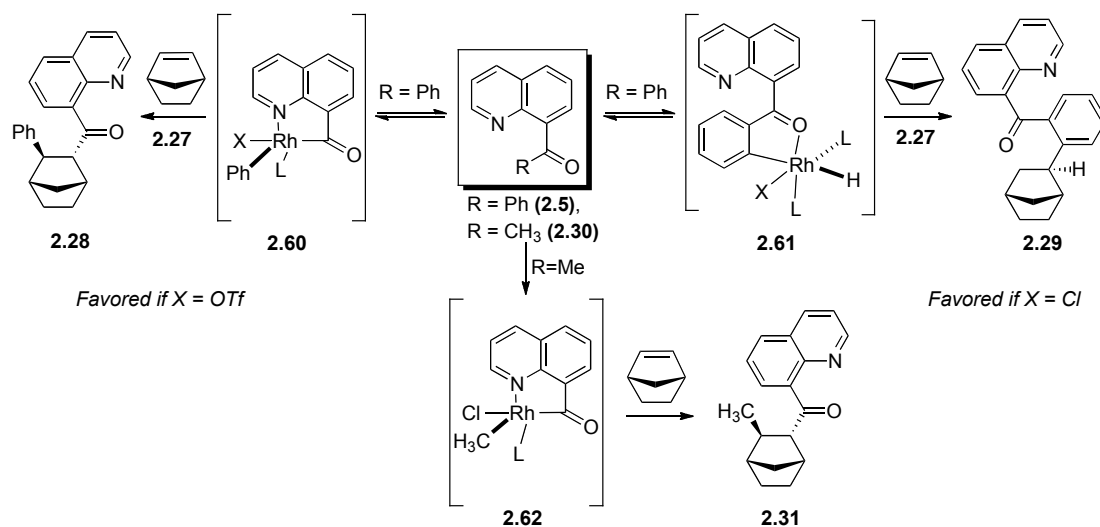
Scheme 9. C–C Sigma-Bond Activation Product Resubmitted to C–H Activation Conditions



Based on our findings and previous results, we presume that **2.5** can form two possible intermediates (**2.60** and **2.61**, Scheme 10). Using the same catalyst/solvent combination as used in previous C–C activation work,^{38,39} we exclusively form the product resulting from C–H activation (**2.29**). Since both **2.60** and **2.61** are accessed under these conditions and since **2.28** and **2.29** do not equilibrate, we conclude that **2.61** is simply more apt toward migratory insertion than **2.60** when chloride is present in a nonpolar solvent. By changing the catalyst counterion (OTf), a mixture of both

(**2.28**) and (**2.29**) activated products was formed [Table 1, entry 4]. Furthermore, by switching to a more polar solvent (THF) with the OTf as counterion, C–C activation pathway is selected exclusively. When R = Me (**2.30**), only the C–C activation (**2.62**) occurs, despite the use of chloride in a nonpolar solvent, since an intermediate analogous to **2.61** cannot form.

Scheme 10. Mechanistic Considerations



2.5 Conclusion

We have reported the activation of an unstrained C–C sigma-bond and subsequent intermolecular carboacylation of a strained alkene to form two new C–C sigma-bonds.⁶² According to our knowledge, this is the first example of its kind in the literature. These results provided a basis for controlling C–C and C–H activation

reaction pathways, which informed future work to develop catalytic C–C activation reactions.

2.6 Experimental Details

General experimental details: All reactions were carried out using flame-dried glassware under a nitrogen or argon atmosphere unless aqueous solutions were employed as reagents or dimethyl formamide was used as a solvent. Tetrahydrofuran (THF) and toluene (PhMe) were dried according to published procedures.¹ Trifluorotoluene, acetonitrile, and 1,2-dichloroethane were distilled prior to use. Toluene was further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. All rhodium complexes were purchased from Strem and used as received. Ketone **2.30** was prepared by a known procedure.² Amine **2.32** was prepared by reduction of the corresponding imide³ and diol **2.34** was prepared by reduction of the corresponding anhydride.⁴ IBX was prepared according to Santagostino.⁵ All other chemicals were purchased from Acros Organics or Sigma-Aldrich and used as received. All rhodium-catalyzed processes were carried out in a Vacuum Atmospheres nitrogen filled glove box in 1 dram vials with PTFE lined caps and heating was applied by aluminum block heaters.

Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates from E. Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulfate/molybdic acid or potassium permanganate/potassium

¹ A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers *Organometallics*, **1996**, *15*, 1518.

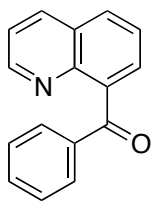
² J.-Y. Legros, J.-C. Fiaud, G. Primault *Tetrahedron*, **2001**, *57*, 2507.

³ T.-Y. Luh, W.-Y. Lin, H.-W. Wang, Z.-C. Liu, J. Xu, C.-W. Chen, Y.-C. Yang, S.-L. Huang, H.-C. Yang, *Chem. Asian J.* **2007**, *2*, 764.

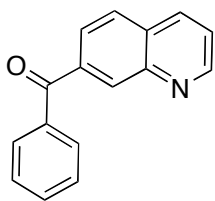
⁴ A. H. Hoveyda, J. J. Van Veldhuizen, D. G. Gillingham, S. B. Garber, O. Kataoka, *J. Am. Chem. Soc.* **2003**, *125*, 12502.

⁵ M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.

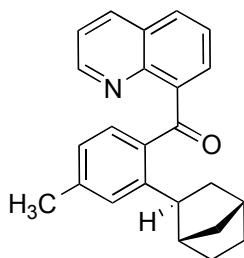
carbonate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck unless otherwise indicated. ^1H NMR (300, 400, and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were obtained on Varian FT NMR instruments. NMR spectra were reported as δ values in ppm relative to chloroform or tetramethylsilane. ^1H NMR coupling constants are reported in Hz; multiplicity was indicated as follows; s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained as films from CH_2Cl_2 or CDCl_3 . Low-resolution mass spectra (LRMS) in EI or CI experiments were performed on a Varian Saturn 2200 GC-MS system, and LRMS and high-resolution mass spectra (HRMS) in electrospray (ESI) experiments were performed on a Bruker BioTOF II.



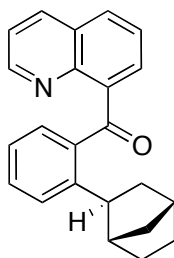
phenyl(quinolin-8-yl)methanone (2.5). A Schlenk tube was charged with a magnetic stir bar, (2-aminophenyl)(phenyl)methanone (3.94 g, 20 mmol), methane sulfonic acid (10.5 mL), 3-nitrobenzene sulfonic acid (2.83 g, 12.5 mmol), and FeSO₄ (167 mg, 12.5 mmol) and heated to approximately 120 °C. Added glycerol (1.8 mL, 25 mmol) and let stir overnight. Added second portion of glycerol (1.8 mL, 25 mmol) was added and allowed to stir for 12 hr. The reaction mixture was cooled to 0 °C and 10 mL of H₂O was added. NaOH pellets were added slowly to the reaction mixture until neutralized. Added KHCO₃ and extracted with Et₂O (3x100 mL). The combined organic portions were dried with Na₂SO₄ and concentrated to give a yellow oil (3.91 g, 16.76 mmol, 84%) R_f = 0.48 (20% EtOAc/Hex); ¹H NMR (300 MHz, CDCl₃) δ 8.84 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.88–7.84 (m, 2H), 7.75 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.56 (dddd, 8.7, 6.6, 1.2, 1.2 Hz, 1H), 7.45–7.39 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.1, 151.0, 146.2, 139.4, 137.9, 136.1, 133.4, 130.3 (2C), 129.8, 128.4, 128.3, 126.0, 121.8; IR (film) 3061, 1670, 1595, 1575, 1495, 1320, 1277 cm⁻¹; LRMS (EI) m/z 233 (M⁺).



phenyl(quinolin-7-yl)methanone (2.55). A Teflon screw cap sealable tube was charged with a magnetic stir bar, (3-aminophenyl)(phenyl)methanone (3.94 g, 20 mmol), methane sulfonic acid (10.5 mL), 3-nitrobenzene sulfonic acid (2.83 g, 12.5 mmol), and FeSO₄ (167 mg, 12.5 mmol) and heated to approximately 120 °C. Added glycerol (1.8 mL, 25 mmol) and let stir overnight. Added second portion of glycerol (1.8 mL, 25 mmol) was added and allowed to stir for 12 hr. The reaction mixture was cooled to 0 °C and 10 mL of H₂O was added. NaOH pellets were added slowly to the reaction mixture until neutralized. Added KHCO₃ and extracted with Et₂O (3x100 mL). The combined organic portions were dried with Na₂SO₄ and concentrated to give a yellow oil (100 mg pure, 0.43 mmol, 2%) R_f = 0.48 (20% EtOAc/Hex); ¹H NMR (300 MHz, CDCl₃) δ 9.01 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.49 (app. t, 1H), 8.25 (ddd, *J* = 8.4, 1.5, 0.9 Hz, 1H), 8.07 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.92–7.89 (m, 2H), 7.64 (tt, *J* = 7.2, 2.1 Hz, 1H), 7.55–7.49 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 196.5, 151.6, 147.5, 138.2, 137.4, 136.1, 133.0, 132.9, 130.6, 130.3, 128.6, 128.5 (2C), 126.5, 123.0; IR (film) 3057, 1657, 1597, 1447, 1287 cm⁻¹; HRMS (ESI) *m/z* 234.3866 (M+H)⁺ (234.0841 calcd for C₁₆H₁₁NO (M+H)⁺).

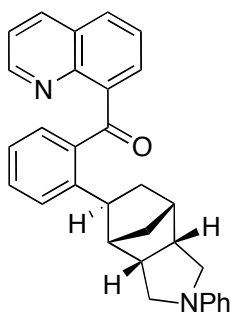


Example Procedure for C–H Activation (2.37): A 1 dram screw cap vial with a PTFE coated screw cap was charged with a magnetic stir bar, phenyl(quinolin-8-yl)methanone (30 mg, 0.12 mmol), norbornene (12 mg, 0.12 mmol) and taken into the glovebox. Add bis(ethylene)-chlororhodium(I)dimer (2.3 mg, 5 mol %) and toluene (0.5 mL). Place in an aluminum block heater for 48 hours at 130 °C. After 48 hours cool to r.t., and filter reaction solution through a pad of celite with excess EtOAc. Concentrate and purify the dark residue by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes) to yield a dark oil (20 mg, 0.058 mmol, 66%): ^1H NMR (300 MHz, CDCl_3) δ 8.94 (dd, $J = 4.2, 1.8$, 1H), 8.20 (m, 1H), 7.95 (m, 1H), 7.70 (m, 2H), 7.55 (m, 2H), 7.45–7.35 (m, 4H), 7.26–7.12 (m, 2H), 3.38–3.33 (m, 1H), 2.36 (s, 1H), 2.30 (s, 1H), 2.20 (s, 3H), 1.73–1.10 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.5, 151.4, 146.2, 145.2, 139.3, 136.2, 134.3, 132.1, 131.7, 130.7, 130.0, 128.6, 126.5, 126.1, 125.7, 121.7, 43.5, 43.4, 40.3, 37.1, 36.8, 30.6, 28.9, 20.9; IR (film) 2951, 2868, 1694, 1653, 1494, 1279 cm^{-1} ; LRMS (EI) m/z 342 (M^+).

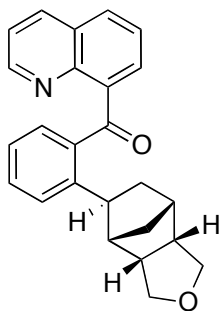


(2-((2S)-bicyclo[2.2.1]heptan-2-yl)phenyl)(quinolin-8-yl)methanone (2.29).

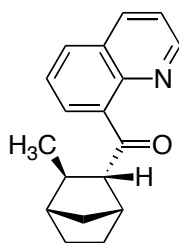
Example Procedure for C–H Activation: phenyl(quinolin-8-yl)methanone (51 mg, 0.22 mmol), norbornene (20.7 mg, 0.22 mmol), and chlorobis(ethylene)rhodium(I)dimer (4.3 mg, 0.022mmol) in 0.65 mL of toluene. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes, gradient) to provide a yellow film (31.5 mg, 0.096 mmol, 44%) $R_f = 0.65$ (20% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.92 (dd, $J = 4.2$, 1.8 Hz, 1H), 8.21 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.96 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.74 (dd, $J = 7.2$, 1.5 Hz, 1H) 7.60–7.40 (m, 4H), 7.32 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.10 (dt, $J = 8.4$, 7.5, 1.2 Hz, 1H), 3.48 (dd, 8.4, 6.0 Hz, 1H), 2.44 (app. s, 1H), 2.34 (app. s, 1H), 2.06–1.66 (m, 3H), 1.50–1.46 (m, 2H), 1.30–1.17 (m, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 200.3, 151.3, 148.1, 146.2, 140.5, 139.3, 136.1, 131.4, 130.7 (2C), 130.0, 128.5, 126.5, 125.7, 124.8, 121.7, 43.8, 43.2, 40.3, 37.1, 36.9, 30.6, 28.9; IR (film) 3061, 2951, 2868, 1668, 1595, 1570, 1495 cm^{-1} ; HRMS (ESI) m/z 328.1701 ($\text{M}+\text{H}^+$) (328.1623 calcd for $\text{C}_{23}\text{H}_{21}\text{NO}$ ($\text{M}+\text{H}^+$)).



Procedure for C–H Activation (2.33): phenyl(quinolin-8-yl)methanone (51 mg, 0.22 mmol), alkene (46.5 mg, 0.22 mmol), and chlorobis(ethylene)rhodium(I)dimer (4.3 mg, 0.022mmol) in 0.65 mL of toluene. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes, gradient) to provide a yellow film (42.9 mg, 0.097 mmol, 44%) $R_f = 0.65$ (20% EtOAc/Hex); ^1H NMR (300 MHz, CDCl_3) δ 8.83 (d, $J = 2.7$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.66 (d, $J = 6.9$ Hz, 1H), 7.51–7.25 (m, 6H), 7.11–7.04 (m, 3H), 6.61 (t, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 8.1$ Hz, 2H), 3.90 (d, $J = 8.7$ Hz, 1H), 3.76 (dd, $J = 8.1, 5.1$ Hz, 1H), 3.36 (d, $J = 9.9$ Hz, 1H), 2.87–2.70 (m, 5H), 2.41 (s, 1H), 1.94–1.72 (m, 3H), 1.44 (d, $J = 9.6$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.5, 151.3, 149.0, 146.9, 146.2, 140.1, 140.0, 136.1, 133.4, 131.6, 130.9, 130.8, 129.9, 129.0 (2C), 128.6, 127.3, 125.7, 125.0, 121.6, 116.3, 113.8, 49.2, 48.9, 48.7, 44.4, 43.5, 42.0, 39.3, 37.3, 30.2; IR (film) 2958, 1668, 1596, 1496, 1276 cm^{-1} ; HRMS (ESI) m/z 445.3098 ($\text{M}+\text{H}$) $^+$ (445.2202 calcd for $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}$ ($\text{M}+\text{H}$) $^+$).

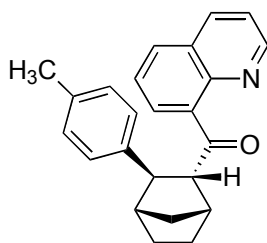


General Procedure for C–H Activation (2.35): phenyl(quinolin-8-yl)methanone (51 mg, 0.22 mmol), alkene (33.9 mg, 0.22 mmol), and chlorobis(ethylene)rhodium(I)dimer (4.3 mg, 0.022mmol) in 0.65 mL of toluene. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes, gradient) to provide a yellow film (35.3 mg, 0.096 mmol, 41%) $R_f = 0.45$ (20% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.92 (dd, $J = 4.2$, 1.8 Hz, 1H), 8.20 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.95 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.74 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.60–7.40 (m, 4H), 7.29 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.09 (ddd, $J = 7.5$, 7.5, 0.9 Hz, 1H), 4.33 (d, $J = 9.9$ Hz, 1H), 3.93–3.85 (m, 2H), 3.38 (dd, $J = 9.3$, 6.6 Hz, 1H), 3.34 (dd, $J = 9.9$, 6.6 Hz, 1H), 2.72–2.52 (m, 3H), 2.38–2.35 (m, 1H), 2.15–2.04 (m, 1H), 1.88 (d, $J = 9.9$ Hz, 1H), 1.87–1.74 (m, 1H), 1.45–1.40 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 200.0, 151.3, 147.6, 146.3, 140.5, 139.5, 136.1, 132.0, 131.1, 130.7, 129.9, 128.6, 127.4, 125.7, 124.9, 121.7, 69.1, 68.8, 47.9, 47.2, 46.1, 41.0, 39.6, 37.4, 30.8; IR (film) 2950, 2847, 1668, 1570, 1265 cm^{-1} ; HRMS (ESI) m/z 370.1794 ($\text{M}+\text{H}^+$) (370.1729 calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_2$ ($\text{M}+\text{H}^+$)).



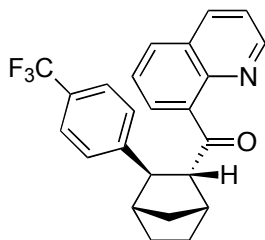
3-methylbicyclo[2.2.1]heptan-2-yl(quinolin-8-yl)methanone (2.31). General

Procedure for C–H Activation: 1-(quinolin-8-yl)ethanone (50 mg, 0.30 mmol), norbornene (33 mg, 0.30 mmol), and chlorobis(ethylene)rhodium(I)dimer (5.85 mg, 0.015 mmol) in 0.6 mL of toluene. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes, gradient) to provide a yellow film (31 mg, 0.117 mmol, 39 %) $R_f = 0.62$ (20% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.95 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.18 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.90 (dd, $J = 9.3, 1.5$ Hz, 1H), 7.70 (dd, $J = 6.9, 1.8$ Hz, 1H), 7.57 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.44 (dd, $J = 8.4, 4.2$ Hz, 1H), 3.67–3.63 (m, 1H), 2.35–2.26 (m, 2H), 1.96 (d, $J = 3.3$ Hz, 1H), 1.65–1.19 (m, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 208.2, 150.5, 145.5, 141.3, 136.1, 130.0, 128.2, 127.7, 126.1, 64.6, 44.1, 41.0, 37.4, 37.2, 29.7, 24.0, 21.6; IR (film) 2951, 2868, 1694, 1495 cm^{-1} ; LRMS (EI) m/z 265 (M^+).



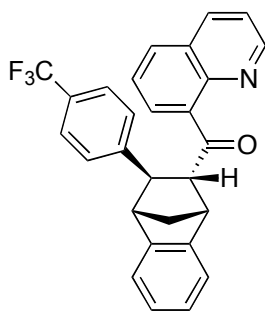
General Procedure for C–C Activation (2.38): A 1 dram screw cap vial with a PTFE lined cap was charged with a magnetic stir bar, quinolin-8-yl(*p*-tolyl)methanone (27.2 mg, 0.11 mmol), norbornene (10.3 mg, 0.11 mmol) and taken into the glovebox. Add bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) and THF (0.325 mL). Place in an aluminum block heater for 24 hours at 100 °C. After 24 hours allow to cool to room temperature, and filter reaction solution through a pad of celite with excess EtOAc. Concentrate and purify the dark residue by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes, gradient) to provide the product of hydroarylation (18, 5.5 mg, 0.016 mmol, 14.7%) and carboacylation as yellow films (19, 5.6 mg, 0.0165mmol, 15.6%) $R_f = 0.59$ (20% EtOAc/Hex); ^1H NMR (300 MHz, CDCl_3) δ 8.86-8.80 (m, 1H), 8.16 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.91-7.89 (m, 1H), 7.80-7.77 (m, 1H), 7.56 (app. t, $J = 7.2$ Hz, 1H), 7.40 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.12 (d, $J = 7.8$ Hz, 1H), 4.45-4.42 (m, 1H), 3.58 (d, $J = 6.3$ Hz, 1H), 2.60-2.56 (m, 1H), 2.44 (m, 1H), 2.33 (s, 3H), 1.79 (d, $J = 9.3$ Hz, 1H), 1.67–1.50 (m, 5H), 1.34-1.26 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.2, 150.6, 145.6, 143.5, 140.8, 136.2, 135.0, 130.5, 129.3, 129.1, 128.5, 128.3, 127.3, 126.2, 121.5, 121.1, 64.3, 46.8, 43.4, 41.2, 38.8,

30.3, 24.6, 21.1; IR (film) 2953, 2870, 1668, 1495 cm^{-1} ; LRMS (CI) m/z 342 (M+H)⁺.



General Procedure for C–C Activation (2.40):

quinolin-8-yl(4 (trifluoromethyl)phenyl)methanone (33.1 mg, 0.11 mmol), norbornene (10.3 mg, 0.11 mmol), and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in 0.325 mL of THF. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002): EtOAc/Hexanes) to provide a yellow film (10.4 mg, 0.0264 mmol, 24 %) $R_f = 0.55$ (20% EtOAc/Hex); ¹H NMR (300 MHz, CDCl₃) δ 8.84-8.82 (m, 1H), 8.17 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 6.6$ Hz, 1H), 7.63-7.49 (m, 5H), 7.41 (dd, $J = 8.4, 3.6$ Hz, 1H), 4.49-4.45 (m, 1H), 3.66 (d, $J = 5.7$ Hz, 1H), 2.62 (d, $J = 3.6$ Hz, 1H), 2.45 (m, 1H), 1.75 (d, $J = 9.3$ Hz, 1H), 1.70-1.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 206.9, 151.3, 150.6, 145.6, 140.5, 136.3, 131.8, 130.7, 128.5, 128.3, 127.8 (2C), 126.3, 125.3 (CF₃, q, $J = 3.4$ Hz), 121.9, 121.7 (2C), 64.4, 47.1, 43.0, 41.2, 38.9, 30.3, 24.5, Data given as it appears on spectra, C–F coupling and incident peaks make it difficult for complete resolution; IR (film) 2957, 2874, 1669 1327 1121 cm^{-1} ; LRMS (CI) m/z 396 (M+H)⁺.



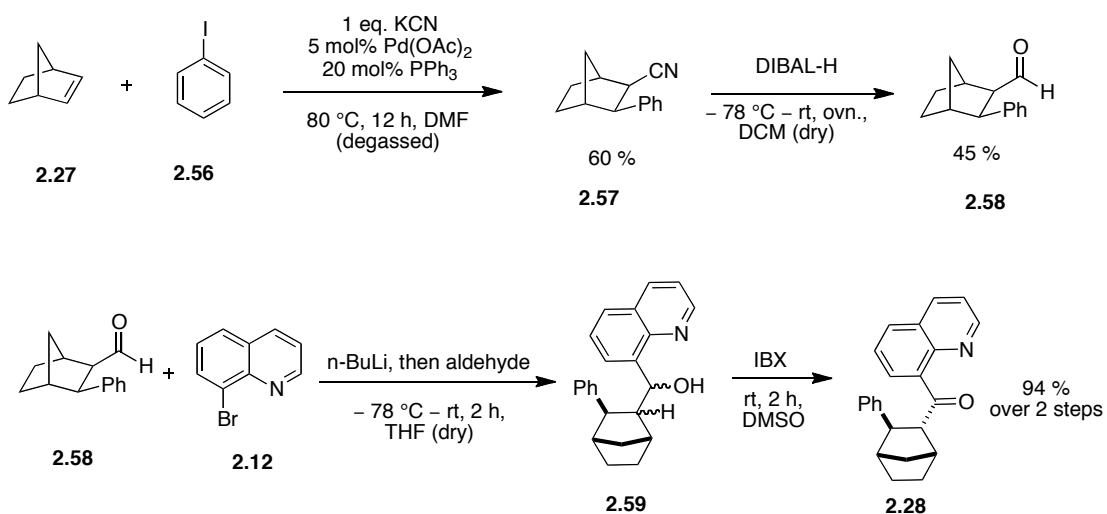
General Procedure for C–C Activation (2.42):

quinolin-8-yl(4 (trifluoromethyl)phenyl)methanone (33.1 mg, 0.11 mmol), alkene (15.6 mg, 0.11 mmol), and bis(1,5-cyclooctadiene)rhodium(I)

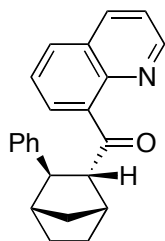
trifluoromethanesulfonate (5.2 mg, 10 mol %) in 0.325 mL of THF. Purified by column chromatography (CombiFlash Companion (Model # 60-5230-002):

EtOAc/Hexanes, gradient) to provide a yellow film (11.9 mg, 0.0268 mmol, 24.4 %)

$R_f = 0.52$ (20% EtOAc/Hex); ¹H NMR (300 MHz, CDCl₃) δ 8.86 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.22 (dd, $J = 8.4, 1.5$ Hz, 1H), 7.97 (dd, $J = 6.6, 3.3$ Hz, 1H), 7.60 (m, 6H) 7.44 (dd, $J = 8.4, 4.2$ Hz, 1H), 7.30 (d, $J = 7.2$ Hz, 1H), 7.16 (app. t, $J = 7.5$ Hz, 1H), 7.06 (app. t, $J = 7.2$ Hz, 1H), 6.72 (d, $J = 7.2$ Hz, 1H), 5.10 (dd, $J = 5.4, 3.9$ Hz, 1H), 3.67-3.65 (m, 2H), 3.46 (d, $J = 3.0$ Hz, 1H), 2.17 (d, $J = 9.3$ Hz, 1H), 1.89 (dd, $J = 9.0, 1.5$ Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 204.7, 151.1, 150.6, 149.4, 148.4, 145.5, 144.3, 139.6, 136.5, 136.2, 131.7, 131.2, 130.5, 130.2, 128.2, 127.2, 126.8, 126.3, 125.9, 125.8, 125.7, 125.5 (CF₃, q, $J = 4.1$ Hz), 122.7, 121.8, 121.7, 121.1, 121.0, 62.4, 49.6, 48.7, 48.5, 47.1, Data given as it appears on spectra, C–F coupling, diastereomer presence, and incident peaks make it difficult for complete resolution; IR (film) 2967, 1669, 1327, 1122 cm⁻¹; LRMS (CI) m/z 444 (M+H)⁺.



The aryl-cyanation of norbornene⁶ and nitrile reduction⁷ were carried out via literature procedures.



3-phenylbicyclo[2.2.1]heptan-2-yl)(quinolin-8-yl)methanone (2.28).

8-Bromoquinoline (7.1 mg, 0.034 mmol) and dry THF (0.2 ml) were added to a flame dried round bottom flask under nitrogen. The flask was stirred and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (2.5M in hexanes) (15 μL , 0.037 mmol) was added dropwise to the round bottom flask over 5 minutes. After 10 minutes, a dry solution of 3-phenylbicyclo[2.2.1]heptane-2-carbaldehyde (10 mg, 0.051 mmol) in THF (dry) (0.2 ml) was added dropwise over 10 minutes. The reaction was kept at $-78\text{ }^{\circ}\text{C}$ for 15

minutes and then removed from the bath and allowed to warm to r.t. After 45 minutes, reaction was quenched with NH₄Cl(sat.) and extracted with EtOAc (3 x 25mL) and washed with brine (1 x 25mL). The combined organic portions were dried with Na₂SO₄ and concentrated to yield a clear oil. Without further purification, the clear oil was taken up in DMSO (1 mL) and IBX (21.4 mg, 0.077 mmol) was added, stirred for 1 hour at r.t. Isopropanol (1 mL) was added and stirred for 40 min. Add H₂O and extract with EtOAc (3 x 25mL). The combined organic portions were dried with Na₂SO₄ and concentrated to yield a clear oil (10.5 mg, 0.032mmol, 94% over 2 steps) R_f = 0.38 (20% EtOAc/Hex); ¹H NMR (300 MHz, CDCl₃) δ 8.87 (dd, *J* = 4.2, 2.1 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.80 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.6-7.2 (m, 7H), 4.47-4.44 (m, 1H), 3.62 (d, *J* = 5.4 Hz, 1H), 2.61 (d, *J* = 2.4 Hz, 1H), 2.45 (s, 1H), 1.80 (d, *J* = 9.6 Hz, 1H), 1.70-1.26 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 207.1, 150.6, 146.5, 145.6, 140.8, 136.2, 130.6, 128.5, 128.4 (2C), 127.6 (2C), 126.2, 125.6, 121.6, 64.3, 47.2, 43.3, 41.2, 38.9, 30.3, 29.9, 24.6; IR (film) 2955, 2865, 1695, 1495 cm⁻¹; HRMS (ESI) *m/z* 327.2796 (M⁺) (327.1623 calcd for C₂₃H₂₁NO (M⁺)). The compound was further characterized by nOe and matched the material prepared by carboacylation in all respects.

CHAPTER 3

3.1 Introduction

Although unstrained carbon-carbon sigma (C–C) bonds can be effectively activated with transition metals, atom-economical reactions with the activated bonds remain extraordinarily rare.⁶³ Accessing the activation of C–C bonds via ring-strain relief⁶⁴ and aromaticity⁶⁵ is much more common. To date, our laboratory remains the only to achieve higher order products from catalytic unstrained C–C activation not involving C–CN bonds.⁶⁶ Although acylquinolines can chelate Rh catalysts promoting C–C activation, *intermolecular* carboacylation reactions suffer from competitive C–H activation (Ch.2; Figure 1, eq. 1)^{66a}, however, *intramolecular* carboacylation of alkenes can be highly chemoselective (eq. 2).^{66b}

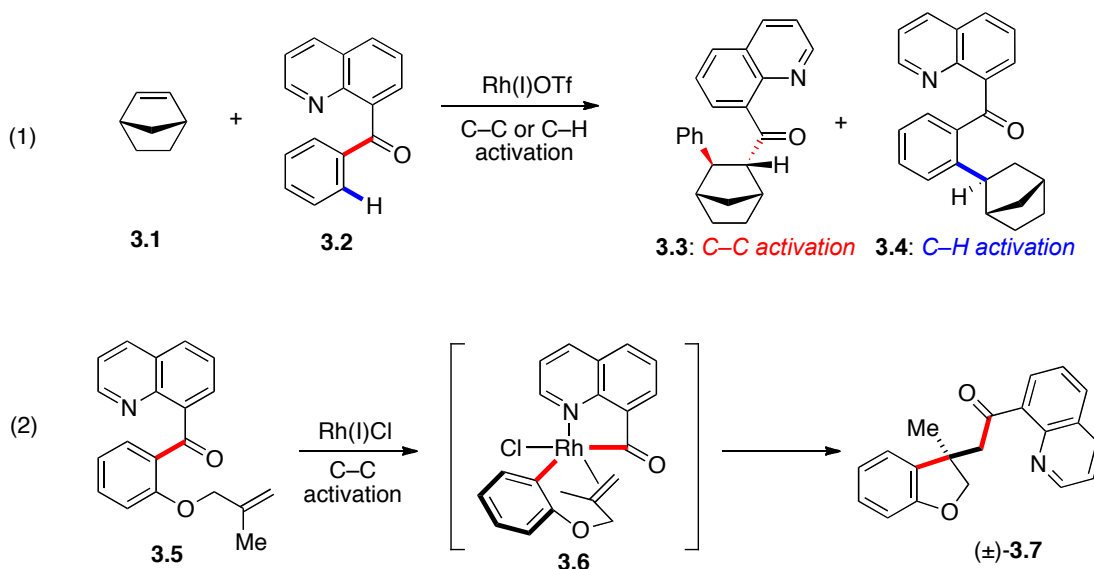
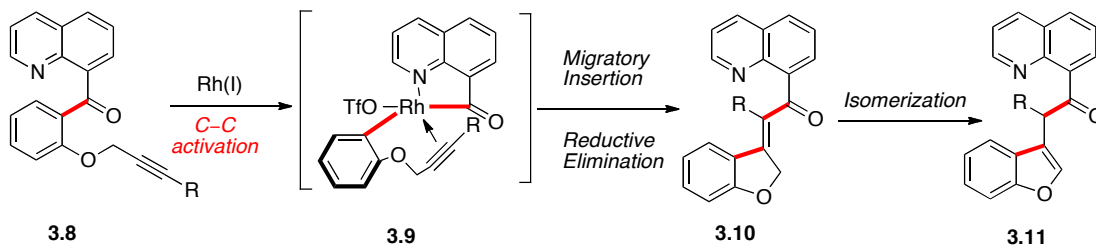


Figure 1. C–C Bond Activation Reactions with 8-Acyl Quinolines

In an effort to better understand the scope of reactivity associated with the activation and functionalization of C–C bonds, we sought to study the intramolecular carboacylation of alkynes (Scheme 1).⁶⁷ Substrates such as **3.8** might be prone to depropargylation, similar to other propargyl ethers, particularly aryl propargyl ethers, that are cleaved in the presence of transition metals (Ni, Ti, Pd).⁶⁸ Indeed, Banerji, Duñach, and the Pal and Yeleswarapu team have successfully exploited this reactivity to provide high yielding depropargylation reactions of amines and ethers.⁶⁹ Kundu reported an interesting metal catalyzed thiol arylation with aryl propargyl thioethers again showing the propensity and potential for aryl-propargyl ether cleavage.⁷⁰ Knowing of these previously reported examples in the chemical literature, we hypothesized that substituted alkynes similar to our previous work with alkenes under the suitable reaction conditions could be used as starting materials C–C sigma-bond activation (**3.9**) and subsequent carboacylation (**3.10**).

In this chapter, it is reported that chemoselectivity for the carboacylation of alkynes (via C–C activation) can be achieved. These competing pathways can be controlled by the appropriate choice of catalyst and solvent with reaction conditions that minimize competitive propargyl-ether cleavage. The predicted carboacylation product, 2,3-dihydrobenzofurans (**3.10**), likely isomerized under the reaction conditions to provide benzofurans **3.11**.

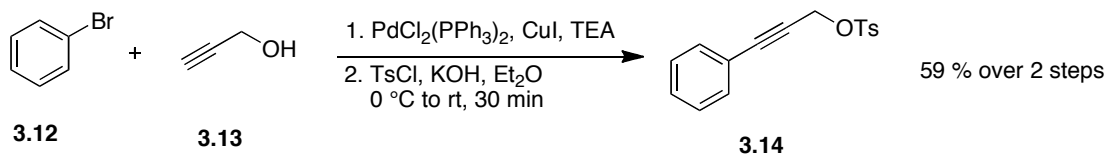
Scheme 1. Proposed C–C Sigma-Bond Activation with Alkynes



3.2 Substrate Synthesis

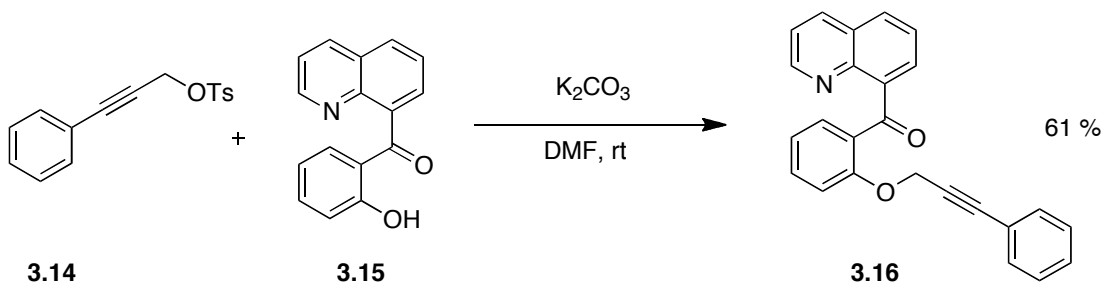
The synthesis of a variety of alkyne-containing 8-acyl quinolines was undertaken using two major routes. The first route allowed for functional group variety on the terminus of the alkyne. This route involved using a halogenated phenyl ring (3.12) and a propargylic alcohol (3.13) to form the substituted alkyne (Scheme 2). An example of this Sonogashira coupling in Scheme 2 with palladium and subsequent tosylation gave a high yielding tosylate (3.14) in 59 % over 2 steps.^{71,72}

Scheme 2. Sonogashira Coupling and Tosylation



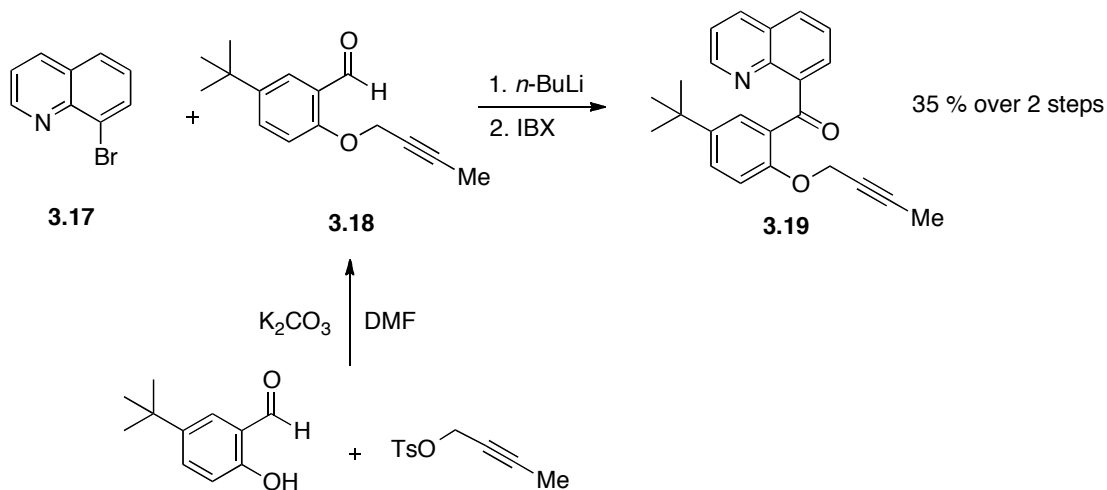
The tosylate (**3.14**) then underwent a substitution reaction (Scheme 3)⁷³ in base with the previously discussed phenolic 8-acyl-quinoline (**3.15**) (Chapter 2, Scheme 3) in 61 % yield forming a suitable substrate (**3.16**) to investigate C–C activation reactions (Scheme 1). This route was also used for alkyl-substituted alkynes similar to the phenyl alkyne **3.14**.

Scheme 3. Nucleophilic Substitution for Substrate Formation



The second route for the synthesis of substrates to be examined in the intramolecular carboacylation of alkynes is shown in Scheme 4. Beginning with the salicylic aldehyde precursor, a substitution reaction with base and the tosylated alkyne with a methyl group at its terminus was performed. This gave the newly substituted alkyne **3.18**.⁷³ A lithium-halogen exchange between 8-bromoquinoline **3.17**⁷⁴ and *n*-BuLi, followed by reaction with aldehyde **3.18** provided the corresponding secondary alcohol, which was oxidized directly with IBX to give the alkyne substrate **3.19**.^{66b}

Scheme 4. Synthesis of Electron-withdrawing and -donating Substrates



The previously discussed routes to alkyne substrates for the proposed carboacylation reaction were not suitable for the substrates in Figure 2. The proposed substrates (3.20, 3.21, 3.22) all suffered from competitive tosylate elimination when undergoing the substitution reaction with base (Scheme 3). No methods were found to allow for the formation despite the use of numerous reaction conditions.

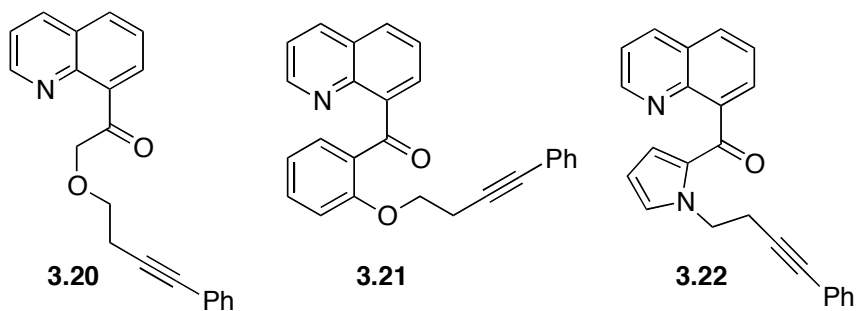


Figure 2. Proposed Substrates for C–C Activation

The substrates shown in Figure 3 were successfully synthesized. Starting alkynes **3.23** and **3.24** were synthesized in a similar manner to Schemes 2 & 3, extending the carbon alkyne tether by an ethylene unit (CH_2CH_2) relative to the substrates in Schemes 3 and 4. Pyrrole derivative **3.25** was synthesized in analogy to a known procedure, as was the aniline **3.26**.^{75,76}

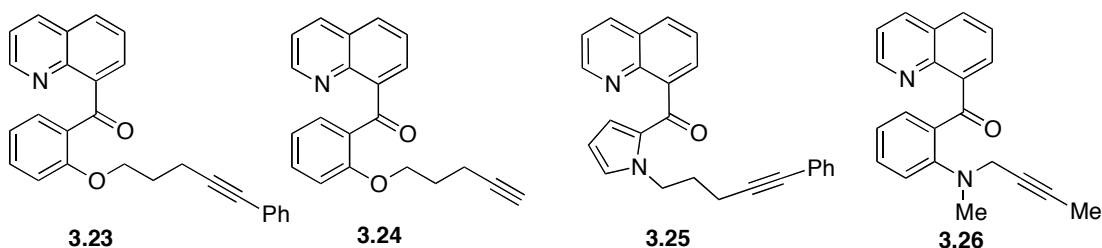
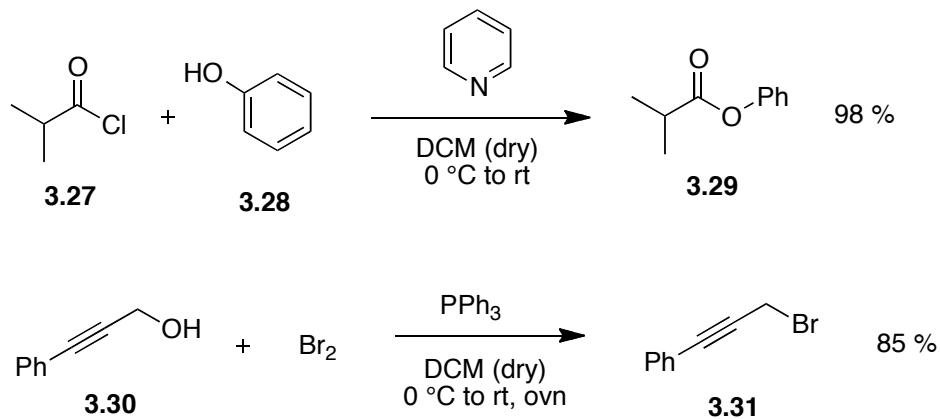


Figure 3. Additional Substrates for Studying C–C Activation/Alkyne Carboacylation

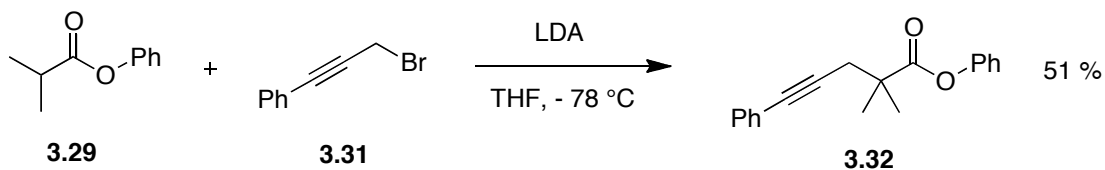
A final substrate was synthesized that was hoped to be able to combine the proposed carboacylation of alkynes (Scheme 1) and the previously developed intramolecular carboacylation of alkenes.^{66b} The proposed molecule would contain appropriately placed units of unsaturation for the tandem cyclization, one from an alkene and the other from an alkyne. The molecule would also contain the quinoline-directing group that had been used previously. The synthesis began with the acid chloride (**3.27**) and phenol (**3.28**) forming the ester (**3.29**), with pyridine as the base in DCM (Scheme 5). With the ester (**3.29**) in hand, the propargyl alcohol (**3.30**) reacted with bromine and triphenylphosphine giving the bromide (**3.31**) for reaction with the ester (**3.29**).⁷⁷

Scheme 5. Esterification and Bromination to form Coupling Partners

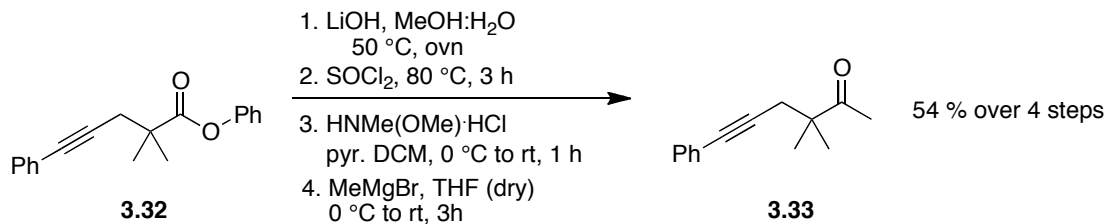


Ester **3.29** and propargyl bromide **3.31** were allowed to react with LDA in THF, giving the ester **3.32** in 51 % yield (Scheme 6). Further functional group manipulation was done to convert ester **3.32** into ketone **3.33** (Scheme 7). The ester **3.32** was hydrolyzed with LiOH in a mixture of MeOH and water. The resulting carboxylic acid was converted to the acid chloride with thionyl chloride.⁷⁸ The acid chloride was transformed to the Weinreb amide and then reacted with methyl Grignard to prepare ketone **3.33**.⁷⁹

Scheme 6. Synthesis of Alkynyl-Ester **3.32**

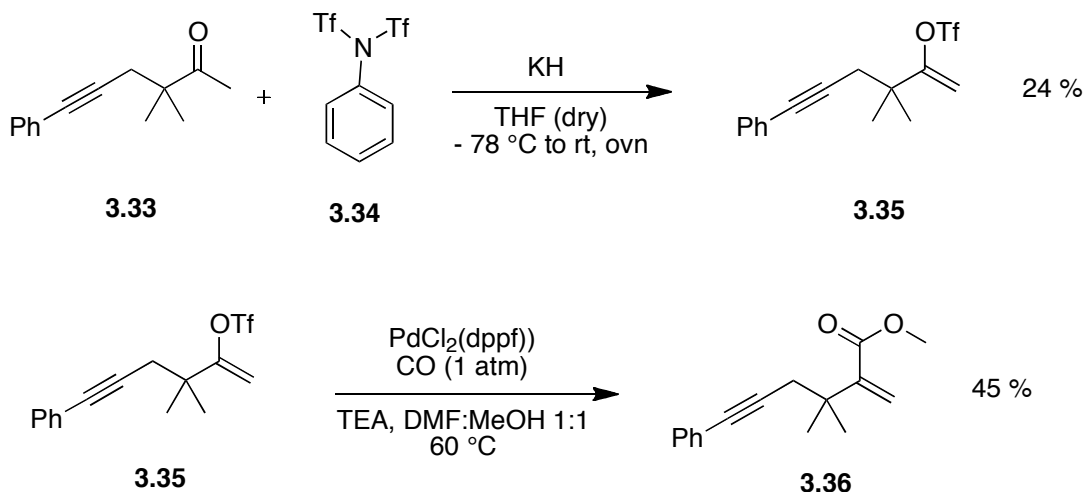


Scheme 7. Synthesis of Ketone 3.33



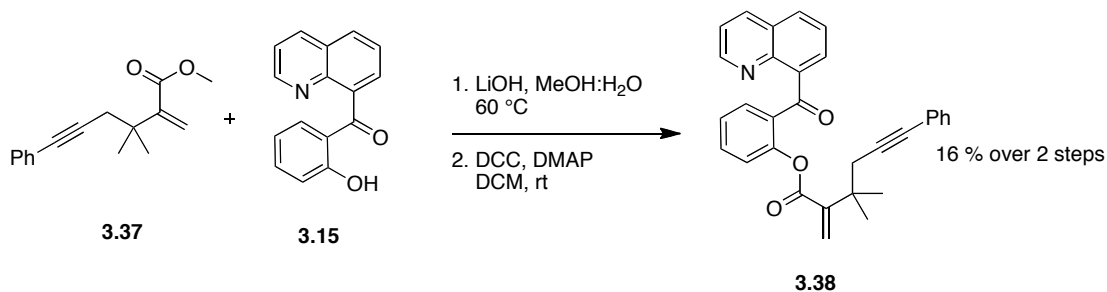
Ketone **3.33** was allowed to react with potassium hydride in the presence of the *N*-phenyl triflamide (**3.34**) to produce the vinyl triflate (**3.35**) (Scheme 8).⁸⁰ The vinyl triflate (**3.35**) was treated with PdCl₂dppf, methanol, and 1 atm of carbon monoxide to prepare the ester **3.36** via carbonylative esterification.⁸¹

Scheme 8. Triflation of Ketone (3.33) and Carbonylation to form 3.37



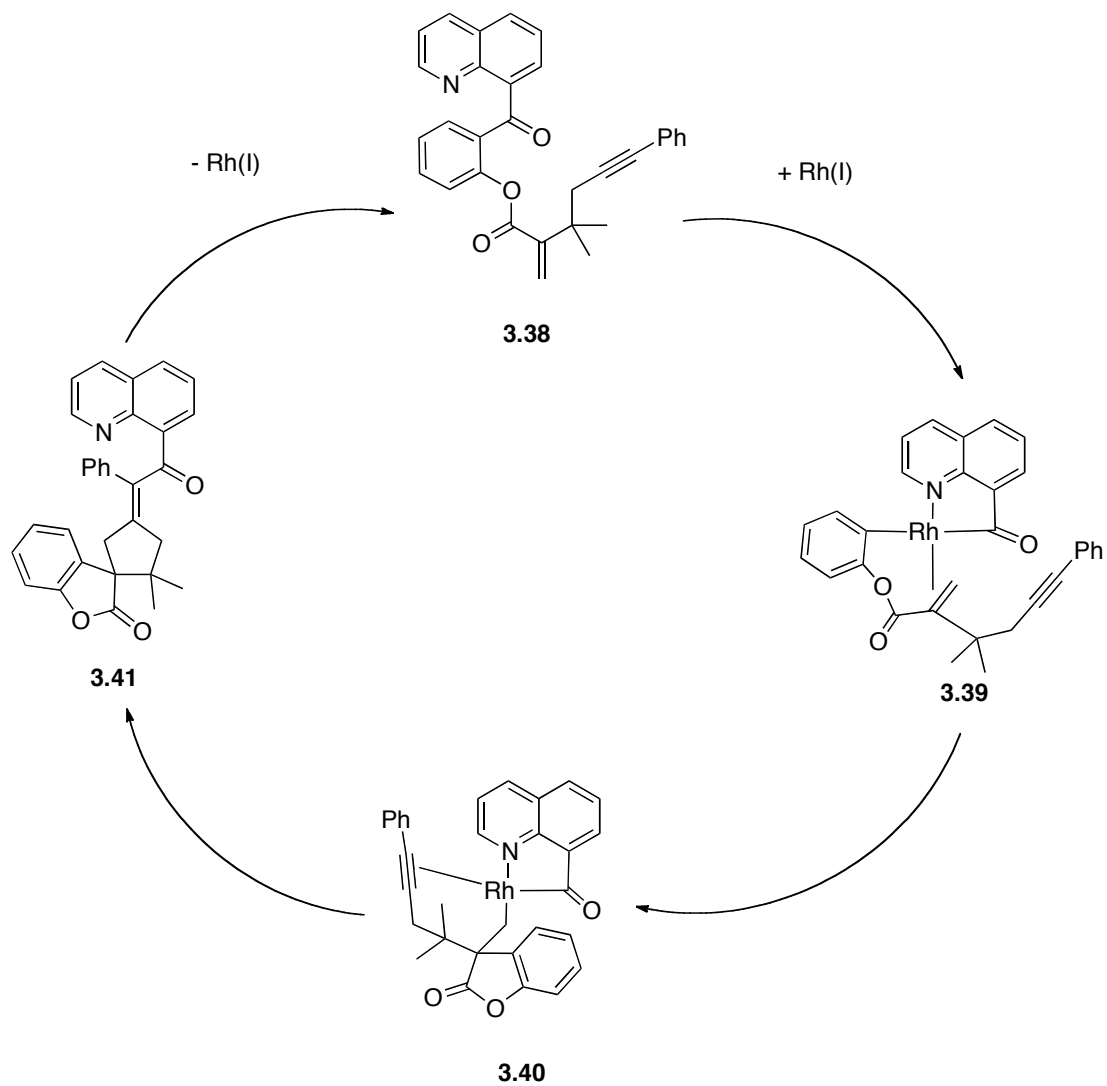
Ester **3.37** was first hydrolyzed to the carboxylic acid using LiOH in a solution of MeOH and water (Scheme 9). The acid was then coupled to the previously synthesized phenolic 8-acylquinoline (**3.15**) using DCC and DMAP, as had been done previously in our laboratories.^{66b} The final product of the reaction was the proposed starting material (**3.38**) for the tandem insertion reaction.

Scheme 9. Hydrolysis and DCC Coupling to form **3.38**



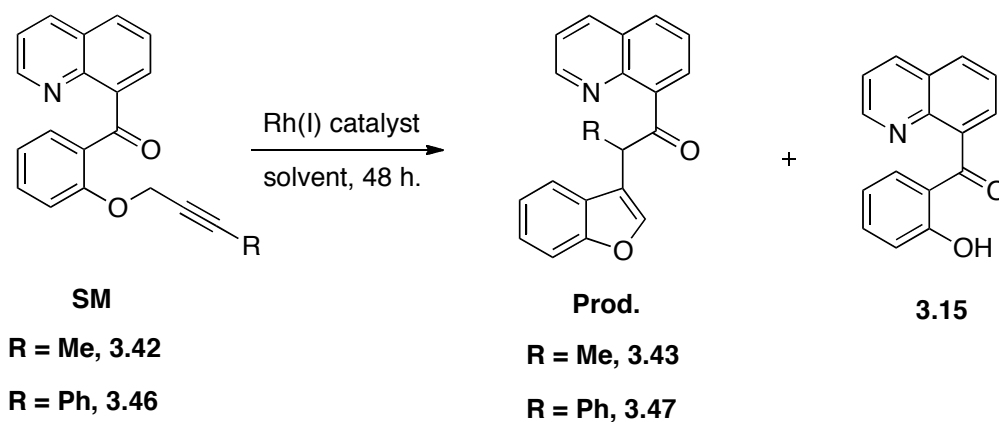
The proposed catalytic cycle for **3.38** is shown in Scheme 10. We predicted that C–C sigma-bond activation would take place giving the metallacycle **3.39**. Following a migratory insertion and reductive elimination, a second C–C sigma-bond activation is possible forming metallacycle **3.40**. If the alkyne is coordinated to the metal center in metallacycle **3.40**, we believed it possible to form two additional C–C bonds from the carboacylation of the alkyne forming the predicted product **3.41**.

Scheme 10. Proposed Double C–C Activation Cycle



3.3 Reaction Optimization and Results

Our initial attempts with terminal alkynes using a variety of Rh catalysts resulted in depropargylation, affording phenol **3.15** (entries 1-3, Table 1). We hoped to circumvent depropargylation by adding alkyl groups (R = Me, Ph) to the alkyne terminus. Despite changes in the substrate, phenol **3.15** remained the major product in the presence of Wilkinson's catalyst (entries 4 and 5). Switching to a catalyst with a less coordinating counter-ion, Rh(OTf)(cod)₂, benzofurans (**Prod.**) were finally observed, albeit in low yields (entries 6 and 7). Following upon the promising result with the Rh(OTf)(cod)₂ catalyst, several solvents were screened (entries 7-11), with the highest yields of **Prod.** observed in THF (entry 11). Using THF, several Rh(I) catalysts were screened (entries 12-15). Ultimately, the original Rh(OTf)(cod)₂ catalyst provided **Prod.** in the highest yield, although another catalyst with a weakly coordination counterion, Rh(BF₄)(cod)₂, performed nearly as well (entry 14). The products were found to be unstable to chromatography, with a rapid Prep-TLC giving similar yields (~ <10 %).

Table 1. Reaction Optimization

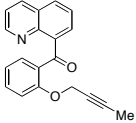
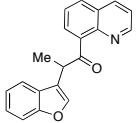
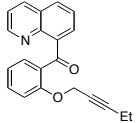
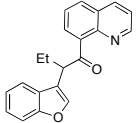
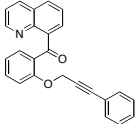
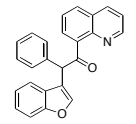
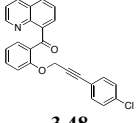
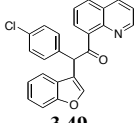
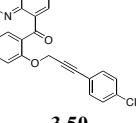
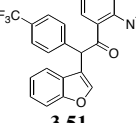
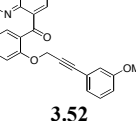
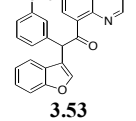
Entry	R	catalyst	mol %	Solvent	Temp.	Yield Prod* (%)	Yield 3.15* (%)	Recovered SM (%)
1	H	RhCl(PPh ₃) ₃	10	toluene	130 °C	0	25	35
2	H	[RhCl(C ₂ H ₄) ₂] ₂	5	toluene	130 °C	0	20	80
3	H	Rh(OTf)(cod) ₂	5	toluene	130 °C	0	90	10
4	Me	RhCl(PPh ₃) ₃	10	toluene	130 °C	0	0	50
5	Ph	RhCl(PPh ₃) ₃	10	toluene	130 °C	0	0	50
6	Me	Rh(OTf)(cod) ₂	10	toluene	130 °C	45	50	5
7	Ph	Rh(OTf)(cod) ₂	10	toluene	130 °C	9	n/a	n/a
8	Me	Rh(OTf)(cod) ₂	10	DCM	130 °C	65	35	0
9	Me	Rh(OTf)(cod) ₂	10	PhCF ₃	130 °C	60	40	0
10	Me	Rh(OTf)(cod) ₂	10	DCM	100 °C	70	20	10
11	Me	Rh(OTf)(cod)₂	10	THF	100 °C	91	5	4
12	Me	RhCl(PPh ₃) ₃	10	THF	100 °C	3	22	75
13	Me	[RhCl(C ₂ H ₄) ₂] ₂	5	THF	100 °C	5	25	70
14	Me	Rh(BF ₄)(cod) ₂	10	THF	100 °C	75	8	17
15	Me	Rh(BF ₄)(norb) ₂	10	THF	100 °C	10	10	80

*Yields determined by ¹H-NMR (4-methoxyacetophenone internal standard)

Using the optimized conditions (Table 1, entry 11), we explored the scope of intramolecular carboacylation of alkynes. We included our initial result with **3.42** converting to **3.43** in 91% yield as a comparison (Table 2, entry 1). Larger alkyne substituents (R = Et (**3.44**), Ph (**3.46**)) also underwent carboacylation, affording

benzofurans **3.45** and **3.47** in lower but acceptable yields (66 and 61% respectively, entries 2 and 3). Having demonstrated that phenyl-substituted alkynes were suitable carboacylation substrates, we proceeded to investigate the stereoelectronic effects of various alkyne substituents upon carboacylation. Reaction of electron-deficient alkynes **3.48** (4-Cl) and **3.50** (4-CF₃) provided benzofurans **3.49** (4-Cl) and **3.52** (4-CF₃) in the highest yields (75 and 73% respectively, entries 4 and 5), while electron-rich alkyne **3.52** (3-OMe) performed much more poorly, providing benzofuran **3.53** in only 33% yield (entry 6).

Table 2. C–C Activation with Alkynes (*para*-Substituted)

Entry	Substrate	Product	Yield*
1	 3.42	 3.43	91
2	 3.44	 3.45	66
3	 3.46	 3.47	61
4	 3.48	 3.49	75
5	 3.50	 3.51	73
6	 3.52	 3.53	33

*Yields determined by $^1\text{H-NMR}$ (4-methoxyacetophenone internal standard)

We investigated the effects of various substituents in the *para* position of the aryl-propargyl ether (Table 3, entries 1-5). Carboacylation of substrates bearing electron-donating substituents **3.54** (*t*-Bu) and **3.56** (OMe) provided benzofurans **3.55** (*t*-Bu) and **3.57** (OMe) in good yield (67 and 72% respectively, entries 1 and 2), while electron-withdrawing substituents **3.58** (NO₂) and **3.60** (Cl) generated benzofurans **3.59** (NO₂) and (Cl) in poor yields (28 and 0%, respectively, entries 3 and 4). The

major by-products of these reactions was phenol and starting material. To our surprise, the presumably electron-withdrawing iodoacetophenone **3.61** provided benzofuran **3.62** in 72% yield (entry 5), comparable to electron-donating substrates containing *t*-Bu (**3.54**) and OMe (**3.56**) substituents. We speculate that substituents that can donate either through sigma-bonds or lone-pair electron back donation improve carboacylation, compared to other electron deficient substituents which promote deproparylation. Despite our attempts to definitively correlate the stereoelectronic effect of *para* substituents to yield, a complete lack of *para* substituent (e.g. **3.42**, entry 1) still provides benzofuran **3.43** in 91% yield, the highest overall. Finally, all the alkynes in Figure 3 were not reactive under the optimized reaction conditions, giving only covered starting material. Also the optimized reaction conditions were not suitable for any of the predicted double insertion product (Schemes 9 & 10) with left over starting material **3.38** being the major component of the crude reaction mixture. Other conditions were tested giving similar results, but a full investigation was not possible with the limited amount of starting material **3.38** available.

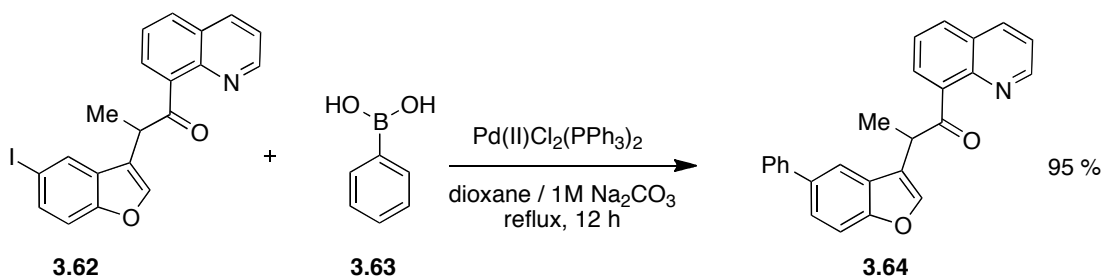
Table 3. C–C Activation with Alkynes (Quinoline Ring Substituted)

Entry	Substrate	Product	Yield*
1	 3.54	 3.55	67
2	 3.56	 3.57	72
3	 3.58	 3.59	28
4	 3.60		0
5	 3.61	 3.62	72

*Yields determined by $^1\text{H-NMR}$ (4-methoxyacetophenone internal standard)

The tolerance of carboacylation to the aryl iodide might allow for subsequent synthetic manipulation. Suzuki cross-coupling of phenyl boronic acid (**3.63**) and benzofuran **3.62** was very clean, providing **3.64** in 95% yield (Scheme 11).

Scheme 11. Iodo-Furan Coupling

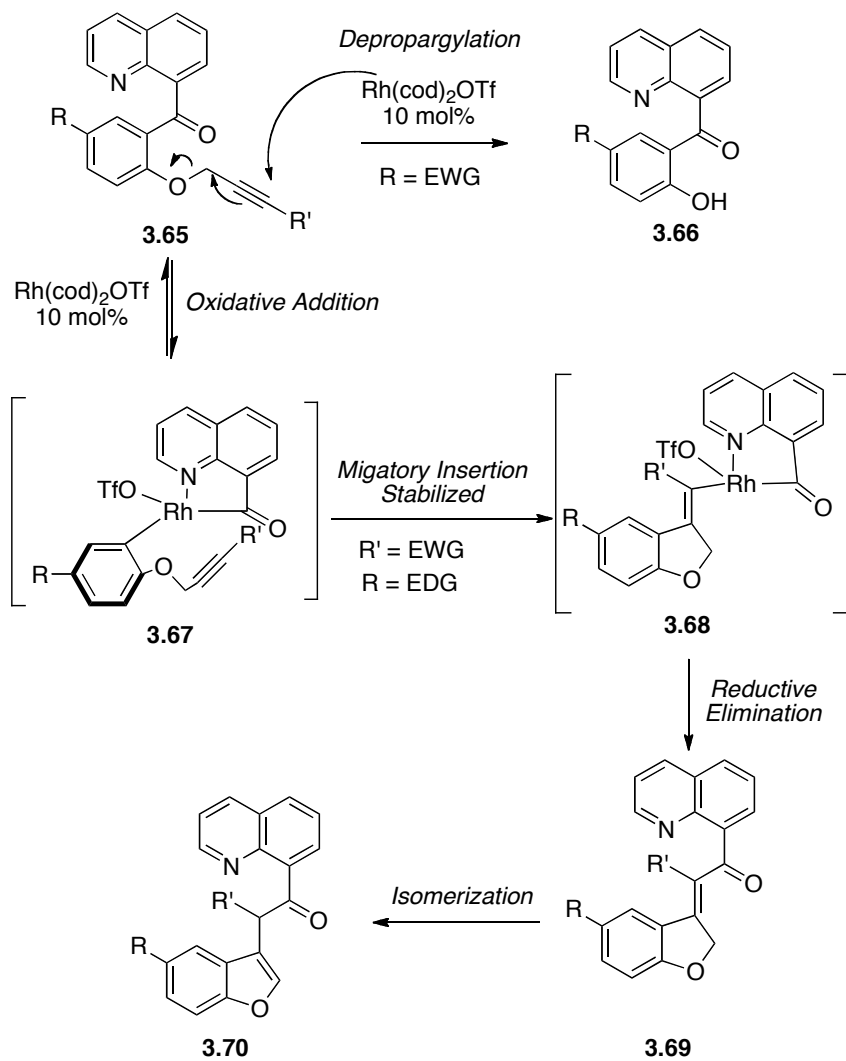


3.4 Mechanistic Considerations

A possible mechanistic rationale for our observations is provided in Scheme 12. Rhodium coordination to the quinoline allows facile oxidative addition into the C–C bond. In fact, we have observed oxidative addition of Rh into C–C bonds even at $-20\text{ }^{\circ}\text{C}$.⁸² Because carboacylation does not occur until the reaction is heated, we propose an equilibrium between starting material **3.65** and **3.67**. Depropargylation likely occurs via an S_N2' mechanism, similar to those proposed for other metal-catalyzed depropargylation reactions giving phenol (**3.66**).^{68,70} The resulting phenoxide would be stabilized by an electron withdrawing group, like NO₂ (**3.58**) or Cl (**3.60**), located *para* to the phenoxide. Carboacylation can be explained by the migratory insertion of the alkyne into the activated bond of **3.67** to form **3.68**.

Reductive elimination would form **3.69**, which readily isomerizes to the benzofuran **3.70**.

Scheme 12. Electronic Considerations for C–C Activation



3.5 Conclusion

In conclusion, we have disclosed conditions that allow the activation of a C–C bond and subsequent intramolecular carboacylation of an alkyne to form two new C–C bonds. These results provide a basis for controlling aryl propargyl-ether cleavage and C–C activation reaction pathways.

3.6 Experimental Details

General experimental details: All reactions were carried out using flame-dried glassware under a nitrogen or argon atmosphere unless aqueous solutions were employed as reagents or dimethyl formamide was used as a solvent. Tetrahydrofuran (THF) and toluene (PhMe) were dried according to published procedures.⁶ Trifluorotoluene, acetonitrile, and 1,2-dichloroethane were distilled prior to use. Toluene was further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. All rhodium complexes were purchased from Strem and used as received. IBX was prepared according to Santagostino.⁷ All other chemicals were purchased from Acros Organics or Sigma-Aldrich and used as received. All rhodium-catalyzed processes were carried out in a Vacuum Atmospheres nitrogen filled glove box in 1 dram vials with PTFE lined caps and heating was applied by aluminum block heaters.

Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates from E. Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulfate/molybdic acid or potassium permanganate/potassium carbonate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck unless otherwise indicated. ¹H NMR (300, 400, and 500 MHz) and ¹³C NMR (75 and 125 MHz) spectra were

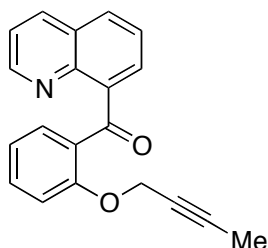
⁶ A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers *Organometallics*, **1996**, *15*, 1518.

⁷ M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.

obtained on Varian FT NMR instruments. NMR spectra were reported as δ values in ppm relative to chloroform or tetramethylsilane. ^1H NMR coupling constants are reported in Hz; multiplicity was indicated as follows; s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained as films from CH_2Cl_2 or CDCl_3 . Low-resolution mass spectra (LRMS) in EI or CI experiments were performed on a Varian Saturn 2200 GC-MS system, and LRMS and high-resolution mass spectra (HRMS) in electrospray (ESI) experiments were performed on a Bruker BioTOF II.

General Procedure for the Synthesis of Alkynes

The phenol **3.15** was synthesized according to a known procedure.⁸



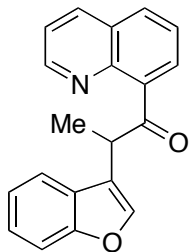
(2-(but-2-yn-1-yloxy)phenyl)(quinolin-8-yl)methanone (**3.42**)

The tosylate (530 mg, 1.65 mmol), phenol **3.15** (370 mg, 1.57 mmol), and K_2CO_3 (435 mg, 3.15 mmol) were combined with DMF (2 mL) in r.b.f and stirred overnight. The mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The crude reaction mixture was purified by flash chromatography (EtOAc:Hex) to provide alkyne: $R_f = 0.32$ (35%

EtOAc/Hex); 1H -NMR (300 MHz; $CDCl_3$): δ 8.76 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.90 (td, $J = 7.9, 1.6$ Hz, 2H), 7.78 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.57 (dd, $J = 8.1, 7.2$ Hz, 1H), 7.47 (ddd, $J = 8.3, 7.3, 1.8$ Hz, 1H), 7.35 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.08 (td, $J = 7.5, 0.8$ Hz, 1H), 6.95-6.92 (m, 1H), 4.08 (q, $J = 2.3$ Hz, 2H), 1.67 (t, $J = 2.3$ Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 196.8, 157.6, 150.3, 146.1, 141.8, 135.8, 133.7, 131.3, 129.83, 129.70, 128.3, 128.0, 126.0, 121.33,

⁸ A. M. Dreis and C. J. Douglas *J. Am. Chem. Soc.* **2009**, *131*, 412.

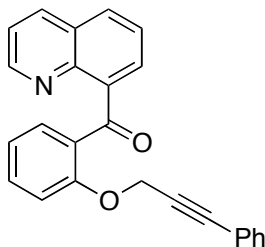
121.28, 113.7, 83.3, 73.2, 56.9, 3.7; IR (film) 3044, 2919, 2349, 1626, 1251 cm^{-1} ;
HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{15}\text{NO}_2 + \text{Na}]^+$ 324.1000, found 324.1033.



2-(benzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.43)

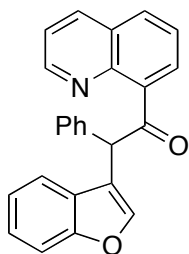
General Procedure for C–C Activation: A 1 dram screw cap vial with a PTFE lined cap was charged with a magnetic stir bar and (2-(but-2-yn-1-yloxy)phenyl)(quinolin-8-yl)methanone (**3.42**) (30.1 mg, 0.1 mmol), and the vial was taken into the glovebox. Bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) and THF (1.0 mL) were added. The vial was placed in an aluminum block heater for 48 hours at 100 °C. After 48 hours, the vial was allowed to cool to room temperature and removed from the glove box. The reaction solution was filtered through a pad of celite with excess EtOAc. The dark residue was concentrated in vacuo and purified by column chromatography (10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (27.4 mg, 0.091 mmol, 91%): $R_f = 0.34$ (20% EtOAc/Hex); $^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 8.99 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.85 (dd, $J = 8.1, 1.4$ Hz, 1H), 7.69 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.47-7.43 (m, 3H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.23-7.22 (m, 1H), 7.18-7.17 (m, 1H), 5.57 (q, $J = 7.1$ Hz, 1H), 1.71 (d, $J = 7.1$ Hz, 4H) ^{13}C NMR (125 MHz, CDCl_3) δ 206.3, 155.5, 150.6, 145.7, 142.4, 139.3, 136.5, 131.0,

129.9, 128.3, 126.2, 124.3 (2C), 122.5, 121.7, 120.5, 120.4, 111.6, 43.6, 16.9; IR (film) 2983, 2923, 1683, 1453 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{15}\text{NO}_2 + \text{Na}]^+$ 324.1000, found 324.1045.



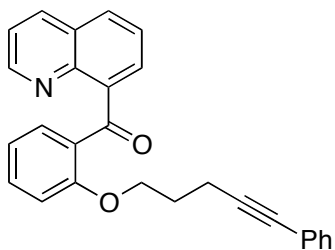
(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)(quinolin-8-yl)methanone (3.46)

$R_f = 0.35$ (35% EtOAc/Hex); ^1H NMR (300 MHz; CDCl_3): δ 8.64 (dd, $J = 4.2, 1.6$ Hz, 1H), 7.91 (ddd, $J = 16.4, 8.0, 1.6$ Hz, 2H), 7.73-7.68 (m, 2H), 7.45-7.34 (m, 2H), 7.20 (app s, 4H), 7.15 (dd, $J = 8.4, 4.2$ Hz, 2H), 7.00 (t, $J = 7.5$ Hz, 1H), 6.90 (d, $J = 8.3$ Hz, 1H), 4.26 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.8, 157.5, 150.5, 146.1, 141.7, 136.0, 133.8, 131.8, 131.4, 130.1, 130.0, 128.8, 128.4 (2C), 128.0, 126.0, 122.3, 121.7, 121.4, 113.8, 86.8, 83.1, 57.2; IR (film) 3054, 2920, 2865, 2238, 1652 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{25}\text{H}_{17}\text{NO}_2 + \text{Na}]^+$ 386.1157, found 386.1126.



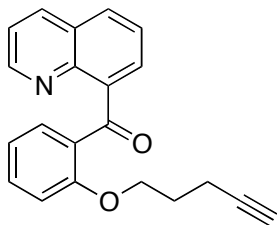
2-(benzofuran-3-yl)-2-phenyl-1-(quinolin-8-yl)ethanone (3.47)

(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)(quinolin-8-yl)methanone (**3.46**) (36.3 mg, 0.1 mmol) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (22.1 mg, 0.061 mmol, 61%): $R_f = 0.37$ (20% EtOAc/Hex); $^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 9.02 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.19 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.88 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.72 (dd, $J = 7.2, 1.4$ Hz, 1H), 7.67–7.65 (m, 1H), 7.60 (d, $J = 0.9$ Hz, 1H), 7.49–7.45 (m, 2H), 7.39–7.36 (m, 3H), 7.29–7.16 (m, 5H), 7.01 (s, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 203.6, 155.5, 150.6, 145.8, 144.0, 139.0, 137.6, 136.6, 131.3, 130.9, 129.5, 128.8, 128.3, 127.9, 127.5, 126.3, 124.4, 122.6, 121.7, 121.0, 119.6, 111.6, 55.3; IR (film) 3067, 2923, 1645, 1548, 1450 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{25}\text{H}_{17}\text{NO}_2 + \text{Na}]^+$ 386.1157, found 386.1131.



(2-((5-phenylpent-4-yn-1-yl)oxy)phenyl)(quinolin-8-yl)methanone (3.23)

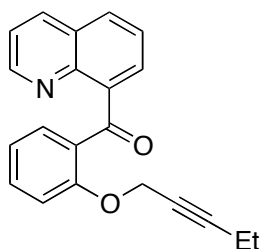
$R_f = 0.39$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.78 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.13 (dd, $J = 8.1, 1.8$ Hz, 1H), 8.01 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.88 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.72 (dd, $J = 7.2, 1.5$ Hz, 1H), 7.55 (app q, $J = 8.1, 7.5$ Hz, 1H), 7.47–7.41 (m, 1H), 7.34–7.29 (m, 3H), 7.27–7.23 (m, 3H), 7.05 (t, $J = 7.5$ Hz, 1H) 6.78 (d, $J = 8.4$ Hz, 1H), 3.62 (t, $J = 6.0$ Hz, 2H), 1.61 (t, $J = 6.9$ Hz, 2H), 1.01 (quint, $J = 6.0$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 197.0, 158.5, 150.5, 145.9, 142.5, 135.9, 134.2, 131.4 (2C), 131.1, 129.6, 128.9, 128.3 (2C), 128.0, 127.7, 127.5, 126.0, 123.7, 121.4, 120.6, 112.2, 89.0, 80.8, 66.2, 27.7, 15.5; IR (film) 3045, 3001, 2349, 1634, 1486 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{27}\text{H}_{21}\text{NO}_2 + \text{Na}]^+$ 414.1470, found 414.1505.



(2-(pent-4-yn-1-yloxy)phenyl)(quinolin-8-yl)methanone (3.24)

$R_f = 0.45$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.81 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.18 (dd, $J = 8.4, 1.8$ Hz, 1H), 8.00 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.91 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.73 (dd, $J = 6.9, 1.5$ Hz, 1H), 7.57 (dd, $J = 15.0, 6.9$ Hz, 1H), 7.47 (dt, J

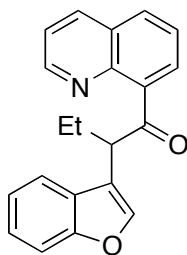
= 15.9, 1.8 Hz, 1H), 7.38 (q, $J = 8.1, 4.2$ Hz, 1H), 7.08 (dt, $J = 7.5, 0.9$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H) 3.61 (t, $J = 11.7, 5.7$ Hz, 2H), 1.81 (t, $J = 5.1, 2.7$ Hz, 1H), 1.41 (dt, $J = 6.9, 2.7$ Hz, 2H), 0.96 (p, $J = 12.9, 6.6$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.0, 158.6, 150.6, 146.0, 142.6, 136.1, 134.2, 131.3, 129.7, 129.0, 128.1, 127.7, 126.1, 121.5, 120.8, 112.3, 83.4, 68.7, 66.2, 27.6, 14.7; IR (film) 3297, 3067, 2940, 2349, 1645, 1595, 1451, 1296 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{21}\text{H}_{17}\text{NO}_2 + \text{Na}]^+$ 338.1157, found 338.1152.



(2-(pent-2-yn-1-yloxy)phenyl)(quinolin-8-yl)methanone (3.44)

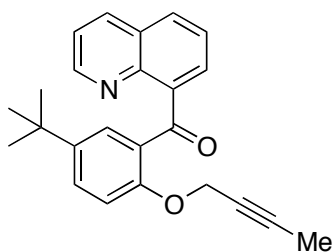
$R_f = 0.36$ (35% EtOAc/Hex); ^1H NMR (500 MHz; CDCl_3): δ 8.77 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.14 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.90 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.87 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.77 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.55 (dd, $J = 8.2, 7.1$ Hz, 1H), 7.45 (ddd, $J = 8.3, 7.3, 1.8$ Hz, 1H), 7.34 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.08–7.05 (m, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 4.09 (t, $J = 2.1$ Hz, 2H), 2.03 (dddd, $J = 9.9, 7.5, 5.1, 2.4$ Hz, 2H), 1.01–1.00 (m, 3H); ^{13}C NMR (75 MHz; CDCl_3): δ 197.3, 158.3, 151.0, 142.2, 136.7, 134.4, 133.5, 132.4, 132.0, 130.4, 129.1, 128.6, 126.6, 121.96, 121.92, 114.4,

89.7, 74.0, 57.6, 14.2, 13.0; IR (film) 2976, 2938, 2240, 1652, 1594, 1294 cm^{-1} ;
HRMS (ESI) m/z calcd for $[\text{C}_{21}\text{H}_{17}\text{NO}_2 + \text{Na}]^+$ 338.1157, found 338.1181.



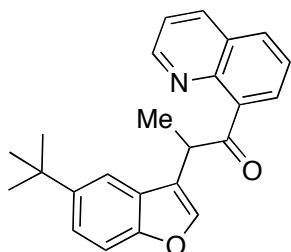
2-(benzofuran-3-yl)-1-(quinolin-8-yl)butan-1-one (3.45)

2-(pent-2-yn-1-yloxy)phenyl(quinolin-8-yl)methanone (**3.44**) (31.5 mg, 0.1 mmol) and bis(1,5- cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (20.8 mg, 0.066 mmol, 66%); $R_f = 0.38$ (20% EtOAc/Hex); ^1H NMR (300 MHz; CDCl_3): δ 8.97 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.85 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.70–7.67 (m, 1H), 7.62–7.59 (m, 1H), 7.47–7.39 (m, 4H), 7.24–7.16 (m, 2H), 5.39 (q, $J = 8.6$ Hz, 1H), 2.47–2.33 (m, 1H), 2.13–1.98 (m, 1H), 1.01 (d, $J = 14.8$ Hz, 3H); ^{13}C NMR (75 MHz; CDCl_3): δ 206.1, 155.4, 150.5, 145.6, 143.1, 139.4, 136.4, 131.0, 129.9, 128.2, 127.5, 126.2, 124.2, 122.5, 121.6, 120.6, 118.3, 111.5, 50.7, 24.6, 12.4; IR (film) 2963, 1699, 1558, 1452, 748 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{21}\text{H}_{17}\text{NO}_2 + \text{Na}]^+$ 338.1157, found 338.1160.



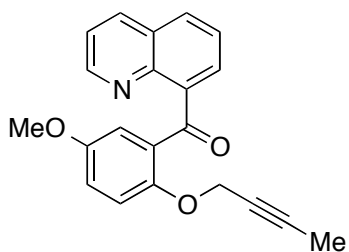
(2-(but-2-yn-1-yloxy)-5-(*tert*-butyl)phenyl)(quinolin-8-yl)methanone (3.54)

$R_f = 0.32$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz; CDCl_3): δ 8.79 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 8.03 (d, $J = 2.6$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.73–7.70 (m, 1H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.53–7.48 (m, 1H), 7.36 (dd, $J = 8.3, 4.2$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 1H), 4.00 (q, $J = 2.3$ Hz, 2H), 1.66 (t, $J = 2.3$ Hz, 3H), 1.34 (s, 9H). $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 196.3, 155.3, 149.7, 145.5, 143.3, 141.9, 135.2, 130.6, 128.7, 127.9, 127.41, 127.39, 127.0, 125.4, 120.6, 112.9, 82.4, 72.8, 59.9, 56.4, 33.8, 30.9, 20.5, 13.7; IR (film) 3044, 2961, 2866, 2244, 1652, 1495, 1262 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{24}\text{H}_{23}\text{NO}_2 + \text{Na}]^+$ 380.1626, found 380.1635.



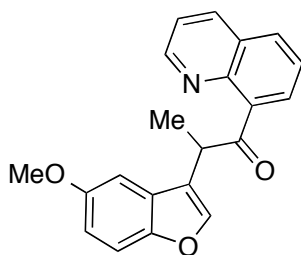
2-(5-(*tert*-butyl)benzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.55)

(2-(but-2-yn-1-yloxy)-5-(*tert*-butyl)phenyl)(quinolin-8-yl)methanone (**3.54**) (35.7 mg, 0.1 mmol) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (23.9 mg, 0.067 mmol, 67%) $R_f = 0.40$ (20% EtOAc/Hex); $^1\text{H NMR}$ (500 MHz; CDCl_3): δ 9.01 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.18 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.85 (dd, $J = 8.1, 1.4$ Hz, 1H), 7.67 (dd, $J = 7.1, 1.3$ Hz, 1H), 7.48–7.46 (m, 1H), 7.44 (dd, $J = 5.6, 2.3$ Hz, 3H), 7.29–7.28 (m, 2H), 5.54 (q, $J = 7.1$ Hz, 1H), 1.72 (d, $J = 7.1$ Hz, 3H), 1.28 (s, 9H). $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 206.8, 153.6, 150.6, 145.68, 145.50, 142.5, 139.5, 136.4, 130.8, 129.8, 128.2, 126.2, 122.2, 121.6, 120.6, 116.4, 110.7, 43.4, 34.8, 31.9 (3C), 16.8; IR (film) 2961, 2869, 1699, 1557, 796 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{24}\text{H}_{23}\text{NO}_2 + \text{Na}]^+$ 380.1626, found 380.1623.



(2-(but-2-yn-1-yloxy)-5-methoxyphenyl)(quinolin-8-yl)methanone (3.56)

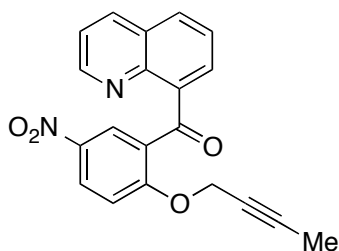
$R_f = 0.35$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz; CDCl_3): δ 8.64 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.02–7.99 (m, 1H), 7.73 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.61 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.41 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.35 (d, $J = 3.2$ Hz, 1H), 7.21 (dd, $J = 8.3, 4.2$ Hz, 1H), 6.88 (dd, $J = 9.0, 3.2$ Hz, 1H), 6.74 (d, $J = 9.0$ Hz, 1H), 3.79 (q, $J = 2.3$ Hz, 2H), 3.67 (s, 3H), 1.50 (t, $J = 2.3$ Hz, 3H); $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 194.1, 151.8, 149.7, 148.0, 143.6, 139.4, 133.6, 128.0, 127.3, 125.78, 125.59, 123.6, 119.0, 118.1, 113.8, 111.9, 80.7, 71.1, 55.6, 53.5, 1.3; IR (film) 3010, 2953, 22.42, 1652, 1494, 1284, 1216 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{21}\text{H}_{17}\text{NO}_3 + \text{Na}]^+$ 354.1106, found 354.1111.



2-(5-methoxybenzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.57)

(2-(but-2-yn-1-yloxy)-5-methoxyphenyl)(quinolin-8-yl)methanone (**3.56**) (33.1 mg, 0.1 mmol) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg,

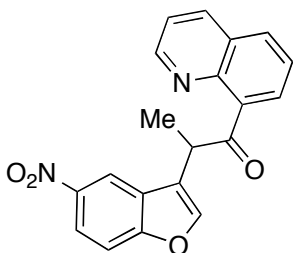
10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (23.8 mg, 0.072 mmol, 72%): $R_f = 0.35$ (20% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz; CDCl_3): δ 9.00 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.19 (dd, $J = 8.3, 1.8$ Hz, 1H), 7.87 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.69 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.49–7.42 (m, 3H), 7.29 (m, 1H), 7.00 (d, $J = 2.6$ Hz, 1H), 6.83 (dd, $J = 8.8, 2.6$ Hz, 1H), 5.56–5.49 (m, 1H), 3.76 (s, 3H), 1.70 (d, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 206.1, 155.9, 155.4, 150.5, 143.1, 139.4, 136.4, 131.0, 129.9, 128.2, 127.5, 126.2, 124.2, 122.5, 121.6, 120.6, 118.3, 111.5, 50.7, 24.6, 12.4; IR (film) 2957, 2922, 1699, 1474 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{21}\text{H}_{17}\text{NO}_3 + \text{Na}]^+$ 354.1106, found 354.1098.



(2-(but-2-yn-1-yloxy)-5-nitrophenyl)(quinolin-8-yl)methanone (3.58)

$R_f = 0.33$ (35% EtOAc/Hex); $^1\text{H NMR}$ (400 MHz; CDCl_3): δ 8.72 (d, $J = 2.9$ Hz, 1H), 8.68 (dd, $J = 4.3, 1.7$ Hz, 1H), 8.37–8.35 (m, 1H), 8.20 (d, $J = 8.3$ Hz, 1H), 7.99–7.95 (m, 2H), 7.65 (d, $J = 7.3$ Hz, 1H), 7.39 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.03 (d, $J = 9.2$ Hz, 1H), 4.20 (t, $J = 2.2$ Hz, 2H), 1.71 (t, $J = 2.3$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 194.6, 161.4, 150.3, 141.7, 139.7, 136.2, 133.0, 131.7, 131.1, 129.7, 128.4, 128.02, 127.89, 126.8, 121.6, 113.1, 84.8, 71.8, 57.3, 3.7; IR (film) 3078, 2922, 2230, 1652,

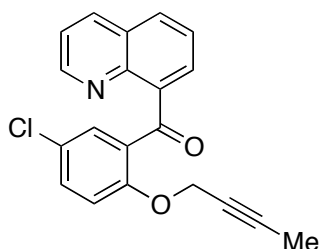
1339, 1278 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_4 + \text{Na}]^+$ 369.0851, found 369.0834.



2-(5-nitrobenzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.59)

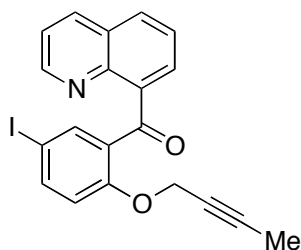
(2-(but-2-yn-1-yloxy)-5-nitrophenyl)(quinolin-8-yl)methanone (**3.58**) (34.6 mg, 0.1 mmol) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25%

EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (9.7 mg, 0.028 mmol, 28%) $R_f = 0.31$ (20% EtOAc/Hex); ^1H NMR (300 MHz; CDCl_3): δ 9.12 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.86 (d, $J = 2.4$ Hz, 1H), 8.22 (ddd, $J = 11.8, 8.7, 2.1$ Hz, 2H), 7.96 (dd, $J = 8.1, 1.5$ Hz, 1H), 7.83 (dd, $J = 7.1, 1.5$ Hz, 1H), 7.74 (s, 1H), 7.59–7.50 (m, 3H), 5.67–5.62 (m, 1H), 1.68 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (75 MHz; CDCl_3): δ 201.2, 153.1, 145.7 (2C), 140.47, 140.32, 133.4, 131.4, 126.3, 124.9, 123.19, 123.14, 121.1, 116.8, 115.1, 112.9, 106.7, 38.1, 24.7, 12.1; IR (film) 2934, 2910, 2846, 1699, 1516, 1342 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_4 + \text{Na}]^+$ 369.0851, found 369.0814.



(2-(but-2-yn-1-yloxy)-5-chlorophenyl)(quinolin-8-yl)methanone (3.60)

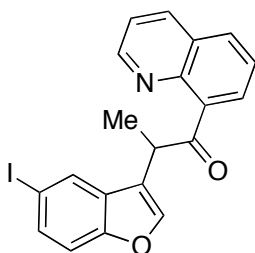
$R_f = 0.34$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz; CDCl_3): δ 8.76 (dd, $J = 4.2, 1.9$ Hz, 1H), 8.18 (dd, $J = 8.4, 1.8$ Hz, 1H), 7.94–7.91 (m, 1H), 7.87 (d, $J = 2.7$ Hz, 1H), 7.83 (dd, $J = 7.1, 1.4$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.43–7.38 (m, 2H), 6.89 (d, $J = 8.9$ Hz, 1H), 4.04–4.02 (m, 2H), 1.69 (t, $J = 2.3$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 195.2, 155.7, 150.2, 141.7, 135.9, 133.2, 132.9, 131.9, 130.5, 130.0, 128.7, 127.88, 127.76, 126.5, 125.9, 121.3, 115.0, 72.6, 57.0, 3.5; IR (film) 3071, 2919, 2230, 1652, 1274 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{ClNO}_2 + \text{Na}]^+$ 358.0611, found 358.0604.



(2-(but-2-yn-1-yloxy)-5-iodophenyl)(quinolin-8-yl)methanone (3.61)

$R_f = 0.31$ (35% EtOAc/Hex); $^1\text{H NMR}$ (300 MHz; CDCl_3): δ 8.75 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.17 (dd, $J = 7.4, 2.1$ Hz, 2H), 7.92 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.81 (dd, $J = 7.1, 1.4$ Hz, 1H), 7.73 (dd, $J = 8.7, 2.3$ Hz, 1H), 7.59 (dd, $J = 8.0, 7.2$ Hz, 1H), 7.38

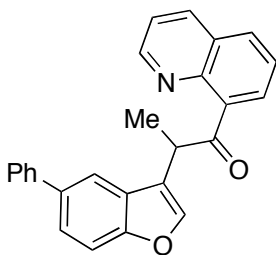
(dd, $J = 8.3, 4.2$ Hz, 1H), 6.71 (d, $J = 8.7$ Hz, 1H), 4.01 (q, $J = 2.3$ Hz, 2H), 1.68 (t, $J = 2.3$ Hz, 3H). ^{13}C NMR (75 MHz; CDCl_3): δ 190.8, 152.6, 145.9, 141.5, 137.4, 136.4, 134.8, 131.4 (2C), 127.6, 125.7, 124.3, 123.4, 121.6, 116.9, 111.4, 79.3, 68.2, 52.4, -0.8 ; IR (film) 2957, 2359, 1648, 1581, 1475, 1276 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{INO}_2 + \text{Na}]^+$ 449.9967, found 449.9986.



2-(5-iodobenzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.62)

(2-(but-2-yn-1-yloxy)-5-iodophenyl)(quinolin-8-yl)methanone (**3.61**) (42.7 mg, 0.1 mmol) and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (5.2 mg, 10 mol %) in THF (1.0 mL). Purified by column chromatography 10%–25% EtOAc/Hexanes) to provide the product of carboacylation as a yellow film (30.7 mg, 0.072 mmol, 72%): $R_f = 0.32$ (20% EtOAc/Hex); ^1H NMR (300 MHz; CDCl_3): δ 9.03 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.21 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.98 (d, $J = 1.4$ Hz, 1H), 7.91 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.74 (dd, $J = 7.1, 1.4$ Hz, 1H), 7.53–7.46 (m, 4H), 7.18 (d, $J = 8.6$ Hz, 1H), 5.55–5.48 (m, 1H), 1.67 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz; CDCl_3): δ 206.0, 154.4, 150.2, 145.2, 142.8, 136.1, 132.4, 130.8, 129.8, 129.5, 129.3 (2C), 127.9, 125.8, 121.4, 119.6, 113.1, 85.7, 42.9, 16.6; IR (film) 2980, 2942, 2360,

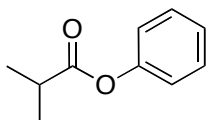
1687, 1449, 797 cm^{-1} ; HRMS (ESI) m/z calcd for $[\text{C}_{20}\text{H}_{14}\text{INO}_2 + \text{Na}]^+$ 449.9967, found 449.9974.



2-(5-phenylbenzofuran-3-yl)-1-(quinolin-8-yl)propan-1-one (3.64)

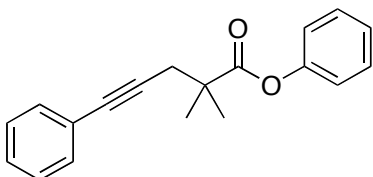
trans-dichlorobis-(triphenylphosphine) palladium (II) (8.4 mg, 0.012 mmol), (2-(but-2-yn-1-yloxy)-5-iodophenyl)(quinolin-8-yl)methanone (**3.62**) (28 mg, 0.06 mmol), and phenyl boronic acid (74 mg, 0.6 mmol) were dissolved in dioxane (6 mL) and stirred at room temperature for 30 min. Aqueous Na_2CO_3 (7 mL, 7.0 mmol) was added as a 1.0 M solution and the reaction was heated to reflux and stirred for 12 hours, at which point the reaction was concentrated in vacuo. The crude product was dissolved in EtOAc and washed with sat. NaCl and dried over anhydrous Na_2SO_4 . Purification via preparatory TLC (20% EtOAc/hexanes) afforded **4** as a light orange oil (22 mg, 95%): $R_f = 0.32$ (20% EtOAc/Hex); ^1H NMR (400 MHz; CDCl_3): δ 9.00–8.96 (m, 1H), 8.17 (dt, $J = 8.2, 2.1$ Hz, 1H), 7.88–7.85 (m, 1H), 7.74–7.70 (m, 2H), 7.54–7.41 (m, 10H), 7.35–7.31 (m, 1H), 5.63–5.57 (m, 1H), 1.77–1.70 (m, 3H). ^{13}C NMR (75 MHz; CDCl_3): δ 206.6, 155.1, 150.6, 145.7, 143.1, 141.8, 139.3, 136.5, 136.2, 131.0, 129.9, 128.8 (2C), 128.3, 127.9, 127.6 (2C), 126.9, 126.2, 124.0, 121.7,

120.7, 119.1, 111.6, 43.5, 16.9. IR (film) 3085, 2974, 2933, 2359, 1699, 1464 cm^{-1} ;
HRMS (ESI) m/z calcd for $[\text{C}_{26}\text{H}_{19}\text{NO}_2 + \text{Na}]^+$ 400.1313, found 400.1265.



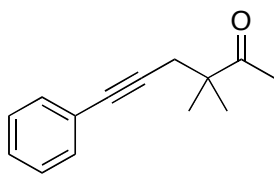
phenyl isobutyrate (3.29)

^1H NMR (300 MHz, CDCl_3) δ 7.39-7.32 (m, 2H), 7.23-7.17 (m, 1H), 7.08-7.05 (m, 2H), 2.79 (septet, $J = 6.9$ Hz, 1H), 1.32-1.29 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.7, 151.0, 129.2 (2C), 125.7, 121.6 (2C), 34.2, 19.0 (2C).



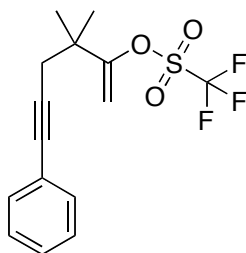
phenyl 2,2-dimethyl-5-phenylpent-4-ynoate (3.32)

^1H NMR (300 MHz, CDCl_3) δ 7.43-7.20 (m, 8H), 7.10-7.07 (m, 2H), 2.81 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.5, 151.1, 131.8, 131.7, 129.6 (2C), 128.7, 128.4 (2C), 128.0, 125.9, 121.7 (2C), 86.5, 83.2, 65.3, 43.2, 31.0, 24.9 (2C).



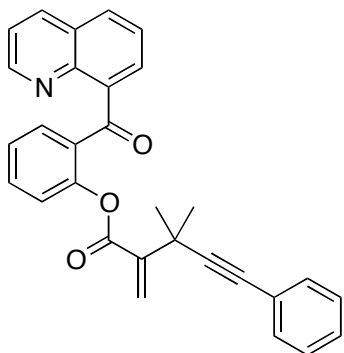
3,3-dimethyl-6-phenylhex-5-yn-2-one (3.33)

^1H NMR (400 MHz, CDCl_3) δ 7.39-7.37 (m, 2H), 7.29-7.27 (m, 3H), 2.61 (s, 2H), 2.23 (s, 3H), 1.29 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 212.5, 131.7, 128.7, 128.4, 128.0, 127.8, 123.7, 86.9, 83.1, 47.9, 42.2, 29.9, 24.3 (2C).



3,3-dimethyl-6-phenylhex-1-en-5-yn-2-yl trifluoromethanesulfonate (3.35)

^1H NMR (400 MHz, CDCl_3) δ 7.40-7.38 (m, 2H), 7.30-7.27 (m, 3H), 5.21 (d, $J = 7.0$ Hz, 1H), 5.08 (d, $J = 7.5$ Hz, 1H), 2.57 (s, 2H), 1.32 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 161.9, 131.8 (2C), 130.2, 128.4 (2C), 128.1, 101.9, 85.7, 84.2, 40.2, 30.9, 25.3 (2C).



2-(quinoline-8-carbonyl)phenyl 3,3-dimethyl-2-methylene-5-phenylpent-4-ynoate (3.38)

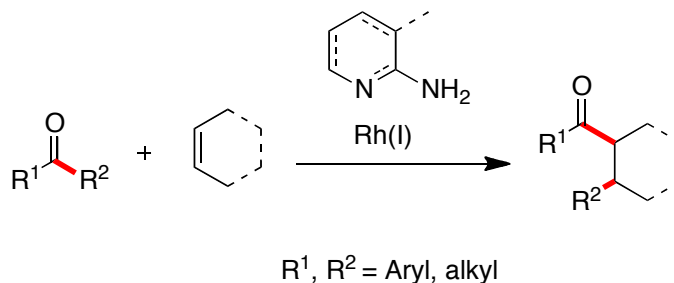
$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 8.83 (dd, $J = 4.2, 1.8$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.85 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.79 (ddd, $J = 7.4, 5.9, 1.5$ Hz, 2H), 7.57-7.50 (m, 2H), 7.40-7.34 (m, 3H), 7.33-7.29 (m, 2H), 7.27-7.25 (m, 3H), 7.10 (dd, $J = 8.1, 0.9$ Hz, 1H), 5.65 (s, 1H), 5.44 (s, 1H), 2.64 (s, 2H), 1.20 (s, 6H); $^{13}\text{C NMR}$ (75 MHz; CDCl_3): δ 195.7, 164.5, 151.0, 149.7, 146.0, 145.0, 139.9, 136.0, 133.4, 132.8, 131.7, 131.6 (2C), 130.6, 129.2, 128.35, 128.3 (2C), 127.7, 126.1, 125.9, 124.1, 123.7, 121.7, 88.1, 82.8, 38.5, 31.6, 27.0 (2C).

CHAPTER 4

4.1 Introduction

The final area of research to be discussed was carried out concurrently with the work discussed in Chapters 2 and 3. However, the work described herein is aimed at developing C–C sigma-bond activation methods that do not require an embedded chelating directing group. Instead, an organic co-catalyst will provide the required chelation for the metal to activate a particular C–C sigma-bond. The goal of this project is to create a more general method based on the reactivity lessons learned in Chapters 2 and 3. Jun and co-workers, as highlighted in Chapter 1, have laid a solid foundation for the use of organic co-catalysts to activate traditionally unreactive bonds. However, most of those examples activated C–H sigma-bonds or did not form more complex products. We hope to extend this work to exclusively activate C–C sigma-bonds and prepare useful products. Thus using ketones without embedded nitrogen directing groups, we hypothesized that condensation of an amine with an appropriately positioned nitrogen directing group could take place, which would facilitate C–C sigma-bond activation. The final product of the proposed C–C sigma-bond activation then would be a ketone as well, a useful synthetic handle when free of directing groups.

Scheme 1. Proposed C–C Sigma-Bond Activation with Organic Co-Catalyst

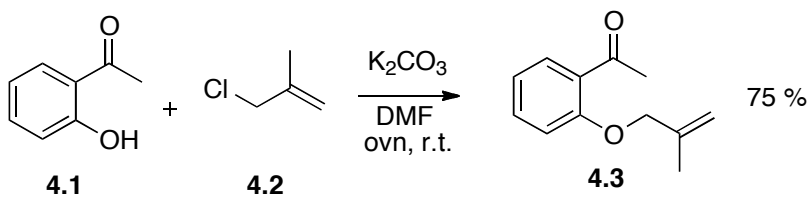


4.2 Results

An initial substrate synthesis for this work is shown in Scheme 2. The substitution reaction between the phenol **4.1** and 1-chloro-2-methylpropene (**4.2**) in DMF gave **4.3** in 75 % yield.⁸³

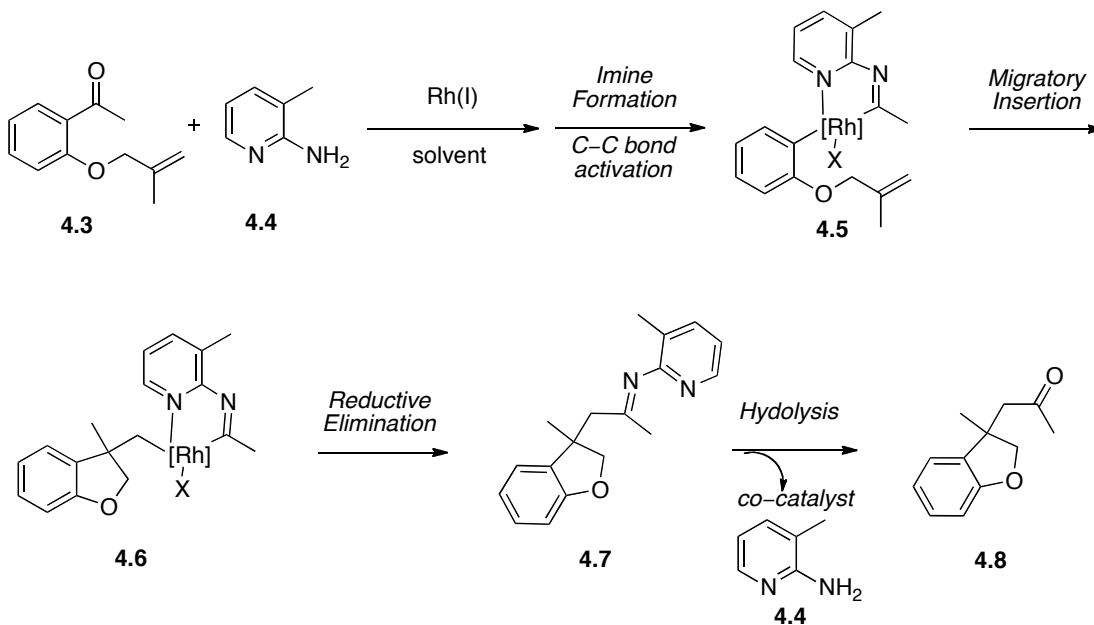
Scheme 2. Synthesis of Substrate for Amine Co–Catalyst C–C Sigma-bond

Activation



The substrate **4.3**, when subjected to the amine co-catalyst **4.4**, should undergo condensation to form the imine, which would be able to facilitate an oxidative addition of a Rh(I) catalyst to a carbon-carbon sigma-bond via chelation giving the 5-membered ring metallacycle **4.5** (Scheme 3). A Lewis acid or Bronsted acid could assist in the formation of the imine necessary for directed chelation. It was then hypothesized that a cyclization would occur via a migratory insertion (**4.6**) followed by reductive elimination giving the newly formed 5-membered ring **4.7**. The final ketone product **4.8** is formed after hydrolysis and regeneration of the amine co-catalyst **4.4**. The driving force for this reaction is the conversion of a C-C π bond to a C-C sigma-bond, an energetic gain of ~ 20 kcal/mol.⁸⁴

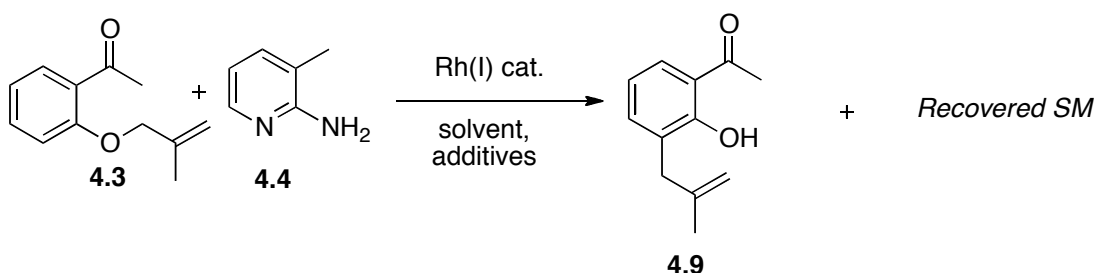
Scheme 3. Proposed Catalytic Cycle using Co-Catalyst 2-Amino-3-Picoline (**4.4**)



Due to the ease with which starting material **4.3** was synthesized, it was immediately used for preliminary C–C sigma-bond activation studies with the amine co-catalyst (**4.4**). Reactions were either done in the glove–box or with schlenk line techniques but none of the predicted product **4.8** was detected in crude product mixtures. A minor component of the crude reaction mixture was a product **4.9** resulting from Claisen rearrangement (Scheme 4)⁸⁵ that was also formed in the absence of a Rh(I) catalyst at the same temperature (150 °C) and reaction time (48 hr). Both the ethylene $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ dimer catalyst and Wilkinson’s catalyst, gave recovered starting material and the Claisen rearrangement product (**4.9**). Based on my reading of Jun’s publications involving organic co-catalysts we hypothesized that imine formation often was the slow step. Conditions were investigated with the intention of alleviating this difficulty.⁸⁶ Both Lewis acids⁸⁷ (AlCl_3 and TiCl_4) or protic acids⁸⁸ (benzoic acid, sulfuric acid, and Montmorillonite K10) were fruitlessly used as additives to facilitate imine formation and therefore carboacylation (**4.3**→**4.8**). Various solvents (THF, DCM, EtOH, and toluene) along with a number of Rh(I) catalysts ($[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$, $\text{RhCl}(\text{PPh}_3)_3$, $\text{Rh}(\text{cod})_2\text{BF}_4$, $\text{Rh}(\text{cod})_2\text{OTf}$) were screened as well to no avail. Jun and co-workers had previously used *n*-BuLi to deprotonate the co-catalyst and form an insoluble imine of **4.4**.⁸⁹ This was also attempted to form the imine with ketone **4.3**, but without success. Finally, transamination of **4.4** with various amines (benzylamine, cyclohexylamine, and hexylamine) and **4.3** was tried similar to numerous variations reported by Jun in

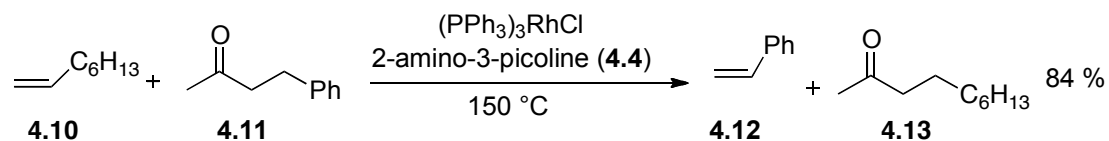
related work.⁹⁰ These experiments also did not yield **4.8**, despite also investigating benzoic acid as an additive. Since the initial substrate (**4.3**) did not lead to the predicted product under a number of reaction conditions and additives similar to Jun's work, a reproduction of the previously published work was done.

Scheme 4. Reaction Screening



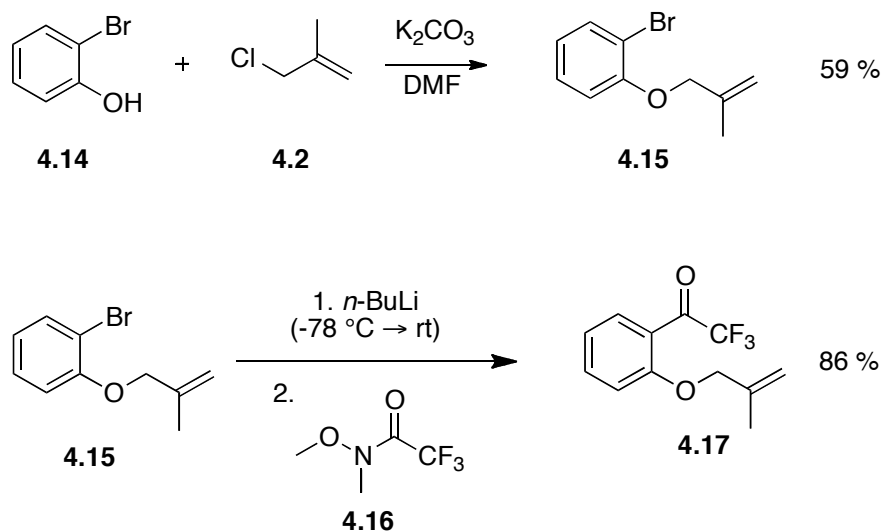
The next step in this project focused on the reproduction of Jun's chemistry (Scheme 5).⁸⁹ 1-Octene (**4.10**), benzylacetone (**4.11**), and 2-amino-3-picoline (**4.4**) were premixed in dry toluene in a glove-box before the addition of rhodium catalyst for 20 minutes at room temperature then Wilkinson's catalyst was added. The resulting mixture was heated at 150 °C for 48 hours affording the product ketone (**4.13**). The premixing was key to the transformation: presumably this step allows for the formation of imine with the ketone (**4.11**) and amine (**4.4**) and was done with our substrates as well. Confident in the reproducibility of Jun's previous C–C sigma-bond activation work with an amine co-catalyst, a new series of substrates was investigated.

Scheme 5. Reproduced Work of Jun and coworkers



Since it is believed that the key step to the C–C sigma-bond activation with co-catalysts such as **4.4** is imine formation, we set out to facilitate its formation by creating a more reactive trifluoroketone. The synthesis of such a substrate is shown in Scheme 6. Phenol **4.14** in the presence of base undergoes a substitution reaction with the 1-chloro-2-methylpropene (**4.2**) in good yield (54%) to give the ether **4.15**. Compound **4.15** then undergoes a lithium-halogen exchange with *n*-BuLi followed by treatment with the Weinreb amide **4.16** to give ketone **4.17**.

Scheme 6. Synthesis of Trifluoroketone **4.17**

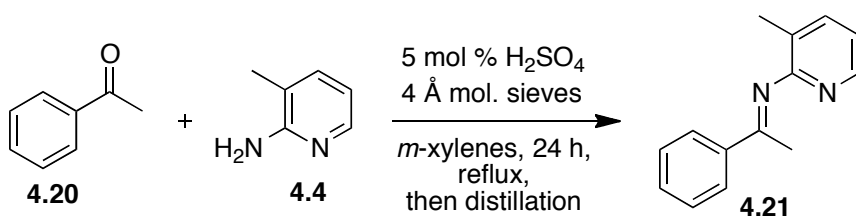


With the trifluoroketone **4.17** being presumably more electrophilic and therefore more likely to form the necessary imine for C–C sigma-bond activation, it was believed that it might be more amenable to carboacylation discussed in Scheme 3. However, before a full screening of catalyst conditions was undertaken, the propensity of **4.17** to form imines with **4.4** was investigated (Scheme 7).

Trifluoroketone **4.17** was heated in d_8 -toluene with amine **4.4** in a J. Young NMR tube. A substantial amount of imine (**4.18**) was observed by ^1H NMR analysis from the terminal alkene protons and methylene shift presumably after imine formation.

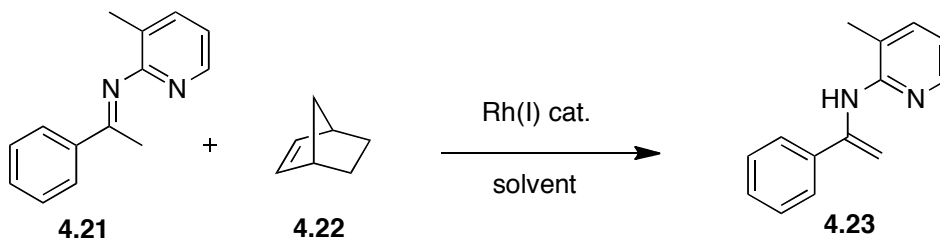
Using acetophenone (**4.20**) with catalytic sulfuric acid and 4 Å molecular sieves in *m*-xylenes at reflux for 24 hours, gave the imine (**4.21**) from amine **4.4** after distillation (Scheme 9).⁹¹

Scheme 9. Independent Imine formation with **4.20**



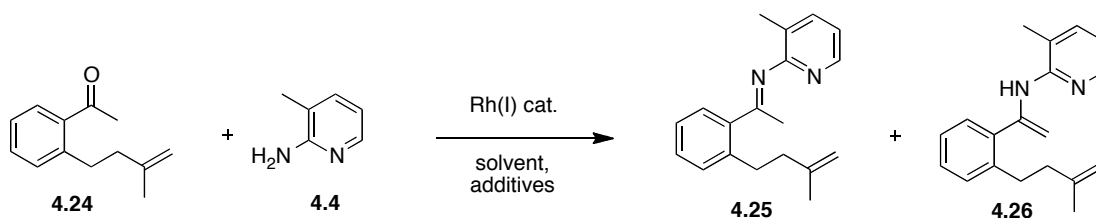
Imine **4.21** was subjected to a number of Rh(I) catalysts, solvents, and mono-dentate phosphine ligands (Scheme 10). Regrettably, none of the Rh(I) catalysts ([RhCl(C₂H₄)₂]₂, RhCl(PPh₃)₃, Rh(cod)₂BF₄, and Rh(cod)₂OTf) examined in two solvents (toluene and THF at temperatures of 130 or 100 °C respectively) gave any intermolecular carboacylation products with norbornene (**4.22**) instead the enamine **4.23** was formed with starting imine **4.21**. Further investigation was done with Wilkinson's catalyst in numerous solvents (DCM, DCE, Acetonitrile, DMF, Trifluorotoluene) to no avail. Finally, attempted reaction of **4.21** and **4.22** with [RhCl(C₂H₄)₂]₂ in THF at 100 °C with mono-dentate phosphine ligands (ie [1,1'-biphenyl]-2-yl-di-*tert*-butylphosphine) also did not give any positive results.

Scheme 10. Reaction Screening with Imine **4.21**



Taking our previous work and the prediction of the rate-determining step being imine formation by Jun in his previous work, a new substrate was tested (Scheme 11). Ketone **4.24** was predicted to be ideal as it could not undergo an intramolecular Claisen rearrangement at high temperatures (Scheme 4), which we had found to be necessary to form imine (Scheme 9). Also the alkene was present within a the starting material for a presumably more facile intramolecular reaction. However, attempted reactions of ketone **4.24** and the co-catalyst **4.4** with rhodium precatalysts did not lead to the predicted cyclic product. Again a series of Rh(I) catalysts ($[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$, $\text{RhCl}(\text{PPh}_3)_3$, $\text{Rh}(\text{cod})_2\text{BF}_4$, and $\text{Rh}(\text{cod})_2\text{OTf}$) with two solvents toluene and THF at temperatures of 130 or 100 °C respectively along with additives aniline and benzoic acid were investigated. These attempts gave a crude mixture with possibly the imine **4.25** or the enamine **4.26** by ^1H NMR from the terminal alkene protons from enamine as well and methyl shift presumably after imine formation, however more work is needed to elucidate the presence of **4.25** or **4.26**.

Scheme 11. Reaction Screening with Alkyl Tethered Alkene



Having had great difficulty with progress using co-catalyst **4.4**, our attention turned to alternative amine co-catalysts (Figure 1). The proline-based amine **4.27** had been used as an efficient organocatalyst previously and was synthesized according to literature precedent.⁹² Other electron rich amines (**4.28**, **4.29**, and **4.30**) were thought to be more nucleophilic than amine **4.4**, but preliminary experiments with amines **4.27-4.30** have not given any promising results with the ether **4.3**. On the contrary, the electron rich amine **4.31** has shown some promising reactivity towards C–C sigma-bond activation.

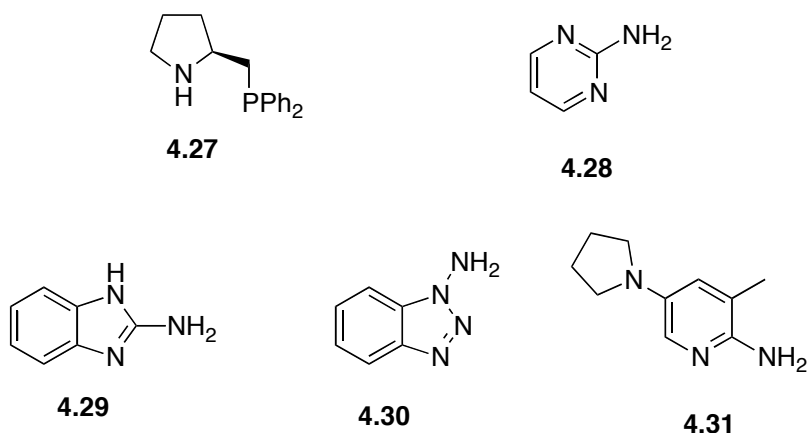
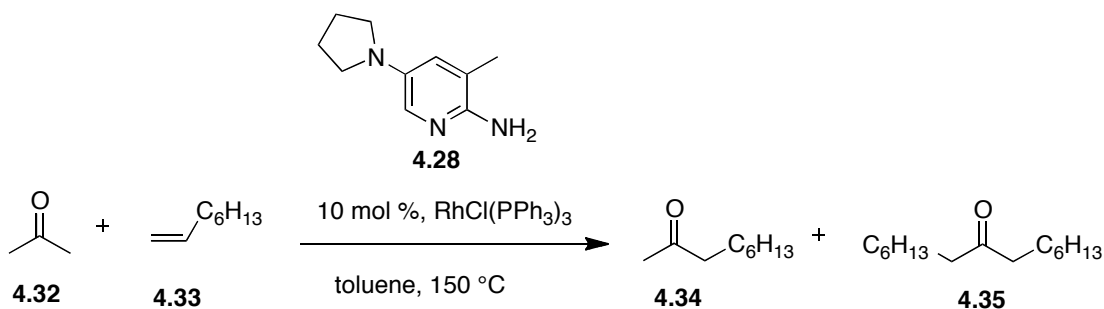


Figure 1. Alternative Amine Co-Catalysts

The more electron rich amino-pyridine **4.31**, which was synthesized in analogy to a known two-step procedure⁹³, was utilized with Jun's previously reported procedure (Scheme 5) and small amount of a double insertion product (**4.35**) was formed. Dr. Sudheer Chava discovered this initial result and also expanded the chemistry to alkyl exchange reactions of acetone (**4.32**) (Scheme 12). To date, it is possible to form both products **4.34** and **4.35** with octene in toluene with Wilkinson's catalyst, but no optimization work has been done to elucidate reaction conditions to control product formation. Also the loss of the methyl groups from acetone (**4.32**) occurs, but we do not see these methyl groups in isolated products. To aid in the future optimization of this reaction with acetone, two standard curves were developed for both products (**4.34** and **4.35**) using GC/MS to allow for rapid product analysis with numerous conditions.

Scheme 12. C–C Sigma-Bond Activation with an Electron Rich Amine

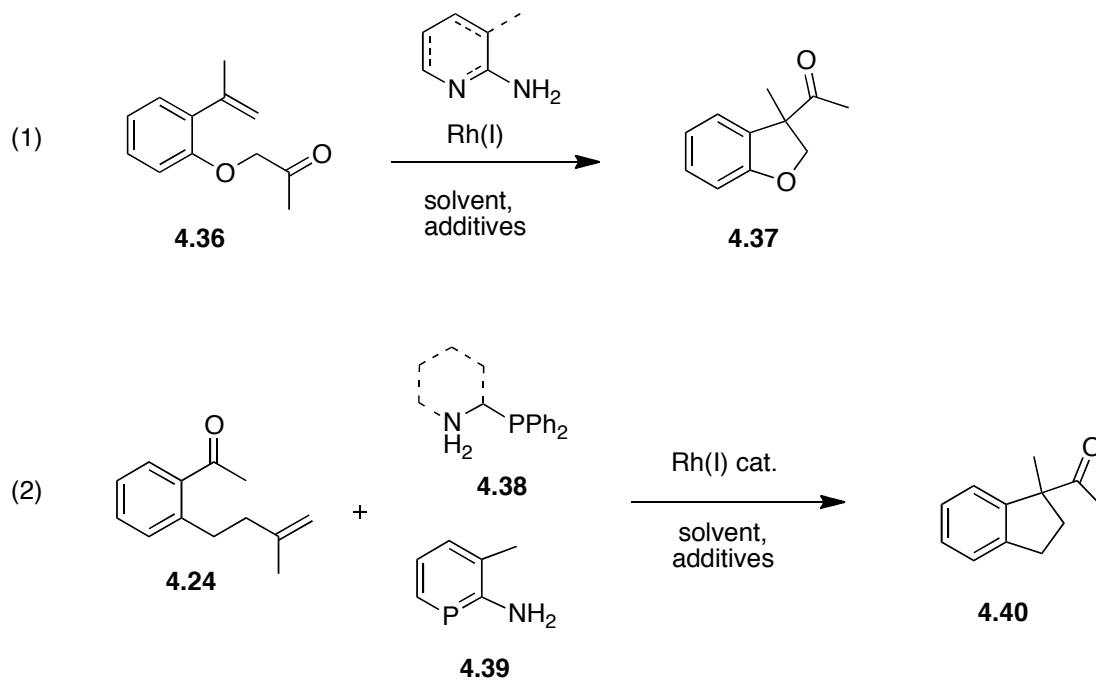


4.3 Conclusion and Future Work

In conclusion, using amine co-catalysts to direct metals toward C–C sigma-bond activation can be a powerful tool in future method development. However, a great deal of optimization is currently needed to overcome challenges associated with the process. Imine formation is currently seen as the hindrance for subsequent activation. With that in mind, the ketone **4.24** (Scheme 11) should be screened more thoroughly with various conditions including with the more reactive co-catalyst **4.28**.

Two final approaches are to design a different substrate for activation or use a different co-catalyst (Scheme 13). Substrate **4.36** should have a more reactive ketone prone to imine formation than aryl ketone. It avoids a Claisen rearrangement (Eq. 1) forming **4.37** as well making it a reasonable substrate to investigate. The final approach would be to examine different co-catalysts (**4.38** and **4.39**) that could coordinate to a metal via a phosphine and help direct C–C sigma-bond activation to cyclic products (**4.40**).

Scheme 13. Future Work



4.4 Experimental Details

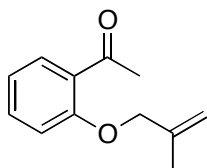
General experimental details: All reactions were carried out using flame-dried glassware under a nitrogen or argon atmosphere unless aqueous solutions were employed as reagents or dimethyl formamide was used as a solvent. Tetrahydrofuran (THF) and toluene (PhMe) were dried according to published procedures.⁹ Trifluorotoluene, acetonitrile, and 1,2-dichloroethane were distilled prior to use. Toluene was further degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glove box. All rhodium complexes were purchased from Strem and used as received. IBX was prepared according to Santagostino.¹⁰ All other chemicals were purchased from Acros Organics or Sigma-Aldrich and used as received. All rhodium-catalyzed processes were carried out in a Vacuum Atmospheres nitrogen filled glove box in 1 dram vials with PTFE lined caps and heating was applied by aluminum block heaters.

Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates from E. Merck. Eluted plates were visualized first with UV light and then by staining with ceric sulfate/molybdic acid or potassium permanganate/potassium carbonate. Flash chromatography was performed using 230–400 mesh (particle size 0.04–0.063 mm) silica gel purchased from Merck unless otherwise indicated. ¹H NMR (300, 400, and 500 MHz) and ¹³C NMR (75 and 125 MHz) spectra were obtained on Varian FT NMR instruments. NMR spectra were reported as δ values in

⁹ A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers *Organometallics*, **1996**, *15*, 1518.

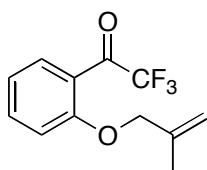
¹⁰ M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.

ppm relative to chloroform or tetramethylsilane. ^1H NMR coupling constants are reported in Hz; multiplicity was indicated as follows; s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained as films from CH_2Cl_2 or CDCl_3 . Low-resolution mass spectra (LRMS) in EI or CI experiments were performed on a Varian Saturn 2200 GC-MS system, and LRMS and high-resolution mass spectra (HRMS) in electrospray (ESI) experiments were performed on a Bruker BioTOF II.



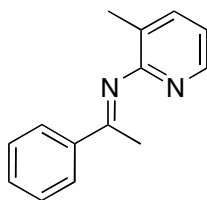
1-(2-((2-methylallyl)oxy)phenyl)ethanone (4.3)

^1H -NMR (300 MHz; CDCl_3): δ 7.73 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.41 (ddd, $J = 8.4, 7.3, 1.9$ Hz, 1H), 6.96 (ddd, $J = 15.1, 7.6, 0.9$ Hz, 2H), 5.11-5.01 (m, 2H), 4.51 (s, 2H), 2.64 (s, 3H), 1.85 (s, $J = 0.5$ Hz, 3H). ^{13}C NMR (75 MHz; CDCl_3): δ 199.7, 158.0, 140.1, 133.5, 130.3, 128.4, 120.6, 113.5, 112.6, 77.6, 77.2, 76.7, 72.3, 31.9, 19.6.



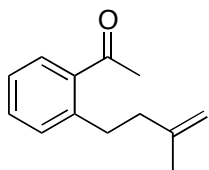
2,2,2-trifluoro-1-(2-((2-methylallyl)oxy)phenyl)ethanone (4.17)

¹H-NMR (300 MHz; CDCl₃): δ 7.57-7.54 (m, 1H), 7.19-7.13 (m, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 44.8 Hz, 2H), 4.10 (s, 2H), 1.74 (s, 3H).



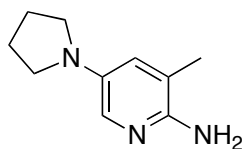
(*E*)-3-methyl-*N*-(1-phenylethylidene)pyridin-2-amine (4.21)

¹H-NMR (400 MHz; CDCl₃): δ 8.29 (d, *J* = 4.8 Hz, 1H), 8.04 (dt, *J* = 6.2, 1.8 Hz, 2H), 7.51-7.42 (m, 6H), 6.96 (dd, *J* = 7.4, 4.9 Hz, 1H), 2.23 (s, 3H), 2.13 (s, 3H).



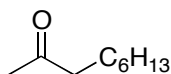
1-(2-(3-methylbut-3-en-1-yl)phenyl)ethanone (4.24)

$^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 7.65 (d, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 7.1$ Hz, 1H), 7.28-7.27 (m, 2H), 4.72 (d, $J = 15.0$ Hz, 2H), 2.99 (t, $J = 8.1$ Hz, 2H), 2.59 (s, 3H), 2.27 (t, $J = 8.1$ Hz, 2H), 1.79 (s, 3H).



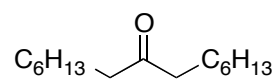
3-methyl-5-(pyrrolidin-1-yl)pyridin-2-amine (4.31)

$^1\text{H-NMR}$ (300 MHz; CDCl_3): δ 7.39 (d, $J = 2.7$ Hz, 1H), 6.72 (d, $J = 3$ Hz, 1H), 3.92 (s, 1H), 3.22-3.18 (m, 4H), 2.14 (s, 3H), 2.00-1.96 (m, 4H).



decan-2-one (4.34)

$^1\text{H-NMR}$ (400 MHz; CDCl_3): δ 2.42 (t, $J = 7.5$ Hz, 2H), 2.13 (s, 3H), 1.57 (t, $J = 7.0$ Hz, 2H), 1.27 (t, $J = 2.4$ Hz, 10H), 0.88 (t, $J = 6.9$ Hz, 3H).



heptadecan-9-one (4.35)

$^1\text{H-NMR}$ (500 MHz; CDCl_3): δ 2.38 (t, $J = 7.5$ Hz, 4H), 1.56 (t, $J = 7.3$ Hz, 4H),

1.31-1.25 (m, 24H), 0.88 (dd, $J = 8.8, 5.2$ Hz, 6H).

¹ (a) Jun, C.-H.; Lee, J. H. Application of C-H and C-C bond activation in organic synthesis. *Pure Appl. Chem.* **2004**, *76*, 577–587. (b) Park, Y. J.; Park, J.-W.; Jun, C.-H., Metal-Organic Cooperative Catalysis in C–H and C–C Bond Activation and Its Concurrent Recovery. *Accounts Chem Res* **2008**, *41*, 222–234. (c) Rybtchinski, B.; Milstein, D., Metal insertion into C-C bonds in solution. *Angew. Chem. Int. Edit.* **1999**, *38*, 870–883. (d) Jun, C.-H., Transition metal-catalyzed carbon-carbon bond activation. *Chemical Society Reviews* **2004**, *33*, 610–618.

² Daugulis, O.; Brookhart, M., Decarbonylation of Aryl Ketones Mediated by Bulky Cyclopentadienylrhodium Bis(ethylene) Complexes. *Organometallics* **2003**, *23*, 527–534.

³ Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S., Ruthenium-Catalyzed Regioselective 1,3-Methylene Transfer by Cleavage of Two Adjacent σ -Carbon–Carbon Bonds: An Easy and Selective Synthesis of Highly Substituted Benzenes. *J. Am. Chem. Soc.* **2005**, *127*, 4186–4187.

⁴ (a) Murakami, M.; Ashida, S.; Matsuda, T., Nickel-Catalyzed Intermolecular Alkyne Insertion into Cyclobutanones. *J. Am. Chem. Soc.* **2005**, *127*, 6932–6933. (b) Kurahashi, T.; de Meijere, A., C–C Bond Activation by Octacarbonyldicobalt: [3+1] Cocyclusations of Methylene cyclopropanes with Carbon Monoxide. *Angew. Chem. Int. Edit.* **2005**, *44*, 7881–7884. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A., Heterocycles from Alkylidenecyclopropanes. *Chem. Rev.* **2003**, *103*, 1213–1270. (d) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S., Palladium-Catalyzed Asymmetric Arylation, Vinylation, and Allenylation of *tert*-Cyclobutanols via Enantioselective C–C Bond Cleavage. *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869. (e) Murakami, M.; Amii, H.; Ito, Y. Selective activation of carbon-carbon bonds next to a carbonyl group. *Nature* **1994**, *370*, 540–541.

⁵ (a) Nakao, Y.; Yada, A.; Ebata, S. Hiyama, T. A. Dramatic Effect of Lewis-Acid Catalysts on Nickel-Catalyzed Carbocyanation of Alkynes *J. Am. Chem. Soc.* **2007**, *129*, 2428–2429. (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. Palladium-Catalyzed Intramolecular Cyanoamidation of Alkynyl and Alkenyl Cyanoforamides *Org. Lett.* **2006**, *8*, 2711–2713. (c) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. Palladium-Catalyzed Cyanoesterification of Norbornenes with Cyanoforamates via the NC–Pd–COOR (R = Me and Et) Intermediate *Org. Lett.* **2005**, *7*, 2639–2641. (d) Nakazawa, H.; Kamata, K.; Itazaki, M. Catalytic C–C bond cleavage and C–Si bond formation in the reaction of RCN with Et₃SiH promoted by an iron complex *Chem. Commun.* **2005**, 4004–4006.

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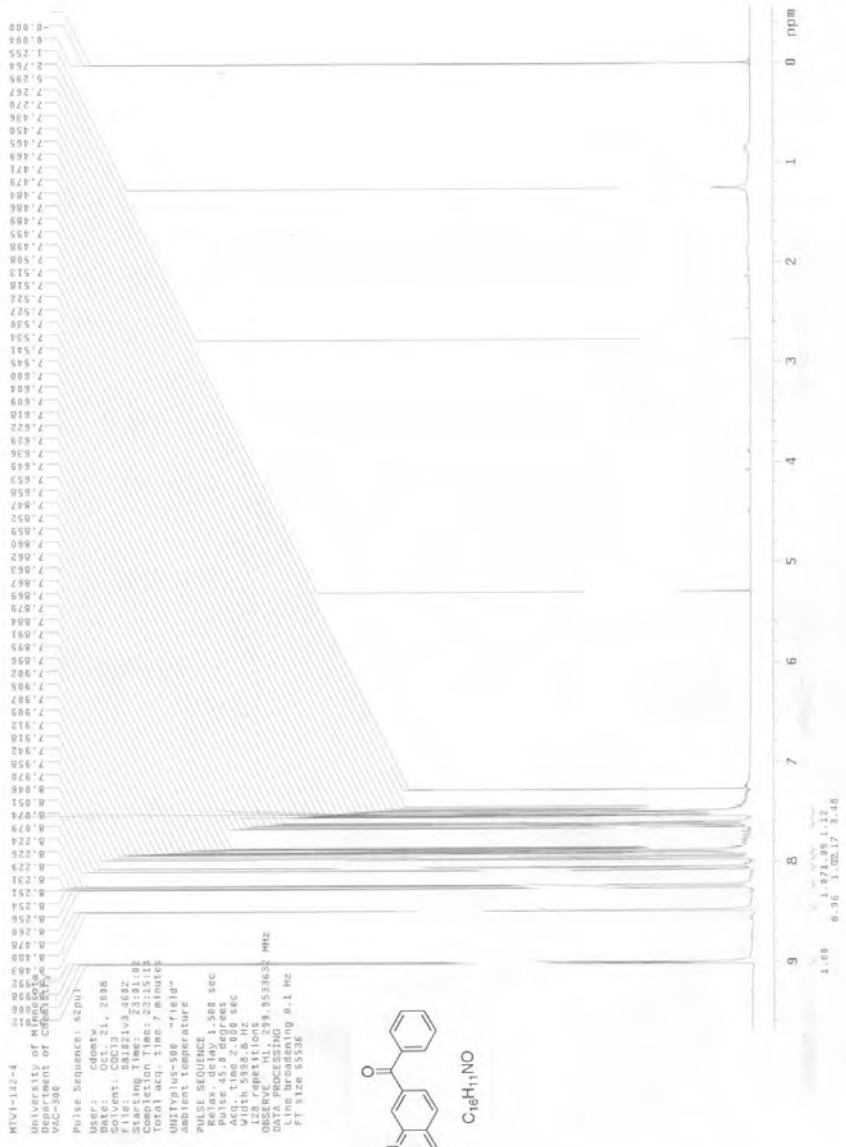
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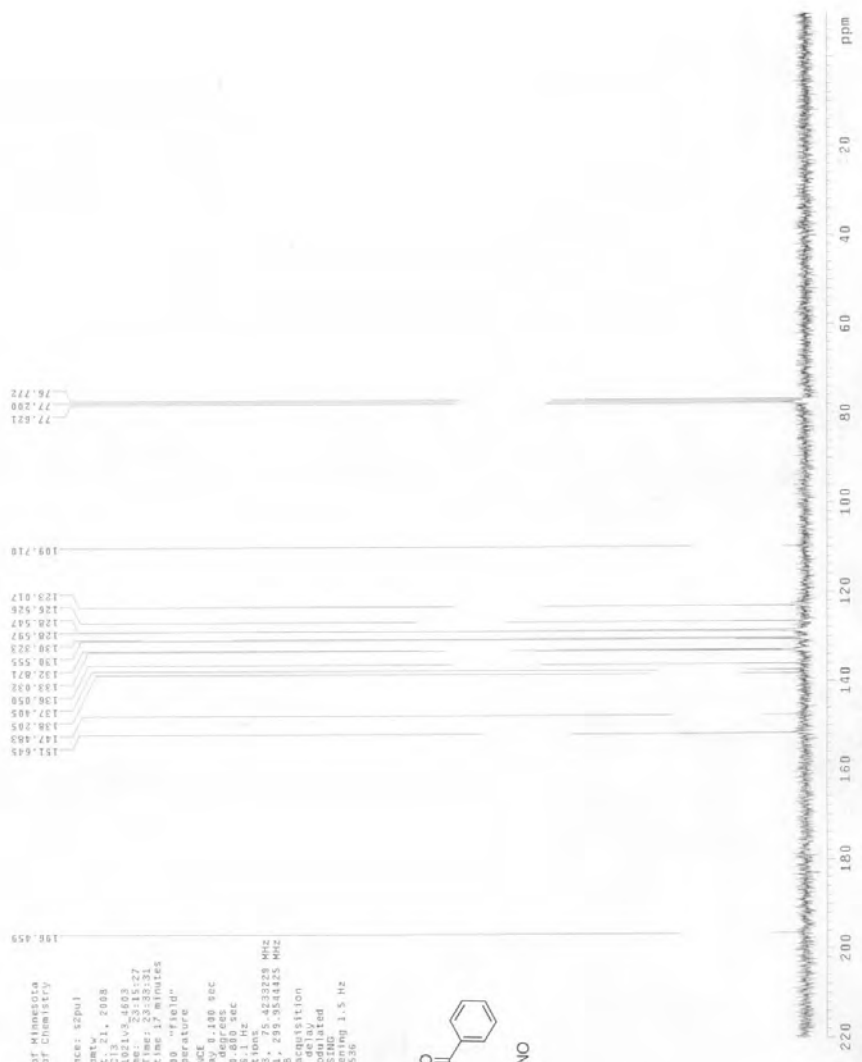
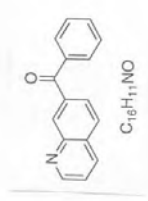
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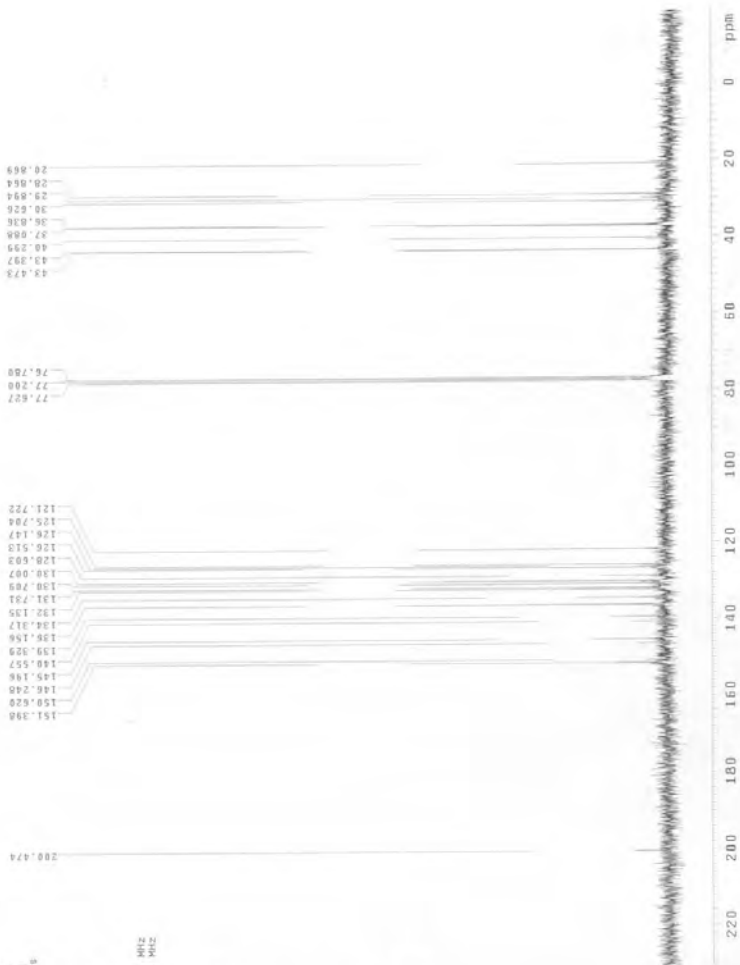
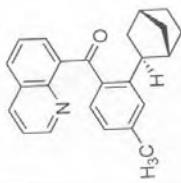


MTHJ-122-4
 University of Minnesota
 Department of Chemistry
 VAC-308
 Pulse sequence: zgpg30
 User: csmc
 Date: Oct. 21, 2008
 Solvent: CDCl3
 Starting Time: 23:15:27
 Completion Time: 23:28:31
 Lock: 198.455 Hz, 1.000 minutes
 Ambient temperature: 100.000 °F
 PULSE SEQUENCE
 relax - delay 0.100 sec
 acq - time 0.500 sec
 width 1.7346 J Hz
 DECOUPLE - H1 - 299.9544425 MHz
 OBSERVE - C13 - 75.4233228 MHz
 on during acquisition
 off during delay
 data: 80000000
 Line broadening 1.5 Hz
 FT size 65536



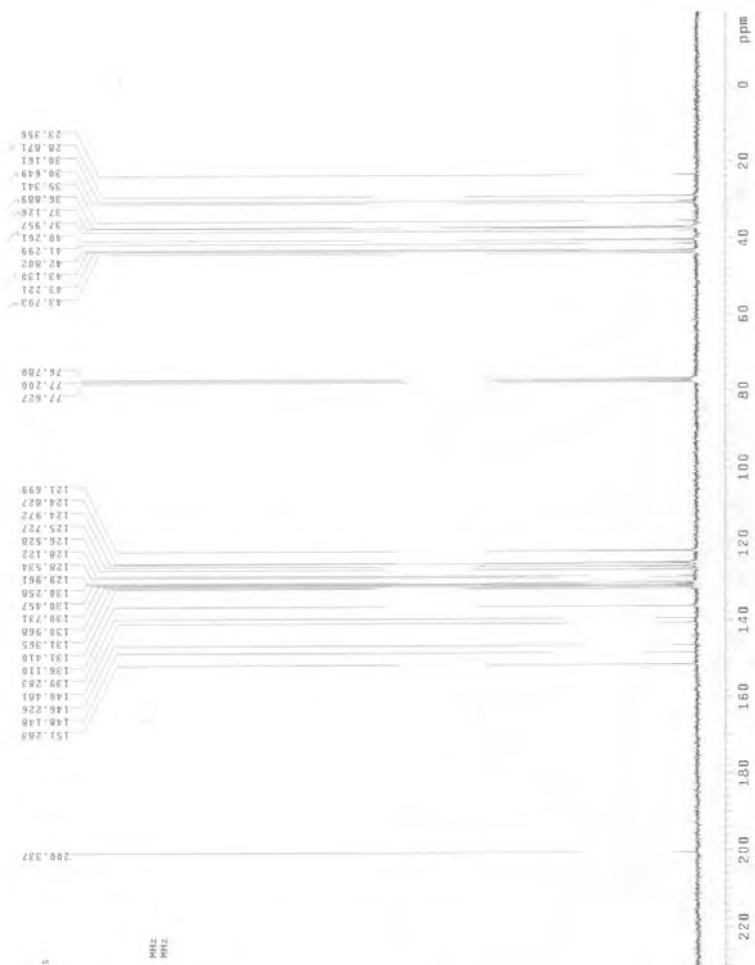
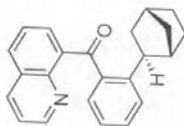
University of Minnesota
Department of Chemistry
VI-388

Pulse Sequence: szpu1
User: cdoakv
Date: 11/11/2009
Solvent: CDCl3
File: Thc-21-3
Completion Time: 11:03:13
Total acq. time 45 minutes
UNITplus-580 "field"
ambient temperature
PULSE PROGRAM: zgpg30
PULSE SEQUENCE: zgpg30, 180 sec
pulse 67.5 degrees
width 11.860 sec
width 11.860 sec
376 repetitions
OBSERVE CH: 13
F2: 101.6254000 MHz
Power 36.00 dB
on during acquisition
WALTZ-16
DATA PROCESSING
SOLVENT: CDCl3 1.5 Hz
FT 5120 45536



University of Minnesota
Department of Chemistry
42-348

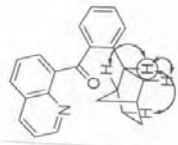
Pulse Sequencer: zgpu
Date: 08/14/2009
Operator: JMB
Solvent: CDCl₃
S1: 100 MHz
S2: 100 MHz
S3: 100 MHz
Completion Time: 11:04:13
Total Acq. Time: 52 minutes
Pulse Program: zgpg30
Pulse Sequence:
Relax: delay 0.100 sec
Pulse 67.5 degrees
Width 12.000 usec
Power 0.00 dB
SFO 100.628125 MHz
1320 repetitions
DECOUPLE: H1, 300.1328468 MHz
SFO 300.1328468 MHz
SFO 100.628125 MHz
WALTZ-16 modulation
OFF during delay
SFO 100.628125 MHz
Line broadening 1.5 Hz
FT 5126 85336



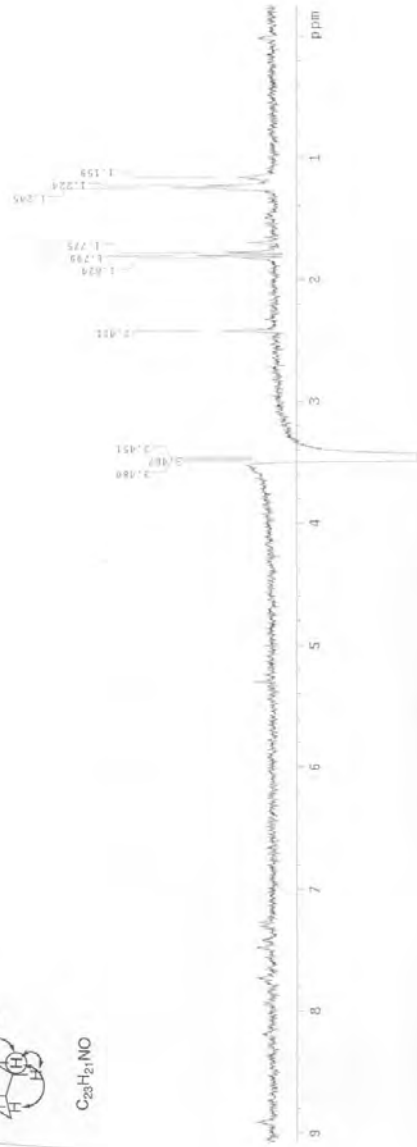
Univ of Minnesota, VI-563

Pulse Sequence: gpcsy

Date: DCI, EA, 2008
Starting Time: 13:21:38
Completion Time: 13:22:48
User: wcl - 50ms 4 scans
Ambient Temperature:
PULSE SEQUENCE: gpcsy
Relax, delay 9.000 sec
1st pulse 91.22 degrees
2nd pulse 91.22 degrees
MIXING 8.530 sec
Acq Time: 0.2 sec
Width 880.0 Hz
3 repetitions
DATA ACQUISITION
DATA PROCESSING
Line broadening 1.0 Hz
FT Size 131072

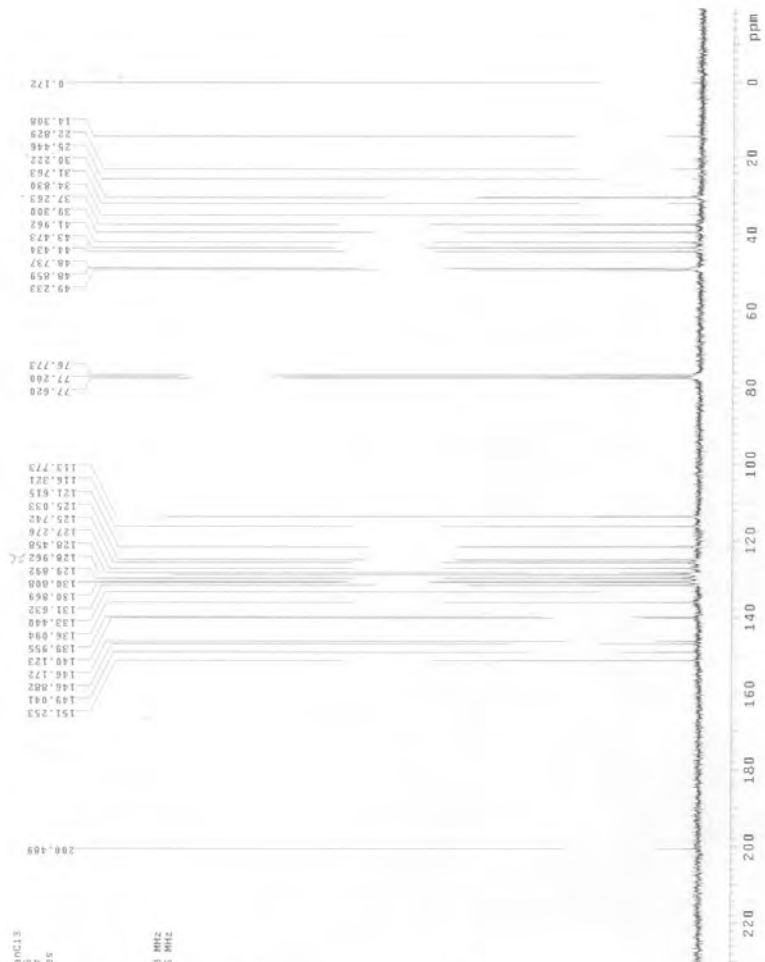
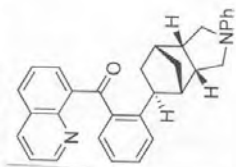


C₂₃H₂₁NO

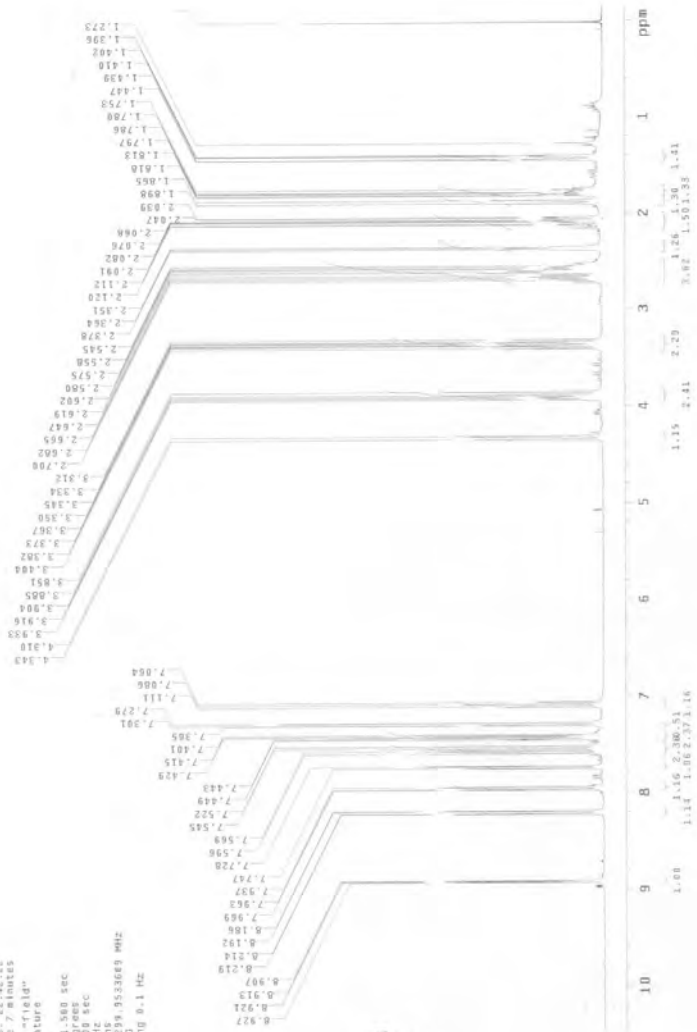
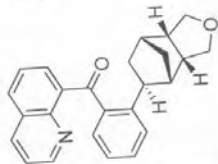


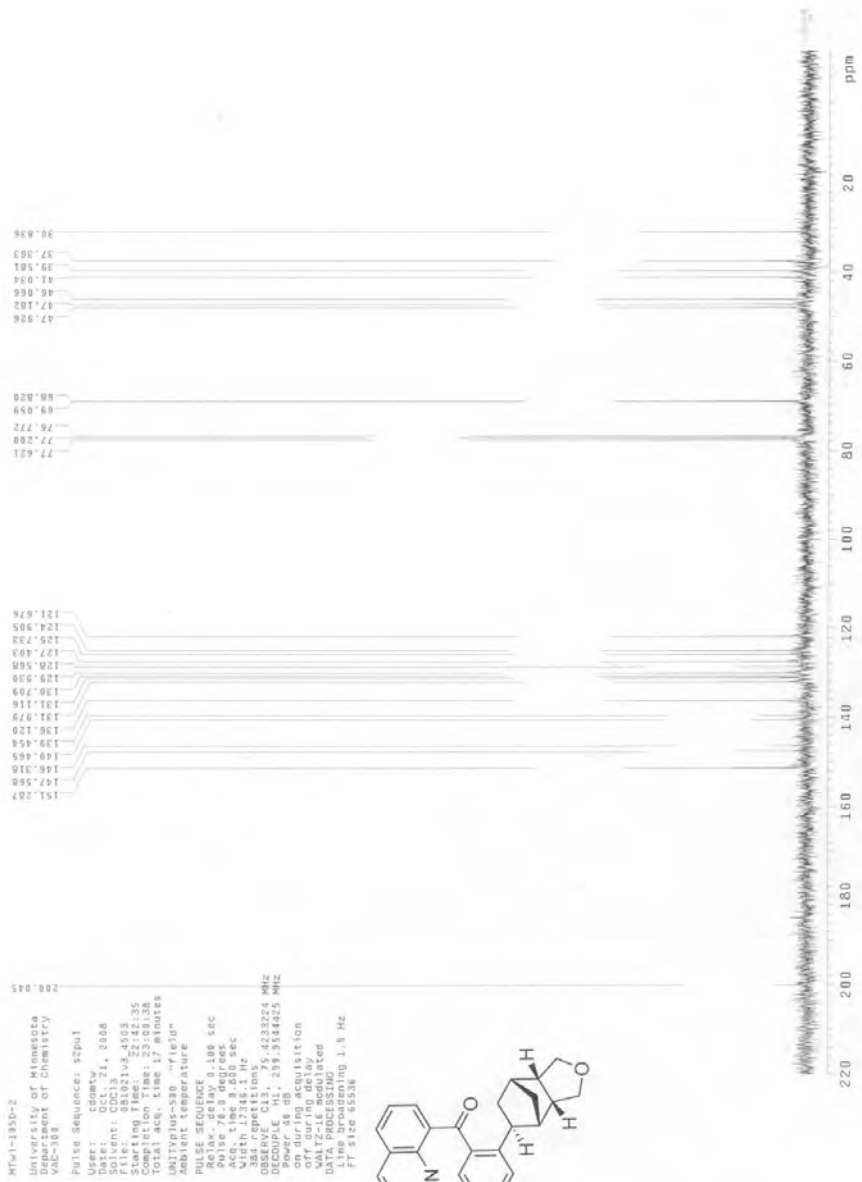
University of Minnesota
Department of Chemistry
VI-388

Pulse Sequence: szpul
User: ceantw
Date: 9/19/2009
Solvent: CDCl3
File: MW-C-H-1hiclep013
Run Time: 11:28:12
Completion Time: 11:28:52
Total acq. time: 9.5 minutes
UNIT value: 0.00 "field"
ambient temperature
P1: 0.00 sec
P2: 0.00 sec
P3: 0.100 sec
Pulse 67.5 degrees
Acq: 180.0 sec
Acq: 180.0 sec
2000 repetitions
DECOR: CL3, 75.47372 MHz
Pulse 38 dB, 30.000000 sec
on during acquisition
WALTZ-16 modulation
DATA PROCESSING
SOLVENT: CDCl3
FT size: 85536



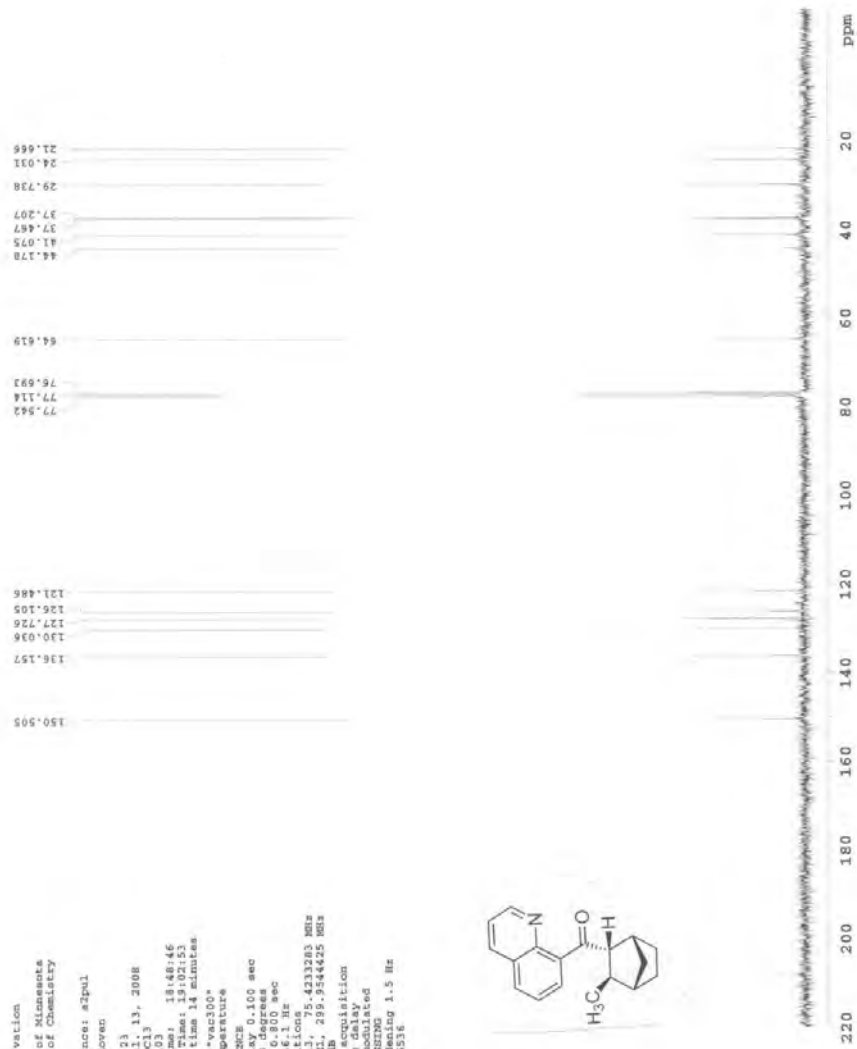
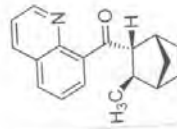
MT-1-183D-C
 University of Minnesota
 Department of Chemistry
 VAC-308
 Pulse sequence: zgpg30
 Date: Dec 21, 2006
 User: cdmw
 Solvent: CDCl3
 Starting Time: 22:27:49
 Completion Time: 22:28:22
 Total Acq Time: 0:44:55
 Lock: None
 Ambient Temperature: 30
 PULSE SEQUENCE
 Relax delay: 1.500 sec
 Acq: 128000
 Width: 5384.6 Hz
 Acq Time: 2.000 sec
 OBSERVE: 1
 OBSERVE F1: 279.5130669 MHz
 DATA PROCESSING
 F1: 279.5130669 MHz
 F2: 125.7615350 MHz





jar oc activation
University of Minnesota
Department of Chemistry
VAC-300

Pulse Sequence: sfpul
User: cdoven
Sample: 1
Scan rate: 23
Date: Jul. 13, 2008
Solvent: CDCl3
Starting Time: 13:48:46
Completion Time: 13:02:53
Total acq. time 14 minutes
UNIT-300 -vac300
SOLVENT: CDCl3
PROC. SEQUENCE
PULSE SEQUENCE
Relax. delay 0.100 sec
Pulse 70.0 degrees
Acq. time 0.100 sec
Mach 17346.1 Hz
300 repetitions
OBSERVE CH1, 75.4233203 MHz
Power 40 dB, 239.5344425 RMS
on during acquisition
off during delay
Mach 17346.1 Hz
DATA PROCESSING
Line broadening 1.5 Hz
Ft size 65536



jar on activation
University of Minnesota
Department of Chemistry
VAC-308

Pulse Sequence: dept

User: cdoven

Sample: 24

Date: Jul 13, 2008

Solvent: CDCl3

Starting Time: 19:03:04

Completion Time: 19:22:10

Total acq. time 31 minutes

UNIT: 300 -ves300-

Acquire temp: 300.2 K

Relax delay: 2.000 sec

Pulse 90.0 degrees

Acq. time 0.800 sec

200 repetitions

OSERVE: C13, 75.4233283 MHz

Power: 40 dB, 299.954425 MHz

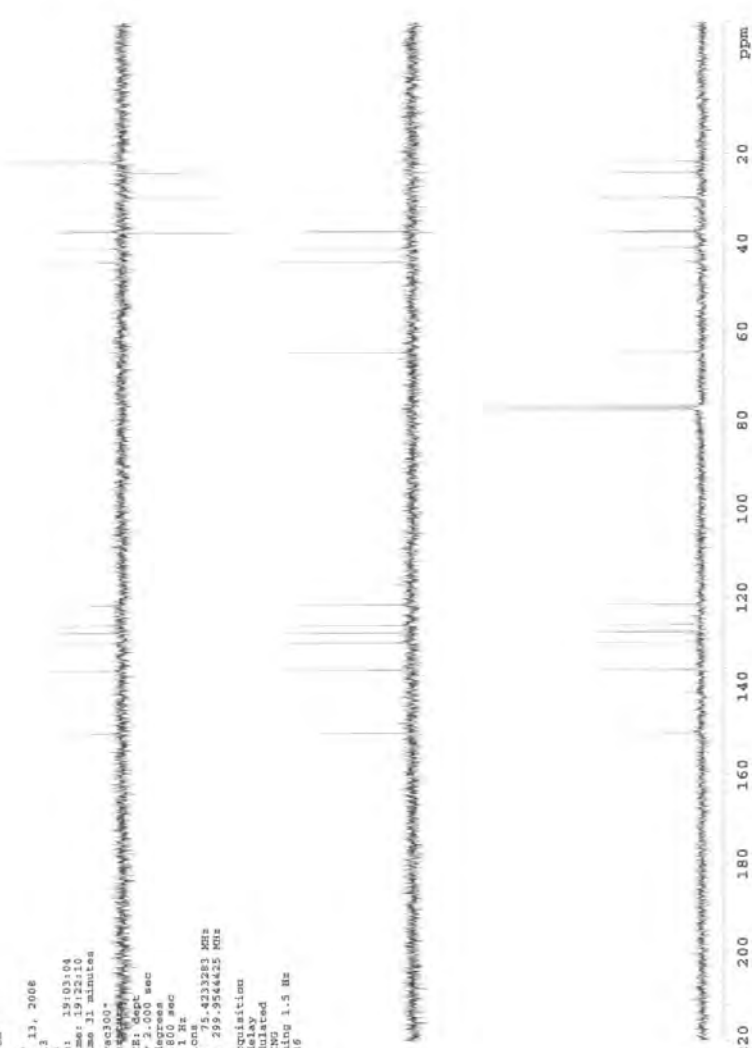
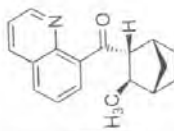
on during acquisition

off during delay

DATA PROCESSING

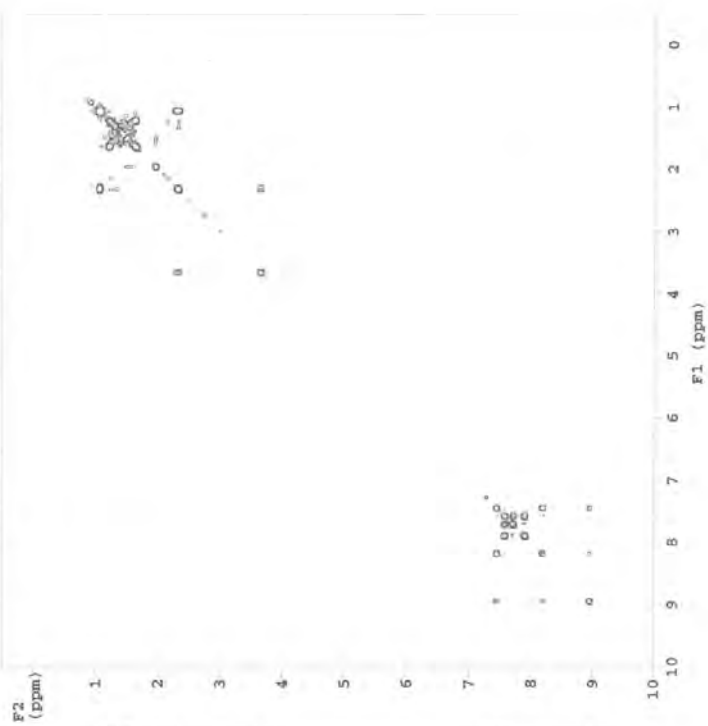
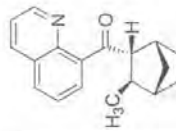
Line broadening 1.5 Hz

FT size 65536



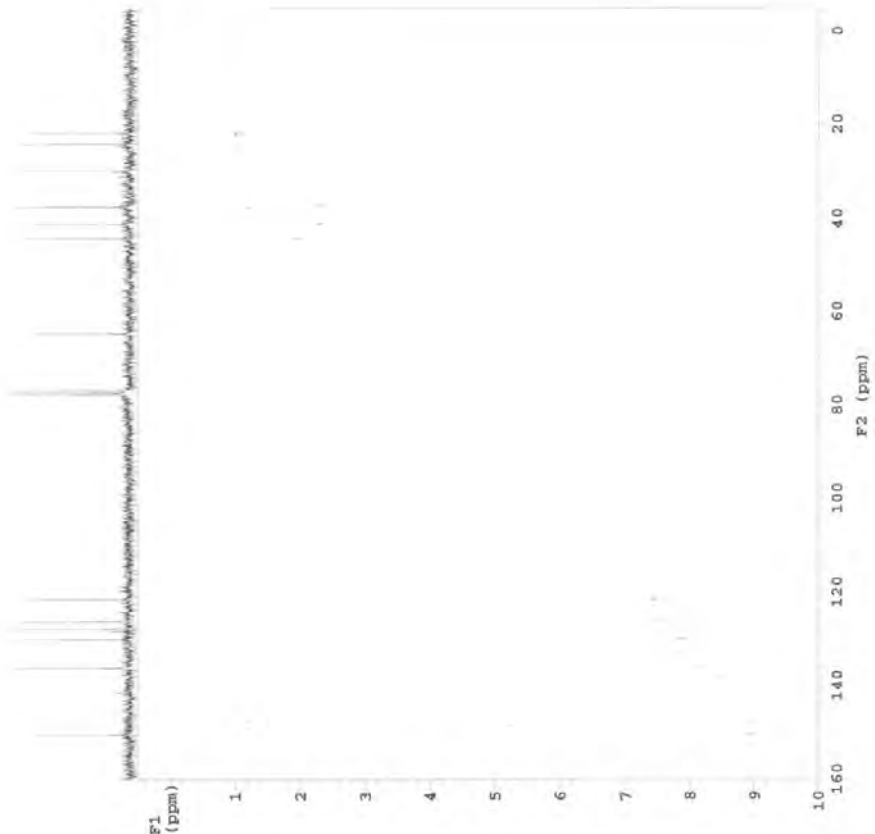
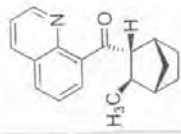
jmc cc activation
University of Minnesota
Department of Chemistry
VAC-300

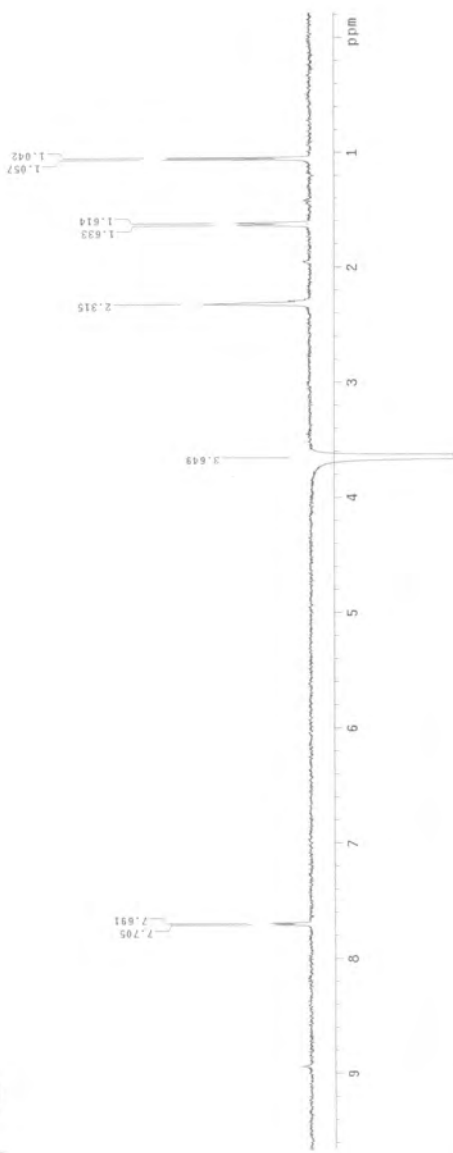
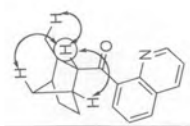
Pulse Sequence: relayh
User: cdovent
Spin rate: 23
Date: Jul. 13. 2008
F1 solvent: DMSO
F2 solvent: DMSO
Starting Time: 19:23:23
Completion Time: 19:42:39
Total acq. time 20 minutes
Ambient temperature
PULSE SEQUENCE: relayh
Relax. delay 1.337 sec
CORY 90-45
Acq. time 163 sec
Width 3149.6 Hz
2D Width 3149.6 Hz
4 repetitions
OBSERVE F1: 299.933609 MHz
DATA PROCESSING
Sine bell 0.030 sec
SI DATA PROCESSING
Sine bell 0.030 sec
FT size 1024 x 1024



jar on activation
 University of Minnesota
 Department of Chemistry
 VAC-300

Pulse Sequence: sfpal
 User: cdvren
 Sample: 23
 Date: Jul. 13, 2008
 Solvent: CDCl3
 Starting Time: 18:48:46
 Completion Time: 19:02:53
 Total acq. time 14 minutes
 UNIRV-300 vsc300
 Ambient temperature
 Relax delay 0.100 sec
 Acq. time 6.800 sec
 Width 1736.1 Hz
 300 repetitions
 192 increments
 Spectrometer: 401303 MHz
 DECOUPLER CH1 209.944435 MHz
 Power 40 dB
 on during acquisition
 of during
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.5 Hz
 FT resolution 0.3 Hz
 Line broadening 0.3 Hz
 FT size 65536 X 1024

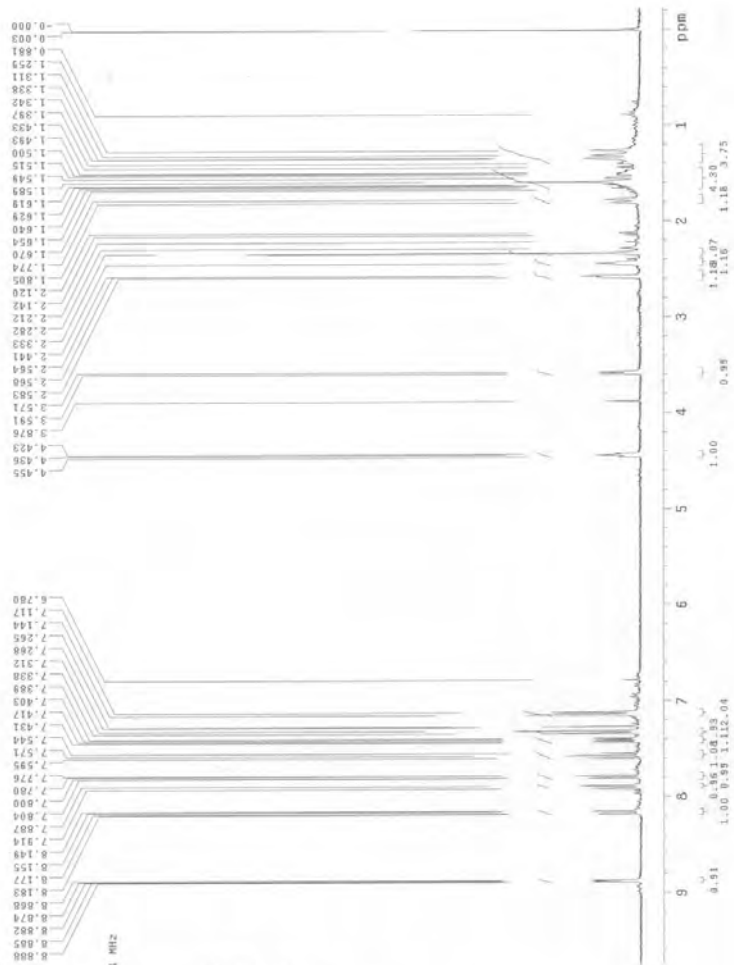
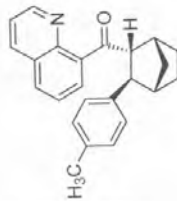




UNIVERSITY of MINNESOTA, VI-300

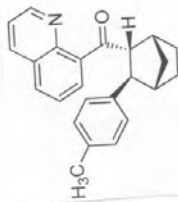
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Date: Mar. 24, 2009
Solvent: CDCl3
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Completion Time: 12:48:01
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Ambient Temperature: 31.571
Relax. delay: 1.500 sec
Acq. time: 4.33 sec
Width: 539.7 Hz
Pulse: 45.0 degrees
Sweep rate: 19.41 Hz/sec
Single scan
Spectral width: 300.1663401 MHz
Resolution: 0.33 Hz
Line broadening: 0.1 Hz
DATA PROCESSING
FT size 131072



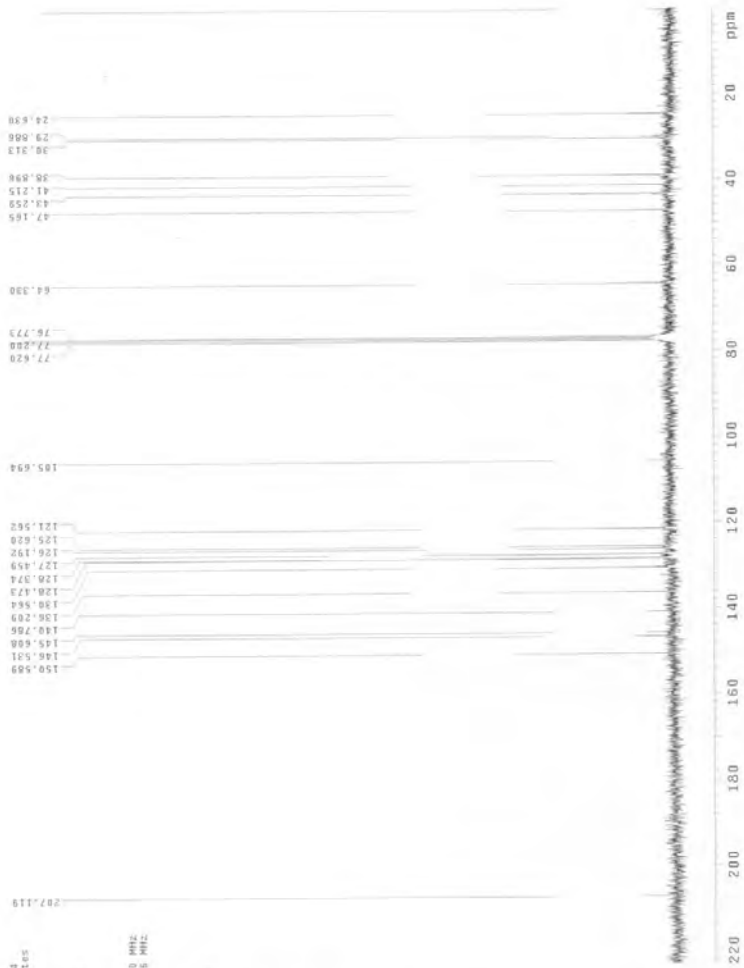
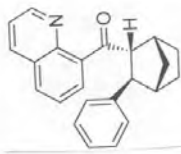
University of Minnesota
Department of Chemistry
VI-589

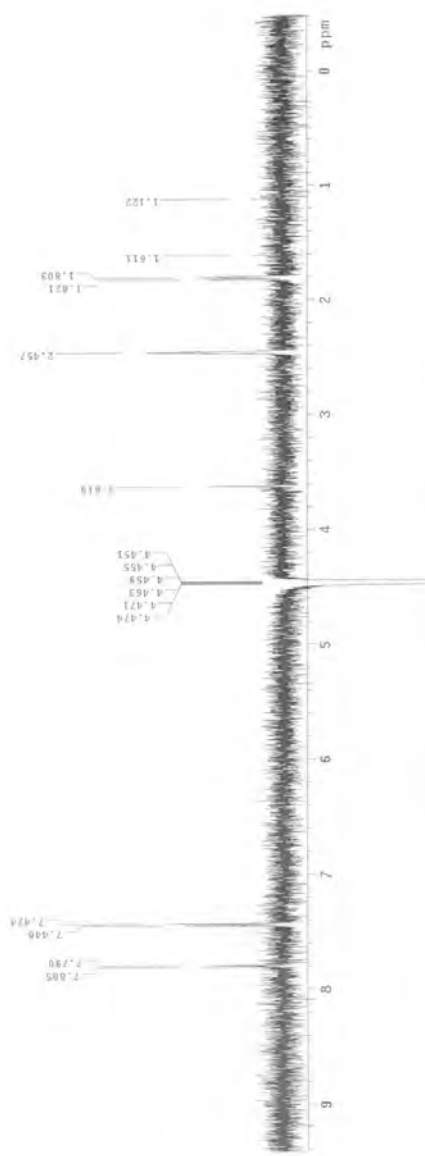
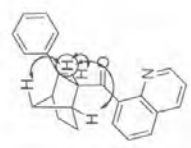
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User: cdmay
Date: 04/24/2009
Solvent: CDCl3
File: MVI-24-14213
Time: 11:58:11
Total Acq. Time: 115 minutes
UNITplus-50 "field"
Ambient Temperature
PULSE SEQUENCE: szpu1
Acq. Time: 115.000 sec
Pulse 1: 1.000 sec
Pulse 2: 0.200 sec
Acq. Time: 0.200 sec
Pulse 1: 1.000 sec
Pulse 2: 0.200 sec
2480 - 0.000 sec
OBSERVE: C13, 75.427356 MHz
PULSE 1: 1.000 sec
Pulse 2: 0.200 sec
on during acquisition
of the sample
DATA PROCESSING
Line Processing: 1.5 Hz
F2 Size: 65536

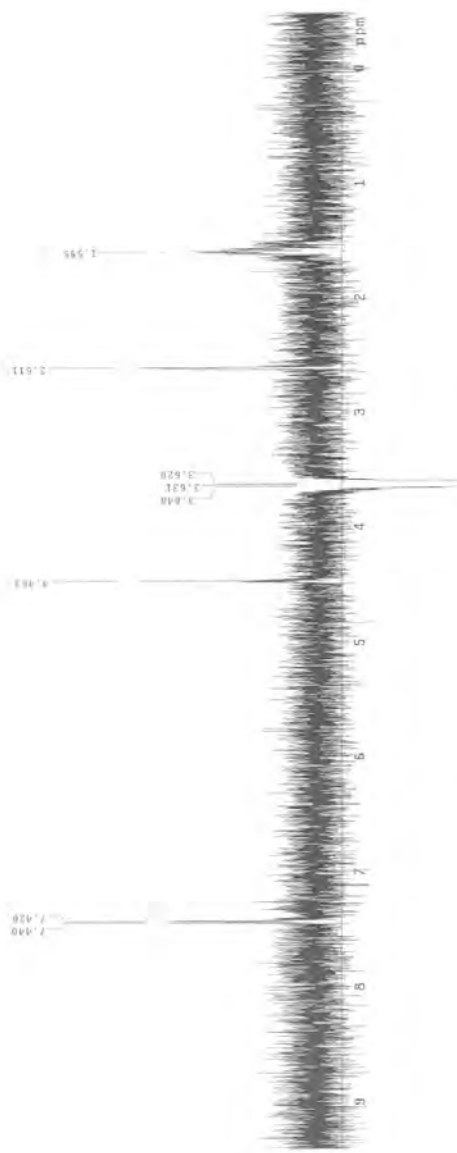
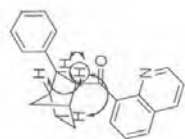


University of Minnesota
Department of Chemistry
05-300

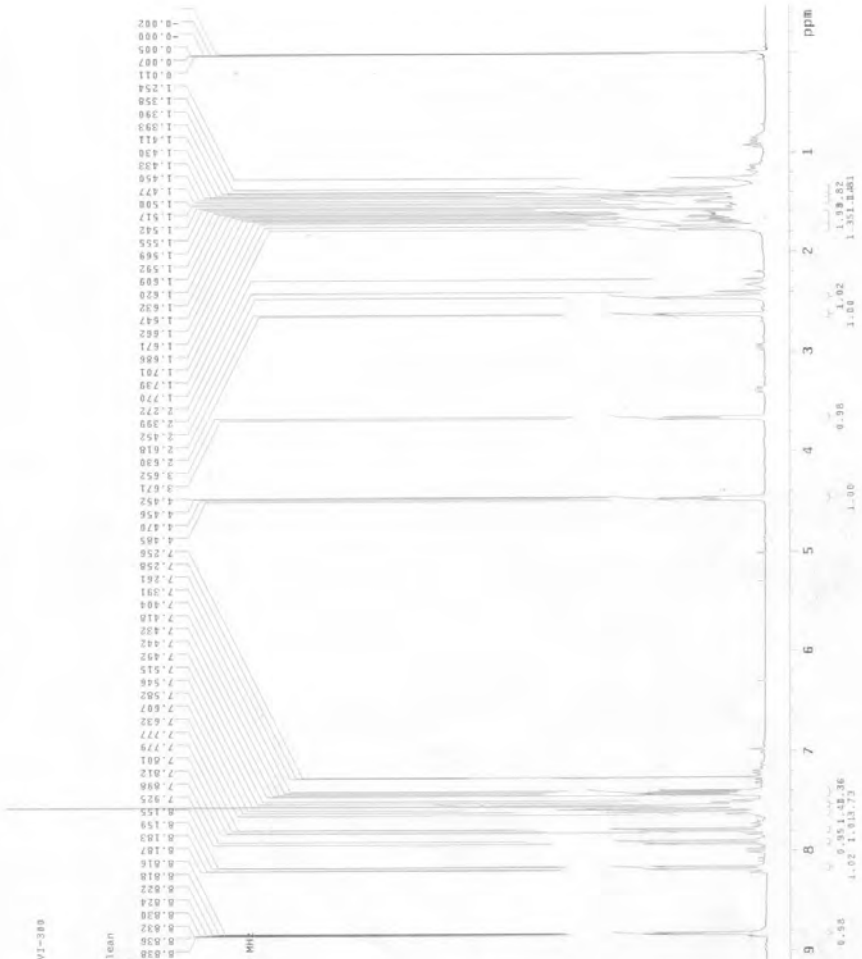
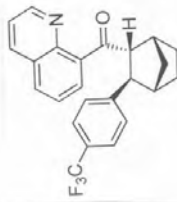
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User: cdooley
Date: Mar 16, 2009
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Acquisition Time: 01:16:05
Inlet Temp: 50 "1010"
Ambient Temperature
PULSE SEQUENCE
Relax delay 0.100 sec
Acq time 0.201 sec
Width 18667.2 Hz
Observer CCL, P5-1773763 MHZ
RECOUPLE: H1, 309.1678468 MHZ
on during acquisition
off during delay
Data collected
DATA PROCESSING
Line broadening 1.5 Hz
FT size 65536





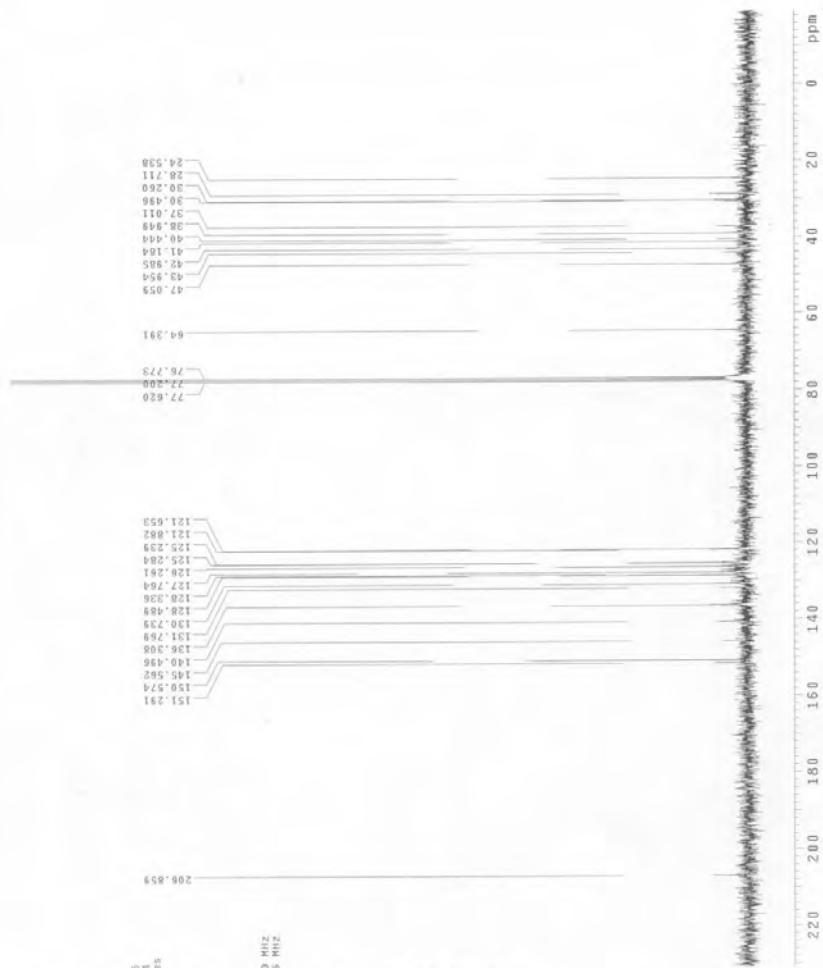
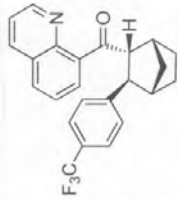


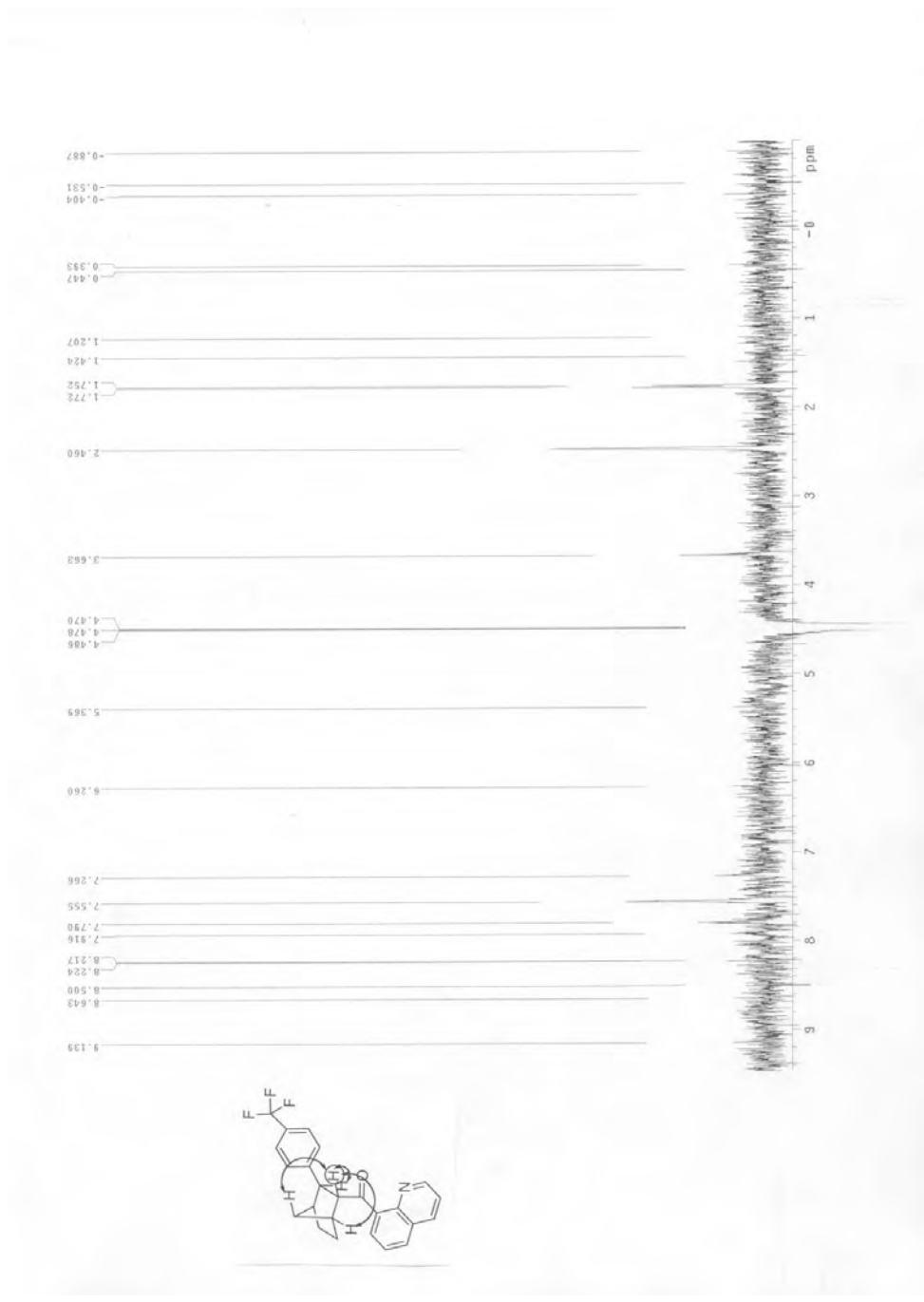
University of Minnesota, VI-389
 Pulse Sequence: zgpg1
 Date: Mar 26, 2005
 Solvent: CDCl3
 Starting Time: 10:38:16
 Completion Time: 10:42:05
 Total Acq. Time: 3 minutes
 Ambient Temperature: 25°C
 PULSE SEQUENCE
 Relax delay: 1.500 sec
 Acquisition time: 3.000 sec
 ACO: 180.000 sec
 Width: 4399.7 Hz
 OBSERVE: 1
 DATA PROCESSING
 Line PROTONS: 6.1 Hz
 FT SIZE: 1310VC

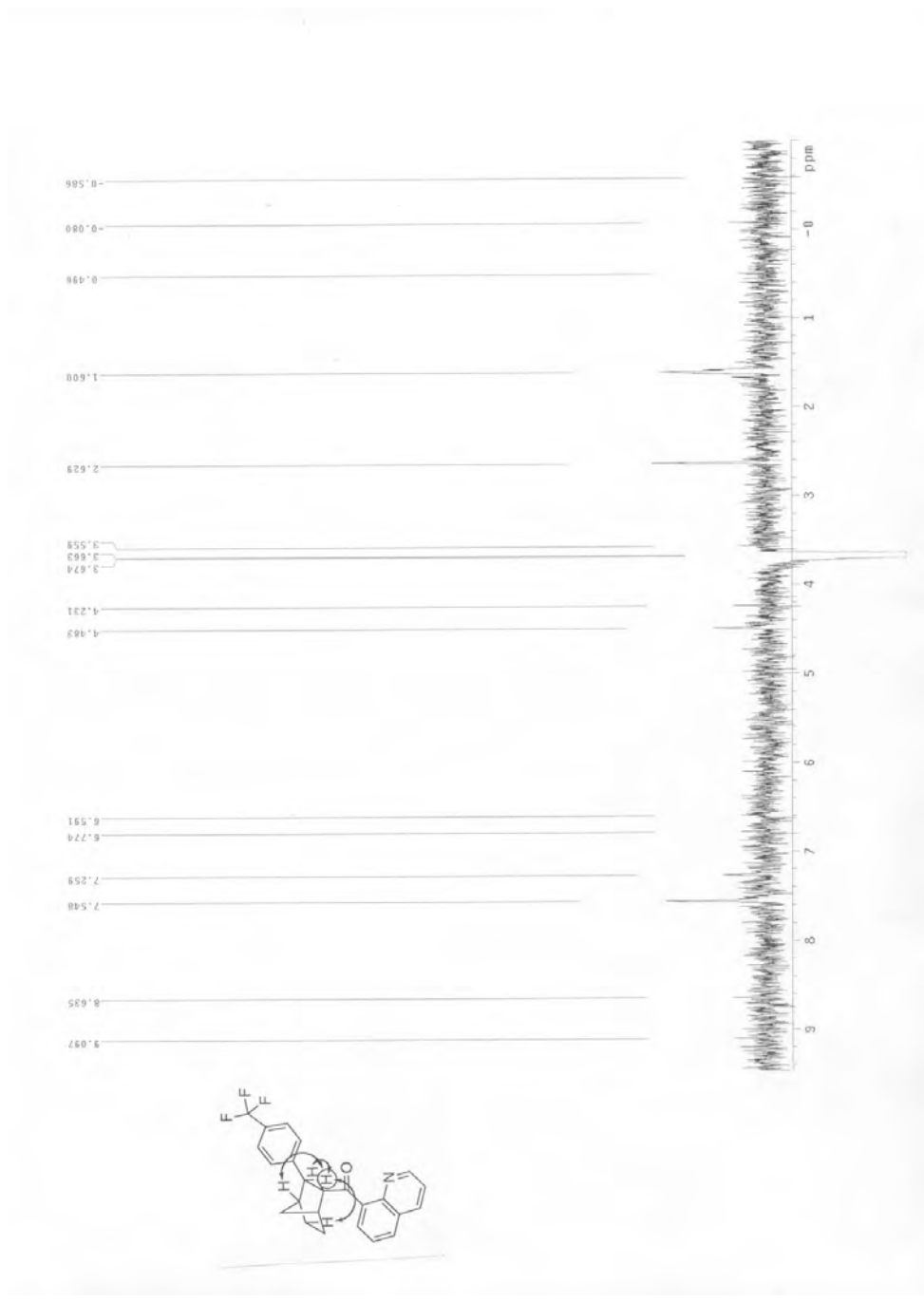


University of Minnesota
Department of Chemistry
VI-590

Pulse Sequence: szpu1
Date: MAR 26, 2000
Solvent: CDCl3
Starting Time: 10:22:55
Total Time: 10:23:00
Total sec. time 07 minutes
UNITYPUS-900 "v1000"
Ambient temperature
PULSE SEQUENCE
Pulse 1: 180 sec
Pulse 2: 7.5 degrees
Acq. time 0.401 sec
Pulse 3: 180 sec
1872 repetitions
OBSERVE C13, 75.472350 MHZ
Power 38 db, 380.1696486 MHZ
on during acquisition
Solving for phase
DATA PROCESSING
Line broadening 1.5 Hz
F1: 16.663550





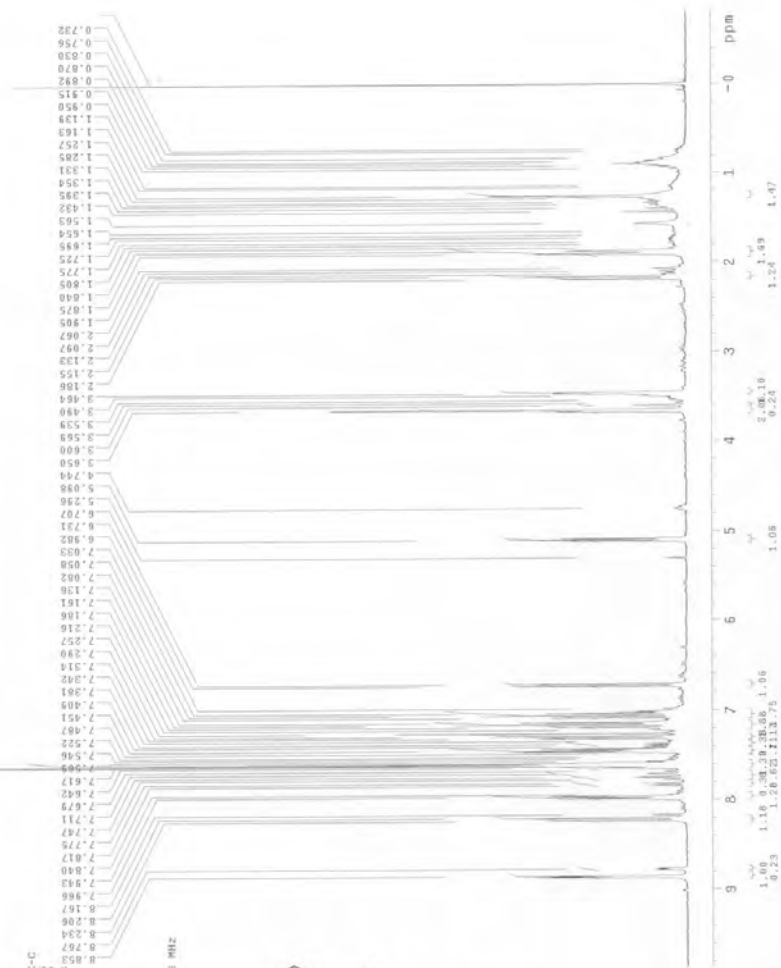
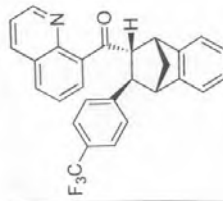


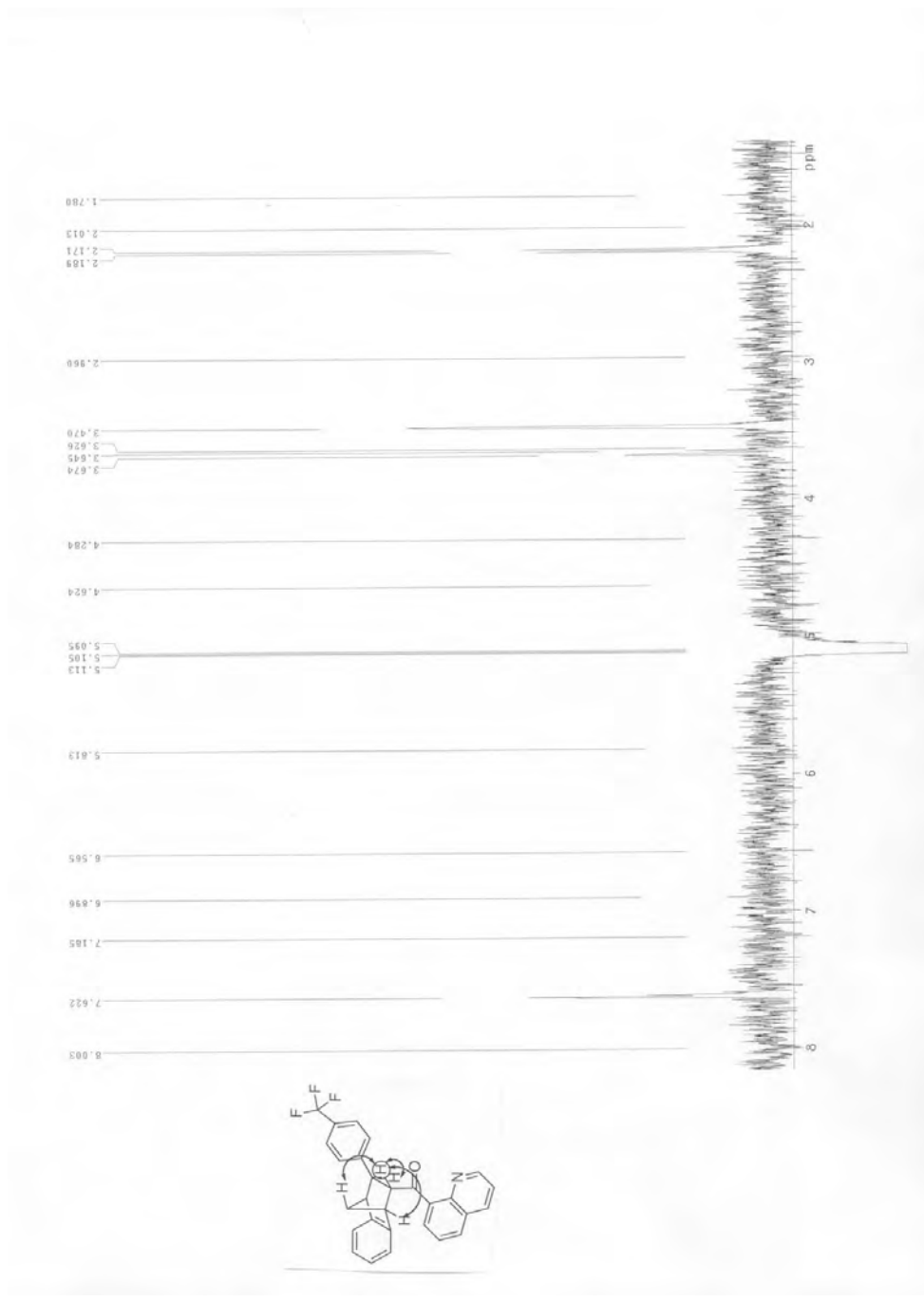
University of Minnesota, VI-308

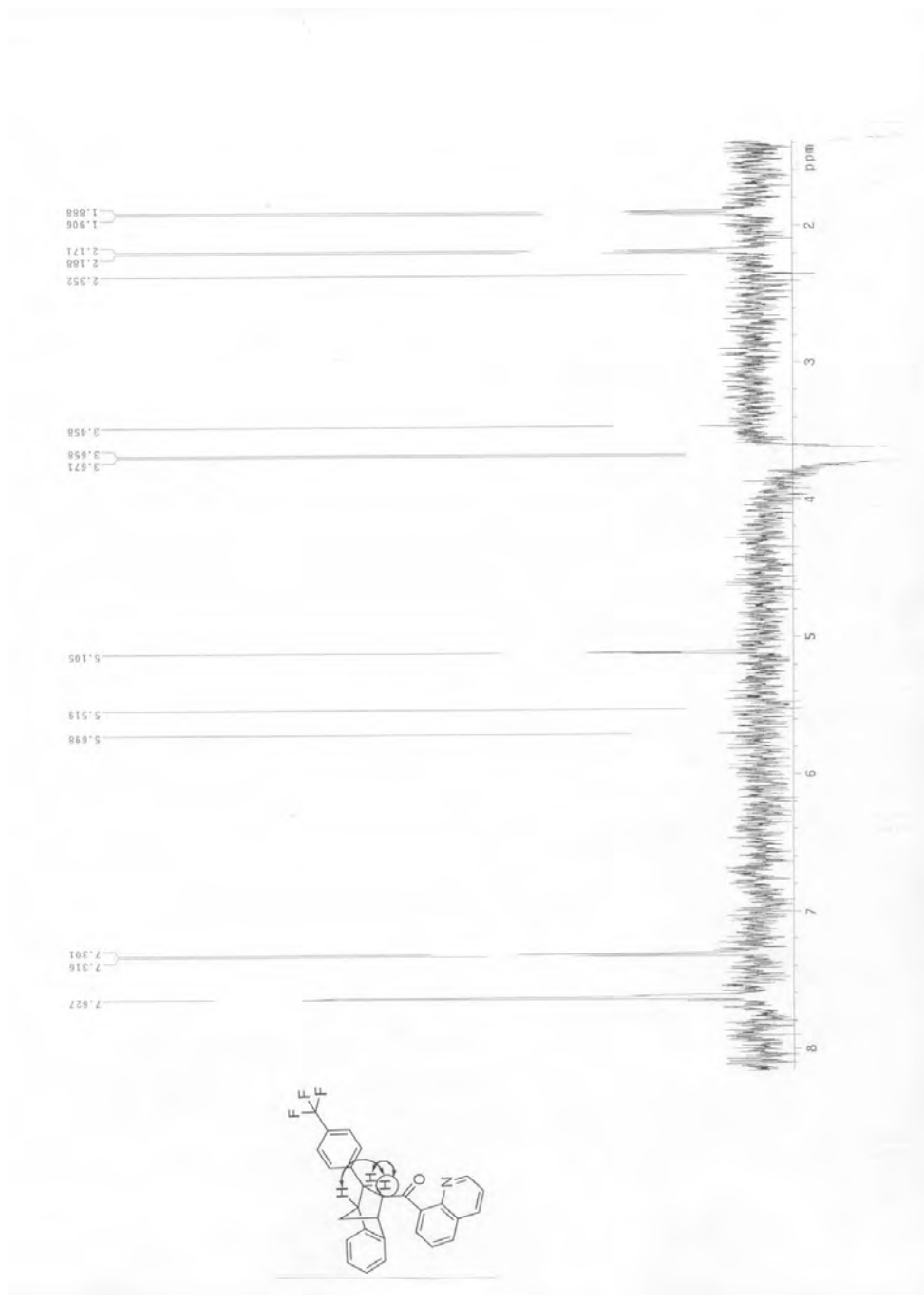
Pulse Sequence: e2pu1

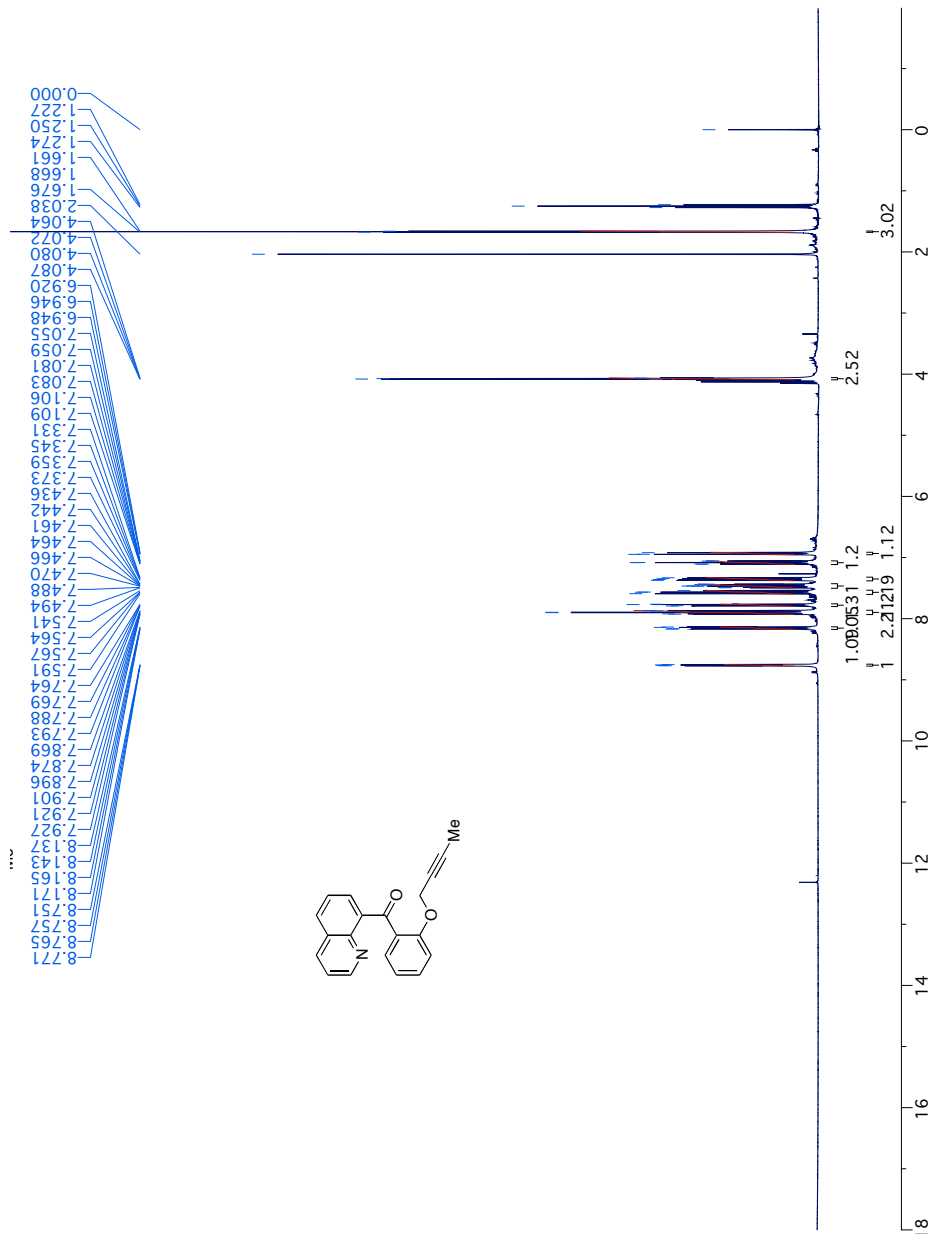
Date: Mar. 28, 2009
Solvent: CDCl3
Starting Time: 12:14:26
Completion Time: 12:16:57
F1 (Acq) Time: 01m46s
F2 (Acq) Time: 01m46s
Ambient Temperature

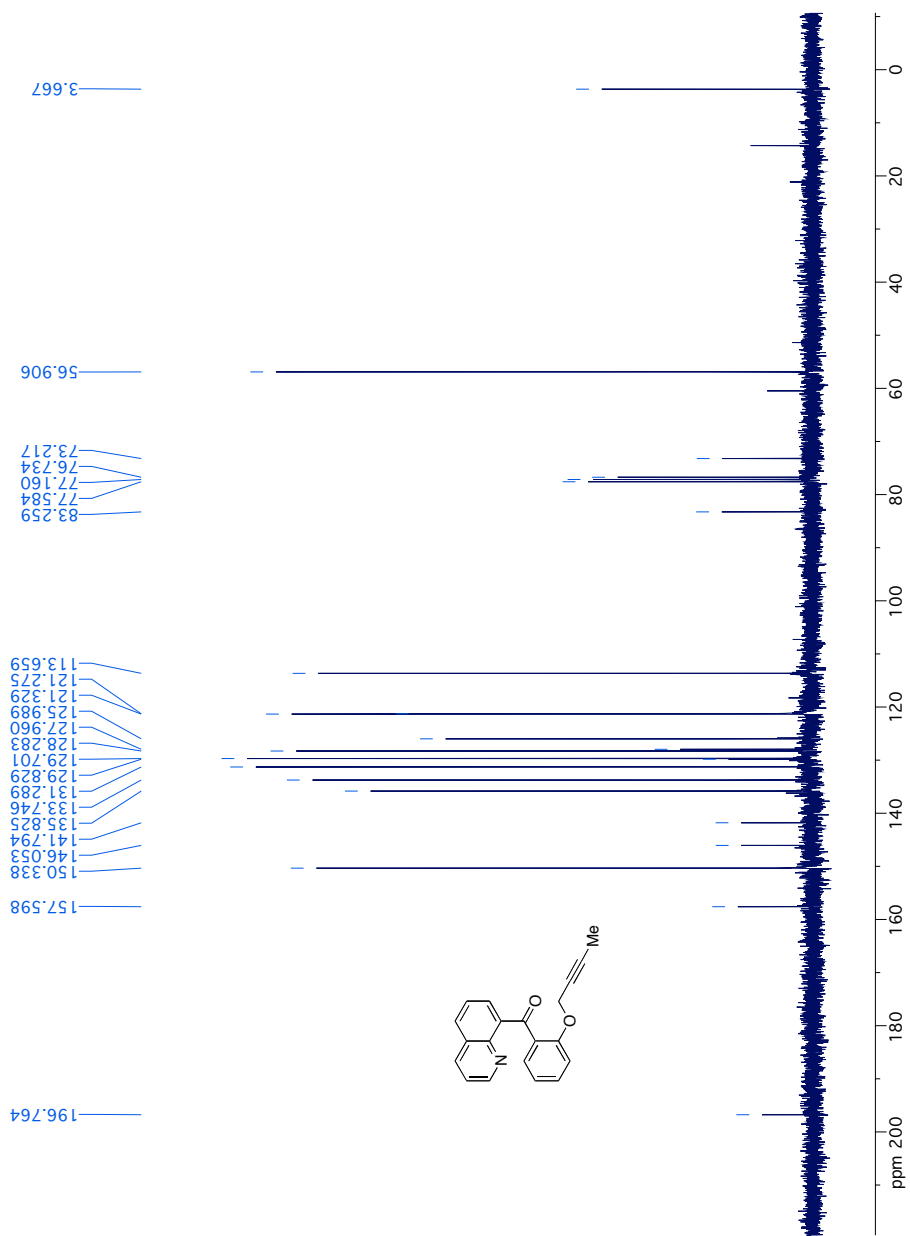
PULSE SEQUENCE
Relax. delay: 1.500 sec
Acq. time: 2.000 sec
Width: 5899.7 Hz
Observed F1: 100.626130 MHz
Observed F2: 300.1663403 MHz
Data Processing
Line Acquisition
F1: 9.126731072

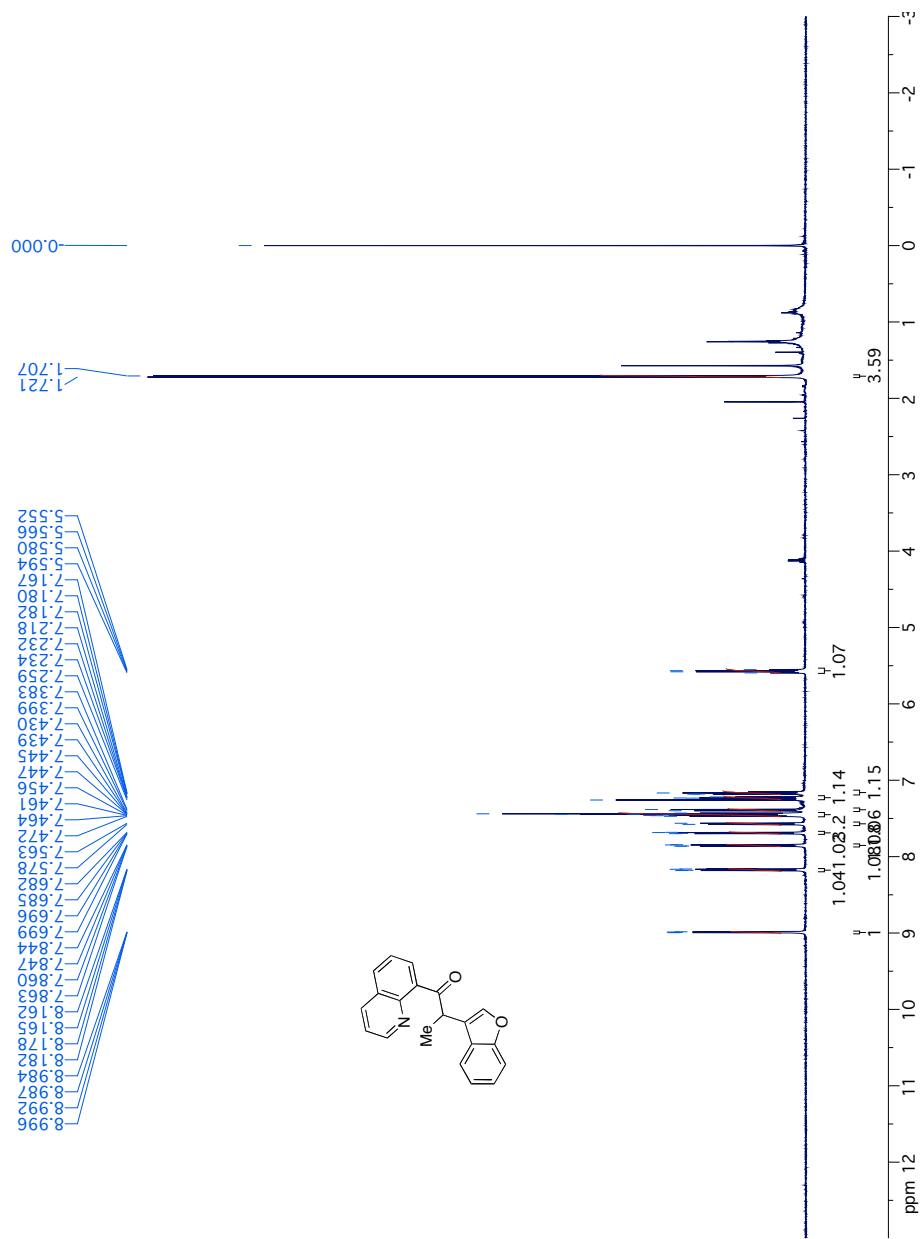




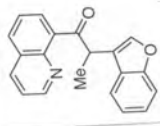




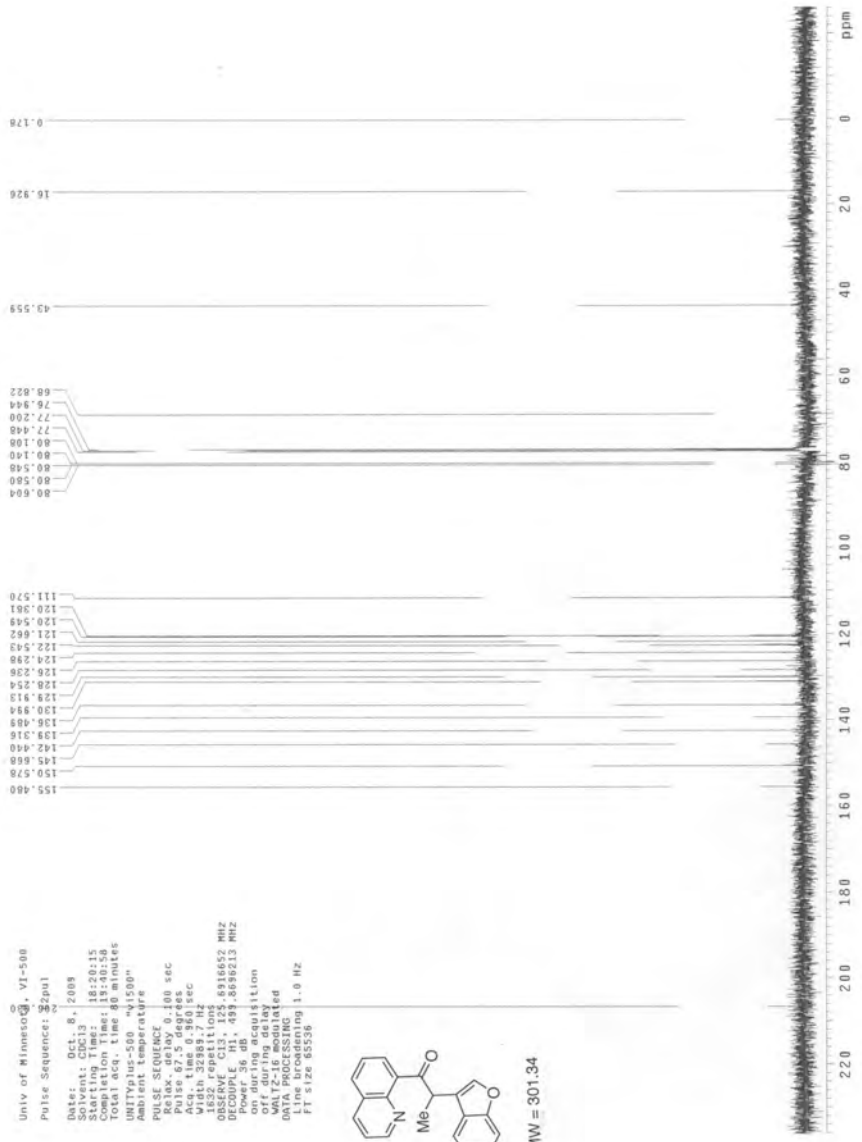


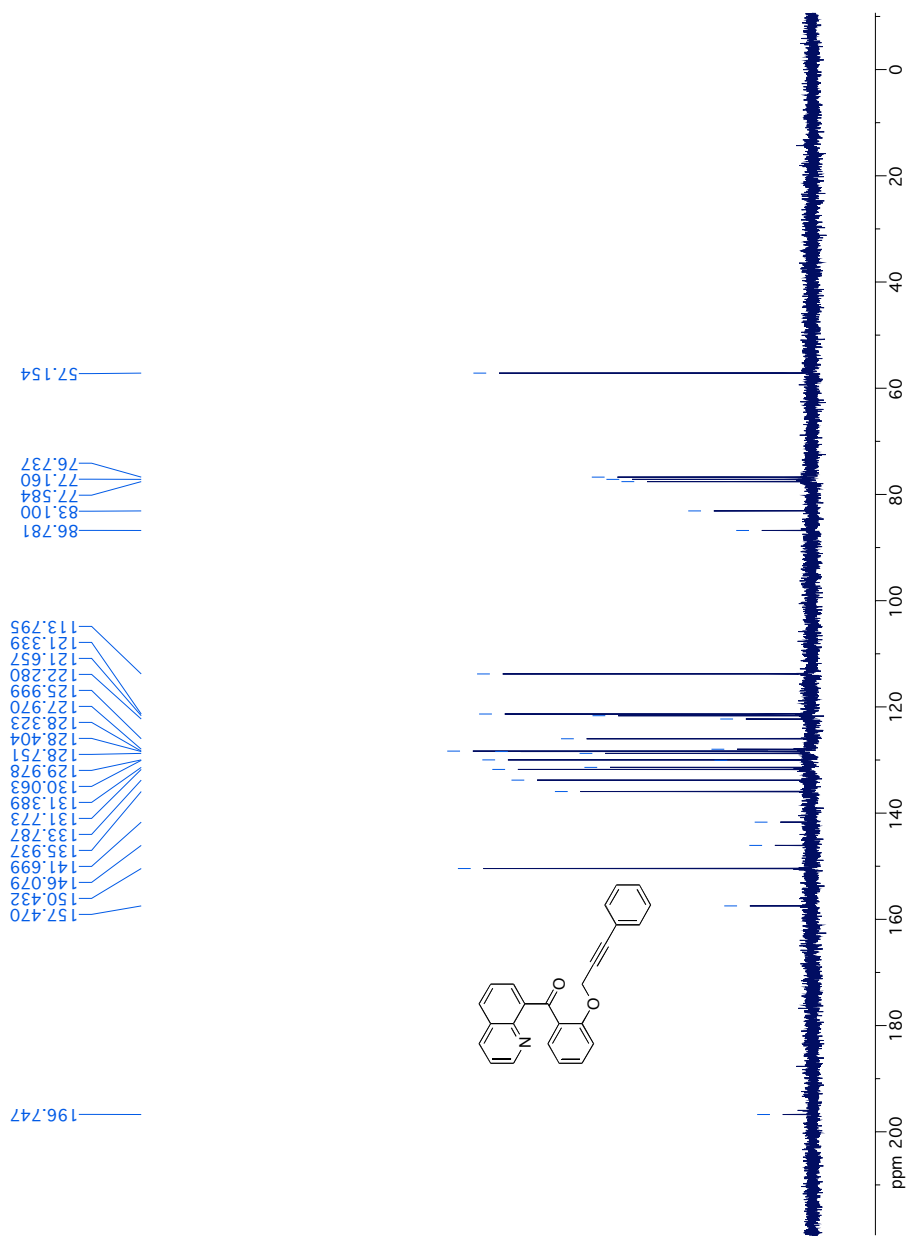


Univ of Minnesota 04_VI-500
 Pulse Sequence: zgpg30
 Date: Oct. 8, 2009
 Solvent: CDCl3
 Acquisition Time: 18:20:15
 Completion Time: 19:40:58
 Total acq. time 80 minutes
 UNITplus-500 -v1500*
 Acquisition Mode: zgpg30
 PULSE SEQUENCE
 Relax. delay 0.100 sec
 Pulse 67.5 degrees
 Width 3289.7 Hz
 1822 repetitions
 DECOUPLE H1, 499.8498215 MHz
 Power 36 dB
 off during delay
 WALTZ-16 modulated
 during acquisition
 Line broadening 1.0 Hz
 FT size 65536

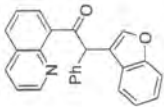


MW = 301.34

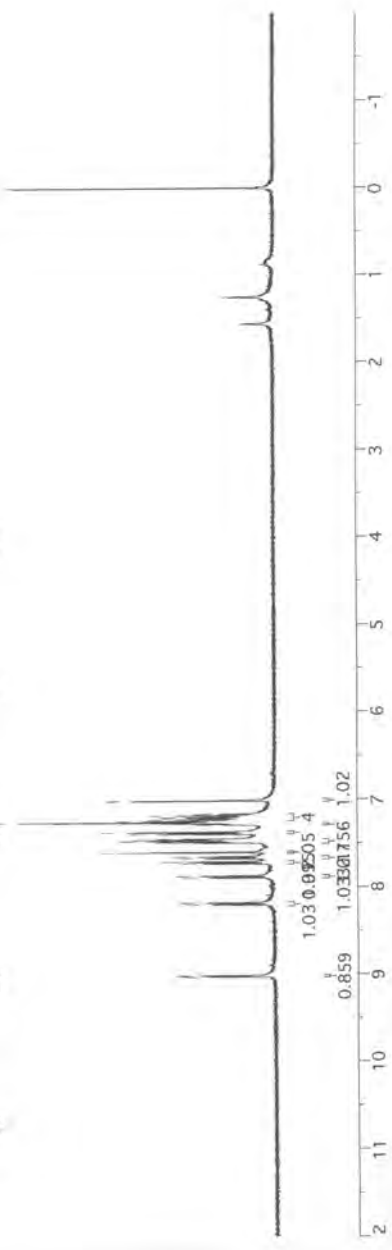
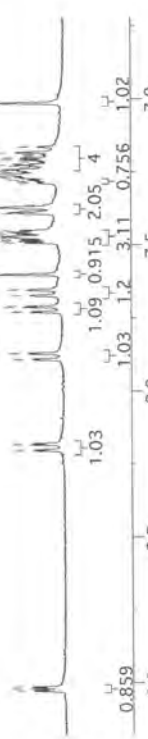


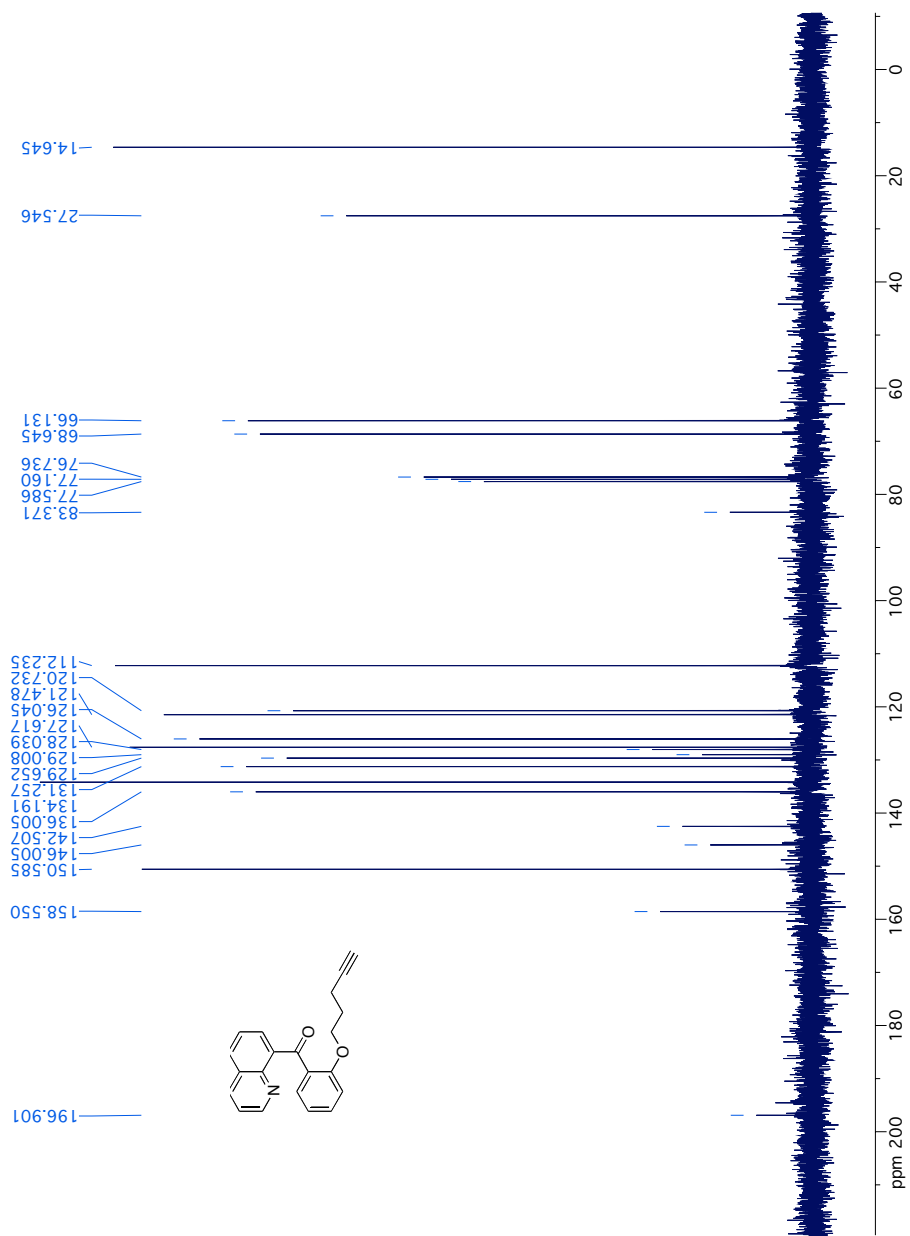


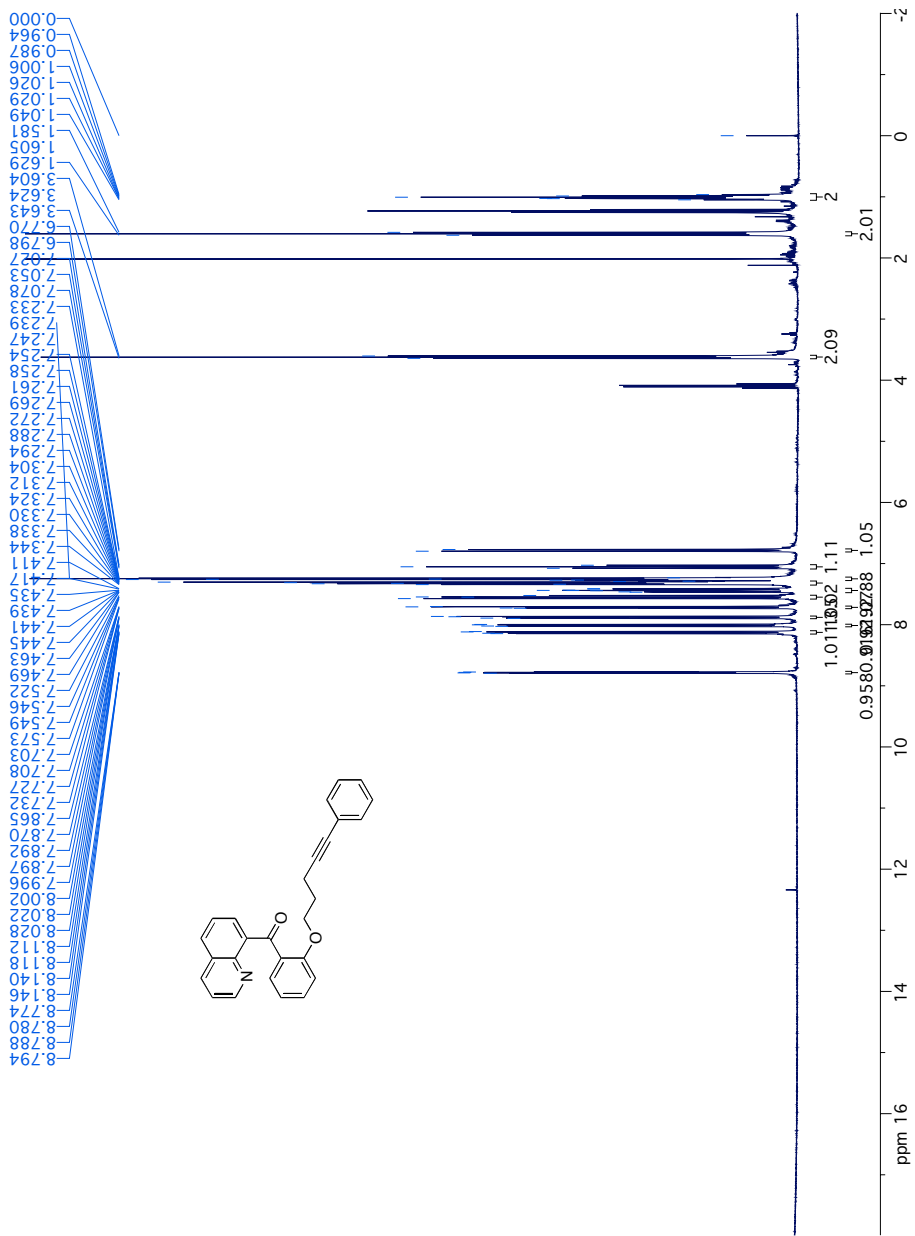
9.028
9.023
9.017
9.013
8.203
8.198
8.188
8.178
7.892
7.889
7.872
7.868
7.730
7.726
7.712
7.708
7.673
7.653
7.652
7.601
7.599
7.487
7.475
7.469
7.466
7.466
7.460
7.456
7.454
7.449
7.391
7.388
7.338
7.332
7.370
7.362
7.287
7.284
7.250
7.249
7.245
7.240
7.238
7.234
7.221
7.214
7.207
7.201
7.199
7.192
7.189
7.181
7.163
7.151
7.013
0.000

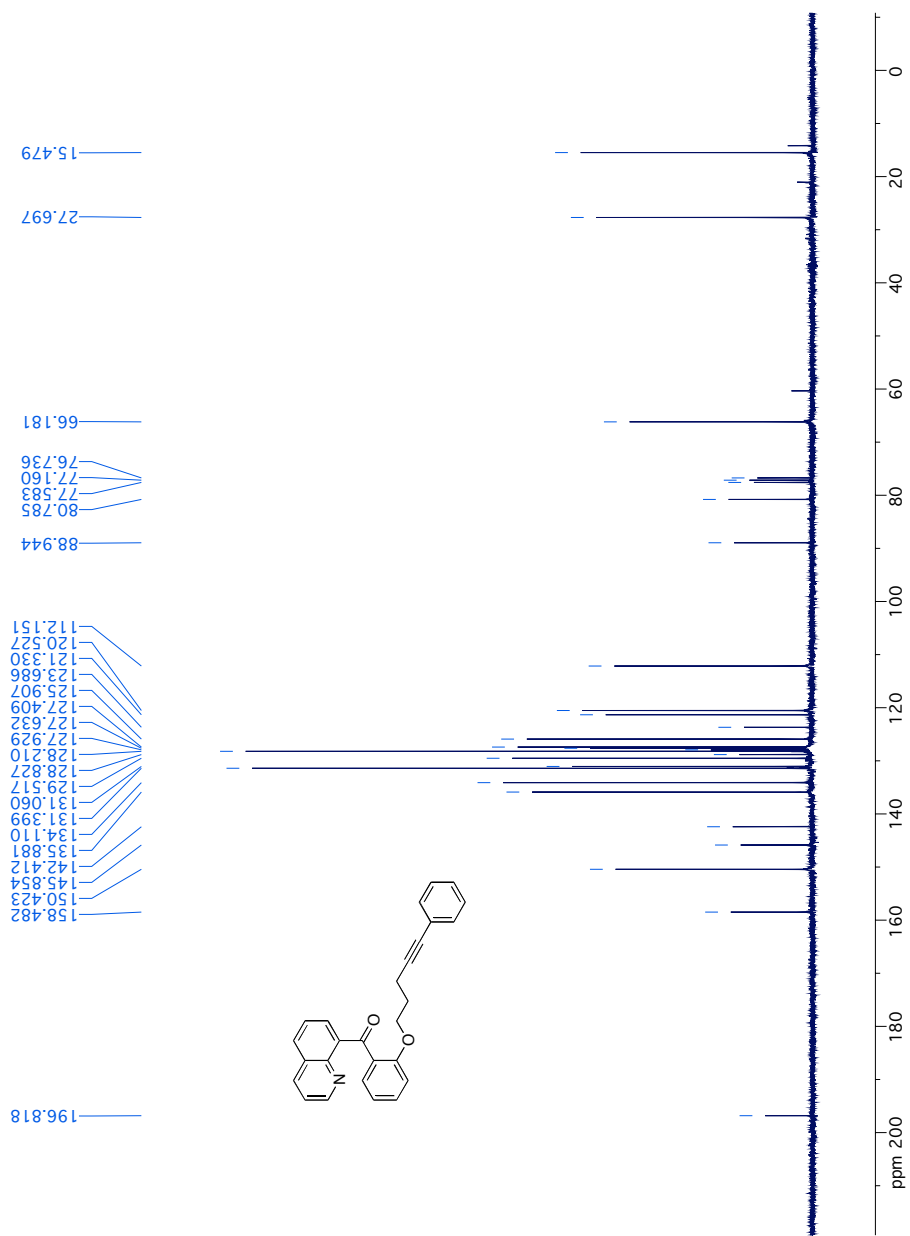


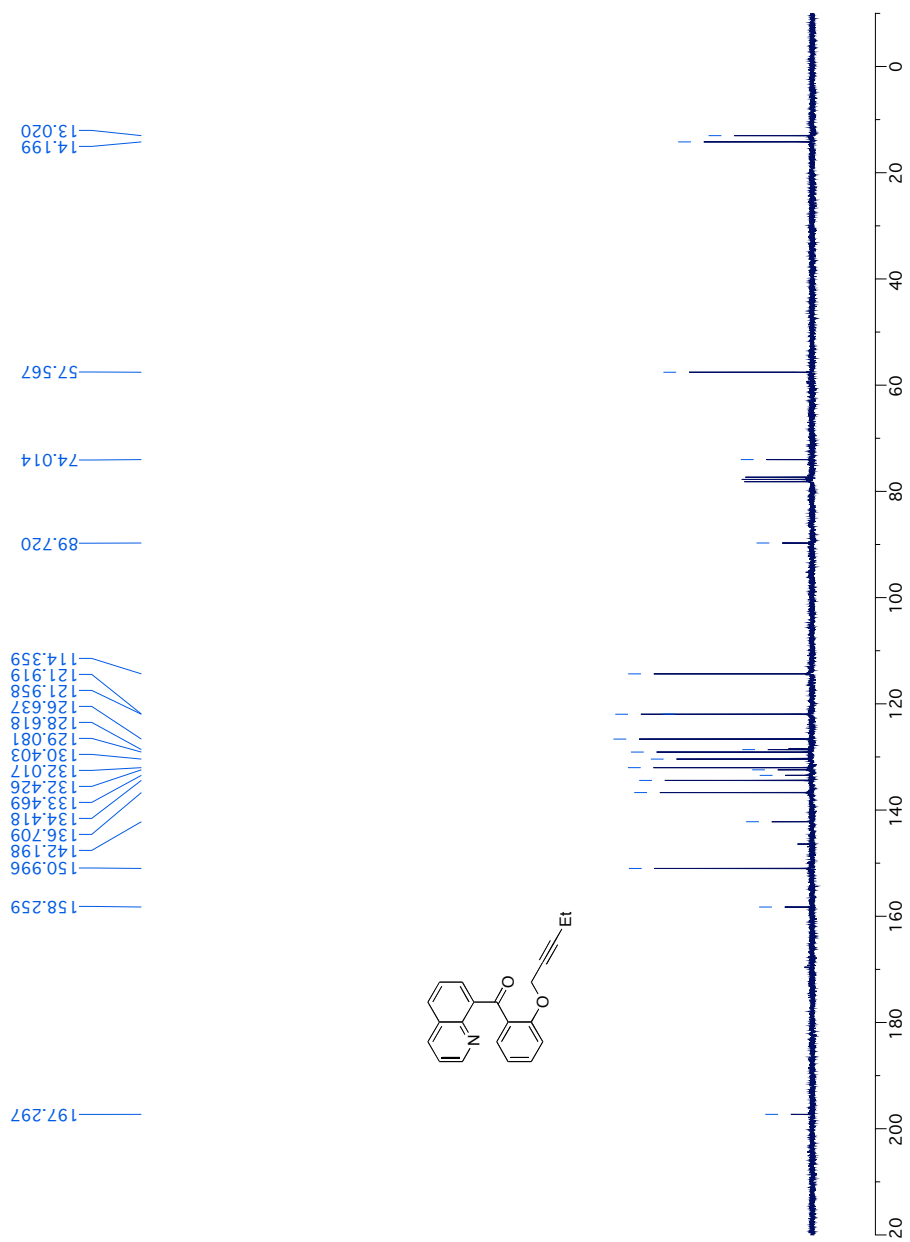
9.028
9.023
9.017
9.013
8.203
8.198
8.188
8.178
7.892
7.889
7.872
7.868
7.730
7.726
7.712
7.708
7.673
7.653
7.652
7.601
7.599
7.487
7.475
7.469
7.466
7.466
7.460
7.456
7.454
7.449
7.391
7.388
7.338
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7.284
7.250
7.249
7.245
7.240
7.238
7.234
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7.214
7.207
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7.189
7.181
7.163
7.151
7.013

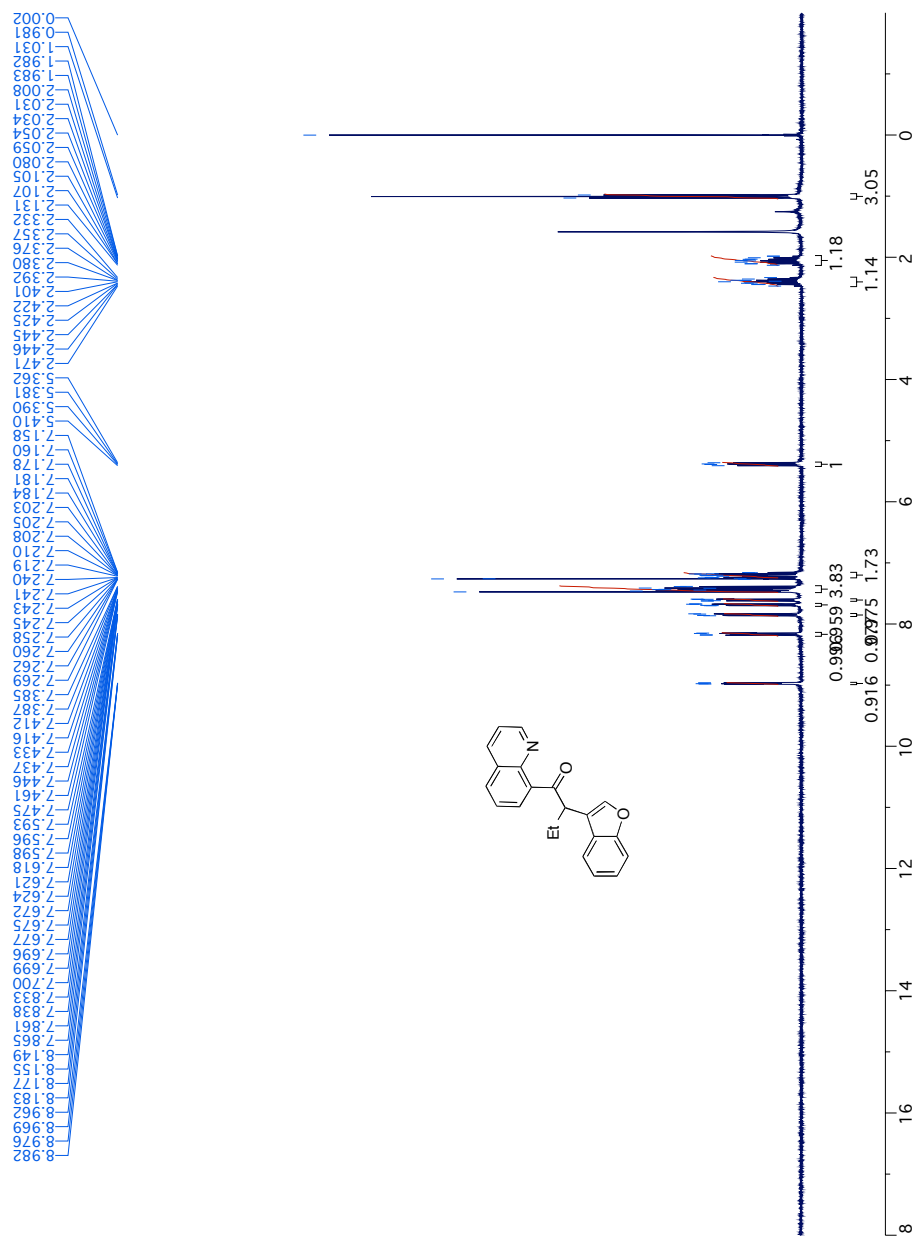


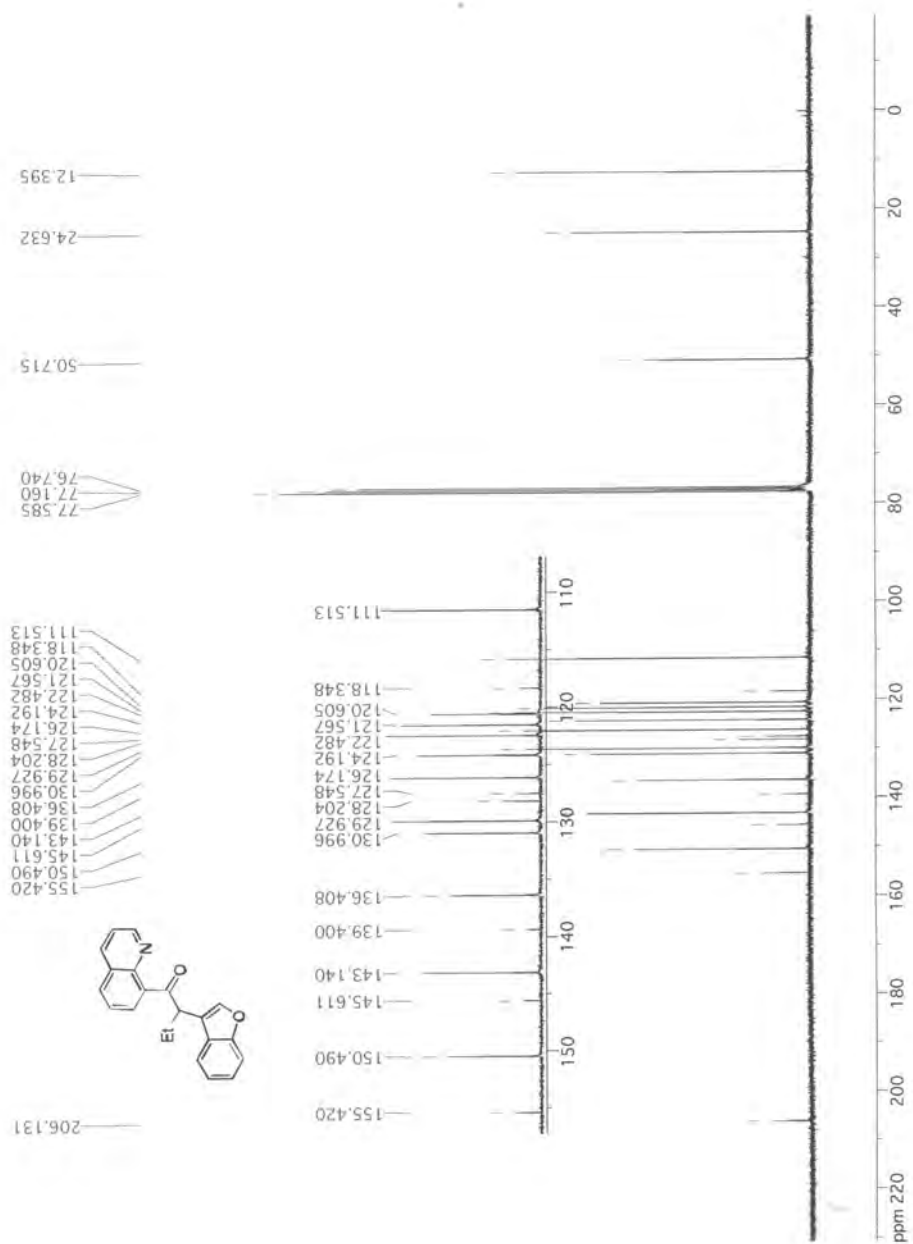


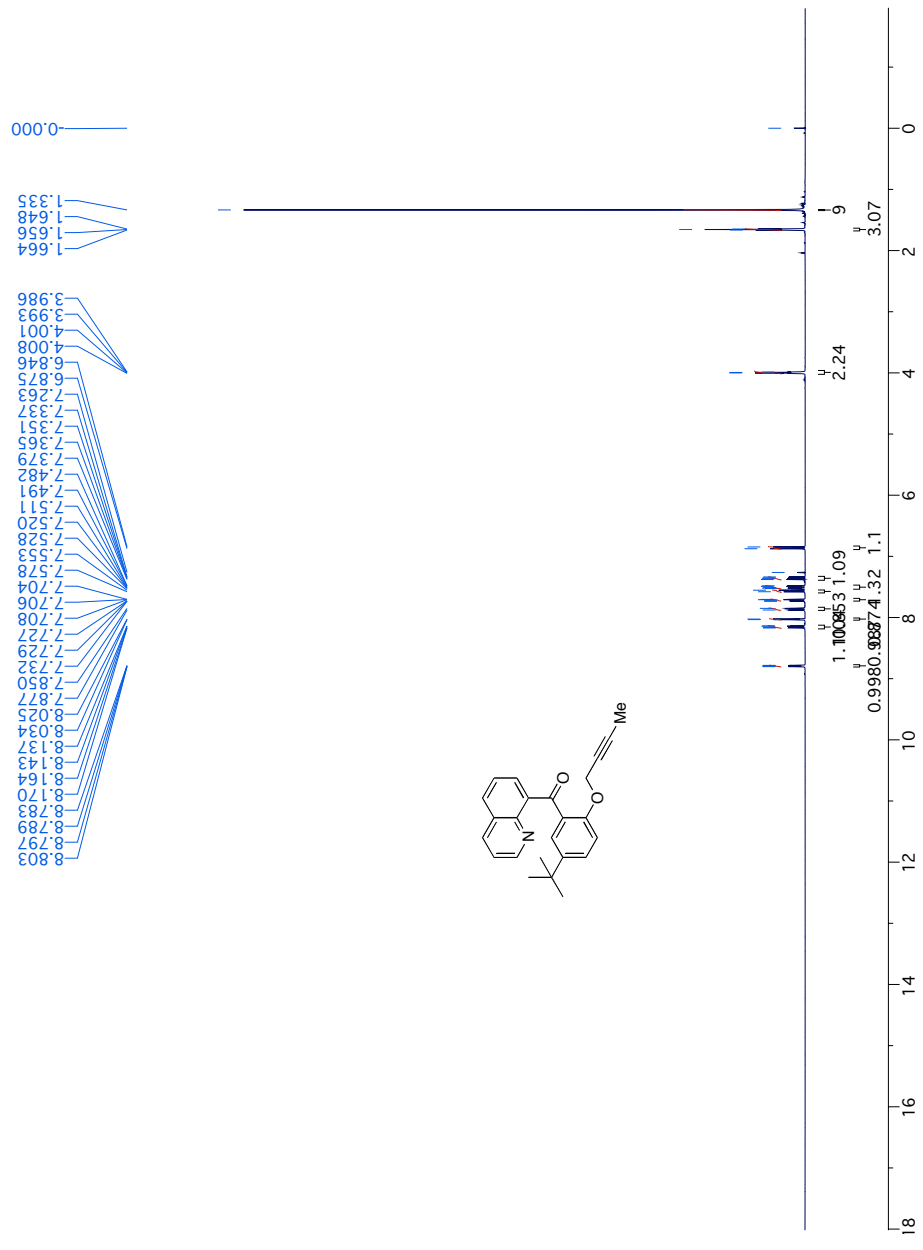


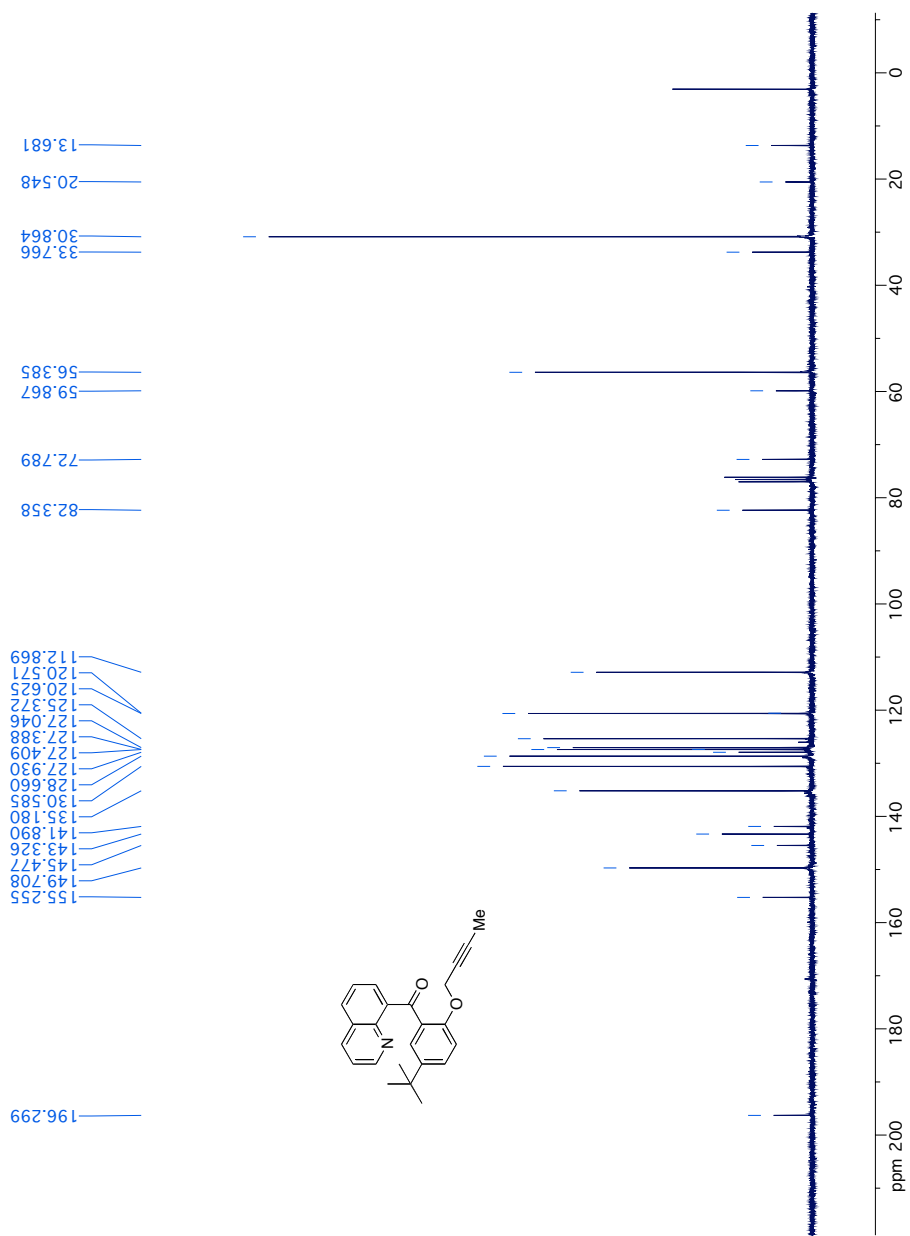


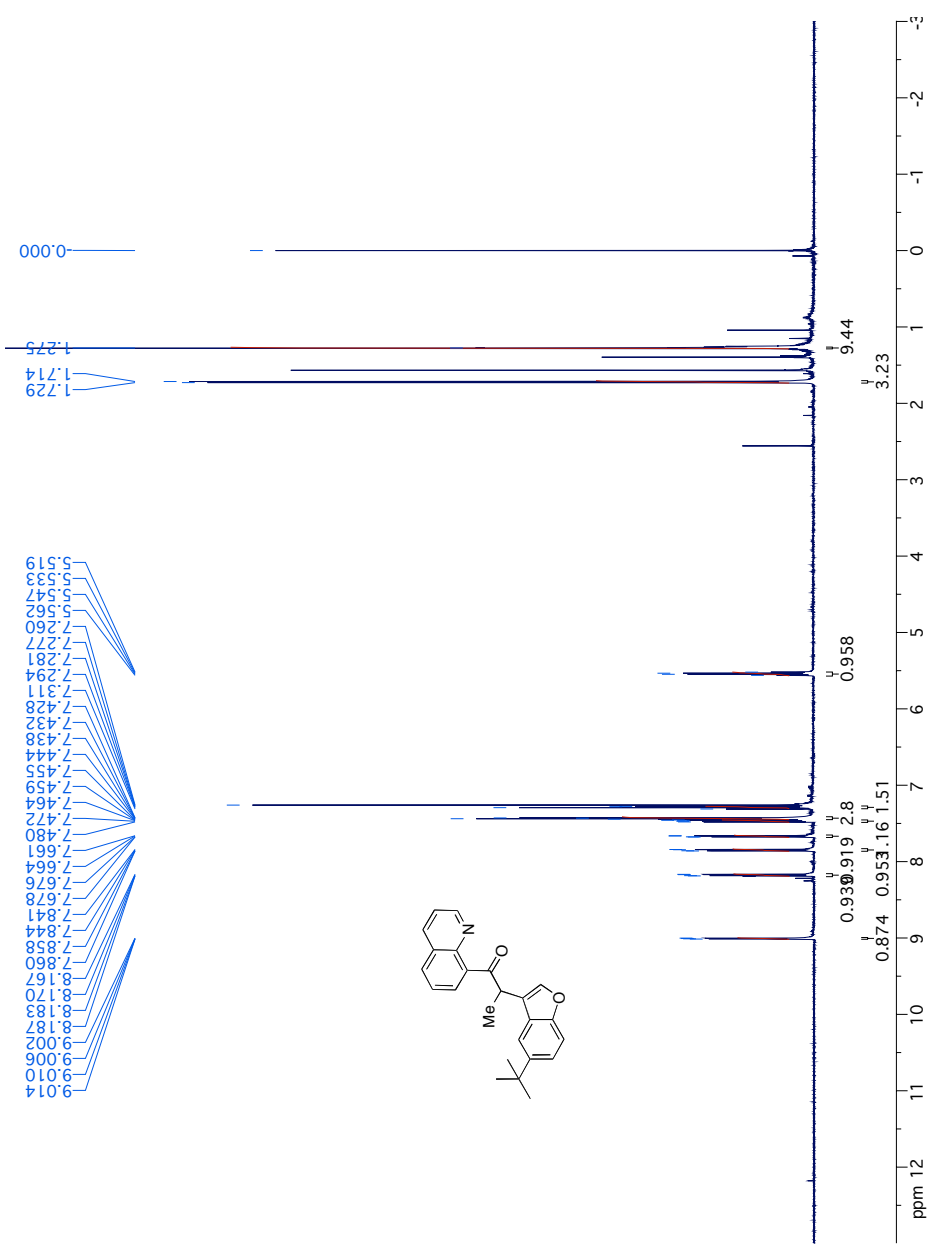


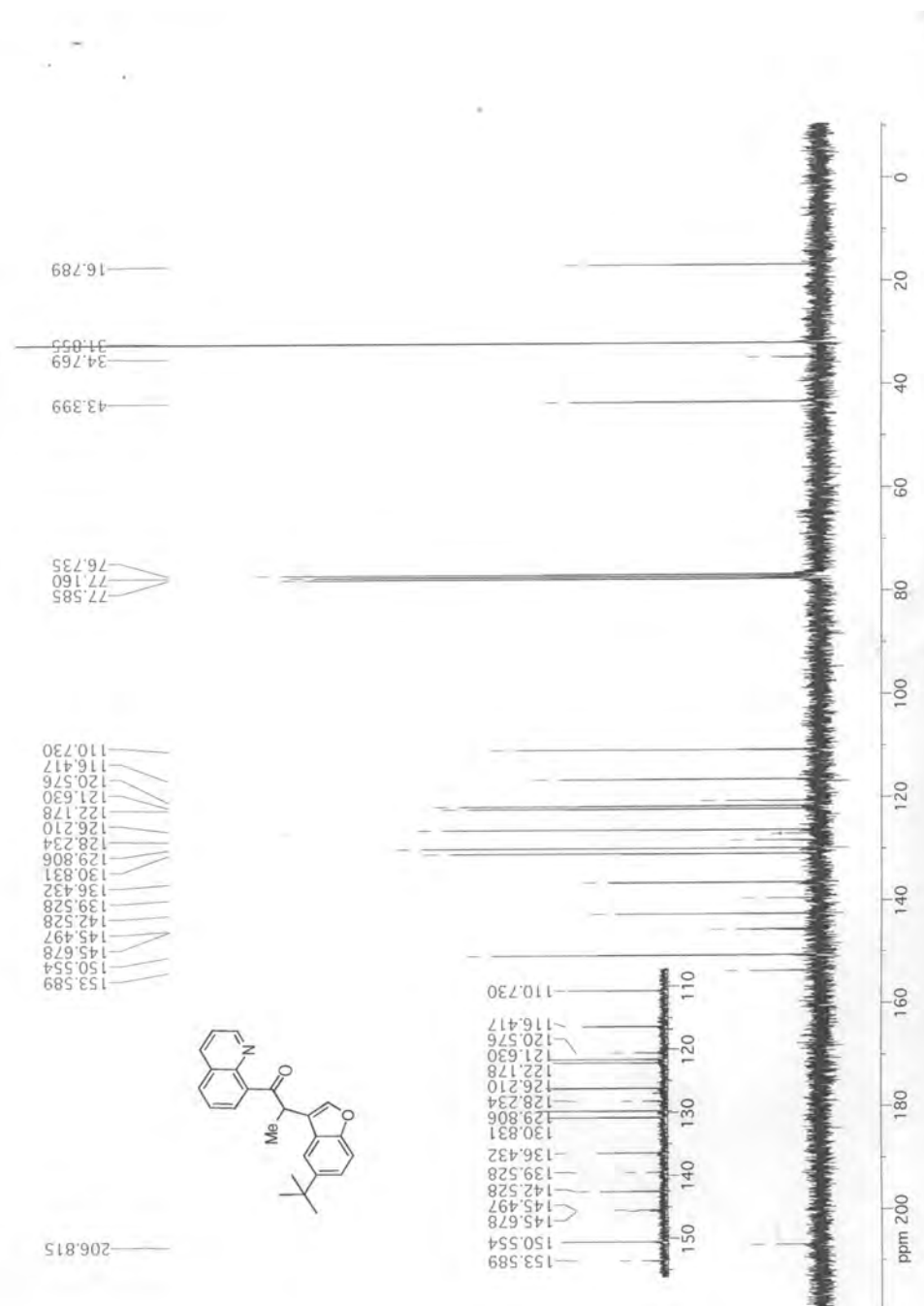


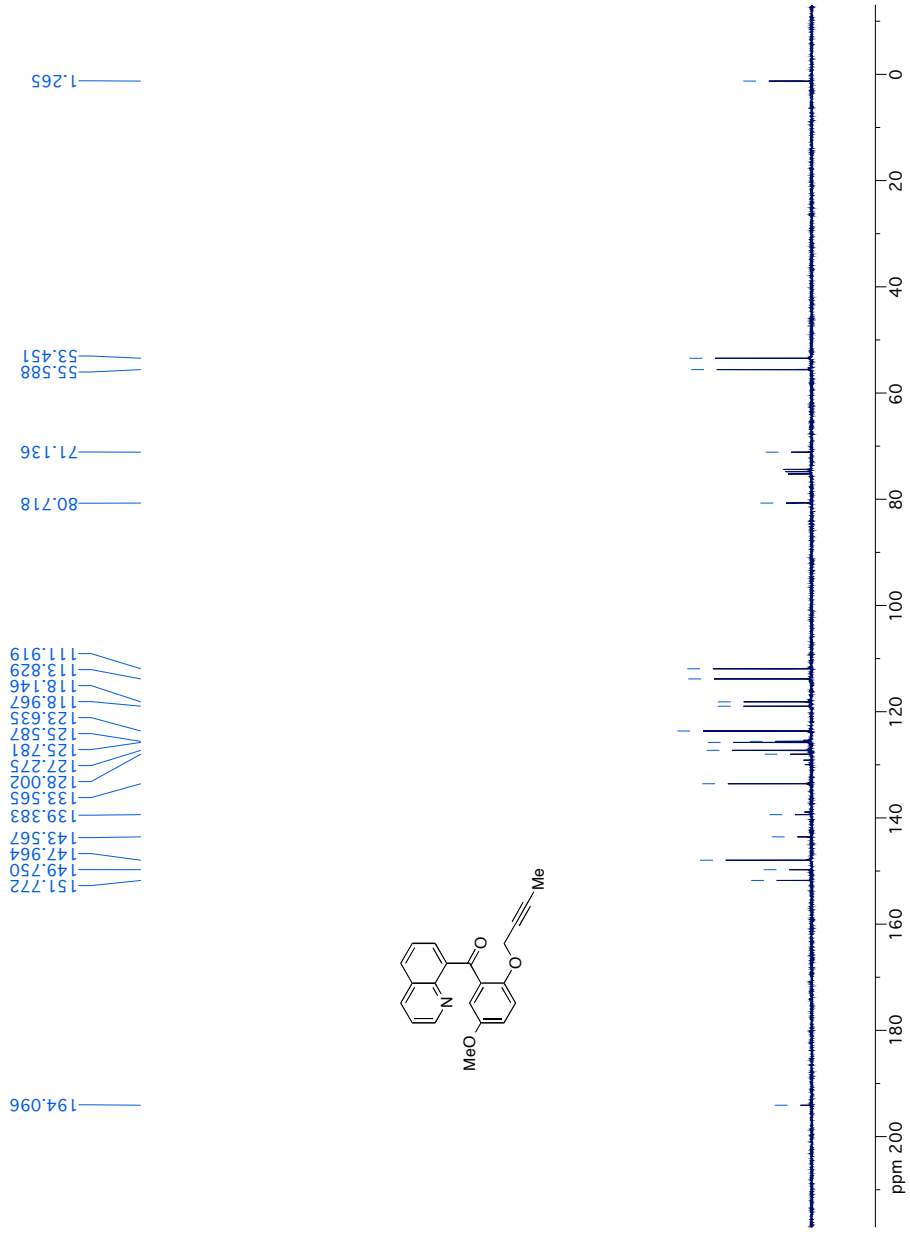
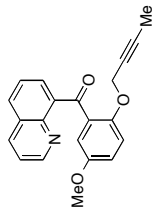


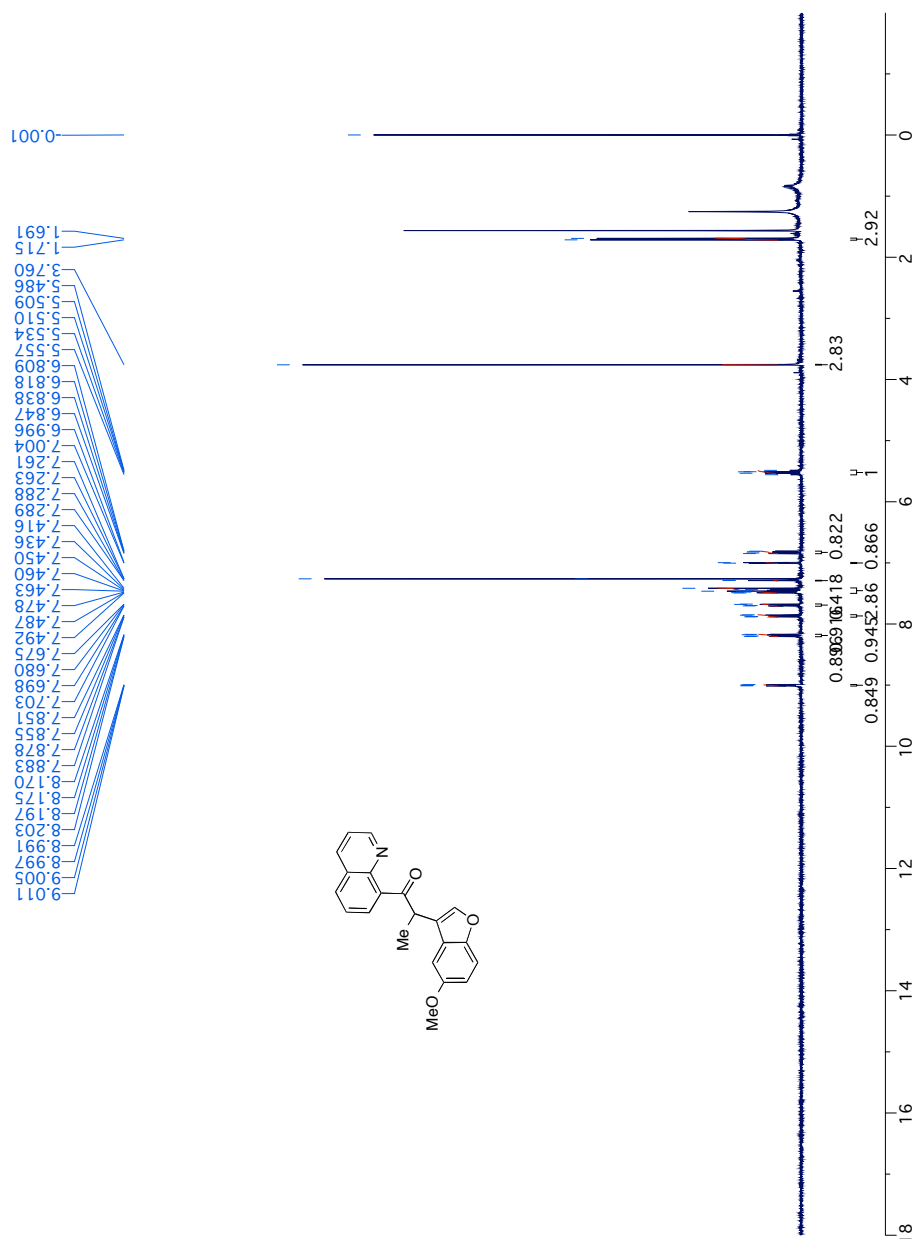


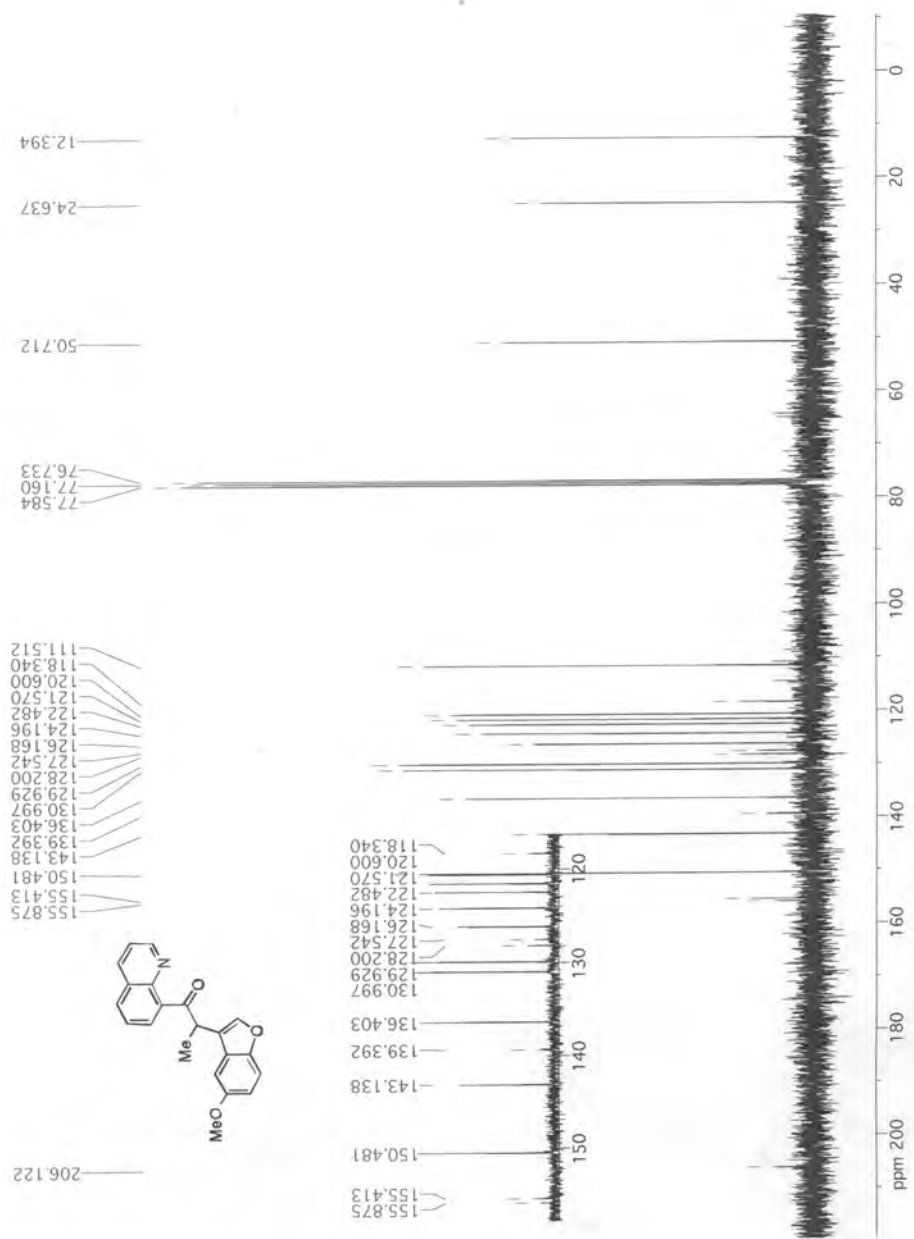


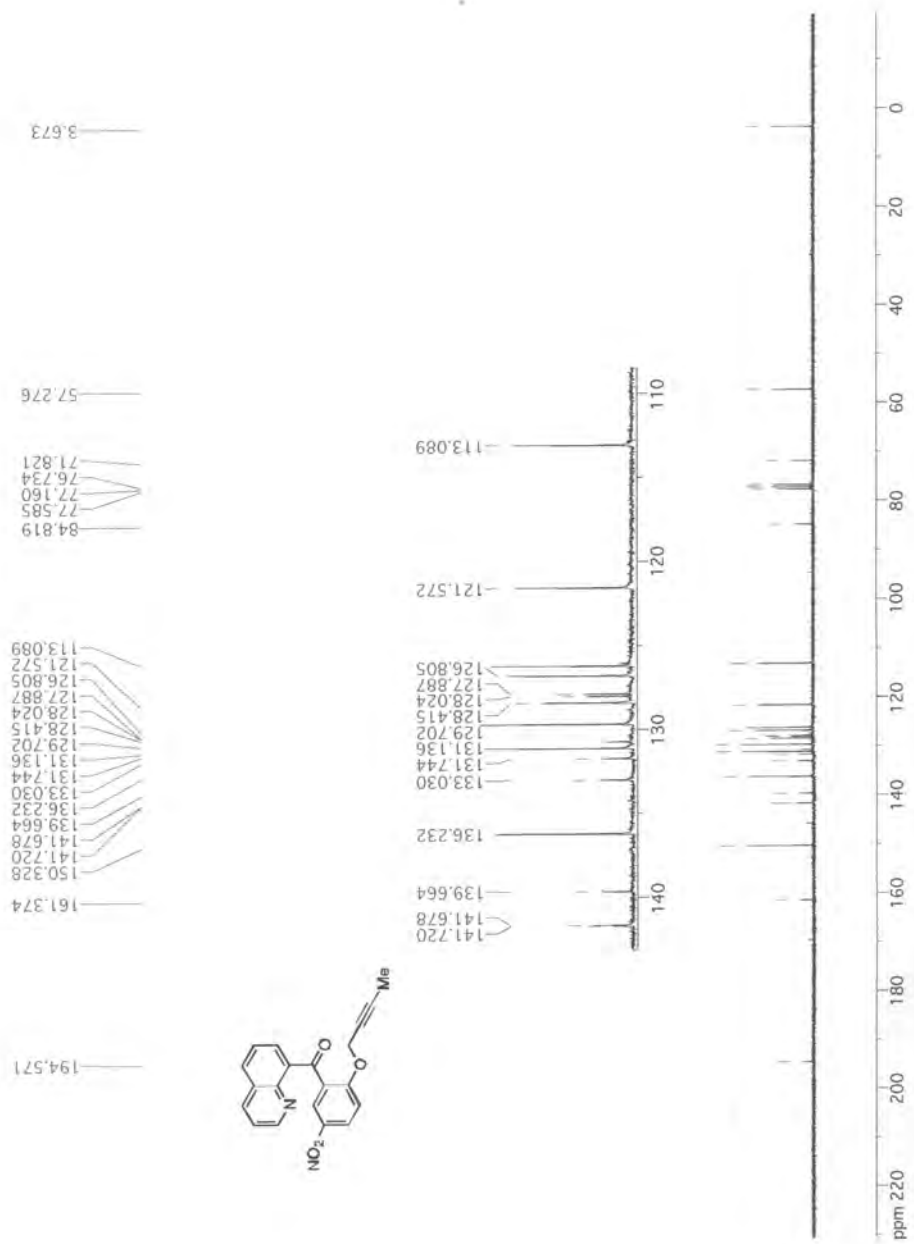


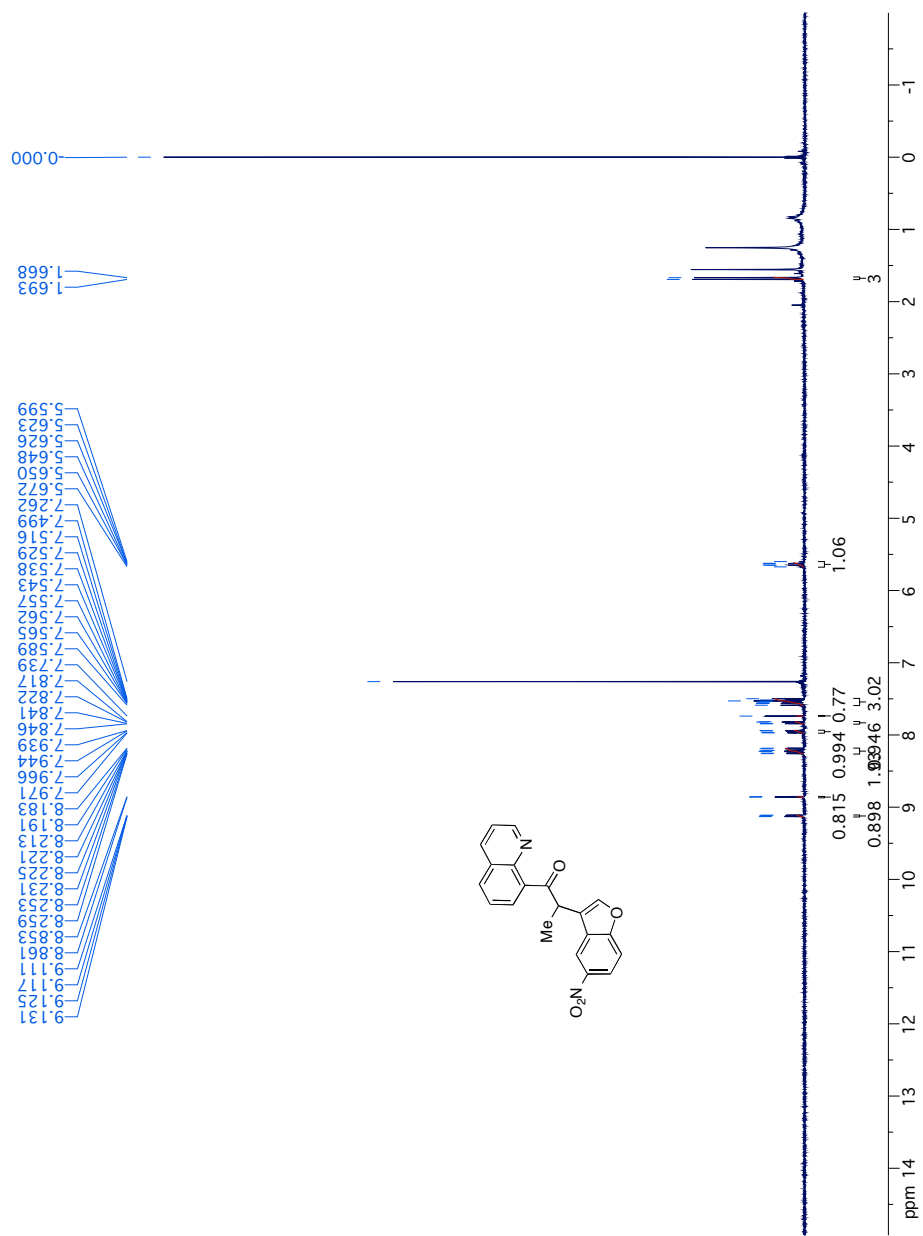


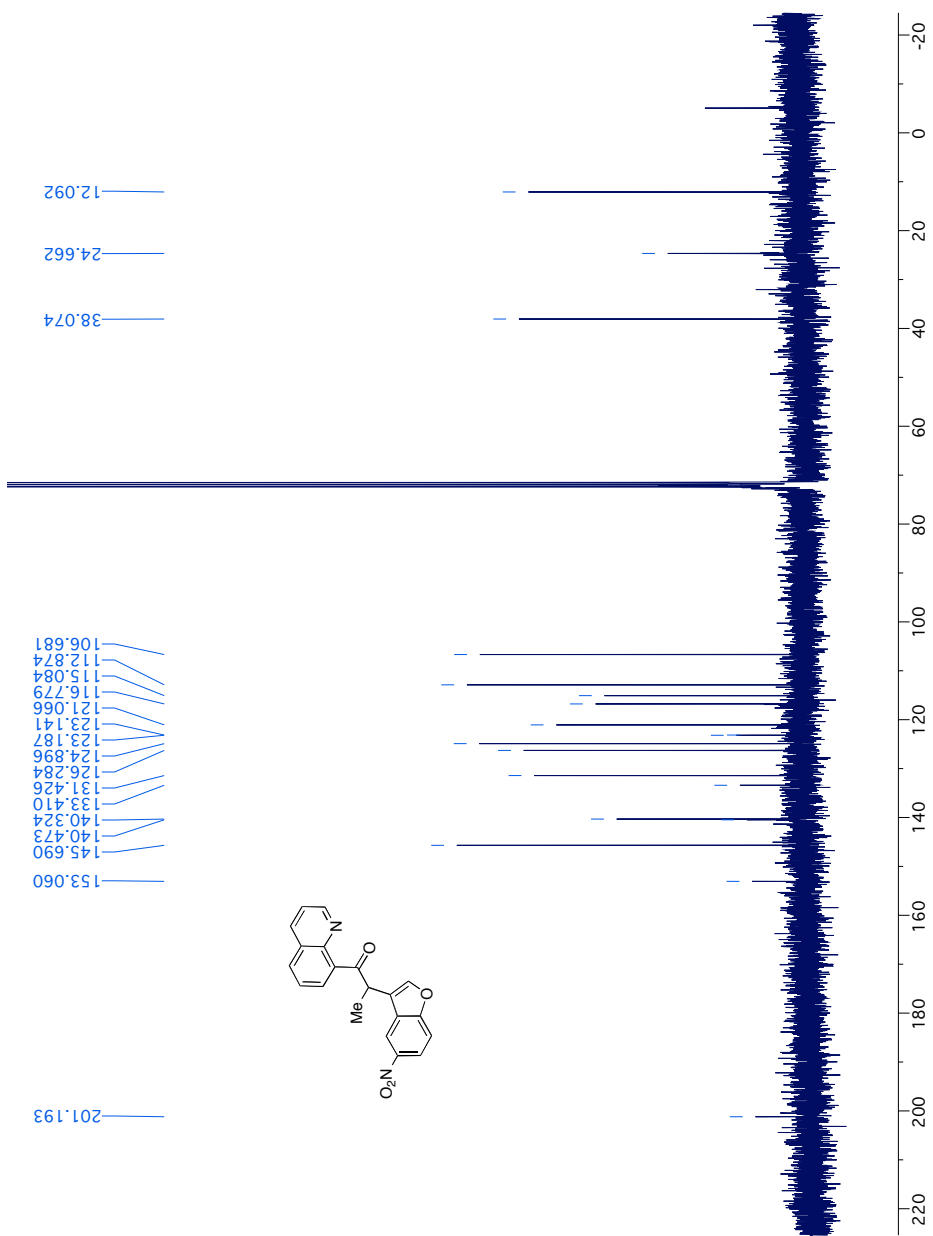


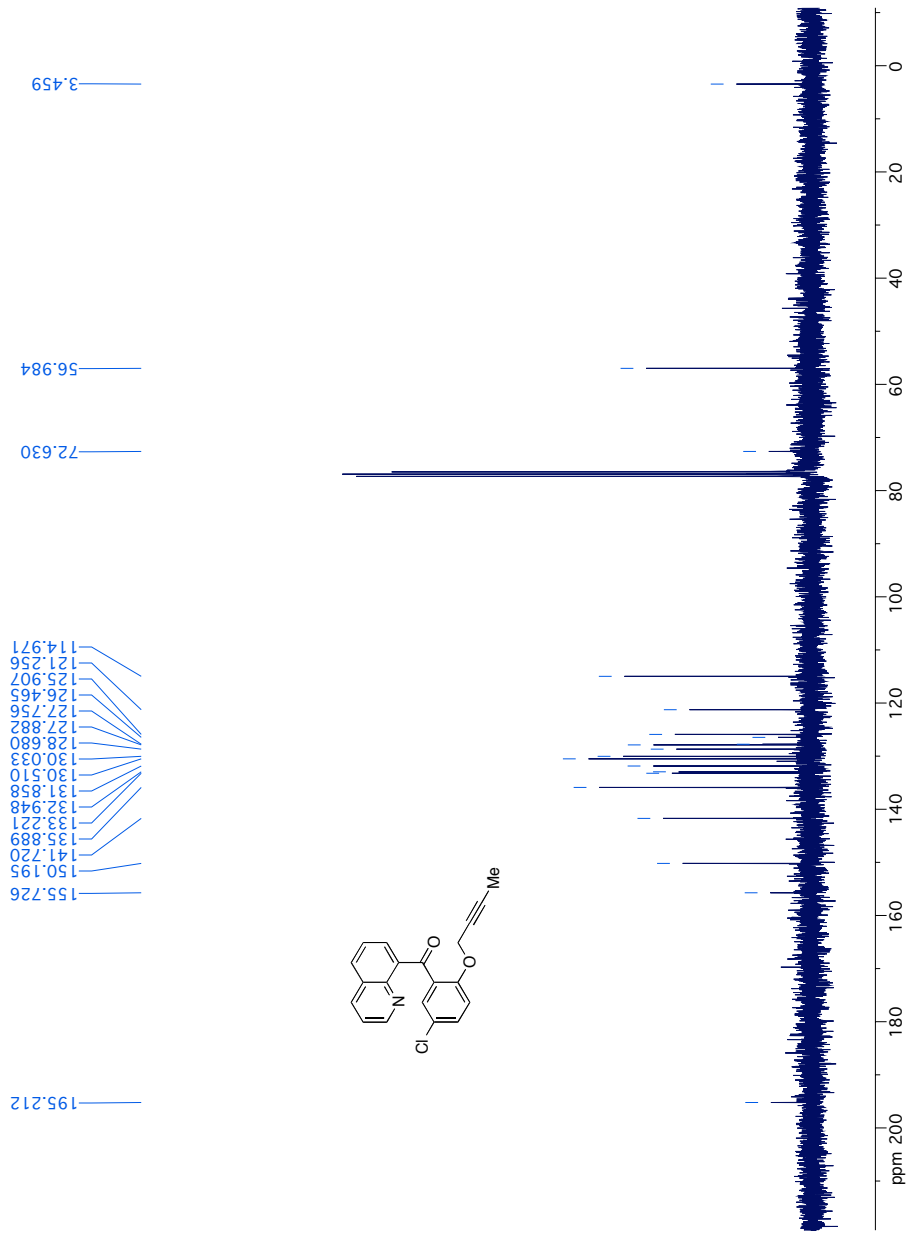


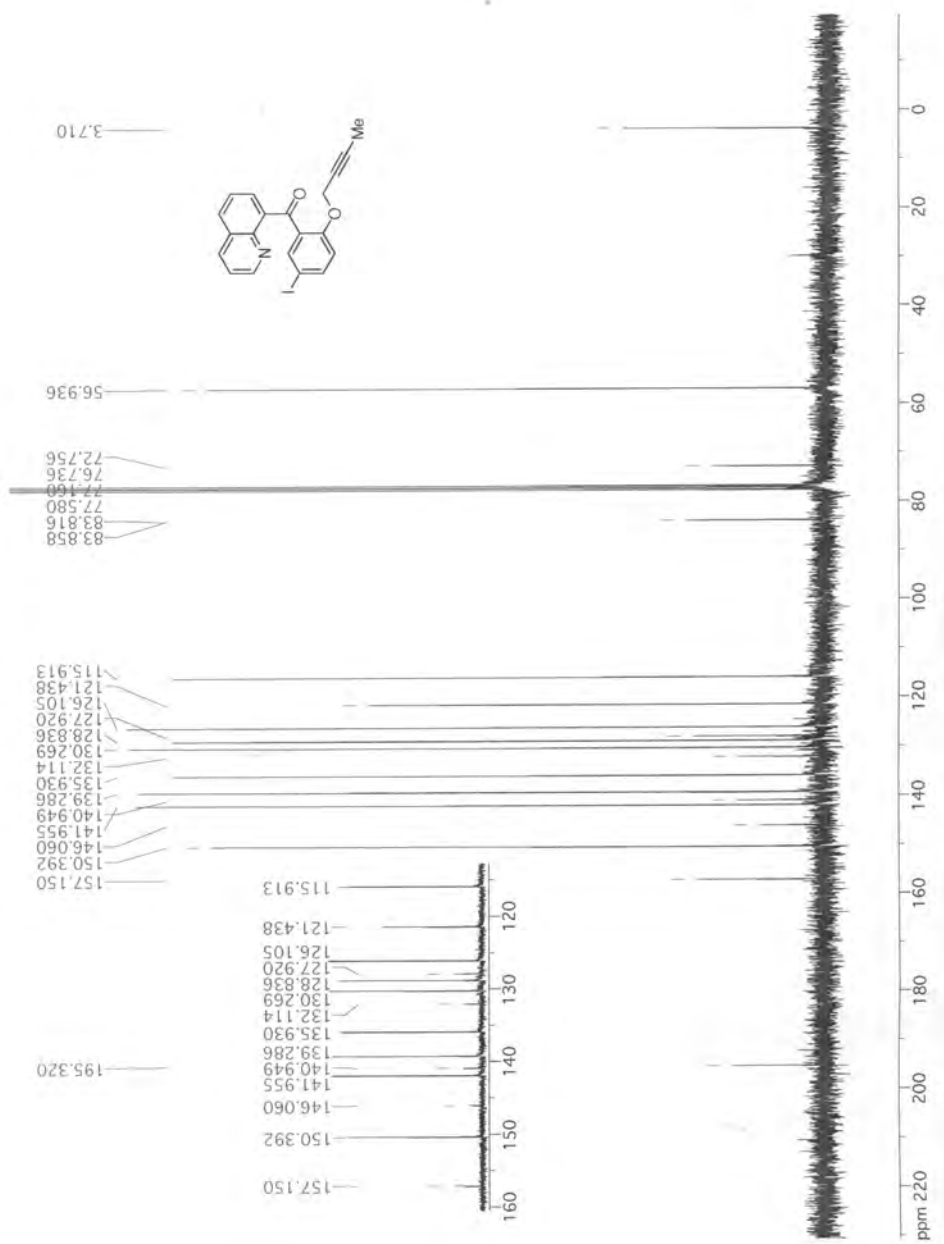


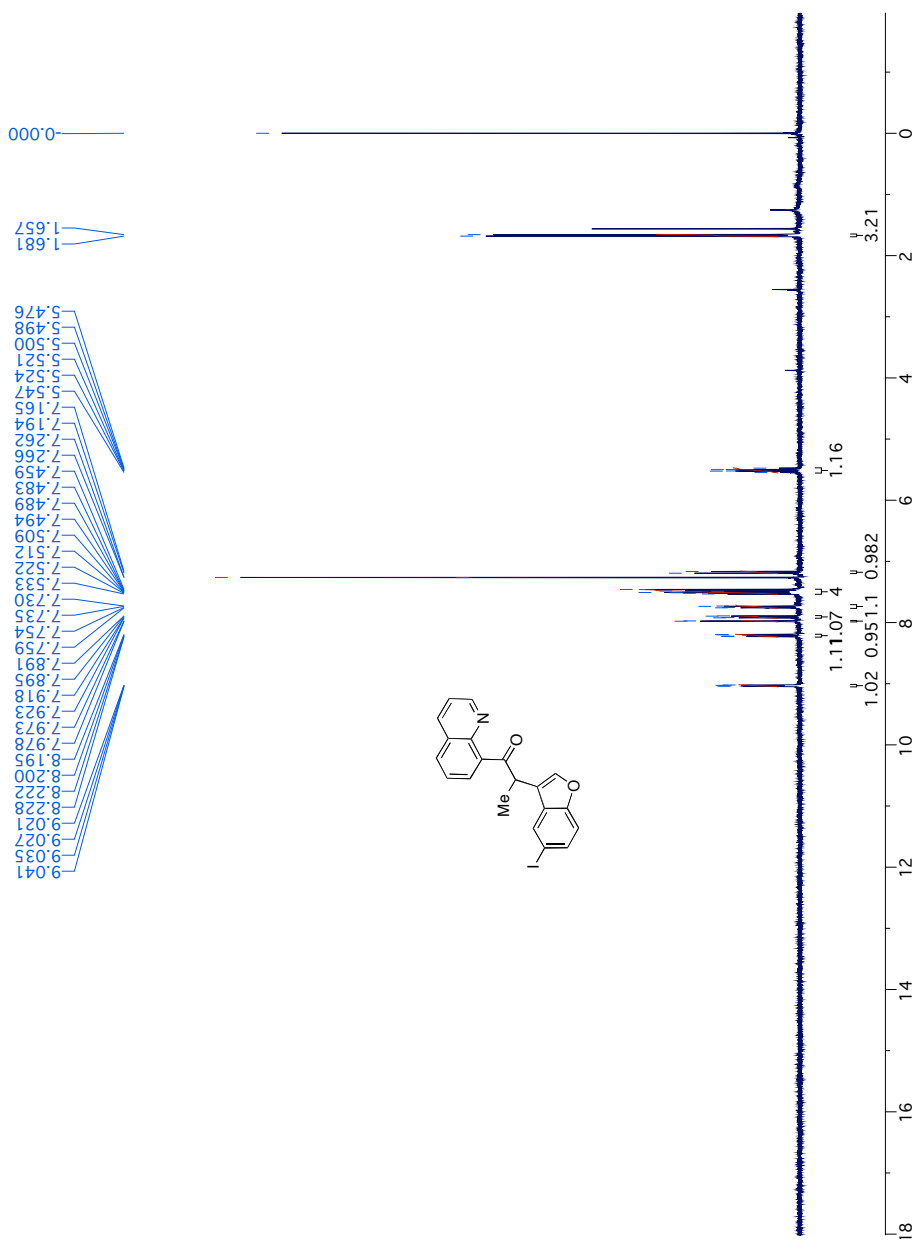


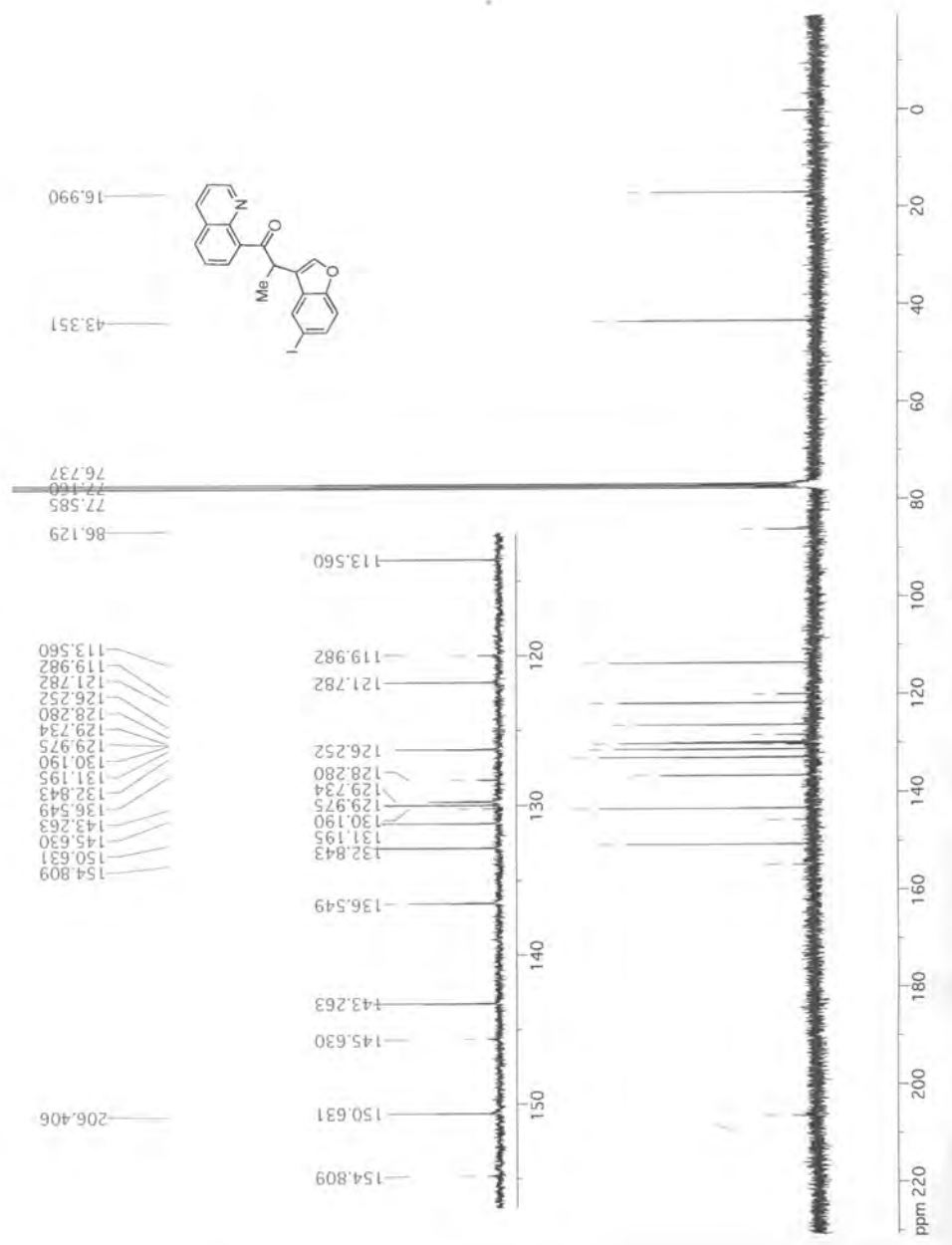


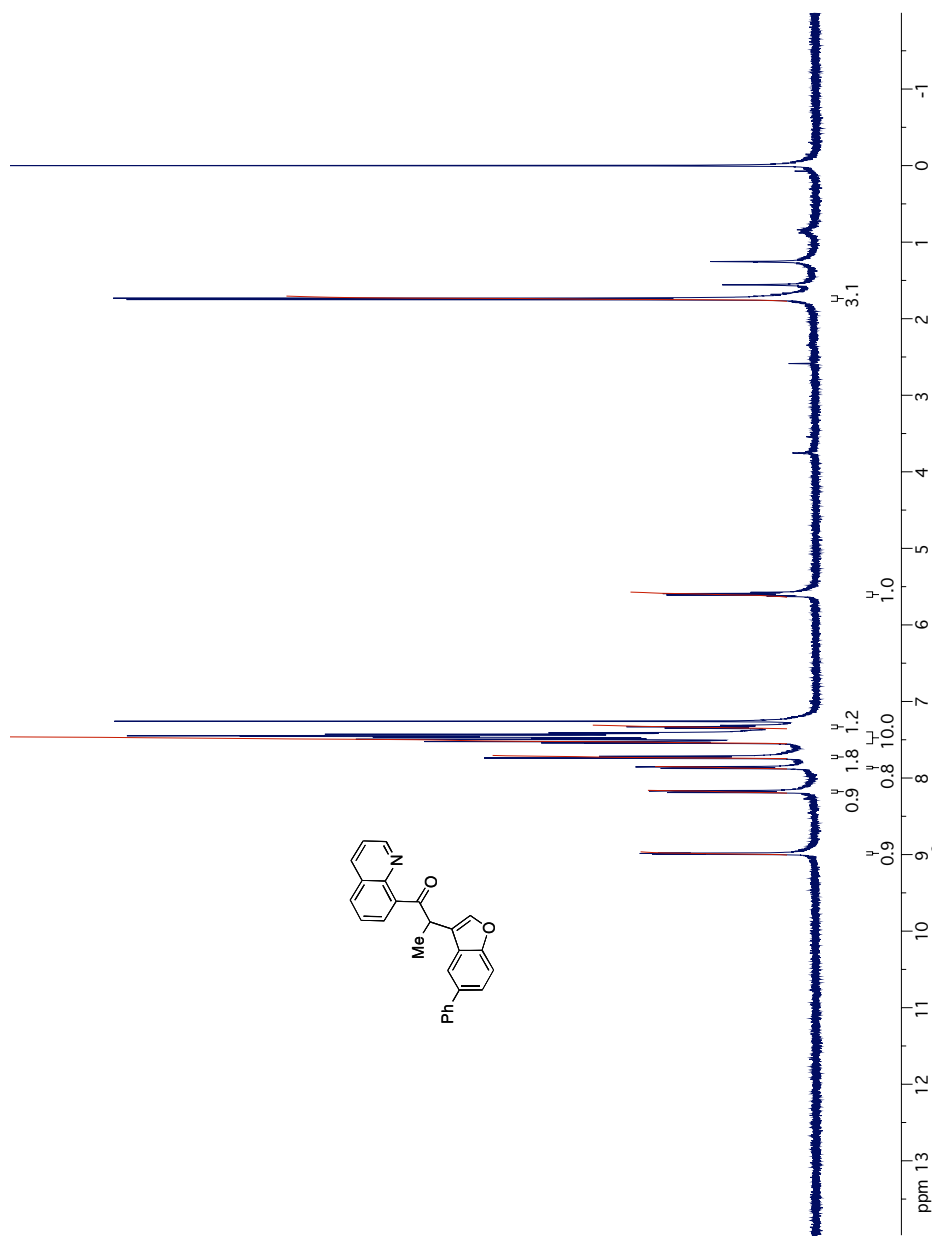


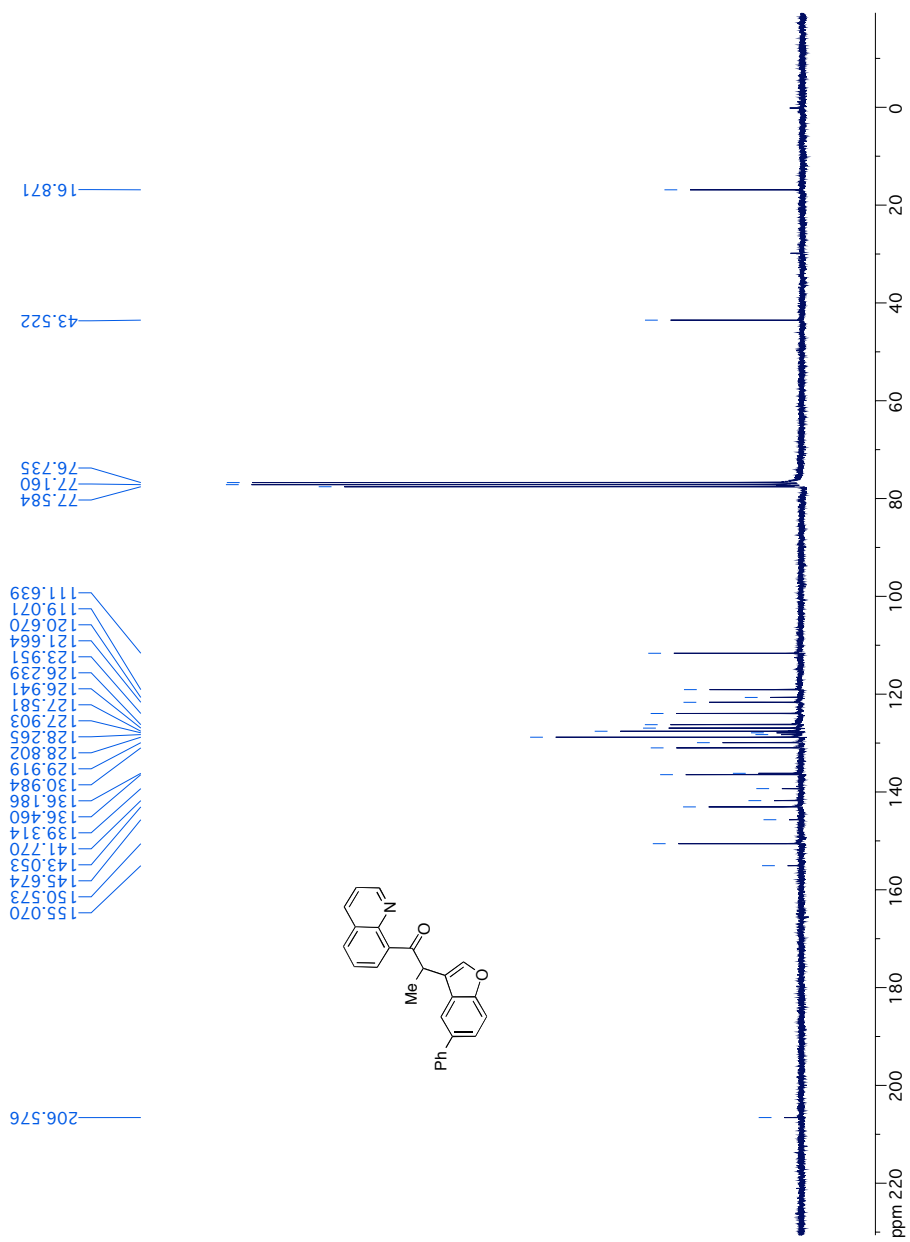




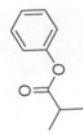




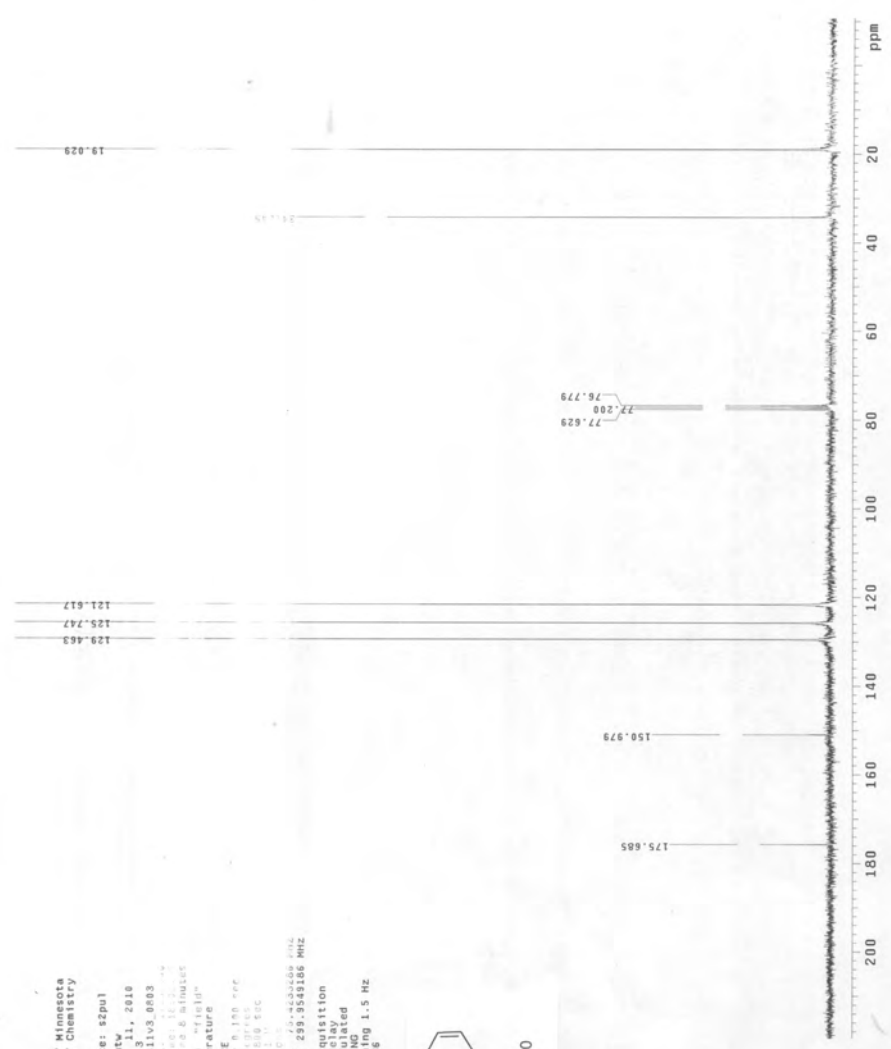




MTVII-69
 University of Minnesota
 Department of Chemistry
 VAC-360
 Pulse Sequence: szpul
 User: cdonw
 Date: Apr 11, 2010
 Time: 10:11:53.0003
 Total SCA: 110.0 minutes
 UNITV0105-503 "fishb"
 Ambient Temperature
 PULSE SEQUENCE
 Acq. time 8.200 SEC
 13C PPM: 11.0
 OBSERVE CH3, 20-ac33000 MHz
 PULSE PRG: zgpg30
 Power 40 dB, 29.9549166 MHz
 on during acquisition
 of the sample by
 VALZ14 (solid)
 DATA PROCESSING
 Line broadening 1.5 Hz
 F1 125.000000



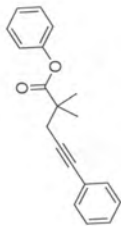
MW = 164.20



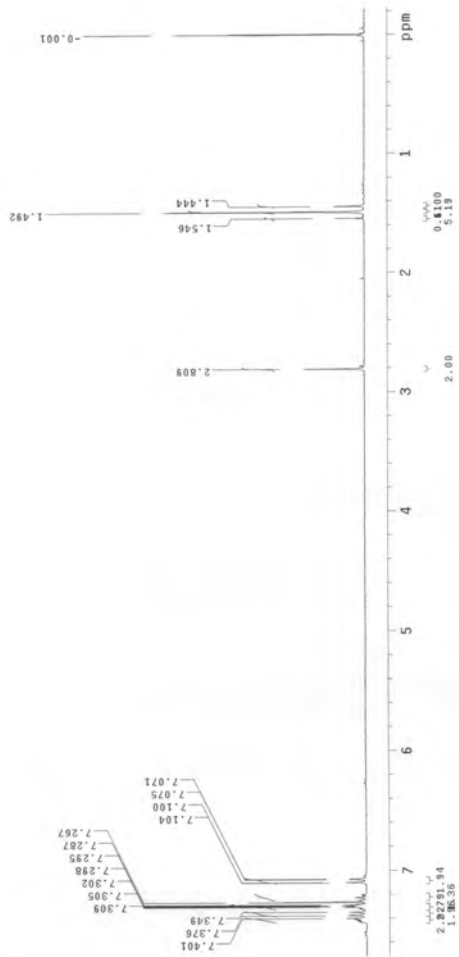
University of Minnesota, VI-300

Pulse Sequence: zgpg30

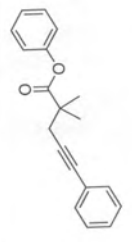
Date: Feb. 19, 2010
Solvent: CDCl3
Completion Time: 17:21:44
Total acq. time: 1 minute
UNITYplus-300 "v1300"
Ambient temperature
Spectral width: 13000 Hz
Relax. delay: 1.500 sec
Pulse: 45.0 degrees
Acq. time: 0.300 sec
Width: 5389.7 Hz
4 repetitions
SPECTROSCOPY: 90.1653401 MHz
DATA PROCESSING: 0.1 Hz
Line broadening: 0.1 Hz
FI size: 131072



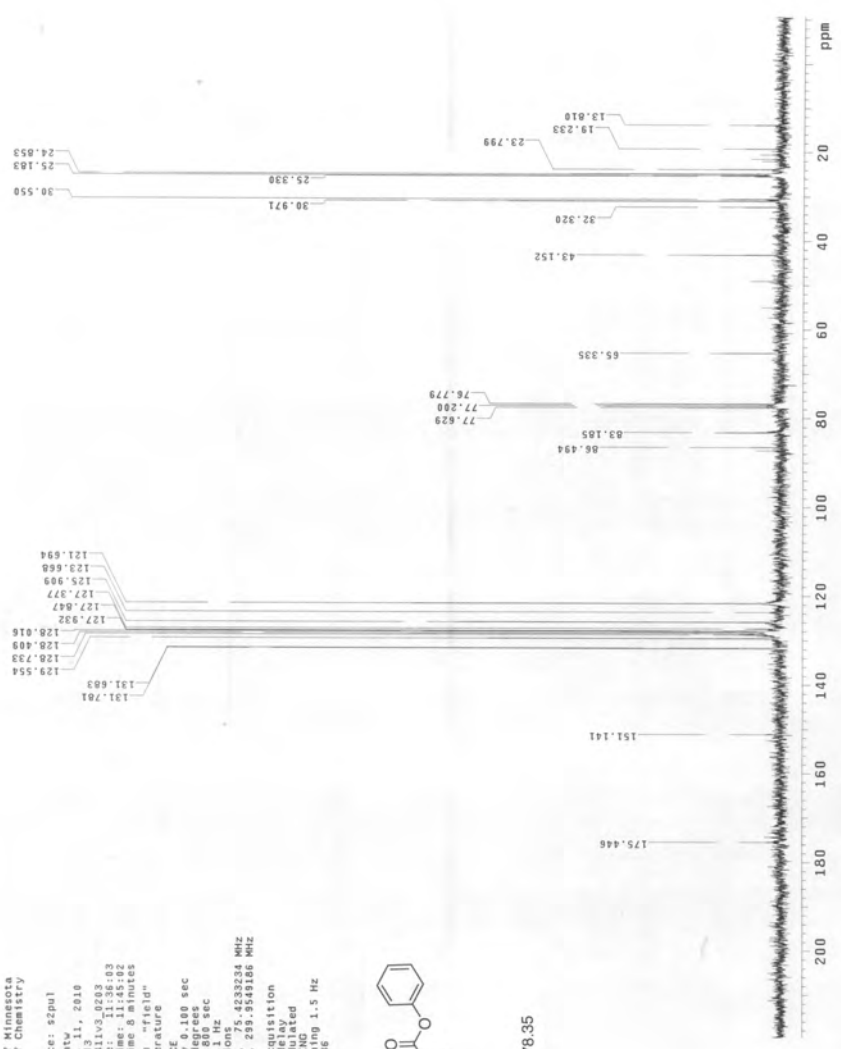
MW = 278.35



MTV11-10316-3
 University of Minnesota
 Department of Chemistry
 VAC-380
 Pulse Sequence: szpu1
 User: cdomw
 Date: Apr. 11, 2010
 File: 100411v3_0203
 Starting Time: 11:38:03
 Total acq. time: 8 minutes
 UNITYplus-500 "field"
 Ambient temperature
 PULSE SEQUENCE
 Pulse width: 100 sec
 Pulse 70 degrees
 Acq. time: 0.800 sec
 192 repetitions
 OBSERVE: C13, 75.423234 MHz
 Power: 40 dB, 239.5949166 MHz
 on during acquisition
 DATA PROCESSING
 FT 124.855310g 1.5 Hz
 FT 124.855310

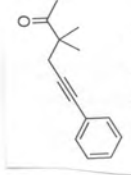


MW = 278.35

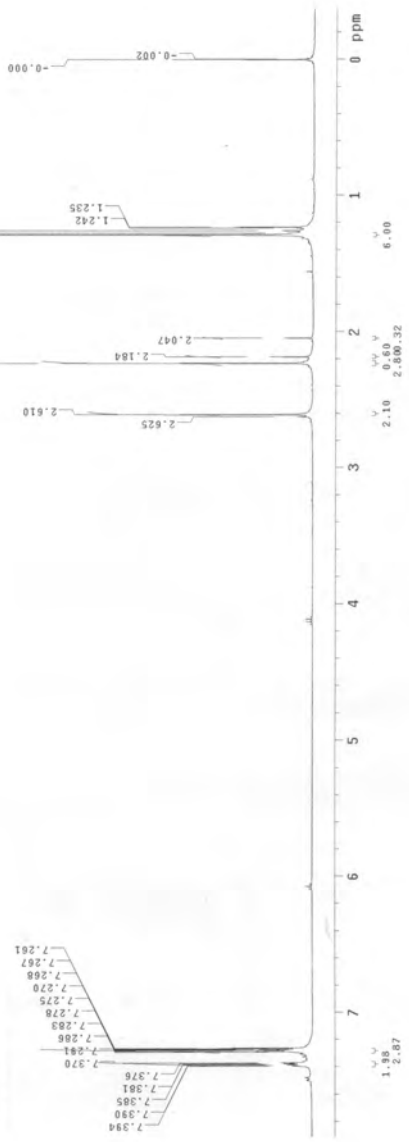


STANDARD 1H OBSERVE

Pulse Sequence: zgpg1
Date: Mar. 3, 2010
Solvent: CDCl3
Scan Time: 17:37:10
Completion Time: 17:38:10
Total acq. time: 1 minute
Multi purpose spectrometer
PULSE SEQUENCE
Relax. delay: 1.500 sec
Pulse: 45.0 degree
Width: 6391.8 Hz
Spectrum
OBSERVE: 400.2874118 MHz
DATA PROCESSING
Line broadening: 0.1 Hz
F1: 315 1319.2



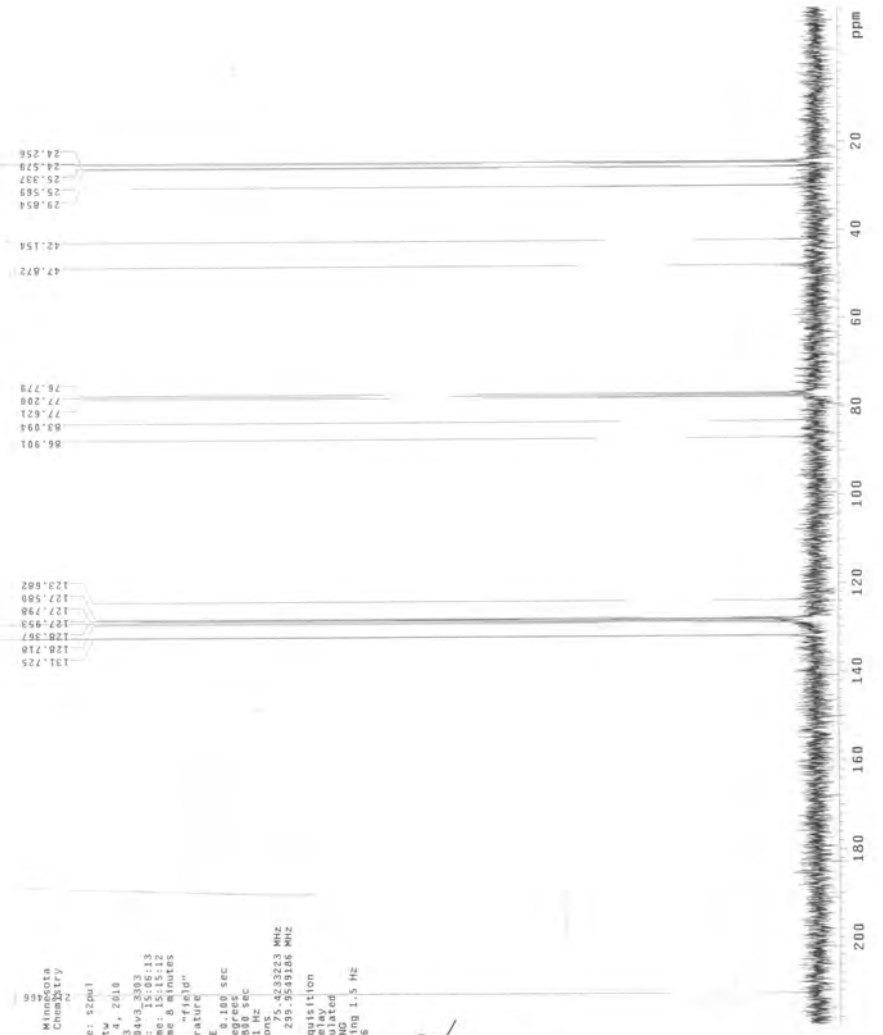
MW = 200.28



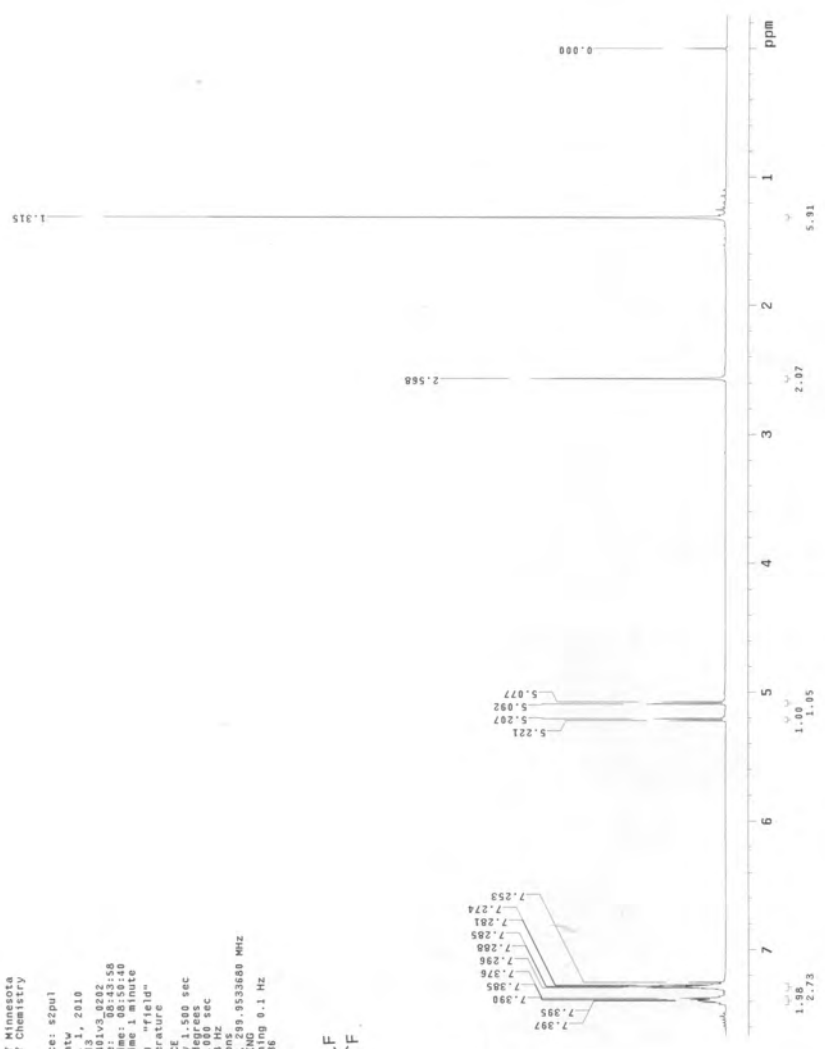
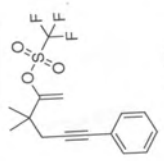
MTH11-08-74-7
 University of Minnesota
 Department of Chemistry
 VAE-380
 660
 Pulse sequence: zgpg1
 Date: Mar 4, 2010
 Solvent: CDCl3
 Starting Time: 15:06:13
 Completion Time: 15:15:12
 Acquisition Time: 8.988
 File name: zgpg1
 Ambient temperature
 PULSE SEQUENCE
 Relax_delay 0.100 sec
 Acq 1.000 sec
 Width 17361.1 Hz
 Acq time 0.088 sec
 OBSERVE C13
 DECOUPLE H1 -239.9549186 MHz
 on during acquisition
 off during delay
 DATA ACQUIRED
 DATA PROCESSING
 Line broadening 1.5 Hz
 FT size 65536



MW = 200.28

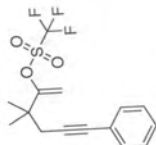


MTW11-99
 University of Minnesota
 Department of Chemistry
 VAC-388
 Pulse Sequence: szpu1
 User: cdomw
 Date: Apr 1, 2010
 Time: 10:03:58
 File: 10040103.0202
 Starting Time: 00:43:58
 Stopping Time: 00:44:00
 Total acq. time: 1 minute
 UNITYplus-500 "field"
 Ambient temperature
 PULSE SEQUENCE
 P1: 1.50 sec
 P2: 4.00 sec
 Pulse 45 degrees
 Acq. time 2.000 sec
 Vcycle: 1024
 16 repetitions
 OBSERVE H1: 299.9533680 MHz
 P1: 1.50000000 sec
 P2: 4.00000000 sec
 Time broadening 0.1 Hz
 FT size 65536

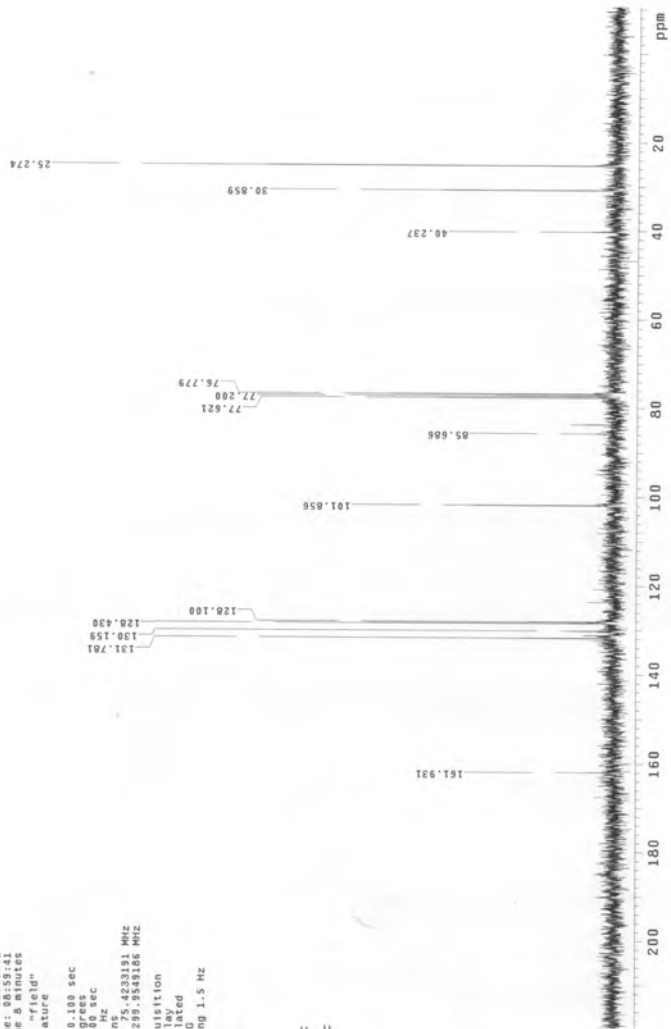


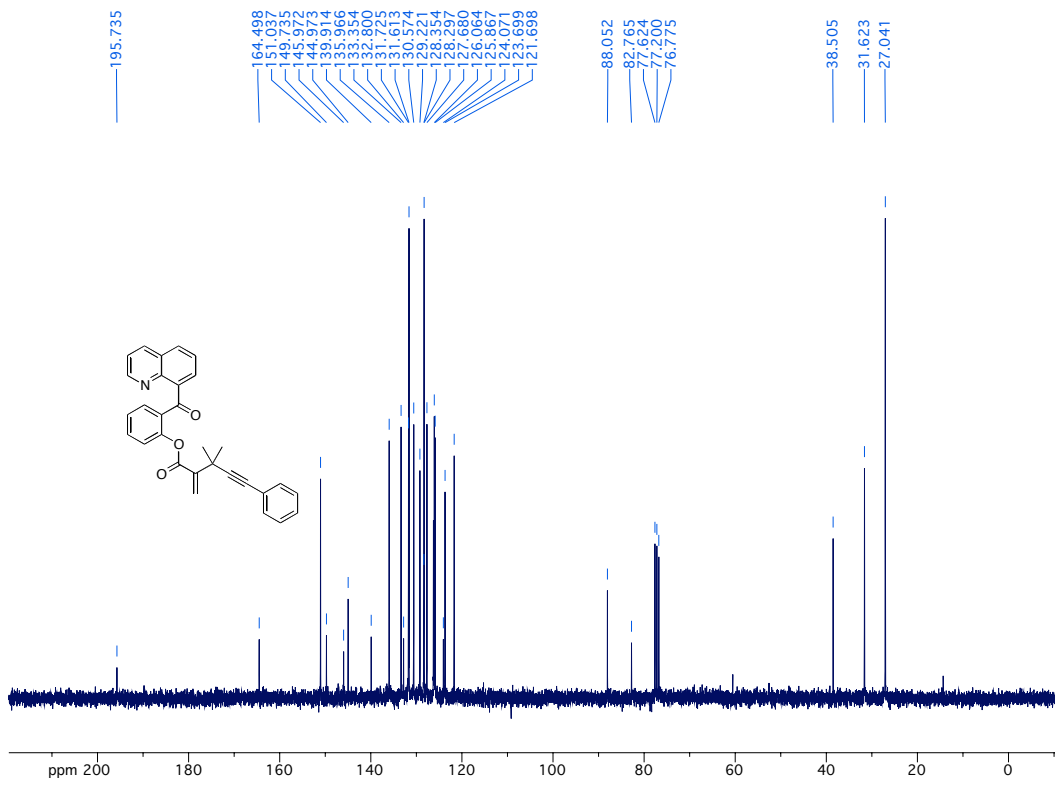
MTW11-99
University of Minnesota
Department of Chemistry
MR-500

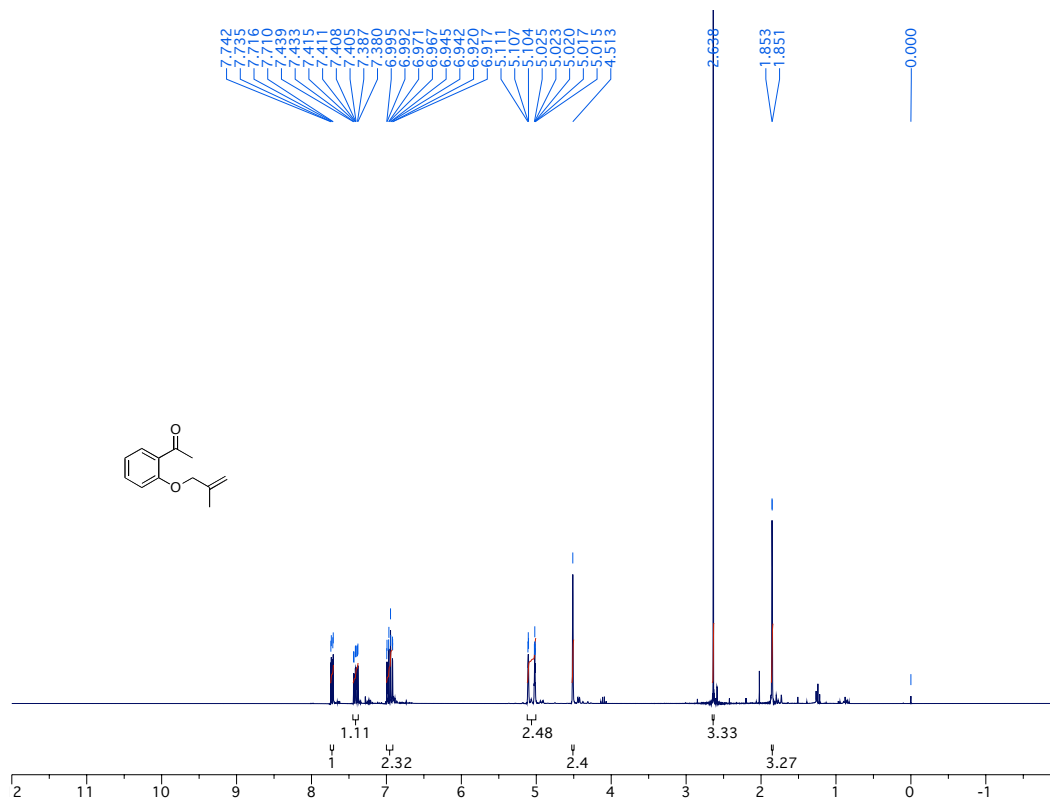
Pulse Sequence: szpu1
User: cdoety
Date: 11/17/99
Solvent: CDCl3
Title: 100401v3_0202
File: 100401v3_0202
Completion Time: 08:58:41
Total acq. time 9 minutes
UNITVul-500 "rfile"
PULSE SEQUENCE
PULSE SEQUENCE
Relax. delay 0.100 sec
Pulse 70.0 degrees
Width 17361.1 Hz
132 repetitions, 4233181 MHz
DECUPLE H1, 299.9548186 MHz
Power 40 dB acquisition
off during delay
WALTZ-16 Modulated
Decoupling
Line broadening 1.5 Hz
FF size 65536

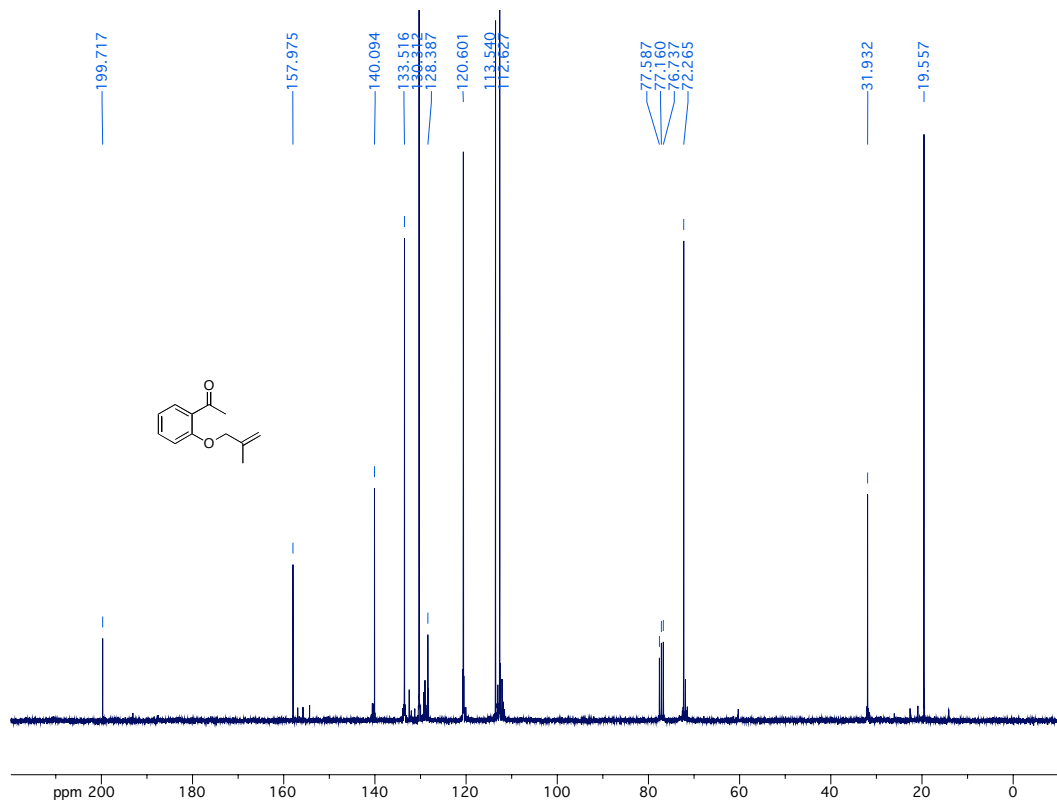


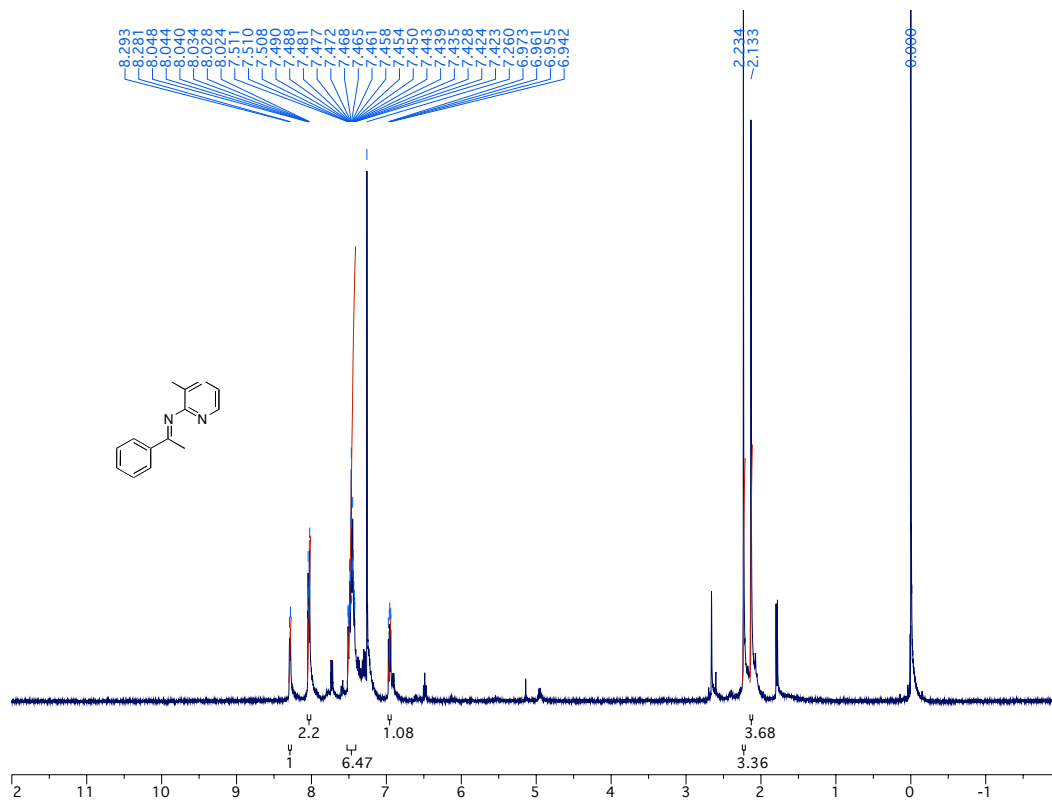
MW = 352.34

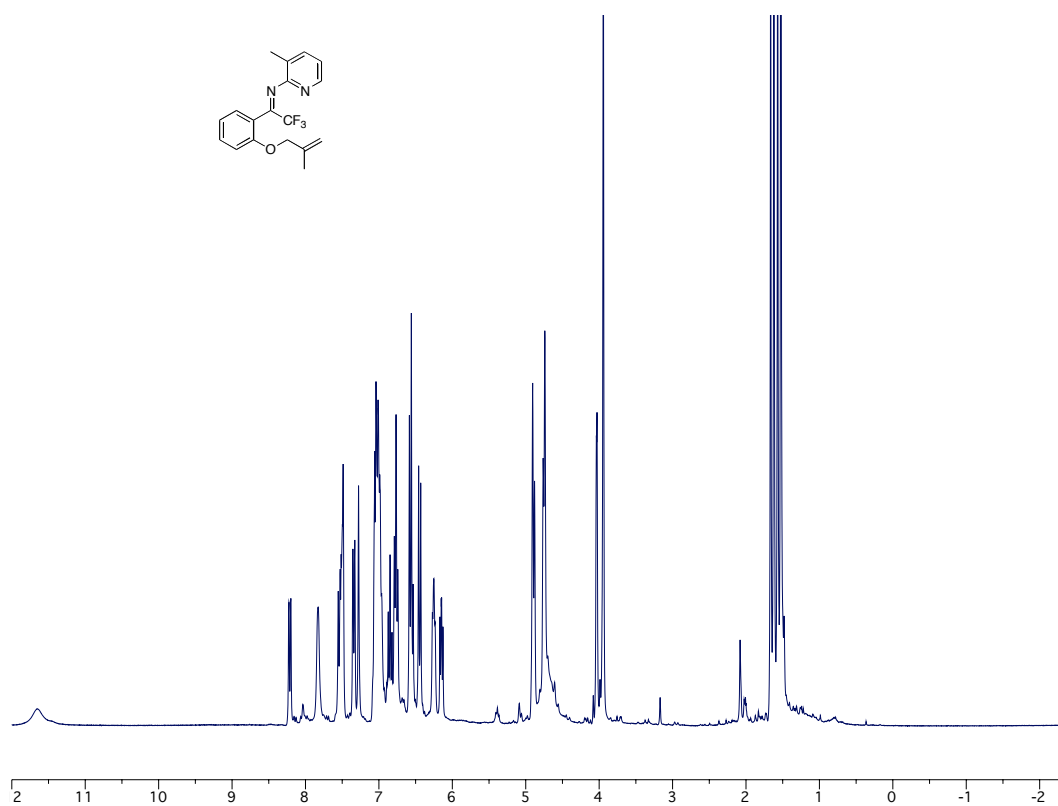


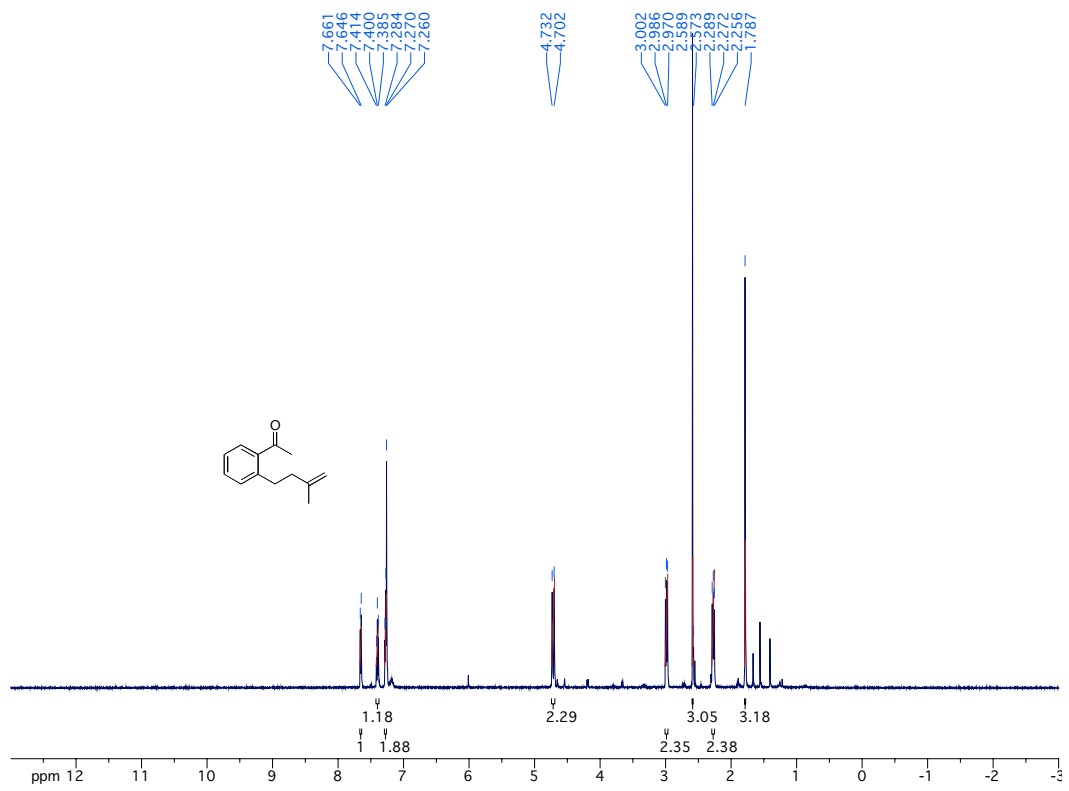










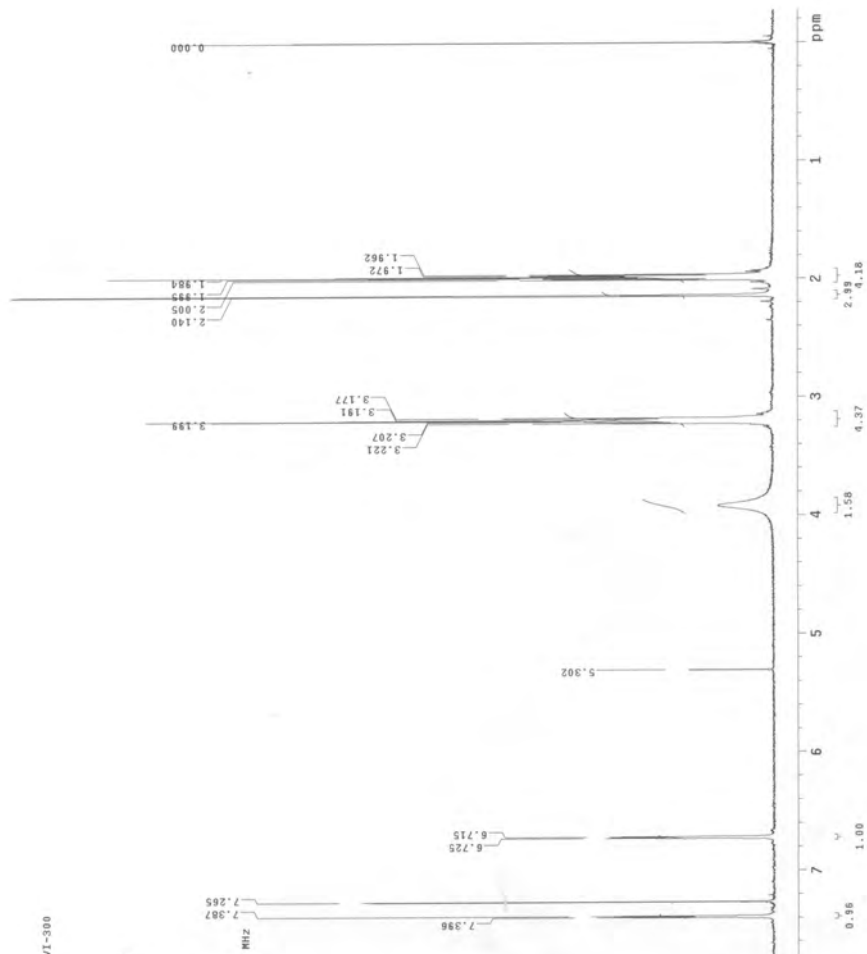
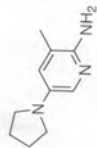


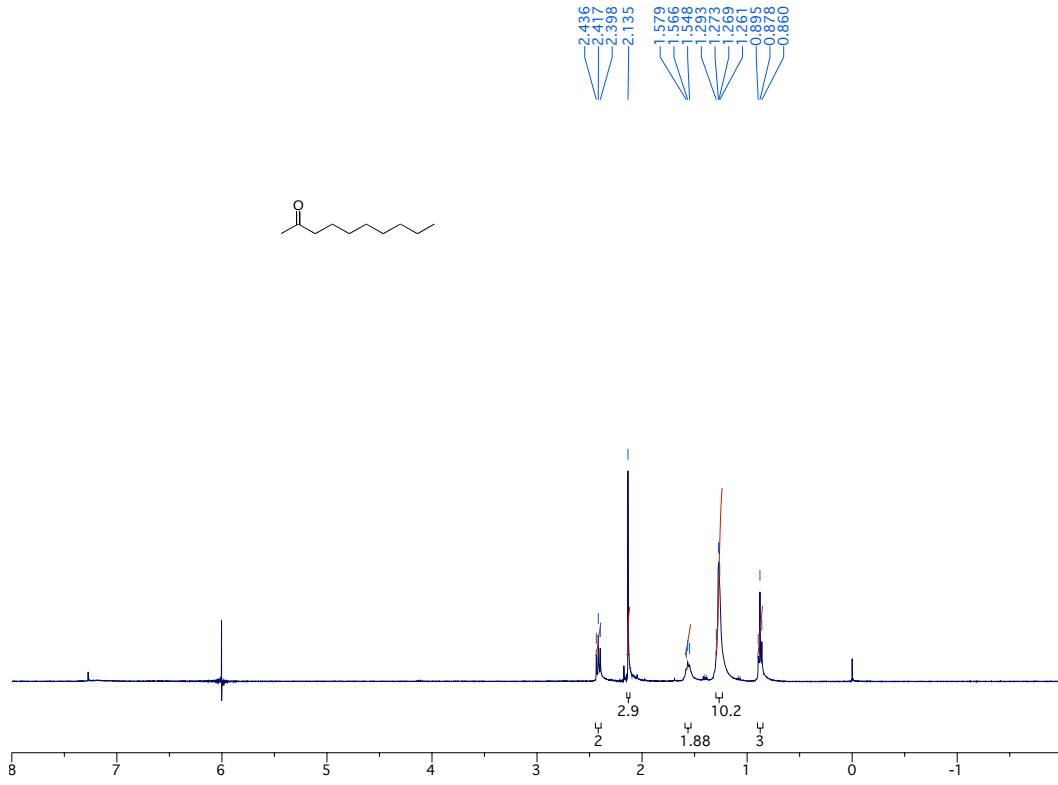
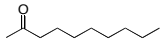
University of Minnesota, VI-300

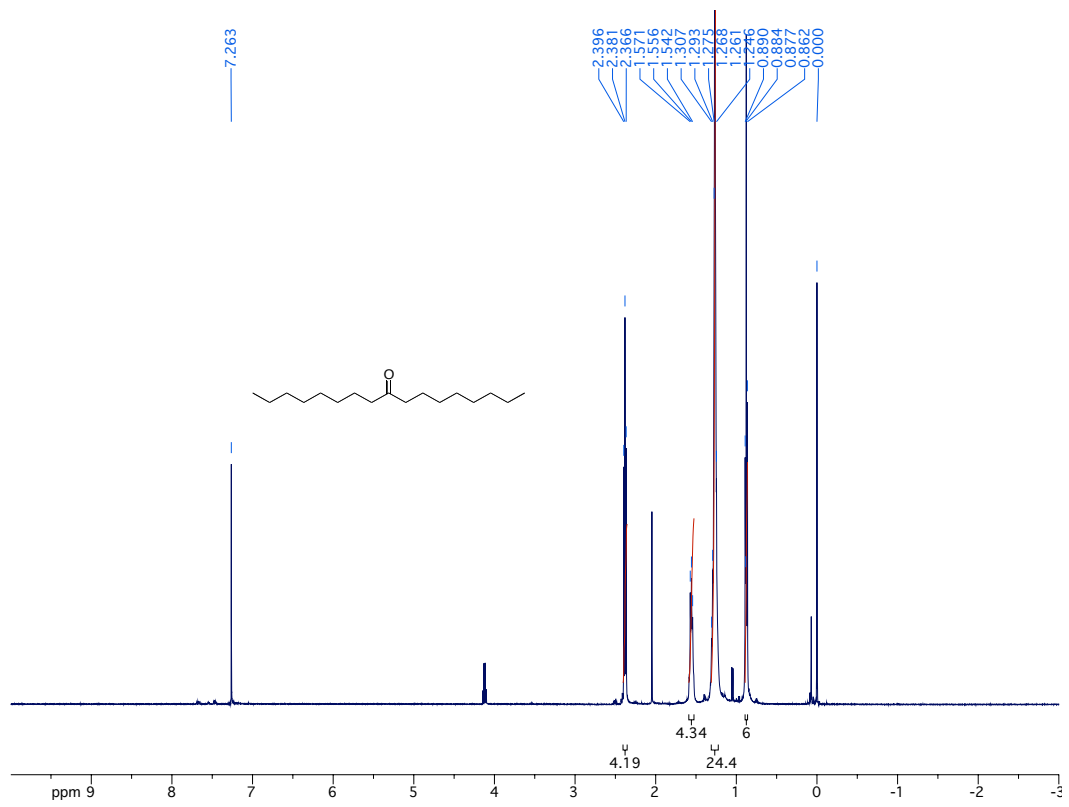
Pulse Sequence: s2pul

Date: Jan. 18, 2011
Run: 1
Starting Time: 16:14:51
Completion Time: 16:15:14
Operator: jk
Solvent: dms
Conc: 0.000 g/ml
WVTX: 0.000 g/ml
Ambient Temperature

PULSE SEQUENCE
Relax. delay 1.500 sec
Acq. time 0.005 sec
Acq. time 2.005 sec
Vp 1.000
Vw 5898.7 Hz
SFO 300.1360172 MHz
OBSERVE F1 300.1683384 MHz
DATA PROCESSING
SFO 300.1360172 MHz
F1 162.831072







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