SYNTHESIS OF NEW AZIRIDINE DERIVATIVES AS POTENTIAL PIPERAZINE PRECURSORS

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SYNTHESIS OF NEW AZIRIDINE DERIVATIVES AS POTENTIAL PIPERAZINE PRECURSORS

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

SYNTHESIS OF NEW AZIRIDINE DERIVATIVES AS POTENTIAL PIPERAZINE PRECURSORS

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Aziridines are three-membered heterocyclic compounds. They have significant properties in organic chemistry and medicinal chemistry. Many natural products have aziridines as medicines to treat various disorders. Especially, they are essential intermediates in the synthesis of heterocyclic frameworks. Moreover, aziridines can be easily transformed into diverse types of biologically active compounds. Other remarkable heterocyclic compounds are piperazines, known as six-membered rings with two nitrogen atoms at 1,4-position in the structure. Similarly, critical pharmacological compounds, especially some antibiotics, contain piperazine structures. Aziridine-fused piperazine precursors are rare compounds due to their extremely high ring strain. They have tremendous potential to be active biological compounds. In addition to that, aziridine-fused piperazine precursors can be easily converted to functionalized piperazine structures. However, the characterizable and isolable ones are limited in the literature. In this study, different aziridines were obtained by using the Gabriel-Cromwell strategy. Starting with aryl vinyl ketones, bromination was done first; then chiral aminoalcohol was reacted with dibromocompound to get chiral aziridines. In order to replace hydroxyl group with amino group, hydroxy group

was tosylated and then reacted with azide. Reduction of azide leads to intramolecular cyclization over the ketone carbonyl. As a result of this cyclization, novel aziridine-fused piperazine imines were obtained in moderate to good yields (36-75%). This strategy can be used for the synthesis of highly functionalized piperazine derivatives.

Keywords: Gabriel-Cromwell Reaction, aziridines, piperazine precursors.

ÖZ

POTANSİYEL PİPERAZİN ÖN MADDELERİ OLARAK YENİ AZİRİDİN TÜREVLERİNİN SENTEZİ

Bayat, Duygu
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Tez Yöneticisi: Prof. Dr. Özdemir Doğan

Temmuz 2022 , 95 sayfa

Aziridinler üç üyeli heterosiklik bileşiklerdir. Organik kimya ve tıbbi kimyada önemli özelliklere sahiptirler. Birçok doğal ürün, çeşitli bozuklukları tedavi etmek için ilaç olarak aziridin içerir. Özellikle heterosiklik bileşiklerin sentezinde önemli ara maddedirler. Ayrıca aziridinler, biyolojik olarak aktif bileşiklerin çeşitli türlerine kolaylıkla dönüştürülebilirler. Diğer dikkat çekici heterosiklik bileşikler, yapısında 1,4-konumunda iki nitrojen atomuna sahip altı üyeli halkalar olarak bilinen piperazinlerdir. Benzer şekilde, kritik farmakolojik bileşikler, özellikle bazı antibiyotikler, piperazin yapıları içerir. Aziridin ile kaynaşmış piperazin öncüleri, son derece yüksek halka gerilimi nedeniyle nadir bileşiklerdir. Aktif biyolojik bileşikler olmak için muazzam bir potansiyele sahiptirler. Buna ek olarak aziridin kaynaşmış piperazin öncüleri fonksiyonel piperazin yapılarına kolayca dönüştürülebilirler. Ancak karakterize edilebilir ve izole edilebilir olanlar literatürde sınırlıdır. Bu çalışmada Gabriel-Cromwell stratejisi kullanılarak farklı aziridin bileşikleri elde edilmiştir. Aril vinil ketonlardan başlanarak önce bromlama tepkimesi yapılmış, sonrasında oluşan dibromo yapısı kiral aminoalkol ile tepkimeye girerek aziridin yapıları elde edilmiştir. Hidroksil grubunun

amino grubuna dönüştürülmesi için önce tosillenmiş, arkasından tosil grubu sodyum azid ile tepkimeye girerek azid yapısı elde edilmiştir. Azid grubunun indirgenmesi aşamasında oluşan amin yapısı keton karbonili üzerinden doğrudan moleküliçi siklizasyona gitmiştir. Bu siklizasyon sonucunda aziridine kaynamış piperazin imin yapıları orta ve iyi denilebilecek verimlerle (%36-75) sentezlenmişlerdir. Bu strateji farklı sübstite grupları olan piperazin yapılarının sentezinde kullanılabilir.

Anahtar Kelimeler: Gabriel-Cromwell Tepkimesi, aziridinler, piperazin öncüleri.

To my mother, my sister, and all women who are struggling...

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SCHEMES

LIST OF ABBREVIATIONS

BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
DEAD	Diethyl azodicarboxylate
t-RNA	Transfer RNA
SN	Nucleophilic substitution
J	Coupling constant
δ	chemical shift
Cbz	Benzyloxycarbonyl
MS	Molecular sieve
dr	Diastereomeric ratio
er	Enantiomeric ratio

CHAPTER 1

INTRODUCTION

Biologically active materials attract attention due to their importance, especially in pharmaceutical science. Various organic molecules are synthesized in this field on both laboratory and industrial scales. Aziridines and their derivatives, some of the potential biologically active molecules, catch deep interest. These small heterocycles play a vital role in organic synthesis. Also, they are known as essential intermediates in synthesizing heterocyclic frameworks with the potential to be natural products showing biological activities and pharmaceutical properties.[1] Piperazines are one of the heterocyclic compounds prepared by using aziridines. They have unique structures with antibacterial activities.[2]

1.1 General look in aziridine

The aziridines are defined as saturated three-membered cyclic compounds having nitrogen and two carbon atoms (Figure 1.1). Aziridine has also been called azacyclopropane and ethylenimine.[3] Aziridine has been recognized as an essential heterocyclic structure used to synthesize precious compounds having biological activities.

Figure 1.1: Structure of the simple aziridine.

There are many natural and synthetic compounds with aziridine rings, such as mitomycins, ficellomycins, and azinomycins (Figure 1.2).[4] Moreover, aziridines possess high reactivity due to their small-ring heterocyclic structure.[5] The high reactivity results from the interior angles of aziridines being 60° which is considerably less than the preferential tetrahedral angle (109.5°). This angle strain makes the aziridine ring unstable and susceptible to nucleophilic attack.

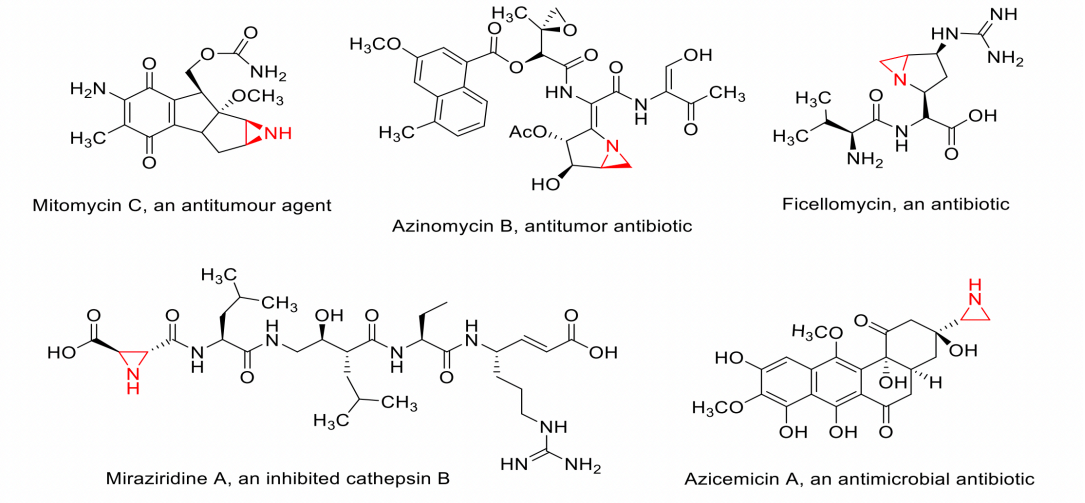

Figure 1.2: Some food and drugs containing an aziridine ring.

Many pharmaceutical compounds can be easily prepared by the ring opening of the aziridine ring. For instance, pseudoephedrine, sphingosine, tamiflu, and oxaliplatin have been synthesized by the opening of the aziridine ring. They are valuable examples of why aziridines are significant synthetic intermediates in organic synthesis (Figure 1.3).

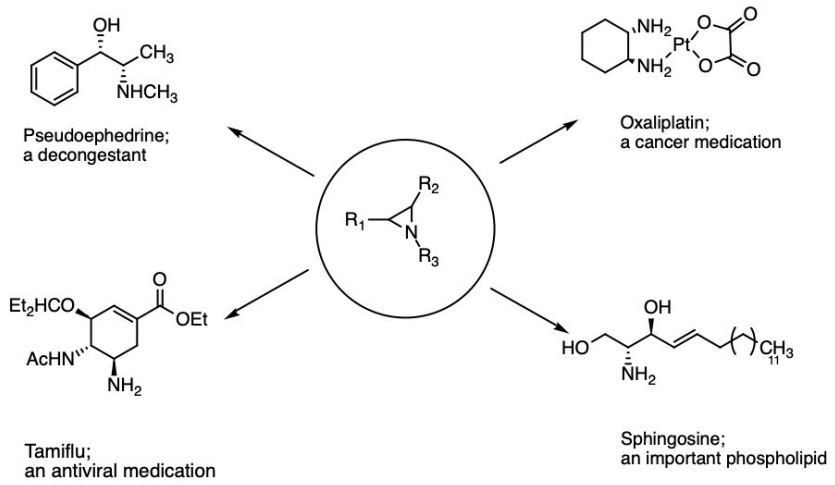

Figure 1.3: Examples of important medicinal compound obtained by ring opening of aziridines.

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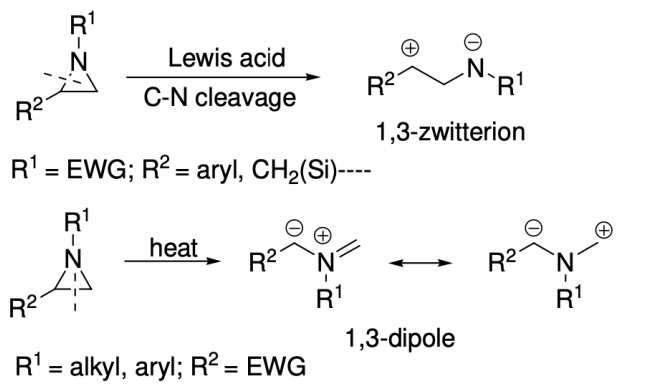
1.2 Heterocycles from aziridines by ring-opening

As mentioned before, low interior angles of the aziridines have ring strain, which facilitates ring opening by nucleophiles. Especially, a variety of nucleophiles lead to ring opening at either its α- or β-position in a regioselective manner. Both C-C or C-N bonds of aziridine rings can undergo cleavage. The regioselectivity in the ring-opening is based on substitution patterns of aziridine ring (Scheme 1.1).[6]

Generally, the electron-withdrawing groups (EWGs) on the ring trigger the cleavage of the C-N bond. On the other hand, the electron-donating groups on the ring drive cleavage of the C-C bond. In addition to these electronic effects, the steric effect favors the nucleophilic attack on the ring.[7]



Scheme 1.1: Cleavage of the C-C and the C-N bonds of aziridine.

As a result of the tendency of the ring-opening of aziridines and subsequent cyclization, the synthetic methodologies for the four-to seven-membered heterocyclic motifs were discovered (Figure 1.4). Azetidines, β-lactams, pyrroles, imidazoles, oxazoles, pyrimidines, pyrazines, oxazines, morpholines, thiomorpholines azepanes, benzodiazepines, benzoxazepines, and benzothiazepines were synthesized by the aforementioned methods.[7]

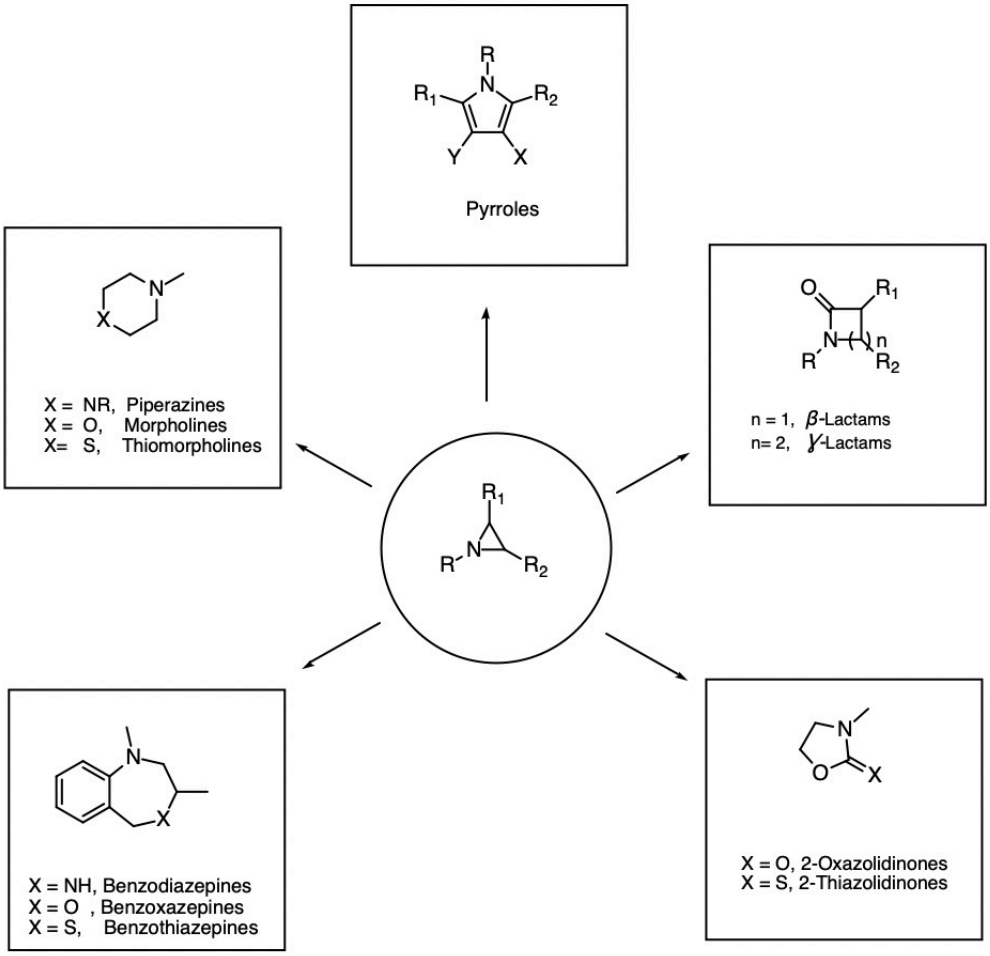
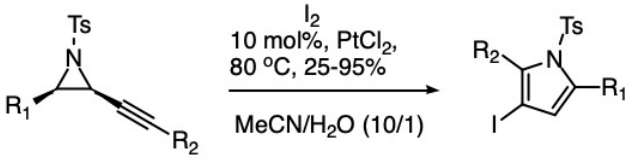


Figure 1.4: Different heterocyclic compounds obtained from aziridines.

1.2.1 Pyrroles

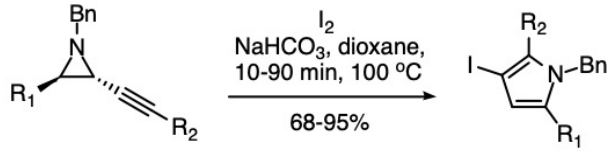
Pyrroles are five-membered heterocyclic aromatic compounds. They can be used as biosynthetic precursors to obtain several natural products, such as heme.[8] Pyrroles can be used in different fields, including material science, non-linear optics, and supramolecular chemistry.[9] Especially, polypyrroles are essential materials for synthesizing molecular sensors and devices.

Pyrroles are also useful components of more complex macrocycles, including porphyrinogens, porphyrins of heme, chlorins, bacteriochlorins, and chlorophylls.[10] The work of Yoshida et al. can be given as an example of pyrrole synthesis from aziridines.[11] As shown in Scheme 1.2, an electrophilic cyclization of *N*-tosyl or *N*-benzyl-substituted propargylic aziridines form 3-iodopyrroles in the presence of platinum used as a catalyst.



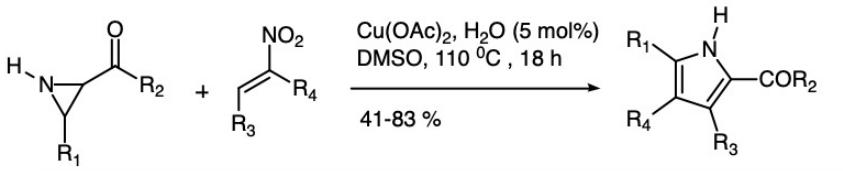
Scheme 1.2: Platinum-catalyzed iodocyclizations of the aziridines to pyrroles.

N-Tosyl-substituted aziridines are activated by coordination of platinum while iodine is preferred for the electrophilic activation of *N*-benzyl-substituted propargylic aziridines (Scheme 1.3).[11]



Scheme 1.3: Iodocyclizations of the aziridines in the presence of iodine.

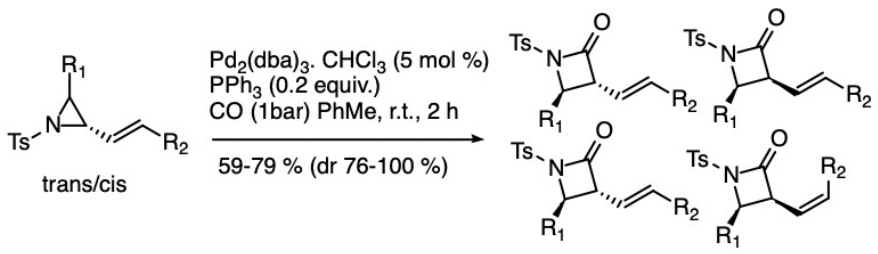
Another efficient method for the synthesis of poly-functionalized pyrroles was performed by Wang et al., which is a cascade of regioselective ring-opening of N-H aziridines followed by [3+2]-cycloaddition with β-nitroolefins under aerobic conditions (Scheme 1.4).[12] In this work, the aziridine ring tends to undergo C–N/C–C bond cleavage, which can be served as a good tool in synthesizing polysubstituted pyrroles. Selective C–C bond cleavage of the aziridine gives azomethine ylide intermediate, and then it reacts with trans-nitroalkenes through a copper-catalyzed [3 + 2] annulation under aerobic conditions.



Scheme 1.4: Copper acetate-catalyzed [3 + 2] annulation reaction of aziridines.

1.2.2 β-Lactams

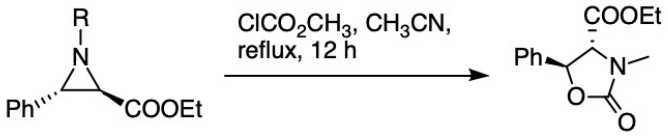
β-Lactams are four-membered cyclic amides, which are the crucial core structures of several antibiotics. Also, they can be utilized as cholesterol absorption inhibitors[13] and β-lactamase inhibitors.[14] Fontana and coworkers have reported α,β-unsaturated aziridines, which undergo Pd-catalyzed carbonylation reactions to give β-lactam derivatives.[15] Four isomeric β-lactams at room temperature were synthesized by using vinylaziridines with carbon monoxide, triphenyl phosphite, and trisdibenzylideneacetone palladium (III) trichloromethane as a catalyst (Scheme 1.5). As a result of this reaction, *trans-(E)*-β-lactam was obtained as the major product. Due to an enantioenriched aziridine, full chirality transfer is achieved. When this reaction was operated under 50 bar CO, the β-lactam in favor of the *trans-(Z)*-isomer was observed.



Scheme 1.5: The palladium-catalyzed carbonylative ring-expansion of vinyl aziridines for the synthesis of β-lactams.

1.2.3 Oxazolidin-2-ones

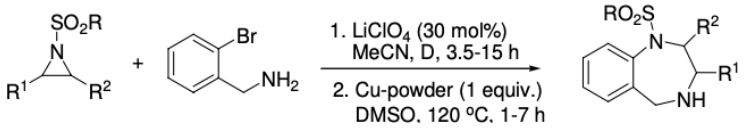
Oxazolidinones exhibiting biological and optical activities are critical organic compounds. Important antibiotics consisting of oxazolidinones show excellent activity against gram-positive bacteria.[16] Some oxazolidinones demonstrate antimicrobial potency for inhibition of bacterial protein synthesis by interacting with the aminoacyl-t-RNA at the site of the ribosome.[17] Because of the importance of oxazolidinone structure, many methods covering aziridine unit as a starting material have been reported to get oxazolidinone molecules. One of them is for development of trans-1,3-oxazolidin-2-ones succeeded by regio- and stereoselective transformation of *trans-N*-alkylaziridine-2-carboxylates in good yields (Scheme 1.6).[18]



Scheme 1.6: Synthesis of oxazolidin-2-ones.

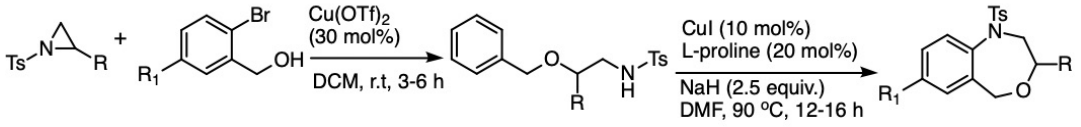
1.2.4 Benzodiazepines and benzoxazepines

Benzodiazepines formed by the fusion of a benzene ring and a diazepine are used as psychoactive drugs such as chlordiazepoxide (Librium).[19] Aziridines are the key molecules for the synthesis of benzodiazepines. Ghorai and coworkers reported that 2,3,4,5-tetrahydro benzodiazepine derivatives could be synthesized successfully from aziridines (Scheme 1.7).[20] They proposed that 2-bromobenzylamine attacks *N*-activated aziridines with a S_N2-type reaction, which is followed by an intramolecular cyclization through Cu-mediated bond formation. Their methods are used to get target molecules in high yields (up to 94% yield) and enantioselectivity (up to 99% ee).



Scheme 1.7: Synthesis of benzodiazepines using *N*-activated aziridines with 2-bromobenzylamine.

Benzoxazepine, oxazepine fused to the benzene ring, is generally considered a biologically and pharmaceutically active structure. Benzoxazepines can also be obtained from aziridine derivatives. Ghorai group has reported a similar reaction starting from *N*-activated aziridines, and 2-bromobenzylalcohol in the presence of a copper catalyst (Scheme 1.8).[21]



Scheme 1.8: Synthesis of benzoxazepines from *N*-activated aziridines and 2-bromobenzylalcohol.

1.3 Overview: Piperazine

Piperazine is a six-membered heterocyclic structure having two nitrogen atoms at 1,4-positions (Figure 1.5). The piperazines are a broad class of chemical compounds with important pharmacological properties.[22] Some antibiotics have the piperazine ring, such as ciprofloxacin, pefloxacin, and rifamycin,[22] are applied in therapeutics.[23] Antimycotic drugs like ketoconazole,[22,24] circulatory system drugs,[25,26] and antiparasitic agents[23] also have piperazine scaffold in their structures. Moreover, some piperazines consist of cephalosporin that are active towards both Gram-positive and Gram-negative bacteria.[27] That's why piperazine synthesis is a critical issue in organic chemistry.

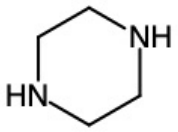


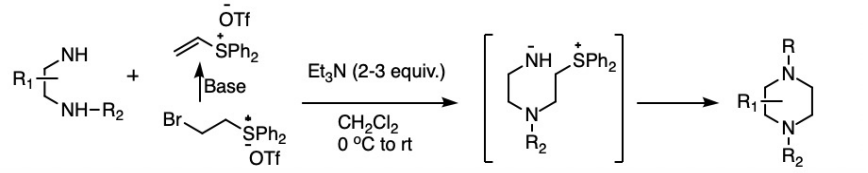
Figure 1.5: Piperazine structure.

1.4 General Methods for Piperazine Synthesis

There are various methods to form piperazines in the literature: *N*-alkylation,[28] reduction of diketopiperazine,[29] transition-metal-catalyzed piperazine synthesis,[30] the borrowing hydrogen strategy,[30] and the reduction of pyrazines.[31] In this section, the relevant researches will be summarized.

1.4.1 *N*-Alkylation

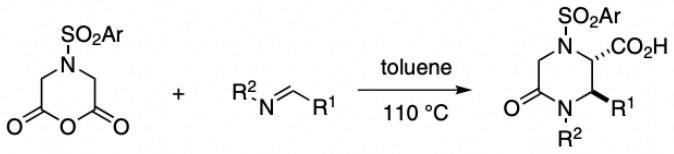
Alkylation of amines is typically a good methodology to synthesize piperazines. The synthesis of piperazines by using the alkylation of 1,2-diamine derivatives was developed by Aggarwal group.[28] They found that the bromoethylsulfonium salt could be a useful annulation agent to get six-membered 1,4-heterocyclic compounds having a piperazine ring (Scheme 1.9).



Scheme 1.9: An annulation reaction for the synthesis of piperazines.

1.4.2 Reduction of (Di)ketopiperazine

In 2015, Krasavin and co-workers introduced the application of the Castagnoli-Cushman reaction with glutaric anhydride analogs.[29] The Castagnoli-Cushman reaction is a remarkable technique to get the piperazines containing heteroatoms in medicinal chemistry. In this strategy, cyclic anhydrides react with different kinds of imines. As a result of the Castagnoli-Cushman reaction, the synthesis of oxopiperazines was possible in high yield and *trans*-stereoselectivity (Scheme 1.10).

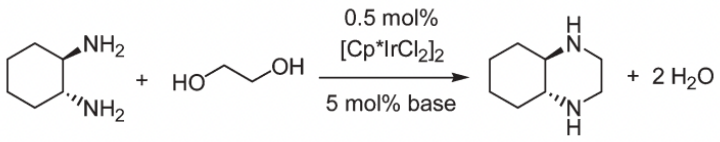


Scheme 1.10: Synthesis of oxopiperazines by the Castagnoli–Cushman reaction.

1.4.3 Borrowing Hydrogen Strategy

For the synthesis of piperazine, borrowing hydrogen strategy is another option. The borrowing hydrogen strategy depends on diamines and diols. Ease of access to commercially available amines and alcohols is the main advantage of this method. Also, it offers a synthesis of piperazine without oxidants and reducing reagents. This reaction provides the desired product in an environmentally-friendly way because the only side product is water.[30]

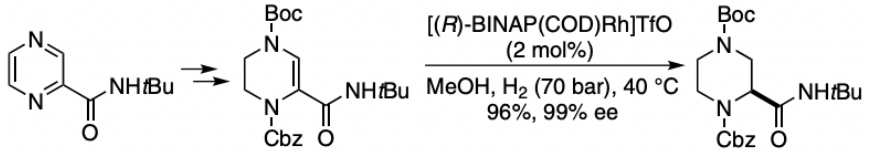
In 2007, Madsen and co-workers reported iridium catalyzed synthesis of piperazines from diols using the borrowing hydrogen concept (Scheme 1.11).[32] Under this catalytic condition, cyclocondensation takes place with different 1,2-diamines and 1,2-diols to yield piperazine derivatives in high yield and stereoselectivity.



Scheme 1.11: Iridium catalyzed synthesis of a bicyclic piperazine from diols.

1.4.4 Reduction of Pyrazine

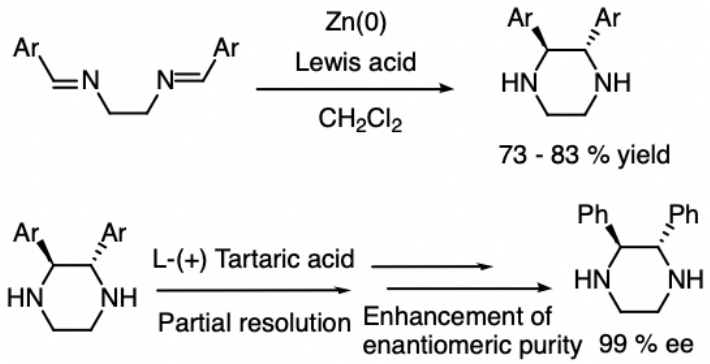
The enantioselective reduction of pyrazines to obtain the piperazines is not an easy process. However, reducing pyrazines through hydrogenation or hydride reaction is a clever and convenient method to synthesize enantioselective piperazines. That was demonstrated by Rossen et al., which is one of the significant applications of reduction of pyrazines (Scheme 1.12).[31] In this process, after partial hydrogenation of the 2-*tert*-butylpyrazine amide, protection of nitrogens with *N*-Boc- and *N*-Cbz groups were carried out. Through asymmetric hydrogenation, using *(R)*-BINAP–Rh chiral catalyst, piperazine amide was obtained in good yields and enantioselectivity.



Scheme 1.12: Asymmetric hydrogenation for the synthesis of a piperazine-2-carboxamide.

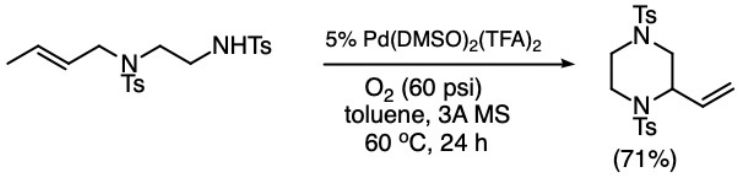
1.4.5 Transition-Metal-Catalyzed/Mediated Piperazine Synthesis

Many transition metals play an important role in the production of piperazines. Copper, palladium, gold, ruthenium, iridium, and zirconium are commonly employed as a catalyst to synthesize piperazine derivatives.[30] Several methods have been published by using transition metal-mediated protocols. For example, Vairaprakash and Periasamy have reported an enantioselective synthesis of 2,3-diarylpiperazine derivatives using the $Ti(O^iPr)_2Cl_2$/Zn reagent.[33] (±)-2,3-diarylpiperazines have been obtained through intramolecular reductive coupling of diimines in the presence of $Ti(O^iPr)_2Cl_2$/Zn in 73-83% yield with dl/meso ratio >99% (Scheme 1.13).



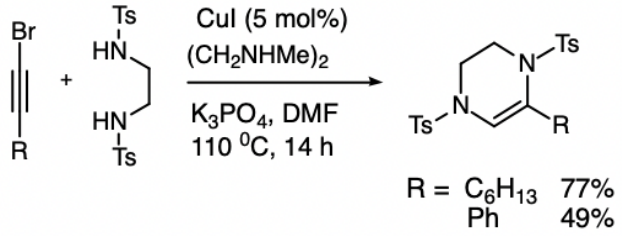
Scheme 1.13: Synthesis of (±)-2,3-diarylpiperazines.

Another study is the Pd(II)-catalyzed oxidative cyclization of alkenes reported by Lu and Stahl. They described the synthesis of six-membered nitrogen heterocycles, including morpholines, piperidines, piperazines, and piperazinones, with a Wacker-type aerobic oxidative cyclization of alkenes.[34] They claimed that $Pd(DMSO)_2(TFA)_2$ was a powerful catalyst for the oxidative cyclization in toluene. Expected products were obtained in good yields by intermolecular oxidative amination of alkenes with Pd(II) catalyst (Scheme 1.14).



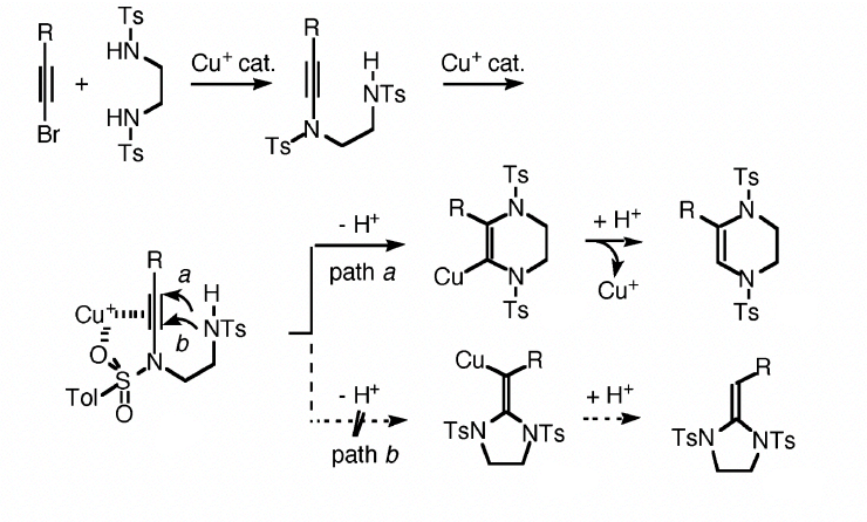
Scheme 1.14: Piperizine synthesis by intermolecular oxidative amination of alkenes with Pd(II) catalyst.

Fukudome et al. reported the copper-catalyzed double amination of haloacetylenes as an alternative way to get unsaturated piperazine compounds as shown in Scheme 1.15.[35]



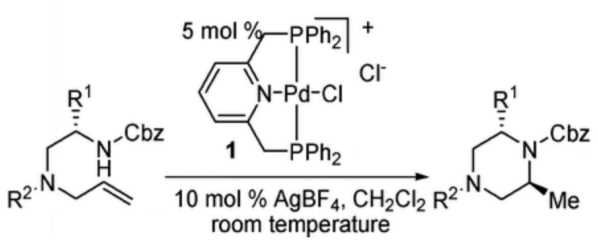
Scheme 1.15: Copper-catalyzed 1,2-double amination of 1-halo-1-alkynes for the synthesis of unsaturated piperazines.

The proposed reaction pathway for this methodology is given in Scheme 1.16. Alkynylation of sulfonamide with halo-acetylene takes place first. Then, amination of the acetylenic bond results. After protonation, the catalytic cycle is completed for the six-membered *N*-heterocyclic structure formation.



Scheme 1.16: The proposed reaction pathway for Cu-catalyzed diamination of alkynes.

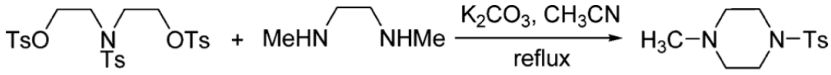
Cochran and Michael have presented a diastereoselective palladium-catalyzed hydroamination reaction for the synthesis of 2,6-disubstituted piperazines.[36] The use of 5 mol% Pd catalyst and 10 mol% $AgBF_4$ provided desired piperazine derivatives in 89-99% yields with excellent diastereoselectivities (Scheme 1.17).



Scheme 1.17: Hydroamination of aminoalkenes for 2,6-disubstituted piperazines.

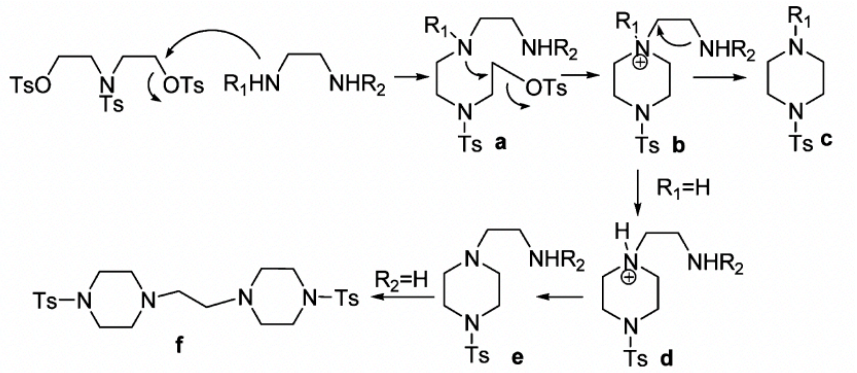
1.4.6 Miscellaneous

Huang et al. have introduced synthesis of *N*-heteroalkyl-*N'*-tosylpiperazines through one-pot cyclization.[37] Distinct diamines having two active primary amine groups are utilized with tosylbis(2-(tosyloxy)ethyl)amine in refluxing acetonitrile with potassium carbonate, which resulted in the formation of ditosylpiperazine derivatives (Scheme 1.18).



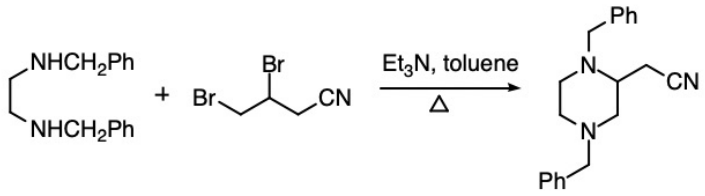
Scheme 1.18: Piperazine synthesis reported by Huang et al.

They proposed the steps involved in this reaction, where intermediate **b** provides piperazine **c** or dipiperazine **f** via intermediates **d** and **e** (Scheme 1.19).



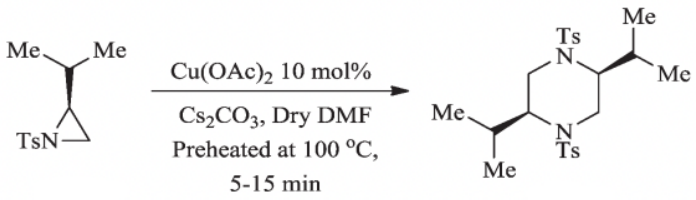
Scheme 1.19: Proposed steps for the formation of piperazine **c** and dipiperazine **f**.

Sengupta et al. have reported a convenient, cheap, and safe method for the synthesis of piperazine by condensation of *N,N'*-dibenzylethylenediamine with 3,4-dibromobutyronitrile in the presence of Et_3N (Scheme 1.20).[38]



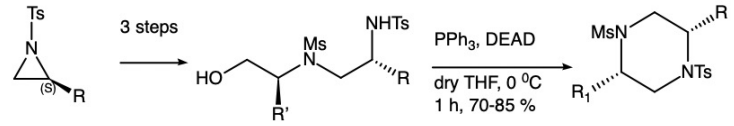
Scheme 1.20: A convenient synthesis of a piperazine derivative.

An example of aziridines used in piperazine synthesis is the study of Manna and Panda.[39] They have reported an efficient synthetic strategy for the synthesis of enantiomerically pure *cis*-2,5-disubstituted chiral piperazines by using $Cu(OAc)_2$, and Cs_2CO_3 at 100 °C (Scheme 1.21).



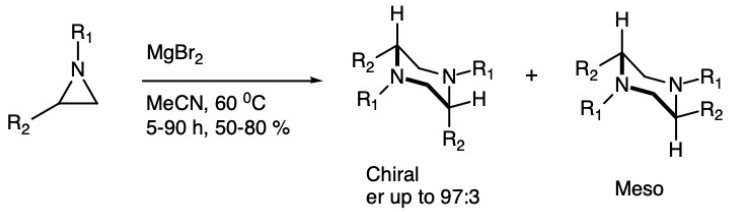
Scheme 1.21: The reaction of asymmetric piperazine synthesis from aziridines.

Another example of piperazine synthesis starting from aziridine was reported by Samanta and coworkers.[40] They have developed four steps synthetic strategy to obtain cis-2,5-disubstituted chiral piperazines by ring opening of chiral aziridines (Scheme 1.22). The critical part of their strategy is the $BF_3.OEt_2$-mediated highly regioselective ring-opening of *N*-Ts chiral aziridines. This protocol explored the construction of the piperazine core framework of the natural product (+)- piperazinomycin.



Scheme 1.22: Synthesis of cis-2,5-disubstituted chiral piperazines by Samanta and coworkers.

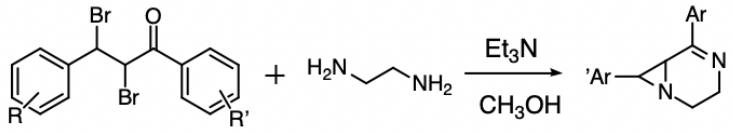
A good example of the enantioselective synthesis of piperazines was reported by Trinchera et al.[41] As a result of using a catalytic amount of a Lewis acid ($MgBr_2$) with *N*-alkyl arylaziridines, a 1:1 mixture of diastereoisomers with the meso compound was obtained in 40% yield with >97:3 enantiomeric ratio (Scheme 1.23).



Scheme 1.23: Enantioselective synthesis of piperazines.

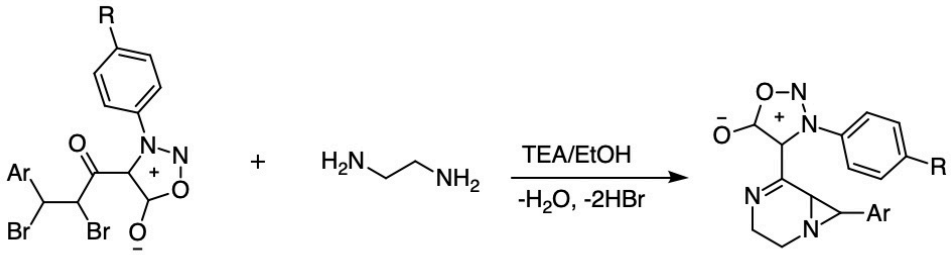
1.4.7 Fused Aziridinyl Piperazine

The structure of 5,7-diaryl-l,4-diazabicyclo[4.4.0]het-4-ene was studied firstly in the literature.[42] Their methodology was associated with the reaction of chalcones with ethylenediamine in the presence of methanol and triethylamine (Scheme 1.24).



Scheme 1.24: The method for synthesis of fused aziridinyl piperazine.

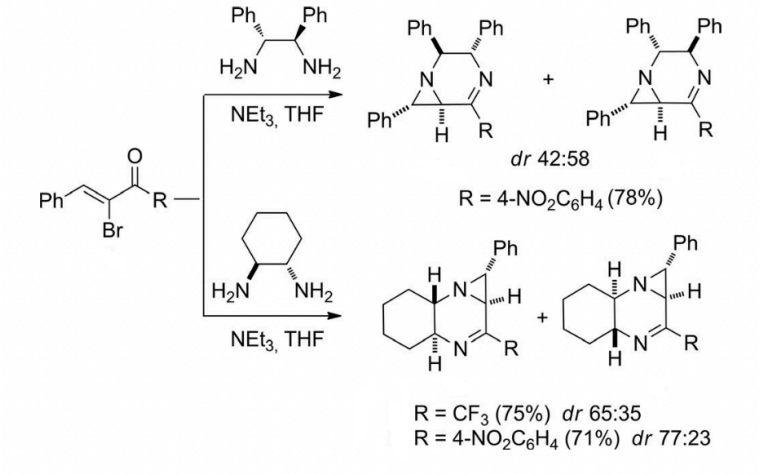
Jyothi et al. have introduced an improved strategy to get aziridines consisting of a sydnone moiety (Scheme 1.25).[43] Sydnones are known as novel mesoionic compounds covering a 1,2,3-oxadiazole ring system. 2,3-dibromo-1-(3-arylsydnone-4-yl)-3-arylpropane-1-ones were preferred as starting materials. As a result of their work, uncommon aziridines consisting of a sydnone moiety and a piperazine framework have been reported.



Scheme 1.25: Synthesis of fused aziridinyl piperazine or aziridines consisting of a sydnone moiety.

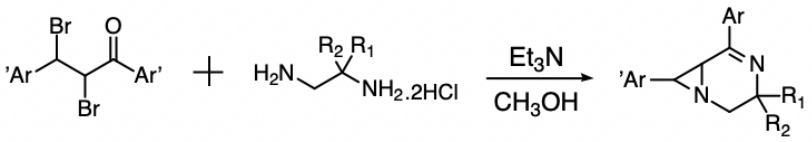
Muzalevskiy et al. have established an effective strategy for the synthesis of 1,4-diazabicyclo [4.1.0] hept-4-enes with N-unsubstituted 1,2-diamines.[44] They have isolated all the heterocyclic products as a single diastereomer (Scheme 1.26). The corre-

sponding 1,4-diazabicyclo[4.1.0]-4-ene derivatives were obtained in good yields for either fluorinated or non-fluorinated bromoenones in high stereoselectivity.



Scheme 1.26: Reaction of 2-bromoenones with chiral diamines.

One of the fundamental ways to synthesize aziridinylpiperazines is related to the use of traditional diamino compounds such as 1,2-phenylenediamine and 1,2- ethylenediamine (Scheme 1.27).[45] To synthesize aziridinylpiperazine derivatives, the bromoderivatives of chalcones were reacted with diamines hydrochloric acid salts in methanol with triethylamine. Cyclopropylethylenediamine and phenylethylenediamine were used to obtain fused aziridinyl piperazine derivatives in 44-69% yield.

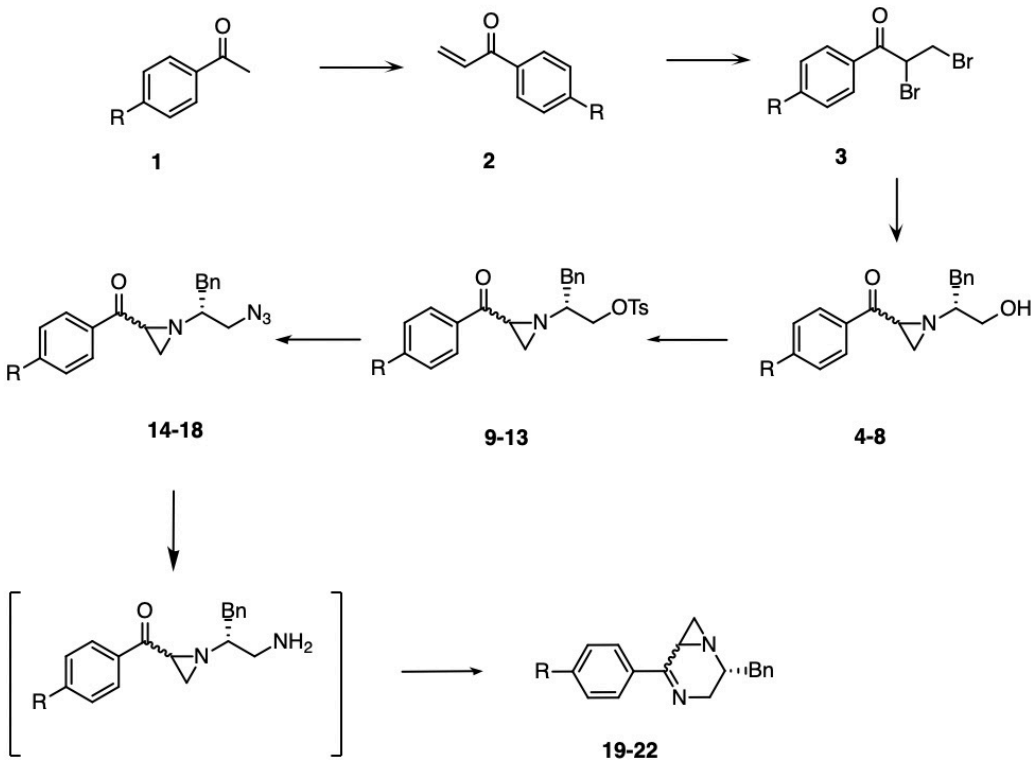


Scheme 1.27: Use of diamines for the synthesis of aziridine fused piperazine.

1.5 Aim of the study

To the best of our knowledge, there is no convenient strategy to prepare aziridine-fused piperazines derivatives. A few examples cover the synthesis of aziridine-fused piperazine precursors via activated aziridines as a starting material in the literature. However, none of these studies was based on systematic aziridine synthesis. Some report the synthesis of particular ones, and the others are limited to a few examples of forms of aziridines in low yields at longer reaction times.

This thesis focuses on synthesizing aziridine-fused piperazine precursors by employing simple reactions (Scheme 1.28). In order to synthesize the derivatives of potentially biologically active aziridine fused-piperazine precursors, we planned to start with aryl-substituted acetophenone derivatives such as acetophenone (**1a**), 4-methyl-acetophenone (**1b**), 4-chloroacetophenone (**1c**), 4-bromoacetophe-none (**1d**), and 4-methoxyacetophenone (**1e**). The next step of our plan was the conversion of acetophenones to aryl vinyl ketones **2** by an aldol reaction. In the third step, simple bromination of aryl vinyl ketones was expected to form dibromo compounds **3**. The reaction of these compounds with *(S)-(-)*-2-amino-3-phenyl-1-propanol via Gabriel-Cromwell reaction was expected to form chiral aziridine derivatives **4-8**.[46,47] Tosylation to form **9-13**, and then S_N2 reaction with azide to get compound **14-18**, followed by azide reduction, were planned to replace hydroxyl group to amino group to yield aziridine bearing free amine. The final step in our plan was the intramolecular condensation to yield **19-22**.



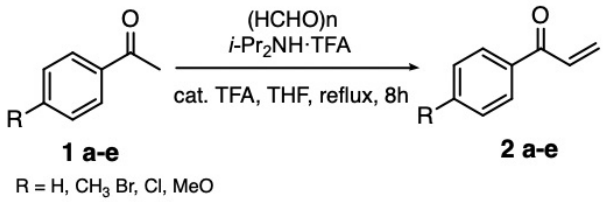
Scheme 1.28: Synthesis plan for the aziridine-fused piperazine precursors.

CHAPTER 2

RESULTS AND DISCUSSION

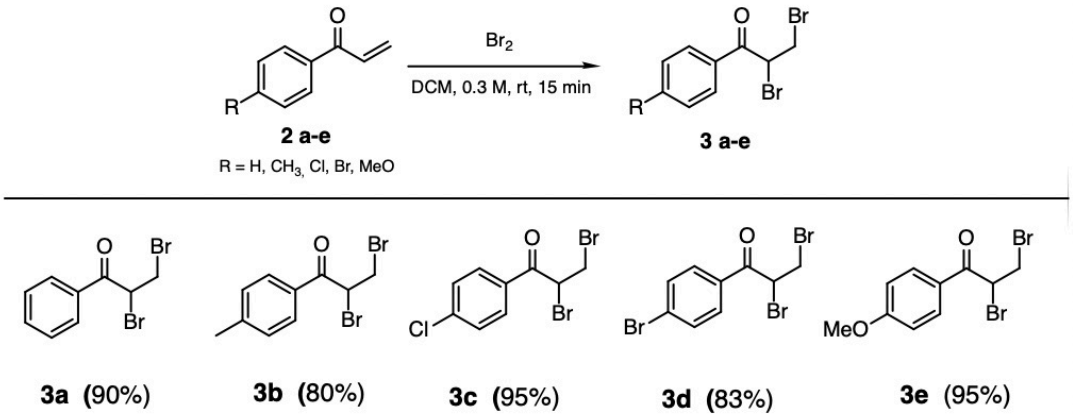
2.1 Synthesis of chiral aziridine

The first step for the preparation of chiral aziridine started with the synthesis of aryl vinyl ketones **2a-e**. To obtain aryl vinyl ketones, different starting materials, acetophenone (**1a**), 4-methyl acetophenone (**1b**), 4-chloro acetophenone (**1c**), 4-bromo acetophenone (**1d**), and 4-methoxy acetophenone (**1e**) were used. Acetophenone derivatives **1a-e** and paraformaldehyde were reacted in dry THF at reflux with trifluoroacetic acid and diisopropylamine (Scheme 2.1). The expected aryl vinyl ketones **2a-e** were obtained in moderate yields, 40, 44, 30, 46, and 35% yield, respectively.[48]



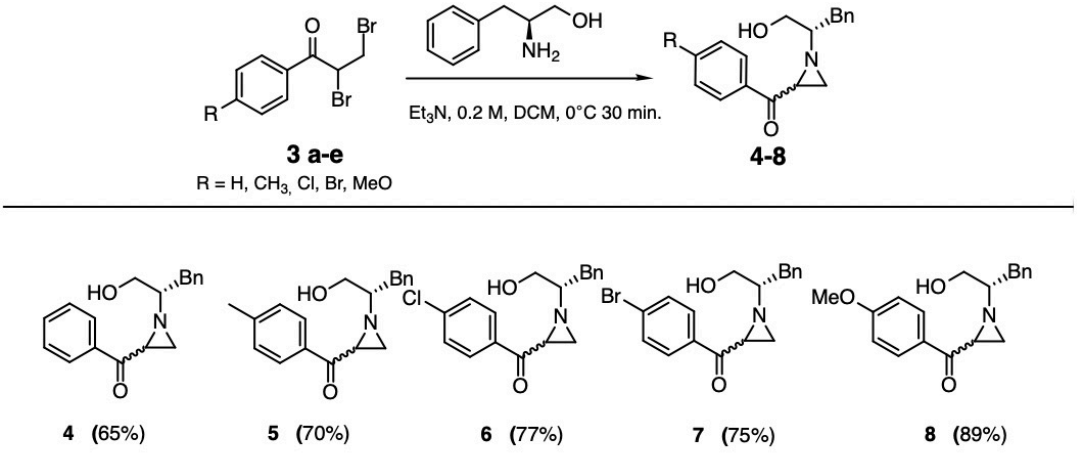
Scheme 2.1: Synthesis of aryl vinyl ketone derivatives **2a-e**.

Aryl vinyl ketones were used as the starting materials in bromination step. Simple bromine addition to vinyl ketones **2a-e** yielded dibromo compounds **3a-e** in high yield (83-95%) after quenching with sodium thiosulfate and extraction with DCM-H_2O. Isolated dibromo compounds were pure enough to be used for the next step, and no further purification was needed after extraction (Scheme 2.2).



Scheme 2.2: Bromination of aryl vinyl ketone derivatives **2a-e**.

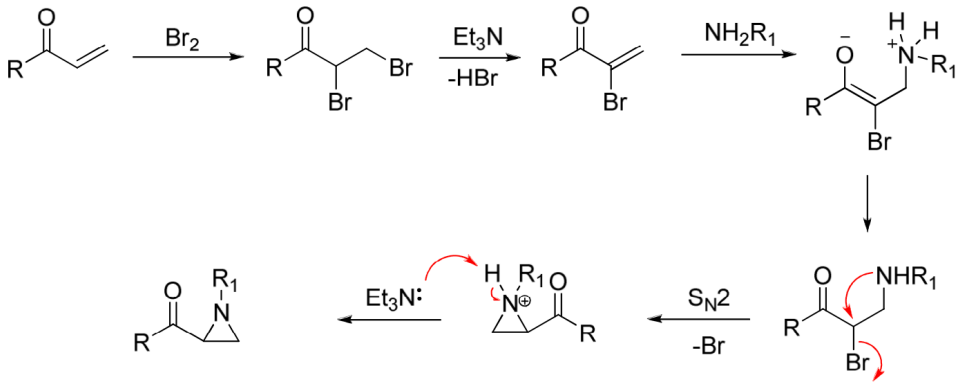
The synthesis of chiral aziridines **4** was achieved in the third step by reacting dibromo compound **3a-e** and the chiral aminoalcohol via Gabriel-Cromwell reaction (Scheme 2.3).



Scheme 2.3: Aziridination of α, β-dibromo ketones by Gabriel-Cromwell reaction.

Aziridination reaction provided the desired products as a mixture of diastereomers **A** and **B**, which were separated by silica column chromatography. Their structures were confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy. IR spectrum of the ketones showed a very intense and broad peak around 3200 cm^{-1} for the hydroxy group. The intense signal around 1670 cm^{-1} was the indication of the ketone carbonyl. Moreover, pres-

ence of carbonyl group was also confirmed by ^{13}C NMR, where the carbonyl carbons resonated between 195-196 ppm depending on the substituent on the aromatic unit.

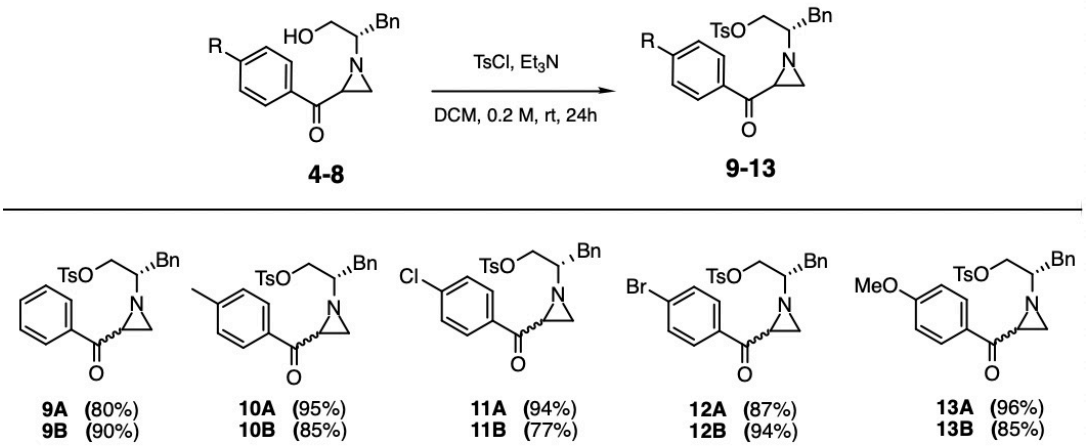


Scheme 2.4: Proposed mechanism for aziridination by Gabriel-Cromwell reaction.

The reaction mechanism shown in Scheme 2.4 was proposed for the aziridination from α-bromovinyl ketone. Simple bromine addition forms a dibromo product which undergoes HBr elimination with Et_3N to yield α-bromo compound. In the next step, conjugate addition of amine, removal of proton followed by S_N2 displacement of bromide completes aziridination mechanism. By using this method and employing a chiral amine, *(S)-(-)*-2-amino-3-phenyl-1-propanol, five new aziridinyl ketones were synthesized as a mixture of diastereomers in 65 to 95% yields.

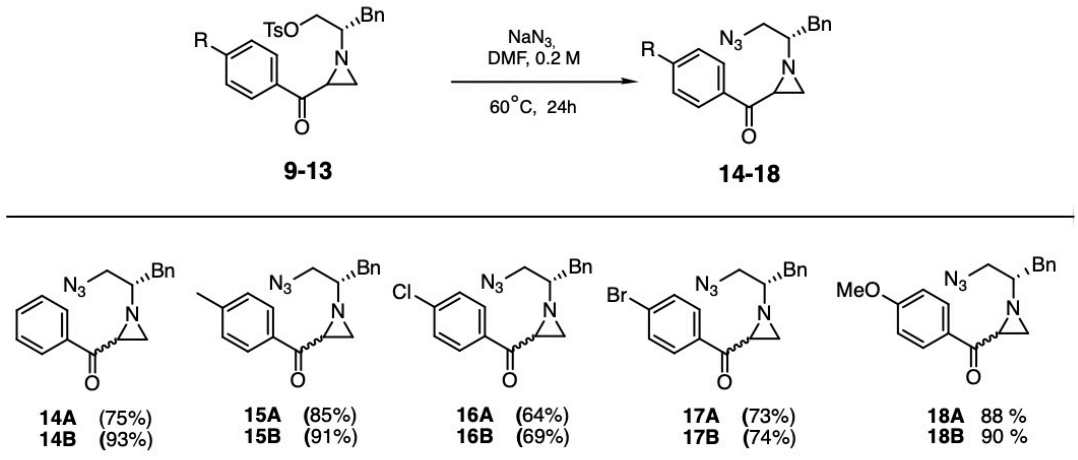
2.2 Synthesis of aziridine fused piperazine precursors

For the synthesis of piperazine precursors, hydroxyl group of aziridines **4-8** was converted to tosylate **9-13** (Scheme 2.5) by simple treatment of alcohol with TsCl in the presence of Et_3N at room temperature in 77-96% isolated yields.



Scheme 2.5: Tosylation of aziridines.

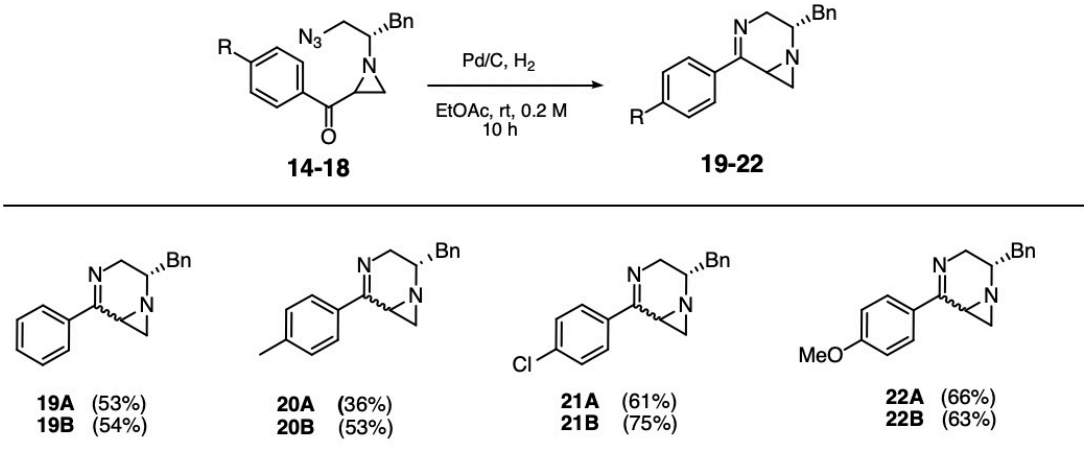
The next step for the piperazine precursors was the conversion of tosylates to azides. For this purpose; tosylates were treated with NaN_3 in DMF at 60 ^oC overnight (Scheme 2.6). This reaction was performed for all the tosylates **9-13** to synthesize the corresponding azides **14-18** in 64-93% yields. The formation of azide was easily confirmed by IR spectroscopy, where azide signal was observed at 2160-2120 cm^{-1} depending on the structure.



Scheme 2.6: Conversion of the tosylates **9-13** to the corresponding azides **14-18**.

For reaching the piperazine precursors, the next step was the reduction of azides to

amines. This step was carried out with 10% Pd/C in EtOAc (Scheme 2.7).



Scheme 2.7: Formation of piperazine precursors **19-22** by reduction of azides.

Reduction of azide did not yield expected amine; instead, aziridine fused piperazine precursors **19-22** were obtained. The structure of the piperazine precursors was confirmed by NMR and IR spectroscopies. In ^{13}C NMR spectrum, ketone carbonyl at around 190 ppm disappeared, and an imine carbon at 165 ppm was observed. In IR spectrum, carbonyl stretching vibration at around 1670 cm^{-1} disappeared and C=N stretching vibration around 1612-1624 cm^{-1}, typical value for imine groups,[42] was observed. Another indication for reduction of azide group was the disappearance of azide signal at 2160-2120 cm^{-1} in IR spectrum. These data are consistent with the literature where similar structures were reported.[45]

We think that as soon as the azide group is reduced, it undergoes intramolecular cyclization by a condensation reaction taking place between intermediate primary amine and ketone carbonyl.

As a result of this intramolecular cyclization, eight novel chiral piperazine precursors were synthesized in up to 75% yield. Although the stereochemistry of starting chiral amino alcohol is known, we have not yet confirmed the stereochemistry at aziridine carbon.

CHAPTER 3

CONCLUSIONS

As a result of this study, novel aziridine fused chiral piperazine precursors were synthesized in 36-75% yield. For the synthesis of these compounds, simple starting materials (aryl methyl ketones) and straightforward reactions (aldol, bromination, conjugate addition, inter and intramolecular S_N2 reactions) were used to obtain reasonably complex tri-substituted chiral piperazine precursors. In future work, absolute stereochemistry will be determined by X-ray analysis, and HRMS will be performed to further prove the structures of the final compounds. In addition, piperazine precursors will be converted to piperazines, and aziridine ring opening reactions will be carried out in due course in our group.

CHAPTER 4

EXPERIMENTAL

4.1 Materials and Instrumentation

All reagents were supplied from Sigma-Aldrich, Across, and Merck. Solvents and reagents were used after they were purified and dried. The reaction mixtures were monitored by TLC (250 lm Silica Gel 60 F254 plates) under UV light at 254 nm. Synthesized products were purified by flash column chromatography on Silica Gel 60 (Merck, 230–400 mesh ASTM). Brucker Spectrospin Avance III DPX-400 instrument at (400 MHz for ^{1}H) and (100 MHz for ^{13}C) relative to TMS was employed to detect ^{1}H and ^{13}C NMR spectra of synthesized compounds. The H NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00). IR spectra were interpreted by using Bruker Platinum ATR-IR instruments.

4.2 General Experimental Procedure

4.2.1 General method for the synthesis of aryl vinyl ketone derivatives

The corresponding acetophenone (1.0 equiv.) and paraformaldehyde (2.0 equiv.) were dissolved in dry THF (1.0 M). Then, diisopropylamine (1.0 equiv.) was added to it. Lastly, trifluoroacetic acid (0.1 equiv.) was added to the reaction mixture. The reaction mixture was stirred at reflux for 2 h. After 2 hours, the color of the reaction converted to transparent. The reaction was left to cool at room temperature. The rest of the paraformaldehyde (2.0 equiv.) was added at room temperature. Then, the reaction mixture was left to stir at reflux for 6 h. The reaction mixture was cooled at room

temperature. The solvent was removed under reduced pressure. It was dissolved in DCM and washed with 1N HCl, 1N NaOH, and brine, respectively. The reaction mixture was dried over Na_2SO_4 and then concentrated under vacuum. The crude product was purified by silica gel column chromatography (Hexane-EtOAc, 20:1). All the data for acetophenone substituted ketones were in accordance with the literature.[48]

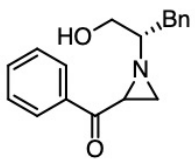
4.2.2 General method for the synthesis of α,β-dibromo ketones

Aryl vinyl ketone **2a** (560 mg, 4.24 mmol) was dissolved in DCM (14 ml). Br_2 (0.2 ml, 4.28 mmol) was added over it. The reaction mixture was left to stir at room temperature for 1 h. It was quenched by a saturated sodium thiosulfate solution. The reaction mixture was extracted with DCM/water. The organic phase was collected and dried over Na_2SO_4. Lastly, it was evaporated under *vacuum*.

4.2.3 General method for the synthesis of chiral aziridine

α,β-dibromo ketone **3a** (1.1 g, 3.8 mmol) was dissolved in DCM (19 ml) and then cooled to 0 ^oC in ice-bath. Et_3N (0.8 ml, 5.7 mmol) was added over the reaction mixture and left to stir for 30 min. (*S*)-(-)-2-Amino-3-phenyl-1-propanol (1.14 g, 7.53 mmol) was added and left to stir at ambient temperature for 15-20 min. TLC demonstrated no starting material was left in the reaction medium. Two stereoisomers were formed (Aziridine **A** and **B**). Then, the reaction was aborted. It was concentrated under *vacuum* and purified by silica gel column chromatography (EtOAc–Hexane).

4.2.3.1 Characterization of (1-((S)-1-hydroxy-3-phenyl propan-2-yl) aziridin-2-yl) (phenyl) methanone (4A, 4B)

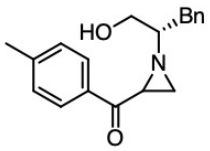


Aziridine ketones **4A-4B** were synthesized according to the general procedure for synthesis of chiral aziridines. It was obtained in 65 % overall yield.

Yellow solid, **4A**, R_f = 0.36 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 2H), 7.92 – 6.94 (m, 8H), 3.79 (dd, J = 12.0, 4.7 Hz, 1H), 3.70 (dd, J = 11.7, 5.6 Hz, 1H), 3.15 (d, J = 4.2 Hz, 1H), 3.00 (dd, J = 13.7, 7.4 Hz, 1H), 2.95 (dd, J = 13.4, 6.5 Hz, 1H), 2.68 (br, 1H), 2.23 (d, J = 3.2 Hz, 1H), 1.96 (s (broad), 1H), 1.66 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 138.6, 136.6, 133.5, 129.5 (2xC), 128.7 (2xC), 128.5 (2xC), 128.4 (2xC), 126.4, 72.4, 64.9, 40.4, 38.0, 35.1. IR (neat, cm^{-1}), 3262, 3058, 2925, 2856, 1687, 1597, 1450, 1400, 1233, 1148, 1047, 878, 760, 696.

Yellow solid, mp: 148-154 ^{o}C, **4B**, R_f = 0.11 (1:1 Hexane/EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.56 (m, 1H), 7.41 (m, 2H), 7.18 (m, 2H), 7.11 (m, 2H), 7.01 (m, 1H), 3.87 (dd, J = 11.2, 4.2 Hz 1H), 3.81 (dd, J = 11.3, 4.0 Hz 1H), 3.03 (d, J = 8.3 Hz, 1H), 3.03 (dd, J = 13.7, 5.2 Hz 1H), 2.92 (dd, J = 13.6, 8.4 Hz 1H), 2.66 (dd, J = 6.6, 3.2 Hz 1H), 2.21 (s, (broad), 1H), 1.93 (d, J = 6.5 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 138.8, 136.6, 133.2, 129.4 (2xC), 128.6 (2xC), 128.4 (2xC), 128.2 (2xC), 126.3, 72.4, 65.4, 39.7, 38.5, 35.7. IR (neat, cm^{-1}), 3283, 2922, 2887, 1673, 1596, 1448, 1400, 1230, 1058, 967, 746, 698.

4.2.3.2 Characterization of (1- ((S) -1-hydroxy -3- phenyl propan -2-yl) aziridin -2-yl) (p-tolyl) methanone (5A, 5B)



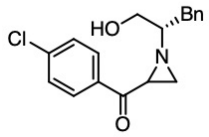
Aziridine ketones **5A-5B** were synthesized according to the general procedure for synthesis of chiral aziridines. It was obtained in 70 % overall yield.

Yellow solid, mp: 110-115 ^{o}C, **5A**, R_f = 0.63 (EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.0 Hz, 2H), 7.34 – 7.30 (m, 2H), 7.27 (m, 5H), 3.77 (dd, J = 11.5, 3.4 Hz 1H), 3.76 (dd, J = 11.5, 3.4 Hz 1H), 3.70 (dd, J = 11.5, 5.0 Hz 1H), 3.13 (dd, J

= 6.7, 3.2 Hz, 1H), 3.03 (dd, *J* = 13.4, 7.5 Hz, 1H), 2.94 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.43 (s, 3H), 2.20 (s, (broad), 1H), 1.94 (m, 1H), 1.62 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 144.3, 138.6, 133.9, 129.4 (2xC), 129.2 (2xC), 128.4 (2xC), 128.3 (2xC), 126.3, 72.4, 64.6, 40.1, 37.8, 35.1, 21.6. IR (neat, cm^{-1}), 3241, 3026, 2923, 2857, 1687, 1493, 1413, 1237, 1180, 1048, 970, 791, 696.

White solid, mp: 136-141 ^{o}C, **5B**, R_f = 0.25 (EtOAc), IR (neat, cm^{-1}), 3278, 3038, 2982, 2917, 2865, 1673, 1605, 1411, 1237, 1058, 1012, 966, 794, 745. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.23 – 7.11 (m, 6H), 7.04 (t, *J* = 7.1 Hz, 1H), 3.84 (dd, *J* = 11.1, 3.9 Hz 1H), 3.78 (dd, *J* = 11.4, 4.7 Hz 1H), 3.03 – 2.96 (m, 1H), 2.91 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.43 (s, 3H), 2.20 (s, (broad), 1H), 1.95 (d, *J* = 4.5 Hz, 1H), 1.89 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 144.1, 138.7, 134.1, 129.4 (2xC), 129.1 (2xC), 128.6 (2xC), 128.3 (2xC), 126.3, 72.3, 65.3, 39.5, 38.4, 35.6, 21.7.

4.2.3.3 Characterization of (4-chloro phenyl) (1-((S) -1- hydroxy -3- phenyl propan -2-yl) aziridin-2-yl) methanone (6A, 6B)



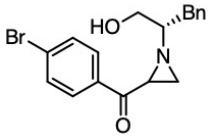
Aziridine ketones **6A-6B** were synthesized according to the general procedure for synthesis of chiral aziridines. It was obtained in 77 % overall yield.

Yellow solid, **6A**, R_f = 0.50 (EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz 2H), 7.37 - 7.22 (m, 5H), 3.74 (m, 2H), 3.10 (dd, *J* = 6.3, 2.9 Hz, 1H), 3.01 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.94 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.20 (d, *J* = 2.3 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.63 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 139.8, 138.5, 134.7, 129.6 (2xC), 129.4 (2xC), 128.8 (2xC), 128.4 (2xC), 126.3, 72.5, 64.7, 40.2, 37.8, 35.2.

Yellow solid, mp: 134-140 ^{o}C, **6B**, R_f = 0.20 (EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 7.3 Hz, 2H), 7.00 (t,

J = 7.5 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 3.84 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.78 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.16 (s, (broad), 1H), 2.93 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.81 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.44 (dd, *J* = 6.5, 3.0 Hz, 1H), 2.11 – 2.07 (m, 1H), 1.90 (d, *J* = 6.7 Hz, 1H), 1.83 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 139.7, 138.9, 134.7, 129.58 (2xC), 129.4 (2xC), 128.7 (2xC), 128.6 (2xC), 126.4, 72.3, 65.5, 39.6, 38.6, 35.7. IR (neat, cm^{-1}), 3280, 2989, 2920, 2868, 1674, 1587, 1407, 1241, 1227, 1091, 1060, 1009, 747, 702.

4.2.3.4 Characterization of (4-bromo phenyl)(1-((S) -1-hydroxy-3- phenyl propan -2-yl) aziridin-2-yl) methanone (7A, 7B)



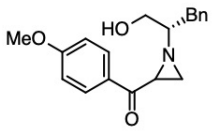
Aziridine ketones **7A-7B** were synthesized according to the general procedure for synthesis of chiral aziridines. It was obtained in 75 % overall yield.

Yellow solid, mp: 143-146 ^{o}C, **7A**, R_f = 0.70 (EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.28 - 7.18 (m, 5H), 3.66 (dd, *J* = 11.3, 3.5 Hz 1H), 3.62 (dd, *J* = 11.1, 5.3 Hz 1H), 3.00 (dd, *J* = 6.6, 3.2 Hz, 1H), 2.90 (dd, *J* = 13.2, 7.3 Hz, 1H), 2.85 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.13 (s, (broad), 1H), 1.90 - 1.87 (m, 1H), 1.55 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 138.5, 135.3, 132.0, 129.9, 129.5, 128.7, 128.5, 126.5, 72.44, 64.9, 40.3, 38.0, 35.2. IR (neat, cm^{-1}), 3235, 3024, 2924, 2858, 1691, 1584, 1408, 1359, 1223, 1047, 1008, 969, 749, 699.

Reddish solid, mp: 130-136 ^{o}C, **7B**, R_f = 0.25 (EtOAc), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 4H), 7.08 (d, *J* = 7.3 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 2H), 6.93 (t, *J* = 7.1 Hz, 1H), 3.77 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.73 (dd, *J* = 11.1, 4.6 Hz, 1H), 2.92 (dd, *J* = 13.7, 4.7 Hz, 1H), 2.81 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.44 (dd, *J* = 6.3, 2.9 Hz, 1H), 2.10 (s, (broad), 1H), 1.89 (m, 1H), 1.82 (d, *J* = 6.6 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 138.7, 135.2, 131.7 (2xC), 129.7 (2xC), 129.3 (2xC), 128.6 (2xC), 128.4, 126.4, 72.2, 65.7, 39.6, 38.6, 35.6. IR (neat, cm^{-1}), 3281, 2985, 2921, 2868,

1673, 1582, 1404, 1241, 1226, 1060, 1007, 965, 747, 707.

4.2.3.5 Characterization of (1-((S)-1-hydroxy -3-phenyl propan-2-yl) aziridin-2-yl) (4-methoxyphenyl) methanone (8A, 8B)



Aziridine ketones **8A-8B** were synthesized according to the general procedure for synthesis of chiral aziridines. It was obtained in 89 % overall yield.

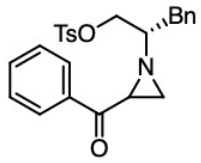
Yellow solid, mp: 144-148 °C, **8A**, R_f = 0.68 (4:0.1 EtOAc/MeOH),^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.30 - 7.20 (m, *J* = 13.9, 6.7 Hz, 5H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.74 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.69 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.05 (dd, *J* = 6.9, 3.2 Hz, 1H), 3.00 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.94 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.21 (d, *J* = 3.2 Hz, 1H), 1.99 – 1.86 (m, 1H), 1.62 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$); 194.4, 163.8, 138.6, 130.6 (2xC), 129.4 (2xC), 128.3 (2xC), 126.3 (2xC), 113.8 (2xC), 72.3, 64.7, 55.4, 40.1, 37.8, 34.7. IR (neat, cm^{-1}), 3241, 3004, 2927, 2857, 1683, 1601, 1421, 1240, 1058, 1025, 970, 797, 700.

Orange solid, mp: 117-125 °C, **8B**, R_f = 0.40 (4:0.1 EtOAc/MeOH), ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.69 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H), 3.85 (dd, *J* = 11.0, 4.0 Hz 1H), 3.79 (dd, *J* = 11.4, 5.1 Hz 1H), 3.01 (dd, *J* = 3,5 Hz, 1H), 2.91 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.63 (d, *J* = 6.8, 3.2 Hz, 1H), 2.20 (br, 1H), 1.96 - 1.93 (m, 1H), 1.88 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 163.6, 138.7, 130.4 (2xC), 129.2 (2xC), 128.4 (2xC), 126.1 (2xC), 113.4 (2xC), 72.3, 65.2, 55.4, 39.2, 38.3, 35.2. IR (neat, cm^{-1}), 3230, 3006, 2921, 2869, 1670, 1600, 1465, 1247, 1179, 1062, 977, 754, 699.

4.2.4 General method for tosylation of hydroxyl-functionalized aziridine

Prepared aziridine **4A** (200 mg, 0.711 mmol) was dissolved in DCM (3.0 ml). Then, Et_3N (0.2 ml, 1.78 mmol) was added to the reaction mixture. Next, TsCl (339 mg, 1.78 mmol) was added over it. It was allowed to stir at room temperature for 24h. The reaction mixture was monitored by TLC. There was no starting material in the reaction medium. The reaction was aborted and purified by silica gel column chromatography (EtOAc–Hexane).

4.2.4.1 Characterization of (2S)-2-(2-benzoyl aziridin-1-yl) -3- phenylpropyl -4- methylbenzenesulfonate (9A, 9B)



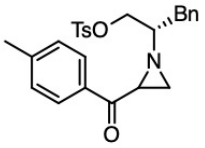
Aziridine ketones **4A-4B** were converted to new aziridine derivatives **9A-9B** bearing a tosylate group according to the general procedure for tosylation of the aziridines.

It was obtained in 80 % yield as yellow oily compound, **9A**, R_f = 0.30 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.4 Hz, 2H), 7.64 (t, J = 7.0 Hz, 1H), 7.58 - 7.45 (m, 4H), 7.37 - 7.25 (m, 4H), 7.22 - 7.13 (m, 3H), 4.14 (dd, J = 10.2, 3.6 Hz, 1H), 4.03 (dd, J = 10.1, 8.0 Hz 1H), 3.28 (dd, J = 6.4, 3.2 Hz, 1H), 2.92 (dd, J = 13.8, 7.1 Hz, 1H), 2.81 (dd, J = 13.9, 6.8 Hz, 1H), 2.38 (s, 3H), 2.31- 2.20 (m, 1H), 2.15 (d, J = 3.0 Hz, 1H), 1.48 (d, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 144.8, 137.1, 136.6, 133.4, 132.0, 129.7 (2xC), 129.2 (2xC), 128.6 (2xC), 128.6 (2xC), 128.4 (2xC), 127.7 (2xC), 126.6, 72.6, 69.3, 39.6, 38.1, 34.8, 21.5. IR (neat, cm^{-1}), 3009, 3262, 1596, 1450, 1353, 1228, 1174, 1004, 970, 838, 751, 696.

It was obtained in 90 % yield as yellow oily compound, **9B**, R_f = 0.25 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.40 – 7.21 (m, 4H), 7.06 - 6.92 (m, 4H), 6.87 (t, J = 6.6 Hz, 1H), 4.12 (dd, J = 10.1, 6.7 Hz, 1H), 4.04 (dd, J = 10.0, 5.4 Hz, 1H), 2.82 (dd, J

= 13.7, 4.2 Hz, 1H), 2.65 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.45 (dd, *J* = 6.7, 3.2 Hz, 1H), 2.38 (s, 3H), 2.20 - 2.06 (m, 1H), 2.00 (d, *J* = 3.0 Hz, 1H), 1.81 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 145.2, 137.3, 136.40, 133.2, 132.6, 130.0 (2xC),129.3 (2xC), 128.7 (2xC), 128.3 (2xC), 128.1 (2xC), 128.0 (2xC), 126.6, 72.4, 68.9, 39.5, 38.8, 35.4, 21.6. IR (neat, cm^{-1}), 3031, 1675, 1596, 1450, 1357, 1233, 1175, 1019, 970, 746, 692.

4.2.4.2 Characterization of (2S)-2-(2-(4-methyl benzoyl) aziridin-1 -yl) -3- phenyl propyl 4-methylbenzenesulfonate (10A, 10B)



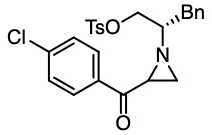
Aziridine ketones **5A-5B** were converted to new aziridine derivatives **10A-10B** bearing a tosylate group according to the general procedure for tosylation of the aziridines.

It was obtained in 95 % yield as yellow oily compound, **10A**, R_f = 0.74 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.27 - 7.13 (m, 5H), 7.11 - 7.06 (m, 4H), 4.06 (dd, *J* = 10.1, 3.6 Hz 1H), 3.93 (dd, *J* = 9.8, 8.3 Hz, 1H), 3.16 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.82 (dd, *J* = 13.9, 7.0 Hz 1H), 2.71 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 2.19 - 2.10 (m, 1H), 2.04 (d, *J* = 2.7 Hz, 1H), 1.37 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 144.9, 144.4, 137.2, 134.3, 132.1, 129.8 (2xC), 129.4 (2xC), 129.4 (2xC), 128.7 (2xC), 128.6 (2xC), 127.8 (2xC), 126.9, 72.8, 69.4, 39.6, 38.3, 34.8, 21.8. IR (neat, cm^{-1}), 3029, 1676, 1604, 1495, 1357, 1234, 1174, 1096, 973, 939, 813, 754, 701.

It was obtained in 85 % yield as yellow oily compound, **10B**, R_f = 0.47 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.9, 2H) 7.02 - 6.98 (m, 4H), 6.94 – 6.87 (m, 1H), 4.12 (dd, *J* = 10.1, 6.6 Hz, 1H), 4.04 (dd, *J* = 10.1, 5.5 Hz 1H), 2.82 (dd, *J* = 13.7, 4.4 Hz 1H), 2.66 (dd, *J* = 13.7, 8.8 Hz 1H), 2.45 (dd, *J* = 6.8, 3.3

Hz 1H), 2.41 (s, 3H), 2.32 (s, 3H), 2.18 – 2.09 (m, 1H), 1.99 (d, J = 6.4 Hz, 1H), 1.80 (d, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 145.1, 144.1, 137.3, 134.0, 132.7, 130.0 (2xC), 129.3 (2xC), 129.0 (2xC), 128.7 (2xC), 128.3 (2xC), 128.0 (2xC), 126.6, 72.4, 69.0, 39.4, 38.7, 35.3, 21.7. IR (neat, cm^{-1}), 3031, 2922, 1673, 1605, 1494, 1356, 1236, 1175, 1097, 968, 814, 751.

4.2.4.3 Characterization of (2S)-2-(2-(4-chlorobenzoyl) aziridin-1- yl)-3-phenyl propyl 4-methylbenzenesulfonate (11A, 11B)



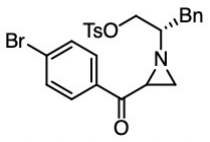
Aziridine ketones **6A-6B** were converted to new aziridine derivatives **11A-11B** bearing a tosylate group according to the general procedure for tosylation of the aziridines.

It was obtained in 94 % yield as yellow oily compound, **11A**, R_f = 0.50 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.7 Hz, 2H), 7.45 - 7.39 (m, 4H), 7.29 – 7.13 (m, 4H), 7.10 - 7.09 (m, 3H), 4.06 (dd, J = 10.2, 3.4 Hz, 1H), 3.96 (dd, J = 10.2, 8.2 Hz, 1H), 3.11 (dd, J = 6.6, 3.3 Hz, 1H), 2.83 (dd, J = 13.9, 7.0 Hz, 1H), 2.71 (dd, J = 13.9, 6.9 Hz, 1H), 2.39 (s, 3H), 2.18 (dd, J = 7.2, 3.3 Hz, 1H), 2.06 (dd, J = 7.2, 3.3 Hz 1H), 1.40 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 145.1, 139.5, 137.1, 134.7, 132.3, 129.8 (2xC), 129.7 (2xC), 129.2 (2xC), 128.9 (2xC), 128.6 (2xC), 127.6 (2xC), 126.8, 72.4, 69.1, 39.7, 37.8, 34.8, 21.4. IR (neat, cm^{-1}), 3029, 1680, 1589, 1357, 1226, 1174, 1092, 947, 940, 836, 749.

It was obtained in 77 % yield as yellow oily compound, **11B**, R_f = 0.45 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H), 7.42 (ddd, J = 18.3, 10.6, 5.6 Hz, 4H), 7.26 – 7.16 (m, 3H), 7.11 (dd, J = 11.8, 7.2 Hz, 4H), 4.07 (m, 1H), 4.02 – 3.90 (m, 1H), 3.14 (ddd, J = 13.2, 6.5, 3.2 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.78 – 2.66 (m, 1H), 2.30 (s, J = 7.6 Hz, 3H), 2.16 (dd, J = 8.8, 6.0 Hz, 1H), 2.08 (dd, J = 12.8, 3.1 Hz, 1H), 1.47 – 1.36 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 163.9, 138.7, 130.7 (2xC), 129.5 (2xC), 128.5 (2xC), 126.4 (2xC), 113.9 (2xC), 72.3, 64.9, 55.3, 40.2, 38.0, 34.8. IR (neat, cm^{-1}), 3029, 2922, 1681, 1589, 1357.58, 1226, 1174,

1091, 969, 837, 813, 748.

4.2.4.4 Characterization of (2S)-2-(2-(4-bromobenzoyl)aziridin-1- yl)-3-phenyl propyl 4-methylbenzenesulfonate (12A, 12B)

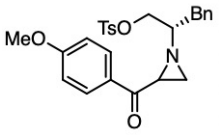


Aziridine ketones **7A-7B** were converted to new aziridine derivatives **12A-12B** bearing a tosylate group according to the general procedure for tosylation of the aziridines.

It was obtained in 87 % yield as yellow oily compound, **12A**, R_f = 0.65 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.30 (dd, J = 14.6, 6.5 Hz, 4H), 7.19 (d, J = 7.2 Hz, 4H), 4.16 (dd, J = 10.2, 3.4 Hz, 1H), 4.05 (dd, J = 10.1, 8.2 Hz, 1H), 3.21 (dd, J = 6.6, 3.2 Hz, 1H), 2.92 (dd, J = 13.9, 7.0 Hz, 1H), 2.80 (dd, J = 13.8, 6.8 Hz, 1H), 2.41 (s, 3H), 2.28 (dd, J = 7.2, 2.8 Hz, 1H), 2.24 (dd, J = 6.8, 3.4 Hz 1H), 1.50 (d, J = 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 145.0, 137.0, 135.3, 132.2, 132.0 (2xC), 130.0 (2xC), 129.9 (2xC), 129.3 (2xC), 128.7, 128.7 (2xC), 127.8, (2xC), 126.9, 72.6, 69.5, 39.8, 38.2, 34.9, 21.9. IR (neat, cm^{-1}), 3028, 2923, 1680, 1584, 1356, 1223, 1174, 1069, 974, 835, 749.

It was obtained in 94 % yield as yellow oily compound, **12B**, R_f = 0.57 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.14 - 6.94 (m, 4H), 6.94 - 6.85 (m, 1H), 4.13 (dd, J = 10.1, 6.7 Hz, 1H), 4.05 (dd, J = 10.1, 5.4 Hz, 1H), 2.83 (dd, J = 13.7, 3.9 Hz, 1H), 2.63 (dd, J = 13.6, 9.5 Hz, 1H), 2.40 (s, 3H), 2.34 (dd, J = 6.6, 3.2 Hz, 1H), 2.19 - 2.10 (m, 1H), 1.99 (d, J = 2.9 Hz, 1H), 1.82 (d, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 145.2, 137.3, 135.1, 132.6, 131.6 (2xC), 130.0 (2xC), 129.6 (2xC), 129.3 (2xC), 128.7 (2xC), 128.5 , 128.0 (2xC), 126.6, 72.6, 69.0, 39.5, 38.4, 34.9, 21.2. IR (neat, cm^{-1}), 2976, 1682, 1584, 1357, 1226, 1069, 968, 837, 748.

4.2.4.5 Characterization of (2S)-2-(2-(4-methoxybenzoyl)aziridi-1- yl)-3-phenyl propyl 4-methylbenzenesulfonate (13A, 13B)



Aziridine ketones **8A-8B** were converted to new aziridine derivatives **13A-13B** bearing a tosylate group according to the general procedure for tosylation of the aziridines.

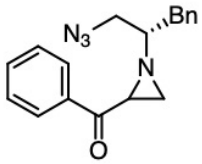
It was obtained in 96 % yield as yellow oily compound, **13A**, R_f = 0.40 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.34 – 7.22 (m, 3H), 7.12 - 7.05 (m, 4H), 6.98 (d, J = 9.0 Hz, 2H), 4.11 (dd, J = 10.1, 3.5 Hz, 1H), 4.00 (dd, J = 10.0, 8.2 Hz, 1H), 3.89 (s, 3H), 3.14 (dd, J = 6.6, 3.3 Hz, 1H), 2.88 (dd, J = 13.9, 7.0 Hz, 1H), 2.79 (dd, J = 13.9, 6.9 Hz, 1H), 2.37 (s, 3H), 2.22 (dd, J = 7.0, 3.5 Hz, 1H), 2.13 (d, J = 3.3 Hz, 1H), 1.43 (d, J = 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 163.9, 144.9, 137.3, 132.1, 130.9 (2xC), 129.9, 129.8 (2xC), 129.4 (2xC), 128.7 (2xC), 127.8 (2xC), 126.8, 113.9 (2xC), 72.8, 69.5, 55.6, 39.4, 38.3, 34.5, 21.6. IR (neat, cm^{-1}), 2979, 1671, 1598, 1357, 1172, 974, 749.

It was obtained in 85 % yield as yellow oily compound, **13B**, R_f = 0.30 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 4.2 Hz, 4H), 6.90 - 6.81 (m, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.22 (dd, J = 10.1, 6.6 Hz, 1H), 4.14 (dd, J = 10.1, 5.5 Hz, 1H), 3.89 (s, 3H), 2.92 (dd, J = 13.7, 4.3 Hz, 1H), 2.75 (dd, J = 13.7, 8.9 Hz, 1H), 2.52 (d, J = 3.1 Hz, 1H), 2.49 (s, 3H), 2.25 - 2.18 (m, 1H), 2.08 (d, J = 3.2 Hz, 1H), 1.87 (d, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ 193.9, 163.5, 145.0, 137.2, 132.5, 130.3 (2xC), 129.9 (2xC), 129.2 (2xC), 128.5 (2xC), 127.9 (2xC), 126.5, 113.4 (2xC), 72.3, 68.8, 55.4, 39.1, 38.5, 35.0, 21.6. IR (neat, cm^{-1}), 2923, 1672, 1598, 1357, 1171, 968, 749.

4.2.5 General method for nucleophilic azidation

Tosyl-attached aziridine **9A** (350 mg, 0.804 mmol) was dissolved in DMF (4.02 ml). NaN_3 (261 mg, 4.02 mmol) was directly added. The reaction mixture was left to stir at 60 °C overnight. Next, it was monitored by TLC. There was no starting material in the reaction medium. The solvent was removed by evaporating at 75 °C for 20 min. The crude product was washed with water and then purified by silica gel column chromatography (EtOAc–Hexane).

4.2.5.1 Characterization of (1-((S)-1-azido-3-phenyl propan-2-yl) aziridin-2-yl) (phenyl) methanone (14A, 14B)



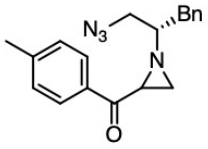
The conversion of tosylate groups **9A-9B** to azide groups **14A-14B** was performed according to the general method for nucleophilic azidation.

It was obtained in 75 % yield as yellow solid, mp: 64 °C, **14A**, R_f = 0.60 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 7.0 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.31 – 7.21 (m, 3H), 3.50 (dd, J = 12.8, 6.7 Hz 1H), 3.46 (dd, J = 12.5, 4.7 Hz, 1H), 3.22 (dd, J = 6.6, 3.3 Hz, 1H), 3.01 (dd, J = 13.7, 6.6 Hz, 1H), 2.93 (dd, J = 13.7, 7.1 Hz, 1H), 2.26 (d, J = 3.2 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.59 (d, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 137.8, 136.8, 133.4, 129.4 (2xC), 128.7 (2xC), 128.6 (2xC), 128.3 (2xC), 126.8, 70.4, 55.3, 40.4, 39.4, 35.3. IR (neat, cm^{-1}),3032, 2982, 2936, 2886, 2100, 1672, 1594, 1408, 1233, 1016, 991, 738, 689.

It was obtained in 93 % yield as yellow solid, **14B**, R_f = 0.52 (4:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.2 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.48 – 7.32 (m, 2H), 7.13 (dt, J = 15.1, 7.5 Hz, 3H), 7.07 – 6.95 (m, 1H), 3.61 (dd, J = 13.8, 4.6 Hz, 1H), 3.50 (dd, J =13.8, 4.6 Hz 1H), 2.98 (dd, J = 13.7, 4.7 Hz, 1H), 2.87 (dd,

J = 8.0, 5.6 Hz, 1H), 2.62 (dd, *J* = 6.1, 2.9 Hz, 1H), 2.24 (d, *J* = 3.2 Hz, 1H), 2.10 – 1.95 (m, 1H), 1.93 (d, *J* = 6.7 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$: δ 195.7, 137.7, 136.4, 133.1, 129.2 (2xC), 128.6 (2xC), 128.3 (2xC), 128.1 (2xC), 126.5, 69.9, 55.3, 39.8, 39.7, 35.6. IR (neat, cm^{-1}), 3028, 2920, 2096, 1680, 1597, 1449, 1400, 1226, 1015, 965, 741, 741, 695.

4.2.5.2 Characterization of (1-((S)-1-azido-3-phenyl propan-2-yl) aziridin-2-yl) (p-tolyl) methanone (15A, 15B)



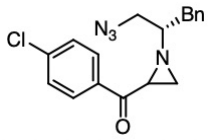
The conversion of tosylate groups **10A-10B** to azide groups **15A-15B** was performed according to the general method for nucleophilic azidation.

It was obtained in 85 % yield as yellow solid, mp: 60-63 °C, **15A**, R_f = 0.60 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.2 Hz,2H), 7.31 – 7.19 (m, 4H), 7.17 – 7.10 (m, 3H), 3.40 (dd, *J* = 12.7, 6.6 Hz, 1H), 3.35 (dd, *J* = 12.9, 5.7 Hz, 1H), 3.10 (dd, *J* = 6.6, 3.3 Hz, 1H), 2.91 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.83 (dd, *J* = 13.8, 7.2 Hz, 1H) 2.35 (s, 3H), 2.15 (d, *J* = 2.3 Hz, 1H), 1.84 (dd, *J* = 11.8, 6.8 Hz 1H), 1.47 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 144.3, 137.9, 134.4, 129.4 (2xC), 129.4 (2xC), 128.6 (2xC), 128.4 (2XC), 126.7, 70.4, 55.3, 40.2, 39.4, 35.2, 21.7. IR (neat, cm^{-1}), 3028, 2921, 2096, 1680, 1597, 1449, 1226, 1015, 741, 695.

It was obtained in 91 % yield as yellow solid, **15B**, R_f = 0.75 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 6.6 Hz, 4H), 6.99 – 6.91 (m, 1H), 3.51 (dd, *J* = 12.4, 6.7 Hz, 1H), 3.39 (dd, *J* = 12.5, 5.4 Hz, 1H), 2.88 (dd, *J* = 13.7, 5.1 Hz, 1H), 2.79 (dd, *J* = 13.7, 8.1 Hz 1H), 2.53 (dd, *J* = 6.8, 3.3 Hz, 1H), 2.34 (s, 3H), 2.16 (d, *J* = 2.0 Hz, 1H), 1.97 (dd, *J* = 11.6, 5.2 Hz 1H), 1.81 (d, *J* = 8.1 Hz 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 144.1, 137.8, 134.1, 129.3 (2xC), 129.1 (2xC), 128.7 (2xC), 128.3 (2xC), 126.6, 70.1, 55.4, 39.9, 39.8, 35.6, 21.7. IR (neat, cm^{-1}), 3033, 2913, 2838, 2102,

1671, 1605, 1441, 1232, 1012, 749, 701.

4.2.5.3 Characterization of (1-((S)-1-azido-3-phenyl propan-2-yl) aziridin-2-yl) (4-chlorophenyl) methanone (16A, 16B)

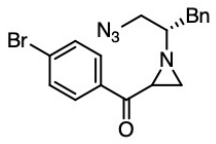


The conversion of tosylate groups **11A-11B** to azide groups **16A-16B** was performed according to the general method for nucleophilic azidation.

It was obtained in 64 % yield as yellow solid, **16A**, R_f = 0.60 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.39 – 7.31 (m, 2H), 7.31 – 7.14 (m, 3H), 3.56 - 3.39 (m, 2H), 3.16 (dd, J = 6.7, 3.3 Hz 1H), 3.00 (dd, J = 13.7, 6.6 Hz 1H), 2.91 (dd, J = 13.8, 7.2 Hz 1H), 2.25 (d, J = 3.2 Hz, 1H), 2.04 – 1.85 (m, 1H), 1.60 (d, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 139.8, 137.5, 134.9, 129.6 (2xC), 129.3 (2xC), 128.9 (2xC), 128.5 (2xC), 126.7, 70.2, 55.2, 40.5, 39.2, 35.1. IR (neat, cm^{-1}), 3028, 2917, 2852, 2828, 2101, 1683, 1589, 1407, 1349, 1227, 1089, 993.

It was obtained in 69 % yield as yellow solid, **16B**, R_f = 0.50 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.41 (m, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.10 - 6.99 (m, 4H), 6.98 – 6.87 (m, 1H), 3.52 (dd, J = 12.5, 6.6 Hz, 1H), 3.41 (dd, J = 12.5, 5.4 Hz, 1H), 2.89 (dd, J = 13.7, 4.5 Hz, 1H), 2.77 (dd, J = 13.7, 8.8 Hz, 1H), 2.42 (dd, J = 6.7, 3.3 Hz, 1H), 2.15 (d, J = 3.2 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.83 (d, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 139.6, 137.8, 134.7, 129.5 (2xC), 129.2 (2xC), 128.6 (2xC), 128.5 (2xC), 126.5, 70.0, 55.6, 40.0, 39.7, 35.4. IR (neat, cm^{-1}), 3028, 2922, 2098, 1681, 1588, 1410, 1287, 1224, 1157, 1090, 1011.

4.2.5.4 Characterization of (1-((S)-1-azido-3-phenyl propan-2-yl) aziridin-2-yl) (4-bromo phenyl) methanone (17A, 17B)

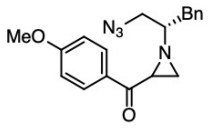


The conversion of tosylate groups **12A-12B** to azide groups **17A-17B** was performed according to the general method for nucleophilic azidation.

It was obtained in 73 % yield as yellow solid, mp: 105.3 °C, **17A**, R_f = 0.64 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 – 7.75 (m, 2H), 7.69 – 7.50 (m, 2H), 7.37 – 7.20 (m, 2H), 7.20 – 7.07 (m, 3H), 3.40 (dd, J = 12.7, 7.0 Hz 1H), 3.37 (dd, J = 12.8, 4.8 Hz 1H), 3.04 (dd, J = 6.6, 3.3 Hz, 1H), 2.90 (dd, J = 13.7, 6.6 Hz, 1H), 2.81 (dd, J = 13.7, 7.2 Hz, 1H), 2.15 (d, J = 2.04 Hz, 1H), 1.87 (dd, J = 11.5, 6.6 Hz, 1H), 1.45 (t, J = 32.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 137.6, 135.4, 132.0 (2xC), 129.7 (2xC), 129.4 (2xC), 128.7 (2xC), 126.8 (2xC), 70.3, 55.3, 40.5, 39.3, 35.2. IR (neat, cm^{-1}), 3075, 3027, 2944, 2915, 2826, 2100, 1682, 1584, 1442, 1348, 1225, 1068.

It was obtained in 74 % yield as yellow solid, mp: 66.2 °C, **17B**, R_f = 0.45 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 - 7.38 (m, 4H), 7.15 - 6.99 (m, 4H), 6.98 - 6.88 (m, 1H), 3.51 (dd, J = 12.5, 6.6 Hz, 1H), 3.41 (dd, J = 12.5, 5.5 Hz, 1H), 2.89 (dd, J = 13.7, 4.5 Hz, 1H), 2.76 (dd, J = 13.7, 8.8 Hz, 1H), 2.41 (dd, J = 6.7, 3.3 Hz, 1H), 2.15 (d, J = 2.0 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.83 (d, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 137.9, 135.1, 131.7 (2xC), 129.7 (2xC), 129.3 (2xC), 128.7 (2xC), 128.4, 126.7, 69.9, 55.5, 40.1, 39.8, 35.6. IR (neat, cm^{-1}), 3031, 2985, 2942, 2908, 2854, 2109, 1672, 1582, 1404, 1357, 1224, 1066, 1001, 982, 752, 702.

4.2.5.5 Characterization of (1-((S)-1-azido-3-phenyl propan-2-yl) aziridin-2-yl) (4-methoxyphenyl)methanone (18A, 18B)



The conversion of tosylate groups **13A-13B** to azide groups **18A-18B** was performed according to the general method for nucleophilic azidation.

It was obtained in 88 % yield as yellow solid, **18A**, R_f = 0.48 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.9 Hz, 1H), 7.38 – 7.20 (m, 3H), 7.01 – 6.94 (m, 2H), 3.90 (s, 2H), 3.49 (dd, J = 12.9, 8.1 Hz 1H), 3.45 (dd, J = 13.0, 5.3 Hz 1H) 3.17 (dd, J = 6.6, 3.3 Hz, 1H), 3.00 (dd, J = 13.7, 6.6 Hz, 1H), 2.92 (dd, J = 13.7, 7.2 Hz, 1H), 2.25 (d, J = 2.1 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.55 (d, J = 5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 163.8, 137.9, 130.7 (2xC), 129.9, 129.4 (2xC), 128.6 (2xC), 126.7, 113.9 (2xC), 70.4, 55.5, 55.3, 40.1, 39.4, 34.9. IR (neat, cm^{-1}), 2922, 2840, 2096, 1575, 1423, 1235, 1169, 1022, 842.

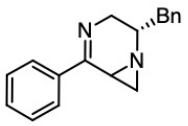
It was obtained in 90 % yield as yellow solid, mp: 60-61 ^{o}C, **18B**, R_f = 0.42 (5:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.9 Hz, 2H), 7.19 – 7.10 (m, 4H), 7.09 - 7.02 (m, 1H), 6.94 – 6.85 (m, 2H), 3.89 (s, 3H), 3.60 (dd, J = 12.4, 6.7 Hz, 1H), 3.48 (dd, J = 12.4, 5.5 Hz, 1H), 2.97 (dd, J = 13.7, 5.0 Hz, 1H), 2.88 (dd, J = 13.7, 8.2 Hz, 1H), 2.58 (dd, J = 6.7, 3.3 Hz, 1H), 2.25 (d, J = 2.0 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.89 (d, J = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 163.6, 137.9, 130.5 (2xC), 129.7, 129.4 (2xC), 128.7 (2xC), 126.6, 113.6 (2xC), 70.1, 55.5, 55.38, 39.8, 39.7, 35.4. IR (neat, cm^{-1}), 2941, 2912, 2843, 2103, 1661, 1594, 1452, 1309, 1237, 1170, 1020, 981, 751, 703.

4.2.6 General method for azide reduction to amine

After completed azidation step, starting material **14A** (166 mg, 0.54 mmol) was dissolved in EtOAc (2.7 ml). Palladium 10 % on carbon powder (32 mg) was added. It was left to stir under hydrogen gas at room temperature for 10 h. The reaction was

aborted. It was filtered via a celite and concentrated in vacuum. Next, it was purified by silica gel column chromatography (EtOAc–Hexane).

4.2.7 Characterization of (2S)-2-benzyl-5-phenyl-1,4-diazabicyclo[4.1.0] hept-4-ene (19A, 19B)

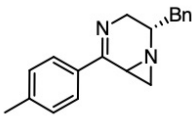


Aziridine-fused piperazine precursors **19A-19B** were isolated according to the general method for azide **14A-14B** reduction to amine.

It was obtained in 53 % yield as white solid, **19A**, R_f = 0.40 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.40 – 7.33 (m, 3H), 7.29 – 7.15 (m, 5H), 3.85 – 3.77 (m, 1H), 3.14 – 3.06 (m, 2H), 3.05 – 2.97 (m, 1H), 2.86 (dd, J = 13.6, 6.5 Hz, 1H), 2.75 (dd, J = 13.6, 5.7 Hz, 1H), 2.17 (d, J = 2.9 Hz, 1H), 2.07 (d, J = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 138.6, 138.1, 138.1, 130.4, 129.2 (2xC), 128.5 (2xC), 128.5 (2xC), 126.6, 126.4 (2xC), 50.5, 47.5, 39.9, 30.5, 25.4. IR (neat, cm^{-1}), 3026, 2914, 2849, 1627, 1492, 1445, 1244, 1065, 999, 751, 694.

It was obtained in 54 % yield as yellow solid, **19B**, R_f = 0.28 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.65 (m, 2H), 7.49 – 7.30 (m, 3H), 7.29 – 7.20 (m, 2H), 7.20 – 7.09 (m, 3H), 3.69 (dd, J = 16.6, 3.3 Hz, 1H), 3.44 (dd, J = 16.6, 5.5 Hz, 1H), 3.08 (dd, J = 8.5, 5.9 Hz, 1H), 2.91 (dd, J = 5.6, 3.5 Hz 1H), 2.85 (dd, J = 13.5, 6.5 Hz 1H) 2.57 (dd, J = 13.5, 6.5 Hz, 1H), 2.21 (d, J = 5.9 Hz, 1H), 2.15 (d, J = 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 139.0, 138.5, 130.4, 129.5 (2xC), 128.5 (2xC), 128.4 (2xC), 126.3, 126.3 (2xC), 54.5, 46.6, 40.7, 30.7, 28.4. IR (neat, cm^{-1}), 3024, 3002, 2929, 2860, 1606, 1665, 1565, 1453, 1250, 1126, 1054, 972, 822, 754, 728.

4.2.8 Characterization of (2S)-2-benzyl-5-(p-tolyl)-1,4- diazabicyclo [4.1.0] hept -4-ene (20A, 20B)

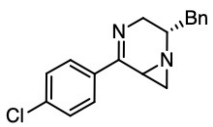


Aziridine-fused piperazine precursors **20A-20B** were isolated according to the general method for azide **15A-15B** reduction to amine.

It was obtained in 36 % yield as yellow liquid, **20A**, R_f = 0.36 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.40 – 7.16 (m, 7H), 3.88 (d, J = 12.9 Hz, 1H), 3.24 – 3.14 (m, 1H), 3.12 (d, J = 3.9 Hz, 1H), 2.95 (dd, J = 13.6, 6.5 Hz, 1H), 2.84 (dd, J = 13.6, 5.7 Hz, 1H), 2.41 (s, 3H), 2.25 (d, J = 3.1 Hz, 1H), 2.15 (d, J = 5.8 Hz, 1H), 1.37 – 1.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.8, 138.1, 135.8, 129.23 (2xC), 129.2 (2xC), 128.5 (2xC), 126.6, 126.4 (2xC), 50.5, 47.5, 39.9, 30.4, 25.4, 21.5. IR (neat, cm^{-1}), 3026, 2923, 2854, 1670, 1604, 1568, 1453, 1235, 1181, 1062, 916, 816, 744, 670.

It was obtained in 53 % yield as yellow liquid, **20B**, R_f = 0.20 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.1 Hz, 2H), 7.27 – 7.11 (m, 7H), 3.63 (dd, J = 16.5, 3.1 Hz, 1H), 3.41 (dd, J = 16.5, 5.4 Hz, 1H), 3.06 – 2.96 (m, 1H), 2.87 (dd, J = 6.5, 3.1 Hz, 1H), 2.55 (dd, J = 13.5, 8.1 Hz, 1H), 2.32 (s, 3H), 2.27 (d, J = 14.0 Hz, 1H), 2.17 (d, J = 5.9 Hz, 1H), 2.09 (d, J = 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 140.5, 139.2, 135.9, 129.4 (2xC), 129.2 (2xC), 128.4 (2xC), 126.4, 126.1 (2xC), 55.1, 46.9, 40.6, 30.5, 28.4, 21.6. IR (neat, cm^{-1}), 3026, 2921, 1667, 1622, 1448, 1385, 1249, 1177, 1056, 973, 950, 770, 747, 731, 694.

4.2.9 Characterization of (2S) -2-benzyl-5- (4-chlorophenyl) -1,4- diazabicyclo [4.1.0] hept-4-ene (21A, 21B)

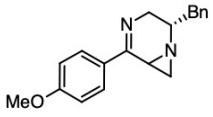


Aziridine-fused piperazine precursors **21A-21B** were isolated according to the general method for azide **16A-16B** reduction to amine.

It was obtained in 61 % yield as white solid, **21A**, R_f = 0.30 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.28 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 8.1 Hz, 1H), 3.89 (d, J = 13.5 Hz, 1H), 3.16 (dd, J = 10.8, 6.4 Hz, 1H), 3.08 (dd, J = 11.04, 8.4 Hz, 1H), 2.94 (dd, J = 13.6, 6.2 Hz 1H), 2.83 (dd, J = 13.7, 5.8 Hz 1H), 2.28 (d, J = 2.6 Hz 1H), 2.23 (dd, J = 7.9, 3.1 Hz, 1H), 2.18 (d, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 137.9, 133.9, 129.2 (2xC), 128.8 (2xC), 128.5 (2xC), 127.8 (2xC), 126.7 (2xC),55.0, 50.5, 39.8, 30.3, 29.7. IR (neat, cm^{-1}), 3028, 2920, 1621, 1591, 1449, 1404, 1250, 1088, 827, 722, 704.

It was obtained in 75 % yield as white solid, **21B**, R_f = 0.25 (3:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.5 Hz 2H), 7.44 (d, J = 8.5 Hz 2H), 7.33 (t, J = 7.5 Hz 2H), 7.24 (m, 3H), 3.78 (dd, J = 16.6, 3.2 Hz, 1H), 3.52 (dd, J = 16.7, 5.6 Hz, 1H), 3.23 - 3.30 (m, 1H), 2.96 (dd, J = 13.6, 6.2 Hz 1H), 2.92 (dd, J = 13.7, 5.8 Hz 1H), 2.66 (dd, J = 13.6, 8.0 Hz, 1H), 2.32 (d, J = 5.8 Hz, 1H), 2.22 (d, J = 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.7, 136.5, 129.2 (2xC), 128.6 (2xC), 128.3 (2xC), 127.5 (2xC), 126.3 (2xC), 54.3, 46.77, 40.6, 30.6, 28.1. IR (neat, cm^{-1}), 3030, 2921, 2856 1617, 1490, 1404, 1250, 1086, 829, 723, 707.

4.2.10 Characterization of (2S)-2-benzyl-5-(4-methoxyphenyl) -1,4- diazabicyclo [4.1.0] hept-4-ene (22A, 22B)



Aziridine-fused piperazine precursors **22A-22B** were isolated according to the general method for azide **18A-18B** reduction to amine.

It was obtained in 66 % yield as yellow solid, mp: 117.0-117.8 °C, **22A**, R_f = 0.36 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.74 (m, 2H), 7.39 – 7.22 (m, 5H), 6.99 – 6.90 (m, 2H), 3.86 (s, 3H), 3.72 (d, J = 2.1 Hz, 1H), 3.13 - 3.02

(m, 2H), 3.06 - 2.93 (m, 1H), 2.94 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.82 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.23 (d, *J* = 3.1 Hz, 1H), 2.11 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 161.3, 138.4, 131.7, 129.2 (2xC), 128.5 (2xC), 127.8 (2xC), 126.5, 113.8 (2xC), 55.4, 50.5, 47.7, 40.0, 30.3, 25.1. IR (neat, cm^{-1}), 3011, 2941, 2898, 2838, 1621, 1456, 1252, 1175, 1021, 961, 940, 751, 736, 716, 699.

It was obtained in 63 % yield as dark-orange solid, mp: 100.9 °C, **22B**, R_f = 0.20 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.19 (m, 5H), 6.97 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 3.72 (dd, *J* =15.9, 3.0 Hz, 1H), 3.52 (dd, *J* = 16.5, 5.4 Hz, 1H), 3.14 - 3.07 (m, 1H), 2.96 (dd, *J* = 6.5 Hz 1H), 2.93 (dd, *J* = 13.8, 6.5 Hz 1H), 2.67 (dd, *J* = 13.5, 8.0 Hz, 1H), 2.28 (d, *J* = 5.9 Hz, 1H), 2.18 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 161.3, 139.0, 131.2, 129.25 (2xC), 128.3 (2xC), 127.6 (2xC), 126.1, 113.6 (2xC), 55.3, 54.9, 46.8, 40.7, 30.8, 28.1. IR (neat, cm^{-1}), 2998, 2931, 2863, 1604, 1453, 1247, 1171, 1128, 973, 952.18, 754, 740, 703.

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APPENDIX

NMR Spectrum of Compounds

NMR Spectrum of Aziridine Ketones

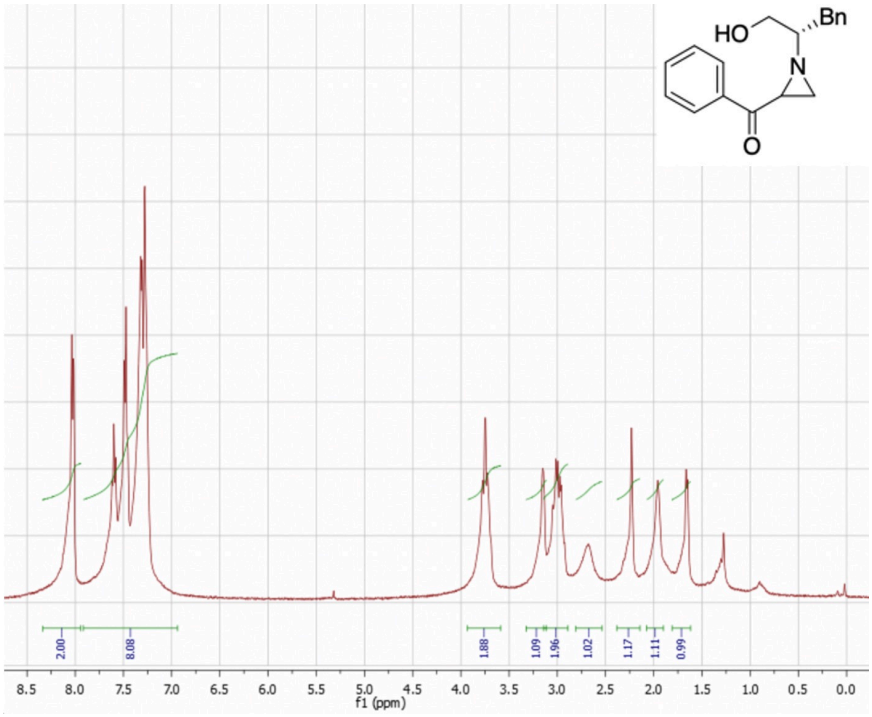

Figure 4.1: ^{1}H NMR Spectrum of Compound **4A**.

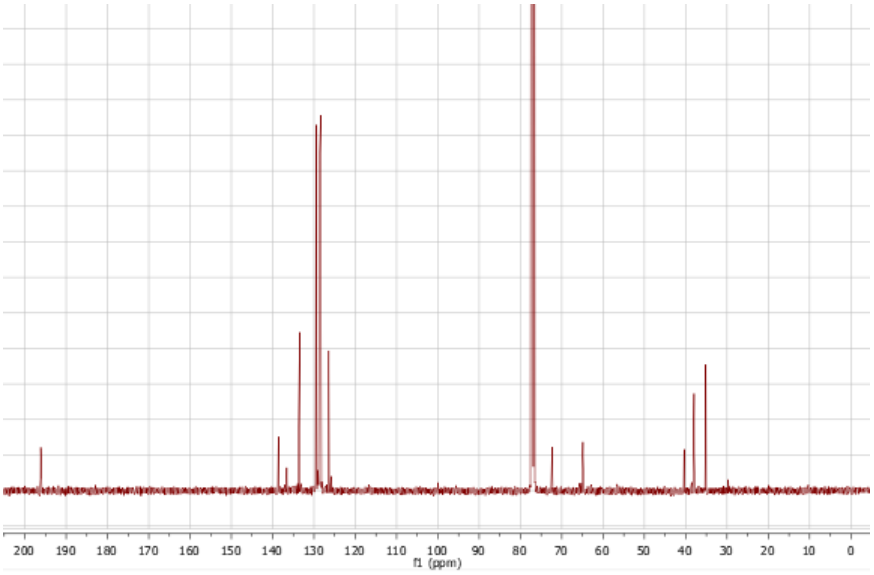

Figure 4.2: ^{13}C NMR Spectrum of Compound **4A**.

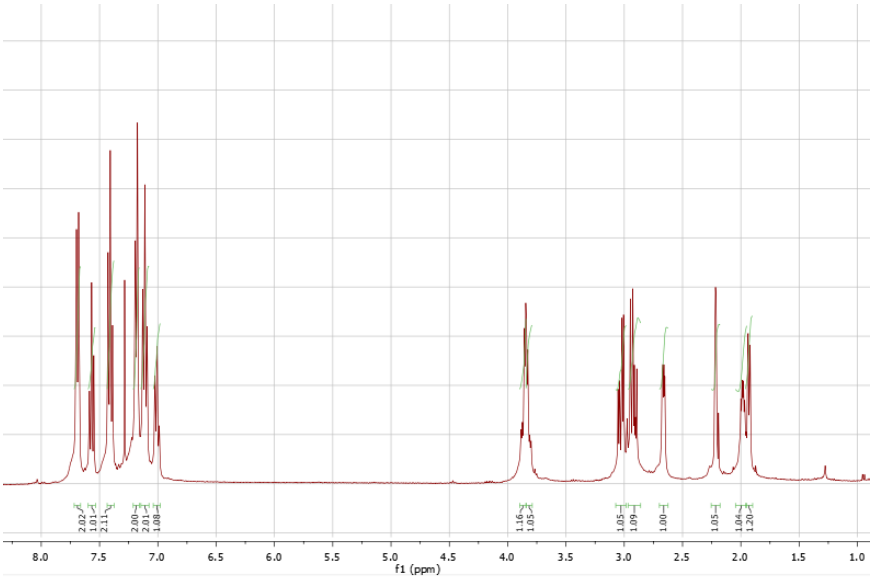

Figure 4.3: ^{1}H NMR Spectrum of Compound **4B**.

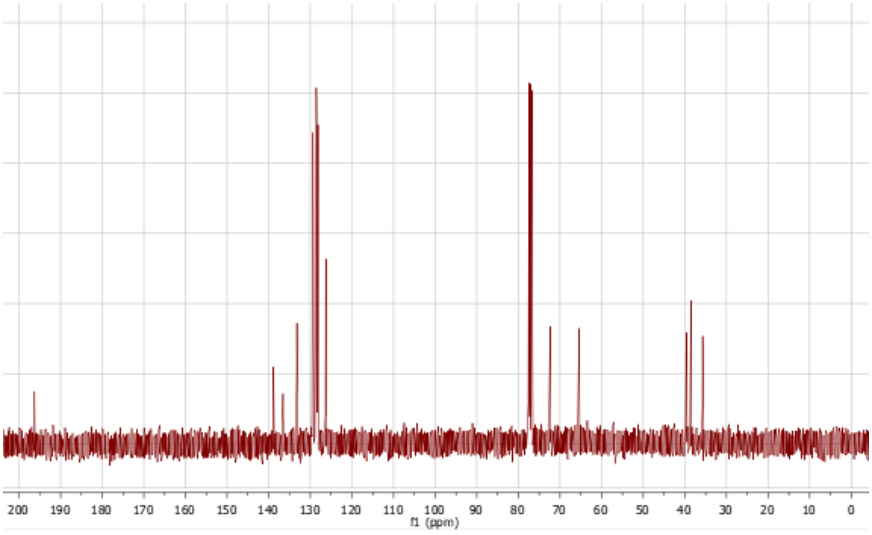

Figure 4.4: ^{13}C NMR Spectrum of Compound **4B**.

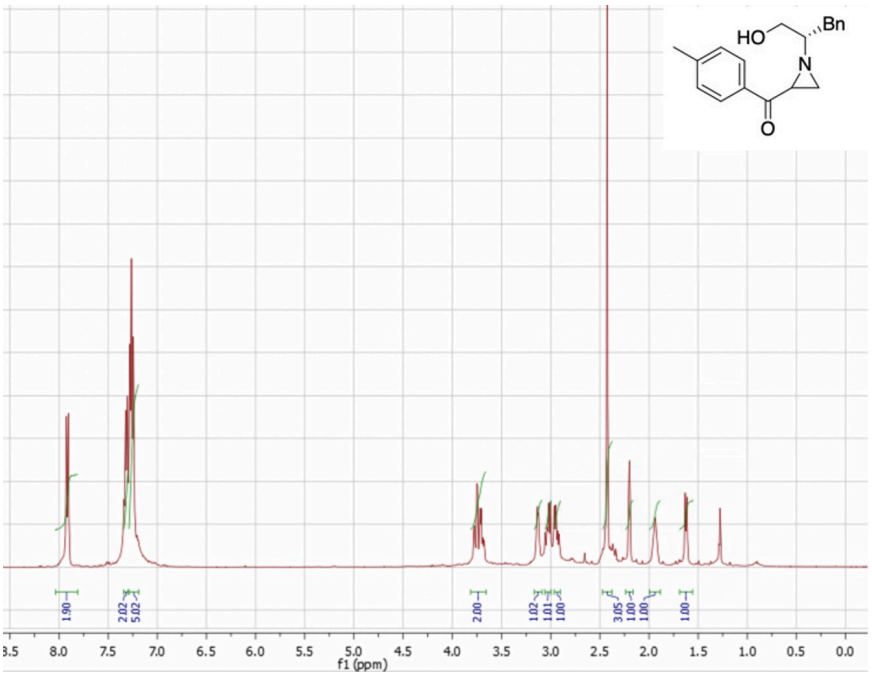

Figure 4.5: ^{1}H NMR Spectrum of Compound **5A**.

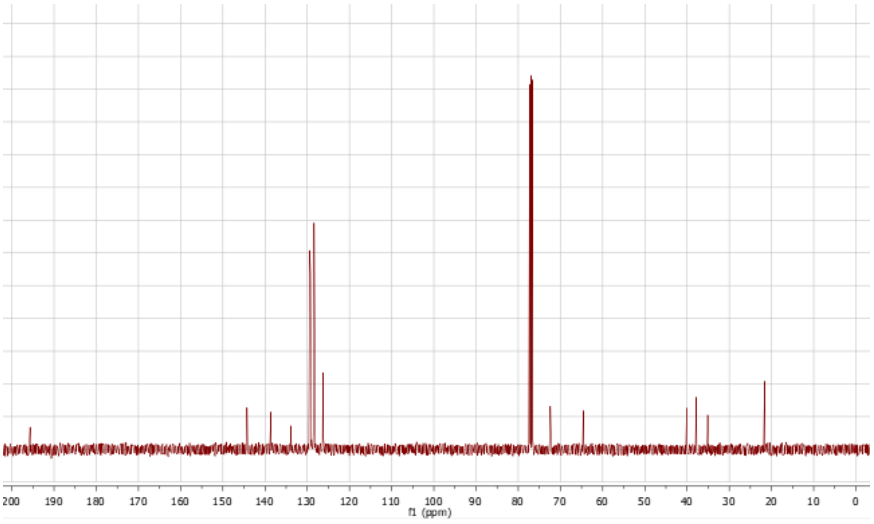

Figure 4.6: ^{13}C NMR Spectrum of Compound **5A**.

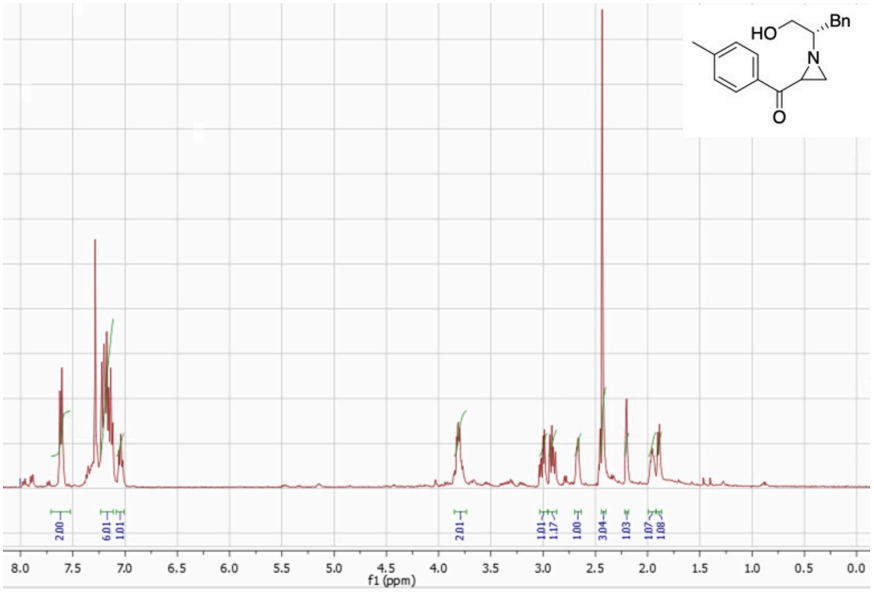

Figure 4.7: ^{1}H NMR Spectrum of Compound **5B**.

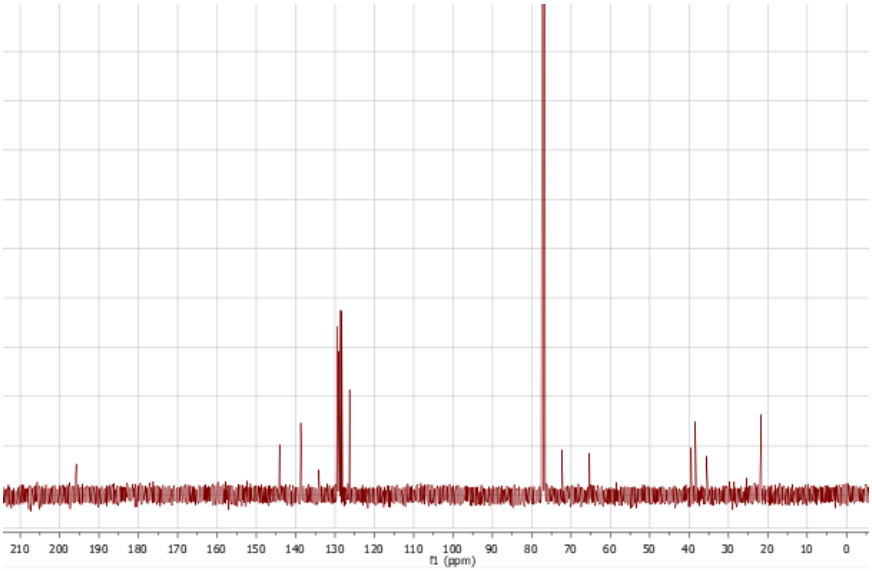

Figure 4.8: ^{13}C NMR Spectrum of Compound **5B**.

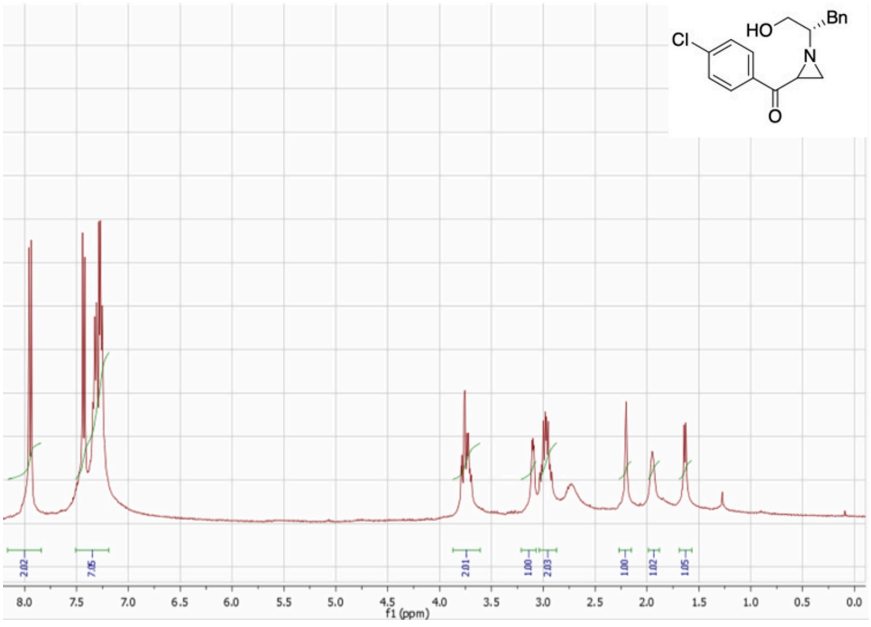

Figure 4.9: ^{1}H NMR Spectrum of Compound **6A**.

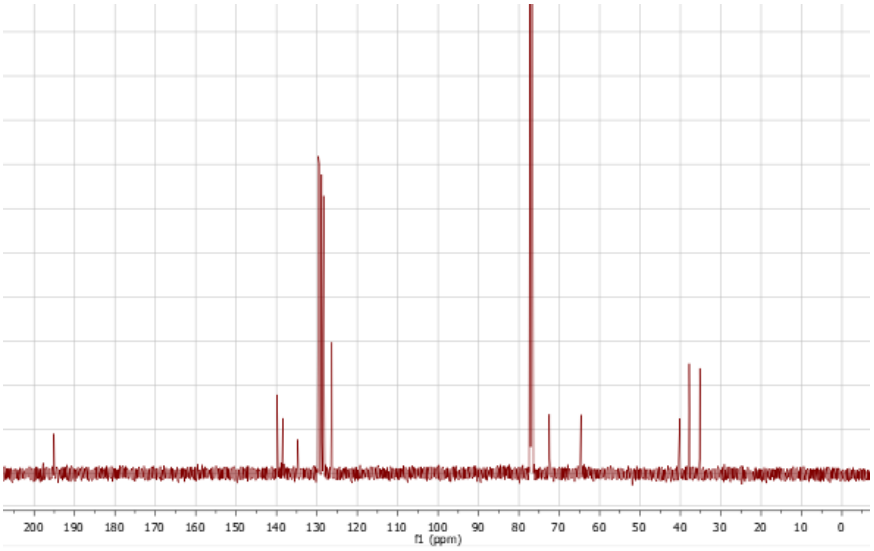

Figure 4.10: ^{13}C NMR Spectrum of Compound **6A**.

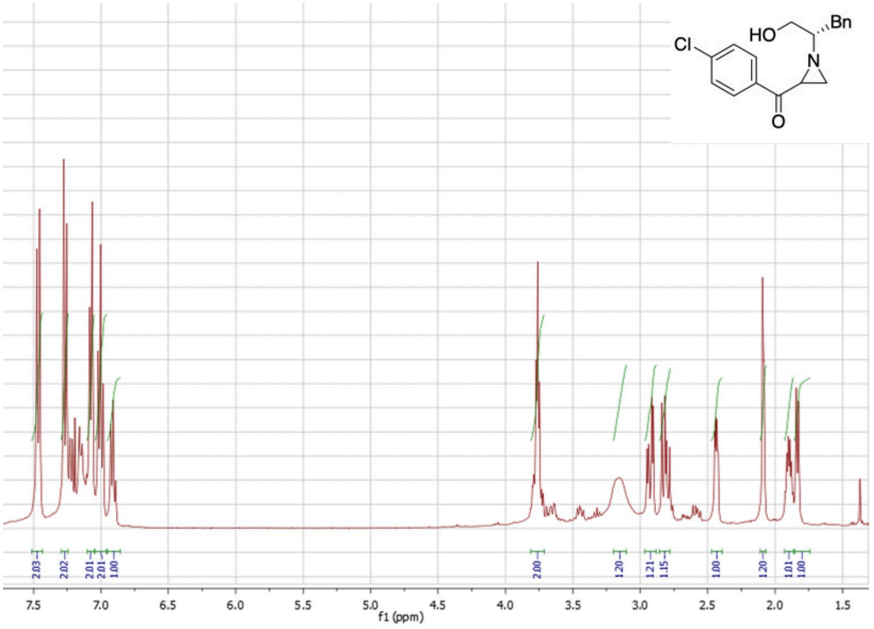

Figure 4.11: ^{1}H NMR Spectrum of Compound **6B**.

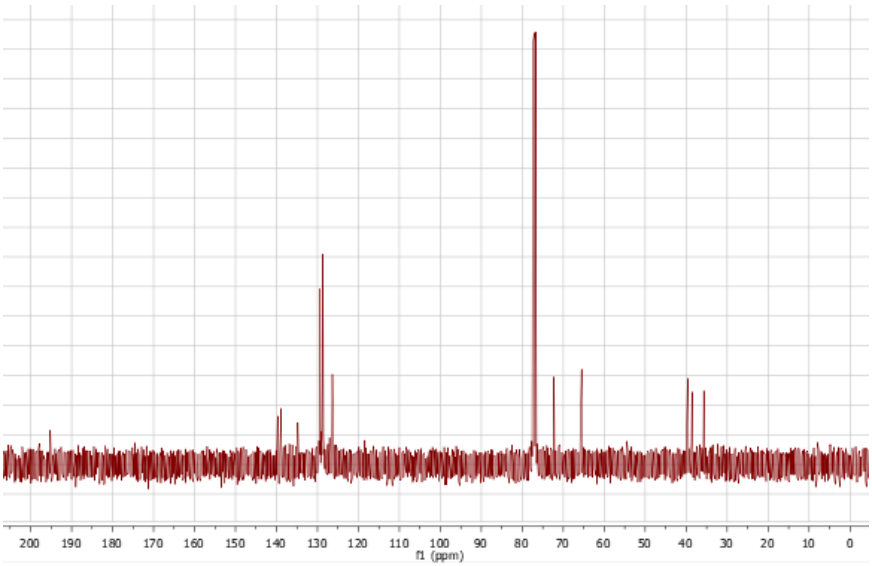

Figure 4.12: ^{13}C NMR Spectrum of Compound **6B**.

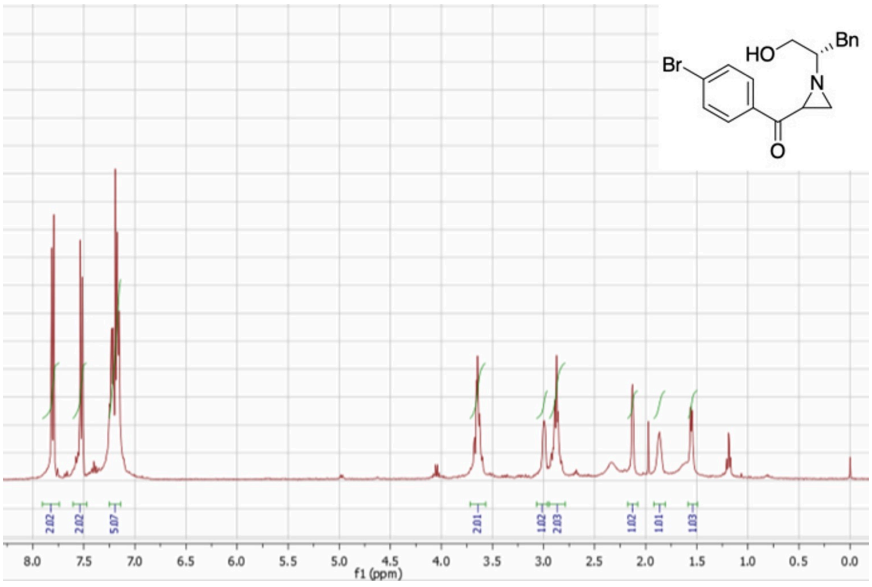

Figure 4.13: ^{1}H NMR Spectrum of Compound **7A**.

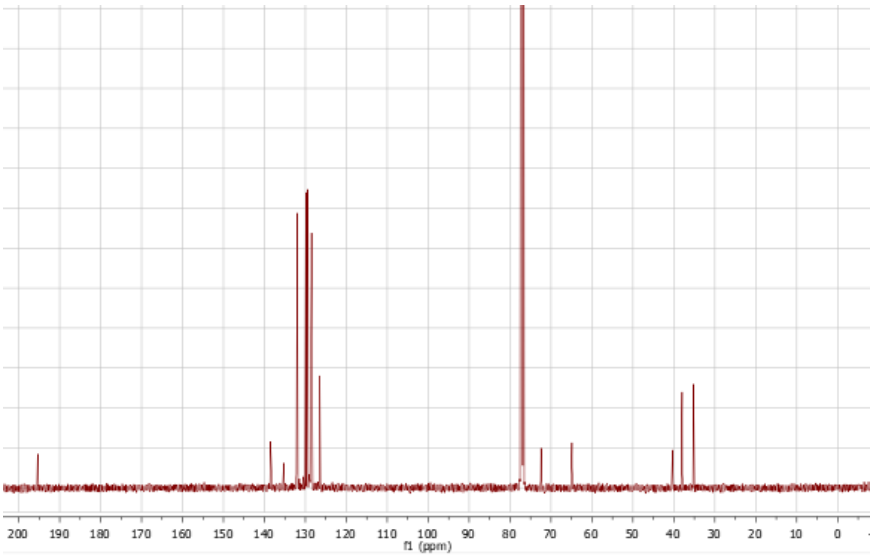

Figure 4.14: ^{13}C NMR Spectrum of Compound **7A**.

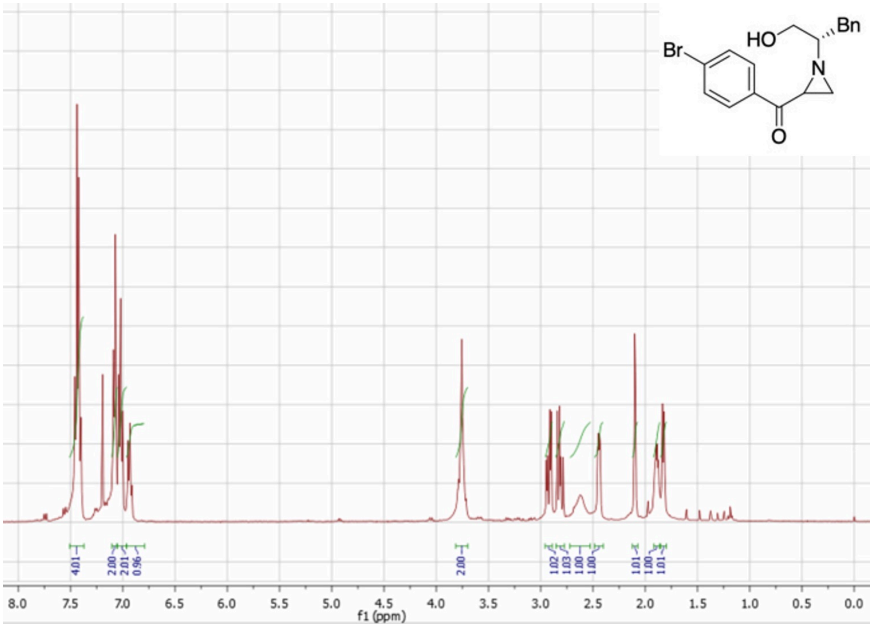

Figure 4.15: ^{1}H NMR Spectrum of Compound **7B**.

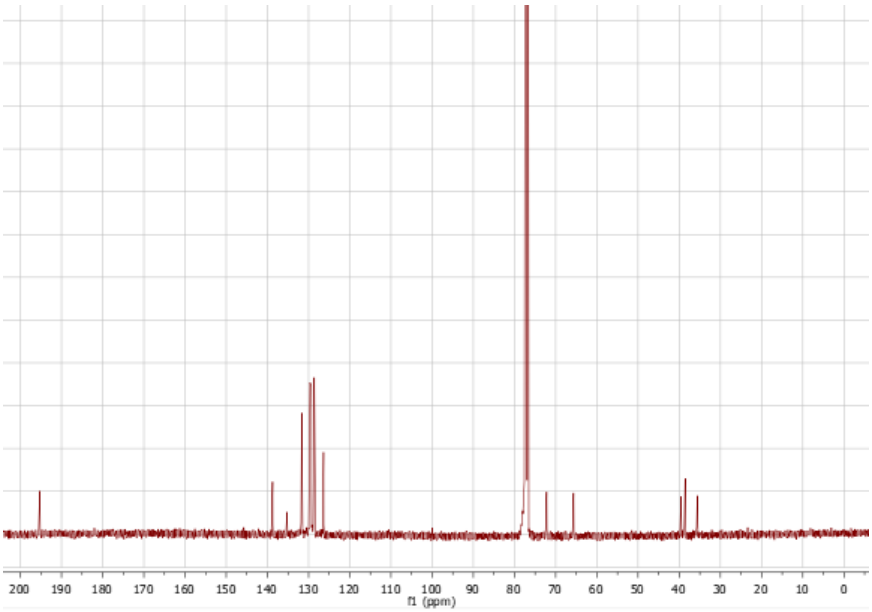

Figure 4.16: ^{13}C NMR Spectrum of Compound **7B**.

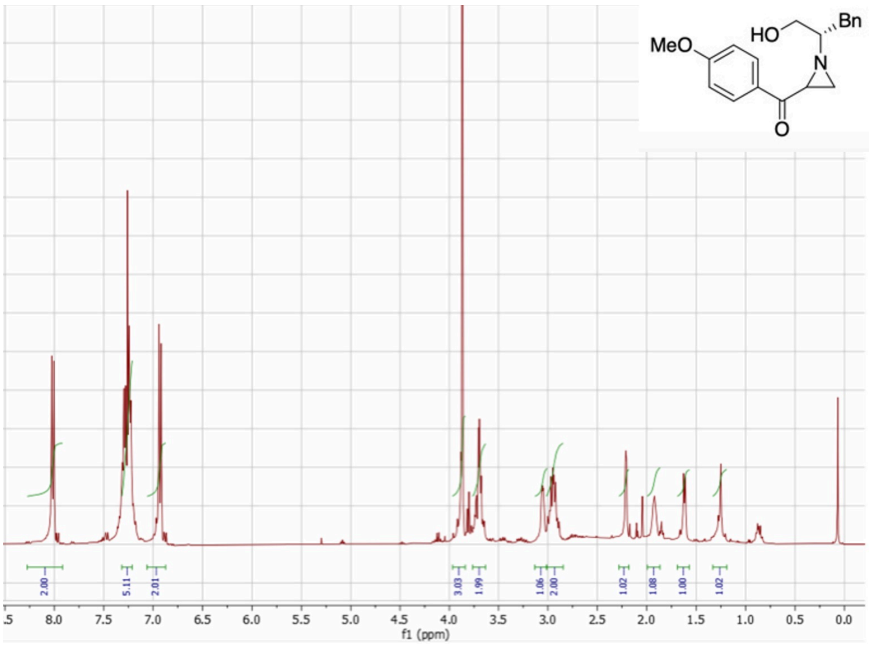

Figure 4.17: ^{1}H NMR Spectrum of Compound **8A**.

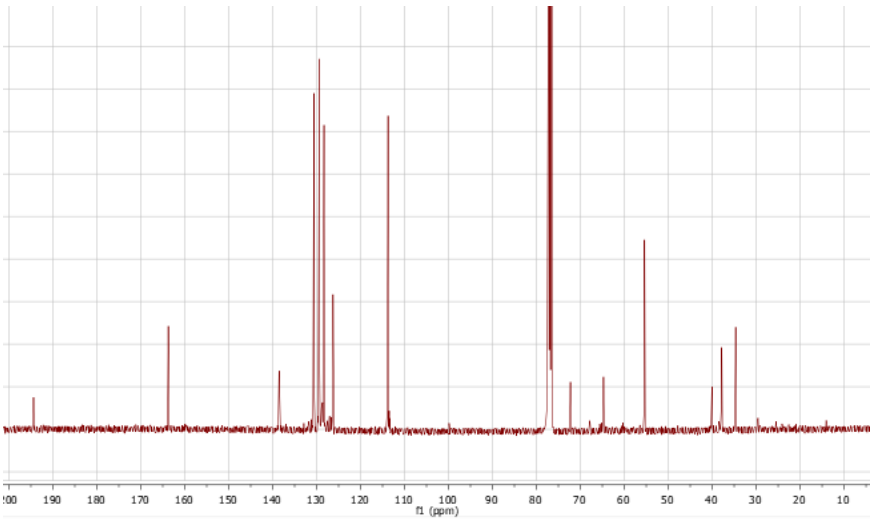

Figure 4.18: ^{13}C NMR Spectrum of Compound **8A**.

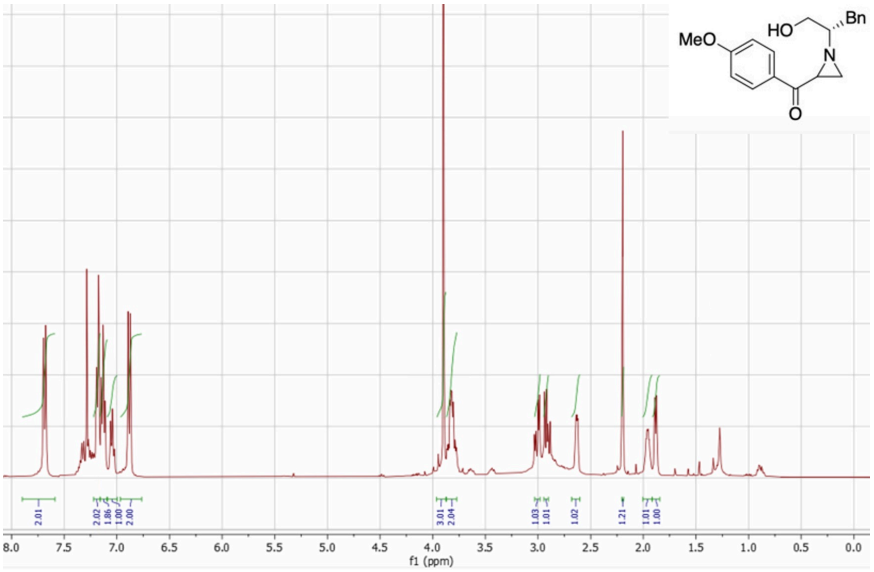

Figure 4.19: ^{1}H NMR Spectrum of Compound **8B**.

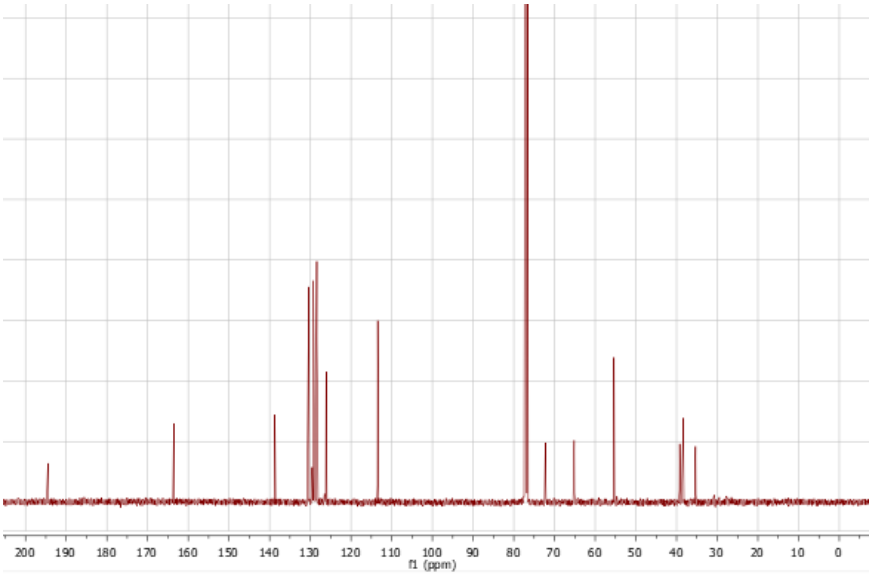

Figure 4.20: ^{13}C NMR Spectrum of Compound **8B**.

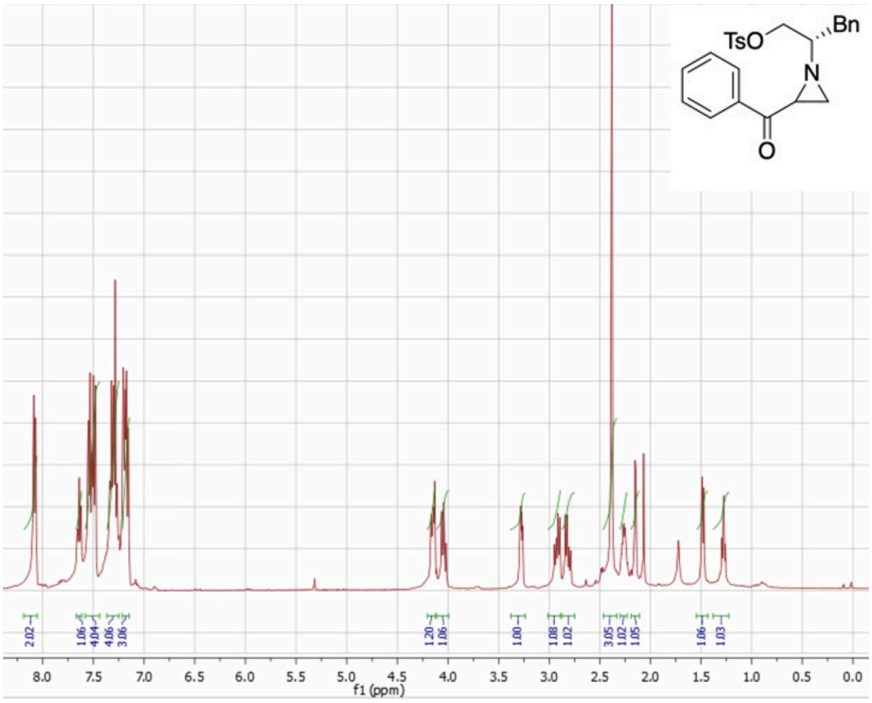

Figure 4.21: ^{1}H NMR Spectrum of Compound **9A**.

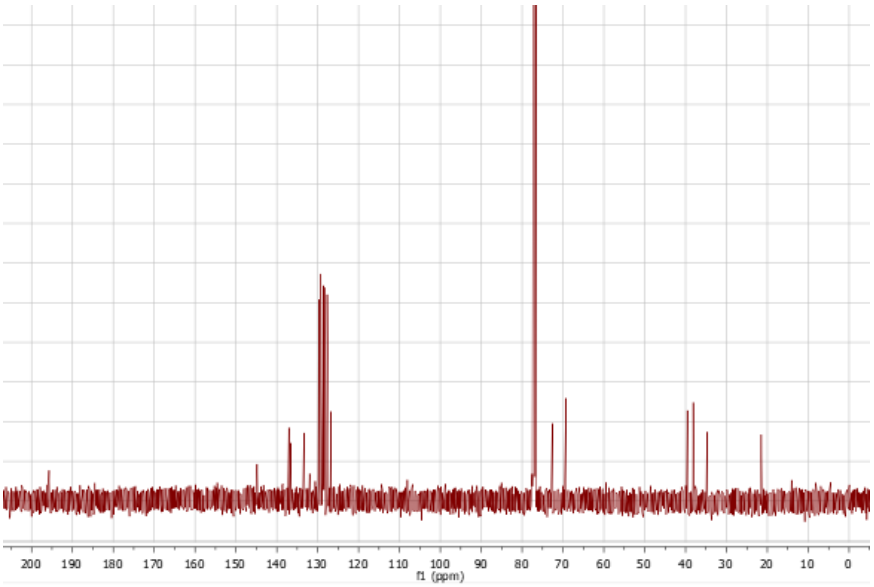

Figure 4.22: ^{13}C NMR Spectrum of Compound **9A**.

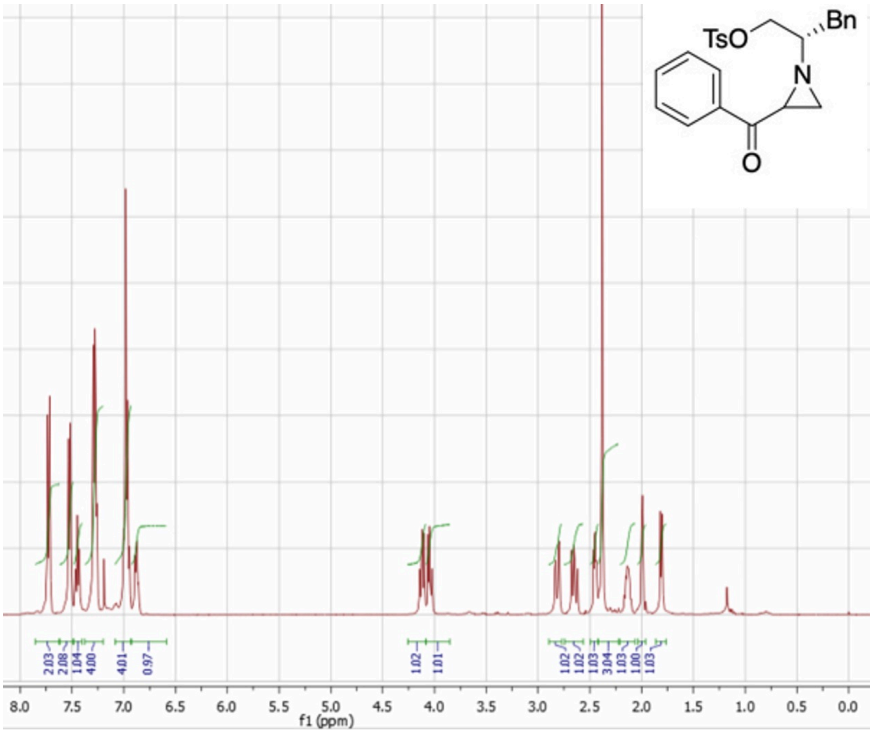

Figure 4.23: ^{1}H NMR Spectrum of Compound **9B**.

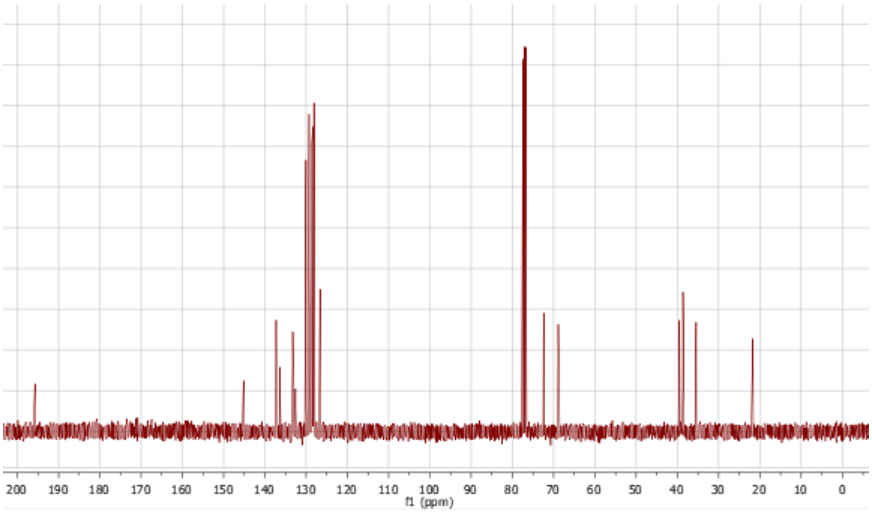

Figure 4.24: ^{13}C NMR Spectrum of Compound **9B**.

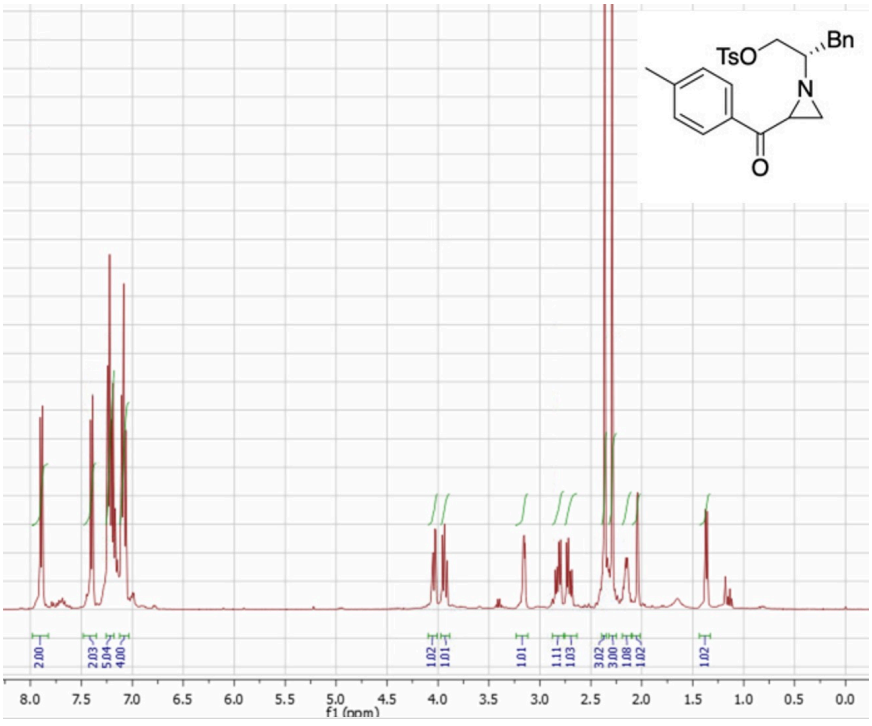

Figure 4.25: ^{1}H NMR Spectrum of Compound **10A**.

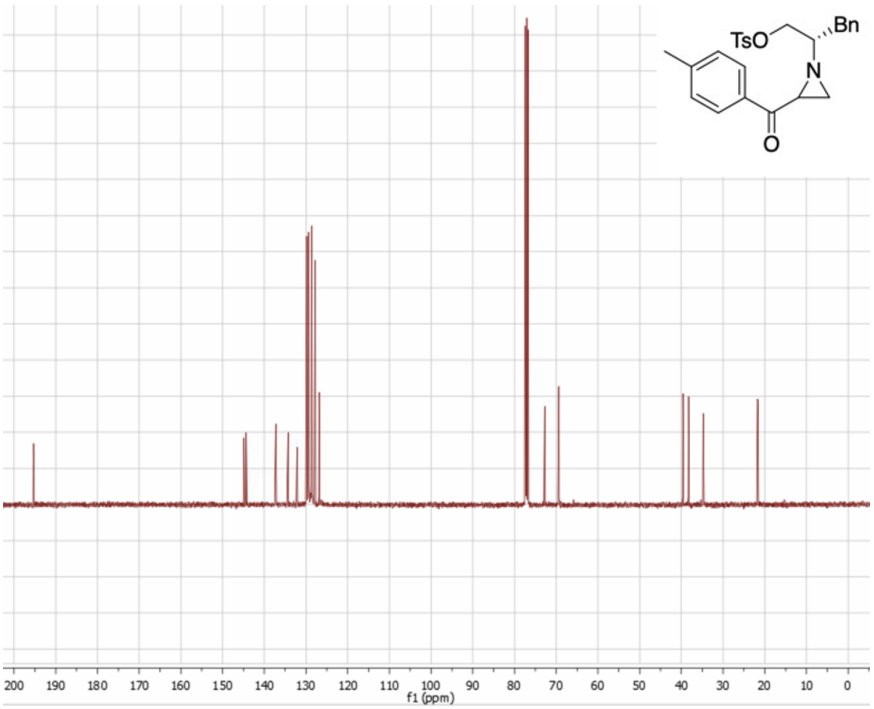

Figure 4.26: ^{13}C NMR Spectrum of Compound **10A**.

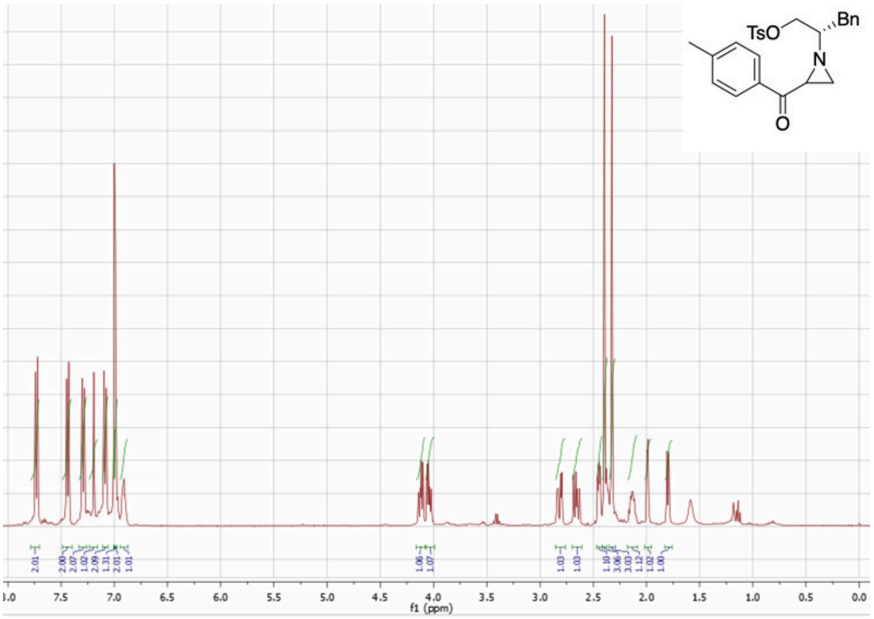

Figure 4.27: ^{1}H NMR Spectrum of Compound **10B**.

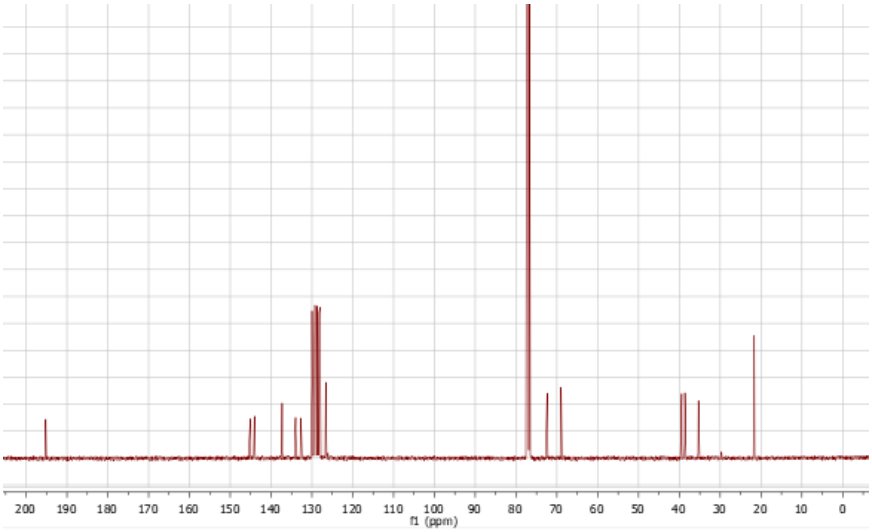

Figure 4.28: ^{13}C NMR Spectrum of Compound **10B**.

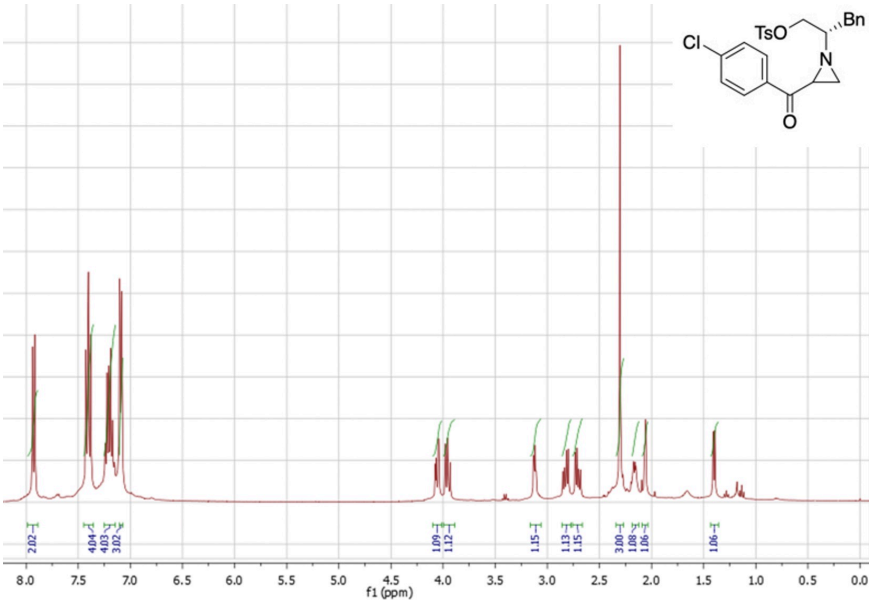

Figure 4.29: ^{1}H NMR Spectrum of Compound **11A**.

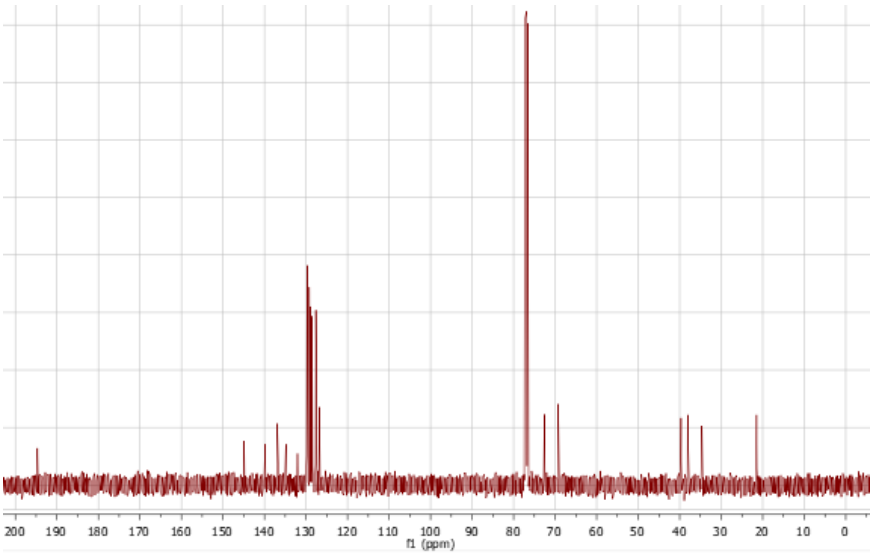

Figure 4.30: ^{13}C NMR Spectrum of Compound **11A**.

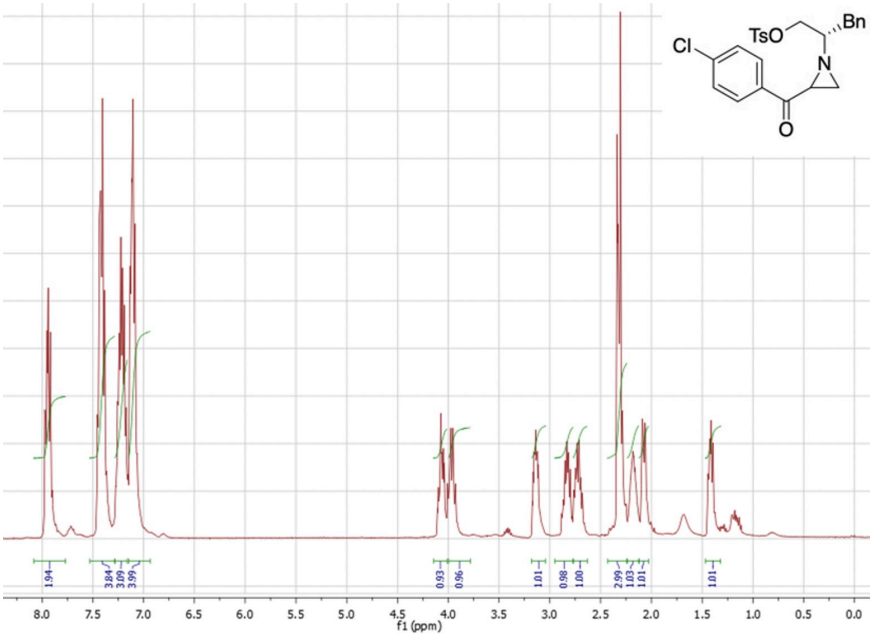

Figure 4.31: ^{1}H NMR Spectrum of Compound **11B**.

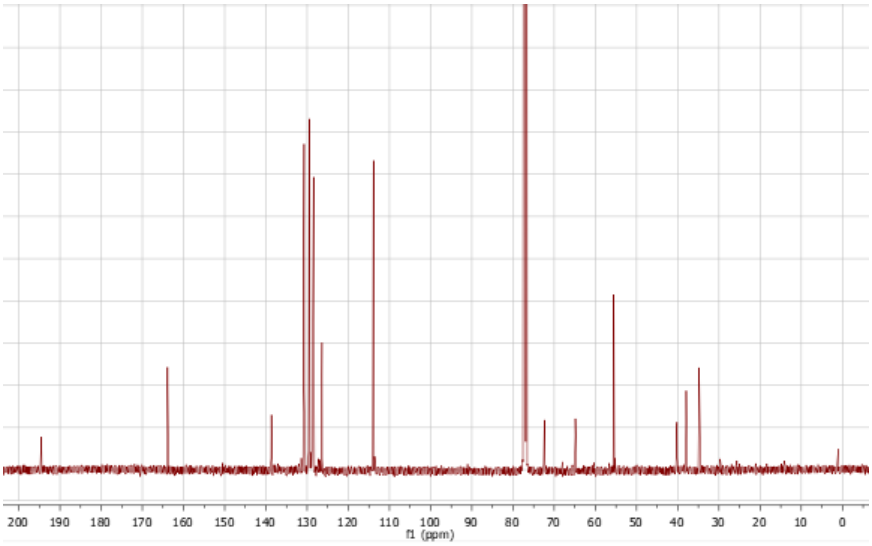

Figure 4.32: ^{13}C NMR Spectrum of Compound **11B**.

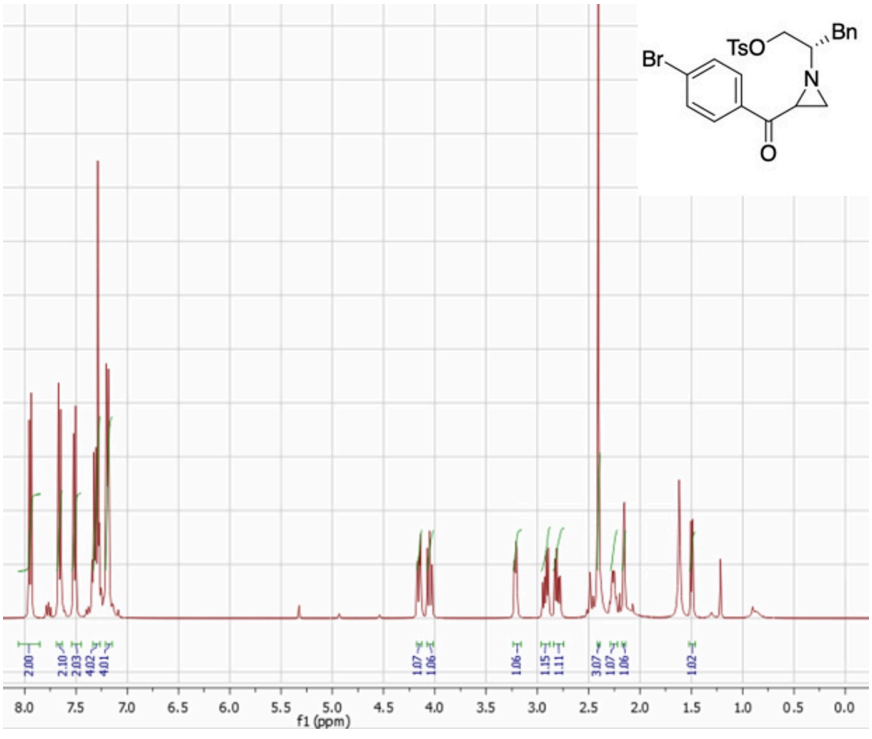

Figure 4.33: ^{1}H NMR Spectrum of Compound **12A**.

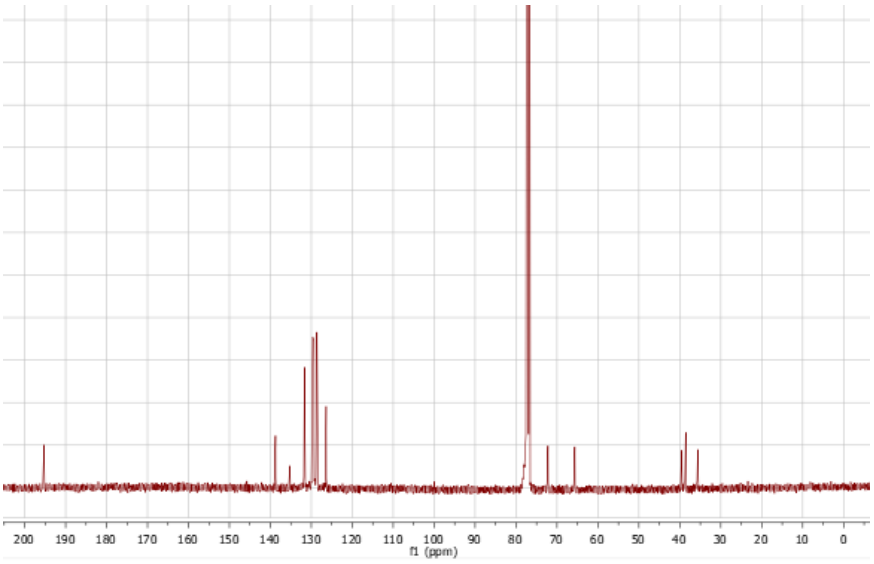

Figure 4.34: ^{13}C NMR Spectrum of Compound **12A**.

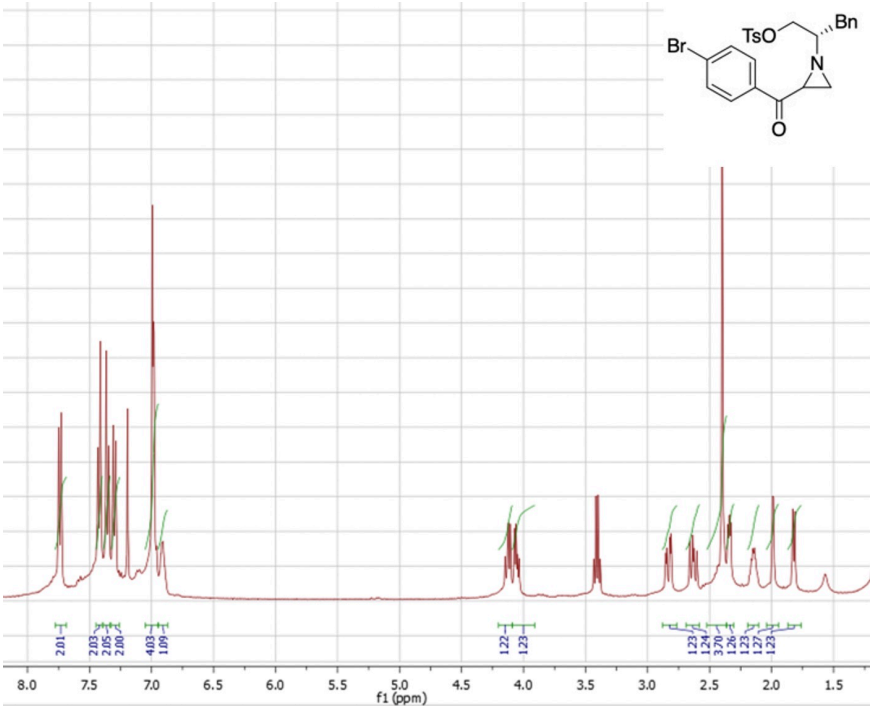

Figure 4.35: ^{1}H NMR Spectrum of Compound **12B**.

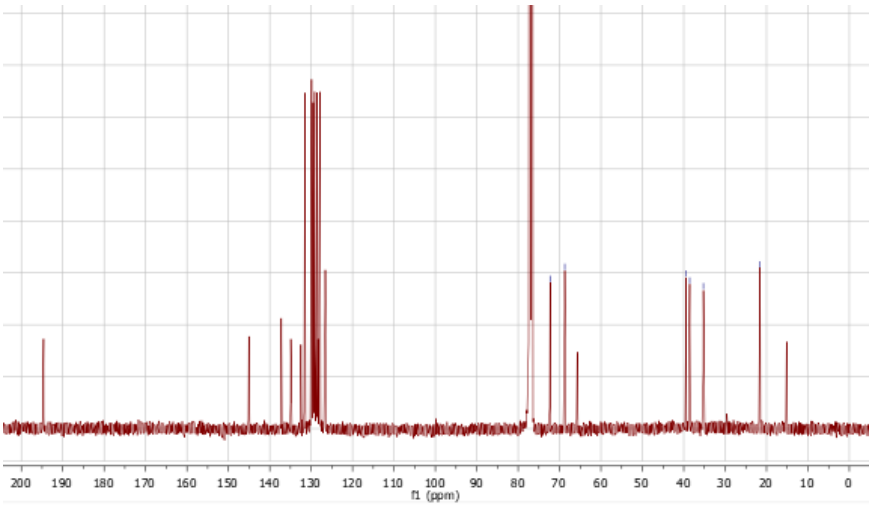

Figure 4.36: ^{13}C NMR Spectrum of Compound **12B**.

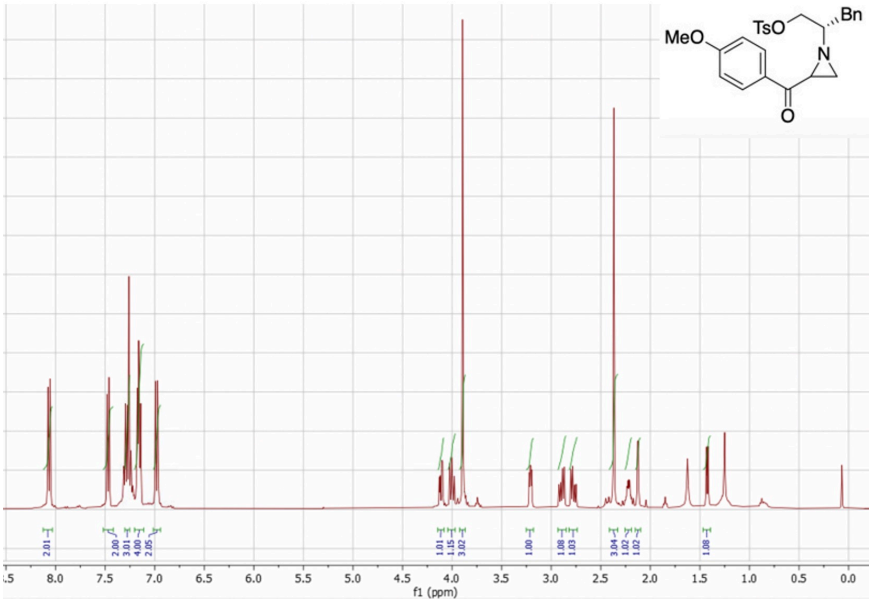

Figure 4.37: ^{1}H NMR Spectrum of Compound **13A**.

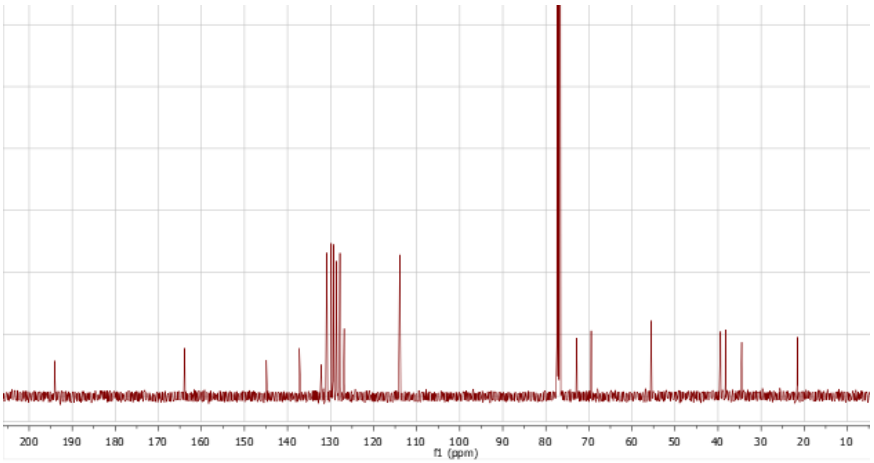

Figure 4.38: ^{13}C NMR Spectrum of Compound **13A**.

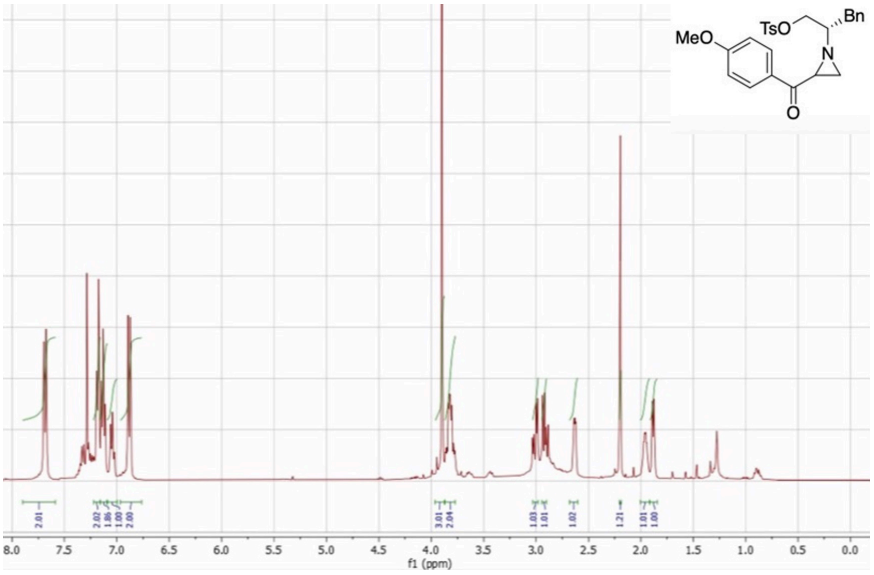

Figure 4.39: ^{1}H NMR Spectrum of Compound **13B**.

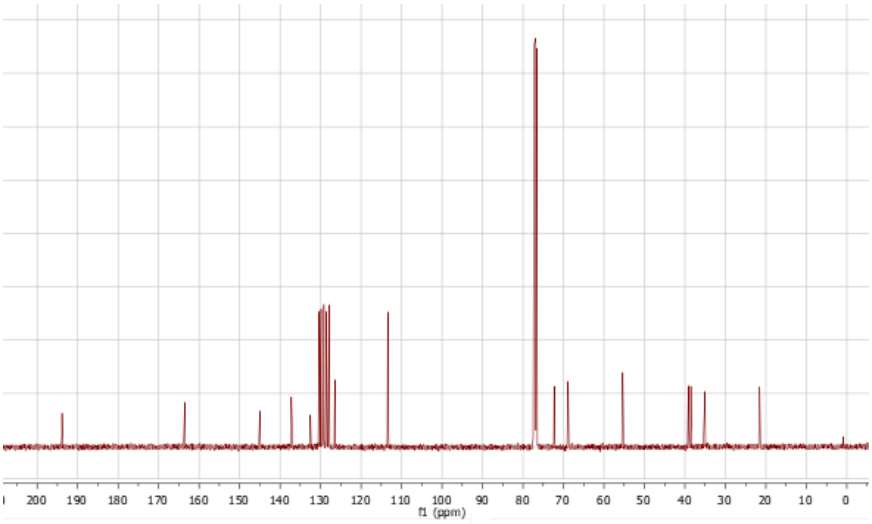

Figure 4.40: ^{13}C NMR Spectrum of Compound **13B**.

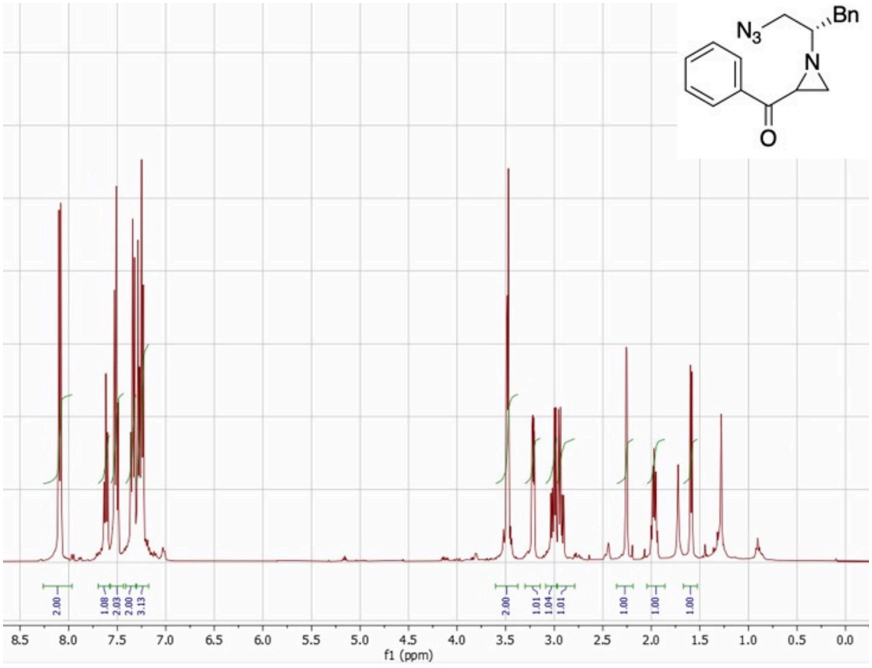

Figure 4.41: ^{1}H NMR Spectrum of Compound **14A**.

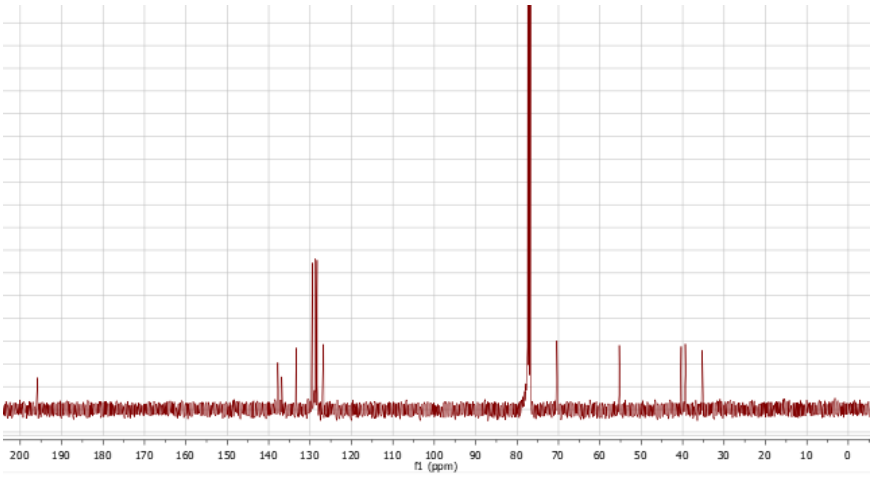

Figure 4.42: ^{13}C NMR Spectrum of Compound **14A**.

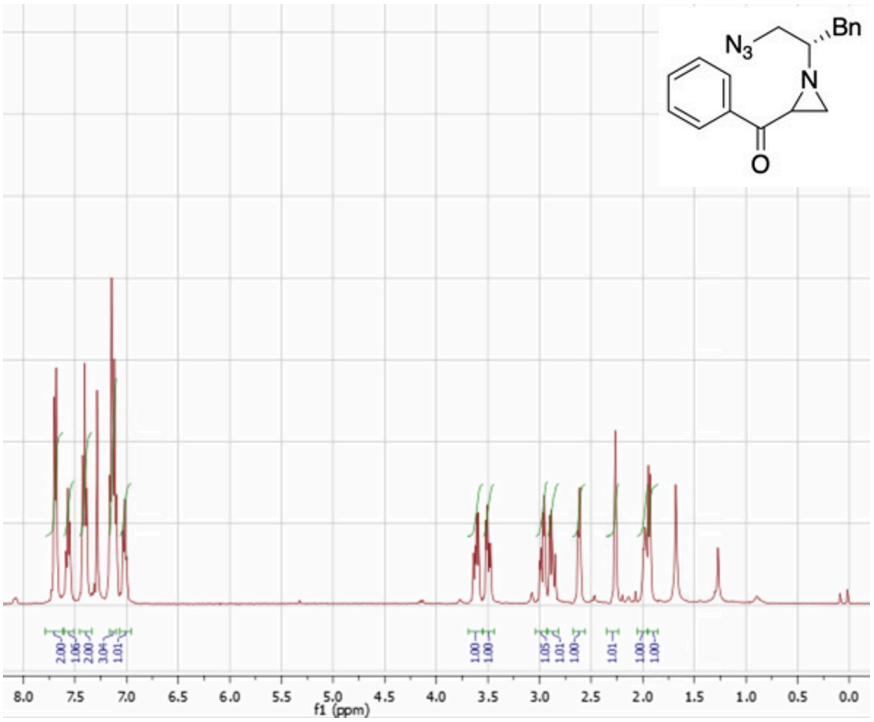

Figure 4.43: ^{1}H NMR Spectrum of Compound **14B**.

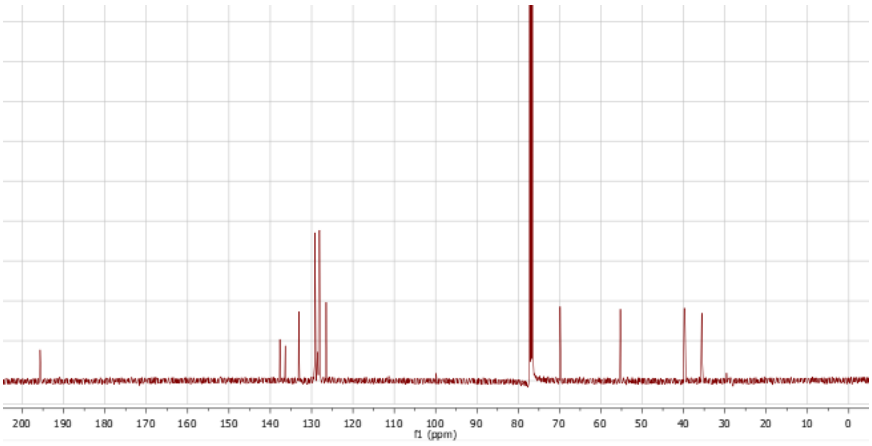

Figure 4.44: ^{13}C NMR Spectrum of Compound **14B**.

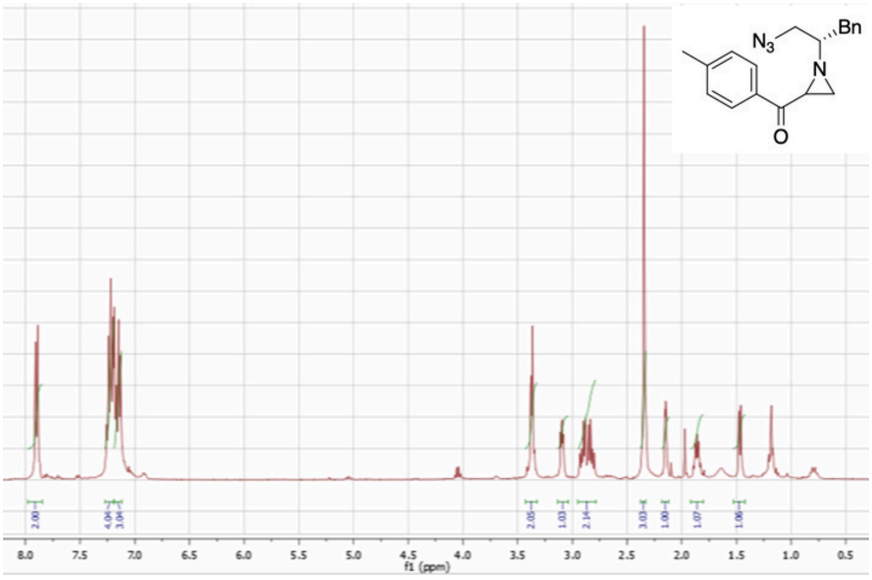

Figure 4.45: ^{1}H NMR Spectrum of Compound **15A**.

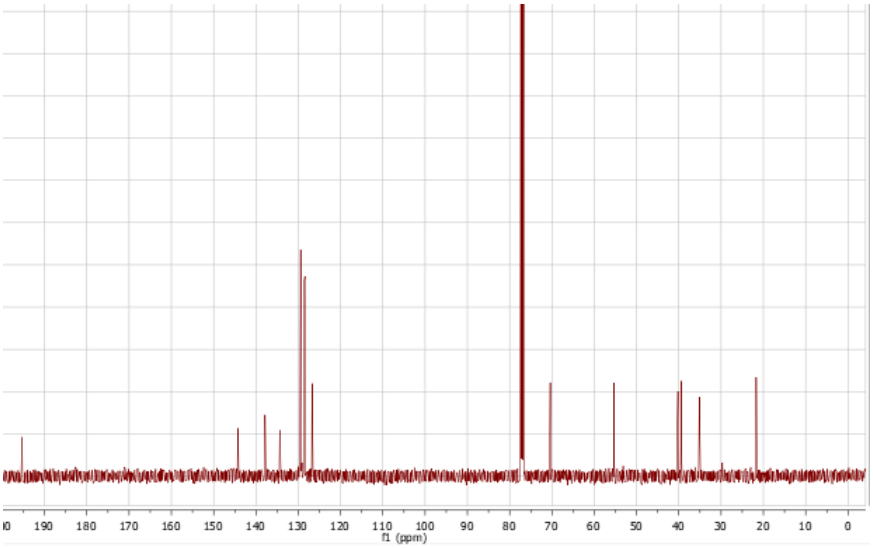

Figure 4.46: ^{13}C NMR Spectrum of Compound **15A**.

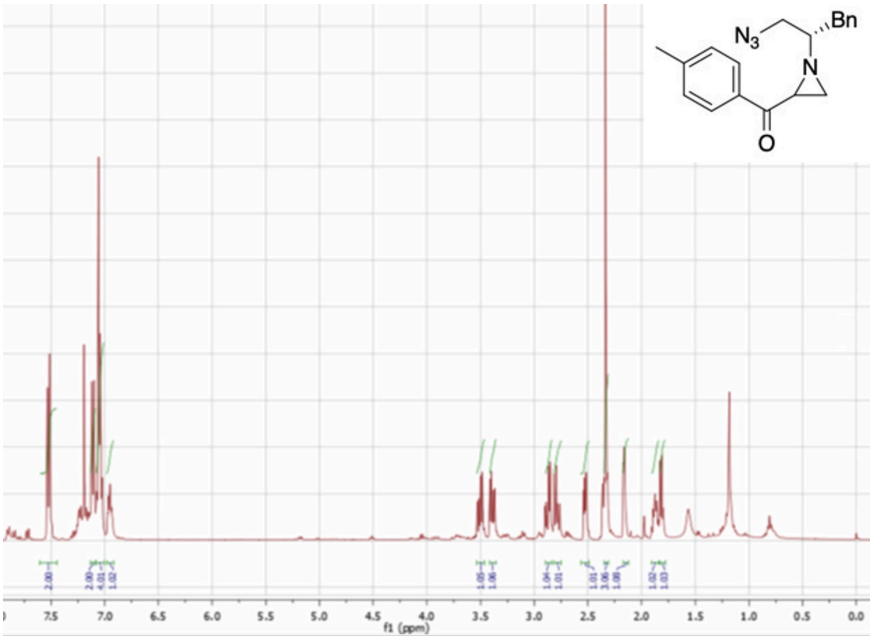

Figure 4.47: ^{1}H NMR Spectrum of Compound **15B**.

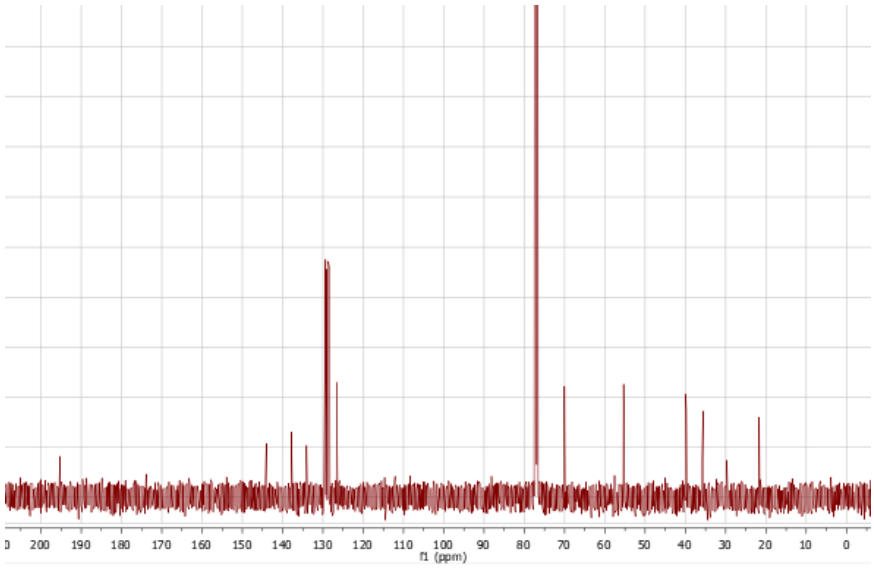

Figure 4.48: ^{13}C NMR Spectrum of Compound **15B**.

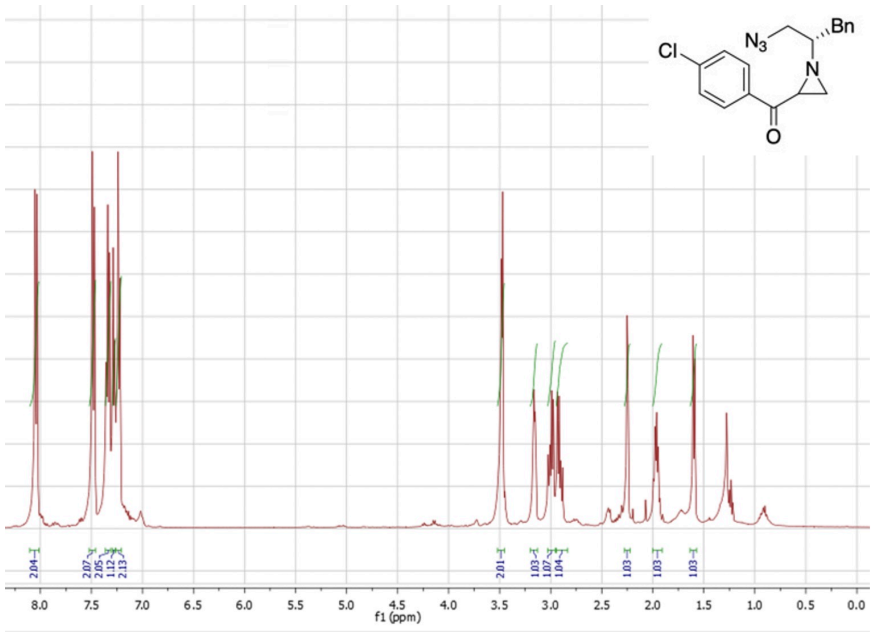

Figure 4.49: ^{1}H NMR Spectrum of Compound **16A**.

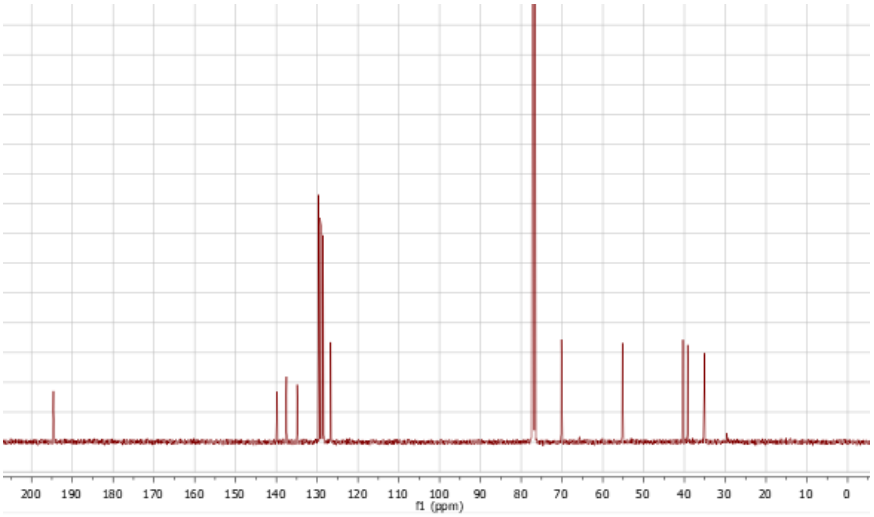

Figure 4.50: ^{13}C NMR Spectrum of Compound **16A**.

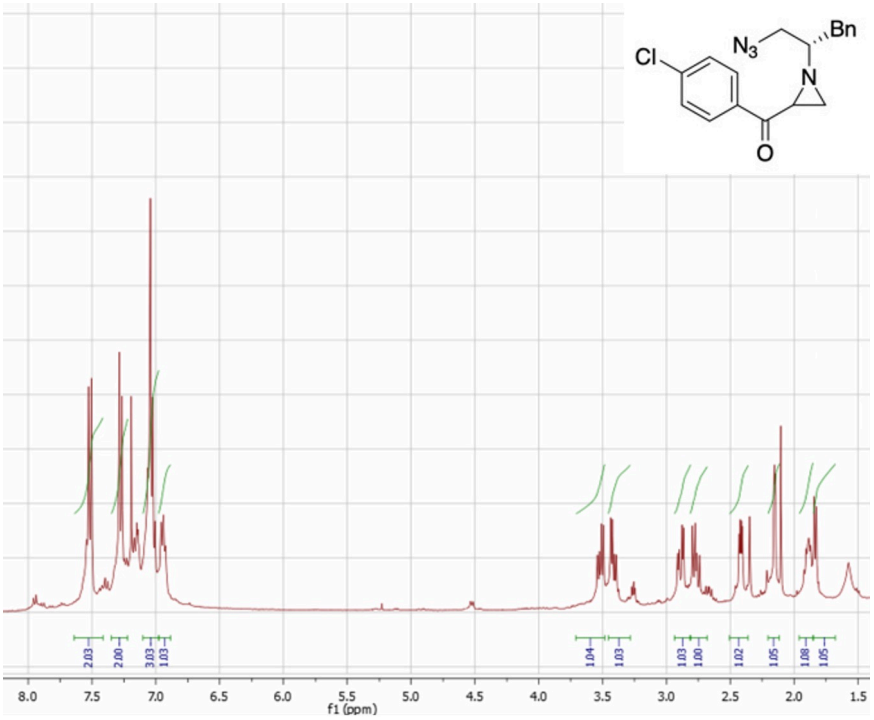

Figure 4.51: ^{1}H NMR Spectrum of Compound **16B**.

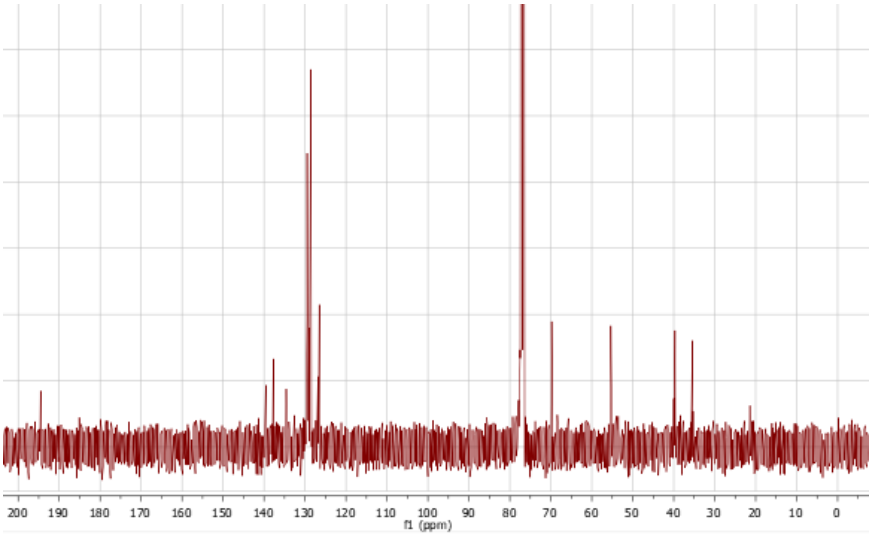

Figure 4.52: ^{13}C NMR Spectrum of Compound **16B**.

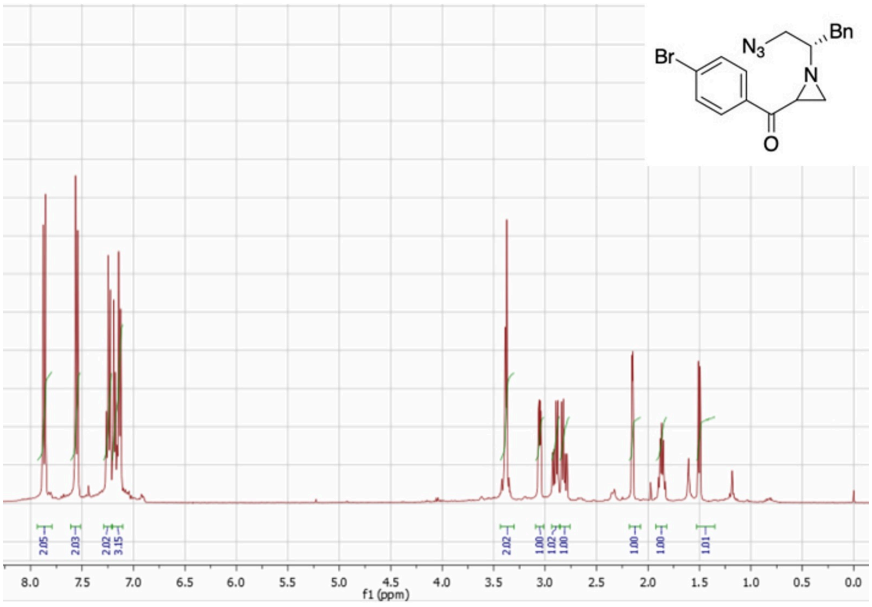

Figure 4.53: ^{1}H NMR Spectrum of Compound **17A**.

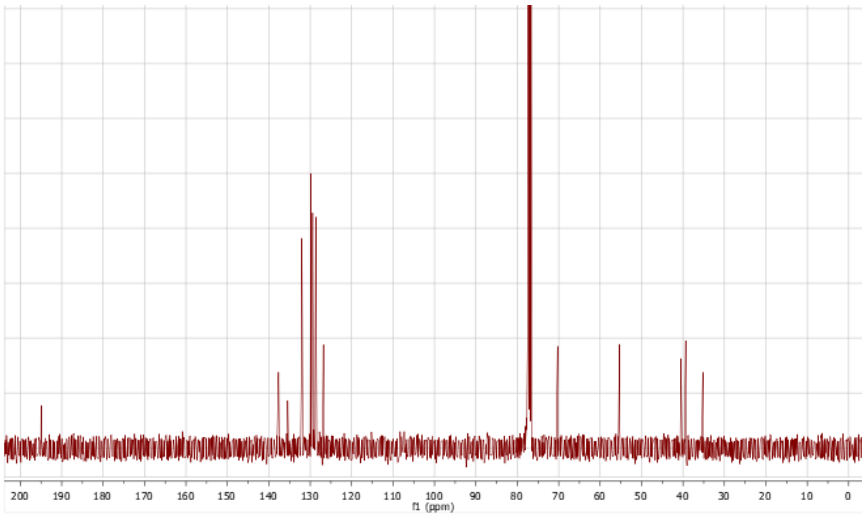

Figure 4.54: ^{13}C NMR Spectrum of Compound **17A**.

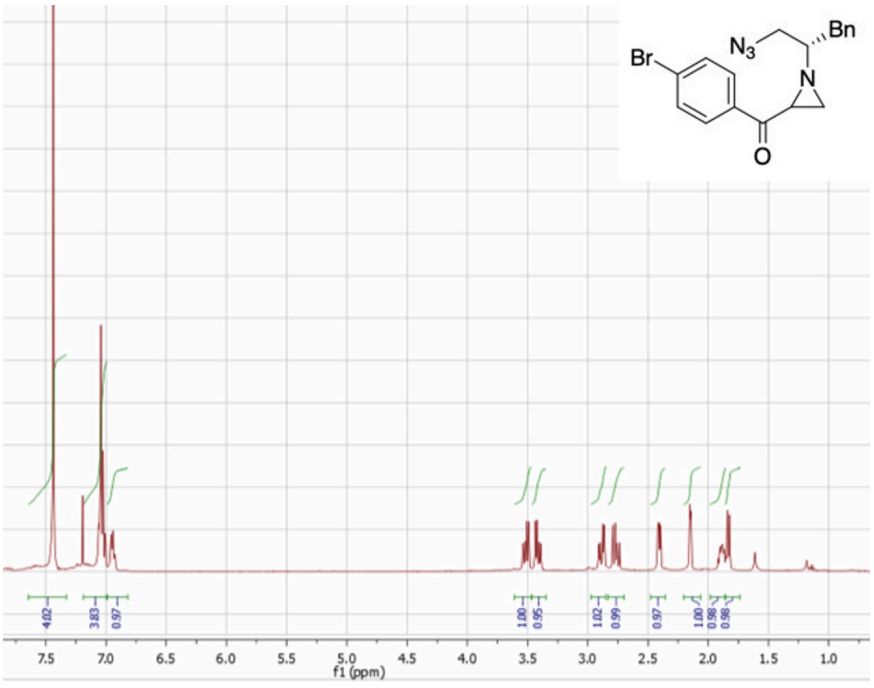

Figure 4.55: ^{1}H NMR Spectrum of Compound **17B**.

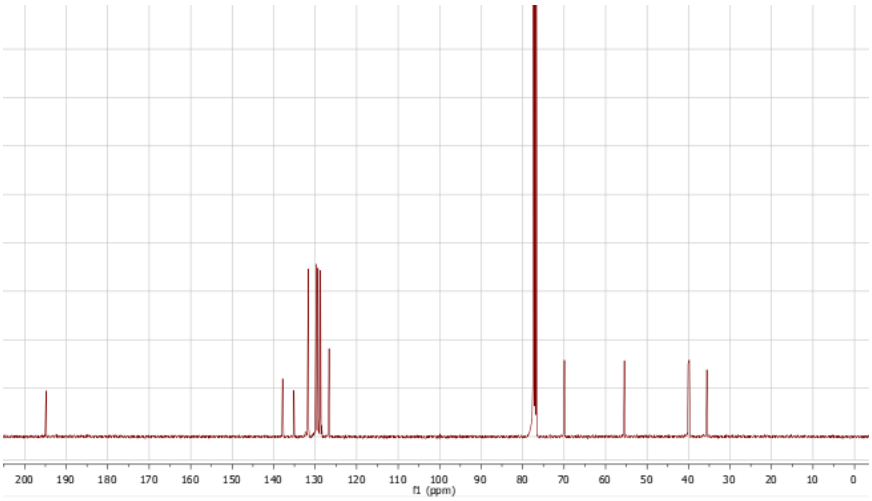

Figure 4.56: ^{13}C NMR Spectrum of Compound **17B**.

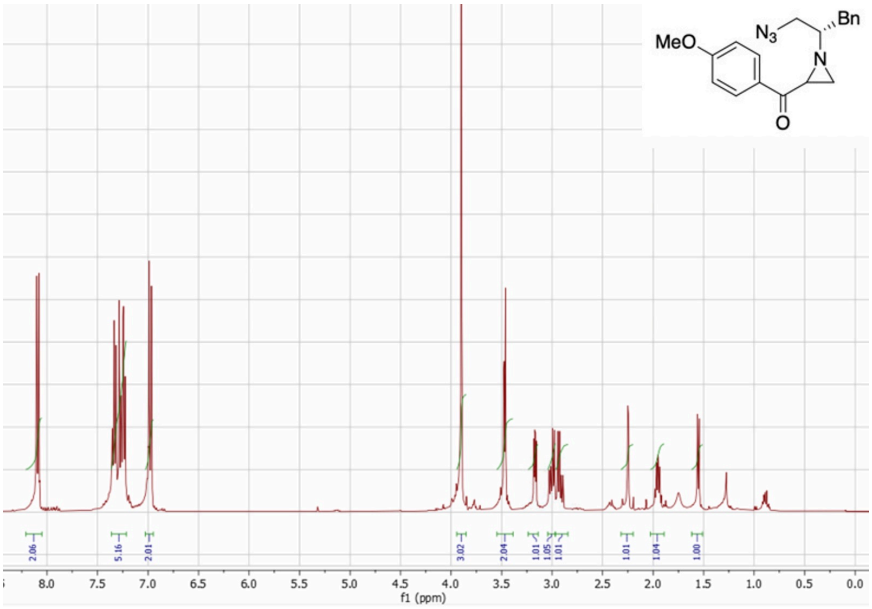

Figure 4.57: ^{1}H NMR Spectrum of Compound **18A**.

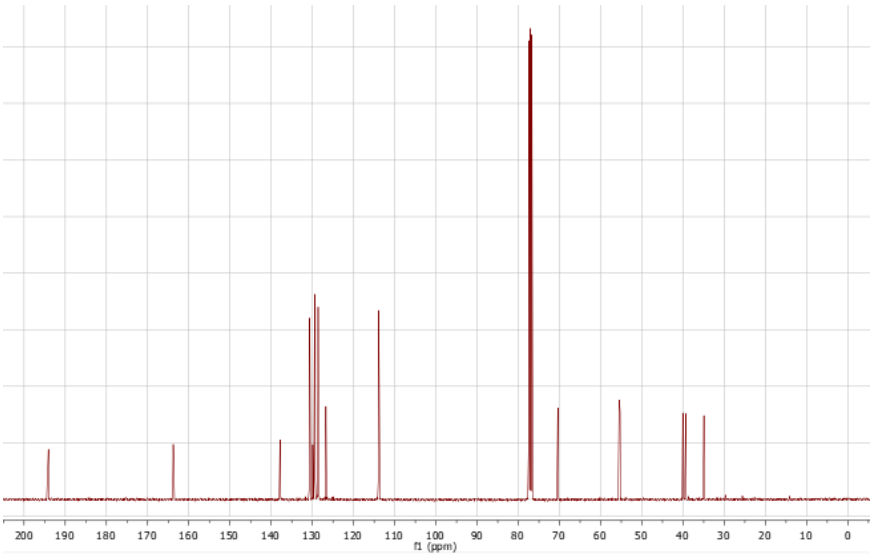

Figure 4.58: ^{13}C NMR Spectrum of Compound **18A**.

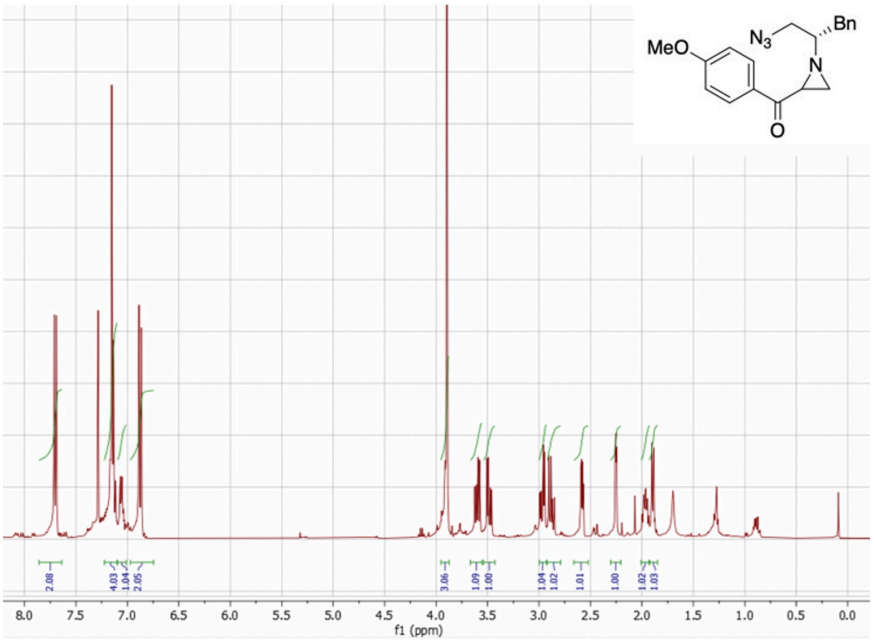

Figure 4.59: ^{1}H NMR Spectrum of Compound **18B**.

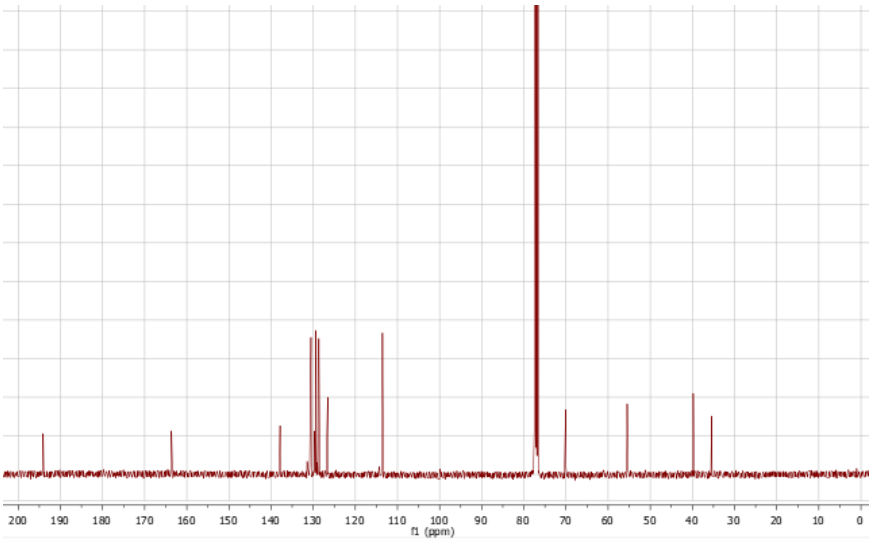

Figure 4.60: ^{13}C NMR Spectrum of Compound **18B**.

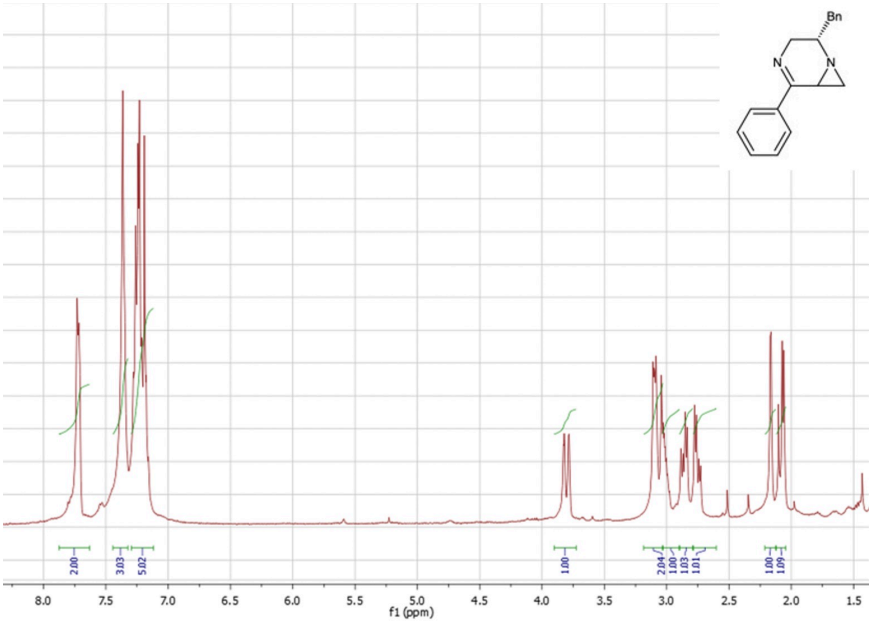

Figure 4.61: ^{1}H NMR Spectrum of Compound **19A**.

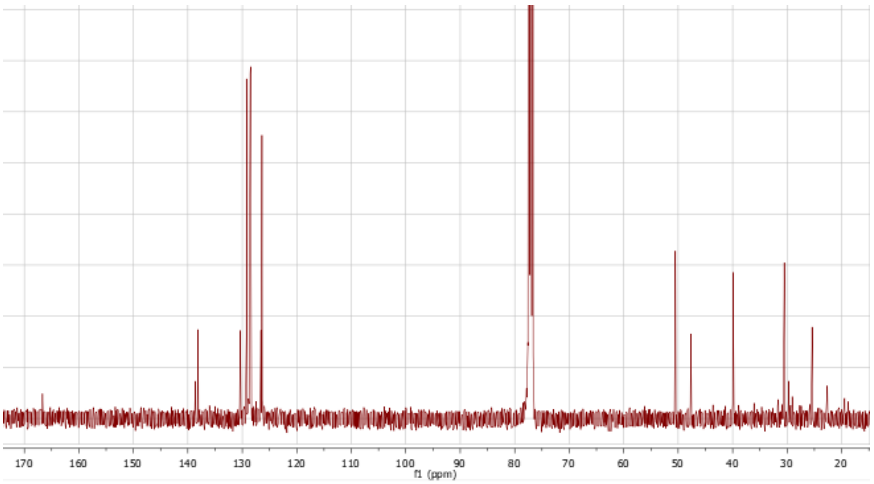

Figure 4.62: ^{13}C NMR Spectrum of Compound **19A**.

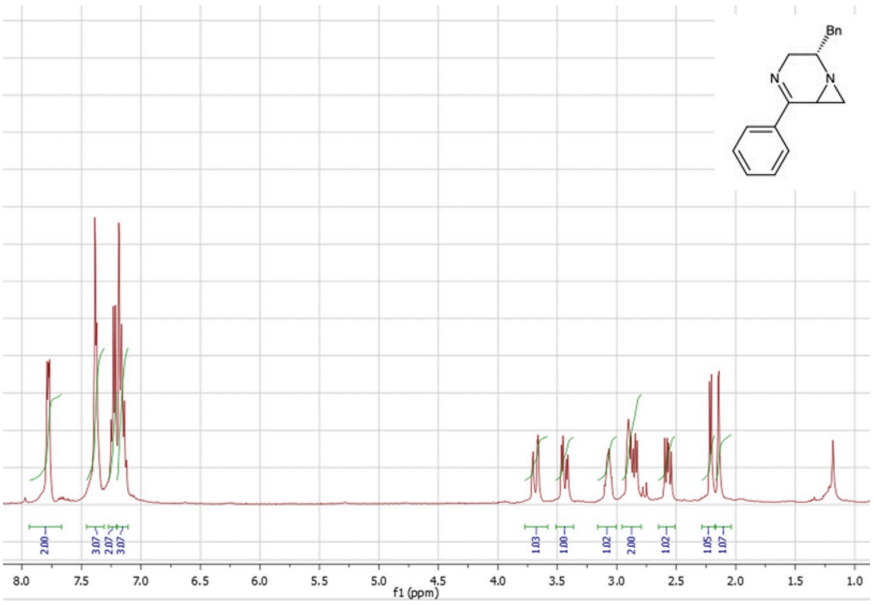

Figure 4.63: ^{1}H NMR Spectrum of Compound **19B**.

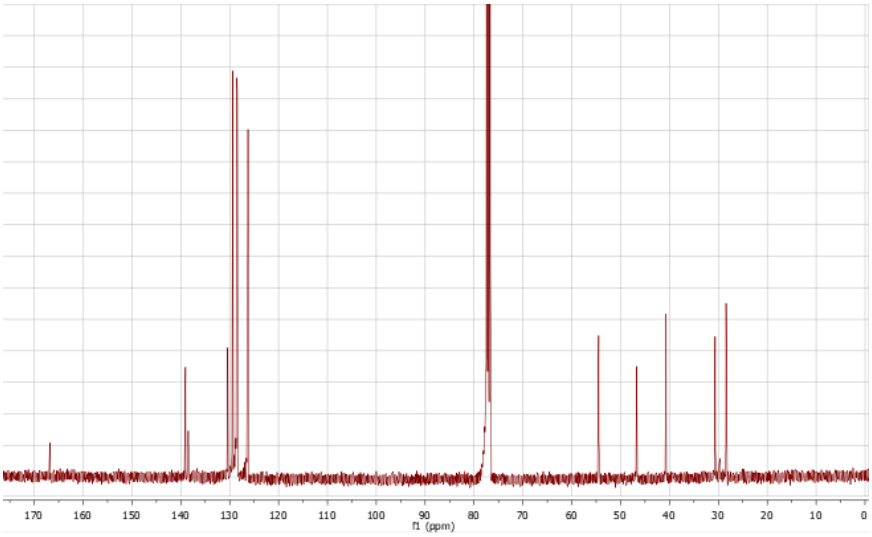

Figure 4.64: ^{13}C NMR Spectrum of Compound **19B**.

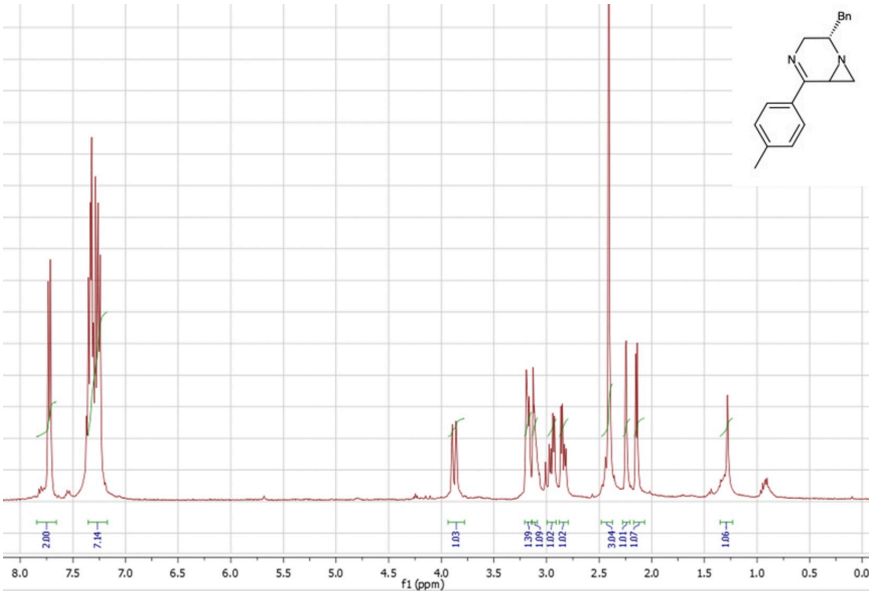

Figure 4.65: ^{1}H NMR Spectrum of Compound **20A**.

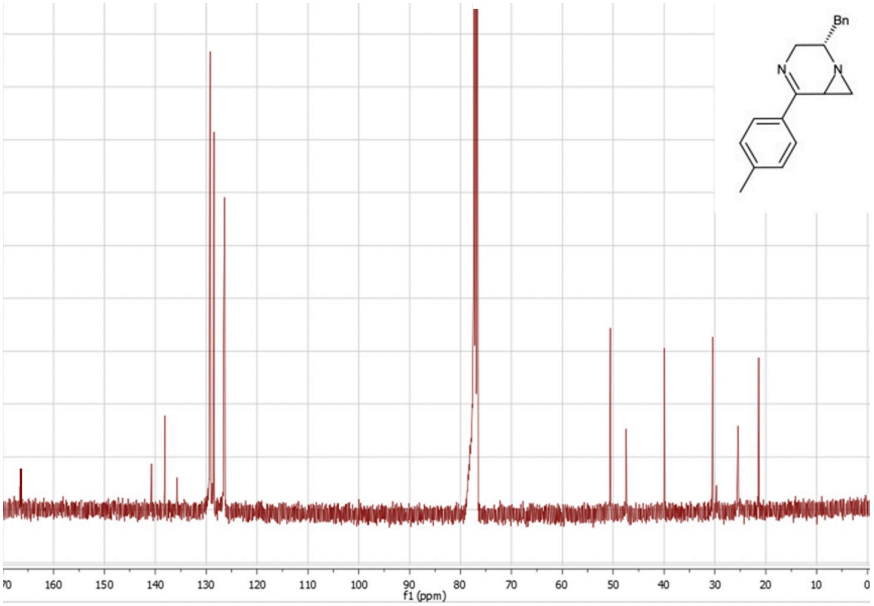

Figure 4.66: ^{13}C NMR Spectrum of Compound **20A**.

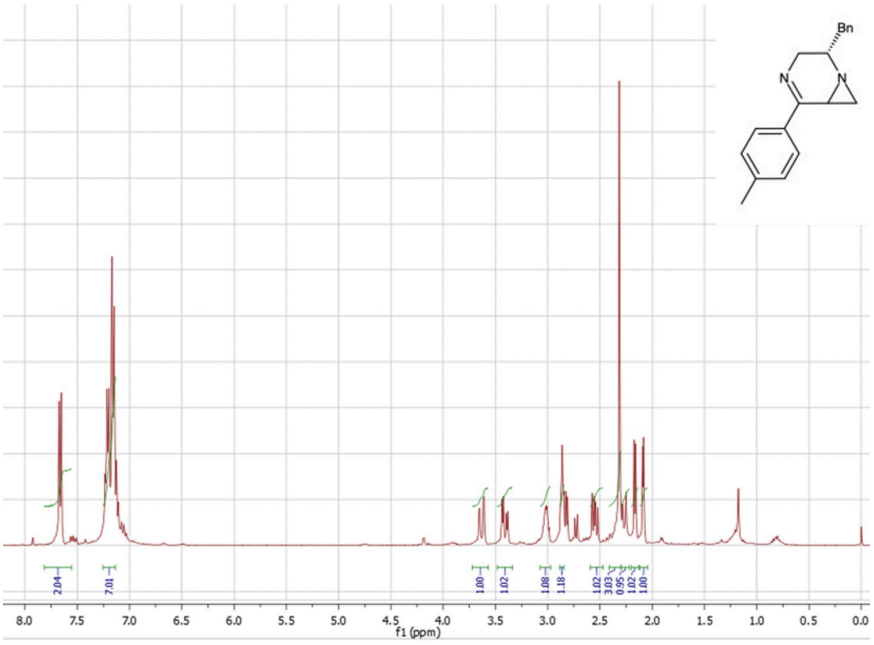

Figure 4.67: ^{1}H NMR Spectrum of Compound **20B**.

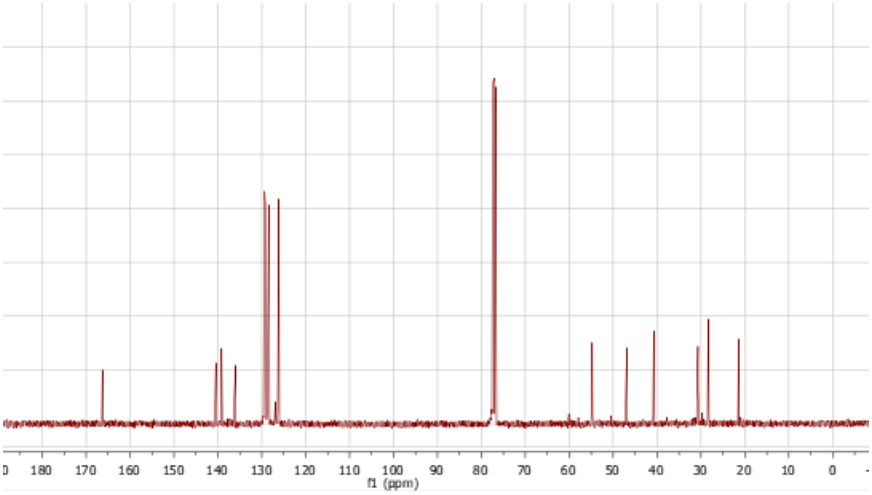

Figure 4.68: ^{13}C NMR Spectrum of Compound **20B**.

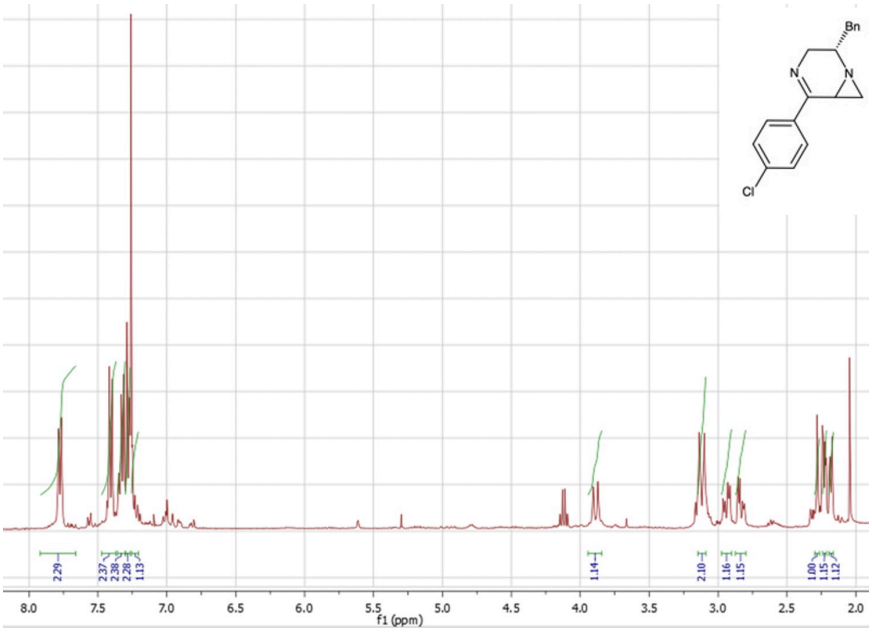

Figure 4.69: ^{1}H NMR Spectrum of Compound **21A**.

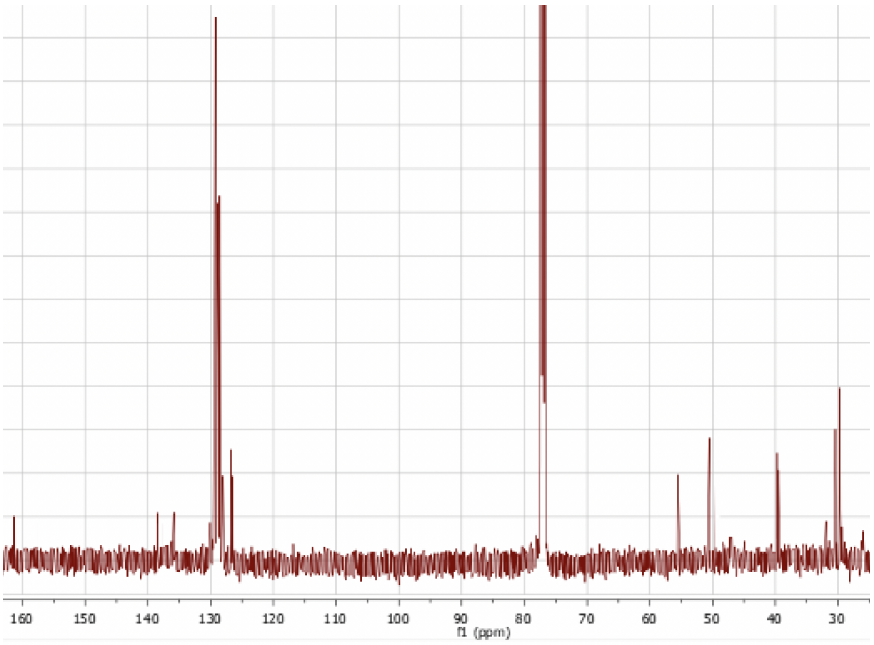

Figure 4.70: ^{13}C NMR Spectrum of Compound **21A**.

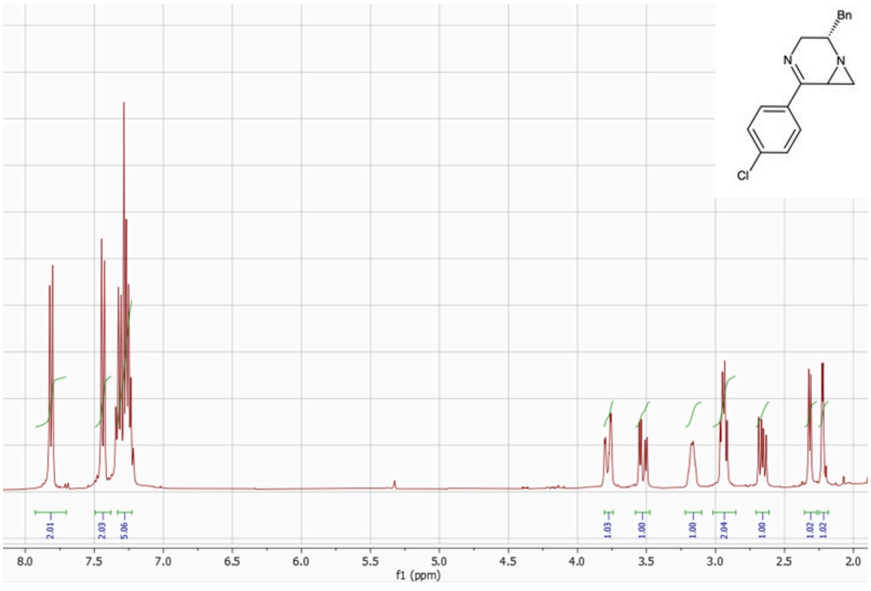

Figure 4.71: ^{1}H NMR Spectrum of Compound **21B**.

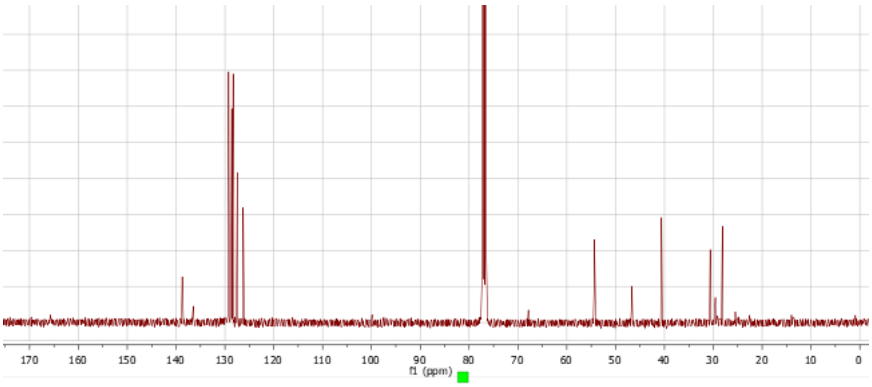

Figure 4.72: ^{13}C NMR Spectrum of Compound **21B**.

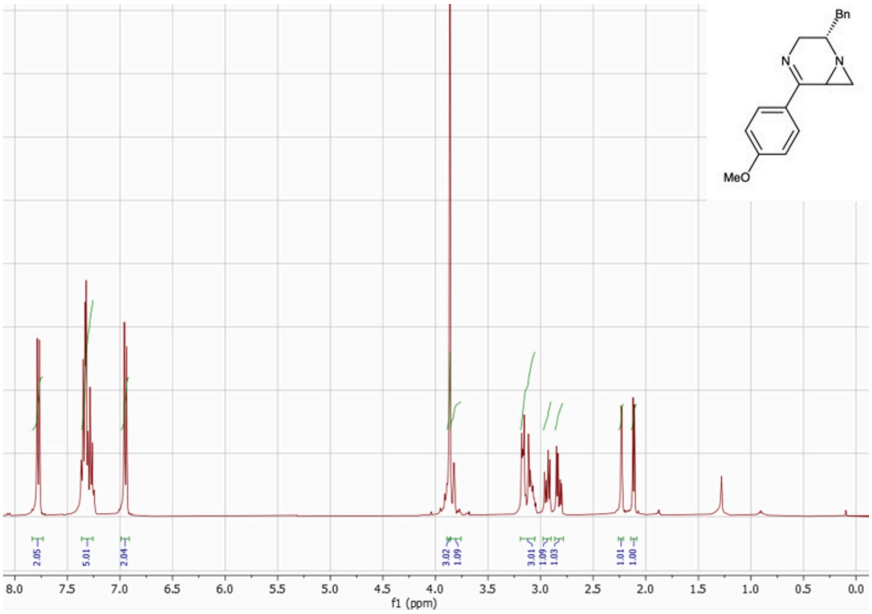

Figure 4.73: ^{1}H NMR Spectrum of Compound **22A**.

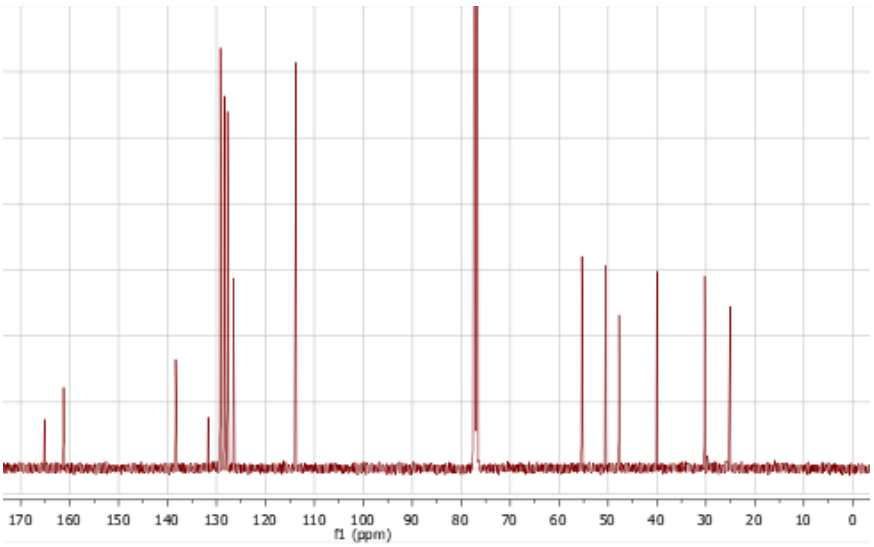

Figure 4.74: ^{13}C NMR Spectrum of Compound **22A**.

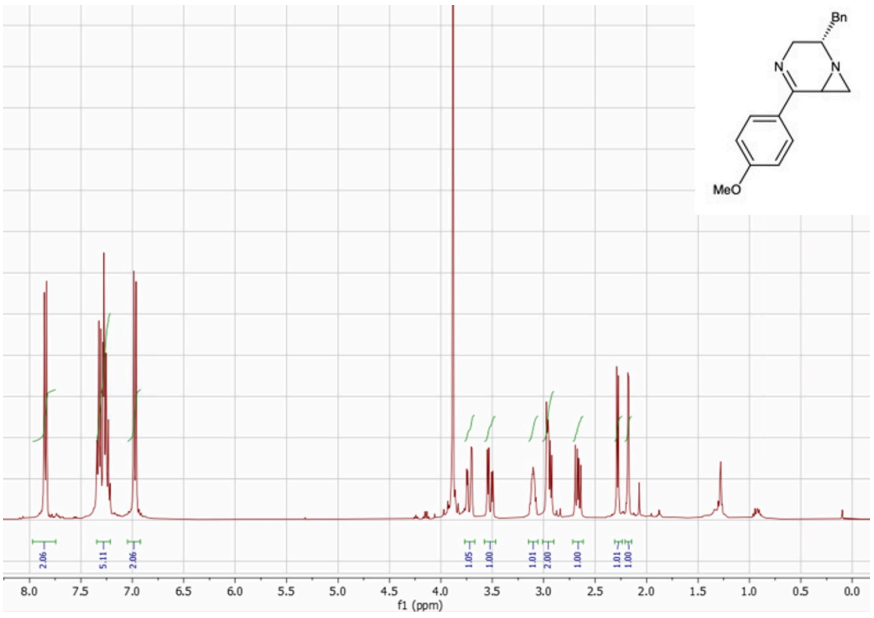

Figure 4.75: ^{1}H NMR Spectrum of Compound **22B**.

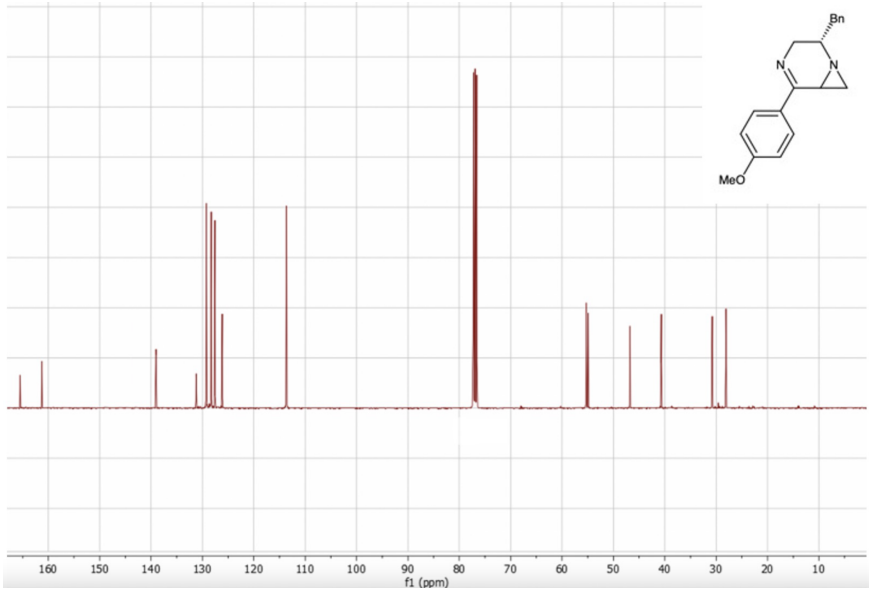

Figure 4.76: ^{13}C NMR Spectrum of Compound **22B**.