1,4–Conjugate Addition with Pyrrole and Indole Enones
&
Propargylic Substitution using Boronic Acids as Nucleophiles with Gallium and Silver Catalysts

by
Amy Elizabeth Boylan

A dissertation submitted to the Department of Chemistry,
College of Natural Sciences and Mathematics
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

Chair of Committee: Jeremy A. May

Committee Member: Scott R. Gilberston

Committee Member: Gregory D. Cuny

Committee Member: Ognjen Miljanic

Committee Member: Arnold Guloy

University of Houston
August 2021

DEDICATION

I would like to dedicate this dissertation to my loving mother, Erika. Her continued love and support to help me pursue my goals has been instrumental in my success. I would also like to thank my Aunt Natalie, who will never know how positively she impacted my life.

ACKNOWLEDGMENTS

First and foremost I would like to thank my advisor, Dr. Jeremy May, for all of his mentorship and guidance over the last five years. I have learned an incredible amount of information during my graduate studies in his group, and I will always be amazed how inspiring he is as a chemist and mentor.

Thank you to all of the wonderful people who I have been able to work alongside in the May lab, Dr. Po-An Chen, Jirong Luo, Bailey Navarez, Hossein Barzegar, Clayton Donald, Po-Kai Peng, Davis Plasko, Dr. Qinxuan Wang. I am also so grateful for the mentorship of Dr. Krit Setthakarn and Dr. Truong Nguyen. I am also so grateful to have known Karlo Sales, who was an amazing chemist and friend and is missed dearly.

Thank you to two of my close friends: Dr. Sasha Sundstrom and Dr. Corie McHale. They are both awesome chemists and friends, and were so supportive throughout my graduate studies. I'd also like to thank my best friend, Dr. Amanda McCord, who I became friends with in an undergraduate organic chemistry lab at Baylor University. We both later moved to Houston after undergraduate to pursue doctorates, M.D. and Ph.D. She was the best roommate and supportive friend throughout this process. I am also thankful to everyone I have meet through the Buffalo Bayou running club. They have particularly made my last year in Houston so enjoyable, especially my friends Monica Esqueda and Joanna Folse.

I am also thankful for my loving boyfriend, Zach Gorman. He has always been supportive, loving, and helpful.

ABSTRACT

This dissertation covers two projects: 1,4–conjugate addition on pyrrole and indole enones, and propargylic substitution using boronic acid as nucleophiles and silver/gallium catalysts.

β-(2-indole)-enones and β-(2-pyrrole)-enones, both historically problematic substrate types with 1,4–conjugate addition reactions, were extensively examined. Analysis of isomer-related reaction-rate trends showed that proximity of a heteroatom to the enone β-carbon was favorable to reaction rate and increased resonance electron donation also increased reaction rate. These enantioselective conjugate addition reactions were ultimately enhanced by using a less electron deficient catalyst and a base additive, ammonium carbonate. After many reactions and substrates were studied, this base was shown to have an advantage effect on enhancing the conjugate addition reaction but had an adverse effect on the starting material, which lead to other side reactions with this conflicted system.

For the second project, three methods have been developed for nucleophilic propargylic substitutions that have been useful in forming tertiary carbons: (IPr)$GaCl_3$/$AgSbF_6$ with boronic acid at 23 °C, $AgSbF_6$ with boronic acid at 40 °C, and $GaCl_3$ with boronic acid at -78 °C. A combination of $AgSbF_6$ and $IPrGaCl_3$ along with boronic acids at lower temperatures have been shown to decrease reaction times for the formation of nucleophilic substitution through the displacement of propargylic alcohols. $GaCl_3$ with boronic acid at -78 °C proved to be the best conditions for the formation of the quaternary carbon centers. An expanded substrate scope and nucleophile scope have been developed for the formation of the tertiary carbon centers and quaternary carbon centers using these three method

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2:

CHAPTER 4:

LIST OF FIGURES

CHAPTER 1:

CHAPTER 2:

CHAPTER 3:

CHAPTER 4:

LIST OF ABBREVIATIONS

aq	aqueous
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BIPHEP	2,2′-bis(diphenylphosphino)-biphenyl
BINOL	1,1᾽-bi-2-naphthol
Bn	benzyl
Boc	tert-butoxycarbonyl
cat	catalyst
Cbz	carboxybenzyl
DCE	dichloroethane
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
FTIR	Fourier-transform infrared spectroscopy
hrs	hour
Het	heteroaryl
HPLC	high-performance liquid chromatography
I	iodine
*i*Pr	isopropyl

Me	methyl
MeOH	methanol
MS	molecular sieves
MOM	methoxymethyl
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PhMe	toluene
Rh	Ruthenium
RT	room temperature
SM	starting material
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TSA	Trichistatin A
9-BBN	9-Borabicyclo(3.3.1.)nonane

CHAPTER 1: CONJUGATE ADDITION REACTIONS AND PYRROLES

1.1 Importance of Pyrroles and Indoles

1.1.1 Pyrroles and Indoles in Pharmaceutical Drugs

Among the thousands of pharmaceutical drugs that are on the market today, many possess heterocycles; specifically a significant percentage have pyrroles and indoles in the cores of their structures.[1] In fact most of the top 200 grossing pharmaceutical drugs of 2019 contain at least one heterocycle. Currently, the second most prescribed pharmaceutical drug is Lipitor®. This compound helps to lower cholesterol levels, has a revenue of $2.096 billion dollars, and has a highly substituted pyrrole (Figure 1.1). Cialis and Lupron earn $891 and $887 million a year, respectively. Both contain multiple heterocycles, including an indole motif.

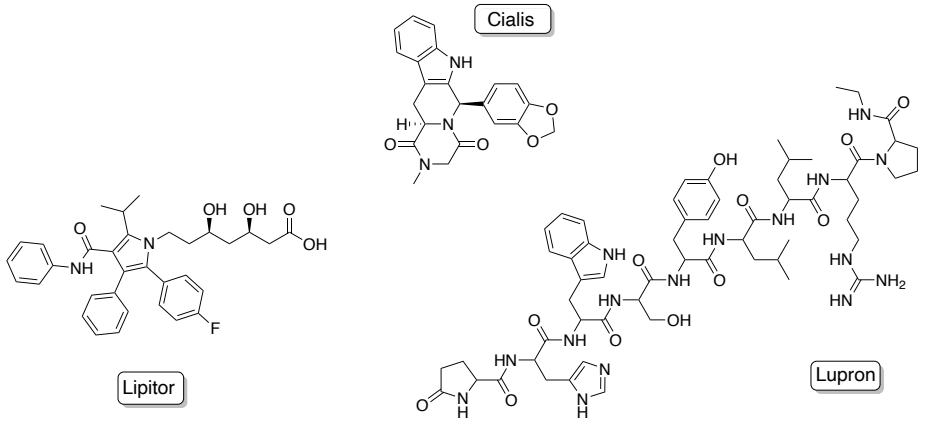


Figure 1.1. Examples of pyrroles & indoles from the top 200 pharmaceutical drugs

Pyrroles appear in a wide variety of drugs with many applications. For example, Sunitinib is a treatment for gastrointestinal stromal tumors (Figure 1.2). Toradol and Tolmetin are both nonsteroidal anti-inflammatory drugs, while pyrvinium is a treatment for pinworms.

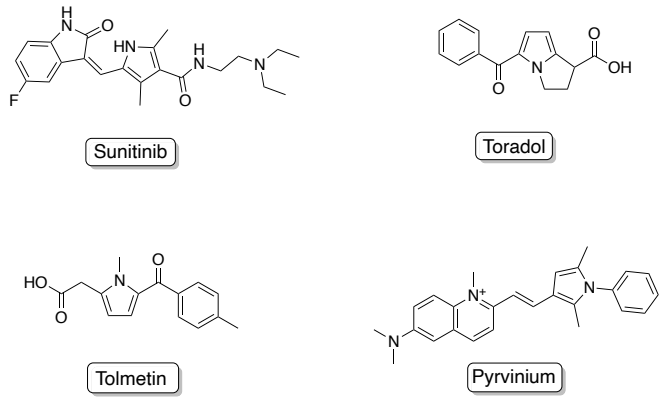


Figure 1.2. Pharmaceutical drugs with pyrroles in their cores

Pyrroles are such useful building blocks for pharmacology that they appear in the active compounds of antitumor, antimalaria, antifungal, antidepressant, antivirus, antiulcer, and insecticidal agents among many other pharmacologically active compounds.[2] These pyrrole motifs are thus valuable to our health and society, and the ability to synthetically access a variety of pyrrole motifs from various methods is important in new drug developments and discoveries. The ability to control stereocenter formation and synthesize heteroaromatic systems has become increasingly important, as the need and desire for greater three-dimensionality in compounds has increased in more recent years.[3–9]

1.1.2 Pyrroles and Indoles in Natural Products

Natural products or analogs of natural products are often sources for drugs.[10] From the years of 1981–2014, 320 of the 1211 new approved drugs were derived from natural products. Often, natural products are isolated from plants or other natural sources in very small quantities; however, many problems arise from the isolation. These problems include: high cost associated with collecting samples, purity of isolation (especially when trying to collect large quantities), long resupply times, as

well as difficulty obtaining large quantities without disrupting or destroying ecosystems.[11]

Once natural product candidates are tested in a variety of assays to see if they have any potential for the treatment of diseases or conditions, it is the job of chemists to find a reasonable synthetic route to make useful quantities of these compounds. Having access to different methods to make compounds can be extremely helpful when one runs into a roadblock in the practical nature of a synthesis.

In Figure 1.3, there are four different retrosynthesis for different natural products that contain a pyrrole in their core structure. The first natural product, rhazinicine, has been shown to mimic the cellular effects of Pacitaxel, a chemotherapy drug.[12] In the first total synthesis of rhazincine, the Gaunt group utilized a strategy of metal catalyzed C–H bond functionalization.[12] In this 11–step synthesis from commercially available starting materials, the overall yield was 9.3%.

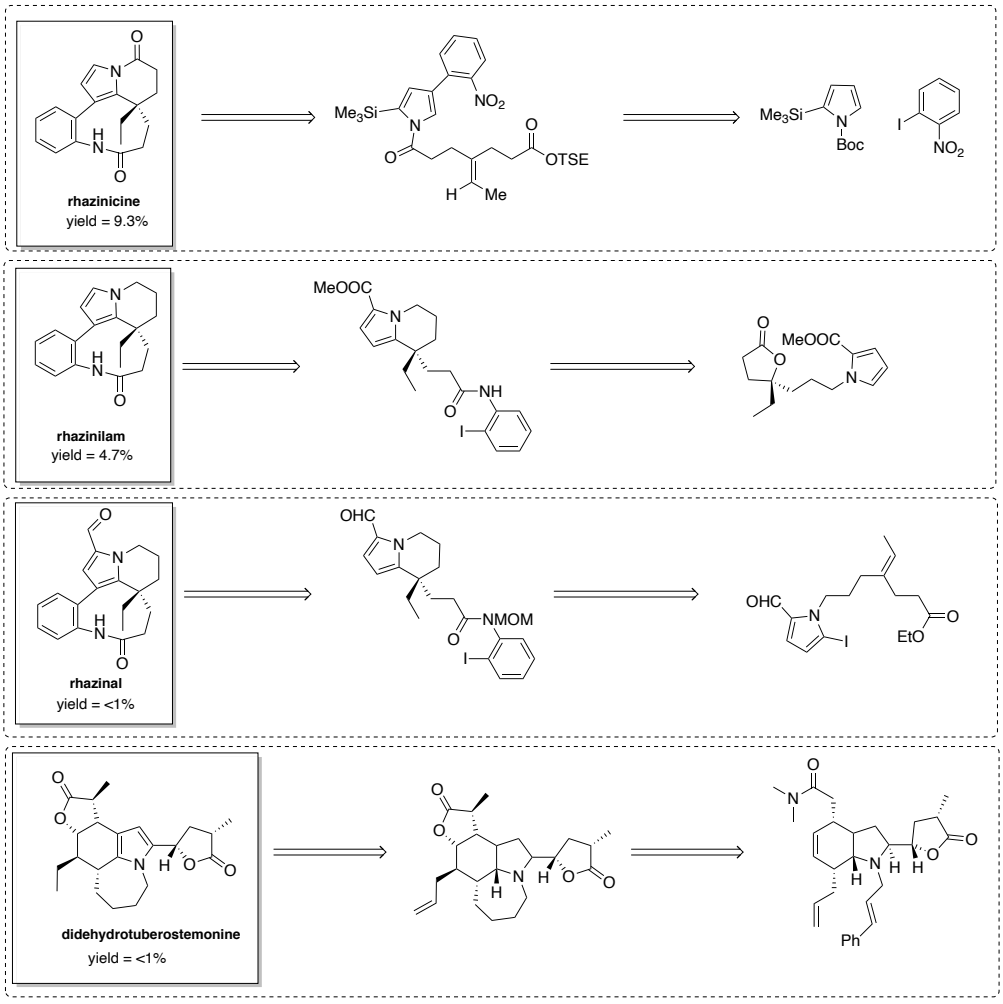


Figure 1.3. Examples of natural products retrosynthesis

The next natural product, rhazinilam, was been made by the Sames lab[13] and the Bowie lab[14]. The Sames lab was the first to publish a synthesis in 2002, and then in 2005 the Bowie lab publish a more concise synthesis of rhazilam. The Sames lab based their synthesis around an intramolecular platinum mediated C–H activation. Although they were able to get fairly good enantioselectivity within their reactions, their overall yields remain low. The Bowie lab was able to complete their total

synthesis in seven steps with a completely different route but the overall yield was similarly low.

The Trauner group published a synthesis of Rhazinal. They utilized a novel oxidative Heck cyclization and palladium-catalyzed direct couplings. Although new methods of synthesis were utilized, the overall yield was extremely low: less than 1% overall. The synthesis of didehydrotuberostemonine was completed by the Spencer group. Their yield was extremely low, however, because they encountered many unstable intermediates.[15]

In each of these synthesizes for pyrrole containing natural products, there are improvements that can still be made. Either new methods to make these structures or different synthetic routes could potentially improve the overall yields. Without the ability to obtain high yields, these natural products are unlikely to be used in applications, such as the large-scale production of drugs, even though they are potentially useful.

Indole based natural products are plentiful. In Figure 1.4, there are examples of terpenoid type natural products with indole cores.[16] Natural products with biological components or activity often include an indole motif.

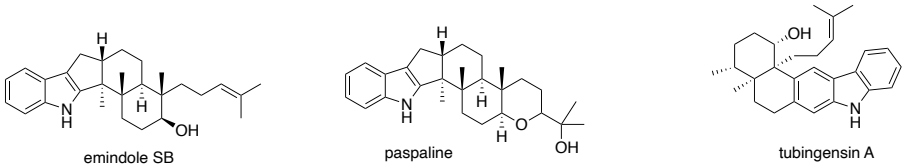


Figure 1.4. Indole based natural products

Natural products also have a lot of value to the chemical community by challenging current synthesis methods which leads to new methodology

developments. They also provide rewards, such as ideas for pharmaceutical drugs targets.

1.2 Origins of Conjugate Addition Reactions

Conjugate addition reactions are a large and diverse class of reactions. In general, they consist of a nucleophilic addition. 1,2 addition is a direct nucleophilic attack to the carbonyl, while a 1,4–addition, or 1,4–conjugate addition, is the nucleophilic attack to an alkene in conjugation with the carbonyl. Depending on the reaction conditions, they can be thermodynamically or kinetically controlled.

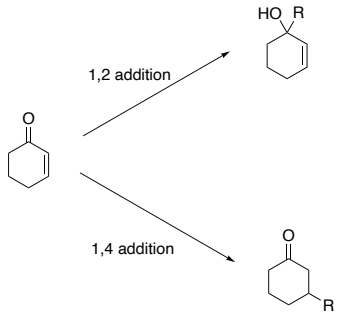


Figure 1.5. 1,2 vs. 1,4–addition

The first reports of conjugate addition reactions date back to 1880 when Arthur Michael started to extensively study them.[17] Arthur Michael, whom discovered the "Michael Addition", determined that a C–C bond could be formed at the electron deficient β-carbon position of a ketone. The enolate serves as a nucleophile to attack the β-position of an α,β- unsaturated ketone compound (Figure 1.6). This results in an 1,4–conjugate addition reaction and a new C–C bond.

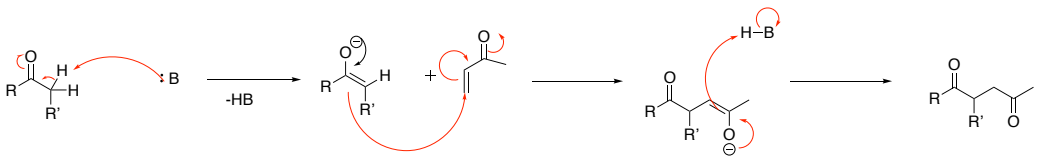


Figure 1.6. Michael reaction

1,4–conjugate addition is a larger category of reactions, in which a nucleophile attacks an α,β-unsaturated carbonyl compound. The nucleophile does not have to be an enolate, like in the Michael Reaction. Grignards and organoboronates are also commonly used as nucleophiles. Although commercially available, Grignards have a few drawbacks as nucleophiles for 1,4–conjugate addition. They are usually more selective for 1,2–addition over 1,4–conjugate addition. They often are difficult to work with since they can be flammable and are often not shelf stable.

1.2.1 Organoboronates as Nucleophiles Without Transition Metal Catalysis

Nearly a hundred years later in 1976, Herbert Brown reported the first conjugate addition with an organoboronate, 9-BBN (Figure 1.7).[18] This reaction provided a practical synthetic route to attach vinyl nucleophiles to methyl vinyl ketones regioselectivity and resulted in a γ,δ-unsaturated ketone. Brown started with an acetylene then reacted it with 9-BBN to generate the organoboronate, then the methyl vinyl ketone was added and the final products were obtained in 66-93% yields overall.

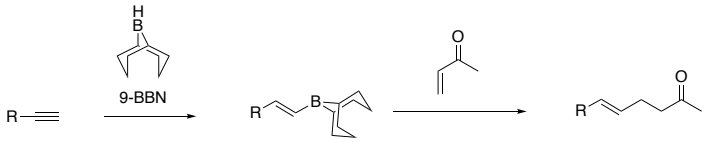


Figure 1.7. Brown's conjugate addition reaction

1.2.2 Enantioselective Conjugate Addition Reactions with Transition Metal Catalysis

Copper-based catalysts with a variety of chiral ligands have been able to promote the 1,4–conjugate addition reactions enantioselectively. Some common types of ligands include oxazoline, TADDOL, and BINOL derivatives.[19] Organozinc nucleophiles, which are unreactive without a copper catalyst, are almost always

required for this reaction system to proceed effectively since they coordinate to the oxygen in the reaction mechanism (Figure 1.8).[20] The large ligands control enantioselectivity in the C-C bond forming step. Only moderate yields of the 1,4–addition products are produced, but the enantioselectivity is very high.

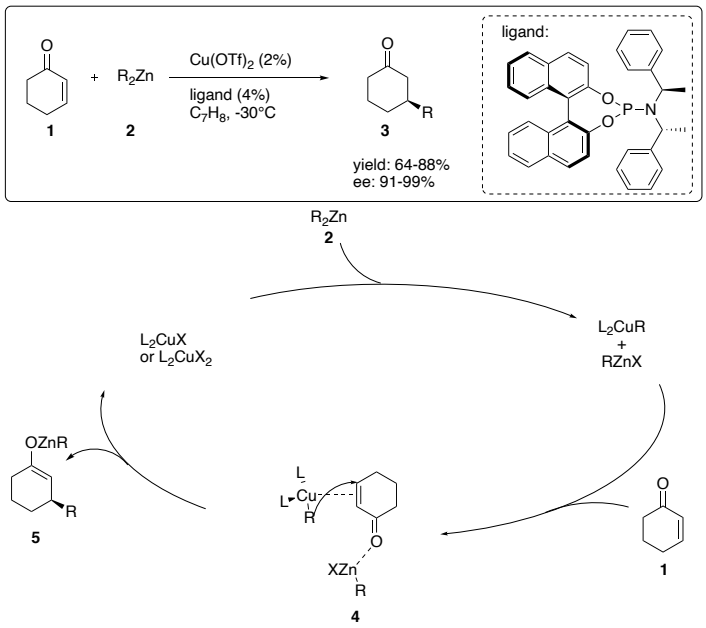


Figure 1.8. Enantioselective copper catalyzed reaction and mechanism

In 1997, Miyaura published the first 1,4–conjugate addition with aryl and alkenyl boronic acids on α,β-unsaturated ketones with a rhodium complex (Figure 1.9).[21] Then shortly thereafter, Miyaura's group developed an asymmetric version of the rhodium complex.[22] They used BINAP as a ligand and a mixed solvent system of dioxane/water heated to reflux temperatures. They were able to get high enantioselectivity, but the yields varied quite a bit from 50-90%. Since then, significant improvements have been made to asymmetric rhodium-catalyzed 1,4–conjugate additions with boronic acids. Many ligands have been developed for

rhodium-catalysis with a variety of nucleophiles as well as on a large scope of substrates.[23]

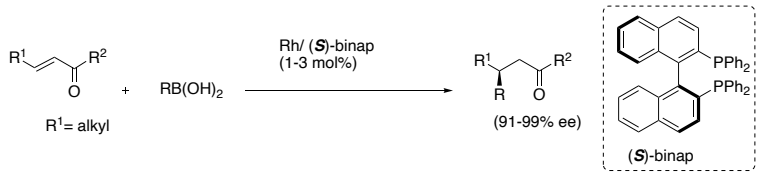


Figure 1.9. First enantioselective rhodium catalyst 1,4-conjugate addition

There are a few other examples of enantioselective conjugate addition reactions with cobalt and nickel based catalysts. These reactions also depend on organozinc nucleophiles instead of boron based nucleophiles. They are also typically limited in substrate and nucleophile scopes, so they are not as powerful of a reaction like the ruthenium or copper catalyzed conjugate addition reactions.

1.3 Conjugate Addition Mechanistic Studies

1.3.1 Early Work with Transition Metal Free and Lewis Acid Free 1,4–Conjugate Additions

Chong's group reported the first transition metal free and Lewis acid free enantioselective 1,4–conjugate addition reaction (Figure 1.10).[24] They were able to catalyze the conjugate addition with a BINOL-derived catalyst. During the C-C bond forming step, they were able to induce enantioselectivity in the product formation. They used boronic esters as the nucleophiles. Through testing various BINOL derivatives, their group found that if the 3 and 3' positions were electron withdrawing groups like iodine, the boron transesterification was facilitated (Figure 1.10). The electron withdrawing groups on the BINOL are most likely affording a more strongly binding "ate" complex formed between the boron and the carbonyl. The BINOL

derived catalysts were both efficient in promoting the enantioenriched product and they have a high turnover, so they are used in catalytic amounts.

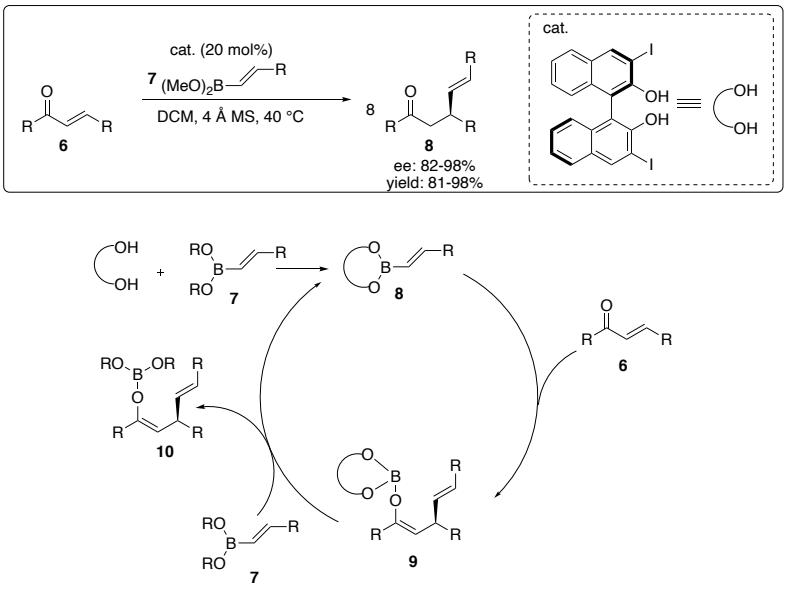


Figure 1.10. An early example of enantioselective organocatalyzed conjugate addition and mechanism

There were a few limitations to this work. First, only alkenyl organoboronates were used as nucleophiles; no alkyl, aryl, or heteroaryl organoboronates were used. The reaction was also slow to complete, with reaction times reported up to about 96 h depending on the nucleophile. However, these reaction conditions were promising since they were fairly mild and were transition metal free. Mild conditions are often sought after for highly complex compounds such as natural products.

1.3.2 May Lab Mechanistic Insights

A mechanism for BINOL-catalyzed conjugate addition reactions with organoboronates was first proposed by Chong.[24,25] Then, Pellegrinet and Goodman worked with DFT calculations to improve the mechanistic understanding.[26–28]

Following all this mechanistic insight, the May group published mechanistic experiements.[29] The 1,4–conjugate addition mechanism starts with the boronate ester **13** forming with the diol of the BINOL-derived catalyst. When the BINOL has electron withdrawing groups in the 3 and 3' locations (the R group), the reactivity is increased because the more electron deficient catalytic complex is able to more tightly bind to the carbonyl of the starting enone. The rate determining step has been proposed to be the C-C bond forming step to get **17**. The stabilization of the developing positive charge by electron donating group would increase stability in the transition state thus lowering the transition state energy which would increase the rate. By contrast, if there was electron withdrawing group then the rate would be decreased. Hammett plot analysis in the May Group confirmed this hypothesis.

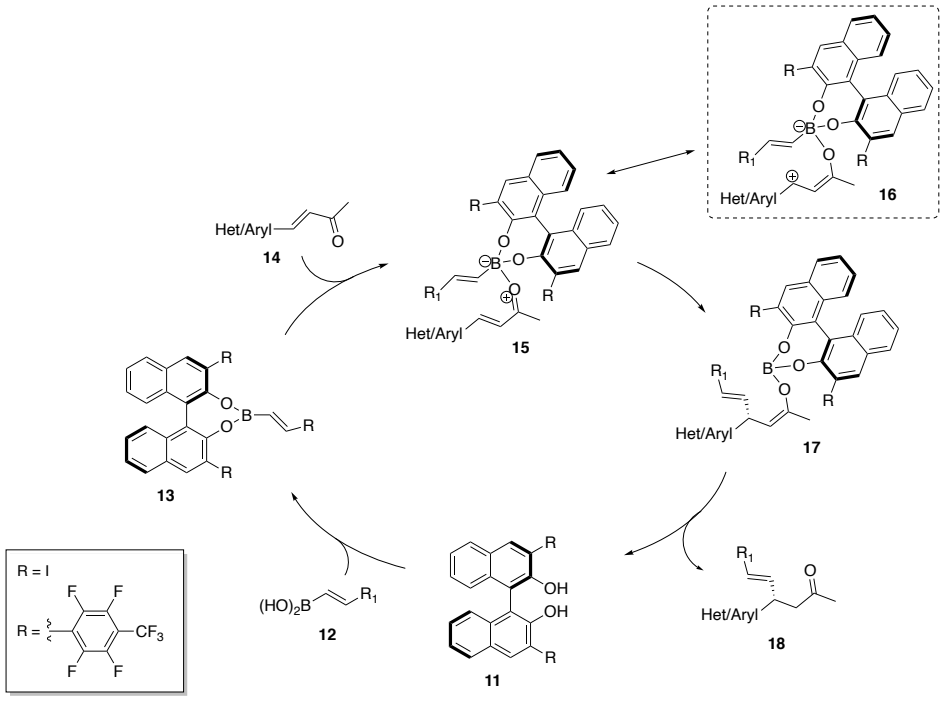


Figure 1.11. Proposed catalytic cycle

1.3.3 Reactivity Trends

In 2015, the May lab looked at reaction rates for the enantioselective conjugate addition with BINOL derived catalyst for the 1,4–conjugate addition reactions with aryl enones.[29] With an electron donating group as X on the aryl ring, **18**, para to the enone, the reactivity is accelerated. If an electron withdrawing group was the X attached to the aryl ring, **18**, then the reaction rate was decelerated. This is unusual since one would predict that substrates with electron donating groups would be less electrophilic. Instead, the effects of rate acceleration are likely related to the cationic charge that is developed in this reaction being stabilized at the benzylic position (Figure 1.12).

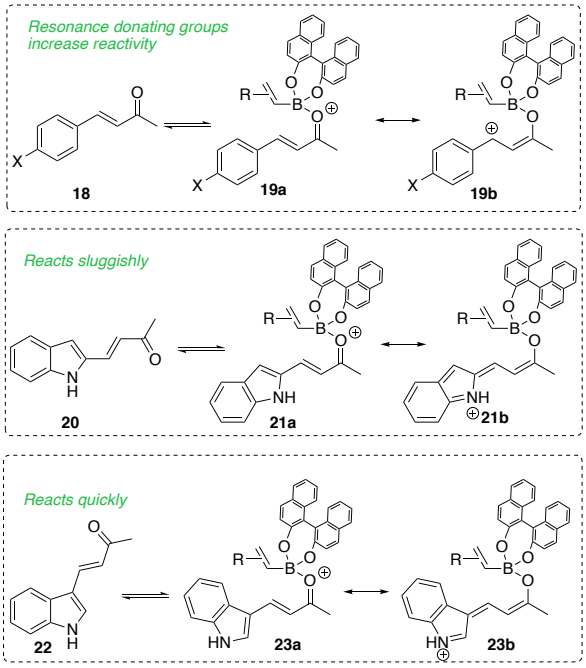


Figure 1.12. May lab mechanistic studies

Now with this insight from these aryl substrates, one would expect that the 3-indole enone **20** to react quicker and the 2-indole enone **22** to react slower. This trend

is confirmed in the Hammett Plot studies. In order for the 2-indole enone to stabilize the cationic charge, the aromaticity of the indole has to be broken. Thus the reaction reacts quickly with the 3-indole enone since the charge can be stabilized without breaking the aromaticity of the indole ring.

1.4 Pyrrole Reactivity

1.4.1 Pyrrole Reactivity Issues

Pyrroles motif have a wide number of applications. Pyrroles are in polymers, natural products, and also pharmaceuticals. Although extremely useful motifs, they are not easy to handle.

Pyrrole itself is a colorless liquid that grows darker in color when exposed to air and it polymerizes when exposed to light. Pyrroles have a lower basicity than amines or pyridines since the lone pair of electrons on nitrogen are delocalized. Pyrroles are very electron rich, which makes them more easily oxidized, even with just atmospheric oxygen. If an electron withdrawing group is added to the ring though, the ring becomes less electron rich and less prone to oxidation. If an electron donating group is added to the ring, the pyrrole becomes even more suspectable to oxidation. The NH and CH protons of pyrrole are somewhat acidic in nature, and when deprotonated with a strong base the pyrrole ring becomes more nucleophilic. Pyrroles are susceptible to electrophile attack. They also can react with countless biomolecules through hydrogen bonding and $\pi - \pi$ stacking. [2]

To combat light-promoted decomposition in synthesis, reaction vessels with pyrroles are covered in aluminum foil to shield them from ambient light. And if being oxygen and light sensitive was not enough, pyrroles are also acid sensitive. In the

presence of acid pyrroles polymerize. The benzannulated counterpart, the indole, is often much more stable because of the stabilizing effects of the aromatic ring fused to pyrrole core. With the added stabilization, indoles tend not to be as light, oxygen, or acid sensitive as the pyrroles.

1.4.2 Potential Side Reactions

The Temelli group developed a copper catalyzed regioselective Friedel-Crafts alkylation of pyrroles (Figure 1.13).[30] Once the alkylation occurred, they could simply do a solvent switch to carbon tetrachloride and heat the reaction mixture to 75 °C. After heating, an intramolecular self-cyclization could occur. The alkylated pyrrole had complete conversion to the hemiacetal **27**. This is evidence for how reactive and nucleophilic the nitrogen of the pyrrole can be, and how easy it is for the pyrrole to react.

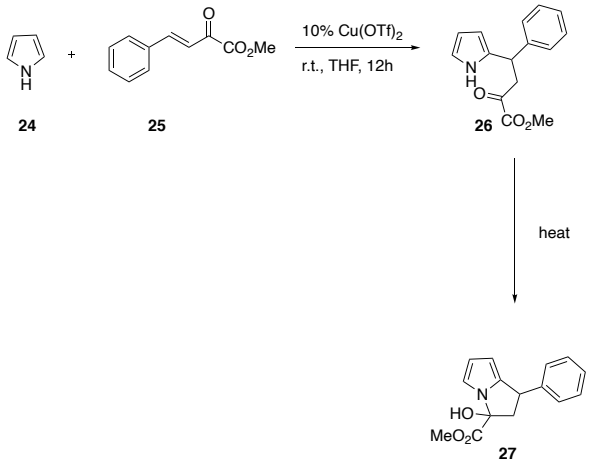


Figure 1.13. Temelli addition reaction

1.4.3 Substitution Trends for Pyrrole

In 2018, the Qui group published an intramolecular Friedel-Craft reaction that was catalyzed by a chiral Brønsted acid to produce six membered spirooxindoles.[31]

Their yields were relativity high for most of the substrates (up to 99%) even when they changed the substituent groups on the aryl ring of the isatin **28** (Figure 1.14). However, when the substituents were changed on the pyrrole of the isatin, they saw that as each substituent was added, the reactivity went down and the yield decreased correspondingly (Figure 1.14, **31-33**). They also observed that the regioselectivity of the reaction decreased significantly. They attribute this poor regioselectivity to be a result of steric hinderance between the chiral phosphoric acid catalyst and the methyl or ethyl substituents. They hypothesized that the low yields are a result of steric hinderance in the proximity of the reactive site as well.

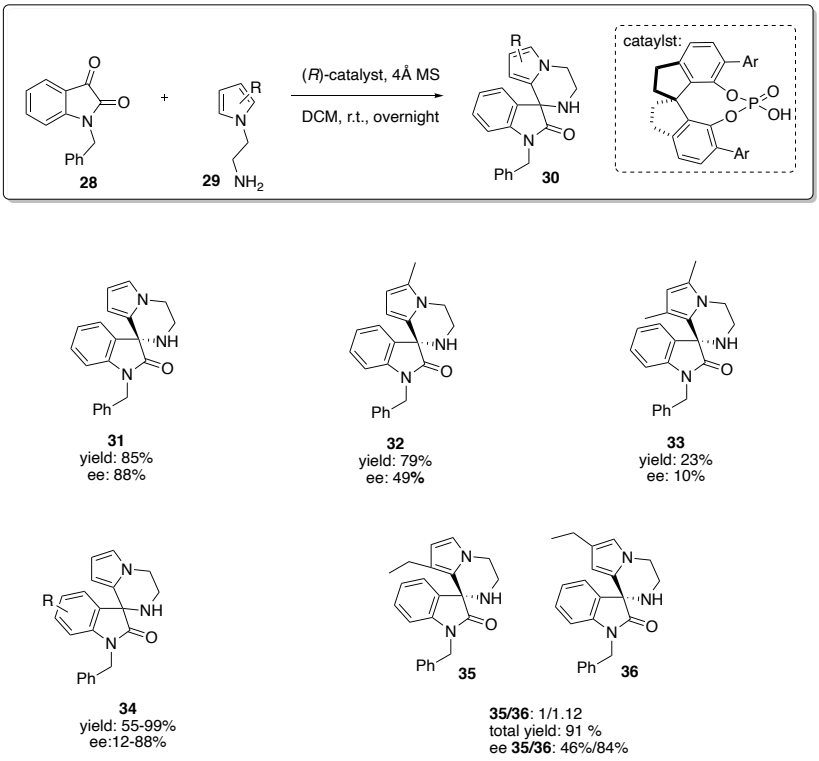


Figure 1.14. Select examples of acid catalyzed asymmetric intramolecular Friedel-Craft reaction

1.5 Conclusion

1,4–Conjugate addition reactions are powerful C–C bond forming reactions. The ability to utilize this reaction on difficult nitrogen bearing heterocycles enones has the potential to help access a variety of complex. Despite the reactive natural of pyrroles motifs they have had valuable applications in the pharmaceutical industry. The study of pyrroles and enantioselective reactions is particularly important, and ability to overcome difficult reactivity issues associated with pyrroles hopefully will lead the ability to access new compounds.

CHAPTER 2: 1,4 CONJUGATE ADDITION WITH PYRROLES AND INDOLES[32]

2.1 Identifying Effective Reaction Conditions

The use of boronate esters and boronic acids as nucleophiles in conjugate additions to enones dates to Suzuki.[33–38] More recent efforts have led to transition metal-catalyzed and organocatalyzed enantioselective versions of this reaction . For the latter cases, examples exist of BINOL-based ligands pioneered by Chong [39–42], α-hydroxy acids reported by Sugiura [43–45,27], and thiourea catalysts from Takemoto.[46] Those reports, however, have primarily dealt with aryl-substituted stereocenter formation, and so they offered little information on how to address heterocycle incorporation and the problematic 2-indole and 2-pyrrole substrates.

The β-indolyl- and β-pyrroyl-enone substrates have historically been problematic substrates. The β-indolyl-enones have deficient reactivity and the β-pyrroyl-enones have hyper reactivity. The goal of this project is maximize the amount of conjugate addition product produced for these difficult substrates.

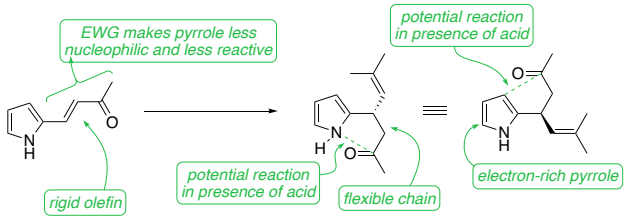


Figure 2.1. β- pyrroyl-enone problems

2.1.1 Synthesis of Catalyst and Starting Materials

Most of the enone substrates are able to be synthesized directly from commercially available starting materials. The pyrrole and indole enones are

synthesized using a classic Wittig reaction with a ketone and an ylide, and the yields are generally high and selective for the *trans*-alkene enone.

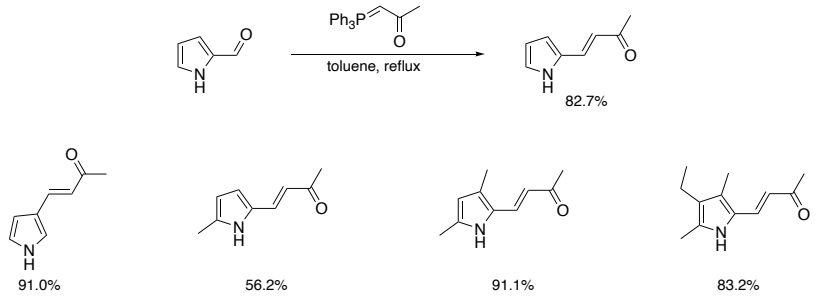


Figure 2.2. Pyrrole Wittig reaction

The catalyst can be made in a 3 step synthesis. Starting with BINOL, the MOM protecting group is used to protect the diols. After protection, *n*-Buli is used to lithiate the 3 and 3' positions and then incorporate iodine. Which is then followed by a deprotection to yield the active electron deficient catalyst.

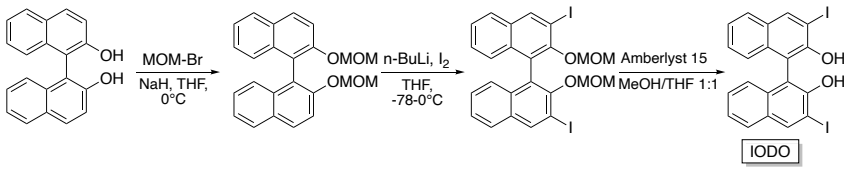


Figure 2.3. BINOL derivated catalyst synthesis

2.2 Results

2.2.1 Reaction Rates

In looking at data collected from the many heteroaromatic substrates that our group has examined, patterns emerged for how the point of enone attachment on furan, pyridine, and imidazole rings affected the reaction rate (Figure 2.1). In the furanyl enone **1**, where the enone is attached at the furan 2-position, the conjugate addition reaction occurs in only 8 h while its counterpart, **2**, which is attached at the 3- position,

does not react completely until after 24 h. Pellegrinet and Goodman established that the initial step in the organocatalyzed conjugate addition mechanism is the formation of a discreet Lewis acid/base adduct between the enone and the catalyst ligated boronate ester. [26,28] One may draw equally viable resonance structures that stabilize the putative Lewis acid/base interaction for the 2- and 3-furan isomers (**8** and **9**, Figure 2.1). [26,28,47] Since the difference in reaction rates was not readily correlated to resonance stabilization, we considered the possibility that proximity to the furan oxygen played a role. Similarly, in β-pyridyl-enones, the reactivity does not correlate to any typical resonance effects in that the 2-pyridine and 4-pyridine substrates do not exhibit similar rates. Rather, the trend also appears correlated with the proximity of the heteroatom to the reacting site, with 2-pyridyl **3** being formed within 3 h and 4-pyridyl **5** taking 21 h for complete reaction. These rates again implicates inductive electronic effects. Recruitment of the Lewis acidic nucleophile by the pyridyl nitrogen in a similar manner to Takemoto's work cannot be fully ruled out, either. For the imidazole substrates **6** and **7**, similar resonance structures may be drawn for either isomer as seen for the furans, so resonance effects did not explain the reactivity difference. Again, having more nitrogens closer to the site of reactivity as seen in the 2-imidizole isomer gave a faster reaction than for the 4-imidazole isomer. Taken together, these substrates suggest that proximity to the inductively electron-withdrawing heteroatom in a heteroaromatic substituent accelerates this conjugate addition. They also exhibited high levels of enantioselectivity.

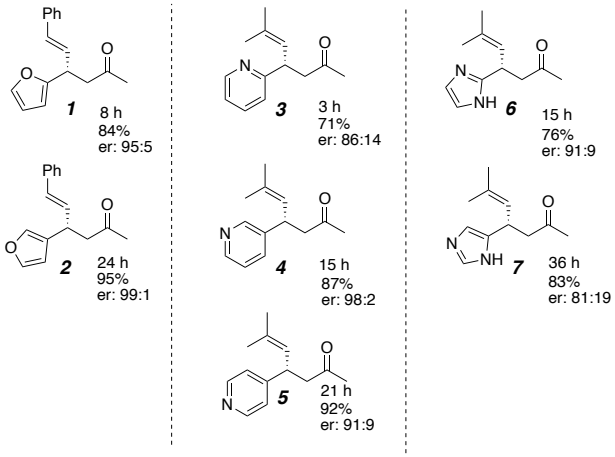


Figure 2.4. Reaction times for series of heteroaromatic substrates

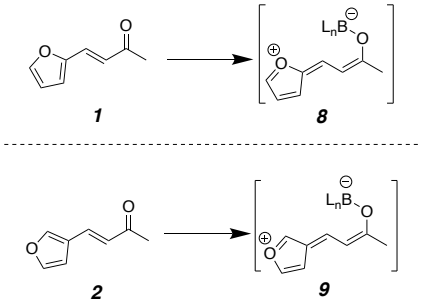


Figure 2.5. Resonance stabilization of Lewis Acid/Base interactions

2.2.2 Reaction Trends with Indoles

However, the trend described in the previous section is opposite that for the indole-substituted enones, where the high-performing 3-indole substrates bear the nitrogen further from the enone β-carbon than the poor-performing 2-indolo-enones (Figure 2.6). Moreover, inconsistent and unpredictable yields of the product of the latter, **11** were routinely obtained. An early explanation for the discrepancy was that the enone **10** has substitution at both the 2- and 3-positions, which would increase steric repulsion at the reactive site. However, control experiments with **12-15** in Figure 6 dispelled that notion since the indole with only 2 substitution worked similarly, **12**, to the indole with both substitution at the 2- and 3- positions, **13**. The inferior

reactivity of the enone **10** was clearly due to the indole position of substitution and therefore more likely to be due to the system's electronics. We reasoned that for these substrates, resonance effects might have played a larger role than the inductive effects seen in Figure 2.4. A relationship study for resonance effects and reaction rates using a Hammett plot analysis of aryl-substituted enones shed some mechanistic insight on what may have been occurring for the indole substrates. [48] In that study, a clear Hammett parameter correlation was seen for electron-donating substituents on the β-aromatic ring accelerating the reaction, which suggested that the stabilization of benzylic cationic charge in **17b** increased the reaction rate, likely because the formation of zwitterionic intermediate **17a** is necessary for the reaction (Figure 2.7). Whereas for the 2/3-furan and 2/4-imidazole substrates the resonance structures for charge stabilization were similar, those for the indoles **12** and **14** are quite different in relative energy because of the additional fused aromatic ring. The 3-indoloenone can stabilize charge with the resonance structure **19b**, which maintains the aromaticity in the fused benzene ring, but similar resonance stabilization in the 2-indoloenone **19b** would require the loss of aromaticity. This phenomenon is the reason behind the well-established Friedel-Crafts reactivity patterns seen for indoles, where electrophilic substitution preferentially occurs at the 3-position. To compensate for this energy difference, we proposed that we needed to make the 2-indoles more electron rich for the key Lewis acid/base interaction illustrated in **21a**.

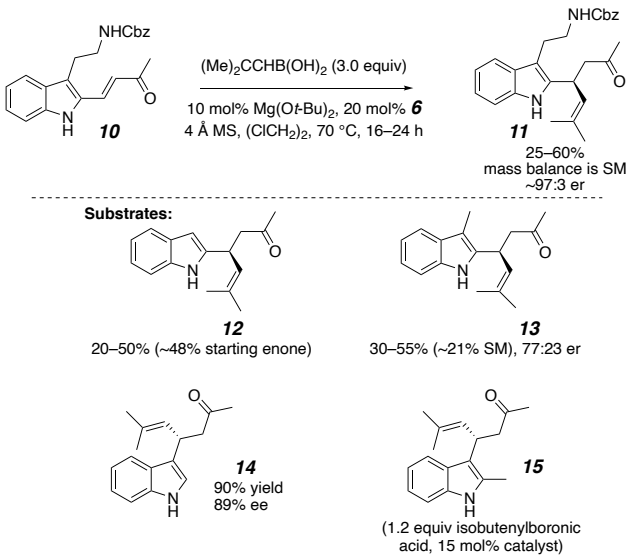


Figure 2.6. Indole control experiments

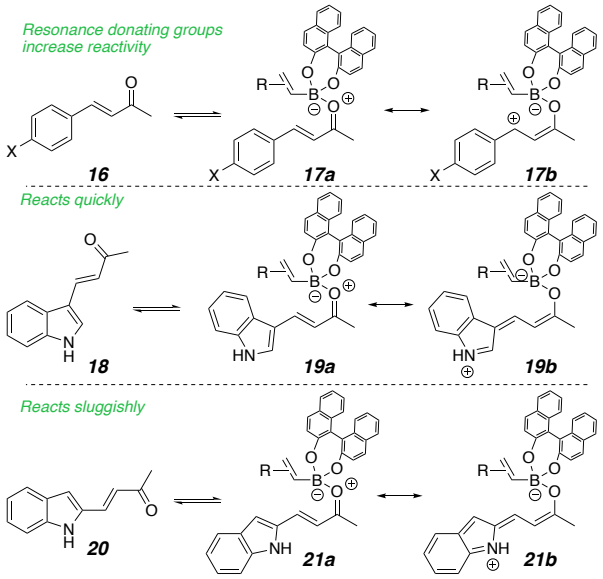


Figure 2.7. Stabilization of the Zwitterionic intermediate

2.2.3 Reaction Trends with Pyrroles

We also looked more closely at the problems with pyrrole substrates. Control experiments showed that the issues stemmed both from the high reactivity found in the starting materials and the even greater instability of the products. As evidence of the latter, when pure ketone **23** was reintroduced to the reaction conditions, it readily

decomposed. When the starting material alone was stirred with base and no other reactants, it also formed a new unstable product which could not be isolated or fully characterized. After the conjugate addition, the pyrrole in **23** is electron rich and nucleophilic, has no protecting group, and bears no steric blocking groups. Various side reactions were consequently seen, such as the pyrrole nitrogen attacking the ketone carbonyl to form a cyclized product that could be observed in the NMR of the crude reaction mixture but was not stable enough to isolate.[49,50] The Lewis acidic catalyst complex was thought to be promoting the side reactions, and so a less electron deficient BINOL catalyst was sought.

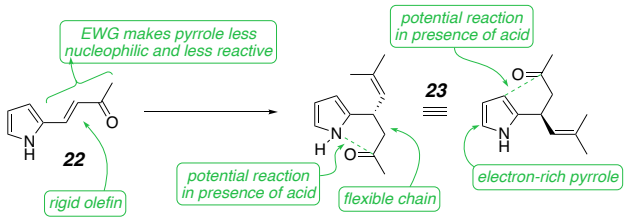


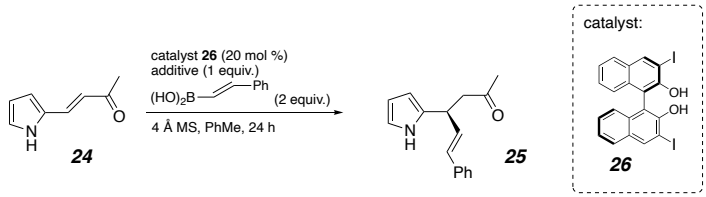
Figure 2.8. Pyrrole problems

2.2.4 Base Additive Hypothesis and Control Experiments

Initially, we thought that a base additive could deprotonate the hydrogen of the pyrrole or indole substituent, at least partially, which would result in greater electron density in the ring. [51,52] That electron density would stabilize benzylic cation development and activate the enone as in Figure 2.7. As a result, we evaluated a variety of bases to test this theory (Table 1). Note that in the original conditions reported for boronic acid nucleophiles (see Figures 2.2 and 2.3), Mg(*t*-BuO)$_2$ is used only in sufficient quantities to deprotonate the catalyst. Moreover, *t*-BuOH replicated its effects, suggesting that the additives function was most likely to serve as a proton transfer agent. The Mg

salt was usually slightly better, so metal coordination or pH adjustment may have played a role in those conditions. Regardless, Mg(*t*-BuO)$_2$ did not provide useful reactivity for 2-indole substrates (**12** and **13**, Figure 2.6). The carbonate bases generally outperformed the other bases in 24 h of reaction (entries **2–6**). More soluble bases, such as Cs_2CO_3 and Na_2CO_3, produced less of the conjugate addition product compared to a less soluble base, such as $(NH_4)_2CO_3$ (entries **3**–**6**). It usually took several h for the $(NH_4)_2CO_3$ to dissolve in the solution. Bases that were stronger also resulted in a significant decrease in yield (entry **8**, **9**, and **17**). Overall, the use of a full equivalent of the $(NH_4)_2CO_3$ and 3,3′-diiodo-BINOL **26** as a catalyst significantly addressed the deficient reactivity of the indole substrates and the hyper reactivity of the pyrrole compounds.

Table 1 Optimizations of additives with 2-pyrrolyl enone



Entry	Additive	Yield
1	$Mg(O\text{-}tBu)_2$	10.2%
2	$(NH_4)_2CO_3$	63.5%
3	K_2CO_3	53.0%
4	Cs_2CO_3	35.3%
5	Li_2CO_3	29.0%
6	Na_2CO_3	4.1%
7	K_3PO_4	34.4%
8	NaHMDS	12.7%
9	LiHMDS	5.9%
10	KOH	4.9%
11	NaOH	4.1%
12	KOtBu	4.0%
13	NaOtBu	2.9%
14	LiOtBu	0%
15	NH_4Cl	1.5%
16	NH_4HSO_4	0%
17	DBU	2.8%

2.2.5 Conjugation Addition Reaction on Pyrrole and Indole Substrates

Since $(NH_4)_2CO_3$ showed much better outcomes for the pyrrole substrate, we tested those conditions on a variety of indole and pyrrole appendid enones, which provided a variety of interesting results (Figure 2.6). We found that when we protected the unsubstituted 2-pyrrolyl-enone **35** we obtained nearly identical results as the unprotected version (**32**). This outcome invalidated our initial hypothesis for the role of a base in deprotonating an indole or pyrrole nitrogen. We also found that as more substituents were incorporated onto the pyrrole, the conjugate addition faltered (**36-**

39). That trend led us to consider other roles that the base might have been playing in reactivity as well as the nature of the problems associated with additional substituents.

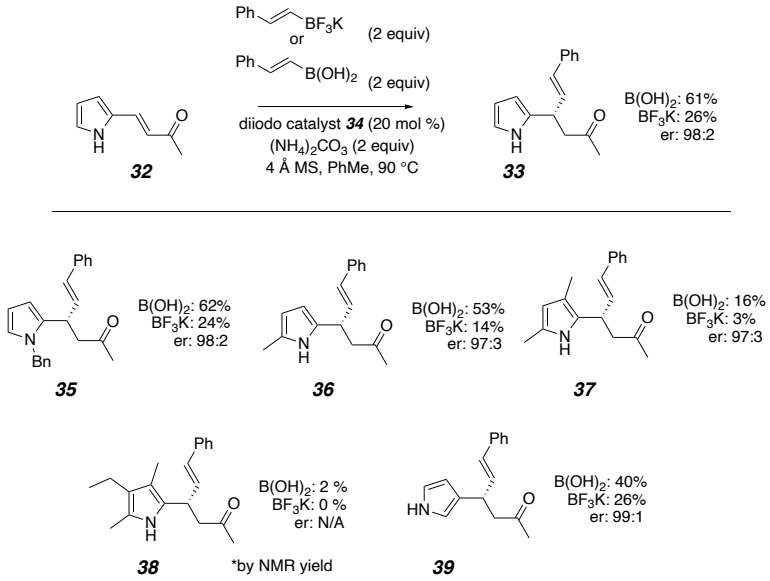


Figure 2.9. Pyrrole substrates

Based on Hammett Plot studies from our group[48], we would expect higher yields for the conjugate addition product for the more substituted pyrroles, since the pyrrole is then more electron rich, which typically results in faster reaction rates. We hypothesize that the lower yields are due to higher reactivity found in the products, which results in the products reacting further. In a control experiment, when the purified products were reintroduced into the reaction conditions, they correspondingly decomposed. Another indication of the reactivity of these substituted pyrrole substrates is that they decompose in ambient lighting more quickly than the unsubstituted starting material **32**. Due to this high reactivity, the most substituted products are not stable enough to be isolated in useful yield. Another possibility for lower yields of the conjugate addition products could be that the extra substituents are causing allylic strain-induced twisting between the ring and the enone, thus breaking

the conjugation and decreasing resonance donation into the enone. With an unactivated enone, the conjugate addition reaction would be less favored over alternative side reactions. Another possibility for decreased conjugate addition yields could be a result of sterics. As more substituents are added to the ring, especially at the 3-position of the pyrrole, greater steric interference could be inhibiting the conjugate addition reaction and allowing more time for side reactions and decomposition to occur. A similar trend with pyrroles has been observed by the Qiu group[53].

Another control experiment was stirring the pyrrolyl-enone with only $(NH_4)_2CO_3$ in toluene without light at 90 °C without a catalyst or organoboron nucleophile; this resulted in an unwanted reaction that produced a side product too unstable to isolate. This indicated to us that the base has both an advantageous effect on the conjugate addition and an adverse effect on the starting material stability, creating a conflicted system. In an effort to avoid starting material decomposition, we tried to premix the catalyst, organoboronate, and the base and then add the pyrrole dropwise, but it resulted in similarly low yields.

Typically, trifluoroborate salts work better in conjugate addition reactions because of their greater stability over their boronic acid counterparts[52,53]. Interestingly though, in all of the pyrrole substrates (Figure 2.6) and some of the indole substrates (Figure 2.7) the boronic acids resulted in higher yields than their trifluoroborate counterparts. These findings led us to believe the base, $(NH_4)_2CO_3$, could also be helping to promote boroxine formation from the boronic acid or maintain a favorable pKa for the conjugate addition reaction to occur.

For the indole substrates in Figure 2.7, $(NH_4)_2CO_3$ also improved the yield for the conjugate addition product. The unsubstituted indoles **30** and **42** resulted in moderate yields with both the boronic acid and trifluoroborate salt. The mono-substituted indoles **41** and **43** resulted in better yields when the trifluoroborate salt nucleophile was used than if the boronic acid was used. Both the pyrrole and indole products were formed with excellent enantioselectivity (Figure 2.6 and 2.7).

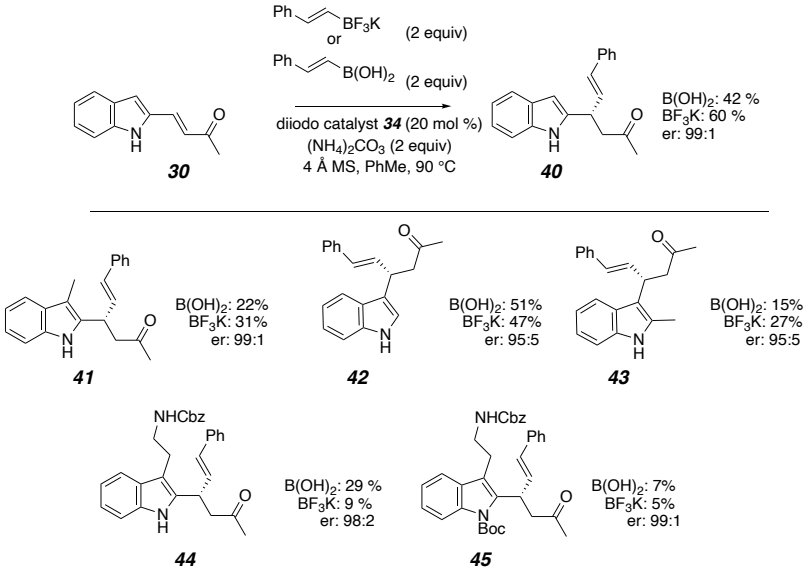


Figure 2.10. Indole substrates

A variety of alkenyl boronic acids also show compatibility with these reaction conditions with the problematic 2-pyrroyl-enone (Figure 2.8). In most cases, the products that were formed in fair to good yields show excellent enantioselectivity (**46-50)**.

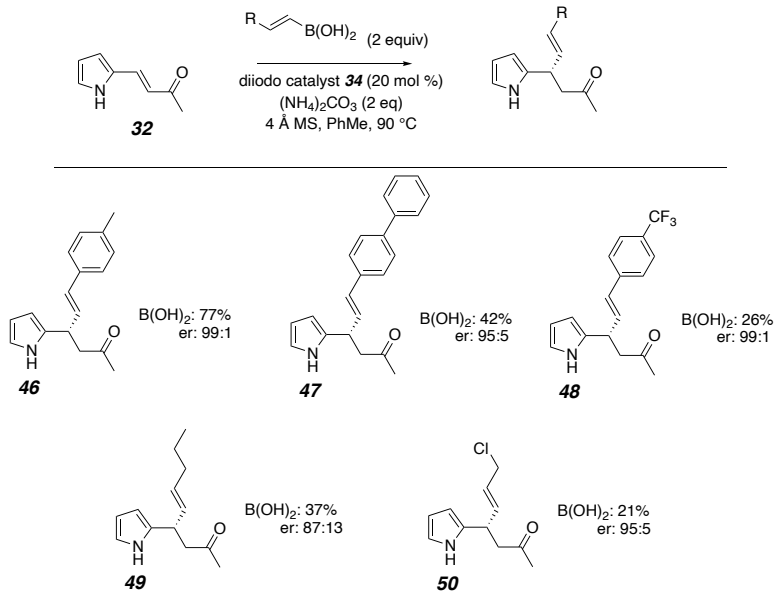


Figure 2.11. 2-pyrrolyl-enone with boronic acids

2.3 Conclusions

Two problematic series of substrates, β-(2-indole)-enones and β-(2-pyrrole)-enones, were thoroughly examined in the enantioselective organocatalyzed conjugate addition of alkenyl boronic acids or trifluoroborates. Analysis of isomer-related reaction rate trends showed that (1) proximity of a heteroatom to the enone β-carbon was favorable to reaction rate and (2) increased resonance electron donation also increased reaction rate. The use of $(NH_4)_2CO_3$ promoted the conjugate addition reaction better than Mg(O*t*-Bu)$_2$ or other additives. The use of a less electron deficient catalyst in conjunction with the new base minimized side product formation and provided the most advantageous environment for the conjugate addition to sensitive substrates to date.

2.4 Experimental Section

2.4.1 Materials and Methods

Commercially available compounds were purchased from Aldrich, Acros, Alfa Aesar, Ark Pharm, and Combi-block and were used without further purification. All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using Cambridge Soft ChemBioDraw Ultra 12.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with an SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-600, JEOL ECA-500 or ECX- 400P spectrometer using residual solvent peak as an internal standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR).

HPLC Columns for Separation of Enantiomers:

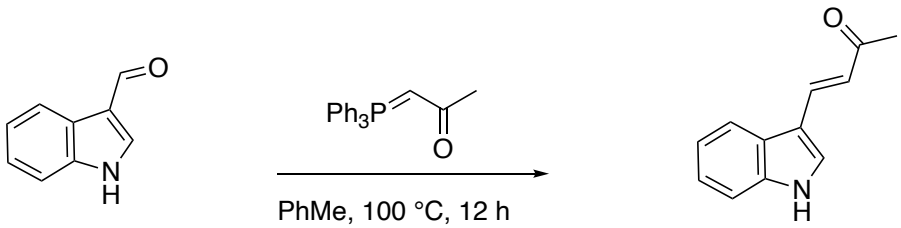
Chiralpak AY-3: Amylose tris-(5-chloro-2-methylphenylcarbamate) coated on 3 μm silica gel, Chiralpak AD-H: Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel, Chiralpak ID: Amylose tris-(3-chlorophenylcarbamate) immobilized on 5 μm silica gel, Chiralcel OJ-H: Cellulose tris-(4-methylbenzoate) coated on 5 μm silica gel, Chiralcel OD-H: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on 5

μm silica gel, Chiralpak AS-H: Amylose tris-[(S)-α-methylbenzylcarbamate) coated on 5 μm silica gel

2.4.2 General Procedure for the Synthesis of Starting Materials (enone)

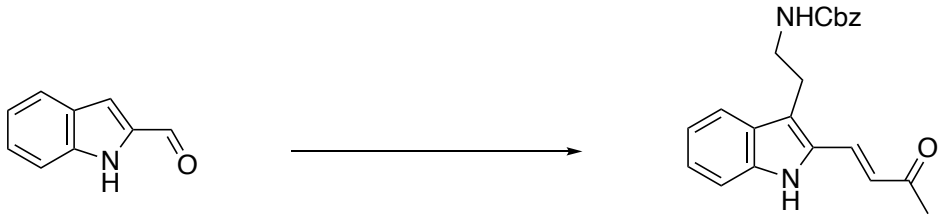
To a flask equipped with a stir bar and a condenser was added carboxaldehyde (2 mmol), 1-(triphenylphosphoranylidene)-2-propanone (1.2 equiv, 764 mg), and toluene (4 ml). The reaction mixture was refluxed for 10 h. After completion, the reaction mixture was concentrated via rotary evaporation. The crude mixture was purified via flash column chromatography with an appropriate eluent on silica gel.

(E)-4-(1H-indol-3-yl)but-3-en-2-one



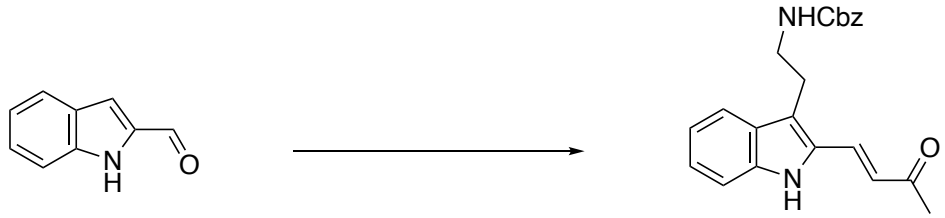
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

benzyl (S,E)-(2-(2-(5-oxo-1-phenylhex-1-en-3-yl)-1H-indol-3-yl)ethyl)carbamate



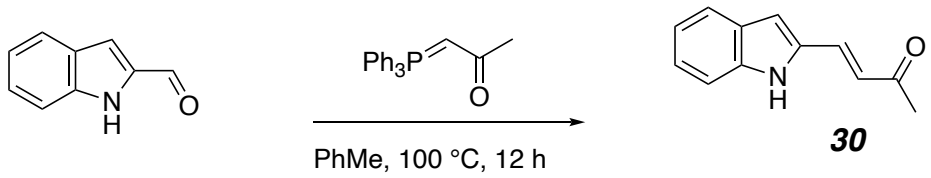
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

Benzyl (E)-(2-(2-(3-oxobut-1-en-1-yl)-1H-indol-3-yl)ethyl)carbamate



The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

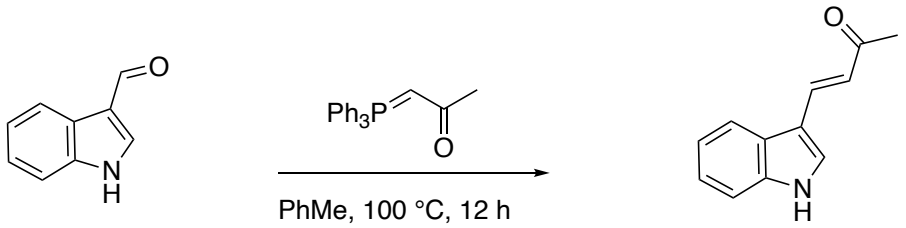
(E)-4-(1H-indol-2-yl)but-3-en-2-one



30

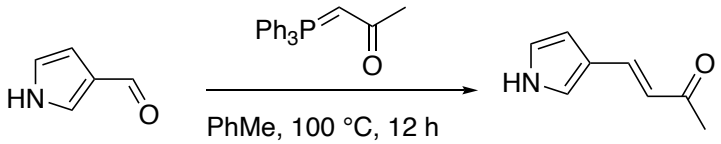
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

(S,E)-4-(1H-indol-3-yl)-6-phenylhex-5-en-2-one



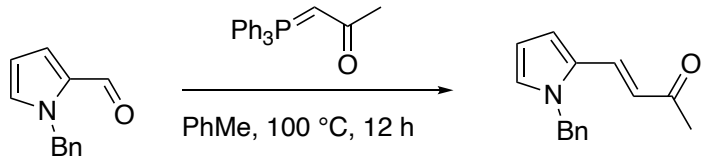
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

(E)-4-(1H-pyrrol-3-yl)but-3-en-2-one



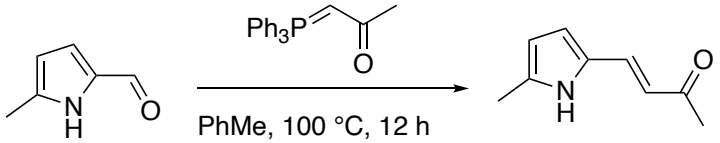
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-30% Ethyl acetate/Hexane and obtained as a white solid. All spectral data were identical to those reported in literature.

(E)-4-(1-benzyl-1H-pyrrol-2-yl)but-3-en-2-one



The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-20% Ethyl acetate/Hexane and obtained as a pale yellow solid. All spectral data were identical to those reported in literature.

(E)-4-(5-methyl-1H-pyrrol-2-yl)but-3-en-2-one



See the general procedure for enone formation above, in addition the reaction was shielded from light by covering reaction and product with aluminum foil. The product will decompose in prolonged exposure to light. 1g of 5-methyl-1*H*-pyrrole-2-carbaldehyde was used. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel. Yield: 56%.

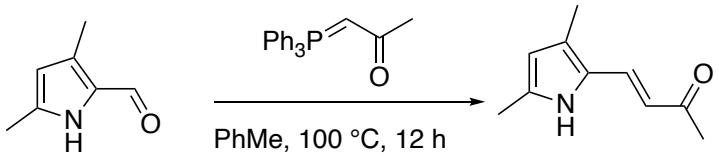
^{1}H-NMR (600 MHz, Benzene-D6) δ 7.18 (s, 2H), 6.39 (s, 1H), 6.34 (s, 1H), 5.93 (s, 1H), 1.96 (s, 3H), 1.33(s, 3H).

^{13}C-NMR (126 MHz, chloroform-d) δ 198.6, 133.6, 121.4, 119.1, 117.6 113.3, 110.8, 110.0, 31.3, 13.9

IR(neat): 3283, 1613, 1560, 1477, 1423, 1358, 1263, 959, 764, 700, 489 cm^{-1}

HRMS-ESI *m*/*z* Calculated for $C_9H_{11}NO$ $[M + H]^+$ 150.0913, found 150.0916.

(E)-4-(3,5-dimethyl-1H-pyrrol-2-yl)but-3-en-2-one



See the general procedure for enone formation above, in addition the reaction was shielded from light by covering reaction and product with aluminum foil. The product will decompose in prolonged exposure to light. 1 g of 3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde was used. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel. Yield: 70%

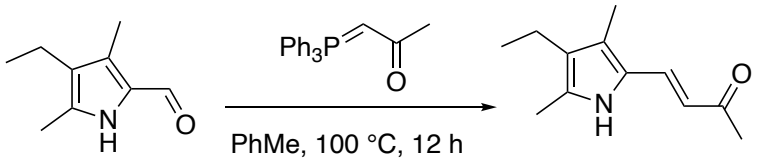
^{1}H-NMR (400 MHz, chloroform-D) δ 8.53 (s, 1H), 7.41 (d, J = 15.6 Hz, 1H), 6.16 (d, J = 16.0 Hz, 1H), 5.89 (d, J = 17.8 Hz, 1H), 2.29 (d, J = 11.2 Hz, 6H), 2.18 (s, 3H), 1.80 (s, 2H)

^{13}C-NMR (101 MHz, chloroform-D) δ 198.4, 131.1, 130.6, 127.2, 112.3, 111.2, 31.1, 13.8, 13.5, 11.5

IR (neat): 3292, 3246, 1600, 1559, 1433, 1358, 1258, 953, 839, 785, 711, 668 cm^{-1}

HRMS-ESI *m/z* Calculated for $C_{10}H_{13}NO$ $[M + Na]^+$ 290.1515, found 290.1525.

(E)-4-(4-ethyl-3,5-dimethyl-1H-pyrrol-2-yl)but-3-en-2-one

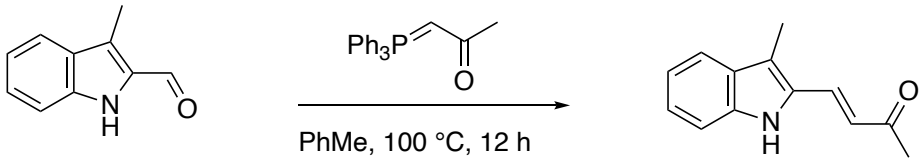


See the general procedure for enone formation above, in addition the reaction was shielded from light by covering reaction and product with aluminum foil. The product will decompose in prolonged exposure to light. 1 g of 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde was used. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel. Yield: 55%

IR(neat): 3254, 2961, 2912, 2855, 1612, 1570, 1444, 1253, 950 cm^{-1}.

HRMS-ESI *m/z* Calculated for $C_{12}H_{17}NO$ $[M + H]^+$ 192.1383, found 192.1386

(E)-4-(3-methyl-1H-indol-2-yl)but-3-en-2-one



A mixture of 3-methyl-1H-indole-2-carbaldehyde (0.1 mmol), but-3-yn-2-one (0.15 mmol), and $Sc(OTf)_3$ (10 mol%) in MeCN (0.5 mL) was stirred at 21 °C for the appropriate time. After complete conversion, as indicated by TLC, the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography with a 5 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

^{1}H NMR (500 MHz, chloroform-D): δ 8.60 (brs, NH), 7.66 (d, J = 16.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H) 7.29 – 7.25 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.50 (d, J = 16.5 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (125 MHz, chloroform-D): δ 198.1, 137.7, 131.1, 129.9, 129.0, 125.4, 122.8, 119.9, 119.9, 119.9, 111.1, 27.4, 9.0.

IR(neat): 3299, 1634, 1598, 1257, 1235, 953, 747, 622, 459 cm^{-1}.

HRMS-ESI *m/z* Calculated for $C_{13}H_{13}NO$ $[M + H]^+$ 200.1070, found 200.1072

2.4.3 Procedure for Boronic Acid Synthesis: 2-methylprop-1-enylboronic acid

To a 250 ml-flask was added LiCl (1.008 g, 24 mmol, 1.2 equiv) and the flask was flamed-dried under high vacuum. The flask was then back-filled with Argon. 0.5 M 2-Methyl-1- propenyl magnesium bromide in THF (40 mL, 20 mmol, 1.0 equiv) and Et_2O (50ml) were added. The solution was cooled to -78 °C. Trimethyl borate (2.5 mL, 22 mmol, 1.1 equiv) was added dropwise and the reaction was allowed to slowly warm to room temperature and stir overnight. The next day it was quenched with 1 M HCl (30 ml) until the reaction mixture became clear and then stirred for 1 h. It was then extracted with Et_2O (3 times), and washed with sat. aqueous $NaHCO_3$ and Brine solution. The organic layer was dried with Na_2SO_4 and then concentrated via rotary evaporation. The crude solid was purified via column chromatography with a 20-30% gradient of ethyl acetate in hexanes as eluent on silica gel to afford a white solid (1.105 g, 11.06 mmol, 55% yield). All spectral properties were identical to those reported in the literature.

2.4.4 General Procedure for 1,4–Conjugate Addition ($Mg(t\text{-}BuO)_2$ as an additive)

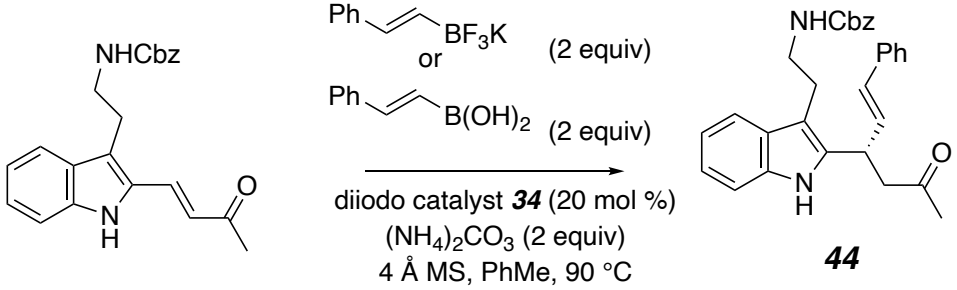
To a flask equipped with a stir bar and a condenser was added 4 Å powdered molecular sieves (100mg) and the flask was flamed-dried under high vacuum. The flask was then back- filled with Argon. The heterocycle-appended enone (0.2 mmol, 1.0 equiv), $Mg(t\text{-}BuO)_2$ (3.4 mg, 0.02 mmol, 0.1 equiv), boronic acid (3 equiv), and BINOL catalyst (0.04 mmol, 0.2 equiv) were then added. Freshly dried toluene (4 mL) was added and the reaction was heated to reflux in a 70 – 78 °C oil bath and allowed to stir at this temperature (see each product for specific reaction times). After completion, methanol was added and the reaction mixture was concentrated via rotary

evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with appropriate eluents. All spectral properties.

2.4.5 General Procedure for 1,4–Conjugate Addition ($(NH_4)_2CO_3$ as an additive)

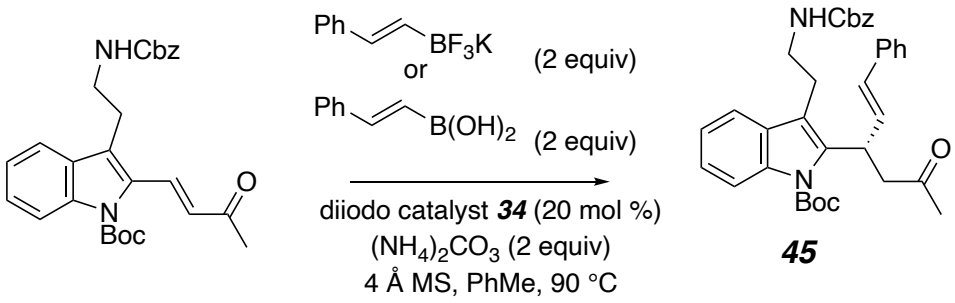
To a flask equipped with a stir bar and a condenser was added 4 Å powdered molecular sieves (100 mg) and the flask was flamed-dried under high vacuum. The flask was then back- filled with Argon. The heterocycle-appended enone (0.2 mmol, 1.0 equiv), $(NH_4)_2CO_3$ (38 mg, 0.4 mmol, 2.0 equiv), boronic acid (2 equiv), and BINOL catalyst (0.04 mmol, 0.2 equiv) were then added. Freshly dried toluene (4 mL) was added and the reaction was heated to 90 °C in an oil bath and allowed to stir at this temperature for 24 h. After completion the reaction mixture was concentrated via rotary evaporation. The crude reaction mixture was then dry-loaded onto silica gel and purified via flash column chromatography on silica gel with eluents of 10-30% ethyl acetate in hexanes.

benzyl (S,E)-(2-(2-(5-oxo-1-phenylhex-1-en-3-yl)-1H-indol-3-yl)ethyl)carbamate



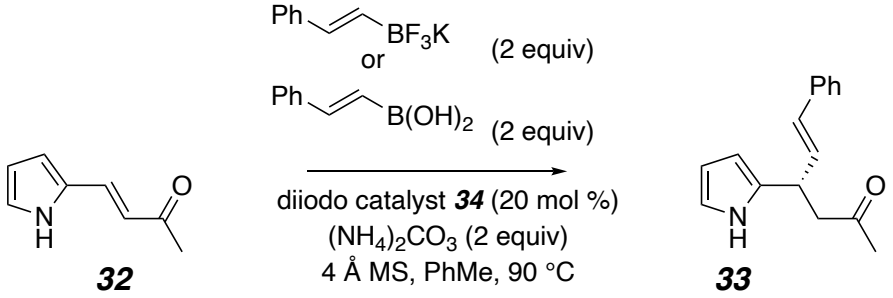
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-20% ethyl acetate/hexane. All spectral data were identical to those reported in literature.

tert-butyl(S,E)-3-(2-(((benzyloxy)carbonyl)amino)ethyl)-2-(5-oxo-1-phenylhex-1-en-3-yl)-1H-indole-1- carboxylate



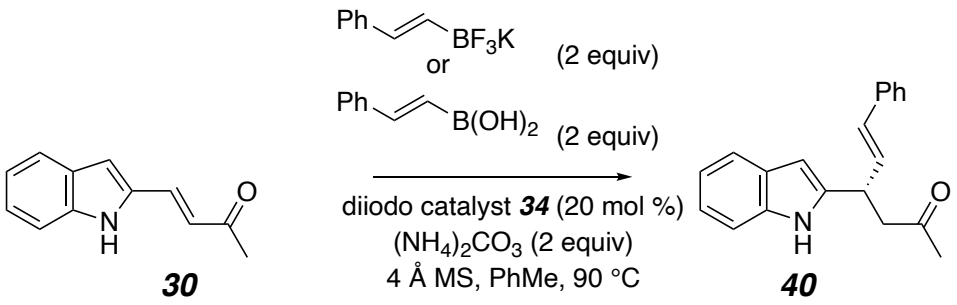
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-20% ethyl acetate/hexane. All spectral data were identical to those reported in literature.

(S,E)-6-phenyl-4-(1H-pyrrol-2-yl)hex-5-en-2-one



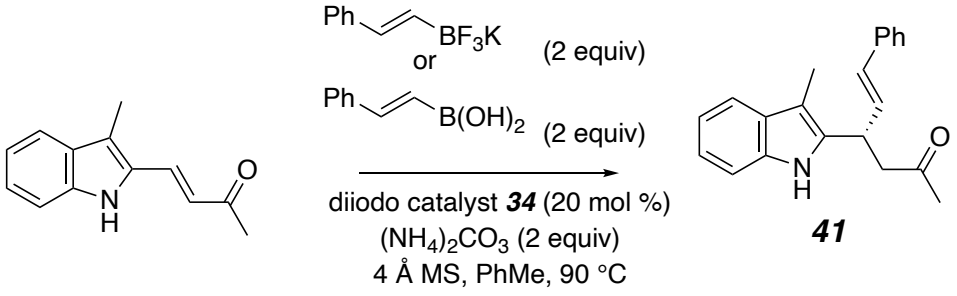
The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-20% ethyl acetate/hexane. All spectral data were identical to those reported in literature.

(S,E)-4-(1H-indol-2-yl)-6-phenylhex-5-en-2-one



The title compound was synthesized following a procedure reported in literature. The title compound was purified by silica gel column chromatography using 10-20% ethyl acetate/hexane. All spectral data were identical to those reported in literature.

(S,E)-4-(3-methyl-1H-indol-2-yl)-6-phenylhex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

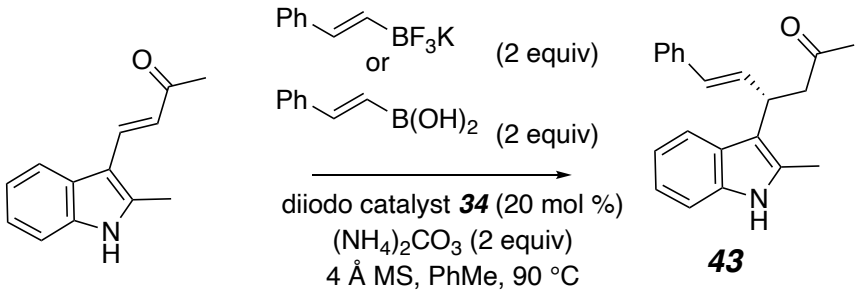
^{1}H-NMR (500 MHz, chloroform-D) δ 8.31 (s, 1H), 7.67 (d, J = 16.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.35-7.27 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 3.50 (s, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 1.36-1.25 (m, 1H)

^{13}C-NMR (101 MHz, chloroform-D) δ 184.5, 138.9, 128.6, 128.4, 127.6, 126.5, 125.8, 124.9, 124.3, 122.9, 121.2, 110.6, 108.7, 74.5, 35.5, 19.0, 13.3

IR(neat): 3090, 3070, 3035, 1477, 1034, 669 cm^{-1}.

HRMS-ESI *m/z* Calculated for $C_{21}H_{21}NO$ $[M + Na]^+$ 326.1515, found 326.1518.

(S,E)-4-(2-methyl-1H-indol-3-yl)-6-phenylhex-5-en-2-one



43

See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

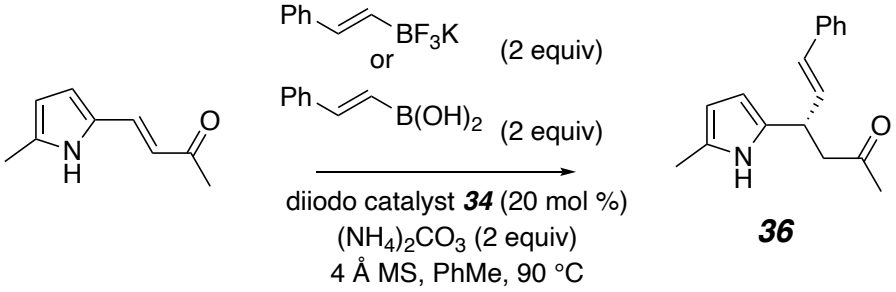
^{1}H-NMR (400 MHz, chloroform-D) δ 7.79 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 6.6 Hz, 3H), 7.18-7.03 (m, 3H), 6.56-6.36 (m, 2H), 4.35 (t, J = 6.5 Hz, 1H), 3.20-3.04 (m, 2H), 2.45 (s, 3H), 2.02 (s, 3H).

^{13}C-NMR (101 MHz, chloroform-D) δ 208.0, 135.5, 132.2, 129.3, 128.5, 128.4, 127.1, 126.3, 121.0, 119.3, 119.2, 110.6, 48.2, 35.1, 30.9, 12.2.

IR(neat): 3091, 3071, 3035, 1477, 1035, 668 cm^{-1}.

HRMS-ESI m/z Calculated for $C_{21}H_{21}NO$ [M + H]$^+$ 326.1515, found 326.1520.

(S,E)-4-(5-methyl-1H-pyrrol-2-yl)-6-phenylhex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

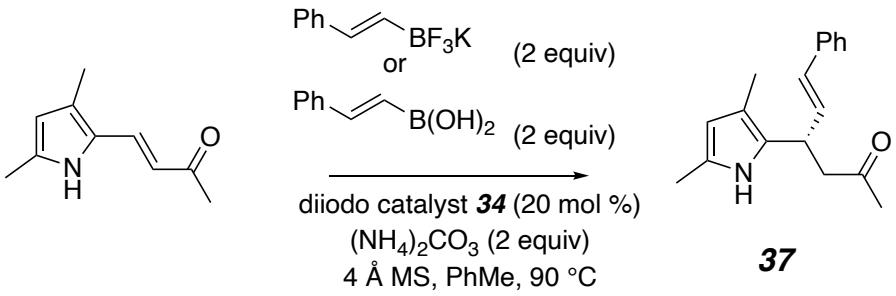
^{1}H-NMR (400 MHz, chloroform-D) δ 8.04 (s, 1H), 7.36-7.28 (m, 4H), 7.23 (d, J = 6.6 Hz, 1H), 6.48 (d, J = 16.2 Hz, 1H), 6.30 (q, J = 7.9 Hz, 1H), 5.78 (d, J = 11.4 Hz, 2H), 4.05-4.01 (m, 1H), 3.03-2.89 (m, 2H), 2.22 (s, 3H), 2.17 (s, 3H)

^{13}C-NMR (101 MHz, chloroform-D) δ 208.2, 131.8, 130.8, 130.5, 128.7, 128.4, 127.6, 127.3, 126.4, 105.7, 104.7, 48.9, 37.0, 30.8, 13.1.

IR(neat): 3090, 3070, 3035, 1959, 1814, 1477, 1034, 668 cm^{-1}.

HRMS-ESI m/z Calculated for $C_{17}H_{19}NO$ [M + Na]$^+$ 276.1359, found 276.1358.

(S,E)-4-(3,5-dimethyl-1H-pyrrol-2-yl)-6-phenylhex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

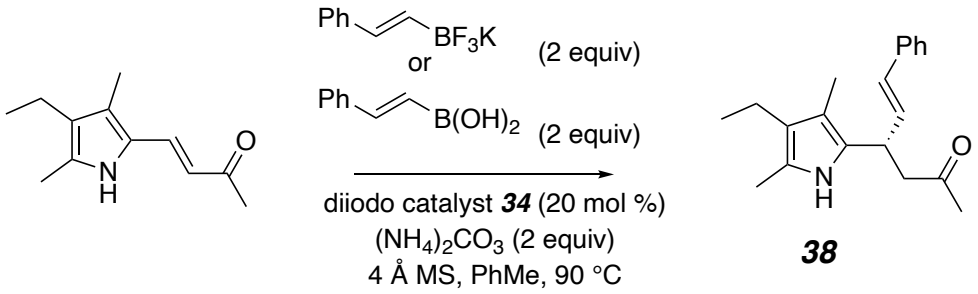
^{1}H-NMR (400 MHz, chloroform-D) δ 7.86 (s, 1H), 7.36-7.28 (m, 5H), 7.22-7.18 (m, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.65 (s, 1H), 4.07 (dd, J = 11.5, 6.3 Hz, 1H), 2.94 (d, J = 6.4 Hz, 2H), 2.19 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H).

^{13}C-NMR (101 MHz, chloroform-D) δ 208.2, 137.1, 130.8, 129.7, 128.6, 127.4, 126.3, 126.0, 114.6, 108.2, 48.5, 35.5, 30.7, 29.8, 13.1, 11.2

IR(neat): 3090, 3070, 3035, 1959, 1814, 1477, 1034, 668 cm^{-1}.

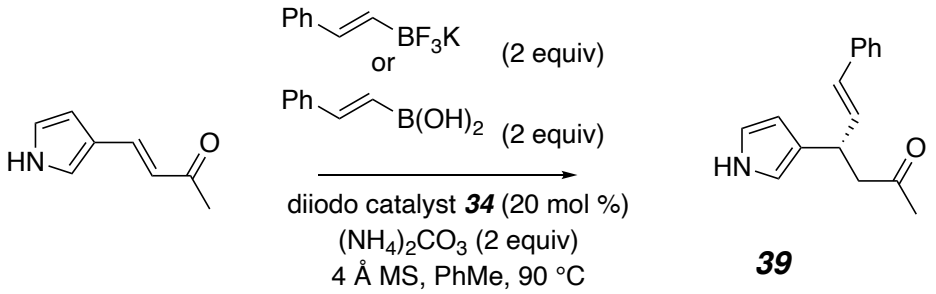
HRMS-ESI m/z Calculated for $C_{18}H_{21}NO$ $[M + Na]^+$ 290.1515, found 290.1525.

(S,E)-4-(4-ethyl-3,5-dimethyl-1H-pyrrol-2-yl)-6-phenylhex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture could not be purified, so an NMR standard, 4-methylnitrobenzoate, was used to obtain the yield. All reactants were added to the reaction mixture along with 0.1 mmol of 4-methylnitrobenzoate. The aryl peaks for the 4-methylnitrobenzoate were compared with the typical quartet around 4.0-4.4 ppm indicating that the beta-bond formed during the conjugate addition reaction.

(S,E)-6-phenyl-4-(1H-pyrrol-3-yl)hex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 30% gradient of ethyl acetate in hexanes as eluent on silica gel.

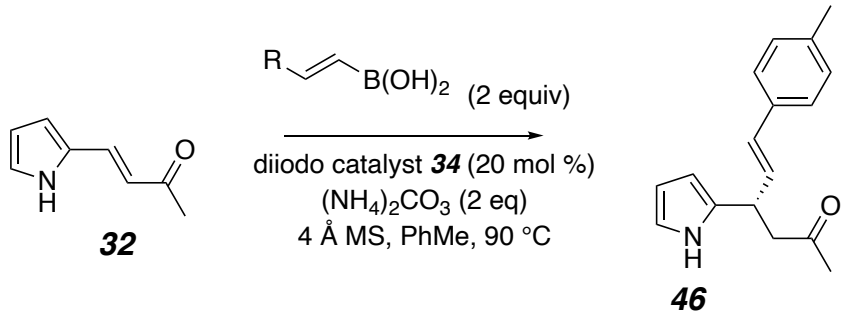
^{1}HNMR (500 MHz, chloroform-D) δ 8.08 (s, 1H), 7.34 (d, J = 7.4 Hz, 2H), 7.28 (d, J = 7.4 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 6.75 (s, 1H), 6.62 (s, 1H), 6.42 (d, J = 15.5 Hz, 1H), 6.30 (q, J = 7.8 Hz, 1H), 6.13 (s, 1H), 4.03 (q, J = 7.3 Hz, 1H), 2.86 (qd, J = 15.8, 7.2 Hz, 2H), 2.12 (s, 3H).

^{13}C-NMR (151 MHz, Benzene-d) δ 204.4, 138.7, 137.3, 133.6, 132.1, 129.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.3, 127.2, 126.6, 126.3, 121.7, 107.6, 106.1, 50.1, 48.3, 35.3, 29.7

IR(neat): 3090, 3080, 3035, 1959, 1814, 1477, 1034, 668 cm^{-1}.

HRMS-ESI m/z Calculated for $C_{16}H_{17}NO$ $[M + Na]^+$ 262.1202, found 262.1208.

(S,E)-4-(1H-pyrrol-2-yl)-6-(p-tolyl)hex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel.

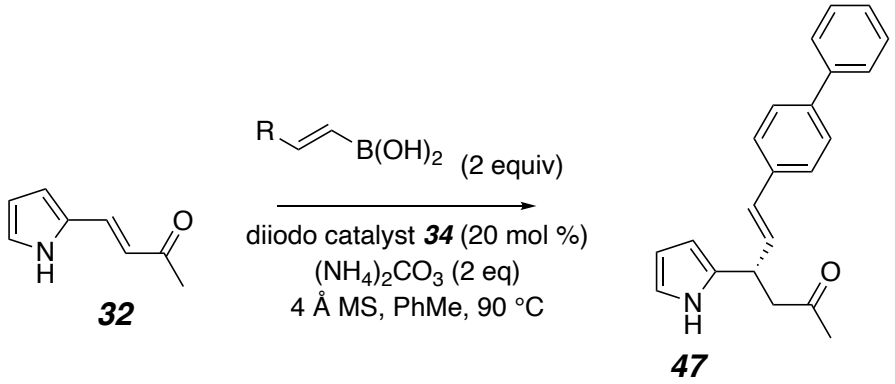
^{1}H-NMR (600 MHz, Benzene-d) δ 7.52 (s, 1H), 7.29–7.22 (m, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.06–7.03 (m, 1H), 6.38–6.23 (m, 2H), 5.98 (d, *J* = 2.7 Hz, 2H), 3.95 (q, *J* = 6.9 Hz, 1H), 2.53–2.34 (m, 2H), 1.93 (t, *J* = 15.5 Hz, 3H), 1.58 (s, 3H)

^{13}C-NMR (151 MHz, Benzene-d) δ 206.0, 134.7, 132.9, 130.2, 129.3, 128.3, 127.9, 127.8, 127.6, 126.4, 116.9, 108.2, 104.9, 48.6, 36.8

IR(neat): 3380, 3022, 2920, 1706, 1512, 1358, 967, 794, 720 cm^{-1}.

HRMS-ESI *m/z* Calculated for $C_{17}H_{19}NO$ $[M + Na]^+$ 276.1359, found 276.1361.

(S,E)-6-([1,1'-biphenyl]-4-yl)-4-(1H-pyrrol-2-yl)hex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel.

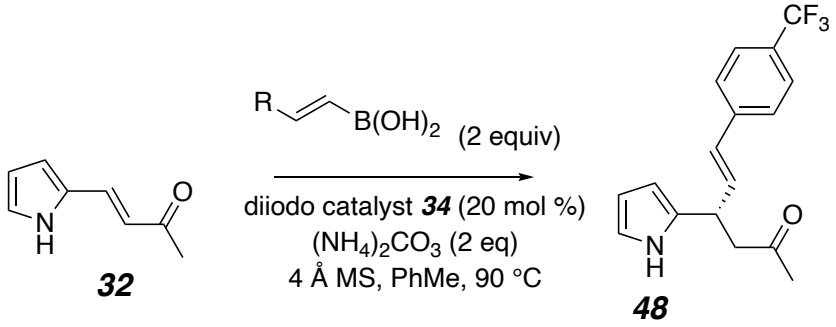
^{1}H-NMR (600 MHz, Benzene-d) δ 7.72 (s, 1H), 7.47 (dd, *J* = 23.7, 7.9 Hz, 4H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 6.9 Hz, 1H), 6.41–6.24 (m, 4H), 6.09 (s, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 2.48 (q, *J* = 8.2 Hz, 1H), 2.35 (dd, *J*= 17.2, 6.2 Hz, 1H), 1.56 (s, 3H)

^{13}C-NMR (151 MHz, chloroform-d) 208.2, 130.7, 128.9, 127.4, 127.0, 126.8, 117.3, 108.2, 104.7, 100.0, 77.3, 77.1, 76.9, 74.8, 49.0, 36.9, 11.3

IR(neat): 3334, 3027, 2925, 1697, 964, 720, 691 cm^{-1}.

HRMS-ESI m/z Calculated for $C_{22}H_{21}NO$ $[M + Na]^+$ 338.1515, found 338.1520.

(S,E)-4-(1H-pyrrol-2-yl)-6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel.

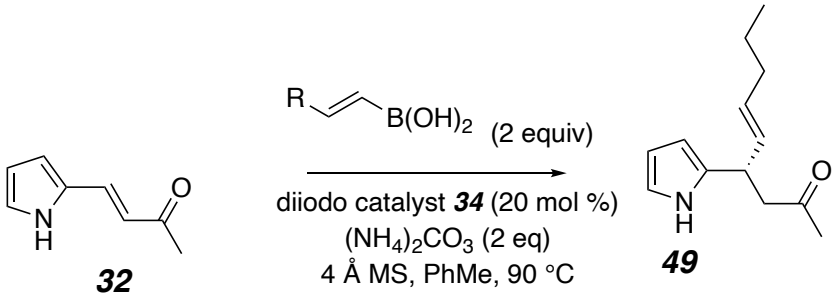
^{1}H-NMR (600 MHz, Benzene-d) δ 7.72 (s, 1H), 7.47 (dd, *J* = 23.7, 7.9 Hz, 4H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 6.9 Hz, 1H), 6.41–6.24 (m, 4H), 6.09 (s, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 2.48 (q, *J* = 8.2 Hz, 1H), 2.35 (dd, *J*= 17.2, 6.2 Hz, 1H), 1.56 (s, 3H)

^{13}C-NMR (151 MHz, chloroform-d) δ 208.0, 133.4, 132.7, 129.4, 126.5, 125.6, 117.4, 108.2, 104.9, 77.3, 77.1, 76.9, 76.8, 48.9, 36.8, 30.7

IR(neat): 3407, 2924, 1704, 1363, 1325, 1222, 529 cm^{-1}

HRMS-ESI m/z Calculated for $C_{17}H_{16}F_3NO$ $[M + H]^+$ 308.1257, found 308.1254.

(S,E)-4-(1H-pyrrol-2-yl)non-5-en-2-one



See the general procedure for enone formation above. The crude reaction mixture was purified via flash column chromatography with a 10 – 20% gradient of ethyl acetate in hexanes as eluent on silica gel.

^{1}HNMR (600 MHz, chloroform-D)δ 8.38 (s, 1H), 6.68 (q, J = 2.3 Hz, 1H), 6.11 (q, J = 3.0 Hz, 1H), 5.88 (s, 1H), 5.55-5.54 (m, 2H), 3.87 (q, J = 6.6 Hz, 1H), 2.90-2.72 (m, 2H), 2.16 (d, J = 20.6 Hz, 3H), 2.02-1.99 (m, 2H), 1.42-1.36 (m, 2H), 0.90-0.87 (m, 3H)

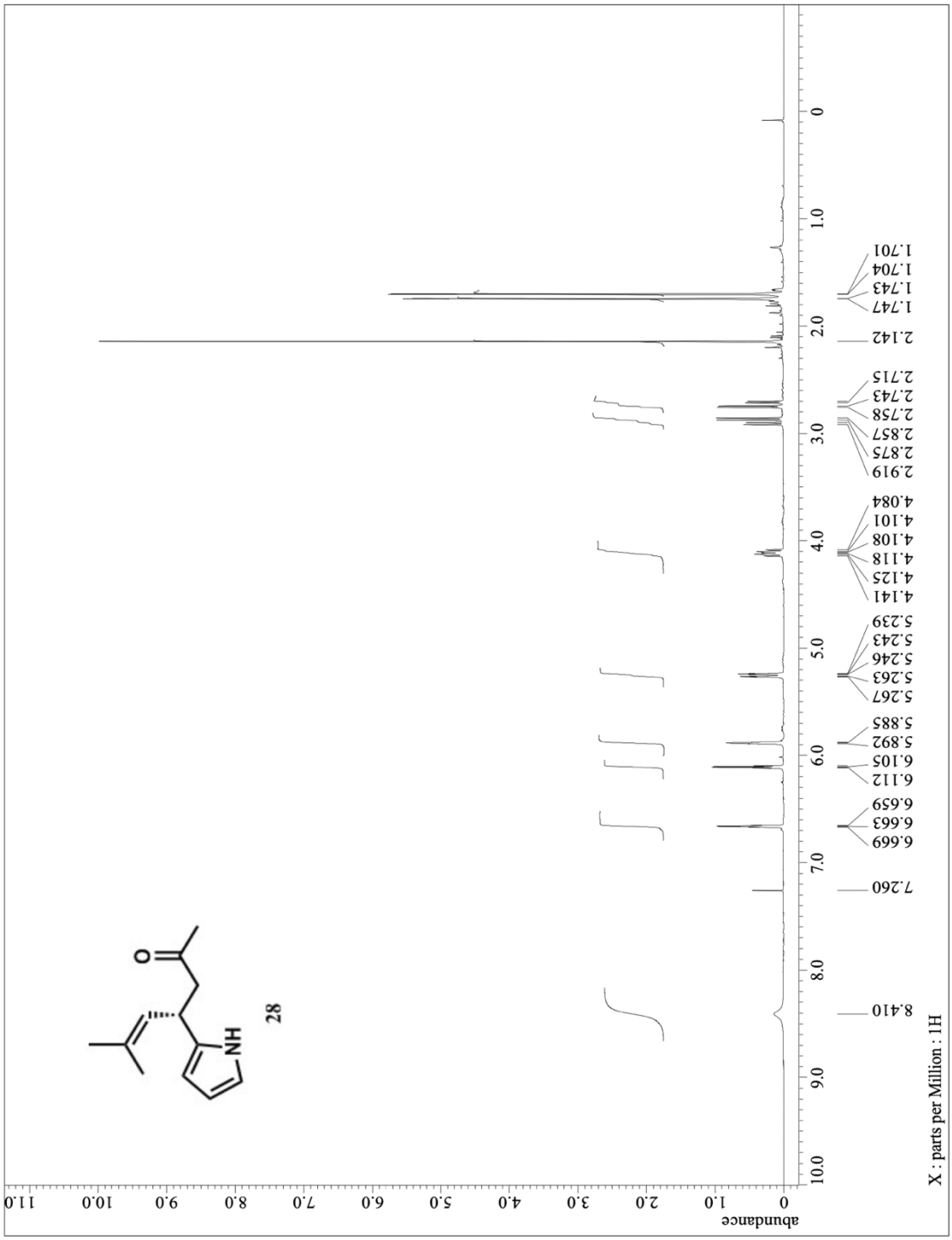
^{13}C-NMR (151 MHz, chloroform-D) δ 208.7, 134.1, 131.8, 130.6, 116.9, 108.0, 104.3, 77.3, 77.1, 76.9, 49.4, 36.7, 34.6, 30.7, 22.6, 13.8

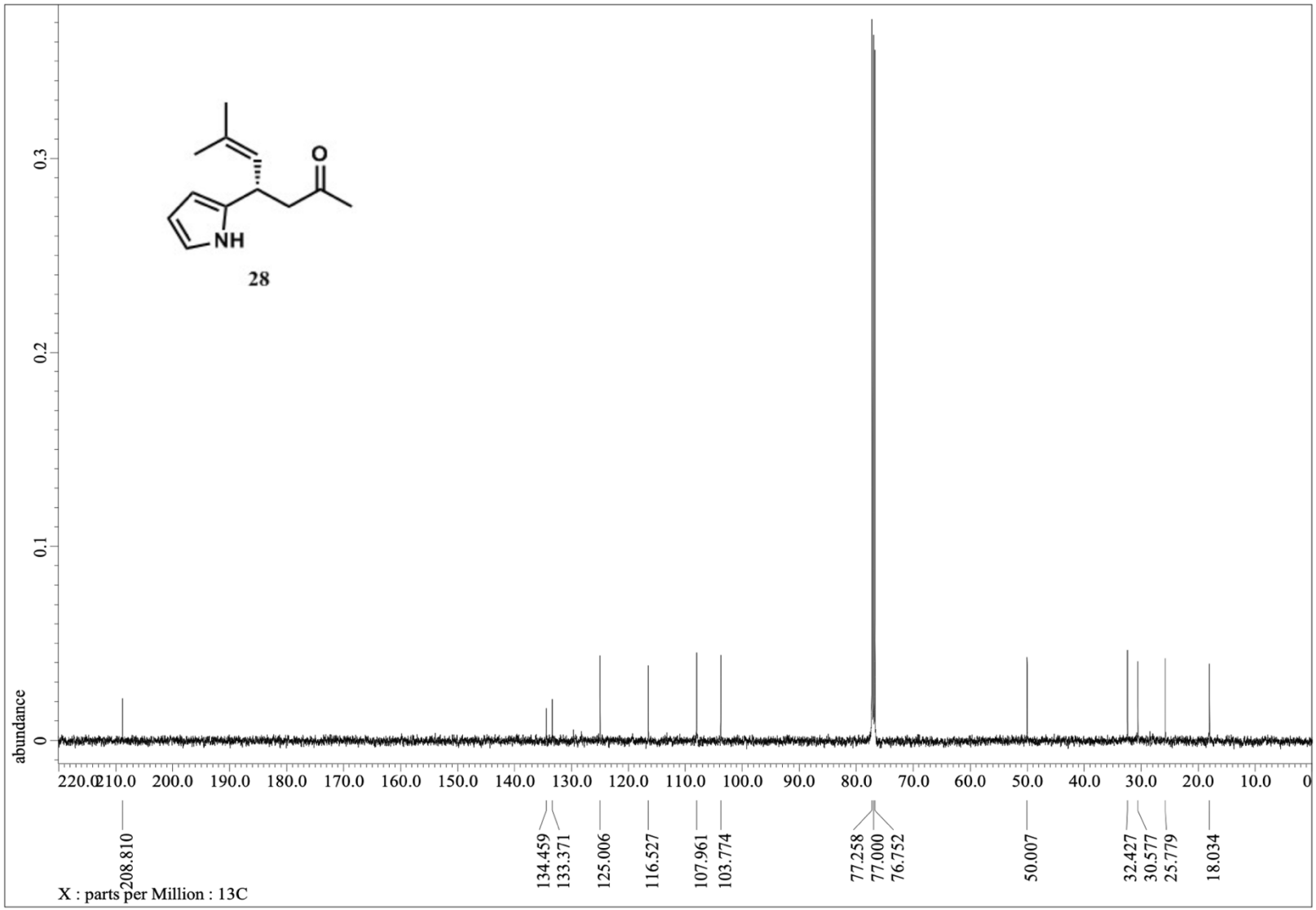
IR(neat): 3378.22, 2957.56, 2927.91, 1704.69, 1357.83, 966.90, 712.07 cm^{-1}.

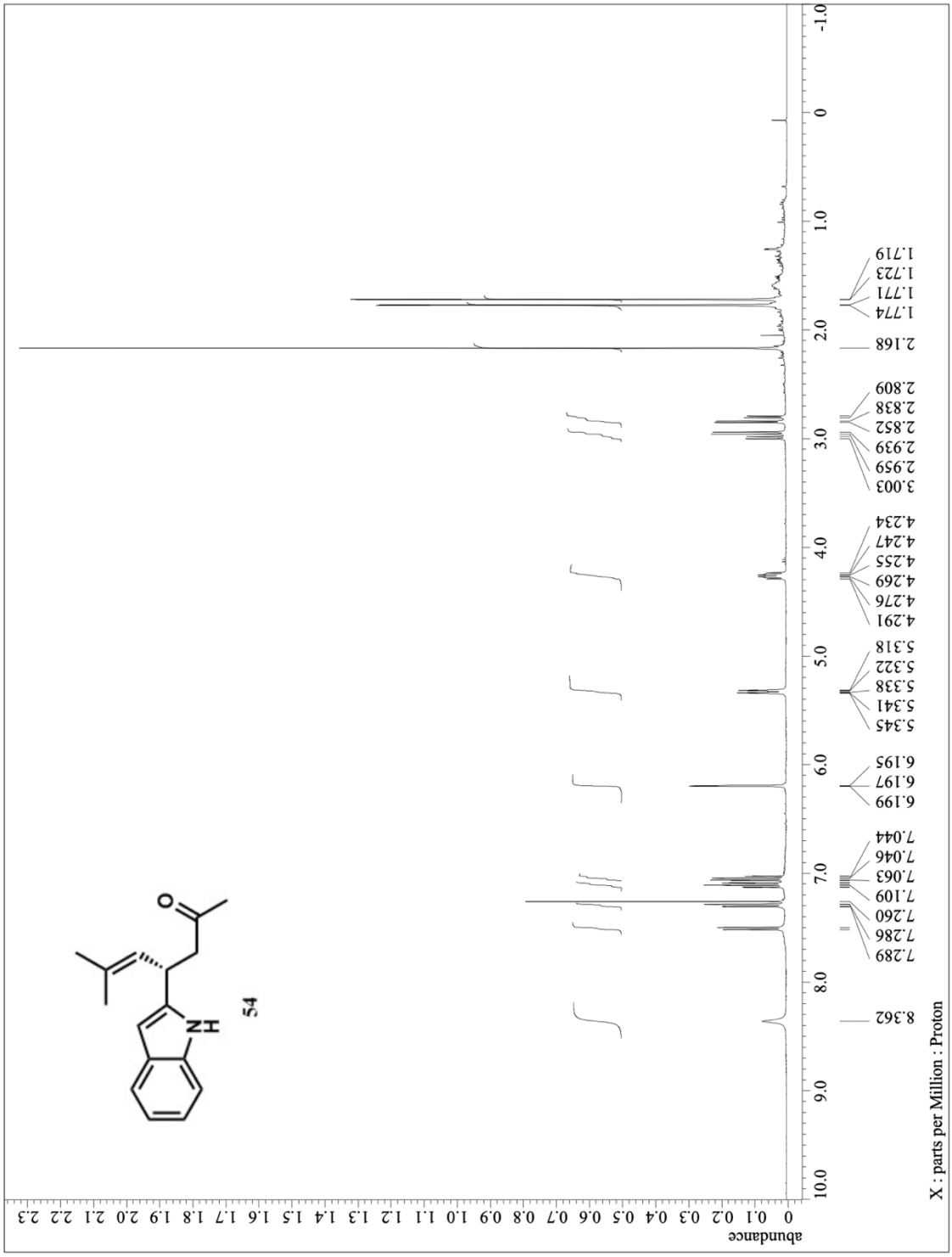
HRMS-ESI *m/z* Calculated for $C_{13}H_{19}NO$ $[M + Na]^+$ 228.1359, found 228.1359.

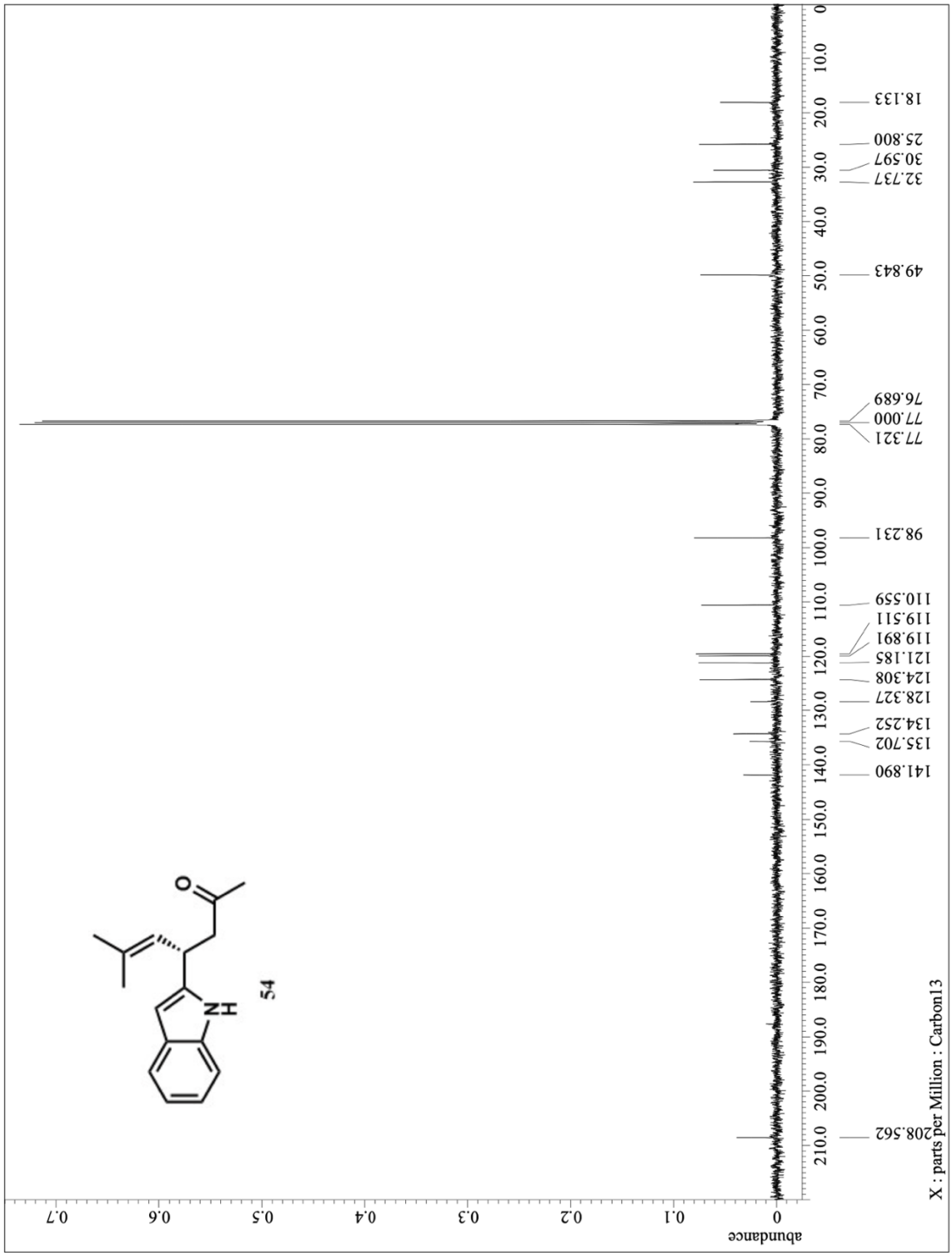
APPENDIX – CHAPTER TWO

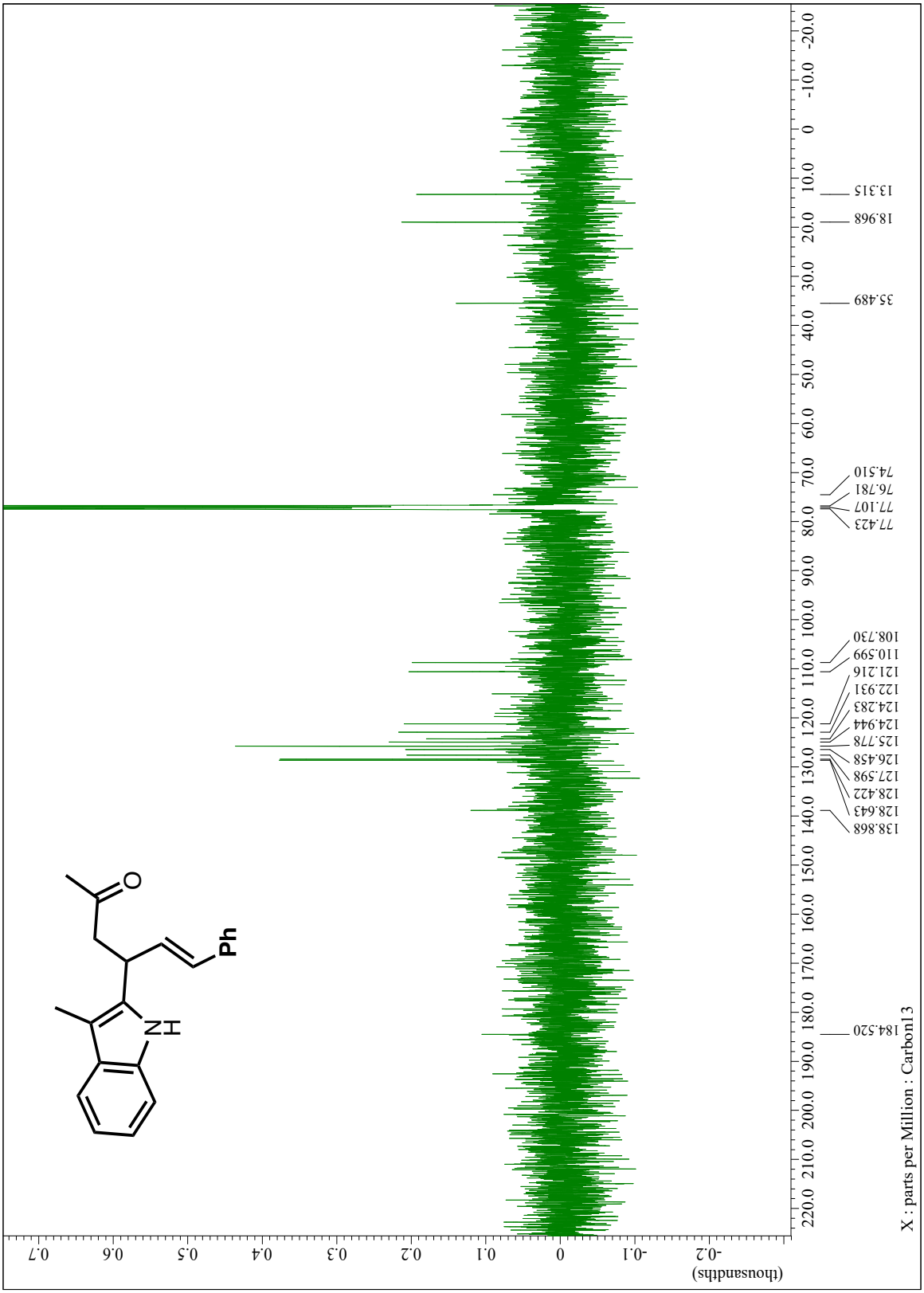
Spectra Relevant to Chapter Two

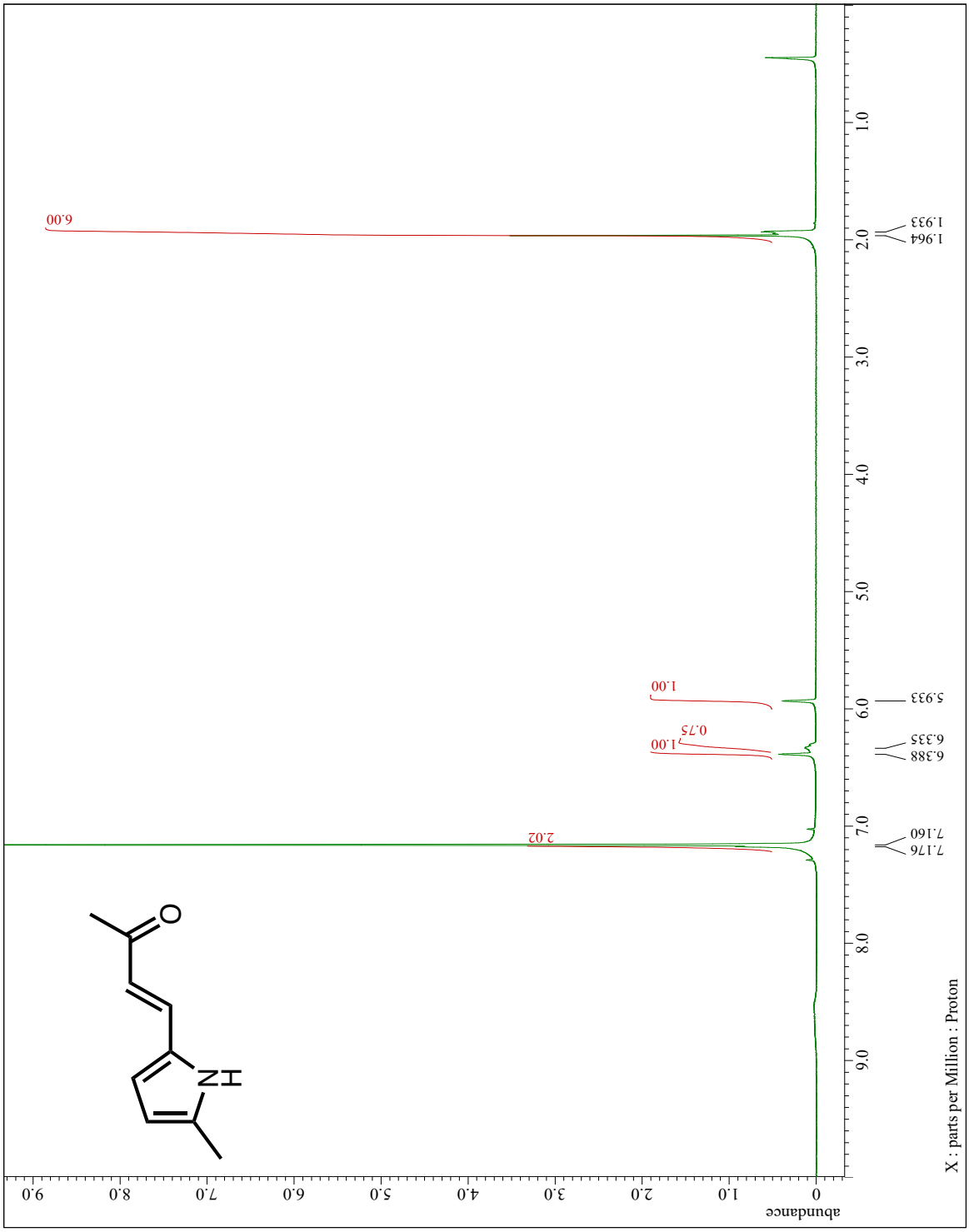

28
NH
O
X : parts per Million : 1H
abundance
8.410
7.260
6.669
6.663
6.659
6.112
6.105
5.892
5.885
5.267
5.263
5.246
5.243
5.239
4.141
4.125
4.118
4.108
4.101
4.084
2.919
2.875
2.857
2.758
2.743
2.715
2.142
1.747
1.743
1.704
1.701


O
NH
28
abundance
0
0.1
0.2
0.3
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
208.810
134.459
133.371
125.006
116.527
107.961
103.774
77.258
77.000
76.752
50.007
32.427
30.577
25.779
18.034
X : parts per Million : 13C


54
X : parts per Million : Proton
abundance
8.362
7.289
7.286
7.260
7.109
7.063
7.046
7.044
6.199
6.197
6.195
5.345
5.341
5.338
5.322
5.318
4.291
4.276
4.269
4.255
4.247
4.234
3.003
2.959
2.939
2.852
2.838
2.809
2.168
1.774
1.771
1.723
1.719


54
abundance
X : parts per Million : Carbon13
208.562
141.890
135.702
134.252
128.327
124.308
121.185
119.891
119.511
110.559
98.231
77.321
77.000
76.689
49.843
32.737
30.597
25.800
18.133

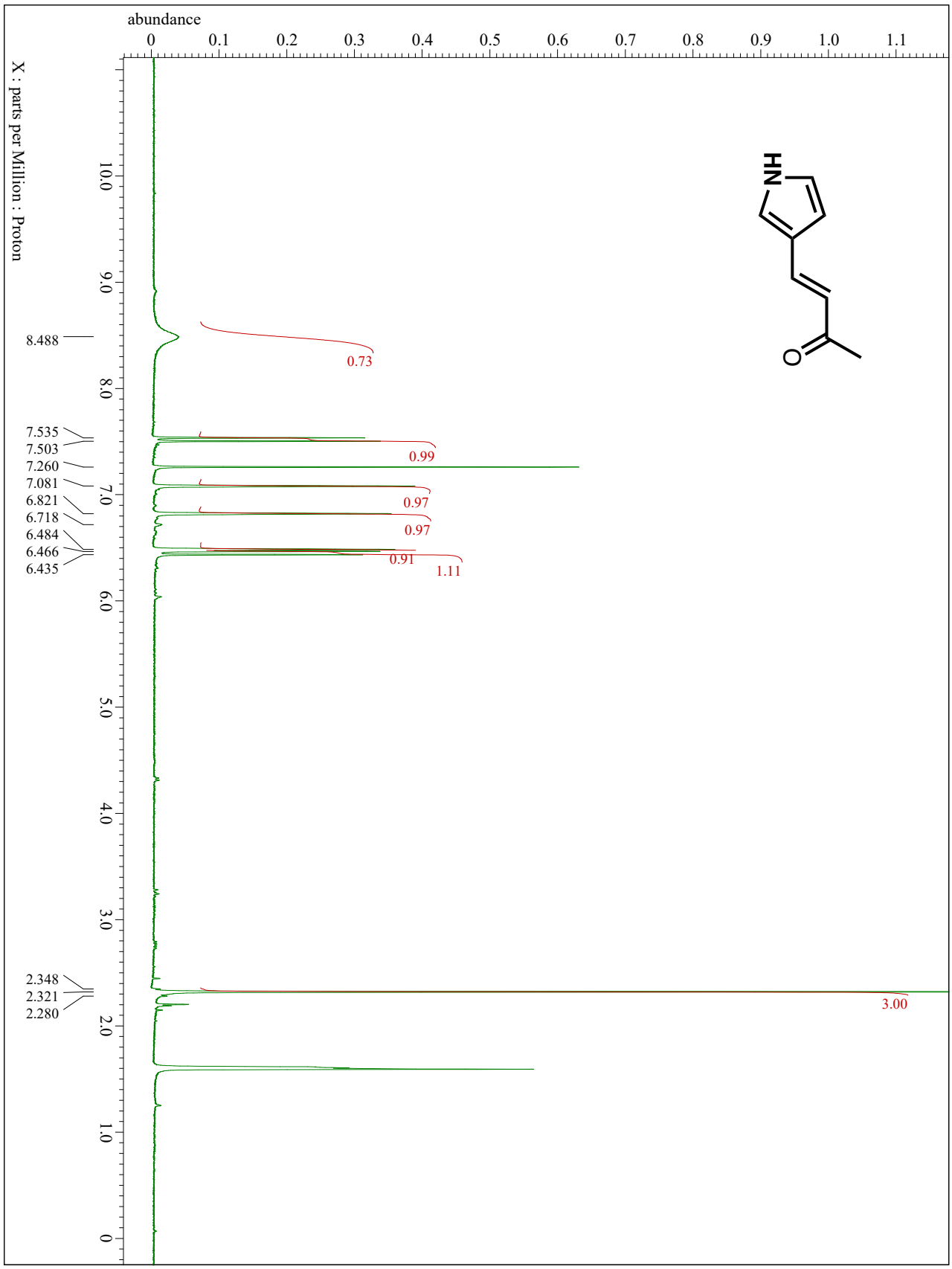

O
NH
Ph
(thousandths)
-0.2
-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
X : parts per Million : Carbon13
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
184.520
138.868
128.643
128.422
127.598
126.458
125.778
124.944
124.283
122.931
121.216
110.599
108.730
77.423
77.107
76.781
74.510
35.489
18.968
13.315

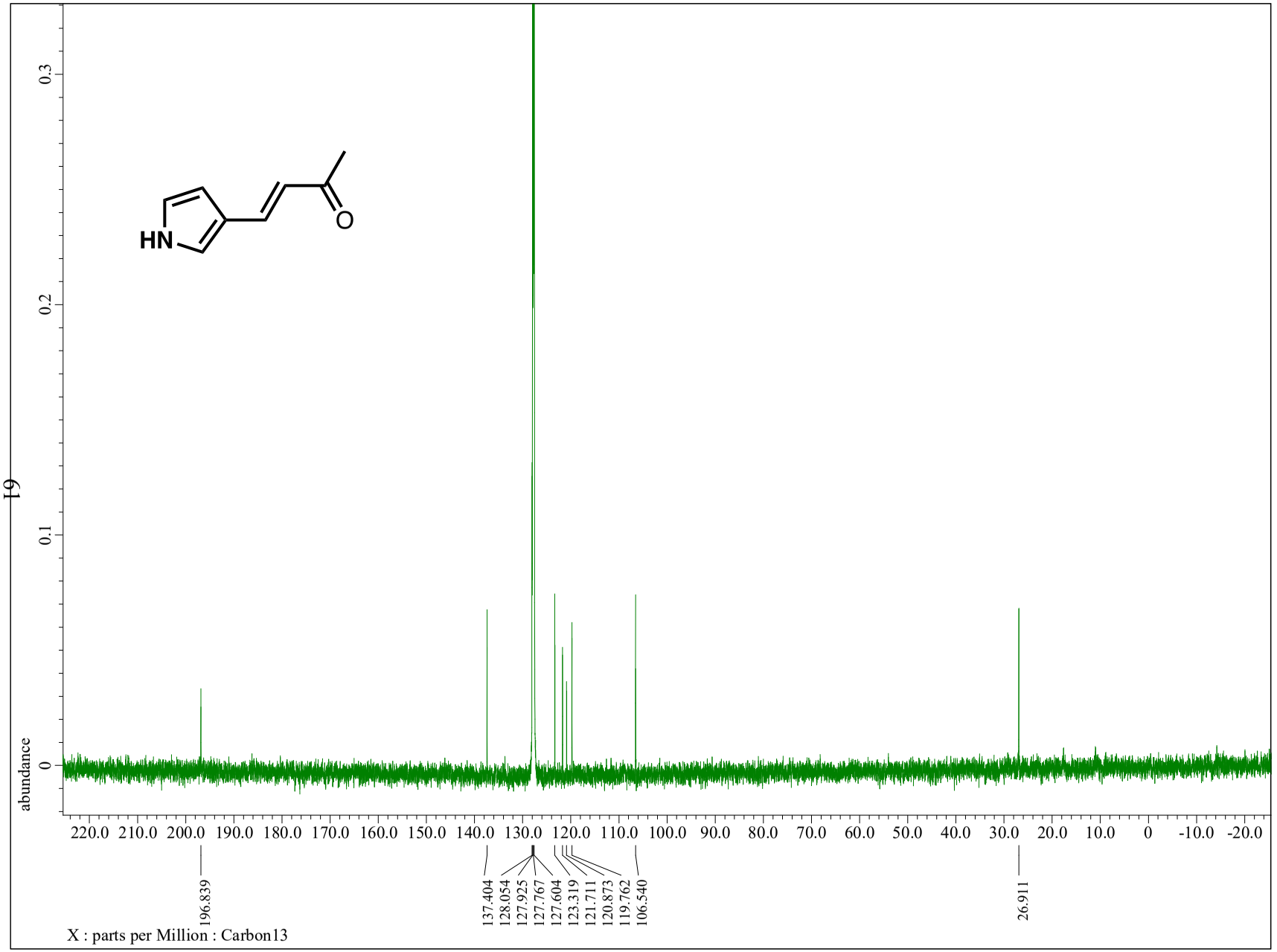

abundance
X : parts per Million : Proton
7.176
7.160
6.388
6.335
5.933
1.964
1.933
2.02
1.00
0.75
1.00
6.00
NH
O

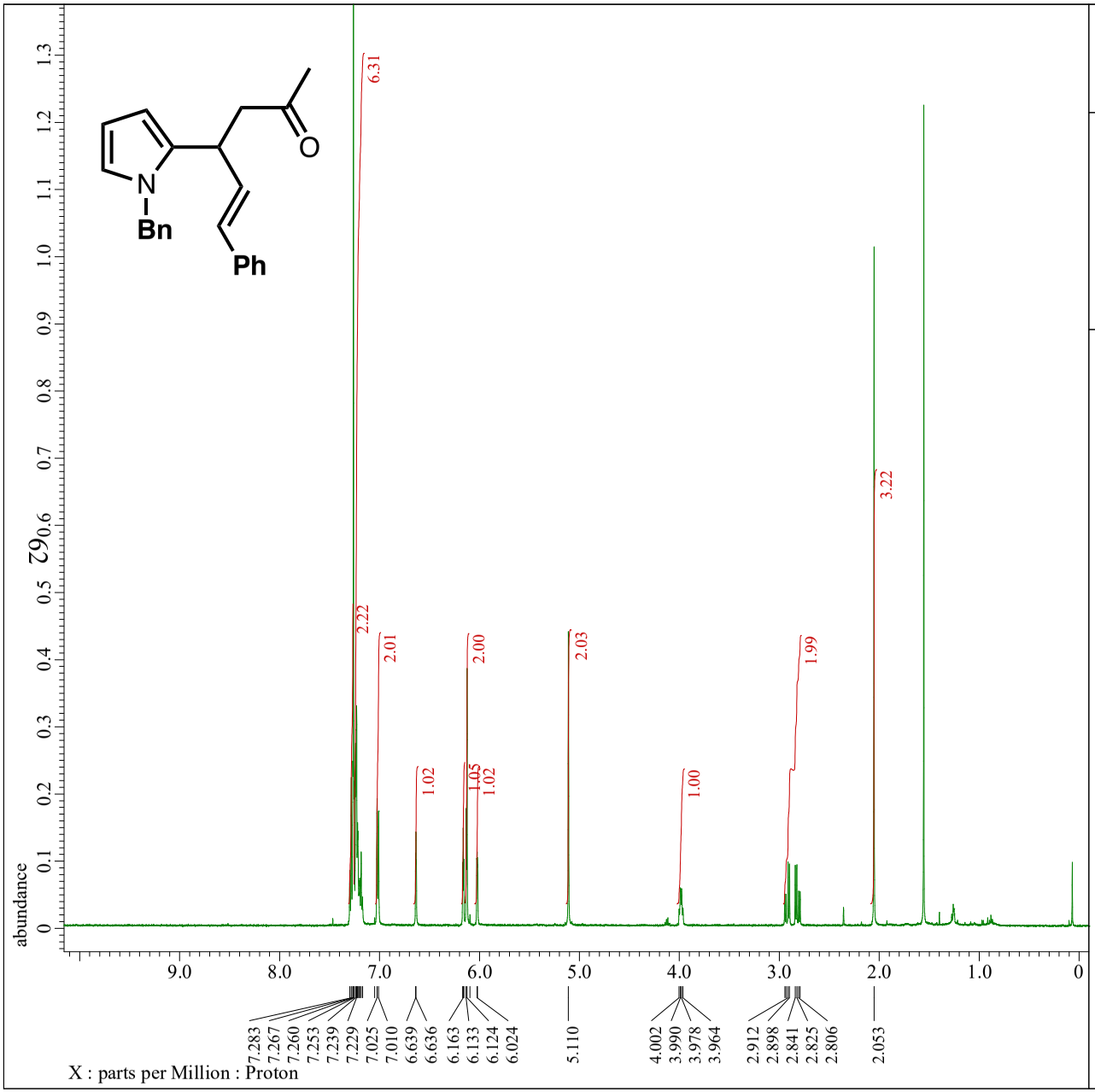
abundance
0
0.1
0.2
0.3
X : parts per Million : Carbon13
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
198.692
133.603
121.362
119.120
117.622
113.262
110.829
110.008
77.388
77.130
76.882
31.257
13.893
O
NH

X : parts per Million : Proton
abundance
8.231
7.424
7.392
7.260
6.112
6.080
5.852
5.849
2.305
2.284
2.174
0.78
1.00
1.00
0.97
2.97
O
NH

(thousandths)
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
X : parts per Million : Carbon13
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
198.376
131.144
130.646
127.234
112.266
111.221
77.433
77.107
76.791
31.148
13.765
13.497
11.465
O
NH


abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
X : parts per Million : Proton
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.488
7.535
7.503
7.260
7.081
6.821
6.718
6.484
6.466
6.435
2.348
2.321
2.280
0.73
0.99
0.97
0.97
0.91
1.11
3.00
NH
O

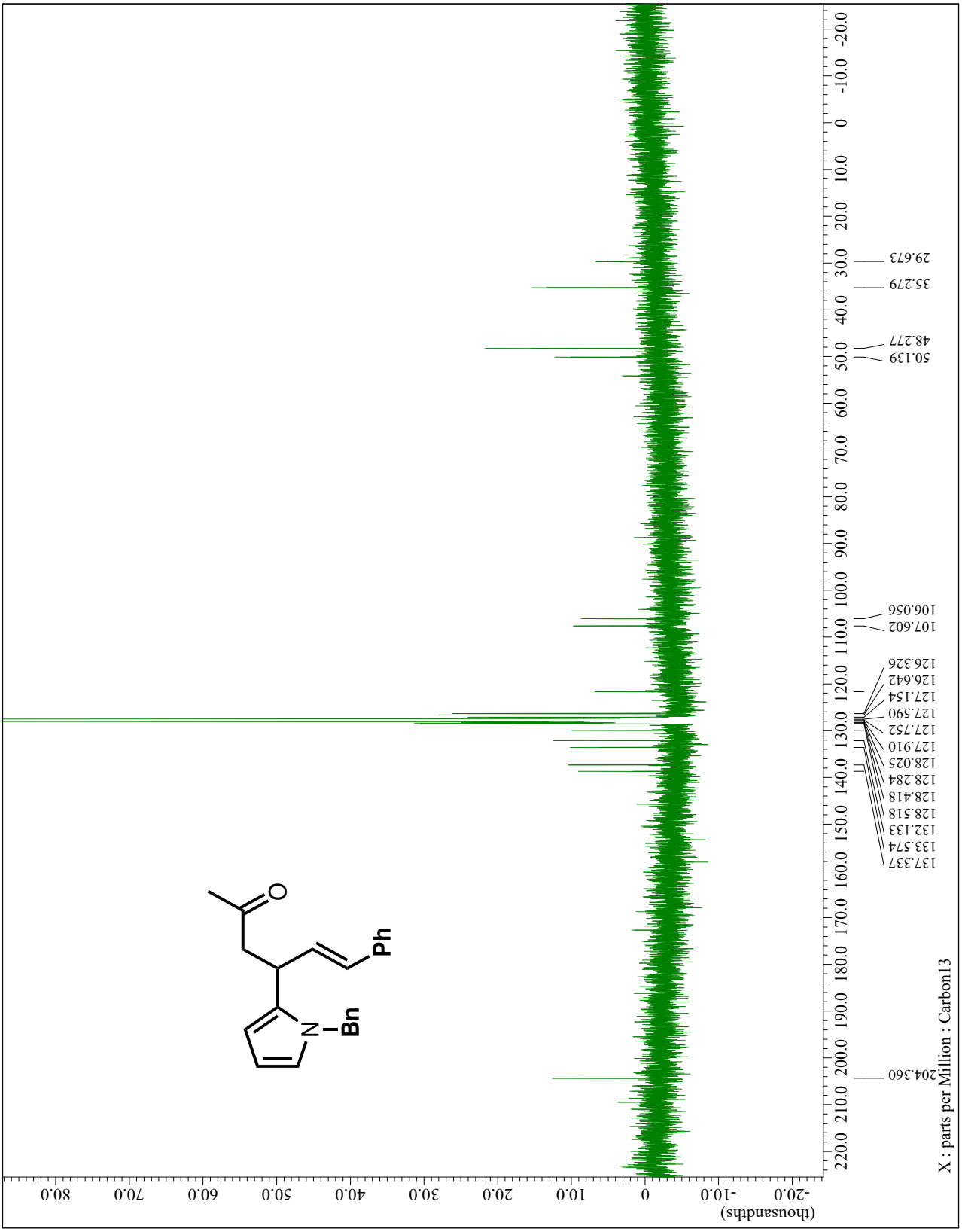

HN
O
abundance
0
0.1
0.2
0.3
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
196.839
137.404
128.054
127.925
127.767
127.604
123.319
121.711
120.873
119.762
106.540
26.911
X : parts per Million : Carbon13



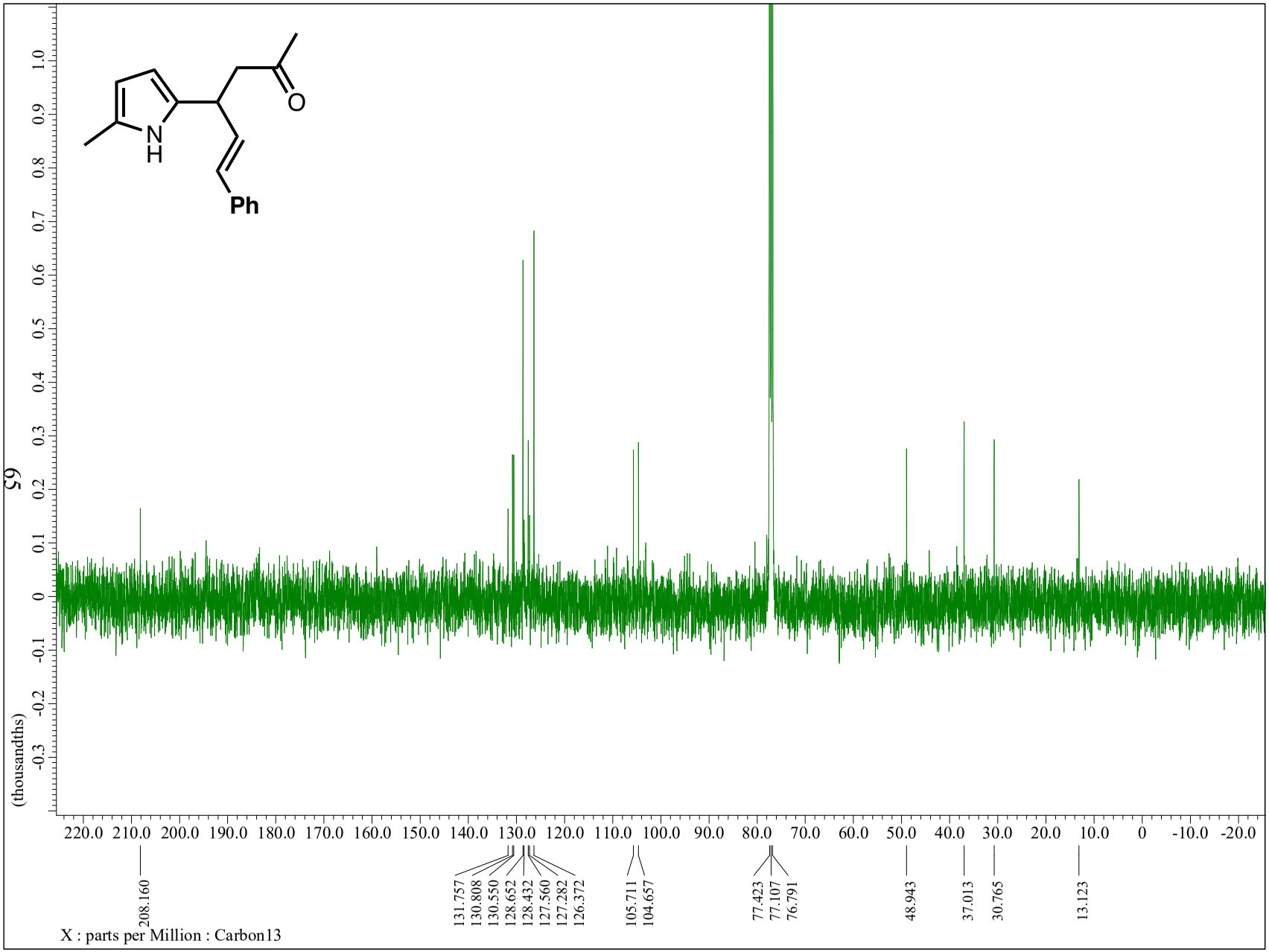
JEOL

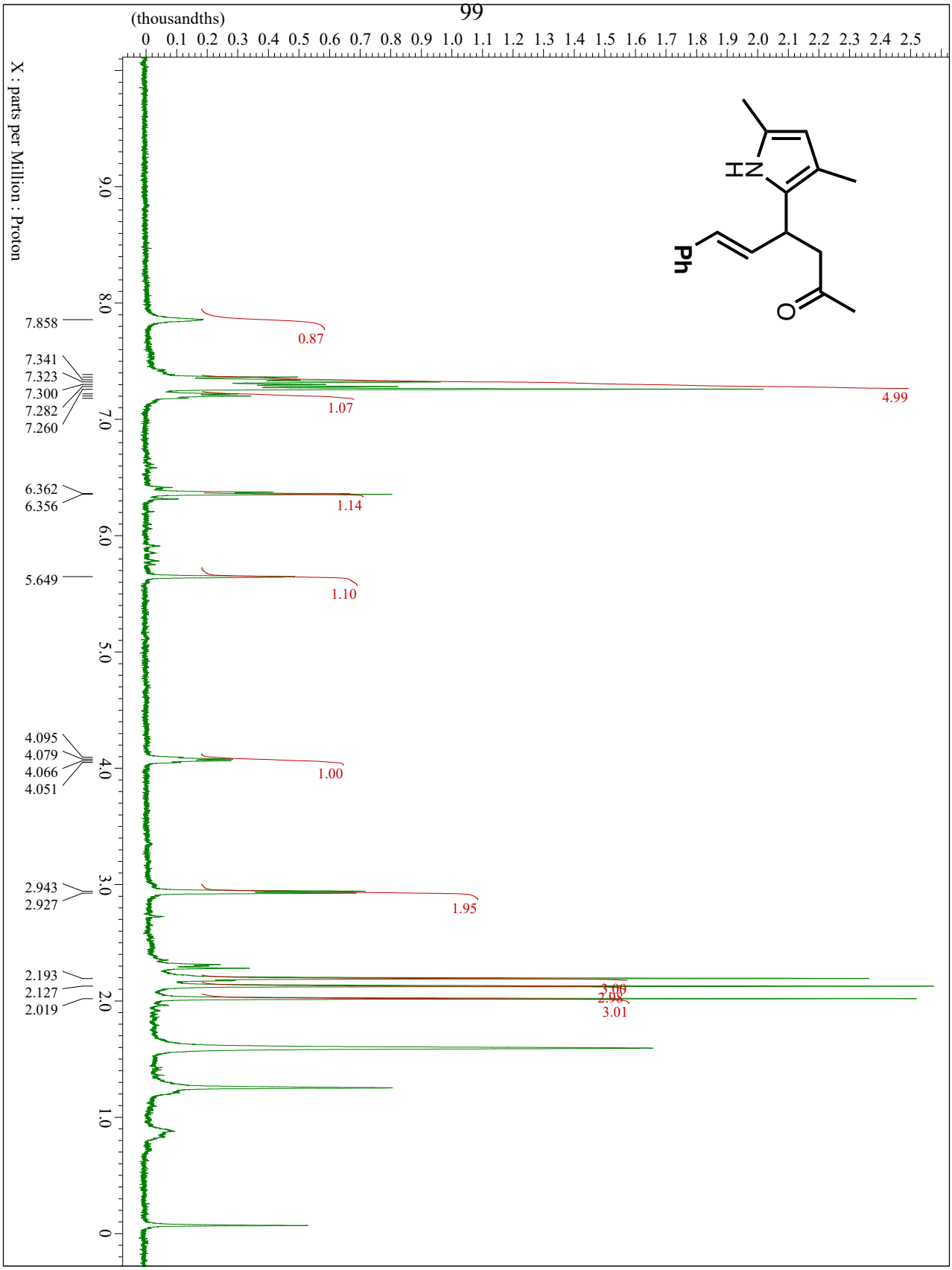
```
---- PROCESSING PARAMETERS ----
dc_balance( 0, FALSE )
sexp( 0.2[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 1 )
fft( 1, TRUE, TRUE )
machinephase
ppm

Derived from: AEB-IV-169_PROTON-2-1.jdf
```

```
Filename          = AEB-IV-169_PROTON-2-2.jd
Author            = May
Experiment        = proton.jxp
Sample_Id         = AEB-IV-169
Solvent           = CHLOROFORM-D
Creation_Time     =  8-OCT-2020 13:06:21
Revision_Time     =  8-OCT-2020 13:14:46
Current_Time      =  8-OCT-2020 13:15:16

Data_Format       = 1D COMPLEX
Dim_Size          = 13107
Dim_Title         = Proton
Dim_Units         = [ppm]
Dimensions        = X
Site              = SERC500
Spectrometer      = DELTA2_NMR

Field_Strength    = 11.7441[T] (500[MHz])
X_Acq_Duration    = 1.74587904[s]
X_Domain          = 1H
X_Freq            = 500.02120543[MHz]
X_Offset          = 5[ppm]
X_Points          = 16384
X_Prescans        = 1
X_Resolution      = 0.57277737[Hz]
X_Sweep           = 9.38438438[kHz]
X_Sweep_Clipped   = 7.50750751[kHz]
Irr_Domain        = Proton
Irr_Freq          = 500.02120543[MHz]
Irr_Offset        = 5[ppm]
Tri_Domain        = Proton
Tri_Freq          = 500.02120543[MHz]
Tri_Offset        = 5[ppm]
Clipped           = FALSE
Scans             = 16
Total_Scans       = 16

Relaxation_Delay = 4[s]
Recvr_Gain        = 46
Temp_Get          = 18.8[dC]
X_90_Width        = 12.4[us]
X_Acq_Time        = 1.74587904[s]
X_Angle           = 45[deg]
X_Atn             = 3[dB]
X_Pulse           = 6.2[us]
Irr_Mode          = Off
Tri_Mode          = Off
Dante_Presat      = FALSE
Initial_Wait      = 1[s]
```

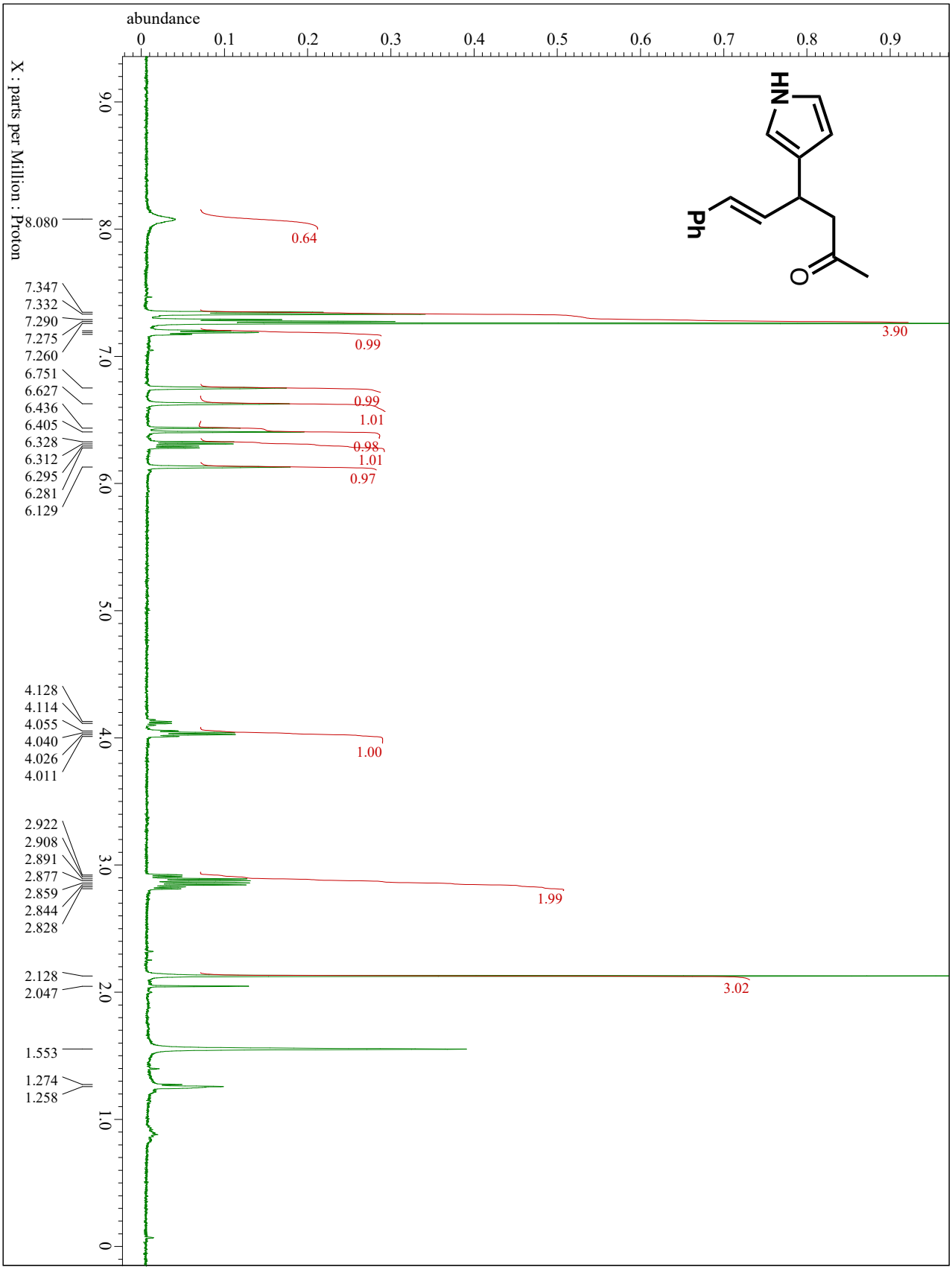

(thousandths)
X : parts per Million : Carbon13
204.360
137.337
133.574
132.133
128.518
128.418
128.284
128.025
127.910
127.752
127.590
127.154
126.642
126.326
107.602
106.056
50.139
48.277
35.279
29.673
Ph
Bn
N
O

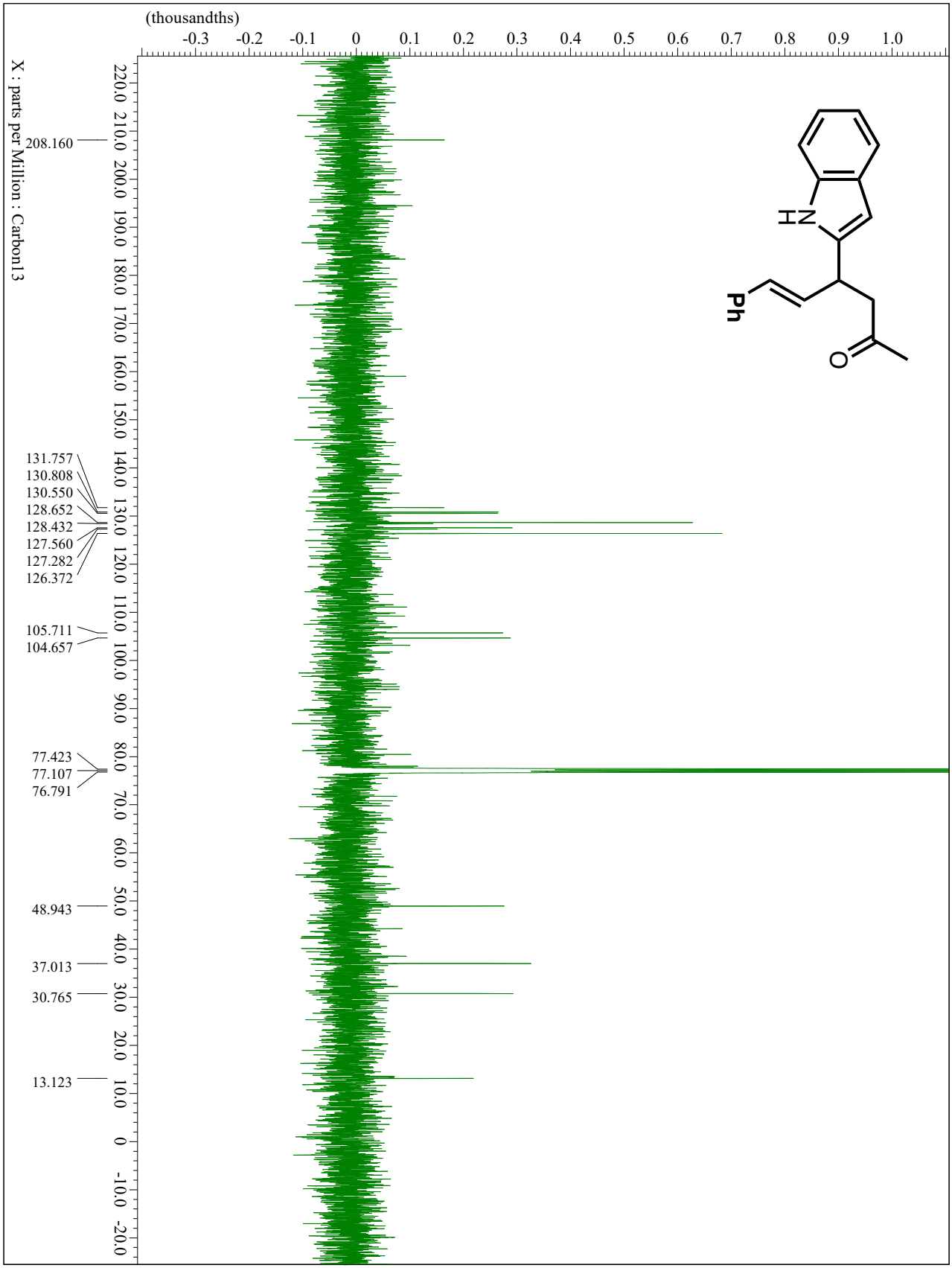
abundance
0
1.0
2.0
3.0
4.0
X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
7.521
7.289
7.236
7.223
7.160
7.134
7.121
7.108
7.058
7.045
7.034
7.026
6.381
6.355
6.287
6.275
6.261
6.248
6.230
5.979
5.975
3.972
3.960
3.949
3.937
2.531
2.518
2.502
2.490
2.383
2.373
2.355
1.956
1.929
1.579
0.79
1.00
2.00
2.00
2.00
2.00
1.00
2.00
3.00
3.00
3.00
O
NH
Ph


S9
(thousandths)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
208.160
131.757
130.808
130.550
128.652
128.432
127.560
127.282
126.372
105.711
104.657
77.423
77.107
76.791
48.943
37.013
30.765
13.123
X : parts per Million : Carbon13
N
H
O
Ph

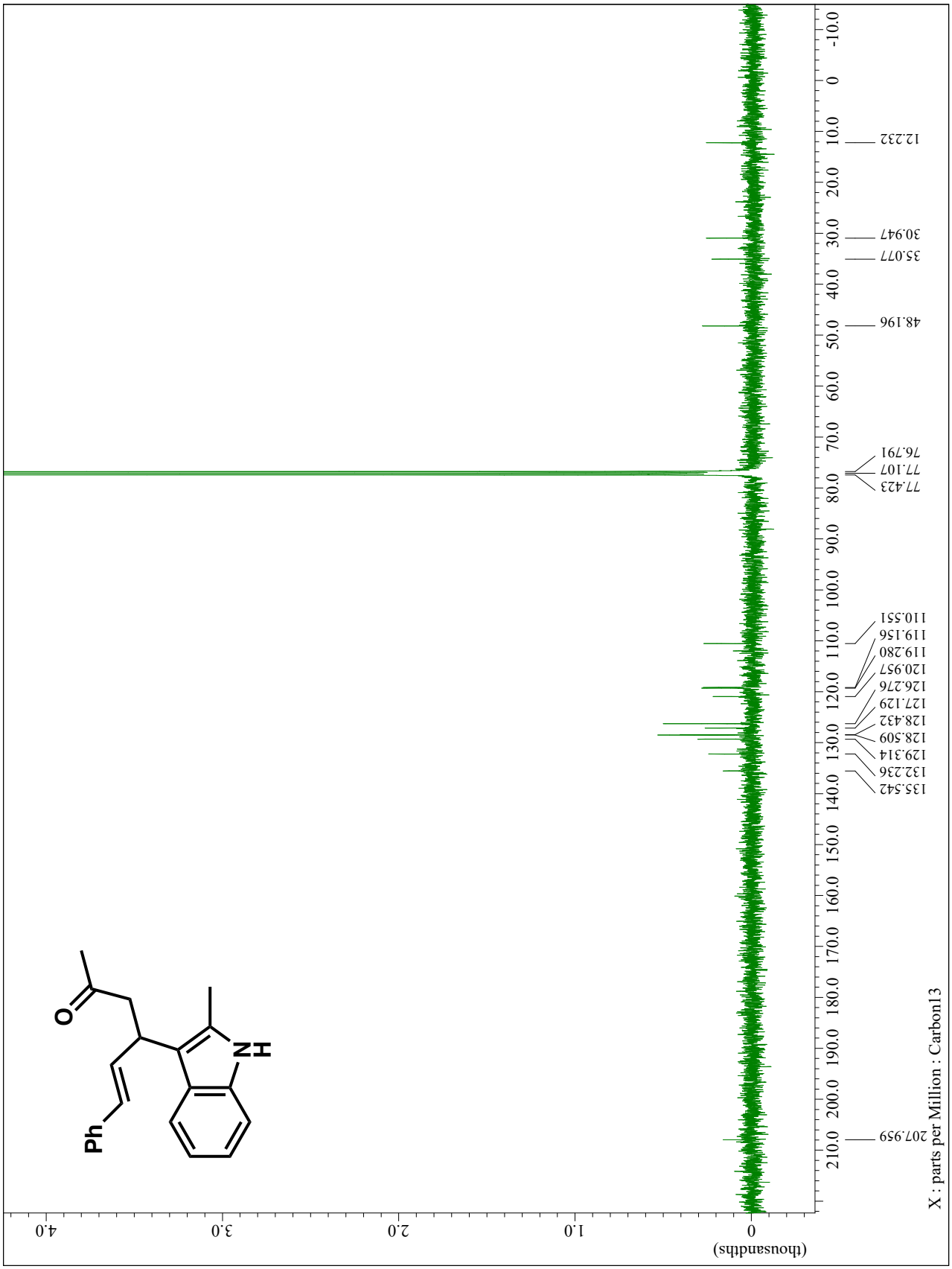

(thousandths)
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5
X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.858
7.341
7.323
7.300
7.282
7.260
6.362
6.356
5.649
4.095
4.079
4.066
4.051
2.943
2.927
2.193
2.127
2.019
0.87
4.99
1.07
1.14
1.10
1.00
1.95
3.00
2.08
3.01
HN
Ph
O

(thousandths)
X : parts per Million : Carbon13
208.151
137.114
130.799
129.678
128.595
127.407
126.324
125.979
114.623
108.184
77.423
77.107
76.791
48.464
35.547
30.707
29.797
13.065
11.216
Ph
HN
O


abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.080
7.347
7.332
7.290
7.275
7.260
6.751
6.627
6.436
6.405
6.328
6.312
6.295
6.281
6.129
4.128
4.114
4.055
4.040
4.026
4.011
2.922
2.908
2.891
2.877
2.859
2.844
2.828
2.128
2.047
1.553
1.274
1.258
0.64
3.90
0.99
0.99
1.01
0.98
1.01
0.97
1.00
1.99
3.02
HN
Ph
O


(thousandths)
-0.3 -0.2 -0.1 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
X : parts per Million : Carbon13
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
208.160
131.757
130.808
130.550
128.652
128.432
127.560
127.282
126.372
105.711
104.657
77.423
77.107
76.791
48.943
37.013
30.765
13.123
HN
Ph
O

O
Ph
NH
(thousandths)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
X : parts per Million : Carbon13
184.520
138.868
128.643
128.422
127.598
126.458
125.778
124.944
124.283
122.931
121.216
110.599
108.730
77.423
77.107
76.781
74.510
35.489
18.968
13.315


(thousandths)
X : parts per Million : Carbon13
207.959
135.542
132.236
129.314
128.509
128.432
127.129
126.276
120.957
119.280
119.156
110.551
77.423
77.107
76.791
48.196
35.077
30.947
12.232
O
NH
Ph

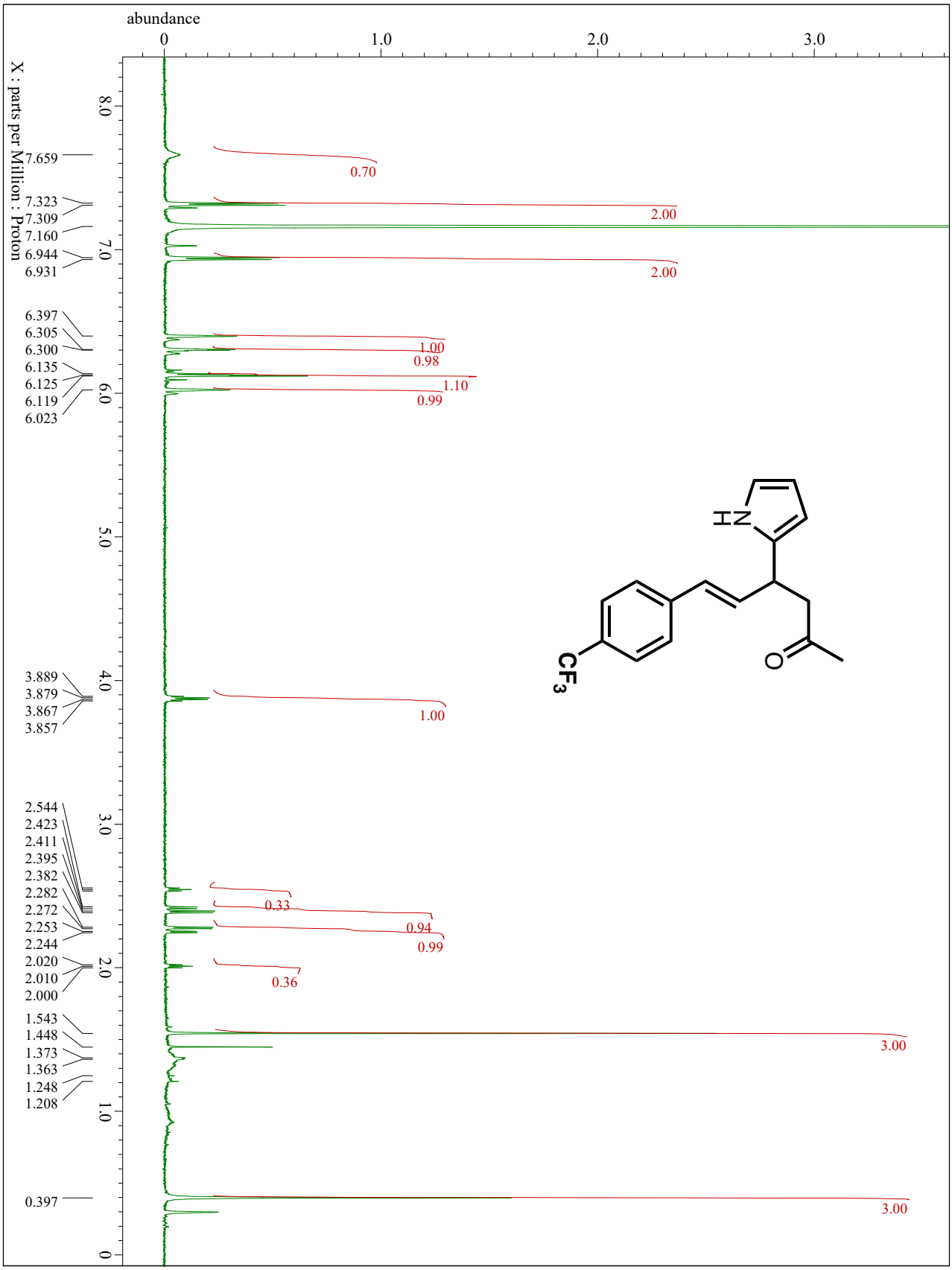
abundance
X : parts per Million : Proton
7.605
7.593
7.124
7.113
7.097
7.009
6.520
6.511
6.493
6.484
6.418
6.391
6.358
4.417
4.407
4.394
4.385
2.894
2.879
2.866
2.852
2.586
2.577
2.558
2.549
2.060
1.444
4.61
3.01
3.00
3.00
1.01
1.00
0.99
1.00
1.00
0.95
0.87
1.00
O
NH
Ph

abundance
X : parts per Million : Proton
0.66
3.10
1.98
3.04
0.89
0.99
1.00
2.02
3.01
3.00
7.702
7.189
7.176
7.160
6.982
6.969
6.394
6.340
6.314
6.303
6.299
6.293
6.216
6.204
6.190
6.063
3.965
3.952
3.941
3.929
2.489
2.476
2.460
2.447
2.360
2.350
2.332
2.321
2.111
1.551
O
NH

(thousandths)
X : parts per Million : Carbon13
205.988
134.661
132.856
130.237
129.284
128.322
127.910
127.752
127.590
126.426
116.890
108.158
104.912
48.560
36.835
O
Zr

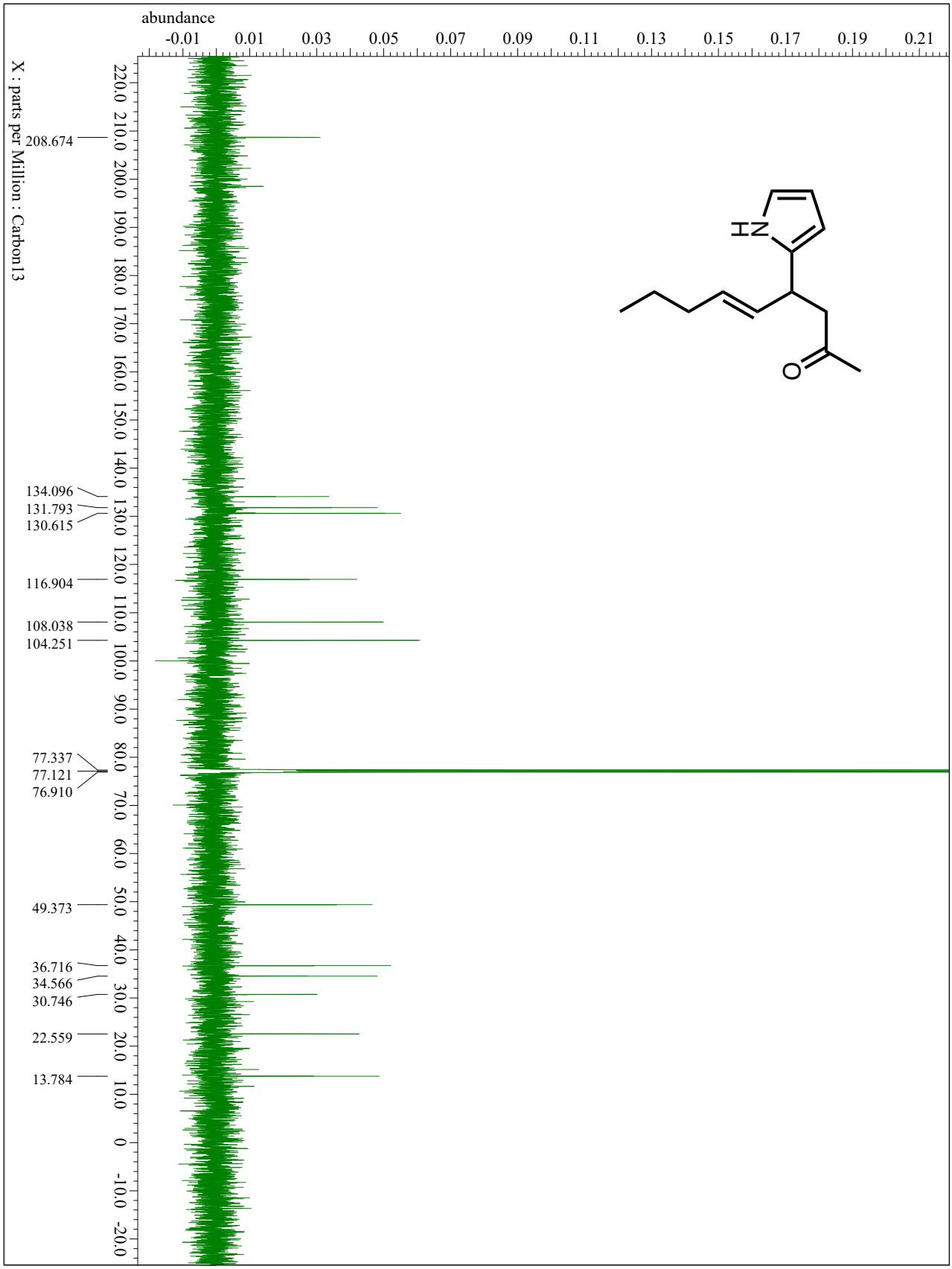
abundance
X : parts per Million : Proton
O
NH
4.00
0.73
1.98
1.99
0.63
3.84
1.03
1.00
3.00
0.99
1.00
1.564
2.333
2.343
2.362
2.372
2.458
2.470
2.486
2.499
3.956
3.967
3.977
3.990
6.088
6.240
6.267
6.279
6.317
6.322
6.327
6.338
6.364
6.412
6.414
7.135
7.146
7.160
7.218
7.231
7.244
7.263
7.277
7.444
7.458
7.484
7.497
7.723

(thousandths)
0
10.0
20.0
30.0
40.0
X : parts per Million : Carbon13
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
208.204
130.663
128.887
127.355
127.010
126.800
117.282
108.196
104.701
100.000
77.327
77.116
76.906
74.814
49.029
36.945
11.290
O
N
H


abundance
0
1.0
2.0
3.0
X : parts per Million : Proton
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.659
7.323
7.309
7.160
6.944
6.931
6.397
6.305
6.300
6.135
6.125
6.119
6.023
3.889
3.879
3.867
3.857
2.544
2.423
2.411
2.395
2.382
2.282
2.272
2.253
2.244
2.020
2.010
2.000
1.543
1.448
1.373
1.363
1.248
1.208
0.397
0.70
2.00
2.00
1.00
0.98
1.10
0.99
1.00
0.33
0.94
0.99
0.36
3.00
3.00
HN
O
CF3

(thousandths)
-10.0
0
10.0
20.0
30.0
40.0
50.0
60.0
X : parts per Million : Carbon13
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
207.984
133.402
132.674
129.423
126.513
125.622
117.440
108.249
104.869
77.327
77.116
76.906
76.767
48.890
36.826
30.746
O
NH
CF3

abundance
X : parts per Million : Proton
8.380
7.260
6.683
6.678
6.676
6.108
6.102
5.878
5.551
5.549
5.546
5.542
5.538
3.885
3.875
3.864
3.852
3.468
3.451
2.875
2.862
2.822
2.812
2.142
2.008
2.005
1.999
1.406
1.393
1.380
0.903
0.890
0.878
0.870
0.87
1.00
1.00
1.00
2.00
1.00
2.00
2.00
3.00
2.00
3.00
O
Zr


abundance
-0.01
0.01
0.03
0.05
0.07
0.09
0.11
0.13
0.15
0.17
0.19
0.21
X : parts per Million : Carbon13
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
208.674
134.096
131.793
130.615
116.904
108.038
104.251
77.337
77.121
76.910
49.373
36.716
34.566
30.746
22.559
13.784
IN
O

BIBLIOGRAPHY:

(1) Top Pharmaceuticals Poster | Njarðarson https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster (accessed 2021 -06 -01).

(2) Ahmad, S.; Alam, O.; Naim, Mohd. J.; Shaquiquzzaman, M.; Alam, M. M.; Iqbal, M. Pyrrole: An Insight into Recent Pharmacological Advances with Structure Activity Relationship. *Eur. J. Med. Chem.* **2018**, *157*, 527–561.

(3) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756.

(4) Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. Route to Three-Dimensional Fragments Using Diversity-Oriented Synthesis. *Proc. Natl. Acad. Sci.* **2011**, *108* (17), 6799–6804.

(5) Hajduk, P. J.; Galloway, W. R. J. D.; Spring, D. R. A Question of Library Design. *Nature* **2011**, *470* (7332), 42–43.

(6) Twigg, D. G.; Kondo, N.; Mitchell, S. L.; Galloway, W. R. J. D.; Sore, H. F.; Madin, A.; Spring, D. R. Partially Saturated Bicyclic Heteroaromatics as an Sp3-Enriched Fragment Collection. *Angew. Chem. Int. Ed.* **2016**, *55* (40), 12479–12483.

(7) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *MedChemComm* **2013**, *4* (3), 515–519.

(8) Prosser, K. E.; Stokes, R. W.; Cohen, S. M. Evaluation of 3-Dimensionality in Approved and Experimental Drug Space. *ACS Med. Chem. Lett.* **2020**, *11* (6), 1292–1298.

(9) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules. *Acc. Chem. Res.* **2015**, *48* (3), 740–751.

(10) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* **2016**, *79* (3), 629–661.

(11) Siddiqui, A. A.; Iram, F.; Siddiqui, S.; Sahu, K. Role of Natural Products in Drug Discovery Process. *Int. J. Drug Dev. Res.* **2014**, *6* (2), 420-451.

(12) Beck, E. M.; Hatley, R.; Gaunt, M. J. Synthesis of Rhazinicine by a Metal-Catalyzed C–H Bond Functionalization Strategy. *Angew. Chem. Int. Ed.* **2008**, *47* (16), 3004–3007.

(13) Johnson, J. A.; Li, N.; Sames, D. Total Synthesis of (−)-Rhazinilam: Asymmetric C−H Bond Activation via the Use of a Chiral Auxiliary. *J. Am. Chem. Soc.* **2002**, *124* (24), 6900–6903.

(14) Bowie, A. L.; Hughes, C. C.; Trauner, D. Concise Synthesis of (±)-Rhazinilam through Direct Coupling. *Org. Lett.* **2005**, *7* (23), 5207–5209.

(15) Wipf, P.; Spencer, S. R. Asymmetric Total Syntheses of Tuberostemonine, Didehydrotuberostemonine, and 13-Epituberostemonine. *J. Am. Chem. Soc.* **2005**, *127* (1), 225–235.

(16) Corsello, M. A.; Kim, J.; Garg, N. K. Indole Diterpenoid Natural Products as the Inspiration for New Synthetic Methods and Strategies. *Chem. Sci.* **2017**, *8* (9), 5836–5844.

(17) Michael, A. Ueber Die Addition von Natriumacetessig- Und Natriummalonsäureäthern Zu Den Aethern Ungesättigter Säuren. *J. Für Prakt. Chem.* **1887**, *35* (1), 349–356.

(18) Jacob, P.; Brown, H. Conjugate Addition of B-Alkenyl-9-Borabicyclo[3.3.1]Nonanes to Methyl Vinyl Ketone. A Convenient Synthesis of .Gamma.,.Delta.-Unsaturated Ketones. *J. Am. Chem. Soc.* **1976**, *98* (24), 7832–7833.

(19) Rossiter, B. E.; Swingle, N. M. Asymmetric Conjugate Addition. *Chem. Rev.* **1992**, *92* (5), 771–806.

(20) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; Vries, A. H. M. de. Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition–Aldol Reactions of Organozinc Reagents. *Angew. Chem. Int. Ed. Engl.* **1997**, *36* (23), 2620–2623.

(21) Sakai, M.; Hayashi, H.; Miyaura, N. Rhodium-Catalyzed Conjugate Addition of Aryl- or 1-Alkenylboronic Acids to Enones. *Organometallics* **1997**, *16* (20), 4229–4231.

(22) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc.* **1998**, *120* (22), 5579–5580.

(23) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* **2003**, *103* (8), 2829–2844.

(24) Wu, T. R.; Chong, J. M. Asymmetric Conjugate Alkenylation of Enones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2007**, *129* (16), 4908–4909.

(25) Turner, H. M.; Patel, J.; Niljianskul, N.; Chong, J. M. Binaphthol-Catalyzed Asymmetric Conjugate Arylboration of Enones. *Org. Lett.* **2011**, *13* (21), 5796–5799.

(26) Pellegrinet, S. C.; Goodman, J. M. Asymmetric Conjugate Addition of Alkynylboronates to Enones: Rationale for the Intriguing Catalysis Exerted by Binaphthols. *J. Am. Chem. Soc.* **2006**, *128* (10), 3116–3117.

(27) Sugiura, M.; Kinoshita, R.; Nakajima, M. O-Monoacyltartaric Acid Catalyzed Enantioselective Conjugate Addition of a Boronic Acid to Dienones: Application to the Synthesis of Optically Active Cyclopentenones. *Org. Lett.* **2014**, *16* (19), 5172–5175.

(28) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. Theoretical Study of the Asymmetric Conjugate Alkenylation of Enones Catalyzed by Binaphthols. *J. Org. Chem.* **2008**, *73* (13), 5078–5089.

(29) Nguyen, T. S.; Yang, M. S.; May, J. A. Experimental Mechanistic Insight into the BINOL-Catalyzed Enantioselective Conjugate Addition of Boronates to Enones. *Tetrahedron Lett.* **2015**, *56* (23), 3337–3341.

(30) Unaleroglu, C.; Aytac, S.; Temelli, B. Copper Triflate Catalyzed Regioselective Alkylation of Pyrrole: Conversion of 2-Alkylated Pyrroles to Novel Pyrrolizine Derivatives by Self-Cyclization. *HETEROCYCLES* **2007**, *71* (11), 2427.

(31) Chen, H.-X.; Zhang, Y.; Zhang, Y.; He, X.; Zhang, Z.-W.; Liang, H.; He, W.; Jiang, X.; Chen, X.; Qiu, L. Synthesis of Six-Membered Spirooxindoles via a Chiral Brønsted Acid-Catalyzed Asymmetric Intramolecular Friedel–Crafts Reaction. *RSC Adv.* **2018**, *8* (65), 37035–37039.

(32) May, J. A.; Boylan, A.; Nguyen, T. S.; Lundy, B. J.; Li, J.-Y.; Vallakati, R.; Sundstrom, S. Rate Dependence on Inductive and Resonance Effects for the Organocatalyzed Enantioselective Conjugate Addition of Alkenyl and Alkynyl Boronic Acids to β-Indolyl Enones and β-Pyrrolyl Enones. *Molecules* **2021**, *26* (6), 1615.

(33) Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. Bf3 Etherate Mediated 1,4-Addition of 1-Alkenyldialkoxyboranes to α,β-Unsaturated Ketones. A Stereoselective Synthesis of γ, δ-Unsaturated Ketones. *Tetrahedron Lett.* **1990**, *31* (2), 247–250.

(34) Fujishima, H.; Takada, E.; Kara, S.; Suzuki, A. Boron Trifluoride Etherate Mediated 1,4-Addition of (1-Alkynyl)Diisopropoxyboranes to α,β-Unsaturated Ketones. A Convenient New Route to 3-Alkynyl Ketone Synthesis. *Chem. Lett.* **2006**, *21* (4), 695–698.

(35) Takada, E.; Hara, S.; Suzuki, A. A Stereoselective Synthesis of Γδ-Unsaturated Ketones Possessing Perfluoroalkyl Groups by Trifluoroborane Etherate Mediated 1,4-Addition Reaction of Alkenyldiisopropoxyboranes to α,β-Unsaturated Ketones. *Tetrahedron Lett.* **1993**, *34* (44), 7067–7070.

(36) Hara, S.; Ishimura, S.; Suzuki, A. Cyanuric Fluoride-Induced 1,4-Addition Reaction of Alkenylboronic Acids to α,β-Unsaturated Ketones. Stereoselective Synthesis of γ,δ-Unsaturated Ketones Having Functionalities. *Synlett* **1996**, *1996* (10), 993–994.

(37) Hara, S.; Shudoh, H.; Ishimura, S.; Suzuki, A. The Regioselective 1,4-Addition Reaction of Alkenylboronic Acids to α,β,A′,B′-Unsaturated Ketones. *Bull. Chem. Soc. Jpn.* **1998**, *71* (10), 2403–2408.

(38) Yoshida, K.; Hayashi, T. Rhodium-Catalyzed Additions of Boronic Acids to Alkenes and Carbonyl Compounds. In *Boronic Acids*; John Wiley & Sons, Ltd, 2006; pp 171–203.

(39) Chong, J. M.; Shen, L.; Taylor, N. J. Asymmetric Conjugate Addition of Alkynylboronates to Enones. *J. Am. Chem. Soc.* **2000**, *122* (8), 1822–1823.

(40) Wu, T. R.; Chong, J. M. Ligand-Catalyzed Asymmetric Alkynylboration of Enones: A New Paradigm for Asymmetric Synthesis Using Organoboranes. *J. Am. Chem. Soc.* **2005**, *127* (10), 3244–3245.

(41) Wu, T. R.; Chong, J. M. Asymmetric Conjugate Alkenylation of Enones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2007**, *129* (16), 4908–4909.

(42) Turner, H. M.; Patel, J.; Niljianskul, N.; Chong, J. M. Binaphthol-Catalyzed Asymmetric Conjugate Arylboration of Enones. *Org. Lett.* **2011**, *13* (21), 5796–5799.

(43) Sugiura, M.; Tokudomi, M.; Nakajima, M. Enantioselective Conjugate Addition of Boronic Acids to Enones Catalyzed by O-Monoacyltartaric Acids. *Chem. Commun.* **2010**, *46* (41), 7799–7800.

(44) Kotani, S.; Osakama, K.; Sugiura, M.; Nakajima, M. A Tertiary Amine as A Hydride Donor: Trichlorosilyl Triflate-Mediated Conjugate Reduction of Unsaturated Ketones. *Org. Lett.* **2011**, *13* (15), 3968–3971.

(45) Grimblat, N.; Sugiura, M.; Pellegrinet, S. C. A Hydrogen Bond Rationale for the Enantioselective β-Alkenylboration of Enones Catalyzed by *O* -Monoacyltartaric Acids. *J. Org. Chem.* **2014**, *79* (14), 6754–6758.

(46) Inokuma, T.; Takasu, K.; Sakaeda, T.; Takemoto*, Y. Hydroxyl Group-Directed Organocatalytic Asymmetric Michael Addition of α,β-Unsaturated Ketones with Alkenylboronic Acids. *Org. Lett.* **2009**, *11* (11), 2425–2428.

(47) Grimblat, N.; Sugiura, M.; Pellegrinet, S. C. A Hydrogen Bond Rationale for the Enantioselective β-Alkenylboration of Enones Catalyzed by O-Monoacyltartaric Acids. *J. Org. Chem.* **2014**, *79* (14), 6754–6758.

(48) Nguyen, T. S.; Yang, M. S.; May, J. A. Experimental Mechanistic Insight into the BINOL-Catalyzed Enantioselective Conjugate Addition of Boronates to Enones. *Tetrahedron Lett.* **2015**, *56* (23), 3337–3341.

(49) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Ethers: Enantioselective Synthesis of Diarylethanes. *J. Am. Chem. Soc.* **2011**, *133* (3), 389–391.

(50) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. Nickel-Catalyzed Cross-Couplings of Benzylic Pivalates with Arylboroxines: Stereospecific Formation of Diarylalkanes and Triarylmethanes. *J. Am. Chem. Soc.* **2013**, *135* (9), 3307–3310.

(51) We Also Examined the Use of an Additional Lewis Acid as Reported by Yu and Mao (Reference 52).

(52) Wang, J.-F.; Meng, X.; Zhang, C.-H.; Yu, C.-M.; Mao, B. Organocatalytic Enantioselective Conjugate Alkynylation of β-Aminoenones: Access to Chiral β-Alkynyl-β-Amino Carbonyl Derivatives. *Org. Lett.* **2020**, *22* (19), 7427–7432.

(53) Chen, H.-X.; Zhang, Y.; Zhang, Y.; He, X.; Zhang, Z.-W.; Liang, H.; He, W.; Jiang, X.; Chen, X.; Qiu, L. Synthesis of Six-Membered Spirooxindoles via a Chiral Brønsted Acid-Catalyzed Asymmetric Intramolecular Friedel–Crafts Reaction. *RSC Adv.* **2018**, *8* (65), 37035–37039.

CHAPTER 3: PROPARGYLIC ALCOHOL SUBSTITUTION

3.1 Utility of Propargylic Alcohols

Propargylic alcohols are very versatile substrates for organic chemistry reactions. They can transform into allenes, be used for C-C bond formations, undergo cyclizations, and much more. In Figure 3.1, there are a few common and useful types of transformations. Propargylic substitution reactions are a very powerful transformation to add a nucleophile adjacent to an alkyne. Once this substituted product is formed, the alkyne can be used to synthesize other compounds that are more complex, such as natural products. Most propargylic substitution reactions result in tertiary carbon formation. There are only a limited number of examples of quaternary carbon center formation and even fewer examples of complex quaternary carbons where R_3 is not a methyl or R_2 and R_3 are not forming a carbocycle.

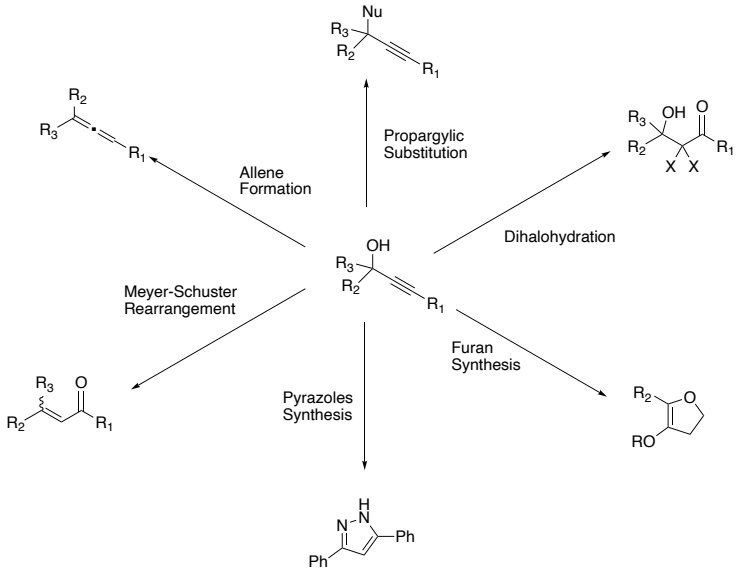


Figure 3.1. Propargylic substitution transformation

3.2 Origins of Propargylic Substitution Reactions

Propargylic alcohols have been used as substrates for a variety of chemical reactions, in which the alcohol is replaced with a nucleophile. The π-system of the alkyne offers a potential for a variety of synthetic transformations as well.

3.2.1 Nicholas Reaction

One of the earliest propargylic substitution reactions is the Nicholas Reaction.[54] In 1977, Nicholas published a four-step sequence that begins with a propargylic alcohol coordinating a cobalt catalyst, $Co_2(CO)_8$ (Figure 3.2). $Co_2(CO)_8$ helps to promote the nucleophilic addition by stabilizing intermediate cationic charge. With the addition of acid, the hydroxyl group is used as the leaving group for an S_N1 reaction. This strategy has a few major drawbacks though. The first is the need for stoichiometric amounts of the cobalt catalyst, which then requires additional steps to remove the catalyst. Ideally, this transformation can be accomplished in a single step more efficiently.

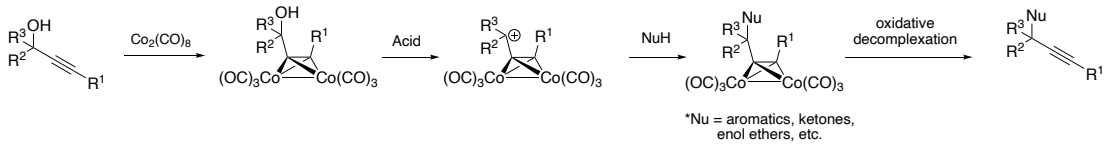


Figure 3.2. Nicholas Reaction

3.2.2 Metal Catalyzed

In 1994, Murahashi's group published the first copper catalyzed propargylic substitution.[55] It used propargylic acetates with a terminal alkynes as the substrates and amines as the nucleophiles. This provided moderate amounts of the substituted propargylic product, around 75% yield. After this catalysis was established, asymmetric versions were developed (Figure 3.3).[56–59] The copper catalyst systems

tend to only work well with amines as nucleophiles and acetates as leaving groups. They also go through an allenylidene intermediate with copper similar to ruthenium catalyzed propargylic substitution reactions. Because of this allenylidene intermediate, the substrates that work well with these catalysts bear a terminal alkyne.

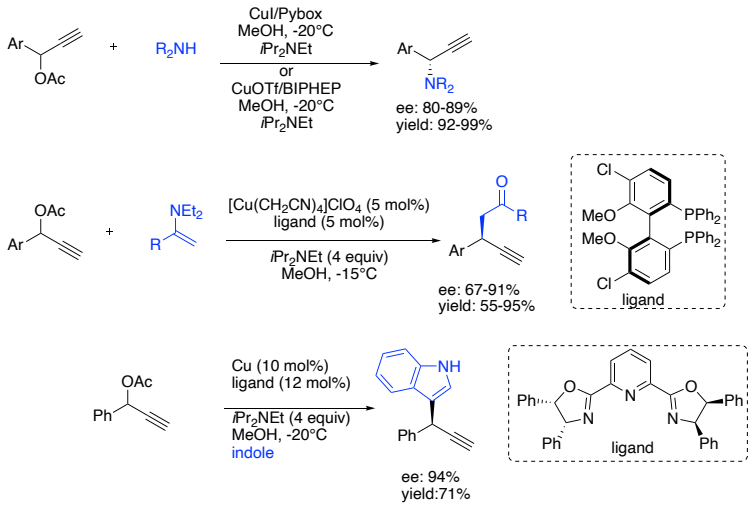


Figure 3.3. Enantioselective copper catalyzed propargylic substitution

Diruthenium catalysts have been used to catalytically mediate propargylic substitution reactions on propargylic substrates using a variety of nucleophiles. Studies of the mechanism have shown that the key intermediate of this reaction is a ruthenium allenylidene **2** (Figure 3.4).[60] A proposed mechanistic pathway is shown in Figure 3.4. The first step of this mechanism is the formation of a vinylidene complex **1** (Figure 3.4) from the reaction of the propargylic alcohol with the ruthenium catalyst. Next, the complex is dehydrated and the allenylidene complex **2** (Figure 3.4) is formed. Which is then followed by an attack of the nucleophile at the γ-carbon, which then leads to another vinylidene complex **3** (Figure 3.4). Then, the vinylidene complex is transformed into the π – alkyne complex **4** (Figure 3.4), and finally the substituted propargylic product is liberated.

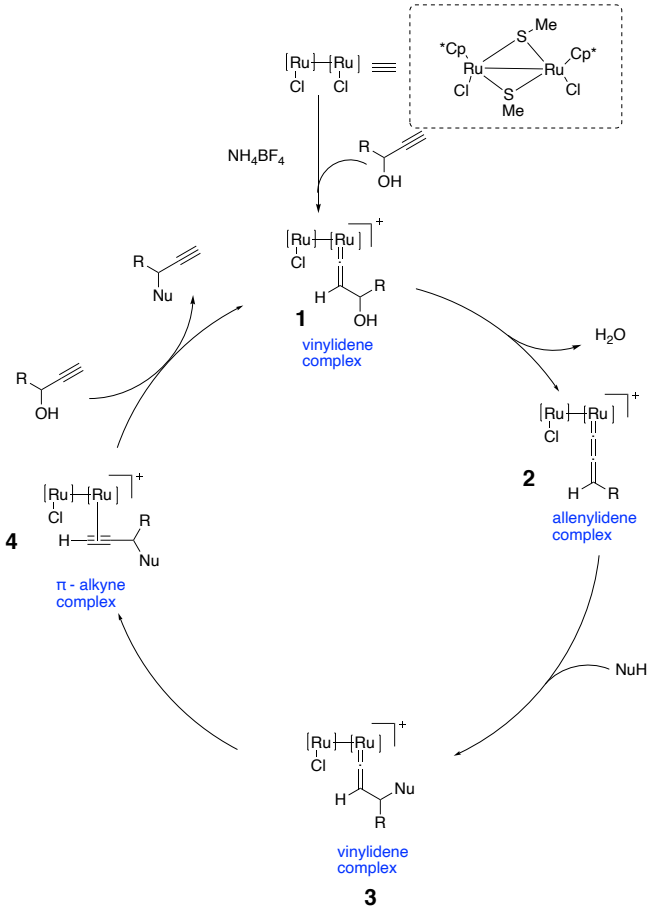


Figure 3.4. Proposed ruthenium catalyzed propargylic substitution reaction pathway

Nishibayashi's group has shown that the diruthenium complex catalyzes the propargylic reaction quite well and that the reaction is tolerant to a variety of functional groups on the nucleophile.[61–67] In Figure 3.5, there is an overview of a variety of substrates and nucleophiles that have worked in fairly good yields. Unfortunately, there are only a limited number of examples that produce quaternary centers, and virtually none that have chiral centers. Another major limitation of ruthenium catalyzed propargylic alcohol substitution reaction is that the alkyne must be a terminal alkyne because of the formation of the vinylidene complex that is formed during the reaction. This limits the utility of this type of reaction for

transformations needed in more complex structures, such as those used in total synthesizes of natural products or in the synthesis of pharmaceutical targets.

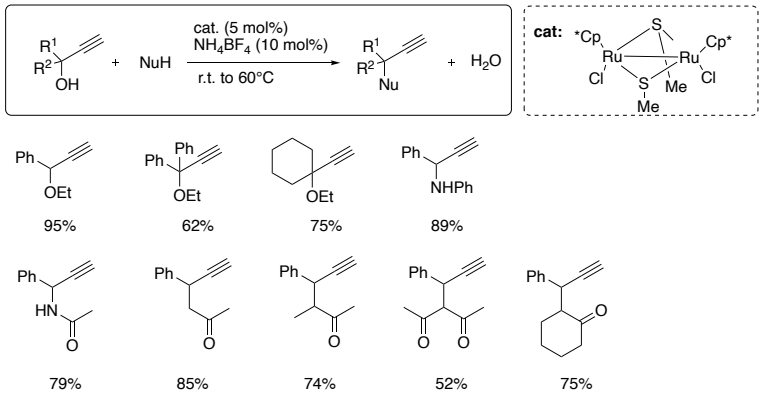


Figure 3.5. Ruthenium catalyzed propargylic substitution

Nishibayashi and co-workers have also developed an enantioselective version of the diruthenium catalyst.[68,69] They found that if the methyl groups on the sulfurs were replaced with phenyl groups and the propargylic alcohol substrate also possessed a phenyl group as one of the "R" groups, the product would be enantioenriched. This is a result of edge to face aromatic $\pi - \pi$ interactions with the phenyl ligand of the catalyst and the phenyl group of the propargylic alcohol.

3.2.3 Acid Catalyzed

In general, both Lewis acids and Brønsted acids can help mediate propargylic substitution reactions with internal alkynes. Unlike the metal mediated propargylic substitution reactions, the Lewis and Brønsted acids are not constrained to metal-allenylidene intermediates so they can be utilized with internal alkynes. That mediates one of the biggest drawbacks of the metal-catalyzed propargylic alcohol/acetate substitution reactions.

The Champagne group used a gold-based Brønsted acid to catalyze nucleophilic addition to an aryl propargylic alcohol. These conditions were compatible with a variety of nucleophiles such as thiols, alcohols, aromatics and allylsilanes. However, this reaction appeared to go through a S_N1 type reaction. They started with an enantioenriched starting material, but the product had 0% ee's since a carbocation is presumably formed during the reaction, so the stereochemical control was lost (Figure 3.6, Eq. 1).[70] Use of *p*–toluenesulfonic acid monohydrate, another common Brønsted acid, also promoted propargylic alcohol substitution (Figure 3.6, Eq. 2).[71] It was compatible with a variety of nucleophiles but the yields varied greatly from 52-90%.

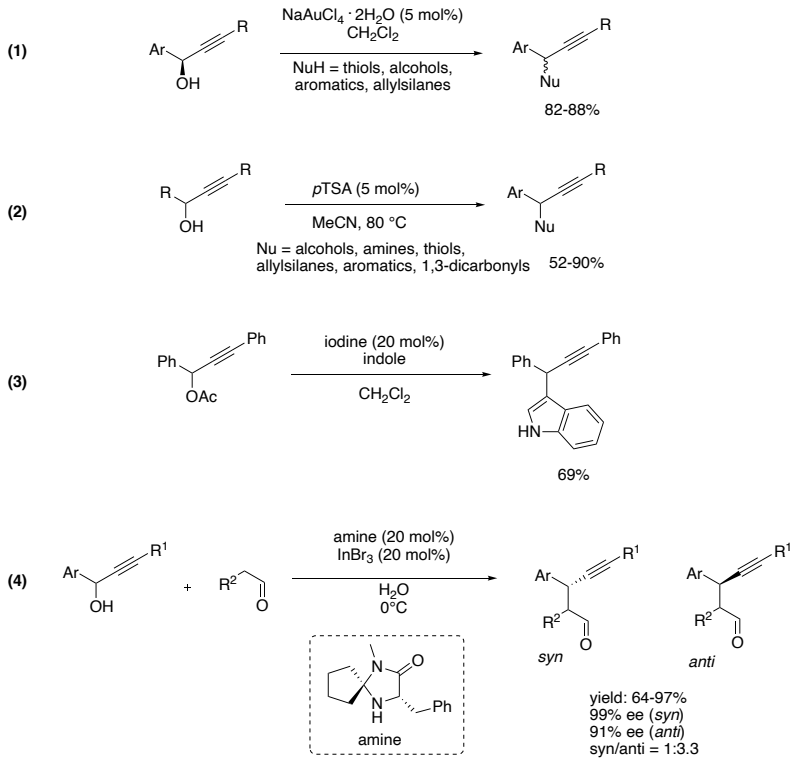


Figure 3.6. Examples of Lewis and Brønsted acid catalyzed propargylic substitution

Mild Lewis acids, such as iodine, can promote propargylic substitution reactions when the leaving group in an acetate (Figure 3.6, Eq. 3).[72] These substitutions work with a few heterocycles as nucleophiles. Unfortunately, iodine is not compatible with many substrates depending on the functional groups present.

Cozzi's group greatly improved the diastereoselectivity of the nucleophilic addition to the propargylic alcohols. They used a Lewis acid $InBr_3$ catalyst as an activator of the propargylic alcohol that had an internal alkyne (Figure 3.4, Eq. 4).[73] By using an amine as an organocatalyst and water as a solvent they were able to obtain high enantioselectivity and increase the diasteroselectivity of the reaction.

Lewis and Brønsted acids tend to work well for propargylic hydroxyls that are also benzylic. This is likely due to the aryl substituent offering increased stabilization of the carbocation formed in a S_N1 type reactions. These reactions tend to result in racemic products. Although there have been significant advances in enantioselective and diastereoselective Lewis acid catalyzed propargylic alcohol substitution reactions, the conditions are often not tolerant of a wide variety of substrates or nucleophiles.

3.2.4 Propargylic Substitution Reactions with Boronic Acids

Propargylic nucleophilic substitutions using boronic acids are still underexplored. In 2005, the Ihara group developed a synthesis with propargylic alcohols and a common cross coupling catalyst, $Pd(PPh_3)_4$, to replace the hydroxyl group with an aryl group.[74] If the R^3 group in alcohol **5** was just a hydrogen (Figure 3.7), they isolated mostly the allene product **6**. If the R^3 was larger like an isopropyl group or phenyl, they saw a mixture of products, **6** and **7** (Figure 3.7). While this

reaction is the first of its kind, it is limited by requiring an aryl boronic acid and offers limited regioselectivity depending on the substrate.

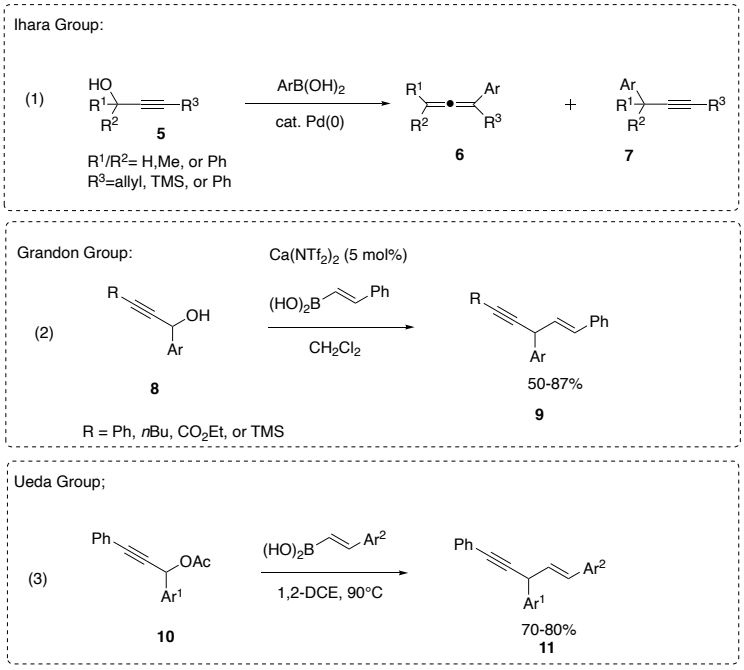


Figure 3.7. Nucleophilic propargylic substitution with boronic acids

Nearly a decade later, Grandon's group came back to this problem and were able to develop a more regioselective reaction (Figure 3.7, Eq. 2).[75] They took a transition metal free approach, and utilized a calcium based catalyst in order to activate the hydroxyl group by forming a six member transition state with the hydroxyl, calcium, and boronic acid. Although this reaction was regioselective, it's boronic acid scope was limited to just (*E*)–styrylboronic acid. In order to exhibit good yields, the hydroxyl group also had to be adjacent to an aryl group.

Ueda's group also utilized boronic acids for nucleophilic propargylic substitution (Figure 3.7, Eq. 3).[76] They did not need to use a metal catalyst for the nucleophilic boronic acid to replace the acetate. Unlike the other two reactions from

the Grandon and the Ihara groups, this reaction takes advantage of using acetate as a leaving group instead of a hydroxyl group. Since they used a better leaving group, OAc, there was not a need for an additional catalyst or additive; however, they did need to heat the reaction to fairly high temperatures for the reaction to proceed. Their reaction conditions only work with aryl propargylic acetate substates and alkenyl boronic acid nucleophiles, since the aryl groups are needed to stabilize the developing cationic charge from the acetate group leaving.

Although these three groups have made significant advancements to nucleophilic propargylic substitution reactions with boronic acids, there are still areas that need improvement. Firstly, none of these conditions with boronic acids are compatible with aliphatic propargylic alcohol substates. They are also not compatible with a wide variety of boronic acids, and all of them depend on the boronic acids having an aryl group.

3.3 Quaternary Carbon Center Construction

In natural product synthesis, one of the fundamental challenges of building more complex structures is the ability to form quaternary carbons. All-carbon quaternary centers are difficult to synthesize because of the steric hinderance of the fully substituted tetrahedral geometry of the carbon. Examples of recently discovered natural products can be seen in Figure 3.8, each of them have been found to have biological activity such as anti-inflammatory (**12**),[77] inhibitory effects on lipopolysaccharide induced nitric oxide production (**13**),[78] anticancer effects (**14**),[79] and opioid receptor agonist (**15**).[80] In the past, carbon bond center formation have come from the strategies where the carbon center acts as a nucleophile, electrophile, or

radical to strategically construct quaternary centers. Unfortunately, there is not a universal method to form these quaternary carbon centers in highly complex natural products. The ability to construct the carbon center depends on each unique case. With the complexity present, and the ability to form quaternary carbon centers by different methods is particularly useful to help solve these problems that arise during multistep synthesizes.

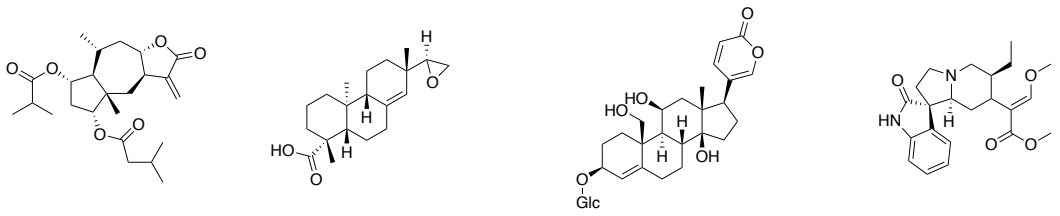


Figure 3.8. Recent published natural product with quaternary carbons[77,78,81]

CHAPTER 4: PROPARGYLIC SUBSTITUTION USING GALLIUM AND SILVER CATLAYSTS AND BORONIC ACIDS

4.1 Limitations and Research Goals

Propargylic substitutions are difficult to achieve with aliphatic alcohols, since the hydroxyl group is a poor leaving group, the intermediates are unstable, and 2 electrophilic sites can lead to an alkyne or allene. Additionally, ruthenium catalyzed nucleophilic substitution with propargylic alcohols have been limited to terminal alkyne substrates. Similarly, copper catalysis only worked well with terminal alkynes because of the allenylidene intermediate that is formed during the reaction. Copper catalyzed nucleophilic substitutions also require a good leaving group such as an acetate. In both ruthenium and copper catalysis, chiral quaternary carbon formations have been virtually non-existent in propargylic nucleophilic substitutions. There are also a very limited number of examples of any type of aliphatic substituents, most examples only work with an aryl substituent next to the propargylic alcohol or acetate. Propargylic alcohols with aliphatic substituents are usually not very productive substrates for nucleophilic substitution reactions because of the competitive elimination pathway.

This project was focused on developing effective reaction conditions to allow for nucleophilic propargylic substitutions with boronic acids, then utilizing these conditions on a variety of substrates with a diverse scope of boronic acid nucleophiles. Another goal of this project was to develop a more “universal” method for arriving at the nucleophilic substitution products. Up to this point, aliphatic propargylic alcohols were not compatible with boronic acids as nucleophiles, since they do not offer

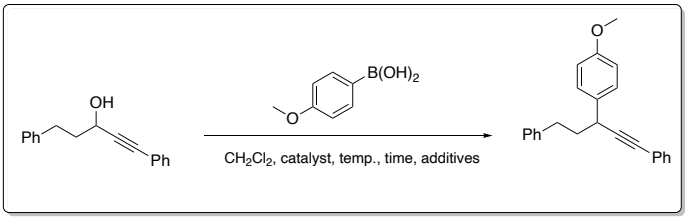
intrinsic stabilization of the cation in the substrate, like aryl propargylic alcohols offer.

4.2 Results

4.2.1 Optimization of Tertiary Carbon Center Formation Reaction Conditions

A co-worker in the May Lab, Dr. Truong Nguyen, optimized the reaction conditions for tertiary carbon formation from secondary aliphatic propargylic alcohols. He started with conditions that had been developed in the May group to facilitate the formation of carbocations from donor/acceptor cyclopropanes.[82] He found that Brønsted acids were ineffective in catalyzing the nucleophilic substitution reaction; the elimination product was formed instead (Table 4.1, entry 1). However, when the catalyst was switched out for a mixed gallium/silver catalyst system (entry 2), the reaction proceeded in just 2 h with 90% yield. In entry 3, that same mixed catalyst system was used but an aryl trifluoroborate salt was used instead of a boronic acid, but the conversion to the product was very low. The $AgSbF_6$ was initially added to generate an active cationic Gallium catalyst. However when $AgSbF_6$ was used alone, the reaction still generated the product in similarly high yield if the reaction was heated slightly to 40 °C and ran for 12 h (Table 4.1, entries **4** and **5**). The higher reactivity of the mixed system indicated that Lewis acidity of cationic gallium complex played a major role in the reaction's outcome. $GaCl_3$ was also examined but maximized at 72% yield after 5 h (Table 4.1, entry **6**).

Table 4.1 Reaction condition evaluation



entry	catalyst (mol%)	temp. (°C)	additive	time (h)	yield[a]
1[b]	Brønsted acids (10-50%)	r.t.	-	24-48	-
2	$IPrGaCl_3$(10%)	0 to r.t.	$AgSbF_6$ (10%)	2	90
3[c]	$IPrGaCl_3$(10%)	0 to r.t.	$AgSbF_6$ (10%)	-	-
4	$AgSbF_6$(10%)	23	-	12	15
5	$AgSbF_6$(10%)	40	-	12	91
6	$GaCl_3$(50%)	0	-	5	72

[a] NMR yields. [b] Brønsted acids = $(n\text{-Bu})_4NHSO_4$, *p*TSA, TFA. [c]Aryl trifluoroborate used instead of aryl boronic acid.

4.2.2 Mechanistic Considerations of Propargylic Substitution Reaction in the May Group with Silver and Gallium Catalysts

Two different mechanistic pathways for the silver and gallium catalyzed propargylic substitution reaction were postulated in Figure 4.1. Two reaction conditions initially worked well for the propargylic substitution reaction were boronic acid nucleophile and $AgSbF_6$ or $(IPr)GaCl_3/AgSbF_6$ catalyst. It was thought that the metal could coordinate with the alkyne and hydroxyl to form the first intermediate **2**. From this intermediate, two mechanistic pathways are plausible. The first is a S_N2 type attack of the nucleophile, which would result in optically active product **3** with an

inversion of stereochemistry. The second possible pathway is a S_N1 type attack, which would pass through carbocation **4** and form the racemic product as a result. In order to test this hypothesis, a co-worker, Dr. Po-An Chen, started with an enantioenriched propargylic alcohol, **1**. Upon completion of the reaction he determined that the final product was racemic, suggesting that the mechanistic pathway goes through the S_N1 type reaction or that the starting material is able to racemize.

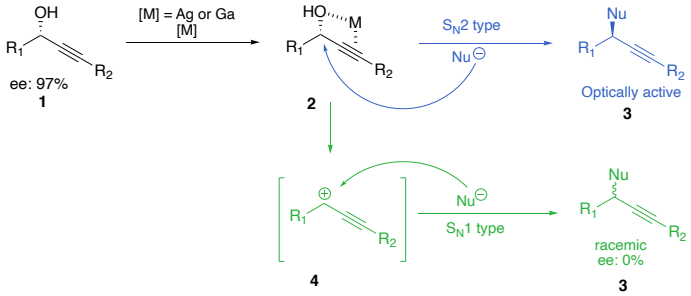


Figure 4.1. Proposed S_N1 vs. S_N2 mechanistic pathways

Interestingly, the trifluoroborate salts did not serve as good nucleophiles in this reaction and did not form the propargylic substitution product. This indicates that the hydroxyl group of the boronic acid might be playing a role in the reaction mechanism. Therefore we propose a different mechanistic pathway, where the metal recruits the acid to produce adduct **9** (Figure 4.2).

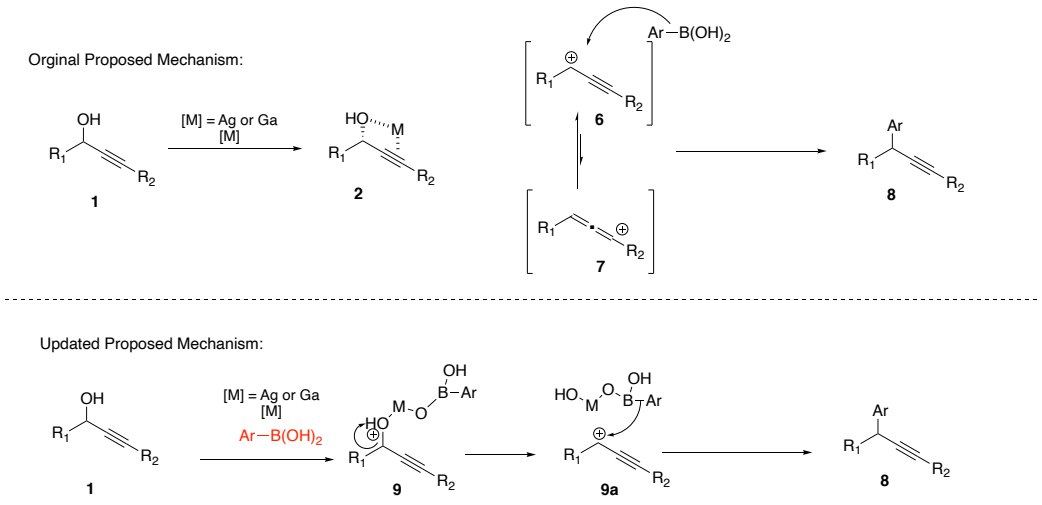


Figure 4.2. Proposed mechanistic pathways

Later, a few control experiments were conducted to further understand the reaction conditions. One of these experiments was replacing the catalyst with HCl to ensure that the $GaCl_3$ is playing a significant role in the reaction and not adventitious acids formed in situ. With HCl in the reaction instead of a gallium or silver catalyst, no nucleophilic substitution was observed. Another control experiment involved replacing the 4-methoxylphenylboronic acid with anisole to see if nucleophilic substitution would still occur. However, no nucleophilic substitution was observed. These experiments further support that the catalysts and the boronic acid play a significant role in the success of the controlled nucleophilic substitution.

4.2.3 Tertiary Carbon Reaction Scope

Most metal catalyzed propargylic substitution reactions require a terminal alkyne in order for the reaction to proceed because of the formation of the vinylidene complex during the reaction. Since $(IPr)GaCl_3$, $AgSbF_6$, and $GaCl_3$ catalysts do not proceed through a similar mechanistic pathway as the ruthenium or copper catalyzed propargylic substitution reactions, they are not constrained to these typical terminal

alkyne substrate systems and are able to react with internal alkynes instead. More recently, a few limited examples of boronic acids as nucleophiles have been used in propargylic substitution reactions to form tertiary carbons, but they typically require R_1 to be a methyl group or an electron rich aryl ring and mainly utilized styrene boronic acid as the nucleophile.[75] However, we have been able to utilize an internal alkyne in the propargylic substitution reaction along with boronic acids in systems where R_1 is a variety of groups, such as bulky groups, aryl groups, alkyl, and alkenyl groups (Figure 4.2). In addition to utilizing a variety of substrates, we have also been able to vary the boronic acids as the nucleophile to form new C-C bonds to access unique tertiary carbon centers (Figure 4.3).

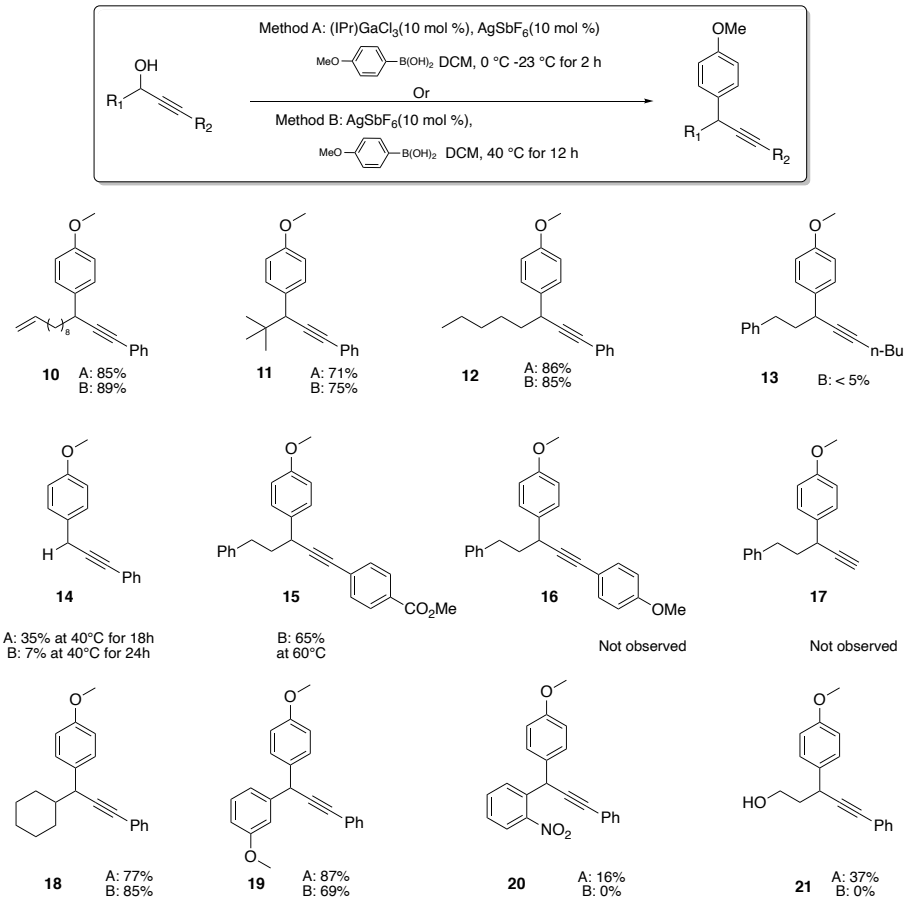


Figure 4.3. Substrate scope

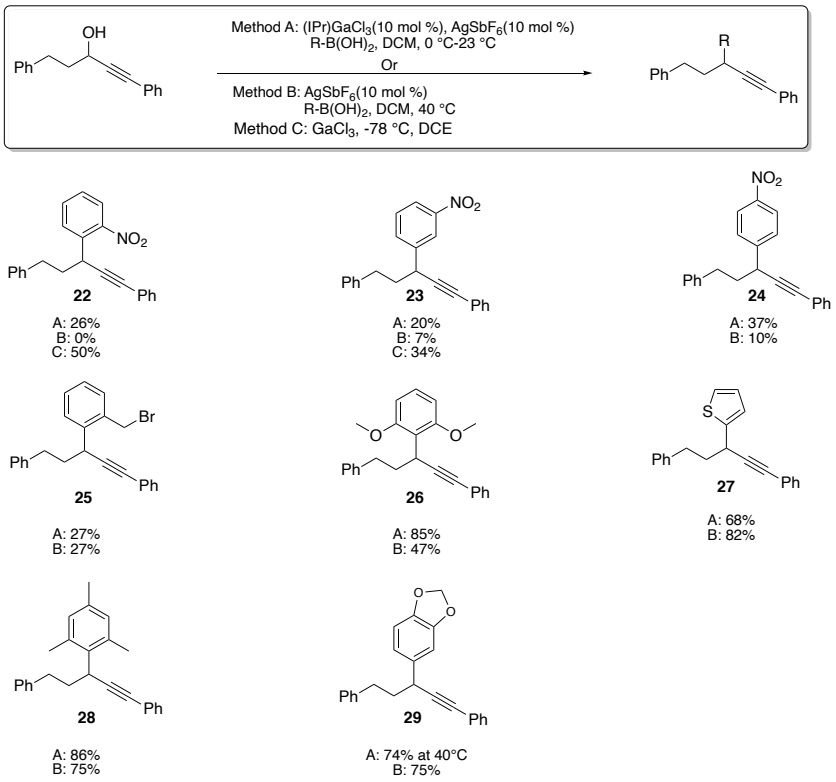


Figure 4.4. Nucleophile scope

Two catalytic conditions, (IPr)$GaCl_3$/$AgSbF_6$ and $AgSbF_6$, were examined with a variety of tertiary propargylic alcohols. Both catalytic conditions were generally compatible with alkyl substituted substrates (Figure 4.3, **11**,**12**, and **18**) and resulted in moderate yields of the propargylated products. When the substituents on the alkyne groups were varied, an electron-poor substrate resulted in a moderate yield when the temperature of the reaction was increased (see Figure 4.3, **15**). When the substrate was electron rich, the corresponding product **16** (Figure 4.3) was not formed, presumably due to the competitive isomerization of the alkyne group to the allene product. The use of a primary propargylic alcohol resulted in a poor yield (see **14**), and substrates bearing a terminal alkyne did not afford any product (see **17**).

Reaction conditions of method A, (IPr)$GaCl_3$/$AgSbF_6$ with boronic acid at 0-23 °C, chemoselectively reacted with the tertiary propargylic alcohol over another hydroxyl present in the same structure (see **21**).

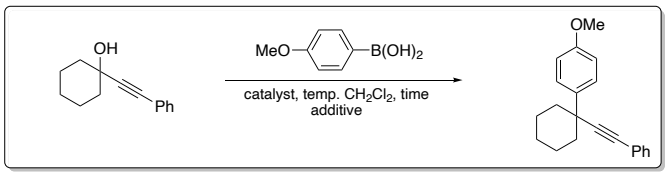
We then began looking into the nucleophile scope. Here we found that electron rich boronic acids, such as those used to form products **26** and **28 (**Figure 4.4), resulted in moderate yields by utilizing the (IPr)$GaCl_3$/$AgSbF_6$ system from method A. The heterocyclic boronic acids tended to result in higher yields (Figure 4.4, **27** and **29**) by implementing method B, $AgSbF_6$ with boronic acid at 40 °C, over method A. For more problematic nucleophiles such as 2-nitrophenyl and 3-nitrophenyl boronic acids, we found that method A and B did not work well since these electron poor boronic acids, tended to be beat out by the competitive elimination pathway. Consequently, we employed a third method, C which was $GaCl_3$ with boronic acid at -78 °C, and were able to improve the reaction which resulted in more of the nucleophilic tertiary substitution products (Figure 4.4, **22** and **23**) than the other two reactions conditions.

4.2.4 Optimization of Quaternary Carbon Center Formation Reaction Conditions

We found out that the above reaction conditions did not carry over well to form quaternary carbon centers. The conditions with (IPr)$GaCl_3$/$AgSbF_6$ as the catalyst no longer worked well with the more hindered tertiary propargylic alcohol, so that the product would be an all carbon center. The yield for this reaction was 14%, and the remaining mass was mostly the elimination product. From here, many other additives and catalysts were examined to improve the yield, including a wide array of

Lewis acids and silver salts, although most resulted in no reaction or elimination. (IPr)$GaCl_3$ was originally analyzed since it was bench stable and was not sensitive to water. Although its precursor, $GaCl_3$, was eventually found to be a better catalyst for quaternary center formation using boronic acid. $GaCl_3$ is very hydroscopic so it cannot be weighed outside of the glovebox without generating hydrochloric acid and quickly. After completing a solvent screen, dichloroethane proved to be a better solvent than the original conditions using dichloromethane.

Table 4.2 Optimization of reaction conditions



entry	catalyst (mol%)	temp. (°C)	additive	time (h)	yield(%)[a]
1	$IPrGaCl_3$(10%)	0 to 23	$AgSbF_6$ (10%)	8	14
2	$IPrGaCl_3$(10%)	0 to 23	$NaBArF^{24}$	18	40
3	$IPrGaBr_3$(10%)	0 to 23	$NaBArF^{24}$	16	51
4	$GaCl_3$(30%)	-78	-	2	66
5[b]	$GaCl_3$(30%)	-78	-	2	71

[a] NMR yields. [b] DCE instead of DCM

4.2.5 Quaternary Carbon Reaction Scope

With the new set of reaction conditions in hand, we started to explore the nucleophile scope. Electron rich boronic acid nucleophiles reacted to form a variety of new quaternary carbon centers, while electron poor nucleophiles, such as 2-nitro phenylboronic acid, only resulted in elimination product and not nucleophilic

substitution. Heteroaryl boronic acid nucleophiles also resulted in some nucleophilic addition but the mass balance was the elimination product. Although these yields are not high, the ability to construct all carbon quaternary centers adjacent to an alkyne is unique to this point.

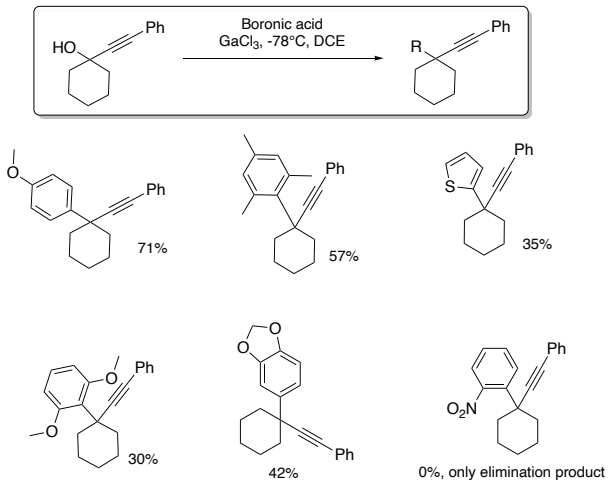


Figure 4.5. Nucleophile scope for quaternary carbon centers

When varying the substrates for quaternary carbon centers, three different products formed. The desired product with a quaternary carbon center, the elimination product, and allene from the nucleophile attacking the alkyne with the π-bond migration. When the starting material has phenyl rings for the R groups instead of a alkyl groups, the elimination product is more difficult to form so we see more formation of the quaternary carbon product. While if one of the R groups is a alkyl group, the elimination product is favored along with the allene derived product. When methoxy groups or halogenated groups are added to the aryl ring, the quaternary product is not produced, and only the elimination and the allene products are observed.

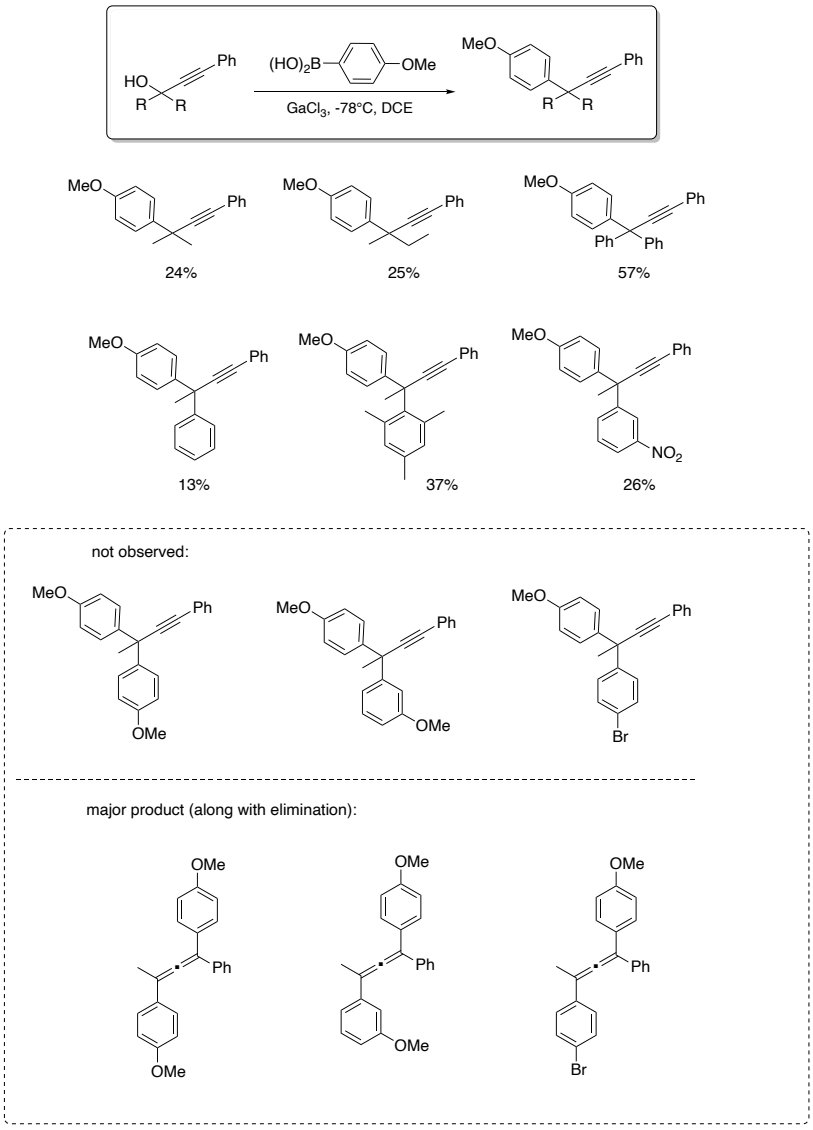


Figure 4.6. Substrate scope

4.3 Conclusions

We have developed a novel method using three different catalyst systems to accomplish the first propargylic substitution reaction between propargylic alcohols that bear alkyl substituents and aryl boronic acids. (IPr)$GaCl_3$/$AgSbF_6$, $AgSbF_6$, and $GaCl_3$ have been used successfully on tertiary propargylic alcohol substrates, while $GaCl_3$ showed to be the best catalyst to date for forming quaternary carbon centers.

This was also the first propargylic substitution reaction between propargylic alcohols and boronic acids to form quaternary carbon centers.

4.4 Experimental Section

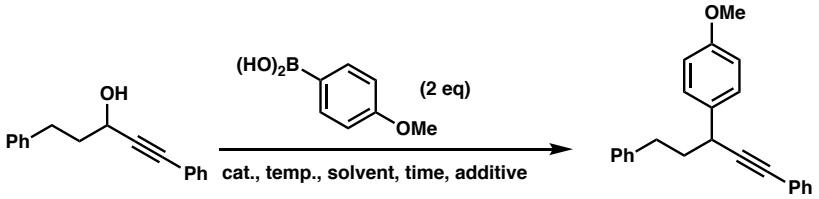
4.4.1 Materials and Methods

Catalyst screens:

NMR yield and ratio calculation:

To the crude product was added methyl-4-nitro-benzoate (9.1 mg, 0.05 mmol, 0.5 equiv) and CDCl3 (0.7 mL). The yield of B was calculated based on ^{1}H NMR peak integration of the proton (δ = 5.81 ppm, t, J = 7.2 Hz, 1H) relative to the methyl group of methyl-4- nitro-benzoate (δ = 3.98 ppm, s, 3H). NMR data was collected using a relaxation delay of 30 s [Experiments were conducted to show that RD (relaxation delay) = 30 s was sufficient to achieve quantitative information.]

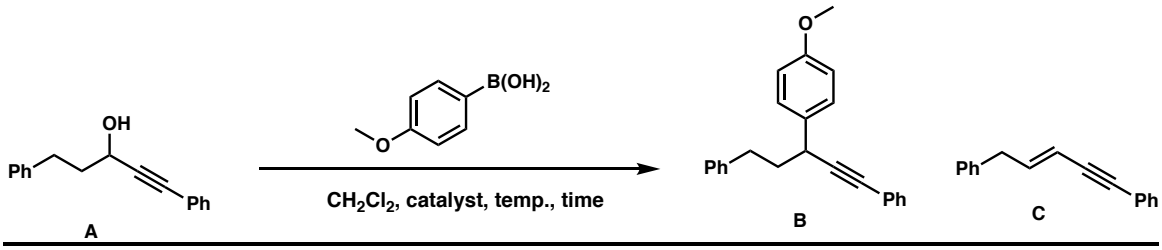
Table 4.3 Screen with secondary alcohols



entry	catalyst	mol %	additive	solvent	temp.	time (h)	yield[a] (%)
1	$iPrGaCl_3$	10	$AgSbF_6$(10 mol %)	DCM	-10 °C	2	90
2[b]	$iPrGaCl_3$	10	$AgSbF_6$(10 mol %)	DCM	-10 °C	24	0
3	$iPrGaCl_3$	10	none	DCM	23 °C	24	0
4	$AgSbF_6$	10	none	DCM	23 °C	12	15
5	$AgSbF_6$	10	none	DCM	40 °C	5	91
6	$GaCl_3$	50	none	DCM	-78 to 23 °C	5	72
7	AgTFA	10	none	DCM	40 °C	24	no reaction
8	AgOTf	10	none	DCM	40 °C	24	no reaction
9	AgF	10	none	DCM	40 °C	24	no reaction
10	$AgSbF_6$	10	none	DCE	40 °C	5	85
11	$AgSbF_6$	10	none	PhCl	40 °C	5	no reaction
12	$AgSbF_6$	10	3Å or 4Å or 5Å MS	DCM	40 °C	24	no reaction
13	$AgSbF_6$	20	iPr-PyBox (40 mol %)	DCM	40 °C	24	no reaction
14	$AgSbF_6$	20	BINAP(20 mol %)	DCM	40 °C	24	no reaction

[a]Determined by crude NMR and TLC; [b]potassium trifluoroborate salt was used instead of boronic acid

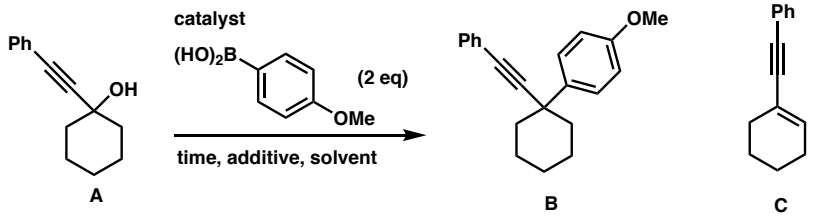
Table 4.4 Screening of Lewis Acids and Bronsted Acids for secondary alcohols



entry	cat. (10 mol %)	additive	Time (h)	temp.	yield[a]
1	$Gd(OTf)_3$	none	48	0 °C to 24 °C	no reaction
2	$CuSO_4$	none	36	0 °C to 40 °C	no reaction
3	LiOTf	none	48	0 °C to 40 °C	no reaction
4	$LiClO_4$	none	48	0 °C to 40 °C	no reaction
5	$LiClO_4$	$(n\text{-}Bu)_4NHSO_4$	48	0 °C to 40 °C	no reaction
6	$Bi(OTf)_3$	none	10	0 °C to 24 °C	C:72%
7	$Cu(OTF)_2$	Pybox (10 mol %)	24	0 °C to 40 °C	major: C
8	$Yb(OTf)_3$	none	36	0 °C to 40 °C	C: 91%
9	$Sb(OTf)_3$	none	42	0 °C to 40 °C	No reaction
10	$Sc(pybox)(OTf)_3$	4Å MS	42	0 °C to 40 °C	no reaction
11	$La(OTf)_3$	none	42	0 °C to 40 °C	no reaction
12	$InCl_3$	none	42	0 °C to 40 °C	major: C
13	$In(OTf)_3$	none	42	0 °C to 24 °C	major: C
14	$InBr_3$	none	42	0 °C to 40 °C	major: C
15	$(n\text{-}Bu)_4NHSO_4$ (30 %)	none	48	24 °C to 40 °C	no reaction
16	*p*TSA	none	48	24 °C to 40 °C	major: C
17	TFA (10-50%)	none	48	24 °C to 40 °C	major: C

[a]Determined by crude NMR and TLC

Table 4.5 Screening conditions for tertiary alcohols by using reported methods

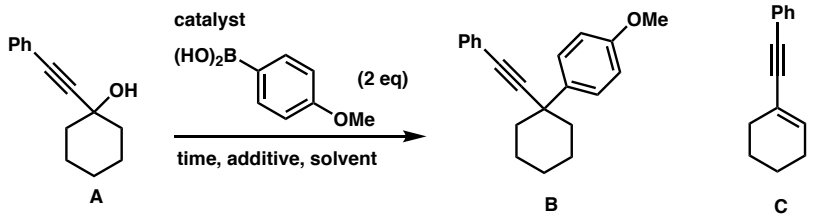


A B C

entry	cat. (10 mol %)	Solvent	temp.	yield[a]
1	$FeCl_3 \cdot H_2O$	DCM	0 °C to 40 °C	no reaction
2	$ZnCl_2$	DCM	0 °C to 40 °C	no reaction
3	$CuBr_2$	$MeNO_2$	0 °C to 40 °C	no reaction
4	CuOTf · ½ benzene	DCM	0 °C to 40 °C	major: C
5	$BiCl_3$	DCM	0 °C to 24 °C	major: C
6	$BiCl_3$	MeCN	0 °C to 40 °C	B + C
7[b]	$BiCl_3$	MeCN	0 °C to 80 °C	no reaction
8	$Ca(NTf_2)_2$/*n*-Bu_4PF_6	DCM	0 °C to 24 °C	B: 8%, C: 85%[c]

[a]Determined by crude NMR and TLC; [b]BF_3K salt was used instead of boronic acid; [c]Isolated yield

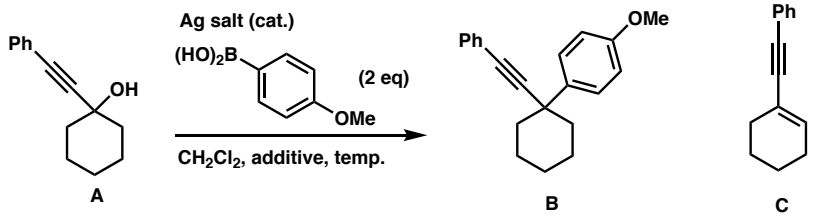
Table 4.6 Screening of Lewis Acid and Bronsted Acid for propargylic substitution of tertiary alcohol



entry	cat. (10 mol %)	additive	Time (h)	temp.	yield[a]
1	$Gd(OTf)_3$	none	29	0 ℃ to 24 ℃	no reaction
2	$CuSO_4$	none	36	0 ℃ to 40 ℃	no reaction
3	LiOTf	none	69	0 ℃ to 40 ℃	no reaction
4	$LiClO_4$	none	39	0 ℃ to 40 ℃	no reaction
5	$LiClO_4$	$(n\text{-}Bu)_4NHSO_4$	39	0 ℃ to 40 ℃	no reaction
6	$Bi(OTf)_3$	none	15	0 ℃ to 24 ℃	major: C
7	$Cu(OTF)_2$	Pybox (10 mol %)	17	0 ℃ to 40 ℃	major: C
8	$Yb(OTf)_3$		50	0 ℃ to 40 ℃	C: 85%
9	$Sb(OTf)_3$	none	24	0 ℃ to 40 ℃	C: 66%
10	$Sc(pybox)(OTf)_3$	4Å MS	40	0 ℃ to 40 ℃	no reaction
11	$La(OTf)_3$	none	52	0 ℃ to 40 ℃	B: 6%; C: 19%[b]
12	$InCl_3$	none	59	0 ℃ to 40 ℃	major: C
13	$In(OTf)_3$	none	20	0 ℃ to 24 ℃	major: C
14	$InBr_3$	none	27	0 ℃ to 40 ℃	B: 14%[b]
15	$Ga(OTf)_3$	none	15	0 ℃ to 24 ℃	major: C
16	$iPrGaCl_3$(17 mol %)	$AgSbF_6$ (10 mol %)	9	0 ℃ to 24 ℃	B: 17%[b]
17	$iPrGaCl_3$	$AgSbF_6$ (17 mol %)	24	0 ℃ to 24 ℃	B: 14%; C: 25%
18	$GaCl_3$ (50 mol %)	none	2	-78 ℃	C: 42 %
19[c]	$GaCl_3$ (50 mol %)	none	2	-78 ℃	C: 66%
20	TFA	none	48	24 ℃ to 40 ℃	no reaction
21	$(n\text{-}Bu)_4NHSO_4$ (30 %)	none	48	24 ℃ to 40 ℃	no reaction
22	*p*TSA	none	48	24 ℃ to 40 ℃	no reaction

[a]Determined by crude NMR and TLC; [b]Isolated yields;[c] starting material added dropwise.

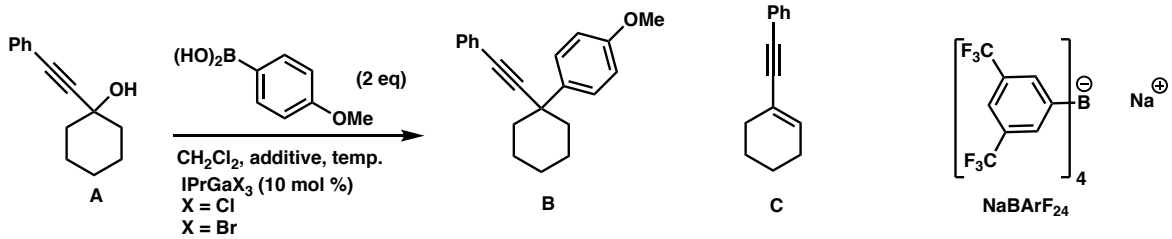
Table 4.7 Silver salts screen for tertiary alcohols



entry	cat.	Time (h)	temp.	yield[a]
1	$AgSbF_6$ (10 mol %)	6	0 °C to 24 °C	B: 14%; C: 25%
2[b]	$AgSbF_6$ (10 mol %)	40	0 °C to 40 °C	no reaction
3[c]	$AgSbF_6$ (10 mol %)	12	0 °C to 24 °C	B: 26%; C: 33%
4[d]	$AgSbF_6$ (15 mol %)	12	0 °C to 24 °C	B: 15%
5	$AgNO_3$ (15 mol %)	18	0 °C to 40 °C	no reaction
6	AgTFA (15 mol %)	24	0 °C to 40 °C	no reaction
7	AgOTf (10 mol %)	24	0 °C to 24 °C	no reaction
8	Ag_2O (10 mol %)	18	0 °C to 40 °C	no reaction
9	$AgPF_6$ (20 mol %)	24	0 °C to 40 °C	no reaction
10	$AgNTf_2$ (10 mol %)	18	0 °C to 24 °C	major: C
11	$AgBF_4$(20 mol %)	13	0 °C to 40 °C	B: 12%

[a]Isolated yield; [b]3Å MS as additive; [c]NH_4PF_6 (10 mol %) as additive; [d]$AgSbF_6$ (15 mol %), yield 15% of product, and no reaction when THF and MeCN were solvents.

Table 4.8 NHC- gallium complexes and additive screen

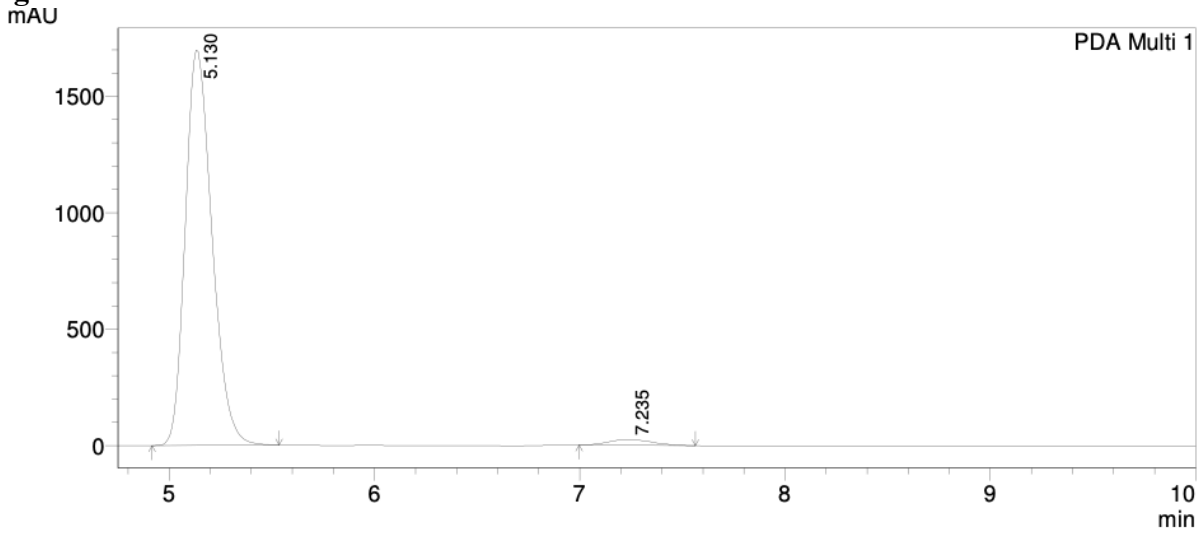


entry	X	additive	temp.	time (h)	yield[a]
1	Cl	$AgPF_6$ (15 mol %)	0 °C to 24 °C	17	B: 18% C: 54%
2	Cl	$NaBArF_{24}$ (12 mol %)	0 °C to 24 °C	18	B: 40%
3	Cl	$NaBArF_{24}$ (20 mol %)	0 °C to 24 °C	40	B: 30%; C: 13%
4	Br	$NaBPh_4$ (20 mol %)	0 °C to 40 °C	24	no reaction
5	Br	$NaBArF_{24}$ (20 mol %)	0 °C to 24 °C	15	B: 51%; C: 5%
6[b]	Br	$NaBArF_{24}$ (20 mol %)	0 °C to 24 °C	12	B + C

[a]Determined by crude NMR and TLC; [b]MeCN as solvent and potassium trifluoroborate salt was used instead of boronic acid

Mechanism Chromatograms:

Figure 4.7. At start of reaction:



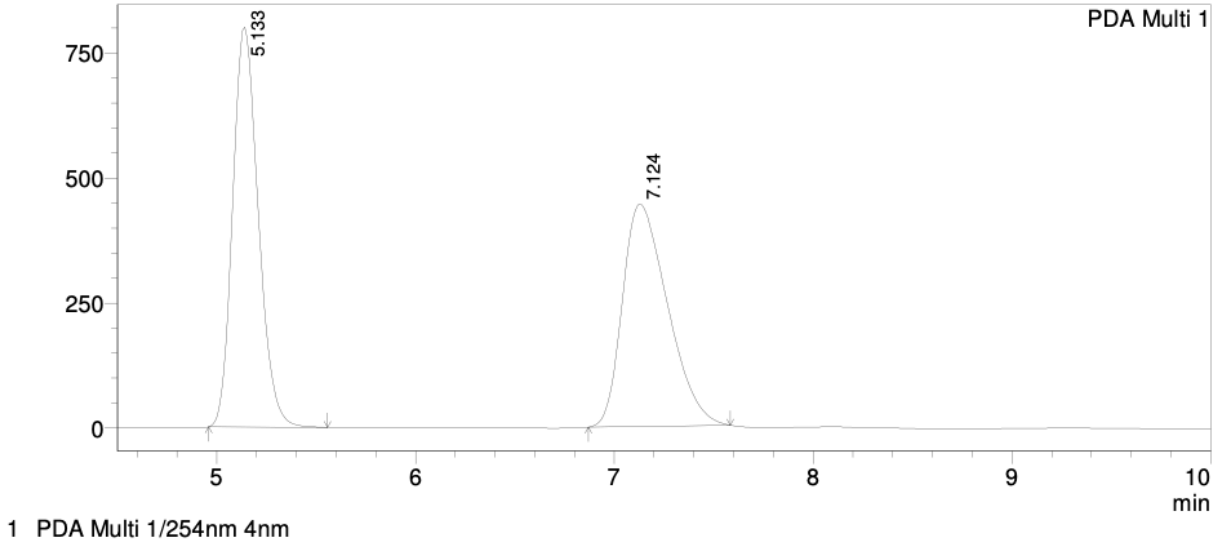
1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.130	15379390	1696473	97.714	98.530
2	7.235	359783	25304	2.286	1.470
Total		15739174	1721778	100.000	100.000

Figure 4.8. After reaction occurred:



PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.133	7172623	799808	50.511	64.225
2	7.124	7027607	445506	49.489	35.775
Total		14200230	1245314	100.000	100.000

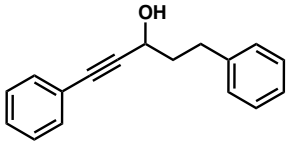
General Materials and Methods: All reactions were carried out in flame- or oven-dried glassware. THF, toluene, dichloroethane and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (EMD Chemicals Inc or Silacel). Preparative plate chromatography was performed on EMD silica gel plates, 60 Å, with UV-254 indicator. Chemical names were generated using CambridgeSoft ChemDraw Professional 14.0. Analysis by HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Chiralpak or Chiralcel (250 mm x 4.6 mm) column (see below for column details). Analytical thin-layer chromatography was performed on EMD silica gel/TLC plates with fluorescent detector 254 nm. The ^{1}H, ^{13}C (^{1}H-broadband decoupled) and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal

standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR; acetone-d6: 2.05 ppm for ^{1}H NMR and 29.8 ppm and 206.3 ppm for ^{13}C NMR). HRMS analyses were performed under contract by University of Houston's mass spectrometric facility (Thermo Exactive + Advion NanoMate, High-resolution Orbitrap MS equipped with a TriVersa NanoMate nano-electrospray (nESI) source) or A&M University via ESI method and using a high-resolution Orbitrap Fusion Tribrid mass spectrometer. Commercially available compounds were purchased from Aldrich, Acros, Alfa Aesar, and Oakwood Chemical, and they were used without further purification.

4.4.2 STARTING MATERIALS SYNTHESIS:

To an oven-dried round-bottom flask equipped with a stir bar was added the corresponding acetylene (1.1 equiv) in THF (0.2 M) under an argon atmosphere. The solution was cooled to -78 °C, and *n*-butyllithium (2.5 M in hexanes, 1.1 equiv) was added dropwise. The resulting mixture was stirred at the same temperature for at least 1 h followed by the addition of the corresponding aldehyde (1.0 equiv). The reaction mixture was allowed to warm up to 24 °C and stirred for 12 h. Once the starting material was consumed as observed by TLC, the reaction was quenched with saturated NH_4Cl and water, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation under reduced pressure, and the crude product was purified by column chromatography on silica gel with an appropriate concentration of ethyl acetate in hexanes as eluent to give the desired product.

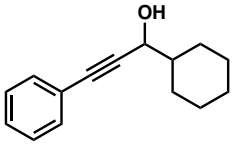
(±)-1,5-Diphenylpent-1-yn-3-ol



SI-1

From dihydrocinnamaldehyde (1.30 mL, 10.00 mmol, 1.0 equiv) and phenylacetylene (1.20 mL, 11.00 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as eluent. The product was obtained in 55% yield (1.299 g) as a colorless oil. R_f: 0.35 in 20% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[83]

1-Cyclohexyl-3-phenylprop-2-yn-1-ol

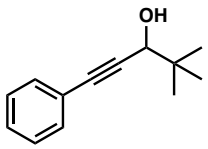


SI-2

From cyclohexanecarboxaldehyde (0.7130 g, 6.39 mmol, 1.0 equiv) and phenylacetylene (0.77 mL, 7.03 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 7% ethyl acetate in hexanes as eluent. The product was obtained in 67% yield (0.9175 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.44–7.42 (m, 2H), 7.31–7.29 (m, 3H), 4.38 (s, 1H),

1.91 (d, J = 12.2 Hz, 1H), 1.80 (d, J = 13.2 Hz, 2H), 1.74–1.60 (m, 1H), 1.35–1.06 (m, 3H). R_f: 0.6 in 20% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[84]

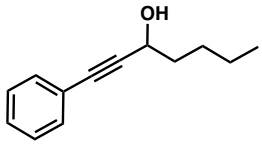
4,4-Dimethyl-1-phenylpent-1-yn-3-ol



SI-3

From trimethylacetaldehyde (0.69 mL, 6.39 mmol, 1.0 equiv) and phenylacetylene (0.77 mL, 7.03 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 3-4% ethyl acetate in hexanes as eluent. The product was obtained in 61% yield (0.7383 g) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.42 (m, 2H), 7.32–7.29 (m, 3H), 4.23 (t, J = 3.0 Hz, 1H), 1.80 (d, J = 6.1 Hz, 1H), 1.06 (s, 9H). R_f: 0.30 in 10% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[85]

1-Phenylhept-1-yn-3-ol

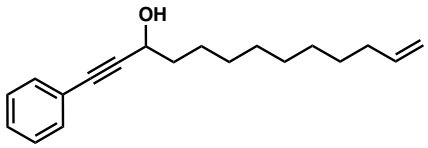


SI-4

From valeraldehyde (0.61 mL, 5.00 mmol, 1.0 equiv) and phenylacetylene (0.60 mL, 5.50 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 5-7% ethyl acetate in hexanes as eluent. The product was obtained in 76% yield (0.7721 g) as a colorless oil. ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.43–7.31 (m, 2H), 7.32–7.25 (m, 3H), 4.59 (q, J = 6.4 Hz, 1H), 1.85–1.76 (m, 3H), 1.55–1.48 (m, 2H), 1.36–1.32 (m, 4H), 0.90 (t, J = 6.8, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7, 128.5, 128.4, 122.7, 90.3, 84.9, 63.1, 38.0, 31.6, 25.0, 22.7, 14.1. R_f: 0.23 in 10% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[86]

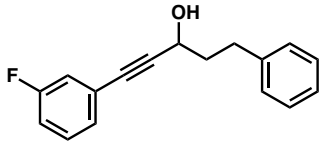
1-Phenyltridec-12-en-1-yn-3-ol



SI-5

From 10-undecenal (1.00 mL, 5.00 mmol, 1.0 equiv) and phenylacetylene (0.60 mL, 5.50 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 5% ethyl acetate in hexanes as eluent. The product was obtained in 20% yield (0.1738 g) as a brown oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.40 (m, 2H), 7.31–7.28 (m, 3H), 5.80 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.00–4.91 (m, 2H), 4.59 (t, J = 6.6 Hz, 1H), 2.05–2.00 (m, 3H), 1.81–1.76 (m, 2H), 1.53–1.47 (m, 2H), 1.36–1.24 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.3, 131.8, 128.4, 128.4, 122.7, 114.2, 90.3, 84.9, 63.1, 38.0, 33.9, 29.6, 29.5, 29.3, 29.2, 29.0, 25.3. R_f: 0.23 in 10% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[87]

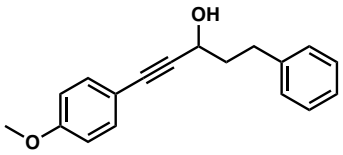
1-(3-Fluorophenyl)-5-phenylpent-1-yn-3-ol



SI-6

From dihydrocinnamaldehyde (0.53 mL, 4.00 mmol, 1.0 equiv) and 1-ethynyl-3-fluorobenzene (0.51 mL, 4.4 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 7-10% ethyl acetate in hexanes as eluent. The product was obtained in 20% yield (0.5237 g) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33– 7.19 (m, 7H), 7.13 (ddd, J = 9.4, 2.5, 1.4 Hz, 1H), 7.03 (tdd, J = 8.6, 2.6, 1.2 Hz, 1H), 4.59 (q, J = 6.5 Hz, 1H), 2.86 (t, J = 7.8 Hz, 2H), 2.17 – 2.109 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4 (d, J = 246.5 Hz), 141.2, 130.0 (d, J = 8.7 Hz), 128.6, 128.6, 127.6 (d, J = 3.2 Hz), 126.1, 124.4 (d, J = 9.4 Hz), 118.6 (d, J = 22.9 Hz), 115.9 (d, J = 21.1 Hz), 90.8, 84.1 (d, J = 3.4 Hz), 62.2, 39.2, 31.5. R_f: 0.16 in 10% ethyl acetate in hexanes.

1-(4-Methoxyphenyl)-5-phenylpent-1-yn-3-ol

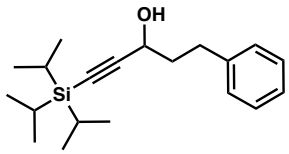


SI-7

From hydrocinnamaldehyde (0.66 mL, 5.00 mmol, 1.0 equiv) and 4-ethynylanisole (0.72 mL, 5.50 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as eluent. The product was obtained in 58% yield (0.7760 g) as a pale

yellow solid. R_f: 0.33 in 20% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[88]

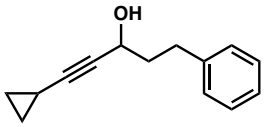
5-Phenyl-1-(triisopropylsilyl)pent-1-yn-3-ol



SI-8

From hydrocinnamaldehyde (0.53 mL, 4.00 mmol, 1.0 equiv) and (triisopropylsilyl)acetylene (0.99 mL, 4.40 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 5-7% ethyl acetate in hexanes as eluent. The product was obtained in 56% yield (0.7128 g) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.26 (m, 2H), 7.21–7.17 (m, 3H), 4.39 (q, J = 6.4 Hz, 1H), 2.81 (t, J = 7.9 Hz, 2H), 2.07–1.96 (m, 2H), 1.76 (d, J = 5.2 Hz, 1H), 1.08 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5, 128.6, 128.5, 362 126.1, 108.5, 86.2, 62.4, 39.7, 31.6, 18.7, 11.2. R_f: 0.33 in 10% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[89]

1-Cyclopropyl-5-phenylpent-1-yn-3-ol

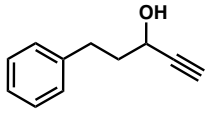


SI-9

From hydrocinnamaldehyde (0.53 mL, 4.00 mmol, 1.0 equiv) and cyclopropylacetylene (0.37 mL, 4.40 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 5-

10% ethyl acetate in hexanes as eluent. The product was obtained in 48% yield (0.3828 g) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.29 (m, 2H), 7.25–7.20 (m, 3H), 4.35 (t, J = 6.5 Hz, 1H), 2.80 (t, J = 7.9 Hz, 2H), 2.09 (br, 1H), 2.06–1.95 (m, 2H), 1.33–1.26 (m, 1H), 0.820.78 (m, 2H), 0.73–0.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5, 128.5, 128.4, 125.9, 89.0, 76.2, 62.0, 39.6, 31.5, 8.3, -0.5. R_f: 0.46 in 20% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[90]

5-Phenylpent-1-yn-3-ol

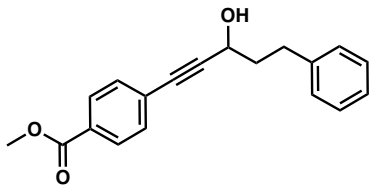


SI-10

To an oven-dried round-bottom flask equipped with a stir bar was added hydrocinnamaldehyde (2.60 mL, 20.00 mmol, 1.0 equiv) and Et_2O (50 mL, 0.4 M) under an argon atmosphere. The solution was cooled to 0 °C, and ethynylmagnesium chloride (0.5 M in THF, 1.5 equiv) was added dropwise. The resulting mixture was stirred for 15 h and allowed to warm up to 24 °C. Once the starting material was consumed, the reaction was quenched with saturated NH_4Cl and water, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation under reduced pressure, and the crude product was purified by column chromatography on silica gel with an 10% ethyl acetate in hexanes as eluent to give the title compound in 61% yield (1.970 g) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31– 7.27 (m, 2H), 7.21–7.18 (m, 3H), 4.37 (td, J = 6.6, 2.1 Hz, 1H), 2.80 (t, J = 7.8 Hz, 2H), 2.50 (d, J = 2.1 Hz, 1H), 2.08–2.00 (m, 2H), 1.87 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 128.6, 126.2, 84.7, 73.5, 61.7, 39.1,

31.3. R_f: 0.33 in 20% ethyl acetate in hexanes. All data were consistent with that presented in the literature.[91]

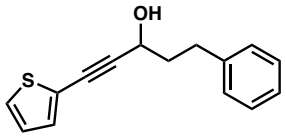
Methyl 4-(3-hydroxy-5-phenylpent-1-yn-1-yl)benzoate



SI-11

From 5-phenylpent-1-yn-3-ol (0.3200 g, 2.00 mmol, 1.0 equiv) and methyl 4-iodobenzoate (0.6290 g, 2.40 mmol, 1.2 equiv), the title compound was synthesized by following General Procedure B. The crude material was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as eluent. The product was obtained in 61% yield (0.3640 g) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.31–7.28 (m, 2H), 7.25–7.18 (m, 3H), 4.60 (q, J = 6.4 Hz, 1H), 3.91 (s, 3H), 2.86 (t, J = 7.8 Hz, 2H), 2.16–2.10 (m, 2H), 1.93 (dd, J = 19.4, 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.6, 141.2, 131.7, 129.8, 129.6, 128.6, 127.3, 126.2, 92.8, 84.6, 62.3, 52.4, 39.2, 31.5. R_f: 0.27 in 20% ethyl acetate in hexanes.

5-Phenyl-1-(thiophen-2-yl)pent-1-yn-3-ol

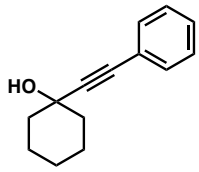


SI-12

From 5-phenylpent-1-yn-3-ol (0.3200 g, 2.00 mmol, 1.0 equiv) and 2-iodothiophene (0.5041 g, 2.40 mmol, 1.2 equiv), the title compound was synthesized by following General Procedure

B. The crude material was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as eluent. The product was obtained in 50% yield (0.2400 g) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.18 (m, 7H), 6.97 (dd, J = 5.2, 3.6 Hz, 1H), 4.60 (q, J = 6.5 Hz, 1H), 2.85 (t, J = 7.8 Hz, 2H), 2.15–2.09 (m, 2H), 1.90 (d, J = 5.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.2, 132.4, 128.6, 128.57, 127.4, 127.1, 126.1, 93.7, 78.7, 62.4, 39.2, 31.5. R_f: 0.46 in 20% ethyl acetate in hexanes.

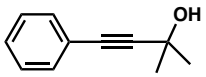
1-(phenylethynyl)cyclohexan-1-ol



SI-13

From cyclohexane (0.86 mL, 8.00 mmol, 1.0 equiv) and cyclopropylacetylene (0.74 mL, 8.80 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude material was purified by column chromatography on silica gel with 5-10% ethyl acetate in hexanes as eluent. The product was obtained in 81% yield (1.280 g) as a yellowish oil. All data were consistent with that presented in the literature.[92]

2-Methyl-4-phenylbut-3-ny-2-ol

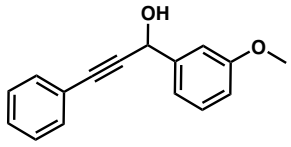


SI-14

To an oven-dried round-bottom flask equipped with a stir bar was added phenylacetylene (2.14 mL, 19.5 mmol, 1.1 equiv) in THF (38 mL, 0.4 M) under an argon atmosphere, the title compound was synthesized by following General Procedure A. The solution was cooled to -

78 °C, and *n*-butyllithium (2.5 M in hexanes, 1.1 equiv) was added dropwise. The resulting mixture was stirred at the same temperature for at least 1 hfollowed by the addition of acetone (1.4 mL, 19.0 mmol, 1.0 equiv). The reaction mixture was allowed to warm up to 24 °C and stirred for 12 h. Once the starting material was consumed, the reaction was quenched with saturated NH_4Cl and water, and the mixture was extracted with ethyl acetate (30 mL x 3). The organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation under reduced pressure, and the crude product was purified by column chromatography on silica gel with 10% ethyl acetate in hexanes as eluent to give the title compound 4.35 in 94% yield (2.870 g) as a low melting point solid. All data were consistent with that presented in the literature.[93]

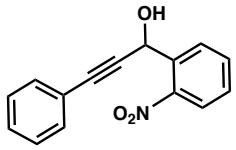
1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-ol



SI-15

From 3-methoxybenzaldehyde (0.870 g, 6.39 mmol, 1.0 equiv) and phenylacetylene (0.77 mL, 7.03 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to produce 78% yield (1.19g). All data were consistent with that presented in literature.[94]

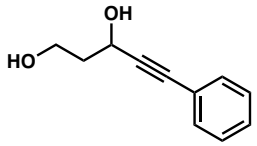
1-(2-nitrophenyl)-3-phenylprop-2-yn-1-ol



SI-16

From 2-nitrobenzaldehyde (0.966 g, 6.39 mmol, 1.0 equiv) and phenylacetylene (0.77 mL, 7.03 mmol, 1.1 equiv), the title compound was synthesized by following General Procedure A. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to produce 63% yield (1.02g). All data were consistent with that presented in literature.[95]

5-phenylpent-4-yne-1,3-diol



SI-27

This compound was synthesized using literature procedures to form the propargylic alcohol above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to produce 23% yield. All data were consistent with that presented in literature.[96]

SYNTHESIS OF PRODUCTS:

4.4.3 General Procedure A: Nucleophilic Substitution for Tertiary Carbons with Ag/Ga

To a flame-dried 7 mL vial was added $IPrGaCl_3$ (12.0 mg, 0.02 mmol, 10 mol %), $AgSbF_6$ (8.0 mg, 0.02 mmol, 10 mol %), and an aryl boronic acid (0.4 mmol, 2 equiv) under an argon atmosphere. The vial was sealed and cooled to 0 °C (ice bath). A solution of a propargylic alcohol (0.2 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was then added dropwise via a syringe. After the reaction completed as monitored by TLC, the crude mixture was absorbed onto silica gel via rotary evaporation under reduced pressure. The product was purified via flash column chromatography on silica gel with a gradient of 0–10% CH_2Cl_2 in hexanes as eluent.

4.4.4 General Procedure B: Nucleophilic Substitution for Tertiary Carbons with Ag

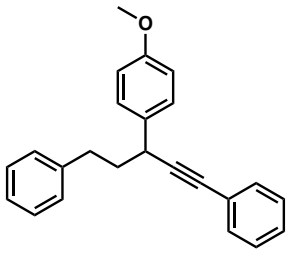
To a flame-dried 7 mL vial was added $AgSbF_6$ (8.0 mg, 0.02 mmol, 10 mol %) and an aryl boronic acid (0.4 mmol, 2 equiv) under an argon atmosphere. A solution of a propargylic alcohol (0.2 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was then added dropwise via a syringe. The reaction was sealed and stirred at 40 °C for about 12 h. After the reaction completed as monitored by TLC, the crude mixture was absorbed onto silica gel via rotary evaporation under reduced pressure. The product was purified via flash column chromatography on silica gel with a gradient of 0–10% CH_2Cl_2 in hexanes as eluent.

4.4.5 General Procedure C: Nucleophilic Substitution for Tertiary and Quaternary Carbons with $GaCl_3$

To a flame-dried 7 mL vial was added $GaCl_3$ (8.0 mg, 0.02 mmol, 10 mol %) in the glove box, then vial was removed, and then a boronic acid was added (0.4 mmol, 2 equiv) under an argon atmosphere, then DCE (2 mL) was added. The reaction was sealed and stirred at -78 °C. A solution of a propargylic alcohol (0.2 mmol, 1 equiv) in DCE (2 mL) was then added

dropwise via a syringe. The reaction was sealed and stirred at -78 °C for about 12 h. After the reaction completed as monitored by TLC, the crude mixture was absorbed onto silica gel via rotary evaporation under reduced pressure. The product was purified via flash column chromatography on silica gel with a gradient of 0–10% ethyl acetate in hexanes as eluent.

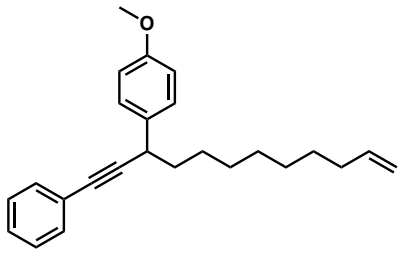
(3-(4-methoxyphenyl)pent-1-yne-1,5-diyl)dibenzene



SI-18

The title compound was synthesized from **SI-1** (47.2 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–10% CH_2Cl_2 in hexanes as eluent, the product was obtained in 90% (58.8 mg) yield with procedure A and 92% (60.1 mg) with procedure B as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.37 – 7.27 (m, 7H), 7.27 – 7.16 (m, 3H), 6.93 – 6.86 (m, 2 H), 3.86 – 3.76 (m, 1H), 3.81 (s, 3H), 2.91 – 2.75 (m, 2H), 2.23 – 2.04 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 158.5, 529 141.8, 134.0, 131.8, 128.6, 128.6, 128.5, 128.4, 127.9, 126.0, 123.9, 114.0, 91.6, 83.7, 55.4, 40.3, 37.02, 33.7. IR: 2931, 1599, 1509, 1245, 1174, 1029, 830, 754, 692 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{24}H_{22}O$ $[M + H]^+$ 327.17, found 327.1743.

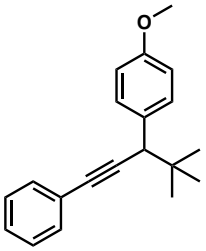
1-methoxy-4-(1-phenyldodec-11-en-1-yn-3-yl)benzene



SI-19

The title compound was synthesized from 1-phenyltridec-12-en-1-yn-3-ol (54 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–10% dichloromethane in hexanes as eluent, the product was obtained in 85% (58.9 mg) yield with procedure A and 89% (61.7 mg) yield with procedure B as a colorless oil. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.43 (d, J = 6.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.29 – 7.28 (m, 3H), 6.87 (d, J = 8.0 Hz, 2H), 5.84 – 5.77 (m, 1H), 4.95 (dd, J = 16.5, 9.6 Hz, 2H), 3.89 – 3.73 (m, 4H), 2.08 – 1.95 (m, 2H), 1.83 – 1.74 (m, 1H), 1.53 – 1.11 (m, 13H), ^{13}C NMR: (151 MHz, $CDCl_3$) δ 158.4, 139.3, 134.6, 131.7, 128.5, 128.3, 127.7, 124.0, 114.2, 113.9, 92.2, 83.1, 55.4, 38.9, 37.7, 33.9, 29.6, 29.62 – 29.16 (m), 29.0, 27.5.

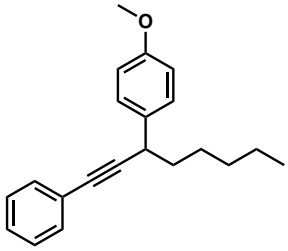
1-(4,4-dimethyl-1-phenylpent-1-yn-3-yl)-4-methoxybenzene



SI-20

The title compound was synthesized from 4,4-dimethyl-1-phenylpent-1-yn-3-ol (37 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–10% dichloromethane in hexanes as eluent, the product was obtained in 71% (39.5 mg) yield with procedure A and 75% (41.8 mg) yield with procedure B as a colorless oil. 1H NMR: (500 MHz, $CDCl_3$) δ 7.47– 7.44 (m, 2H), 7.33 – 7.26 (m, 5H), 6.89 – 6.84 (m, 2H), 3.81 (s, 3H), 3.59 (s, 1H), 1.03 (s, 9H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.5, 131.7, 131.6, 130.7, 128.3, 127.7, 124.2, 113.1, 91.7, 83.7, 55.4, 49.6, 35.6, 27.8.

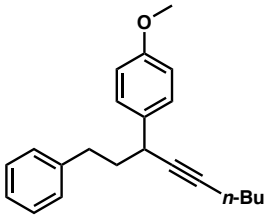
1-methoxy-4-(1-phenyloct-1-yn-3-yl)benzene

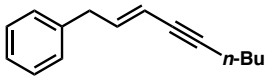


SI-21

The title compound was synthesized from 1-phenyloct-1-yn-3-ol (40 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–10% dichloromethane in hexanes as eluent, the product was obtained in 86% (50.3 mg) yield with procedure A and 85% yield (49.7 mg) with procedure B as a colorless oil. ^1H NMR: (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.31 – 7.30 (m, 2H), 7.31 – 7.27 (m, 3H), 6.92 – 6.86 (m, 2H), 3.85 – 3.76 (m, 1H), 3.84 (s, 3H), 1.86 – 1.73 (m, 2H), 1.60 – 1.40 (m, 2H), 527 1.38 – 1.26 (m, 4H), 0.91– 0.84 (m, 3H) ^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.4, 134.6, 131.7, 128.5, 128.3, 127.8, 124.0, 113.9, 92.2, 83.0, 55.4, 38.8, 37.7, 31.6, 27.2, 22.7, 14.2.

1-methoxy-4-(1-phenylnon-4-yn-3-yl)benzene & (*E*)-non-2-en-4-yn-1-ylbenzene

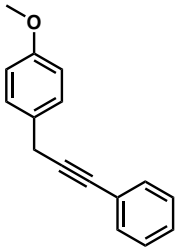




SI-22 **SI-23**

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–10% gradient of DCM in hexanes, **SI-22** was observed in trace amounts (<5%) by NMR and the elimination product **SI-23** was observed in 84% (33.3 mg) yield . All data for **SI-23** were consistent with that presented in literature.[97]

1-methoxy-4-(3-phenylprop-2-yn-1-yl)benzene

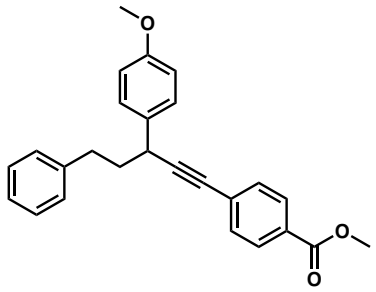


SI-24

The title compound was synthesized from 3-phenylprop-2-yn-1-ol (26 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with 5% Et_2O in hexanes as eluent, the product was obtained in 35% (15.6 mg) yield with procedure A as a colorless oil. ^1H NMR: (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.32 – 7.29 (m, 5H), 6.90 – 6.84 (m, 2H), 3.80 (s, 3H), 3.77 (s, 2H). HRMS-

ESI *m/z* Calculated for $C_{16}H_{14}O$ $[M + H]^+$ 223.11, found 223.1117.Spectra data were consistent to those reported in the literature.[98]

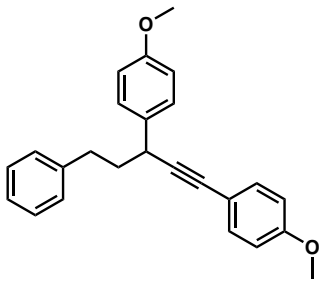
methyl 4-(3-(4-methoxyphenyl)-5-phenylpent-1-yn-1-yl)benzoate

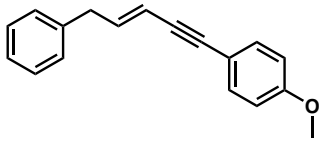


SI-25

The title compound was synthesized from methyl 4-(3-hydroxy-5-phenylpent-1-yn-1-yl)benzoate (60 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–5% Et_2O in hexanes as eluent, the product was obtained in 65% (50.0 mg) yield with procedure B as a colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.00 – 7.96 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 6.9 Hz, 1H), 7.35 – 7.27 (m, 4H), 7.22 – 7.18 (m, 3H), 6.91 – 6.86 (m, 2H), 3.92 (s, 3H), 3.83 – 3.77 (m, 4H), 2.88 – 2.70 (m, 2H), 2.24 – 1.91 (m, 2H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 166.8, 158.6, 141.6, 133.5, 131.7, 129.5, 129.2, 128.6, 128.6, 128.5, 126.1, 114. 1, 95.1, 83.0, 55.4, 52.3, 40.0, 37.1, 33.6. IR: 2950, 1722, 1603,1511, 1276, 1108, 698 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{26}H_{24}O_3$ $[M + H]^+$ 385.17, found 385.1798.

4,4'-(5-phenylpent-1-yne-1,3-diyl)bis(methoxybenzene) & (*E*)-1-methoxy-4-(5-phenylpent-3-en-1-yn-1-yl)benzene

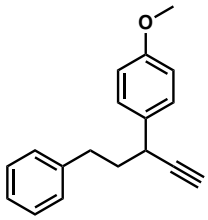


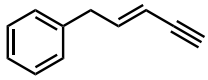


SI-26 **SI-27**

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–10% gradient of DCM in hexanes, **SI-26** was not observed and the elimination product **SI-27** was observed in 88% (49.2 mg) yield . All data for **SI-27** were consistent with that presented in literature.[99]

1-methoxy-4-(5-phenylpent-1-yn-3-yl)benzene & (*E*)-pent-2-en-4-yn-1-ylbenzene

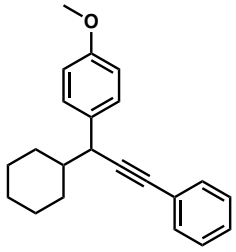




SI-28 **SI-29**

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 1–10% gradient of DCM in hexanes, **SI-28** was not observed and the elimination product **SI-29** was observed in 91% (25.9 mg) yield . All data for **SI-29** were consistent with that presented in literature.[100]

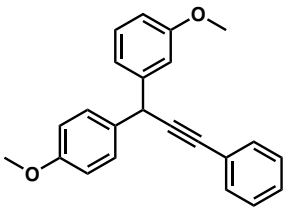
1-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)-4-methoxybenzene



SI-30

The title compound was synthesized from 1-cyclohexyl-3-phenylprop-2-yn-1-ol (40.8 mg, 0.2 mmol, 1 equiv) and 4-methoxyl boronic acid (60.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 5–10% dichloromethane in hexanes as eluent, the product was obtained in 77% (46.9 mg) yield with procedure A and 85%(51.7 mg) yield with procedure B as a colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.33 – 7.26 (m, 5H), 6.91 – 6.82 (m, 2H), 3.87 (s, 3H), 3.65 (d, J = 6.7 Hz, 1H), 1.88 – 1.86 (m, 1H), 1.73 – 1.71 (m, 2H), 1.68 – 526 1.61 (m, 3H) 1.28 – 1.04 (m, 5H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.4, 133.0, 131.7, 129.3, 128.3, 127.7, 124.1, 113.6, 91.2, 83.9, 55.4, 44.8, 44.3, 31.7 , 29.7, 26.5, 26.5, 26.4. All data for **SI-30** were consistent with that presented in literature.[101]

1-methoxy-3-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)benzene

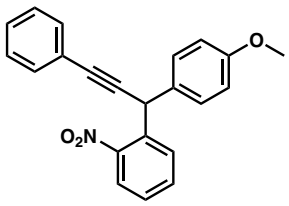


SI-31

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in

hexanes as eluent on silica gel to yield 87% (57.1 mg) with procedure A and 69% (43.2 mg) with procedure B. All data were consistent with that presented in literature.[102]

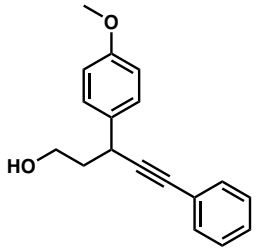
1-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-2-nitrobenzene



SI-32

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 16% (10.5 mg) with method A. All data were consistent with that presented in literature.[102]

3-(4-methoxyphenyl)-5-phenylpent-4-yn-1-ol

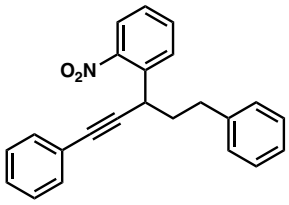


SI-33

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 37% (19.6 mg) with procedure A. ^{1}H-NMR (600 MHz, CHLOROFORM-D) δ 7.76 (d, J = 8.2 Hz, 2H), 7.46-7.45 (m, 2H), 7.34-7.31 (m, 3H), 6.88 (d, J = 8.2 Hz, 2H), 5.16 (t, J = 5.2 Hz, 1H), 4.41 (s, 1H), 4.18 (d, J = 6.2 Hz, 1H), 3.82 (s, 3H), 2.36-2.17 (m, 2H). ^{13}C-NMR (151 MHz, chloroform-D) δ 161.9, 135.7, 131.9, 128.7,

128.4, 122.4, 113.2, 88.1, 84.9, 77.3, 77.1, 76.9, 61.8, 59.9, 55.2, 33.2, 29.8 IR: 2926, 2250, 1603, 1302, 1245, 1141, 905, 690, 663 cm^{-1} HRMS-ESI *m/z* Calculated for $C_{18}H_{18}O_2$ $[M + H]^+$ 267.13, found 267.1373.

(3-(2-nitrophenyl)pent-1-yne-1,5-diyl)dibenzene



SI-34

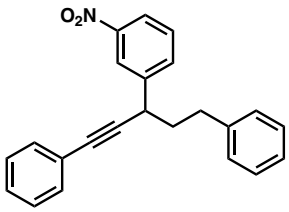
See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluenton silica gel to yield 26% (17.6 mg) with method A and 27% (17.8 mg) with method C . ^{1}H-NMR (600 MHz, chloroform-D) δ 7.41-7.26 (m, 10H), 7.19 (dt, J = 43.8, 7.0 Hz, 4H), 4.73 (t, J = 6.5 Hz, 1H), 2.90 (t, J = 7.6 Hz, 2H), 2.19 (dtd, J = 37.9, 14.0, 7.7 Hz, 2H). ^{13}C-NMR (151 MHz, acetone-D6) δ 141.6, 131.7, 131.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 126.0, 125.9, 122.9, 122.6, 88.9, 87.9, 86.0, 66.7, 37.7, 31.3. IR: 2924, 1489, 1070, 1047, 754, 690 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{23}H_{19}NO_2$ $[M + H]^+$ 342.14, found 342.1452.

Table 4.9 Screen of solvents

entry	cat.	solvent	temp.	yield (%)[a]
1	$GaCl_3$(10 mol%)	DCE	-78 °C	48
2	$GaCl_3$(10 mol%)	MeCN	-78 °C	0, 92% elimination
3	$GaCl_3$(10 mol%)	DCM	-78 °C to 0°C	3, 88% elimination
4	$GaCl_3$(10 mol%)	PhMe	-78 °C to 0°C	no reaction
5	$GaCl_3$(10 mol%)	MeOH	-78 °C to 0°C	no reaction

[a]Determined by crude NMR and TLC

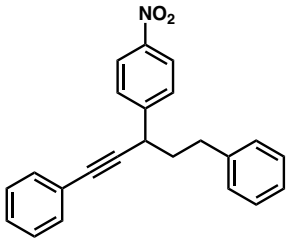
(3-(3-nitrophenyl)pent-1-yne-1,5-diyl)dibenzene



SI-35

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 20% (13.6 mg) with procedure A, 7% (4.8 mg) with procedure B, and 34% (25.2 mg) with procedure C. ^{1}H-NMR (600 MHz, chloroform-D) δ 7.45-7.28 (m, 10H), 7.25-7.15 (m, 4H), 4.74 (t, J = 6.5 Hz, 1H), 2.91 (t, J = 7.9 Hz, 2H), 2.26-2.13 (m, 2H). ^{13}C-NMR (151 MHz, chloroform-D) δ 141.7, 131.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 125.9, 122.8, 109.8, 88.1, 86.1, 77.3, 77.1, 76.9, 67.1, 67.0, 37.6, 31.6, 29.8 IR: 2923, 2853, 2358, 1599, 1490, 1454, 1071, 1044, 905, 728, 698 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{23}H_{19}NO_2$ $[M + H]^+$ 342.14, found 342.1452.

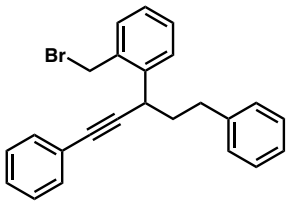
(3-(4-nitrophenyl)pent-1-yne-1,5-diyl)dibenzene



SI-36

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 37% (25.2 mg) with procedure A and 10% (6.8 mg) with procedure B. All data were consistent with that presented in literature.[102]

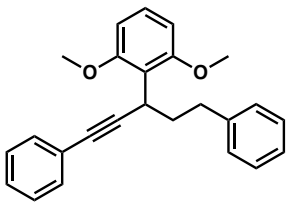
(3-(2-(bromomethyl)phenyl)pent-1-yne-1,5-diyl)dibenzene



SI-37

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 27% (21.1 mg) with method A and 27% (20.0 mg)with method B. ^{1}H-NMR (600 MHz, chloroform-D) δ 7.48-7.47 (m, 2H), 7.31 (td, J = 14.9, 7.3 Hz, 7H), 7.24-7.19 (m, 3H), 6.89 (d, J = 8.2 Hz, 2H), 5.30 (s, 1H), 3.81 (s, 2H), 2.83 (q, J = 7.3 Hz, 2H), 2.18-2.09 (m, 2H). ^{13}C-NMR (151 MHz, chloroform-D) δ 158.5, 141.8, 134.0, 131.8, 128.6, 128.6, 128.5, 128.3, 127.9, 126.0, 123.8, 114.0, 91.6, 83.7, 55.4, 55.4, 40.3, 37.0, 33.7, 29.8 IR: 3027, 2925, 2855, 2360, 1692, 1599, 1510, 1246, 1175, 1030, 906, 728, 691 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{24}H_{21}Br$ $[M + H]^+$ 390.08, found 390.0811.

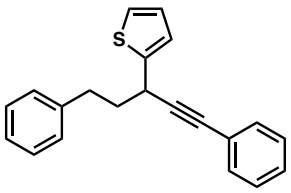
(3-(2,6-dimethoxyphenyl)pent-1-yne-1,5-diyl)dibenzene



SI-38

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to yield 85% (60.6 mg) with procedure A, and 47%(24.2 mg) (with procedure B. ^{1}H-NMR (400 MHz, chloroform-D) δ 7.52-7.46 (m, 3H), 7.29 (m, 3H), 7.23-7.17 (m, 7H), 6.45 (d, J = 14.3 Hz, 2H), 4.23 (s, 1H), 3.79 (s, 6H), 2.85 (d, J = 27.5 Hz, 2H), 2.06 (d, J = 44.7 Hz, 2H). ^{13}C-NMR (126 MHz, chloroform-D) δ 160.9, 157.2, 142.2, 131.8, 130.0, 129.0, 128.6, 128.3, 127.7, 125.8, 122.7, 106.2, 104.2, 100.5, 98.5, 82.9, 55.5, 55.4, 38.3, 33.8, 30.9. IR: 2945, 1596, 1475, 1320, 1234, 1100, 788, 692 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{25}H_{24}O_2$ $[M + H]^+$ 357.18, found 357.1849.

2-(1,5-diphenylpent-1-yn-3-yl)thiophene

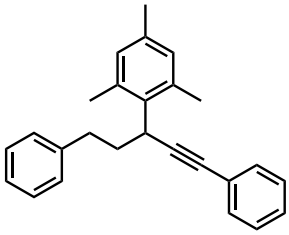


SI-39

The title compound was synthesized from **SI-1** (47.2 mg, 0.2 mmol, 1 equiv) and 2-thiophene boronic acid (51.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 5−10% CH_2Cl_2 in hexanes as eluent, the product was obtained in 68% (41.1 mg) yield with procedure A and 82% (49.7 mg) with procedure B as a colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.52 – 7.44 (m, 2H), 7.34 – 7.28 (m, 5H), 7.25 – 7.19 (m, 4H), 7.05 – 7.01 (m, 1H), 6.97 – 6.95 (m, 1H), 4.14 (t, J = 7.1 Hz, 1H), 3.05 – 2.61 (m, 2H), 2.26 – 2.22 (m, 2H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 145.5, 141.4, 131.8, 128.7, 128.5, 128.3, 128.1, 126.7, 126.1, 124.5, 124.0, 123.5, 90.4, 83.6, 40.2, 33.4, 33.0. IR: 3026,

1737, 1724, 1661, 1365, 1230, 1217, 699 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{21}H_{18}S$ $[M + H]^+$ 303.11, found 303.1202.

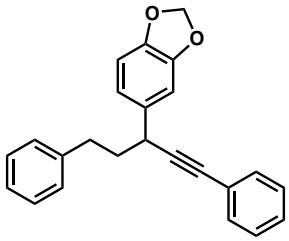
(3-mesitylpent-1-yne-1,5-diyl)dibenzene



SI-40

The title compound was synthesized from **SI-1** (47.2 mg, 0.2 mmol, 1 equiv) and mesitylene boronic acid (66.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 0–10% CH_2Cl_2 in hexanes as eluent, the product was obtained in 86% (58.2 mg) yield with procedure A and 75% (50.7 mg) with procedure B as a colorless oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 7.3, 2.1 Hz, 2H), 7.35 – 7.18 (m, 8H), 6.84 (s, 2H), 4.20 (dd, J = 10.3, 5.3 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.86 – 2.78 (m, 1H), 2.46 – 2.30 (m, 1H), 2.63 – 2.12 (br, 6H), 2.25 (s, 3H), 2.00 – 1.85 (m, 1H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 141.6, 136.1, 134.8, 131.6, 130.1(br), 128.7, 128.5, 128.3, 127.7, 126.1, 124.2, 91.4, 83.0, 36.0, 34.1, 31.8, 20.8. IR: 2917, 1598, 1489, 1452, 850, 523, 495 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{26}H_{26}[M + H]^+$ 339.21, found 339.2107.

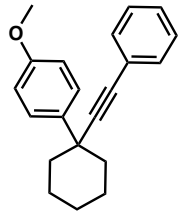
5-(1,5-diphenylpent-1-yn-3-yl)benzo[d][1,3]dioxole



SI-41

The title compound was synthesized from **SI-1** (47.2 mg, 0.2 mmol, 1 equiv) and 3,4-(methylenedioxy)phenylboronic acid (66.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 5–10% CH_2Cl_2 in hexanes as eluent, the product was obtained in 74% (50.2 mg) yield with procedure A and 75% (51.1 mg) with procedure B as a colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.36 – 7.27 (m, 5H), 7.25 – 7.16 (m, 3H), 6.94 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.0, 1.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H), 3.76 (dd, J = 8.5, 530 6.1 Hz, 1H), 2.88 – 2.72 (m, 2H), 2.20 – 2.01 (m, 2H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 147.8, 146.4, 141.7, 135.9, 131.8, 128.6, 128.5, 128.4, 128.0, 126.0, 123.7, 120.7, 108.3, 108.1, 101.1, 91.3, 83.8, 40.4, 37.5, 33.6. IR: 3025, 2923, 1735, 1485, 1441, 1244, 1038, 933, 755, 691 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{24}H_{20}O_2$ $[M + H]^+$ 341.15, found 341.1536.

1-Methoxy-4-(1-(phenylethynyl)cyclohexyl)benzene and (cyclohex-1-en-1-ylethynyl)benzene

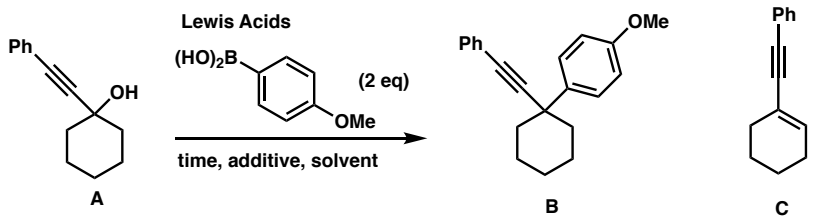


SI-42

SI-43

From 1-(phenylethynyl)cyclohexanol (40.0 mg, 0.20 mmol, 1.0 equiv) and 4-methoxypenylboronic acid (60.0 mg, 0.40 mmol, 2.0 equiv), the title compound as obtained by following either General Procedure C or D. The crude material was purified by column chromatography on silica gel with 0.2% ethyl acetate in hexanes as eluent. The product 4.26 was obtained in 50% yield (29.4 mg) as a yellow oil. NMR data for product **SI-24**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.54 (m, 2H), 7.47–7.46 (m, 2H), 7.31–7.27 (m, 3H), 6.89–6.87 (m, 2H), 3.80 (s, 3H), 2.00–1.89 (m, 4H), 1.79–1.70 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1, 139.5, 131.7, 128.3, 127.7, 127.12, 124.2, 113.6, 94.5, 85.5, 55.4, 41.7, 39.6, 25.9, 23.9. R_f: 0.56 in 10% ethyl acetate in hexanes. NMR data for elimination product **SI-25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.40 (m, 2H), 7.31–7.25 (m, 3H), 6.21 (tt, J = 3.9, 1.8 Hz, 1H), 2.22 (ddd, J = 8.1, 4.1, 2.4 Hz, 2H), 2.14 (ddt, J = 8.7, 6.0, 2.7 Hz, 2H), 1.71–1.58 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 135.3, 131.5, 128.3, 127.8, 123.8, 120.8, 91.3, 86.8, 29.3, 25.9, 22.4, 21.6. All data for the elimination product were consistent with that presented in the literature. [103]

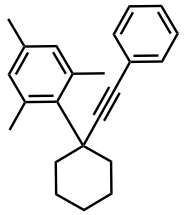
Table 4.10 Screen of conditions



entry	cat.	solvent	temp.	yield of B (%)[a]
1	$GaCl_3$(10 mol%)	DCE	-78 °C	68
2	$GaCl_3$(20 mol%)	DCE	-78 °C	66
3	$GaCl_3$(30 mol%)	DCE	-78 °C	55
4	$GaCl_3$(50 mol%)	DCE	-78 °C	40
5	$GaCl_3$(1 eq.)	DCE	-78 °C	36
6	$GaCl_3$(10 mol%)	DCE	0 °C	42
7	$GaCl_3$(10 mol%)	DCE	50°C	0, elimination: 93%
8	$GaCl_3$(10 mol%)	MeCN	-78 °C	30
9	$GaCl_3$(10 mol%)	DCM	-78 °C to 0°C	51
10	$GaCl_3$(10 mol%)	PhMe	-78 °C to 0°C	no reaction
10	$GaCl_3$(10 mol%)	MeOH	-78 °C to 0°C	no reaction

[a]Determined by crude NMR and TLC

1,3,5-trimethyl-2-(1-(phenylethynyl)cyclohexyl)benzene

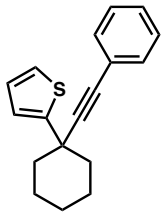


SI-44

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 57% (34.2 mg). ^{1}H-NMR (600 MHz, chloroform-D) δ 7.43 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.97 (s, 2H), 6.87 (d, J = 7.9 Hz, 1H), 6.63 (s, 1H), 2.35 (s, 3H), 2.12 (s, 6H), 1.96-1.87 (m, 5H), 1.64 (q, J = 12.4 Hz, 2H), 1.50 (d, J = 13.7 Hz, 2H). ^{13}C-NMR (151 MHz, chloroform-D)

δ 153.9, 143.5, 140.7, 140.5, 136.8, 136.7, 132.4, 128.1, 126.6, 125.1, 121.8, 120.5, 77.3, 77.1, 76.9, 53.4, 34.8, 26.2, 25.0, 21.2, 20.2. IR: 2925, 2855, 1448, 905, 850, 750, 729 cm^{-1} HRMS-ESI *m*/*z* Calculated for $C_{23}H_{26}$ $[M + H]^+$ 303.21, found 303.2107.

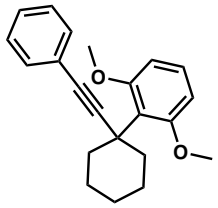
2-(1-(phenylethynyl)cyclohexyl)thiophene



SI-45

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 35% (18.1 mg). ^{1}H NMR: (500 MHz, Chloroform-D) δ 7.52 – 7.44 (m, 2H), 7.34 – 7.28 (m, 5H), 7.25 – 7.19 (m, 4H), 7.05 – 7.01 (m, 1H), 6.97 – 6.95 (m, 1H), 4.14 (t, *J* = 7.1 Hz, 1H), 3.05 – 2.61 (m, 2H), 2.26 – 2.22 (m, 2H). ^{13}C-NMR (151 MHz, Acetone-D6) δ 206.3, 205.9, 205.5, 205.5, 205.3, 205.2, 150.2, 134.9, 131.5, 131.2, 128.5, 128.1, 128.0, 123.6, 121.9, 93.5, 91.1, 86.6, 84.5, 40.8, 40.0, 30.1, 29.9, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.8, 28.6, 28.6, 25.4, 23.5 IR: 2928, 1739, 1442, 1230, 755, 458 cm^{-1} HRMS-ESI *m*/*z* Calculated for $C_{18}H_{18}S$ $[M + H]^+$ 267.12, found 267.1202.

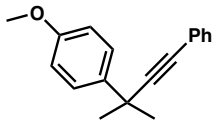
1,3-dimethoxy-2-(1-(phenylethynyl)cyclohexyl)benzene



SI-46

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 30% (19.3 mg). All data were consistent with that presented in literature. [104]

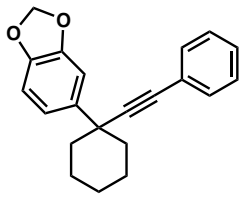
1-methoxy-4-(2-methyl-4-phenylbut-3-yn-2-yl)benzene



SI-47

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 1–10% gradient of DCM in hexanes as eluent on silica gel to give a yield of 24% (12.0 mg). All data were consistent with that presented in literature.[105]

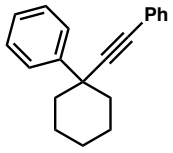
5-(1-(phenylethynyl)cyclohexyl)benzo[*d*][1,3]dioxole



SI-48

The title compound was synthesized from **SI-13** (47.2 mg, 0.2 mmol, 1 equiv) and 3,4-(methylenedioxy)phenylboronic acid (66.0 mg, 0.4 mmol, 2 equiv). After purification via flash column chromatography with a gradient of 5–10% CH_2Cl_2 in hexanes as eluent, the product was obtained in 74% (50.2 mg) yield with procedure A and 75% (51.1 mg) with procedure B as a colorless oil. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 2H), 7.36 – 7.27 (m, 5H), 7.25 – 7.16 (m, 3H), 6.94 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.0, 1.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H), 3.76 (dd, J = 8.5, 530 6.1 Hz, 1H), 2.88 – 2.72 (m, 2H), 2.20 – 2.01 (m, 2H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 147.8, 146.4, 141.7, 135.9, 131.8, 128.6, 128.5, 128.4, 128.0, 126.0, 123.7, 120.7, 108.3, 108.1, 101.1, 91.3, 83.8, 40.4, 37.5, 33.6. IR: 3025, 2923, 1735, 1485, 1441, 1244, 1038, 933, 755, 691 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{24}H_{20}O_2$ $[M + H]^+$ 341.15, found 341.1536.

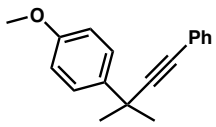
((1-phenylcyclohexyl)ethynyl)benzene



SI-49

The title compound **SI-49** was not synthesized from the procedures A, B, or C, only the elimination product **SI-43** was observed.

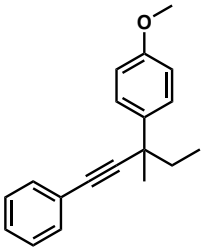
1-methoxy-4-(2-methyl-4-phenylbut-3-yn-2-yl)benzene



SI-50

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 1–10% gradient of DCM in hexanes as eluent on silica gel to give a yield of 24% (12.0 mg). All data were consistent with that presented in literature.[105]

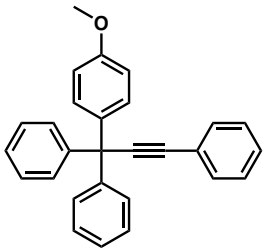
1-methoxy-4-(3-methyl-1-phenylpent-1-yn-3-yl)benzene



SI-51

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 25% (13.1 mg). ^{1}H-NMR (600 MHz, acetone-D6) δ 7.53 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.37 (q, J = 6.6 Hz, 3H), 6.92 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 1.92-1.88 (m, 2H), 1.61 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (151 MHz, acetone-D6) δ 158.4, 137.1, 131.5, 128.7, 128.5, 127.9, 127.2, 123.9, 113.5, 95.0, 83.7, 54.6, 40.9, 37.0, 9.5 IR: 2966, 2929, 1874, 1598, 1510, 1249, 756, 691 cm^{-1}. HRMS-ESI *m*/*z* Calculated for $C_{19}H_{20}O$ $[M + H]^+$ 265.15, found 265.1587.

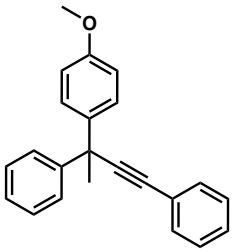
(1-(4-methoxyphenyl)prop-2-yne-1,1,3-triyl)tribenzene



SI-52

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 57% (42.8 mg) . All data were consistent with that presented in literature.[106]

(3-(4-methoxyphenyl)but-1-yne-1,3-diyl)dibenzene



SI-53

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in

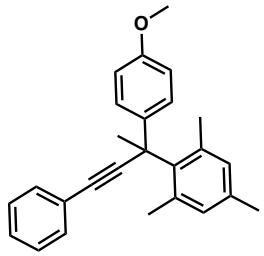
hexanes as eluent on silica gel to give a yield of 13% (7.9 mg). All data were consistent with that presented in literature.[107]

Table 4.11 Screen of conditions

entry	cat.	solvent	temp.	yield (%)[a]
1	$GaCl_3$(10 mol%)	DCE	-78 ℃	13
2	$GaCl_3$(10 mol%)	MeCN	-78 ℃	0, elimination: 92%
3	$GaCl_3$(10 mol%)	DCM	-78 ℃ to 0℃	0, elimination: 93%
4	$GaCl_3$(10 mol%)	PhMe	-78 ℃ to 0℃	no reaction
5	$GaCl_3$(10 mol%)	MeOH	-78 ℃ to 0℃	no reaction
6	$GaCl_3$(10 mol%)	DCE	0 ℃	0, elimination: 88%
7	$GaCl_3$(10 mol%)	DCE	40℃	0, elimination: 92%

[a]Determined by crude NMR and TLC

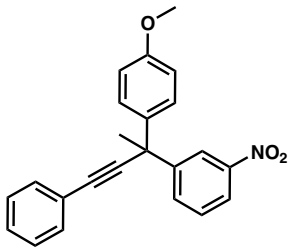
2-(2-(4-methoxyphenyl)-4-phenylbut-3-yn-2-yl)-1,3,5-trimethylbenzene



SI-54

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 37% (26.1 mg). ^{1}H-NMR (600 MHz, acetone-D6) δ 7.65 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.25-7.17 (m, 5H), 7.13 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 8.9 Hz, 1H), 6.49 (s, 1H), 3.75 (s, 3H), 2.86 (s, 3H), 1.40 (s, 9H). ^{13}C-NMR (151 MHz, chloroform-D) δ 158.3, 152.4, 150.6, 144.7, 142.8, 137.7, 136.3, 129.5, 128.9, 128.2, 127.8, 126.5, 126.4, 125.5, 125.0, 123.0, 114.0, 113.6, 63.6, 55.3, 33.1, 29.5. IR:3058, 2952, 2867, 2360, 1599, 1392, 1246, 1178, 1033, 612, 748, 539 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{26}H_{26}O$ $[M + H]^+$ 355.20, found 355.2056.

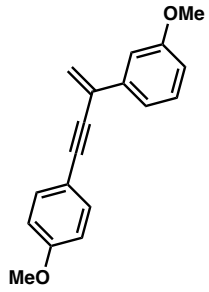
1-(2-(4-methoxyphenyl)-4-phenylbut-3-yn-2-yl)-3-nitrobenzene

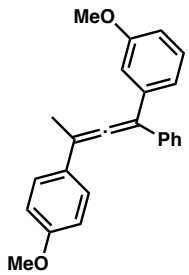


SI-55

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 26% (18.5 mg). l. ^{1}H-NMR (600 MHz, acetone-D6) δ 8.31 (d, J = 123.0 Hz, 1H), 8.12 (dd, J = 27.1, 7.9 Hz, 1H), 7.88 (dd, J = 119.9, 7.9 Hz, 1H), 7.70-7.39 (m, 9H), 6.94 (d, J = 8.2 Hz, 1H), 3.79 (s, 3H), 2.12 (s, 2H), 1.88 (s, 2H). ^{13}C-NMR (151 MHz, acetone-D6) δ 158.4, 137.1, 131.5, 128.7, 128.5, 127.9, 127.2, 123.9, 113.5, 95.0, 83.7, 54.6, 40.9, 37.0, 9.5. IR: 2932, 2835, 1606, 1526, 1508, 1349, 1249, 1180, 1030, 772, 687 cm^{-1}. HRMS-ESI *m/z* Calculated for $C_{23}H_{19}NO_3$ $[M + H]^+$ 358.14, found 358.1438.

1-methoxy-3-(4-phenylbut-1-en-3-yn-2-yl)benzene & 1-methoxy-3-(4-phenylbut-1-en-3-yn-2-yl)benzene

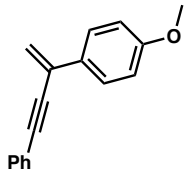


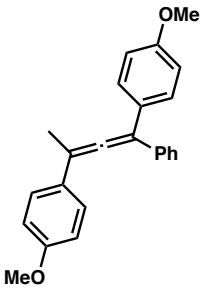


SI- 56 **SI- 57**

See the general procedure C for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 65% (30.4 mg) of **SI-56** and 28% (12.9 mg) of **SI-57**. All data were consistent with that presented in literature. [74,108]

1-methoxy-4-(4-phenylbut-1-en-3-yn-2-yl)benzene & 4,4'-(1-phenylbuta-1,2-diene-1,3-diyl)bis(methoxybenzene)

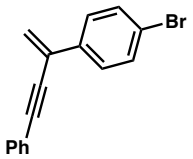




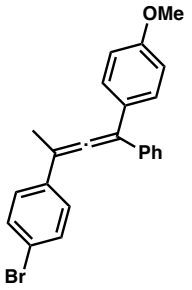
SI- 58 **SI-59**

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 70% (32.6 mg) of **SI-58** and 26% (17.4 mg) yield of **SI-59**. All data were consistent with that presented in literature.[74,108]

1-bromo-4-(4-phenylbut-1-en-3-yn-2-yl)benzene & 1-bromo-4-(4-(4-methoxyphenyl)-4-phenylbuta-2,3-dien-2-yl)benzene



SI-60



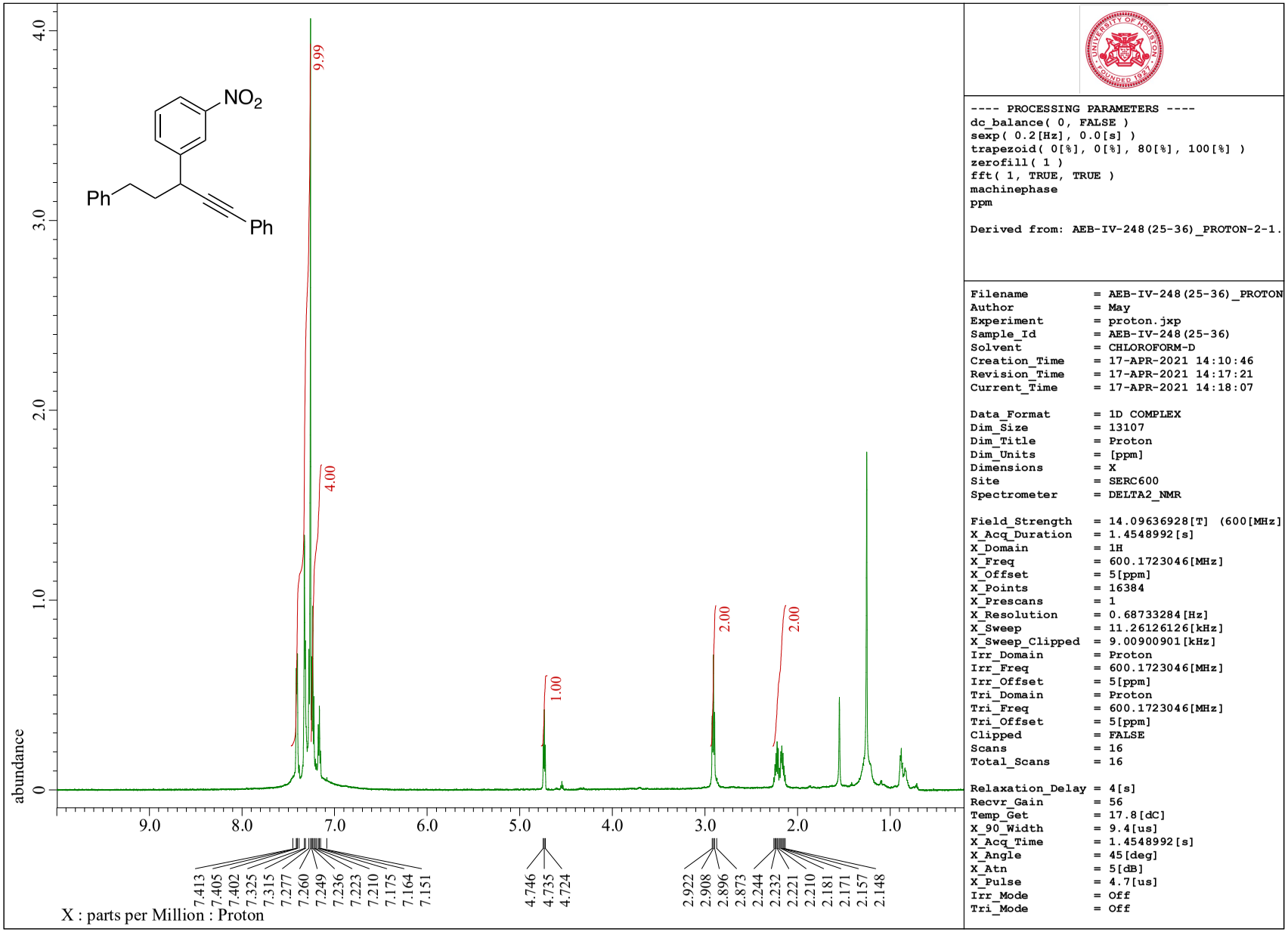
SI-61

See the general procedure for nucleophilic substitution reactions above. The crude reaction mixture was purified via flash column chromatography with a 5–20% gradient of DCM in hexanes as eluent on silica gel to give a yield of 82% (46.2mg) for **SI-60** and 15% (8.1%) of **SI-61**. All data were consistent with that presented in literature.[74,108]

APPENDIX – CHAPTER FOUR

Spectra Relevant to Chapter Four

Ph
7.436
7.424
7.260
7.243
7.231
7.219
7.195
7.182
7.170
6.966
6.875
6.862
6.634
2.354
2.119
1.961
1.939
1.920
1.910
1.892
1.873
1.667
1.646
1.625
1.605
1.513
1.490
6.00
5.00
3.00
2.00
2.00
1.00
1.00
1.00
1.00
1.00
abundance
X : parts per Million : Proton




```
---- PROCESSING PARAMETERS ----
dc_balance( 0, FALSE )
sexp( 0.2[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 1 )
fft( 1, TRUE, TRUE )
machinephase
ppm

Derived from: AEB-IV-248(25-36)_PROTON-2-1.
```

```
Filename          = AEB-IV-248(25-36)_PROTON
Author            = May
Experiment        = proton.jxp
Sample_Id         = AEB-IV-248(25-36)
Solvent           = CHLOROFORM-D
Creation_Time     = 17-APR-2021 14:10:46
Revision_Time     = 17-APR-2021 14:17:21
Current_Time      = 17-APR-2021 14:18:07

Data_Format       = 1D COMPLEX
Dim_Size          = 13107
Dim_Title         = Proton
Dim_Units         = [ppm]
Dimensions        = X
Site              = SERC600
Spectrometer      = DELTA2_NMR

Field_Strength    = 14.09636928[T]  (600[MHz]
X_Acq_Duration    = 1.4548992[s]
X_Domain          = 1H
X_Freq            = 600.1723046[MHz]
X_Offset          = 5[ppm]
X_Points          = 16384
X_Prescans        = 1
X_Resolution      = 0.68733284[Hz]
X_Sweep           = 11.26126126[kHz]
X_Sweep_Clipped   = 9.00900901[kHz]
Irr_Domain        = Proton
Irr_Freq          = 600.1723046[MHz]
Irr_Offset        = 5[ppm]
Tri_Domain        = Proton
Tri_Freq          = 600.1723046[MHz]
Tri_Offset        = 5[ppm]
Clipped           = FALSE
Scans             = 16
Total_Scans       = 16

Relaxation_Delay  = 4[s]
Recvr_Gain        = 56
Temp_Get          = 17.8[dC]
X_90_Width        = 9.4[us]
X_Acq_Time        = 1.4548992[s]
X_Angle           = 45[deg]
X_Atn             = 5[dB]
X_Pulse           = 4.7[us]
Irr_Mode          = Off
Tri_Mode          = Off
```

Br
Ph
Ph
7.00
3.01
2.01
2.00
0.78
2.15
2.00
2.01
3.812
5.302
7.482
7.479
7.470
7.346
7.332
7.320
7.309
7.296
7.283
7.259
7.236
7.223
7.212
7.199
6.895
6.881
2.851
2.841
2.827
2.814
2.181
2.167
2.159
2.145
2.135
2.123
2.112
2.097
2.088
abundance
X : parts per Million : Proton

abundance
X : parts per Million : Proton
Ph
O
HO
3.03
2.00
2.01
2.01
1.00
0.99
1.00
3.00
2.01
7.770
7.757
7.460
7.451
7.447
7.336
7.317
7.306
7.253
6.887
6.874
5.172
5.164
5.155
4.409
4.187
4.177
3.818
2.353
2.347
2.340
2.330
2.324
2.317
2.223
2.214
2.207
2.199
2.191
2.184

abundance
X : parts per Million : Proton
MeO
Ph
3.00
2.00
3.00
2.00
3.00
3.00
3.786
2.050
1.906
1.899
1.894
1.886
1.882
1.615
0.922
0.909
0.898
7.540
7.526
7.500
7.488
7.386
7.375
7.363
7.352
6.923
6.908

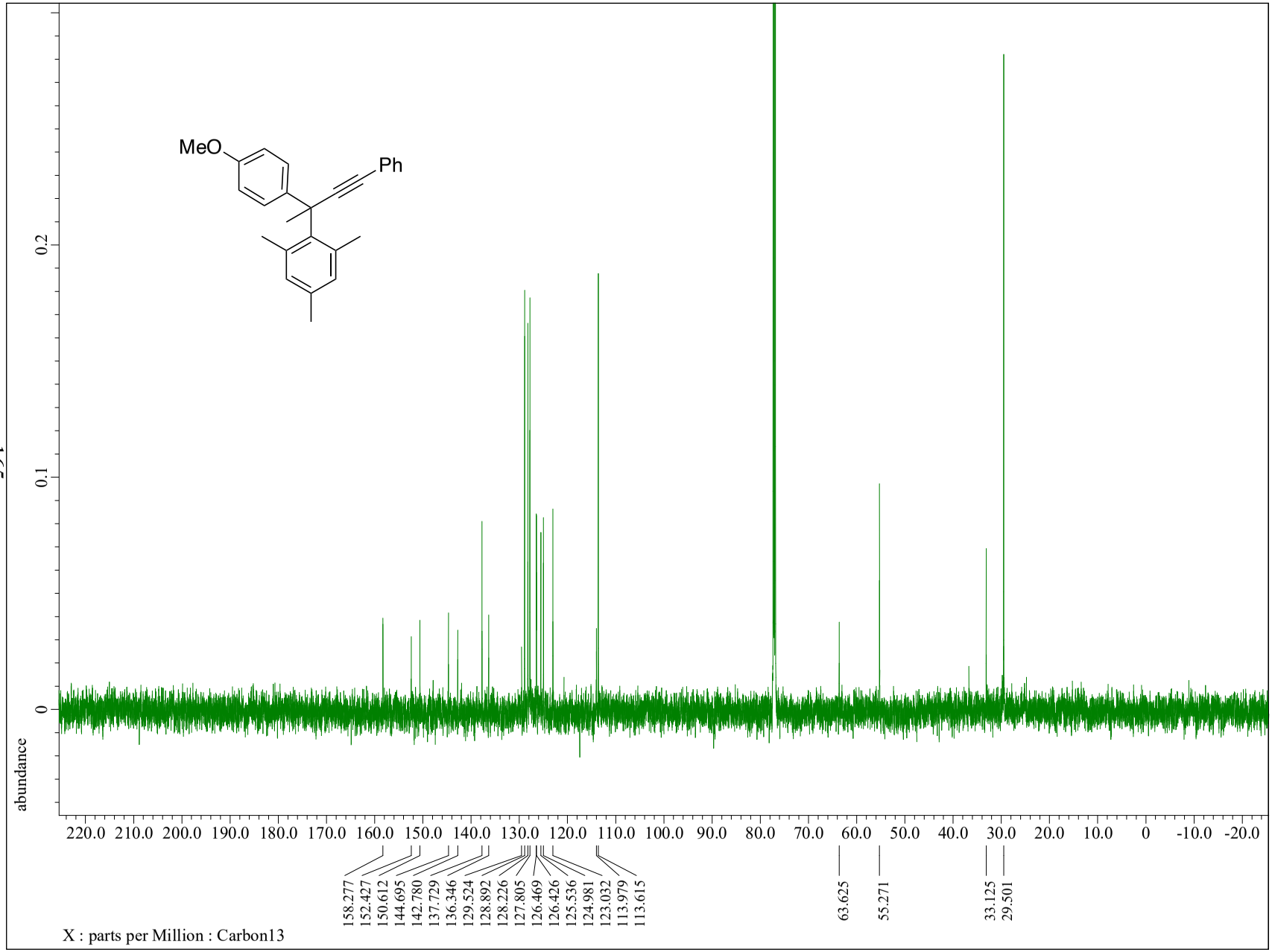
abundance
X : parts per Million : Proton
10.02
4.02
2.00
2.01
1.00
NO2
Ph
Ph
7.407
7.398
7.395
7.319
7.308
7.298
7.271
7.258
7.250
7.241
7.230
7.217
7.168
7.156
4.740
4.730
4.718
2.916
2.902
2.890
2.238
2.227
2.216
2.203
2.191
2.187
2.175
2.164
2.151

abundance
X : parts per Million : Proton
9.00
3.00
3.00
5.00
1.00
1.00
1.00
1.00
1.00
1.403
2.050
2.857
3.747
6.495
6.800
6.815
7.126
7.141
7.168
7.181
7.194
7.210
7.223
7.226
7.238
7.267
7.279
7.292
7.347
7.359
7.639
7.652

Ph
153.887
143.455
140.741
140.468
136.781
136.710
132.377
128.083
126.603
125.086
121.773
120.480
77.341
77.131
76.920
53.419
34.791
26.241
24.963
21.214
20.242
X : parts per Million : Carbon13
abundance

abundance
0
0.1
0.2
0.3
X : parts per Million : Carbon13
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
161.910
135.656
131.922
128.691
128.384
122.405
113.213
88.079
84.896
77.327
77.116
76.906
61.801
59.858
55.157
33.182
29.812
O
Ph
OH

NO2
Ph
Ph
(thousandths)
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : Carbon13
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
141.693
131.917
128.767
128.705
128.657
128.605
128.576
128.451
128.351
128.279
125.919
122.778
109.800
88.127
86.121
77.317
77.107
76.896
67.063
66.996
37.582
31.598
29.807


165
MeO
Ph
abundance
0
0.1
0.2
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
158.277
152.427
150.612
144.695
142.780
137.729
136.346
129.524
128.892
128.226
127.805
126.469
126.426
125.536
124.981
123.032
113.979
113.615
63.625
55.271
33.125
29.501
X : parts per Million : Carbon13

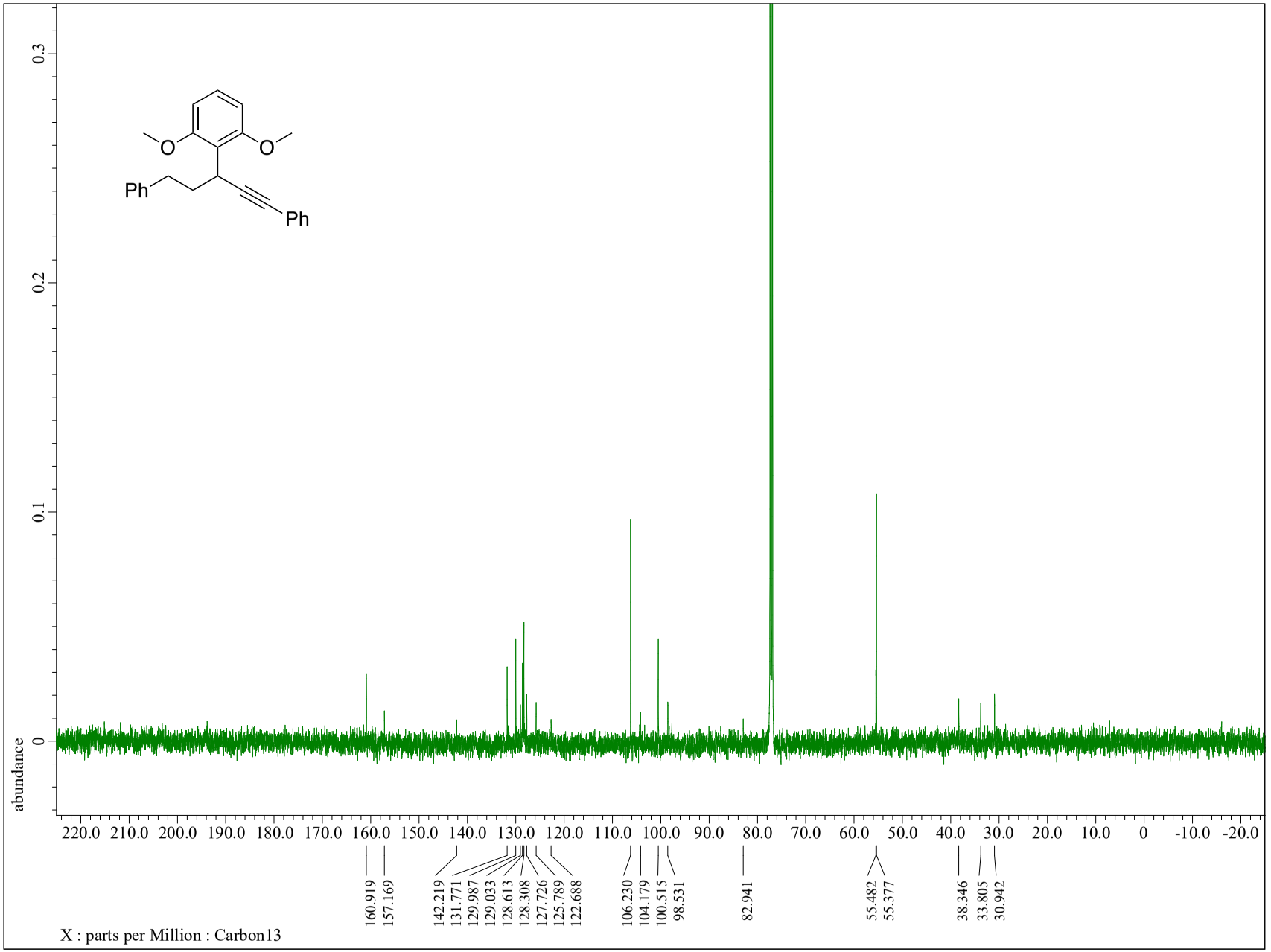
MeO
Ph
(thousandths)
X : parts per Million : Carbon13
158.377
137.141
131.477
128.729
128.504
127.944
127.221
123.913
113.491
95.012
83.704
54.625
40.890
36.955
9.538

abundance
X : parts per Million : Carbon13
22.315
54.994
54.721
110.025
112.246
113.888
114.171
121.414
121.519
121.672
121.816
127.566
128.092
128.619
128.787
128.892
129.801
131.539
133.047
133.411
140.104
MeO
Ph
NO2

abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
X : parts per Million : Carbon13
158.492
141.779
134.034
131.760
128.638
128.571
128.490
128.341
127.896
125.995
123.841
113.984
91.608
83.665
55.420
55.386
40.316
37.017
33.666
29.827
Br
Ph
Ph

(thousandths)
X : parts per Million : Carbon13
206.323
205.930
205.519
205.461
205.332
205.198
150.244
134.852
131.477
131.238
128.514
128.116
127.973
123.626
121.941
93.451
91.134
86.629
84.465
40.756
40.014
29.530
29.410
29.281
29.156
29.027
28.898
28.769
28.639
23.493
Ph
S

abundance
0
0.1
0.2
0.3
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
X : parts per Million : Carbon13
31.344
37.678
66.699
86.030
87.902
88.869
122.644
122.908
125.928
125.962
128.322
128.360
128.437
128.485
128.504
128.523
128.562
128.595
128.667
131.664
131.740
141.593
NO2
Ph
Ph


O
O
Ph
Ph
abundance
0.3
0.2
0.1
0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
160.919
157.169
142.219
131.771
129.987
129.033
128.613
128.308
127.726
125.789
122.688
106.230
104.179
100.515
98.531
82.941
55.482
55.377
38.346
33.805
30.942
X : parts per Million : Carbon13

BIBLIOGRAPHY:

(54) Nicholas, K. M. Chemistry and Synthetic Utility of Cobalt-Complexed Propargyl Cations. *Acc. Chem. Res.* **1987**, *20* (6), 207–214.

(55) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. Copper(I)-Catalyzed Amination of Propargyl Esters. Selective Synthesis of Propargylamines, 1-Alken-3-Ylamines, and (Z)-Allylamines. *J. Org. Chem.* **1994**, *59* (9), 2282–2284.

(56) Asymmetric Copper-Catalyzed Propargylic Substitution Reaction of Propargylic Acetates with Enamines. *Org. Lett.* **2009**, 11, 20, 4612–4615

(57) Copper-Catalyzed Asymmetric Propargylic Substitution Reactions of Propargylic Acetates with Amines. *Angew. Chem. Int. Ed.* **2008**, *47* (20), 3781–3783.

(58) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. Enantioselective Copper-Catalyzed Propargylic Amination. *Angew. Chem. Int. Ed.* **2008**, *47* (20), 3777–3780.

(59) Detz, R. J.; Abiri, Z.; le Griel, R.; Hiemstra, H.; van Maarseveen, J. H. Enantioselective Copper-Catalysed Propargylic Substitution: Synthetic Scope Study and Application in Formal Total Syntheses of (+)-Anisomycin and (−)-Cytoxazone. *Chem. – Eur. J.* **2011**, *17* (21), 5921–5930.

(60) Nishibayashi, Y.; Wakiji, I.; Hidai, M. Novel Propargylic Substitution Reactions Catalyzed by Thiolate-Bridged Diruthenium Complexes via Allenylidene Intermediates. *J. Am. Chem. Soc.* **2000**, *122* (44), 11019–11020.

(61) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Uemura, S. Novel Method for the Preparation of Enantiomerically Pure Propargylic Substituted Compounds. *Organometallics* **2005**, *24* (17), 4106–4109.

(62) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. Preparation of Alkanechalcogenolate- and Benzenechalcogenolate-Bridged Diruthenium Complexes and Their Catalytic Activity toward Propargylation of Acetone with Propargylic Alcohol. *Organometallics* **2004**, *23* (21), 5100–5103.

(63) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Hidai, M.; Uemura, S. Preparation of a Series of Chalcogenolate-Bridged Diruthenium Complexes and Their Catalytic Activities toward Propargylic Substitution Reactions. *Organometallics* **2004**, *23* (1), 26–30.

(64) Nishibayashi, Y.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. Synthesis of Diruthenium Complexes Containing Chiral Thiolate-Bridged Ligands and Their Application to Catalytic Propargylic Alkylation of Propargylic Alcohols with Acetone. *Organometallics* **2003**, *22* (4), 873–876.

(65) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. Ruthenium-Catalyzed Propargylation of Aromatic Compounds with Propargylic Alcohols. *J. Am. Chem. Soc.* **2002**, *124* (40), 11846–11847.

(66) Nishibayashi, Y.; Wakiji, I.; Hidai, M. Novel Propargylic Substitution Reactions Catalyzed by Thiolate-Bridged Diruthenium Complexes via Allenylidene Intermediates. *J. Am. Chem. Soc.* **2000**, *122* (44), 11019–11020.

(67) Yoshiaki Nishibayashi, *; Masato Yoshikawa, †; Youichi Inada, †; Masanobu Hidai, ‡ and; Sakae Uemura*, †. Ruthenium-Catalyzed Cycloaddition between Propargylic Alcohols and Cyclic 1,3-Dicarbonyl Compounds via an Allenylidene Intermediate *J. Org. Chem.* 2004, 69, 10, 3408–3412.

(68) Kanao, K.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. Ruthenium-Catalyzed Enantioselective Propargylation of Indoles with Propargylic Alcohols. *Synthesis* **2008**, *2008* (23), 3869–3873.

(69) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. Ruthenium-Catalyzed Enantioselective Propargylation of Aromatic Compounds with Propargylic Alcohols via Allenylidene Intermediates. *Angew. Chem. Int. Ed.* **2007**, *46* (34), 6488–6491.

(70) Georgy, M.; Boucard, V.; Campagne, J.-M. Gold(III)-Catalyzed Nucleophilic Substitution of Propargylic Alcohols. *J. Am. Chem. Soc.* **2005**, *127* (41), 14180–14181.

(71) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. Metal-Free Catalytic Nucleophilic Substitution of Propargylic Alcohols. *Eur. J. Org. Chem.* **2006**, *2006* (6), 1383–1386.

(72) Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Mandal, S. S.; Reddy, J. S. S.; Yadav, J. S. Iodine-Catalyzed C- and O-Nucleophilic Substitution Reactions of Aryl-Propargyl Methanols. *Tetrahedron Lett.* **2007**, *48* (46), 8120–8124. https://doi.org/10.1016/j.tetlet.2007.09.123.) Sinisi, R.; Vita, M. V.; Gualandi, A.; Emer, E.; Cozzi, P. G. SN1-Type Reactions in the Presence of Water: Indium(III)-Promoted Highly Enantioselective Organocatalytic Propargylation of Aldehydes. *Chem. – Eur. J.* **2011**, *17* (27), 7404–7408.

(74) Yoshida, M.; Gotou, T.; Ihara, M. Palladium-Catalyzed Direct Coupling Reaction of Propargylic Alcohols with Arylboronic Acids. *Tetrahedron Lett.* **2004**, *45* (29), 5573–5575.

(75) Lebœuf, D.; Presset, M.; Michelet, B.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. CaII-Catalyzed Alkenylation of Alcohols with Vinylboronic Acids. *Chem. – Eur. J.* **2015**, *21* (31), 11001–11005.

(76) Ueda, M.; Nakakoji, D.; Morisaki, T.; Ryu, I. Transition-Metal-Catalyst-Free Cross-Coupling Reaction of Secondary Propargylic Acetates with Alkenyl- and Arylboronic Acids. *Eur. J. Org. Chem.* **2017**, *2017* (47), 7040–7045.

(77) Xue, P.-H.; Zhang, N.; Liu, D.; Zhang, Q.-R.; Duan, J.-S.; Yu, Y.-Q.; Li, J.-Y.; Cao, S.-J.; Zhao, F.; Kang, N.; Qiu, F. Cytotoxic and Anti-Inflammatory Sesquiterpenes from the Whole Plants of Centipeda Minima. *J. Nat. Prod.* **2021**, *84* (2), 247–258.

(78) Kim, J. G.; Lee, J. W.; Le, T. P. L.; Han, J. S.; Kwon, H.; Lee, D.; Hong, J. T.; Kim, Y.; Lee, M. K.; Hwang, B. Y. Diterpenoids and Diacetylenes from the Roots of Aralia Cordata with Inhibitory Effects on Nitric Oxide Production. *J. Nat. Prod.* **2021**, *84* (2), 230–238.

(79) Langat, L.; Langat, M. K.; Wetschnig, W.; Knirsch, W.; Mulholland, D. A. Antiproliferative Bufadienolides from the Bulbs of Drimia Altissima. *J. Nat. Prod.* **2021**.

(80) Chear, N. J.-Y.; León, F.; Sharma, A.; Kanumuri, S. R. R.; Zwolinski, G.; Abboud, K. A.; Singh, D.; Restrepo, L. F.; Patel, A.; Hiranita, T.; Ramanathan, S.; Hampson, A. J.; McMahon, L. R.; McCurdy, C. R. Exploring the Chemistry of Alkaloids from Malaysian Mitragyna Speciosa (Kratom) and the Role of Oxindoles on Human Opioid Receptors. *J. Nat. Prod.* **2021**.

(81) Wang, K.; Zhou, X.-Y.; Wang, Y.-Y.; Li, M.-M.; Li, Y.-S.; Peng, L.-Y.; Cheng, X.; Li, Y.; Wang, Y.-P.; Zhao, Q.-S. Macrophyllionium and Macrophyllines A and B, Oxindole Alkaloids from *Uncaria Macrophylla*. *J. Nat. Prod.* **2011**, *74* (1), 12–15.

(82) Nguyen, T. N.; May, J. A. Tertiary and Quaternary Carbon Formation via Gallium-Catalyzed Nucleophilic Addition of Organoboronates to Cyclopropanes. *Org. Lett.* **2018**, *20* (1), 112–115.

(83) Xu, Z.; Mao, J.; Zhang, Y. Highly Enantioselective Alkynylation of Aldehydes Catalyzed by a New Oxazolidine–Titanium Complex. *Org. Biomol. Chem.* **2008**, *6* (7), 1288–1292.

(84) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. Diastereoselective Syn or Anti Opening of Propargylic Epoxides. Synthesis of α-Allenic Alcohols. *Tetrahedron* **1991**, *47* (9), 1677–1696.

(85) Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Kawamura, T.; Uemura, S. Oxovanadium Complex-Catalyzed Aerobic Oxidation of Propargylic Alcohols. *J. Org. Chem.* **2002**, *67* (19), 6718–6724.

(86) Bellina, F.; Colzi, F.; Mannina, L.; Rossi, R.; Viel, S. Reaction of Alkynes with Iodine Monochloride Revisited. *J. Org. Chem.* **2003**, *68* (26), 10175–10177.

(87) Wadhwa, K.; Chintareddy, V. R.; Verkade, J. G. P(PhCH2NCH2CH2)3N: An Efficient Lewis Base Catalyst for the Synthesis of Propargylic Alcohols and Morita−Baylis−Hillman Adducts via Aldehyde Alkynylation. *J. Org. Chem.* **2009**, *74* (17), 6681–6690.

(88) Pennell, M. N.; Turner, P. G.; Sheppard, T. D. Gold- and Silver-Catalyzed Reactions of Propargylic Alcohols in the Presence of Protic Additives. *Chem. – Eur. J.* **2012**, *18* (15), 4748–4758.

(89) Smith, S. W.; Fu, G. C. Nickel-Catalyzed Negishi Cross-Couplings of Secondary Nucleophiles with Secondary Propargylic Electrophiles at Room Temperature. *Angew. Chem. Int. Ed.* **2008**, *47* (48), 9334–9336.

(90) Boussonnière, A.; Bénéteau, R.; Zimmermann, N.; Lebreton, J.; Dénès, F. Radical Cyclization of α-Bromo Aluminum Acetals onto Alkenes and Alkynes (Radic[Al] Process): A Simple Access to γ-Lactols and 4-Methylene-γ-Lactols. *Chem. – Eur. J.* **2011**, *17* (20), 5613–5627.

(91) Linderman, R. J.; Jamois, E. A.; Tennyson, S. D. Synthesis of and Analysis of Thiol Additions to .Beta.-Alkyl-.Alpha.,.Beta.-Unsaturated Trifluoromethyl Ketones. *J. Org. Chem.* **1994**, *59* (5), 957–962.

(92) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. Catalytic Alkynylation of Ketones and Aldehydes Using Quaternary Ammonium Hydroxide Base. *J. Org. Chem.* **2003**, *68* (9), 3702–3705.

(93) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. Palladium-Catalyzed Hydrovinylation of Vinyl Triflates with Alkynes An Approach to the Synthesis of 3-Vinylfuran-2(5H)-Ones. *Eur. J. Org. Chem.* **1999**, *1999* (12), 3305–3313.

(94) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. New Formulas for Organozincate Chemistry. *J. Am. Chem. Soc.* **1998**, *120* (20), 4934–4946.

(95) Batey, R. A.; Thadani, A. N.; Smil, D. V. Potassium Alkenyl- and Aryltrifluoroborates: Stable and Efficient Agents for Rhodium-Catalyzed Addition to Aldehydes and Enones. *Org. Lett.* **1999**, *1* (10), 1683–1686.

(96) Allart, E. A.; Christie, S. D. R.; Pritchard, G. J.; Elsegood, M. R. J. Preparation of Highly Substituted Tetrahydropyrans via a Metal Assisted Dipolar Cycloaddition Reaction. *Chem. Commun.* **2009**, No. 47, 7339–7341.

(97) Li, H.; Alexakis, A. Enyne Chlorides: Substrates for Copper-Catalyzed Asymmetric Allylic Alkylation. *Angew. Chem. Int. Ed.* **2012**, *51* (4), 1055–1058.

(98) Torregrosa, R. R. P.; Mendis, S. N.; Davies, A.; Tunge, J. A. Palladium-Catalyzed Decarboxylative Benzylation of Acetylides and Enolates. *Synthesis* **2018**, *50* (16), 3205–3216.

(99) Chuang, D.-W.; El-Shazly, M.; Chen, C.-C.; Chung, Y.-M.; D. Barve, B.; Wu, M.-J.; Chang, F.-R.; Wu, Y.-C. Synthesis of 1,5-Diphenylpent-3-En-1-Yne Derivatives Utilizing an Aqueous B-Alkyl Suzuki Cross Coupling Reaction. *Tetrahedron Lett.* **2013**, *54* (38), 5162–5166.

(100) Cheng, L.-J.; Cordier, C. J. Catalytic Nucleophilic Fluorination of Secondary and Tertiary Propargylic Electrophiles with a Copper–N-Heterocyclic Carbene Complex. *Angew. Chem. Int. Ed.* **2015**, *54* (46), 13734–13738.

(101) Fürstner, A.; Méndez, M. Iron-Catalyzed Cross-Coupling Reactions: Efficient Synthesis of 2,3-Allenol Derivatives. *Angew. Chem. Int. Ed.* **2003**, *42* (43), 5355–5357.

(102) Kabalka, G. W.; Yao, M.-L.; Borella, S. Substitution of Hydroxyl Groups with Alkynyl Moieties Using Alkynylboron Dihalides: An Efficient Approach to Secondary Alkylacetylene Derivatives. *Org. Lett.* **2006**, *8* (5), 879–881.

(103) Stille, J. K.; Simpson, J. H. Stereospecific Palladium-Catalyzed Coupling Reactions of Vinyl Iodides with Acetylenic Tin Reagents. *J. Am. Chem. Soc.* **1987**, *109* (7), 2138–2152.

(104) Niggemann, M.; Meel, M. J. Calcium-Catalyzed Friedel–Crafts Alkylation at Room Temperature. *Angew. Chem. Int. Ed.* **2010**, *49* (21), 3684–3687.

(105) Liu, X.; Liu, R.; Dai, J.; Cheng, X.; Li, G. Application of Hantzsch Ester and Meyer Nitrile in Radical Alkynylation Reactions. *Org. Lett.* **2018**, *20* (21), 6906–6909.

(106) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. Pd-Catalyzed Three-Component Coupling of N-Tosylhydrazone, Terminal Alkyne, and Aryl Halide. *J. Am. Chem. Soc.* **2010**, *132* (39), 13590–13591.

(107) Martins, G. M.; Back, D. F.; Kaufman, T. S.; Silveira, C. C. SeCl2-Mediated Approach Toward Indole-Containing Polysubstituted Selenophenes. *J. Org. Chem.* **2018**, *83* (6), 3252–3264.

(108) Kim, J.-H.; Lee, D.-H.; Jun, B.-H.; Lee, Y.-S. Copper-Free Sonogashira Cross-Coupling Reaction Catalyzed by Polymer-Supported N-Heterocyclic Carbene Palladium Complex. *Tetrahedron Lett.* **2007**, *48* (40), 7079–7084.