AZOMETHINE YLIDE MEDIATED INVERSION OF CONFIGURATION OF QUATERNARY CARBON: CONVERTING *TRANS* TO *CIS* IMIDAZOLINES

By

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ABSTRACT

AZOMETHINE YLIDE MEDIATED INVERSION OF CONFIGURATION OF QUATERNARY CARBON: CONVERTING *TRANS* TO *CIS* IMIDAZOLINES

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Biological functions of small molecules are often closely related to their stereochemistry. Stereoisomers of the same scaffolds can sometimes show complementary biological responses, as exemplified by the *cis*- and *trans*-4,5-diaryl-2-imidazolines. Chapter I summarizes the recent progress of researches on application and synthesis of 2-imidazolines. Chapter II describes an efficient synthetic methodology of converting *trans*-4,5-diaryl-2-imidazolines to the corresponding *cis*-4,5-diaryl-2-imidazolines. This methodology features mild reaction conditions and a simple one-pot two-step procedure.

This thesis is dedicated to my beloved mother, Yu Qin, for her love and encouragement.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my advisor, Professor Jetze J. Tepe for offering me the opportunity to work in his research group and on such an exciting project. Professor Tepe paid close attention to developing and improving my ability to think independently. His confidence and encouragement to me have made my study in Michigan State University an enjoyable experience. Under his mentorship, I completed this thesis for my Master of Science degree.

I would like to extend my appreciation to my committee members for their advices. Through discussing chemistry with them, I learned how to apply the knowledge from the textbooks into practice. I also acknowledge Dr. Dan Holmes (NMR) and Dr. Richard Staples (X-ray analysis) for their constant technical support during my graduate studies. I am very grateful to my group members for their assistance during my laboratory struggles.

Two years have elapsed quickly. Tepe research group, chemistry department and Michigan State University campus have made happy memories in my mind. They are just like many oil paintings that never fade and will be treasured in my memory corridor.

I would like to thank my family, especially my dear mother, for their love, encouragement and support. Thank you for standing by me all the time.

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LIST OF SYMBOLS OR ABBREVIATIONS

Ar – Aryl

Boc – *tert*-Butyloxycarbonyl

Cbz – Carbobenzyloxy

COSY – Correlation spectroscopy

CSA – Camphorsulfonic acid

DABCO – 1,4-Diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM – Dichloromethane

DFT – Density functional theory

DIPEA – *N*, *N*-diisopropylethylamine

DMAP – 4-(*N*, *N*-dimethylamino)pyridine

DMSO – Dimethyl sulfoxide

EDCI – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Et – Ethyl

HMBC – Heteronuclear multiple-bond correlation spectroscopy

HMQC – Heteronuclear correlation through multiple quantum coherence

HRMS – High resolution mass spectrometry

IBX – 2-iodoxybenzoic acid

I-κB – Inhibitory kappa B

Me – Methyl

NBS – *N*-bromosuccinimide

NF-κB – Nuclear factor kappa B

Ni – Nickel

NMR – Nuclear magnetic resonance

NOESY – Nuclear Overhauser effect spectroscopy

Pd – Palladium

Ph – Phenyl

ROESY – Rotating-frame Overhauser effect spectroscopy

THF – Tetrahydrofuran

TMS – Trimethylsilyl

Ts – Tosyl

CHAPTER I

INTRODUCTION TO 2-IMIDAZOLINES

A. Overview of imidazolines

Nitrogen-containing heterocycles constitute the core structures of many biologically active natural products and pharmaceuticals.[1] Among these heterocycles, imidazolines hold important positions. The term imidazoline refers to any of the dihydroimidazoles, which are the reduced forms of the corresponding imidazoles (Figure I-1).[2,3,4]

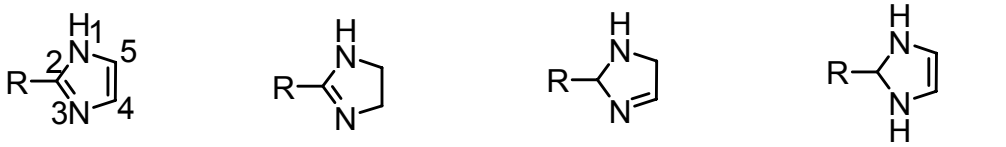
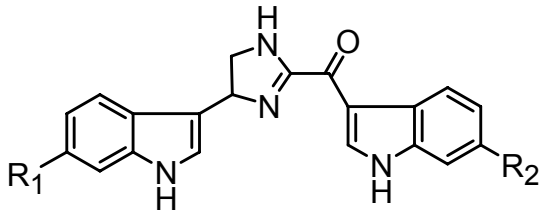


Figure I-1. Imidazole and imidazoline structures.

B. Biological significance of 2-imidazolines

2-imidazolines are the most important class among the above three classifications and this thesis will focus on them. 2-imidazoline structures can be found in many natural products. For instance, three novel bis(indole)-based alkaloids, Spongotines A, B and C, have recently been isolated from the marine sponge *Spongosorites* sp. (Figure I-2) and their structures were determined through close analysis of a combination of ^{1}H, ^{13}C, COSY, HMBC and ROESY NMR spectra together with fragmentation modes in mass data.[5] One unique feature of these structures is that the two indole rings are connected through an 2-imidazoline ring and a ketone

functionality, which is different from the same class of natural products isolated previously.[6] Among them, Spongotines A and C display marginal cytotoxicity towards five human solid tumor cell lines.



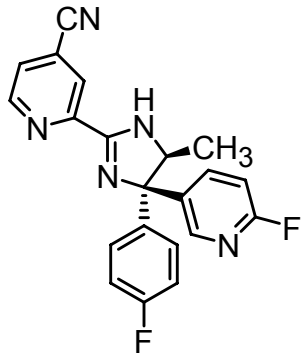
Spongotine A R_1=Br, R_2=H

Spongotine B R_1=H, R_2=Br

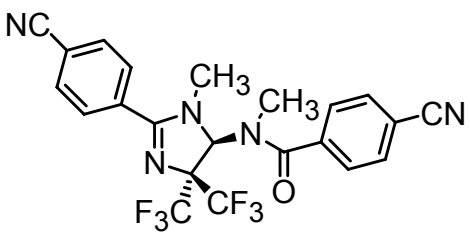
Spongotine C R_1=Br, R_2=Br

Figure I-2. Structures of Spongotines A, B and C.

Many other pharmaceutically-relevant compounds also contain 2-imidazolines as core structures, as shown in Figure I-3. Examples include Neuropeptide Y (NPY) Y5 receptor antagonists that have potential as antiobesity drugs,[7] cholesterol acyltransferase (ACAT) inhibitors,[8] estrogen receptor (ER) ligand,[9] and α_2-adrenoreceptor modulators with high antinociceptive activity.[10]



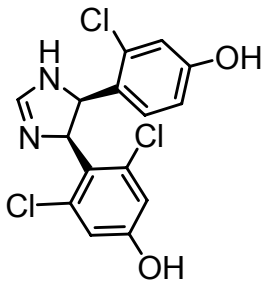
NPY Y5 receptor antagonist



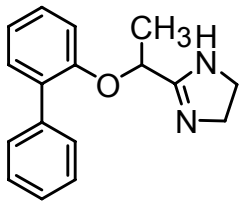
ACAT inhibitor

Figure I-3. Representative pharmaceutically important 2-imidazolines.

Figure I-3 (cont'd)

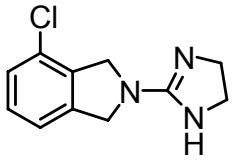


Estrogen receptor modulator

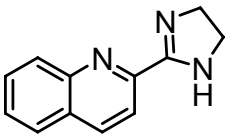


α_2-adrenoreceptor

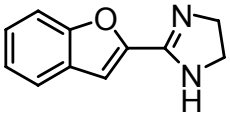
Imidazoline receptors (containing three receptors I_1, I_2 and I_3) are binding sites which have high affinity for imidazoline-containing compounds.[11] Imidazoline receptor I_1 is related to controlling blood pressure and imidazoline receptor I_2 is believed to be involved in modulating pain. So detailed investigation of compounds targeting imidazoline receptor I_2 provides potential opportunities for the discovery of novel effective analgestics. Several imidazoline receptor I_2 ligands are shown in Figure I-4. Imidazoline receptor I_3 might be responsible for regulating insulin secretion and its specific action mechanism is still under investigation.



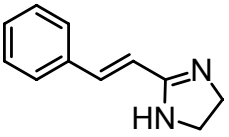
4-chloro-2-(4,5-dihydro-1*H*-imidazol-2-yl)isoindoline



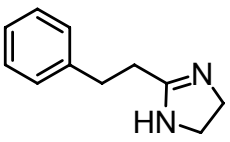
2-(4,5-dihydro-1*H*-imidazol-2-yl)quinoline



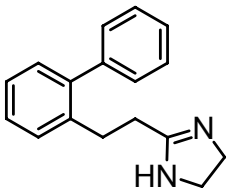
2-(benzofuran-2-yl)-4,5-dihydro-1*H*-imidazole



(*E*)-2-styryl-4,5-dihydro-1*H*-imidazole



2-phenethyl-4,5-dihydro-1*H*-imidazole



Diphenylzoline

Figure I-4. Representative imidazoline receptor I_2 ligands.

C. Utilization of 2-imidazolines in asymmetric catalysis

The progress of transition-metal-based asymmetric reactions depends on the development of efficient chiral catalysts and ligands. The results of using 2-imidazoline-based chiral ligands in asymmetric synthesis turn out to be promising and some elegant work has been summarized below.

In the field of asymmetric synthesis, a number of C_2-symmetric chiral bis(oxazoline) ligand-metal complexes have been utilized to catalyze enantiospecific carbon-carbon bond formation.[12] In light of these successes, chemists have synthesized and studied analogous ligands based on imidazolines. One advantage of imidazoline-based ligands is that different substituents can be attached at their N-1 sites, which can not only fine-tune electronic effects, but also influence the steric interactions of their complexes with substrates.[4,13] In 2004, Casey and coworkers synthesized two types of tricyclic bis(imidazoline) ligands with 5,6,5 and 5,7,5 skeletons respectively (Figure I-5).

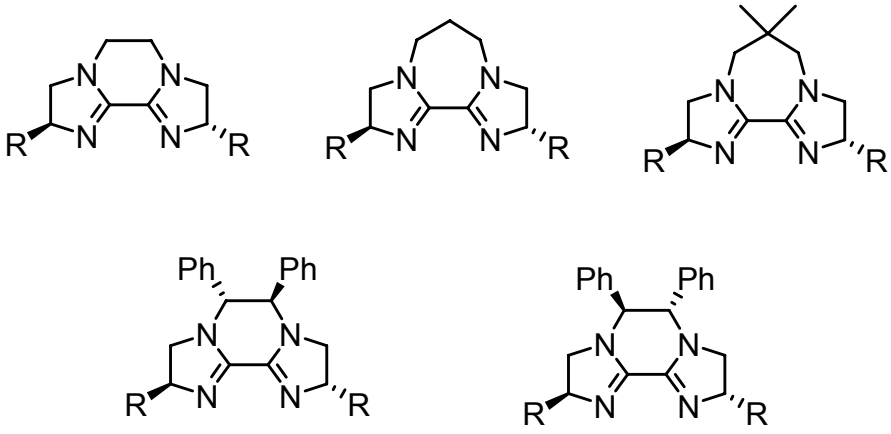
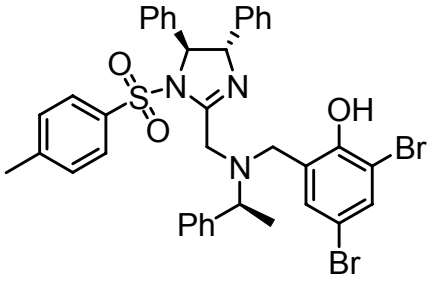


Figure I-5. Synthesized chiral bis(imidazoline) ligands.

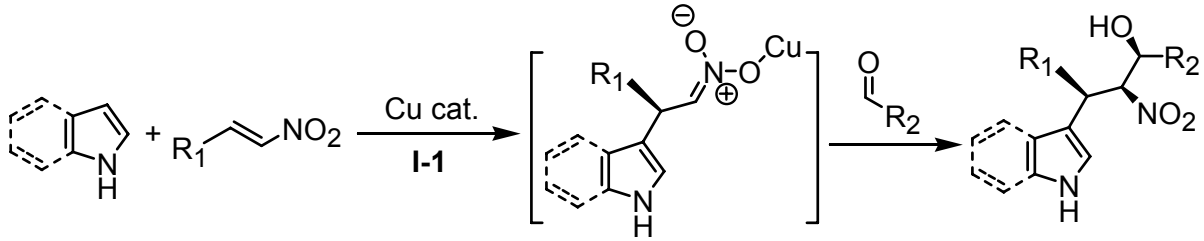
Asymmetric palladium-catalyzed allylation reactions of malonate were used to test the effects of these bis(imidazoline) ligands on inducing enantioselectivity.[14] The

results showed that for this reaction bis(imidazoline) ligand complexes are more effective than bis(oxazoline) ligands.

Arai and coworkers synthesized a 2-imidazoline-containing chiral ligand **I-1** and by combining it with copper catalysts, they developed a unique chiral imidazoline-aminophenol-copper catalyst system.[15] With this catalyst system a tandem catalytic asymmetric sequence that connects Friedel-Craft reaction with the Henry reaction has been realized to afford optically pure structural motifs incorporating indoles and pyrroles (Scheme I-1).



I-1



Scheme I-1. A tandem catalytic asymmetric sequence utilizing imidazoline ligand.

In 2011, Gong, Song and coworkers synthesized several chiral PCN pincer Pd(II) and Ni(II) complexes with chiral imidazolines as N donors (Figure I-6) to evaluate their catalytic behaviors in asymmetric hydrophosphination of α,β-unsaturated enones by diphenylphosphines (Scheme I-2).[16] Among the four pincer complexes tested, Pd pincer **I-2** successfully afforded the expected chiral 1,4 phosphine addition products in moderate to high yields and *ee* values.

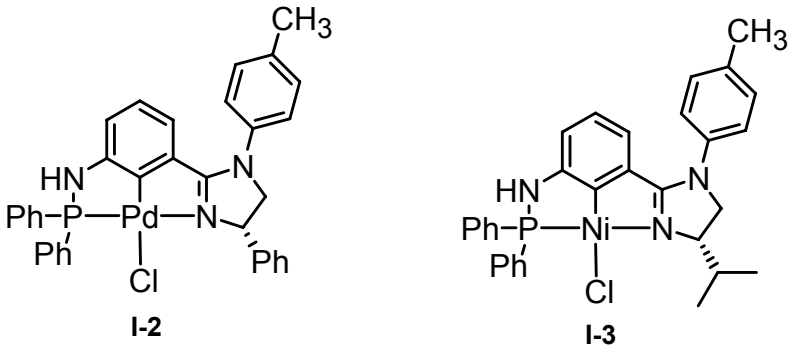
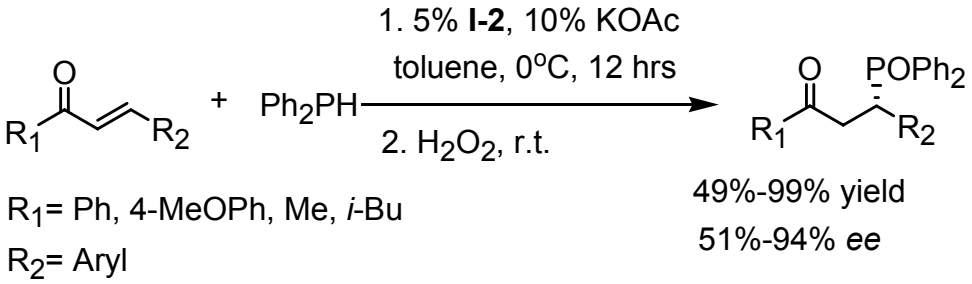


Figure I-6. Two representative chiral PCN pincer Pd(II) and Ni(II) complexes.

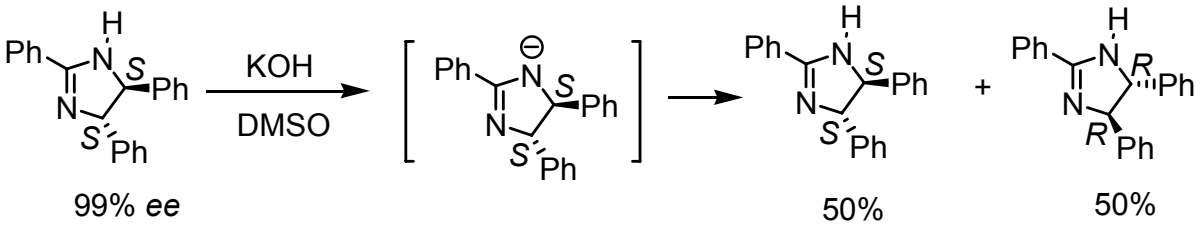


Scheme I-2. Chiral Pd pincer-catalyzed 1,4 addition reaction.

D. Racemization of chiral imidazolines

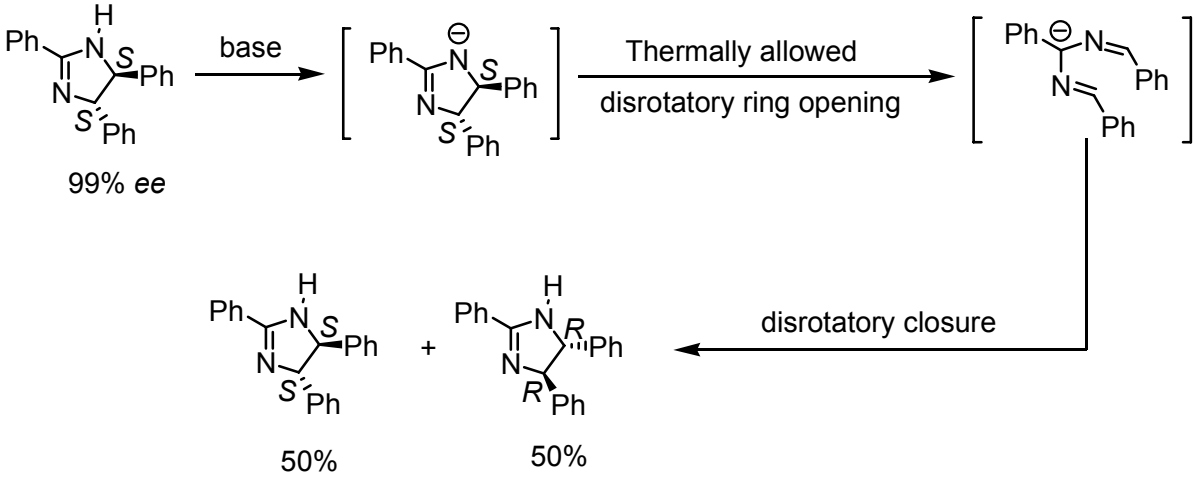
Due to the extensive research on the synthesis and application of imidazolines, especially their explosive development in the field of chiral ligands, some in-depth insights about the properties of these molecules are required. The racemization of chiral imidazolines is one of them and will be discussed below.

In 2008, researchers of Boehringer-Ingelheim Pharmaceuticals unexpectedly found that chiral imidazolines in DMSO solution can undergo racemization under strong basic conditions, during their preparation of relevant chiral phosphinoimidazoline ligands (Scheme 1-3).[17]



Scheme I-3. Racemization of chiral imidazoline.

Subsequent experiments show that nitrogen substituents prevent this racemization process. No racemization is observed if nitrogen bears a substituent, such as tosyl or methyl. Moreover, a number of amine bases, such as triethylamine, DABCO, DBU, DMAP do not promote this racemization. Based on these findings, the following possible mechanism has been put forward to account for this phenomenon. The overall process is proposed to be a disrotatory pericyclic ring-opening and ring-closure sequence.



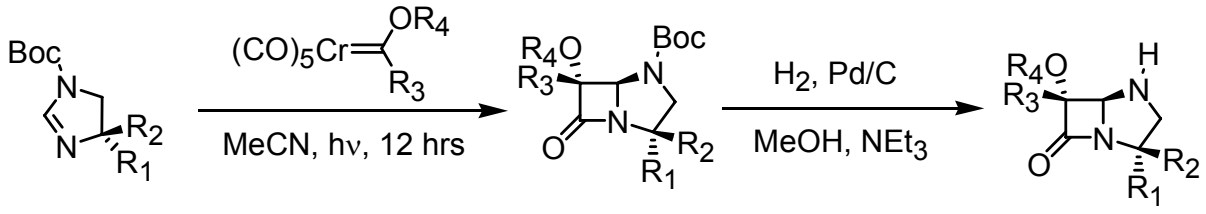
Scheme I-4. Possible mechanism of racemization of chiral imidazoline.

The same group of researchers recently applied online vibrational circular dichroism (VCD), chemometrics and DFT calculations into the investigation of this racemization transformation, calculating activation energies of the transition states and finding that aromatic substituents on the two chiral carbons are necessary for the

overall racimization.[18]

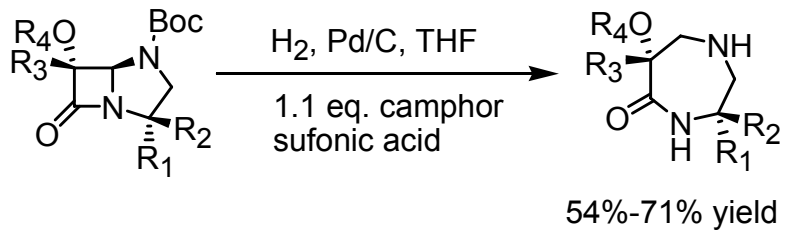
E. Application of 2-imidazolines in organic synthesis

One common synthetic application of 2-imidazolines is to convert them via oxidation into the corresponding 2-imidazoles, which are core structural motifs in many biologically-relevant compounds. In addition to that, 2-imidazolines serve as important synthetic intermediates, which readily convert into a number of useful organic moieties. Hegedus and coworkers synthesized a series of optically active 4-disubstituted 2-imidazolines from optically active amino acids, then utilized them to prepare azapenams through a photolysis reaction mediated by alkoxycarbene chromium complexes (Scheme 1-5).[19]



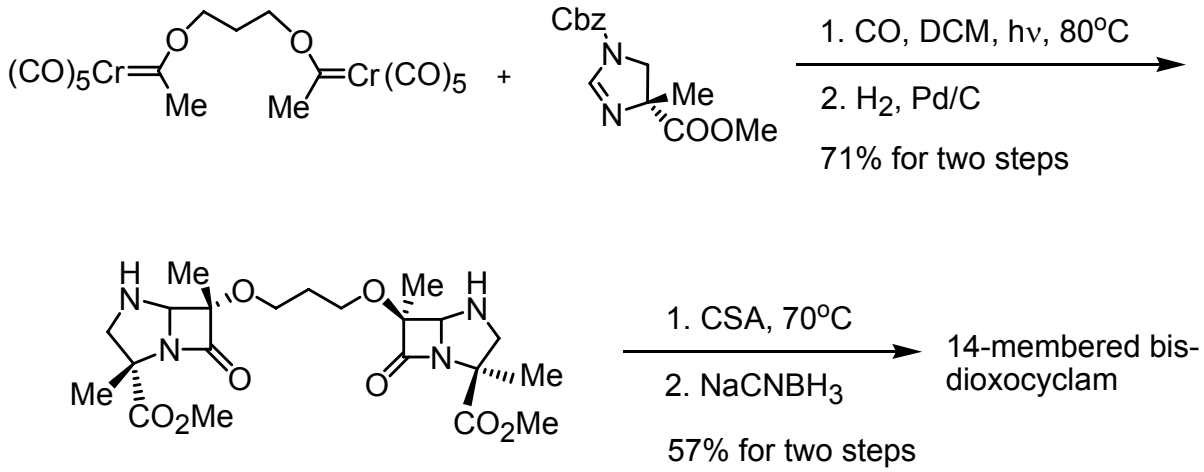
Scheme I-5. Chromium-mediated synthesis of azapenams.

Interestingly enough, when the deprotection step of the Boc group was carried out under acidic conditions, a unique class of hexahydrodiazepinone compounds was obtained as shown in Scheme 1-6 in moderate yields. Few synthetic methods are available to approach these molecular architectures, so this azapenam-based isomerization provides a convenient way to synthesize these seven-membered rings, whose biological properties might be worthy of further investigations.



Scheme I-6. Conversion from azapenams to hexahydrodiazepinones.

Encouraged by these elegant results, the same group successfully prepared a family of fourteen-membered tetraazamacrocyclic bisdioxocyclam-type compounds via the bis-chromium alkoxycarbene complex-mediated photocycloaddition reaction using 4-disubstituted 2-imidazolines as starting materials (Scheme 1-7). These macrocycles have potential applications in metal coordination chemistry research, biology and magnetic resonance imaging.[20]



Scheme I-7. Synthesis of 14-membered bisdioxocyclam.

F. Application of 2-imidazolines in other related fields

2-imidazolines not only hold important positions in the traditional organic chemistry fields as illustrated above, but their applications also extend into other relevant chemistry disciplines, which will be briefly discussed.

Synthetic peptides have been explored as lead compounds for drug development and 2-imidazolines are unique as amide-bond replacements: they have two heteroatoms in the core scaffolds, possible hydrogen bonding interactions and similar steric sizes, which are all quite similar to the amide bonds in peptides. Jones and Gilbert elegantly prepared one peptide mimetic of CCK-4 (residues 30-33 of cholecystokinin), the C-terminus tetrapeptide that replaces the crucial amide bond between tryptophan and norleucine with synthetic 2-imidazolines (Figure I-7).[21] Then the same researchers tested the *in vitro* binding affinities of these pseudopeptides to the CCK-A and CCK-B receptors, revealing that the synthesized analogues have higher binding to the CCK-B receptor.

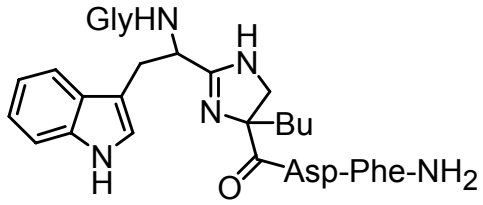


Figure I-7. Pentapeptide mimic with synthetic 2-imidazoline incorporated.

Not limited to peptidomimetics, 2-imidazolines can also find applications in analytical chemistry. Recently Zhang and coworkers synthesized 2-imidazoline molecules with the aid of microwave heating under solvent-free conditions and immobilize them into silica surface by polymerization to make a novel 2-imidazoline-based stationary phase for use in chromatography.[22]

G. Synthesis of 2-imidazolines

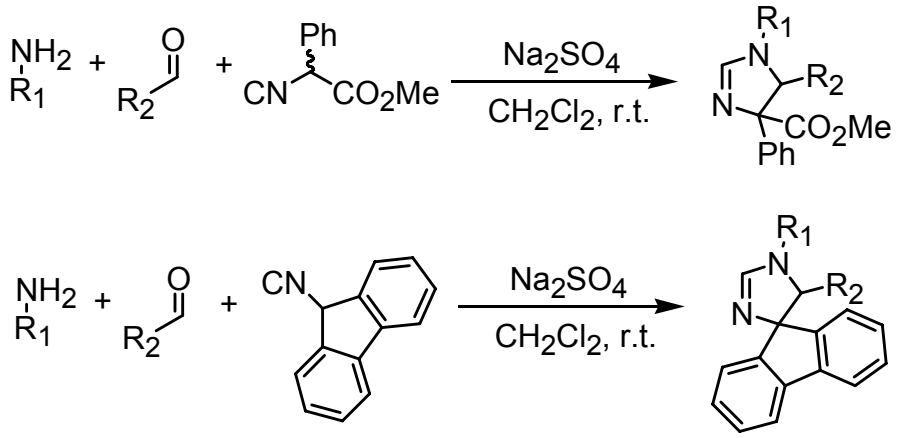
Given the significance of 2-imidazoline-based structures in pharmaceutical and chemistry fields, efficient synthetic methodologies are urgently needed to produce

these scaffolds for further application investigations. In recent years, many novel approaches towards the 2-imidazoline scaffolds have been accomplished by different research groups, which will be discussed in detail below.

G.1 Multicomponent synthesis of 2-imidazolines

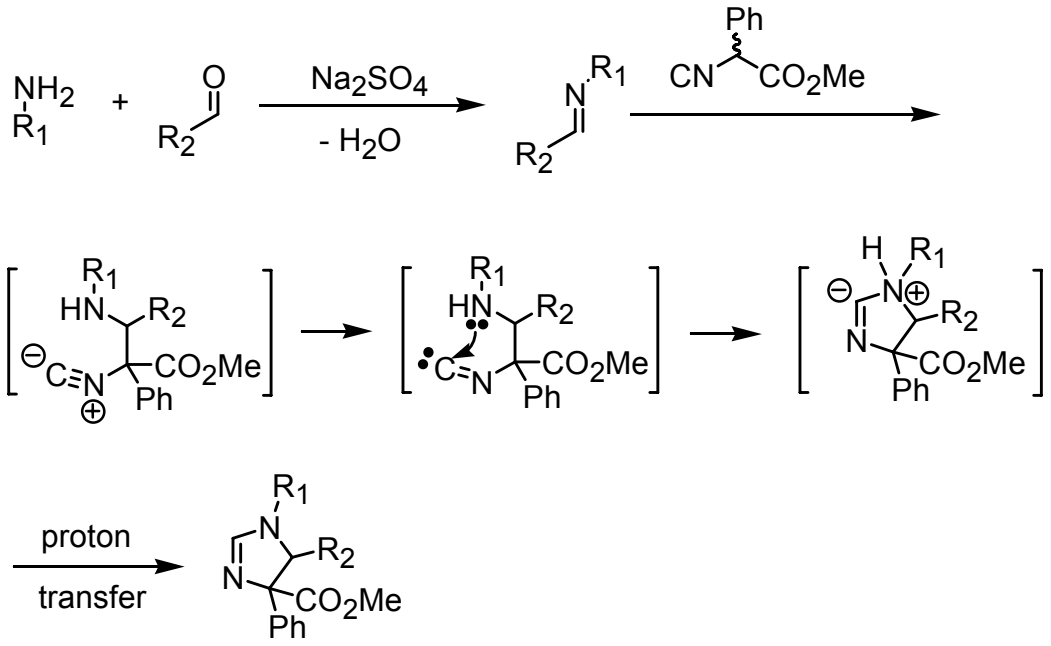
A basic method to synthesizing imidazolines in the past was to assemble the necessary straight chain intermediates first, which can be induced to cyclize into the desired five-membered imidazoline rings under the reaction conditions.[3] Taking advantage of the rapid development of multicomponent synthetic methodologies,[23] imidazolines can be assembled much more efficiently. Compared with the relatively old synthetic routes, the differences lie in that the required intermediates are quickly prepared by combining several simple readily available building blocks instead of time-consuming stepwise synthesis. As for the choice of appropriate substrates, isocyanides and nitriles, both bearing a carbon-nitrogen triple bond that can be incorporated into the skeletal structure of the final imidazoline ring, are among the most favorite starting materials.

In 2003, Orru and coworkers developed a mild three-component synthesis of highly substituted 2-imidazolines from amines, aldehydes and isocyanides with an acidic α-hydrogen (Scheme 1-8).[24]



Scheme I-8. Three component of synthesis of 2-imidazolines.

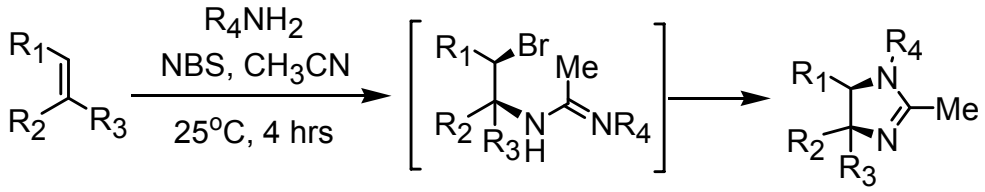
They proposed an aldol-type condensation between the isocyanide and the *in situ* formed imine as the key carbon-carbon bond-forming step, which is followed by ring closure to afford the 2-imidazoline (Scheme I-9).



Scheme I-9. Mechanism of the multicomponent reaction.

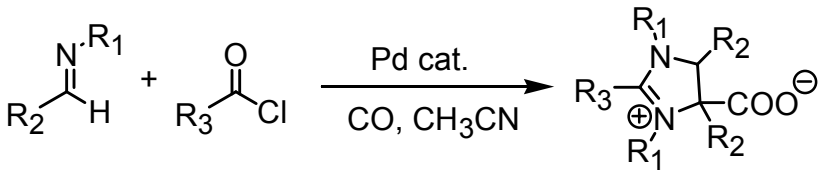
Two years later, the same group published a more detailed paper on their work.[25] They determined two influencing factors for this methodology: the reactivity of isocyanides and the steric hindrance in the *in situ* formed imines. They found that the less reactive isocyanides can participate in the reaction with the help of silver acetate.

Very recently, Yeung and coworkers successfully made a range of 2-imidazoline derivatives by one-pot *N*-bromosuccinimide (NBS)-induced cascade reactions between olefins, amines and nitriles under ambient temperature (Scheme I-10).[26] This methodology utilizes readily available reagents and features the convenient reaction operation of just mixing reaction substrates in acetonitrile. The reaction can stop at the amidine intermediates, which potentially allows other useful synthetic transformations.



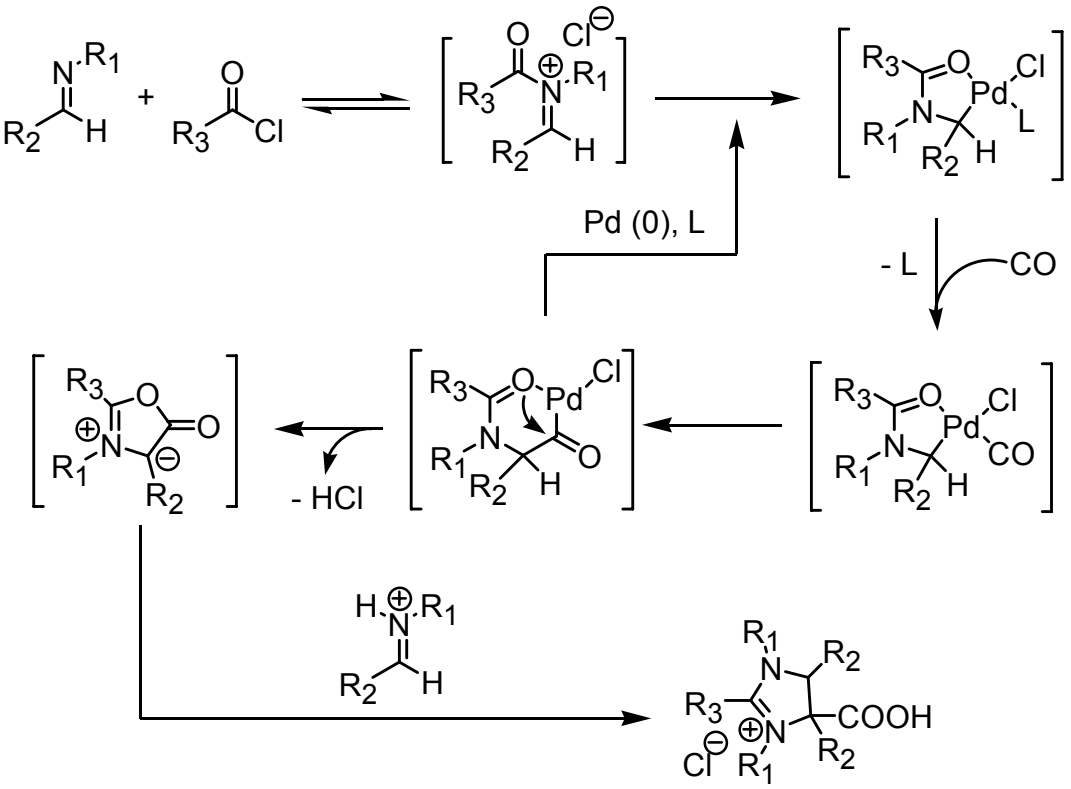
Scheme I-10. NBS-mediated cascade synthesis of 2-imidazolines.

Transition metals are also helpful in promoting assembly of a variety of heterocycles by combining several reaction substrates. Arndtsen and coworkers approached the synthesis of a range of diversified 2-imidazoline carboxylates via palladium-catalyzed multicomponent condensation between imines, acid chlorides and carbon monoxide (Scheme I-11).[27]



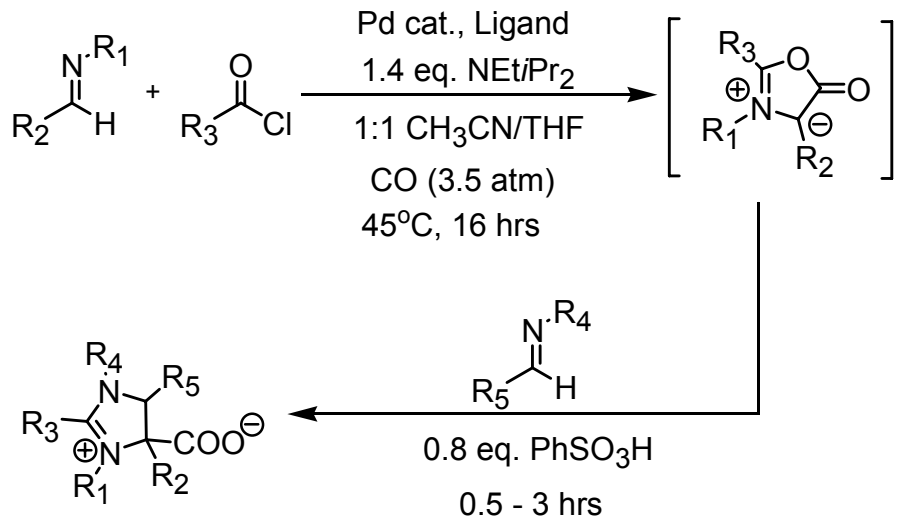
Scheme I-11. Palladium-catalyzed synthesis of 2-imidazoline carboxylates.

They proposed the following mechanism to account for the formation of the 2-imidazoline carboxylates (Scheme I-12).



Scheme I-12. Proposed mechanism for the generation of imidazoline carboxylates.

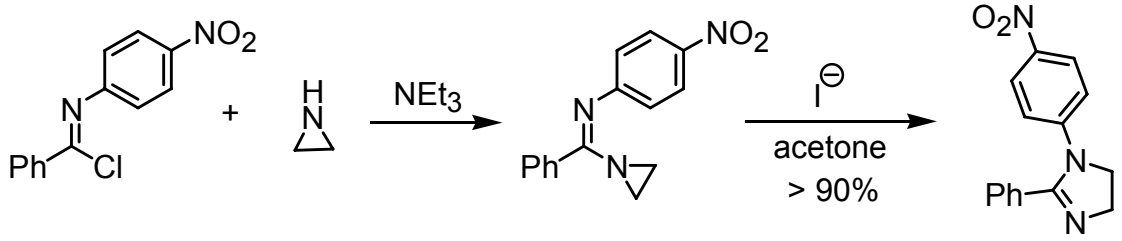
One limitation of the above reaction is that the same imine has been incorporated twice into the 2-imidazoline carboxylate products, resulting in the same R_1 substituent on both nitrogen and the same R_2 substituent on the carbons 4 and 5. Arndtsen and coworkers successfully modified their methodology to incorporate two different imines into the final products, thus giving more diversified 2-imidazolines and making this reaction more powerful as shown in Scheme I-13.[28]



Scheme I-13. 2-imidazoline carboxylates formation via usage of two different imines.

G.2 Synthesis of 2-imidazolines via ring expansion of aziridine

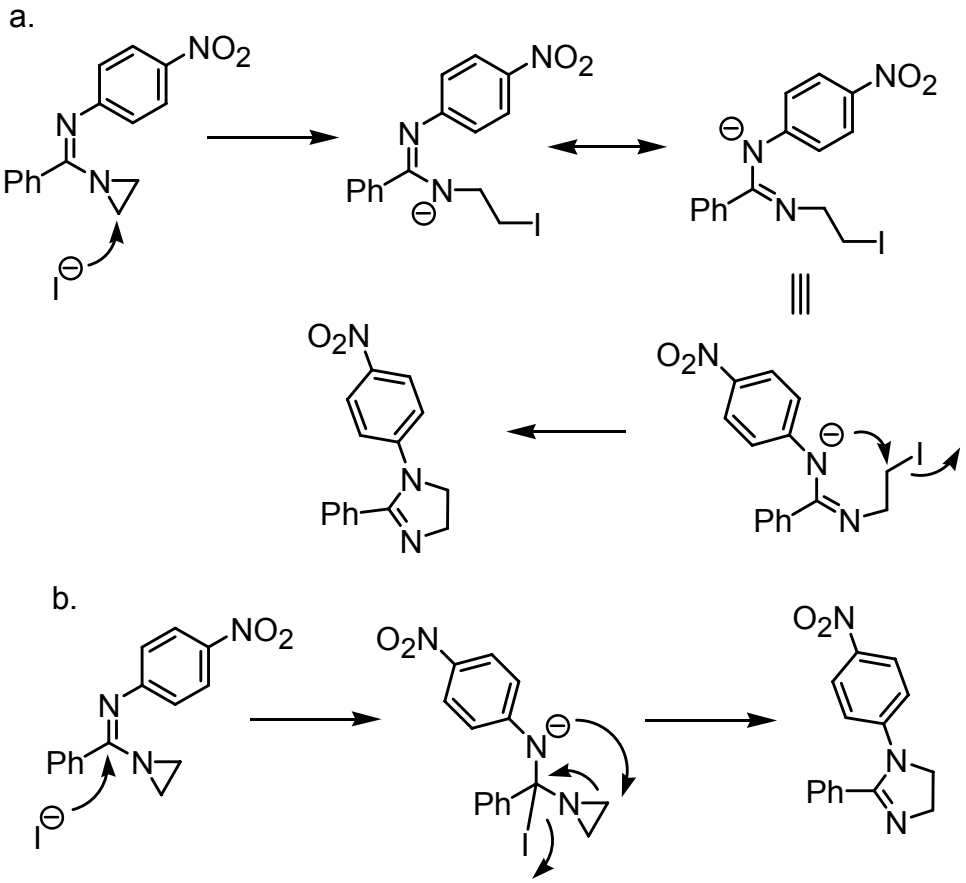
Aziridines have served as versatile synthetic intermediates in many synthetic transformations and they can be readily converted into imidazolines through ring expansion. As early as 1960, Heine and coworker successfully employed iodide anion to isomerize 1-(*N*-p-nitrophenylbenzimidoyl)aziridine into 1-p-nitrophenyl-2-phenyl-2-imidazoline (Scheme I-14).[29]



Scheme I-14. Rearrangement of 1-arylbenzimidoylazirdine into 2-imidazoline.

The authors put forward the following two possible reaction pathways for the above isomerization (Scheme I-15). In one case, the iodide anion opens the three-membered aziridine ring, followed by ring closure by the other nitrogen atom with iodide serving as a leaving group (Pathway a, Scheme I-15). In the other case,

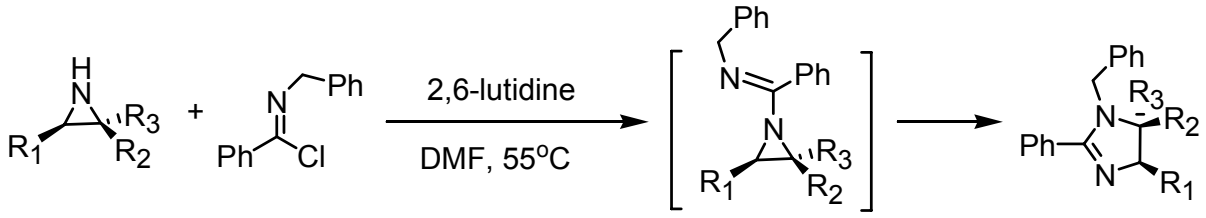
iodide might attack the carbon atom of benzimidoyl moiety to generate an intermediate with tetrahedral configuration, which then cyclizes into the 2-imidazoline ring, kicking off the iodide anion simultaneously (Pathway b, Scheme I-15). This pathway involves a disfavored 5-endo-tet cyclization, which renders it a weak mechanism candidate.



Scheme I-15. Two possible mechanisms of rearrangement of 1-arylbenzimidoylaziridine into 2-imidazoline.

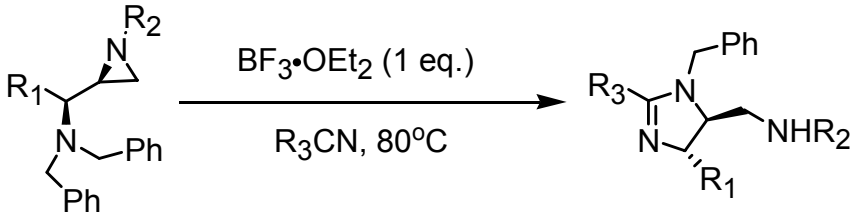
In Heine and coworker's reaction, the benzimidoylaziridine intermediate was isolated and the overall reaction constituted a two-step synthetic sequence. Recently our group developed a convenient one-pot ring expansion synthesis of highly substituted 2-imidazolines from aziridines and imidoyl chlorides in a stereospecific

and regioselective manner (Scheme I-16).[30] Only one regioisomer was produced and the stereochemistry in the starting aziridines was retained in the products. A variety of different functional groups are tolerated on the starting aziridines, ranging from aryl, vinyl, alkyl groups to ester and ketone functionalities.



Scheme I-16. One-pot synthesis of 2-imidazolines from aziridines and imidoyl chlorides.

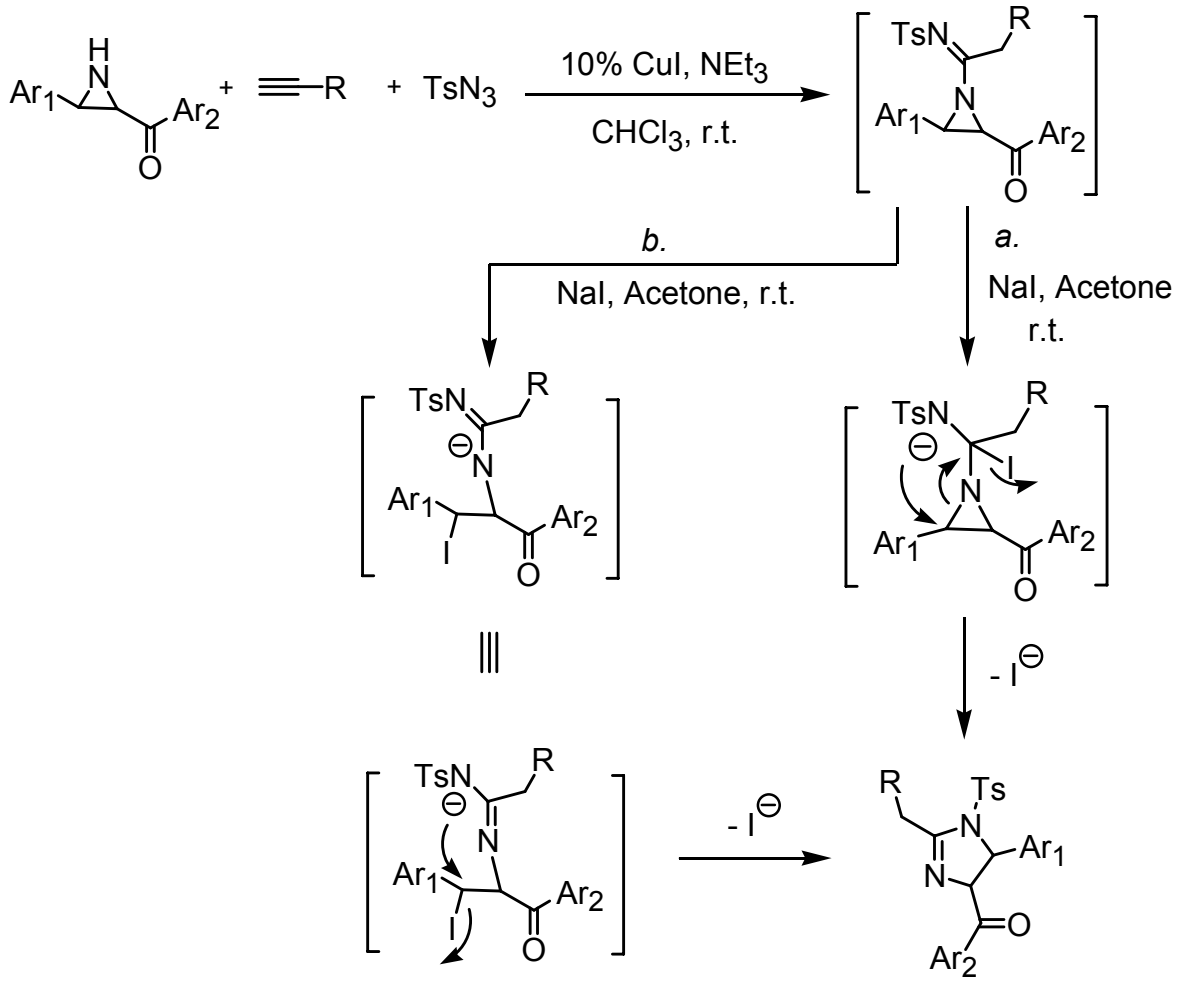
In 2004 Concellon and coworkers reported their synthesis of enantiopure 2,4,5-trisubstituted 2-imidazolines via a Ritter reaction of chiral aziridines and nitriles activated by Lewis acid.[31] The opening of the aziridine ring is regioselective and stereoselective, rendering a variety of alkyl and aryl-substituted 2-imidazolines (Scheme I-17).



Scheme I-17. Synthesis of 2,4,5-trisubstituted 2-imidazolines via a Ritter reaction.

Recently Liang and coworkers documented their efforts to synthesize 4-ketone substituted 2-imidazolines by coupling terminal alkynes, sulfonyl azides and *N*-unsubstituted aziridines (Scheme I-18).[32] They proposed pathway a for the formation of the 2-imidazoline products, which in my opinion is a weak mechanism

candidate as a disfavored 5-endo-tet cyclization is involved. Instead pathway b might be a more reasonable mechanism for this reaction (Scheme I-18). The intermediate aziridines can be isolated, opening the door for some other possible useful synthetic manipulations.



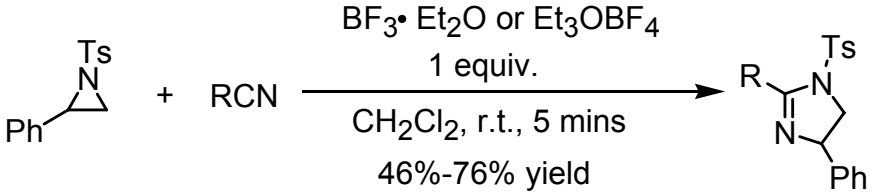
Scheme I-18. One-pot copper-catalyzed synthesis of 4-ketone substituted 2-imidazolines via a three-component coupling.

Preparation of a series of 4-ketone substituted 2-imidazolines with simultaneous conversion of the starting *trans*- to the final *cis*- configuration is the subject of this thesis, which will be covered in more details in Chapter II. To put a brief comparison, the methodology presented in Chapter II involves oxidation of intermediate alcohols

to install the ketone functionality. In contrast to Liang and coworkers' work, the ketone functionality comes directly from the aziridine starting materials. In addtion, in terms of substituent scope, Liang's reaction only allows Ar_2 (Scheme I-18) to be aromatic groups, but the methodology in this thesis is able to introduce alkyl and heteroaromatic groups at this position.

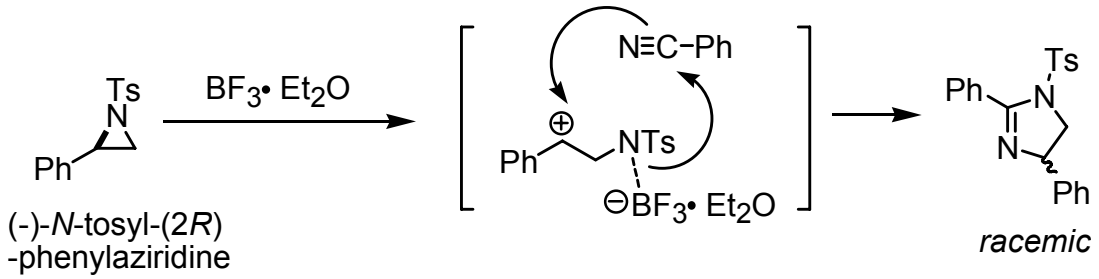
G.3 Synthesis of 2-imidazolines via cycloaddition

In 2004, Singh and coworkers reported a simple and efficient synthesis of 2,4-disubstituted 2-imidazolines via [3+2] cycloaddition reaction of aziridines and nitriles under Lewis acid (Scheme I-19).[33] This reaction proceeds quickly under ambient temperature (less than 5 minutes) and has a broad scope on the choice of nitrile reactant. But one limitation is that a stoichiometric amount of Lewis acid catalyst is required for this reaction to be completed in short time and give good yields.



Scheme I-19. [3+2] cycloaddition reaction of aziridines and nitriles.

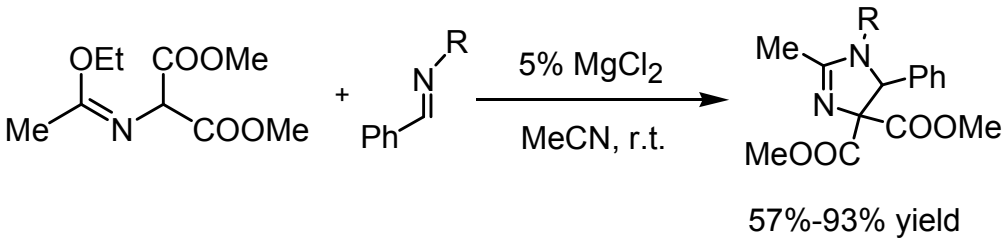
The authors proposed a [3+2] cycloaddition mechanism and tested it by using a chiral starting aziridine. They obtained racemic products, supporting the generation of a benzylic carbocation intermediate as shown in Scheme I-20.



(-)-*N*-tosyl-(2*R*)
-phenylaziridine

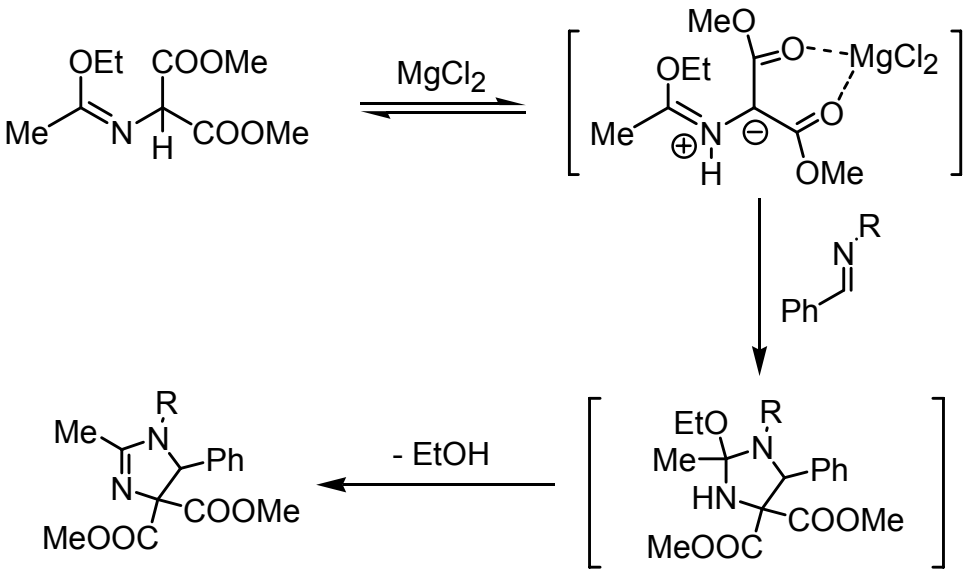
Scheme I-20. Proposed mechanism for the [3+2] cycloaddition process.

In the same year, Johnson and coworkers found that *N*-malonic imidates undergo a $MgCl_2$-catalyzed [3+2] cycloaddition with imines to give 4-diester substituted 2-imidazolines in good to excellent yields (Scheme I-21).[34] This methodology can be also applied to the synthesis of the corresponding oxazolines and pyrrolines when the imine dipolarophiles are replaced with aldehydes and olefins respectively.



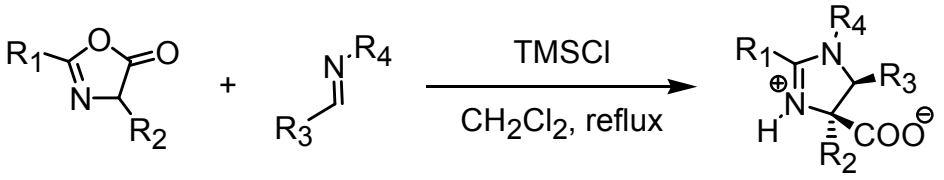
57%-93% yield

Proposed mechanism:



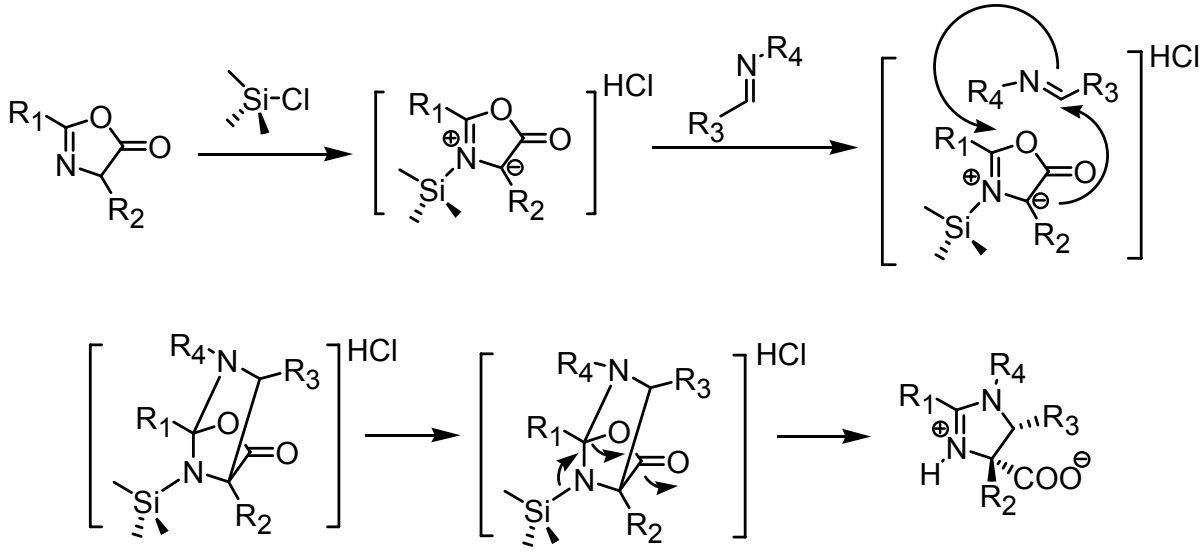
Scheme I-21. $MgCl_2$-catalyzed [3+2] cycloaddition between imidates and imines.

Our group pioneered in developing a Lewis acid-mediated [3+2] cycloaddition reaction between oxazolones[35] and preformed imines to afford the 2-imidazoline scaffolds with four-point diversity.[36,37] Chlorotrimethylsilane (TMSCl) was chosen as the capable Lewis acid catalyst after a series of screening tests (Scheme I-22).



Scheme I-22. One-pot synthesis of 2-imidazolines from oxazolones.

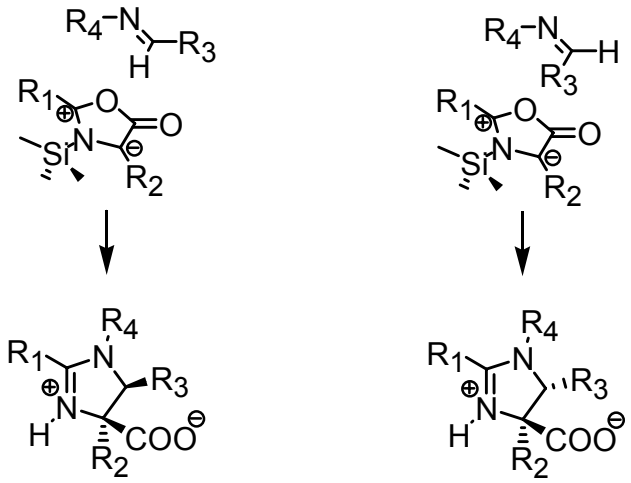
The mechanism is believed to be a [3+2] cycloaddition process. The Lewis acid first coordinates to the nitrogen of oxazolones to increase the equilibrium concentration of the Münchnones intermediates, then the key [3+2] cycloaddition reaction follows to give a bicyclic adduct, which transforms into the final 2-imidazolines retaining a carboxylate group at the 4 position (Scheme I-23).



Scheme I-23. Proposed mechanism of one-pot synthesis of 2-imidazolines.

The diastereoselectivity of this reaction has been found to be substrate-controlled, by changing the electronic nature of substituents R_1 and R_2 in

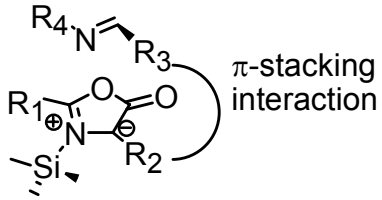
the oxazolone moiety (Scheme I-23), both *syn*- and *anti*- 2-imidazolines can be prepared (with respect to substituents R_2 and R_3, Scheme I-23). When R_1 is an aryl group, exclusively *anti*-2-imidazolines are obtained. It is believed that steric hindrance between the bulky silicon moiety and the R_3 substituent plays a key role in determining this diastereoselectivity, disfavoring the exo approach and rendering the *anti* products (Scheme I-24).[37]



Scheme I-24. Mechanistic rationale for *anti* selectivity of 2-aryl-oxazolones.

In contrast, in order to yield the *cis*-2-imidazolines as the major products, R_1 needs to be alkyl group and simultaneously R_2 has to be aryl group. It is also found that if both R_1 and R_2 are alkyl groups, a mixture of diastereomers are produced. Electronic effect of R_3 substituent seems to have some influence on the diastereoselectivity of this reaction as well. Electron-withdrawing groups favor the formation of *syn* products more than electron-donating groups. Based on these observations, possible π-stacking interaction between aryl R_2 and R_3 substituents is proposed as a reasonable explanation for favoring the exo approach of imines to

oxazolones, which results in the observed reversal of the diastereoselectivity in the products (Scheme I-25).

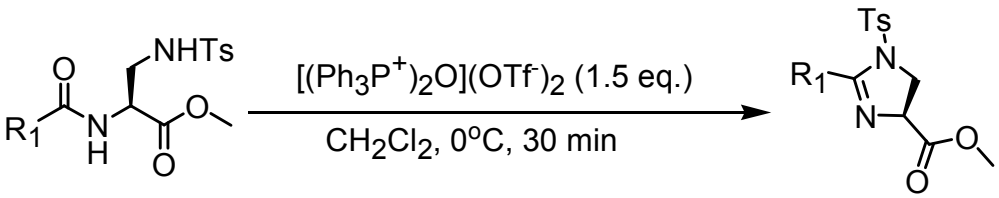


R_1=alkyl, R_2=aryl

Scheme I-25. Mechanistic rationale for *syn* selectivity of 2-alkyl-4-aryl-oxazolones.

G.4 Miscellaneous methods for synthesis of 2-imidazolines

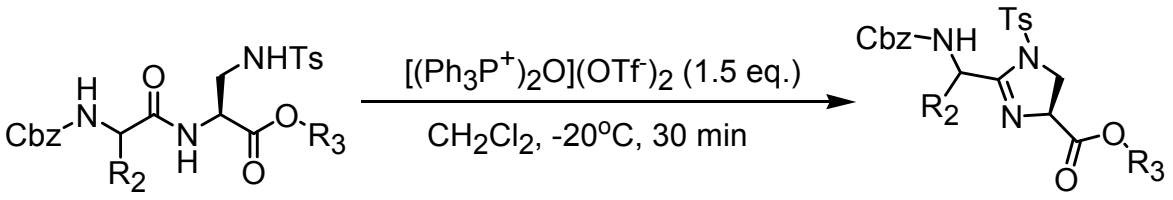
There exist many other successful syntheses of 2-imidazoline-containing molecules that fall beyond the above classification. In 2004, Kelly and coworkers reported a bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate-mediated enantiospecific synthesis of imidazolines and imidazoline-based amino acids from dipeptide precursors (Scheme I-26 and 1-27).[38] Good to excellent yields and enantiomeric excess were achieved in these methodologies. The imidazoline-based amino acids can be oxidized into the corresponding imidazole-containing amino acids, which have been further manipulated to be incorporated into macrolactam-related natural product analogues.



90%-97% yield

86%-99% *ee*

Scheme I-26. Bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate-mediated synthesis of imidazolines**.**



71%-88% yield
>99:1 dr
98%-99.5% *ee*

Scheme I-27. Bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate-mediated synthesis of imidazoline-derived amino acids**.**

REFERENCES

REFERENCES

1. (a) Godoi, B.; Schumacher, R. F. Synthesis of heterocycles via electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev.* **2011**, *111*, 2937-2980. (b) Roughley, S. D.; Jordan, A. M. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **2011**, *54*, 3451-3479.

2. Ferm, R. J.; Riebsomer, J. L. The Chemistry of the 2-imidazolines and imidazolidines. *Chem. Rev.* **1954**, *54*, 593-613.

3. Crouch, D. R. Synthetic routes toward 2-substituted 2-imidazolines. *Tetrahedron*. **2009**, *65*, 2387-2397.

4. Liu, H.; Du, D. M. Recent progress in the synthesis of 2-imidazolines and their applications in homogeneous catalysis. *Adv. Synth. Catal.* **2009**, *351*, 489-519.

5. (a) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Cho, H. Y.; Jung, J. H. Bisindole alkaloids of the Topsentin and Hamacanthin classes from a marine sponge *Spongosorites* sp. *J. Nat. Prod.* **2007**, *70*, 2-8. (b) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.-O.; Sim, C. J.; Im, K. S.; Jung, J. H. Cytotoxic bisindole alkaloids from a marine sponge *Spongosorites* sp. *J. Nat. Prod.* **2005**, *68*, 711-715. (c) Tsujii, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. Topsentin, bromotopsentin, and dihydrodeoxybromotopsentin: antiviral and antitumor bis(indolyl)imidazoles from Caribbean deep-sea sponges of the family Halichondriidae. Structural and synthetic studies. *J. Org. Chem.* **1988**, *53*, 5446-5453. (d) Guinchard, X.; Vallee, Y.; Denis, J.-N. Total syntheses of brominated marine sponge alkaloids. *Org. Lett.* **2007**, *9*, 3761-3764. (e) Murai, K.; Morishita, M.; Nakatani, R.; Kubo, O.; Fujioka, H.; Kita, Y. Concise total synthesis of (-)-Spongotine A. *J. Org. Chem.* **2007**, *72*, 8947-8949.

6. (a) Sato, H.; Tsuda, M.; Watanabe, K.; Kobayashi, J. Rhopaladins A-D, new indole alkaloids from marine tunicate *Rhopalaea* sp. *Tetrahedron*. **1998**, *54*, 8687-8690. (b) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. New bisindole alkaloids of the Topsentin and Hamacanthin classes from the Mediterranean marine sponge *Rhaphisia lacazei*. *J. Nat. Prod.* **2000**, *63*, 447-451. (c) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. Hamacanthins A and B, new antifungal bisindole alkaloids from the deep-water marine sponge, *Hamacantha* sp. *J. Nat. Prod.* **1994**, *57*, 1437-1441.

7. Sato, N.; Ando, M.; Ishikawa, S.; Jitsuoka, M.; Nagai, K.; Takahashi, H.; Sakuraba,

A.; Tsuge, H.; Kitazawa, H.; Iwaasa, H.; Mashiko, S.; Gomori, A.; Moriya, R.; Fujino, N.; Ohe, T.; Ishihara, A.; Kanatani, A.; Fukami, T. Discovery of tetrasubstituted imidazolines as potent and selective Neuropeptide Y Y5 receptor antagonists: reduced human ether-a-go-go related gene potassium channel binding affinity and potent antiobesity effect. *J. Med. Chem.* **2009**, *52*, 3385-3396.

8. Li, H. Y.; DeLucca, I.; Boswell, G. A.; Billheimer, J. T.; Drummond, S.; Gillies, P. J.; Robinson, C. Design, synthesis and structure-activity relationship studies of novel 4,4-bis(trifluoromethyl)imidazolines as Acyl-CoA: cholesterol acyltransferase (ACAT) inhibitors and antihypercholesterolemic agents. *Bioorg. Med. Chem.* **1997**, *5*, 1345-1361.

9. (a) Rauch, M.; Busch, S.; Gust, R. Investigations on the effects of basic side chains on the hormonal profile of (4*R*,5*S*)/(4*S*,5*R*)-4,5-bis(4-hydroxyphenyl) -2-imidazolines. *J. Med. Chem.* **2005**, *48*, 466-474. (b) Schlenk, M.; Ott, I.; Gust, R. Cobalt-alkyne complexes with imidazoline ligands as estrogenic carriers: synthesis and pharmacological investigations. *J. Med. Chem.* **2008**, *51*, 7318-7322. (c) Gust, R.; Keilitz, R.; Schmidt, K. Investigations of new lead structures for the design of selective estrogen receptor modulators. *J. Med. Chem.* **2001**, *44*, 1963-1970.

10. Gentili, F.; Bousquet, P.; Brasili, L.; Caretto, M.; Carrieri, A.; Dontenwill, M.; Giannella, M.; Marucci, G.; Perfumi, M.; Piergentili, A.; Quaglia, W.; Rascente, C.; Pigini, M. α_2-Adrenoreceptors profile modulation and high antinociceptive activity of (*S*)-(-)-2- [1-(biphenyl-2-yloxy)ethyl]-4,5-dihydro-1*H*-imidazole. *J. Med. Chem.* **2002**, *45*, 32-40.

11. (a) Li, J. X.; Zhang, Y. N. Imidazoline I_2 receptors: Target for new analgesics? *European Journal of Pharmacology.* **2011**, *658*, 49-56. (b) Nikolic, K.; Agbaba, D. Imidazoline antihypertensive drugs: selective I_1-imidazoline receptors activation. *Cardiovascular Therapeutics* **2011**, 1-8.

12. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. C_2-symmetric chiral bis(oxazoline)-metal complexes in catalytic asymmetric synthesis. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.

13. Du, X.; Liu, H.; Du, D. M. Synthesis and application of diphenyl sulfide linked bis(imidazoline) ligands: dramatic electronic effect of ligands on catalytic behavior. *Eur. J. Org. Chem.* **2011**, *4*, 786-793.

14. (a) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Mueller-Bunz, H.; Wilkes, P. Preparation of enantiopure biimidazoline ligands and their use in asymmetric catalysis. *Org. Biomol. Chem.* **2004**, *2*, 1995-2002. (b) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. A novel general route for

the preparation of enantiopure imidazolines. *J. Org. Chem.* **2002**, *67*, 3919-3922.

15. (a) Arai, T.; Yokoyama, N.; Yanagisawa, A. A library of chiral imidazoline-aminophenol ligands: discovery of an efficient reaction sphere. *Chem.-Eur. J.* **2008**, *14*, 2052-2059. (b) Arai, T.; Awata, A.; Wasai, M.; Yokoyama, N.; Masu, H. Catalytic asymmetric Friedel-Crafts/protonation of nitroalkenes and *N*-heteroaromatics. *J. Org. Chem.* **2011**, *76*, 5450-5456.

16. (a) Yang, M. J.; Liu, Y. J.; Gong, J. F.; Song, M. P. Unsymmetrical chiral PCN pincer Palladium(II) and Nickel(II) complexes with aryl-based aminophosphine-imidazoline ligands: synthesis via aryl C-H activation and asymmetric addition of diarylphosphines to enones. *Organometallics* **2011**, *30*, 3793-3803. (b) Wu, L. Y.; Hao, X. Q.; Xu, Y. X.; Jia, M. Q.; Wang, Y. N. ; Gong, J. F.; Song, M. P. Chiral NCN pincer Pt(II) and Pd(II) complexes with 1,3-bis(2′-imidazolinyl)benzene: synthesis via direct metalation, characterization, and catalytic activity in the Friedel-Crafts alkylation reaction. *Organometallics* **2009**, *28*, 3369-3380.

17. Busacca, C. A.; Bartholomeyzik, T.; Cheekoori, S.; Grinberg, N.; Lee, H.; Ma, S.; Saha, A.; Shen, S.; Senanayake, C. H. On the Racemization of chiral imidazolines. *J. Org. Chem.* **2008**, *73*, 9756-9761.

18. Ma, S.; Busacca, C. A.; Fandrick, K. R.; Bartholomeyzik, T.; Haddad, N.; Shen, S.; Lee, H.; Saha, A.; Yee, N.; Senanayake, C.; Grinberg, N. Directly probing the racemization of imidazolines by vibrational circular dichroism: kinetics and mechanism. *Org. Lett.* **2010**, *12,* 2782-2785.

19. Hegedus, L. S.; Betschart, C. Synthesis of azapenams, diazepinones, and dioxocyclams via the photolytic reaction of chromium alkoxycarbene complexes with imidazolines. *J. Am. Chem. Soc.* **1992**, *114*, 5010-5017.

20. (a) Hsiao, Y.; Hegedus, L. S. Synthesis of optically active imidazolines, azapenams, dioxocyclams, and bis-dioxocyclams. *J. Org. Chem.* **1997**, *62*, 3586-3591. (b) Dumas, S.; Lastra, E.; Hegedus, L. S. Synthesis and metal complexation reactions of bis-dioxocyclams from photochemical reaction of bis-chromium alkoxycarbene complexes with imidazolines. *J. Am. Chem. Soc.* **1995**, *117*, 3368-3379.

21. (a) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R. C. F. Imidazolines as amide bond replacements. *Tetrahedron* **1995**, *51*, 6315-6336. (b) Jones, C. F.; Ward, G. J. Amide bond isosteres: imidazolines in pseudopeptide chemistry. *Tetrahedron Lett.***1988**, *29*, 3853-3856. (c) Gilbert, I. H.; Rees, D. C.; Richardson, R. S. Amide bond replacements: incorporation of a 2,5,5-trisubstituted imidazoline into dipeptides and into a CCK-4 derivative. *Tetrahedron Lett.***1991**, *32*, 2277-2280.

(d) Jones, R. C. F.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. Synthesis of a homochiral α,α-disubstituted α,β-diamino-acid. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1661-1664.

22. Li, Y.; Feng, Y.; Chen, T.; Zhang, H. X. Imidazoline type stationary phase for hydrophilic interaction chromatography and reversed-phase liquid chromatography. *Journal of Chromatography A* **2011**, in press.

23. (a) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. 1,3-dicarbonyl compounds in stereoselective domino and multicomponent reactions. *Tetrahedron*: *Asymmetry* **2010**, *21*, 1085-1109. (b) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. Multiple multicomponent macrocyclizations (MiBs): a strategic development toward macrocycle diversity. *Chem. Rev.* **2009**, *109*, 796-814.

24. Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. Novel multicomponent reaction for the combinatorial synthesis of 2-imidazolines. *Org. Lett.* **2003**, *5*, 3759-3762.

25. Bon, R. S.; Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. Multicomponent synthesis of 2-imidazolines. *J. Org. Chem.* **2005**, *70,* 3542-3553.

26. Zhou, L.; Zhou, J.; Tan, C. K.; Chen, J.; Yeung, Y. Y. *N*-Bromosuccinimide initiated one-pot synthesis of imidazoline. *Org. Lett.* **2011**, *13*, 2448-2451.

27. Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. The use of carbon monoxide and imines as peptide derivative synthons: a facile palladium-catalyzed synthesis of α-amino acid derived imidazolines. *Angew. Chem. Int. Ed.* **2001**, *40*, 3228-3230.

28. Worrall, K.; Xu, B.; Bontemps, S.; Arndtsen, B. A. A palladium-catalyzed multicomponent synthesis of imidazolinium salts and imidazolines from imines, acid chlorides, and carbon monoxide. *J. Org. Chem.* **2011**, *76,* 170-180.

29. Heine, H. W.; Bender, H. S. The isomerization of some aziridine derivatives. III. A new synthesis of 2-imidazolines. *J. Org. Chem.* **1960**, *25*, 461-463.

30. Kuszpit, M. R.; Wulff, W. D.; Tepe, J. J. One-pot synthesis of 2-imidazolines via the ring expansion of imidoyl chlorides with aziridines. *J. Org. Chem.* **2011**, *76*, 2913-2919.

31. Concellon, J. M.; Riego, E.; Suarez, J. R.; Garcia-Granda, S.; Dıaz, M. R. Synthesis of enantiopure imidazolines through a Ritter reaction of 2-(1-aminoalkyl)aziridines with nitriles. *Org. Lett.* **2004**, *6*, 4499-4501.

32. Han, Y.; Xie, Y. X.; Zhao, L. B.; Fan, M. J.; Liang, Y. M. Synthesis of highly substituted 2-imidazolines through a three-component coupling reaction. *Synthesis* **2008**, *1*, 87-93.

33. Prasad, B. A. B.; Pandey, G.; Singh, V. K. Synthesis of substituted imidazolines via [3+2]-cycloaddition of aziridines with nitriles. *Tetrahedron Lett* **2004**, *45*, 1137-1141.

34. (a) Bowman, R. K.; Johnson, J. S. Lewis acid catalyzed dipolar cycloaddtions of activated imidate. *J. Org. Chem.* **2004**, *69*, 8537-8540. (b) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. Lewis acid-promoted carbon−carbon bond cleavage of aziridines: divergent cycloaddition pathways of the derived ylides. *J. Am. Chem. Soc.* **2004**, *126*, 2294-2295.

35. Fisk, J. S.; Mosey, R. A.; Tepe, J. J. The diverse chemistry of oxazol-5-(4H)-ones. *Chem. Soc. Rev.* **2007**, *36*, 1432-1440.

36. (a) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. Highly diastereoselective multicomponent synthesis of unsymmetrical imidazolines. *Org. Lett.* **2002**, *4*, 3533-3535. (b) Peddibhotla, S.; Tepe, J. J. Multicomponent synthesis of highly substituted imidazolines via a silicon mediated 1,3-dipolar cycloaddition. *Synthesis* **2003**, *9*, 1433-1440.

37. Sharma, Vasudha; Tepe, Jetze J. Diastereochemical diversity of imidazoline scaffolds via substrate controlled TMSCl-mediated cycloaddition of azlactones. *Org. Lett.* **2005,** *7*, 5091-5094.

38. (a) You, S. L.; Kelly, J. W. Highly efficient enantiospecific synthesis of imidazoline-containing amino acids using bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. *Org. Lett.* **2004**, *6*, 1681-1683. (b) You, S. L.; Kelly, J. W. Total Synthesis of Dendroamide A: oxazole and thiazole constructionusing an oxodiphosphonium salt. *J. Org. Chem.* **2003**, *68*, 9506-9509.

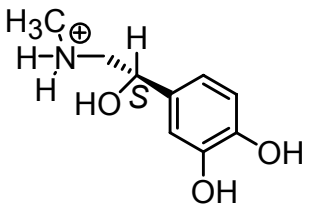
CHAPTER II

AZOMETHINE YLIDE MEDIATED INVERSION OF CONFIGURATION OF QUATERNARY CARBON: CONVERTING *TRANS* TO *CIS* IMIDAZOLINES

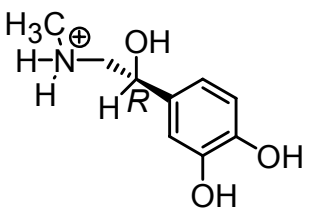
A. Introduction

The stereochemistry of small molecules is often key to their biological functions. The two enantiomers of one drug molecule can show different chemical and pharmacological properties in the chiral environments of living systems due to their differences in three dimensional space.

Epinephrine (also known as adrenaline), a hormone secreted by the adrenal glands in times of stress, is used for the treatment of some heart diseases, asthma or allergic reactions.[1] The two enantiomers of epinephrine are quite different in their biological activity. (-)-Epinephrine is much more active than the corresponding (+)-epinephrine, as the interaction of the benzylic hydroxyl group with the α–adrenoreceptor plays a key role in potency difference of the two stereoisomers (Figure II-1).



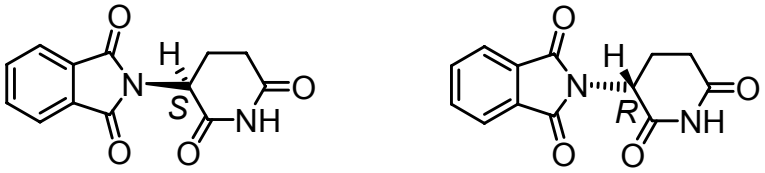
(-)-Epinephrine



(+)-Epinephrine

Figure II-1. Chemical structures of (+) and (-)-Epinephrine.

Another representative case is associated with the notorious compound thalidomide (Figure II-2). Thalidomide, which was developed in West Germany in the 1950s, was prescribed for relieving nausea for pregnant women. Unfortunately it later became one of nightmares in the pharmaceutical history as severely teratogenic side effects or even death were observed in thousands of babies in more than forty countries, whose mothers took thalidomide in their stage of pregnancy.[2] Thalidomide was given as a racemate to pregnant women but it turned out that only the *S* enantiomer has the sedative effect for the morning sickness. In sharp contrast, the *R* enantiomer caused severe birth defect. Again the delicate stereochemistry difference of this small molecule on just one carbon atom renders them quite opposite in their biological consequences.



Sedative *Teratogenic*

Figure II-2. Enantiomers of thalidomide.

Cis- and *trans*- stereoisomers of the same scaffolds can also behave significantly differently in some cases. Interestingly enough, sometimes they can show opposite but complementary biological responses towards the same disease. A case in point is the 4,5-diaryl-2-imidazolines, which are the focus of this dissertation. Nutlins, which are representatives of *cis*-4,5-diaryl-2-imidazolines (Figure II-3), disrupt the binding of

the E3-ligase MDM2 to the pro-apoptotic transcription factor p53, resulting in activating apoptotic pathways in cancer cells.[3]

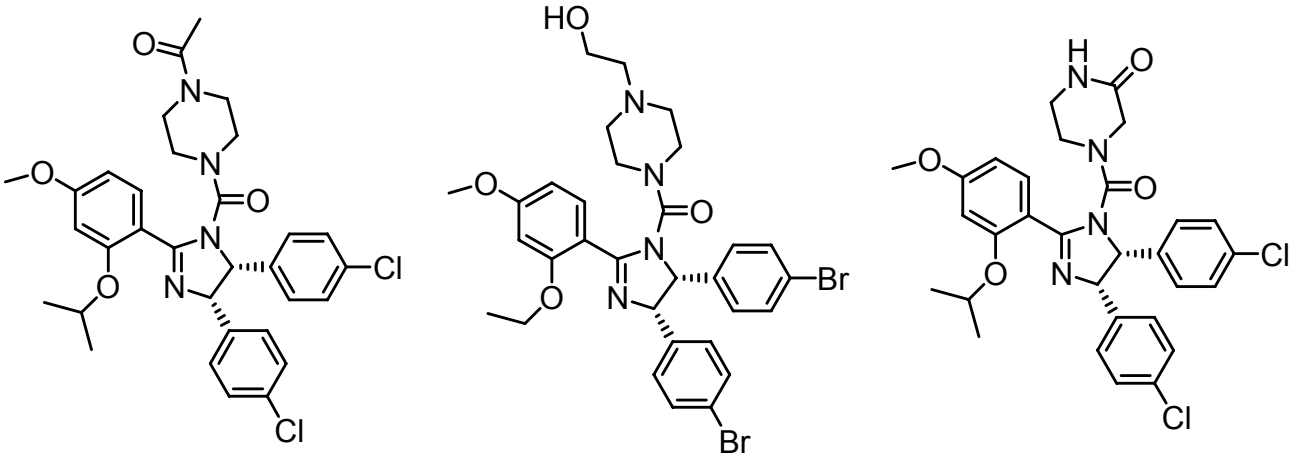
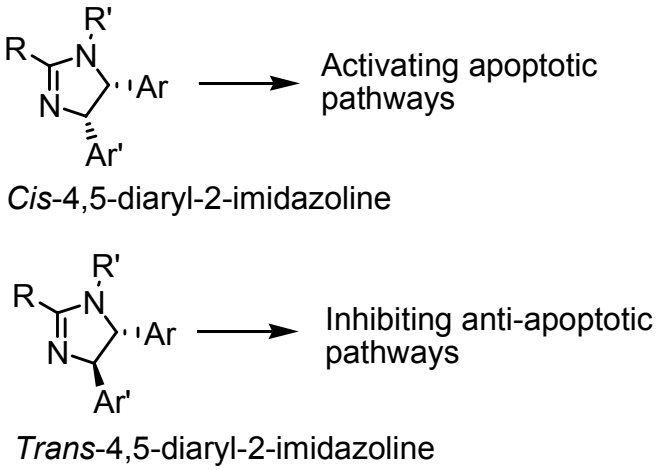


Figure II-3. Three representative Nutlins.

Amazingly enough, the corresponding *trans*-4,5-diaryl-2-imidazolines, which have been developed in our laboratory, have been found to inhibit the anti-apoptotic transcription factor NF-κB, thus inhibiting anti-apoptotic pathways (Scheme II-1).[4,5]



Scheme II-1. Biological responses to *cis*- and *trans*-4,5-diaryl-2-imidazolines.

B. Inhibition of NF-κB-mediated gene transcription

Nuclear factor kappa B (NF-κB) proteins are mammalian transcription factors and are responsible for regulating many genes in the body that are controlling a variety of cellular processes, such as expression of many inflammatory cytokines, chemokines, immune receptors and cell surface adhesion molecules (E-selectin, ICAM-1 and VCAM-1 for instance).[6] In mammalian cells, five proteins of NF-κB family have been identified: RelA (p65), c-Rel, RelB, NF-κB1 (p50 and its precursor p105) and NF-κB2 (p52 and its precursor p100).[7] These proteins can form a number of homodimers and heterodimers and the general term NF-κB traditionally refers to the heterodimer p50/p65. The specificity and selectivity of some DNA control elements are controlled by the NF-κB family.

NF-κB exists in inactivated form in cytoplasm associated with its inhibitory protein I-κB. Numerous stimuli, including physical stress, oxidative stress, a large range of bacteria or viruses and even exposure to certain chemicals, can activate NF-κB and the general activation pathway has been summarized in Figure II-4. The cellular stimuli first lead to activation of IκB kinase (IKK), which phosphorylates two serines (S32 and S36) on IκB proteins. Then the phosphorylated IκB is followed by ubiquitinylation process and degraded by the 26S proteasome. Degradation of IκB releases the active NF-κB, which translocates into the nucleus and initiates the gene transcription process by its binding with specific DNA control elements.[8]

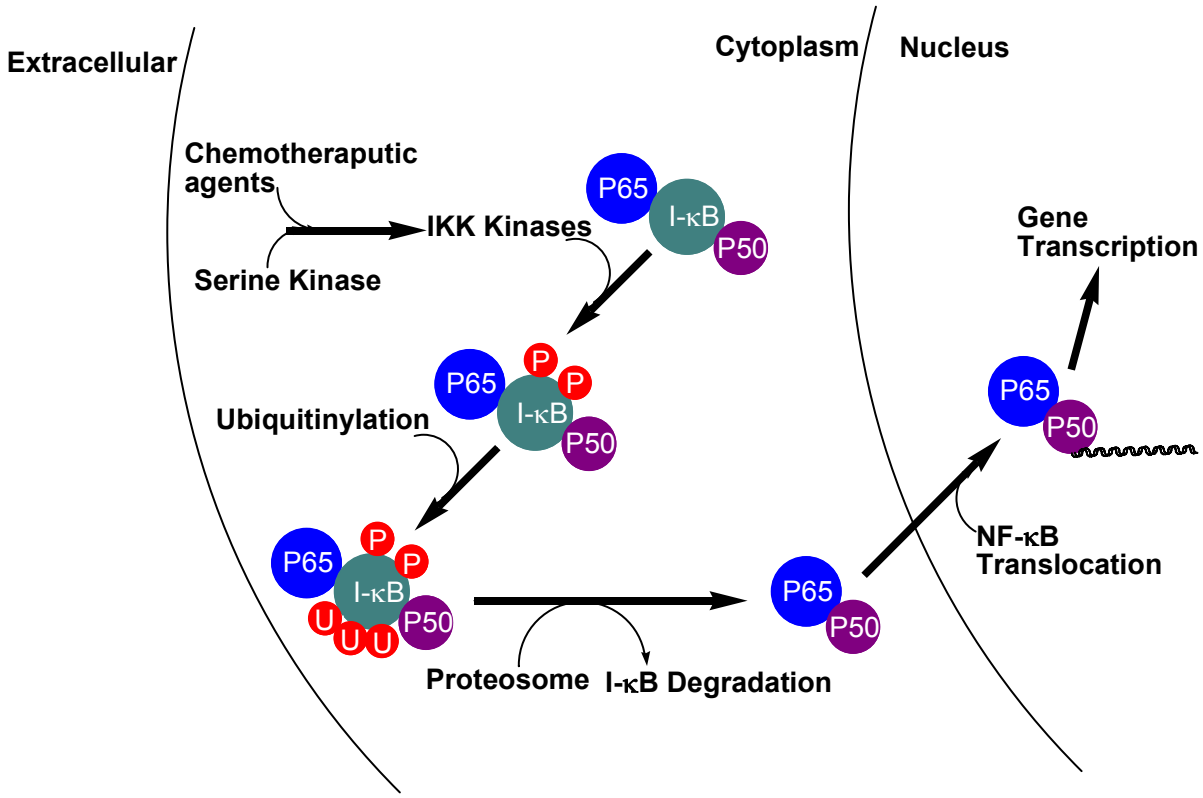


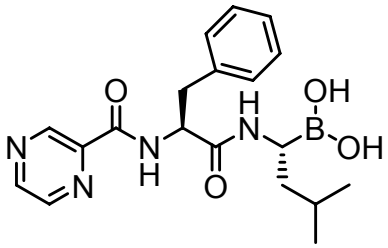
Figure II-4. NF-κB activation pathway by external stimuli.

(For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this thesis.)

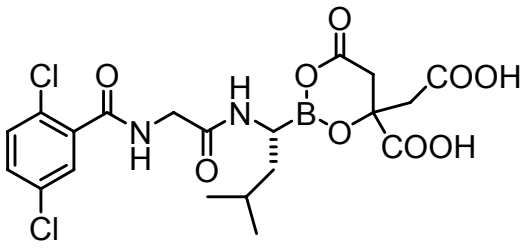
As NF-κB plays a crucial role in the regulation of many genes that are closely related to the physiological processes in the body, it has become an increasingly important target to develop the relevant therapeutics to tackle many disease states of human beings, such as cancer, asthma, arthritis and so on. From the general NF-κB activation pathway shown above, if IκB is not degraded, the whole pathway will be shut down. One common approach to inhibit the activation of NF-κB is to inhibit the function of the essential 26S proteasome. A number of small molecule 26S proteasome inhibitors have been developed.

Bortezomib (PS-341 or Velcade), developed in this context by Millenium

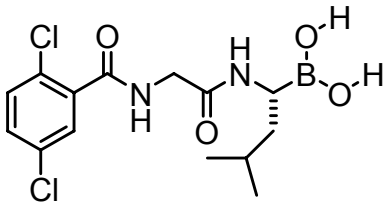
Pharmaceuticals (Cambridge, MA) is one representative 26S proteasome inhibitor. Bortezomib (Figure I-9), as a dipeptidyl boronic acid, has high specificity for the 26S proteasome and has been approved by the United States Food and Drug Administration (FDA) to be clinically used for the treatment of multiple myeloma.[9,10] Recently MLN9708 (Figure II-5) is being evaluated by the same pharmaceutical company to be a second-generation 26S proteasome inhibitor. When exposed to aqueous solutions or plasma, MLN9708 hydrolyzes to MLN2238 immediately, which is the real active form and investigated to be potent, selective and reversible proteasome inhibitor.[11] Several other known 26S proteasome inhibitors have been shown in Figure II-5 as well, including MG-132 and two natural products (+) Lactacystin and Salinosporamide A.[12,13]



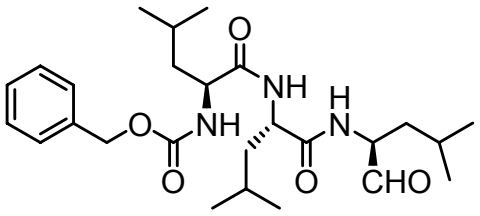
Bortezomib



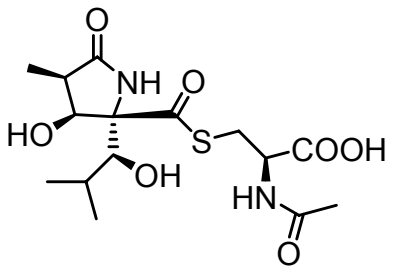
MLN9708



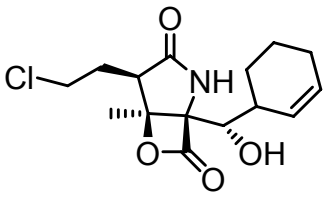
MLN2238



MG-132



(+) Lactacystin

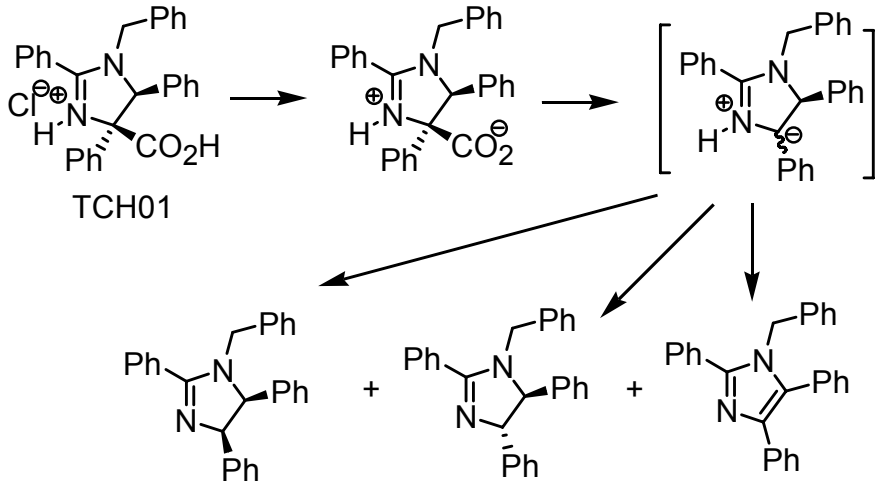


Salinosporamide A

Figure II-5. Examples of small molecule 26S proteasome inhibitors.

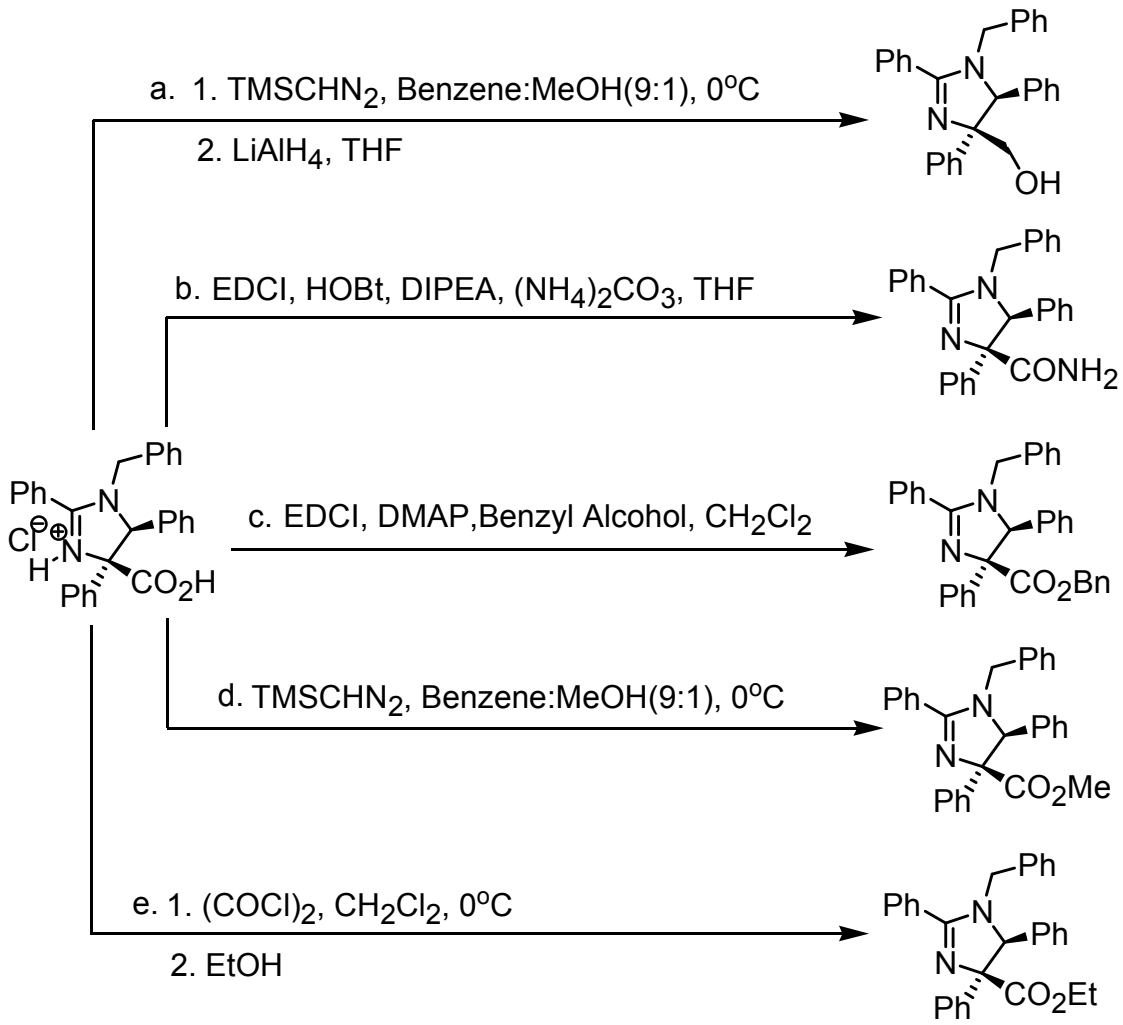
C. Highly-functionalized 2-imidazolines as potent inhibitors of NF-κB-mediated gene transcription

In 2004, our group reported the preparation of a new class of 2-imidazoline-based NF-κB inhibitors, which dramatically enhance the anticancer efficacy of the chemotherapeutic agent Camptothecin (CPT).[14] Among these synthesized 2-imidazolines, TCH01 is the most active in cell culture. But it is not very stable and transforms into the corresponding zwitterion, which can decarboxylate to give *cis* or *trans* dihydroimidazolines and imidazole via an azomethine ylide intermediate (Scheme II-2). The instability of TCH01 might account for the inconsistent activity when it is tested in cell culture and human whole blood. In order to address this instability and pursue the further clinical potential of these 2-imidazolines, appropriate chemical transformations are necessary.



Scheme II-2. Decarboxylation of the parent 2-imidazoline.

The carboxylic acid group in the imidazoline molecule provides a good platform for more diverse synthetic manipulations. A series of 2-imidazoline derivatives have been synthesized and evaluated biologically in our laboratory (Scheme II-3).[15] The parent 2-imidazoline hydrochloride salt, reacted with $TMSCHN_2$ in benzene and methanol (9:1) as a mixture of solvents to give the corresponding methyl ester derivative (d, Scheme II-3). Reduction of the methyl ester with $LiAlH_4$ afforded a primary alcohol (a, Scheme II-3). Two more ester derivatives, benzyl and ethyl ester-substituted 2-imidazolines were prepared with conditions shown in c and e of Scheme II-3. Finally an amide functional group was installed (b, Scheme II-3). After the biological testing, the ethyl-ester substituted 2-imidazoline was found to be stable against hydrolysis and potent in inhibiting NF-κB-mediated gene transcription. Furthermore, the two enantiomers of the ethyl-ester substituted 2-imidazoline were separated via chiral HPLC and were further evaluated for their individual activity. The results showed that the (*R*, *R*) enantiomer is slightly more potent than the (*S*, *S*) counterpart at inhibiting NF-κB-mediated gene transcription.



Scheme II-3. Derivatization of the parent 2-imidazoline.

In order to obtain a more detailed understanding of structure-activity relationship of these highly substituted 2-imidazolines, a series of relevant 2-imidazoline derivatives have been prepared using the 1,3-dipolar cycloaddition protocol between oxazolones and imines pioneered in our laboratory as described previously. The three R substituents (R_1 to R_3) and the carboxyl acid moiety constitute a 2-imidazoline scaffold with four-point variability (Figure II-6). The optimization of this scaffold was the focus of other members of the Tepe research lab.[16]

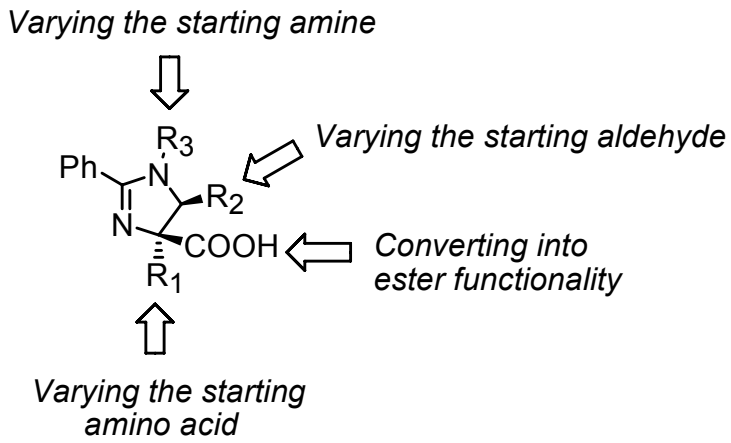
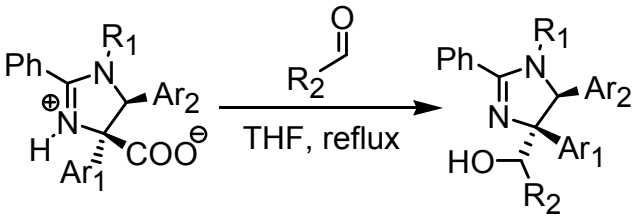


Figure II-6. Diversity-oriented synthesis of *trans*-2-imidazolines.

D. Overview of Chapter II

As both *cis*- and *trans*-2-imidazolines enjoy significance biologically and synthetically, an efficient synthetic methodology to realize the transformation between the two stereoisomers would facilitate synthesis of these useful scaffolds, rendering them much more available for biological screening. This chapter describes the development of a mild and easy-to-operation synthetic methodology, which focuses on the formation of highly substituted *cis*-4,5-diaryl-2-imidazolines through converting the corresponding *trans*-4,5-diaryl-2-imidazolines (Scheme II-4).

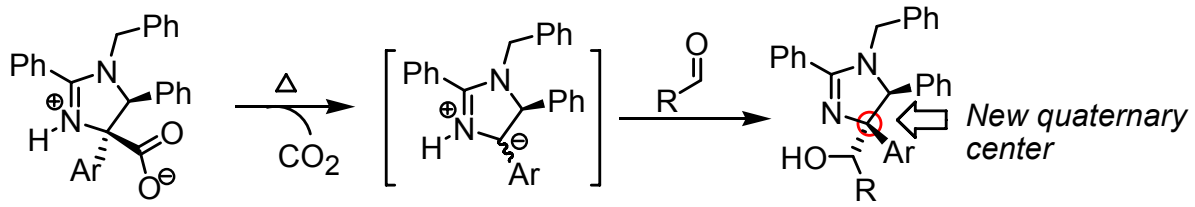


Scheme II-4. Conversion of *trans*- to *cis*-4,5-diaryl-2-imidazolines.

E. Proposed hypothesis

The starting *trans*-4,5-diaryl-2-imidazoline contains a reactive carboxylic acid, which

can be lost under thermal heating. We hypothesized that the mild thermal decarboxylation of the *trans*-4,5-diaryl-2-imidazoline zwitterion generates a reactive azomethine ylide intermediate, which can be trapped with aldehydes to yield the *cis*-4,5-diaryl-2-imidazoline (Scheme II-3).



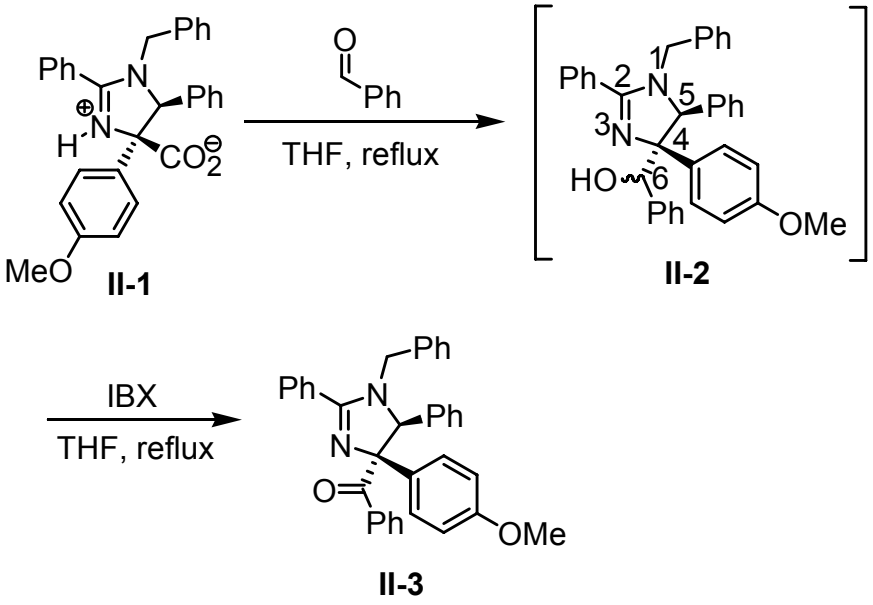
***Trans*-4,5-diaryl-2-imidazoline** **Azomethine Ylide** ***Cis*-4,5-diaryl-2-imidazoline**

Scheme II-5. Synthesis of the *cis*-4,5-diaryl-2-imidazoline.

F. Results and discussion

F.1 Initial attempt of the proposed hypothesis

To test this hypothesis, *trans*-4,5-diaryl-2-imidazoline **II-1** was refluxed in THF in the presence of benzaldehyde for two hours. In order to avoid producing a mixture of diastereomers at carbon 6, the resulting intermediate alcohol **II-2** was oxidized with IBX[17,18] during work-up to afford the much more stable new 4-ketone-disubstituted 2-imidazoline derivative **II-3** in a 77% overall yield as a single diastereomer (Scheme II-4).



Scheme II-6. Conversion of *cis*-4,5-diaryl-2-imidazolines **II-1** to its *trans* counterpart.

The relative stereochemistry of the *para*-methoxy phenyl and the phenyl at the 4 and 5 position of the product **II-3** has been unambiguously determined to be *cis* on the basis of X-ray crystallography (Figure II-7).

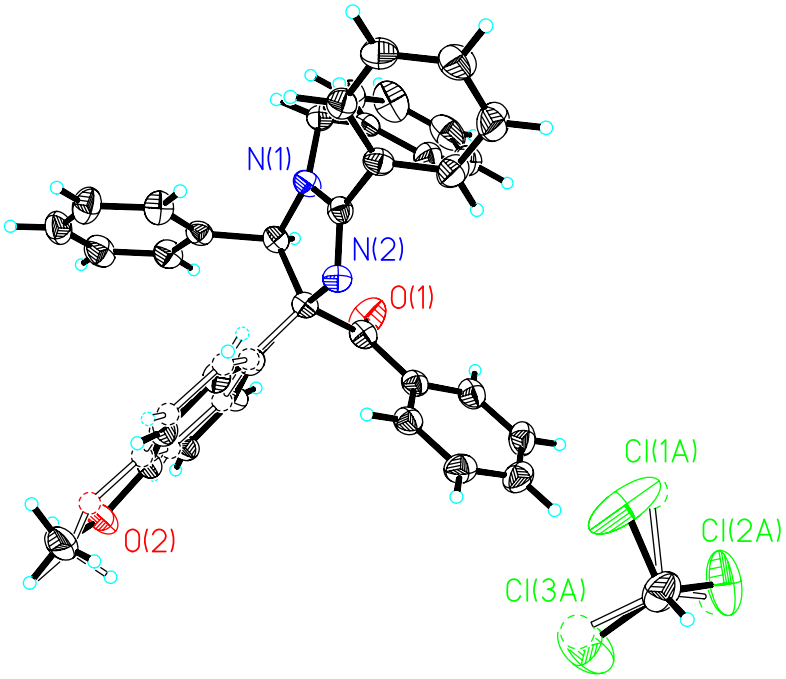


Figure II-7. X-ray crystal structure of **II-3**.

To rationalize the stereochemical outcome obtained, it is envisioned that benzaldehyde prefers to approach the azomethine ylide intermediate from the opposite direction of the 5-position phenyl group in order to minimize the steric interaction with it, which leads to the observed stereochemistry (Figure II-8).

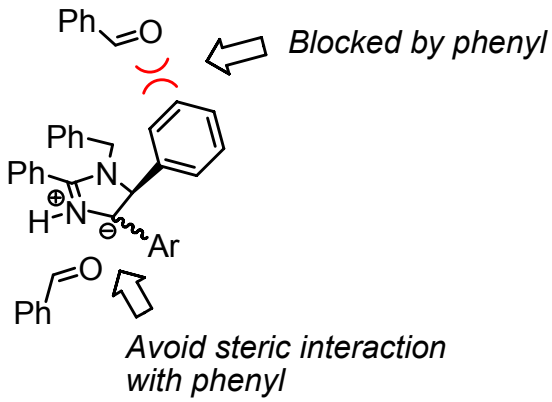
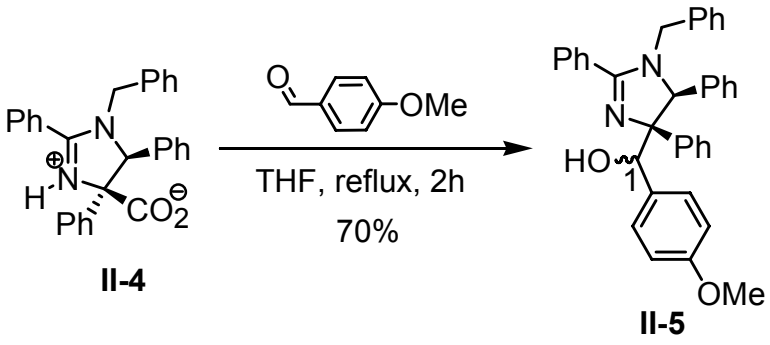


Figure II-8. Model that explains the stereochemical outcome.

F.2 Isolation of the intermediate alcohol

The following reaction has been conducted and the two resulting alcohol diastereomers (varies at carbon 1, Scheme II-7) have been isolated in a 1:1 ratio.



II-4 **II-5**

Scheme II-7. Preparation of intermediate alcohol **II-5**.

A series of 2D NMR experiments (gHMQC and gHMBC) were carried out to assign the characteristic hydrogen and carbon signals of one of the two

diastereomers (Diastereomer II). The results have been summarized in Figure II-9, Table II-1 and Table II-2 respectively. Moreover, gNOESY experiments were also conducted to give insight into the spatial configuration of the two product molecules.

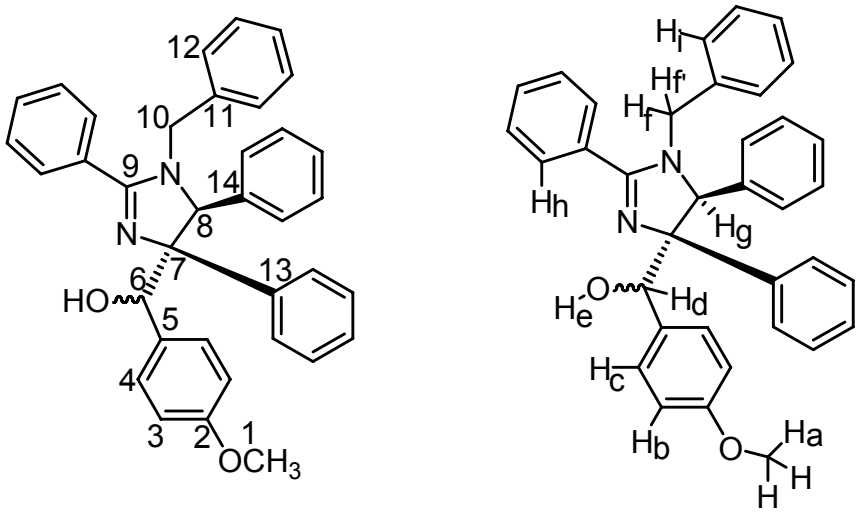


Figure II-9. Numbering systems for **II-5** used in Table II-1 and Table II-2**.**

Carbon #	Chemical Shift δ (ppm)	gHMQC Correlations (to hydrogen)	gHMBC Correlations (to hydrogen)
1	55.21	a	None
2	159.19	None (quaternary)	a,b,c
4	130.49	None (quaternary)	d
6	79.62	d	c,g
7	81.07	None (quaternary)	d,g
8	69.43	g	d,f,f’
9	166.42	None (quaternary)	f,f’,g,h
10	48.50	f,f’	i
11	134.54	None (quaternary)	f,f’
12	127.43	i	f,f’
13	139.29	None (quaternary)	d,g
14	136.13	None (quaternary)	g

Table II-1. Summarized results of ^{13}C, HMQC and HMBC spectra of Diastereomer II.

Proton #	Chemical Shift δ (ppm)	Multiplicity & Coupling Constant J (Hz)	Hydrogen Integration
a	3.82	s	3
b	6.76-6.80	m	4
c	7.18-7.27	m	6
d	5.06	s	1
f	4.45	d, J = 15.5	1
f'	3.57	d, J = 16	1
g	5.09	s	1
h	7.71-7.73	m	2
i	6.76-6.80	m	4

Table II-2. Summarized results of ^{1}H spectra of Diastereomer II.

All the results of these 2D NMR experiments (gHMQC and gHMBC) are consistent with the expected structure of alcohol intermediate **II-5**. Based on the successful assignment of characteristic hydrogens and carbons of diastereomer II, it is easier to interpret the gNOESY data obtained on this molecule. As seen from Figure II-10, it is expected that hydrogen d and g could "see" each other in gNOESY. However, this characteristic signal was not detected in gNOESY spectra of diastereomer II (Figure II-11, right).

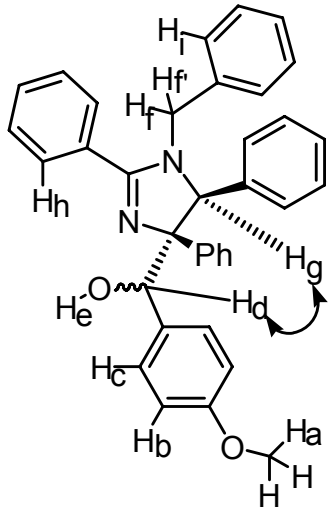


Figure II-10. Expected characteristic gNOESY signal of Diastereomer II of **II-5**.

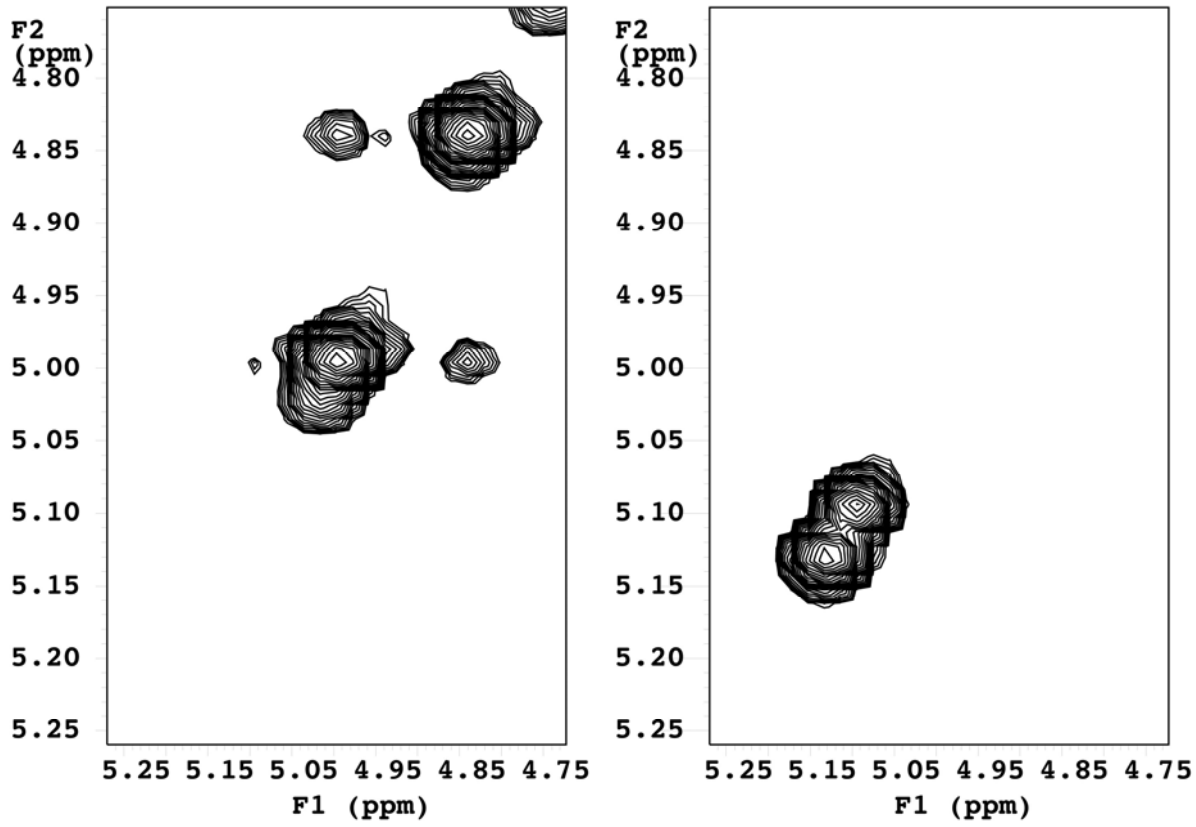


Figure II-11. gNOESY of alcohol intermediate **II-5**.

But fortunately enough, the same gNOESY experiment conducted on the other diastereomer (Diastereomer I) shows clear coupling between the two characteristic hydrogen (*δ*4.81 and 4.97 respectively, Figure II-11, left). Moreover, X-ray crystal

structure of Diastereomer II was obtained to further prove the relative stereochemistry (Figure II-12).

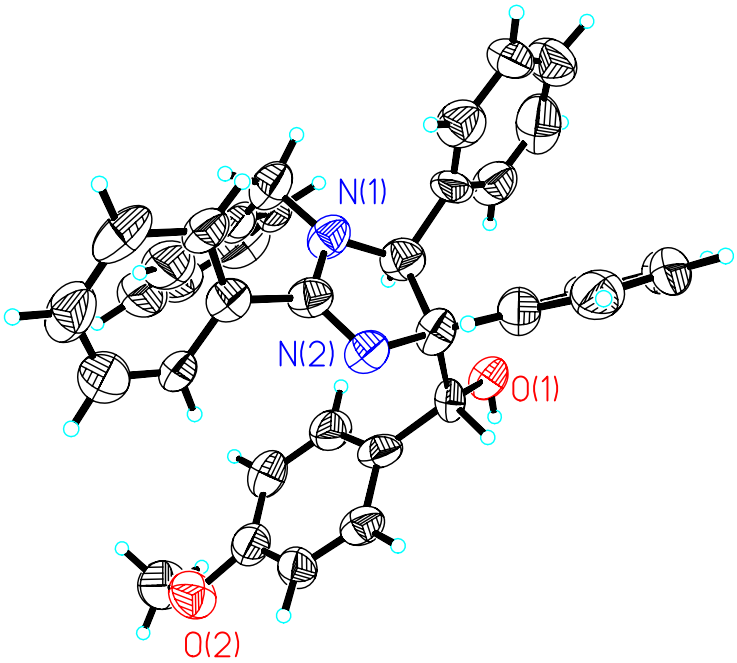
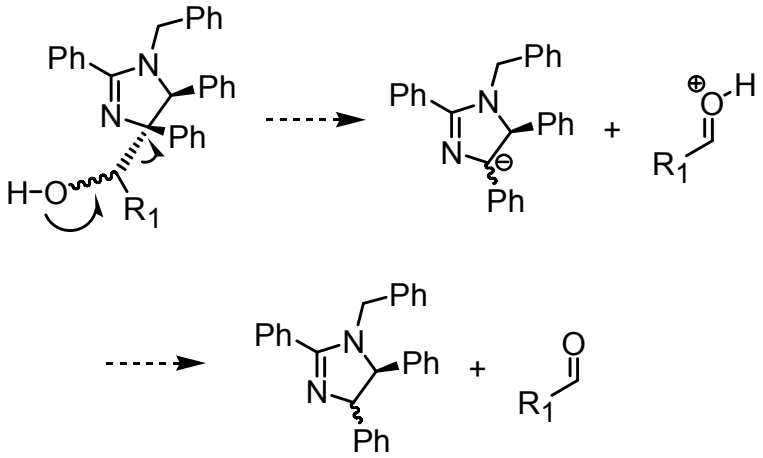


Figure II-12. X-ray crystal structure of Diastereomer II of **II-5**.

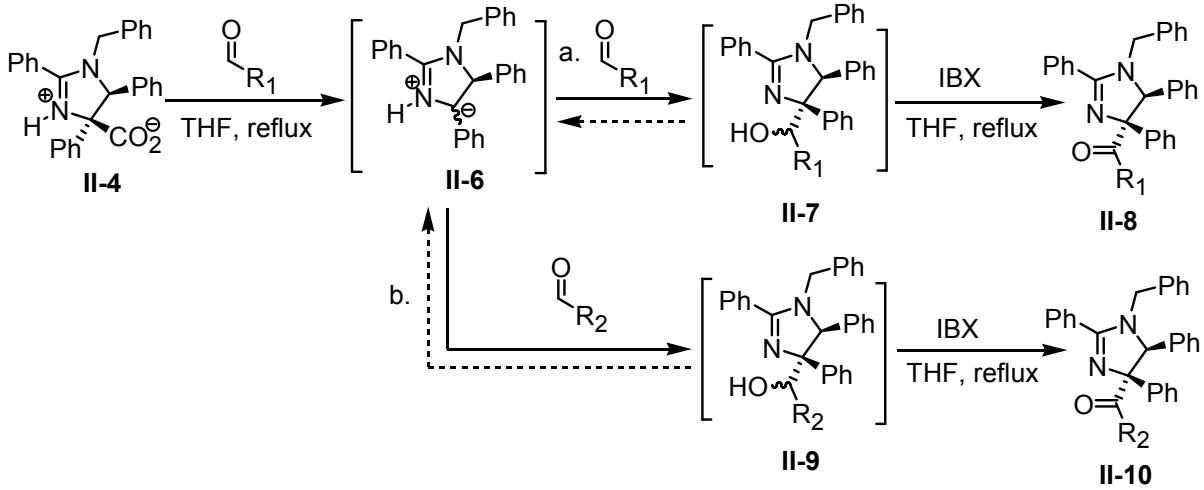
F.3 Control experiments to test the reversibility of the nucleophilic step

In the initial design of this conversion, another factor to consider oxidizing the intermediate alcohol is to prevent a possible retroaldol-type reaction (Scheme II-8).



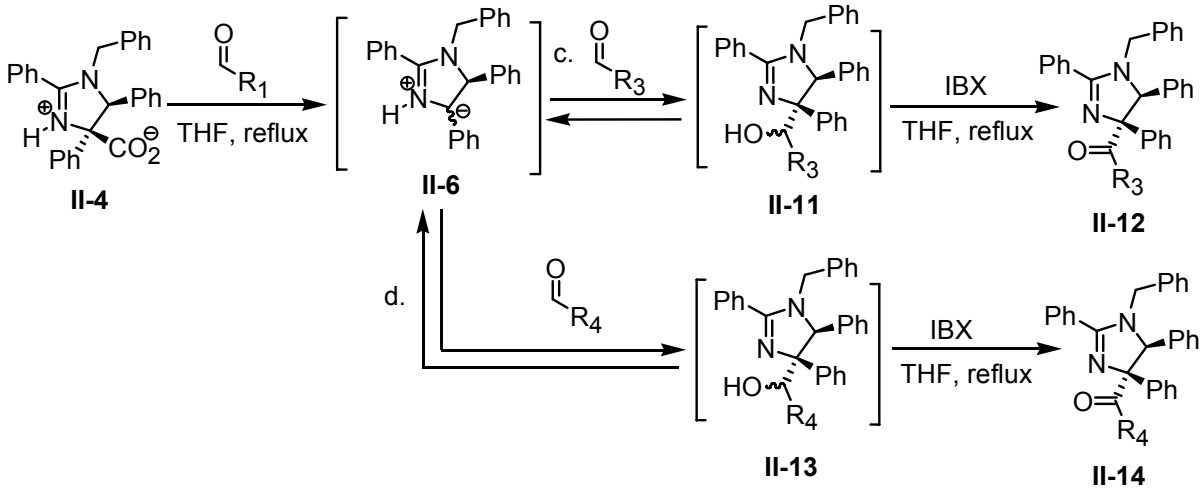
Scheme II-8. Proposed retroaldol-type reaction of intermediate alcohol.

In order to verify whether the nucleophilic addition step of azomethine ylide towards aldehyde is reversible or not, the following control experiments have been put forward. The idea behind these experiments is summarized as follows: if the formation of the intermediate alcohol is irreversible (dashed arrows stand for irreversibility of the reaction step, Scheme II-9), after a period of reaction time, a second aldehyde (R_2CHO) is added to the reaction system, the pathway a should dominate, which will afford only one ketone **II-8** that incorporates the first aldehyde (R_1CHO).



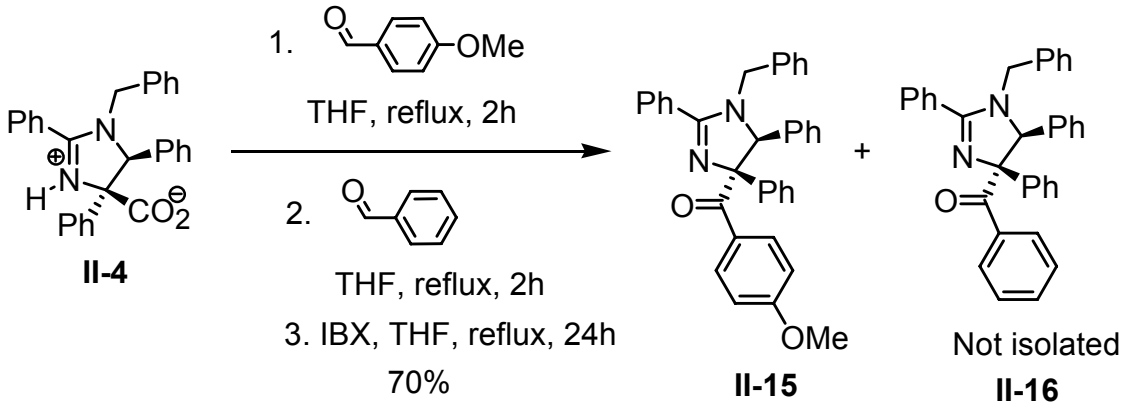
Scheme II-9. Proposed irreversible formation of intermediate alcohol.

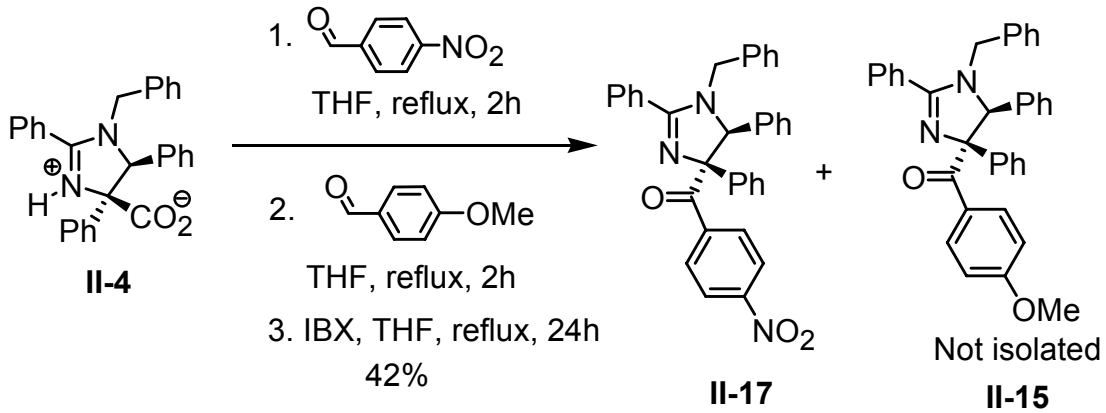
In contrast, if the formation of the intermediate alcohol is reversible (Scheme II-10), still after a period of reaction time, a second aldehyde (R_2CHO) is added to the reaction system, both pathways c and d should dominate, which will in this situation afford two ketones **II-12** and **II-14** which incorporate both aldehydes (R_3CHO and R_4CHO).



Scheme II-10. Proposed reversible formation of intermediate alcohol.

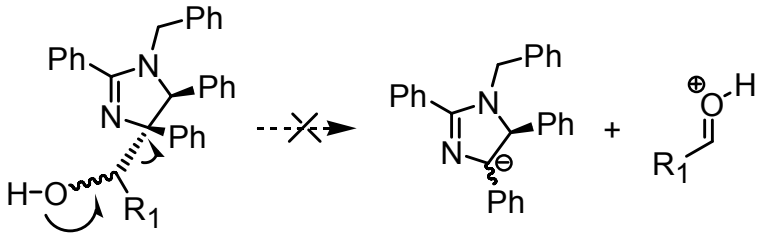
The above ideas have been tested and the results are presented in Scheme II-11.





Scheme II-11. Testing reversibility of nucleophilic addition step.

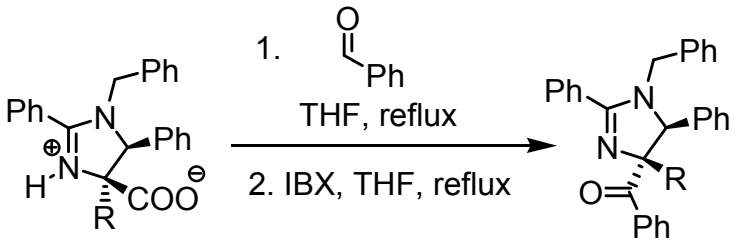
From the results of the above two control experiments, it is clear that the formation of the intermediate alcohol is irreversible (Scheme II-12).

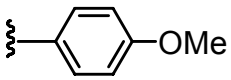
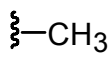


Scheme II-12. Irreversible formation of intermediate alcohol.

F.4 Scope of the methodology

The scope of this methodology has been evaluated afterwards. *Trans*-4,5-diaryl-2-imidazolines containing various substitutions α- to the carboxylate were tested (Table II-3). Of the α -substituents tested, both electron rich and poor aryl groups rendered the products efficiently. However alkyl substituents did not provide the desired products, but resulted mainly in recovery of starting material and imidazole.

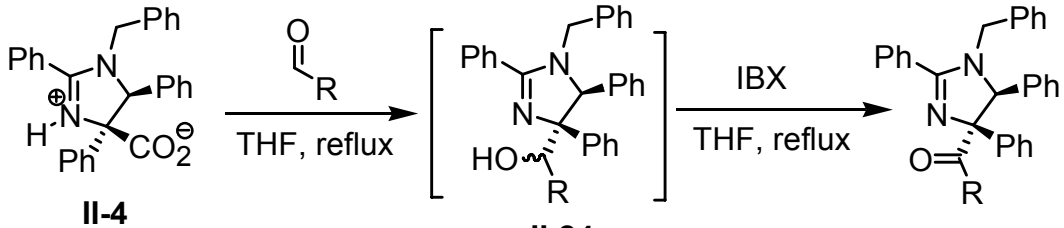


Entry	Starting Imidazoline	Product Imidazoline	R	Yield(%)[a]
1	**II-1**	**II-3**		77
2	**II-4**	**II-16**		86
3	**II-18**	**II-19**		53
4	**II-20**	**II-21**		0
5	**II-22**	**II-23**		0

a. isolated yield.

Table II-3. Variation of starting imidazolines.

To further explore the scope of this methodology, imidazoline **II-4** has been reacted with a variety of aldehydes. To our satisfaction, moderate to excellent yields of the *cis*-4,5-diaryl-2-imidazolines were obtained in all cases (Table II-4). Aromatic (Entry 1-6), heteroaromatic (entry 7) and aliphatic (entry 8-9) aldehydes all successfully undergo this conversion. The steric hindrance appears to play a role in this transformation as the relatively hindered aldehyde, isobutyraldehyde (entry 9), was incorporated in the product in only moderate yield.



II-4 **II-24**

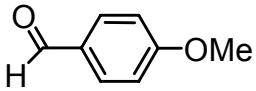
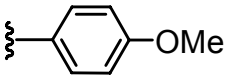
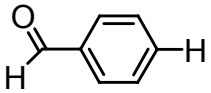
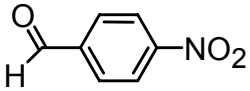
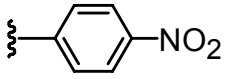
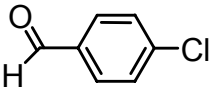
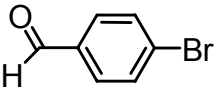
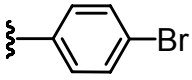
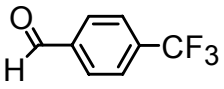
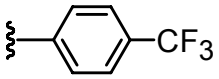
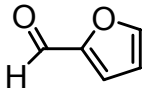
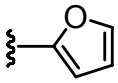
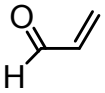
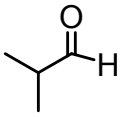
Entry	Compound	Aldehyde	R	Yield(%)[a]
1	**II-15**			72
2	**II-16**			86
3	**II-17**			45
4	**II-25**			58
5	**II-26**			67

Table II-4. Variation of aldehydes.

Table II-4. (cont'd)

6	**II-27**			68
7	**II-28**			90
8	**II-29**			69
9	**II-30**			32

a. isolated yield.

G. Conclusion

In conclusion, we have taken advantage of the decarboxylation of the starting imidazolines to generate the reactive azomethine ylide *in situ* to facilitate the transformation from the initial *trans*-4,5-diaryl-2-imidazolines into their *cis* counterparts. A quaternary carbon is formed in this process. This conversion from *trans*- to *cis*- 2-imidazolines allows efficient access to both classes of biologically important scaffolds.

H. Experimental procedures

H.1 General methods

Reactions were carried out in flame-dried glassware under nitrogen atmosphere. All reactions were magnetically stirred and monitored by TLC with 0.25 μm pre-coated silica gel plates using UV light to visualize the compounds. Column chromatography was carried out on Silica Gel 60 (230-400 mesh) supplied by EM Science. Yields refer

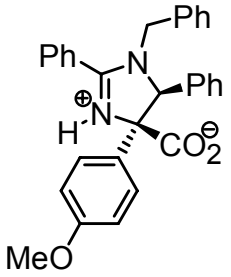
to chromatographically and spectroscopically pure compounds. Infrared spectra were recorded on a Galaxy Series FTIR3000 spectrometer and reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus-500 or 600 spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent ($CDCl_3$: 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). The following abbreviations are used to denote the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Melting points were measured using an electrothermal capillary melting point apparatus and are uncorrected.

H.2 Materials

Reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous dichloromethane and benzene were dispensed from a delivery system which passes the solvents through a column packed with dry neutral alumina. Anhydrous tetrahydrofuran (THF) was distilled from sodium using benzophenone as an indicator for the presence of water. Anhydrous chlorotrimethylsilane was distilled from calcium hydride. The following aldehydes were purchased from Sigma Aldrich and used as received: benzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-(trifluoromethyl)benzaldehyde, 2-furylaldehyde, 90% acrolein solution, isobutyraldehyde. IBX was prepared according to a reported literature procedure.[19]

H.3 Characterization data

Compound II-1: *dl*-(4S,5S)-1- benzyl-4-(4-methoxyphenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid

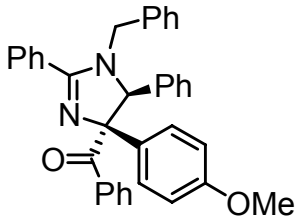


II-1

To 50 mL of anhydrous benzene was added benzyl amine (0.44 g, 4.1 mmol) and benzaldehyde (0.44 g, 4.1 mmol) sequentially. Then the solution was refluxed under nitrogen for overnight and then concentrated *in vacuo*. The resulting residue was redissolved in 50 mL of anhydrous dichloromethane. Then 4-(4-methoxyphenyl)-2-phenyloxazol-5(4H)-one (1.1 g, 4.1 mmol) and chlorotrimethylsilane (0.58 g, 5.3 mmol) were added to the solution sequentially. The mixture was refluxed under nitrogen for 24 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in 50 mL ethyl acetate producing a white solid precipitate, which was filtered through 25 mL fritted funnel. The solid was suspended in 50 mL of dichloromethane and washed with saturated sodium bicarbonate solution (1 x 50 mL) and brine solution (1 x 50 mL) and then dried over sodium sulfate. The solution was concentrated *in vacuo* and the resulting crude solid was purified via recrystallization (dichloromethane/hexane) to afford 1.1 g (60% yield) of the title compound as a white crystalline solid. (m.p.= 133-135 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ3.76 (d, J=15.5 Hz, 1H), 3.76 (s, 3H), 4.58 (d, J=15.5 Hz, 1H),

4.88 (s, 1H), 6.62 (d, *J*=7.0 Hz, 2H), 6.73 (d, *J*=8.0 Hz, 2H), 7.06-7.09 (m, 2H), 7.14-7.17 (m, 1H), 7.29-7.37 (m, 7H), 7.46-7.49 (m, 1H), 7.58 (d, *J*=7.0 Hz, 2H), 7.70 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 48.58, 55.23, 75.40, 79.12, 113.65, 126.98, 127.93, 128.09, 128.31, 128.77, 128.80, 128.82, 129.05, 129.13, 129.16, 132.52, 134.17, 135.34, 136.32, 159.05, 164.82, 168.70. IR (KBr): 3396 cm^{-1}, 3027 cm^{-1}, 2856 cm^{-1}, 1642 cm^{-1}, 1539 cm^{-1}; HRMS calcd for $C_{30}H_{27}N_2O_3(M^+$+H): 463.2022. Found: 463.2011.

Compound II-3: *dl*-((4R,5S)-1-benzyl-4-(4-methoxyphenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazol-4-yl)(phenyl)methanone

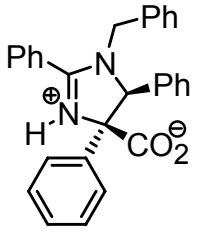


II-3

dl-(4S,5S)-1-benzyl -4-(4-methoxyphenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole -4-carboxylic acid II-1 (0.38 g, 0.82 mmol) was dissolved in 10 mL anhydrous THF and benzaldehyde (0.44 g, 4.1 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.57 g, 2.0 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 18% ethyl acetate, 80% hexane, 2% triethyl amine) to afford 330 mg (77% yield) of the title

compound as a white crystalline solid. (m.p.= 68 – 70 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ3.59 (s, 3H), 3.92 (d, J=16 Hz, 1H), 4.70 (d, J=16 Hz, 1H), 5.91 (s, 1H), 6.48-6.50 (m, 2H), 6.93-6.95 (m, 4H), 7.01-7.09 (m, 5H), 7.24-7.27 (m, 5H), 7.34-7.37 (m, 1H), 7.43-7.47 (m, 3H), 7.66-7.67 (m, 2H), 8.13-8.15 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 49.36, 54.95, 69.11, 87.47, 113.24, 127.00, 127.43, 127.54, 127.70, 127.73, 128.36, 128.44, 128.60, 128.80, 128.81, 130.13, 131.29, 131.40, 131.58, 131.76, 135.71, 136.80, 137.41, 158.31, 165.66, 197.40; IR (KBr): 3062 cm^{-1}, 3030 cm^{-1}, 2917 cm^{-1}, 1673 cm^{-1}; HRMS calcd for $C_{36}H_{31}N_2O_2$(M^++H): 523.2386. Found: 523.2370.

Compound II-4: *dl*-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid

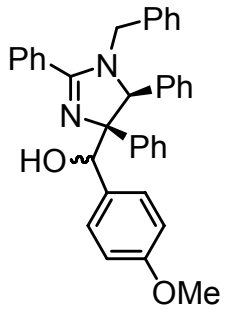


II-4

To 50 mL of anhydrous benzene was added benzyl amine (0.71 g, 6.5 mmol) and benzaldehyde (0.68 g, 6.5 mmol) sequentially. Then the solution was refluxed under nitrogen for overnight and then concentrated *in vacuo*. The resulting residue was redissolved in 50 mL of anhydrous dichloromethane. Then 2,4-diphenyloxazol-5(4H)-one (1.5 g, 6.5 mmol) and chlorotrimethylsilane (0.94 g, 8.7 mmol) were added to the solution sequentially. The mixture was refluxed under

nitrogen for 12 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in 50 mL ethyl acetate producing a white solid precipitate, which was filtered through 25 mL fritted funnel. The solid was suspended in 50 mL of dichloromethane and washed with saturated sodium bicarbonate solution (1 x 50 mL) and brine solution (1 x 50 mL) and then dried over sodium sulfate. The solution was concentrated *in vacuo* and the resulting crude solid was purified via recrystallization (dichloromethane/hexane) to afford 0.9 g (32% yield) of the title compound as a white crystalline solid. The ^{1}H and ^{13}C spectra match the literature report.[20]

Compound II-5: *dl*-(4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-methoxyphenyl)methanol

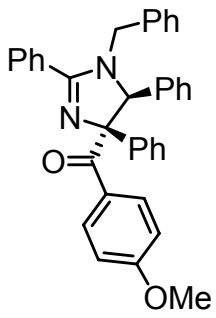


II-5

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.10 g, 0.23 mmol) was dissolved in 10 mL anhydrous THF and 4-methoxybenzaldehyde (0.15 g, 1.1 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Then the solution was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 50% ethyl acetate, 50% hexane-49% ethyl acetate, 49% hexane, 2% acetic acid) to

afford 0.084 g (70% yield) of the title compound as a white solid (a mixture of diastereomers). Diastereomer I: (m.p.= 162–164 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.72 (d, *J*=15.5 Hz, 1H), 3.71 (s, 3H), 4.58 (d, *J*=15.5 Hz, 1H), 4.81 (s, 1H), 4.97 (s, 1H), 6.60-6.61 (m, 2H), 6.79-6.90 (m, 9H), 7.03-7.05 (m, 4H), 7.31-7.33 (m, 4H), 7.50-7.52 (m, 3H), 7.71-7.73 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 48.96, 55.09, 70.08, 80.12, 82.45, 112.69, 125.66, 126.20, 126.78, 127.21, 127.35, 127.69, 128.01, 128.19, 128.61, 128.66, 128.82, 128.89, 129.34, 129.79, 130.24, 131.98, 136.80, 158.77, 165.21. IR (thin film): 3185 cm^{-1}, 3061 cm^{-1}, 3029 cm^{-1}, 2961 cm^{-1}, 2926 cm^{-1}, 1495 cm^{-1}; HRMS calcd for $C_{36}H_{33}N_2O_2(M^{+}+H)$: 525.2542. Found: 525.2526. Diastereomer II: (m.p.= 168–170 ^{o}C).^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.57 (d, *J*=16 Hz, 1H), 3.82 (s, 3H), 4.45 (d, *J*=15.5 Hz, 1H), 5.06 (s, 1H), 5.09 (s, 1H), 6.67 (broad, s, 2H), 6.76-6.80 (m, 4H), 6.87-6.88 (m, 2H), 6.95-6.99 (m, 4H), 7.18-7.26 (m, 6H), 7.50-7.56 (m, 3H), 7.71-7.73 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 48.50, 55.21, 69.43, 79.62, 81.07, 113.10, 126.45, 127.08, 127.43, 127.64, 127.93, 128.14, 128.42, 128.53, 128.66, 128.96, 130.49, 131.13, 131.38, 134.54, 136.13, 139.29, 159.19, 166.42. IR (thin film): 3399 cm^{-1}, 2956 cm^{-1},2924 cm^{-1}, 2853 cm^{-1}, 1457 cm^{-1}; HRMS calcd for $C_{36}H_{33}N_2O_2(M^{+}+H)$: 525.2542. Found: 525.2559.

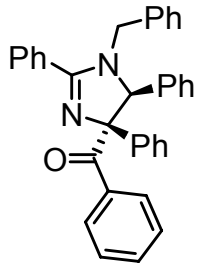
Compound II-15: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-methoxyphenyl)methanone



II-15

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.30 g, 0.70 mmol) was dissolved in 10 mL anhydrous THF and 4-methoxybenzaldehyde (0.48 g, 3.5 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.51 g, 1.8 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 5% ethyl acetate, 93% hexane, 2% triethyl amine) to afford 0.26 g (72% yield) of the title compound as a white solid. (m.p.= 144–146 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.68 (s, 3H), 3.86 (d, *J*=15.5 Hz, 1H), 4.62 (d, *J*=15.5 Hz, 1H), 5.90 (s, 1H), 6.65-6.67 (m, 2H), 6.82-6.88 (m, 5H), 6.91-6.96 (m, 7H), 7.17-7.18 (m, 3H), 7.38-7.40 (m, 3H), 7.61-7.63 (m, 2H), 8.09-8.11 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 49.47, 55.21, 69.15, 87.96, 112.95, 126.41, 126.92, 127.25, 127.44, 127.60, 127.64, 127.81, 128.37, 128.47, 128.66, 128.90, 130.15, 131.50, 133.98, 136.88, 137.54, 137.53, 139.99, 162.63, 165.68, 195.66. IR (KBr): 3089 cm^{-1}, 3028 cm^{-1}, 2907 cm^{-1}, 1669 cm^{-1}, 1598 cm^{-1}; HRMS calcd for $C_{36}H_{31}N_2O_2$ (M^++H): 523.2386. Found: 523.2368.

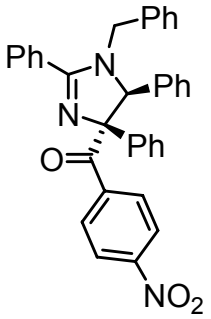
Compound II-16: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(phenyl)methanone



II-16

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.12 g, 0.28 mmol) was dissolved in 10 mL anhydrous THF and benzaldehyde (0.15 g, 1.4 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.19 g, 0.70 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 10% ethyl acetate, 88% hexane, 2% triethyl amine) to afford 118 mg (86 % yield) of the title compound as a colorless oil. ^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.91 (d, *J*=15.5 Hz, 1H), 4.68 (d, *J*=15.5 Hz, 1H), 5.93 (s, 1H), 6.88-6.94 (m, 5H), 6.97-7.03 (m, 6H), 7.21-7.25 (m, 6H), 7.32-7.35(m, 3H), 7.43-7.46 (m, 3H), 7.65-7.66 (m, 2H), 8.11-8.12 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 49.22, 68.82, 87.79, 126.51, 126.99, 127.14, 127.50, 127.62, 127.66, 127.67, 127.70, 128.48, 128.70, 128.75, 128.81, 130.25, 131.09, 131.43, 131.93, 135.36, 136.67, 137.18, 139.40, 165.89, 196.99. IR (thin film): 3026 cm^{-1}, 2932 cm^{-1}, 1680 cm^{-1}, 1589 cm^{-1}; HRMS calcd for $C_{35}H_{29}N_2O$ (M^++H): 493.2280. Found: 493.2300.

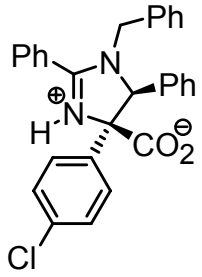
Compound II-17: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-nitrophenyl)methanone



II-17

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.12 g, 0.28 mmol) was dissolved in 10 mL anhydrous THF and 4-nitrobenzaldehyde (0.21 g, 1.4 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.19 g, 0.70 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 10% ethyl acetate, 88% hexane, 2% triethyl amine) to afford 68 mg (45% yield) of the title compound as a yellow solid. (m.p.= 80–82 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.92 (d, *J*=15.5 Hz, 1H), 4.71 (d, *J*=15.5 Hz, 1H), 5.90 (s, 1H), 6.90-7.07 (m, 12H), 7.27-7.29 (m, 3H), 7.45-7.50 (m, 3H), 7.64-7.66 (m, 2H), 8.03-8.06 (m, 2H), 8.27-8.30 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 49.21, 68.73, 87.49, 122.77, 127.04, 127.14, 127.34, 127.68, 127.72, 127.87, 128.00, 128.58, 128.59, 128.70, 128.83, 130.56, 130.68, 132.30, 136.44, 136.53, 138.43, 140.56, 149.35, 166.45, 195.21. IR (KBr): 3060 cm^{-1}, 3029 cm^{-1}, 2922 cm^{-1}, 1684 cm^{-1}, 1522 cm^{-1}; HRMS calcd for $C_{35}H_{28}N_3O_3$ (M^++H): 538.2125. Found: 538.2147.

Compound II-18: *dl*-(4S,5S)-1-benzyl-4-(4-chlorophenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid

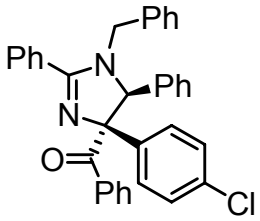


II-18

To 50 mL of anhydrous benzene was added benzyl amine (0.21 g, 1.9 mmol) and benzaldehyde (0.21 g, 1.9 mmol) sequentially. Then the solution was refluxed under nitrogen for overnight and then concentrated *in vacuo*. The resulting residue was redissolved in 50 mL of anhydrous dichloromethane. Then 4-(4-chlorophenyl)-2-phenyloxazol-5(4H)-one (0.52 g, 1.9 mmol) and chlorotrimethylsilane (0.27 g, 2.5 mmol) were added to the solution sequentially. The mixture was refluxed under nitrogen for 20 hours. The solution was concentrated *in vacuo* and the resulting residue was resuspended in 50 mL ethyl acetate producing a white solid precipitate, which was filtered through 25 mL fritted funnel. The solid was suspended in 50 mL dichloromethane and washed with saturated sodium bicarbonate solution (1 x 50 mL) and brine solution (1 x 50 mL) and then dried over sodium sulfate. The solution was concentrated *in vacuo* and the resulting crude solid was purified via recrystallization (dichloromethane/hexane) to afford 0.38 g (43% yield) of the title compound as a white crystalline solid. (m.p.= 114-116 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ3.71 (d, *J*=15.5 Hz, 1H), 4.56 (d, *J*=15.5 Hz, 1H), 4.75 (s, 1H), 6.55 (d, *J*=8

Hz, 2H), 7.02-7.15 (m, 5H), 7.23-7.27 (m, 2H), 7.32-7.33 (m, 5H), 7.41-7.44 (m, 1H), 7.56-7.58 (m, 2H), 7.66 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (150 MHz) ($CDCl_3$): *δ*: 48.53, 75.10, 78.43, 122.57, 126.88, 127.21, 128.10, 128.40, 128.90, 128.93, 128.95, 129.08, 129.20, 129.28, 133.03, 133.17, 133.44, 135.81, 141.59, 164.54, 167.80. IR (KBr): 3409 cm^{-1}, 3025 cm^{-1}, 1641 cm^{-1}, 1537 cm^{-1}; HRMS calcd for $C_{29}H_{24}N_2O_2Cl$ (M^++H): 467.1526. Found: 467.1521.

Compound II-19: *dl*-((4R,5S)-1-benzyl-4-(4-chlorophenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazol-4-yl)(phenyl)methanone

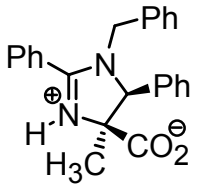


II-19

dl-(4S,5S)-1-benzyl -4-(4-chlorophenyl)-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-18 (0.17 g, 0.37 mmol) was dissolved in 10 mL anhydrous THF and benzaldehyde (0.20 g, 1.9 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.28 g, 1.0 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 8% ethyl acetate, 90% hexane, 2% triethyl amine) to afford 0.1 g (53% yield) of the title compound as a white crystalline solid. (m.p.= 60–62 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): *δ*3.91 (d,

J=15.5 Hz, 1H), 4.69 (d, *J*=16 Hz, 1H), 5.91 (s, 1H), 6.89-6.98 (m, 8H), 7.04-7.08 (m, 3H), 7.23-7.27 (m, 5H), 7.34-7.38(m, 1H), 7.43-7.48 (m, 3H), 7.64-7.66 (m, 2H), 8.10-8.12 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): *δ*: 49.46, 69.12, 87.58, 127.36, 127.58, 127.72, 127.80, 127.85, 127.95, 128.54, 128.71, 128.72, 128.73, 128.85, 130.35, 131.16, 131.44, 132.09, 132.56, 135.42, 136.67, 137.08, 138.33, 166.03, 196.91. IR (KBr): 3061 cm^{-1}, 3029 cm^{-1}, 2924 cm^{-1}, 1675 cm^{-1}, 1487 cm^{-1}; HRMS calcd for $C_{35}H_{28}N_2OCl$ (M^++H): 527.1890. Found: 527.1881.

Compound II-20: *dl*-(4S,5S)-1-benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid

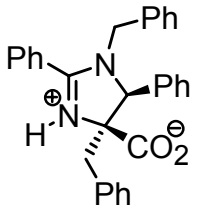


II-20

To 50 mL of anhydrous benzene was added benzyl amine (0.43 g, 4.0 mmol) and benzaldehyde (0.42 g, 4.0 mmol) sequentially. Then the solution was refluxed under nitrogen for overnight and then concentrated *in vacuo*. The resulting residue was redissolved in 50 mL of anhydrous dichloromethane. Then 4-methyl-2-phenyloxazol-5(4H)-one (0.70 g, 4.0 mmol) and chlorotrimethylsilane (0.56 g, 5.2 mmol) were added to the solution sequentially. The mixture was refluxed under nitrogen for 6 hours and then stirred overnight at room temperature. The solution was concentrated *in vacuo* and the title compound (0.35 g, 24% yield) was precipitated using 50 mL ethyl acetate. The ^1H and ^{13}C spectra match the literature

report.[21]

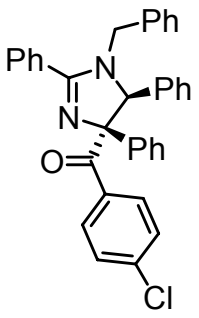
Compound II-22: *dl*-(4S,5S)-1,4-dibenzyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid



II-22

To 50 mL of anhydrous benzene was added benzyl amine (0.73 g, 6.8 mmol) and benzaldehyde (0.71 g, 6.8 mmol) sequentially. Then the solution was refluxed under nitrogen for overnight and then concentrated *in vacuo*. The resulting residue was redissolved in 50 mL of anhydrous dichloromethane. Then 4-benzyl-2-phenyloxazol-5(4H)-one (1.7 g, 6.8 mmol) and chlorotrimethylsilane (0.94 g, 8.7 mmol) were added to the solution sequentially. The mixture was refluxed under nitrogen for 8 hours and then stirred overnight at room temperature. The mixture was washed with 50 mL distilled water and the organic layer was collected and dried over sodium sulfate. The solution was concentrated *in vacuo* and the title compound (0.76 g, 25% yield) was precipitated using dichloromethane: ether (1:3). The ^{1}H and ^{13}C spectra match the literature report.[21]

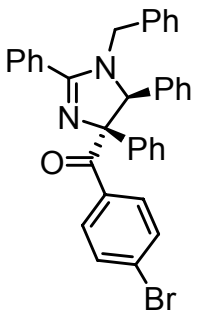
Compound II-25: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-chlorophenyl)methanone



II-25

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.10 g, 0.24 mmol) was dissolved in 10 mL anhydrous THF and 4-chlorobenzaldehyde (0.17 g, 1.2 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.17 g, 0.60 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 1:2 diethyl ether: hexane) to afford 74 mg (58% yield) of the title compound as a white solid. (m.p.= 58 – 60 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ3.92 (d, J=15.5 Hz, 1H), 4.69 (d, J=15.5 Hz, 1H), 5.96 (s, 1H), 6.87-7.03 (m, 12H), 7.21-7.34 (m, 5H), 7.41-7.47 (m, 3H), 7.65-7.67 (m, 2H), 8.13-8.14 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 49.19, 68.79, 87.75, 126.50, 126.98, 127.11, 127.48, 127.61, 127.65, 127.66, 127.67, 128.46, 128.68, 128.74, 128.79, 130.24, 131.05, 131.41, 131.92, 135.32, 136.64, 137.14, 139.37, 165.88, 196.96. IR (thin film): 3062 cm^{-1}, 2963 cm^{-1}, 1679 cm^{-1}, 1579 cm^{-1}; HRMS calcd for $C_{35}H_{28}N_2OCl$ (M^++H): 527.1890. Found: 527.1881.

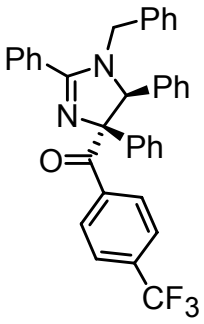
Compound II-26: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-bromophenyl)methanone



II-26

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.12 g, 0.28 mmol) was dissolved in 10 mL anhydrous THF and 4-bromobenzaldehyde (0.26 g, 1.4 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.20 g, 0.70 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 50% dichloromethane, 50% hexane) to afford 0.11 g (67% yield) of the title compound as a white solid. (m.p.= 48 – 50 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ 3.92 (d, J=15.5 Hz, 1H), 4.68 (d, J=15.5 Hz, 1H), 5.91 (s, 1H), 6.88-7.05 (m, 12H), 7.23-7.26 (m, 3H), 7.35-7.37 (m, 2H), 7.44-7.48 (m, 3H), 7.65-7.67 (m, 2H), 8.02-8.04 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 49.23, 68.73, 87.63, 126.69, 127.09, 127.19, 127.56, 127.72, 127.73, 127.78, 128.52, 128.77, 128.78, 130.37, 130.95, 130.99, 133.12, 134.03, 136.59, 136.97, 139.14, 166.06, 195.81. IR (KBr): 3057 cm^{-1}, 1652 cm^{-1}, 1635 cm^{-1}; HRMS calcd for $C_{35}H_{28}N_2OBr$ (M^++H): 571.1385. Found: 571.1399.

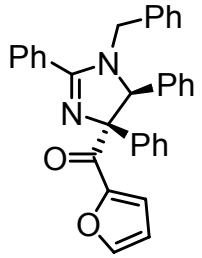
Compound II-27: *dl*- ((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(4-(trifluoromethyl)phenyl)methanone



II-27

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.12 g, 0.28 mmol) was dissolved in 10 mL anhydrous THF and 4-(trifluoromethyl)benzaldehyde (0.25 g, 1.4 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.20 g, 0.70 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 30% ethyl acetate, 70% hexane) to afford 107 mg (68% yield) of the title compound as a white solid. (m.p.= 60 – 62 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$): δ 3.92 (d, J=15.5 Hz, 1H), 4.69 (d, J=16 Hz, 1H), 5.91 (s, 1H), 6.91-7.05 (m, 12H), 7.24-7.27 (m, 3H), 7.43-7.49 (m, 5H), 7.64-7.66 (m, 2H), 7.65-7.67 (m, 2H), 8.22 (d, J =8.5 Hz, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 49.22, 68.76, 87.64, 123.73 (q, J=1084 Hz, 1C), 124.65 (q, J=14.5 Hz, 1C), 126.84, 127.14, 127.20, 127.61, 127.71, 127.79, 127.88, 128.55, 128.75, 128.79, 130.43, 130.89, 131.66, 132.05 (q, J=130 Hz, 1C), 136.56, 136.82, 138.33, 138.80, 166.23, 195.85. IR (KBr): 3083 cm^{-1}, 3031 cm^{-1}, 1686 cm^{-1}, 1615 cm^{-1}; HRMS calcd for $C_{36}H_{28}N_2OF_3$ (M^++H): 561.2154. Found: 561.2133.

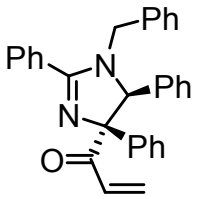
Compound II-28: *dl*-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)(furan-2-yl)methanone



II-28

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.10 g, 0.24 mmol) was dissolved in 10 mL anhydrous THF and 2-furylaldehyde (0.11 g, 1.2 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.17 g, 0.60 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 49% ethyl acetate, 49% hexane, 2% triethyl amine) to afford 104 mg (90% yield) of the title compound as a white solid. (m.p.= 57 – 59 ^{o}C). ^{1}H NMR (500MHz) ($CDCl_3$). δ3.82 (d, J=16 Hz, 1H), 4.57 (d, J=16 Hz, 1H), 5.85 (s, 1H), 6.21 (dd, J_1=3.5 Hz, J_2=1.5 Hz, 1H), 6.82-7.01 (m, 12H), 7.13-7.19 (m, 4H), 7.35-7.40 (m, 4H), 7.60-7.62 (m, 2H); ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 49.13, 68.17, 86.64, 111.80, 122.50, 126.58, 127.13, 127.28, 127.44, 127.53, 127.54, 127.72, 128.53, 128.67, 128.69, 128.84, 130.20, 131.14, 136.56, 136.99, 139.51, 146.12, 150.51, 165.88, 186.10. IR (KBr): 3021 cm^{-1}, 2935 cm^{-1}, 1672 cm^{-1}, 1587 cm^{-1}; HRMS calcd for $C_{33}H_{27}N_2O_2$ (M^++H): 483.2073. Found: 483.2094.

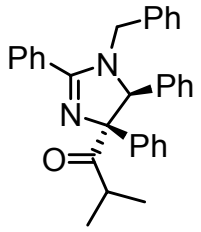
Compound II-29: *dl*-1-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)prop-2-en-1-one



II-29

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (0.10 g, 0.24 mmol) was dissolved in 10 mL anhydrous THF and acrolein (0.075 g, 1.2 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (0.16 g, 0.60 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography (silica gel, 20% ethyl acetate, 78% hexane, 2% triethyl amine) to afford 73 mg (69% yield) of the title compound as a colorless oil. ^{1}H NMR (500MHz) ($CDCl_3$): δ3.84 (d, J=16 Hz, 1H), 4.60 (d, J=16 Hz, 1H), 5.57 (d, J=10.5 Hz, 1H), 5.78 (s, 1H), 6.38 (dd, J_1=1.5 Hz, J_2=17.5 Hz, 1H), 6.70 (dd, J_1=10.5 Hz, J_2=17.5 Hz, 1H), 6.92-7.02 (m, 12H), 7.25-7.29 (m, 3H), 7.47-7.48 (m, 3H), 7.67-7.68 (m, 2H). ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 48.93, 67.36, 86.59, 126.82, 127.21, 127.42, 127.45, 127.67, 127.80, 127.81, 128.12, 128.53, 128.54, 128.74, 130.23, 130.93, 131.05, 133.57, 136.60, 136.94, 137.66, 166.30, 194.67. IR (thin film): 3025 cm^{-1}, 2961 cm^{-1}, 1689 cm^{-1}, 1593 cm^{-1}; HRMS calcd for $C_{31}H_{27}N_2O$ (M^++H): 443.2118. Found: 443.2127.

Compound II-30: *dl*-1-((4R,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazol-4-yl)-2-methylpropan-1-one



II-30

dl-(4S,5S)-1-benzyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid II-4 (90 mg, 0.21 mmol) was dissolved in 10 mL anhydrous THF and isobutyraldehyde (72 mg, 1.0 mmol) was added to the solution. Then the solution was heated to reflux for 2 hours. Heating was then paused and IBX (150 mg, 0.52 mmol) was added. The solution was refluxed for 24 hours and then filtered through 25 mL fritted funnel. The filtrate was concentrated *in vacuo* and the resulting residue was purified via column chromatography twice with different eluent systems (the first column: silica gel, 30% ethyl acetate, 68% hexane, 2% triethyl amine; the second column: silica gel, 33% diethyl ether, 65% hexane, 2% triethyl amine;) to afford 31 mg (32% yield) of the title compound as a colorless oil. ^{1}H NMR (500MHz) ($CDCl_3$): δ0.73 (d, J=7 Hz, 3H), 1.12 (d, J=7 Hz, 3H), 3.76 (d, J=15.5 Hz, 1H), 4.52 (d, J=16 Hz, 1H), 3.12 (m, 1H), 5.60 (s, 1H), 6.87-6.98 (m, 12H), 7.17-7.22 (m, 3H), 7.41-7.43 (m, 3H), 7.62-7.64 (m, 2H). ^{13}C NMR (125 MHz) ($CDCl_3$): δ: 20.39, 21.34, 36.66, 49.25, 67.93, 88.74, 126.73, 127.16, 127.47, 127.50, 127.51, 127.79, 127.99, 128.54, 128.55, 128.81, 128.96, 130.17, 131.46, 136.98, 137.58, 137.73, 165.83, 212.30. IR (thin film): 3062 cm^{-1}, 3030 cm^{-1}, 2927 cm^{-1}, 1708 cm^{-1}, 1448 cm^{-1}; HRMS calcd for $C_{32}H_{31}N_2O$ (M^++H): 459.2436.

Found: 459.2433.

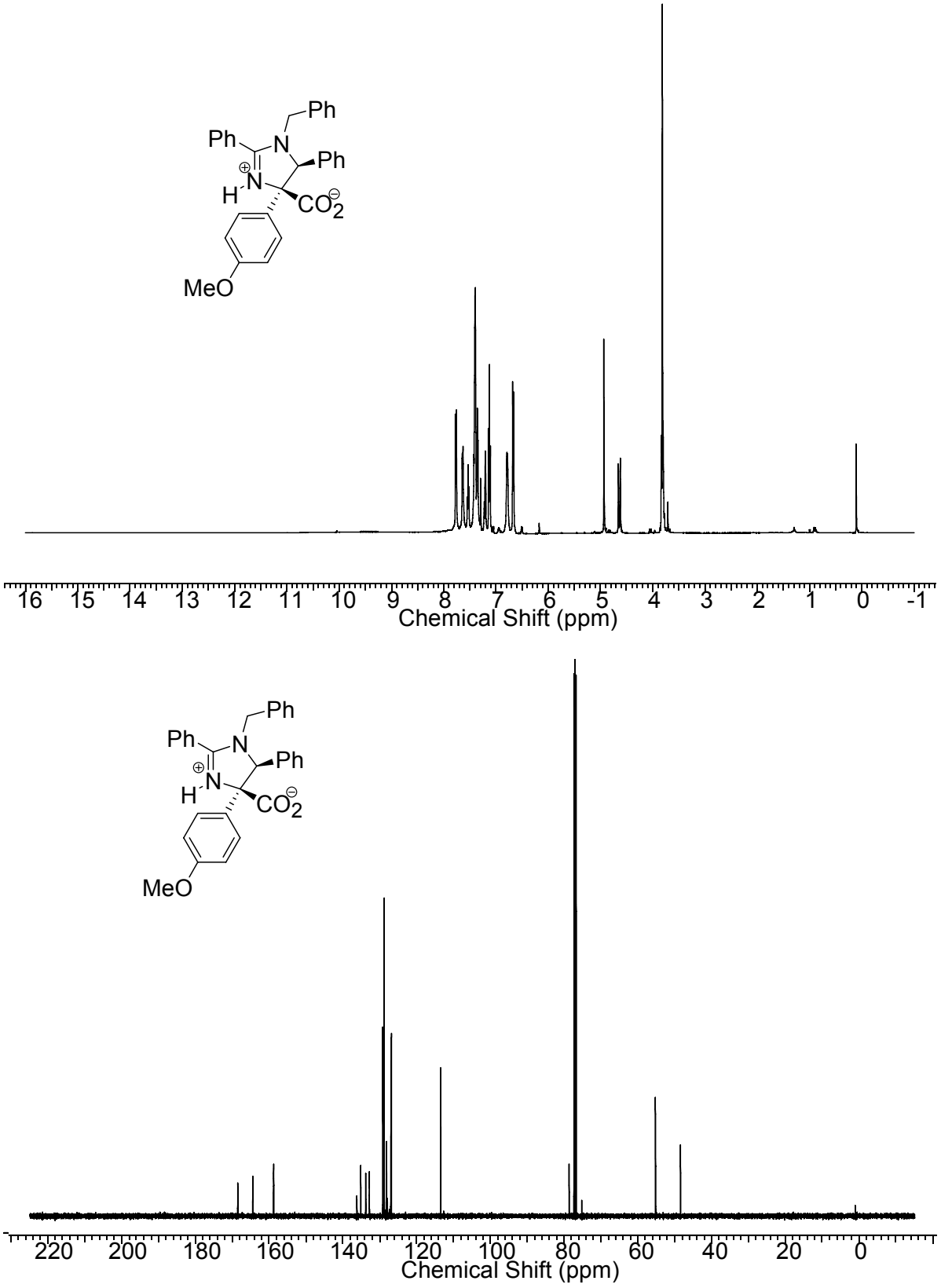


Figure II-13. NMR spectra of imidazoline **II-1**.

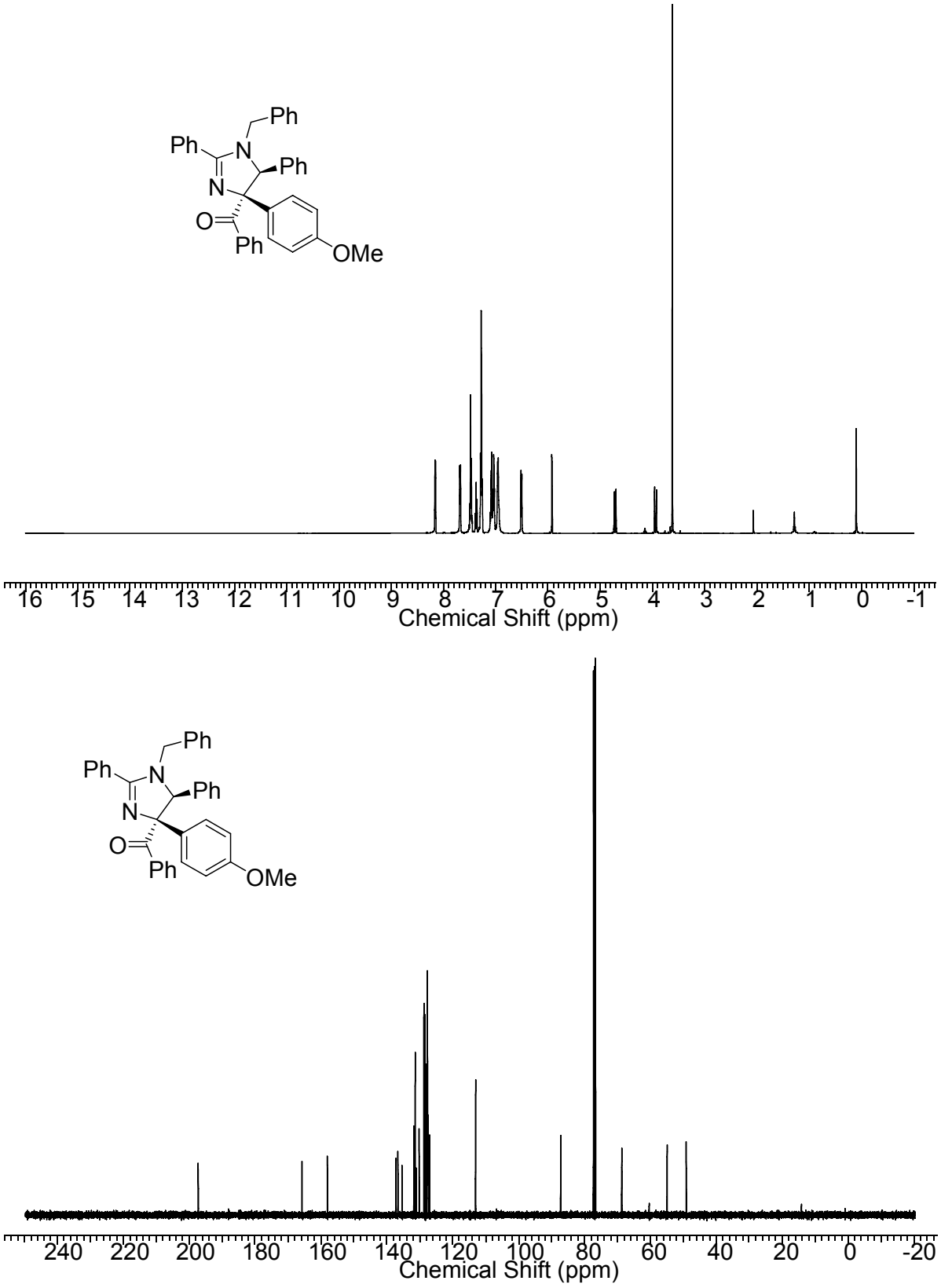


Figure II-14. NMR spectra of imidazoline **II-3**.

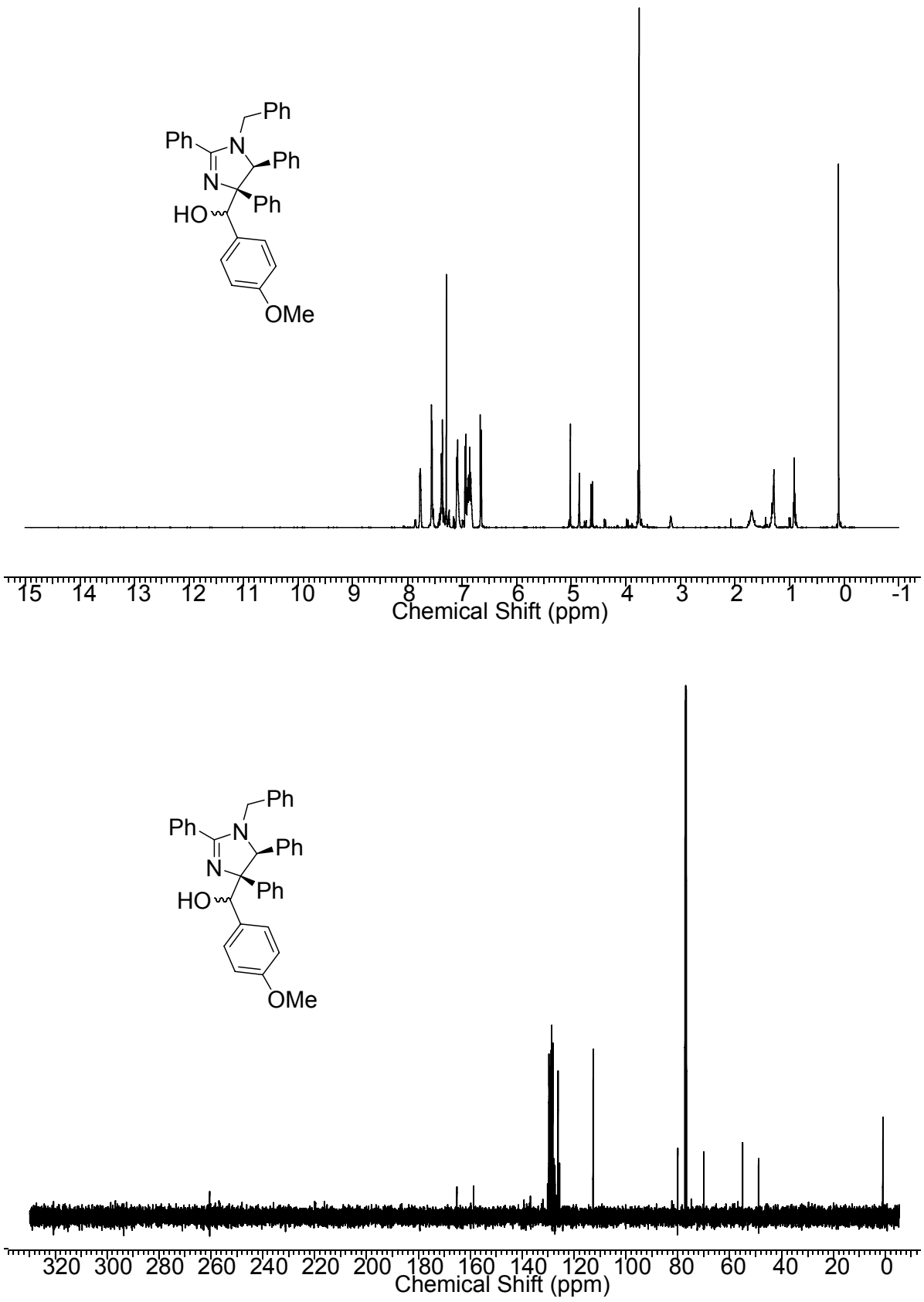
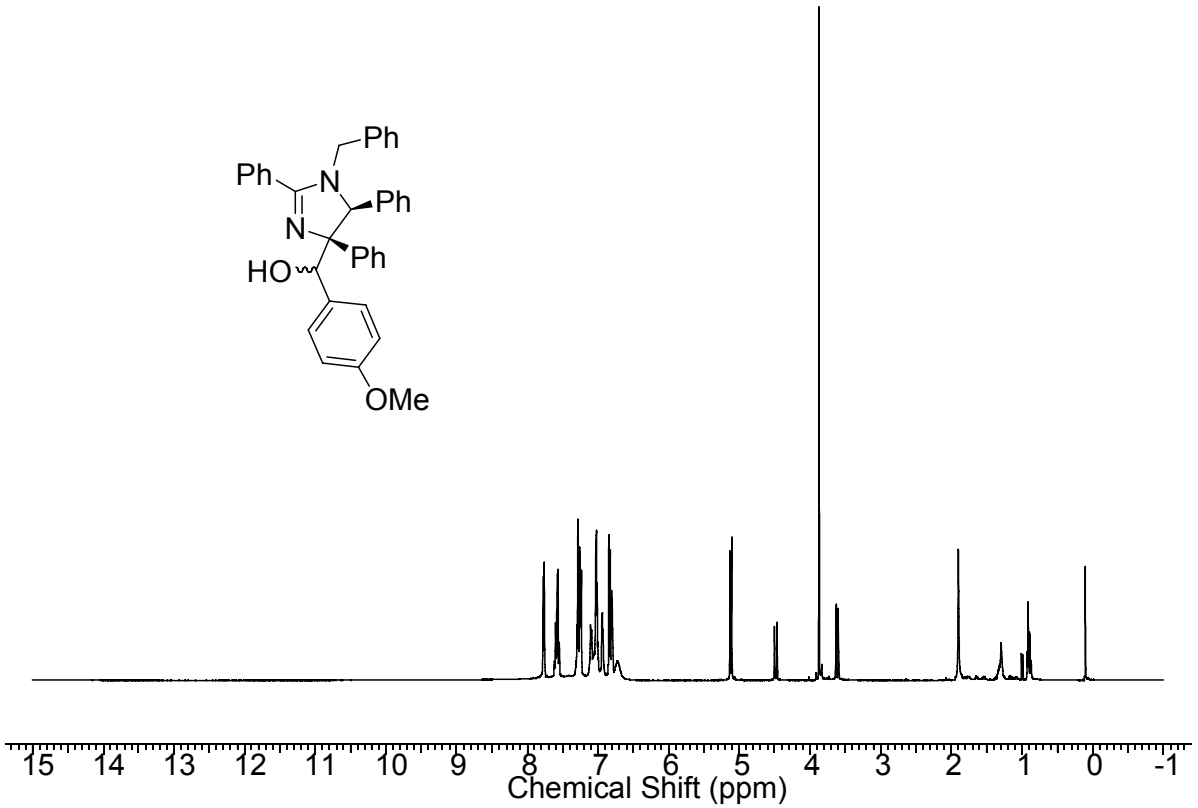


Figure II-15. NMR spectra of diastereomer I of imidazoline **II-5**.



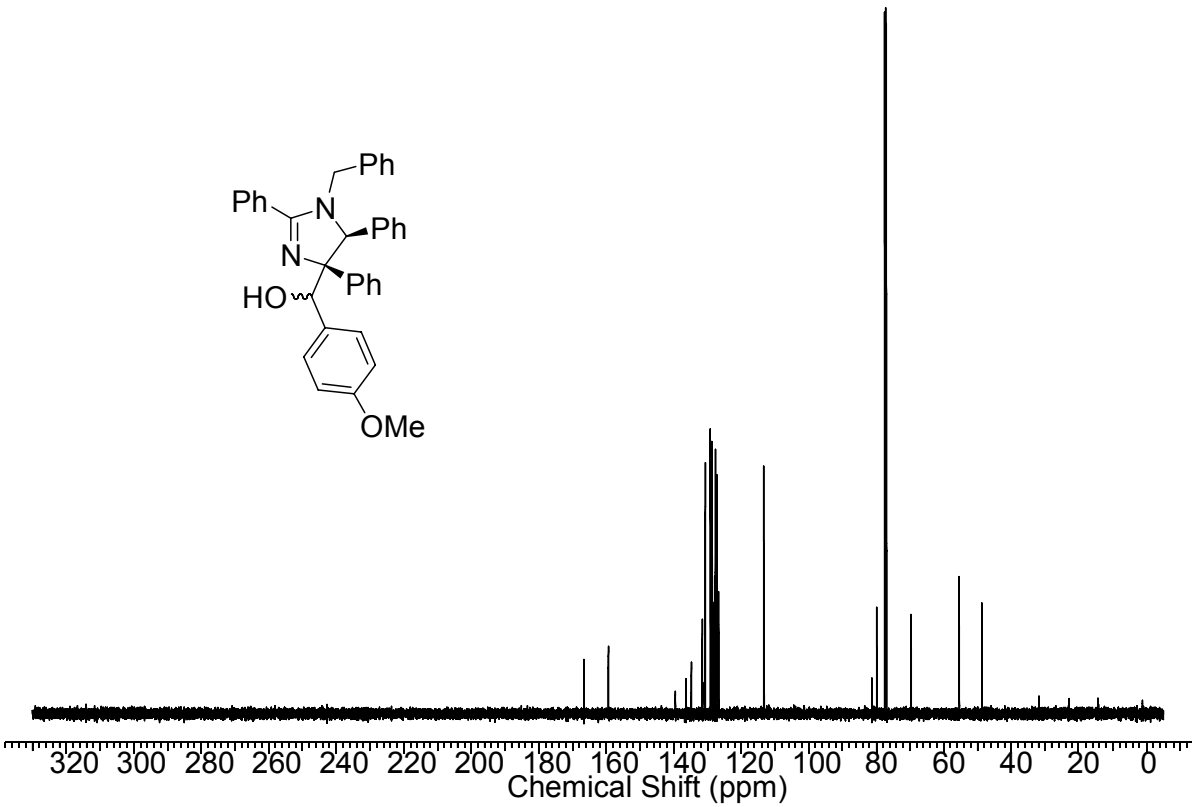


Figure II-16. NMR spectra of diastereomer II of imidazoline **II-5**.

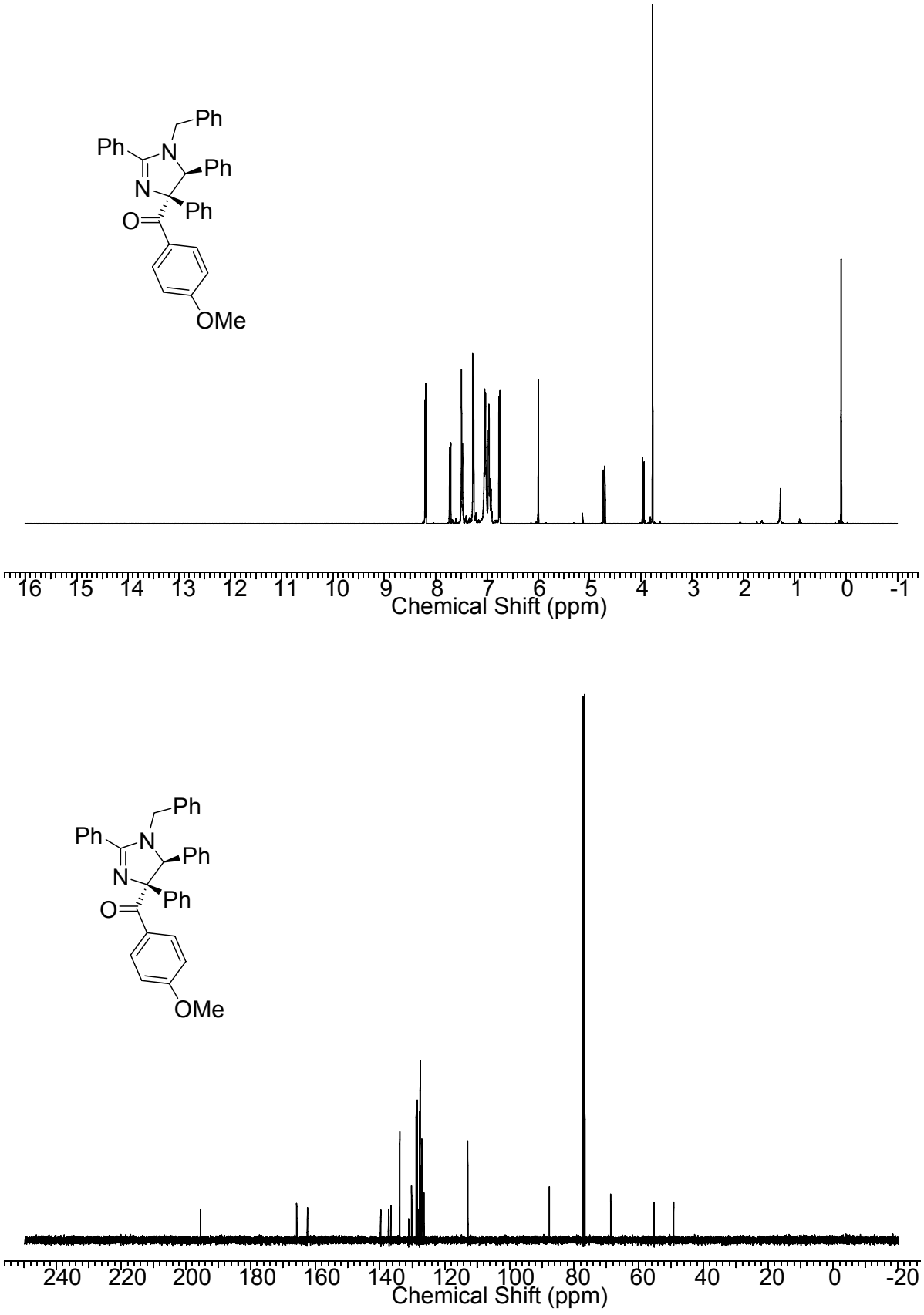
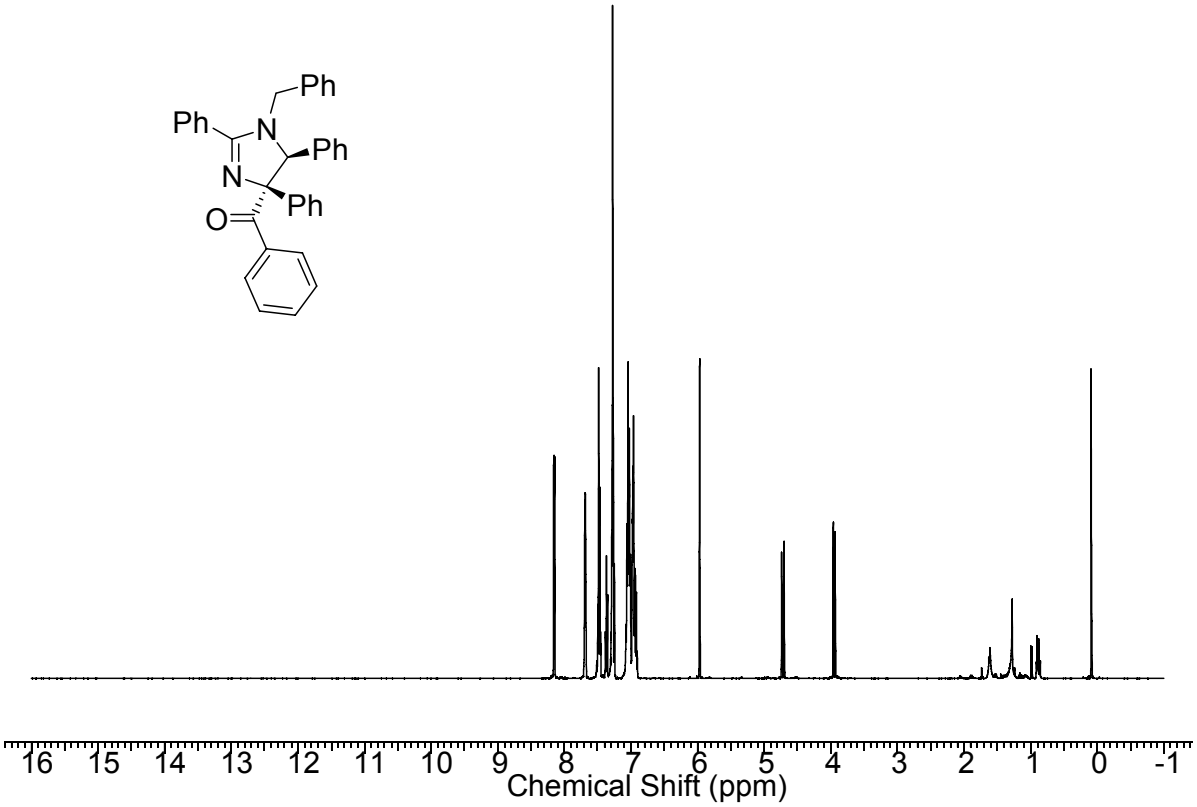


Figure II-17. NMR spectra of imidazoline **II-15**.



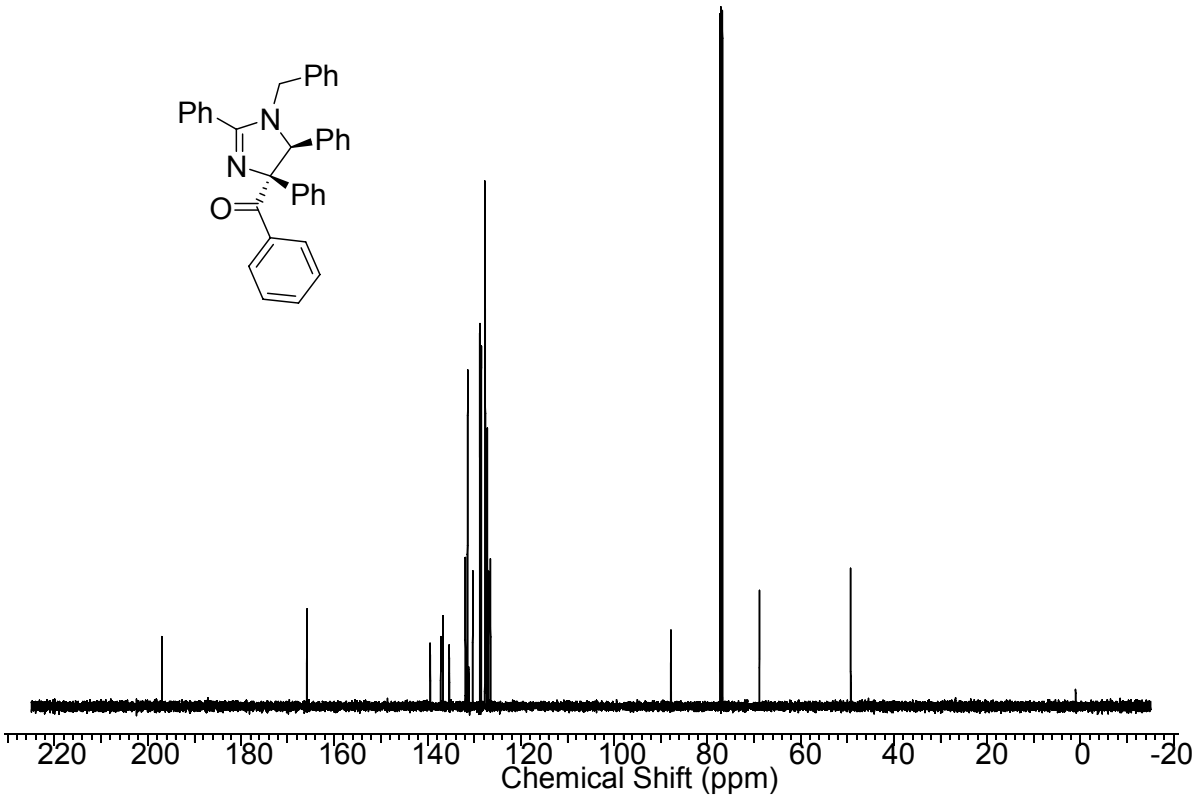


Figure II-18. NMR spectra of imidazoline **II-16**.

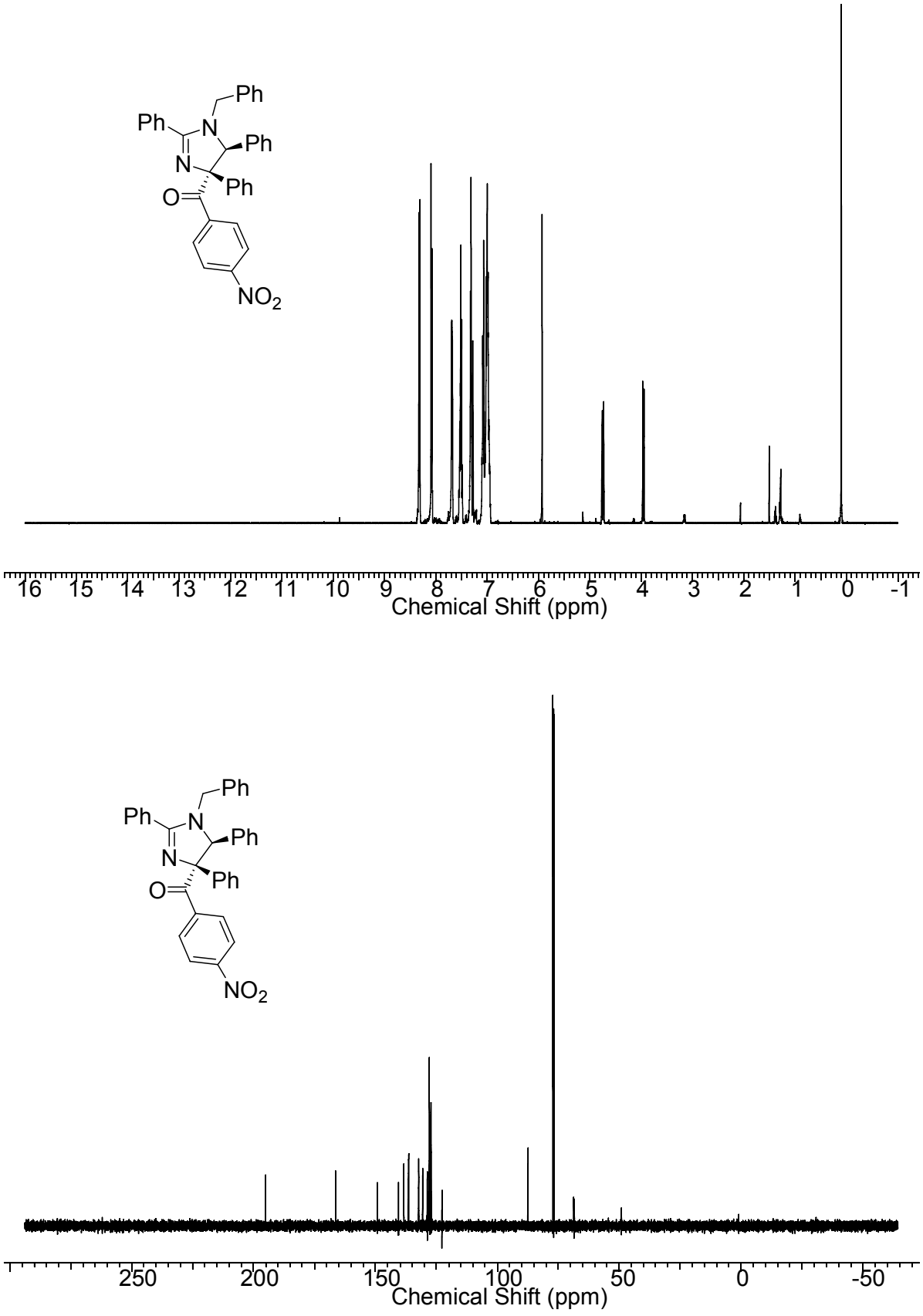
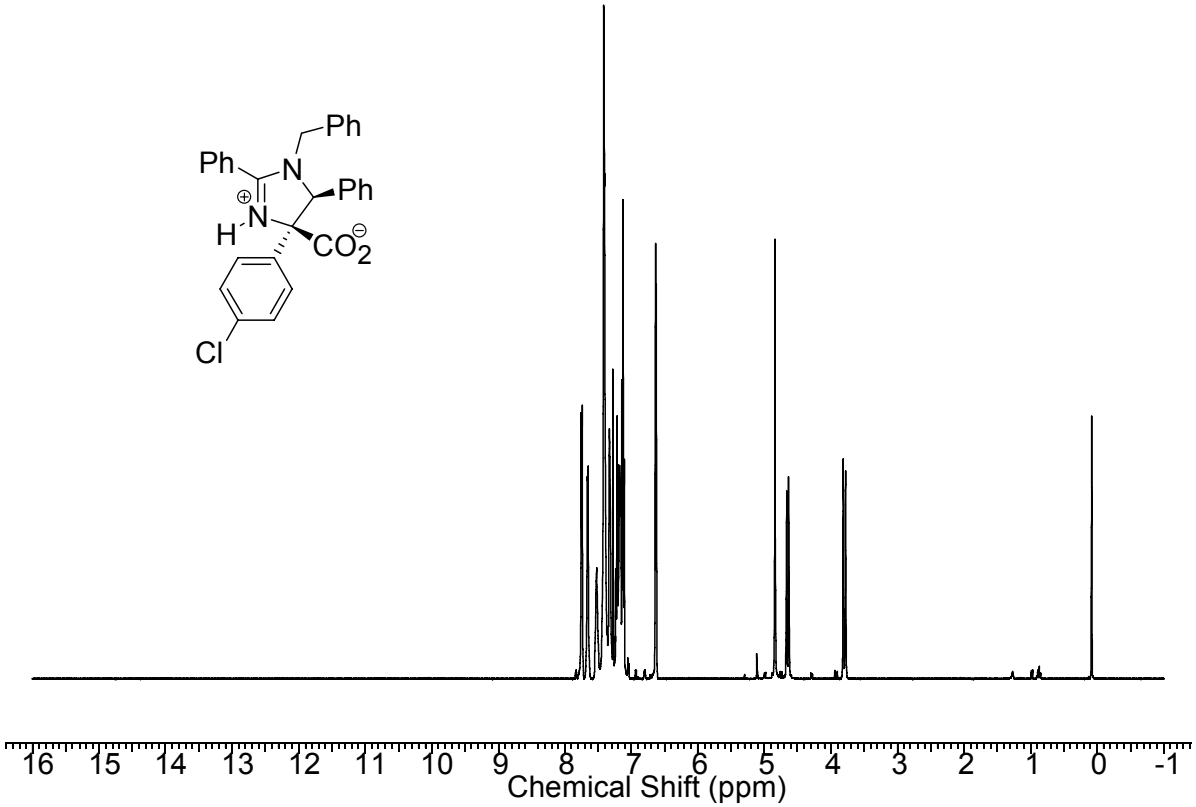


Figure II-19. NMR spectra of imidazoline **II-17**.



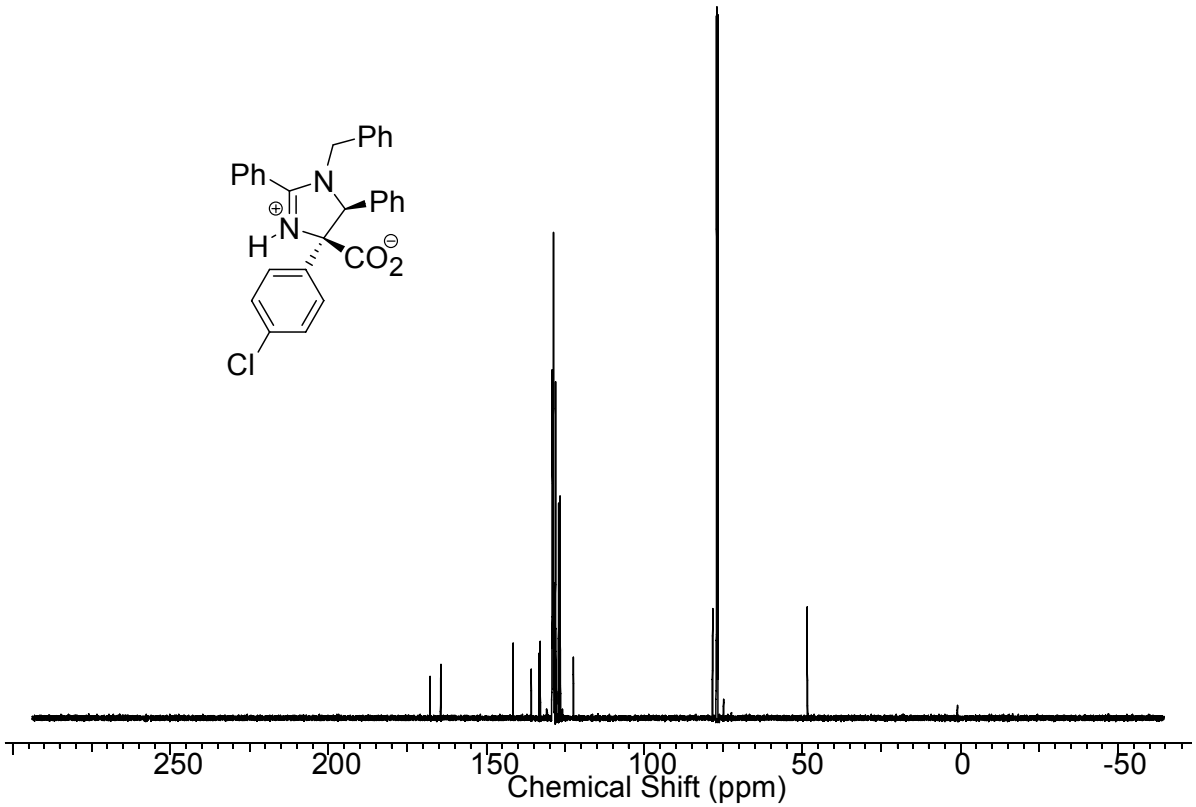
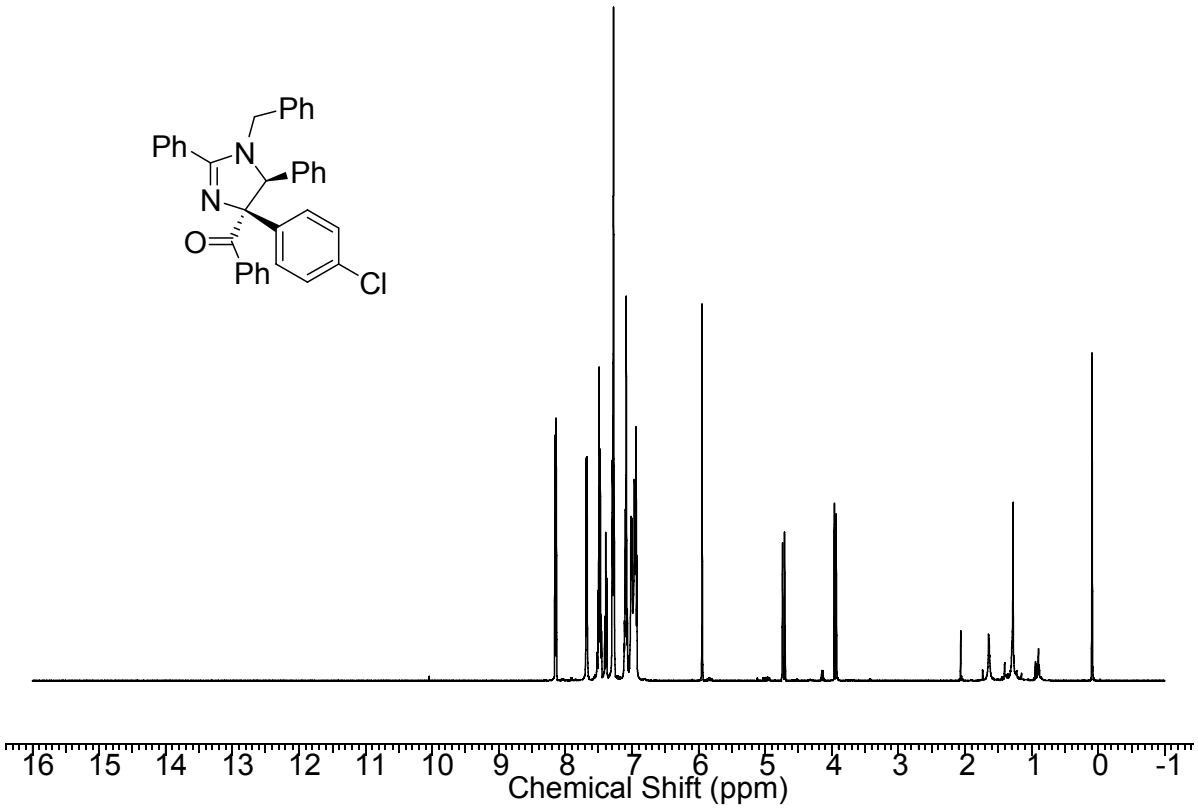


Figure II-20. NMR spectra of imidazoline **II-18**.



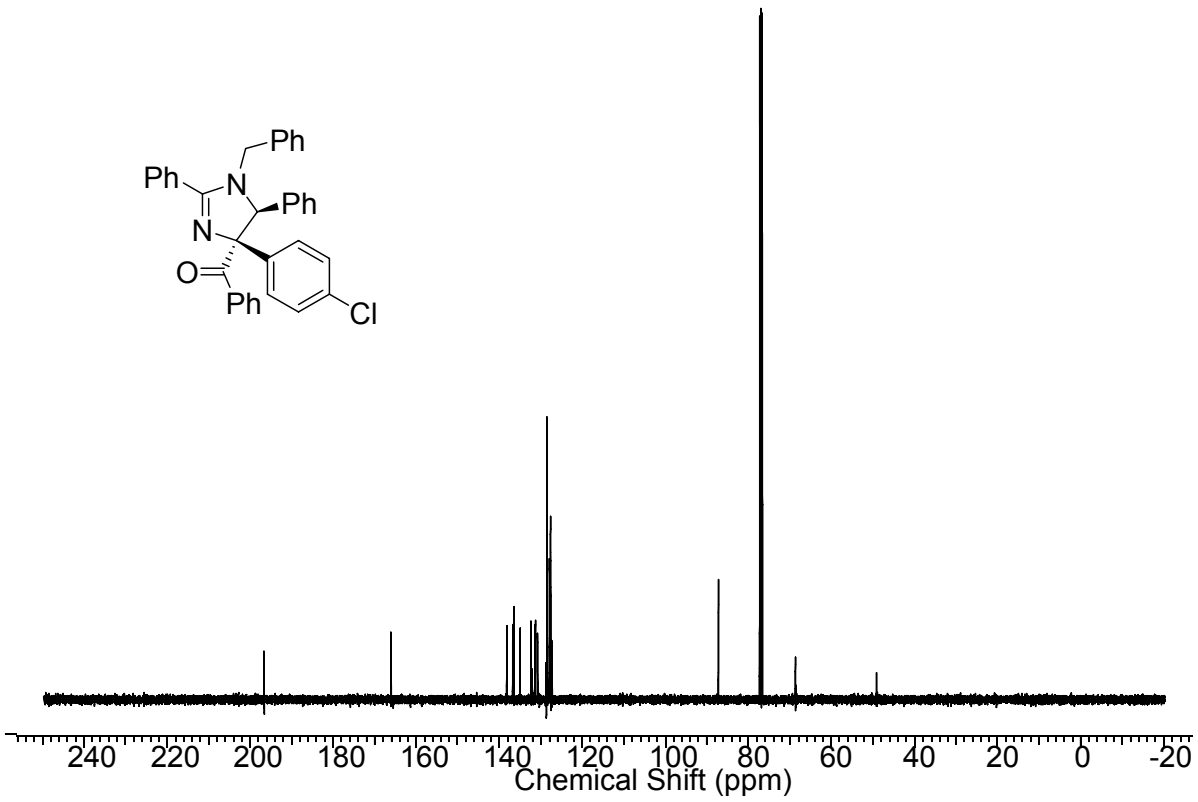


Figure II-21. NMR spectra of imidazoline **II-19**.

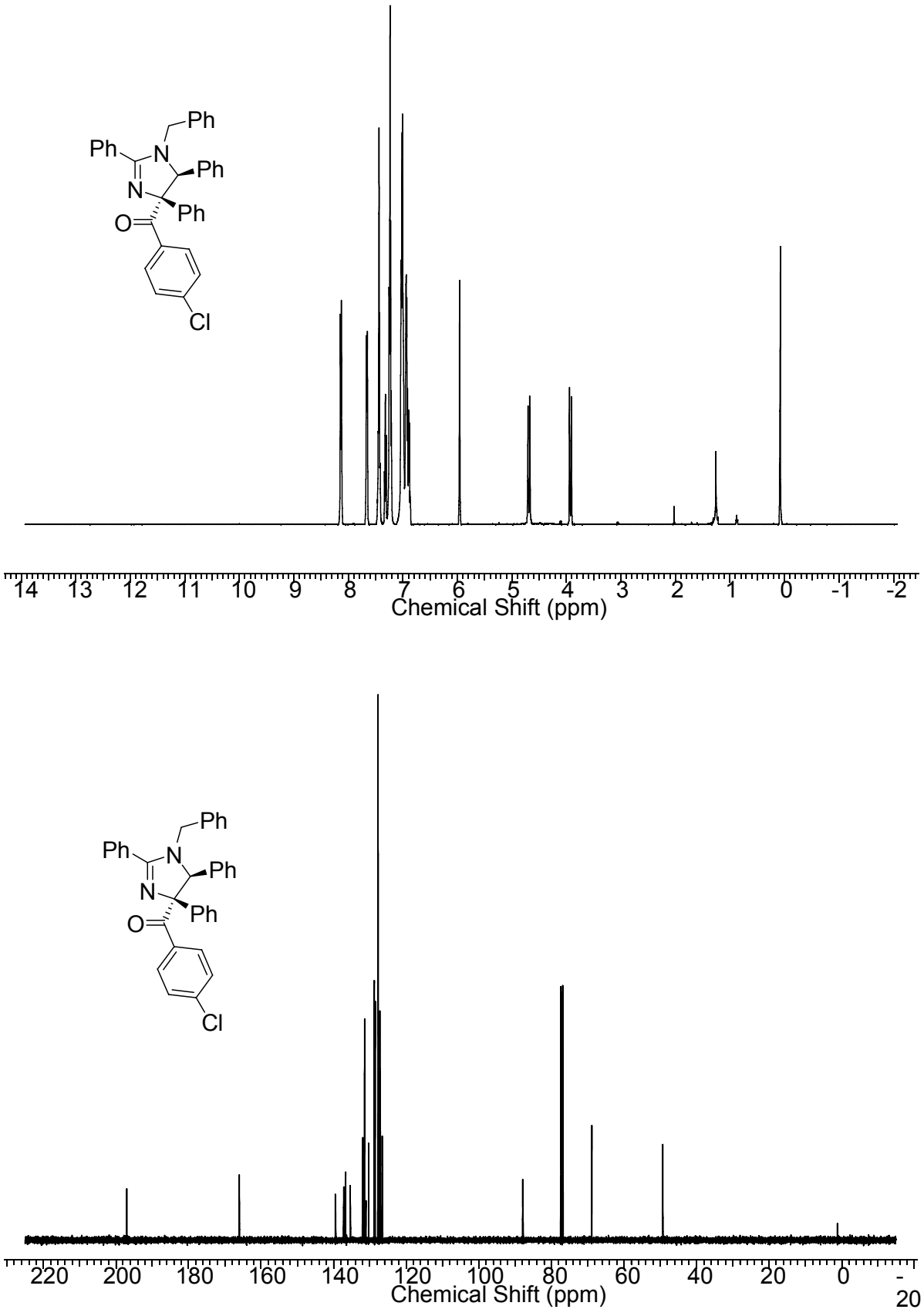
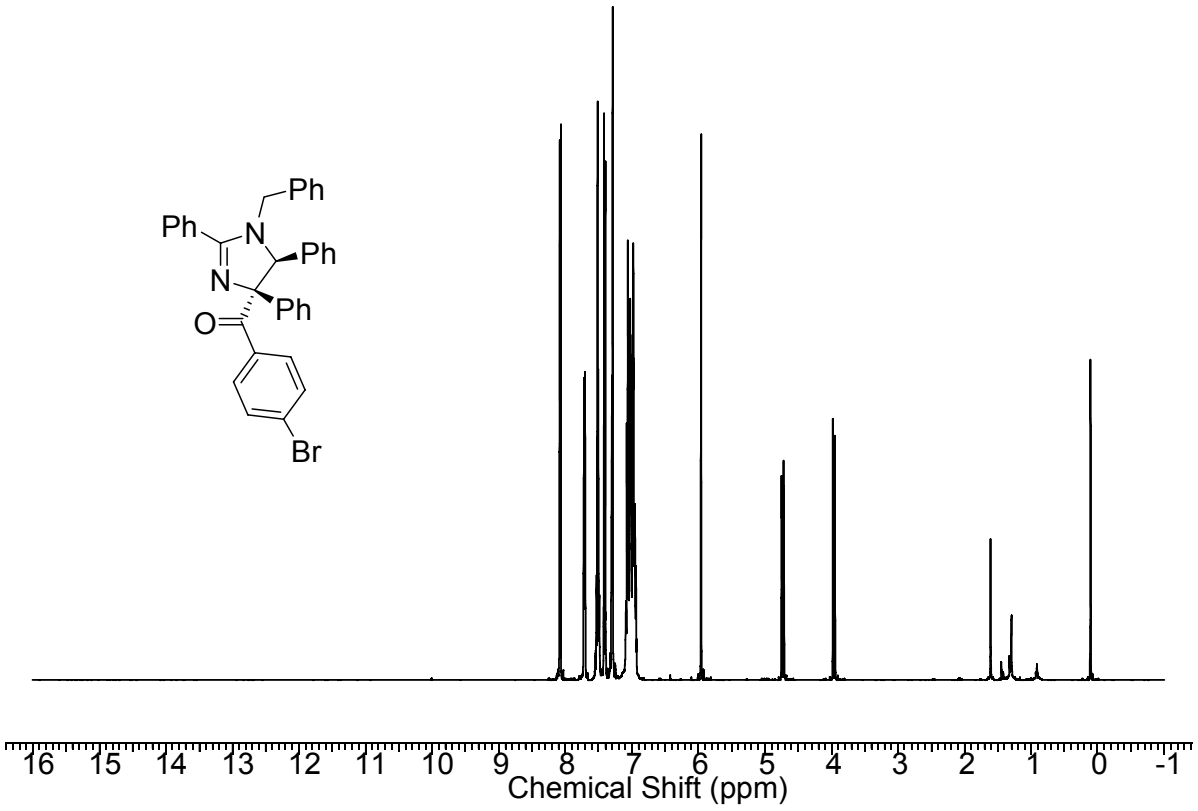


Figure II-22. NMR spectra of imidazoline **II-25**.



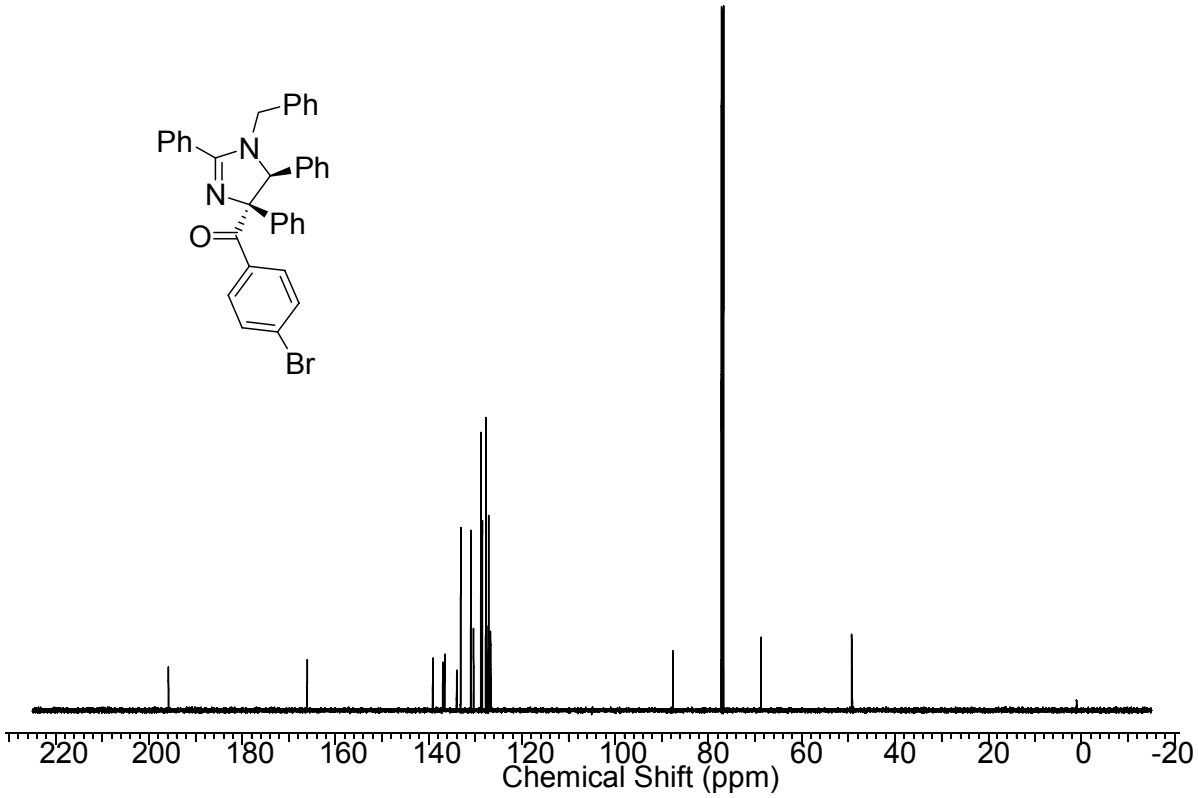
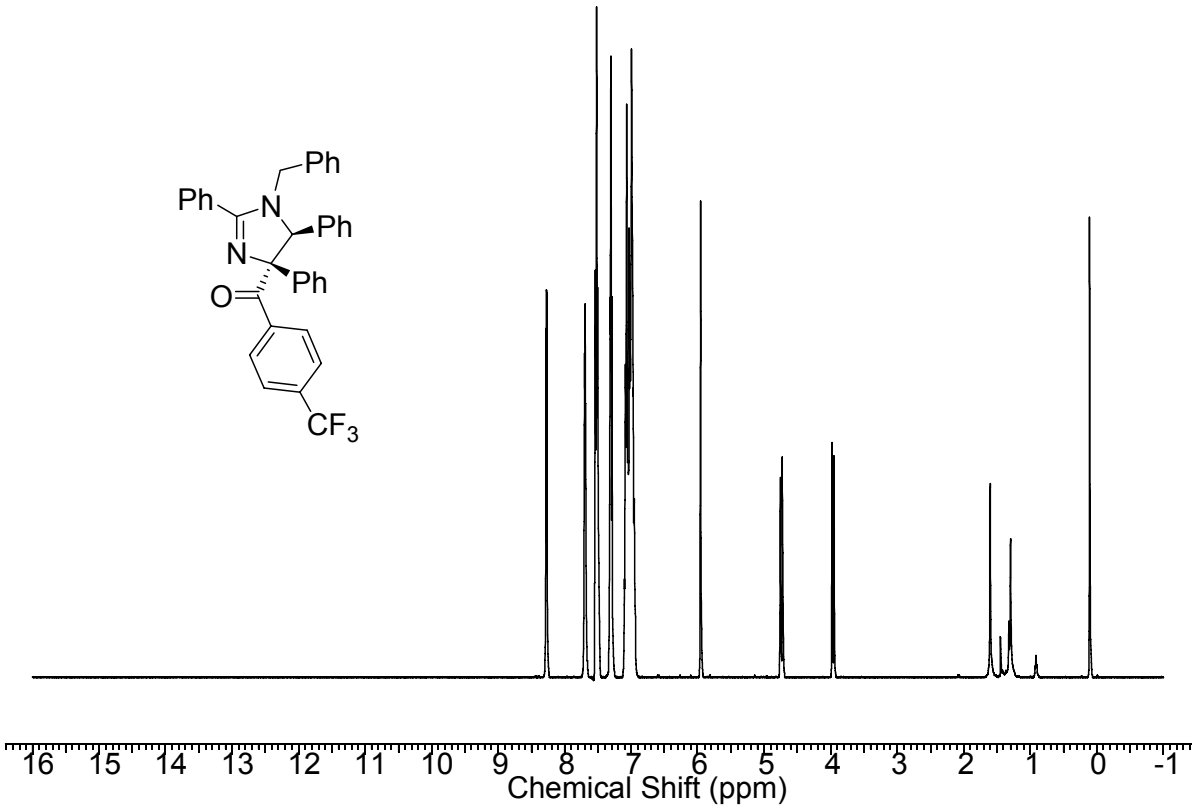


Figure II-23. NMR spectra of imidazoline **II-26**.



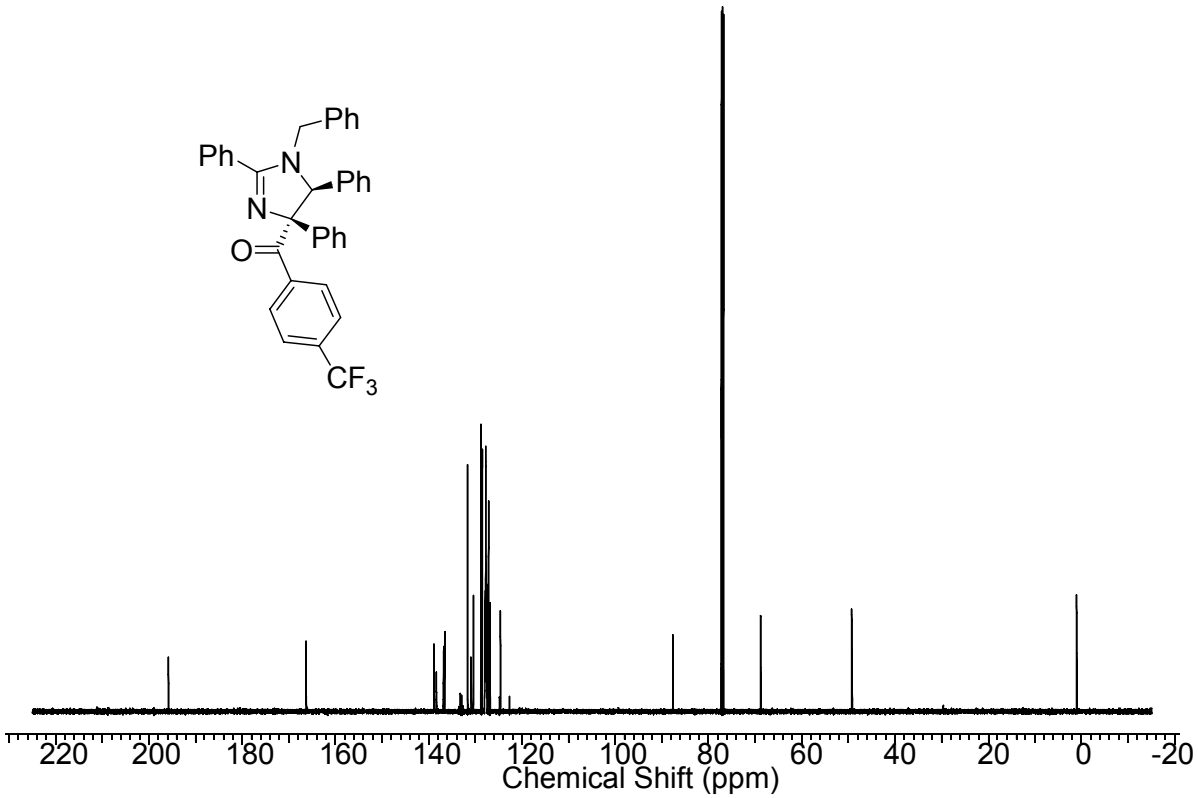


Figure II-24. NMR spectra of imidazoline **II-27**.

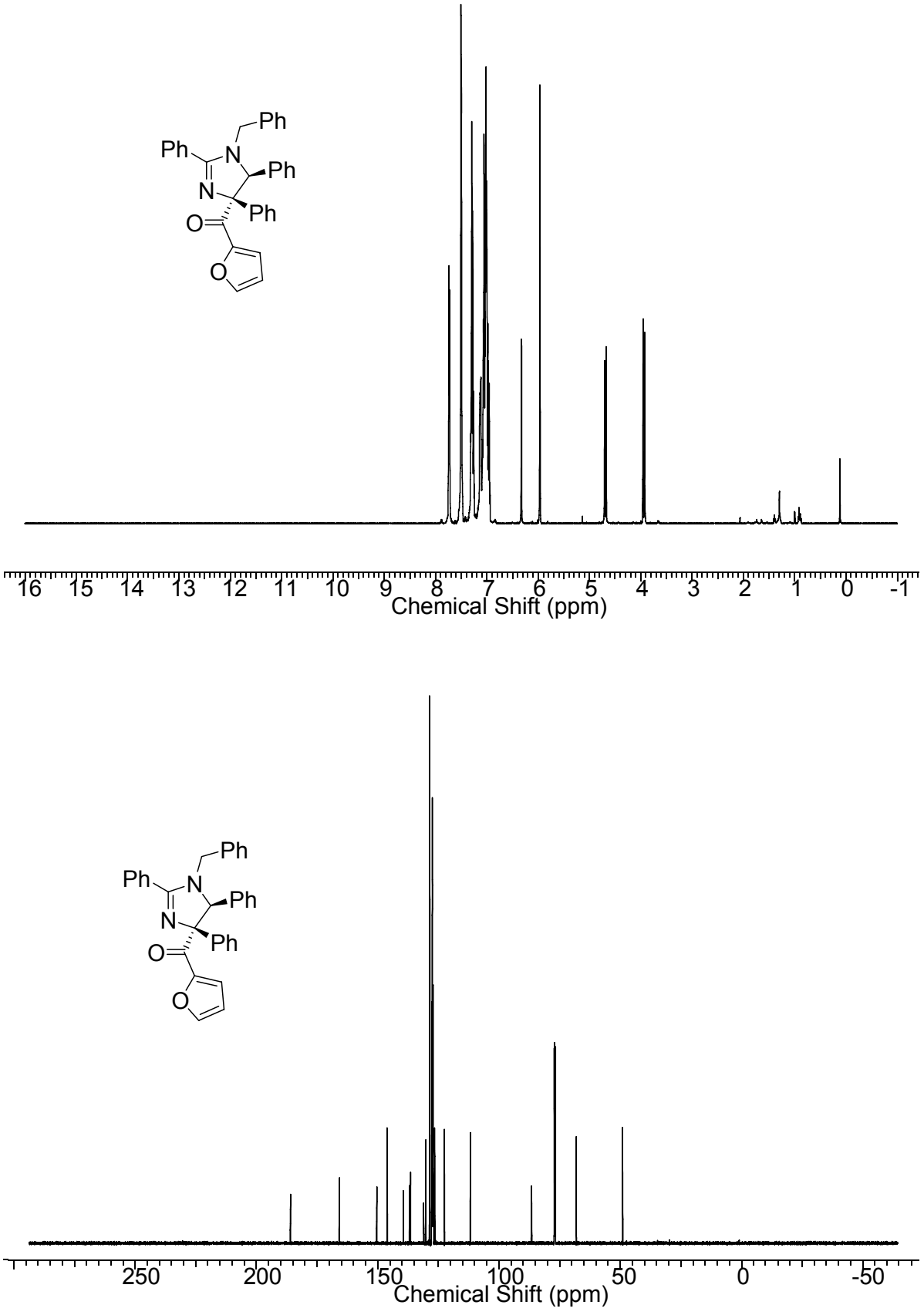


Figure II-25. NMR spectra of imidazoline **II-28**.

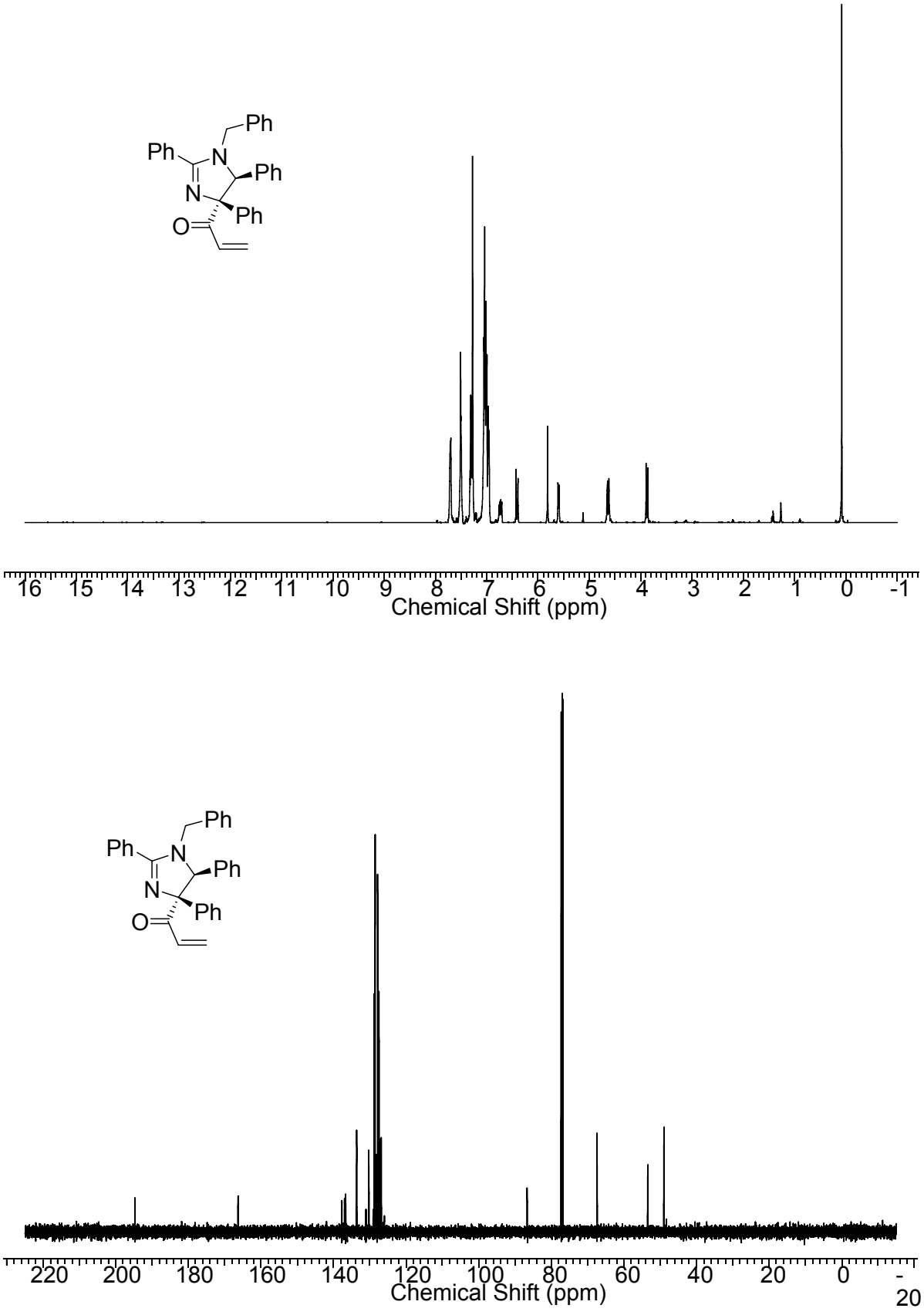


Figure II-26. NMR spectra of imidazoline **II-29**.

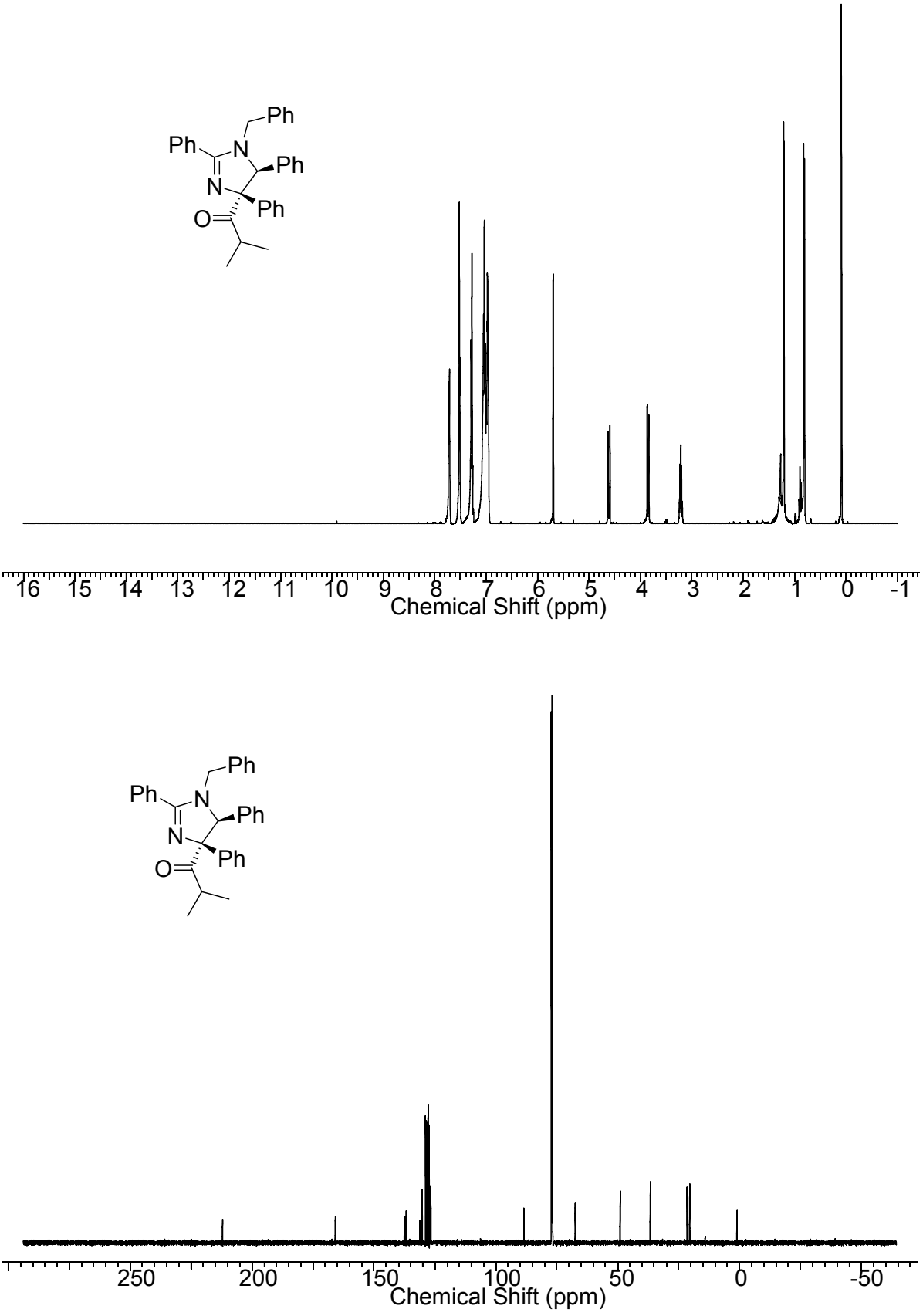


Figure II-27. NMR spectra of imidazoline **II-30**.

H.4 gNOESY spectra of II-5 (Diastereomer I)

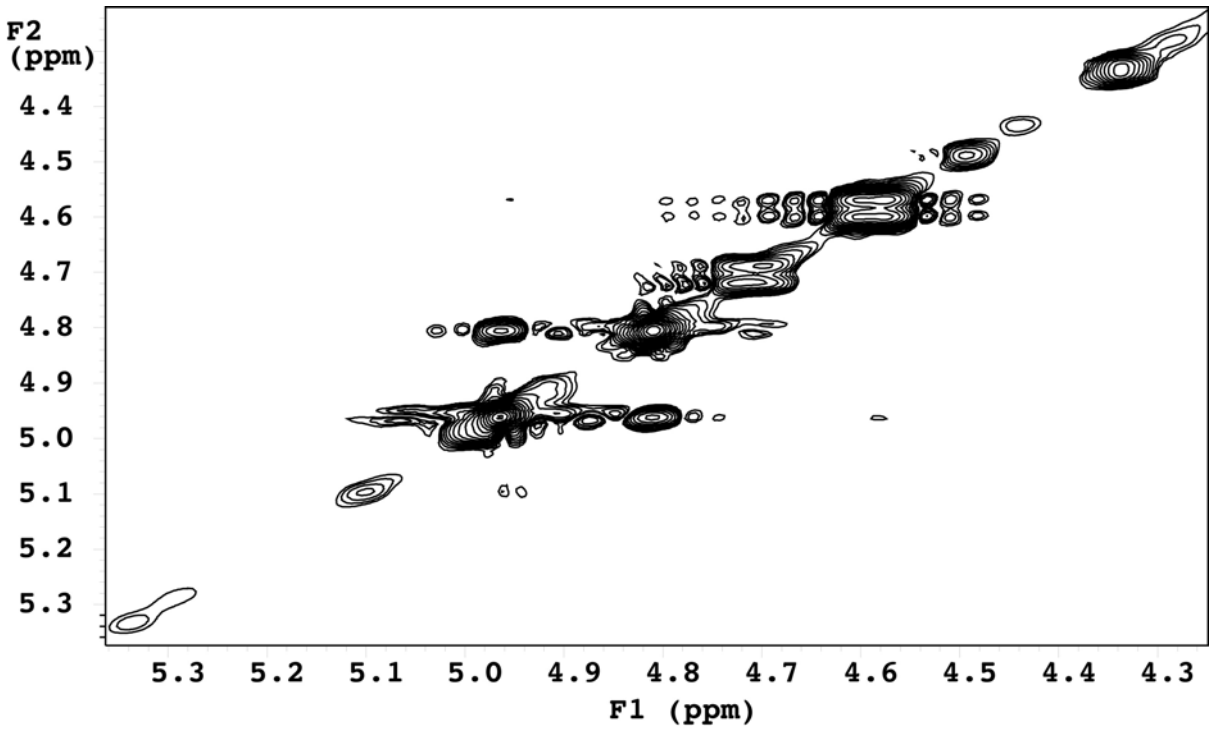


Figure II-28. gNOESY spectra of diastereomer I of **II-5**.

H.5 X-ray Crystallographic Data for II-1, II-3, II-19, II-28

X-ray Crystallographic Data for compounds **II-1, II-3**, **II-19** and **II-28** has been deposited at the Cambridge Crystallographic Data Centre and allocated the corresponding deposition numbers.

REFERENCES

REFERENCES

1. Rice, P. J.; Miller, D. D.; Sokoloski, T. D.; Patil, P. N. Pharmacologic implications of α-adrenoreceptor interactive parameters for epinephrine enantiomers in the rat vas deferens. *Chirality* **1989**, *1*, 14-19.

2. (a) Macpherson, G. R.; Franks, M.; Tomoaia-Cotisel, A.; Ando, Y.; Price, D. K.; Figg, W. D. Current status of thalidomide and its role in the treatment of metastatic prostate cancer. *Critical reviews in oncology/hematology.* **2003**, *46*, S49-S57. (b) Stephens, T. D.; Bunde, C. J. W.; Fillmore, B. J. Mechanism of action in Thalidomide teratogenesis. *Biochemical Pharmacology* **2000**, *59*, 1489-1499.

3. Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science* **2004**, *303*, 844-848.

4. Sharma, V.; Lansdell, T. A.; Peddibhotla, S.; Tepe, J. J. Sensitization of tumor cells toward chemotherapy: enhancing the efficacy of Camptothecin with imidazolines. *Chem. Biol.* **2004**, *11*, 1689-1699.

5. Sharma, V.; Peddibhotla, S.; Tepe, J. J. Sensitization of cancer cells to DNA damaging agents by imidazolines. *J. Am. Chem. Soc.* **2006**, *128*, 9137-9143.

6. Li, X.; Stark, G. R. NFκB-dependent signaling pathways. *Experimental Hematology.* **2002**, *30*, 285-296.

7. (a) Perkins, N. D. The Rel/ NF-κB family: friend and foe. *Trends Biochem. Sci.* **2000**, *25*, 434-440. (b) Grossmann, M.; O'Reilly, L. A.; Gugasyan, R.; Strasser, A.; Adams, J. M.; Gerondakis, S. The anti-apoptotic activities of Rel and RelA required during B-cell maturation involve the regulation of Bcl-2 expression. *EMBO* **2000**, *19*, 6351-6360.

8. (a) Baldwin, A. S. The NF-κB and IκB proteins: new discoveries and insights. *Annu. Rev. Immunol.* **1996**, *14*, 649-681. (b) Lin, Y. C.; Brown, K.; Siebenlist, U. Activation of NF-kappaB requires proteolysis of the inhibitor I kappa B-alpha: signal-induced phosphorylation of I kappa B-alpha alone does not release active NF-kappaB. *Proc. Natl. Acad. Sci.* **1995**, *92*, 552-556.

9. O'Connor, O. A.; Wright, J. Moskowitz, C.; Muzzy, J.; MacGregor-Cortelli, B.; Stubblefield, M.; Straus, D.; Portlock, C.; Hamin, P.; Choi, E.; Dumetrescu, O; Esseltine, D.; Trehu, E.; Adams, J.; Schenkein, D.; Zelenetz, A. D. Phase II clinical experience with the novel Proteasome inhibitor Bortezomib in patients with indolent

non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. *Journal of Clinical Oncology* **2005**, *23*, 676-684.

10. (a) Bunn, P. A. The Potential role of Proteasome inhibitors in the treatment of lung cancer. *Clin. Cancer Res.* **2004**, 10, 4263-4265. (b) Roué, G.; Pérez-Galán, P.; Mozos, A. López-Guerra, M.; Xargay-Torrent, S.; Rosich, L; Saborit-Villarroya, L.; Normant, E.; Campo, E.; Colomer, D. The Hsp90 inhibitor IPI-504 overcomes bortezomib resistance in mantle cell lymphoma in vitro and in vivo by down-regulation of the prosurvival ER chaperone BiP/Grp78. *Blood* **2011**, *117*, 1270-1279.

11. Edmund, E.; Lee, E. C.; Cao, Y.; Bannerman, B.; Fitzgerald, M.; Berger, A.; Yu, J.; Yang, Y.; Hales, P.; Bruzzese, F.; Liu, J.; Blank, J.; Garcia, K.; Tsu, C.; Dick, L.; Fleming, P.; Yu, L.; Manfredi, M.; Rolfe, M.; Bolen, J. Evaluation of the Proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res.* **2010**, *70*, 1970-1980.

12. Pajonk, F.; Grumanny, T.; McBride, W. H. The Proteasome inhibitor MG-132 protects hypoxic SiHa cervical carcinoma cells after cyclic hypoxia/reoxygenation from ionizing radiation. *Neoplasia* **2006**, *8*, 1037-1041.

13. (a) O'Connor, O. A. Apoptosis: from biology to therapeutic targeting. *Ann. Oncol.* **2011**, *22*, 76-79. (b) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatakeyama, S. A concise route to (+)-Lactacystin. *J. Org. Chem.* **2004**, *69*, 7765-7768. (c) Hogan, P. C.; Corey, E. J. Proteasome inhibition by a totally synthetic β-lactam related to Salinosporamide A and Omuralide. *J. Am. Chem. Soc.* **2005**, *127*, 15386-15387.

14. (a) Sharma, V.; Lansdell, T. A.; Peddibhotla, S.; Tepe, J. J. Sensitization of tumor cells toward chemotherapy: enhancing the efficacy of Camptothecin with imidazolines. *Chem. Biol.* **2004**, *11*, 1689-1699. (b) Sharma, V.; Peddibhotla, S.; Tepe, J. J. Sensitization of cancer cells to DNA damaging agents by imidazolines. *J. Am. Chem. Soc.* **2006**, *128*, 9137-9143.

15. Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Hupp, C. D.; Friebe, T. L.; Hovde, S.; Jones, D. A.; Dyer, R. D.; Henry, W. R.; Tepe, J. J. Nuclear factor-κB mediated inhibition of cytokine production by imidazoline scaffolds. *J. Med. Chem.* **2009**, *52*, 1302-1309.

16. Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Tepe, J. J. Structural-activity relationship study of highly-functionalized imidazolines as potent inhibitors of nuclear transcription factor-κB mediated IL-6 production. *Bioorg. Med. Chem.* **2009**, *17*, 3093-3103.

17. (a) Lapitskaya, M. A.; Vasiljeva, L. L. Pivnitsky, K. K. *o*-Iodoxybenzoic acid in dimethylformamide as a convenient reagent for the oxidation of alcohols to aldehydes

and ketones. *Mendeleev Commun.* **2008**, *18*, 309-311. (b) Uyanik, M.; Akakura, M.; Ishihara, Kazuaki. 2-Iodoxybenzenesulfonic acid as an extremely active catalyst for the selective oxidation of alcohols to aldehydes, ketones, carboxylic acids, and enones with Oxone. *J. Am. Chem. Soc.* **2009**, *131*, 251-262.

18. (a) Kuhakarn, C.; Kittigowittana, K.; Pohmakotr, M.; Reutrakul, V. IBX/*n*-Bu_4NBr/CH_2Cl_2-H_2O: a new mild system for selective oxidation of secondary alcohols. *Tetrahedron* **2005**, *61*, 8995-9000. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T.; *o*-Iodoxybenzoic acid (IBX) as a viable reagent in the manipulation of nitrogen- and sulfur-containing substrates: scope, generality, and mechanism of IBX-mediated amine oxidations and dithian deprotection. *J. Am. Chem. Soc.* **2004**, *126*, 5192-5201.

19. Frigerio, M.; Santagostino, M.; Sputore, S. A user-friendly entry to 2-iodoxybenzoic acid (IBX). *J. Org. Chem.* **1999**, *64*, 4537-4538.

20. Kahlon, D. K.; Lansdell, T. A.; Fisk, J. S.; Hupp, C. D.; Friebe, T. L.; Hovde, S.; Jones, D. A.; Dyer, R. D.; Henry, W. R.; Tepe, J. J. Nuclear factor-κB mediated inhibition of cytokine production by imidazoline scaffolds. *J. Med. Chem.* **2009**, *52*, 1302-1309.

21. Sharma, V.; Tepe, J. J. Diastereochemical diversity of imidazoline scaffolds via substrate controlled TMSCl-mediated cycloaddition of azlactones. *Org. Lett.* **2005**, *7*, 5091-5094.