THESIS

THE ENANTIOSELECTIVE RHODIUM CATALYZED [2+2+2] CYCLOADDITION OF ALKENYL ISOCYANATES WITH DIARYL ACETYLENES AND 1,2-DISUBSTITUTED ALKENYL ISOCYANATES

Submitted by

Mark Emil Oinen

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Master of Science

Colorado State University

Fort Collins, Colorado

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WE HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER OUR SUPERVISION BY MARK EMIL OINEN ENTITLED THE ENANTIOSELECTIVE RHODIUM CATALYZED [2+2+2] CYCLOADDITION OF ALKENYL ISOCYANATES WITH DIARYL ACETYLENES AND 1,2-DISUBSTITUTED ALKENYL ISOCYANATES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE.

Committee on Graduate work

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Robert M. Williams

_____

Matthew Kipper

_____

Advisor: Tomislav Rovis

_____

Chair: Ellen R. Fisher

ABSTRACT OF THESIS

THE ENANTIOSELECTIVE RHODIUM CATALYZED [2+2+2] CYCLOADDITION OF ALKENYL ISOCYANATES WITH DIARYL ACETYLENES AND 1,2-DISUBSTITUTED ALKENYL ISOCYANATES

Elaborating upon the recent discovery of a [2+2+2] rhodium-catalyzed cycloaddition of alkenyl isocyanates with various alkynes, the scope of this rhodium-catalyzed cycloaddition with diaryl acetylenes was explored. The reaction with pentenyl isocyanate and diaryl acetylenes utilizing $[Rh(C_2H_4)Cl]_2$ and 3,3'-substituted BINOL phosphoramidites as a catalyst predominantly affords vinylogous amide type products. Investigation into product selectivity reveals that both electronic and steric factors of the ligand have an influence on the product selectivity. Information gleaned from these studies allowed for a change in product selectivity for formation of lactam products with diaryl acetylenes. Selectivity for lactam product is at best 1:1.5 with BINOL phosphites. Vinylogous amide products are formed selectively (>20:1) in the cycloaddition using a variety of BINOL based phosphoramidites.

Using 3,3' substituted BINOL based phosphoramidites promising enantioselectivies are obtained in the cycloaddition of diaryl acetylenes and pentenyl isocyanate. In the course of this investigation an interesting effect of substrate on the enantioselectivity was noticed. The ee of the reaction is highly dependent upon the nature of the diaryl acetylene. It was revealed that substrate affects the enantioselectivity by playing the role of spectator ligand in the reaction. Elucidation of the mechanism of the

role of this spectator ligand was done by characterization of intermediates, kinetic analysis of the reaction rate and competition experiments between substrates.

This effect of spectator ligands was exploited in a synthetically viable way to yield products with high and consistent enantioselectivities. By employing methyl nicotinate, a non-participating spectator ligand, as a stoichiometric additive synthetically useful enantioselectivities can be achieved.

Finally, limitations existed within the scope of both alkynes and alkenyl isocyanates on the scope of the rhodium catalyzed [2+2+2] cycloaddition. Acetylene dicarboxylates, and 1,2-disubstituted alkenyl isocyanates were reaction partners that failed to provide cycloadducts under current reaction conditions. In both cases, the resultant cycloadduct would be interesting as they could provide additional synthetic handles for further manipulation of cycloadducts. Identification of undesired byproducts in these reactions allowed for the development of reaction conditions to reduce their formation of these by-products. The reduction in the formation of benzenoids formed from alkyne trimerization allowed for the production of mixtures of lactam and vinylogous amide products using acetylene dicarboxylates. With 1,2-disubstituted alkenyl isocyanates the implementation of reaction conditions which lead to the suppression of 2-pyridone lead to successful formation of the lactam products.

Mark Emil Oinen
Department of Chemistry
Colorado State University
Fort Collins, CO 80523
Spring 2010

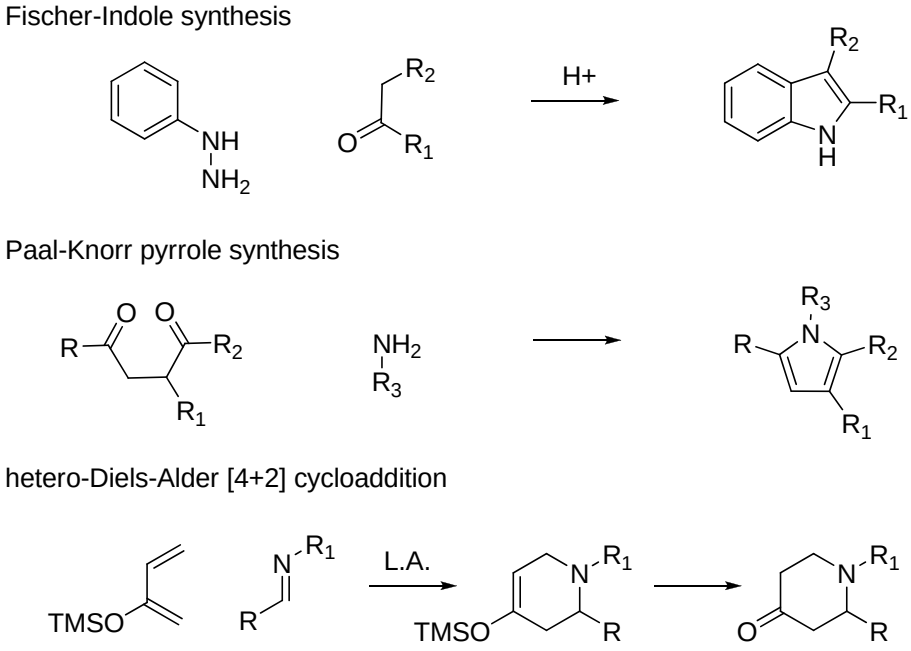
Chapter 1

The Development of the Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates with Diaryl Acetylenes

1.1 Introduction

The utilization in drug development of nitrogen-containing heterocycles provides impetus for research into efficient methods for their synthesis. One rapid approach to the construction of heterocycles is the formation of multiple bonds in a single transformation. Classic examples of these methods for the formation of heterocycles are the Fischer indole synthesis, the Paal-Knorr pyrrole synthesis and the hetero-Diels-Alder cycloaddition (Fig. 1).

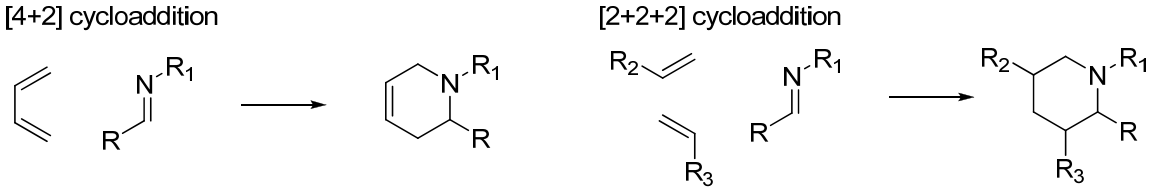
Figure 1.



In each of these examples a heterocycle is formed by the formation of multiple bonds in a single reaction. In each of these examples important heterocycles are formed

which are important pharmacophores in drug molecules. Cycloadditions are a powerful synthetic method due to their ability to synthesize molecules of greater complexity from simple starting materials. The Diels-Alder reaction, a [4+2] cycloaddition to form six-membered rings has proven perhaps the most powerful method for creating stereodefined and sterically congested cores of natural products in organic synthesis. A natural extension of the Diels-Alder reaction is the [2+2+2] cycloaddition in which three separate π-components are brought together to form the three bonds of a six-membered ring. The change in complexity of a molecule is directly related to the number of bonds formed in a reaction. In theory three-component cycloadditions offer the opportunity for a greater change in complexity than two-component cycloadditions, like the Diels-Alder, due to their ability to form more bonds (Fig. 2).

Figure 2.

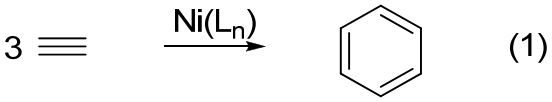


In comparison to the Diels-Alder, cycloadditions between three π–components that create complex heterocyclic cores with controlled for regio- and stereoselectivity are rare. While Diels-Alder reactions can be thermally promoted, the challenges to a three-component cycloaddition are the entropic penalty of bringing three distinct molecules together at precisely the right time, or the instability of reactive intermediates along the pathway to the desired products. Therefore it is necessary to lower these barriers to activation by the intervention of some catalyst.

Metals are in a unique position to overcome the energetic barriers to three-component cycloaddition reactions. First the organization about the metal center of up to

6 ligands allows for ligand-metal interactions. These interactions account for the thermodynamically disfavorable loss of entropy associated with the organization of these components about the metal center. Second, metals by their ability to access multiple oxidation states, are able to undergo oxidative cyclization reactions. The metallacycles which are afforded by these oxidative cyclization reactions provide stabilization of intermediates in the cycloaddition by the formation of metal-carbon σ-bonds.

The first example of a cycloaddition which implicated the possibility of a metal's role in organizing three separate π-components about a metal to form a cyclic system was elucidated by Reppe in 1942 (Eq. 1).[1]

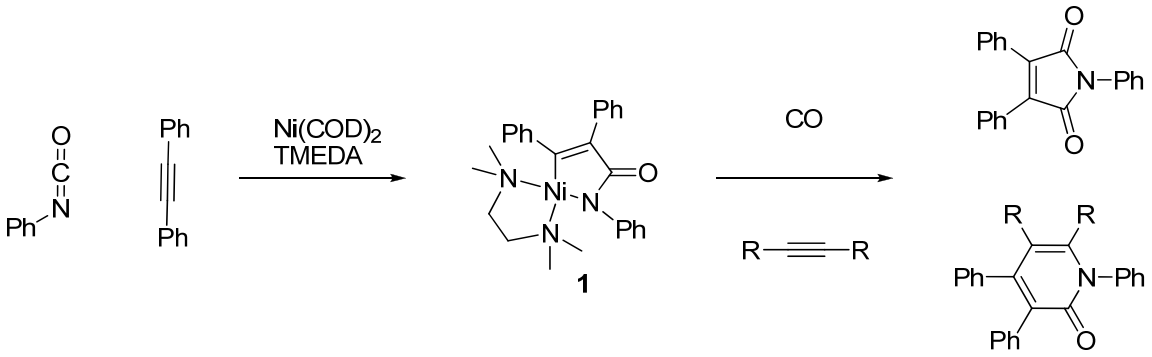


(1)

Reppe used a nickel catalyst to effect the trimerization of acetylene to form benzene. Early trimerization chemistry was effective only for simple symmetrical benzenoid structures. Further functionalization of the alkyne starting materials or use of heterocombinations of alkynes led to mixtures of regioisomers. This investigation was of fundamental importance as it suggested that the intermediacy of a metallacycle had lowered the barrier of activation of trimerization.

The utilization of isocyanates as one of the π–components introduces a heteroatom in the cyclic final product. Hoberg demonstrated the viability of this synthetic strategy by showing the stability of metallacyles, such as **1**, as synthetic intermediates, and further showing that these metallacyles could incorporate a third π–component to yield nitrogen-containing heterocycles (Fig. 3).[2]

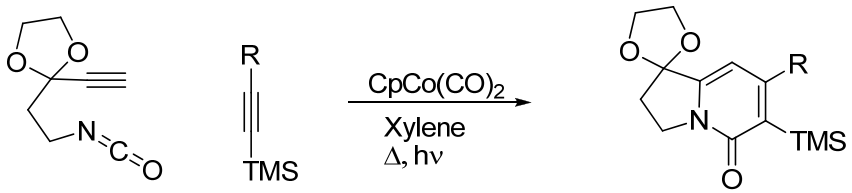
Figure 3.



Nickellacycle **1**, formed from phenyl isocyanate and diphenylacetylene, was isolated as a single regioisomer. Metallacycle **1** was used as an intermediate in the cycloaddition reaction to form two types of nitrogen containing heterocycles, maleimides and pyridones. Although this represents an efficient synthetic process, one drawback to this methodology is the stoichiometric use of nickel metal. Substoichiometric catalyst loadings are desirable because of increased efficiency, lower cost and the elimination of difficulties associated with removing metals from the product.

The first successful catalytic version of a three component cycloaddition utilizing isocyanates was published by Volhardt in 1984. A cobalt carbonyl complex proved an effective precatalyst for the cycloaddition between an alkynyl isocyanate and an alkyne that afforded bicyclic 2-pyridone type products (Fig. 4).[3]

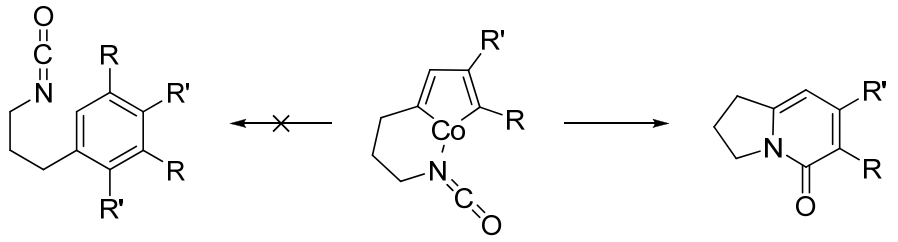
Figure 4.



Using a variety of trimethylsilyl (TMS) substituted alkynes; Vollhardt was able to show excellent regioselectivity of insertion of the alkyne. Vollhardt employed an alkynyl

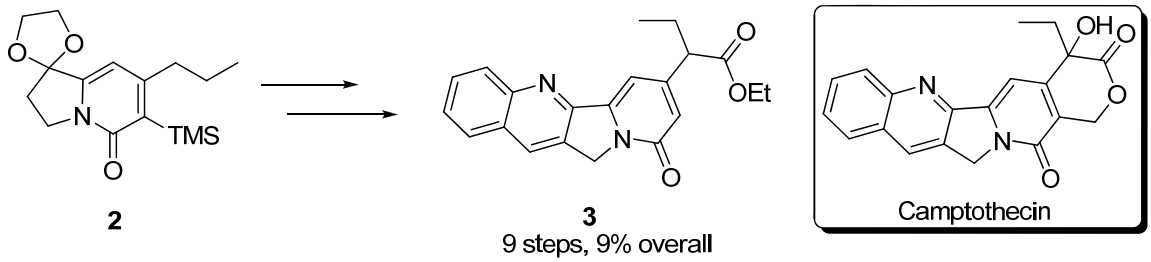
tethered isocyanate which allowed for rapid insertion of the isocyanate and avoided the competing alkyne trimerization (Fig. 5).

Figure 5

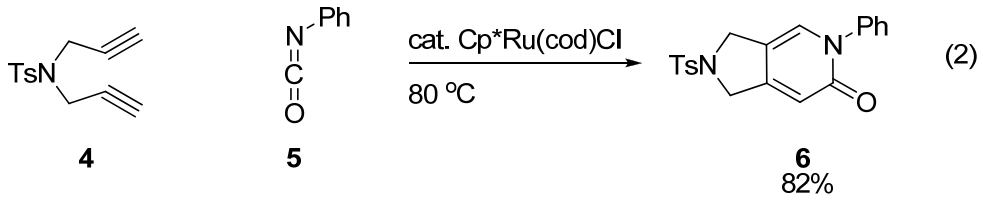


Vollhardt and coworkers applied this methodology to the total synthesis of a natural product, Camptothecin. Utilizing cycloadduct **2** Vollhardt was able to synthesize compound **3** which represents a formal total synthesis of Camptothecin.[4] This synthesis proceeded in 9 steps and 9% overall yield (Fig. 6).

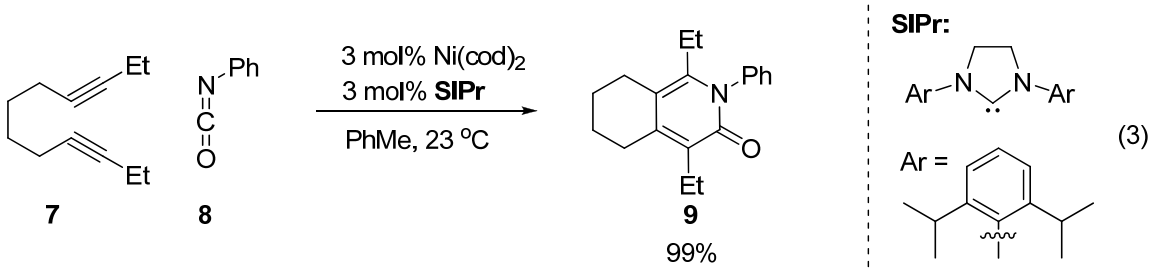
Figure 6



Since Vollhardt's work using a relatively inexpensive cobalt catalyst others have investigated pyridone forming cycloadditions using other transition metals. In 2001, Itoh reported a ruthenium catalyst capable of forming pyridone products from diynes (Eq. 2).[5]

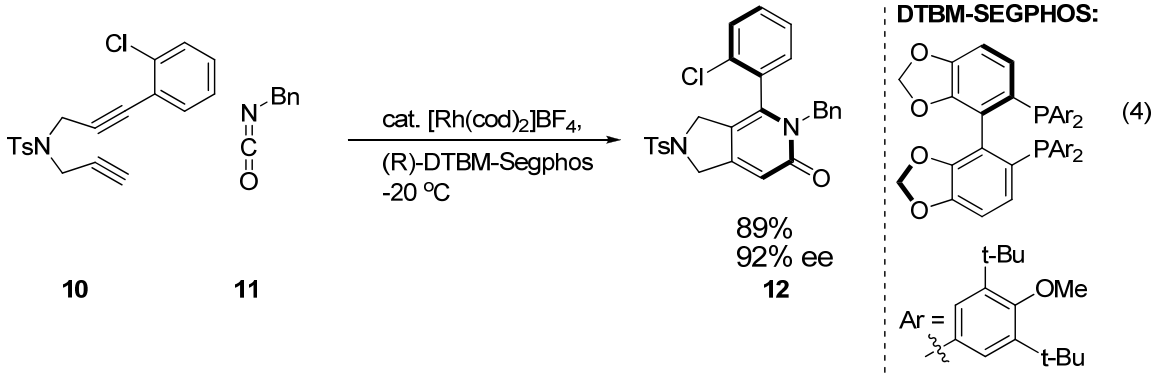


These products provided complementary regioselectivity to Vollhardt's synthesis of bicyclic 2- pyridone systems. Louie[6] also reported a cycloaddition using internal diynes and a nickel/N-heterocyclic carbene catalyst system in 2004 (Eq. 3).



(3)

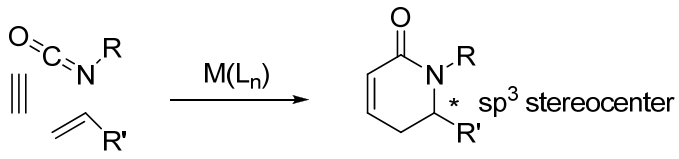
The most exciting recent innovation in this area was an asymmetric pyridone synthesis by Tanaka in 2005 using a rhodium catalyst.[7] Tanaka exploited an ortho-substituted aryl diyne to synthesize atropisomeric pyridone products in good yields and excellent enantioselectivity (eq. 4).



(4)

Approximately the same time as Tanaka was developing his asymmetric rhodium catalyzed [2+2+2] cycloaddition, Robert Yu was working hard in his investigation of another asymmetric rhodium catalyzed [2+2+2] cycloaddition. Our lab's innovation was that we envisioned an isocyanate, alkyne and an alkene to generate a sp^3 carbon stereocenter rather than product with axial chirality(Fig 7).

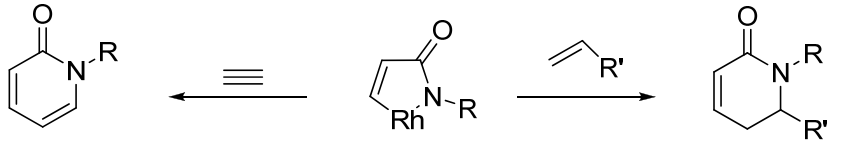
Figure 7.



While the incorporation of nitrogen into molecules to form heterocyclic products is important in drug discovery and design so too is the synthesis of enantiomerically pure molecules. "The worldwide sales of single-isomer chiral drugs have increased from 1 percent in 1985 to 12 percent in 2000".[8] A search revealed that the literature was wanting for efficient methods to construct such ring systems enantioselectively. Most current methods to do so would required multiple steps and chiral pool materials.[9] The prevelance of this motif in natural products, such as quinolizidine and indolizidine alkaloids also made this area of research attractive.

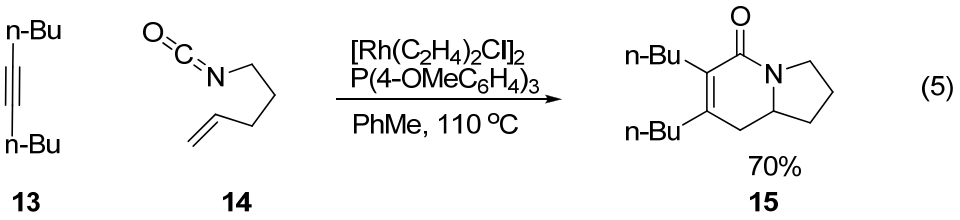
One of the challenges in developing this reaction is the incorporation of an alkene in preference to an alkyne. Incorporation of the alkyne to form pyridones had already been demonstrated to be a facile process (*vide supra*). Competitive insertion to a rhodium lactam metallacycle of a second equivalent of alkyne in preference to an olefin would provide pyridone products (Fig. 8).

Figure 8



To circumvent the formation of these unwanted byproducts the olefin was tethered to the isocyanate. This promoted the olefin insertion in preference to the alkyne by making it an intramolecular rather than intermolecular reaction. Utilizing a rhodium pre-catalyst and

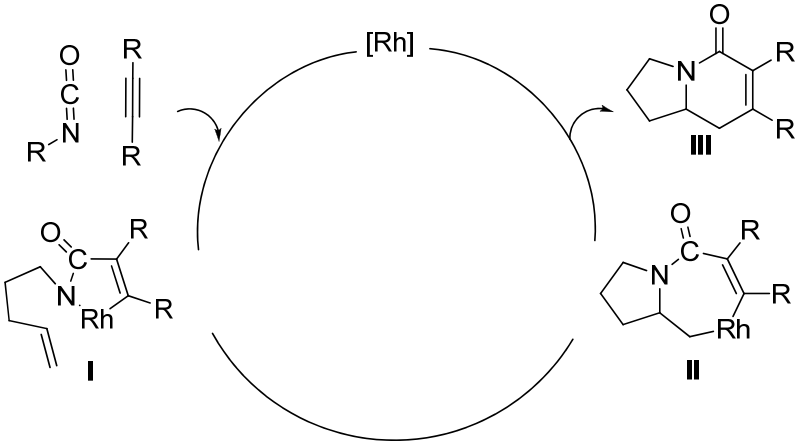
triaryl phosphine ligands, this strategy was put into practice to affect the desired three component cycloaddition in 2006 (Eq. 5). [10]



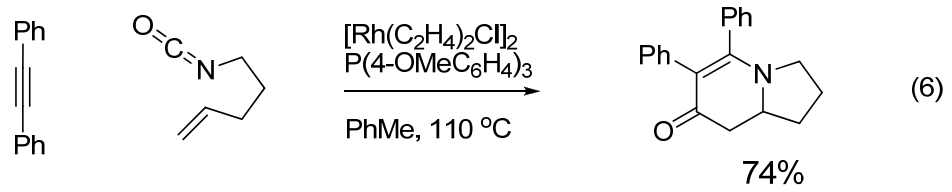
13 **14** **15** (5)

The mechanism for the formation of product **15** appeared to be straightforward. Experiments suggested that it proceeds through initial oxidative cyclization to form rhodalactam metallacyle **I**. Following oxidative cyclization, olefin insertion occurs to give metallacycle **II** which undergoes reductive elimination to give lactam product **III** (Fig. 9).

Figure 9.

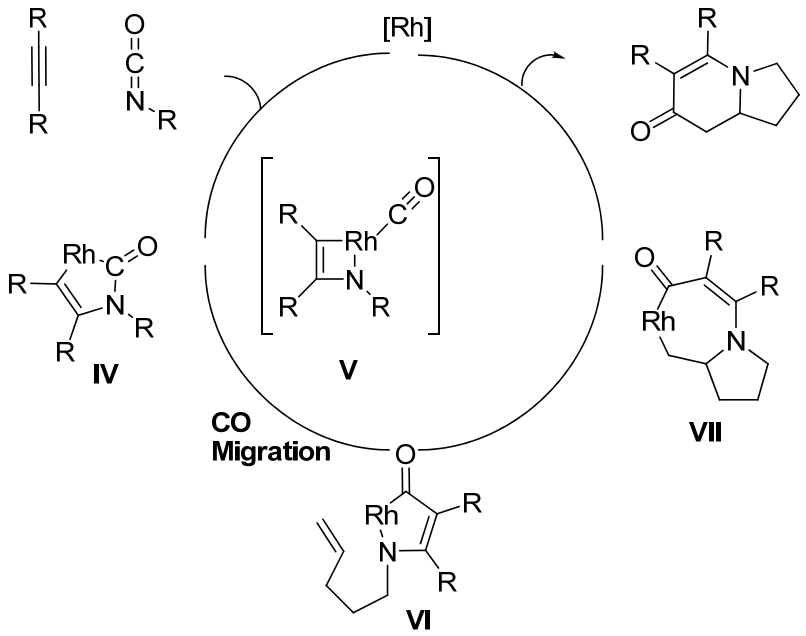


During the expansion of the substrate scope it was revealed that internal diaryl acetylenes, such as **16** gave a wholly separate class of products like **17**, labeled as "vinylogous amide" (Eq. 6).



The mechanism for the formation of vinylogous amide is similar to that of lactam. Oxidative cyclization forms rhodalactam metallacyle **IV**. Metallacyle **IV** is formed such that the carbon-oxygen double bond of the isocyanate ends up α to the rhodium metal center. The major change in the mechanism results from the regiochemistry of the oxidative cyclization which allows for a CO migration process to occur. CO migration is believed to occur through a rhodacyclobutene carbonyl intermediate like **V**. Insertion of the carbonyl ligand on the opposite side of the metallacycle gives rise to intermediate **VI**. This intermediate is now poised to undergo an olefin insertion to give intermediate **VII**. Reductive elimination from metallacycle **VII** affords vinylogous amide product (Fig. 10).

Figure 10.

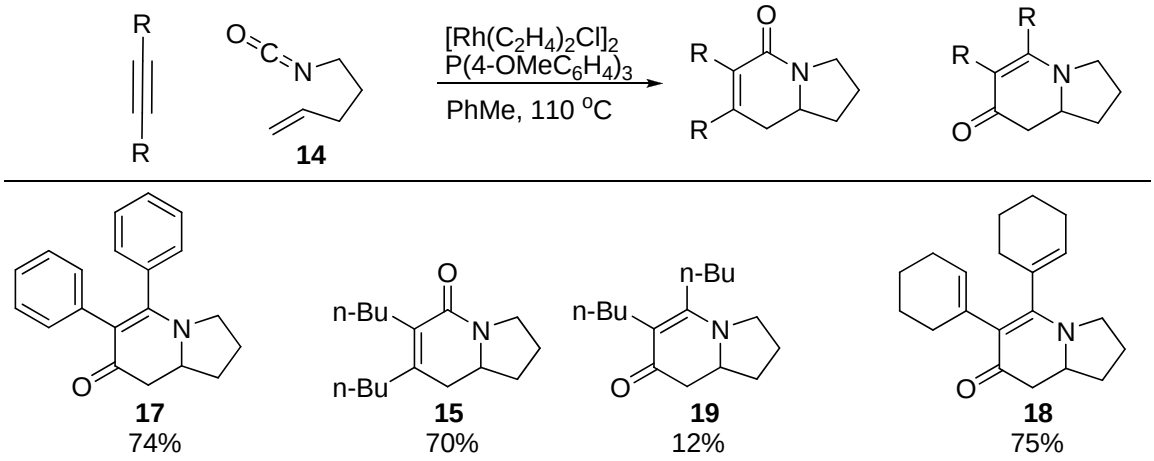


It was quite exciting that the problem that was now faced was a reaction that appeared to give two different types of products selectively. Moreover since this selectivity appeared to be substrate dependent, investigations would need to be carried out to determine the factors responsible for product selectivity.

1.2 Vinylogous Amide Selectivity with Diphenyl Acetylene

A curiousity arose that the reaction displayed substrate dependent product selectivity.[10] Diphenyl acetylene **16** gave exclusive formation (>20:1) of vinylogous amide, whereas 5-decyne gave mostly lactam product **15** (~7:1) (Table 1).

Table 1.

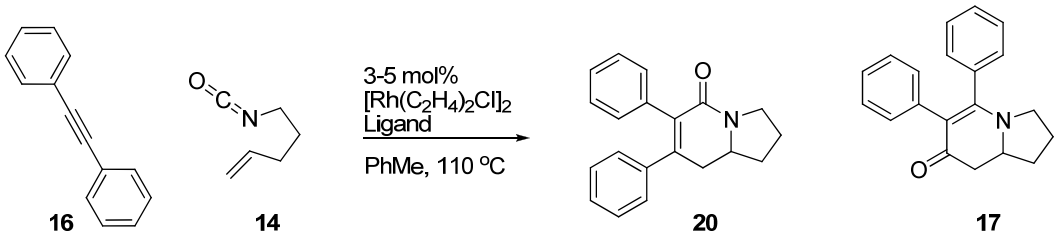


Furthermore dicyclohexenyl acetylene gave only vinylogous amide product **18**. This result suggested that sterics may be influential in product determination in this reaction. Before we could investigate the effect of substrate on the reaction we were curious as to whether the catalyst could control the product selectivity.

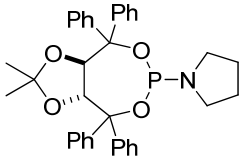
Phosphines and phosphoramidites were effective as ligands for rhodium in this reaction. A number of different ligands were screened with diphenyl acetylene **18**. Both Taddol based phosphoramidites **L1-L6** and a number of BINOL based phosphoramidites

L7-L13 afforded only vinylogous amide product **17** with diphenyl acetylene **18** (Table 2).

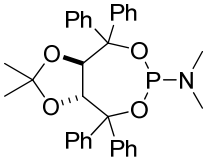
Table 2



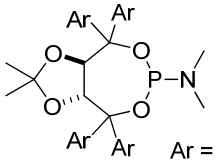
TADDOL Ligands



L1
<1:20
72%

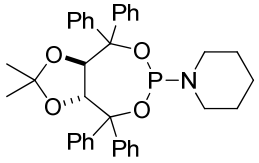


L2
<1:20
71%

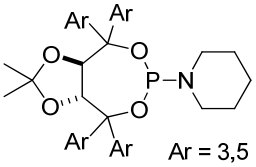


Ar = 3,5 Me C_6H_3

L3
<1:20
47%



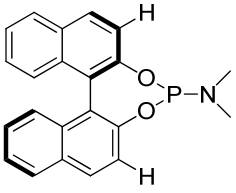
L4
<1:20
62%



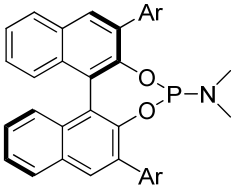
Ar = 3,5 Me C_6H_3

L5
<1:20
67%

BINOL Ligands

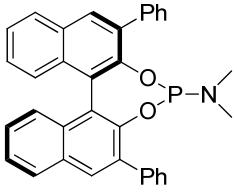


L6
<1:20
74%

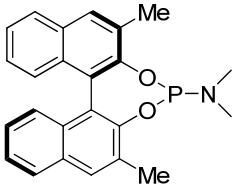


L7
<1:20
73%

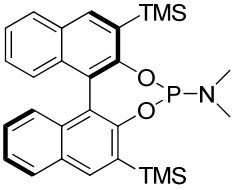
Ar = 3,4 OMe C_6H_3



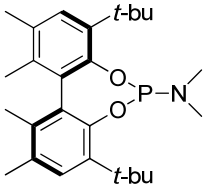
L8
<1:20
64%



L9
<1:20
74%



L10
<1:20
68%



L11
<1:20
76%

While this set of ligands **L1-L11** had proven useful to affect product selectivity with other substrates (*vide infra*) with dipheyl acetylene product selectivity was invariant. Since it appeared that substrate biased this reaction to a greater extent than catalyst we hoped that by understanding this bias it might be possible to reverse product selectivity to favor lactam product. To develop a model for product selectivity with diphenyl acetylene we looked back at previous work done in the group which gave us insight into the product selectivity with terminal alkyl alkynes.

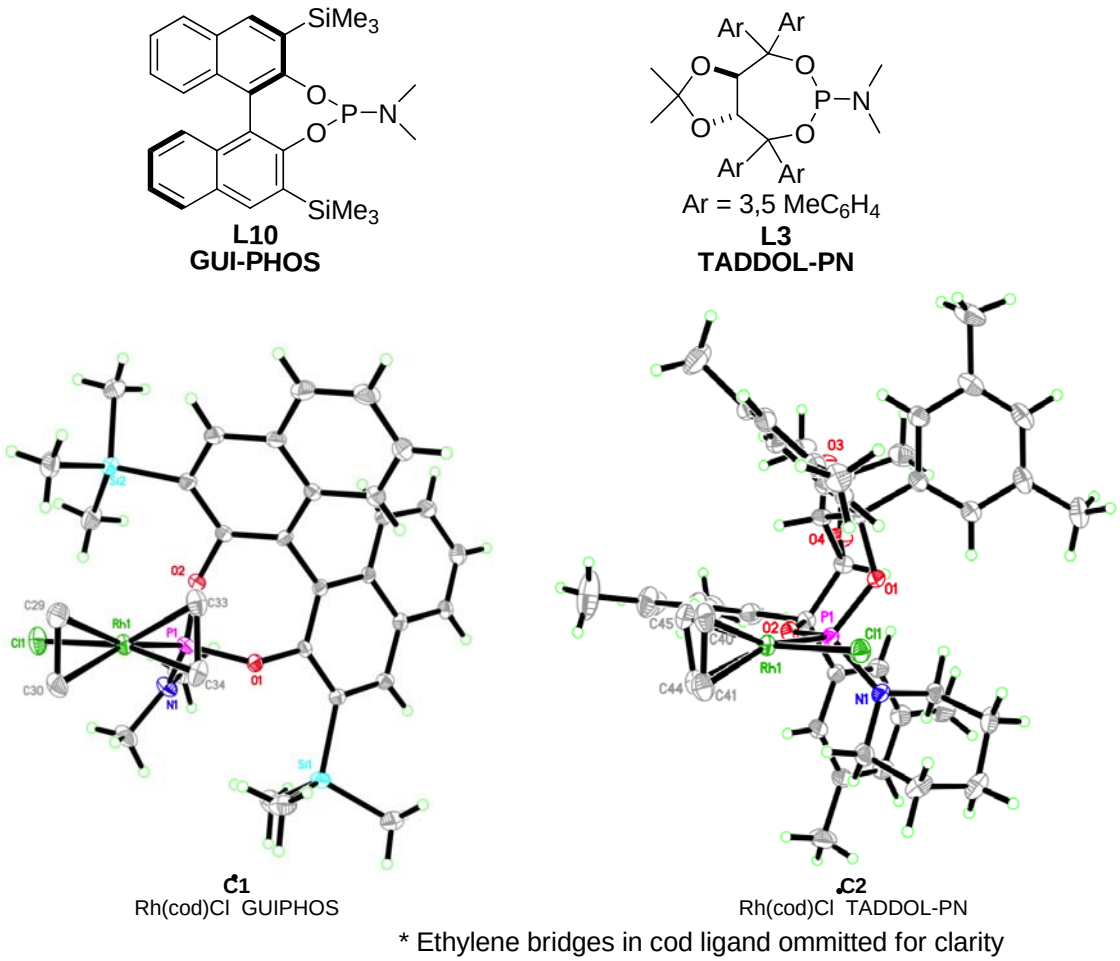
1.3 Product Selectivity using Terminal Alkyl Acetylenes

Because terminal alkyl acetylenes show variation of product selectivity with ligand this system was the first to be explored to study the effects of catalyst structure on product selectivity. Product selectivities of lactam:vinylogous amide could vary from >20:1 to 1:14 depending upon the combination of substrate and ligand.[11] Over the past year a model for product selectivity was developed for terminal alkyl acetylenes which reflect both the effect of rhodium-ligand interactions as well as the steric effects of alkyne structure. This model is presented here since the product selectivity with terminal alkyl acetylenes provides a good model for the product selectivity with internal diaryl acetylenes.

Two effects will be predominant in determining product selectivity with diaryl acetylenes: the interaction between rhodium and the ligand and the sterics of the substrate. To understand rhodium-ligand interaction a number of rhodium-cyclooctadiene phosphoramidite complexes [Rh(cod)**L**Cl] (**L** = Phosphoramidite) were synthesized and

crystallized. Complexes with both TADDOL based phosphoramidite complex, **C1**, and BINOL based phosphoramidite complex, **C2**, were synthesized (Fig. 11).

Figure 11

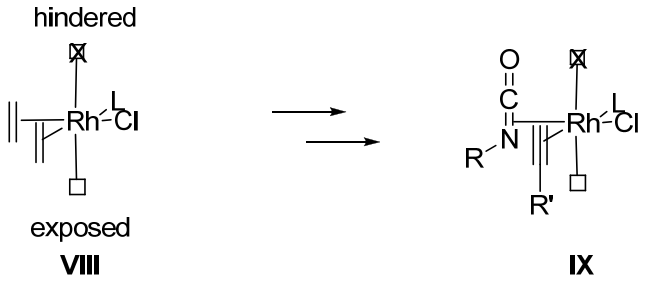


* Ethylene bridges in cod ligand ommitted for clarity

The isolation and characterization of these complexes allowed us to hypothesize how the ligand-metal interactions might be controlling product selectivity. In each of the complexes the substituents in the back bone of the ligand (The phenyl ring in **L3**, and the TMS group in **L10**) sat above the plane of the square planar rhodium (I) complex. The subtituents on these ligands act to block one of the faces of the rhodium metal, while leaving the opposite face exposed. If these x-ray crystal structures mimic the conformation of the rhodium complex in toluene solution then a complex like **VIII** with

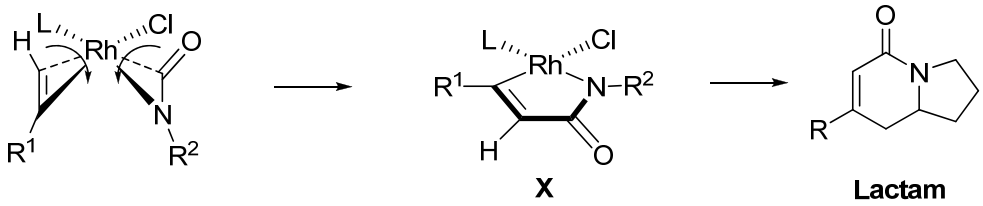
two spectator ligands (alkynes or ethylenes) would lead to the precursor to oxidative cyclization, **IX** (Fig. 12).

Figure 12.



The disposition of the ligand blocks one face of the complex **IX. T**his orients the small groups of each of the cycloaddition partners towards the hindered face of the rhodium complex in order to avoid a steric interaction. From **IX** the oxidative cyclization can occur only two ways to give the regiochemistry observed with terminal alkyl acetylenes. Oxidative cyclization can occur via rotation of the two π-components inward or outward. Inward rotation of the two π-components places both the nitrogen atom of the isocyanate and the substituent of the alkyne α to the metal as in the metallacycle **X** (Fig. 13). This metallacycle **X** cannot undergo CO migration and will lead to lactam products.

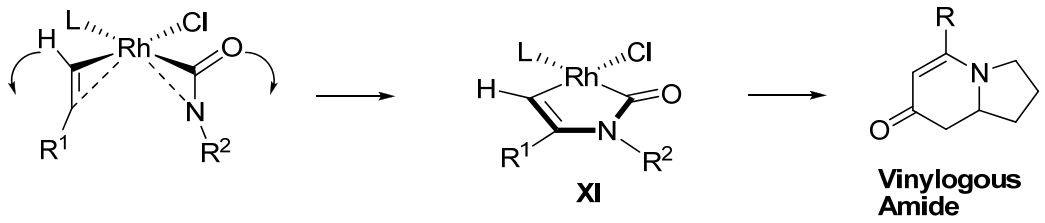
Figure 13



Rotation in the opposite direction of the two π-components places the carbonyl of the isocyanate and the terminal hydrogen of the alkyne α to the metal as in the metallacycle

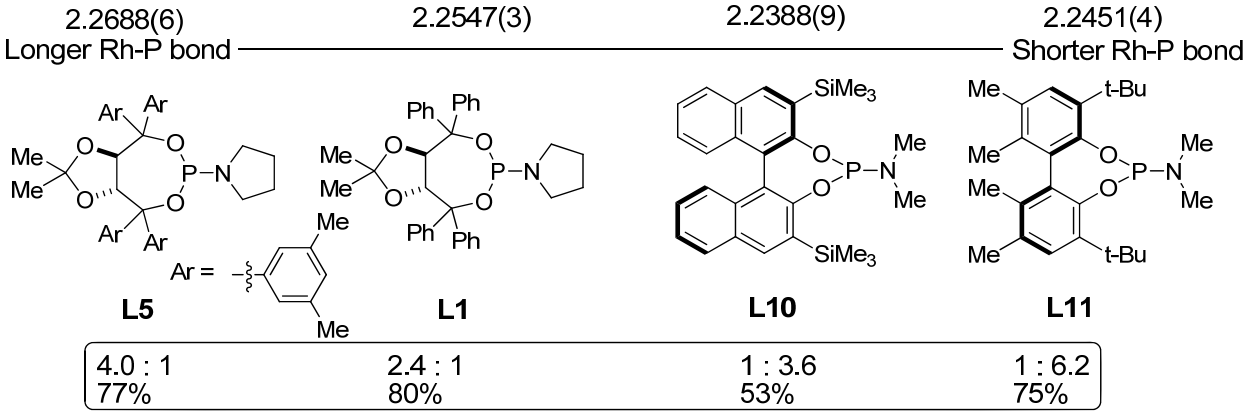
XI (Fig. 14). Metallacycle **XI** allows for CO migration and leads to vinylogous amide products.

Figure 14



Kevin Oberg and Derek Dalton compared the rhodium-phosphorous bond lengths obtained from these crystal structures of [Rh(cod)**L**Cl] complexes to the product selectivities obtained in the reaction with 1-octyne. Shorter Rh-P bond lengths should show a greater steric interaction between the metal center and the substrate while longer Rh-P bond lengths should have a smaller interaction (Table 4).

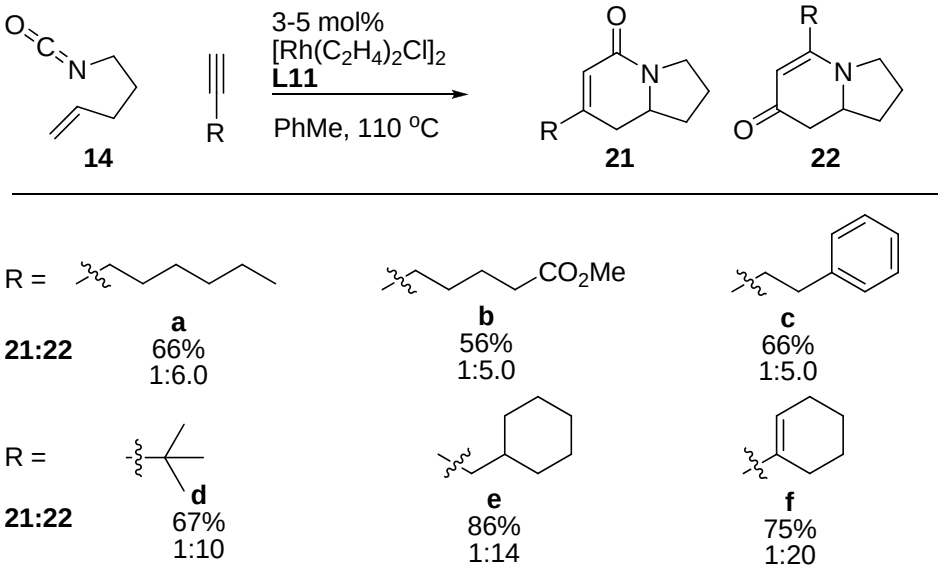
Table 4



The correlation between Rh-P bond lengths and product selectivities with 1-octyne seems to suggest that the shorter Rh-P bond distance the greater amount of vinylogous amide product. Thus a more sterically crowded metal center may lead to steric interactions that favor formation of a metallacycle that leads to vinylogous amide product.

Robert during his investigations of the reaction with terminal alkynes observed that by varying the substituent on the alkyl alkyne it appeared that the size of the substituent also played a role in product selectivity. To determine if a steric interaction between the substrate and the metal complex contributed to product selectivity the size of the substituent on the substrate was varied (Table 5).

Table 5

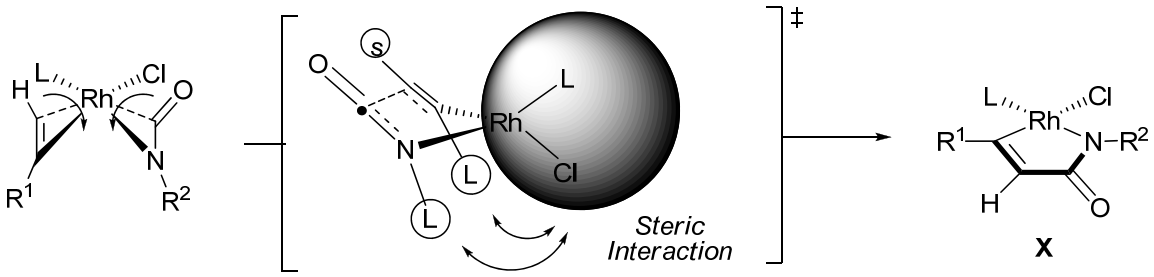


Smaller alkyl groups on the alkyne favored lactam (1-octyne) while larger groups favored the vinylogous amide product (1-cyclohexenyl acetylene). This correlates well with the data regarding the Rh-P bond length and suggests that steric interactions between the substrate and the catalyst do play a large role in product selectivity.

A model was developed to explain how the steric interaction between the substituent on the alkyne and the metal catalyst effect which metallacycle was preferred. In the rotational model of the oxidative cyclization there are a couple of steric interactions that might explain the selective metallacycle formation. The formation of the

lactam metallacyle via the outward rotation requires a strong steric interaction between the substituent on both the alkyne and isocyanate with the bulky metal center (Fig. 15).

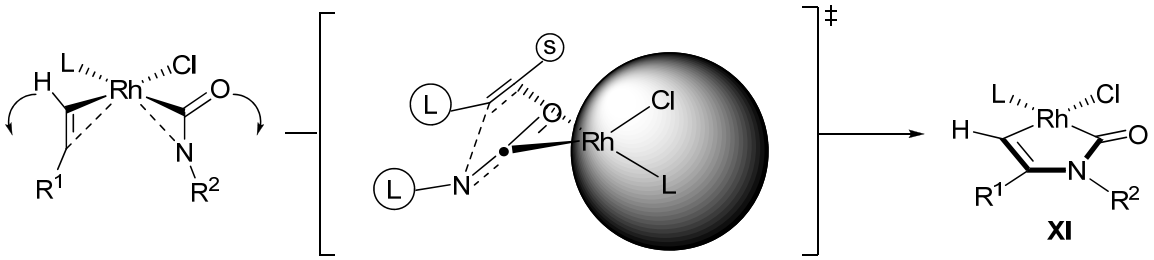
Figure 15



This steric interaction is caused by the two substituents being brought in close proximity to the metal-ligand complex as they are brought into the xy plane of the catalyst to form metallacycle **X.**

In the formation of vinylogous amide metallacycle with the inward rotation of the components the substituents are moving farther away from the metal as they become coplanar with the catalyst's xy plane. This pathway introduces significantly less strain in the transition state and leads to the formation of vinylogous amide product (Fig. 16).

Figure 16



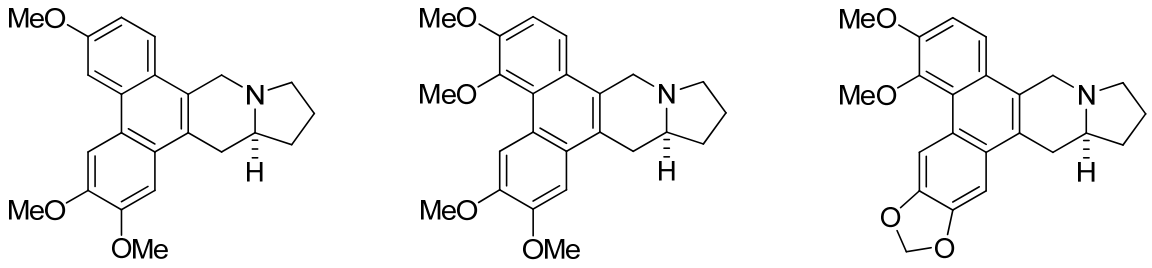
This model for terminal aryl acetylenes describes a situation in which a steric interaction between the substrate and the metal-ligand complex dictates the partitioning between two

metallacycles leading to two different products. In the next section we will attempt to apply this model by analogy to the case of diaryl acetylenes. By understanding the reasons for product selectivity we hope to be able to overcome the biases in the system so that we can form either product lactam or vinylogous amide, selectively.

1.4 Product Selectivity with Diaryl Acetylenes

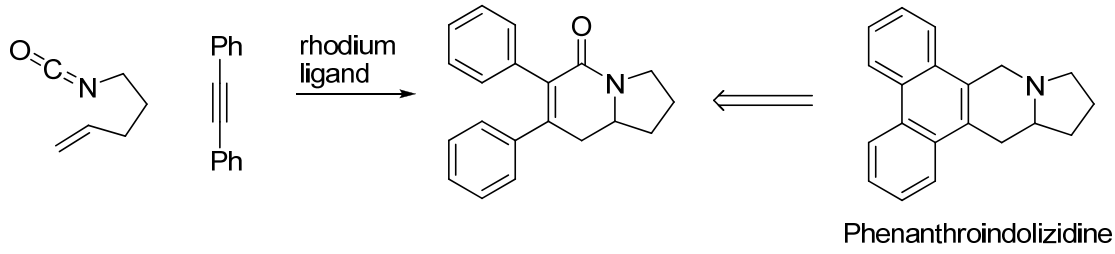
A driving force for development of a cycloaddition with diaryl acetylenes was to utilize this methodology in the rapid construction of cytotoxic phenantroindolizidine alkaloids. (Fig.17).[12]

Figure 17



A synthesis of these alkaloids would demonstrate the power and efficiency of this methodology. These alkaloids bear a close resemblance to the lactam type of cycloadduct formed from pentenyl isocyanate (Fig.18).

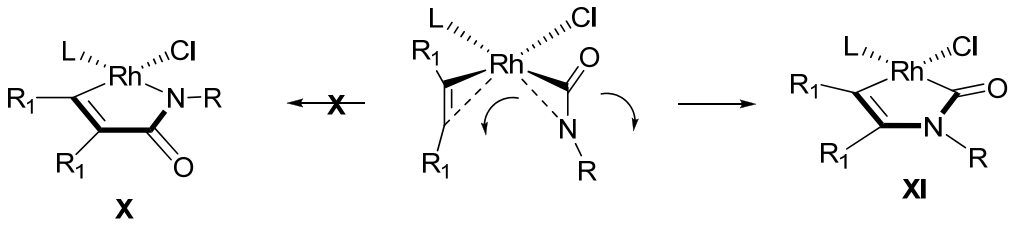
Figure 18



Altering the product selectivity of the cycloaddition with diaryl acetylenes to favor lactam products would allow for development of a concise synthesis of these phenanthroindolizidine alkaloids.

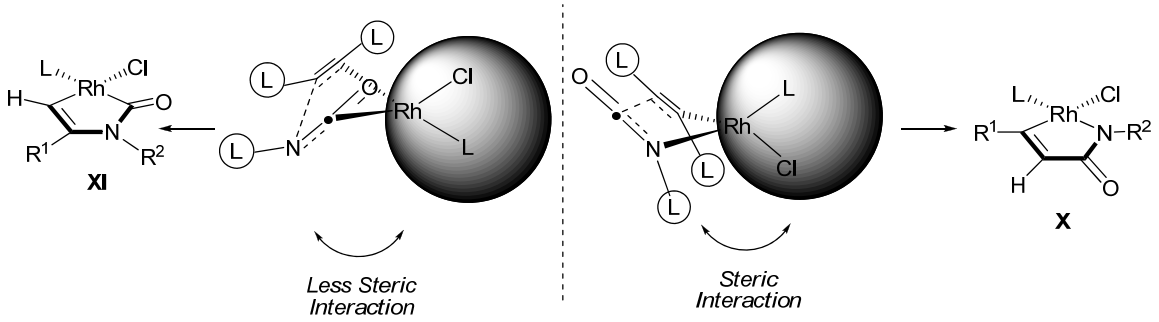
Steric interactions primarily influenced the product selectivity with terminal alkyl acetylenes. The model developed with terminal alkyl acetylenes was used as a framework for product selectivity with diaryl acetylenes. In the model with terminal alkyl acetylenes it was determined that rotation of the π-components either inward or outward would determine which product was formed. Diaryl acetylenes are symmetrical, thus the product selectivity is determined in this case only by the rotation of the isocyanate during the oxidative cyclization since either substituent of the acetylene has equal steric and electronic environments (Fig. 19).

Figure 19



Our initial screen of ligands revealed only vinylogous amide type products and no lactam product was observed (*vide supra*). Diaryl acetylenes have large substituents on both sides of the alkyne therefore the discriminating factor for which metallacycle forms must be the steric interaction between the isocyanate and the metal center (Fig. 20).

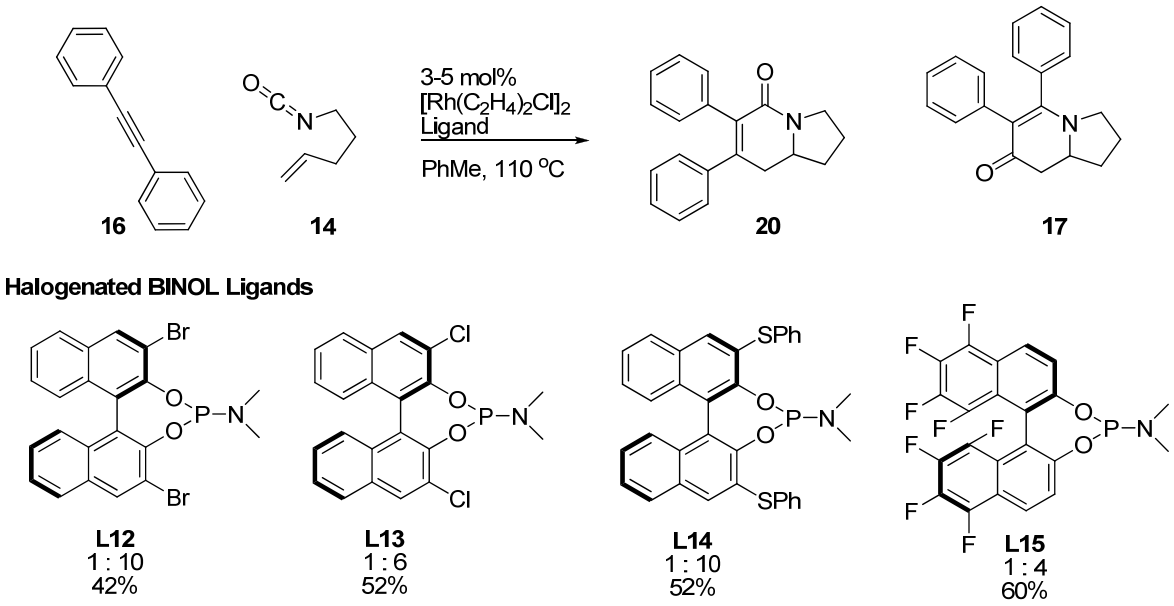
Figure 20



Thus, when in the transition state towards lactam metallacycle **X** the isocyanate undergoes rotation which places the substituent towards the metal center which disfavors oxidative cyclization. In the other case, the formation of vinylogous amide metallacycle **XI** occurs through a transition state which places the less bulky oxygen atom closer to the metal center.

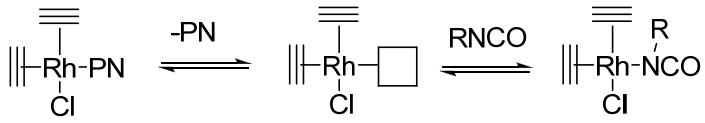
During the investigation with BINOL phosphoramidites, it was discovered that one particular ligand set did afford some lactam product with diphenylacetylene. Ligand **L12**, a phosphoramidite substituted with bromine at the 3, 3' position, did afford a small amount of lactam product with diphenyl acetylene (Table 3). As a result we also looked at the effect of other halogens (**L13, L15**) on the BINOL backbone and the effect on product selectivity (Table 6).

Table 6



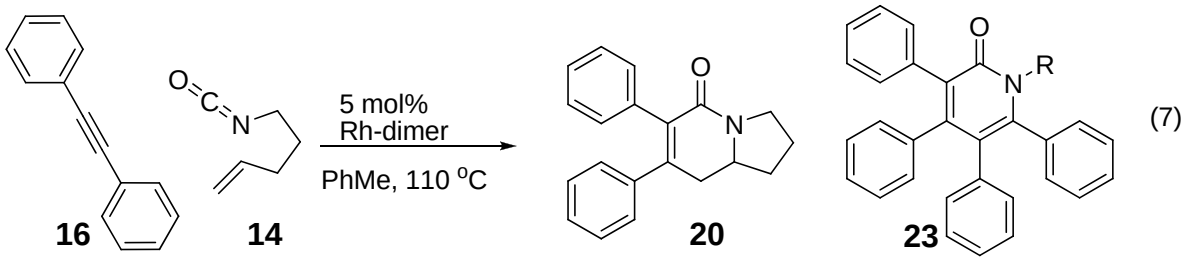
Though MONOPHOS, **L6** (Table 2), gave product selectivity favoring vinylogous amide (<1:20) yet ligands **L12-14** favored formation of the lactam product. The effect of these substituents upon the dihedral angle of BINOL most likely would make the BINOL ligands sterically more bulky as F_8-BINOL has a torsional angle 1.7° greater than BINOL itself.[13] Though it would be expected that substitution at these positions would make the ligand more bulky and therefore favor vinylogous amide product, yet this ligand allowed a shift towards formation of lactam product. A more electron deficient ligand would presumably cause a shorter Rh-P bond length which would affect the product selectivity by favoring vinylogous amide to an even greater extent (Table 4). One way in which these ligands could be functionally smaller with the 3, 3' substituents would be if the ligands favored a dissociative equilibrium (Fig. 21).

Figure 21



PN = Phosphoramidite ligand

A more electron deficient ligand would favor the dissociative equilibrium because the decreased electron donating character of the phosphorous lone pair. If lactam is formed by an unligated rhodium complex then the reaction of diphenylacetylene **16** and pentenyl isocyanate **14** run in the absence of ligand should yield lactam product. When this reaction was run only in the presence of the carbonyl or ethylene rhodium dimers lactam product **20** and pyridone products **23** were isolated (Eq. 7).



with $[Rh(C_2H_4)_2Cl]_2$	22%	29%
with $[Rh(CO)_2Cl]_2$	28%	32%

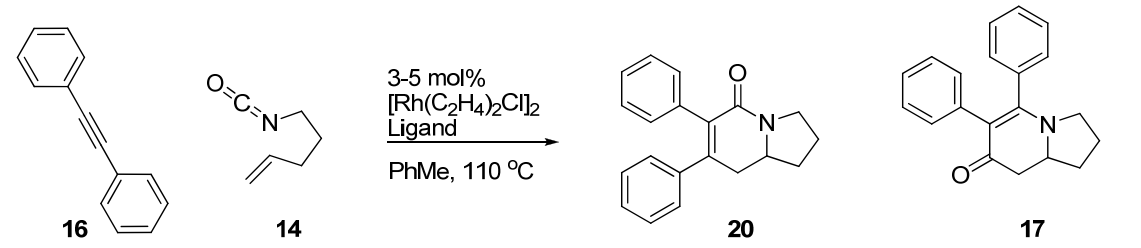
(7)

This suggested that this equilibrium was relevant. It also provided support for our model of product selectivity by showing that by decreasing the size of the metal catalyst the ratio of lactam product was increased. Perhaps if a smaller ligand was used product selectivity with diaryl acetylenes could be made to favor lactam.

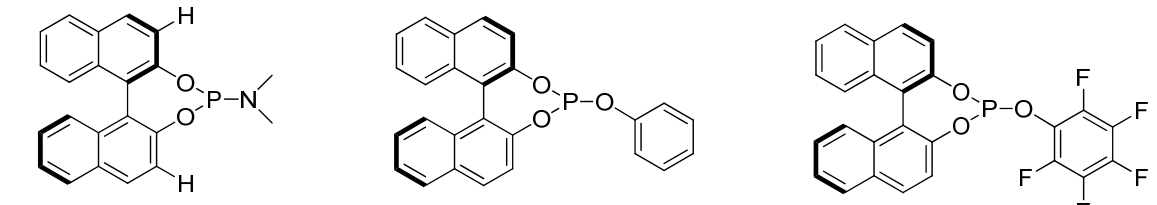
Phosphite ligands are smaller sterically than phosphoramidites, since phosphites have only one substituent on the oxygen as opposed to two substituents on nitrogen. Comparing A-values also suggested that an –OR group was smaller in size than a $-NR_2$ group (A-value NMe_2 = 2.1, OC_6H_5 = 0.65).[14] These ligands were synthesized and did

afford a greater amount of lactam product when diaryl acetylenes were used as the alkyne coupling component (Table 7).

Table 7



BINOL Phosphite Ligands



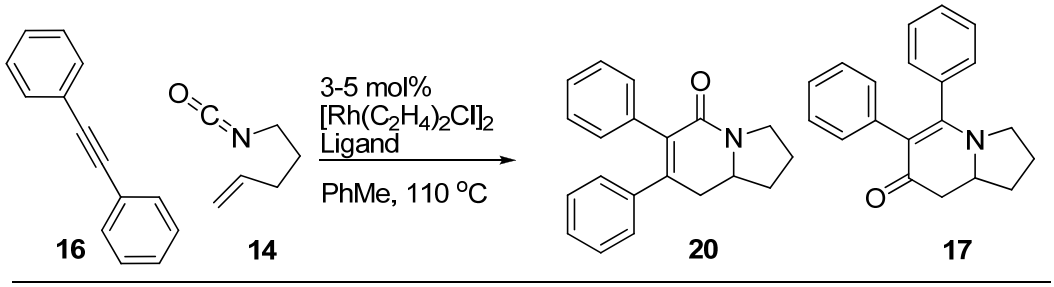
L7
<1:20
74%

L16
1 : 4
55%

L17
1 : 2
57%

The product selectivity obtained using BINOL based phosphites gave a higher product ratio favoring lactam reflecting the smaller size of phosphite ligands. Achiral phosphine ligands were examined as well to demonstrate how smaller the size of a ligand would favor greater lactam selectivity. Comparing Tolman's parameter of ligand size, phosphorous cone angle,[15] shows a correlation between decreasing cone angle and increasing lactam product selectivity (Table 8).

Table 8

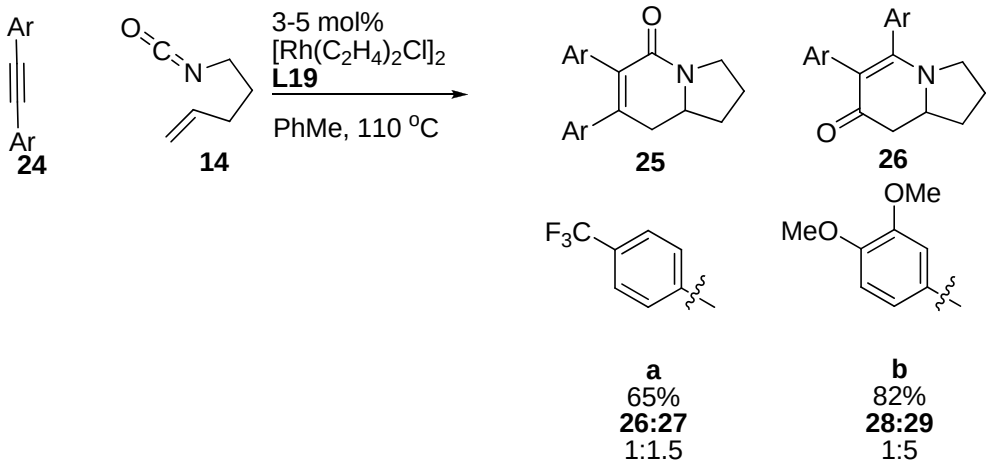


Tolman Cone Angle	145°	129°	110°	
	PPh_3	$P(Oi\text{-}Pr)_3$	$P(OEt)_3$	$P(OCH_2CF_3)_2$
	<1:20	$P(OCH(CF_3)_2$ 1:8	1:3	1:2
	72%	45%	62%	78%

Smaller ligands appear to give increased lactam selectivity; however, by decreasing the size of the phosphorus ligands we have decreased the ability to transfer chirality from the ligand to the substrate.

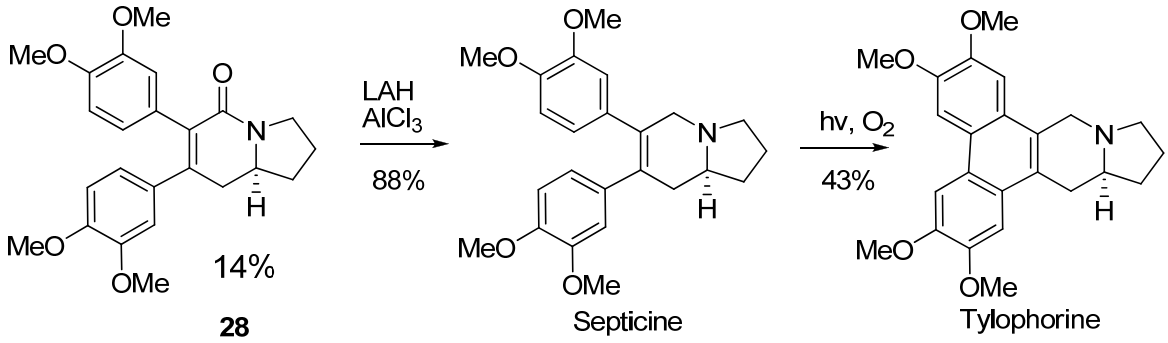
Briefly the effects of substrate on the product selectivity were explored. When the reaction was run with ligand **L19** in the presence of either electron-rich or electron-poor diaryl acetylenes there was an effect on the product ratio (Table 9).

Table 9.



Electron deficient trifluoromethylphenyl acetylene **24** favored lactam product to a greater extent than with diphenyl acetylene, **16**. When dimethoxyphenyl acetylene **25** was used the product selectivity was eroded. Unfortunately, this acetylene would be most relevant to the phenanthrolizidine natural products. This result suggested that this ligand design was not general at changing the product selectivity with diaryl acetylenes. However, lactam product **28** obtained from the reaction with **25** does constitute a formal synthesis of both Septicine and Tylophorine as reported by Kibiyashi (Scheme 1).[16]

Scheme 1



Because of the limited ability to form the desired products in good ratio and enantioselectively further investigations into this area are not ongoing.

1.6 Conclusion

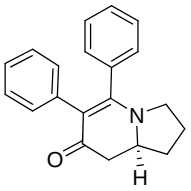
In this first chapter the development of a rhodium-catalyzed cycloaddition of alkenyl isocyanates with diaryl acetylenes has been described. Placed within a historical context this cycloaddition is important due to the fact that we have been able to use an olefin as a component in this cycloaddition. The incorporation of an olefin as the cycloaddition component allows for the generation of a sp^3 stereocenter in the product which may provide an interesting and valuable scaffold for drug discovery and invention. In this initial investigation we have looked at the effect of catalyst environment on product selectivity. The factors which can be manipulated to affect product selectivity with diaryl acetylenes have been identified and suggest that catalyst control of product selectivity is possible though it has not been achieved presently. As well, a ligand, GUIPHOS, **L10** provides promising yields and product selectivities favoring vinylogous amide

Chapter 1 Experimental

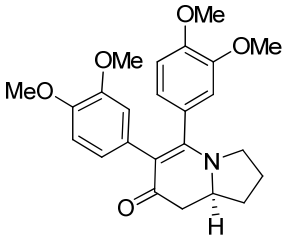
The Development of the Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates with Diaryl Acetylenes

General Methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Acetonitrile (certified ACS grade) and triethylamine (peptide synthesis grade) were purchased from Fisher Scientific and used without further purification. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and KMnO4 followed by heating. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from CDCl3 taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Alkyne **16** were purchased from Aldrich Chemicals Co. and used without further purification, Alkynes **24a,b** were prepared via literature procedure[17] Alkenyl isocyanate **14** was synthesize by the procedure below.[18] 5-hexenoic acid, 6-heptenoic acid, and diphenyl phosphoryl azide were purchased from Aldrich Chemicals Co. $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. Ligand **L1-L5** was prepared as described in the literature.[2,19] Ligands **L6-L15** were prepared as described in the literature.[20] Ligands **L16**,**L17** were prepared as described in the literature.[21] Complexes **C1** and **C2** were prepared as described in the literature.[22]

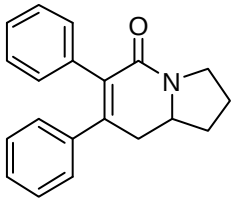
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and diaryl acetylenes: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N_2) glove box. A solution of alkyne (1.0 eq, 0.128 mmol) and isocyanate (1.5 eq, 0.193 mmol) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 ^{o}C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated *in vacuo*, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.



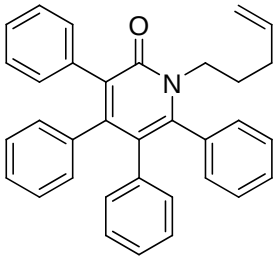
5,6-diphenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (17).
The general procedure yielded a light yellow solid (95% yield): Rf = 0.13 (1:1 EtOAc/Hex); $[\alpha]_D^{20}$ = 632.5 HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.1 minutes, Minor: 13.8 minutes, 230 nm detection light, *ee* = 93%;^{1}H NMR (400 MHz, CDCl3) δ 7.04 – 7.30 (m, 5H), 7.00 (m, 2H), 6.88 –6.94 (m, 3H), 4.14 (dddd, 1H, *J* = 6.8, 6.8, 6.8, 13.6 Hz), 3.40 (ddd, 1H, *J* = 4.0, 7.5, 11.5 Hz), 3.11 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.67 (dd, 1H, *J* = 15.6, 15.6 Hz), 2.59 (dd, 1H, *J* = 5.3, 16.0 Hz), 2.35 (m, 1H), 1.94 – 2.03 (m, 1H), 1.73 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) 189.9, 161.1, 136.7, 135.9, 132.2, 128.9, 128.2, 127.4, 125.3, 112.4, 57.8, 50.1, 42.1, 32.5, 24.4; IR (NaCl, CDCl3) 1617, 1528, 1450, 1383, 1304, 1091 cm-1;HRMS $[C_{20}H_{20}NO]$+ calcd 290.1545. Found 290.1545 (FAB+).



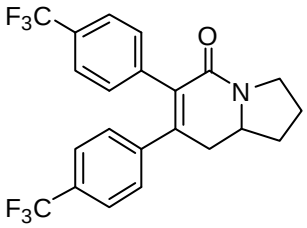
5,6-bis(3,4-dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one
(26b). The general procedure yielded a light yellow solid (98% yield): Rf = 0.14 (EtOAc); ^{1}H NMR (400 MHz, CDCl3)□6.54 – 7.20 (m, 6H), 4.11 (dddd, 1H, *J* = 6.5, 6.5, 6.5, 12.9 Hz), 3.71-3.65 (s, 12H), 3.43 (m, 1H), 3.10 (m, 1H), 2.64 (dd, 1H, *J* = 15.8, 15.8 Hz), 2.55 (dd, 1H, *J* = 4.5, 15.8 Hz), 2.31 (m, 1H), 1.91 – 2.01 (m, 1H), 1.71 – 1.90 (m, 2H); 13C NMR (100 MHz, CDCl3)□189.9, 161.0, 159.8, 157.1, 133.0, 130.6, 129.3, 128.2, 113.6, 113.1, 111.8, 57.5, 55.3, 55.2, 50.3, 42.0, 32.3, 24.5; IR (NaCl, CHCl3) 1590, 1531, 1372, 1299, 970 cm-1; HRMS [C24H28NO4]+ calcd 409.1947. Found 409.1950 (FAB+).



6,7-diphenyl-2,3,8,8a-tetrahydroindolizin-5(1H)-one (20)
The general procedure yielded a light yellow solid (28% yield): Rf = 0.5 (EtOAc); ^{1}H NMR (400 MHz, CDCl3) δ 6.78 – 7.18 (m, 10H), 3.95 (dddd, 1H, *J* = 5.2, 5.3, 9.5, 13.9 Hz), 3.65 (ddd, 1H, *J* = 2.1, 9.0, 11.7 Hz), 3.43 (ddd, 1H, *J* = 7.5, 9.1, 10.1 Hz), 2.74 (m, 2H), 2.23 (ddd, 1H, *J* = 5.5, 5.3, 13.8 Hz), 2.01-2.13 (m, 1H), 1.61 – 1.90 (m, 2H); 13C NMR (100 MHz, CDCl3)δ 164.1, 145.4, 140.7, 140.4, 137.4, 136.1, 131.6, 131.2, 129.1, 128.5, 128.1, 127.6, 126.9, 126.7, 125.3, 55.9,45.0, 37.7, 34.0, 23.4; IR (NaCl, CHCl3) 1644, 1593, 1450, 1352, 1327 cm^{-1}; HRMS [C20H20NO]+ calcd 290.1545. Found 290.1547 (FAB+).



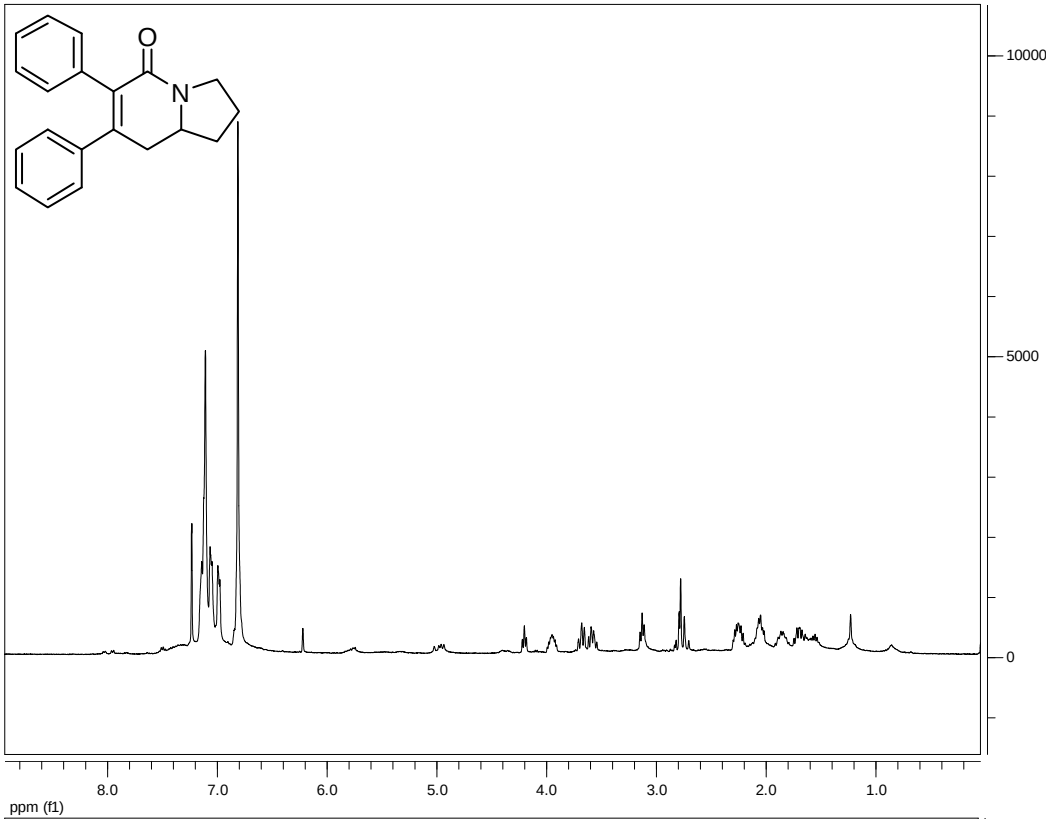
1-(pent-4-enyl)-3,4,5,6-tetraphenylpyridin-2(1H)-one(23) The general procedure yielded a light yellow solid (32% yield): Rf = 0.7 (EtOAc); ^{1}H NMR (400 MHz, CDCl3) δ 7.15-7.28 (m, 10H), 6.65-6.88(m, 10H) 5.54 (m, 1H), 4.82 (dm, 1H, *J* =11.7 Hz), 3.83 (t, 2H, *J* = 6.2 Hz) 1.90 (dt, 2H, *J* = 6.8, 7.0 Hz), 1.80 (tt, 2H, *J* = 7.0, 7.2 Hz); 13C NMR (100 MHz, CDCl3) δ 161.8, 138.2, 137.5, 136.5, 131.9, 131.2, 130.2, 130.0, 128.6, 128.5, 128.1, 127.5, 127.1, 127.0, 126.6, 126.4, 125.9, 115.1 IR (NaCl, CHCl3) 1622, 1585, 1370, 1364, 1321 cm^{-1}; HRMS [C24H30NO]+ calcd 461.2249. Found 461.2245 (FAB+).



6,7-bis(4-(trifluoromethyl)phenyl)-2,3,8,8a-tetrahydroindolizin-5(1H)-one (25a). The general procedure yielded a light yellow solid (26% yield): R_f = 0.3 (EtOAc); ^{1}H NMR (400 MHz, CDCl3) δ 7.15-7.4 (d, 4H, *J* = 8 Hz), 7.17 (d, 2H, *J* = 8 Hz), 7.08 (d, 2H, *J* = 8 Hz) 3.97 (dddd, 1H, *J* = 4.8, 5.2, 8.9, 12.9 Hz), 3.69 (ddd, 1H, *J* = 2.4, 8.9, 10.5 Hz), 3.58 (ddd, 1H, *J* = 7.5, 9.1, 10.1 Hz), 2.79 (m, 2H), 2.31 (ddd, 1H, *J* = 5.4, 5.7, 12.8 Hz), 2.15-2.05 (m, 1H), 1.80 – 1.95 (m, 1H), 1.65– 1.75 (m, 1H) ^{13}C NMR (100 MHz, CDCl3) δ 163.0, 145.1, 143.5, 139.2, 133.5, 131.5, 129.8, 129.2, 128.7, 125.6, 125.4, 124.8, 124.8, 55.8, 45.1, 37.6, 33.9, 23.3 IR (NaCl, CHCl3) 1642, 1585, 1439, 1353, 1321 cm^{-1}; HRMS [C24H30NO]+ calcd 426.1214 Found 426. 1217 (FAB+).

Procedure for the synthesis of 5-isocyanatopent-1-ene (14) A dry, 100 mL, single-necked, round-bottom flask (note 1), equipped with a Teflon-covered magnetic stirring bar, was charged with 10.1 g of 5-hexenoic acid (88.4 mmol) , 20 mL of dichloromethane in a single neck 100 mL round bottom flask was added 13.6 ml of Et_3N (97.3 mmol) slowly. The flask was placed in an ice/water bath and allowed to cool to 0 ^{o}C. Diphenylphosphorylazide (DPPA) 21.8 mL (97.3 mmol 1.1 eq) was added via syringe pump over the course of one hour. The temperature of the ice/water bath was monitored and maintained at 0 ^{o}C over the course of the reaction. The reaction was monitored by TLC and considered done after the disappearance of starting material (usually 4 to 5 hours). A silica gel column was prepared using 150 g silica gel dissolved in hexanes using at 4 inch wide column and then preeluted using hexanes. The crude reaction mixture was placed directly on the silica gel column using a minimum amount of dichloromethane (5 ml) was used to wash the reaction flask. The mixture was then eluted using 150 ml of hexanes followed by 1-1.5 L of 20:1 Hexanes/EtOAc. The acyl azide was the first compound which eluted and can be identified by UV (Rf = 0.8, 20:1 Hexanes/EtOAc).[23] The fractions

containing acyl azide were collected. The solvent was removed by rotary evaporator in a room temperature water bath until there was approximately 50 mL of a solution remaining. This solution was transferred to a flame-dried 100 mL round-bottom flask. This flask was fitted with an air condenser or vigreux column, septa and a large gauge needle outlet connected to a bubbler to monitor gas evolution. While monitoring nitrogen evolution the solution was slowly heated at 30 ^{o}C. The temperature was raised slowly over 4 hours no more than 5 degrees over two hours. It was then heated between 40-50 ^{o}C over another four hours. After 8 hours the remainder of the solvent was removed by rotary evaporator in a room temperature water bath. The procedure yielded 7.8 g of **5-isocyanatopent-1-ene (14)** 79% yield. Yields were obtained in the range of 70-81%) using this procedure.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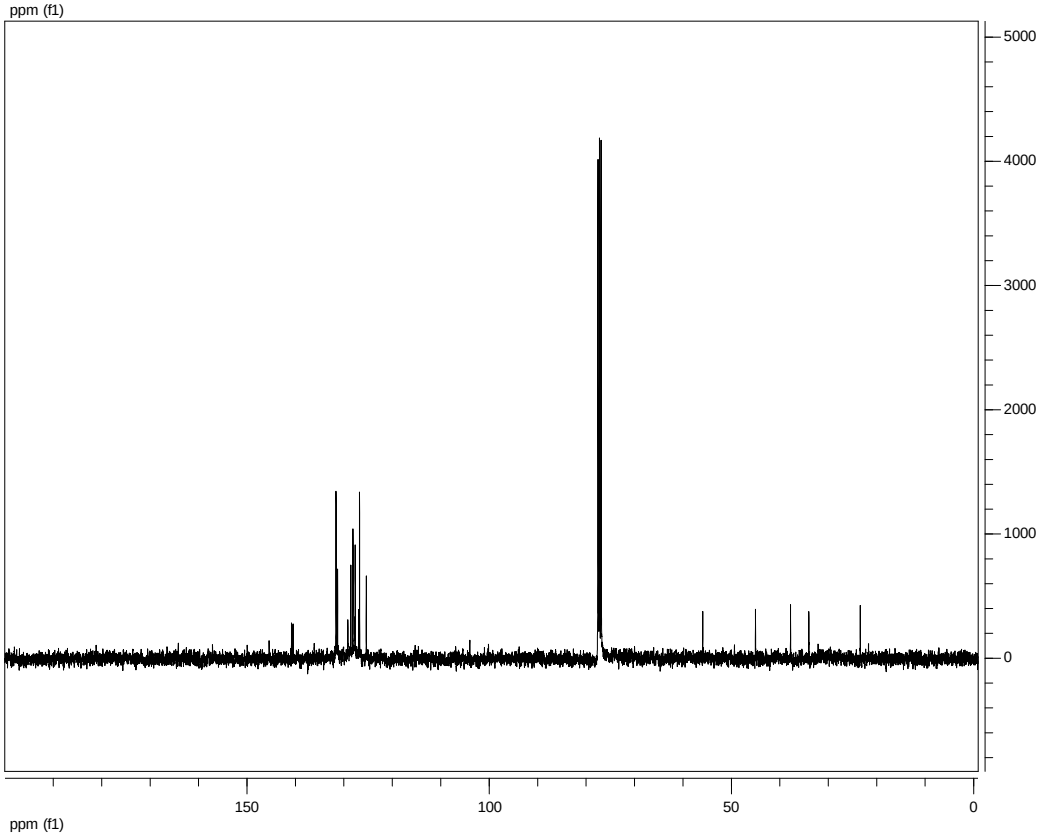
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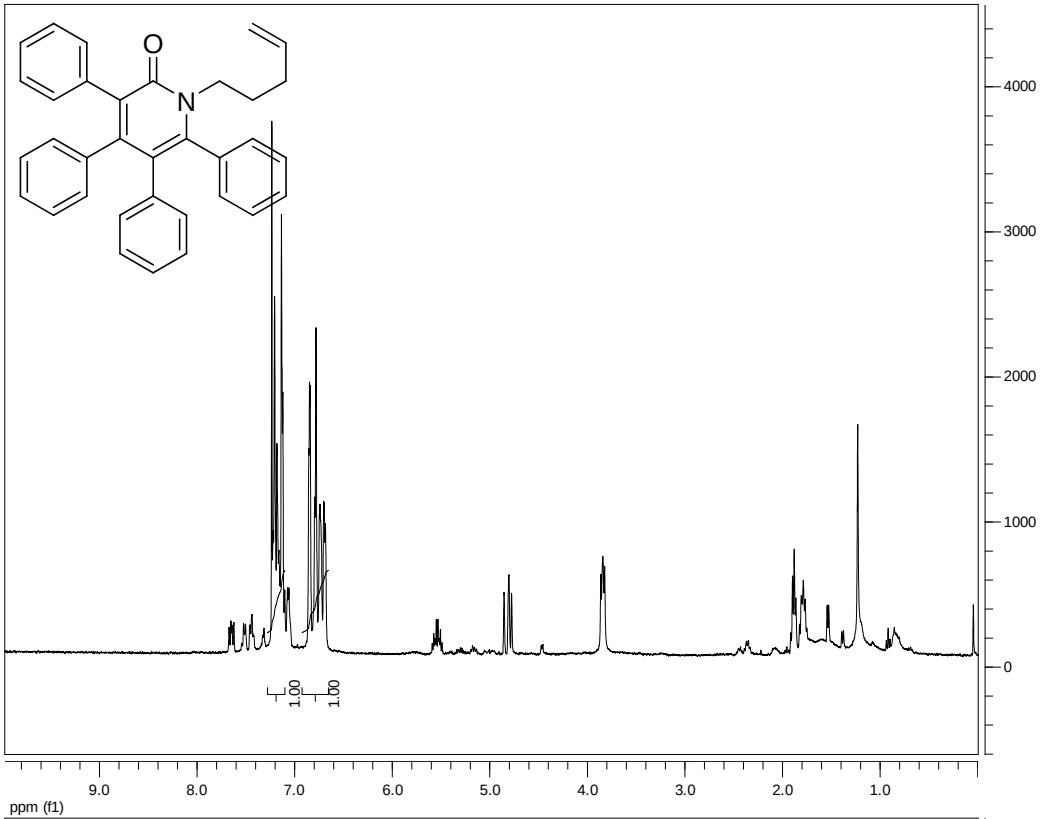
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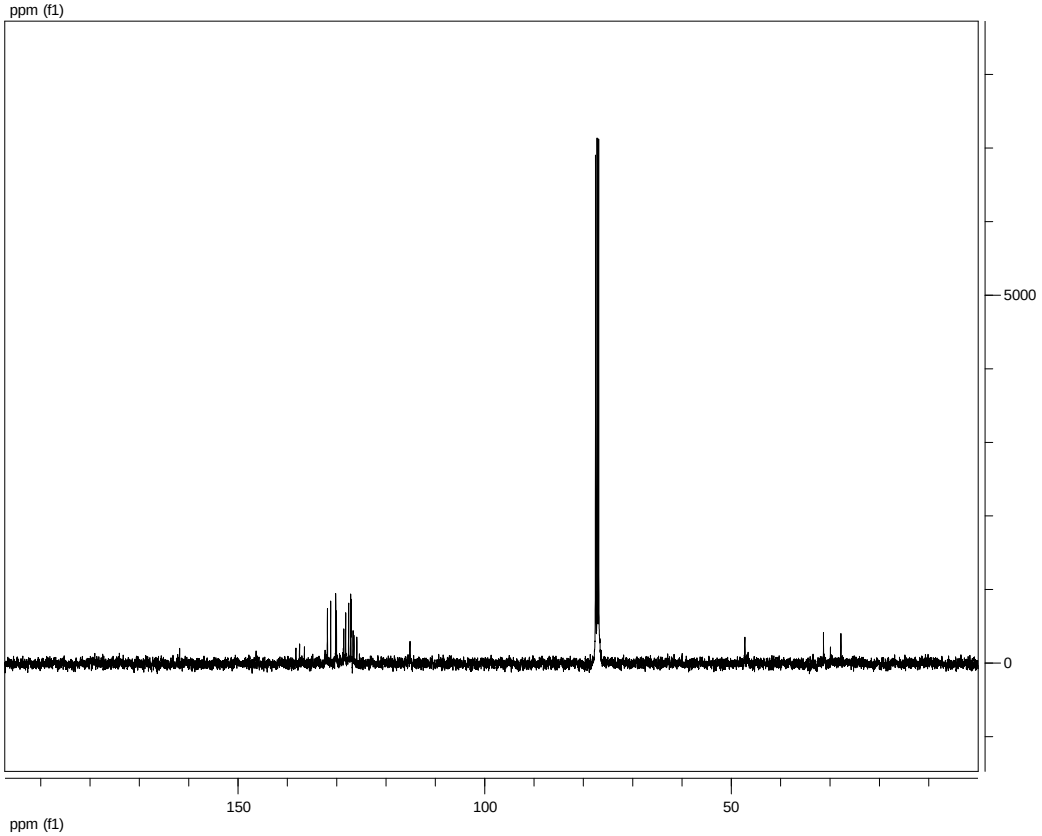
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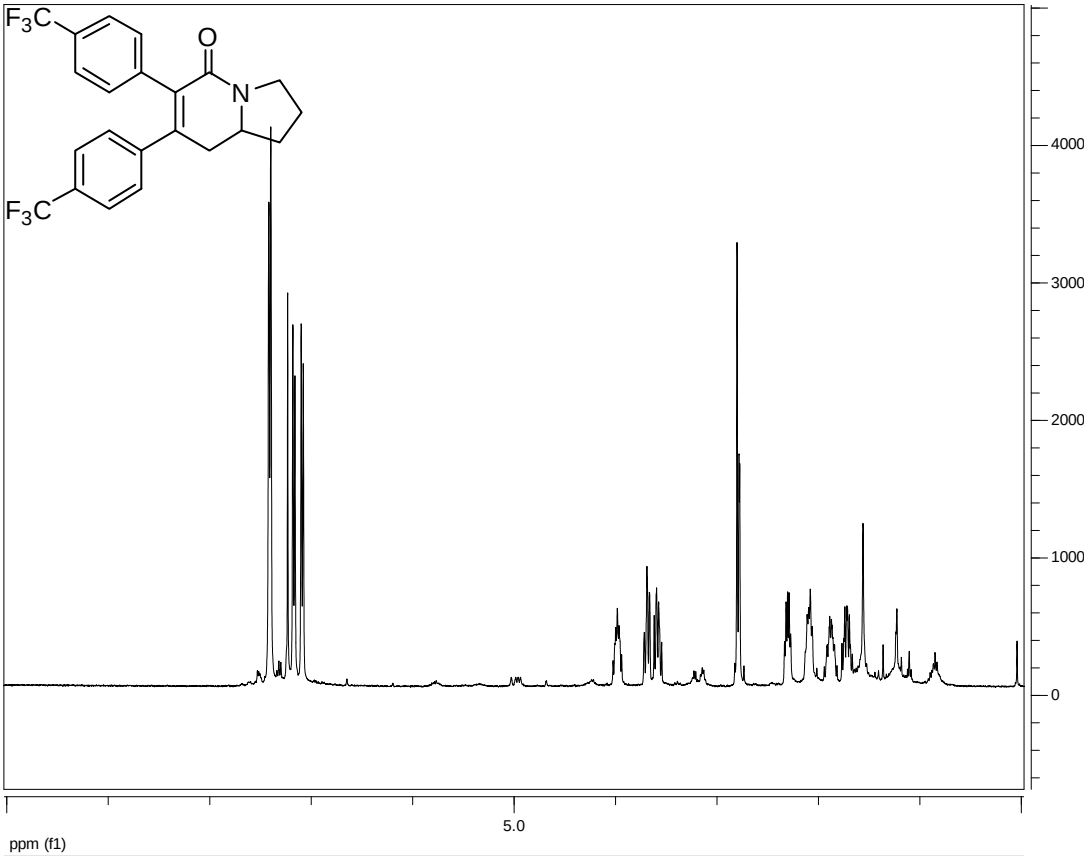
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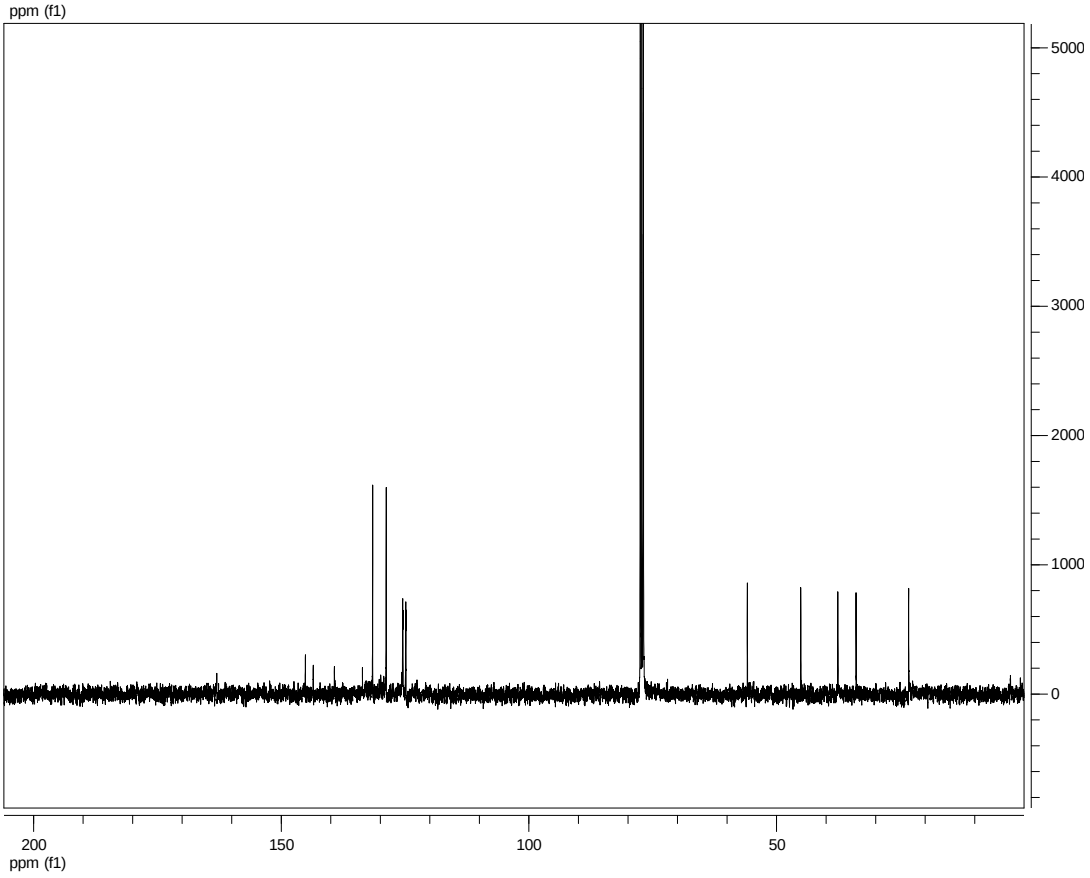
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[23] Excess DPPA can also be observed by TLC in 20:1 Hexanes/EtOAc (Rf = 0.25)

Chapter 2.

The Use of Additives in the Optimization of the Enantioselective Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates with Diaryl Acetylenes

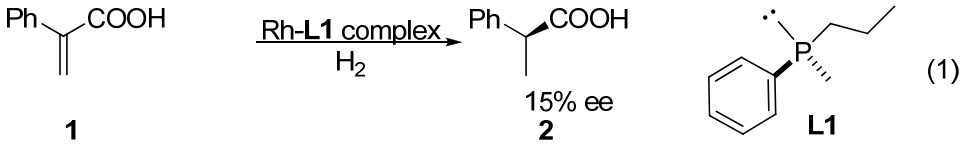
2.1 Background

Metal catalysis is uniquely fit to overcome the difficulties associated with three component cycloaddition reactions. A transition metal bringing together multiple components for a cycloaddition reaction, acts like a stage, bringing together actors, who play the various roles in a play. In catalysis, as in a play, there may be a need for supporting roles, those which provide embellishments and flourishes upon a piece, and which may take a great performance and make it the masterpiece. In their variety of coordination numbers and coordination environments, metals allow for these "supporting roles", by open coordination sites, where non-crucial chemical entities can become involved and alter the reaction course. This ballet of equilibrium exists between short-lived reaction intermediates can alter both reaction efficiency and selectivity. Furthermore these entities can also leave clues with which one can learn intimate details about the reaction mechanism. In this chapter we will describe the observation of such an effect, where a non-participating chemical entity has become involved, and alters both the reaction course and our mechanistic understanding.

2.1.1 Rhodium Catalyzed Hydrogenation

This story really begins with the advent of the asymmetric rhodium-catalyzed hydrogenation of olefins. Asymmetric hydrogenation was recognized for its power and utility fifty years ago and even today investigations into this reaction are still ongoing.

A breakthrough in asymmetric catalysis took place in 1968 with the discovery by Knowles[1] that p-chiral monodentate phosphines acting as ligands on rhodium were able to catalyze the hydrogenation to form enantioenriched carboxylic acids from α-substituted acrylic acids (Eq.1).

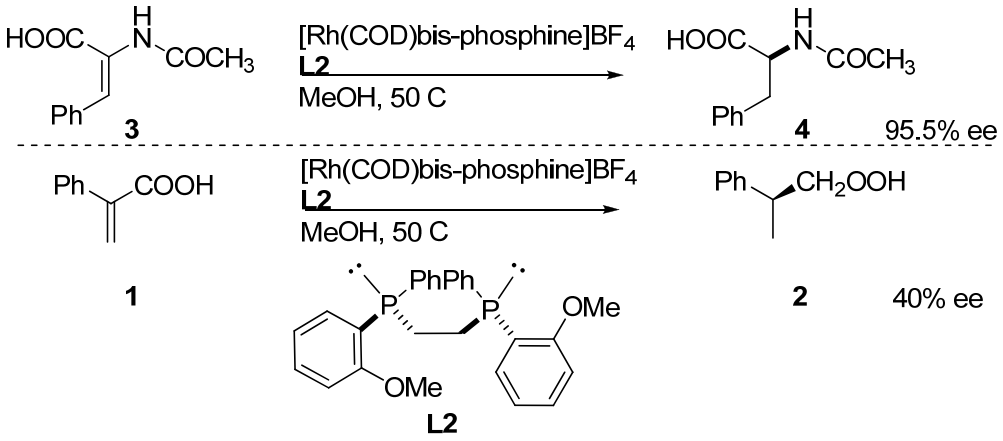


1 **2** **L1**

Historically this was an important advance as enantioselective reactions during this time were not as prevalent or as well explored as they are now. Furthermore this represented a reaction yielding product of increased optical purity with a chiral transition metal catalyst.

A second technological advancement for asymmetric rhodium catalysis came a few years later using a chiral bidentate phosphine **L2**, which gave very high enantioselectivities (>95%) in the hydrogenation of dehydroaminoacids **3**.[2] On the basis of these results it was suggested that bidentate phosphine ligands allowed for greater stereocontrol in this hydrogenation (Fig. 1).

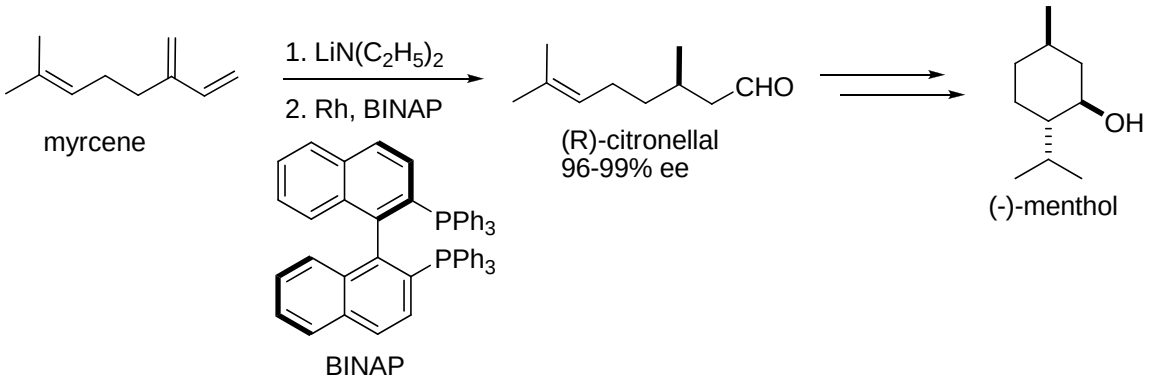
Figure 1



In this example the stereochemistry is controlled better by a chelating bidentate phosphine ligand rather than two single ligands occupying two coordination sites because rotation is restricted with the chelating ligand bound to rhodium.

Ultimately this research culminated in the realization of catalytic asymmetric hydrogenations using both rhodium and ruthenium with BINAP. The implementation of BINAP type ligands allowed for high levels of asymmetric induction. The importance of these reactions can be seen by the recognition of Knowles and Noyori with the 2001 Nobel Prize, as well as in industry by the efficient kiloton scale synthesis of (R)-citronellal and (-)-menthol employing this methodology (Scheme 1).[3]

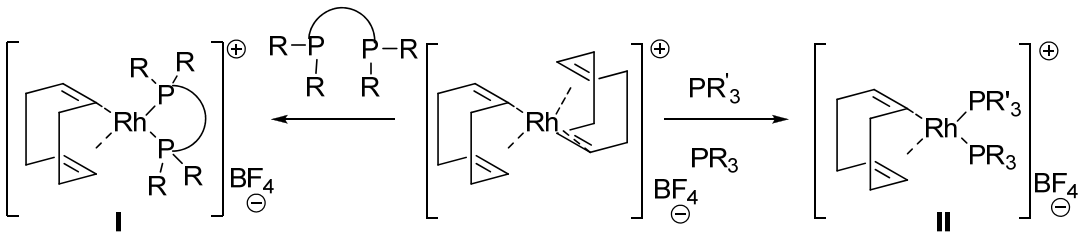
Scheme 1



2.1.2 Asymmetric Rhodium Catalysis Using Combinations of Chiral Ligands

Rhodium hydrogenation catalysis suffered for many years from a dogma that the use of bis-phosphines was necessary to obtain high enantioselectivity in reductions. Combinatorial methods have recently been applied to this problem to investigate the viability of using combinations of chiral ligands instead of bidentate phosphines to obtain optimum enantioselectivity for specific substrates. Rhodium catalyzed hydrogenations are proposed to start from a precatalyst like cationic cod complex **I**. Optimization of the enantioselectivitiy of any hydrogenation reaction for a given substrate should therefore be possible using combinations of monodentate phosphine ligand as in complex **II** (Fig. 2).

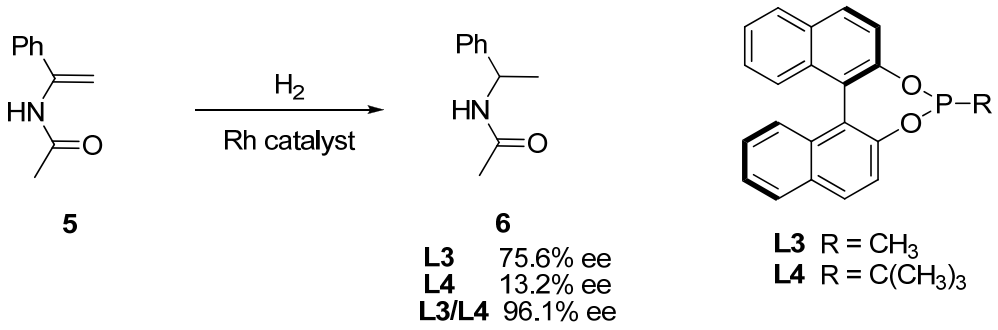
Figure 2



This strategy would be beneficial by avoiding the costly synthesis of specially designed bidentate phosphine ligands. For a given set of monodentate ligands, modifying the amine, alkoxy or carbon substituent of a phosphoramidite, phosphite or phosphinites

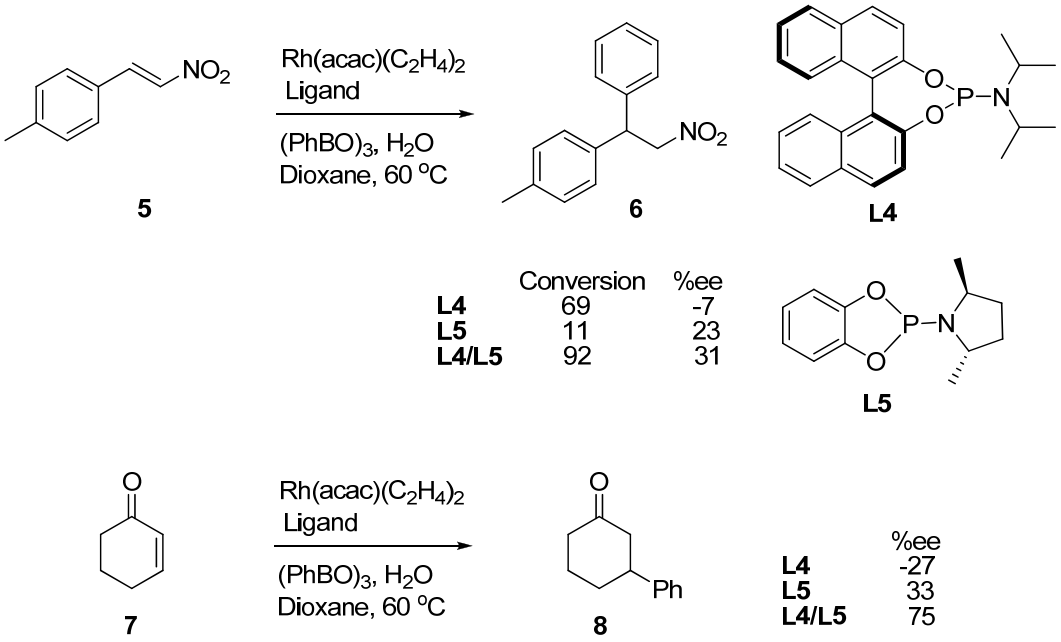
ligands are trivial.[4] Reetz has shown that high enantioselectivities, above and beyond those obtained with any single ligand, can be obtained in the hydrogenation of **5** through screening combinations of relatively simple BINOL phosphinites (Fig. 3). [5]

Figure 3



The combination of two different chiral ligands in many cases achieves greater enantioselectivities than when those individual ligands are used alone. The effective use of combinations of chiral phosphoramidite ligands has been shown in rhodium catalyzed conjugate additions to nitro alkenes[6] and cyclohexenones[7] (Fig. 4).

Figure 4

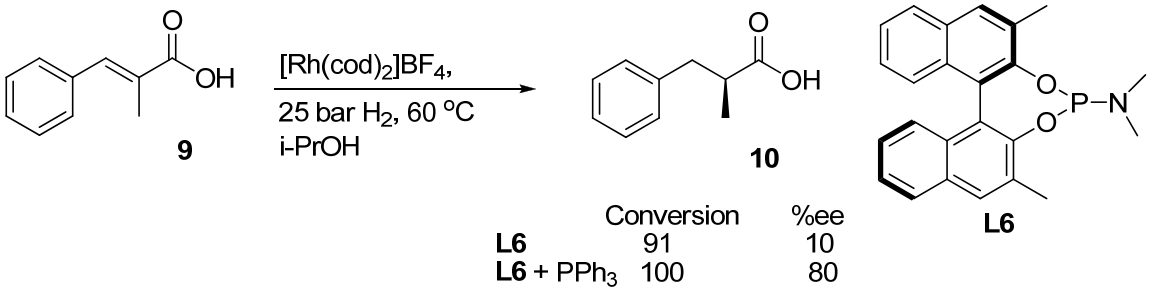


In most of these cases this synergistic effect occurs as a result of a combination of one sterically "large" ligand and one "small" ligand. While one ligand appears to control the absolute sense of stereoinduction, the other ligand may function to block the other face of the rhodium catalyst from approaching substrate, thereby allowing for greater control of the "small" ligand. If this hypothesis were true combinations of an achiral ligand and a chiral ligand should provide the same synergistic effects. Due to their ease of synthesis, the use of combinations of achiral ligands would be a more attractive synthetic solution.

2.1.3 Asymmetric Rhodium Catalysis Using a Combination of Chiral and Achiral Ligands

Feringa has been able to show the application of achiral ligands to have an influence on the enantioselectivity. By making a single face sterically inaccessible the achiral ligand promotes the asymmetric reaction by forcing a stronger interaction with the substrate and the chiral ligand. In the hydrogenation of α-methyl cinnamic acid **9** using monodentate phosphoramidite **L6** the enantioselectivity was increased dramatically in the presence of triphenyl phosphine (Fig. 5).[8]

Figure 5



The use of achiral ligands does present some problems in catalysis. The presence of achiral ligands may form an achiral rhodium complex, which promotes a racemic background reaction. Feringa was able to address this problem. When the reaction was monitored by ^{31}P NMR, a homocomplex [$Rh(PPh_3)_2$] as well as heterocomplex [$Rh(PPh_3)$**L6**] were formed. The ratios of the respective complexes were controlled by stoichiometry. A 2:1 ratio of **L6** to PPh_3 lead to the complete formation of heterocomplex [$Rh(PPh_3)$PN] and completely suppresses the racemic reaction. The rationale for the increase in enantioselectivity and efficiency in the presence of PPh_3 is due to the fact that the complex formed from ligand **L6** incorporates only a single phosphoramidite. Therefore the heterocomplex is more electron-rich, leading to increased efficiency, as well as more sterically bulky, leading to higher ee.

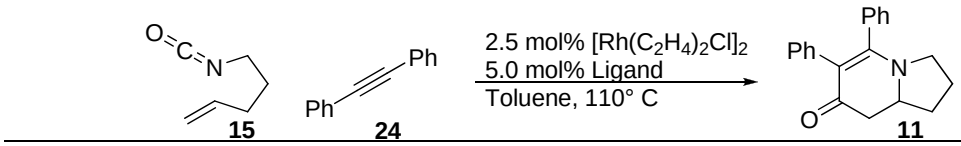
All of the reactions presented in this section are significant as they show that additives can affect the enantioselectivity of a rhodium catalyzed process. What is notable in these cases is that this "additive effect" was the result of changing the composition of a rhodium (I) precatalyst which thereby changes the nature of the rhodium catalyst as it enters the catalytic cycle. Given the coordination chemistry of rhodium perhaps it would be possible to alter selectivity by interception by an additive of an intermediate within the catalytic cycle.

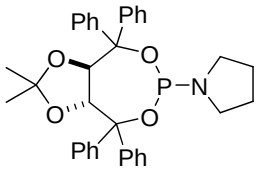
2.2 The Enantioselective Rhodium Catalyzed [2+2+2] Reaction of Diaryl Acetylenes and the Discovery of an "Additive" Effect.

Having successfully generated vinylogous amide cycloadducts using diaryl acetylenes with a sp^3 carbon stereocenter we wanted to control the enantioselectivity of

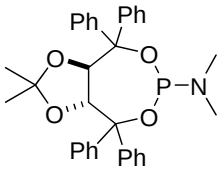
the reaction. TADDOL based phosphoramidites with diphenyl acetylene gave poor enantioselectivities (Table 1). BINOL phosphoramidites were shown to be effective in the asymmetric rhodium catalyzed hydrogenation when these ligands were employed in the reaction.[9] BINOL based phosphoramidites out performed the TADDOL ligands, with respect to enantioselectivity in the cycloaddition with diphenyl actylene.

Table 1





L7
72%
9% ee



L8
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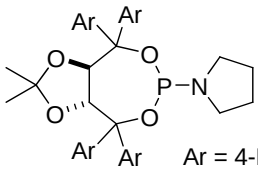
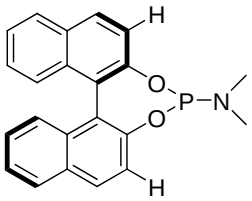
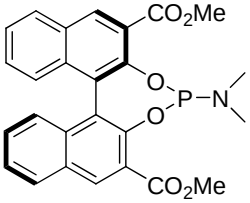
12% ee



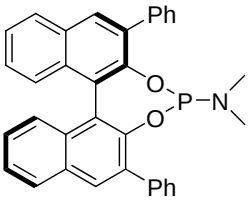
L9
71%
17%ee



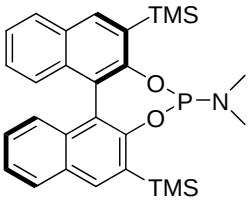
L10
74%
39% ee



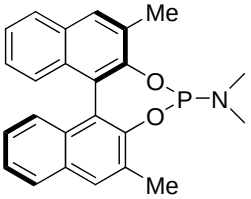
L11
68%
61% ee



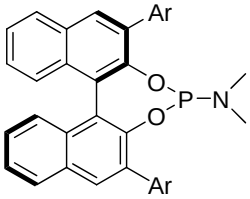
L12
64%
83%ee



L13
68%
84%ee

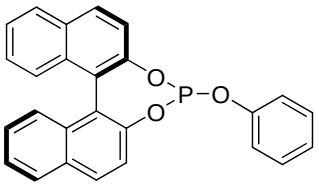


L14
74%
61% ee

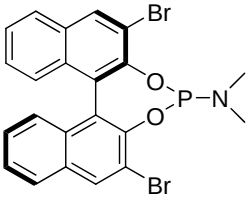


L15
73%
89% ee

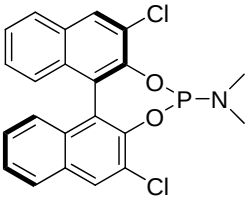
Ar = 3,4-OMe C_6H_3



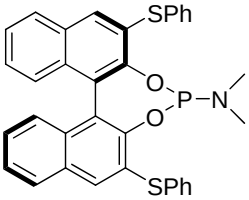
L16
44%
20% ee



L17
38%
53% ee



L18
43%
46% ee

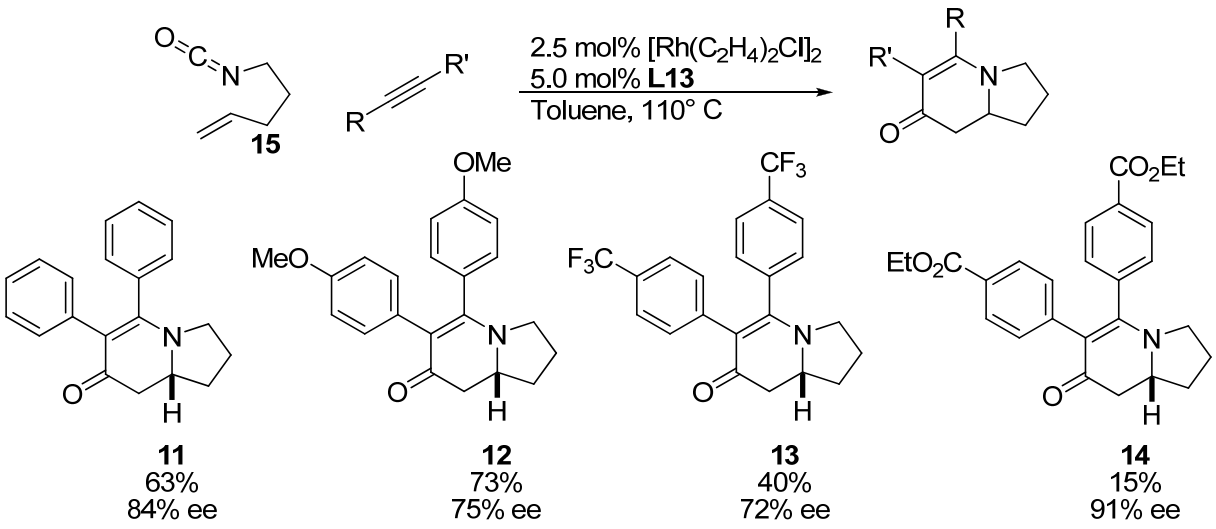


L19
47%
72% ee

Especially promising results were obtained by using 3, 3'-substituted BINOL phosphoramidites. Though aryl substituted BINOL **L15** did provide slightly higher ees

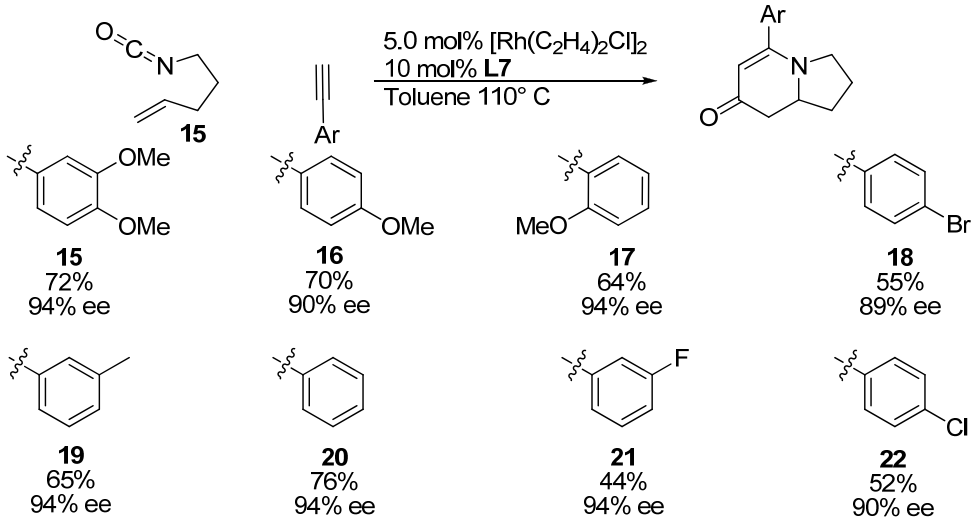
than the 3, 3' substituted TMS ligand **L13** the use of the latter ligand was more attractive due to a shorter synthesis. The enantioselectivity of this cycloaddition with other diaryl acetylenes was examined with ligand **L13** (Table 2).

Table 2.



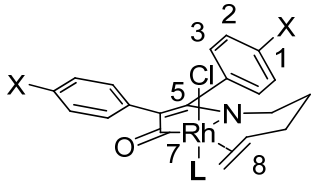
Notably, the enantioselectivity of the products seemed to vary dramatically with the substrate. When the only variable between substrates was the para-substituent on the diaryl acetylene, enantioselectivities differed by almost 20% (72-91%). These results were compared to the results obtained from the enantioselective reaction of terminal aryl acetylenes using TADDOL-based phosphoramidite **L7** (Table 3) and differed substantially.[10]

Table 3.



With ligand **L7** enantioselectivities are high across a range of different terminal aryl acetylenes, consistent, and independent of the aryl substituent. Results obtained with diarylacetylenes and ligand **L13** suggested that there was a difference in the mechanism of enantioselectivity between these systems. Olefin insertion sets the stereocenter adjacent to the nitrogen and is the enantiodeterming step of the reaction. Our research thus far suggested that intermediate **III** was a viable precursor to olefin insertion (Fig. 6).

Figure 6



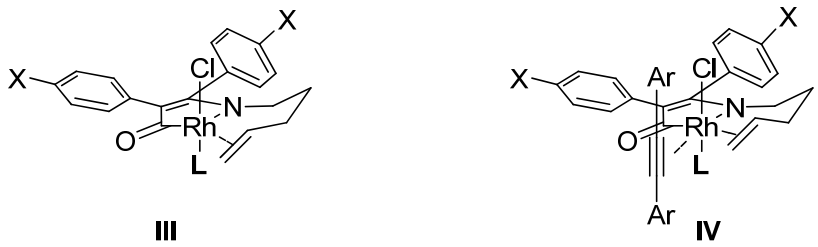
III

Explaining these changes in enantioselectivity based on para-substituents from either steric or electronic effects was difficult. Rationalizing these differences from a steric perspective would require an effect of the para substituent on the aryl rings on the

forming stereocenter which is 8 atoms removed. Stereocontrol from such a distal element would be unusual. Electronic influence of the substituent on metallacycle **III** would be small due to poor communication through the π system as the aryl rings would be bent out of the plane to avoid $A_{1,3}$ interactions.

Looking more closely at the coordination chemistry complex **III** is a 5-coordinate rhodium (III) species this affords a 16-electron complex. An octahedral 18-electron rhodium (III) complex would be more stable. Data from the cambridge crystallographic database suggests that six-coordinate octahedral rhodium (III) complexes are the most common.[11] Given this information it is possible that a six-coordinate octahedral rhodium (III) complex like **IV** may be an intermediate prior to olefin insertion (Fig. 7).

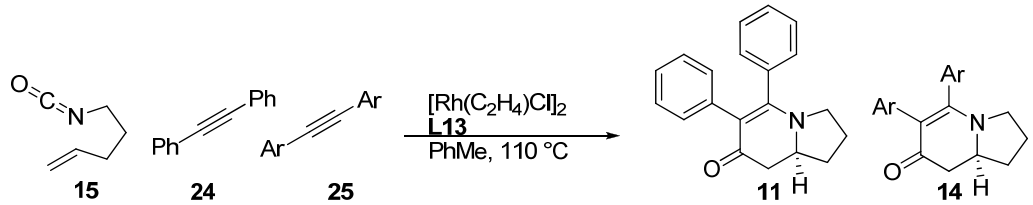
Figure 7



In complex **IV** a second equivalent of alkyne substrate is acting as a spectator ligand. If substrate were involved in the olefin insertion as a spectator ligand this could explain the dramatic change in enantioselectivity between substrates. Electronically, the spectator ligand would have a more fluid electronic communication between the alkyne and rhodium than the aryl rings would through the metallacycle. Sterically, the alkyne might exert a greater influence on olefin coordination or ligand geometry. Enantioselectivity could be determined by the length of this rhodium-alkyne bond and its effect on the forming stereocenter.

A competition experiment was designed in which two separate diarylacetylenes were placed in the same reaction mixture and the ee was measured. The hypothesis that a complex like **IV** undergoes olefin insertion would be confirmed by a difference in enantioselectivity of either of the products formed. A difference in ee suggests one substrate is bound to the rhodium during the enantiodifferentiating step of the other substrate. Table 3 shows the reaction of diphenyl acetylene **24** with isocyanate **15** in the presence of alkyne **25**. The enantioselectivity of product **11** is increased from 84% ee to 92% ee suggesting that alkyne **25** is involved in the enantiodetermining step for the formation of **11**.

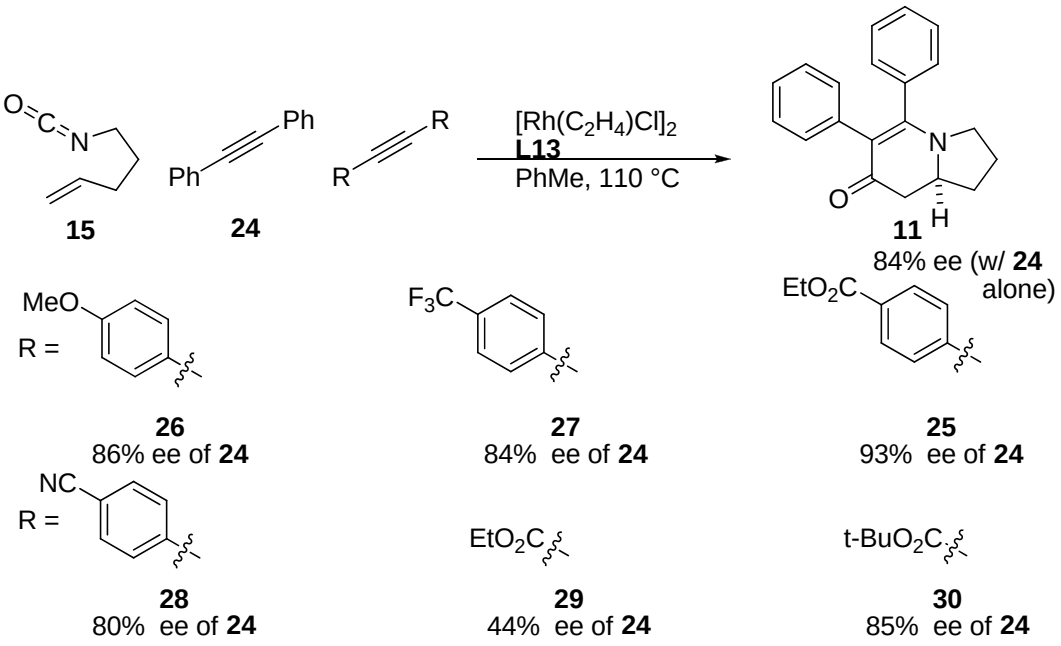
Table 3



15	**24**	**25**	**11**	**14**
	1.0	-	84% ee	-
	-	1.0	-	91% ee
	0.6	0.6	92% ee	91% ee

This competition experiment was performed with additional alkynes to determine the effect they had on the reaction with diphenyl acetylene 24 (Table 4).

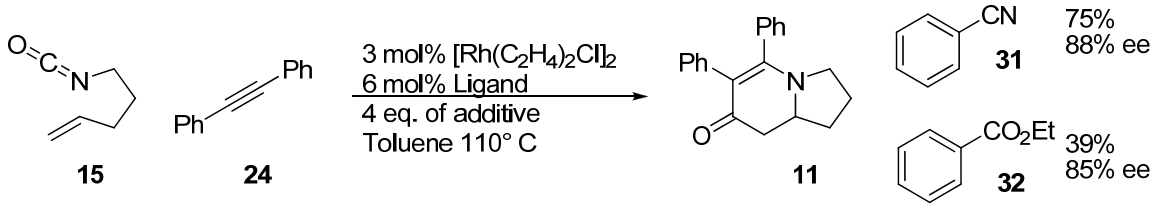
Table 4



Alkynes **26** and **27** did not show a significant change in the % ee. These alkynes may act similar to **24** as a spectator ligand. Acetylene dicarboxylate **29** decreased the enantioselectivity of the reaction; however an increase in the size of the substituents hindered the ability of **30** to act as a spectator ligand and the ee of **11** was restored. Both ester **25** and nitrile **28** substituted alkynes gave product **11** with different ee. Although alkynes **25** and **28** might be expected to perform similarly because they are both strong π-acids, the possibility exists for alkyne **28** to coordinate through the nitrile moiety, which may significantly affect how it changes the ee.

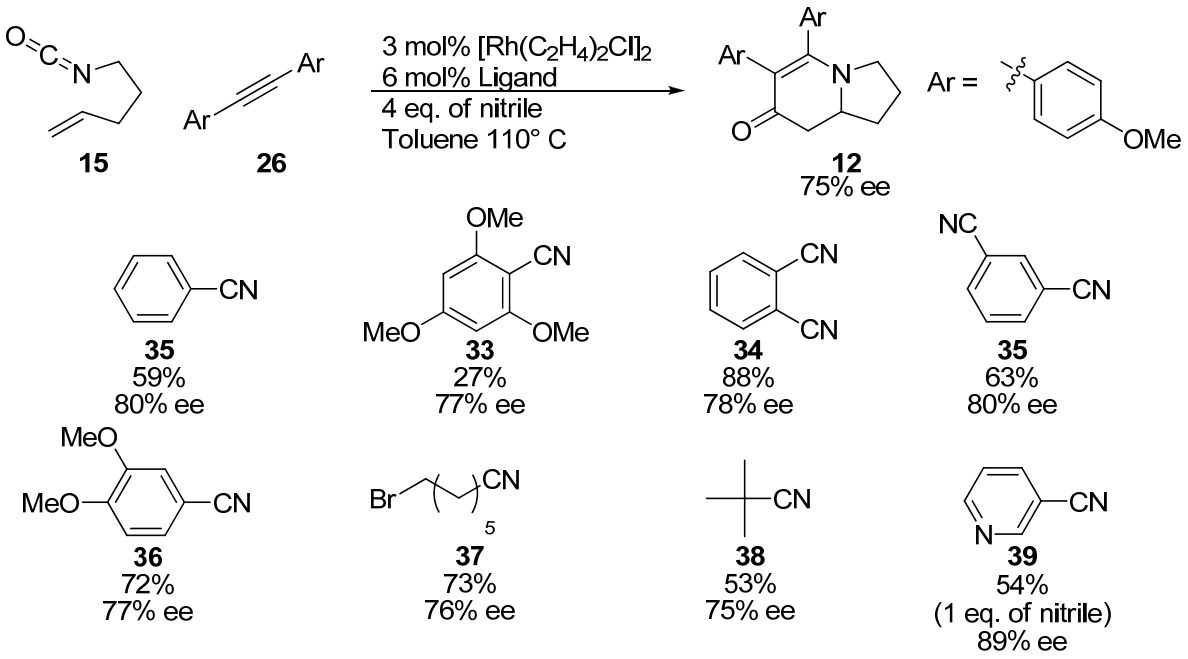
The competition between **25**, and **28-30** with diphenyl acetylene made it clear that the alkyne was affecting the enantioselectivity. To test whether this effect was due to coordination of the alkyne, ester or nitrile functional groups control experiments were run with nitrile **31** or ester **32** (Fig. 8).

Figure 8



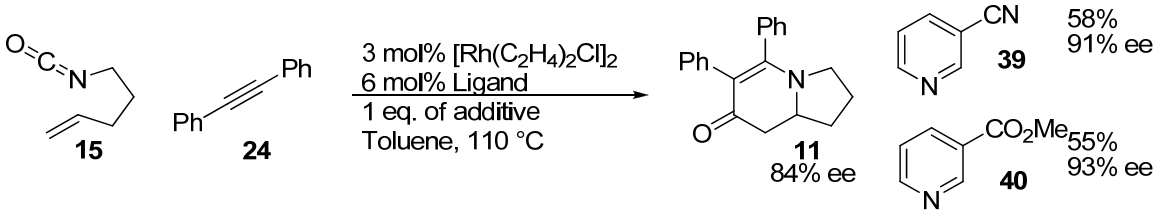
Interestingly in the reaction with added nitrile **31** there was an increase in enantioselectivity (88%) while with the benzyl ester there was no increase (85%). This result implied that there was coordination of the nitrile to the rhodium. Additionally, no cycloadduct were observed that incorporate nitrile **31**. The enhancement of the ee using a nitrile represented a result in which ees were altered by something that did not participate in the reaction. Thus, we focused on use of a spectator ligand, instead of substrate, as it avoids the formation of cycloadducts that need to be separated. In an effort to improve this effect and determine to what extent sterics and electronics played a role in the ability of nitriles to affect the enantioselectivity, nitriles were subjected as additives to the reaction (Table 5).

Table 5.



Use of Alkyne **26** in this screen would allow us to distinguish greater changes in enantioselectivity. There seemed to be little difference between the effect of the substituents and the change in ee. Perhaps we had obtained a maximum of the effect of nitriles on ee. Yet, when nitrile **39** was added to the reaction it resulted in a 14% change in ee. This additive also contains a pyridine, which raised a concern that either the pyridine or the nitrile might be coordinating to the rhodium. To test whether the pyridine was coordinating, the nitrile was replaced by the non-coordinating but electron withdrawing methyl ester **40** (Fig. 9).

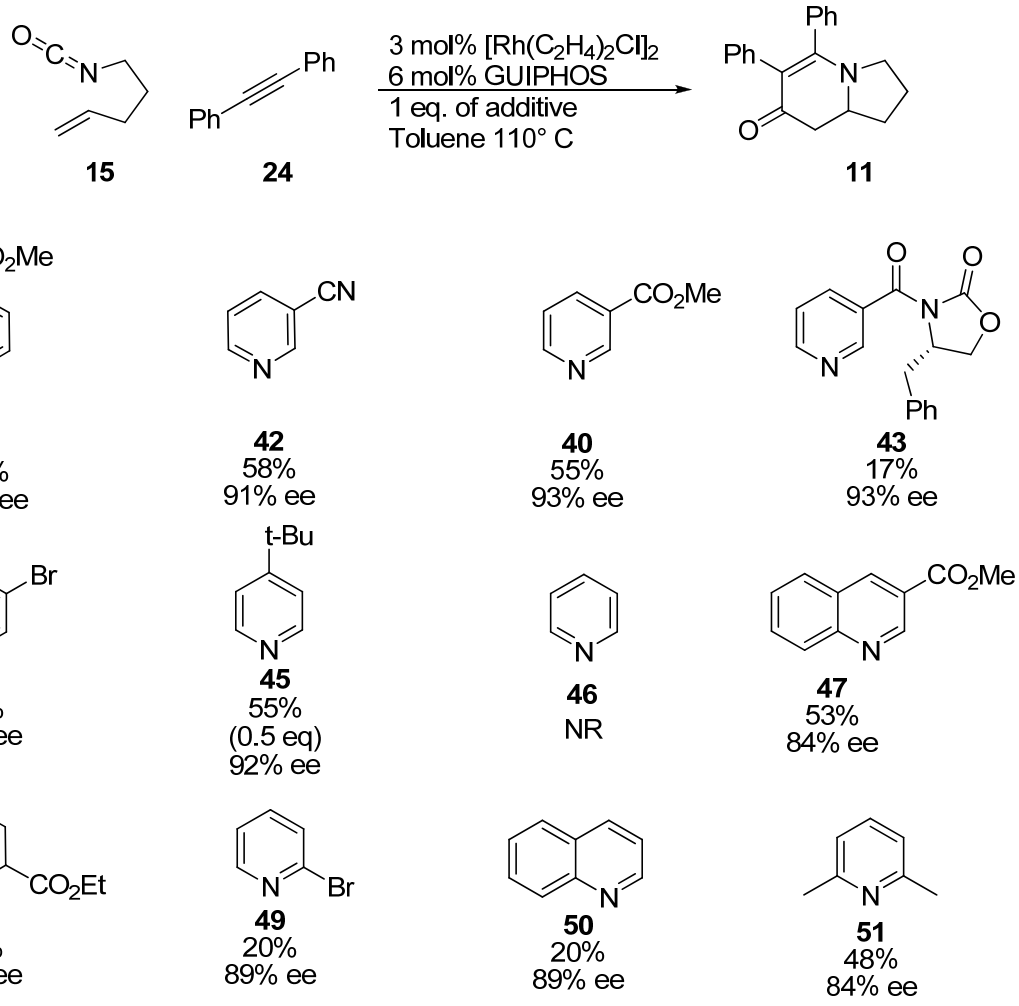
Figure 9



High enantioselectivity was obtained with **40** confirming that the pyridine moiety is crucial for the high enantioselectivity obtained with these types of additives.

With the discovery that pyridines as well as nitriles affected the enantioselectivity a structure activity relationship study with substituted pyridines was performed (Table 6).

Table 6



The enatioselectivity appears to have reached its apex at 93% ee, as more electron rich pyridines **44**-**46** and more electron withdrawing **42** give lower ees and lower yields. Pyridine **46** completely inhibits the reaction. Pyridines **47**- **51** with substituents ortho to the lewis basic nitrogen affect the ee only in some cases. This suggests that there is

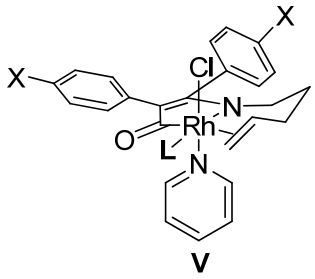
hindered coordination of ortho substituted pyridines. Pyridine **49** with a longer carbon-bromine bond at the 2-position changes the ee slightly and does not completely inhibit the conversion to product.

In this section both pyridines and nitriles have been identified as non-participating additives which enhance the enantioselectivity. Nitriles could be used in great excess (4 eq.) without deleterious effects on the yield; however, they do not have a large effect on enantioselecitivty. Pyridines were used as a stoichiometric additive which give a dramatic increase in the ee of the product. Though major drawbacks existed, using a single equivalent of additive and non-optimized yields, we had identified that exogenous additives that do not participate in the reaction could be used in the cycloaddition with diaryl acetylenes in order to achieve synthetically useful enantioselectivities.

2.3.1 The Dilemma of the Additive Effect

Different additives had been explored for their effect on the enantioselectivity of the reaction, although the fundamental understanding of how they changed the catalyst was not clear. To affect the enantioselectivity of the reaction must the additive be present during the enantiodetermining step? Since olefin insertion creates the carbon-nitrogen bond to the stereocenter enantiodetermination must occur during olefin insertion. Additive bound to a rhodium complex prior to olefin insertion would look like complex **V** (Fig. 10).

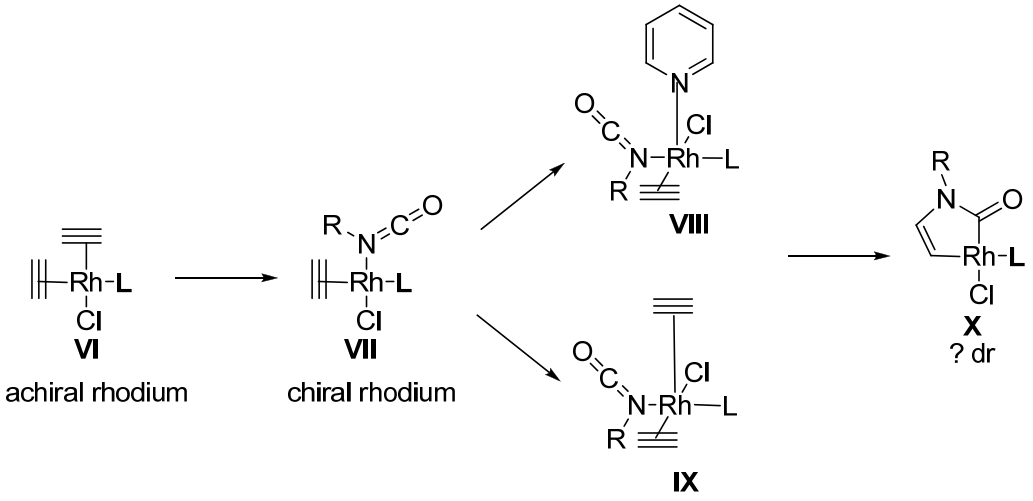
Figure 10



V

Enantioselectivity could be affected at other points in the mechanism. One of the caveats of asymmetric metal catalyzed reactions is that asymmetry of the metal catalyst is transferred to the substrate. Therefore the enantioselectivity could be imparted during the formation of an intermediate metal complex prior to coordination of the substrate, and the resulting ee could depend on the diastereoselectivity of the formation of this metal complex. In our case the rhodium metal becomes chiral before the olefin is involved (VII, Fig. 11).

Figure 11



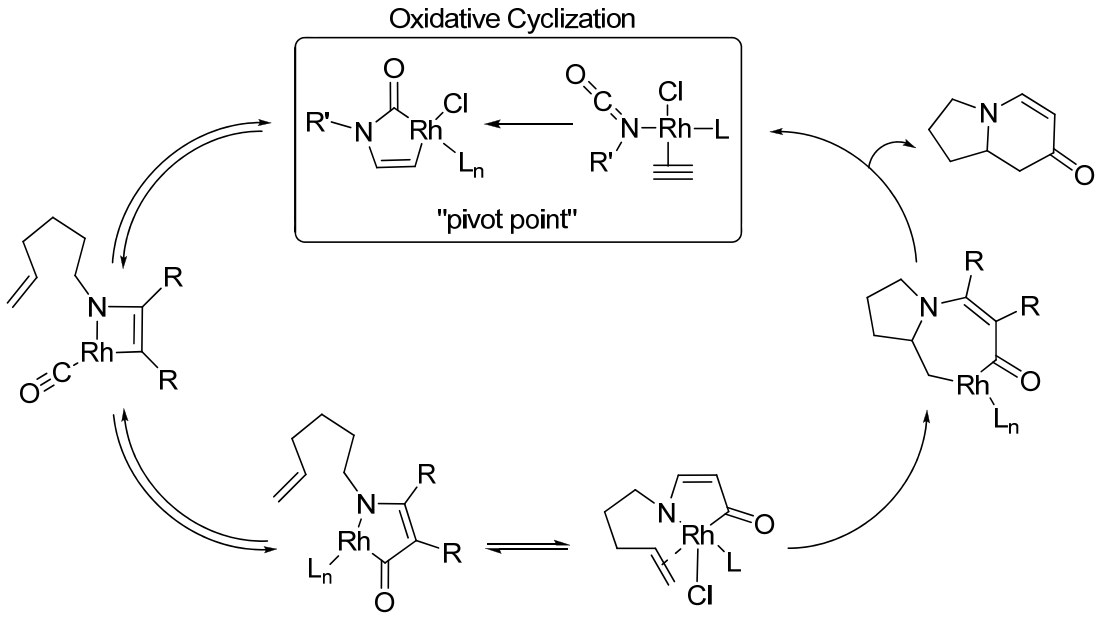
One alternative mechanism that was proposed was that the additive could be coordinating to a chiral rhodium (I) intermediate **VII** prior to the oxidative cyclization. Coordination of the additive or substrate would give rise to two intermediates **VIII** and **IX**. The

coordination of the additive at this stage could alter the relative diastereoselectivity of intermediate **X** that forms after oxidative cyclization. If the intermediate is stereochemically rigid the diatereoselectivity of **X** ultimately influences the ee of the product. Further more if this is true it is possible that dissociation of the additive occurs after oxidative cyclization and the additive is not present during the enantiodetermining olefin insertion.

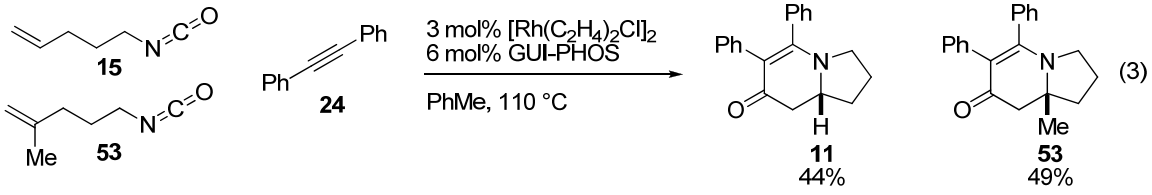
Distinguishing between whether the additive affects the oxidative addition, olefin insertion or both would be important. If the additive affects the rhodium (I) complex that underwent oxidative cyclization this would be analogous to effects observed by Feringa and others (section 2.1). In each of those cases the presence of a combination of chiral ligands or chiral and achiral ligands leads to "hetero" rhodium (I) complex which undergoes the reaction with greater efficiency and enantioselectivity than the "homo" rhodium (I) complex.

The question that needed to be answered was whether or not the additive affects oxidative cyclization of a rhodium (I) intermediate**.** Thus, oxidative cyclization was chosen as a "pivot point" to distinguish whether the additive affects the reaction prior to oxidative cyclization (a rhodium (I) intermediate) or after oxidative cyclization (a rhodium (III) intermediate). This seemed a reasonable "pivot point" as oxidative cyclization was suspected as the turn over limiting step. Therefore it seemed reasonable to separate the mechanism into these two distinct parts (Fig. 12).

Figure 12



First an experiment was designed to test whether oxidative cyclization was turn over limiting. A competition experiment was performed in which a mixture of isocyanates **15** and **53** were subjected to the reaction with diphenyl acetylene **24** (eq. 3).



The results of this competition experiment show that there is no preference for either alkenyl isocyanate in the oxidative cyclization. If the oxidative cyclization were reversible and the olefin insertion was the turn-over limiting step we would expect a bias

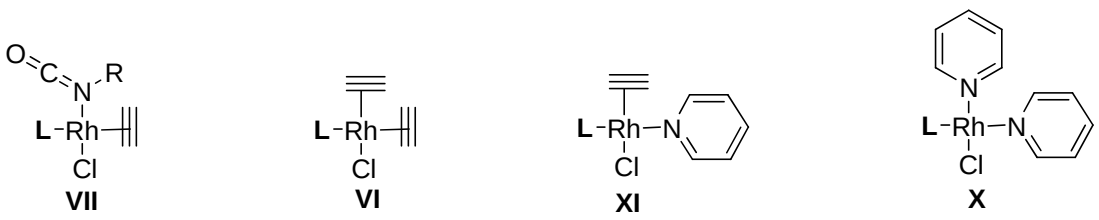
for incorporation of the terminal isocyanate over the 1,1-disubstitued isocyanate of 100:1.[12] Since there is no bias in the product distribution this suggests that the oxidative cyclization is the first irreversible step and turn-over limiting.

Oxidative cyclization being turn-over limiting now allows us to separate the reaction into two regimes. First the kinetically visible regime constitutes all the steps that occur prior to oxidative cyclization. Second there is a kinetically invisible regime which constitutes the steps that occur in the reaction after oxidative cyclization.

2.3.2 The Composition of Rhodium (I) Precursors and the Effect of Additives Prior to Oxidative Cyclization

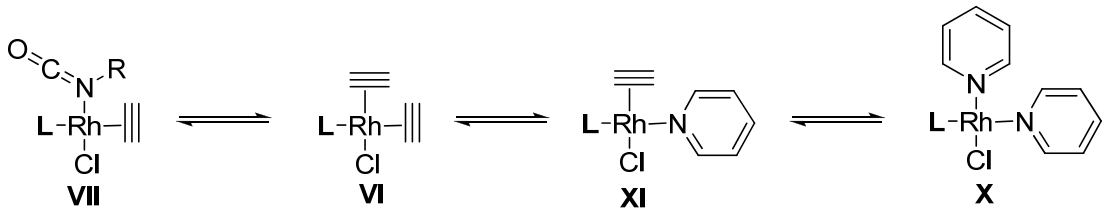
Next the investigation focused on what information we could glean about the composition of rhodium (I) intermediates in the kinetically visible regime. Through ^{31}P NMR studies a rhodium complex made from the combination of 1 eq. of $[Rh(C_2H_4)_2Cl]_2$ with 1 eq. of GUIPHOS and 2 eq. of diphenyl acetylene **24** lead was observed.[13] This data was most consistent with monomeric phosphoramidite complex **VI** (^{31}P δ 134 ppm, J = 288 hz). Upon addition of isocyanate **15** to complex **VI** no change was observed by NMR under standard reaction conditions suggesting that complex **VII** is not involved in a relevant equilibrium (Fig. 13).

Figure 13



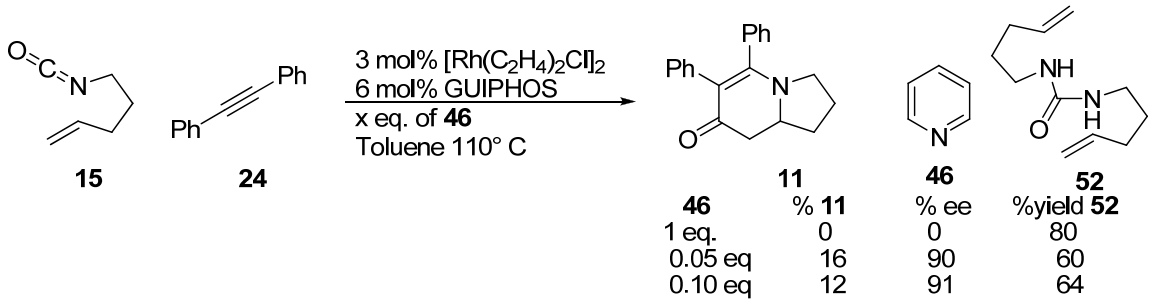
Two other complexes were generated from the combination of $[Rh(C_2H_4)_2Cl]_2$ with 1 eq. of GUIPHOS, the first with 2 eq. of methyl nicotinate **40** and the second with one equivalent of **24** and 1 equivalent of **40**. In the former case only one complex is observed which is assigned as monomeric complex **X** (^{31}P δ 146 ppm, J = 258 hz) and in the latter case both **VI**, **X** and a third complex assigned as **XI** (^{31}P δ 143 ppm, J = 258 hz) is observed (Fig. 12).[14] Complexes **VI**, **XI** and **X** exist in an equilibrium with each other ultimately leading to a complex which is able to undergo oxidative cyclization (Fig. 14).

Figure 14



A key observation was made with respect to the ability of the additives to affect the oxidative cyclization, that pyridine **46** appears to inhibit the reaction. No product was obtained in the presence of one equivalent of pyridine **46**; as well, decreased yields were obtained in the presence of **40**. It was possible that the equilibrium favoring complexes **XI** and **X** was inhibiting oxidative cyclization by shutting down any pathways leading to **VII**. Decreasing the concentration of pyridine **46** increased the yield of desired product (Table 7).

Table 7.

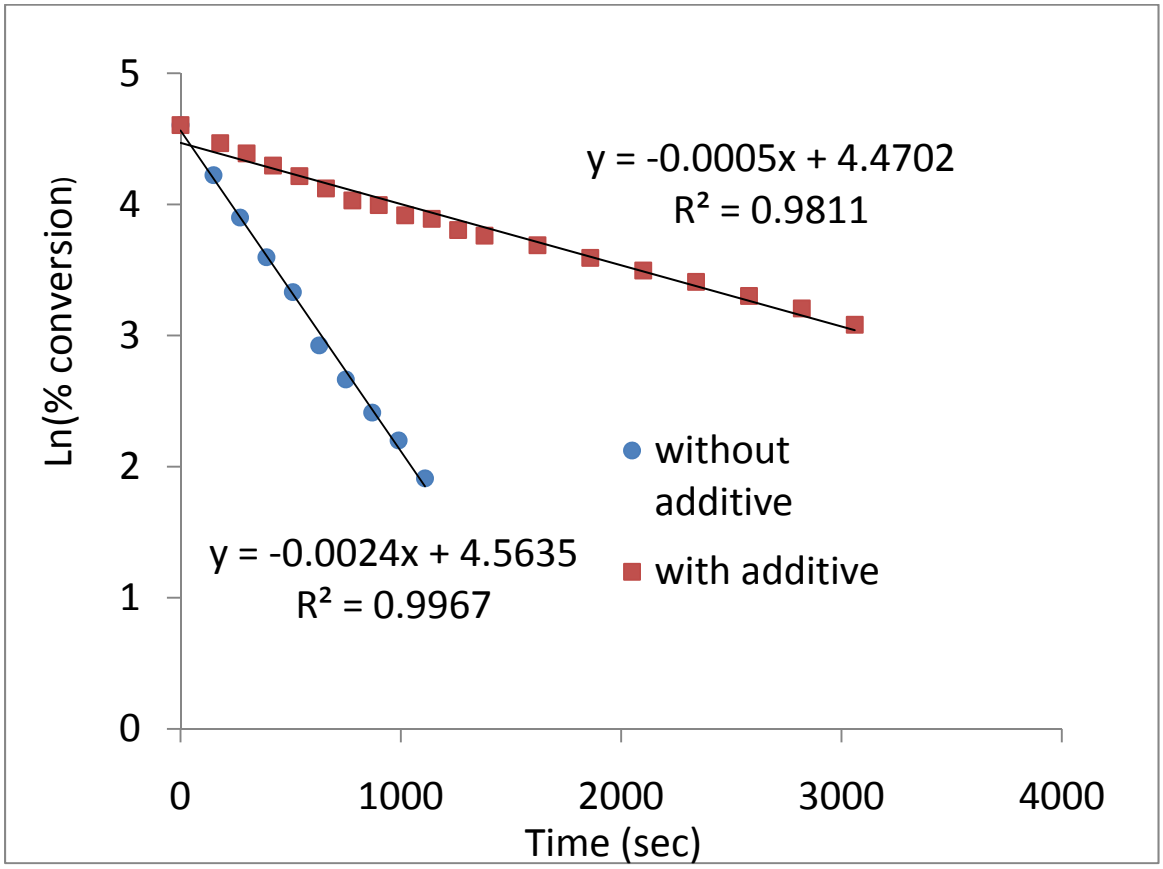


46	% 11	% ee	%yield 52
1 eq.	0	0	80
0.05 eq	16	90	60
0.10 eq	12	91	64

The major byproduct in the failed reactions was urea **52**. Increasing the amount of pyridine in the reaction yields greater amounts of urea **52**. The urea may be formed from a background reaction with adventitious water.[15] This background reaction takes place because pyridine **40** is able to occupy multiple coordination sites on rhodium. This favors formation of complexes **XI** and **X**, and inhibits coordination of the isocyanate to form a complex like **VII** which undergoes oxidative cyclization (*vide infra*).[16]

If pyridine type additives are inhibiting the rate of the oxidative cyclization, then the observed rate of the reaction in the presence of additive should be slower. The rate of the reaction was measured via the disappearance of alkyne **55**, 3,3'-fluorodiphenylacetylene, using ^{19}F NMR. Graph 1 shows the results of this study showing the log of the disappearance of starting material **55** versus time both in the presence and absence of methyl nicotinate **40**.

Graph 1

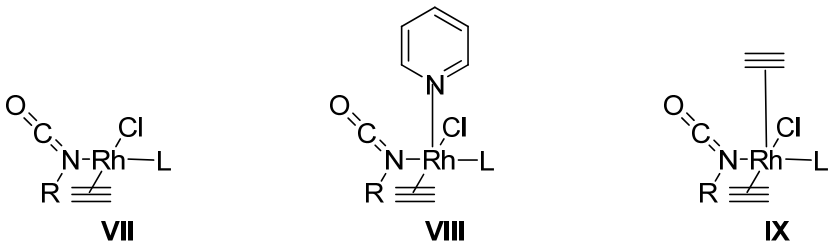


The slope of the line without the additive is much steeper than with which implies that the consumption of alkyne in the reaction without the additive is much faster. This confirms that the reaction is slower in the presence of methyl nicotinate **40**.

The composition of the complex which underwent oxidative cyclization between the isocyanate and alkyne was still unknown. Oxidative cyclization could be occurring to either a four-coordinate comples like **VII** or a five-coordinate complex like **VIII** or **IX** (Fig 15). Complexes like **VIII** and **IX** accommodate a fifth ligand and allow for the possibility that the additive or substrate is affecting the enantioselectivity of the reaction by coordination to an intermediate prior to oxidative cyclization. In order to distinguish

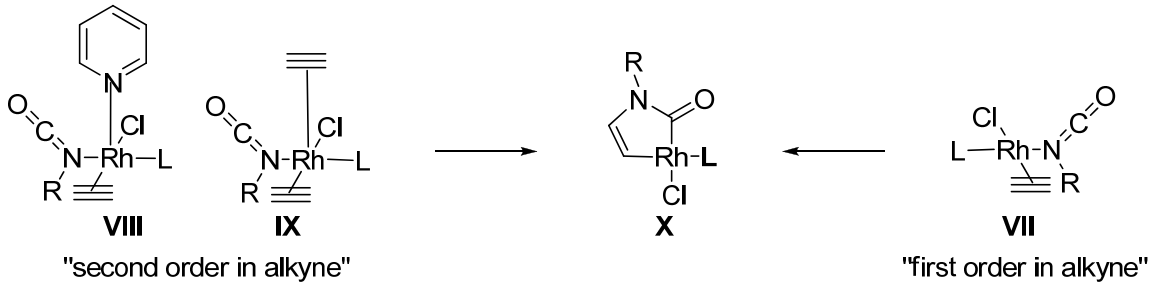
whether the additive is affecting the oxidative cyclization we need to show whether oxidative cyclization can occur to intermediates like **VIII** or **IX**.

Figure 15



The dependence of alkyne in the rate law will be different if intermediate **VII** or **IX** are the rhodium complexes which undergo oxidative cyclization(Scheme 2).

Scheme 2



If oxidative cyclization occurs to a five-coordinate intermediate like **IX** then the reaction would appear to be second order in alkyne. A first order dependence on alkyne would be indicative that a four-coordinate intermediate like **VII** is undergoing oxidative cyclization.

The shape of the data from graph 1 is linear confirming that the reaction is first order in alkyne. If the reaction were second order in alkyne this data would show curvature; therefore intermediate **VII** is the most plausible intermediate to undergo oxidative cyclization. This data is in agreement with the equilibrium proposed (Fig. 14)

on the basis of the ^{31}P NMR studies and the studies demonstrating the inhibitory affect of the pyridine **46** (Table 7).

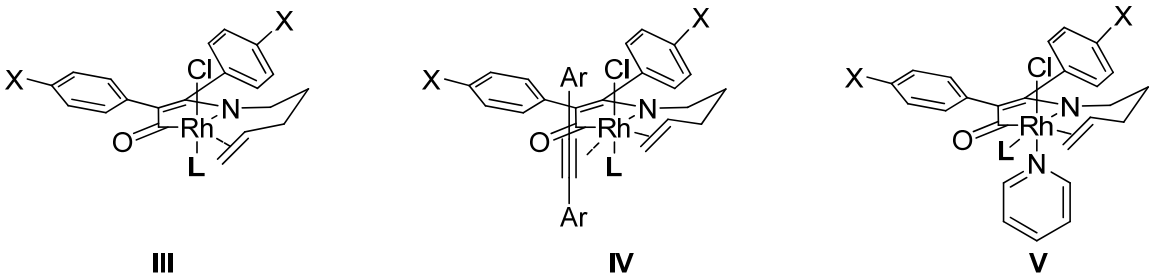
Both alkynes and exogenous additives presumably affect the enantioselectivity of the reaction through a similar mechanism. The first order dependence of alkyne suggests that both the alkyne and the additive affect the enantioselectivity of the reaction by altering a reaction intermediate that occurs after the oxidative cyclization. This conclusion was important because it distinguished this additive effect from the additive effects which were discussed in section 2.1. In those cases the presence of a combination of chiral ligands or chiral and achiral ligands leads to a "hetero" rhodium (I) complex which undergoes the asymmetric reaction with greater efficiency and enantioselectivity than the "homo" rhodium (I) complex. In our case we had now shown that the additive inhibits the oxidative cyclization thereby slowing the efficiency and that it was affecting a rhodium (III) complex which existed in the "kinetically invisible regime". This data now allowed us to probe further the likely composition of intermediates leading to enantioselecitivity.

2.3.2 The Composition of Rhodium (III) Precursors and the Effect of Additives After Oxidative Cyclization

The data now correlates well with the hypothesis that the additive effect was due to coordination of the additive to a rhodium (III) species prior to olefin insertion. Three possibilities of rhodium (III) intermediates responsible for enantioselectivity existed. A five-coordinate rhodium intermediate **III** with no additional ligand bound, a six-

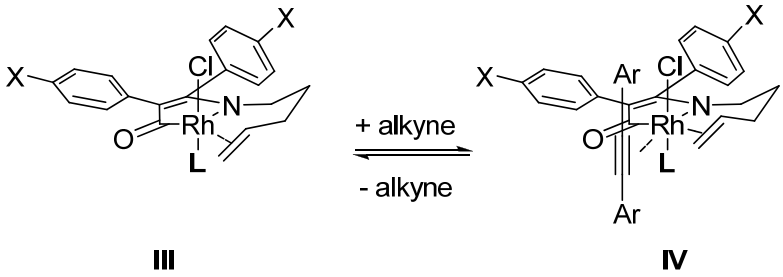
coordinate rhodium intermediate **IV** with substrate acting as a spectator ligand and a six-coordinate rhodium intermediate **V** with additive acting as a spectator ligand (Fig. 16).

Fig 16



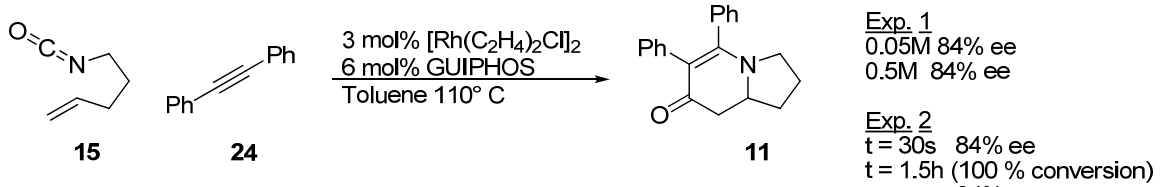
Competition between 5-coordinate complex **III** with no spectator ligand and 6-coordinate complex **IV** could potentially complicate the mechanism as enantioselectivity would be highly dependent on reaction concentration (Fig. 17).

Figure 17



One qualitative piece of evidence that argued against a competition between **III** and **IV** was the fact that ees were reproducible. Table 8 documents two experiments that show complex **III** does not undergo olefin insertion and is not relevant to enantioselectivity.

Table 8

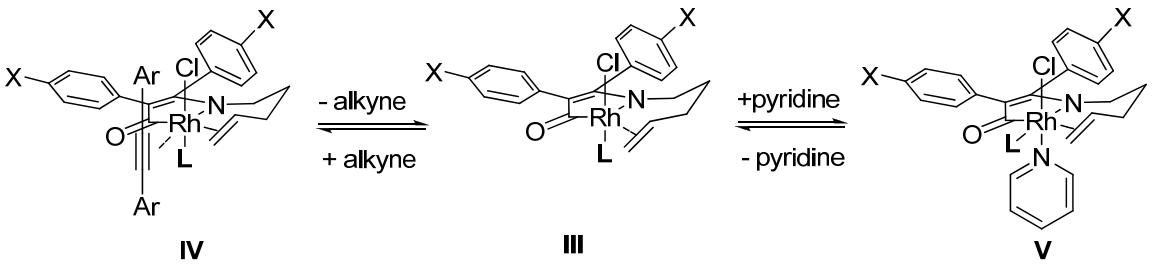


First when the reaction is run over a ten-fold concentration variation (normal = 0.2M),

there is no change in % ee of the product. If there was a competition for olefin insertion between **III** and **IV** the % ee may be dependent on the concentration of alkyne reflecting the partitioning between these two complexes for olefin insertion. Under dilute conditions the % ee should reflect the enantioselectivity of olefin insertion to **III** and under more concentrated conditions the ee should reflect the enantioselectivity of olefin insertion to **IV**. A second experiment examines the enantioselectivity of the reaction over time. When the reaction is run at normal concentrations and the % ee is monitored over time, the % ee of the first aliquot is the same as the % ee of the last, and 84% ee was obtained for all data points. Since the concentration of alkyne is changing over the course of the reaction if a competition existed between **III** and **IV** we would expect the % ee to increase over time. Both of these experiments support the fact that intermediate **III** does not undergo olefin insertion.

Competition between **IV** and **V** should be dependent on both concentration and coordinating ability of the additive (Fig. 18).

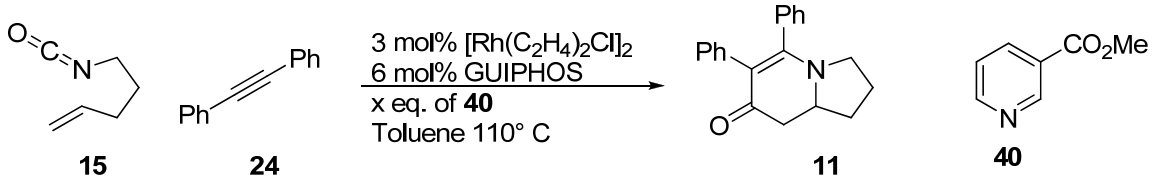
Figure 18



A change in enantioselectivity based on the ability of the pyridine to coordinate has been observed (Table 6) where ortho substitution of the pyridine prevents coordination to rhodium and therefore additives such as **47**, **48** and **51** do not show a change in enantioselectivity. Competition between **IV** and **V** would also be demonstrated by how

well the pyridine was able to compete with the alkyne for coordination to rhodium. By decreasing the concentration of the pyridine it would be expected that the enantioselectivity would drop due to a greater concentration of **IV** over **V**. Table 8 demonstrates the effect of additive concentration on the enantioselectivity of the reaction.

Table 8.

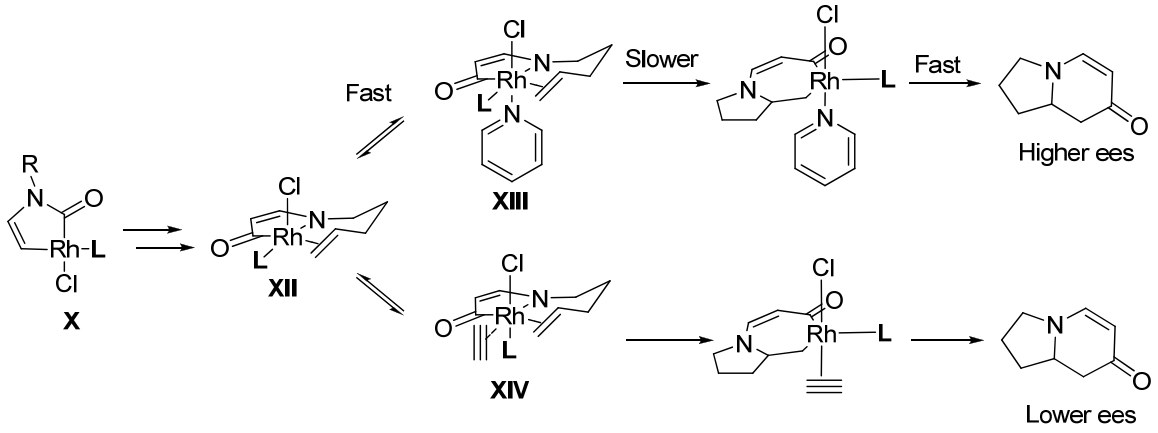


15 **24** **11** **40**

eq. of **40**	Yield	%ee
0.05	53	86
0.1	47	87
0.2	27	89
0.4	52	91
0.8	45	93

Titration of the additive to show higher enantioselectivity at greater concentrations of **40** is consistent with the hypothesis that equilibrium between two different 6-coordinate rhodium species **IV** and **V** is established after oxidative cyclization **(**Fig 18). Though the precise structure of fluxional rhodium intermediates **IV** or **V** is not known it is consistent with the data that these intermediates are 6-coordinate rhodium (III) intermediates which directly precede enantioselective olefin insertion (Fig 19).

Figure 19

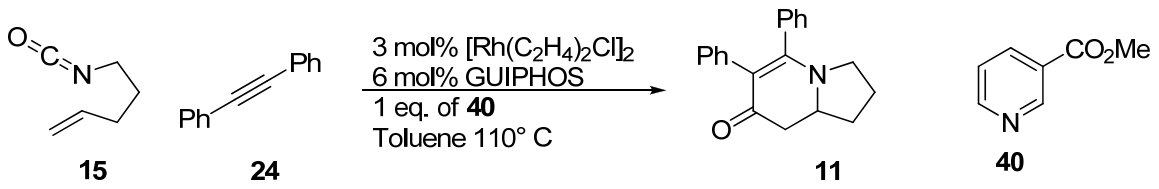


These intermediates **XIII** and **XIV** are presumably short-lived and high energy but their fluxional nature and rapidly established equilibrium can be seen because of the ability of the catalyst to distinguish between **XIII** and **XIV** in the olefin insertion step. Thus the additive allows for higher enantioselectivities in the reaction by "choice" of different rhodium (III) intermediates **XIII** or **XIV**.

2.4 Scope of the Additive Effect

With the information regarding the mechanism of the additive effect in hand the reaction was optimized with diaryl acetylenes. Initially, adverse effects on the yield of the reaction were found using a single equivalent of additive. Titration studies of the additive (Table 7 and 8) showed that a large proportion of alkyne **24** still remained and that most of the isocyanate starting material **15** that had not been converted into product **11** had become urea **52**. Since the oxidative cyclization was rate-determining and this depended on both the concentration of alkyne and isocyanate in order to avoid urea formation the reaction was optimized with respect to equivalents of isocyanate (Table 9).

Table 9

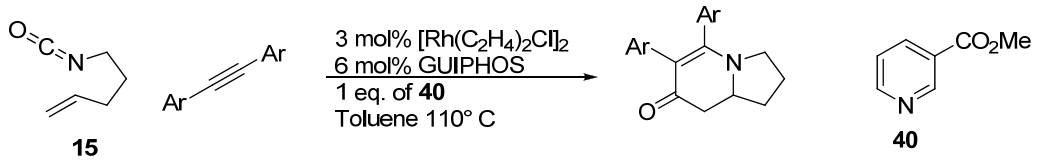


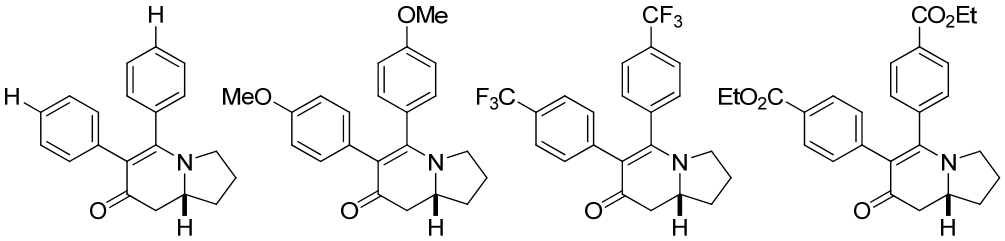
15 **24** **11** **40**

eq. of **15**	Yield	%ee
1.0	39	93
1.2	62	93
1.4	89	93
1.5	95	93
1.6	93	93

It appeared that 1.5 equivalents of isocyanate **15** were optimal to obtain quantitative conversion with diaryl acetylenes. The % ee with respect to equivalents of methyl nicotinate **40** had already been optimized using 1 eq. (Table 8). Since there was no observation of competitive side reactions with the diarylacetylene **24** these optimized conditions were used to investigate the full substrate scope of the reaction. A number of diarylacetylenes were used in order to investigate the scope of this additive effect and to show this effect to be general that the enantioselectivities of a wide variety of substrates can be brought into a synthetically useful range (Table 10).[17]

Table 10



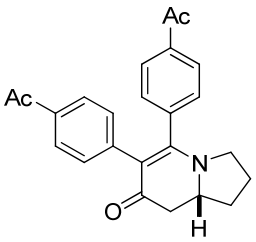


11
95%
93% ee
(84% ee)

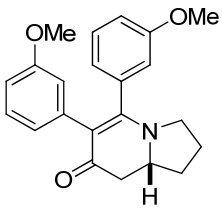
12
93%
91% ee
(75% ee)

13
28%
93% ee
(72% ee)

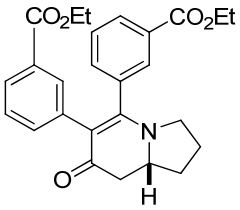
14
92%
93% ee
(91% ee)



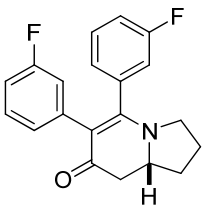
56
95%
90% ee
(84% ee)



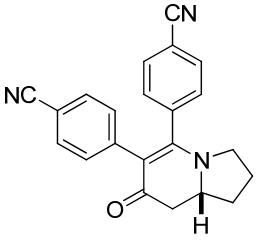
57
93%
92% ee
(85% ee)



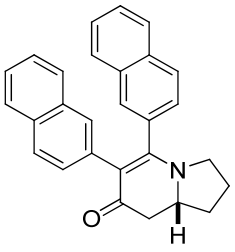
58
92%
93% ee
(91% ee)



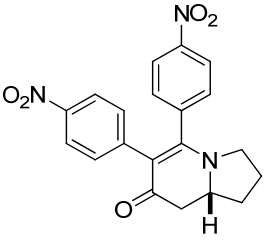
59
80%
93% ee
(68% ee)



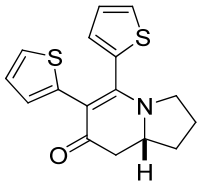
60
70%
62% ee
(62% ee)



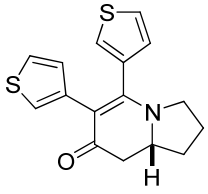
61
92%
91% ee
(86% ee)



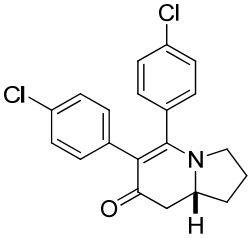
62
70%
86% ee
(90% ee)



63
92%
93% ee
(91% ee)



64
92%
93% ee
(91% ee)



65
71%
92% ee
(76% ee)

Trying to extend this effect to other substrates proved that this effect is not as general as we had hoped. Methyl nicotinate **40** was able to increase ee with aryl propiolates (eq. 4).

15 **68** **69**
36%
91% ee
(86% ee)

(4)

However this was not the case with terminal alkynes (eq. 5)

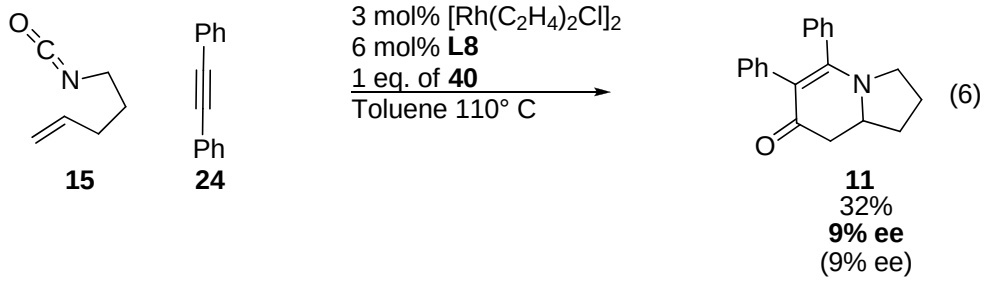
15 **70** **20**
55%
40% ee
(40% ee)

(5)

There appears to be both a steric and electronic element to the ability of a substrate to be subject to the additive effect. The result with terminal acetylenes is not suprising. There is an apparent difference in the nature of enantioselectivity with terminal alkynes than with diaryl acetylenes. This can be illustrated by the fact that while TADDOL ligands give poor ees (9%) with diphenylacetylene **14** while terminal alkynes give consistently high ees (88-94%) with TADDOL based phosphoramidites (Table 2). Furthermore with GUIPHOS, **L10** diphenyl acetylene give high ees (84%), while with terminal acetylenes, **70** only modest (40%) ee is obtained. These differences could be due to something as simple as ligand and substrate complex conformation, or could be due as well to the coordination geometry of rhodium intermediates dependent on substrate.

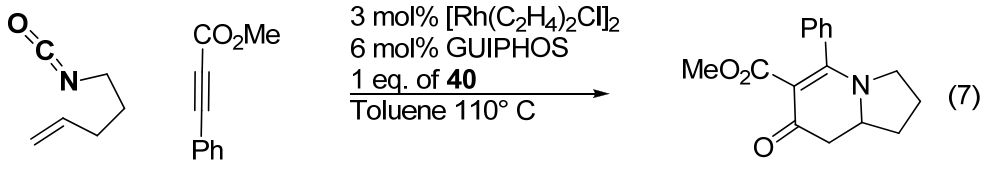
The effect of additives on the enantioselectivity outside of the BINOL based phosphoramidites also is problematic. Cycloaddition of diaryl acetylenes using

TADDOL-based phosphoramidite **L8** showed no change in ee in the presence of methyl nicotinate **40** (Eq. 6).



15 **24** **11**
32%
9% ee
(9% ee)

The failure of the additive effect is likely the result of poor enantioselectivity with this substrate and ligand set. It would be hard to imagine that an achiral spectator ligand could dramatically change the difference in the diastereomeric transition states, when the ligand itself is incapable of imparting a significant difference. To test this hypothesis an experiment was performed to look at the enantioselectivity of the reaction of methyl-phenyl propiolate and ligand **L8** in the presence and absence of methyl nicotinate **40** (Eq. 7).



15 **68** **69**
58%
88% ee
(73% ee)

This substrate ligand combination which provides products of high enantioselectivity (73%)[18] does show an effect of **40** on the ee of the product, which suggests that TADDOL as well as BINOL based phosphoramidites are subject to the effects of additives.

In this chapter the mechanism of the effect of substrate and exogenous additives on the rhodium catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and diaryl

acetylenes has been elucidated. This additive effect represents a heretofore undescribed type of effect of achiral additives on an enantioselective rhodium catalyzed reaction. By distinguishing it mechanistically from other effects of additives in rhodium-catalyzed reactions additional possibilities for manipulating asymmetric rhodium catalysis have been identified. With the knowledge that this mechanism provides into the mechanism additional strategies for exploiting additives in asymmetric rhodium catalyzed reactions can be envisioned.

Chapter 2 Experimental

The Use of Additives in Optimization of the Enantioselective Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates with Diaryl Acetylenes

General Methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Acetonitrile (certified ACS grade) and triethylamine (peptide synthesis grade) were purchased from Fisher Scientific and used without further purification. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and KMnO4 followed by heating. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (□, ppm) from deuterated chloroform (CDCl3) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from CDCl3 taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Alkyne **2a** and compounds **29-51** were purchased from Aldrich Chemicals Co. and used without further purification. Diaryl acetylenes were prepared via literature procedure.[19] Alkenyl isocyanates **15** and **53** can be synthesized by the procedure previously describe. 5-hexenoic acid, 6-heptenoic acid, and diphenyl phosphoryl azide were purchased from Aldrich Chemicals Co. $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. Ligand **L7-L9** were prepared as described in the literature.[20] Ligand **L10-L19** were prepared as described in the literature.[21]

General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and diaryl acetylenes: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne (1.0 eq, 0.128 mmol) and isocyanate (1.5 eq, 0.193 mmol) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

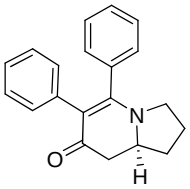
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and diaryl acetylenes using additives: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne (1.0 eq, 0.128 mmol), isocyanate (1.5 eq, 0.193 mmol) and compound **4d** (1.0 eq, 0.128) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution to typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

Procedure for the competition reaction of Rh-catalyzed [2+2+2] cycloaddition of pentenyl isocyanate diphenyl acetylene and bis(4-carboxyethyl phenyl) acetylene: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0069 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0138 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne **2a** (1.0 eq, 0.140 mmol), bis(4-carboxyethyl phenyl) acetylene **2f** (1.0 eq, 0.140 mmol) and 5-Isocyanato-2-methyl-pent-1-ene **1** (1.0 eq, 0.231 mmol) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure products **3a** and **3f** in 41% and 23 % yields respectively.

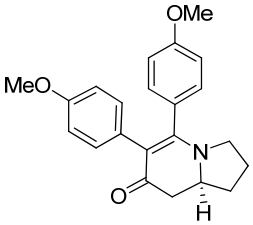
Procedure for the competition reaction of Rh-catalyzed [2+2+2] cycloaddition of 5-Isocyanato pent-1-ene and 5-Isocyanato-2-methyl-pent-1-ene and diphenyl acetylene: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0055 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0110 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne **2a** (1.0 eq, 0.184 mmol), 5-Isocyanato pent-1-ene **1** (1.0 eq, 0.184 mmol) and 5-Isocyanato-2-methyl-pent-1-ene **1a** (1.0 eq, 0.184 mmol) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of Toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure products **3a** and **4** in 44% and 49 % yields respectively.

Procedure for monitoring the disappearance of Bis(3-fluorophenyl) acetylene 2n in the Rh-catalyzed [2+2+2] cycloaddition of 5-Isocyanato pent-1-ene without additive:
An oven-dried nmr tube was flushed with argon. In an inert atmosphere (N2) glove box a 1 dram vial was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0055 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0110 mmol), alkyne **2n** (1.0 eq, 0.184 mmol) and 1-Fluoronapthalene (10 □L, 0.077 mmol) as an internal standard. 0.250 mL of D_8-toluene was used to dissolve, the rhodium precatalyst, ligand and alkyne, and the solution was transferred to the nmr tube. The reaction was placed in the NMR tube and inside the NMR and slowly heated over ten minutes to 90^o C. Data was collected without isocyanate at T=0. The NMR tube was removed and injected with 5-Isocyanato pent-1-ene **1** (1.0 eq, 0.184 mmol) in 0.150 ml of D_8-toluene. NMRs were subsequently taken at periods of 2 minutes and then 5 minutes until the reaction was greater than 90% conversion.

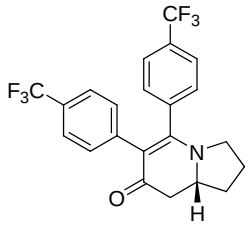
Procedure for monitoring the disappearance of Bis(3-fluorophenyl) acetylene 2n in the Rh-catalyzed [2+2+2] cycloaddition of 5-Isocyanato pent-1-ene with methyl nicotinate:
An oven-dried nmr tube was flushed with argon. In an inert atmosphere (N2) glove box a 1 dram vial was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0055 mmol) and the phosphoramidite ligand **L** 3.9 mg (0.06 eq, 0.0110 mmol), alkyne **2a** (1.0 eq, 0.187 mmol), methyl nicotinate (0.5 eq, 0.094 mmol) and 1-Fluoronapthalene(10 □L, 0.077 mmol) as an internal standard. 0.250 mL of D_8-toluene was used to dissolve, the rhodium precatalyst, ligand, alkyne, and methyl nicotinate and the solution was transferred to the NMR tube. The reaction was placed in the NMR tube and slowly heated over ten minutes to 90^o C. Data was collected without isocyanate at T=0. The NMR tube was removed and injected with 5-Isocyanato pent-1-ene **1** (1.0 eq, 0.184 mmol) and 5-Isocyanato-2-methyl-pent-1-ene **1b** (1.0 eq, 0.560 mmol) in 0.150 ml in D_8-toluene. NMRs were subsequently taken at periods of 2 minutes and then 5 minutes until the reaction was greater than 80% conversion.



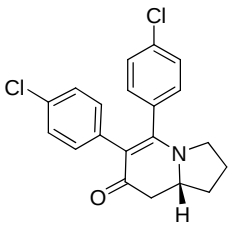
5,6-diphenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (11). The general procedure yielded a light yellow solid (95% yield): R_f = 0.13 (1:1 EtOAc/Hex); $[\alpha]_D^{20}$ = + 632.5 HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.1 minutes, Minor: 13.8 minutes, 230 nm detection light, *ee* = 93%; ^{1}H NMR (400 MHz, $CDCl_3$) 7.04 – 7.30 (m, 5H), 7.00 (m, 2H), 6.88 –6.94 (m, 3H), 4.14 (dddd, 1H, *J* = 6.8, 6.8, 6.8, 13.6 Hz), 3.40 (ddd, 1H, *J* = 4.0, 7.5, 11.5 Hz), 3.11 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.67 (dd, 1H, *J* = 15.6, 15.6 Hz), 2.59 (dd, 1H, *J* = 5.3, 16.0 Hz), 2.35 (m, 1H), 1.94 – 2.03 (m, 1H), 1.73 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 189.9, 161.1, 136.7, 135.9, 132.2, 128.9, 128.2, 127.4, 125.3, 112.4, 57.8, 50.1, 42.1, 32.5, 24.4; IR (NaCl, $CDCl_3$) 1617, 1528, 1450, 1383, 1304, 1091 cm^{-1};HRMS $[C_{20}H_{20}NO]^+$ calcd 290.1545. Found 290.1545 (FAB+).



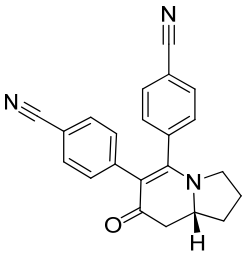
5,6-bis(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (12). The general procedure yielded a light yellow solid (98% yield): R_f = 0.21 (EtOAc); $[\alpha]_D^{20}$ = + 559.4 (c =1.5, THF) HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.1 minutes, Minor: 13.8 minutes, 230 nm detection light, *ee* = 91% ^{1}H NMR (400 MHz, $CDCl_3$) 6.54 – 7.20 (m, 8H), 4.11 (dddd, 1H, *J* = 6.5, 6.5, 6.5, 12.9 Hz), 3.71 (s, 3H), 3.65 (s, 3H), 3.43 (m, 1H), 3.10 (m, 1H), 2.64 (dd, 1H, *J* = 15.8, 15.8 Hz), 2.55 (dd, 1H, *J* = 4.5, 15.8 Hz), 2.31 (m, 1H), 1.91 – 2.01 (m, 1H), 1.71 – 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 189.9, 161.0, 159.8, 157.1, 133.0, 130.6, 129.3, 128.2, 113.6, 113.1, 111.8, 57.5, 55.3, 55.2, 50.3, 42.0, 32.3, 24.5; IR (NaCl, $CHCl_3$) 1598, 1521, 1440, 1301, 1030 cm^{-1}; HRMS $[C_{22}H_{24}NO_3]^+$ calcd 350.1756. Found 350.1761 (FAB+).



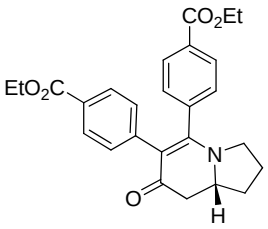
5,6-bis(4-trifluoromethylphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (13) The general procedure yielded a dark yellow solid (74% yield) R_f = 0.20 EtOAc $[\alpha]_D^{20}$ = + 448 (c = 1.2, THF) HPLC analysis – Chiracel OD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 11.14 minutes, Minor: 12.53 minutes, 254 nm detection light, *ee* = 80% ^{1}H NMR (400 MHz, $CDCl_3$) 7.62 – 7.4 (m, 3H), 7.30 (d, 2H, J=8 Hz), 7.14-7.06(m, 1H), 7.02 (d, 2H, J = 8 Hz) 4.19 (dddd, 1H, *J* = 7.2, 7.2, 7.2, 14.4 Hz), 3.40 (ddd, 1H, *J* = 4.0, 7.2, 11.6 Hz), 3.12 (ddd, 1H, *J* = 7.6, 7.6, 10.8 Hz), 2.73-2.63 (m, 2H) 2.41 (m, 1H, Hz2.1-1.8 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) 189.6, 159.4, 140.0, 138.0, 132.2, 131.5, 129.6, 125.7, 124.6, 111.6, 58.2, 50.3, 41.8, 32.5, 29.9, 24.5; IR (NaCl, $CHCl_3$) 2924, 1630, 1534, 1455, 1406,1325,1164,1066 cm^{-1}; HRMS $[C_{22}H_{18}F_6NO]$ calcd. 426.1214 Found (426.1212) (ESI+).



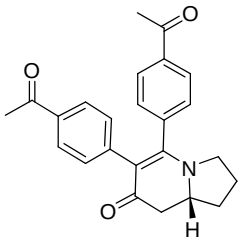
5,6-bis(4-chlorophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (65).
The general procedure yielded a light yellow solid (71% yield) R_f = 0.25 (EtOAc); $[\alpha]_D^{20}$ = + 591.0 (c = 0.3, THF); HPLC analysis – Chiracel OD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 12.5 minutes, Minor: 16.0 minutes, 254 nm detection light, *ee* = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) 6.76 – 7.32 (m, 8H), 4.12 (dddd, 1H, *J* = 7.2, 7.2, 7.2, 14.4 Hz), 3.39 (ddd, 1H, *J* = 4.3, 7.5, 11.5 Hz), 3.09 (ddd, 1H, *J* = 7.5, 7.5, 11.1 Hz), 2.63 (dd, 1H, *J* = 16.0, 16.0 Hz), 2.61 (dd, 1H, *J* = 6.6, 16.0 Hz), 2.35 (dddd, 1H, *J* = 4.3, 6.7, 6.7, 6.7 Hz), 1.95 – 2.04 (m, 1H), 1.73 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ™ 189.5, 160.0, 135.3, 134.9, 133.9, 133.3, 131.2, 130.6, 130.3, 128.8, 127.8, 111.4, 57.9, 50.3, 41.7, 32.4, 24.4; IR (NaCl, $CHCl_3$) 1614, 1516, 1440, 1301, 1086 cm^{-1}; HRMS $[C_{20}H_{18}Cl_2NO]_+$ calcd 358.0765. Found 358.0755 (ESI+).



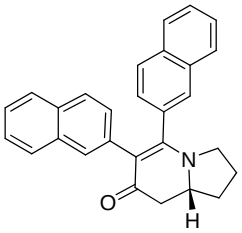
5,6-bis(4-cyanophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (60). The general procedure yielded a orange solid (70% yield) R_f = 0.17 EtOAc $[\alpha]_D^{20}$ = + 403.6 (c = 0.3, THF) HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 34.06 minutes, Minor: 40.91 minutes, 254 nm detection light, *ee* = 62%.^{1}H NMR (400 MHz, $CDCl_3$) 7.66-7.62 (m, 1H), 7.48-7.40 (m, 1H), 7.30 (d, 2H, J = 8 Hz), 7.05-7.02 (m, 1H), 6.96 (d, 2H, J = 8 Hz), 4.17 (dddd, 1H, J = 8, 8, 8, 15.6 Hz), 3.39 (ddd, 1H, J = 4, 7.2, 11.2), 3.09 (ddd, 1H, 7.2, 7.2, 15.2 Hz), 2.70-2.60 (m, 2H), 2.45-2.35 (m, 1H), 2.09-1.76 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) 189.3, 158.9, 141.3, 139.6, 132.7, 132.5, 132.3, 131.4, 130.1, 129.8, 119.3, 117.9, 113.6, 111.3, 109.0, 58.2, 50.3, 41.6, 32.3, 24.5 IR (NaCl, $CHCl_3$) 2969, 2876, 2224, 1628, 1528, 1455,1301, 1127, 731 cm^{-1}; HRMS $[C_{26}H_{18}NO_5]^+$ calcd. 340.1372 Found (340.1375) (ESI+).



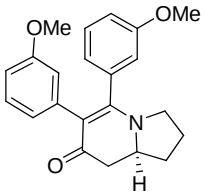
5,6-bis(4-carboethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one.(14) The general procedure yielded a dark yellow solid (92% yield) R_f = 0.21 EtOAc $[\alpha]_D^{20}$ = + 447.6 (c = 0.3, THF) HPLC analysis – Chiracel OD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 34.06 minutes, Minor: 40.91 minutes, 254 nm detection light, *ee* = 93%. ^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (d, 1H, J = 6.8 Hz), 7.72 (d, 1H, J = 7.2 Hz), 7.63 (d, 2 H, J = 8.4 Hz), 7.31 (d, 1H, J = 6.8 Hz), 6.95 (d, 1H, J = 7.2 Hz), 6.91 (d, 1H, 8.4 Hz), 4.26 (q, 2, J = 9 Hz), 4.20 (q, 2H, J = 7.2), 4.11 (m, 1H) 3.33 (ddd, 1H, 4.2 Hz, 7.4 Hz, 11.5 Hz), 3.02 (ddd, 1H, J=7.5 Hz, 7.5 Hz, 11 Hz), 2.59 (m, 2H), 2.30 (ddd, J=6 Hz, 10.8 Hz, 17.3 Hz), 1.96-1.74(m, 3H), 1.28(t, 3H, 7.15), 1.24(t, 3H, 7.15) ^{13}C NMR (100 MHz, $CDCl_3$) 189.4, 170.0, 166.9, 165.9, 160.0, 141.6, 139.8, 131.9, 131.1, 129.9, 129.5, 129.3, 129.1, 128.8, 127.2, 61.5, 60.8, 58.0, 50.2, 42.0, 32.5, 29.9, 24.5,14.5; IR (NaCl, $CHCl_3$) 2977, 2928, 2873, 1712, 1631, 1528, 1273, 1101, 1020 cm^{-1}; HRMS $[C_{26}H_{28}NO_5]^+$ calcd. 433.1889 Found (433.1882) (ESI+).



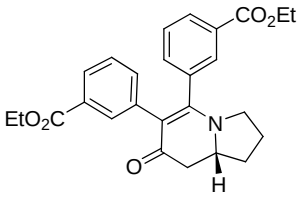
5,6-bis(4-acetylphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (56) The general procedure yielded a light yellow solid (95% yield): R_f = 0.13 (EtOAc); $[\alpha]_D^{20}$ = + 513.9 (c = 1.3, THF); HPLC analysis – Chiracel OD-H column 70:30 hexane:iPrOH, 1.0 ml/min, Major: 17.7 minutes, Minor: 23.3 minutes, 254 nm detection light, *ee* = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (broad d, 1H, *J* = 7.0), 7.67 (broad d, 1H, *J* = 7.2), 7.59 (d, 2H, *J* = 8.3), 7.39 (broad d, 1H, *J* = 6.8), 7.03 (broad d, 1H, *J* = 7.5), 6.98 (d, 2H, *J* = 8.3), 4.17 (dddd, 1H, *J* = 7.0, 7.0, 7.0, 14.1 Hz), 3.40 (ddd, 1H, *J* = 4.3, 7.5, 11.6 Hz), 3.08 (ddd, 1H, *J* = 7.5, 7.5, 11.1 Hz), 2.67 (dd, 1H, *J* = 15.3, 15.3 Hz), 2.61 (dd, 1H, *J* = 6.1, 15.8 Hz), 2.52 (s, 3H), 2.44 (s, 3H), 2.38 (dddd, 1H, *J* = 4.3, 6.6, 6.6, 6.6 Hz), 2.01 (m, 1H), 1.75 – 1.96 (m, 2H); $_{13}$C NMR (100 MHz, $CDCl_3$) ™ 198.3, 197.4, 189.6, 159.9, 142.0, 140.0, 137.5, 134.1, 132.1, 129.6, 129.4, 128.8, 128.3, 127.7, 111.7, 58.1, 50.3, 41.8, 32.4, 26.8, 26.7, 24.5; IR (NaCl, $CHCl_3$) 1680, 1619, 1521, 1429, 1301, 1040 cm^{-1}; HRMS $[C_{24}H_{24}NO_3]^+$ calcd 374.1756. Found 374.1739 (ESI+).



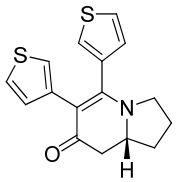
5,6-bis(naphthyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one(61). The general procedure yielded a dark yellow solid (95% yield) R_f = 0.25 $[\alpha]_D^{20}$ = + 428.8 (c = 1.2, THF); HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 15.0 minutes, Minor: 12.8 minutes, 254 nm detection light, *ee* = 91% ^{1}H NMR (400 MHz, $CDCl_3$) 7.8 – 7.0 (m, 14H), 4.25-4.10 (m, 1H), 3.5-3.25 (m, 1H), 3.2-3.0 (m, 1H), 2.76-2.5 (m, 2H), 2.38-2.27 (m, 1H), 1.98-1.6 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 190.2, 161.2, 133.4,131.7, 130.7, 128.8, 128.6, 128.4, 128.2, 127.9, 127.8, 127.4, 127.2, 127.0, 126.9, 126.7, 126.6, 126.4, 125.1, 124.9, 112.5, 58.0, 50.6, 42.1, 32.5, 24.4; IR (NaCl, $CHCl_2$) 3052, 2962, 2925, 2872, 1620, 1520, 1438, 1368, 1300, 1238, 746 cm^{-1}; HRMS $[C_{28}H_{23}NO]^+$ calcd 389.1780. Found 349.1788 (ESI+)



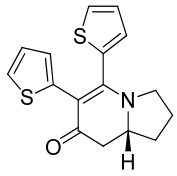
5,6-bis(3-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (57). The general procedure yielded a light yellow solid (93% yield): R_f = 0.21 (EtOAc); $[\alpha]_D^{20}$ = + 396.9 (c = 1.6, THF) HPLC analysis – Chiracel AD-H column 85:15 hexane:iPrOH, 1.0 ml/min, Major: 13.1 minutes, Minor: 14.4 minutes, 254 nm detection light, *ee* = 92% ^{1}H NMR (400 MHz, $CDCl_3$) 6.46 – 7.18 (m, 8H), 4.12 (dddd, 1H, *J* = 6.8, 6.8, 6.8, 13.6 Hz), 3.50 – 3.76 (m, 6H), 3.43 (m, 1H), 3.14 (ddd, 1H, *J* = 7.5, 7.5, 10.9 Hz), 2.65 (dd, 1H, *J* = 15.7, 15.7 Hz), 2.57 (dd, 1H, *J* = 5.3, 15.9 Hz), 2.34 (m, 1H), 1.94 – 2.03 (m, 1H), 1.73 – 1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 189.9, 160.7, 159.4, 158.9, 138.2, 137.1, 129.4, 128.3, 124.8, 121.4, 117.2, 114.6, 111.8, 57.9, 55.4, 55.2, 50.1, 42.1, 32.5, 24.4; IR (NaCl, $CHCl_3$) 1614, 1521, 1460, 1419, 1312, 1045 cm^{-1}; HRMS $[C_{22}H_{23}NO_3]^+$ calcd 349.1678. Found 349.1667 (ESI+) .



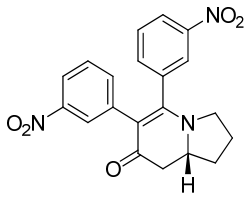
5,6-bis(3-carboethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one(58). The general procedure yielded a dark yellow solid (97% yield) R_f =0.20 EtOAc $[\alpha]_D^{20}$ = + 430.3 (c = 1.2, THF); HPLC analysis – Chiracel OD-H column 70:30 hexane:iPrOH, 1.0 ml/min, Major: 10.9 minutes, Minor: 14.0 minutes, 254 nm detection light, *ee* = 93% ^{1}H NMR (400 MHz, $CDCl_3$) 7.99 – 7.96 (m, 1H), 7.85 (d, 1H, J= 7.2 Hz), 7.65 – 7.63 (m, 1H), 7.60 (d, 1H, J= 7.2 Hz), 7.57-.7.53 (m, 1H), 7.40-7.32 (m, 1H), 7.18-7.05(m, 2H), 4.4-4.1(m, 5H), 3.5-3.25 (m, 1H), 3.2-3.0 (m, 1H), 2.673 (t, J=16, 15 Hz), 2.64-2.5 (m, 1H), 2.45-2.35 (m, 1H), 2.05-1.70 (m, 3H) 1.41-1.2 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) 189.7, 166.9, 160.0, 136.7, 135.7, 133.7, 133.4, 133.1, 130.6, 130.0, 129.7, 128.7, 128.5, 127.6, 126.7, 111.7, 61.5, 60.7, 57.9, 50.1, 41.9, 32.4, 24.4, 14.4; IR (NaCl, $CHCl_3$) 3065, 2978, 2873, 2238, 1715, 1627, 1530, 1455, 1261 cm^{-1}; HRMS $[C_{26}H_{28}NO_5]^+$ calcd. 433.1889 Found (433.1892) (ESI+).



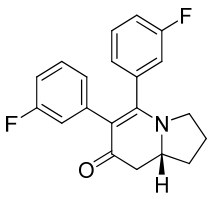
5,6-bis(3-thiophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (64) The general procedure yielded a orange solid (94% yield) R_f = 0.30 EtOAc $[\alpha]_D^{20}$ = + 480 (c = 0.5, THF) HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 16.76 minutes, Minor: 17.93 minutes, 254 nm detection light, *ee* = 86% ^{1}H NMR (400 MHz, $CDCl_3$) 7.19-7.12 (m 2H) 6.97-6.94 (m, 1H), 6.81 (d, 1H, J = 4.8 Hz), 6.77 (m, 1H), 6.63 (d, 1H, J=4.8 Hz), 4.10 (dddd, 1H, J = 6.8, 6.8, 6.8, 13.6), 3.55 (ddd, 1H, J = 7.2,7.2,12), 3.22 (ddd, 1H, *J* = 7.2, 7.2, 11.2 Hz), 2.67-2.54 (m, 2H), 2.36-2.28 (m, 1H), 2.04-1.71 (m, 3H) ^{13}C NMR (100 MHz), $CDCl_3$ 189.2, 156.5 136.3 136.1 130.2 128.2, 127.1, 125.9, 123.1, 122.9, 107.46, 57.4, 50.5, 41.7, 32.0, 24.1 IR (NaCl, $CHCl_3$) 3093, 3964, 2877,1614, 1538, 1504, 1454,1408, 1285, 770 cm^{-1}; HRMS $[C_{16}H_{16}NOS_2]^+$ calcd. 302.0595 Found (302.0598) (ESI+).



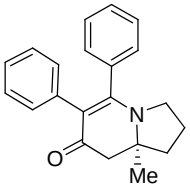
5,6-bis(2-thiophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (63) The general procedure yielded a orange solid (91% yield) R_f = 0.30 EtOAc $[\alpha]_D^{20}$ = + 180 (c = 0.8, THF) HPLC analysis – Chiracel AS-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 20.06 minutes, Minor: 24.84 minutes, 254 nm detection light, *ee* = 19% ^{1}H NMR (400 MHz, $CDCl_3$) 7.55 (d, 1H, J = 5.2) 7.04 (d, 1H, J = 4.8 Hz), 6.99 (d, 1H, J = 3.2 Hz), 6.93 (t, 1H, J = 4 Hz), 6.73 (t, 1H, J=4 Hz), 6.49 (d, 1H, J = 3.2 Hz), 4.14 (dddd, 1H, J = 6.4, 6.4, 6.4, 12.8), 3.70-3.65 (m, 1H), 3.31-3.28 (m, 1H), 2.69-2.55 (m, 2H), 2.34 (dddd, 1H, J= 6.8, 6.8, 6.8, 12.8), 2.05-1.75 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$ 189.1, 154.2, 138.2, 136.2, 130.3, 128.8, 127.1, 127.0, 125.8, 124.3, 113.6, 106.8, 57.3, 50.9, 41.9, 31.9, 24.5 IR (NaCl, $CHCl_3$) 3097, 2978, 2933, 2879, 1614, 1531, 1495, 1286 cm^{-1}; HRMS $[C_{16}H_{16}NOS_2]^+$ calcd. 302.0595 Found (302.0594) (ESI+).



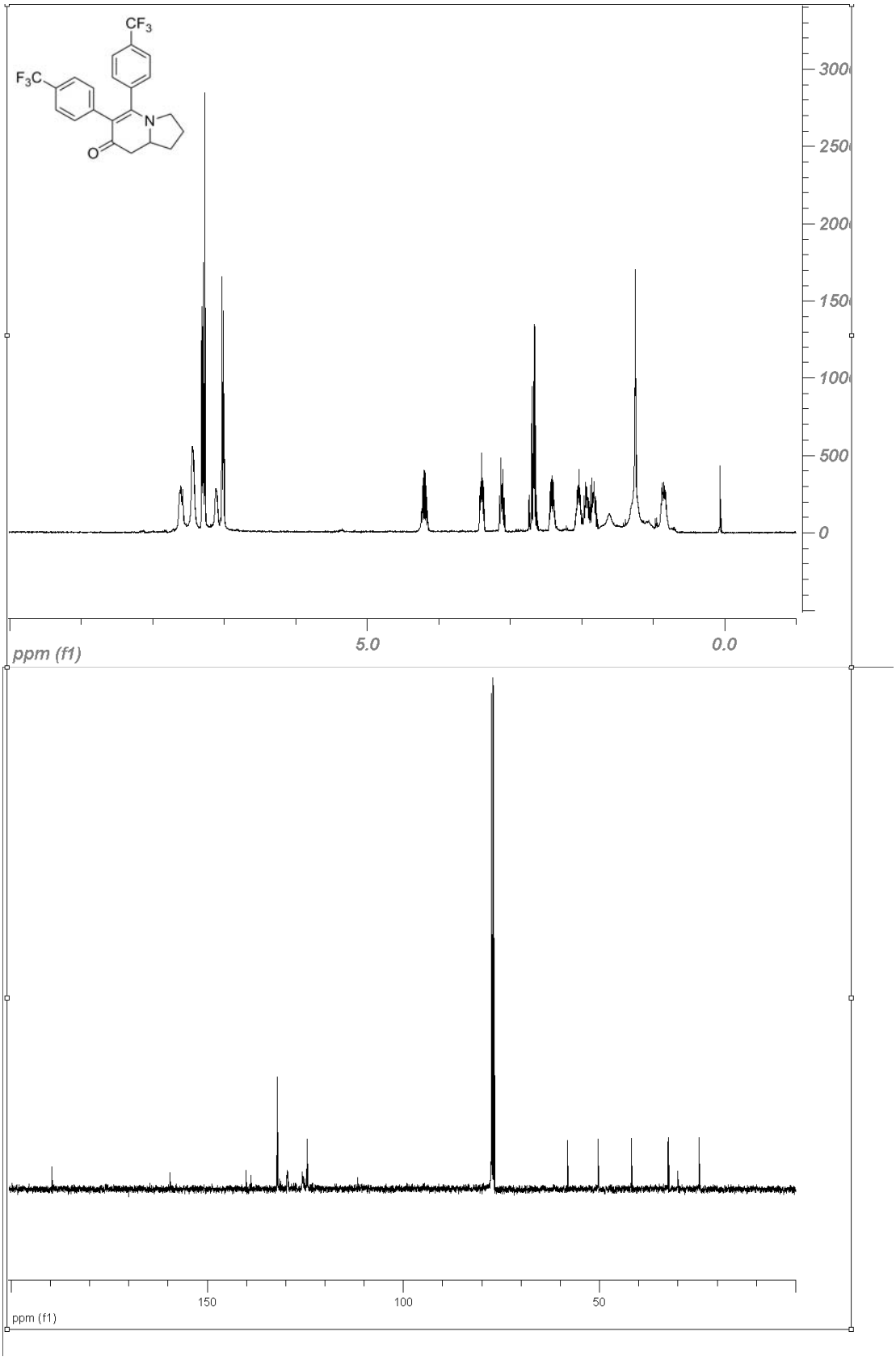
5,6-bis(3-nitrophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (63) The general procedure yielded a orange solid (70% yield) R_f = 0.20 EtOAc $[\alpha]_D^{20}$ = HPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 18.6 minutes, Minor: 20.3 minutes, 254 nm detection light, *ee* = 90% ^{1}H NMR (400 MHz, $CDCl_3$) 8.22-7.20 (m, 8H) 4.21 (m, 1H), 3.47-3.36 (m, 1H), 3.17-3.12 (m, 1H), 2.74-2.59 (m, 2H), 2.44-2.42 (m, 1H) 1.97-1.79 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) 189.3, 158.3, 148.3, 136.6, 135.0, 132.2, 130.1, 128.6, 128.5, 126.9, 124.4, 124.0, 120.8, 120.7,111.1, 58.3, 50.3, 41.6, 32.4, 24.4, IR (NaCl, $CHCl_3$) 3081, 2963, 2925, 2873, 1628, 1578, 1532, 1451, 1348, 1310, 911 HRMS $[C_{20}H_{18}N3O5]^+$ calcd. 379.1168 Found (379.1170) (ESI+)



5,6-bis(3-fluorophenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (65) The general procedure yielded a yellow solid (80% yield) R_f = 0.30 EtOAcHPLC analysis – Chiracel AD-H column 80:20 hexane:iPrOH, 1.0 ml/min, Major: 7.56 minutes, Minor: 9.06 minutes, 254 nm detection light, *ee* = 93% ^{1}H NMR (400 MHz, $CDCl_3$) 7.25-6.80 (m, 6H) 6.82 (t, 1H, J = 6 Hz), 6.70 (t, 1H, J = 8.8 Hz), 4.10 (dddd, 1H, J = 6.8, 6.8, 6.8, 14), 3.38 (ddd, 1H, J = 4.4, 4.4, 7.6), 3.12 (ddd, 1H, *J* = 7.6, 7.6, 10.8 Hz), 2.67-2.53 (m, 2H), 2.38-2.30 (m, 1H), 2.03-1.72 (m, 3H) ^{13}C NMR (100 MHz), $CDCl_3$ 189.9, 164.0, 162.0, 161.5, 160.0, 159.6,133.6, 133.5, 132.4, 131.7, 131.3, 115.7, 114.5, 111.6, 57.7,50.1, 41.9, 32.4, 24.4IR (NaCl, $CHCl_3$) 2971,2876, 1629, 1529, 1449, 1306, 1220 cm^{-1}; HRMS $[C_{16}H_{16}NOF_2]^+$ calcd. 302.0595 Found (302.0594) (ESI+).



5,6-diphenyl-8a-methyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (53). The procedure for competition between isocyanates yielded a yellow solid (49% yield) R_f = 0.60 EtOAc HPLC analysis – Chiracel AD-H column 90:10 hexane:iPrOH, 1.0 ml/min, Major: 13.8 minutes, Minor: 13.2 minutes, 254 nm detection light, *ee* = 98% ^{1}H NMR (400 MHz, $CDCl_3$) 7.3-6.8 (m, 10H) 3.45 (m, 1H), 3.07 (m, 1H), 2.87 (d, 1H *J* = 9 Hz), 2.49 (d, 1H *J* = 9Hz), 2.1-1.85 (m, 4H), 1.47 (s, 3H) ^{13}C NMR (100 MHz), $CDCl_3$ 189.7, 159.6,136.7, 132.1, 131.9, 129.4, 129.2, 129.0, 128.2, 128.0, 127.4, 125.2, 111.6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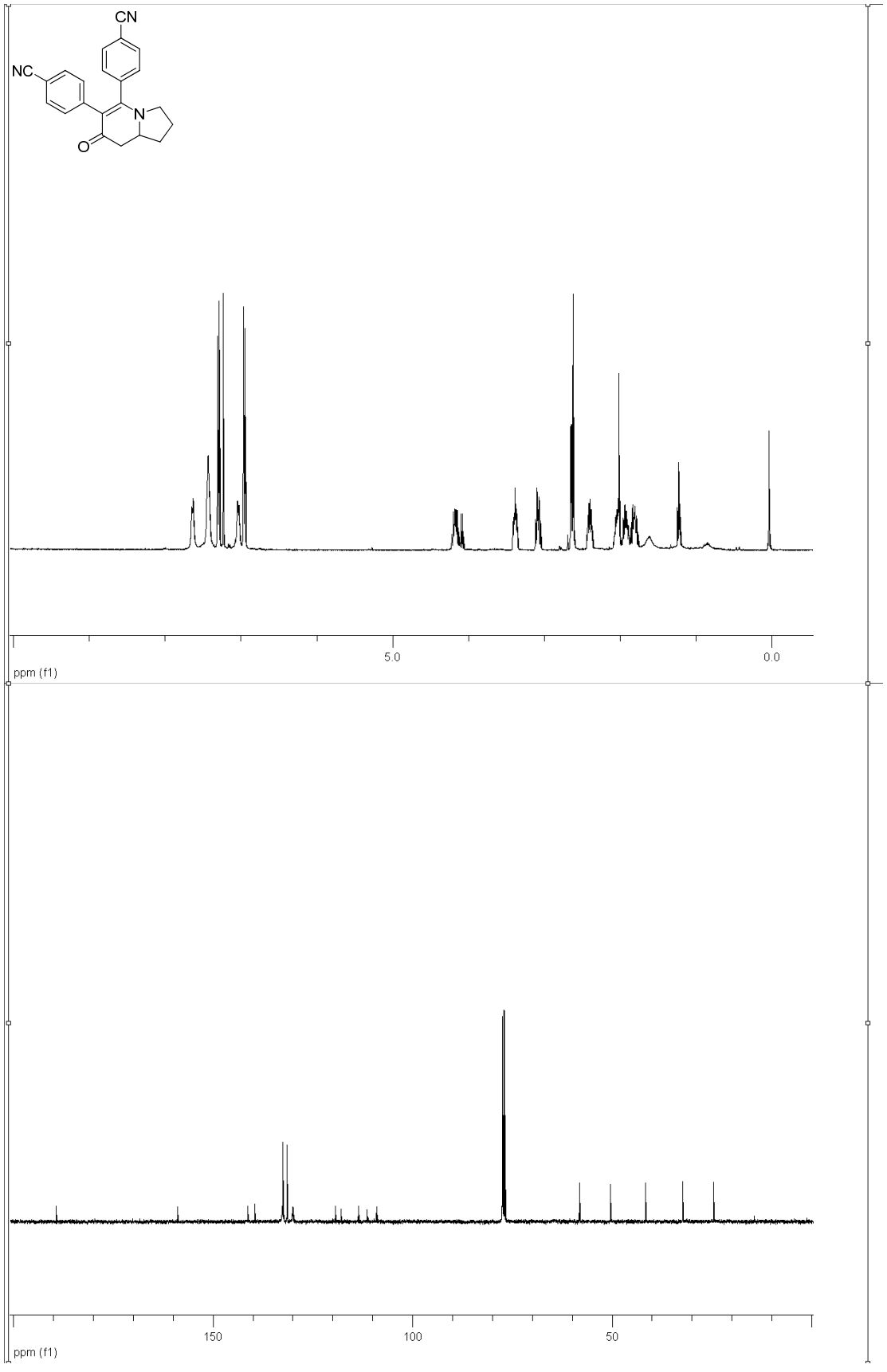
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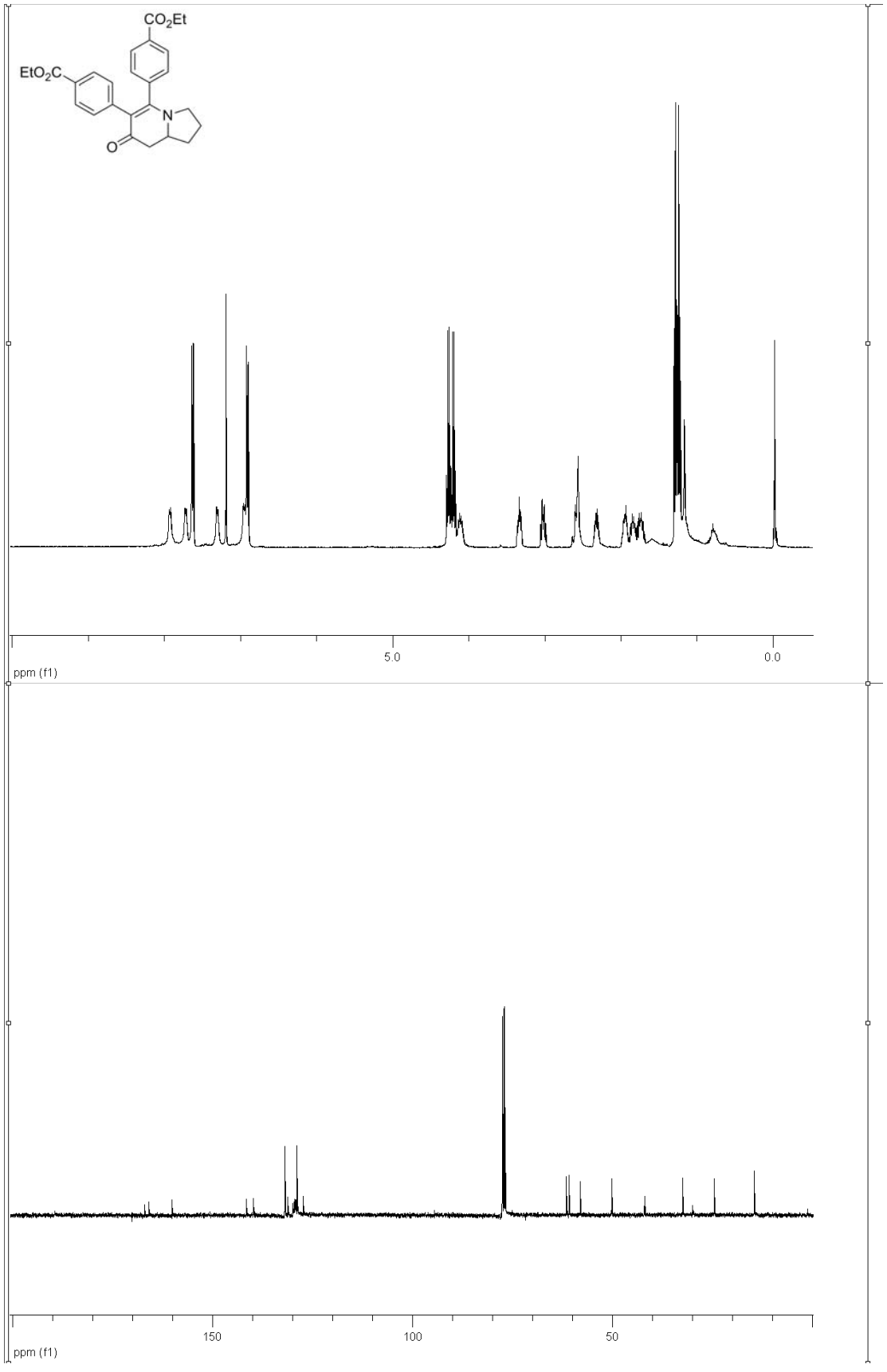
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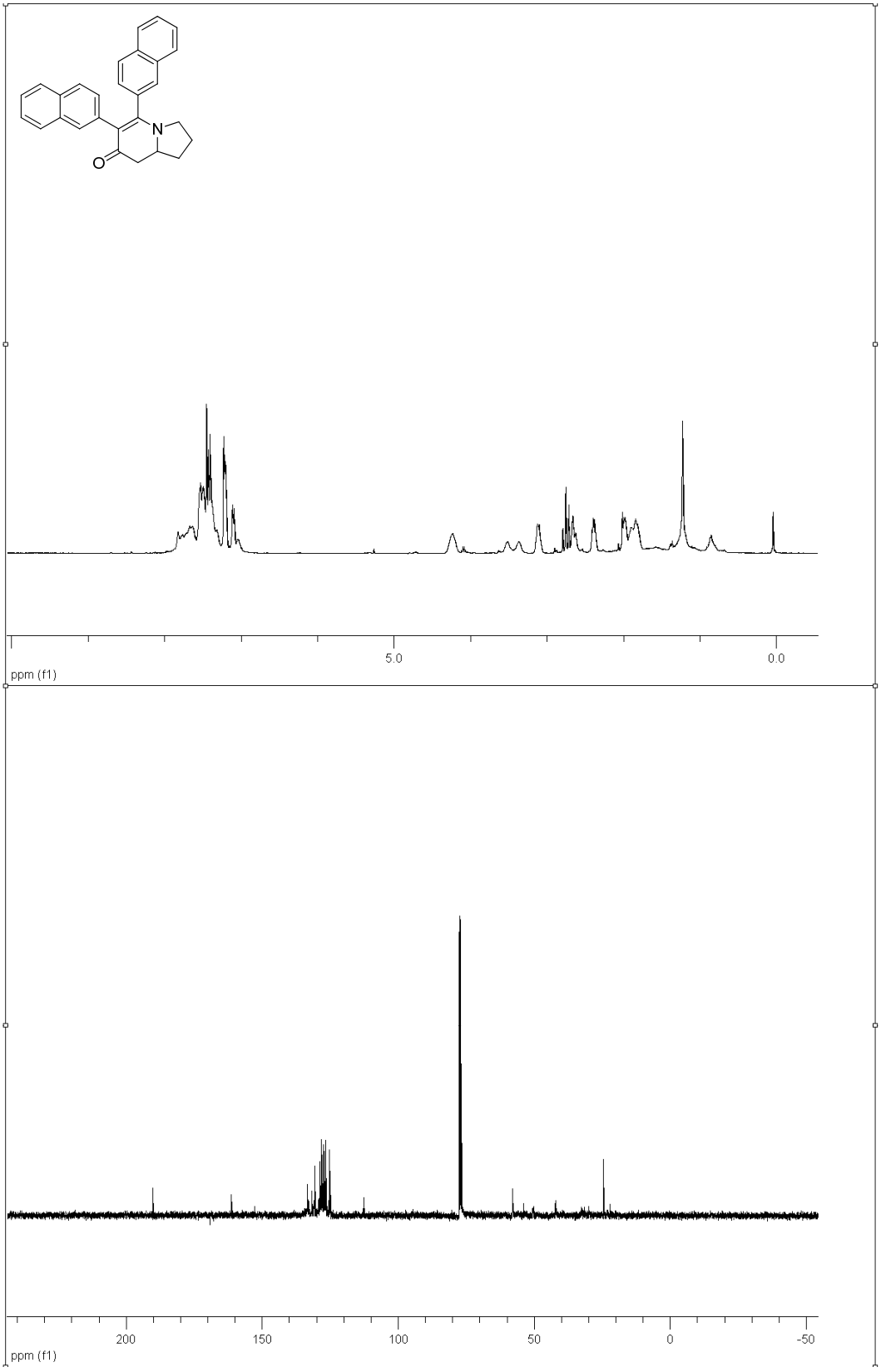
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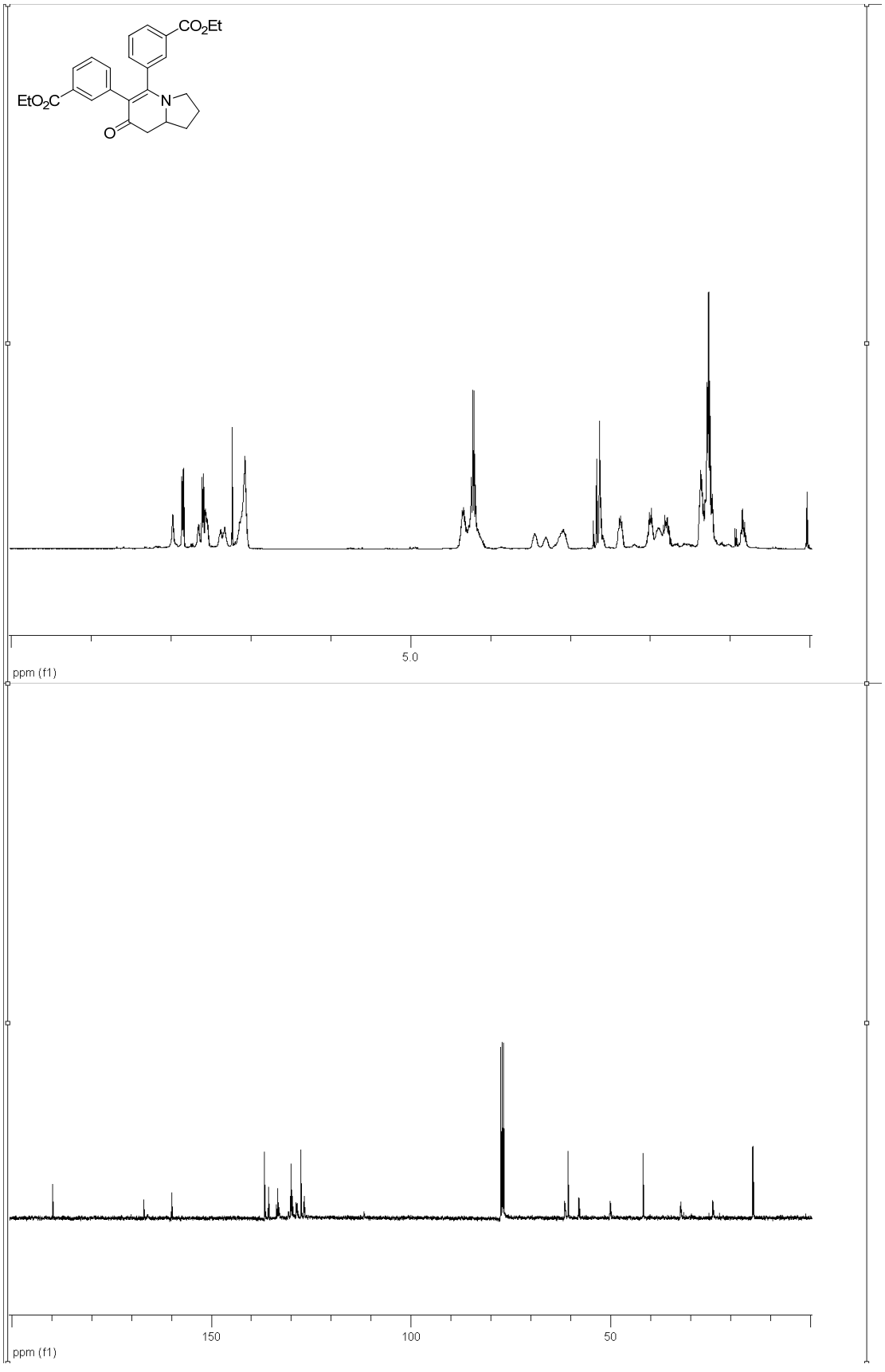
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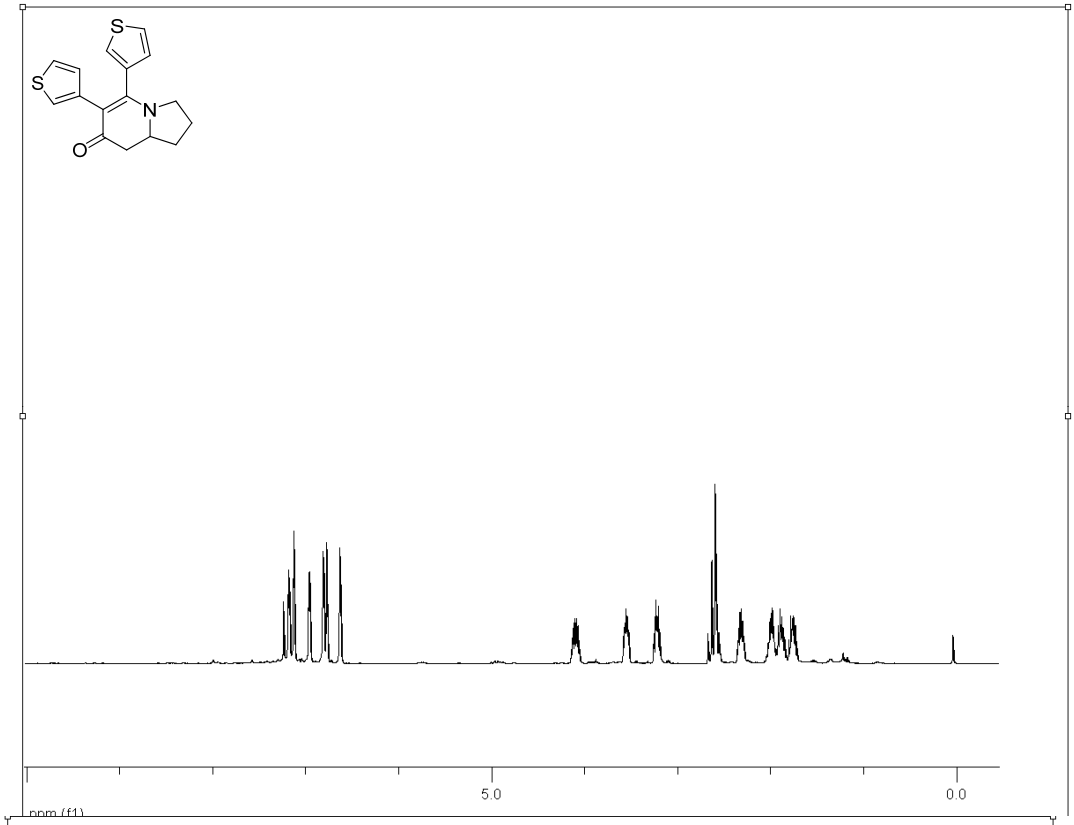
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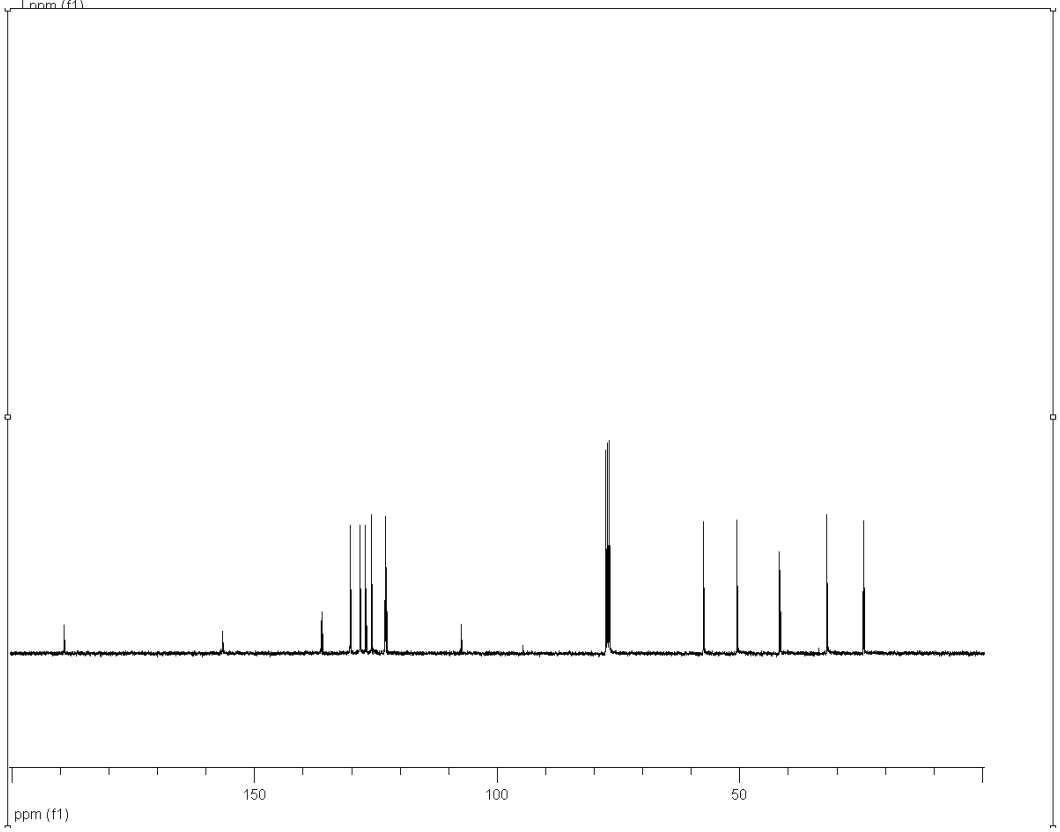
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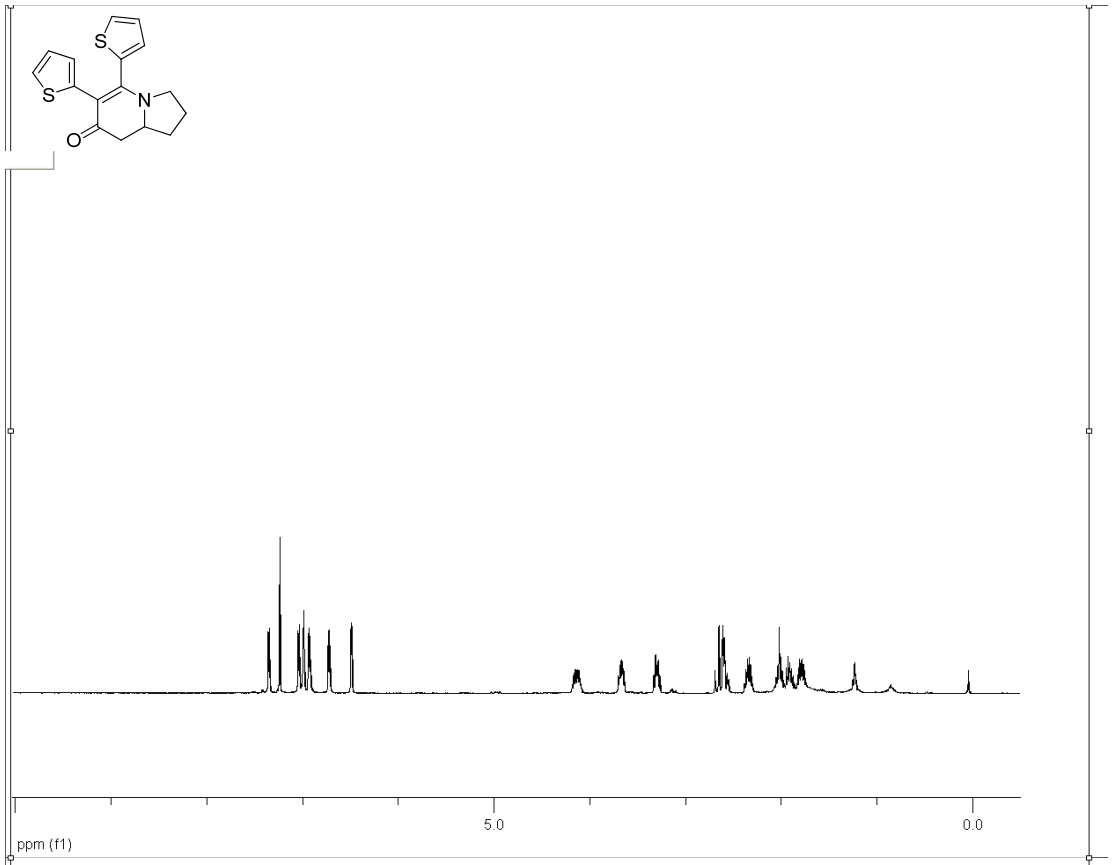
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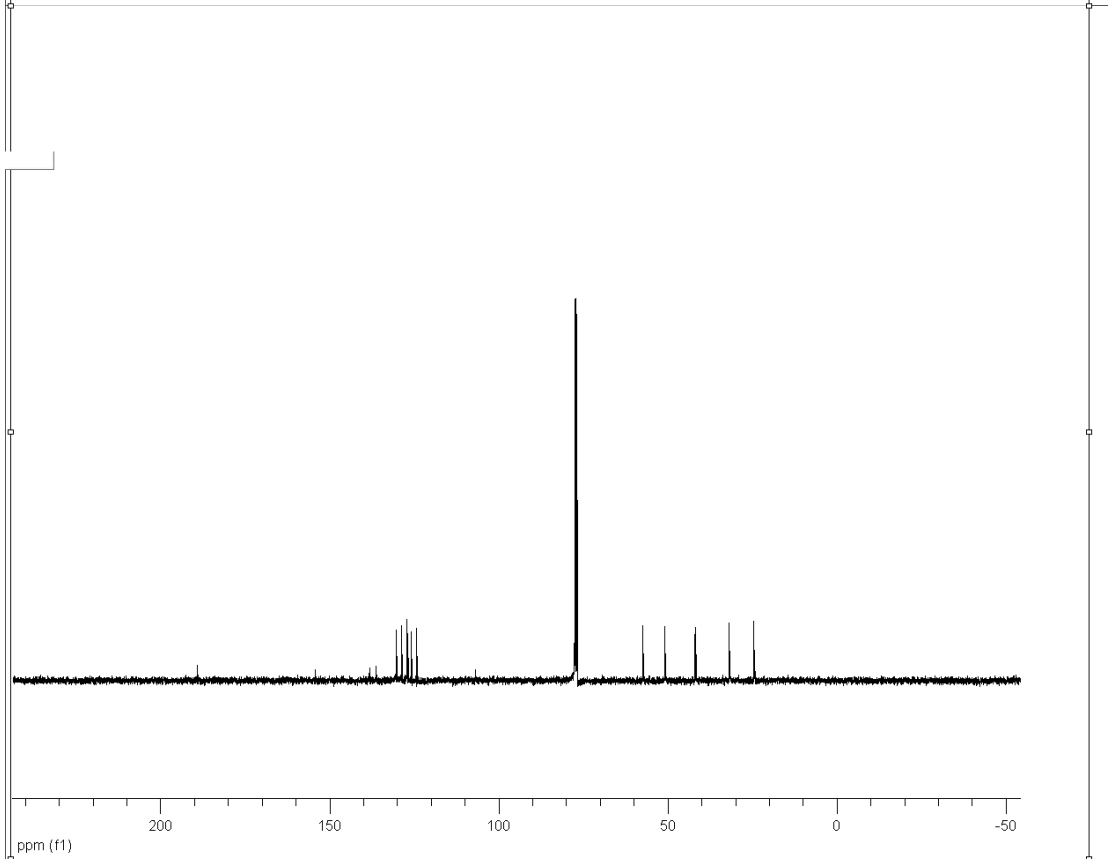
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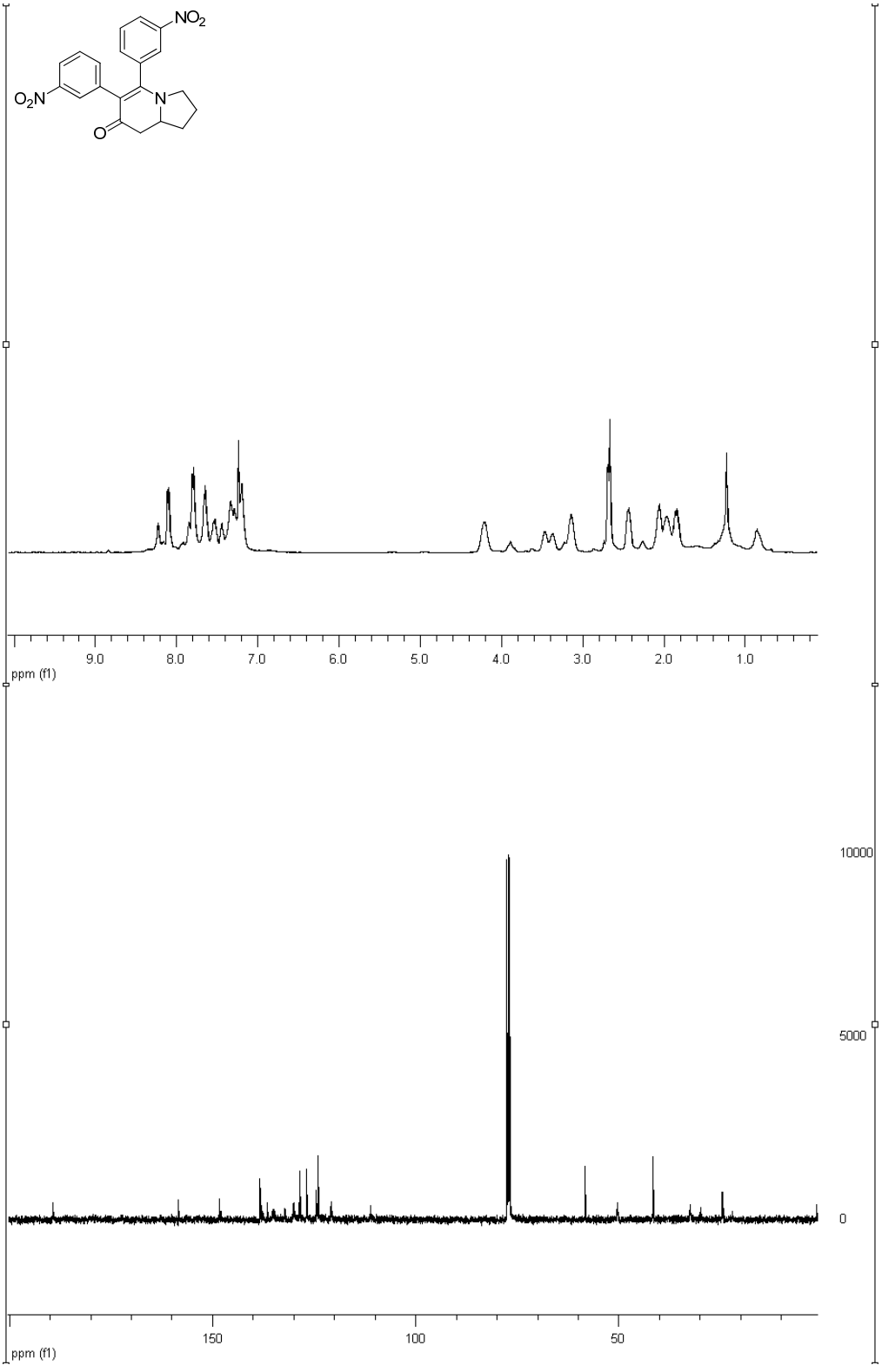
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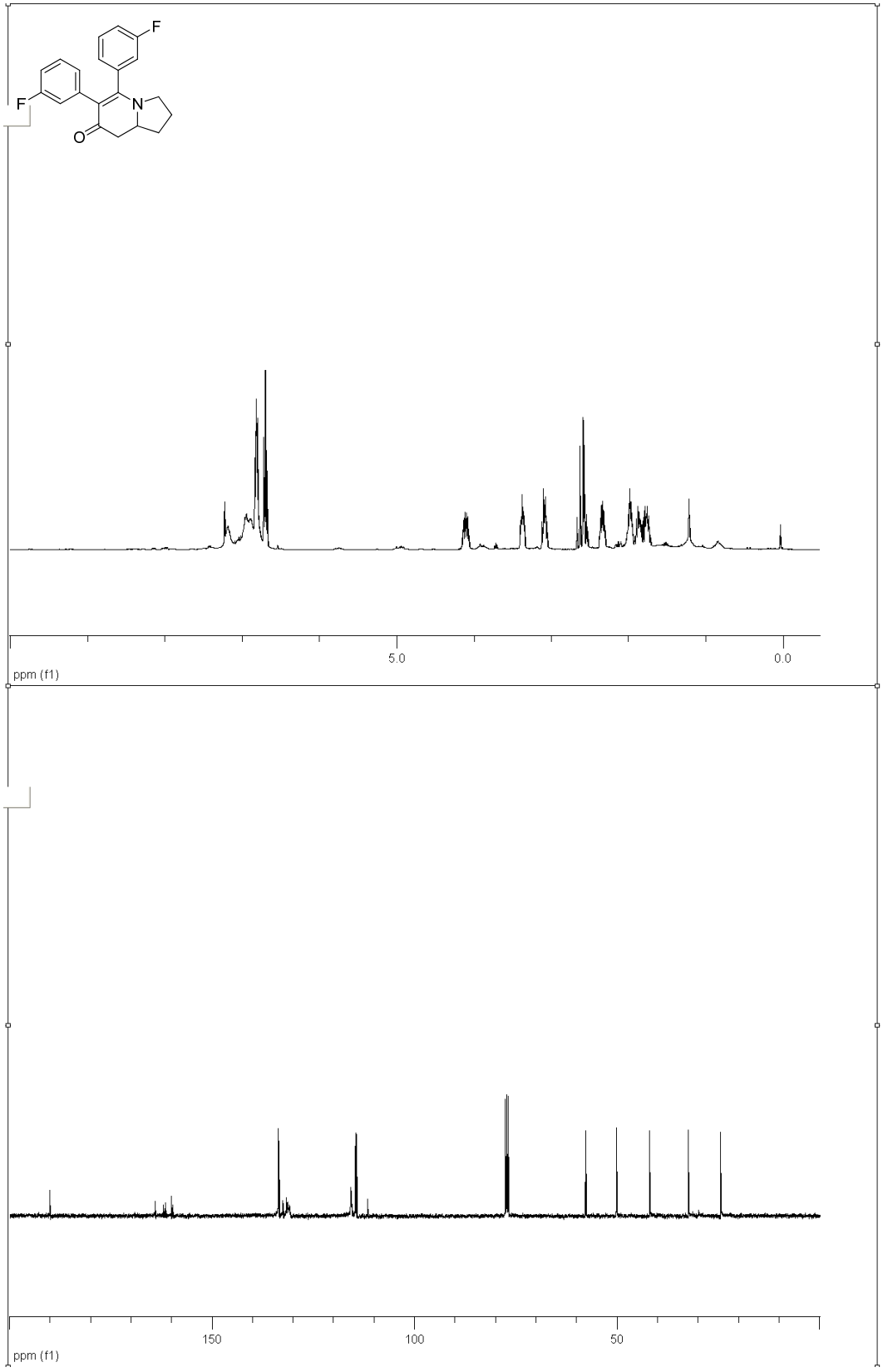
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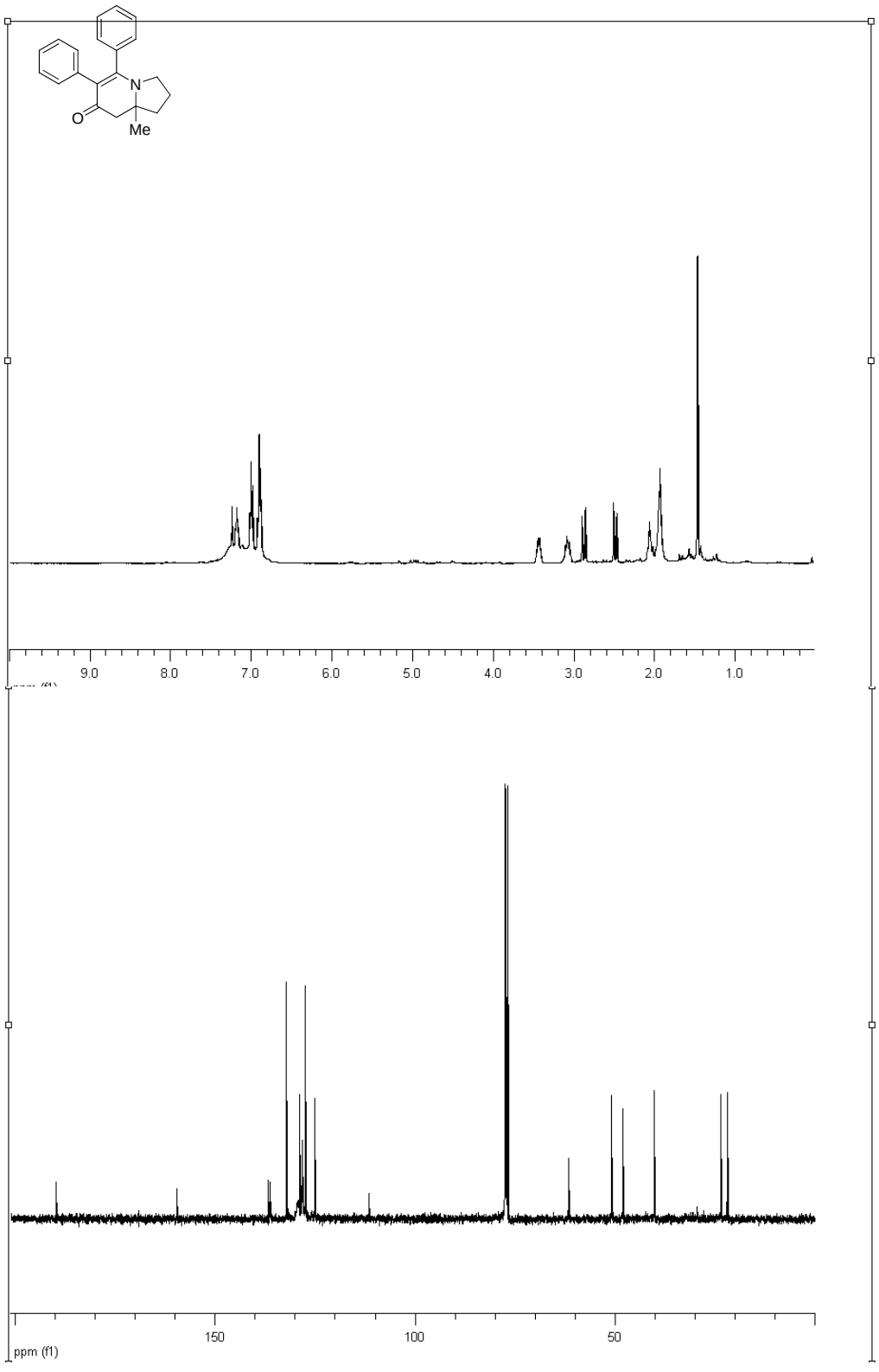
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[1] W. S. Knowles, M. J. Sabacky *Chem. Commun.* **1968**, 1445
[2] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem Soc*. **1975**, 2567
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[11] A search of the Cambridge Crystallographic Database revealed 738 six-coordinate monomeric rhodium (III) complexes but only 106 five-coordinate and three four-coordinate complexes.
[12]This is based on the equilibrium constants for coordination of the two types of olefins to rhodium. Schurig, V. *Inorg. Chem.* **1986**, 25, 945
[13] No change in this complex was observed upon addition of isocyanate **15** at room temperature.
[14] Upon addition of **15** no complexes of the type **VII** were observed.
[15] Urea **52** is normally recovered in the case of slower reaction or no reaction and indicates an inefficient catalyst turnover.
[16] It should be noted that the reaction run in the presence of pyridine type additives but without phosphoramidite ligand yields no product.
[17] Numbers in Parantheses indicate the % ee which was observed in the absence of any additive.
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Chapter 3

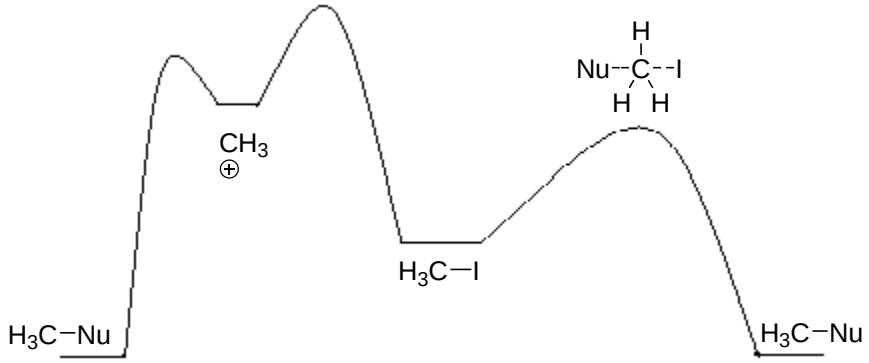
The Expansion of the Scope of the Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates.

3.1 Introduction

As chemists, nature can be our most formidable foe or our closest companion. On a daily basis we strive to understand how it works and to use that understanding to our advantage. As organic chemists we focus on tackling synthetic challenges. Predominantly this involves observing modes of reactivity and applying these paradigms to different systems to obtain new reactivity. For some the boundaries of envisioned reactivity can be boundless, constrained only to the edge of the paper. Ultimately it is our ambition to take these ideas from the two dimensional graphite concoctions to three dimensional liquid suspensions that drives us to innovation. This primordial understanding suggests a world of infinite possibilities, but in this world of infinite possibilities, there is one certainty, we can't change the course of nature, but only fit our will to accept what nature will give us.

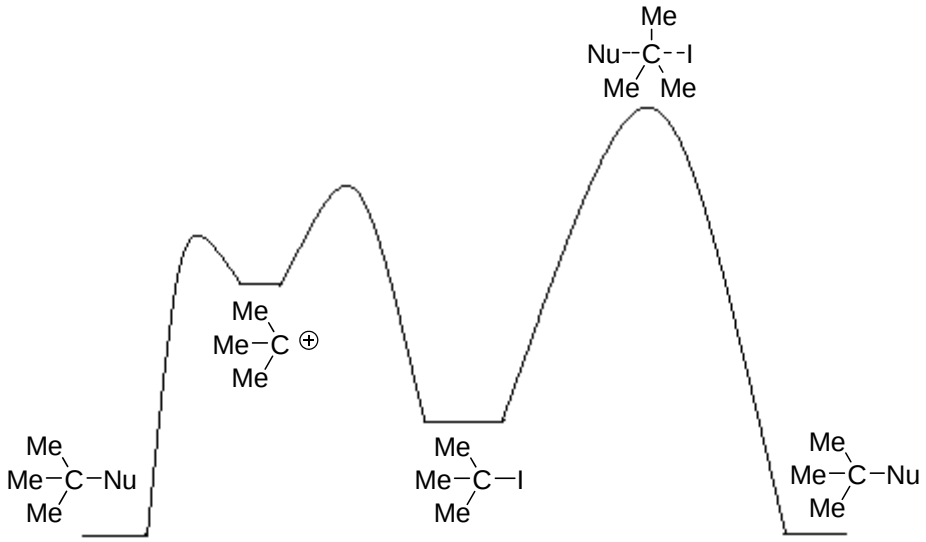
The way that nature makes choices is taught to us from the beginning when we learn the story of the substitution reaction. The substitution reaction can occur through two pathways with either unimolecular or bimolecular rate determining step. When our electrophile is methyl iodide we know that it will go through a bimolecular pathway (Fig. 1).

Figure 1



It is our nature to change the fate of things. Of course as scientists we know that we must sometimes be observers, not actors. By manipulating the choice that we give nature we can allow it to take a different path. In the substitution reaction, by increasing the size of the electrophile (t-butyl iodide instead of methyl iodide) the bimolecular pathyway requires greater energy than the unimolecular pathway (Fig. 2).

Figure 2

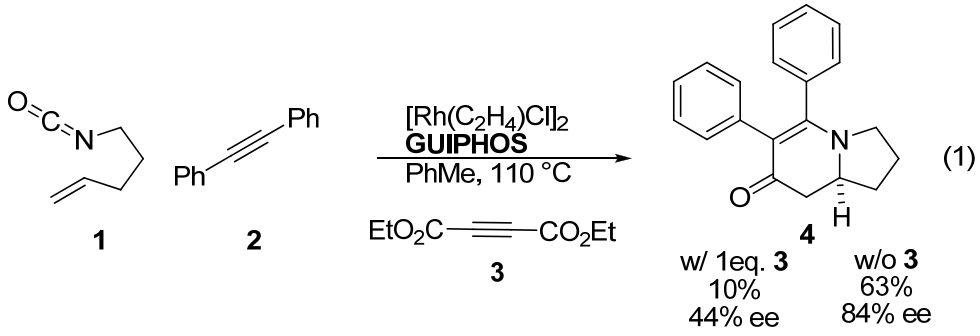


Nature's preference for the lower energy pathway remains the same; we have just changed the outcome by changing the choice. Though in theory this approach is simple, in practice finding a solution to a problem can become complex.

In the following chapter two synthetic challenges were overcome by changing conditions such that nature had to make a different choice. In each case we presented the problem such that nature would chose to follow the desired reaction pathway. In this way we have been able to expand the substrate scope of the rhodium catalyzed [2+2+2] cycloaddition with alkenyl isocyanates to include acetylene dicarboxylates as an alkyne component and 1,2 disubstituted olefins on the alkenyl isocyanate.

3.2 The Case of Acetylene Dicarboxylates.

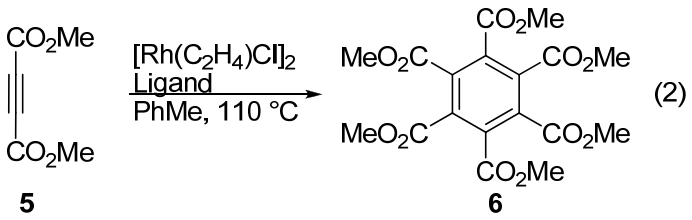
The use of acetylene dicarboxylates, like **3**, as an alkyne component was attractive as the incorporation of this type of alkyne yields a highly functionalized cycloadduct. Furthermore such an electron deficient alkyne presented a synthetic challenge. Previously it was reported the reaction of diphenyl acetylene **2** in the presence of diethyl acetylene dicarboxylate **3** had shown that the acetylene dicarboxylate had participated in the reaction by affecting the enantioseleectivity (Eq.1). Although very low yield of the desired cycloadduct **4** was obtained in the presence of **3**, no cycloadduct from alkyne **3** was isolated.



(1)

Under my supervision an undergraduate researcher, Sarah Collins, had occasion to examine the reaction with acetylene dicarboxylates. Alkyne **3** was coordinating to rhodium and affected the course of the reaction by altering the ee. Others had reported, and I had also observed, that under our standard reaction conditions no cycloadduct was obtained from **3**. It was known in the literature that [2+2+2] cycloadditions with terminal alkynes and acetylene dicarboxylates using a rhodium catalyst were possible.[1] A cursory search of the literature also revealed that acetylene dicarboxylates were known to

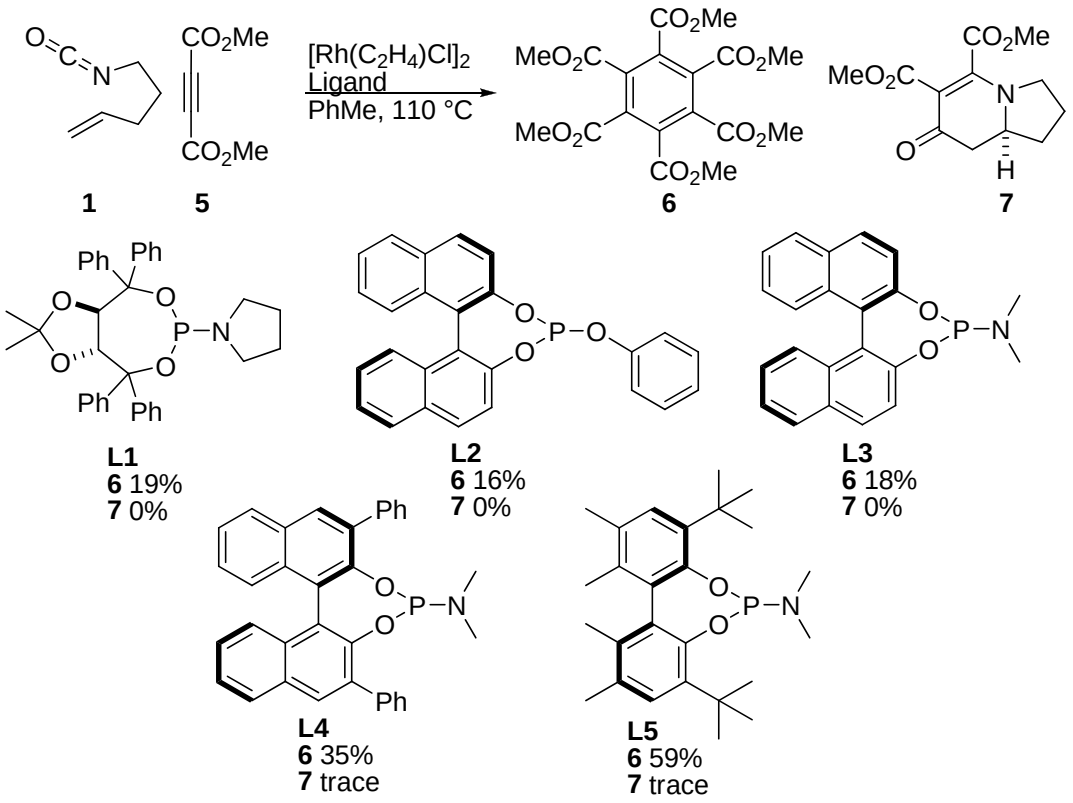
undergo a [2+2+2] cycloaddition to provide a trimer **6** in the presence of a metal catalyst (Eq. 2).[2]



5 **6** (2)

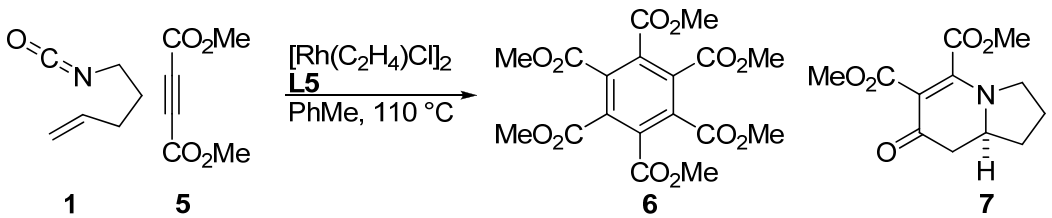
Product **6** was deceptively simple; by ^{1}H NMR and TLC it looks identical to starting material. Using melting points and also by ^{13}C NMR we were able to distinguish the trimer **6** from alkyne **5**. Being able to distinguish the trimer **6** the reaction with alkenyl isocyanate **1** dimethyl acetylene dicarboxylate (DMAD) **5** using our standard reaction conditions was investigated (Table 1).[3]

Table 1



Predominately the trimer **6** was isolated; however using ligands **L4** and **L5** a small amount of the desired adduct **7** was isolated. The appearance of a large amount of trimer in the reaction with **L5** suggested that that **L5** was the optimum ligand for cycloaddition with this substrate. Investigations were carried out to see if formation of the trimer could be decreased while increasing the formation of desired cycloadduct (Table 2).

Table 2.



1 **5** **6** **7**

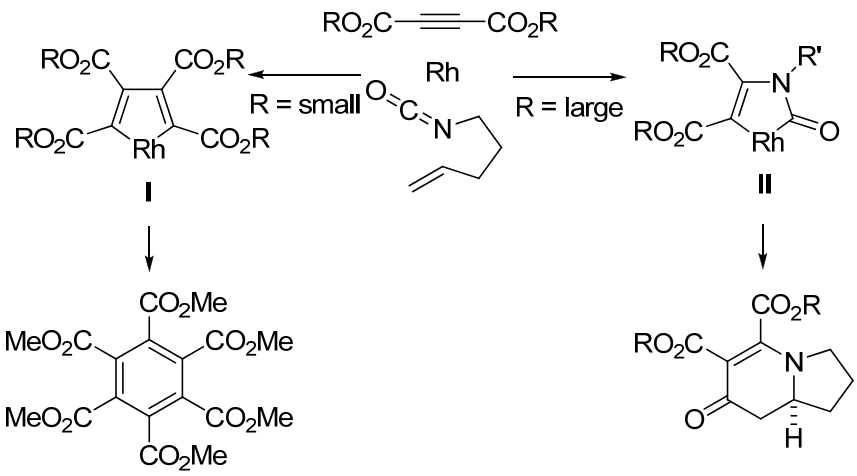
Entry	Isocyanate (eq.)	Yield (%)	Yield (%)
1	2	44	12
2	3	41	13
3[a]	3	17	14
4[b]	3	9	14

[a] slow addition of **5**. [b] $[Ir(cod)Cl]_2$ was used instead of rhodium dimer

By increasing the amount of isocyanate **1** there was an increase the amount of desired cycloadduct **7** which was formed (entries 1, 2). DMAD **5** was added via slow addition which decreased the amount of trimer **6** but did not increase the amount of cycloadduct **7**. In entry 4 it was thought that the use of a less reactive pre-catalyst $[Ir(cod)Cl]_2$ might increase the yield of the desired cycloadduct.

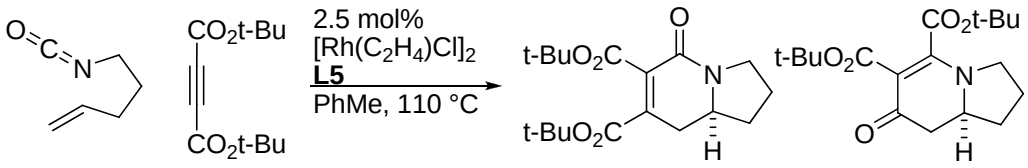
Trimer formation could be discouraged by utilizing a sterically bulky group on the acetylene dicarboxylate. This should disfavor oxidative cyclization between two alkynes which ultimately leads to trimer **6** and should favor the oxidative cyclization between isocyanate and alkyne which leads to product **7** (Fig. 3).

Figure 3



This hypothesis was also encouraged by our models for product selectivity (ch. 1) which suggested the catalyst was sensitive to the sterics of the substrate. To test this hypothesis an alkyne with much bulkier substituents, di-tert-butyl acetylene dicarboxylate (DTAD) was used in the reaction (Table 3).

Table 3

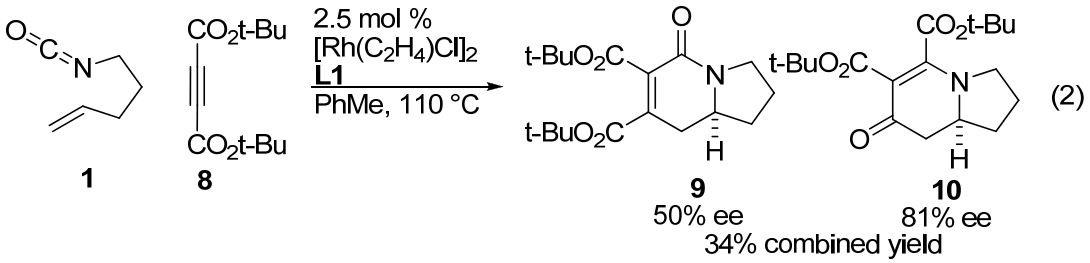


1 **8** **9** **10**

Entry	Isocyanate (eq.)	Alkyne (eq.)	Combined Yield (%)
1	2	1	29
2	3	1	43
3	1	3	21[a]
4	3	1	56[b]

[a]13% of trimer was also isolated. [b] 5 mol% of catalyst was used

Indeed with the larger alkyne a decrease in trimer formation as well as an increase in the formation of cycloadducts **9** and **10**. The cycloadducts were obtained as a mixture of **9** and **10** in approximately a 1:2 ratio. Increasing the equivalents of alkyne **8** lead to a small amount of trimer formation (entry 3). Increased catalyst loading increased the combined product yield to 56% (entry 4). The one drawback to this approach was that the two cycloadducts **9** and **10** became inseperable. Ligand **L1** at the same time provided the two products in low yield and good enantioselectivity (eq. 2).



(2)

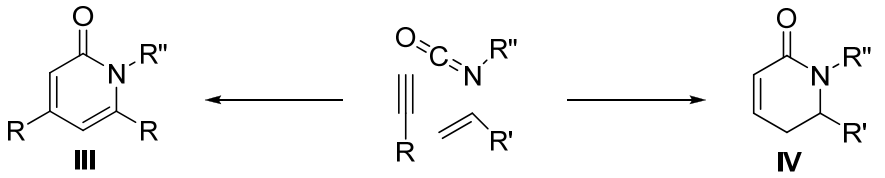
Through careful isolation and characterization an undesired byproduct, the alkyne trimer, was isolated and identified. Substrate design decreased the formation of alkyne trimer which caused a concomitant increase in formation of the desired cycloadducts. We have shown that acetylene dicarboxylates can be used as the alkyne coupling partner to afford a densely functionalized indolizidine core. Work to derivatize and utilize these cycloadducts is ongoing.

Section 3.3 Exploiting the Additive Effect to Shut Down Pyridone Formation

The formation of pyridones using 2+2+2 cycloadditions with transition metal catalysts has been well explored (Ch. 1.1). Our group was able to expand the area of transition metal catalyzed [2+2+2] cycloadditions by utilizing olefins as a coupling partner to form

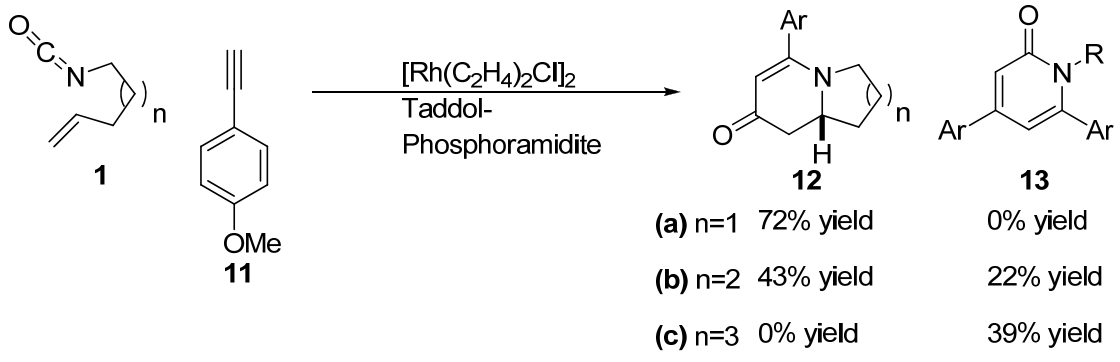
dihydropyridone products **IV** in preference to pyridone **III** in the presence of alkynes (Fig. 4).

Figure 4



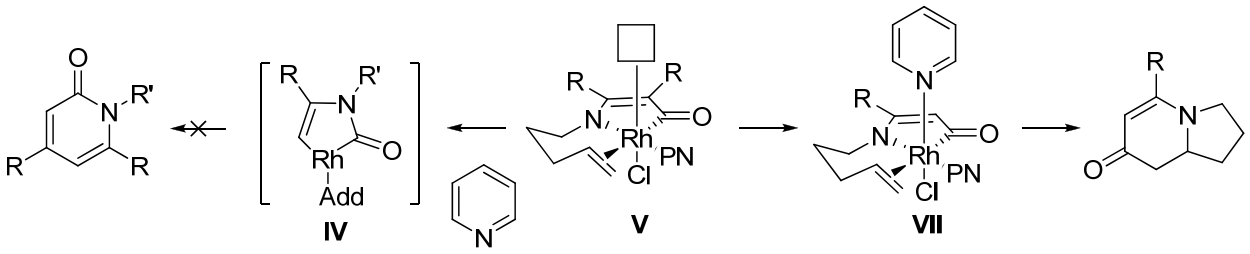
Tethering the alkene to the isocyanate proved a successful strategy in promoting the formation of products like **IV** while avoiding pyridone products **III**. Yet today the intermolecular cycloaddition between isocyanate, alkyne and alkene still remains elusive. In systems where the olefin insertion became less favorable pyridone products were formed instead of the desired cycloadduct. For example as the tether length was increased in the cycloaddition with terminal aryl isocyanates the yield of desired cycloadduct product decreased along with an increase in formation of pyridone (Fig 5).[4]

Figure 5



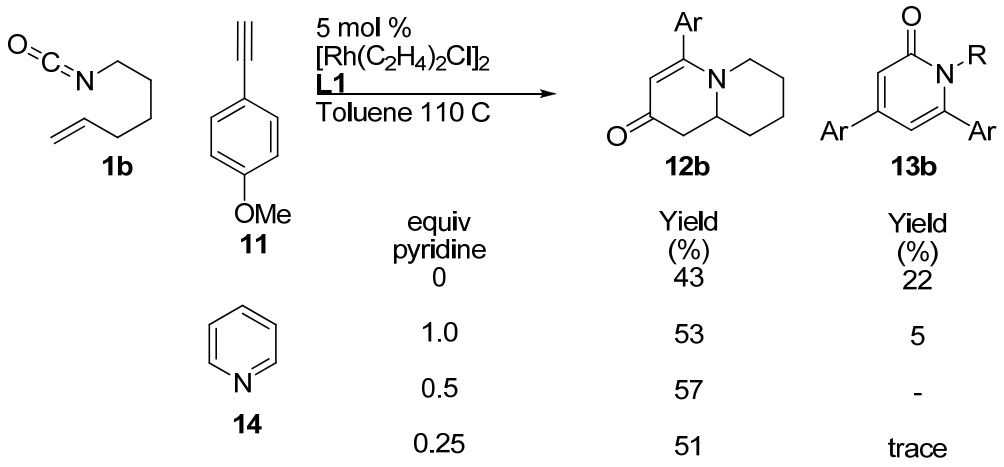
Pyridone arises from competitive insertion of a second alkyne into a metallacycle formed from isocyanate and alkyne like **VI**. Using an additive we were able to intercept a 6-coordinate rhodium intermediate like **VII** (Fig. 6).

Figure 6



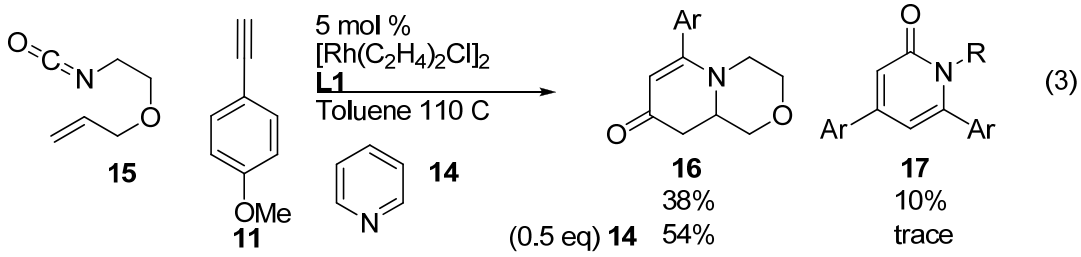
If the additive was present in solution perhaps it would compete with alkyne for this open coordination site to yield complexes like **VII** instead of **VI**. If the additive, instead of the alkyne, was bound at this stage this should slow the formation of pyridone in favor of the desired cycloadduct.The reaction of hexenyl isocyanate with p-methoxy phenyl acetylene was chosen as a test system because we were able to isolate pyridone under these conditions (Table 3). Terminal acetylenes were chosen because internal acetylenes did not show pyridone formation. As well pyridine **14** was chosen as an additive because it did not appear to inhibit this system.

Table 3



equiv pyridine	Yield (%) 12b	Yield (%) 13b
0	43	22
1.0	53	5
0.5	57	-
0.25	51	trace

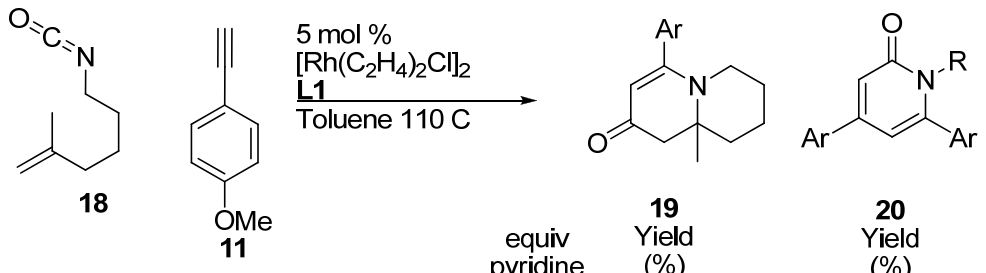
These experiments show a slight increase in the yield of the desired cycloadduct **12b** with a decrease in the amount of pyridone **13b** formed. Using 0.5 equivalents of **14** lead to the highest yields. A second substrate was tested to see the affect of pyridine **14** on the reaction (eq. 3).



With isocyanate **15** an increase in yield in the presence of pyridine was observed. 0.5 equivalents gave a small increase but the additive did not dramatically change the yield.

Next isocyanate **18** was chosen because it consistently gave low yields of vinylogous amide product **19** and higher yields of pyridone **20**. When this isocyanate was used in conjunction with pyridine inconclusive results were obtained (Table 4).

Table 4

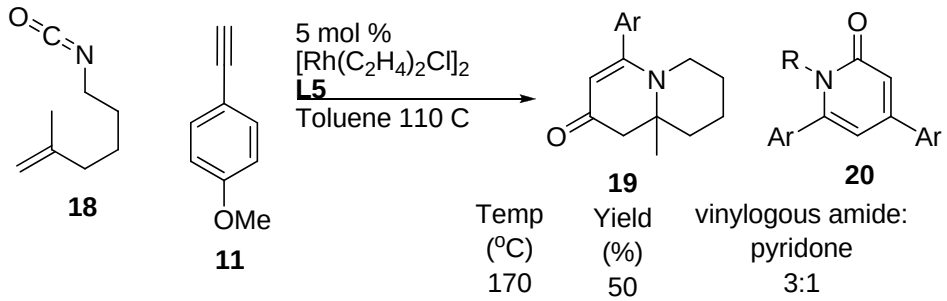


equiv pyridine	**19** Yield (%)	**20** Yield (%)
0	31	26
1.0	23	20
0.5	25	17
0.25	33	30

The dramatic increase in isolated yield that we had hoped for had not been obtained, and furthermore yields of both cycloadduct and pyridone were very inconsistent in this system. Given these inconsistencies in yields it was difficult to say whether the additive was having the desired effect. Since yields were not reproducible and the increase in efficiency of the reaction was not substantial, these experiments did not justify the continued use of an exogenous additive for the reduction of pyridone.

During these investigations it was discovered how pyridone could be reduced by manipulating reactions conditions. By inreasing temperature, decreasing the concentration of alkyne **11** or by using slow addition the yield of **19** increased while decreasing the amount of pyridone **20** (Table. 5).

Table 5



Temp (°C)	Yield (%)	vinylogous amide: pyridone
170	50	3:1
150	36	3:1
110	30[a]	2:1
110	42[b]	4:1

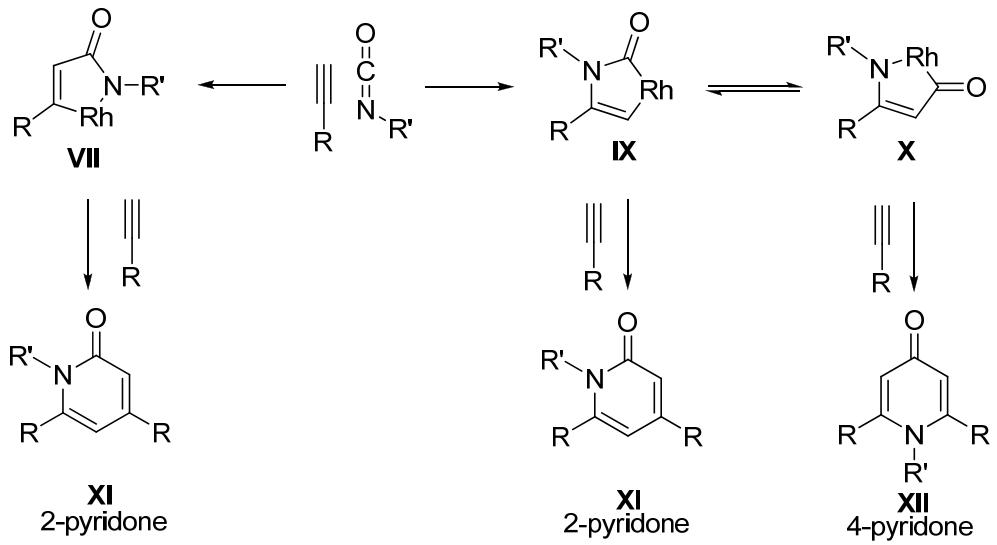
[a] Reaction run at 0.005M [b] reaction run with slow addition of alkyne

In our continued search to expand the scope of this cycloaddition we looked at the mechanism of pyridone formation for ways to that it might be possible to shut this reaction down.

3.4 Mechanism of pyridone formation.

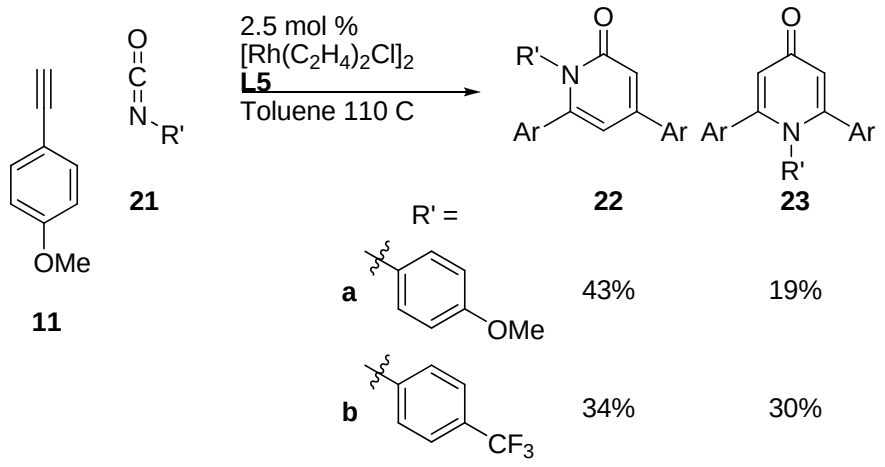
A closer look at the mechanism for pyridone formation revealed that pyridones could form from any one of three metallacycles (Fig. 7).

Figure 7



One interesting question that this mechanism raised is whether the observed 2-pyridone is formed from vinylogous amide metallacycle **IX** or lactam metallacycle **VII**? Kevin Oberg had recently investigated the pyridone-forming reaction and some of his experiments shed light on this question.[5] One result that gave a key insight into which pathway lead to pyridone was the isolation of a 4-pyridone product. By varying the electronics on a series of aryl isocyanates a new 4-pyridone product was isolated (Table 6).

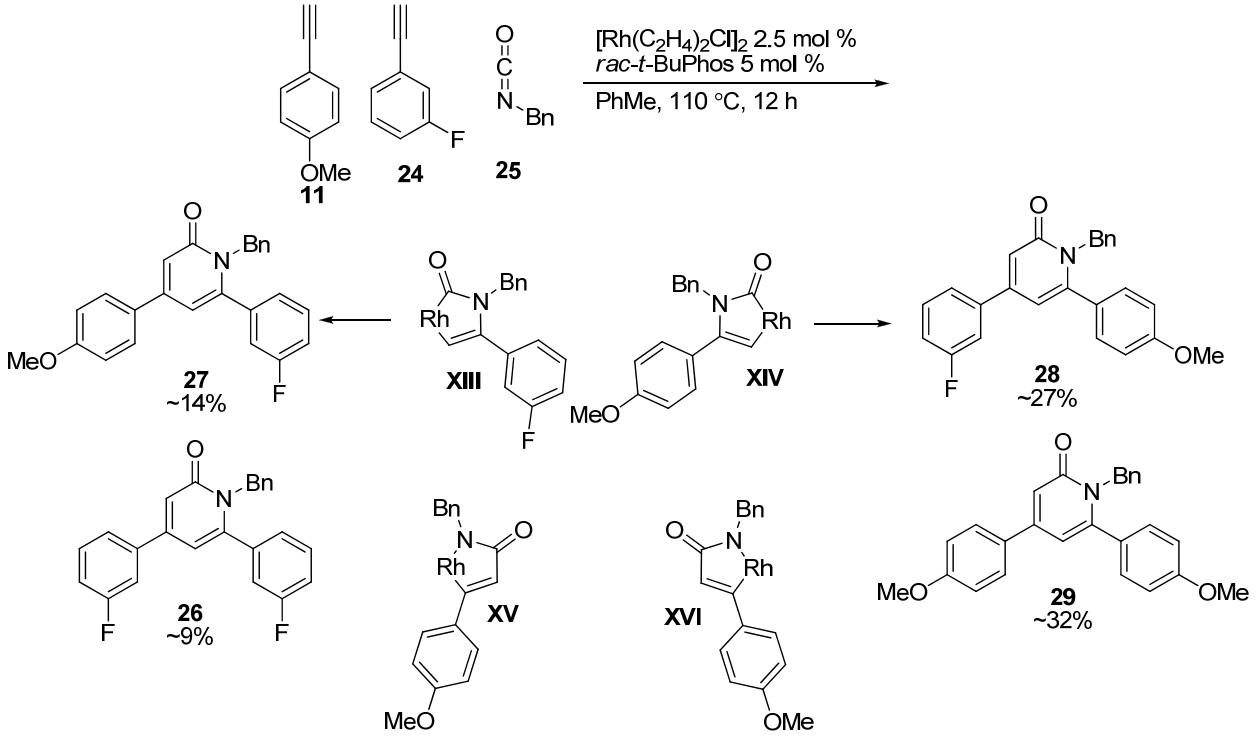
Table 6



With electron-rich isocyanates the pyridone forming reaction favored the 2-pyridone product while with electron-deficient isocyanates the reaction was unselective and formed either pyridone in a 1:1 ratio. The isolation of these pyridones in different ratios but comparable yields suggests that both pyridones likely arise from the same metallaycle. If this were true it would imply that pyridones arise through vinylogous amide metallacycle **IX** rather than lactam metallacycle **VII**. The effect of substrate electronics on product ratio may be the result of a perturbation to the equilibrium between metallacycle **IX** and **X** rather than affecting the oxidative cyclization reaction.

A second experiment was performed to look at the competition between two alkynes in the pyridone forming reaction.[6] When the reaction of benzyl isocyanate **25** was run in the presence of 1 equivalent of both electron-deficient **24** and electron-rich acetylene **11** the following product ratios were obtained. (Fig. 8)

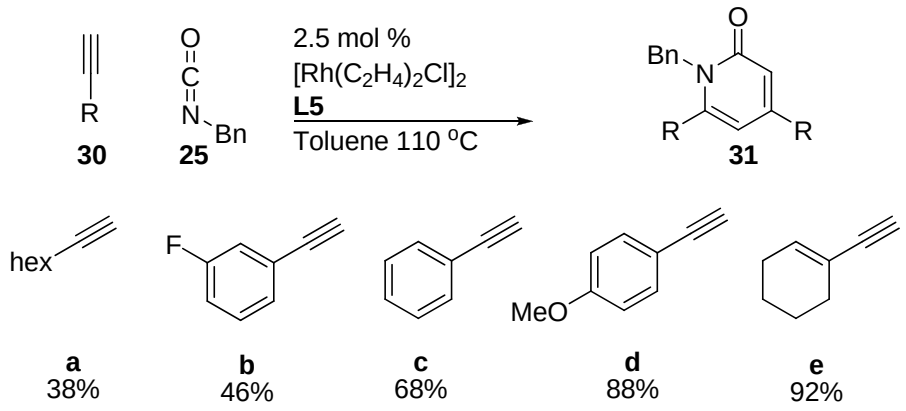
Figure 8



If we assume that oxidative cyclization occurs faster with an electron-rich than an electron-poor alkyne than the products formed in the greatest amount should reflect a metallacycle that initially formed between alkyne **11** and isocyanate **25**. Under this assumption since we obtain product **28** in greater proportions than product **27** this suggests that the 2-pyridones are forming from metallacycles **XIII**, **XIV** rather than the corresponding lactam type metallacycles **XV**, **XVI**. If these products were formed from the lactam metallacycles we would expect the opposite bias in the product distribution.

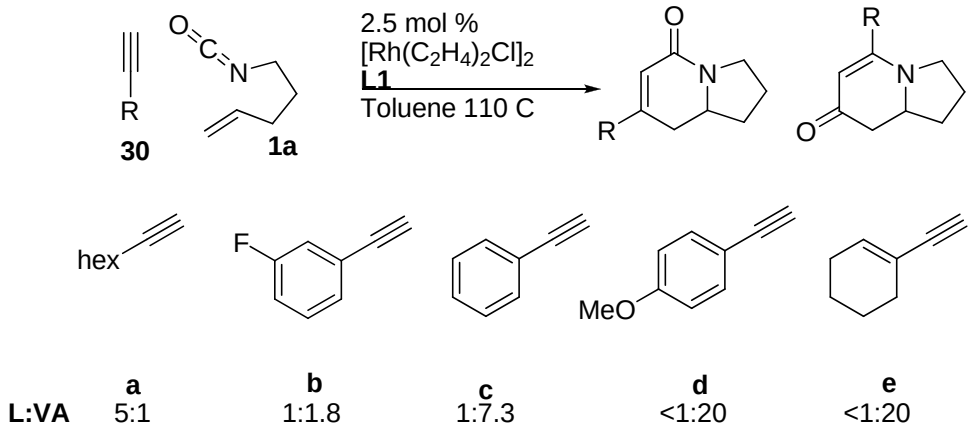
Finally the efficiency of the pyridone reaction appeared to be dependent on substrate. The reaction proved to be very efficient with substrates aryl and cyclohexenyl acetylenes (**24c-e**) but not as efficient with **24a,b (**Fig. 9).

Figure 9



If the product yields in the pyridone reaction are correlated to the ratio of lactam:vinylogous amide type products which are found in the reaction of pentenyl isocyanate the more the ratio favors vinylogous amide product the greater the yield of the pyridone reaction (Fig. 10).[7]

Figure 10



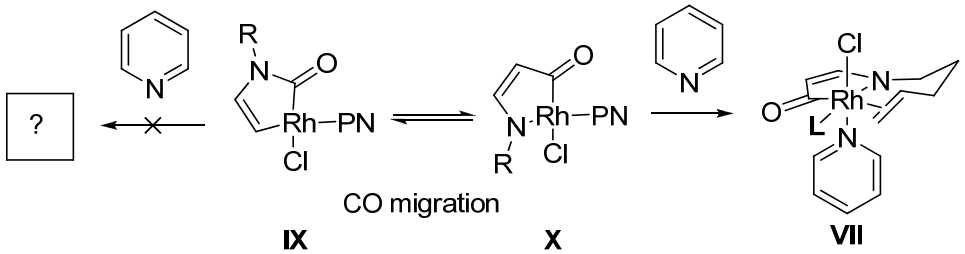
These low effeciencies can be explained if the only vinylogous amide metallacycle **IX** leads to pyridone and lactam metallacyle **VII** leads to an unproductive pathway.

Each of these three studies leads us to believe that pyridone products are formed through vinylogous amide metallacycle **IX** rather than through lactam metallacycle **VII**. Next we wondered if it would be possible to put this hypothesis to the test by using our knowledge of the mechanism of pyridone formation to shutdown pyridone and encourage cycloaddition with an alkene.

3.5 Shutting Down Pyridone Formation to Form New Cycloadducts

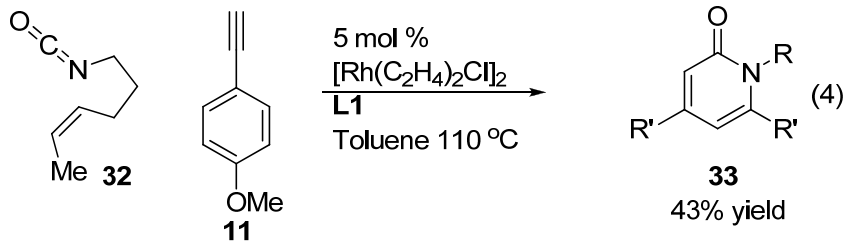
Given the mechanism for formation of 2-pyridone proceeds through vinylogous amide metallacycle it is not surprising that we had difficulty in showing an effect of the additive on the formation of 2-pyridone. From the results of our additive study we can only know that the additive becomes involved with intermediate **VII** (Fig. 11). Yet pyridone is formed earlier in the mechanism from a metallacycle which precedes CO migration.

Figure 11



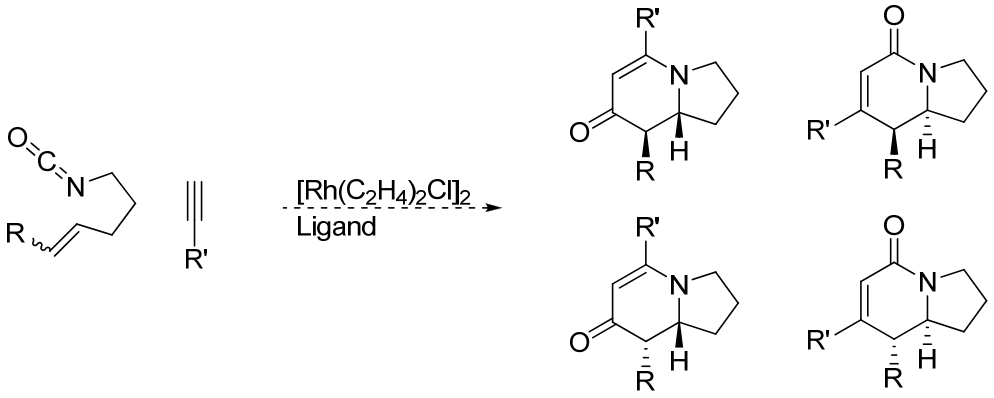
For the additive to interrupt the formation of 2-pyridone it would need to coordinate to an intermediate like **IX**. First we have no evidence that this is possible. Secondly if the additive did coordinate to **IX** it might very well interfere with the CO migration process, since CO migration requires an open coordination site. By coordinating to **IX** and preventing CO migration the additive would also be preventing the olefin insertion. Therefore we would not expect to see a change in the ratio of product to 2-pyridone.

The study of the pyridone reaction did yield some valuable insight into ways that we can suppress the formation of 2-pyridone. Reaction of 1-octyne (Fig. 9) showed that formation of 2-pyridone was suppressed in systems which predominantly lead to formation of lactam cycloadduct. By using reaction conditions which favored lactam cycloadduct the amount of pyridone formed should be reduced and therefore lead to an increase in the yield of olefin insertion cycloadduct. One system that never yielded the desired olefin insertion product from was the 1,2 disubstituted alkenyl isocyanates. Only pyridone was ever isolated from these reactions (Eq. 4).[8]



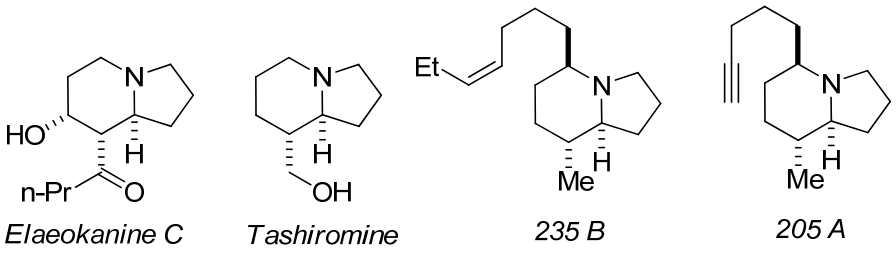
The use of 1,2 disubstituted alkenyl isocyanates would be a synthetically useful extension of this methodology since by using stereochemically defined olefins we should be able to form cycloadducts with two vicinal stereocenters (Fig. 12).

Figure 12

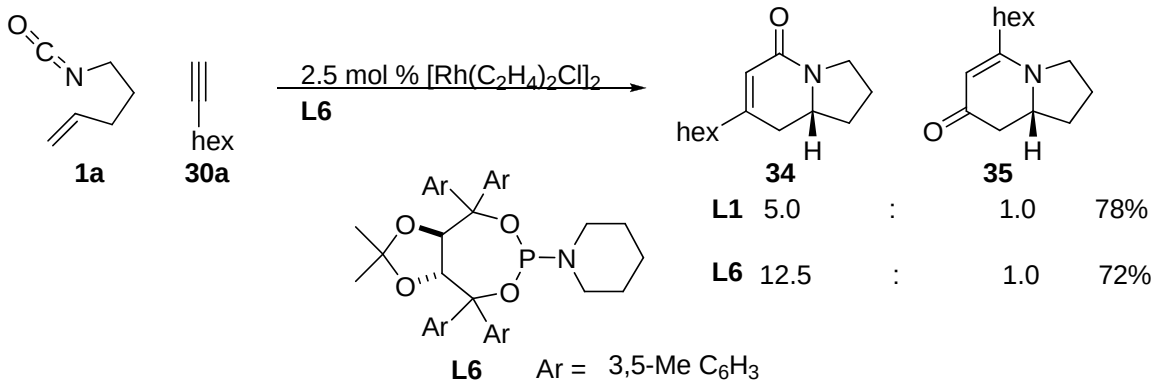


This method would allow us to access two different diastereomers of two different products for a total of 4 different compounds and their enantiomers. This variety of products as well as the functional handles on both the alkyne and the alkene makes this a versatile method for making densely functionalized indolizidine cores. In addition to the flexibility of this method incorporation of 1,2 disubstituted alkenes would potentially allow us rapid entry to synthesis of a number of indolizine alkaloid natural products (Fig. 13).

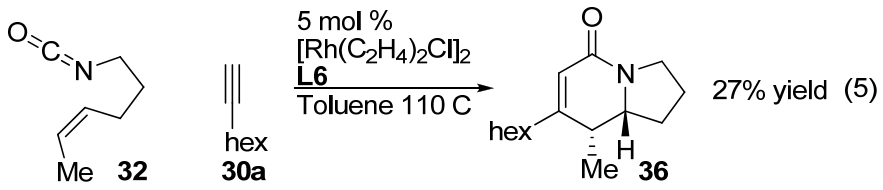
Figure 13



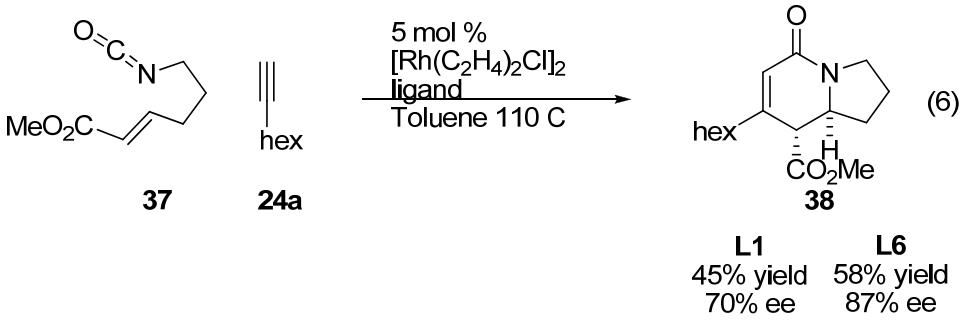
To test our hypothesis we would want to find a system that had very good lactam selectivity. As a substrate we chose 1-octyne **30a** which favored lactam to vinylogous amide 5:1 using ligand **L1**. However ligand **L6** gave even greater selectivity favoring lactam than **L1**.



Our hypothesis indicated that this system with the greatest lactam selectivity should yield less 2-pyridone. The smaller amount of 2-pyridone should allow for competitive insertion of the 1,2 disubstituted olefin into the lactam metallacycle. When a methyl 1,2 disubstituted alkenyl isocyanate **25** was reacted with octyne **30a** the desired cycloadduct was isolated (Eq. 5).



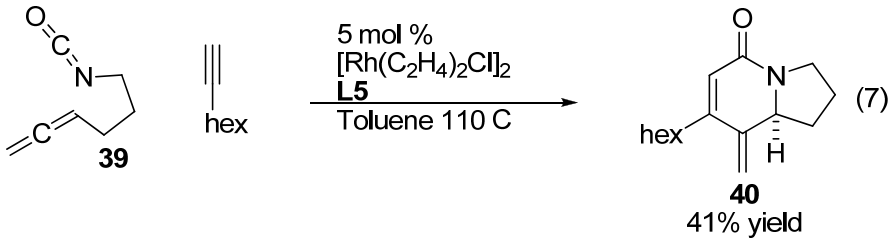
Under these reaction conditions no 2-pyridone product was isolated. Optimization of reactions conditions: concentration, stoichiometry, solvent and temp did not yield any greater amount of product. Methyl substitution on the alkene of the isocyanate appeared to be the only alkyl substituent tolerated. By varying the electronics the propensity of the olefin to bind to the rhodium should be increased. Replacing the methyl substituent with a methyl ester on the alkenyl isocyanate **37** yielded cycloadduct **38** in this reaction (Eq. 6).



Much higher yields were obtained with this isocyanate **31** with an electron deficient olefin. The higher yields in this case are presumably due to more facile coordination of this olefin as well as the reactivity of the Micheal acceptor.

Since methyl or methyl esters seemed to be the only groups tolerated at the 2-position of the alkene sterics at the 2-position of the alkene were obviously important. The success with isocyanates **25** and **33** suggested that allenes might work as a π-component in the reaction. Allenes from a steric perspective should be smaller than the

methyl substitutent on **25**; as well it should be a weaker π-bond than an alkene and should be reactive in this system. When isocyanate **39** was used under these conditions we isolated the desired lactam product **40** (Eq. 7).



This result allowed us access to lactam product **40** which is an interesting product with a functional handle which has a large potential to yield different types of indolizidine cores which we have not been able to access easily.

In this chapter I have shown how extending the utility of the rhodium catalyzed cycloaddition of alkenyl isocyanates has been possible by the identification of byproducts. Upon identification of unwanted byproducts strategies were developed to have the intended effect of decreasing the formation of these byproducts in order to increase the formation of desired cycloadducts. This strategy was applied successfully in the case of the cycloaddition of acetylene dicarboxylates, the cycloaddition of 1,2-disubstituted alkenyl isocyanates and the cycloaddition of allenyl isocyanates.

Chapter 3 Experimental

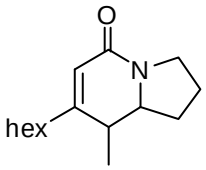
The Expansion of the Scope of the Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates.

General Methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Acetonitrile (certified ACS grade) and triethylamine (peptide synthesis grade) were purchased from Fisher Scientific and used without further purification. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and KMnO4 followed by heating. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (□, ppm) from deuterated chloroform (CDCl3) taken as 7.26 ppm (300 MHz) or 7.23 ppm (400 MHz), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from CDCl3 taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Alkyne **2, 3, 5, 8, 11** and compounds **14** were purchased from Aldrich Chemicals Co. and used without further purification. Alkenyl isocyanates **1a,b,c 15,18, 32, 37, 39** can be synthesized by the procedure previously describe from the corresponding carboxylic acid.. 5-hexenoic acid, 6-heptenoic acid, and diphenyl phosphoryl azide were purchased from Aldrich Chemicals Co. $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemical, Inc. and used without further purification. Ligand **L1, L6** were prepared as described in the literature.[9] Ligand **L2-L5** were prepared as described in the literature.[10]

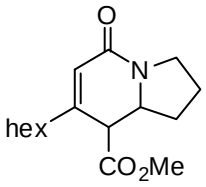
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alkenyl isocyanates and terminal acetylenes using pyridine: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L1** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne (1.0 eq, 0.128 mmol), isocyanate (1.5 eq, 0.193 mmol) and compound **14** (1.0 eq, 0.128) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution to typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

General procedure for the Rh-catalyzed [2+2+2] cycloaddition of 1,2 disubstituted alkenyl isocyanates and terminal acetylenes: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L6** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne (1.0 eq, 0.128 mmol) and isocyanate (1.5 eq, 0.193 mmol) in 3 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 3 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. An additional 1 ml of toluene to rinse any remaining isocyanate and alkyne was used and added to the reaction. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.

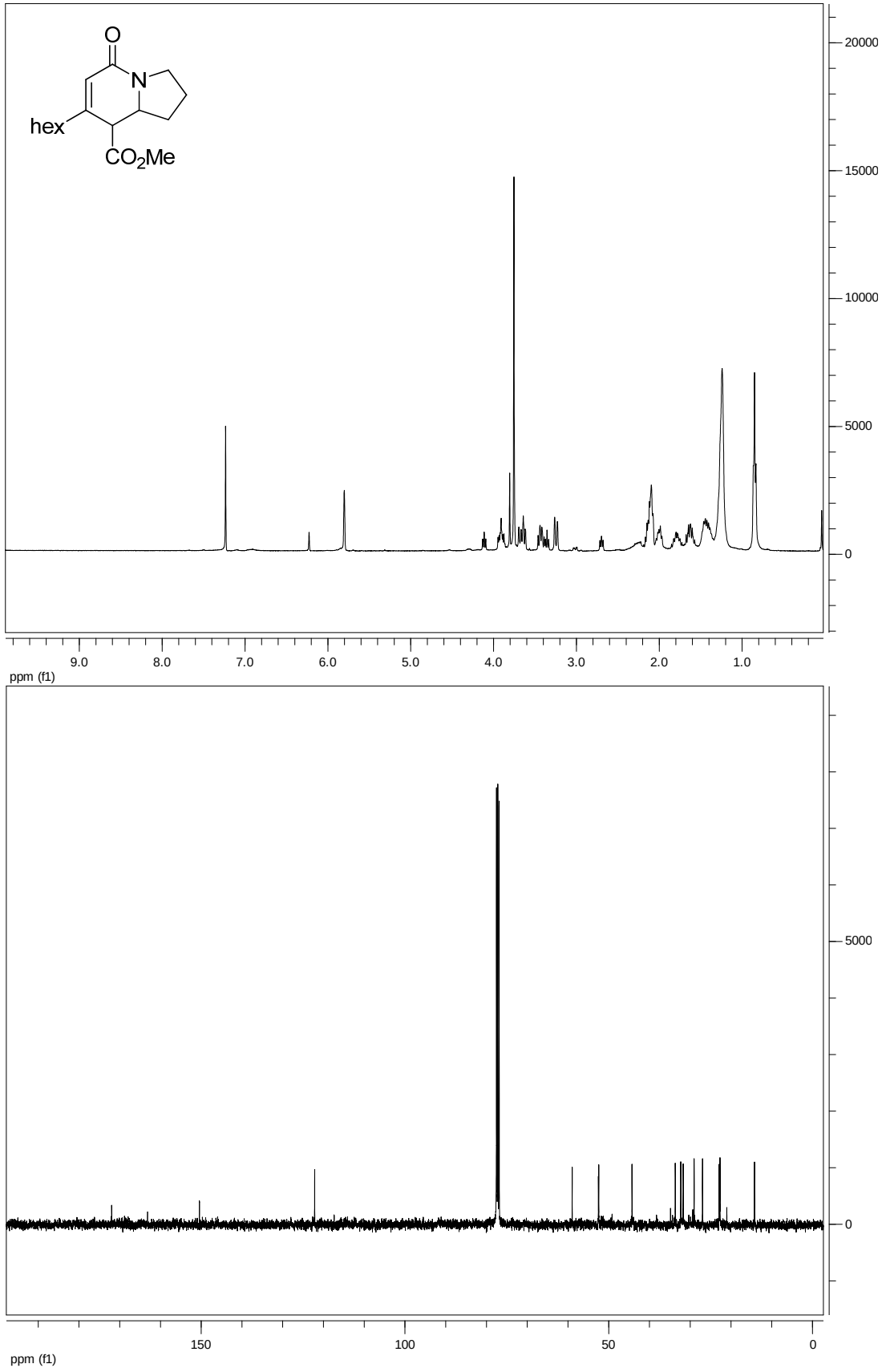
General procedure for the Rh-catalyzed [2+2+2] cycloaddition of alleneyl isocyanates and terminal acetylenes: An oven-dried 10 mL round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.03 eq, 0.0038 mmol) and the phosphoramidite ligand **L6** 3.9 mg (0.06 eq, 0.0077 mmol), and was fitted with an oven-dried reflux condenser in an inert atmosphere (N2) glove box. A solution of alkyne (8.0 eq, 1.0 mmol) and isocyanate (1.0 eq, 0.193 mmol) in 1 ml of toluene was prepared. This solution was placed under an atmosphere of argon. The 1 mL solution of toluene was then added via syringe to the flask containing the rhodium catalyst. A solution of isocyanate (1.0 eq, 0.125 mmol) in 3 ml of toluene was prepared. The 3 mL solution of toluene was then added slowly via syringe over 2 hours to the reaction flask. The resulting solution was heated to 110 □C in an oil bath, and maintained at reflux for *ca.* 16 h. The reaction mixture was cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 100% ethyl acetate). Evaporation of solvent afforded the analytically pure product.



7-hexyl-8-methyl-2,3,8,8a-tetrahydroindolizin-5(1H)-one (36) The general procedure yielded a light yellow solid (58% yield): Rf = 0.30 (EtOAc); characterized as a mixture of diastereomers ^{1}H NMR (400 MHz, CDCl3) δ 5.70(s, 1H), 5.30(s, 1H), 3.73 (dddd, 1H *J* = 5.7, 5.7, 10.2, 11.3 Hz), 3.59-3.70 (m, 1H), 3.20-3.50 (m, 4H), 2.20-2.31 (m, 2H), 2.08-2.20 (m, 2H), 1.88-2.03 (m, 2H), 1.70-1.85 (m, 2H), 1.40-1.61 (m, 2H), 1.20-1.40 (m, 16H); 1.10(d, 6H, *J* = 7 Hz) 0.80-0.90 (m, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 160.2, 157.3, 120.6, 119.1, 77.8, 77.5, 77.4, 77.2, 76.8, 63.0, 59.7, 44.5, 44.4, 38.9, 35.6, 34.8, 33.2, 33.0, 31.8, 31.7, 29.2, 29.1, 28.3, 27.5, 27.3, 23.5, 23.0, 22.7, 14.6, 14.2; IR (NaCl, CHCl3) 1585, 1574 1535, 1320, 1311, 980 cm-1; HRMS [C16H26NO3]+ calcd 236.1936 Found 236.1939 (FAB+).



(8R,8aS)-methyl 7-hexyl-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-8-carboxylate (37) The general procedure yielded a light yellow solid (58% yield): Rf = 0.44 (EtOAc); ^{1}H NMR (400 MHz, CDCl3) δ 5.80(s, 1H), 3.90 (dddd, 1H, J=6.2, 6.2, 10.8, 10.8) 3.75 (s, 3H), 3.68 (m, 1H), 3.3-3.48 (m, 2H), 2.64 (dd, 1H, *J* = 15.8, 15.8 Hz), 2.55 (dd, 1H, *J* = 4.5, 15.8 Hz), 2.20-2.31 (m, 3H), 1.99– 2.11 (m, 1H), 1.61 – 1.85 (m, 2H); 1.20-1.40 (m, 8H); 0.80-0.90 (m, 3H) ^{13}C NMR (100 MHz, CDCl3) δ 171.9, 163.1, 150.4, 122.1, 77.8, 76.8, 58.9, 52.5, 49.1, 44.2, 38.2, 34.8, 32.3, 31.8, 30.3, 26.9 IR (NaCl, CHCl3) 1586, 1575 1532, 1322, 1311, 970 cm-1; HRMS [C16H26NO3]+ calcd 280.1834 Found 280.1837 (FAB+).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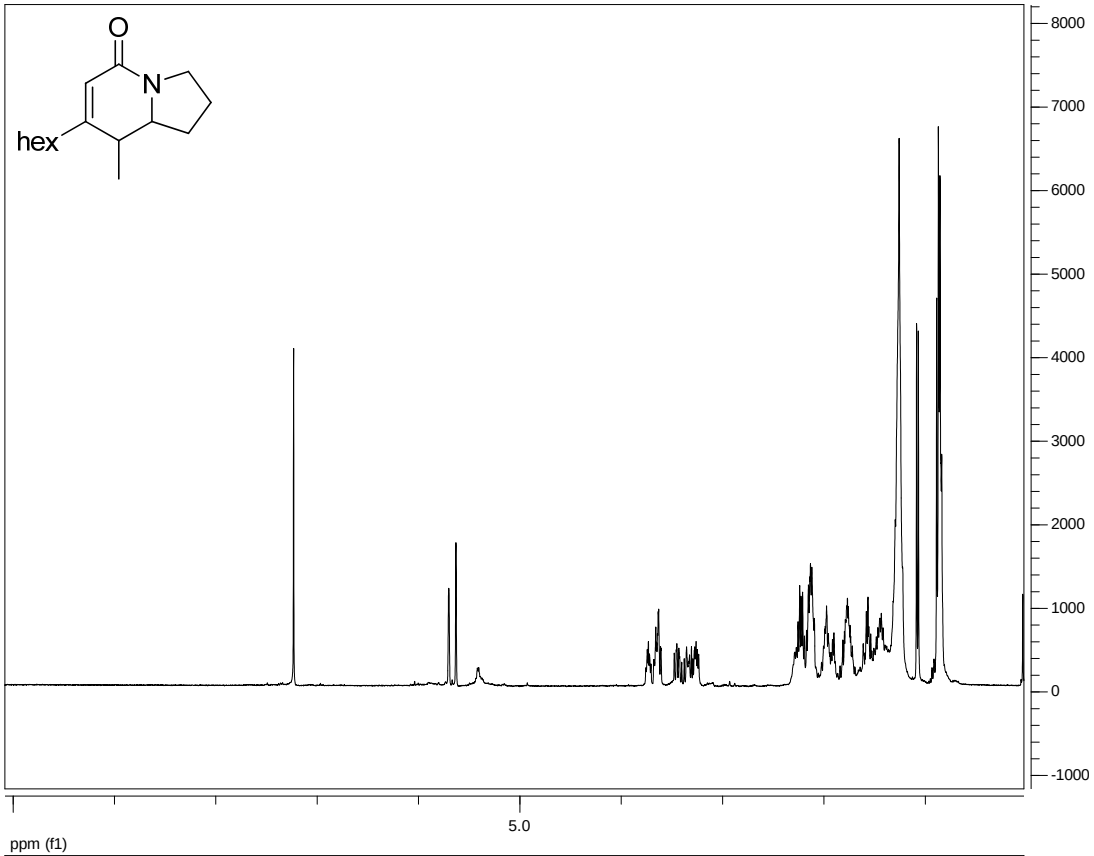
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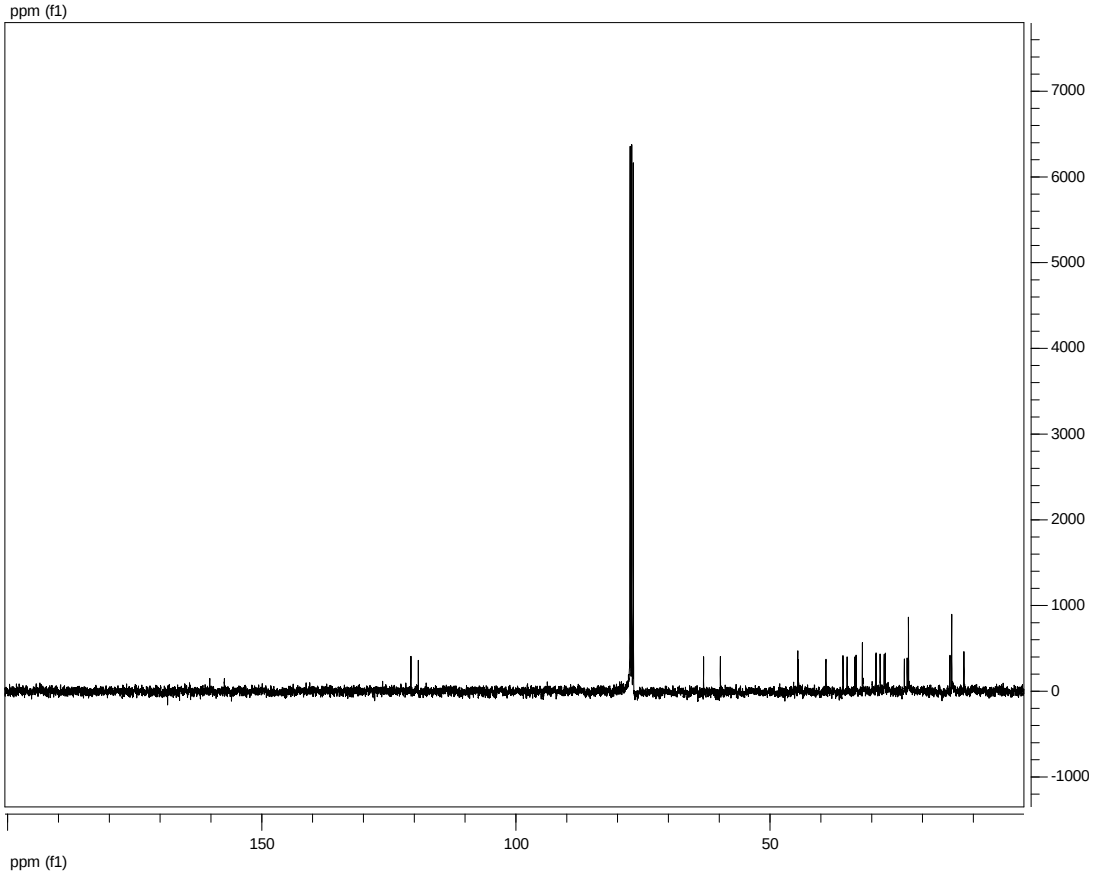
5.0
ppm (f1)


7000
6000
5000
4000
3000
2000
1000
0
-1000
150
100
50
ppm (f1)

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