ENANTIOSELECTIVE ARYLATION AND VINYLATION OF ALLYLIC BROMIDES CATALYZED BY GUANIDINIUM AND COPPER(I) SALT

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Abstract

The work during my Ph.D period was devoted to develop the asymmetric cross coupling reactions in the presence of chiral guanidinium catalyst. A series of guanidine-derived organocatalysis was developed in Prof Tan Choon Hong's lab, showing great efficiency in asymmetric transformations.

The thesis presented here is divided into three chapters, mainly discussing the exploration of enantioselective Csp^3-Csp^2 cross coupling to give optically active products in the presence of metal complex and chiral guanidinium catalyst.

Chapter 1 of this thesis introduces the development of methodology for asymmetric Csp^3-Csp^2 cross coupling catalyzed by transition metals, assorted by types of electrophiles and nucleophiles employed in the reactions. Different transition metal complexes and ligands are discussed and compared in terms of capacity and disadvantage in asymmetric Csp^3-Csp^2 cross coupling. Proposal and objectives are raised at the end of Chapter 1 to address the possibility of using copper(I) salt and guanidinium for the reaction.

The following part in Chapter 2 is the detailed investigation of asymmetric Csp^3-Csp^2 cross coupling catalyzed by copper(I) complex and guanidinium catalyst. An array of cyclic allylic bromides were transformed to corresponding arylated or vinylated products in good yields and high enantioselectivity. Mechanistic exploration of the cross coupling process involves: (1) *X*-Ray crystal structure and reactivity of guanidinium cuprate complex; (2) ^{63}Cu NMR spectrum to observe the interaction between copper(I) complex and other reagents; (3) "Hard" nucleophilic attack pathway determined by change in the stereoselectivity of asymmetric allylic arylation process.

Chapter 3 describes the extension of the developed methodology from cyclic bromides to various prochiral acyclic bromides, giving a wider substrate scope of S_N2' products in good enantioselectivity. The results illustrate the practicality of our catalyst system in asymmetric allylic substitution with various substrates.

List of Schemes and Tables

Chapter 1

Chapter 2

Chapter 3

Abbreviations and Nomenclature

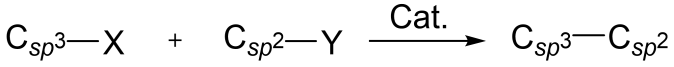
Standard abbreviations and IUPAC nomenclature are used throughout this thesis. Less common usages are as follows.

PG	Pentanidinium
BG	Bisguanidinium
CG	Bicyclicguanidinium
Tol	Toluene
DCM	Dichloromethane
THF	Tetrahydrofuran
Hex	Hexane
DME	Dimethoxyethane
DMI	1,3-Dimethyl-2-imidazolidinone
O.R.	Optical rotation
ee	Enantiomeric excess
sec	Secondary
rt	Room temperature

Chapter One

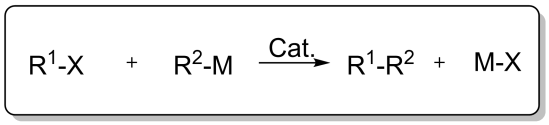
Introduction

Asymmetric Csp^3-Csp^2 Cross Coupling



1.1 Introduction

Transition metal catalyzed cross-coupling reaction (Scheme 1.1) is one of the most important organic transformations in synthetic chemistry because it provides a broad array of methods for C-C bond construction to create sophisticated organic compounds.[1] The significance of these methods is acknowledged by 2010 Nobel Prize in Chemistry awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their contribution in developing Pd-catalyzed cross coupling reactions.[2]



Cat.= transition metal catalyst Ni^0 or Pd^0
M= Sn, Zn, Mg, B, Si, Li...

Scheme 1.1 Transition-metal-catalyzed cross coupling.

Asymmetric cross coupling has been explored extensively by many groups as it allows the formation of chiral C-C bond for synthesizing optically active compounds. Among all different types of C-C bonds, the ubiquitous existence of chiral Csp^3-Csp^2 bond in many important natural products and biologically active molecules leads to continuous interest in developing enantioselective methodology for its effective construction.[3] Although Ni- or Pd-catalyzed cross coupling reactions have been extensively examined for over forty years, their catalytic capacity in the enantioenriched formation of Csp^3-Csp^2 bond proves effective only in the last decade.[4]

Among all the organometallic reagents which are usually used as cross coupling partners including organotin (Stille coupling)[5], organozinc (Nigeshi coupling)[6], organomagnesium (Kumada coupling)[7], organoboron (Suzuki-Miyaura coupling)[8], organosilicon (Hiyama–Denmark coupling)[9] and organolithium (Fringa's work)[10], only a few have been demonstrated as suitable reagents for enantioselective Csp^3-Csp^2 cross coupling. It is usually difficult to achieve high selectivity, especially when using those highly reactive partners. On the other hand, Ni and Pd dominate the use of transition metal catalyst for

Csp^3-Csp^2 cross coupling, the pursuit of using less reactive reagents and other cheap transition metal catalyst for higher atom economy and environmental sustainability never stops.[11]

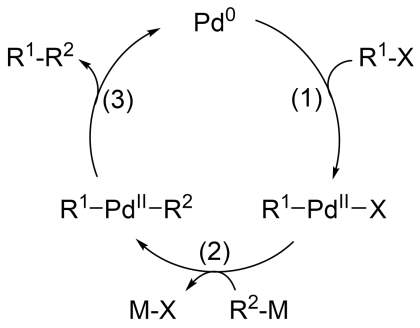
Herein, a summary for the development of enantioselective Csp^3-Csp^2 cross coupling based on the types of cross coupling partners is presented, covering mainly those reported work with good selectivity. Initiated with an overlook of the general mechanism, the following discussion is divided into three subsections: 1) Csp^3 nucleophile and Csp^2 electrophile cross coupling; 2) Csp^2 nucleophile and Csp^3 electrophile cross coupling; 3) Csp^2 nucleophile and Csp^3 acyclic allylic electrophile cross coupling, which is also described as transition-metal-catalyzed enantioselective allylic substitution (EAS) at γ position to give chiral S_N2' product. In each subsection, categories based on the reagent type are shown. While most examples in the discussion are enantioselective versions of cross coupling which utilize racemic starting material, selected examples of efficient enantiospecific Csp^3-Csp^2 cross coupling which use chiral starting material are also listed for complement. However, cross-dehydrogenative-coupling[12] (CDC reaction) with external oxidant, Ni catalyzed reductive cross coupling[13] with external reductant, and C-H activation cross coupling[14] are not included herein.

1.2 General Mechanism of Cross Coupling

Cross coupling reactions involves a broad range of C–C bond formation processes where organometallic nucleophiles couple with organic electrophiles catalyzed by late transition metal complexes. It is widely accepted that the mechanism of classical transition-metal-catalyzed cross coupling reactions involves three basic steps.[5,15] A general mechanism of palladium-catalyzed cross coupling proceeding via a Pd^0/Pd^{II} catalytic cycle is shown here for illustration in Scheme 1.2.

The three basic steps includes: (1) An initial oxidative addition of organic electrophile (**R^1–X**, usually a halide or pseudohalide such as triflate, alcohol, or

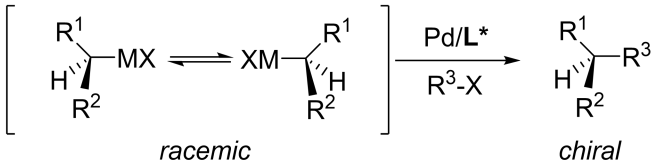
carbonate) to an electron-rich Pd^0-species, producing an organo-Pd^{II} complex (**R^1-Pd^{II}-X**); (2) Transmetallation of an organometallic reagent (**R^2-M**, M=Mg, Zn, Sn, Li, B, Si...) results in the formation of a new organo-Pd^{II} complex (**R^1-Pd^{II}-R^2**); (3) Reductive elimination at Pd^{II} center to form carbon–carbon bond, release the desired cross coupling product (**R^1–R^2**), and at the meantime, regenerate the active Pd^0-species. Approximate relative order of reactivity of organic halides in oxidative addition to Pd^0 has been estimated as: allyl, propargyl > benzyl, acyl > alkenyl, alkynyl > aryl >> simple alkyl. The rate determining step is believed to be the transmetallation of organometallic reagent, which has been extensively explored with great details.[16]



(1) oxidative addition (2) transmetalation (3) reductive elimination
R^1,R^2=alkyl, aryl, alkenyl; X=I, Br, Cl, OTf, etc.

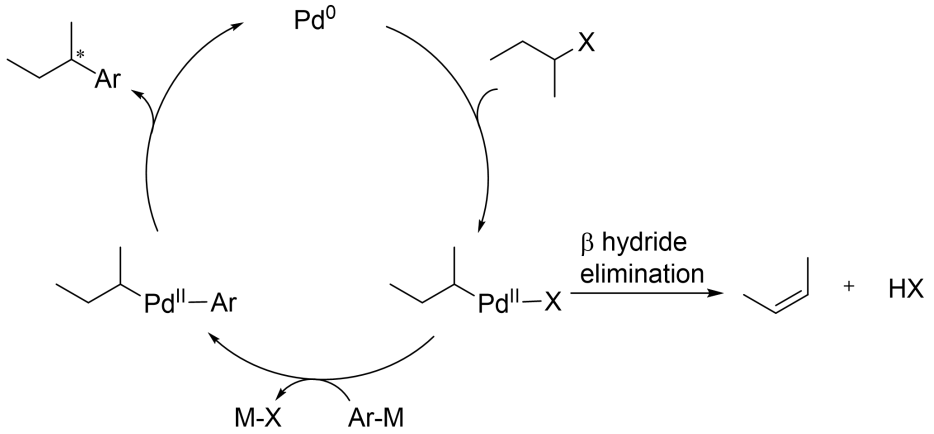
Scheme 1.2 Catalytic cycle of transition-metal-catalyzed cross coupling.

Asymmetric Csp^3-Csp^2 cross coupling reactions with chiral catalyst in early years mostly used alkyl organometallic reagent as nucleophile and aryl halide as electrophile.[17] If secondary (*sec*-) alkyl organometallic nucleophiles are employed (Scheme 1.3), the enantioselectivity can be achieved via the kinetic resolution of organometallic reagent, transforming a racemic mixture of the *sec*-alkyl organometallic reagent into an optically active product. If the cross coupling occurs at a rate comparable to the racemization of organometallic reagents, the desired enantiomerically enriched Csp^3-Csp^2 cross coupling product thus can be formed with a full conversion of the *sec*-alkyl organometallic reagent.



Scheme 1.3 Asymmetric cross coupling with chiral catalyst.

However, the development of asymmetric cross coupling to give chiral C*sp*^{3}-C*sp*^{2} bond is quite slow since its initial discovery. Secondary alkyl metallic reagents are typically slower than the primary alkyl reagents to undergo transmetallation to Pd or other metal center for its steric bulkiness.[17] Similarly, *sec*-alkyl electrophiles are more difficult to undergo oxidative addition to electron-rich metal center compared with aryl and alkenyl halides, as C*sp*^{3}-X bonds are more electron-rich than C*sp*^{2}-X bonds.[18] Since no π electrons are available to interact with the empty *d* orbitals of metal center, the alkylmetallic intermediate formed upon either oxidative addition or transmetallation is substantially less stable than an aryl or alkenyl metal species.[19] Thus the alkylmetallic intermediate tends to undergo side reactions, such as β hydride elimination or hydrodehalogenation, which can outcompete both intermolecular transmetallation and reductive elimination (Scheme 1.4). Thus, *sec*-alkyl substrates (either as electrophiles or nucleophiles) were not widely used as suitable cross coupling partners for cross-coupling reactions, especially the asymmetric version.



Scheme 1.4 General catalytic cycle for cross coupling with *sec*-alkyl electrophiles.

Nevertheless, with the continuous development of fundamental aspects in the methodology, especially efficient ligands, a great number of asymmetric C*sp*^{3}-C*sp*^{2}

cross couplings involving *sec*-alkyl reagents[20] have been achieved in the last decade. The development of these new methodologies is significantly expanding the scope of transition-metal-catalyzed processes. In next section, recent important development in enantioselective Csp^3-Csp^2 cross coupling using either activated or non-activated secondary electrophiles will be discussed.

1.3 Enantioselective C*sp*^{3}-C*sp*^{2} Cross Coupling

In this section, discussion is divided into three subsections based on the role of C*sp*^{3} alkyl coupling partners. In the first part, the *sec*-alkyl organometallic reagents **C*sp*^{3}-M** function as nucleophiles, which undergo transmetallation to transition metal center and then couple with various *sp*^{2}-hybridized electrophiles **C*sp*^{2}-X**, such as aryl, vinyl and acyl. Configurational liability of *sec*-alkyl metallic reagents (M=Mg, Zn, Li)[21] allows the racemization of two enantiomers (Scheme 1.3). Therefore the chirality of transition metal complex will control the formation of chiral carbon center through the fast equilibrium of certain intermediate. Specifically, the mechanism of several Pd-catalyzed cross coupling reactions using stabilized nucleophiles has been described by Trost as dynamic kinetic asymmetric transformations (DYKAT).[22]

In the second part, *sec*-alkyl halides **C*sp*^{3}-X** function as electrophiles, which undergo oxidative addition to metal center and couple with *sp*^{2}-hybridized nucleophile **C*sp*^{2}-M**. Activated *sec*-alkyl halides which are substituted by electron withdrawing group (EWG) are mostly employed in such cross couplings.

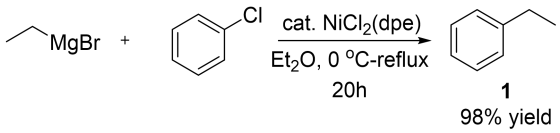
In the third part, *sp*^{2}-hybridized nucleophiles **C*sp*^{2}-M** attacked the γ position of prochiral acyclic allylic substrates to provide chiral S_N2' product in the presence of chiral metal catalysis.

1.3.1 Enantioselective C*sp*^{3}-C*sp*^{2} Cross Coupling Using C*sp*^{3}-M

1.3.1.1 *sec*-Alkyl Magnesium Reagents

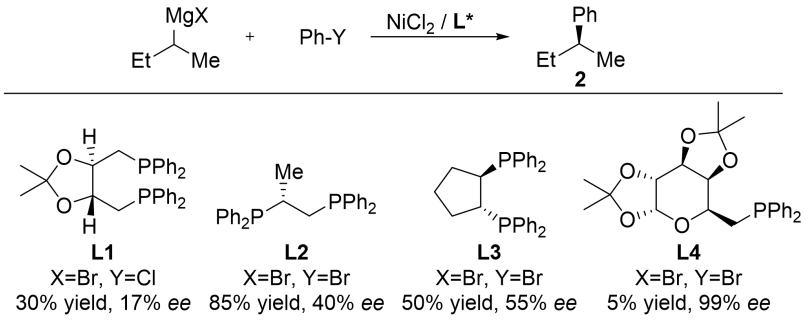
The first example of C*sp*^{3}-C*sp*^{2} cross coupling was first reported by Kumada and Tamao in 1972 (Scheme 1.5).[4a] Ni-catalyzed C*sp*^{3}-C*sp*^{2} cross coupling between ethyl Grignard reagent and phenyl chloride was achieved. The desired product ethylbenzene **1** was obtained with 98% yield in the presence of catalytic amount of $NiCl_2$(dpe) complex (dpe=1,2-bis(diphenylphosphino)ethane). This exciting discovery has emerged as a simple protocol for efficient C*sp*^{3}-C*sp*^{2} cross

coupling, which is also referred as Grignard coupling.[23] Since the *sec*-alkyl Grignard reagents can be easily prepared from commercial available organohalides with low cost, the enantioselective Grignard coupling was soon explored and reported from 1973.



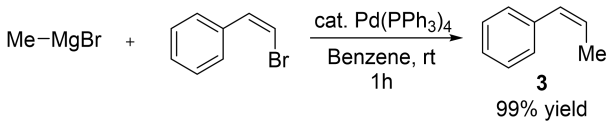
Scheme 1.5 First example of Ni-catalyzed Csp^3-Csp^2 cross coupling.

With Ni or Pd complex as catalyst, the enantioselective construction of Csp^3-Csp^2 bond was achieved by utilizing various chiral phosphine ligands (Scheme 1.6). Early efforts were mainly focused on developing chiral Ni complex as catalyst. Diphosphine ligand **L1** was reported by Consiglio[24] and Kumada[25] respectively to deliver low enantioselectivity around 17% *ee* for (*S*)-*sec*-butylbenzene **2**. Further improvement was achieved with revised ligands.[26] Diphosphine ligand **L2**[27] and **L3**[28] gave increased *ee* to 40% and 55% while carbohydrate-derived ligand **L4**[29] was also reported to help build chiral Csp^3-Csp^2 bond with excellent 99% *ee*, although with very poor yield in only 5%.



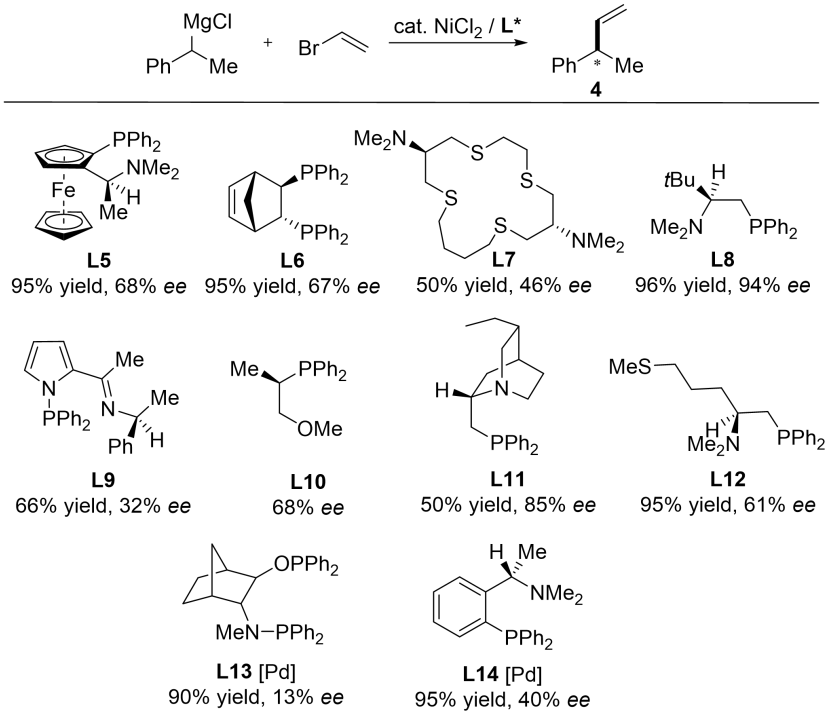
Scheme 1.6 Enantioselective Kumada coupling with phenyl electrophiles.

In 1975, the first palladium-catalyzed Csp^3-Csp^2 Grignard coupling was realized by Murahashi and co-workers (Scheme 1.7).[30] In the presence of catalytic $Pd(PPh_3)_4$, (*Z*)-prop-1-en-1-ylbenzene **3** can be synthesized almost quantitatively using methyl Grignard reagent and (*Z*)-vinyl bromide with full retention of configuration.



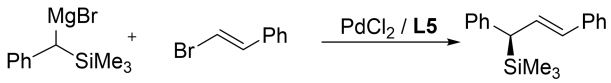
Scheme 1.7 First example of Pd-catalyzed Csp^3-Csp^2 Grignard coupling.

Accompanied with the pioneer work on Csp^3-Csp^2 Grignard coupling using aryl halide as sp^2-hybridized electrophile, the study using on vinyl electrophile emerged soon as well. A number of chiral ligands (Scheme 1.8) were designed for Ni-catalyzed enantioselective Csp^3-Csp^2 Grignard coupling between α-methylbenzyl Grignard reagents and vinyl bromides. The chiral ferrocenyl aminophosphine ligand **L5** was first employed together with Ni by Hayashi and Kumada to deliver the desired chiral product **4** in 68% *ee*.[31] The authors postulated a coordination of the dimethylamino group in **L5** to Mg, forming a diastereomeric complex with the Grignard species. The stereoselectivity of the reaction is determined in the transmetallation step. The ligand **L5** was later successfully combined with $PdCl_2$ for cross coupling of 1-silyl-substituted alkyl Grignard reagent **5** with vinyl halides, giving chiral product **6** in 95% *ee* (Scheme 1.9).[31d]



Scheme 1.8 Enantioselective Grignard coupling with vinyl bromide.

Comparable yield and enantioselectivity of **4** was observed when Norphos **L6** was employed in the transformation.[32] Macro cyclic sulfide derived ligand **L7** was also capable of catalyzing this reaction though with lower efficiency.[33] Kumada and co-workers redesigned the β-dimethylaminoalkylphosphine ligand **L8**, which showed high reactivity of 96% yield and 94% *ee* for the same reaction.[34] Further variation in the backbone of chiral phosphine ligands **L9-L12** showed no significant improvement in terms of yield and selectivity.[35-38] Pd complexes with **L13** or **L14** also showed moderate capacity for the asymmetric coupling.[39,40]

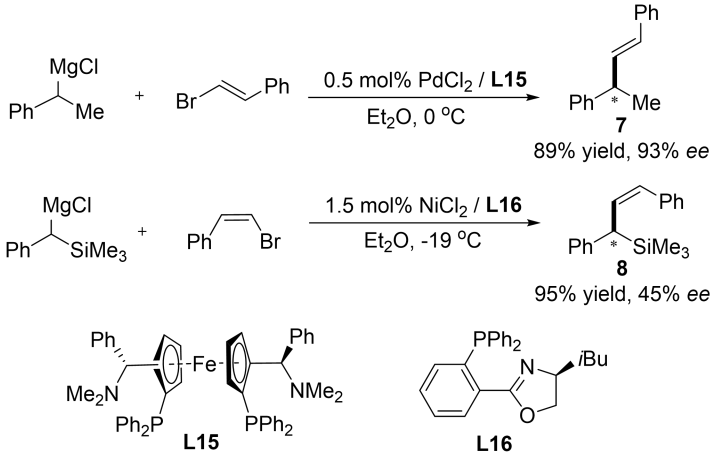


5 **6**

93% yield, 95% *ee*

Scheme 1.9 Pd-catalyzed enantioselective Grignard coupling.

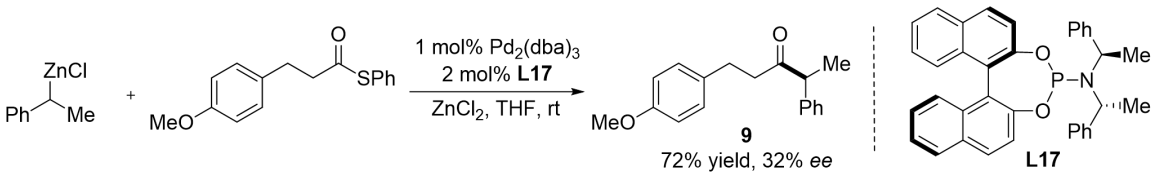
Configuration of substrates can be retained during Csp^3-Csp^2 cross coupling reactions.[41] In the presence of $PdCl_2$ and ferrocenyl P, N-ligand **L15**, (*E*)-styryl bromide was successfully coupled with *sec*-alkyl magnesium reagent to afford (*E*)-but-1-ene-1,3-diyldibenzene **7** in 89% yield and 93% *ee* with retention of configuration (Scheme 1.10).[42] When (*Z*)-styryl bromide was employed with **5**, $NiCl_2$ and a phosphinoaryl oxazoline ligand **L16** was used as catalyst to deliver corresponding product **8** with high yield and decreased *ee* in 45%.[43]



Scheme 1.10 Enantioselective Grignard coupling with retention of configuration.

1.3.1.2 *sec*-Alkyl Zinc Reagents

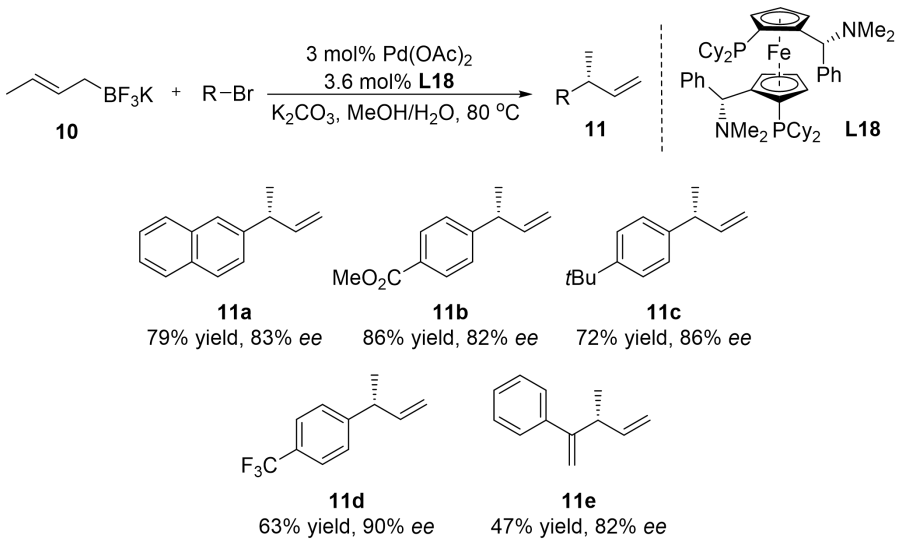
In 1977, organozinc reagent was demonstrated by Negishi to undergo cross coupling with aryl halide to give C-C bond formation.[44] However, only one example of enantioselective cross coupling utilizing *sec*-alkyl zinc reagent and thioester was reported in 2014 (Scheme 1.11), with the alkyl-acyl coupled product **9** obtained in only 32% *ee*.[45] This asymmetric version of Fukuyama cross coupling[46] was catalyzed by $Pd_2(dba)_3$ (dba=dibenzylideneacetone) and a monodentate phosphoramidite ligand **L17**.



Scheme 1.11 Pd-catalyzed asymmetric Fukuyama cross coupling.

1.3.1.3 *sec*-Alkyl Boron Reagents

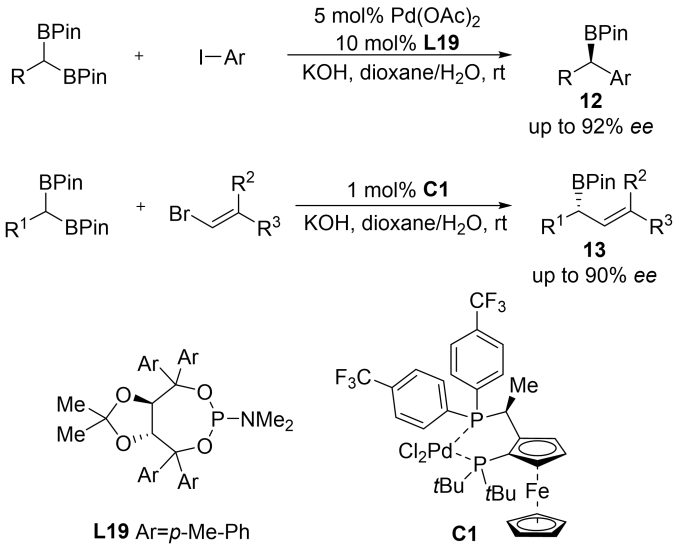
Suzuki coupling is a powerful methodology for C-C bond construction where organoboron reagents are coupled with organic electrophiles in the presence of base catalyzed by transition metal complex.[8] There are continuous reports on the enantiospecific conversion of chiral *sec*-alkyl boron reagents.[47] However, examples of non-chiral alkylboron reagent for asymmetric cross coupling controlled by chiral catalyst are rare. In 2006, the allylic potassium 2-butenyltrifluoroborates **10** which contain allyl Csp^3 nucleophiles were reported to couple effectively with aryl or vinyl bromides catalyzed by $Pd(OAc)_2$ and Josiphos **L18** with K_2CO_3 as base (Scheme 1.12).[48] Due to the stability of organoborates, MeOH and H_2O mixture was used as solvent for the reaction with ease.



Scheme 1.12 Enantioselective cross coupling of alkyl borates with aryl or vinyl bromides.

Both aryl and vinyl bromides were suitable electrophiles for this transformation, with chiral Csp^3-Csp^2 products **11** obtained in up to 90% *ee*. Diverse aromatic rings with different substitutions, such as ester group, steric bulky *t*Bu group and electron withdrawing CF_3 group, can be installed to give product **11a-d**, while vinyl group was coupled to give **11e** in a lower 47% yield and 82% *ee*. A cationic Pd^{II} intermediate [Ph-Pd-**L**]$^+$ was proposed to be formed before transmetallation with **10**, however the detailed enantiodiscrimination mechanism is not clear.

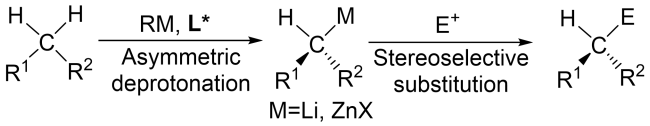
The work using *sec*-alkyl boron reagent for direct asymmetric cross coupling with sp^2-hybridized nucleophiles was presented in 2014 by Morken (Scheme 1.13).[49] The geminal bis(boronates) which contain two BPin group on one carbon were used as *sec*-alkyl nucleophiles. In the presence of $Pd(OAc)_2$ and chiral monodentate P,N-ligand **L19**, aryl iodides were coupled with bis(boronates) to give chiral products **12** with up to 92% *ee*. When vinyl bromides were employed as sp^2-hybridized nucleophiles, an air-stable complex **C1** was prepared in advance. It was found that only 1 mol% of **C1** was capable enough to show high efficiency for Csp^3-Csp^2 cross couplings, giving alkyl-vinyl coupled products **13** with up to 90% *ee* as well. The two reactions used similar mild conditions with dioxane and H_2O as solvent at room temperature, which demonstrated the superior property of organoboron reagents in such transformations.



Scheme 1.13 Enantioselective cross coupling of geminal bis(boronates).

1.3.1.4 *sec*-Alkyl Lithium Reagents

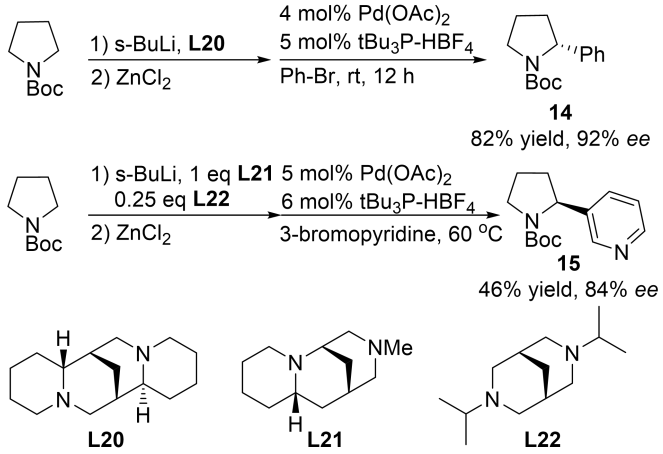
Organolithium reagents are widely used in organic synthesis since they are either commercially available with cheap price, or readily accessible through simple protocol. The direct use of alkyl lithium reagent for cross coupling with sp^2-hybridized nucleophiles only emerged in recent years upon Fringa's pioneering work.[50] Asymmetric cross coupling with *sec*-alkyl organolithium species usually occurs via the enantiospecific substitution with electrophiles after asymmetric deprotonation by lithium base in the presence of a chiral auxiliary or chiral ligand (Scheme 1.14).[51]



Scheme 1.14 Asymmetric deprotonation by organolithium reagent.

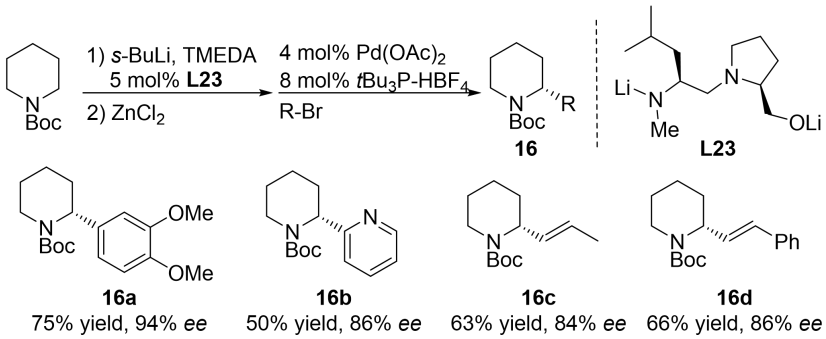
In most cases, enantioenriched alkyl lithium intermediate can be converted to alkyl zinc intermediate which is more configurationally stable for higher selectivity in subsequent substitution.[51-53] Through this method, N-Boc-pyrrolidine was effectively coupled with phenyl bromide to afford chiral product **14** in 92% *ee* with

aid of chiral auxiliary **L20** (Scheme 1.15). Furthermore, heteroaryl nucleophile like pyridine can also be employed to produce **15** in 84% *ee* with **L21** and **L22**.



Scheme 1.15 Stoichiometric chiral auxiliary for asymmetric deprotonation.

The utilization of catalytic amount of chiral ligand insteand of stoimectric chiral auxiliary was reported in 2011 (Scheme 1.16).[54] With only 5 mol% of chiral ligand **L23**, Gawley and co-workers realized the asymmetric Csp^3-Csp^2 cross coupling of N-Boc-2-lithiopiperidine. Various sp^2-hybridized nucleophiles including aryl, heterocycle or vinyl can be utilized to product enantiopure products **16** in 84-94% *ee*, though the overall yields were only moderate.



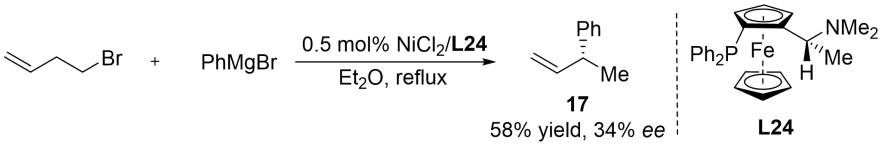
Scheme 1.16 Catalytic chiral ligand for asymmetric deprotonation.

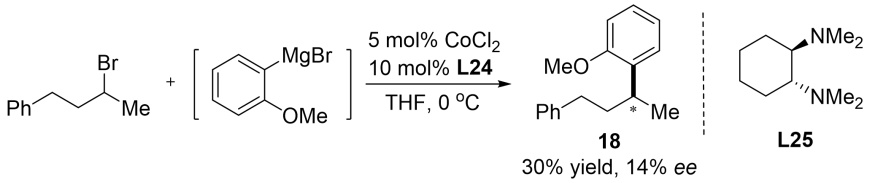
1.3.2 Enantioselective Csp^3-Csp^2 Cross Coupling Using Csp^3-X

In section 1.3.1, excellent reports on asymmetric Csp^3-Csp^2 cross coupling reactions have been discussed, which use aryl and vinyl halides as electrophiles. Compared with these Csp^2-hybridized electrophiles, *sec*-alkyl Csp^3-hybridized electrophiles are less suitable for such reactions since they are more electron-rich and thus more difficult to undergo oxidative addition to metal center. In addition, the alkylmetallic intermediate formed via oxidative addition is substantially less stable if no π electrons are available to interact with *d* orbitals of metal. Thus, the use of *sec*-alkyl electrophiles for asymmetric Csp^3-Csp^2 cross coupling reactions is considered challenging. In recent decade, with the development of numerous chiral ligands, such transformations now can be achieved in good selectivity, albeit mostly with activated *sec*-alkyl substrates. Detailed discuss of reactions in this category is presented as follows, assorted by types of the nucleophilic coupling partner.

1.3.2.1 sp^2-Hybridized Organomagnesium Reagents

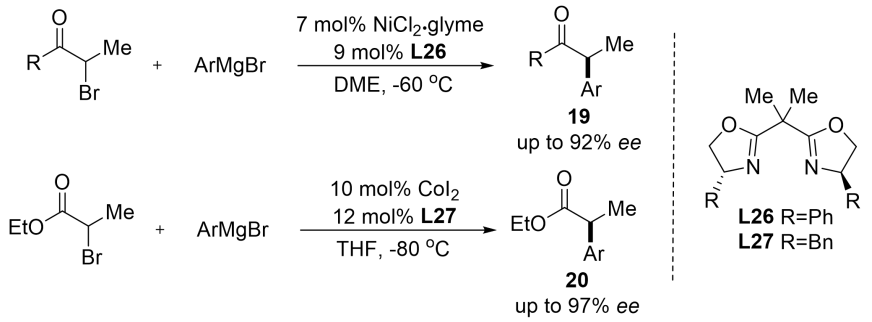
Soon after the discovery of cross coupling using alkyl Grignard reagent as nucleophile, Kumada and co-workers also investigated the use of alkyl bromide as electrophile (Scheme 1.17). However, only 58% yield and 34% *ee* of branched arylated product **17** was obtained with $NiCl_2$ and ferrocenyl aminophosphine ligand **L24**,[55] which indicated the difficulty in developing this methodology. A chiral diamine ligand **L25** was later reported to work with $CoCl_2$, facilitating the formation of chiral product **18** with only 14% *ee* from *in situ* formed organomagnesium reagent.[56] The enantioselective cross coupling with non-activated alkyl halides still remains as challenging task.





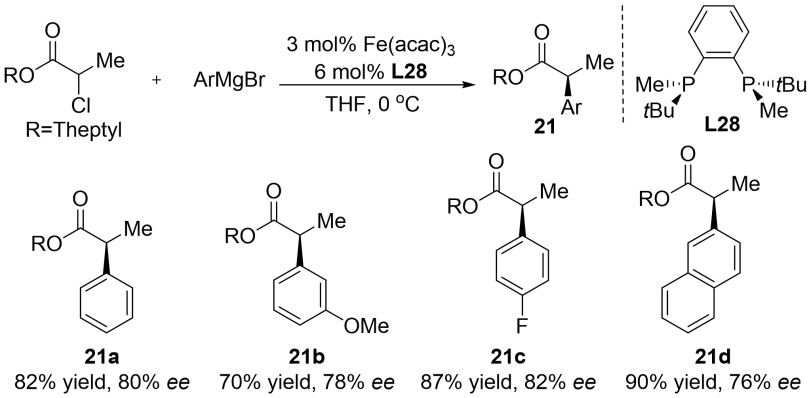
Scheme 1.17 Grignard coupling with non-activated alkyl bromides.

Exciting progress was reported by Fu in 2010 using activated secondary bromides (Scheme 18). The use of Ni(II) and Bis(oxazoline) **L26** furnished the asymmetric Kumada coupling product **19** from α-carbonyl bromides at −60 °C.[57] A similar ligand **L27** was later employed with Co(II) for highly selective transformation of racemic α-ester bromides at a lower temperature of −80 °C.[58]



Scheme 1.18 Ni-catalyzed Grignard coupling of α-carbonyl bromides.

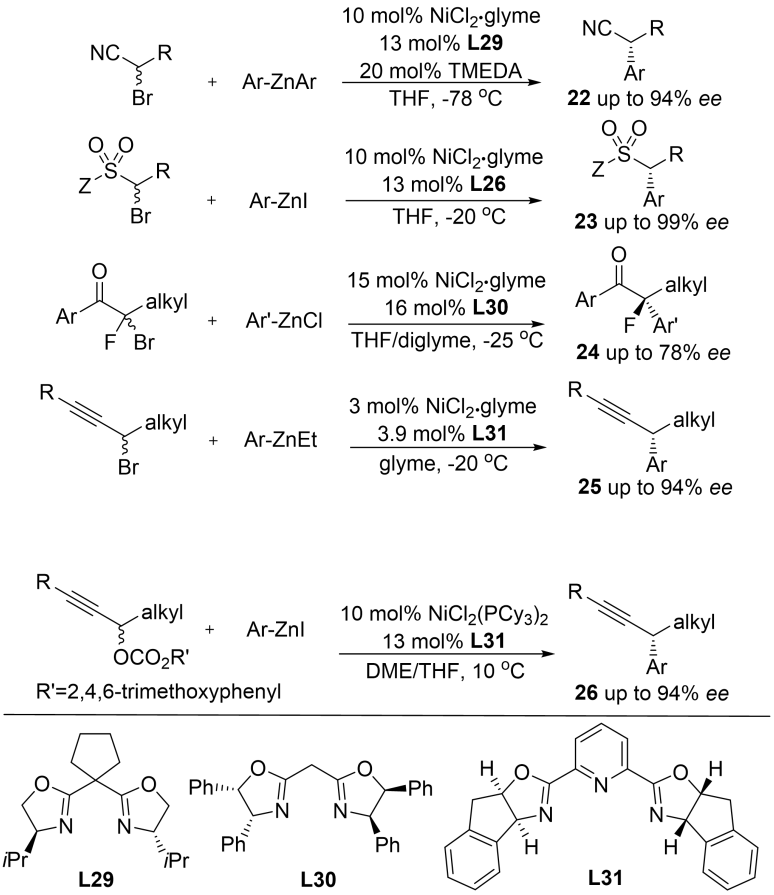
An example of improved methodology was reported by Nakamura's work in 2015 (Scheme 1.19).[59] With the cheap $Fe(acac)_3$ complex and **L28** as catalyst, the reaction can be conducted at 0 °C which excluded the need of low temperature. In addition, the more stable α-ester chlorides were used as substrates instead of bromides to produce α-arylated esters **21**, althought the overall yield and enantioselectivity were not excellent.



Scheme 1.19 Fe-catalyzed Grignard coupling of α-carbonyl chlorides.

1.3.2.2 sp^2-Hybridized Organozinc Reagents

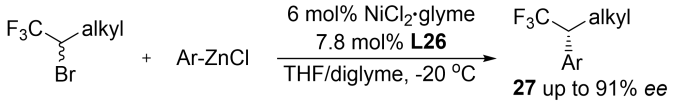
Upon Fu's initial work on enantioconvergent alkyl-alkyl cross coupling reactions of activated *sec*-alkyl bromide with sp^3-hybridized organozinc reagent[60], they later established a series of asymmetric transformations on diverse *sec*-alkyl halides with sp^2-hybridized nucleophiles.[61]



Scheme 1.20 Ni-catalyzed Negishi coupling of activated *sec*-alkyl substrates.

Activated *sec*-alkyl bromides were successfully coupled with arylzinc reagents in high efficiency in the presence of Ni(II) salt (Scheme 1.20). In the presence of different bis(oxazoline) ligands, racemic secondary bromides with cyanide or sulfone as activating group were converted to alkyl-aryl products **22-23** with high selectivity, while tertiary bromides with a carbonyl substitution gave decreased *ee* values of product **24** in up to 78%. The *sec*-alkyl bromides and carbonates bearing an alkyne substitution were also good coupling partners with

arylzinc reagents by Ni(II)/**L31**. Various products **25** and **26** in similar structure were obtained in high enantioselectivity.

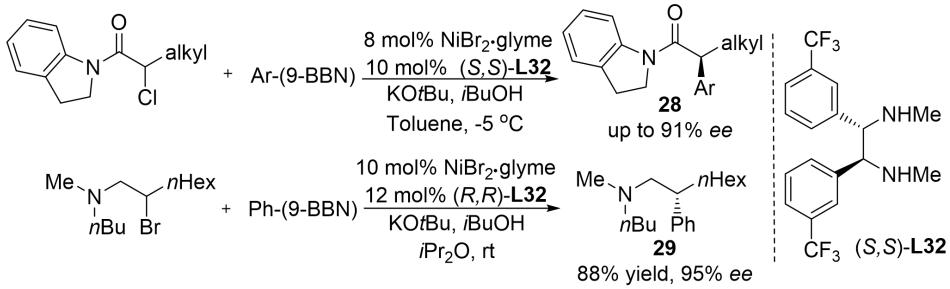


Scheme 1.21 Ni-catalyzed Negishi coupling of CF_3-substituted bromides.

However, Csp^3-Csp^2 cross coupling of non-activated alkyl bromides with organozinc reagents is still challenging. Exciting progress has been reported in 2015 by using Ni(II)/**L26** catalytic system (Scheme 1.21).[61f] The secondary bromides bearing a CF_3 group and an alkyl substituent were successfully arylated at －20 °C to deliver the enantioenriched fluorinated products **27** in up to 91% *ee*. Since the enantiodiscrimination process between a CF_3 group and an alkyl group is usually assumed to be very difficult, this work represented the significant attempt of Csp^3-Csp^2 cross coupling using non-activated alkyl bromides.

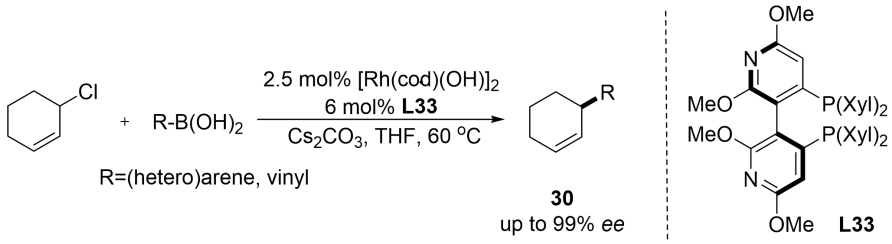
1.3.2.3 sp^2-Hybridized Organoboron Reagents

Asymmetric Suzuki cross coupling of racemic *sec*-alkyl halides using arylboron reagents Ar-(9-BBN) was achieved in Ni/diamine catalyst system with KO*t*Bu as base.[62] The first example was reported in 2010 on racemic α-chloroamide. Aryl groups with different electron density were installed to give optically active α-arylated amides **28** in good selectivity (Scheme 1.22). The other enantiomer of **L32** was later employed in similar condition to transform α-amino sec-alkyl bromides into enantioenriched arylated product **29** with 95% *ee* at room temperature.



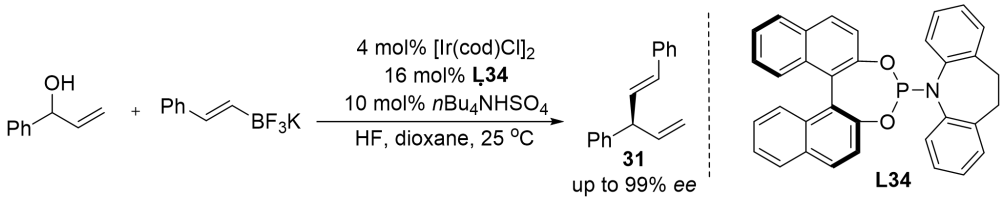
Scheme 1.22 Ni-catalyzed Suzuki coupling of aryl-9BBN.

High functional group tolerance of organoboron acids and their stability against moisture and air allow the successful expansion of sp^2-hybridized nucleophile scope to heteroarene and vinyl. Fletcher reported the Rh complex and chiral diphosphine ligand catalyzed arylation and vinylation of cyclic allylic chlorides using various boronic acids (Scheme 1.23). Both Xyl-P-PHOS **L33** and BINAP were found to be effective ligands in the reaction.[63]



Scheme 1.23 Rh-catalyzed Suzuki coupling of alkyl chloride with boronic acids.

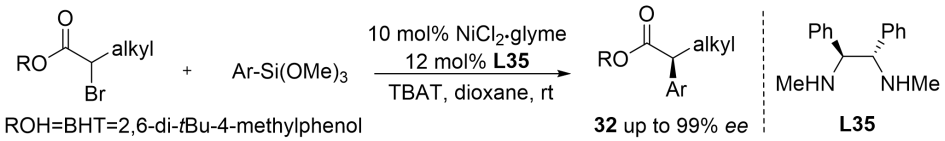
Carreira reported a highly enantioselective and regioselective vinylation of racemic allylic alcohols catalyzed by Ir/**L34** with aid of Brønsted acid promoters (Scheme 1.24).[64] Under the mild condition, multi-substituted potassium alkenyltrifluoroborates were employed as sp^2-hybridized nucleophiles in the reaction, giving optically active 1,4-dienes **31** as products. Two key intermediates described as (η^2-allylic alcohol)iridium(I) and (η^3-allyl)iridium(III) were prepared and characterized to further comprehend the catalytic cycle.[64b]



Scheme 1.24 Ir-catalyzed asymmetric vinylation of allylic alcohols.

1.3.2.4 sp^2-Hybridized Organosilicon Reagents

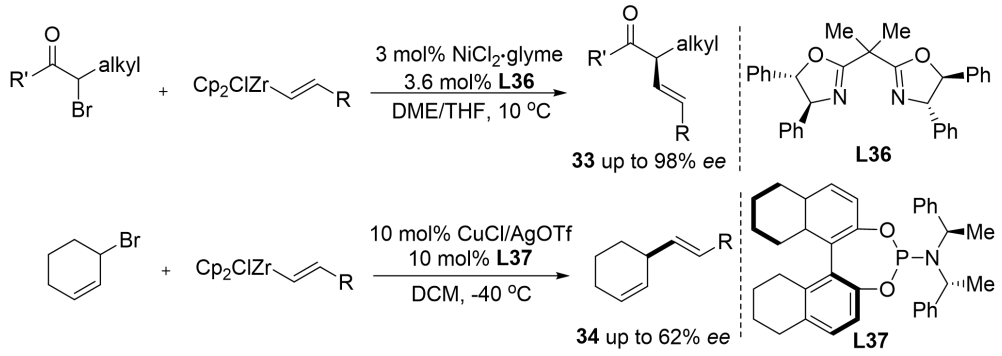
Racemic versions of Hiyama cross coupling of secondary alkyl electrophiles and aryl silanes have been reported with Ni or Rh as catalyst.[65] However, the only enantioselective example was demonstrated by Fu in 2008 with Ni/**L35** catalyst in the presence of TBAT (Tetrabutylammonium difluorotriphenylsilicate) as a fluoride promoter (Scheme 1.25).[65] The racemic α-bromo esters were coupled with aryl- or vinyl-Si(OMe)$_3$ to give moderate yield and high *ee* of desired products **32**, although a very bulky substituent R of ester group is still of necessity for the high enantioselectivity.[66]



Scheme 1.25 Ni-catalyzed asymmetric Hiyama coupling.

1.3.2.5 *sp*^{2}-Hybridized Organozirconium Reagents

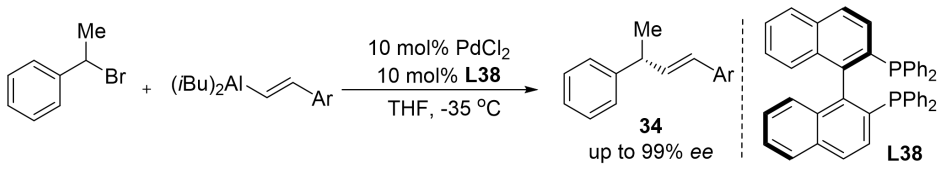
The synthetic transformations involving organozirconium reagents are usually for the installation of alkenyl group since alkenylzirconium reagents can be easily prepared by treating alkyne substrates with Cp_2ZrHCl in THF. As for its asymmetric cross coupling with secondary halides, Fu's Ni/bis(oxazoline) catalyst system showed great capacity on α-carbonyl bromides. The α-vinylated ketones **33** were achieved with up to 98% *ee* at 10 °C with alkenylzirconium reagents (Scheme 1.26).[67] Another CuCl/**L37** catalyzed reaction also showed potential for asymmetric version, with maximum 62% *ee* of vinylation product **34** obtained from cyclic allylic bromide at −40°C (Scheme 1.26).[68]



Scheme 1.26 Asymmetric vinylation of *sec*-alkyl bromides with organozirconium reagents.

1.3.2.6 *sp*^{2}-Hybridized Organoaluminum Reagents

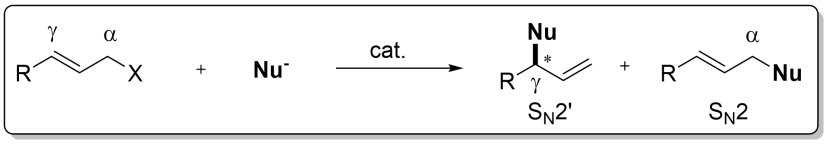
Although organoaluminum reagents have been effectively used for cross coupling reaction to form C-C bond, its cross coupling with alkyl electrophiles is quite rare. A non-chiral cross coupling between benzylic bromides and *sp*-hybridized aluminum catalyzed by Ni complex was reported in 2011 by Gau and co-workers.[69] The only example of asymmetric cross coupling between alkyl electrophile and *sp*^{2}-hybridized nucleophile from organoaluminum was achieved with $PdCl_2$ and BINAP **L38** as catalyst (Scheme 1.27).[70] At −35 °C, secondary benzylic bromides reacted with aryl-substituted alkenylaluminum reagents to afford chiral products **34** in good yield and high enantioselectivity up to 99% *ee*.



Scheme 1.27 Asymmetric vinylation of *sec*-alkyl bromides with organoaluminium reagents.

1.3.3 Asymmetric Cross Coupling of Allylic Halide or Pseudohalide

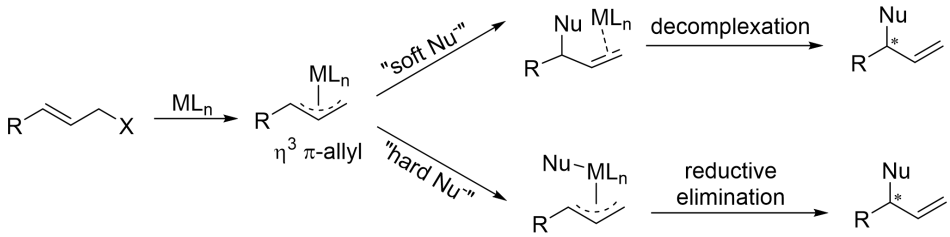
Enantioselective allylic substitution (EAS) is an efficient C-C bond-forming reaction for preparing optically active compounds.[71] In the presence transition metal catalysis, allylic substrates can couple with sp^2-hybridized nucleophiles at α or γ position to afford Csp^3-Csp^2 coupled S_N2 or S_N2' product. The latter will generate a chiral center at γ position, which indicates the potential of this methodology in synthesizing enantioenriched compounds (Scheme 1.28). Tertiary or quaternary carbon center formed in such reactions bearing multiple aryl or vinyl groups are valuable structural motifs which are often found in pharmaceuticals or natural products.[72] A summary of EAS process using different nucleophilic organometallic reagents (M=Mg, Zn, Al, Li, B...) catalyzed by copper complex or other transition metals will be presented herein.



Scheme 1.28 Enantioselective allylic substitution.

Mechanism of asymmetric allylic substitution was discussed by Trost in Pd-catalyzed reactions.[73] "Soft" or "hard" nucleophilic attack was proposed to explain the stereoselectivity of γ-substituted product (Scheme 1.29). In a Pd catalyzed reaction, oxidative addition of allylic substrate to Pd gives the η^3 π-allyl complex which can be then attacked via either "soft" or "hard" nucleophilic pathway. Stabilized or "soft" nucleophile will attack the γ position of allyl-palladium complex directly, followed by decomplexation to afford product in

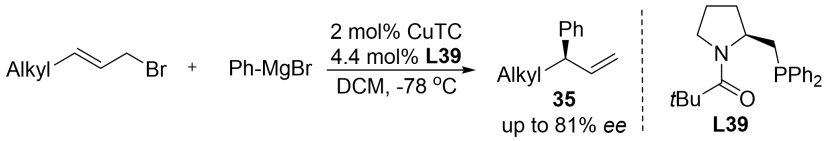
a net retention of stereochemistry. In contrast, unstabilized or “hard” nucleophile will first transmetallate to the metal center, followed by reductive elimination to give final product with a net inversion of stereochemistry.



Scheme 1.29 Soft/hard nucleophilic attack in enantioselective allylic substitution.

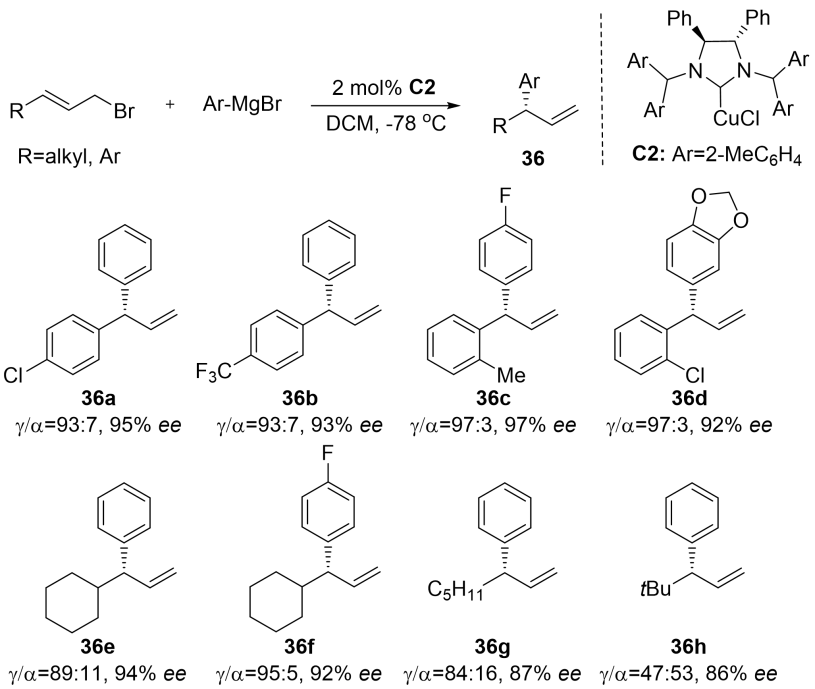
1.3.3.1 sp^2-Hybridized Organomagnesium Reagents

Arylmagnesium reagent was first reported by Tomioka for EAS reaction with aliphatic allylic bromides (Scheme 1.30).[74a] At −78 °C, the γ-phenylated product **35** was obtained exclusively in up to 81% *ee* with CuTC (TC=thiophene-2-carboxylate) and an amidophosphane ligand **L39** as catalyst. However, for cinnamyl-type substrates, same catalysis system would only afford the mixture of γ- and α-products (84:16 as highest γ/α ratio).



Scheme 1.30 Cu-catalyzed enantioselective allylic phenylation of aliphatic bromide with Grignard reagent.

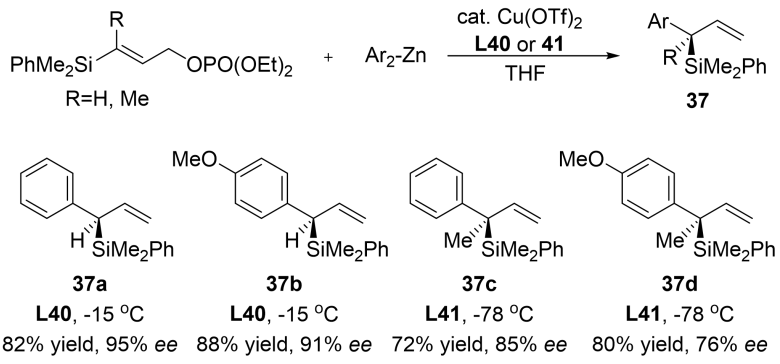
Later, the design of a new Cu-NHC complex **C2** helped effectively improve the γ/α selectivity and enantioselectivity for cinnamyl-type allylic bromides (Scheme 1.31). Various substituted aryl allylic bromides were arylated to give **36a-d** in high efficiency. While for aliphatic allylic bromides, the reaction proceeded smoothly to afford **36e-h** but with generally lower enantioselectivity.[74b,c]

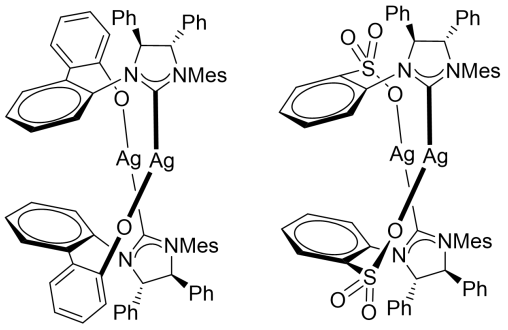


Scheme 1.31 Cu-catalyzed enantioselective allylic arylation of cinnamyl bromides.

1.3.3.2 *sp*^{2}-Hybridized Organozinc or Organoaluminum Reagents

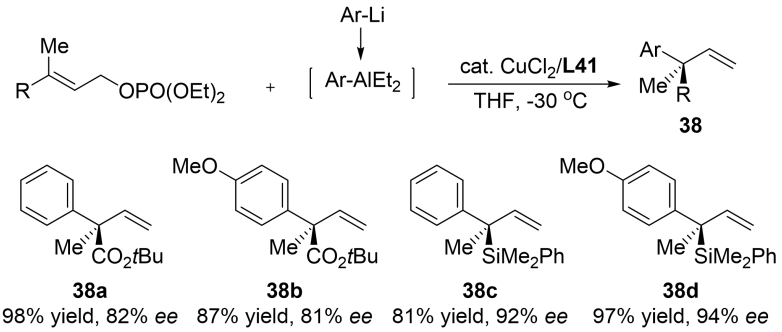
Organozinc reagents were demonstrated as effective *sp*^{2}-hybridized nucleophiles for EAS reaction by Hoveyda.[75] NHC ligand **L40** or **L41**[76] were combined with Cu(II) salt to catalyze the asymmetric arylation reaction of allylic phosphate substrates. Silyl-substituted enantioenriched products **37a-b** bearing a tertiary carbon center were prepared with arylzinc reagents in moderate yield and good *ee* (Scheme 1.32). However, low temperature of －78 °C was necessary for high enantioselectivity of products **37c-d** bearing a quaternary carbon center.





Scheme 1.32 Cu-catalyzed enantioselective allylic arylation with organozinc reagents.

Similarly, organoaluminum reagents were also employed successfully in the above system as sp^2-hybridized nucleophiles by the same group. Ester- or silyl-substituted allylic phosphates were coupled successfully with *in situ* prepared organoaluminum reagents to produce chiral products **38** bearing quaternary carbon center. $CuCl_2$ instead of $Cu(OTf)_2$ was used to show higher reactivity with ligand **L41**. However, this reaction suffers the problem of a very limited scope of both coupling partners (Scheme 1.33).

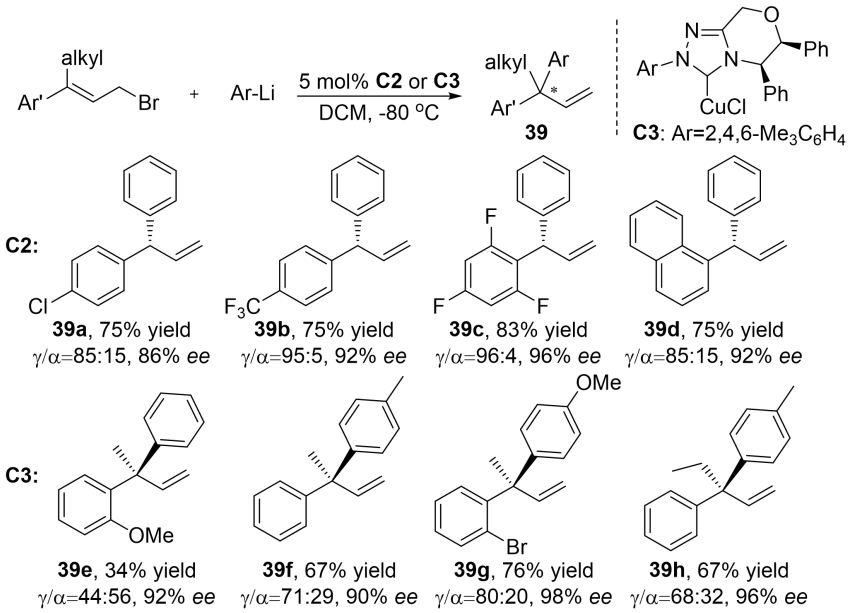


Scheme 1.33 Cu-catalyzed enantioselective allylic arylation with organoaluminum reagents.

1.3.3.3 sp^2-Hybridized Organolithium Reagents

The direct employment of organolithium reagents for EAS reactions of cinnamyl-type allylic bromides was recently achieved by Feringa with aid of Cu-NHC catalysis **C2** or **C3** (Scheme 1.34).[77] Readily availability of aryl lithium reagents allowed a wide substrate scope for products **39a-d** albeit a very low

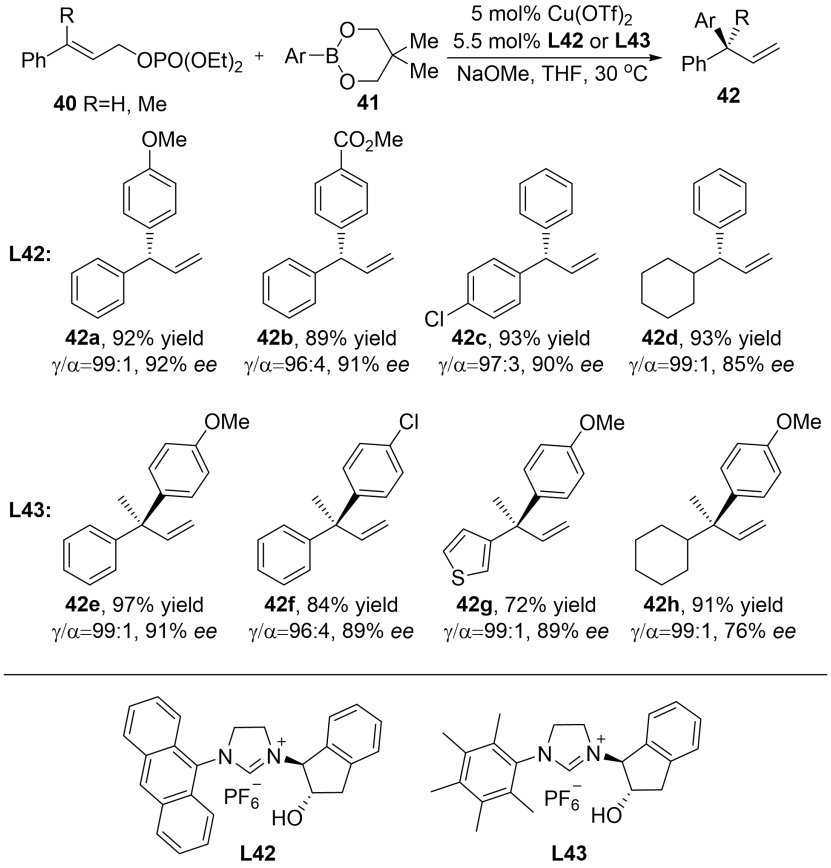
reaction temperature — 80 °C was required for high enantioselectivity. For the synthesis of products **39e-h** bearing a quaternary carbon center, significant decrease of regioselectivity was observed by lower γ/α ratio, although the enantioselectivity of γ-substituted products remained high.



Scheme 1.34 Cu-catalyzed enantioselective allylic arylation with organolithium reagents.

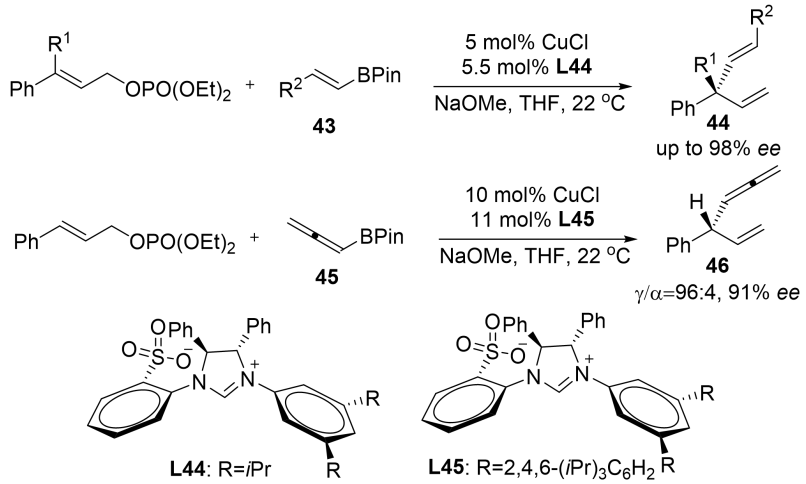
1.3.3.4 *sp*²-Hybridized Organoboron Reagents

Due to the readily availability, stability against air and moisture, and high functionality diversity, boronic acids and its derivatives have gained great interest as nucleophiles for EAS reaction. Hayashi and co-workers have utilized Cu-NHC complexes to catalyze the allylic arylation with aryl boronic neopentylglycol esters **41**.[78] In the presence of Mauduit-type chiral NHC ligand **L42** or **L43**, cinnamyl phosphates **40** were transformed to tertiary and quaternary arylated products **42** with high efficiency at ambient temperature (Scheme 1.35).



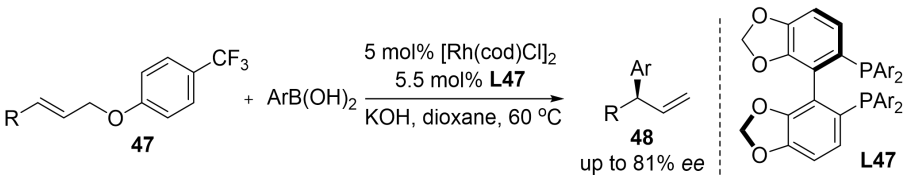
Scheme 1.35 Cu-catalyzed enantioselective allylic arylation with boronic esters.

Vinyl boronic pinacol esters **43** is also a suitable reagent for this reaction. Hoveyda designed the anionic NHC ligand **L45** and with Copper together as catalyst for highly efficient vinylation of prochiral phosphates (Scheme 1.36). The highly functional group tolerated variation of substituents on the vinyl group allows the methodology to be applied smoothly for natural product synthesis.[79] A allenylboronic acid pinacol ester **45** was also used under the same condition with a revised ligand **L46** for the asymmetric installation of allene group to γ position.



Scheme 1.36 Cu-catalyzed enantioselective allylic substitution with vinyl- or allene-boronic esters.

However, compared with boronic esters, very few example using sp^2-hybridized boronic acids was reported for asymmetric allylic substitution. In 2016, Sato and co-workers used Rh and diphosphine ligand **L46** (R'=3,5-*t*Bu-4-MeOC_6H_2) as catalyst for EAS reaction with a moderate enantioselectivity in up to 81% ee (Scheme 1.37).[80] The allylic esters **47** underwent the cleavage of C-O bond to couple with aryl boronic acid, giving γ-arylated **48** as optically active products. Although copper complexes with NHC ligands were effective with several boronic esters, example of boronic acids used in EAS reactions with copper catalyst has not been reported yet.



Scheme 1.37 Rh-catalyzed enantioselective allylic arylation with boronic acids.

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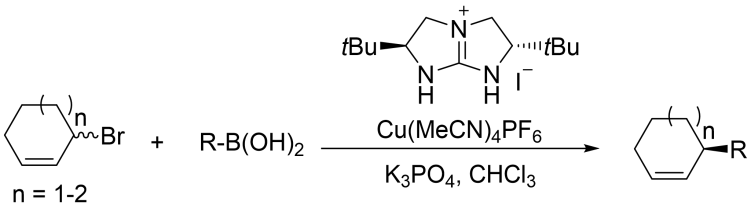
Chapter Two

Asymmetric Csp^3-Csp^2 Cross Coupling with Cyclic Allylic Bromides and Boronic Acids



2.1 Overview: Asymmetric Allylic Cross Coupling with Racemate

Asymmetric Csp^3-Csp^2 cross coupling has emerged as a powerful methodology of C-C bond construction, which is still under extensive exploration for higher selectivity and efficiency by many groups. Among all the work, enantioselective allylic substitution (EAS) is of much interest to us since the substrates are easily accessible and products are mostly valuable building blocks for subsequent transformations. However, based on the above discussion in Section 1.3.3, methodology for EAS reaction still needs further improvement in the following aspects:

I. Variation of nucleophiles: Most of the sp^2-hybridized nucleophiles employed in EAS reaction are mainly organometallic reagents, which need to be prepared *in situ* or in advance. And most organometallic reagents have very low functional group tolerance. The development of organoboron reagents is actually attracting more attention due to their stability against air or moisture, and high functional group tolerance at the same time.

II. Other transition metal catalyst: Late transition metals (including Pd, Rh, Ir, etc.) are dominant in the metal catalyst for EAS reactions. Compared with other metals, Cu stands out as an ideal choice because it's cheap and readily available. And Cu-NHC complex has been well demonstrated to be highly effective in several allylic alkylation reactions via S_N2' pathway.

III. Mild conditions: Highly enantioselective EAS reactions have been achieved by using different organometallic reagents but almost all of them required very low temperature to afford high enantioselectivity. The development of organoboron reagents allows the reactions to be conducted at ambient temperature with excellent efficiency but a strong base is needed to *in situ* generate the Cu-NHC complex from its precursors.

Phase-transfer catalyst has long been recognized as an efficient approach for asymmetric transformations through ionic interaction between charged species. Our group recently developed pentanidinium (**PG**) and bisguanidinium (**BG**) as efficient ion pair catalyst for enantioselective alkylation[1a] and oxidation[1b-d]. The

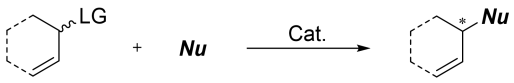
precise stereo-control of anionic species including permanganate, tungstate, molybdate and silicate exhibited by chiral guanidinium cations encouraged us to extend the system to organocuprate $[CuR_2]^-$ species[2] for asymmetric transformations.

Therefore, in this project, we sought to develop the methodology for asymmetric Csp^3-Csp^2 cross coupling reaction catalyzed by Cu and guanidinium complex under mild condition, that is at ambient temperature and weak base used. sp^2-hybridized boronic acids are utilized as nucleophiles and guanidine-derived chiral catalyst can combine with Cu salt to help produce high regio- and enantioselectivity. The detailed objectives are:

a. Develop the methodology of Csp^3-Csp^2 cross coupling reactions catalyzed by Cu salt and guanidinium.
b. Synthesize and analyze diverse chiral Csp^3-Csp^2 cross coupling products from racemic allylic bromides and boronic acids.
c. Demonstrate the synthetic value of the methodology via transforming products to other useful building blocks in synthetic chemistry.
d. Analyze the intermediate and pathway of the reaction to propose the possible mechanism.

A particularly powerful class of EAS reaction (see Section 1.3.3) allows the conversion of racemic allylic substrates into single enantiomer products, instead of using prochiral materials (Scheme 2.1). Trost and co-workers reported a series of reactions in this type catalyzed by Pd, which are generally defined as dynamic kinetic asymmetric transformations (DYKAT) in terms of mechanism.[3] Different nucleophiles are utilized for Pd-catalyzed DYKAT process to form chiral C-C, C-N, C-O bond.[4] However, there are only scarce successful examples of DYKAT processes utilizing sp^2-hybridized nucleophiles. Diverse boronic acids were reported as sp^2-hybridized nucleophiles for allylic arylation of racemic cyclic chlorides by Fletcher, with Rh/phosphine ligand complex as catalyst which is quite expensive.[5] Although copper was well demonstrated to catalyze the asymmetric allylic substitution of prochiral substrates via S_N2' pathway, the only known Cu-catalyzed allylic substitution of racemate with sp^2-hybridized nucleophiles is

the coupling of *in situ* prepared alkenylzirconocene nucleophiles with cyclic allyl bromides by Fletcher in 2015, yet with the maximum enantioenrichment as 62% *ee*.[6]



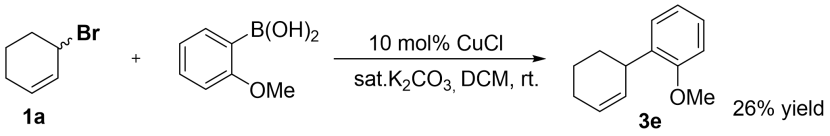
Scheme 2.1 Conversion of racemic allylic substrate to single chiral enantiomer.

It would be interesting to use copper salt as catalyst in the asymmetric allylic substitution where boronic acids are employed as nucleophiles instead of organometallic reagents. And it is still challenging to obtain highly enantioselective allyl substitution with sp^2-hybridized nucleophiles in the presence of Cu. Thus, we initiated our work by studying the reaction between cyclic allylic substrates with boronic acid to afford single enantiomer product using copper. The methodology involving Cu(I) and guanidinium complex was developed after careful screening of reaction parameters including Cu salt, guanidinium catalyst, base, solvent, temperature and reagent ratio, which was later successfully applied to produce various Csp^3-Csp^2 products with high enantioselectivity.

2.2 Reactivity and Condition

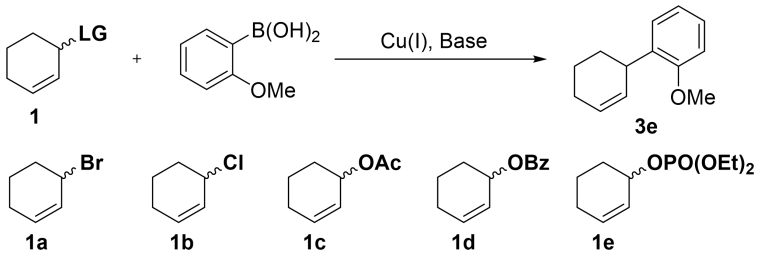
2.2.1 Cyclic Allylic Bromides: Synthesis and Properties

3-bromocyclohex-1-ene (**1a**) was first tested for the arylation with (2-methoxyphenyl)boronic acid with catalytic amount of CuCl as model reaction (Scheme 2.2). In the presence of excess saturated aqueous K_2CO_3, the desired product 2'-methoxy-1,2,3,4-tetrahydro-1,1'-biphenyl (**3e**) was obtained successfully, though in only 26% yield based on GC-MS analysis.



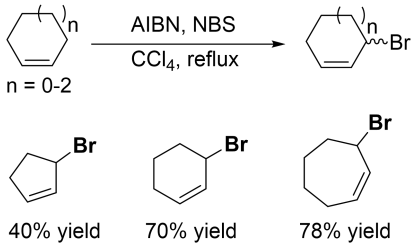
Scheme 2.2 Initial attempt with CuCl for allylic arylation reaction.

However, change of allylic bromide to other allylic substrates with different leaving groups (**1b-1e**), such as -Cl[7], -OAc[8], -OBz[9] or -OPO(OEt)$_2$[9], lead to almost no product formed in the model reaction (Scheme 2.3). Allylic bromides were found to be the only effective substrate as the electrophilic cross coupling partner in the system.



Scheme 2.3 Racemic allylic substrates with different leaving groups.

Therefore, a series of racemic cyclic allylic bromides were prepared via radical substitution of allylic C-H bond (Scheme 2.4).[10] The allylic C-H bond is particularly weak because the radical formed through the homolytic cleavage of C-H bond is stabilized by resonance.[11] 3-bromocyclopent-1-ene and 3-bromocyclohept-1-ene were synthesized via same procedure and purified by vacuum distillation in 40% yield and 78% yield respectively. All allylic bromides prepared in this project are not quite stable at ambient temperature especially 3-bromocyclopent-1-ene, which reacted quite fast in model reaction with majority decomposed in the above conditions.

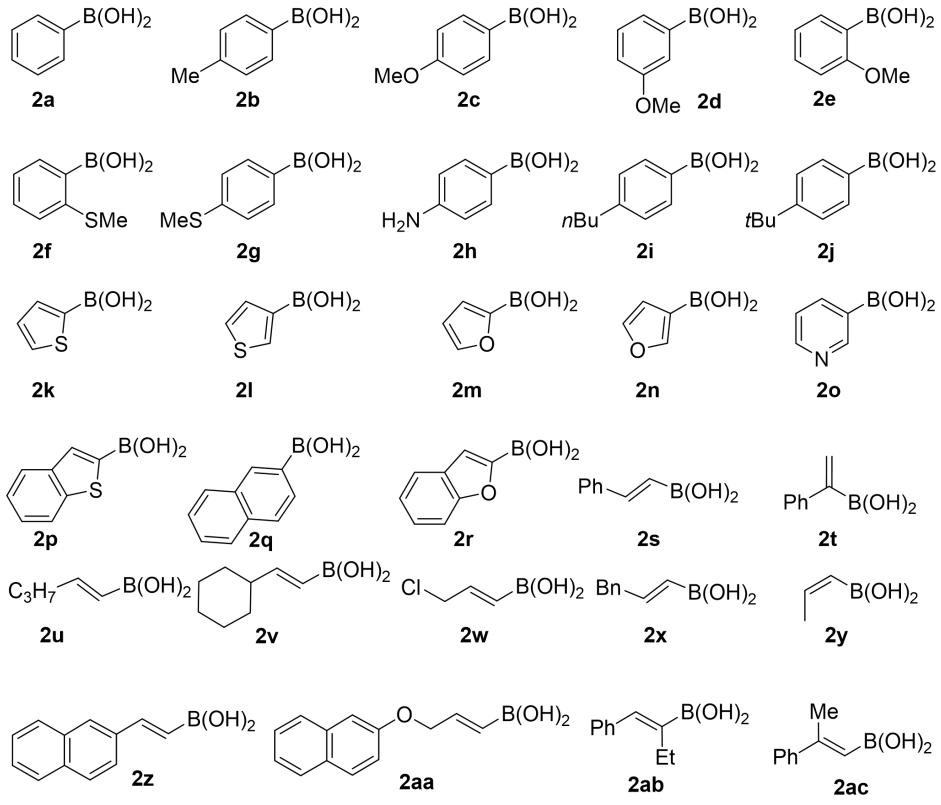


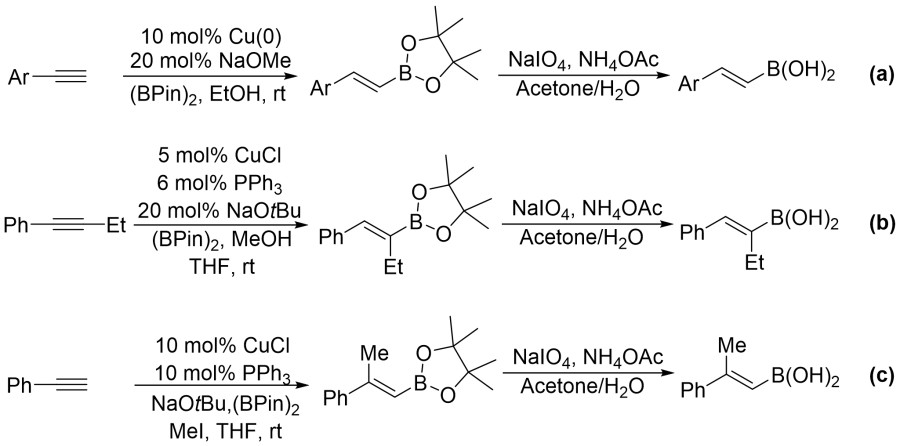
Scheme 2.4 Synthesis of cyclic racemic allylic bromides.

2.2.2 Boronic Acids: Synthesis and Properties

The *sp*^{2}-hybridized boronic acids mainly comprise ary-, heteroaryl- and vinyl-boronic acids. Most of aryl boronic acids listed in Scheme 2.5 are commercial available with diverse functional groups, including aryl group with

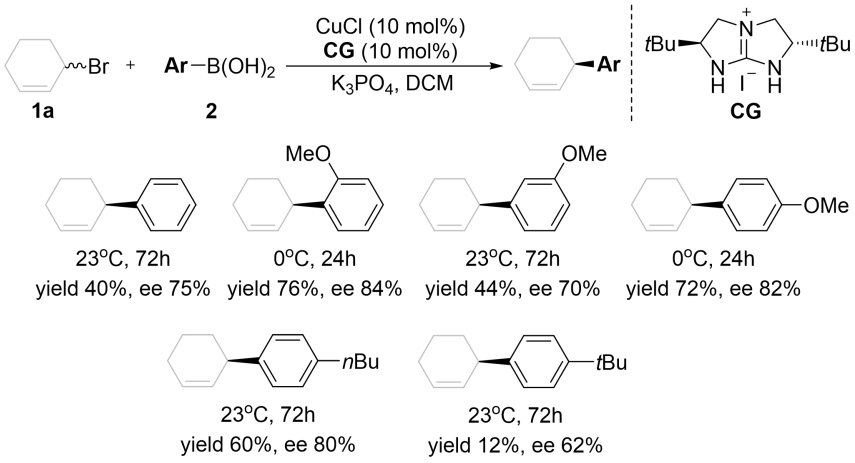
different substituents (**2a-2j**), heterocyle group (**2k-2r**) and vinyl group with substituents (**2s-2y**). Nevertheless, several vinyl boronic acids need to be prepared in advance with ease through hydroboration and hydrolysis of alkynes.[12] (*E*)-(2-(naphthalen-2-yl)vinyl)boronic acid (**2z**) and (*E*)-(3-(naphthalen-2-yloxy)prop-1-en-1-yl)boronic acid (**2aa**) were prepared from corresponding terminal alkynes (Scheme 2.6a).[13] Cu(0) catalyzed ligand-free hydroboration was conducted with bis(pinacolato)diboron $(BPin)_2$ in high efficiency, which was followed by acidic hydrolysis to afford the desired vinyl boronic acids.[14] Tri-substituted boronic acids (**2ab** and **2ac**) were also synthesized from either di-substituted[15] or terminal alkynes[16]. MeOH was used as proton source to capture the alkenylcopper intermediate (Scheme 2.6b) while MeI as methyl source (Scheme 2.6c). All crude boronic acids were used directly for subsequent reactions after acidic hydrolysis without further purification.





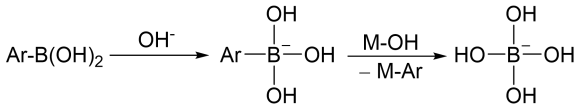
Scheme 2.5 Variation of sp^2-hybridized boronic acids.

Primary test using all the available boronic acids in the reaction with **1a** (10 mol% CuCl and CG as catalyst) revealed that electron density on the ary ring and steric bulkiness of boronic acids affected the profile significantly (Scheme 2.6). For example, the reactions utilizing phenylboronic acid (**2a**) and (*meta*-methoxyphenyl)boronic acid (**2d**) gave much decreased reaction rate and conversion than (*para*-methoxyphenyl)boronic acid (**2c**) and (*otho*-methoxyphenyl)boronic acid (**2e**), probably due to electron deficient nature of aryl ring in **2a** and **2d**. Furthermore, (4-(*tert*-butyl)phenyl)boronic acid (**2j**) which contains a *t*Bu group at the *para* position lead to trace amount of desired product while a *n*Bu-substituted one (**2i**) proceeded smoothly. The steric bulkiness of *t*Bu is assumed to affect the transmetallation from boronic acid to metal center.[13] Therefore, the scope of boronic acids for this allylic arylation reaction with copper guanidinium catalyst is limited to those with electron sufficient and less bulky substituents.



Scheme 2.6 Primary test with aryl boronic acids.

Transmetallation process involves the transferring of aryl or vinyl group from boronic acid to metal center, which requires a base in presence to facilitate (Scheme 2.7).[17] Saturated aqueous K_2CO_3 solution was initially used in our reaction while screening of other bases such as Na_2CO_3, K_3PO_4 and CsF was later conducted as well. It was found that strong bases like KO*t*Bu or NaOH only lead to hydrolysis of bromide **1a** to the corresponding allylic alcohol, with no desired cross coupling product formed. Weak bases such as $NaHCO_3$ or Na_2HPO_4 were not strong enough to activate the boronic acid, leaving all substrates intact. Detailed screening of bases and its effect on conversion and enantioselectivity will be discussed in Section 2.2.4.

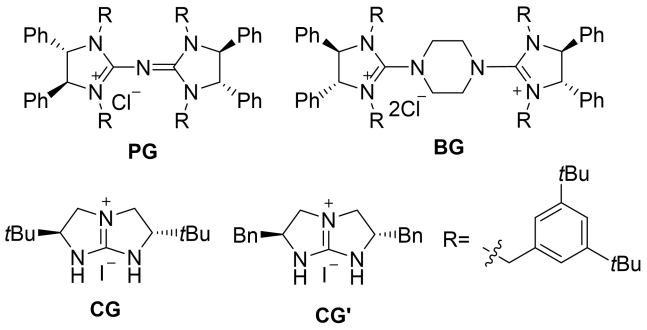


Scheme 2.7 Base activation of boronic acids followed by transmetallation.

2.2.3 Guanidinium Catalyst: Synthesis and Properties

Guanidinium-based chiral catalysis has long been widely reported as efficient organocatalysis for asymmetric synthesis. Our group recently developed pentanidinium (**PG**), bisguanidinium (**BG**) and cyclic guanidinium (**CG**) as efficient ion pair catalyst for enantioselective alkylation[18] and oxidation[19] (Scheme 2.8). The precise stereo-control of anionic species including enolate,

permanganate, tungstate, molybdate and silicate exhibited by chiral guanidinium cations encouraged us to extend the system to organocuprate $[CuR_2]^-$ species[20] for asymmetric transformations.



Scheme 2.8 Chiral guanidinium catalyst.

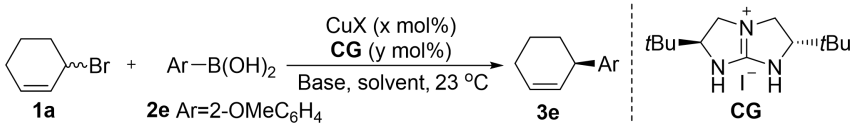
For the asymmetric allylic arylation with boronic acid, these guanidinium-based catalyst were tested for the catalytic capacity. **PG** and **BG** were found to deliver low reactivity with less than 30% yield and around 20% *ee* of arylation product. Change of their substitution group R to other aryl group didn't help improve the reactivity.

On the contrary, both **CG** and its Bn-substituted version **CG'** could give the desired cross coupling product with improved yield and selectivity. Thus in the following condition screening section, **CG** and **CG'** were used as chiral catalyst to combine with selected copper salt under different conditions.

2.2.4 Condition Screening of Asymmetric Allylic Arylation

A batch of model reactions between **1a** and **2e** were carried out with different parameters including base, copper salt, solvent and reagent ratio (Table 2.1). In the presence of 10 mol% CuCl and **CG**, saturated K_2CO_3 or K_3PO_4 aqueous solution were utilized as base, but only low yield and poor enantioselectivity of desired product was observed (Entry 1,2). A significant amount of bromide and boronic acid were hydrolyzed with aqueous base solution, which lead to the direct use of solid base. Strong base like KOH gave no desired product, while several other solid bases including K_2CO_3, CsF and K_3PO_4 were able to afford improved result while the enantioselectivity still remained moderate (Entry 3-6). **CG'**, the Bn-substituted

version of **CG**, gave slightly lower selectivity in the reaction than the original (Entry 6). Since Cu(II) salts gave much decreased reaction rate and yield of the desired product, a screening of Cu(I) salts was conducted and $Cu(MeCN)_4PF_6$ was found to be the best option (Entry 5-8). And the ratio of copper salt against **CG** affected the enantioselectivity obviously (Entry 9-12). Finally, the optimized condition was determined for the reaction: 3 mol% $Cu(MeCN)_4PF_6$, 6 mol% **CG**, 2 eq $RB(OH)_2$ and 4 eq K_3PO_4 in $CHCl_3$ at room temperature.



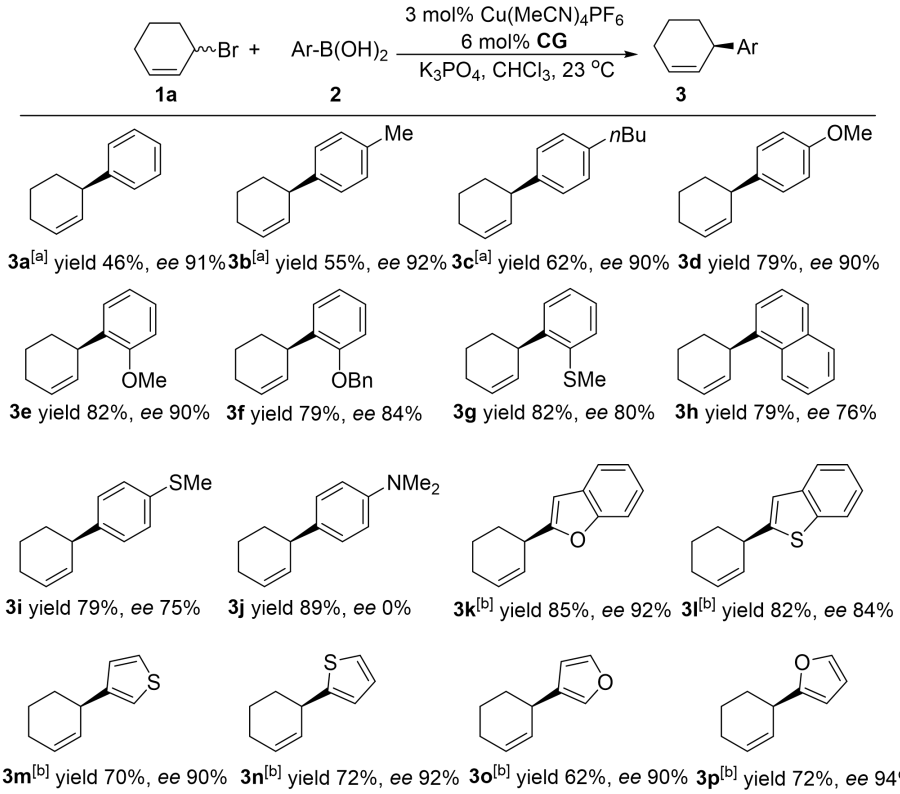
Entry	CuX/ x mol%	Catalyst/ y mol%	Base	Yield (%)[a]	*ee* (%)[b]
1	CuCl (10)	**CG** (10)	sat K_2CO_3	24	15
2	CuCl (10)	**CG** (10)	sat K_3PO_4	15	20
3	CuCl (10)	**CG** (10)	KOH	n.d.	-
4	CuCl (10)	**CG** (10)	K_2CO_3	48	12
5	CuI (10)	**CG** (10)	CsF	57	27
6	CuCl (10)	**CG** (10)	K_3PO_4	75	43
7	CuCl (10)	**CG'** (10)	K_3PO_4	43	32
8	CuTC (10)[c]	**CG** (10)	K_3PO_4	75	53
9	$Cu(MeCN)_4PF_6$ (10)	**CG** (10)	K_3PO_4	72	70
10[d, e]	$Cu(MeCN)_4PF_6$ (5)	**CG** (5)	K_3PO_4	70	85
11[d]	$Cu(MeCN)_4PF_6$ (20)	**CG** (5)	K_3PO_4	68	55
12[d,f]	$Cu(MeCN)_4PF_6$ (3)	**CG** (6)	K_3PO_4	82	90

Table 2.1 Condition screening of asymmetric allylic arylation. Reaction was carried out with **1a** (0.05 mmol), **2e** (0.10 mmol) and base (0.2 mmol) in CH_2Cl_2 (0.4 mL) for 48 h at room temmperature. [a] GC yield, 1,1'-biphenyl used as an internal standard. [b] Determined by GC-MS analysis with chiral column. The absolute configuration was determined by comparison with reported example. [c] CuTC=Copper 2-thiophenecarboxylate. [d] $CHCl_3$ was used instead of CH_2Cl_2. [e] Reaction was carried out at 0 °C for 72h. [f] Reaction was carried out under N_2 atmosphere.

2.3 Results and Discussion

2.3.1 Asymmetric Allylic Arylation of 3-Bromocyclohex-1-ene

With the optimized reaction conditions in hand, the substrate scope of aryl boronic acids was explored in reaction with **1a** and the results were summarized in Scheme 2.9. Phenylboronic acid and its alkyl-substituted derivatives, such as methyl or *n*butyl, reacted smoothly to give optical pure arylated products **3a-3c** with over 90% *ee*. Alkoxyl-substituted aryl boronic acids also showed good reactivity in the reaction and either *ortho*- or *para*-methoxyl subtitution didn't obviously affect the selectivity, with **3d** and **3e** obtained respectively with high *ee*. Thiomethyl substitution on phenyl ring of boronic acid lead to lower *ee* values of 80% for *ortho*-substituion (**3g**) and 75% *ee* for *para*-substituion (**3i**). However, a dimethylamino substitution only generate a complete racemic product **3j** though with a good yield, which indicates the possible coordination of long pair of N atom to copper center. Besides phenyl ring, 1-naphthylboronic acid was also used but gave a slightly decreased *ee* value of the product **3h** in 76%.

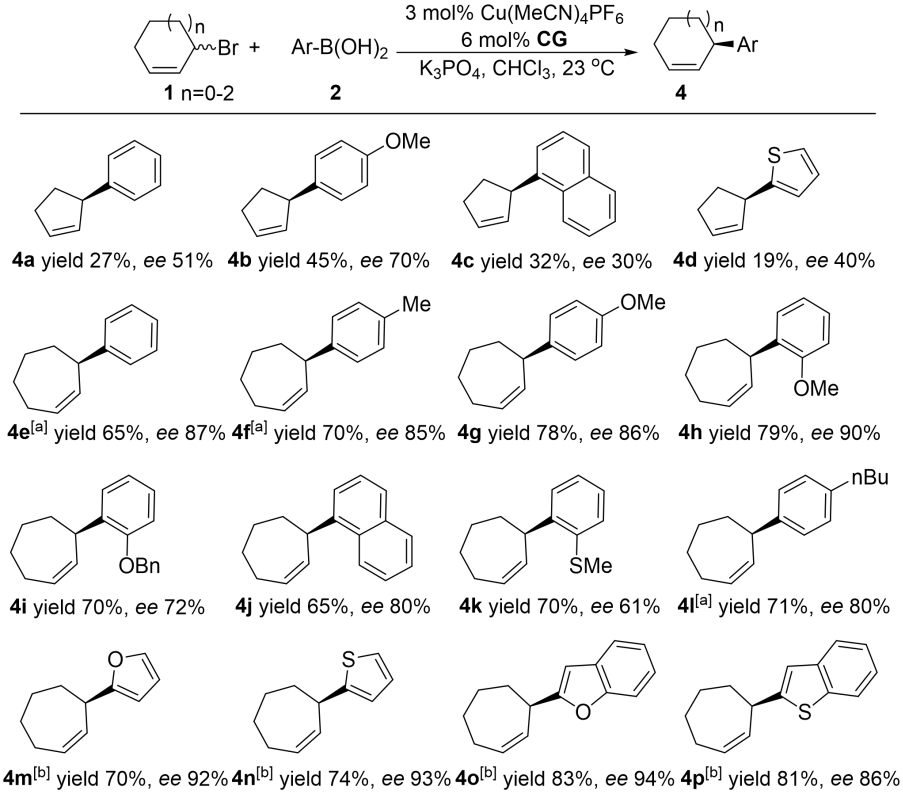


Scheme 2.9 Substrate scope of aryl boronic acids for asymmetric allylic arylation of **1a**. Reaction was carried out with **1a** (0.3 mmol), **2** (0.6 mmol) and K_3PO_4 (0.12 mmol) in $CHCl_3$ (1.5 mL) at room temperature. [a] 8 mol% Cu(I) and 10 mol% **CG** was used. [b] Reactions were carried out at 0 °C.

Heteroarene boronic acids were also employed with ease to display high reactivity towards **1a** under standard conditions. The background reaction between heteroarene boronic acids and **1a** was strong in the absence of **CG**, maybe because of their high electron density. Thus in order to obtain optimized enantioselectivity of the desired products, reaction temperature for reactions involving heteroarene boronic acids was decreased to 0 °C, which to some extent might help suppress the background reaction by Cu(I) itself or homocoupling byproduct.[21] With this revised condition, different heterocycles including benzofuran, benzothiophene, 2-furan, 3-furan, 2-thiophene and 3-thiophene were successfully installed to give corresponding products **3k-3p** with high efficiency. However, when pyridine boronic acid was used, almost no desired product was detected in the mixture, indicating again the possible coordination of long pair on N atom to metal center.

2.3.2 Asymmetric Allylic Arylation of Different Bromides

As asymmetric allylic arylation was successfully achieved with **1a**, other cyclic allylic bromides with different ring sizes were soon tested under the identical condition (Scheme 2.10). 3-bromocyclopent-1-ene **1f** itself is not very stable which underwent decomposition or hydrolysis if exposed to light or moisture at room temperature. Since **1f** is quite active, its reaction with aryl boronic acids proceeded very fast as well under standard condition. Therefore, not surprisingly, only gave poor yield and moderate *ee* of desired product **4a-4d** were obtained. Excess amount of **1f** against boronic acid would help improve the yield of desired product but hardly affect the enantioselectivity.



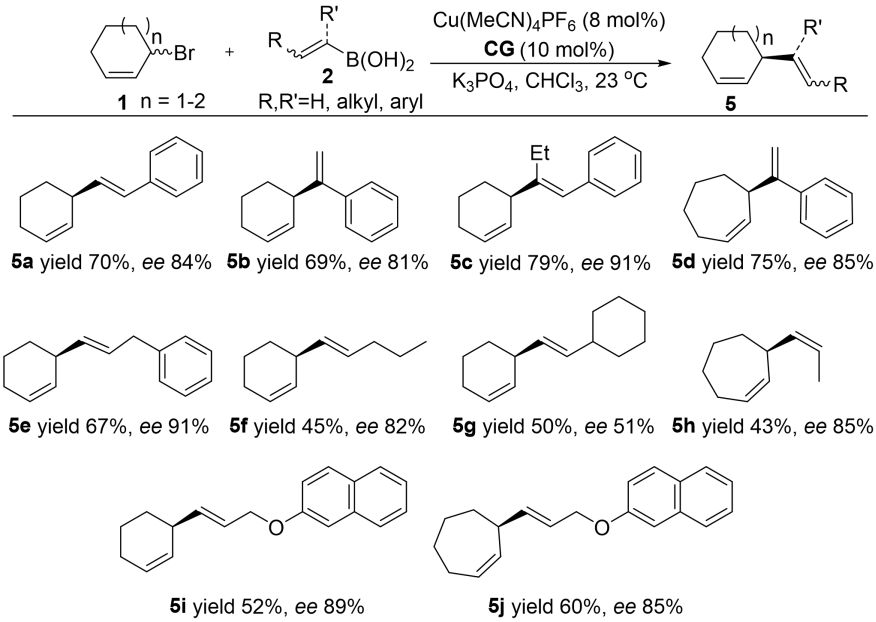
Scheme 2.10 Substrate scope of aryl boronic acids with different allylic bromides. Reaction was carried out with **1** (0.3 mmol), **2** (0.6 mmol) and K_3PO_4 (1.2 mmol) in $CHCl_3$ (1.5 mL) for 48 h at room temperature. [a] 8 mol% Cu(I) and 10 mol% **CG** was used. [b] Reactions were carried out at 0 °C.

Later, 3-bromocyclohept-1-ene **1g** with seven-member ring was employed to expand the scope. To our delight, asymmetric allylic arylation occurred smoothly

with **1g**, which gave comparable results as six-member ring substrate. With various substitutions on the aryl ring of boronic acids, arylated products **4e-4l** were all obtained with moderate yield and good *ee*. Elimination of HBr from **1g** to give cyclohepta-1,3-diene was observed on GC-MS, which was a major reason of the moderate yield. With the active heteroarene boronic acids, desired products **4m-4p** were also achieved with high enantioselectivity.

2.3.3 Asymmetric Allylic Vinylation of Cyclic Allylic Bromides

Besides aryl and heteroarene, vinyl boronic acids can also be used as sp^2-hybridized nucleophiles in our reaction, which afforded 1,4-skipped dienes as products **5** (Scheme 2.11). 10 mol% **CG** was found to be necessary for high selectivity of the asymmetric vinylation reaction. Both of (*E*)-styrylboronic acid and its regio-isomer (1-phenylvinyl)boronic acid were installed to cyclic allylic substrate to give **5a** and **5b** with 84% and 81% *ee* respectively. Tri-substituted (*E*)-(1-phenylbut-1-en-2-yl)boronic acid used as coupling partner showed no negative effect on yields and enantioselectivity of desired product **5c**. Vinylation of seven-member ring bromide also showed satisfying result, leading to formation of **5d** in 85% *ee*.



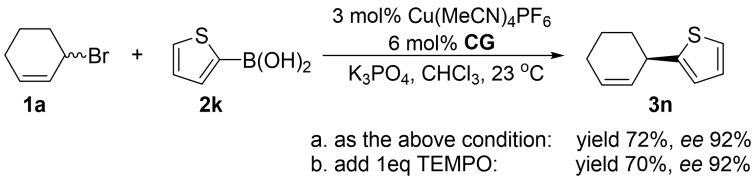
Scheme 2.11 Substrate scope of vinyl boronic acids with different allylic bromides.

Alkyl-substituted vinyl boronic acids were also effective coupling partner with allylic bromides. A vinyl boronic acid with the Bn substitution reacted smoothly with **1a** to produce **5e** in 91% *ee* while aliphatic ones showed decreased efficiency in the reaction, with **5f** and **5g** obtained with only 82% and 51% *ee*. Furthermore, (*Z*)-prop-1-en-1-ylboronic acid with a (*Z*)-configuration could lead to 85% *ee* of corresponding product **5h**. Finally, a vinyl boronic acid with ether substitution were employed for asymmetric vinylation of both **1a** and **1g**, giving desired vinylated products **5i** and **5j** with good *ee*. However, the homo-coupling of alkyl-substituted vinyl boronic acid to conjugated dienes cannot be suppressed under the standard conditions, which is the major problem leading to moderate yield of the desired product.

2.4 Mechanism Exploration

2.4.1 Radical Trap

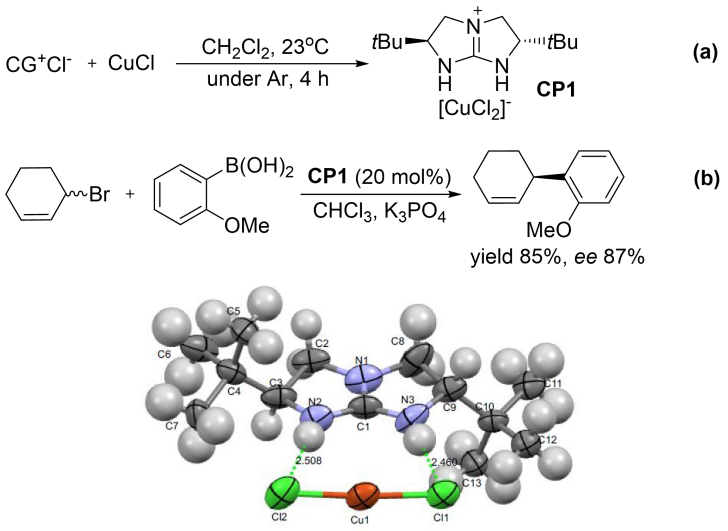
Radical trap experiments were conducted via adding TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) into the reaction of **1a** with thiophen-2-ylboronic acid **2k** (Scheme 2.12). Under standard condition, was obtained as 72% yield and 92% ee. Meanwhile, the addition of extra 1eq TEMPO into the reaction didn't obviously affect the results, with only slight decrease in the yield of product. It is assumed that no active radical species was present in the reaction based on the radical trap experiments. In other words, the reaction might not proceed via radical pathway.



Scheme 2.12 Radical trap experiments.

2.4.2 *X*-ray Crystallography

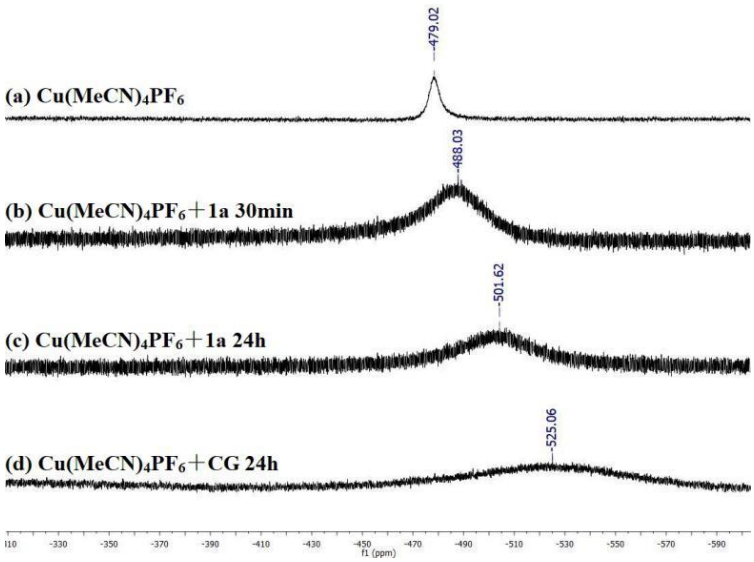
In order to gain more information about the mechanism of the enantioselective allylic substitution with cyclic bromides catalyzed by Cu(I) and **CG** in the presence of base, complex **CP1** was prepared by mixing CuCl and CG^+Cl^- at room temperature. The crystal structure of complex **CP1** was later characterized by *X*-ray crystallography (Scheme 2.12a). An anionic cuprate species $[CuCl_2]^-$ was determined which cooperated with guanidinium cation via ionic interaction. Complex **CP1** was later used to replace the combination of $Cu(MeCN)_4PF_6$ and **CG** in the standard condition to verify its catalytic capacity. Desired arylation product was obtained in 85% yield and 87% *ee*, which proved **CP1** to be an active intermediate in the reaction (Scheme 2.12b). The enantioselectivity of arylation process was proposed to be controlled by chiral guanidinium cation over organocuprate species formed in the reaction.



Scheme 2.13 Identification of guanidinium cuprate complex as a key catalytic intermediate.

2.4.3 ^{63}Cu NMR Study

Much efforts have been devoted to work on identification or isolation of copper-associated intermediates involving either nucleophile or halide electrophile in nucleophilic substitution reactions, but generally unfruitful. In 1988, Kennedy and co-workers utilized ^{63}Cu NMR spectrum to detect the weak interaction between $Cu(MeCN)_4BF_4$ and various 2-haloarylazo compounds. The exchange equilibria of $Cu(MeCN)_4^+$ with solvents or ligands were demonstrated by changes in chemical shift and peak width of ^{63}Cu resonance. Given the fact that stable Cu-associated intermediate could hardly be isolated, ^{63}Cu NMR spectrum could be a means to probe the interaction between Cu(I) complex and substrates or organocatalysis in our reaction.[22]

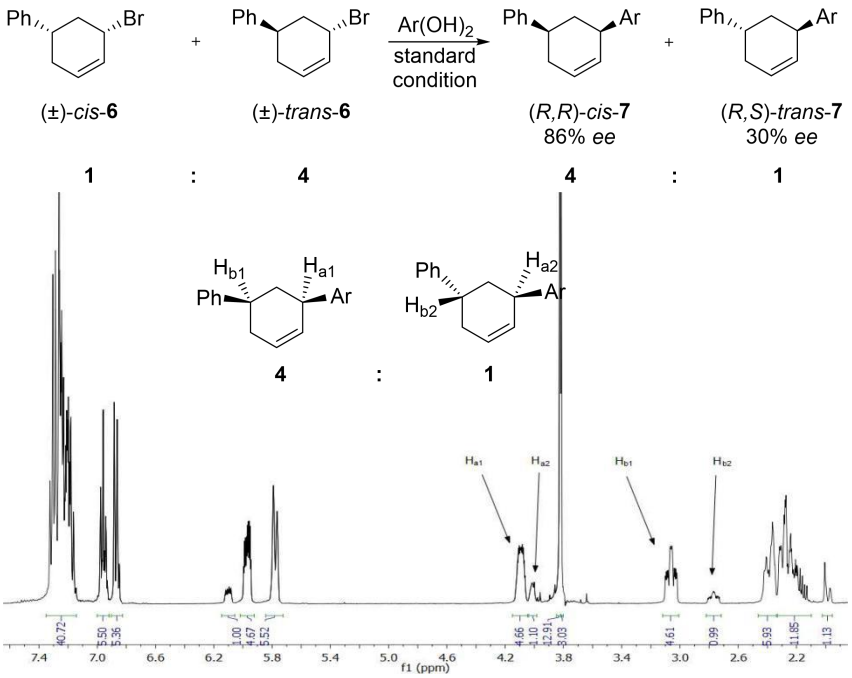


Scheme 2.14 ^{63}Cu NMR spectrum of copper complex in different conditions.

A batch of experiments on the interaction between Cu(I) complex and other reagents in our reaction were carried out and the resulting ^{63}Cu NMR spectrum are shown in Scheme 2.13. First of all, $Cu(MeCN)_4PF_6$ complex was dissolved in CD_3CN, giving the chemical shift of －479ppm which is a sharp peak on ^{63}Cu NMR spectrum (Scheme 2.14a). Next, a mixture of $Cu(MeCN)_4PF_6$ and cyclic allylic bromide **1a** with 1:1 ratio in CD_3CN for 30min led to upfield shift of ^{63}Cu resonance to －488ppm and the width of the peak increased (Scheme 2.14b), probably showing the interaction between Cu(I) salt and allylic bromide. In contrast, mixture of $Cu(MeCN)_4PF_6$ with aryl boronic acid didn't cause any shift or width change of ^{63}Cu peak. After $Cu(MeCN)_4PF_6$ and **1a** reacted for 24 hours, the ^{63}Cu resonance shifted further to －501ppm (Scheme 2.14c), indicating the slow coordination of **1a** to $Cu(MeCN)_4PF_6$. A mixture of $Cu(MeCN)_4PF_6$ and **CG** was dissolved in CD_3CN and ^{63}Cu resonance displayed a significant upfield shift to －525ppm (Scheme 2.14d). The notable broad ^{63}Cu peak implied the possible coordination of iodide with copper center, which is in concordance with structure of **CP1**.

2.4.4 Stereoselectivity of Allylic Arylation

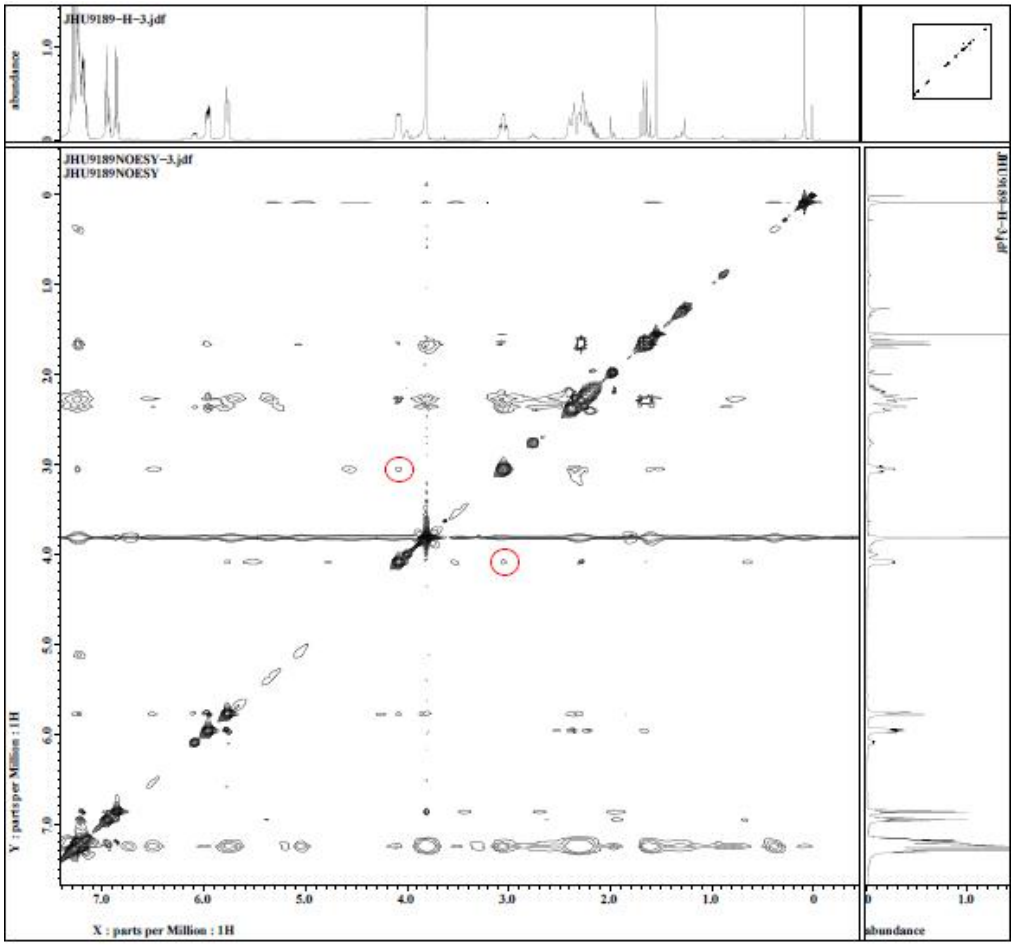
In terms of mechanism, how the enantioselectivity is induced is essential to understand the asymmetric allylic arylation process. In Pd catalyzed EAS reactions, most of nucleophiles employed are stabilized or "soft", which will attack the π-allyl-M intermediate externally to form product. However, for non-stabilized nucleophiles, they are usually thought to attack the metal center first in a manner of inner sphere coordination, followed by reductive elimination to afford product with a net reversion of configuration. The enantiodiscrimination occurs within the coordination sphere of the intermediate. Therefore, the change of stereochemistry during the reaction can help differentiate the nucleophilic attack pathway.



Scheme 2.15 Stereoselectivity of allylic arylation.

Since it's difficult to synthesize enantiopure allylic bromides, phenyl-substituted allylic bromide **6** (with a *cis/trans* ratio of 1:4) was prepared for diastereoselective allylic arylation to gain mechanistic insight (Scheme 2.15). Under standard condition with $Ar(OH)_2$ (**2e**, Ar=2-methoxylphenyl), the mixture of *cis/trans* bromide **6** was arylated smoothly to afford the corresponding product **7**. Configuration of product **7** was found to be a net inversion of starting material with

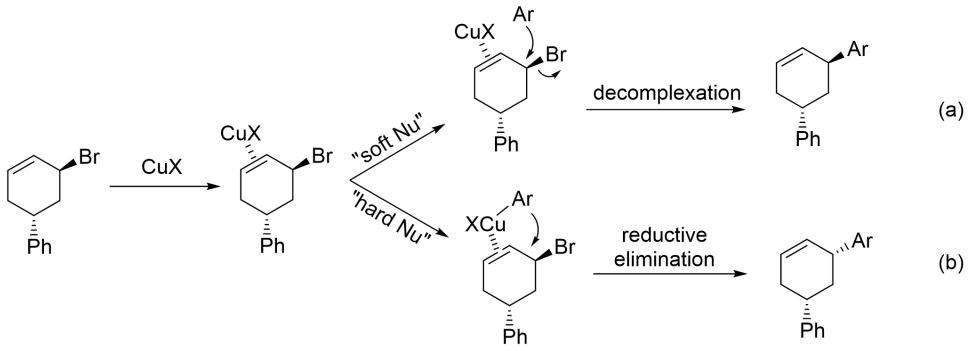
a *cis/trans* ratio of 4:1 determined by ^{1}H NMR. The cross peak of H_{a1} (4.10 ppm) and H_{b1} (3.07 ppm) in NOESY spectrum helped confirm the *cis*-configuration of major product (Scheme 2.16).



Scheme 2.16 NOESY spectrum of arylated product **7**.

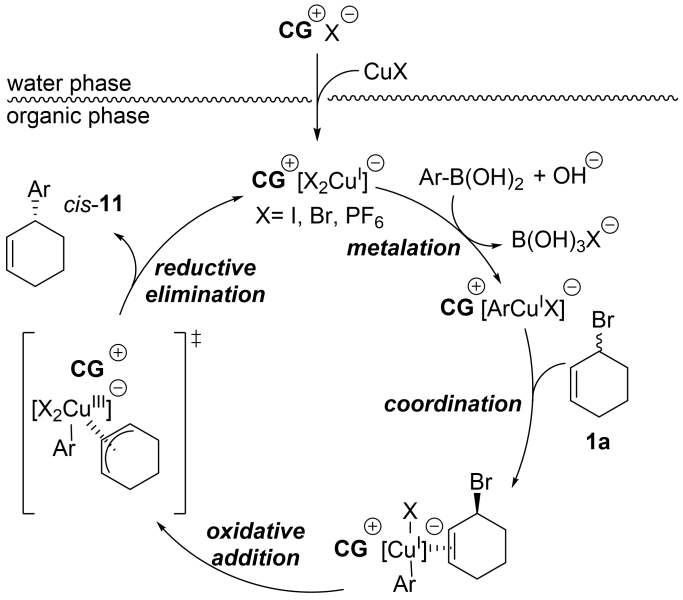
The difference between "soft" and "hard" nucleophilic attack pathway is shown in Scheme 2.17. In "soft" nucleophilic attack pathway, the "soft" nucleophile will attack directly at the carbon center and kick out the leaving group of the Cu-π-allyl complex, resulting in the double inversion of stereo-configuration and giving retention of the dr structure. However, in "hard" nucleophilic attack pathway, the "hard" nucleophile will attack the Cu center first and then undergo reductive elimination to give the product, which will result in the inversion of stereo-configuration in the product. The inversion of stereo-configuration in the

asymmetric allylic arylation of **6** indicated that aryl nucleophile from boronic acid in this Cu catalyzed reaction might attack the allyl-Cu intermediate via the "hard" nucleophile pathway, where it bounded to Cu center first and then underwent reductive elimination to give final product. Furthermore, enantioenrichment of *cis*- and *trans*-**7** was not identical, where the *cis*-**7** was determined with 86% *ee* but trans-**7** was 30% *ee*. The steric hindrance of **CG**-associated Cu complex and related intermediate might affect the enantiodiscrimination process significantly.



Scheme 2.17 "Soft/Hard" nucleophilic attack of aryl nucleophile from boronic acid.

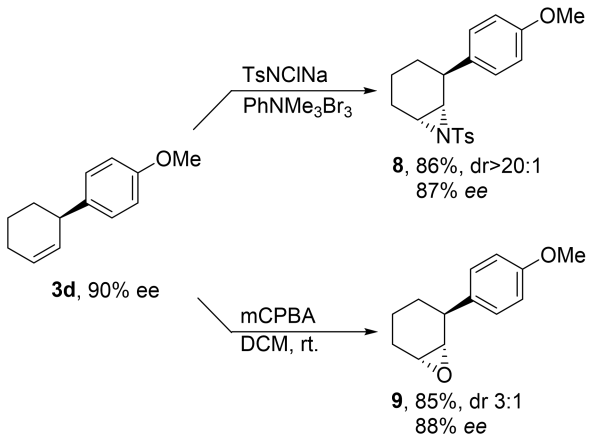
Based on the above mechanistic exploration, a plausible mechanism for the asymmetric allylic arylation reaction catalyzed by Cu(I) and **CG** was proposed as Scheme 2.18. An ionic complex $\mathbf{CG}^{+}CuX_2^{-}$ was formed upon interface of solvents, which underwent ligand exchange process with sp^2-nucleophile from boronic acid in basic condition. Attachment of metal center to allylic moiety and oxidative addition to form the Cu-π-allyl complex allowed the racemization of substrate. Under the control of configuration of **CG**, the asymmetric functionalized product was obtained upon reductive elimination and meanwhile, the Cu-**CG** catalyst was re-generated. Though this is a plausible mechanism cycle for this asymmetric allylic arylation and vinylation reaction, another pathway where guanidinium salt was deprotonated in the basic condition and functioned as coordination ligand to copper metal cannot be fully excluded. Further mechanistic investigation and computational calculation with kinetic data would be helpful to verify the reaction pathway.



Scheme 2.18 Proposed mechanism of the asymmetric allylic arylation reaction catalyzed by Cu(I) and CG.

2.5 Diastereoselective Transformations of Products

Optically active products from the enantioselective allylic substitution can be further transformed diastereoselectively to various organic molecules (Scheme 2.19). Olefin **3d** can be exploited with chloramine T trihydrate to produce aziridine **8** in the presence of trimethylphenylammonium tribromide as catalyst.[23] Alternatively, a simple procedure was conducted for oxidation of the olefin **3d** with *m*-CPBA, giving access to epoxide product **9** with good yield and selectivity.[23]



Scheme 2.19 Stereoselectivity transformations of allylic arylated product **3d**.

2.6 Conclusion

In summary, the methodology for highly enantioselective arylation and vinylation of allylic bromides with wide substrate scope is described.

Racemic cyclic allylic bromides in different ring size were cross coupled with sp^2-hybridized nucleophiles from boronic acids and then transformed to one single enantiomer catalyzed by Cu(I) complex and **CG** with K_3PO_4 as base in $CHCl_3$. Variation of the boronic acids ranges from (hetero)aryl to substituted vinyl groups.

Mechanism experiments including *X*-ray crystallography and ^{63}Cu NMR were conducted to explore the details in the mechanism. Anionic cuprate complex with guanidinium cation was recognized as active intermediate and interaction between copper salt and allylic bromides was observed. Hard nucleophilic attack pathway is proposed based on stereochemistry of the reaction, while other details in the mechanism still remain unclear. The utilization of readily available boronic acids and mild reaction conditions emphasize the practicality and great potential of our methodology for organic synthesis of valuable chiral motifs.

However, those electron deficient sp^2-hybridized nucleophiles cannot be employed in this methodology, which might require further modification of the reaction system including structure of chiral catalyst and reaction profiles.

2.7 Experimental Section

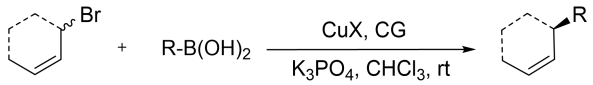
General Information and Materials

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 (400 MHz) or AV300 (300 MHz) spectrometer at 23 ^{o}C. ^{63}Cu NMR was recorded on a JEOL ECA400 spectrometer at 23 ^{o}C. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets), m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplets. Splitting patterns that could not be easily interpreted are designated as multiplets (m) or broad (br). Chemical shifts are recorded as δ in units of parts per million (ppm). The residual solvent peak (7.26 ppm for $CDCl_3$ and 1.94 ppm for CD_3CN) was used as an internal reference. High resolution mass spectrometry (HRMS) was performed on Waters Q-TOF Premier mass spectrometer and reported in units of mass of charge ratio (*m/z*) within 5ppm error. Enantiomeric excess (*ee*) values were determined by chiral HPLC analysis on Shimadzu LC-20AT and LC-2010CHT HPLC workstations with Chiralpak® columns; Or, by chiral GC-MS on Shimadzu GCMS-QP2010 SE GC-MS station with chiral GC columns. Chiral GC methods are described as: initial temp ^{o}C (hold time min) - rate of temperate increase - middle temperature ^{o}C (hold time min) - rate of temperate increase - final temp ^{o}C (hold time min). Optical rotations were measured at 23 ^{o}C using a 1 mL cell with a 1 cm path length on a Jasco P1030 digital polarimeter and are reported as follows: $[\alpha]^{t}_{D}$. Flash chromatography was performed using basified Merck silica gel 60 with distilled solvents. Thin-layer chromatography (TLC) was carried out on Merck 60 F254 silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp or aqueous basic $KMnO_4$ stain. Procedures involving air- or moisture-sensitive materials were conducted with degassed solvents under an inert atmosphere of N_2 or argon using standard Schlenk techniques.

Solvents used in this work including THF, toluene, acetonitrile, hexane and dichloromethane were distilled over drying agent under N_2 atmosphere. Degassed $CHCl_3$ was produced by freeze-pump-thaw technique and stored under N_2 atmosphere. Unless stated otherwise, all other reagents are commercially available

and used without further purification as purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar or TCI. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. All racemic enantiomers were prepared with 20 mol% $Cu(MeCN)_4PF_6$ as catalyst in $CHCl_3$.

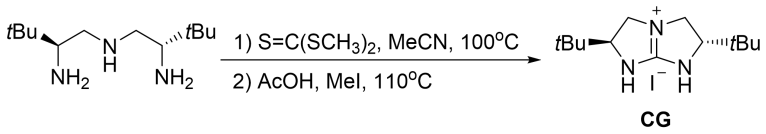
General Procedure: Cu-catalyzed Enantioselective Allylic Substitution



Catalytic amount of $Cu(MeCN)_4PF_6$, CG, boronic acid (2 eq) and K_3PO_4 (4 eq) were placed into a 25 ml Schlenk tube equipped with a stir bar. After replacing the air with N_2 atmosphere, degassed $CHCl_3$ was added into the tube via syringe followed by addition of allylic bromide (1 eq). The mixture was then stirred at ambient temperature. Upon full conversion, add water and hexane into mixture to dilute. Extract the mixture with hexane, and dry the organic phase over Na_2SO_4. Solvent was removed *in vacuo* and flash column chromatography was conducted with Hex/EA to give desired product.

2.7.1 Preparation of Catalyst and Substrates

Preparation of Cyclic Guanidinium Catalyst:

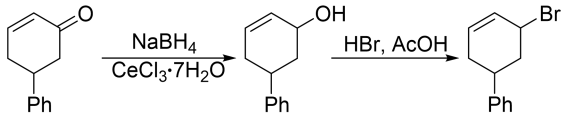


CG and **CG'** were prepared according to known literature procedure.[22] For *t*Bu-substituted **CG**: to a solution of free amine (300 mg, 1.4 mmol) in nitromethane (3 ml), dimethyl trithiocarbonate (190 µl, 1.25 eq) was added dropwise. The mixture was then heated to reflux at 100 °C for 2 h when free amine was all consumed. The mixture was allowed to cool to room temperature. Acetic acid (320 µl, 4 eq) and MeI (260 µl, 2 eq) were added in sequence. The mixture was heated again to reflux at 110 °C for 3 h and then stir at room temperature

overnight. The solvent was removed under vacumn and concentrated mixture was purified by flash column chromatography (MeOH/DCM 100:1) to give product **CG** as yellow solid in 55 % yield. It was stored at room temperature in anhydrous atmosphere. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 2H), 4.21 – 4.11 (m, 2H), 3.43 (t, *J* = 9.2 Hz, 2H), 3.28 (dd, *J* = 9.2, 6.8 Hz, 2H), 0.97 (s, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* 167.2, 72.8, 48.6, 33.9, 25.8.

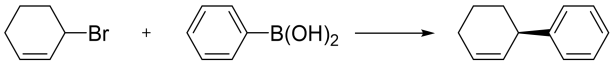
Preparation of Allylic Bromides

3-bromocyclohept-1-ene (**1g**) was prepared according to literature.[10] Under N_2 atmosphere, to a solution of NBS (7.8 g, 43 mmol, 1 eq) and benzoyl peroxide (50 mg, 0.4 mmol, 0.01 eq) in CCl_4 (20 mL) was added cycloheptene (5 ml, 43 mmol, 1 eq). The mixture was then heated to reflux at 85 ºC for 1 h. An aliquot of mixture was checked on GC-MS to monitor conversion. Upon completion, the mixture was cooled to 0 ºC and then filtered through a pad of Celite. Solid was washed with Hexane. The filtrate was washed with 5% aq.$NaHCO_3$, dried over Na_2SO_4 and concentrated under vacuum. Fractional distillation under reduced pressure gave a colourless oil (90% pure with impurity of cyclohepta-1,3-diene), which was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ1.43 – 1.54 (1H, m), 1.75 – 1.91 (2H, m), 1.94 – 2.09 (2H, m), 2.14 – 2.26 (3H, m), 4.91 – 4.96 (1H, m), 5.83 – 5.88 (1H, m), 5.92 – 5.98 (1H, m); **^{13}C NMR** (101 MHZ, $CDCl_3$): δ 26.4, 26.7, 28.3, 36.3, 53.8, 132.3, 135.5 ppm.

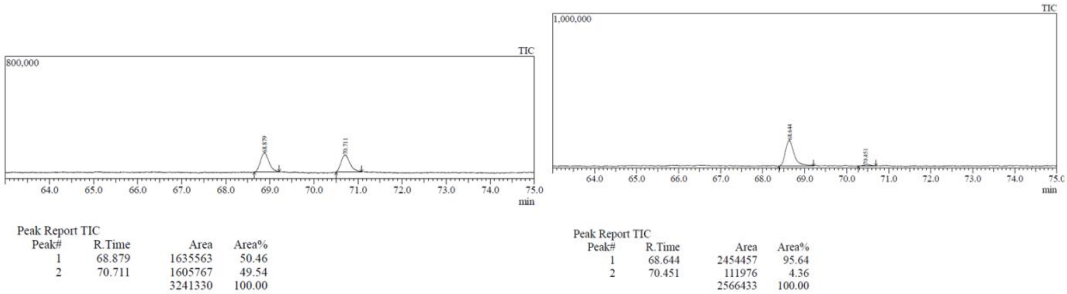


3-bromo-1,2,3,6-tetrahydro-1,1'-biphenyl (**6**) was prepared through reduction and bromination according to literature.[26] A mixture of *trans/cis* isomers was obtained in a ratio of 4:1 which was used for arylation directly without further purification.

2.7.2 Characterization and Spectra of Cyclic Products



(R)-1,2,3,4-tetrahydro-1,1'-biphenyl (3a): Following the general procedure using phenylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The corresponding product was obtained in 46% yield as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 5.89 (ddd, *J* = 9.8, 6.0, 3.6 Hz, 1H), 5.72 (dd, *J* = 10.0, 2.1 Hz, 1H), 3.41 (m, 1H), 2.09 (m, 2H), 2.06 – 1.96 (m, 1H), 1.80 – 1.70 (m, 1H), 1.68 – 1.52 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.6, 130.1, 128.3, 128.2, 127.7, 125.9, 41.8, 32.6, 25.0, 21.2. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +132.6 (c=2.18 in CH_2Cl_2, 91 % *ee*). **HRMS** (ESI) m/z calcd. for $C_{12}H_{15}$ $[M+H]^+$: 159.1174, found: 159.1172. **Enantiomeric excess** of 91% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-110 °C (20 min)-15-160 °C (1 min), major enantiomer t_R= 68.6 min; minor enantiomer t_R= 70.4 min].



Peak Report TIC

Peak#	R.Time	Area	Area%
1	68.879	1635563	50.46
2	70.711	1605767	49.54
		3241330	100.00

Peak Report TIC

Peak#	R.Time	Area	Area%
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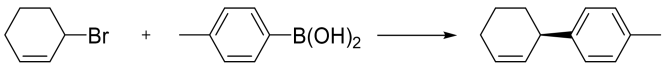
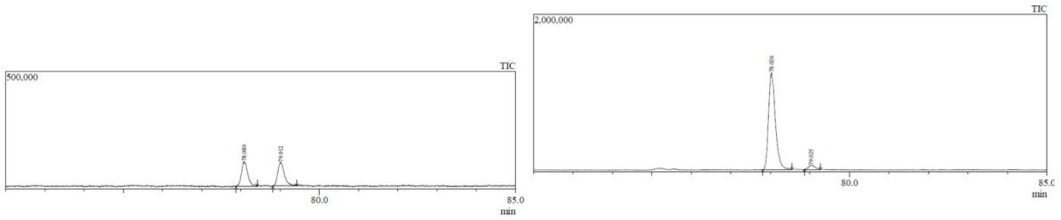
2	70.451	111976	4.36
		2566433	100.00



(R)-4'-methyl-1,2,3,4-tetrahydro-1,1'-biphenyl (3b): Following the general procedure using *p*-tolylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The corresponding product was obtained in 55% yield as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (s, 4H), 5.88 (ddd, *J* = 9.7, 6.0, 3.5 Hz, 1H), 5.74 – 5.68 (m, 1H), 3.38 (ddt, *J* = 8.0, 5.3, 2.7 Hz, 1H), 2.33 (s, 3H), 2.14 – 2.05 (m, 2H), 2.05 – 1.94 (m, 1H), 1.82 – 1.70 (m, 1H), 1.68 – 1.51 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 135.4, 130.4, 128.9, 128.1, 127.6, 41.4, 32.7, 25.0,

21.2, 21.0. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +137.8 (c=0.68 in CH_2Cl_2, 92 % *ee*). **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}$ $[M+H]^+$: 173.1330, found: 173.1326. **Enantiomeric excess** of 92% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-135 °C (1min)-15-160 °C (1 min), major enantiomer t_R= 78 min; minor enantiomer t_R= 79 min].

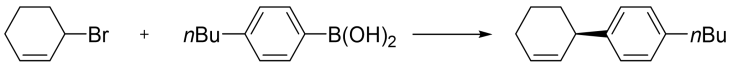


Peak Report TIC

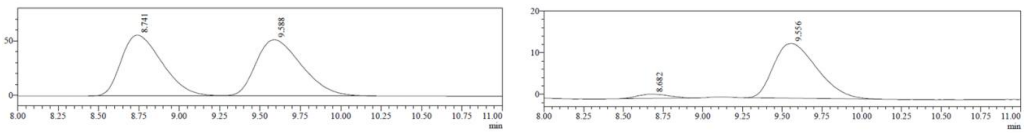
Peak#	R.Time	Area	Area%
1	78.080	1158771	49.32
2	79.012	1190946	50.68
		2349717	100.00

Peak Report TIC

Peak#	R.Time	Area	Area%
1	78.026	14824815	96.04
2	79.025	611510	3.96
		15436325	100.00



(R)-4'-butyl-1,2,3,4-tetrahydro-1,1'-biphenyl (3c): Following the general procedure using (4-butylphenyl) boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The corresponding product was obtained in 62% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +120.3 (c=1.58 in CH_2Cl_2, 90 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 4H), 5.89 (ddd, *J* = 9.8, 5.9, 3.5 Hz, 1H), 5.73 (ddd, *J* = 10.1, 4.1, 2.0 Hz, 1H), 3.39 (ddt, *J* = 8.0, 5.3, 2.7 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.16 – 2.06 (m, 2H), 2.04 – 1.96 (m, 1H), 1.79 – 1.70 (m, 1H), 1.68 – 1.51 (m, 4H), 1.37 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8, 140.5, 130.5, 128.3, 128.1, 127.6, 41.4, 35.3, 33.7, 32.6, 25.0, 22.4, 21.2, 14.0. **HRMS** (ESI) m/z calcd. for $C_{16}H_{23}$ $[M+H]^+$: 215.1800, found: 215.1801. **Enantiomeric excess** of 90% was determined by chiral HPLC [chiral column OJH; methods: Eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 9.5 min; minor enantiomer t_R= 8.7 min].

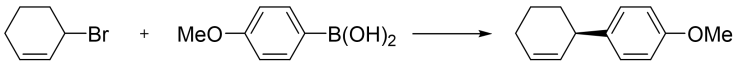


Peak Table

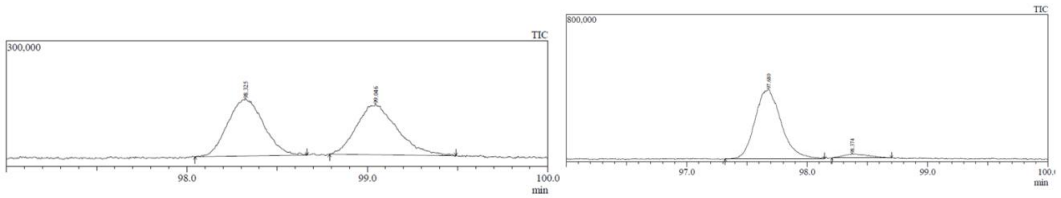
Peak#	Ret. Time	Height	Area	Area%
1	8.740	13131	228811	49.993
2	9.589	11932	228871	50.007
Total		25052	457682	100.000

Peak Table

Peak#	Ret. Time	Height	Area	Area%
1	8.682	966	13675	5.156
2	9.556	13193	250644	94.844
Total		14159	264270	100.000



(R)-4'-methoxy-1,2,3,4-tetrahydro-1,1'-biphenyl (3d): Following general procedure using (4-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 79% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +94.6 (c=1.12 in CH_2Cl_2, 90 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 2H), 6.90 – 6.80 (m, 2H), 5.89 (ddt, *J* = 9.8, 5.9, 3.0 Hz, 1H), 5.69 (ddt, *J* = 15.0, 10.8, 2.2 Hz, 1H), 3.80 (s, 3H), 3.42 – 3.31 (m, 1H), 2.13 – 2.05 (m, 2H), 2.00 (m, *J* = 13.2, 7.1, 4.1 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.63 (m, *J* = 8.5, 6.1, 4.9, 2.2 Hz, 1H), 1.58 – 1.49 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.9, 138.8, 130.5, 128.6, 128.1, 113.7, 55.3, 41.0, 32.7, 25.0, 21.1. **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279, found: 189.1283. **Enantiomeric excess** of 90% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-140 °C (15 min)-15-160 °C (1 min), major enantiomer t_R= 97.6 min; minor enantiomer t_R= 98.3 min].

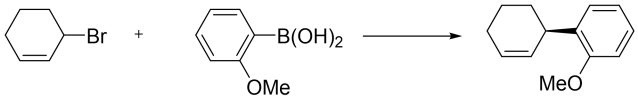


Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	98.325	136841	1889901	50.20
2	99.046	121445	1874586	49.80
		258286	3764487	100.00

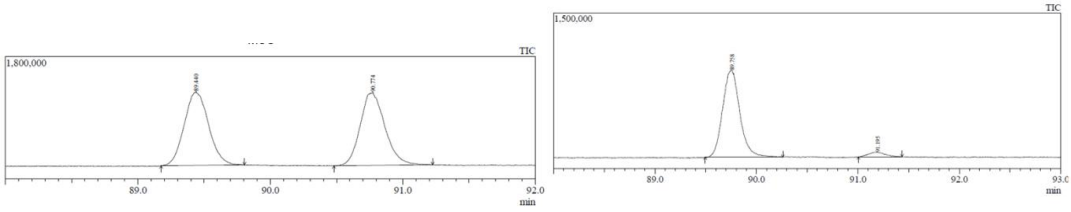
Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	97.680	377628	5658590	94.76
2	98.374	22936	312923	5.24
		400564	5971513	100.00



(R)-2'-methoxy-1,2,3,4-tetrahydro-1,1'-biphenyl (3e) : Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 82% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +65.4 (c=2.85 in CH_2Cl_2, 90 % *ee*). [reported -41.2 (c=1.88 in $CHCl_3$) for *S* in 74% *ee*].[26] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 12.1, 4.6 Hz, 2H), 6.94 (dd, *J* = 10.8, 4.1 Hz, 1H), 6.88 (d, *J* = 7.8

Hz, 1H), 5.93 (ddd, *J* = 9.7, 5.9, 3.5 Hz, 1H), 5.69 (dd, *J* = 10.1, 2.2 Hz, 1H), 3.92 – 3.87 (m, 1H), 3.85 (s, 3H), 2.14 – 2.07 (m, 2H), 2.07 – 1.97 (m, 1H), 1.77 – 1.59 (m, 2H), 1.59 – 1.48 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 134.5, 130.3, 128.5, 128.4, 126.9, 120.3, 110.2, 55.3, 34.2, 30.2, 25.2, 21.0. **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279, found: 189.1287. **Enantiomeric excess** of 90% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-140 °C (15 min)-15-160 °C (1 min), major enantiomer t_R= 89.7 min; minor enantiomer t_R= 91.1 min].

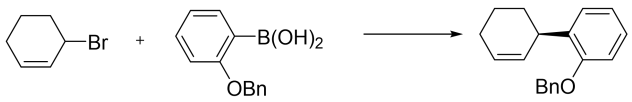


Peak Report TIC

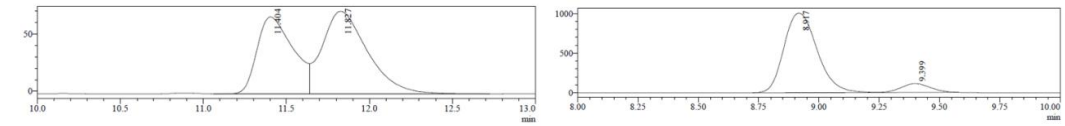
Peak#	R.Time	Height	Area	Area%
1	89.440	1094678	13832015	49.86
2	90.774	1080438	13910774	50.14
		2175116	27742789	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	89.758	837471	9888013	95.02
2	91.195	44998	518669	4.98
		882469	10406682	100.00



(R)-2'-(benzyloxy)-1,2,3,4-tetrahydro-1,1'-biphenyl (3f): Following general procedure using (2-(benzyloxy) phenyl)boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 79% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +19.3 (c=2.27 in CH_2Cl_2, 84 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.47 – 7.39 (m, 2H), 7.36 (ddd, *J* = 8.5, 4.4, 1.3 Hz, 1H), 7.28 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.21 (td, *J* = 7.9, 1.8 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.00 – 5.93 (m, 1H), 5.78 – 5.71 (m, 1H), 5.14 (s, 2H), 4.06 – 3.96 (m, 1H), 2.20 – 2.04 (m, 3H), 1.80 – 1.60 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 137.6, 134.9, 130.3, 128.8, 128.6, 128.5, 127.7, 127.0, 127.0, 120.7, 111.7, 69.9, 34.6, 30.2, 25.2, 21.0. **HRMS** (ESI) m/z calcd. for $C_{19}H_{21}O$ $[M+H]^+$: 265.1592, found: 265.1597. **Enantiomeric excess** of 84% was determined by chiral HPLC [chiral column IA-3; methods: Eluting solvent: 1% IPA in hexane, flow speed: 0.5 ml/min; major enantiomer t_R= 8.9 min; minor enantiomer t_R= 9.4 min].



Peak Table

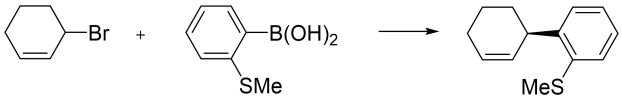
PDA Ch4 271nm

Peak#	Ret. Time	Height	Area	Area%
1	11.404	67408	1021625	42.694
2	11.827	72340	1371300	57.306
Total		139748	2392925	100.000

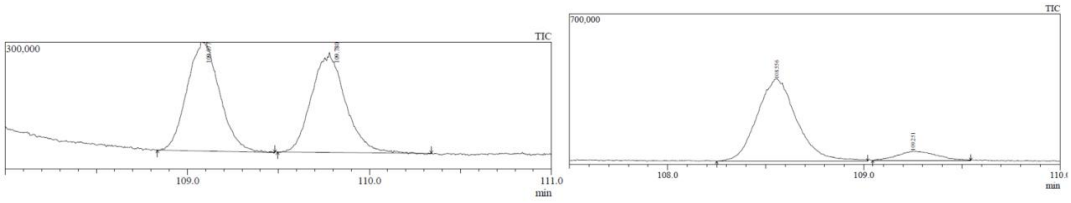
Peak Table

PDA Ch4 270nm

Peak#	Ret. Time	Height	Area	Area%
1	8.917	362030	3174190	91.838
2	9.399	33168	282089	8.162
Total		395198	3456279	100.000



(R)-methyl(1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-yl)sulfane (3g)： Following general procedure using (2-methylthiophenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 82% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +5.4 (c=0.85 in CH_2Cl_2, 80 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 3H), δ 7.15 – 7.12 (m, 1H), δ 5.96 – 5.91 (m, 1H), δ 5.67 – 5.64 (m, 1H), 3.90 – 3.85 (m, 1H), 2.47 (s, 3H), 2.10 – 2.08 (m, 3H), 1.71 – 1.64 (m, 2H), 1.55 – 1.49 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 136.7, 129.9, 128.7, 127.8, 126.7, 125.7, 125.0, 38.1, 30.4, 25.1, 21.0, 16.1. **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}S$ $[M+H]^+$: 205.1051, found: 205.1050. **Enantiomeric excess** of 80% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-140 °C (15 min)-15-160 °C (1 min), major enantiomer t_R= 109 min; minor enantiomer t_R= 109.7 min].

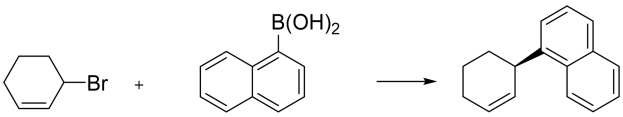


Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	109.077	262931	3207626	51.37
2	109.780	237429	3036745	48.63
		500360	6244371	100.00

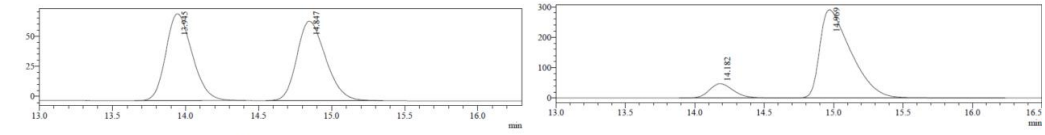
Peak Report TIC

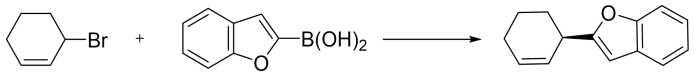
Peak#	R.Time	Height	Area	Area%
1	108.556	382462	5364706	90.23
2	109.251	43880	580677	9.77
		426342	5945383	100.00



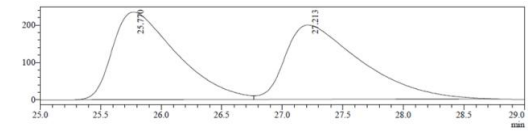
(R)-1-(cyclohex-2-en-1-yl)naphthalene (3h)： Following general procedure using naphthalen-1-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol%

CG. The corresponding product was obtained in 79% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +7.2 (c=0.75 in CH_2Cl_2, 76 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8Hz, 1H), 7.88 (d, *J* = 8Hz, 1H), 7.73 (d, *J* = 8Hz, 1H), 7.52 – 7.39 (m, 4H), 6.03 – 6.01 (m, 1H), 5.85 – 5.83 (m, 1H), 4.25 – 4.23 (m, 1H), 2.21 – 2.16 (m, 3H), 1.79 – 1.67 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.9, 134.0, 131.4, 130.2, 128.9, 128.8, 125.7, 125.4, 125.3, 125.1, 123.4, 37.0, 30.9, 25.3, 20.9. **HRMS** (ESI) m/z calcd. for $C_{16}H_{17}$ $[M+H]^+$: 209.1330, found: 209.1332. **Enantiomeric excess** of 76% was determined by chiral HPLC [chiral column IB3; methods: Eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 14.9 min; minor enantiomer t_R= 14.1 min].





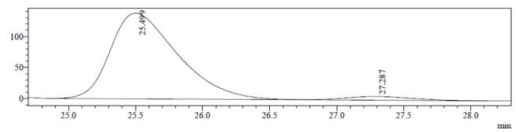
(R)-2-(cyclohex-2-en-1-yl)benzofuran (3k): Following general procedure using benzofuran-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 85% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +133.8 (c=4.4 in CH_2Cl_2, 92 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 1H), 7.49 – 7.44 (m, 1H), 7.27 – 7.18 (m, 2H), 6.42 (t, J = 0.8 Hz, 1H), 5.99 – 5.92 (m, 1H), 5.92 – 5.85 (m, 1H), 3.68 – 3.61 (m, 1H), 2.16 – 2.06 (m, 3H), 1.96 – 1.87 (m, 1H), 1.84 – 1.74 (m, 1H), 1.73 – 1.63 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1, 154.8, 129.5, 128.9, 126.4, 123.2, 122.4, 120.4, 110.9, 101.8, 77.4, 77.1, 76.7, 35.4, 28.0, 25.0, 20.4. **HRMS** (ESI) m/z calcd. for $C_{14}H_{15}O$ $[M+H]^+$: 199.1123, found: 199.1124. **Enantiomeric excess** of 92% was determined by chiral HPLC [chiral column IE; methods: Eluting solvent: hexane, flow speed: 0.3 ml/min; major enantiomer t_R= 25.5 min; minor enantiomer t_R= 27.2 min].



Peak Table

PDA Ch2 230nm

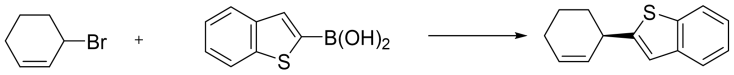
Peak#	Ret. Time	Height	Area	Area%
1	25.770	234301	8618835	49.939
2	27.213	198603	8660049	50.061
Total		432905	17298884	100.000



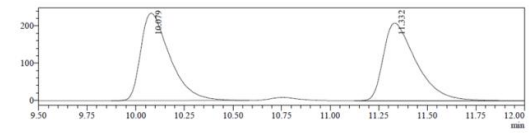
Peak Table

PDA Ch2 230nm

Peak#	Ret. Time	Height	Area	Area%
1	25.499	137763	4806569	95.914
2	27.287	5945	204740	4.086
Total		143708	5011309	100.000



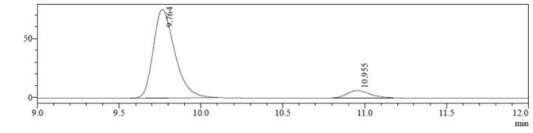
(R)-2-(cyclohex-2-en-1-yl)benzothiophene (3l): Following general procedure using benzothiophen-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 80% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +119.3 (c=1.48 in CH_2Cl_2, 84 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.24 (m, 2H), 7.07 (s, 1H), 5.97 – 5.84 (m, 2H), 3.80 – 3.73 (m, 1H), 2.21 – 2.08 (m, 3H), 1.89 – 1.78 (m, 2H), 1.72 – 1.64 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.2, 140.1, 139.2, 129.0, 128.9, 124.0, 123.4, 122.8, 122.2, 120.0, 77.3, 77.0, 76.7, 37.4, 31.9, 25.0, 20.6. **HRMS** (ESI) m/z calcd for $C_{14}H_{15}S$ $[M+H]^+$: 215.0894, found: 215.0895. **Enantiomeric excess** of 84% was determined by chiral HPLC [chiral column IB-3; methods: Eluting solvent: hexane, flow speed: 0.8 ml/min; major enantiomer t_R= 10 min; minor enantiomer t_R= 11 min].



Peak Table

PDA Ch4 280nm

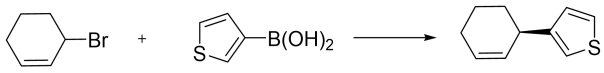
Peak#	Ret. Time	Height	Area	Area%
1	10.079	235113	2444391	50.015
2	11.332	207913	2442956	49.985
Total		443026	4887346	100.000



Peak Table

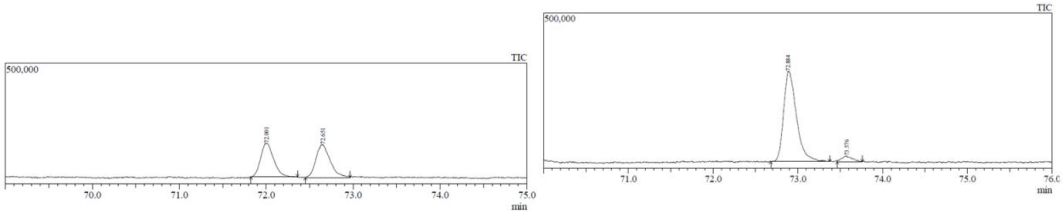
PDA Ch4 280nm

Peak#	Ret. Time	Height	Area	Area%
1	9.764	75028	6880821	91.909
2	10.955	6347	605574	8.091
Total		81375	7486656	100.000



(R)-2-(cyclohex-2-en-1-yl)thiophene (3m): Following general procedure using thiophen-3-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +79.8 (c=3.88 in CH_2Cl_2, 90 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.02 – 6.94 (m, 2H), 5.89 – 5.80 (m, 1H), 5.80 – 5.73 (m, 1H), 3.50 (m,

1H), 2.03 – 1.96 (m, 3H), 1.78 – 1.66 (m, 1H), 1.66 – 1.56 (m, 2H). **^{13}C NMR** (101 MHz, CDCl3) δ 147.2, 129.9, 127.9, 127.5, 125.2, 119.9, 36.9, 31.2, 25.0, 20.8. **HRMS** (ESI) m/z calcd. for $C_{10}H_{13}S$ $[M+H]^+$: 165.0738, found: 165.0740. **Enantiomeric excess** of 90% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-124 °C (1 min)-15-160 °C (1 min), major enantiomer t_R= 72.8 min; minor enantiomer t_R= 73.6 min].

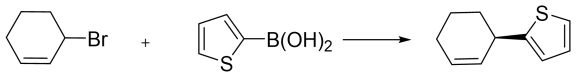


Peak Report TIC

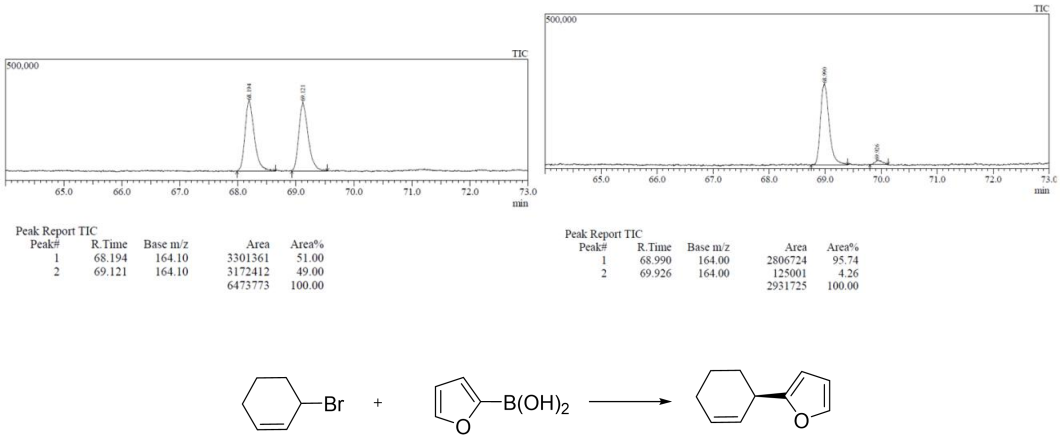
Peak#	R.Time	Base m/z	Area	Area%
1	72.001	135.05	1487374	50.24
2	72.651	135.05	1473205	49.76
			2960579	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	72.884	164.05	3051114	95.20
2	73.576	135.00	153786	4.80
			3204900	100.00



(R)-2-(cyclohex-2-en-1-yl)thiophene (3n): Following general procedure using thiophen-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 72% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +94.3 (c=8.38 in CH_2Cl_2, 91 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 – 7.11 (m, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (d, *J* = 3.4 Hz, 1H), 5.88 – 5.76 (m, 2H), 3.69 (s, 1H), 2.13 – 2.03 (m, 3H), 1.81 – 1.69 (m, 2H), 1.69 – 1.59 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.2, 129.9, 127.9, 127.5, 125.2, 119.9, 36.9, 31.2, 25.0, 20.8. **HRMS** (ESI) m/z calcd. for $C_{10}H_{13}S$ $[M+H]^+$: 165.0738, found: 165.0738. **Enantiomeric excess** of 91% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-120 °C(1 min)-15-160 °C(1 min), major enantiomer t_R= 68.1 min; minor enantiomer t_R= 69.1 min].



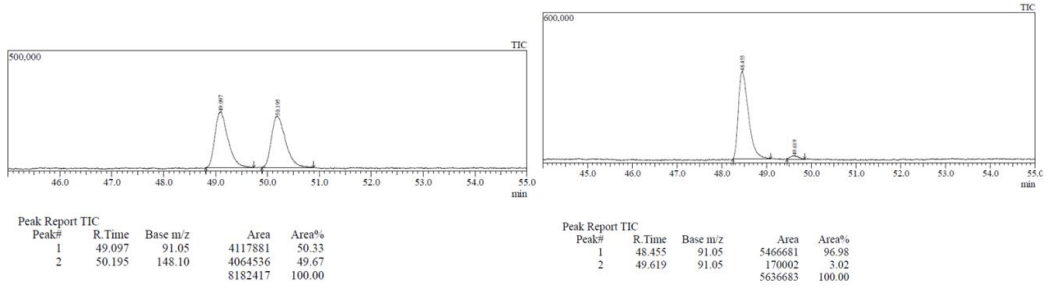
Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	68.194	164.10	3301361	51.00
2	69.121	164.10	3172412	49.00
			6473773	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	68.990	164.00	2806724	95.74
2	69.926	164.00	125001	4.26
			2931725	100.00

(R)-2-(cyclohex-2-en-1-yl)furan (3p): Following general procedure using furan-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 72% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +84.9 (c=3.54 in CH_2Cl_2, 94 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.0 Hz, 1H), 6.29 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.99 (d, *J* = 3.1 Hz, 1H), 5.90 – 5.81 (m, 1H), 5.77 (ddd, *J* = 10.0, 4.7, 2.1 Hz, 1H), 3.52 – 3.42 (m, 1H), 2.10 – 2.02 (m, 2H), 2.01 – 1.93 (m, 1H), 1.81 – 1.68 (m, 2H), 1.61 (dtd, *J* = 9.1, 6.4, 3.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0, 140.9, 128.8, 127.1, 109.9, 104.4, 35.0, 28.2, 24.9, 20.5. **HRMS** (ESI) m/z calcd. for $C_{10}H_{13}O$ $[M+H]^+$: 149.0966, found: 149.0970. **Enantiomeric excess** of 94% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-95 °C (10 min)-15-160 °C (1 min), major enantiomer t_R= 48.5 min; minor enantiomer t_R= 49.6 min].

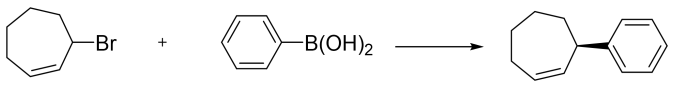


Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	49.097	91.05	4117881	50.33
2	50.195	148.10	4064536	49.67
			8182417	100.00

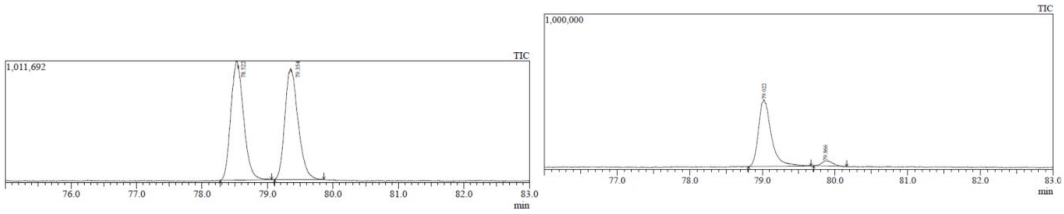
Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	48.455	91.05	5466681	96.98
2	49.619	91.05	170002	3.02
			5636683	100.00



(R)-3-phenylcyclohept-1-ene (4e): Following general procedure using phenylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The

corresponding product was obtained in 65% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +21.4 (c=0.52 in CH_2Cl_2, 87 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 5.87 – 5.82 (m, 1H), 5.78 – 5.74 (m, 1H), 3.54 – 3.52 (m, 1H), 2.27 – 2.20 (m, 2H), 1.97 – 1.92 (m, 1H), 1.86 – 1.79 (m, 1H), 1.78 – 1.62 (m, 3H), 1.50 – 1.44 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.9, 142.1, 137.1, 134.9, 131.6, 128.4, 127.2, 125.8, 47.1, 36.2, 30.2, 28.0, 27.0. **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}$ $[M+H]^+$: 173.1330, found: 173.1332. **Enantiomeric excess** of 87% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min), major enantiomer t_R= 79 min; minor enantiomer t_R= 79.9 min].

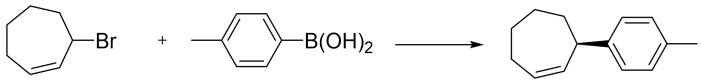


Peak Report TIC

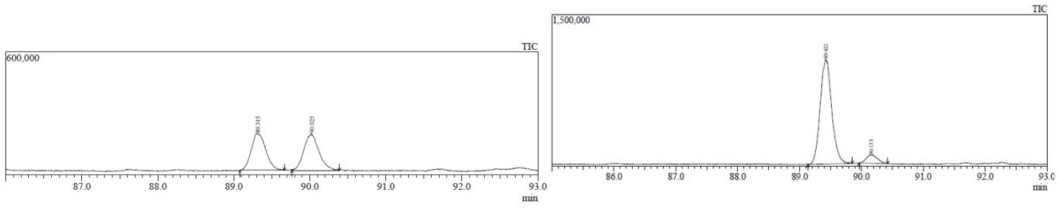
Peak#	R.Time	Height	Area	Area%
1	78.522	991484	13435327	50.93
2	79.354	924616	12946105	49.07
		1916100	26381432	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	79.022	429139	5214487	93.79
2	79.866	33616	345073	6.21
		462755	5559560	100.00



(R)-3-(p-tolyl)cyclohept-1-ene (4f): Following general procedure using p-tolylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +29 (c=1.04 in CH_2Cl_2, 85 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 4H), 5.86 – 5.81 (m, 1H), 5.77 – 5.74 (m, 1H), 3.51 – 3.49 (m, 1H), 2.34 (s, 3H), 2.33 – 2.20 (m, 2H), 1.96 – 1.91 (m, 1H), 1.85 – 1.64 (m, 4H), 1.49 – 1.44 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 137.3, 135.2, 131.5, 129.1, 127.1, 46.7, 36.3, 30.2, 28.8, 27.1, 21.0. **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}$ $[M+H]^+$: 187.1487, found: 187.1486. **Enantiomeric excess** of 85% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min), major enantiomer t_R= 79 min; minor enantiomer t_R= 79.9 min].

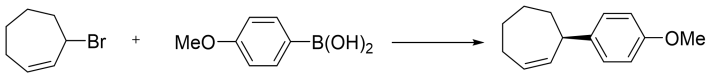


Peak Report TIC

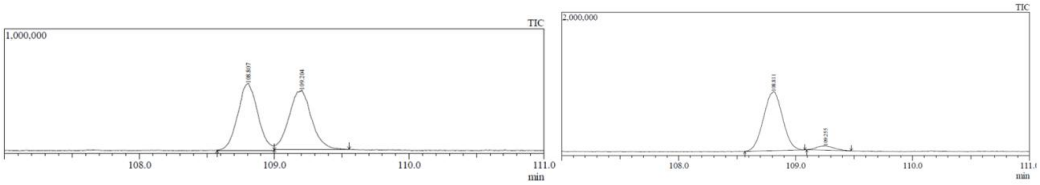
Peak#	R.Time	Area	Area%
1	89.315	2396550	49.42
2	90.025	2452379	50.58
		4848929	100.00

Peak Report TIC

Peak#	R.Time	Area	Area%
1	89.421	13425337	92.69
2	90.155	1059405	7.31
		14484742	100.00



(R)-3-(4-methoxyphenyl)cyclohept-1-ene (4g): Following general procedure using (4-methoxyphenyl)boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 75% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +35.4 (c=2.52 in CH_2Cl_2, 88 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 2H), 6.90 – 6.82 (m, 2H), 5.90 – 5.81 (m, 1H), 5.80 – 5.72 (m, 1H), 3.81 (s, 3H), 3.58 – 3.46 (m, 1H), 2.32 – 2.17 (m, 2H), 1.99 – 1.89 (m, 1H), 1.88 – 1.60 (m, 4H), 1.55 – 1.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 140.1, 137.4, 131.4, 128.1, 113.8, 55.3, 46.3, 36.4, 30.1, 28.8, 27.0. **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436, found: 203.1439. **Enantiomeric excess** of 88% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min), major enantiomer t_R= 108.5 min; minor enantiomer t_R= 108.9 min].

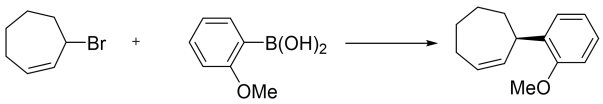


Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	108.807	537884	5541176	50.14
2	109.204	478282	5509284	49.86
		1016166	11050460	100.00

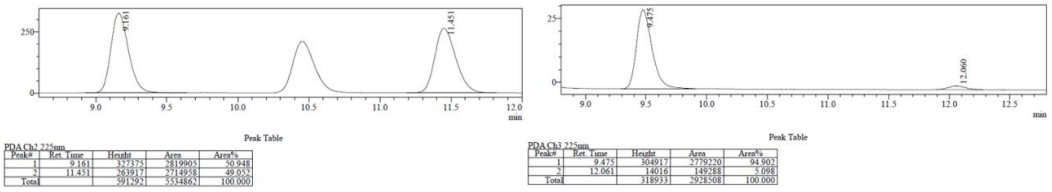
Peak Report TIC

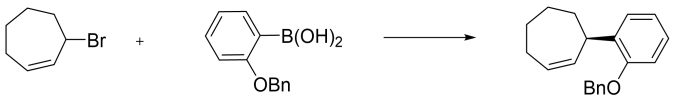
Peak#	R.Time	Height	Area	Area%
1	108.811	823772	9331334	93.76
2	109.255	61766	621203	6.24
		885538	9952537	100.00



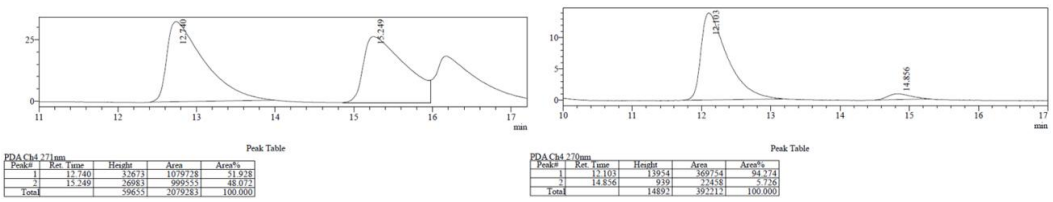
(R)-3-(2-methoxyphenyl)cyclohept-1-ene (4h): Following general procedure using (2-methoxyphenyl)boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6

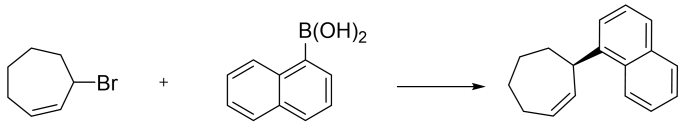
mol% **CG**. The corresponding product was obtained in 79% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +15 (c=0.4 in CH_2Cl_2, 90 % *ee*).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.92 – 5.80 (m, 1H), 5.77 – 5.69 (m, 1H), 4.05 – 3.93 (m, 1H), 3.84 (s, 3H), 2.33 – 2.22 (m, 2H), 1.98 – 1.89 (m, 1H), 1.84 – 1.73 (m, 3H), 1.73 – 1.63 (m, 1H), 1.56 – 1.42 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 137.2, 136.0, 131.2, 128.1, 126.8, 120.6, 110.5, 55.5, 39.7, 34.7, 30.3, 28.8, 27.3. **HRMS** (ESI) m/z calcd. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1436, found: 203.1427. **Enantiomeric excess** of 90% was determined by chiral HPLC [chiral column IB3; methods: Eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 9.5 min; minor enantiomer t_R= 12 min].



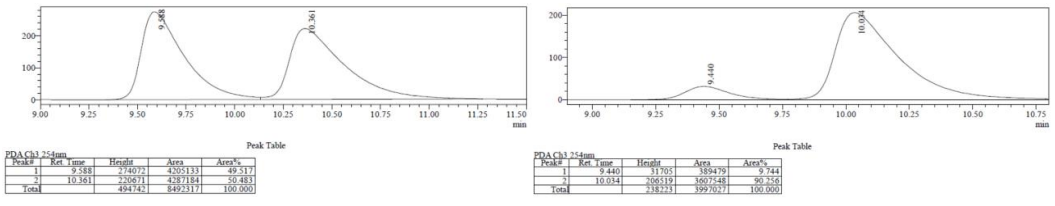


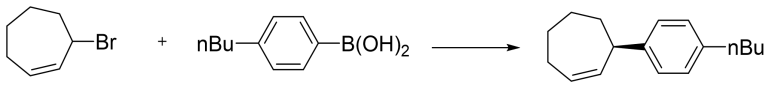
(R)-3-(2-(benzyloxy)phenyl)cyclohept-1-ene (4i): Following general procedure using (2-(benzyloxy)phenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = – 8 (c=2.02 in CH_2Cl_2, 89 % ee). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.44 – 7.38 (m, 2H), 7.36 – 7.25 (m, 1H), 7.22 – 7.12 (m, 1H), 7.00 – 6.91 (m, 1H), 5.94 – 5.83 (m, 2H), 5.83 – 5.75 (m, 1H), 5.12 (s, 1H), 4.13 – 4.02 (m, 2H), 2.32 – 2.20 (m, 2H), 1.99 – 1.89 (m, 1H), 1.86 – 1.74 (m, 3H), 1.73 – 1.61 (m, 1H), 1.53 – 1.43 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5, 137.6, 137.0, 136.4, 131.3, 128.5, 128.2, 127.6, 127.0, 126.8, 121.0, 112.2, 70.1, 40.1, 34.7, 30.3, 28.8, 27.3. **HRMS** (ESI) m/z calcd. for $C_{20}H_{23}O$ $[M+H]^+$: 279.1749, found: 279.1761. **Enantiomeric excess** of 89% was determined by chiral HPLC [chiral column IE; methods: Eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 12 min; minor enantiomer t_R= 15 min].





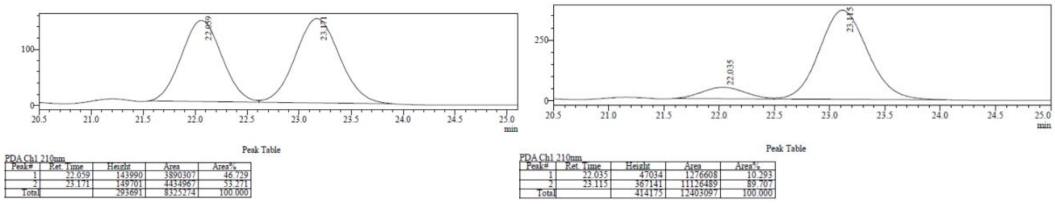
(R)-1-(cyclohept-2-en-1-yl)naphthalene (4j): Following general procedure using p-tolylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 65% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23} = -32.2$ (c=1.17 in CH_2Cl_2, 80 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8 Hz, 1H), 7.88 (dd, *J* = 8, 16 Hz, 1H), 7.73 (dd, *J* = 8, 16 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.47 – 7.43 (m, 2H), 5.94 – 5.90 (m, 1H), 5.87 – 5.83 (m, 1H), 4.31 – 4.29 (m, 1H), 2.37 – 2.33 (m, 2H), 2.08 – 1.90 (m, 3H), 1.89 – 1.85 (m, 1H), 1.81 – 1.76 (m, 1H), 1.58 – 1.52 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 137.4, 134.1, 131.5, 131.1, 128.9, 126.5, 125.6, 125.3, 124.0, 123.9, 42.7, 35.0, 30.8, 28.9, 27.2. **HRMS** (ESI) m/z calcd. for $C_{17}H_{19}$ $[M+H]^+$: 223.1487, found: 223.1485. **Enantiomeric excess** of 80% was determined by chiral HPLC [chiral column IE; methods: Eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 10min; minor enantiomer t_R= 9.4 min].





(R)-3-(4-butylphenyl)cyclohept-1-ene (4l): Following general procedure using p-tolylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG**. The corresponding product was obtained in 71% yield as a colorless oil. **HRMS** (ESI) m/z calcd for $C_{14}H_{19}O$ $[M+H]^+$: 229.1956, found: 229.1950. **Enantiomeric excess**

of 79% was determined by chiral HPLC [chiral column IE; methods: Eluting solvent: hexane, flow speed: 0.2 ml/min; major enantiomer t_R= 23.1 min; minor enantiomer t_R= 22 min].

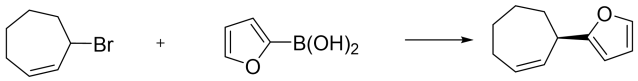


Peak Table

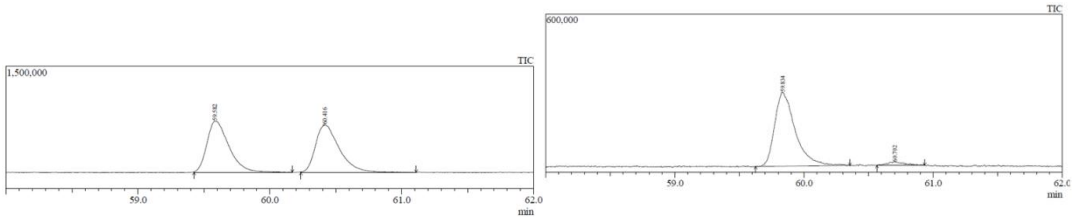
Peak#	Ret. Time	Height	Area	Area%
1	22.059	143990	3890307	46.729
2	23.171	149701	4434967	53.271
Total		293691	8325274	100.000

Peak Table

Peak#	Ret. Time	Height	Area	Area%
1	22.035	47034	1276608	10.293
2	23.115	367141	11126489	89.707
Total		414175	12403097	100.000



(R)-2-(cyclohept-2-en-1-yl)furan (4m): Following general procedure D using furan-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG** at 0°C. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +74.5 (c=3.08 in CH_2Cl_2, 92 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 1H), 6.30 – 6.28 (m, 1H), 6.04 – 6.03 (m, 1H), 5.93 – 5.83 (m, 2H), 3.67 – 3.65 (m, 1H), 2.22 – 2.17 (m, 2H), 1.97 – 1.90 (m, 2H), 1.75 – 1.65 (m, 3H), 1.54 – 1.43 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 140.8, 133.3, 132.5, 109.9, 103.9, 39.9, 32.6, 29.8, 28.6, 26.9. **HRMS** (ESI) m/z calcd. for $C_{11}H_{15}O$ $[M+H]^+$: 163.1123, found: 163.1118. **Enantiomeric excess** of 92% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-110 °C (1 min)-15-160 °C (1 min), major enantiomer t_R= 59.4 min; minor enantiomer t_R= 60.3 min].

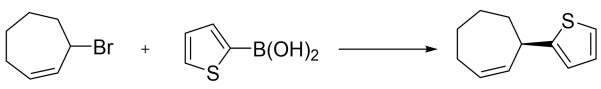


Peak Report TIC

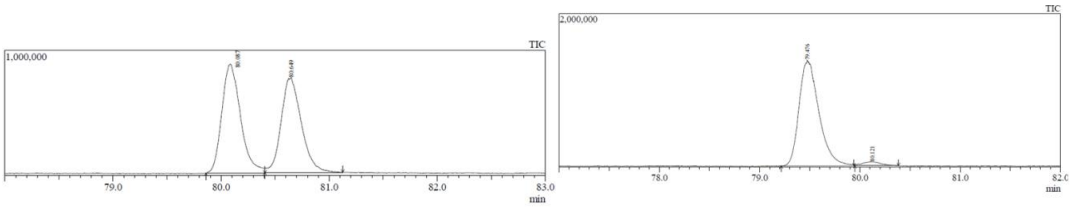
Peak#	R.Time	Height	Area	Area%
1	59.582	720321	8267264	49.52
2	60.416	673268	8429008	50.48
		1393589	16696272	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	59.834	281885	3096267	96.04
2	60.702	13999	127648	3.96
		295884	3223915	100.00



(R)-2-(cyclohept-2-en-1-yl)thiophene (4n): Following general procedure using thiophen-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG** at 0°C. The corresponding product was obtained in 74% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +53.1 (c=3.57 in CH_2Cl_2, 93 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.01 – 5.79 (m, 2H), 3.99 – 3.86 (m, 1H), 2.28 – 2.17 (m, 2H), 2.04 – 1.92 (m, 2H), 1.89 – 1.80 (m, 1H), 1.77 – 1.66 (m, 2H), 1.55 – 1.45 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 136.4, 132.0, 126.6, 122.9, 122.8, 41.7, 36.5, 29.7, 28.7, 26.9. **HRMS** (ESI) m/z calcd. for $C_{11}H_{15}S$ $[M+H]^+$: 179.0894, found: 179.0896. **Enantiomeric excess** of 93% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-133 °C (1 min)-15-160 °C (1 min), major enantiomer t_R= 80.0 min; minor enantiomer t_R= 80.6 min].

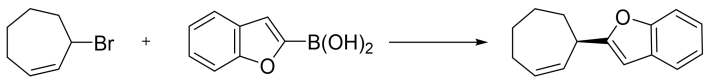


Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	80.087	871655	10498127	51.75
2	80.649	760784	9788677	48.25
		1632439	20286804	100.00

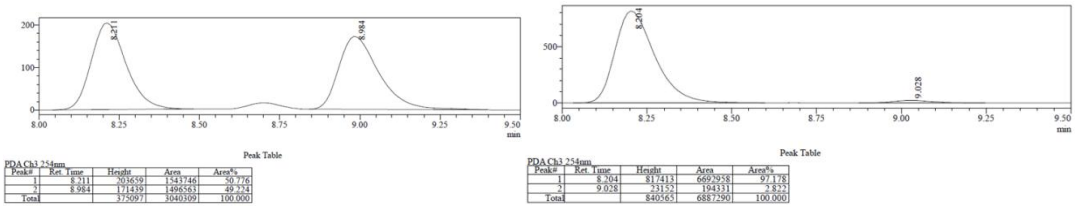
Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	79.476	1381739	18855113	96.61
2	80.121	52011	661361	3.39
		1433750	19516474	100.00



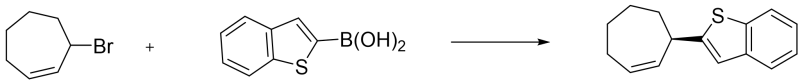
(R)-2-(cyclohept-2-en-1-yl)benzofuran (4o): Following general procedure using benzofuran-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG** at 0°C. The corresponding product was obtained in 83% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +61.5 (c=5.15 in CH_2Cl_2, 94 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 1H), 7.49 – 7.42 (m, 1H), 7.27 – 7.18 (m, 2H), 6.47 (t, J = 0.9 Hz, 1H), 6.04 – 5.94 (m, 2H), 3.87 – 3.78 (m, 1H), 2.35 – 2.19 (m, 2H), 2.13 – 2.04 (m, 1H), 2.03 – 1.86 (m, 2H), 1.84 – 1.67 (m, 2H), 1.60 – 1.45 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.3, 154.8, 133.2, 132.6, 128.9, 123.2, 122.5, 120.4, 110.9, 101.3, 40.4, 32.4, 29.8, 28.7, 26.9. **HRMS** (ESI) m/z calcd. for

$C_{15}H_{17}O[M+H]^+$: 213.1279, found: 213.1284. **Enantiomeric excess** of 94% was determined by chiral HPLC [chiral column IB3; methods: Eluting solvent: hexane, flow speed: 0.8 ml/min; major enantiomer t_R= 8.2 min; minor enantiomer t_R= 9.0 min].

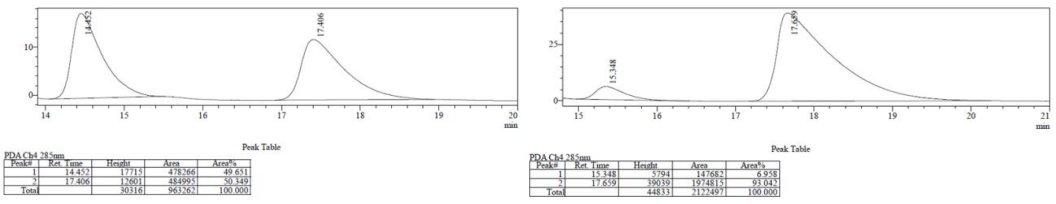


PDA Ch3 254nm					
Peak#	Ret. Time	Height	Area	Area%	
1	8.211	203659	1543746	50.776	
2	8.984	171439	1496563	49.224	
Total		375097	3040309	100.000	

PDA Ch3 254nm					
Peak#	Ret. Time	Height	Area	Area%	
1	8.204	817413	6692958	97.178	
2	9.028	23152	194331	2.822	
Total		840565	6887290	100.000	

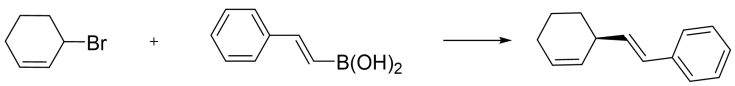


(R)-2-(cyclohep-2-en-1-yl)benzothiophene (4p): Following general procedure using benzo[b]thiophen-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG** at 0°C. The corresponding product was obtained in 81% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +58.4 (c=3.92 in CH_2Cl_2, 86 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.31 (dtd, *J* = 14.9, 7.2, 1.2 Hz, 2H), 7.08 (s, 1H), 5.96 – 5.88 (m, 2H), 3.95 (d, *J* = 9.3 Hz, 1H), 2.32 – 2.18 (m, 2H), 2.12 – 2.02 (m, 1H), 1.99 – 1.89 (m, 2H), 1.83 – 1.68 (m, 2H), 1.65 – 1.49 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.6, 140.1, 139.2, 135.3, 132.6, 124.1, 123.5, 122.9, 122.2, 119.5, 42.4, 35.9, 29.5, 28.7, 26.9. **HRMS** (ESI) m/z calcd. for $C_{15}H_{17}S[M+H]^+$: 229.1051, found: 229.1042. **Enantiomeric excess** of 86% was determined by chiral HPLC [chiral column IE; methods: eluting solvent: hexane, flow speed: 0.8 ml/min; major enantiomer t_R= 17 min; minor enantiomer t_R= 15 min].

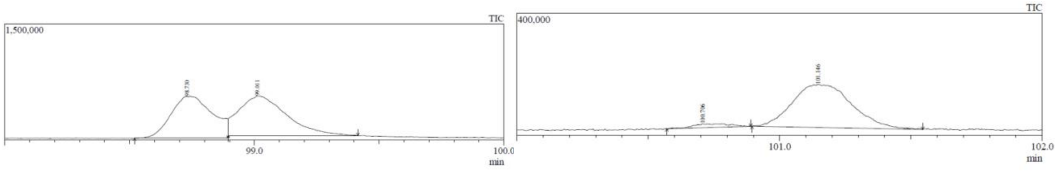


PDA Ch4 285nm					
Peak#	Ret. Time	Height	Area	Area%	
1	14.452	17715	478266	49.651	
2	17.406	12601	484995	50.349	
Total		30316	963262	100.000	

PDA Ch4 285nm					
Peak#	Ret. Time	Height	Area	Area%	
1	15.348	5794	147682	6.958	
2	17.659	39039	1974815	93.042	
Total		44833	2122497	100.000	



(*R*,*E*)-(2-(cyclohex-2-en-1-yl)vinyl)benzene (5a): Following general procedure using (*E*)-styrylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0°C. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +271 (c=1.14 in CH_2Cl_2, 84 % *ee*). [reported -78.8 (c=0.65 in $CHCl_3$) for *S* in 96% *ee*].[26a] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 7.4 Hz, 1H), 5.84 – 5.77 (m, 1H), 5.68 – 5.61 (m, 1H), 2.96 (m, 1H), 2.06 – 1.99 (m, 2H), 1.94 – 1.83 (m, 1H), 1.80 – 1.69 (m, 1H), 1.64 – 1.47 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8, 134.7, 129.5, 129.0, 128.5, 128.1, 126.9, 126.0, 38.7, 29.3, 25.1, 20.5. **HRMS** (ESI) m/z calcd. for $C_{14}H_{17}$ $[M+H]^+$: 185.1330, found: 185.1327. **Enantiomeric excess** of 90% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-135 °C (1 min)-25-160 °C (1 min), major enantiomer t_R= 101.1 min; minor enantiomer t_R= 100.7 min].

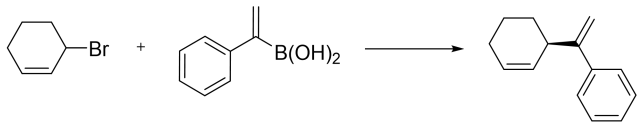


Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	98.730	141.10	6308433	48.03
2	99.011	141.10	6826594	51.97
			13135027	100.00

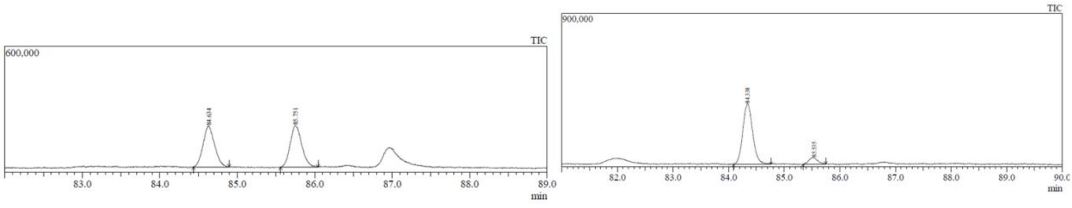
Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	100.706	141.15	114083	4.86
2	101.146	141.10	2233655	95.14
			2347738	100.00



(R)-(1-(cyclohex-2-en-1-yl)vinyl)benzene (5b): Following general procedure using (1-phenylvinyl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0°C. The corresponding product was obtained in 69% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +45 (c=0.5 in CH_2Cl_2, 81 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.29 – 7.21 (m, 1H), 5.90 – 5.81 (m, 1H), 5.76 – 5.66 (m, 1H), 5.30 (d, *J* = 1.4 Hz, 1H), 5.06 (s, 1H), 3.37 (m, 1H), 2.05 – 2.00 (m, 2H), 1.87 – 1.75 (m, 1H), 1.73 – 1.63 (m, 1H), 1.61 – 1.50 (m, 1H), 1.50 – 1.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.5,

142.0, 129.7, 128.3, 128.2, 127.2, 126.6, 113.1, 39.9, 28.4, 25.3, 20.3. **HRMS** (ESI) m/z calcd. for $C_{14}H_{17}$ $[M+H]^+$: 185.1330, found: 185.1331. **Enantiomeric excess** of 83% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-140 °C (1 min)-15-160 °C (1 min), major enantiomer t_R= 84.3 min; minor enantiomer t_R= 85.5 min].

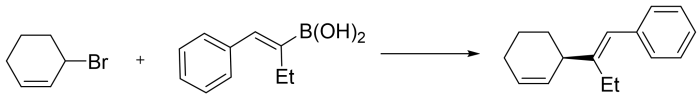


Peak Report TIC

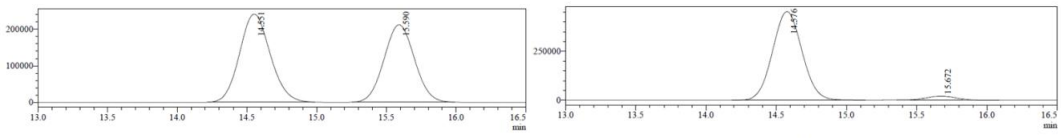
Peak#	R.Time	Area	Area%
1	84.634	2012141	49.24
2	85.751	2073865	50.76
		4086006	100.00

Peak Report TIC

Peak#	R.Time	Area	Area%
1	84.338	4378092	91.41
2	85.535	411418	8.59
		4789510	100.00



(*R*,*E*)-(2-(cyclohex-2-en-1-yl)but-1-en-1-yl)benzene (5c): Following general procedure using (*Z*)-(1-phenylbut-1-en-2-yl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 78% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +35 (c=0.36 in CH_2Cl_2, 91 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34– 7.30 (m, 2H), 7.30– 7.24 (m, 2H), 7.21–7.180 (m, 1H), 6.26 (s, 1H), 5.86 (dt, J = 6.4 Hz, 1H), 5.66 (dd, J = 10 Hz, 1H), 2.96 (m, 1H), 2.47 – 2.42 (m, 1H), 2.21 – 2.15 (m, 1H), 2.08 (m, 2H), 1.93 – 1.89 (m, 1H), 1.79 – 1.76 (m, 1H), 1.63 – 1.56 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6, 138.8, 130.4, 128.5, 128.1, 128.1, 125.8, 125.3, 41.6, 29.0, 25.3, 23.5, 20.8, 13.6. **HRMS** (ESI) m/z calcd for $C_{14}H_{17}$ $[M+H]^+$: 185.1330, found: 185.1331. **Enantiomeric excess** of 91% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.3 ml/min; major enantiomer t_R= 14.6 min; minor enantiomer t_R= 15.6 min].



Peak Table

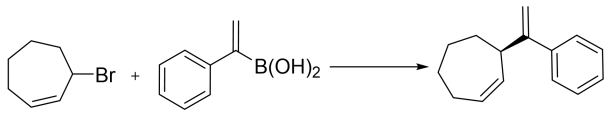
PDA Ch3 247nm

Peak#	Ret. Time	Height	Area	Area%
1	14.551	240765	3693835	53.419
2	15.590	211387	3220190	46.581
Total		452152	6913025	100.000

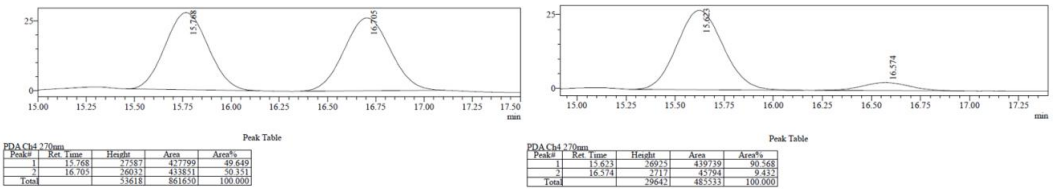
Peak Table

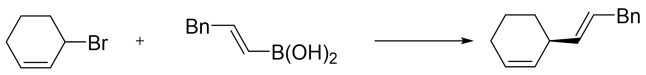
PDA Ch3 247nm

Peak#	Ret. Time	Height	Area	Area%
1	14.576	452114	6609931	95.487
2	15.672	20887	312391	4.513
Total		473001	6922323	100.000



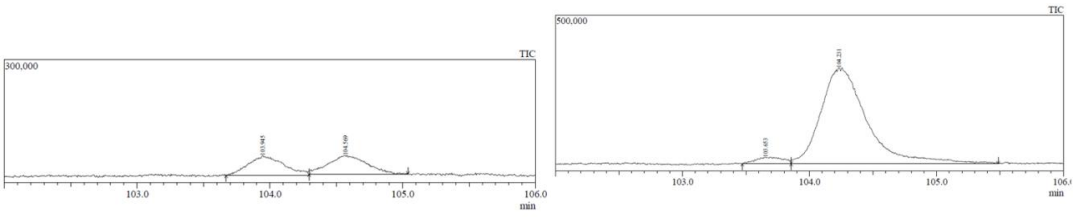
(R)-3-(1-phenylvinyl)cyclohept-1-ene (5d): Following general procedure using (1-phenylvinyl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 75% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +12.7 (c=3.8 in CH_2Cl_2, 81 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 5.86 (dtd, *J* = 7.9, 6.0, 2.1 Hz, 1H), 5.75 (dd, *J* = 11.3, 4.5 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 5.14 (t, *J* = 1.1 Hz, 1H), 3.50 (m, 1H), 2.24 – 2.16 (m, 2H), 1.95 – 1.86 (m, 1H), 1.85 – 1.77 (m, 1H), 1.75 – 1.64 (m, 1H), 1.63 – 1.55 (m, 2H), 1.52 – 1.42 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 147.2, 142.2, 136.2, 131.7, 128.2, 127.2, 126.6, 112.3, 45.3, 32.9, 29.6, 28.6, 27.0. **HRMS** (ESI) m/z calcd. for $C_{15}H_{19}$ $[M+H]^+$: 199.1487, found: 199.1492. **Enantiomeric excess** of 81% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.3 ml/min; major enantiomer t_R= 15.6 min; minor enantiomer t_R= 16.6 min].





(*R*,*E*)-(3-(cyclohex-2-en-1-yl)allyl)benzene (5e): Following general procedure using (*E*)-(3-phenylprop-1-en-1-yl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 67% yield as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23}$ = +148.1 (c=1.32 in CH_2Cl_2, 91 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.20 – 7.18 (m, 3H), 5.73 – 5.69 (m, 1H), 5.59 – 5.54 (m, 2H), 5.76 – 5.66 (m, 1H), 3.36 (d, *J* = 8 Hz, 2H), 2.78 (m, 1H), 1.99 – 1.96 (m, 2H), 1.82 – 1.79 (m, 1H), 1.69 – 1.68 (m, 1H), 1.56 – 1.53 (m, 1H), 1.43 – 1.40 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0,

135.9, 130.1, 128.5, 128.3, 1228.1, 127.5, 125.9, 39.0, 38.2, 29.3, 25.1, 20.6. **HRMS** (ESI) m/z calcd. for $C_{15}H_{19}$ $[M+H]^+$: 199.1487, found: 199.1495. **Enantiomeric excess** of 91% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (30 min), major enantiomer t_R= 104 min; minor enantiomer t_R= 103 min].

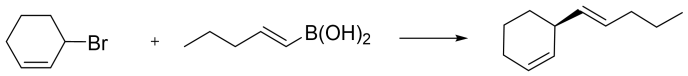


Peak Report TIC

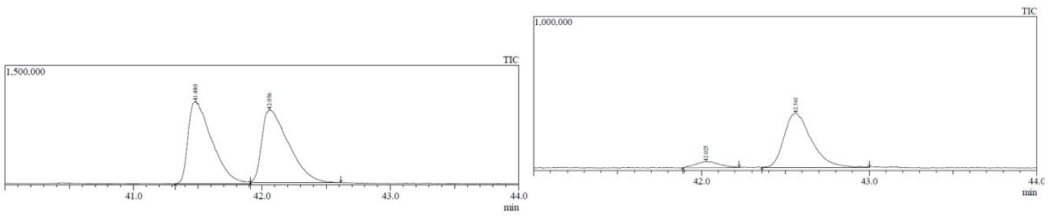
Peak#	R.Time	Height	Area	Area%
1	103.945	47929	869165	48.59
2	104.569	45479	919555	51.41
		93408	1788720	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	103.653	21227	307766	3.84
2	104.231	308153	7714421	96.16
		329380	8022187	100.00



(*S*,*E*)-3-(pent-1-en-1-yl)cyclohex-1-ene (5f): Following general procedure using (*E*)-pent-1-en-1-ylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 45% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +160.1 (c=1.85 in CH_2Cl_2, 82 % *ee*). [lit. +93.6 (c=1.18 in $CHCl_3$) for analogue 98% *ee*].[26b] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.71 (dtd, *J* = 9.7, 3.6, 2.4 Hz, 1H), 5.55 (ddd, *J* = 10.0, 4.7, 2.2 Hz, 1H), 5.46 – 5.30 (m, 2H), 2.77 – 2.67 (m, 1H), 2.02 – 1.91 (m, 4H), 1.83 – 1.72 (m, 1H), 1.73 – 1.61 (m, 1H), 1.59 – 1.47 (m, 1H), 1.44 – 1.30 (m, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.4, 130.6, 129.5, 127.2, 38.3, 34.7, 29.5, 25.1, 22.7, 20.6, 13.6. **HRMS** (ESI) m/z for $C_{14}H_{17}$ $[M+H]^+$: 151.1487, found: 151.1489. **Enantiomeric excess** of 82% was determined by chiral GC-MS [chiral column Rt®-bDEXse (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min), major enantiomer t_R= 42.6 min; minor enantiomer t_R= 42 min].

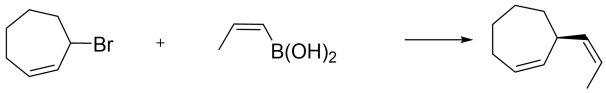


Peak Report TIC

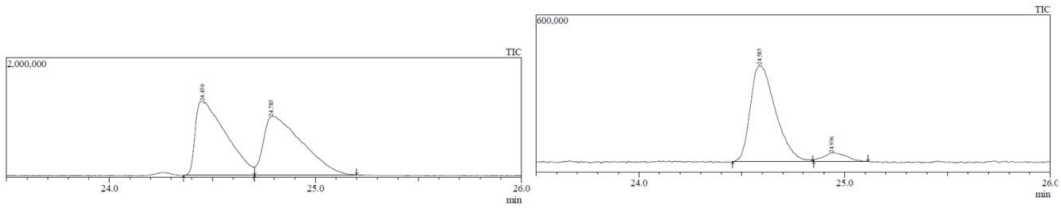
Peak#	R.Time	Height	Area	Area%
1	41.480	1035927	13250798	50.02
2	42.056	919703	13240265	49.98
		1955630	26491063	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	42.025	40394	378457	8.79
2	42.561	350765	3928013	91.21
		391159	4306470	100.00



(*S*,*Z*)-3-(prop-1-en-1-yl)cyclohept-1-ene (5h): Following general procedure using (*Z*)-prop-1-en-1-ylboronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 45% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +45.3 (c=1.05 in CH_2Cl_2, 85 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 10.1, 5.1 Hz, 1H), 5.57 – 5.43 (m, 2H), 5.43 – 5.31 (m, 1H), 3.23 (m, 1H), 2.21 – 2.09 (m, 2H), 2.01 – 1.90 (m, 1H), 1.74 – 1.64 (m, 2H), 1.62 (d, *J* = 6.6 Hz, 3H), 1.58 (m, 1H), 1.47 – 1.31 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.1, 135.9, 131.3, 122.1, 38.1, 34.2, 30.3, 28.9, 27.1, 12.8. **HRMS** (ESI) m/z calcd. for $C_{10}H_{17}[M+H]^+$: 137.1330, found: 137.1324. **Enantiomeric excess** of 85% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-100 °C (1 min)-15-160 °C (1 min), major enantiomer t_R= 24.5 min; minor enantiomer t_R= 24.9 min].

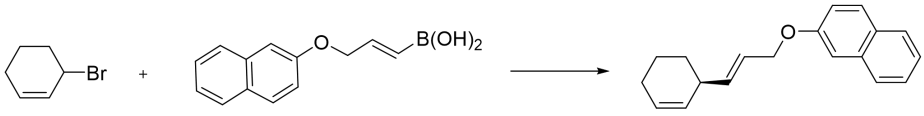


Peak Report TIC

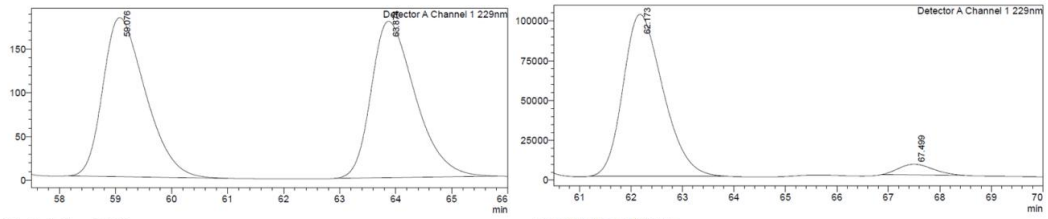
Peak#	R.Time	Height	Area	Area%
1	24.450	1243232	12834626	50.08
2	24.785	979826	12793989	49.92
		2223058	25628615	100.00

Peak Report TIC

Peak#	R.Time	Height	Area	Area%
1	24.585	369756	3130511	92.49
2	24.936	33583	254321	7.51
		403339	3384832	100.00



(*R*,*E*)-2-((3-(cyclohex-2-en-1-yl)allyl)oxy)naphthalene (5i): Following general procedure using (*E*)-(3-(naphthalen-2-yloxy)prop-1-en-1-yl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 62% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +127.3 (c=1.45 in CH_2Cl_2, 89 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 16.9, 8.1 Hz, 3H), 7.49 – 7.41 (m, 1H), 7.38 – 7.29 (m, 1H), 7.21 – 7.12 (m, 2H), 5.91 – 5.83 (m, 1H), 5.82 – 5.73 (m, 2H), 5.62 (dd, *J* = 10.1, 2.5 Hz, 1H), 4.62 (d, *J* = 5.7 Hz, 2H), 2.89 (m, 1H), 2.04 – 1.98 (m, 2H), 1.90 – 1.81 (m, 1H), 1.73 (m, 1H), 1.63 – 1.53 (m, 1H), 1.47 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.7, 139.2, 134.6, 129.4, 129.2, 129.0, 128.2, 127.6, 126.7, 126.3, 124.1, 123.6, 119.1, 107.0, 68.9, 38.1, 28.9, 25.1, 20.5. **HRMS** (ESI) m/z calcd. for $C_{19}H_{21}O$ $[M]^+$: 265.1592, found: 265.1598. **Enantiomeric excess** of 89% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 62 min; minor enantiomer t_R= 67 min].

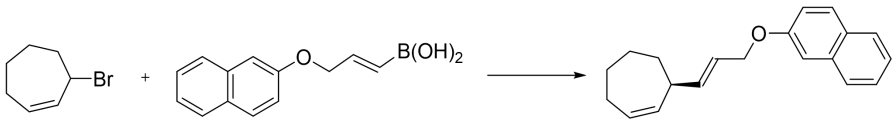


Detector A Channel 1 229nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	59.076	9573539	181509	50.429	49.574
2	63.874	9738196	178421	49.571	50.426
Total		19311735	359930	100.000	100.000

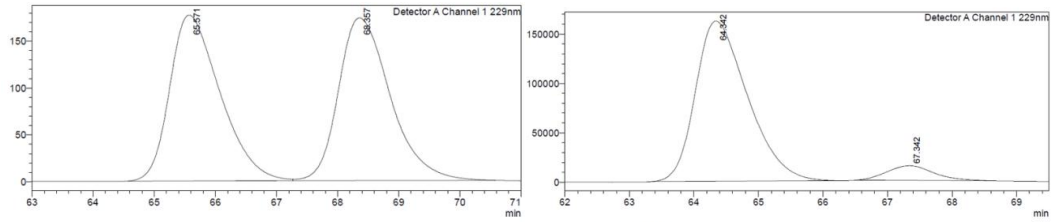
Detector A Channel 1 229nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	62.173	5467377	101497	93.828	94.682
2	67.499	307101	6677	6.172	5.318
Total		5774478	108173	100.000	100.000



(*R*,*E*)-2-((3-(cyclohept-2-en-1-yl)allyl)oxy)naphthalene (5j): Following general procedure using (*E*)-(3-(naphthalen-2-yloxy)prop-1-en-1-yl)boronic acid, catalyzed by 8 mol% $Cu(MeCN)_4PF_6$ and 10 mol% **CG** at 0 °C. The corresponding product was obtained in 70% yield as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +33.2 (c=1.01 in CH_2Cl_2, 85 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.67 (m, 3H), 7.46 – 7.39 (m, 1H), 7.37 – 7.29 (m, 1H), 7.20 – 7.13 (m, 2H), 5.95 (dd, *J* = 15.5, 7.4 Hz, 1H), 5.85 – 5.74 (m, 2H), 5.64 (dd, *J* = 11.0, 4.5 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 2H), 3.05 (m, 1H), 2.19 – 2.09 (m, 2H), 1.96 – 1.86 (m, 1H), 1.77 – 1.70 (m, 1H), 1.67 – 1.57

(m, 2H), 1.53 – 1.42 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.7, 139.4, 134.7, 134.5, 132.0, 129.3, 129.0, 127.6, 126.7, 126.3, 123.6, 123.5, 119.1, 107.0, 68.9, 42.9, 33.5, 29.5, 28.7, 27.0. **HRMS** (ESI) m/z calcd. for $C_{20}H_{23}O$ $[M+H]^+$: 279.1749, found: 279.1738. **Enantiomeric excess** of 85% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 64 min; minor enantiomer t_R= 67 min].

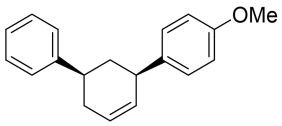


Detector A Channel 1 229nm

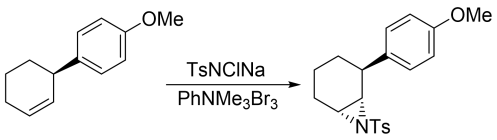
Peak#	Ret. Time	Area	Height	Height%	Area%
1	65.571	10109536	176645	50.496	49.763
2	68.357	10205988	173177	49.504	50.237
Total		20315523	349822	100.000	100.000

Detector A Channel 1 229nm

Peak#	Ret. Time	Area	Height	Height%	Area%
1	64.342	9092836	162234	91.722	92.544
2	67.342	732578	14642	8.278	7.456
Total		9825414	176877	100.000	100.000

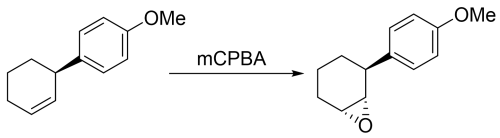


(*R,R*)-4-methoxy-1',2',3',4'-tetrahydro-1,1':3',1''-terphenyl (7): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 7H), 7.00 – 6.92 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.00 – 5.93 (m, 1H), 5.78 (d, *J* = 9.9 Hz, 1H), 4.14 – 4.05 (m, 1H), 3.82 (s, 3H), 3.11 – 2.99 (m, 1H), 2.38 (dd, *J* = 14.7, 4.3 Hz, 1H), 2.33 – 2.12 (m, 2H), 1.66 (dd, *J* = 23.7, 12.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.0, 147.0, 134.3, 130.9, 128.4, 127.6, 127.5, 127.1, 126.9, 126.0, 120.7, 110.3, 55.4, 41.1, 38.0, 36.5, 34.0. **HRMS** (ESI) m/z calcd. for $C_{19}H_{24}O$ $[M+H]^+$: 264.1514, found: 264.1510. **Enantiomeric excess** was determined by chiral HPLC [chiral column IB3; method: eluting solvent: hexane, flow speed: 0.5 ml/min; (*R,R*)-*cis*-**7**: major enantiomer t_R= 18.4 min; minor enantiomer t_R= 20.4 min. (*R,S*)-*trans*-**7**: major enantiomer t_R= 16.4 min; minor enantiomer t_R= 15.6 min].



(*1S,2S,6R*)-2-(4-methoxyphenyl)-7-tosyl-7-azabicyclo[4.1.0]heptane (8): Under N_2 atmosphere, olefin **3d** (37.0 mg, 0.2 mmol) and chloramine T trihydrate (84 mg,

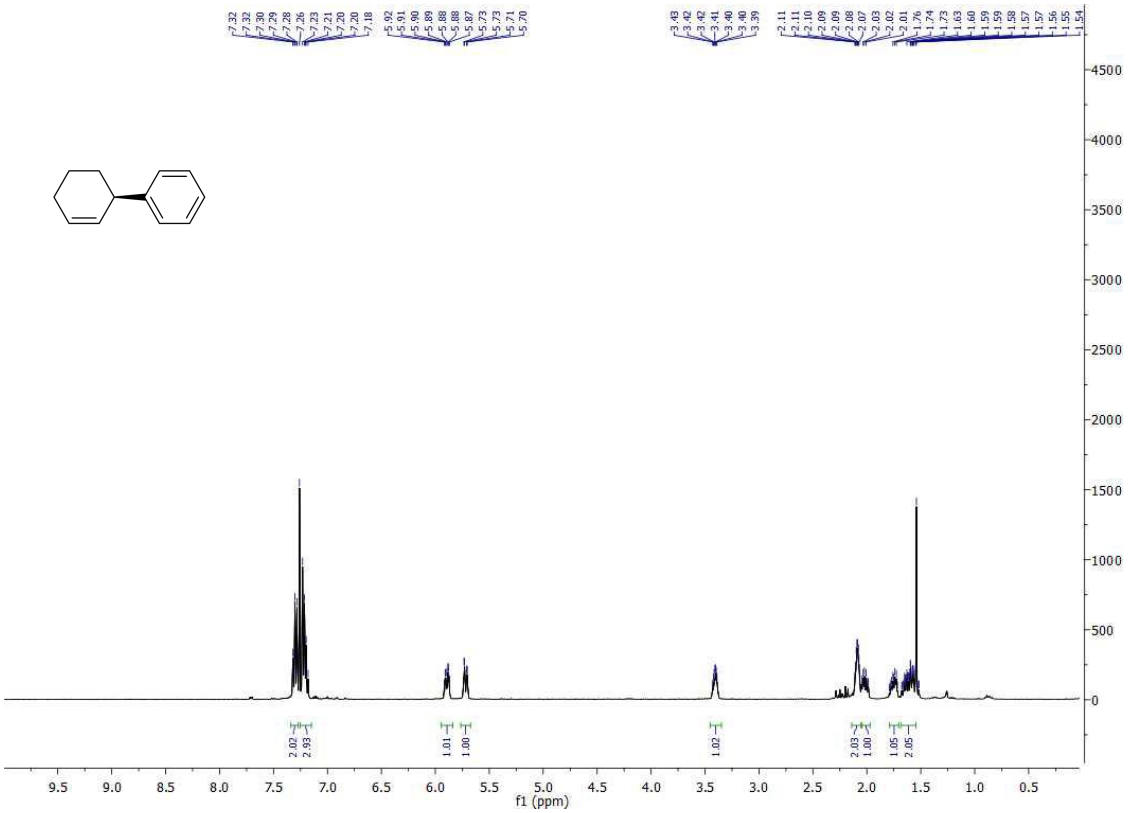
0.3 mmol) were dissolved in acetonitrile, followed by addition of trimethylphenylammonium tribromide (7 mg, 0.01 mmol). The mixture was then stirred at ambient temperature and monitored by TLC for conversion. Upon full conversion, the mixture was filtered through celite and wash with DCM. The filtrate was concentrated under reduced pressure and then loaded on to silica gel flash column chromatography to get pure product **8** (57mg, 80% yield). **Opt. Rot**.: $[\alpha]_{589}^{23}$ = −2.66 (c=1.13 in CH_2Cl_2, 87 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.18 – 3.12 (m, 1H), 3.01 (d, *J* = 6.9 Hz, 1H), 2.98 – 2.90 (m, 1H), 2.45 (s, 3H), 2.03 – 1.91 (m, 1H), 1.82 – 1.71 (m, 2H), 1.47 – 1.32 (m, 2H), 1.30 – 1.15 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.3, 144.2, 136.3, 135.7, 129.7, 128.4, 127.7, 114.0, 55.3, 44.4, 40.5, 39.1, 29.6, 23.0, 21.6, 17.2. **HRMS** (ESI) m/z calcd. for $C_{20}H_{24}O_3NS$ $[M+H]^+$: 358.1477, found: 358.1481. **Enantiomeric excess** was determined by chiral HPLC [chiral column IA3; methods: eluting solvent: 5% IPA/hexane, flow speed: 1 ml/min; major enantiomer t_R= 20.9 min; minor enantiomer t_R= 24.9 min].



(*1S,2S,6R*)-2-(4-methoxyphenyl)-7-oxabicyclo[4.1.0]heptane (9): Under N_2 atmosphere, to a solution of olefin **3d** (37.0 mg, 0.2 mmol) in DCM was added mCPBA (64 mg, 0.3 mmol). The mixture was stirred overnight and monitored by TCL. Upon finish, it was concentrated and purified by silica gel flash column chromatography to get the product **9** (30 mg, 75% yield). **Opt. Rot**.: $[\alpha]_{589}^{23}$ = + 6.1 (c=2.05 in CH_2Cl_2, 88 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H), 6.91 – 6.83 (m, 2H), 3.80 (s, 3H), 3.31 – 3.28 (m, 1H), 3.16 (d, *J* = 3.7 Hz, 1H), 3.10 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.14 (dt, *J* = 15.0, 4.7 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.46 – 1.36 (m, 2H), 1.30 – 1.19 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2, 136.4, 128.8, 114.0, 56.4, 55.3, 52.8, 40.4, 29.9, 24.6, 16.9. **HRMS** (ESI) m/z calcd. for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1228, found: 205.1229. **Enantiomeric excess** was determined by chiral HPLC [chiral column ODH; methods: eluting

solvent: 0.5% IPA/hexane, flow speed: 0.3 ml/min; major enantiomer t_R= 12.8 min; minor enantiomer t_R= 13.8 min].

^{1}H NMR:



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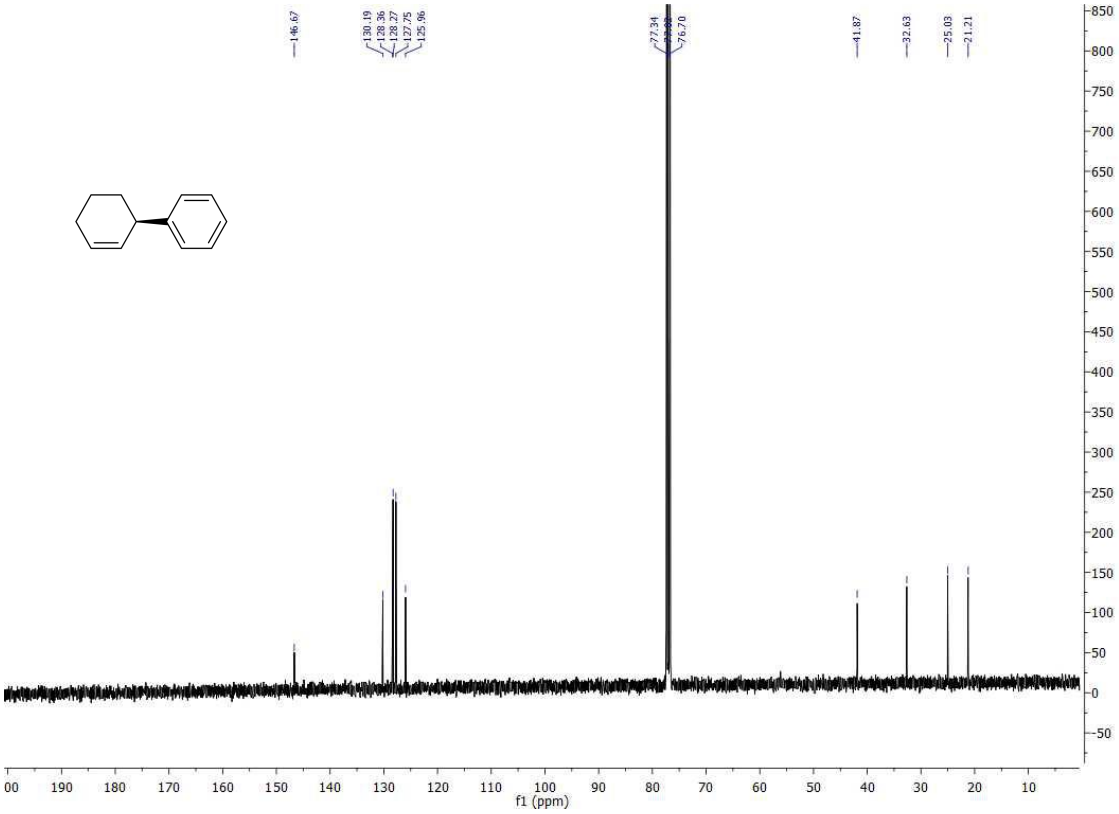

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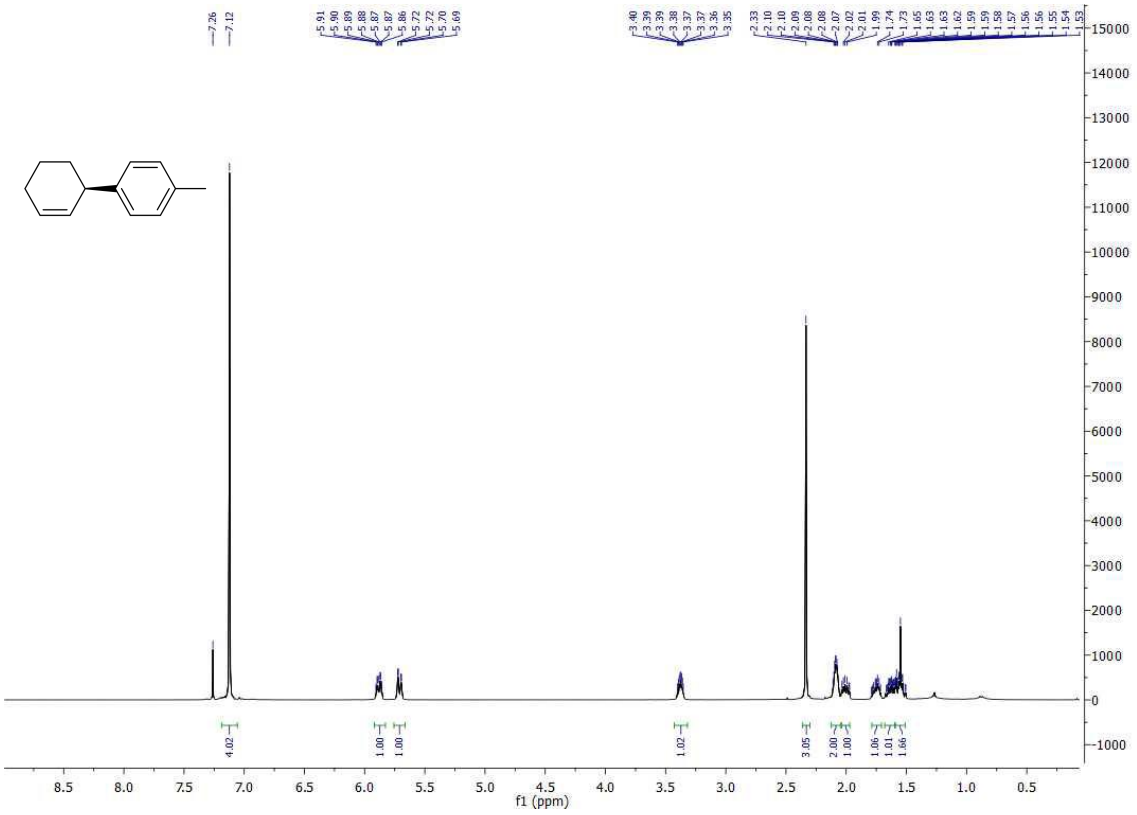

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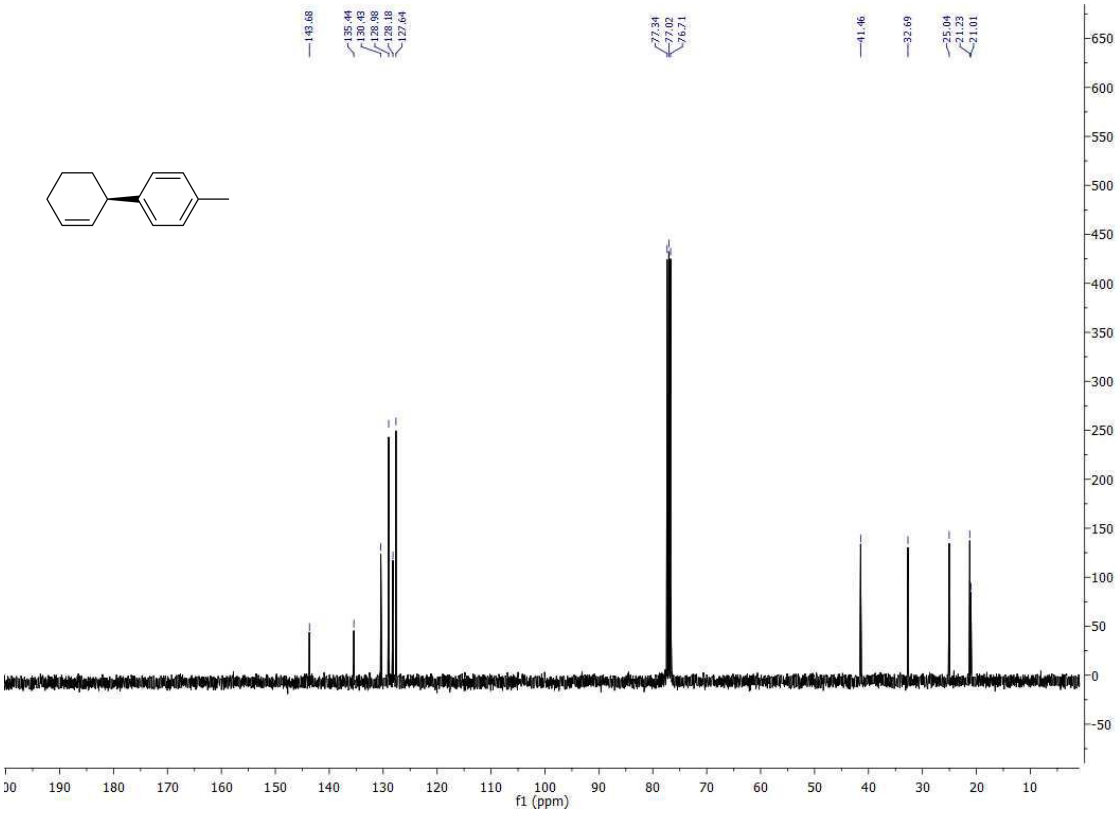

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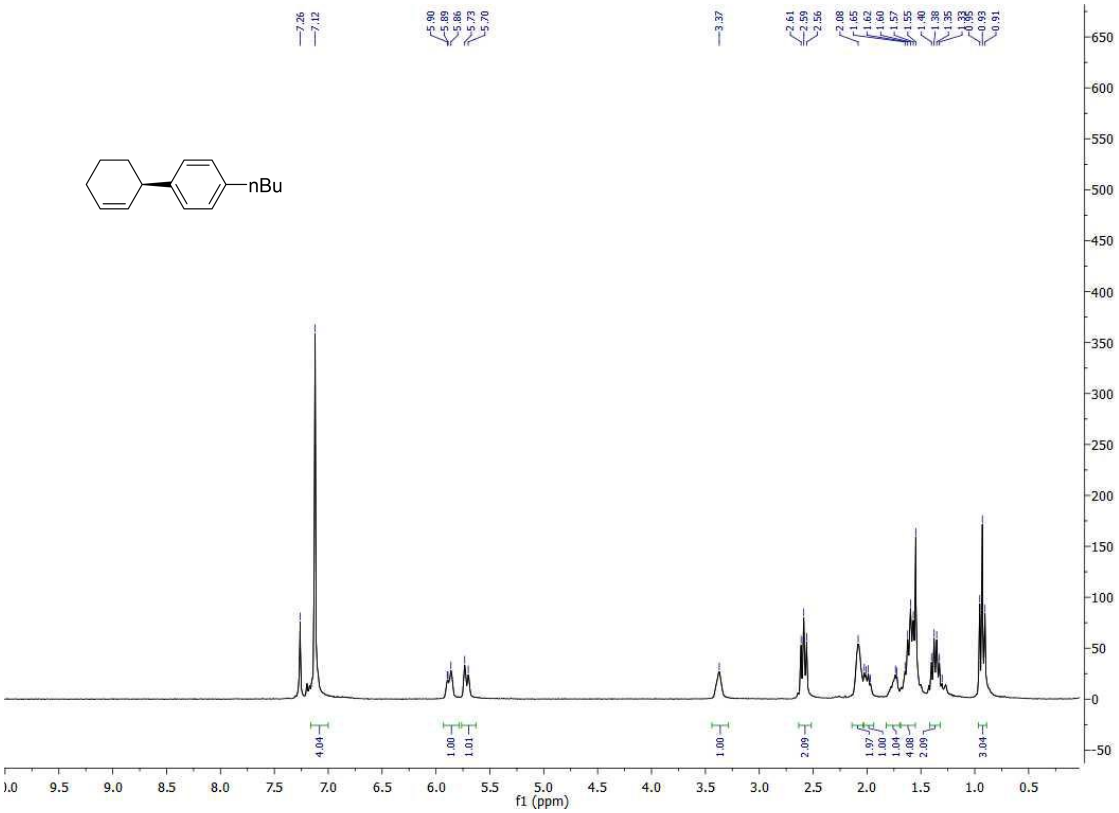

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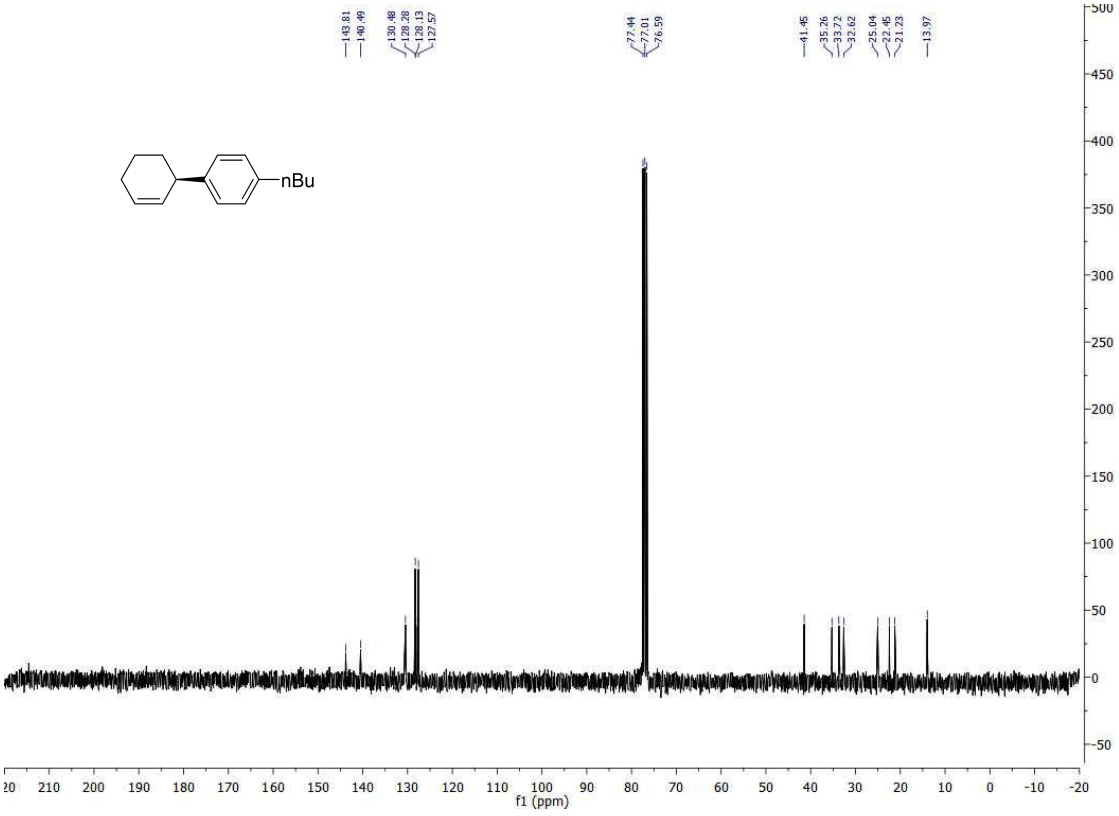

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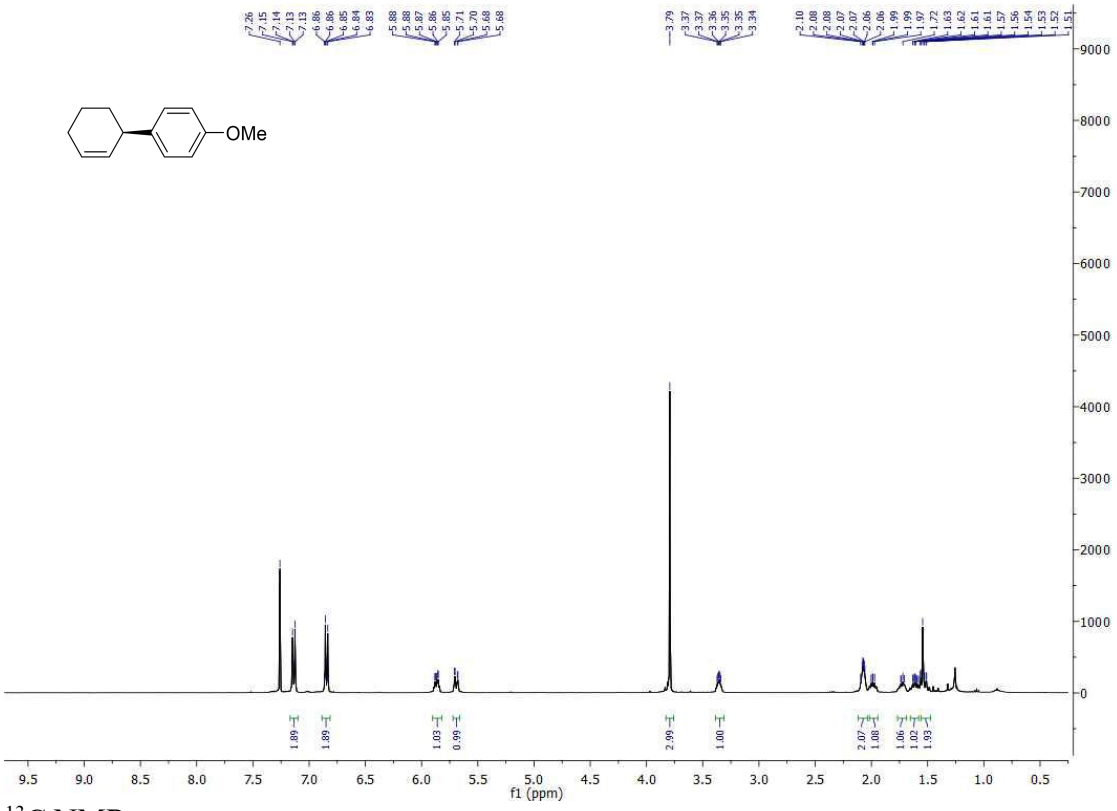

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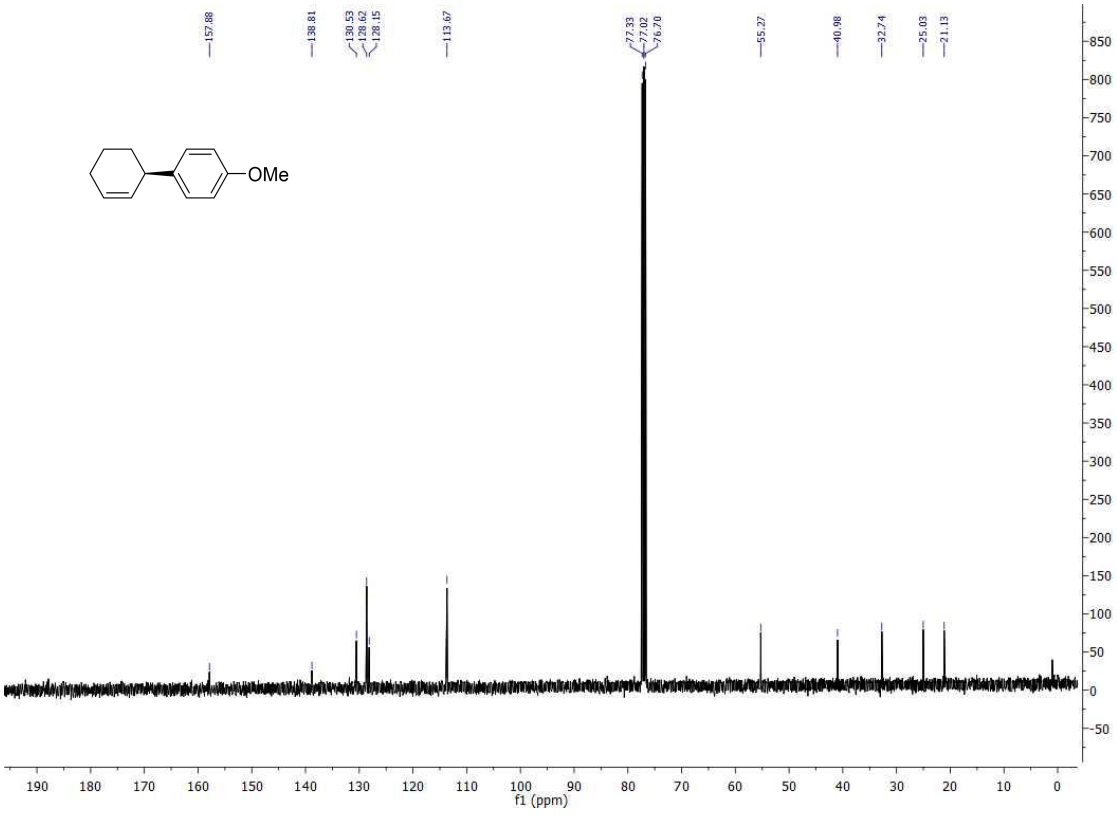

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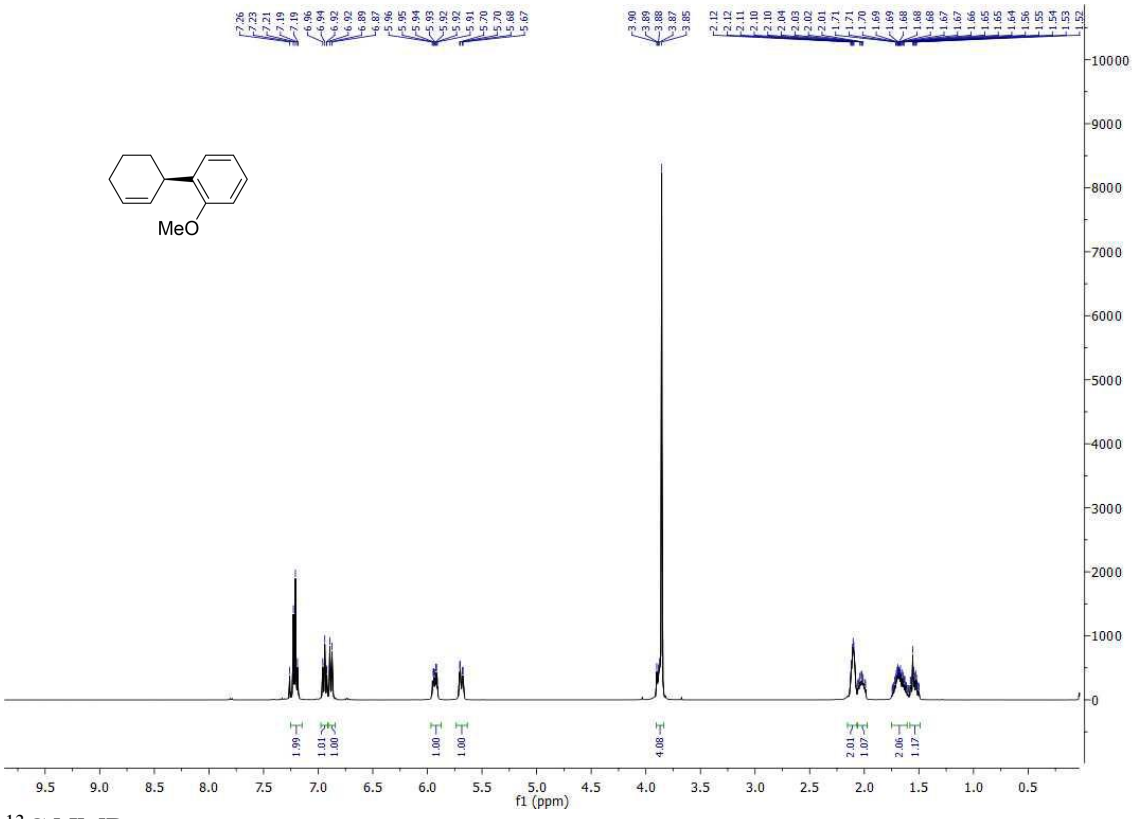

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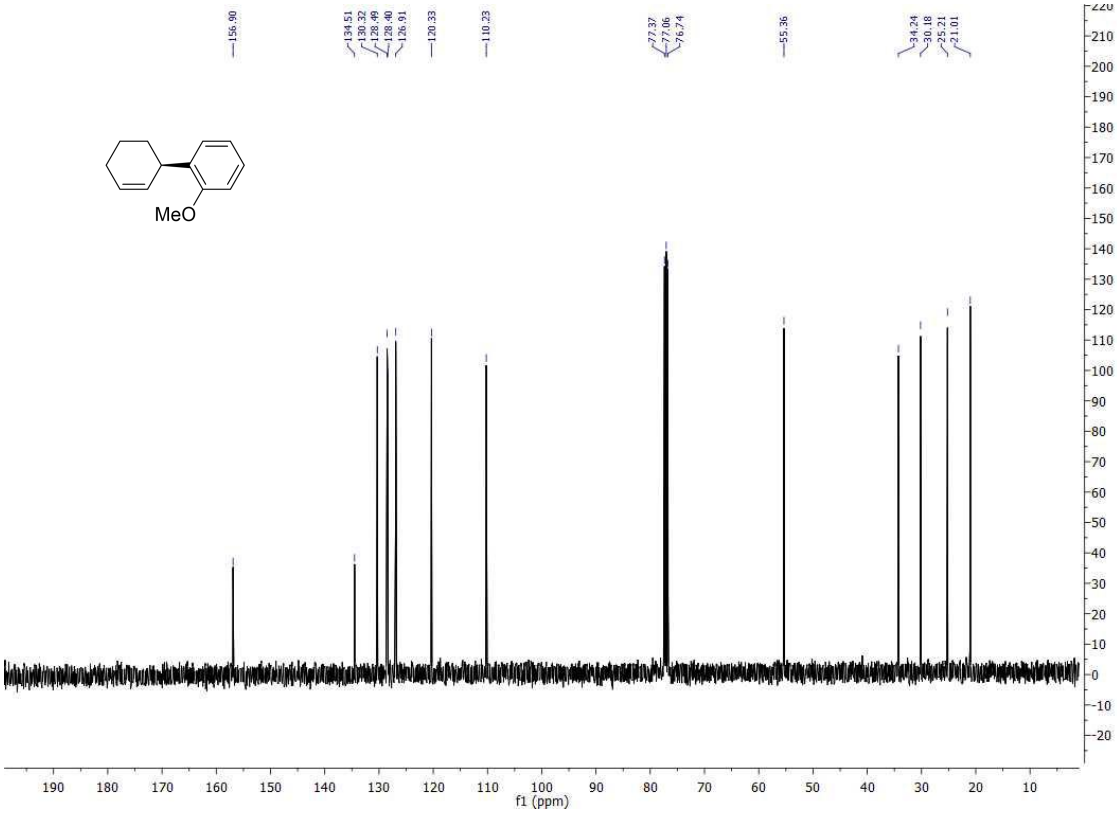

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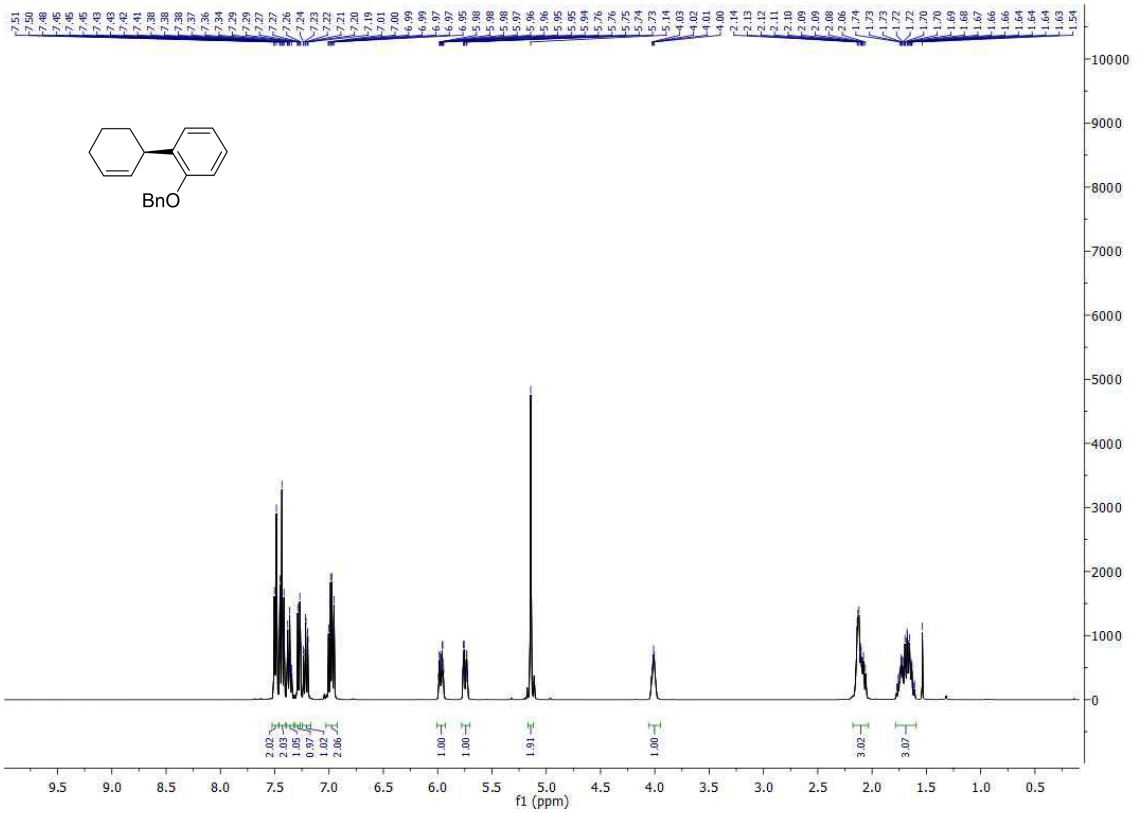

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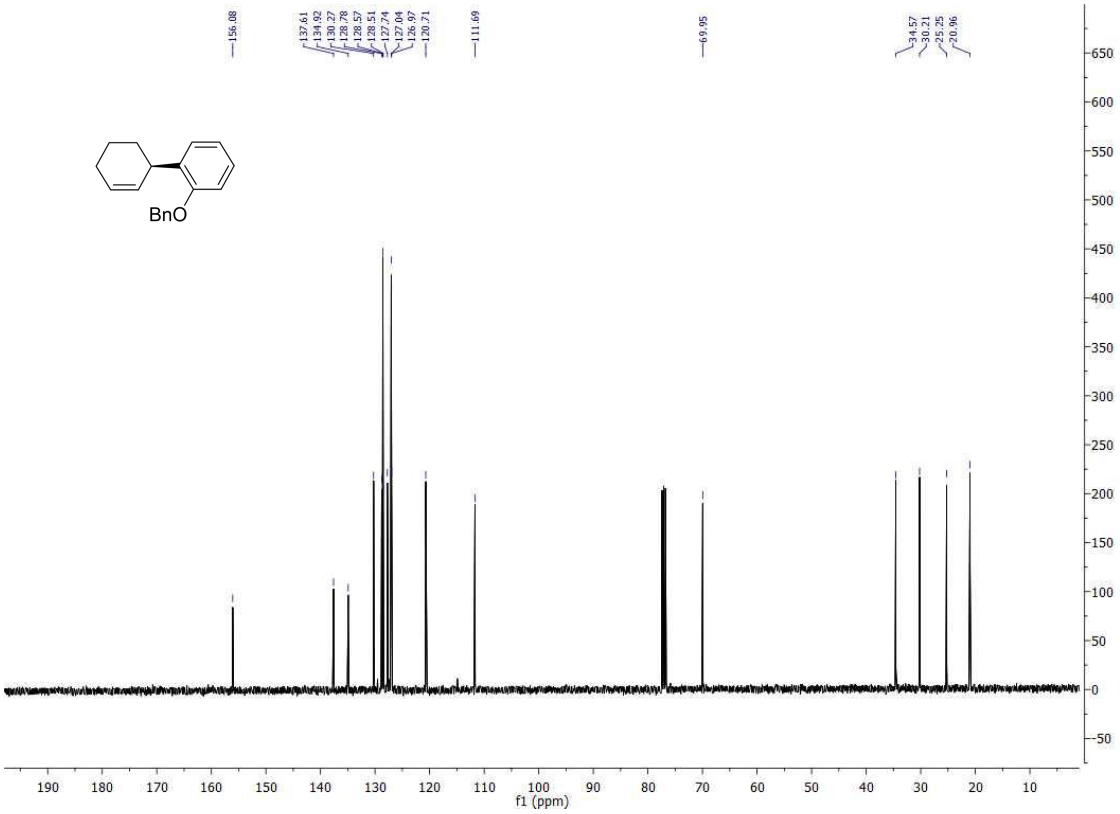

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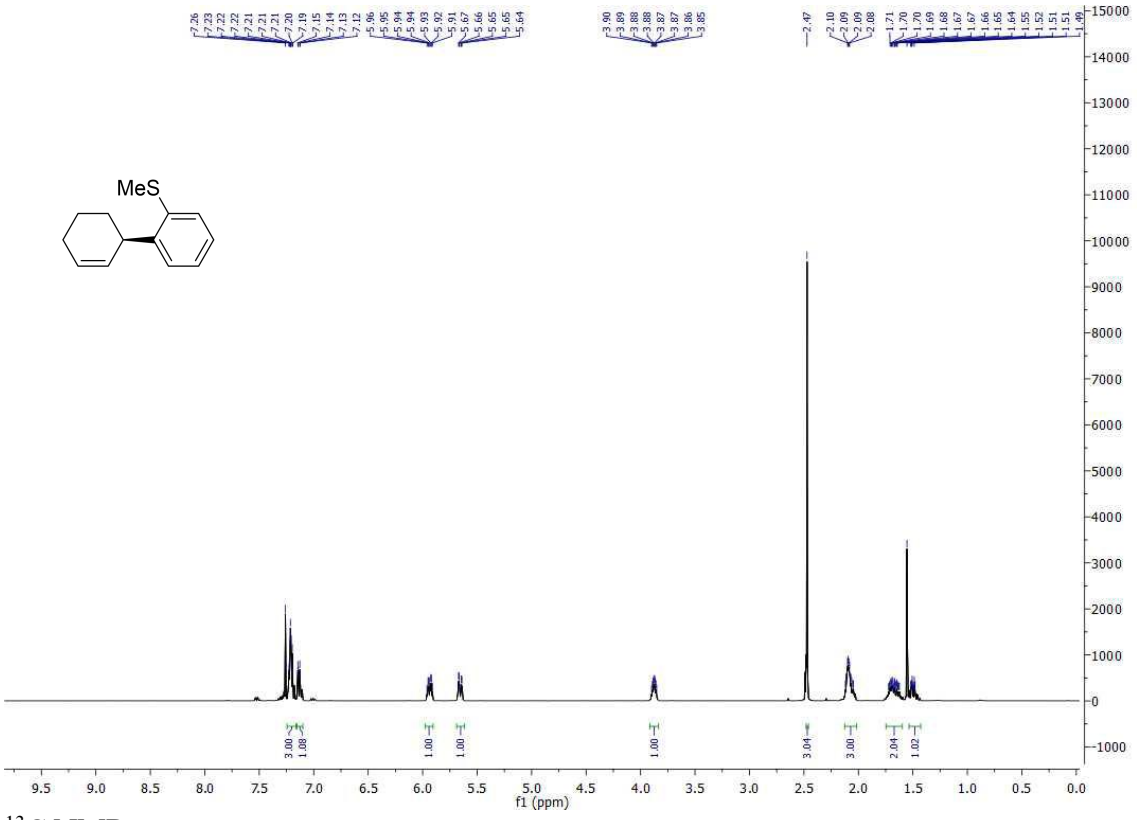

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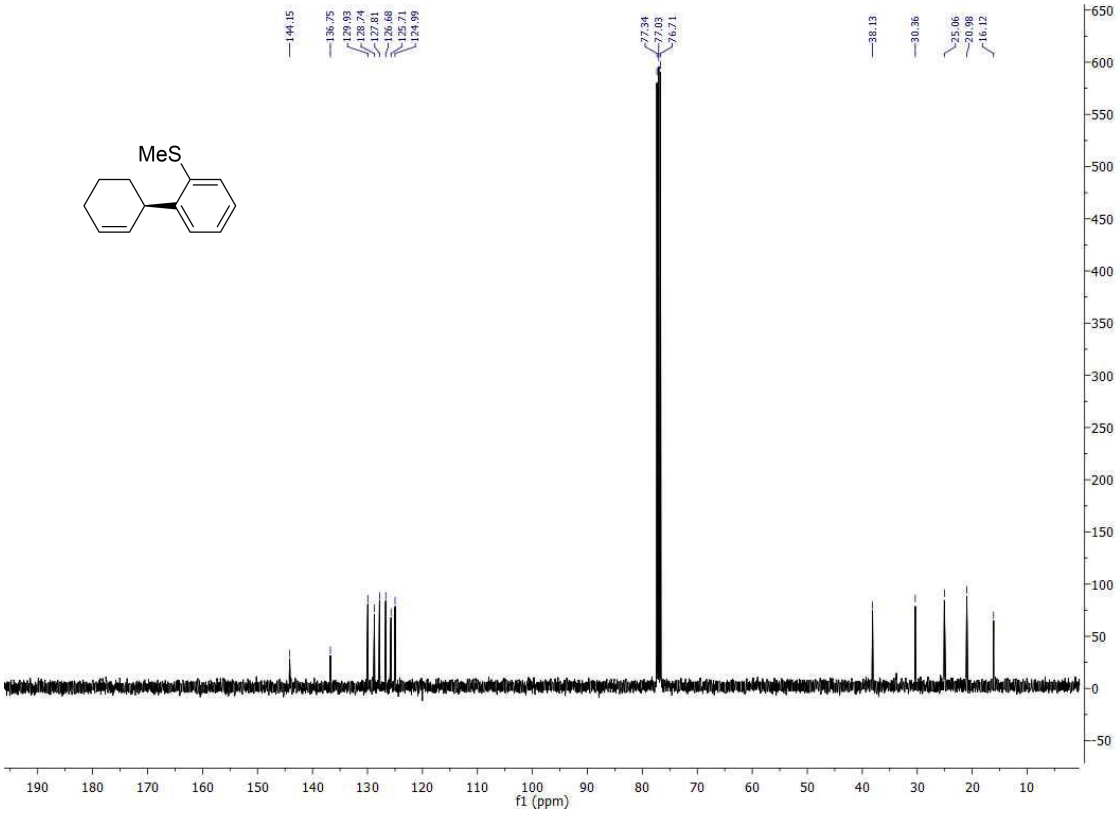

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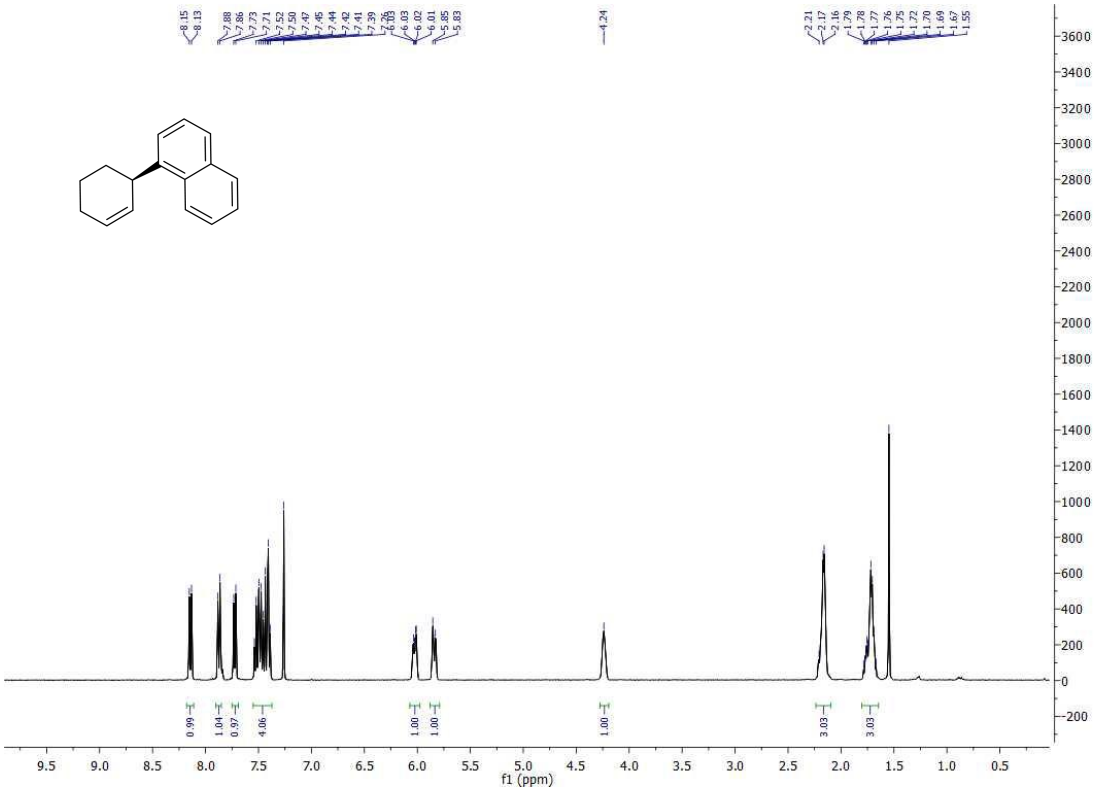

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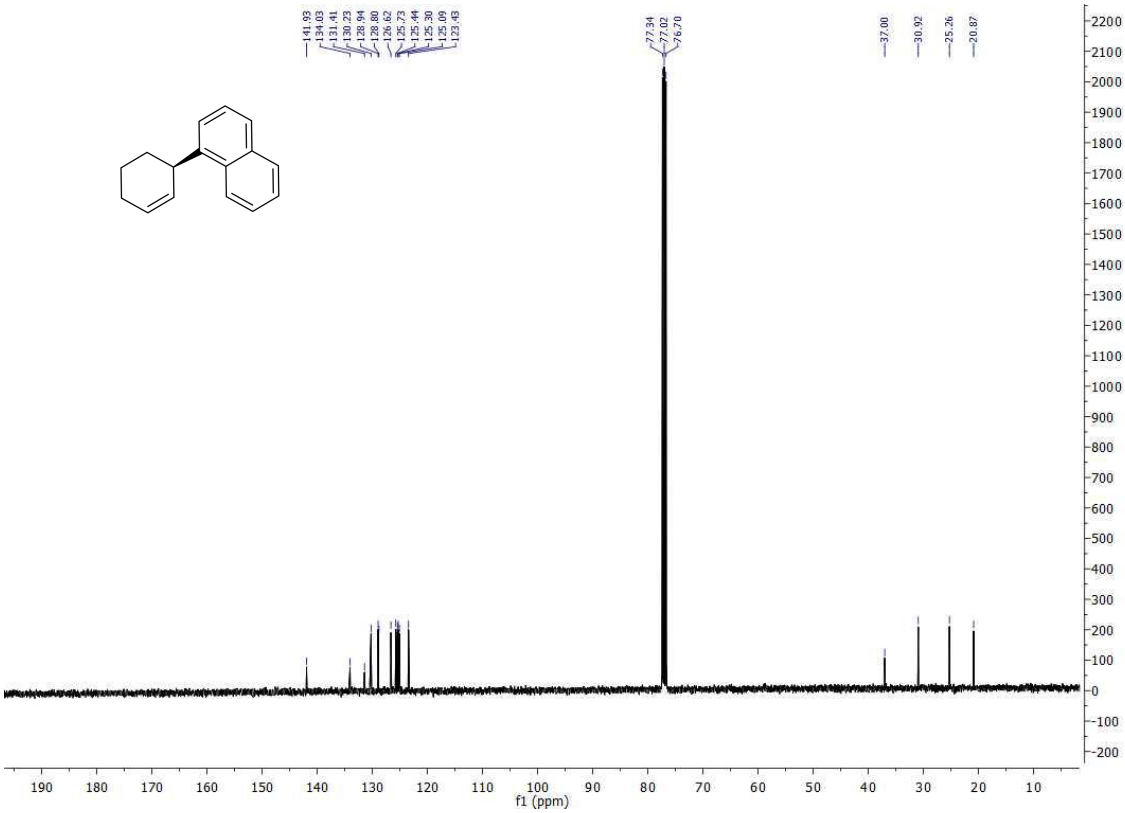

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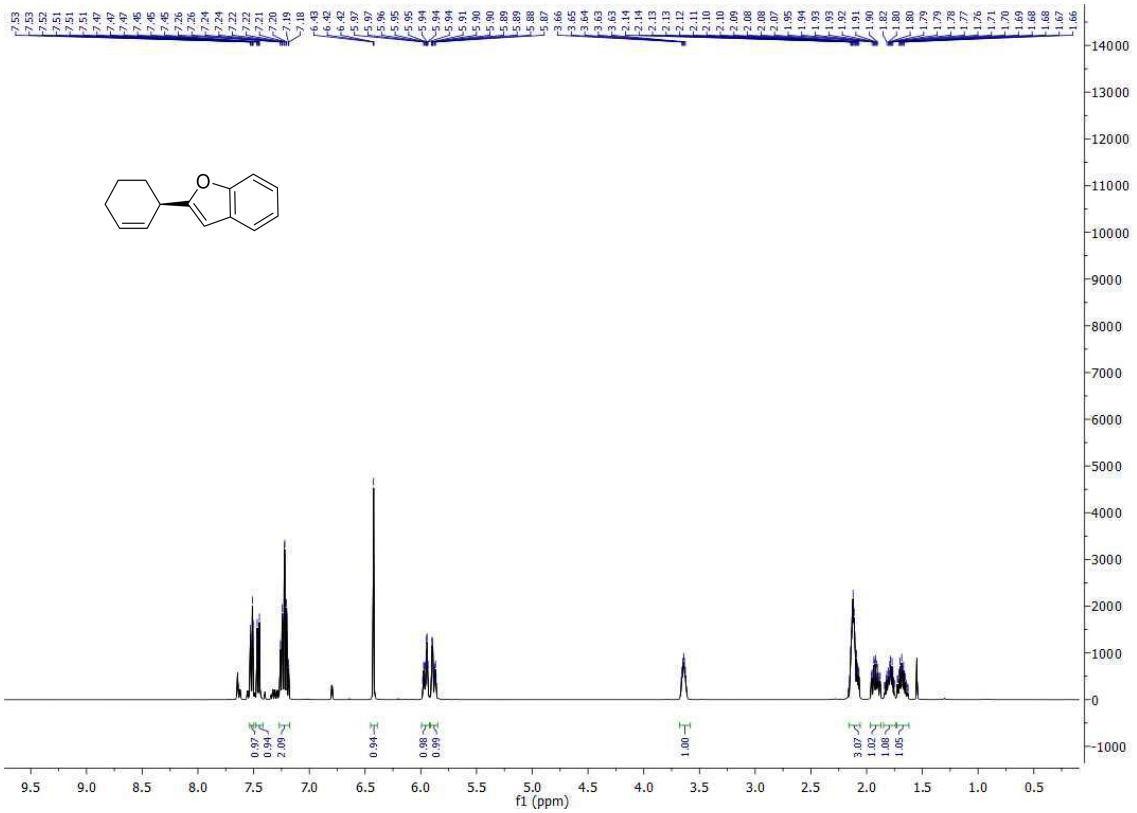

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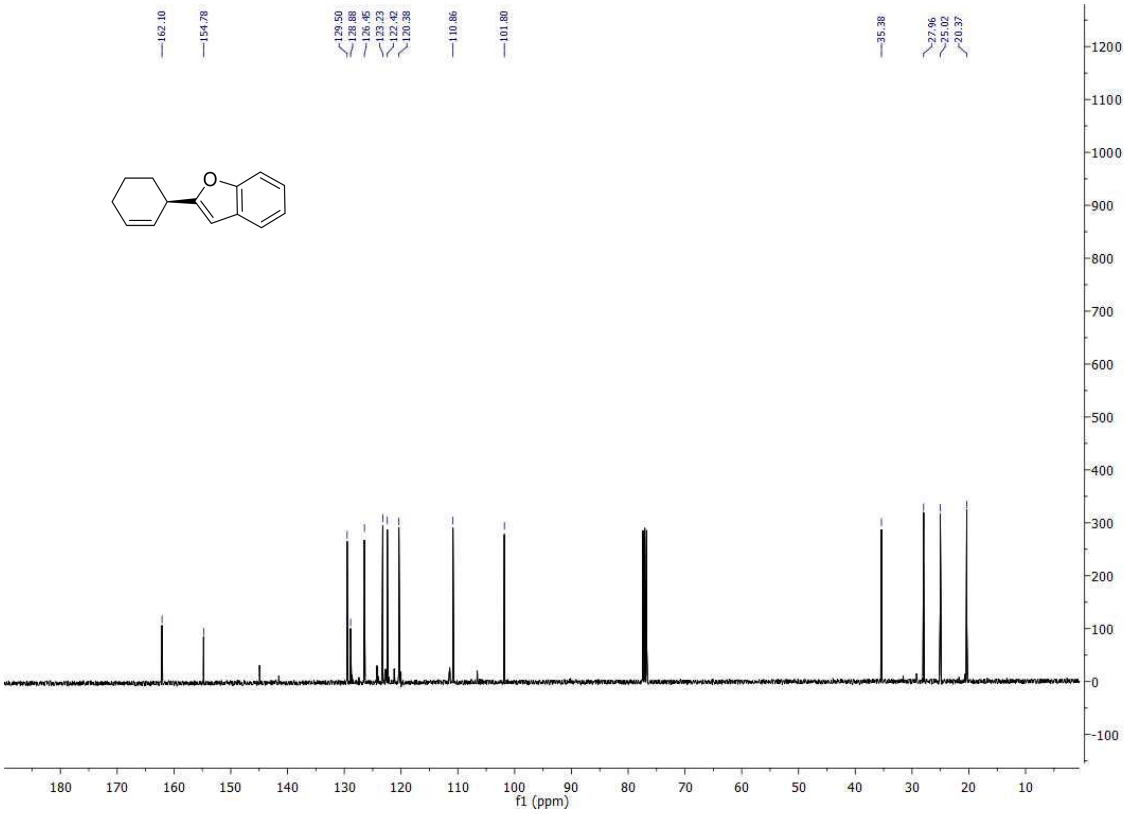

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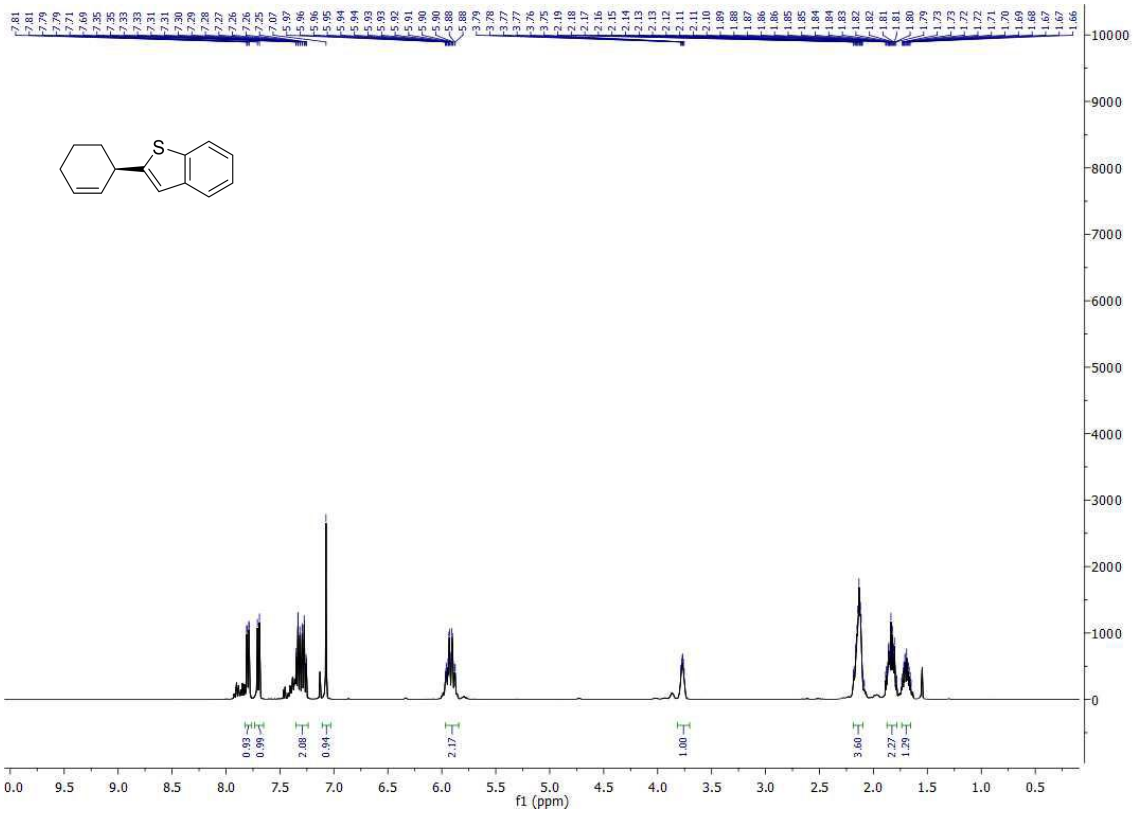

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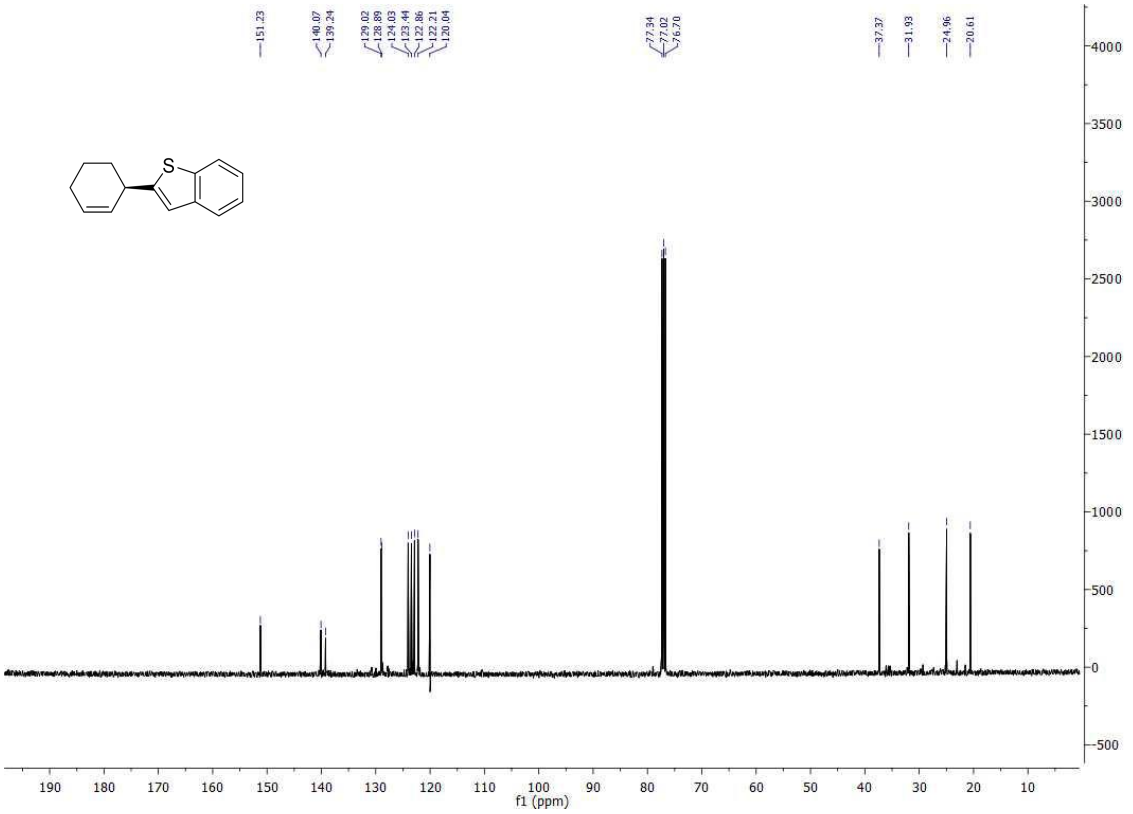

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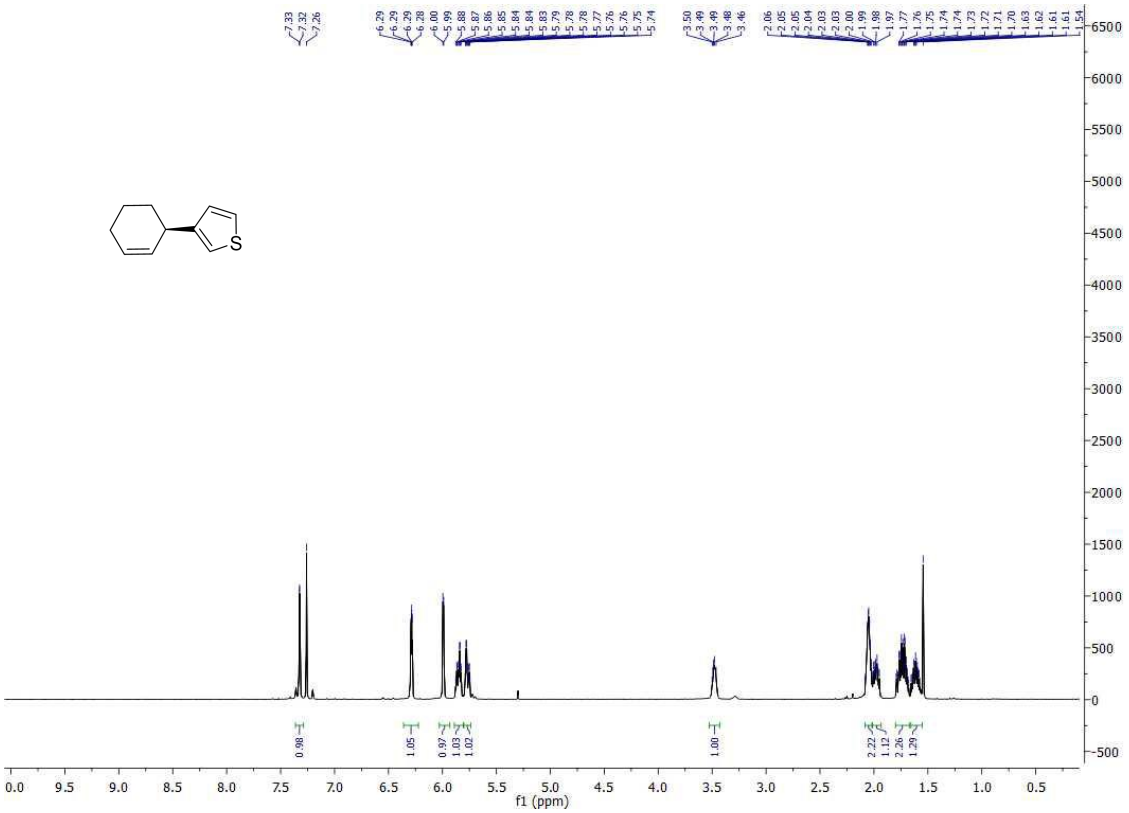

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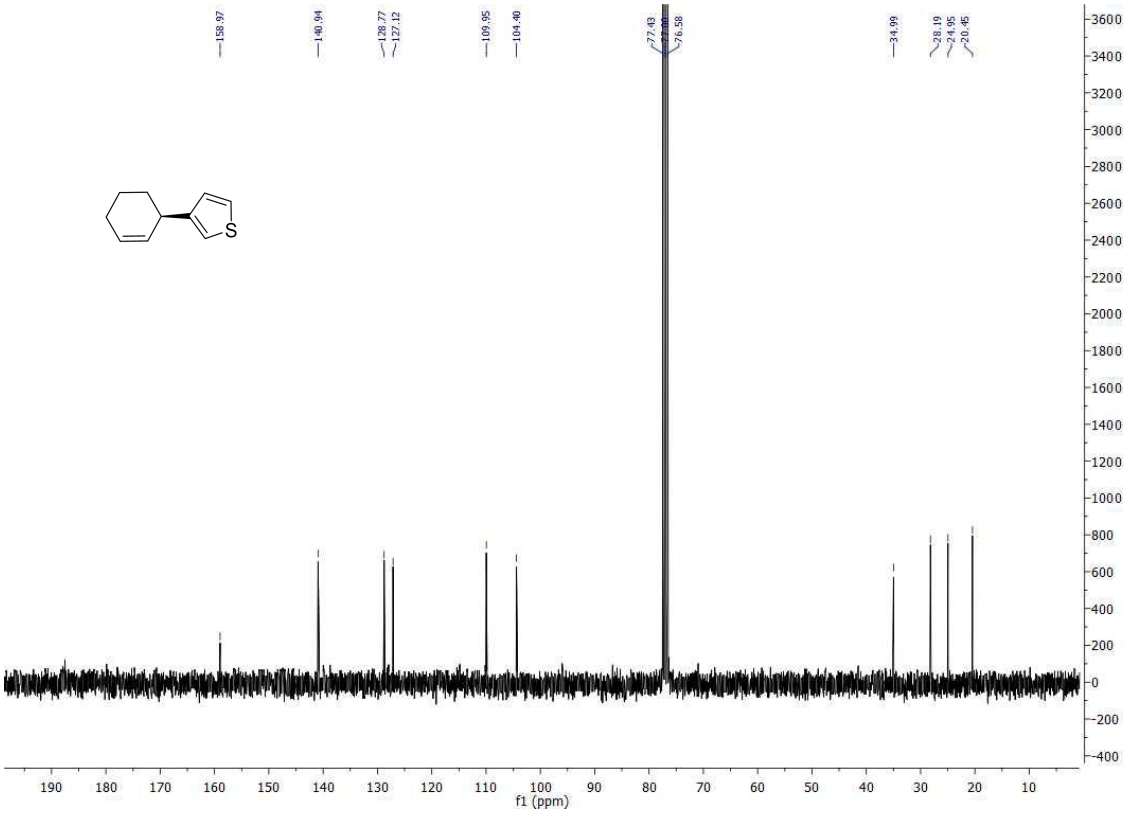

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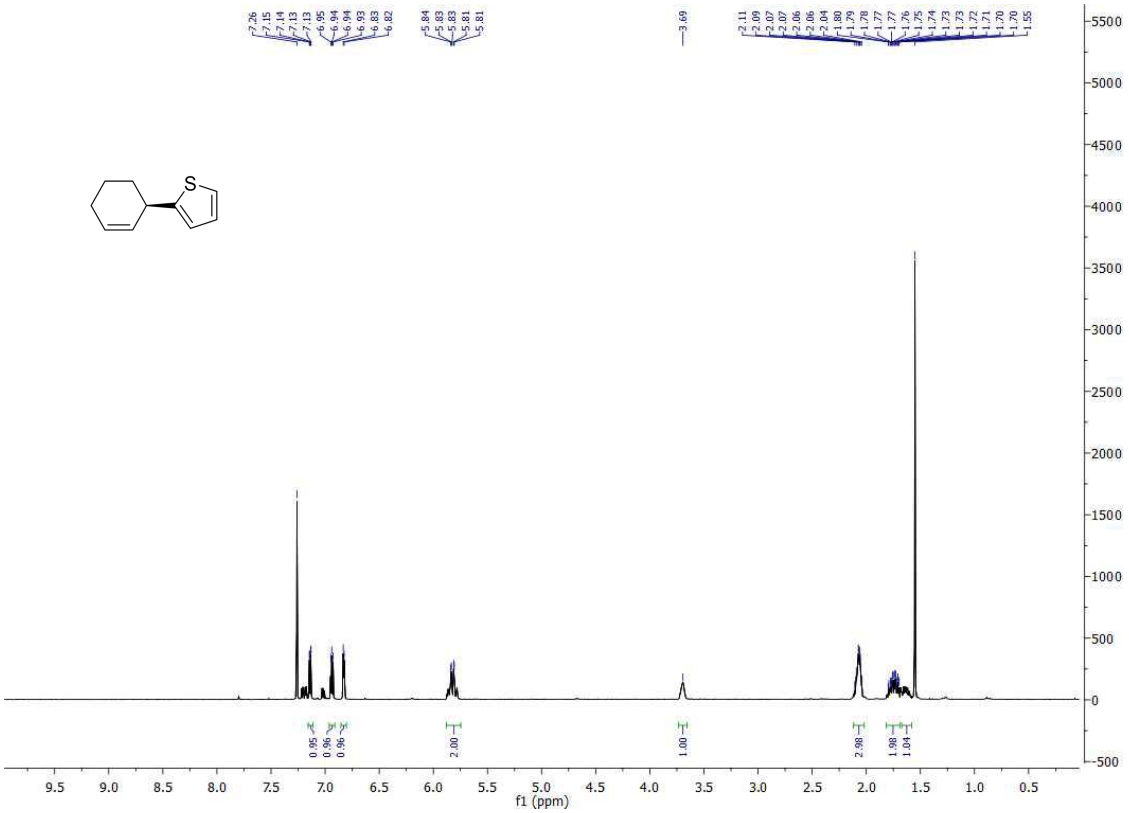

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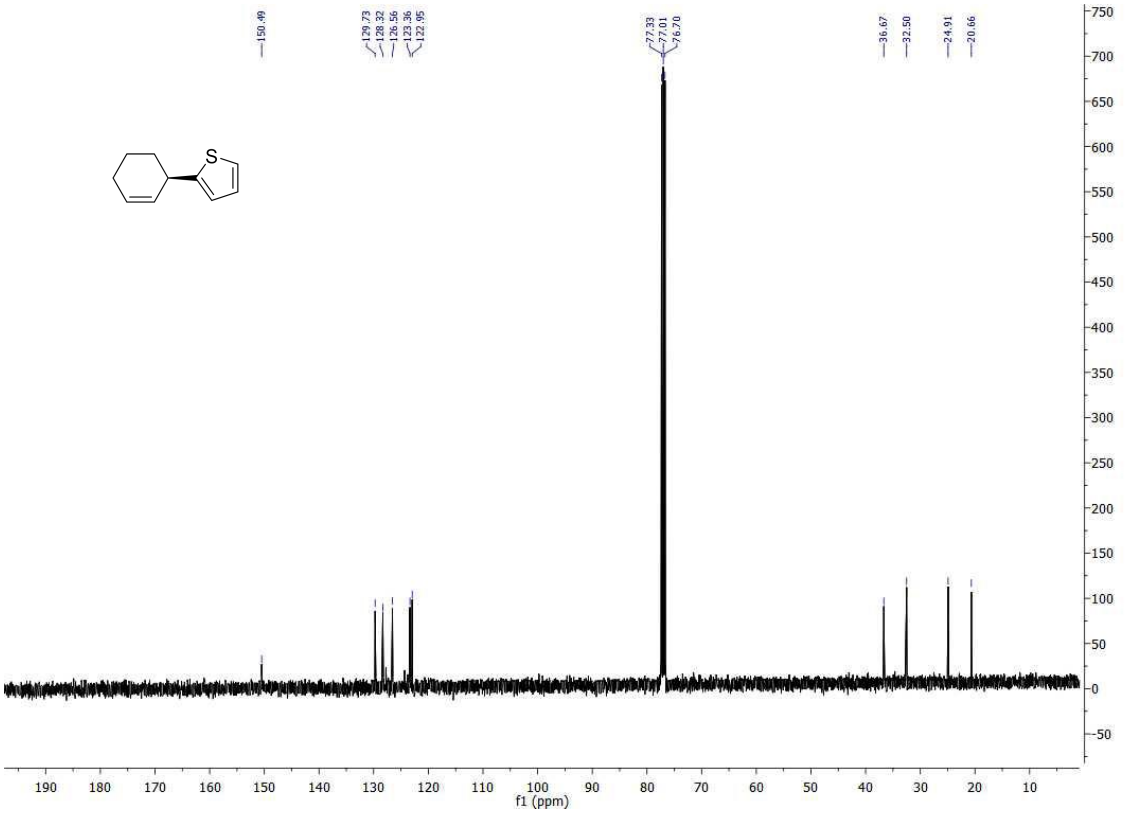

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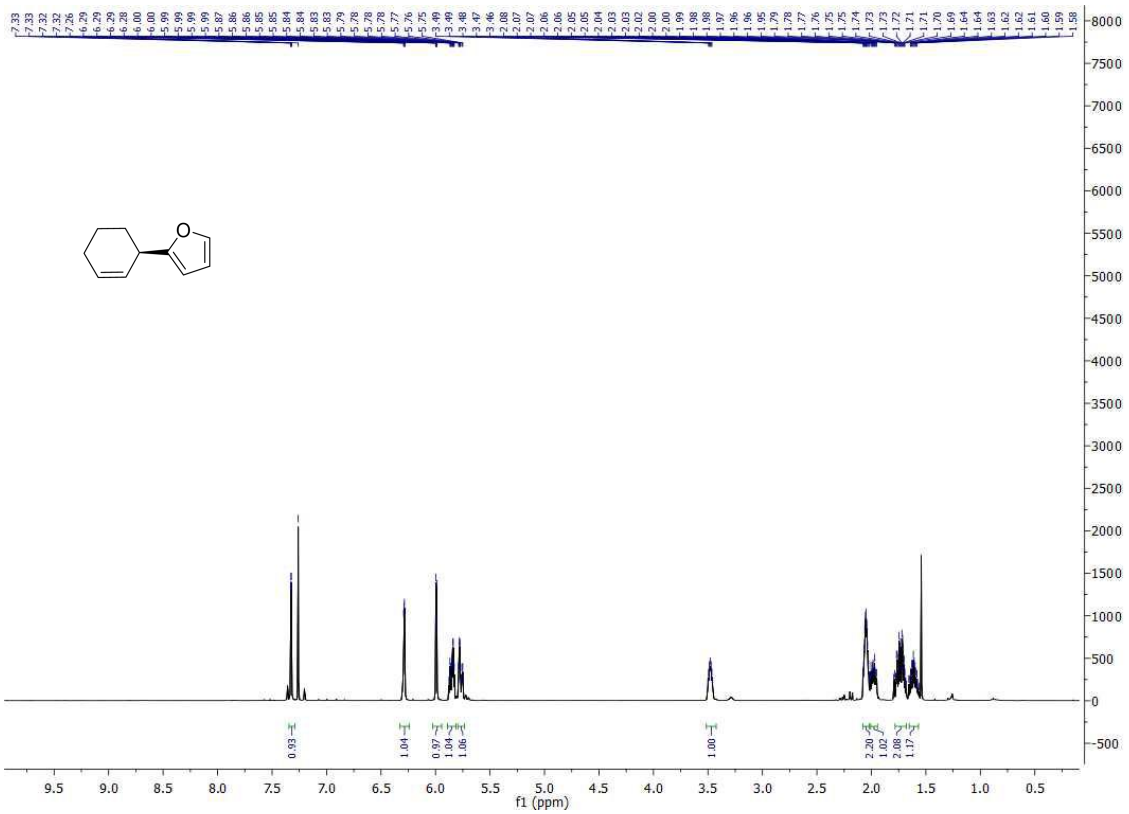

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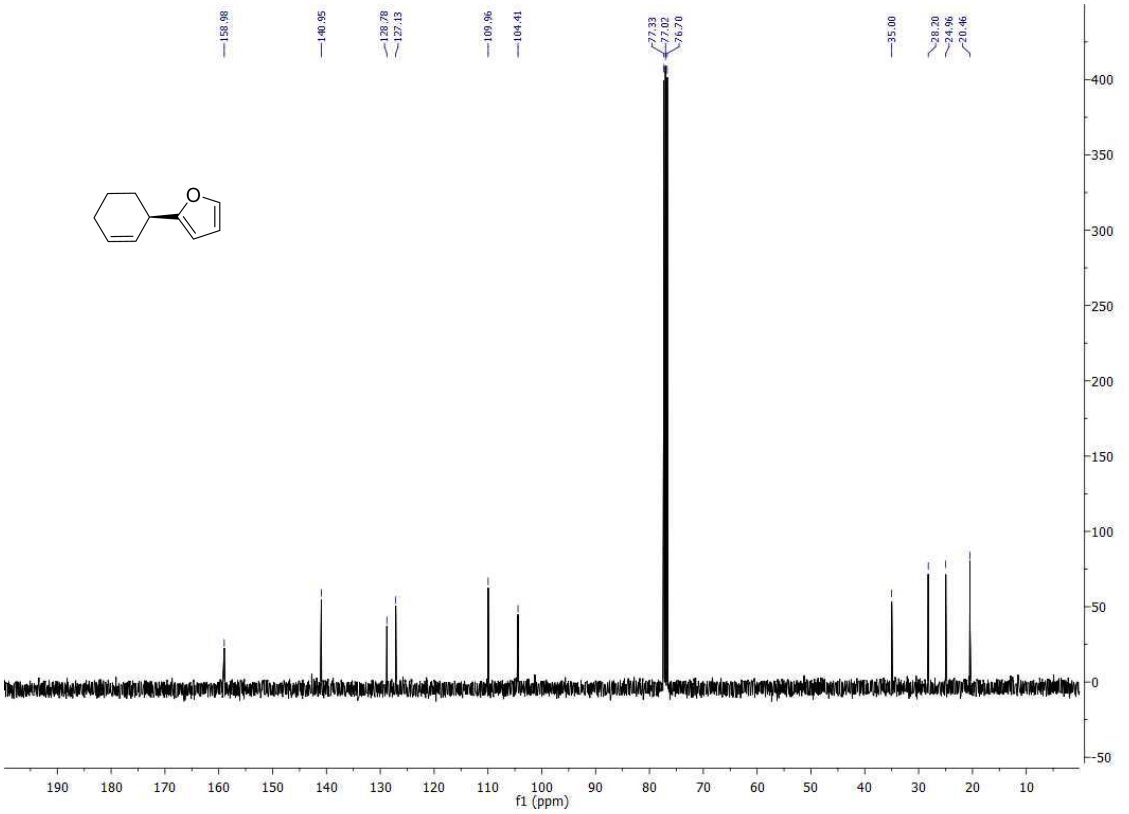

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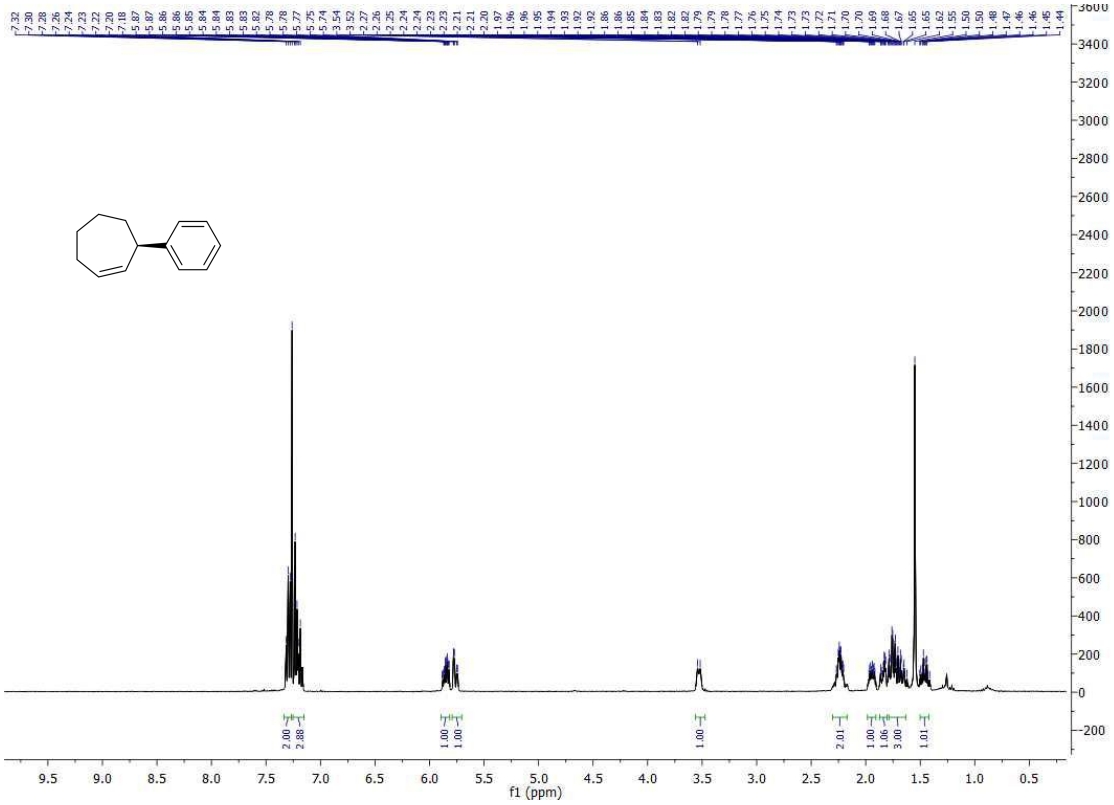

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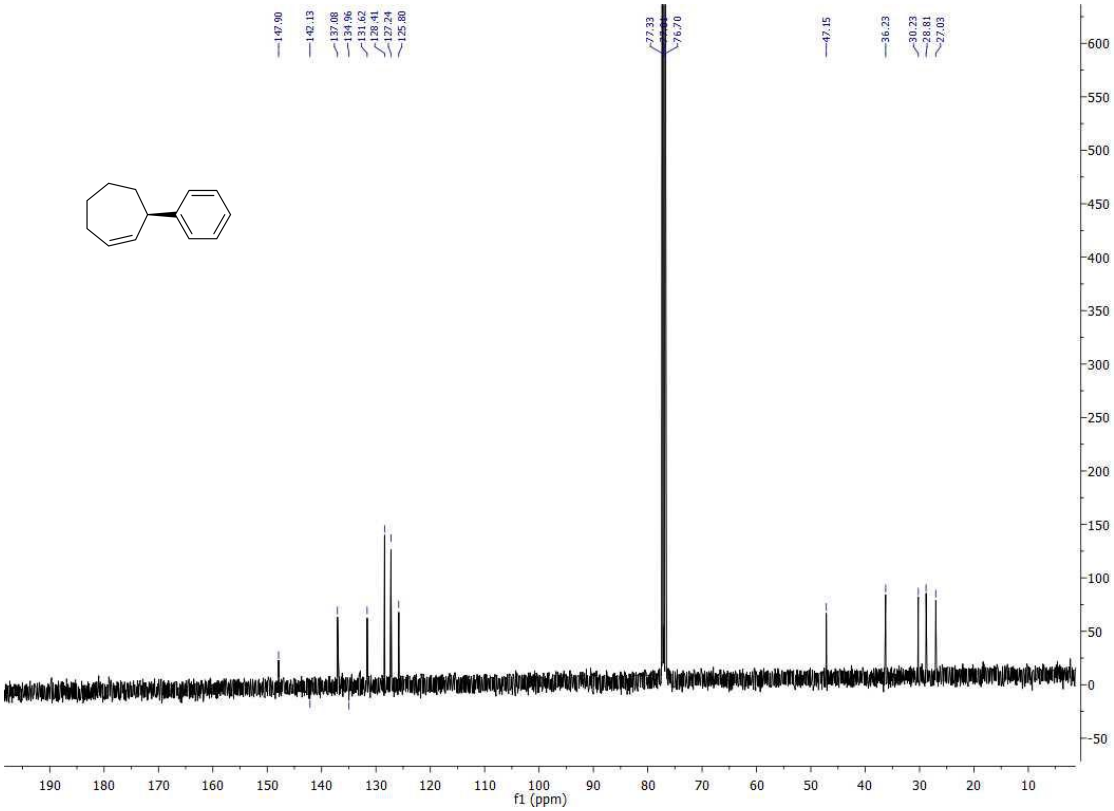

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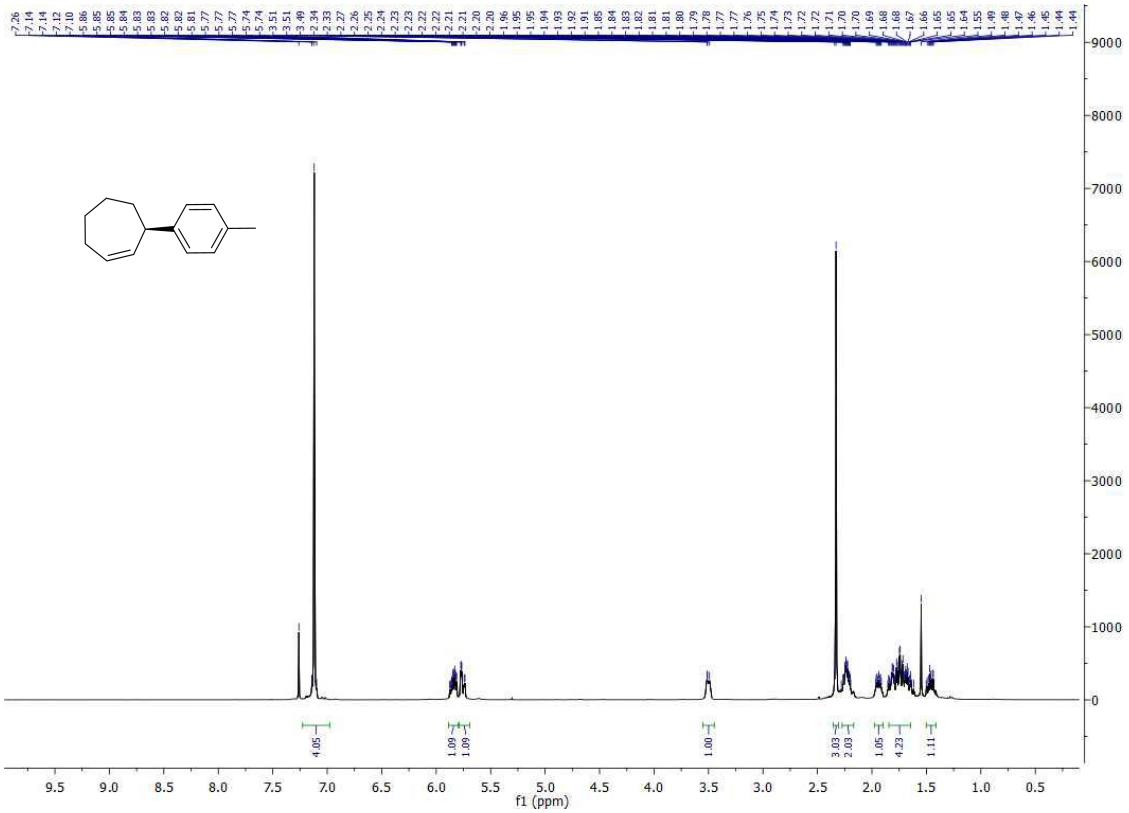

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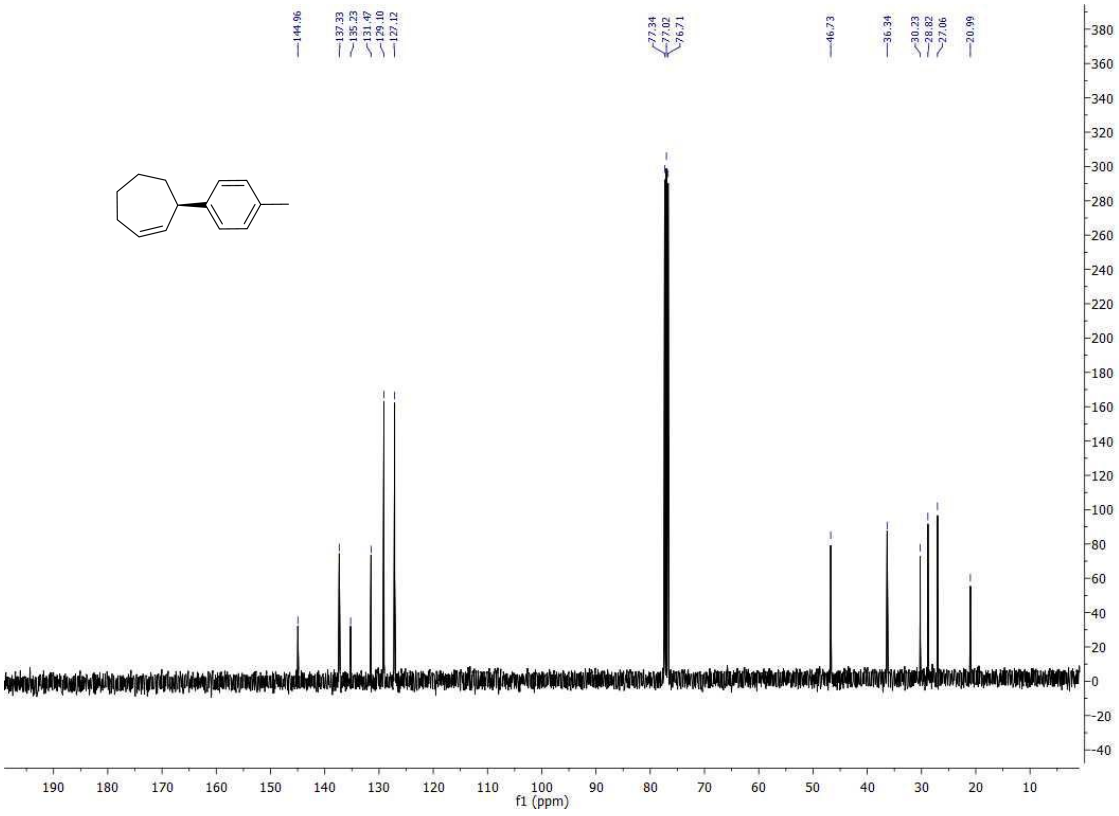

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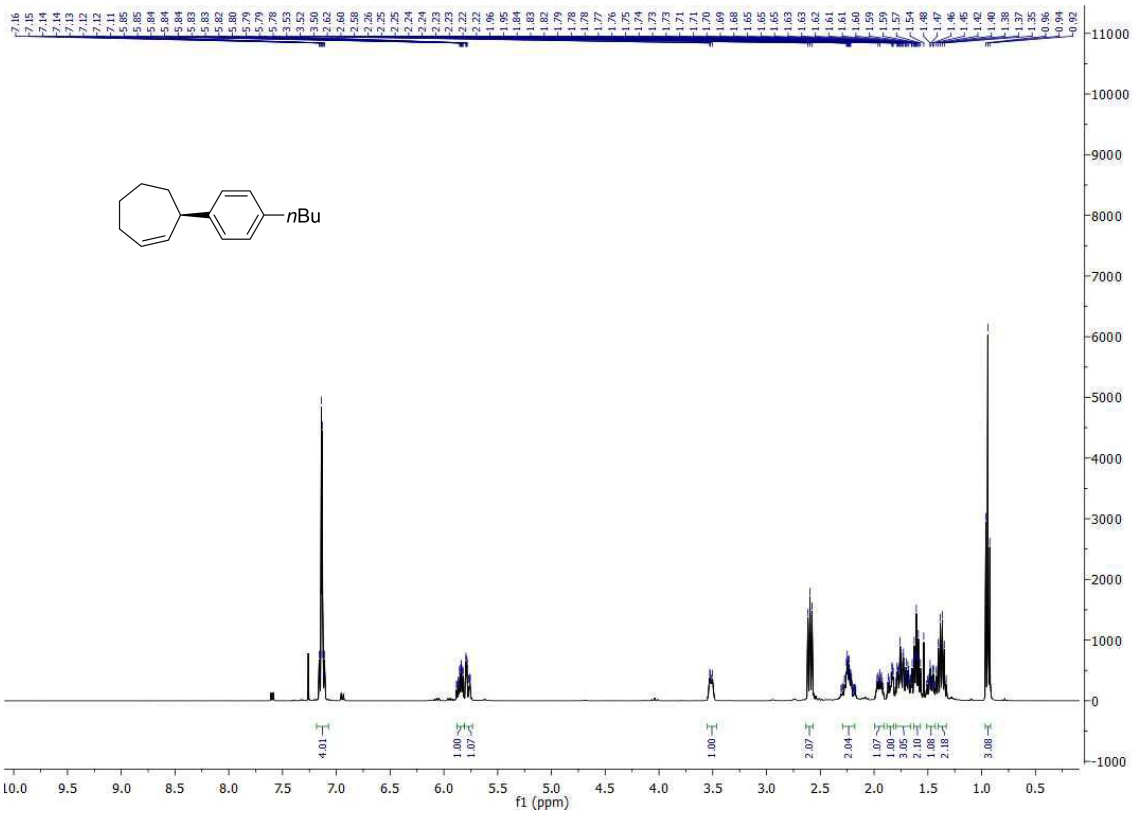

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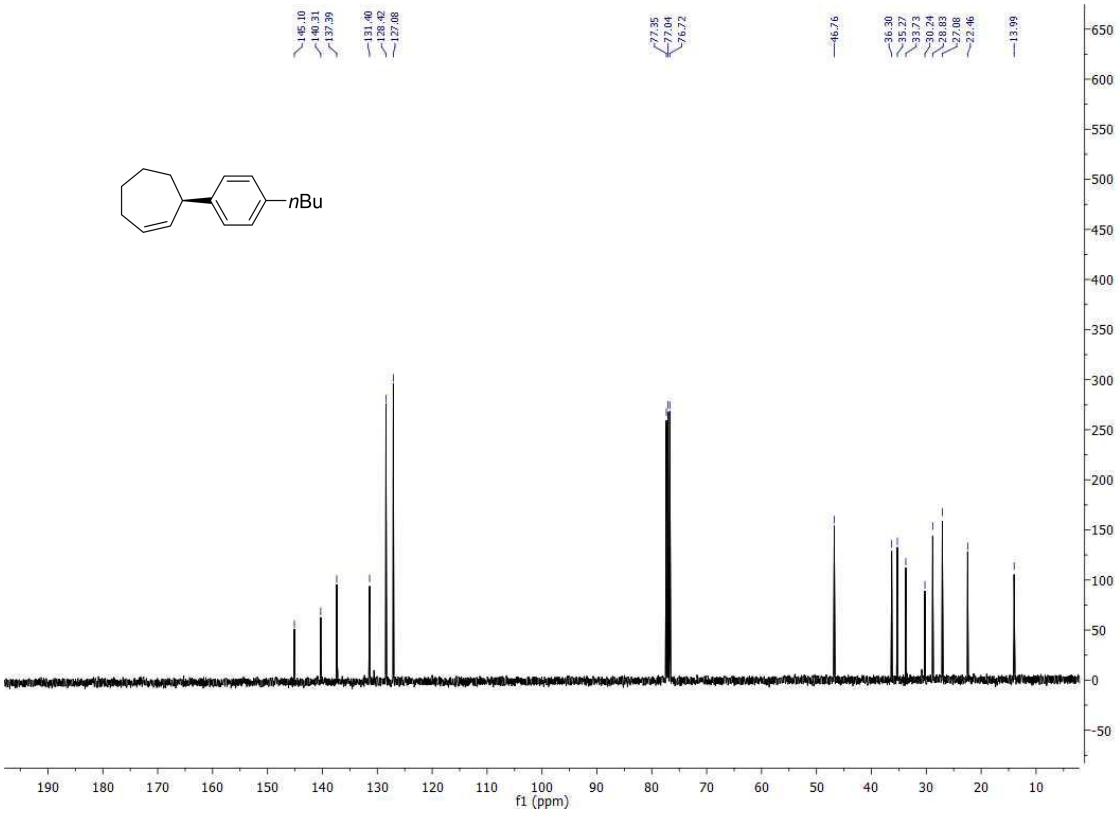

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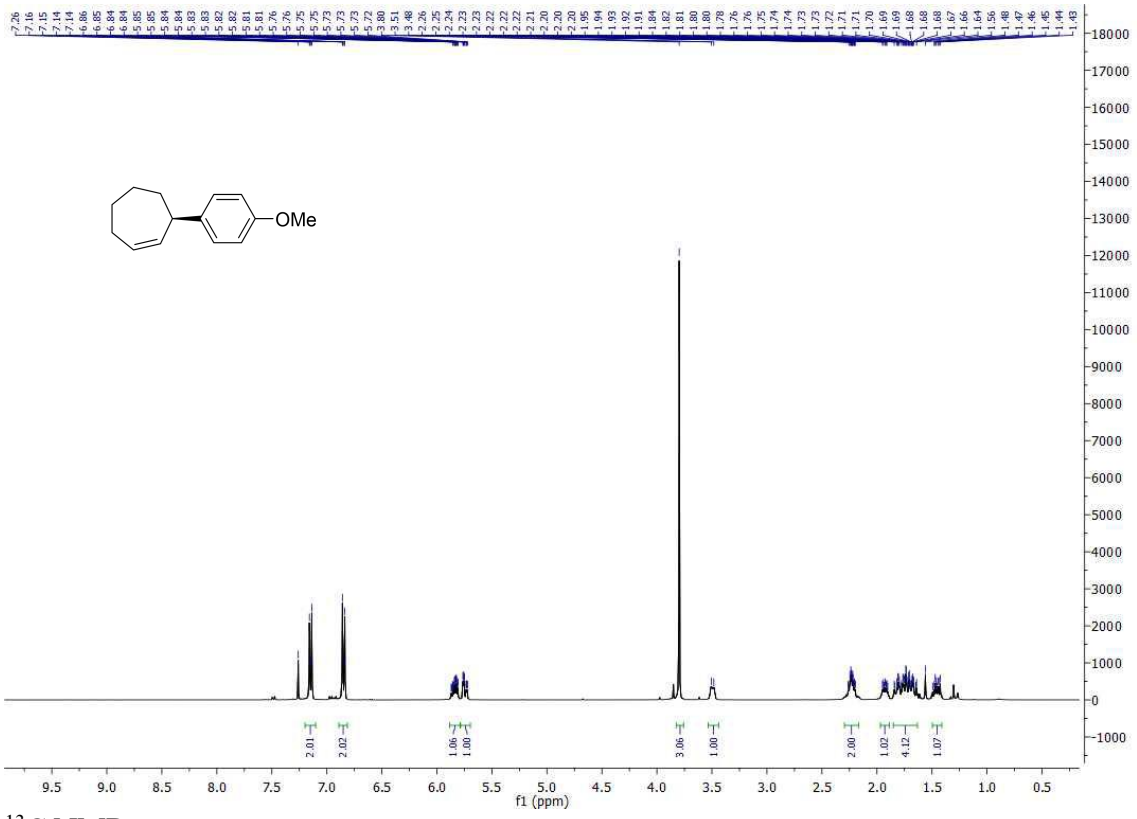

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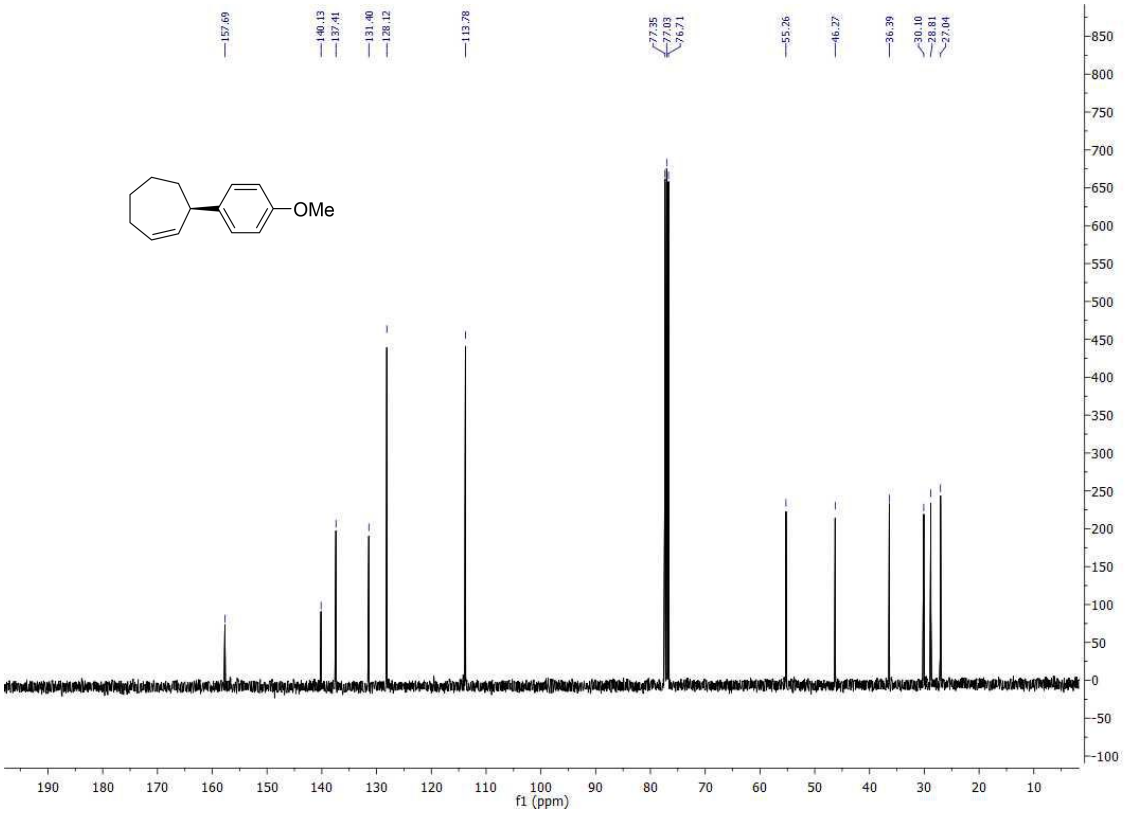

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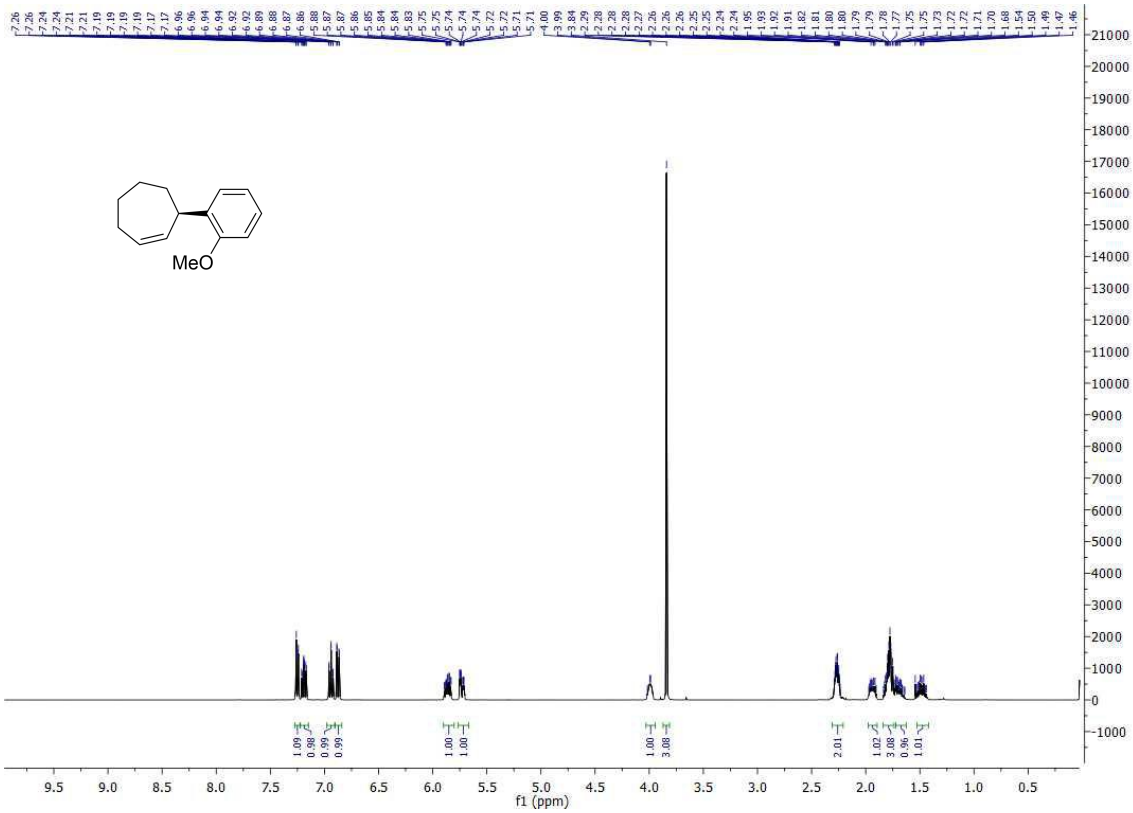

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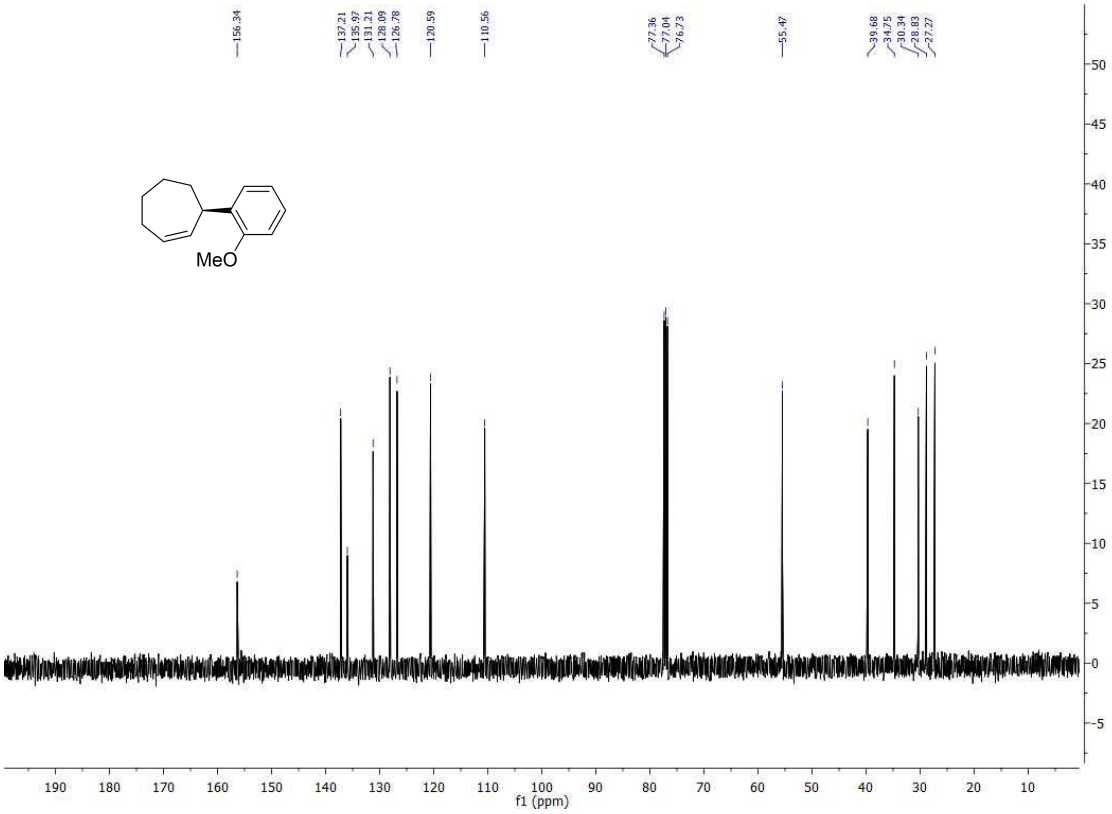

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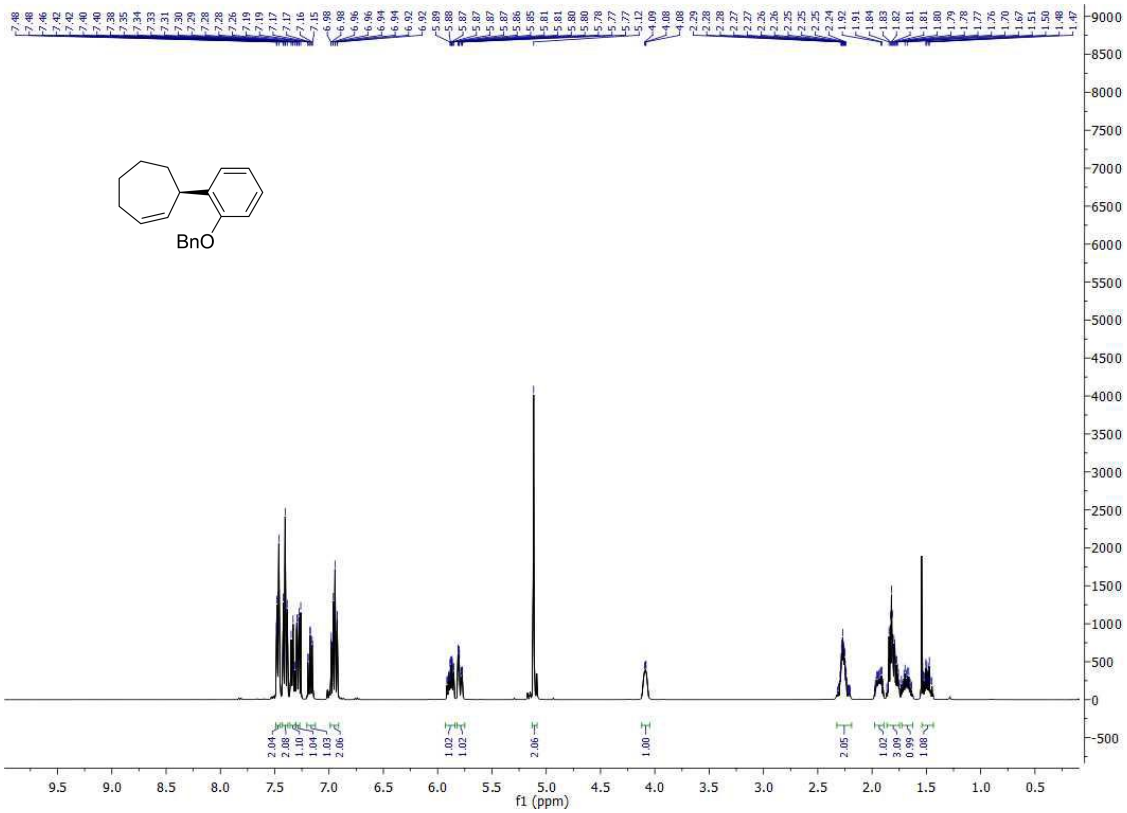

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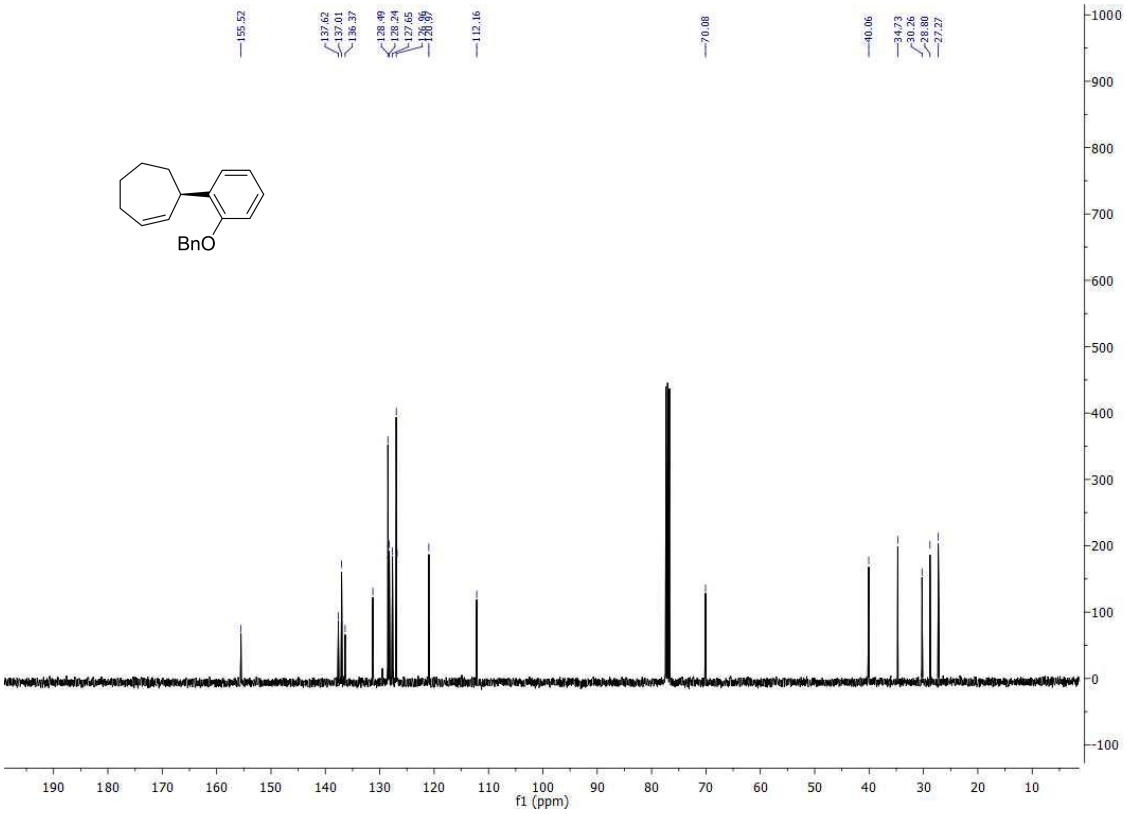

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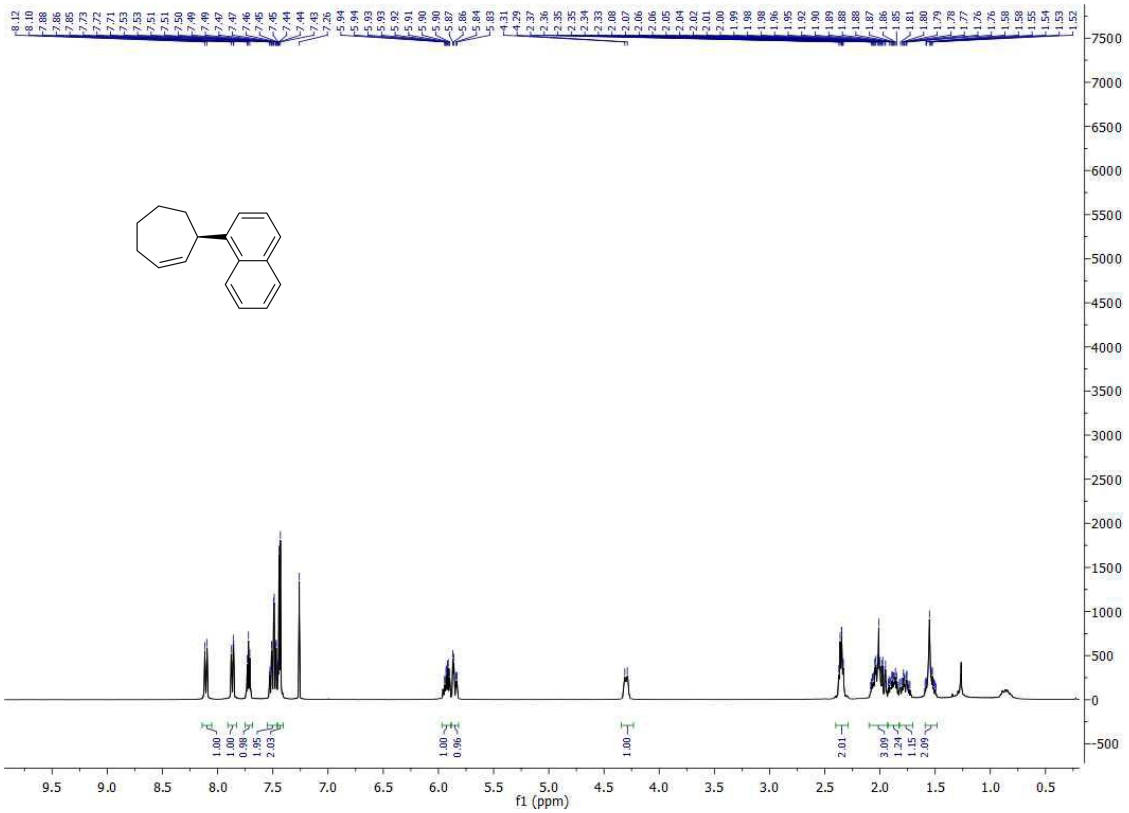

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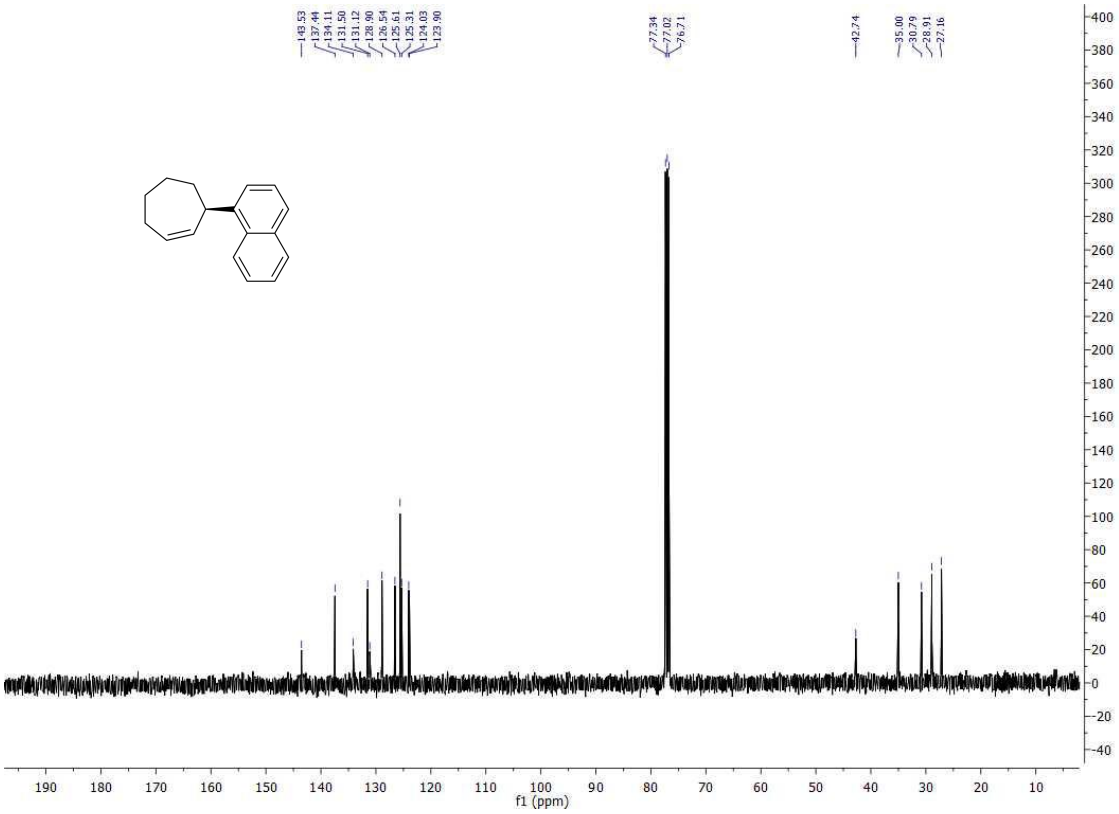

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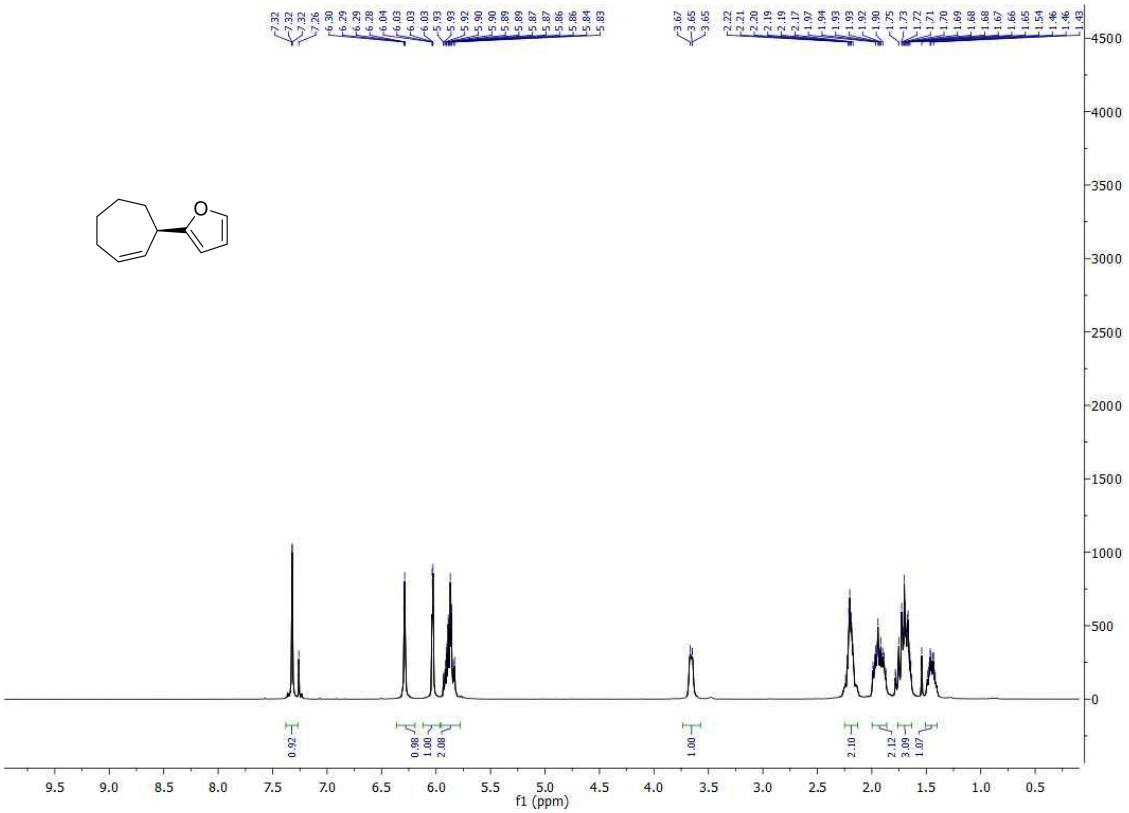

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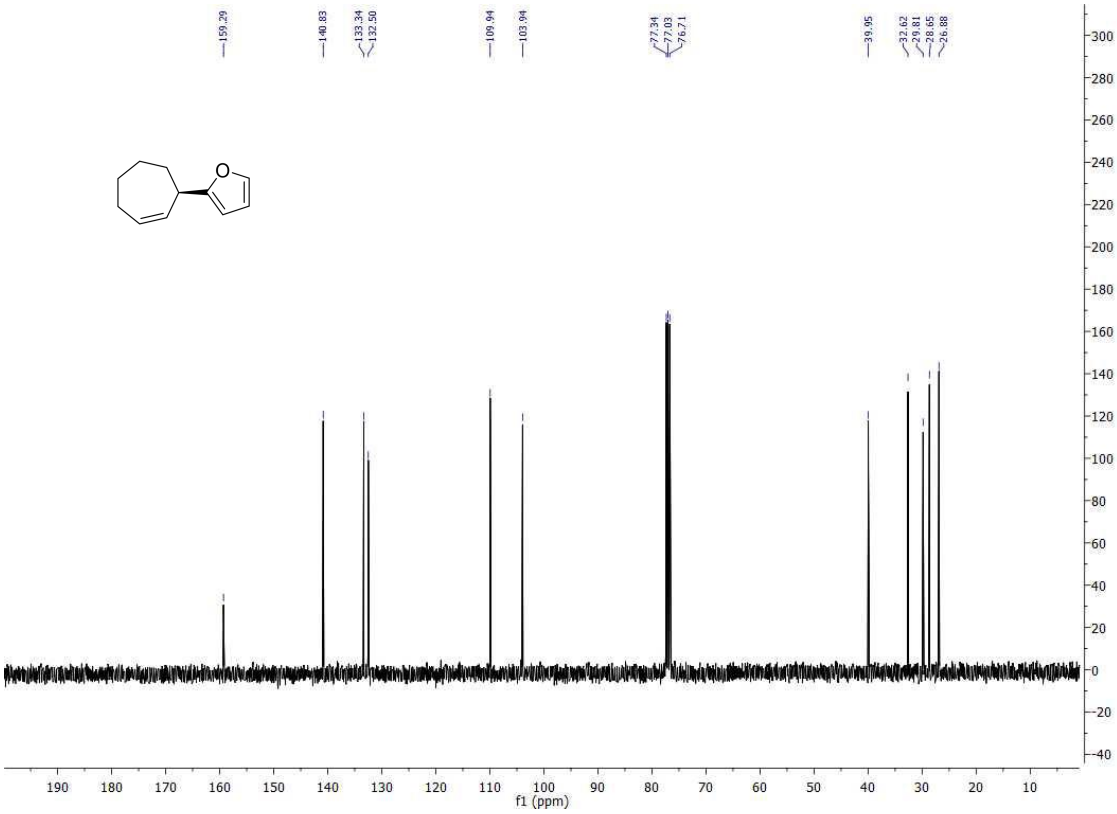

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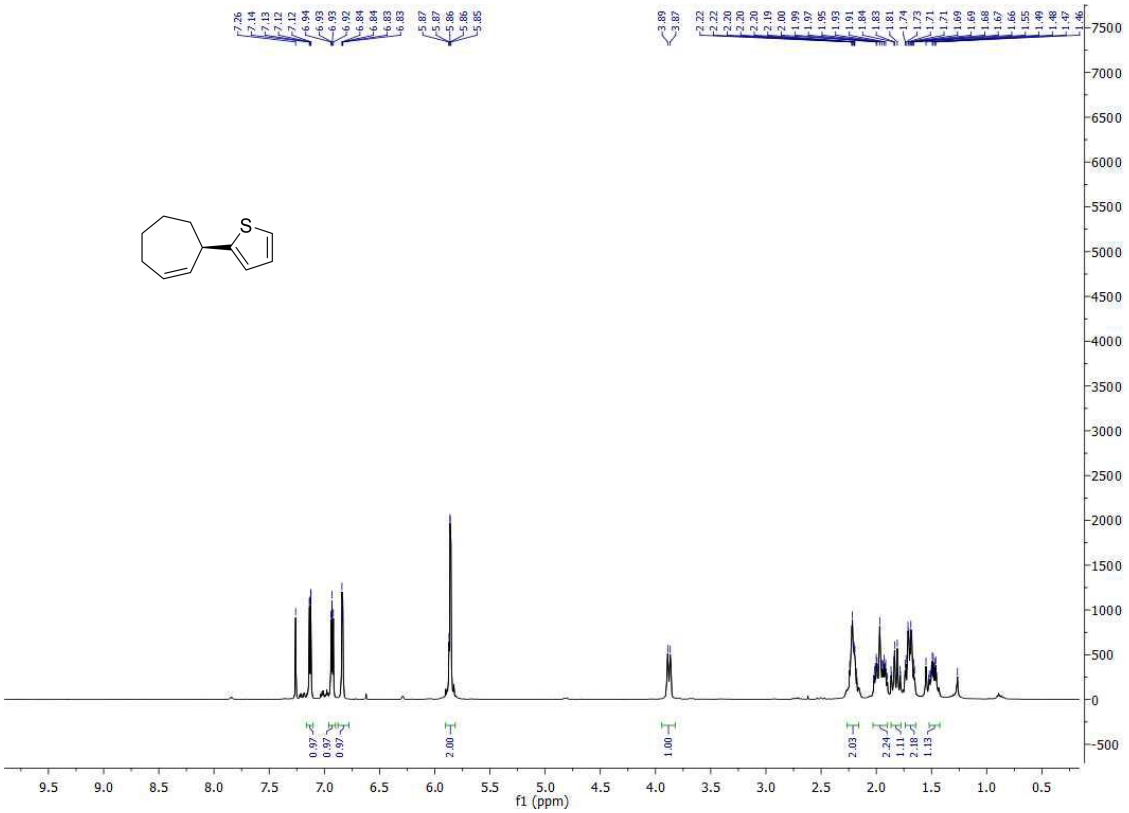

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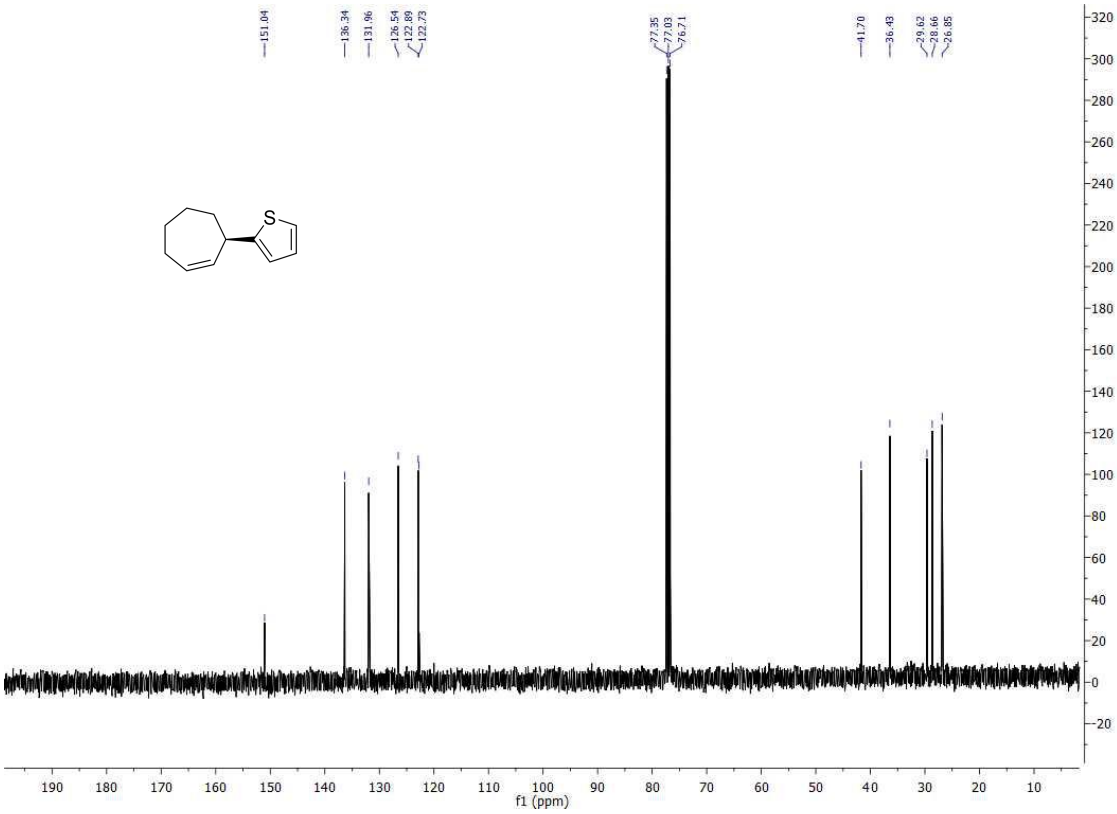

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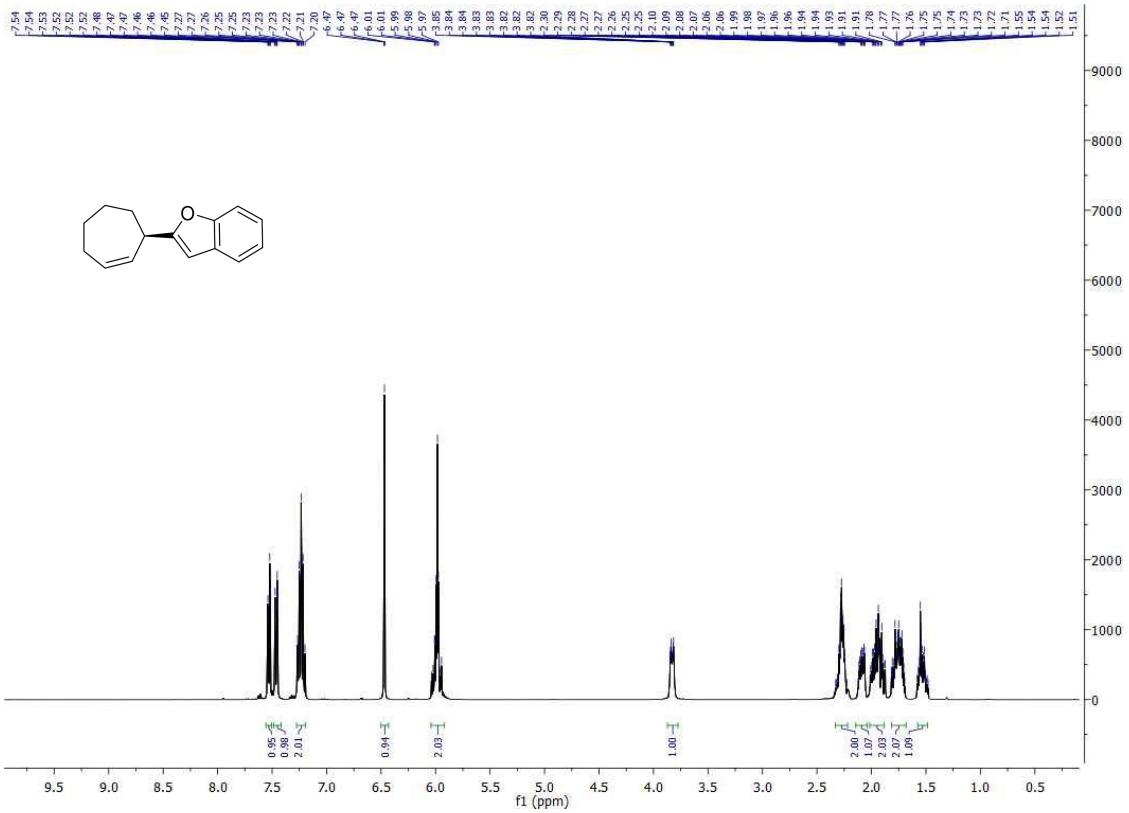

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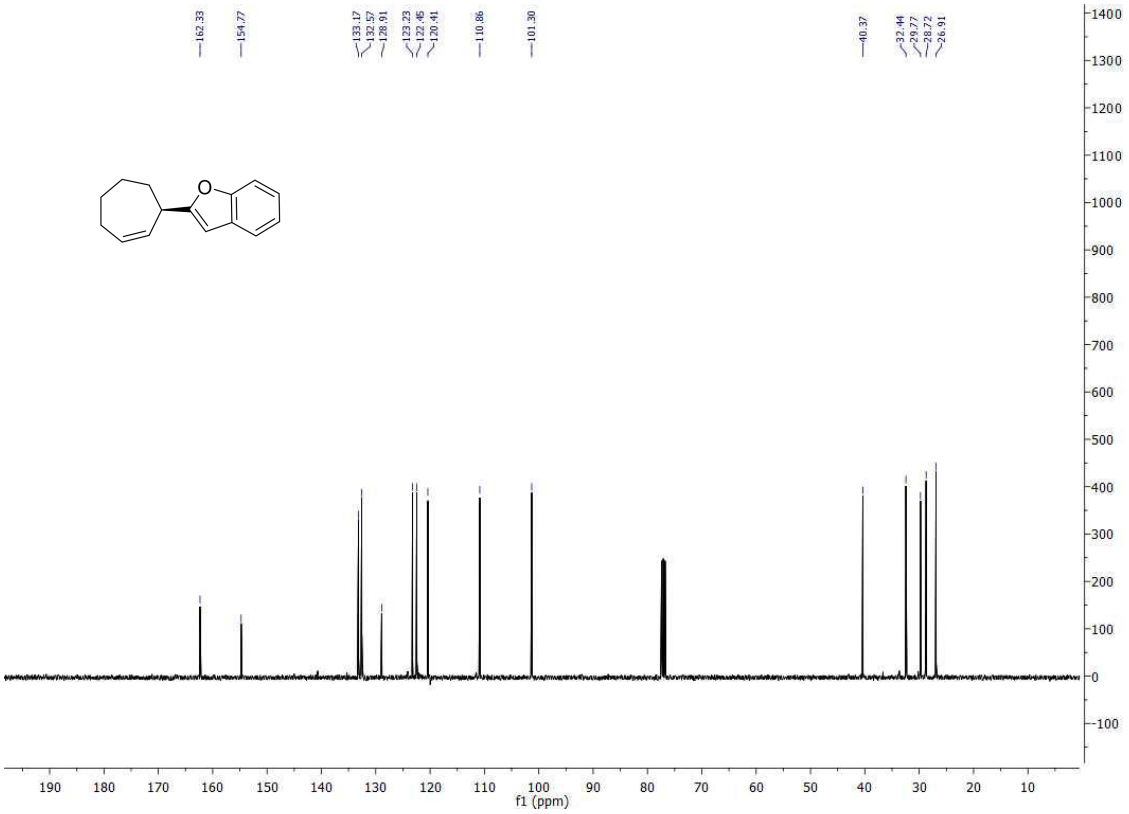

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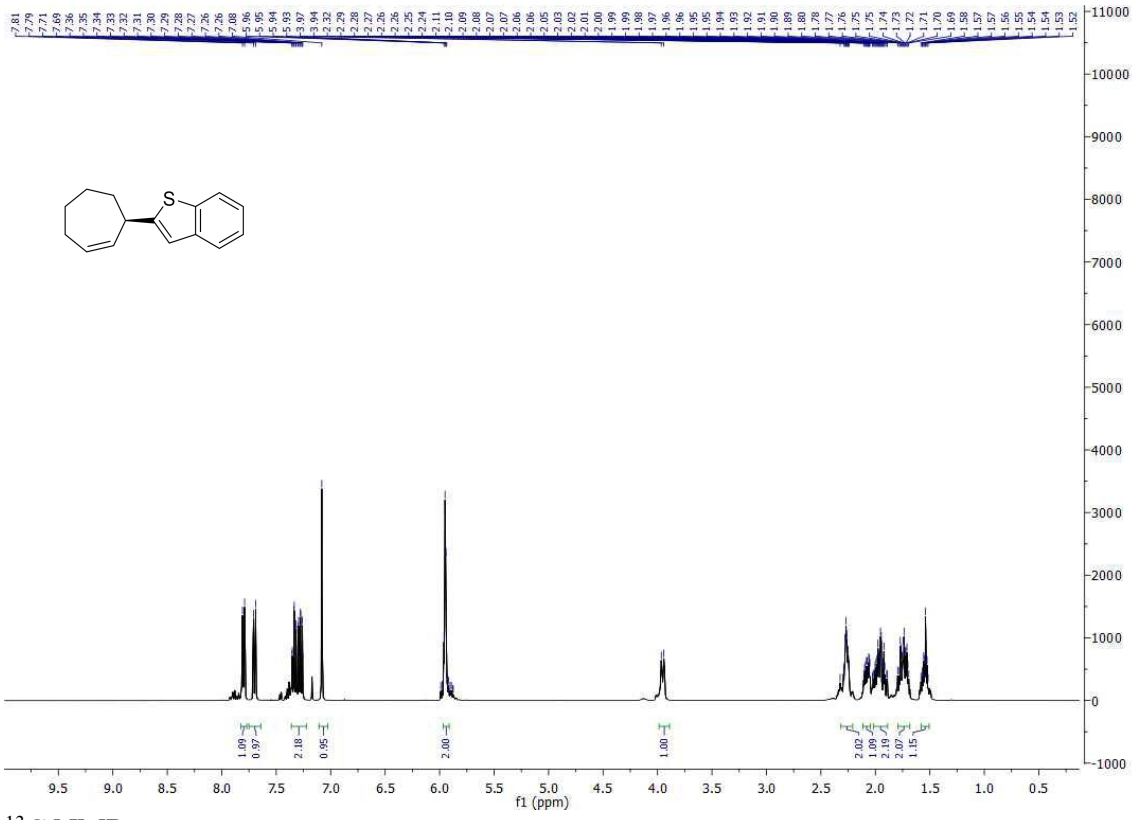

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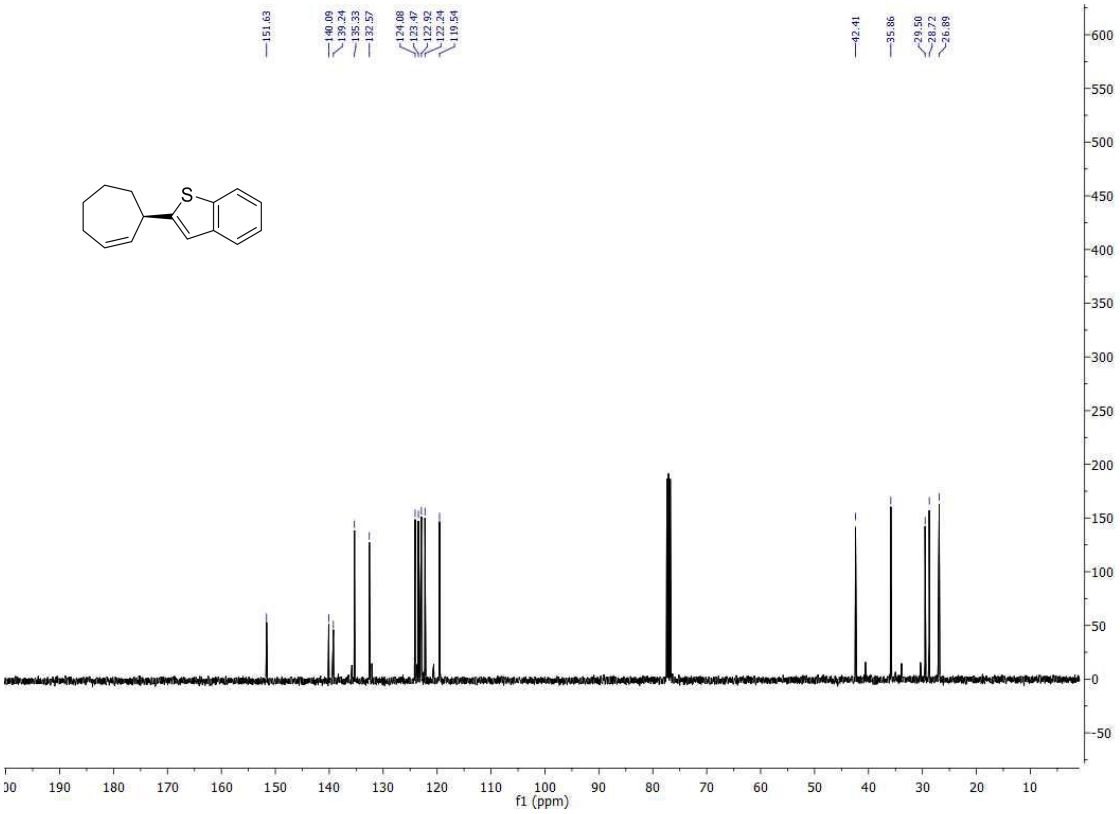

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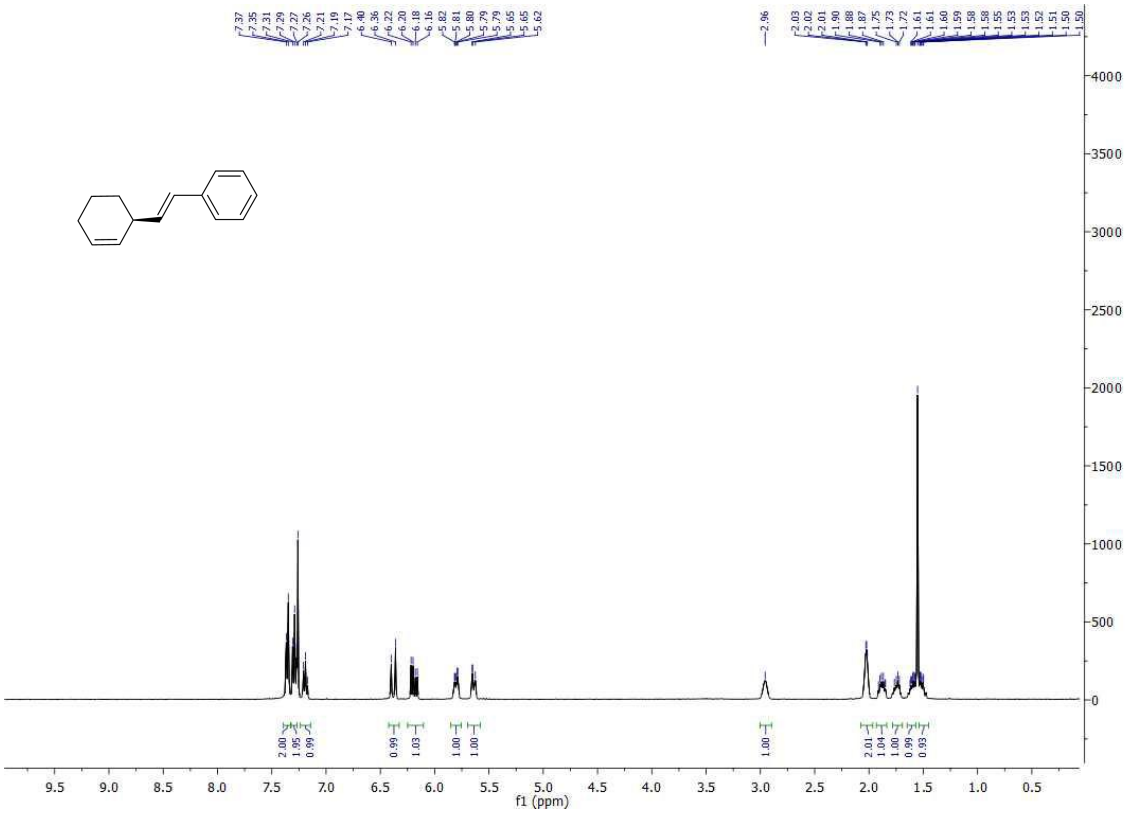

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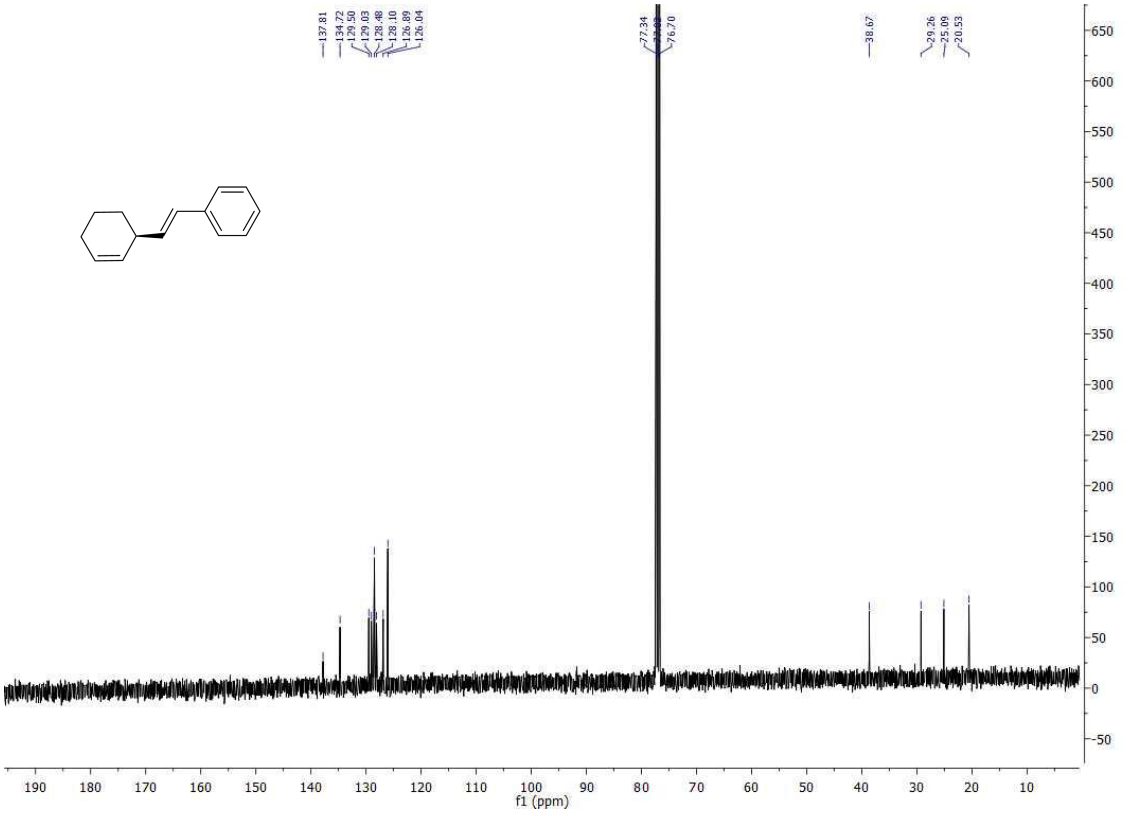

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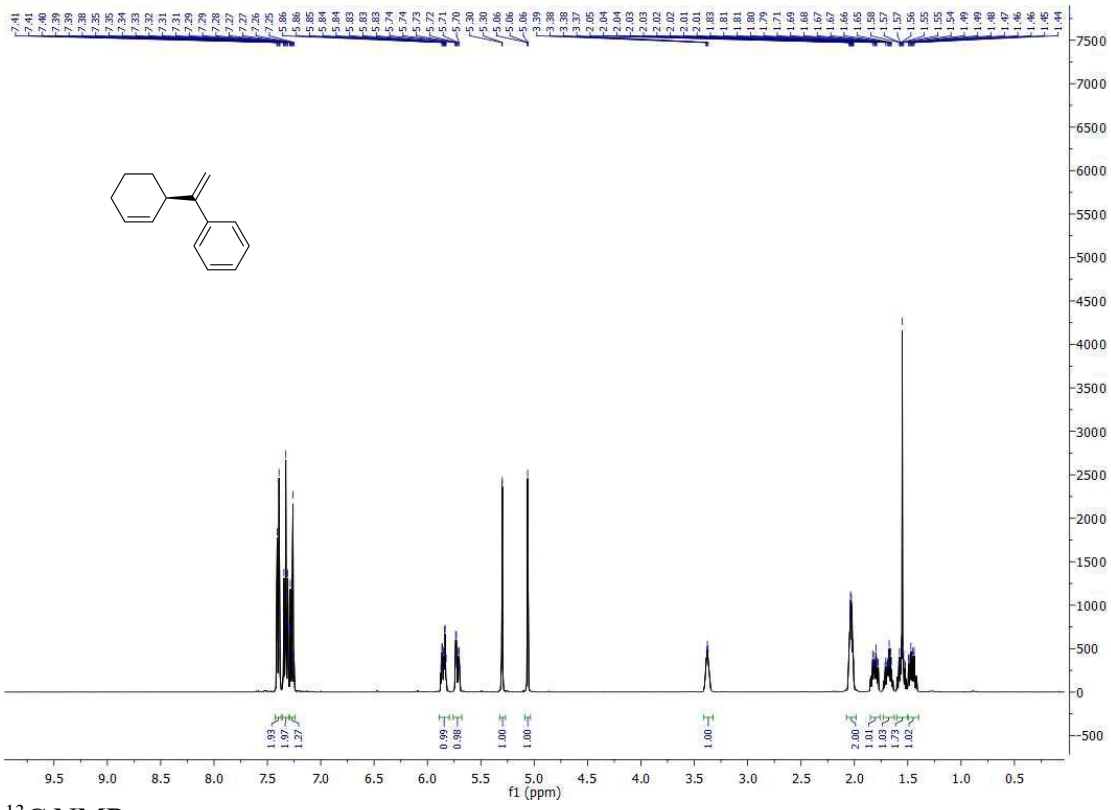

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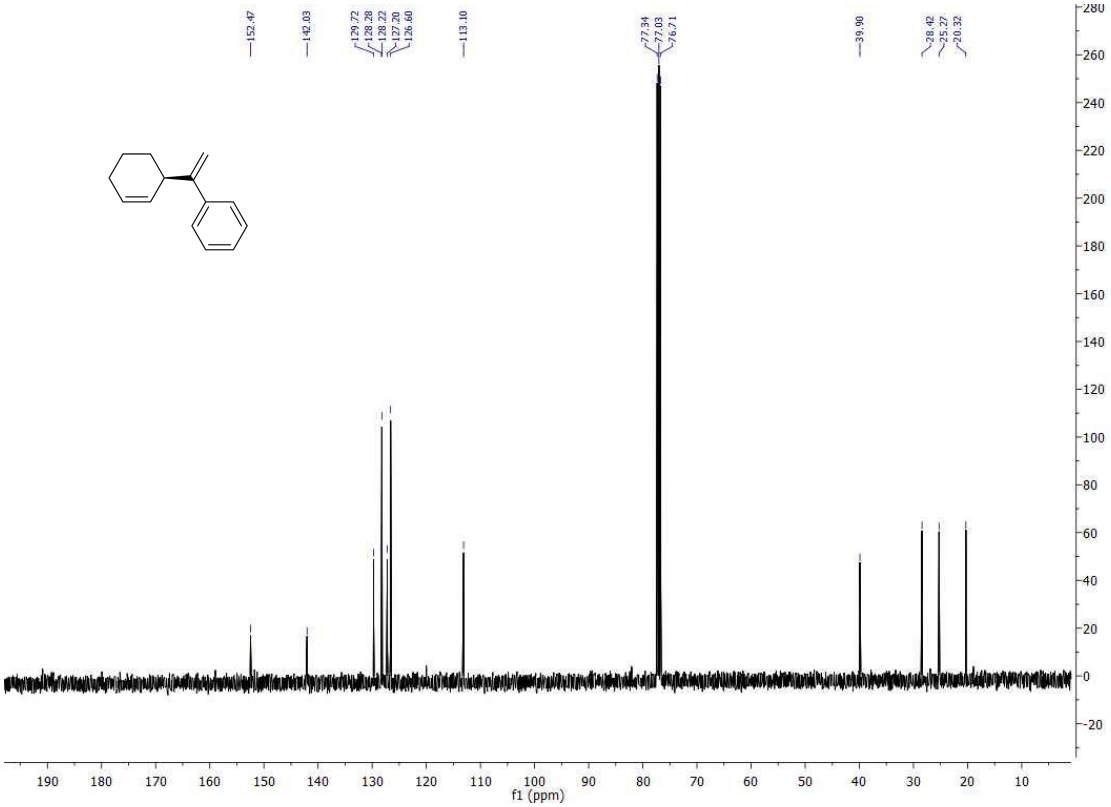

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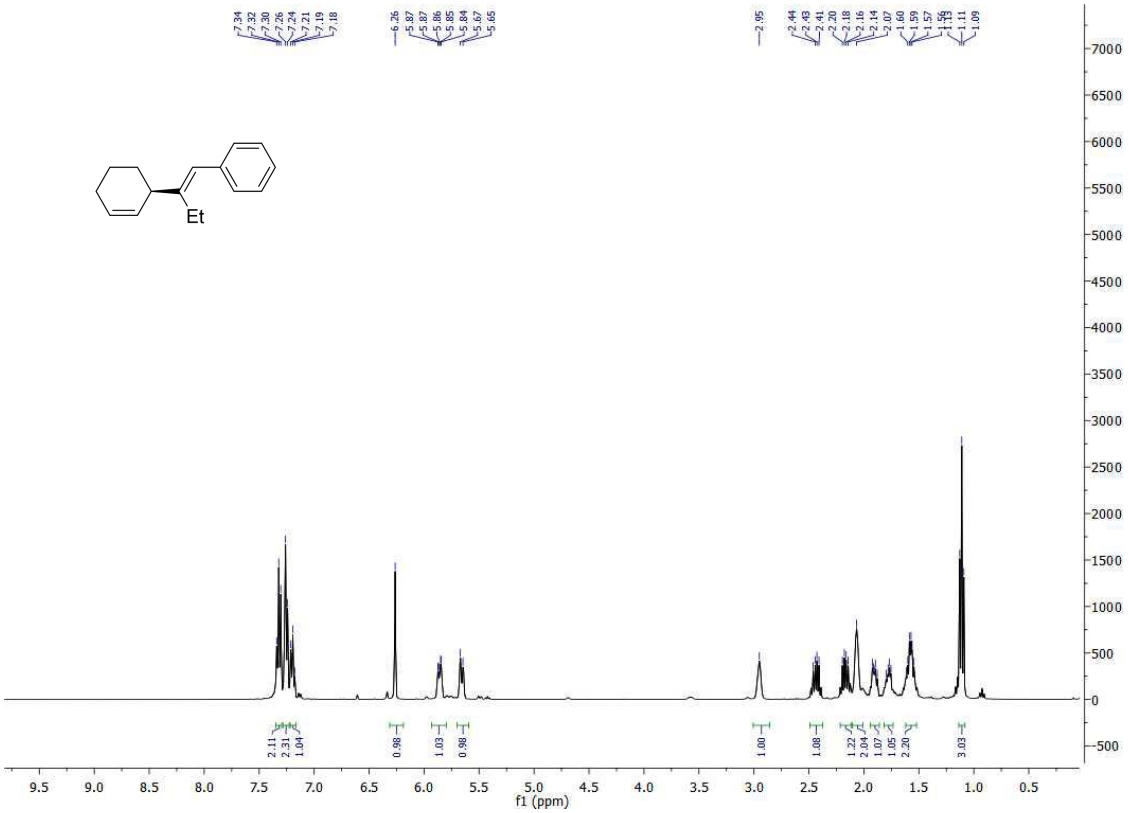

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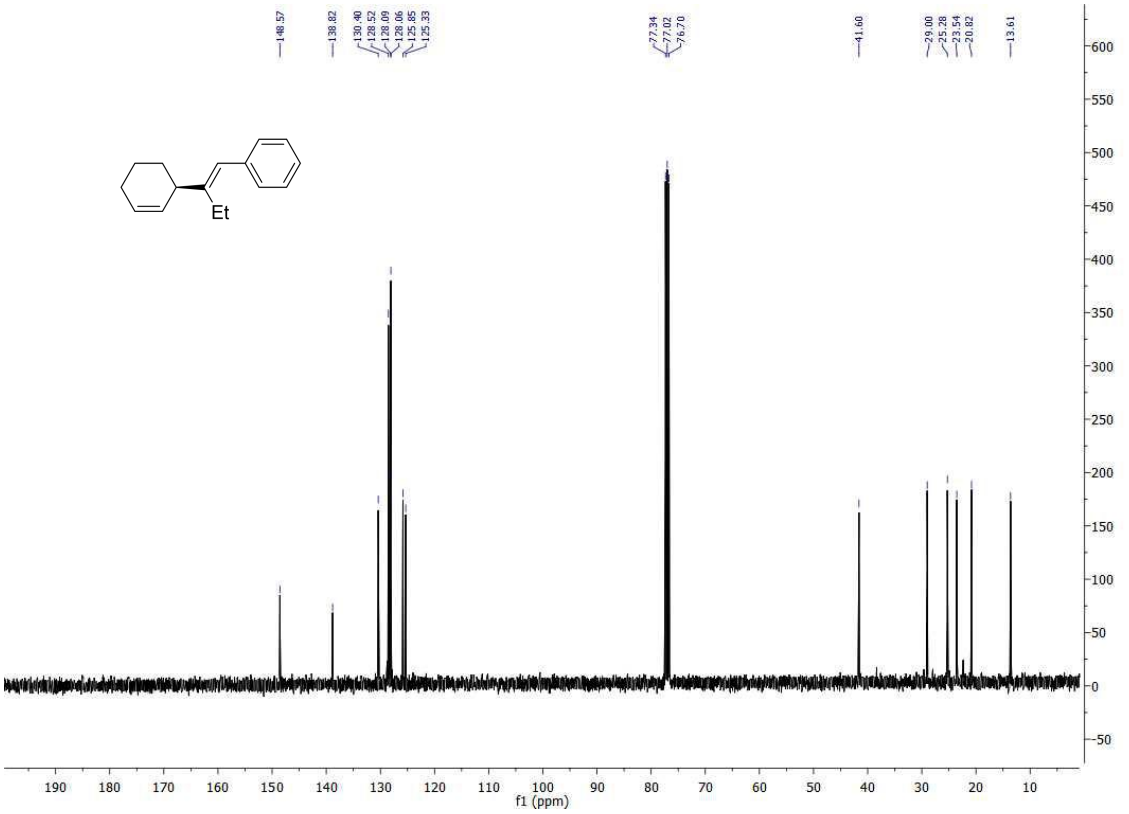

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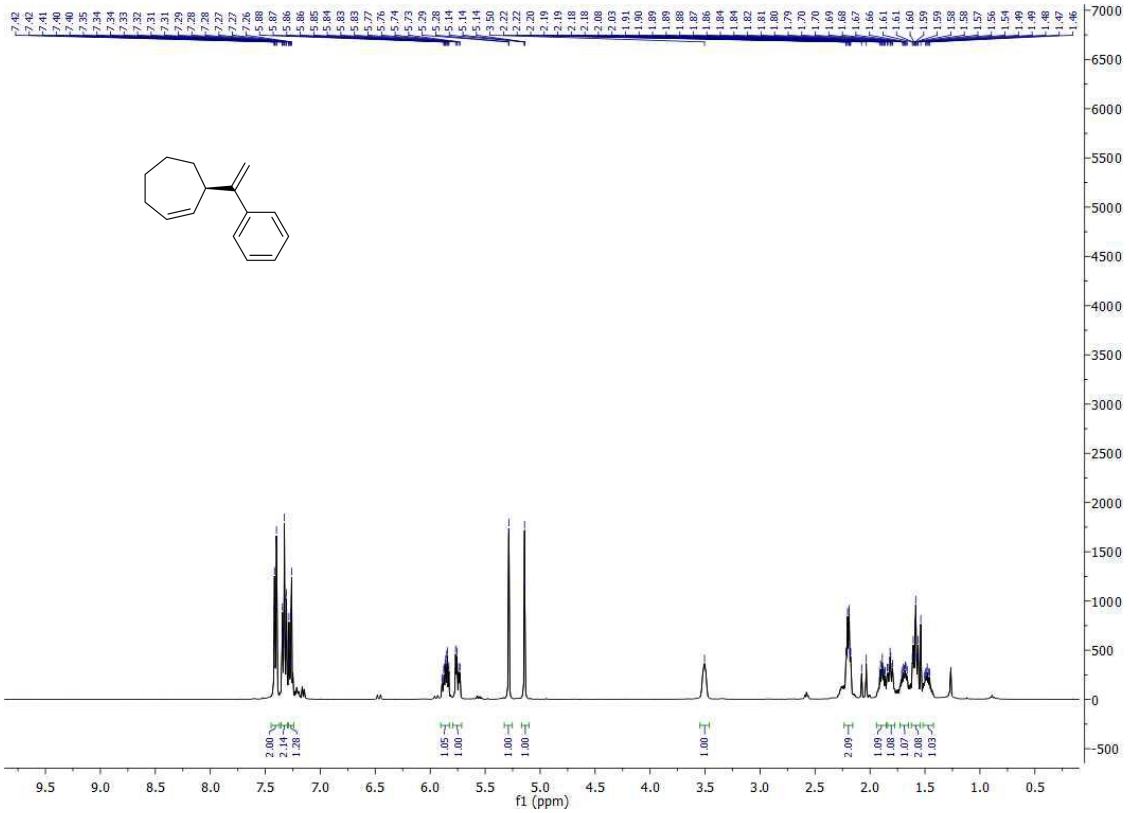

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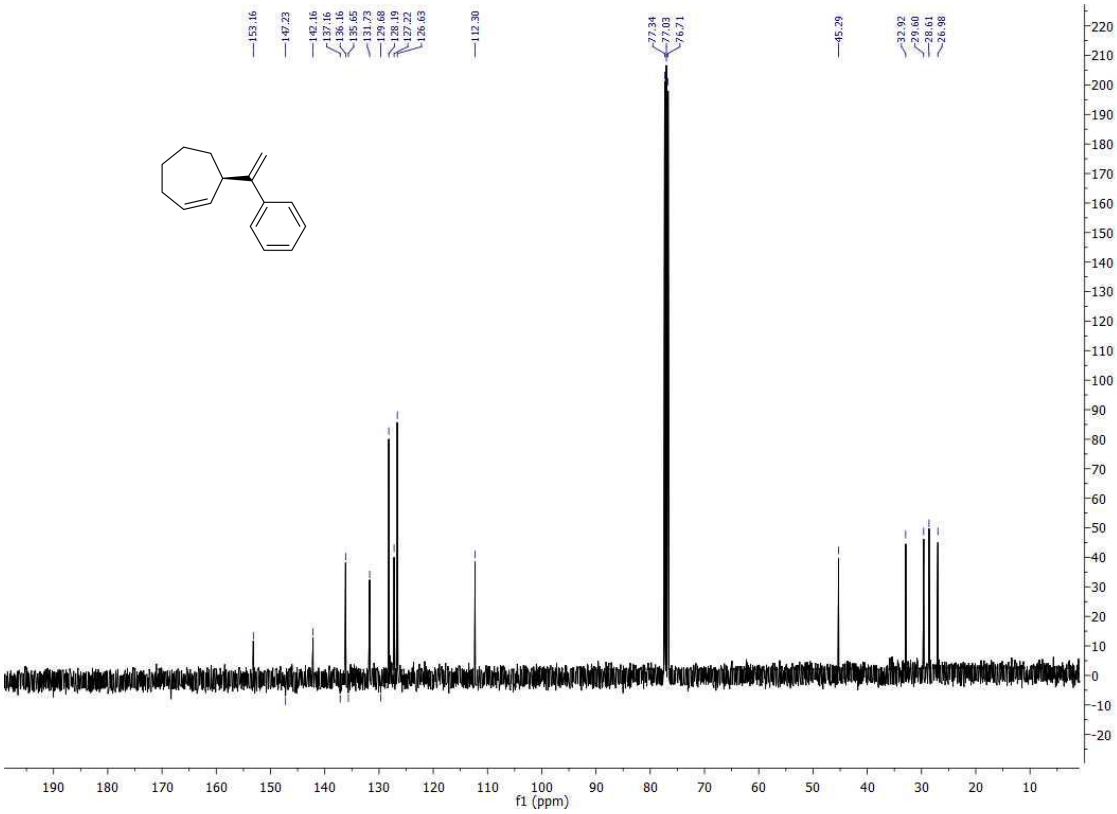

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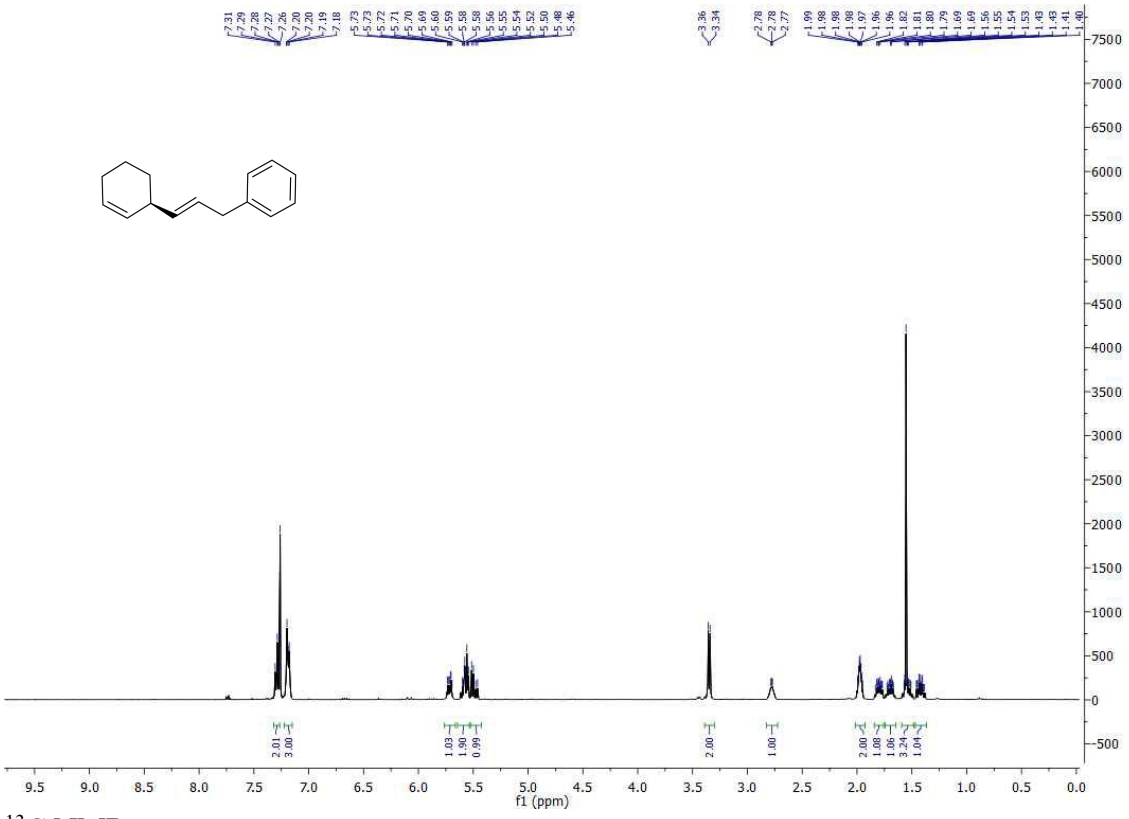

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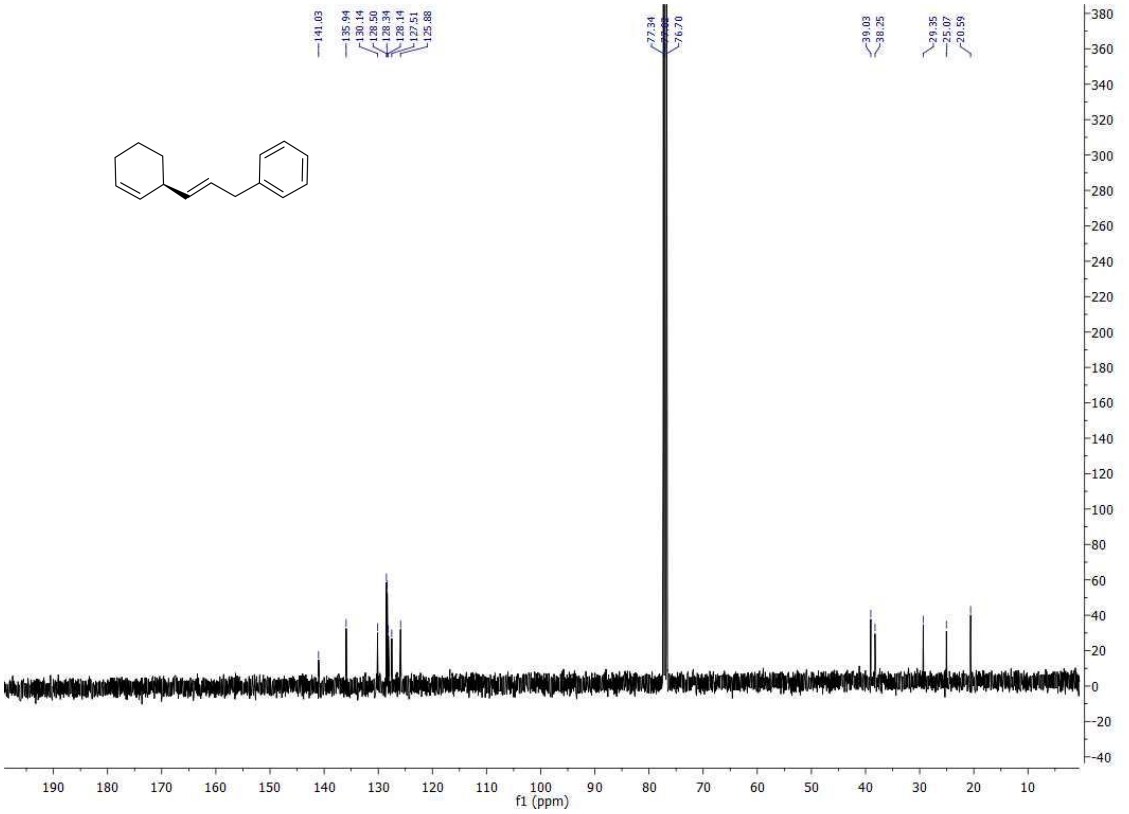

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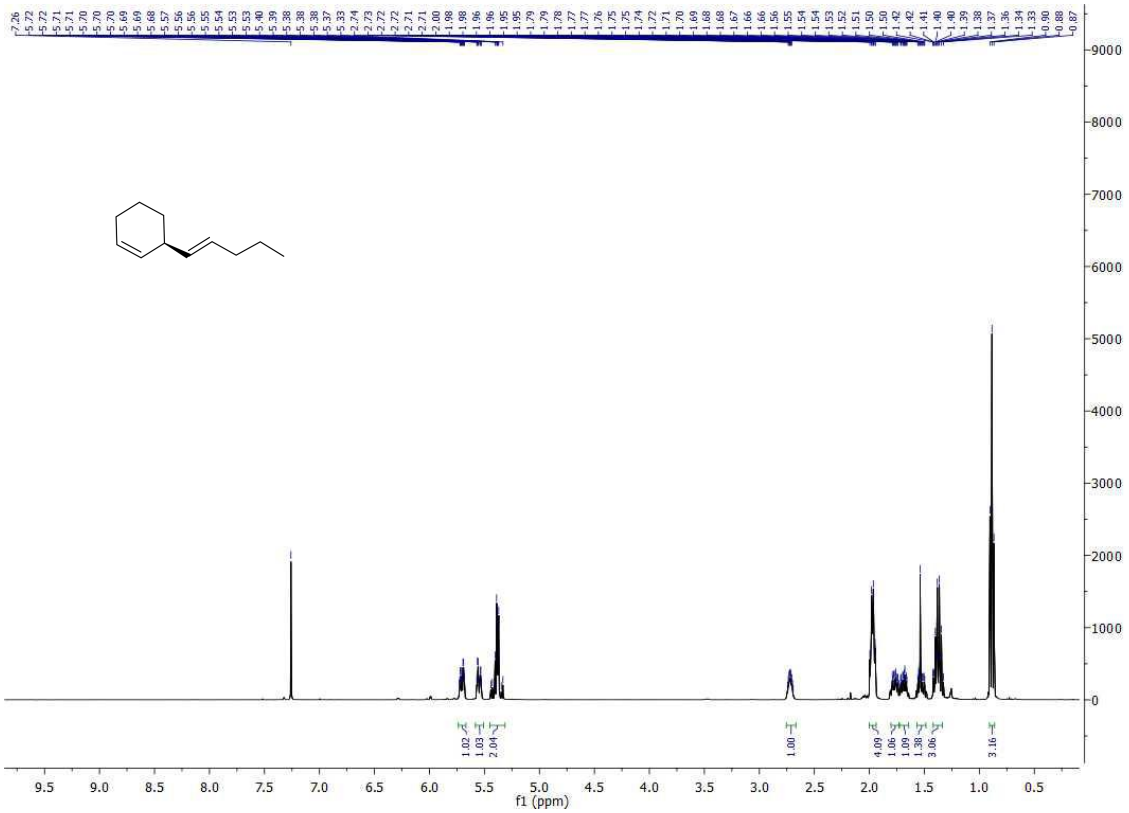

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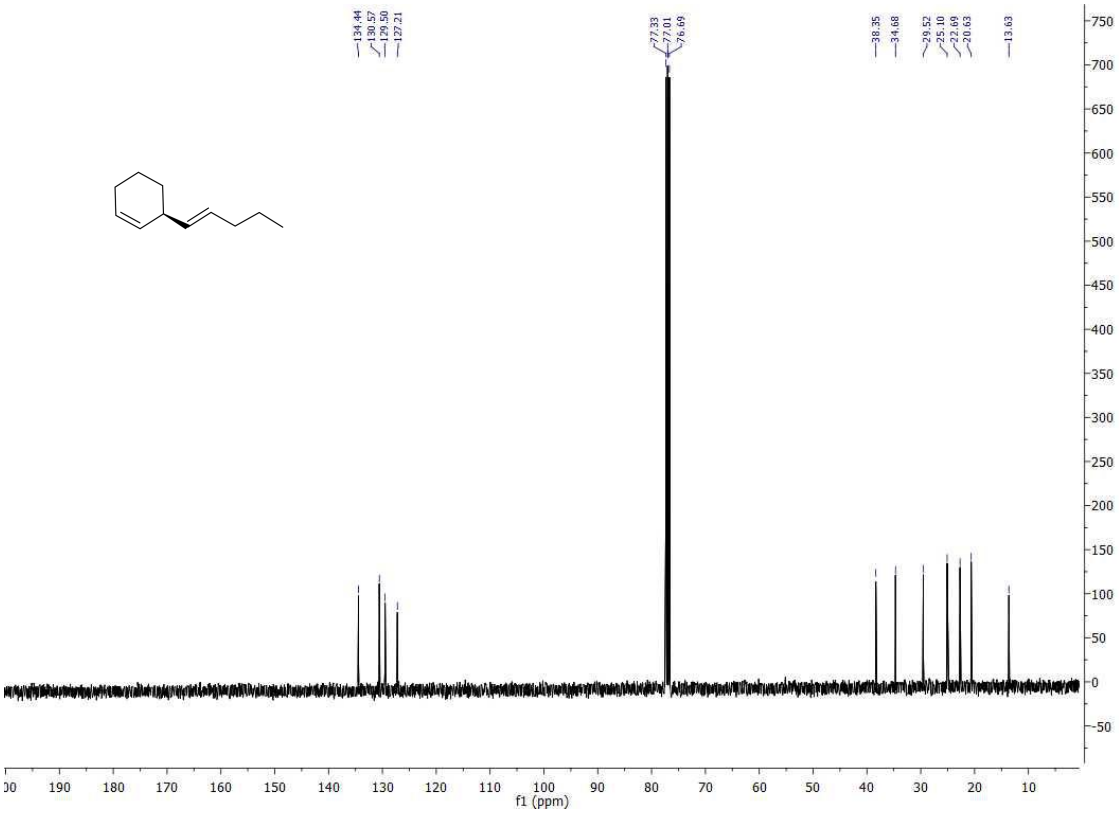

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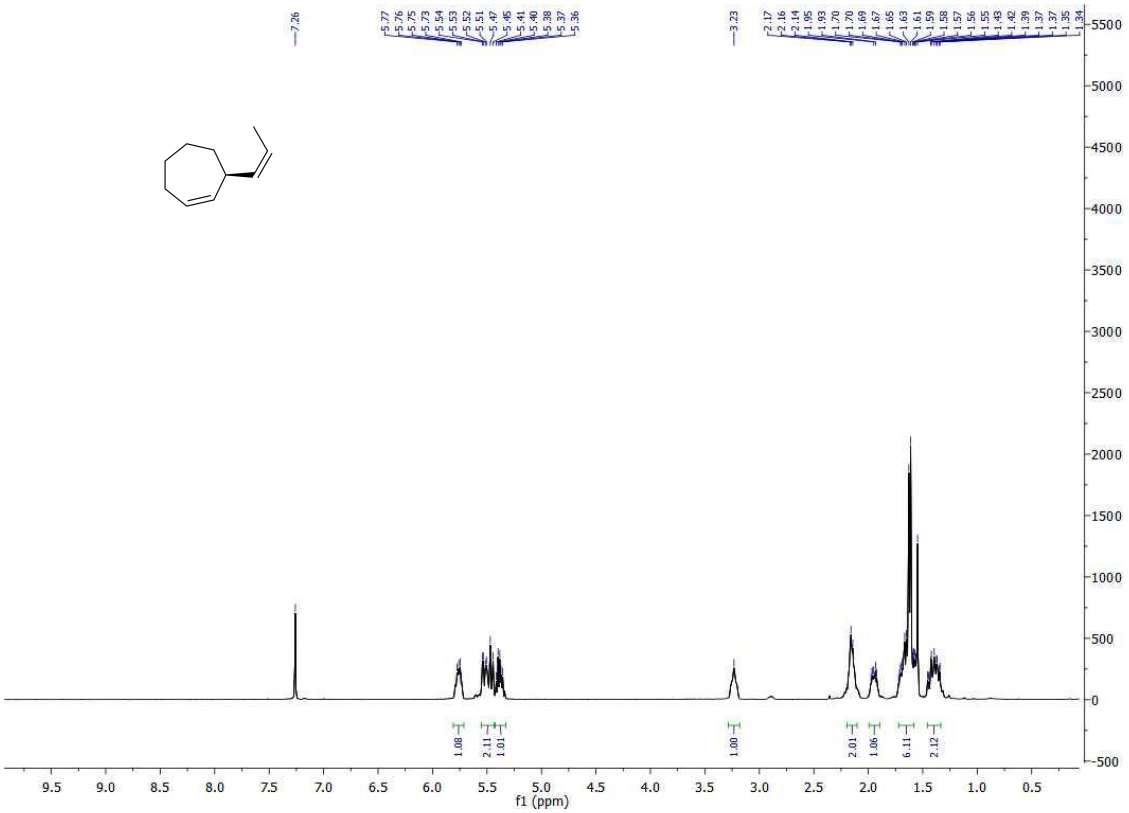

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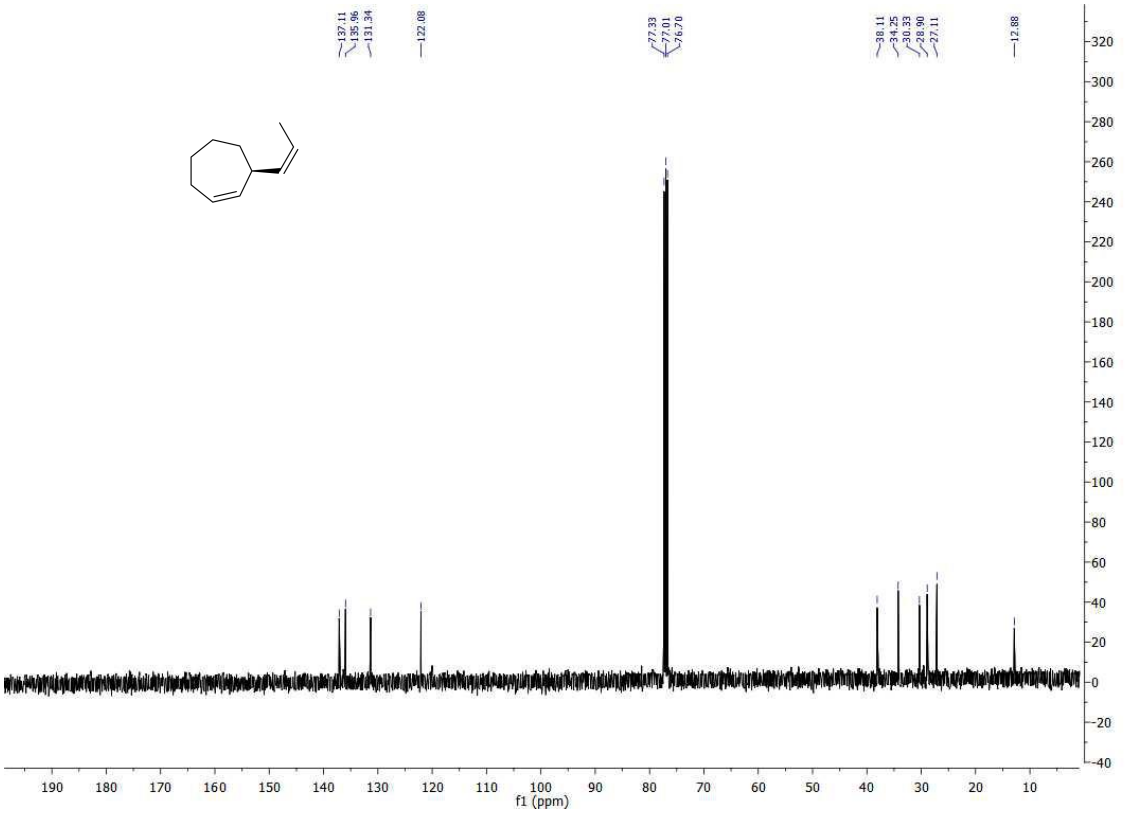

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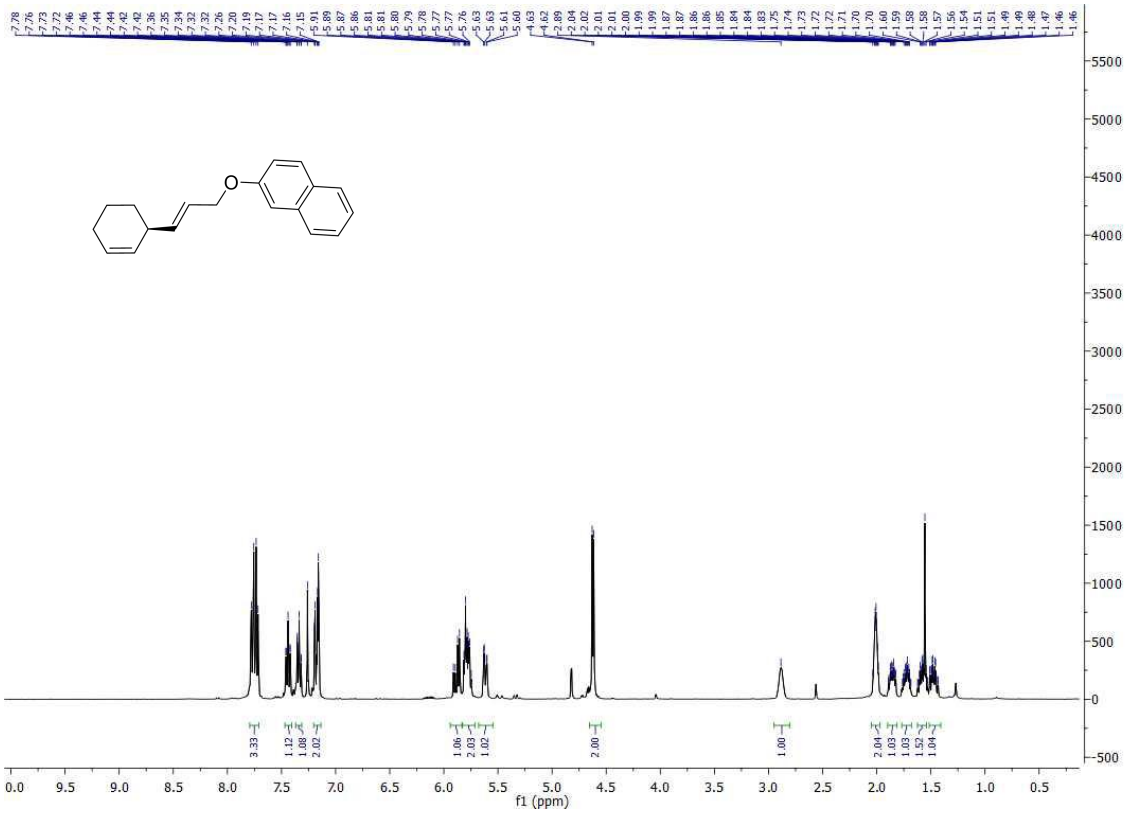

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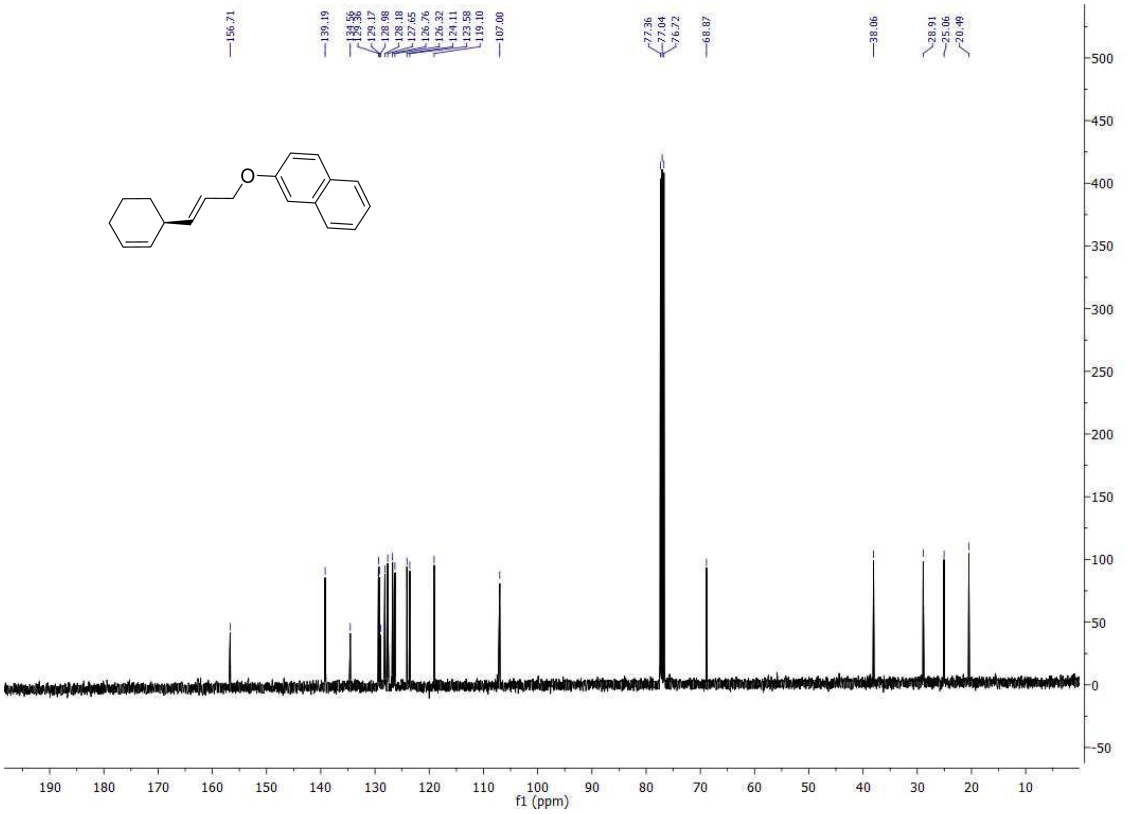

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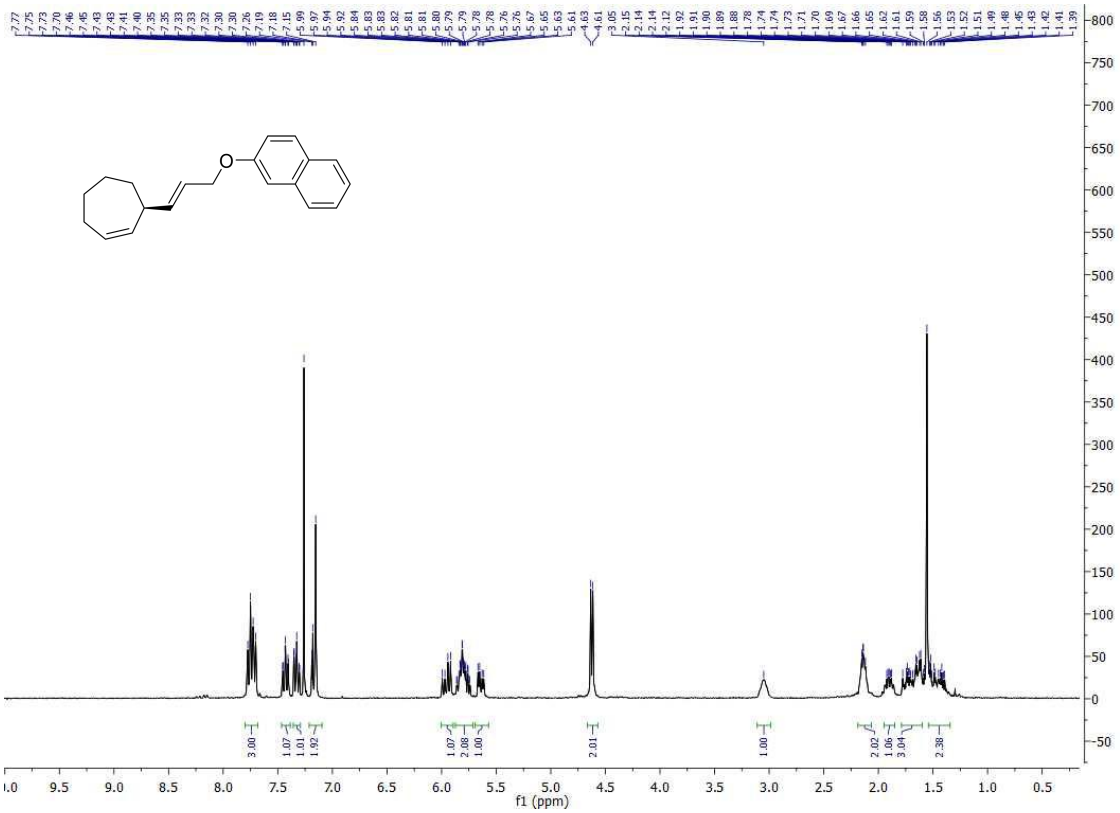

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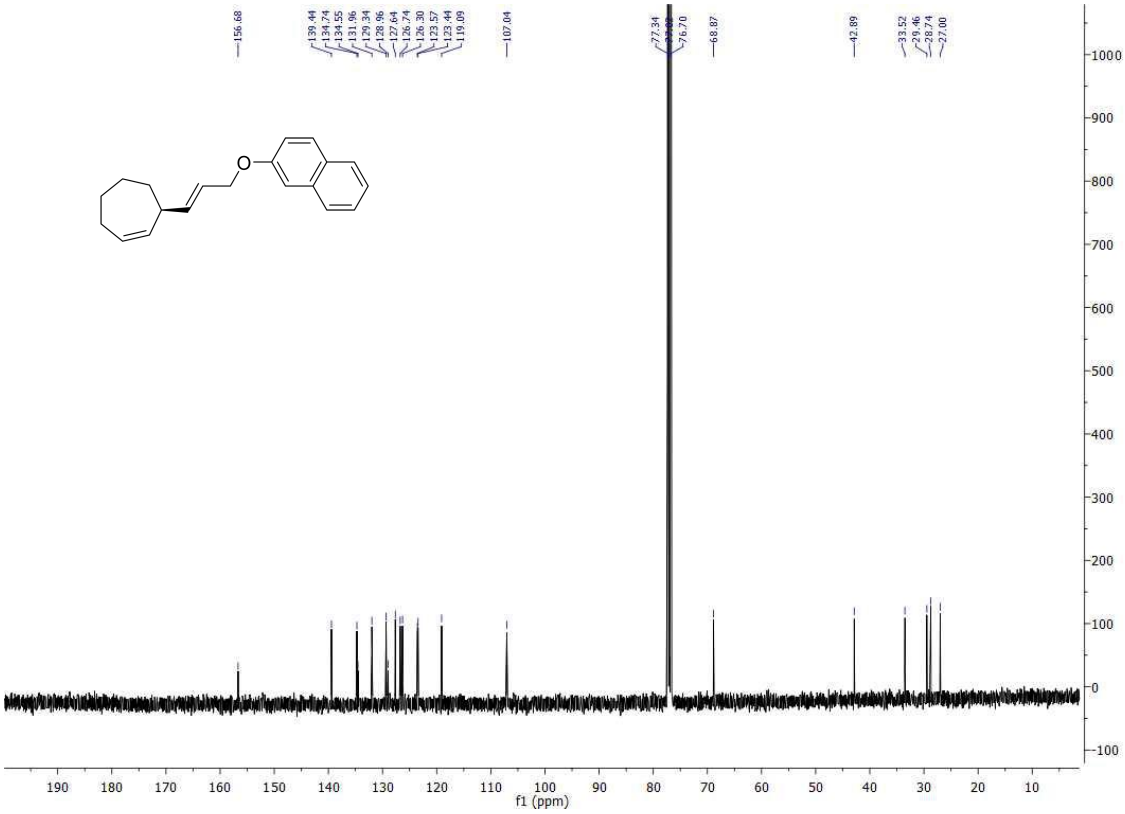

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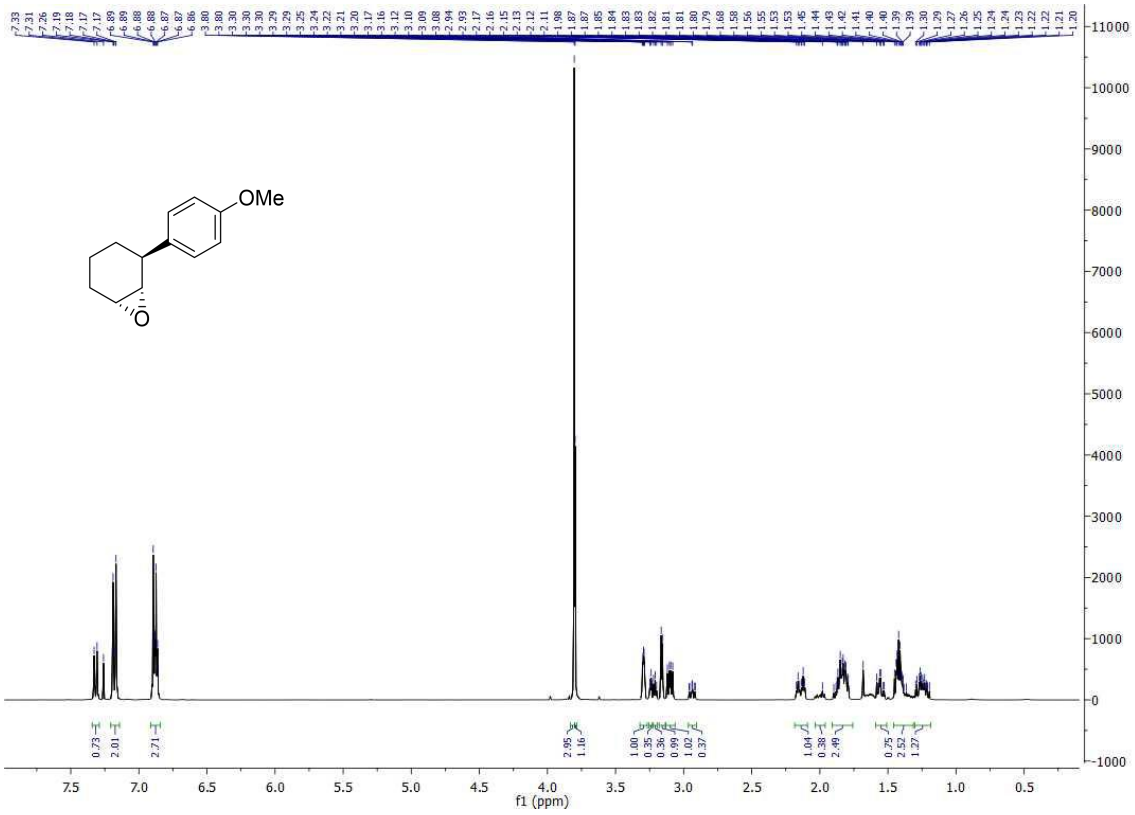

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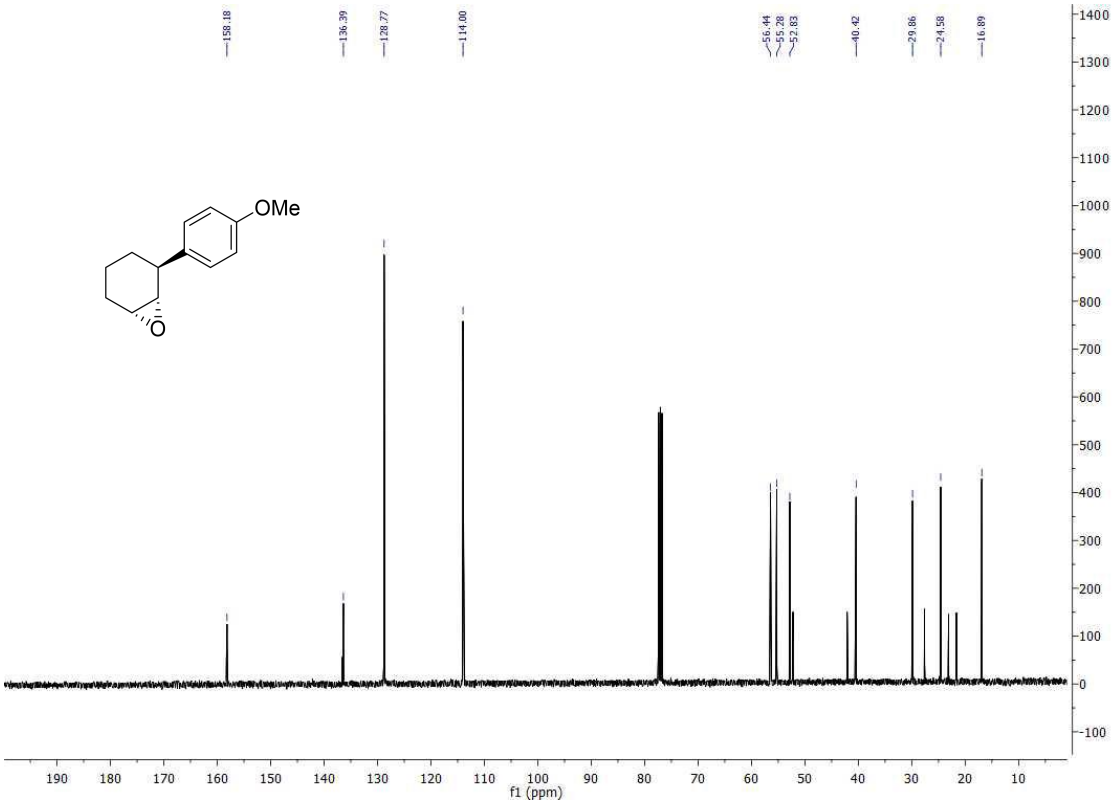

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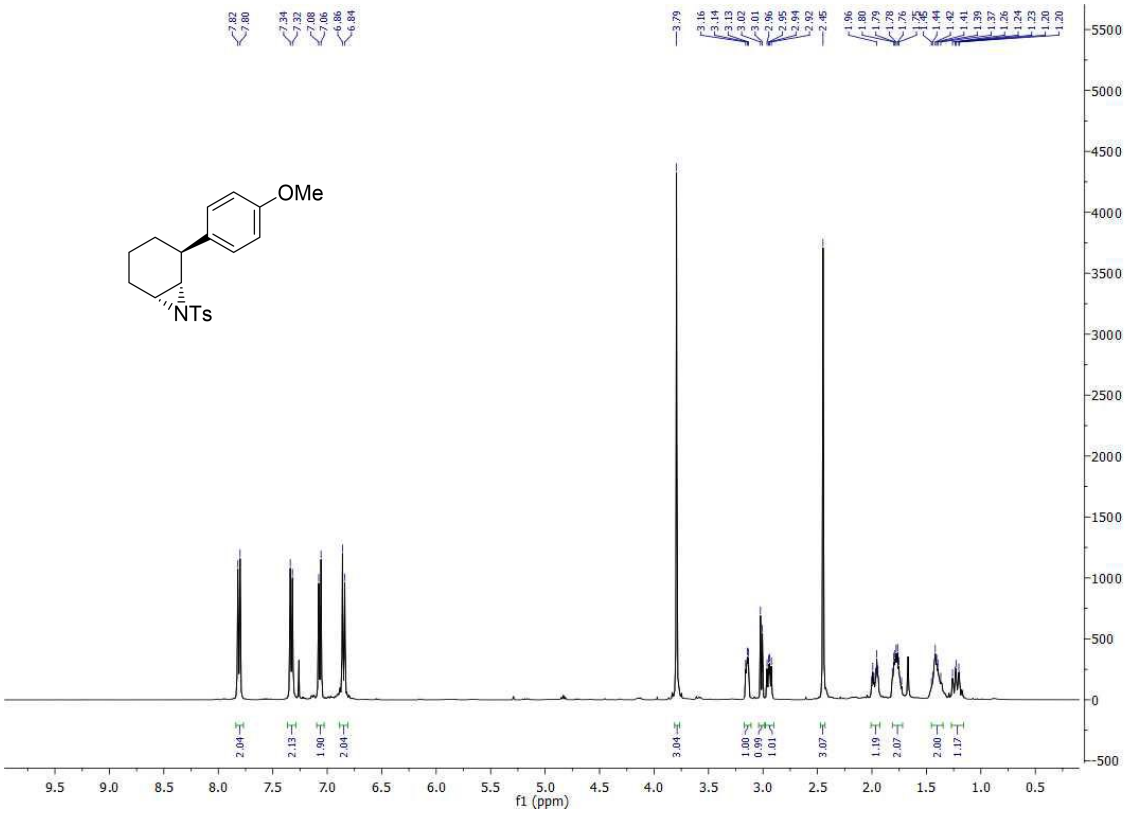

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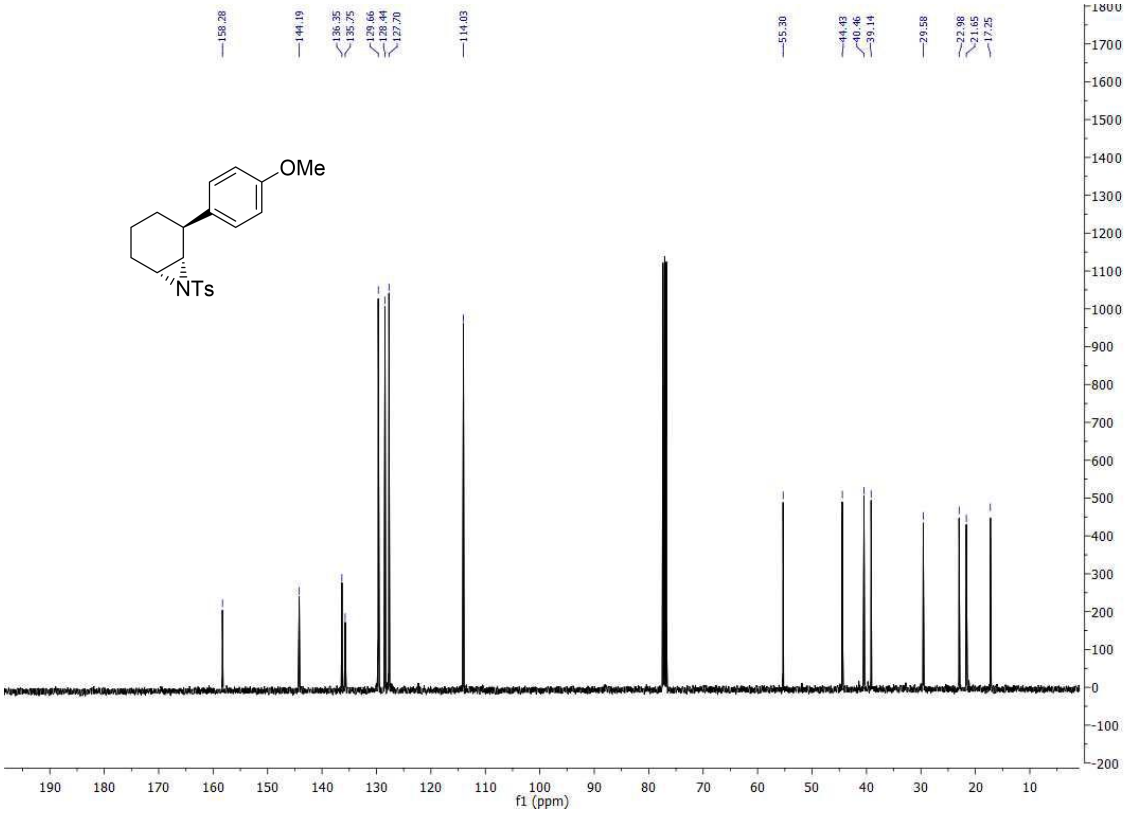

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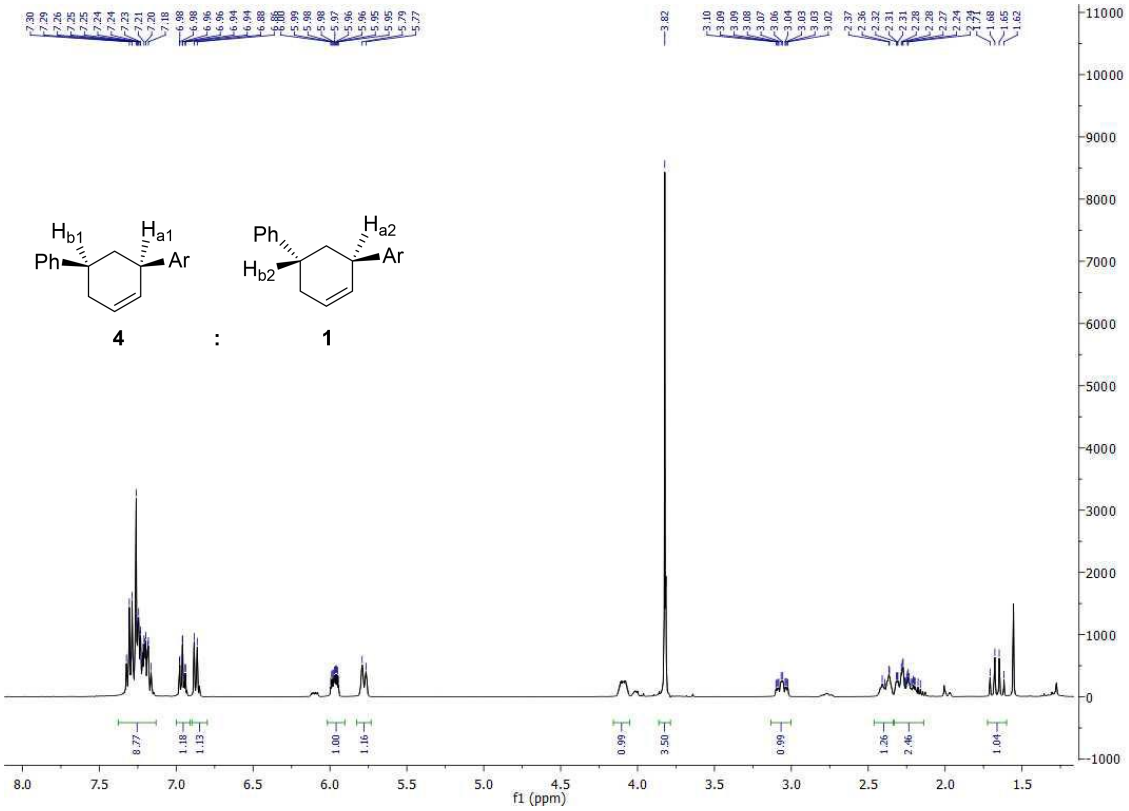

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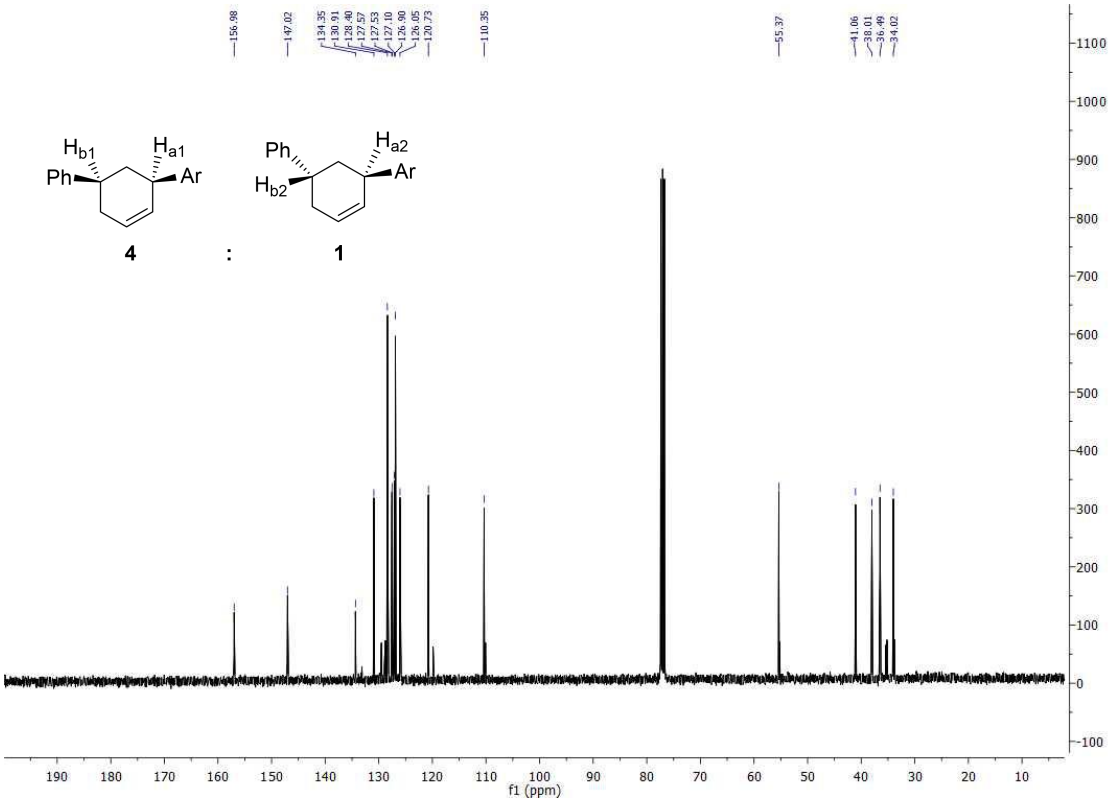

X-Ray Crystal Data

Chemical formula	C13H26Cl2CuN3
Formula weight	358.81 g/mol
Temperature	123(2) K
Wavelength	1.54178 Å
Crystal size	0.020 x 0.260 x 0.340 mm
Crystal habit	colorless plate
Crystal system	monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 12.2576(10) Å α = 90°
	b = 9.2057(6) Å β = 90.282(6)°
	c = 15.2983(12) Å γ = 90°
Volume	1726.2(2) Å3
Z	4
Density (calculated)	1.381 g/cm3
Absorption coefficient	4.554 mm-1
F (000)	752

2.8 Reference

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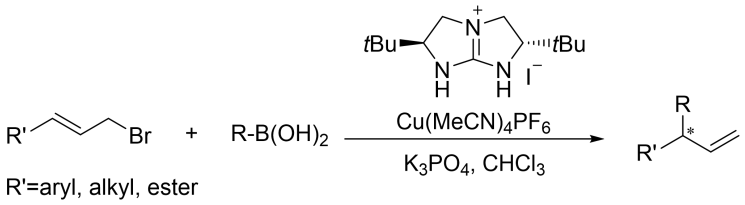
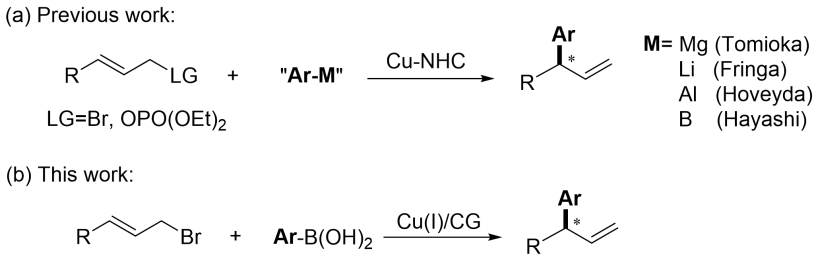
Chapter Three

Enantioselective Allylic Substitution of Prochiral Acyclic Bromides with Boronic Acids



3.1 Overview: Allylic Arylation of Acyclic Bromides

Copper-catalyzed enantioselective allylic arylation reactions (see Section 1.3.3) have been extensively explored by Tomioka (organomagnesium reagents), Fringa (organolithium reagents), Hoveyda (organoaluminum reagents) and Hayashi (organoboron reagents). Generally, excellent regio- and enantioselectivity were achieved whereas catalyst used in all the above work was dominated by Cu-NHC complexes.[1] For organometallic reagents including Mg, Al and Li, reaction profiles normally require a rather low temperature for high selectivity. While for organoboron reagents, reactions can normally be conducted at room temperature with comparable selectivity, which is attractive for practical use, especially industrial application. The attempt to use readily available and environmentally benign organoboron reagents instead of organometallic reagents is still challenging but worth efforts. On the other hand, in copper-catalyzed EAS reactions using non-NHC ligand, only one example of phosphine ligand used for sp^2-hybridized organozirconium reagents was reported by Fletcher.[2] Exploration to use other catalyst system other than Cu-NHC is also interesting which might help expand the substrate types to a wide range.



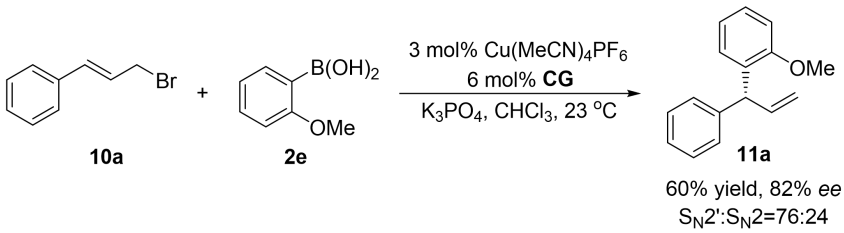
Scheme 3.1 Asymmetric allyl arylation catalyzed by Cu(I).

The successful EAS reaction of cyclic allyl bromides (see Chapter 2) leads us to probe the possibility of utilizing the established methodology for that of prochiral acyclic substrates, which can give access to more synthetically diverse molecules. Therefore, an array of acyclic allylic bromides were chosen for the test and promising results were demonstrated as follows. This work also showed that Cu(I) and guanidinium catalyst system could be a great alternative of Cu-NHC complex in asymmetric Csp^3-Csp^2 cross coupling reactions.

3.2 Enantioselective Allylic Substitution

3.2.1 Enantioselective Allylic Arylation

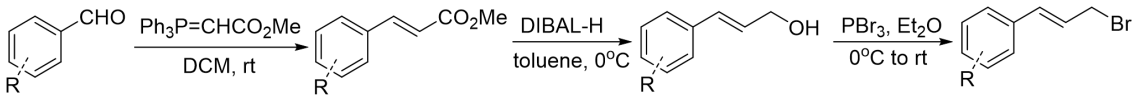
Cinnamyl bromide **10a** was initially tested for the asymmetric allylic arylation with aryl boronic acid **2e**. Results were shown in Scheme 3.2.

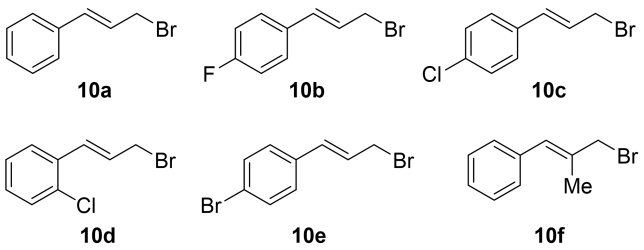


Scheme 3.2 Asymmetric allylic arylation of cinnamyl bromide.

In the standard condition where catalytic amount of $Cu(MeCN)_4PF_6$ and **CG** was used, **10a** was reacted with (2-methoxyphenyl)boronic acid **2e** and successfully transformed to arylated product. The optically active S_N2' product **11a** was obtained in 82% *ee*, together with S_N2 product in a ratio of 76:24. While in reported work by Fringa in 2016, (2-methoxyphenyl)lithium reagent was used for the identical transformation catalyzed by Cu-NHC complex and the desired product was obtained in only 26% *ee*.[3]

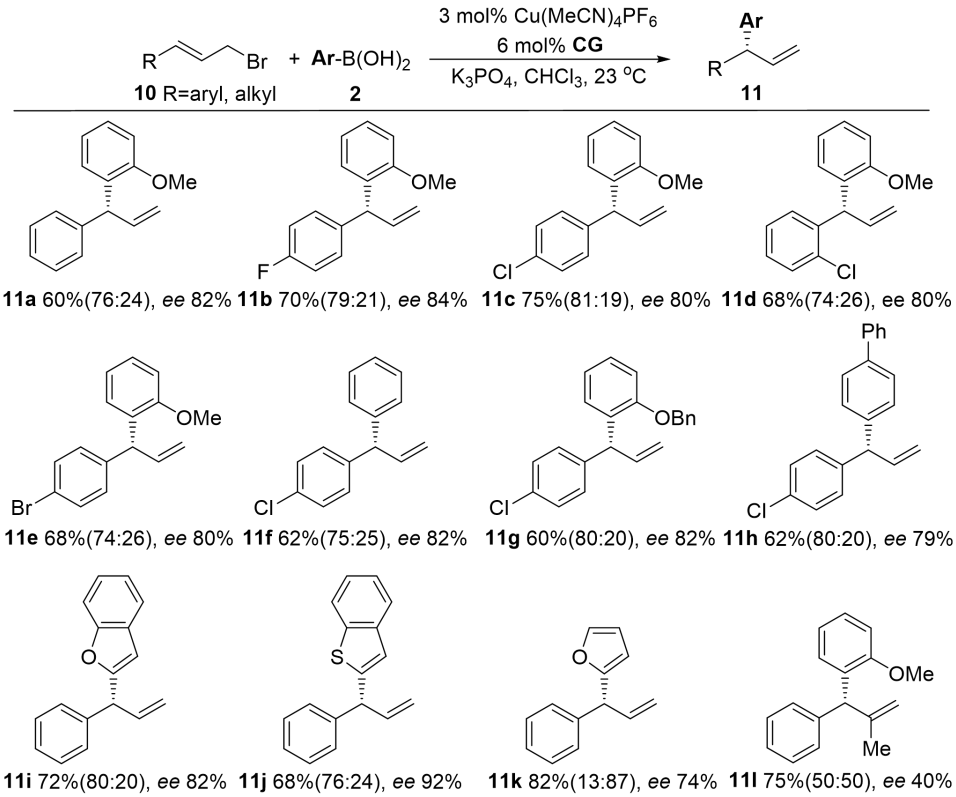
However, the moderate regioselectivity towards S_N2' product in our reaction was not significantly improved when further changes were made to condition parameters including copper salt, base, solvent and temperature. This indicates that enantio- and regio-discrimination process of the reaction strongly depended on the structure of chiral guanidinium and related intermediates.





Scheme 3.3 Synthesis of cinnamyl bromide derivatives.

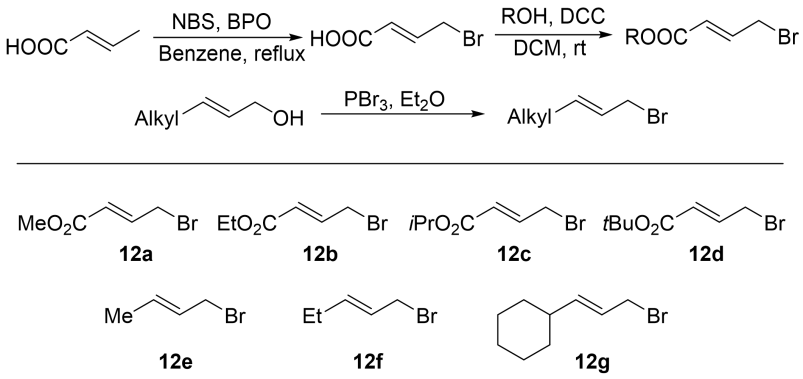
A series of cinnamyl bromide derivatives **10b-f** were prepared (Scheme 3.3) according to literature procedure.[4] They were later screened under the identical condition for enantioselective arylation reaction (Scheme 3.4). Substrates with halogen substitution on the phenyl ring reacted smoothly with **2e** to generate desired S_N2' products **11b**, **11c** and **11e** in a similar regioselectivity with **11a**. *Ortho*-substituted cinnamyl bromide showed little negative effect on the results, giving S_N2' product **11d** in 80% *ee*. Alkoxyl- and aryl-substitution of the aryl boronic acids on different positions was also tolerated which affords **11f-h** in good enantioselectivity as expected.



Scheme 3.4 Enantioselective allylic arylation of cinnamyl bromide derivatives. Results of each product are shown as: yield % (S_N2':S_N2), *ee* value.

Furthermore, heteroarene boronic acids were found to be suitable substrates in the profile as well, installing benzofuran group in 82% *ee* and benzothiophene in 92% *ee*. However, to our disappointment, when 2-furan boronic acid was employed in the same condition, quite poor regioselectivity with S_N2':S_N2 ratio of 13:87 was observed whereas desired S_N2' product **11k** was produced in moderate 74% *ee*. Tri-substituted cinnamyl bromide **10f** was later tried and desired geminal di-substituted terminal olefin **11l** was obtained in only 40% ee and still poor regioselectivity, implying that steric effect plays a crucial role in the enantiodiscrimination process.

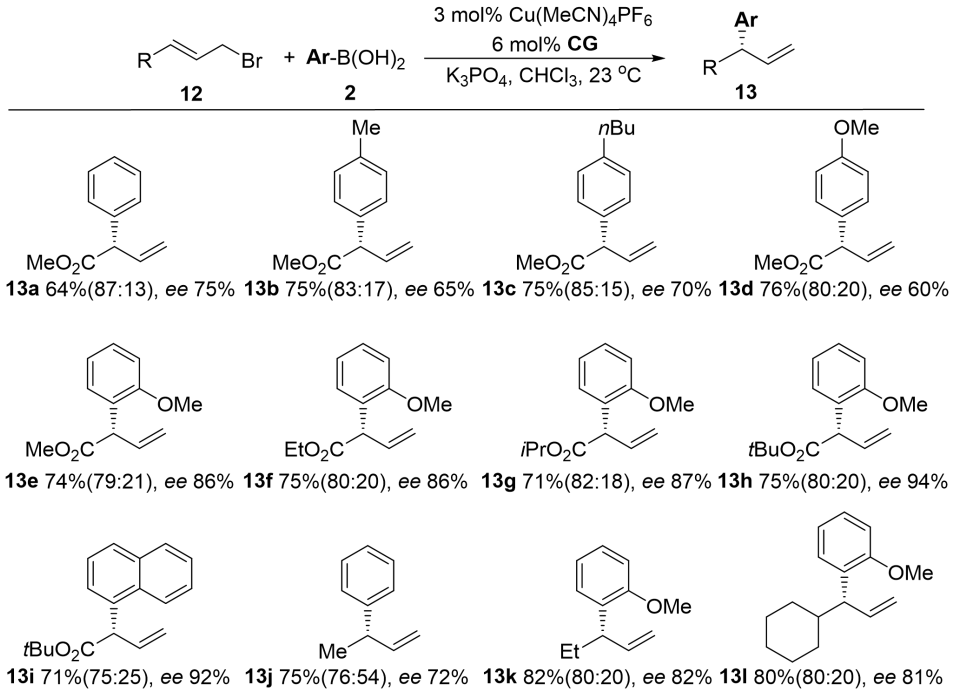
Upon established the EAS reaction of cinnamyl bromide derivatives in Cu(I) and **CG** system, expansion of scope of allylic bromides was later tried to ester- and alkyl-substituted allylic bromides (Scheme 3.5).[5] Different ester-substituted bromides **12a-d** with variation in steric bulkiness of ester group were prepared via radical allylic substitution of acid followed by esterification. Alkyl-substituted allylic bromides **12e-g** were prepared by bromination of corresponding allylic alcohols.



Scheme 3.5 Synthesis of ester- and alkyl-substituted bromides.

All the above allylic bromides **12** were then successfully utilized to show good reactivity in asymmetric allylic arylation catalyzed by Cu(I) and **CG** (Scheme 3.6). First of all, commercial available methyl 4-bromocrotonate **12a** was reacted with alkoxyl- and alkyl-substituted aryl boronic acids under standard condition.

The reactions proceeded smoothly to give arylated S_N2' products **13a-d** in moderate *ee* around 70%. (2-Methoxyphenyl)boronic acid **2e** showed the highest selectivity among all aryl boronic acids, leading the formation of **13e** in 86% *ee*. Increased bulkiness of the carboxylic ester group didn't decrease the enantioselectivity significantly, giving **13f-h** with up to 94% *ee*. Bromide **12d** was also reacted with naphthalen-1-ylboronic acid to afford **13i** in 92% *ee*, showing the positive effect of steric bulkiness in the reaction. To our pleasure, aliphatic substituted allylic bromides were found to show good reactivity in the reaction as well, producing **13j-l** in good enantioselectivity.



Scheme 3.6 Enantioselective allylic arylation of various acyclic bromides. Results are shown as: yield % (S_N2':S_N2), *ee* value.

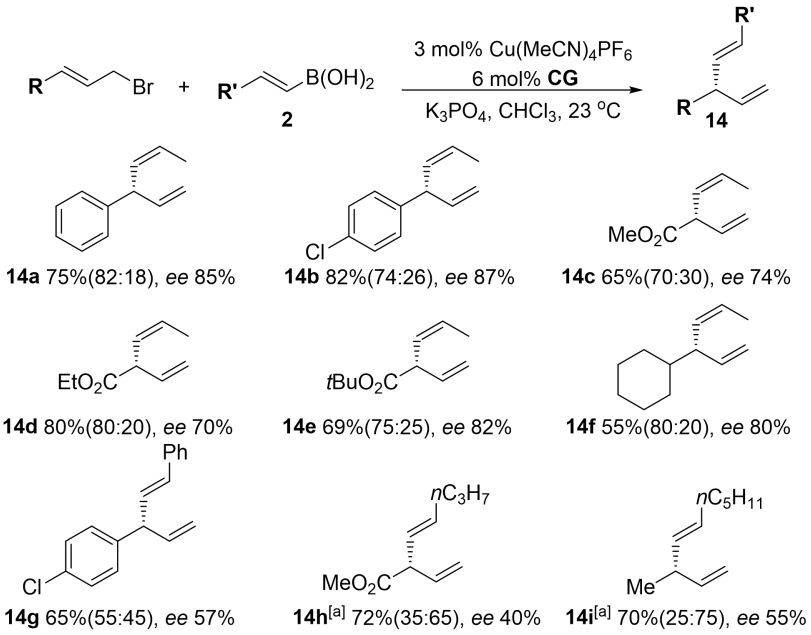
3.2.2 Enantioselective Allylic Vinylation

Effective enantioselective allylic arylation where aryl group as sp^2-hybridized nucleophile is installed at the γ position has been reported be several groups since 2008. However, vinyl group as sp^2-hybridized nucleophile has been less explored probably due to its lower availability in organometallic reagents. Indeed, only several vinyl boron reagents including borates, esters and acids have been used for

EAS reactions.

Here we also applied our catalyst system to the enantioselective allylic vinylation of acyclic bromides. Results are shown in Scheme 3.7. The prop-1-en-1-ylboronic acid **2y** bearing a (*Z*)-configuration was used for the vinylation. Cinnamyl bromide **10a** was well functionalized with (*Z*)-vinyl to produce S_N2' product **14a** in 85% *ee* and good regioselectivity. A *para*-substituted Cl atom didn't affect the result obviously, giving corresponding product **14b** in 87% *ee*. To our delight, (*Z*)-vinyl was smoothly reacted with either ester- or alkyl-substituted allylic bromides to give good enantioselectivity of **14c-f**.

In contrast, vinyl boronic with (*E*)-configuration delivered poor result. Phenyl-substituted (*E*)-vinyl group was installed with only 57% *ee* in the S_N2' product **14g**, which was similar to the poor enantioselectivity in alkyl-substituted vinylation product **14h-i**. Increase of catalyst loading didn't help improve the results obviously and decrease of reaction temperature only led to slow reaction rate.



Scheme 3.7 Enantioselective allylic vinylation of various acyclic bromides. Results are shown as: yield % (S_N2':S_N2), *ee* value. [a]: GC yield.

As was shown in section 3.2.1 and 3.2.2, the enantioselective arylation and vinylation of prochiral acyclic allylic bromides with Cu(I)/CG catalyst generally

proved to be effective while the enantioselectivity was not excellent which requires further exploration. Several aspects regarding to the reaction are listed as below which can be considered for achieving improvement.

1. Catalyst structure. As was shown by the different catalytic capacity of CG and CG' in Table 2.1, the substituent on guanidinium structure affects the reactivity significantly. Variation on the substituent group of guanidinium catalyst might help improve the enantioselectivity during the chirality-generated procedure. Further, the cyclic structure of guanidinium catalyst can also be varied to rigid cycle or flexible cycle based on different ring size for different reactivity.

2. Copper salt. Different copper(I) salt with various coordination ligands can be screened for the reaction. Similar in Table 2.1, obvious improvements can be obtained when copper salt was changed. A better coordination environment might help establish the efficient enantioselective process, which might deliver better selectivity.

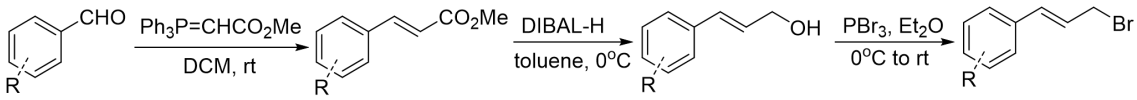
3. Reaction conditions. Reaction parameters including concentration, temperature and solvent can be screened for acyclic substrates since the stability of the reactive intermediate might rely strongly on them.

3.3 Conclusion

In summary, we have described here an enantioselective arylation and vinylation of prochiral acyclic allylic bromides with Cu(I)/CG catalyst in the presence of K_3PO_4 in $CHCl_3$. Several types of acyclic allyl bromides with aryl, ester or alkyl substitution were all suitable substrates for the enantioenriched transformation. Interesting structures such chiral 1,4-skipped dienes were synthesized with the easy protocol, excluding low temperature condition or the use of strong base. Indeed, the reaction condition is identical to the direct arylation and vinylation of cyclic allylic bromides in Chapter 2, showing the excellent capability of the catalyst system. However, both the regio- and enantioselectivity of the desired S_N2' products were not excellent, which requires further modification of reaction profiles, especially the structure of **CG** catalyst.

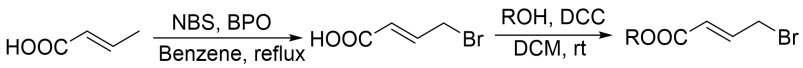
3.4 Experimental Section

3.4.1 Preparation of Cinnamyl Bromide Derivatives



Mixture of benzaldehyde (1 eq) and methyl 2-(triphenylphosphoranylidene)acetate (1.05 eq) in DCM was stirred overnight at rt. Residue was triturated with hexane/Et_2O. Filter, concentrate and purify by silica gel chromatography to give α,β-unsaturated ester. To a solution of ester (1 eq) in DCM was added DIBAL-H (1 M in toluene, 2.2 eq) slowly at －78 °C. After 2 h, quench reaction with 10% aq.NaOH. Extract with DCM for three times. Organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give allylic alcohol. To a solution of allylic alcohol in Et_2O was added PBr_3 (1 eq) dropwise at 0 °C. Mixture was then poured into aq.$NaHCO_3$. Extract with Et_2O and organic layers were washed with aq.$Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and concentrated to give crude product was used without purification.

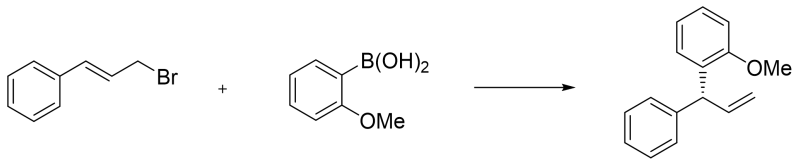
3.4.2 Preparation of 4-Bromocrotonates



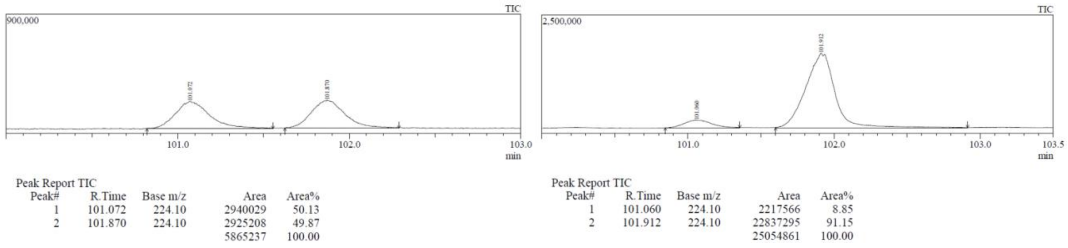
The 4-bromocrotonates were prepared according to literature procedure. (1) To a solution of crotonic acid (1 eq) in benzene was added NBS (1.03 eq) and BPO (0.01 eq). The mixture was heated to reflux for 2 h and then cooled to 5 °C. Filter and wash with cold toluene. Concentrated residue was extracted with refluxing hexane for three times. Recrystalization in hexane gave the 4-bromocrotonic acid as white colorless solid. (2) 4-bromocrotonic acid (1 eq) was dissolved in DCM. ROH (1.1 eq) and DMAP (0.1 eq) were added into mixture and then cooled to 0 °C. DCC (1.05 eq) was added slowly. The mixture was stirred overnight at rt. Upon full conversion, mixture was filtered and washed with DCM. The filtrate was

concentrated and purified by flash column chromatography (Hex/EA 100:1) to give 4-bromocrotonates.

3.4.3 Characterization and Spectra of Acyclic Products



(*R*)-1-methoxy-2-(1-phenylallyl)benzene (11a): Following general procedure catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 60% yield (S_N2':S_N2=76:24) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +6.8 (c=0.88 in CH_2Cl_2, 82 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.26 – 7.19 (m, 4H), 7.19 – 7.14 (m, 1H), 6.95 (td, *J* = 7.5, 0.8 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.38 – 6.28 (m, 1H), 5.26 – 5.16 (m, 2H), 4.95 (dt, *J* = 17.1, 1.6 Hz, 1H), 3.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.0, 143.2, 140.5, 131.8, 129.3, 128.7, 128.1, 127.6, 126.0, 120.5, 116.0, 110.9, 77.4, 77.1, 76.7, 55.6, 47.6. **HRMS** (ESI) m/z calcd. for $C_{16}H_{17}O$ $[M+H]^+$: 225.1279, found: 225.1282. **Enantiomeric excess** of 82% was determined by chiral HPLC [chiral column IA3; methods: eluting solvent: hexane, flow speed: 0.5 ml/min; major enantiomer t_R= 11.7 min; minor enantiomer t_R= 12.5 min].



Peak Report TIC

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			5865237	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
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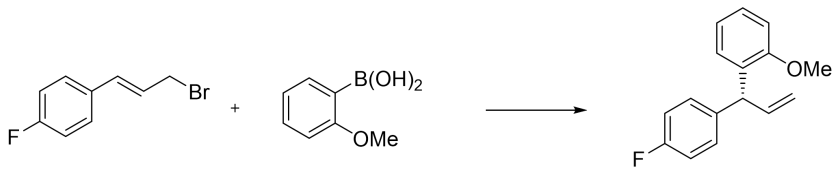
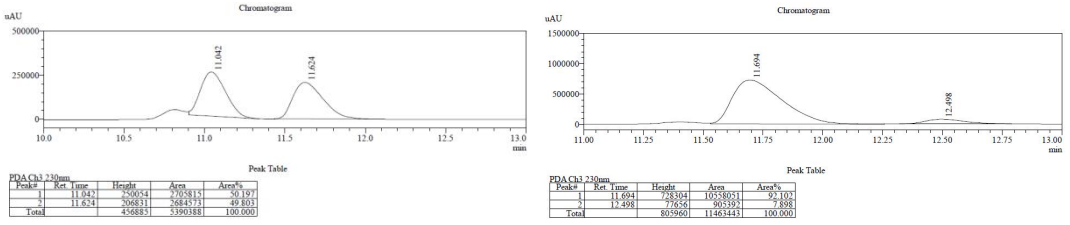
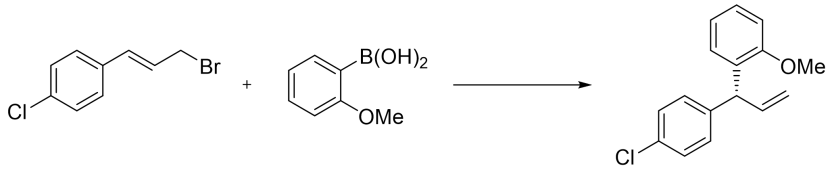
2	101.912	224.10	22837295	91.15
			25054861	100.00



(*R*)-1-(1-(4-fluorophenyl)allyl)-2-methoxybenzene (11b): Following general procedure catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 70% yield (S_N2':S_N2=79:21) as a colorless

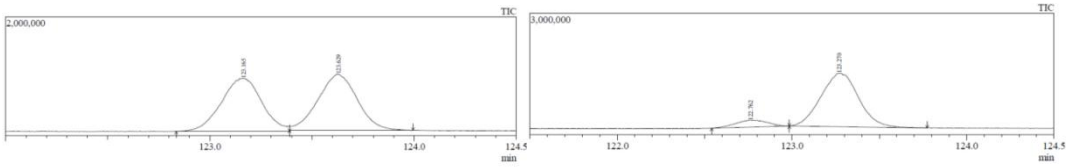
oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = −8.89 (c=1.8 in CH_2Cl_2, 84 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 1H), 7.17 – 7.12 (m, 3H), 7.00 – 6.92 (m, 3H), 6.88 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.36 – 6.22 (m, 1H), 5.22 (dt, *J* = 10.2, 1.5 Hz, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 4.92 (dt, *J* = 17.1, 1.6 Hz, 1H), 3.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.5, 160.1, 156.9, 140.3, 131.6, 130.1, 130.0, 129.1, 127.7, 120.5, 116.2, 114.9, 114.7, 110.9, 55.5, 46.9. **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}FO$ $[M+H]^+$: 243.1185, found: 243.1194. **Enantiomeric excess** of 84% was determined by chiral HPLC [chiral column IA3; methods: eluting solvent: hexane, flow speed: 0.5 ml/min; major enantiomer t_R= 11.7 min; minor enantiomer t_R= 12.5 min].





(*R*)-1-(1-(4-chlorophenyl)allyl)-2-methoxybenzene (11c): Following general procedure catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 75% yield (S_N2':S_N2=81:19) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ =+2.2 (c=1.4 in CH_2Cl_2, 80 % *ee*). [reported +5.0 (c=1 in $CHCl_3$) for *R* analogue in 26% *ee*][3a]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.20 – 7.11 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.27 – 6.17 (m, 1H), 5.57 (d, *J* = 5.8 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 140.5, 138.9, 134.5, 130.4, 129.9, 129.5, 129.2, 127.8, 127.4, 126.4, 120.3, 116.5, 110.8, 55.7, 44.3. **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}OCl$ $[M+H]^+$: 259.0890, found: 259.0888. **Enantiomeric excess** of 80% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25

μm df); methods: 50 ºC (1 min)-1-175 ºC (1 min); major enantiomer t_R= 123.2 min; minor enantiomer t_R= 122.7 min].



Peak Report TIC

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			25000821	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
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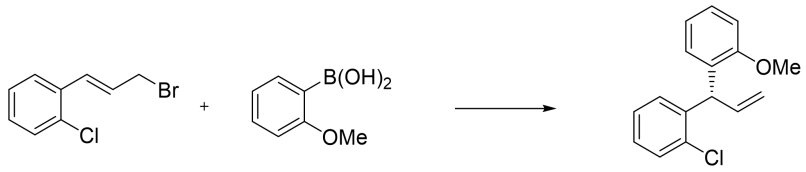
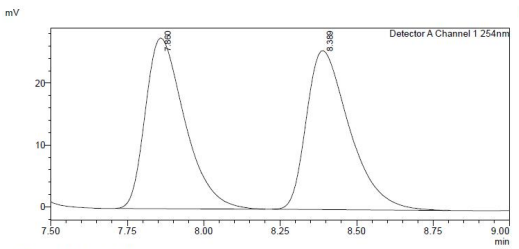
2	123.270	258.10	19902827	90.07
			22096778	100.00



(*S*)-1-chloro-2-(1-(2-methoxyphenyl)allyl)benzene (11d): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 68% yield (S_N2':S_N2=74:26) as a colorless oil. **Opt. Rot**.: $[\alpha]_{589}^{23} = -24.7$ (c=1.75 in CH_2Cl_2, 84 % ee). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.14 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.32 – 6.16 (m, 1H), 5.57 (d, *J* = 5.8 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 140.5, 138.9, 134.5, 130.4, 129.9, 129.5, 129.2, 127.8, 127.4, 126.4, 120.3, 116.5, 110.8, 55.7, 44.3. **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}OCl$ $[M+H]^+$: 259.0890, found: 259.0889. **Enantiomeric excess** of 80% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 8.2 min; minor enantiomer t_R= 7.8 min].



Detector A Channel 1 254nm

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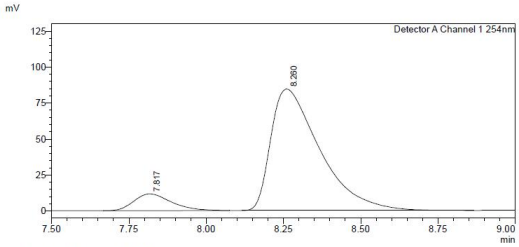

Detector A Channel 1 254nm

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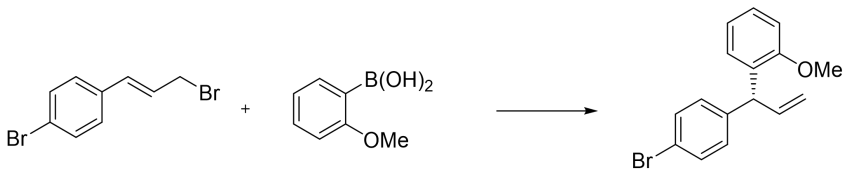
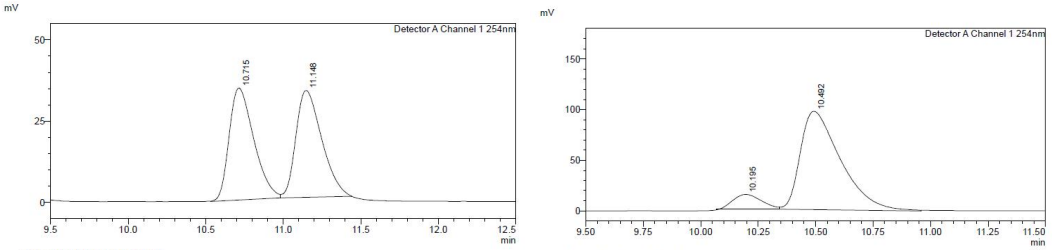
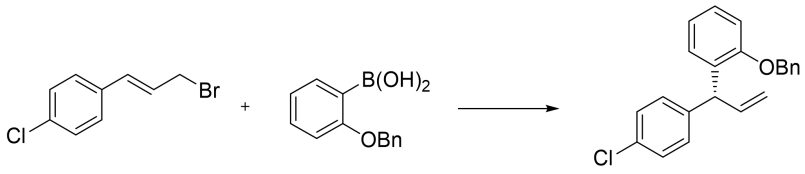


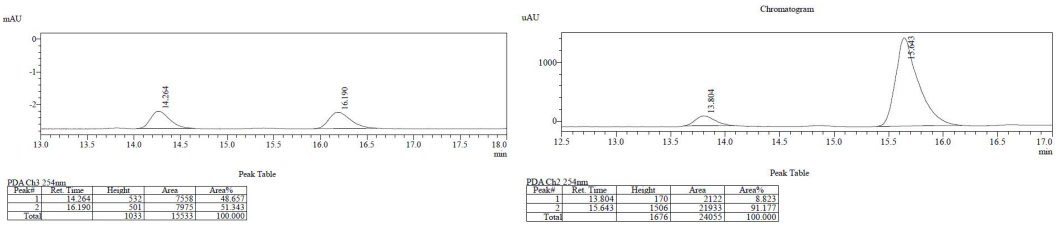
(*R*)-1-(1-(4-bromophenyl)allyl)-2-methoxybenzene (11e): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 68% yield (S_N2':S_N2=74:26) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +2.8 (c=2.67 in CH_2Cl_2, 80 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.33 – 6.20 (m, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 5.10 (d, *J* = 6.5 Hz, 1H), 4.91 (d, *J* = 17.1 Hz, 1H), 3.75 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 142.2, 139.9, 131.2, 130.4, 129.1, 127.8, 120.5, 119.8, 116.5, 110.8, 55.5, 47.2. **HRMS** (ESI) m/z calcd. for $C_{16}H_{16}OBr$ $[M+H]^+$: 303.0385, found: 303.0372. **Enantiomeric excess** of 80% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.8 ml/min; major enantiomer t_R= 10.5 min; minor enantiomer t_R= 10.2 min].

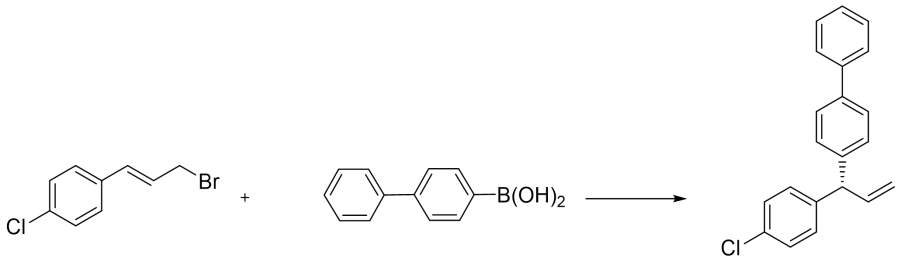




(*R*)-1-(benzyloxy)-2-(1-(4-chlorophenyl)allyl)benzene (11g): Following general procedure using (2-(benzyloxy)phenyl)boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 60% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +18.7 (c=2.16 in

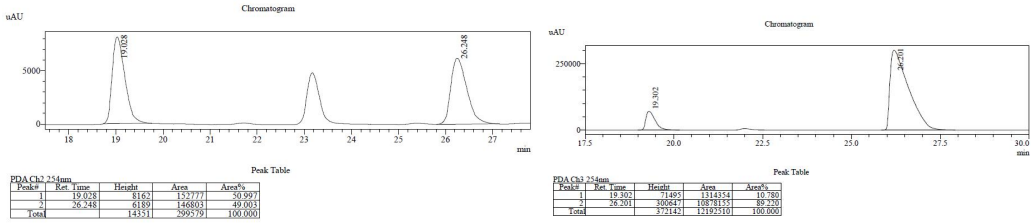
CH_2Cl_2, 82 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.24 – 7.14 (m, 6H), 7.08 (dd, *J* = 6.2, 4.5 Hz, 2H), 6.97 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.31 – 6.22 (m, 1H), 5.22 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.13 (d, *J* = 6.6 Hz, 1H), 4.99 (d, *J* = 3.3 Hz, 2H), 4.91 (dt, *J* = 17.1, 1.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.9, 141.7, 139.9, 137.0, 131.7, 131.6, 130.1, 129.2, 128.4, 128.2, 127.8, 127.3, 120.8, 116.6, 112.0, 70.0, 47.7. **HRMS** (ESI) m/z calcd. for $C_{22}H_{19}OCl$ $[M+H]^+$: 335.1203, found: 335.1193. **Enantiomeric excess** of 82% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 15.6 min; minor enantiomer t_R= 13.8 min].

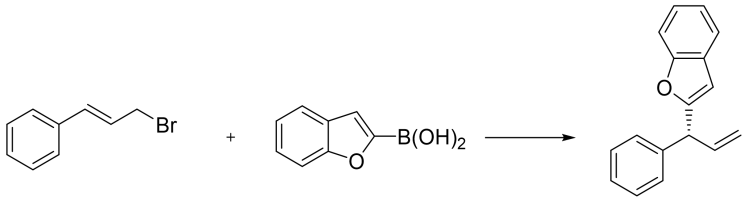




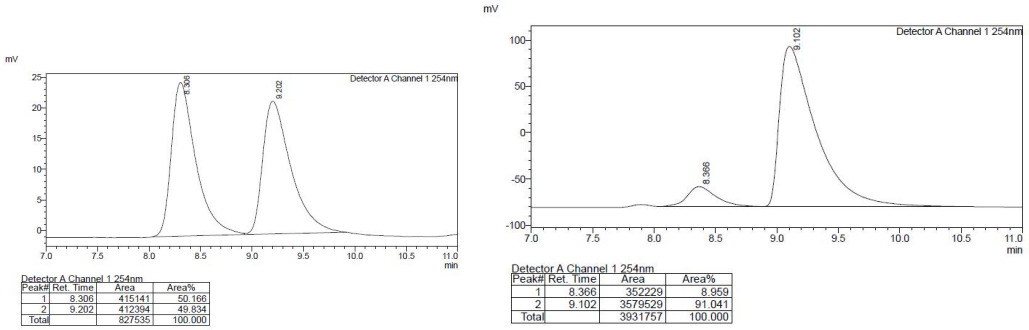
(*S*)-4-(1-(4-chlorophenyl)allyl)-1,1'-biphenyl (11h): Following general procedure using [1,1'-biphenyl]-4-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 62% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +7.9 (c=0.52 in CH_2Cl_2, 80 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 4H), 7.43 (m, 2H), 7.36 – 7.31 (m, 1H), 7.31 – 7.27 (m, 2H), 7.23 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.29 (m, 1H), 5.27 (dt, *J* = 10.2, 1.2 Hz, 1H), 5.03 (dt, *J* = 17.1, 1.4 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.9, 141.7, 140.8, 140.1, 139.5, 132.3, 123.0, 128.9, 128.7, 128.6, 127.3, 127.2, 127.0, 116.8, 54.0. **HRMS** (ESI) m/z calcd. for $C_{21}H_{17}Cl$ $[M+H]^+$: 305.1097, found: 305.1101. **Enantiomeric excess** of 80% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane,

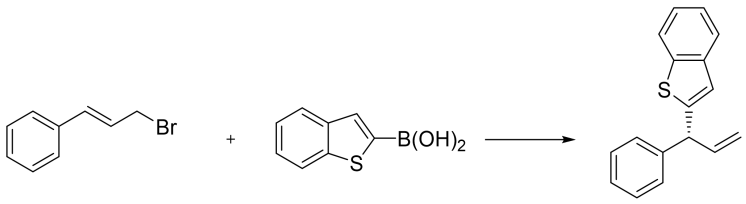
flow speed: 1 ml/min; major enantiomer t_R= 26.2 min; minor enantiomer t_R= 19.3 min].



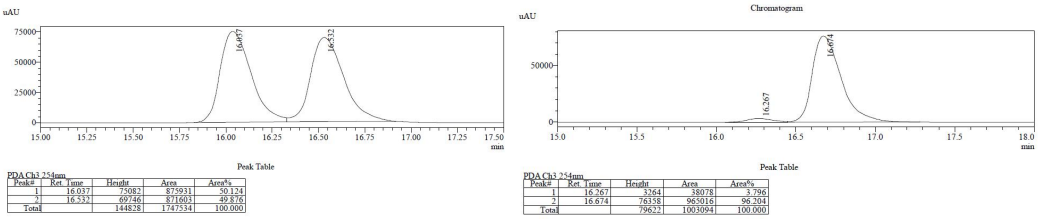


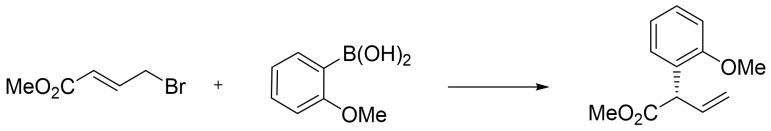
(*S*)-2-(1-phenylallyl)benzofuran (11i): Following general procedure using benzofuran-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 72% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ =−4.7 (c=0.4 in CH_2Cl_2, 82 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 1H), 7.43 – 7.39 (m, 1H), 7.36 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 7.24 – 7.11 (m, 2H), 6.45 (t, *J* = 0.9 Hz, 1H), 6.34 – 6.24 (m, 1H), 5.28 (dt, *J* = 10.1, 1.2 Hz, 1H), 5.14 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.87 (d, *J* = 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 155.0, 140.2, 137.4, 128.6, 128.4, 127.8, 127.1, 123.6, 122.6, 120.6, 117.3, 111.1, 103.8. **HRMS** (ESI) m/z calcd. for $C_{17}H_{14}O$ $[M+H]^+$: 235.1123, found: 235.1133. **Enantiomeric excess** of 82% was determined by chiral HPLC [chiral column IC; methods: eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 9.1 min; minor enantiomer t_R= 8.3 min].





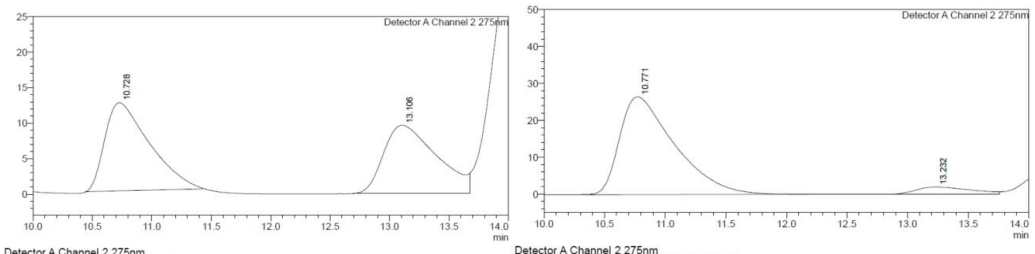
(*R*)-2-(1-phenylallyl)benzo[b]thiophene (11j): Following general procedure using benzothiophen-2-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 68% yield (S_N2':S_N2=76:24) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +6.2 (c=1.04 in CH_2Cl_2, 92 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.22 (m, 7H), 7.02 (s, 1H), 6.40 – 6.30 (m, 1H), 5.29 (dt, *J* = 10.1, 1.1 Hz, 1H), 5.19 (dt, *J* = 17.0, 1.3 Hz, 1H), 4.97 (d, *J* = 7.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 142.3, 139.8, 139.5, 128.6, 128.3, 127.1, 124.1, 123.8, 123.2, 122.2, 121.7, 116.9, 51.2. **HRMS** (ESI) m/z calcd for $C_{17}H_{14}S$ $[M+H]^+$: 251.0894, found: 251.0900. **Enantiomeric excess** of 92% was determined by chiral HPLC [chiral column IB3; methods: eluting solvent: hexane, flow speed: 0.7 ml/min; major enantiomer t_R= 16.6 min; minor enantiomer t_R= 16.2 min].





methyl (*S*)-2-(2-methoxyphenyl)but-3-enoate (13e): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 70% yield (S_N2':S_N2=79:21) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +65.6 (c=1.94 in CH_2Cl_2, 86 % *ee*). **^{1}H NMR** (400 MHz, CDCl3) δ 7.31 – 7.20 (m, 2H), 6.95 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.21 (ddd, J = 17.7, 10.1, 7.7 Hz, 1H), 5.21 (d, J = 10.2 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 4.64 (d, J = 7.7 Hz, 1H), 3.82 (s,

3H), 3.69 (s, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 173.1, 158.9, 135.9, 130.1, 129.0, 117.2, 114.1, 55.3, 54.8, 52.2. **HRMS** (ESI) m/z calcd for $C_{12}H_{14}O_3$ $[M+H]^+$: 207.1021, found: 207.1022. **Enantiomeric excess** of 86% was determined by chiral HPLC [chiral column ASH; methods: eluting solvent: hexane:IPA=99:1, flow speed: 0.5 ml/min; major enantiomer t_R= 10.7 min; minor enantiomer t_R= 13.2 min].



Detector A Channel 2 275nm

Peak#	Ret. Time	Area	Area%
1	10.728	324780	52.307
2	13.106	296134	47.693
Total		620915	100.000

Detector A Channel 2 275nm

Peak#	Ret. Time	Area	Area%
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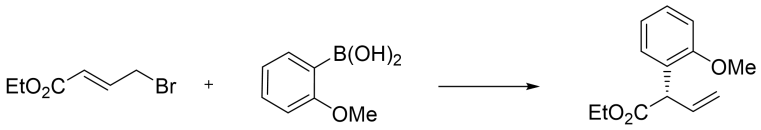
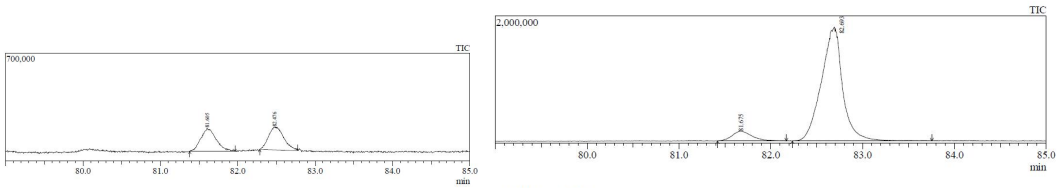
2	13.232	61138	6.829
Total		895234	100.000



ethyl (*S*)-2-(2-methoxyphenyl)but-3-enoate (13f): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 75% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +46.2 (c=1.9 in CH_2Cl_2, 85 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 6.99 – 6.94 (m, 1H), 6.94 – 6.87 (m, 1H), 6.28 – 6.17 (m, 1H), 5.23 (dt, *J* = 10.2, 1.1 Hz, 1H), 5.14 (dt, *J* = 17.2, 1.3 Hz, 1H), 4.64 (d, *J* = 7.7 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 156.7, 135.1, 129.0, 128.4, 127.0, 120.7, 117.4, 110.7, 60.8, 55.5, 49.7, 14.2. **HRMS** (ESI) m/z calcd. for $C_{13}H_{16}O_3$ $[M+H]^+$: 221.1178, found: 221.1179. **Enantiomeric excess** of 85% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min), major enantiomer t_R= 82.6 min; minor enantiomer t_R= 81.6 min].

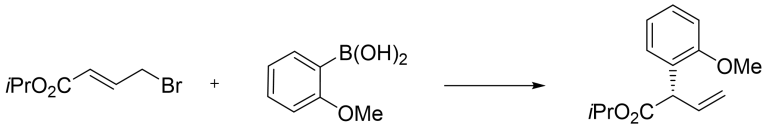


Peak Report TIC

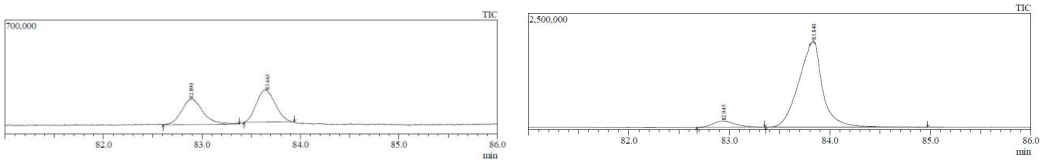
Peak#	R.Time	Base m/z	Area	Area%
1	81.605	147.10	1624862	50.17
2	82.476	147.10	1613969	49.83
			3238831	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	81.675	147.10	2310124	7.40
2	82.693	147.10	28925943	92.60
			31236067	100.00



iso-propyl (*S*)-2-(2-methoxyphenyl)but-3-enoate (13g): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 71% yield (S_N2':S_N2=82:18) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +24.1 (c=5.04 in CH_2Cl_2, 87 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.24 – 6.10 (m, 1H), 5.19 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 5.04 (dt, *J* = 12.6, 6.2 Hz, 1H), 4.56 (d, *J* = 7.7 Hz, 1H), 3.81 (s, 3H), 1.20 (dd, *J* = 12.3, 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 156.7, 135.2, 128.9, 128.3, 127.9, 120.6, 117.3, 110.6, 68.0, 55.4, 49.9, 21.7, 21.6. **HRMS** (ESI) m/z calcd. for $C_{14}H_{18}O_3$ $[M+H]^+$: 235.1334, found: 235.1333. **Enantiomeric excess** of 87% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-160 °C (1 min); major enantiomer t_R= 83.8 min; minor enantiomer t_R= 82.9 min].



Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	82.890	147.10	2356065	47.23
2	83.663	147.10	2632457	52.77
			4988522	100.00

Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
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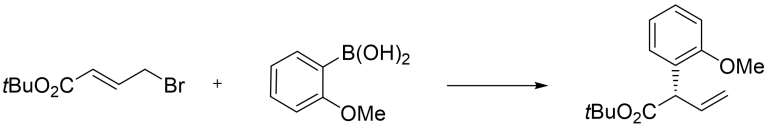
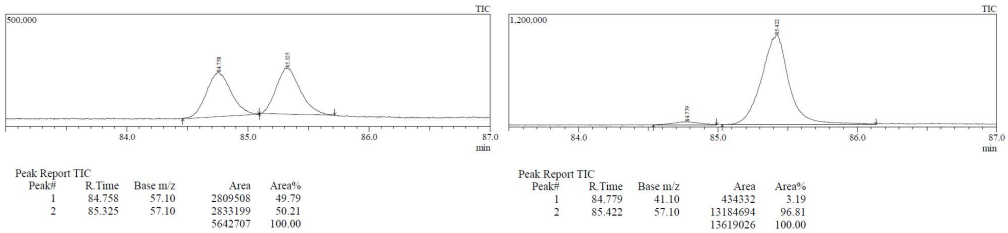
2	83.840	147.15	30728526	93.54
			32849461	100.00



***tert*-butyl (*S*)-2-(2-methoxyphenyl)but-3-enoate (13h):** Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol%

$Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 75% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +25.5 (c=1.63 in CH_2Cl_2, 94 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.25 – 6.13 (m, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.0, 156.7, 146.0, 135.5, 128.9, 128.2, 120.6, 117.0, 110.6, 80.6, 55.4, 50.6, 28.0. **HRMS** (ESI) m/z calcd. for $C_{15}H_{20}O_3$ $[M+H]^+$: 249.1491, found: 249.1499. **Enantiomeric excess** of 94% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-165 °C (1 min); major enantiomer t_R= 85.4 min; minor enantiomer t_R= 84.7 min].

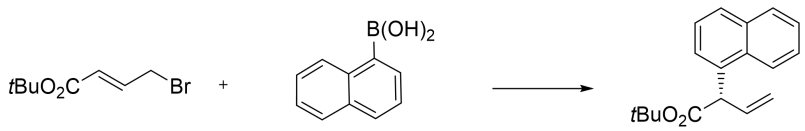


Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	84.758	57.10	2809508	49.79
2	85.325	57.10	2833199	50.21
			5642707	100.00

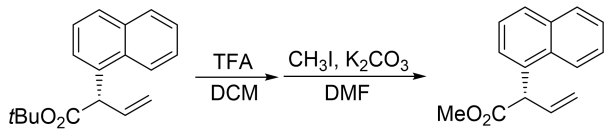
Peak Report TIC

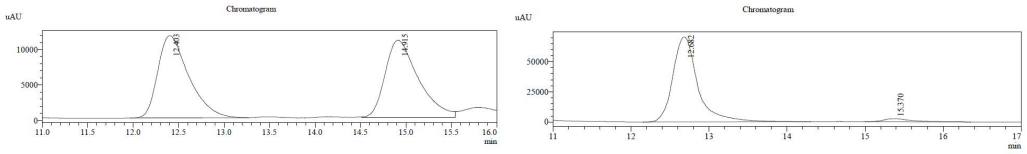
Peak#	R.Time	Base m/z	Area	Area%
1	84.779	41.10	434332	3.19
2	85.422	57.10	13184694	96.81
			13619026	100.00

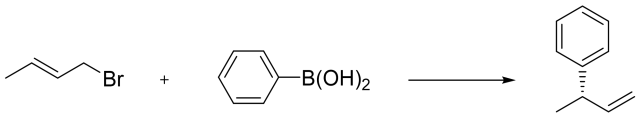


***tert*-butyl (S)-2-(2-methoxyphenyl)but-3-enoate (13i):** Following general procedure using naphthalen-1-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 77% yield (S_N2':S_N2=75:25) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +3.72 (c=0.86 in CH_2Cl_2, 92 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.84 (m, 2H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.52 – 7.43 (m, 3H), 7.34 – 7.27 (m, 1H), 6.40 – 6.29 (m, 1H), 5.26 (dt, *J* = 10.3, 1.1 Hz, 1H), 5.16 (dt, *J* = 17.2, 1.2 Hz, 1H), 4.97 (d, *J* = 7.3 Hz, 1H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.9, 135.6, 128.9, 128.3, 127.8, 126.1, 125.8, 125.6, 125.6, 125.5, 125.3, 123.6, 117.6, 81.3, 52.8, 27.9. **HRMS** (ESI) m/z calcd for $C_{18}H_{21}O_2$ $[M+H]^+$: 285.1491, found: 285.1486. **Enantiomeric excess** of 92% was determined by chiral HPLC after being converted to the corresponding methyl ester.[7] [chiral column AD-H; methods:

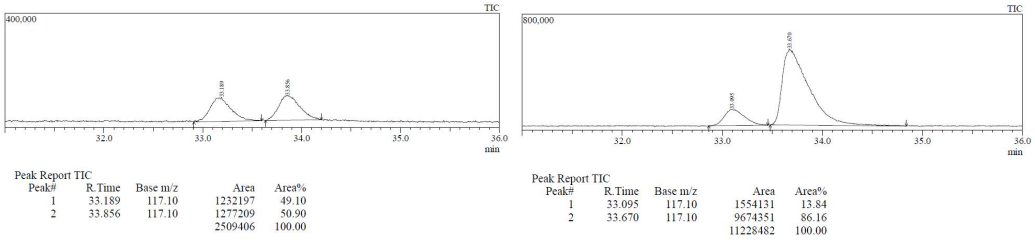
eluting solvent: 99.5:0.5=hexane:IPA, flow speed: 0.7 ml/min; major enantiomer t_R= 12.6 min; minor enantiomer t_R= 15.3 min].

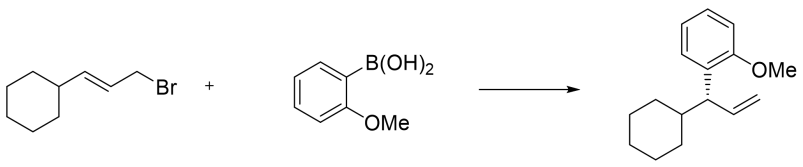




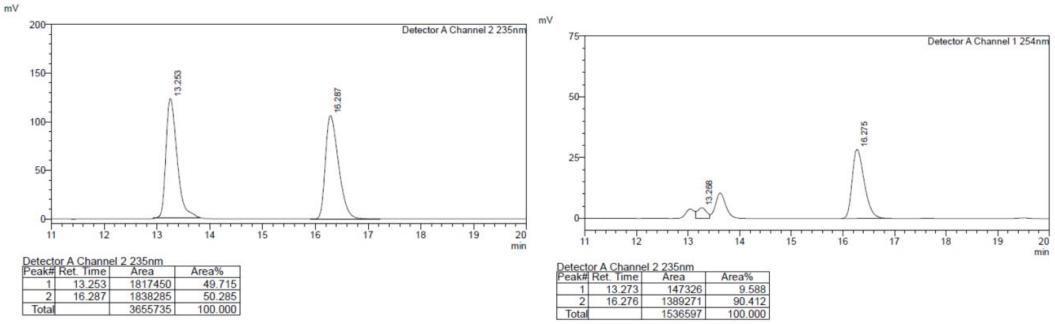


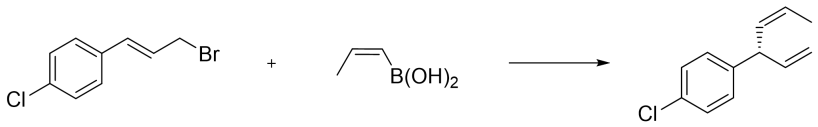
(*S*)-but-3-en-2-ylbenzene (13j): Following the general procedure with 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. Product was obtained in 75% yield (S_N2':S_N2=46:54) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23} = +9.8$ (c=0.49 in CH_2Cl_2, 72 % *ee*) for mixture. [reported –3 (c=0.5 in $CHCl_3$) for *R* in 70% *ee*].[3b] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 6.09 – 5.97 (m, 1H), 5.12 – 5.01 (m, 2H), 3.54 – 3.44 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.6, 143.3, 128.5, 128.4, 127.3, 126.1, 113.1, 43.2, 20.7. **HRMS** (ESI) m/z calcd for $C_{10}H_{12}$ $[M+H]^+$: 132.0939, found: 132.0935. **Enantiomeric excess** of 72% was determined by chiral GC [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-165 °C (1 min); major enantiomer t_R= 33.6 min; minor enantiomer t_R= 33.1 min].





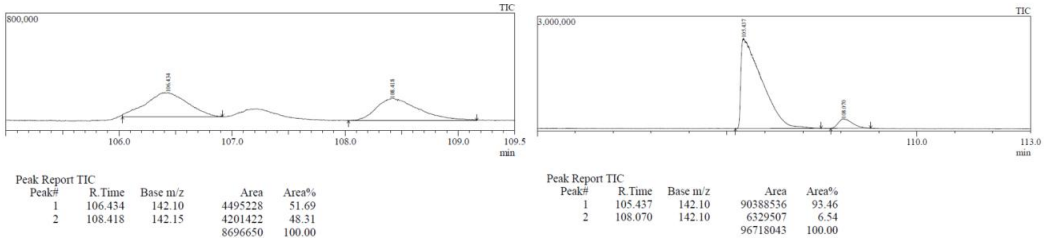
(*R*)-1-(1-cyclohexylallyl)-2-methoxybenzene (13l): Following general procedure using (2-methoxyphenyl) boronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 80% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = + 356 (c=1.53 in CH_2Cl_2, 81 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 2H), 6.92 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.11 – 5.97 (m, 1H), 5.06 – 4.95 (m, 2H), 3.82 (s, 3H), 3.45 (t, *J* = 9.3 Hz, 1H), 1.92 (d, *J* = 13.0 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.69 – 1.58 (m, 3H), 1.41 (d, *J* = 12.0 Hz, 1H), 1.30 – 1.19 (m, 1H), 1.19 – 1.07 (m, 2H), 0.99 – 0.89 (m, 1H), 0.89 – 0.78 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1, 141.0, 132.6, 128.5, 126.7, 120.6, 114.8, 110.9, 55.5, 49.9, 41.1, 31.5, 31.2, 26.6, 26.5, 26.4. **HRMS** (ESI) m/z calcd for $C_{16}H_{23}O$ $[M+H]^+$: 231.1747, found: 231.1749. **Enantiomeric excess** of 81% was determined by chiral HPLC [chiral column IA3; methods: eluting solvent: hexane, flow speed: 0.5 ml/min; major enantiomer t_R= 11.7 min; minor enantiomer t_R= 12.5 min].





(*S*,*Z*)-1-chloro-4-(hexa-1,4-dien-3-yl)benzene (14b): Following general procedure using (*Z*)-prop-1-en-1-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 89% yield (S_N2':S_N2=74:26) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +25.2 (c=1.3 in CH_2Cl_2, 87 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 7.19 – 7.12 (m, 2H), 6.00 – 5.87 (m, 1H), 5.67 – 5.57 (m, 1H), 5.56 – 5.43 (m, 1H), 5.14 – 5.03 (m, 1H), 4.36 – 4.27 (m, 1H), 1.68 (d, *J* = 1.7 Hz, 3H). **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 139.9, 131.1, 129.0, 128.6, 128.5, 127.2, 125.1, 115.0, 46.0, 13.0. **HRMS** (ESI) m/z calcd. for $C_{12}H_{14}Cl$ $[M+H]^+$: 193.0784, found: 193.0785. **Enantiomeric excess** of 87% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-165 °C (1 min); major enantiomer t_R= 105.4 min; minor enantiomer t_R= 108 min].

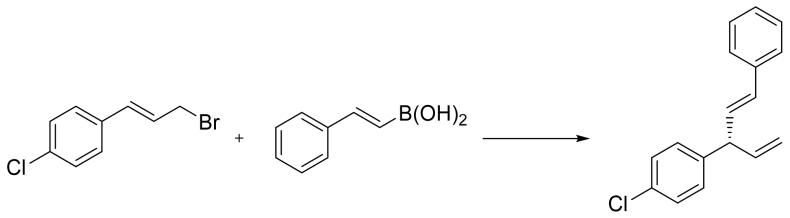


Peak Report TIC

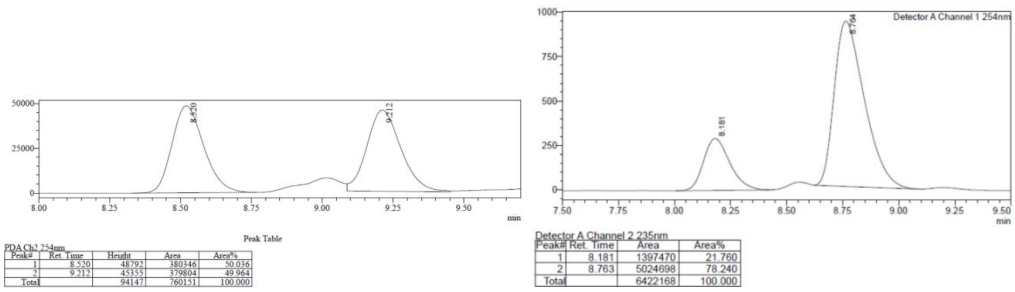
Peak#	R.Time	Base m/z	Area	Area%
1	106.434	142.10	4495228	51.69
2	108.418	142.15	4201422	48.31
			8696650	100.00

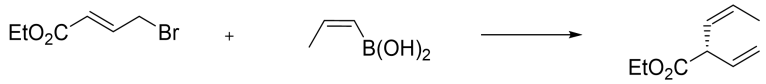
Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
1	105.437	142.10	90388536	93.46
2	108.070	142.10	6329507	6.54
			96718043	100.00

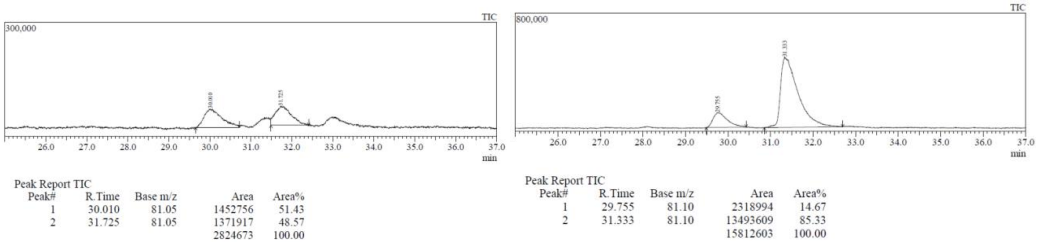


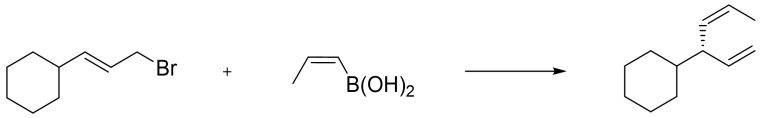
(*S*,*E*)-1-chloro-4-(1-phenylpenta-1,4-dien-3-yl)benzene (14c): Following general procedure using (*E*)-styrylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 89% yield (S_N2':S_N2=74:26) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +40 (c=0.5 in CH_2Cl_2, 56 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.27 (m, 4H), 7.25 – 7.18 (m, 3H), 6.45 – 6.31 (m, 2H), 6.13 – 6.01 (m, 1H), 5.21 (dt, *J* = 10.2, 1.3 Hz, 1H), 5.14 (dt, *J* = 17.2, 1.4 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 139.6, 137.2, 132.3, 131.2, 131.1, 129.5, 128.7, 128.6, 127.4, 126.3, 116.1, 51.7. **HRMS** (ESI) m/z calcd. for $C_{17}H_{16}Cl$ $[M+H]^+$: 255.0941, found: 255.0948. **Enantiomeric excess** of 56% was determined by chiral HPLC [chiral column IB; methods: eluting solvent: hexane, flow speed: 1 ml/min; major enantiomer t_R= 9.2 min; minor enantiomer t_R= 8.5 min].





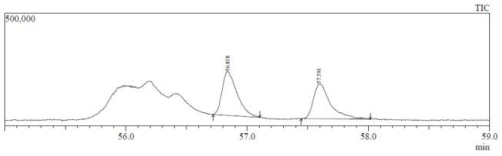
Ethyl (*S,Z*)-2-vinylpent-3-enoate (14e): Following general procedure using (*Z*)-prop-1-en-1-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 75% yield (S_N2':S_N2=80:20) as a colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +17.8 (c=1.4 in CH_2Cl_2, 70 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.99 – 5.86 (m, 1H), 5.71 – 5.62 (m, 1H), 5.56 – 5.47 (m, 1H), 5.20 – 5.10 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.03 (t, J = 8.1 Hz, 1H), 1.66 (dd, J = 6.8, 1.6 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 134.9, 127.2, 126.16, 116.5, 60.9, 47.9, 14.1, 13.0. **HRMS** (ESI) m/z calcd. for $C_9H_{15}O_2$ $[M+H]^+$: 155.1072, found: 155.1066. **Enantiomeric excess** of 70% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (1 min)-1-165 °C (1 min); major enantiomer t_R= 31.3 min; minor enantiomer t_R= 30 min].





(*R,Z*)-hexa-1,4-dien-3-ylcyclohexane (14h): Following general procedure using (*Z*)-prop-1-en-1-ylboronic acid, catalyzed by 3 mol% $Cu(MeCN)_4PF_6$ and 6 mol% **CG**. The corresponding product was obtained in 89% yield (S_N2':S_N2=74:26) as a

colorless oil. **Opt. Rot.**: $[\alpha]_{589}^{23}$ = +11.5 (c=0.4 in CH_2Cl_2, 80 % *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.74 – 5.64 (m, 1H), 5.56 – 5.47 (m, 1H), 5.35 – 5.25 (m, 1H), 4.99 – 4.96 (m, 1H), 4.95 – 4.92 (m, 1H), 2.82 (m, 1H), 1.77 – 1.64 (m, 5H), 1.62 (d, *J* = 1.8 Hz, 3H), 1.29 – 1.12 (m, 4H), 0.99 – 0.85 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.6, 131.8, 124.0, 113.8, 47.8, 42.2, 31.0, 30.3, 26.6, 26.5, 26.5, 13.1. **HRMS** (ESI) m/z calcd for $C_{12}H_{21}$ $[M+H]^+$: 165.1643, found: 165.1642. **Enantiomeric excess** of 80% was determined by chiral GC-MS [chiral column Rt®-BDM (30 m, 0.25 mmID, 0.25 μm df); methods: 50 °C (45 min)-1-160 °C (1 min); major enantiomer t_R= 56.6 min; minor enantiomer t_R= 57.5 min].



Peak Report TIC

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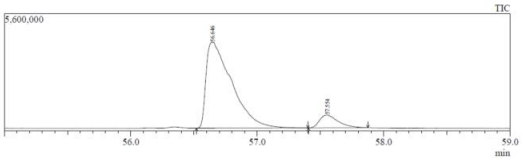
2	57.591	55.05	1515434	47.58
			3184983	100.00



Peak Report TIC

Peak#	R.Time	Base m/z	Area	Area%
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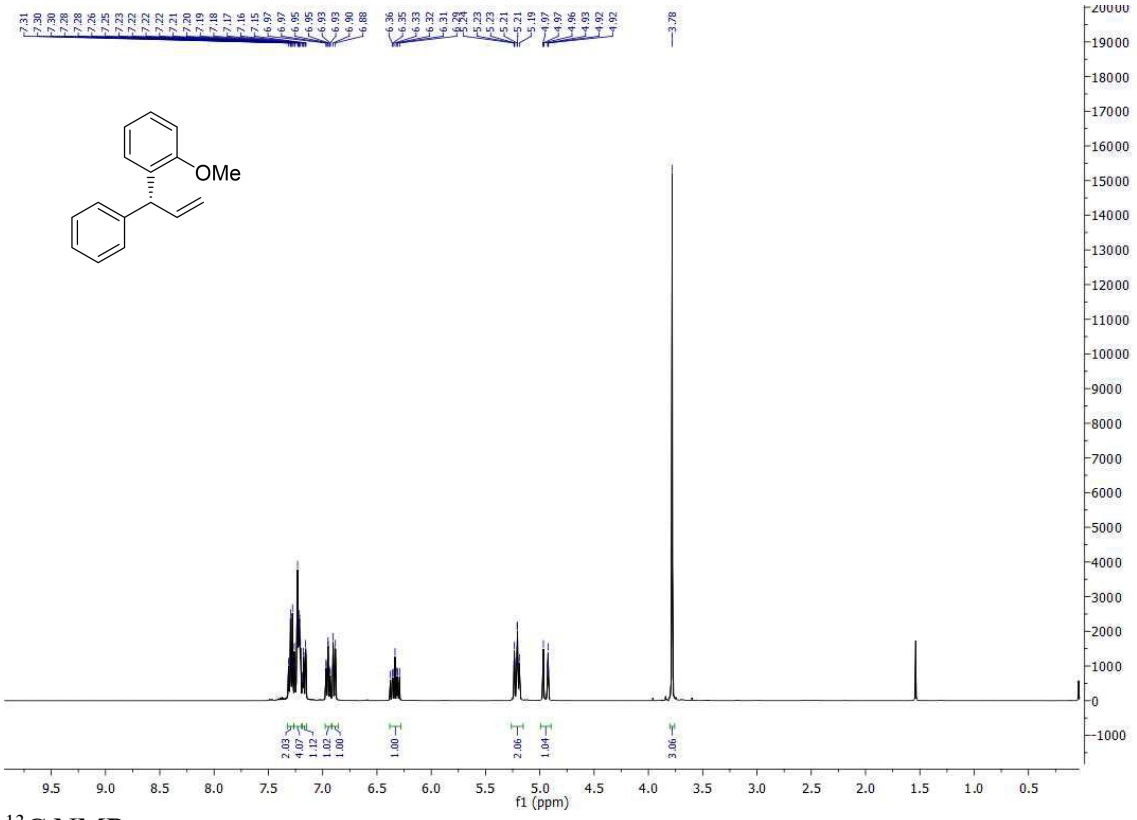
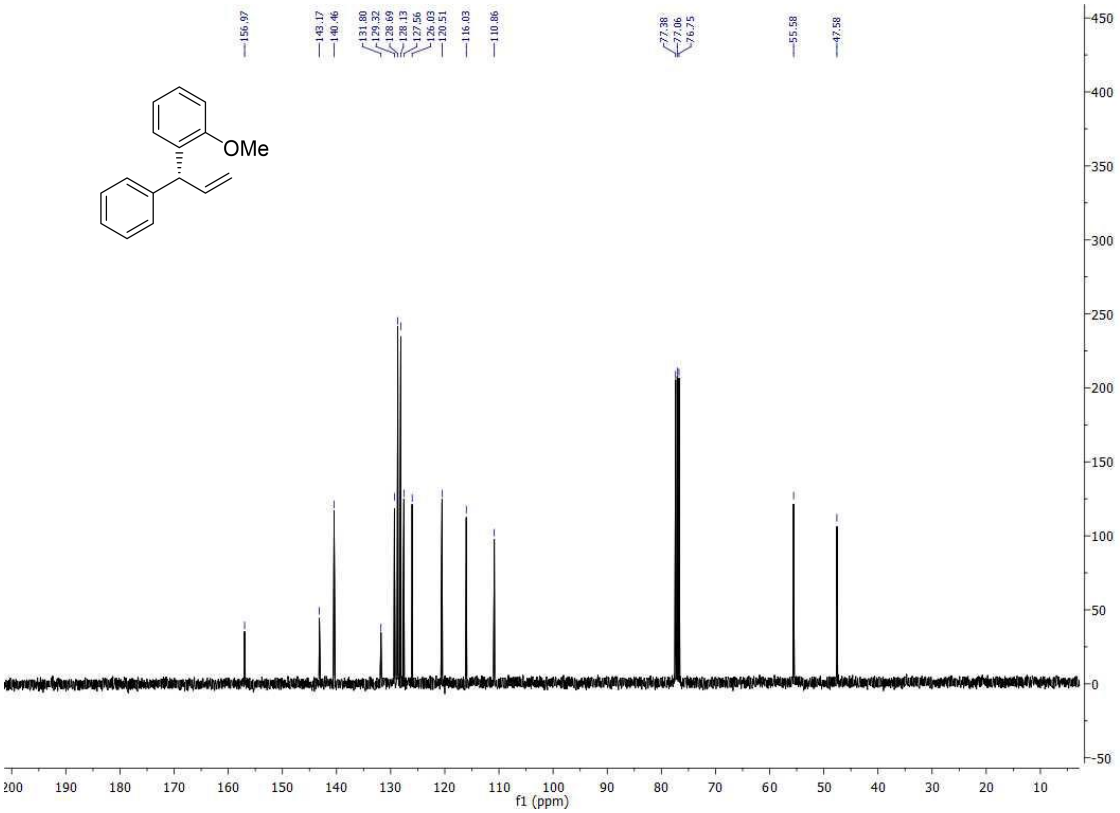
2	57.554	55.10	6355191	9.73
			65338040	100.00

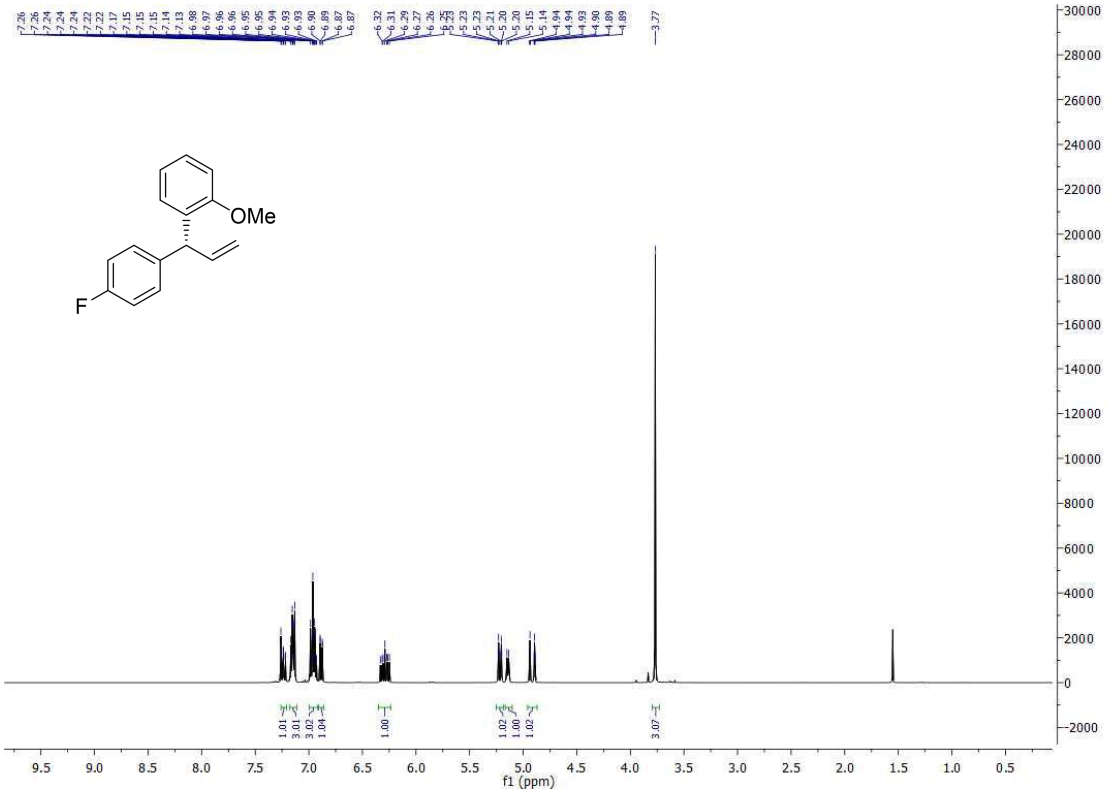
^{1}H NMR:



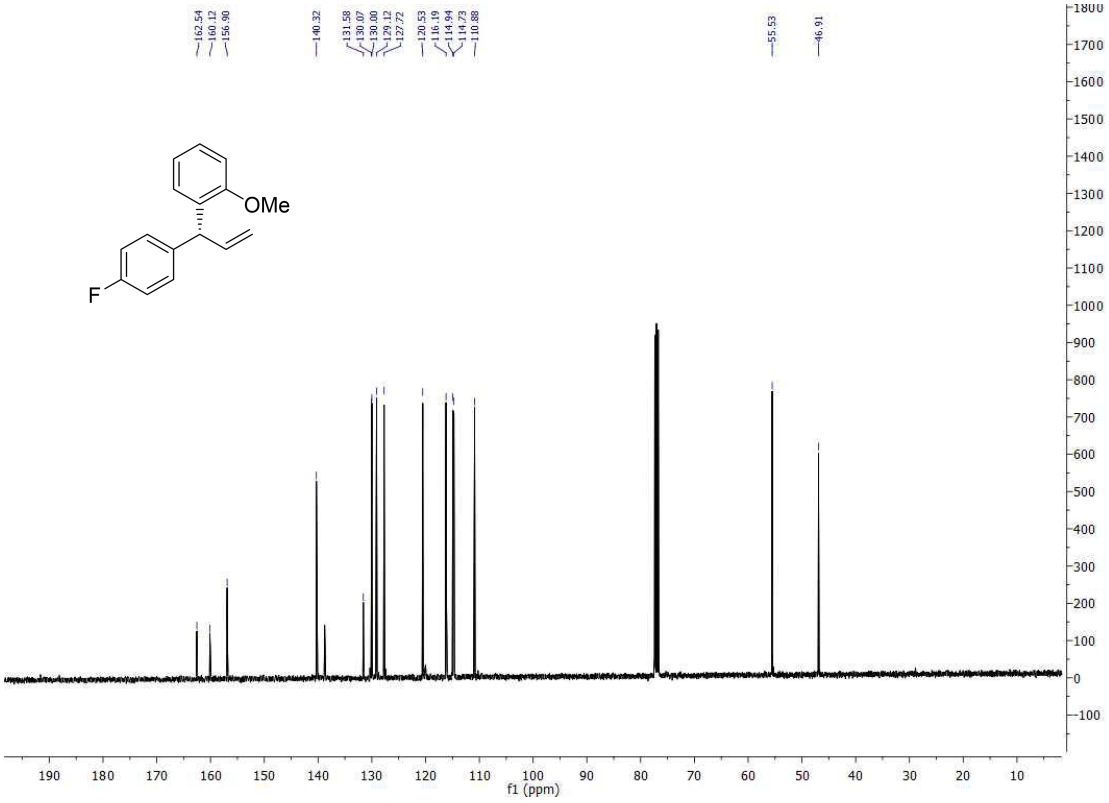
^{13}C NMR:



^{1}H NMR:



^{13}C NMR:



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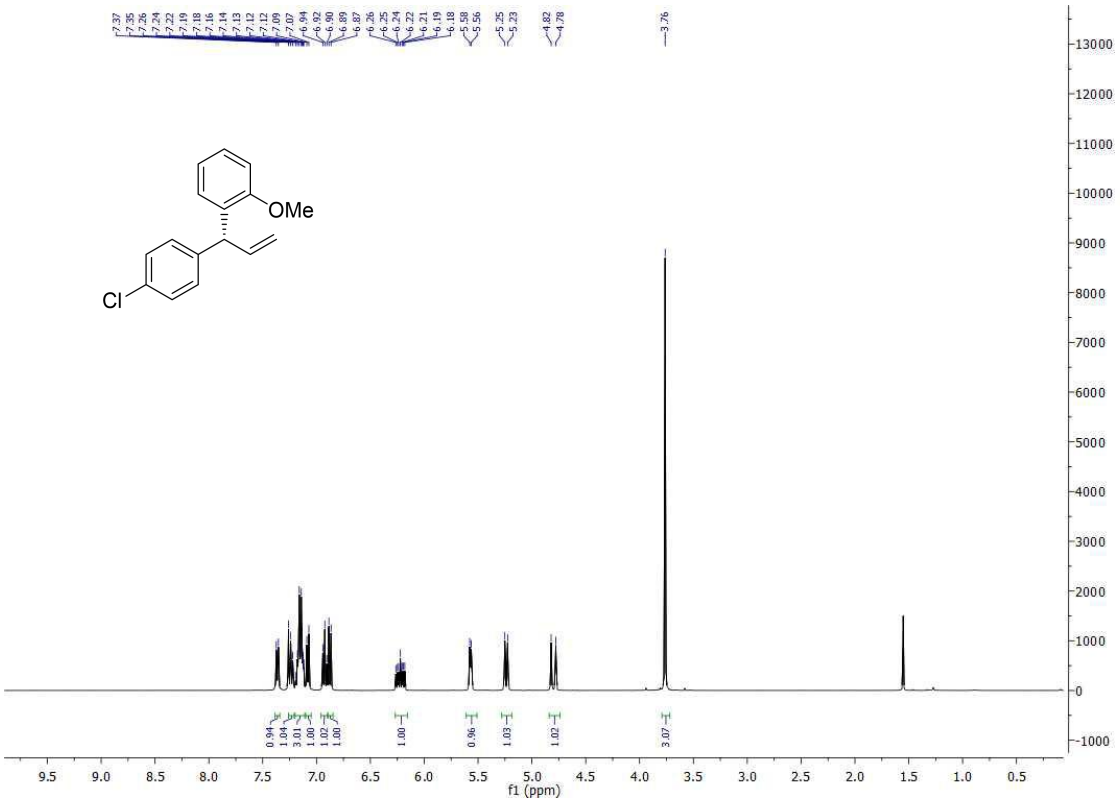
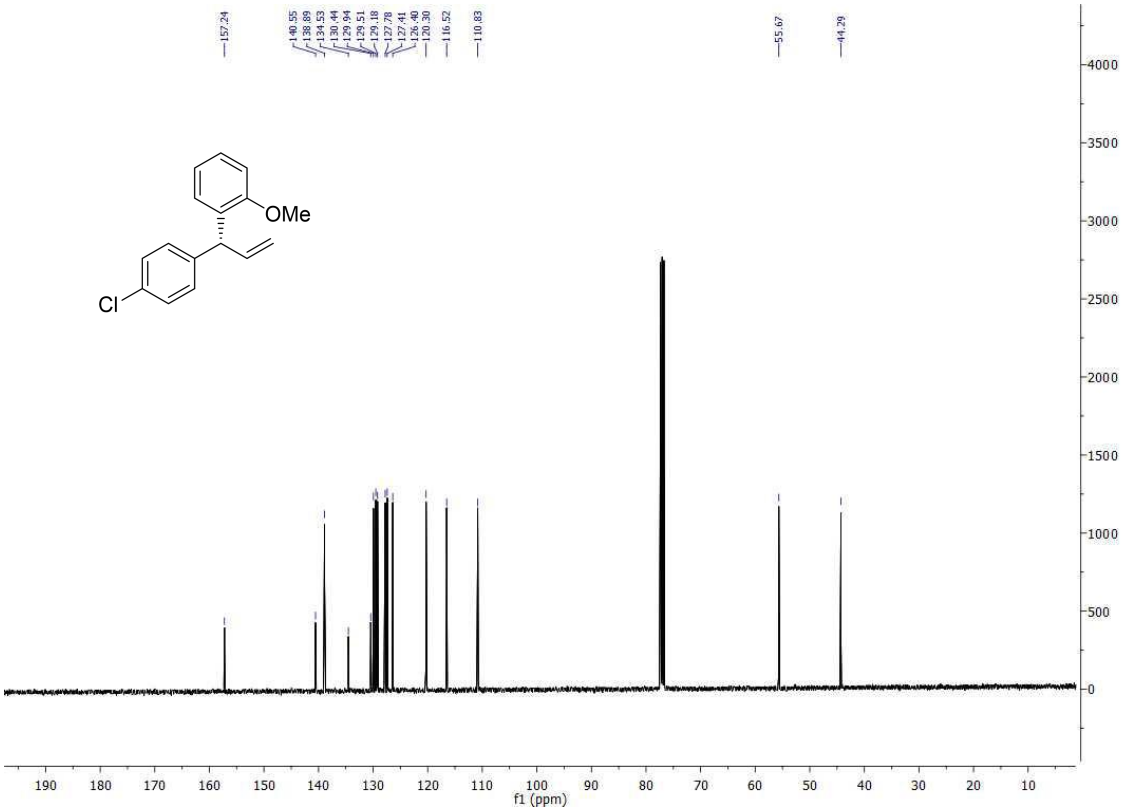


^{13}C NMR:



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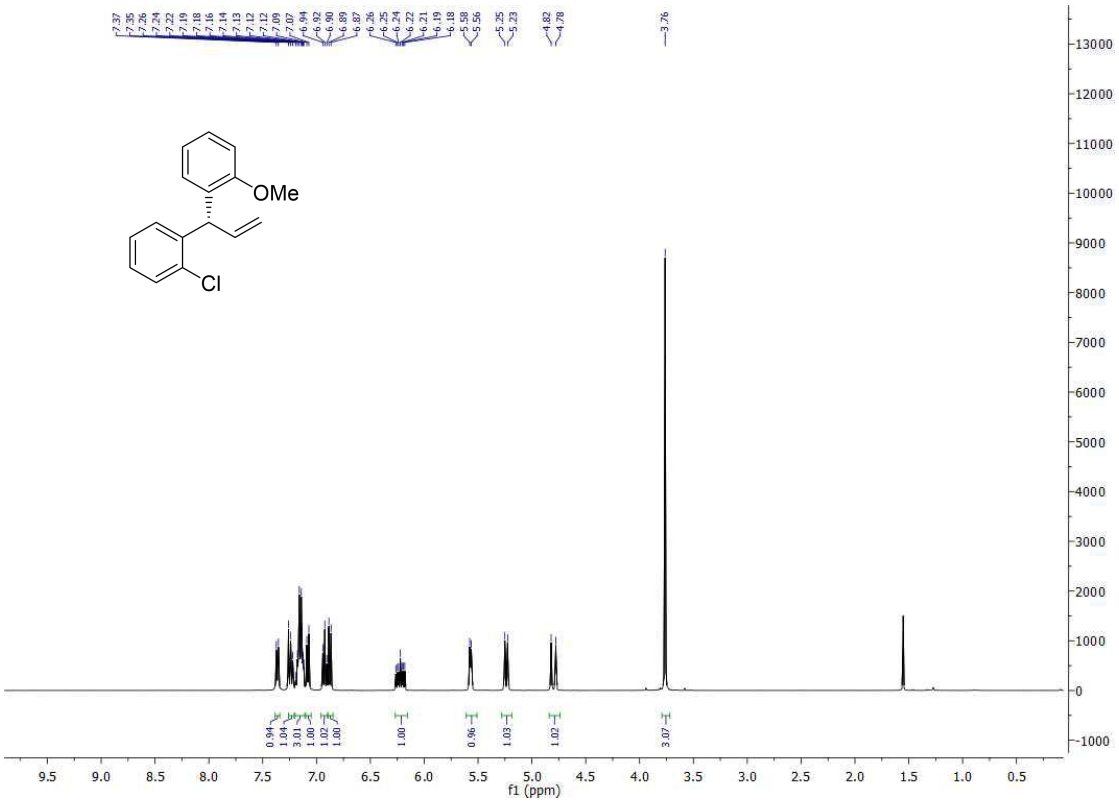

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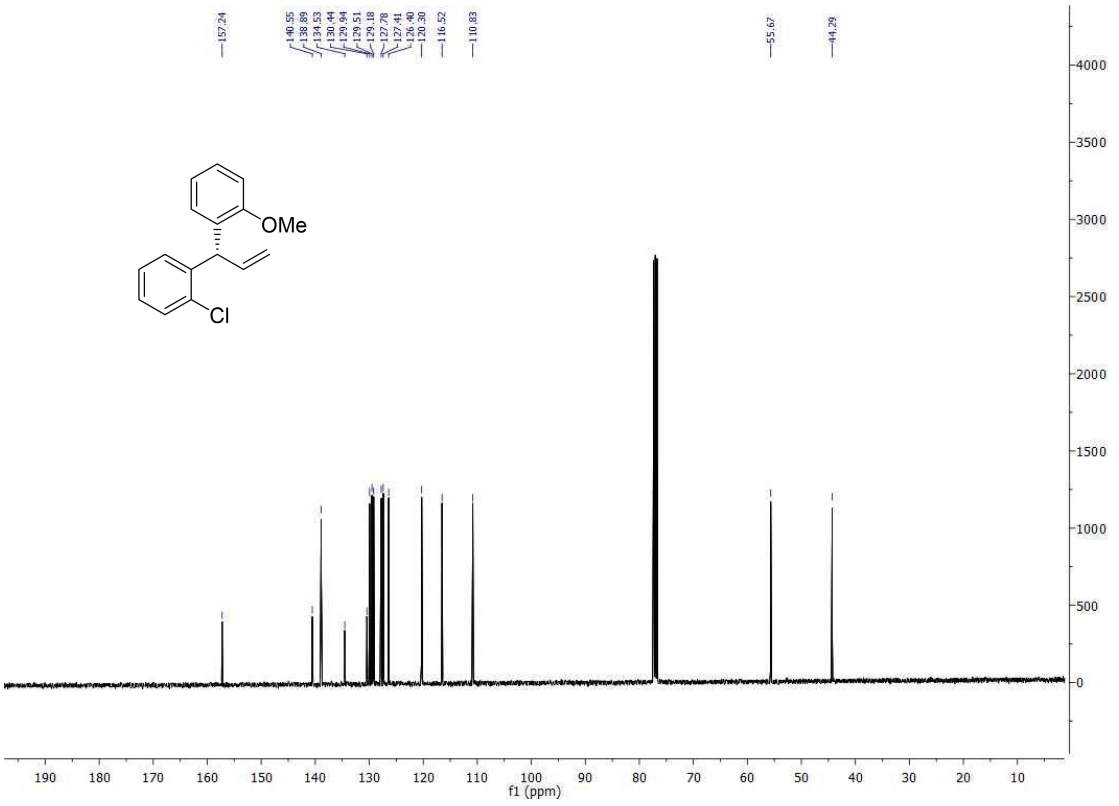

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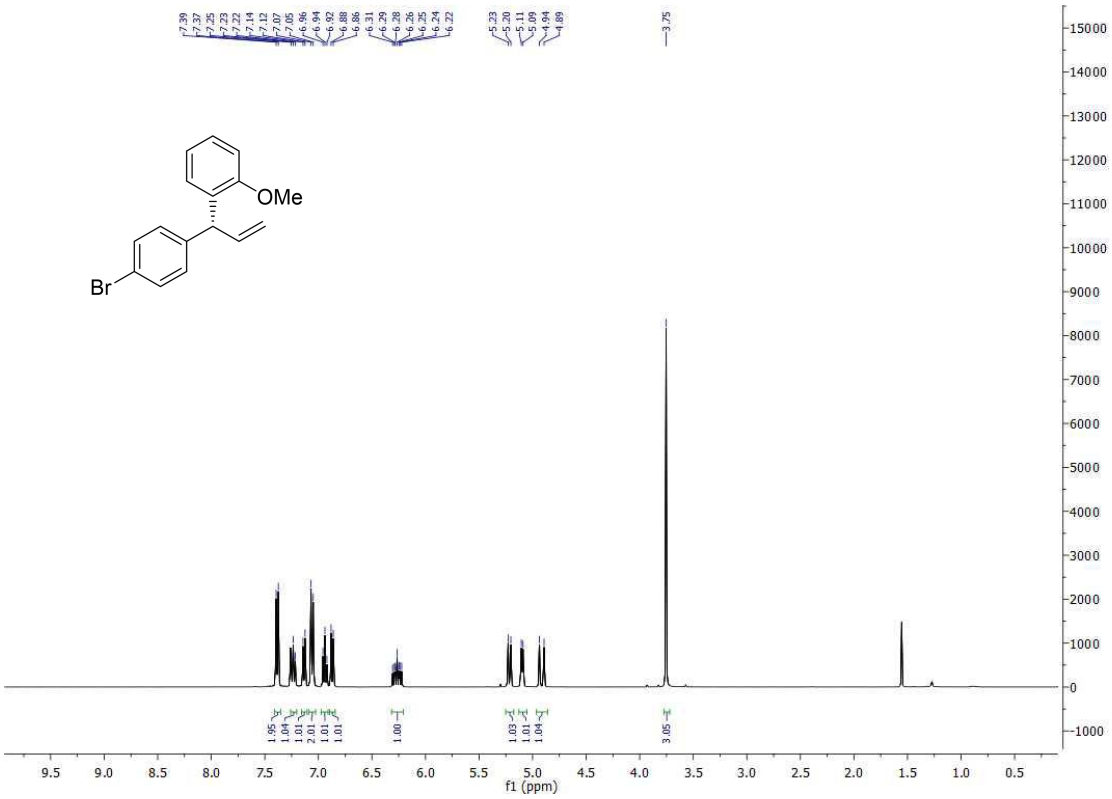

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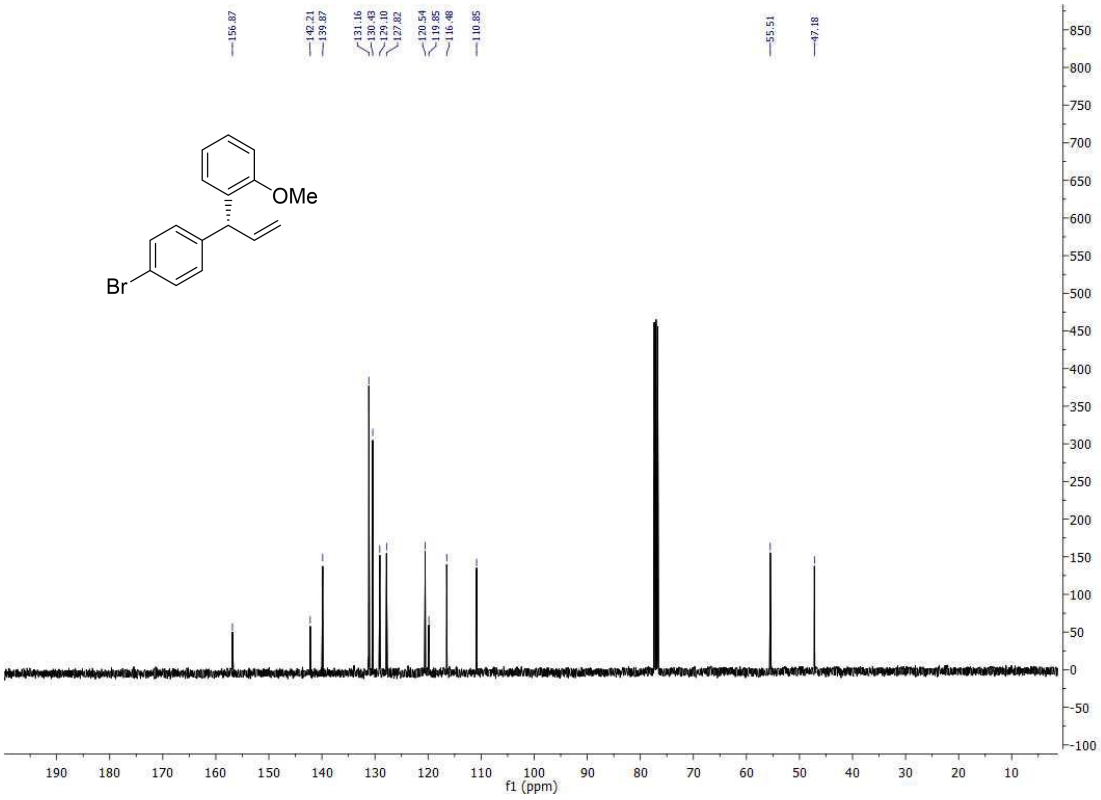

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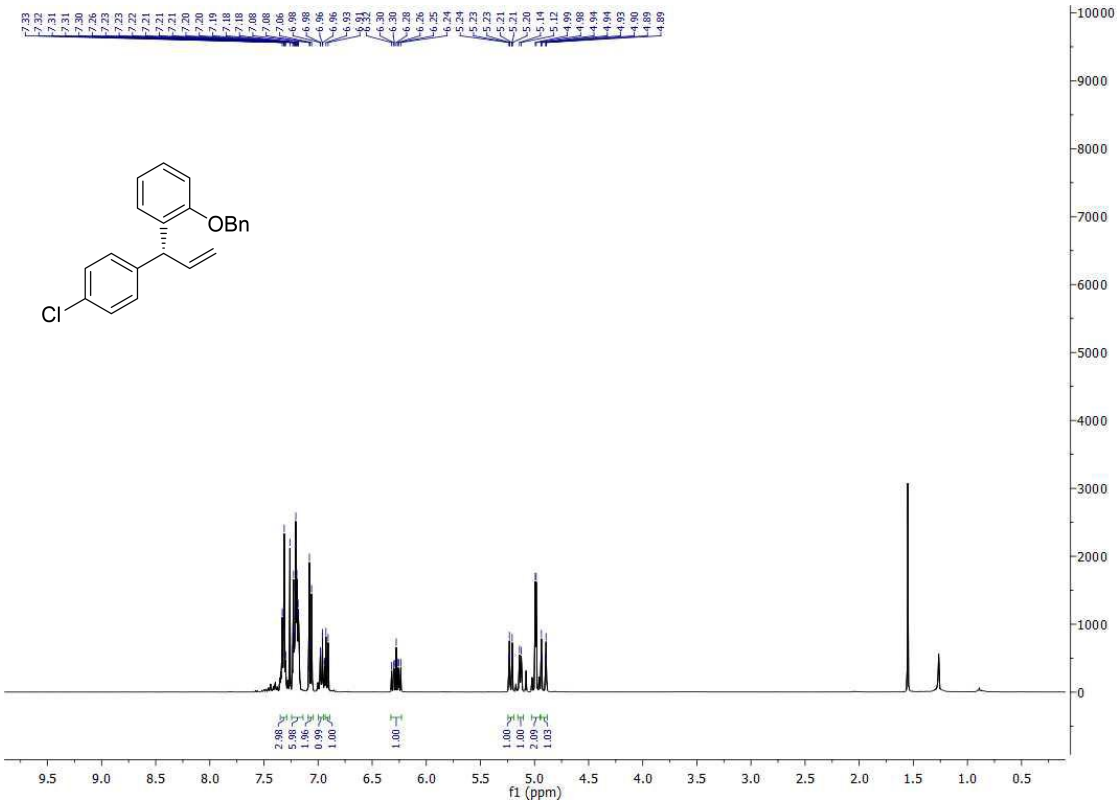

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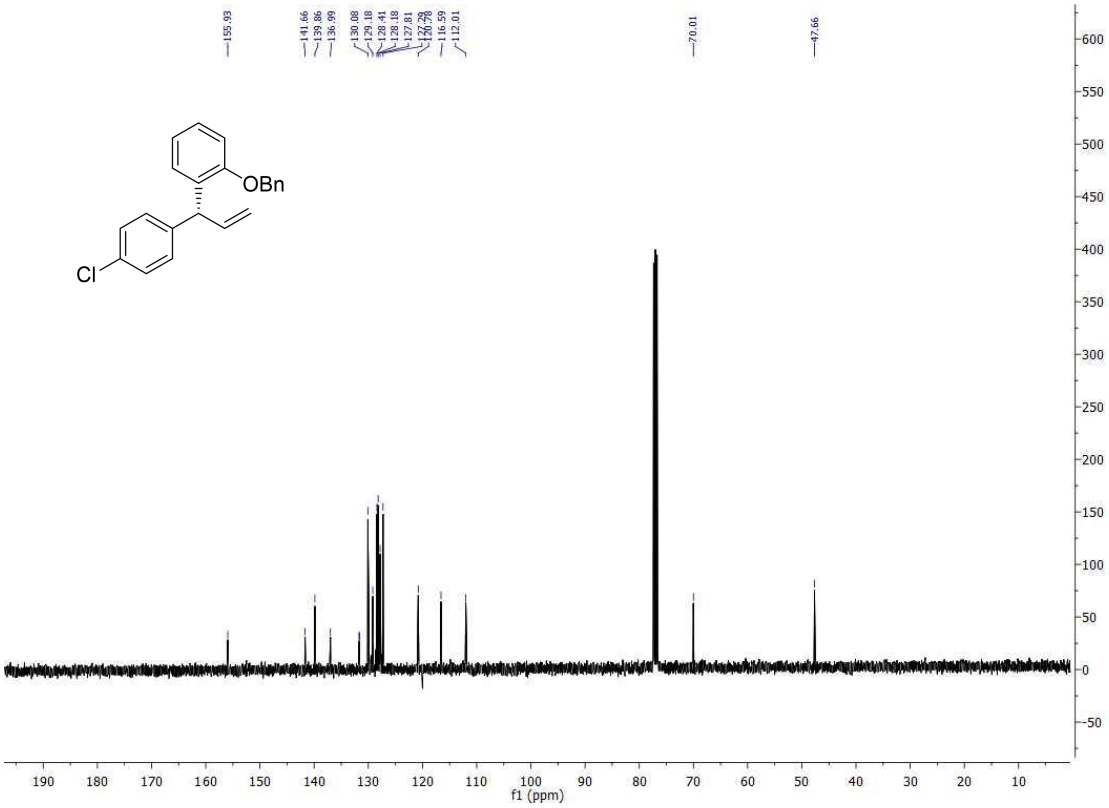

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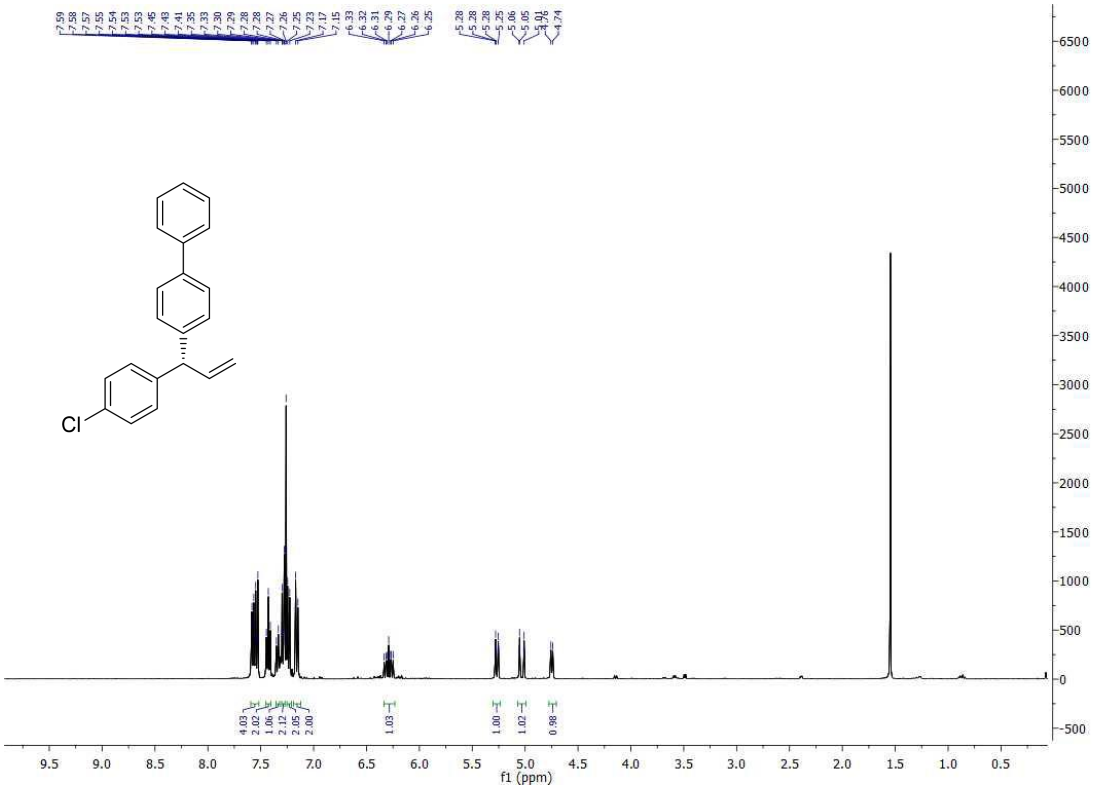
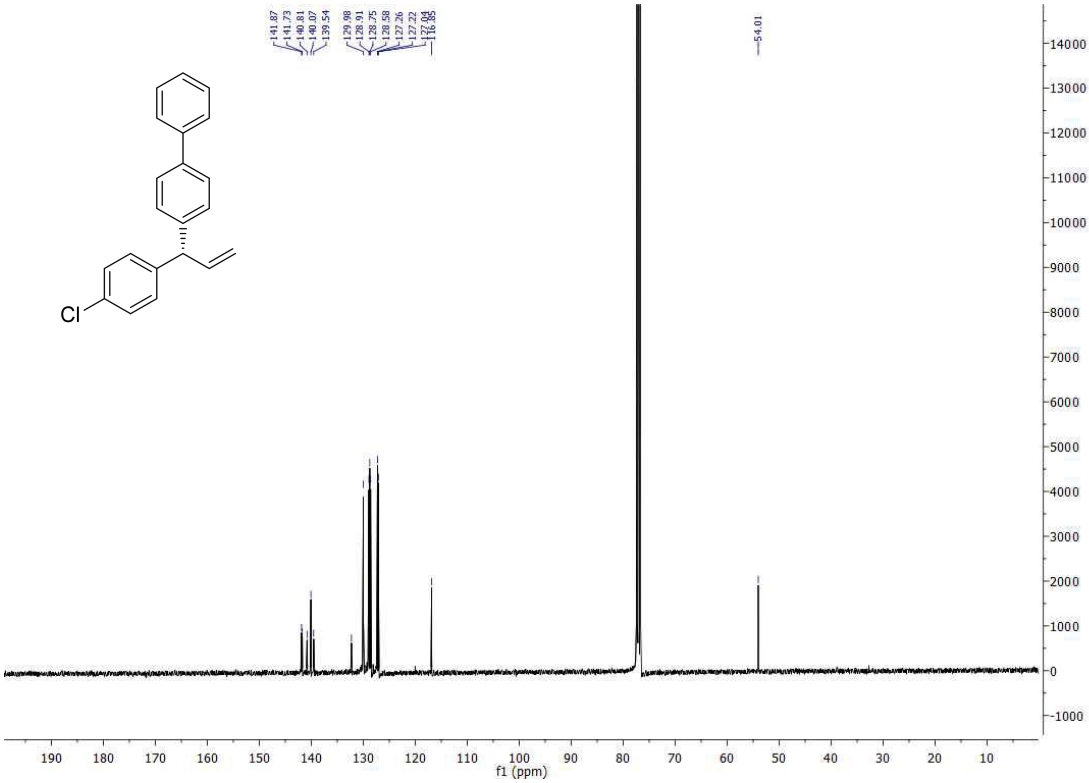


^{13}C NMR:



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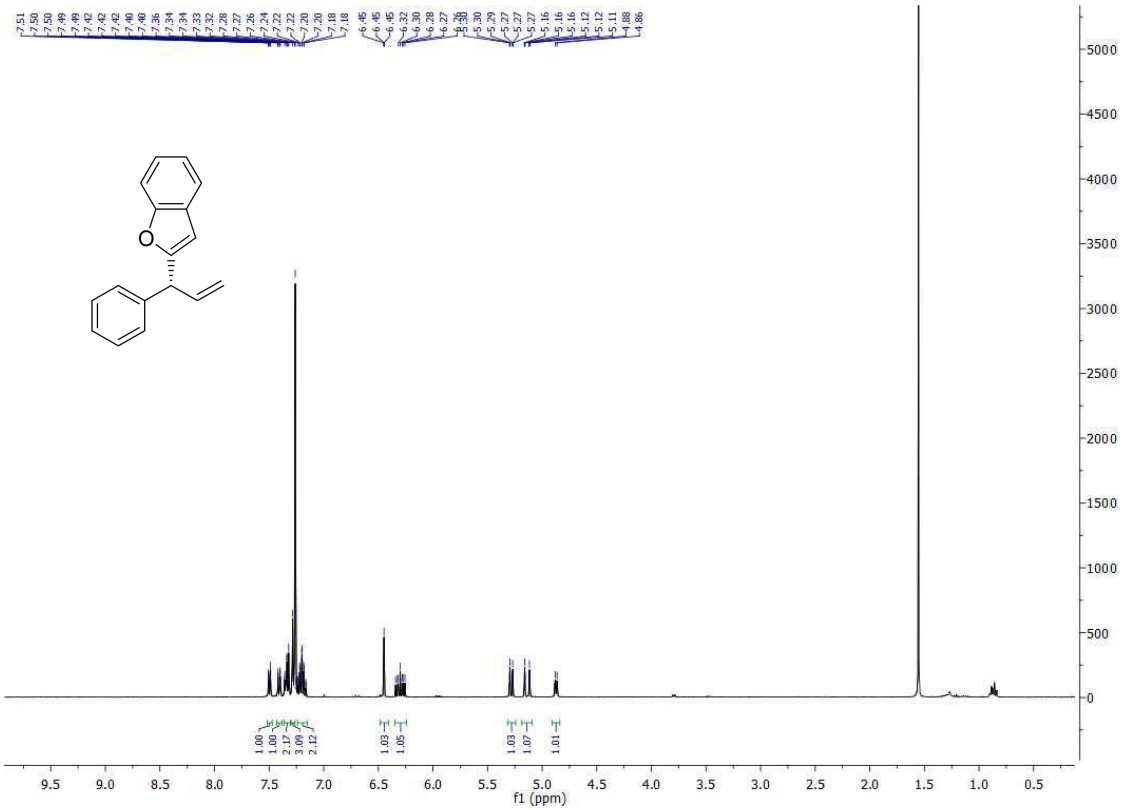

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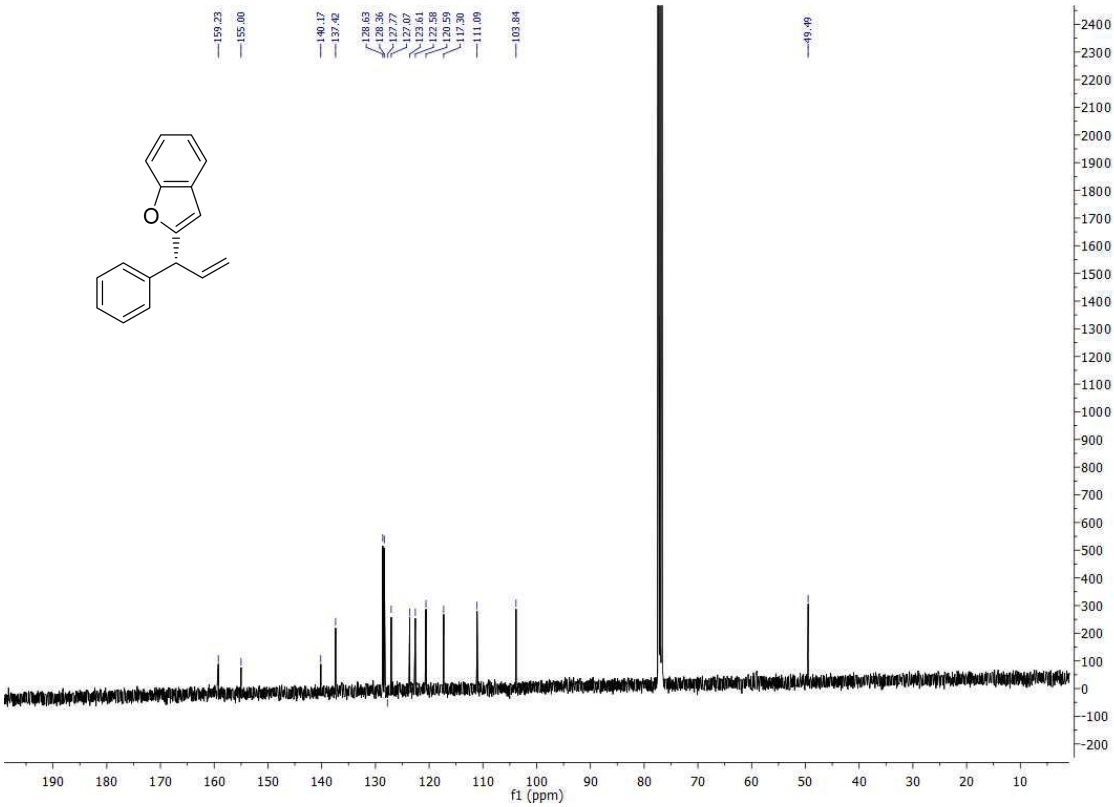

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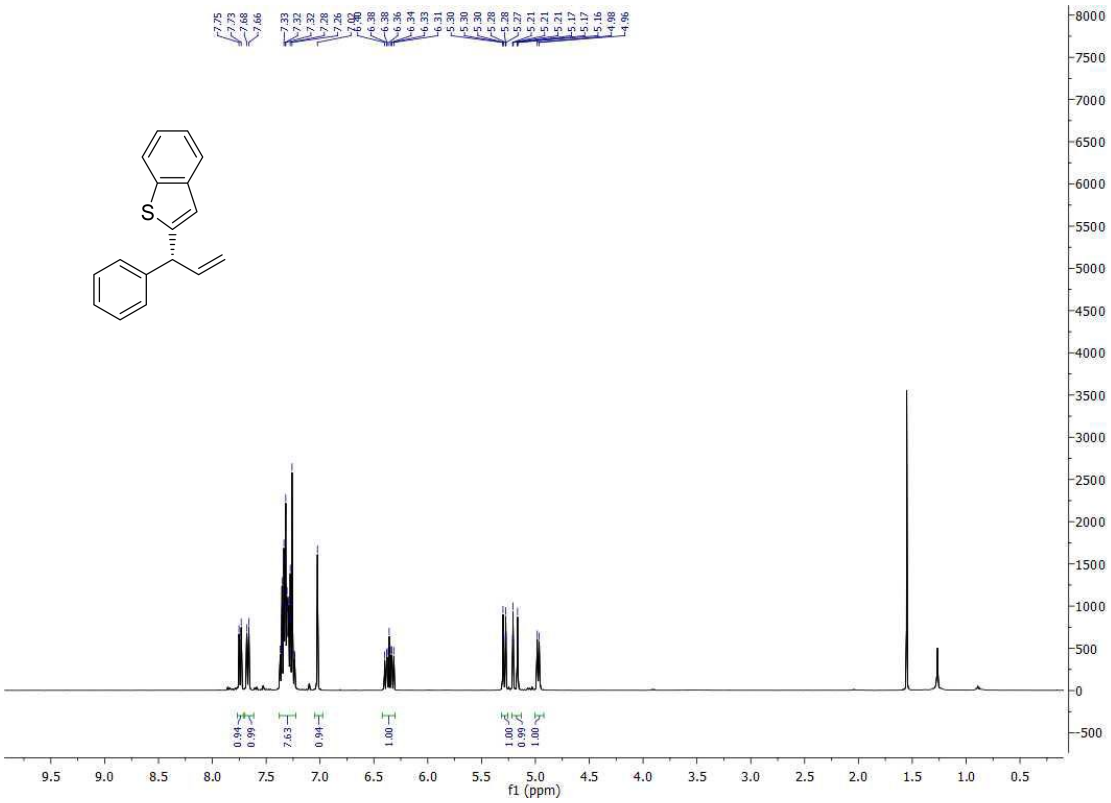
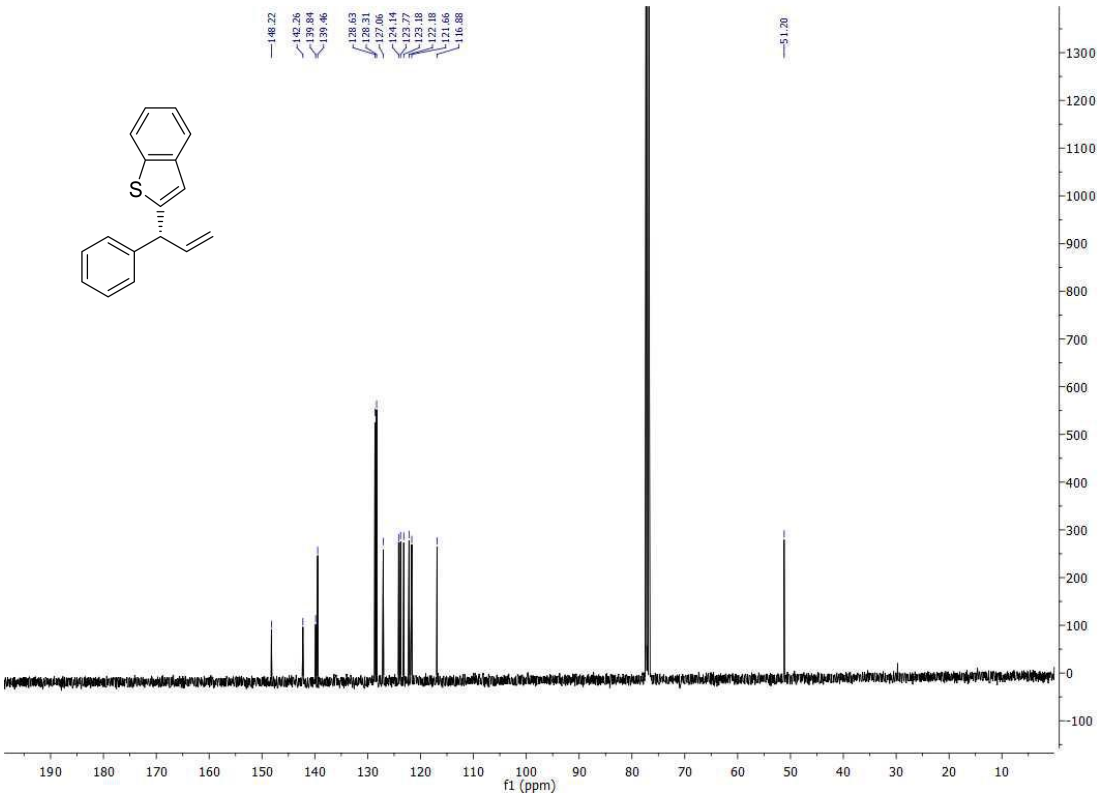
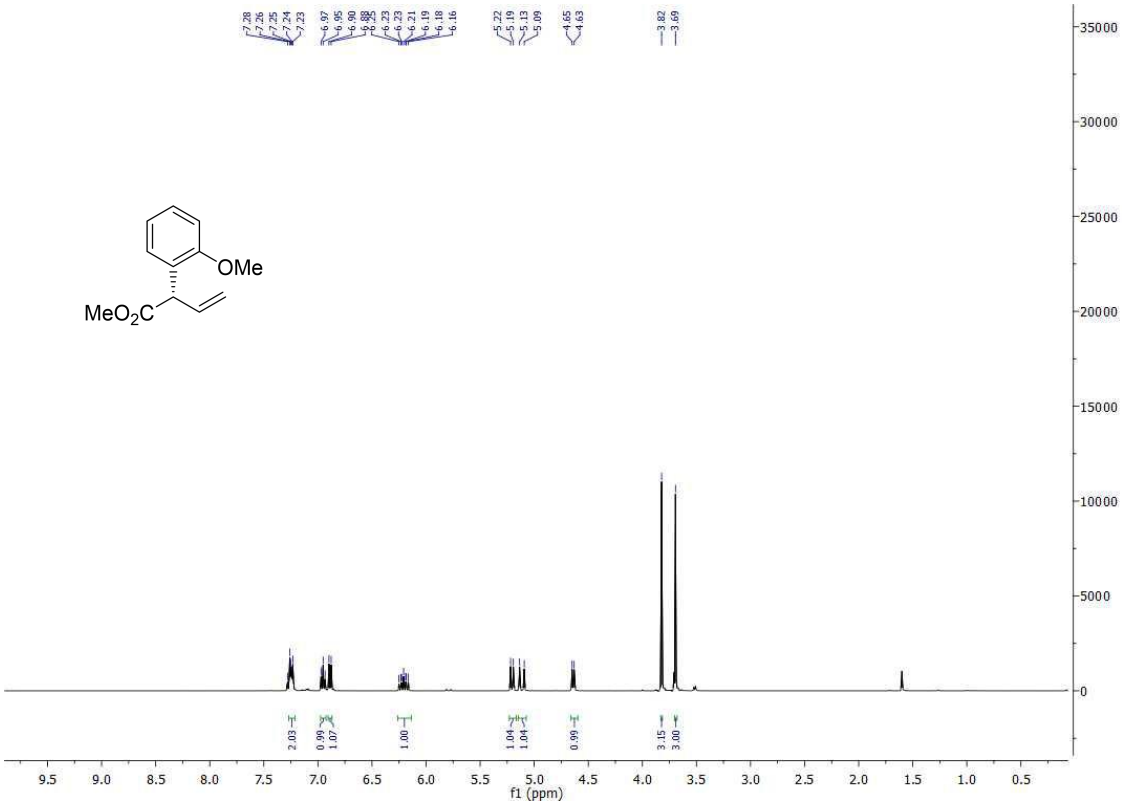


^{13}C NMR:



^{1}H NMR:



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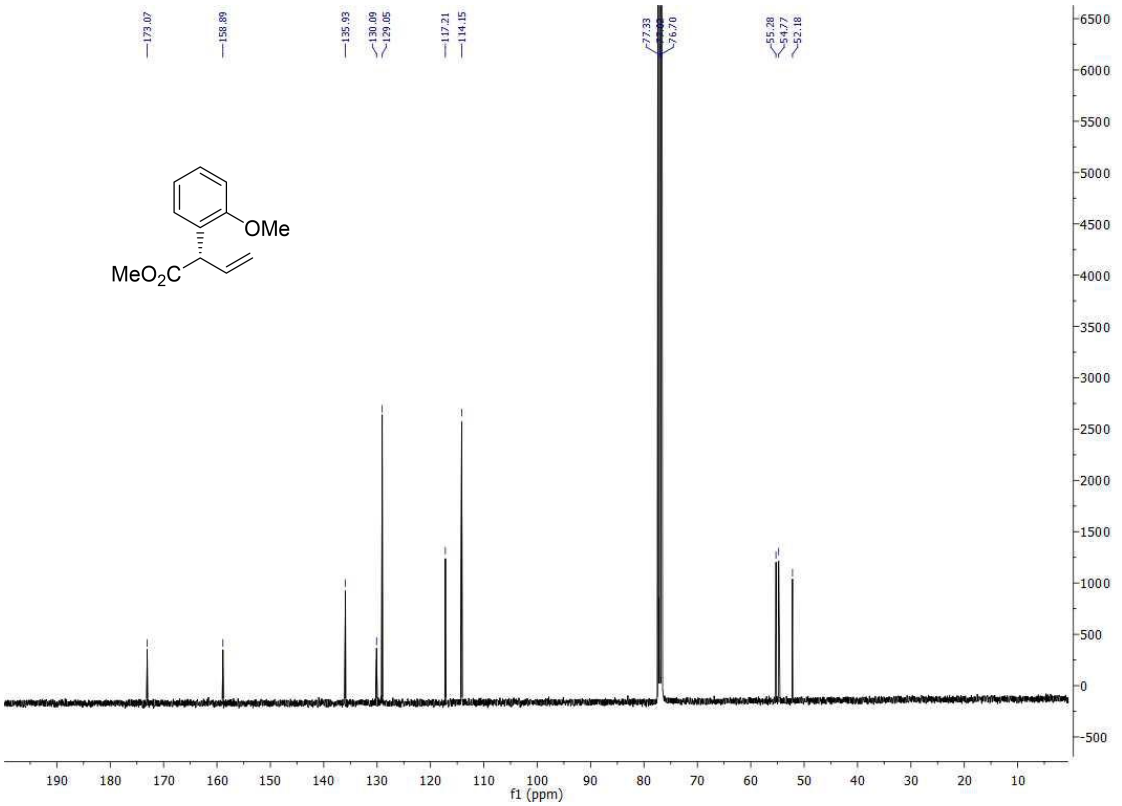

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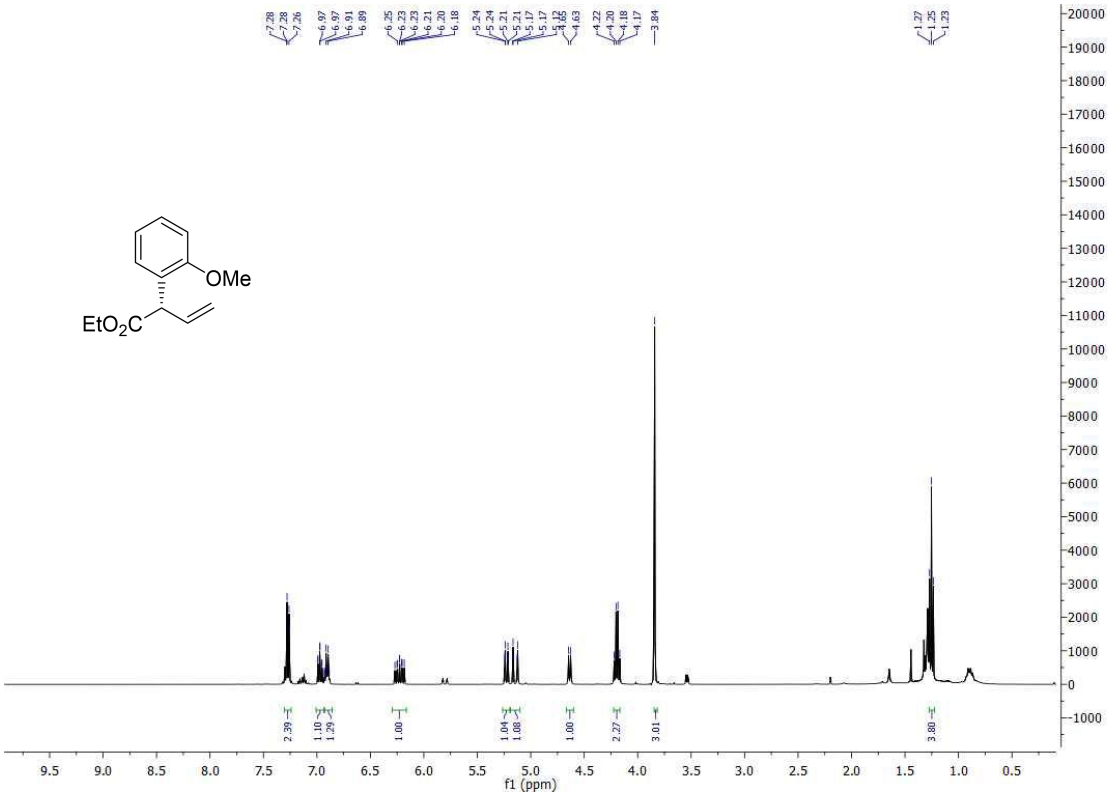

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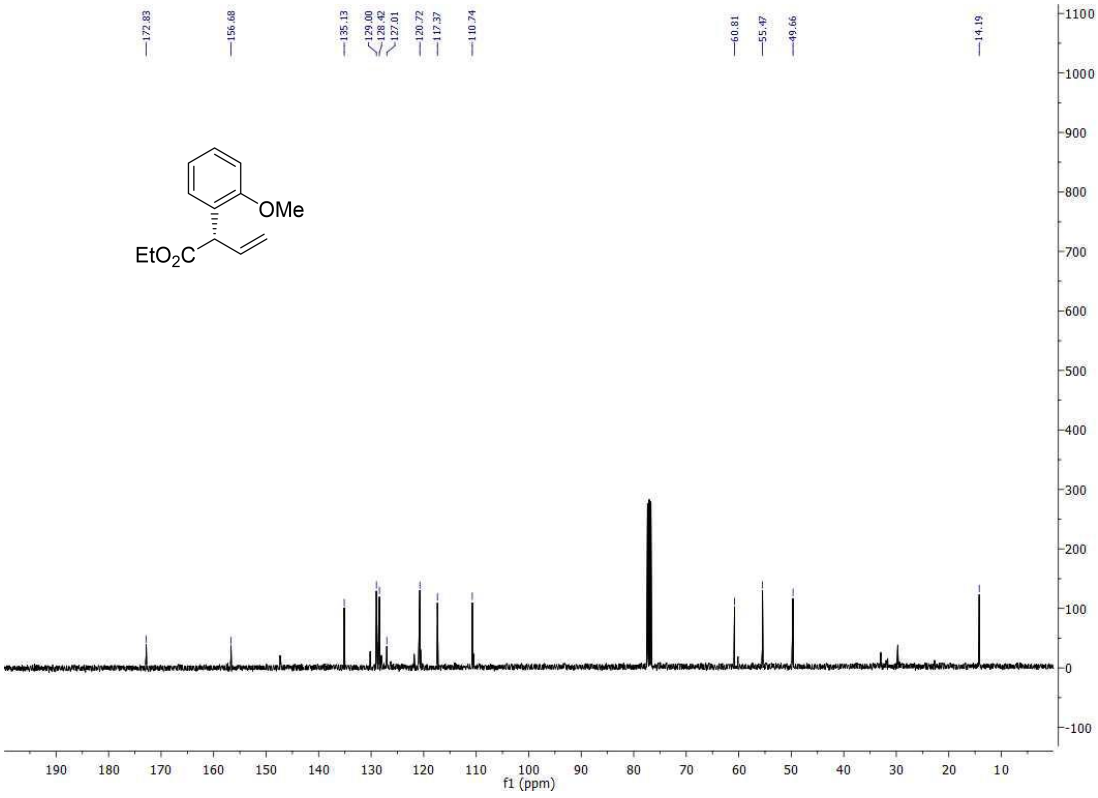

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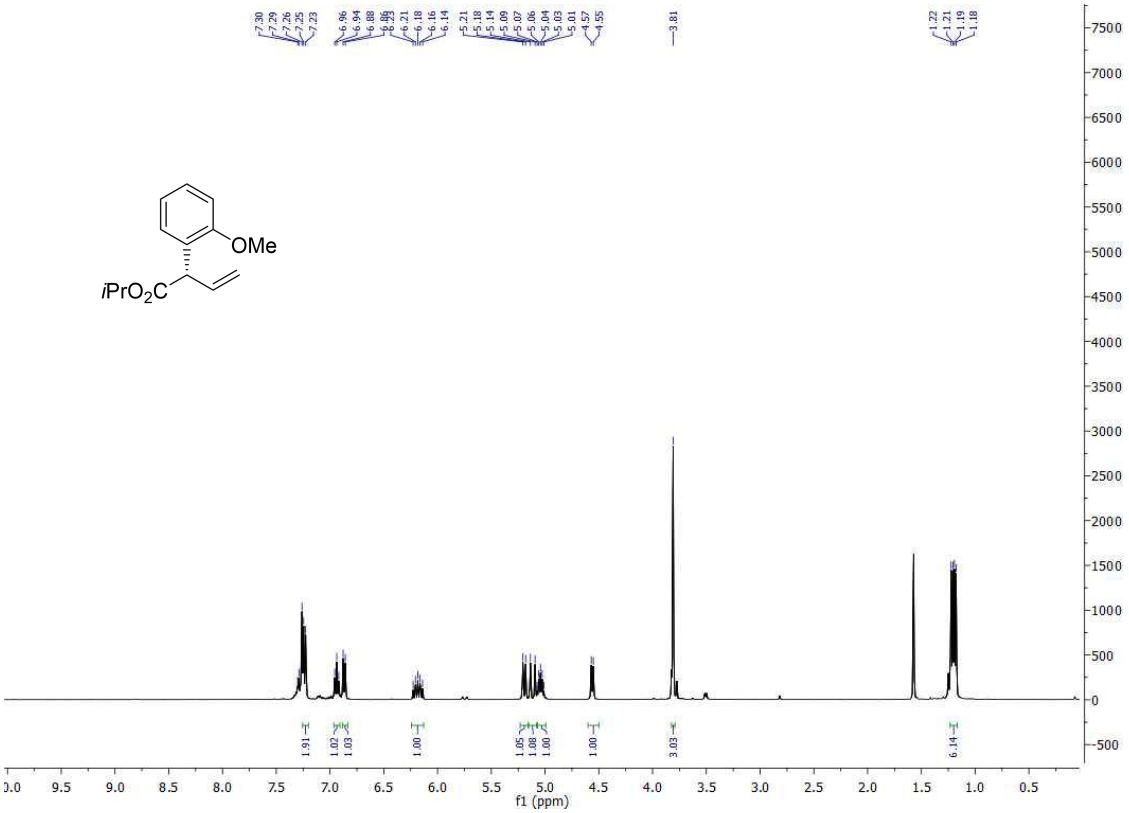
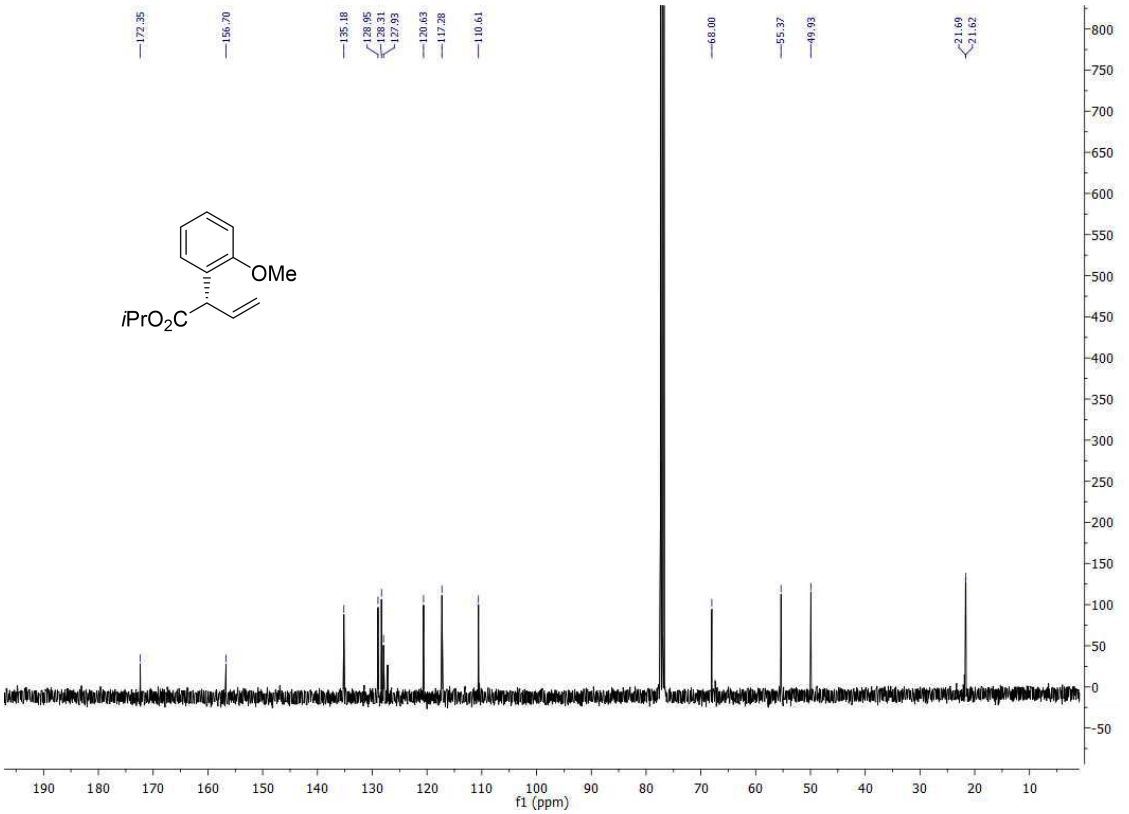


^{13}C NMR:



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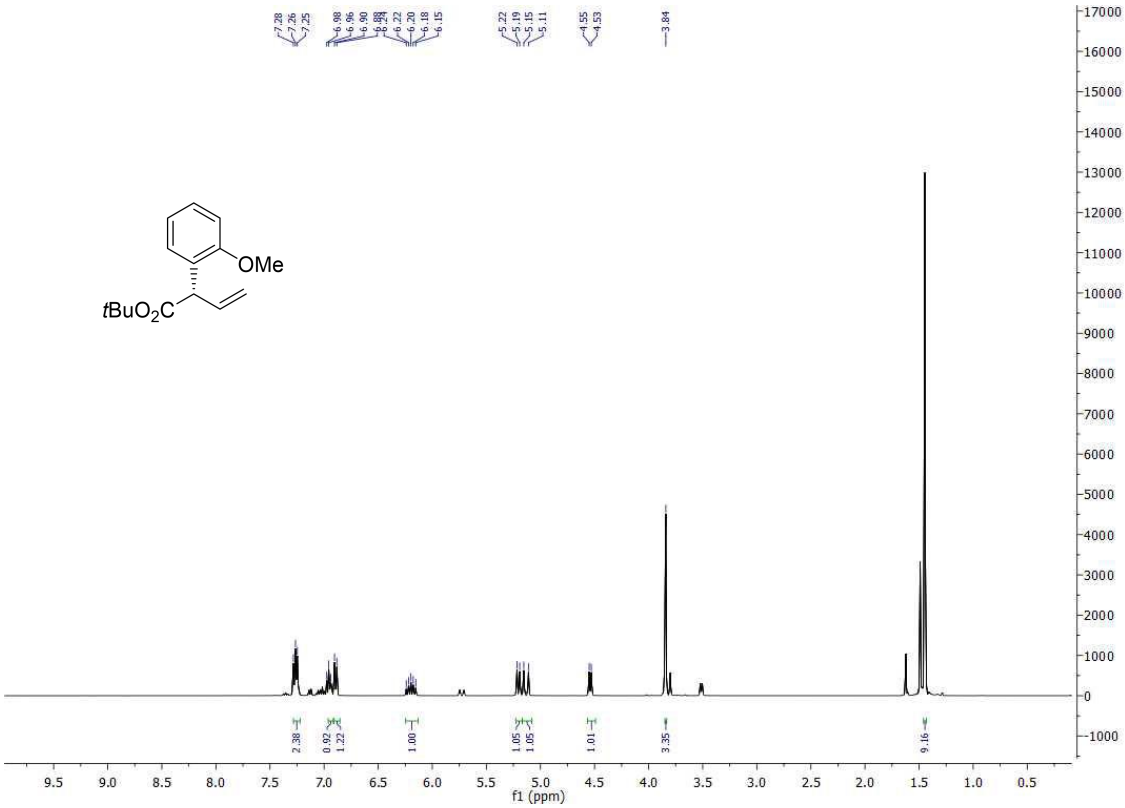

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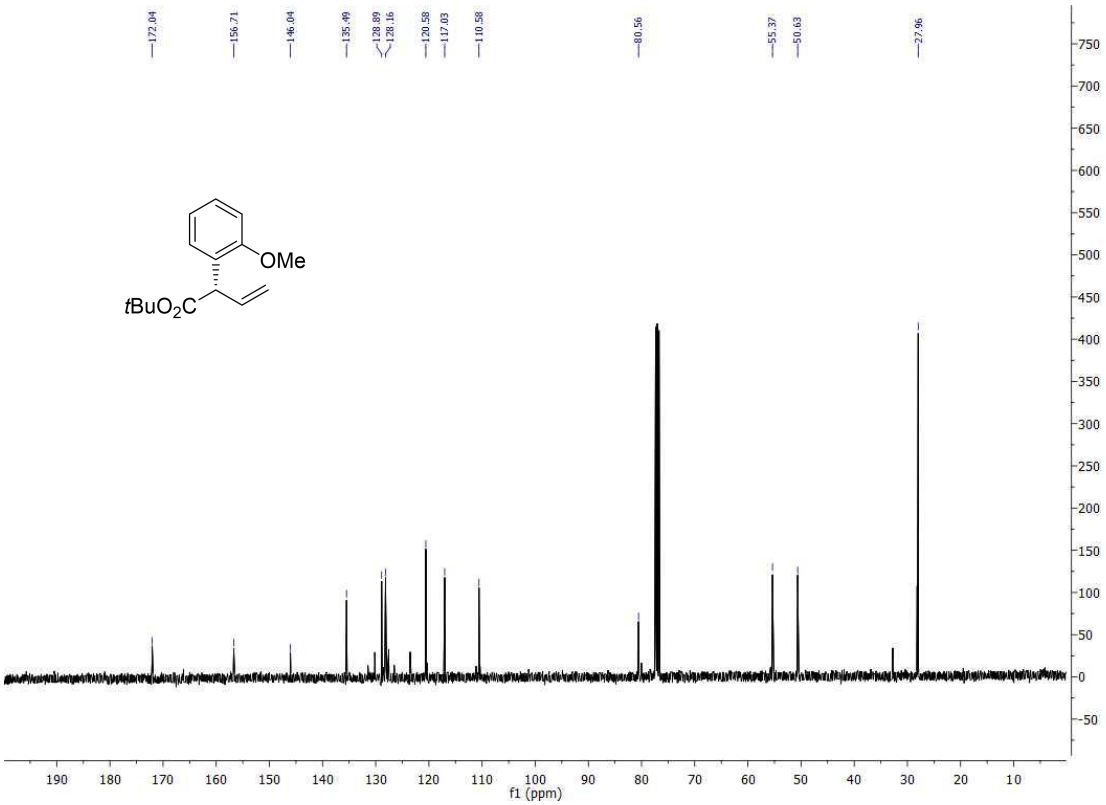

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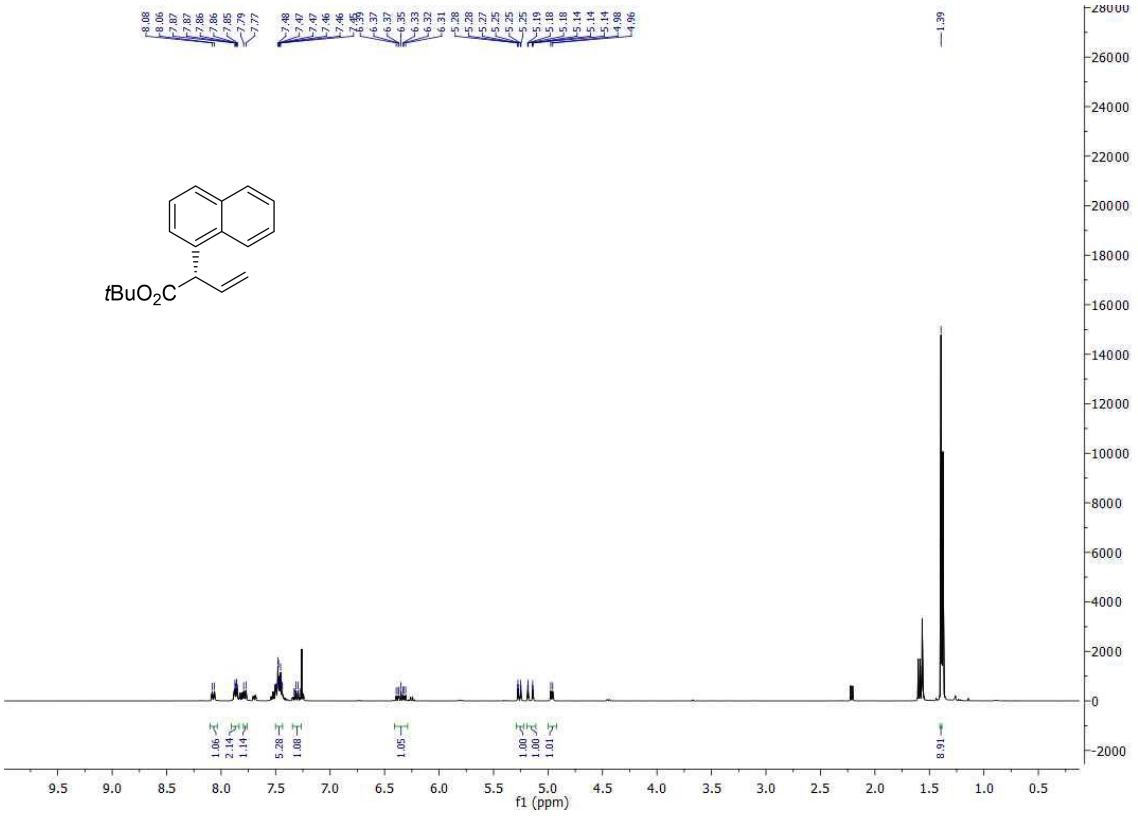

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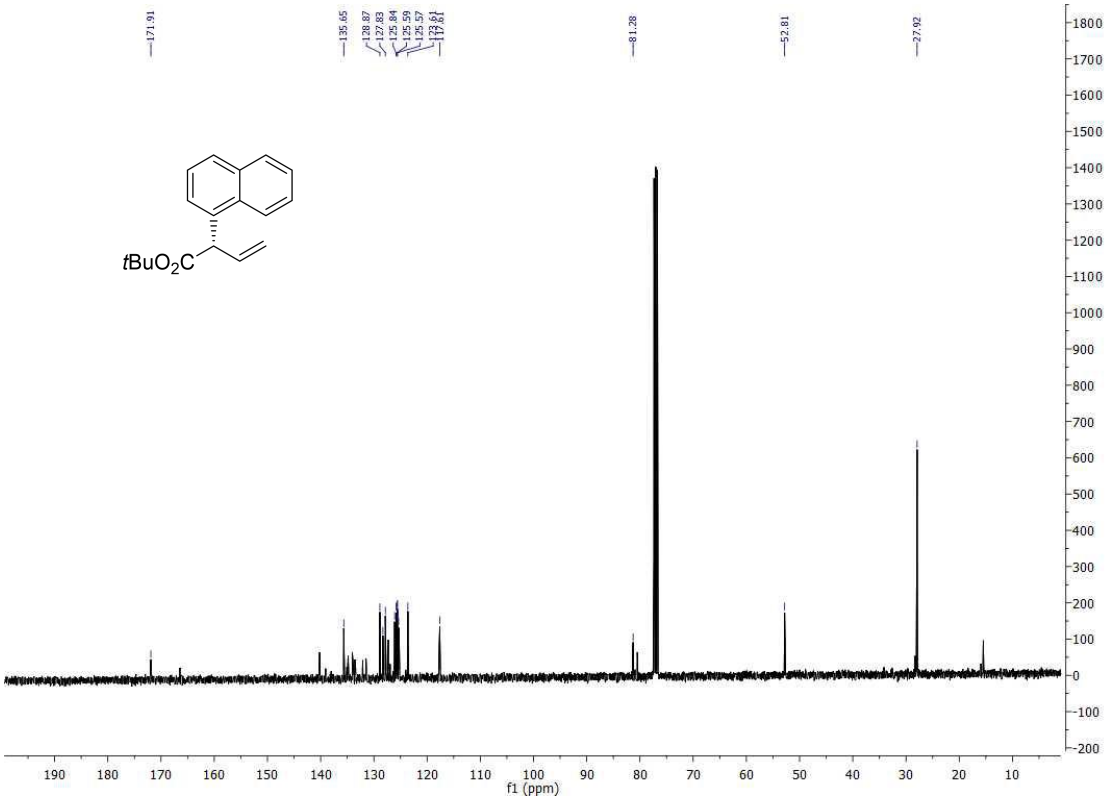

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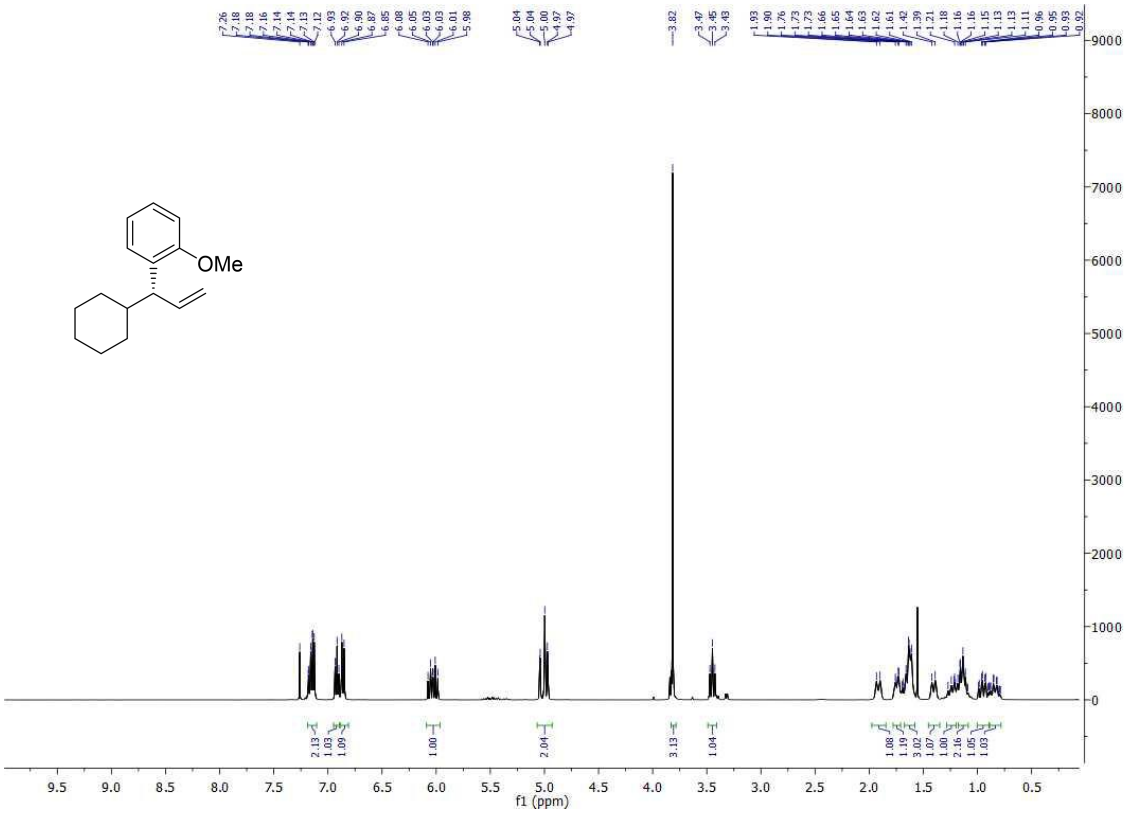

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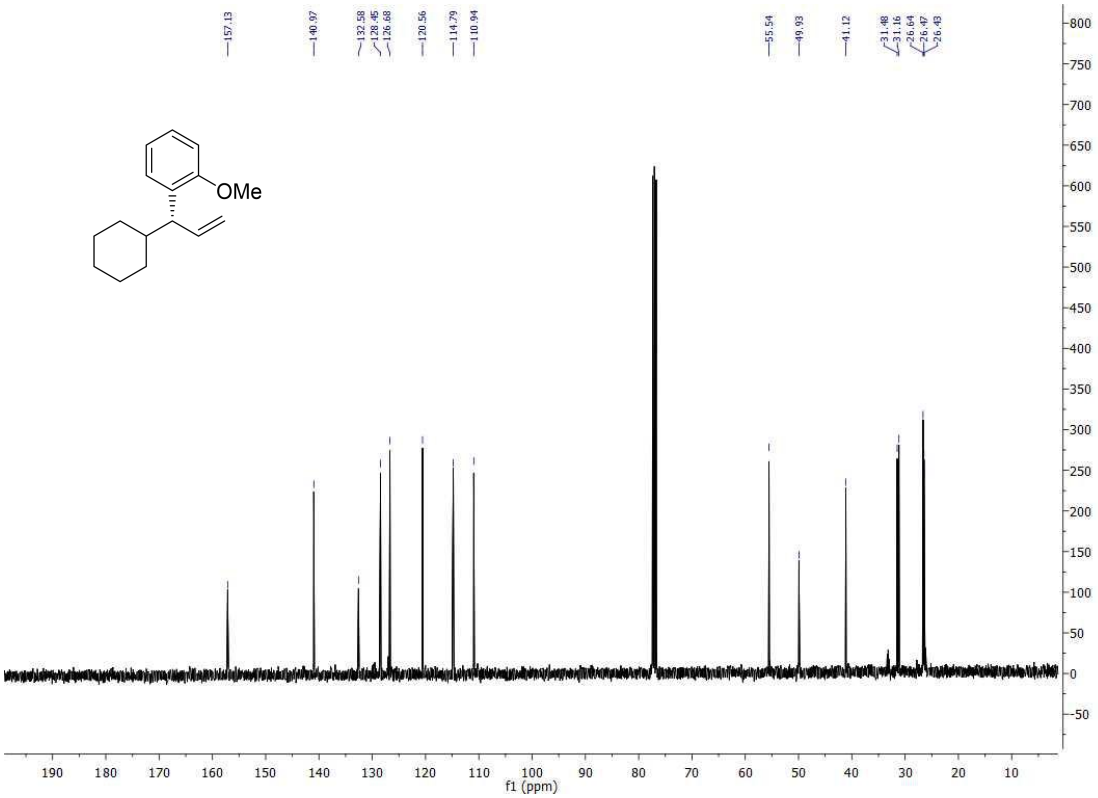
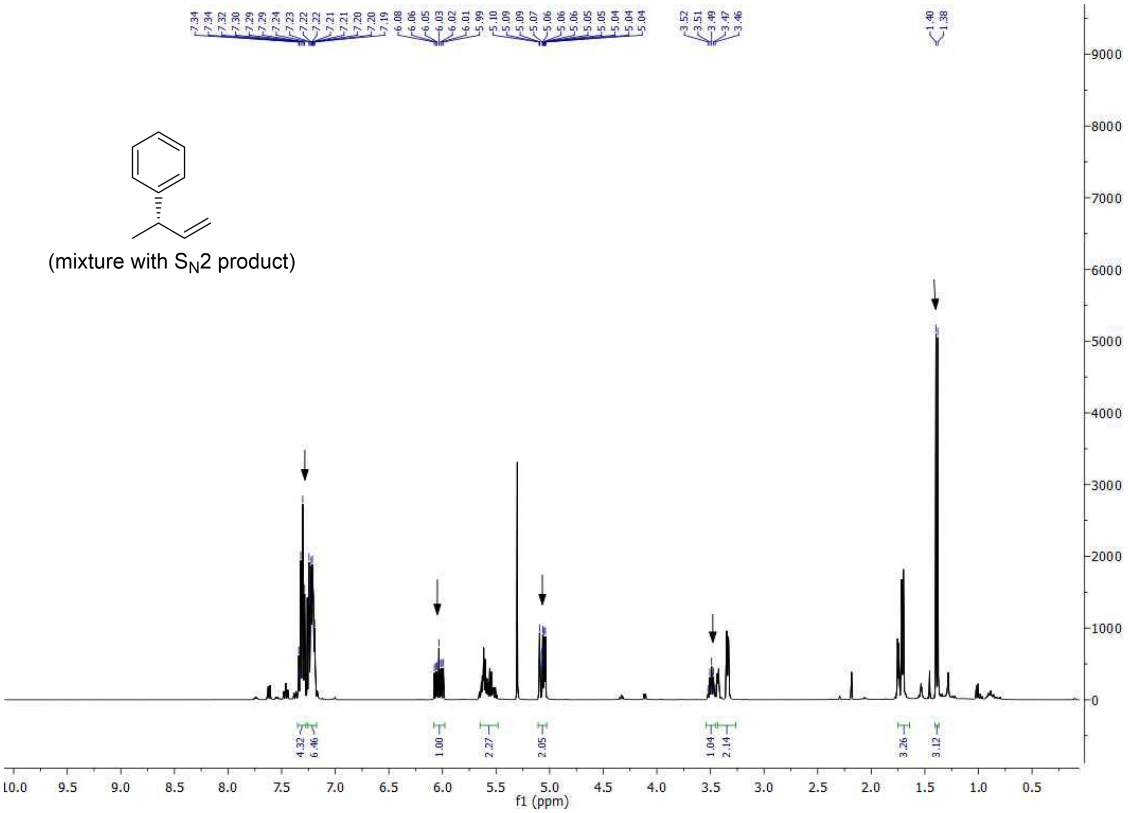


^{1}H NMR:



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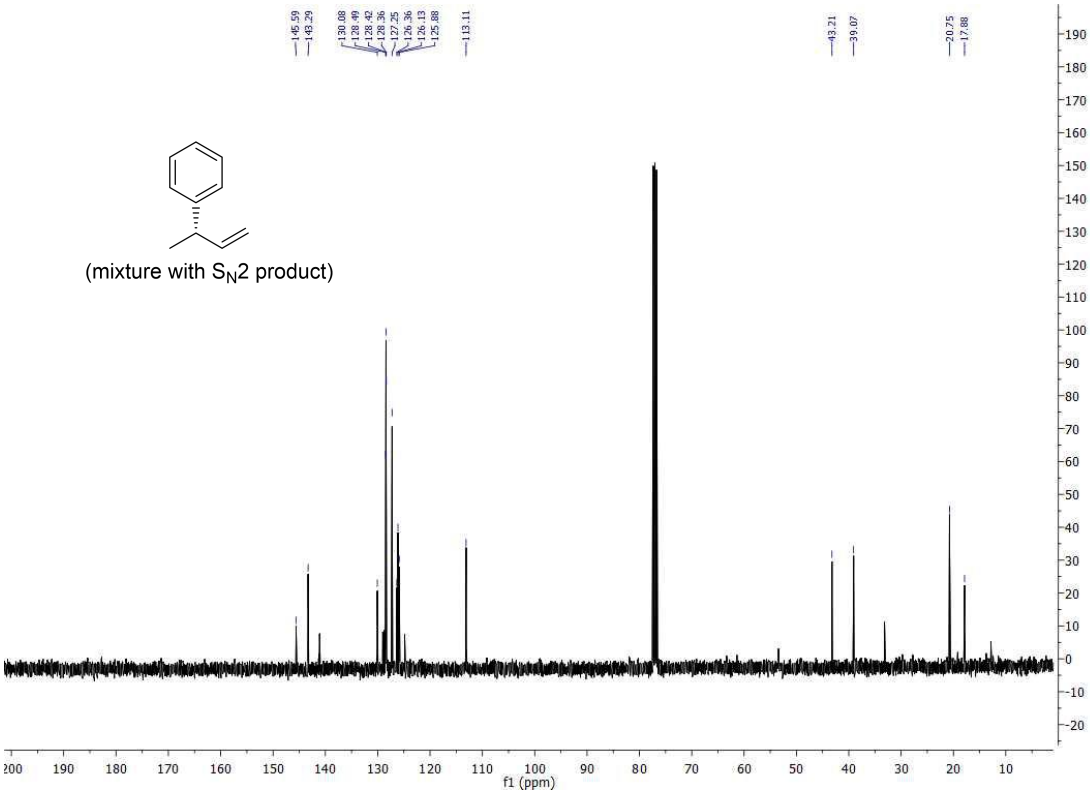

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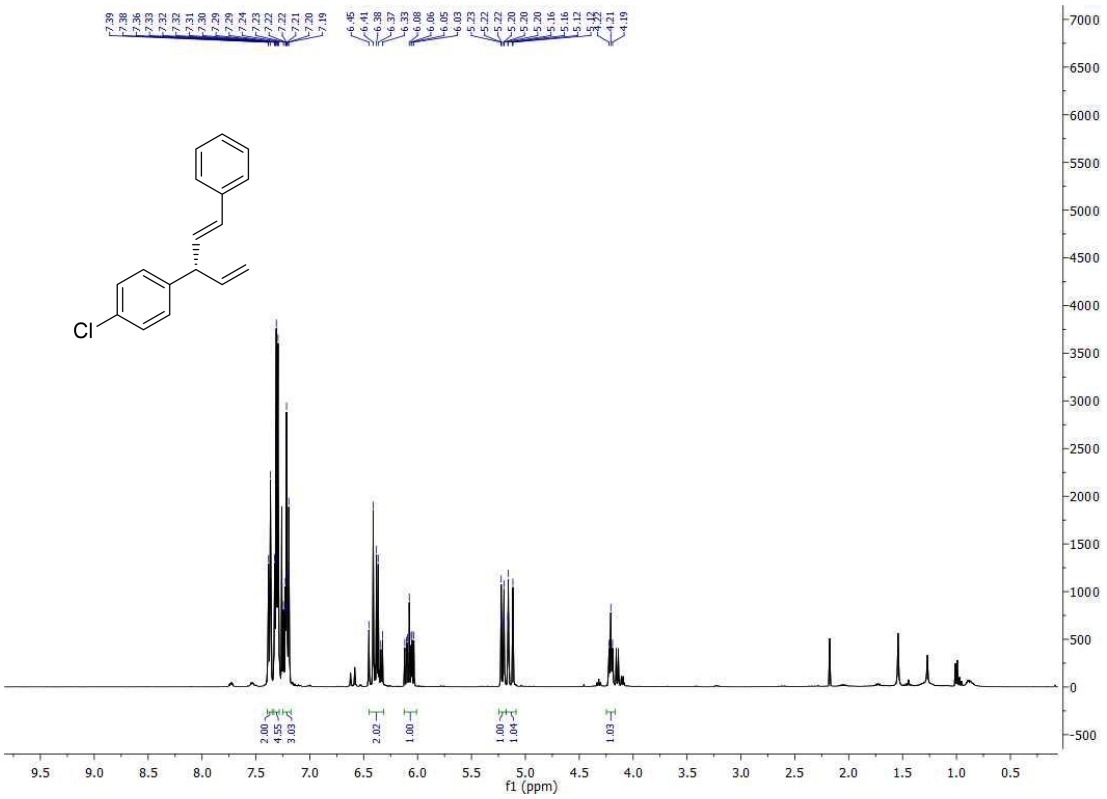

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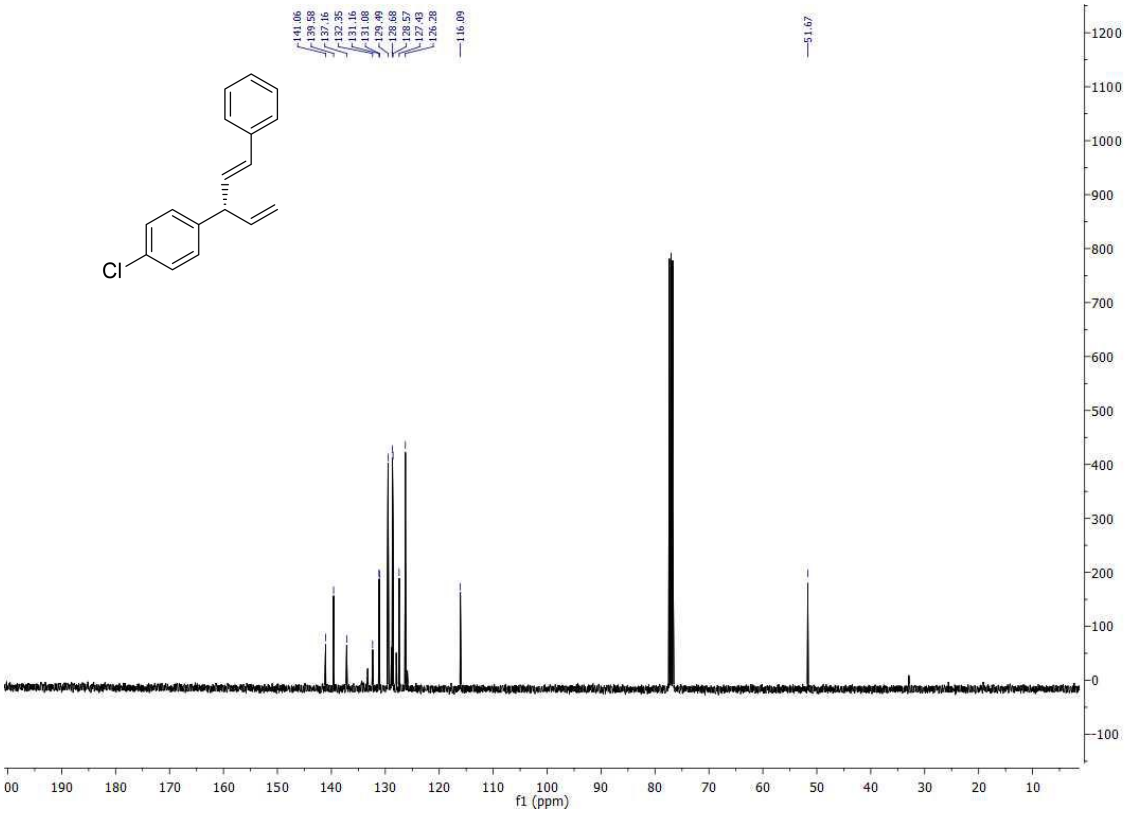
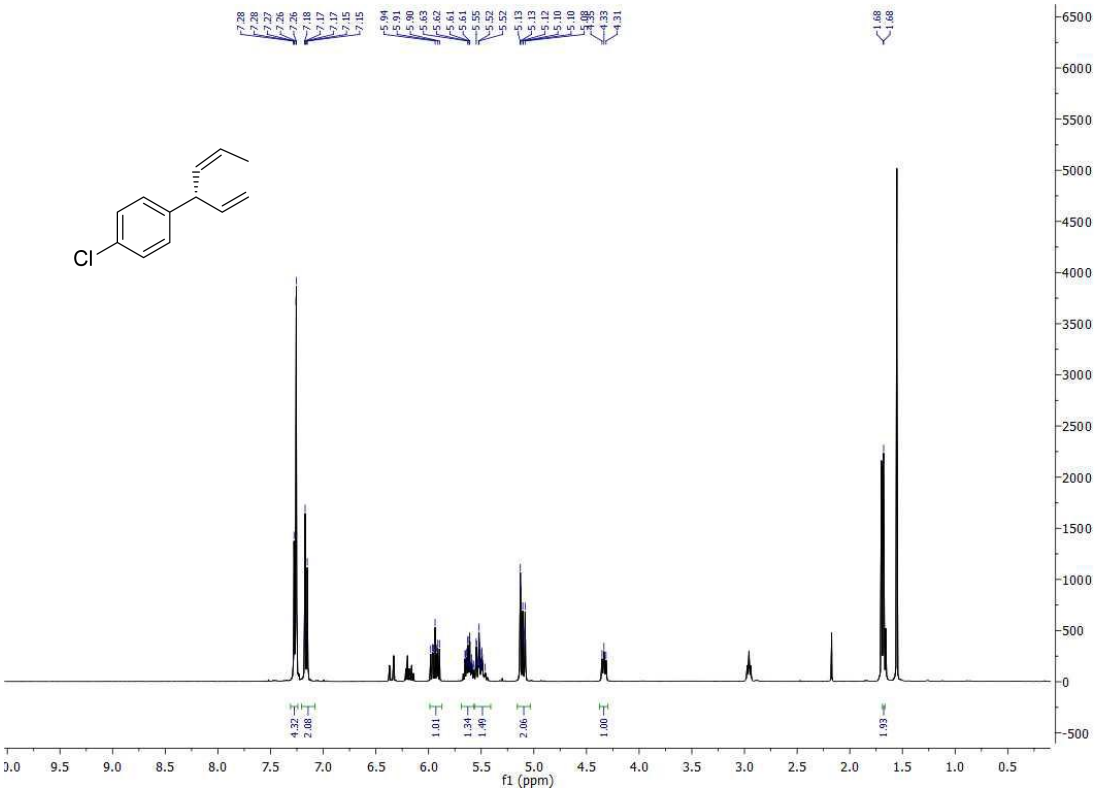


^{1}H NMR:



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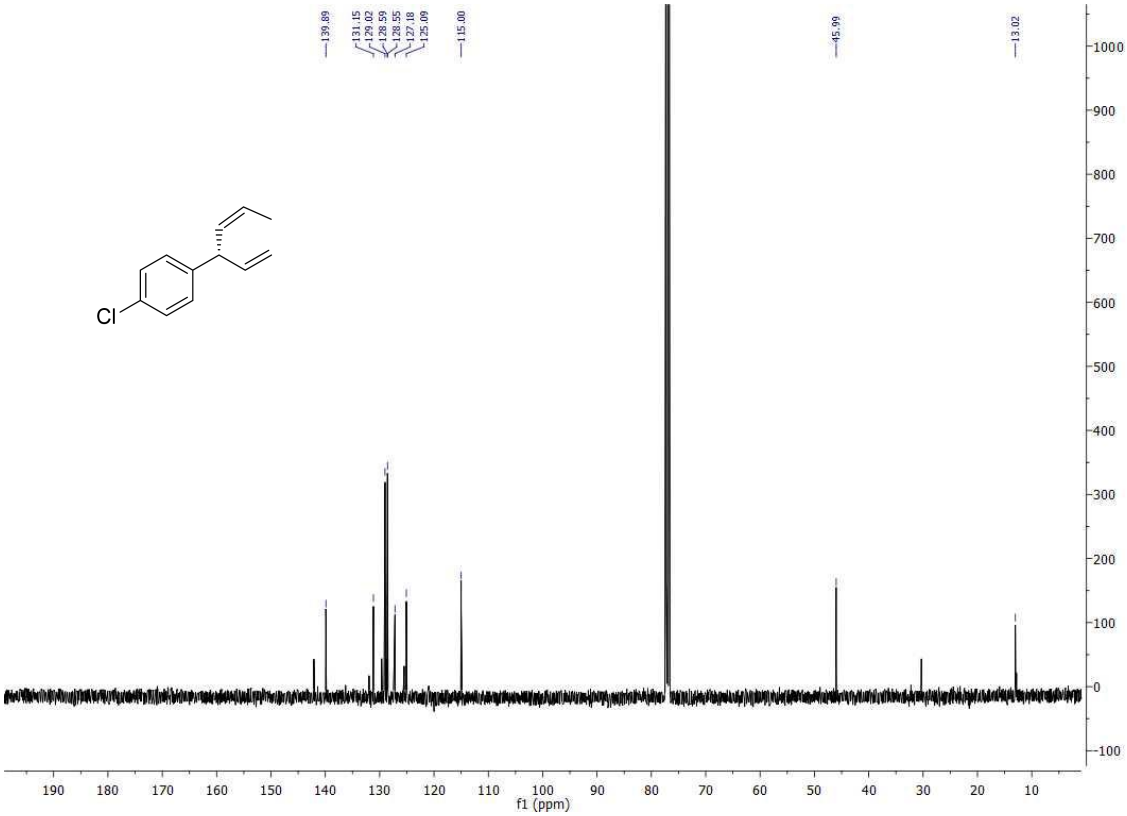

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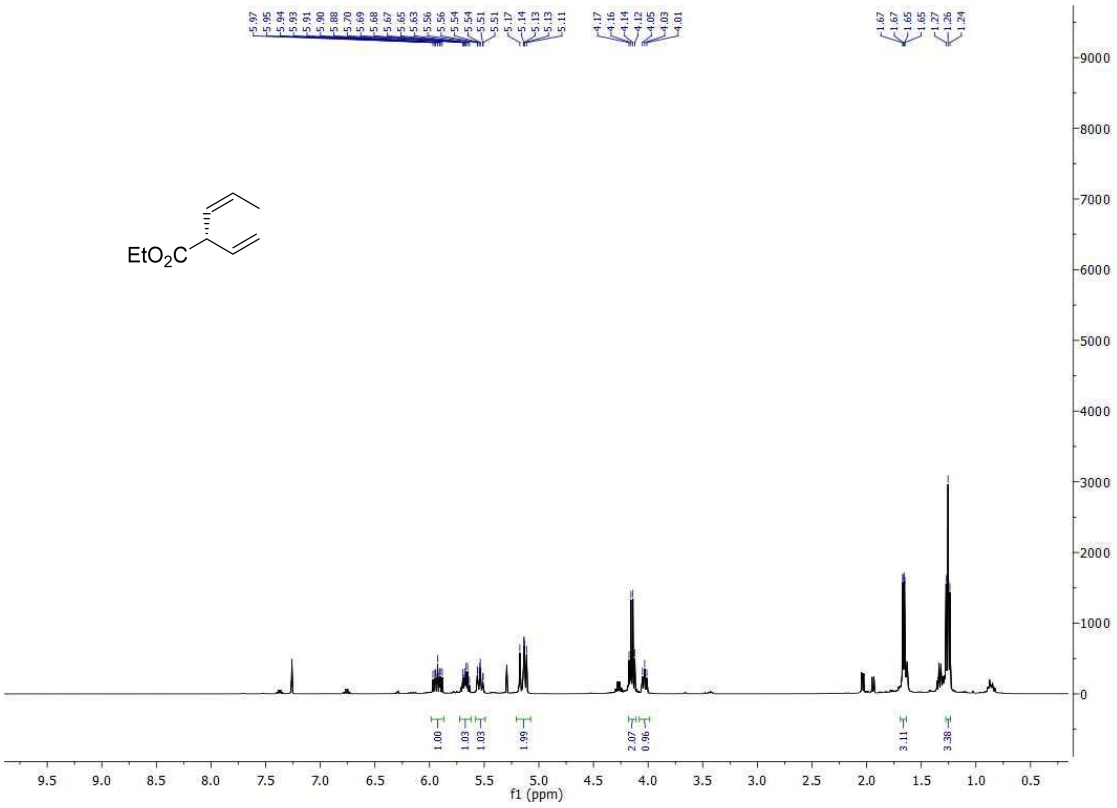

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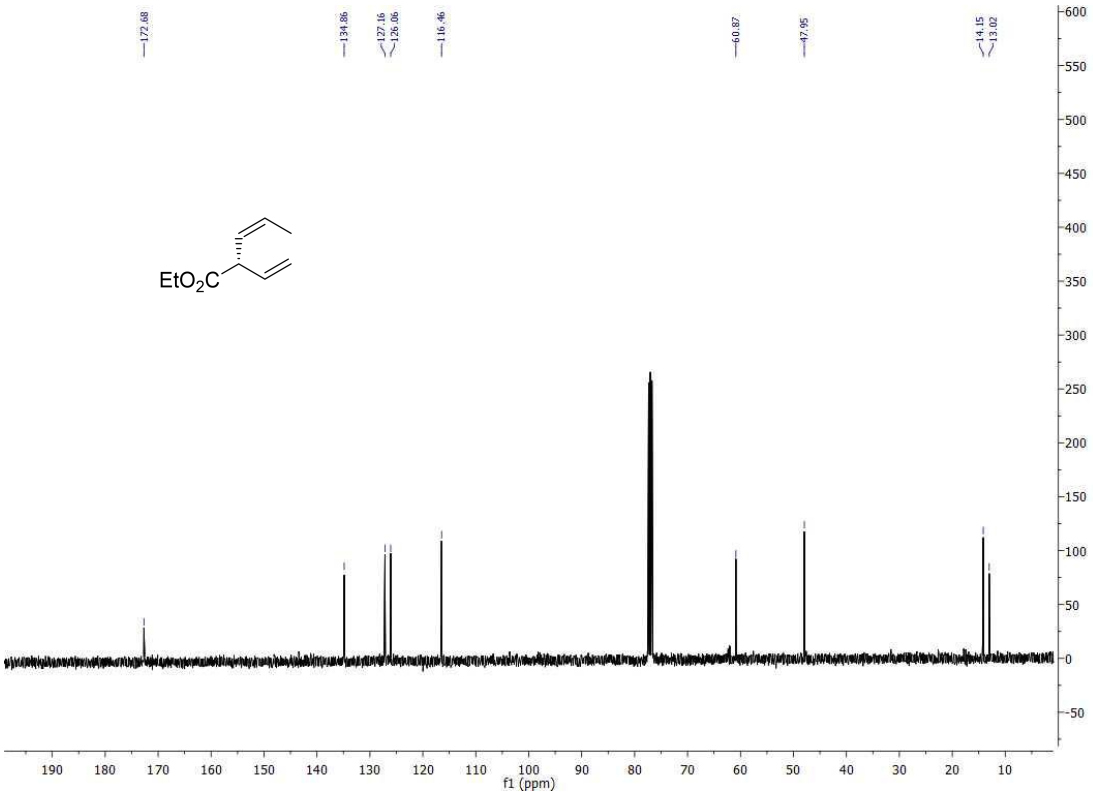

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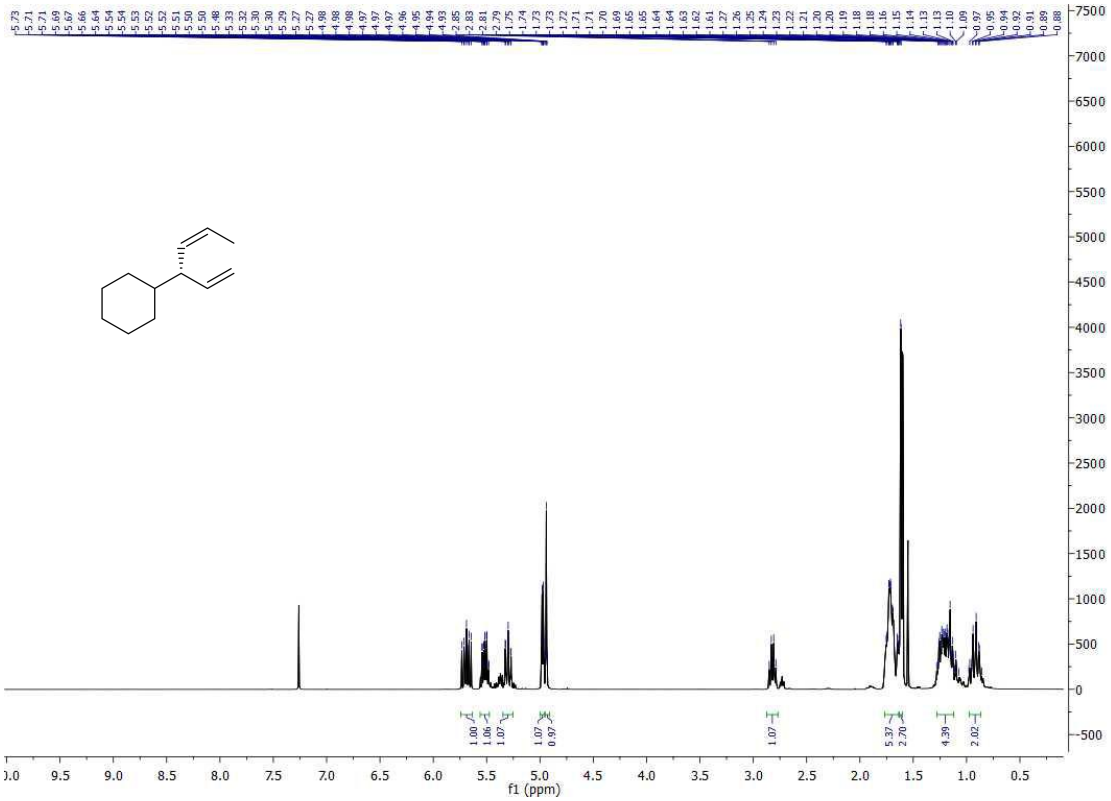

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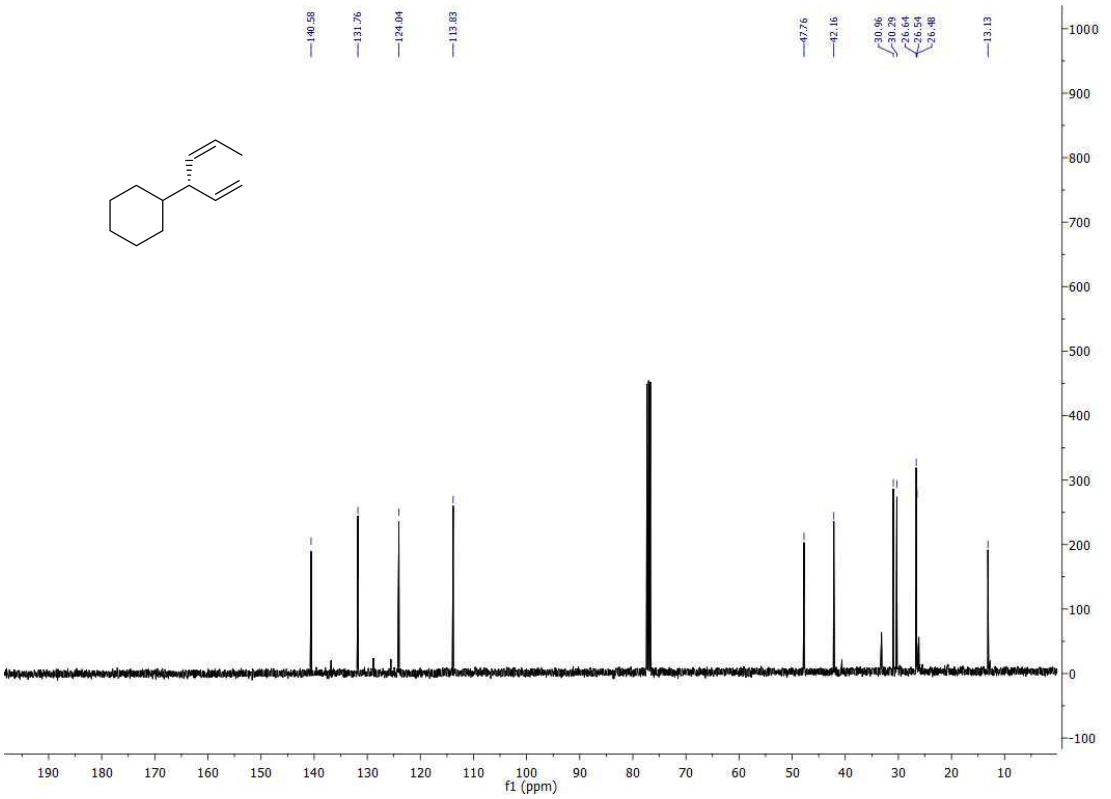

3.5 Reference

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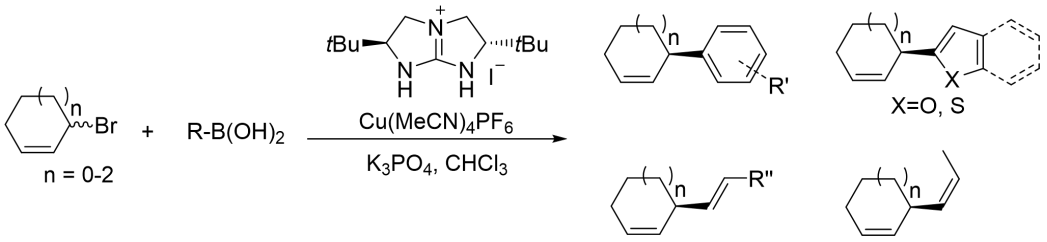
Outlook and Summary

The research work presented in this thesis comprises of two major parts, focusing on the development of enantioselective construction of Csp^3-Csp^2 bond catalyzed by copper complex and guanidinium salt under mild condition.

The first part of the work discussed the detailed investigation of asymmetric Csp^3-Csp^2 cross coupling reaction catalyzed by copper(I) complex and guanidinium catalyst. An array of cyclic allylic bromides in five-, six- or seven-member ring were transformed to the corresponding Csp^3-Csp^2 cross coupling products in good yield and high enantioselectivity. Various nucleophiles from boronic acids were employed, including aryl, heteroarene and vinyl groups. Mechanism exploration by *X*-ray, ^{63}Cu NMR and stereoselectivity of asymmetric allylic arylation process supported a "hard" nucleophilic attack pathway in the reaction.



The second part of the thesis described the extension of the developed methodology from cyclic bromides to various acyclic bromides, giving a broader scope of S_N2' products with good enantioselectivity. Though the regio- and enantio-selectivity of the reaction with prochiral acyclic allylic bromides was generally moderate, the results illustrated the capacity of our catalyst system in enantioselective allylic substitution with a wide range of bromide substrates.