SYNTHESIS OF IMIDAZOLINES FROM AZIRIDINES

By

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Chemistry

2010

ABSTRACT

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The majority of the work in this thesis presents a new method to syntheisize imidazolines from both chiral and racemic aziridines. The purpose of synthesizing such heterocycles was for there known biological activity. Previous research in the Tepe group has developed a method to diastereoselectively synthesize racemic imidazolines from the trimethyl silyl chloride mediated (3 +2) cycloaddition of imines with azlactones. This methodology allowed access to variety of imidazolines that have been shown to inhibit NF-κB mediated gene transcription. An SAR study has been conducted in our research group on this class of compounds. The ability of the imidazolines to inhibit NF-κB mediated gene transcription was measured by human cervical epithelial (HeLa) cells and human whole blood. The result of these studies has determined which functional groups were essential for efficient inhibition of NF-κB. These studies have also determined that one imidazoline enantiomer was much more potent inhibitor than the other. Although our research group has created a diastereoselective method to synthesize imidazolines there was still not a method to synthesize chiral imidazolines. Due to the cost, time, and inefficiencies of separation of racemic imidazolines by chiral HPLC and resolution an enatioselective method was needed. This thesis represents the progress towards an enantioselective synthesis of imidazolines.

This thesis is dedicated to my parents Sandra Kuszpit and Kenneth Kuszpit. They have always supported me in everything I have pursued in my life.

ACKNOWLEDGEMENTS

I would like to thank my father, Ken Kuszpit, and my mother Sandy Kuszpit. I would also like to thank my brother, Greg Kuszpit, for his support and love. I wish also to thank my old friends and the new friendships that I have made during my time here at Michigan State University. I would not have been successful without the support and encouragement from my new friends that I have made during my graduate studies here. I would also like to thank my girlfriend, Beth Girnys, for standing by me in both the good and the bad times of graduate school.

I would like to express my gratitude to my graduate advisor, Dr. Jetze J. Tepe, for giving me the opportunity to conduct research in his group. He took time to listen to my thoughts about my career and my research project. I liked Dr. Tepe's research style, he allowed me to pursue my own ideas and learn from my mistakes. I believe this research style was the best way for me to grow as a scientist.

I would also like to thank my advisory committee Dr. Aaron Odom, Dr. James Jackson, and Dr. William Wulff. Of my advisory committee I would like to especially thank Dr. Wulff. The research in this thesis has been done in collaboration with Dr. Wulff. He provided me with the knowledge of aziridine chemistry carried out in his research group. In addition Dr. Wulff provided me with the catalysts necessary to conduct my research and his door was always open whenever I had questions.

I would also like to acknowledge Munmun Mukherjee, Aman Desai, and Anil Kumar Gupta they were extremely helpful to me in answering the questions I had about

aziridine chemistry. I would also like to show my appreciation to Tom Jurek, Sarah Marshall, and Aman Kulshrestha they were also very helpful. Finally, I would like to express my graditude to current and former members of the Tepe group for their help and support, particularly Dr. Jason Fisk, Brandon Dutcher, Rahmen Saleem, Dr. Adam Mosey, and Dr. Daljinder Kahlon.

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LIST OF SYMBOLS AND ABBREVIATIONS

Bh- Benzhydryl

DABCO- 1,4-diazabicyclo[2.2.2]octane

DCE- Dichloroethane

DCM- Dichloromethane

DMAP- 4-dimethylamino pyridine

DME- Dimethoxy ethane

DMF- Dimethyl formamide

DMSO- Dimethyl sulfoxide

EC50- Half maximal effective concentration

EDCI- Ethyldimethylaminopropyl carbodiimide

HeLa- Human cervical epithelial

HRMS- High resolution mass spectrometry

I-κB- Inhibitory kappa B

LA- Lewis Acid

MSOH- Methanesulfonic acid

NBS- N-Bromosuccinimide

NCS- N-Chlorosuccinimide

NIS- N-Iodosuccinimide

NF-κB- Nuclear transcription factor kappa B

SAR- Structure activity relationship

TfOH- Triflic acid

THF- Tetrahydrofuran

TNF-α- Tumor necrosis factor alpha

Ts- Tosyl

$TMSN_3$- Trimethyl silyl Azide

TMSCl- Trimethyl silyl chloride

TEA- Triethyl amine

CHAPTER 1

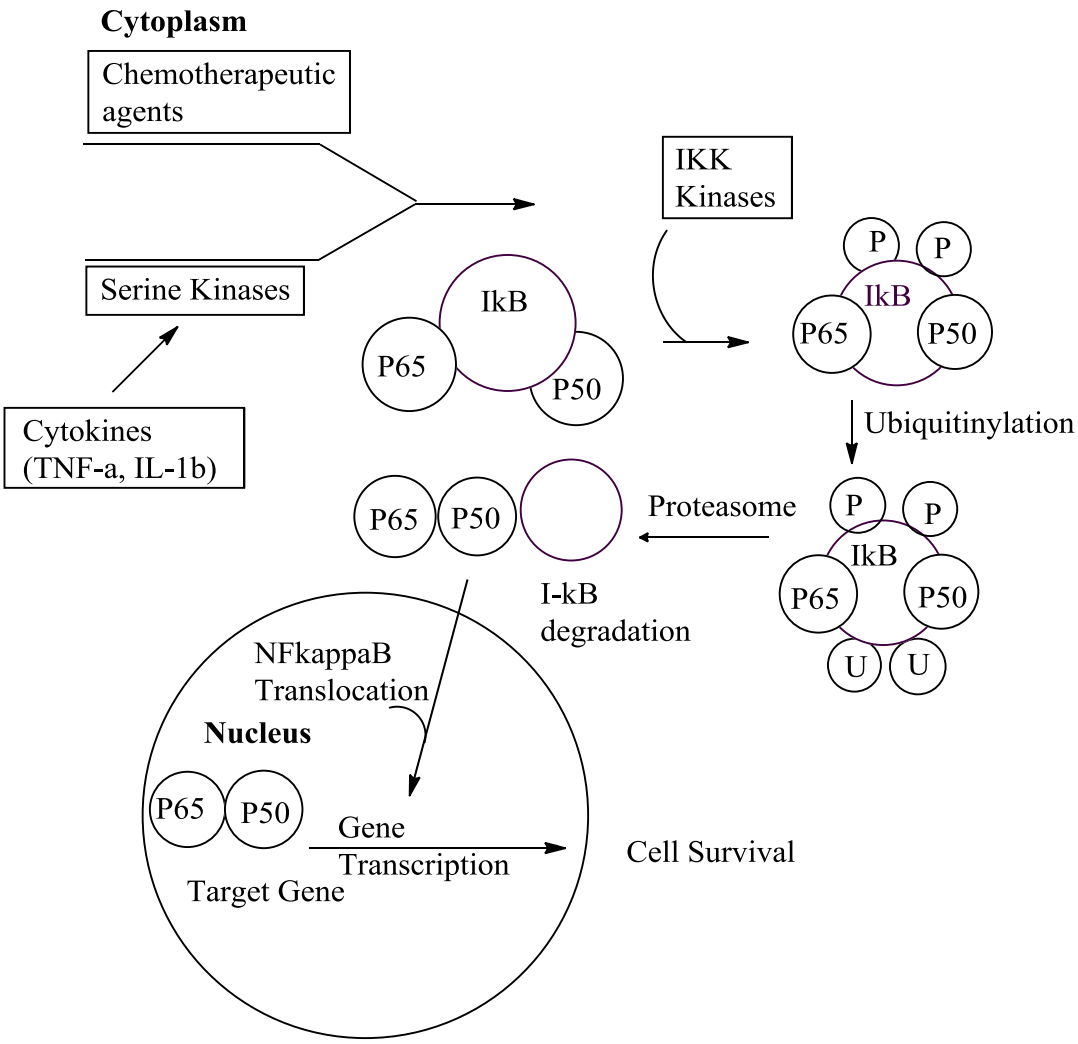
INHIBITION OF NF-κB GENE TRANSCRIPTION BY IMIDAZOLINES

Apoptosis (programmed cell death) is a defense defensive mechanism to remove infected, mutated, or damaged cells.[1] Traditional cancer treatment uses ionizing radiation or chemotherapy to induce apoptosis in cancer cells.[1] One example is Camptothecin which is a DNA topoisomerase I inhibitor and induces a stable ternary topoisomerase I-DNA cleavable complex.[1] This complex is recognized as damaged DNA and initiates a programmed cell death signaling pathway.[1] Another chemotherapy drug, Cisplatin, covalently bonds to DNA base pairs, which induces a similar signaling pathway to that of camptothecin.[1] Unfortunately, Camptothecin and Cisplatin also initiate DNA repair signaling pathways.[1] Cellular resistance has been the result of activation of anti-apoptotic (cell survival) signaling pathways. One of the cell survival pathways activated by Camptothecin and Cisplatin is NF-κB, and as a result the efficacy of chemotherapy is reduced.

NF-κB is a mammalian transcription factor responsible for the regulation of many genes,[2-3] such as those associated with stress,[4] inflammatory stimuli,[5] anti-apoptosis,[6] and apoptosis.[7] Misregulation of NF-κB mediated gene transcription is associated with many diseases, such as rheumatoid arthritis,[8] inflammatory bowel disease,[9-11] and cancer.[12-13] In most mammalian cells, NF-κB exists as either a p50/p50 homodimer or a

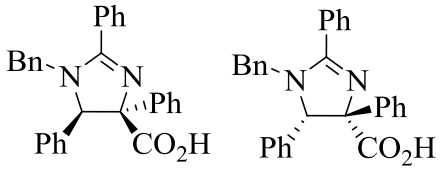
p50/p65 heterodimer. In non-stimulated normal cells, NF-κB is located in the cytoplasm and bound by I-κB.[14] The NF-κB pathway can be activated by the correct extracellular signal, such as cytokines TNF-α and IL-1ß, as seen in scheme 1-1.[3,5,15-17] IKK kinases phosphorylate I-κB on serine residues 32 and 36,[18-19] followed by ubiquitinylation and degradation of I-κB by the 26S proteosome.[20-21] After degradation of I-κB, NF-κB is released and allows for its translocation into the nucleus.[22] Inside the nucleus, NF-κB binds to various DNA control elements and initiates gene transcription and thus cell survival (Scheme 1-1).[23-26]

New chemotherapeutic methods have moved towards a combination of inducers of apoptosis and inhititors of cancer cell survival pathways. There has been a search for small molecules that can either selectively induce apoptosis or inhibit cell survival pathways in cancer cells to prevent cellular chemoresistance.[1] One focus of the Tepe group has been the development of inhibitors of cancer cell survival pathways to improve traditional chemotherapy. The Tepe group has created small molecule imidazolines, which have been shown to inhibit the cancer cell survival signaling pathway mediated by NF-κB.[1,23-24] Therefore, imidazolines inhibit the NF-κB pathway, resulting in sensitization of cancer cells to chemotherapeutic agents like Camptothecin, and subsequent reduction of chemoresistance.[1,23-24]



Scheme 1-1: Activation of NF-κB Pathway

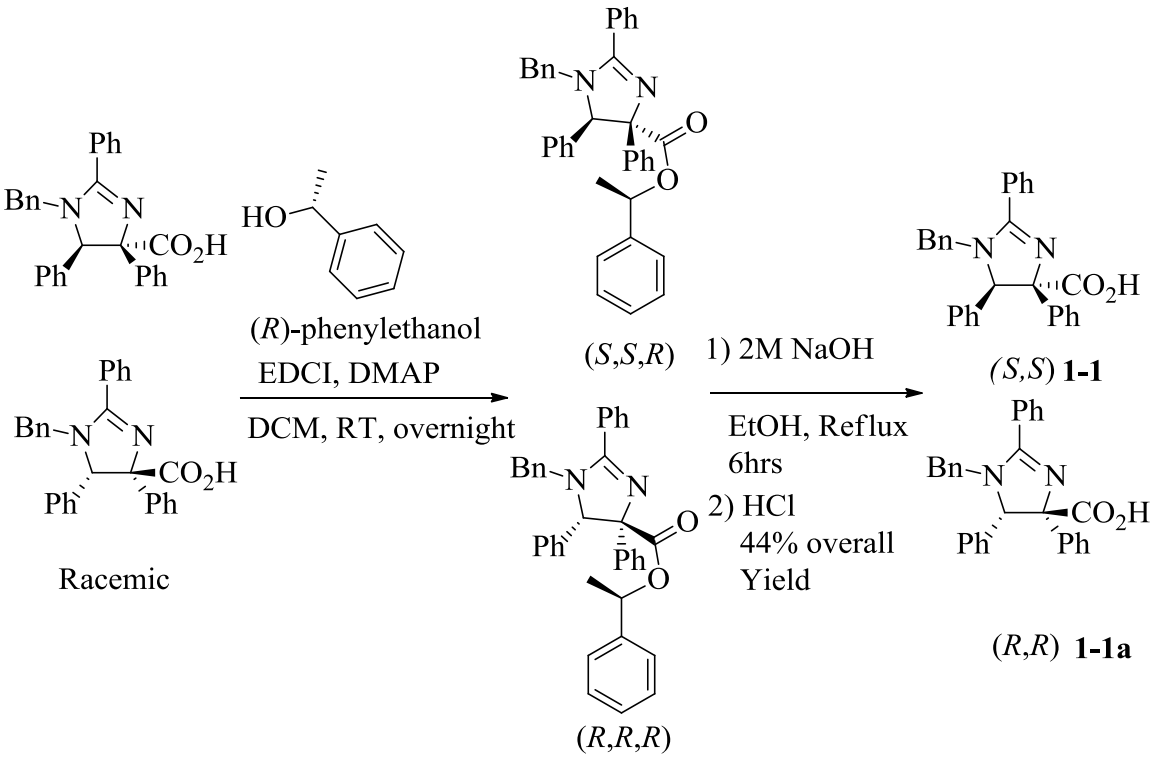
The Tepe lab has prepared a class of imidazoline scaffolds as potent inhibitors of NF-κB mediated gene transcription. Inhibition of NF-κB has been shown to proceed by modulation of I-κB-α degradation by inhibition of the 26S proteasome, although the precise molecular target within the 26S proteasome is still unknown at this time.[1,25] Racemic imidazolines were first developed in our laboratory by a 1,3-dipolar cycloaddition reaction between azlactones and imines.[26] Compounds **1-1** and **1-1a** were shown to be inhibitors of NF-κB.[27]



(*R*,*R*) **1-1**

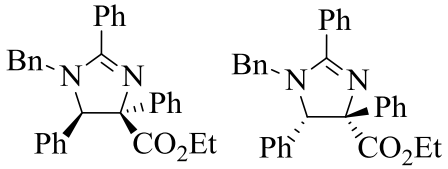
(*S*,*S*) **1-1a**

Previously, the two enantiomers have been separated by resolution with R(+)-1-phenylethanol to yield two diastereomeric esters. The esters were then separated by column chromatography and the resolving agent was removed to yield each pure enantiomer (Scheme 1-2).[27]



Scheme 1-2: Resolution of Compounds **1-1** and **1-1a**.[1]

Resolution of the enantiomers of compound **1-1** was also accomplished by transformation of the carboxylic acid of compound **1-1** to the ethyl ester and separation on chiral HPLC. However, only small amounts of the compound could be separated at a time using this method. Since compounds **1-1** and **1-1a** are prone to spontaneous decarboxylation, they were transformed into the ethyl ester.[23,27] The resulting compounds **1-2** and **1-2a** were the lead compounds developed in our lab.[23]



(*R*,*R*) **1-2** EC_{50} = 1.6 μM IC_{50} = 0.6 μM

(*S*,*S*) **1-2a** EC_{50} = 2.9 μM IC_{50} = 0.7 μM

Imidazolines **1-2** and **1-2a** were measured for their ability to inhibit NF-κB mediated gene transcription by using a luciferase based reporter assay in human cervical epithelial (HeLa) cells. Cells were pretreated for 30 minutes with compound **1-2** or **1-2a** (20 to 0.5 μM) followed by treatment with the cytokine TNF-α, which initiated the NF-κB pathway. This caused degradation of I-κB and translocation into the nucleus, where it initiated transcription of genes, including those needed for the production of the enzyme luciferase. Luciferase production was evaluated after 8 hours by a luminometer. From this data the EC_{50} values for compounds **1-2** and **1-2a** were determined to be 1.6 μM and 2.9 μM, respectively.

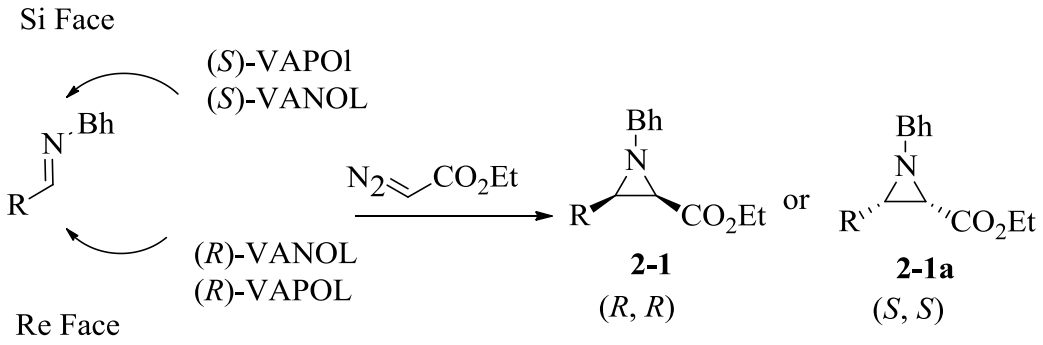
Since the discovery of the lead compounds, an SAR study has shown which functional groups on the imidazoline scaffold were essential for inhibition of NF-κB.[23-24] The Tepe group has also determined that the enantiomers of the lead compound were not equally potent inhibitors of NF-κB. The (*R,R*) enantiomer was a more potent inhibitor of NF-κB mediated gene transcription than the (*S,S*) enantiomer.[12,23] Separation of the enantiomers **1-1** and **1-1a** by resolution or chiral HPLC methods is very expensive and time consuming. Clearly, an enantioselective synthesis of imidazolines would not require the enantiomers to be separated, assuming the enantioselectivity of the reaction was greater than 98% enantiomeric excess (ee) at this time. A new methodology may be able to introduce new functional groups onto the imidazoline scaffold, while still maintaining the proper stereochemistry. The ultimate goal would be to not only synthesize chiral imidazolines, but to synthesize chiral imidazolines that are more potent inhibitors of NF-κB mediated gene transcription than the lead compound. The work in the proceeding chapters show the progress made towards a new methodology to synthesize imidazolines enantioselectively.

CHAPTER 2

ENANTIOSELECTIVE HALOGENATION OF AZIRIDINES

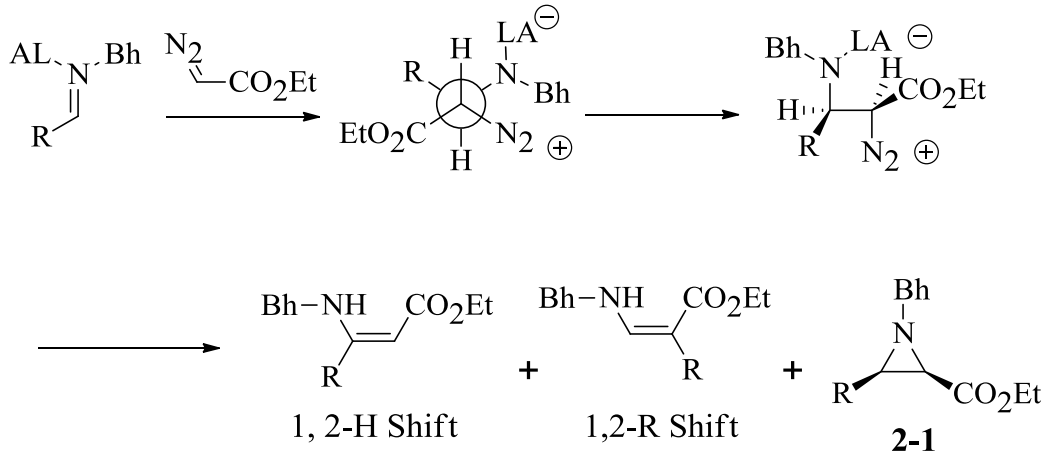
Wulff Aziridine Methodology

The synthesis of chiral aziridines has been extensively studied by Wulff and coworkers.[28-33] One of the first aziridines that were synthesized asymmetrically by Wulff and coworkers were benzhydryl aziridines.[28] These aziridines had an ethyl carboxylate at the C-2 position and a variety of different substituents (R) were possible at the C-3 position of the aziridine ring. The benzhydryl aziridines were produced by reaction of imines with ethyl diazoacetate in the presence of a chiral Lewis acid (LA). The chiral LA was created by the reaction between chiral VAPOL or VANOL with triphenyl borate in the presence of a trace amount of water (Scheme 2-3).[32] The exact mechanism of the aziridination reaction is not known, but Wulff and coworkers depicted one possible mechanism.[32] If the chiral LA was produced from (*S*)-VAPOL or (*S*)-VANOL, the chiral LA would coordinate to the imine from the Si face to produce the (*R*,*R*) enantiomer (compound **2-1**). Similarly, if the chrial LA was produced from chiral (*R*)-VAPOL and (*R*)-VANOL, the chiral LA would coordinate to the imine from the Re face to yield the (*S*,*S*) enantiomer (compound **2-1a**) (Scheme 2-1).[32]



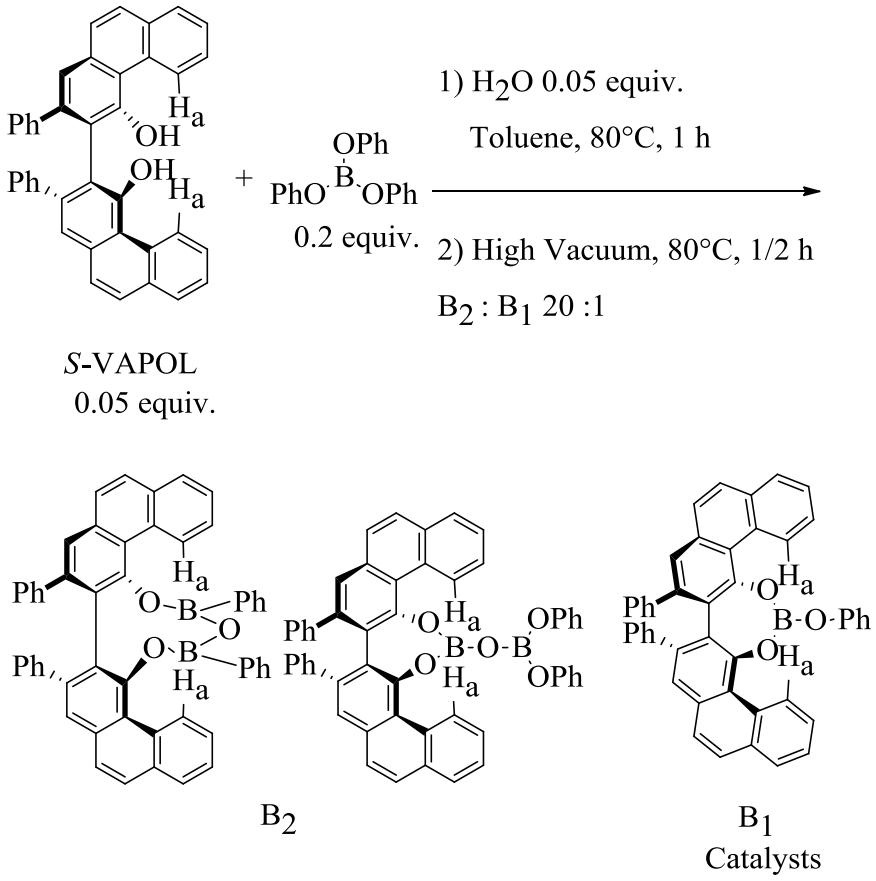
Scheme 2-1: Enantioselective Synthesis of Benzhydryl Aziridines

The synthesis of **2-1** with the chiral LA derived from (*S*)-VAPOL or (*S*)-VANOL is depicted in the Newman projection below (Scheme 2-2).[32] Both the R group and the ethyl ester are shown to be in a gauche relationship to one another. In the mechanism Wulff and coworkers proposed, initially the chiral LA coordinates to the imine nitrogen atom from the Si face.[32] Since the imine bond is now activated by the chiral LA, the ethyl diazoacetate will then nucleophilically attack the carbon atom of the imine bond from the Re face, breaking the carbon-nitrogen pi bond. The nitrogen lone pair of electrons can now attack at the C-2 position to substitute the N_2 group and yield compound **2-1**.[32] Although a small amount of enamines were also formed in the aziridination reaction due to a 1,2-H shift and a 1,2-R shift, the benzhydryl aziridines were still synthesized in great yields and high enantiomeric excesses (Scheme 2-2).[32]



Scheme 2-2: Possible Aziridination Mechanism

The Wulff group has shown that there are actually several LA catalyst species possible (Scheme 2-3). They discovered that the catalyst species defined as B_2, but not B_1 was the key to the high enantioselectivity. These catalysts were able to be distinguished by ^{11}B NMR, as well as the proton labeled as H_a (Scheme 2-3) of B_2 and B_1 was distinguished by ^{1}H NMR.[32] From this NMR data, the ratio of the two different catalyst species defined as B_2:B_1 was calculated.[32] Wulff and coworkers have changed the ratio of VAPOL or VANOL, triphenyl borate, and water to determine the optimal conditions to form the greatest ratio of B_2 to B_1. They have also determined the best solvent, time, and temperature for selective LA catalyst formation. Their best results are shown in scheme 2-3, where they selectively formed B_2 over B_1 in a 20:1 ratio.



Scheme 2-3: Catalyst Species Present in the Aziridination Reaction[32]

Besides optimum catalyst conditions, Wulff and coworkers have also determined the optimal solvent, time, and temperature for the benzhydryl aziridination reaction.[32] The benzhydryl aziridines (**2-1** or **2-1a**) were synthesized in toluene at room temperature with only a catalytic amount of chiral VAPOL or VANOL. Their results are summarized in Table 2-1.[32]

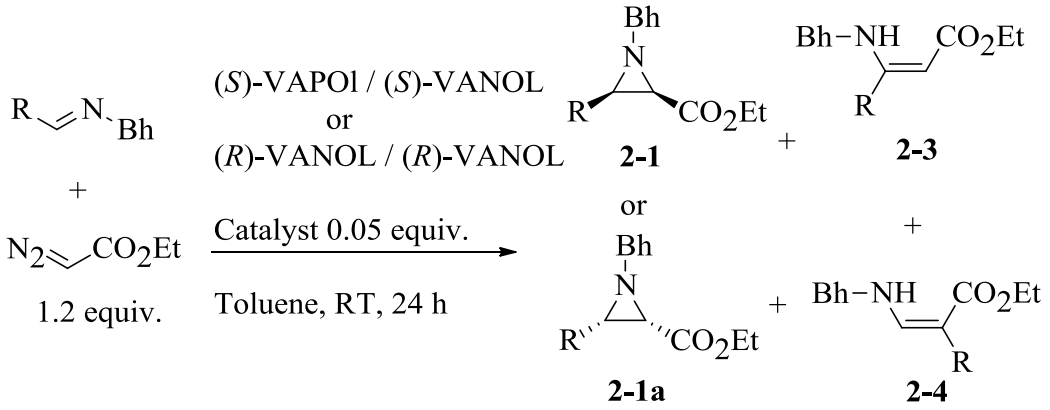
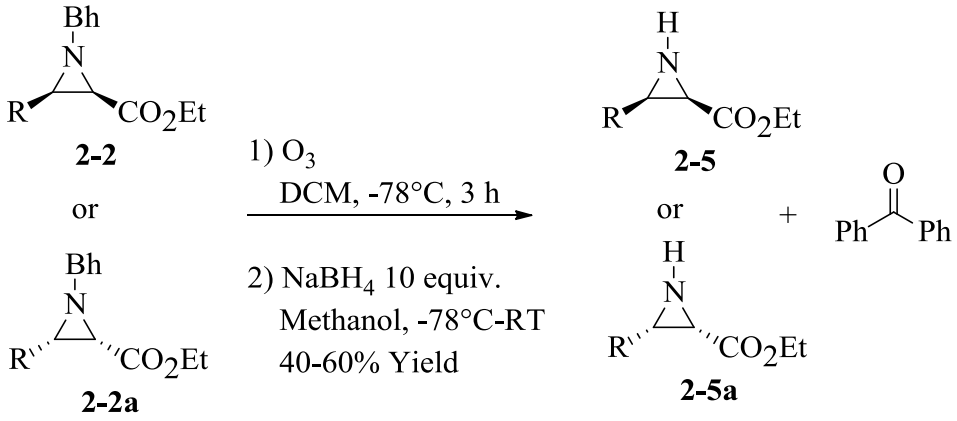


Table 2-1: Synthesis of Benzhydryl Aziridines[32]

Entry	R	Ligand	% Yield **2-1** or **2-1a**	% ee	*Cis*: *Trans*	% Yield **2-3**+**2-4**
1	1-naphthyl	(*S*)-VAPOL	76	93	34:1	<1
2	1-naphthyl	(*R*)-VANOL	80	93	51:1	2
3	Ph	(*S*)-VAPOL	82	94	≥ 50:1	<1
4	Ph	(*R*)-VANOL	87	93	100:1	2
5	*o*-MeC_6H_4	(*S*)-VAPOL	63	91	10:1	14
6	*o*-MeC_6H_4	(*R*)-VANOL	67	90	12:1	11
7	*p*-MeC_6H_4	(*S*)-VAPOL	80	92	≥ 50:1	<1
8	*p*-MeC_6H_4	(*R*)-VANOL	79[a]	94	1.6:1	2
9	*o*-BrC_6H_4	(*S*)-VAPOL	37	82	1.9:1	10
10	*o*-BrC_6H_4	(*R*)-VANOL	43	82	20:1	24
11	*p*-BrC_6H_4	(*S*)-VAPOL	78[a]	90	≥ 20:1	< 1
12	*p*-BrC_6H_4	(*R*)-VANOL	86	94	15:1	14
13	*p*-$NO_2C_6H_4$	(*S*)-VAPOL	79[b]	79	100:1	< 1
14	*p*-$NO_2C_6H_4$	(*R*)-VANOL	86	89	≥ 100:1	< 1
15	*p*-$MeOC_6H_4$	(*S*)-VAPOL	51[ac]	86	6:1	23
16	*p*-$MeOC_6H_4$	(*R*)-VANOL	61	87	34:1	< 1
17	3,4-$(OAc)_2C_6H_3$	(*S*)-VAPOL	87	89	100:1	6
18	3,4-$(OAc)_2C_6H_3$	(*R*)-VANOL	84	93	≥ 100:1	< 1
19	*n*-propyl	(*S*)-VAPOL	40	81	14:1	7
20	*n*-propyl	(*R*)-VANOL	54	77	14:1	19
21	Cyclohexyl	(*S*)-VAPOL	73	81	≥ 50:1	< 1
22	Cyclohexyl	(*R*)-VANOL	79	82	≥ 50:1	6

[a] Solvent was 4:1 toluene: DCM. [b] Reaction time was 48hrs. [c] 78% Conversion. [d] 93% conversion.

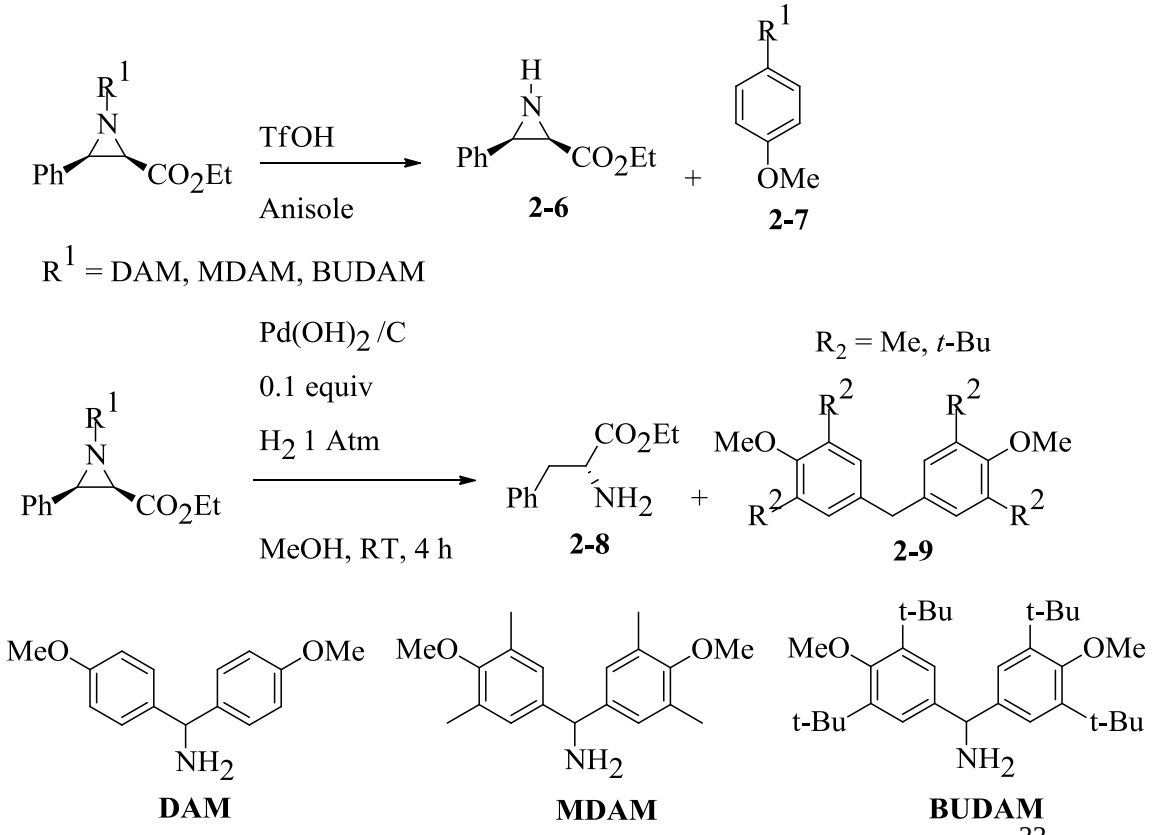
Aziridines are synthetically useful molecules for both aziridine ring opening and ring expansion reactions. However, in either case the aziridine nitrogen protecting group often determines the reactivity of the aziridine. Once the nitrogen protecting group is removed, the free aziridine may be substituted with other protecting group to give the desired reactivity. Thus, a method to remove the benzhydryl protecting group would be synthetically useful. Wulff and coworkers have also created such a methodology. The benzhydryl aziridines can be deprotected by oxidation with ozone in DCM at -78°C to yield compounds **2-5** or **2-5a** and benzophenone (Scheme 2-4).[29]



Scheme 2-4: Deprotection of Benzhydryl Aziridines[29]

Other aziridine protecting groups derived from the respective amines have been developed by the Wulff group such as bis(4-methoxyphenyl)methanamine (DAM), bis(4-methoxy-3,5-dimethylphenyl)methanamine (MDAM), and bis(3,5-di-tert-butyl-4-methoxyphenyl)methanamine (BUMAM).[31,33] The aziridination reaction of imines protected with the DAM, MDAM, and BUDAM groups gave even higher enantiomeric

excesses than imines protected with the benzhydryl group. The BUDAM imines have given the overall highest ee and yield for various aziridine-2-carboxylates substituted at the C-3 position of the aziridine ring.[33] These protecting groups can be removed by reaction with hydrogen and Pearlman's catalyst.[28,31] Alternatively, the DAM, BUDAM, and MDAM protecting groups can be removed with TfOH in anisole to yield compounds **2-6** and **2-7**.[33] However, if the aziridine was substituted with a phenyl at C-3 position then the MDAM, DAM, and BUDAM protecting groups could only be removed with TfOH in anisole. Pearlman's catalyst and hydrogen broke the bond between C-3 position and the nitrogen atom leading to compounds **2-8** and **2-9** (Scheme 2-5, Table 2-2).[31]

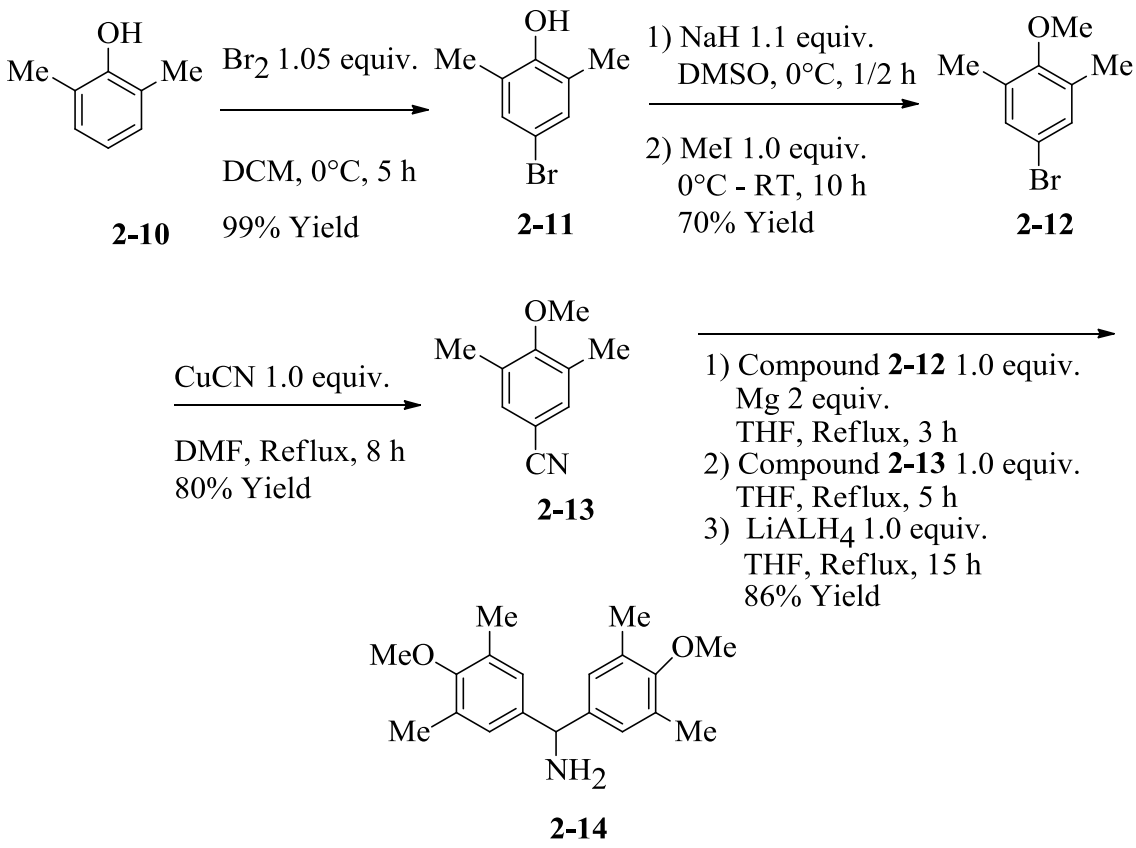


Scheme 2-5: Deprotection of N-DAM, N-MDAM, and N-BUDAM Aziridines[33]

Tabel 2-2: Deprotection with TfOH[33]

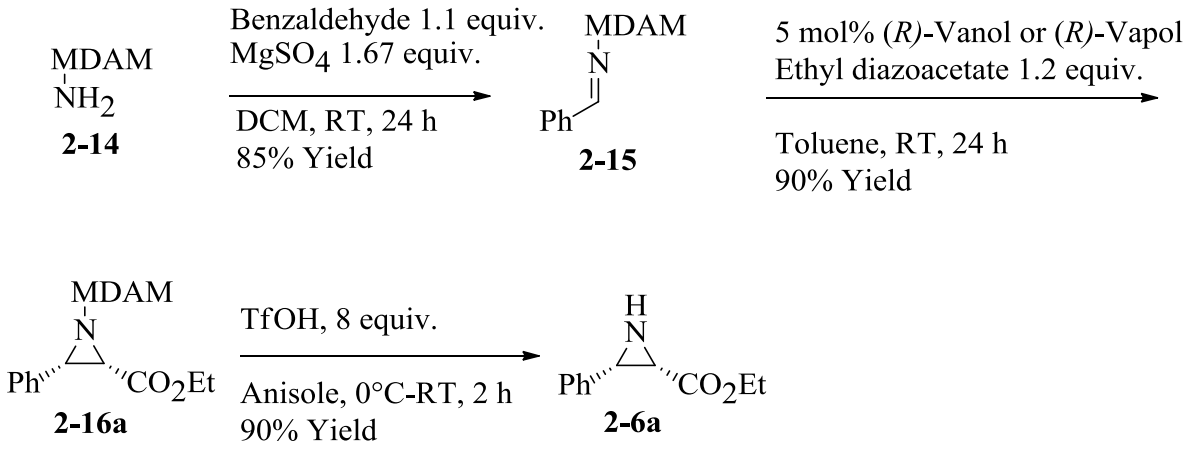
Entry	R^1	TfOH equiv.	Temp °C	Time h	% Yield
1	DAM	5	25	0.67	99
2	MDAM	8	25	2	97
3	BUDAM	8	25	2	97

The electron donating substituents on the DAM, MDAM, and BUDAM protection groups made a very stable carbocation upon treatment of the respective aziridine with TfOH.[28] Wulff and coworkers determined that anisole quenched the carbocation and was the key to obtain a high yield in the deprotection of the N-DAM, N-MDAM, and N-BUDAM aziridines. In contrast, the benzhydryl protecting group could not be removed with TfOH.[28-29] TfOH and anisole was a general method to deprotect the DAM, MDAM, or BUDAM aziridines regardless of the substituent at the C-3 position of the aziridine ring. This methodology allowed direct access to compounds **2-6** or its enantiomer **2-6a** and the necessary starting material for an enantioselective synthesis of imidazolines. When the enantioselective synthesis of imidazolines was initially pursued, the MDAM amine compound **2-14** was chosen in preference to the DAM amine and BUDAM amine. The MDAM amine was synthesized according to the procedure provided by Wulff (Scheme 2-6).[33]



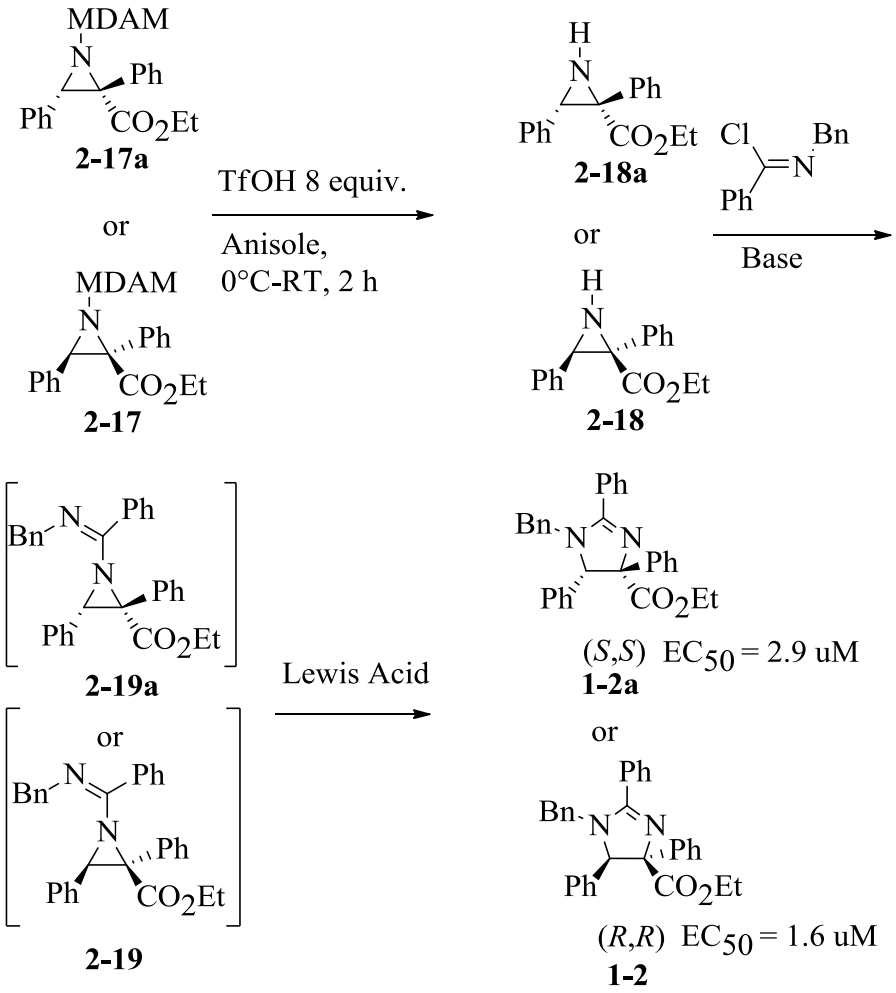
Scheme 2-6: Synthesis of Bis(4-methoxy-3-5-dimethylphenyl)methanamine[31,33]

Next, by following the experimental procedures provided by Wulff and coworkers[31,33] the MDAM amine was reacted with benzaldehyde to yield the imine compound **2-15**. The reaction of compound **2-15** with ethyl diazoacetate and (*S*)-VANOL or (*S*)-VAPOL (*R*)-VANOL and (*R*)-VAPOL were not available at the time) yielded the aziridine **2-16a**.[32] Lastly, deprotection of the MDAM group with TfOH yielded the aziridine **2-6a** in 90% yield (Scheme 2-7).



Scheme 2-7: Synthesis of (2S,3S)-ethyl 3-phenylaziridine-2-carboxylate [32-33]

However, the target imidazoline **1-2** contained a phenyl group at the C-5 position. The proposed method to synthesize imidazolines from aziridines was by a LA promoted isomerization of imidoyl aziridines **2-19** or **2-19a** (Scheme 2-8). The aziridine needed for this imidazoline would be compound **2-18** or **2-18a**, depending on which imidazoline enantiomer was desired. This would require deprotection of compound **2-17** or **2-17a**. However, compound **2-17** or **2-17a** could not be synthesized by Wulff's aziridine chemistry. They determined that the ethyl diazoacetate could only have a hydrogen atom at the C-2 position. Thus, the aziridine could only be mono-substituted at the C-2 carbon of the aziridine ring. Wulff and coworkers have not reported a synthesis of C-2 di-substituted chiral aziridines.[28-33]



Scheme 2-8: Proposed Enantioselective Synthesis of Lead Imidazolines

Wulff and coworkers have also reported an enantioselective alkylation of aziridines.[30] The benzhydryl aziridines were reacted with lithium diisoproyl amine (LDA) at -78°C to generate a lithium enolate which was treated with various electrophiles. Alkylation of aziridines has been extremely rare and there have been very few reported examples.[30] The problems frequently encountered are self condensation with the ester or instability of the lithium enolate leading to aziridine ring opening.[34]

The alkylation methodology was completely enantioselective to the less hindered face of the aziridine (Table 2-3).[30]

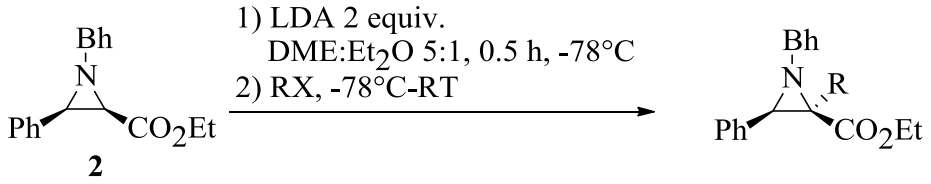


Table 2-3: Enantioselective Alkylation of Aziridines [30]

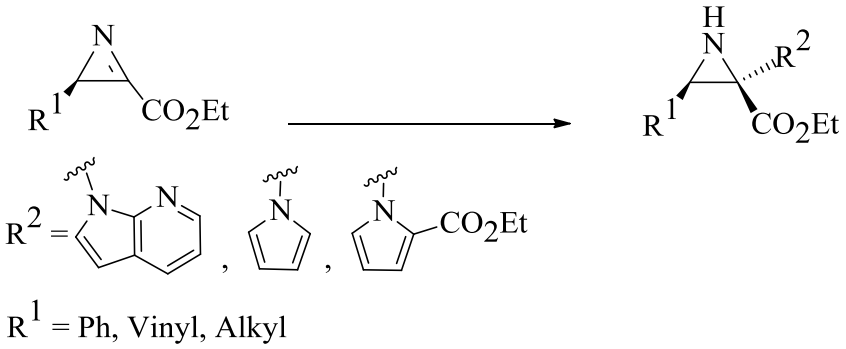
Entry	RX	% Yield	Entry	RX	% Yield
1	MeI	82	5	BnBr	33
2	*n*-$C_8H_{17}I$	50	6	BuSnCl	73[a]
3	CH_2=$CHCH_2Br$	61	7	PhCHO	95[b]
4	MOMCl	63	8	*n*-C_3H_7CHO	89[b]

[a] 18% of yield was the O-alkylated product. [b] 1:1 mixture of diastereomers at carbinol carbon.

However, it was not possible to place a phenyl group at the C-2 position of the aziridine ring with the alkylation methodology reported by Wulff and coworkers.[30]

Literature Precedent for Synthesis of Azirines

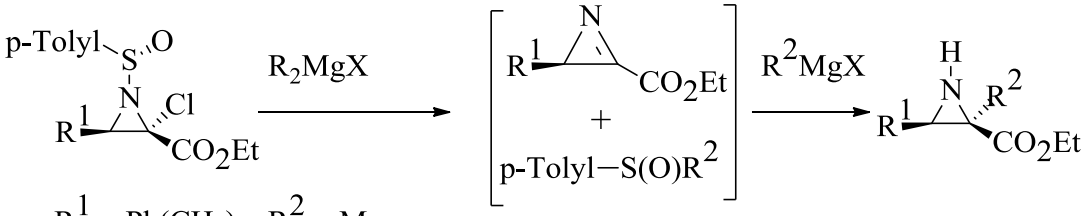
One possible way to place a phenyl group at C-2 position of the aziridine ring to yield aziridines **2-18** or **2-18a** was through an azirine. Literature has shown that azirines undergo nucleophilic substitution to yield aziridines stereoselectively.[34-36] The nucleophile attacks the less sterically hindered face of the azirine. The reactions of azirines with Grignard reagents are typically carried out at -78°C in THF. The reaction of nitrogen containing heterocycles with azirines can also occur at room temperature with potassium carbonate (Scheme 2-9).[34]



R^1 = Ph, Vinyl, Alkyl

Scheme 2-9: Nucleophilic Addition to Azirines

Literature has also shown that C-2 halo-aziridines substituted with nitrogen protecting groups that are very electron withdrawing form azirines when reacted with strong nucleophiles like Grignard reagents.[36] For example, when p-tolylsulfinyl was attached to the aziridine nitrogen, the nucleophile attacked the p-tolylsulfinyl group instead of the ester.[36-37] An azirine was formed in situ by elimination of a chlorine atom followed by nucleophilic attack of a second equivalent of Grignard reagent to the less sterically hindered face of the azirine (Scheme 2-10).[37]



R^1 = Ph$(CH_2)_4$, R^2 = Me

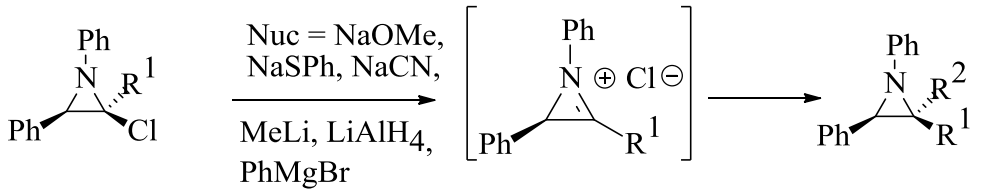
R^1 = Ph$(CH_2)_4$, R^2 = Ph

R^1 = Ph$(CH_2)_4$, R^2 = CH_2=CH

R^1 = *i*-Pr, R^2 = Ph

Scheme 2-10: Enantioselective Substitution of Azirines[37]

Another literature example has a phenyl group on the aziridine nitrogen atom and a chlorine atom at the C-2 position of the aziridine ring.[38-39] The chlorine atom was substituted with a variety of nucleophiles. This substitution reaction occurred through an azirinium cationic intermediate (Scheme 2-11).[38-39]

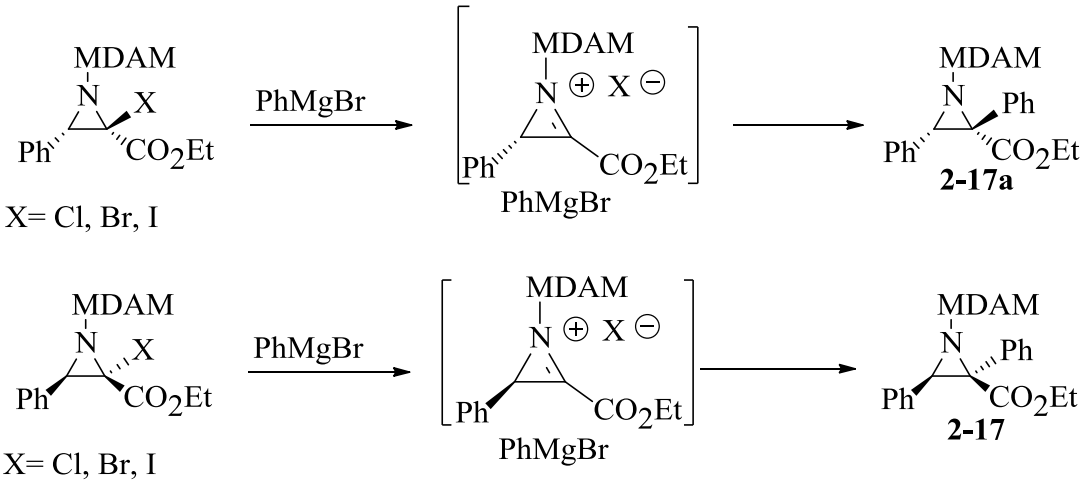


R^1 = H, Me

R^2 = OMe, SPh, CN,
Me, H, Ph

Scheme 2-11: Nucleophilic Substitution of 2-chloro-aziridines[38-39]

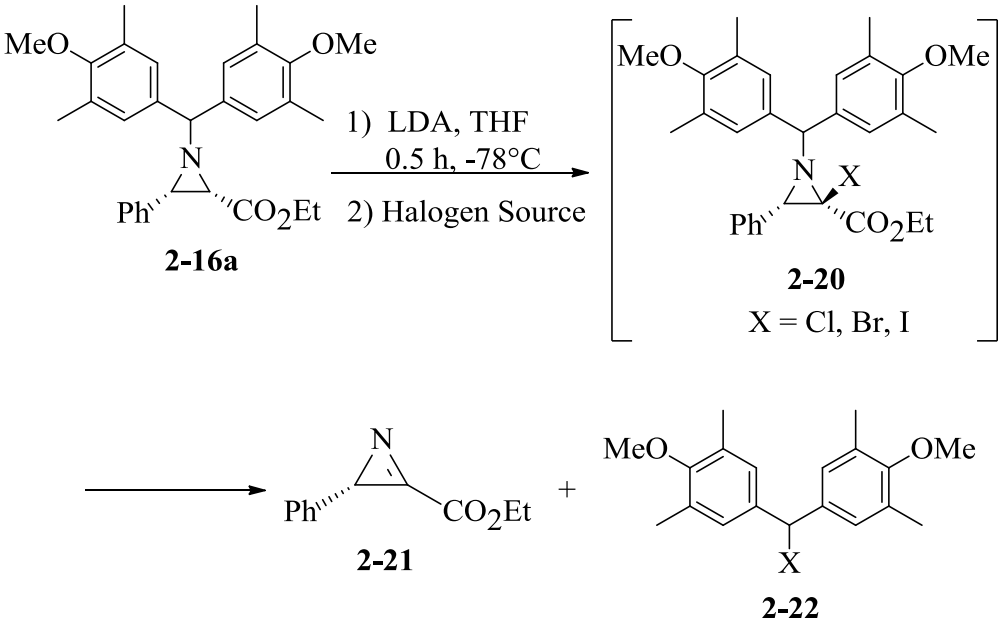
One would think that if the MDAM-ethyl 3-phenylaziridine-2-carboxylate had a halogen atom on C-2 position of the aziridine ring that substitution with phenyl magnesium bromide would be possible. The reaction would be presumed to go through an azirinium cationic intermediate. However, no literature examples have been reported for the substitution of C-2-halo-aziridines with an ester group at the C-2 position. This reaction would yield the aziridines **2-17** and **2-17a** needed for the proposed ring expansion to imidazolines **1-2** and **1-2a** (Scheme 2-12).



Scheme 2-12: Proposed Nucleophilic Substitution of 2-halo-N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

Halogenation of N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

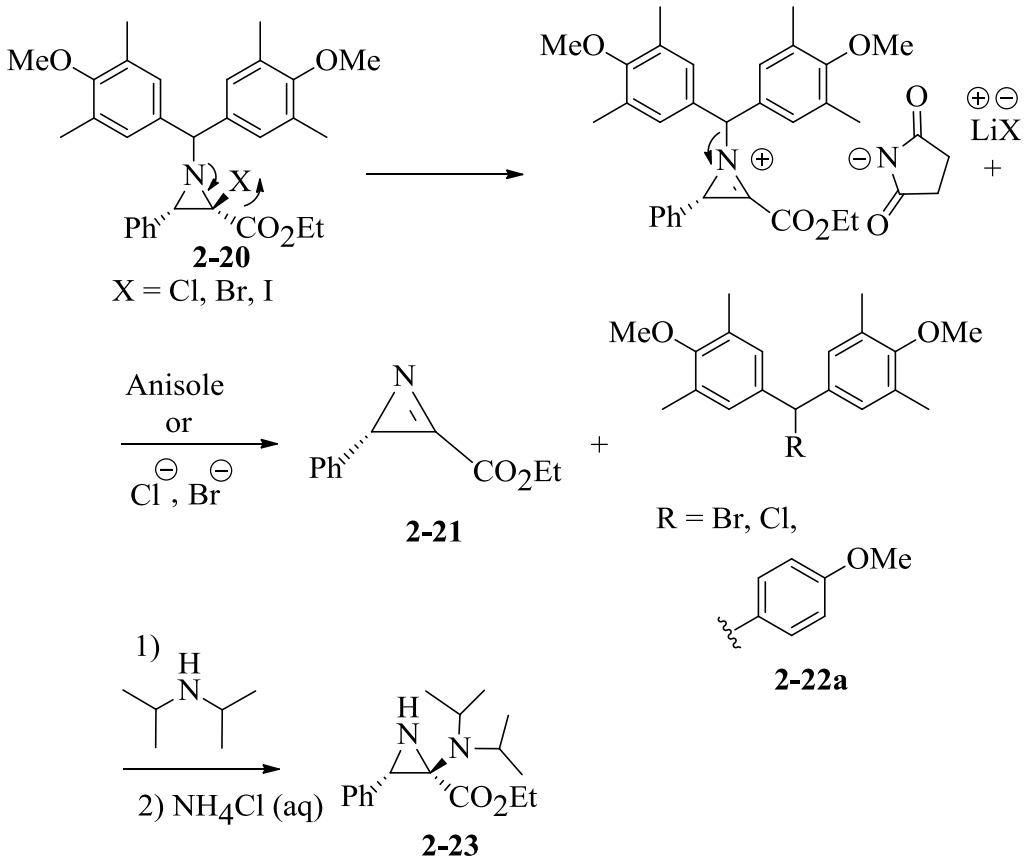
One possible way to halogenate N-MDAM-ethyl-3-phenyl-2-carboxylate would be to use the alkylation methodology reported by Wulff and coworkers.[30] However, their methodology has never reported the halogenation of a lithium enolate through an electrophilic halogen source. One would propose that the reaction of compound **2-16a** with LDA followed by reaction with a halogen source like N-Bromosuccinimide (NBS) or N-Chlorosuccinimide (NCS) would successfully halogenate compound **2-16a**. However, it is possible that compound **2-20** would not exist as a stable molecule, and instead could react further to form compound **2-22** and the ethyl 2-phenyl-2H-azirine-3-carboxylate (**2-21**) (Scheme 2-13).



Scheme 2-13: Proposed Halogenation of **2-16a**

Initial experimental results for the reaction of compound **2-16a** with NBS or NCS seemed to be successful (Table 2-4, entry 2). Compound **2-16a** was reacted with LDA at -78°C in THF to give a dark yellow colored solution due to the presence of the lithium enolate. When the NBS or NCS was added, the solution immediately turned red, presumably due to the formation of the MDAM carbocation. This implied that after compound **2-16a** was brominated to form compound **2-20** it was unstable. As a result, the bond between the aziridine nitrogen atom and the MDAM benzyl carbon broke to produce the MDAM carbocation and elimination of the halogen, to produce the azirine compound **2-21** (Scheme 2-14). After the reaction solution was warmed to room temperature, the red color due to the MDAM carbocation was absent. However, only trace amounts of compound **2-21** was present in the reaction mixture (Table 2-4, entry 2). These results were repeated after the reaction solution turned red again, but instead of warming the solution to room temperature the solution was transferred into anisole at -

78°C (Table 2-4, entry 3). The anisole quenched the MDAM carbocation and the red color disappeared. The crude ^{1}H NMR showed evidence for the formation of compound **2-21**. The aliphatic methine proton of compound **2-22a** was present in the ^{1}H NMR which confirmed that the MDAM protecting group had been removed and quenched with anisole. However, the ^{1}H NMR also showed that the diisopropyl amine may have undergone nucleophilic substitution with compound **2-21** to yield compound **2-23** (Table 2-4, entry 3) (Scheme 2-14).



Scheme 2-14: Azirine Formation through Halogenation of N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

Literature has shown that most azirines cannot be isolated by column chromatography due to decomposition, but are stable enough to be isolated by purification by aqueous extractions.[34-35] Compounds **2-23** and **2-21** were also too unstable to be isolated in pure form by column chromatography. A variety of reaction conditions were attempted to better understand the reaction in hope of isolating only compounds **2-21**, or **2-23** as a single component. The results of the reaction of **2-16a** with NBS or NCS are shown below in Table 2-4.

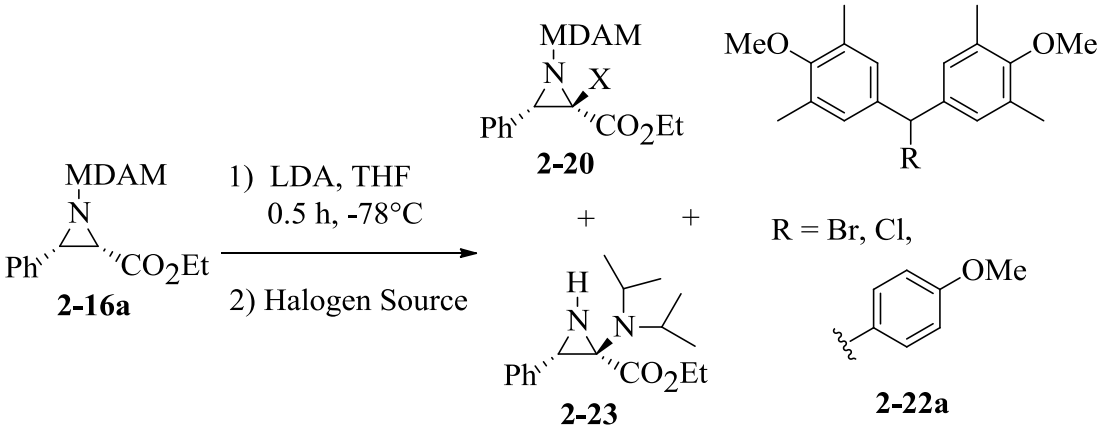


Table 2-4: Attempted Halogenation Reactions of N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

Entry	Base equiv.	Solvent	Temp ° C	Time h	Electrophile equiv.	Nucleophile equiv.	Results
1	LDA, 1.1	THF	-78-RT	12	NBS, 2.0	None	Only **2-16a**
2	LDA, 2	THF	-78-RT	12	NBS, 3.0	None	Mixture
3	LDA, 2	THF	-78-RT	4	NBS, 3.0	None	Mixture
4	LDA, 2	THF	-78-RT	4	NBS, 3.0	MeMgBr, 5.0	Mixture
5	LDA, 2	THF/ Anisole	-78	4	NBS, 3.0	MeMgBr, 5.0	Mixture
6	NaH, 2	THF	RT	1	D_2O, excess	None	No enolate
7	LiH, 2	THF	RT	1	D_2O, excess	None	No enolate
8	LiHMDS, 2	THF	RT	1	D_2O, excess	None	No enolate
9	NaHMDS, 2	THF	RT	1	D_2O, excess	None	No enolate
10	LiH, 2	THF/ HMPA	RT	1	D_2O, excess	None	No enolate
11	LDA, 2	THF	-78-RT	16	NBS, 3.0	None	Mixture
12	LDA, 2	THF	-78-RT	16	NCS, 3.0	None	Mixture
13	LDA, 2	THF	-78-RT	1	NBS, 3.0	None	Mixture
14	LDA, 2	THF	-78	1	NBS, 2.0	None	Mixture
15	LDA, 2	THF	-78-RT	0.75	NCS, 2.0	None	Mixture
16	LDA, 2	THF	0-RT	0.75	NBS, 2.0	None	Mixture
17	LDA, 2	THF	-78	2.5	NCS, 2.0	None	Mixture

In attempt to stop the formation of compound **2-23**, instead of warming the reaction to room temperature the reaction was carried out at -78°C for 4 hours after the NBS was added to the lithium enolate of compound **2-16a**. The solution turned red once again and 5 equivalents of MeMgBr were added to quench the MDAM cation and to react with compound **2-20**. Assuming that the MeMgBr reaction would proceed through an azirinium cationic intermediate as mentioned in the literature for other 2-halo-aziridines the methyl group should have substituted the bromine atom.[38-39] After the addition of the MeMgBr the reaction was maintained at -78°C for 0.5 hours, slowly warmed to room temperature, and quenched with NH_4Cl (Table 2-4, entry 4). Unfortunately, the reaction did not yield the desired product, but instead a complicated mixture of products. This reaction was repeated, almost identically to entry 4 above, except that the solvent was a 1:1 mixture of anisole and THF (Table 2-4, entry 5). An aliquot of the reaction mixture was taken and quenched at -78°C with NH_4Cl, extracted into ether, dried with $MgSO_4$, and concentrated under reduced pressure. The ^1H NMR indicated the MDAM protecting group was removed because compound **2-22a** was present. In both reactions (Table 2-4, entries 4 and 5) a singlet appeared at about 5.5 ppm in the ^1H NMR due to the methine benzyl proton, indicating that the anisole did not have an effect on the reaction, but instead the bromine atom had attacked the MDAM carbocation. Five equivalents of MeMgBr were added and the solution was stirred for 0.5 hours at -78°C (Table 2-4, entry 5). The reaction was quenched at -78°C with NH_4Cl, but again a mixture of products was formed (entry 5). Since diisopropyl amine

seemed to be a nucleophile in the reaction, other bases were tried, but they all were unable to deprotonate the alpha proton to form the aziridine enolate (Table 2-4, entries 5-9). Entries 10 through 16 had different halogen sources, reaction times, and reaction temperatures in attempt to yield compound **2-20** or **2-23** as a single component, but none of the reaction conditions were successful.

Attempts to isolate the ethyl 2-phenyl-2H-azirine-3-carboxylate (**2-21**) in one step or reaction of compound **2-21** with a Grignard reagent was not successful. Instead the focus became trying to just halogenate compound **2-16a** at the C-2 position of the aziridine ring. There have not been any methods reported to halogenate aziridine enolates. It would seem that NBS and NCS would halogenate compound **2-16a** very well because they are both very strong electrophilc sources of bromine and chlorine respectively. However, iodine, carbon tetrabromide, and carbon tetrachloride have also been used to halogenate lithium enolates of other substrates, but no examples have been reported for aziridine enolates.[40-41] A variety of electrophilic sources of chlorine, bromine, and iodine and reaction conditions were screened to find a method to halogenate compound **2-16a**. Compound **2-16a** was successfully chlorinated with carbon tetrachloride. Both the chloro-hydantion and NCS did not yield compound **2-24**, but instead gave a complicated mixture of products and an unreacted amount of compound **2-16a**. (Table 2-5).

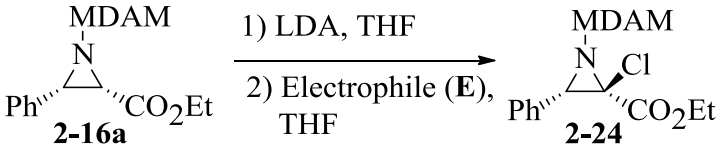


Table 2-5: Chlorination of N-MDAM-ehtyl-3-phenylaziridine-2-carboxylate

Entry	LDA Equiv	Temp° C	**E**	**E** Equiv.	Time h	% **2-16a** ^{1}H NMR integration	% **2-24** ^{1}H NMR integration
1	2	-78	NCS	3	0.75	51	0
2	2	-78	Cl-hydantion	3	0.75	49	0
3	3	-78	CCl_4	3.3	0.75	0	68
4	3	-78-RT	CCl_4	3.3	0.75	0	60
5	2	-78	CCl_4	3	0.75	0	68

Bromination of **2-16a** was also successful with carbon tetrabromide, but again the bromo-hydantion and NBS did not brominate compound **2-16a**, but instead gave a complicated mixture of products and an un-reacted amount of compound **2-16a**. (Table 2-6).

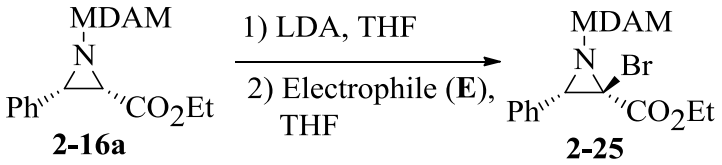


Table 2-6: Bromination of N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

Entry	LDA equiv.	Temp °C	**E**	**E** equiv.	Time h	% **2-16a** ^{1}H NMR integration	% **2-25** ^{1}H NMR Integration
1	2	-78	NBS	3	0.75	50	0
2	2	-78	Br-hydantion	3	0.75	100	0
3	2	-78	Br_2	3	0.75	Trace	67
4	2	-78	CBr_4	3	0.75	0	68

Lastly, iodination at the C-2 position of compound **2-16a** was also possible. N-Iodosuccinimide (NIS) and iodine were both screened and both electrophilic iodine

sources yielded product. However, iodine was a better source of electrophilic iodine than NIS (Table 2-7).

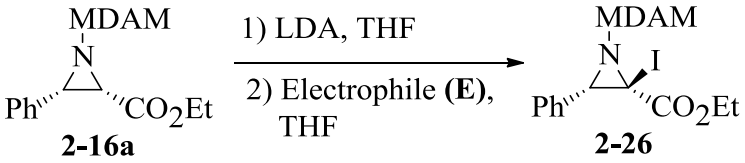


Table 2-7: Iodination of N-MDAM-ethyl-3-phenylaziridine-2-carboxylate

Entry	LDA Equiv.	Temp °C	Electrophile	Electrophile Equiv.	Time h	% **2-16a** ^{1}H NMR Integration	% **2-26** ^{1}H NMR Integration
1	2	-78	NIS	3	0.75	0	53
2	3	-78	I_2	3.3	0.75	0	60
3	2	-78	I_2	3	0.75	0	62
4	2	-78	I_2	1.1	0.75	Trace	60
5	2	-78	I_2	2.2	0.75	0	60
6	2	-78	I_2	1.2	0.75	0	0[a]
7	2	-78	NIS	3	1.0	0	0[b]
8	2	-78	I_2	3	2.0	0	60
9	2	-78	I_2	3	0.75	0	62[c]

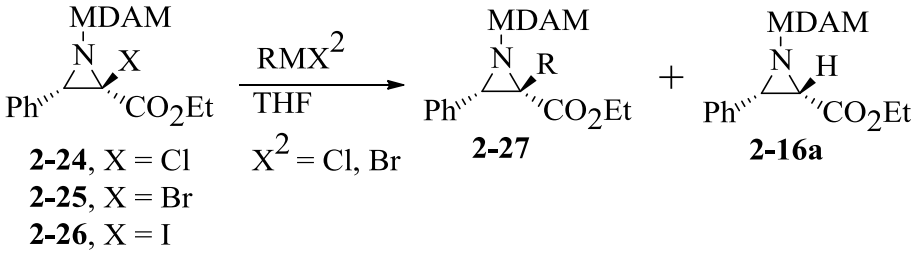
[a] Added lithium enolate to iodine in THF. [b] Added enolate to NIS in THF. [c] Ether was used as the solvent.

Carbon tetrachloride, carbon tetrabromide, and iodine were the best chlorine, bromine, and iodine sources to yield compounds **2-24**, **2-25**, and **2-26** respectively. Bromine left a trace amount of **2-16a** due to the protochemical reaction of bromine with light (Table 6, entry 3). Initial attempts to purify compounds **2-24**, **2-25**, and **2-26** by chromatography on silica gel, neutral alumina, or basic alumina resulted in decomposition. Instead the yields of the reactions were approximated by measuring the integration of the proton at the C-3 position of compound **2-16a** to the proton at the C-3 position of compounds **2-24**, **2-25**, and **2-26** in the crude ^{1}H NMR spectra. In all the halogenation reactions, the

electrophile was added to the lithium enolate of compound **2-16a** at-78°C. In attempt to further optimize the reaction and hopefully increase the yield, the lithium enolate of compound **2-16a** was added to the halogen source. However, this resulted in 0% yield of compound **2-26**, indicating that the order of addition was important (Table 2-7, entries 6 and 7). Surprisingly, the halide succinimides and halide hydantions were very poor in the halogenation of aziridines. Perhaps iodine, carbon tetrabromide, and carbon tetrachloride were successful because they were sterically less hindered than the halide succinimides and halide hydantions.

Aziridine Coupling Reactions

Reaction of the 2-halo-ethyl-3-phenylaziridine-2-carboxylate with Grignard reagents, cuprates, or alkyl zinc reagents failed. The reaction did not go through an azirinium cationic intermediate as predicted in Scheme 2-12 (Table 2-8).



2-24, X = Cl
2-25, X = Br
2-26, X = I

X^2 = Cl, Br

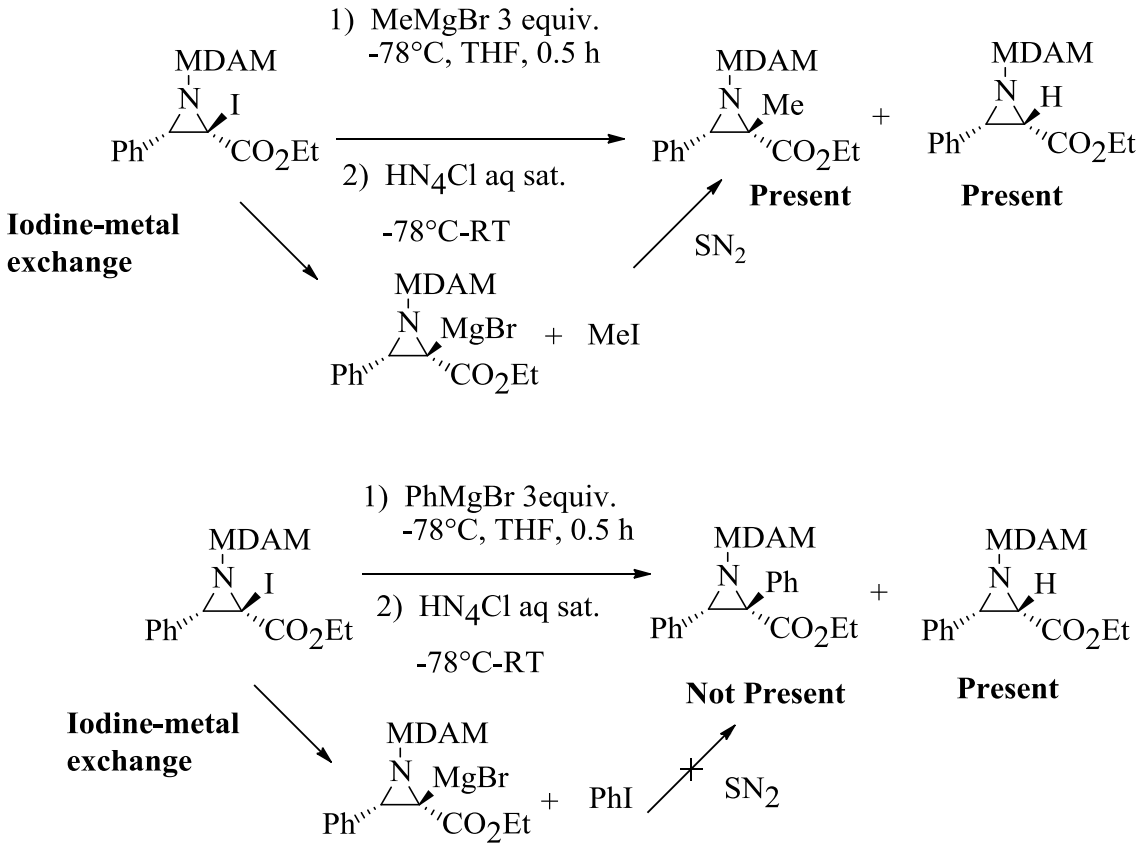
2-27

2-16a

Table 2-8: Reaction of Halo-aziridines with Metal Reagents

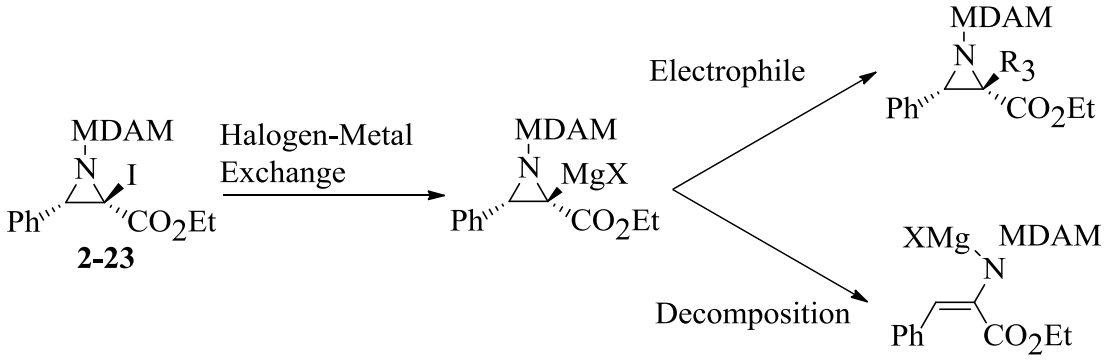
Entry	X	RMX^2	Reagent Equiv.	Temp°C	Time h	Result
1	Cl	MeMgBr	3	-78, -15	0.5	No rxn
2	Cl	MeMgBr	5	-78- RT	0.5	No rxn
3	Cl	MeMgBr	10	Reflux	0.5	Rxn at ester
4	Br	MeMgBr	5	-78 - 0	0.5	No rxn
5	Br	MeMgBr	5	-78 - RT	0.5	No rxn
6	Br	MeMgBr	5	Reflux	0.5	Rxn at ester
7	I	MeMgBr	3	-78	0.5	Ratio **2-27**:**2-16a** 4:1, 45% Yield
8	I	PhMgBr	3	-78	0.5	Only **2-16a**
9	I	$Me_2CuMgBr$	5	-78	0.5	No rxn
10	Br	MeZnCl	5	-78 - RT	5.0	No rxn

Instead, compound **2-26** gave metal-iodine exchange and compounds **2-24** and **2-25** did not react until refluxed in THF, which gave reaction at the carbonyl group. Compound **2-26** gave metal-iodine exchange with MeMgBr followed by alkylation of the in *situ* formation of methyl iodide (Scheme 2-15). This gave methylation of the magnesium enolate at C-2 position as well as compound **2-16a** due to a trace amount of water in 45% overall yield with a 4:1 ratio of compound **2-27** to compound **2-16a** (entry 7). Reaction of compound **2-26** with phenyl magnesium bromide gave magnesium-iodide exchange only and phenyl iodide, which could not undergo substitution at the sp^2 carbon center of iodobenzene (Entry 8). When this reaction was quenched with NH_4Cl, compound **2-16a** was the major component along with some decomposition products (Entry 8).



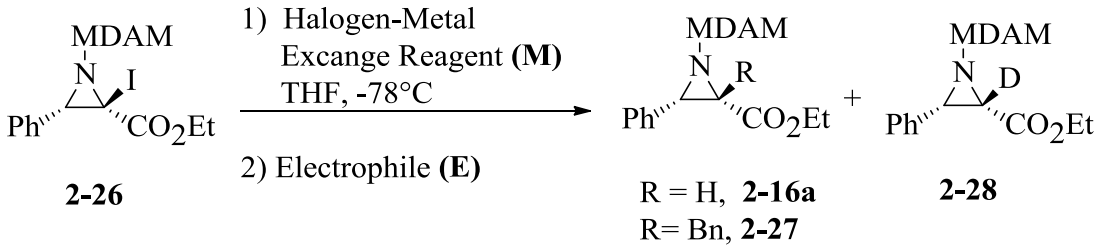
Scheme 2-15: Halogen Metal Exchange and Alkylation of Compound **2-26**

The magnesium enolate could be generated at -78°C by magnesium-iodine exchange and either was alkylated or decomposed as the reaction slowly warmed to room temperature (Scheme 2-16).



Scheme 2-16: Reaction Pathway for Magnesium Enolate of Compound **2-26**

To confirm that compound **2-26** went via a halogen metal exchange mechanism followed by alkylation with methyl iodide, compound **2-26** was reacted at -78°C in THF with *i*-prMgCl or CH_2=CHMgCl both reagents caused halogen-metal exchange. Once the magnesium enolate was formed, it was quenched with CD_3OD to install a deuterium atom at the C-2 position of the aziridine ring. Coupling by halogen metal exchange with CH_2=CHMgCl and reaction with benzyl bromide was attempted. The reaction worked to benzylate the C-2 position of the aziridine ring in low yield (Table 2-9, entry 5).



2-26

R = H, **2-16a**
R= Bn, **2-27**

2-28

Table 2-9: Alkylation through Halogen-metal Exchange

Entry	Temp ° C	Time h	**M**	**M** equiv.	**E**	Electrophile Equiv.	Result
1	-78	0.5	Mg^0	2.0	D_2O	Excess	Decomposition
2	-78	0.5	*i*-PrMgCl	1.0	CD_3OD	Excess	Only **2-26**
3	-78	0.5	*i*-PrMgCl	3.0	CD_3OD	Excess	Only **2-28**
3	-78–RT	15	*i*-PrMgCl	3.0	CD_3OD	Excess	**2-28** and Decomposition
4	-78	0.5	CH_2=CHMgCl	3.0	CD_3OD	Excess	Only **2-28**
5	-78–RT	4	CH_2=CHMgCl	3.0	BnBr	3.0	**2-27**, 30% Yield

It was a disappointment that the coupling reaction went through iodine-metal exchange and not through an azirinium cationic intermediate. One more final attempt to synthesize aziridine **2-17a** was attempted through Suzuki coupling reactions. Gregory C. Fu, among others, has shown that simple alpha-haloesters can be coupled with boronic

acids or 9BBN reagents via Suzuki coupling conditions even if the coupling substrate contains beta hydrogen atoms.[42-46] In the hope of avoiding beta-hydride elimination, coupling reactions with **2-26** and phenyl boronic acid were attempted, but gave a complex mess of products (Table 2-10).

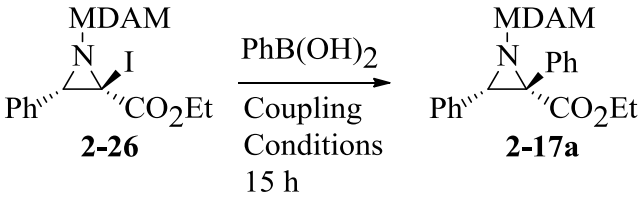


Table 2-10: Attempted Suzuki Cross-coupling Reactions

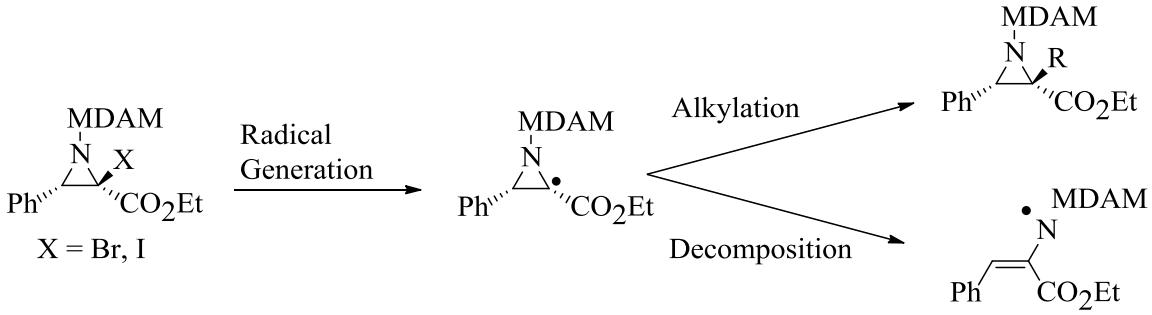
Entry	PhB $(OH)_2$ equiv.	Solvent	Metal equiv.	Ligand equiv.	Base equiv.	Temp °C	Result
1	1.2	Toluene/ water (2equiv.)	$Pd(OAc)_2$ 0.3	$P(O\text{-}tolyl)_3$ 3.0	K_3PO_4 5.0	80	Dec.
2	1	Toluene/ water (2equiv.)	$Ni(PPh_3)_4$ 0.3	None	K_3PO_4 2.0	80	No rxn
3	1	Toluene	$Pd(PPh_3)_4$ 0.3	None	K_3PO_4 2.0	80	Dec.
4	1.5	*t*-Amyl alcohol	$Pd(OAc)_2$ 0.4	$P(t\text{-}bu)_2Me$ 0.8	KOt-Bu_3	RT	Dec.
5	1.5[a]	DMF: H_2O 4:1	$Pd(OAc)_2$ 0.2	PPh_3 1	K_2CO_3 1.2	RT	Dec.

[a] 0.8eqs of Bu_4NCl was also added

Not even trace amounts of compounds **2-17a** or **2-26** could be identified by mass spectrometry. All of the Suzuki coupling reactions led to aziridine ring opening except for entry 2. Presumably, aziridine ring opening occurred by beta-hydride elimination or coordination of the aziridine nitrogen lone pair of electrons to the palladium. Beta-hydride elimination seemed to be the obvious occurrence, since the palladium and the

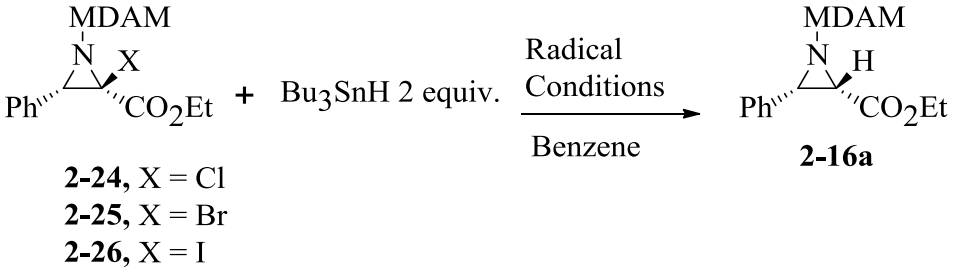
iodine atom were on the same side of the aziridine ring after the oxidative addition of compound **2-26** to the palladium had occurred. The iodine atom was also at a sterically hindered site, so the bulky phosphine ligands attached to the palladium would most likely be dissociated, leaving an open site on the palladium for C-H activation and subsequent beta-hydride elimination to occur.

In an attempt to find some synthetic usefulness for the 2-halo-aziridines (compounds **2-24**, **2-25**, and **2-26**), radical reactions were attempted. The goal was to try to create new substituents at the C-2 position of the aziridine ring besides the substituents that could be accessed through the asymmetric aziridine alkylation chemistry reported by Wulff and coworkers.[30] Radical coupling reactions of compounds **2-25** and **2-26** could either proceed by decomposition or alkylation (Scheme 2-17).



Scheme 2-17: Reaction Pathway for the Radical of Compound **2-25** or **2-26**

First, the 2-halo-aziridines were reacted with tributyl tin hydride and various initiators to determine if a stable radical could be produced and replaced with a hydrogen atom. The benzene used in all of these reactions was degassed by the freeze pump thaw method (Table 2-11).



2-24, X = Cl
2-25, X = Br
2-26, X = I

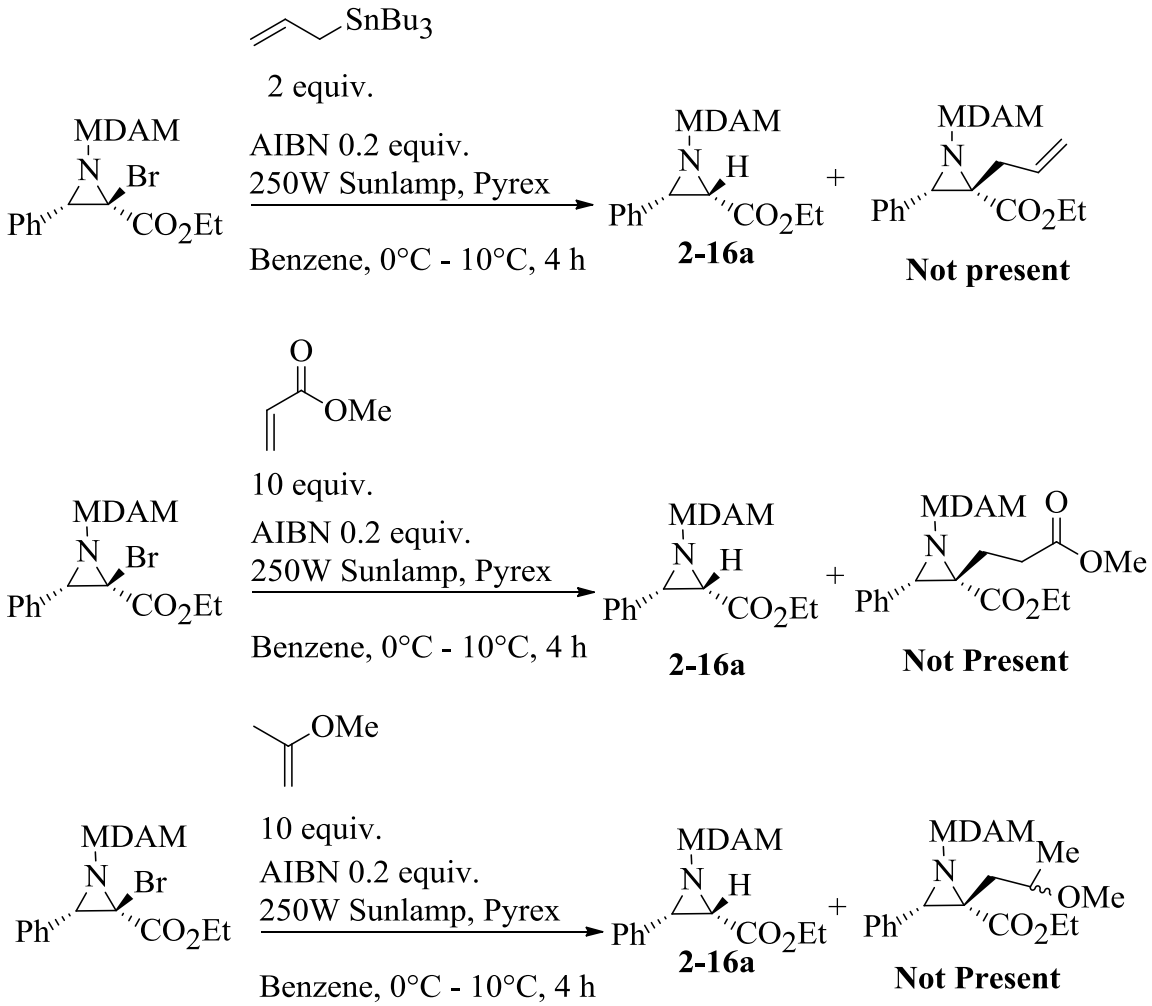
Table 2-11: Radical Reduction of 2-Halo-aziridines

Entry	X	Initiator Initiator equiv.	Initiator method	Temp °C	Time h	Glass ware	Result
1	I	None	250W Sunlamp	R.T.	2	Pyrex	Only **2-26**, no decomposition
2	I	None	Thermal	80	2	Pyrex	Decomposition
3	I	AIBN 0.2	Thermal	80	2	Pyrex	Decomposition, trace **2-16a**
4	Br	Me_6Sn_2 0.15	UV reactor	RT	5	Quartz	Decomposition
5	Br	AIBN 0.2	250W Sunlamp	0 - 10	2	Pyrex	Only **2-25**, No decomposition
6	I	AIBN 0.2	250W Sunlamp	0 - 10	2	Pyrex	Only **2-26**, No decomposition
7	Br	AIBN 0.2	250W Sunlamp	0 - 10	2	Quartz	**2-16a** only, 80% Yield
8	I	AIBN 0.2	250W Sunlamp	0 - 10	2	Quartz	**2-16a** only, 80% Yield
9	Br	None	250W Sunlamp	0 - 10	2	Quartz	Ratio **2-16a** : **2-25**, 1:1 Conversion by ^{1}H NMR

The reaction of **2-26** with tributyl tin hydride with or without azobisisobutyronitrile (AIBN) resulted in decomposition (entries 2 and 3). The issue seemed to be that a radical needed to be created at low temperatures to avoid aziridine ring opening, while most of the methods to generate radicals require at least 60°C with AIBN. Other radical initiators require even harsher conditions. A 250 watt sunlamp with quartz glassware was able to generate a stable aziridine radical at 0°C. Pyrex would reflect the light from the sunlamp and was not effective unless the sunlamp heated the flask to about 60°C, to cause thermal

initiation instead of photochemical initiation. A stable radical could be formed from both compound **2-25** and **2-26** (entries 7 and 8).

Initial results showed that a stable radical could be generated without decomposition to give compound **2-16a**. This seemed encouraging because if a stable radical could be generated, then it could react with either an electrophilic or nucleophilc substrate. However, attempts to couple the aziridine with both electrophilic and nucleophilic substrates were not successful. Instead, the only product that could be identified was compound **2-16a** (Scheme 2-18).



Scheme 2-18: Attempted Radical Coupling Reactions

Ideally, once the 2-halo-aziridine radical was formed, it would react with a substrate and the resulting radical would then be quenched with tributyl tin hydride to give the products shown in Scheme 2-18. Instead, the tributyl tin hydride just reduced the 2-bromo-aziridine to compound **2-16a**. The 2-bromo-aziridine was reduced too fast to compound **2-16a** and did not allow enough time for the aziridine radical to react with the substrate first. In attempt to avoid the formation of **2-16a**, the tributyl tin hydride was added with a syringe pump over several hours, but still there was not any desired products formed and only compounds observed were compounds **2-16a**, **2-25** or **2-26**.

Deprotection of 2-halo-aziridines

All of the previous coupling reactions of 2-halo-aziridines were not successful to produce the desired aziridines (compounds **2-18** or **2-18a**) to synthesize the target imidazolines (compounds **1-1** or **1-1a**). Compounds **2-18** or **2-18a** could be synthesized by reaction of compound **2-30** or **2-31** with PhMgBr. The deprotection of compound **2-24** would lead to the formation of either compound **2-30** or **2-31**. Deprotection of compound **2-24** by the standard procedure provided by Wulff [33] with TfOH in anisole led to aziridine ring opening and further decomposition (Table 2-12, entry 1).

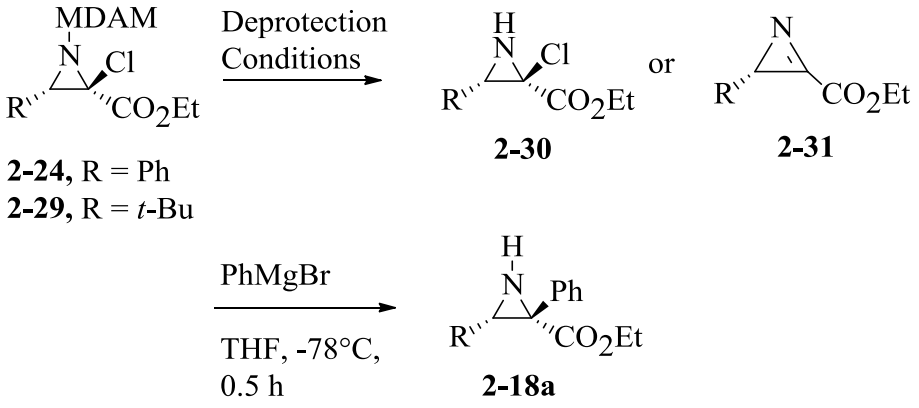
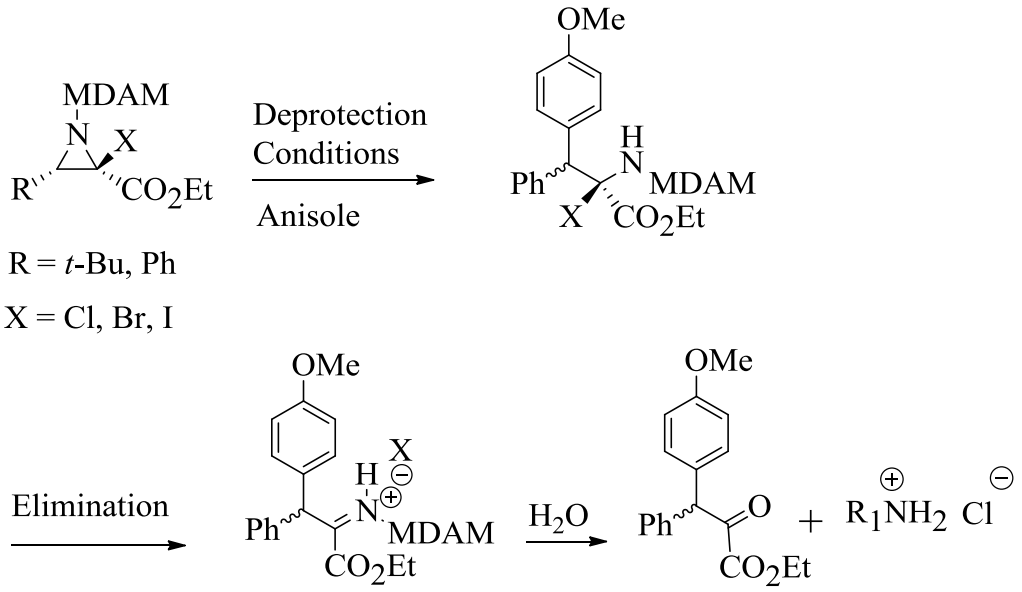


Table 2-12: Deprotection of 2-Halo-aziridines

Entry	R	Reagent	Reagent equiv.	Temp°C	Time h	% Yield **2-30** or **2-31**
1	Ph	TfOH	8	RT	2	0[a]
2	Ph	TfOH	1	RT	2	0[a]
3	Ph	TfOH	1	-40-RT	1	0[a]
4	Ph	TFA	1	RT	1	No rxn
5	Ph	MSOH	1	RT	1	No rxn
5	Ph	TFOH, Et_3SiH	4,4	0	0.5	0[a]
6	Ph	MSOH, Et_3SiH	4,4	0	0.5	0[a]
7	*t*-butyl	TfOH	1	-40-RT	1	0[a]

[a] Aziridine ring opening had occurred.

Deprotection of compounds **2-25** and **2-26** with TfOH or TFA lead to a very complicated mixture of products. Deprotection of compound **2-24** with weaker acids like TFA and methanesulfonic acid gave no reaction (entries 4 and 5). Even with a *t*-butyl group at the C-3 position of the aziridine ring instead of a phenyl group (compound **2-29**) deprotection was not possible (entry 6). Shown below in Scheme 2-19 was a possible explanation to what occurred during these deprotection reactions shown in table 2-12.



Scheme 2-19: Attempted Deprotection of Compounds **2-24**, **2-25**, and **2-26**

The halogen atom at the C-2 position of the aziridine ring must have pulled the lone pair of electrons into the p-orbital between the C-2 position and the nitrogen atom, causing high aziridine ring strain. Once the aziridine nitrogen atom was protonated, the strain energy was relieved by the aziridine ring opening. As a result, deprotection of the 2-halo-aziridines was not possible.

Conclusion

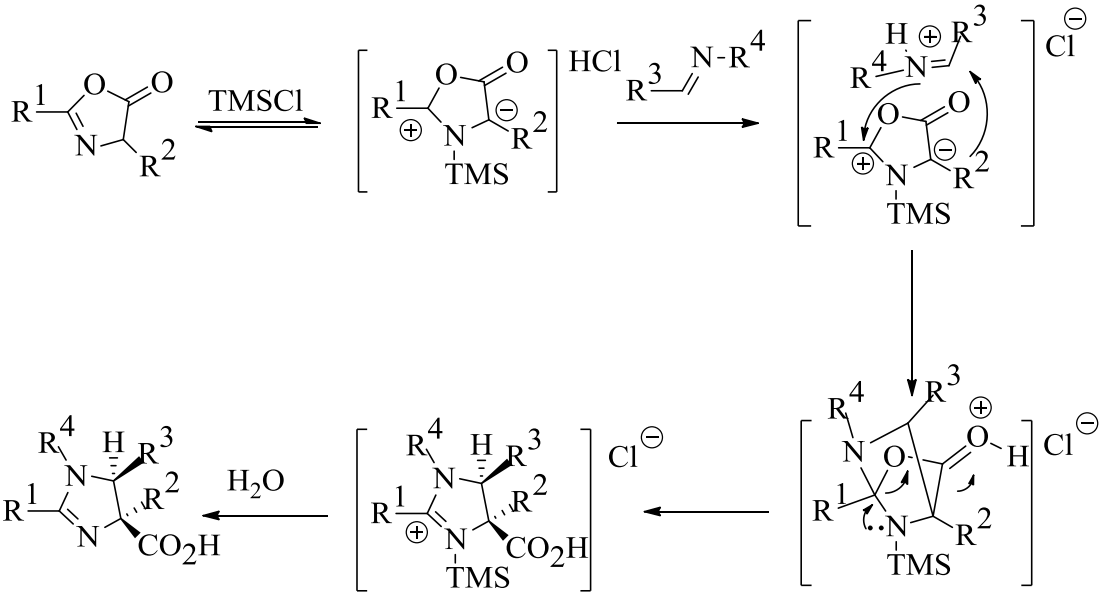
A methodology to halogenate N-MDAM aziridines at the C-2 position has been successful. However, all attempts to couple a Sp^2 carbon to the C-2 position of the ring were not fruitful. Also, deprotection of the MDAM group was not successful without opening the aziridine ring. The application of these halo-aziridines to the synthesis of useful molecules has not yet been achieved.

CHAPTER 3

RING EXPANSION OF AZIRIDINES TO IMIDAZOLINES

Previous Methods to Synthesize Imidazolines

Imidazolines have been previously synthesized in the Tepe group by the reaction of azlactones with imines.[1-3] These reactions proceed through a 1,3-dipolar cycloaddition of dipolarophiles (azlactones) with dienophiles (imines) mediated by TMSCl. The reaction of azlactones with imines yielded both the *syn* and the *anti* diastereomers with respect to R_2 and R_3.[1-3] Scheme 3-1 shows the formation for the anti stereoisomer.



Scheme 3-1: Mechanism for the Synthesis of Imidazolines from Azlactones with Imines[1-3]

The selectivity of the *syn* and *anti* imidazoline stereoisomers could be controlled by changing the electronics of the R_1 substituent. For example, if the R_1 substituent was a

phenyl group, the 1,3-dipole was stabilized to result in the *anti* stereoisomer as the major product (Table 3-1, entry 1). However, if the R_1 substituent was a methyl group, then the 1,3-dipole was not stabilized and as a result the *syn* imidazoline stereoisomer was formed exclusively (entry 4). Thus the *syn* and *anti* imidazoline stereoisomer selectivity was determined by the amount of resonance stabilization of the carbocation in the 1,3-dipole (Table 3-1).[47]

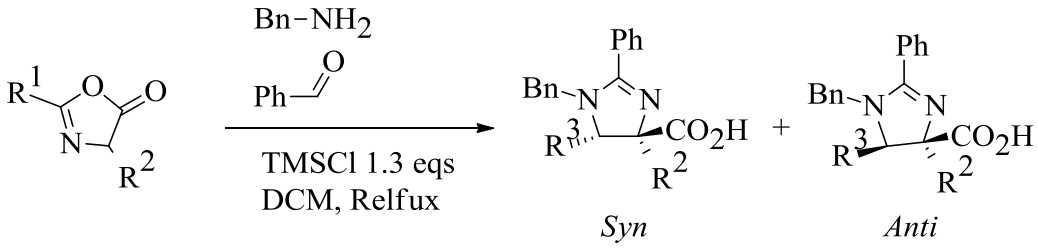


Table 3-1: Syn:Anti Imidazoline selectivity as a Function of 1,3-dipole Stabilization

Entry	R^1	R^2	% Yield	*Syn*:*Anti*
1	Ph	Me	75	5:95
2	Bn	Me	76	33:67
3	Me	Me	12	50:50
4	Me	Ph	72	90:10

The *anti* imidazoline stereoisomer was formed as the major product in most cases. From a biological standpoint, the Tepe group was generally only interested in the *anti* imidazolines, since the *anti* stereoisomers have been shown to inhibit NF-κB.[1,23-24] The scope of the Tepe imidazoline methodology was quite broad and tolerated a variety of different functional groups. Some of the examples are highlighted in Table 3-2.[48]

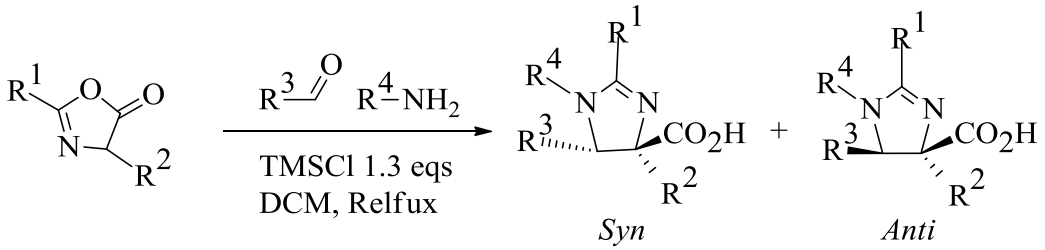


Table 3-2: Scope of Methodology for the Synthesis of Imidazolines from Azlactones with Imines

R^1	R^2	R^3	R^4	Yield *Anti*	Ratio *Anti*:*Syn*
Ph	Me	Ph	Bn	75	95:5
Ph	Me	4-methoxyphenyl	Bn	78	95:5
Ph	Me	Ph	4-fluorophenyl	74	95:5
Ph	Me	CO_2Et	4-fluorophenyl	72	95:5
Ph	Me	Ph	H	71	95:5
Ph	Ph	Ph	Bn	30	75:25
Ph	Me	Ph	CO_2Me	70	95:5
Ph	Me	4-pydridinyl	Bn	76	-
Ph	Ph	CO_2Et	4-fluorophenyl	68	95:5
Ph	Indole-3-methyl	Ph	Bn	68	95:5

Another reported methodology to synthesize imidazolines was through the ring expansion of tosyl aziridines with nitriles in the presence of a LA. Typical Lewis acids (LAs) used were boron trifluoride diethyl etherate, copper triflate, zinc triflate, and scandium triflate.[4-5] One of the advantages of this method was that it was a very simple and efficient way to synthesize racemic imidazolines. This was a solvent free method to synthesize imidazolines. A tosyl aziridine was simple combined with a nitrile in a catalytic amount of a LA to yield a variety of imidazolines.[4-5] Thus the purification and isolation of the product was simple. The yields were modest, as seen from some examples below in Table 3-3.

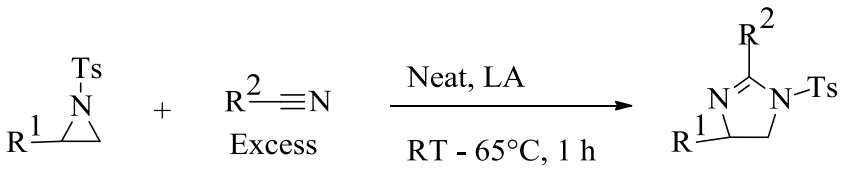


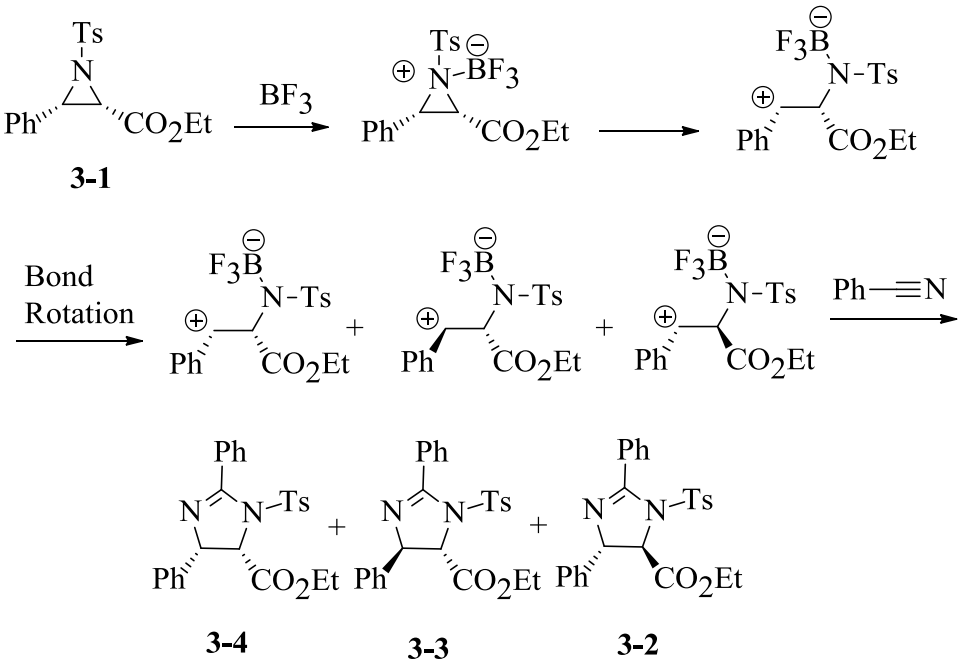
Table 3-3: Ring Expansion of Tosyl Aziridines with Nitriles[4-5]

Entry	R^1	R^2	% Yield
1	Ph	Ph	67
2	Ph	Me	75
3	Ph	Bn	63
4	Ph	3-methoxy Bn	49
5	Ph	4-Fluoro Bn	51
6	4-MePh	Me	77
7	4-ClPh	Me	72
8	4-MePh	Ph	62
9	4-ClPh	Ph	61

However, one of the drawbacks to this method was that the tosyl group had to be removed to functionalize the N-1 position of the imidazoline ring. Tosyl groups can be easily removed by reaction with elemental sodium in naphthalene.[49] Once the tosyl group has been removed the imidazolines can be acylated or alkylated. Due to the resonance between N-1, C-2, and N-2 positions of the imidazoline ring at least two different imidazoline regioisomers can be formed when alkylated or acylated. This would result in a mixture of two different regioisomers.[50-51]

Literature has shown that the LA catalyzed ring expansion of aziridines proceeds by an SN_1 mechanism through the most stable carbocation.[50-51] There have not been any examples of the ring expansion of compound **3-1** or similar compounds with nitriles have been reported by this method. The reaction of compound **3-1** with benzonitrile in

the presence of a catalytic amount of boron trifluoride diethyl etherate would be expected to yield 3 products (Scheme 3-2).

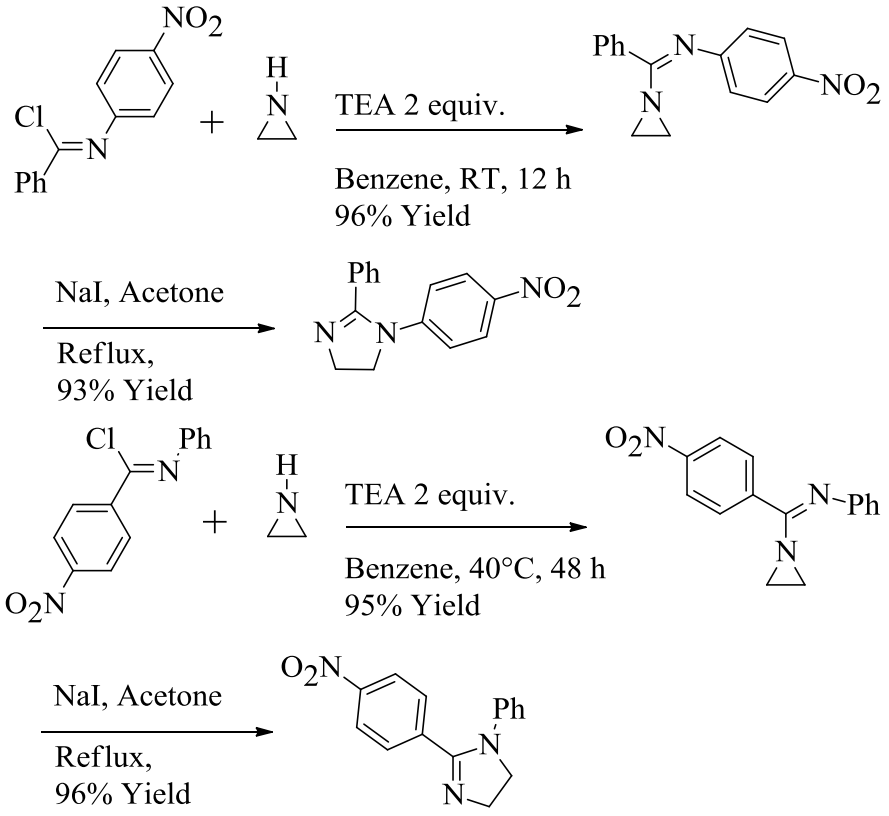


Scheme 3-2: Proposed Ring Expansion of ethyl 3-phenyl-1-(phenylsulfonyl)aziridine-2-carboxylate with Benzonitrile

One would not expect compound **3-1** to open at C-2 position, but instead to open at C-3 position due to the greater carbocation stability when reacted with boron trifluoride diethyl etherate. The enantioselectivity of the reaction could be lost due to bond rotation during the carbocation intermediate (Scheme 3-2). The *trans*-stereoisomers, compounds **3-2** and **3-3** would be expected to be the major products. However, the *cis*-stereoisomer, compound **3-4**, could be formed if the benzonitrile can react with the carbocation before the C-2-C-3 bond rotation from the *cis*-conformation to the *trans*-conformation can occur. Furthermore, deprotection of the tosyl group and alkylation or acylation would lead to a mixture of imidazoline regioisomers. One would believe that the synthesis of

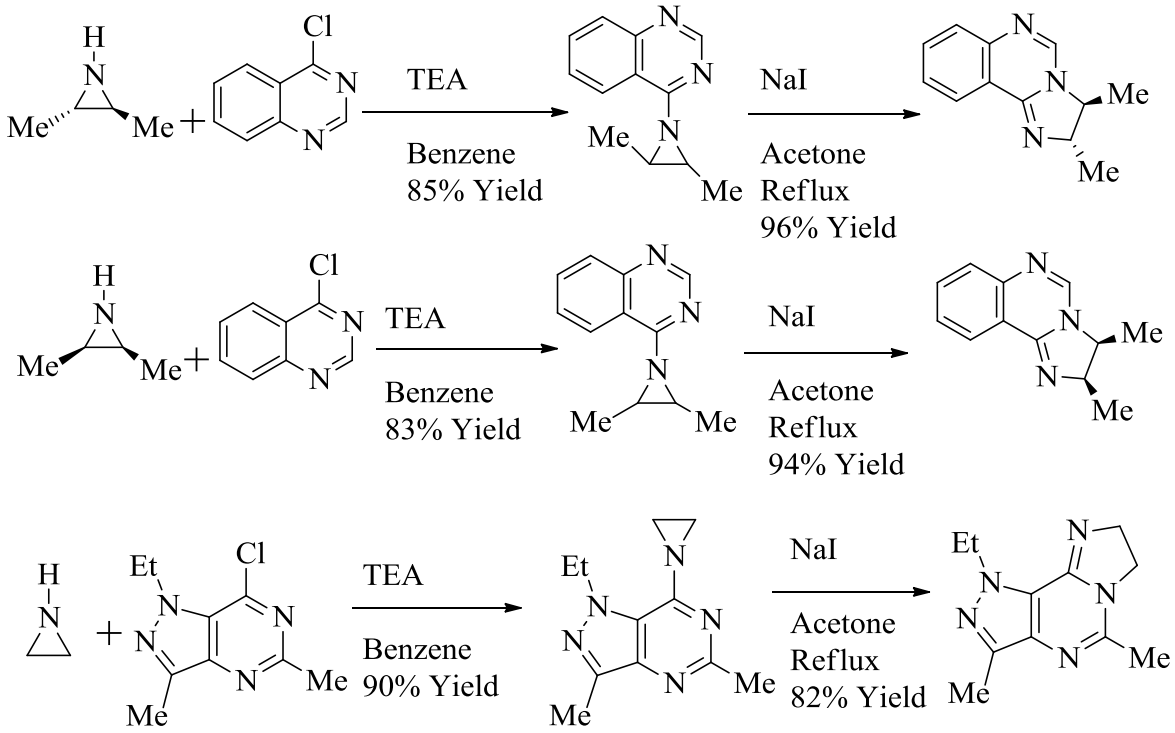
substituted imidazolines enantioselectively with nitriles would be problematic and therefore was never pursued through this method.

Another method to synthesize imidazolines from aziridines is through imidoyl aziridines. To date only two imidazolines have been reported to be synthesized by the isomerization of imidoyl aziridines.[52] There have not been any examples reported for the regioselective isomerization of imidoyl aziridines to imidazolines. Also, there have not been any examples reported for the izomerization of chiral imidoyl aziridines to chiral imidazolines (Scheme 3-3).



Scheme 3-3: Isomerization of Imidoyl Aziridines to Imidazolines[52]

Imidoyl chlorides have also been used to make heterocycles such as substituted 2,3-dihydroimidazo[1,2-c]quinazolines and substituted 7,8-dihydro-3-methyl-lH-imidalzo[1-2-c]pyrazolo[3,4-e]pyrimidines (Scheme 3-4).[53-54]



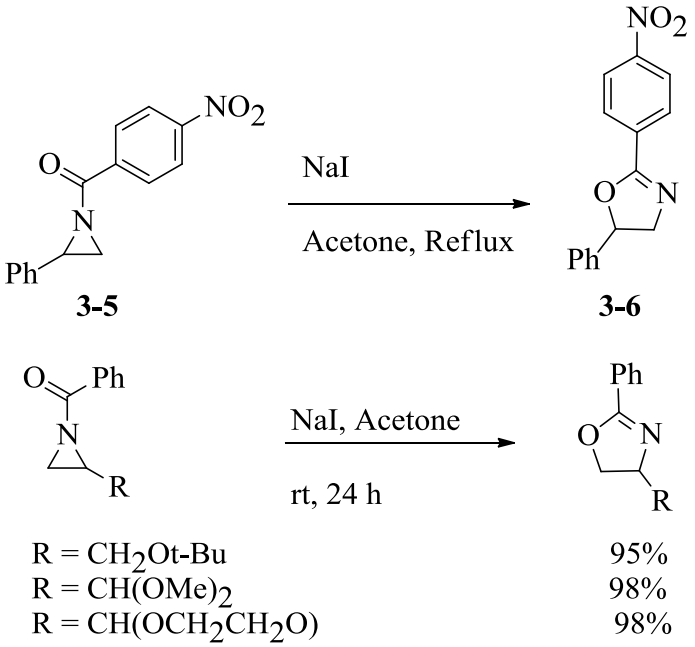
Scheme 3-4: Isomerization of Imidoyl Aziridines to Quinazolines and Pyrimidines

2,3-dimethyl aziridine and aziridine underwent reaction with imidoyl chlorides in the presence of triethyl amine in benzene to give the corresponding intermediates respectively. The triethyl ammonium hydrogen chloride salt was removed by precipitation out of ether and filtration. These intermediates were isomerized by refluxing in acetone with sodium iodide. The authors claim the reaction proceeded by two SN_2 reactions to give double inversion and an overall retention of stereochemistry. First, the iodide anion opened the aziridine ring to give inversion, and then the ring

expansion occurred by the nitrogen atom displacing the iodine atom through a second inversion.[53-54]

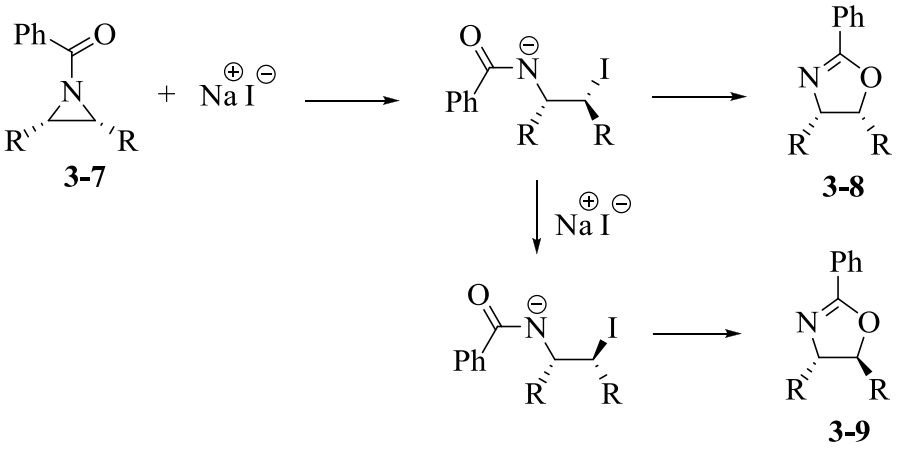
Previous Methods to Synthesize Oxazolines from aziridines

Isomerization of acyl and benzoyl aziridines to oxazolines has been accomplished by the sodium iodide method in solvents such as acetone, MeCN, and DMF. For example, (4-nitrophenyl)(2-phenylaziridin-1-yl)methanone, compound **3-5**, was isomerized with sodium iodide in acetone to yield compound **3-6**. The iodide anion attacked the most electropositive and sterically hindered carbon atom of the aziridine ring which was at the C-3 position and not the C-2 position (Scheme 3-5).[55] Other literature examples of 2-alkyl aziridines have also shown that the iodine anion will attack the C-3 position of the aziridine ring as well. Although the C-3 position of the aziridine ring did not contain an electron-withdrawing phenyl group like in the above example, it was still the most electropositive position of the aziridine ring due to the electron donating substituent at the C-2 position (Scheme 3-5).[56]



Scheme 3-5: Isomerization of acyl aziridines

Formation of oxazolines, like imidazolines, has been considered to proceed by two SN_2 reactions (Scheme 3-5).[57] For example, compound **3-7** first underwent attack by an iodine anion to open the aziridine ring, followed by attack of the oxygen anion to form the *cis* oxazoline compound **3-8**. However, one problem that can arise in these reactions was the loss of stereochemistry due to the fact that the iodide atom may be displaced by another iodide atom in a SN_2 fashion to cause inversion at that carbon. Then attack of the oxygen atom occurs to substitute the iodine atom to form the *trans*-oxazoline, compound **3-9**, instead of the *cis*-oxazoline compound **3-8**. (Scheme 3-6).



Scheme 3-6: Formation of *cis* and *trans* Oxazolines through the Sodium Iodide Isomerization

Therefore, isomerization of *cis*-N-benzoyl aziridines proceeded through a net retention of stereochemistry. In order to minimize the formation of the other *trans* stereoisomer, only a catalytic amount of sodium iodide was needed.[57]

There have been also been literature examples of isomerization of acyl and benzoyl aziridines to oxazolines with LA. One example that has been reported used a catalytic amount of aluminum trichloride.[58] The isomerization of acyl and benzoyl aziridines to oxazolines has also been reported by reaction in chloroform at room temperature.[59] This particular example used a chiral auxillary to direct the stereochemistry at the C-3 position of the aziridine ring.[59] Reaction in DCM even at reflux gave very little yield (Table 3-4, entry 4), but reaction in chloroform gave almost quantitative yields (entries 1 and 2). One possible explanation as to why chloroform worked so well was that it may have contained trace amounts of hydrochloric acid from photochemical decomposition with light. Isomerization of acyl aziridines also occurred with boron trifluoride diethyl etherate in DCM (Table 3-4, entry 5).[59]

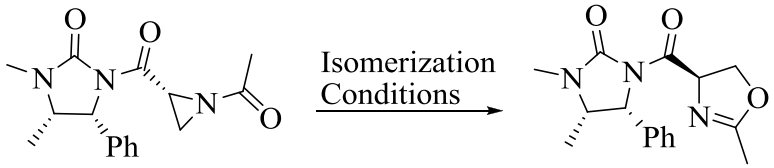


Table 3-4: Isomerization of Acyl Aziridines to Oxazolines

Entry	Solvent	Temp. °C	LA	Time h	% Yield
1	$CHCl_3$	RT	None	20	95
2	$CHCl_3$	Reflux	None	2	95
3	THF	Reflux	None	20	6
4	DCM	Reflux	None	18	7
5	DCM	-78	BF_3OEt_2, Cat.	4	85

The isomerization of benzoyl and acyl aziridines with various LAs are presumed to occur by coordination to the pyramidal lone pair of electrons on the aziridine nitrogen by an azaphilic metal.[60] On the other hand, use of an oxophilic metal will coordinate to the oxygen atom of the carbonyl group and activate the benzoyl aziridine for nucleophilic attack (Table 3-5).[60]

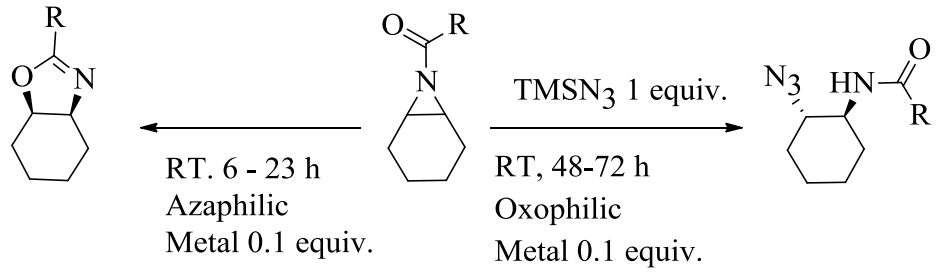
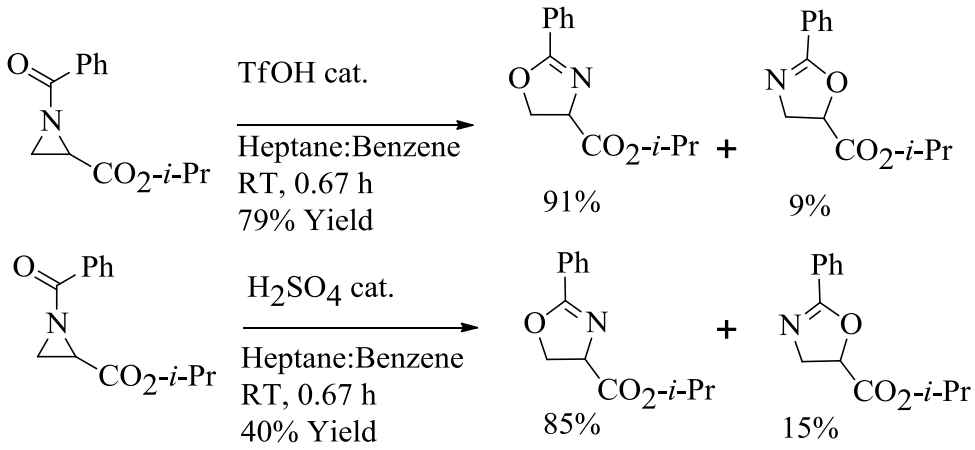


Table 3-5: Isomerization of Benzoyl Aziridines to Oxazolines with LAs[60]

Entry	Solvent	Metal	Metal Type	R	% Yield
1	DCM	Yb(biphenol)OTf	Oxophilic	p-MeO-C_6H_4	84
2	THF	$Ti(O\text{-}i\text{-}Pr)_4$	Oxophilic	Ph	64
3	THF	$Zr(Cp)_2(SbF_6)_2$	Oxophilic	Ph	57
4	DCM	Yb(biphenol)OTf	Oxophilic	Ph	72
5	THF	$Ti(O\text{-}i\text{-}Pr)_4$	Oxophilic	Ph	67

6	THF	$Zr(Cp)_2(SbF_6)_2$	Oxophilic	Ph	58
7	DCM	Yb(biphenol)OTf	Oxophilic	*p*-F-C_6H_4	75
8	DCM	Yb(biphenol)OTf	Oxophilic	*p*-CF_3-C_6H_4	80
9	THF/DME 20:1	$Cu(OTf)_2$	Azaphilic	*p*-MeO-C_6H_4	89
10	THF/DME 20:1	$Sn(OTf)_2$	Azaphilic	*p*-MeO-C_6H_4	83
11	THF/DME 20:1	$Zn(OTf)_2$	Azaphilic	*p*-MeO-C_6H_4	63
12	THF/DME 20:1	$Cu(OTf)_2$	Azaphilic	Ph	80
13	THF/DME 20:1	$Sn(OTf)_2$	Azaphilic	Ph	30
14	THF/DME 20:1	$Zn(OTf)_2$	Azaphilic	Ph	74
15	THF/DME 20:1	$Cu(OTf)_2$	Azaphilic	*p*-F-C_6H_4	80
16	THF/DME 20:1	$Sn(OTf)_2$	Azaphilic	*p*-F-C_6H_4	79
17	THF/DME 20:1	$Zn(OTf)_2$	Azaphilic	*p*-F-C_6H_4	60
18	THF/DME 20:1	$Cu(OTf)_2$	Azaphilic	*p*-CF_3-C_6H_4	76
19	THF/DME 20:1	$Sn(OTf)_2$	Azaphilic	*p*-CF_3-C_6H_4	67
20	THF/DME 20:1	$Zn(OTf)_2$	Azaphilic	*p*-CF_3-C_6H_4	62

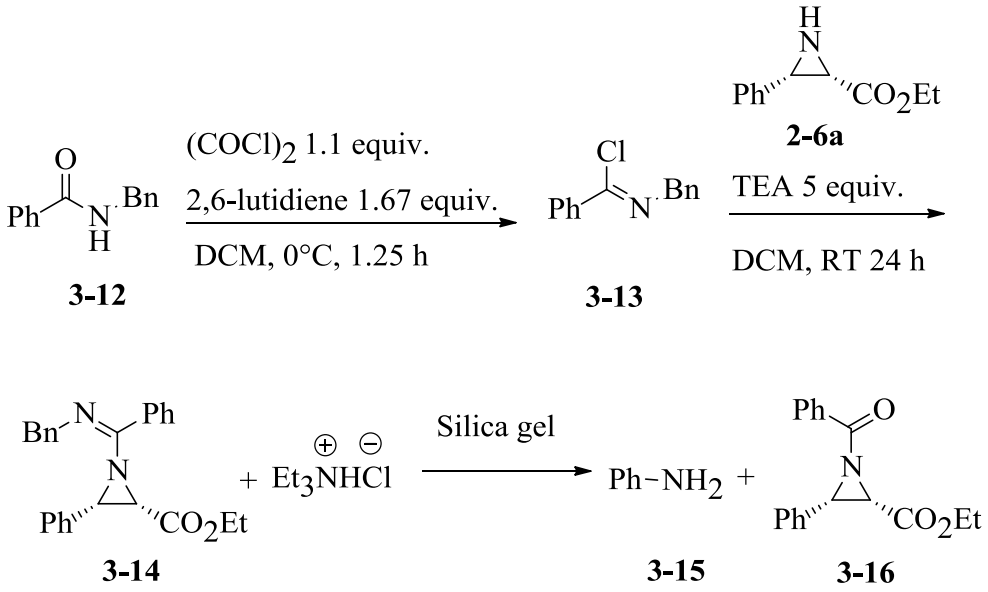
There have been few reported examples of the isomerization of acyl or benzoyl aziridines to oxazolines with Bronsted acids. One reported example employs sulfuric or triflic acid and has shown that a mixture of regioisomers was formed.[56] The major oxazoline formed in each example was due to the aziridine ring opening at the C-3 position to give the more stable carbocation. Obviously, the aziridine ring opening at the C-2 position resulted in the formation of a much less stable carbocation and and as a result was the minor product in both examples shown below (Scheme 3-7).[56]



Scheme 3-7: Bronsted Acid isomerization of Acyl Aziridines

Isomerization of Imidoyl Aziridines through LAs, Bronsted Acids and Sodium Iodide

Methods to synthesize imidoyl chlorides have typically employed thionyl chloride, phosphorous pentachloride, or oxalyl chloride.[61-63] Oxalyl chloride was superior to both thionyl chloride and phosphorous pentachloride to produce **3-13** with the greatest yield and shortest reaction time. Initial attempts to make the imidoyl aziridine, compound **3-14,** was by substitution of ethyl-3-phenylaziridine-2-carboxylate with (Z)-N-benzylbenzimidoyl chloride in DCM with triethylamine (TEA) present in excess. The ^{1}H NMR of compound **3-14** was complicated because compound **3-14** existed as two rotational isomers. Purification of by column chromatography caused hydrolysis of the imidoyl group to benzyl amine (**3-15**) and (2*S*,3*S*)-ethyl 1-benzoyl-3-phenylaziridine-2-carboxylate (**3-16**) (Scheme 3-8).



Scheme 3-8: Synthesis of compound **3-16**

Since column chromatography was not sufficient, the solvent was removed and the triethyl ammonium hydrochloride salt (Et_3NHCl) was precipitated with ethyl acetate and removed by filtration. The product was concentrated under reduced pressure and then placed under high vacuum with heating to about 50°C to remove the excess triethyl amine. The product was carried on to the next reaction without further purification. The ring expansion of the imidoyl aziridine, compound **3-14**, to imidazolines was attempted with various LAs (Table 3-6).

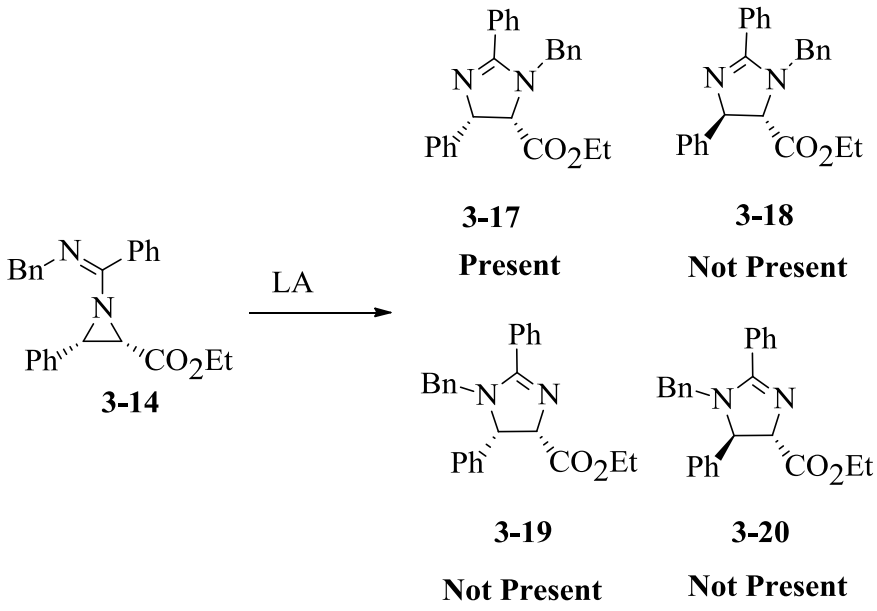


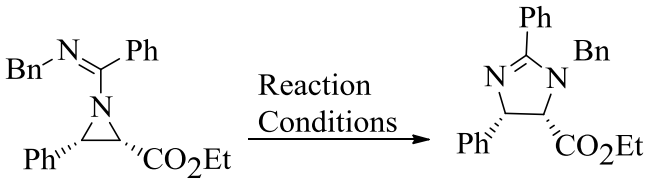
Table 3-6: LA Isomerization of Imidoyl Aziridine Compound **3-14**

Entry	Solvent	LA	LA equiv.	Temp. °C	Time h	% Yield **3-17**
1	DCM	BF_3	0.5	RT	24	No Rxn
2	DCM	BF_3	3.0	RT	36	No Rxn
3	$CHCl_3$	BF_3	5.0	Reflux	46	37
4	$CHCl_3$	BF_3	2.0	Reflux	19	24
5	THF	$AlCl_3$	0.5	RT	24	No Rxn
6	THF	$AlCl_3$	1.5	Reflux	48	No Rxn
7	THF	$MgBr_2$	0.5	Reflux	48	No Rxn
8	THF	$ZnOTf_2$	0.5	RT	24	Dec.
9	THF	$ScOTf_3$	0.5	RT	24	Dec.
10	THF	$YbOTf_3$	0.5	RT	24	Dec.
11	THF	$CuBr_2$	0.5	RT	24	Dec.
12	$CHCl_3$	BF_3, NaI	5.0, 1.0	Reflux	64	32

The isomerization of compound **3-14** was not observed in DCM or tetrahydrofuran at room temperature. The only LA that was successful was boron trifluoride diethyl etherate to yield compound **3-17** in low yield. Other LAs like the

metal triflates and $CuBr_2$ gave no reaction, but upon workup with sat. aq. $NaHCO_3$ gave hydrolysis of compound **3-14** to compounds **3-15** and **3-16** (entries 8-11).

Only the *cis* imidazoline stereoisomer, compound **3-16**, was formed in chloroform at reflux with boron trifluoride diethyl etherate with or without sodium iodide (entries 3,4, and 12). Unfortunately, the desired imidazoline, compound **3-19**, was not formed in any of the reaction conditions. However, there was not any evidence for the formation of either *trans*-imidazoline stereoisomers, compounds **3-18** or **3-20**. Isomerization to compound **3-17** was also attempted without a LA and the Et_3NHCl from the previous reaction was again removed prior to reaction (Table 3-7).



3-14 **3-17**

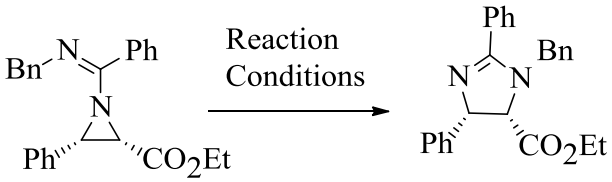
Table 3-7: Isomerization of Imidoyl Aziridines without LAs

Entry	Solvent	Additive	Additive equiv.	Temp. °C	Time h	% Yield **3-17**
1	$(CH_2Cl)_2$	None	0	Reflux	72	Dec.
2	$CHCl_3$	None	0	Reflux	15	22
3	$CHCl_3$	None	0	Reflux	72	No Rxn
5	$CHCl_3$	NaI	1.0	Reflux	22	40
6	Acetone	NaI	0.8	RT	24	No Rxn
7	Acetone	NaI	0.8	Reflux	24	41
8	Acetone	NaI	10	Reflux	24	30

Entry 2 showed that the imidazoline **3-17** could be synthesized without any LA. Entry 3 contradicted entry 2 because it gave no reaction under the same conditions. This seemed to indicate that perhaps trace hydrochloric acid catalyzed the reaction. As stated

previously, trace hydrochloric acid can form due to the photochemical decomposition of chloroform with light. The imidoyl aziridine, compound **3-14**, could be isomerized into compound **3-17** by reaction with sodium iodine in acetone (Entries 6-8).

All the previous reaction conditions employed gave only mediocre yields of compound **3-17**. In an effort to increase the yield of compound **3-17**, isomerization was attempted with a Bronsted acid. Isomerization of **3-14** with triflic acid was not successful and instead gave a complicated mixture of products (Table 3-8).



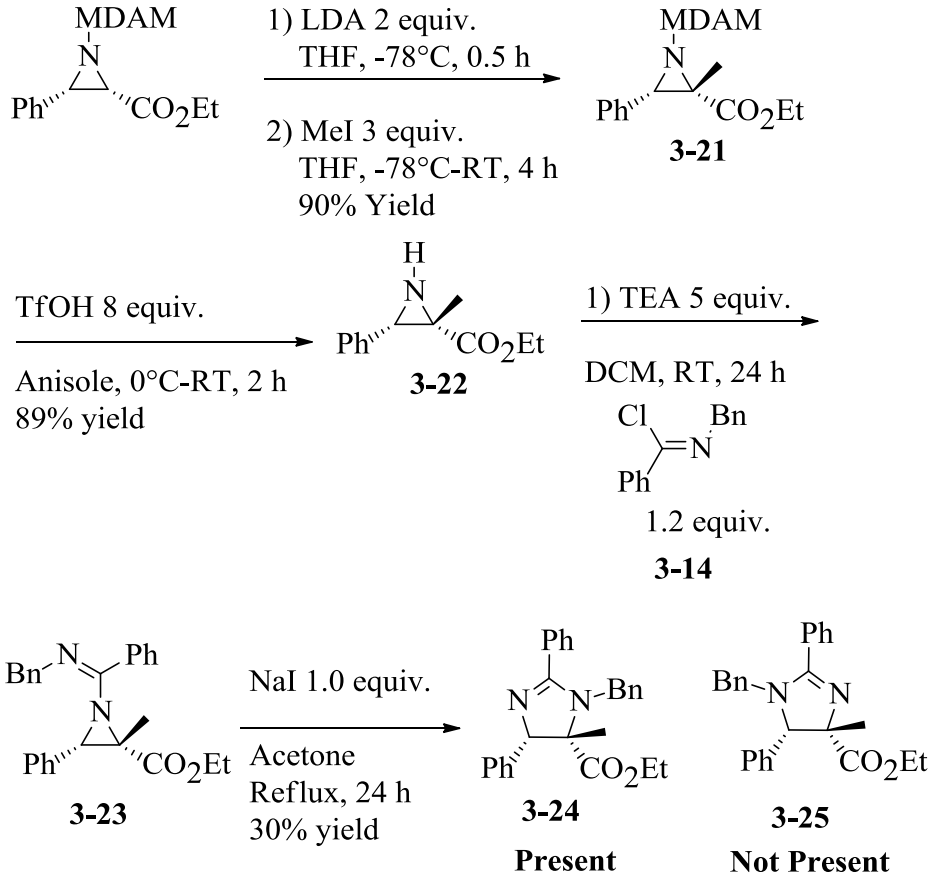
3-14 **3-17**

Table 3-8: Bronsted Acid Isomerizaton of Imidoyl Aziridines

Entry	Solvent	Acid	Acid equiv.	Result
1	DCM	TfOH	1.5	Dec.
2	Heptane	TfOH	1.5	Dec.
3	DCM	TfOH	0.3	Dec.

The identity of compound **3-17** was confirmed by previously reported literature data.[64] The coupling constants between the CH protons at the C-4 and C-5 positions of compound **3-17** were 12 Hz which indicated *cis* coupling, instead of 6 Hz, which would have indicated *trans* coupling.[64] NOE data by irradiation of the proton at the C-4 position showed absorption of the proton at the C-5 position. Irradiation of the benzyl protons showed absorption of the proton at the C-5 position and not at the C-4 position. The C-4 proton was further downfield than the C-5 proton.

Further evidence for the regioselectivity of the reaction could be gathered by methylation at the C-5 position of compound **3-17** and then by comparison of this product to the reported literature data for compound **3-25**. Compound **3-22** was synthesized by known procedures provided by Wulff and coworkers.[30,32] Another imidoyl aziridine, compound **3-24,** was synthesized in 30% overall yield (2 steps) by substitution with (Z)-N-benzylbenzimidoyl chloride and isomerization with sodium iodide in acetone (Scheme 3-6). The racemic synthesis of **3-25** has been reported by the Tepe group (Scheme 3-9).[48]

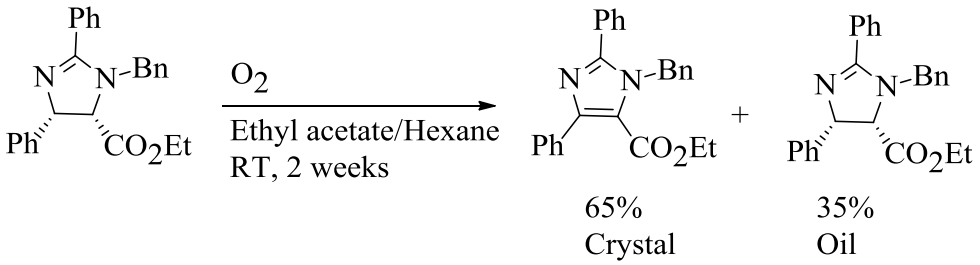


Scheme 3-9: Synthesis of compound **3-24**

Isomerization of **3-23** yielded compound **3-24**, not **3-25**. The identity of compound **3-24** was verified by comparing the NMR data to the Tepe literature reported NMR data for compound **3-25**. Since the NMR spectra did not match, this indicated that compound **3-24** was synthesized instead of compound **3-25**. The NOE data of compound **3-24** provided that the phenyl and the ethyl ester had a *cis* relationship to one another. NOE of compound **3-24** also confirmed that the proton at the C-4 position and the methyl at the C-5 position were *cis* to one another. The regiochemistry was confirmed by irradiation of the benzyl protons, which showed a signal at the methyl protons at the C-5 position and not the proton at the C-4 position.

The ring expansion reaction to compounds **3-17** and **3-24** were counter intuitive results. Therefore, in order to confirm the identity of compound **3-17** an x-ray crystal structure of compound **3-17** was obtained and solved by Dr. Richard J. Staples. Compound **3-17** was a viscous oil and an attempt to grow a crystal was carried out in a mixture of ethyl acetate and hexane in a glass vial. A crystal finally formed after approximately two weeks. Unfortunately, compound **3-17** had undergone oxidation with air to form ethyl 1-benzyl-2,4-diphenyl-1H-imidazole-5-carboxylate. The imidazole was the only compound identified by x-ray crystallography because compound **3-17** never crystallized, but instead remained as an oil and as a result did not undergo diffraction when analyzed by x-ray crystallography. Consequently only the imidazole was seen by x-ray crystallography. The crystal was dissolved in $CDCl_3$ and analyzed by ^1H NMR and it was evident that oxidation had occurred, but there was still some amount of compound **3-16** present. The ^1H NMR showed a mixture of 65% ethyl 1-benzyl-2,4-

diphenyl-1H-imidazole-5-carboxylate and 35% of compound **3-16** by integration of the two methyl groups.



Despite the oxidation of compound **3-17** to an imidazole the regiochemistry of the ring expansion reaction can still be confirmed by the crystal structure. However, the stereochemistry was believed to be the *cis*-stereoisomer, but was not with 100% certainty.

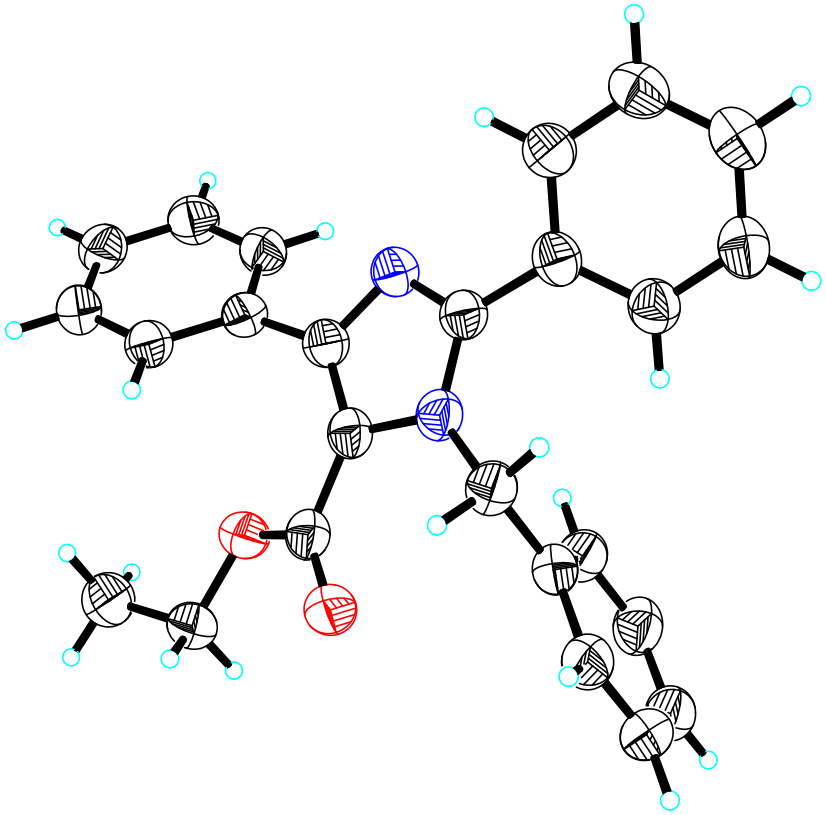
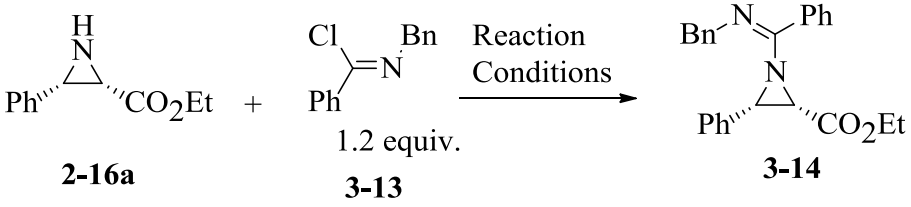


Figure 3-1: Crystal Structure of Oxidized Compound **3-17**

The yields of imidazolines **3-24** and **3-17** were low and the impurities present were difficult to identify due to the rotational isomers of the imidoyl aziridines. The optimal reaction conditions to form compound **3-14** were therefore investigated (Table 3-9).



2-16a **3-13** **3-14**

Table 3-9: Optimization of Intermediate Imidoyl Aziridine

Entry	Base	Base equiv.	Solvent	Temp °C	Time h	Comments
1	TEA	6	Benzene	RT	48	Still **2-16a** present
2	TEA	6	Benzene	RT	20	Still **2-16a** present
3	TEA	6	Benzene	Reflux	20	Decomposition
4	TEA	10	DCM	RT	12	Still **2-16a** present
5	TEA	6	DCM	Reflux	5	Rxn Complete
6	Hünig's Base	6	DCM	Reflux	5	Rxn Complete
7	KO-t-bu	1.2	THF	0°C-RT	20	Decomposition
8	NaH	1.2	THF	0°C-RT	20	Still **2-16a** present

Compound **3-14** was synthesized in the highest yield by refluxing in DCM with six equivalents of TEA. The ^{1}H NMR spectrum showed the absence of (3*S*,2*S*)-ethyl-3-phenylaziridine-2-carboxylate. The excess TEA was removed by high reduced pressure for several hours to yield crude compound **3-14** and Et_3NHCl. To better understand the role of sodium iodide and the Et_3NHCl in the isomerization of compound **3-14** into compound **3-17** the following reactions were conducted (Table 3-10).

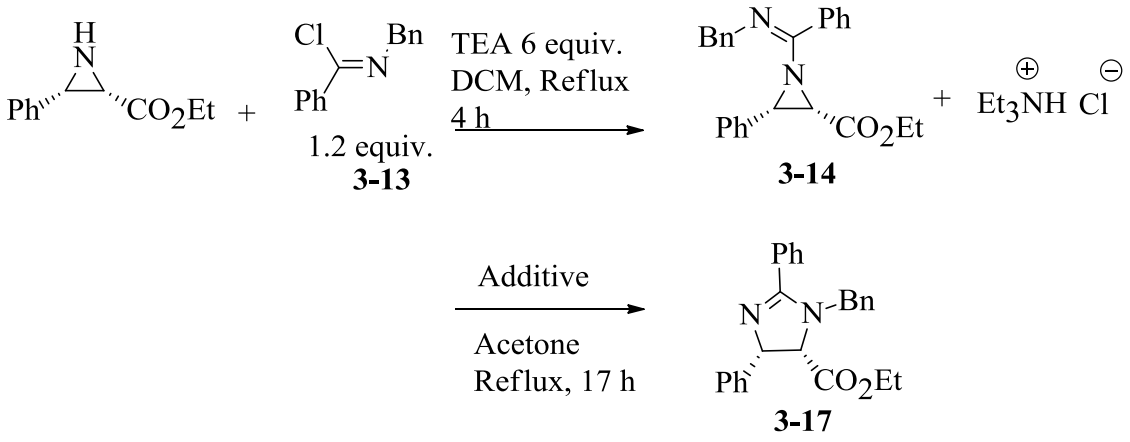
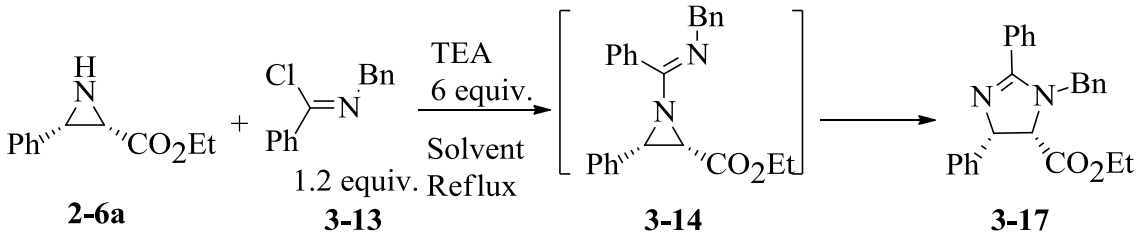


Table 3-10: Isomerization to (4*S*,5*S*)-ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate

Entry	Solvent	Time h	Temp.	Additive	% Yield **3-17**
1	Acetone	17	Reflux	NaI 1 equiv. Et_3NHCl 1.2 equiv.	20
2	Acetone	17	Reflux	Et_3NHCl 1.2 equiv.	25
3	Acetone	17	Reflux	Trace Et_3NHCl	22
4	Acetone	17	Reflux	None	0

The first isomerization reaction of compound **3-14** was carried out in acetone with sodium iodide and Et_3NHCl. The second reaction, entry 2, proved that sodium iodide was not needed and only triethyl Et_3NHCl was needed to isomerize compound **3-14** into compound **3-17**. The third reaction, entry 3, was carried out with only a trace amount of Et_3NHCl and the last reaction, entry 4, was without any sodium iodine or Et_3NHCl. The Et_3NHCl was removed by filtration before refluxing in acetone. Reaction 4 gave no reaction, but entry 3 gave compound **3-17** in low yield. This seemed to indicate that a weak acid like Et_3NHCl, which has a pKa of approximately 10, catalyzed the isomerization of compound **3-14** into compound **3-17**.

The yield of compound **3-17** was very low because the imidoyl chloride, compound **3-14**, was very water sensitive. The low yield was from hydrolysis of **3-14** into compounds **3-15** and **3-16**. It was difficult to isolate the intermediate compound **3-14** and manipulate it without it being contaminated with trace amounts of water. So instead of isolating compound **3-14**, the imidazoline **3-17** was synthesized in one step from (3*S*, 2*S*)-ethyl-3-phenylaziridine-2-carboxylate (**2-6a**) (Table 3-11).



2-6a **3-13** **3-14** **3-17**

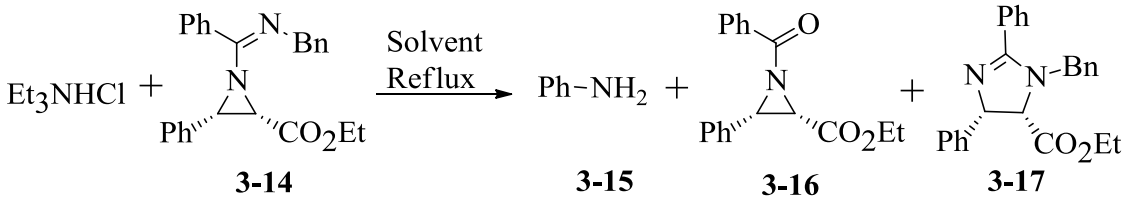
Table 3-11: One Step Synthesis of (4*S*,5*S*)-ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate

Entry	Solvent	Time h	% Yield **3-17**	Comments
1	DCM	24	0	Only **3-14**
2	$CHCl_3$	72	Trace	Major component was **3-14**
3	DCM	4	0	Only **3-14**
4	Acetone	17	23	Major component was **3-14**
5	1,4 Dioxane	17	20	Major component was **3-14**

Only trace amounts of compound **3-17** was formed by refluxing in DCM (entries 1, 3). The reaction was also carried out in acetone and 1,4 dioxane to synthesize compound **3-17** in only 20-23% yield. The reaction stopped at the intermediate, compound **3-14**, in DCM or $CHCl_3$. These reactions (Entries 1-3) were monitored by ^1H NMR to show that the reaction shut down once approximately 20% imidazoline was formed in only approximately 4 hours. The rest of the reaction mixture was compound **3-14,** which did not convert into compound **3-17** even with additional reaction time. It seemed that excess TEA shut down the reaction and stopped it at the intermediate imidoyl aziridine.

Since the reaction seemed to require a weak acid to undergo the ring expansion to the imidazoline **3-17**, excess TEA would decrease the probability of a proton from Et_3NHCl reacting with the intermediate compound **3-14**.

Compound **3-14** was synthesized by refluxing in DCM for 5 hours with 6 equivalents of TEA. The solution was concentrated under reduced pressure and excess TEA was removed by heating under high vacuum. This crude product contained product **3-14** and Et_3NHCl. The Et_3NHCl was not removed and the crude product, compound **3-14**, was refluxed in various solvents to give imidazoline **3-17** along with some hydrolysis to yield compounds **3-15** and **3-16** (Table 3-12).



3-14 **3-15** **3-16** **3-17**

Table 3-12: Two Step Synthesis of (4*S*,5*S*)-ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate

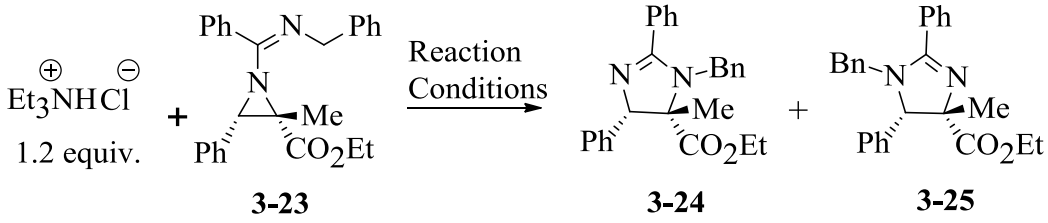
Solvent	Time h	% **3-14** ^{1}H NMR	% **3-16** ^{1}H NMR	% **3-17** ^{1}H NMR	% Yield **3-17**
Acetone	12	0	31	68	50
Acetone with Molecular Sieves	12	0	25	75	52
THF	36	0	24	74	55

The yield of compound **3-17** was improved, but still a trace amount of water was responsible for hydrolysis of compound **3-14**.

Unfortunately and unexpectedly, in all the reactions employed so far only the undesirable regioisomer was synthesized by the ring expansion of compound **3-14** to compound **3-17**. Similarly, the ring expansion of compound **3-23** gave only compound

3-24 and not compound **3-25 (**Table 3-13). One would expect that the intermediate **3-23** would break at the N-C-3 bond to make a benzyl carbocation and would not break at the N-C-2 bond to give an alpha ester carbocation. However compound **3-25** was not synthesized and was an unexpected result. The exact mechanism of the ring expansion of the intermediate imidoyl aziridines to imidazolines was not clear.

Compound **3-24** had a much higher EC_{50} value than compound **3-25** upon testing against the 20S proteasome in the Tepe lab by Teresa A. Lansdell, which indicated that the imidazoline regiochemistry was very important (see Table 3-17). In order to improve the regiochemisty of the ring expansion reaction, the solvent and reaction temperature was studied. Isomerization of compound **3-23** to compounds **3-24** and **3-25** was carried out in solvents of varying polarity with 1.2 equivalents of Et_3NHCl (formed from the synthesis of compound **3-23**). (Table 3-13).



3-23 **3-24** **3-25**

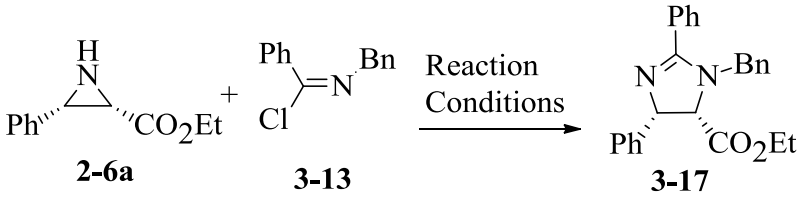
Table 3-13: Regiochemistry Selectivity as a Function of Solvent and Temperature

Solvent	Temp (°C)	^{1}H NMR % **3-24**	^{1}H NMR % **3-25**	Polarity index
DMF	80	85	15	6.4
Acetone	60	100	0	5.1
Dioxane	60	No rxn	No rxn	4.8
Dioxane	80	75	25	4.8
Dioxane	110	67	33	4.8
Toluene	110	63	37	2.4

The data from Table 3-13 seemed to indicate that lower temperatures and polar solvents tend to favor compound **3-24** and non-polar solvents and higher temperatures favored compound **3-25**, but unfortunately the effects were not that drastic.

Optimization and Scope of One Pot Synthesis of Imidazolines

Synthesis of imidazolines in one step from aziridines would be more efficient than trying to manipulate the water sensitive and acid sensitive intermediate imidoyl aziridines. Although the undesirable regioisomer was synthesized, a method to synthesize imidazolines in decent yields in one step from aziridines has been successful nonetheless (Table 3-14).



2-6a **3-13** **3-17**

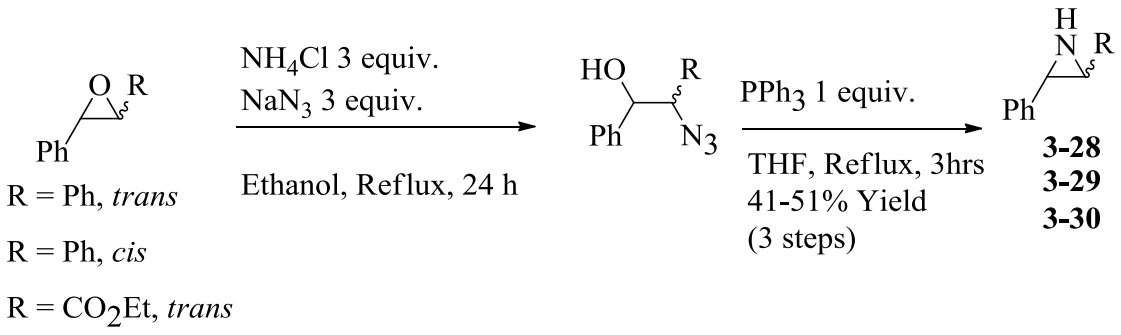
Table 3-14: Optimization of Imidazoline (4S,5S)-ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate

Entry	Temp °	Solvent	Rxn	Base	**3-13**	Base	% Yield
1	55	DCM	12	Hunig'sBase	1.5	6	0[a]
2	80	Toluene	12	TEA	1.5	2.4	0[a]
3	80	Toluene	9	DABCO	1.5	1.2	0[a]
4	80	Toluene	21	2,6-lutidine	1.5	1.5	20
5	80	Acetone	21	2,6-lutidine	1.5	1.5	37
6	80	MeCN	21	2,6-lutidine	1.5	1.5	20[b]
7	80	DMSO	21	2,6-lutidine	1.5	1.5	5[b]
8	80	DMF	9	2,6-lutidine	1.5	1.5	46
9	55	DMF	9	2,6-lutidine	1.5	1.5	32
10	RT	DMF	23	2,6-lutidine	1.5	1.5	10[b]
10	RT	DMF	117	2,6-lutidine	1.5	1.5	33[b]
11	RT	DMF	23	2,6-lutidine	1.5	7.5	38[b]
11	RT	DMF	44	2,6-lutidine	1.5	7.5	60[b]
11	RT	DMF	117	2,6-lutidine	1.5	7.5	67[b]
12	RT	DMF	65	Pyridine	1.5	7.5	62[b]
13	RT	DMF	65	DMAP	1.5	7.5	0[b]
14	55	DMF	21	2,6-lutidine	1.3	6.5	35
15	40	DCM	21	2,6-lutidine	1.1	5.5	46
16	55	DMF	21	2,6-lutidine	1.1	5.5	50
17	80	DMF	21	2,6-lutidine	1.1	5.5	47
18	80	DCM	21	2,6-lutidine	1.1	5.5	39
19	80	DCE	21	2,6-lutidine	1.1	5.5	37
20	55	DMF	21	2,6-lutidine	1.1	5.5	50[bc]
21	80	DMF	21	NaOAc	1.1	1.1	0
22	55	DMF	21	2,6-lutidine	1.1	5.5	50[bd]
23	130	DMF	3	2,6-lutidine	1.1	5.5	20[b]
24	55	DMF	6	2,6-lutidine	1.2	6	52
25	55	DMF	6	none	1.2	6	0

[a] The reaction stopped at the intermediate compound 3-14. [b] Yield based on the crude ^{1}H NMR. [c] The imidoyl chloride was added over 4 hours with a syringe pump to compound **2-6a**, DMF, and 2,6-lutidine. [d] Compound **2-6a** was added over 4 hours with a syringe pump to the DMF, compound **3-13**, and 2,6-lutidine

A bulky base like 2,6-lutidine was the key in synthesizing the imidazoline **3-17**. Other bases stopped the reaction at the intermediate compound **3-14** (entries 1-3). Excess of other bases like TEA would actually inhibit the formation of compound **3-17** and would stop at the intermediate compound **3-14**. A variety of solvents were screened and DMF was found to be the best as compared to the other solvent at 80°C (entries 4-7, 17-19). To minimize the formation of impurities the optimal temperature was determined to be 55°C (entry 16). If the reaction was carried out at 80°C in DMF a new impurity (was not present of 55°C) formed and the new impurity was hard to remove by column chromatography (entry 8). The ring expansion reaction to compound **3-17** did occur very slowly at room temperature. An excess amount of 2,6-lutidine was not necessary, but increased the reaction rate. Two reactions were monitored by ^{1}H NMR at room temperature and the reaction with 7.5 equivalents of 2,6-lutidine was faster than the reaction with 1.5 equivalents (entries 10, 11). An excess amount of 2,6-lutidine did not inhibit the reaction rate like other bases employed. The reaction went to completion very fast at elevated temperatures in DMF, but a significant amount of decomposition occurred as well (entry 23). The formation of another impurity formed when excess amount of compound **3-13** was used. If too little of compound **3-13** was used, it would be hydrolyzed to form benzyl benzamide due to residual water in the reaction mixture instead of reacting with (3*S*, 2*S*)-ethyl-3-phenylaziridine-2-carboxylate (**2-6a**). Changing the order of addition of either the imidoyl chloride to the aziridine in DMF with 2,6-lutidine or the aziridine to the imidoyl chloride in DMF with 2,6-lutidine had very little effect on the yield (entries 20, 22). The best yield obtained was 52% yield of only one imidazoline (Entry 24).

Other aziridines were synthesized to determine if the ring expansion would be successful. Racemic aziridines, compounds **3-28**, **3-29**, and **3-30** were synthesized by known literature procedures (Scheme 3-10).



Scheme 3-10: Synthesis of Racemic Aziridines

Since, the ring expansion of the imidoyl aziridine compound **3-14** to compound **3-17** had given the undesirable regioisomer one solution to this problem was to use a symmetrical aziridine. Compounds **3-28** and **3-29** were symmetrical aziridines so obviously the regiochemisty of the aziridine ring expansion reaction would not matter in this case.

One of the key requirements for the imidazolines to be potent inhibitors of NF-κB was to have *trans*-phenyl groups at the C-4 and C-5 positions of the imidazoline ring. In order to test the scope of the ring expansion reaction of aziridines to imidazolines, other imidoyl chlorides had to be synthesized. Therefore, a variety of amides were synthesized from the corresponding acid chlorides and amines (Table 3-15).

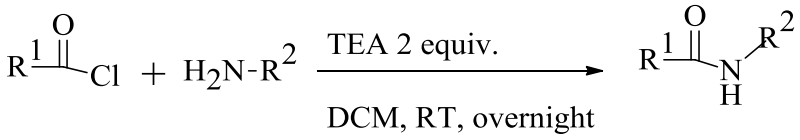


Table 3-15: Synthesis of Amides

R^1	R^2	#	% Yield	R^1	R^2	#	% Yield
p-MeO-C_6H_4	Bn	**3-31**	90	Ph	*p*-MeO-C_6H_4	**3-39**	93
Ph	Bn	**3-32**	95	Ph	Ph	**3-40**	92
p-F-C_6H_4	Bn	**3-33**	90	Ph	CH_2CO_2Me	**3-41**	56[c]
p-NO_2-C_6H_4	Bn	**3-34**	92	Ph	PMB	**3-42**	94
CH_2=CH_2	Bn	**3-35**	93[a]	Ph	Cy	**3-43**	97
Cy	Bn	**3-36**	34[b]	Ph	Me	**3-44**	63[d]
Me	Bn	**3-37**	95	Ph	*t*-bu	**3-45**	95
Py	Bn	**3-38**	35[b]	H	Cy		NA[e]

[a] Added acid chloride dropwise over 10 minutes to the amine at 0°C. [b] Converted the corresponding carboxylic acid into acid chloride by reaction with 1 equiv. of TEA and 1 equiv. of oxalyl chloride. [c] The amine was as the HCl salt, 3 equiv. of TEA was used. [d] Used 6 equiv. of $MeNH_3Cl$ and 6 equiv. of TEA at -10°C. [e] Purchased from Aldrich.

These amides were converted into imidoyl chlorides by reaction with oxalyl chloride in DCM. The reactions were monitored by ^{1}H NMR in $CDCl_3$ to determine the optimum reaction time. After the disappearance of the amide proton, the solution was concentrated under reduced pressure at room temperature to remove the DCM. DMF and compound **3-28** were added and the reaction flask was heated with an oil bath to 55°C (Table 3-16).

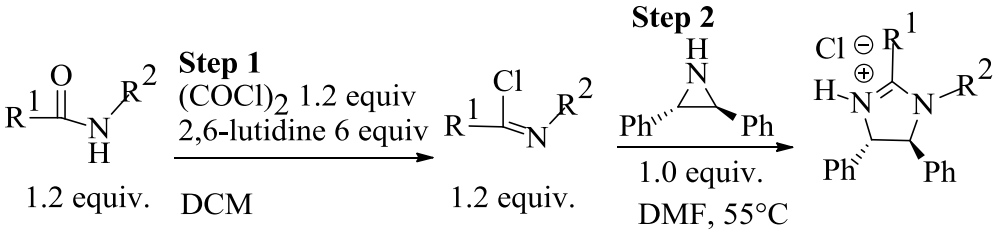


Table 3-16: One Pot Synthesis of racemic *trans*-imidazolines

Entry	R^1	R^2	#	Step 1 Time h	Step 1 Temp °C	Step 2 Time h	Step 2 Temp °C	% Yield
1	*p*-MeO-C_6H_4	Bn	3-46	1.25	0	6	85	59
2	*p*-MeO- C_6H_4	Bn	3-46	1.25	0	9	55	57
3	Ph	Bn	3-47	1.25	0	6	85	59
4	Ph	Bn	3-47	1.25	0	9	55	55
5	*p*-F-C_6H_4	Bn	3-48	1.25	RT	9	55	43
6	*p*-NO_2- C_6H_4	Bn	3-49	6	RT	6	85	0
7	*p*-NO_2- C_6H_4	Bn	3-49	6	RT	6	55	0
8	Py	Bn	3-50	1.25	80[a]	6	85	0
9	Py	Bn	3-50	1.25	80[a]	6	55	0
11	Cy	Bn	3-51	1.25	RT	6	85	47
12	Cy	Bn	3-51	1.25	RT	6	55	67
13	Me	Bn	3-52	1.25	0	6	85	48
14	Ph	*p*-MeO-C_6H_4	3-53	1.25	RT	13	55	0[b]
15	Ph	Ph	3-54	1.25	RT	6	85	0
16	Ph	CH_2CO_2Me	3-55	1.25	RT	6	85	0
17	Ph	PMB	3-56	1.25	0	9	55	53
19	Ph	Me	3-57	1.25	0	9	55	60
20	Ph	*t*-bu	3-58	1.25	0	9	55	0[b]
21	H	Cy	3-59	1.25	0	6	55	0[b]

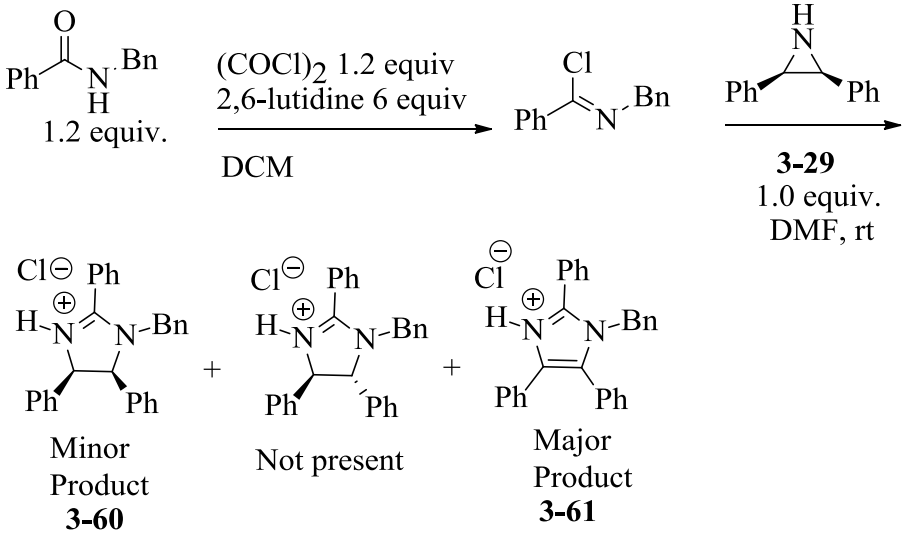
[a] PCl_5 in toluene was used to synthesize the imidoyl chloride. [b] Analysis of a reaction aliquot proved that the desired product was present by ^{1}H NMR, but decomposed upon workup and purification.

The imidazolines were formed as salts due to the basic nitrogen atom and the acidic conjugate acid of 2,6-lutidine. The reactions were quenched with $NaHCO_3$ and

purified by column chromatography. Some imidazolines were unstable and had to be purified under very basic column chromatography conditions. Imidazolines **3-53**, **3-58**, and **3-59** were present by ^{1}H NMR of the crude reaction solution, but decomposed upon workup and purification by column chromatography even under basic conditions.

Cis-diphenyl aziridine, compound **3-29**, was treated with (Z)-N-benzylbenzimidoyl chloride in DMF at 55°C, but resulted in 0% yield. However, when this reaction was repeated at room temperature for 3 days a small amount of imidazoline **3-60** was formed in only traceable yield. The two phenyl groups at C-4 and C-5 were *cis* to one another, and this stereochemistry was verified by the reported literature data.[23]

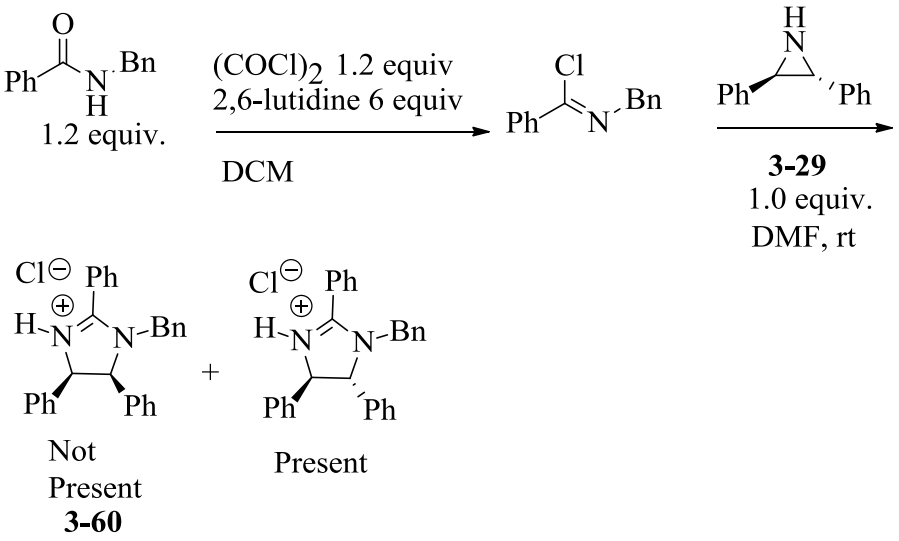
The yield for compound **3-60** was so low due to the ability of the *cis*-imidazoline to oxidize to an imidazole compound **3-61** (Scheme 3-11).



Scheme 3-11: Synthesis of *cis*-(4,5)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole

The *trans*-stereoisomer was not present which indicated that the reaction preserved its stereochemistry. Similarly, the *trans*-aziridine (compound **3-30**) also preserved its

stereochemistry under the ring expansion to give only the *trans*-imidazoline stereoisomer **3-62** (Scheme 3-12).



Scheme 3-12: Synthesis of ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate

An x-ray crystal structure of compound **3-57** was solved by Dr. Richard J. Staples. The crystal showed disorder which was 50:50 in both molecules observed in the asymmetric cell. In both enantiomers there was free rotation about the bond between the phenyl group at the C-2 position of the imidazoline ring and the second carbon atom (C-2) of the imidazoline ring. A crystal structure of compound **3-57** was obtained to prove the stereochemistry of the imidazoline was the *trans*-stereoisomer not the *cis*-stereoisomer as well as to prove the identity of the imidazoline. Based on the x-ray crystal structure of compound **3-57** all of the other imidazolines in Table 3-16 were all determined to be the *trans*-stereoisomer as well. The coupling constant of the protons at the C-4 and C-5 positions of the imidazoline ring were consistently between 8.0 to 10 Hz for the *trans*-imidazolines in table 3-16. The coupling constant between the protons at the C-4 and C-5 positions of the imidazoline ring of the *cis*-imidazoline **3-60** was 11 Hz.

Comparison of compounds **3-60** and **3-47** the coupling constant between the protons at the C-4 and C-5 positions were 8.5 Hz for the *cis*-stereoisomer and 11 Hz for the *trans*-stereoisomer.

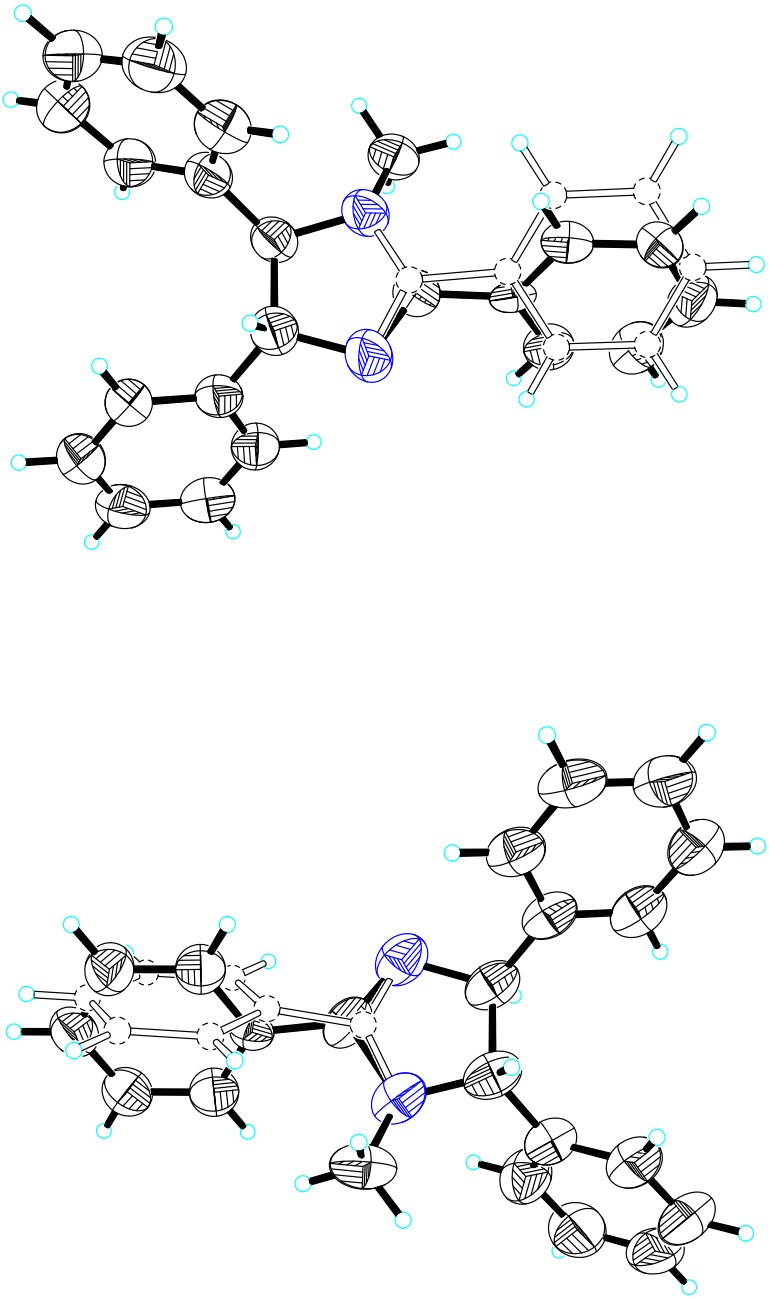
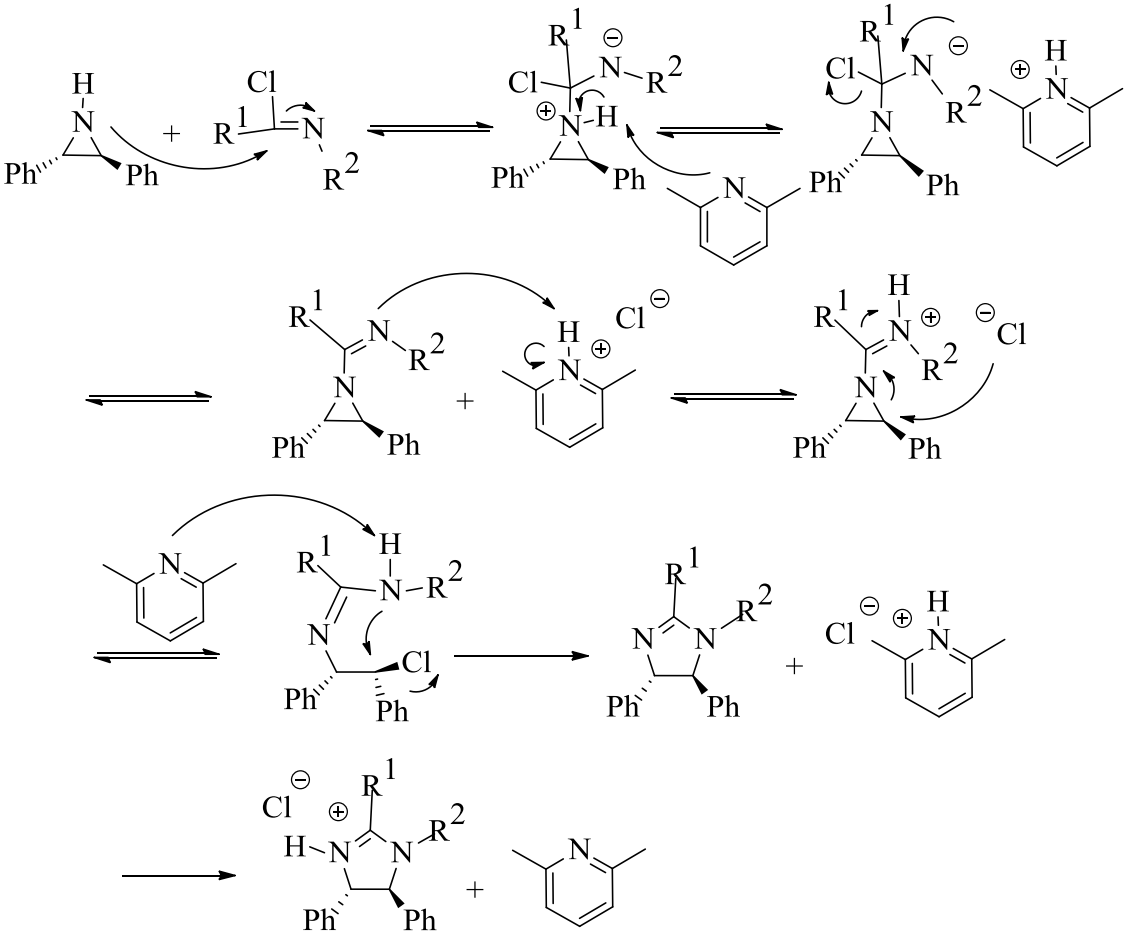


Figure 3-2: Crystal Structure of Racemic Imidazoline **3-57**.

Based on the retention of stereochemistry of the isomerization of *trans*-2,3-diphenyl aziridine and *cis*-2,3-diphenyl aziridine, one possible mechanism could be depicted as in Scheme 10. The conjugate acid of 2,6-lutidine would act as a weak Bronstead acid to protonate the imidoyl aziridine intermediate therefore making it an even better electron withdrawing group. This would allow the chlorine atom to open the aziridine ring in an SN_2 fashion, followed by the attack of the nitrogen lone pair in a second SN_2 reaction to close the ring in a Baldwin 5-exo-tet cyclization mode (Scheme 13).



Scheme 3-13: Proposed Mechanism for One Pot Synthesis of *trans*-imidazolines

The *trans*-2,3-diphenyl aziridines were measured using a 20S proteasome assay by Theresa A. Lansdell. The peptide substrate used was Suc-LLVY-AMC for ChT-L activity and the Fluorescence was measured. From this data the EC_{50} values were determined and the results for the imidazolines are summarized in Table 3-17 below. A few of the imidazolines in Table 3-17 are approximately as potent as the lead compounds **1-1** and **1-1a** previously developed in the Tepe lab.

Table 3-17: CT-L Proteolysis of the 20S Proteasome

#	EC_{50} (μM)	Std. Error	#	EC_{50} (μM)	Std. Error
1-2	2.38	0.05	**3-52**	1.53	0.08
3-46	0.85	0.02	**3-56**	0.68	0.04
3-47	1.61	0.05	**3-57**	5.48	0.10
3-48	4.76	0.12	**3-17**	3.51	0.07
3-51	0.51	0.04	**3-62**	4.03	0.07

Conclusion

A new one-pot methodology to synthesize an imidazoline from an aziridine has been developed. The scope of the imidazoline methodology will be further evaluated to other functional groups at the C-4 and C-5 positions of the imidazoline ring besides ethyl esters and phenyl groups. The methodology will also be extended further to 2,2 di-substituted and 3,3 di-substituted aziridines. Unfortunately, the undesirable imidazoline regioisomer with a phenyl at the 4-position and an ethyl ester at the 5-position of the imidazoline ring was synthesized. The regiochemistry was important for the imidazoline to have a low EC_{50} value. Hopefully, the methodology can be further developed to become more regioselective to yield the desirable imidazoline regioisomer. The methodology will be applied to enantiopure aziridines to determine if they yield an

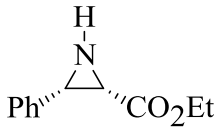
enantiopure imidazoline as expected based on the proposed mechanism. These imidazolines will be test for their ability to inhibit NF-κB mediated gene transcription.

EXPERIMENTAL

General

Acetonitrile, triethyl amine, anisole, and DMF were distilled from calcium hydride under nitrogen. Toluene, 1,4-dioxane, benzene, and DCM were purified through a column packed with dry alumina. THF and ether were distilled from sodium under nitrogen. Acetone, 1,2-dichloroethane, and chloroform were distilled from calcium sulfate under nitrogen. All other reagents and solvents were purchased from Aldrich, Alfa Aesar, or TCI and used without further purification. (*R*)-VANOL and (*R*)-VAPOL were provided by Dr. William D. Wulff. All flasks were oven dried overnight in an oven and cooled under argon or nitrogen. All reactions were monitored by TLC with 0.25 μM precoated silica gel plates and UV light was used to visualize the compounds. Column chromatography silica gel was provided by EM Science (230-400 mesh). All NMR spectra were recorded on a Varian Unity Plus-500 or 300 spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Melting points were determined on a Mel-Temp apparatus with a microscope attachment. HRMS were obtained at the Mass Spectrometry Facility of Michigan State University with a JEOL JMS HX-110 mass spectrometer.

Compound 2-6a: (2*S*,3*S*)-ethyl 3-phenylaziridine-2-carboxylate

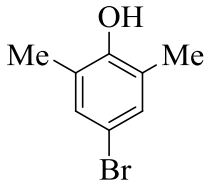


MDAM (2*S*, 3*S*)-ethyl 3-phenylaziridine-2-carboxylate (0.83 g, 1.8 mmol) and 19 mL dried anisole was added to a 25 mL oven dried round bottom flask under argon. The 25

mL round bottom flask was cooled to 0°C and TfOH (1.25 mL, 14.0 mmol) was added with a syringe. The solution turned a dark red color due to the MDAM carbocation formation. The 25 mL round bottom flask was taken out of the ice bath and allowed to react for 2 hours at room temperature. The reaction was quenched with 20 mL of sat. aq. $NaHCO_3$. The organic phase was removed and the aqueous phase was extracted with ether (20 mL x 3). The combined organic extracts were washed with brine (40 mL x 2), dried over $MgSO_4$, and filtered. The organic layer was concentrated by reduced pressure at room temperature to remove the ether and then by high vacuum to remove the majority of the anisole. Heating to remove the anisole caused decomposition to occur. The compound was purified by column chromatography (R_f = 0.13, 1: 1 hexane: ether) to give a light yellow solid. The compound could be further purified by recrystallization from 1:1 ether: hexane to give a white solid, 90% yield, mp 66-67°C. The compound matched the reported literature data.[33]

^{1}H NMR (300 MHz) $CDCl_3$: 1.04 (3H, t, J = 7.1 Hz), 1.73 (1H, br, s), 3.04 (1H, d, 1H, J = 6.1 Hz), 3.52 (1H, d, J = 6.1 Hz), 3.99-4.05 (2H, m), 7.27-7.40 (5H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 13.96, 29.73, 37.23, 61.13, 127.51, 127.65, 128.04, 134.82, 169.04.

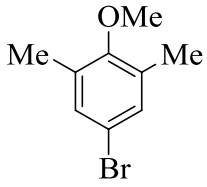
Compound 2-11: 4-bromo-2,6-dimethylphenol



A 500 mL 3-neck round bottom flask was equipped with a rubber septum, an addition funnel, and a gas outlet valve. 2,6-dimethyl phenol (50 g, 0.249 mol) and 200 mL of DCM were added to the round bottom flask. The addition funnel was charged with 22 mL Br_2. The round bottom flask was placed in an ice bath and the Br_2 was added over the course of 80 minutes. A gas outlet valve was attached to a 1M solution of NaOH in a 1L Erlenmeyer flask. The solution was stirred for an additional 20 minutes at 0°C. The solution was warmed to room temperature and 50 mL of saturated sodium thiosulfate and 344 mL $NaHCO_3$ were added. The organic phase was separated and the aqueous phase was extracted with DCM (50 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an orange solid in 99% yield mp 78-79°C. The compound matched the reported literature data.[33]

^{1}H NMR (500 MHz) $CDCl_3$: 2.16 (6H, s), 4.47 (1H, s), 7.08 (2H, s); ^{13}C NMR (125 MHz) ($CDCl_3$): 15.97, 112.25, 125.48, 131.24, 151.56.

Compound 2-12: 4-bromo-2-methoxy-1,3-dimethylbenzene

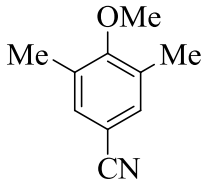


A 1000 mL 3-neck round bottom flask under nitrogen was charged with NaH (11.8g, 0.124 mol) and 250 mL DMSO and the solution was cooled to 0°C. In another round bottom flask 4-bromo-2,6-dimethylphenol (25g, 0.124 mol) was dissolved in 50 mL DMSO. The 4-bromo-2,6-dimethylphenol solution was transferred to the NaH solution

over the course of 30 minutes with a syringe and the solution was stirred at 0°C for an additional 20 minutes. Methyl iodine (44mls, 0.373 mol) was added to the round bottom flask over the course of 10 minutes. The solution was left to react and warm to room temperature overnight. Hexane (85 mL) was added to the round bottom flask and the solution was cooled to 0°C. The solution was poured into a 1L Erlenmeyer flask containing 115 mL hexane. Water (115 mL) was poured into the 1L Erlenmeyer flask and the solution was transferred into a 2L sep. funnel. The organic phase was removed and the aqueous phase was extracted with hexane (45 mL x 4). The organic extracts were combined and washed with water (75 mL x 4). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the product was vacuum distilled to give a colorless liquid. The vacuum was not strong enough so some polymerization occurred reducing the yield to 70% as a colorless liquid. The compound matched the reported literature data.[33]

^{1}HNMR (300 MHz) $CDCl_3$: 2.30 (6H, s), 3.74 (3H, s), 7.19 (2H, s); ^{13}C NMR (75 MHz) ($CDCl_3$): 15.06, 60.72, 113.22, 126.61, 131.80, 155.51.

Compound 2-13: 4-methoxy-3,5-dimethylbenzonitrile

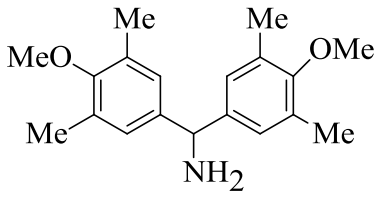


Copper cyanide (4.66 g, 0.029 mol), 5-bromo-2-methoxy-1,3-dimethylbenzene (9.3 g, 0.029 mol), and 95 mL of DMF were added to a 250 mL round bottom flask under an argon atmosphere. The solution was refluxed for 24 hours, then cooled to room

temperature, and poured into a 1L Erlenmeyer flask submerged in ice containing 21 mL ethane-1,2-diamine and 468 mL water. The solution was transferred to a sep. funnel and the organic phase was removed. The aqueous phase was extracted with toluene (50 mL x 4). The organic phase was washed with 100 mL 6% aq. NaCN and then water (50 mL x 2). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown solid. The product was recrystallized twice from hexane to give an off white solid in 80% yield, mp 47-48°C. The compound matched the reported literature data.[33]

^{1}H NMR (300 MHz) $CDCl_3$: 2.26 (6H, s), 3.73 (3H, s), 7.29 (2H, s); ^{13}C NMR (75 MHz) $CDCl_3$: 15.80, 59.62, 107.18, 118.83, 132.37, 132.57, 160.69.

Compound 2-14: bis(4-methoxy-3,5-dimethylphenyl)methanamine

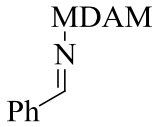


5-bromo-2-methoxy-1,3-dimethylbenzene (8.8 g, 0.041 mol), THF (105 mL), Mg^0 (2.5g, 0.083 mol), and a few crystals of iodine were added to a 250 mL round bottom flask under nitrogen. The solution was refluxed for 3 hours and cooled to room temperature. This solution was transferred via syringe to a 500 mL round bottom flask under nitrogen. 4-methoxy-3,5-dimethylbenzonitrile (6 g, 0.041 mol) and THF (100 mL) was added to another 250 mL round bottom flask under nitrogen. This solution was transferred to the 500 mL round bottom flask via a syringe. The reaction solution was refluxed for 5 hours

and then cooled to room temperature. $LiAlH_4$ (1.6g, 0.041 mol) and THF (25 mL) was added to a 50 mL round bottom flask and this solution was transferred to the reaction flask via a syringe. The round bottom flask was refluxed for 15 hours and cooled to room temperature. The reaction was quenched with water (13mL), 1.3 mL 10% NaOH, and then with water (1,3 mL). The salts were removed by reduced pressure filtration through celite and the celite was washed with THF until the yellow color disappeared. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give yellow oil. The oil was dissolved in ether and 12M HCl was added until all of the amine had been converted into the HCl salt. The compound was triturated, filtered, and washed with 100 mL ether. The solid compound was added to a sep. funnel with 200 mL ether and 1M NaOH until the pH was basic. The organic phase was separated, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a light yellow solid in 86% yield mp 58-60°C. The compound matched the reported literature data.[33]

^{1}H NMR (300 MHz) $CDCl_3$: 1.73 (2H, br), 2.32 (12H, s), 3.75 (6H, s), 5.06 (1H, s), 7.07 (4H, s); ^{13}C NMR (75 MHz) $CDCl_3$: 16.08, 58.77, 58.49, 126.96, 130.54, 140.87, 155.65.

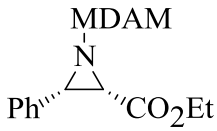
Compound 2-15: MDAM Phenylmethanimine



Bis(4-methoxy-3-5-dimethylphenyl)methanamine (1 g, 3.34 mmol), $MgSO_4$ (0.81 g, 5.59 mmol), DCM (30 mL), and benzaldehyde (0.37 mL, 3.67 mmol) were added to a 50 mL round bottom flask under argon. The solution was stirred at room temperature for 18 hours. The $MgSO_4$ was removed by reduced pressure filtration and the filtrate was concentrated under reduced pressure to give a yellow solid. The solid was put under an argon atmosphere in a 50 mL round bottom flask and 6 mL hexane was added. The solution was brought to reflux and the solids were triturated to give an off white solid precipitate with a yellow colored hexane solution. The solution was allowed to cool to room temperature and sit for 45 minutes. The hexane was decanted and the solids were dried under reduced pressure to give an off white solid in 84% yield mp 60-61°C. The compound matched the reported literature data.[33]

^{1}H NMR (300 MHz) $CDCl_3$: 2.30 (6H, s), 3.74 (3H, s), 7.19 (2H, s); ^{13}CNMR (75 MHz) ($CDCl_3$): 15.06, 60.72, 113.22, 126.61, 131.80, 155.51.

Compound 2-16a: MDAM (2*S*, 3*S*)-ethyl 3-phenylaziridine-2-carboxylate



(*R*)-Vanol (62 mg, 0.129 mmol), triphenylborate (164 mg, 0.517 mmol), and 6 mL toluene were added to a 50 mL round bottom flask under argon. The solution was heated to 85°C for 1 hour. The solution was cooled to room temperature and the toluene was removed under reduced pressure. The round bottom flask was heated to 85°C under high vacuum for an additional 30 minutes to give light orange oil. The round bottom flask

was purged with argon. N-benzylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine (1.0 g, 2.58 mmol) and toluene (6 mL) were added to the 50 mL round bottom flask. The solution turned dark yellow due to a catalyst complex with the imine. The round bottom flask was put under argon and ethyl diazoacetate (0.36 mL, 3.1 mmol) was added via syringe. The solution released nitrogen gas rapidly and was stirred for 24 hours. Hexane (45 mL) was added to the reaction solution and the solution was concentrated under reduced pressure to give a light yellow sticky solid. The compound was purified by column chromatography R_f = 0.33 (20:20:1) hexane: DCM: EtOAc to give a foam-like solid 90% yield mp 55-59°C. The compound matched the reported literature data.[33]

^{1}H NMR (300 MHz) $CDCl_3$: 1.07 (3H, t, J = 6.9 Hz), 2.28 (3H, s), 2.34 (3H, s), 2.63 (1H, d, J = 6.9 Hz), 3.18 (1H, d, J = 6.9 Hz), 3.70 (3H, s), 3.77 (4H, s), 4.02 (2H, m), 7.18 (2H, s), 7.21-7.31 (5H, M), 7.43 (2H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz) $CDCl_3$: 13.97, 16.14, 16.20, 46.21, 48.17, 59.47, 59.53, 60.48, 76.97, 127.19, 127.35, 127.68, 127.75, 127.80, 130.58, 135.23, 137.78, 137.94, 155.87, 156.02, 168.01 (one sp^2 carbon not found).

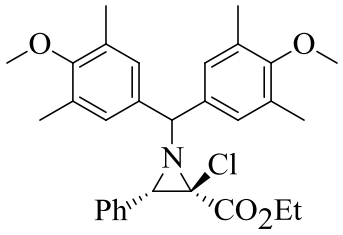
Typical procedure to halogenate aziridines (2-24, 2-25, 2-26)

To a 25 mL round bottom flask was added (2*S*,3*S*)-ethyl 1-((4-methoxy-3,5-dimethylphenyl)(4-methoxy-3-methylphenyl)methyl)-3-phenylaziridine-2-carboxylate (200 mg, 0.423 mmol) and THF (3 mL). To another 25 mL round bottom flask was added THF (3 mL) and diisopropyl amine (136 μL, 0.973 mmol). The diisopropyl amine solution was cooled to -78°C for 15 minutes. Butyl lithium (530 μL, 0.847 mmol) was

added dropwise with a syringe to the diisopropyl amine solution. This solution was maintained at -78°C for 5 minutes and then warmed to 0°C for 15 minutes. Both the aziridine solution and the LDA solutions were cooled to -78°C for 15 minutes. To another 25 mL round bottom flask was added either carbon tetrachloride (120 μL, 1.27 mmol), carbon tetrabromide (840 mg, 1.27 mmol), or Iodine (333 mg, 1.27 mmol) and THF (6 mL). The hood lights were turned off and the solution was wrapped with aluminium foil and cooled to -78°C. The aziridine solution was added with a cannula to the LDA solution. The addition time took about 3 minutes the solution turned immediately dark yellow due to the enolate formation. The reaction was kept at -78°C for 30 minutes. The solution containing the carbon tetrabromide, carbon tetrachloride, or iodine was added to the aziridine solution with a cannula at -78°C. The addition time took about 5 minutes and the solution turned a dark brown color. The solution was wrapped with aluminium foil and kept at -78°C for 45 minutes. At that time sat. aq. NH_4Cl (3 mL) was added when carbon tetrabromide or carbon tetrachloride was the electrophile or aq. sodium thiosulfate (3 mL) was added if the electrophile was iodine. The solution was taken out of the dry ice bath and left to warm to room temperature. The solution was poured into a sep. funnel with ether (10 mL) and water (10 mL). The aqueous phase was separated and extracted with ether (3 x 10 mL). The organic extracts were combined, rinsed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by saturating silica gel with excess TEA. The excess TEA was removed under reduced pressure to give the silica gel as a powder again. The product was purified by 3% TEA: 97% hexanes $R_f = 0.35$. Without

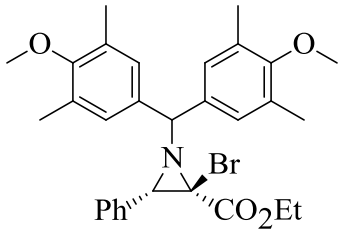
neutralizing the silica gel with TEA the compound would decompose and stayed on the column.

Compound 2-24: (2*R*,3*S*)-ethyl 2-chloro-1-((4-methoxy-3,5-dimethylphenyl)(4-methoxy-3-methylphenyl)methyl)-3-phenylaziridine-2-carboxylate



Light yellow oil; 68% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.03 (3H, t, J = 7 Hz), 2.19 (3H, s), 2.31(3H, s), 3.29 (1H, s), 3.64 (3H, s), 3.73 (3H, s), 4.03 (2H, m), 4.63 (1H, s), 7.11 (2H, s), 7.30-7.29 (3H, m), 7.34-7.37 (4H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 13.77 (CH_3), 16.09 (CH_3), 16.30 (CH_3), 53.61 (CH), 59.49 (CH_3), 59.56 (CH_3), 62.01 (CH_2), 64.84 (C), 70.48 (CH), 127.17 (CH), 127.28 (CH), 127.78 (CH), 127.86 (CH), 128.20 (CH), 130.47 (C), 130.67 (C), 134.12 (C), 137.17 (C), 137.75 (C), 155.90 (C), 156.16 (C), 164.35 (C). IR (NaCl, $CDCl_3$) 2934.10, 1745.80, 1485.38, 1221.10, 1016.62; HRMS: Calculated for $C_{30}H_{35}ClNO_4$ (M^+): 508.2255; Found 508.2262.

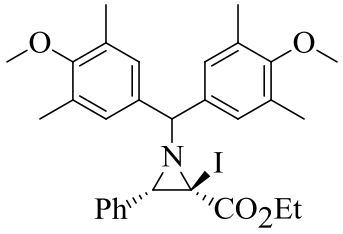
Compound 2-25: (2*R*,3*S*)-ethyl 2-bromo-1-((4-methoxy-3,5-dimethylphenyl)(4-methoxy-3-methylphenyl)methyl)-3-phenylaziridine-2-carboxylate



Foam-like solid; 62% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.98 (3H, t, J = 7 hz), 2.13 (6H, s), 2.28 (6H, s), 3.27 (1H, s), 3.59 (3H, s), 3.70 (3H, s), 4.01 (2H, m), 4.43 (1H, s),

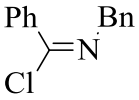
7.05 (2H, s), 7.19-7.25 (3H, m), 7.30-7.33 (4H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 13.71 (CH_3), 16.02 (CH_3), 16.27 (CH_3), 53.03 (CH), 57.73 (C), 59.41 (CH_3), 59.48 (CH_3), 61.92 (CH_2), 73.39 (CH), 127.02 (CH), 127.35 (CH), 127.74 (CH), 127.90 (CH), 128.16 (CH), 130.36 (C), 130.61 (C), 134.55 (C), 136.99 (C), 137.50 (C), 155.85 (C), 156.10 (C), 163.93 (C); IR (NaCl, $CDCl_3$) 2926.39, 1741.94, 1485.38, 1219.17, 1016.62; HRMS: Calculated for $C_{30}H_{35}BrNO_4$ (M^+): 552.1749; Found 552.1752.

Compound 2-26: (2R,3S)-ethyl 2-iodo-1-((4-methoxy-3,5-dimethylphenyl)(4-methoxy-3-methylphenyl)methyl)-3-phenylaziridine-2-carboxylate



Foam-like solid; 45% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.95 (3H, t, J = 7 Hz), 2.12 (3H, s), 2.29 (3H, s), 3.27 (1H, s), 3.58 (3H, s), 3.68 (3H, s), 3.92 (1H, s), 3.96 (2H, m), 7.05 (2H, s), 7.19-7.22 (3H, m), 7.28-7.32 (2H, m), 7.36 (2H, s); ^{13}C NMR (125 MHz) $CDCl_3$: 14.02 (CH_3), 16.43 (CH_3), 16.62 (CH_3), 37.72 (C), 54.33 (CH), 59.76 (CH_3), 59.85 (CH_3), 62.15 (CH_2), 79.11 (CH), 127.23 (CH), 128.02 (CH), 128.28 (CH), 128.59 (CH), 130.70 (C), 130.95 (C), 135.67 (C), 137.17 (C), 137.51 (C), 156.23 (C), 156.42 (C), 164.37 (C); IR (NaCl, $CDCl_3$) 2922.53, 1736.16, 1485.38, 1219.17, 1016.62; HRMS: Calculated for $C_{30}H_{35}INO_4$ (M^+): 600.1611; Found 600.1619.

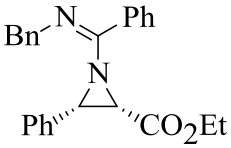
Compound 3-13: (Z)-N-benzylbenzimidoyl chloride



Benzyl benzamide (200 mg, 0.95 mmol) and DCM (4 mL) was added to a 10 mL round bottom flask under argon. The round bottom flask was cooled to 0°C and 2,6-lutidine (0.132 mL, 1.58 mmol) was added to the round bottom flask via a syringe. Oxalyl chloride (0.098 mL, 1.14 mmol) and DCM (1 mL) was added to a 20 mL glass vial. This solution was added dropwise to the reaction solution over the course of 2 minutes. CO and CO_2 bubbled out to the solution and the reaction was stirred at 0°C for 1.25 hours. The DCM was removed by reduced pressure at room temperature to give a yellow solid. The round bottom flask was put under argon and hexane (4 mL) was added via a syringe. The solution was mixed at 0°C for 1 hour. The salts were removed by vacuum filtration through a plug of celite. The hexane was removed under reduced pressure at room temperature to give light yellow colored oil in 80% yield. The product could not be purified any further due to rapid hydrolysis to benzyl benzamide with water from the air. The compound matched the reported literature data.[65]

^{1}H NMR (300MHz) $CDCl_3$: 4.9 (2H, s), 7.12-7.5 (8H, m), 8.08 (2H, d, J = 7 Hz).

Compound 3-14: (2*S*,3*S*)-ethyl 1-((Z)-(benzylimino)(phenyl)methyl)-3-phenylaziridine-2-carboxylate



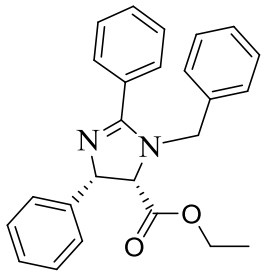
(2*S*,3*S*)-ethyl 3-phenylaziridine-2-carboxylate (50 mg, 0.262 mmol) was added to a 10 mL round bottom flask under argon. TEA (0.218 mL, 1.57 mmol), (Z)-N-benzylbenzimidoyl chloride (73 mg, 0.314 mmol), and DCM (5 mL) were added to the round bottom flask. The solution was refluxed for 5 hours. The DCM was removed

under reduced pressure and the excess TEA was removed on high vacuum while heating to 50°C. The crude product was dissolved in ether and the salts were filtered away through a celite pad. The solution was concentrated under reduced pressure to give yellow oil. This product was used immediately without further purification for isomerization into compound **3-17** by Lewis acids, NaI, and Bronstead Acids.

General procedure for synthesis of imidazolines

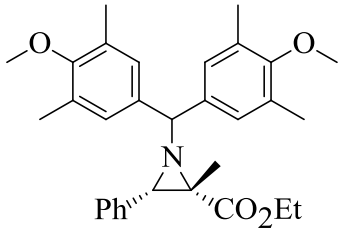
To a 10 mL round bottom flask under argon was added the desired amide (1.2eqs, 0.62 mmol), 2,6-lutidine (0.27 mL, 3.08 mmol), and DCM (4 mL). The solution was either cooled to 0°C or left at room temperature depending on the amide (see Table 3-16). In a 20 mL glass vial was added DCM (1 mL) and oxalyl chloride (0.054mL, 0.62 mmol). The oxalyl chloride solution was added to the round bottom flask over 3 minutes with a syringe. The solution was reacted for the desired time (see Table 3-16) and then the solvent was removed on under reduced pressure at room temperature. This gave the crude product as a mixture of the desired imidoyl chloride (see Table 3-16), excess 2-6-lutidine, which was the not removed at all under reduced pressure (bp 144°C), and 2,6-lutidine hydrogen chloride. This round bottom flask was then placed under argon again and the desired aziridine (100 mg, 0.51 mmol) and DMF (4 mL) were added. The solution was heated to 55°C for the desired time (see Table 3-16).

Compound 3-17: (4*S*,5*S*)-ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate



50:50 Ethyl acetate:hexane; R_f = 0.35; Oil; 52% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 0.76 (3H, t, J = 7 Hz), 3.55 (2H, m), 4.15 (1H, d, J = 15.5 Hz), 4.42 (1H, d, J = 12 Hz), 4.68 (1H, d, J = 15.5 Hz), 5.55 (1H, d, J = 12 Hz), 7.08-7.27 (10H, m), 7.43-7.44 (3H, m), 7.71-7.72 (2H, m); ^{13}C NMR and DEPT (75 MHz) $CDCl_3$: 13.36 (CH_3), 49.94 (CH_2), 60.39 (CH_2), 67.03 (CH) 71.32 (CH), 127.33 (CH), 127.51 (CH), 127.58 (CH), 127.65 (CH), 127.96 (CH), 128.42 (CH), 128.57 (CH), 129.99 (CH), 130.52 (CH), 130.70 (C), 136.25 (C), 139.00 (C), 146.33 (C), 169.79 (C); IR (NaCl, $CDCl_3$) 3075.00, 2980.45 1738.08, 1597.26, 1496.95, 1452.58, 1406.29, 1194.09, 1132.36, 1018.54; HRMS: Calculated for $C_{25}H_{25}N_2O_2$ (M^+): 385.1916; Found 385.1922.

Compound 3-21: (2R,3R)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-methyl-3-phenylaziridine-2-carboxylate

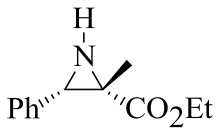


THF (27 mL) and diisopropyl amine (0.54 mL, 4.07 mmol) were added to a 100 mL round bottom flask under argon. The solution was cooled to -78°C and butyl lithium (1.54 mL, 3.69 mmol) was added. The solution was stirred at -78°C for 5 minutes. The solution was warmed to 0°C for 15 minutes and then cooled back to -78°C. (2*R*,3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate (0.9 g, 1.85 mmol) and THF (27 mL) were added to another 50 mL round bottom flask. This solution was cooled to -78°C and transferred to the LDA solution with a cannula. The reaction solution was stirred at -78°C for 30 minutes. Methyl iodine (0.36 mL, 5.55

mmol) was added to the reaction solution with a syringe. The solution was stirred at -78°C while allowing too slowly warm up to room temperature over 4 hours. The reaction was quenched with sat. aq. $NaHCO_3$. The organic phase was removed and the aqueous phase was extracted with ether (50 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to give a foam-like solid 1:5 ethyl acetate: hexane R_f = 0.2, 90% yield.

^{1}HNMR (300 MHz) $CDCl_3$: 0.993 (3H, t, J = 7.2 Hz), 1.57 (3H, s), 2.25 (3H, s), 2.30 (3H, s), 2.97 (1H, s), 3.67 (3H, s), 3.75 (3H, s), 4.30 (1H, s), 7.19-7.37 (9H, m); HRMS: Calculated for $C_{31}H_{38}NO_4$ (M^+): 488.2828; Found 488.2828.

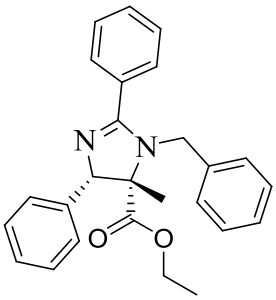
Compound 3-22: (2R,3R)-ethyl 2-methyl-3-phenylaziridine-2-carboxylate



Procedure was identical to that of compound **2-6a**. Compound was purified by column chromatography to give yellow oil (R_f = 0.18, 1:3 ethyl acetate: hexane) 89% yield. The compound matched the reported literature data.[31]

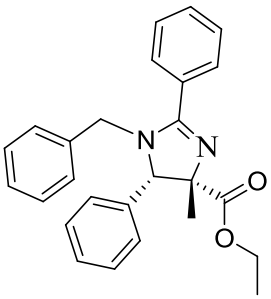
^{1}H NMR (300 MHz) $CDCl_3$: 0.96 (3H, J = 7.2 Hz), 1.68 (3H, s), 2.0 (1H, s, br) 3.25 (1H, s), 3.95 (2H, q, J = 6.9 Hz) 7.30-7.33 (5H, m); ^{13}C NMR (300 MHz) $CDCl_3$: 13.90, 20.12, 42.89, 47.62, 61.33, 127.67, 127.61, 128.05, 135.49, 171.04.

Compound 3-24: (4*S*,5*S*)-ethyl 1-benzyl-5-methyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate



50:50 Ethyl acetate: hexane; R_f = 0.45; Oil; 30% yield; ^{1}H NMR ($CDCl_3$): 0.90 (3H, t, 7 Hz), 1.60 (3H, s), 3.63(2H, m), 3.93 (1H, d, J = 17 Hz), 4.75 (1H, d, J = 17 Hz), 5.15 (1H, s), 7.24-7.43(13H, m), 7.61 (2H, dd, J = 8 Hz, J = 1.5 Hz); ^{13}C NMR and DEPT (500 Mz) $CDCl_3$ 13.85 (CH_3), 23.06 (CH_3), 49.52 (CH_2), 61.26 (CH_2), 73.32 (CH), 79.59 (C), 127.19 (CH), 127.34 (CH), 127.85 (CH), 127.97 (CH), 128.13 (CH), 128.47 (CH), 128.61 (CH), 128.68 (CH), 130.05 (CH), 131.58 (C), 136.25 (C), 139.40 (C), 146.33 (C), 167.47 (C); IR (NaCl, $CDCl_3$): 3074.80, 2979.12, 1730.37, 1653.21, 1616.55, 1597.26, 1576.04, 1496.95, 1448.73, 1394.71, 1356.13; HRMS: Calculated for $C_{26}H_{27}N_2O_2$ (M^+): 399.2073; Found 399.2077.

Compound 3-25: (4*S*,5*S*)-ethyl 1-benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylate

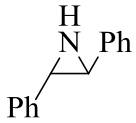


Compound has been previously reported by the Tepe group.[48]

^{1}H NMR (300 MHz) $CDCl_3$: 0.84 (3 H, t, J = 7.2 Hz), 1.57 (3 H, s), 3.60 (2 H, q, J = 7.2 Hz), 3.85 (1 H, d, J = 15.3 Hz), 4.32 (1 H, s), 4.74 (1 H, d, J = 15.3 Hz), 6.98 (2 H, dd, J_1

= 6.9 Hz, J_2 = 2.1 Hz), 7.27–7.35 (8 H, m), 7.49–7.51 (2H, m), 7.76–7.79 (2 H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 13.80, 27.13, 49.12, 60.06, 71.31, 127.98, 128.03,128.12, 128.67, 129.02, 129.11, 130.96, 136.40,136.80, 166.11, 171.78

Compound 3-28: trans-2,3-diphenylaziridine



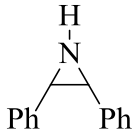
Trans-stillbene (5 g, 0.028 mol), DCM (120 mL) and mCPBA (11.23 g, 0.067 mol), were added to a 250 mL round bottom flask under nitrogen, (1 equiv. gave incomplete reaction due to partial decomposition of the mCPBA). The solution was mixed at room temperature overnight. The DCM was removed under reduced pressure and the solid was partitioned between ethyl acetate and washed with aq. $NaHCO_3$ (3x 50 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude *trans*-stillbene oxide was used without further purification. The *trans*-stillbene oxide was dissolved in 150 ml EtOH. NaN_3 (2.7 g, 0.084 mol) and NH_4Cl (2.23 g, 0.084 mol) were added. This gave the NH_4Cl and NaN_3 as a suspension which was heated to 65°C for 24 hours. The reaction was then cooled to 0°C and the solids were filtered off and the solution was concentrated under reduced pressure. The crude azide alcohol was used without further purification. The azide alchol was dissolved in 100 mL THF and PPh_3 (6.75 g, 0.025 mol) was added. The solution was refluxed for 3 hours. The solution was cooled to room temperature and the solvent was removed under reduced pressure to give yellow oil. Ether was added to precipitate out the majority of the triphenyl phosphine oxide. The solution was put in the fridge for ½

hour and the solids were removed by vacuum filtration. The ether was removed under reduced pressure and the product was purified by flash chromatography 100% ether R_f = 0.8, 51% yield (3steps). The product was only on the column for approximately 20 minutes, longer times caused the compound to decompose rapidly.

The compound matched the reported literature data.[66-68]

^{1}H NMR (300 MHz) $CDCl_3$: 1.57 (1H, s, br), 3.05 (2H, s), 7.20-7.32 (10H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 43.95, 125.77, 127.59, 128.88, 139.88.

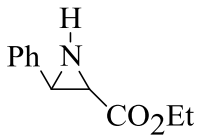
Compound 3-29: *cis*-2,3-diphenylaziridine



Procedure was the same as for **3-28** except that *cis*-stillbene (0.612 g, 3.14 mmol) was used instead of *trans*-stillbene. R_f = 0.8, 100% ether, 41% yield (3 steps). The compound was only on the column for approximately 20 minutes or else decomposition occurred very rapidly. The compound matched the reported literature data.[66-68]

^{1}H NMR (300 MHz) $CDCl_3$: 1.66 (1H, s), 3.64 (2H, s), 7.17-7.32 (10H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 39.68, 126.44, 127.49, 127.81, 136.52.

Compound 3-30: ethyl 3-phenylaziridine-2-carboxylate



To a 250 mL round bottom flask under nitrogen was added KOEt (8.8 g, 0.15 mol) and 100 mL anhydrous EtOH. The solution was cooled to -10°C, benzaldehyde (10.53 mL, 0.11 mol) and ethyl chloroacetate (11.1 mL, 0.15 mol) were mixed together in a small

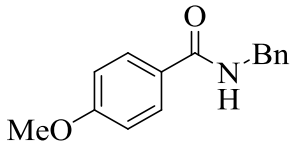
beaker and the solution was added with a syringe over 5 minutes to the KOEt/EtOH solution will keeping the temperature < -5°C. The solution was mixed at -5°C for 2 hours and then at room temperature for 5 hours. The solution was concentrated under reduced pressure. The crude ethyl 3-phenyloxirane-2-carboxylate was transformed into ethyl 3-phenylaziridine-2-carboxylate by the same procedure as for compound **3-28**. The compound matched the reported literature data.[69-70]

Oil; 48% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.26 (3H, t, 7 Hz), 1.90 (1H, s, br), 2.54 (1H, s), 3.21 (1H, s), 4.21 (2H, m), 7.21-7.28 (5H, m); ^{13}C NMR (500 MHz) $CDCl_3$: 14.03, 39.33, 40.21, 61.59, 126.01, 127.59, 128.29, 137.77, 171.54.

General procedure for the synthesis of Amides (Table 3-15)

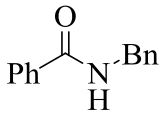
The scale was typically based on 2 g of the amide based on a 100 % yield reaction. The desired amine (1 equiv.), DCM (50 mL), and TEA (2 equiv.) were added to a 250 mL round bottom flask under nitrogen. The desired acid chloride (1 equiv.) was added dropwise to the reaction solution. The solution was stirred at room temperature overnight. The DCM was removed under reduced pressure and the crude product was dissolved with EtOAc (50 mL). The reaction solution was extracted with 2M HCL (2x 20 mL, 2M NaOH (2x 20 mL), washed with 40 mL brine, and dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give a solid.

Compound 3-31: N-benzyl-4-methoxybenzamide



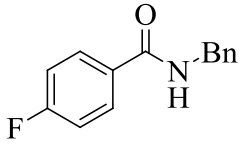
Compound matched the reported literature data.[71] white solid; mp 128-129°C; 90% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.74 (3H, s), 4.53 (2H, d, J = 6 Hz), 6.34 (1H, s, br), 6.81 (2H, d, J = 9 Hz), 7.16-7.25 (5H, m), 7.66 (2H, d, J = 9 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 43.92, 55.31, 113.65, 126.61, 127.38, 127.76, 128.62, 128.76, 138.45, 162.12, 166.87.

Compound 3-32: N-benzylbenzamide



Compound matched the reported literature data.[71] white solid; mp 104-106°C; 95% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.65 (2H, d, J = 5.5 Hz), 6.37 (1H, s, br), 7.27-7.50 (8H, m), 7.77 (2H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 43.87, 126.95, 127.33, 127.67, 128.39, 128.56, 131.33, 134.28, 138.24, 167.39.

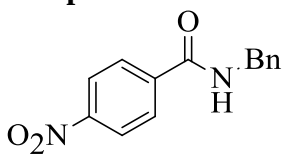
Compound 3-33: N-benzyl-4-fluorobenzamide



The compound matched the literature data[72] with the exception that the reported literature data labeled the $^{2}J_{CF}$ = 21 Hz at a chemical shift of 115.45 ppm, but this ^{13}C NMR has a $^{2}J_{CF}$ = 51.9 Hz at 115.45 ppm. white solid; mp 143-144°C; 90% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.53 (2H, d, J = 6 Hz), 6.37 (1H, s, br), 7.04-7.27 (2H, m), 7.27-7.35 (5H, m), 7.78-7.81 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 44.04, 115.46 ($^{2}J_{cf}$

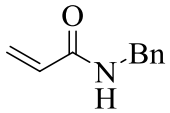
= 51.9Hz), 127.52, 127.74, 128.68, 129.26, 129.33, 138.08, 163.64, 166.01 ($^{1}J_{cf}$ = 215.1 Hz).

Compound 3-34: N-benzyl-4-nitrobenzamide



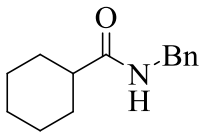
Compound matched the reported literature data.[71] yellow solid; mp 144-146°C, 92% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.65 (2H, d, J = 5.5 Hz), 6.47 (1H, s, br), 7.30-7.38 (5H, m), 7.91-7.94 (2H, m), 8.25-8.27 (2H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 44.40, 123.76, 127.88, 127.90, 128.17, 128.88, 137.44, 139,88, 149.58, 165.39.

Compound 3-35: N-benzylacrylamide



The compound matched the reported literature data.[73] white solid, mp 67-68°C, 93% yield; ^{1}H NMR (300 MHz) $CDCl_3$: 4.45 (2H, d, J = 5.7 Hz), 5.60 (1H, dd, J_1 = 10 Hz, J_2 = 1.8 Hz), 6.15 (1H, dd, J_1 = 17.1 Hz, J_2 = 10 Hz), 6.30 (1H, dd, J_1 = 17.1 Hz, J_2 = 1.8 Hz), 7.22-7.32 (5H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 43.44, 126.37, 127.34, 127.70, 128.60, 130.96, 138.27, 166.06.

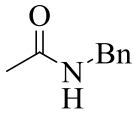
Compound 3-36: N-benzylcyclohexanecarboxamide



Missing 1 aliphatic carbon signal, but matches the reported literature data.[74]

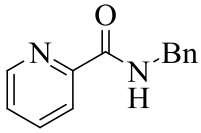
white solid; mp 114-115°C; 34 % yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.20-1.26 (3H, m), 1.40-1.47 (2H, m), 1.64-1.66 (1H, m), 1.75-1.78 (2H, m), 1.85-1.87 (2H, m), 2.06-2.11 (1H, m), 4.40 (2H, d, J = 6 Hz), 7.22-7.32 (5H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 25.64, 29.62, 43.19, 45.39, 127.24, 127.55, 128.53, 138.57,175.92.

Compound 3-37: N-benzylacetamide



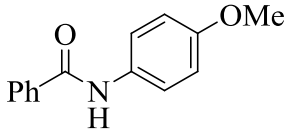
The compound matched the reported literature data.[75] white solid; mp 62-63°C; 95% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.96 (3H, s), 4.38 (2H, d, J = 6Hz), 5.98 (1H, s, br), 7.26-7.31 (5H, M); ^{13}C NMR (125 MHz) $CDCl_3$: 23.03, 43.56, 127.34, 127.68, 128.55, 138.55, 138.24, 169.97.

Compound 3-38: N-benzylpicolinamide



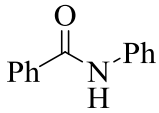
The compound matched the reported literature data.[76] light brown solid, mp 81-82°C, 35% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.58 (2H, d, J = 6 Hz), 7.16-7.33 (6H, m), 7.73-7.76 (1H, m), 8.12-8.14 (1H, m) 8.29 (1H, s, br), 8.41-8.43 (1H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 43.38, 122.24, 126.08, 127.35, 127.73, 128.59, 137.23, 138.17, 147.98, 149.78, 164.14.

Compound 3-39: N-(4-methoxyphenyl)benzamide



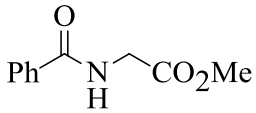
The compound matched the reported literature data.[77] light yellow solid; mp 162-163°C, 93% Yield; ^{1}H NMR (300MHz) $CDCl_3$: 3.79 (3H, s), 6.90 (2H, d, J = 9 Hz), 7.45-7.46 (5H, m), 7.78 (1H, s, br), 7.83 (2H, d, J = 9 Hz). ^{13}C NMR (75 MHz) $CDCl_3$: 55.63, 113.34, 122.19, 127.12, 128.82, 131.27, 132.12, 135.30, 156.90, 165.91.

Compound 3-40: N-phenylbenzamide



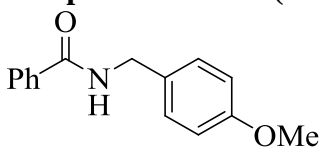
The compound matched the reported literature data (commercially available). white solid; mp 161-162°C; 92% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 7.12-7.16 (1H, m), 7.34-7.37 (2H, m), 7.45-7.48 (2H, m), 7.52-7.56 (1H, m), 7.64 (2H, d, J = 7.5 Hz), 7.82 (1H, s, br), 7.85 (2H, d, J = 8 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 120.21, 124.56, 127.00, 128.77, 129.08, 131.81, 135.01, 137.93, 165.73.

Compound 3-41: methyl 2-benzamidoacetate



Compound matched the reported literature data.[78] white solid; mp 81-82°C; 56% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.79 (3H, s), 4.24 (2H, d, J = 5.5 Hz), 6.65 (1H, s, br), 7.41-7.44 (2H, m), 7.49-7.52 (1H, m), 7.80 (2H, d, J = 9 Hz). ^{13}C NMR (125 MHz) $CDCl_3$: 41.59, 52.26, 127.01, 128.44, 131.65, 133.56, 167.50, 170.43.

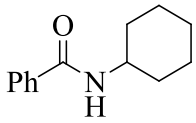
Compound 3-42: **N**-(4-methoxybenzyl)benzamide



The compound matched the reported literature data.[79] white solid; mp 93-94°C; 94%

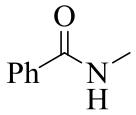
Yield; ^{1}H NMR (300 MHz) $CDCl_3$: 3.78 (3H, s), 4.57 (2H, d, J = 5.7 Hz), 6.36 (1H, s, br), 6.68 (2H, d, J = 9 Hz), 7.28 (2H, M), 7.40 (3H, M) 7.75 (2H, d, J = 9 Hz); ^{13}C NMR (75 MHz) $CDCl_3$: 43.34, 54.95, 113.75, 126.74, 128.14, 128.88, 130.28, 113.07, 134.26, 158.82, 167.31.

Compound 3-43: N-cyclohexylbenzamide



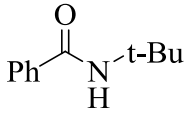
The compound matched the reported literature data.[80] white solid; mp; 146-147°C, 97% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.20-1.29 (3H, m), 1.39-1.48 (2H, m), 1.65-1.69 (1H, m), 1.75-1.80 (2H, m), 2.03-2.06 (2H, m), 3.99-4.03 (1H, m), 6.06 (1H, s, br), 7.41-7.50 (3H, m), 7.77 (2H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz) $CDCl_3$: 25.16, 25.82, 33.47, 48.91, 127.08, 128.72, 131.44, 135.40, 166.85.

Compound 3-44: N-methylbenzamide



The compound matched the reported literature.[81] white solid; mp; 80-82°C; 63% yield; ^{1}H NMR (300 MHz) $CDCl_3$: 3.03 (3H, d, J = 8 Hz), 6.42 (1H, s, br), 7.44-7.46 (3H, m), 7.78-7.81 (2H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 26.75, 126.93, 128.41, 131.25, 134.35, 168.37.

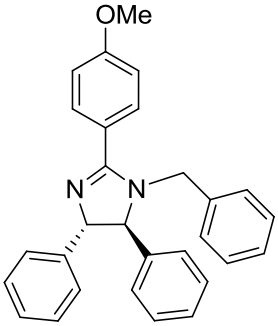
Compound 3-45: N-tert-butylbenzamide



Compound matched the reported literature data.[82] white solid; mp 151-153°C; 95%

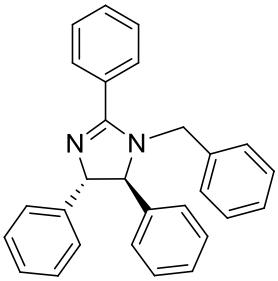
Yield; ^{1}H NMR (300 MHz) $CDCl_3$: 1.45 (9H, s), 5.95 (1H, s, br), 7.35-7.47 (3H, m), 7.68-7.72 (2H, m); ^{13}C NMR (75 MHz) $CDCl_3$: 28.91, 51.62, 126.70, 128.50, 131.10, 135.95, 169.6.

Compound 3-46: 1-benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole



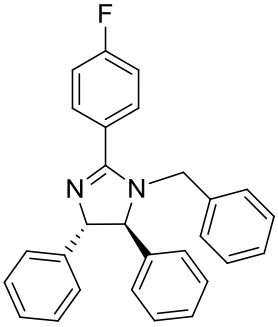
50:50 Ethyl acetate: hexane; R_f = 0.4; Oil, 59% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.88 (3H, s), 4.02 (1H, d, J = 16 Hz), 4.42 (1H, d, J = 8.5 Hz), 4.82 (1H, d, J = 15.5 Hz), 5.04 (1H, d, J = 8.5 Hz), 6.99 (2H, dd, J = 7.5 Hz, J = 2.5 Hz), 7.07 (2H, d, J = 9 Hz), 7.15 (2H, d, J = 7 Hz), 7.38-7.32 (8H, m), 7.37-7.43 (3H, m), 7.84 (2H, d, J = 9 Hz); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 49.67 (CH_2), 55.24 (CH_3), 72.54 (CH), 76.54 (CH), 114.06 (CH), 122.25 (C), 126.53 (CH), 127.02 (CH), 127.08 (CH), 127.51 (CH), 127.83 (CH), 127.86 (CH), 128.36 (CH), 128.42 (CH), 128.84 (CH), 130.20 (CH), 135.98 (C), 141.24 (C), 143.31 (C), 161.30 (C), 165.69 (C); IR (NaCl, $CDCl_3$) 3028.63, 1686.00, 1612.70, 1512.30, 1454.51, 1251.96, 1172.87, 1028.19; HRMS: Calculated for $C_{29}H_{27}N_2O$ (M^+): 419.2123; Found 419.2123.

Compound 3-47: 1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole



50:50 Ethyl acetate: hexane; R_f = 0.4; Oil; 55% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.97 (1H, d, J = 15.5 Hz), 4.38 (1H, d, J = 8.5 Hz), 4.75 (1H, d, J = 15.5 Hz), 5.04 (1H, d, J = 8.5Hz), 6.98 (2H, dd, J_1 = 8 Hz, J_2 = 2 Hz), 7.14 (2H, dd, J_1 = 8 Hz, J_2 = 1.5 Hz), 7.22-7.40 (11H, m), 7.51-7.53 (3H, m), 7.84-7.86 (2H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 49.49 (CH_2), 72.45 (CH), 77.72 (CH), 126.58 (CH), 126.88 (CH), 126.99 (CH), 127.32 (CH), 127.64 (CH), 127.80 (CH), 128.24 (CH), 128.30 (CH), 128.48 (CH), 128.52 (CH), 128.72 (CH), 130.00 (CH), 131.11 (C), 136.23 (C), 141.63 (C), 143.72 (C), 165.82 (C). IR (NaCl, $CDCl_3$) 3028.63, 2922.53, 1614.62, 1595.00, 1572.18, 1495.02, 1448.73, 1406.29, 1358.06, 1278.97, 1026.26; HRMS: Calculated for $C_{28}H_{25}N_2$ (M^+): 389.2023; Found 389.2023.

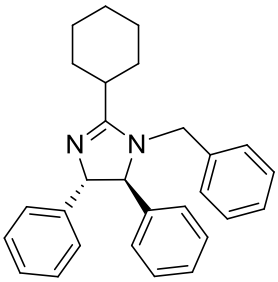
Compound 3-48: 1-benzyl-2-(4-fluorophenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole



20:77:3 Ethyl acetate:hexane:TEA; R_f = 0.26; Oil; 43% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 4.05 (1H, d, J = 15.5 Hz), 4.41 (1H, d, J = 8.5 Hz), 4.71 (1H, d, J = 15.5 Hz),

5.04 (1H, d, J = 8.5 Hz), 6.97 (2H, dd, J_1 = 9.5 Hz, J_2 = 3.5 Hz), 7.14-7.44 (15H, m), 7.87 (2H, m). ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 50.11 (CH_2), 73.11 (CH), 78.24 (CH), 116.18 ($J_{C/F}$ = 86.5 Hz) (CH), 127.05 (CH), 127.40 (CH), 127.48 (CH), 127.8 (C), 127.89 (CH), 128.16 (CH), 128.23 (CH), 128.74 (CH), 128.85 (CH), 129.21 (CH), 131.01 ($J_{C/F}$ = 33 Hz) (CH), 136.64 (C), 142.06 (C), 144.09 (C), 163.10 (C), 165.10 ($J_{C/F}$ = 119.5 Hz) (C) IR (NaCl, $CDCl_3$) 3030.56, 2957.25, 2922.53, 1612.70, 1512.38, 1495.02, 1452.58, 1414.00, 1224.95, 1155.51, 1076.42; HRMS: Calculated for $C_{28}H_{24}FN_2$ (M^+): 407.1929; Found 407.1927.

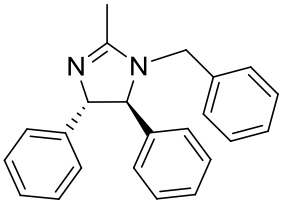
Compound 3-51: 1-benzyl-2-cyclohexyl-4,5-diphenyl-4,5-dihydro-1H-imidazole



50:50 Ethyl acetate:hexane; R_f = 0.35; Oil; 67% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.24-1.26 (3H, m), 1.67-1.77 (2H, m), 1.84-1.92 (3H, m), 2.01-2.08 (2H, m), 2.42-2.48 (1H, m), 3.87 (1H, d, 16.5 Hz), 4.19 (1H, d, J = 8 Hz), 4.55 (1H, d, J = 16 Hz), 4.83 (1H, d, J = 8 Hz). ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 25.93 (CH_2), 26.15 (CH_2), 26.37 (CH_2), 30.56 (CH_2), 31.88 (CH_2), 36.62 (CH), 47.23 (CH_2), 72.70 (CH), 76.76 (CH), 126.57 (CH), 126.89 (CH), 127.09 (CH), 127.12 (CH), 127.35 (CH), 127.74 (CH), 128.36 (CH), 128.62 (CH), 128.82 (CH), 137.04(C), 141.85(C), 144.30(C), 169.92 (C); IR (NaCl, $CDCl_3$) 3028.63, 2928.32, 2853.08, 1603.05, 1495.02, 1450.65, 1356.13,

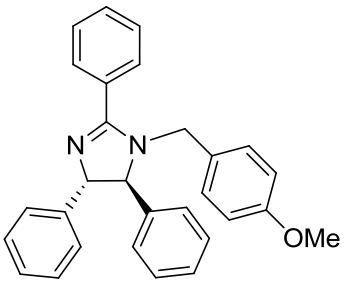
1265.46, 1174.80, 1028.19; HRMS: Calculated for $C_{28}H_{31}N_2$ (M^+): 395.2487; Found 395.2494.

Compound 3-52:



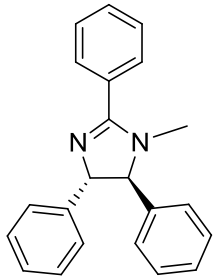
Silica gel was saturated in TEA and concentrated under reduced pressure to yield dry silica again. 95:5 Ethyl acetate:TEA; R_f = 0.3. Silica gel that was not neutralized with TEA resulted in 0% yield. Oil; 48% yield; ^{1}H NMR (500 MHz) $CDCl_3$: 2.23 (3H, s), 3.93 (1H, d, J = 16.5 Hz), 4.29 (1H, d, J = 9 Hz), 4.51 (1H, d, J = 16.5 Hz), 4.84 (1H, d, J = 9 Hz), 7.05 (2H, d, J = 7.5 Hz), 7.13 (2H, m), 7.17-7.35 (11H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 14.75 (CH_3), 47.82 (CH_2), 72.99 (CH), 77.32 (CH), 126.63 (CH), 126.87 (CH), 127.12 (CH), 127.26 (CH), 127.33 (CH), 127.73 (CH), 128.29 (CH), 128.58 (CH), 128.70 (CH), 136.65 (C), 141.04 (C), 143.57 (C), 162.94 (C); .IR (NaCl, $CDCl_3$) 3028.63, 1616.55, 1495.02, 1452.58, 1419.79, 1354.20, 1028.19; HRMS: Calculated for $C_{23}H_{23}N_2$ (M^+): 327.1861; Found 327.1867.

Compound 3-56: 1-benzyl-2-methyl-4,5-diphenyl-4,5-dihydro-1H-imidazole



50:50 Ethyl acetate:hexane; R_f = 0.40; Foam-like solid; 53% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.78 (3H, s), 3.89 (1H, d, J = 15Hz), 4.37 (1H, d, J = 9Hz), 4.70 (1H, d, J = 15.5Hz), 5.01 (1H, d, J = 8.5Hz), 6.76 (2H, dd, 6.5Hz, J = 2Hz), 6.87 (2H, dd, J = 8.5Hz, J = 2Hz), 7.15 (2H, dd, J = 8.5Hz, J = 1.5Hz), 7.24-7.43 (8H, m), 7.53 (3H, m), 7.85 (2H, m); ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 49.06 (CH_2), 55.12 (CH_3), 72.38 (CH), 77.89 (CH), 113.80 (CH), 126.75 (CH), 126.93 (CH), 127.13 (CH), 127.66 (CH), 128.31 (CH), 128.56 (CH), 128.67 (CH), 128.79 (CH), 129.24 (CH), 130.03 (CH), 131.43 (C), 141.86 (C), 143.91 (C), 158.90 (C), 165.95 (C) (Missing 1 quaternary carbon signal); IR (NaCl, $CDCl_3$) 3028.63, 2928.32, 1612.70, 1595.33, 1512.36, 1448.73, 1248.10, 1174.80, 1028.19; HRMS: Calculated for $C_{29}H_{27}N_2O$ (M^+): 419.2123; Found 419.2125.

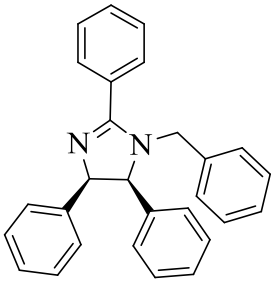
Compound 3-57: 1-methyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole



50:50 Ethyl acetate: hexane; R_f = 0.35; Foam-like semi-solid; 60% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 2.73 (3H, s), 4.26 (1H, d, J = 10 Hz), 4.96 (1H, d, J = 10 Hz), 7.27-7.41 (10H, m), 7.46 (3H, m), 7.74 (2H, m). ^{13}C NMR and DEPT (125 MHz) $CDCl_3$: 34.98 (CH_3), 77.81 (CH), 78.62 (CH), 126.89 (CH), 127.08 (CH), 127.11 (CH), 127.82 (CH), 128.39 (CH), 128.45 (CH), 128.56 (CH), 128.85 (CH), 130.01 (CH), 131.29(C), 141.90(C), 144.05(C), 167.00 (C); IR (NaCl, $CDCl_3$) 3061.42, 3028.63, 1613.70,

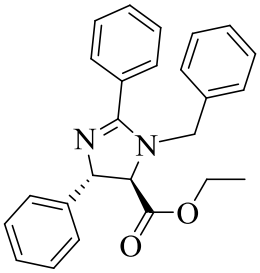
1570.20, 1498.95, 1440.73, 1367.00, 1344.56, 1278.97, 1082.91; HRMS: Calculated for $C_{22}H_{21}N_2$ (M^+): 313.1705; Found 313.1707.

Compound 3-60: *cis*-(4, 5)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole



Compound matched the reported literature data.[23] 50:50 Ethyl acetate: hexane; R_f = 0.4; Oil; 5% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 3.84 (1H, d, J = 16 Hz), 4.76 (1H, d, J = 16 Hz), 4.91 (1H, d, J = 11 Hz), 5.55 (1H, d, J = 11 Hz), 6.91-7.81 (20H, m); ^{13}C NMR (125 MHz) $CDCl_3$: 49.0, 68.4, 72.9, 126.2, 127.1, 127.3, 127.5, 127.8, 127.9, 127.9, 128.1, 128.5, 128.6, 128.7, 130.2, 131.2, 136.6, 136.8, 139.3, 167.1; HRMS: Calculated for $C_{28}H_{25}N_2$ (M^+): 385.1916; Found 385.1918.

Compound 3-62: ethyl 1-benzyl-2,4-diphenyl-4,5-dihydro-1H-imidazole-5-carboxylate



50:50 Ethyl acetate: hexane; R_f = 0.4; Oil; 38% Yield; ^{1}H NMR (500 MHz) $CDCl_3$: 1.27 (3H, t, J = 7 Hz), 3.97 (1H, d, J = 7.5 Hz), 4.19 (2H, m), 4.42 (1H, d, J = 15.5 Hz), 4.61 (1H, d, J =15.5 Hz), 5.28 (1H, d, J = 7.5 Hz), 7.09 (2H, dd, J_1 = 6Hz, J_2 = 1.5Hz), 7.22-7.31 (10H, m), 7.48 (3H, m), 7.80 (2H, m); ^{13}C NMR (500 MHz) $CDCl_3$: 14.12,

51.32, 61.26, 69.92, 72.30, 126.58, 127.28, 127.67, 127.91, 128.43, 128.57, 128.58, 128.75, 130.29, 130.61, 136.32, 143.23, 165.81, 172.10; IR: 3063.35, 2980.40, 1741.94, 1616.55, 1574.11, 1496.95, 1448.73, 1402.43, 1234.60, 1176.73, 1024.33; HRMS: HRMS: Calculated for $C_{25}H_{25}N_2O_2$ (M^+): 389.2023; Found 389.2027

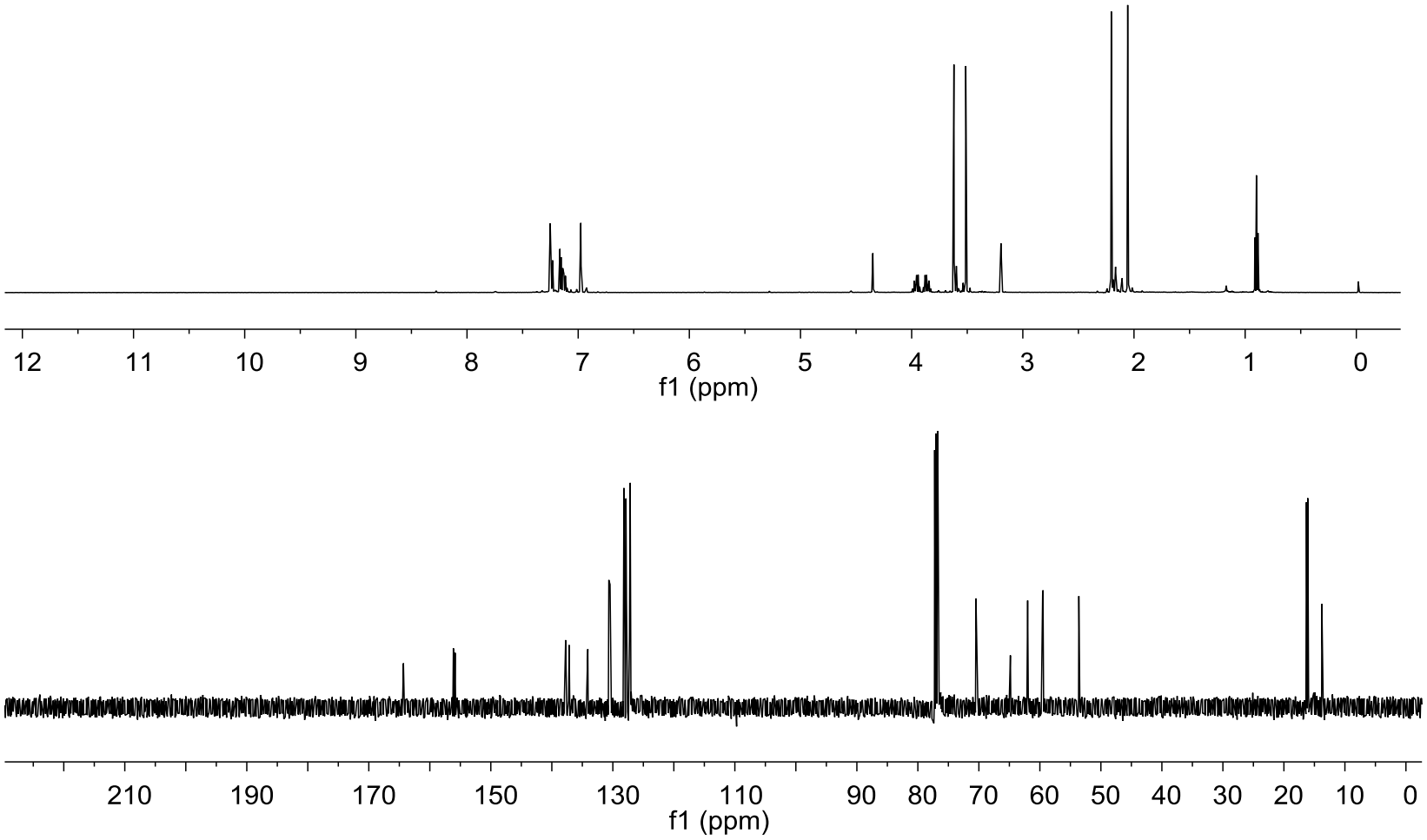


Figure 2-1: ^{1}HNMR and ^{13}C NMR of Compound **2-24**

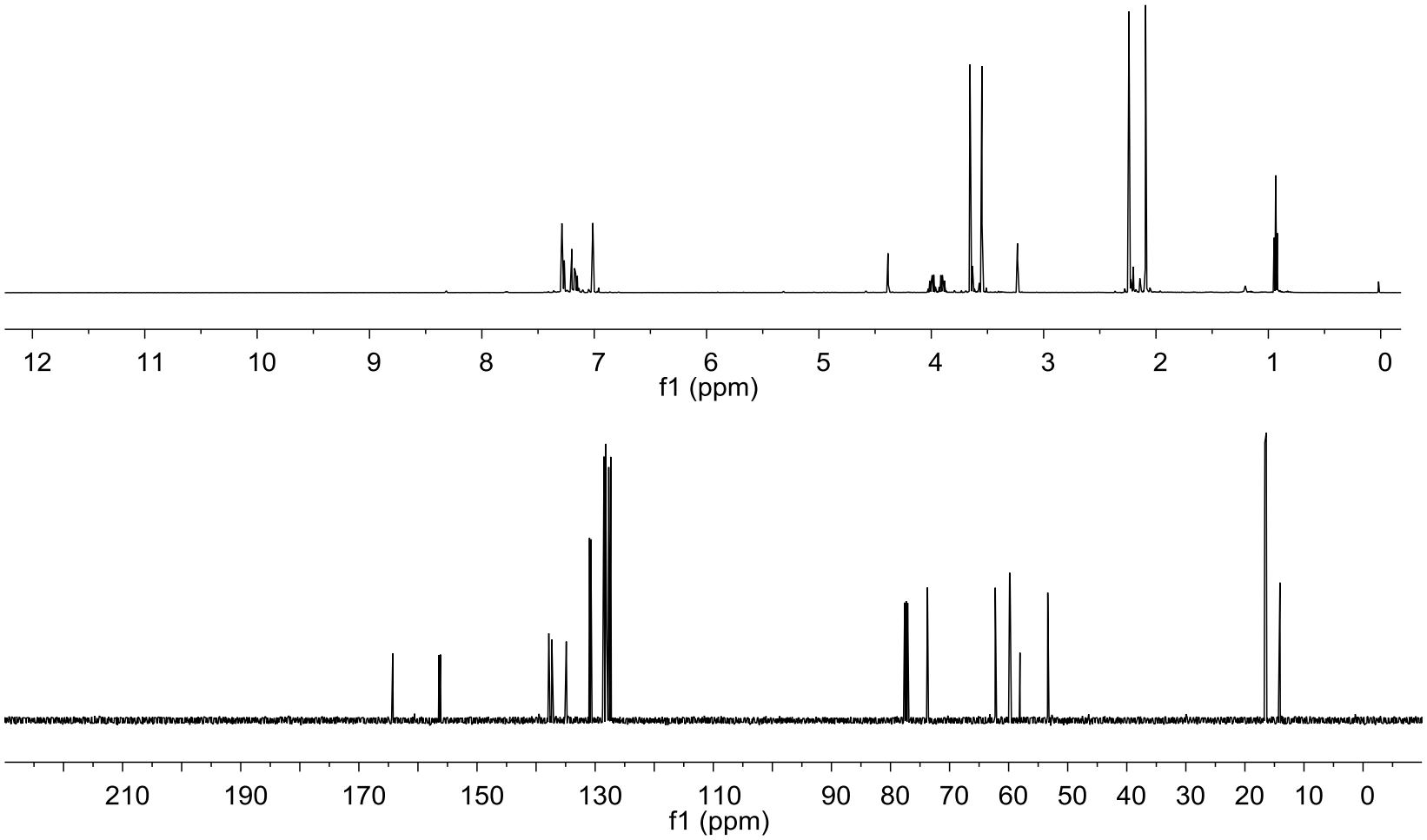


Figure 2-2: ^{1}HNMR and ^{13}C NMR of Compound **2-25**

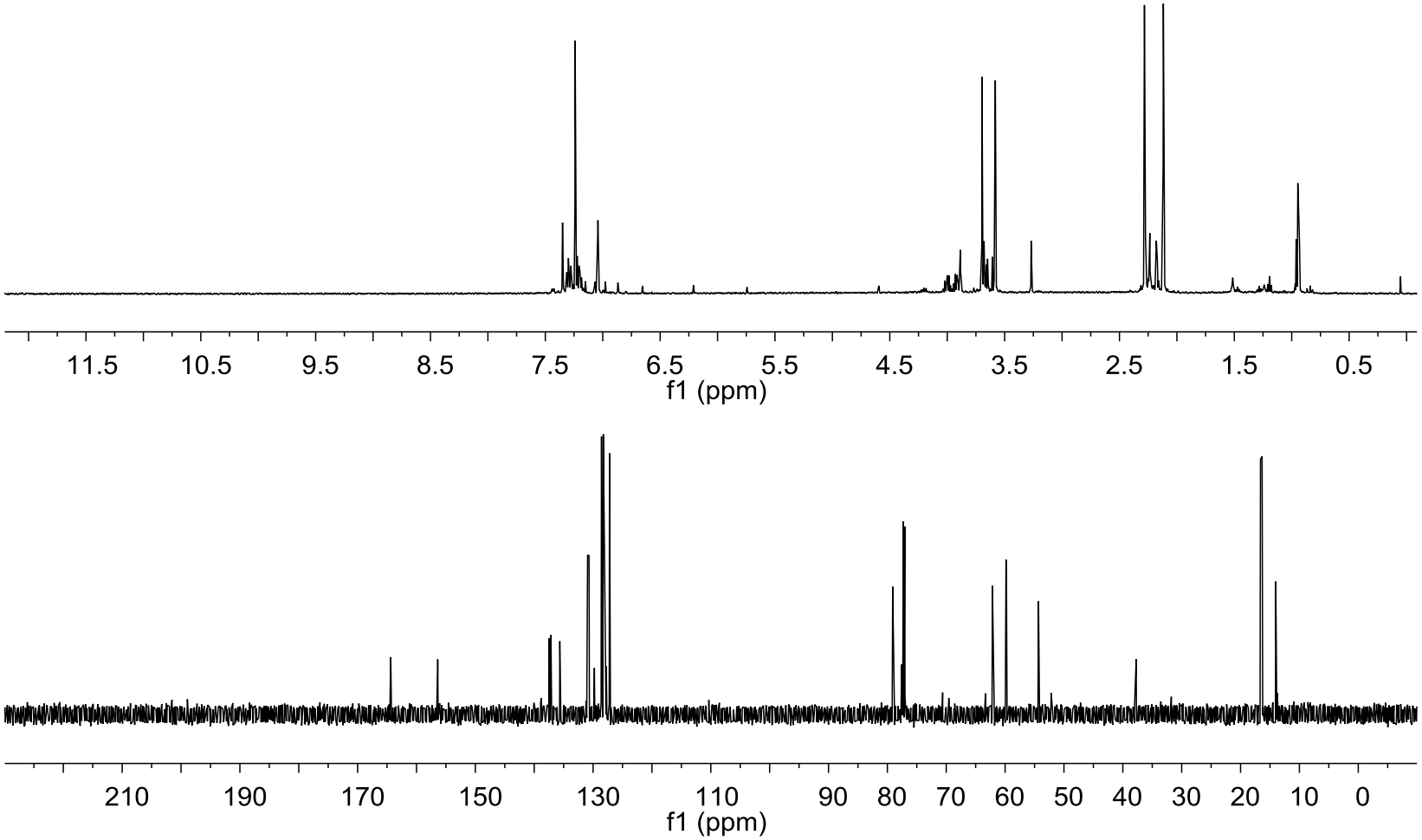


Figure 2-3: ^{1}HNMR and ^{13}C NMR of Compound **2-26**

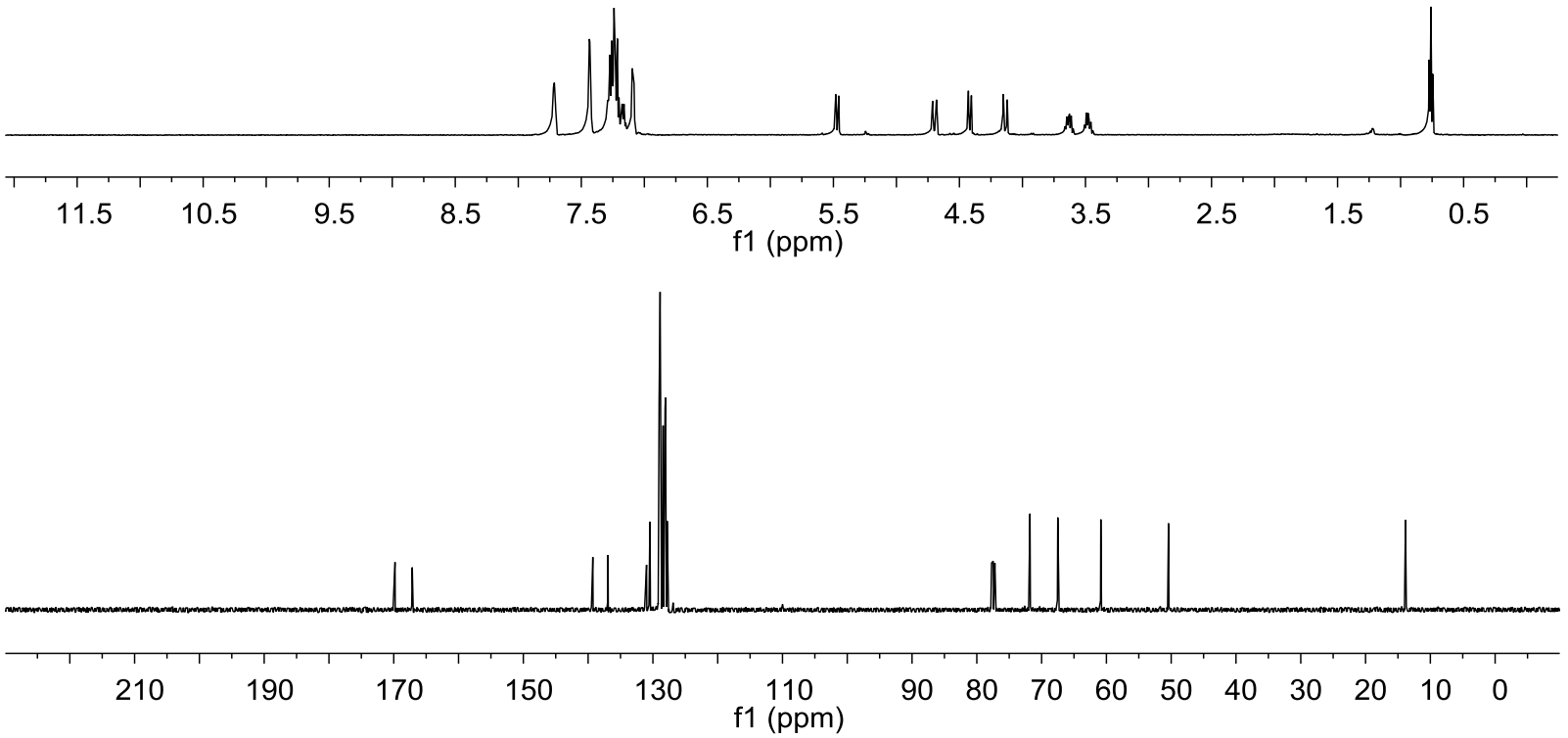


Figure 3-3: ^{1}HNMR and ^{13}C NMR of Compound **3-17**

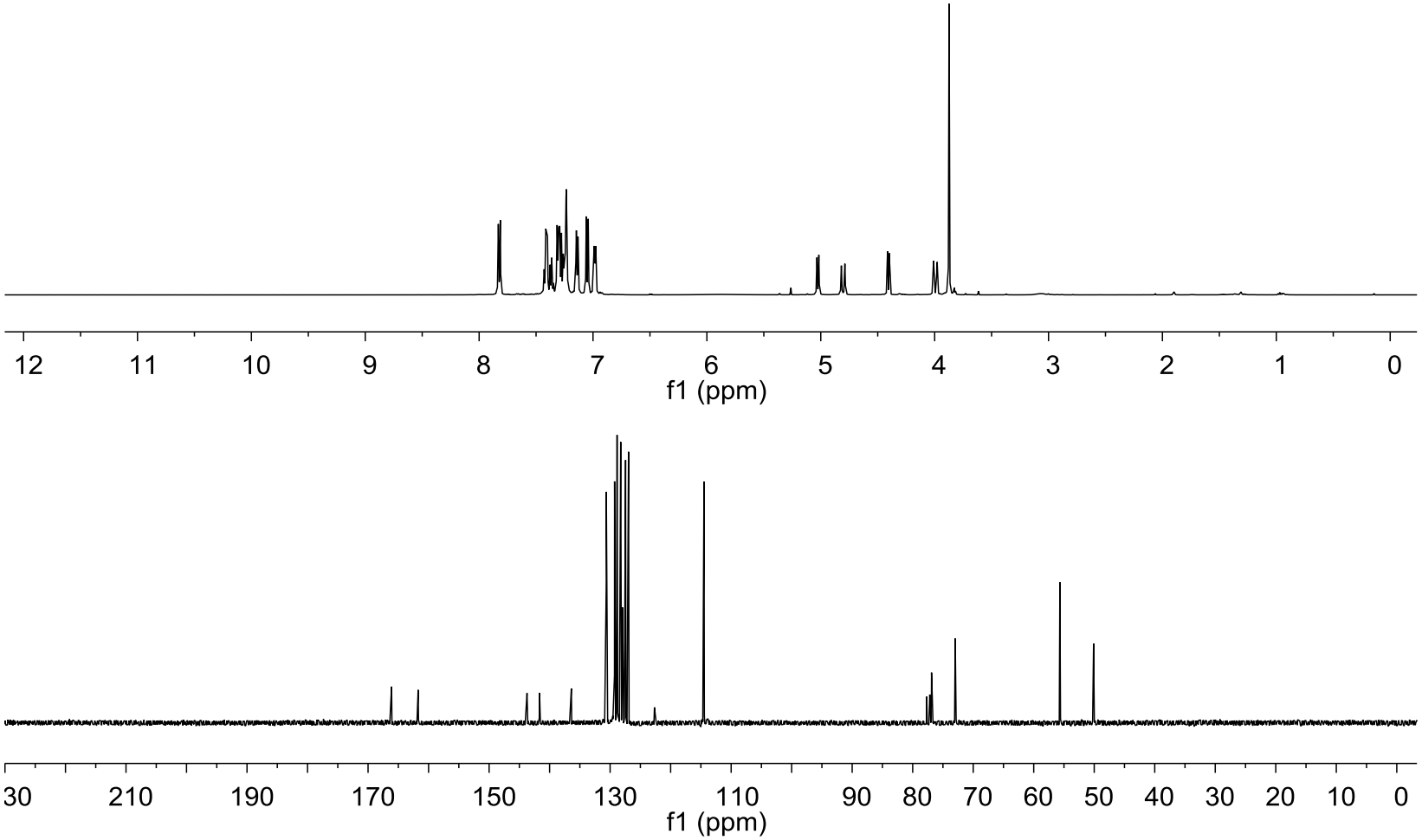


Figure 3-4: ^{1}HNMR and ^{13}C NMR of Compound **3-46**

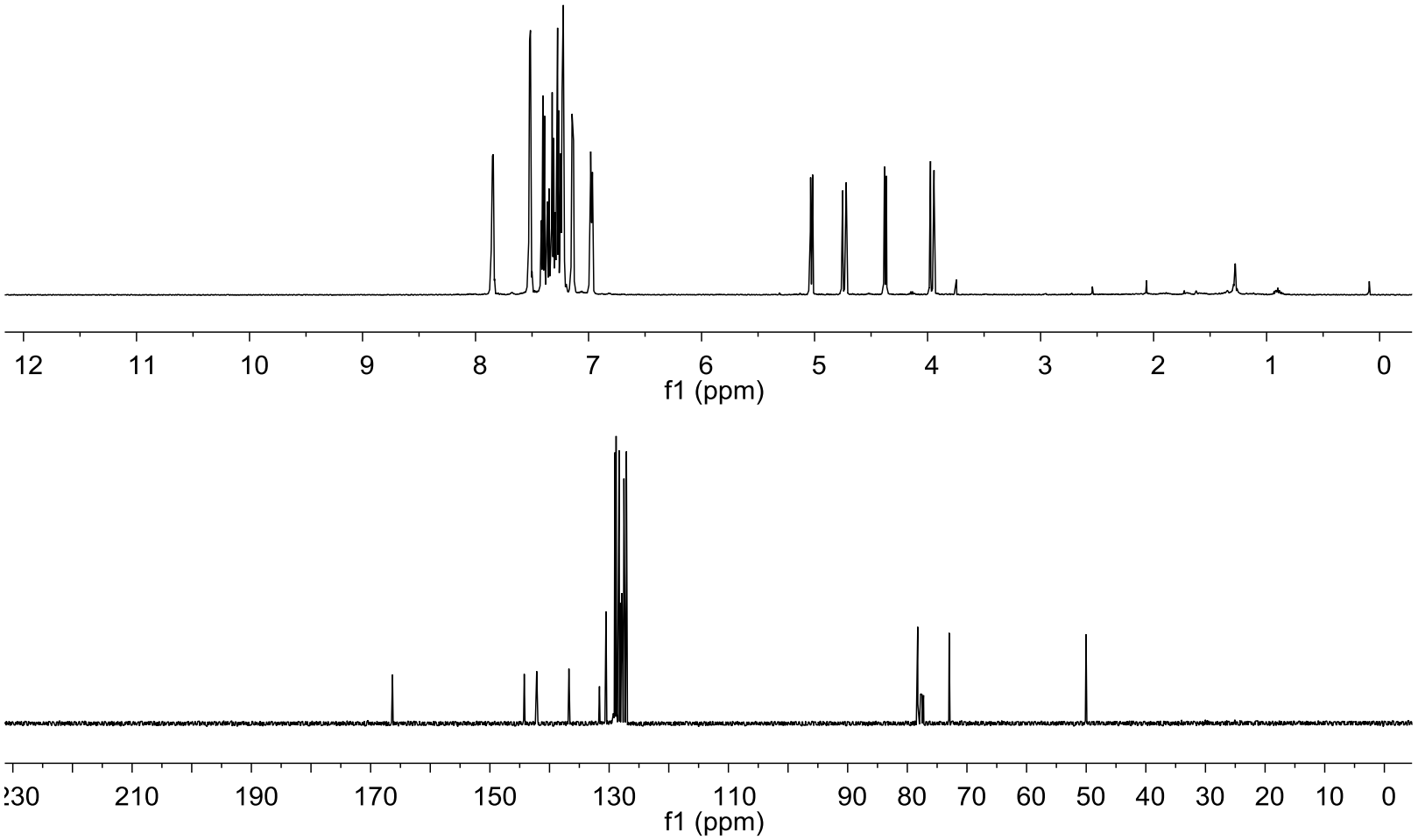


Figure 3-5: ^{1}HNMR and ^{13}C NMR of Compound **3-47**

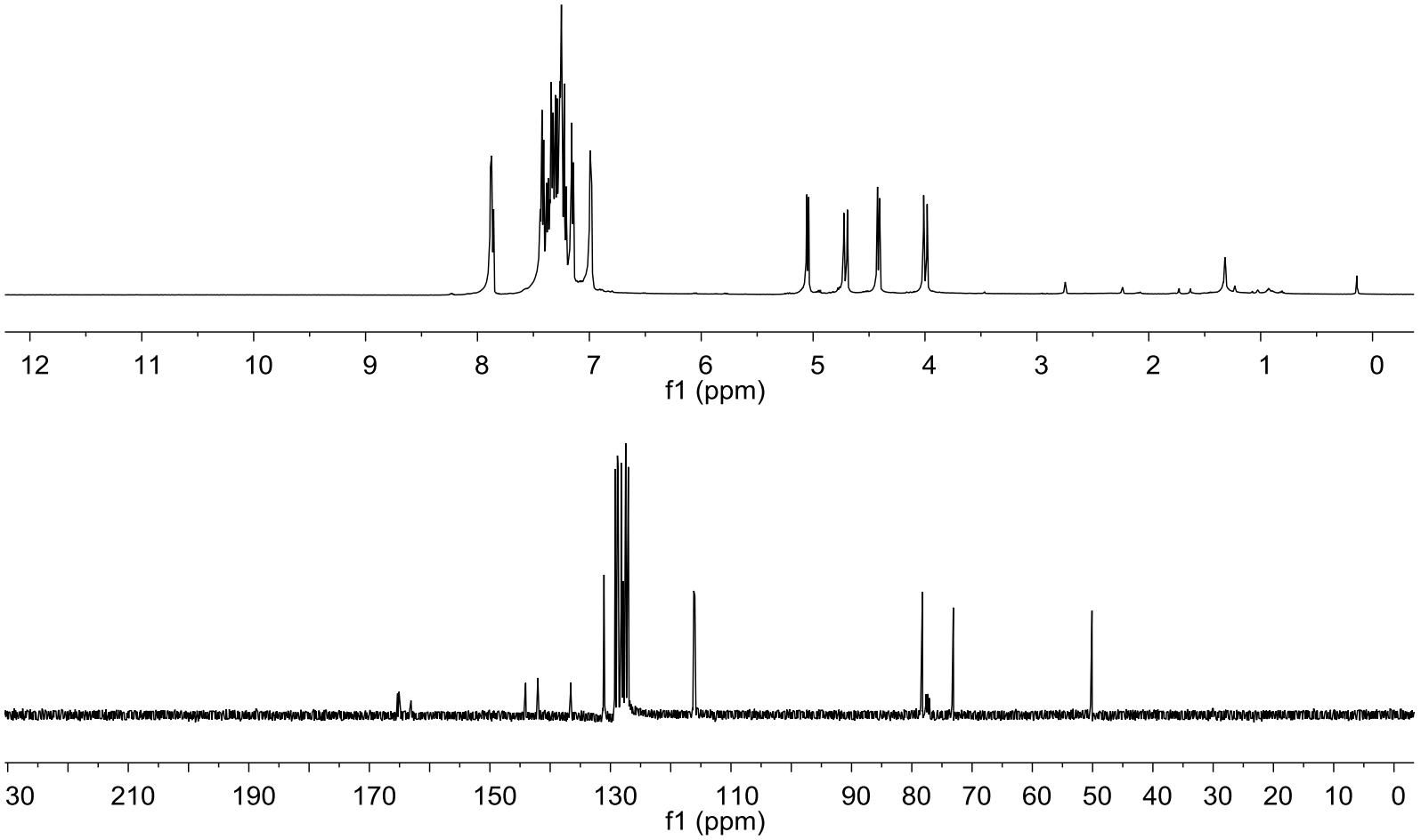


Figure 3-6: ^{1}HNMR and ^{13}C NMR of Compound **3-48**

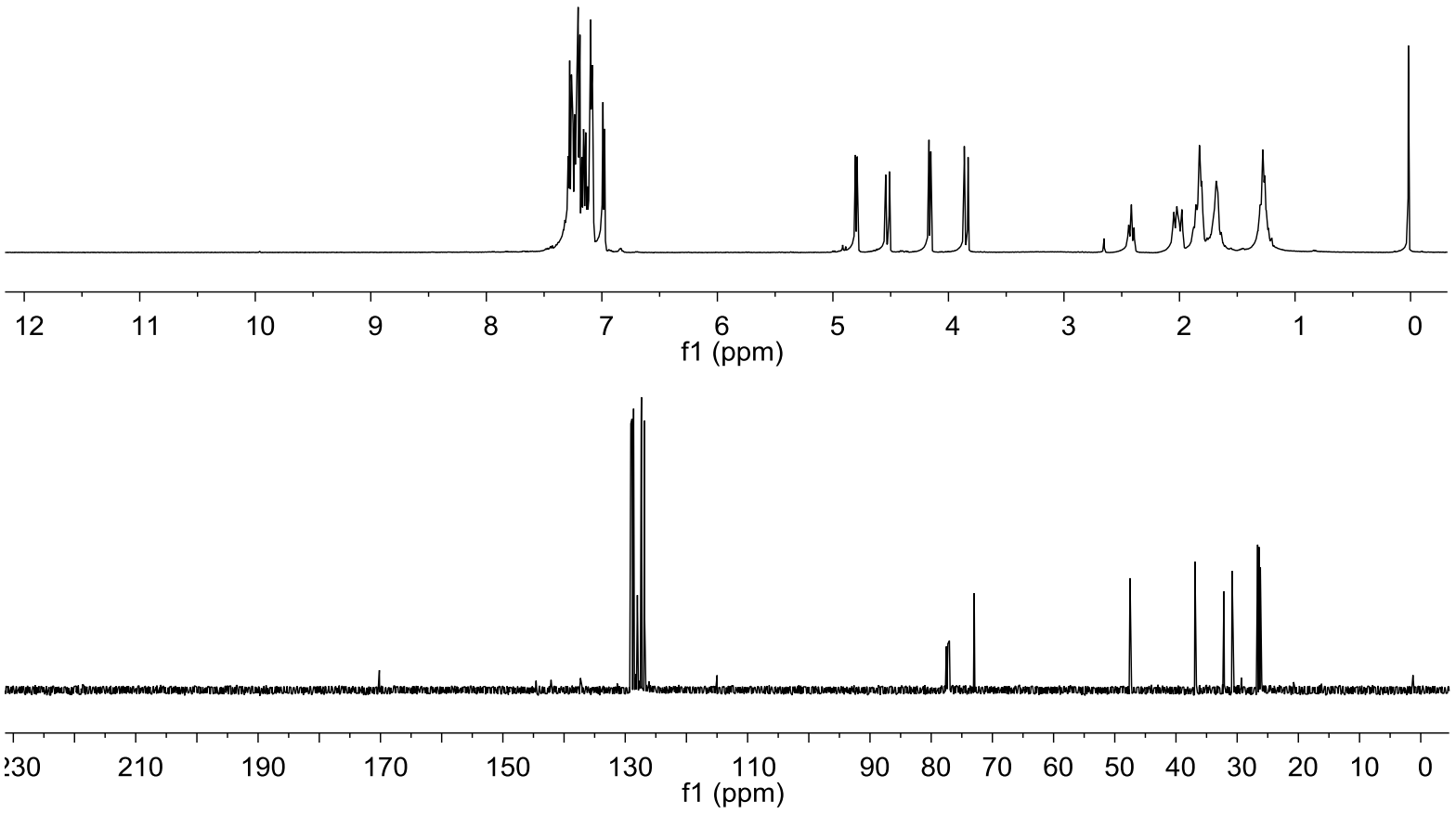


Figure 3-7: ^{1}HNMR and ^{13}C NMR of Compound **3-51**

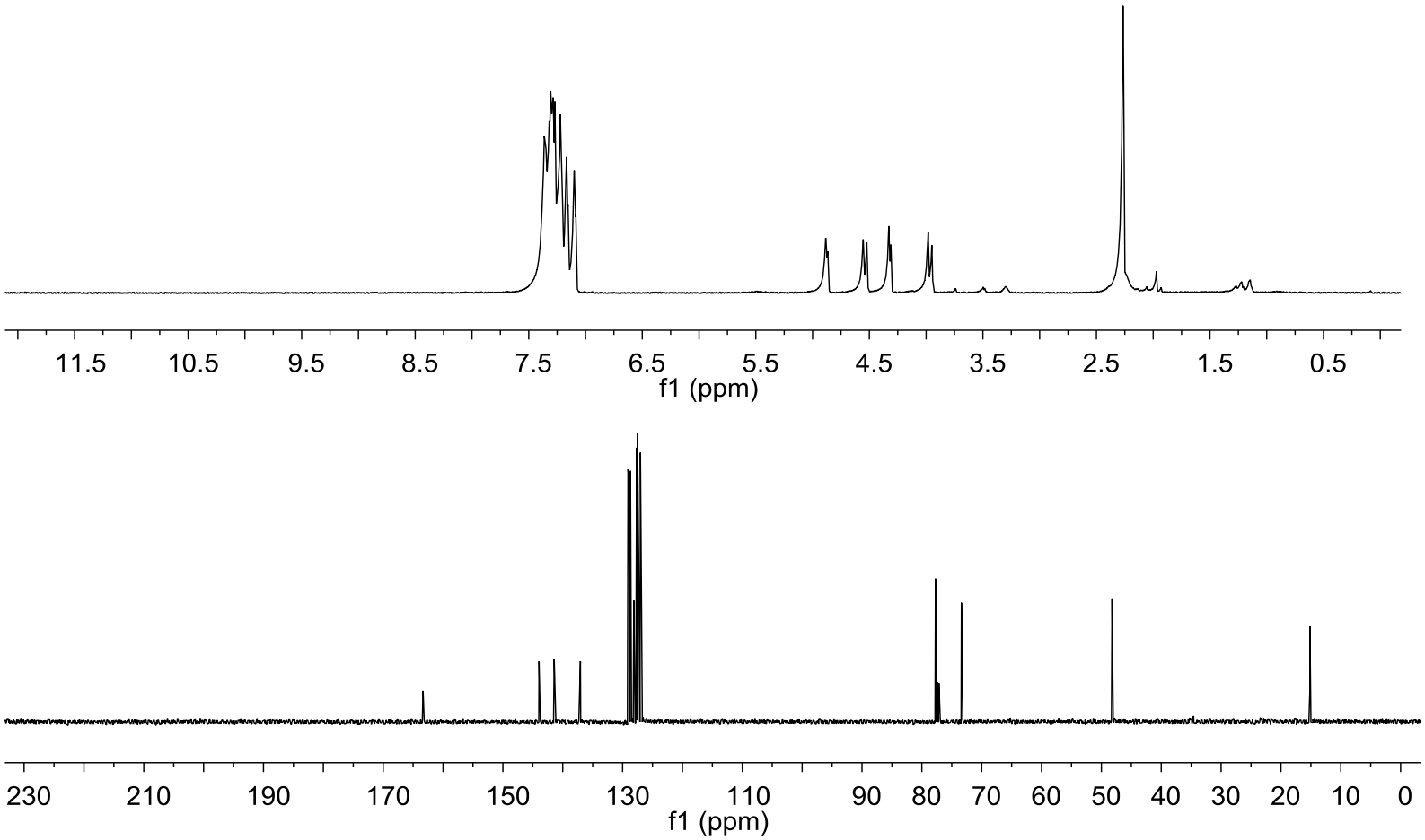


Figure 3-8: ^{1}HNMR and ^{13}C NMR of Compound **3-52**

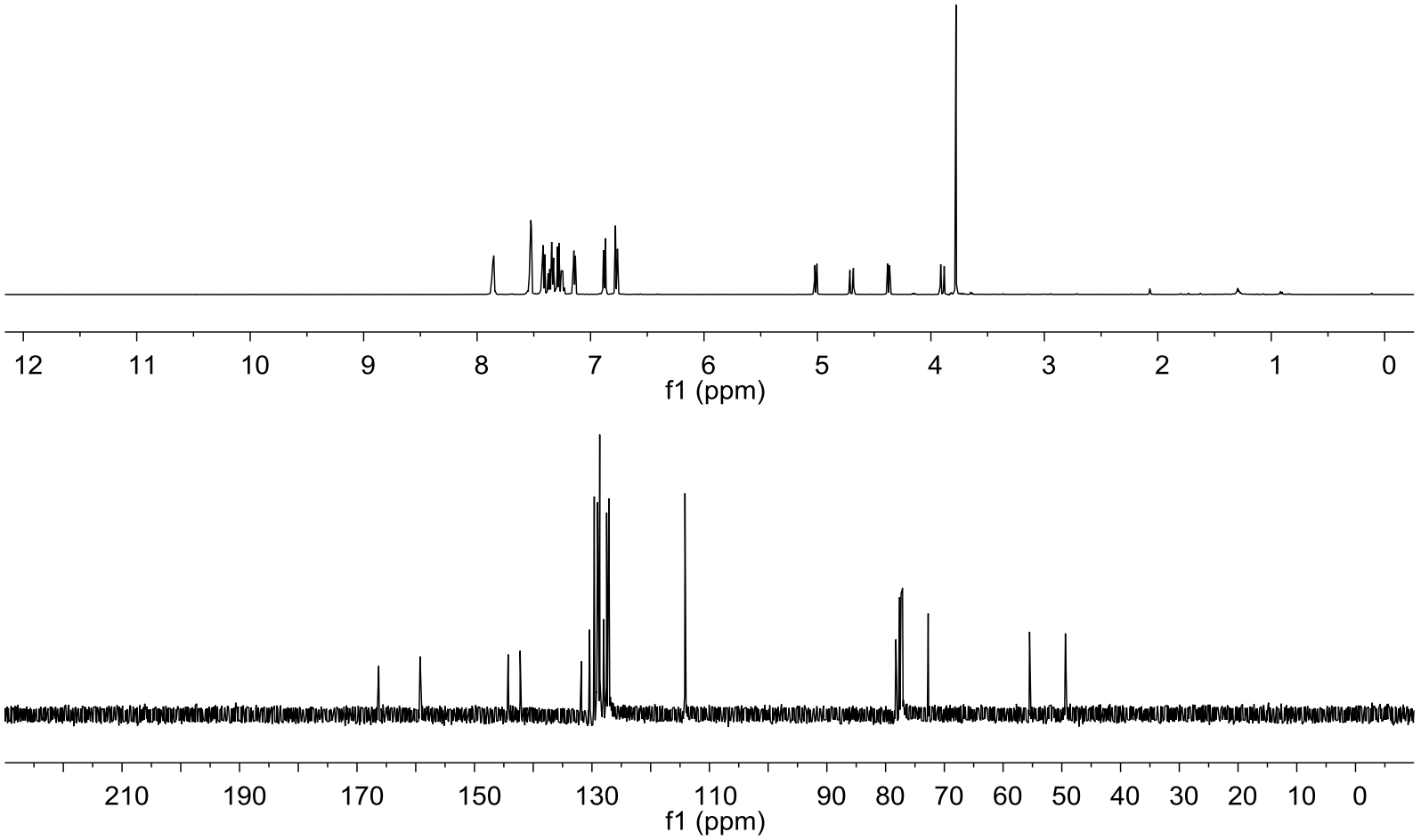


Figure 3-9: ^{1}HNMR and ^{13}C NMR of Compound **3-56**

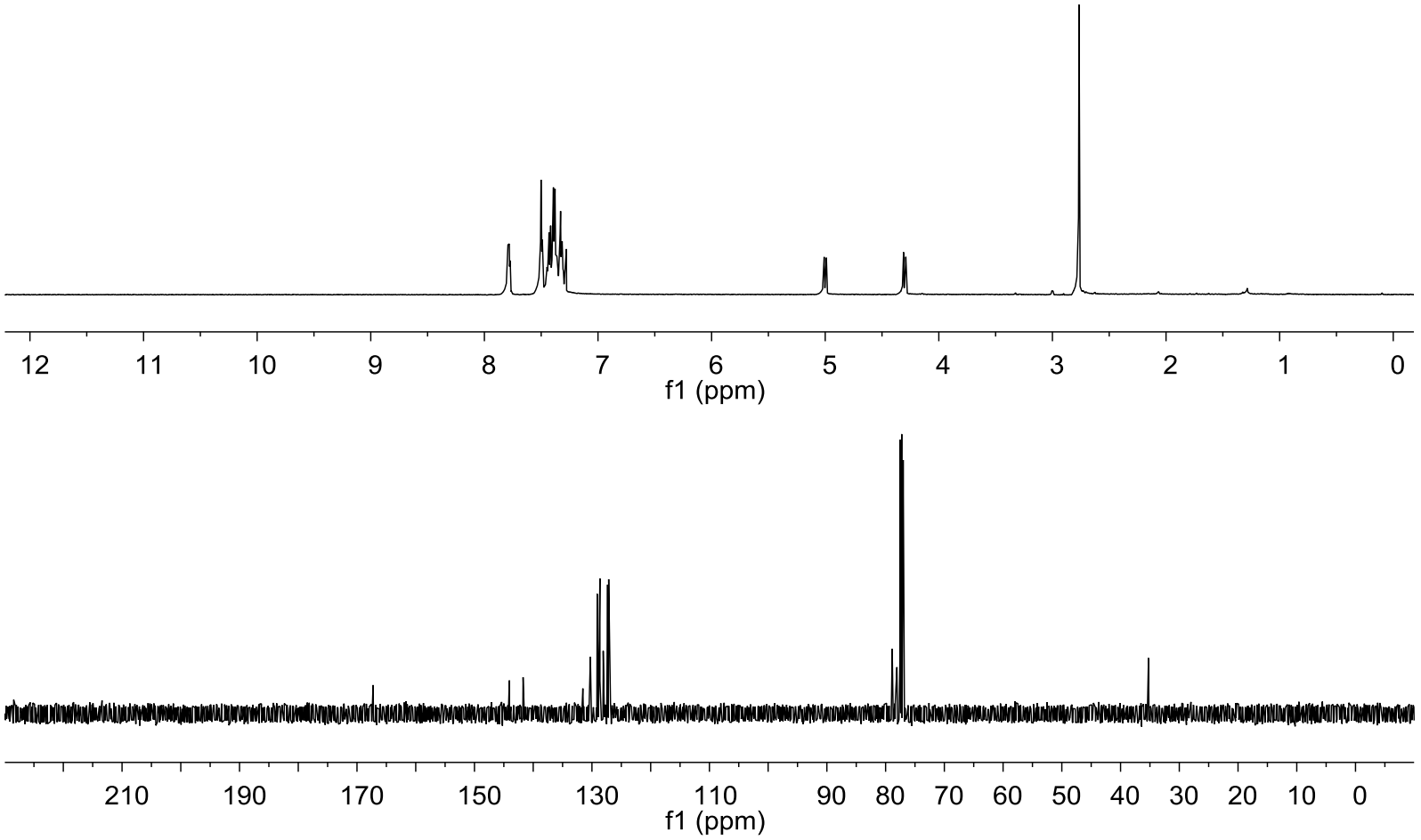


Figure 3-10: ^{1}HNMR and ^{13}C NMR of Compound **3-5**

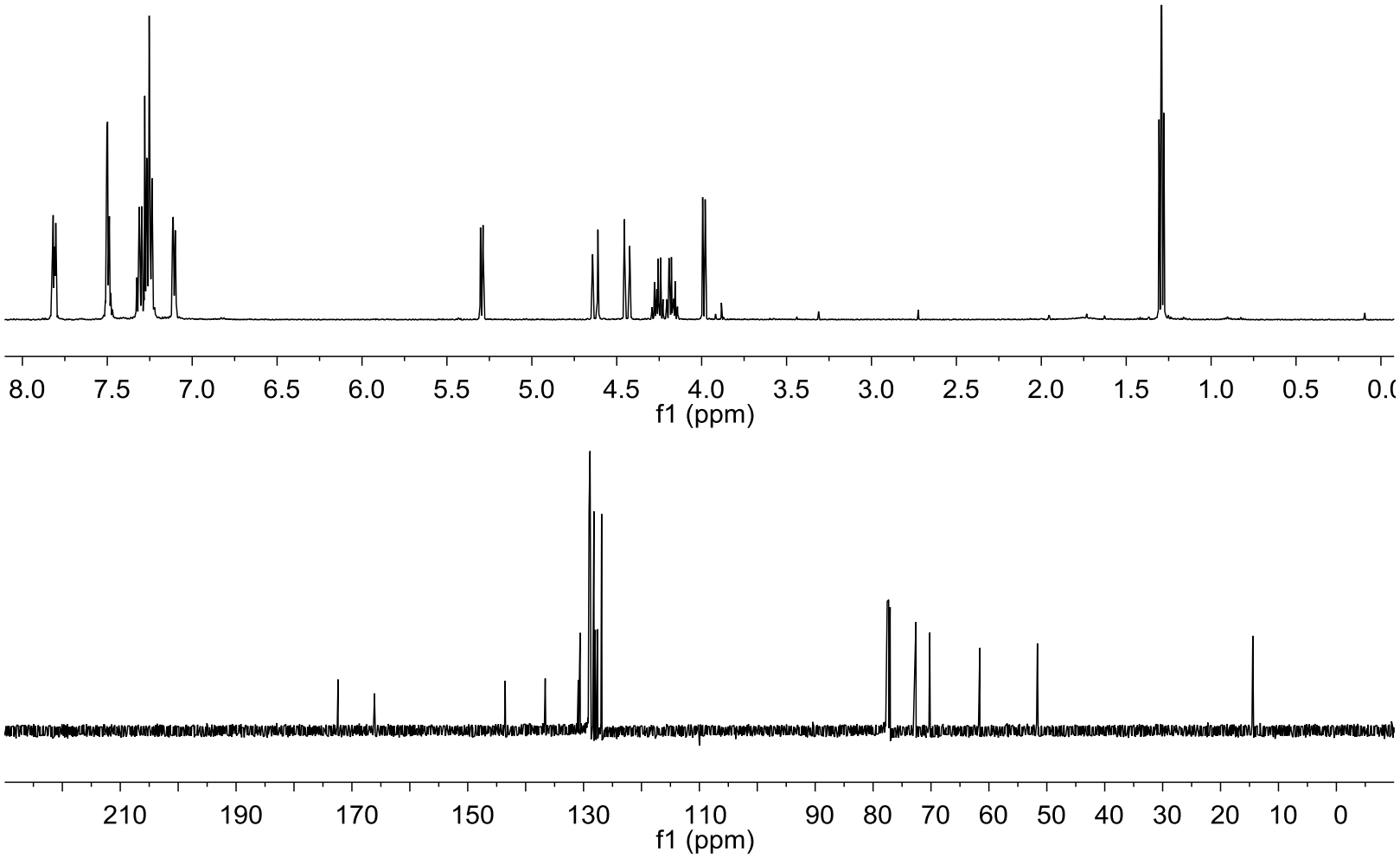


Figure 3-11: ^{1}HNMR and ^{13}C NMR of Compound **3-6**

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